SYNTHETIC STRATEGIES TOWARDS (+)-L-733,060, BRUGUIEROLS AND NATURAL/SYNTHETIC LACTONES AND DDQ MEDIATED DEPROTECTION OF N-ALLYLIC AMINES

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IN

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BY

SHIJO K. CHERIAN

UNDER THE GUIDANCE OF

DR. PRADEEP KUMAR

DIVISION OF ORGANIC CHEMISTRY
CSIR-NATIONAL CHEMICAL LABORATORY
PUNE-411008, INDIA

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CSIR-NATIONAL CHEMICAL LABORATORY

Dr. Homi Bhabha Road, Pune-411 008, India

Dr. Pradeep Kumar
Scientist G, FNASc
Organic Chemistry Division
CSIR-National Chemical Laboratory
Pune-411008, India

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

CERTIFICATE

This is to certify that the work presented in the thesis entitled "**Synthetic Strategies Towards (+)-L-733,060, Bruguierols and Natural/Synthetic Lactones And DDQ Mediated Deprotection of N-Allylic Amines**" submitted by **Shijo K. Cherian** was carried out by the candidate at National Chemical Laboratory, Pune under my supervision. Such materials as obtained from other sources have been duly acknowledged in the thesis.

(Dr. Pradeep Kumar)
Research Guide

September 2013

CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled "**Synthetic Strategies Towards (+)-L-733,060, Bruguierols and Natural/Synthetic Lactones And DDQ Mediated Deprotection of N-Allylic Amines**" submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune has not been submitted by me to any other university or institution. This work was carried out at CSIR-National Chemical Laboratory, Pune, India.

Shijo K. Cherian **September 2013**
Senior Research Fellow
Organic Chemistry Division
CSIR-National Chemical Laboratory
Pune-411008, India

Dedicated to

Adhvay, Adith, Annu, Amma

&

Chacha

The greatest challenge to any thinker is stating the problem in a way that will allow a solution.

Bertrand Russell

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It is a great pleasure to express my thanks and appreciations towards the people who have in many ways assisted me to reach this stage. First of all I would like to express my deep sense of gratitude to my research guide, Dr. Pradeep Kumar, for introducing me to this fascinating field of Organic Chemistry, also for his support and guidance throughout my association with him. This thesis would have not been possible without his help, support and most importantly, the wholeheartedness. I will never forget his encouraging words and patience when my motivation was at a low. I preserve an everlasting gratitude for him.

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Shijo K. Cherian

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Chapter 5

Chemoselective Deprotection of N-Allylic Amines using DDQ

Abbreviations

Ac	-	Acetyl
ACN	-	Acetonitrile
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
Bn	-	Benzyl
BnBr	-	Benzyl bromide
$BH_3 \cdot Me_2S$	-	Boron dimethyl sulfide complex
Boc	-	*tert*-Butoxy carbonyl
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
BuLi	-	Butyl lithium
Cat.	-	Catalytic
$CDCl_3$	-	Deuterated chloroform
DBU	-	1,8-Diazabicyclo[5.4.0]undecene-7
DCM	-	Dichloromethane
$(DHQ)_2PHAL$	-	1,4-Bis(dihydroquinin-9-*O*-yl)phthalazine
$(DHQD)_2PHAL$	-	1,4-Bis(dihydroquinindin-9-*O*-l)phthalazine
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	-	Diisobutylaluminiumhydride
DMP	-	2,2-Dimethoxypropane
DMF	-	*N, N′*-Dimethylformamide
DMAP	-	*N,N′*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
ee	-	Enantiomeric excess
equiv.	-	Equivalents
EtOH	-	Ethanol
Et	-	Ethyl
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
Hz	-	Hertz

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

General remarks

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

Abstract

The thesis entitled **"Synthetic Strategies Towards (+)-L-733,060, Bruguierols and Natural/Synthetic Lactones And DDQ Mediated Deprotection of N-Allylic Amines"** is divided into five chapters.

Chapter 1: Introduction to Sharpless asymmetric epoxidation, Jacobsen's hydrolytic kinetic resolution (HKR) and proline-catalysed reactions.

Chapter 2: Studies towards enantioselective synthesis of (+)-L-733,060 and (+)-CP-99,994 using Sharpless asymmetric epoxidation.

Chapter 3: Formal synthesis of verbalactone and its monomer via two different hydrolytic kinetic resolution strategies.

Chapter 4: Enantiomeric synthesis of substituted chiral γ-butyrolactones from aldehydes via proline-catalysed sequential lactonization reaction and proline-catalysed enantiomeric synthesis of Bruguierol A and Bruguierol B.

Chapter 5: Chemoselective deprotection of *N*-Allylic amines using DDQ.

Chapter 1: Introduction to Sharpless asymmetric epoxidation (AE), Jacobsen's hydrolytic kinetic resolution (HKR) and proline-catalysed reactions.

This chapter gives a brief introduction to Sharpless asymmetric epoxidation (AE), Jacobsen's hydrolytic kinetic resolution (HKR) and proline-catalysed reactions.

The ultimate goal of organic synthesis is to assemble a given organic compound (target molecule) from readily available starting materials and reagents in the most efficient way.[1] It is more elegant and economical to prepare just wanted isomer by asymmetric synthesis and through inexpensive catalytic processes. It is especially useful in the case of carbon-

hetero atom bond formation reaction, since the resulting functionality can be readily manipulated to produce many important different classes of compounds.

The oxidation of olefins is considered as the single most versatile, powerful and reliable class of transformation in organic synthesis. The Sharpless epoxidation[2] is a popular laboratory process that is both enantioselective and catalytic in nature. It employs inexpensive reagents and involves various important substrates (allylic alcohols) and products (epoxides) in organic synthesis. It also demonstrates unusually wide applicability because of its insensitivity to many aspects of substrate structure.[3] The wide scope application of this transformation arises not only from the utility of epoxide compounds but also from the subsequent regiocontrolled and stereocontrolled nucleophilic substitution (ring-opening) reactions of the derived epoxy alcohol. These, through further functionalization, allow access to an impressive array of target molecules in enantiomerically pure form.[4]

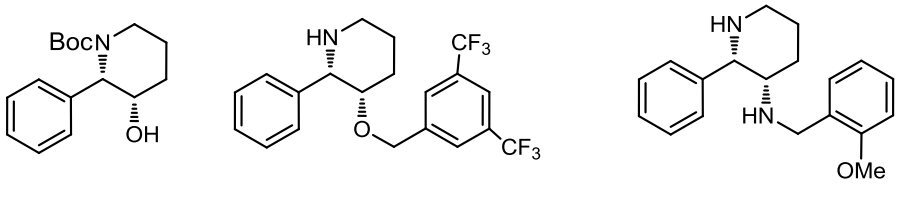
The hydrolytic kinetic resolution[5] (HKR) of terminal epoxides catalyzed by chiral (salen) Co^{III}(OAc) complex affords both recovered epoxide and 1,2-diol product in highly enantioenriched form. The HKR provides general access to useful, highly enantioenriched chiral building blocks that are otherwise difficult to access, from inexpensive racemic materials. The HKR has seen rapid adoption as the method of choice for the preparation of a variety of terminal epoxides in enantioenriched form, and a large number of applications in target oriented synthesis have been reported already.[6]

The field of asymmetric organocatalysis is rapidly growing and attracts an increasing number of research groups around the world. In this connection, proline, an abundant, inexpensive amino acid available in both enantiomeric forms, has emerged as arguably the most practical and versatile organocatalyst.[7-8] The organocatalytic asymmetric α-aminoxylation of aldehydes and ketones with proline as catalyst is a highly enantioselective means of preparation of α-hydroxy carbonyl compounds and their derivatives.[9] Proline-catalyzed sequential transformations is an emerging research field in organic synthesis as synthesis of complex organic molecules could be accessible in one-pot procedure. Recently a variety of such transformations has been developed by different research groups.[10]

These methods have contributed to more advances in research not only in chemistry but also in material science, biology and medicine. This work gives access to new molecules needed to investigate hitherto undiscovered and unexplained phenomena in the molecular world. In this chapter, we have described aforementioned catalytic reactions. During the course of our research work we have prepared chiral epoxides and lactones and successfully employed these synthetic intermediate towards the synthesis of (+)-L-733,060, (+)-CP-99,994, Bruguierols A and B, Verbalactone and its monomer.

<u>Chapter 2:</u> Studies towards enantioselective synthesis of (+)-L-733,060 and (+)-CP-99,994 using Sharpless asymmetric epoxidation.

The search for non-peptide antagonists of the NK1 receptor led to the discovery of 2,3-disubstituted piperidine derivatives L-733,060 **2**[11] and CP-99,994 **3**[12] (Figure 1). They have excellent affinity and selectivity with human NK1 receptors and possess potent antiemetic activity.[13] They are expected to act as remedy for a wide range of diseases, including arthritis, asthma and migraines.[14] Structure activity relationship studies have shown that the *cis* relationship between C2 and C3 substituents on the piperidine ring of **2** and **3** is required for optimum binding activity.[15] The present study describes our endeavors towards the synthesis of compound **2** and **3** from commercially available cinnamyl alcohol. In this strategy the chirality was introduced by Sharpless asymmetric epoxidation (AE) and piperidine ring formation was achieved by one pot Staudinger/aza-Wittig reaction.[16]



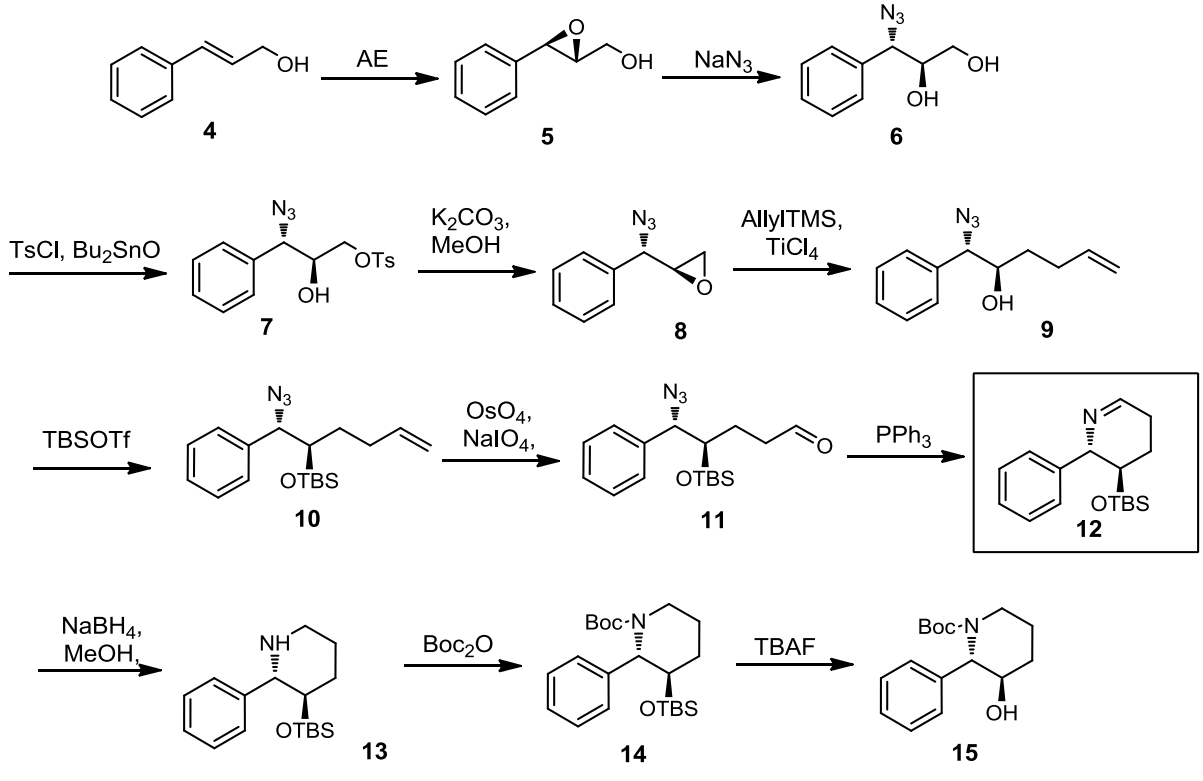
1 (+)-L-733,060 **2** (+)-CP-99,994 **3**

Figure 1: Structures of 2-aryl-3-hydroxypiperidine and 2-aryl-3-aminopiperidine derivatives

As shown in Scheme 1, the synthesis of **2** and **3** were initiated by AE of commercially available cinnamyl alcohol **4** to afford *trans*-epoxide **5**.[17] The regioselective epoxide opening of **5** with NaN_3 gave a single regio-isomer **6**.[18] The regioselective primary monotosylation of diol **6** with tosyl chloride and catalytic Bu_2SnO, furnished compound **7** which on base

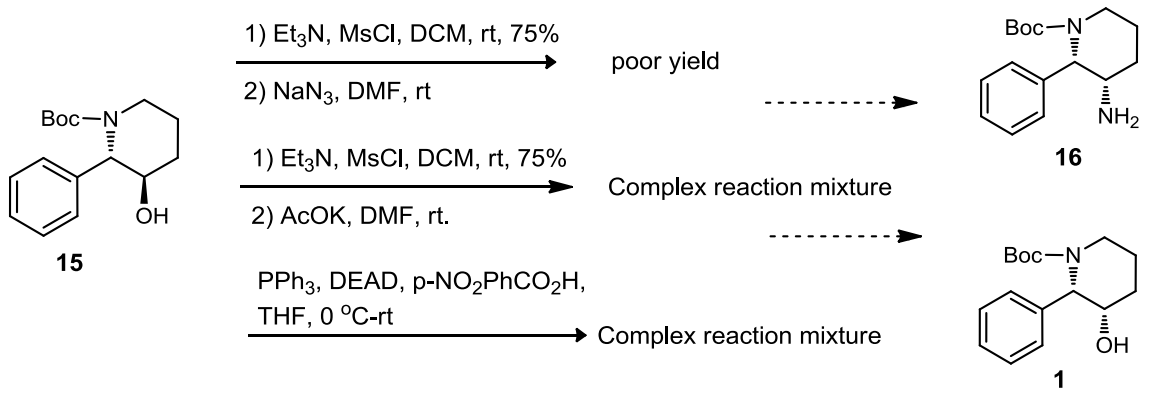
treatment in presence of K_2CO_3 in methanol furnished azido epoxide **8.** The chain elongation through regioselective ring opening of epoxide **8** by allylation is achieved after several trials. Finally we could improve the yield of **9** by using 3 equivalents of allylsilane with slow addition of freshly distilled $TiCl_4$.

The subsequent protection of secondary hydroxyl group in **9** as TBS ether **10** was successfully carried out using TBS triflate and 2,6-lutidine[19]. The oxidation of olefin[20]**10** gave the crucial azido-aldehyde intermediate **11** required for the one pot Staudinger/aza-Wittig reaction. Without further purification of aldehyde **11**, Staudinger reduction was performed. The resulting aza-ylide was condensed intramolecularly with aldehyde to provide a six membered imine **12**. The *in situ* reduction of imine with $NaBH_4$ and methanol in the same reaction medium provided the free amine **13** in good yield. Subsequently the free amine **13** was protected as Boc derivative **14** and TBS was selectively deprotected using TBAF to obtain compound **15**[21] in 90% yields (Scheme 1).



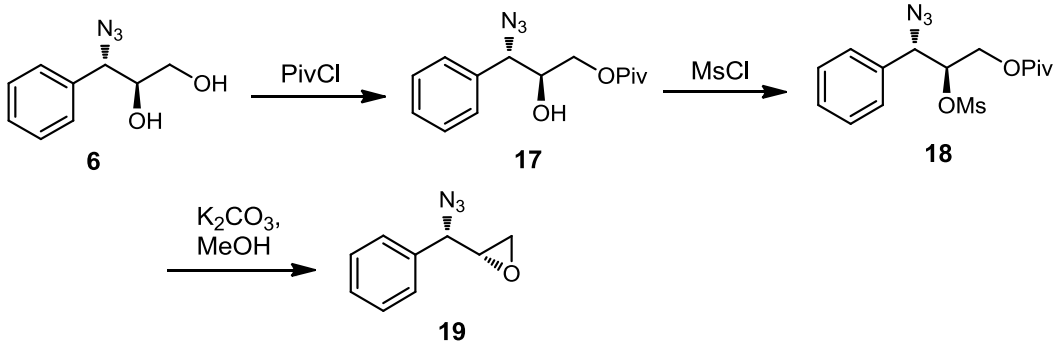
Scheme 1: Synthesis of *trans*-2-aryl-3-hydroxypiperidine

Since various attempts[22] to make required *cis*-1,2- configuration from **15** failed at this stage (Scheme 2)**,** we decided to invert the hydroxy to the required configuration at the early stage of the synthesis, that is, before the formation of the piperidine ring.



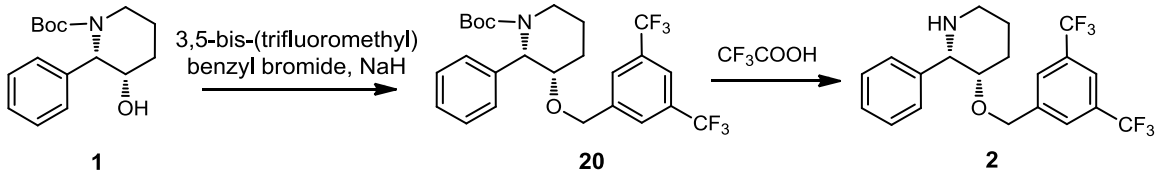
Scheme 2: Various attempts to make required *cis*-2-aryl-3-hydroxypiperidine from **15**

The desired *cis*-configuration was achieved through a three-step sequence involving the chemoselective pivalation[23] of diol **6**, mesylation of secondary hydroxyl **17** using MsCl and final treatment of crude mesylate **18** with K_2CO_3 in methanol to furnish the appropriately oriented *cis* azido-epoxide **19** (Scheme 3). Once we accomplished the desired *cis* configuration, we completed the synthesis of N-Boc protected *syn*-3-hydroxy-2-phenylpiperidine **1** from **19** through previously established route.



Scheme 3: Synthesis of *cis* azido-epoxide **19**

Having constructed the piperidine ring with the desired *syn*-stereochemistry, *O*-alkylation of **1** with 3,5-bis(trifluoromethyl)benzyl bromide in the presence of NaH was performed[24] to give **20**. Finally *N*-Boc deprotection of **20** using TFA furnished the target molecule **2** in good yields (Scheme 4).

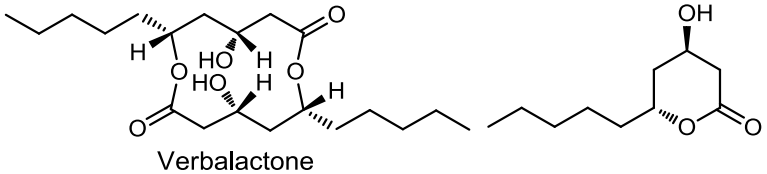


1 20 2

Scheme 4: Synthesis of (+)-L-733,060 **2**

<u>Chapter 3:</u> Formal synthesis of verbalactone and its monomer via two different hydrolytic kinetic resolution strategies

Verbalactone **21**[25] is a novel macrocyclic dimer lactone isolated from the roots of *Verbascum undulatum* Lam., a biennial plant that belongs to the family Scrophulariaceae (Figure 2). It is the first example of a 1,7-dioxacyclodecane unit being present in the ring system of a natural product. This compound exhibited interesting antibacterial activity against three Gram-positive bacteria with optimum activity MIC = 62.5 µg/mL and five Gram-negative bacteria with optimum activity MIC = 125 µg/mL.[26] The structure and the absolute stereochemistry of **21** (4*R*,6*R*,10*R*,12*R*,4,10-dihydroxy-2,8-dioxo-6,12-dipentyl-1,7-dioxocyclodecane) were determined by spectral methods and chemical correlation. Verbalactone 2**1** is a dimer of lactone **22** [(+)-(3*R*,5*R*)-3-hydroxy-5-decanolide], a secondary metabolite isolated from *Cephalosporium recifei*[27] (Figure 2). The lactone moiety 2**2** is identical to the lactone unit in compactin, mevinolin etc., a potent inhibitor of the enzyme HMG-CoA reductase.[28] Therefore the monomer **22** has also been the synthetic target of considerable interest.[29]



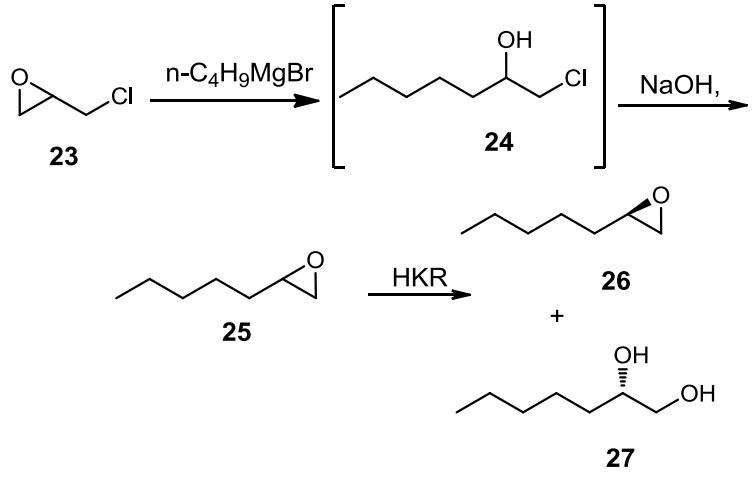
Verbalactone **21** **22**

Figure 2: Structure of Verbalactone and its monomer

This chapter is further divided into two sections.

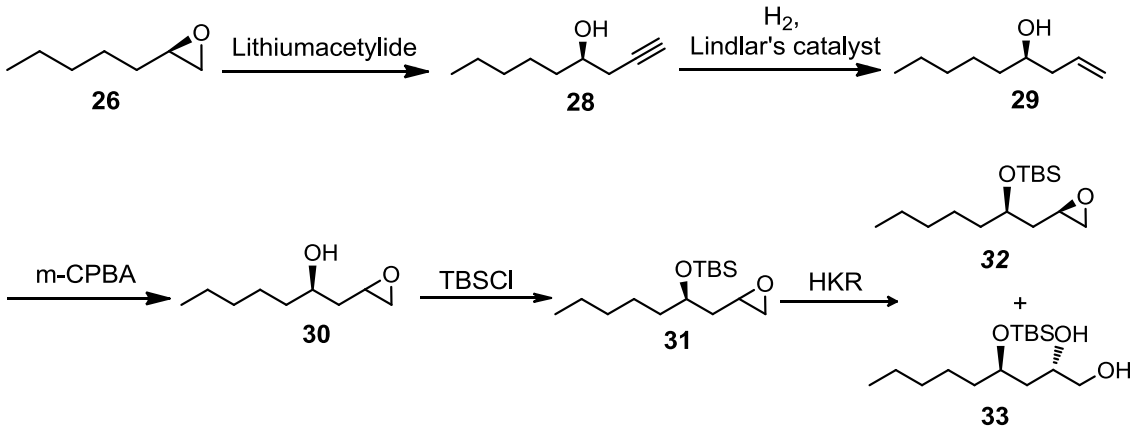
Section A: Formal synthesis of verbalactone and its monomer via iterative hydrolytic kinetic resolution

The synthesis of verbalactone **21** commenced from commercially available racemic epichlorohydrin **23** as depicted in Scheme 5. Racemic epoxide **25** from epichlorohydrin **23** was prepared by two step process. Then epoxide **25** was resolved with (*R,R*)-salen-Co-(OAc) complex (0.5 mol%) and water (0.55 equiv.) in THF (0.55 equiv.) to give the *R*-epoxide **26**[30] in 45% yield with 99% ee, and *S*-diol **27**[25] in 43% yield with 99.5% ee (Scheme 5).



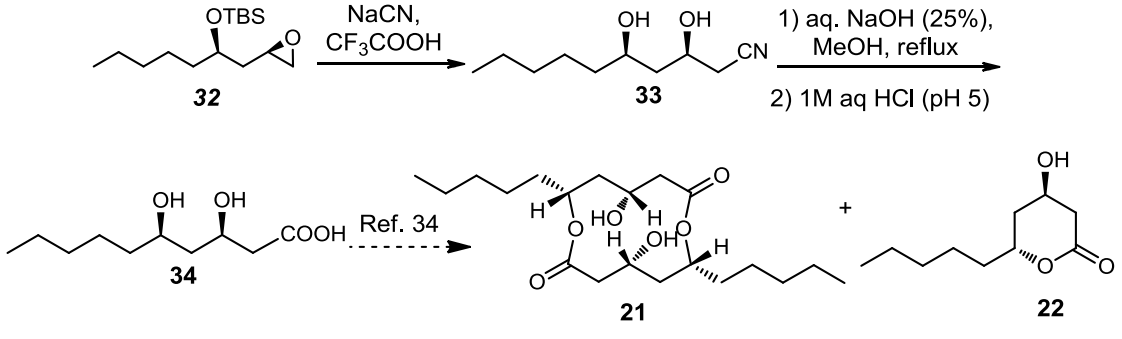
Scheme 5. Synthesis of *R*-epoxide **26** and *S*-diol **27** by HKR

With enantiomerically pure epoxide **26** in hand, our next task was to construct the *syn*-1,3-diol. The homoallylic alcohol **29** was prepared by a two-step reaction sequence from **26**. The epoxide **26** was treated with excess of lithiumacetylide followed by partial hydrogenation of the resultant acetylene **28** with Lindlar's catalyst[31] to afford the homoallylic alcohol **29** in excellent yield. The epoxidation of homoallylic alcohol **29**, followed by hydroxyl group protection as the TBS ether produced the epoxide **31** in favour of the desired *syn*-isomer (*syn*:*anti*/ 1.3:1) (Scheme 6). To synthesise the diastereomerically pure epoxide by means of Jacobson's hydrolytic kinetic resolution, the epoxide **31** was treated with (*R,R*)-salen-Co-(OAc) complex (0.5 mol%) and water (0.55 equiv.) in THF (0.55 equiv.) to afford the epoxide **32**[32] as a single diastereomer in 45% yield and the diol **33** in 47% yield. Epoxide **32** could easily be separated from the more polar diol **33** by silica gel column chromatography.



Scheme 6: Synthesis of the epoxide **32** and the diol **33** via HKR.

The regioselective ring opening of epoxide **32** was carried out with NaCN[33] in the presence of trifluroacetic acid in ethanol at 50 ^{o}C to give the cyanoalcohol **33** with concomitant removal of the TBS group. Finally, the hydrolysis of nitrile was effected by treatment of **33** with 25% aqueous NaOH in methanol followed by acidic work up at pH 5 with HCl to furnish the acid **34** in good yield. As the subsequent transformations of **34** to target molecules 2**1** and 2**2** under varied conditions have already been reported,[34] the formal synthesis of 2**1** and **22** was completed (Scheme 7).

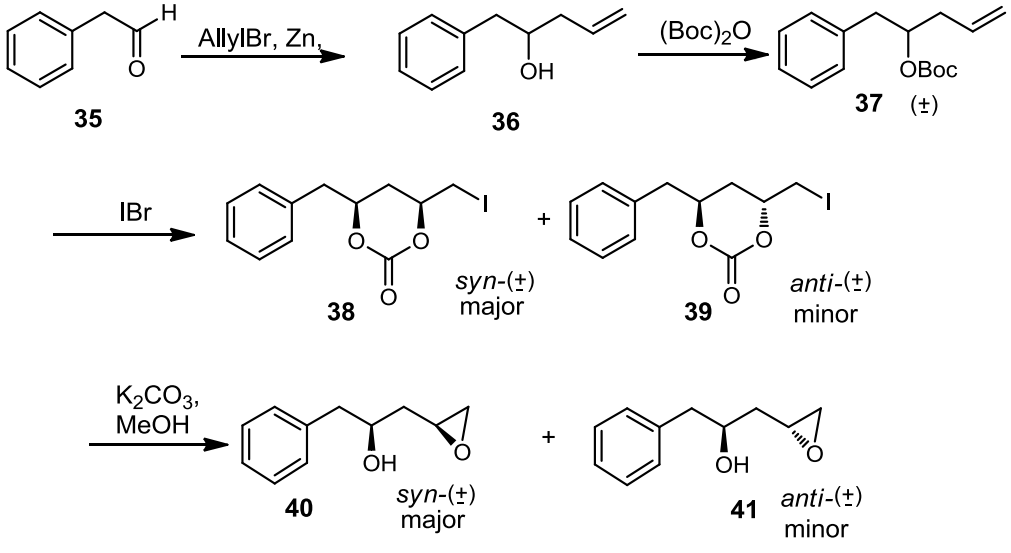


Scheme 7: Formal synthesis of verbalactone 2**1** and monomer **22**

Section B: A Revised Strategy for the synthesis of chiral epoxyalcohol, a precursor of verbalactone by combination of diastereoselective iodine induced electrophilic cyclization and hydrolytic kinetic resolution

Our revised strategy initiated with synthesis from Barbier-type[35] allylation of phenyl acetaldehyde **35** to homoallylic alcohol **36** (Scheme 8). To establish the second stereogenic

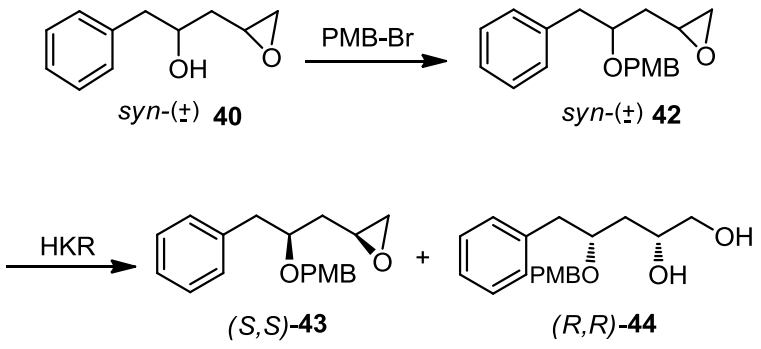
center with an excellent level of diastereoselectivity, we decided to apply a three-step sequence.[36] Accordingly first we prepared the homoallylic *tert*-butyl carbonate **37** from the corresponding alcohol **36** using BOC_2O[37] and DMAP in CCl_4. With substantial amount of BOC protected homoallylic alcohol **37** in hand we then further proceeded to explore the stereoselective outcome of iodocyclization[36] reaction in different reaction conditions. Cyclic iodo carbonates **38** and **39** were converted into the corresponding epoxy alcohols **40** and **41** by treatment with 3 equiv. of K_2CO_3 in methanol at room temperature (Scheme 8). Reaction was completed after 2 h to furnish the desired *syn*-epimer **40** with excellent diastereoselectivity.



Scheme 8: Synthesis of the racemic *syn*-epoxide **40**

With *syn*-racemic epoxide **40** in hand, our next aim was to synthesize the *syn*-(*S,S*)-epoxide through the Jacobsen's hydrolytic kinetic resolution method. Direct introduction of epoxide **40** to HKR reaction was a failure. So we decided to protect the free hydroxyl group of **40** before HKR reaction. We protected the hydroxyl group of homoallylic alcohol **40** as PMB ether **42** using PMB-bromide. In order to get the required (*S,S*)-hydroxyl epoxide **43**, racemic *syn*-epoxide **42** was treated with (*S,S*)-salen-Co-(OAc) complex (0.5 mol%) and water (0.7 equiv.) in THF (0.7 equiv.) to afford the epoxide **43** as a single stereoisomer (determined from the ^1H and ^{13}C NMR spectral analysis) in 43% yield and the diol **44** in 45% yield. Epoxide **43** could easily be separated from the more polar diol **44** through silica gel column

chromatography. The enantiomeric purity of the epoxide **43** was estimated to be >98% by chiral HPLC analysis. Compound **43** can lead to a formal synthesis of verbalactone **1**.



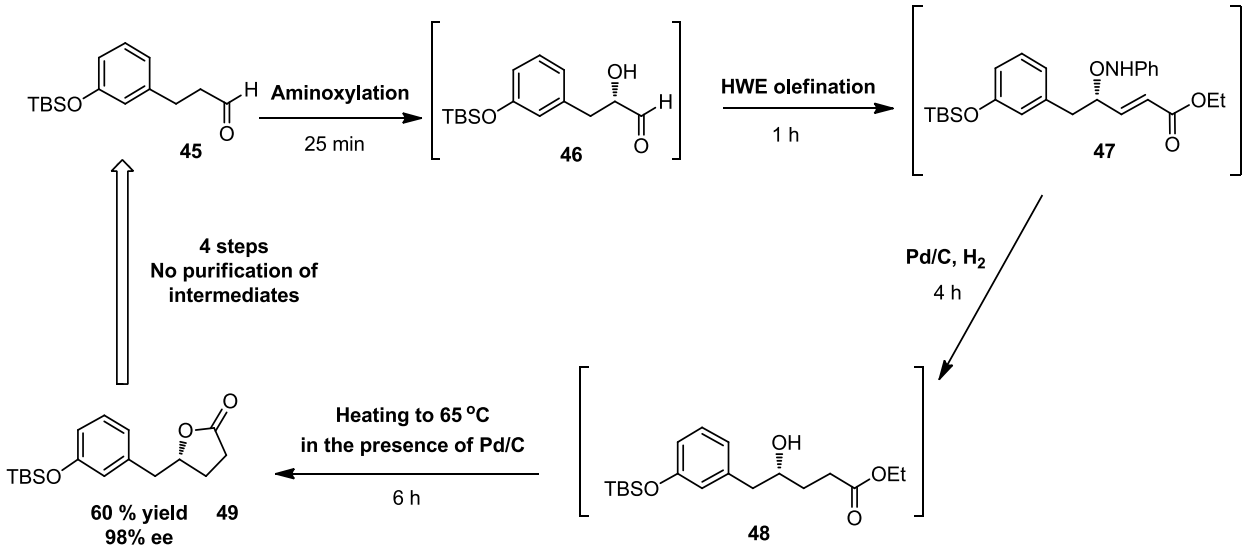
Scheme 9: Resolution of *syn*-epoxide **40** by HKR

<u>Chapter 4:</u> Enantiomeric synthesis of substituted chiral γ-butyrolactones from aldehydes via proline catalysed sequential lactonization reaction and proline catalysed enantiomeric synthesis of Bruguierol A and Bruguierol B

This chapter is further divided into two sections.

Section A: Enantiomeric synthesis of substituted chiral γ-butyrolactones from aldehydes via proline catalysed sequential lactonization reaction

Optically active γ-butyrolactones have attracted much attention owing to their presence in a large variety of biologically active compounds such as alkaloids, antibiotics, pheromones, and flavor components. They have great importance in the areas of pharmaceuticals, agrochemicals, flavor components, material and in polymer productions.[38] Interest in the synthesis of these and other applications of γ-butyrolactones has fueled and stimulated the effort to develop improved methodology for the construction of substituted γ-butyrolactones in an enantioselective manner. Therefore, it is not surprising that various biological and chemical methods have been described in the literature to access the important ring systems in optically active forms.[39]



Scheme 10: Synthetic Strategy for the preparation of substituted chiral γ-butyrolactone **49** from aldehyde **45** via proline catalysed sequential lactonization.

The preparation of optically pure hydroxy esters or acids and their conversion to lactones are important processes in organic syntheses as a result of the significance of such molecules.[40] We have devised a novel and practical sequential asymmetric α-aminoxylation/Wadsworth-Emmons-Horner olefination; tandem reduction/cyclization reaction of aldehydes for the synthesis of optically active substituted γ-butyrolactone (Scheme 10). For making a practical and efficient approach to the stereocontrolled synthesis of γ-butyrolactones, we examined various reaction conditions to standardize our methodology.

The advantages of the sequential process include the following: (1) all starting materials are readily available; (2) the *O*-amino-substituted unsaturated ester that is formed after sequential α-aminoxylation and HWE olefination can be isolated in good yield and is converted to γ-butyrolactone without requiring a separate column purification step, (3) the procedure is very easy to operate under the ordinary lab conditions; (4) both (*R*)- and (*S*)-substituted γ-butyrolactone can be made since either enantiopure form of the proline is commercially available. The synthetic utility of this protocol was further demonstrated by the asymmetric synthesis of Bruguierol A and Bruguierol B (Section B).

Section B: Proline-catalysed enantiomeric synthesis of Bruguierol A and Bruguierol B

In 2005, Sattler and co-workers isolated and disclosed an unusual family of aromatic-C-glycoside natural products termed bruguierols A-C from the stem of the Bruguiera gymmorrhiza mangrove tree[41](Figure 3).

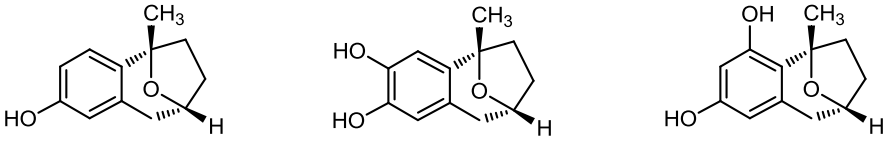
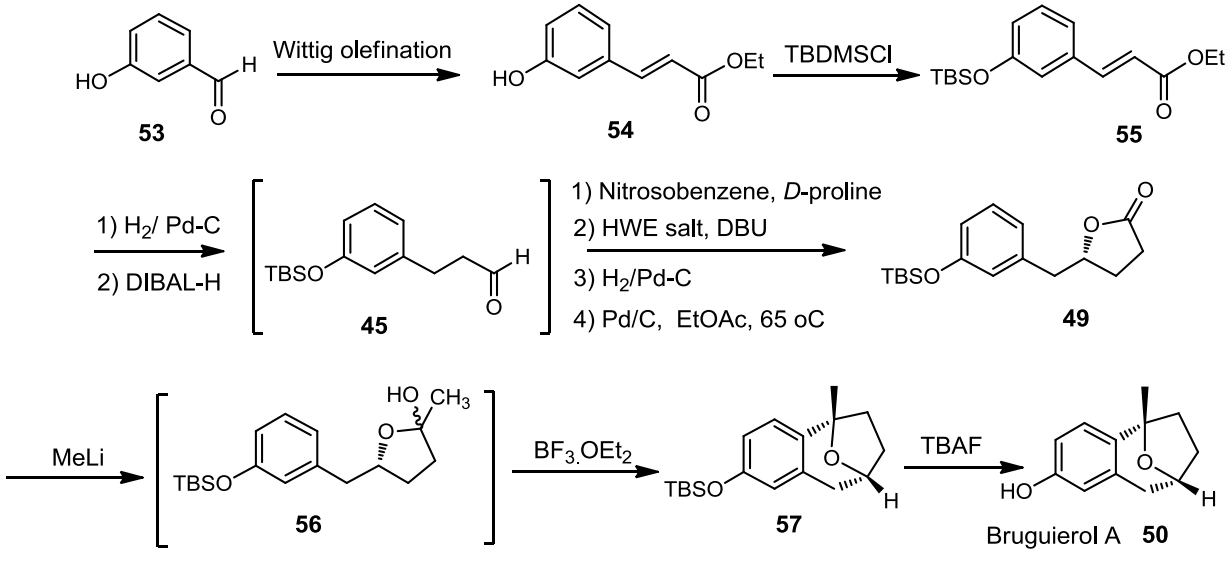


Figure 3: Structure of Bruguierols

The structure of these natural products is characterized by a 2,3-benzofused 8-oxabicyclo[3.2.1]octane core. Additionally, the aromatic ring is substituted with one (bruguierol A) or two hydroxyl groups (bruguierols B and C). Thus, the development of a flexible strategy to access these natural products or analogues could be highly interesting in finding new broad spectrum antibiotics.[42]

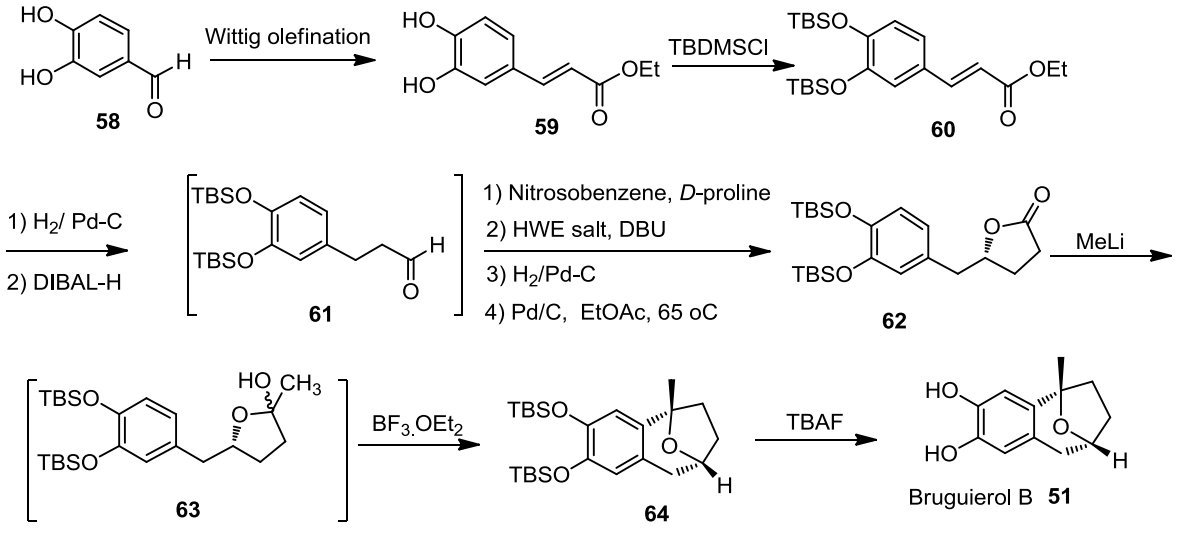
Synthesis of Bruguierol A



Scheme 11: syntheses of Bruguierol A **50**

We have developed a new asymmetric synthetic strategy for Bruguierol A **50** and Bruguierol B **51**. In this strategy the chirality was introduced by proline catalysed sequential lactonization reaction and 2,3-benzofused 8-oxabicyclo[3.2.1]octane core was achieved by intramolecular Friedel-Crafts alkylation.[42b] The treatment of lactone **49** with 1.3 equiv. of MeLi in Et_2O quantitatively furnished lactol **57**, which was then sequentially treated with $BF_3.OEt_2$ and allowed to react at -20 °C for 3 h. An intramolecular trap of the incipient oxocarbenium cation by means of a Marson type Friedel-Crafts alkylation[43] provided the protected bruguierol A **57** in good yield. Later TBS ether was deprotected using a standard protocol (Scheme 11). We also synthesized Bruguierol B to ensure the flexibility of our synthetic strategy (Scheme 12).

Synthesis of Bruguierol B



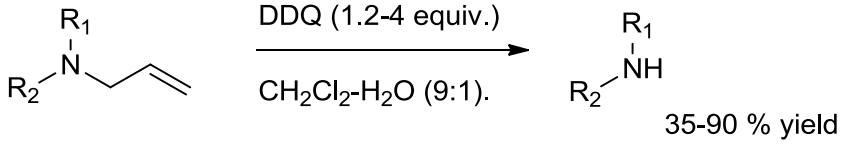
Scheme 12: syntheses of Bruguierol B

Chapter 5: Chemoselective Deprotection of *N*-Allylic Amines using DDQ

Protecting groups often play a crucial role in many complex synthetic strategies. The proper selection of efficient protecting groups, as well as the search of selective deprotection methodologies, still remains crucial issues in modern organic chemistry.[44] In particular, among the plethora of alternatives, the use of allyl moieties for the protection of amines is becoming more and more popular as methods of amines into carbamates or to a lesser extent into amides. In contrast to classical protecting groups such as Boc (*tert*-butoxycarbonyl),

FMOC (9-fluorenylmethyl carbamate), tosylamide, etc.; allyl groups remain inert under both acidic and basic conditions. But as reported later on, they can be cleaved upon treatment with strong bases.[45] However, those basic conditions are rather tough and incompatible with base-sensitive functional groups. Except for a few miscellaneous methods, transition-metal-catalyzed reactions (essentially Pd and Rh) are currently the most efficient and selective strategies for the deprotection of *N*-allylamines[46], but selectivity can still be a problem, since *O*-allyl derivatives are cleaved faster than *N*-allyl derivatives in most cases. An important drawback of the π-allyl–palladium methodology is the requirement of stoichiometric amounts of a nucleophilic compound, which acts as the allyl group scavenger. New procedures involving Grubbs-type catalysts are also emerged.[47] But still selectivity remains the problem with these methods. Reductive metals also fall into same position.[48]

2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ) is a high potential quinone which has found extensive synthetic applications in organic synthesis.[49] Since *O*-allyl ethers are cleaved in the presence of DDQ[50], this reaction occurs in a rather complex multistep pathway, has not been developed further into a method of synthetic interest for the cleavage of allylic C-N bonds.[51] Our studies shows that DDQ mediated *N*-deallylation could be a promising methodology in organic synthesis.



R_1 and R_2 = Allyl, Bn, Boc, Cyclohexyl, PMB, trans-Cinnamyl, Phenyl, $C_{15}H_{31}$, C_6H_{13}, Ts, Propagyl etc

Figure 4: Chemoselective Deprotection of Allylic Amines using DDQ

Deprotection of *N*-allyl group was examined in several solvent systems. The best result was obtained using CH_2Cl_2-H_2O (9:1). The reaction in other solvents such as CH_3CN-H_2O and Toluene-H_2O proceeded more slowly. Solvent systems like THF-H_2O and EtOAc-H_2O resulted in complex reaction mixtures. This reaction is only achieved in the presence of water. When water was not added, only a trace amount of the desired product was obtained.

This method constitutes a new procedure for deprotection of *N*-allyl group with the considerable advantage of being under neutral conditions.

References:

1. Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis: Targets, Strategies*, *Methods*. II Ed.; VCH Publishers: Weinheim, **1996**, 4.
2. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
3. (a) For a review, see: Johnson, R. A.; Sharpless, K. B. Catalytic Asymmetric Epoxidation of Allylic Alcohols. In *Catalytic Asymmetric Synthesis;* Ojima. I. Ed.; VCH Publishers: New York, **1993**, 103; (b) Woodard, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc*. **1991**, *113*, 106.
4. Lin, Guo-Qiang; Li, Yue-Ming; Chan, A.S.C. Asymmetric Oxidation., In *Principles and Applications of Asymmetric Synthesis*; John Wiley & Sons, Inc. **2001**, *chapter 4*, 195.
5. (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936; (b) Schaus, S. E; Jacobsen, E. N; *J. Am. Chem. Soc.* **2002**, *124*, 1307.
6. For review: Kumar, P.; Naidu, V.; Gupta, P. *Tetrahedron* **2007**, *63*, 2745.
7. Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726; (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138; (c) Houk, K. N.; List, B., Eds.; *Acc. Chem. Res*. **2004**, *37*, 8; (d) List, B.; Bolm, C., Eds.; *Adv. Synth. Catal*. **2004**, 346; (e) *Asymmetric Organocatalysis*; Berkessel, A., Gröger, H., Eds.; Wiley-VCH: Weinheim, **2005**; (f) List, B., Seayad, *J. Org. Biomol. Chem*. **2005**, *3*, 719.
8. For a review on proline-catalyzed asymmetric reactions see: List, B. *Tetrahedron* **2002**, *58*, 5573.
9. (a) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett*. **2003**, *44*, 8293; (b) Zhong, G. *Angew. Chem., Int. Ed*. **2003**, *42*, 4247; (c) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed*. **2003**, *43*, 1112; (d) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2003**, *125*, 10808; (e) Cordova, A.; Sunden, H.; Bøgevig, A.; Johansson, M.; Himo, F. *Chem. A-Eur. J*. **2004**, *10*, 3673.
10. (a) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F. III *Org. Lett*. **2003**, *5*, 1685; (b) Zhong, G.; Yu, Y. *Org. Lett*. **2004**, *6*, 1637; (c) Zhao, G. –L.; Liao, W, -W.; Cordova,

A. *Tetrahedron Lett*. **2006**, *47*, 4929; (d) Liao, W. –W.; Ibrahem I.; Cordova A. *Chem. Commun*. **2006**, 674; (e) Kotkar, S. P.; Chavan V. B.; Sudalai A. *Org. Lett*. **2007**, *9*, 1001.

11. (a) Baker, R.; Harrison, T.; Hollingworth, G. J.; Swain, C. J.; Williams, B. J. EP0528 495A1, 1993; (b) Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 2545.
12. Desai, M. C.; Lefkwitz, S. L.; Thadeo, P. F.; Longo, k. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911.
13. Watson, J. W.; Gonsalves, S. F.; Fossa, A. A.; Mc Lea, S.; Seeger, T.; Obach, S.; Andrews, P. L. R. *Br. J. Pharmacol*. **1995**, *115*, 84; (b) Zaman, S.; Woods, A. J.; Watson, J. W.; Reynolds, D. J. M.; Andrews, P. L. R. *Neuropharmacology* **2000**, *39*, 316.
14. (a) Lotz, M.; Vaughan, J. H.; Carson, D. A. *Science* **1987**, *235*, 893; (b) Moskowitz, M.A. *Trends Pharmacol. Sci*. **1992**, *13*, 307; (c) Takenchi, Y.; Berkley Shand, E, F.; Beusen, D. D.; Marshall, G. R. *J. Med. Chem*. **1998**, *41*, 3609; (d) Swain, C. J. *Prog. Med. Chem*. **1998**, *35*, 57.
15. Boks, G. J.; Tollenacre, J. P.; Kroon, J. *Bioorg. Med. Chem*. **1997**, *5*, 535.
16. (a) Williams, D. R.; Fromhold, M. G.; Earley, J. D. *Org. Lett*. **2001**, *3*, 2721; (b) Menand, M.; Blais, J. –C.; Valery, J. –M.; Xie, J. *J. Org. Chem*. **2006**, *71*, 3295.
17. Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc*. **1987**, *109*, 5765.
18. Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem*. **1988**, *53*, 5185.
19. Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett*. **1981**, ***22***, 3455.
20. Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett*. **2004**, *6*, 3217.
21. Li, G. –I.; Zahao, G. *Org. Lett*. **2006**, *8*, 633.
22. (a) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, *23*, 1977; (b) Mitsunobu, O. *Synthesis* **1981**, 1; (c) Lipshutz, B. H.; Miller, T. A. *Tetrahedron Lett.* **1990**, *31*, 5253.
23. (a) Takao, K.-I.; Ochiai, H.; Yoshida, K.-I.; Hashizuka, T.; Koshimura, H.; Tadano, K. –I.; Ogawa, S. *J. Org. Chem*. **1995**, *60*, 8179; (b) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 45.
24. Bhaskar, G.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 915.

25. Magiatis, P.; Spanakis, D.; Mitaku, S.; Tsitsa, E.; Mentis, A.; Harvala, C. *J. Nat. Prod.* **2001**, *64*, 1093.
26. Doshida, J.; Hasegawa, H.; Onuki, H.; Shimidzu, N. *J. Antibiot.* **1996**, *49*, 1105.
27. Vesonder, R. F.; Stodola, F. H.; Rohwedder, W. K. *Can. J. Biochem*. **1972**, *50*, 363.
28. Endo, A. J. *J. Med. Chem*. **1985,** *28*, 401**.**
29. (a) Romeyke, Y.; Keller, M.; Kluge, H.; Grabley, S.; Hammann, P. *Tetrahedron* **1991**, *47*, 3335; (b) Takano, S.; Setoh, M.; Ogasawara, K. *Tetrahedron Asymmetry* **1992**, *3*, 533; (c) Bennett, F.; Knight, D.; Fenton, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1543; (d) Bennett, F.; Knight, D. *Heterocycles* **1989**, *29*, 639; (e) Yang, Y.-L.; Falck, J. R. *Tetrahedron Lett.* **1982**, *23*, 4305.
30. Gupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 849.
31. Lindlar, H.; Dubuis, R. *Organic Syntheses*, *Wiley, New York* **1973**, *Collect. Vol. V*, 880.
32. Sabitha, G.; Bhaskar, V.; Yadav, J. S. *Synth. Commun*. **2008**, *38*, 3129.
33. Laker, F. J.; Hager, L. P. *J. Org. Chem*, **1996**, *61*, 3923.
34. (a) Salunke, G. B.; Shivakumar, I.; Gurjar, M. K. *Tetrahedron Lett*. **2009**, *50,* 2048; (b) Gogoi, S.; Barua, N. C.; Kalita, B. *Tetrahedron Lett*. **2004**, *45*, 5577; (c) Allais, F.; Louvel, M-C.; Cossy, J. *Synlett* **2007**, *3*, 451; (d) Sabitha, G.; Bhaskar, V.; Yadav, J. S. *Synth. Commun*. **2008**, *38*, 3129.
35. Barbier, P. *Compt. Rend.* **1890**, *130*, 1322.
36. (a) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.: Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013; (b) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.: Academic: Orlando, Florida, **1984**; *Vol. 3*, 411. For analogous iodine-induced cyclirations of lithium carbonates, see: (c) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. J. Chem. Sot., *Chem. Commun*. **1981**, 465. (d) Bongini, A.: Cardillo, G.; Orena, M.; Porzi. G.; Sandri, S. *J. Org. Chem.* **1982,** *47*, 4626; (e) Lipshutz, B. H.; Kozlowski, J. A. *J. Org. Chem*. **1984**, *49*, 1147; (f) Lipshutz, B. H.; Barton, J. C. *J. Org. Chem.* **1988**, *53*, 4495.
37. For *O*-BOC protection, see: (a) Houlihan, F.; Bouchard, F.; Fre´chet, J. M. J.; Willson, C. G. *Can. J. Chem*. **1985**, *63*, 153; (b) Losse, G.; Süptitz, G. *Synthesis* **1990**, 1035.

38. (a) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1869; (b) Donnelly, D. M. X.; Meegan, M. J. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon: New York, **1984**; Vol. 4, 657; (c) Devon, T. K.; Scott, A. I. In *Handbook of Naturally Occurring Compounds*; Academic Press: New York, **1975**; *Vol. 1*, 249.

39. (a) Katoh, T.; Nishide, K.; Node, M.; Hiroo, O. *Heterocycles*, **1999**, *50*, 833; (b) Drioli, S.; Felluga, F.; Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E.; *J. Org. Chem.* **1998**, *63*, 2385; (c) Vassilev, V. P.; Uchiyama, T.; Kajimoto, T.; Wong, C. H. *Tetrahedron Lett.* **1995**, *36*, 5063; (d) Takahata, H.; Uchida, Y.; Momose, T. *J. Org. Chem.* **1994**, *59*, 7201; (e) Miyazaki, Y.; Hotta, H.; Sato, F. *Tetrahedron Lett.* **1994**, *35*, 4389; (f) Tsuda, M.; Shigemori, H.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 3503.

40. (a) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377; (b) Wang, Z.; Meng, X. J.; Kabalka, G. W. *Tetrahedron Lett.* **1991** *32*, 4619; (c) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97.

41. Han, L.; Huang, X.; Sattler, I.; Moellmann, U.; Fu, H.; Lin, W.; Grabley, S. *Planta Med.* **2005**, *71*, 160.

42. (a) Ramana, C. V.; Salian, S. R.; Gonnade, R. G. *Eur. J. Org. Chem*. **2007**, 5483; (b) Solorio, D. M.; Jennings, M. P. *J. Org. Chem*. **2007**, *72*, 6621; (c) Wu, J.-Z.; Zhen, Z. B.; Zhang, Y. H.; Wu, Y. K. *Acta Chim. Sinica* **2008,** *66*, 2138; (d) Fananás, F. J.; Fernández, A.; Cevic, D.; Rodríguez, F. *J. Org. Chem*. **2009**, *74*, 932; (e) Hu, B.; Xing, S.; Ren, J.; Wang, Z. *Tetrahedron* **2010**, *66*, 5671; (f) Sarkar, D.; Venkateswaran, R. V. *Tetrahedron Lett.* **2011**, *52*, 3232.

43. Marson, C. M.; Campbell, J.; Hursthouse, M. B.; Malik, K. M. A. *Angew. Chem. Int. Ed.* **1998**, *37*, 1122.

44. (a) Greene, T.; Wuts, P. G. *Protective Groups in Organic Syntheses*, 3rd ed., Wiley, New York, **1999**; (b) Kocienski, P. J. *Protecting Groups*, Thieme, Stuttgart, **1994**; (c) Guibé, F. *Tetrahedron* **1997**, *53*, 13509.

45. (a) Rivière, M.; Lattes, A. *Bull. Soc. Chim. Fr.* **1968**, 4430; (b) Price, C. C.; Snyder, W. H. *Tetrahedron Lett.* **1962**, 69; (c) Gigg, R.; Conant, R. *Carbohydr. Chem.* **1982**, *100*, C5–C9, and references cited therein.

46. (a) Liu, Q.; Marchington, A. P.; Boden, N.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 511; (b) Carless, H. A. J.; Haywood, D. J. *J. Chem. Soc., Chem.*

Commun. **1980**, 980; (c) Boss, R.; Scheffold, R. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 558; (d) Krompiec, S.; Pigulla, M.; Krompiec, M.; Baj, S.; Mrowiec-Bialon, J.; Kasperczyk, J. *Tetrahedron Lett.* **2004**, *45*, 5257.

47. (a) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Org. Lett.* **2001**, *3*, 3781; (b) Alcaide, B.; Almendros, P.; Alonso, J. M. *Chem. Eur. J.* **2003**, *9*, 5793; (c) Alcaide, B.; Almendros, P.; Alonso, J. M.; Luna, A. *Synthesis* **2005**, 668.
48. (a) Talukdar, S.; Banerji, A. *J. Indian Chem. Soc.* **1997**, *74*, 842; (b) Rele, S.; Chattopadhyay, S.; Nayak, S. K. *Tetrahedron Lett.* **2001**, *42*, 9093.
49. Walker, D.; Hiebert, J. D. *Chem. Rev*. **1967**, *67*, 153.
50. Yadav, J. S.; Chandrasekhar, S.; Sumithra, G.; Kache, R. *Tetrahedron Lett.* **1996**, *37*, 6603.
51. Bertrand, M.; Escoubet, S.; Gastaldi, S. *Eur. J. Org. Chem*. **2005**, 3855.

Chapter-1

Introduction to Sharpless asymmetric epoxidation, Jacobsen's hydrolytic kinetic resolution (HKR) and proline-catalysed reactions

1.1. ASYMMETRIC EPOXIDATION (AE)

1.1.1. Introduction

The construction of nature's molecules in the laboratory from atoms and/or simple molecules, a process often known as total synthesis, is one of the most demanding human practices. The beneficial impact of this field on health and welfare of society is beyond question, particularly when we make the connection between science and civil progress via technology.[1] The unlimited variation in structures and the constant discovery of new molecules keep the field of natural product synthesis so attractive and vibrant.

The ultimate goal of organic synthesis is to assemble a given organic compound (target molecule) from readily available starting materials and reagents in the most efficient way. It is more elegant and economical to prepare just wanted isomer by asymmetric synthesis and through inexpensive catalytic processes. It is especially useful in the case of carbon-hetero atom bond formation reaction, since the resulting functionality can be readily manipulated to produce many important different classes of compounds.

The oxidation of olefins is considered as the single most versatile, powerful and reliable class of transformation in organic synthesis. The processes for the selective oxidation of olefins have long been among the most useful tools for day-to-day organic synthesis. The pioneering work of K. B. Sharpless on 'chirally catalyzed oxidation reactions' viz. the asymmetric epoxidation (AE)[2] developed in early 1980 and asymmetric dihydroxylation (AD)[3] in early 1990 and newly developed asymmetric aminohydroxylation (AA)[4] in 1995, bagged him the 'Nobel Prize'(in part) in Chemistry (2001).

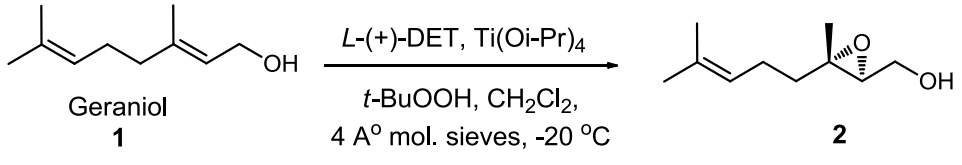
1.1.2. Asymmetric Epoxidation of Allylic Alcohols

Epoxides are versatile and important intermediates in organic chemistry. The strain of three membered heterocyclic ring makes them accessible to a large variety of reagents. Asymmetric epoxidation of allylic alcohols was once one of the leading areas of investigation in synthetic organic chemistry, mainly due to the fact that very high enantioselective induction for a wide range of substrates is possible using several classes of reagents.[5] Today, the most successful asymmetric epoxidation reaction is the titanate-mediated epoxidation of

allylic alcohols, or Sharpless epoxidation, which enables the achievement of an enantiomeric excess of over 90% in most cases.[6]

The Sharpless epoxidation is a popular laboratory process that is both enantioselective and catalytic in nature. Not only does it employ inexpensive reagents and involve various important substrates (allylic alcohols) and products (epoxides) in organic synthesis, but it also demonstrates unusually wide applicability because of its insensitivity to many aspects of substrate structure. The wide scope application of this transformation arises not only from the utility of epoxide compounds but also from the subsequent regiocontrolled and stereocontrolled nucleophilic substitution (ring-opening) reactions of the derived epoxy alcohol. These, through further functionalization, allow access to an impressive array of target molecules in enantiomerically pure form.[5]

Since its discovery in 1980[6], the Sharpless expoxidation of allylic alcohols has become a benchmark classic method in asymmetric synthesis. A wide variety of primary allylic alcohols have been epoxidized with over 90% optical yield and 70-90% chemical yield using TBHP (*t*-BuOOH) as the oxygen donor and titanium isopropoxide-diethyl tartrate (DET, the most frequently used dialkyl tartrate) as the catalyst. Notably, this reaction exhibits high levels of enantioselectivity. Like other metal catalyzed epoxidations, this reaction also proceeds under mild conditions with good chemical yield and with high regio-and chemoselectivity (Scheme 1).



Geraniol
1

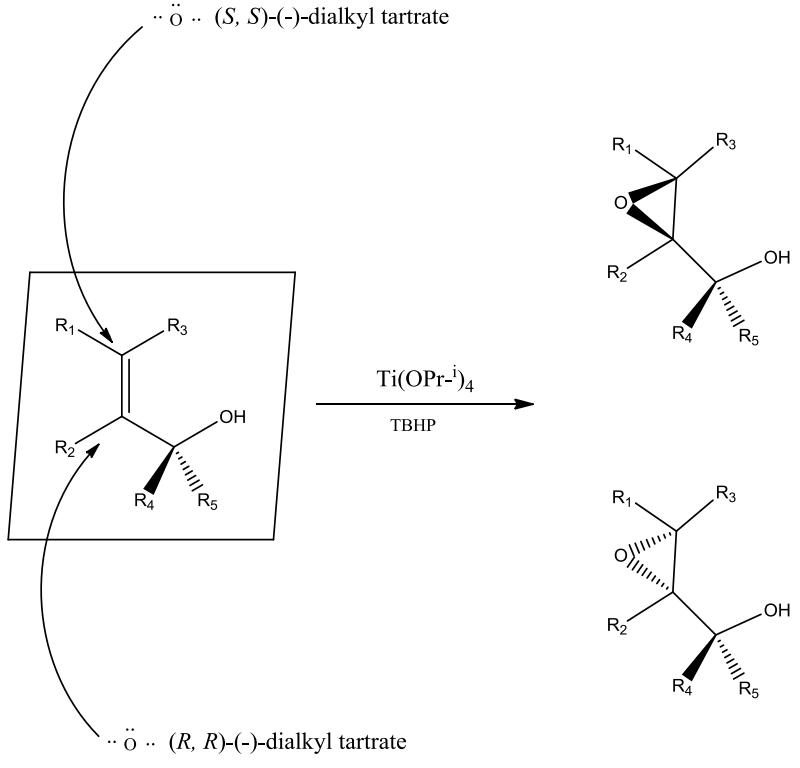
2

Scheme 1: A representative example of Sharpless asymmetric epoxidation

1.1.3. The Empirical rule for predicting high enantiofacial selectivity

The combination of $Ti(OPr^i)_4$, a dialkyl tartrate, and *tert*-butyl hydroperoxide epoxidizes most allyic alcohols in good chemical yield and with predictably high enantiofacial selectivity according to the empirical rule illustrated in Scheme 2. When an allylic alcohol

(R^4, R^5 = H) is drawn in a plane with the hydroxymethyl group positioned at the lower right, the delivery of oxygen occurs from the bottom side of the olefin to give the (2*S*)-epoxide if an (*R*,*R*)-dialkyl tartrate is used as the chiral auxiliary. When an (*S*,*S*)-dialkyl tartrate is employed, oxygen is delivered from the top side. The enantiofacial selectivity of the reaction is > 90% *ee* for substrate without a Z-olefinic substituent (R^3 = H). The degree of facial selectivity for a Z-allylic alcohol depends on the nature of the Z substituent R^3. The enantioselectivity for substrate with unbranched R^3 substituents ranges from 80 to 94% *ee*, but that for substrates with branched substituent is lower.[7]



Scheme 2: The mnemonic device for predicting the face selectivity

1.1.4. Mechanism

Sharpless suggested that epoxidation was catalysed by a single Ti center in a dimeric complex with a C_2-symmetric axis. Molecular weight measurement, infrared spectroscopy, and ^1H, ^{13}C, and ^{17}O NMR spectrometry all suggest that such a dinuclear structure is dominant in the solution phase (Figure 1).[8]

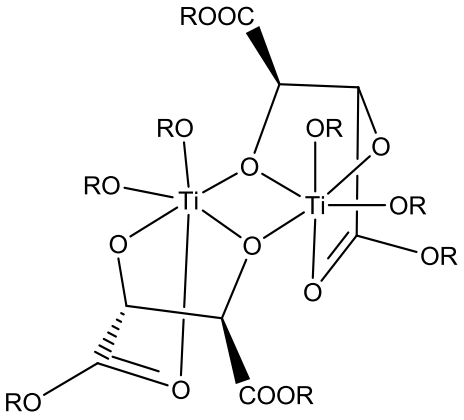
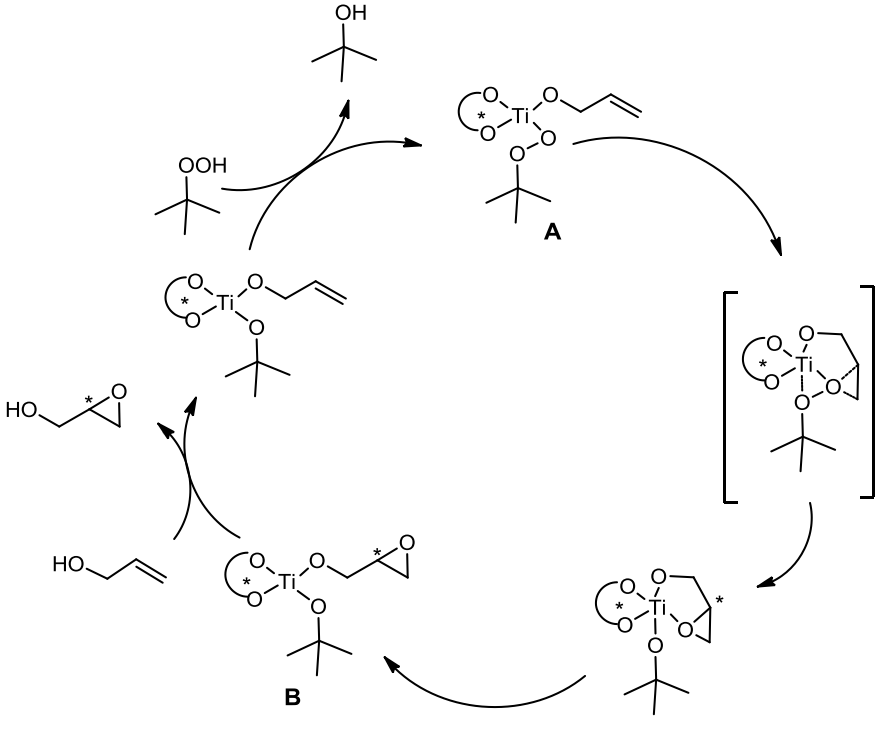


Figure 1: Structure of dinuclear Ti-tartrate complexes

Metal alkoxides generally undergo rapid ligand exchange with alcohols. When a metal alkoxide, an allylic alcohol, and an alkyl hydroperoxide are mixed, ligand exchange occurs to afford a mixture of complexes. It is believed that the species containing equal moles of Ti and tartrate is the most active catalyst.[9] Among them, only species such as **A** bearing both allylic alkoxide and alkyl hydroperoxide groups, are responsible for the epoxidation (Scheme 3).



Scheme 3: Mechanism of Ti-catalyzed Sharpless epoxidation

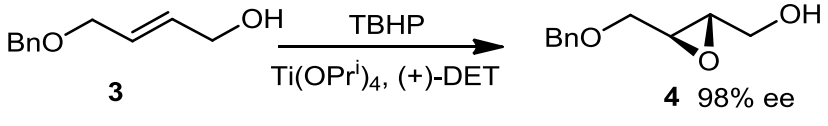
As shown in Scheme 3, the reaction proceeds via a Ti(IV) mixed-ligand complex A bearing allyl alkoxide and TBHP anions as ligands. The alkyl peroxide is electrophilically activated by bidentate coordination to the Ti(IV) center. Oxygen transfer to the olefinic bond occurs to provide the complex B, in which Ti(IV) is coordinated by epoxy alkoxide and *t*-butoxide. In complex **B**, alkoxide products are replaced by allylic alcohol and TBHP to regenerate complex **A** and complete the catalytic cycle. It seems clear that enantioselectivity is controlled by the chiral ligands on Ti(IV), which determines the conformation of the coordinated allylic alcohol. The exact nature of the catalytic species remains only partially understood.

1.1.5. Modification of Sharpless Epoxidation- The 4A^o Molecular Sieves System

The initial procedure for the Sharpless reaction required a stoichiometric amount of the tartrate-Ti complex promoter. In the presence of 4 A^o molecular sieves, the asymmetric reaction can be achieved with a catalytic amount of titanium tetraisopropoxide and DET. This can be explained by the fact that the molecular sieves may remove the co-existing water in the reaction system and thus avoid catalyst deactivation.[10]

1.1.6. The Characteristics of Sharpless Epoxidation[5]

For the asymmetric epoxidation of achiral allyl alcohols, high *ee* can normally be obtained. For example, in Scheme 4, asymmetric epoxidation of the achiral allylic alcohol **3** provides epoxyl alcohol **4** with a selectivity of 99:1.

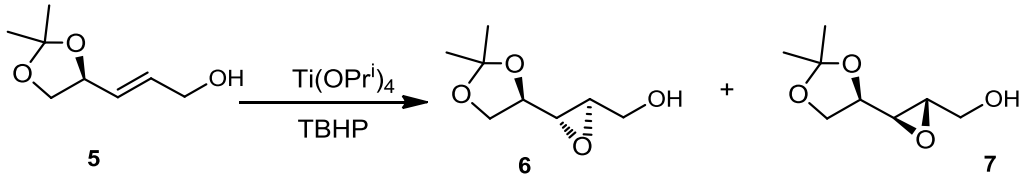


3 **4** 98% ee

Scheme 4

The idea of double asymmetric induction is also applicable to asymmetric epoxidation. In the case of asymmetric epoxidation involving double asymmetric induction, the enantioselectivity depends on whether the configurations of the substrate and the chiral ligand are matched or mismatched. For example, treating **5** with titanium tetraisopropoxide

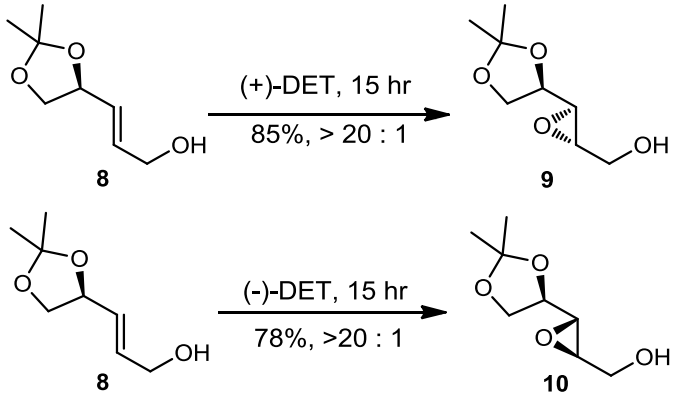
and *t*-butyl hydroperoxide without (+)- or (-)-diethyl tartrate yields a mixture of epoxy alcohols **6** and **7** in a ratio of 2.3:1 (Scheme 5). In a double asymmetric reaction, asymmetric epoxidation reaction of **5** with (+)- or (-)-diethyl tartrate proceeds smoothly to provide the epoxides **6** and **7** in ratios of 1:22 and 90:1, referring to the mismatched and matched cases, respectively (Scheme 5).



In the absence of tartrate **6:7**= 2.3 : 1
In the presence of (+)-DET, mismatched, **6:7**= 1: 22
IIn the presence of (-)-DET, matched, **6:7**= 90 : 1

Scheme 5: Double asymmetric induction

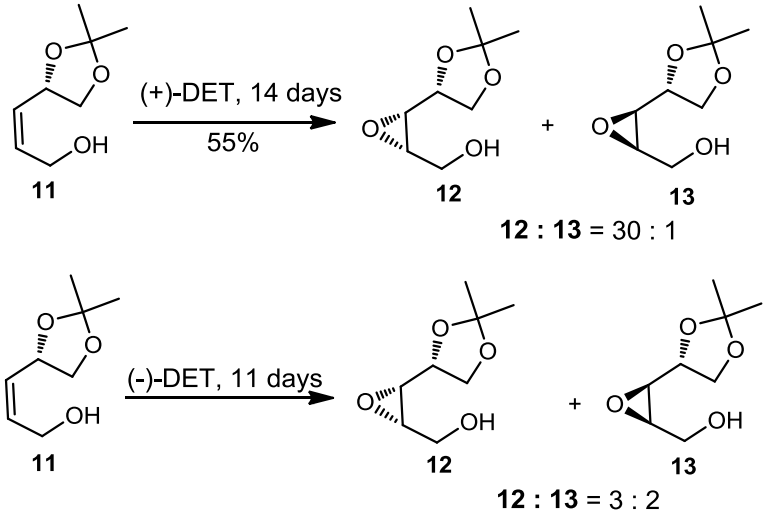
In Sharpless epoxidation reactions, (*Z*)-substituted allylic alcohols react much more slowly than the corresponding (*E*)-substituted substrates, and sometimes the reaction is sensitive to the position of pre-existing chirality in the selected substrate.



Scheme 6: (*E*)-substituted substrate

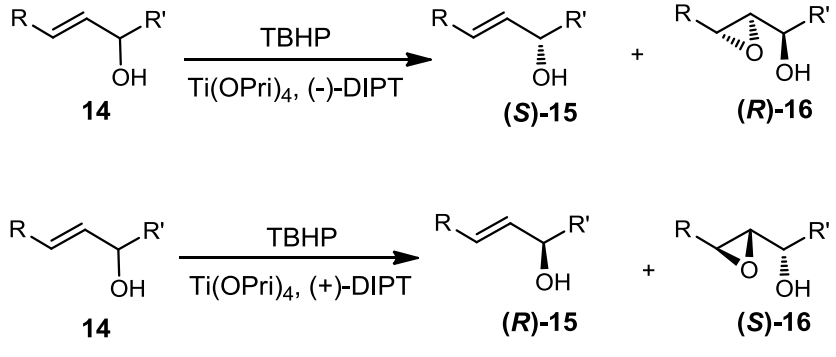
For instance, in the presence of (+)-DET, chiral (*E*)-allylic alcohol **8** undergoes epoxidation in 15 hours to give product **9** as the major product with a diastereomeric ratio of >20:1. As for reaction with (-)-DET, **10** is then obtained, also with a diastereoselectivity of >20:1 (Scheme 6). In the case of (*Z*)-allylic alcohol **11**, however, it takes 2 weeks to get product **12**

in a ratio of **12:13** = 30:1 for matched pairs, while the epoxide **12** is obtained in the much lower ratio of **12:13** = 3:2 for mismatched pairs (Scheme 7).



Scheme 7: (*Z*)-substituted substrate

Like the vanadium-based epoxidation reaction, the Sharpless reaction intrinsically favours 1,2-anti products. With a racemic allylic alcohol, one of the enantiomers reacts faster, and this rate differentiation step can be used to selectively epoxidize the more reactive enantiomer in the presence of its antipode. In general, by reducing the amount of TBHP to 0.6 equivalent in a reaction system, the same reaction can be used to kinetically resolve secondary allylic alcohols (Scheme 8).[11]



Scheme 8: Kinetic resolution of secondary allylic alcohols

1.1.7. Conclusion

In summary, the following characteristics describe the effectiveness of this epoxidation reaction.[5]

Simplicity: All the ingredients are inexpensive and commercially available.

Reliability: It succeeds with most allylic alcohols, although bulky substituents are deleterious.

High optical purity: Optical purity of the product is generally >90% *ee* and usually >95% *ee*.

Predictable absolute stereochemistry: Thus far, when dealing with a prochiral allylic alcohol substrate, no exception to the rules has been observed.

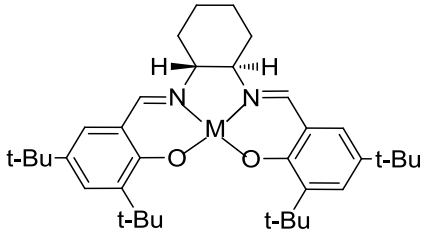
Relative insensitivity to pre-existing chiral centers: In allylic alcohols with pre-existing chiral centers, the diastereofacial preference of the chiral titanium-tartrate catalyst is often strong enough to override diastereofacial preferences inherent in the chiral olefinic substrate.

Versatility of 2,3-epoxy alcohols as intermediates: New selective transformations widen the utility and significance of the reaction.

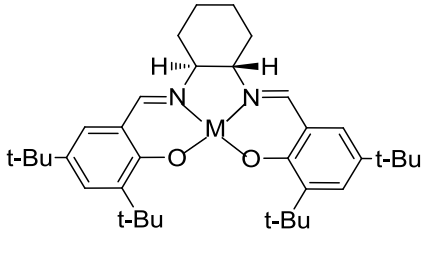
1.2. HYDROLYTIC KINETIC RESOLUTION (HKR)

1.2.1. Introduction

Enantiopure epoxides are valuable intermediates in organic synthesis. Their corresponding vicinal diols, which can be either transformed into the epoxide itself or used as highly reactive cyclic sulfates or sulfites, are similarly valuable epoxide-like building blocks.[12] This, essentially, is due to the versatility of the oxirane function, which can be chemically transformed into numerous—more elaborated—enantiopure intermediates en route to biologically active targets.[13] Since those epoxides that are produced naturally are typically complex compounds available only in limited amounts. So nature's chiral pool has not proven to be a useful direct source of optically active epoxides for use in organic synthesis. Instead, enantio-enriched epoxides have been accessed indirectly from the chiral pool via multistep procedures.[14]These, however, tend to be inherently inefficient, and the range of epoxides available by this approach is also quite limited. The identification of catalytic asymmetric olefin oxidation methods has been an area of active research for several decades, and the advances made in this field have increased greatly the number of enantiomerically enriched epoxides available for use in organic synthesis.[15] Despite these considerable advances in asymmetric catalytic synthesis of epoxides, no general methods have been identified for the direct preparation of highly enantio-enriched 1-oxiranes, arguably the most valuable class of epoxides for organic synthesis.[16]. Recently Jacobsen had discovered the (salen)Co complex **17** (Figure 2) catalyzed efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides (Scheme 9).[17]

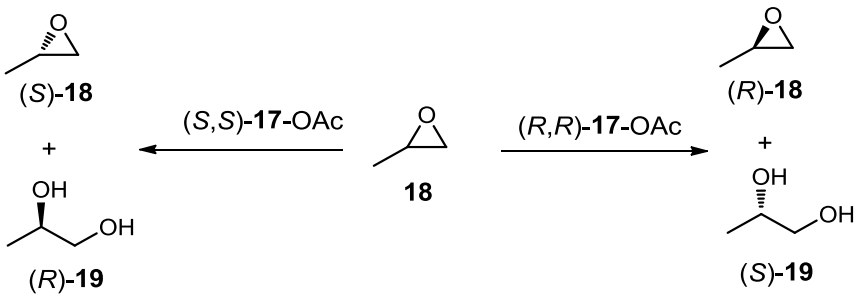


M = Co: (*R*,*R*)-**17**
M = Co-OAc: (*R*,*R*)-**17**-OAc



M = Co: (*S*,*S*)-**17**
M = Co-OAc: (*S*,*S*)-**17**-OAc

Figure 2. Jacobsen catalysts



Scheme 9: Hydrolytic kinetic resolution of propylene oxide

One of the most attractive features of kinetic resolution processes in general is the fact that the enantiomeric composition of unreacted substrate can be controlled by adjusting the degree of conversion, and virtually enantiopure material can be obtained at appropriately high conversions. Resolution strategies have always played a central role in the preparation of optically active compounds.[18] However, and particularly recently, great effort has been directed toward avoiding such approaches due to what is perceived to be their inherent inelegance and inefficiency. This is due to the fact that, except in those rare cases where both enantiomers can be employed productively, resolutions have a maximum yield of 50% based on racemic starting material. In that respect, they can be seen as displaying inherently poor atom economy.[19] However, Jacobsen's catalytic method appeared to hold considerable promise with regard to meeting all of the criteria for kinetic resolution to be practical.[20]

1.2.2. The Characteristics of Hydrolytic Kinetic Resolution

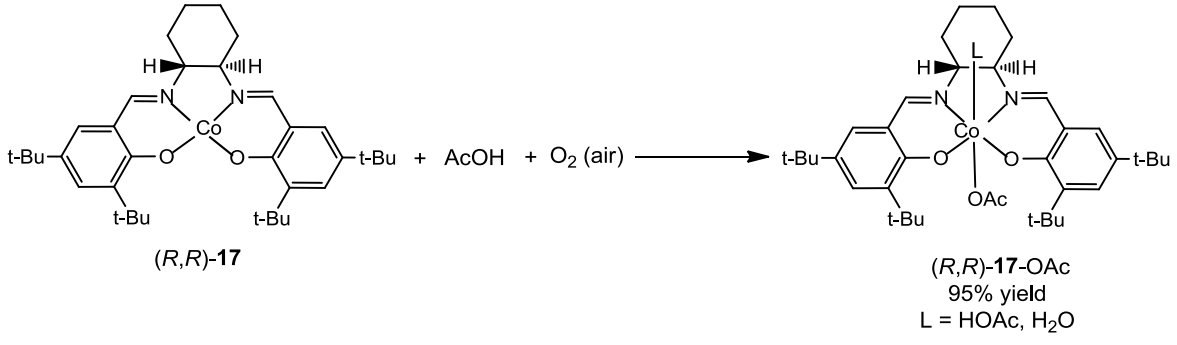
Racemic 1,2-epoxides are generally available directly from commercial suppliers at low cost or are obtainable in one step from inexpensive olefins or aldehydes. In fact, certain racemic epoxides, such as propylene oxide, epichlorohydrin, styrene oxide, and butadiene monoepoxide, are commodity chemicals and are no more expensive than common organic solvents.[21] The ligands for catalyst **17** had previously been commercialized and manufactured on a ton scale in the context of (salen)Mn epoxidation catalysts.[22] The cobalt analogues (*R*,*R*)-**17** and (*S*,*S*)-**17** proved equally accessible, and these are also now available in bulk.[23] The catalyst is used at low loadings and can be recycled repeatedly. The HKR can be run effectively on milligram to multiton scale.[21]

Epoxides can be recovered in >99% *ee* and good-to-excellent yield. The HKR also provided useful enantio-enriched 1,2-diols, including many that are otherwise not readily accessible

using existing asymmetric dihydroxylation methods.[24] Separation of ring-opened diol product from unreacted epoxide is carried out easily by distillation or extraction. Reactions are carried out under solvent-free conditions for certain substrates. In other cases, one volume equivalent of solvent provides better results. In general, very high volumetric productivities are attainable.[21]The water is perhaps the ideal reagent for effecting the resolution reaction: it is inexpensive and safe, and the rate of the ring-opening reaction can be controlled simply by modulating the rate of addition of water to the epoxide-catalyst mixture.[25] Reactions are run at 0±25 °C.

1.2.3. Preparation of Catalyst and General Experimental Considerations

Both enantiomers of the (salen)Co(II) complex **17** are available commercially on research or commercial scale,[23] or they can be prepared from the commercially available ligands using $Co(OAc)_2$. The Co(II) complex **17** is catalytically inactive, however, and it must be subjected to one-electron oxidation to produce a (salen)Co(III) X complex prior to the HKR. This may be done conveniently by aerobic oxidation in the presence of a mild Brönsted acid. Water alone was found not to mediate the oxidation reaction, but a screen of additives revealed that acetic acid was effective and that the corresponding Co(III) **17**.OAc is convenient for use in HKR reactions both in terms of its preparation and reactivity. Two useful methods for the generation of complex **17**.OAc have been developed (Scheme 10).[21]



Scheme 10: Preparation of catalyst

Method A- This method involves isolation of **17**.OAc as a crude solid prior to the HKR. The Co(II) complex **17** is dissolved in toluene to generate *ca*. 1 M solution, and acetic acid (2 equiv) is added. The resulting solution is stirred open to air at room temperature for 30 min, during which time the color of the mixture changes from orange to dark brown. All volatile

materials are removed in vacuum, affording **17**.OAc as a brown solid residue that can be used without further purification.

Method B- This method involves in situ generation of **17**.OAc under HKR conditions by suspension of the Co(II) complex **17** in epoxide or epoxide/solvent and addition of HOAc under an aerobic atmosphere.

For certain substrates such as 1-hexene oxide, catalyst prepared by either method leads to essentially identical results. In these situations, *in situ* catalyst generation (method B) is preferable since the procedure avoids an extra solvent removal step. On the other hand, catalyst prepared by method A was found to be more effective with less reactive substrates (vide infra) and was applicable to all substrates examined. Therefore, if HKR did not afford epoxide in >99% *ee* with catalyst prepared by method B after optimization of solvent and catalyst loading, then catalyst prepared by method A was employed (table 1).[21]

Entry	Epoxide substituent	Cat. Loading (mol %)	Cat. Oxidation method	Solvent	Reaction time (h)	Isolated yield (%)
1	CH_3	0.2	A	-	18	46
2	$(CH_2)_3CH_3$	0.5	B	-	18	43
3	$(CH_2)_{11}CH_3$	0.5	A	*i*-PrOH	24	42
4	$(CH_2)_2CH{=}CH_2$	0.5	B	THF	18	43
5	CH_2Ph	0.5	B	THF	18	46
6	*c*-C_6H_{11}	0.5	B	THF	18	44
7	*t*-C_4H_9	2.0	A	(±)-1,2-hexanediol	48	41

Table 1: Hydrolytic Kinetic Resolution (HKR) of Aliphatic Terminal Epoxides

Aside from the method of generation of **17**.OAc, the only reaction parameters in the HKR that required optimization for individual substrates were catalyst loading and choice of solvent. With few exceptions, epoxide of >99% *ee* could be obtained using 0.55 equiv. of water relative to racemate. Relatively small epoxides with some degree of water solubility could be resolved effectively without added solvent. However, the HKR of more lipophilic substrates did benefit from inclusion of a water miscible organic solvent such as tetrahydrofuran (THF), 2-propanol, or 1,2-hexanediol (table 1). In general, one volume of solvent relative to racemic epoxides was sufficient to allow efficient HKR. Catalyst loadings

of 0.5 mol% or lower relative to racemic epoxide were effective for many substrates, but epoxides bearing sterically hindered or unsaturated substituents often required more catalyst (up to 2 mol%) to attain complete resolution (table 1). Reactions were initiated at 0 °C and then allowed to warm to room temperature with continued stirring for 12-18 h. The corresponding 1,2-diols were produced in good-to-high enantiomeric excess using 0.45 equiv of H_2O.[21]

1.2.4. Mechanism

The extraordinarily high levels of selectivity observed in the HKR raise interesting questions about the mechanism of catalysis. Preliminary kinetic studies were carried out on the HKR of 1-octene oxide. The reaction follows a second-order dependence on catalyst concentration, consistent with a mechanism wherein two discrete catalyst molecules cooperate to activate both the electrophile (epoxide) and the nucleophile (water).[26] Compelling evidence for a similar bimetallic mechanism has been obtained in the asymmetric ring-opening of epoxides by azide nucleophiles catalyzed by related chromium-containing catalysts.[27] It is noteworthy that bimetallic catalysis is apparently operative with such distinct classes of reactions, and it hints at the possible generality of such a mechanism. The reactants may be sandwiched between two chiral catalyst units which results the extraordinary levels of enantioselection in ring opening reactions. This insight has led to the design and development of multimeric (salen)Co catalysts with dramatically enhanced reactivities and in some cases improved enantioselectivities in epoxide ring opening reactions.[28]

1.2.5. Catalyst Recycling

The possibility of recycling a catalyst has obvious practical appeal, particularly in cases where the catalyst is precious due to cost or limited availability. Catalyst **17** is prepared in bulk from low-cost components, and as a result it is quite inexpensive relative to most chiral catalysts. On the other hand, the HKR employs reactants (racemic epoxide, water, minimal if any solvent) that impact the cost of the overall process to an almost negligible extent in many cases, and as a result the catalyst is a significant contributor to the material costs. Accordingly, efforts were directed toward identifying practical methods for effecting catalyst recovery and recycling.[21]

The catalyst has been shown to be recyclable through several reactions with no diminishment in either reactivity or enantioselectivity. As a result of the large boiling point differences between epoxides and diols, the products can be distilled directly from the reaction vessel and isolated in pure form leaving only the catalyst residue. The solid residue remaining in the reaction vessel was found to have the characteristic red-brick color of the reduced (salen)CoII complex **17**. Reoxidation to **17**.OAc with air and AcOH led to catalyst with undiminished levels of reactivity and selectivity.[21] Furthermore, it has been shown that the catalyst can be attached to solid supports with no deleterious effect on activity or selectivity, making its recovery and reuse even simpler.[26b]

1.2.6. Conclusion

The HKR provides a straightforward method for the preparation of a wide assortment of terminal epoxides in highly enantioenriched form and in many cases there exist no practical alternatives for accessing these valuable chiral building blocks. The HKR has seen rapid adoption as the method of choice for the preparation of a variety of terminal epoxides in enantioenriched form, and a number of applications in target oriented synthesis have been reported already.[29]In addition, the commercial manufacture of enantioenriched propylene oxide, epichlorohydrin, and styrene oxide using HKR methodology has been implemented, thereby reducing the cost of these useful chiral building blocks.[23]

1.3. PROLINE CATALYSED ASYMMETRIC α-AMINOXYLATION

1.3.1. Introduction

Organocatalysis is a relatively new and popular field within the domain of stereoselective synthesis. Although chemical transformations that use organic catalysts have been documented sporadically over the past century, it was not until the early 2000s that the field of organocatalysis was born.[30] It is triggered by the ground-breaking work of List, MacMillan, and others in the early 2000s, the last ca. ten years have seen exponential growth of the field of asymmetric organocatalysis. Iminium and enamine-based organocatalysis now enables cycloadditions, Michael additions, aldol reactions, nucleophilic substitutions, and many other transformations with excellent enantioselectivity; new generations of phase-transfer catalysts give almost perfect enantiomeric excesses at low catalyst loadings; chiral ureas and thioureas are extremely enantioselective catalysts for addition of a variety of nucleophiles to aldehydes and imines; and so forth.[31] Overall, asymmetric organocatalysis has matured in recent few years into a very powerful, practical, and broadly applicable third methodological approach in catalytic asymmetric synthesis. It is now widely accepted that organocatalysis is one of the main branches of enantioselective synthesis, and those who are involved in the synthesis of chiral molecules consider organocatalysis to be a fundamental tool in their catalysis toolbox.[32]

Organocatalysis is the catalysis of chemical transformations using a purely organic molecule, which is composed of mainly carbon, hydrogen, nitrogen, sulfur, and phosphorus, and does not contain any metals. Organocatalysts have several advantages. They are usually robust, inexpensive and readily available, and non-toxic. Because of their inertness toward moisture and oxygen, demanding reaction conditions, for example inert atmosphere, low temperatures, absolute solvents, etc., are, in many instances, not required. Because of the absence of transition metals, organocatalytic methods seem to be especially attractive for the preparation of compounds that do not tolerate metal contamination, e.g. pharmaceutical products.[31] Organic molecules not only have ease of manipulation and a “green” advantage but also can be very efficient catalysts. Several aspects of organocatalysis will undoubtedly attract researcher’s attention. Tremendous efforts will continue to be directed towards the

discovery and design of catalysts with better efficiency, new reactivities and greater turnover numbers (Figure 3).[31]

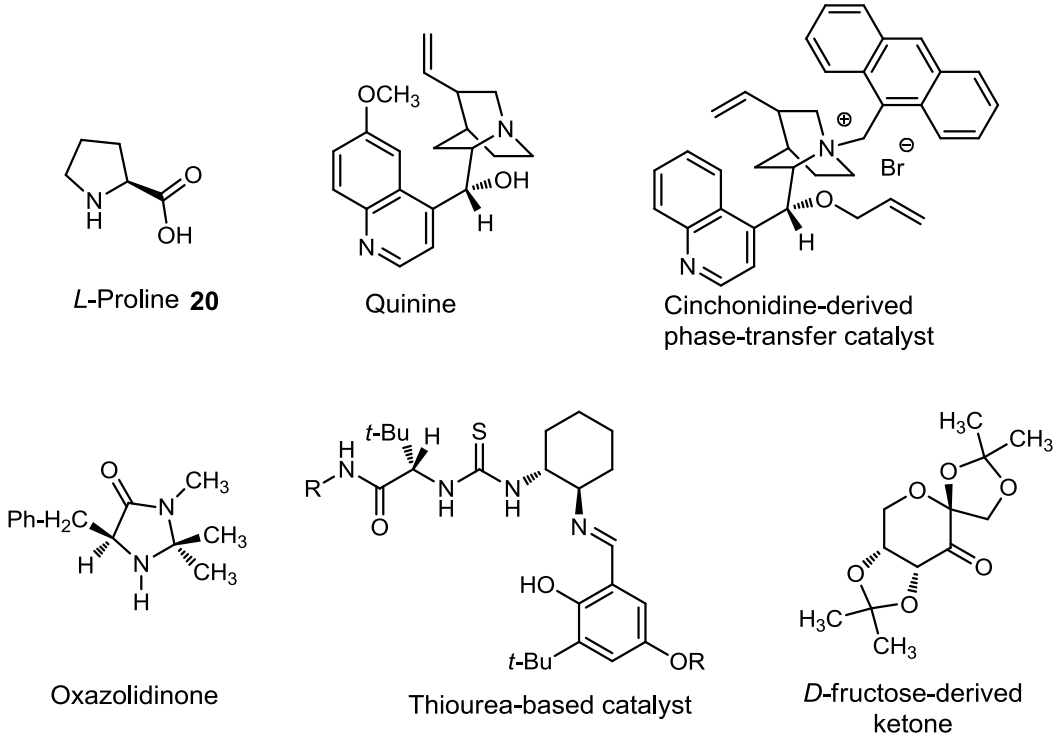


Figure 3: A selection of typical organocatalysts

Proline **20** has been defined as a "universal catalyst" because of its high utility in variety of asymmetric organic transformations.[33] Proline **20** is the only natural amino acid with a secondary amine functionality, which raises the pKa value and better nucleophilicity as compared to other amino acids. It can act as a nucleophile to carbonyl groups (iminium intermediate) or Michael acceptors (enamines). It can be regarded as a bifunctional catalyst as the secondary amine acts as Lewis base and the acid group acts as Bronsted acid (Figure 4). The high stereoselectivity in the proline-catalyzed reactions is possibly due to its formation of organized transition states with many hydrogen bonding frameworks.[33] Proline is not the only molecule to promote catalysis, but it still seems to be one of the best in the diversity of transformations. It is known to catalyze aldol,[34] Diels-Alder,[35] Michael addition[36] and α-functionalization[37] among many other organic transformations.[33] Particularly proline-

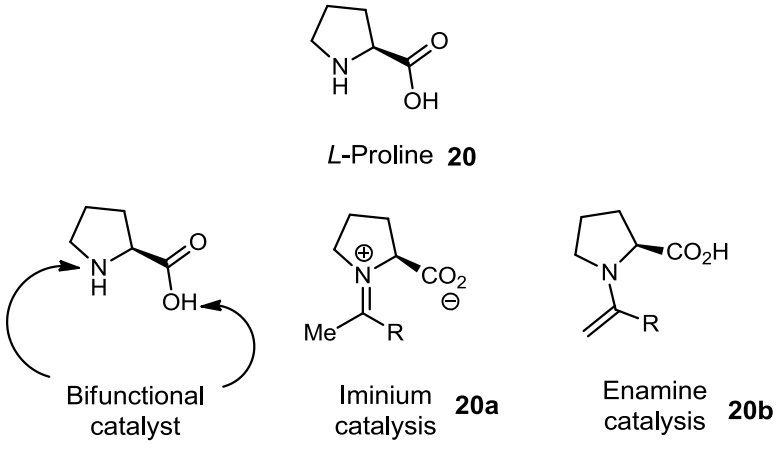
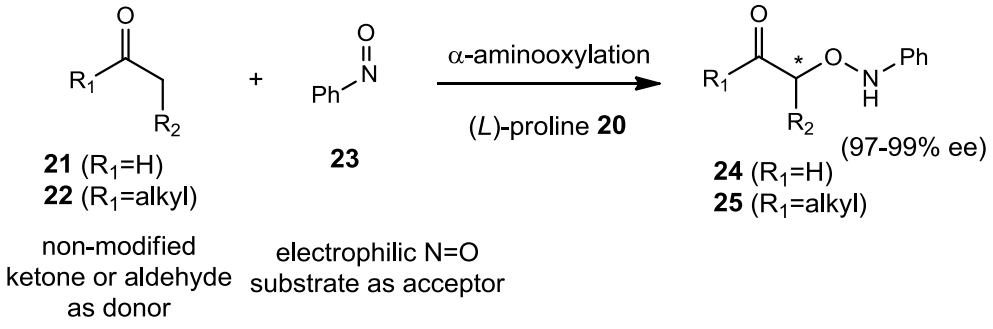


Figure 4: Modes of proline catalysis

catalysed α-aminoxylation[38] of carbonyl compounds has emerged as powerful method because chiral building materials can be synthesized in effective manner starting from easily available materials.

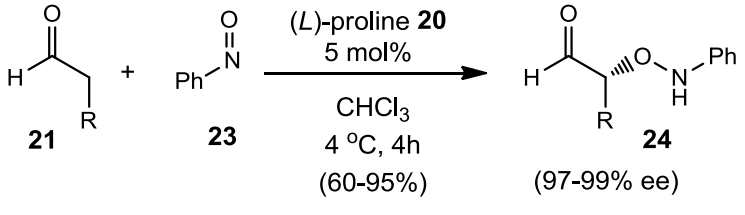
1.3.2. Proline catalyzed α-aminoxylation

Optically active α-hydroxyaldehydes and ketones are important intermediates in organic synthesis as they are direct precursors to 1,2-diols. Because of this utility many methods have been developed for their preparation. For the synthesis of optically active α-hydroxyaldehydes, transformations from chiral natural sources such as amino acids, sugars, and chiral α–hydroxy acids are widely used.[39] Several methods using asymmetric catalytic reactions are known, including the asymmetric dihydroxylation of enol ethers developed by Sharpless et al.[40], the asymmetric epoxidation of silyl enol ethers with a chiral dioxirane,[41] and the asymmetric epoxidation of enol ethers with a chiral Mn-Salen catalyst.[42] Most of these preparations, however, require multiple manipulations, and no direct method from the corresponding aldehyde or ketone has been available. Recently, proline has been found to be an excellent asymmetric catalyst for α-aminoxylation[38] of carbonyl compounds. The reaction with nitrosobenzene forms the α-phenylaminoxy carbonyl both regio- and enantioselectively in good to excellent yields. The directness of the approach to α–hydroxyl carbonyls, the generality of the proline mediated nitrosoaldol reaction, which permits great flexibility in flexibility in selection of aldehydes and ketones.[43]



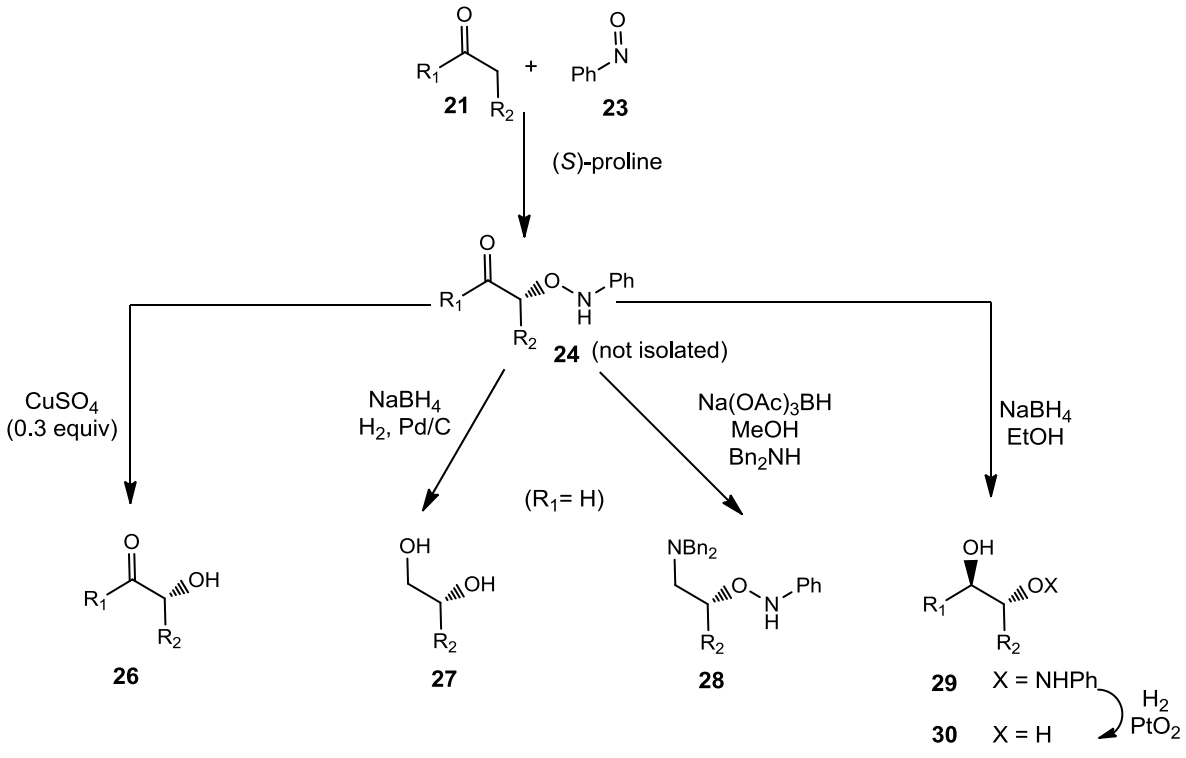
Scheme 11: The concept of the α-aminoxylation reaction

Aldehydes are usually unsuitable donors in enamine reactions because they undergo competing self-condensation. In a hydroxylations this undesired reaction can be minimized when nitrosobenzene is used as the acceptor (Scheme 11). The superior reactivity of nitrosobenzene causes a dramatic decrease in self-aldolization and enables the use of a nearly equimolar amount of the aldehyde.[38] These reactions are anomalously rapid relative to other proline-catalyzed reactions. Another interesting facet of the transformation is the *O*-selective attack of the enamine; in contrast, nitroso-aldol reactions proceed through selective attack at the N-atom.[44] The products were obtained in good to high yields and excellent enantioselectivity in the range 97–99% *ee* were obtained, irrespective of the pattern of substitution of the aldehydes (Scheme 12).[43] The nitrosoaldehyde can be converted to various functional groups by sequential transformations (Scheme 13).[43]



R= Me, nBu, *i*Pr, Ph, CH_2-CH=CH_2, CH_2Ph, $(CH_2)_3$OTIPS

Scheme 12: Enantioselective *L*-proline-catalyzed α-aminoxylation of aldehydes



Scheme 13: Synthetic applications of the α-aminoxylation of aldehydes and ketones

1.3.3. Mechanism

The mechanism of the α-aminoxylation reaction is shown in figure 5. The observed enantioselectivitiy of the catalytic α-aminoxylation of aldehydes can be rationalized by invoking an enamine mechanism operating through a chair transition state where the *Si* face of an α-enamine formed from the aldehyde and *L*-proline approaches the less hindered oxygen atom of nitrosobenzene to provide a chiral α-aminoxyaldehyde with *R*-configuration.[45] Since proline is commercially available in both enantiopure forms, a one pot sequential catalytic α-aminoxylation of aldehydes followed by *in situ* reduction with $NaBH_4$ affords *R*- or *S*-configured 1,2-diol units (the secondary alcohol "protected" by an *O*-amino group) with excellent enantioselectivities and in good yields.

Only *O*-alkylation is observed in all cases. Proline provides an additional directing features to ensure attack at the oxygen atom due to the presence of the carboxyl group which may favour a transition state **A** with an intramolecular hydrogen bond stabilized by the enhanced Brønsted basicity of the nitrogen atom (Figure 5).[43]

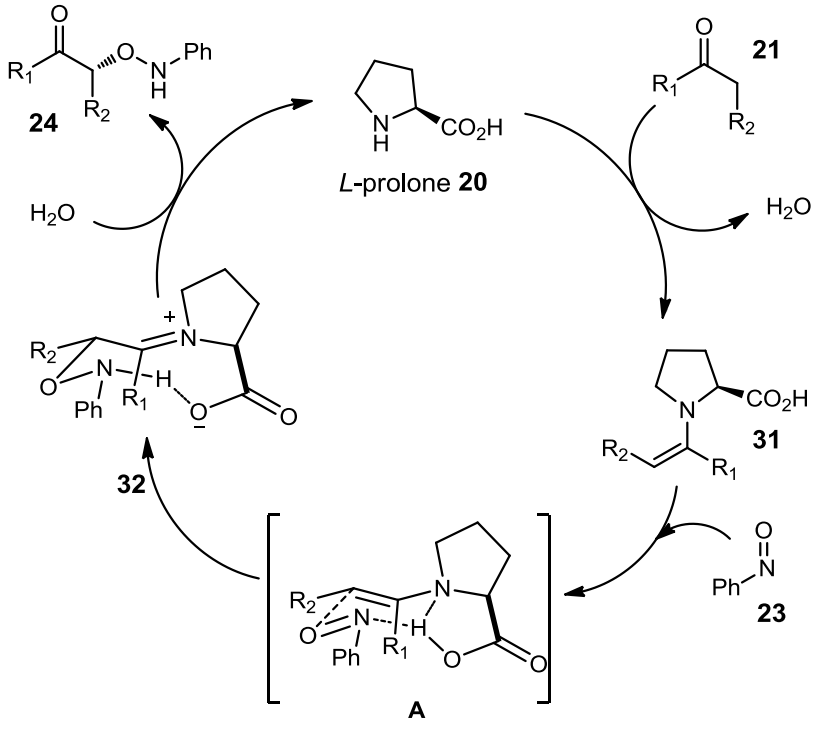


Figure 5: Proposed mechanism of the α-aminoxylation reaction

Model **A** has been proposed essentially in the same, but independent, way by the groups of MacMillan,[38d] Hayashi,[38a] and Zhong,[38b] and it follows the previously reported mechanistic considerations for *L*-proline-catalyzed reactions. This mechanism is in accordance with the proposed reaction mechanism for the aldol reaction.

1.3.4. Conclusion

In summary, the organocatalytic asymmetric α-aminoxylation of aldehydes and ketones with proline as catalyst is a highly enantioselective means of preparation of α-hydroxy carbonyl compounds, and their derivatives. The versatility of the reactions have impressive advantages that should facilitate the synthesis of many useful small molecules possessing not only the α-hydroxycarbonyl unit but also other functionalities such as diols or amino alcohols. Undoubtedly, all these possibilities provide synthetic tools for the asymmetric synthesis of collections of molecules with high levels of diversity directed to diversity-oriented synthesis.

1.4. Reference

1. Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis: Targets, Strategies*, *Methods*. II Ed.; VCH Publishers: Weinheim, **1996**, 4.
2. (a) For a review, see: Johnson, R. A.; Sharpless, K. B. Catalytic Asymmetric Epoxidation of Allylic Alcohols. In *Catalytic Asymmetric Synthesis;* Ojima. I. Ed.; VCH Publishers: New York, **1993**, 103; (b) Woodard, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc*. **1991**, *113*, 106.
3. (a) Kolb, H. C.; Sharpless, K. B. Asymmetric Dihydroxylation. In *Transition Metals for Organic Synthesis*, Beller, M.; Bolm, C. Vol *2*, II. Ed; VCH Publishers; New York, **1998**, 219; (b) Lohray, B. B. *Tetrahedron: Asymmetry* **1992,** *3*, 1317.
4. Kolb, H. C.; Sharpless, K. B. Asymmetric Aminohydroxylation. In *Transition Metals for Organic Synthesis*; Beller, M.; Bolm, C. Vol *2* II. Ed; VCH Publishers: New York, **1998**, 243.
5. Lin, Guo-Qiang; Li, Yue-Ming; Chan, A.S.C. Asymmetric Oxidation., In *Principles and Applications of Asymmetric Synthesis*; John Wiley & Sons, Inc. **2001**, *chapter 4*, 195.
6. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
7. (a) Wood, R. D.; Ganem, B. *Tetrahedron Lett.* **1982**, *23*, 707. (b) Erickson, T. J. *J. Org. Chem.* **1986**, *51*, 934.
8. (a) Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113; (b) Potvin, P. G.; Bianchet, S. *J. Org. Chem.* **1992**, *57*, 6629.
9. Woodard, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc*. **1991**, *113*, 106.
10. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
11. Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.
12. Lohray, B. B.; *Synthesis* **1992**, *11,* 1035.
13. (a) Epothilones: Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325; (b) FR901464: Nakajima, H.; Takase, S.; Terano, H.; Tanaka, H. *J. Antibiot.* **1997**, *50*, 96.

14. For examples, see: (a) Larchevêque, M.; Petit, Y. *Tetrahedron Lett.* **1987**, *28*, 1993; (b) Larchevêque, M.; Henrot, S. *Tetrahedron* **1990**, *46*, 4277; (c) de March, P.; Figueredo, M.; Font, J.; Monsalvatje, M. *Synth. Commun.* **1995**, *25*, 331; (d) Adiyaman, M.; Khanapure, S. P.; Hwang, S. W.; Rokach, J. *Tetrahedron Lett.* **1995**, *36*, 7367.
15. (a) Katsuki, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, **1999**, Chapter 18.1; (b) Rossiter, B. E. in *Asymmetric Synthesis*, Vol. 5; Morrison, J. D., Ed.; Academic Press: New York, **1985**, Chapter 7; (c) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, **1993**, Chapter 4.1; (d) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1. Reviews: (e) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, **1999**, Chapter 18.2; (f) Katsuki T. *Coord. Chem. Rev.* **1995**, *140*, 189; (g) Jacobsen, E. N. In *Comprehensive Organometallic Chemistry II*, Vol. 12; Wilkinson, G., Stone, F. G. A., Abel, E. W., Hegedus, L. S., Eds.; Pergamon: New York, **1995**, 1097. For asymmetric dihydroxylation routes, see: (h) Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515. For asymmetric reduction methods, see: (i) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1991**, *56*, 442.
16. For the most enantioselective methods developed to date involving synthetic catalysts: (a) Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333; (b) Collman, J. P.; Wang, Z.; Straumanis, A.; Quelquejeu, M.; Rose, E. *J. Am. Chem. Soc.* **1999**, *121*, 460. For methods involving biocatalysts, see: (c) Botes, A. L.; Weijers, C. A. G. M.; Botes, P. J.; van Dyk, M. S. *Tetrahedron: Asymmetry* **1999**, *10*, 3327 and references therein; (d) Goswami, A.; Totleben, M. J.; Singh, A. K.; Patel, R. N. *Tetrahedron: Asymmetry* **1999**, *10*, 3167, and references therein.
17. (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936; (b) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org.Chem*. **1998**, *63*, 6776.
18. (a) Wistuba, D.; Schurig, V.; *J. Chromatogr. A* **2000**, *875*, 255; (b) Collet, A.; *Enantiomer* **1999**, *4*, 157.
19. Trost, B. M.; *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 259.

20. For an in depth discussion of practical considerations in kinetic resolution reactions, see: Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5.
21. Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.
22. (a) Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939; (b) Larrow, J. F.; Jacobsen, E. N. *Org. Synth*. **1997**, *75*, 1.
23. For information, see: http://www.rhodiachirex.com.
24. (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483; (b) Schroder, M. *Chem*. *Rev*. **1980**, *80*, 187; (b) Becker, H.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1996**, *35*, 448.
25. While it may be assumed that an "ideal" resolution would involve no added reagents i.e., an enantiomer undergoing selective isomerization or polymerizations the rate of such transformation may be difficult to control because of the exothermicity ($\Delta E >$ 30 kcal/mol) associated with epoxide ring opening. This is a special concern with reactions carried out on a large scale. The fact that the rate of nucleophile addition can be adjusted to control reaction rate therefore has significant practical advantages.
26. (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science*, **1997**, *277*, 936; (b) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147.
27. Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am.Chem. Soc*. **1996,** *118*, 10924.
28. Jacobsen, E. N. *Acc. Chem. Res.* **2000,** *33*, 421.
29. For review: Kumar, P.; Naidu, V.; Gupta, P. *Tetrahedron* **2007**, *63*, 2745.
30. Hechavarria Fonseca, M. T.; List, B.; *Angew. Chem., Int. Ed*. **2004**, *43*, 3958.
31. Berkessel, A.; Groger, H. In *Asymmetric Organocatalysis – From Biomimetic Concepts to Applications in Asymmetric Synthesis* WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, **2005,** *Chapter 1*, 1.
32. Pellissier, H. *Tetrahedron* **2007**, *63*, 9267.
33. List, B. *Tetrahedron* **2002**, *58*, 5573.
34. List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc*. **2000**, *122*, 2395.
35. (a) Sabitha, G.; Fatima, N.; Reddy, E.V.; Yadav, J. S. *Adv. Synth. Catal*. **2005**, *347*, 1353; (b) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F. III *Synlett* **2003**, 1910.
36. Hechavarria Fonseca, M. T.; List, B.; *Angew. Chem., Int. Ed*. **2004**, *43*, 3958.

37. For α-functionalization reviews: (a) Franzen, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjarsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2005**, *127*, 18296; (b) Guillena, G.; Ramon, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465.
38. (a) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett*. **2003**, *44*, 8293; (b) Zhong, G. *Angew. Chem., Int. Ed*. **2003**, *42*, 4247; (c) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed*. **2003**, *43*, 1112; (d) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2003**, *125*, 10808; (e) Cordova, A.; Sunden, H.; Bøgevig, A.; Johansson, M.; Himo, F. *Chem. A-Eur. J*. **2004**, *10*, 3673.
39. Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Shoji, M. *J. Org. Chem.* **2004**, *69*, 5966.
40. (a) Morikawa, K.; Park, J.; Andersson, P. G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc*. **1993**, *115*, 8463; (b) Hashiyama, T.; Morikawa, K.; Sharpless, K. B. *J. Org. Chem*. **1992**, *57*, 5067.
41. (a) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett*. **1998**, *39*, 7819; (b) Adam, W.; Fell, R. T.; Saha-Moller, C. R.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1998**, *9*, 397.
42. (a) Fukuda, T.; Katsuki, T. *Tetrahedron Lett*. **1996**, *37*, 4389; (b) Adam, W.; Fell, R. T.; Stegmann, V. R.; Saha-Moller, C. R. *J. Am. Chem. Soc*. **1998**, *120*, 708.
43. Merino, P.; Tejero, T.; *Angew. Chem., Int. Ed*. **2004**, *43*, 2995.
44. (a) Momiyama, H.; Yamamoto, H. *Org. Lett.* **2002**, *4*, 3579; b) Momiyama, N.; Yamamoto, H.; *J. Am. Chem. Soc.***2004**, *126*, 6498.
45. Berkessel, A.; Groger, H. In *Asymmetric Organocatalysis – From Biomimetic Concepts to Applications in Asymmetric Synthesis* WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, **2005,** *Chapter 7*, 249.

Chapter-2

Studies towards enantioselective synthesis of (+)-L-733,060 and (+)-CP-99,994 using Sharpless asymmetric epoxidation

Studies towards enantioselective synthesis of (+)-L-733,060 and (+)-CP-99,994 using Sharpless asymmetric epoxidation

2.1. Introduction

The peptide neurotransmitter, Substance P (SP) involves a variety of biological actions such as pain transmission, vasodilation, smooth muscle contraction and neurogenic inflammation.[1]This tachykinin family peptide member binds preferentially to the NK1 receptor. The search for non-peptide antagonists of the NK1 receptor led to the discovery of 2,3-disubstituted piperidine derivatives L-733,060[2] **2** and CP-99,994[3] **3** (Figure 1). They have excellent affinity and selectivity with human NK1 receptors and possess potent antiemetic activity.[4] They are expected to act as remedy for a wide range of diseases, including arthritis, asthma and migraines.[5] Recent studies have shown that (+)-L-733,060 **2** can act both as an antitumor agent and as a promising new target for the treatment of retinoblastoma.[5 e,f]

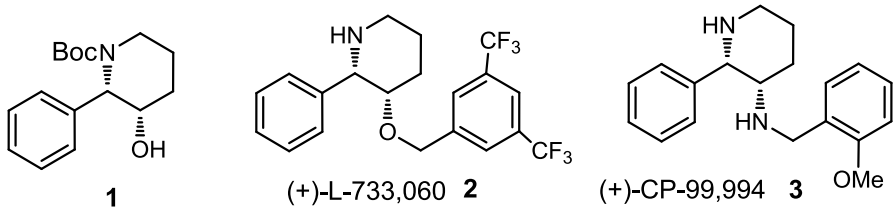


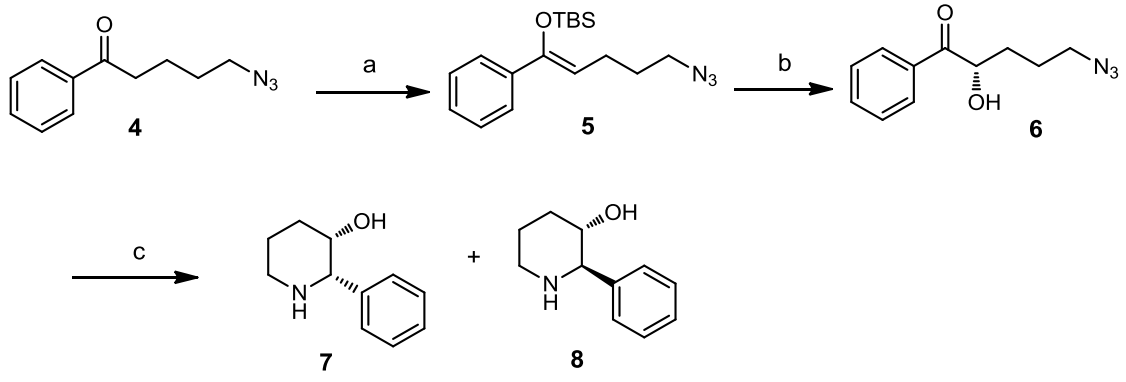
Fig. 1: Structures of 2-aryl-3-hydroxypiperidine and 2-aryl-3-aminopiperidine derivatives

2.2. Review of Literature

In recent years, there have been several reports on the synthesis and structural modification studies of the above compounds. Structure activity relationship studies have shown that the *cis* relationship between C_2 and C_3 substituents on the piperidine ring of **2** and **3** is required for optimum binding activity.[6] Routes leading to valuable intermediate **1**, compound **2** and **3** mainly rely on racemic synthesis followed by resolution techniques[2b,7a,7c] or lengthy asymmetric synthesis of **1** and **2** reported in recent literatures.[7,8] Some of the interesting and important synthetic routes to (+)-L-733,060 **2** are described below.

Stadler *et al.* (1999)[7a]

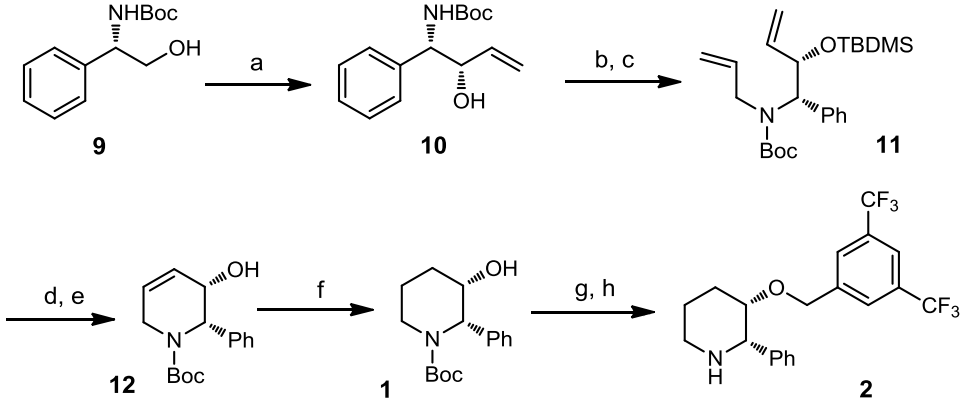
In this synthetic approach, Stadler utilized Sharpless asymmetric dihydroxylation to generate chirality. The AD reaction of **5** provided **6** which was subjected to hydrogenolytic condition leading to a mixture of *cis*- and *trans*-isomers **7** and **8** which was separated by crystallization to yield **7** (Scheme 1).[7a]



Scheme 1: *Reaction conditions*: (a) Et_3N, TBDMS-Cl, CH_3CN, 84%; (b) K_3FeCN_6, K_2CO_3, CH_3SONH_2, OsO_4, $(DHQ)_2PHAL$, H_2O/*t*-BuOH ; (c) Pd/C, MeOH.

Rao *et al.* (2003)[7b]

Rao *et al.* have achieved the synthesis of (+)-L-733,060 (**2**) starting from *N*-Boc protected amino alcohol **9,** which was subjected to Swern oxidation, followed by chelation controlled addition of vinyl magnesium bromide to give allylic alcohol **10** (Scheme 2).

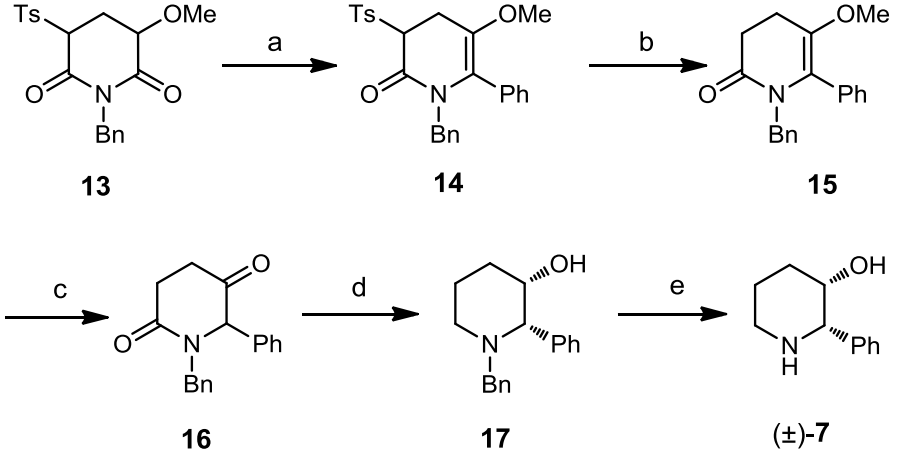


Scheme 2: *Reaction conditions*: (a) DMSO, $(COCl)_2$, *i*-Pr_2NEt, CH_2Cl_2; then CH_2=CHMgBr, THF, 2 h, 90%; (b) TBDMSCl, imid., CH_2Cl_2, 24 h, 90%; (c) allyl bromide, NaH, DMF, 0- 25 ºC, 24 h, 90%; (d) TBAF-AcOH, THF, 0- 25 ºC, 24 h, 85%; (e) Grubbs' catalyst, CH_2Cl_2, 25 ºC, 6 h, 82%; (f)10% Pd/C, H_2, EtOH, 4 h, 65%; (g) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, DMF, 80%; (h) TFA, CH_2Cl_2, 79%.

Protection of allylic alcohol **10** as silyl ether followed by *N*-allylation of the amine resulted in diene **11**, which upon ring closing metathesis using Grubbs' catalyst gave the unsaturated piperidine moiety **12**. The catalytic hydrogenation of olefin **12** furnished the intermediate **1** in 65% yield (Scheme 2). [7b]

Chang *et al.* (2005)[7c]

Chang *et al.* have employed a new method of addition of Grignard reagent onto glutarimide **13** for the synthesis of racemic 3-hydroxy-2-phenyl piperidine (±)-**7**. Accordingly, addition of phenyl magnesium bromide to glutarimide **13** followed by trapping the resulted OH group with Ac_2O proceeded regioselectively to provide the enol ether **14** in 82% yield.



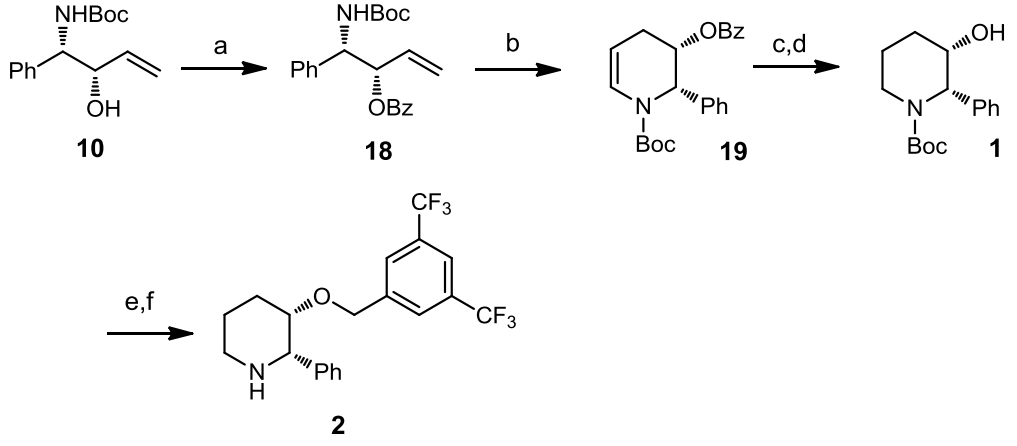
Scheme 3: *Reaction conditions*: (i) NaH, PhMgBr, THF, 25 ºC, 1 h, 82%; (ii) Na-Hg, MeOH, 25 ºC, 90%; (iii) BBr_3, CH_2Cl_2, -78 ºC, 90%; (iv) $LiAlH_4$, THF, reflux, 87%; (v) $Pd(OH)_2$, H_2, MeOH, 25 ºC, 90%.

Removal of the sulfonate ester group was achieved using Na/Hg to obtain enol ether **15**, which was hydrolysed by using BBr_3 that afforded ketolactam **16.** The reduction of ketolactam **16** with $LiAlH_4$ gave piperidine **17**. Benzyl group was deprotected to produce racemic 3-hydroxy-2-phenyl piperidine **7** (Scheme 3).[7c]

Oshitari *et al.* (2006)[7d]

Oshitari *et al.* have achieved the synthesis of (+)-L-733,060 **2** starting from optically active amino alcohol **10**. Esterification of the free alcohol group with benzoyl chloride gave the

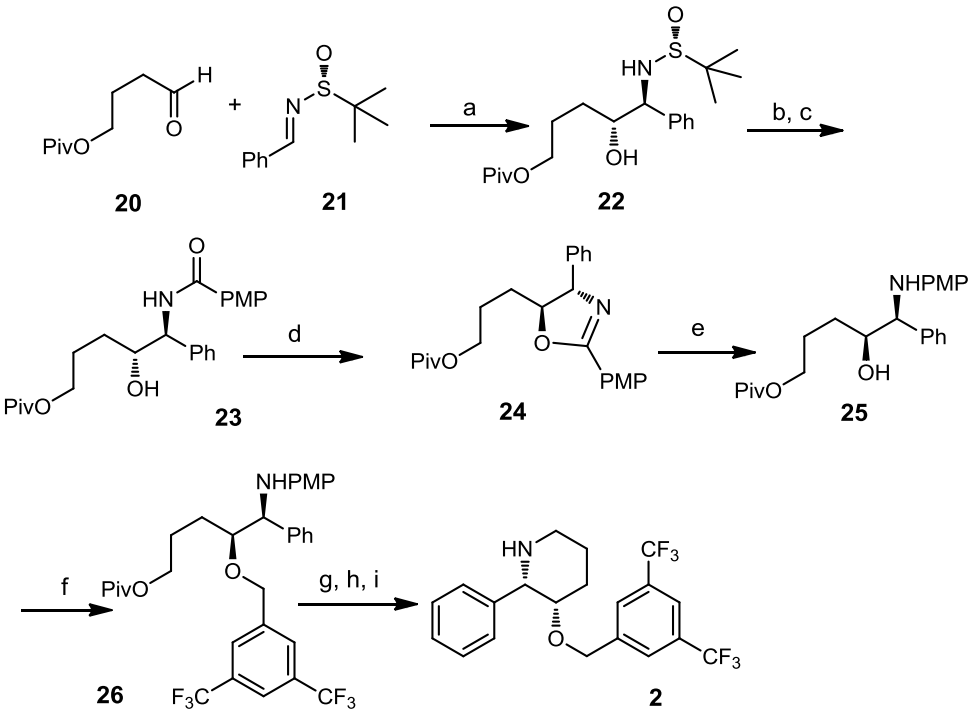
protected amino alcohol **18**. One carbon extension and ring closure to obtain enamine **19** was achieved in one-pot *via* $Rh(acac)(CO)_2$-catalyzed hydroformylation of olefin **18**. Hydrogenation of C=C bond in **19** followed by hydrolysis gave the intermediate **1** which was converted to (+)-L-733,060 **2** *via* standard reaction sequences (Scheme 4).



Scheme 4: *Reaction conditions*: (a) BzCl, pyridine, 25 °C, 10 h; (b) $Rh(acac)(CO)_2$ (3 mol%), biphephos (6 mol%), CO/H_2 (5 atm), THF, 65 °C, 5 h; (c) 10% Pd/C, H_2 (1 atm), EtOH, 25 °C, 20 h; (d) 1M NaOH, MeOH: 1,4-dioxane (1:2), 25 °C, 1 h; (e) 3,5-$(CF_3)_2C_6H_3CH_2Br$, NaH, THF: DMF (1: 3), 0 °C, 6 h; (f) TFA, 25 °C, 1.5 h, $NaHCO_3$.

Wang *et al.* (2008)[7e]

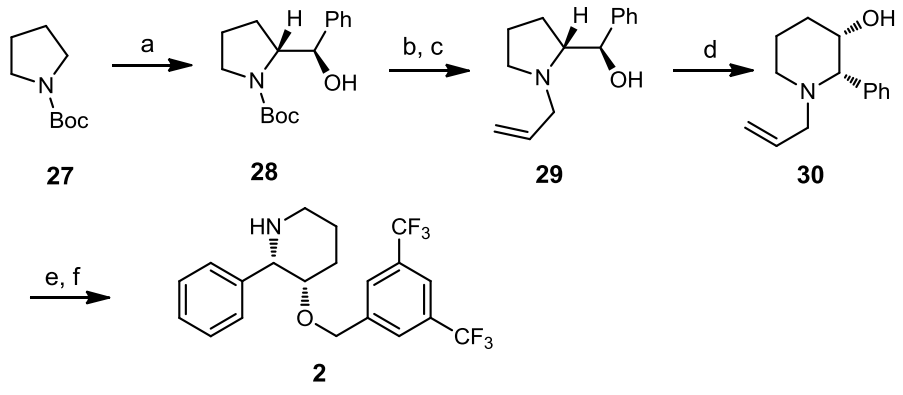
Wang *et al*. employed the reductive coupling of 4-pivaloxybutanal **20** with (*R*)-phenyl *N*-*tert*-butanesulfinyl imine **21** in the presence of SmI_2 to afford amino alcohol **22** with desired stereochemistry. Removal of the chiral auxiliary followed by selective *N*-acylation with 4-methoxybenzoic anhydride afforded amide **23**. Mesylation of free alcohol group of **23** furnished oxazoline **24** in 85% yield, with complete inversion of configuration at C-2. Reductive ring-opening of oxazoline **24** ($NaBH_3CN$, HOAc, 40 °C) gave *syn*-1,2-amino alcohol **25** in excellent yield. Selective *O*-alkylation with 3,5-bis(trifluromethyl)benzyl bromide provided **26** in 82% yield. The intermediate **26** was converted to (+)-L-733,060 **2** by standard reaction sequences (Scheme 5).[7e]



Scheme 5: *Reaction conditions*: **(**a) SmI_2, ^tBuOH, -78 ^oC, 78%; (b) HCl, MeOH; (c) $(PMPCO)_2O$, Et_3N, CH_2Cl_2, 88%; (d) MsCl, Et_3N, CH_2Cl_2, 85%; (e) $NaCNBH_3$, AcOH, 90%; (f) NaH, 3,5-bis(trifluoromethyl)benzyl bromide, TBAI, DMF, 82%; (g) NaOMe, MeOH; (h) MsCl, Et_3N, CH_2Cl_2, 78%; (i) DDQ, CH_2Cl_2, 0 ^oC.

O'Brien *et al.* (2008)[7f]

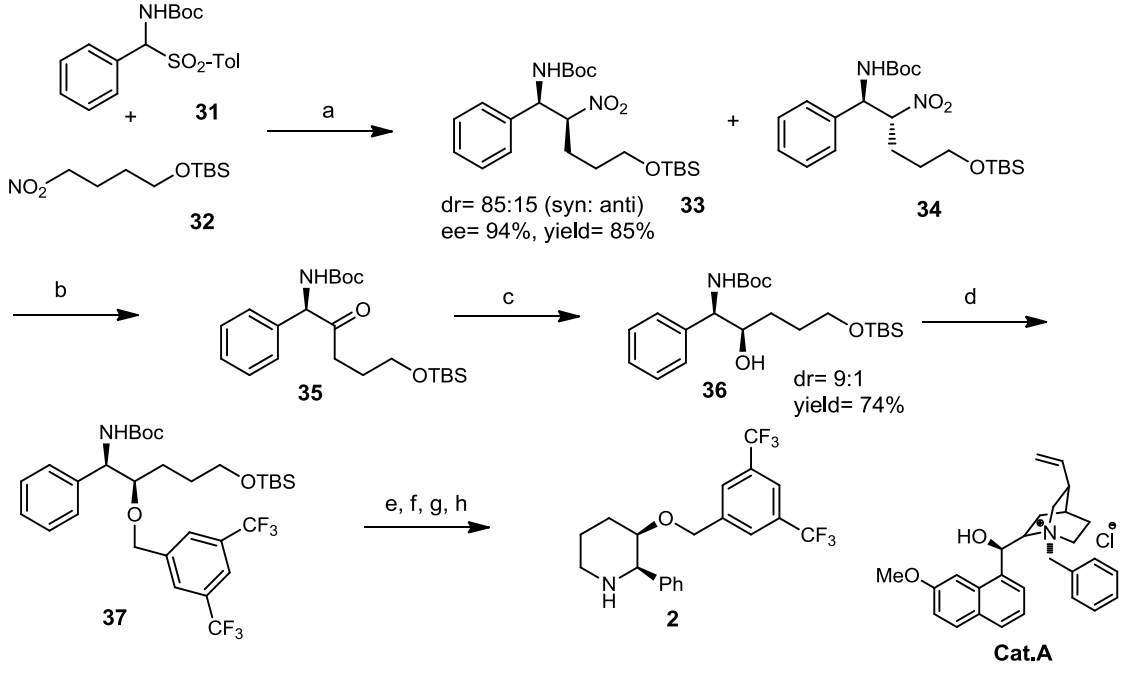
O'Brien *et al*. have reported synthesis of (+)-L-733,060 using catalytic asymmetric deprotonation of *N*-Boc pyrrolidine **27**as a key step. *N*-Boc pyrrolidine **27** was subjected to asymmetric deprotonation by using *s*-BuLi, (-)-sparteine to give the organolithium reagent, which was subsequently trapped with benzaldehyde to afford alcohol **28** with dr = 3:1 (*syn*: *anti*). Deprotection of Boc group in alcohol **28** followed by its treatment with allyl bromide in presence of K_2CO_3 gave *N*-allylated alcohol **29** in 58% yield. The *N*-allylated alcohol **29** was subjected to ring-expansion with TFAA followed by hydrolysis to give piperidine derivative **30** in 83% yield. *O*-Benzylation of **30** was achieved by using NaH and the corresponding benzyl bromide. Finally, *N*-deallylation was achieved with Pd(0) and *N*,*N*′-dimethylbarbituric acid to give (+)-L-733,060 **2** (Scheme 6).[7f]



Scheme 6: *Reaction conditions*: (a) i) *s*-BuLi, (-)-sparteine, LiDMAE, Et_2O, -78 °C; ii) PhCHO, 64% (3:1 dr). (b) TFA, CH_2Cl_2, 25 °C, 16; (c) K_2CO_3, AllylBr, MeCN, 25 °C, 6 h, 58%; (d) $(CF_3CO)_2O$, Et_3N, THF, reflux, 72 h, then aq NaOH, 83%; (e) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, THF, 0 °C, 30 min; (f) $Pd(PPh_3)_4$, *N*,*N*′-dimethylbarbituric acid CH_2Cl_2, 25 °C, 24 h.

Kumaraswamy *et al* (2011)[7g]

Kumaraswamy *et al.* has accomplished an efficient enantioselective synthesis of (+)-L-733,060 by catalytic enantioselective aza-Henry reaction.



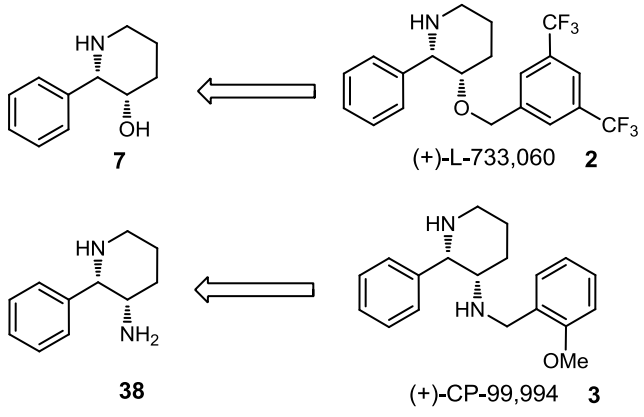
Scheme 7: *Reaction conditions*: (a) Cat A (15 mol %), CsOH. H_2O (1.3 equiv.), toluene (0.8 M), -55 °C, 44 h; (b) $NaNO_2$ (6 equiv.), DMF/H_2O (7:1), 45 °C, 12 h; (c) $NaBH_4$, $CeCl_3$. $7H_2O$, -78 °C to -40 °C; (d) (i) NaH, TBAI, THF, (ii) *3,5*-bis trifluromethyl benzyl bromide, 12 h, rt; (e) TBAF, 0 °C, THF; (f) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (g) TFA, CH_2Cl_2; (h) Et_3N, MeOH, 2 h, 60 °C.

The reaction of N-Boc-sulfone **31** with nitro compound **32** employing phase transfer catalyst A resulted the *syn* product **33** in 85% yield with 85:15 diastereomeric ratio in favour. Oxidation of nitro functionality in **33** by Gissot's protocol led to keto compound **35** in 68% yield. Then, the amino ketone **35** was reduced with $NaBH_4$ under Luche's conditions to furnish a *syn* selective (dr = 9:1) secondary alcohol **36** (74%). Hydroxyl protection of **36** with 3,5-bis-triflouromethyl benzyl bromide under basic conditions resulted in a separable pure *syn*-isomer **36** (74% yield) and then following deprotection of TBS led to a primary alcohol in 80% yield. Mesylation of primary alcohol followed by removal of N-Boc group with TFA resulted in TFA salt. Subsequent cyclization under basic condition afforded the desired compound **2** in 65% isolated yield over three steps (Scheme 7).[7g]

2.3. Present work

Objective

2,3-Disubstituted piperidines are found in numerous natural products and are common subunits in several drug candidates.[9] 3-Hydroxy-2-phenylpiperidine **7** and 3-amino-2-phenylpiperidine **38** are important intermediates in the synthesis of non-peptidic substance P antagonists, (Scheme 8) which binds preferentially to the neurokinin-1 (NK-1) receptor. Neurokinin 1 (NK1) antagonists are a novel class of medications that possesses unique antidepressant[10] anxiolytic,[11] and antiemetic properties. The discovery of neurokinin 1 (NK1) receptor antagonists was a turning point in the prevention of nausea and vomiting associated with cancer chemotherapy.[12] The compound **7** and **38** are precursors to the NK-1 receptor antagonist **2** and **3**. The *cis*-relationship between the two substituents on the piperidine ring is essential for high-affinity binding to the human NK1 (hNK1) receptor.[6]

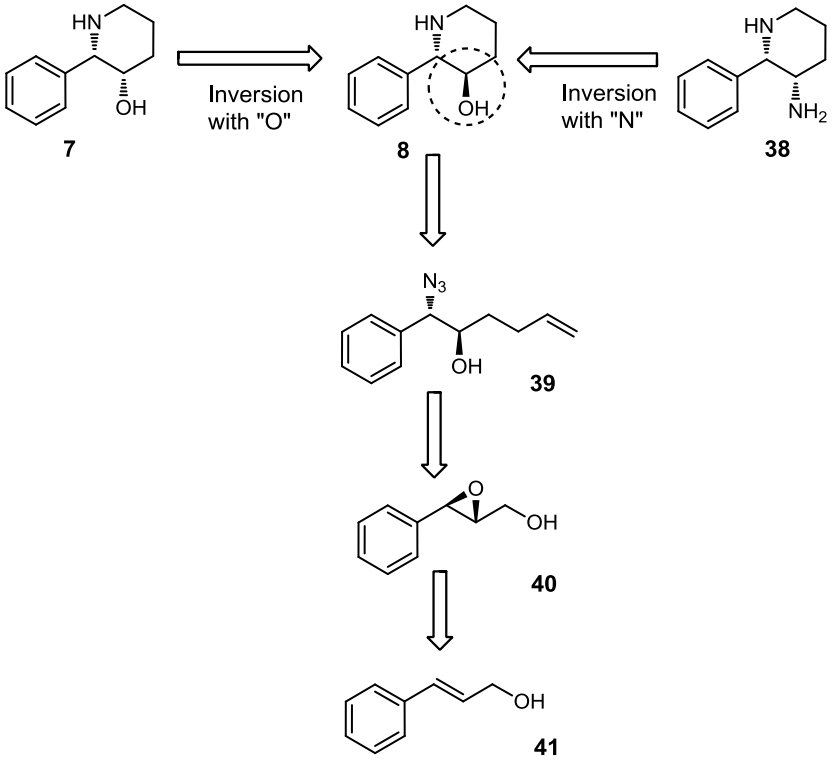


Scheme 8: Retrosynthetic Analysis of (+)-L-733,060 and (+)-CP-99,994

In continuation of our research program aimed at developing enantioselective synthetic routes to amino alcohols,[13] we became interested in devising a general, flexible, and efficient route to **2** and **3.** The present study describes our endeavors towards the synthesis of compound **2** and compound **3** from commercially available cinnamyl alcohol. In this strategy the chirality was introduced by Sharpless asymmetric epoxidation (AE)[14] and piperidine ring formation was achieved by one pot Staudinger/aza-Wittig reaction.[15]

2.4. Results and discussion

Our initial approach for the synthesis of compound **7** and **38** was envisioned *via* the retrosynthetic route as shown in Scheme 9. The *trans*-3-Hydroxy-2-phenylpiperidine **8** was thought to be the common intermediate which can easily be obtained from cinnamyl alcohol **41**.

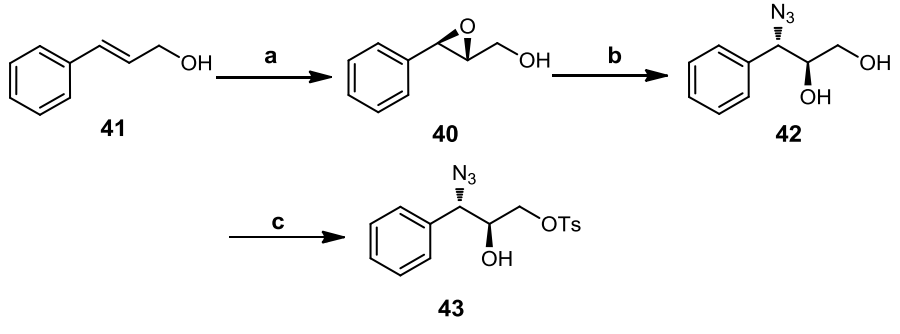


Scheme 9: Retrosynthetic Analysis of *cis*-3-Hydroxy-2-phenylpiperidine and *cis*-3-Amino-2-phenylpiperidine

The key to this route lies in the inversion of the configuration of the hydroxyl in **8** by appropriate *N*- and *O*-nucleophiles, respectively, to furnish *syn*-1,2-diamine **38** and *syn*-1,2-

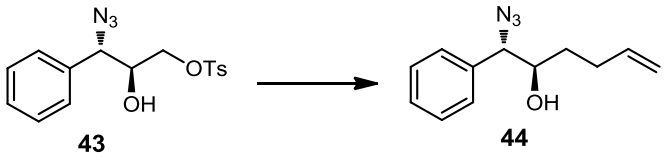
amino alcohol **7** structural units. Conceptually, this approach complements the Sharpless asymmetric aminohydroxylation reaction[16] and asymmetric diamination reaction.[17] Moreover, it provides facile access to important 2,3-disubstituted piperidine derivatives[18] of all four possible configurations.

As shown in Scheme 10, the synthesis of (+)-L-733,060 was initiated by AE of commercially available cinnamyl alcohol **41** to afford *trans*-epoxide **40** in 89% yield with >99% ee. (After recrystallisation) $[\alpha]_D^{27}$ = +48.66 (*c* 2.4, $CHCl_3$) {lit.[14] $[\alpha]_D^{25}$ = –49.6 (*c*2.4, $CHCl_3$) for (–)-**40**}. The epoxide peaks appeared at δ 3.23-3.27 (m, 1H), 3.94-3.95 (d, *J* = 2.1 Hz, 1H) ppm in ^{1}H NMR spectrum. The ^{13}C NMR spectrum of **40** showed upfield carbons of epoxide at δ 55.5, 61.2 ppm. The regioselective epoxide opening of **40** with NaN_3 gave a single regio-isomer **42** in excellent yield.[19] The IR spectrum illustrated the azide group stretching frequency at 2099 cm^{-1}. Our next aim was to convert the free primary hydroxy group of **42** into a leaving group such as *p*-toluene sulphate derivative using tosyl chloride. The regioselective primary monotosylation of this diol **42** with tosyl chloride and catalytic Bu_2SnO, furnished compound **43** in excellent yield. The appearance of peak at δ 2.46 ppm in ^{1}H- NMR shows the presence of tosyl group (Scheme 10).



Scheme 10: *Reagents and conditions:* (a) (*S*,*S*)-(–)-DET, Ti(OPr-*i*)$_4$, TBHP, MS 4Å, CH_2Cl_2, –20 °C, 3 h, 89%; (b) NaN_3, NH_4Cl, MeOH:H_2O (8:1), 65 °C, 5 h, 98%; (c) TsCl, Et_3N, Bu_2SnO, DCM, 91%.

With the tosylate **43** in hand our next aim was to displace tosyl group with suitable allyl reagent to elongate the chain, towards this end we tried various conditions to displace the tosyl group using allyl magnesium bromide. This attempt, however, was unsuccessful. The results are summarized in Table 1.

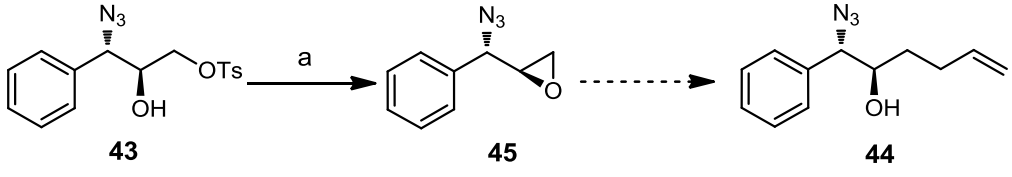


Scheme 11: Allyl displacement of tosyl group

Entry	Reaction conditions	Yield % of 44
1	Allylmagnesium bromide, (2.5 equiv.), CuI, THF, -30 °C, 12 h.	–
2	Allylmagnesium bromide, (2.5 equiv.), CuI, THF, -78 °C, 12 h.	-
3	Allylmagnesium bromide, (3 equiv.), CuI, Et_2O, -78 °C, 12 h.	-
4	Allylmagnesium bromide, (3.5 equiv.), Et_2O, 25 °C, 24 h.	<5
5	Allylmagnesium bromide, (3.5 equiv.), THF, 60 °C, 48 h.	<5

Table 1: *Reagents and conditions*: Allylmagnesium bromide, various additives, solvent.

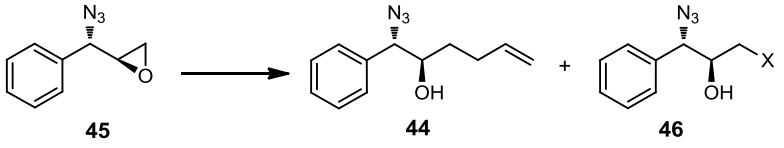
Since all these reactions failed to work, we then looked at the possibility of regioselective ring opening of corresponding epoxide with an allyl reagent. Base treatment of compound **43** in presence of K_2CO_3 in methanol furnished azide epoxide **45**. The appearance of multiplet in the range of δ 2.77-2.79 (dd, *J*= 4.6, 2.7 Hz, 1H), 2.83-2.84 (m, 1H), 3.28-3.30 (m, 1H) ppm in ^{1}H- NMR confirmed the presence of epoxide. The ^{13}C NMR spectrum of **45** showed upfield carbons of epoxide at δ 44.8, 54.7 ppm.



Scheme 11: *Reagents and conditions:* (a) K_2CO_3, MeOH, rt, 1 h, 82%.

With substantial amount of epoxide **45** in hands, our next aim was to elongate the chain through regioselective ring opening of epoxide **45** by allylation (Scheme 12). The results are

summarized in Table 2. To our delight, the anticipated allyl opened product **44** was achieved after several trials.



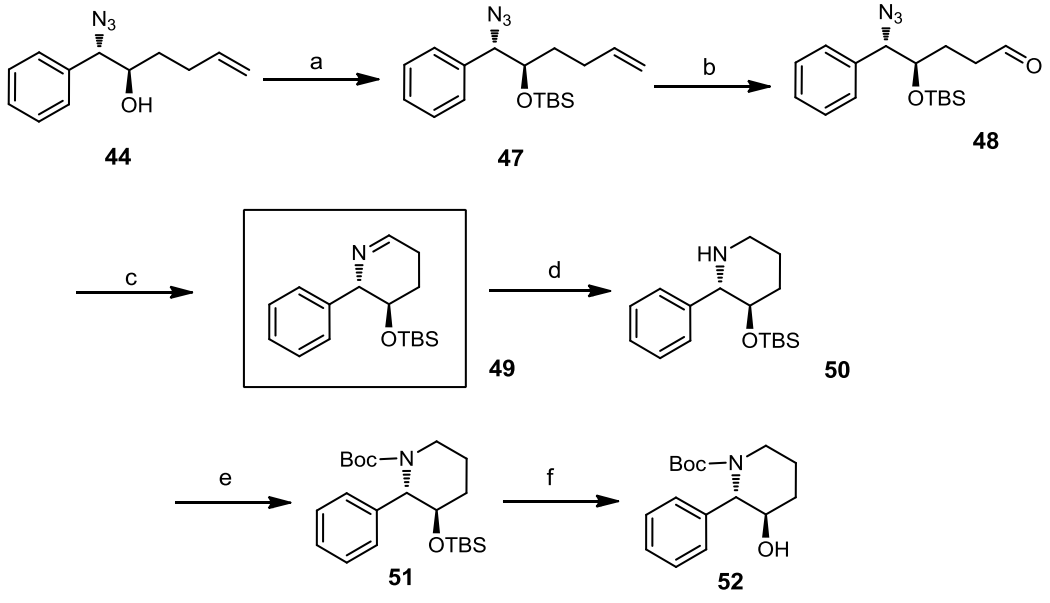
Scheme 12: Allyl opening of epoxide

Entry	Reaction conditions	Yield % of 44	Yield % of 46
1	Allylmagnesium bromide, CuI, THF, 0 °C–rt, 12 h	–	90% X=Br, I
2	Allyltrimethylsilane, $BF_3.OEt_2$, CH_2Cl_2, –78 °C, 2 h.	5%	75% X= OH
3	Allyltrimethylsilane, $BF_3.OEt_2$, CH_2Cl_2, –30 °C–0 °C, 3 h.	8%	60% X=OH
4	Allyltributylstannane, $TiCl_4$, CH_2Cl_2, –78 °C, 1 h.	–	90% X=Cl
5	Allyltrimethylsilane (1 equiv.), $TiCl_4$, CH_2Cl_2, –78 °C, 1 h.	55%	25% X=Cl
6	Allyltrimethylsilane (3 equiv.), $TiCl_4$, CH_2Cl_2, –78 °C, 1 h.	65%	10% X=Cl

Table 2: Allyl opening of epoxide **45** by different nucleophiles under various reaction conditions

Opening of epoxide **45** with allylmagnesium bromide[20a] (Table 2, entry 1) resulted only halide opened byproducts. Similarly the use of $BF_3.OEt_2$ with allylsilane was also disappointing as it resulted in a poor yield of the desired product **44** (Table 2, entry 2 and 3) along with the hydroxy opened product **45** as major one. The reaction with allylstannane and $TiCl_4$ in CH_2Cl_2 at –78 °C[20b] (Table 2, entry 4) also failed to give the allylated product **44**. The use of 1:1 equivalent amounts of allylsilane and $TiCl_4$ in CH_2Cl_2 at –78 °C resulted **44** in moderate yield (Table 2, entry 5). Finally we could improve the yield of **44** by using 3 equivalents of allylsilane with slow addition of freshly distilled $TiCl_4$ (Table 2, entry 6). The appearance of olefinic protons in the range of δ 4.97-5.0 (m, 1H), 5.06-5.07 (m, 1H), 5.75-5.84 (m, 1H) ppm as multiplet confirmed the formation of the product. The ^{13}C NMR

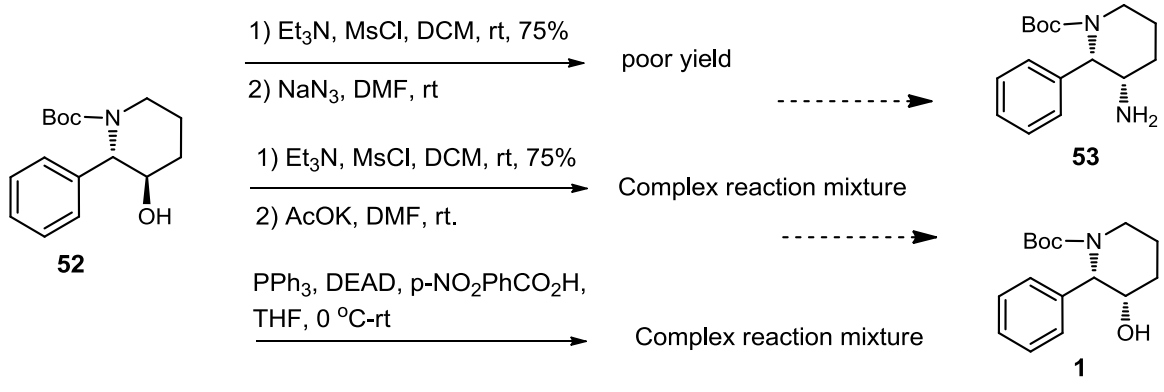
spectrum of **44** showed olefinic carbons at δ 115.1 and 137.9 ppm. The subsequent protection of secondary hydroxyl group as TBS ether was successfully carried out using TBS triflate and 2,6-lutidine[21] to afford **47** in 95% yield.(Scheme 13)



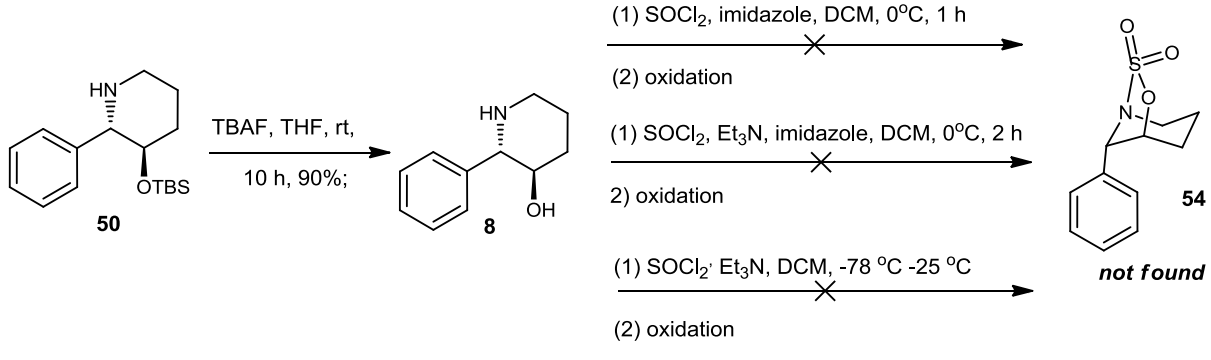
Scheme 13: *Reagents and conditions:* (a) TBSOTf, 2,6-lutidine, 0 °C, 1 h, 95%; (b) OsO_4, $NaIO_4$, 2,6-lutidine, 1,4-Dioxane: H_2O (3:1), 0 °C, 3 h; (c) PPh_3, THF, rt, 16 h; (d) $NaBH_4$, MeOH, 0 °C, 30 min, (65% yield from **47)**; (e) Boc_2O, Et_3N, CH_2Cl_2, 2 h, 95%; (f) TBAF, THF, 0 °C–rt, 10 h, 90%.

According to our synthetic strategy, compound **47** had all the ideal functionalities to carry out the required heterocyclic ring formation reaction. The oxidation of olefin[22]**47** gave the crucial azido-aldehyde intermediate **48** required for the one pot Staudinger/aza-Wittig reaction.[15] Without further purification of aldehyde **48**, Staudinger reduction was performed by the addition of triphenylphosphine to azido-aldehyde **48** in dry THF. The resulting aza-ylide was condensed intramolecularly with aldehyde to provide a six membered imine **49**. The *in situ* reduction of imine with $NaBH_4$ and methanol in the same reaction medium provided the free amine **50** in good yield. IR spectrum of **50** showed strong NH-stretching at 3343 cm^{-1} and disappearance of the azide group stretching peak. In ^1H and ^{13}C NMR spectrum of **50** showed absence of olefin peaks. Subsequently the free amine **50** was protected as Boc derivative and TBS was selectively deprotected using TBAF to obtain compound **52**[23] in 90% yields. (Scheme 13) Its ^{13}C NMR spectrum displayed signals at δ 155.2 and 79.6 indicating the presence of Boc carbonyl (-N**C**O-) and *tert*-butyl carbon (Me_3**C**-O) groups respectively. IR spectrum of **52** showed strong hydroxyl absorption at 3447 cm^{-1}.

At this stage, we decided to invert the hydroxy of **52** to the required configuration, that is, from *trans*- to *cis*-configuration. Initial attempts to displace the mesylate of **52** with N-nucleophiles resulted in unsatisfactory yield (<10%). When **52** was subject to conventional Mitsunobu condition (PPh_3, DEAD, *p*-NO_2PhCO_2H, THF, 0 ^oC-rt)[24] or the routine two-step sequence ($MsCl/Et_3N$, then AcOK/DMF)[25] to introduce the hydroxyl function, complex mixtures resulted. (Scheme 14)



Scheme 14: Various attempts to invert the hydroxyl group

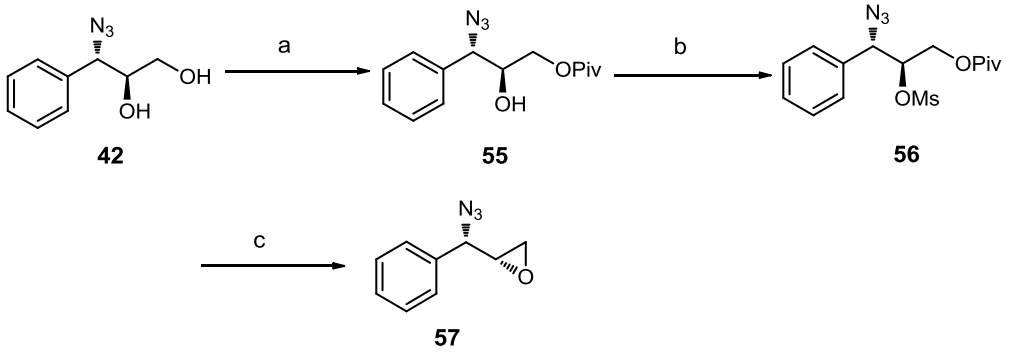


Scheme 15: Various attempts to make cyclic sulfate **54**

This may be partly due to the instability of the mesylate at elevated temperatures and partly to the bulk of the *N*-Boc protection which might favor other reaction pathways over the substitution by the weakly nucleophilic acetate anion (Scheme 14). Since all these reactions failed to work, we then looked at the possibility of inverting the hydroxyl through a cyclic

sulfate intermediate. Various attempts to make cyclic sulfate[26] from **50** also failed to give the desired product **54**. (Scheme 15)

In order to establish the desired *cis* configuration, we planned a three-step sequence involving the chemoselective pivalation[27] of diol **42**, mesylation of secondary hydroxyl **55** using MsCl, and final treatment of crude mesylate **56** with K_2CO_3 in methanol to furnish the appropriately oriented *cis*-azido-epoxide **57** in overall 80% yield (Scheme 16). Chemoselectivity of pivalation in **55** is increased by choosing 1:1 Pyridine: DCM solvent system. (Table 3)

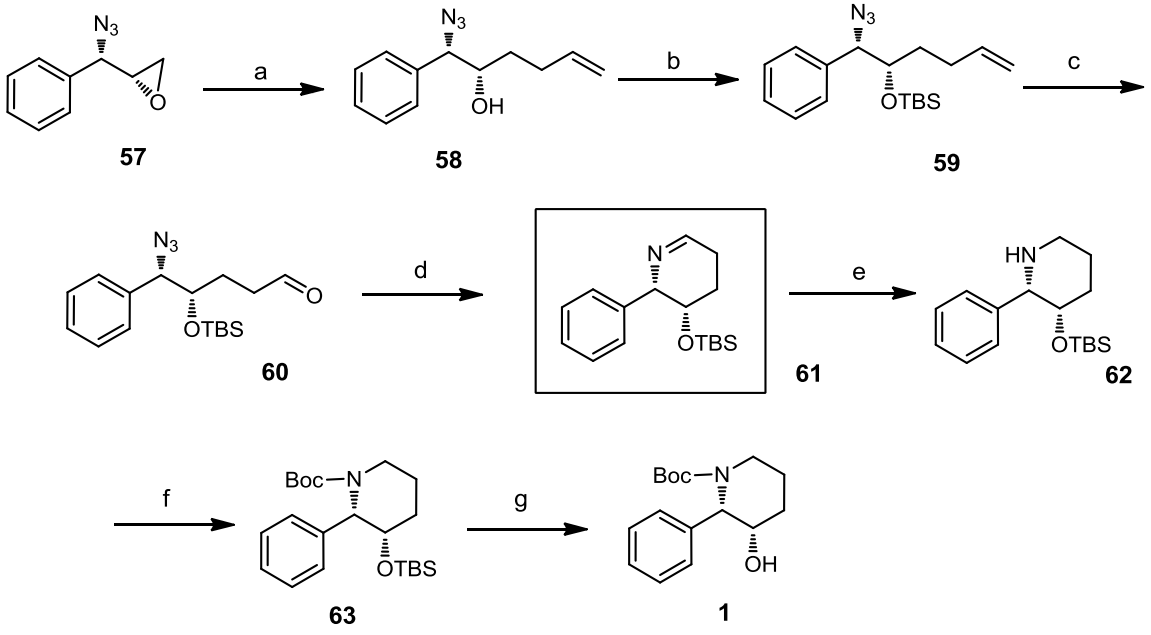


Scheme 16: *Reagents and conditions:* (a) PivCl, Py:CH_2Cl_2 (1:1), 0 ^oC–rt, 5 h ; (b) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 ^oC–rt, 1 h; (c) K_2CO_3, MeOH, rt, overnight, 80% (overall 3 steps).

Entry	Reaction conditions	Yield % of product 55
1	PivCl, Et_3N, DCM 0^oC 30 min.	50%
2	PivCl, Py, 0^oC-rt 3 days	10%
3	PivCl, Py:DCM (1:1) 0^oC- rt, 5 h	85%

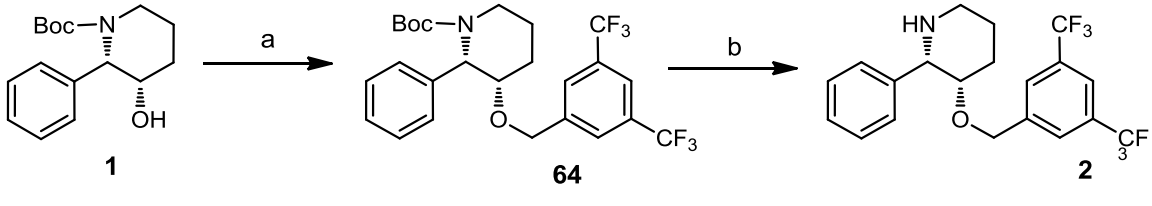
Table 3: *Reagents and conditions*: Pivolyl Chloride, Base and solvents.

Once we accomplished the desired *cis* configuration, we completed the synthesis of *N*-Boc protected *syn*-3-Hydroxy-2-phenylpiperidine **1** from **57** through previously established route (Scheme 17).



Scheme 17: *Reagents and conditions:* (a) Allyltrimethylsilane (3 equiv.), $TiCl_4$, CH_2Cl_2,–78 °C, 1 h, 65%; (b) TBSOTf, 2,6-lutidine, 0 °C, 1 h, 95%; (c) OsO_4, $NaIO_4$, 2,6-lutidine, 1,4-Dioxane: H_2O (3:1), 0 °C, 3 h; (d) PPh_3, THF, rt, 16 h; (e) $NaBH_4$, MeOH, 0 °C, 30 min, (65% yield from **59**); (f) Boc_2O, Et_3N, CH_2Cl_2, 2 h, 95%; (g) TBAF, THF, 0 °C–rt, 10 h, 90%.

Having constructed the piperidine ring with the desired *syn*-stereochemistry, *O*-alkylation of **1** with 3,5-bis(trifluoromethyl)benzyl bromide in the presence of NaH was performed to give **64** {$[\alpha]^{25}_D$ +31.40 (*c* 1.0, $CHCl_3$); lit.[7b] $[\alpha]^{25}_D$ +30.38 (*c* 1.55, $CHCl_3$)}. Finally *N*-Boc deprotection of **64** using TFA furnished the target molecule **2** in good yields. {$[\alpha]^{25}_D$ +36.20 (*c* 0.66, $CHCl_3$); [lit.[7b] $[\alpha]^{25}_D$ +34.29 (*c* 1.32, $CHCl_3$]} (Scheme 18). The physical and spectroscopic data of **2** were in full agreement with those reported.[7b]



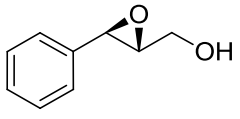
Scheme 18: *Reagents and conditions:* (a) 3,5-bis-(trifluoromethyl)benzyl bromide, NaH, dry DMF, 80 °C, 12 h, 78%; (b) CF_3COOH, MeOH, rt, 12 h, 70%.

2.5. Conclusion

In conclusion, a flexible and a highly enantioselective synthesis of (+)-L-733,060 has been achieved by employing Sharpless asymmetric epoxidation and one pot Staudinger/aza-Wittig reaction as key steps. The synthetic strategy described herein has significant potential for further extension to other NK1 receptor antagonists. Currently studies are in progress in this direction.

2.6. Experimental Section

(2*R*,3*R*)-(3-Phenyl-oxiranyl)-methanol (40)



To a stirred solution of (*S,S*)-(–)-diisopropyl tartrate (0.83 mL, 0.92 g, 3.91 mmol) in CH_2Cl_2 (450 mL) at –20 °C, 2.8 g activated powdered 4Å molecular sieves, Ti(OPr-*i*)$_4$ (0.78 mL, 0.74 g, 2.61 mmol) and 3 M solution of TBHP in toluene (34.78 mL, 104.34 mmol) were added sequentially. The mixture was allowed to stir at –20 °C for 1 h and then a solution of of freshly distilled (*E*)-3-phenyl-2-propenol **41** (cinnamyl alcohol) (7.0 g, 52.17 mmol) in 10 mL of CH_2Cl_2 was added dropwise over 30 min. After 3h at –20 °C, the reaction was quenched at –20 °C with 10% aqueous solution of NaOH saturated with NaCl (4.2 mL). After diethyl ether (60 mL) was added the cold bath was allowed to warm to 10 °C, stirring was maintained at 10 °C while $MgSO_4$ (5 g) and Celite (500 mg) were added. After another 15 minutes of stirring, the mixture was allowed to settle and clean solution was filtered through a pad of Celite and washed with diethyl ether. Azeotropic removal of TBHP with toluene at reduced pressure and finally subjection to high vacuum gave **40** as yellow oil. Recrystallization from petroleum ether/diethylether at –20 °C gave yellow crystals of **40**.

Yield: 6.97 g (89%)

Mol. Formula: $C_9H_{10}O_2$

Melting point: 53.5-54 °C

$[\alpha]_D^{27}$: +48.66 (*c* 2.4, $CHCl_3$)

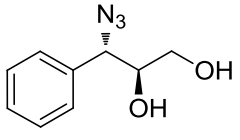
IR ($CHCl_3$, cm^{-1}): ν_{max} 3428, 3017, 2927, 2871, 1606, 1462, 1392, 1256, 1108, 1068, 1027, 881, 863, 840, 758.

^{1}H NMR (200 MHz, $CDCl_3$): 2.26 (brs, 1H), 3.23-3.27 (m, 1H), 3.77-3.85 (dd, *J* = 12.8, 4.6 Hz, 1H), 3.94-3.95 (d, *J* = 2.1Hz, 1H), 4.03-4.11 (dd, *J* = 12.76, 2.3 Hz, 1H), 7.2-7.42 (m, 5H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 55.5, 61.2, 62.4, 127.5, 128.0, 128.2, 136.4 ppm.

Analysis: Calcd.: C, 71.98; H, 6.71. **Found:** C, 71.94; H, 6.82.

(2*S*,3*S*)-3-Azido-3-phenyl-propane-1,2-diol (42)



The epoxy alcohol **40** (6.0 g, 39.95 mmol), NaN_3 (5.19 g, 79.90 mmol) and NH_4Cl (4.27 g, 79.90 mmol) in a solvent mixture of methanol (32 mL) and water (4 mL) was warmed at 65 ^oC for 5 hours. The reaction mixture was cooled and solid was filtered. The filtrate was concentrated to a residue which was taken into ethyl acetate, washed with brine and water, dried and concentrated to give a syrup which was purified by column chromatography (eluent: petroleum ether/EtOAc 7:3) to yield yellow liquid **42**.

Yield: 7.56 g (98%).

Mol. Formula: $C_9H_{11}N_3O_2$

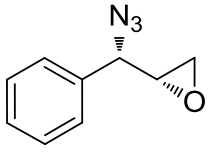
$[\alpha]_D^{27}$: +166.32 (*c* 1.2, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3392, 3032, 2932, 2871, 2099, 1602, 1493, 1454, 1384, 1100, 1039, 877, 828, 759.
^{1}H NMR (200 MHz, $CDCl_3$): δ 3.38 (brs, 2H), 3.58-3.75 (m, 2H), 3.78-3.86 (m, 1H), 4.57-4.61 (d, *J* = 7.1 Hz, 1H), 7.32-7.47 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 62.8, 66.9, 73.9, 127.7, 128.7, 128.9, 136.0 ppm.

Analysis Calcd.: C, 55.95; H, 5.74; N, 21.75; **Found:** C, 55.91; H, 5.73; N, 21.84.

(2*R*,3*S*)-2-(Azido-phenyl-methyl)-oxirane (57)



The diol **42** (7.0 g, 36.23 mmol) was dissoled in dry pyridine (40 mL) and dry CH_2Cl_2 (40 mL) at 0 ^oC under argon and pivaloyl chloride (4.44 mL, 36.23 mmol) was added dropwise over a period of 30 minutes. The mixture was stirred at room temperature for 5 hours. Concentration followed by azeotropic removal of pyridine gave compound **55** which was used in the next reaction without any further purification.

Compound **55** was then dissolved in dry CH_2Cl_2 (30 mL) under argon and treated with MsCl (2.80 mL, 36.23 mmol), Et_3N (6.0 mL, 43.34 mmol), and a catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 1 hour then quenched with water. The water layer was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a crude product **56**, which was dissolved in MeOH (20 mL) and treated with K_2CO_3 (5.0 g, 36.23 mmol). This mixture was stirred overnight at room temperature and then filtered through Celite. Removal of the volatiles under reduced pressure, followed by column chromatography on silica gel (eluent: petroleum ether/EtOAc 19:1) produced the epoxide **57** as a yellow liquid.

Yield: 5.08 g, overall yield 80% from **42**

Mol. Formula: $C_9H_9N_3O$

$[\alpha]_D^{27}$: +138.99 (c 1.1, $CHCl_3$)

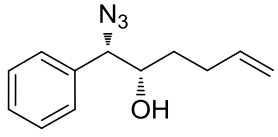
IR ($CHCl_3$, cm^{-1}): ν_{max} 3019, 2927, 2106, 1601, 1493, 1455, 1251, 1123, 863, 758.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.77-2.79 (dd, *J*= 4.6, 2.7 Hz, 1H), 2.83-2.84 (m, 1H), 3.28-3.30 (m, 1H), 4.28-4.29 (d, *J*= 6 Hz, 1H), 7.39-7.45 (m, 5H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 44.8, 54.7, 66.8, 127.2, 128.8, 128.9, 135.73 ppm.

Analysis: Calcd.: C, 61.70; H, 5.18; N, 23.99%. **Found:** C, 61.81; H, 5.15; N, 23.91%.

(1*S*,2*S*)-1-Azido-1-phenyl-hex-5-en-2-ol (58)



To a stirred solution of **57** (3.0 g, 17.12 mmol) and allylTMS (8.16 g, 51.37 mmol) in CH_2Cl_2 (50 mL) at –78 ºC, a solution of $TiCl_4$ (1.88 mL, 17.12 mmol) in CH_2Cl_2 (35 mL) was added through the cold inner surface of the flask over a period of 30 min. The mixture was stirred at the temperature for 1 h and the cold bath removed. Subsequently, 30% aqueous $NaHCO_3$ (5 mL) and ether (50 mL) were added, and the mixture stirred vigorously while being allowed to come to room temperature. The organic phase was separated, washed with brine, dried over Na_2SO_4 and purified by silica gel column chromatography (eluent: petroleum ether/EtOAc 20:1) to give **58** as a yellow liquid.

Yield: 2.42 g (65%)

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

$[\alpha]_D^{27}$: +178.41 (c 1.0, $CHCl_3$)

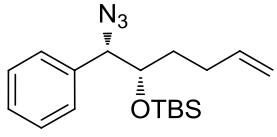
IR ($CHCl_3$, cm^{-1}): ν_{max} 3430, 3031, 2977, 2921, 2103, 1640, 1603, 1493, 1453, 1080, 995, 913, 874, 757, 701.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45-1.52 (m, 1H), 1.62-1.67 (m, 1H), 1.84 (brs, 1H), 2.14-2.16 (m, 1H), 2.24-2.28 (m, 1H), 3.80-3.84 (m, 1H), 4.49-4.50 (d, *J*= 5.8 Hz, 1H), 4.97-5.00 (m, 1H), 5.06-5.07 (m, 1H), 5.75-5.84 (m, 1H), 7.36-7.44 (m, 5H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7, 31.6, 70.5, 73.5, 115.12, 127.95, 128.5, 128.7, 136.13, 137.97 ppm.

Analysis: Calcd.: C, 66.34; H, 6.96; N, 19.34; **Found:** C, 66.27; H, 6.91; N, 19.36.

(1*S*,2*S*)-[1-(Azido-phenyl-methyl)-pent-4-enyloxy]-tert-butyl-dimethyl-silane (59)



2,6-Lutidine (2.45 mL, 21.17 mmol) was added to a stirred solution of **58** (2.30 g, 10.58 mmol) in anhydrous CH_2Cl_2 (20 mL). After the solution was cooled to 0 ^oC with an ice-bath, TBSOTf (3.65 mL, 15.87 mmol) was added to it. The mixture was stirred for 1 hour, then quenched with saturated NH_4Cl (10 mL), extracted with Et_2O (3 x 15 mL), and dried over anhydrous Na_2SO_4. After concentration, the crude product was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc 30:1) to afford compound **59**, as a brown liquid.

Yield: 3.33 g (95%).

Mol. Formula: $C_{18}H_{29}N_3OSi$

$[\alpha]_D^{27}$: +75.26 (*c* 1.1, $CHCl_3$)

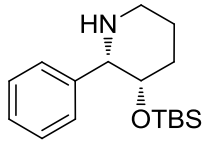
IR ($CHCl_3$, cm^{-1}): ν_{max} 3018, 2954, 2930, 2896, 2858, 2105, 1640, 1603, 1472, 1453, 1361, 1256, 1104, 1058, 976, 888, 837, 758.

^{1}H NMR (200 MHz, $CDCl_3$): δ –0.06 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.47-1.57 (m, 1H), 1.66-1.78 (m, 1H), 2.10- 2.13 (m, 1H), 2.18-2.27 (m, 1H), 3.88-3.96 (m, 1H), 4.56-4.59 (d, *J* = 5.05 Hz, 1H), 4.92-4.94 (m, 1H), 4.97-5.04 (m, 1H), 5.67-5.87 (m, 1H), 7.30-7.41 (m, 5H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ –4.7, –4.6, 18.0, 25.7, 28.9, 31.5, 69.7, 75.4, 114.5, 127.8, 128.0, 128.3, 137.1, 138.3 ppm.

Analysis: Calcd.: C, 65.21; H, 8.82; N, 12.67; **Found:** C, 65.24, H, 8.83; N, 12.65.

(2*S*, 3*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-phenyl-piperidine (62)



To a solution of compound **59** (1.50 g, 4.52 mmol) in dioxane-water (3:1, 20 mL) were added 2,6-lutidine (1.05 mL, 9.04 mmol), OsO_4 (0.1M solution in toluene, 0.78 mL, 0.023 g, 0.09 mmol) and $NaIO_4$ (3.87 g, 18.08 mmol). The reaction was stirred at 25 ^oC for 3 hours. After the reaction was complete, water (10 mL) and CH_2Cl_2 (20 mL) were added. The organic layer was separated, and the water layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. After concentration compound **60** was used in the next reaction without any further purification.

To a solution of compound **60** at room temperature in THF (200 mL) was added solid PPh_3 (4.74 g, 18.08 mmol). The reaction was allowed to stir at room temperature for 16 hours until all starting aldehyde was consumed. $NaBH_4$ (0.43 g, 11.30 mmol) and MeOH (0.51 mL, 11.30 mmol) were added at 0 ^oC. After stirring for 30 min, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuum. Purification by neutralized silica gel column chromatography (eluent: CH_2Cl_2/MeOH 100:1) afforded compound **62** as a pale yellow oil.

Yield: 0.86 g, (65% yield**)**

Mol. Formula: $C_{17}H_{29}NOSi$

$[\alpha]_D^{27}$: +51.50 (*c* 1.1, MeOH);

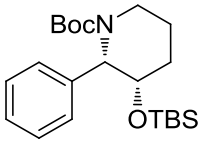
IR ($CHCl_3$, cm^{-1}): 3343, 3019, 2930, 2857, 1603, 1472, 1106, 931, 887, 758.

^{1}H NMR (200 MHz, $CDCl_3$): δ –0.47 (s, 3H), –0.14 (s, 3H), 0.75 (s, 9H), 1.50-1.83 (m, 3H), 2.08-2.17 (m, 1H), 2.24 (brs, 1H), 2.70-2.83 (m, 1H), 3.12-3.18 (m, 1H), 3.41-3.46 (d, *J* = 8.7 Hz, 1H), 3.52-3.59 (m, 1H), 7.27-7.49(m, 5H) ppm.

^{13}C NMR (500 MHz, $CDCl_3$): δ –5.7, –4.9, 17.8, 25.3, 25.6, 35.3, 46.7, 69.3, 73.9, 127.3, 127.9, 128.4, 142.6 ppm.

Analysis: Calcd.: C, 70.04; H, 10.03; N, 4.80; **Found:** C, 70.05; H, 10.01; N, 4.82.

(2*S*,3*S*)-1-[3-(*tert*-Butyl-dimethyl-silanyloxy)-2-phenyl-piperidin-1-yl]-2,2-dimethyl-propan-1-one (63)



To a suspension of compound **62** (0.60 g, 2.06 mmol) in CH_2Cl_2 (10 ml) was added Et_3N (0.43 mL, 3.09 mmol). The mixture was cooled to 0 ^oC and $(Boc)_2O$ (0.71 mL, 3.09 mmol) was added drop wise with stirring. Then the mixture was warmed to room temperature and stirred for 2 hours. The reaction was quenched with saturated NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3 x 15 mL), dried over anhydrous Na_2SO_4. After concentration under reduced pressure, compound was purified by silica gel column chromatography (eluent; petroleum ether/EtOAc 8:1) to give **63** as a pale yellow oil.

Yield: 0.77 g (95%).

Mol. Formula: $C_{22}H_{37}NO_3Si$

$[\alpha]_D^{27}$: +18.43 (*c* 1.1, $CHCl_3$)

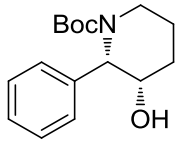
IR ($CHCl_3$, cm^{-1}): 3023, 3018, 2979, 2955, 1696, 1602, 1495, 1418, 1367, 1257, 1168, 1137, 984, 876, 851, 756.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.14 (s, 3H), 0.92 (s, 9H), 1.50 (s, 9H), 1.66-1.68 (m, 2H), 1.79-1.81 (m, 1H), 1.93-1.96 (m, 1H), 2.71-2.78 (m, 1H), 3.95-3.98 (d, *J* = 13 Hz, 1H), 4.06-4.11 (m, 1H), 5.40-5.41 (d, *J* = 4.5 Hz, 1H), 7.23-7.35 (m, 3H), 7.58-7.60 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ –5.0, –4.9, 17.9, 23.9, 25.7, 28.3, 28.6, 38.6, 58.6, 71.8, 79.6, 126.4, 127.8, 128.4, 138.8, 155.2 ppm.

Analysis: Calcd.: C, 67.47; H, 9.52; N, 3.58; **Found:** C, 67.43; H, 9.51; N, 3.61.

(2*S*,3*S*)-1-(3-Hydroxy-2-phenyl-piperidin-1-yl)-2,2-dimethyl-propan-1-one (1)



To a solution of **63** (0.60 g, 1.53 mmol) in anhydrous THF (20 mL) was added TBAF (2.30 mL, 1M in THF, 2.30 mmol) successively with stirring. The mixture was stirred for 10 h, then quenched with water (10 mL) at 0 ºC and diluted with CH_2Cl_2 (20 mL). After being stirred for about 10 minutes, the solution was extracted with CH_2Cl_2 (3 x 15 mL), dried over anhydrous Na_2SO_4. After concentration, the crude product was purified by silica gel chromatography (eluent: petroleum ether/EtOAc 8:2) to afford product **1**, as a yellow oil.

Yield: 0.38 g (90%).

Mol. Formula: $C_{16}H_{23}NO_3$

$[\alpha]_D^{27}$: +37.50 (*c* 1.0, $CHCl_3$).

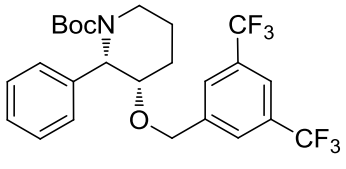
IR ($CHCl_3$, cm^{-1}): 3447, 3018, 2979, 2955, 1676, 1602, 1495, 1418, 1367, 1327, 1168, 1137, 984, 876, 851, 756.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24-1.91 (m, 5H), 1.45 (s, 9H), 2.78-2.93 (td, *J* = 13.1, 3.3 Hz, 1H), 4.04-4.13 (m, 1H), 4.49-4.53 (m, 1H), 5.34-5.38 (m, 1H), 7.13-7.35 (m, 5H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 23.9, 25.9, 28.3, 39.9, 60.24, 67.4, 80.1, 126.3, 126.8, 128.8, 138.1, 156.7 ppm.

Analysis: Calcd.: C, 69.29; H, 8.36; N, 5.05%. **Found:** C, 69.31; H, 8.32; N, 5.01%.

(2*S*,3*S*)-1-(*tert*-Butyoxycarbonyl)-2-phenyl-3-[(3,5)bis(trifluoromethyl) benzyloxy]piperidine (64)



To a stirred solution of sodium hydride (0.020 mg, 60% dispersion in mineral oil, 0.83 mmol) and dry DMF (3 mL) at 0 ^{o}C, was added a solution of **1** (0.2 g, 0.72 mmol) and 3,5-bis(trifluoromethyl)benzyl bromide (0.22 g, 0.72 mmol) in dry DMF (2 mL). The reaction mixture was stirred for 12 h at 80 ^{o}C. The reaction was quenched with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel column (eluent: petroleum ether/EtOAc 7:3) to provide **64** as a colourless oil.

Yield: 0.28 g (78%).

Mol. Formula: $C_{25}H_{27}F_6NO_3$

$[\alpha]_D^{27}$: +31.40 (*c* 1.0, $CHCl_3$)

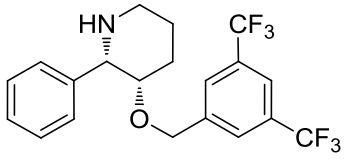
IR ($CHCl_3$, cm^{-1}): ν_{max} 2945, 1644, 1381, 1345, 1253, 1172, 875, 665.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48 (s, 9H), 1.54-2.01 (m, 4H), 2.81-2.96 (ddd, *J* = 11.2, 9.8, 4.6 Hz, 1H), 3.81–3.97 (m, 2H), 4.64-4.68 (d, *J* = 11.4 Hz, 1H), 4.74-4.76 (d, *J* = 12.2 Hz, 1H), 5.68 (brs, 1H), 7.20–7.30 (m, 3H), 7.34–7.41 (m, 2H), 7.60 (s, 2H), 7.70 (s, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.1, 25.9, 28.3, 39.9, 54.3, 68.8, 78.7, 80.1, 121.1, 123.3 (q, *J*= 272 Hz), 126.3, 126.8, 127.6, 128.6, 131.4 (q, *J*= 33.5 Hz), 138.1, 141.1, 156.7 ppm.

Analysis: Calcd.: C, 59.64 ; H, 5.41 ; N, 2.78; **Found:** C, 59.61 ; H, 5.38; N, 2.76.

(2*S*,3*S*)-2-Phenyl-3[(3,5)bis (trifluoromethyl)benzyloxy]piperidine (2)



To an ice-bath solution of **64** (0.10 g, 0.20 mmol) in dry CH_2Cl_2 (5 mL) was added trifluoroacetic acid (15 μL, 0.20 mmol). The reaction mixture was stirred at room temperature for 12 h and then quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2

(3 x 15 mL). The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent; $CH_3OH/CHCl_3$ 1:9) to give **2**, as colourless viscous liquid.

Yield: 0.056 g yield (70%).

Mol. Formula: $C_{20}H_{19}F_6NO$

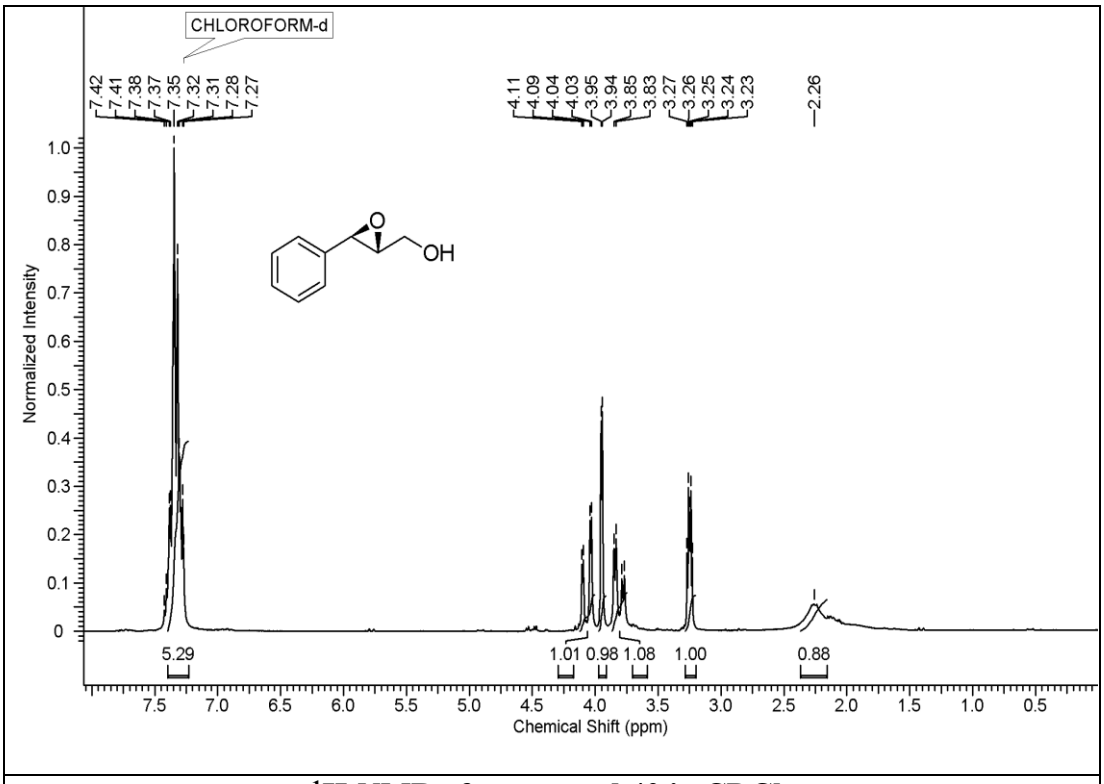
$[\alpha]_D^{25}$: $[\alpha]_D^{25}$ = +36.20 (*c* 0.66, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 2950, 1370, 1277, 1170, 1123, 877, 663.

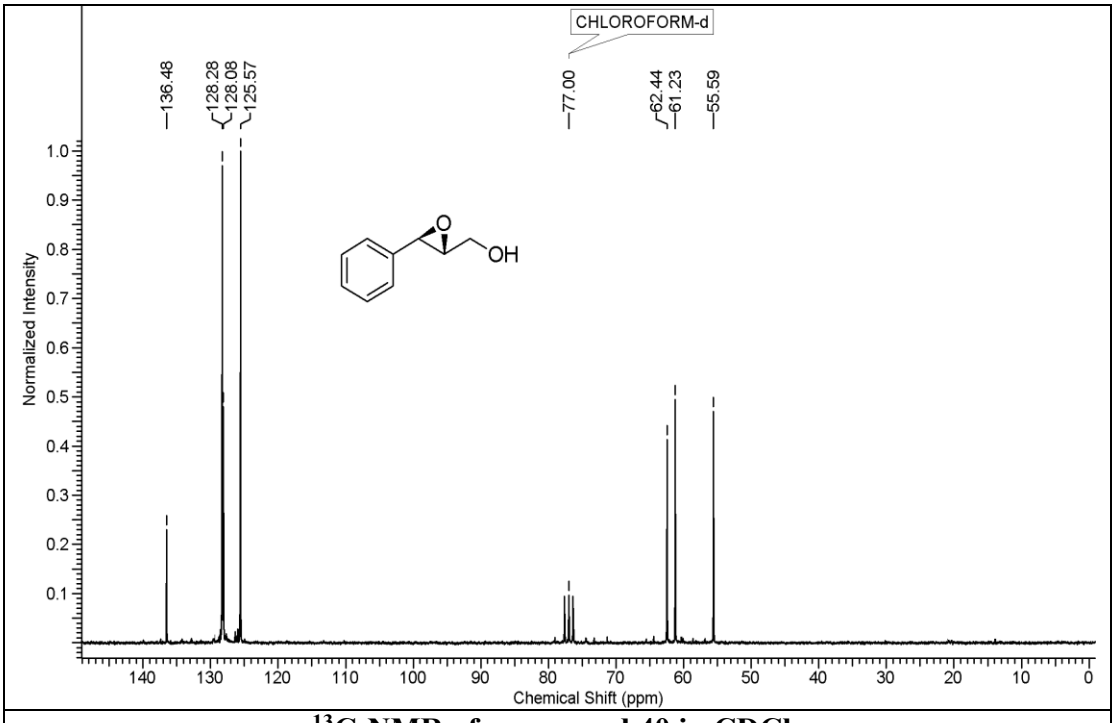
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.49-1.84 (m, 3H), 2.13-2.16 (m, 1H), 2.23-2.24 (m, 1H), 2.82-2.92 (td, *J*=12.3, 2.5 Hz, 1H), 3.27-3.32 (brd, *J*=12.5 Hz, 1H), 3.68 (brs, 1H), 3.84 (brs, 1H), 4.14-4.18 (d, *J* = 12.2 Hz, 1H), 4.51-4.55 (d, *J* = 12.2 Hz, 1H), 7.30-7.44 (m, 5H), 7.47 (s, 2H), 7.69 (s, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.2, 28.2, 46.7, 64.0, 69.3, 77.3, 121.2, 123.1 (q, *J*= 271 Hz), 126.6, 127.3, 127.9, 128.4, 132.4 (q, *J*= 32.5 Hz), 142.1, 142.4 ppm.

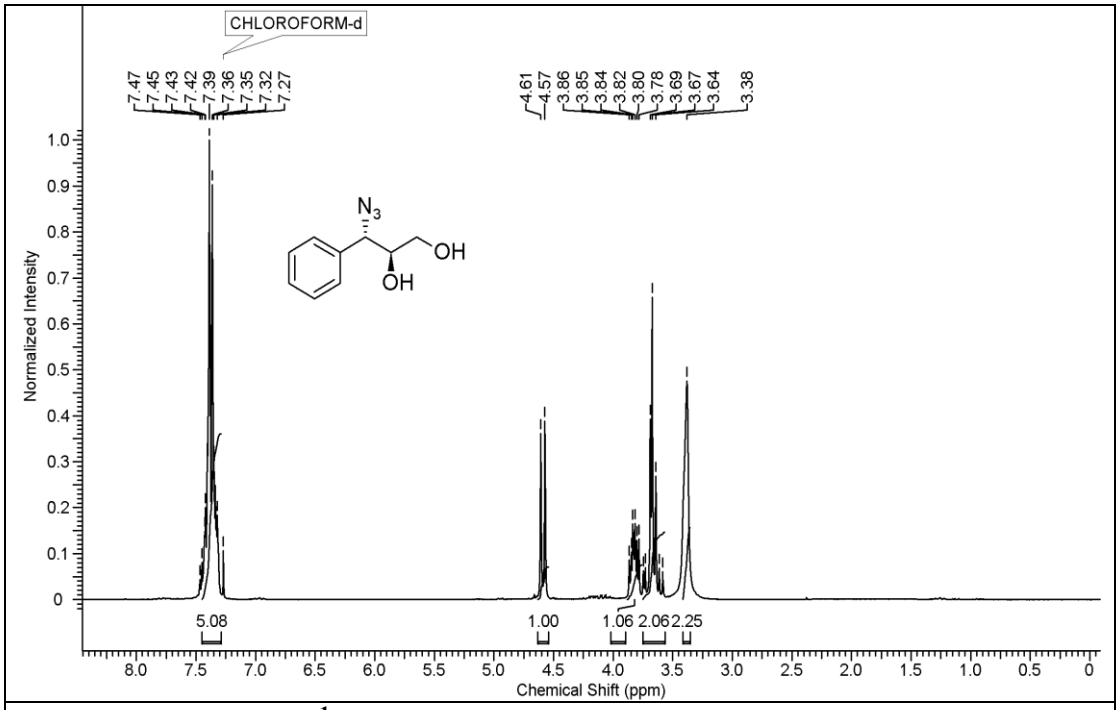
2.7. Spectra



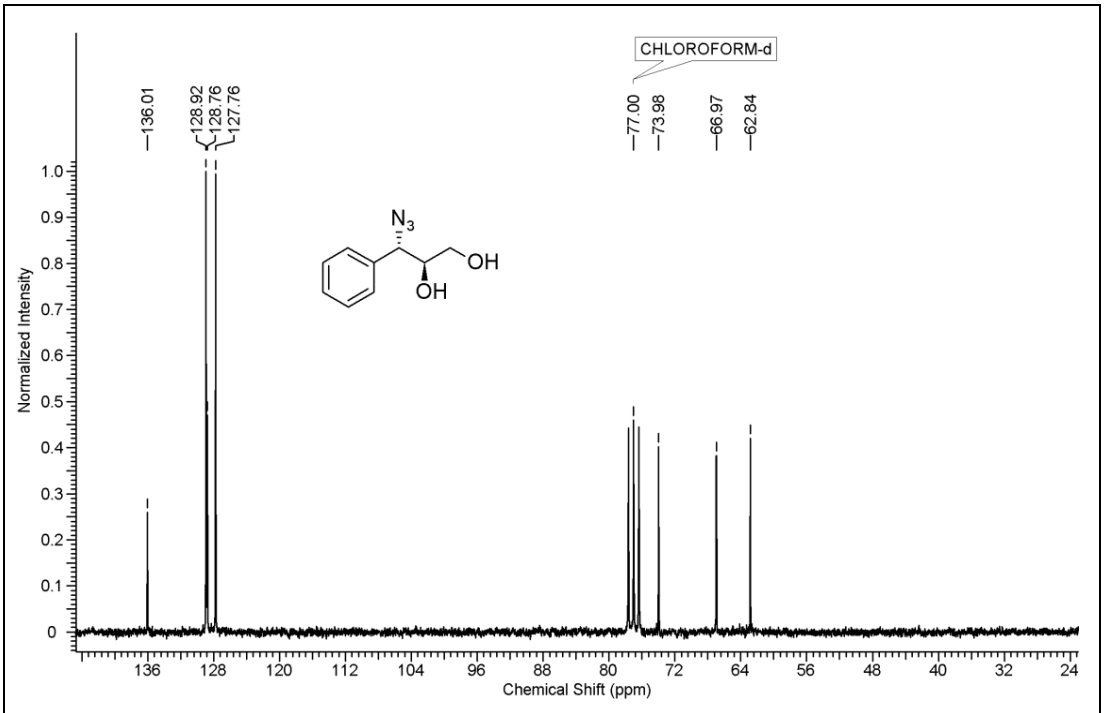
^{1}H-NMR of compound 40 in $CDCl_3$



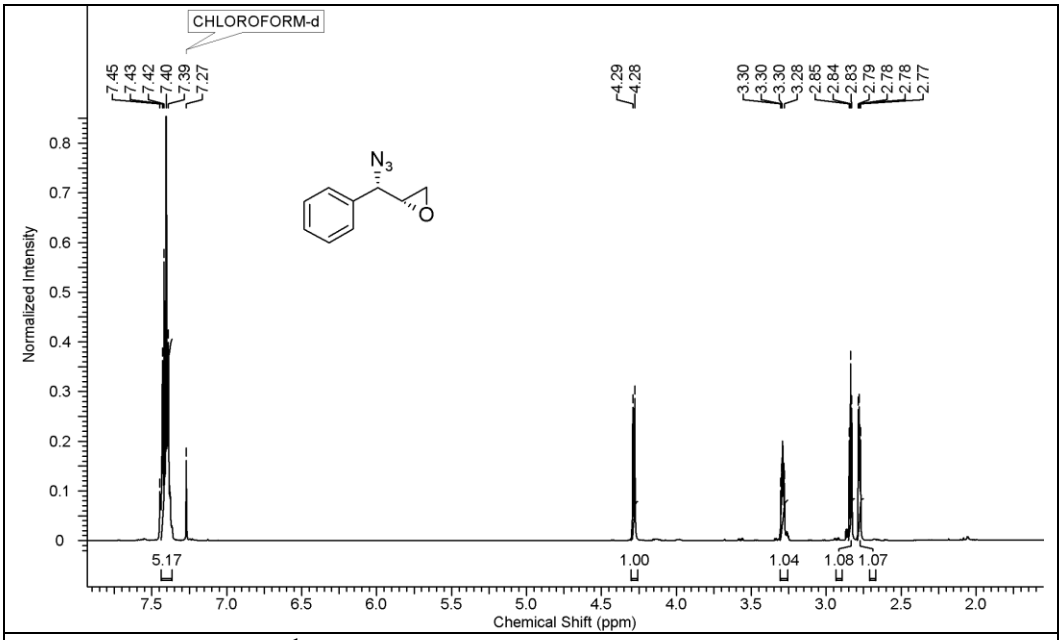
^{13}C-NMR of compound 40 in $CDCl_3$



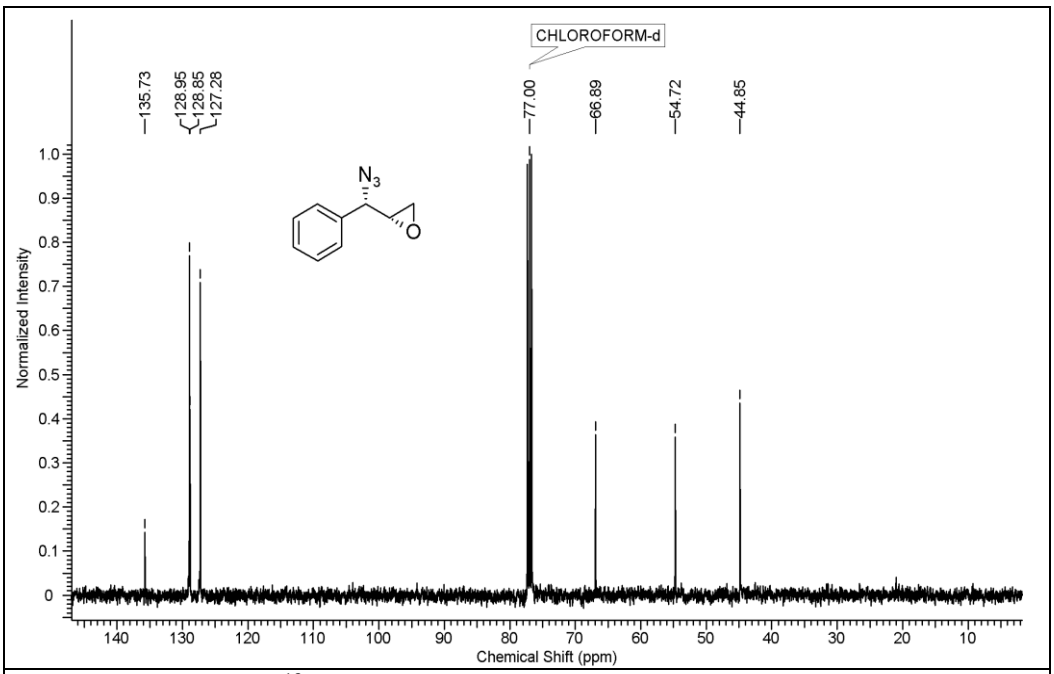
^{1}H-NMR of compound 42 in $CDCl_3$



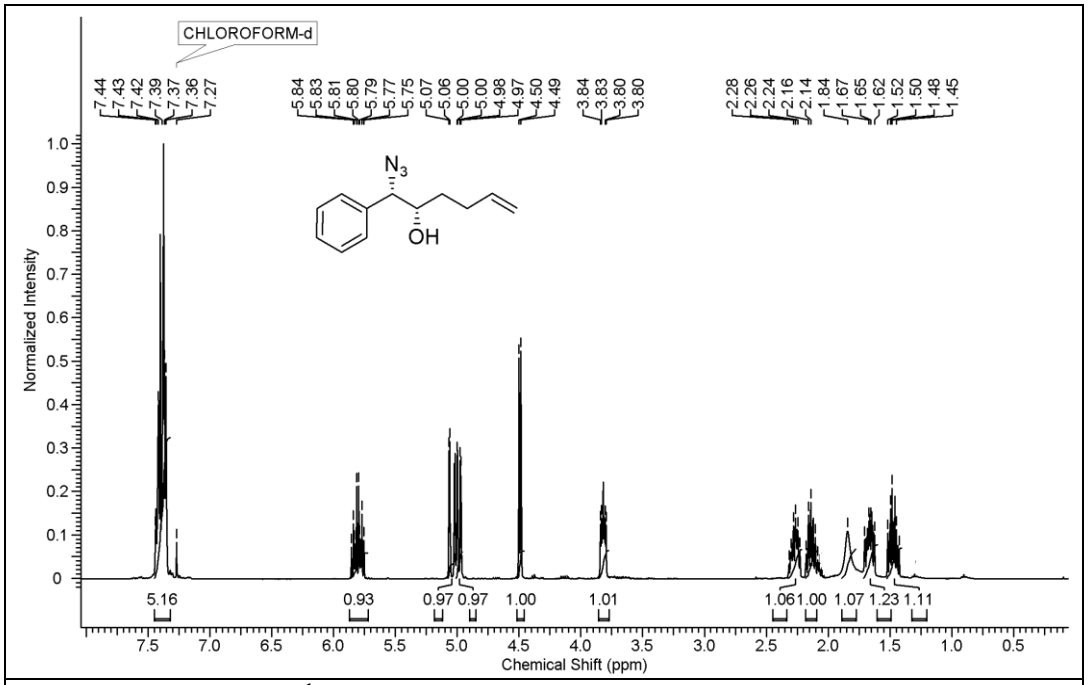
^{13}C-NMR of compound 42 in $CDCl_3$



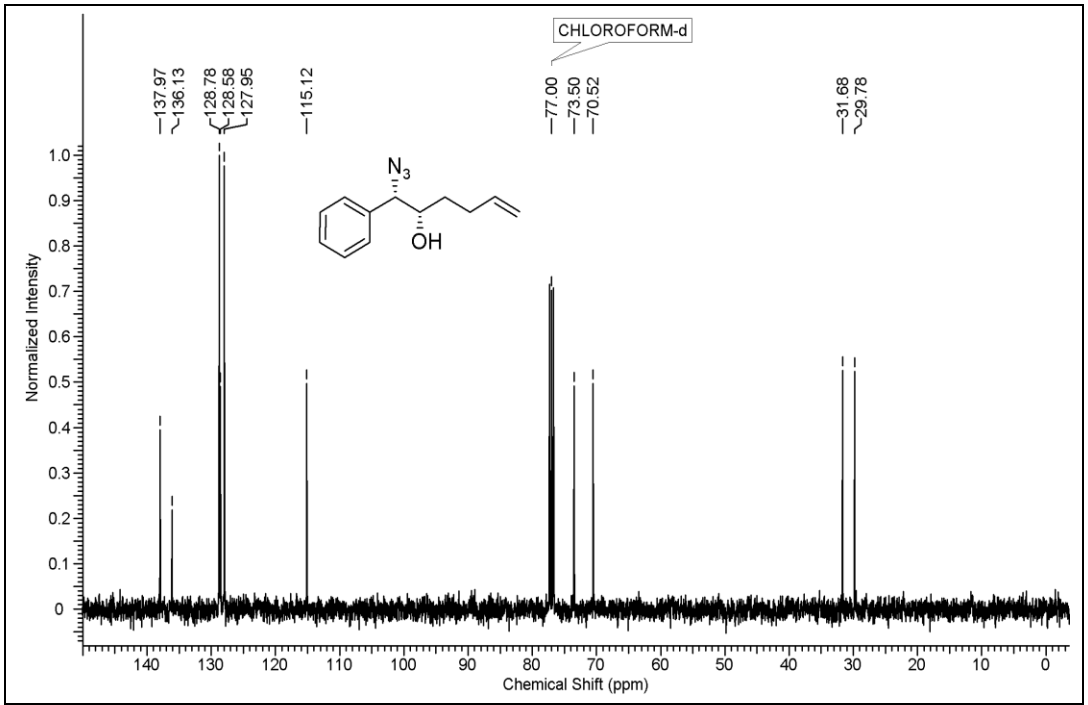
^{1}H-NMR of compound 57 in $CDCl_3$



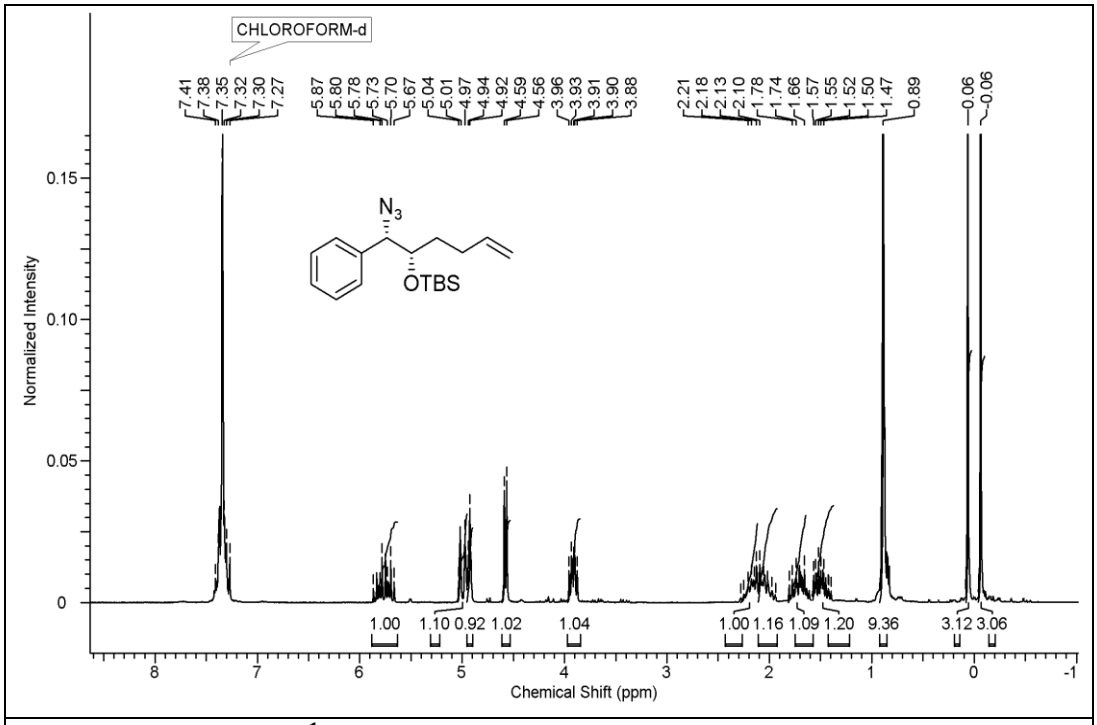
^{13}C-NMR of compound 57 in $CDCl_3$



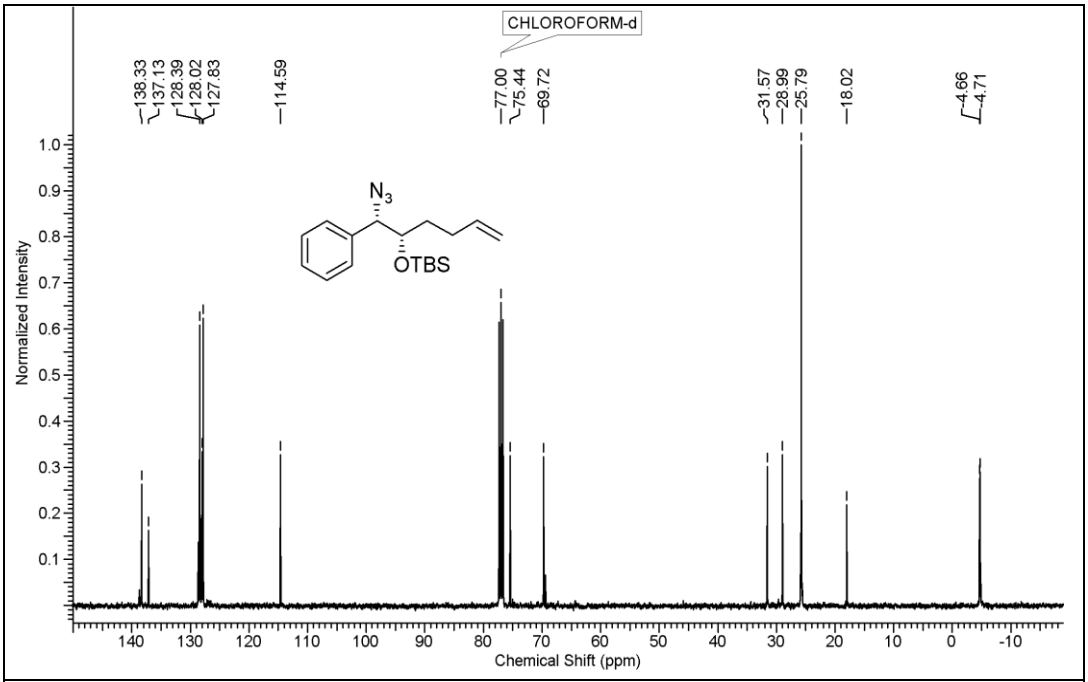
^{1}H-NMR of compound 58 in $CDCl_3$



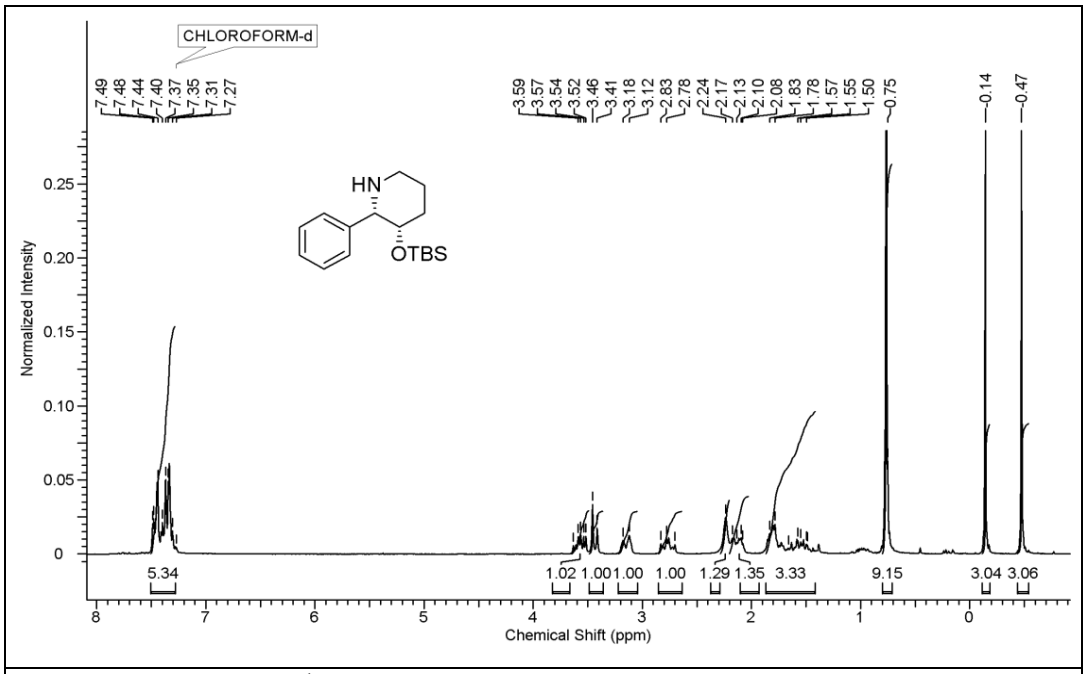
^{13}C-NMR of compound 58 in $CDCl_3$



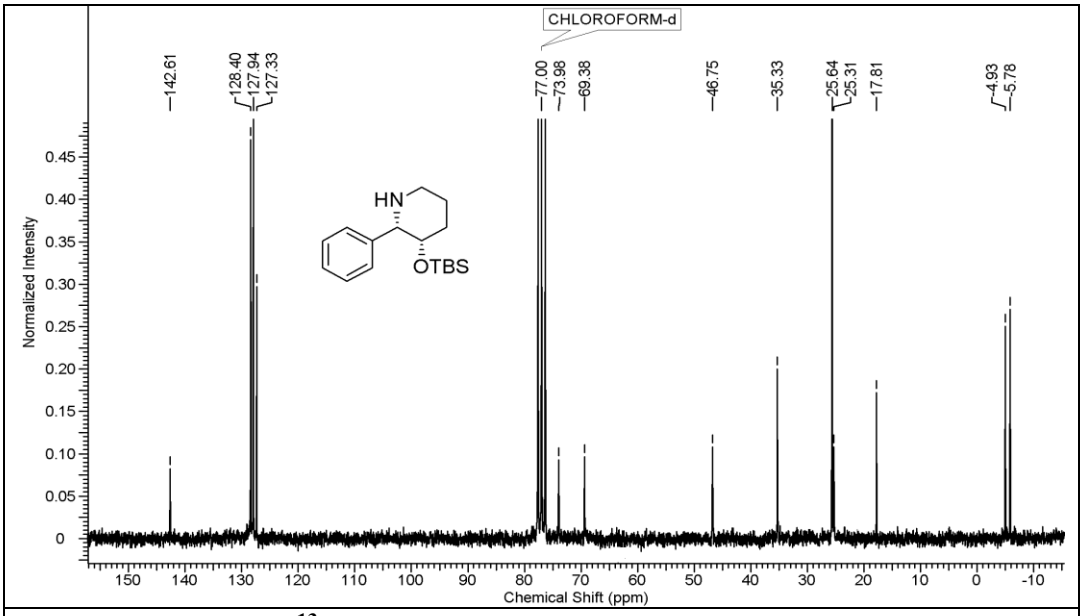
^{1}H-NMR of compound 59 in $CDCl_3$



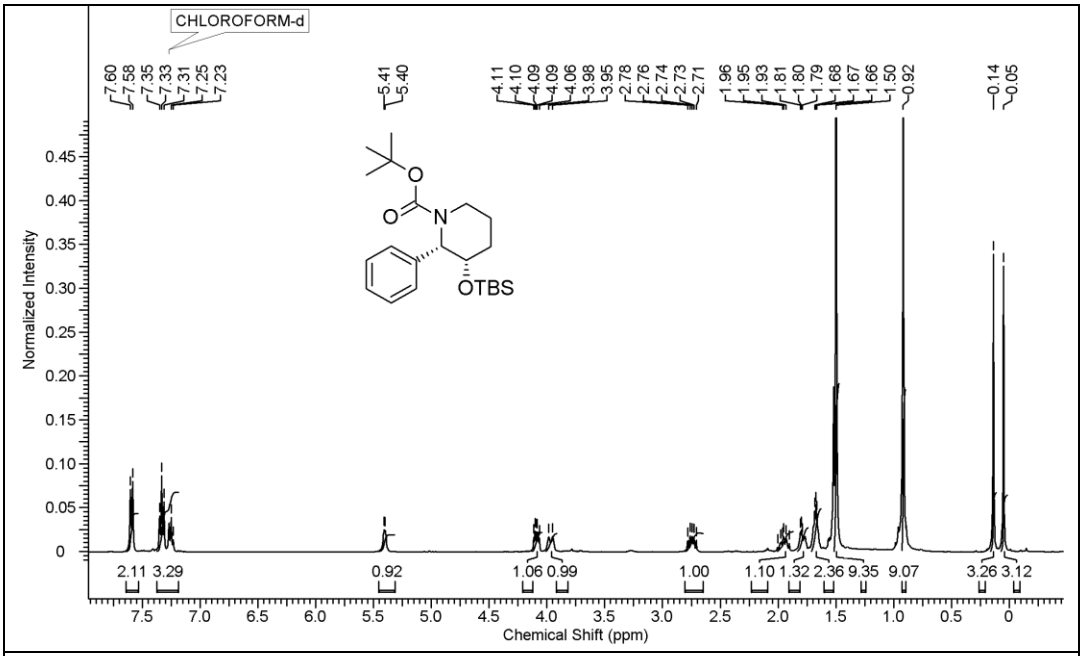
^{13}C-NMR of compound 59 in $CDCl_3$



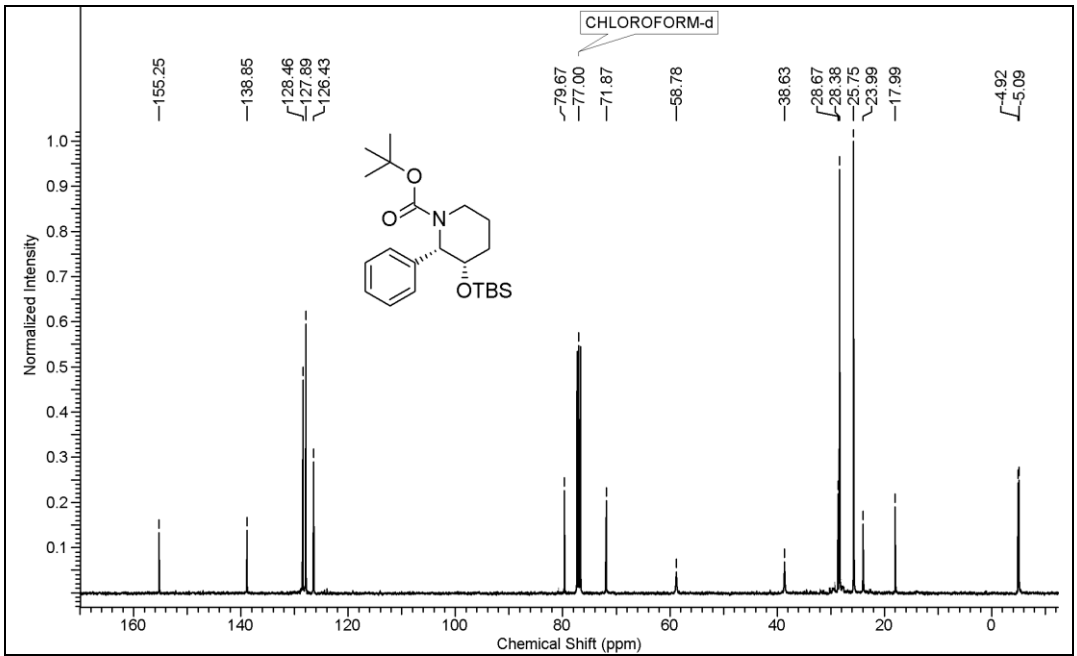
^{1}H-NMR of compound 62 in $CDCl_3$



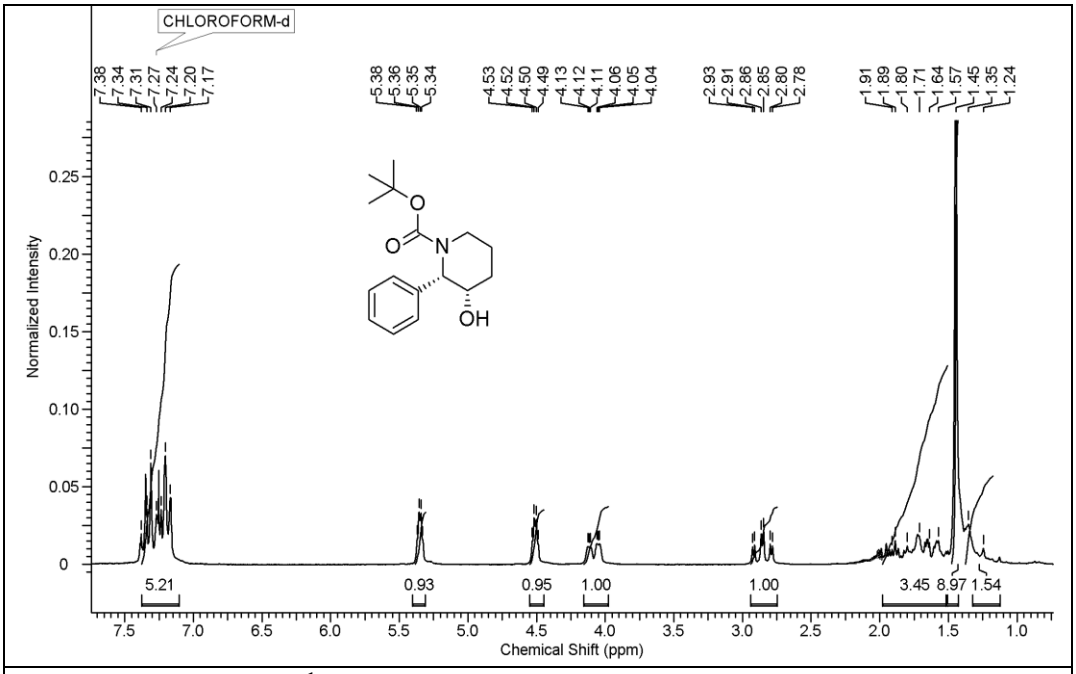
^{13}C-NMR of compound 62 in $CDCl_3$



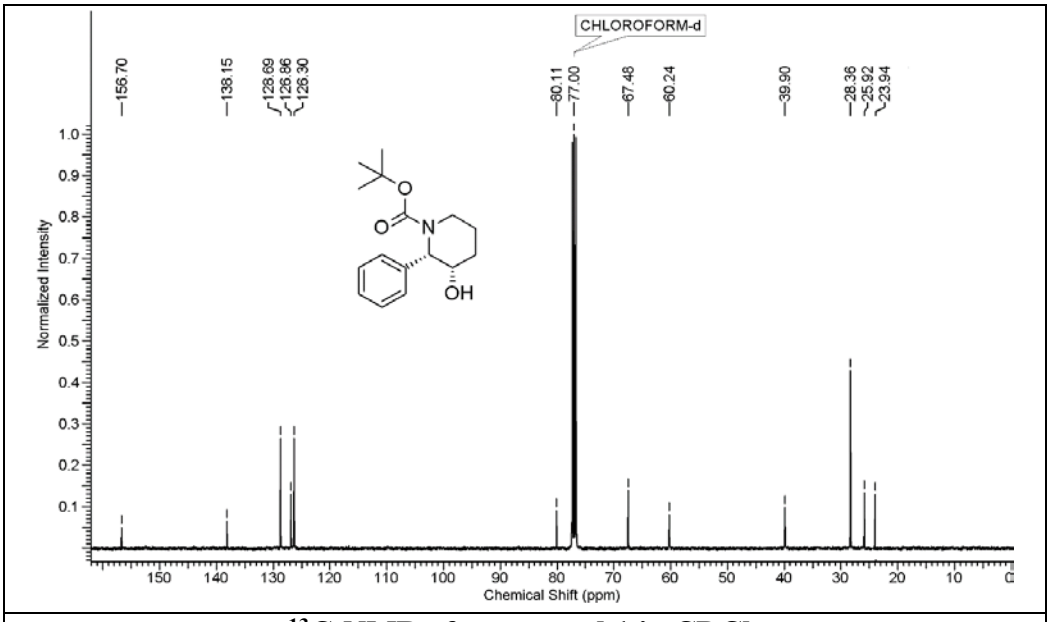
^{1}H-NMR of compound 63 in $CDCl_3$



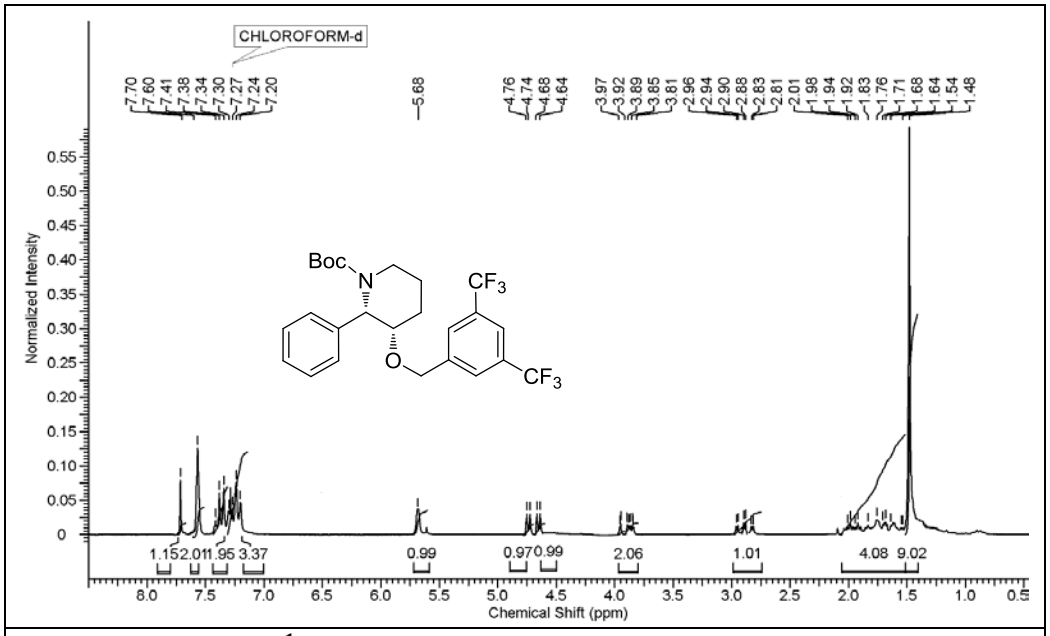
^{13}C-NMR of compound 63 in $CDCl_3$



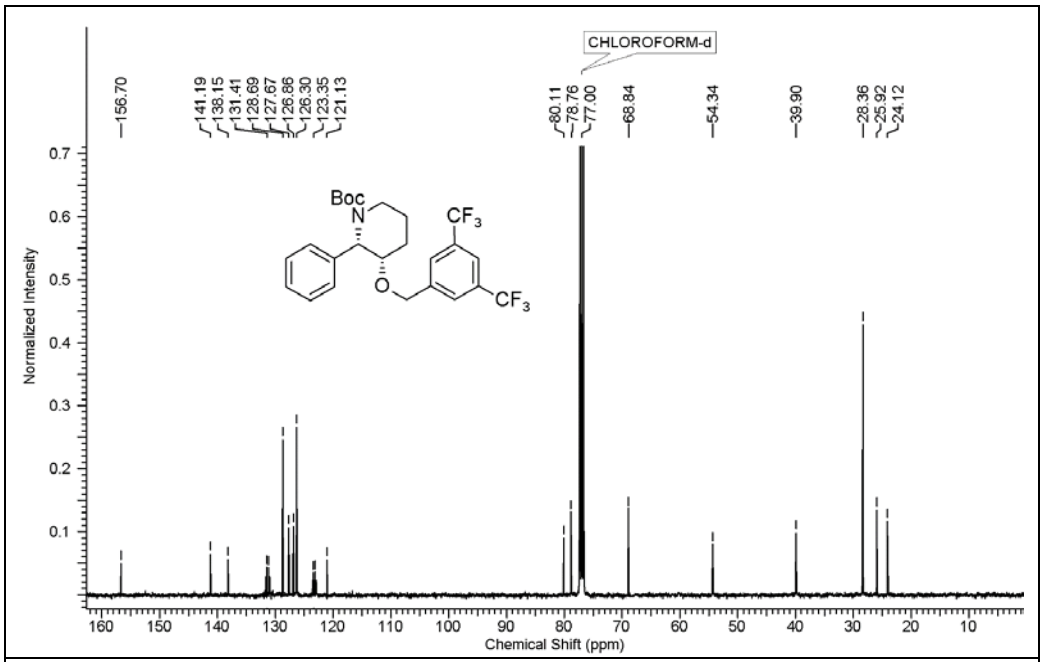
^{1}H-NMR of compound 1 in $CDCl_3$



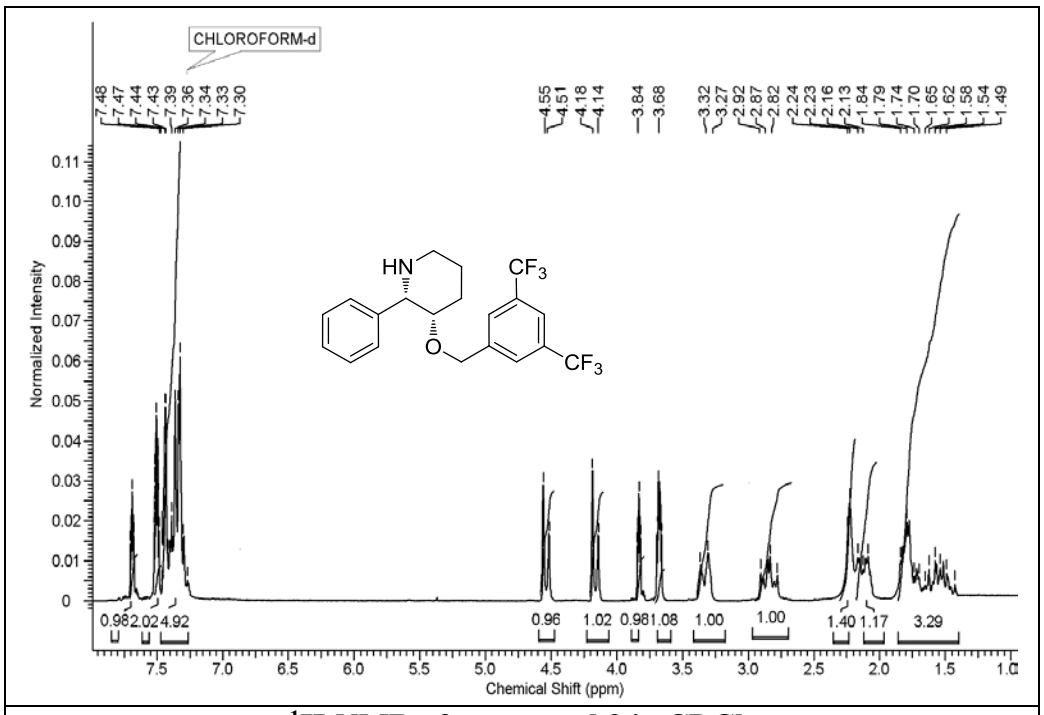
^{13}C-NMR of compound 1 in $CDCl_3$



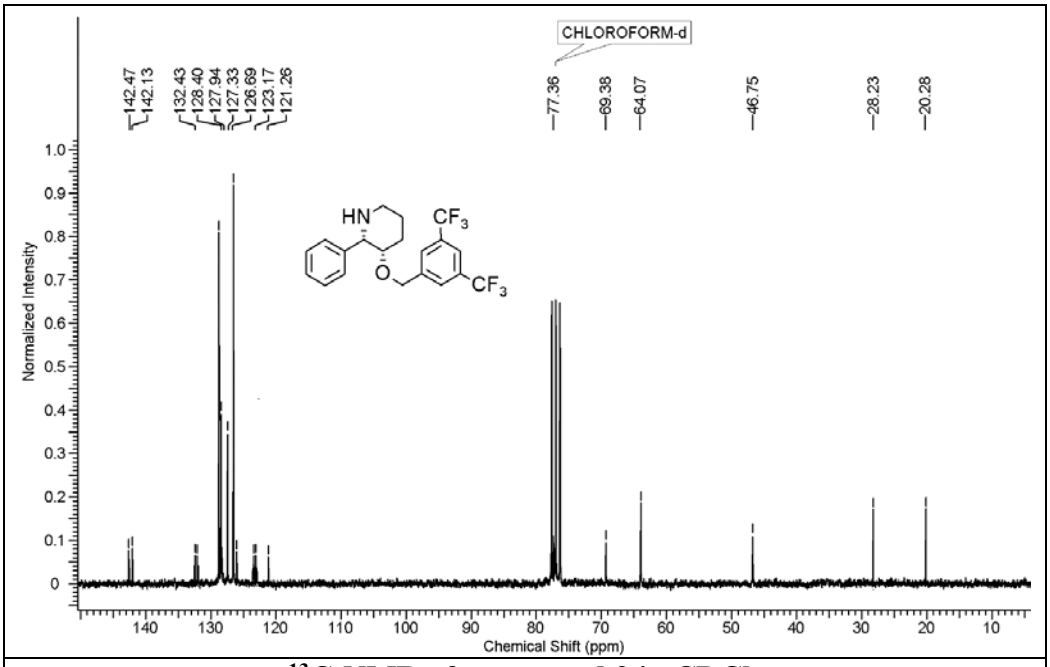
^{1}H-NMR of compound 64 in $CDCl_3$



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



^{1}H-NMR of compound 2 in $CDCl_3$



^{13}C-NMR of compound 2 in $CDCl_3$

2.8. References

1. (a) von Euler, V. S.; Gaddum, J. H. *J. Physiol*. **1931**, *72*, 577; (b) Chang, M. M.; Leeman, S.E. *J. Biol. Chem*. **1970**, *245*, 4784; (c) Pernow, B. *Phamacol. Rev*. **1983**, *35*, 85; (d) Naanishi, S. *Physiol. Rev*. **1987**, *67*, 1117; (e) Vaught, J. *Life Sci*. **1988**, *43*, 1419; (f) Lotz, M.; Vaughan, J. H.; Carson, D. A. *Science* **1988**, *241*, 1218; (g) Perianan, A.; Snyderman, R.; malfroy, B. *Biochem. Biophy. Res. Commun*. **1989**, *161*, 520; (h) Snijdelaar, D. G.; Dirksen, R.; Slappendd, R.; Crul, B. J. P. *Eur. J. Pain* **2000**, *4*, 121; (i) Datar, P.; Srivastava, S.; Coutinho, E.; Govil, G. *Curr. Top. Med. Chem*. **2004**, *4*, 75.
2. (a) Baker, R.; Harrison, T.; Hollingworth, G. J.; Swain, C. J.; Williams, B. J. EP0528 495A1, 1993; (b) Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 2545.
3. Desai, M. C.; Lefkwitz, S. L.; Thadeo, P. F.; Longo, k. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911.
4. Watson, J. W.; Gonsalves, S. F.; Fossa, A. A.; Mc Lea, S.; Seeger, T.; Obach, S.; Andrews, P. L. R. *Br. J. Pharmacol*. **1995**, *115*, 84; (b) Zaman, S.; Woods, A. J.; Watson, J. W.; Reynolds, D. J. M.; Andrews, P. L. R. *Neuropharmacology* **2000**, *39*, 316.
5. (a) Lotz, M.; Vaughan, J. H.; Carson, D. A. *Science* **1987**, *235*, 893; (b) Moskowitz, M.A. *Trends Pharmacol. Sci*. **1992**, *13*, 307; (c) Takenchi, Y.; Berkley Shand, E, F.; Beusen, D. D.; Marshall, G. R. *J. Med. Chem*. **1998**, *41*, 3609; (d) Swain, C. J. *Prog. Med. Chem*. **1998**, *35*, 57; (e) Muñoz, M.; Rosso, M.; Pérez, A.; Coveñas, R.; Rosso, R.; Zamarriego, C.; Soult, J, A.; Montero, I. *Invest. Ophthalmol. Vis. Sci.* **2005**, *46*, 2567; (f) Miguel, M.; Marisa, R.; Rafael, C. *Lett. Drug Des. Discov.* **2006**, *3*, 323.
6. Boks, G. J.; Tollenacre, J. P.; Kroon, J. *Bioorg. Med. Chem*. **1997**, *5*, 535.
7. (a) Stadler, H.; Bos, M. *Heterocycles* **1999**, *51*, 1067; (b) Bhaskar, G.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 915; (c) Tsai, M.-R., Chen, B.-F., Cheng, C.-C., Chang, N.-C. *J. Org. Chem*. **2005**, *70*, 1780; (d) Oshitari, T.; Mandai, T. *Synlett* **2006**, 3395; (e) Liu, R.-H., Fang, K., Wang, B., Xu, M.-H., Lin, G.-Q. *J. Org. Chem*. **2008**, *73*, 3307; (f) Bilke, J, L.; Moore, S, P.; O'Brien, P.; Gilday, J. *Org. Lett.* **2009**, *11*, 1935; (g) Kumaraswamy, G.; Pitchaiah, A. *Tetrahedron* **2011**, *67*, 2536.

8. (a) Takahashi, K.; Nukano, H.; Fujita, R. *Tetrahedron Lett*. **2005**, *46*, 8927; (b) Huang, P. Q.; Liu, L. X.; Wei, B. G.; Ruan, Y. P. *Org*. *Lett*. **2003**, *5*, 1927; (c) Yoon, Y.-J.; Joo, J. –E.; Lee, K. –Y.; Kim, Y. –H.; Oh, C. –Y.; Ham, W.-H. *Tetrahedron Lett*. **2005**, *46*, 739; (d) Lee, J.; Hoang, T.; Lewis, S.; Weissman, S. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett*. **2001**, *42*, 6223; (e) Tsuritani, N.; Yamuda, K.; Yoshikawa, N.; Shibaski, M. *Chem. Lett*. **2002**, 276; (f) Kandula, S. R. V.; Kumar, P. *Tetrahedron: Asymmetry* **2005**, *16*, 3579; (g) Lemine, A.; Grenon, M.; Pourashraf, C.; Charette. A. B. *Org*. *Lett*. **2004**, *6*, 3517; (h) Bodas, M. S.; Upadhyay, P. K.; Kumar, P. *Tetrahedron Lett*. **2004**, *45*, 987.
9. For leading reviews, see: (a) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561; (b) Kotti, S. R. S. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101.
10. Varty, G.B.; Cohen-Williams M. E.; Hunter J.C. *Behavioural Pharmacology* **2003**, *14*, 87.
11. Varty G. B.; Cohen-Williams M. E.; Morgan C. A. *Neuropsychopharmacology* **2002**, *27*, 371.
12. Hesketh, P. J. *Supportive Care in Cancer* **1994**, *12*, 550.
13. (a) Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1035; (b) Gupta, P.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 4231; (c) Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1957; (d) Kondekar. N. B.; Kandula, S.V.; Kumar, P. *Tetrahedron Lett*. **2004**, *45,* 5477; (e) Pandey, S. K.; Kandula, S. V.; Kumar, P. *Tetrahedron Lett*. **2004**, *45,* 5877; (f) Gupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 9641; (g) Kumar, P.; Bodas, M. S. *J. Org. Chem*. **2005**, *70*, 360.
14. Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc*. **1987**, *109*, 5765.
15. (a) Williams, D. R.; Fromhold, M. G.; Earley, J. D. *Org. Lett*. **2001**, *3*, 2721; (b) Menand, M.; Blais, J. –C.; Valery, J. –M.; Xie, J. *J. Org. Chem*. **2006**, *71*, 3295.
16. (a) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451; (b) Bruncko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1483.

17. (a) Mun˜iz, K.; Nieger, M. *Synlett* **2003**, 211; (b) Mun˜iz, K.; Nieger, M.; Mansikkama¨iki, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5958; (c) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 11688.
18. For related reviews, see: (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701; (b) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953.
19. Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem*. **1988**, *53*, 5185.
20. (a) Boto, A.; Betancor, C.; Prange, T.; Suavez, E. *J. Org. Chem*. **1994**, *59*, 4393; (b) Imai, T.; Nishida, S. *J. Org. Chem.* **1990**, *55*, 4849.
21. Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett*. **1981**, ***22***, 3455.
22. Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett*. **2004**, *6*, 3217.
23. Li, G. –I.; Zahao, G. *Org. Lett*. **2006**, *8*, 633.
24. (a) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, *23*, 1977; (b) Mitsunobu, O. *Synthesis* **1981**, 1.
25. Inversion of *syn*-1,2-amino alcohols to *anti*-1,2-amino alcohols has been reported using Mitsunobu reaction: Lipshutz, B. H.; Miller, T. A. *Tetrahedron Lett.* **1990**, *31*, 5253.
26. Khanjin N. A.; Hesse M. *Helv. Chem. Acta.* **2003***, 86,* 2028.
27. (a) Takao, K.-I.; Ochiai, H.; Yoshida, K.-I.; Hashizuka, T.; Koshimura, H.; Tadano, K. –I.; Ogawa, S. *J. Org. Chem*. **1995**, *60*, 8179; (b) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453.

Chapter-3

Formal synthesis of verbalactone and its monomer via two different hydrolytic kinetic resolution strategies

Formal synthesis of verbalactone and its monomer via two different hydrolytic kinetic resolution strategies

3.1. Introduction

Verbalactone **1** is a novel macrocyclic dimer lactone isolated from the roots of *Verbascum undulatum* Lam., a biennial plant that belongs to the family Scrophulariaceae.[1] It is the first example of a 1,7-dioxacyclodecane unit being present in the ring system of a natural product. This compound exhibited interesting antibacterial activity against three Gram-positive bacteria with optimum activity MIC = 62.5 μg/mL and five Gram-negative bacteria with optimum activity MIC = 125 μg/mL.[2] The structure and the absolute stereochemistry of **1** [(+)-(*4R,6R,10R,12R*)-4,10-dihydroxy-2,8-dioxo-6,12-dipentyl-1,7-dioxocyclodecane]were determined by spectral methods and chemical correlation. Verbalactone **1** is a dimer of lactone **2** [(+)-(3*R*,5*R*)-*3*-hydroxy-*5*-decanolide], a secondary metabolite isolated from *Cephalosporium recifei*[3a] (Fig. 1). The lactone moiety **2** is identical to the lactone unit in compactin, mevinolin etc., a potent inhibitor of the enzyme HMG-CoA reductase.[3b] Therefore the monomer **2** has also been the synthetic target of considerable interest.[4]

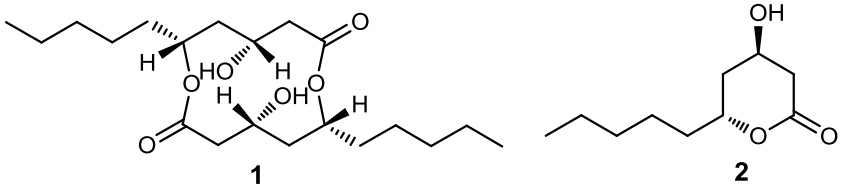


Figure 1: Structure of Verbalactone and its monomer

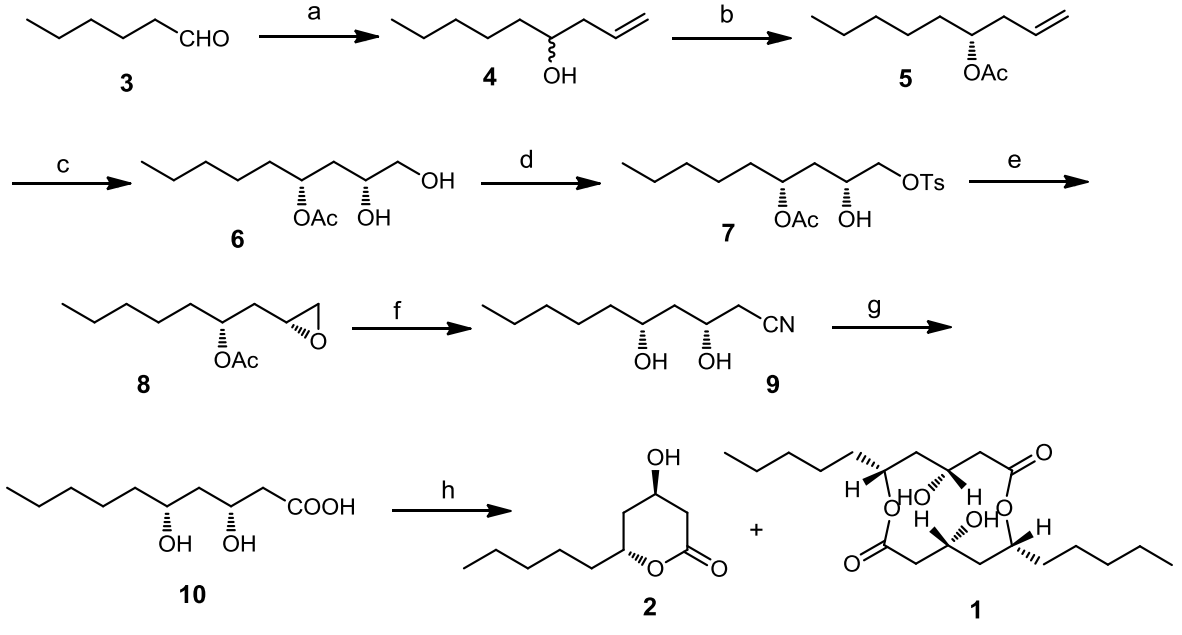
3.2. Review of Literature

So far there are more than ten synthetic routes reported for the construction of verbalactone **1** and its monomer **2**. These approaches achieved the *syn*-1,3-diol moiety either from enantiomerically pure precursors obtained from carbohydrates[5] and other chiral pool materials[6] or asymmetric synthesis using enzymatic kinetic resolution,[7] enantioselective allylmetalations,[8] Sharpless asymmetric dihydroxylation,[7] asymmetric epoxidation[9,6] and α-

aminoxylation[10] etc. Most of these approaches utilize the Yamaguchi macrolactonization for the final ring construction. A few them are reviewed.

Barua *et al.* (2004)[7]

Barua *et al.* reported the first total synthesis of verbalactone via enzymatic kinetic resolution, Sharpless asymmetric dihydroxylation and a Yamaguchi macrolactonization (Scheme 1). A Barbier-Grignard reaction with hexanal **3** afforded the homoallylic alcohol (±)-**4** in 90% yield. The homoallylic acetate was prepared by *trans*-esterification of (±)-**4** with Amano lipase from Pseudomonas fluorescens, an enzymatic kinetic resolution technique, giving *R*-**5** in 47% yield and with an enantiomeric excess of 94%. Next asymmetric dihydroxylation of *R*-**5** was effected to give a diastereoisomeric mixture of **6** in a diastereoisomeric ratio of 85:15. The required isomer *R*-**6** was monotosylated and converted into the epoxide *R*-**8** in 72% yield by treatment with NaOH.

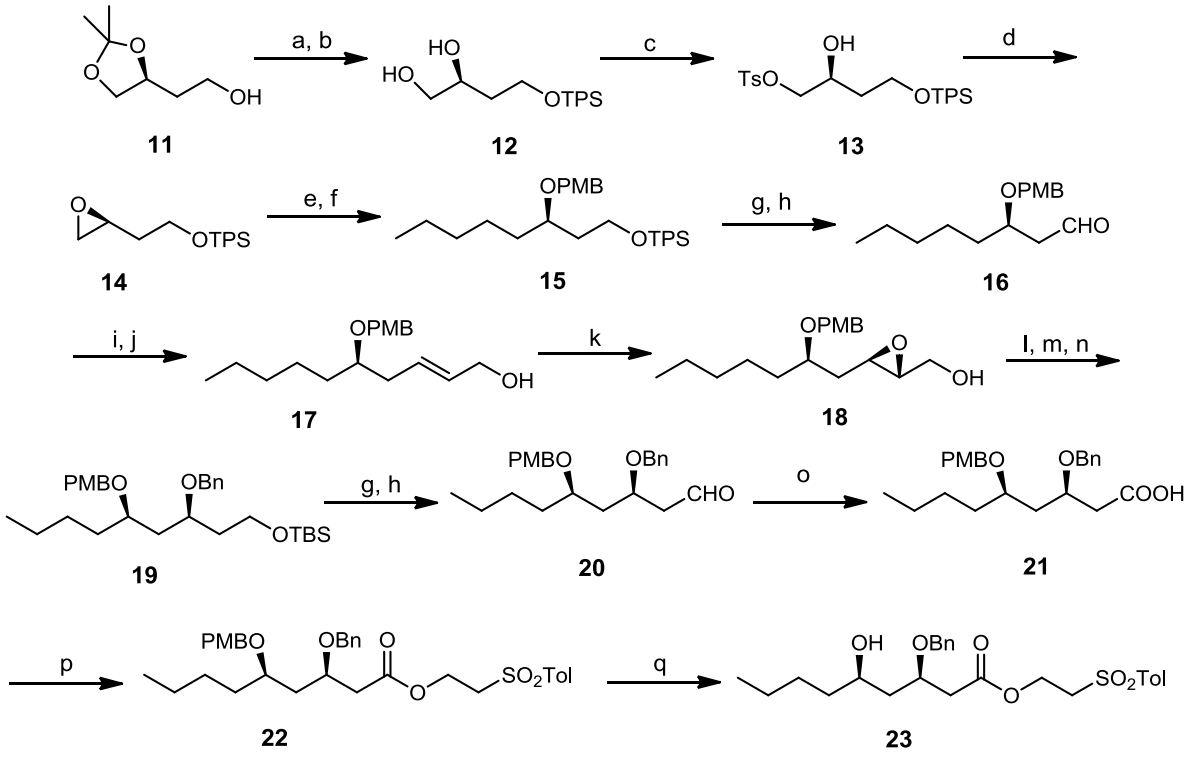


Scheme 1: *Reagents and conditions*: (a) allyl bromide, Zn, THF, aq NH_4Cl, rt, 1 h, 90%; (b) Amano Lipase from Pseudomonas fluorescens, hexane, rt, 26 h, 47%; (c) $K_3Fe(CN)_6$, K_2CO_3, $(DHQD)_2PHAL$, OsO_4, *t*-BuOH–water (1:1), 0 °C, 24 h, 88%; (d) TsCl/Py, CH_2Cl_2, rt, 27 h, 75%; (e) NaOH (2M soln in water), Et_2O, 15 h, rt, 72%; (f) $MgSO_4.7H_2O$, NaCN, dry MeOH, reflux, 6 h, 74%; (g) aqueous NaOH (25%), MeOH, reflux, 1M aq HCl (pH 5), 77%; (h) (i) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, 1.5 h; (ii) DMAP (20 equiv.), toluene, reflux, 4 h, 58%.

Treatment of *R*-**8** with NaCN and $MgSO_4$ in refluxing dry methanol gave cyanoalcohol *R*-**9** in 74% yield. During this step the acetate group in *R*-**8** was hydrolyzed under the reaction conditions. Hydrolysis of the cyanoalcohol *R*-**9**, was carried out followed by acidic work-up (pH 5) to give **10** in 77% yield. The pH during hydrolysis was carefully controlled to avoid the formation of the monomeric lactone **2** which was observed at pH 2. In the final step, lactonization of **10** to give the dimeric lactone **1** was successfully achieved by Yamaguchi's method in 58% yield and with >95% ee. In this step, a small amount of the monomeric lactone **2** (30%) was also formed (Scheme 1).[7]

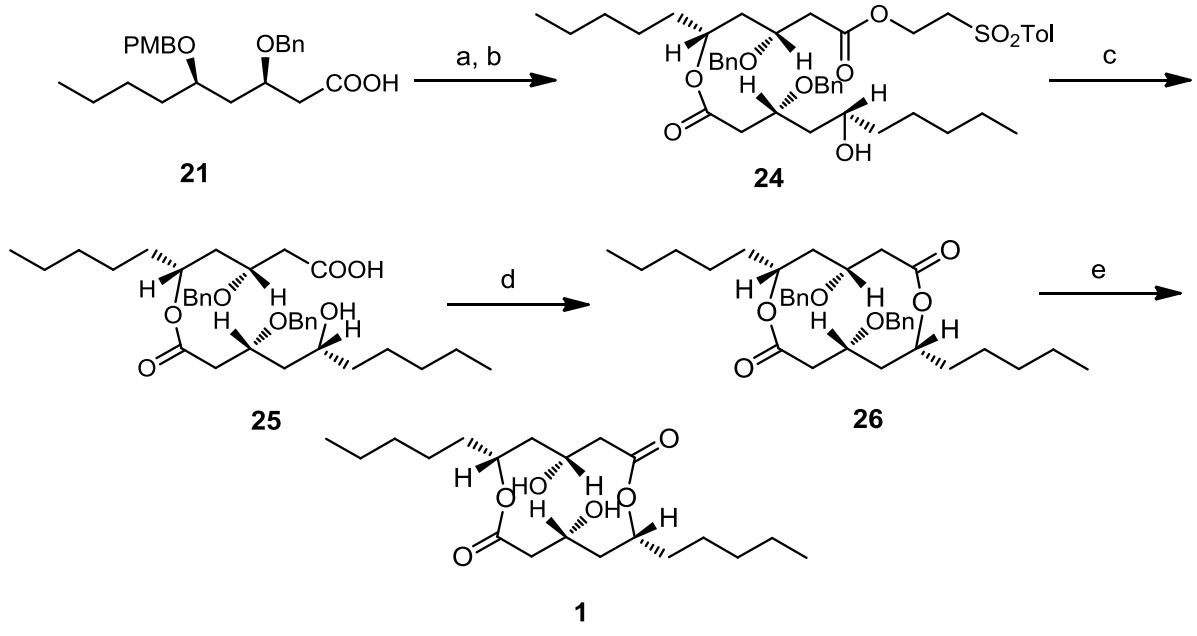
Sharma *et al.* (2004)[6]

Sharma et al. achieved total synthesis of verbalactone starting from *L*-malic acid. The basic strategy for the synthesis was to utilize the lone stereocenter in malic acid as C-*5* and to introduce the C-*3* hydroxyl of the target molecule by an asymmetric Sharpless epoxidation. Starting from known alcohol **11** derived from *L*-malic acid, TBDPS protection followed by hydrolysis gave the diol **12**. Selective tosylation of **12** with *p*-TsCl furnished **13**, which was reacted with base to give the epoxide **14**. Selective opening of **14** with CuI and *n*-BuLi followed by protection with PMBBr gave **15** in 85% yield. Alcohol resulted from desilylation of **15** was oxidized under Swern conditions to give aldehyde **16**. Homologation of **16** afforded ester which on reduction using DIBAL-H furnished the alcohol **17**. The Sharpless asymmetric epoxidation of **17** exclusively gave the epoxide **18** in 83% yield. Regioselective reductive opening of **18**, followed by silylation and subsequent benzylation of the secondary alcohol using NaH and BnBr gave **19**. Deprotection of the TBDMS ether in **19** with TBAF and subsequent oxidation under Swern conditions furnished the corresponding aldehyde **20**, which on further oxidation gave **21** in 83% yield. Having completed the synthesis of the key fragment **21**, it was subjected to esterification with *p*-toluenesulfonylethanol to afford ester **22**. Oxidative deprotection of the PMB group in **22** using DDQ gave the hydroxy ester **23**, a coupling fragment with segment **21**, in 73% yield (Scheme 2).[6]



Scheme 2: *Reagents and conditions:* (a) TBDPSCl, imidazole, CH_2Cl_2, rt, 5h; (b) 60% aq AcOH, rt, 12h; (c) *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C, 10h; (d) K_2CO_3, MeOH, rt, 2h; (e) CuI, *n*-BuLi, dry ether, 0 °C, 2h; (f) PMBBr, NaH, THF, 0 °C-rt, 5h; (g) TBAF, CH_2Cl_2, rt, 10h; (h) $(COCl)_2$ DMSO, Et_3N, CH_2Cl_2, -78 °C, 3h; (i) $Ph_3PCHCOOMe$, benzene, reflux, 2h; (j) DIBAL-H, CH_2Cl_2, rt, 3h; (k) (-)-DIPT, $Ti(Oi\text{-}Pr)_4$ cumene hydroperoxide, 4A˚MS, CH_2Cl_2, -20 °C, 3h; (l) $NaAlH_2(OCH2CH2OMe)_2$, THF, 0 °C, 5h; (m) TBDMSCl, imidazole, CH_2Cl_2 rt, 6h; (n) BnBr, NaH, THF, 0 °C-rt, 4h; (o) $NaClO_2$, 30% H_2O_2, *t*-BuOH/H_2O (2:1), 0 °C-rt, 10h; (p) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, $HOCH_2CH_2SO_2Ar$, DMAP, toluene, rt, 16h; (q) DDQ, CH_2Cl_2/H_2O (19:1), 0 °C-rt, 5h.

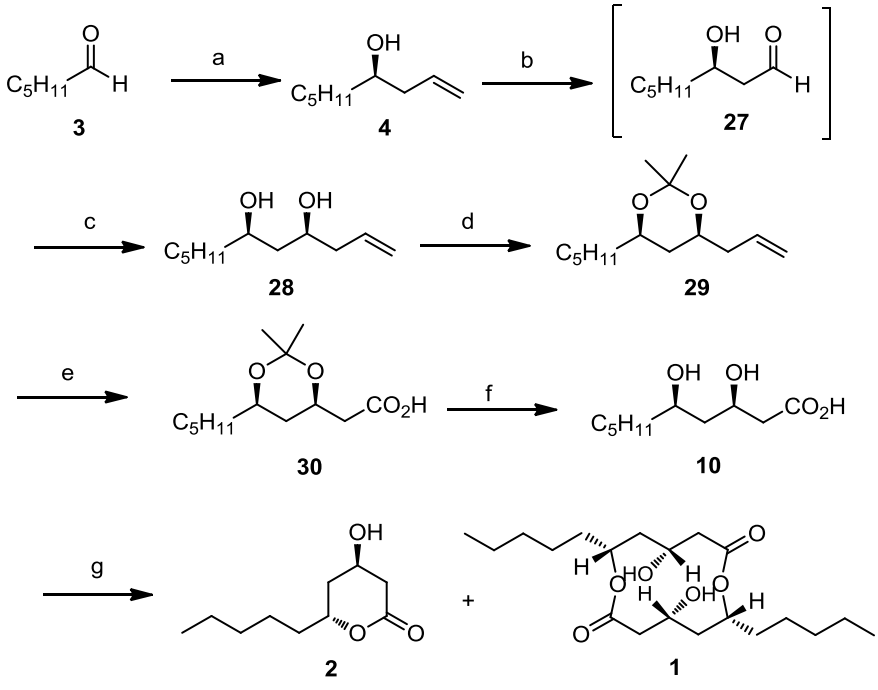
Esterification of acid **21** with alcohol **23** under Yamaguchi conditions followed by PMB deprotection furnished **24** in 69% yield (Scheme 3).[6] Selective cleavage of the *p*-toluenesulfonylethyl group in **24** was effected with DBN to give seco acid **25** (68%), which on lactonization under Yamaguchi conditions afforded **26** in 61% yield. Finally deprotection of the benzyl groups in **26** was effected with $TiCl_4$ (1 equiv.) in CH_2Cl_2 at 0 °C to give verbalactone **1** (Scheme 3).[6]



Scheme 3: *Reagents and conditions:* (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, **23**, DMAP, toluene, rt, 20h; (b) DDQ, CH_2Cl_2/H2O (19:1), rt, 3h; (c) DBN, benzene, rt, 12h; (d) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene, 90 ºC, 24h; (e) $TiCl_4$, CH_2Cl_2, 0 ºC, 1h.

Cossy *et al* (2007)[8a]

Cossy *et al* synthesized Verbalactone from commercially available hexanal **3** by enantio- and diastereoselective allylmetalation and a Yamaguchi macrolactonization. The synthesis started with the preparation of the homoallylic alcohol **4** from hexanal with an enantiomeric excess of 98%, by using the allylborane, (–)-Ipc_2BAllyl (Scheme 4). Compound **4** was then submitted to an oxidative cleavage to afford the β-hydroxyaldehyde **27** in quantitative yield. When the crude aldehyde **27** was immediately treated with a premixed solution of allyltrimethylsilane and $SnCl_4$ in CH_2Cl_2 at –78 °C, a mixture of two 1,3-diols was obtained in a ratio of 93:7 in favour of the *syn*-1,3-diol **28**. Later diols were protected as acetonide **29**. Oxidation of **29** allowed the formation of the (*R*,*R*)-dioxolane **30** in 77% yield. The deprotection of **30** was successfully achieved by treatment with a catalytic amount of CSA in MeOH as **10** was isolated in 80% yield accompanied by a small amount of lactone **2**. Finally, the synthesis of verbalactone **1** was successfully completed using Yamaguchi's macrolactonization (Scheme 4).[8a]

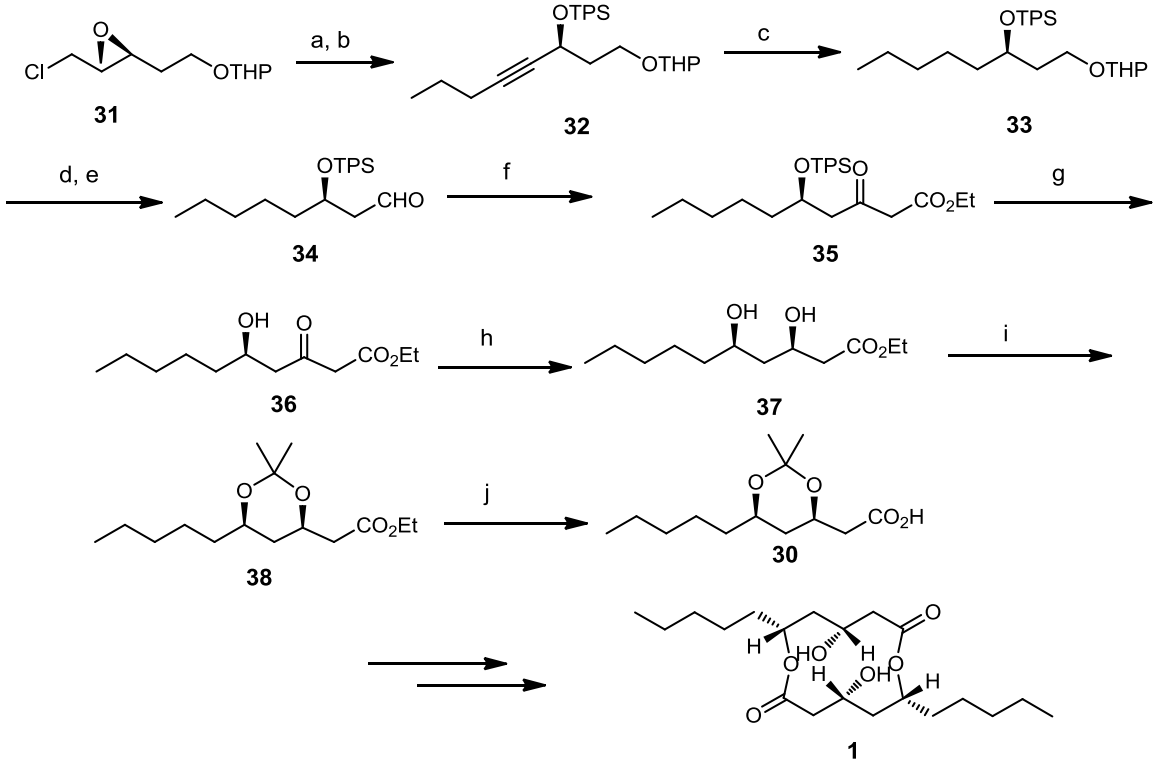


Scheme 4: *Reagents and conditions:* (a) (–)-DIPCl, AllylMgCl, Et_2O, –78 °C, 87%, 98% ee; (b) OsO_4, $NaIO_4$, *2,6*-lutidine, dioxane–H_2O 3:1, r.t., quant.; (c) $AllylSiMe_3$, $SnCl_4$, CH_2Cl_2, –78 °C, 74% from **4**, dr = 93:7; (d) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, r.t., 95%; (e) $RuCl_3$, $NaIO_4$, CH_2Cl_2–MeCN–H_2O, 77%; (f) cat. CSA, MeOH, r.t., 80%; (g) (*i*) 2,4,6-trichlorobenzoylchloride, Et_3N, THF, r.t., 3 h; (*ii*) DMAP (30 equiv.), toluene, reflux, 4 h, 49%.

Yadav *et al.* (2008)[9]

Yadav *et al* reported a formal synthesis of verbalactone starting with the known 2,3-epoxychloride **31**. The 2,3-epoxychloride **31** was directly converted into an alkylated chiral acetylenic carbinol in 80% yield in one-pot by subjecting it to a base-induced opening with Li metal in liquid NH_3 in THF, and the resulting alkynol without isolation was treated with 1-bromopropane and later secondary hydroxyl was protected as silyl ether **32**. Hydrogenation of triple-bond compound **32** with 10% Pd/C in EtOAc at room temperature for 4 h yielded a saturated compound **33** in 90% yield followed by deprotection of the THP group and oxidation with iodoxbenzoic acid in DMSO to afford aldehyde **34**. Treatment of aldehyde **34** with ethyl diazoacetate in the presence of a catalytic amount of tin(II) chloride at room temperature led to the formation of β-keto ester **35** in 75% yield. Selective deprotection of TBDPS ether group was done using TBAF to produce δ–hydroxy-β-ketoester **36** in 90%

yield. The stereoselective reduction of δ–hydroxy-β-ketoester **36** to the corresponding *syn*-1,3-diol **37** was achieved using catecholborane (3.0 equiv.) in THF at -10 °C in 92% yield with high diastereoselectivity (*syn:anti*/ 99:1). Diol **37** was transformed into the corresponding acetonide derivative **38**. The intermediate **38** was converted into the acid **30** by hydrolysis using 4N NaOH in EtOH at rt maintaining pH at 6.0 for 1 h by keeping the protecting group intact (Scheme 5).[9]

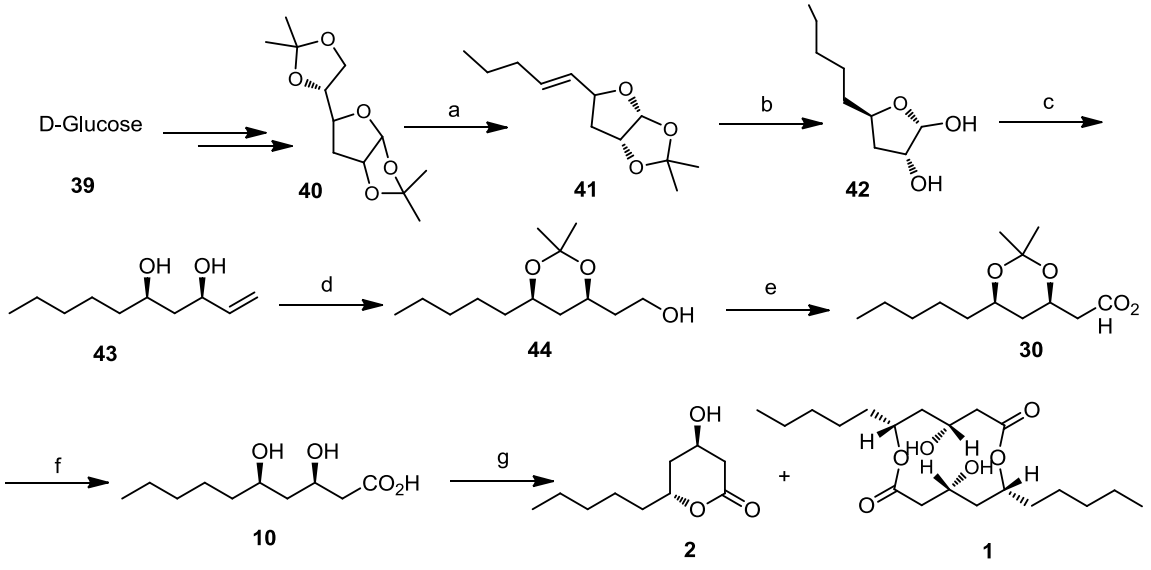


Scheme 5: *Reagents and conditions:* (a) Li/liq NH_3, ferric nitrate (catalyst), dry THF, -33 °C, 2 h, then propyl bromide, -33 °C, 6 h, 80%; (b) TBDPSCl, imidazole, DCM, 0 °C -rt, 1 h, 90%; (c) 10% Pd/C, EtOAc, H_2, rt, 4h, 90%; (d) PPTS, methanol, rt, 2 h, 86%; (e) IBX, DMSO, DCM, 0 °C -rt, 3h, 80%; (f) anhyd. $SnCl_2$, $N_2CHCOOEt$, DCM, 0 °C -rt, 6 h, 75%; (g) TBAF, THF, 1 h, 90%; (h) catecholborane, dry THF, -10 °C, 4 h, 92%; (i) *2,2*-DMP, PPTS, dry acetone, 85%; (j) 4N NaOH, EtOH, rt, 1 h, pH 6.0, 78%.

Gurjar *et al.* (2009)[5b]

Gurjar *et al*. described a carbohydrate-based strategy for the total synthesis of verbalactone **1**. The synthesis started with the preparation of 3-deoxy-1,2,5,6-di-*O*-isopropylidene- α-D-glucofuranose **40** from D-glucose. Selective deprotection of the 5,6-*O*-isopropylidene group of **40** afforded the C5–C6 diol in 94% yield. Oxidative cleavage by using sodium

metaperiodate followed by subsequent Wittig olefination provided alkene **41** in the ratio 3:7 (E/Z) (Scheme 6).



Scheme 6: *Reagents and conditions:* (a) (i) 0.8% aq H_2SO_4, MeOH, rt, 16 h, 95%; (ii) $NaIO_4$ on silica gel, CH_2Cl_2, 96%; (iii) $C_4H_9P^+Ph_3Br^-$, *n*-BuLi, THF, 0 °C, 81%; (b) (i) Raney-Ni, ethanol, 98%; (ii) 4% aq H_2SO_4, THF, 60 °C, 3 h, 94%; (c) $CH_3P^+Ph_3I^-$, n-BuLi, THF, 0 °C-rt, 80%; (d) (i) CSA (cat), 2,2-dimethoxypropane, CH_2Cl_2, 0 °C, 15 min, 98%; (ii) BH_3-DMS, THF, 0 °C, 4 h, 76%; (e) (i) Dess–Martin periodinane, CH_2Cl_2, 0 °C-rt, 1 h, 92%; (ii) $NaClO_2$, $NaH_2PO_4.2H_2O$, 30% H_2O_2, *t*-BuOH:H_2O (3:1), 0 °C-rt, 3 h, 95%; (f) CSA (5 mol %), MeOH, rt, 30 min, 80%; (g) (i) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, 3 h; (ii) DMAP (30 equiv.), toluene, reflux, 4 h, 60% (over two steps).

Hydrogenation of alkene **41** using Raney-Ni in ethanol and then hydrolysis of the 1,2-*O*-isopropylidine group afforded the diastereomeric lactol **42**. One-carbon Wittig homologation of lactol **42** with in situ-generated methylenetriphenyl phosphorane yielded *syn*-1,3-diol **43**. The *syn*-1,3-diol **43** was transformed quantitatively into its isopropylidene derivative. Selective hydroboration of this acetonide derivative of **43** with BH_3-DMS reagent afforded primary alcohol **44** in 76% yield. The alcohol **44** on treatment with Dess–Martin periodinane gave the corresponding aldehyde, which on further oxidation gave acid **30**. The unmasking of the 1,3-isopropylidene group was achieved by treating **30** with cat. CSA in anhydrous methanol and by carefully controlling the pH during work-up to provide the *(3R,5R)-3,5*-dihydroxydecanoic acid **10**. Finally, the synthesis of verbalactone **1** was successfully completed using Yamaguchi's macrolactonization to obtain verbalactone **1** in 60% yield from **10** along with monomer lactone **2** (Scheme 6).[5b]

3.3. SECTION A:

Formal synthesis of verbalactone and its monomer via iterative hydrolytic kinetic resolution

3.3.1. Present work

Objective

The stereoselective synthesis of 1,3-polyol arrays is one of the most important topics in organic chemistry because of the ubiquity of 1,3-polyols in various biologically active natural products and drugs, such as polyene macrolide antibiotics.[11] Thus, numerous strategies for their synthesis have been developed with great success.[12] Many highly stereocontrolled 1,3-asymmetric induction reactions[13] have been developed that mainly rely on 1,3-*syn*[14] or *anti*[15]-selective ketone reduction using borane reagents, intramolecular addition of the acetal to olefins,[16] inter- or intramolecular addition of silyl reagents to olefins such as hydrosilylation,[17] and intramolecular allylsilylation to carbonyl groups.[18] In contrast to the diversity of asymmetric reactions that are employed for the introduction of the first chirality, only a few chiral reagents or chiral catalysts are applied for stereoselective elongation of 1,3-polyol arrays due to crucial matched or mismatched effects caused by the substrate chirality. Among the above mentioned asymmetric reactions, chiral auxiliary controlled aldol reaction[19] allyl addition using chiral borane or titanium reagents [20] and catalytic asymmetric epoxidation of allylic alcohols[21] are commonly used for 1,3-polyol synthesis.

To synthesize 1,3-polyol natural products and their analogues, a highly versatile synthetic method that makes all possible stereoisomers freely accessible with the same efficiency is required. Scheme 7 shows our general synthetic strategy to construct the *syn*-and *anti*-1,3-polyol system which is based on a three-step reaction sequence[22h] employing iterative epoxidation, hydrolytic kinetic resolution (HKR)[23] and vinylation. Accordingly, the racemic epoxide can easily be derived from the corresponding olefin by oxidation. In order to install the first stereogenic centre, the hydrolytic kinetic resolution (HKR) can be performed on the racemic epoxide **47** using Jacobsen's catalyst **45** and **46** (Figure 2).

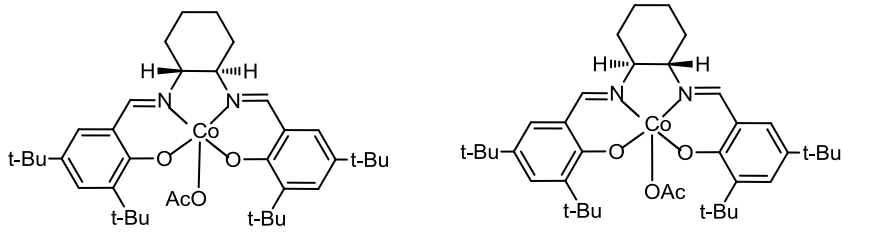
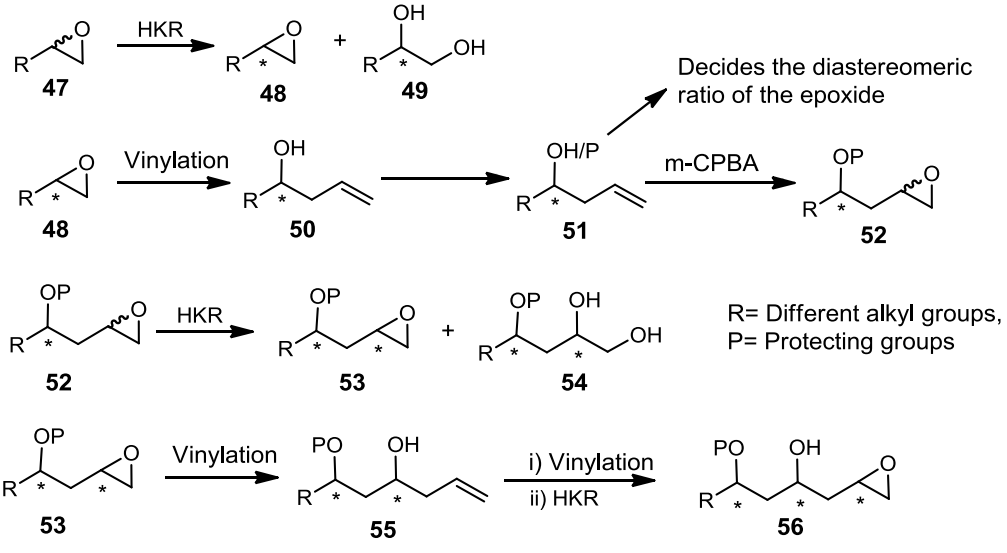


Figure 2: Jacobson catalysts for HKR

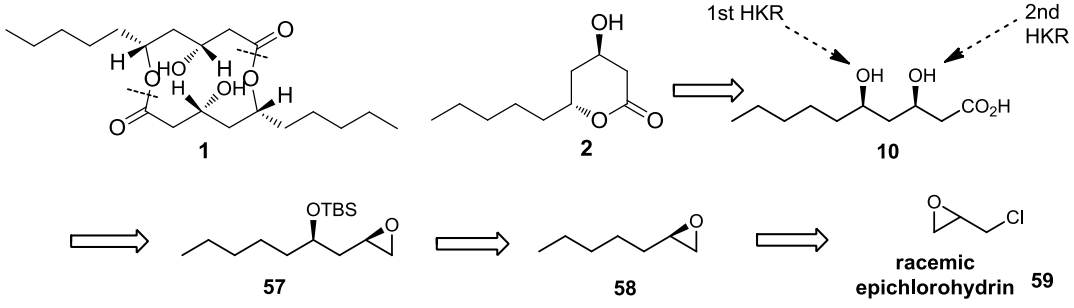


Scheme 7: General synthetic strategy to the synthesis of 1,3-polyols.

The ring opening of chiral epoxide **48** with vinylmagnesium bromide would provide the homoallylic alcohol **50** as precursor for the epoxidation and subsequent HKR. The homoallylic alcohol **51** can then be subjected to epoxidation with *m*-CPBA to get a mixture of diastereomeric epoxide **52**. The diastereomeric ratio in epoxidation reaction would depend on whether the hydroxyl group is free or protected. The HKR can subsequently be performed on the diastereomeric epoxide to obtain the enantiopure epoxide **53** which by iterative vinylation and epoxidation would eventually lead to the 1,3-polyol system. The *syn*-and *anti*-configuration of 1,3-polyol moiety can be manipulated simply by changing the Jacobsen's catalyst in the hydrolytic kinetic resolution step (Scheme 7).

Interesting structural complexity and our continued interest in the area of synthesis of bioactive natural products containing 1,3-polyol systems[22] prompted us to devise a simple and concise route to verbalactone **1** and its monomer **2**. In this procedure, we report the enantioselective synthesis of **1** and **2**, employing iterative hydrolytic kinetic resolution (HKR).

Retrosynthetic Analysis of Verbalactone

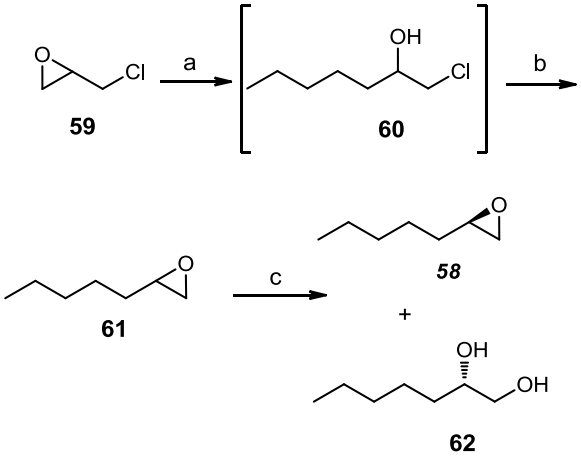


Scheme 8: Retrosynthetic Analysis of Verbalactone **1** and monomer **2**

A common approach to the synthesis of verbalactone **1** features, dissecting the molecule at two junctions as shown in Scheme 8. The retrosynthetic analysis shown above indicated that verbalactone **1** can easily be synthesized exploiting Yamaguchi's macrolactonization[24] on the key monomer seco-acid, (3*R*,5*R*)-3,5-dihydroxy decanoic acid **10**. The *syn*-1,3-configuration of the hydroxyl functionalities can be fixed by the use of Jacobsen catalyst **45** in iterative Hydrolytic Kinetic Resolution of subsequent racemic epoxides.

3.3.2. Results and Discussion

The synthesis of verbalactone **1** commenced from commercially available racemic epichlorohydrin **59** as depicted in Scheme 9. The treatment of **59** with butylmagnesium bromide in the presence of CuI at -30 ^{o}C was a clean reaction. Once we confirmed the complete conversion of epichlorohydrin **59** from TLC, we quenched the reaction, extracted with diethyl ether and subsequently treated the crude sample with pulverized NaOH in diethyl ether for two hours. Racemic epoxide **61** was then distilled from the reaction mixture (135 ^{o}C at 760 Torr.) in an overall 82% yield from epichlorohydrin **59**.

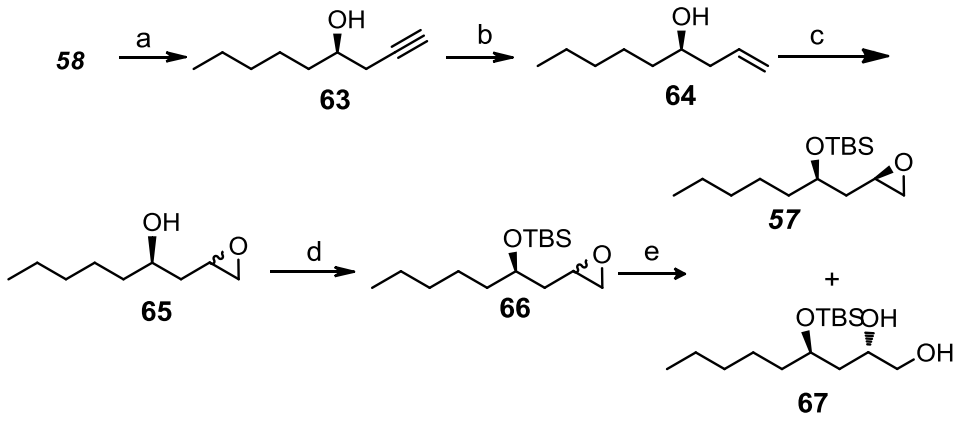


Scheme 9: *Reagents and conditions*: (a) *n*-C_4H_9MgBr, Et_2O, CuI, -30 ^oC, overnight; (b) NaOH, Et_2O, 0 ^oC, 2 h, 82%; (c) (*R,R)*-salen-Co-(OAc) **45** (0.5 mol%), dist. H_2O (0.55 equiv.), 0 ^oC, 16 h, (45% for **58**, 43% for **62**).

The epoxide peaks appeared at δ 2.45-2.46 (d, *J*= 5.1 Hz, 1H), 2.74-2.75 (d, *J*= 5.0 Hz, 1H), 2.88-2.90 (m, 1H) in ^1H NMR spectrum. The ^{13}C NMR spectrum of **61** showed upfield carbons of epoxide at δ, 46.9 and 50.2 ppm. Then epoxide **61** was resolved with (*R,R*)-salen-Co-(OAc) complex **45** (0.5 mol%) and water (0.55 equiv.) in THF (0.55 equiv.) to give the *R*-epoxide **58**[25] in 45% yield with 99% ee, $[\alpha]_D^{25}$ +9.6 (*c* 1, $CHCl_3$) and *S*-diol **62**[25] in 43% yield with 99.5% ee, $[\alpha]_D^{25}$ -15.9 (*c* 1.67, EtOH) (Scheme 9).

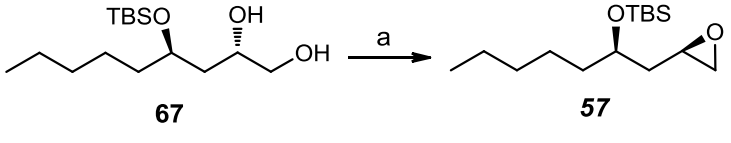
With enantiomerically pure epoxide **58** in hand, our next task was to construct the *syn*-1,3-diol. Thus treatment of epoxide **58** with vinylmagnesium bromide in the presence of CuI provided the homoallylic alcohol **64** only in low yield. As an alternative to this method, we employed a two-step reaction sequence. Thus the epoxide 5**8** was treated with excess of lithiumacetylide followed by partial hydrogenation of the resultant acetylene **63** with Lindlar's catalyst[26] to afford the homoallylic alcohol **64** in excellent yield. The ^1H NMR spectrum of **64** gave olefin peaks at δ 5.08-5.18 (m, 1H), 5.73-5.94 (m, 1H) ppm.

We then proceeded to explore the stereoselective outcome of the epoxidation reaction with and without hydroxyl group protection. To this end, the hydroxyl group of homoallylic alcohol **64** was first protected as TBS ether, followed by epoxidation with *m*-CPBA to give a mixture of two diastereomers (*anti*:*syn*; 2.5:1) with the desired *syn*-isomer of **66** as the minor component.



Scheme 10: *Reagents and conditions*: (a) LiC≡CH–ethylene diamine, DMSO, 0 °C to rt, 2 h, 86%; (b) H_2, Lindlar's catalyst, EtOAc, 30 min. 98%; (c) *m*-CPBA, CH_2Cl_2, rt, overnight, 96%; (d) TBSCl, imidazole, CH_2Cl_2, rt, 6 h, 94%; (e) (*R,R)*-salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55 equiv.), 0 °C, 24 h, (45% for **57,** 47% for **67**).

In contrast, the epoxidation of homoallylic alcohol **64** produced the epoxide **65** in favour of the desired *syn*-isomer (*syn*:*anti*/ 1.3:1) (Figure 3). The two diastereomers could not be differentiated on TLC. The next step in the synthesis was to construct the diastereomerically pure epoxide by means of Jacobson's hydrolytic kinetic resolution (Scheme 10). For that, initially we protected the hydroxyl group as the TBS ether, then the epoxide **66** was treated with (*R,R*)-salen-Co-(OAc) complex **45** (0.5 mol%) and water (0.55 equiv.) in THF (0.55 equiv.) to afford the epoxide **57**[9] as a single diastereomer (determined by ^1H and ^{13}C NMR spectral analysis) in 45% yield and the diol **67** in 47% yield. Epoxide **57** could easily be separated from the more polar diol **67** by silica gel column chromatography. As the HKR method provided the desired epoxide **57** along with unwanted diol **67** in almost equal amounts, we converted the diol **67** into the required epoxide **57** (Scheme 11) by means of an internal nucleophilic substitution of a secondary mesylate.[27]



Scheme 11. *Reagents and conditions*: (a) (i) PivCl, Et_3N, Cat. DMAP, rt, 2 h; (ii) MsCl, Et_3N, DMAP, 0 °C to rt, 1 h; (iii) K_2CO_3, MeOH, rt, overnight, (60% for three steps).

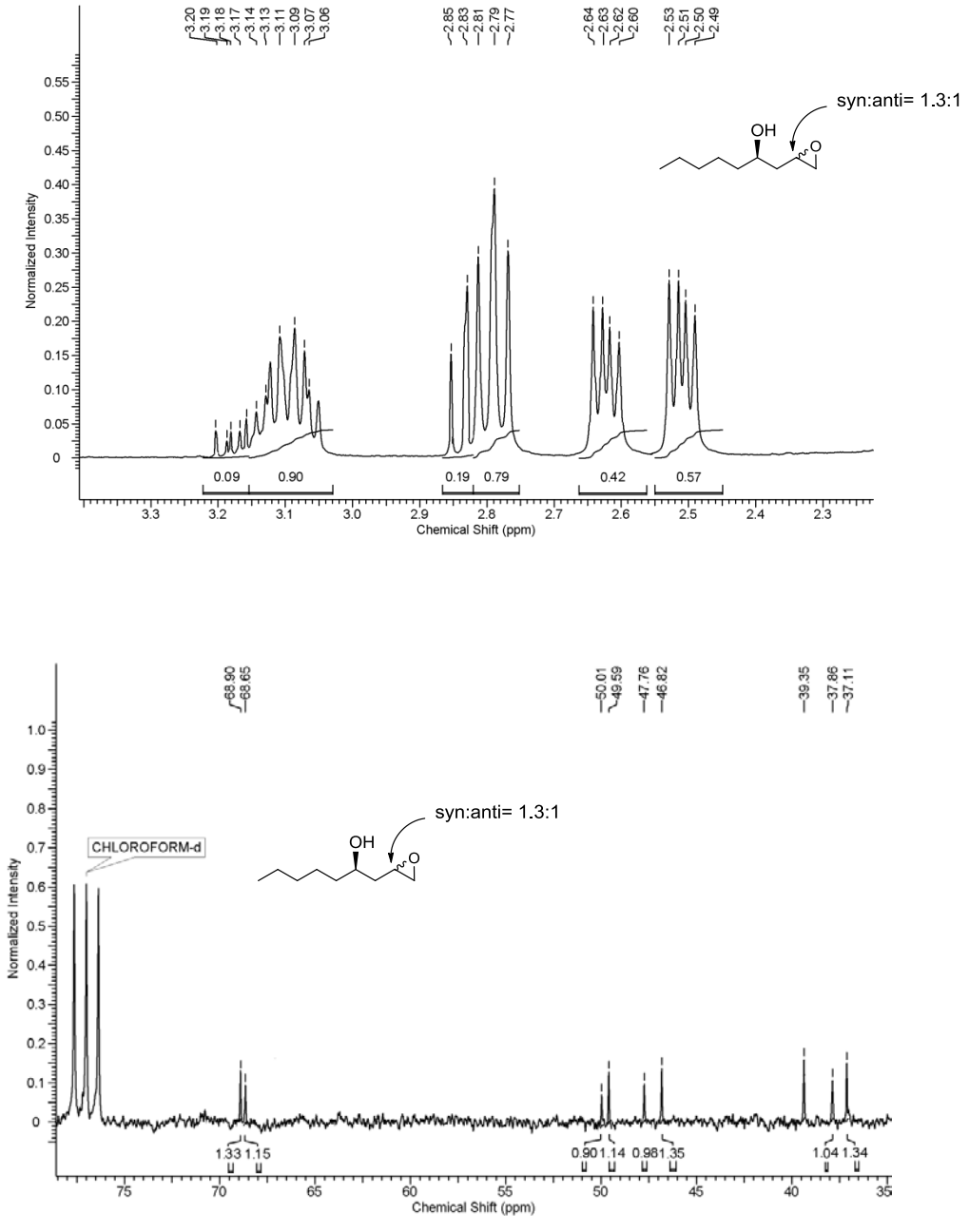
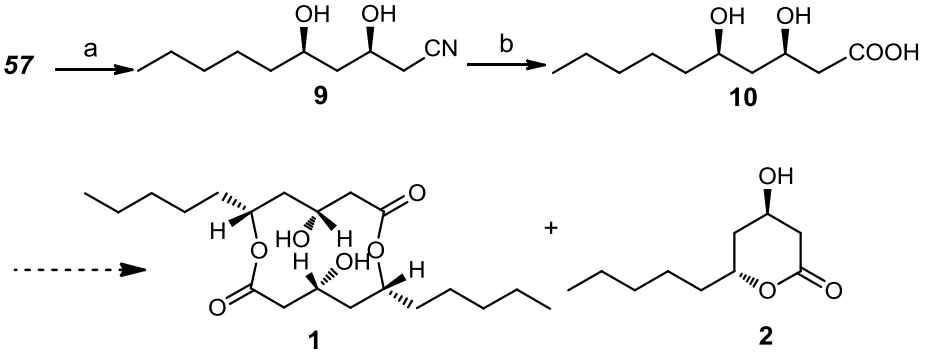


Figure 3: Partial ^{1}H NMR and ^{13}C NMR spectra of diastereomeric mixture (*syn*:*anti*/ 1.3:1) **65**

With substantial amount of **57** in hand**,** we then further proceeded towards the synthesis of **1** (Scheme 12). To this end, the regioselective ring opening of epoxide **57** was carried out with NaCN[28] in the presence of trifluroacetic acid in ethanol at 50 ^{o}C to give the cyanoalcohol **9** with concomitant removal of the TBS group. The IR spectrum illustrated the nitrile group stretching frequency at 2250 cm^{-1}. The ^{13}C NMR spectrum showed nitrile carbon peak at δ

117.7 ppm. Finally, the hydrolysis of nitrile was effected by treatment of **9** with 25% aqueous NaOH in methanol followed by acidic work up at pH 5 with HCl to furnish the acid **10** in good yield. The spectral and analytical data of **10** were in full agreement with the reported compound. {$[\alpha]_D^{25}$ +14.1 (*c* 0.2, $CHCl_3$); lit. $[\alpha]_D^{25}$ +14.3 (*c* 0.23, $CHCl_3$)[5c]}. The IR spectrum illustrated the carbonyl stretching frequency at 1713 cm^{-1} featuring the acidic functionality. The ^{13}C NMR spectrum showed carbonyl peak at δ 176.4 ppm. As the subsequent transformations of **10** to target molecules **1** and **2** under varied conditions have already been reported,[5b,7,8a,9] the formal synthesis of **1** and **2** was completed (Scheme 12).



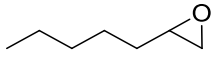
Scheme 12. *Reagents and conditions*: (a) NaCN, CF_3COOH, EtOH, 50 °C, 10 h, 90%; (b) aqueous NaOH (25%), MeOH, reflux, 6 h., then 1M aq HCl (pH 5), 78%.

3.3.3. Conclusion

In conclusion, a practical and enantioselective synthesis of verbalactone **1** and its monomer **2** has been achieved using iterative hydrolytic kinetic resolution as the key step. The synthetic strategy described for **1** and **2** might be easily amenable for the preparation of other isomers simply by changing the catalyst in the hydrolytic kinetic resolution.

3.3.4. Experimental Section

2-Pentyloxirane (61)



To a mixture of (±)–epichlorohydrin **59** (5g, 54.05 mmol) and CuI (0.2058g, 1.0 mol) in diethylether (60 mL) at -30 ^{o}C, a diethylether solution of n-butylmagnesium bromide which was prepared from Mg (3.94g, 162.1mmol), n-Butyl bromide(14.918g, 108.1 mmol), 1,2-dibromoethane (4 drops) and diethylether (30mL) was added dropwise. The mixture was stirred for overnight and poured into a mixture of saturated aqueous NH_4Cl solution and ethylacetate with vigorous stirring, extracted with ethylacetate and organic layer was washed with brine (75 mL), and dried over anhydrous Na_2SO_4. Finally solvent was removed under reduced pressure. Without purification, crude **60** was subjected to next operation.

NaOH (2.38g, 59.74mol) is added to the solution of chlorohydrin **60** (6g, 39.82mmol) in 25 mL diethylether in a flask fitted with distillation head. The mixture was stirred for 1 hour and the epoxide **61** distilled over as a colourless liquid. (135 ^{o}C at 760 Torr.)

Yield: 4.18 g, (92%)

Mol. Formula: **$C_7H_{14}O$**

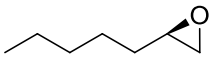
IR ($CHCl_3$, cm^{-1}): ν_{max} 3015, 2960, 2931, 2860, 1479, 1467, 1410, 1380, 1260, 1133, 1022, 916, 850, 828.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86-0.92 (t, *J*= 7 Hz, 3H), 1.25-1.42 (m, 8H), 2.45-2.46 (d, *J*= 5.1 Hz, 1H), 2.74-2.75 (d, *J*= 5.0 Hz, 1H), 2.88-2.90 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) δ 13.9, 22.5, 25.1, 31.7, 37.3, 46.9, 50.2 ppm.

Analysis: Calcd.: C, 73.63; H, 12.36; **Found:** C, 73.57; H, 12.43.

***(2R)*-Pentyloxirane (*58*)**



A solution of epoxide **61** (3g, 26.27mmol) and (*R,R*)-salen-Co(III)-OAc **45** (0.087 g, 0.13 mmol) in THF (0.25 mL) was stirred at 0 ºC for 5 min, and then distilled water (0.26mL, 14.82mmol) was added. The reaction was allowed to warm to rt and stir 16 hours. (*R*)-*1*,*2*-epoxyheptane **58** was isolated as a colourless liquid by vacuum transfer at 0.25 torr. into a cooled (-78 ºC) receiving flask and diol **62** by purified by silica gel column chromatography eluting with light petroleum : EtOAc (3:2) to provid the diol **62** as a brown color liquid as a single enantiomer.

Yield: 1.35 g, (45%)

Mol. Formula: $C_7H_{14}O$

$[\alpha]_D^{25}$: +9.6 (*c* 1, $CHCl_3$).

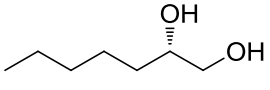
IR ($CHCl_3$, cm^{-1}): ν_{max} 3016, 2959, 2931, 2860, 1478, 1467, 1410, 1379, 1260, 1130, 1022, 916, 850, 828.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86-0.92 (t, *J*= 7 Hz, 3H), 1.25-1.43 (m, 8H), 2.45-2.46 (d, *J*= 5.1 Hz, 1H), 2.74-2.75 (d, *J*= 5.0 Hz, 1H), 2.88-2.90 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 22.5, 25.1, 31.7, 37.3, 46.9, 50.2 ppm.

Analysis: Calcd.: C, 73.63; H, 12.36; **Found:** C, 73.59; H, 12.34.

***(S)*-Heptane-1,2-diol (62)**



Yield: 1.49g, (43%)

Mol. Formula: $C_7H_{16}O_2$

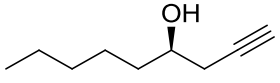
$[\alpha]_D^{25}$: -15.9 (*c* 1.67, EtOH)

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

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.82-0.88 (t, *J*= 7.1Hz, 3H), 1.30-1.55 (m, 8H), 2.96 (brs, 2H), 3.33-3.55 (m, 1H), 3.69-3.72 (m, 1H), 3.73-3.81 (m, 1H) ppm.
^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 22.4, 25.2, 31.7, 45.6, 63.4, 71.6 ppm.

Analysis: Calcd.: C, 63.60; H, 12.20; **Found:** C, 63.64; H, 12.21.

***(R)*-Non-1-yn-4-ol (63)**



To a solution of **58** (1.2 g, 10.50 mmol) in DMSO (5 mL) at 0 °C, lithiumacetylide-EDA complex (1.45 g, 15.76 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 30 min and 2 hours at room temperature. The excess of reagent was quenched with 0.3 N H_2SO_4 and extracted with EtOAc, washed with water, brine, dried (Na_2SO_4), concentrated. The residue was purified by silica gel chromatography by eluting with light petroleum ether: EtOAc (9.5:1) to afford **63** as brown liquid.

Yield: (1.09 g, 86 %).

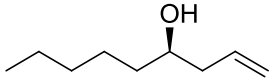
Mol. Formula: $C_9H_{16}O$

$[\alpha]_D^{27}$: +23.5 (*c* 1, $CHCl_3$).
IR ($CHCl_3$, cm^{-1}): ν_{max} 3436, 3309, 2860, 2119, 1467, 1381, 1216, 1123, 1038, 759, 668, 640.
^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.85-0.92 (t, *J*= 6.5 Hz, 3H), 1.30-1.54 (m, 8H), 2.03 (brs, 1H), 2.05-2.06 (d, *J*= 2.6 Hz, 1H), 2.32-2.46 (m, 2H), 3.69-3.81 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 22.4, 25.1, 27.1, 31.6, 36.0, 69.7, 70.5, 80.9 ppm.

Analysis: Calcd.: C, 77.09; H, 11.50; **Found:** C, 77.11; H, 11.47.

***(R)*-Non-1-en-4-ol (64)**



Compound **63** (1.1g, 7.84mmol), Lindlar catalyst (10 mg) and quinoline (0.2mL) in ethylacetate (10 mL) were stirred under hydrogen atmosphere for 30 min. The catalyst was filtered, concentrated and the residue extracted with ethyl acetate, it was washed with 1N HCl, water, dried (Na_2SO_4) and purified by silica gel column chromatography eluting with light petroleum: EtOAc (9.5:1) to give **64** as pale yellow liquid.

Yield: 1.09g, (98 %).
Mol. Formula: $C_9H_{18}O$

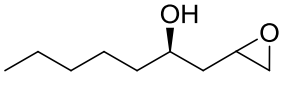
$[\alpha]_D^{27}$: +7.87 (*c* 1.1, $CHCl_3$).
IR ($CHCl_3$, cm^{-1}): ν_{max} 3351, 2926, 2854, 1641, 1589, 1457, 1378, 1259, 1156, 999, 836.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86-0.92 (t, *J*= 6.4 Hz, 3H), 1.25-1.44 (m, 8H), 2.98 (brs, 1H), 2.13-2.30 (m, 2H), 3.57-3.70 (m, 1H), 5.08-5.18 (m, 1H), 5.73-5.94 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 22.5, 25.1, 31.7, 36.2, 41.4, 70.3, 117.7, 134.8 ppm.

Analysis: Calcd.: C, 76.00; H, 12.76; **Found:** C, 76.06; H, 12.79.

***(2R)*-1-(Oxiran-2-yl)heptan-2-ol (65)**



To a stirred solution of olefin **64** (1 g, 7.03 mmol) in CH_2Cl_2 (15mL) at 0 ^oC *m*-CPBA (50%) (3.63g, 10.54mmol) was added. The reaction mixture was stirred at room temperature for

overnight and quenched by saturated $NaHCO_3$ solution, extracted with CH_2Cl_2, washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography using pet ether/EtOAc (9:1) as eluent to yield the epoxide **65** as a colourless liquid in diastereomeric mixture (1.3:1).

Yield: 1.06g, (96%)

Mol. Formula: $C_9H_{18}O_2$

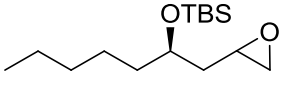
IR ($CHCl_3$, cm^{-1}): ν_{max} 3410, 2959, 2933, 2867, 1476, 1467, 1410, 1379, 1260, 1130, 1022, 913, 851, 828.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85-0.92 (t, *J*= 6.5 Hz, 3H), 1.25-1.58 (m. 8H), 1.81-1.90 (m, 2H), 2.12 (brs, 1H), 2.49-2.64 (m, 1H), 2.77-2.85 (m, 1H), 3.09-3.19 (m, 1H), 3.86-3.95 (m, 1H)) (mixture of diastereomers) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 22.5, 24.6, 31.8, 37.1, 37.8, 39.3, 46.8, 47.7, 49.5, 50.0, 68.6, 68.9 (mixture of diastereomers) ppm.

Analysis: Calcd.: C, 68.31; H, 11.47; **Found:** C, 68.34; H, 11.44.

***tert*-Butyldimethyl(((*2R*)-1-(oxiran-2-yl)heptan-2-yl)oxy)silane (66)**



To a stirred solution of alcohol **65** (1 g, 6.31 mmol) in CH_2Cl_2 (20 mL), imidazole (0.86g, 1.26 mmol) and *t*-butyl dimethylchlorosilane (1.1430 g, 7.58 mmol) was added at 0 ^oC and reaction was stirred at room temperature for 6 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 x 25 mL). The extract was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (20:1) as eluent provided **66** as a colorless liquid.

Yield: 1.62g, (94%)

Mol. Formula: $C_{15}H_{32}O_2Si$

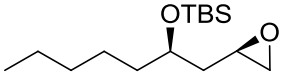
IR ($CHCl_3$, cm^{-1}): ν_{max} 2959, 2931, 2860, 1478, 1467, 1410, 1379, 1260, 1130, 1022, 916, 850, 828.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.90-0.95 (m, 12H), 1.26 (brs, 8H), 1.47-1.66 (m, 2H), 2.45-2.51 (m, 1H), 2.74-2.81 (m, 1H), 3.02-3.06 (m, 1H), 3.78-3.92 (m, 1H) (mixture of diastereomers) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.7, 13.9, 22.5, 24.6, 25.8, 29.6, 31.8, 37.1, 37.8, 40.1, 46.8, 47.7, 49.5, 50.0, 70.1, 70.3 (mixture of diastereomers) ppm.

Analysis: Calcd.: C, 66.11; H, 11.84; **Found:** C, 66.09; H, 11.81.

***tert*-Butyldimethyl(((R)-1-((R)-oxiran-2-yl)heptan-2-yl)oxy)silane (*57*)**



A solution of epoxide **66** (1.3 g, 4.71 mmol) and (*R,R*)-salen-Co(III)-OAc **45** (0.015 g, 0.023 mmol) in THF (0.05 mL) was stirred at 0 ^oC for 5 min, and then distilled water (0.047 mL, 2.62mmol) was added slowly. After stirring for 24 h, it was concentrated and purified by silica gel column chromatography using pet ether: EtOAc (20:1) to afford **57** as a yellow colour liquid. Continued chromatography with pet ether/EtOAc (3:2) provided the diol **67** as a brown color liquid as a single diastereomer.

Yield: 0.58g, (45%)

Mol. Formula: $C_{15}H_{32}O_2Si$

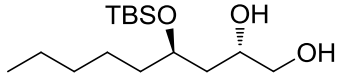
$[\alpha]_D^{27}$: +4.1 (c 2.1, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 2959, 2931, 2860, 1478, 1467, 1410, 1379, 1260, 1130, 1022, 916, 850, 828.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.90-0.96 (m, 12H), 1.26 (brs, 8H), 1.47-1.67 (m, 2H), 2.45-2.51 (m, 1H), 2.74-2.82 (m, 1H), 3.02-3.06 (m, 1H), 3.78-3.92 (m, 1H) ppm.
^{13}C NMR (50 MHz, $CDCl_3$): δ -4.7, 13.9, 22.5, 24.6, 25.8, 29.6, 31.8, 37.1, 40.1, 46.8, 49.5, 70.3 ppm.

Analysis: Calcd.: C, 66.11; H, 11.84; **Found:** C, 66.12; H, 11.81.

***(2S,4R)*-4-((*tert*-Butyldimethylsilyl)oxy)nonane-1,2-diol (67)**

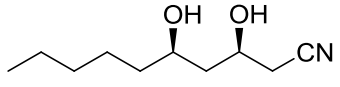


Yield: 0.64g, (47%)
Mol. Formula: $C_{15}H_{34}O_3Si$

$[\alpha]_D^{27}$: -14.87 (c 1, $CHCl_3$)
IR ($CHCl_3$, cm^{-1}): ν_{max} 3410, 2956, 2930, 1580, 1463, 1380, 1288, 1256, 1123, 1074, 836, 759.
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.90 (m, 12 H), 1.26-1.28 (m, 8H), 1.52-1.62 (m, 2H), 2.89 (brs, 2H), 3.45-3.52 (m, 1H), 3.60-3.64 (m, 1H), 3.96-4.11 (m, 1H), 4.27-4.34 (m, 1H) ppm.
^{13}C NMR (50 MHz, $CDCl_3$): ^{13}C NMR ($CDCl_3$, 50MHz): δ -4.7, 13.9, 22.5, 24.3, 25.3, 25.7, 31.8, 31.9, 37.8, 39.0, 67.1, 68.8, 71.4 ppm.

Analysis: Calcd.: C, 62.01; H, 11.80; **Found:** C, 62.06; H, 11.83.

***(3S,5R)*-Dihydroxydecanenitrile (9)**



NaCN (0.2697g, 5.5mmol) was suspended in 3.0 mL of ice-cold ethanol and trifluoroacetic acid (0.2725 mL, 3.6 mmol) was added slowly, followed by compound **57** (0.5 g, 1.8 mmol). The flask was hermetically sealed and heated to 50 ^{o}C for 14 hrs. The solution was cooled, concentrated and triturated with 20 mL of ether and 10 mL of brine. Extraction of the aqueous phase with ether (3× 20 mL), drying over Na_2SO_4 and evaporation of ether was followed by purification by silica gel column chromatography eluting with light petroleum: EtOAc (10:3) to give **9** as a pale yellow liquid.

Yield: 0.3g, (90 %)

Mol. Formula: $C_{10}H_{19}NO_2$

$[\alpha]_D^{25}$: +8.1 (*c* 0.25, $CHCl_3$)

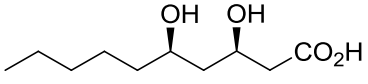
IR ($CHCl_3$, cm^{-1}): ν_{max} 3436, 3290, 2923, 2250, 1645, 1456, 1080 ppm.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85-0.92 (m, 3H), 1.24-1.46 (m, 8H), 1.59-1.78 (m, 2H), 2.51-2.54 (d, *J*= 5.7 Hz, 2H), 3.34 (brs, 2H), 3.38-3.91 (d, *J*= 5.8 Hz, 1H), 4.15-4.18 (d, *J*= 5.7 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.7, 22.3, 23.8, 25.7, 32.5, 38.0, 43.1, 67.2, 69.0, 117.7 ppm.

Analysis: Calcd.: C, 64.83; H, 10.34; N, 7.56; **Found:** C, 64.81; H, 10.37; N, 7.57.

***(3R,5R)-3,5*-Dihydroxydecanoic acid (10)**



1mL of 25% aqueous NaOH is added to the solution of **9** (0.25g, 1.3 mmol) in 4 mL MeOH and mixture was refluxed for 8 hours. The reaction mixture was poured into ice-water, and the pH was adjusted to 5 with 1 N HCl. The aqueous layer was extracted with ethyl acetate (25 mL). The organic layer was washed with water, dried (Na_2SO_4). The solvent was removed under reduced pressure to give **10** as a colourless semisolid.

Yield: 0.21 g, (78%)

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

$[\alpha]_D^{25}$: +14.1 (*c* 0.2, $CHCl_3$)

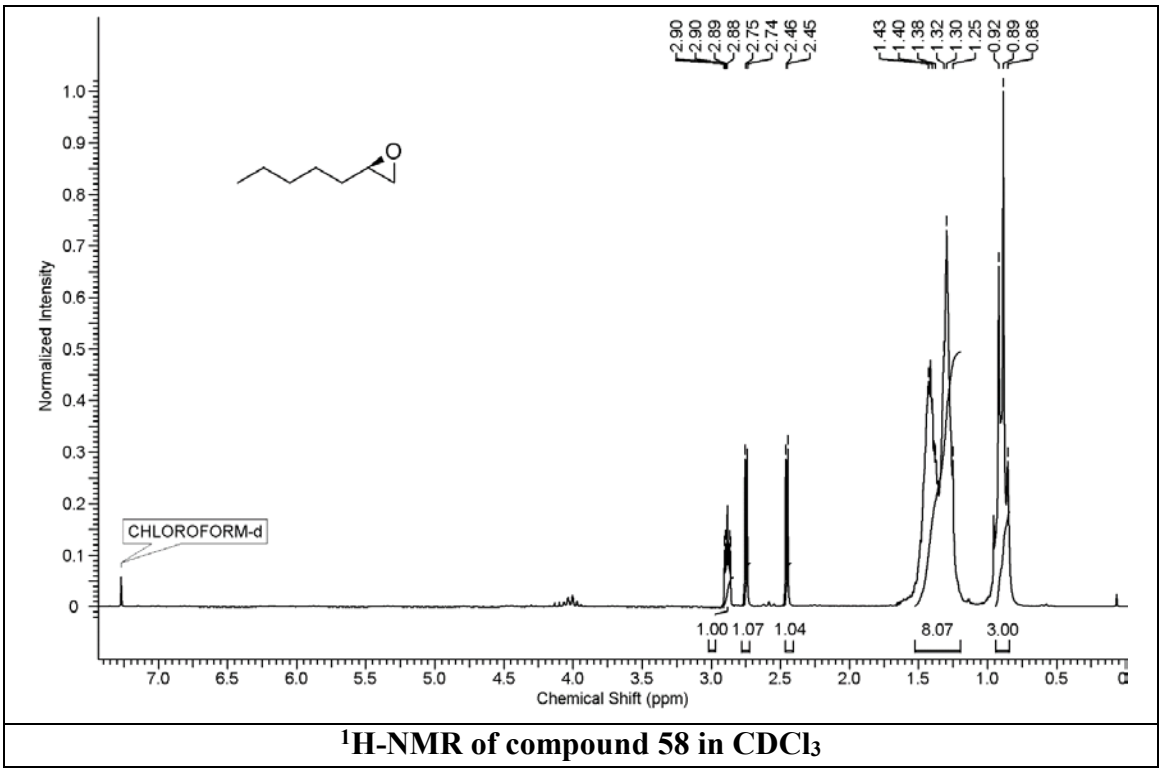
IR ($CHCl_3$, cm^{-1}): ν_{max} 3371, 3031, 2107, 1713, 1071 ppm.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85-0.91 (t, *J*= 6.01 Hz, 3H), 1.28-1.46 (m, 8H), 1.59-1.78 (m, 2H), 2.11-2.32 (m, 1H), 2.41-2.51 (m, 1H), 2.91 (brs, 2H), 3.19-3.27 (m, 1H), 3.29-3.54 (m, 1H), 10.89 (brs, 1H) ppm.

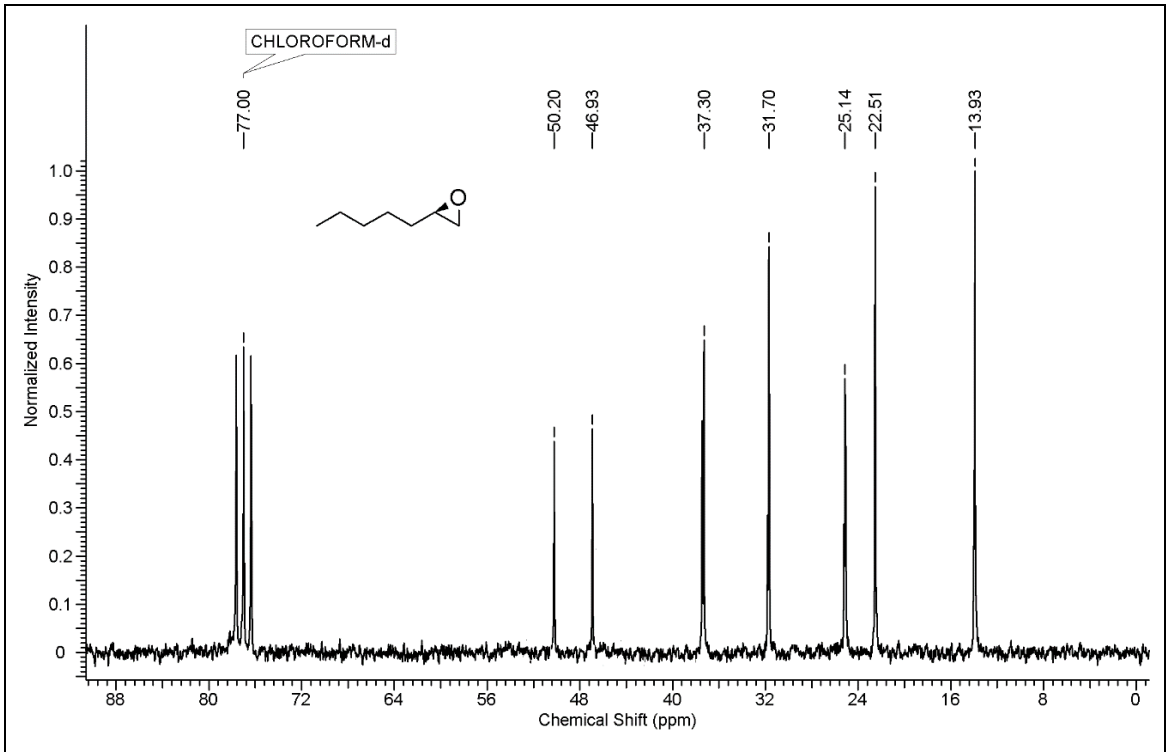
^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 22.5, 23.2, 31.9, 41.9, 44.8, 65.9, 69.2, 176.4 ppm.

Analysis: Calcd.: C, 58.80; H, 9.87; **Found:** C, 58.83; H, 9.86.

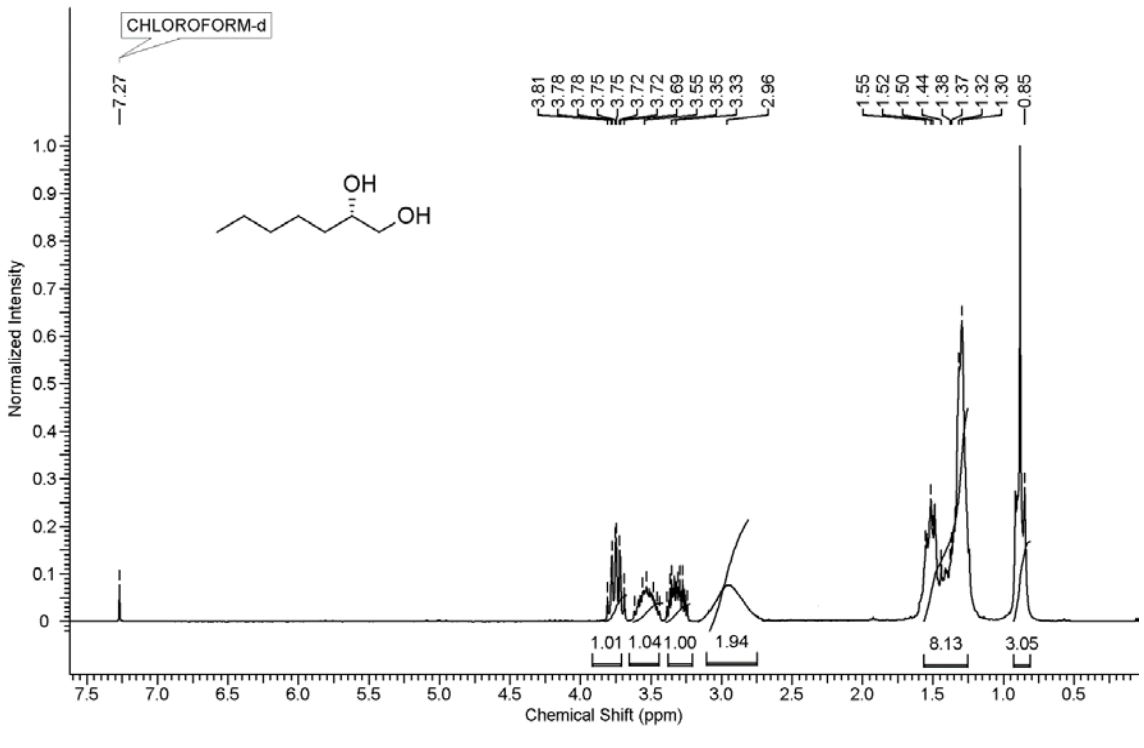
3.3.5. Spectra



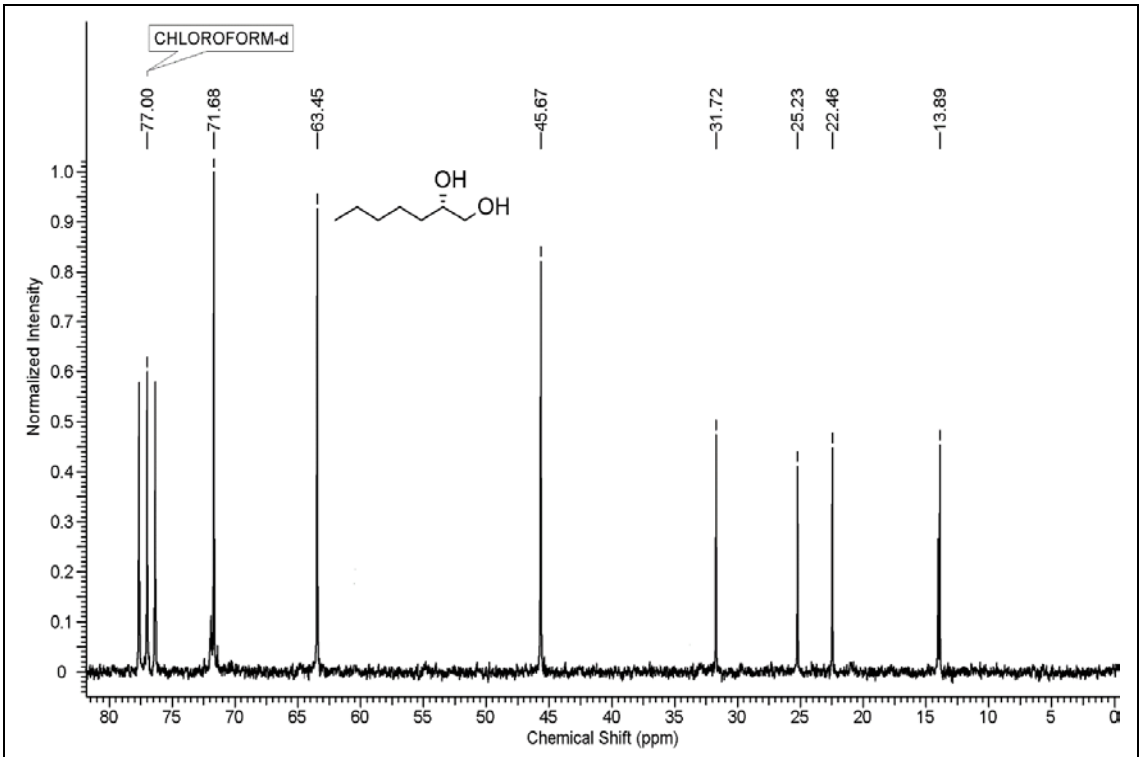
^{1}H-NMR of compound 58 in $CDCl_3$



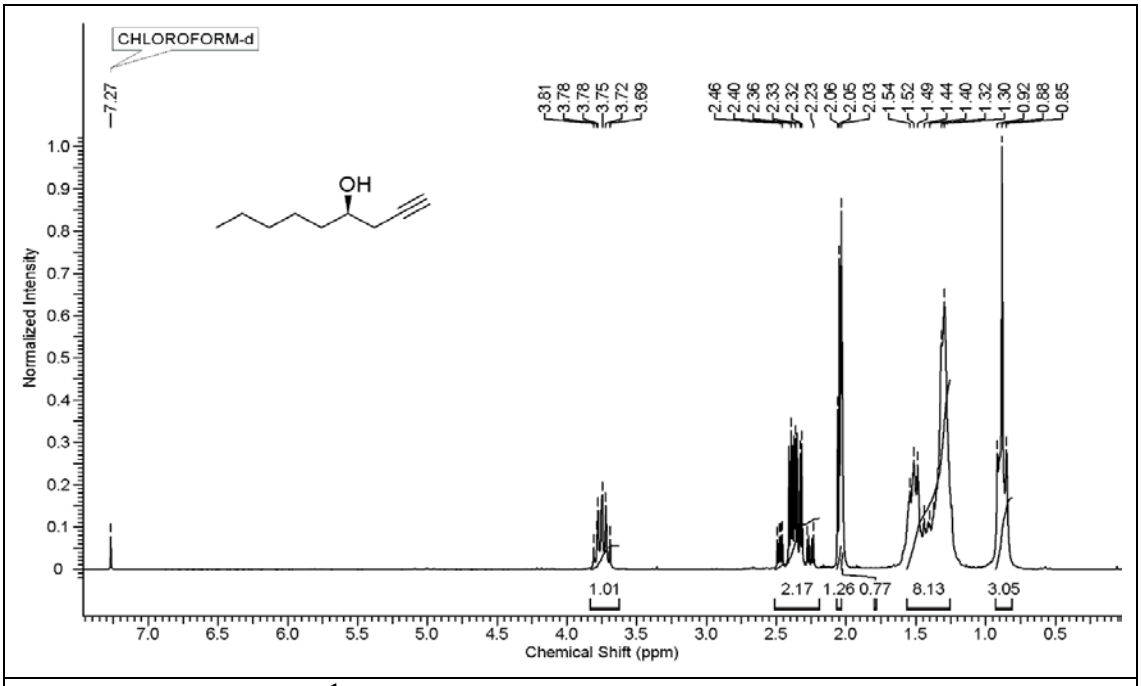
^{13}C-NMR of compound 58 in $CDCl_3$



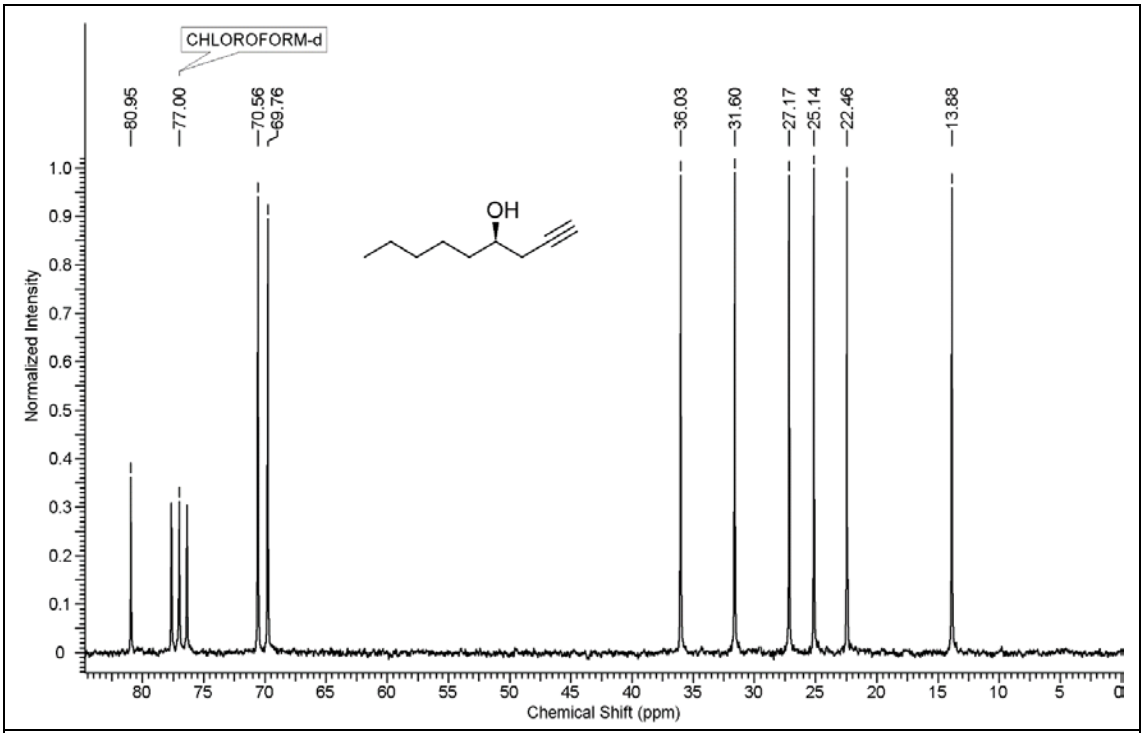
^{1}H-NMR of compound 62 in $CDCl_3$



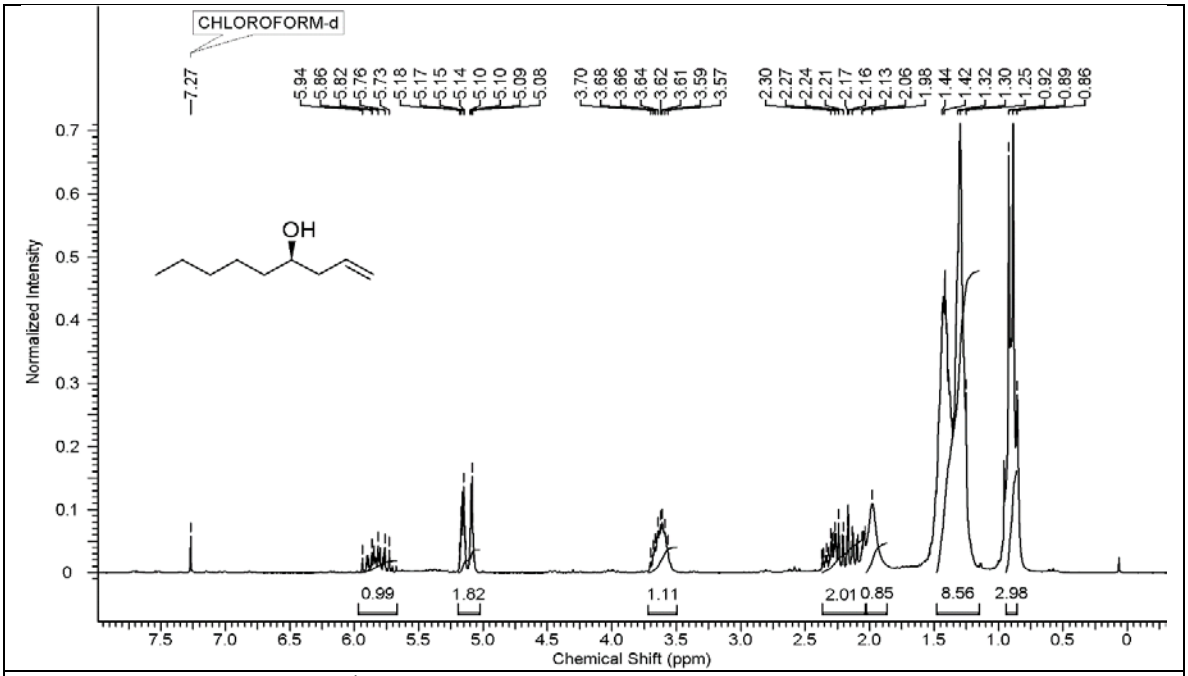
^{13}C-NMR of compound 62 in $CDCl_3$



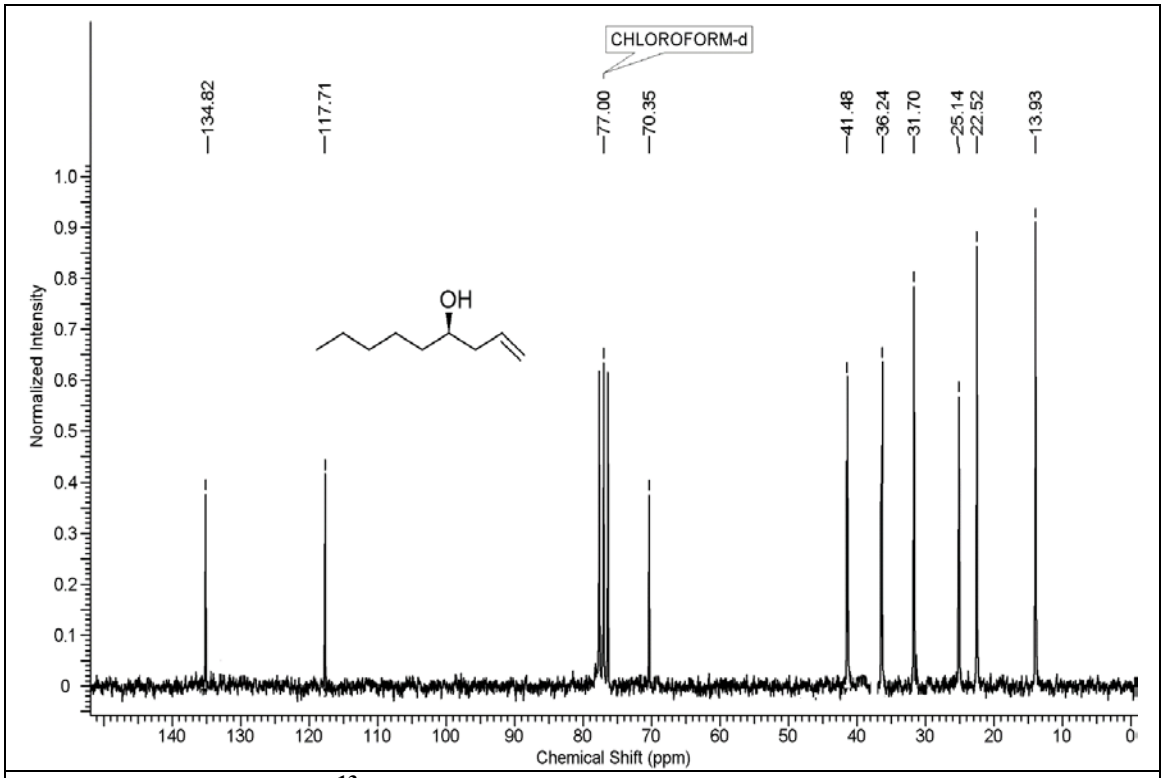
^{1}H-NMR of compound 63 in $CDCl_3$



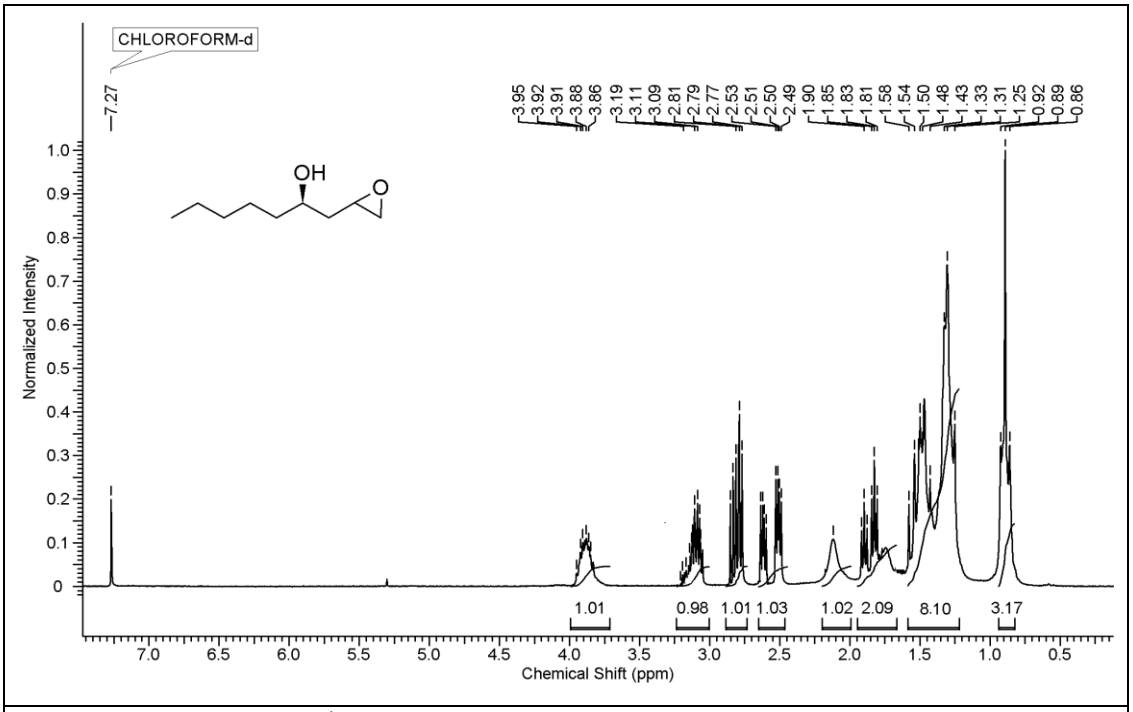
^{13}C-NMR of compound 63 in $CDCl_3$



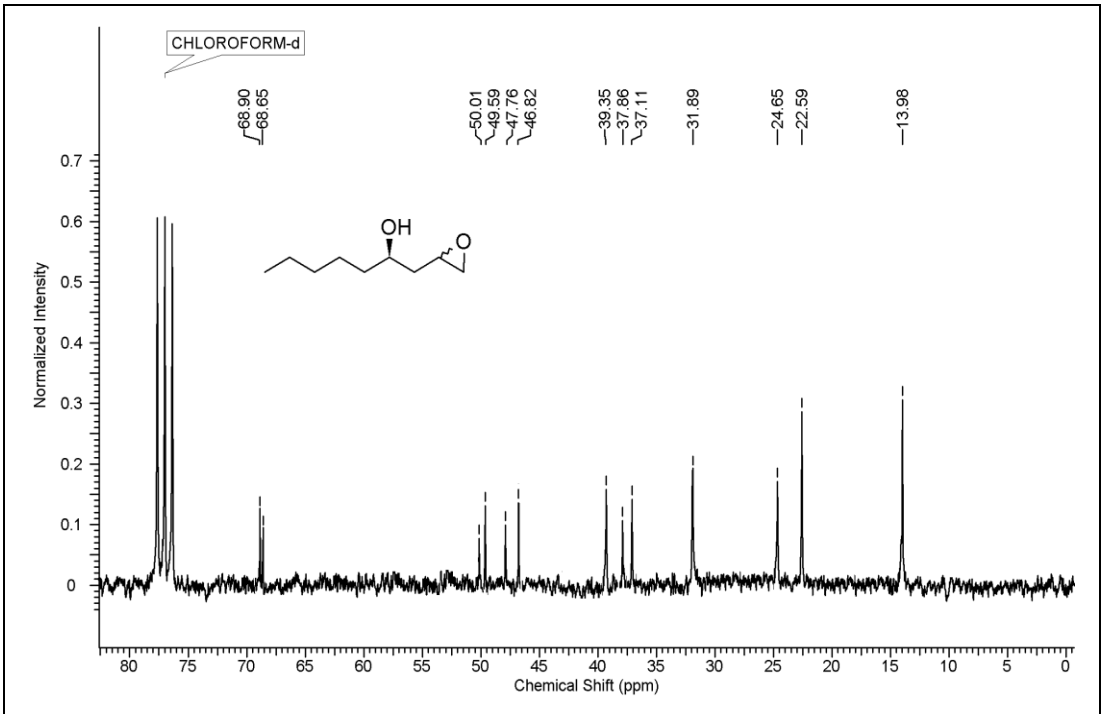
^{1}H-NMR of compound 64 in $CDCl_3$



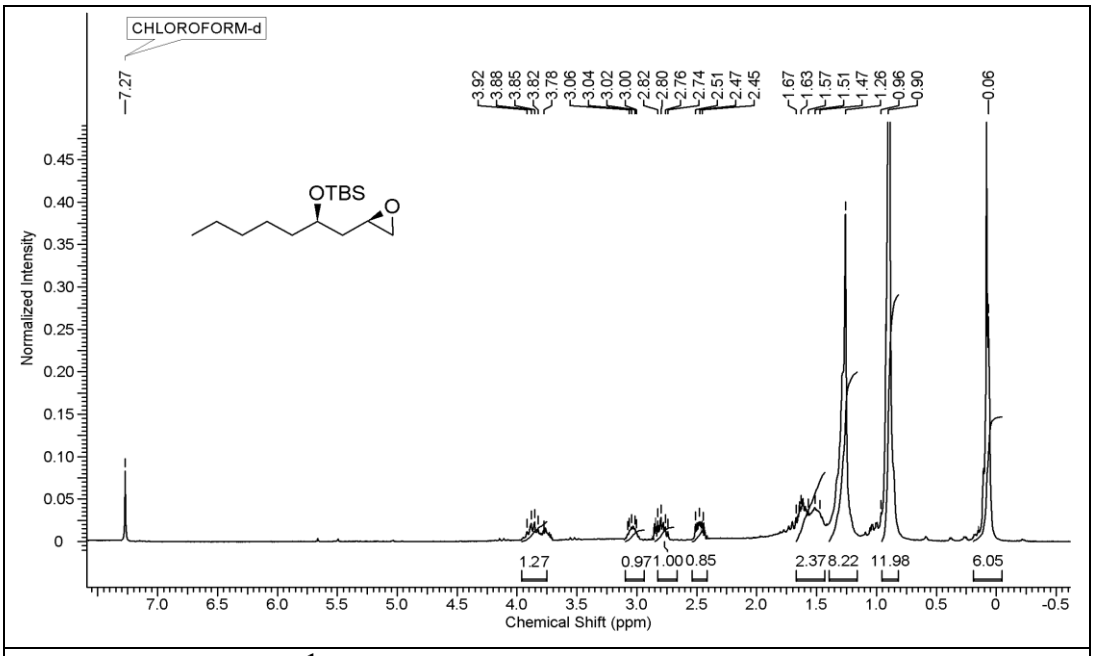
^{13}C-NMR of compound 64 in $CDCl_3$



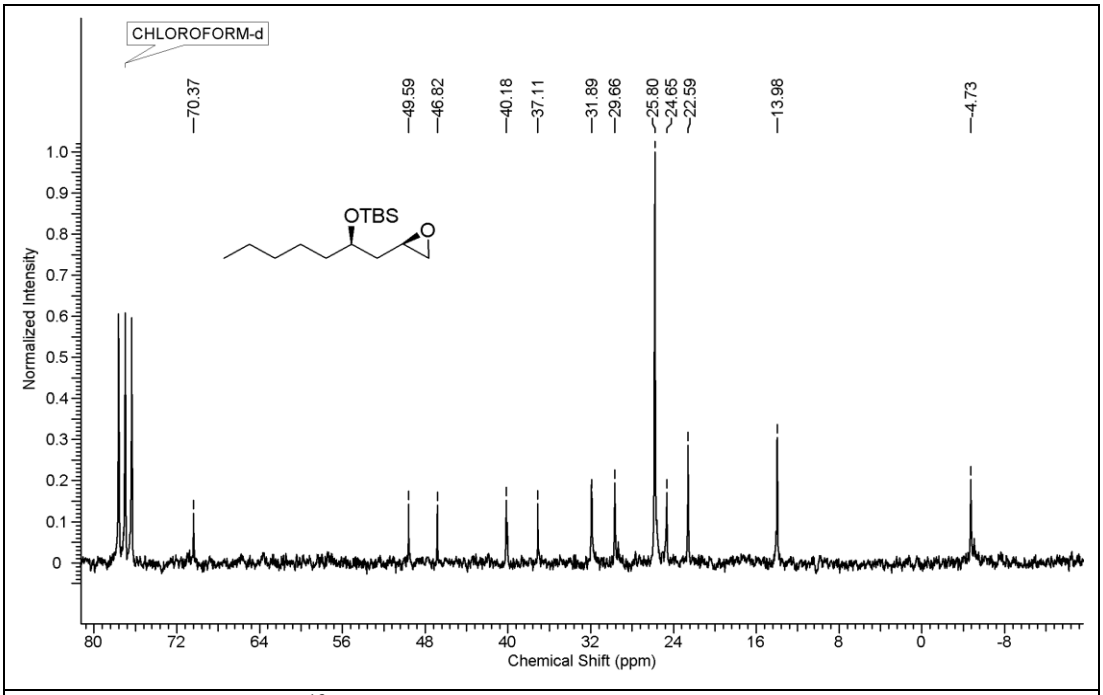
^{1}H-NMR of compound 65 in $CDCl_3$



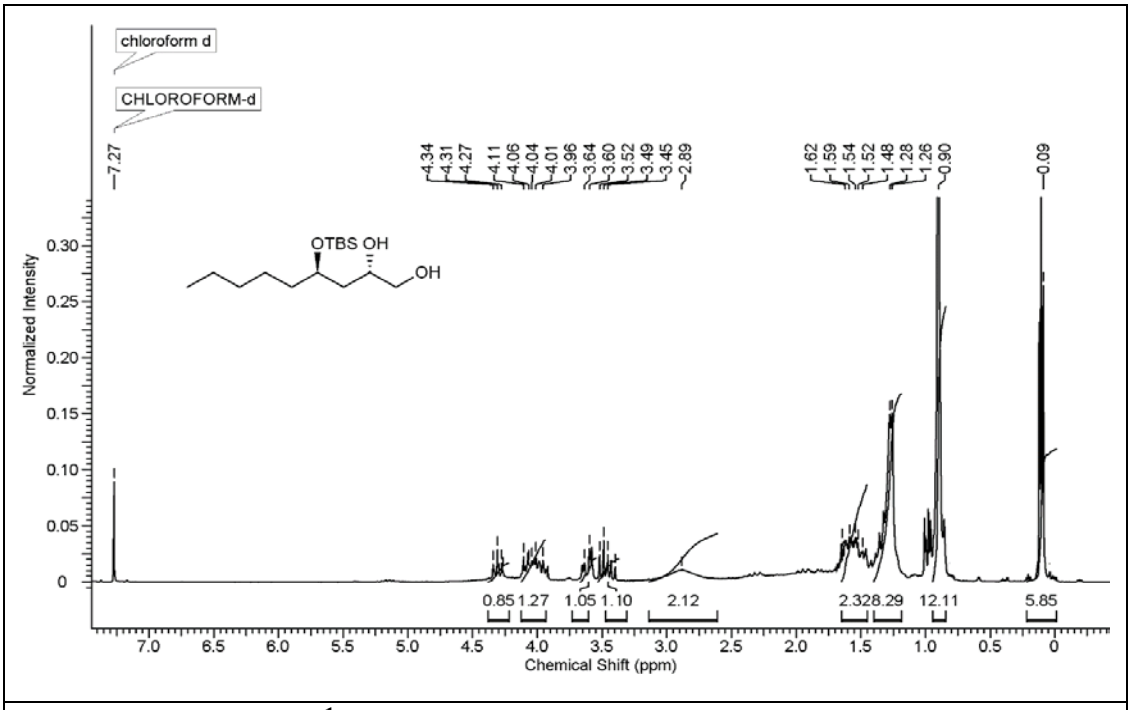
^{13}C-NMR of compound 65 in $CDCl_3$



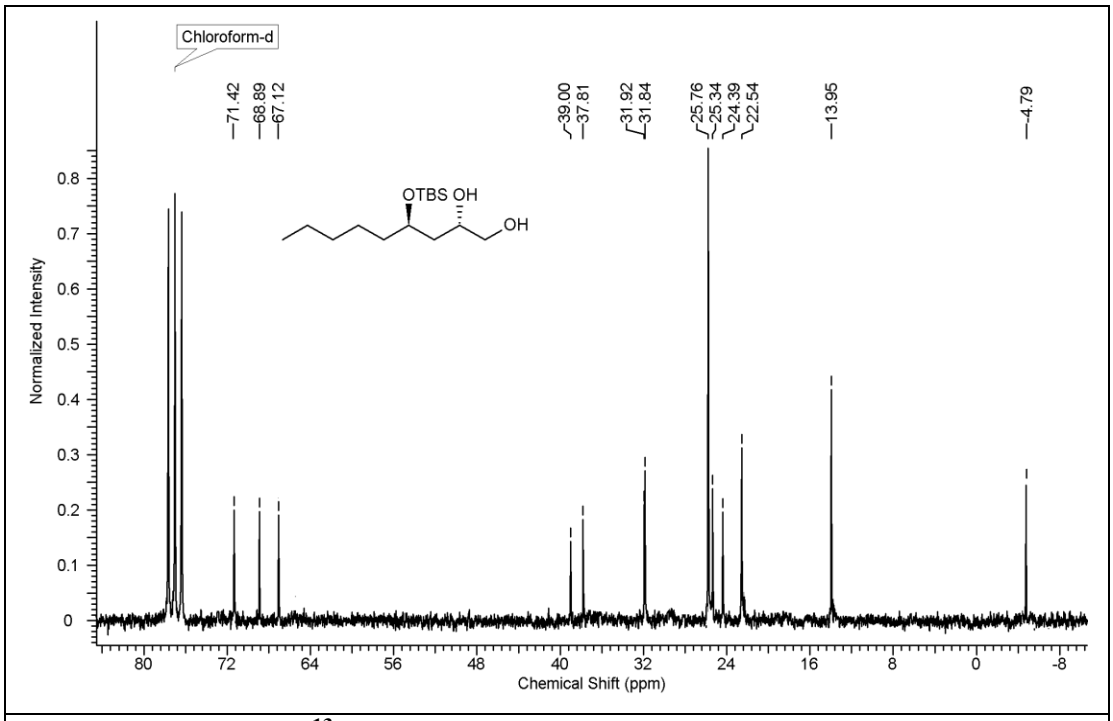
^{1}H-NMR of compound 57 in $CDCl_3$



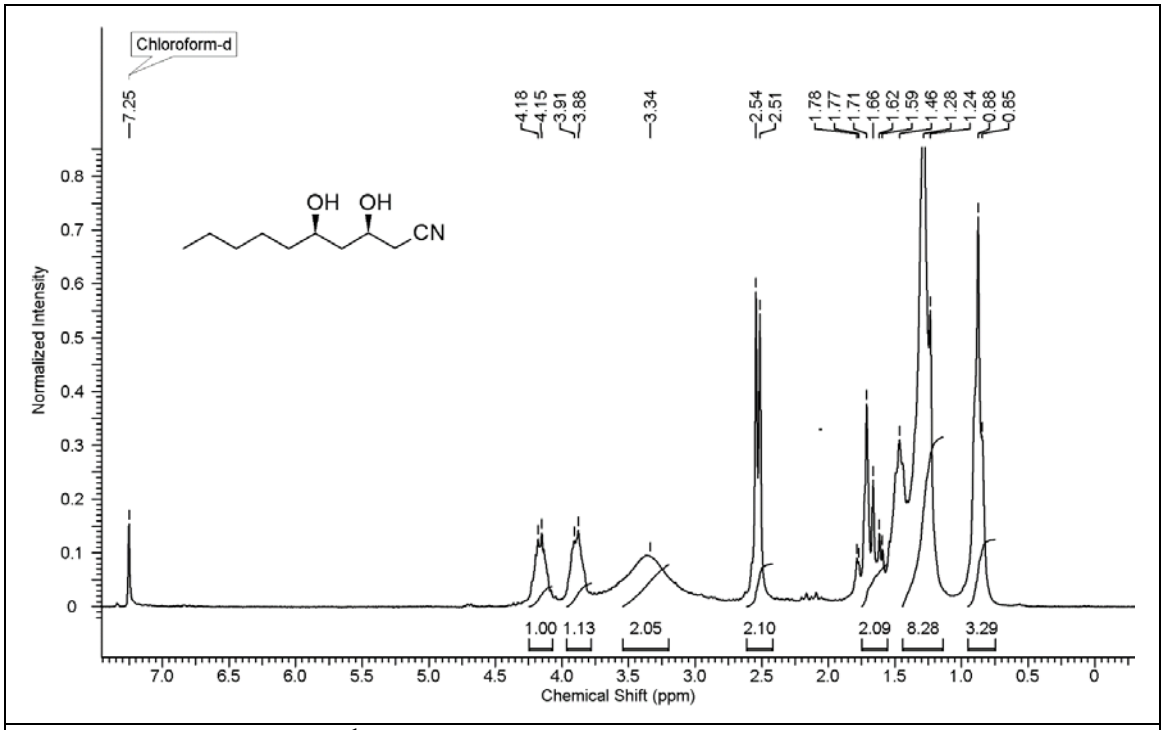
^{13}C-NMR of compound 57 in $CDCl_3$



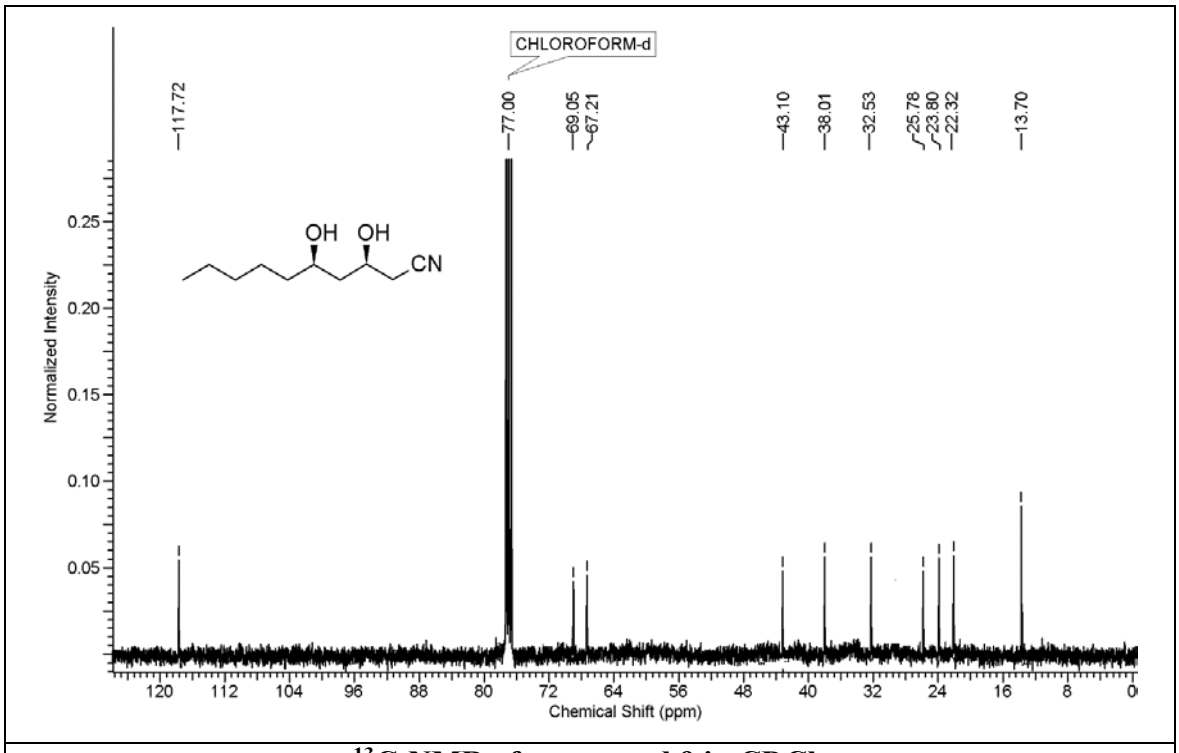
^{1}H-NMR of compound 67 in $CDCl_3$



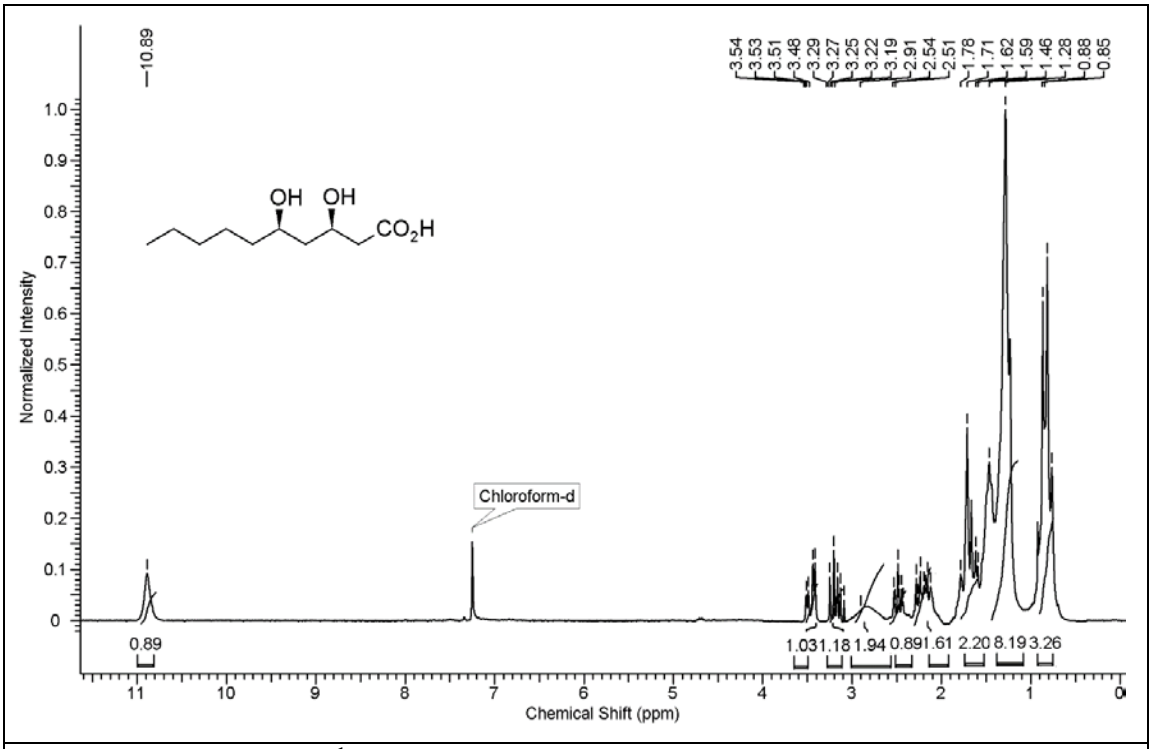
^{13}C-NMR of compound 67 in $CDCl_3$



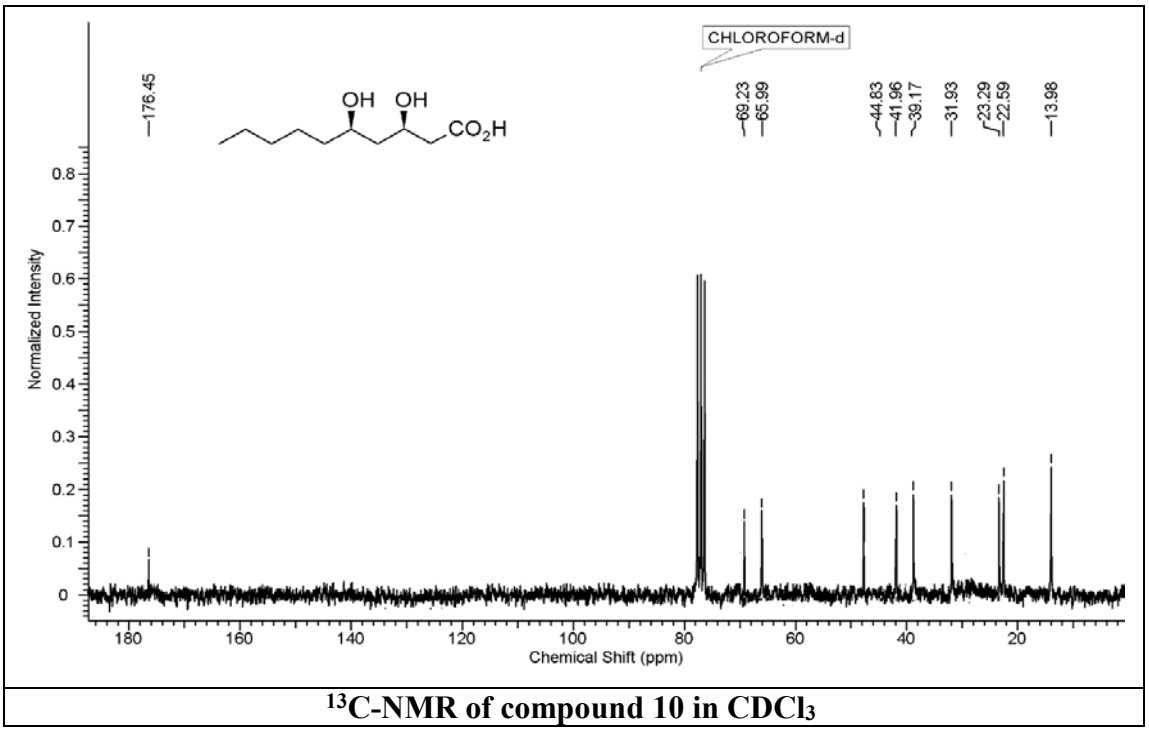
^{1}H-NMR of compound 9 in $CDCl_3$



^{13}C-NMR of compound 9 in $CDCl_3$



^{1}H-NMR of compound 10 in $CDCl_3$



^{13}C-NMR of compound 10 in $CDCl_3$

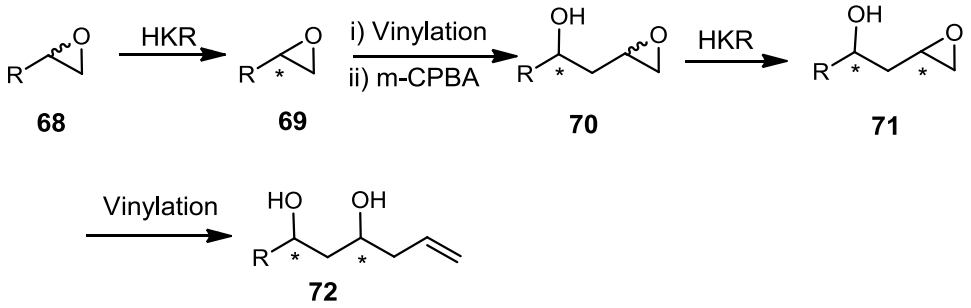
3.4. SECTION B:

A Revised Strategy for the synthesis of chiral epoxyalcohol, a precursor of verbalactone by combination of diastereoselective iodine induced electrophilic cyclization and hydrolytic kinetic resolution

3.4.1. Present work

Objective

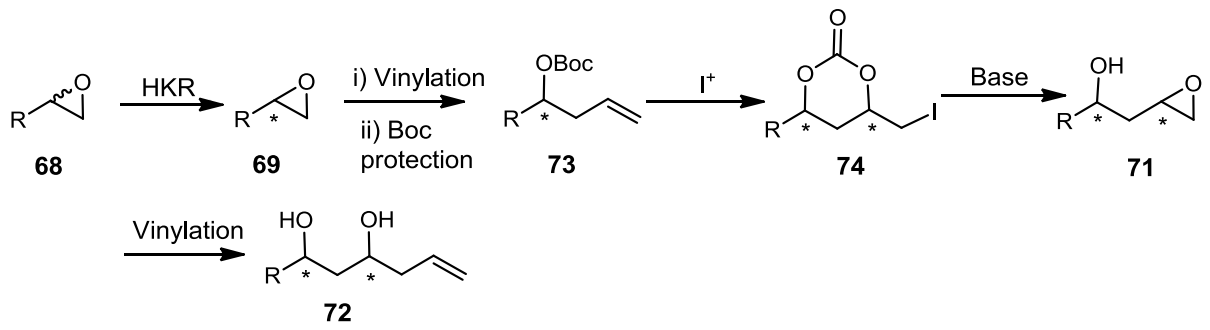
Optically active *syn*- and *anti*-1,3-polyols are ubiquitous structural motifs in various biologically active compounds.[11] Fascinated by their broad range of biological activity and structural diversity in compounds ranging from simple carbohydrate to complex alkaloid and polyketides, synthetic chemists continue to pursue their synthesis and the development of new methodologies.[12] In previous section we have discussed a general synthetic strategy developed in our group for the construction of *syn*/*anti*-1,3-polyol systems using iterative HKR (Scheme 13).[22h] This general and flexible synthetic strategy was subsequently utilized in the synthesis of natural products with a broad range of biological activity.[22b]



Scheme 13: Iterative HKR strategy to the synthesis of 1,3-polyols

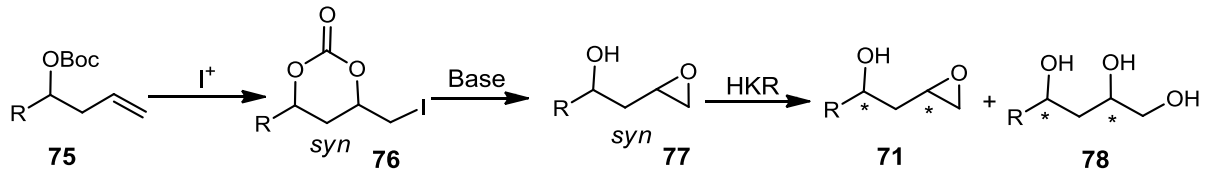
In last section we have discussed a practical and enantioselective synthesis of verbalactone **1** and its monomer **2** using iterative hydrolytic kinetic resolution as the key step (Scheme 8). Even though the previous synthetic strategy was simple, straight forward and used easily accessible reagents, we encountered some difficulties. Many of the initial intermediates were highly volatile. Usage of sodium cyanide for the opening of epoxides and its hydrolysis at higher pH was heedful. Iterative kinetic resolution steps caused huge material losses and persuaded with additional steps to recover the material back.

With this aspects in mind, we considered a modified protocol for the *syn*-1,3-polyol system which is based on a sequence using iodine-induced diastereoselective electrophilic cyclization of the Boc protected homoallylic alcohol which led to the *syn*-epoxy alcohol **71**.[22h] This modified protocol avoids the iterative usage of HKR (Scheme 14).



Scheme 14: Combination of HKR and diastereoselective iodocyclization strategy to the synthesis of 1,3-polyols

Based on above strategy, we envisioned an alternative approach to chiral 1,3-diol synthesis that utilizes kinetic resolution of racemic *syn*-2-hydroxy-1-oxirane derivatives. In this strategy, the relative stereochemistry between the alcohol and the epoxide groups is established prior to the HKR step and in this way a single asymmetric reaction can be used to form the key enantiomerically pure 2-hydroxy-1-oxirane intermediates.[29] (Scheme 15)

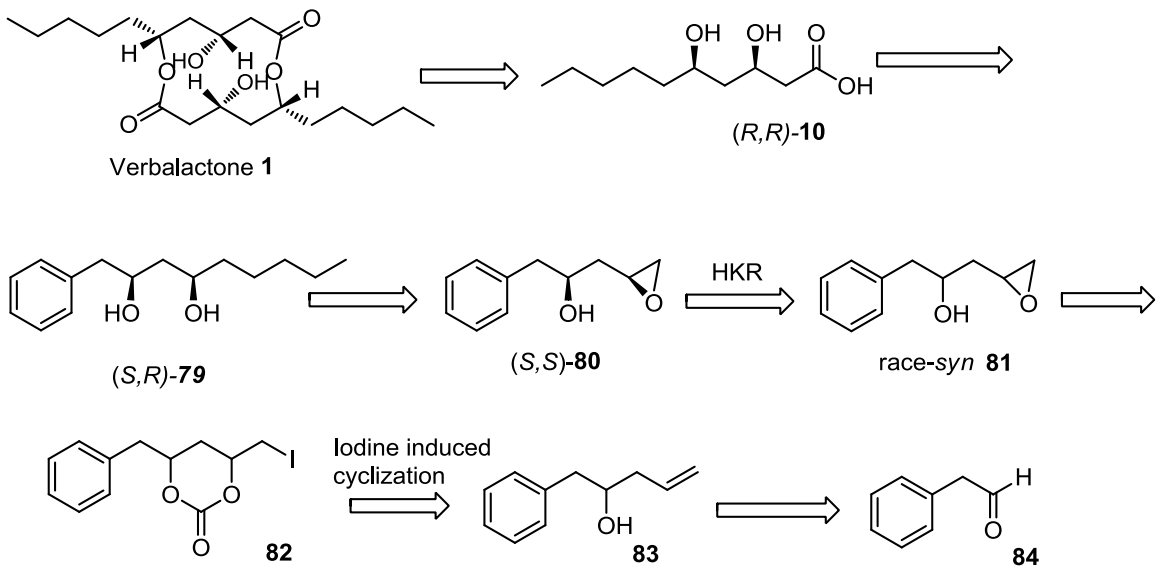


Scheme 15: Reversed HKR and diastereoselective iodocyclization strategy to the synthesis of 1,3-polyols.

Retrosynthetic Analysis of Verbalactone 1

Our new approach to the synthesis of verbalactone **1** as delineated in Scheme 16 indicated that verbalactone **1** could be constructed by exploiting Yamaguchi's macrolactonization of key monomer seco acid, (3*R*,5*R*)-3,5-dihydroxy decanoic acid **10** which could be accomplished by the *n*-butyl Grignard opening of epoxide **80** and aryl ring oxidation of

resulted diol **79**. The HKR of *syn*-racemic epoxide **81** which could be prepared from iodine induced electrophilic cyclization of racemic homoallylic alcohol **83**, might give enantiomeric pure *syn*-epoxide **80**. The racemic homoallylic alcohol **83** could easily be synthesised from phenyl acetaldehyde **84**.



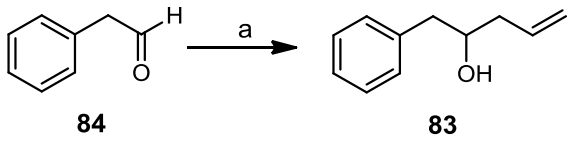
Scheme 16: New retrosynthetic Analysis of Verbalactone **1**

3.4.2. Results and Discussion

We initiated synthesis from Barbier-type allylation of phenyl acetaldehyde **84** (Scheme 17). The combined reaction of an aldehyde or ketone, alkyl halide (preferably allyl or propargyl halide) and appropriate metal in suitable solvent system is known as Barbier reaction.[30] The generation of organometallic reagent is *in situ* unlike Grignard reaction where initial generation of organometallic reagent is compulsory. In this procedure all three components; the allyl halide, the aldehyde/ketone and the metal are mixed together and allowed to react. Mg was used as metal in original Barbier reaction, but thereafter many more metals such as Zn, Sn, In, Pb, Fe, etc. were found applicable with promising results.

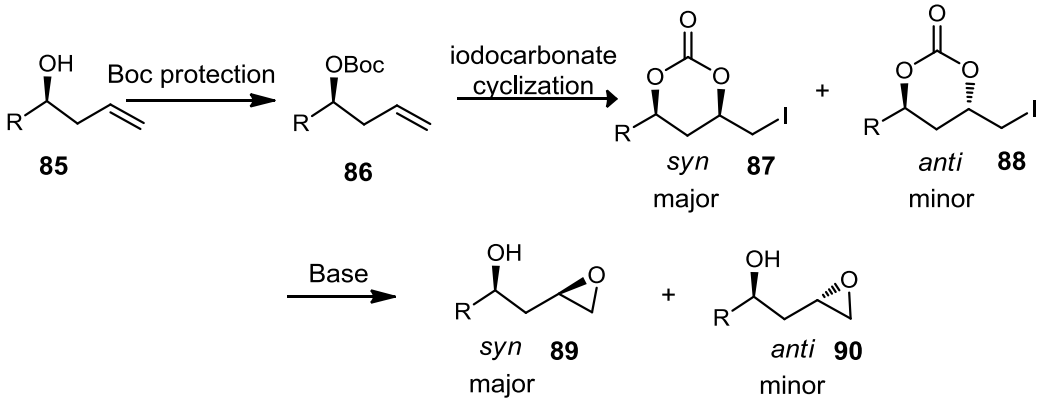
The use of aqueous media for Barbier-type reaction offers considerable advantages such as practical convenience of not having to handle inflammable and anhydrous organic solvents, the tedious deprotection-protection processes for certain acidic hydrogen containing functional groups and its easy work up. The replacement of water by saturated aq. NH_4Cl solution enhanced the efficiency of reactions.[31] The Barbier-type reaction of **84** was carried

out with allyl bromide in presence of Zn in a mixture of THF and saturated aq. NH_4Cl solution (2:1) at 0 °C to rt[32]. Gratifyingly, this reaction afforded the alcohol **83** in an excellent yield of 82% (Scheme 17).[25] The appearance of olefinic protons in the range of δ 5.17-5.24 (m, 2H) and 5.85-5.96 (m, 1H) ppm as multiplet confirmed the formation of the product. The ^{13}C NMR spectrum of **83** showed olefinic carbons at δ 118.0 and 134.6 ppm.



Scheme 17: *Reagents and conditions*: (a) AllylBr, Zn, THF: NH_4Cl (2:1), 0 °C to rt, 3 h, 82%.

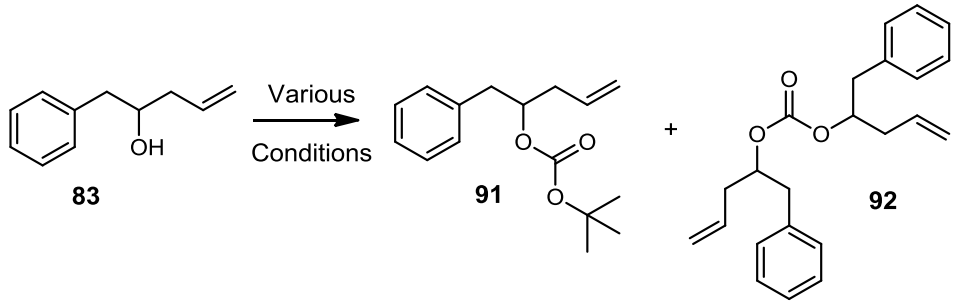
With homoallylic alcohol **83** in hand, our next aim was to construct the *syn*-1,3-diol. Whereas the stereoselective epoxidation of allytic alcohols has become a cornerstone of modern synthetic methodo1ogy[33], the analogous transformation of homoallylic substrates remains generally unsatisfactory.[34] The iodine-induced electrophilic cyclization of homoallylic *t*-butyl carbonates was introduced as an effective alternative in the early 1980s.[35] As illustrated in Scheme 18, the resultant six-membered iodocarbonates **87** and **88** are versatile intermediates which readily furnish epoxy alcohols[35a] **89** and **90**. To establish the second stereogenic center with an excellent level of diastereoselectivity, we decided to apply this three-step sequence. (Scheme 18)



Scheme 18: The iodine-induced electrophilic cyclization of homoallylic *t*-butyl carbonates

Following this methodology, the homoallylic *tert*-butyl carbonate **91** has to be prepared from the corresponding alcohol **83** (Scheme 19). $(Boc)_2O$ is widely applied to introduce the *tert*-butoxycarbonyl (Boc) protecting group.[36]Usually alcohols do not react with $(Boc)_2O$

even in the presence of a base like Et_3N. The addition of a catalytic amount (0.1-0.4 equiv.) of DMAP led to immediate reaction of alcohols.[37] The reaction of homoallylic alcohol **83** in MeCN at room temperature with $(Boc)_2O$ (1.1 equiv.)/DMAP (0.4 equiv.) gave the *O*-Boc derivative **91** with an unexpected symmetrical carbonate **92** in ratio of 1:1 (Table 1, entry 1). The IR spectrum of **91** showed absence of hydroxyl group, Boc carbonyl appeared at 1740 cm^{-1}. ^{13}C NMR spectra showed the Boc-carbonyl at δ 153.2 and *t*-butyl carbon at δ 81.8 and three methyl carbons at δ 27.8 ppm. Compound **92** lacks these *t*-butyl carbon peaks, but have Boc-carbonyl at δ 159.9 ppm.



Scheme 19: Preparation of homoallylic *tert*-butyl carbonate

Entry	Reaction conditions	Total Yield 91 and 92	Ratio of 91: 92
1	$(Boc)_2O$ (1.1 equiv.), DMAP (0.4 equiv.), MeCN, rt, 5h.	70%	50:50
2	$(Boc)_2O$ (2 equiv.), DMAP (0.4 equiv.), MeCN, rt, 5h.	79%	55:45
3	$(Boc)_2O$ (1.2 equiv.), DMAP (0.1 equiv.), MeCN, rt, 12h.	55%	55:45
4	$(Boc)_2O$ (1.2 equiv.), DMAP (1 equiv.), MeCN, rt, 1h.	85%	35:65
5	$(Boc)_2O$ (1.2 equiv.), DMAP (0.4 equiv.), MeCN, 0 ^oC, 18h.	35%	50: 50

Table 1. *O*-Boc protection of **83** by $(Boc)_2O$ in MeCN under various reaction conditions.

An excess of $(Boc)_2O$ (1.2-2 equiv.) was used in order to ascertain that formation of the symmetric carbonates is not the result of lack of $(Boc)_2O$. The ratio of products **91** and **92** was not influenced by the amount of $(Boc)_2O$ (Table 1, entry 2). Similarly, the amount of

DMAP (0.1-0.4 equiv.) also did not affect the ratio of **91** and **92** in MeCN (Table 1, entry 3). Adding more equivalent of DMAP (0.5-1 equiv.) increased the rate of the reaction as well as formation of side product **92** (Table 1, entry 4). Lowering of temperature even up to 0 ^{o}C was found to decrease the reaction rate drastically (Table 1, entry 5).

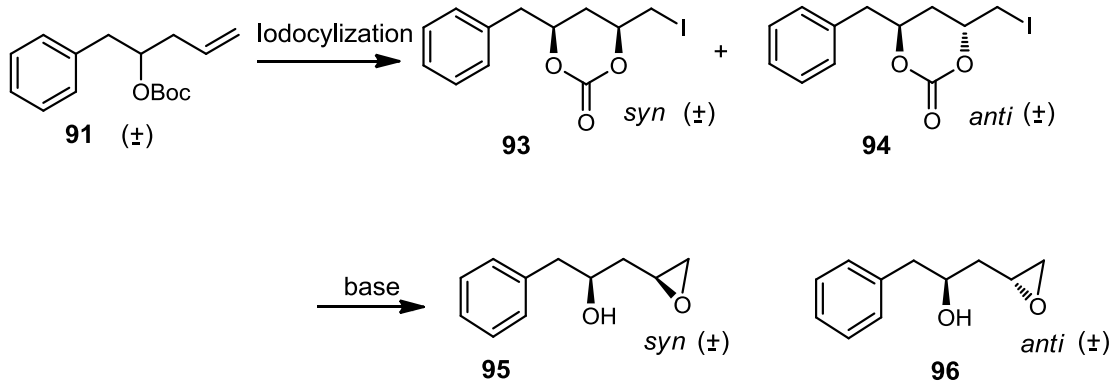
We tried this reaction in different solvents like DCM, chloroform, THF, 1,4-dioxane (polar solvents) toluene, cyclohexane and CCl_4 (non-polar solvents) for improving the yield of *O*-Boc product (Table 2). The use of non-polar solvents improved the rate as well as selectivity of the reaction. This may reflect a preferred solubility of the *O*-Boc product compared to the alcohol in nonpolar solvent.[38] Among choice of non-polar solvents, CCl_4 is found to be the best solvent for Boc protection of hydroxyl group at room temperature compared to toluene, cyclohexane etc (Table 2, entry 3). The amount of *O*-Boc product was improved from 50:50 ratio of **91**:**92** to 90:10 in CCl_4 at room temperature. Even though lowering the concentration of DMAP decreased the rate of the reaction, we limited DMAP to 0.1 equivalents to increase the selectivity. Addition of 1 equivalent of Et_3N to the reaction mixture helped to improve the rate of the reaction (Table 2, entry 4). All this precautions led us to attain more than 80% yield of required *O*-Boc product **91**.

Entry	Reaction conditions	Total Yield 91 and 92	Ratio of 91: 92
1	$(Boc)_2O$ (1.2 equiv.), DMAP (0.4 equiv.), 1,4-dioxane , rt, 5h.	65%	50:50
2	$(Boc)_2O$ (1.2 equiv.), DMAP (0.4 equiv.), Toluene , rt, 5h.	80%	75:25
3	$(Boc)_2O$ (1.2 equiv.), DMAP (0.4 equiv.), CCl_4, rt, 12h.	84%	85:15
4	$(Boc)_2O$ (1.2 equiv.), DMAP (0.1 equiv.), Et_3N (1 equiv.) CCl_4, rt, 6h.	90%	90:10
5	$(Boc)_2O$ (1.2 equiv.), MeIm (0.8 equiv.), Toluene, 0 ^{o}C, 5h.	80%	75:25

Table 2. *O*-Boc protection of **83** by $(Boc)_2O$ under various solvents.

The use of *N*-methylimidazole (MeIm) as catalyst instead of DMAP in above reaction conditions did not show any drastic improvements in selectivity (Table 2, entry 5). In some cases, isolation of new side products with imidazole moiety indicates that sometimes MeIm reacted not only as a catalyst but also as a reactant.[38]

With substantial amount of Boc protected homoallylic alcohol **91** in hand we then further proceeded to explore the stereoselective outcome of iodocyclization reaction in different reaction conditions (Scheme 20 and Table 3). First we carried out the Bartlett's original iodocyclization protocol[35a] reaction in a homogeneous acetonitrile solution of carbonate **91** at -20 ^{o}C for 6 h by adding 2.5 equivalent of I_2 dissolved in acetonitrile (Table 3, entry 1).

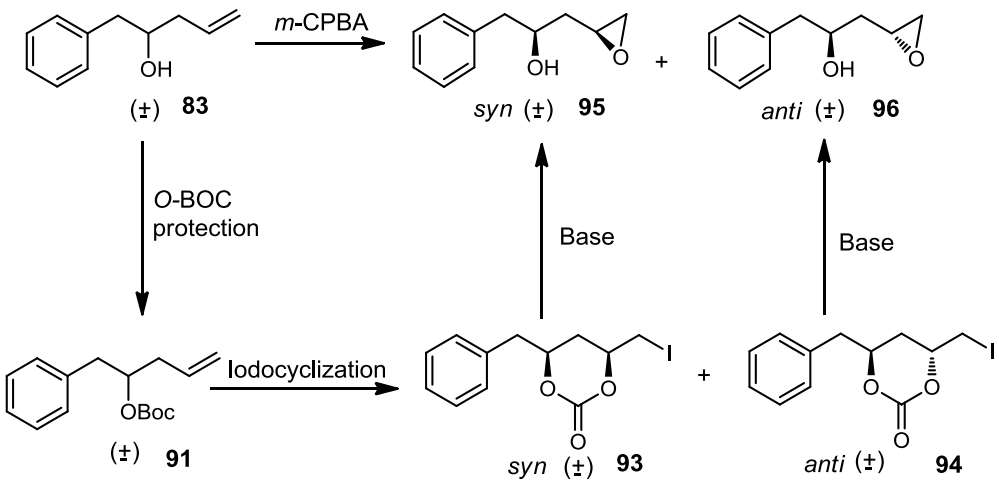


Scheme 20: The iodine-induced electrophilic cyclization of **91**

The cyclic iodo carbonates **93** and **94** were obtained in good yield. The stereostructures of cyclic iodo carbonates were established by conversion into the corresponding epoxy alcohols **95** and **96**. Cyclic iodo carbonates **93** and **94** were converted into the corresponding epoxy alcohols by treatment with 3 equiv. of K_2CO_3 in methanol at room temperature (Scheme 20). Reaction was completed after 2 h to furnish the desired *syn*-epimer **95** with 16:1 diastereoselectivity (Table 3, entry 1). The hydrolysis proceeds with retention of the stereostructure present in the starting iodo carbonate. The diastereomeric ratios of the epoxy alcohols recovered after hydrolysis always corresponded to the ratio of the iodo carbonate starting material.[39] The assigned stereochemistry of epoxy alcohol **95** was confirmed by comparison of ^{1}H NMR and ^{13}C NMR spectra with that of a known mixture obtained by epoxidation of the corresponding alcohol **83** with *m*-CPBA (Scheme 21).

Entry	Reaction conditions	Total Yield 95 and 96	Ratio of 95: 96
1	i) I_2, CH_3CN, -20 °C, 6 h ii) K_2CO_3, MeOH, rt, 2h,	68%;	16:1
2	i) NIS, CH_3CN, -40 °C to-0 °C , 20 h ii) K_2CO_3, MeOH, rt, 2h,	60%	8:1
3	i) IBr, CH_3CN, -20 °C, 15 min ii) K_2CO_3, MeOH, rt, 2h,	74%	12:1
4	i) IBr, CH_2Cl_2, -20 °C, 15 min ii) K_2CO_3, MeOH, rt, 2h	70%	14:1
5	i) IBr, CH_2Cl_2, -80 °C, to -85 °C 15 min ii) K_2CO_3, MeOH, rt, 2h	80%	16:1
6	i) IBr, Toluene, -80 °C, to -85 °C 4 h ii)K_2CO_3, MeOH, rt, 2h	85%	25:1
7	i) ICl, CH_2Cl_2, -80 °C, to -85 °C 30 min ii) K_2CO_3, MeOH, rt, 2h	77%	12:1

Table 3. The iodine-induced electrophilic cyclization of **91** under various conditions.



Scheme 21: Parallel synthesis of hydroxyl epoxides **95** and **96**

The ^{1}H NMR spectrum of mixtre **95** and **96** showed absence of olefin protons at δ 5.11-5.19 (m, 2H) and 5.75-5.96 (m, 1H). The diastereomeric epoxide peaks appeared at δ 2.54-2.56

(m, 1 H), 2.62-2.64 (m, 1/16 proton) and 3.13-3.18 (m, 1H), 3.20-3.24 (m, 1/16 proton) in ^{1}H NMR spectrum. In ^{13}C NMR spectrum, **95** showed upfield carbons of epoxide at δ 46.4, 50.2 and other stereocentre at δ 70.9 ppm. The anti-isomer **96**'s peaks appeared at δ 47.0 and 70.0 as a diastereomeric mixture in NMR (Figure 4). The *syn* isomer **95** was obtained as major component.

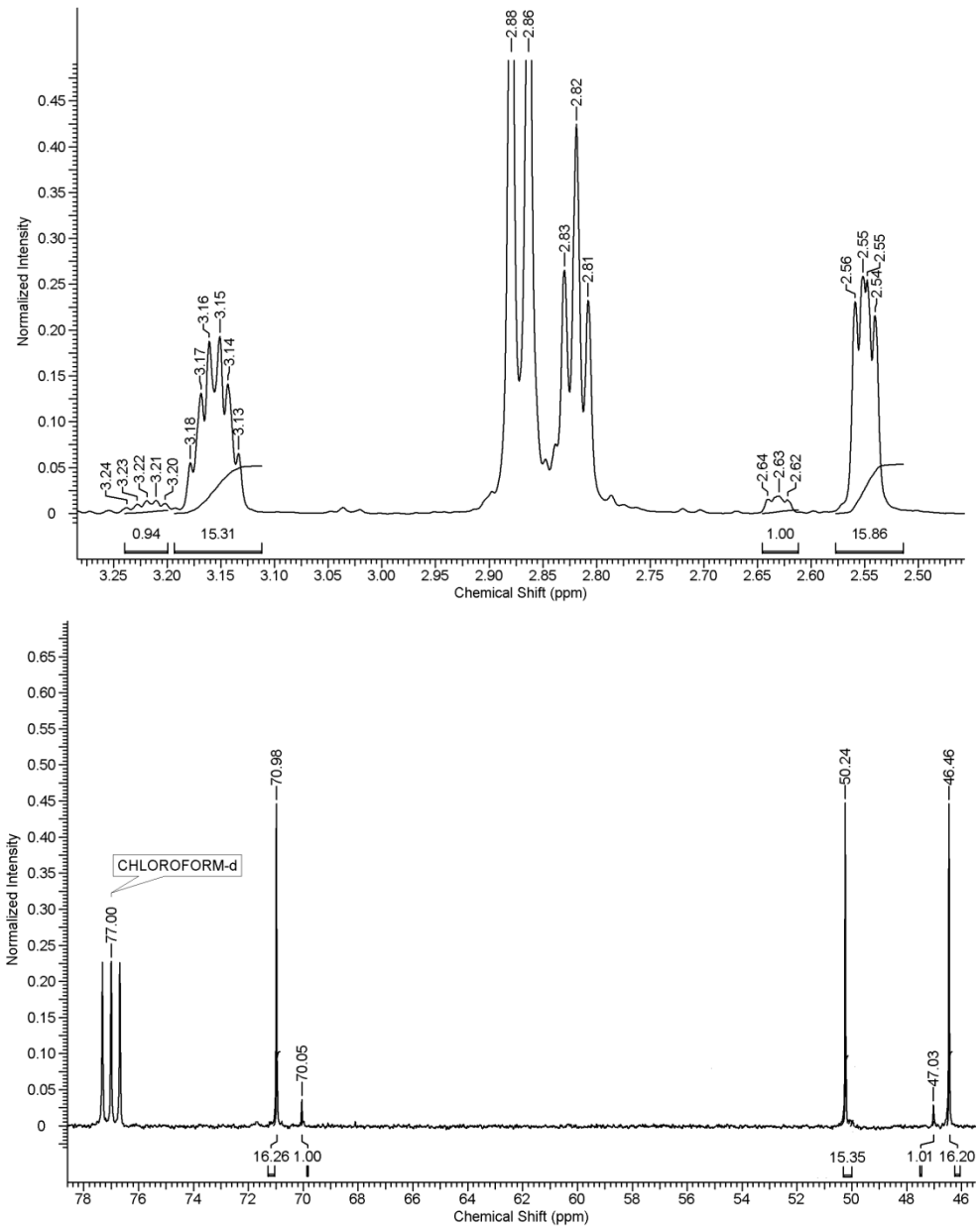


Figure 4: Partial ^{1}H NMR and ^{13}C NMR spectra of diastereomeric mixture **95** and **96** showing ratio 16:1 **(**Reaction condition table 3, entry 1)

We anticipated that the isomer ratio **95:96** could be improved by lowering the reaction temperature, but even at -20 ^{o}C the cyclization proceeded relatively slowly, suggesting that a more electrophilic reagent might be required. Next we carried out the diastereoselective

iodocyclization of *O*-Boc using *N*-iodosuccinimide[40] in CH_3CN at low temperature (-40 °C to 0 °C) followed by base induced hydrolysis in methanol to furnish the required epoxide **95** significantly lower in selectivity than Barlett's original conditions (Table 3, entry 2). It took 20 hours to complete the iodocyclization reaction and yielded 60% overall yield. This result sets the stage for investigation of new powerful electrophilic reagents, solvents and lower temperatures for improving *syn*-diastereoselectivity.

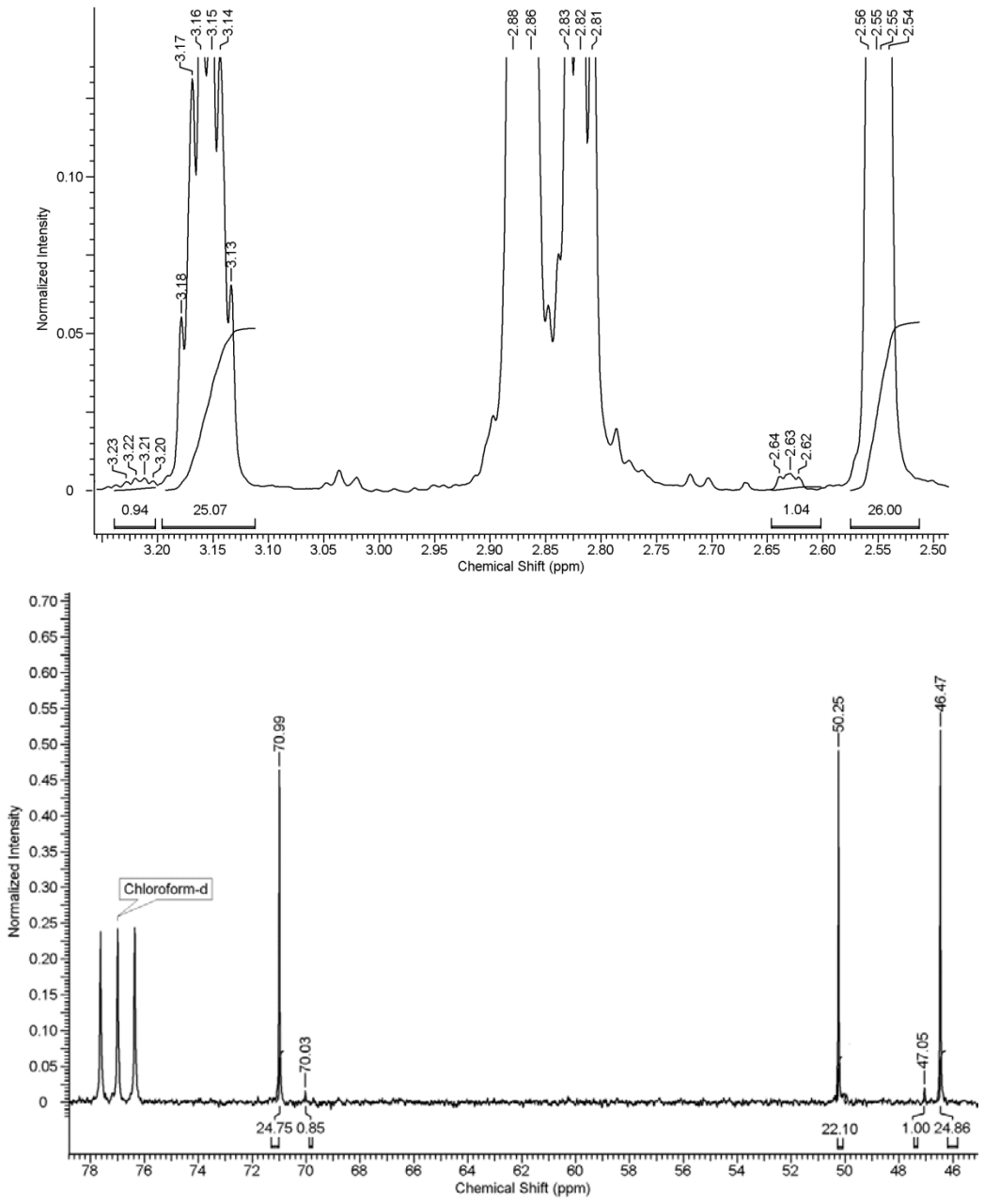
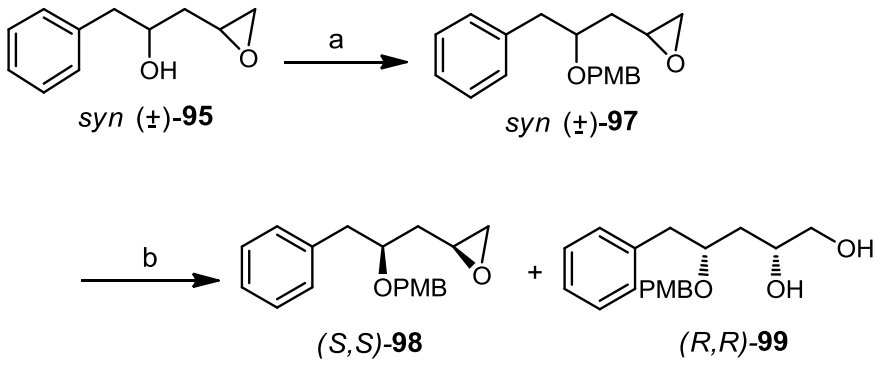


Figure 5: Partial ^{1}H NMR and ^{13}C NMR spectra of diastereomeric mixture **95** and **96** showing ratio 25:1 **(**Reaction condition table 3, entry 6)

Iodine monobromide and Iodine monochloride are potent electrophiles toward olefinic bonds than molecular iodine. [39] IBr is more soluble in CH_3CN and CH_2Cl_2 than nonpolar solvents. Although the IBr cyclizations in both CH_3CN and CH_2Cl_2 at -20 °C and in CH_2Cl_2 at -85 °C were less selective than the Bartlett method (Table 3, entry 3-5), IBr in toluene proved to be more selective (Table 3, entry 6) (figure 5).

The enhancement achieved with iodine monobromide in toluene at -80 to -85 °C thus derives from both temperature and solvent effects.[39]The modest toluene solubility of IBr at low temperature necessitated a 4 h reaction time for cyclization of **91**. Finally we noticed that iodine monochloride showed lower selectivity than IBr under similar conditons (Table 3, entry 7). In all cases diastereomeric ratio is determined by ^{1}H NMR and ^{13}C NMR analysis of crude epoxide mixtures with a known mixture[39] obtained by epoxidation of the corresponding alcohol **83** with *m*-CPBA (Scheme 21).

With syn-racemic epoxide **95** in hand, our next aim was to synthesize the *syn*-(*S,S*)-chiral epoxide **98** through the Jacobsen's hydrolytic kinetic resolution method. Direct introduction of epoxide **95** to HKR reaction[22] was a failure. So we decided to protect the free hydroxyl group of **95** before HKR reaction. Our attempts to protect the hydroxyl as TBS ether group using either TBSCl or TBSOTf gave poor yields. Later we protected the hydroxyl group of homoallylic alcohol **95** as PMB ether **97** using PMB-bromide (Scheme 22).

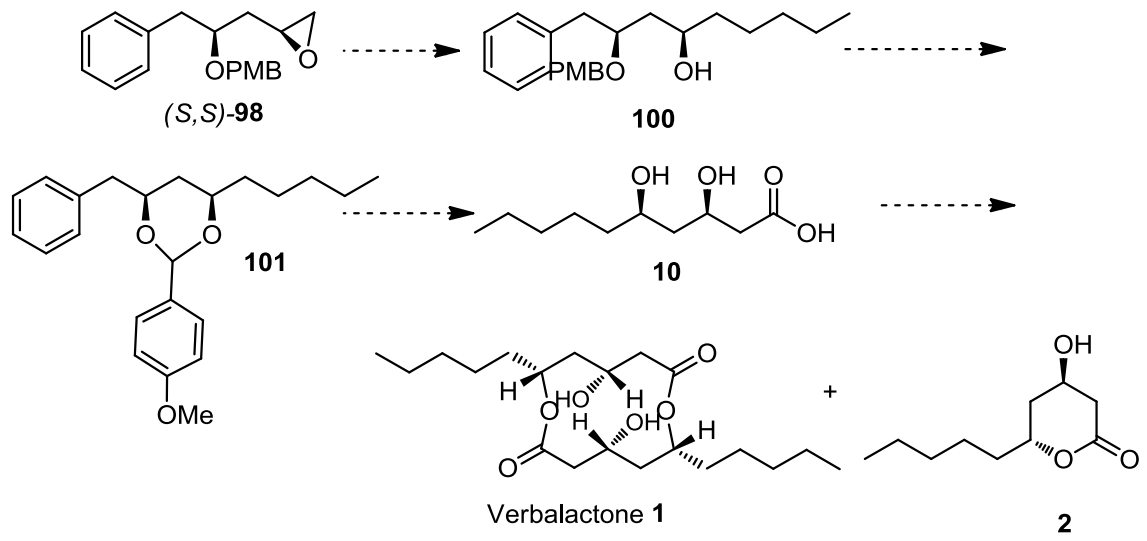


Scheme 22: *Reagents and conditions*: (a) PMB-Br, NaH, THF, 0 °C to rt, 3h, 85%; (b) (*S,S)*-salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.7 eq), THF, 0 °C to rt, 18 h. (40% for **98**, 45% for **99)**.

In order to get the required *(S,S)*-hydroxyl epoxide **98**, racemic *syn*-epoxide **97** was treated with (*S,S)*-salen-Co-(OAc) complex **46** (0.5 mol%) and water (0.7 equiv.) in THF to afford the epoxide **98** as a single stereoisomer (determined from the ^{1}H and ^{13}C NMR spectral

analysis) in 40% yield and the diol **99** in 45% yield. Epoxide **98** could easily be separated from the more polar diol **99** through silica gel column chromatography. The enantiomeric purity of the epoxide **98** was estimated to be >98% by chiral HPLC analysis using Chiracel OD-H (250 cm x 4.6 mm), IPA–PE(10:90), wavelength 214 nm, 1mL/min, Retention time (min): 14.92 (minor) and 16.51 (major).

Compound **98** can lead to the formal synthesis of verbalactone **1** by sequence of reaction shown in scheme 23. We could further proceed with the synthesis of **1** by opening of the epoxide **98** with any *n*-Butyl nucleophilic reagent. The free hydroxy group of **100** could be protected as *p*-methoxybenzylidene ketal **101** by DDQ oxidation of neighbouring PMB ether[41] in **100**. Later required seco acid **10** could be prepared by aryl ring oxidation of **101** with $RuCl_3$ and $NaIO_4$.[42] The conversion of seco acid **10** to verbalactone **1** by Yamaguchi's macrolactonization is documented in literature.[5b,7,8a,9] The synthesis of compound **10** from **98** in order to achieve the formal synthesis of verbalactone **1** is currently under progress in our laboratory.



Scheme 23: Proposed scheme for the completion of verbalactone **1**

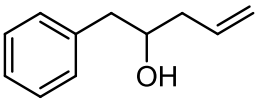
3.4.3. Conclusion

We have developed conceptually new and shortest synthetic route for the synthesis of (*S,S*)-**98**, a precursor for verbalactone **1** by HKR and diastereoselective iodocyclization, a methodology developed from our group. Another important feature of this synthesis is the preparation of enantiomerically pure *syn*-2-hydroxy-1-oxirane intermediates by single

kinetic resolution step. We feel that our present approach is general in nature and can be useful to design diverse the synthetic routes to *syn*-1,3-polyols. Currently studies are in progress in this direction.

3.4.4. Experimental Section

1-Phenylpent-4-en-2-ol (83)



To a mixture of **84** (7.0 g, 58.33 mmol) and allyl bromide (8.1 mL, 93.32 mmol) in THF-saturated aq. NH_4Cl solution (80 mL : 40 mL) was added Zinc dust (6.1 g, 93.32 mmol) slowly in portions at 0 ^oC, and stirred for 30 min at same temperature. Then the mixture was warmed to room temperature and stirred for another 2.5 hours. The reaction mixture was filtered through a Celite pad, extracted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated to give a syrup which was purified by column chromatography (eluent: petroleum ether/EtOAc 96:4) to yield pale yellow liquid **83**.

Yield: 7.74 g (82%)
Mol. Formula: $C_{11}H_{14}O$

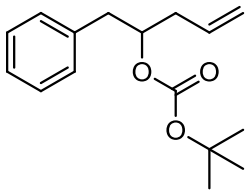
IR ($CHCl_3$, cm^{-1}): ν_{max} 3430, 3077, 3028, 2925, 1640, 1603, 1495, 1454, 1119, 1079, 915, 745, 700.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.91 (brs, 1H), 2.26-2.39 (m, 2H), 2.71-2.90 (m, 2H), 3.90-3.97 (m, 1H), 5.17-5.24 (m, 2H), 5.85-5.98 (m, 1H), 7.28-7.41 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 41.1, 43.2, 71.6, 118.0, 126.4, 128.4, 129.3, 134.6, 138.3 ppm.

Analysis: Calcd.: C, 81.44; H, 8.70; **Found:** C, 81.41; H, 8.72.

***tert*-Butyl (1-phenylpent-4-en-2-yl) carbonate (91)**



To a solution of alcohol **83** (7 g, 43.21mmol), $(Boc)_2O$ (11.9 mL, 51.85 mmol) and Et_3N(6.0 mL, 43.21 mmol) in CCl_4 (80 mL) at room temperature was added DMAP (0.528g, 4.32 mmol). After 6 h of stirring, the solvent was evaporated under reduced pressure. The residue was taken up in EtOH (45 mL) and imidazole (14.71 g, 216.05 mmol) was added. The resulting mixture was stirred at room temperature for 15 min and then CH_2Cl_2 was added. The organic layer was washed with water, dried (Na_2SO_4) and concentrated. Purification of the crude product by silica gel column chromatography using pet ether/EtOAc (98:2) as eluent afforded **91** as a colourless liquid.

Yield: 9.17g (81%)

Mol. Formula: $C_{16}H_{22}O_3$

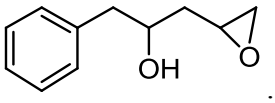
IR ($CHCl_3$, cm^{-1}): ν_{max} 3076, 3028, 2982, 2934, 1740, 1594, 1475, 1458, 1394, 1369, 1291, 758.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43-1.53 (m, 9H), 2.35-2.42 (m, 2H), 2.86-3.03 (dd, *J*= 6.4, 5.2 Hz, 2H), 4.93-4.99 (quin, *J*= 6.4 Hz, 1H), 5.11-5.19 (m, 2H), 5.75-5.96 (m, 1H), 7.24-7.33 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.8, 38.0, 40.2, 77.8, 81.8, 118.1, 126.6, 128.5, 129.6, 133.6, 137.4, 153.2 ppm.

Analysis: Calcd.: C, 73.23; H, 8.45; **Found:** C, 73.25; H, 8.44

1-(Oxiran-2-yl)-3-phenylpropan-2-ol (95)



To a solution of carbonate **91** (9g, 34.35 mmol) in toluene (125 mL) at –85 ºC was slowly added a solution of IBr (1 M in CH_2Cl_2, 11.36g, 54.96 mmol). After being stirred at –85 ºC for 4 h, the resulting mixture was quenched with 20% aqueous $Na_2S_2O_3$ and 5% aqueous $NaHCO_3$ solution (1/1) and diluted with ether (50 mL). The aqueous phase was extracted with ether (2 x 100 mL). The organic extracts were washed with brine, dried over anhydrous Na_2SO_4. After concentration, compound **93** was used in the next reaction without any further purification.

To a crude mixture of cyclic carbonate **93** in anhydrous MeOH (100 mL) at room temperature was added K_2CO_3 (14.24 g, 103.05 mmol) and the reaction was stirred for 2 h. The mixture was diluted with ether (50 mL) and quenched with saturated aqueous $Na_2S_2O_3$ and saturated aq. $NaHCO_3$ solution (1/1). The aqueous phase was extracted with ether (3 x 50 mL). The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Purification of the crude product by silica gel column chromatography using pet ether/EtOAc (80:20) as eluent afforded the epoxide **95** as a colourless liquid.

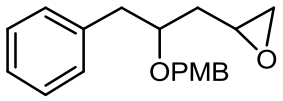
Yield: 5.19g (85%)
Mol. Formula: $C_{11}H_{14}O_2$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3422, 3060, 3027, 2920, 1602, 1496, 1454, 1254, 1081, 878, 748, 701.
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.62-1.66 (m, 1H), 1.89-1.98 (m, 1H), 2.26 (brs, 1H), 2.54-2.57 (dd, *J*= 4.9, 2.8 Hz, 1H), 2.80-2.82 (m, 1H), 2.84-2.88 (d, *J*= 6.9 Hz, 2H), 3.14-3.16 (m, 1H), 4.11-4.20 (m, 1H), 7.27-7.40 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 38.7, 43.7, 46.4, 50.2, 70.9, 126.4, 128.4, 129.3, 137.9 ppm.

Analysis: Calcd.: C, 74.13; H, 7.92; **Found:** C, 74.11; H, 7.93.

2-(2-((4-Methoxybenzyl)oxy)-3-phenylpropyl)oxirane (97)



To a solution of **95** (5 g, 28.08 mmol) in dry THF (50 mL) was added sodium hydride (60%, 1.42 g, 42.12 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 °C. To this was added slowly *p*-methoxybenzyl

bromide (4.5 mL, 30.88 mmol) and *tetra n*-butylammonium iodide (1.03 g, 2.80 mmol) with further stirring for 2.5 h at room temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with water (3 x 100 mL), brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (90:10) as eluent furnished **97** as a colourless oil.

Yield: 7.11g (85%)
Mol. Formula: $C_{19}H_{22}O_3$

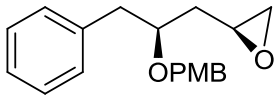
IR ($CHCl_3$, cm^{-1}): ν_{max} 3079, 3060, 3031, 2920, 1602, 1496, 1453, 1250, 1040, 932, 878.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.64-1.72 (m, 1H), 1.92-2.03 (m, 1H), 2.56-2.60 (m, 1H), 2.82-2.84 (m, 2H), 2.87-2.90 (m, 1H), 3.15-3.17 (m, 1H), 3.54-3.67 (m, 1H), 3.84 (s, 3H), 4.62 (s, 2H), 6.78-6.87 (m, 2H), 6.94-7.01 (m, 2H), 7.31-7.41 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 36.9, 41.8, 46.4, 49.6, 54.8, 70.2, 75.6, 113.9, 126.4, 128.4, 129.3, 129.8, 130.6, 137.9, 157.9 ppm.

Analysis: Calcd.: C, 76.48; H, 7.43; **Found:** C, 76.43; H, 7.41.

***(S)*-2-(*(S)*-2-((4-Methoxybenzyl)oxy)-3-phenylpropyl)oxirane (98)**



Racemic *syn*-epoxide **97** (7.0 g, 23.49 mmol), THF (295 μL) were added to (*S,S*)-Salen-Co-OAc catalyst (77.9 mg, 0.117 mmol, 0.5 mol%) and the solution was cooled to 0 °C. Every 5 min, H_2O (60 μL) was added until 295 μL (0.7 equiv., 16.44 mmol) had been added; after another 5 min the ice bath was removed and the reaction was stirred at room temperature for 18 h. The reaction mixture was concentrated and purified through silica gel column chromatography using petroleum ether/EtOAc (90:10) as eluent to furnish the epoxide (*S,S*)-**98** as a single stereoisomer as a colourless liquid. Continued chromatography with petroleum ether/EtOAc (55:45) provided the diol (*R,R*)-**99** as a pale yellow colour liquid.

Yield: 2.8 g (40%)

Mol. Formula: $C_{19}H_{22}O_3$

$[\alpha]_D^{25}$: + 34.6 (*c* 1.0, $CHCl_3$).

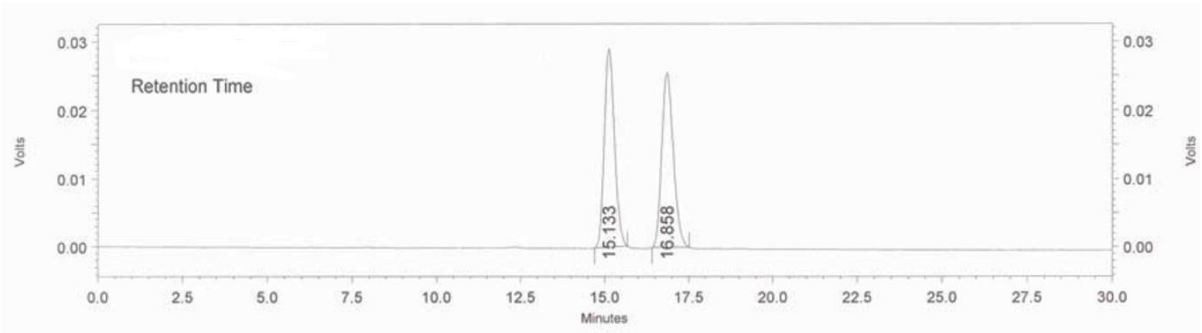
IR ($CHCl_3$, cm^{-1}): ν_{max} 3079, 3060, 3031, 2920, 1602, 1496, 1453, 1250, 1041, 932, 878.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.64-1.72 (m, 1H), 1.92-2.03 (dt, *J*= 14.4, 4 Hz, 1H), 2.56-2.60 (dd, *J*= 4.9, 2.8 Hz, 1H), 2.82-2.84 (m, 2H), 2.87-2.90 (m, 1H), 3.15-3.18 (m, 1H), 3.54-3.67 (m, 1H), 3.84 (s, 3H), 4.62 (s, 2H), 6.78-6.85 (m, 2H), 6.94-7.01 (m, 2H), 7.31-7.43 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 36.9, 41.8, 46.4, 49.6, 54.8, 70.2, 75.6, 113.9, 126.4, 128.4, 129.3, 129.8, 130.6, 137.9, 157.9 ppm.

Analysis: Calcd.: C, 76.48; H, 7.43; **Found:** C, 76.44; H, 7.42.

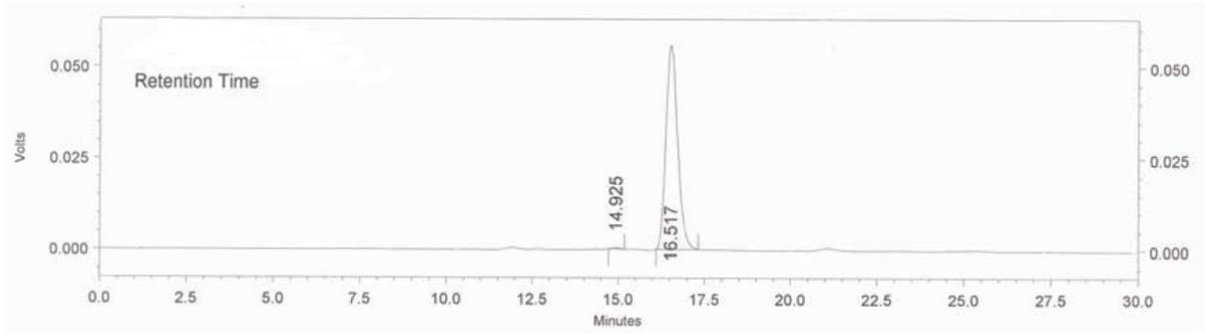
Racemic **97** chromatograph



Pk #	Retention Time	Area	Area %	Height	**Height Percent**
1	15.133	615876	49.979	29004	**53.21**
2	16.858	616391	50.021	25506	**46.79**
Totals		1232267	100.000	54510	**100.00**

Column**:** Chiracel OD-H (250 cm x 4.6 mm)
Mobile phase**:** IPA–PE (10:90)
Wavelenth**:** 214 nm
Flow**:** 1 mL/min
Concentration**:** 0.51 mg/0.25 mL mobile phase
Injection vol.**:** 20 µL

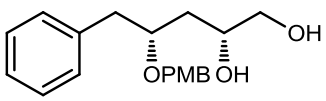
Chiral **98** chromatograph



Pk #	Retention Time	Area	Area %	Height	**Height Percent**
1	14.925	5376	0.403	359	**0.64**
2	16.517	1329750	99.597	55816	**99.36**
Totals		1335126	100.000	56175	**100.00**

Column**:** Chiracel OD-H (250 cm x 4.6 mm)
Mobile phase**:** IPA–PE (10:90)
Wavelenth**:** 214 nm
Flow**:** 1 mL/min
Concentration**:** 0.49 mg/0.25 mL mobile phase
Injection vol.**:** 20 µL

(*2R,4R*)-4-((4-Methoxybenzyl)oxy)-5-phenylpentane-1,2-diol (99)



Yield: 3.34g (45%)

Mol. Formula: $C_{19}H_{24}O_4$

$[\alpha]_D^{25}$: + 43.9 (*c* 0.9, $CHCl_3$)

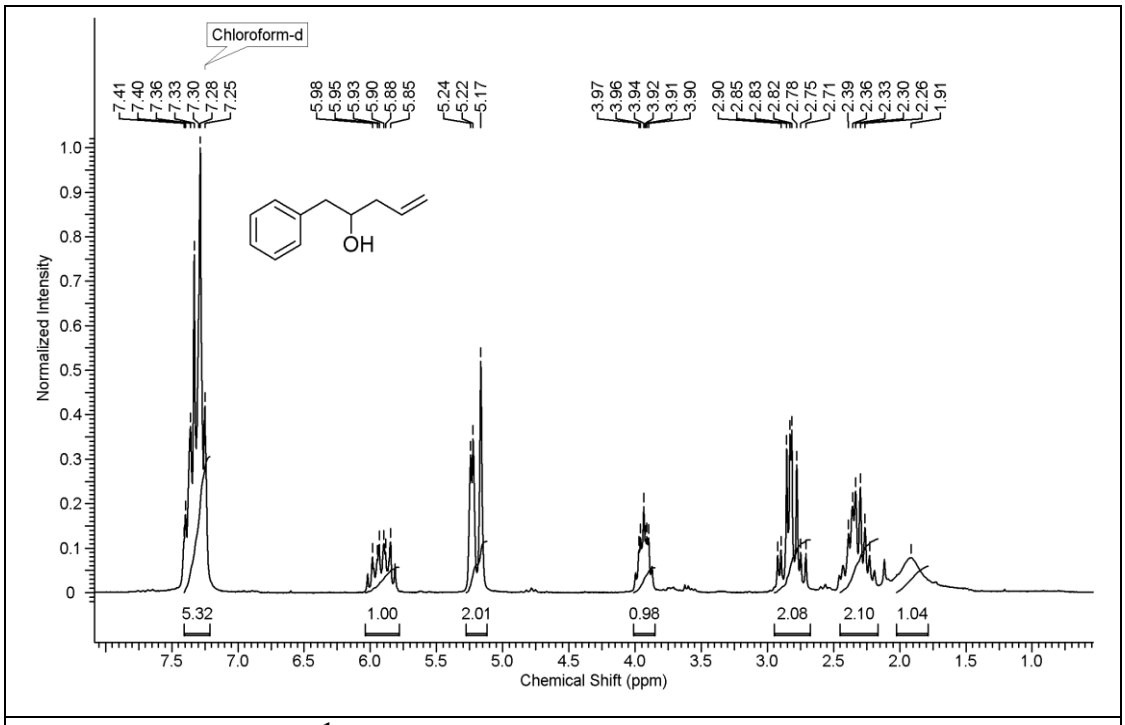
IR ($CHCl_3$, cm^{-1}): ν_{max} 3424, 3080, 3061, 3028, 2954, 1604, 1496, 1463, 1255, 1040, 932, 848.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.61-1.77 (m, 2H), 2.83-2.89 (t, *J*= 6.1 Hz, 2H), 3.36-3.44 (m, 2H), 3.68 (brs, 2H), 3.84 (s, 3H), 4.02-4.25 (m, 2H), 4.62 (s, 2H), 6.78-6.88 (m, 2H), 6.92-6.99 (m, 2H), 7.30-7.42 (m, 5H) ppm.

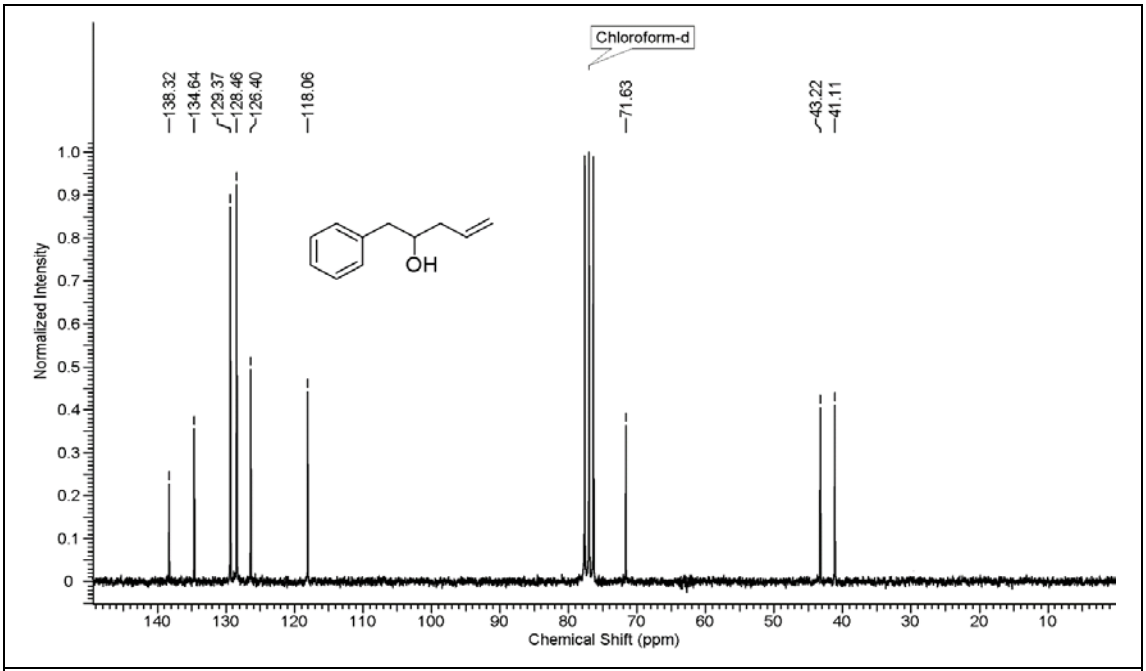
^{13}C NMR (50 MHz, $CDCl_3$): δ 37.7, 42.8, 54.8, 66.3, 70.9, 71.5, 75.5, 114.0, 126.4, 128.4, 129.3, 129.9, 130.8, 137.9, 158.0 ppm.

Analysis: Calcd.: C, 72.13; H, 7.65; **Found:** C, 72.09; H, 7.64.

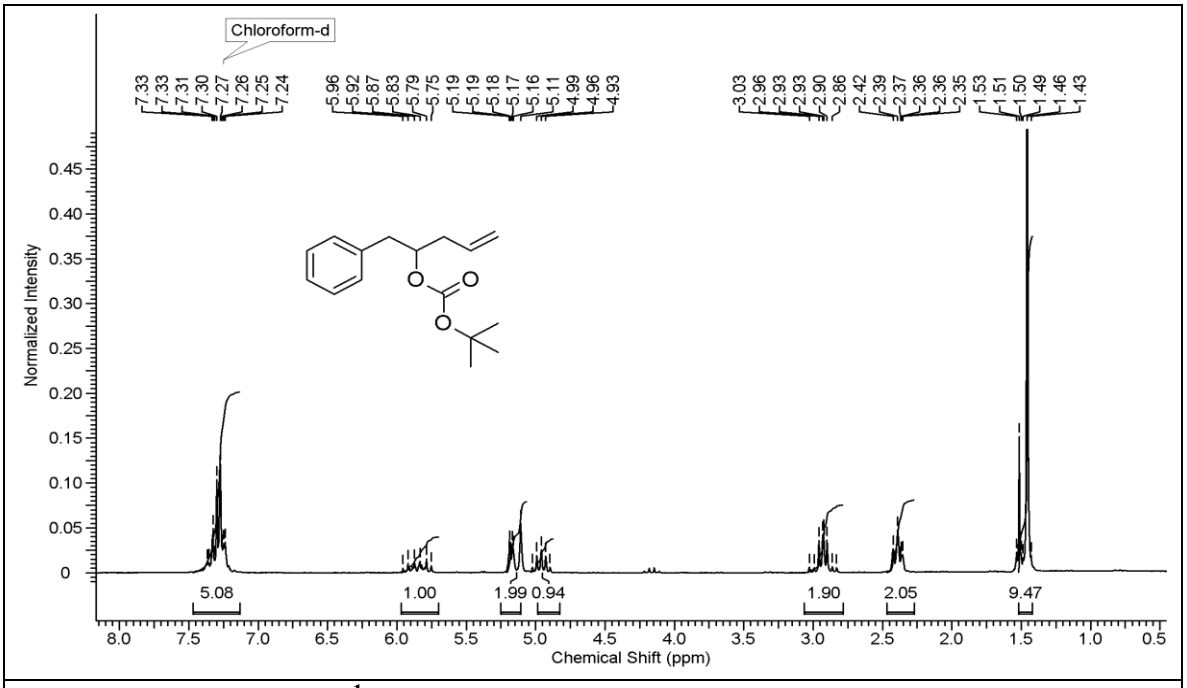
3.4.5. Spectra



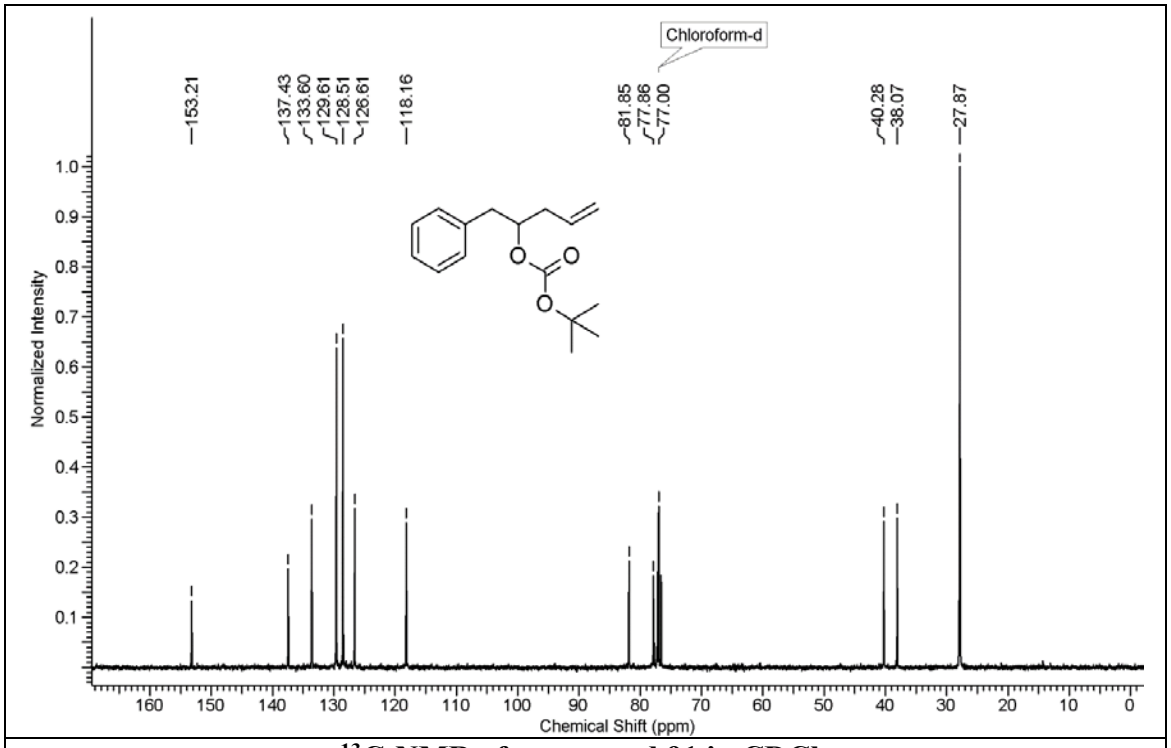
^{1}H-NMR of compound 83 in $CDCl_3$



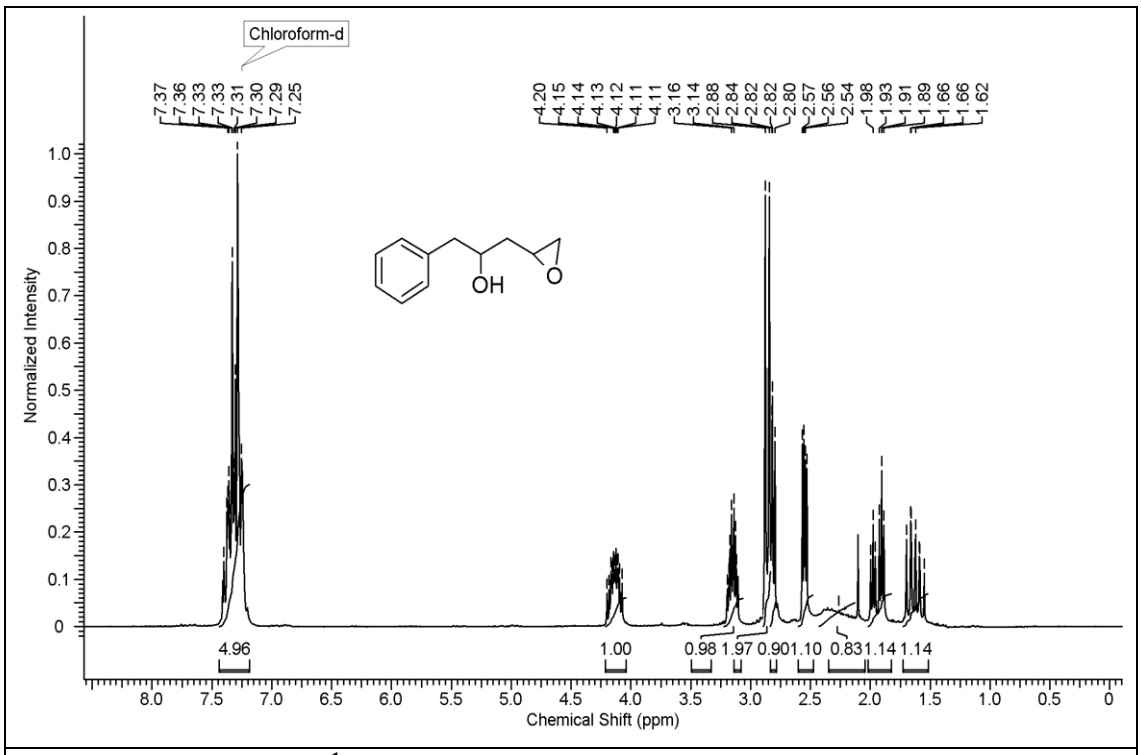
^{13}C-NMR of compound 83 in $CDCl_3$



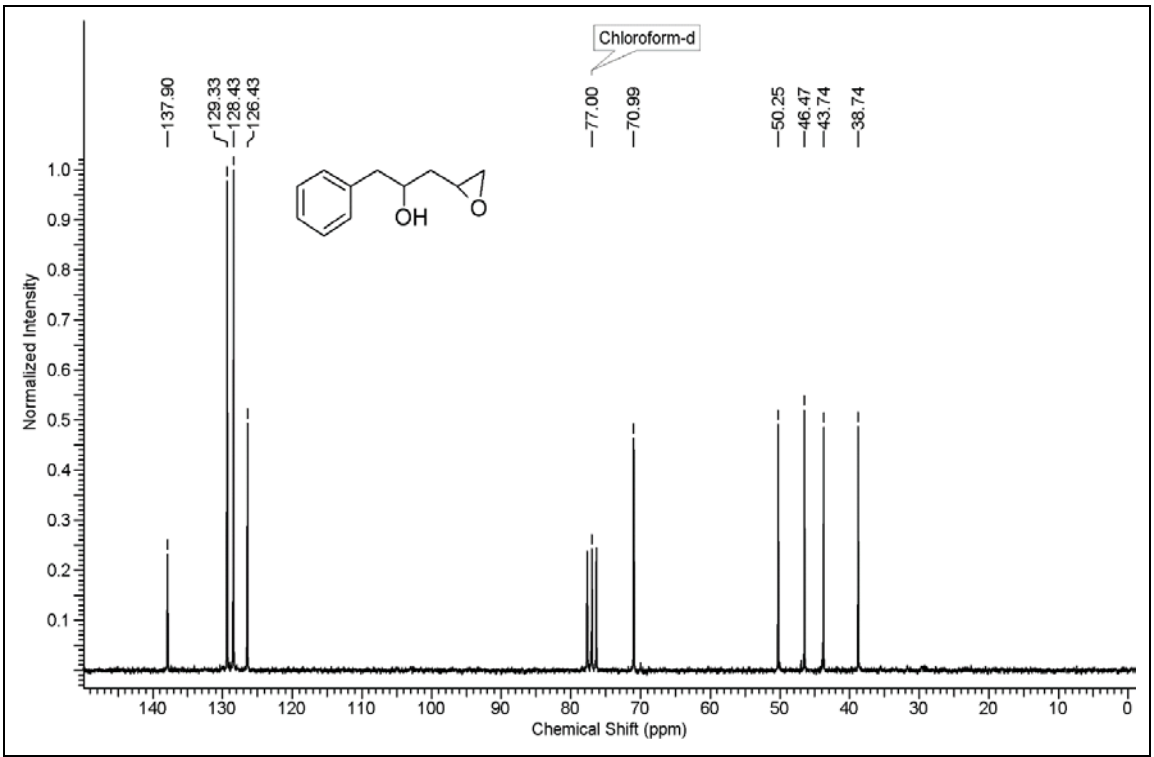
^{1}H-NMR of compound 91 in $CDCl_3$



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



^{1}H-NMR of compound 95 in $CDCl_3$



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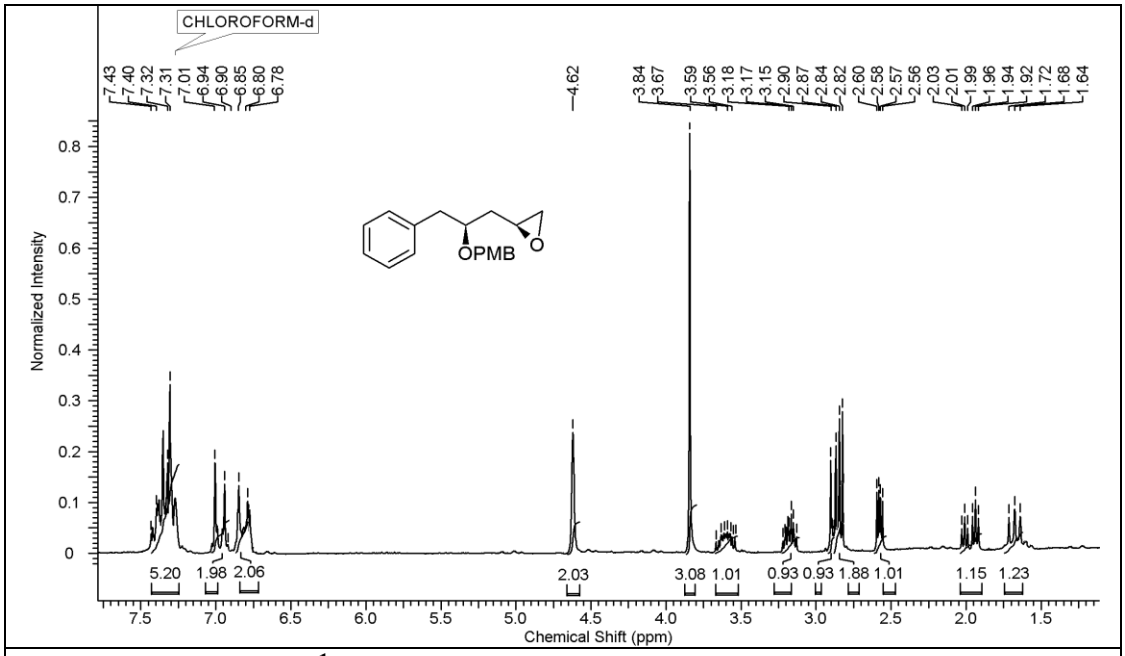

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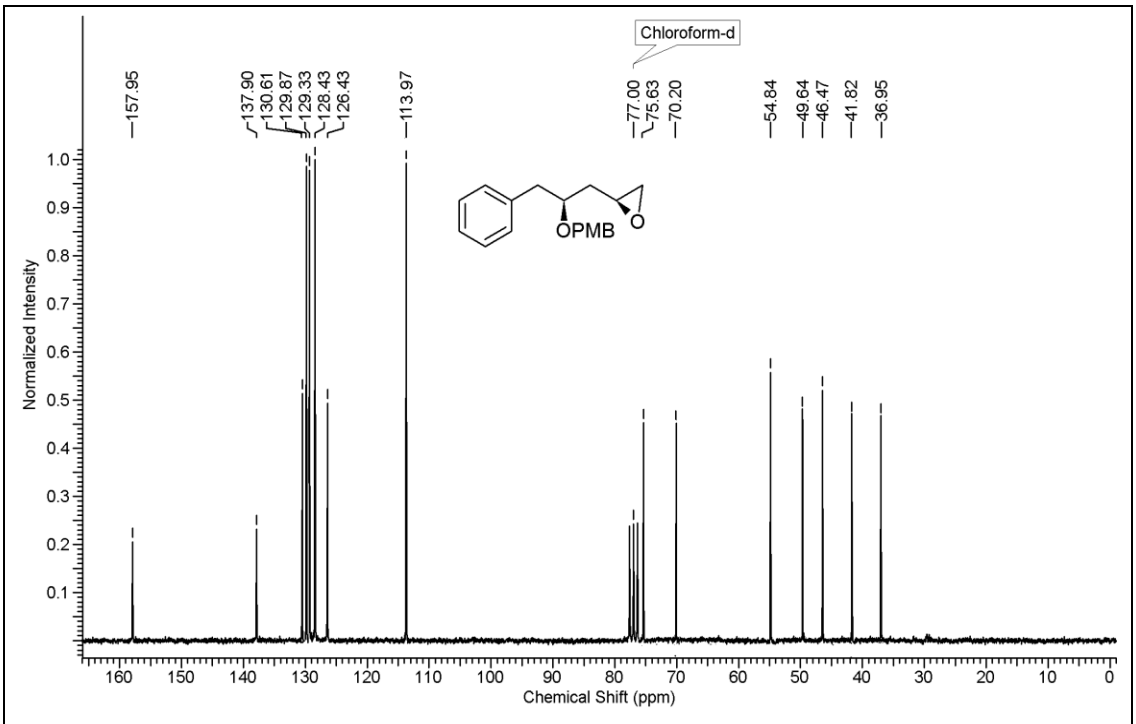

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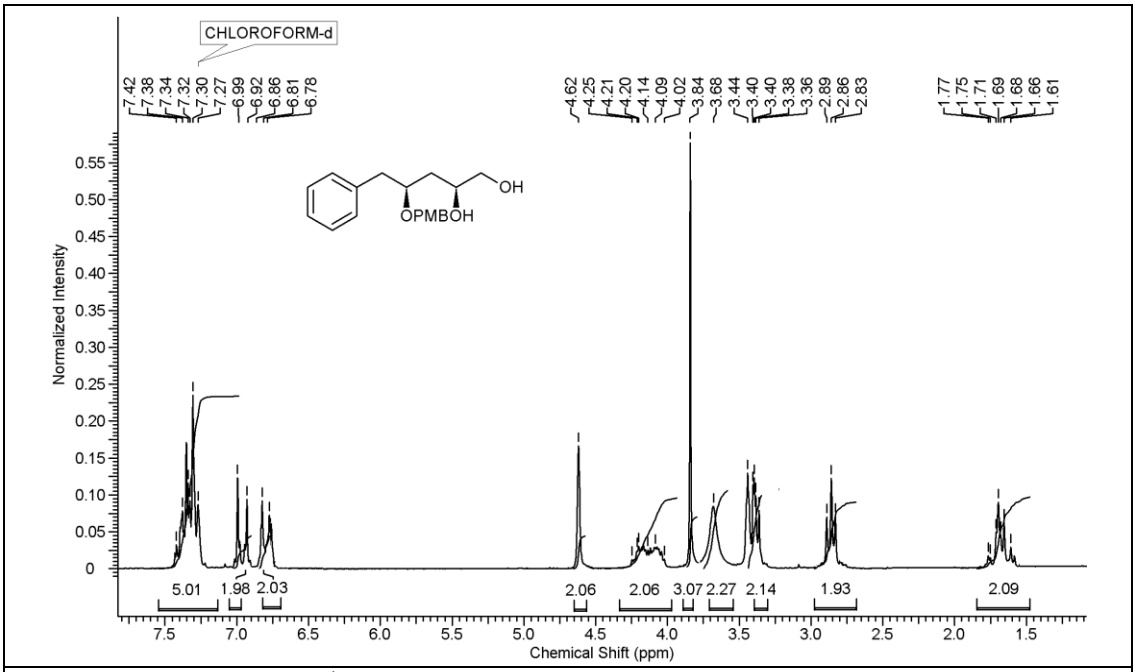

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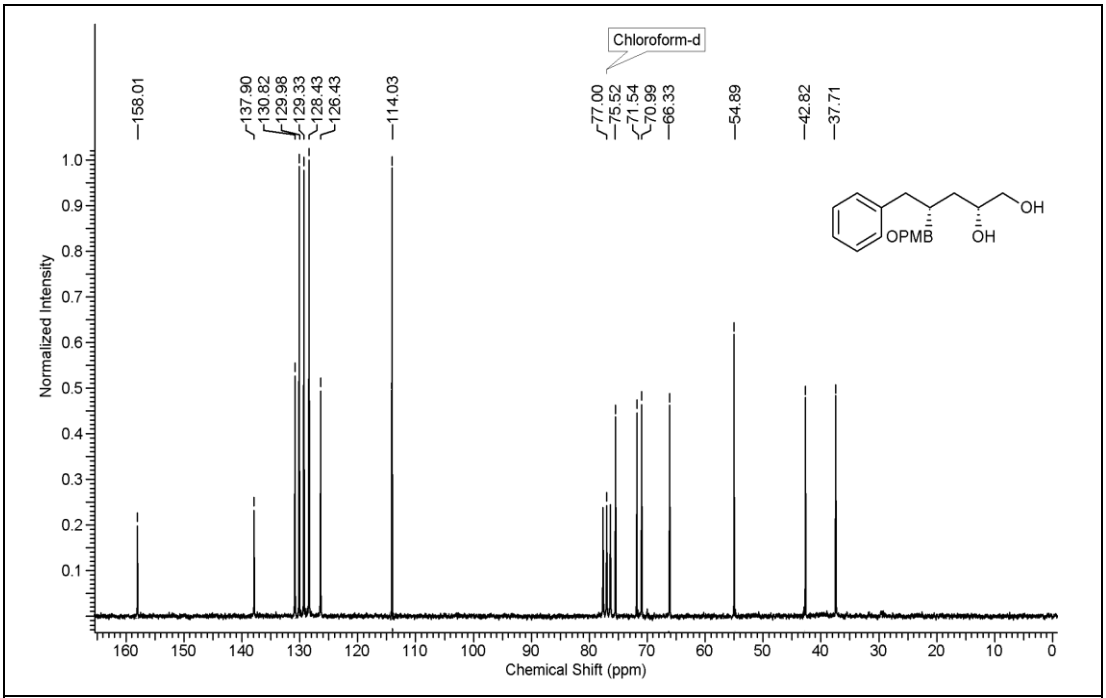


^{13}C-NMR of compound 99 in $CDCl_3$

3.5. Reference

1. Magiatis, P.; Spanakis, D.; Mitaku, S.; Tsitsa, E.; Mentis, A.; Harvala, C. *J. Nat. Prod.* **2001**, *64*, 1093.
2. Doshida, J.; Hasegawa, H.; Onuki, H.; Shimidzu, N. *J. Antibiot.* **1996**, *49*, 1105.
3. (a) Vesonder, R. F.; Stodola, F. H.; Rohwedder, W. K. *Can. J. Biochem*. **1972**, *50*, 363; (b) Endo, A. J. *J. Med. Chem*. **1985,** *28*, 401**.**
4. (a) Romeyke, Y.; Keller, M.; Kluge, H.; Grabley, S.; Hammann, P. *Tetrahedron* **1991**, *47*, 3335; (b) Takano, S.; Setoh, M.; Ogasawara, K. *Tetrahedron Asymmetry* **1992**, *3*, 533; (c) Bennett, F.; Knight, D.; Fenton, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1543; (d) Bennett, F.; Knight, D. *Heterocycles* **1989**, *29*, 639; (e) Yang, Y.-L.; Falck, J. R. *Tetrahedron Lett.* **1982**, *23*, 4305.
5. (a) Wu, J-Z.; Gao, J.; Ren, G-B.; Zhen, Z-B.; Zhang, Y.; Wu, Y. *Tetrahedron* **2009***, 65* 289; (b) Salunke, G. B.; Shivakumar, I.; Gurjar, M. K. *Tetrahedron Lett*. **2009**, *50,* 2048; (c) Garg, A.; Singh, V. K. *Tetrahedron* **2009**, *65,* 8677.
6. Sharma, G. V. M.; Reddy, C. G. *Tetrahedron Lett*. **2004**, *45*, 7483.
7. Gogoi, S.; Barua, N. C.; Kalita, B. *Tetrahedron Lett*. **2004**, *45*, 5577.
8. (a) Allais, F.; Louvel, M-C.; Cossy, J. *Synlett* **2007**, *3*, 451; (b) Das, B.; Laxminarayana, K.; Krishnaiah, M.; Kumar, D. N. *Hel. Chim. Acta.* **2009**, *92* 1840.
9. Sabitha, G.; Bhaskar, V.; Yadav, J. S. *Synth. Commun*. **2008**, *38*, 3129.
10. Harbindu, A.; Kumar, P. *Synthesis*, **2011,** *12,* 1954.
11. (a) Omura, S.; Tanaka, H. *Macrolide Antibiot.* **1984**, 351; (b) Sternberg, S. *Science* **1994**, *266*, 1632; (c) Rychnovsky, S. D. *Chem. Rev*. **1995**, *95*, 2021.
12. (a) Schenider, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 1375; (b) Hoffmann, W. H. *Angew. Chem. Int. Ed*. **2003**, *42*, 1096.
13. A highly stereocontrolled 1,5-asymmetric induction. See: Evans, D. A.; Côtè, B.; Coleman, P. J.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10893.
14. (a) Narasaka, K.; Pai, F.G. *Tetrahedron* **1984**, *40,* 2233; (b) Chen, K.; Hardmann, G. E.; Prasad, K.; Repic, O.; *Tetrahedron Lett*. **1987**, *28*, 155.
15. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc*. **1988**, *110*, 3560.
16. (a) Evans, D. A.; Gaucht-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446; (b) Miyazawa, M.; Matsuoka, E.; Sasaki, S.; Oonuma, S.; Maruyama, K.; Miyashita, M. *Chem. Lett.* **1998**, 56; (c) Sarraf, S. T.; Leighton, J. L. *Org. Lett*. **2000**, *2*, 403.

17. (a) Ito, Y.; Suginome, M. *Pure Appl. Chem*. **1996**, *68*, 505; (b) Shneider, C.; Rehfeuter, M. *Chem. Eur. J.* **1999**, *5*, 2850; (c) O'Malley, S. J. Leighton, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 2915; (d) Shneider, C.; Tolksdorf, F.; Rehfeuter, M. *Synlett* **2002**, *12*, 2098; (e) Powell, S. A.; Tenenbaum, J. M.; Woerpel, K. *J. Am. Chem. Soc*. **2002**, *124*, 12 648.
18. Zacuto, M. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 8587.
19. For recent examples of a chiral auxiliary controlled aldol reaction in 1,3-polyol syntheses, see: (a) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866; (b) Evans, D. A.; Howard, P. Ng.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127; (c) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322; (d) Cowden, C. J.; Peterson, I. *Org. React*. **1997**, *51*, 1; (e) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res*. **2000**, *33*, 325; (f) Enders, D.; Hundertmark, T. *Tetrahedron Lett.* **1999**, *40*, 4169; (g) Narkevitch, V.; Shenk, K.; Vogel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 1806; (h) Kiyooka, S.; Hena, M. A.; Yabukami, T.; Murai, K.; Goto, F. *Tetrahedron Lett*. **2000**, *41*, 7511; (i) Peterson, I.; Collet, L. A. *Tetrahedron Lett.* **2001**, *42*, 1187.
20. For recent examples of allyl addition using chiral borane or titanium reagents in 1,3-polyol syntheses, see: (a) Paterson, I.; Wallace, D. J.; Gibson, K. R.; *Tetrahedron Lett*. **1997**, *38*, 8911; (b) Barrett, A. G. M.; Braddock, D. C.; de-Koning, P D.A.; White, J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 375; (c) Greer, P. B.; Donaldson, W. A. *Tetrahedron Lett*. **2000**, *41*, 3801; (d) Bouzbouz, S.; Cossy, *J. Org. Lett*. **2000**, *2*, 3975; (e). Dreher, S. D.; Leighton, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 341.
21. For recent examples of catalytic asymmetric epoxidation of allylic alcohols in 1,3-polyol syntheses, see: (a) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem*. **1982**, *47*, 1378; (b) Schreiber, S. L.; Goulet, M. T. *J. Am. Chem. Soc*. **1987**, *109*, 8120; (c) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res*. **1994**, *27*, 9; (d) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc*. **2002**, *124*, 8188; (e) Gerber-Lemaire, S.; Vogel, P. *Eur. J. Org. Chem*. **2003**, 2959.
22. For the applications of HKR see review: (a) Kumar, P.; Naidu, S. V.; Gupta, P. *Tetrahedron* **2007**, *63*, 2745; (b) Kumar, P; Gupta, P. *Synlett* **2009**, 1367; (c) Kumar, P.; Naidu, S. V.; Gupta, P. *J. Org. Chem.* **2005**, *70*, 2843; (d) Kumar, P ; Gupta, P.; Naidu, S. V. *Chem. Eur. J.* **2006**, *12*, 1397 ; (e) Kumar, P.; Naidu, S. V. *J. Org. Chem.* **2006**, *71*, 3935; (f) Pandey, S. K.; Kumar, P. *Eur. J. Org. Chem.* **2007**, 369; (g) Pandey, S. K.; Pandey, M.; Kumar, P.

Tetrahedron Lett. **2008**, *49*, 3297; (h) Gupta, P.; Kumar, P. *Eur. J. Org. Chem.* **2008**, 1195; (i) Tripathi, D.; Kumar, P. *Tetrahedron Lett*. **2008**, *49*, 7012.

23. (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936; (b) Schaus, S. E.; Brnalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 4876.
24. Inanaga, J.; Hirata, K.; Sacki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
25. Gupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 849.
26. Lindlar, H.; Dubuis, R. *Organic Syntheses*, *Wiley, New York* **1973**, *Collect. Vol. V*, 880.
27. (a) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453; (b) Takao, K.; Ochiai, H.; Yoshida, K.; Hashizuka, T.; Koshimura, H.; Tadano, K.; Ogawa, S. *J. Org. Chem*. **1995**, *60*, 8179;
28. Laker, F. J.; Hager, L. P. *J. Org. Chem*. **1996**, *61*, 3923.
29. Kim, Y.-J.; Tae, J. *Synlett* **2006**, 61.
30. Barbier, P. *Compt. Rend.* **1890**, *130*, 1322.
31. (a) Petrier, C.; Luche, J.-L. *J. Org. Chem.* **1985**, *50,* 910; (b) Luche, J.-L.; Einhorn, C. *J. Organomet. Chem.***1987**, *322,* 177.
32. Gurjar, M. K.; Reddy, D. S. *Tetrahedron Lett*. **2002**, *43*, 295.
33. (a) For a review of diastereoselective oxidation of allylic alcohols, see: Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1883**, *39*, 2323; (b) For a review of Sharpless asymmetric epoxidation, see: Pfenninger, A. *Synthesis* **1886**, 89.
34. (a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136; (b) Tsuzuki, K.; Nakajima, Y.; Watanabe, T.; Yanagiya, M.; Matsumoto, T. *Tetrahedron Lett*. **1978**, 989; (c) Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690; (d) Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem*. **1984**, *49*, 3707; (e) Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett*. **1987**, *28*, 6191.
35. (a) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.: Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013; (b) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.: Academic: Orlando, Florida, **1984**; *Vol. 3*, 411. For analogous iodine-induced cyclization of lithium carbonates, see: (c) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. J. Chem. Sot., *Chem. Commun*. **1981**, 465; (d) Bongini, A.: Cardillo, G.; Orena, M.; Porzi. G.; Sandri, S. *J. Org. Chem.* **1982,** *47*, 4626; (e) Lipshutz, B. H.; Kozlowski, J. A. *J. Org. Chem*. **1984**, *49*, 1147; (f) Lipshutz, B. H.; Barton, J. C. *J. Org. Chem.* **1988**, *53*, 4495.

36. For *O*-BOC protection, see: (a) Houlihan, F.; Bouchard, F.; Fre´chet, J. M. J.; Willson, C. G. *Can. J. Chem*. **1985**, *63*, 153; (b) Losse, G.; Süptitz, G. *Synthesis* **1990**, 1035.
37. Pozdnev, V. F. *Int. J. Peptide Protein Res*. **1992**, *40*, 407.
38. Basel, Y.; and Hassner, A. *J. Org. Chem.* **2000**, *65,* 6368.
39. Duan, J. J.-W.; Sprengeler, P. A.; Smith, A. B., III. *J. Org. Chem.* **1993**, *58*, 3703.
40. Taylor, R. E.; Jin, M. *Org. Lett.* **2003**, *5*, 4959.
41. Oikawa,Y.; Yoshioka, T.; Yonemitsu,O. *Tetrahedron Lett.* **1982**, *23*, 889.
42. Kim, I. S.; Ryu, C. B.; Li, Q. R.; Zee, O. P.; Jung, Y. H. *Tetrahedron Lett.* **2007**, *48*, 6258.

Chapter-4

Enantiomeric synthesis of substituted chiral γ-butyrolactones from aldehydes via proline-catalysed sequential lactonization reaction and proline-catalysed enantiomeric synthesis of Bruguierol A and Bruguierol B

4.1. SECTION A: Enantiomeric synthesis of substituted chiral γ-butyrolactones from aldehydes via proline-catalysed sequential lactonization reaction

4.1.1. Introduction

Organic reactions are traditionally viewed as linear and stepwise processes in which isolation and purification of key intermediates often lead to reduced yields. The main issue now is the efficiency of a synthesis. The costly protecting-group strategies and lengthy purification procedures after each synthetic step are hampering the current status of organic chemistry.[1] The relationship between structural complexity and the number of steps in a synthesis must be improved. Multistep syntheses with more than 20 steps have to be avoided, because they are neither economically nor ecologically justifiable. The modern syntheses must deal carefully with our resources and our time, must reduce the amount of waste formed, should use catalytic transformations and must avoid all toxic reagents and solvents. One of the ways to fulfil these goals is the development and use of domino and tandem processes.[2]These process would be the transformation of two or more bond-forming reactions under identical reaction conditions, in which the latter transformations take place at the functionalities obtained in the former bond forming reactions.[3] While it is desirable that the whole process proceeds without changing the conditions, raising the temperature or adding a reagent may be allowed.[2a]

Nicolaou noted that the descriptors *domino*, *cascade*, *tandem*, and *sequential* are often used indistinguishably from one another in the literature.[4] Indeed, a variety of opinions exist on how such reactions should be classified. According to Tietze, a domino (or cascade) reaction is defined as a process in which two or more bond-forming transformations occur based on functionalities formed in the previous step. Furthermore, no additional reagents, catalysts, or additives can be added to the reaction vessel, nor can reaction conditions be changed.[3] Denmark further posits that most domino reactions, as defined by Tietze, fall under the broader category of tandem processes.[5] Other tandem reactions that are not cascades involve the isolation of intermediates, a change in reaction conditions, or the addition of reagents or coupling partners. Others classify domino reactions with even stricter conditions.[6]

Tandem sequential reactions require the addition of the second reagent for the tandem process in a separate step. To qualify as a tandem reaction, the first stage must create the functionality in the product to enable it to engage in the second reaction. The intermediate may be isolable, though this is not a necessity.[5] The quality and importance of these reactions can be correlated to the number of bonds generated in such a process and the increase of complexity. They can be performed as single-, two- and multicomponent transformations. The reactions can be performed in solution, as well as on solid support and their use in automated synthesis is also possible.[3d] Tandem reactions are not a new invention − indeed, nature has been using this approach for billions of years.[3f]

Tandem reactions have gained wide acceptance, because they increase synthetic efficiency by decreasing the number of laboratory operations required and the quantities of chemicals and solvents used.[2b] These reactions can be considered to fall under the banner of "green chemistry" i.e. only a single reaction solvent, workup procedure, and purification step may be required to provide a product that would otherwise have to be made over the course of several individual steps.

4.1.2. Review of Literature

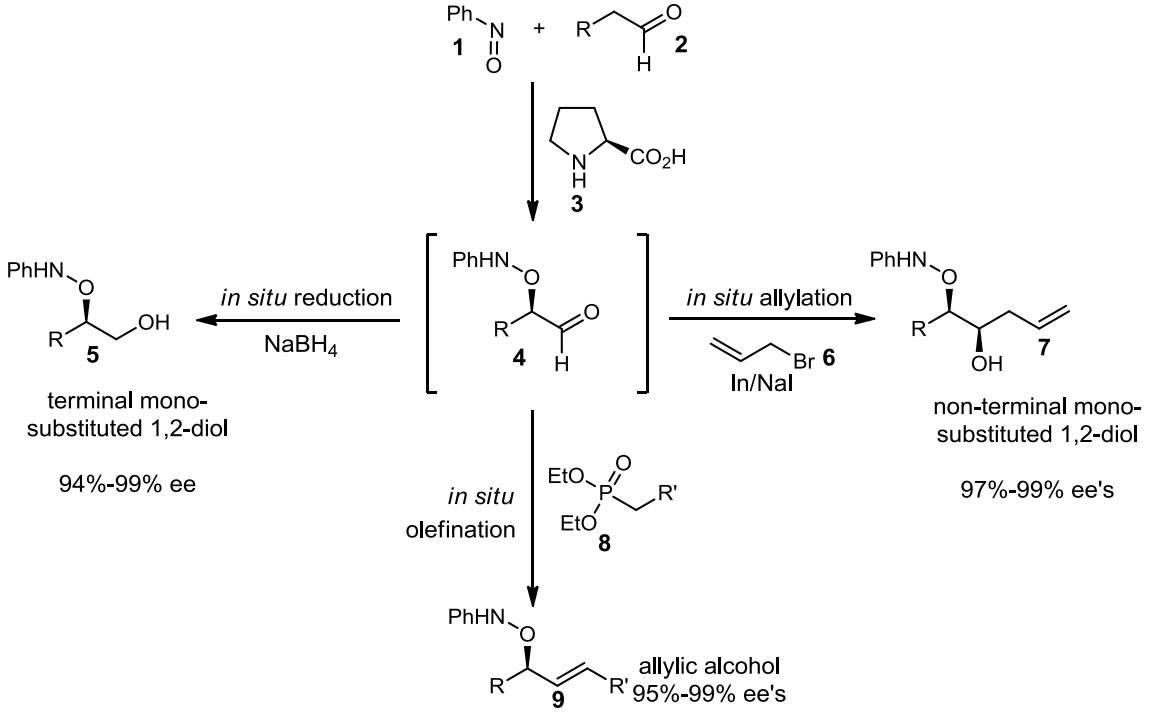
The ability to create complex molecules in only a few steps has long been the dream of chemists. Now with the development of tandem reactions, the dream has become almost true for the laboratory chemist. Today, this new way of thinking represents a clear change of paradigm in organic synthesis, with tandem reactions being frequently used not only in basic research but also in applied chemistry.[3f] For the design and performance of tandem reactions, it is of paramount importance that the functionalities react in a fixed chronological order to allow the formation of defined molecules. This can be done by steric or electronic differentiation. The application of tandem reactions to natural products synthesis represents a particularly demanding task, but the results can be both stunning and instructive.[3f]

The synthesis of optically active chiral compounds, which play an important role in medicine and materials, is one of the most fascinating aspects of modern organic synthesis. The use of tandem reactions in asymmetric synthesis is increasing constantly. The design and development of new asymmetric tandem reactions is regarded as a great intellectual

challenge for organic chemists. The rational design of an asymmetric tandem reaction is a complex action, requiring imagination, knowledge and creativity.[2a] The increasing number of publications regarding the applications of this type of reactions paints a comprehensive picture for their real possibilities in organic synthesis, offering the advantages of atom economy, simple procedures, and savings in cost and time.[2b]

Proline in tandem reactions

Organocatalysis is rapidly growing research field in organic synthesis and has the advantage of being highly selective and reducing synthetic manipulation. It is often associated with mild and simple reaction conditions that are appealing because of easy handling, cost and safety issues. Proline in the recent past has been defined as a "universal catalyst" because of its utility in different reactions providing rapid, catalytic, atom-economical access to enantiomerically pure products.



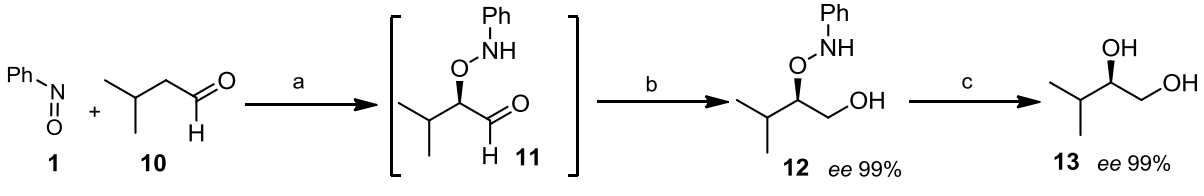
Scheme 1: Strategy for in situ trapping of the reactive *a*-aminoxy aldehyde intermediates

This small molecule can catalyze numerous reactions such as the aldol, Mannich, Michael addition, Robinson annulation, Diels-Alder, α-functionalization, α-amination, and α-aminoxylation reactions. The reactive aldehyde intermediates formed in various proline

catalysed reactions can be efficiently trapped and transformed *in situ* without requiring a separate preparative step.[1,7] For example, in the case of direct catalytic asymmetric α-aminoxylation of aldehydes by using enantiopure proline as the catalyst and nitrosobenzene as the oxygen source[8], the α-aminoxy aldehyde generated during the reaction could not be isolated in good yields, indeed they could be converted to terminal 1,2-diols by in situ reduction of α-aminoxy aldehyde[9]or they could be converted to nonterminal 1,2-diol by *in situ* indium promoted allylation of α-aminoxy aldehyde[10] or to be converted to allylic alcohols by the subsequent Wadsworth-Emmons-Horner olefination of α-aminoxy aldehyde[11] (Scheme 1).

Zhong *et al*. (2003)[9]

Zhong *et al*. reported the first direct catalytic enantioselective α-aminoxylation of aldehydes which provides a facile route to enantiopure α-aminoxyaldehyde intermediates. Although the α–aminoxy aldehyde intermediates formed in the reaction could not be isolated in good yields, they proposed a one-pot sequence of catalytic α-aminoxylation of aldehydes followed by in situ reduction with $NaBH_4$, to afford optically active 1,2-diol units with excellent enantioselectivities (*ee* values from 94 to 99%) and good yields (54–86%).[9] The reaction of isovaleraldehyde **10**, nitrosobenzene **1**, and *L*-proline **3** in DMSO was completed in just 10 min. After that in situ conversion of the intermediate **11** into the more stable 2-aminoxy alcohol **12** by reduction with sodium borohydride was carried out in the mixed solvent of DMSO and ethanol. The corresponding product **12** was then isolated in good yield (82%, one pot in two steps) and with excellent enantioselectivity (99% *ee*). Catalytic hydrogenation of the alcohol **12** over platinum dioxide (Adams catalyst) in THF cleaved the O-N bond of **12** to furnish diol **13** with 95% yield (Scheme 2).

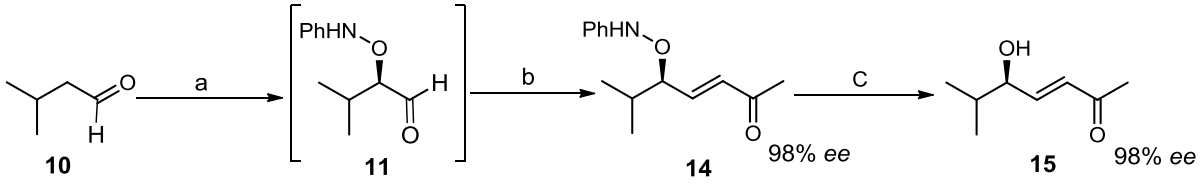


Scheme 2: *Reactions and conditions*: (a) *L*-proline, DMSO, rt, 10 min; (b) $NaBH_4$, EtOH, 82%; (c) H_2/Adams cat. (15 mol %), THF, rt, 2h, 95%.

Zhong *et al.* (2004)[11]

Zhong *et al.* developed sequential asymmetric α-aminoxylation/Wadsworth-Emmons-Horner olefination of aldehydes for the synthesis of optically active *O*-amino-substituted allylic alcohols.[11] This process displayed a wide substrate scope and was compatible with functionalities such as aryl, alkenyl, benzyloxy, or amido groups. Excellent enantioselectivities (with 95-99% *ee*) and good yields (52-81%) were achieved in all cases. The α-aminoxylation of valeraldehyde was carried out by following procedure (Scheme 3).

A mixture of valeraldehyde **10** (1.2 equiv.), nitrosobenzene **1** (1.0 equiv.), and *L*-proline **3** (20 mol %) was stirred in the solvent DMSO at room temperature for 10 min. Then, the following in situ olefination was started with addition of diethyl (*2*-oxopropyl)phosphonate (1.5 equiv) and cesium carbonate (1.5 equiv). The stirring of the reaction mixture was kept at room temperature for 30 min. As a result, the corresponding amino-substituted allylic alcohol **14** was isolated as the major product in 43% yield and with 98% ee by flash column chromatography on silica gel. Later removal of the *N*-phenylamino group from **14** was achieved by the copper (II)-catalyzed N-O bond cleavage, which gave the allylic alcohol **15** as a product in 66% yield (Scheme 3). The N-O bond cleavage reaction did not result in any loss in enantiomeric purity.

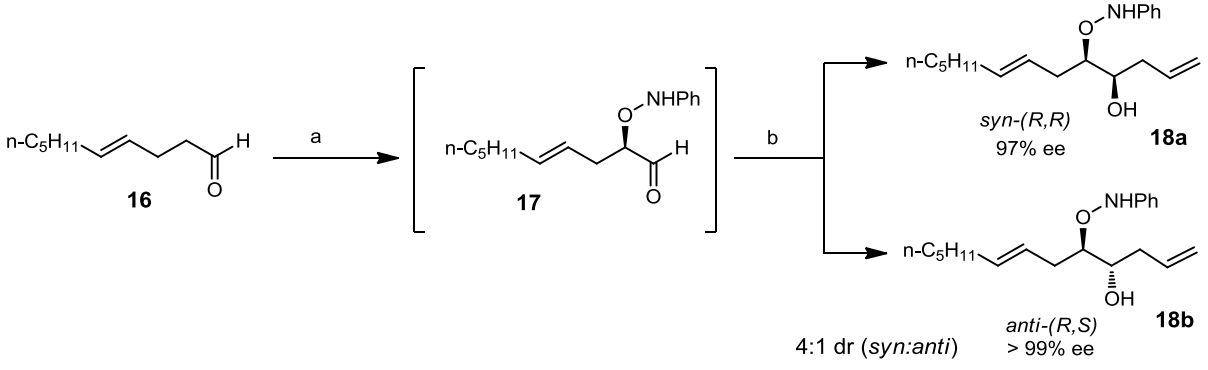


Scheme 3: *Reactions and conditions*: (a) nitrobenzene, *L*-proline, DMSO, rt, 10 min; (b) diethyl(*2*-oxopropyl)phosphonate, $CsCO_3$, 30 min, 43%; (c) $Cu(OAc)_2$ (30 mol%) ethanol, rt, 12 h, 66%.

Zhong *et al.* (2004)[10]

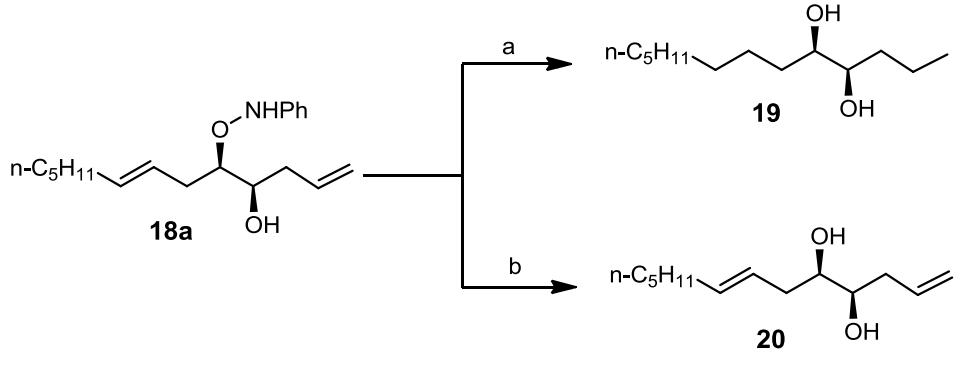
Zhong *et al*. developed a tandem proline catalyzed asymmetric α-aminoxylation of aldehydes and subsequent *in situ* indium promoted allylation for the conversion of aldehydes to both *syn*- and *anti*-mono amino-substituted 1,2-diols in in good yields (65–82%) with excellent enantioselectivities (*ee*'s from 97% to > 99%).[10]

The experiments were conducted by stirring *trans*-4-decenal **16** (1.2 equiv.), nitrosobenzene **1** (1.0 equiv.) and *L*-proline **3** (20 mol %) in DMSO at room temperature for 15 minutes (Scheme 4). After that allyl bromide **6** (1.5 equiv.), indium (1.5% equiv.) and sodium iodide (1.5 equiv.) were added and the reaction mixture was kept stirring for 3–5 minutes. The allylation in the solvent DMSO was completed in just 5 minutes and the products **18a** (*syn*) and **18b** (*anti*) were isolated in good yield (70%) with the diastereoselectivity 4:1 (*syn*/*anti*) (Scheme 4).



Scheme 4: *Reactions and conditions*: (a) nitrosobenzene, *L*-proline, DMSO, 15 min; (b) allylbromide, In, NaI, rt, 5 min, 70%.

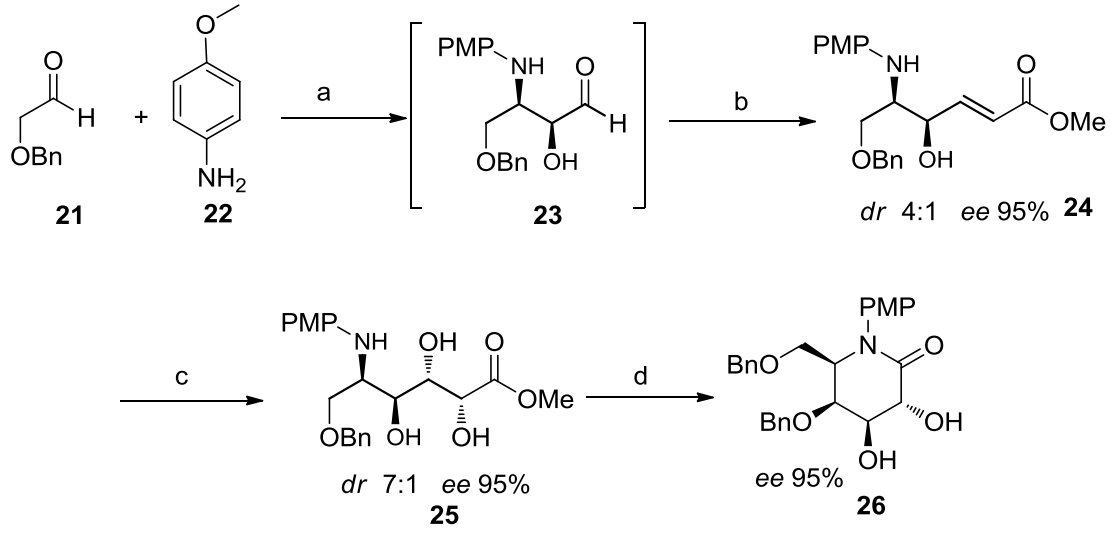
Removal of the *N*-phenylamino group from product **18a** was achieved either by catalytic hydrogenation or by the copper(II) catalyzed N–O bond cleavage reaction. The catalytic hydrogenation of the **18a** over platinum dioxide (Adams catalyst) cleaved the N–O bond, but at the same time it also reduced the two C=C bonds in the molecule affording the diol **19** as product in 84% yield. The copper(II) catalyzed N–O bond cleavage gave unsaturated diol **20** as product in 63% yield (Scheme 5). It should be pointed out that both N–O bond cleavage reactions did not result in any loss in enantiomeric purity.



Scheme 5: *Reactions and conditions*: (a) H_2/adams catalyst (15 mol %), ethanol, rt, 40 min, 84%; (b) $Cu(OAc)_2$ (30 mol%), ethanol, rt, 24 h, 63%.

Cordova *et al.* (2006)[12]

Cordova *et al.* reported a concise de novo synthesis of amino- and iminosugar synthesis based on one-pot tandem organocatalytic asymmetric Mannich–Wittig-olefination reactions utilizing an α-oxyaldehyde as the aldehyde component followed by diastereoselective hydroxylation.[12] The orthogonally protected galactolactams **26** were prepared with high stereoselectivity using this protocol (Scheme 6). The α-benzyloxyacetaldehyde **21** (3 equiv.) reacted with with *p*-anisidine **22** (1 equiv.) in the presence of a catalytic amount of (*S*)-proline (30 mol %) in DMF.

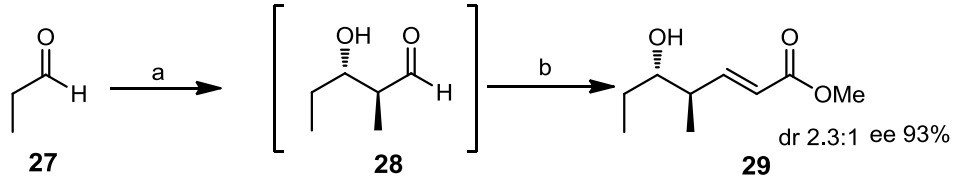


Scheme 6: *Reactions and conditions*: (a) (*S*)-proline, DMF, rt, 48 h; (b) DBU, LiCl, $(EtO)_2POCH_2COOMe$, DMF, rt, 64%; (c) cat. OsO_4, NMO, acetone–H_2O 9:1, rt, 67%; (d) AcOH, MeOH, reflux, 74%.

After 48 h of stirring at room temperature, LiCl (2.2 equiv.), the alkyl diethylphosphonoacetate (2.2 equiv.) and DBU (2.2 equiv.) were added to the reaction mixture. The reaction was quenched after 1.5 h and the desired orthogonally protected vicinal amino alcohol **24** isolated in 64% yield with 4:1 dr and 95% *ee*. Later **24** was catalytically dihydroxylated to furnish galactonic acid **25**. The subsequent ring-closure of **25** yielded the desired galactolactam **26** with 95% *ee* (Scheme 6).

Cordova *et al.* (2006)[13]

Cordova *et al.* developed a one-pot; proline catalysed asymmetric tandem cross-aldol/Horner–Wittig–Emmons reactions to assemble polyketide and carbohydrate derivatives in good yield with 93–98% *ee*.[13] The propionaldehyde **27** (2 mmol) was added to a stirred solution of (*S*)-proline (10 mol %) in DMF (0.5 mL). After 15 h of vigorous stirring at 4 ^{o}C, the temperature was increased to room temperature and LiCl (1.5 mmol), methyl 2-(diethoxyphosphoryl)-acetate (1.5 mmol) and DBU (1.5 mmol) were added to the reaction mixture. After stirring for 4 h at room temperature, the reaction mixture was passed directly through a silica gel column to give the pure natural product mycinonic acid ester **29** in 52% yield with 2.3:1 dr (*anti:syn*) and 93% *ee* (Scheme 7).



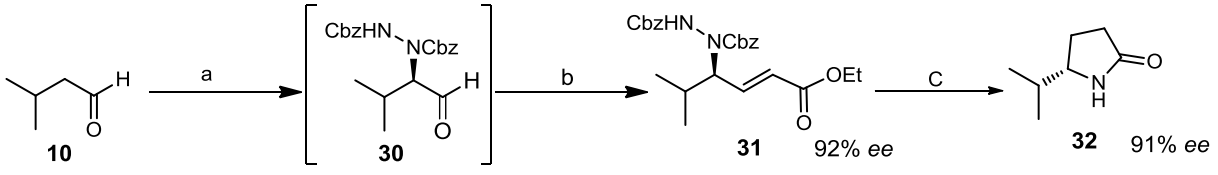
Scheme 7: *Reactions and conditions*: (a) (*S*)-proline, DMF, 4 ^{o}C, 15 h; (b) $(EtO)_2POCH_2COOMe$, LiCl, DBU, rt, 4h, 52%.

Sudalai *et al.* (2007)[14]

Sudalai *et al.* developed a one-pot procedure for obtaining highly enantioselective synthesis of *γ*-amino-*α,β*-unsaturated esters using tandem α-amination/Horner-Wadsworth-Emmons (HWE) olefination of aldehydes.[14] The potential of this reaction has been demonstrated by the synthesis of important optically active 2-pyrrolidinone derivatives **32** in good yields. They examined the scope of several aldehydes bearing different functionalities under the optimized reaction conditions. In all cases studied, the *γ*-amino-*α,β*-unsaturated esters were obtained in excellent yields (80-88%) and high enantioselectivities (92-99% *ee*'s).

The α-amination of valeraldehyde **10** was conducted by using dibenzyl azodicarboxylate (DBAD) as a nitrogen source and *L*-proline **3** as a catalyst to obtain the α-amino aldehyde **30** (Scheme 8). Because *α*-amino aldehydes are prone to racemization, the in situ olefination of **30** was carried out by the addition of triethyl phosphonoacetate (1.5 equiv.) and LiCl (1.5 equiv.) in the presence of DBU (1 equiv.) produced **31** in 80% yield with high

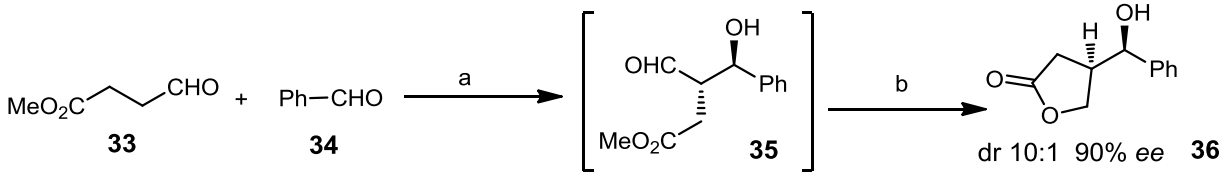
enantioselectivity (92% *ee*). Later a single-step transformation of **31** under hydrogenation conditions (Raney nickel, H_2, 60 psig) provided the 2-pyrrolidone **32** in 70% yields (91% *ee*) (Scheme 8).



Scheme 8: *Reactions and conditions*: (a) DBAD (1 equv.), *L*-proline (10 mol %), CH_3CN, 0-10 ^oC, 3h; (b) triethyl phosponoacetate (1.5 equiv.), LiCl (1.5 equiv.), DBU (1 equiv.), 45 min, 80%; (c) Raney-Ni, MeOH, H_2 (60 psig), 12 h, 70%.

Hajra et al. (2008)[15]

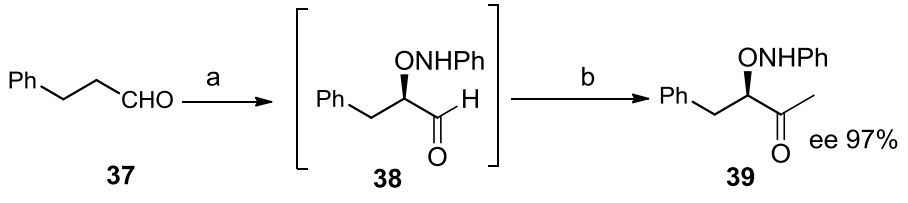
Hajra *et al.* reported a one-pot, proline catalysed asymmetric tandem cross-aldol reaction of methyl-4-oxobutyrate **33** and a variety of aldehydes followed by reduction with $NaBH_4$ for the synthesis of 4-(hydroxyalkyl)-γ-butyrolactones with high diastereo (dr > 24:1) and enantioselectivity (*ee* > 99%).[15] The reaction of methyl-4-oxobutyrate **33** and benzaldehyde **34** in the presence of *L*-proline **3** as a catalyst was carried out in dry DMF at 4 ^oC under an argon atmosphere (Scheme 9). Addition of 4-oxobutyrate **33** to the reaction mixture was performed through a micro syringe pump during 22 h to avoid its self-aldol reaction. After an additional 4 h of stirring, the resulting mixture was diluted with methanol at 4 ^oC, $NaBH_4$ (0.5 equiv.) was then added portion wise. This was followed by stirring at 35-40 ^oC for 1 h. Work up of the reaction mixture afforded β-hydroxyphenylmethyl-γ-butyrolactone **36** with high diastereo (10:1) and enantioselectivity (*ee* 90%) in 47% yield (Scheme 9).



Scheme 9: *Reactions and conditions*: (a) *L*-proline, DMF, 4 ^oC, 26 h; (b) $NaBH_4$, MeOH, 4 ^oC- 35 ^oC, 1 h, 47%.

Wang *et al.* (2009)[16]

Wang *et al.* have developed a general method for the synthesis of 3-hydroxyl-2-alkanones via tandem organocatalytic aminoxylation of aldehydes and chemoselective diazomethane homologation.[16] The tandem aminoxylation/homologation of various aldehydes was examined. The sequential reactions were carried out conveniently in one pot, without isolation of the intermediates, in moderate to good yields over two steps. The *ee*'s of all products were excellent, indicating that no racemization occurred during the CH_2N_2-induced rearrangement. The potential of this reaction has been demonstrated by the synthesis of a key intermediate for the synthesis of Epothilones, in high ee. The first step of tandem sequence was the aminoxylation of 3-phenylpropanal **37** using *L*-proline **3**, nitrosobenzene **1** in DMF for 10 minutes (Scheme 10). The next step was homologation of aldehyde **38** to methyl ketone **39** via reaction with diazomethane. The anhydrous magnesium salts increased the chemoselectivity to a useful level of 6:1 with enhanced yields of ketone (Scheme 10).

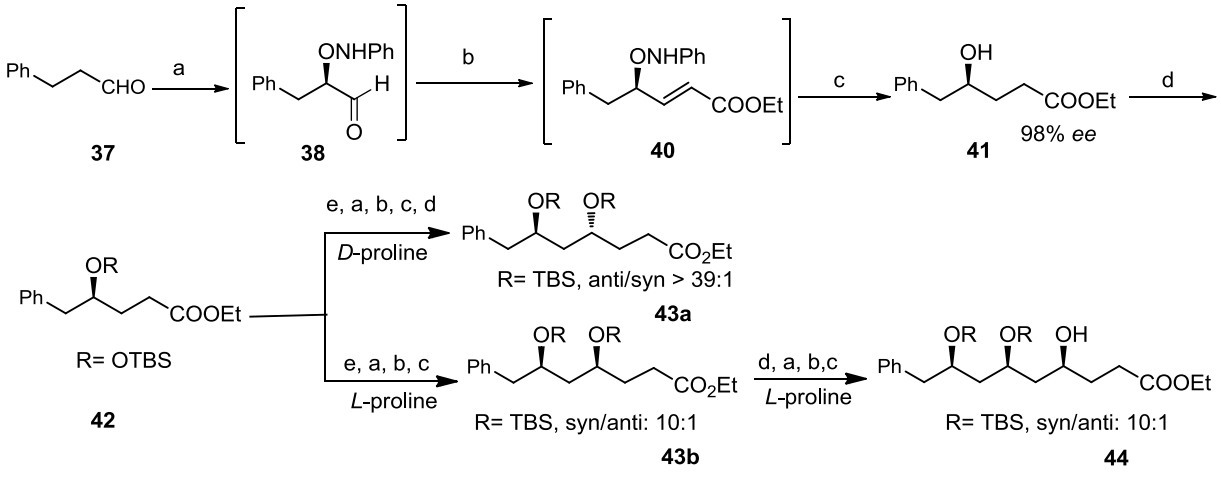


Scheme 10: *Reactions and conditions*: (a) PhNO, *L*-proline, DMSO, rt, 10 min; (b) CH_2N_2, Et_2O, $MgCl_2$, rt, 60%.

Kumar *et al.* (2009) [17]

Kumar *et al.* developed a method to access both *syn/anti*-1,3-polyols by iterative use of proline-catalyzed tandem α-aminoxylation and HWE olefination of aldehydes reported by Zhong *et al*.[11] This iterative sequence is particularly attractive because of mild reaction conditions; the overall short reaction sequence involving four steps and two column purifications per iteration and the stereochemical outcome of the reaction can be predicted on the basis of the catalyst used. The synthetic utility of this protocol was further demonstrated by the asymmetric synthesis of a pheromone component, (*2S,3S*)-2-hydroxyhexylcyclopentanone.[17]

The iteration procedure starts with synthesis of γ-hydroxy ester **41** in a tandem fashion (Scheme 11). The commercially available phenyl propanal **37** was subjected to sequential α-aminoxylation followed by HWE-olefination reaction; it furnished *O*-amino-substituted allylic alcohol **40**. To minimize handling of intermediates and its time-consuming purification, the crude product obtained after workup was directly subjected to hydrogenation conditions using catalytic amounts of Pd/C to furnish the γ-hydroxy ester **41** in good yield. Later the free hydroxy group of γ-hydroxy ester **41** was protected as TBS ether using TBSOTf to furnish compound **42** and proceeded toward the first cycle of iteration (Scheme 11). Each cycle of iteration consists of four steps, viz. DIBAL-H reduction of ester to aldehyde, sequential α-aminoxylation, HWE olefination, and H_2-Pd/C reduction, followed by TBS protection of the hydroxy group to eventually furnish the TBS protected γ-hydroxy ester with excellent diastereoselectivites (39:1 for *anti*-isomer **43a** and 10:1 for *syn*-**43 b**) (Scheme 11).



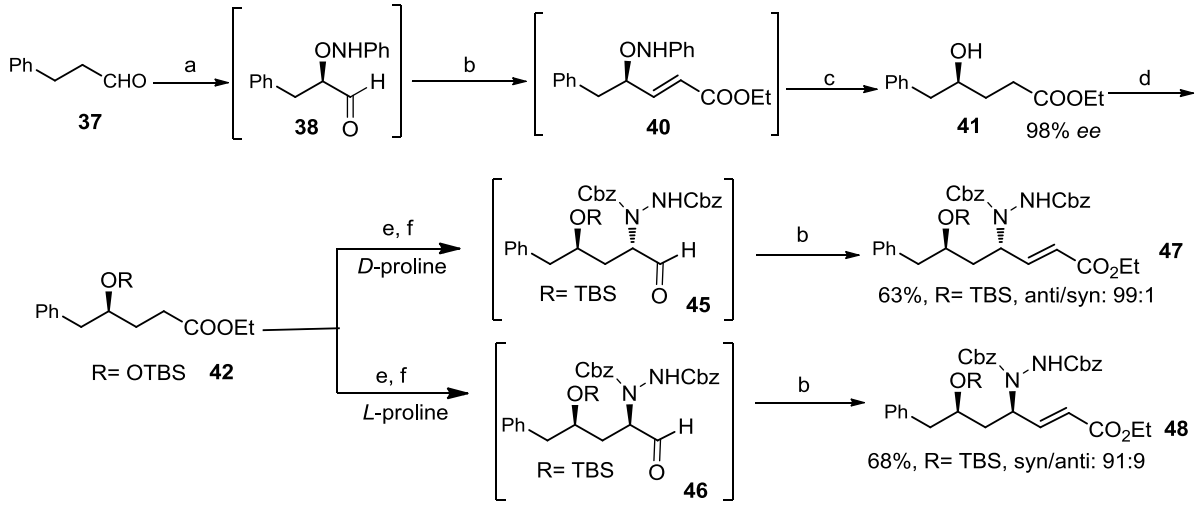
Scheme 11: *Reactions and conditions*: (a) Nitrosobenzene, *L*-proline, DMSO; (b) HWE salt, DBU, LiCl, CH_3CN; (c) H_2/Pd-C, EtOAc; (d) TBSOTf, 2,6-Lutidine, DCM; (e) DIBAL-H, DCM, -78 °C.

By subjecting *syn*-diol **43b** to a second cycle of iteration using the *L*-proline-catalyzed sequence of reactions, the diastereomerically pure triol **44** (10:1) was obtained in 88% yield (Scheme 11).

Kumar *et al.* (2010)[18]

Kumar *et al.* developed a general method for asymmetric synthesis of both *syn*/*anti*-1,3-amino alcohols using proline-catalyzed sequential α-aminoxylation/α-amination and

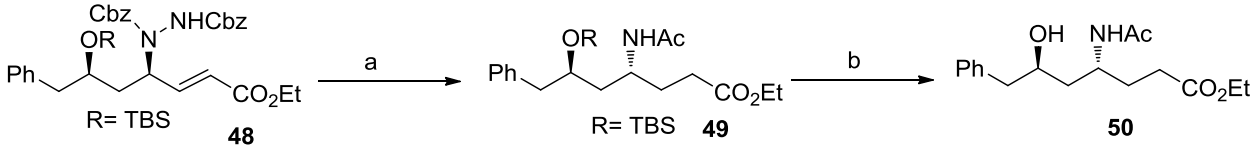
Horner-Wadsworth-Emmons (HWE) olefination of aldehydes as the key step. By using this method, a short synthesis of a bioactive molecule, (*R*)-1-((*S*)-1-methylpyrrolidin-2-yl)-5-phenylpentan-2-ol, is also accomplished.[18] The synthesis of 1,3-amino alcohols initiated with synthesis of protected *γ*-hydroxy esters **42** by the tandem α-aminoxylation and HWE olefination of aldehydes, a protocol developed by Kumar *et al*.[17] The commercially available phenyl propanal **37** on sequential α-aminoxylation and subsequent HWE olefination using triethyl phosphonoacetate, followed by hydrogenation using a catalytic amount of Pd/C, furnished the *γ*-hydroxy ester **41** in good yields (71%) and excellent enantioselectivities (98% *ee*). The free hydroxy group of *γ*-hydroxy ester was protected as TBS ether using TBSCl (Scheme 12).



Scheme 12: *Reactions and conditions*: (a) Nitrosobenzene, *L*-proline, DMSO; (b) HWE salt, DBU, LiCl, CH_3CN; (c) H_2/Pd-C, EtOAc; (d) TBSOTf, 2,6-Lutidine, DCM; (e) DIBAL-H, DCM, -78 °C; (f) DBAD, *D*/*L*-proline , CH_3CN, 0-10 °C, 3h.

The second stage, the introduction of amine functionality at the 3-position with respect to the hydroxy group initiated with the DIBAL-H reduction of ester **42** furnished the corresponding aldehyde which was then subjected to α-amination using commercially available dibenzyl azodicarboxylate (DBAD) as a nitrogen source and D/L-proline as a catalyst to furnish the α-amino aldehyde **45** and **46**, which on *in situ* trapping by triethyl phosphonoacetate (HWE olefination) in the presence of DBU furnished the *anti/syn*-1,3-amino alcohols **47** and **48** (Scheme 12).

For further synthetic manipulation, the *N-N* bond of substituted hydrazine **48** was easily cleaved with concomitant reduction of the double bond using freshly prepared Raney-Ni, and free amine was converted into its acetate derivative using Ac_2O. Subsequent silyl deprotection using TBAF furnished compound **50** in 67% yield, over three steps (Scheme 13).



Scheme 13: *Reactions and conditions*: (a) (i) H_2, Raney Ni, MeOH/AcOH, 24 h; (ii) Ac_2O, Et_3N, DMAP, DCM, 2 h; (b) TBAF, THF, 0 ^oC, 2 h.

4.1.3. Present work

Objective

γ-Butyrolactones **51** are a very common structural element in organic compounds, present in about 10% of all natural products.[19] They are present in a large variety of biologically active compounds such as alkaloids, antibiotics, pheromones, and flavour components (Figure 1).[20] A wide variety of naturally occurring mono-, di- and trisubstituted monocyclic γ-butyrolactones are known (Figure1). The physiological activity of these γ-lactones often depends on the optical purity and absolute configuration[21], which underlines the necessity for efficient and flexible routes to chiral lactones. They display a broad biological profile including strong antibiotic, antihelmitic, antifungal, antitumor, antiviral, antiinflammatory and cytostatic properties, which makes them interesting lead structures for new drugs. They also have great importance in the areas of agrochemicals, flavor components, material and in polymer productions.[22]

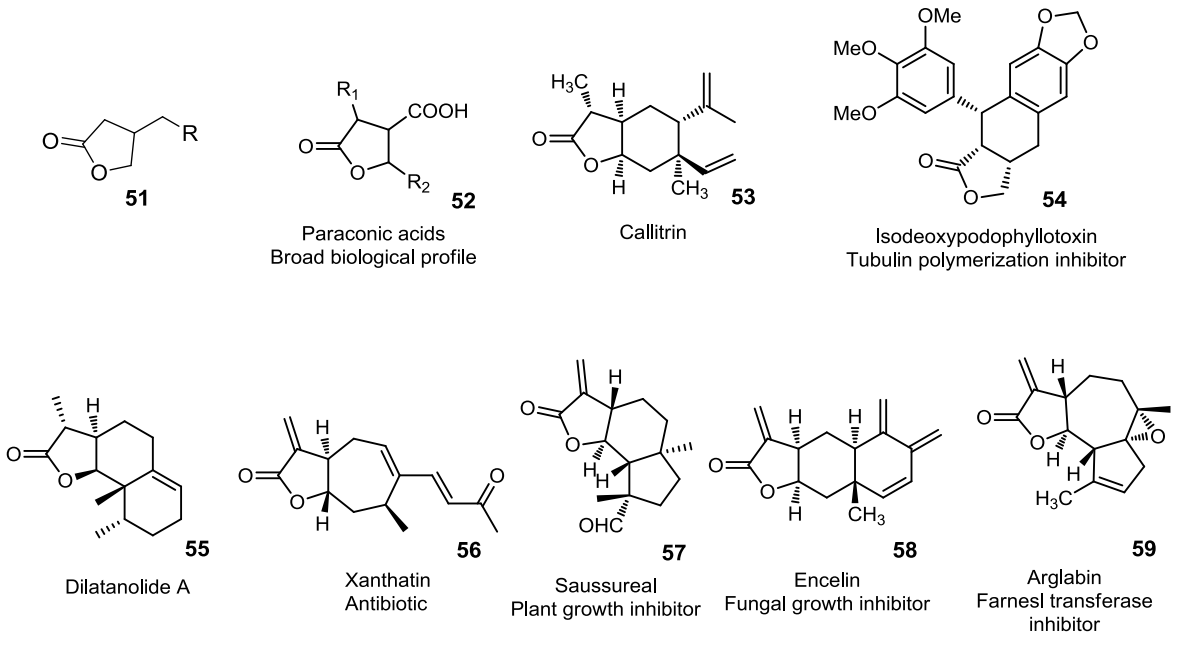
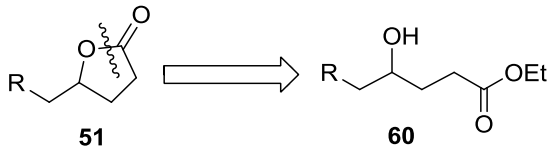


Figure 1: Representative examples of monocyclic, bicyclic and tricyclic γ-butyrolactone natural products

Since the lactone moiety represents a bifunctional structural element in which both functions can be selectively elaborated, lactones also represent valuable building blocks for synthesis. These wide applications of γ-butyrolactones has stimulated and fueled the effort to develop improved methodology for the construction of substituted γ-butyrolactones in an enantioselective manner.[23]These include diastereoselective conjugate addition to chiral butenolides,[24] asymmetric radical reaction,[25] dichloroketene addition to optically active alkenyl sulfoxide,[26] chiral auxiliary directed alkylation,[27] from *L*-malic acid via chiral *N*-alkyl-unsaturated-γ-lactams[28] and from *L*-glutamic acid,[29] and enzymatic resolution.[30] Catalytic asymmetric hydrogenation of itaconic acid derivatives followed by chemoselective reduction-lactonization[31] and chiral Rh(II)- catalyzed enantioselective intramolecular C-H insertion of alkyl diazoacetates[32] are the catalytic asymmetric synthesis of lactone **51**. The retrosynthetic disconnection on the cyclic ester functionality obviously reveals a 4-hydroxycarbonyl compound **60** as an acyclic synthon for a γ–butyrolactone (Scheme 14). The preparation of optically pure hydroxy esters **60** or acids and their conversion to lactones **51** are important processes in organic syntheses as a result of the significance of such molecules.[33] In contrast to the highly advanced methodology available for the synthesis of 3-hydroxycarbonyl compounds by aldol reactions, the analogous homoaldol reaction is much

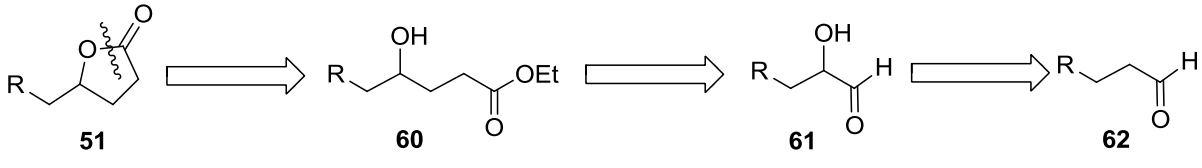
more difficult because of the inherent stability problems such as self-condensation commonly associated with homoenolates.[34]



Scheme 14: Retrosynthetic analysis of optically active γ-butyrolactones

Retrosynthetic Analysis of substituted γ–butyrolactone

In our continuing effort in the development of mild, practical methods for catalytic asymmetric synthesis, we have recently developed a practical and efficient iterative approach to prepare enantiomerically pure both *syn/anti*-1,3-polyols via proline-catalyzed sequential reactions (Scheme 11).[17] The γ-hydroxy ester **60** could be easily prepared from corresponding achiral aldehyde **62** through this protocol, the sequential reactions of α-aminoxylation followed by HWE-olefination reaction and finally Pd/C hydrogenation reaction (Scheme 15).



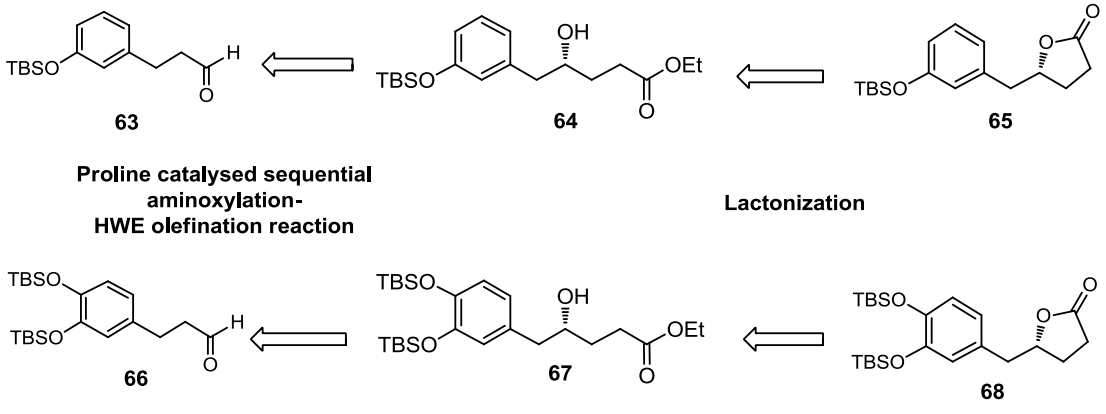
Scheme 15: Retrosynthetic scheme of optically active γ-butyrolactones through sequential reactions

Any reaction conditions which spontaneously lactonize the γ-hydroxy ester **60** into γ-butyrolactone **51** could definitely add an additional benefit to above retrosynthetic scheme (Scheme 15). In this chapter, we report an extended application of our protocol: a one-pot synthesis of enantiopure γ-butyrolactones from commercially available and inexpensive starting materials. The motivation of this study emanates from the view that this would permit an easy access to functionalised chiral lactones and thereby provide potential

intermediates for the synthesis of various natural products by way of several synthetic transformations.

4.1.4. Results and discussion

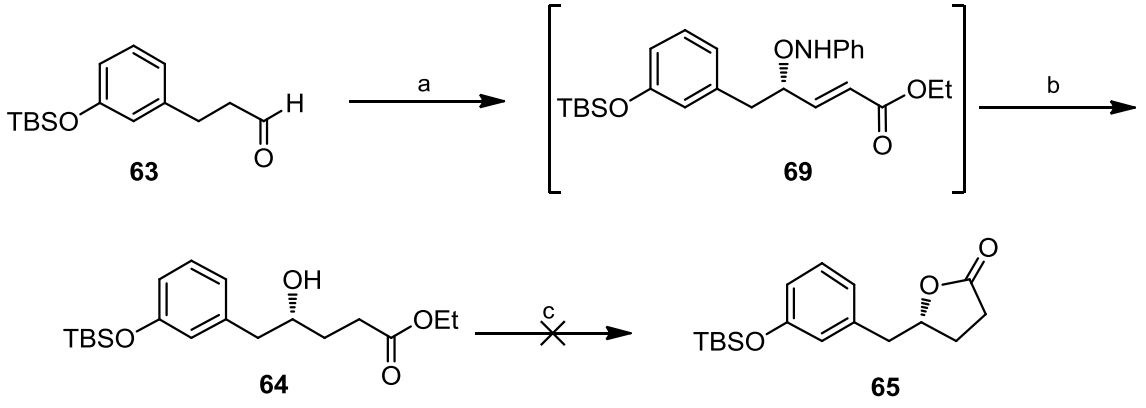
Organocatalytic domino reactions catalyzed by amines, especially by proline are widespread. The capability to tolerate numerous functional groups makes proline ideal for the design of new asymmetric organocatalytic domino reactions, although its scope is mainly limited to carbonyl systems.[1] In continuation of our interest in organocatalysis and our ongoing effort to expand the synthetic utility of sequential α-aminoxylation, HWE olefination reaction catalysed by proline[35], we have recently accomplished the syntheses of Bruguierol A and Bruguierol B (Section B).



Scheme 16: Retrosynthetic scheme for chiral intermediate **65** and **68**

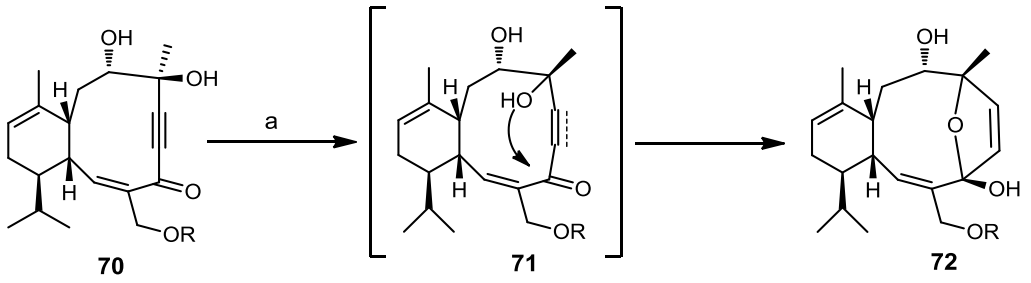
The lactones **65** and **68** were the key intermediates in the synthesis. Our initial approach for the synthesis of lactones **65** and **68** was envisioned as shown in Scheme 16. Lactones **65** and **68** was thought to be easily obtained by lactonizing *γ*-hydroxy esters **64** and **67**, which in turn could be prepared from sequential α-aminoxylation, HWE olefination reaction of the corresponding aldehydes **63** and **66**. Thus as shown in Scheme 17, synthesis of lactone **65** began with the OTBS protected aldehyde **63**, which was subjected to sequential α-aminoxylation (*D*-proline as a catalyst) followed by HWE olefination reaction and hydrogenation using a catalytic amount of Pd/C to furnish the γ-hydroxy ester **64** in 65% yield. We then focused on the lactonization of *γ*-hydroxy esters **64** by treating with catalytic *p*-TSA in MeOH[17, 18] as well as in DCM. But to our disappointment, some portion of OTBS

was deprotected during the reaction and we ended up with mixture of products. Then we attempted the lactonization of γ-hydroxy ester **64** into lactone **65** by using catalytic amount of 1 M HCl at 0 °C, which led to complete deprotection of OTBS. The same result has been found in the case of γ-hydroxy ester **67** during lactonization process.



Scheme 17: *Reagents and conditions*: (a) (i) Nitrosobenzene, *D*-proline, DMSO, 30 min, (ii) HWE salt, DBU, LiCl, CH_3CN, 1h; (b) (i) H_2/Pd-C, EtOAc, 4h, 65% over 2 steps; (c) cat. *p*-TSA, MeOH, 4 h.

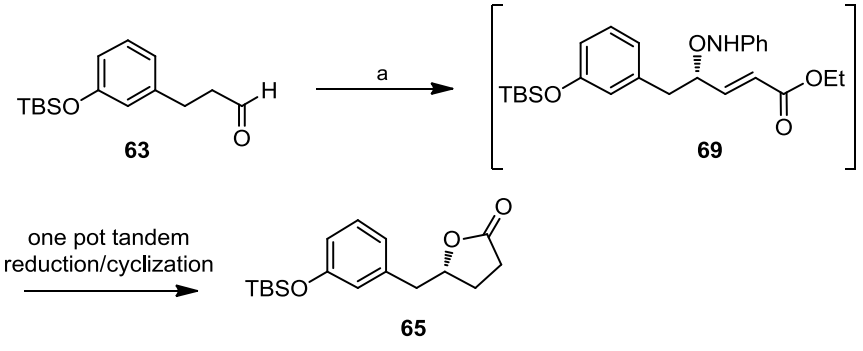
On the other hand we observed that prolonging the catalytic hydrogenation reaction using H_2/Pd-C in EtOAc resulted some spontaneously lactonized product **65** as a minor product (<10%) along with **64**. Several asymmetric domino reactions including a reduction as the key step are reported in the literature.[2] For example, Nicolaou *et al*. have developed a powerful asymmetric reduction cyclisation sequences in order to prepare important biological products such as eleutherobin (Scheme 18).[36] These observations finally led us to investigate the possibility of combining a tandem reduction/cyclization reaction to our previously established proline catalysed sequential α-aminoxylation/HWE olefination reaction. We reasoned that this method could make it possible to skip a number of steps in the total synthesis of Bruguierols A and B (Section B).



Scheme 18: *Reagents and conditions*: (a) H_2-Lindlar, Toluene, 78%.

In order to study the influence of reaction conditions on the lactonization of **64** to **65**, OTBS substituted phenyl propanal **63** was used as a model substrate. The α-aminoxylation of compound **63** was subjected to our previously established conditions. A mixture of aldehyde **63** (1 equiv.), nitrosobenzene (1equiv.), and *D*-proline (40 mol %) was stirred in the solvent DMSO at room temperature for 25 min, then cooled to 0 °C. Thereafter, a premixed and cooled (0 °C) solution of triethylphosphonoacetate (3 equiv.), DBU (3 equiv.), and LiCl (3 equiv.) in CH_3CN was added quickly at 0 °C. The resulting mixture was allowed to warm to room temperature over 1 h and quenched by addition of ice pieces. The acetonitrile was evaporated under vacuum and crude reaction mixture extracted with Et_2O. The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated in vacuum to give crude product **69** which was directly subjected to next step without purification (Scheme 19).

With the desired *O*-amino-substituted γ-hydroxyester **69** in hand, attention was directed to the one pot tandem reduction/cyclization reaction. Each trial reactions was carried out in 1 g scale. First we tried hydrogenation of crude **69** in ethyl acetate using 10 mol% Pd/C for 14 hours at room temperature (Table 1, entry 1). We monitored the tandem reduction/cyclization reaction using ^{1}H NMR spectroscopy.



Scheme 19: *Reagents and conditions*: (a) (i) Nitrosobenzene, *D*-proline, DMSO, 25 min; (ii) HWE salt, DBU, LiCl, CH_3CN 1h.

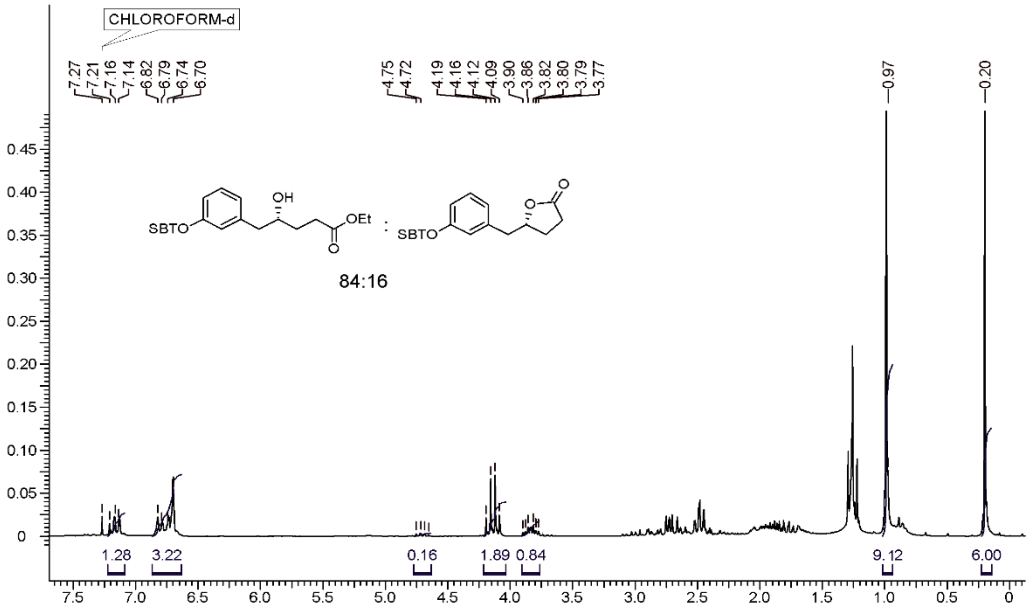


Figure 2: Crude ^{1}H NMR spectra of mixture **64** and **65** showing ratio 84:16 **(**Reaction condition table 1, entry 1)

Figure 2 shows that saturated γ-hydroxyester **64** and lactonized product **65** formed in 84:16 ratio. The disappearance of triplet peak at δ 1.21-1.28 (3H); quartet peak at δ 4.09-4.19 (2H), multiplet at δ 3.77-3.90 (1H) and appearance of a multiplet peak at δ 4.72-4.75 (1H) in ^{1}H NMR confirmed the formation of compound **65**.

Further, we anticipated that the experimental conditions necessary to achieve the lactonization might be quite vigorous. Practically, protic solvents were found to be optimal, providing adequate temperature control and favourable reaction rates. So we tried our next reaction in ethanol at room temperature (Table 1, entry 2). But to our disappointment even after 24 hours only 9% lactonized product could be obtained (Figure 3). In the next reaction, we stopped the hydrogenation within 5 hours after monitoring the completion of reduction reaction in TLC, then crude mixture was extracted and heated in ethanol at 60 ^{o}C for 15 hours to give lactonization product up to 55% yield (Table 1, entry 3) (Figure 4).

Entry	Reaction conditions	Yield of 64 in %	Yield of 65 in %
1	10 mol % Pd/C, H_2, EtOAc, rt, 14 h	84	16
2	10 mol % Pd/C, H_2, EtOH, rt, 24 h	91	09
3	(1) 10 mol % Pd/C, H_2, EtOH rt, 5 h. (2) EtOH, 60 ^oC, 15 h	45	55
4	(1) 10 mol % Pd/C, H_2, EtOAc, rt, 6 h (2) Pd/C, EtOAc, 60 ^oC, 6 h	25	75
5	(1) 10 mol % Pd/C, H_2, EtOAc, rt, 6 h (2) Pd/C, EtOAc, 60 ^oC, 12 h	14	86
6	(1) 20 mol % Pd/C ,H_2, rt, 4 h (2) Pd/C, EtOAc, 65 ^oC, 6 h	**7**	**93**

Table 1. One pot tandem reduction/cyclization of compound **69**

When the reaction was further investigated in ethyl acetate, it was observed that heating the reduced mixture in the same pot of Pd/C facilitated the lactonization reaction much faster than previous conditions (Table 1, entry 4) (Figure 5). Later we improved the yield by either stirring the reaction mixture at longer time (Table 1, entry 5) (Figure 6) or by adding 20 mol% Pd/C (Table 1, entry 6) (Figure 7). In TLC, these products **64** and **65** shows a small difference in R_f value, (0.61 for **64** and 0.55 for **65** in 40% ethyl acetate in petroleum ether) but we easily separated the mixture using flash chromatography (400 mesh silica). The disappearance of peaks, a triplet peak at δ 1.21-1.28 (3H); quartet peak at δ 4.08-4.19 (2H) and appearance of a multiplet peak at δ 4.69-4.75 (1H) in ^1H NMR confirmed the formation of compound **65**. In IR spectrum, a shift of carbonyl group stretching frequency from 1731 cm^{-1} to 1772 cm^{-1} confirmed the formation of saturated 5-membered lactone **65** (Scheme 19). Thus, through four sequential reactions and one column purification (Scheme 19), *γ*-butyrolactone **65** was obtained in 60 % yield and 98% ee.[37]

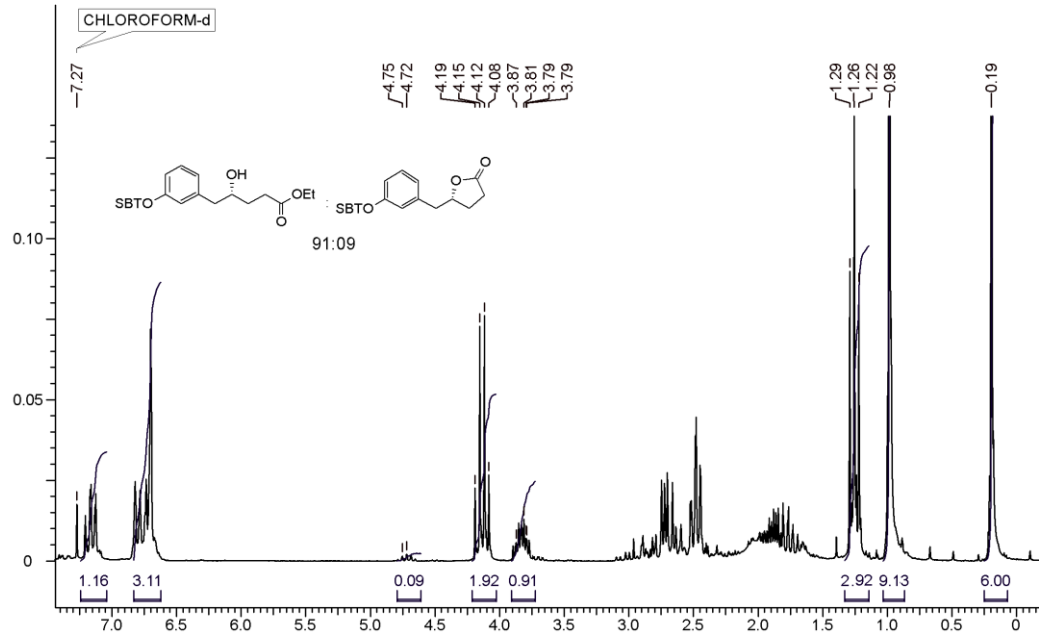


Figure 3: Crude ^{1}H NMR spectra of mixture **64** and **65** showing ratio 91:09 **(**Reaction condition table 1, entry 2)

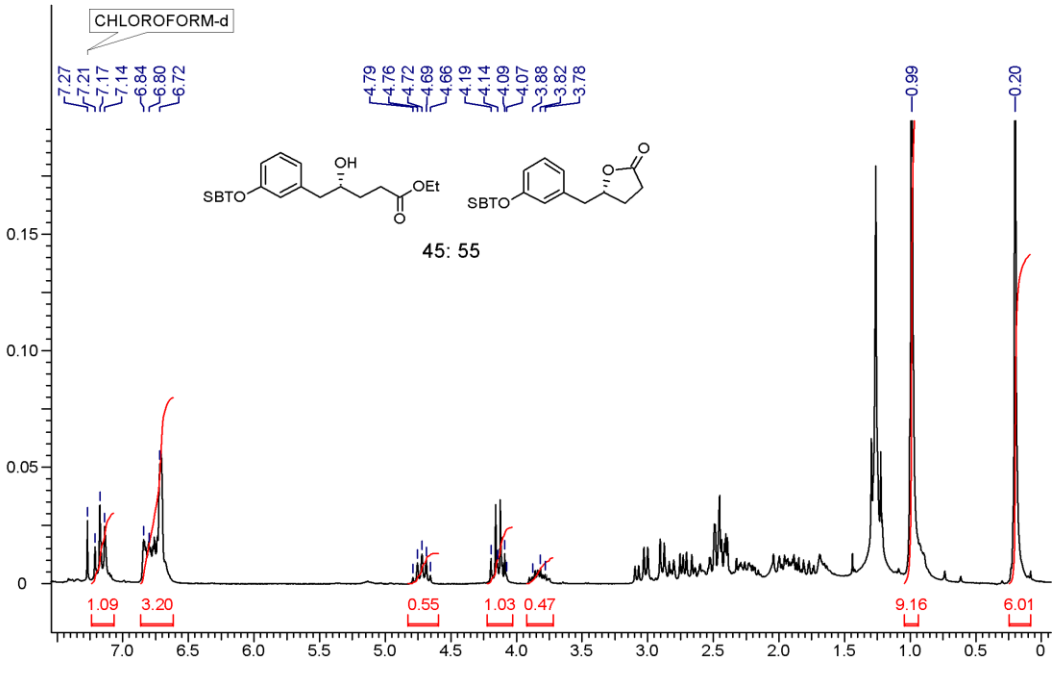


Figure 4: Crude ^{1}H NMR spectra of mixture **64** and **65** showing ratio 45:55 **(**Reaction condition table 1, entry 3)

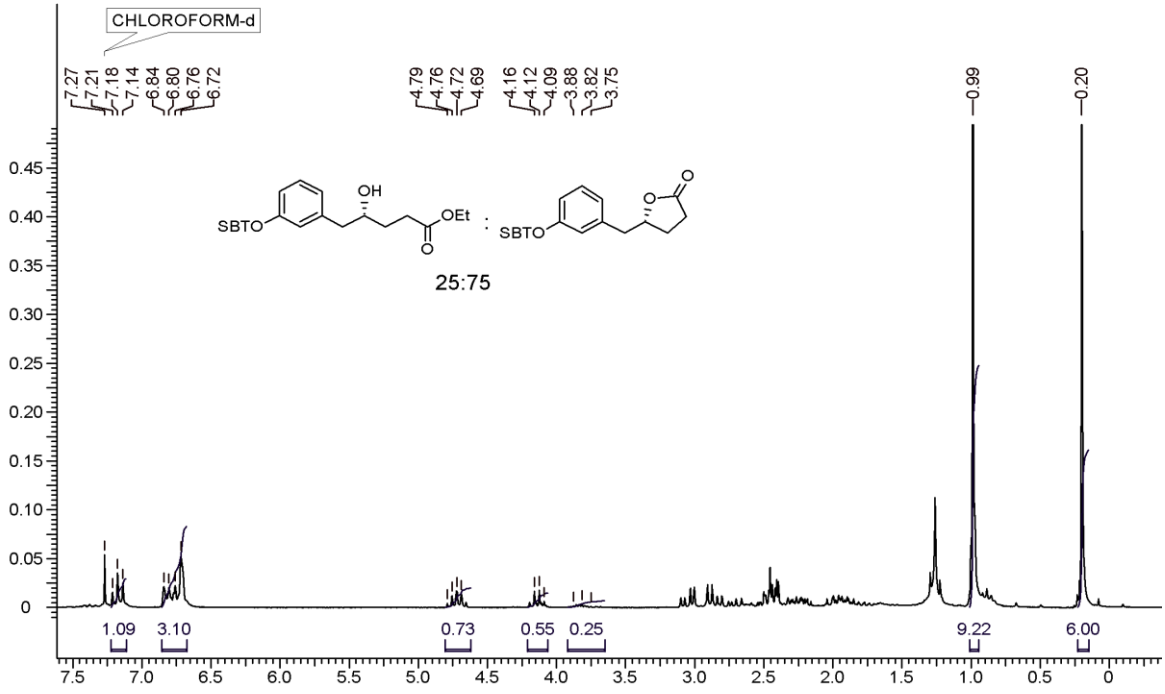


Figure 5: Crude ^{1}H NMR spectra of mixture **64** and **65** showing ratio 25:75
(Reaction condition table 1, entry 4)

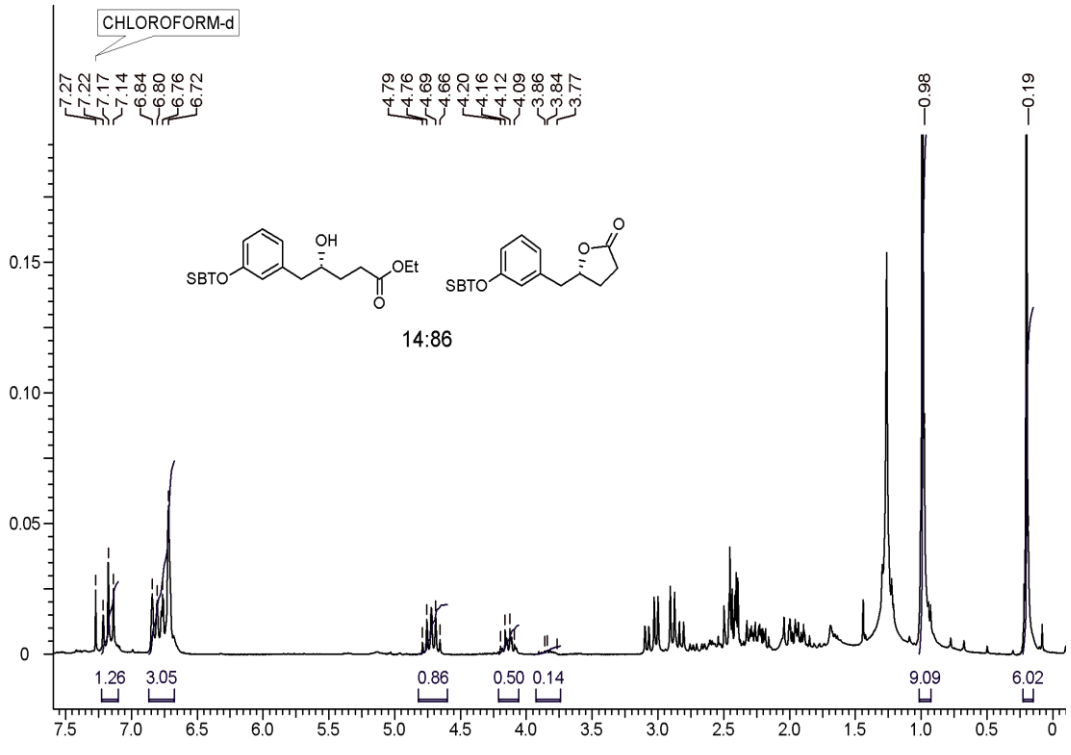


Figure 6: Crude ^{1}H NMR spectra of mixture **64** and **65** showing ratio 14:86
(Reaction condition table 1, entry 5)

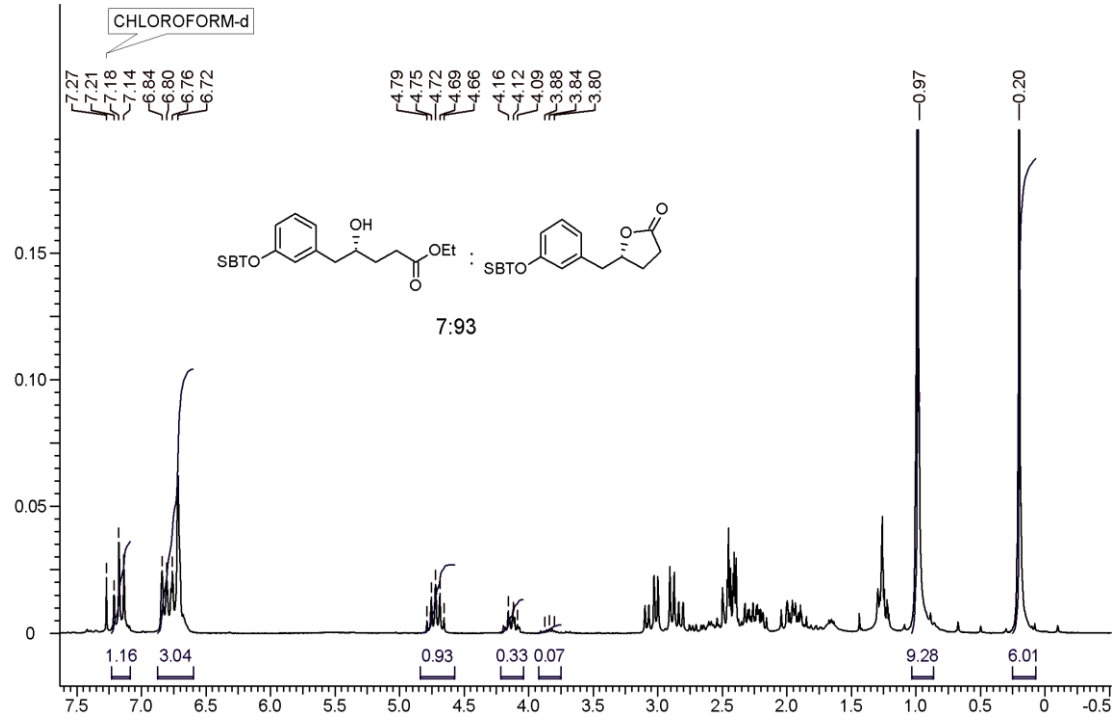
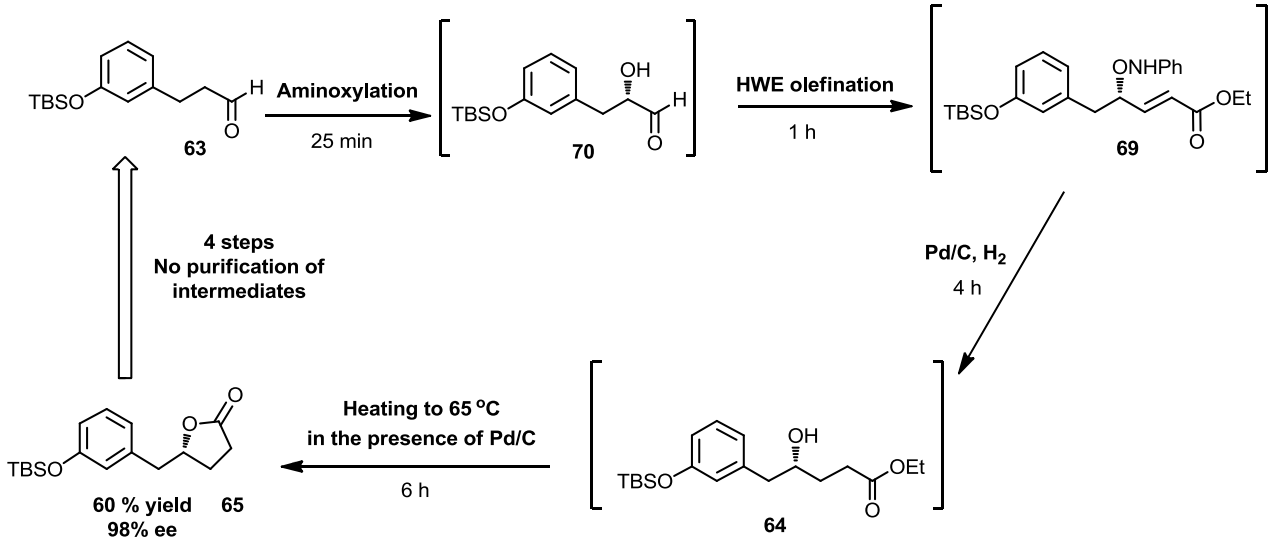
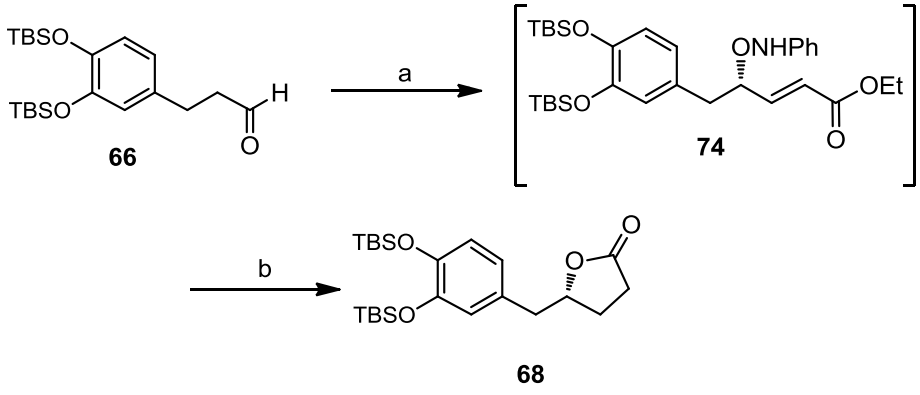


Figure 7: Crude ^{1}H NMR spectra of mixture **64** and **65** showing ratio 7:93
(Reaction condition table 1, entry 6)



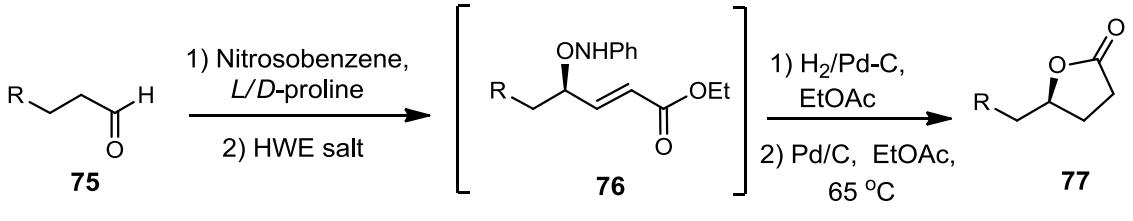
Scheme 20: Synthetic Strategy for the preparation of substituted chiral γ-butyrolactone **65** from aldehyde **63** via proline catalysed sequential lactonization

To test the generality of the one-pot method we also investigated the preparation of lactone **68** from **66** (Scheme 21). The proline catalysed sequential lactonization reaction of crude aldehyde **66** provided the substituted enatiopure γ-butyrolactone **68** in overall 45% yield and 96% ee.[38]



Scheme 21: *Reagents and conditions*: (a) (i) Nitrosobenzene, *D*-proline, DMSO, 30 min; (ii) HWE salt, DBU, LiCl, CH_3CN, 1h; (b) (i) H_2/Pd-C, EtOAc, 3h; (ii) Pd/C, EtOAc, 65 ^oC, 10 h (45 % over 4 steps).

We further explored the scope of this sequential lactonization reaction by using various aliphatic aldehydes bearing different functionalities. It was found that the process displayed a wide substrate scope and was compatible with various aromatic and aliphatic functionalities (Scheme 22). Excellent enantioselectivities (with 95-99% *ee*s) and good yields (60-75%) were achieved in all cases (Table 2). The stereochemistry and *ee* of this tandem transformation was assigned according to the previous reports.[17, 18]



Scheme 22: Synthesis of of substituted chiral γ-butyrolactone **77 a-e** from aldehyde **75 a-e** via proline catalysed sequential lactonization

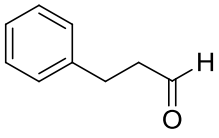
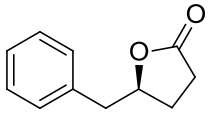
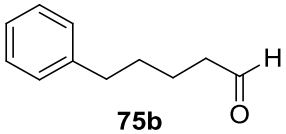
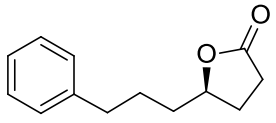
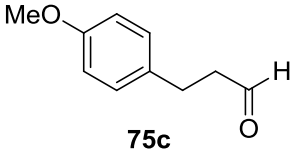
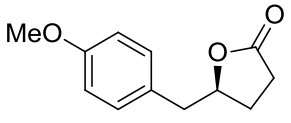
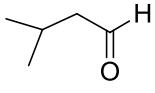
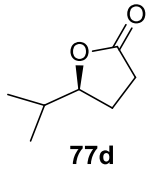
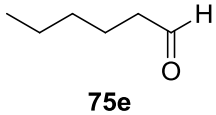
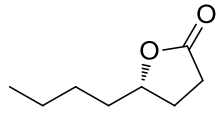
Entry	Substrate 75	Catalyst	Product 77	Yield %
1	 **75a**	*L*-proline	 **77a**	70
2	 **75b**	*L*-proline	 **77b**	65
3	 **75c**	*L*-proline	 **77c**	75
4	 **75d**	*L*-proline	 **77d**	70
5	 **75e**	*D*-proline	 **77e**	62

Table 2: Synthesis of of substituted chiral γ-butyrolactone **77 a-e** from aldehyde **75 a-e**

4.1.5. Conclusion

In conclusion, we have developed a novel, practical sequential asymmetric α-aminoxylation/Wadsworth-Emmons-Horner olefination; tandem reduction/cyclization reaction of aldehydes for the synthesis of optically active substituted γ-butyrolactone. The advantages of the sequential process include the following: (1) all starting materials are readily available; (2) the *O*-amino-substituted unsaturated ester that is formed after sequential α-aminoxylation and HWE olefination can be isolated in good yield and is

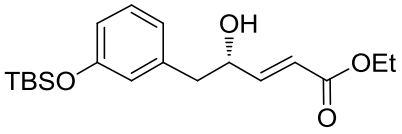
converted to γ-butyrolactone without requiring a separate column purification step, (3) the procedure is very easy to operate under the ordinary lab conditions; (4) both (*R*)- and (*S*)-substituted γ-butyrolactone can be made since either enantiopure form of the proline is commercially available. The synthetic utility of this protocol was further demonstrated by the asymmetric synthesis of Bruguierol A and Bruguierol B (Section B).

4.1.6. Experimental Section

General Experimental Procedure for the proline-catalysed sequential lactonization reaction

To a solution of aldehyde (10 mmol, 1 equiv.) and nitroso benzene (1-1.1 equiv.) in anhydrous DMSO (15 mL) was added *L/D*-proline (20-40 mol%) at 25 °C. The mixture was vigorously stirred for 25 min under argon (the colour of the reaction changed from green to yellow during this time), then cooled to 0 °C. Thereafter, A premixed and cooled (0 °C) solution of triethylphosphonoacetate (3 equiv.), DBU (3 equiv.) and LiCl (3 equiv.) in CH_3CN (15 mL) was added quickly (1-2 min) at 0 °C. The resulting mixture was allowed to warm to room temperature over 1 h, and quenched by addition of ice pieces. The acetonitrile was evaporated under vacuum. This reaction mixture was then poured into water (50 mL) and extracted with Et_2O (3×50 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated in vacuum to give crude product which was directly subjected to next step without purification. To the crude unsaturated ester in ethyl acetate was added Pd-C (20%) under hydrogenation conditions. After 2-4 hours of stirring, hydrogen atmosphere was removed and continued the stirring of reaction mixture at elevated temperature (60-65 ^oC) for another 6-10 hours. On completion of reaction (until ^1H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of celite and concentrated in vacuum to give γ-butyrolactone. The crude product was then purified by using flash column chromatography using pet ether and EtOAc.

(*S*,*E*)-Ethyl 5-(3-((tert-butyldimethylsilyl)oxy)phenyl)-4-hydroxypent-2-enoate (69)



Mol. Formula: $C_{19}H_{30}O_4Si$

$[\alpha]_D^{25}$: -3.36 (*c*1.2, $CHCl_3$)

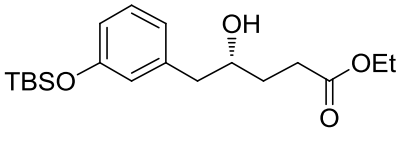
IR ($CHCl_3$, cm^{-1}): ν_{max} 3427, 2897, 2931, 2859, 1714, 1658, 1602, 1585, 1486, 1277, 1160, 977, 840, 757, 695.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.20 (s, 6H), 0.99 (s, 9H), 1.26-1.33 (t, *J*= 7.1 Hz, 3H), 1.95 (brs, 1H), 2.68-2.79 (m, 1H), 2.85-2.96 (m, 1H), 4.15-4.26 (q, *J*= 7.1 Hz, 2H), 4.49-4.54 (m, 1H), 6.02-6.11 (dd, *J*= 15.7, 1.8 Hz, 1H), 6.71-6.84 (m, 3H), 6.96-7.06 (dd, *J*= 15.7, 4.5 Hz, 1H), 7.15-7.19 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.4, 14.1, 18.1, 25.6, 43.0, 60.4, 71.6, 118.5, 120.5, 121.2, 122.3, 129.5, 138.2, 148.8, 155.8, 166.5 ppm.

Analysis: Calcd.: C, 65.10; H, 8.63; **Found:** C, 65.14; H, 8.67.

(*R*)-Ethyl 5-(3-((tert-butyldimethylsilyl)oxy)phenyl)-4-hydroxypentanoate (64)



Mol. Formula: $C_{19}H_{32}O_4Si$

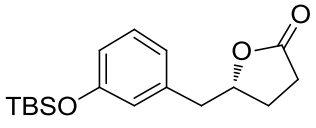
IR ($CHCl_3$, cm^{-1}): ν_{max} 3420, 3029, 2894, 2957, 2931, 2859, 1738, 1604, 1585, 1486, 1444, 1274, 1160, 1004, 970, 839, 782, 665.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.19 (s, 6H), 0.97 (s, 9H), 1.22-1.29 (t, *J*= 7.1 Hz, 3H), 1.74-1.92 (m, 2H), 2.05 (brs, 1H), 2.45-2.49 (m, 2H), 2.66-2.75 (m, 2H), 3.74-3.88 (m, 1H), 4.08-4.19 (q, *J*=7.1 Hz, 2H), 6.70-6.82 (m, 3H), 7.13-7.17 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.4, 14.1, 18.1, 25.6, 28.5, 33.6, 41.4, 60.0, 68.7, 119.0, 120.9, 122.0, 129.5, 140.0, 155.8, 173.3 ppm.

Analysis: Calcd.: C, 64.73; H, 9.15; **Found:** C, 64.71; H, 9.14.

(*R*)-5-(3-((*tert*-Butyldimethylsilyl)oxy)benzyl)dihydrofuran-2(3*H*)-one (65)



Yield: 0.755 g from 1 g (60% over 4 steps)

Mol. Formula: $C_{17}H_{26}O_3Si$

$[\alpha]_D^{25}$: -5.52 (*c* 3.4, $CHCl_3$)

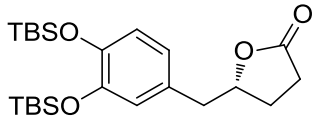
IR ($CHCl_3$, cm^{-1}): ν_{max} 3019, 2956, 2931, 1772, 1604, 1583, 1486, 1444, 1278, 1161, 1007, 971, 781, 664.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.20 (s, 6H), 0.99 (s, 9H), 1.90-2.00 (m, 1H), 2.22-2.25 (m, 1H), 2.41-2.50 (m, 2H), 2.83-2.89 (dd, *J*= 13.8, 6.5 Hz, 1H), 3.02-3.07 (dd, *J*=13.8, 5.8 Hz, 1H), 4.69-4.75 (m, 1H), 6.71-6.76 (m, 2H), 6.81-6.83 (m, 1H), 7.15-7.19 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.4, 18.1, 25.6, 27.0, 28.6, 41.1, 80.7, 118.6, 121.2, 122.4, 129.5, 137.2, 155.8, 176.9 ppm.

Analysis: Calcd.: C, 66.62; H, 8.55; **Found:** C, 66.60; H, 8.53.

(*R*)-5-(3,4-bis((*tert*-Butyldimethylsilyl)oxy)benzyl)dihydrofuran-2(3*H*)-one (68)



Yield: 0.495 g from 1 g (45 % over 4 steps)

Mol. Formula: $C_{23}H_{40}O_4Si_2$

$[\alpha]_D^{25}$: +1.36 (*c,* 1.4, $CHCl_3$)

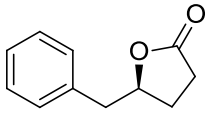
IR ($CHCl_3$, cm^{-1}): ν_{max} 3021, 2953, 2890, 2858, 1770, 1601, 1583, 1484, 1447, 1270, 1161, 1017, 975, 664.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.20 (s, 12 H), 0.98 (s, 18 H), 1.92-2.02 (m, 1 H), 2.16-2.30 (m. 1H), 2.36-2.52 (m, 2 H), 2.73-2.84 (m, 1H), 2.92-3.02 (m, 1H), 4.61-4.74 (m, 1H), 6.63-6.79 (m, 3H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.0, 18.3, 25.9, 27.0, 28.6, 41.4, 80.7, 121.0, 121.3, 121.4, 131.6, 145.1, 145.9, 176.9 ppm.

Analysis: Calcd.: C, 63.25; H, 9.23; **Found**: C, 63.23; H, 9.27.

(*S*)-5-Benzyldihydrofuran-2(3*H*)-one (77a)



Yield: 0.92 g from 1 g (70 % over 4 steps)

Mol. Formula: $C_{11}H_{12}O_2$

$[\alpha]_D^{25}$: +38.34 (*c* 1.5, $CHCl_3$)

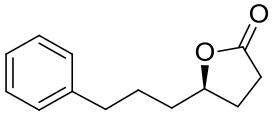
IR ($CHCl_3$, cm^{-1}): ν_{max} 3019, 2953, 2890, 2858, 1772, 1601, 1583, 1494, 1447, 1270, 1161, 1022, 970, 663.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.97-2.08 (m, 1H), 2.31-2.44 (m, 1H), 2.46-2.56 (m, 2H), 2.94-3.20 (m, 2H), 4.74-4.87 (m, 1H), 7.27-7.44 (m, 5 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.2, 28.1, 41.7, 81.7, 127.1, 128.5, 136.5, 177.4 ppm.

Analysis: Calcd.: C, 74.98; H, 6.86; **Found:** C, 74.89; H, 6.83;

(*R*)-5-(3-Phenylpropyl)dihydrofuran-2(3*H*)-one (77b)



Yield: 0.82 g from 1 g (65 % over 4 steps)
Mol. Formula: $C_{13}H_{16}O_2$

$[\alpha]_D^{25}$: +27.86 (*c* 1, $CHCl_3$).

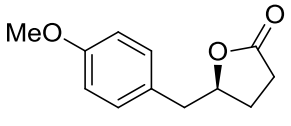
IR ($CHCl_3$, cm^{-1}): ν_{max} 3021, 2995, 2890, 2858, 1769, 1605, 1583, 1484, 1447, 1273, 1161, 890, 690

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.76-1.79 (m, 1H), 1.84-1.89 (m, 2H), 1.93-1.95 (m, 2H), 2.37-2.43 (dq, *J*= 13.0, 6.8 Hz, 1 H), 2.60-2.63 (dd, *J*=9.5, 7.0 Hz, 2H), 2.75-2.78 (m, 2H), 4.56-4.62 (m, 1 H), 7.27-7.31 (m, 3 H), 7.36-7.40 (m, 2 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.9, 27.9, 28.7, 35.0, 35.4, 80.7, 125.8, 128.3, 141.5, 177.1 ppm.

Analysis: Calcd.: C, 76.44; H, 7.90. **Found:** C, 76.40; H, 7.91.

(*S*)-5-(4-Methoxybenzyl)dihydrofuran-2(3*H*)-one (77c)



Yield: 0.94 g from 1 g (75 % over 4 steps)

Mol. Formula: $C_{12}H_{14}O_3$

$[\alpha]_D^{25}$: +10.12 (*c* 0.5, $CHCl_3$)

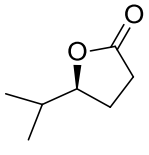
IR ($CHCl_3$, cm^{-1}): ν_{max} 3021, 2890, 2858, 1770, 1601, 1583, 1484, 1447, 1273, 1250, 1161, 1040, 905, 770.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.88-2.05 (m, 1H), 2.23-2.47 (m, 3 H), 2.89-2.98 (m, 2 H), 3.79 (s, 3 H), 4.63-4.76 (m, 1 H), 6.83-6.87 (m, 2 H), 7.12-7.17 (m, 2 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.8, 28.5, 40.1, 55.0, 80.8, 113.8, 127.7, 130.3, 158.4, 177.1 ppm.

Analysis: Calcd.: C, 69.88; H, 6.84. **Found:** C, 69.91; H, 6.85.

(*S*)-5-iso-Propyldihydrofuran-2(3*H*)-one (77d)



Yield: 1 g from 1 g (70 % over 4 steps)

Mol. Formula: $C_7H_{12}O_2$

$[\alpha]_D^{25}$:+34.54 (*c* =1.2, $CHCl_3$).

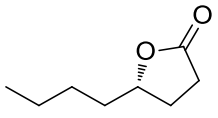
IR ($CHCl_3$, cm^{-1}): ν_{max} 2856, 2731, 1771, 1385, 1270, 1181, 1007, 978, 721.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.92-0.94 (d, *J*=6.8 Hz, 3 H), 1.01-1.03 (d, *J*= 6.8 Hz, 3H), 1.81-1.95 (m, 2H), 2.20-2.29 (dq, *J*= 13.1, 6.5 Hz, 1H), 2.50-2.65 (m, 2H), 4.16-4.22 (q, *J*= 7.3 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 17.2, 18.3, 25.5, 29.1, 32.9, 85.8, 177.3 ppm.

Analysis: Calcd.: C, 65.60; H, 9.44; **Found:** C, 65.53; H, 9.39.

(*S*)-5-Butyldihydrofuran-2(3*H*)-one (77e)



Yield: 0.88 g from 1 g (62 % over 4 steps)

Mol. Formula: $C_8H_{14}O_2$

$[\alpha]_D^{25}$: - 8.73 (*c* 1.5, $CHCl_3$)

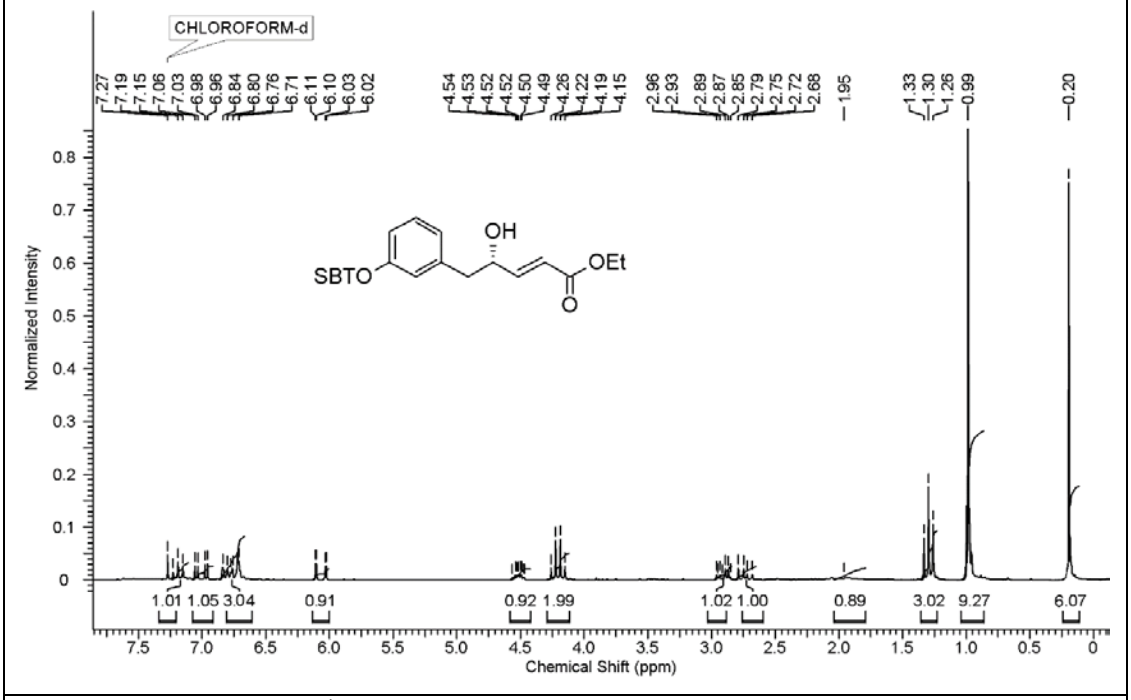
IR ($CHCl_3$, cm^{-1}): ν_{max} 2934, 2897, 2858, 1773, 1464, 1447, 1273, 1183, 890.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87-0.94 (t, *J* = 7.2 Hz, 3H), 1.25-1.36 (m, 4H), 1.67-1.72 (m, 2H), 1.77-1.90(m, 2H), 2.32-2.41(m, 1H), 2.51-2.58 (m, 2H), 4.73-4.87 (m, 1H) ppm.

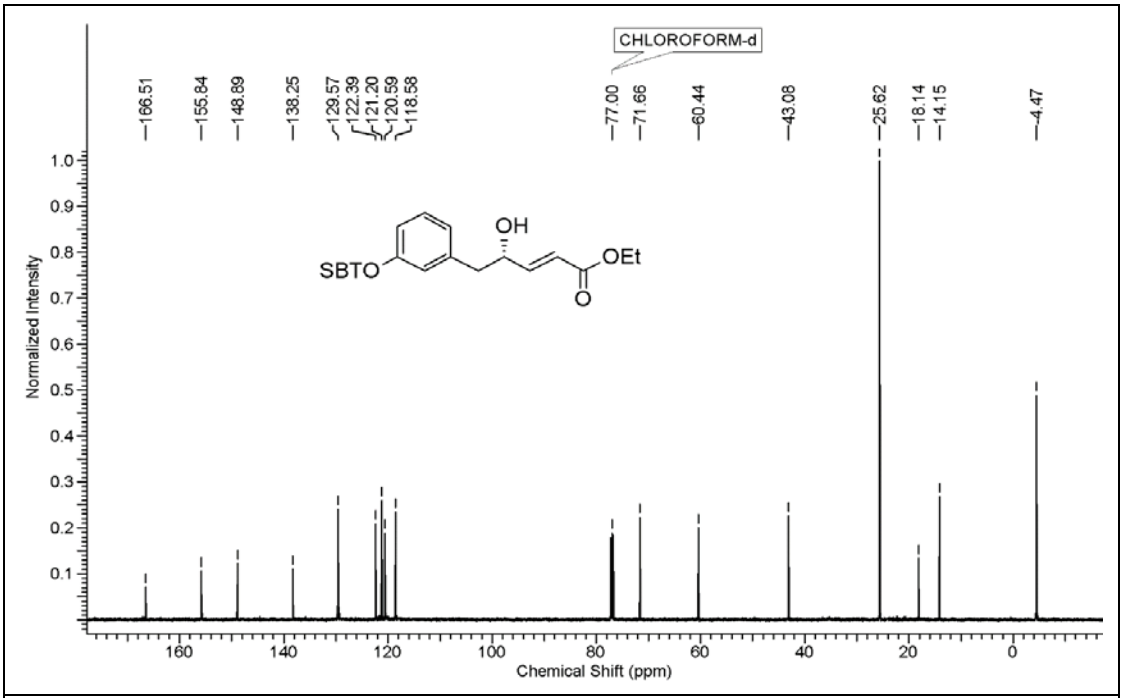
^{13}C NMR (100 MHz, $CDCl_3$): *δ* 13.9, 21.2, 22.4, 28.3, 28.8, 33.0, 80.9, 177.4 ppm.

Analysis Calcd. C, 67.57; H, 9.92; Found C, 67.51; H, 9.87.

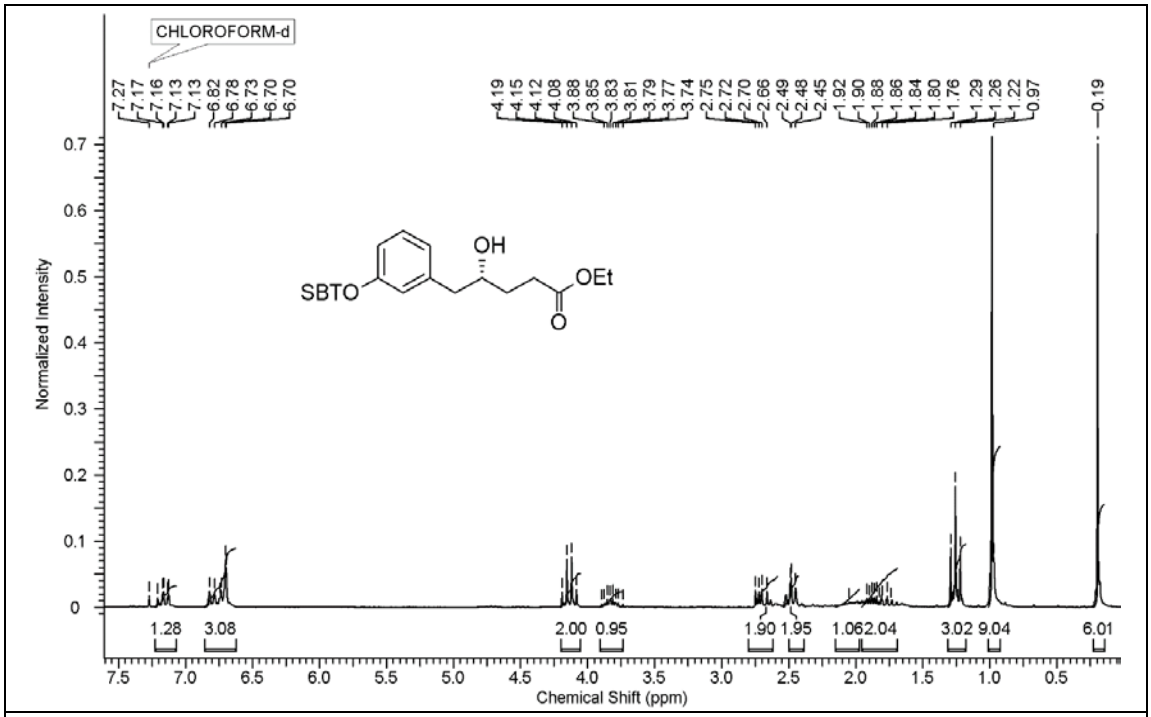
4.1.7. Spectra



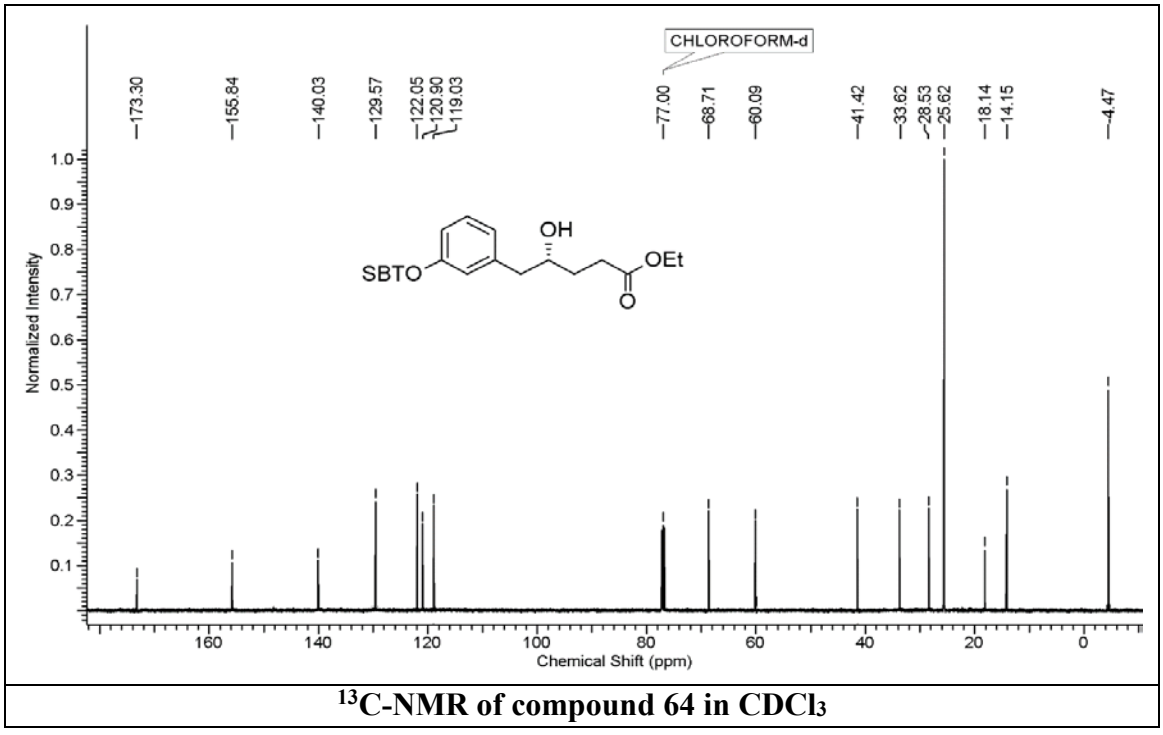
^{1}H-NMR of compound 69 in $CDCl_3$



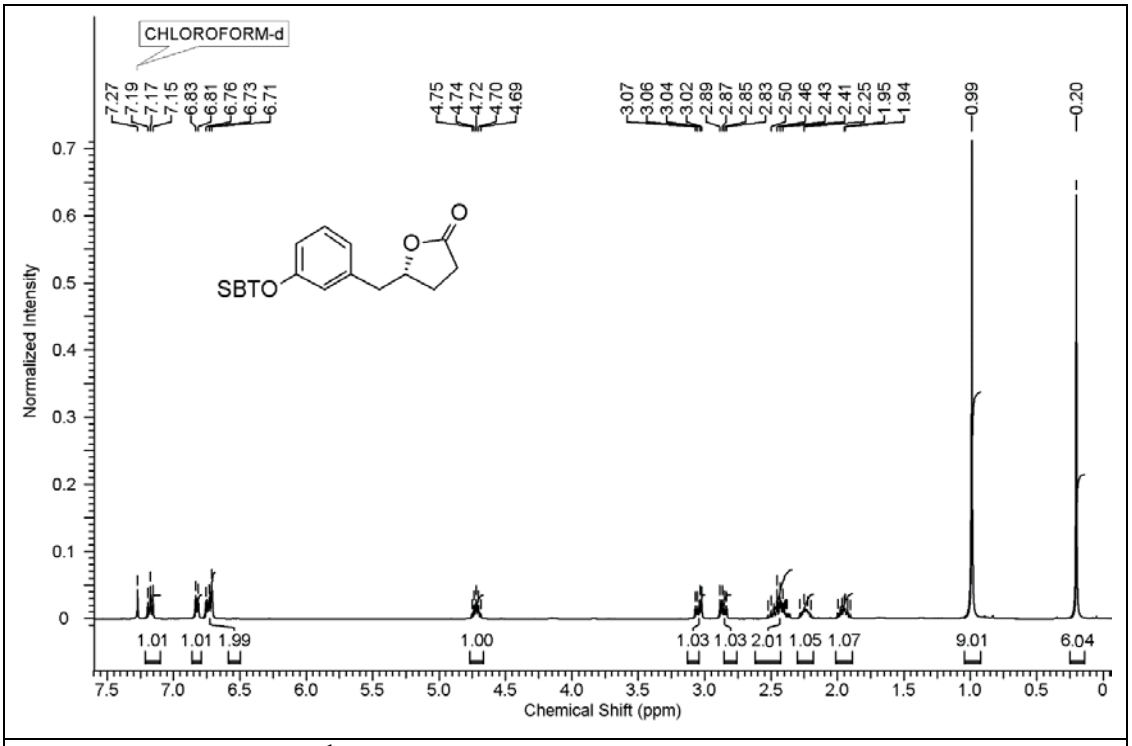
^{13}C-NMR of compound 69 in $CDCl_3$



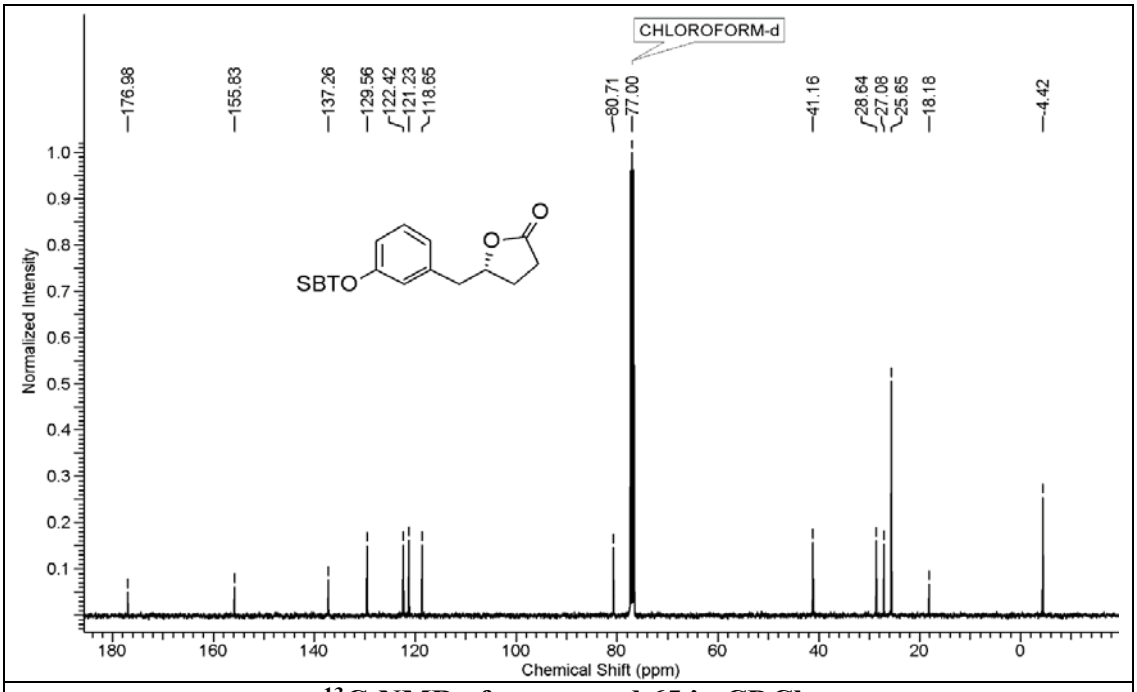
^{1}H-NMR of compound 64 in $CDCl_3$



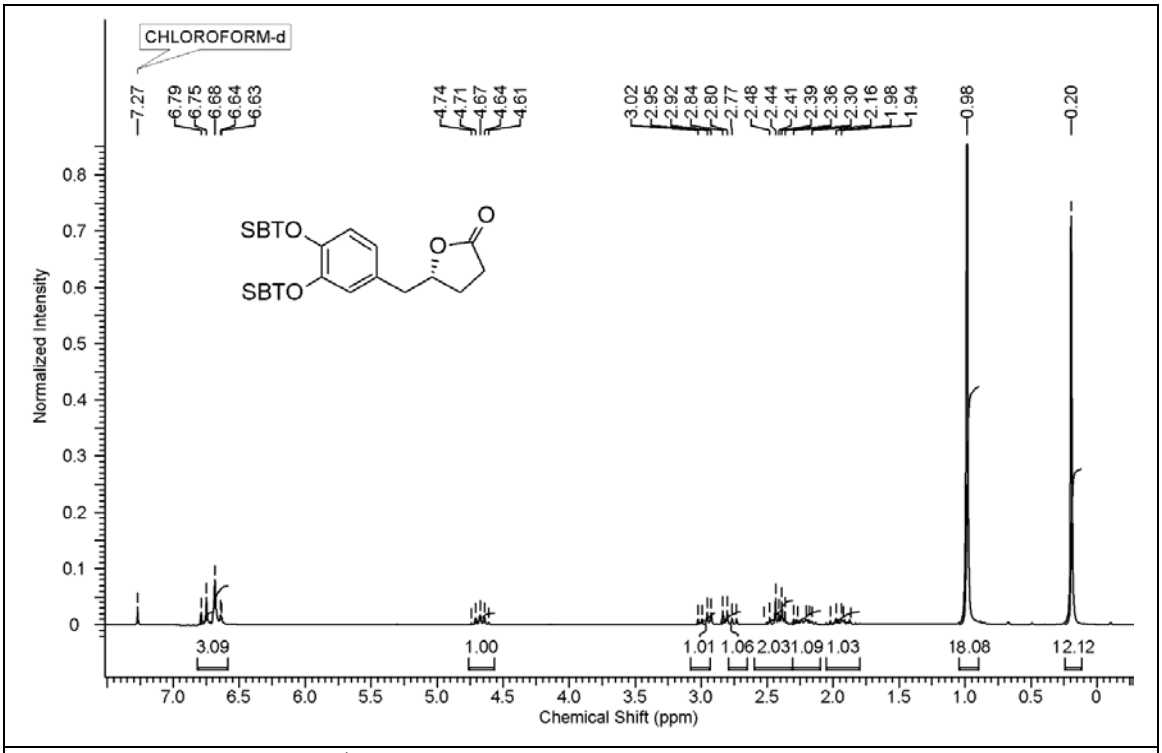
^{13}C-NMR of compound 64 in $CDCl_3$



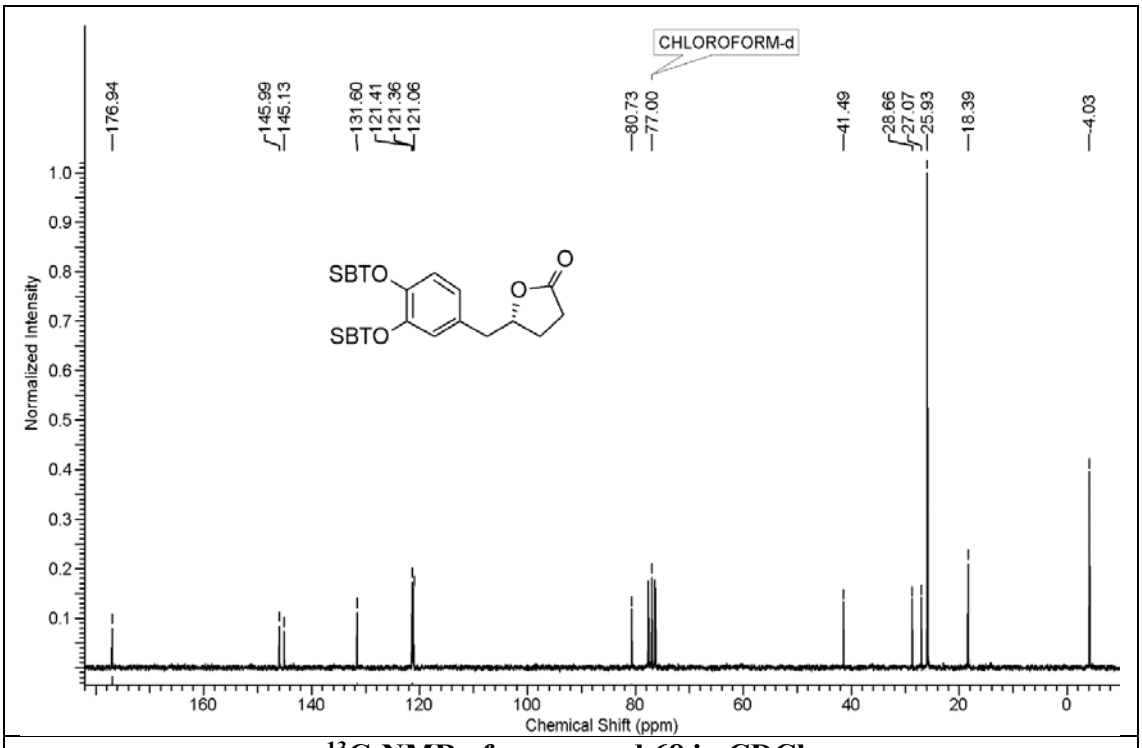
^{1}H-NMR of compound 65 in $CDCl_3$



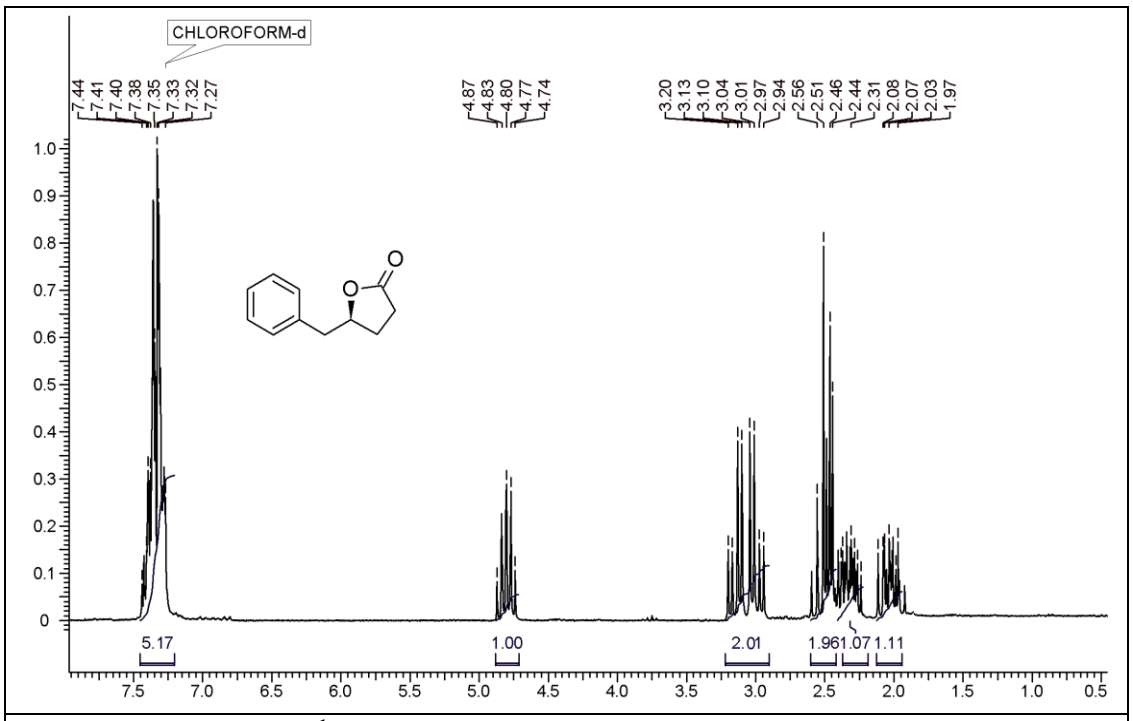
^{13}C-NMR of compound 65 in $CDCl_3$



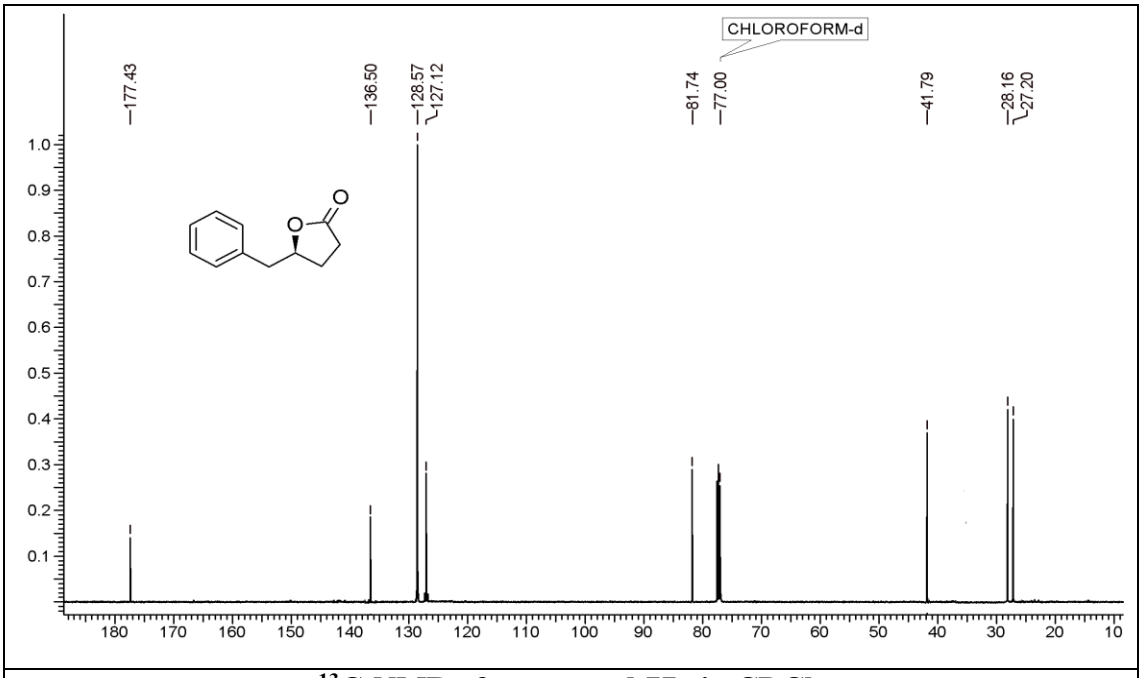
^{1}H-NMR of compound 68 in $CDCl_3$



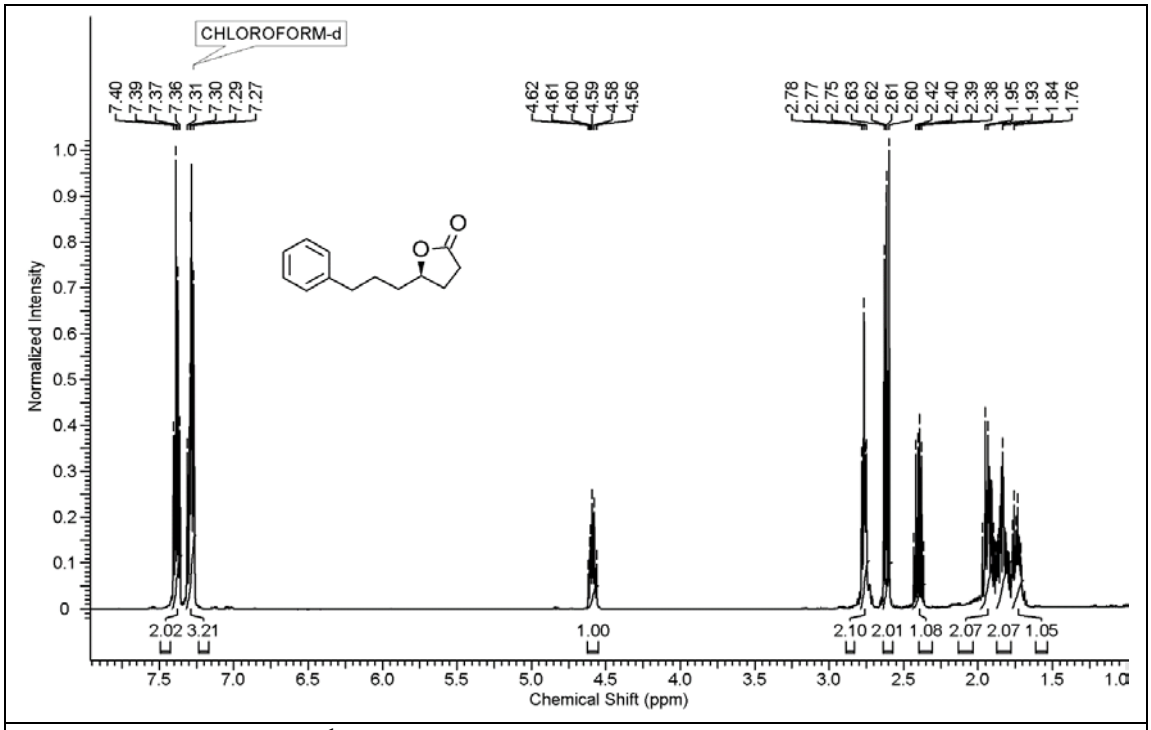
^{13}C-NMR of compound 68 in $CDCl_3$



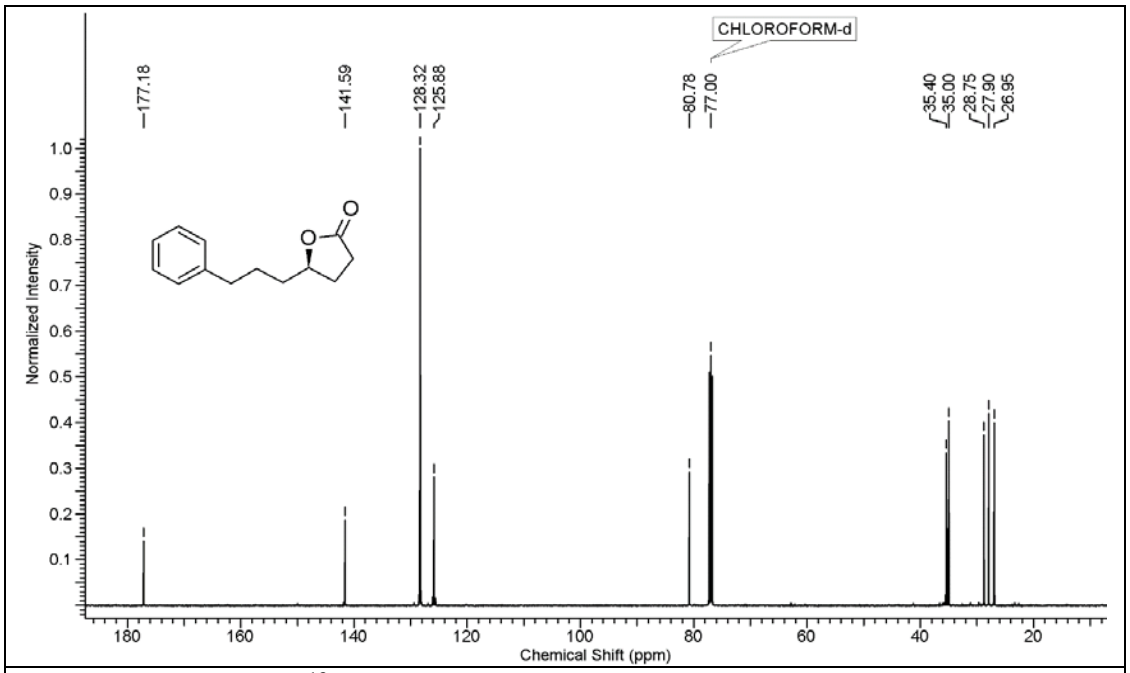
^{1}H-NMR of compound 77a in $CDCl_3$



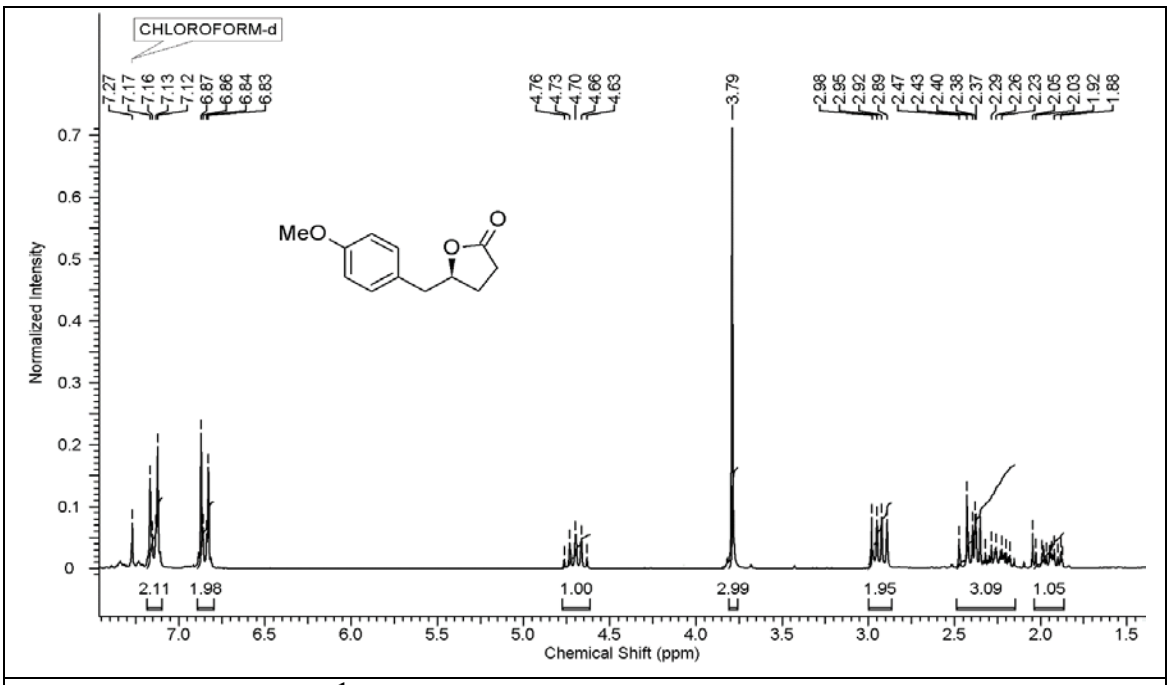
^{13}C-NMR of compound 77a in $CDCl_3$



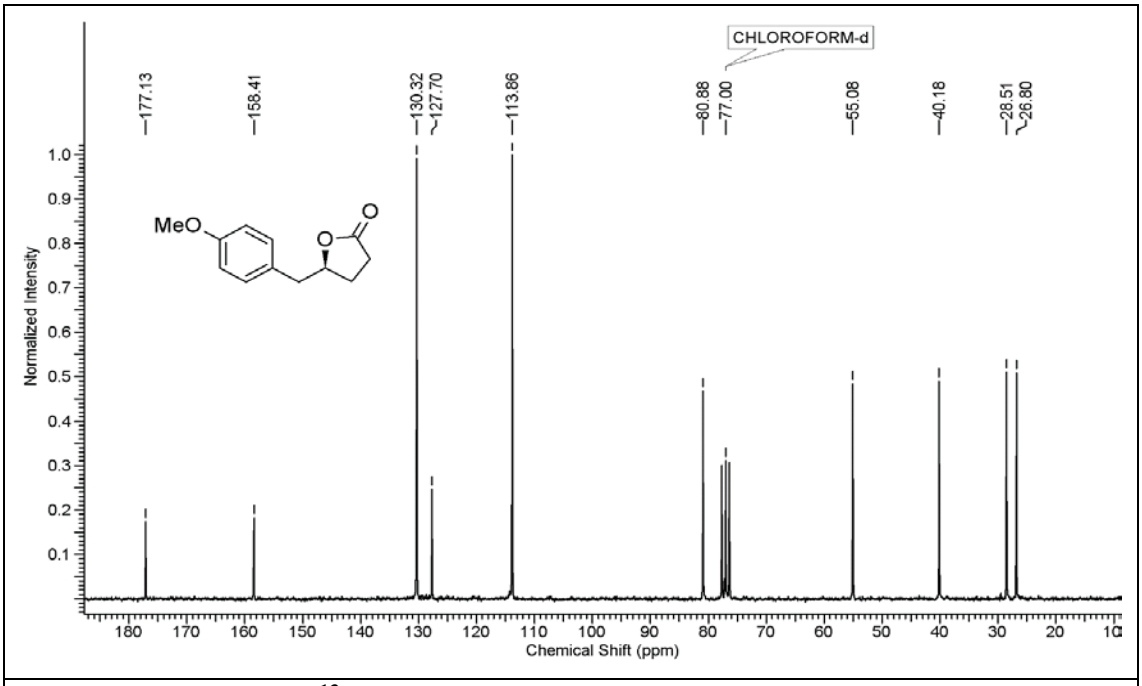
^{1}H-NMR of compound 77b in $CDCl_3$



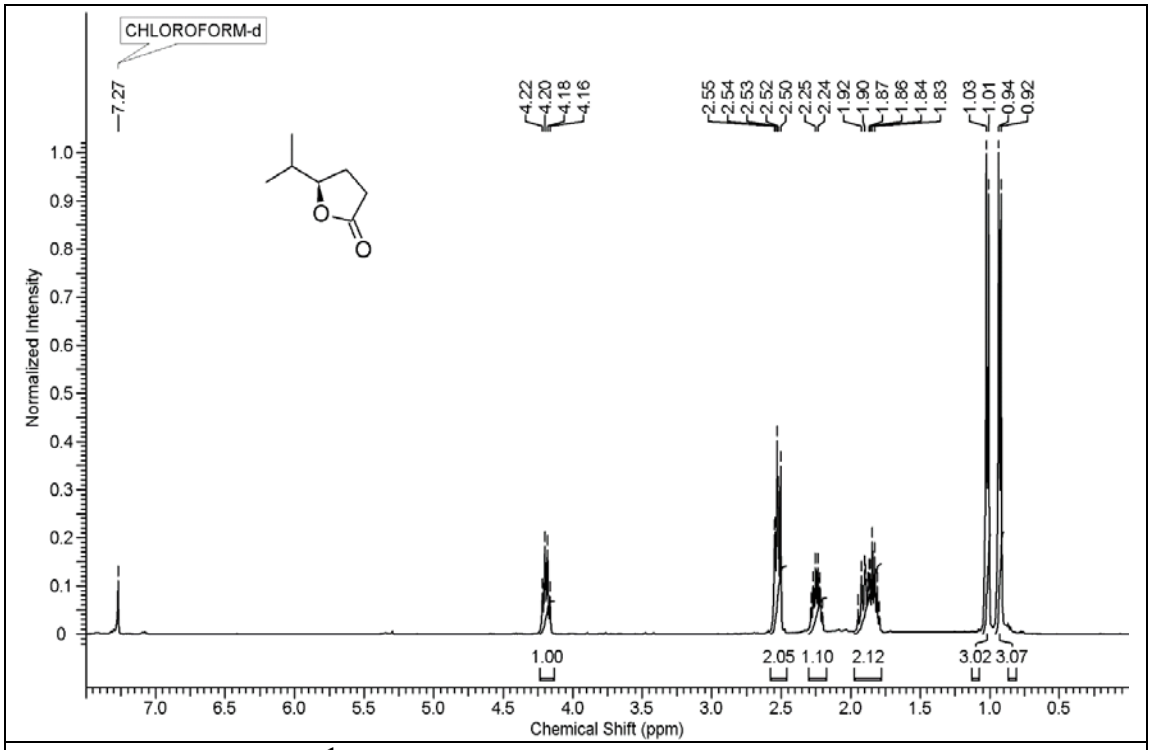
^{13}C-NMR of compound 77b in $CDCl_3$



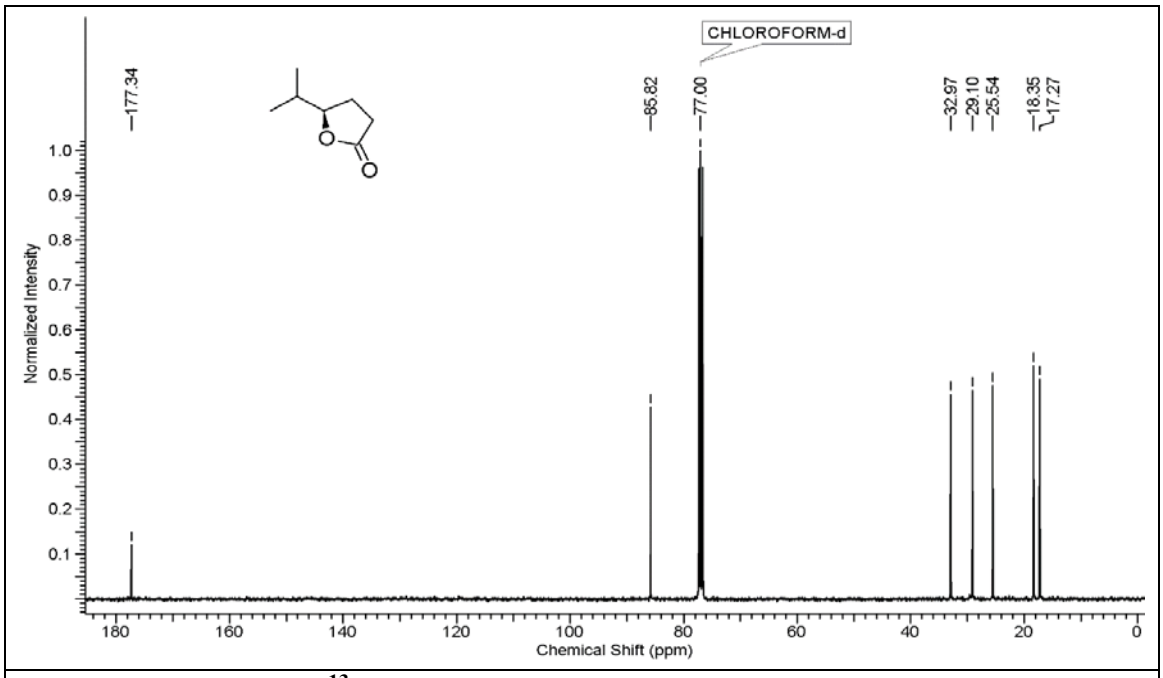
^{1}H-NMR of compound 77c in $CDCl_3$



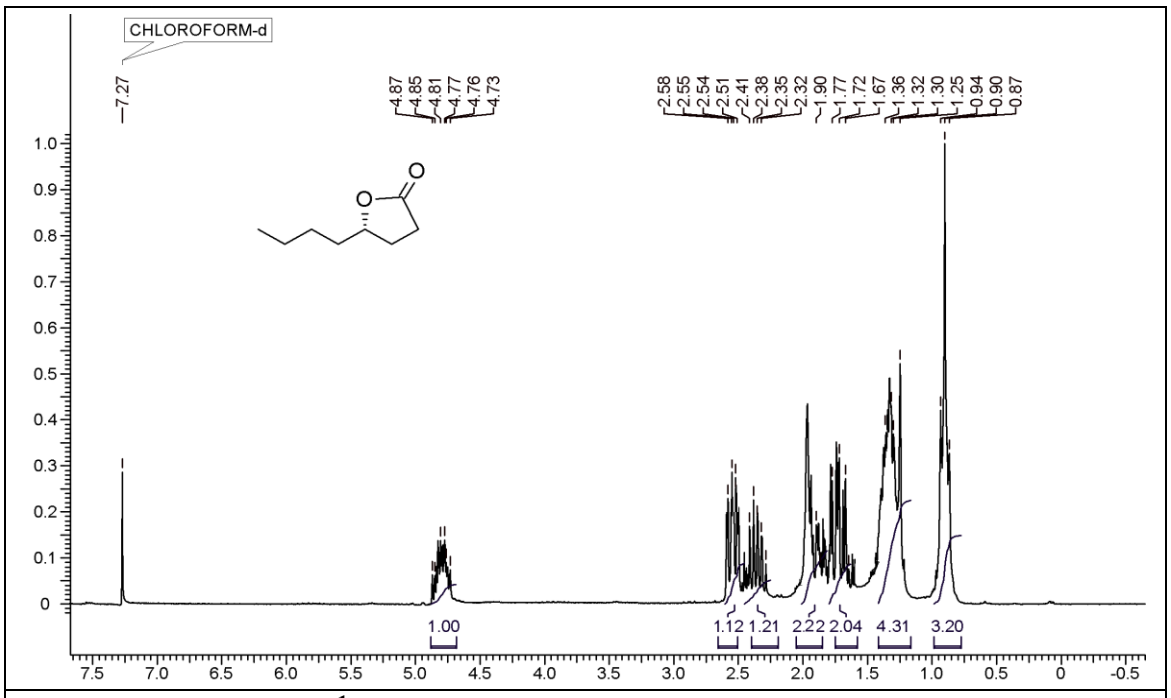
^{13}C-NMR of compound 77c in $CDCl_3$



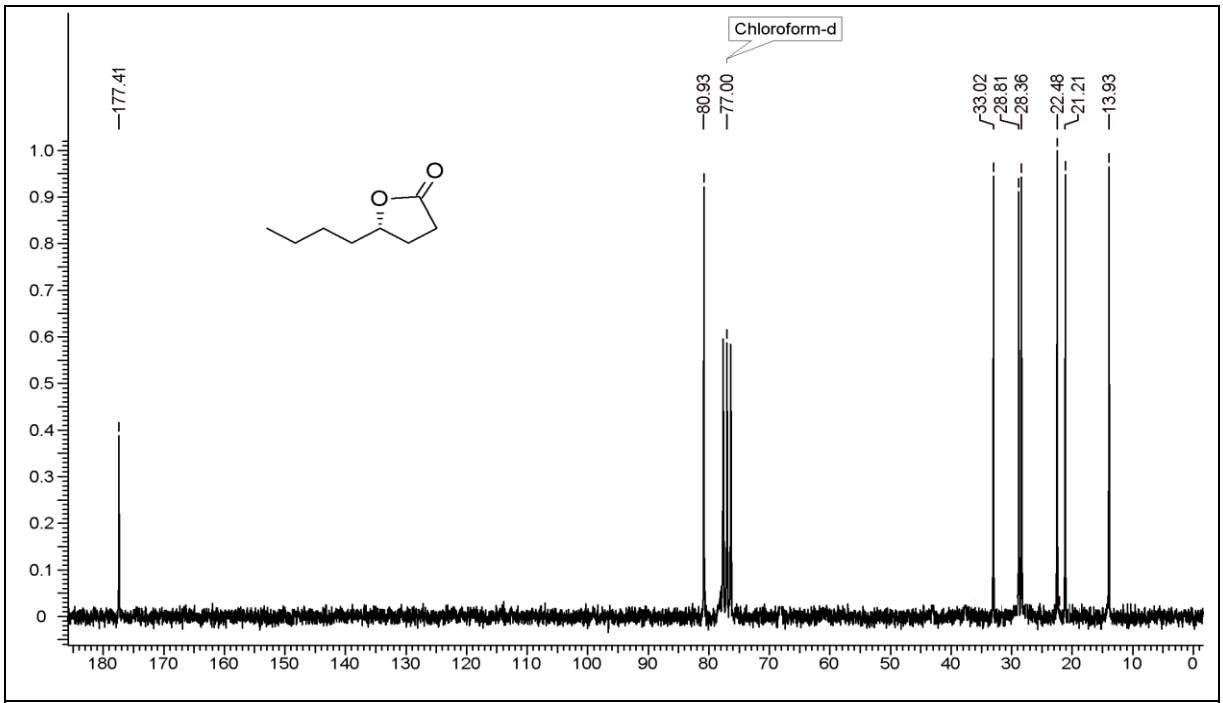
^{1}H-NMR of compound 77d in $CDCl_3$



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



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



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

4.1.8. Reference

1. Enders, D.; Grondal, C.; Hüttl M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570.
2. (a) Pellissier H. *Tetrahedron* **2006**, *62*, 1619; (b) Pellissier H. *Tetrahedron* **2006**, *62*, 2143.
3. (a) Tietze, L.F.; Beifuss, U. *Angew. Chem. Int. Ed. Engl*. **1993**, *32*, 131; (b) Tietze, L.F. *Chem. Rev*. **1996**, *96*, 115; (c) Tietze, L.F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304; (d) Tietze, L.F.; Lieb, M. E. *Curr. Opin. Chem. Biol.* **1998**, *2*, 363; (e) Tietze, L.F.; Rackelmann, N. *Pure Appl.Chem.* **2004**, *76*, 1967; (f) Tietze, L. F.; Brasche, G.; Gerike, K. *Domino Reactions in Organic Chemistry*, Wiley-VCH, Weinheim, **2006**.
4. Nicolaou, K.C.; Edmonds, D.J.; Bulger, P.G. *Angew. Chem. Int. Ed*. **2006**, *45*, 7134.
5. Denmark, S.E.; Thorarensen, A. *Chem. Rev*. **1996**, *96*, 137.
6. (a) Chapman, C.J.; Frost, C.G. *Synthesis* **2007**, *1*, 1; (b) Fogg, D.E.; dos Santos, E.N. *Coord. Chem. Rev*. **2004**, *248*, 2365.
7. For reviews on organocatalytic tandem reactions, see: (a) reference 1; (b) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037; (c) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477
8. For a comprehensive review on α-aminoxylation see: Merino, P.; Tejero, T. *Angew. Chem. Int. Ed* **2004**, *43*, 2995 and references cited therein.
9. Zhong, G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4247.
10. Zhong, G. *Chem. Commun.* **2004**, *5*, 606.
11. Zhong, G.; Yu, Y. *Org. Lett.* **2004**, *6*, 1637.
12. Liao, W–W.; Ibrahem I.; Cordova A. *Chem. Commun*. **2006**, *6*, 674.
13. Zhao, G–L.; Liao, W-W.; Cordova, A. *Tetrahedron Lett*. **2006**, *47*, 4929.
14. Kotkar, S. P.; Chavan V. B.; Sudalai A. *Org. Lett.* **2007**, *9*, 1001.
15. Hajra, S.; Giri, A. K. *J. Org. Chem.* **2008**, *73*, 3935.
16. Yang, L.; Liu, R-H.;Wang, B.; Weng, L-L.; Zheng, H. *Tetrahedron Lett*. **2009**, *50*, 2628.
17. Kondekar, N. B.; Kumar, P. *Org. Lett.* **2009**, *11*, 2611.
18. Jha, V.; Kondekar, N.B.; Kumar, P. *Org. Lett.* **2010**, *12*, 2762.
19. (a) Hoffmann, H.M.R.; Rabe, J. *Angew Chem Int Ed.* **1985**, *24*, 94; (b) Koch, S. S. C.; Chamberlin, A. R. *In Studies in Natural Products Chemistry*; Att-ur-Rahman, Ed.; Elsevier Science: New York, **1995**; *Vol. 16*, 687.
20. Seitz, M.; Reiser, O. *Current Opinion in Chemical Biology* **2005**, *9*, 285.

21. Silverstein, R. M. In *Semiochemistry, Flavors and Pheromones*; Proceedings ACS Symposium; Acree, T. E., Ed.; W. de Gruyter and Co.: Berlin. **1985**,121.

22. (a) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1869; (b) Donnelly, D. M. X.; Meegan, M. J. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon: New York, **1984**; *Vol. 4*, 657; (c) Devon, T. K.; Scott, A. I. In *Handbook of Naturally Occurring Compounds*; Academic Press: New York, **1975**; *Vol. 1*, 249.

23. (a) Katoh, T.; Nishide, K.; Node, M.; Hiroo, O. *Heterocycles* **1999**, *50*, 833; (b) Drioli, S.; Felluga, F.; Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E.; *J. Org. Chem.* **1998**, *63*, 2385; (c) Vassilev, V. P.; Uchiyama, T.; Kajimoto, T.; Wong, C. H. *Tetrahedron Lett.* **1995**, *36*, 5063; (d) Takahata, H.; Uchida, Y.; Momose, T. *J. Org. Chem.* **1994**, *59*, 7201; (e) Miyazaki, Y.; Hotta, H.; Sato, F. *Tetrahedron Lett.* **1994**, *35*, 4389; (f) Tsuda, M.; Shigemori, H.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 3503.

24. (a) Posner, G. H.; Kogan, T. P.; Haines, S. R.; Frye, L. L. *Tetrahedron Lett.* **1984**, *25*, 2627; (b) van Oeveren, A.; Jansen, J. F. G. A.; Feringa, B. L. *J. Org. Chem.* **1994**, *59*, 5999; (c) Rehnberg, N.; Magnusson, G. *J. Org. Chem.* **1990**, *55*, 4340.

25. (a) Sibi, M. P.; Liu, P.; Ji, J.; Hajra, S.; Chen, J. *J. Org. Chem.* **2002**, *67*, 1738; (b) Fischer, J.; Reynolds, A. J.; Sharp, L. A.; Sherburn, M. S. *Org. Lett.* **2004**, *6*, 1345.

26. (a) Achiwa, K. *Heterocycles* **1979**, *12*, 515; (b) Kosugi, H.; Tagami, K.; Takahashi, A.; Kanna, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 935.

27. (a) Kosch, S. S. C.; Chamberlin, A. R. *J. Org. Chem.* **1993**, *58*, 2725; (b) Sibi, M. P.; Liu, P.; Johnson, M. D. *Can. J. Chem.* **2000**, *78*, 133; (c) de L Vanderlei, J. M.; Coelho, F.; Almedia, W. P. *Synth. Commun.* **1998**, *28*, 3047.

28. Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron* **1992**, *48*, 3313.

29. (a) Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1979**, *20*, 3315; (b) Tomioka, K.; Koga, K. *Heterocycles* **1979**, *12*, 1523; (c) Tomioka, K.; Ishiguro, T.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 652; (d) Tomioka, K.; Cho, Y.-S.; Sato, F.; Koga, K. *J. Org. Chem.* **1988**, *53*, 4094.

30. (a) Boissin, P.; Dahol, R.; Brown, E. *Tetrahedron Lett.* **1989**, *30*, 4371; (b) Brown, E.; Dawgan, A. *Tetrahedron Lett.* **1985**, *26*, 3997; (c) Gaboury, J. A.; Sibi, M. P. *J. Org. Chem.* **1993**, *58*, 2173; (d) Honda, T.; Kimura, N.; Sato, S.; Kato, D.; Tominaga, H. *J. Chem. Soc., Perkin Trans 1* **1994**, 1043.

31. (a) Morimoto, T.; Chiba, M.; Achiwa, K. *Tetrahedron Lett.* **1989**, *30*, 735; (b) Tanaka, M.; Mukaiyama, C; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. J. *Org. Chem* **1995**, *60*, 4339; (c) Landais, Y.; Robi, J. P.; Leburn, A. *Tetrahedron* **1991**, *47*, 3787.
32. (a) Doyle, M. P.; van Oeveren, A.; Westrum, L. J.; Protopopova, M. N.; Clayton, T. W., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 8982; (b) Doyle, M. P.; Bode, J. W.; Lynch, V. J.; Protopopova, M. N.; Simonsen, S. H.; Zhou, Q.-L. *J. Org. Chem.* **1995**, *60*, 6654; (c) Bode, J. W.; Protopopva, M. N.; Zhou, Q.-L.; Doyle, M. P. *J. Org. Chem.* **1996**, *61*, 9146.
33. (a) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377; (b) Wang, Z.; Meng, X. J.; Kabalka, G. W. *Tetrahedron Lett.* **1991** *32*, 4619; (c) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97.
34. Seitz, M.; Reiser, O. *Current Opinion in Chemical Biology* **2005**, *9*, 285.
35. Kumar, P.; Dwivedi, N. *Acc. Chem. Res.* **2013**, *46*, 289 and references cited therein.
36. (a) Nicolaou, K. C.; Xu, J.; Kim, S.; Ohshima, T.; Hosokawa, S.; Pfefferkorn, J. *J. Am. Chem. Soc.* **1997**, *119*, 11353; (b) Nicolaou, K. C.; van Delft, F.; Ohshima, T.; Vourloumis, D.; Xu, J.; Hosokawa, S.; Pfefferkorn, J.; Kim, S.; Li, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 2520.
37. HPLC: Chiracel OD-H column (2-Propanol: petroleum ether = 5:95, flow rate 1.0 mL/min, λ = 214 nm). Retention time (min): 12.16 (minor) and 16.69 (major). The racemic standard was prepared from racemic *γ*-hydroxy ester, *ee* 98%.
38. HPLC: Chiracel OD-H column (2-Propanol: petroleum ether = 5:95, flow rate 1.0 mL/min, λ = 214 nm). Retention time (min): 11.26 (minor) and 15.39 (major). The racemic standard was prepared from racemic *γ*-hydroxy ester, *ee* 96%.

4.2. SECTION B:

Proline-catalysed enantiomeric synthesis of Bruguierol A and Bruguierol B

4.2.1. Introduction

In 2005, Sattler *et al.* isolated an unusual family of aromatic *β*-C-glycoside natural products termed Bruguierols A-C (1-3) from the stem of the Bruguiera gymmorrhiza mangrove tree which was collected from the coast of Xiamen in the south of China (Figure 1)[1]. The structure of these natural products is characterized by a 2,3-benzofused 8-oxabicyclo[3.2.1]octane core. Additionally, the aromatic ring is substituted with one hydroxyl group in bruguierol A **1** or two hydroxyl groups in both bruguierols B **2** and C **3**. Amongst the three, bruguierol C **3** showed moderate activity against Gram-positive and Gram-negative bacteria including mycobacteria and resistant strains (MICs 12.5 μgmL^{-1}) (Figure 1).[1]

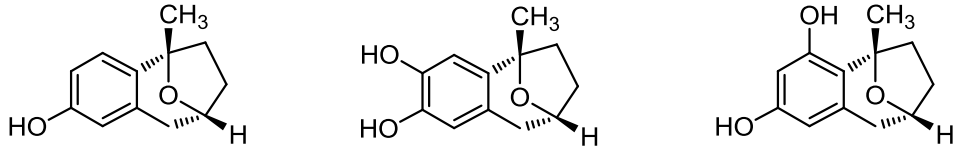


Figure 1: Structure of Bruguierols

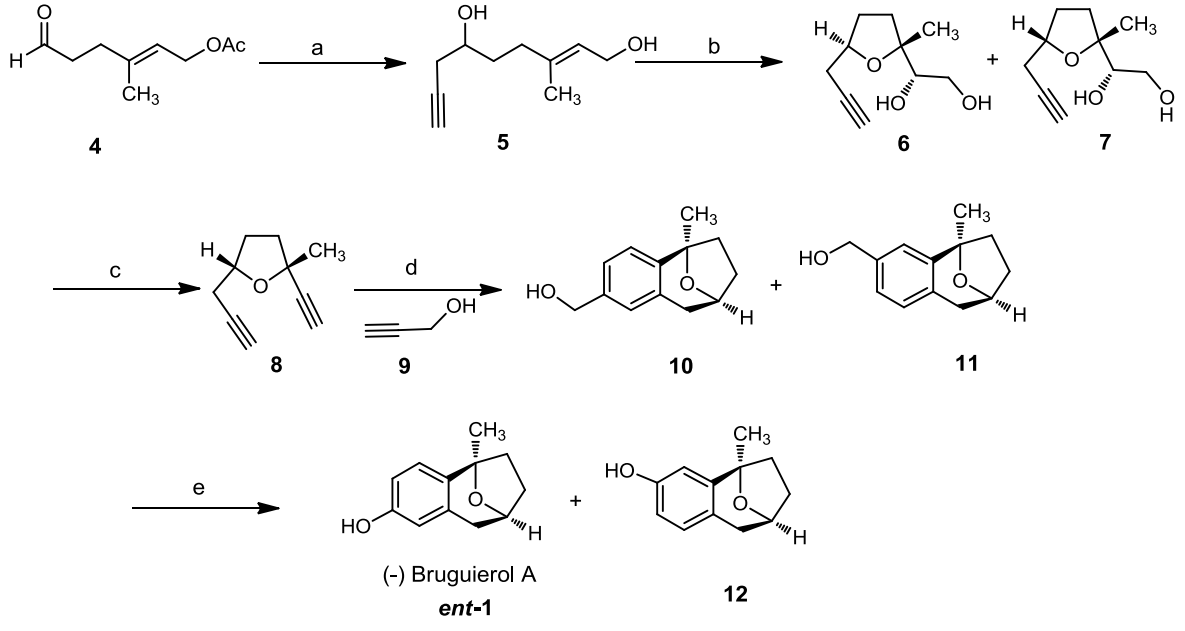
4.2.2. Review of Literature

With the interesting structural features and potential biological activities, synthesis of bruguierols began to attract attention from the synthetic community. Up to now, there are six synthetic routes reported for the total synthesis of bruguierols. In 2007, Ramana and co-workers reported the application of [2+2+2] alkyne cyclotrimerisation as the key step for the total synthesis of (-)-bruguierol A *ent*-**1**.[2] Jennings and co-workers have completed the total synthesis of (+)-bruguierol C **3** by diastereoselective capture of an in situ generated oxocarbenium ion via an intramolecular Friedel-Crafts alkylation.[3] Wu and co-workers have completed the total synthesis of racemic bruguierol A (±)-**1** in 2008 via a similar intramolecular Friedel-Crafts annulation method.[4] The key bridged cyclic frame work was

constructed by using an intramolecular Friedel-Crafts alkylation with a ketal as the alkylating agent. Fananás and co-workers have applied an efficient tandem intramolecular hydroalkoxylation-hydroarylation reaction for the construction of the key bridged cyclic framework to the total synthesis of bruguierol A **1**.[5] Wang and co-workers accomplished the total synthesis of racemic bruguierol A **(±)-1** via novel $Sc(OTf)_3$-catalyzed intramolecular [3+2] cycloaddition of cyclopropane 1,1-diester.[6] In 2011, Venkateswaran and co-workers reported the synthesis of racemic bruguierol A **(±)-1** by employing ring closing metathesis as a key step to generate the benzoxabicyclo[3.2.1]octane ring system.[7]

Ramana *et al*. (2007)[2]

Ramana *et al*. synthesised (–)-bruguierol A ***ent*-1** by employing a cross alkyne cyclotrimerisation reaction. The synthesis started with the propargylation of known 6-acetyloxy-4-methylhex-4-enal **4** under Barbier conditions (Scheme 1) to afford **5**.

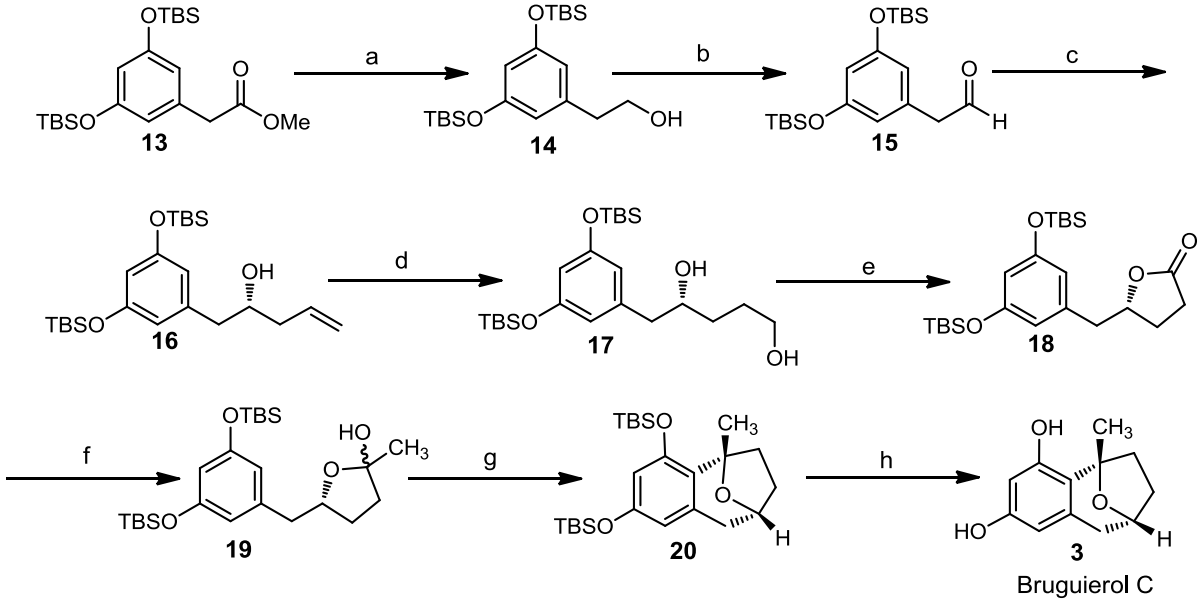


Scheme 1 : *Reaction conditions*: (a) (i) propargyl bromide, Zn, saturated aqueous NH_4Cl, THF, 0 °C-rt, 2 h, 87%; (ii) K_2CO_3, methanol/water, r.t., 4 h, 90%; (b) *L*-(+)-DIPT, $Ti(OiPr)_4$, *t*BuOOH, DCM, –20 °C, 6 h, 90%; (c) (i) silica-supported $NaIO_4$, DCM, rt, 2 h; (ii) dimethyl-1-diazo-2-oxopropylphosphonate, K_2CO_3, methanol, rt, 4 h, 82%; (d) propargyl alcohol, $Rh(PPh_3)_3Cl$, toluene/ethanol, 80 °C, 67%; (e) (i) MnO_2, DCM, rt, 5 h; (ii) m-CPBA, DCM, 0 °C-rt, 4 h; (iii) aq. NaOH, THF, 2 h, (33% from three steps).

The following Sharpless asymmetric epoxidation reaction gave easily separable isomeric furans **6** and **7** in 90% yield and with 91% and 90% *ee* respectively. The $NaIO_4$-mediated cleavage of required *cis* furan diol **7** followed by treatment of the intermediate aldehyde with the Ohira–Bestmann reagent gave key diyne **8** in 82% yield. The benzene-fused 8-oxabicyclo[3.2.1]octane system of bruguierol was constructed by a rhodium-catalysed [2+2+2] cyclotrimerisation reaction of diyne with propargyl alcohol to give 1:1 inseparable regioisomeric mixtures **10**/**11** in moderate yields. Oxidation of the mixture **10** and **11** with MnO_2 followed by treatment with *m*-CPBA provided (-)-bruguierol A (*ent*-**1**) and **12** in 33% overall yield (Scheme 1).[2]

Jennings *et al.* (2007)[3]

Jennings *et al.* have completed the total synthesis of (+)-bruguierol C **3** in 7 linear steps from the known compound **13** and the key step involved was diastereoselective capture of an in situ generated oxocarbenium ion via an intramolecular Friedel-Crafts alkylation (Scheme 2). The synthesis of the required homoallylic alcohol **16** was achieved through asymmetric allylboration of **17** utilizing Brown's Ipc based allylborane reagent.

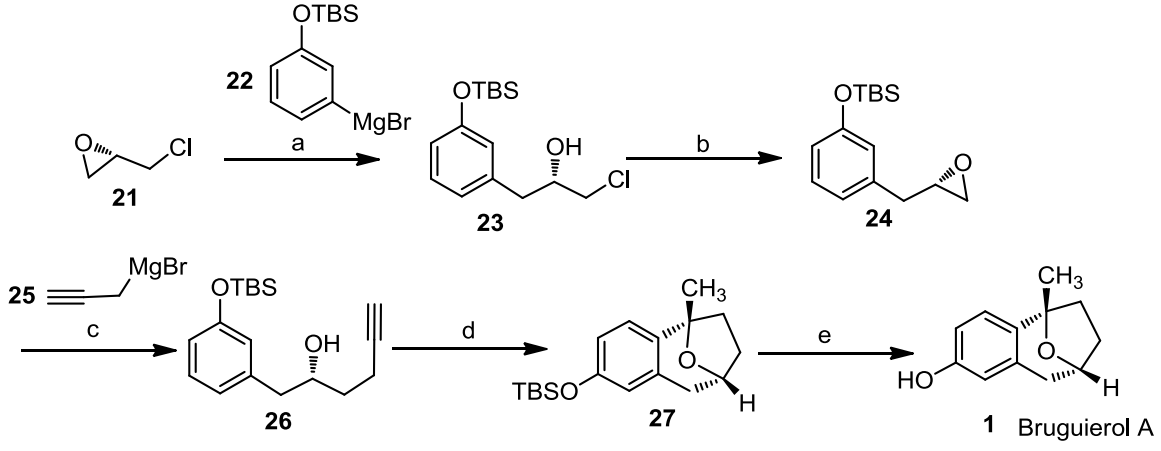


Scheme 2 : *Reaction conditions*: (a) $LiAlH_4$, THF, 91%; (b) PCC, DCM, 85%; (c) (+)-Ipc_2Ballyl, THF, 70%; (d) $(Cy)_2BH$, NaOH, H_2O_2, 91%; (e) TPAP-NMO, DCM, 68%; (f) MeLi, THF; (g) $BF_3.OEt_2$, DCM, 58%; (h) TBAF, THF, 85%.

Later homoallylic alcohol **16** was subjected to hydroboration using dicyclohexyl borane followed by basic oxidation to provide the diol **17** in 91% yield. The selective oxidation of the primary alcohol moiety of diol **17** to the aldehyde followed by intramolecular cyclization to the lactol and further oxidation to the obligatory lactone **18** was accomplished by means of Ley's TPAP-NMO protocol in 68% yield. The treatment of lactone **18** with 1.3 equivalent of MeLi in THF quantitatively furnished lactol **19**, which was then sequentially treated with $BF_3.OEt_2$ to provide the desired *β-C*-glycoside product **20** with an overall 58% yield from lactone **18**. Finally the treatment of **20** with 3 equivalent of TBAF at room temperature in THF furnished the (+)-bruguierol C **3** in 85% yield (Scheme 2). [3]

Fananás *et al.* (2009)[5]

Fananás *et al.* reported the total synthesis of bruguierol A **1** based on a platinum-catalyzed tandem intramolecular hydroalkoxylation-hydroarylation reaction for the construction of 2,3-benzofused 8-oxabicyclo[3.2.1]octane skeleton. The synthesis of bruguierol A **1** started from commercially available (*S*)-epichlorydrin **21** (Scheme 3).



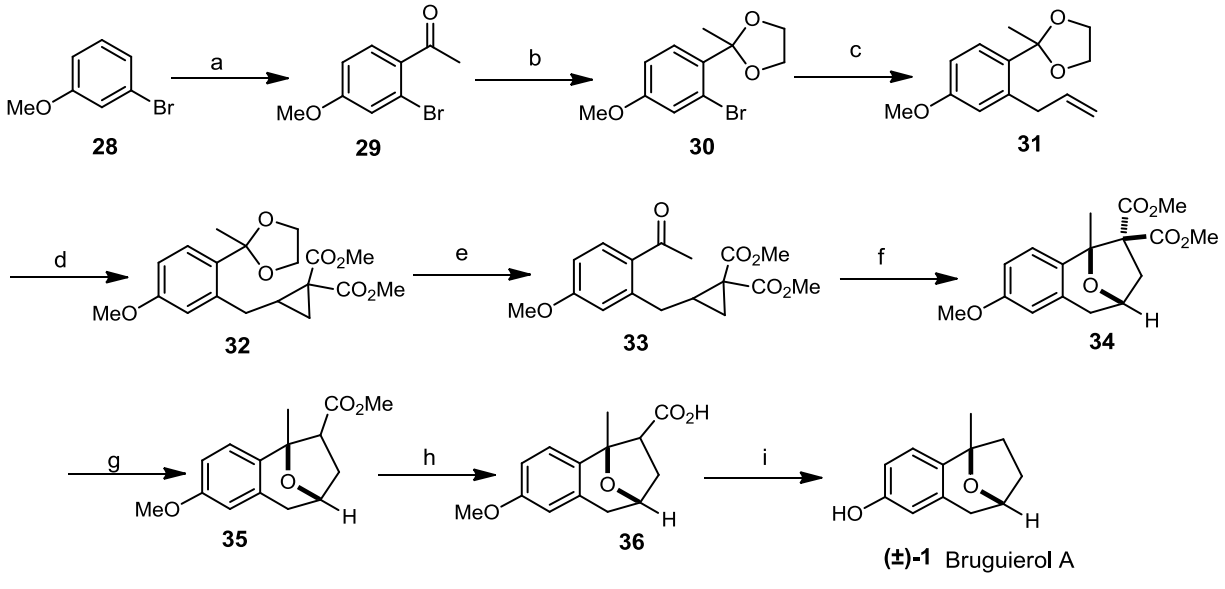
Scheme 3: *Reaction conditions:* (a) compound **22**, Et_2O, 0 °C- rt, 92%; (b) MeLI, THF, -78 °C-rt, 92%; (c) propargylmagnesium bromide **25**, Et_2O, 0 °C- rt, 90%; (d) 5 mol% $PtCl_4$, CH_2Cl_2, rt, 94%; (e) TBAF, THF, rt, 96%.

The first reaction implies the ring opening of the epoxide **21** by reaction with the Grignard reagent **22** to give the chlorohydrin derivative **23** in 92% yields. Further reaction of this alcohol with methyllithium furnishes the new epoxide **24** in 92% yields. The reaction of this epoxide with propargylmagnesium bromide **25** provides the desired pentynol derivative **25**

in 90% yields as a single regioisomer. The pentynol derivative **25** was subjected to the intramolecular hydroalkoxylation-hydroarylation reaction by using $PtCl_4$ as catalyst in dichloromethane at room temperature. Under these conditions the protected bruguierol A **27** was obtained in 94% yield. Subsequent treatment of **27** with TBAF in THF afforded the natural product bruguierol A **1** in 96% yield (Scheme 3).[5]

Wang *et al.* (2010)[6]

Wang *et al. have* accomplished the total synthesis of (±)-bruguierol A (±)-**1** in 10-steps from commercially available 3-bromoanisole **28**. The unique 8-oxabicyclo[3.2.1]octane core skeleton of this natural product was constructed via a novel $Sc(OTf)_3$-catalyzed intramolecular [3+2] cycloaddition of cyclopropane-1,1-diester **33** (Scheme 4).

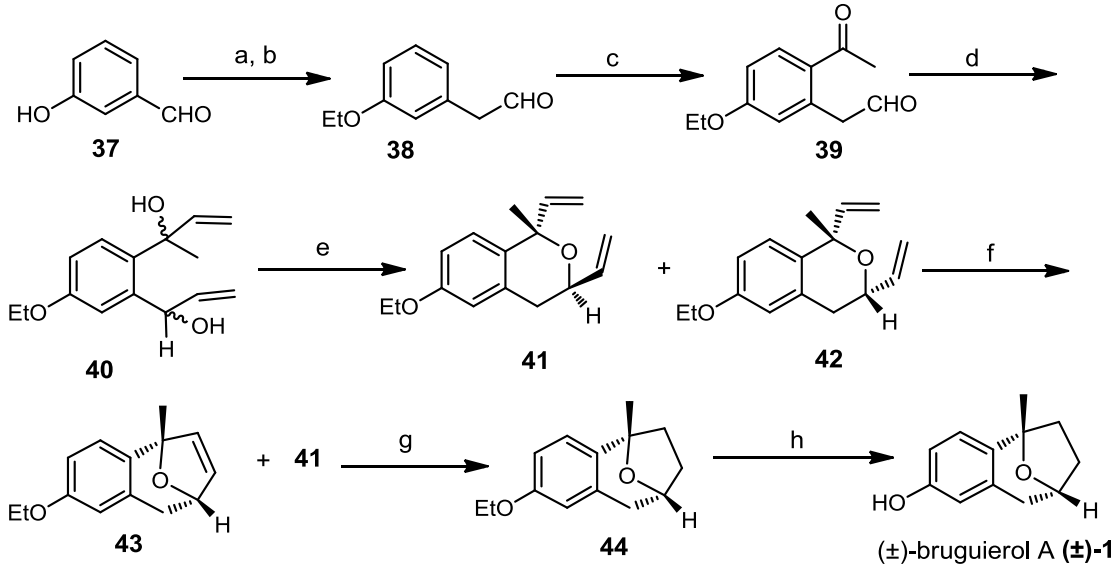


Scheme 4 : *Reaction conditions*: (a) $AlCl_3$, CH_3COCl, 72%; (b) p-TsOH, ethylene glycol, 94%; (c) *t*-BuLi, Et_2O, allyl bromide, 64%; (d) $N_2{=}C(CO_2Me)_2$, $Rh_2(esp)_2$, 77%; (e) 1 M HCl, THF, rt, 95%; (f) $Sc(OTf)_3$, DCE, 98%; (g) LiCl, wet DMSO, 160 ^oC, 88%; (h) LiOH, MeOH, H_2O, THF, 88%; (i) (*i*) Barton decarboxylation (*ii*) NaSEt, DMF, 70% (two steps).

Cyclopropanation of **31** with diazodimethyl-malonate in the presence of $Rh_2(esp)_2$ afforded cyclopropane-1,1-diester **33**. Krapcho decarboxylation of **34** afforded the corresponding monoester **35**, which was then saponified to afford carboxylic acid **36** in 88% yield. Finally, the total synthesis of (±)-bruguierol A (±)-**1** was achieved after the Barton decarboxylation and demethylation (Scheme 4).[6]

Venkateswaran *et al.* (2011)[7]

Venkateswaran *et al.* reported the synthesis of (±)-bruguierol A (±)-**1** by employing ring closing metathesis as a key step to generate the benzoxabicyclo[3.2.1]octane ring system. The synthesis started from *m*-ethoxybenzaldehyde **37** which was subjected to homologation employing a Wittig reaction to furnish aldehyde **38** (Scheme 5). This aldehyde **38** was subjected to a Friedel–Crafts acylation to afford the desired keto-aldehyde **39** in 60% yield. Interaction of this keto-aldehyde **39** with an excess of vinylmagnesium bromide furnished diol **40** as a mixture of isomers. The acid catalysed cyclisation of diol **40** provided two products **41**/**42** in 1:1 ratio. However separation of this mixture was rendered difficult (Scheme 5).



Scheme 5 : *Reaction conditions*: (a) K_2CO_3, acetone, EtI, reflux, 3 h, 90%; (b) potassium *tert*-butoxide, methoxymethyltriphenyl phosphonium chloride, THF, -5 °C to rt, 1 h followed by 2 M HCl, THF, rt, 4 h, 80% (for two steps); (c) CH_3COBr, $AlBr_3$, DCM, 0 °C to rt, 2 h, 60%; (d) vinylmagnesium bromide (2 equiv.), THF, 0 °C to rt, 1 h; (e) 1 M H_2SO_4, THF, rt, 30 min, 60% (for two steps); (f) Grubbs' 2nd generation (0.005 mol), DCM, rt, 7 h, 47%; (g) $Rh(PPh_3)_3Cl$, H_2, rt, 11 h, 98%; (h) EtSNa, DMF, 110 °C,12 h, 86%.

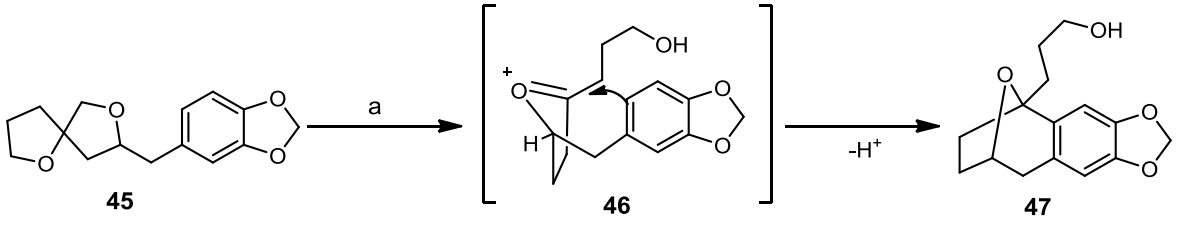
It was found that treatment of the diene mixture **41**/**42** with Grubbs 2nd generation catalyst resulted in a mixture of the expected cyclized product **43** in 47% yield and the uncyclized diene **41**. Selective hydrogenation of the double bond was achieved by Wilkinson catalyst to provide *O*-ethylbruguierol A **44** in quantitative yield. Finally de-ethylation of **44** by treatment

with sodium ethylmercaptide in DMF afforded (±)-bruguierol A (±)-**1** in 78% yield as a crystalline solid (Scheme 5).[7]

4.2.3. Present work

Objective

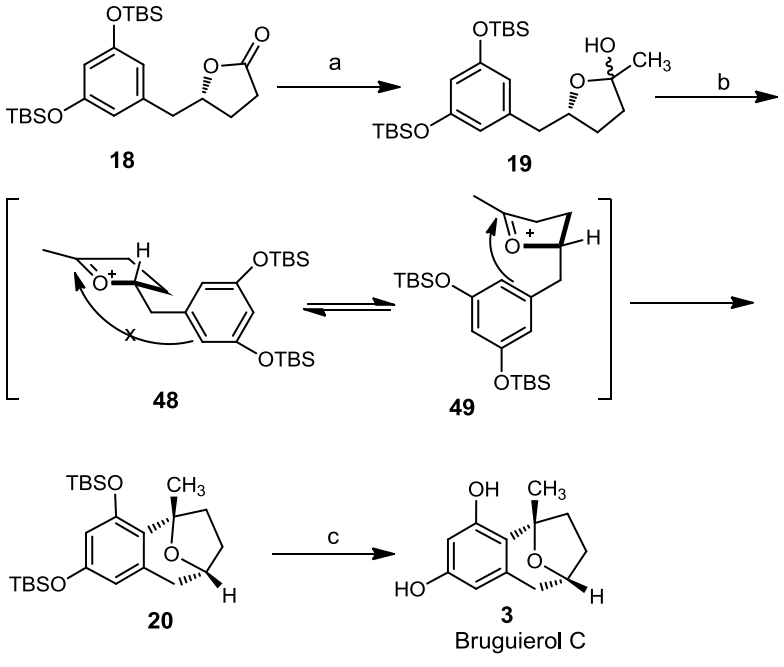
The interesting structural features of bruguierols encouraged us to make them as our synthetic targets. Based on the fact that bruguierol C **3** exhibits activity against both Gram-positive and Gram-negative bacteria, one could envision further investigations of analogues or hybrids of bruguierols for broad spectrum of antibiotics.[3] Aromatic fused bicyclic systems present in bruguierols are very difficult to access and there are very few synthetic methods available. Among those strategies intramolecular Friedel-Crafts alkylation is most frequently used in literature. Fan *et al.*[8a] reported first examples of Friedel-Crafts alkylation using spiro-ketals as alkylating agents and accessed benzene fused 8-oxabicyclo[3.2.1]octane system. The ketal carbonyl carbon is first activated by either protonation or coordination to a Lewis acid. Slightly more than one equivalent of $BF_3.OEt_2$ in THF at refluxing temperature were found to be the most satisfactory conditions to achieve the desired cyclization. The formation of bicyclic system was satisfactorily explained through an oxonium intermediate **46** which immediately undergoes cyclization to **47**(Scheme 6).



Scheme 6: *Reaction conditions*: (a) $BF_3.OEt_2$, THF, 89%.

Marson *et al.*[8b] also developed a similar approach to benzene fused 8-oxa bicyclo[3.2.1]octane ring system based on $SnCl_4$-catalysed intramolecular Friedel–Crafts alkylation with hemistannyl acetals (formed *in situ* from epoxides) as alkylating agents. Jennings *et al.*[3] have completed the total synthesis of (+)-bruguierol C **3** by means of a similar intramolecular Friedel-Crafts alkylation trap of the incipient oxocarbenium cation **49**. The oxocarbenium cation produced via a sequential methylation of lactone **18** followed by

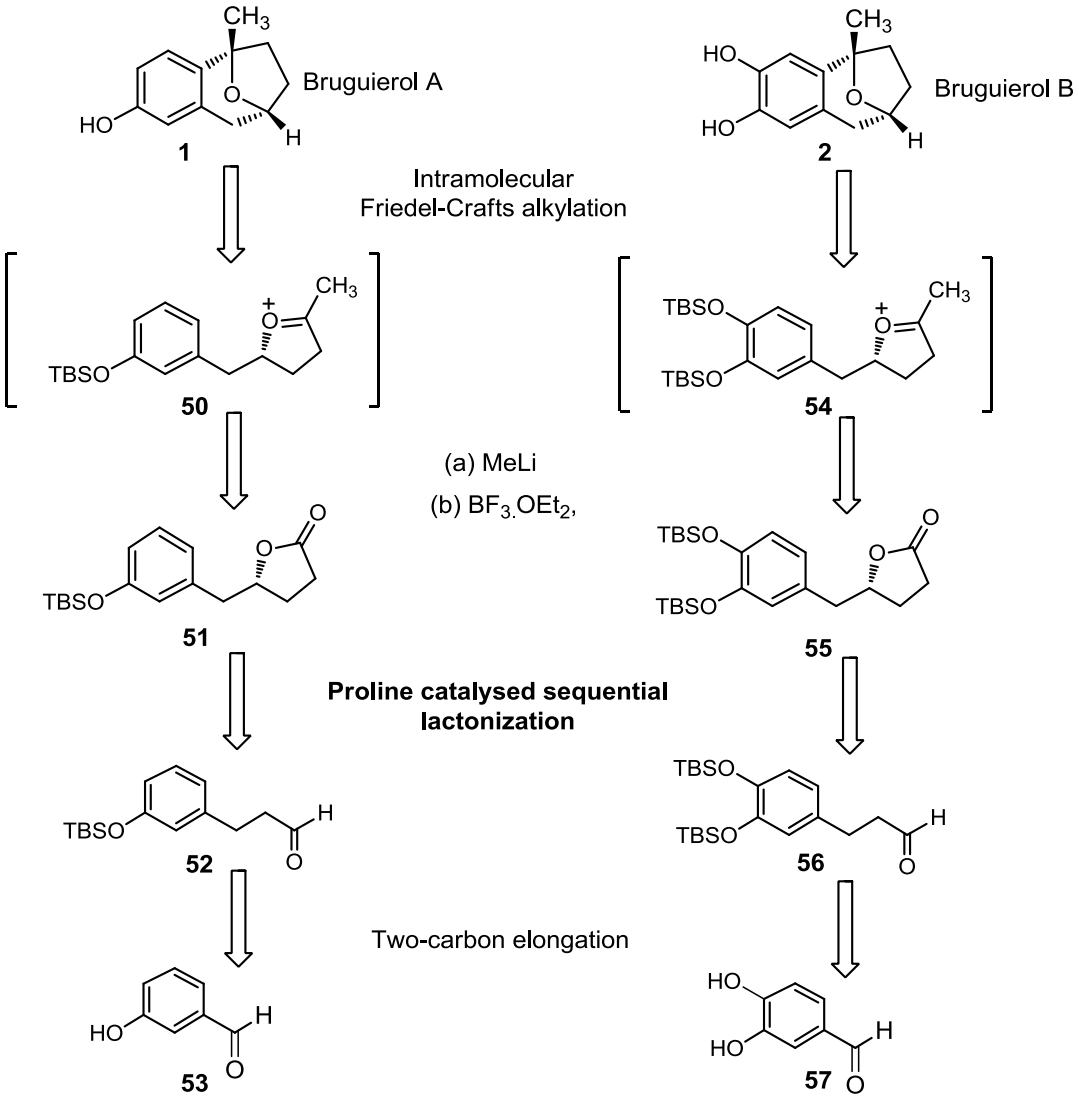
treatment of lactol **19** with an appropriate Lewis acid $BF_3.OEt_2$ (Scheme 7). This class of enatiopure *γ*-butyrolactones could be readily prepared from corresponding prochiral aldehydes via our recently established proline catalysed sequential lactonization reaction (Section A).



Scheme 7 : *Reaction conditions*: (a) MeLi, THF; (b) $BF_3.OEt_2$, DCM, 58%; (c) TBAF, THF, 85%.

Retrosynthetic Analysis of Bruguierol A and Bruguierol B

The great structural variety of γ-butyrolactone frameworks found in nature makes them attractive scaffolds for combinatorial synthesis, as has been successfully demonstrated recently with natural product classes.[9] The diversity of their biogenetic origins suggests that this structure may also be one of the key elements in various biosynthesis.[10] Optically pure substituted γ-butyrolactones have been employed as synthons/intermediates for acquiring many biologically important compounds such as antitumor antibiotic (+)-hitachimycin,[11a] an aggregation pheromone *R*-(-)-sulcatol,[11b] antileukaemic liganans (+)-*trans*-burseran and (-)-isostegane,[11c] a natural product dihydromevinolin[11d] etc. In continuation of our interest in developing enantioselective syntheses of bioactive molecules[12], we considered attempting at the syntheses of Bruguierol A **1** and Bruguierol B **2** from corresponding optically active *γ*-butyrolactones **51** and **55**.



Scheme 8: Retrosynthetic route for the syntheses of Bruguierol A and Bruguierol B

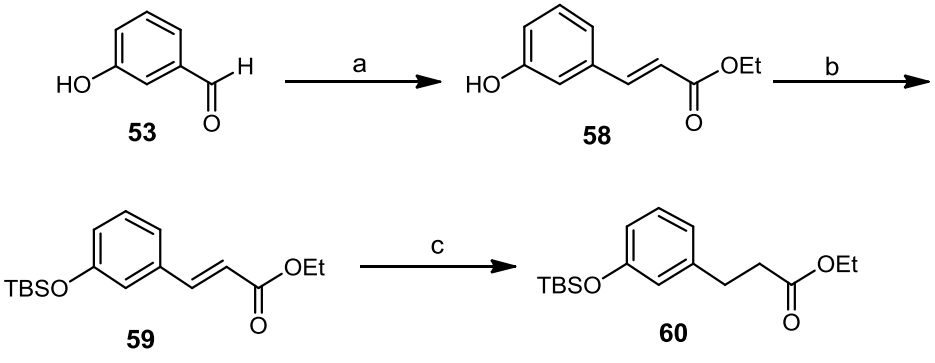
As depicted in the synthetic plan (Scheme 8), bruguierol A **1** and B **2** can be accessed from the suitably substituted chiral lactones **51** and **55** through diastereoselective capture of the incipient oxocarbenium cations **50** and **54** by means of a Marson type Friedel-Crafts alkylation.[8b] Lactones **51** and **55** could be easily obtained from the corresponding prochiral aldehydes **52** and **56** via sequential lactonization reaction involving proline catalyzed α-aminoxylation of carbonyl compound followed by Horner-Wadsworth-Emmons (HWE) olefination and catalytic Pd/C hydrogenation/cyclization reaction (Section A). The aldehydes **52** and **56** in turn could be easily synthesized from the commercially available 3-

hydroxybenzaldehyde **53** and 3,4-dihydroxybenzaldehyde **57** by two-carbon chain elongation.

4.2.4. Results and discussion

Synthesis of of Bruguierol A

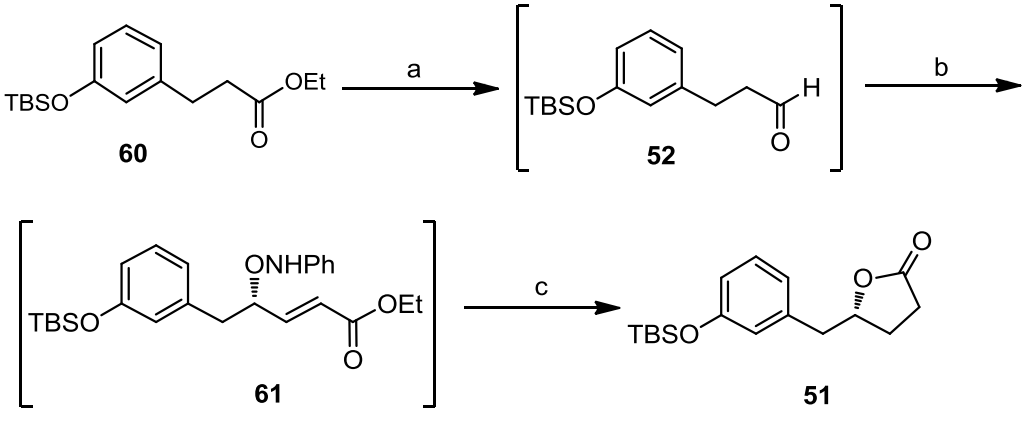
Our first focus was the synthesis of the required lactone **51** for our proline catalysed sequential lactonization reaction. We envisioned that the saturated aldehyde **52** could easily be prepared from commercially available *3*-hydroxybenzaldehyde **53** through Wittig olefination and reduction of corresponding ester to aldehyde. Thus as shown in Scheme 9, synthesis of ester **60** starts from the reaction of **53** with (ethoxycarbonylmethylene) triphenylphosphorane in dry THF at room temperature to afford the *α,β*-unsaturated ester **58** in 90% yield. Appearance of peaks at δ 6.41-6.49 (d, *J* = 16 Hz, 1H) and at δ 7.64-7.72 (d, *J* = 16 Hz, 1H) in ^{1}H NMR and peak at 1716 cm^{-1} in IR spectrum confirmed the formation of the compound **58**.



Scheme 9: *Reagents and conditions*: (a) PPh_3=CHCOOEt, dry THF, rt, 24 h, 90 %; (b) TBDMSCl, Imidazole, DCM, 8 h, 95%; (c) H_2/ Pd-C, EtOAc, 4h, 96%.

In order to achieve the synthesis of target compound **1** from **58**, we required a suitable phenol protecting group for further synthetic manipulation. The compound **58** was protected as TBS ether by treating with TBSCl and imidazole in DCM. The signals corresponding to TBS group was observed at δ 0.27 (s, 6H), 1.05 (s, 9H) as singlets in ^{1}H NMR spectrum. Later double bond of **59** is reduced by hydrogenation using 10% Pd/C to give **60** in 96% yield. The disappearance of olefin peaks at δ 6.42-6.50 (d, *J*= 16 Hz, 1H) and 7.65-7.73(d, *J*= 16 Hz, 1H) in ^{1}H NMR spectrum and shift of carbonyl group stretching frequency from 1716 cm^{-1} to 1731 cm^{-1} confirmed formation of saturated ester **60** (Scheme 9).

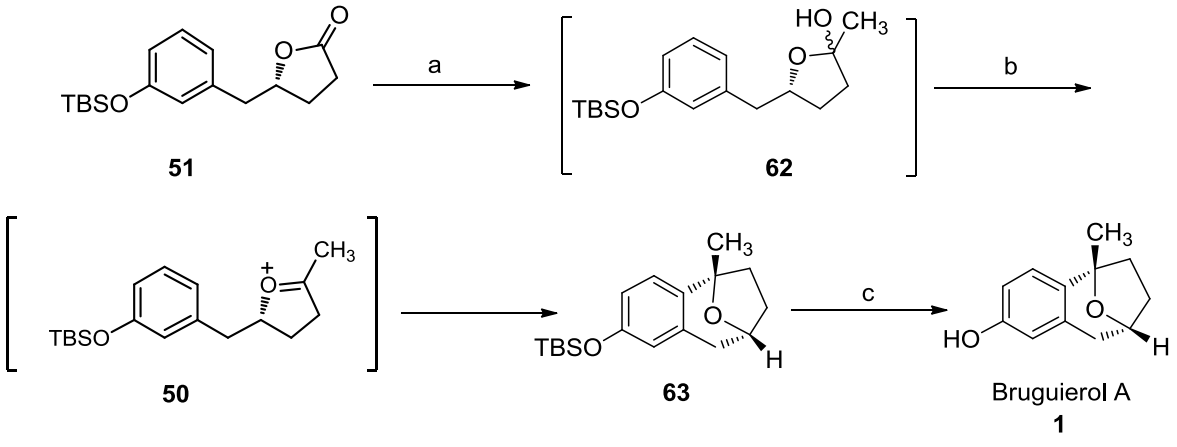
With substantial amount of saturated ester **60** in hand, our next aim was to synthesize chiral *γ*-butyrolactone **51** through the proline-catalysed sequential lactonization reaction. As illustrated in Scheme 10, the DIBAL-H reduction of ester **60** furnished the corresponding aldehyde **52** which was directly used in the lactonization sequential reactions without further purification. The crude aldehyde **52** was subjected to sequential α-aminoxylation (D-proline as a catalyst) followed by HWE-olefination reaction, to furnish *O*-amino-substituted allylic alcohol **61**. In an effort to minimize handling of intermediates and its time-consuming purification, the crude product obtained after workup was directly subjected to hydrogenation conditions using catalytic amounts of Pd/C for four hours. After that hydrogen atmosphere was replaced by argon gas and prolonged the stirring at elevated temperature (60-65 ºC) to afford the enatiopure *γ*-butyrolactone **51** in good yield.



Scheme 10: *Reagents and conditions*: (a) DIBAL-H, DCM, -78 °C, 45 min; (b) (i) Nitrosobenzene, *D*-proline, DMSO, 30 min, (ii) HWE salt, DBU, LiCl, CH_3CN, 1h; (c) (i) H_2/Pd-C, EtOAc, 4h; (ii) Pd/C, EtOAc, 65 ºC, 6 h, 60% over 3 steps.

The disappearance of peaks, a triplet peak at δ 1.21-1.28 (3H); quartet peak at δ 4.08-4.19 (2H) and appearance of a multiplet peak at δ 4.69-4.75 (1H) in ^{1}H NMR confirmed the formation of compound **51**. In IR spectrum, a shift of carbonyl group stretching frequency from 1731 cm^{-1} to 1772 cm^{-1} confirmed the formation of saturated 5-membered lactone **51** (Scheme 10). Thus, using five sequential reactions and one column purification, *γ*-butyrolactone **51** was obtained in 60 % yield and 98% ee.[13]

Once we accomplished the desired lactone **51**, we completed the synthesis of bruguierol A **1** by adopting Jennings's method[3], which was used in the total synthesis of bruguierol C **3**. This method follows a three-step reaction sequence- alkylation, oxocarbenium ion formation and final intramolecular Friedel-Crafts alkylation (Scheme 7). First we treated the lactone **51** with MeLi in anhydrous Et_2O to furnish lactol **62**, which was then sequentially treated with $BF_3.OEt_2$ at -20 ^oC for 2 hours to provide the desired 2,3-benzofused 8-oxabicyclo[3.2.1]octane core product **63** with an overall 60% from lactone **51**. The treatment of lactol **62** with Lewis acid $BF_3.OEt_2$ incipiently produced the oxocarbenium cation **50**, which was diastereoselectively captured by means of a Marson type intramolecular Friedel-Crafts alkylation [8b] provided the protected natural product bruguierol A **63** (Scheme 11).

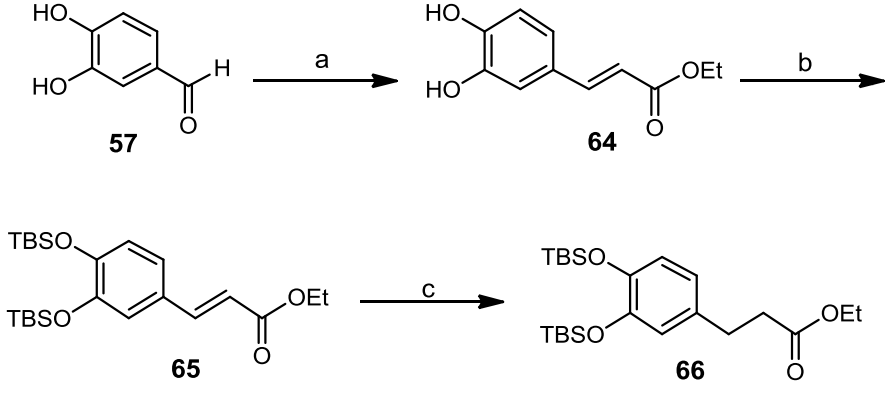


Scheme 11: *Reagents and conditions*: (a) MeLi, Et_2O 1.5 h, -78 ^oC, 1.5 h; (b) $BF_3.OEt_2$, DCM, -20 ^oC, 2h, 60% over 2 steps; (c) TBAF, THF, rt, 2 h, 90%.

The ^1H, ^{13}C NMR (including DEPT) and IR spectra confirmed the structure of compound **63**.[1] For example, the two geminal benzylic protons show different splitting patterns in the ^1H NMR spectrum (δ 2.44-2.48 (d, *J*= 16.3 Hz, 1H); 3.30-3.34 (dd, *J*= 16.3, 4.8 Hz, 1H)) because they have different dihedral angles with respect to the bridgehead proton.[14] Finally the treatment of **63** with 1.2 equiv of TBAF at rt in THF furnished the natural product **1** in a respectable 90 % yield. The spectral data (^1H NMR, ^{13}C NMR, IR) and optical rotation ($[\alpha]_D^{25}$: + 14.8 (*c* 0.3, MeOH)) of synthetic (+)-bruguierol A **1** were in full agreement with the natural product.[1]

Synthesis of of Bruguierol B

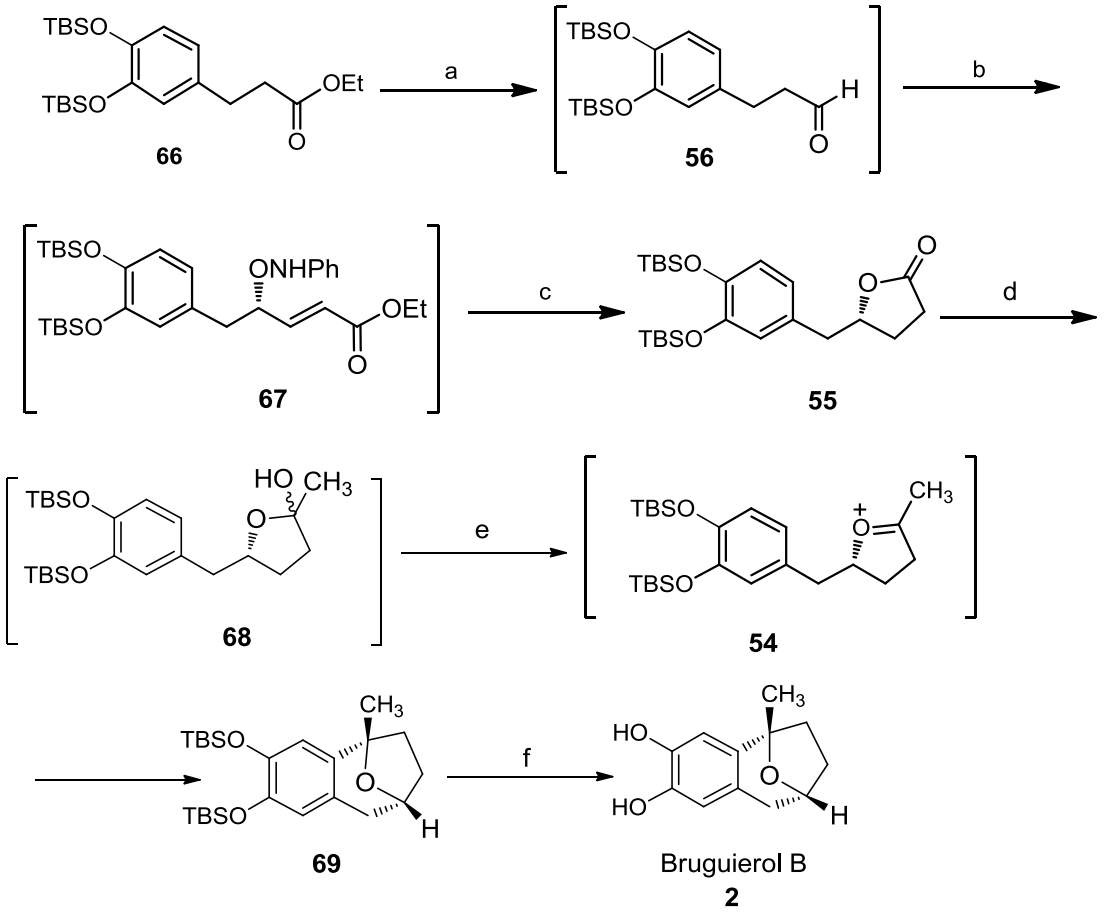
After successfully applying the sequential lactonization reaction for the synthesis of (+)-bruguierol A **1** we next focused our attention on its higher hydroxy analogue (+)- bruguierol B **2**. The synthetic pathway towards bruguierol B **2** follows an exactly similar strategy of bruguierol A **1** synthesis. We accomplished the synthesis of bruguierol B **2** from **57** through previously established route. As shown in Scheme 12, synthesis of ester **66** starts from the two carbon elongation from 3,4-dihydroxybenzaldehyde **57.** Due to the limited solubility of compound **57** in dry THF, we tried a one pot Wittig reaction in aqueous media.[15] The mixing of the aldehyde to the solution of PPh_3, ethylbromoacetate in saturated aqueous $NaHCO_3$ under room temperature afforded the *α,β*-unsaturated ester **64** in 80% yield. Appearance of peaks at δ 6.38-6.46 (d, *J*= 15.9 Hz, 1H) and at 7.67-7.75 (d, *J*= 15.9 Hz, 1H) in ^{1}H NMR and peak at 1716 cm^{-1} in IR spectrum confirmed the formation of the compound **64**. Later the phenolic hydroxyl groups in compound **64** was protected as TBS ethers by treating with 2 equivalents of TBDMSCl and imidazole in DCM and later double bond of **65** is reduced by hydrogenation using 10% Pd/C to give **66** in 90% yield. The disappearance of olefin peaks (δ 6.32-6.40 (d, *J*= 15.8 Hz, 1 H), 7.61-7.69 (d, *J*= 15.8 Hz, 1H) ppm.) in ^{1}H NMR spectrum and shift of carbonyl group stretching frequency from 1716 cm^{-1} to 1738 cm^{-1} confirmed the formation of saturated ester **66** (Scheme 12).



Scheme 12: *Reagents and conditions*: (a) PPh_3, $BrCH_2COOEt$, sat. $NaHCO_3$, 0 ^oC-rt , 6 h, 80 %; (b) TBDMSCl, Imidazole, DCM, 0 ^oC-rt, 12 h, 90%; (c) H_2/ Pd-C, EtOAc, rt, 4h, 90%.

Our next aim was the synthesis of optically active γ-butyrolactone **55** from saturated ester **66** through the proline-catalysed sequential lactonization reaction. As illustrated in Scheme 13, the DIBAL-H reduction of ester **66** to aldehyde **56** and subsequent proline catalysed

sequential lactonization reaction of crude aldehyde **56** provided the substituted enantiopure *γ*-butyrolactone **55** in in overall 45% yield and 96% ee.[16]



Scheme 13: *Reagents and conditions*: (a) DIBAL-H, DCM, -78 °C, 45 min; (b) (i) Nitrosobenzene, D-proline, DMSO,30 min; (ii) HWE salt, DBU, LiCl, CH_3CN; 1h; (c) (i) H_2/Pd-C, EtOAc; 3h; (ii) Pd/C, EtOAc, 65 °C, 10 h, (45 % over 4 steps); (d) MeLi, Et_2O, 3h, -78 °C, 1.5 h; (e) $BF_3.OEt_2$, DCM, 2h, -20 °C, 50%; (f) TBAF, THF, rt, 3h, 90%.

The NMR and IR spectra confirmed the formation of saturated 5-membered lactone **55**. (Scheme 13). Later we treated the lactone **55** with MeLi in anhydrous Et_2O furnished lactol **68**, which was sequentially treated with Lewis acid $BF_3.OEt_2$ generated to furnish oxocarbenium cation **54** which was captured in diastereoselective manner by intramolecular Friedel-Crafts annulation[8b] to provide the protected natural product bruguierol B **69**. The ^1H, ^{13}C NMR, DEPT and IR spectra confirmed the presence of 2,3-benzofused 8-oxabicyclo[3.2.1]octane core in compound **69**.[1] Finally the treatment of **69** with 2.2 equiv.

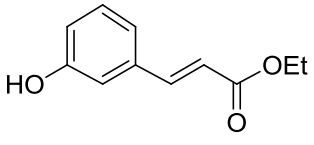
of TBAF at rt in THF furnished the natural product **2** in good yield. The spectral data and optical rotation ($[\alpha]_D^{25}$: + 8.3 (*c* 0.1, MeOH)) of synthetic (+)-bruguierol B **2** were in full agreement with the literature.[1]

4.2.5. Conclusion

In conclusion, proline-catalysed sequential lactonization reactions have been successfully applied towards the synthesis of Bruguierol A **1** and Bruguierol B **2**. The present methods are easily amenable for the synthesis of various monosubstituted γ-butyrolactones in an enantioselective manner which can be employed as synthons/intermediates for acquiring many biologically important compounds. Currently studies are under progress in this direction.

4.2.6. Experimental Section

(*E*)-Ethyl 3-(3-hydroxyphenyl)acrylate (58)



To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (15.66 g, 45.03 mmol) in dry THF (150 mL) was added a solution of the aldehyde **53** (5.0 g, 40.94 mmol) in dry THF (50 mL). The reaction mixture was stirred for 24 h at room temperature. It was then concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (92:8) as eluent to afford the *α,β*-unsaturated olefin **58** as a colourless solid with an *E:Z* ratio of 95:5 and the mixture was used directly for the next step.

Yield: 7.07 g (90%)
Mol. Formula: $C_{11}H_{12}O_3$

Melting point: 74.7 °C

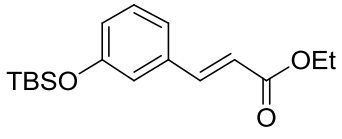
IR ($CHCl_3$, cm^{-1}): ν_{max} 3385, 3030, 2982, 1716, 1637, 1583, 1370, 1191, 855, 785, 679.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35-1.42 (t, *J*= 7.1 Hz, 3H), 4.26-4.37 (q, *J*= 7.1 Hz, 2H), 5.32 (brs, 1H), 6.41-6.49 (d, *J*=16 Hz, 1H), 6.89-6.94 (m, 1H), 7.04-7.06 (m, 1H), 7.13-7.16 (m, 1H), 7.27-7.35 (m, 2H), 7.64-7.72 (d, *J*=16 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 60.7, 114.5, 117.4, 118.4, 120.6, 130.0, 135.8, 144.5, 156.1, 167.3 ppm.

Analysis: Calcd.: C, 68.74; H, 6.29; **Found:** C, 68.71; H, 6.28.

(*E*)-Ethyl 3-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)acrylate (59)



To a stirred solution of phenol **58** (5.0 g, 26.01 mmol) in CH_2Cl_2 (25 mL) was added imidazole (2.47 g, 36.41 mmol). To this solution *t*-butyl dimethylchlorosilane (4.31 g, 28.61 mmol) was added at 0 ^oC and reaction was stirred at room temperature for 8 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 x 50 mL). The extract was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (98:2) as eluent provided **59** as a colourless liquid.

Yield: 7.57g, (95%).
Mol. Formula: $C_{17}H_{26}O_3Si$

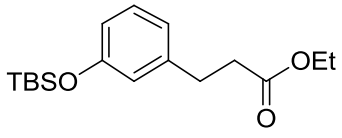
IR ($CHCl_3$, cm^{-1}): ν_{max} 3027, 2956, 2031, 2859, 1716, 1638, 1579, 1473, 1281, 1176, 1038, 842, 784, 682.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.27 (s, 6H), 1.05 (s, 9H), 1.37-1.44 (t, *J*= 7.1 Hz, 3H), 4.28-4.38 (q, *J*= 7.1 Hz, 2H), 6.42-6.50 (d, *J*=16 Hz, 1H), 6.90-6.95 (m, 1H), 7.05-7.07 (m, 1H), 7.16-7.24 (m, 1H), 7.32-7.35 (m, 1H), 7.65-7.73 (d, *J*=16 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.4, 14.2, 18.1, 25.5, 60.4, 118.3, 119.2, 121.3, 122.0, 129.7, 135.8, 144.4, 155.9, 166.8 ppm.

Analysis: Calcd.: C, 66.62; H, 8.55; **Found:** C, 66.61; H, 8.55.

Ethyl 3-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)propanoate (60)



To a solution of olefin **59** (3.0 g, 9.78 mmol) in ethyl acetate (30 mL) was added 10% Pd/C (0.09 g), and reaction mixture was stirred under hydrogen atmosphere for 4 hrs at room temperature. After completion of reaction as indicated by TLC, the reaction mixture was filtered through a celite pad and the filtrate was concentrated in vacuum. Silica gel column chromatography using petroleum ether/EtOAc (98:2) as eluent afforded the compound **60** as a colourless liquid.

Yield: 2.89 g (96%)
Mol. Formula: $C_{17}H_{28}O_3Si$

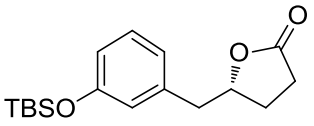
IR ($CHCl_3$, cm^{-1}): ν_{max} 3030, 2957, 2931, 2859, 1731, 1603, 1587, 1486, 1274, 1159, 969, 839, 782, 695.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.20 (s, 6H), 0.99 (s, 9H), 1.21-1.28 (t, *J*=7.1 Hz, 3H), 2.56-2.64 (m, 2H), 2.86-2.94 (m, 2H), 4.08-4.19 (q, *J*= 7.1 Hz, 2H), 6.68-6.70 (m, 2H), 6.78-6.82 (m, 1H), 7.10-7.18 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.5, 14.1, 18.1, 25.6, 30.7, 35.7, 60.2, 117.7, 119.9, 121.2, 129.2, 142.0, 155.6, 172.7 ppm.

Analysis: Calcd.: C, 66.19; H, 9.15; **Found:** C, 66.14; H, 9.11.

(*R*)-5-(3-((*tert*-Butyldimethylsilyl)oxy)benzyl)dihydrofuran-2(3*H*)-one (51)



To a solution of ethyl ester **60** (2.5 g, 8.10 mmol) in CH_2Cl_2 (50 mL), was added DIBAL-H (3.87 mL 2.3 M solution in toluene, 8.91 mmol) at -78 °C under argon atmosphere. The reaction was stirred at this temperature for 40 min, then a solution of tartaric acid (15 mL) was added. The resulting mixture was stirred for 15 min and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic layers were dried (Na_2SO_4), and evaporated under reduced pressure to give aldehyde **52** as a colourless liquid, which was directly used in the next step without further purification.

To a solution of crude phenyl propanal **52** (~8.10 mmol) and nitroso benzene (0.86 g, 8.10 mmol) in anhydrous DMSO (15 mL) was added *D*-proline (0.37 g, 3.24 mmol) at 20 °C. The mixture was vigorously stirred for 25 min under argon (the colour of the reaction changed from green to yellow during this time), then cooled to 0 °C. Thereafter, a premixed and cooled (0 °C) solution of triethylphosphonoacetate (4.86 mL, 24.3 mmol), DBU (3.62 mL, 24.3 mmol) and LiCl (1.03g, 24.3 mmol) in CH_3CN (15 mL) was added quickly (1-2 min) at 0 °C. The resulting mixture was allowed to warm to room temperature over 1 h and quenched by addition of ice pieces. The acetonitrile was evaporated under vacuum. This reaction mixture was then poured into water (50 mL) and extracted with Et_2O (3×50 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated in vacuum to give crude product **61** which was directly subjected to next step without purification. To the crude unsaturated ester **61** in ethyl acetate was added Pd-C (20%) under hydrogenation conditions. After 4 hours of stirring, hydrogen atmosphere was replaced by argon gas and continued the stirring of reaction mixture at elevated temperature (60-65 ^oC) for another 6 hours. On completion of reaction (until ^1H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of celite and concentrated in vacuum to give substituted *γ*-butyrolactone **51**. The crude product was then

purified by using flash column chromatography using pet ether: EtOAc (93:7) as eluent to give **51** as a colourless liquid.

Yield: 1.5 g (60% over 4 steps)
Mol. Formula: $C_{17}H_{26}O_3Si$

$[\alpha]_D^{25}$: -5.52 (*c* 3.4, $CHCl_3$)

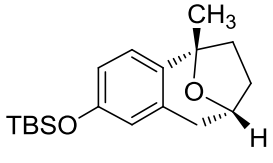
IR ($CHCl_3$, cm^{-1}): ν_{max} 3019, 2956, 2931, 1772, 1604, 1583, 1486, 1444, 1278, 1161, 1007, 971, 781, 664.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.20 (s, 6H), 0.99 (s, 9H), 1.90-2.00 (m, 1H), 2.22-2.25 (m, 1H), 2.41-2.50 (m, 2H), 2.83-2.89 (dd, *J*= 13.8 Hz, 6.5, 1H), 3.02-3.07 (dd, *J*=13.8, 5.8 Hz, 1H), 4.69-4.75 (m, 1H), 6.71-6.76 (m, 2H), 6.81-6.83 (m, 1H), 7.15-7.19 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.4, 18.1, 25.6, 27.0, 28.6, 41.1, 80.7, 118.6, 121.2, 122.4, 129.5, 137.2, 155.8, 176.9 ppm.

Analysis: Calcd.: C, 66.62; H, 8.55; **Found:** C, 66.60; H, 8.53.

***tert*-Butyldimethyl(((5*S*,8*R*)-5-methyl-6,7,8,9-tetrahydro-5*H*-5,8 epoxybenzo[7]annulen-2-yl)oxy)silane (63)**



To a solution of lactone **51** (1g, 3.26 mmol) dissolved in anhydrous Et_2O (25 mL) was added MeLi (2.6 mL, 1.6 M solution in DEE, 4.24mmol) drop wise under argon at -78 °C. The reaction was left stirring for 1.5 h until starting material was consumed at which time the reaction was quenched with NH_4Cl. The aqueous layer was then extracted (3 x 50 mL) with Et_2O. The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, which afforded the crude lactol **62**. To a solution of

crude lactol **62** dissolved in 25 mL of CH_2Cl_2 was added $BF_3.OEt_2$ (0.81 mL, 6.52 mmol) dropwise under argon at -20 ^oC. The solution was left stirring for 2 h and the reaction was quenched with sat. NH_4Cl. The aqueous layer was then extracted (3x50 mL) with Et_2O. The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude product **63**. Silica gel column chromatography using petroleum ether/EtOAc ((98:2) as eluent afforded the compound **63** as a colourless liquid.

Yield: 0.59 g (60% over two steps)
Mol. Formula: $C_{18}H_{28}O_2Si$

$[\alpha]_D^{25}$: + 28.8 (*c* 0.7, $CHCl_3$)

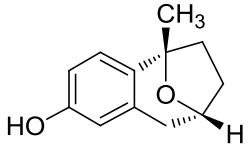
IR ($CHCl_3$, cm^{-1}): ν_{max} 3020, 2979, 2931, 2858, 1609, 1575, 1496, 1487, 1420, 1265, 1154, 1093, 1031, 982, 838, 757, 679.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.19 (s, 6H), 0.98 (s, 9H), 1.64-1.74 (m, 1H), 1.71(s, 3H), 1.81-1.87 (m, 1H), 1.98-2.02 (m, 1H), 2.22-2.28 (m, 1H), 2.44-2.48 (d, *J*= 16.3 Hz, 1H), 3.30-3.34 (dd, *J*= 16.3, 4.8 Hz, 1H), 4.70-4.73 (t, *J*=6.3 Hz, 1H), 6.55 (s, 1H), 6.60-6.62 (d, *J*= 8.5 Hz, 1H), 7.00-7.01 (d, *J*=8.5 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.4, 18.1, 22.8, 25.6, 30.4, 37.5, 42.9, 74.2, 80.2, 117.4, 120.3, 123.6, 133.1, 136.9, 154.4 ppm.

Analysis: Calcd.: C, 71.00; H, 9.27; **Found:** C, 71.03; H, 9.24.

(5*S*,8*R*)-5-Methyl-6,7,8,9-tetrahydro-5*H*-5,8-epoxybenzo[7]annulen-2-ol (1)



To a solution of protected natural product **63** (0.3 g, 0.98 mmol) dissolved in THF (20 mL) was added TBAF (1.2 mL, 1M solution in THF, 1.18 mmol) dropwise at rt. The reaction was left stirring for 2 h and the reaction was quenched with sat. NH_4Cl. The aqueous layer was then extracted (3x25 mL) with EtOAc. The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, which afforded the crude product **1**. Flash chromatography using petroleum ether/EtOAc (91:9) afforded (+)-bruguierol A **1** as a white solid.

Yield: 0.170 g (90 %)
Mol. Formula: $C_{12}H_{14}O_2$

Melting point: 132.6 ^oC

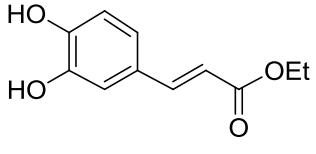
$[\alpha]_D^{25}$: + 14.8 (*c* 0.3, MeOH) {reported value **$[\alpha]_D^{25}$:** +14.4 (*c* 0.3, $CHCl_3$)}
IR ($CHCl_3$, cm^{-1}): ν_{max} 3390, 3021, 2980, 2933, 2856, 1610, 1575, 1496, 1472, 1234, 1154, 1117, 1091, 994, 817, 778, 679.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.69-1.75 (m, 1H), 1.72 (s, 3H), 1.83-1.89 (m, 1H), 1.98-2.03 (m, 1H), 2.23-2.29 (m, 1H), 2.43-2.47 (d, *J*= 16.5 Hz, 1H), 3.29-3.33 (dd, *J*= 16.5, 4.9 Hz, 1H), 4.72-4.75 (t, *J*=6.0 Hz, 1H), 5.68 (brs, 1H), 6.53 (s, 1H), 6.54-6.62 (dd, *J*= 8.2 Hz, 2.4, 1H), 7.00-7.02 (d, *J*=8.5 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 22.8, 30.4, 37.5, 42.9, 74.2, 80.5, 112.9, 115.6, 123.9, 133.3, 136.1, 154.4 ppm.

Analysis: Calcd.: C, 75.76; H, 7.42; **Found:** C, 75.71; H, 7.43.

(*E*)-Ethyl 3-(3,4-dihydroxyphenyl)acrylate (64)



To a solution of PPh_3 (15.2 g, 57.9 mmol), Ethyl bromoacetate (5.6 mL, 50.6 mmol) in saturated aqueous $NaHCO_3$ (180 mL) was added aldehyde **57** (5 g, 36.2mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 6 hours. Then the pH of reaction mixture was adjusted to ~5.5 using H_2SO_4 (1 M). The aqueous phase was extracted with EtOAc (3 x 75 mL). The combined organic layers were washed with water (3 x 100 mL), brine, dried (Na_2SO_4) and concentrated. The residual oil was purified by silica gel column chromatography using petroleum ether/EtOAc (80:20) as eluent to afford the *α,β*-unsaturated olefin **64** as a colourless solid with an *E:Z* ratio of 90:10 which was used directly in the next step.

Yield: 6.0 g (80%)
Mol. Formula: $C_{11}H_{12}O_4$

Melting point: 148.2 °C

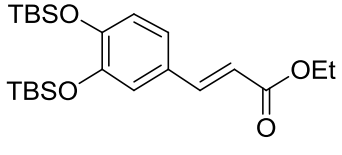
IR ($CHCl_3$, cm^{-1}): ν_{max} 3663, 3346, 3030, 2982, 1716, 1601, 1584, 1372, 1193, 857, 790, 680.

^{1}H NMR (200 MHz, DMSO): δ 1.50-1.57 (t, *J*=7.1 Hz, 3H), 4.37-4.48 (q, *J*= 7.2 Hz, 2H), 5.80 (brs, 2H), 6.38-6.46 (d, *J*= 15.9 Hz, 1H), 7.01-7.27 (m, 3H). 7.67-7.75 (d, *J*= 15.9 Hz, 1H) ppm.

^{13}C NMR (50 MHz, DMSO): δ 14.1, 59.7, 114.1, 115.5, 121.2, 125.8, 144.7, 145.3, 147.9, 166.9 ppm.

Analysis: Calcd.: C, 63.45; H, 5.81; **Found:** C, 63.43; H, 5.83.

(*E*)-Ethyl 3-(3,4-bis((*tert*-butyldimethylsilyl)oxy)phenyl)acrylate (65)



To a stirred solution of phenol **64** (5.0 g, 24.01 mmol) in CH_2Cl_2 (50 mL) was added imidazole (4.90 g, 72.04 mmol). To this solution *t*-butyl dimethylchlorosilane (7.96 g, 52.82 mmol) was added at 0 ^oC and reaction was stirred at room temperature for 12 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 x 50 mL). The extract was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (96:4) as eluent provided **65** as a colourless solid.

Yield: 9.45 g (90 %)
Mol. Formula: $C_{23}H_{40}O_4Si_2$

Melting point: 106.5 ^oC

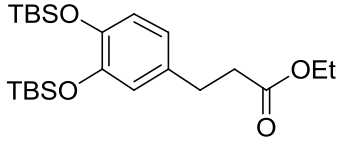
IR ($CHCl_3$, cm^{-1}): ν_{max} 3027, 2931, 2896, 2859, 1716, 1635, 1568, 1510, 1472, 1289, 1162, 1126, 1042, 983, 906, 840, 694.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.24 (s, 12 H), 1.03 (s, 18 H), 1.26-1.33 (t, *J*= 7.2 Hz, 3 H), 4.13-4.24 (q, *J*= 7.2 Hz, 2H), 6.32-6.40 (d, *J*= 15.8 Hz, 1 H), 6.95-7.03 (m, 2 H), 7.21 (s, 1H), 7.61-7.69 (d, *J*= 15.8 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.0, 14.3, 18.4, 25.8, 60.2, 115.8, 120.3, 121.1, 122.2, 128.0, 144.5, 147.1, 149.3, 167.2 ppm.

Analysis: Calcd.: C, 63.25; H, 9.23; **Found:** C, 63.24; H, 9.21

Ethyl 3-(3,4-bis((tert-butyldimethylsilyl)oxy)phenyl)propanoate (66)



To a solution of olefin **65** (5.0 g, 11.4 mmol) in ethyl acetate (50 mL) was added 10% Pd/C (0.1 g), and reaction mixture was stirred under hydrogen atmosphere for 4 hrs at room

temperature. After completion of reaction as indicated by TLC, the reaction mixture was filtered through a celite pad and the filtrate was concentrated in vacuum. Silica gel column chromatography using petroleum ether/EtOAc (98:2) as eluent afforded the compound **66** as a colourless viscous liquid.

Yield: 4.5 g (90%)

Mol. Formula: $C_{23}H_{42}O_4Si_2$

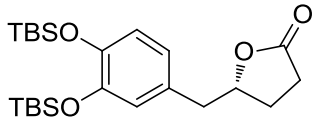
IR ($CHCl_3$, cm^{-1}): ν_{max} 3027, 2957, 2931, 2896, 1738, 1606, 1576, 1511, 1472, 1295, 1254, 1159, 907, 839, 781, 690.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.19 (s, 12 H), 0.97 (s, 18 H), 1.20-1.28 (t, *J*= 7.2 Hz, 3H), 2.51-2.59 (m, 2H), 2.79-2.87 (m, 2H), 4.07-4.18 (q, *J*=7.1 Hz, 2H), 6.60-6.76 (m, 3H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.1, 14.1, 18.3, 25.9, 30.2, 36.1, 60.2, 120.8, 121.0, 121.1, 133.6, 145.1, 146.5, 172.9 ppm.

Analysis: Calcd.: C, 62.96; H, 9.65; **Found**: C, 62.91; H, 9.66.

(*R*)-5-(3,4-bis((*tert*-Butyldimethylsilyl)oxy)benzyl)dihydrofuran-2(3*H*)-one (55)



To a solution of ethyl ester **66** (4 g, 9.11 mmol) in CH_2Cl_2 (50 mL), was added DIBAL-H (4.35 mL, 2.3 M solution in toluene, 10.02 mmol) at -78 °C under argon atmosphere. The reaction was stirred at this temperature for 45 min, then a solution of tartaric acid (20 mL) was added. The resulting mixture was stirred for 15 min and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic layers were dried (Na_2SO_4), and evaporated under reduced pressure to give aldehyde **56** as a colourless liquid, which was directly used in the next step without further purification.

To a solution of crude **56** (~9.11 mmol) and nitroso benzene (0.88 g, 8.19 mmol) in anhydrous DMSO (20 mL) was added *D*-proline (0.21 g, 1.82 mmol) at 20 °C. The mixture was vigorously stirred for 30 min under argon (the colour of the reaction changed from green to yellow during this time), then cooled to 0 °C. Thereafter, a premixed and cooled (0 °C) solution of triethylphosphonoacetate (5.46 mL, 27.3 mmol), DBU (4.07 mL, 27.3 mmol) and LiCl (1.15g, 27.3 mmol) in CH_3CN (20 mL) was added quickly (1-2 min) at 0 °C. The resulting mixture was allowed to warm to room temperature over 1 h and quenched by addition of ice pieces. The acetonitrile was evaporated under vacuum. This reaction mixture was then poured into water (50 mL) and extracted with Et_2O (3×50 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated in vacuum to give crude product **67** which was directly subjected to next step without purification. To the crude unsaturated ester **67** in ethyl acetate was added Pd-C (20%) under hydrogenation conditions. After 3 hours of stirring, hydrogen atmosphere was removed and continued the stirring of reaction mixture at elevated temperature (60-65 ^oC) for another 10 hours. On completion of reaction (until ^1H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of celite and concentrated in vacuum to give substituted *γ*-butyrolactone **55**. The crude product was then purified by using flash column chromatography using pet ether: EtOAc (94:6) as eluent to give **55** as a colourless liquid.

Yield: 1.8 g (45 % over 4 steps)

Mol. Formula: $C_{23}H_{40}O_4Si_2$

$[\alpha]_D^{25}$: +1.36 (*c,* 1.4, $CHCl_3$)

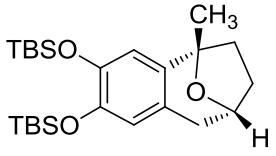
IR ($CHCl_3$, cm^{-1}): ν_{max} 3021, 2953, 2890, 2858, 1770, 1601, 1583, 1484, 1447, 1270, 1161, 1017, 975, 664.

^1H NMR (200 MHz, $CDCl_3$): δ 0.20 (s, 12 H), 0.98 (s, 18 H), 1.92-2.02 (m, 1 H), 2.16-2.30 (m. 1H), 2.36-2.52 (m, 2 H), 2.73-2.84 (m, 1H), 2.92-3.02 (m, 1H), 4.61-4.74 (m, 1H), 6.63-6.79 (m, 3H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.0, 18.3, 25.9, 27.0, 28.6, 41.4, 80.7, 121.0, 121.3, 121.4, 131.6, 145.1, 145.9, 176.9 ppm.

Analysis: Calcd.: C, 63.25; H, 9.23; **Found**: C, 63.23; H, 9.27.

(((5*S*,8*R*)-5-Methyl-6,7,8,9-tetrahydro-5*H*-5,8-epoxybenzo[7]annulene-2,3-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) (69)



To a solution of lactone **55** (1g, 2.28 mmol) dissolved in anhydrous Et_2O (20 mL) was added MeLi (1.85 mL, 1.6 M solution in DEE, 2.97 mmol) dropwise under argon at -78 ^oC. The reaction was left stirring for 1.5 h until starting material was consumed at which time the reaction was quenched with NH_4Cl. The aqueous layer was then extracted (3 x 50 mL) with Et_2O. The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, which afforded the crude lactol product **68**. To a solution of crude lactol **68** dissolved in 25 mL of CH_2Cl_2 was added $BF_3.OEt_2$ (0.56 mL, 4.56 mmol) dropwise under argon at -20 ^oC. The solution was left stirring for 2 h and the reaction was quenched with sat. NH_4Cl. The aqueous layer was then extracted (3x50 mL) with Et_2O. The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude product **69**. Silica gel column chromatography using petroleum ether/EtOAc (99:1) as eluent afforded compound **69** as a colourless liquid.
Yield: 0.5 g (50 % over 2 steps)
Mol. Formula: $C_{24}H_{42}O_3Si_2$

$[\alpha]_D^{25}$: + 19.4 (*c* 0.5, $CHCl_3$)

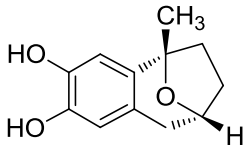
IR ($CHCl_3$, cm^{-1}): ν_{max} 3020, 2979, 2931, 2898, 1609, 1515, 1496, 1420, 1275, 1184, 1093, 1081, 982, 894, 767.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.16 (s, 12 H), 0.98 (s, 18H), 1.66 (s, 3H), 1.72-1.73 (m, 1H), 1.76-1.79 (m, 1H), 1.88-1.94 (m, 1H), 1.98-2.41 (m, 2H), 3.19-3.30 (dd, *J*= 16.7, 5.0 Hz, 1H), 4.67-4.73 (t, *J*= 6.4 Hz, 1H), 6.51 (s, 1H), 6.62 (s, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.3, 18.2, 22.9, 25.7, 30.5, 37.6, 43.0, 74.3, 81.5, 117.5, 118.3, 127.7, 128.3, 144.0, 144.9 ppm.

Analysis: Calcd.: C, 66.30; H, 9.74; **Found:** C, 66.33; H, 9.71.

(5*S*,8*R*)-5-Methyl-6,7,8,9-tetrahydro-5*H*-5,8-epoxybenzo[7]annulene-2,3-diol (2)



To a solution of protected natural product **69** (0.2 g, 0.46 mmol) dissolved in THF (10 mL) was added TBAF (1.01 mL, 1M solution in THF, 1.01 mmol) dropwise at rt. The reaction was left stirring for 3 h and the reaction was quenched with sat. NH_4Cl. The aqueous layer was then extracted (3x25 mL) with EtOAc. The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, which afforded the crude product **2**. Flash chromatography using petroleum ether/EtOAc (55:45) afforded (+)-bruguierol B **2** as a white solid.

Yield: 0.085 g (90%)
Mol. Formula: $C_{12}H_{14}O_3$

$[\alpha]_D^{25}$: + 8.3 (*c* 0.1, MeOH)

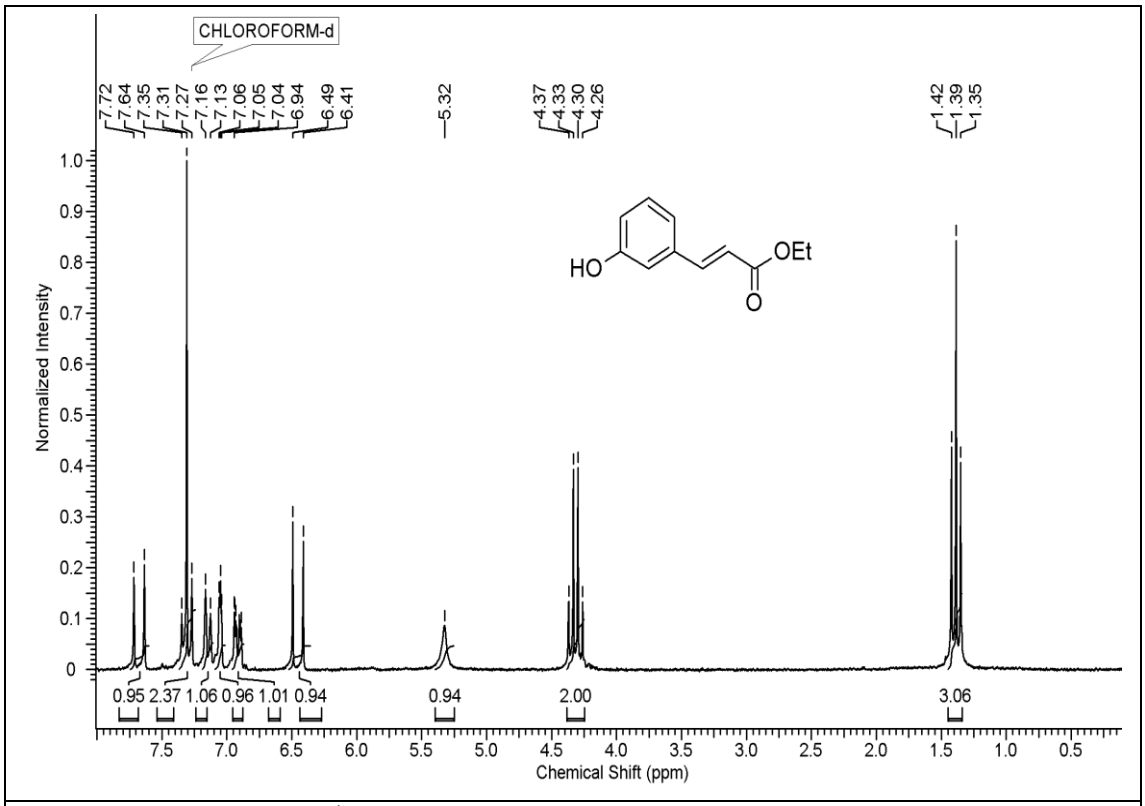
IR ($CHCl_3$, cm^{-1}): ν_{max} 3290, 3019, 2933, 2856, 1608, 1518, 1494, 1442, 1294, 1164, 1113, 1091, 990, 867.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.66 (s, 3H), 1.72-1.99 (m, 3H), 2.20-2.41(m, 2H), 3.19-3.30 (dd, *J*= 16.4, 4.7 Hz, 1H), 4.67-4.74 (m, 1H), 5.71 (brs, 2H), 6.51 (s, 1H), 6.62 (s, 1H) ppm.

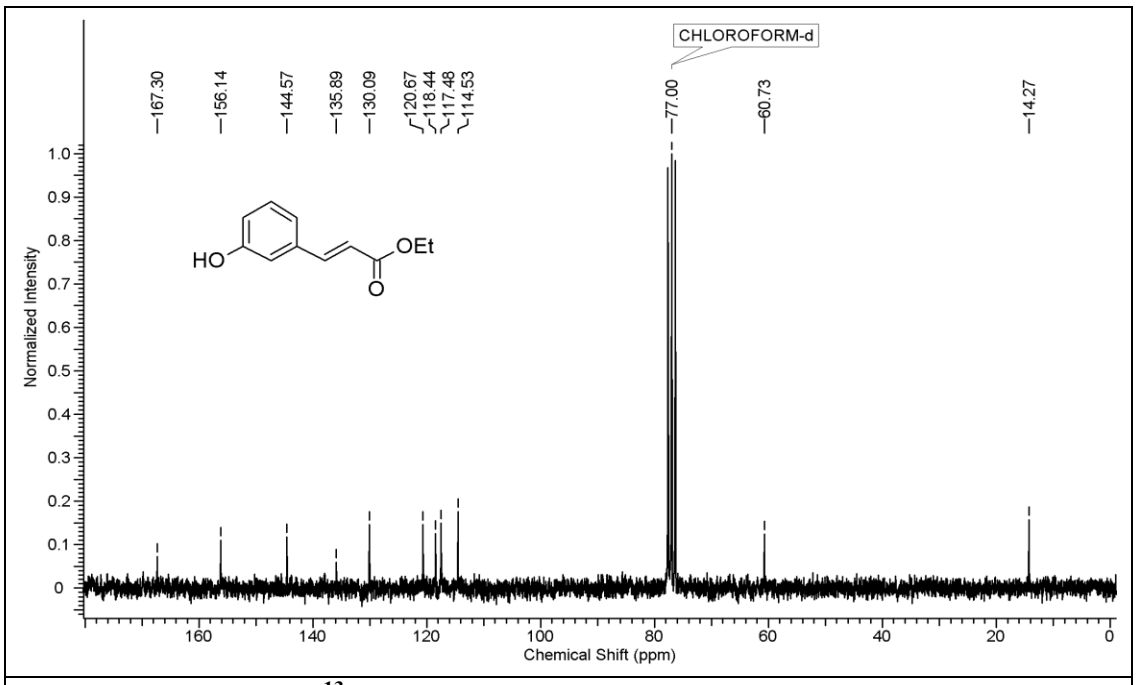
^{13}C NMR (50 MHz, $CDCl_3$): δ 22.9, 30.5, 37.6, 43.0, 74.3, 81.6, 115.0, 115.7, 128.2, 128.8, 142.0, 142.7 ppm.

Analysis: Calcd.: C, 69.88; H, 6.84; **Found:** C, 69.86; H, 6.85.

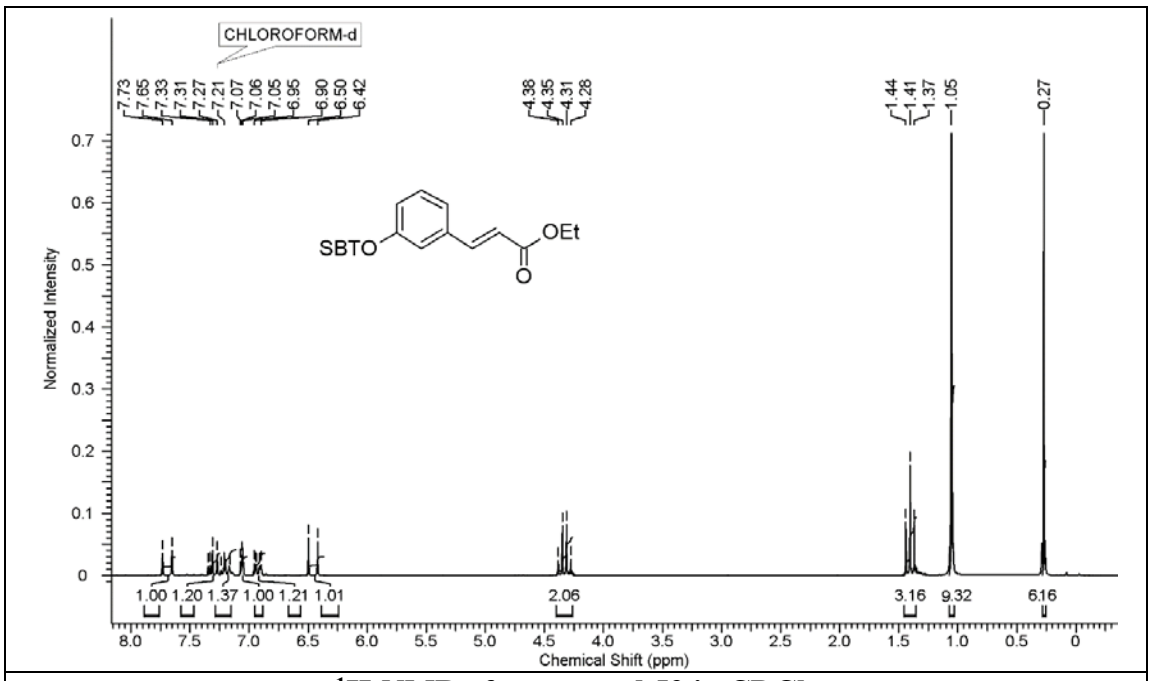
4.2.7. Spectra



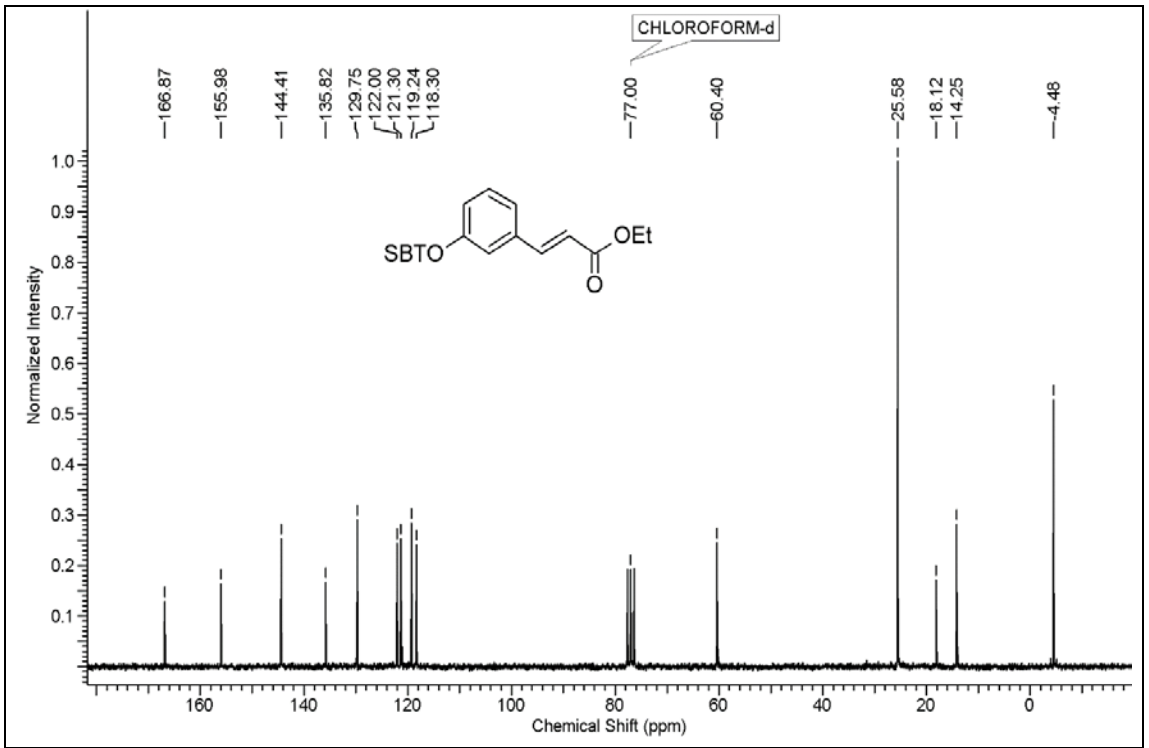
^{1}H-NMR of compound 58 in $CDCl_3$



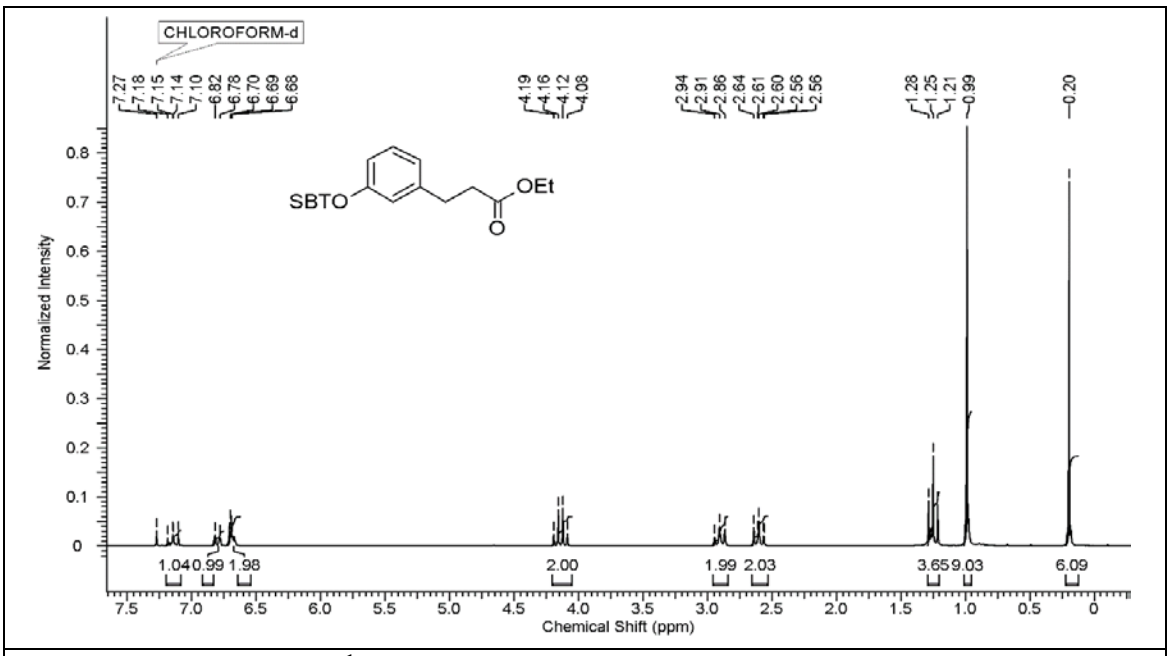
^{13}C-NMR of compound 58 in $CDCl_3$



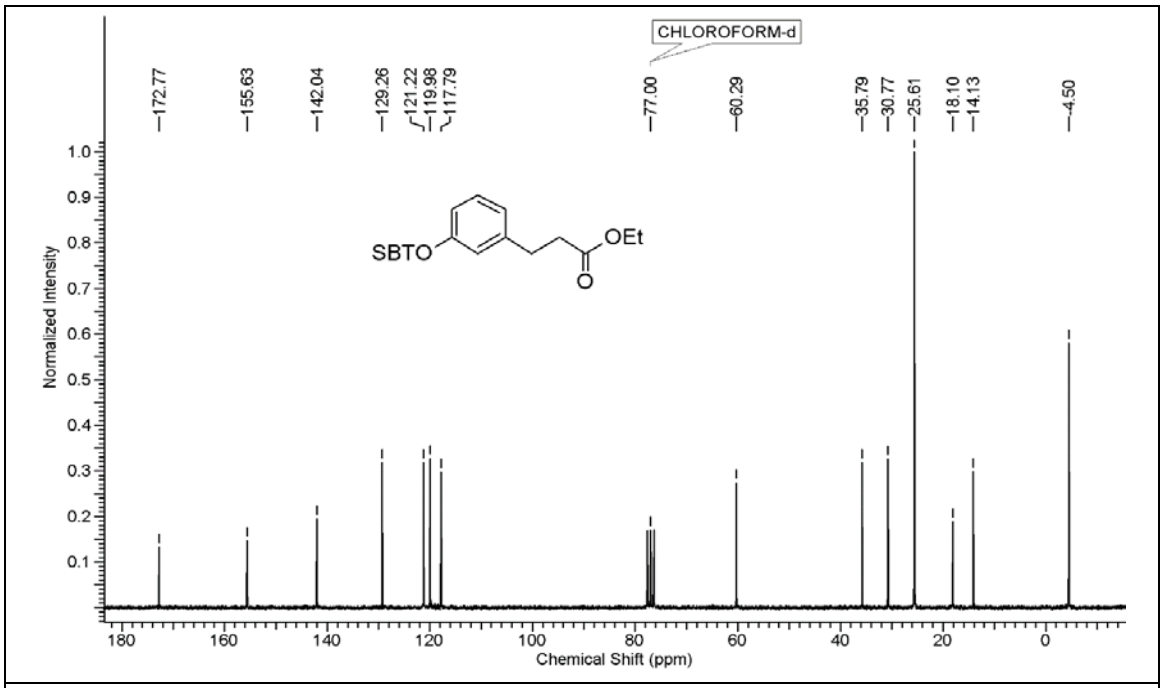
^{1}H-NMR of compound 59 in $CDCl_3$



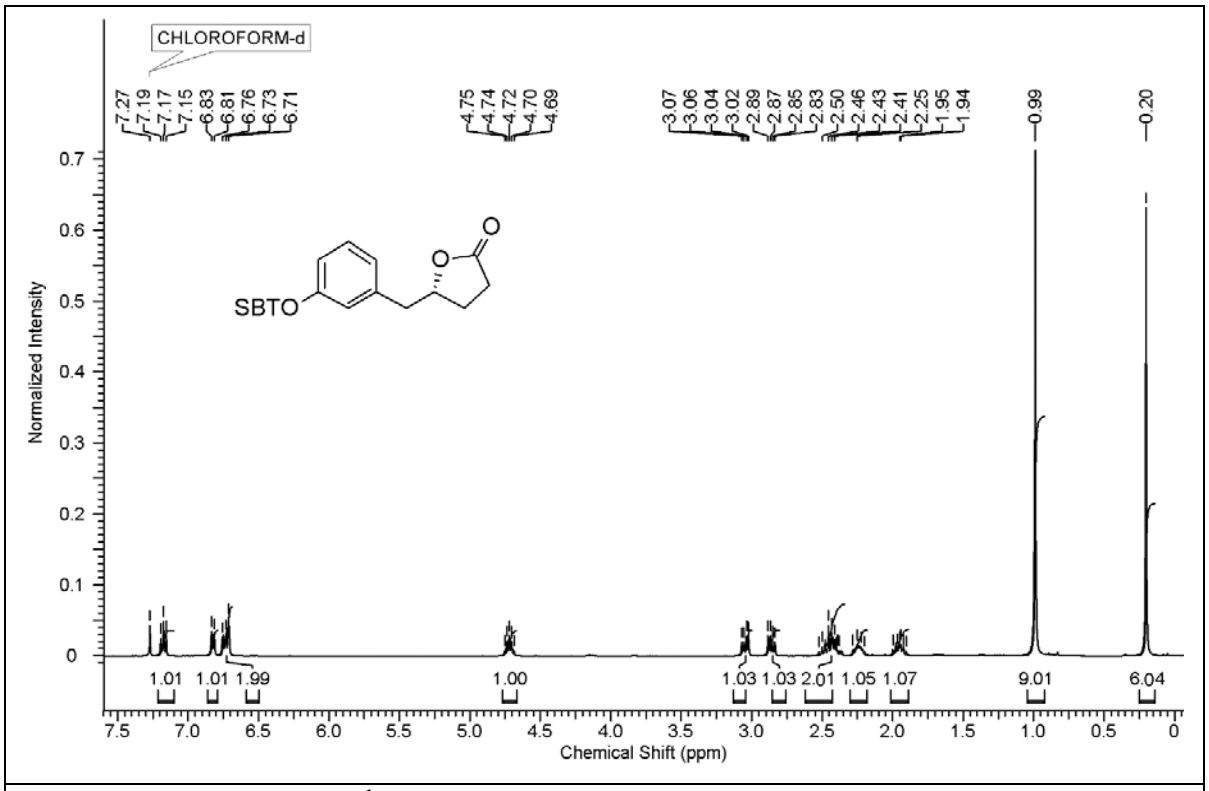
^{13}C-NMR of compound 59 in $CDCl_3$



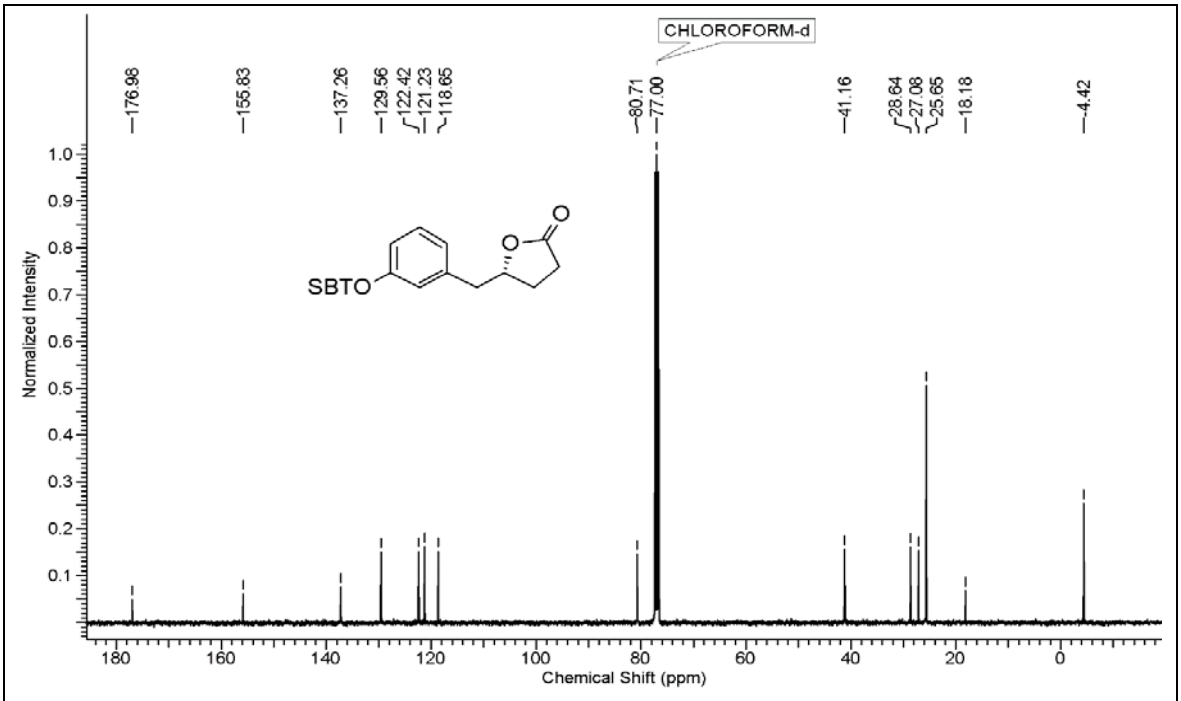
^{1}H-NMR of compound 60 in $CDCl_3$



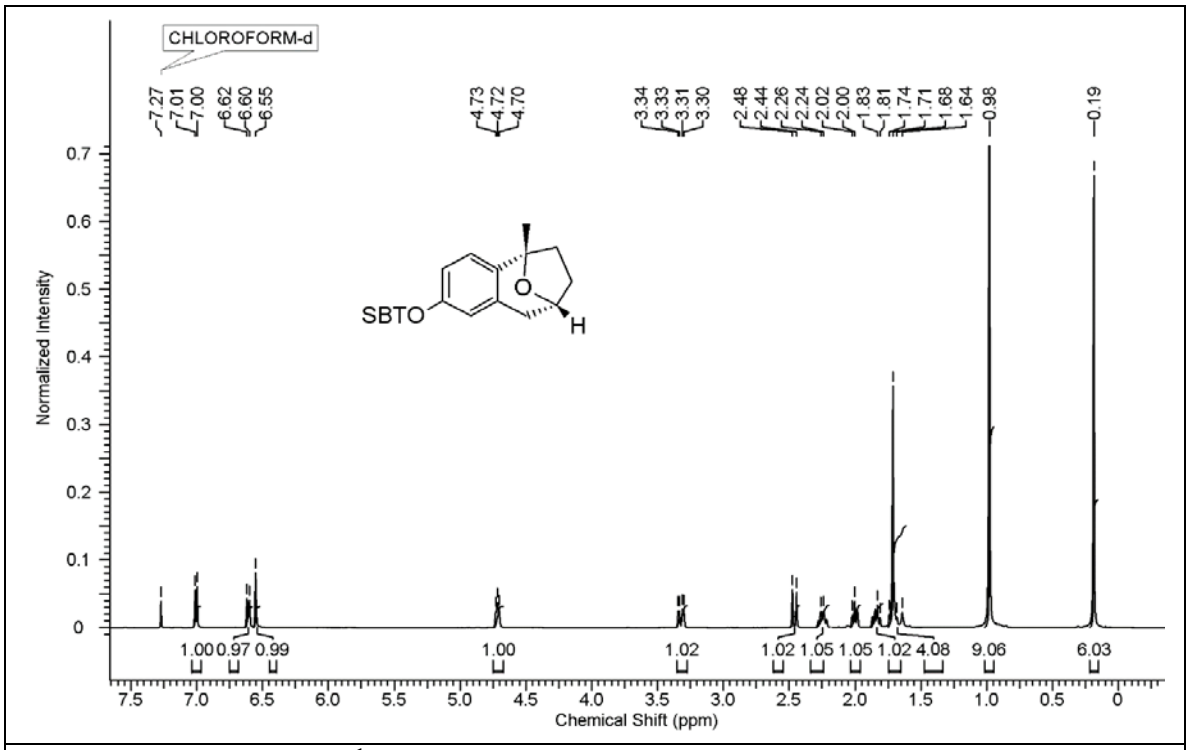
^{13}C-NMR of compound 60 in $CDCl_3$



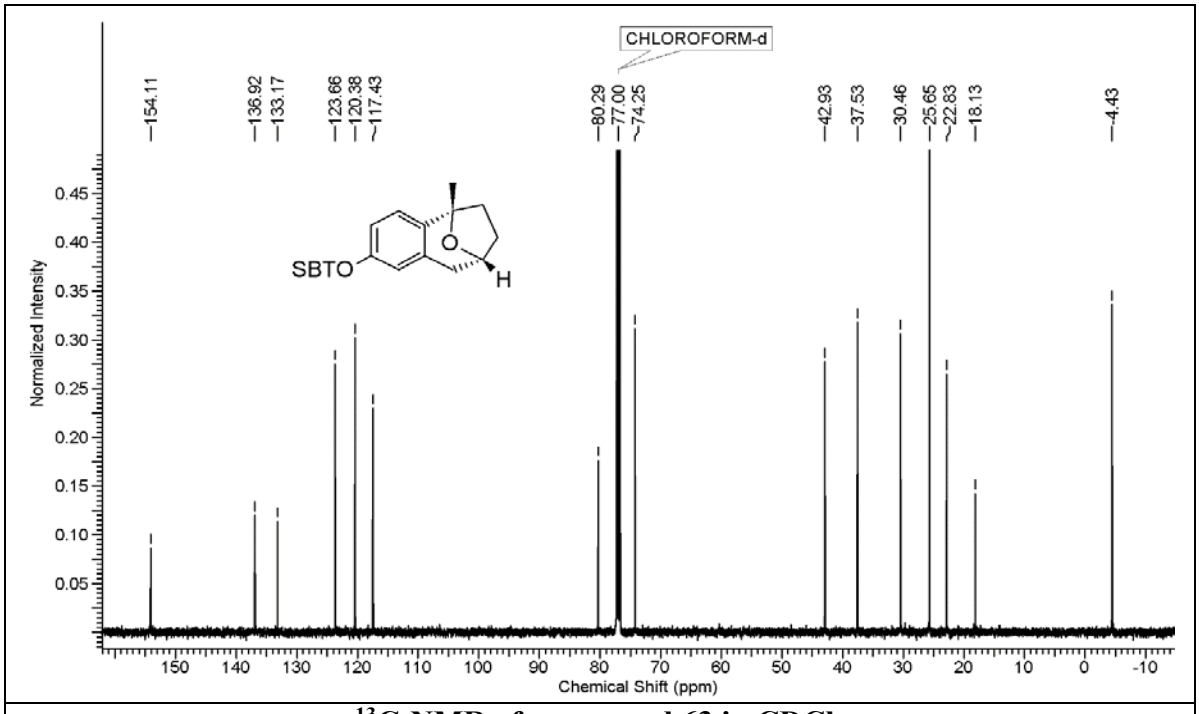
^{1}H-NMR of compound 51 in $CDCl_3$



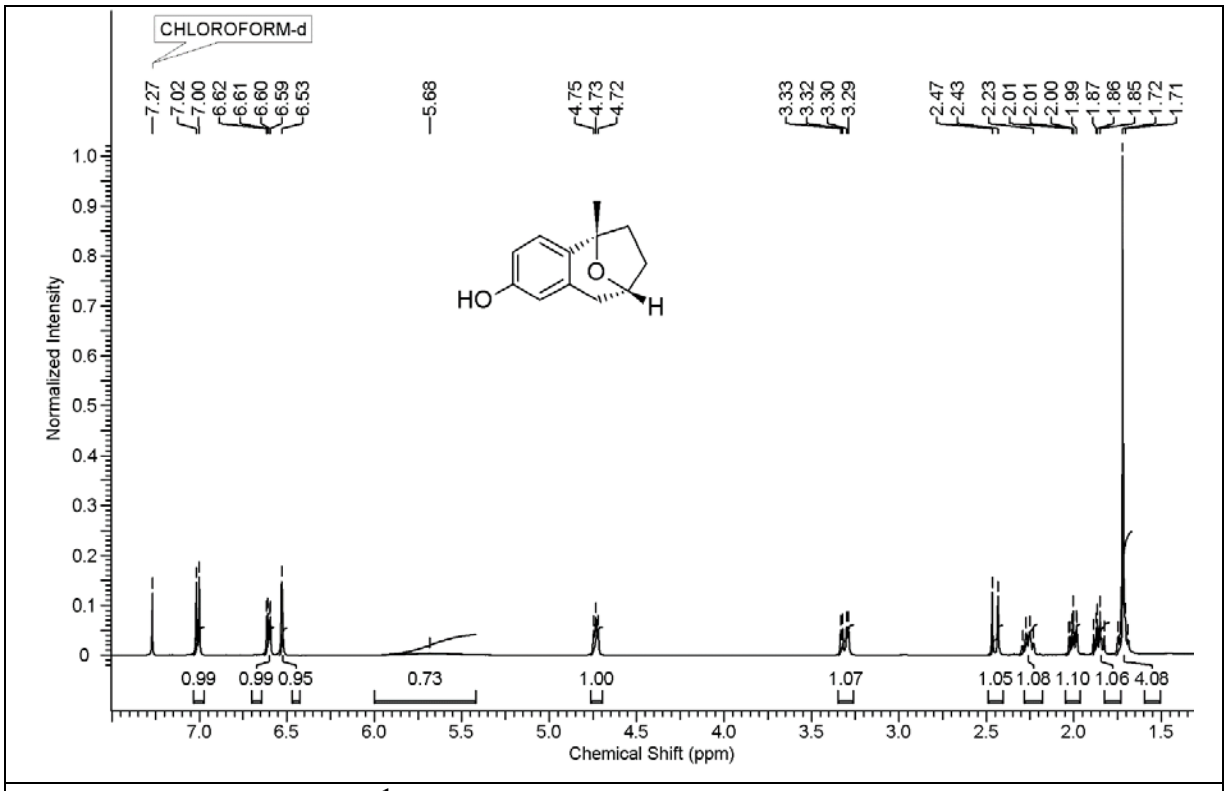
^{13}C-NMR of compound 51 in $CDCl_3$



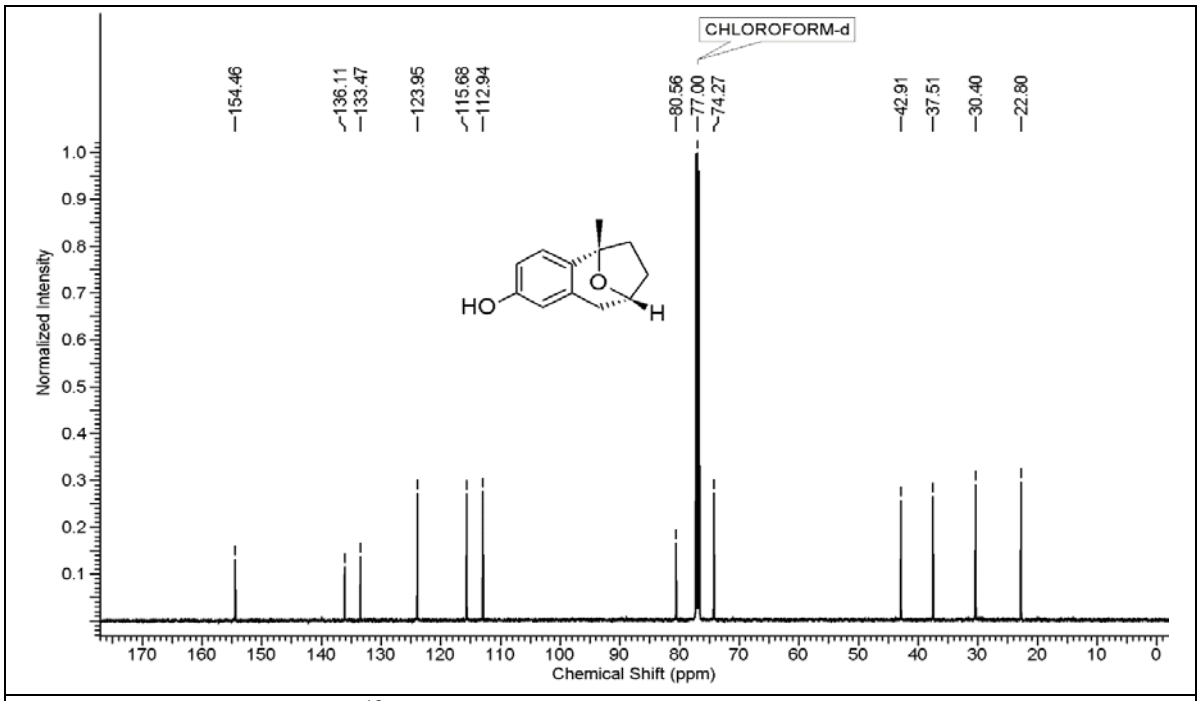
^{1}H-NMR of compound 63 in $CDCl_3$



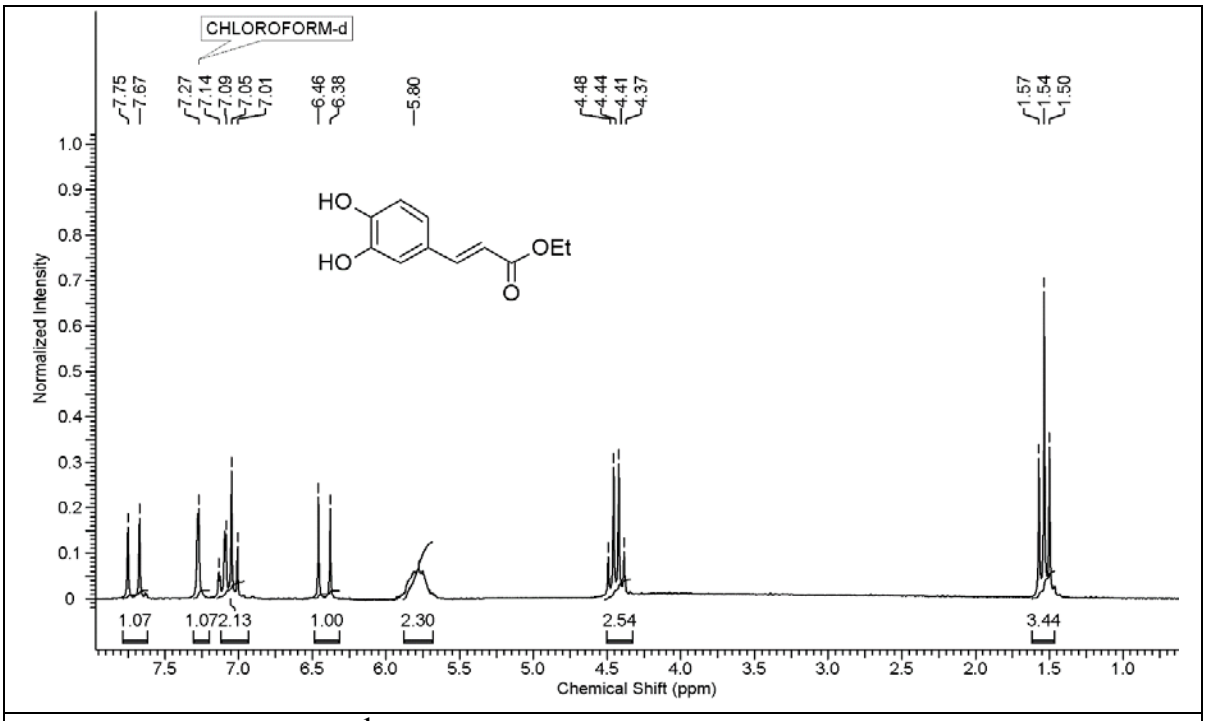
^{13}C-NMR of compound 63 in $CDCl_3$



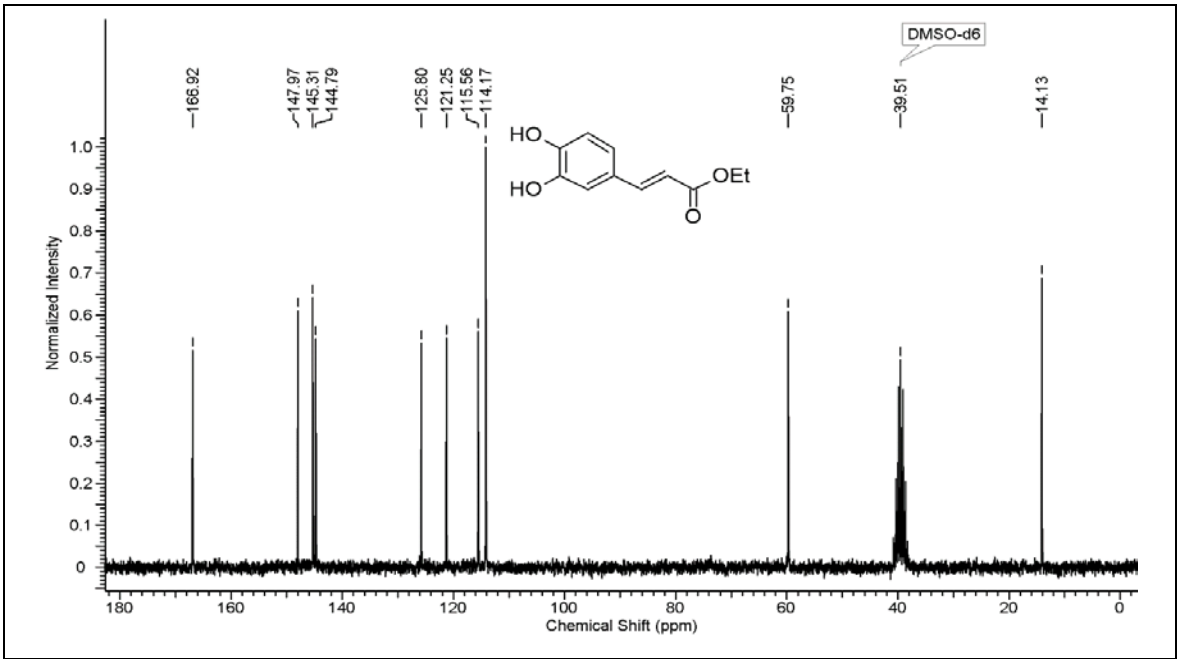
^{1}H-NMR of compound 1 in $CDCl_3$



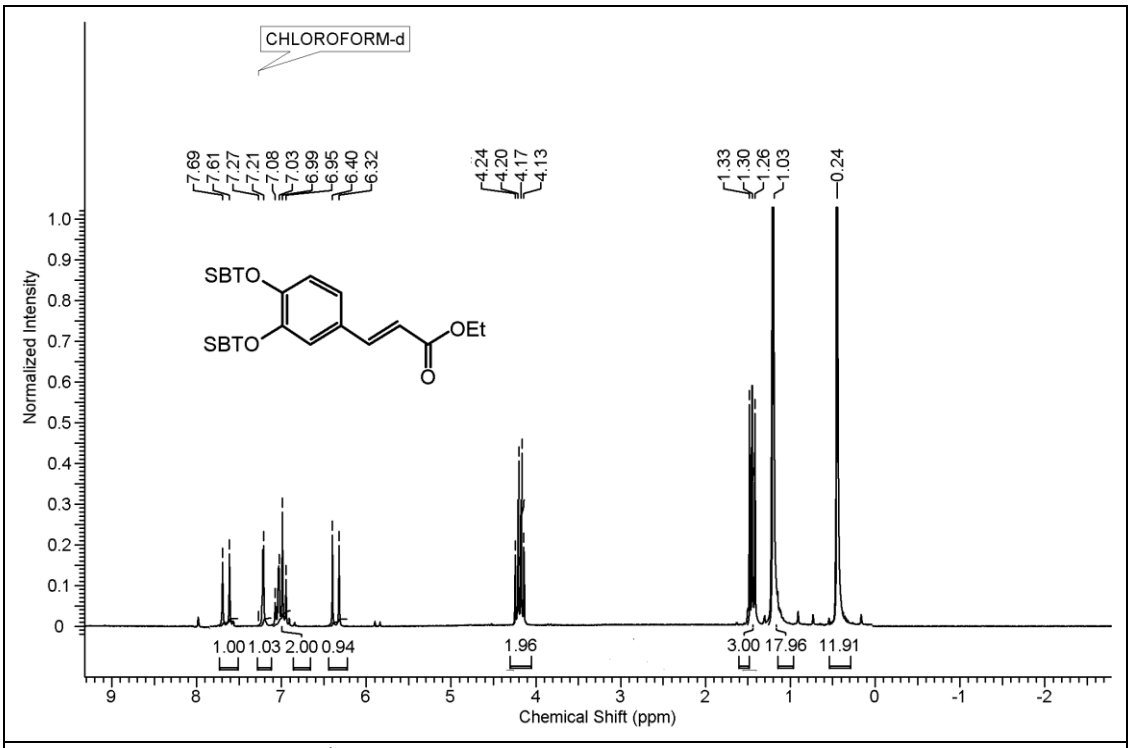
^{13}C-NMR of compound 1 in $CDCl_3$



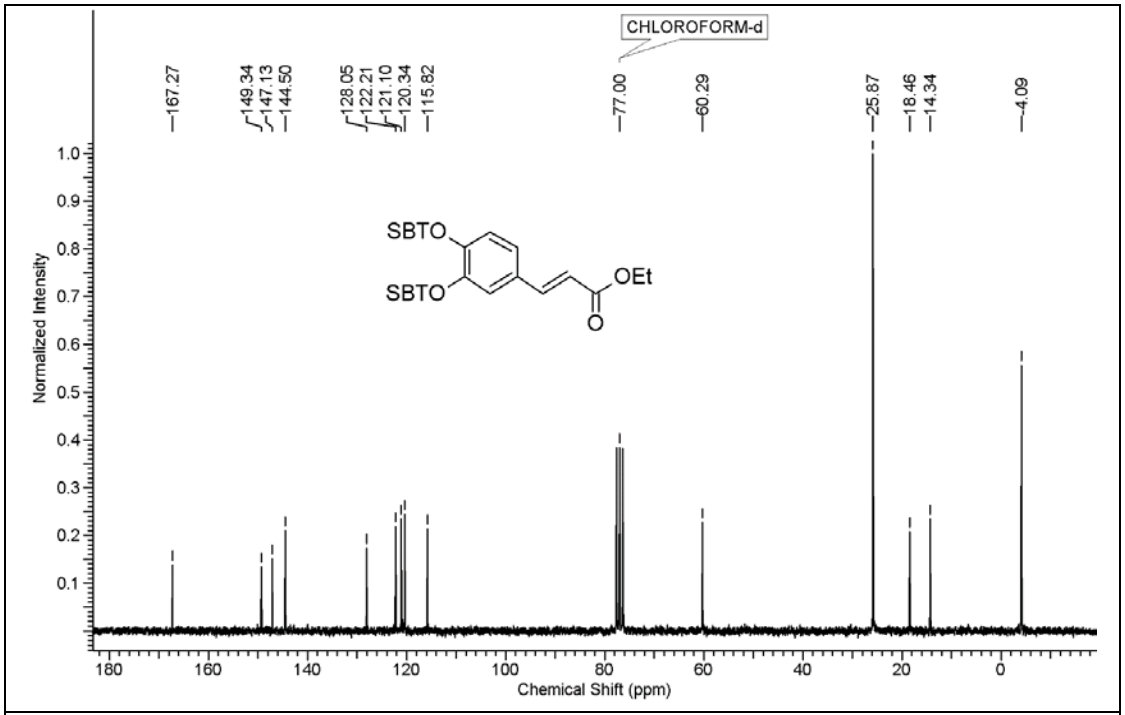
^{1}H-NMR of compound 64 in $CDCl_3$



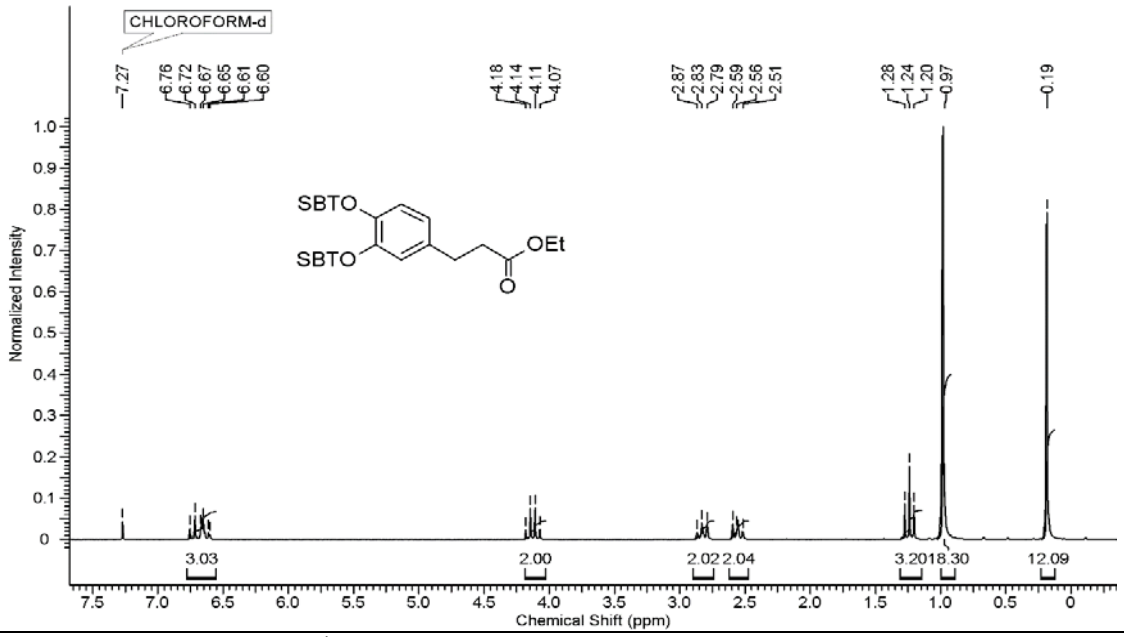
^{13}C-NMR of compound 64 in DMSO-d6



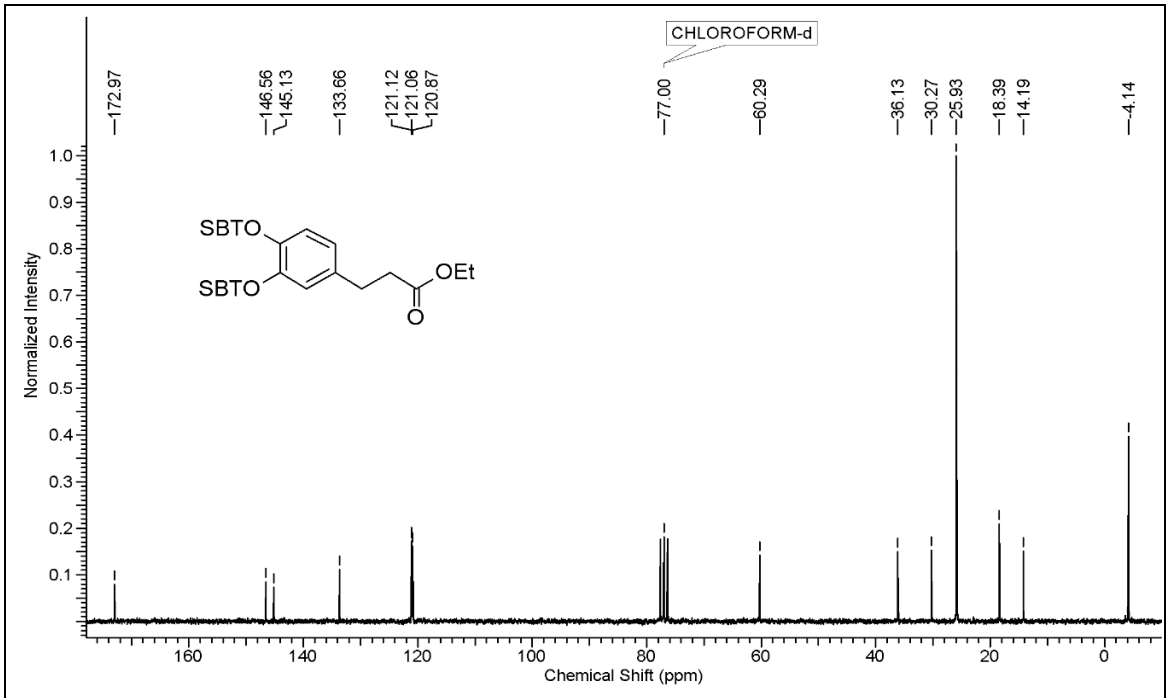
^{1}H-NMR of compound 65 in $CDCl_3$



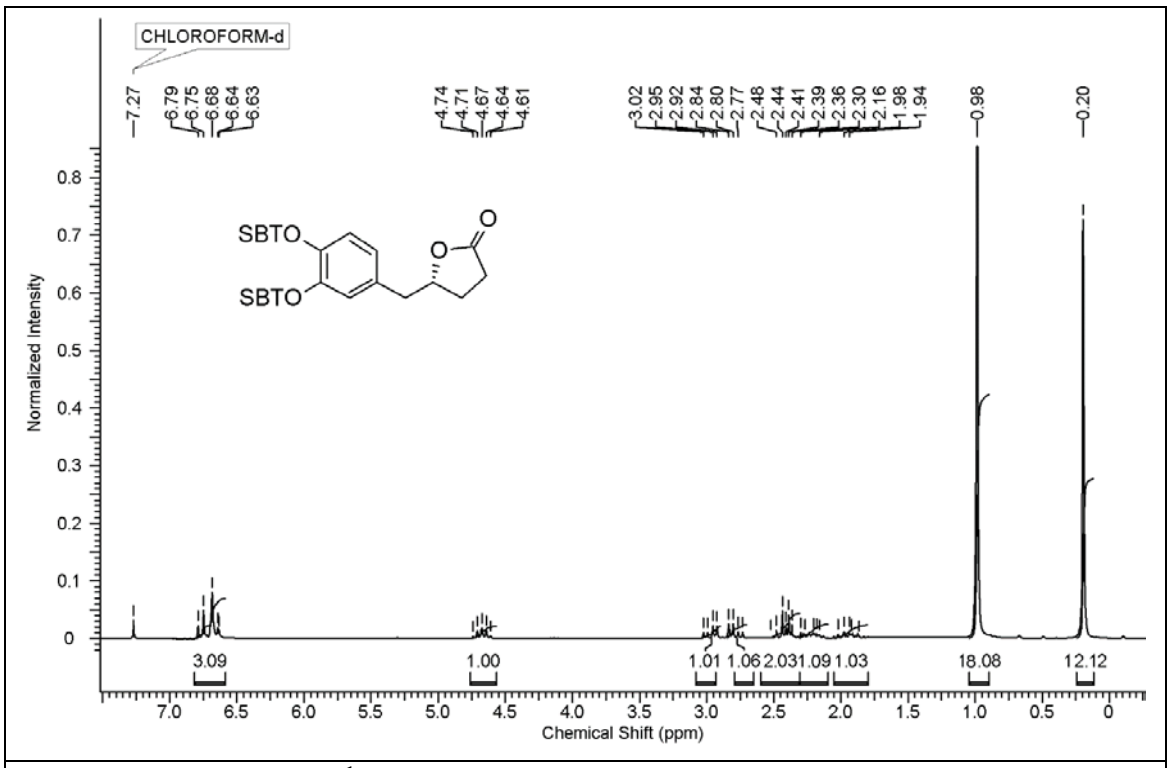
^{13}C-NMR of compound 65 in $CDCl_3$



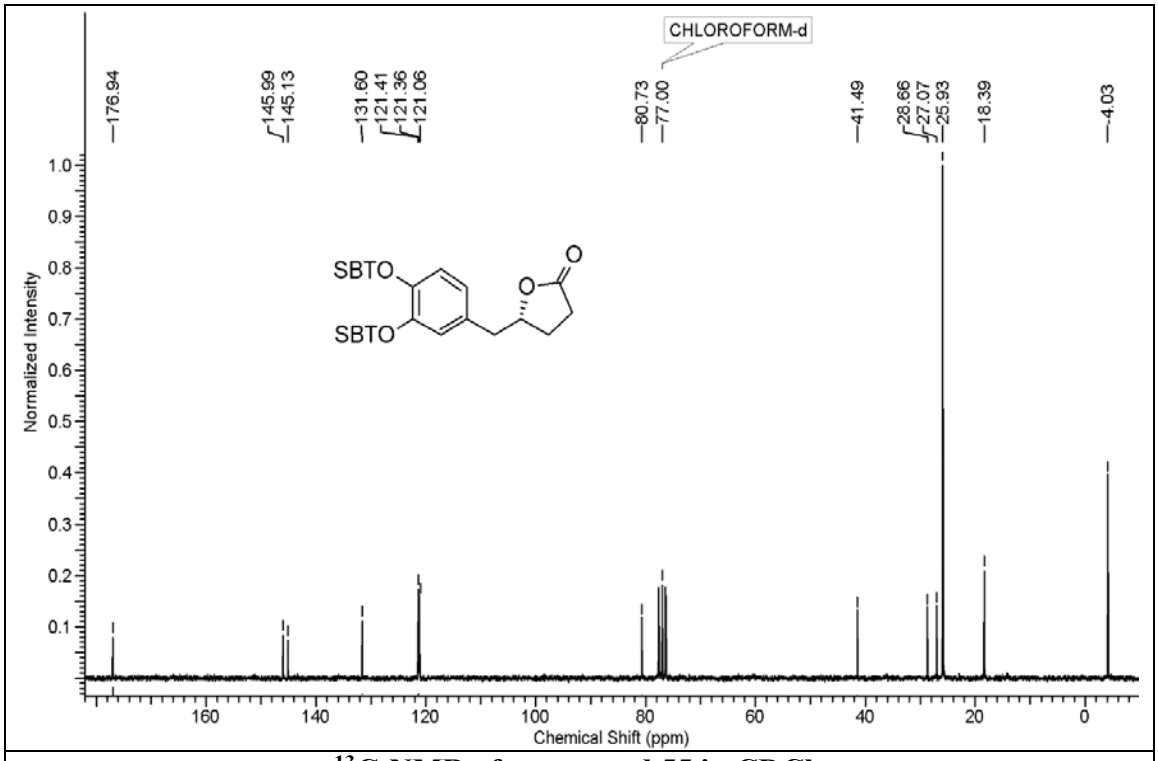
^{1}H-NMR of compound 66 in $CDCl_3$



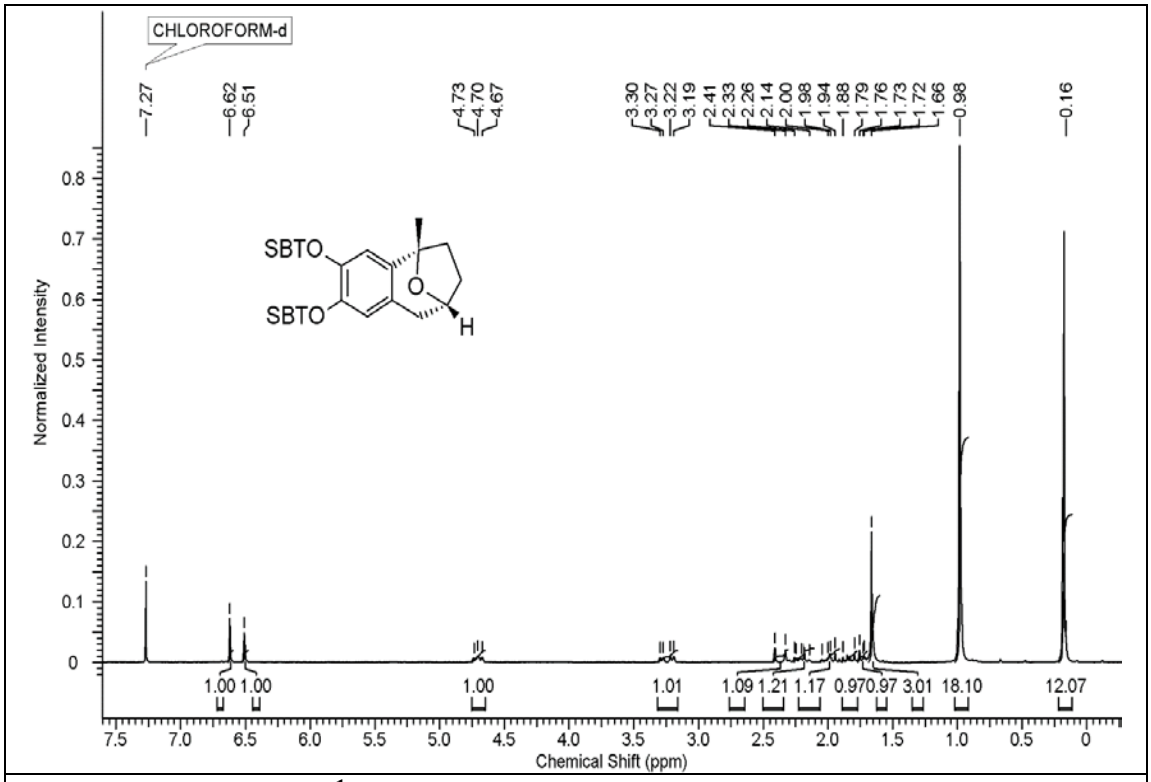
^{13}C-NMR of compound 66 in $CDCl_3$



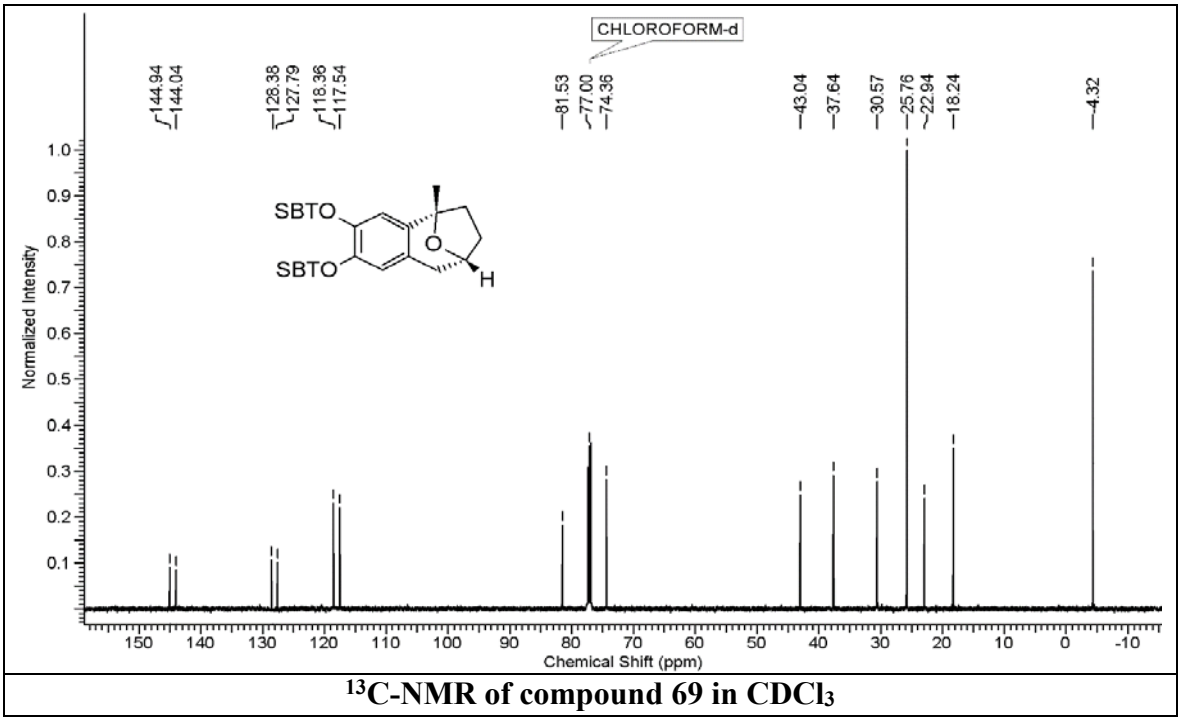
^{1}H-NMR of compound 55 in $CDCl_3$



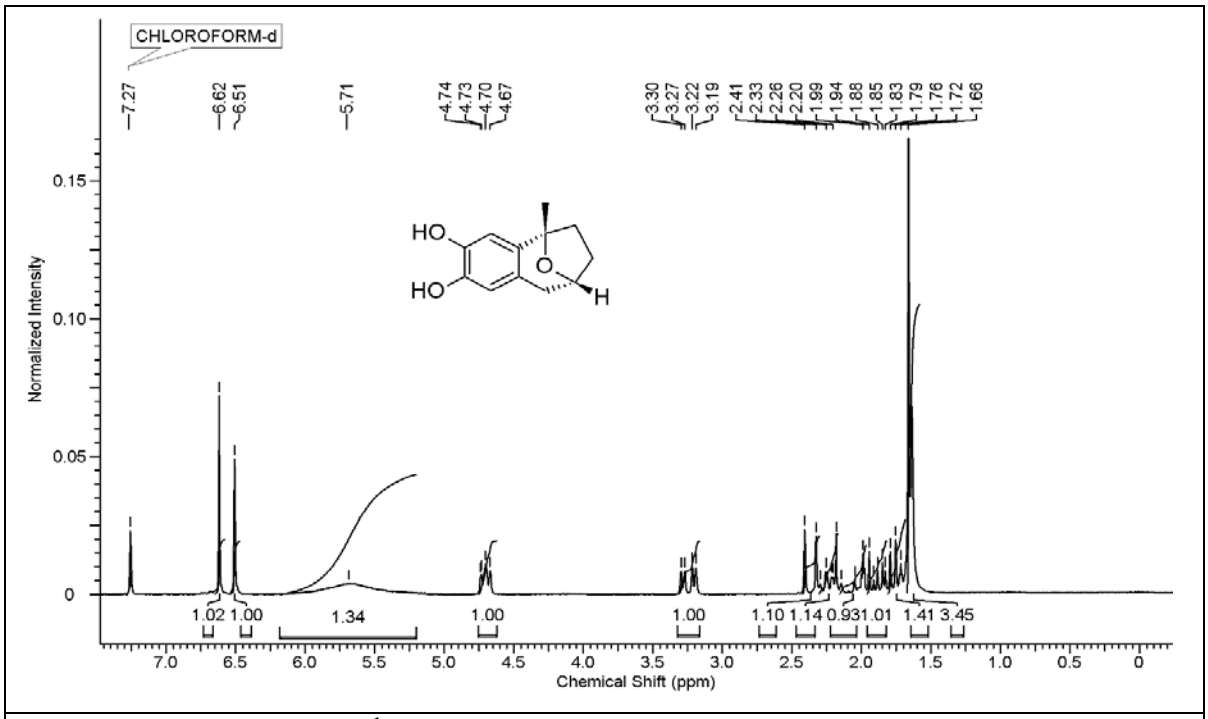
^{13}C-NMR of compound 55 in $CDCl_3$



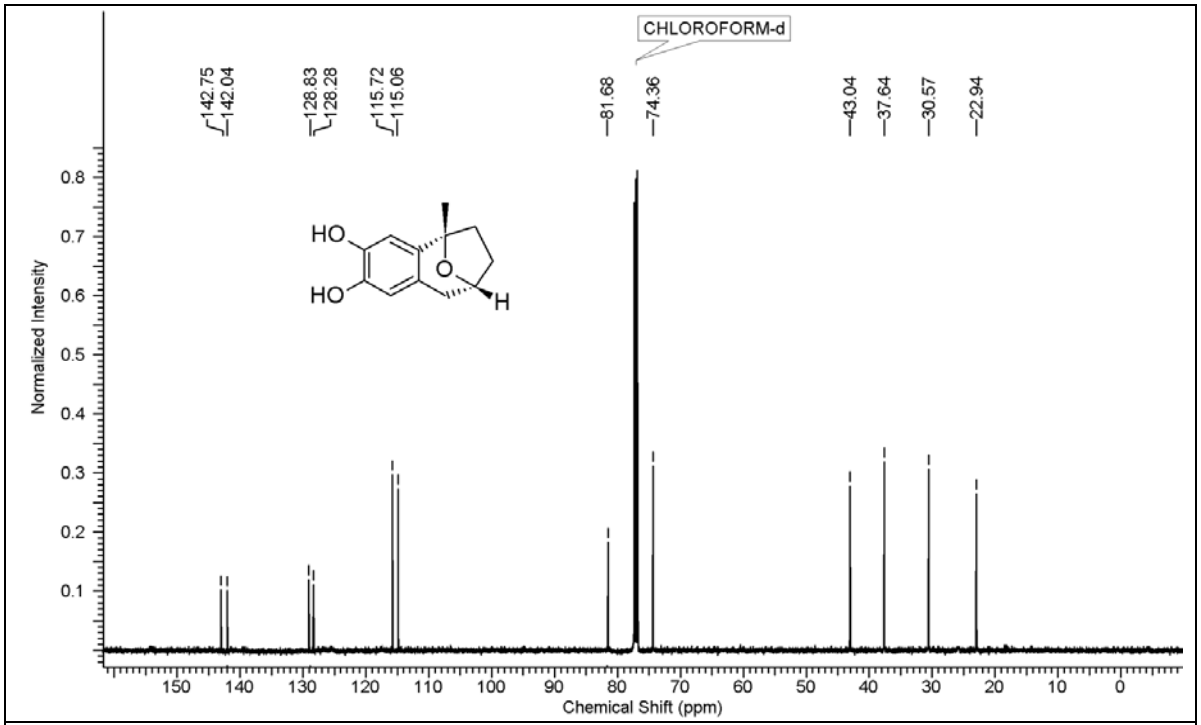
^{1}H-NMR of compound 69 in $CDCl_3$



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



^{1}H-NMR of compound 2 in $CDCl_3$



^{13}C-NMR of compound 2 in $CDCl_3$

4.2.8. References:

1. Han, L.; Huang, X.; Sattler, I.; Moellmann, U.; Fu, H.; Lin, W.; Grabley, S. *Planta Med,* **2005**, *71,* 160.
2. Ramana, C. V.; Salian, S. R.; Gonnade, R. G. *Eur. J. Org. Chem*. **2007**, 5483.
3. Solorio, D. M.; Jennings, M. P. *J. Org. Chem*. **2007**, *72*, 6621.
4. Wu, J.-Z.; Zhen, Z. B.; Zhang, Y. H.; Wu, Y. K. *Acta Chim. Sinica* **2008,** *66*, 2138.
5. Fananás, F. J.; Fernández, A.; Cevic, D.; Rodríguez, F. *J. Org. Chem*. **2009**, *74*, 932.
6. Hu, B.; Xing, S.; Ren, J.; Wang, Z. *Tetrahedron* **2010**, *66*, 5671.
7. Sarkar, D.; Venkateswaran, R. V. *Tetrahedron Lett.* **2011**, *52*, 3232.
8. (a) Fan, J-F.; Wu, Y.; Wu, Y-L. *J. Chem. Soc. Perkin Trans. 1* **1999**, 1189; (b) Marson, C. M.; Campbell, J.; Hursthouse, M. B.; Malik, K. M. A. *Angew. Chem. Int. Ed.* **1998**, *37*, 1122.
9. (a) Hall, D.G.; Manku, S.; Wang, F. *J. Comb. Chem.* **2001**, *3*, 125; (b) Abel, U.; Koch, C.; Speitling, M.; Hansske, F.G. *Curr. Opin. Chem. Biol.* **2002**, *6*, 45; (c) Arya, P.; Joseph, R.; Chou, D. T. H. *Chem. Biol.* **2002**, *9*, 145.
10. (a) Maier, M. S.; Marimon, D. I. G.; Stortz, C. A.; Adler, M. T. *J. Nat. Prod.* **1999**, *62*, 1565; (b) Lee, S.-C.; Brown, G. D. *J. Nat. Prod.* **1998**, *61*, 29; (c) Chen, S.-Y.; Joullie´, M. M. *J. Org. Chem.* **1984**, *49*, 2168; (d) Brown, H. C.; Kulkarni, S. V.; Racherla, U. S. *J. Org. Chem.* **1994**, *59*, 365, and references therein.; (e) Schmitz, W. D.; Messerschmidt, N. B.; Romo, D. *J. Org. Chem.* **1998**, *63*, 2058.
11. (a) Smith, A. B.; Rano, T. A.; Chida, N.; Sulikowaski, G. A.; Wood, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 8008; (b) Mori, K. *Tetrahedron* **1975**, *31*, 3011; (c) Kiyoshi, T.; Tsuneo, I.; Koga, K. *J. Chem. Soc. Chem. Commun.* **1979**, 652; (d) Blackwell, C. M.; Davidson, A. H.; Lewis, C. N.; Todd, R. S.; Roffey, J. A. *J. Org. Chem.* **1992**, *57*, 5596.
12. (a) Show, K.; Gupta, P.; Kumar, P. *Tetrahedron Asymmetry* **2011**, *22,* 1212; (b) Jha, V.; Kondekar, N. B.; Kumar, P. *Org. Lett.* **2010**, *12*, 2762; (c) Dubey, A.; Puranik, V. G.; Kumar, P. *Org. Bio.Chem.* **2010**, *8*, 5074; (d) Tripathi, D; Pandey S. K.; Kumar, P. *Tetrahedron* **2009**, *65*, 2226; (e) Dubey, A.; Kumar, P *Tetrahedron Lett.* **2009**, *50*, 3425; (f) Pandey, S. K.; Pandey, M.; Kumar, P. *Tetrahedron Lett*. **2008**, *49*, 2397; (g) Gupta, P.; Kumar, P. *Eur. J. Org. Chem*. **2008**, 1195; (h) Tripathi, D.; Kumar, P. *Tetrahedron Lett.* **2008**, *49*, 7012. (i) Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 6149; (j)

Gupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett*. **2004**, *45*, 849; (k) Naidu, S. V.; Gupta, P.; Kumar, P. *Tetrahedron Lett.* **2005**, *46*, 2129.

13. HPLC: Chiracel OD-H column (2-Propanol: petroleum ether = 5:95, flow rate 1.0 mL/min, λ = 214 nm). Retention time (min): 12.16 (minor) and 16.69 (major). The racemic standard was prepared from racemic *γ*-hydroxy ester, *ee* 98%.
14. Description of the coupling of bridge-head protons can be found in *Stereochemistry*: *Fundamentals and Methods* Kagan, H. B. Ed. George Thieme Publishers, Stuttgart, **1977**, *vol. 1*.
15. Ei-Batta, A.; Jiang, C.; Zhao, W.; Anness, R.; Cooksy, A. L.; Bergdahl, M. *J. Org. Chem.* **2007**, *72*, 5244.
16. HPLC: Chiracel OD-H column (2-Propanol: petroleum ether = 5:95, flow rate 1.0 mL/min, λ = 214 nm). Retention time (min): 11.26 (minor) and 15.39 (major). The racemic standard was prepared from racemic *γ*-hydroxy ester, *ee* 96%.

Chapter-5

Chemoselective deprotection of N-Allylic amines using DDQ

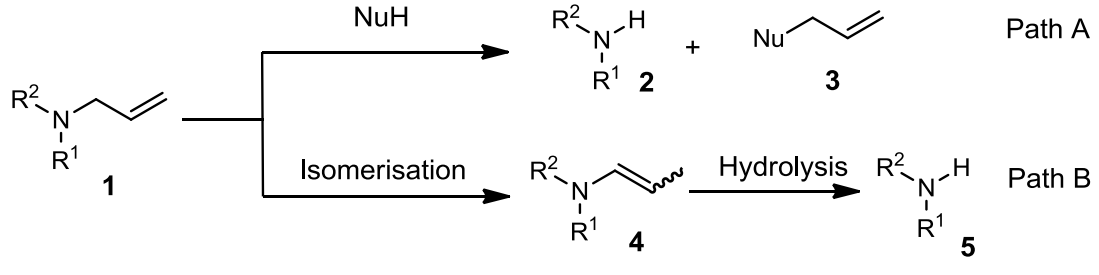
Chemoselective Deprotection of *N*-Allylic Amines using DDQ

5.1. Introduction

Protecting groups often play a crucial role in many complex synthetic strategies. The proper selection of efficient protecting groups, as well as the search of selective deprotection methodologies, still remains crucial issues in modern organic chemistry.[1] These processes are particularly relevant in the chemistry of amines since they generally constitute unavoidable steps in a great variety of organic transformations including the synthesis of natural products and other polyfunctional complex molecules.[1] In particular, among the plethora of alternatives, the use of allyl moieties for the protection of amines is becoming more and more popular as methods of amines into carbamates or to a lesser extent into amides. In contrast to classical protecting groups such as Boc (*tert*-butoxycarbonyl), FMOC (9-fluorenylmethyl carbamate), tosylamide *etc*., allyl groups remain inert under both acidic and basic conditions. But as reported later on, they can be cleaved upon treatment with strong bases.[2]

5.2. Review of Literature

The *N*-deallylation methodologies can be roughly classified into two groups according to their mechanistic features.[3] The methods belonging to the first group procedures are based on nucleophilic substitution reactions, where the amine unit **2** becomes a leaving group (Scheme 1, path A). The second group procedures are based on the isomerization of the allylamine into an enamine **4**, which is subsequently cleaved upon acidic hydrolysis (Scheme 1, path B).

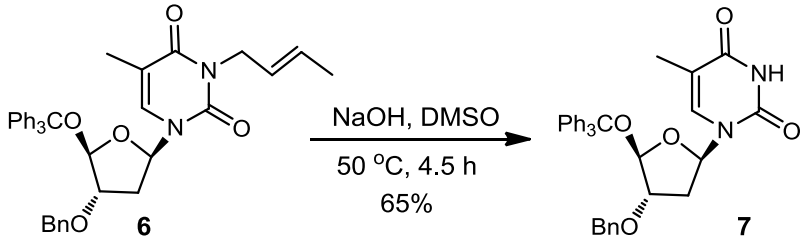


Scheme 1: Strategies used for deprotection of *N*-allylamines

Early reports demonstrated that allylamines can be isomerized into enamines upon treatment with strong bases. However, basic conditions are rather tough and generally cannot be used under catalytic conditions. The use of a stoichiometric amount of a strong base is incompatible with base-sensitive functional groups.[4]Alternatively, the migration of the double bond can be performed under milder conditions involving transition metals catalysis[5] (essentially Pd and Rh) or free-radical processes.[6] Among the latter, new procedures involving Grubbs-type catalysts also have emerged.[7]A few of them are reviewed.

Caperelli *et al.* (1997)[8]

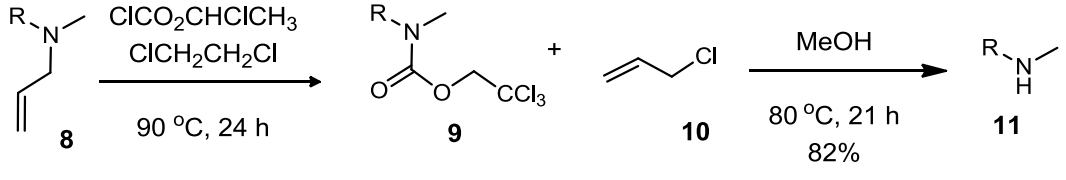
Caperelli *et al.* have used NaOH at 50 °C in DMSO to deprotect the *N*-crotylthymine moiety in a carbocyclic analog of 2-deoxyribonucleoside **6,** where migration of the double bond occurs concomitantly to the hydrolysis of resulting enamines. The *N*-propargyl group can also be removed by refluxing in 1 N NaOH (Scheme 2).[8]



Scheme 2

Charles *et al.* (1983)[9]

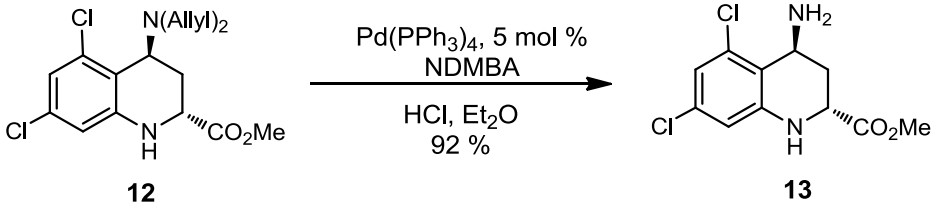
Charles *et al.* performed deallylation upon treatment with chloroformate providing a two-step procedure to release secondary amines. The first step leads to a carbamate **9**, which is cleaved upon heating at reflux in methanol (Scheme 3).[9] Vinyl and trichloroethyl chloroformates are among the best reagents for this purpose since their oxygenated moieties are very good leaving groups. It should be noted that *N*-debenzylation is faster under these experimental conditions than *N*-deallylation.



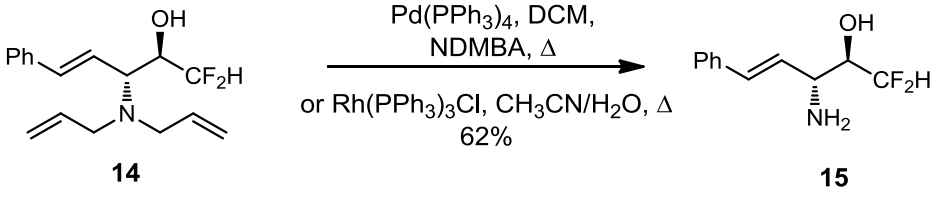
Scheme 3

Guibé *et al.* (1993)[10]

Guibé *et al.* has developed a very efficient method for the deprotection of monoallylamines and diallylamines based on a Pd(0) catalyst and *N,N*-dimethylbarbituric acid (NDMBA) (Scheme 4).[10] The number of recorded examples suggests that this is probably the most efficient and widely employed procedure. It is also possible to cleave the *N*-allyl group selectively in the presence of an α-branched allylic chain **14**. (Scheme 5)[11]



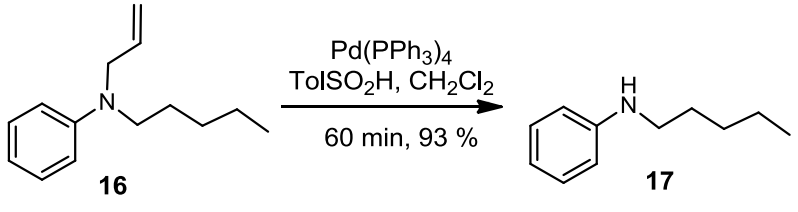
Scheme 4



Scheme 5

Nagakura *et al.* (1997)[12]

Nagakura *et al.* modified Pd(0) protocol by sulfinic acids or their salts have been used in the presence of a catalytic amount of [$Pd(PPh_3)_4$] (Scheme 6). This procedure is efficient to cleave both C–N and C–O allylic bonds.

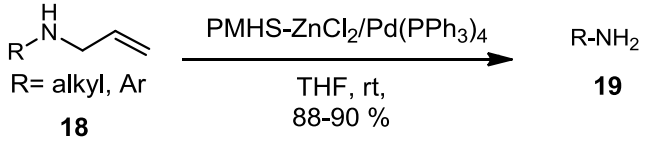


Scheme 6

The procedure involving [$Pd(PPh_3)_4$] in dichloromethane or in a THF/MeOH mixture in the presence of $ArSO_2Na$ allows the cleavage of allyl, methallyl, crotyl, and cinnamyl ethers, and the cleavage of allyloxycarbonyl (alloc) derivatives and allyl esters as well.

Chandrasekhar *et al.* (2001)[13]

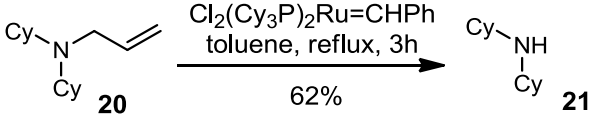
Chandrasekhar *et al.* demonstrated that association of [$Pd(PPh_3)_4$] with poly(methylhydrosiloxane)(PMHS) in the presence of $ZnCl_2$ has cleaved allyl ethers, allyl esters, and allylamines. *N*-Benzyl, *N*-Boc, and *N*-Cbz derivatives were found to be stable under these reaction conditions (Scheme 7).



Scheme 7

Alcaide *et al.* (2001)[7]

Alcaide *et al*. have reported the catalytic deprotection of allylic amines by using Grubbs' carbene. The deallylation mechanism involves ruthenium-catalyzed isomerization followed by hydrolysis of the enamine intermediate. The treatment of tertiary allylamine in the presence of 5 mol % $Cl_2(Cy_3P)_2RudCHPh$ in toluene at 110 °C for 3 h gave deallylated products (Scheme 8). Tertiary allylamines bearing a variety of substituents were smoothly deallylated by Grubbs' carbene to give the corresponding *N*-deprotected amines.

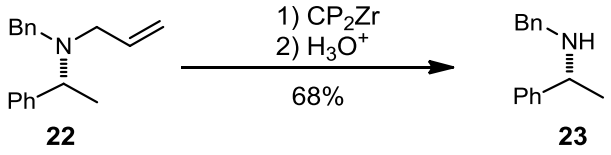


Scheme 8

Hauzawa *et al.* (1993)[14]

Hauzawa *et al*. achieved the cleavage of *N*-Allylamines by treatment with one equivalent of zirconocene at room temperature (Scheme 9). Both allyl ethers and allylamines are cleaved

under these peculiar conditions, but since the rate constants for the two processes are quite different, it is possible to cleave the C– O bond selectively without breaking the C–N bond.

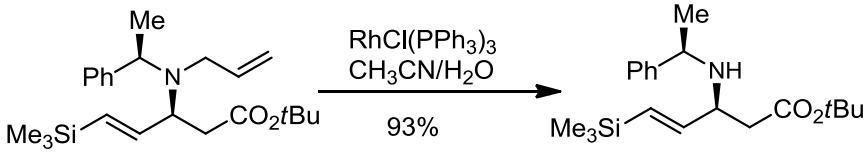


22 **23**

Scheme 9

Davies *et al.* (2003)[15]

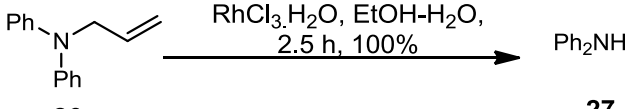
Davies *et al.* have reported *N*-deallylation using Wilkinson's catalyst in aqueous acetonitrile. This method is probably among the most frequently used because of its ability to differentiate between different protecting groups of amines. It is possible to deprotect the *N*-allyl group in the presence of an α-branched allylic chain and in the presence of *N*-benzyl nitrogen protecting groups (Scheme 10).



24 **25**

Scheme 10

Marquet, *et al*.[16] showed that in some cases, $RhCl_3 \cdot H_2O$, used under the same conditions as Wilkinson's catalyst, leads to very good results, and this procedure has been claimed to be superior because of its better reproducibility (Scheme 11).

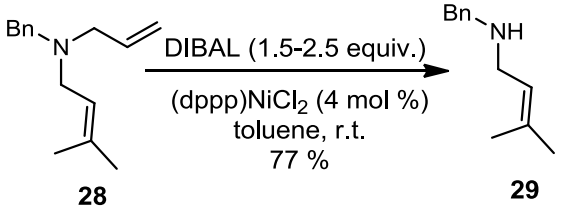


26 **27**

Scheme 11

Ogasawara *et al.* (1998)[17]

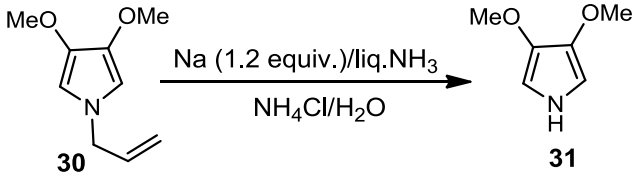
Ogasawara *et al*. demonstrated the deprotection of a series of allylic tertiary amines, including aliphatic, benzylic, aromatic, and heteroaromatic compounds which is catalyzed by dichlorobis(diphenylphosphanyl) propane nickel [$NiCl_2$(dppp)] in the presence of DIBAL, at 0 °C in toluene (Scheme 12). It is worth noting that the reaction is chemoselective. The allyl group is removed selectively and the prenyl group is recovered unchanged.



Scheme 12

Meyer *et al.* (1999)[6d]

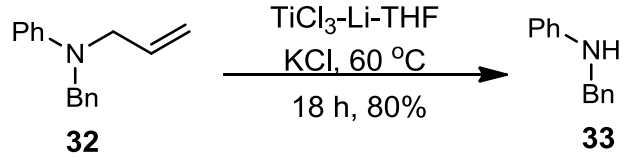
Meyer *et al.* employed the Birch reduction conditions to *N*-allylpyrrole derivatives for *N*-allyl deprotection (Scheme 13). It should be noted that *O*-allyl, *O*-benzyl, and *N*-benzyl derivatives are all cleaved under these conditions.



Scheme 13

Nayak *et al.* (2001)[6b]

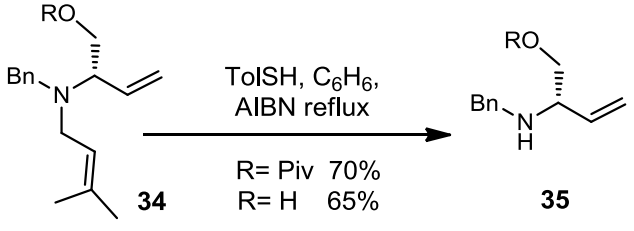
Nayak *et al.* applied low-valent titanium (LVT) to amines to cleave C–N bonds by electron transfer. This methodology, which allows the allyl chain cleaved faster than the benzyl group under such conditions, although yields are moderate. Substantial improvement of the yield can be achieved by adding an inorganic salt such as KCl to the reaction medium (Scheme 14). The cleavage of allyl- and benzylamines is slower than the cleavage of the corresponding ethers.



Scheme 14

Bertrand *et al.* (2002)[6e]

Bertrand *et al*. reported a 1,3-hydrogen shift leading to an enamine by the thiyl radical. Subsequent hydrolytic treatment allows primary or secondary amines to be released. The reaction can be performed in the presence of either a stoichiometric or a catalytic amount of thiol. These conditions apply to allyl, crotyl, prenyl, and cinnamyl derivatives, although prenyl groups are cleaved slightly faster. The prenyl group can be removed selectively in the presence of α-branched allylic groups (Scheme 15).



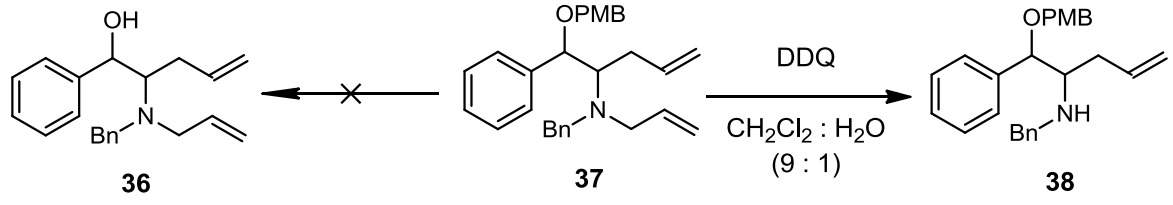
Scheme 15

5.3. Present work

Objective

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[18] is a powerful oxidizing agent and has proved to be a versatile reagent for various synthetic organic transformations. Apart from its well-known applications as a dehydrogenating and oxidizing agent, in recent years it has found number of other applications including C–C, C–O and C–N bond-formation reactions and deprotection of various functional groups including cleavage of linker molecules from its solid support.[19]

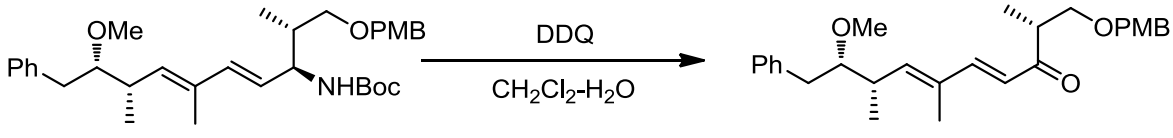
During one of our on-going project directed toward the asymmetric synthesis of natural products and derivatives of biological interest[20], we have observed a clean cleavage of *N*-allyl amine in compound **37** instead of expected PMB ether deprotection[21] with DDQ in CH_2Cl_2-H_2O mixture (Scheme 16).



36 **37** **38**

Scheme 16

Armstrong *et al.* has reported a similar incident during their total synthesis of Motuporin (Nodularin-V). [22] They observed that allylic NHBoc in **39** was converted to a ketone **40** during attempted PMB cleavage (Scheme 17).



39 **40**

Scheme 17

A careful literature survey has revealed that DDQ has previously never been utilised effectively for *N*-deallylation of amines.

5.4. Results and Discussion

The choice of protecting groups is one of the decisive factors in the successful realization of a complex, demanding synthetic project. The protecting groups used influence the length and efficiency of the synthesis and are often responsible for its success or failure.[23] The allyl moiety is a protecting group that permits orthogonal protection strategies with a wide range of protecting groups. It is readily removable and its compatibility with a range of other functional groups, the allyl protecting group has become established in protecting group

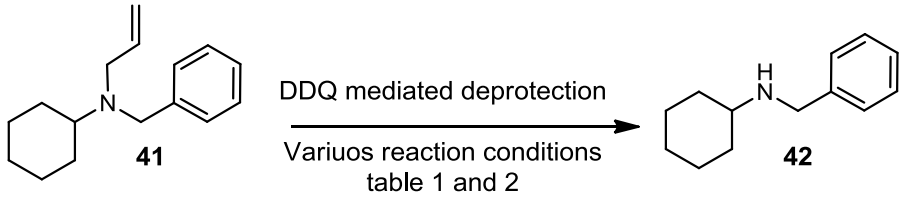
chemistry and is finding increasing application in the synthesis of complex natural products.[23]

It is undeniable that transition-metal-catalyzed methods[5] are the most widely admitted methods for allyl group deprotection. But selectivity can still be a problem, since *O*-allyl derivatives are cleaved faster than *N*-allyl derivatives in most cases. Reductive metals are not selective either.[6] An important drawback of the π-allyl–palladium methodology is the requirement of stoichiometric amounts of a nucleophilic compound, which acts as the allyl group scavenger. Selectivity is also a problem with chloroformate-mediated processes[9], which are capable of cleaving different types of N–C bonds. New procedures involving Grubbs-type catalysts are also emerged in recent years.[7] But still selectivity remains the problem with these methods. Therefore we were interested in the development of an alternative *N*-deallylation method that can smoothly provide free amines.

The high oxidation potential (E_0) of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) has resulted in the extensive use of this compound as a dehydrogenating agent in organic synthesis.[24] Even though *O*-allyl ethers are oxidatively cleaved in the presence of DDQ[25], this reaction has not been developed further into a method of synthetic interest for the cleavage of *N*-allylic bonds.[26] The examples of the quinone mediated oxidation of amines are limited. In general, primary and secondary aliphatic amines undergo nucleophilic displacement reactions with halogen-containing quinone oxidants, whereas aliphatic tertiary amines are known to react by way of a charge transfer complex to give enamines.[27] Our studies shows that DDQ mediated *N*-deallylation of amine could be a promising methodology in organic synthesis. The mild cleavage condition broadens the synthetic applications of *N*-allyl amines and the high selectivity observed in the presence of other functionalities extends its utility as an orthogonal protecting group.

Our studies began with the reaction of a series of allyl substrates on aliphatic, alicyclic and benzylic amines. From the literature, we learned that *O*-allylic ethers are easily deprotected at room temperature by 1.2 equivalent of 2,3-dichloro-5,6-dicyanoquinone (DDQ) in a solvent mixture of CH_2Cl_2-H_2O (9:1).[25] This solvent system has an additional merit, that is, weakly acidic $DDQH_2$ (2,3-dichloro-5,6-dicyanohydroquinone) precipitated from the

solution as the reaction proceeded because $DDQH_2$ is almost insoluble in both dichloromethane and water, and the reaction medium was consequently kept almost neutral all through the reaction.[28] This is sometimes very important in the case of substrates bearing acid-sensitive functional and protecting groups.



Scheme 18

We performed the reactions choosing compound **41** as a model substrate (Scheme 18). The DDQ which recrystallized from toluene-hexane solvent mixture was used in all oxidative deallylation reactions. The reaction conditions we initially identified were mild (1.2 equiv DDQ, non-dried solvent, open to air and room temperature). DDQ was added to a solution of **41** in dichloromethane-water (9: 1) (table 1, entry 1). and the resulting dark red solution stirred at room temperature overnight, during which time a pale yellow hydroquinone derivative was precipitated. The reaction proceeded without difficulty.

Entry	Solvent system	DDQ (Equivalent)	Reaction time (hrs.)	Deprotection of 41 in %
1	CH_2Cl_2-H_2O (9:1)	1.2	12	92
2	CH_2Cl_2-H_2O (97:3)	1.2	22	70
3	CH_2Cl_2	1.2	48	trace
4	Hexane-H_2O (9:1)	1.2	24	0
5	Dioxane-H_2O (9:1)	1.2	10	Complex mixture
6	THF-H_2O (9:1)	1.2	12	Complex mixture
7	Toluene-H_2O (9:1)	1.2	36	45
8	$CHCl_3$-H_2O (9:1)	1.2	24	60
9	EtOAc-H_2O (9:1)	1.2	12	Complex mixture
10	MeOH-H_2O (9:1)	1.2	6	Complex mixture
11	CCl_4-H_2O (9:1)	1.2	24	20
12	MeCN-H_2O (9:1)	1.2	14	85

Table 1: Oxidative cleavage of compound **41** with DDQ in various solvents at room temperature

The IR spectrum of **41** exhibits a characteristic sharp band of medium intensity at 1641 cm^{-1} (C=C stretching vibration). This band is useful for monitoring the deprotection reaction of *N*-allyl amine. It was found that correct work-up of the reactions was very important. The optimised procedure involved extraction with several portions of CH_2Cl_2 and washing with saturated sodium bicarbonate solution, followed by loading the residual solution (after removal of the volatiles) directly onto a short basic alumina flash column, eluting with hexane–CH_2Cl_2 afforded a nearly quantitative yield of *N*-deallylated secondary amines **42** (table 1, entry 1).

This reaction is only achieved in the presence of water. Decrease of the water ratio somewhat lowered the yields and increased the reaction time (table 1, entry 2). In the absence of water, most of compound **41** was recovered (table 1, entry 3). The reaction was studied in a variety of solvents and results are summarized in table **1.** No desired deallylation product was observed when the reaction was carried out in hexane-water (table 1, entry 4). The reaction could proceed in THF, toluene, $CHCl_3$, MeOH, CCl_4, MeCN, EtOAc and dioxane (table 1, entries 5–12). However, considerable amounts of undesired products were formed in THF, MeOH, EtOAc and dioxane (table 1, entries 5, 6, 9 and 10). The rate of the reaction became slower when $CHCl_3$, CCl_4 or toluene were used as the solvents (table 1, entries 7, 8 and 11). Interestingly, the speed and yield of the reaction in MeCN were comparable with those in CH_2Cl_2 (table 1, entry 12). Based on the above investigations; CH_2Cl_2 was preferred as the reaction media from the practical point of view.

A stoichiometric amount of DDQ would be sufficient for this oxidation, but the reactions progressed slowly, probably because of competitive aqueous decomposition of DDQ.[19b] To circumvent this problem, the DDQ was added in small portions in every twenty minutes (3–4 portions) and this helped us to achieve high yields. Variation in the number of equivalents of DDQ was then assayed. Usually 20% excess of DDQ brought about a large reduction in reaction time (table 2, entries 1 and 2). Starting material was reclaimed when less than 1 equivalent of DDQ was used (table 2, entry 3). When the concentration of the reaction mixture was examined between 0.4 and 0.02 M, the best combination of rate and ease of handling was found at 0.1 M of substrate. Attempt to conduct the reaction at lower

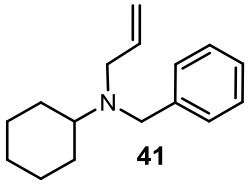
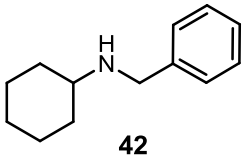
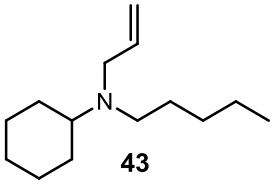
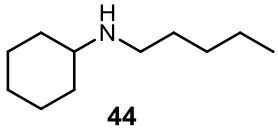
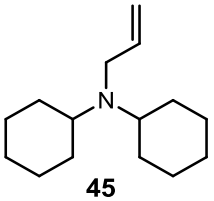
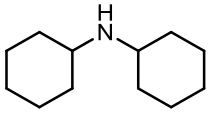
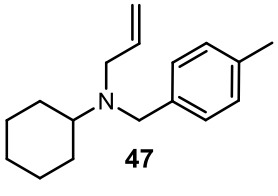
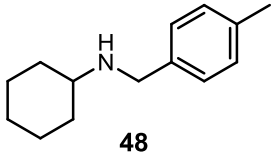
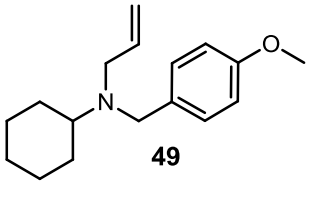
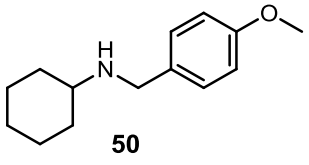
temperature than room temperature slow down the reaction considerably (table 2, entry 4). A further increase of temperature above room temperature did a significantly faster conversion, but the yield of deallylated amine was just a little lower (table 2, entry 5).

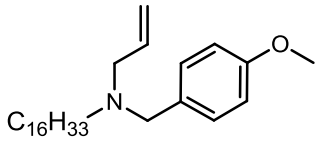
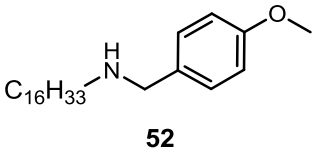
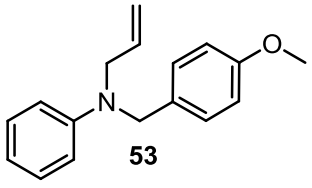
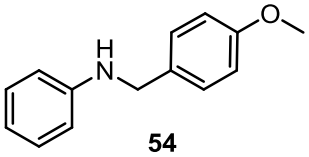
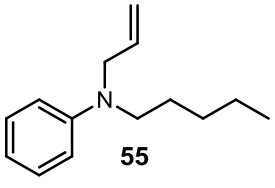
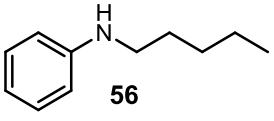
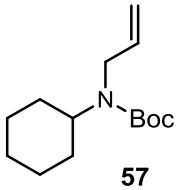
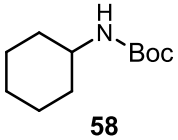
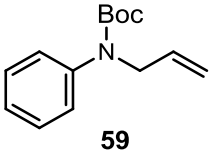
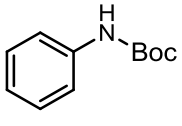
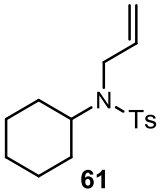
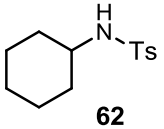
Entry	Reaction conditions	Reaction time (hrs)	Deprotection of 41 in %
1	1.2 equiv. DDQ, CH_2Cl_2-H_2O (9:1) r.t.	12	92
2	1 equiv. DDQ, CH_2Cl_2-H_2O (9:1) r.t.	18	80
3	0.8 equiv. DDQ, CH_2Cl_2-H_2O (9:1) r.t.	20	45
4	1.2 equiv. DDQ, CH_2Cl_2-H_2O (9:1) 0 ^oC	24	35
5	1.2 equiv. DDQ, MeCN-H_2O (9:1) 70 ^oC	6	78

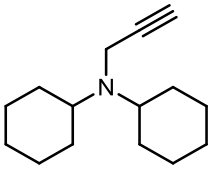
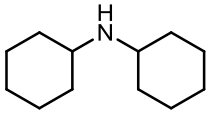
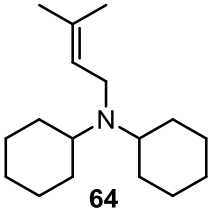
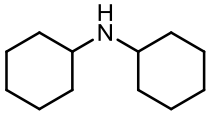
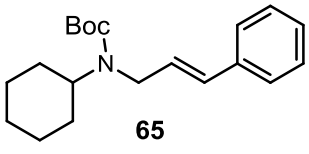
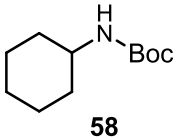
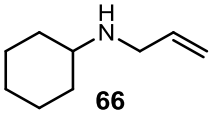
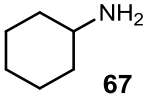
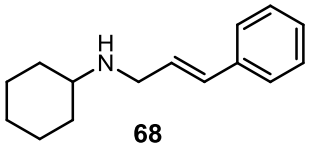
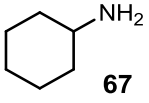
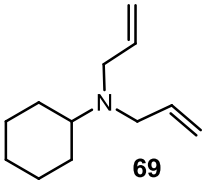
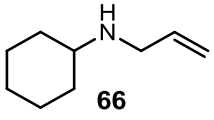
Table 2: Oxidative cleavage of compound **41** with DDQ in various reaction conditions

With the optimized reaction conditions established, various substrates were subjected to this deallylation reaction (Table 3). The reaction proceeded without any difficulty. Regardless of the aliphatic, alicyclic, or benzylic allyl amine substrates used to give the corresponding secondary amines in satisfactory yields with specific removal of the *N*-allyl group. During this study, *N*-benzyl (NBn), *N*-*t*-butyl carbamate (NBoc) and *N*-Tosylamide (NTs) groups were found to be stable to the reaction conditions (table 3, entries 1, 4, 9, 10, 11 and 14). Indeed, some selective deprotection of *N*-allyl group in the presence of *N*-PMB group could be achieved under certain conditions (table 3, entries 5, 6 and 7). Deallylation of *N*-Tosyl and *N*-Boc protected amine systems (table 3, entries 9, 10 and 11) required longer reaction time and higher equivalents of oxidant DDQ (1.5-2.5 equiv.). It has been observed that *N*-cinnamyl and *N*-prenyl systems (table 3, entries 13 and 14) deprotected much faster than *N*-allyl substrates. But cleavage of *N*- prpargyl amine **63** (table 3, entry 12) resulted a complex reaction mixture.

Table 3: Oxidative cleavage of various *N*-allyl amines with DDQ in CH_2Cl_2-H_2O (9:1) at room temperature

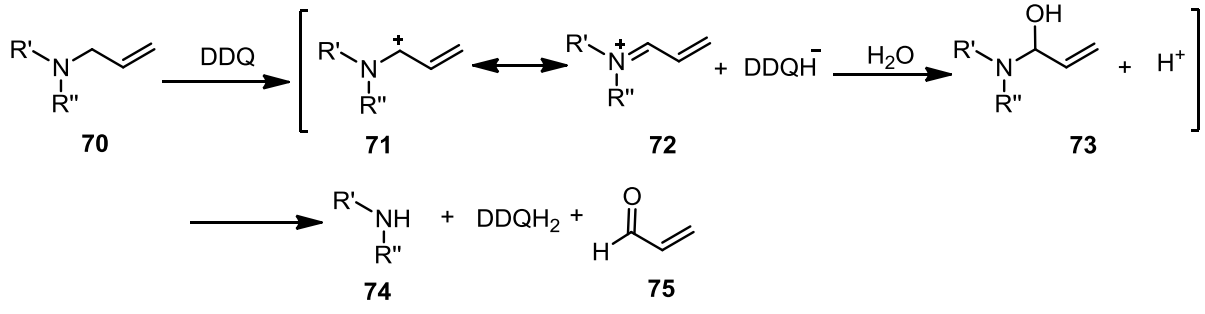
Entry	Substrate	Product	Reaction time (hrs.)	% Yield
1	 **41**	 **42**	12	92
2	 **43**	 **44**	18	85
3	 **45**	 **46**	18	90
4	 **47**	 **48**	12	80
5	 **49**	 **50**	6	55

Entry	Substrate	Product	Reaction time (hrs.)	% Yield
6	 **51**	 **52**	7	50
7	 **53**	 **54**	3	35
8	 **55**	 **56**	8	75
9	 **57**	 **58**	18	80
10	 **59**	 **60**	14	74
11	 **61**	 **62**	24	60

Entry	Substrate	Product	Reaction time (hrs.)	% Yield
12	 **63**	 **46**	14	Complex mixture
13	 **64**	 **46**	4	95
14	 **65**	 **58**	4	85
15	 **66**	 **67**	24	20
16	 **68**	 **67**	16	65
17	 **69**	 **66**	48	A mixture of **66:67**

Extrapolation of the deprotection of tertiary allyl amines to secondary allyl amines is not obvious. Even through secondary amine *N*-cinnamylcyclohexanamine **68** gave cyclohexanamine **67** in 65 % yields (table 3, entry 16), conversion of *N*-allylcyclohexanamine **66** to cyclohexanamine **67** under the same reaction condition was very slow (table 3, entry 15). When *N,N*-diallylcyclohexanamine **69** was treated under the same procedure (table 3, entry 17), we got a mixture of compounds **66**:**67** even after 2 days, suggesting that secondary *N*-allylamines would require stronger reaction conditions to be cleaved.

Mechanism of the reaction is not very clear to us. Mechanistically, the oxidation/deprotection *N*-allyl amine with DDQ must follow the same pathway as that involved in the cleavage of prenyl ethers, cinnamyl ethers or OPMB, which has been well studied.[29] A possible mechanism is shown in Scheme 19.



Scheme 19

The reaction must proceed by hydride abstraction from the activated methylene of **70** by DDQ followed by trapping the iminium ion **72** by water giving a hemiaminal **73** which decomposes to give a 2^{o} amine, $DDQH_2$ and acrylaldehyde **75**. A heteroatom such as nitrogen, oxygen, or sulfur atom located at the α-position activates the adjacent allylic sp^3 C-H bond and further stabilizes the *in situ* formed intermediate.

The oxidative cation formation appears to proceed (Scheme 19) through a sequence of radical cation formation followed by hydrogen atom abstraction. DDQ is a well-known electron acceptor and forms charge transfer (CT) complexes with a variety of donors.[30] When a solution of *N*-allyl amine was combined with DDQ, we usually observed a immediate colour changes in reaction mixture that is likely a charge-transfer complex formation.

Even through DDQ is a mild and efficient oxidant, it has some disadvantage like removal of its by-product (2,3-dichloro-5,6-dicyanohydroquinone-$DDQH_2$) is sometimes cumbersome. In order to overcome these difficulties, Sharma *et al.* have reported a method for regeneration of DDQ using $Mn(OAc)_3$ as reoxidant.[31]. We tested this method during the cleavage of compound **41,** but failed to see any initial promising result.

The preparation of *tert*-*N*-allyl amines derivatives used in this study deserves some comment. As previously reported in the literature[32], the direct allylation of the amino group with allyl bromide in the presence of a base (diisopropylamine in toluene, NaH in THF or K_2CO_3 in MeCN) afforded most of *tert*-*N*-allyl amines.

5.5. Conclusion

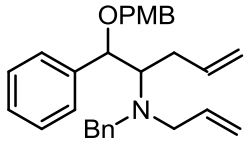
The use of DDQ in dichloromethane–water provides a mild and efficient one-step deallylation of tertiary *N*-ally amines. The new method is well suited to selective deprotection of a wide variety of orthogonally protected tertiary amine derivatives, and its application permits novel manipulation of more complex allyl protecting groups. Application of the present method to secondary amines and use of catalytic amount of DDQ in reactions are currently underway in our group.

5.6. Experimental Section

General Experimental Procedure for the Oxidative Cleavage of *N*-allyl amine:

To a stirred solution of the *N*-allyl amine (1 mmol) dissolved in 9 mL of CH_2Cl_2 and 1 mL of water, DDQ (1.2 equiv.) were added intermittently in 3-4 portions. Reaction progress was monitored by TLC. Upon consumption of the *N*-allyl amine, 2,3-dichloro-5,6-dicyanohydroquinone($DDQH_2$) was filtered. A saturated $NaHCO_3$ solution was added to the filtrate and the aqueous phase was extracted twice with CH_2Cl_2. Drying over Na_2SO_4, evaporation to dryness gave a material that was purified by flash column chromatography using neutral or basic Alumina as stationary phase and petroleum ether–CH_2Cl_2 as eluent. The compounds were characterized by comparison with authentic samples and by spectral data.

***N*-Allyl-*N*-benzyl-1-((4-methoxybenzyl)oxy)-1-phenylpent-4-en-2-amine (37)**



Mol. Formula: $C_{29}H_{33}NO_2$

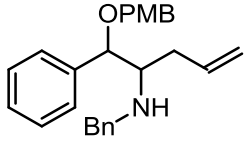
IR ($CHCl_3$, cm^{-1}): ν_{max} 3069, 3029, 3003, 2956, 2933, 1676, 1642, 1598, 1500, 1460, 1246, 1036, 818.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.36-2.64 (m, 2H), 3.04-3.16 (m, 2H), 3.30-3.37 (m, 1H), 3.60 (s, 2H), 3.86 (s, 3H), 4.25-4.33 (m, 1H), 4.67 (s, 2H), 4.98-5.13 (m, 4H), 5.63-5.87 (m, 2H), 6.91-6.95 (d, *J*=8.7, 2H), 7.19-7.42 (m, 12H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 30.5, 53.3, 54.1, 55.0, 63.6, 70.1, 80.5, 113.6, 115.1, 116.2, 126.4, 127.0, 127.1, 127.8, 128.0, 128.5, 129.3, 130.3, 137.6, 138.2, 140.4, 141.3, 159.0 ppm.

Analysis Calcd.; C, 81.46; H, 7.78; N, 3.28; **Found:** C, 81.45; H, 7.73; N, 3.26.

***N*-Benzyl-1-((4-methoxybenzyl)oxy)-1-phenylpent-4-en-2-amine (38)**



Yield: 78%

Mol. Formula: $C_{26}H_{29}NO_2$

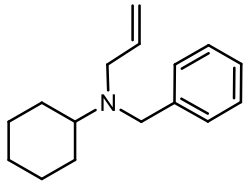
IR ($CHCl_3$, cm^{-1}): ν_{max} 3439, 3067, 3025, 3001, 2954, 2933, 1676, 1597, 1503, 1464, 1249, 1136, 816.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.23-2.43 (m, 2H), 2.89 (brs, 1H), 3.58-3.60 (m, 1H), 3.73 (s, 2H), 3.81 (s, 3H), 4.20-4.26 (m, 1H), 4.48 (s, 2H), 5.04-5.12 (m, 2H), 5.72-5.92 (m, 1H), 6.85-6.90 (d, *J*= 8.7 Hz, 2H), 7.16-7.38 (m, 12H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.6, 50.9, 55.2, 61.1, 70.4, 81.4, 113.7, 117.4, 127.2, 127.6, 127.8, 128.3, 128.5, 129.5, 129.6, 130.3, 135.5, 139.4, 159.2 ppm.

Analysis Calcd.: C, 80.59; H, 7.54; N, 3.61; **Found:** C, 80.58; H, 7.51; N, 3.58.

***N*-Allyl-*N*-benzylcyclohexanamine (41)**



Mol. Formula: $C_{16}H_{23}N$

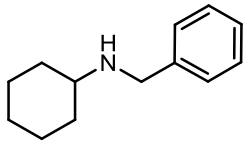
IR ($CHCl_3$, cm^{-1}): ν_{max} 3081, 3063, 2928, 2853, 1641, 1602, 1493, 1450, 1416, 1263, 1122, 915, 735, 697.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.16-1.36 (m, 5H), 1.64-1.77 (m,1H), 1.82-1.87 (m, 4H), 2.55-2.59 (m, 1H), 3.11-3.15 (dt, *J*= 6.1, 1.3 Hz, 2H), 3.63 (s, 2H), 5.07-5.21 (m, 2H), 5.77-5.93 (ddt, *J*= 17.2, 10.1, 6.1Hz, 1H), 7.24-7.39 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.1, 26.4, 28.9, 53.0, 53.5, 58.6, 115.8, 126.3, 127. 9, 128.3, 137.7, 141.3 ppm.

Analysis: Calcd.: C, 83.79; H, 10.11; N, 6.11; **Found:** C, 83.71; H, 10.14; N, 6.09.

***N*-benzylcyclohexanamine (42)**



Yield: 92%

Mol. Formula: $C_{13}H_{19}N$

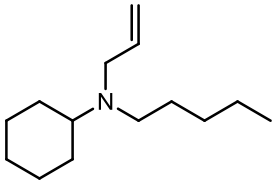
IR ($CHCl_3$, cm^{-1}): ν_{max} 3435, 3071, 3065, 2980, 2933, 2854, 1580, 1455, 1372, 1264, 1212, 1119, 758.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10-1.23 (m, 5H), 1.57-1.60 (m, 1H), 1.69-1.72 (m, 2H), 1.89-1.92 (d, *J*=11.8 Hz, 2H), 2.17 (brs, 1H), 2.46-2.50 (m, 1H), 3.79 (s, 2H), 7.21-7.23 (m, 1H), 7.27-7.30 (m, 4H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.9, 26.0, 33.2, 50.7, 56.0, 126.8, 128.1, 128.3, 140.3 ppm.

Analysis: Calcd.: C, 82.48; H, 10.12; N, 7.40; **Found:** C, 82.58; H, 10.11; N, 7.38.

***N*-Allyl-*N*-pentylcyclohexanamine (43)**

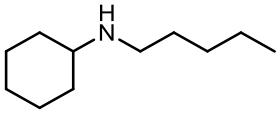


Mol. Formula: $C_{14}H_{27}N$

IR ($CHCl_3$, cm^{-1}): ν_{max} 2931, 2857, 2796, 1640, 1444, 1384, 1271, 1114, 989, 891.
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88-0.92 (m,3H), 1.13-1.39 (m, 9H), 1.66-1.75 (m, 4H), 1.99-2.03 (m, 3H), 2.44-2.54 (m, 1H), 2.92 (br, 2H),3.01-3.04 (d, *J*=6.1 Hz, 2H), 5.00-5.16 (m, 1H), 5.24-5.31 (t, *J*=7.1 Hz, 1H), 5.70-5.90 (m, 1H) ppm.
^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.3, 26.3, 27.3, 28.6, 30.4, 32.2, 52.5, 55.8, 57.9, 115.2, 138.0 ppm.

Analysis Calcd.: C, 80.31; H, 13.00; N, 6.69; **Found:** C, 80.29; H, 13.07; N, 6.65.

***N*-Pentylcyclohexanamine (44)**



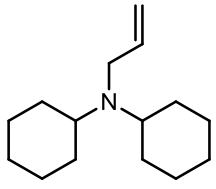
Yield: 85%

Mol. Formula: $C_{11}H_{23}N$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3567, 2932, 2853, 2798, 1444, 1384, 1275, 1124, 889
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.83-0.91 (m, 3H), 1.11-1.15 (m, 4H), 1.29-1.33 (m, 5H), 1.73-1.97 (m, 4H), 2.00-2.04 (m, 3H), 2.43-2.52 (m, 1H), 2.99-3.02 (m, 2H), 3.86 (brs, 1H) ppm.
^{13}C NMR (50 MHz, $CDCl_3$): δ 13.6, 21.7, 25.6, 25.9, 28.7, 29.7, 30.7, 31.5, 49.5, 54.4 ppm.

Analysis Calcd.: C, 78.03; H, 13.69; N, 8.27; **Found:** C, 78.08; H, 13.61; N, 8.34.

***N*-Allyl-*N*-cyclohexylcyclohexanamine (45)**



Mol. Formula: $C_{15}H_{27}N$

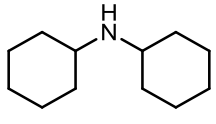
IR ($CHCl_3$, cm^{-1}): ν_{max} 2929, 2853, 2712, 2666, 1729, 1625, 1449, 1271, 1116, 912, 756.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.03-1.06 (m, 2H), 1.15-1.25 (m, 8H), 1.56-1.59 (br, 2H), 1.69-1.74 (m, 8H), 2.52-2.57 (m, 2H), 3.18-3.20 (d, *J*=5.8 Hz, 2H), 4.95-4.98 (d, *J*=10.1 Hz, 1H), 5.10-5.15 (dd, *J*=17.1, 1.8 Hz, 1H), 5.77-5.85 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.2, 26.3, 31.7, 49.2, 57.6, 114.2, 140.4 ppm.

Analysis Calcd.: C, 81.38; H, 12.29; N, 6.33; **Found:** 81.33; H, 12.31; N, 6.35.

Dicyclohexylamine (46)



Yield: 90%

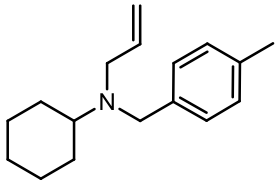
Mol. Formula: $C_{12}H_{23}N$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3357, 2928, 2853, 2713, 1728, 1605, 1578, 1449, 1295, 1159, 758.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.09-1.24 (m, 10H), 1.58-1.71 (m, 3H), 1.73-1.74 (m, 4H), 1.87-1.90 (m, 3H), 2.59-2.65 (m, 2H), 3.75 (brs, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.7, 26.3, 34.8, 52.8 ppm.

***N*-Allyl-*N*-(4-methylbenzyl)cyclohexanamine (47)**

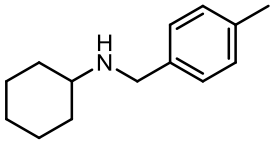


Mol. Formula: $C_{17}H_{25}N$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3021, 2937, 2851, 1738, 1644, 1601, 1483, 1457, 1416, 1278, 913.
^{1}H NMR (200 MHz, $CDCl_3$): 1.14-1.35 (m, 5H), 1.63-1.68 (m, 1H), 1.80-1.90 (m, 4H), 2.38 (s, 3H), 2.56-2.63 (m, 1H), 3.15-3.18 (d, *J*=6.1 Hz, 2H), 3.63 (s, 2H), 5.06-5.12 (dd, *J*=10.1, 1.9 Hz, 1H), 5.16-5.25 (dd, *J*=17.2, 1.8 Hz, 1H), 5.87-5.97 (m, 1H), 7.13-7.17 (d, *J*=7.6 Hz, 2H), 7.27-7.31 (d, *J*=7.6 Hz, 2H) ppm.
^{13}C NMR (50 MHz, $CDCl_3$): δ 21.0, 26.1, 26.4, 28.9, 52.9, 53.2, 58.5, 115.7, 128.2, 128.7, 135.8, 137.9, 138.2 ppm.

Analysis Calcd.: C, 83.89; H, 10.35; N, 5.75; **Found:** C, 83.84; H, 10.36; N, 5.81.

***N*-(4-Methylbenzyl)cyclohexanamine (48)**



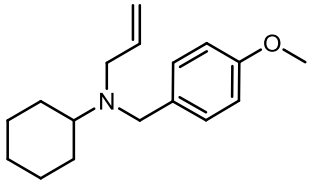
Yield: 80%
Mol. Formula: $C_{14}H_{21}N$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3498, 3022, 2939, 2856, 1739, 1601, 1489, 1434, 1415, 1271, 1135, 945.
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.09-1.28 (m, 4H), 1.73-1.78 (m, 2H), 1.89-1.94 (m, 4H), 2.35 (s, 3H), 2.42-2.56 (m, 1H), 3.77 (s, 2H), 4.63 (s, 1H), 7.12-7.24 (m, 4H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.9, 24.8, 26.0, 33.2, 50.4, 55.8, 127.9, 128.9, 136.2, 137.4 ppm.

Analysis Calcd.: C, 82.70; H, 10.41; N, 6.89; **Found:** C, 82.72; H, 10.45; N, 6.81.

***N*-Allyl-*N*-(4-methoxybenzyl)cyclohexanamine (49)**



Mol. Formula: $C_{17}H_{25}NO$

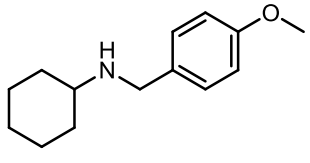
IR ($CHCl_3$, cm^{-1}): ν_{max} 3073, 3002, 2929, 2853, 1699, 1640, 1611, 1509, 1450, 1246, 1167, 1038, 913, 817, 758

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.07-1.27 (m, 5H), 1.56-1.61 (m, 1H), 1.73-1.82 (m, 4H), 2.48-2.53 (m, 1H), 3.06-3.10 (dt, *J*=6.1, 1.3 Hz, 2H), 3.53 (s, 2H), 3.77 (s, 3H), 4.99-5.05 (ddt, *J*=10.1, 2.2, 1.2 Hz, 1H), 5.08-5.17 (m, 1H), 5.73-5.89 (ddt, *J*= 16.9, 10.4, 6.2 Hz, 1H), 6.79-6.84 (d, *J*=8.7 Hz, 2H), 7.21-7.26 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.0, 26.4, 28.8, 52.8(2C) 55.0, 58.4, 113.3, 115.7, 129.3, 133.0, 137.7, 158.2 ppm.

Analysis Calcd.: C, 78.72; H, 9.71; N, 5.40; **Found:** C, 78.75; H, 9.70; N, 5.34.

***N*-(4-Methoxybenzyl)cyclohexanamine (50)**



Yield: 55%

Mol. Formula: $C_{14}H_{21}NO$

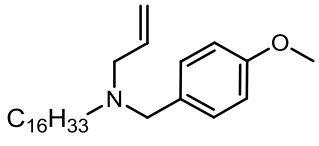
IR ($CHCl_3$, cm^{-1}): ν_{max} 3435, 3073, 3001, 2931, 2854, 1700, 1612, 1508, 1450, 1245, 1169, 1037, 819, 753.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.97-1.26 (m, 5H), 1.35-1.42 (m, 1H), 1.52-1.80 (m, 4H), 2.44-2.56 (m, 1H), 3.52 (s, 2H), 3.73 (s, 3H), 4.16 (brs, 1H), 6.75-6.80 (d, *J*= 8.6 Hz, 2H), 7.20-7.23 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 23.2, 25.5, 29.6, 49.9, 55.6, 57.5, 112.9, 126.5, 130.2, 157.8 ppm.

Analysis Calcd.: C, 76.67; H, 9.65; N, 6.39; **Found:** C, 76.66; H, 9.61; N, 6.40.

***N*-Allyl-*N*-(4-methoxybenzyl)hexadecan-1-amine (51)**



Mol. Formula: $C_{27}H_{47}NO$

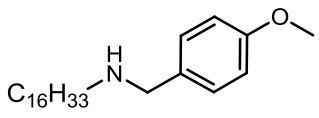
IR ($CHCl_3$, cm^{-1}): ν_{max} 3073, 2975, 2853, 1728, 1642, 1612, 1511, 1645, 1248, 1170, 1039, 914, 818, 759.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86-0.92 (m, 3H), 1.17-1.34 (m, 28H), 2.36-2.44 (m, 2H), 3.04-3.07 (d, *J*= 6.3 Hz, 2H), 3.51 (s, 2H), 3.81 (s, 3H), 5.11-5.22 (m, 2H), 5.82-5.96 (ddt, *J*= 17, 10.3, 6.4 Hz, 1H), 6.83-6.87 (m, 2H), 7.22-7.27 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.6, 26.9, 27.3, 29.3, 29.5, 29.6, 31.9, 53.2, 55.1, 56.5, 57.2, 113.4, 116.9, 129.9, 131.6, 136.1, 158.4 ppm.

Analysis Calcd.: C, 80.74; H, 11.79; N, 3.49; **Found:** C, 80.69; H, 11.77; N, 3.5.

***N*-(4-Methoxybenzyl)hexadecan-1-amine (52)**



Yield: 50%

Mol. Formula: $C_{24}H_{43}NO$

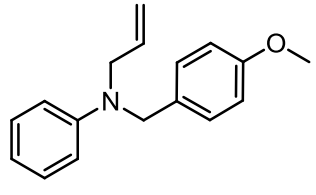
IR ($CHCl_3$, cm^{-1}): ν_{max} 3478, 3071, 2975, 2852, 1728, 1612, 1511, 1645, 1248, 1171, 1039, 817, 760.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87-0.93 (m, 3H), 1.37-1.35 (m, 29H) 2.49-2.57 (m, 2H), 3.61(s, 2H), 3.82 (s, 3H), 6.84-6.88 (m, 2H), 7.23-7.28 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 12.3, 20.9, 25.1, 25.6, 27.6, 27.8, 27.9, 30.2, 51.5, 53.4, 55.5, 111.7, 128.2, 129.9, 156.7 ppm.

Analysis Calcd.: C, 79.72; H, 11.99; N, 3.87; **Found:** C, 79.74; H, 11.95; N, 3.92.

***N*-Allyl-*N*-(4-methoxybenzyl)aniline (53)**



Mol. Formula: $C_{17}H_{19}NO$

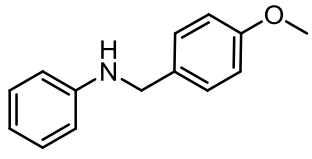
IR ($CHCl_3$, cm^{-1}): ν_{max} 3061, 3003, 2931, 3834, 1725, 1642, 1598, 1500, 1460, 1266, 1036, 921, 818, 747.

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.84 (s, 3H), 4.03-4.05 (d, *J*= 14.5 Hz, 2H), 4.54 (s, 2H), 5.19-5.21 (t, *J*= 1.8 Hz, 1H), 5.25-5.28 (m, 1H), 5.84-6.02 (m, 1H), 6.70-6.71 (m, 1H), 6.79-6.80 (m, 2H), 6.89-6.93 (m, 2H), 7.207.21 (m, 2H), 7.24-7.28 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 52.7, 53.2, 55.1, 112.3, 113.8, 116.16, 116.3, 127.6, 129.0, 130.6, 133.6, 148.8, 158.4 ppm.

Analysis Calcd.: C, 80.60; H, 7.56; N, 5.53%; **Found:** C, 80.63; H, 7.54; N, 5.50%.

***N*-(4-Methoxybenzyl)aniline (54)**



Yield: 35%

Mol. Formula: $C_{14}H_{15}NO$

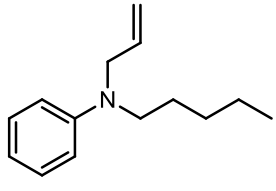
IR ($CHCl_3$, cm^{-1}): ν_{max} 3419, 3061, 3002, 2934, 3834, 1725, 1596, 1501, 1460, 1266, 1036, 816.

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.82 (s, 3H), 4.24 (brs, 1H), 4.41 (s, 2H), 6.71-6.77 (m, 3H), 6.89-6.90 (m, 2H), 7.17-7.27 (m, 4H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 49.2, 55.1, 112.3, 113.8, 115.0, 127.6, 129.0, 132.3, 148.8, 158.4 ppm.

Analysis Calcd.: C, 78.84; H, 7.09; N, 6.57; **Found:** C, 78.81; H, 7.11; N, 6.59.

***N*-Allyl-*N*-pentylaniline (55)**



Mol. Formula: $C_{14}H_{21}N$

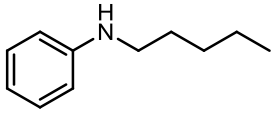
IR ($CHCl_3$, cm^{-1}): ν_{max} 3056, 3007, 2931, 2796, 1749, 1642, 1443, 1384, 1270, 1071, 1039, 914, 891.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.93-0.95 (m, 3H), 1.33-1.35 (m, 4H), 1.44-1.49 (m, 2H), 2.29 (m, 2H), 3.01-3.04 (d, *J*= 6.1 Hz, 2H), 5.00-5.16 (m, 2H), 5.24-5.31 (t, *J*= 7.1 Hz, 1H), 5.70-5.87 (m, 1H), 6.61-6.72 (m, 3H), 7.16-7.27 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 22.3, 30.8, 32.1, 52.3, 55.5, 112.1, 115.8, 125.4, 128.8, 133.6, 149.1 ppm.

Analysis Calcd.: C, 82.70; H, 10.41; N, 6.89; **Found:** C, 82.73; H, 10.45; N, 6.84.

***N*-Pentylaniline (56)**



Yield: 75%

Mol. Formula: $C_{11}H_{17}N$

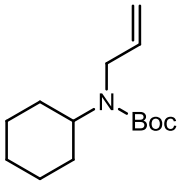
IR ($CHCl_3$, cm^{-1}): ν_{max} 3414, 3049, 3006, 2931, 1750, 1443, 1384, 1271, 1074, 1040, 890.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90-0.96 (m, 3H), 1.33-1.49 (m, 3H), 1.61-1.71 (m, 2H), 2.06-2.11 (m, 1H), 2.92 (m, 2H), 4.10 (brs, 1H), 6.58-6.72 (m, 3H), 6.96-7.27 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.4, 31.0, 32.0, 49.8, 112.8, 127.3, 129.1, 148.6 ppm.

Analysis Calcd.: C, 80.93; H, 10.50; N, 8.58; **Found:** C, 80.89; H, 10.54; N, 8.5.

***tert*-Butyl allyl(cyclohexyl)carbamate (57)**



Mol. Formula: $C_{14}H_{25}NO_2$

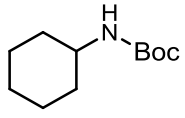
IR ($CHCl_3$, cm^{-1}): ν_{max} 2986, 2931, 2821, 2713, 1720, 1658, 1647, 1454, 1416, 1263, 912.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.02-1.05 (m, 1H), 1.28-1.29 (m, 4H), 1.41 (s, 9H), 1.56-1.59 (m, 1H), 1.66-1.73 (m, 4H), 3.67 (brs, 2H), 3.90 (brs, 1H), 4.99-5.08 (m, 2H), 5.72-5.76 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.4, 25.8, 28.3, 31.0, 45.1, 54.8, 79.1, 114.9, 136.3, 155.3 ppm.

Analysis Calcd.: C, 70.25; H, 10.53; N, 5.85; **Found:** C, 70.29; H, 10.51; N, 5.85.

***tert*-Butyl cyclohexylcarbamate (58)**



Yield: 80%

Mol. Formula: $C_{11}H_{21}NO_2$

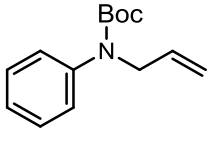
IR ($CHCl_3$, cm^{-1}): ν_{max} 3356, 2984, 2934, 2822, 2713, 1720, 1658, 1452, 1416, 1263, 830.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.05-1.36 (m, 5H), 1.44 (s, 9H), 1.58-1.71 (m, 3H), 1.90-1.95 (m, 2H), 3.39-3.42 (m, 1H), 4.43 (brs, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.8, 25.4, 28.3, 33.4, 49.3, 78.8, 155.1 ppm.

Analysis Calcd.: C, 66.29; H, 10.62; N, 7.03; **Found:** C, 66.25; H, 10.64; N, 7.07.

***tert*-Butyl allyl(phenyl)carbamate (59)**



Mol. Formula: $C_{14}H_{19}NO_2$

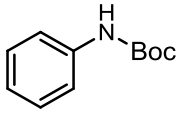
IR ($CHCl_3$, cm^{-1}): ν_{max} 3073, 3041, 3027, 2976, 2851, 1730, 1658, 1642, 1454, 1416, 1264, 913.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 4.31-4.33 (m, 2H), 5.14-5.24 (m, 2H), 5.83-5.92 (m, 1H), 7.02-7.08 (m, 2H), 7.17-7.21 (m, 1H), 7.23-7.58 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 28.3, 49.0, 80.1, 117.7, 126.6, 128.8, 129.7, 130.9, 143.4, 155.5 ppm.

Analysis Calcd.: C, 72.07; H, 8.21; N, 6.00; **Found:** C, 72.03; H, 8.24; N, 5.98.

***tert*-Butyl phenylcarbamate (60)**



Yield: 74%

Mol. Formula: $C_{11}H_{15}NO_2$

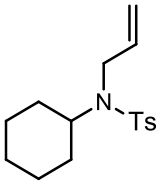
IR ($CHCl_3$, cm^{-1}): ν_{max} 3416, 3073, 3040, 3023, 2976, 2841, 1728, 1658, 1454, 1415, 1261, 937.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 4.48 (brs, 1H), 6.91-6.97 (m, 2H), 7.06-7.10 (m, 1H), 7.41-7.47 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 28.3, 79.13, 122.4, 127.0, 128.9, 137.9, 152.3 ppm.

Analysis Calcd.: C, 68.37; H, 7.82; N, 7.25; **Found:** C, 68.30; H, 7.85; N, 7.23.

***N*-Allyl-*N*-cyclohexyl-4-methylbenzenesulfonamide (61)**



Mol. Formula: $C_{16}H_{23}NO_2S$

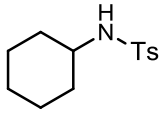
IR ($CHCl_3$, cm^{-1}): ν_{max} 3063, 3042, 3027, 2986, 2941, 2819, 2713, 1720, 1639, 1454, 1420, 1251, 1142, 1030, 914.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.09-1.23 (m, 5H), 1.57-1.60 (m, 1H), 1.69-1.72 (m, 4H), 2.39 (s, 3H), 2.56-2.63 (m, 1H), 3.15-3.18 (d, *J*= 6.1 Hz, 2H), 5.06-5.12 (dd, *J*= 10.1, 1.9 Hz, 1H), 5.16-5.25 (dd, *J*= 17.3, 1.7 Hz, 1H), 5.81-5.97 (m, 1H), 7.25-7.27 (d, *J*= 8 Hz, 2H), 7.73-7.75 (d, *J*=8.1 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.4, 25.4, 25.8, 28.3, 49.3, 55.1, 115.2, 125.7, 127.3, 127.6, 137.1, 140.6 ppm.

Analysis Calcd.: C, 65.49; H, 7.90; N, 4.77; **Found:** C, 65.43; H, 7.92; N, 4.74.

***N*-Cyclohexyl-4-methylbenzenesulfonamide (62)**



Yield: 60%

Mol. Formula: $C_{13}H_{19}NO_2S$

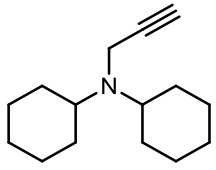
IR ($CHCl_3$, cm^{-1}): ν_{max} 3412, 3063, 3042, 3027, 2986, 2941, 2819, 2713, 1720, 1454, 1420, 1250, 1140, 1032.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.13-1.26 (m, 5H), 1.49-1.52 (m, 1H), 1.61-1.65 (m, 2H), 1.73-1.75 (m, 2H), 2.43 (s, 3H), 3.09-3.16 (m, 1H), 4.67 (brs, 1H), 7.28-7.30 (d, *J*= 8.1 Hz, 2H), 7.76-7.78 (d, *J*= 8.3 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.4, 24.9, 26.0, 33.2, 50.7, 128.1, 128.3, 137.5, 141.3 ppm.

Analysis Calcd.: C, 61.63; H, 7.56; N, 5.53; **Found:.** C, 61.64; H, 7.58; N, 5.51.

***N*-Cyclohexyl-*N*-(prop-2-yn-1-yl)cyclohexanamine (63)**



Mol. Formula: $C_{15}H_{25}N$

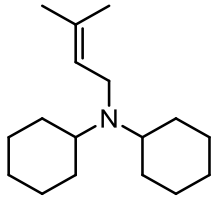
IR ($CHCl_3$, cm^{-1}): ν_{max} 3264, 2929, 2857, 2702, 2666, 2265, 1729, 1447, 1271, 1116, 1013, 747**.**

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.16-1.28 (m, 9H), 1.55-1.58 (br, 2H), 1.72-1.82 (m, 9H), 2.10 (s, 1H), 2.71-2.76 (m, 2H), 3.44 (s, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.9, 26.1, 30.9, 34.6, 57.1, 70.8, 83.5 ppm.

Analysis Calcd.: C, 82.13; H, 11.49; N, 6.39; **Found:** C, 82.16; H, 11.45; N, 6.37.

***N*-Cyclohexyl-*N*-(3-methylbut-2-en-1-yl)cyclohexanamine (64)**



Mol. Formula: $C_{17}H_{31}N$

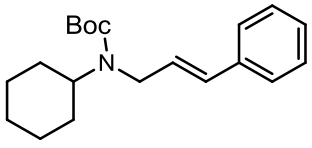
IR ($CHCl_3$, cm^{-1}): ν_{max} 2929, 2853, 2701, 2666, 1729, 1662, 1447, 1271, 1116, 916**.**

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.97-1.19 (m, 10H), 1.50-1.52 (m, 2H), 1.53 (s, 3H), 1.60-1.65 (m, 8H), 1.78 (s, 3H), 2.46-2.50 (m, 2H), 3.12-3.13 (d, *J*= 6.5 Hz, 2H), 5.14-5.27 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 18.4, 25.5, 26.3, 26.5, 26.8, 27.0, 31.9, 35.1, 44.5, 53.2, 58.3, 127.1, 132.4 ppm.

Analysis Calcd.: C, 81.86; H, 12.53; N, 5.62; **Found:** C, 81.84; H, 12.54; N, 5.63.

***tert*-Butyl cinnamyl(cyclohexyl)carbamate (65)**



Mol. Formula: $C_{20}H_{29}NO_2$

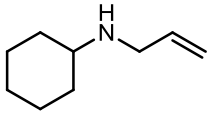
IR ($CHCl_3$, cm^{-1}): ν_{max} 3074, 3027, 2976, 2930, 2851, 2806, 1730, 1658, 1647, 1454, 1416, 1261, 912.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.99-1.25 (m, 4H), 1.37 (s, 9H), 1.64-1.70 (m, 4H), 1.83-1.89 (m, 2H), 2.58-2.73 (m, 1H), 3.69-3.72 (dd, *J*= 6.1, 0.9 Hz, 2H), 6.17-6.28 (m, 1H), 6.32-6.49 (m, 1H), 7.14-7.34 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.5, 26.6, 28.8, 32.6, 49.4, 58.1, 79.8, 126.7, 127.7, 128.9, 129.3, 131.4, 137.6, 154.0 ppm.

Analysis Calcd.: C, 76.15; H, 9.27; N, 4.44; **Found:** C, 76.11; H, 9.28; N, 4.42.

***N*-Allylcyclohexanamine (66)**



Mol. Formula: $C_9H_{17}N$

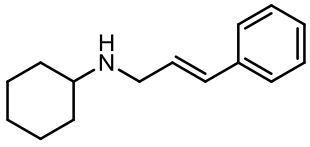
IR ($CHCl_3$, cm^{-1}): ν_{max} 3430, 2977, 2929, 2851, 2806, 1730, 1642, 1450, 1416, 1261, 914, 758.

^{1}H NMR (200 MHz, $CDCl_3$): δ 125-1.41 (m, 4H), 1.49-1.74 (m, 6H), 2.41-2.52 (m, 1H), 3.80-3.92 (m, 2H), 4.45 (brs, 1H), 5.04-5.22 (m, 2H), 5.69-5.89 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.0, 24.3, 26.9, 50.8, 56.8, 114.1, 135.4 ppm.

Analysis Calcd.: C, 77.63; H, 12.31; N, 10.06; **Found:** C, 77.61; H, 12.29; N, 10.09.

***N*-Cinnamylcyclohexanamine (68)**



Mol. Formula: $C_{15}H_{21}N$

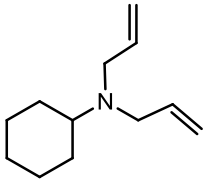
IR ($CHCl_3$, cm^{-1}): ν_{max} 3430, 3074, 3027, 2977, 2929, 2851, 2806, 1730, 1655, 1454, 1416, 1261, 914.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.98-1.24 (m, 5H), 1.59-1.69 (m, 4H), 1.82-1.86 (m, 2H), 2.39-2.51 (m, 1H), 3.35-3.38 (dd, *J*= 6.1, 0.9 Hz, 2H), 6.20-6.31 (m, 1H), 6.41-6.49 (m, 1H), 7.14-7.33 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.9, 26.0, 33.4, 48.78, 56.0, 126.0, 127.1, 128.3, 128.7, 130.8, 130.8, 137.0 ppm.

Analysis Calcd.: C, 83.67; H, 9.83; N, 6.50; **Found:** C, 83.68; H, 9.80; N, 6.53.

***N,N*-Diallylcyclohexanamine (69)**



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

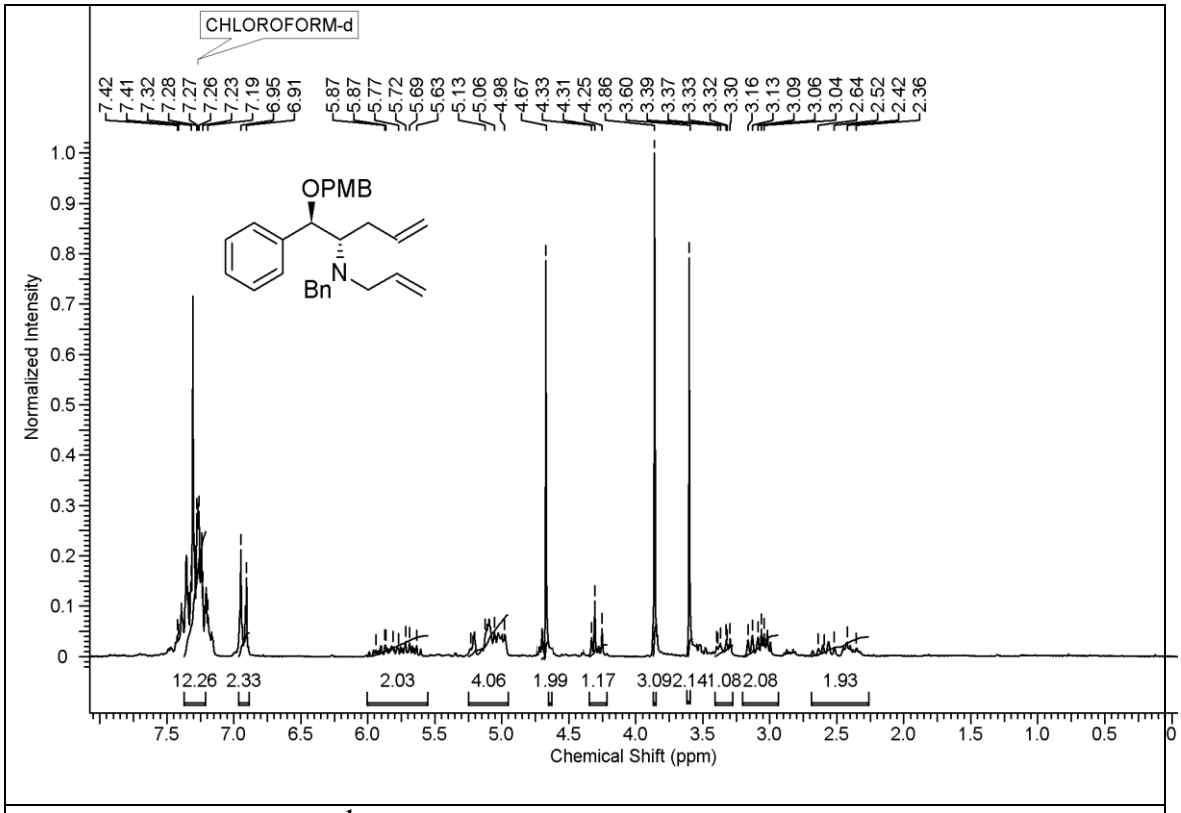
IR ($CHCl_3$, cm^{-1}): ν_{max} 2976, 2929, 2854, 2806, 1728, 1642, 1450, 1416, 1261, 915, 758.

^{1}H NMR (200 MHz, $CDCl_3$): δ 115-1.25 (m, 5H), 1.57-1.64 (m, 1H), 1.76-1.79 (m, 4H), 2.48-2.58 (m, 1H), 3.10-3.11 (t, *J*= 1.3 Hz, 2H), 3.13-3.14 (t, *J*= 1.3 Hz, 2H), 5.04-5.05 (m, 1H), 5.09-5.11 (m, 2H), 5.18-5.20 (m, 1H), 5.74-5.91 (m, 2H) ppm.

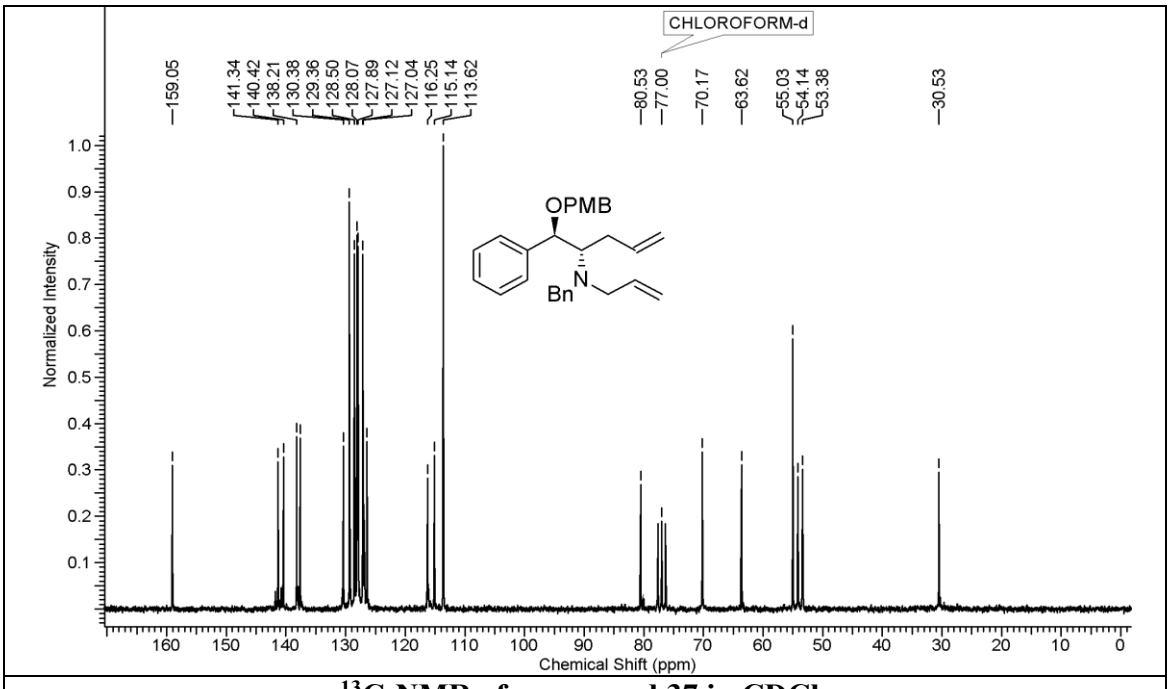
^{13}C NMR (50 MHz, $CDCl_3$): δ 26.0, 26.3, 28.9, 52.8, 58.8, 116.1, 137.4 ppm.

Analysis Calcd.: C, 80.38; H, 11.81; N, 7.81; **Found:** C, 80.37; H, 11.80; N, 7.83.

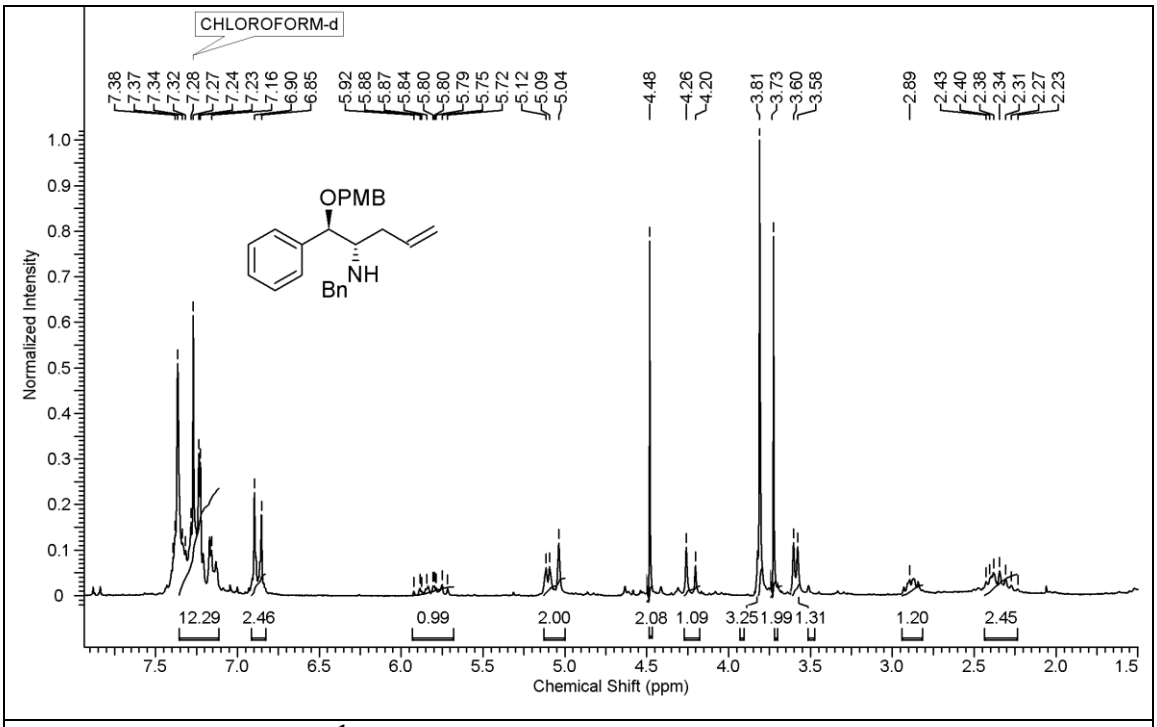
5.7. Spectra



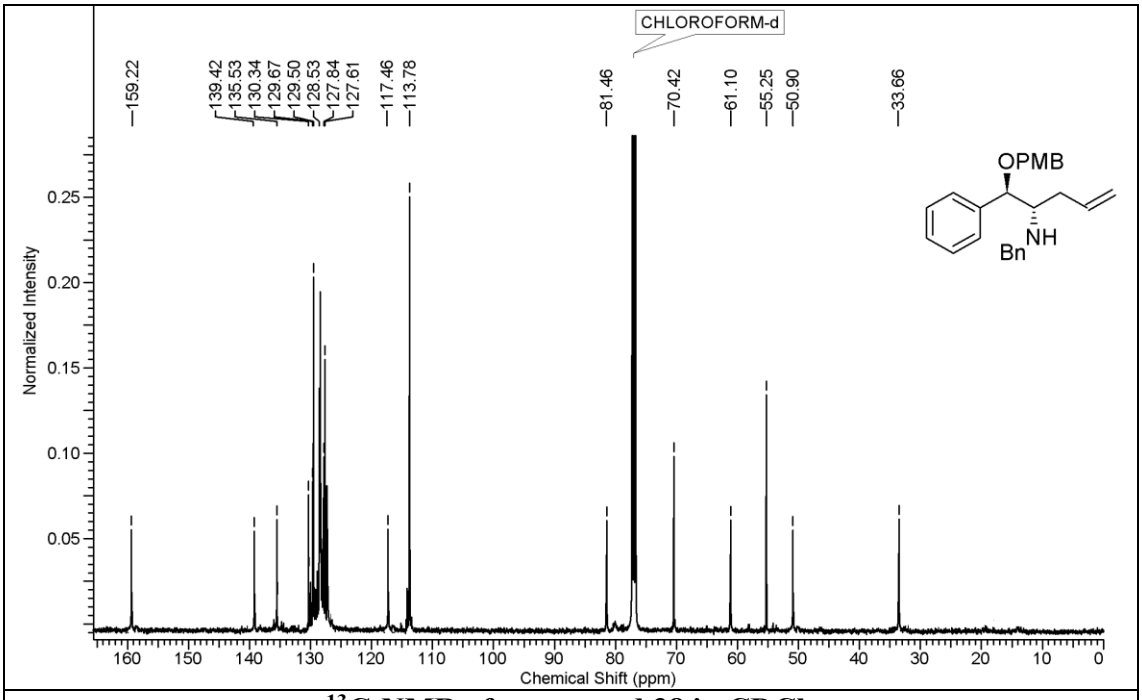
^{1}H-NMR of compound 37 in $CDCl_3$



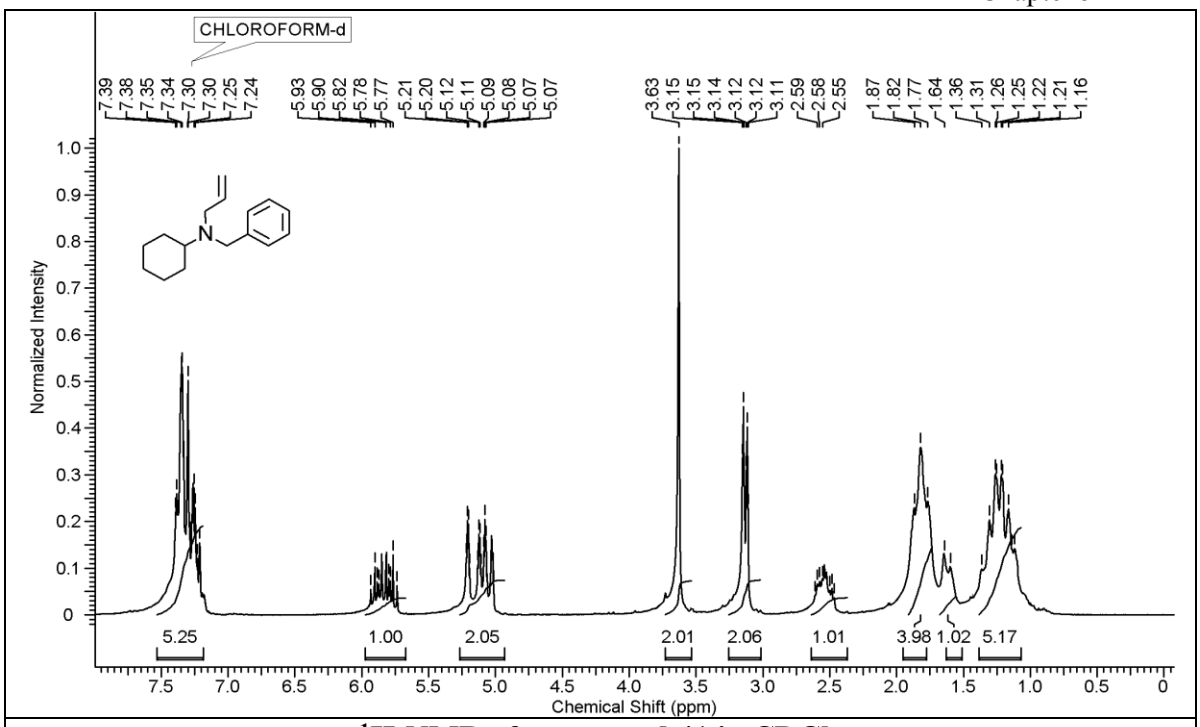
^{13}C-NMR of compound 37 in $CDCl_3$



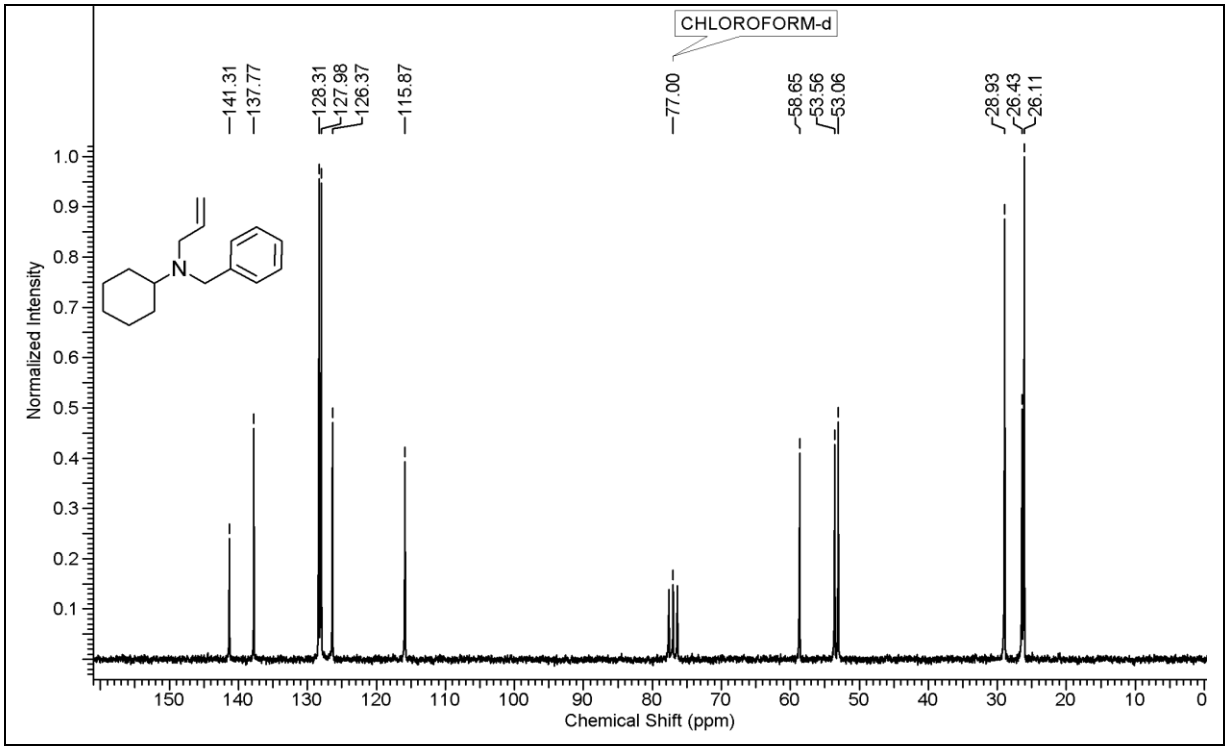
^{1}H-NMR of compound 38 in $CDCl_3$



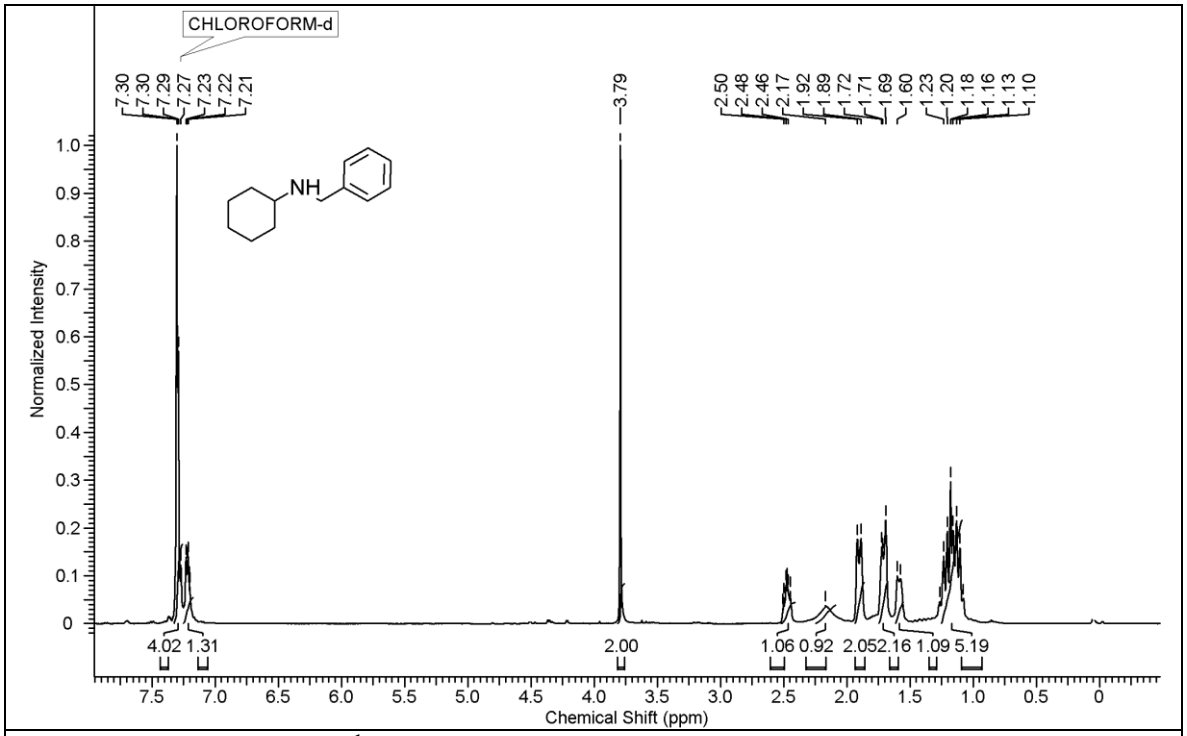
^{13}C-NMR of compound 38 in $CDCl_3$



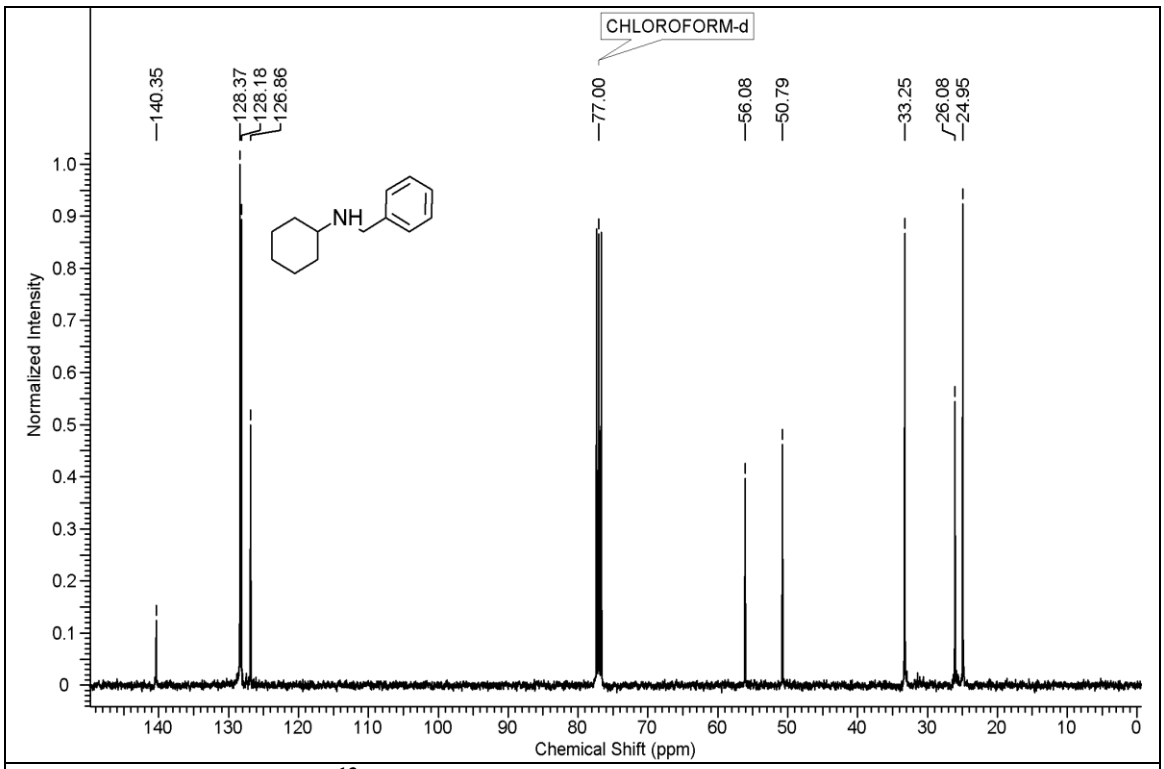
^{1}H-NMR of compound 41 in $CDCl_3$



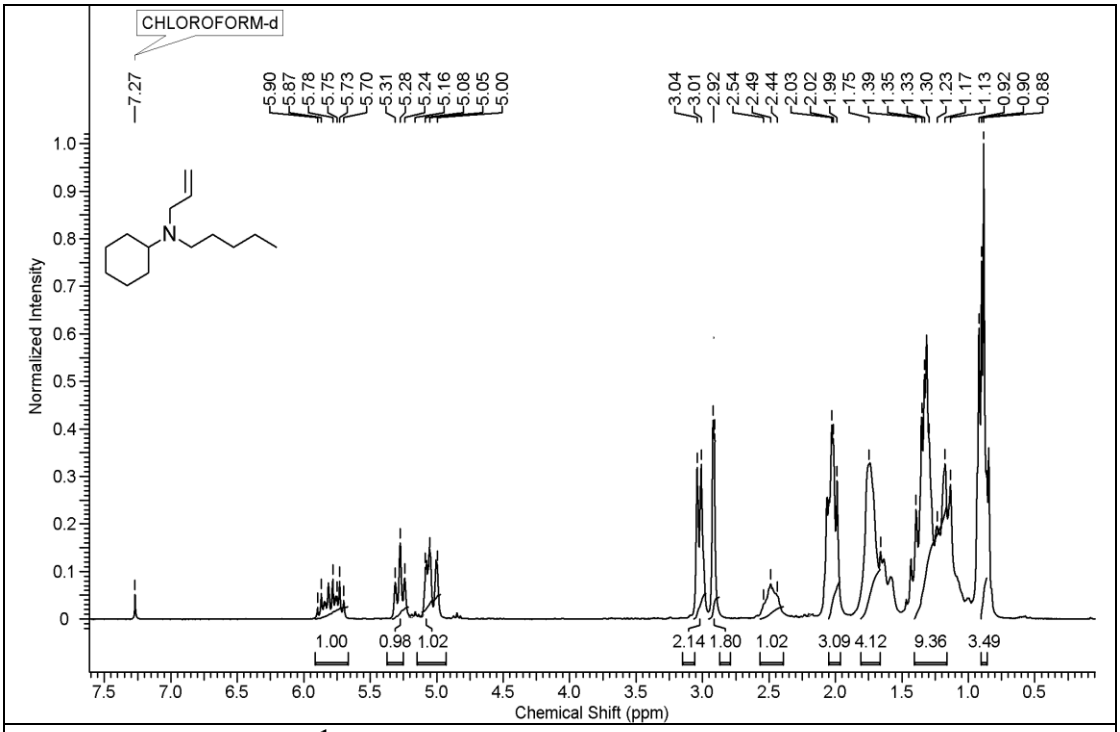
^{13}C-NMR of compound 41 in $CDCl_3$



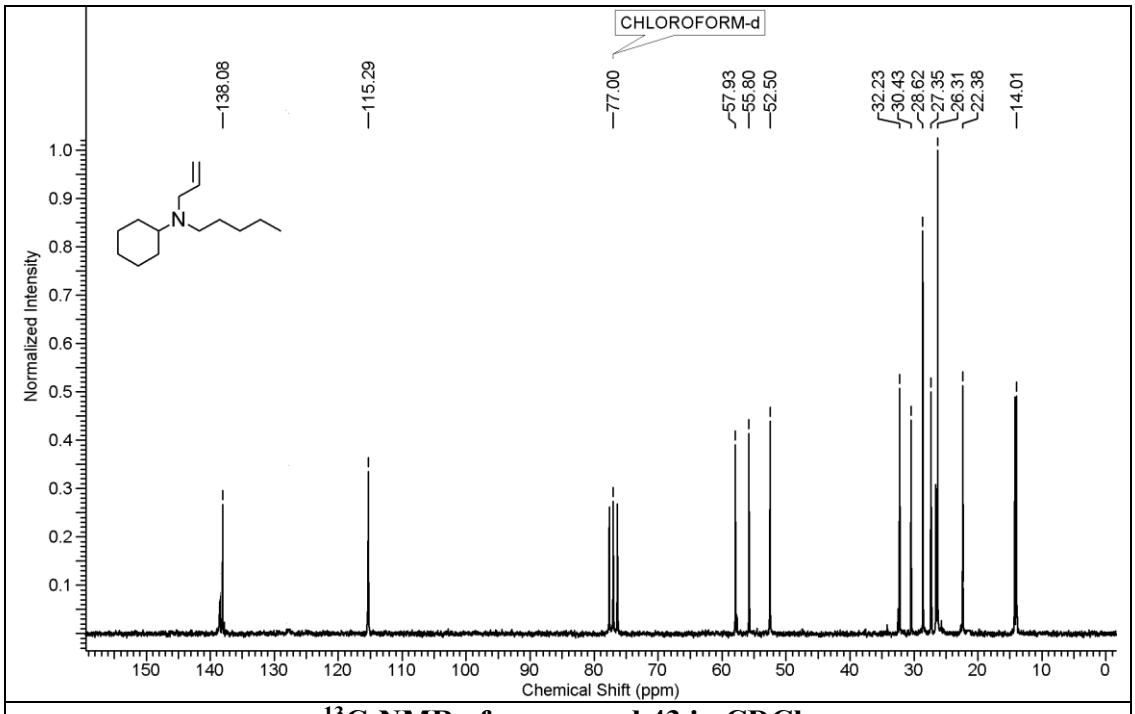
^{1}H-NMR of compound 42 in $CDCl_3$



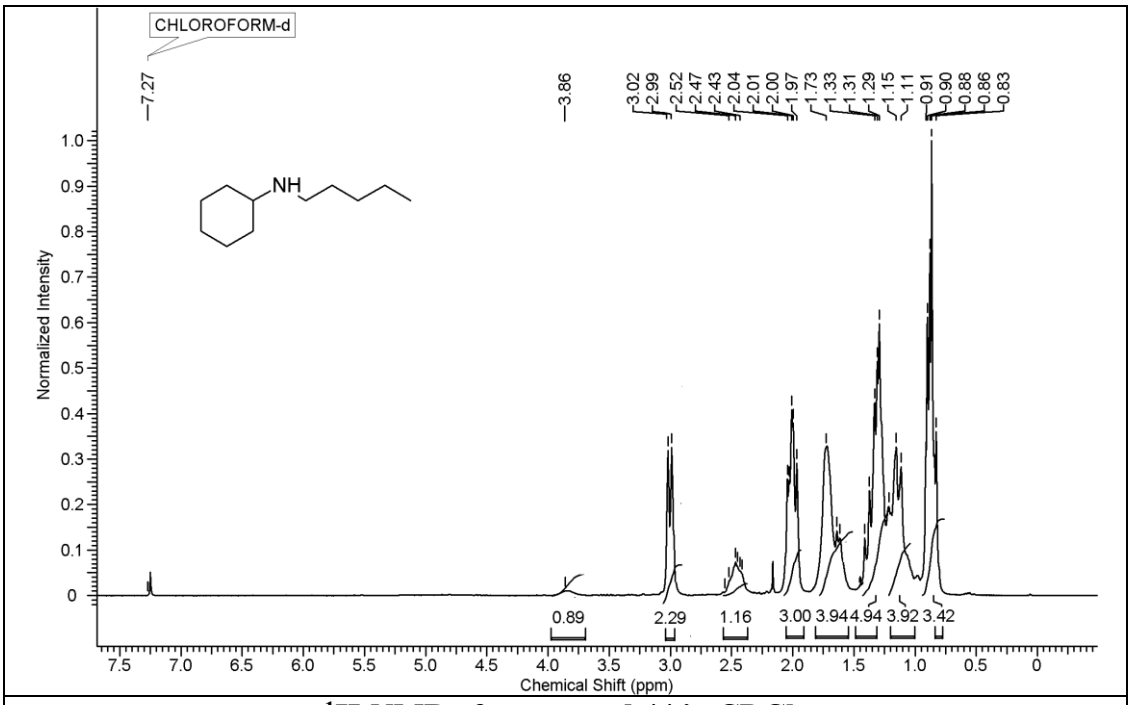
^{13}C-NMR of compound 42 in $CDCl_3$



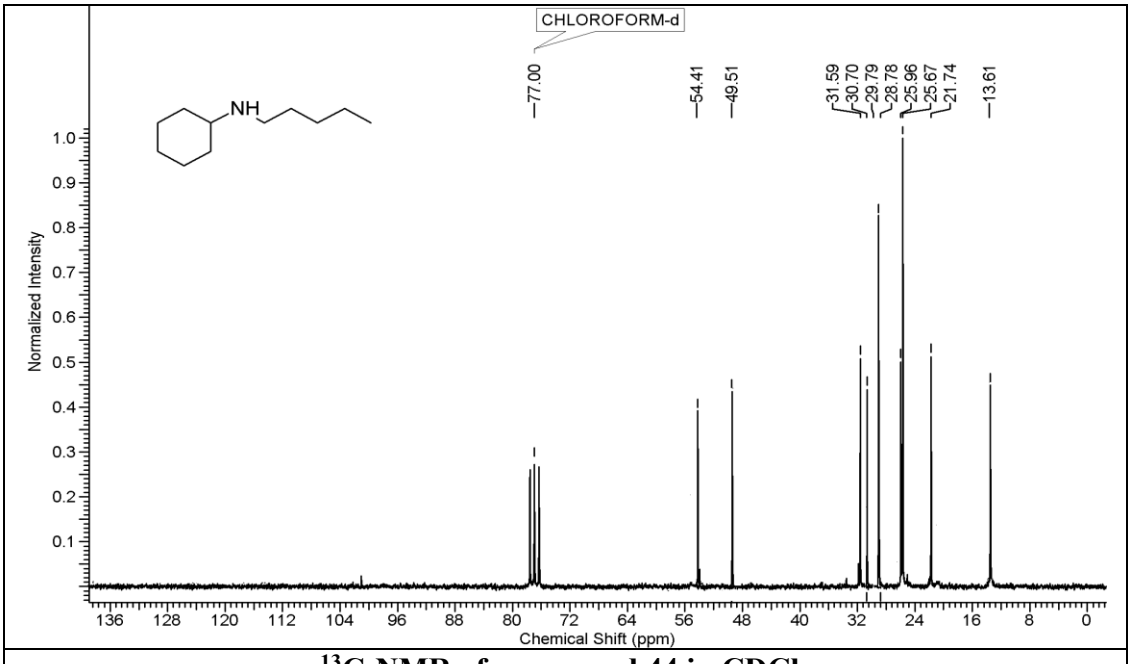
^{1}H-NMR of compound 43 in $CDCl_3$



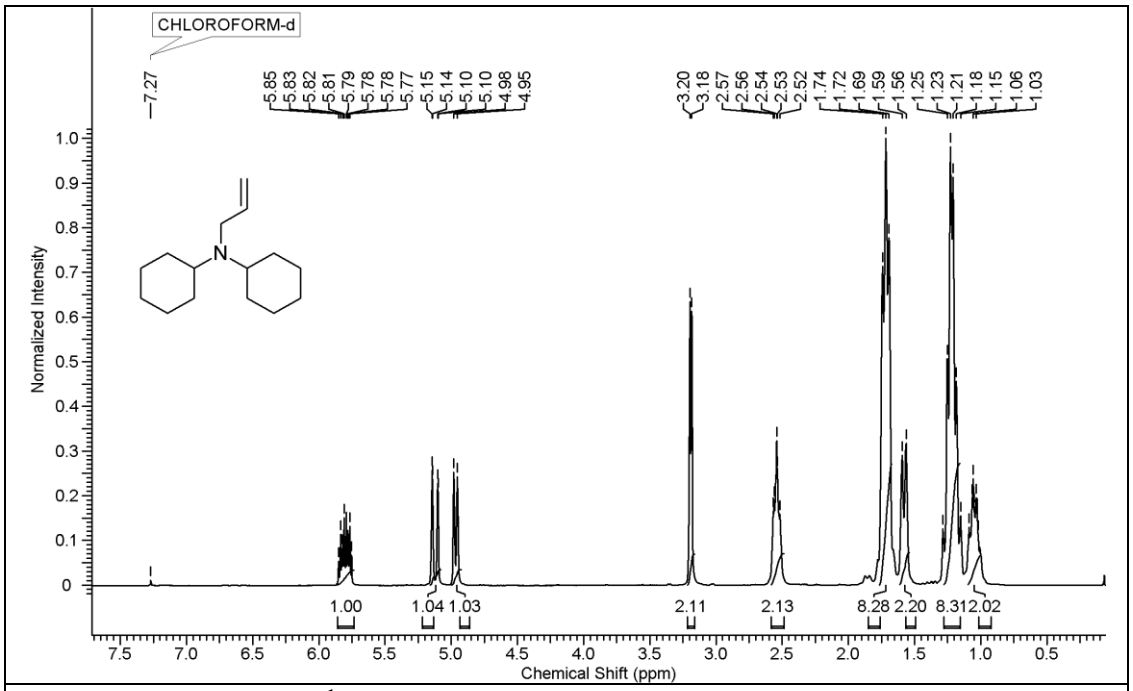
^{13}C-NMR of compound 43 in $CDCl_3$



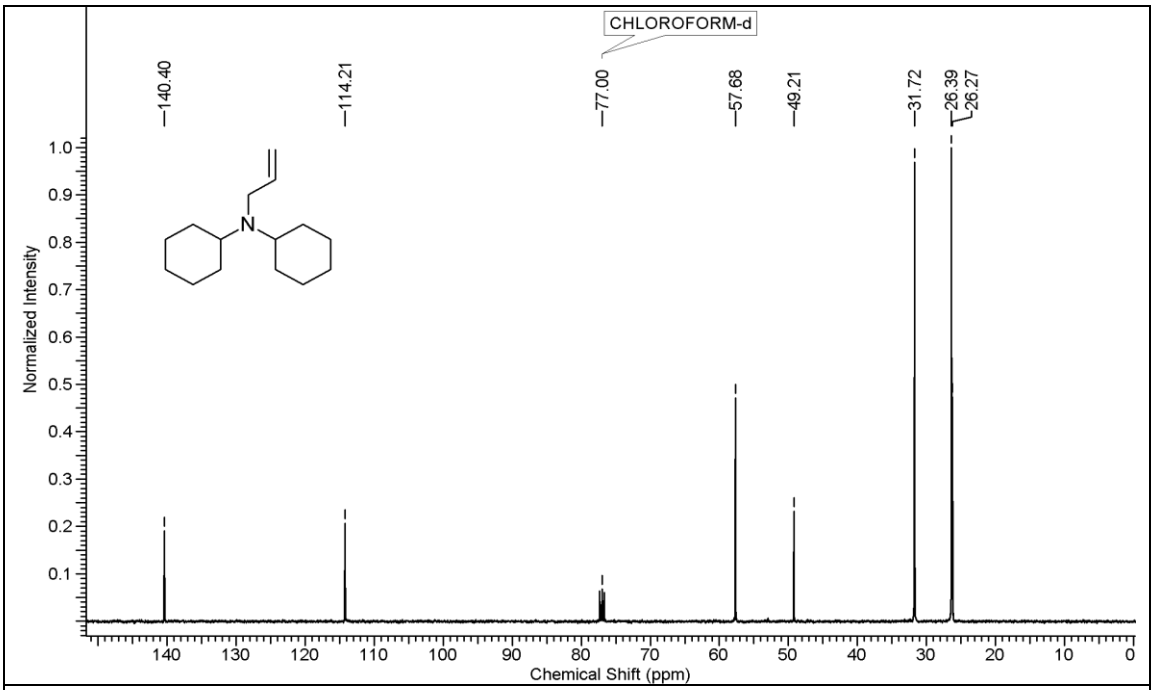
^{1}H-NMR of compound 44 in $CDCl_3$



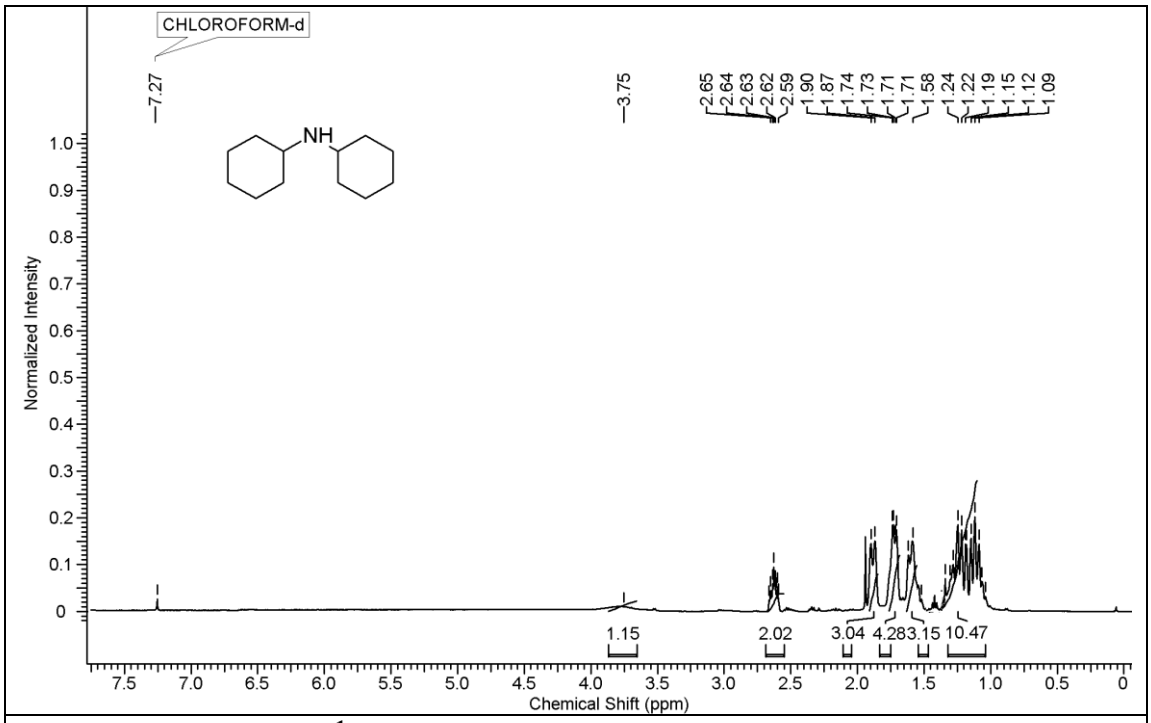
^{13}C-NMR of compound 44 in $CDCl_3$



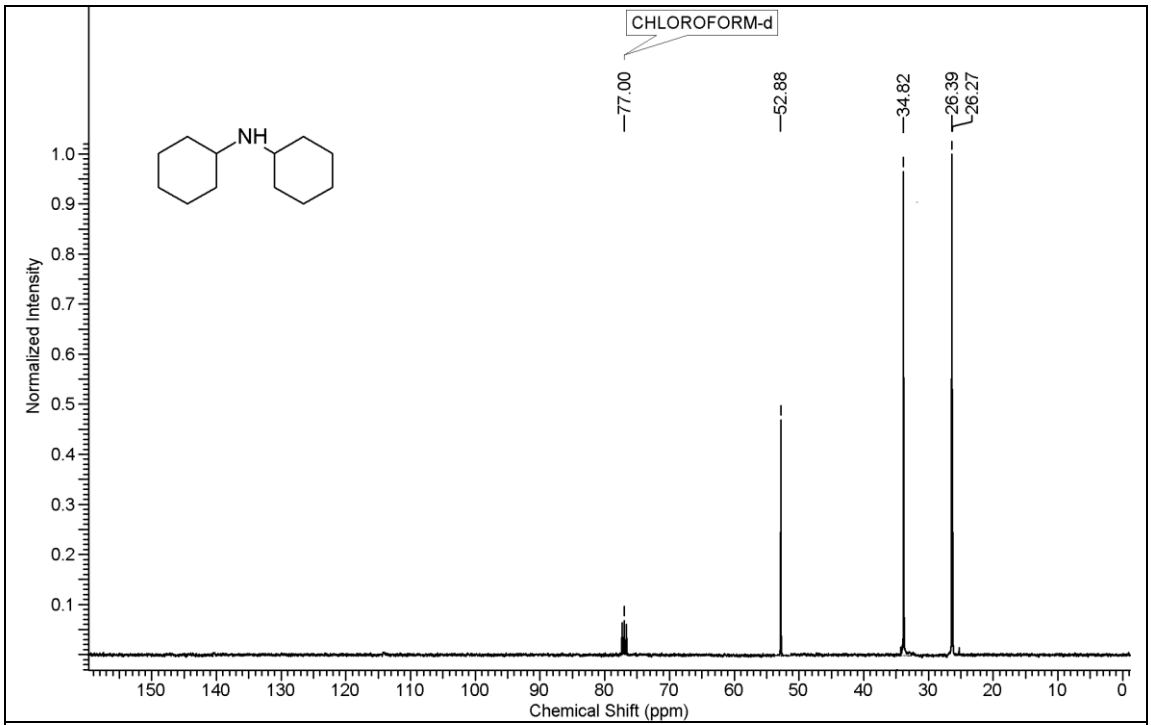
^{1}H-NMR of compound 45 in $CDCl_3$



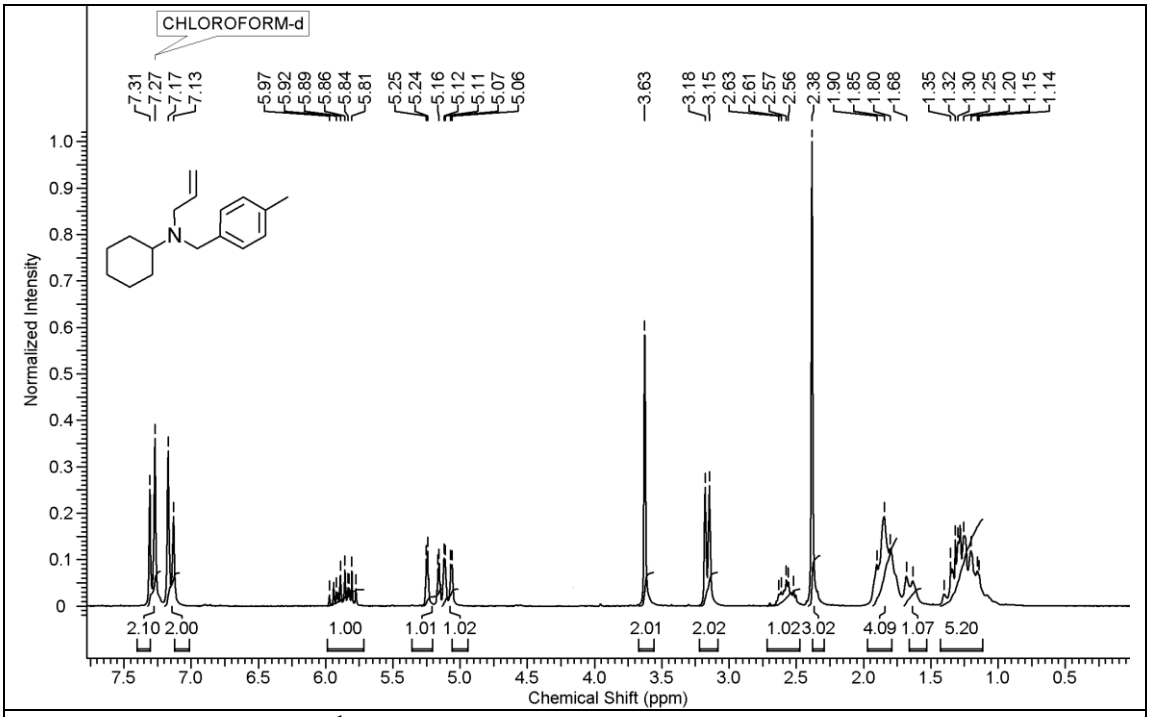
^{13}C-NMR of compound 45 in $CDCl_3$



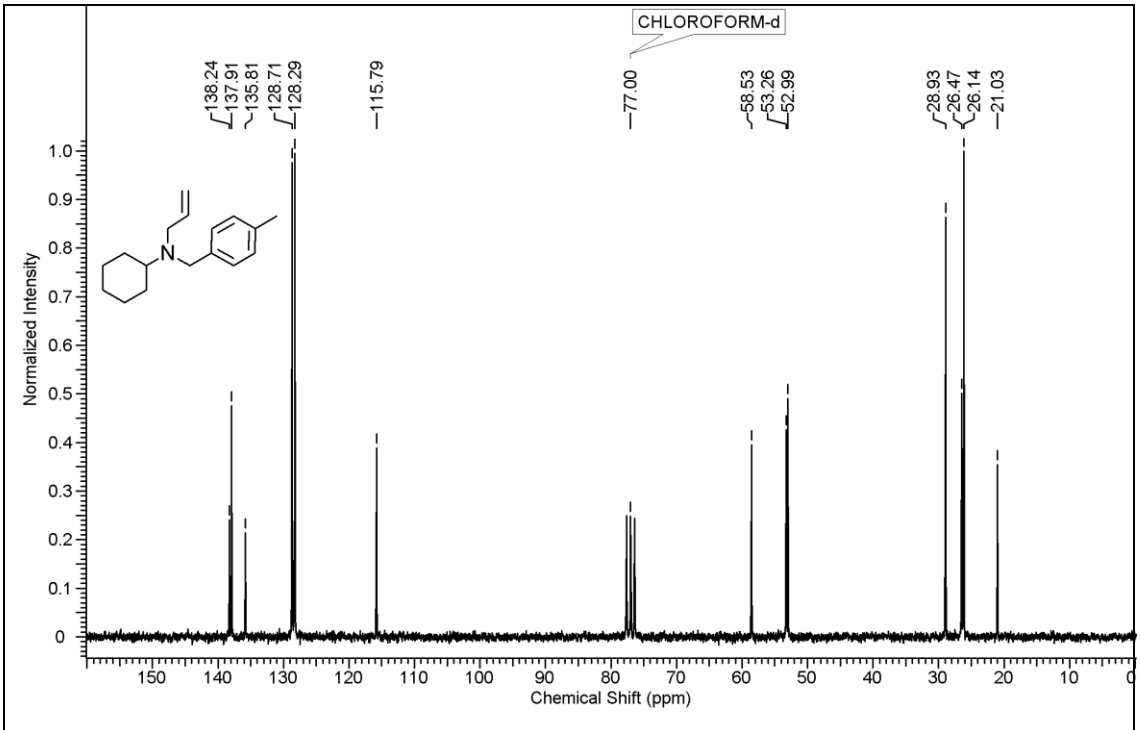
^{1}H-NMR of compound 46 in $CDCl_3$



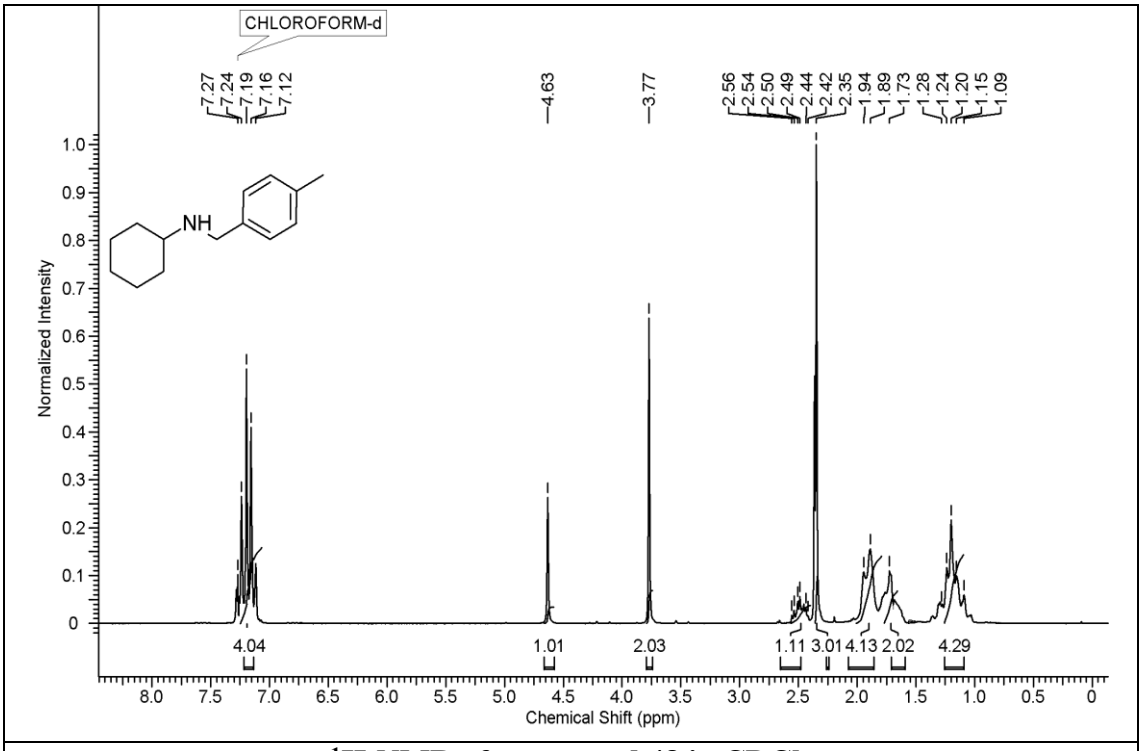
^{13}C-NMR of compound 46 in $CDCl_3$



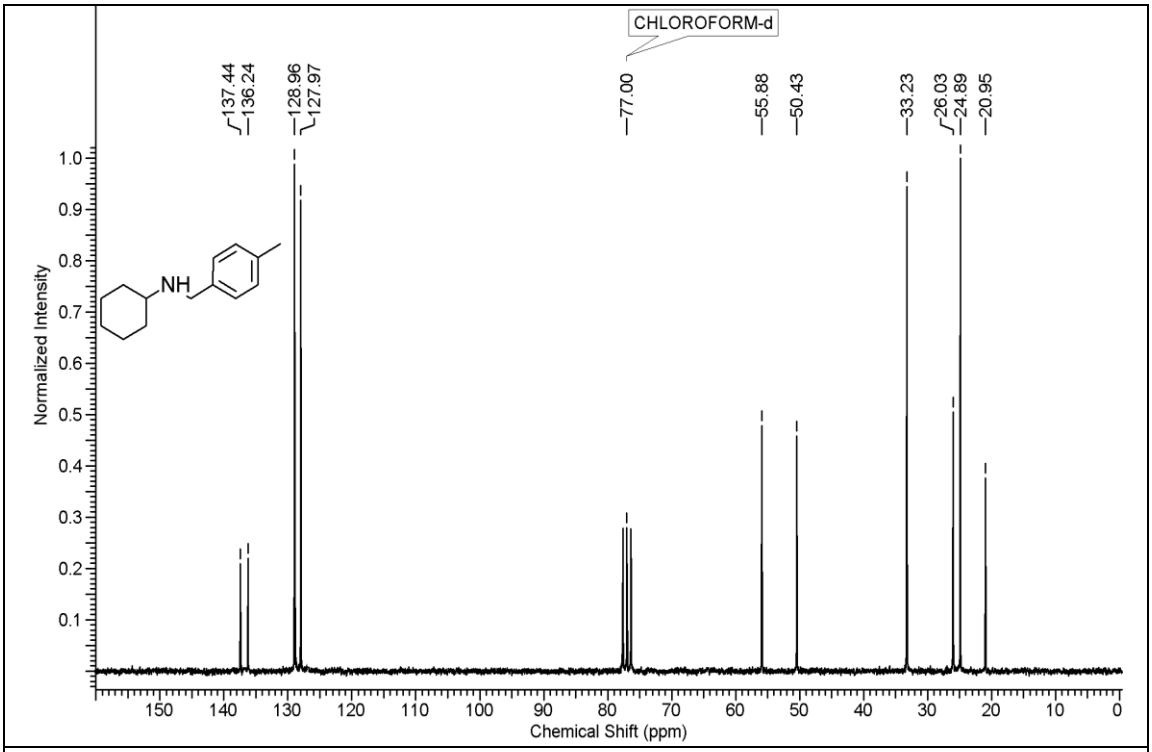
^{1}H-NMR of compound 47 in $CDCl_3$



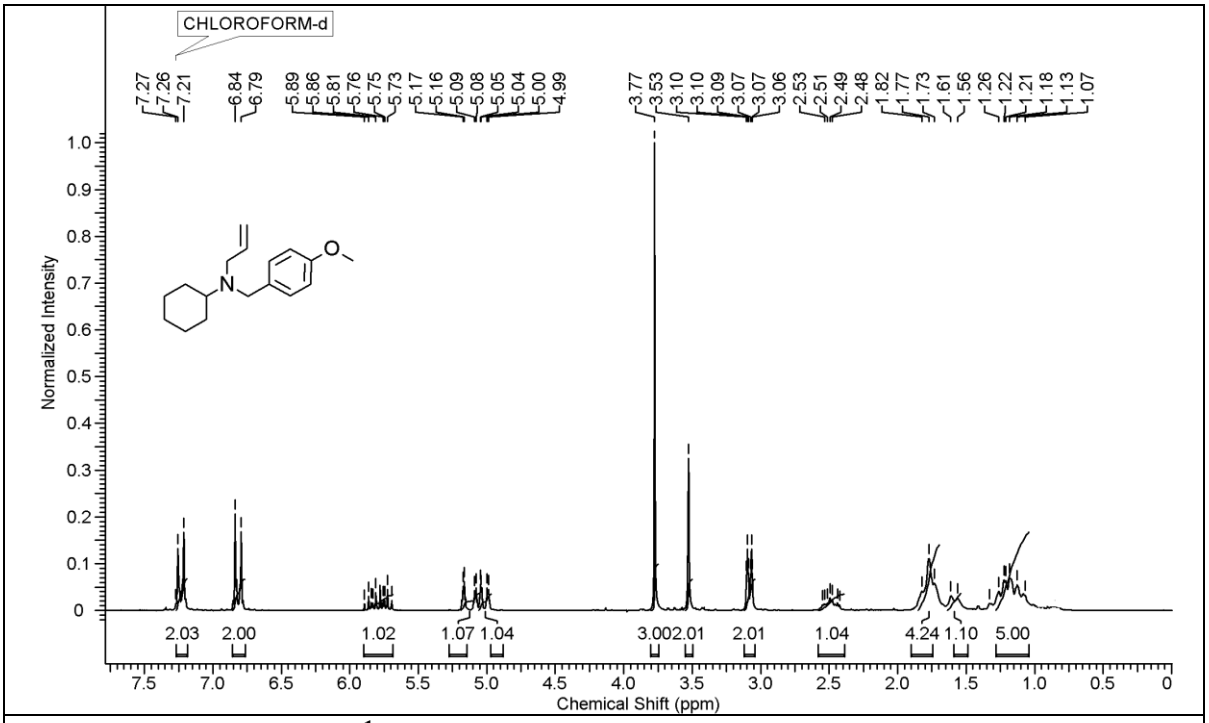
^{13}C-NMR of compound 47 in $CDCl_3$



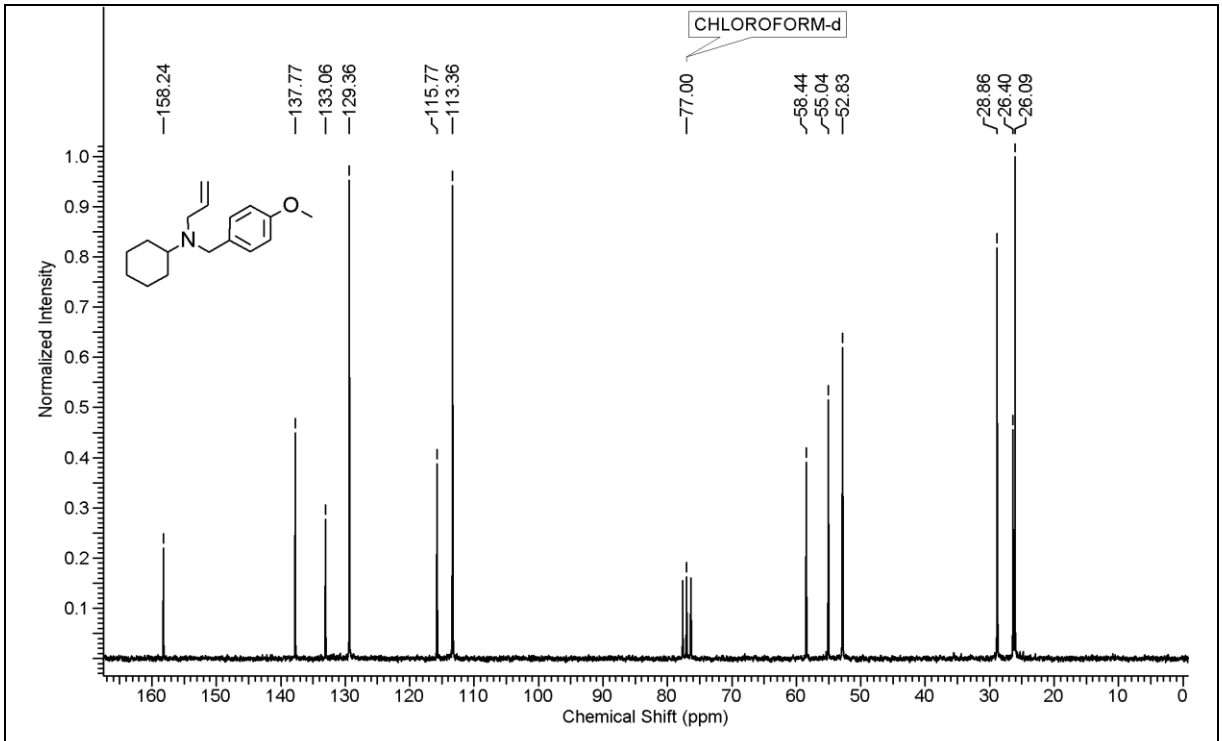
^{1}H-NMR of compound 48 in $CDCl_3$



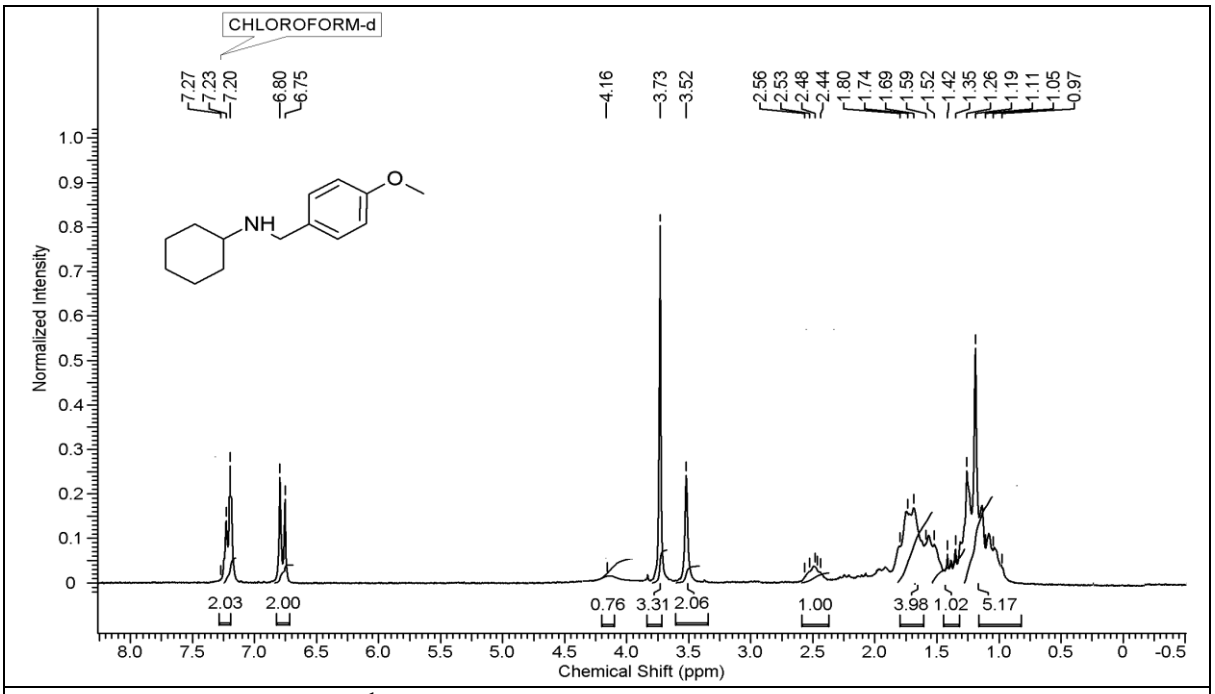
^{13}C-NMR of compound 48 in $CDCl_3$



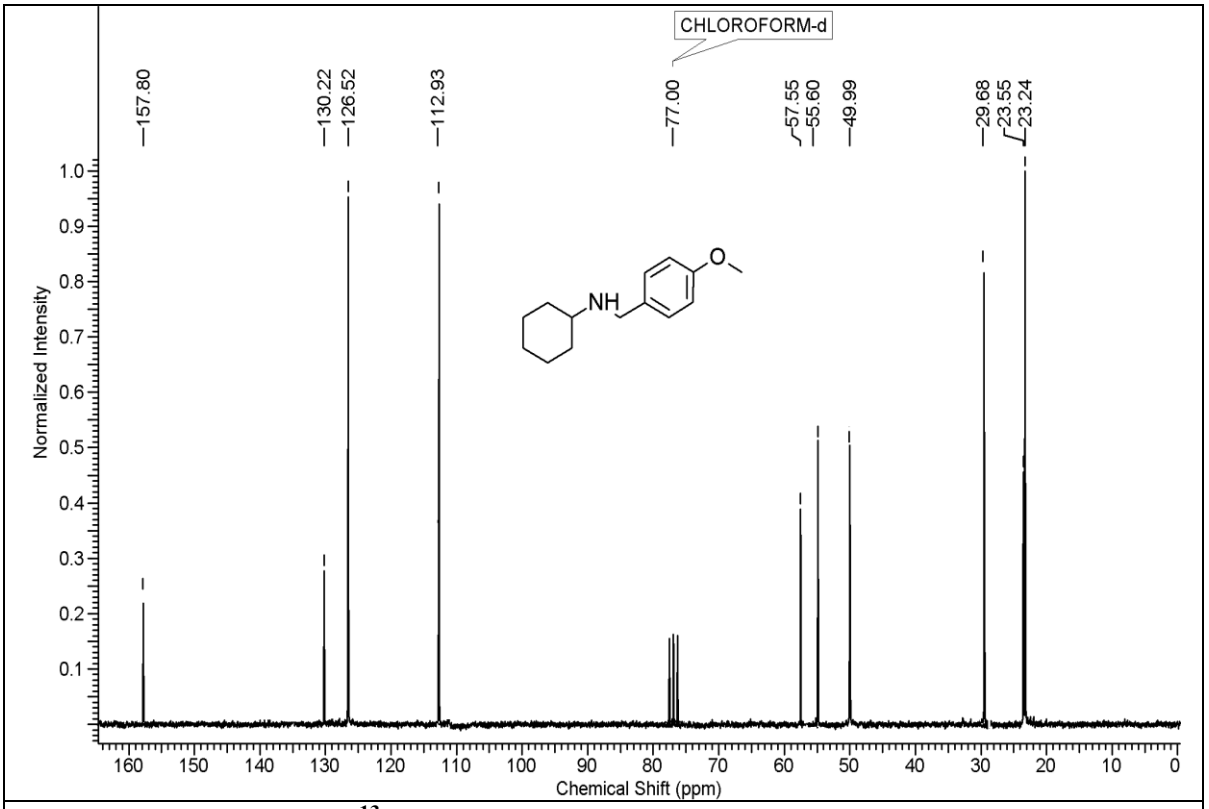
^{1}H-NMR of compound 49 in $CDCl_3$



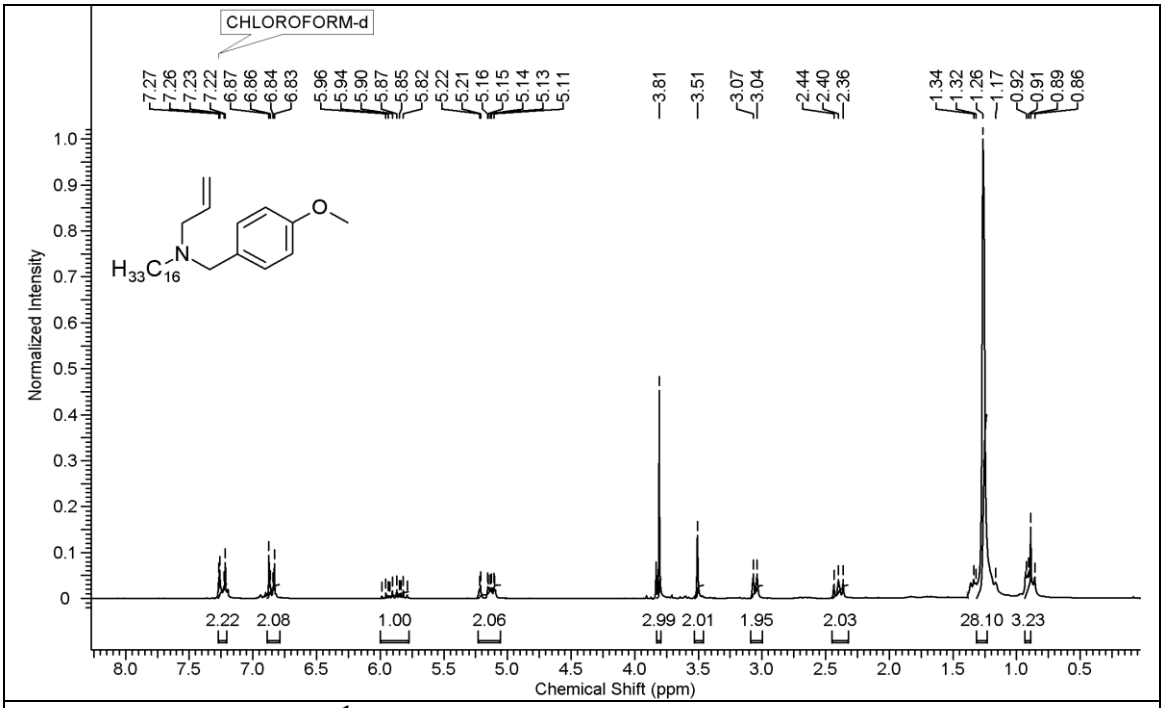
^{13}C-NMR of compound 49 in $CDCl_3$



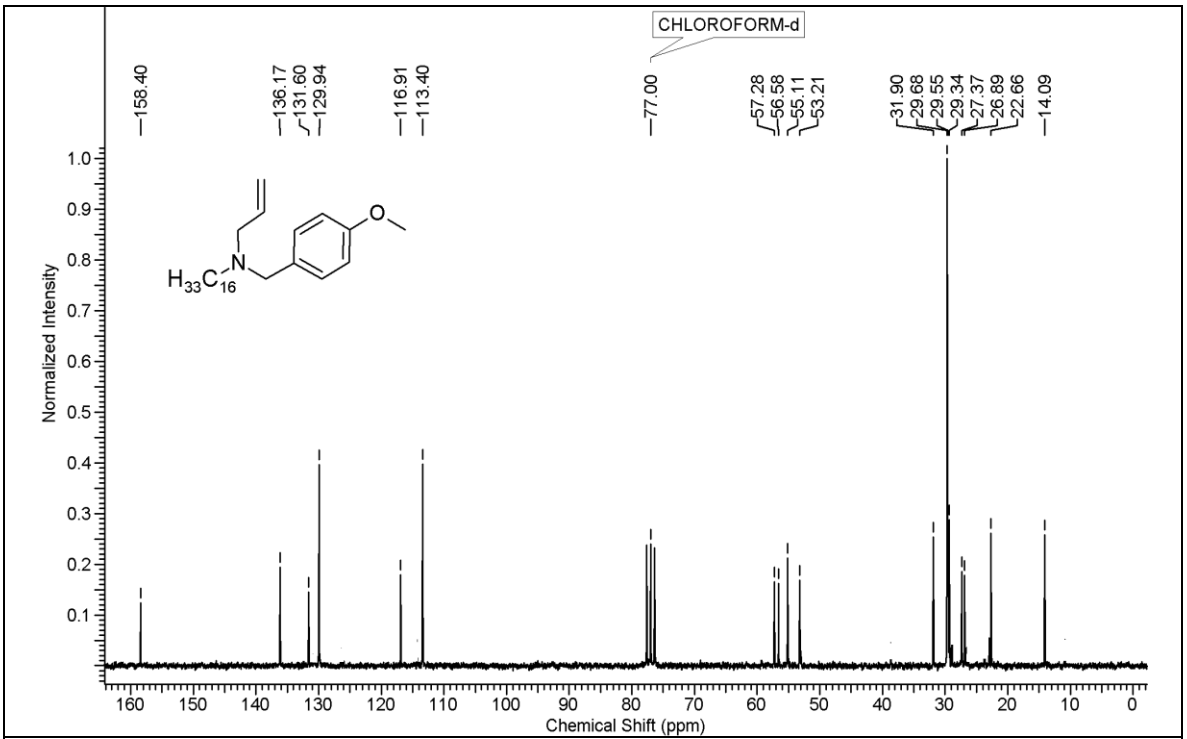
^{1}H-NMR of compound 50 in $CDCl_3$



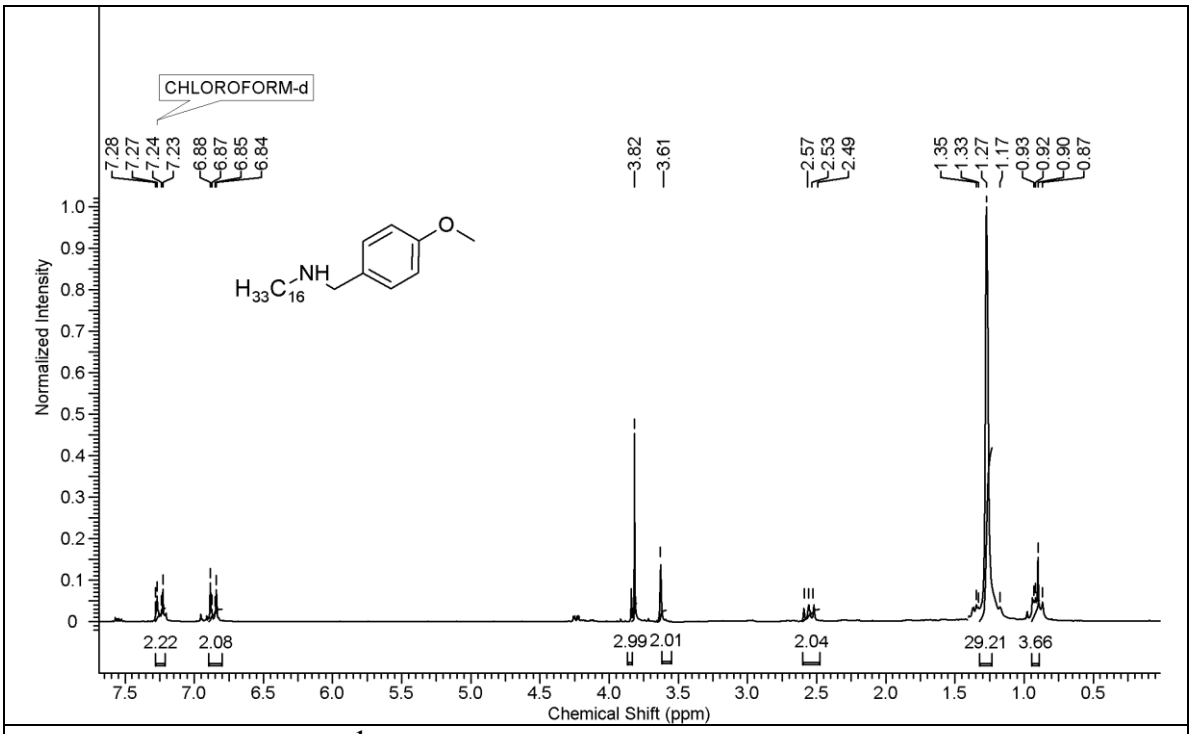
^{13}C-NMR of compound 50 in $CDCl_3$



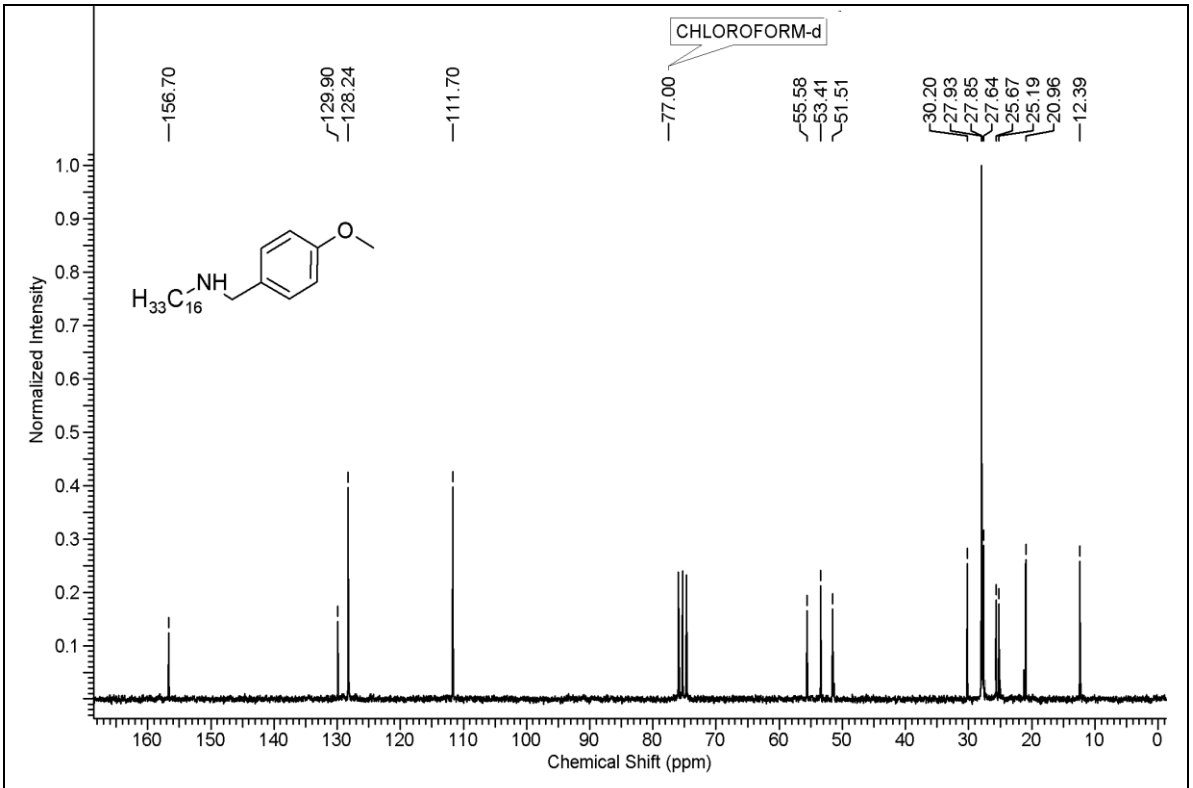
^{1}H-NMR of compound 51 in $CDCl_3$



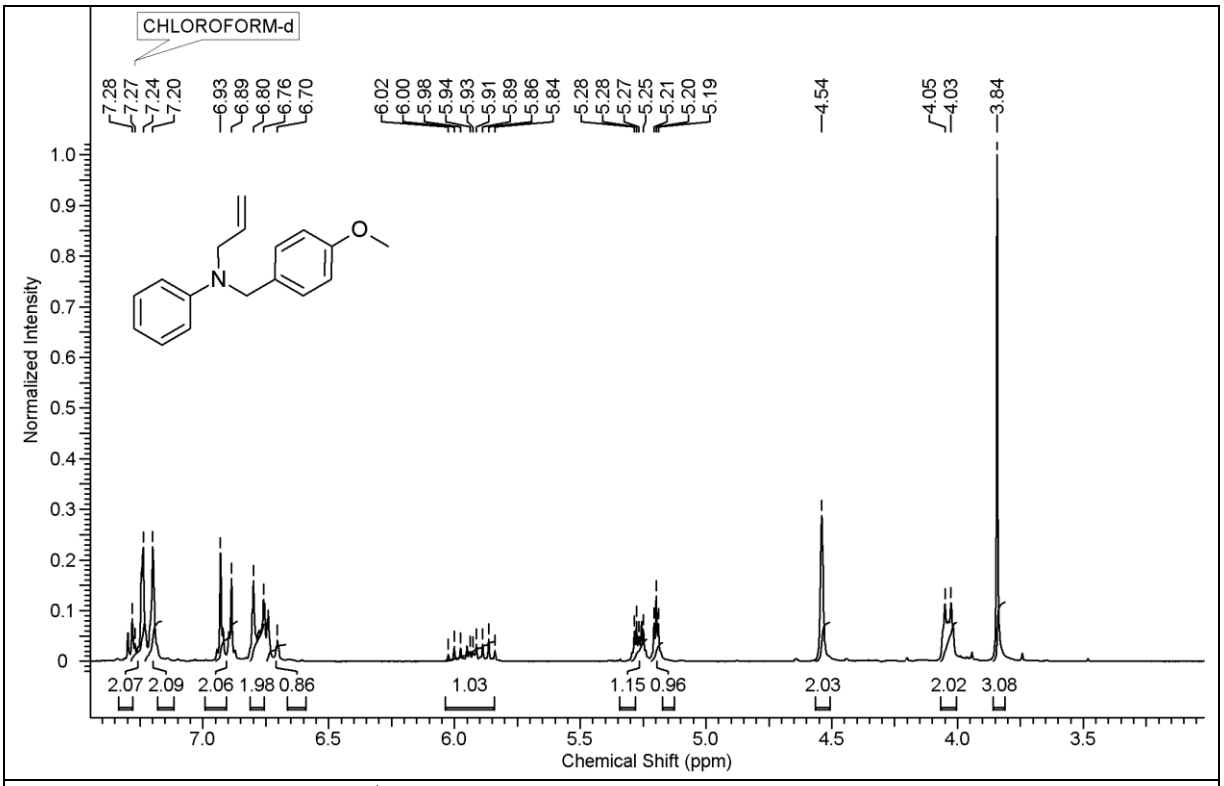
^{13}C-NMR of compound 51 in $CDCl_3$



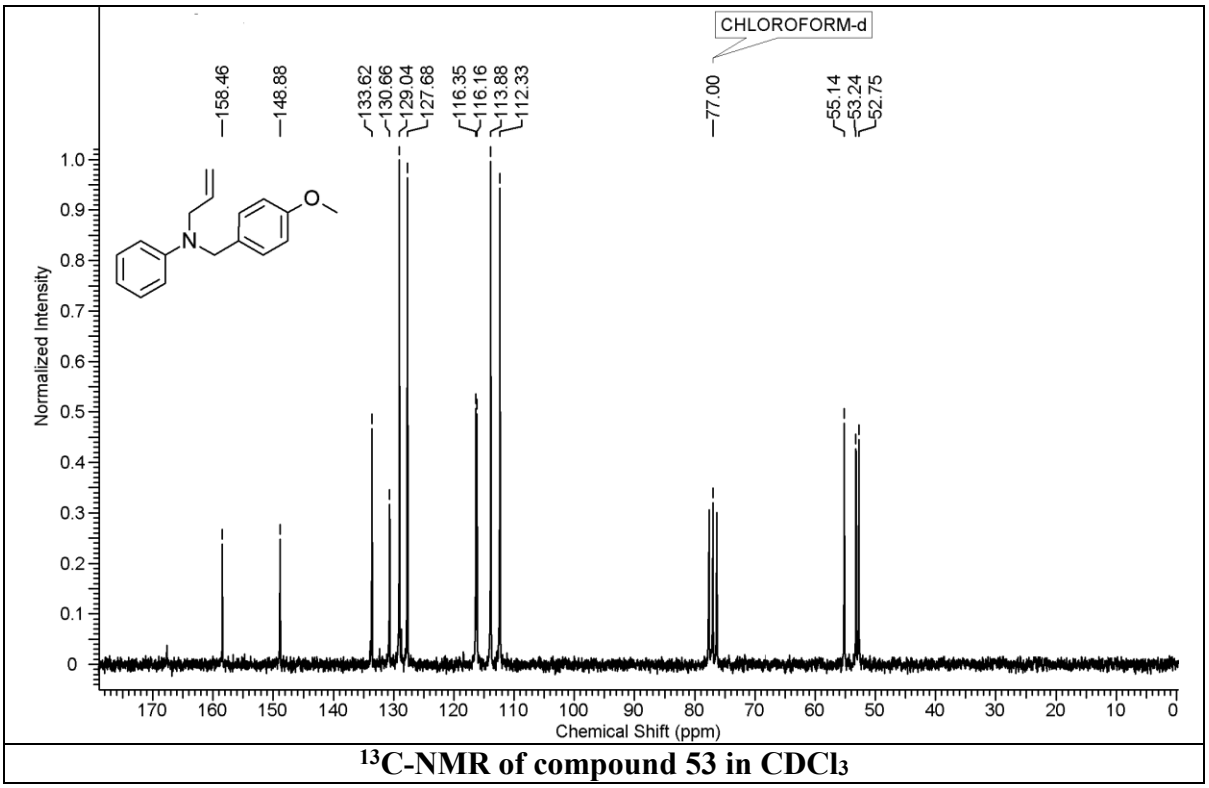
^{1}H-NMR of compound 52 in $CDCl_3$



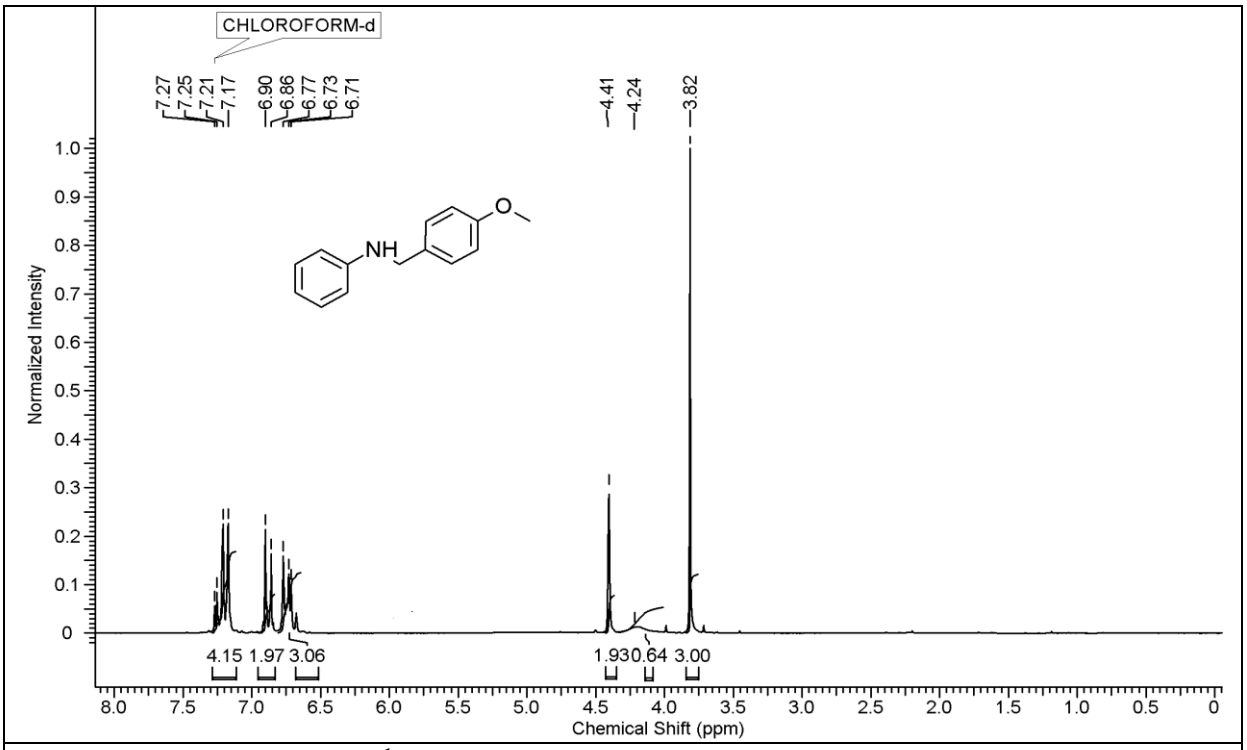
^{13}C-NMR of compound 52 in $CDCl_3$



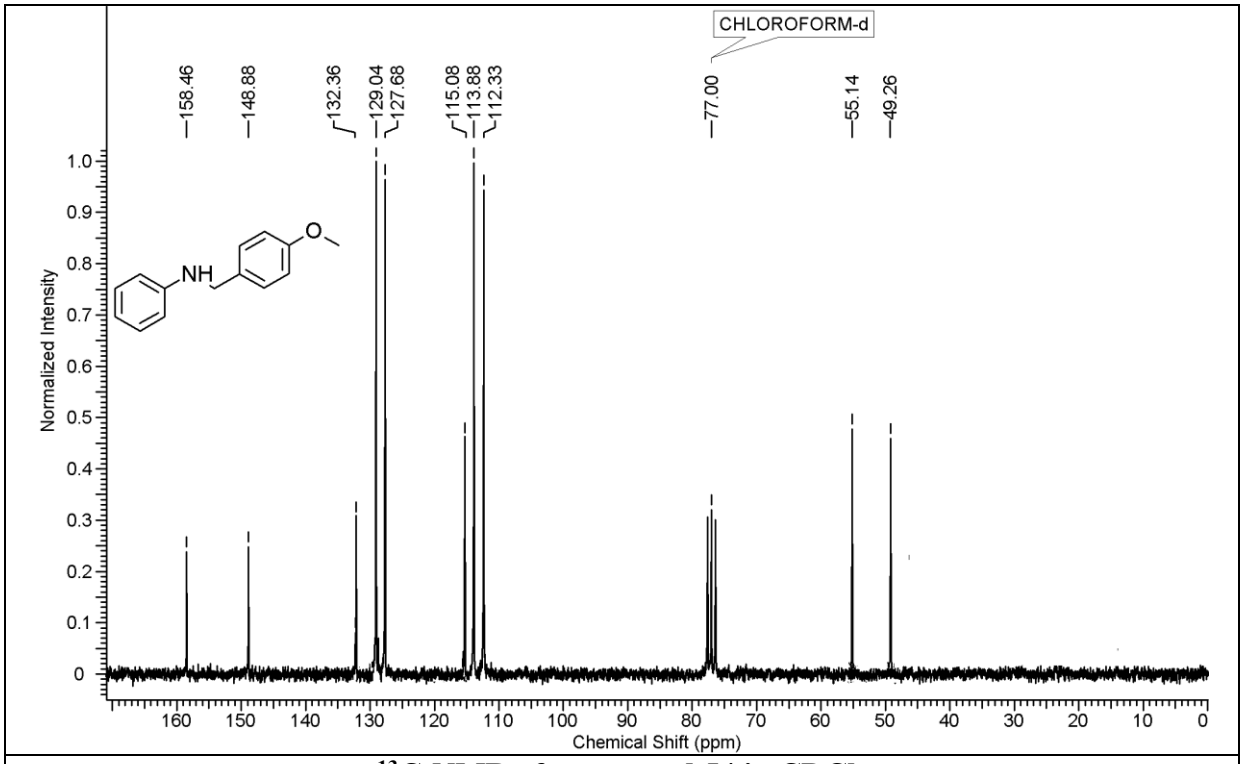
^{1}H-NMR of compound 53 in $CDCl_3$



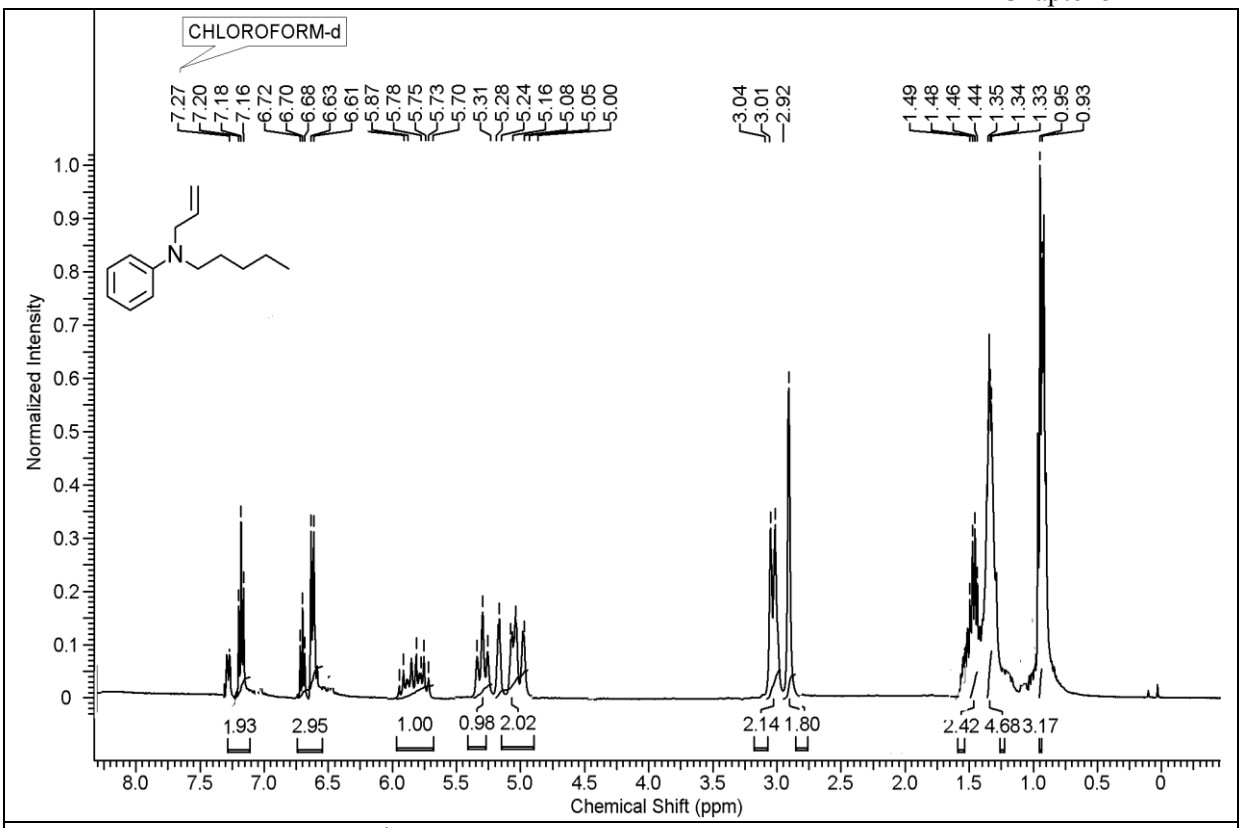
^{13}C-NMR of compound 53 in $CDCl_3$



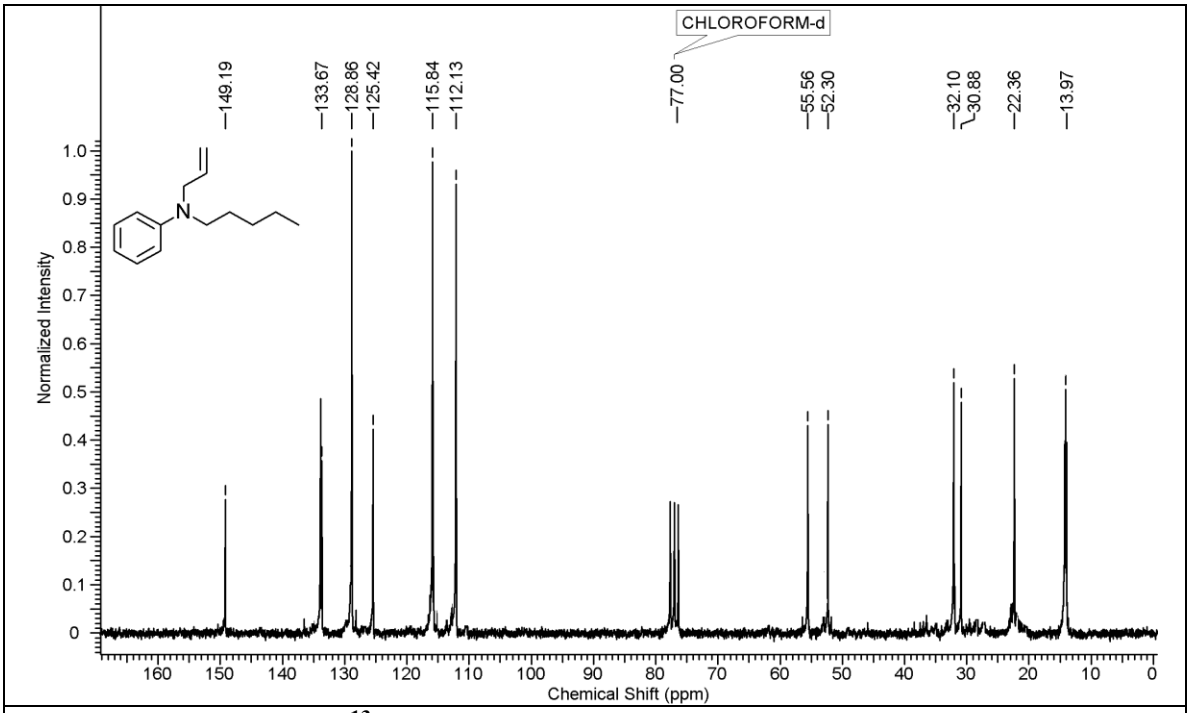
^{1}H-NMR of compound 54 in $CDCl_3$



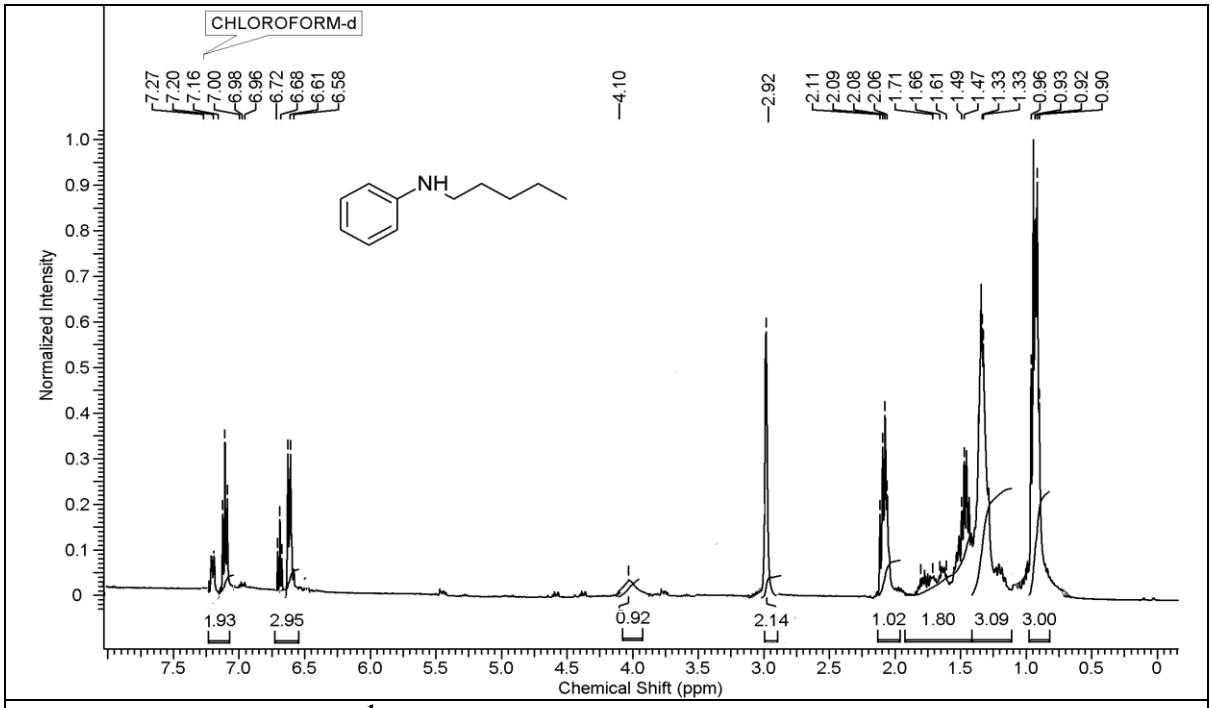
^{13}C-NMR of compound 54 in $CDCl_3$



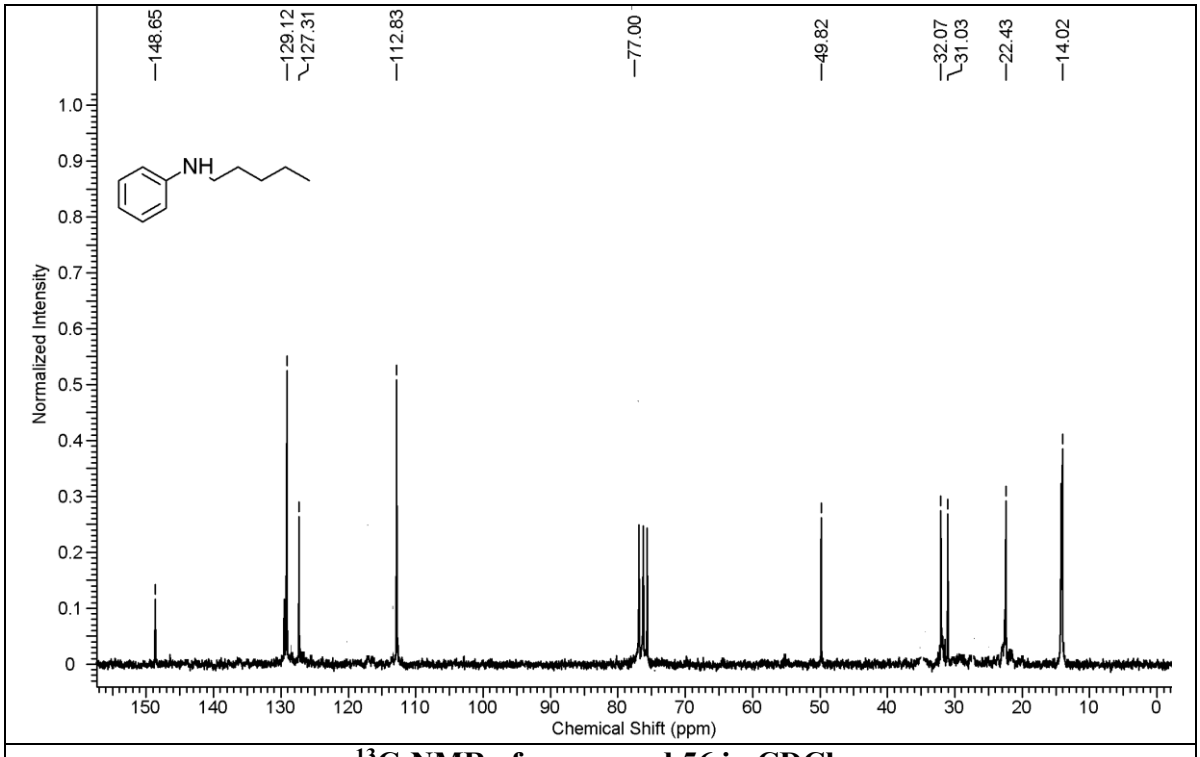
^{1}H-NMR of compound 55 in $CDCl_3$



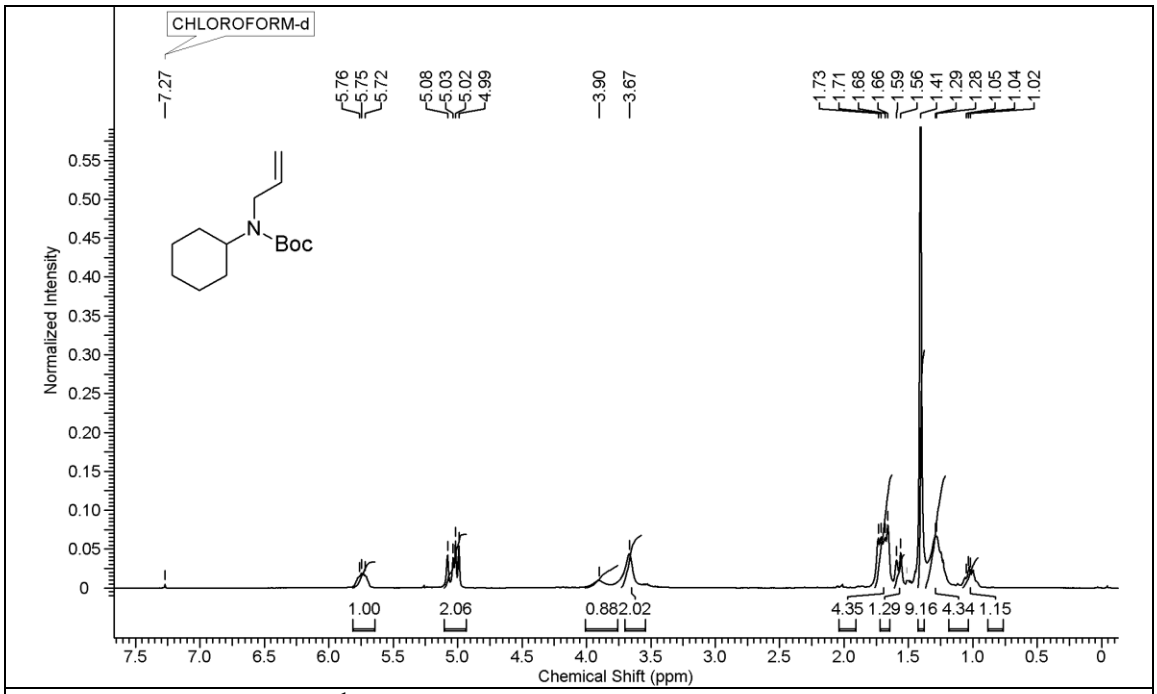
^{13}C-NMR of compound 55 in $CDCl_3$



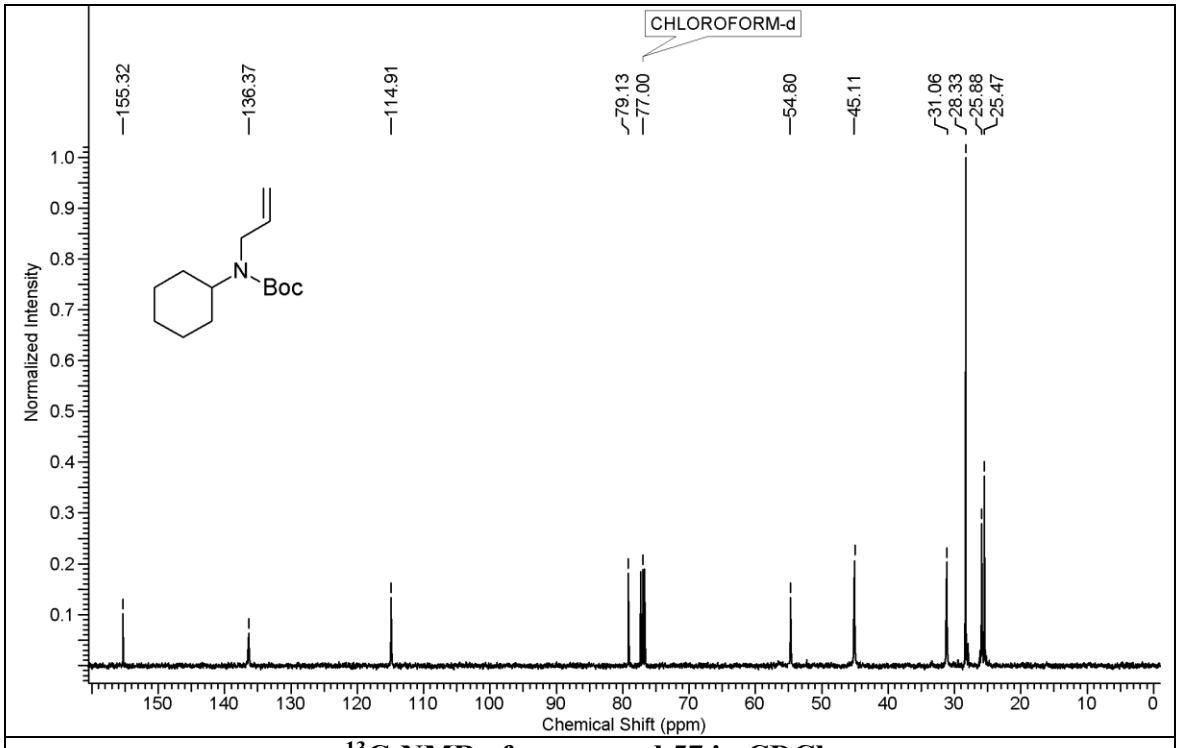
^{1}H-NMR of compound 56 in $CDCl_3$



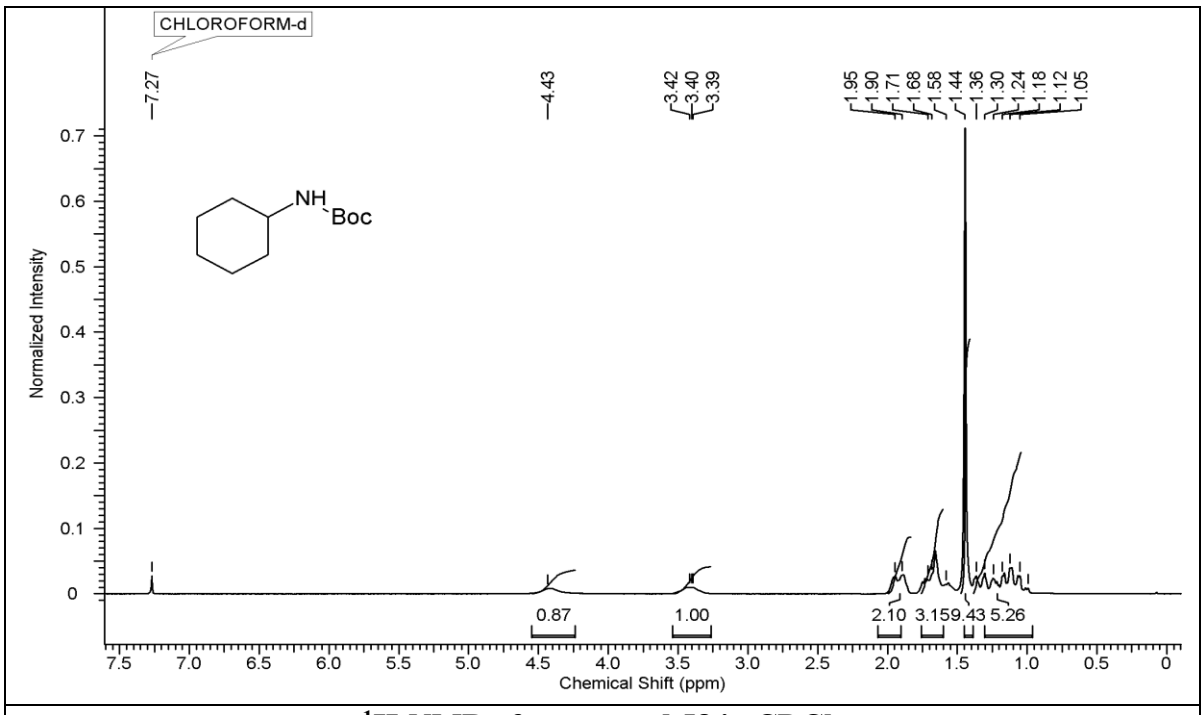
^{13}C-NMR of compound 56 in $CDCl_3$



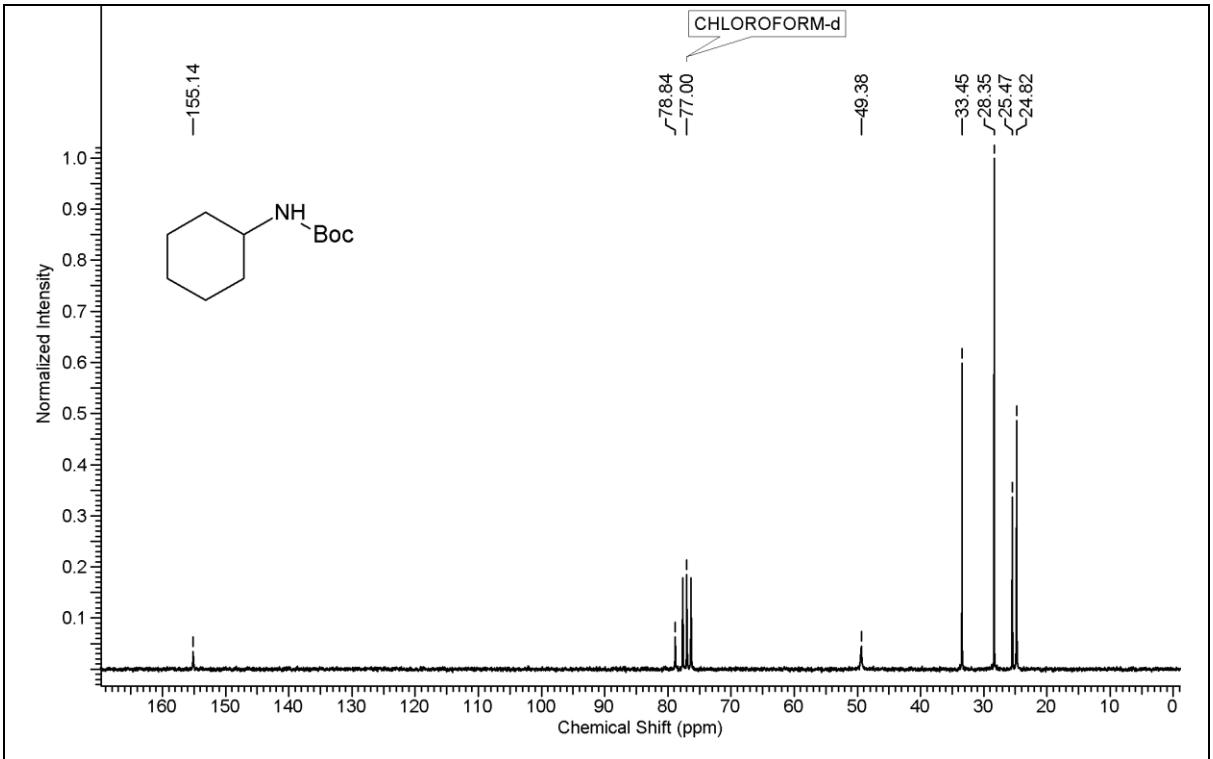
^{1}H-NMR of compound 57 in $CDCl_3$



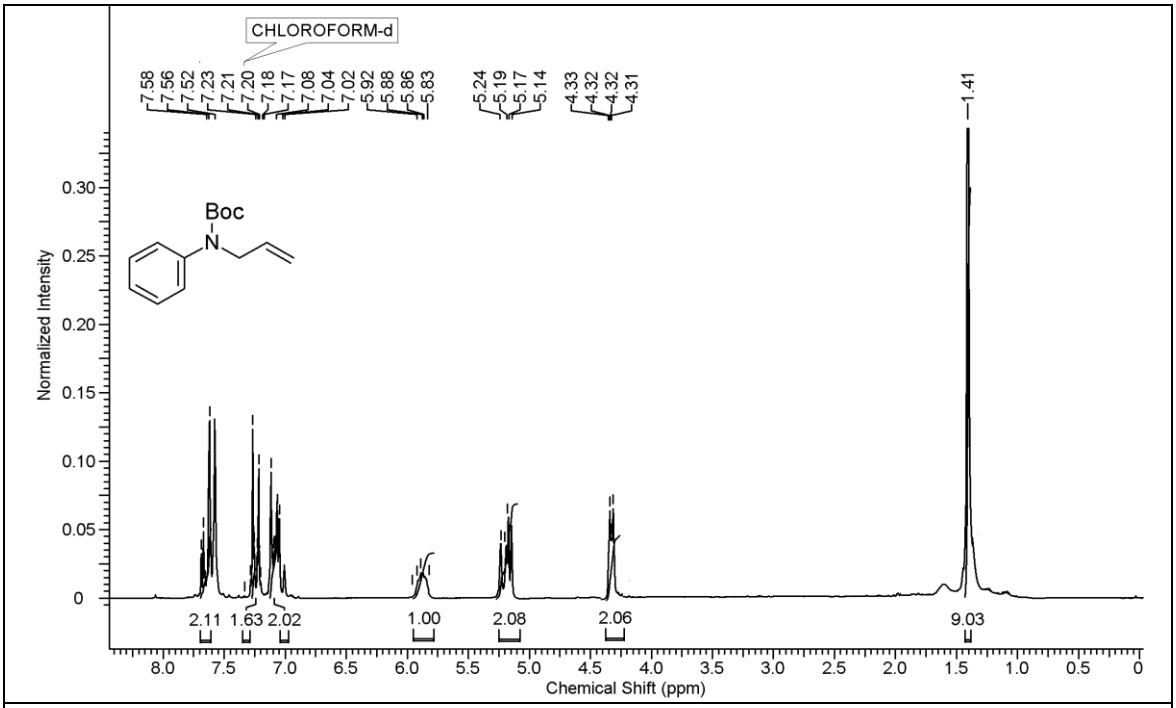
^{13}C-NMR of compound 57 in $CDCl_3$



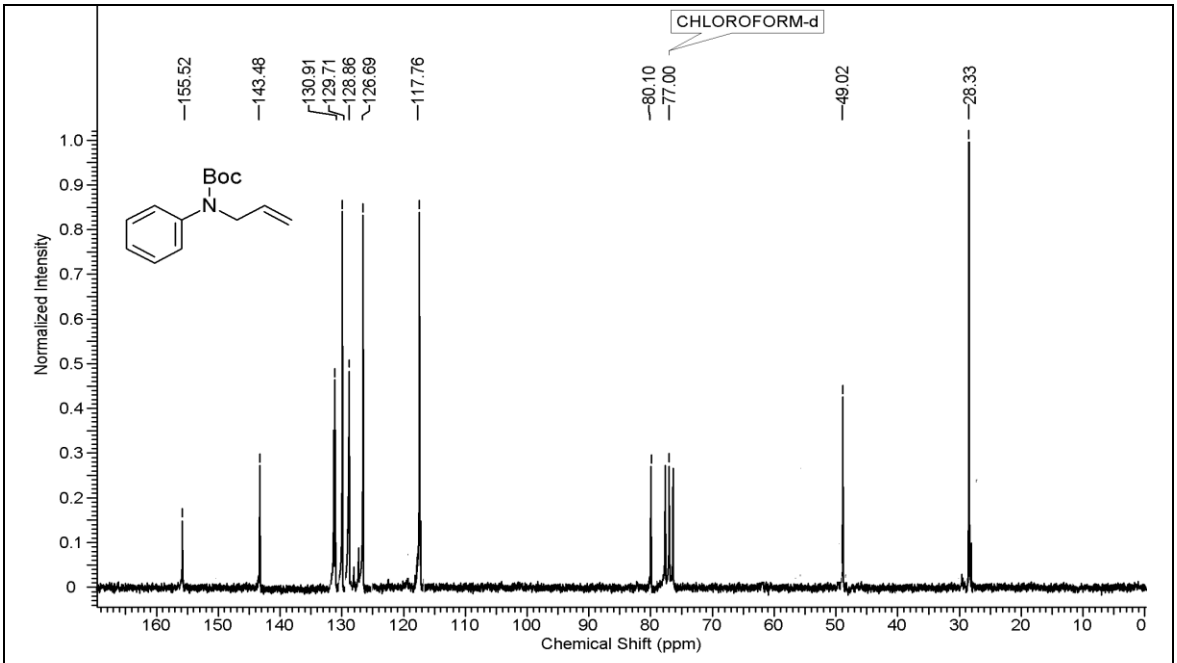
^{1}H-NMR of compound 58 in $CDCl_3$



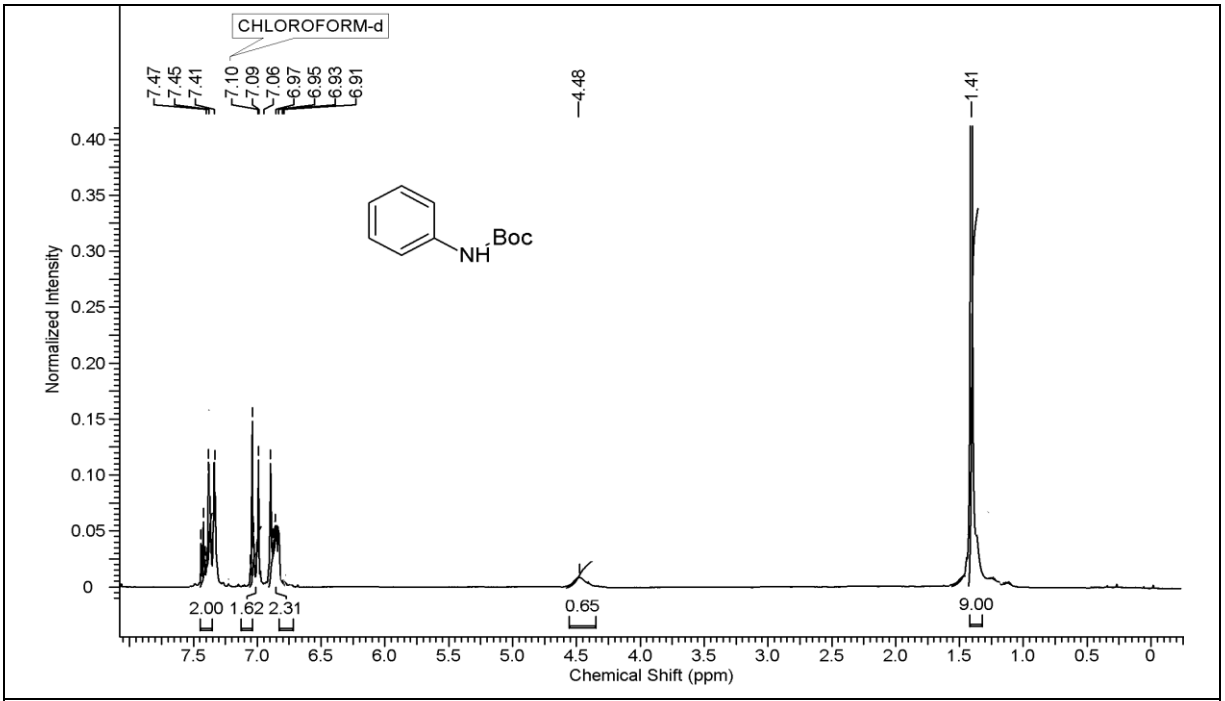
^{13}C-NMR of compound 58 in $CDCl_3$



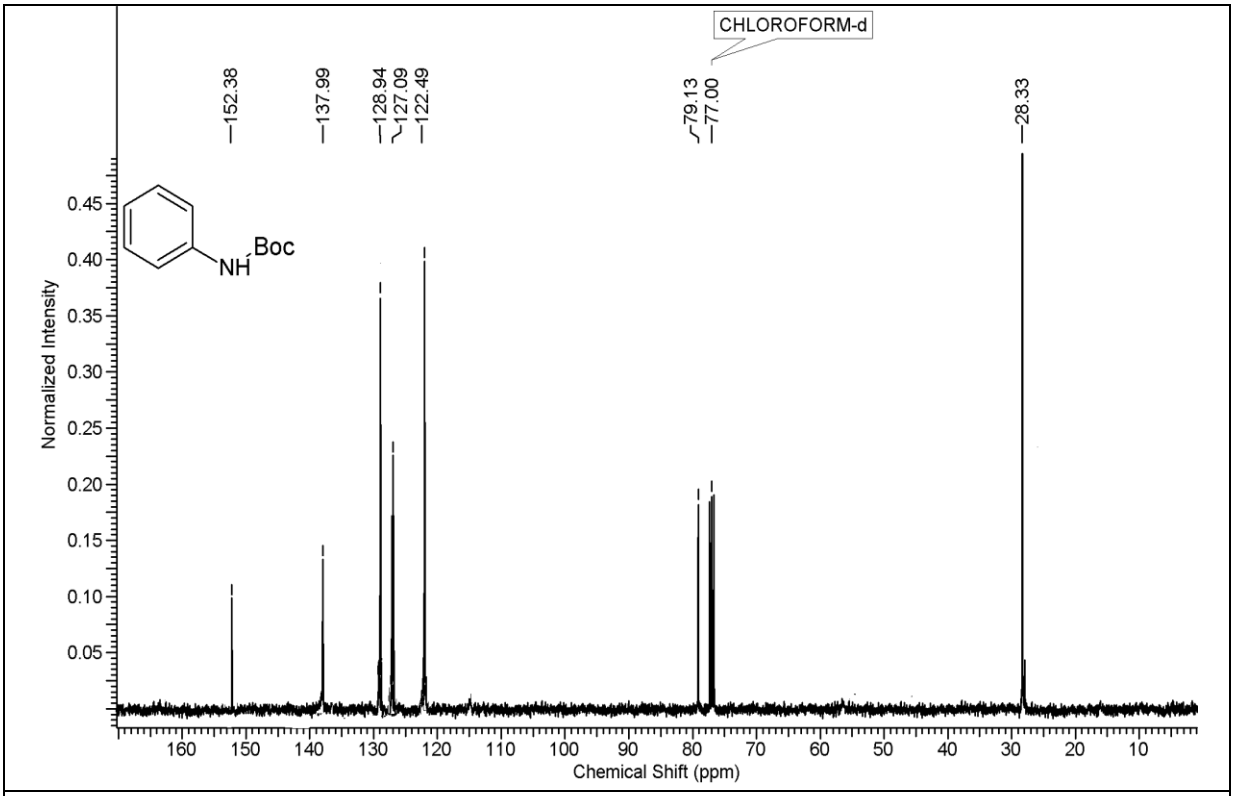
^{1}H-NMR of compound 59 in $CDCl_3$



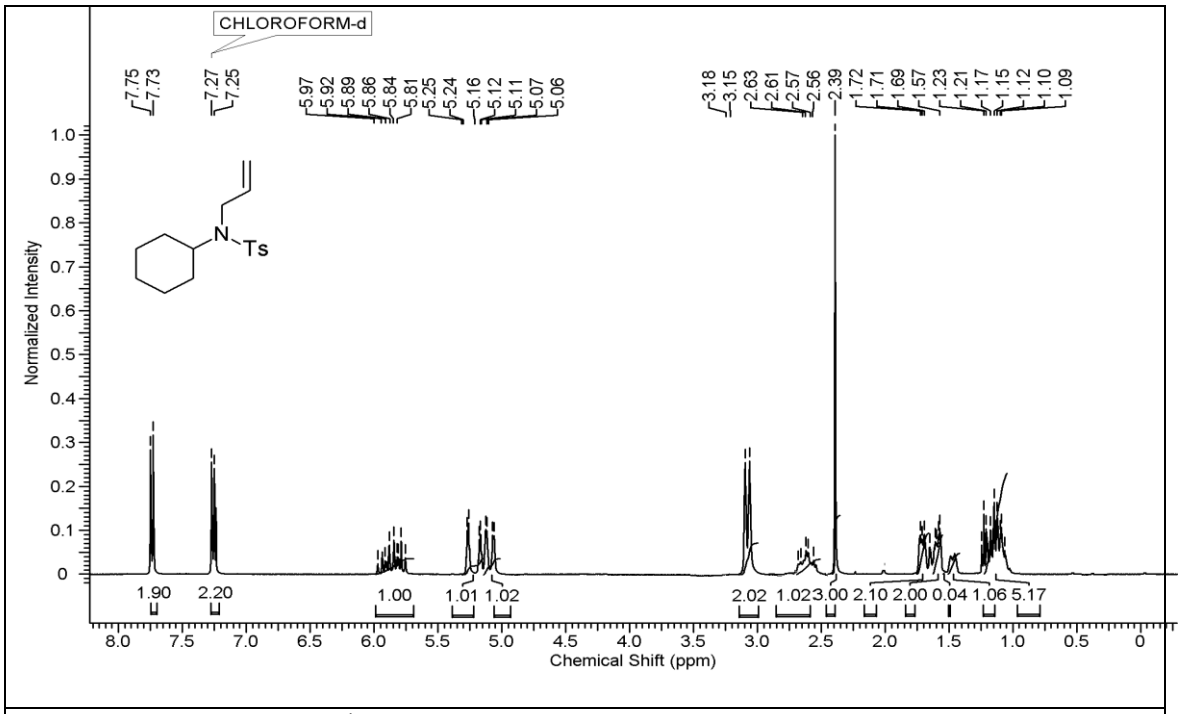
^{13}C-NMR of compound 59 in $CDCl_3$



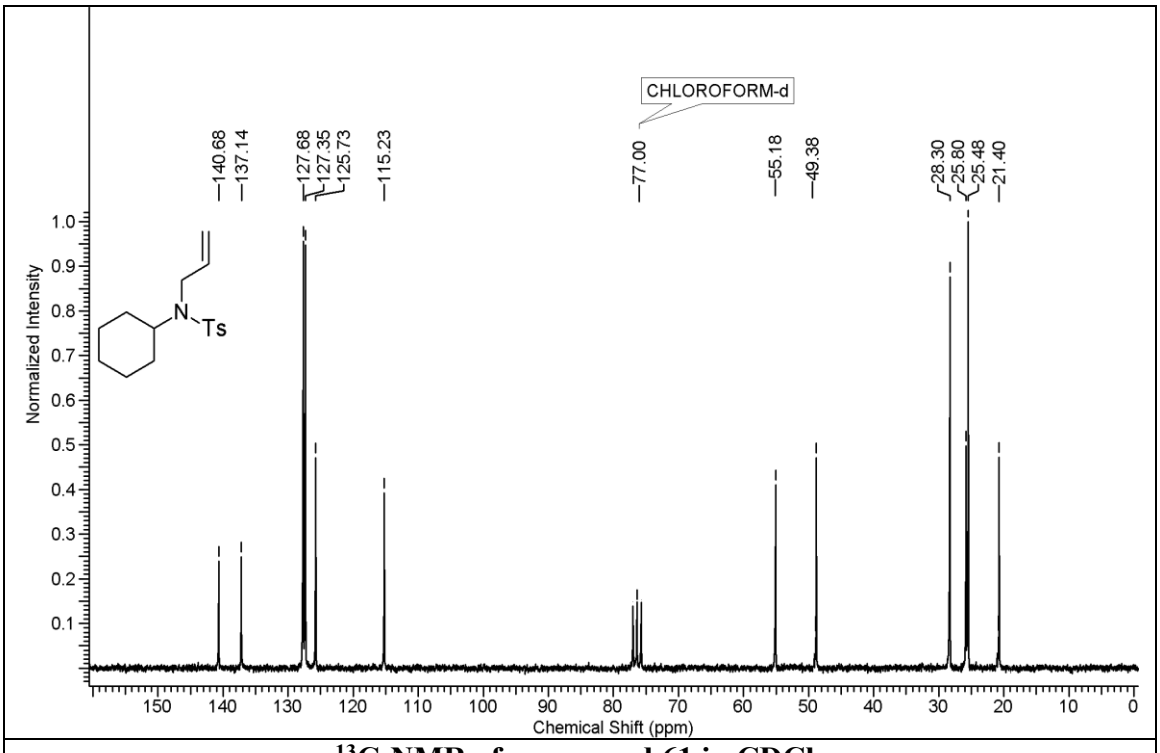
^{1}H-NMR of compound 60 in $CDCl_3$



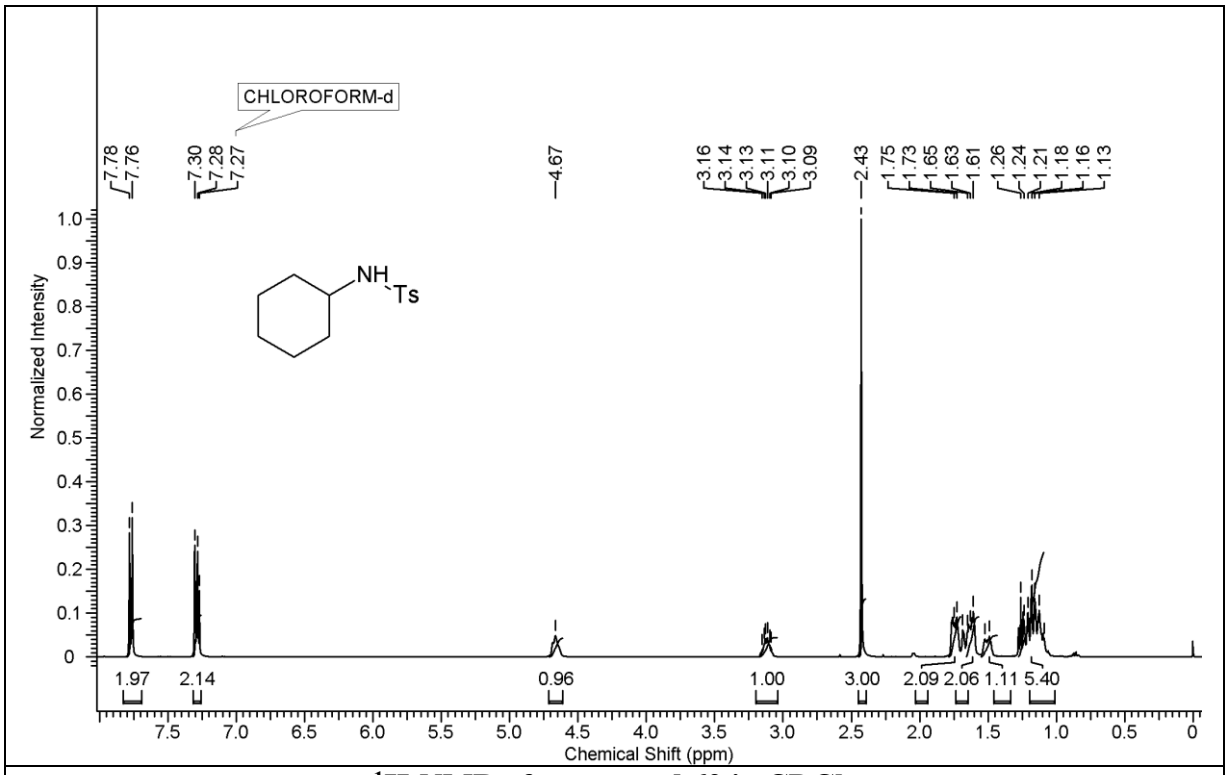
^{13}C-NMR of compound 60 in $CDCl_3$



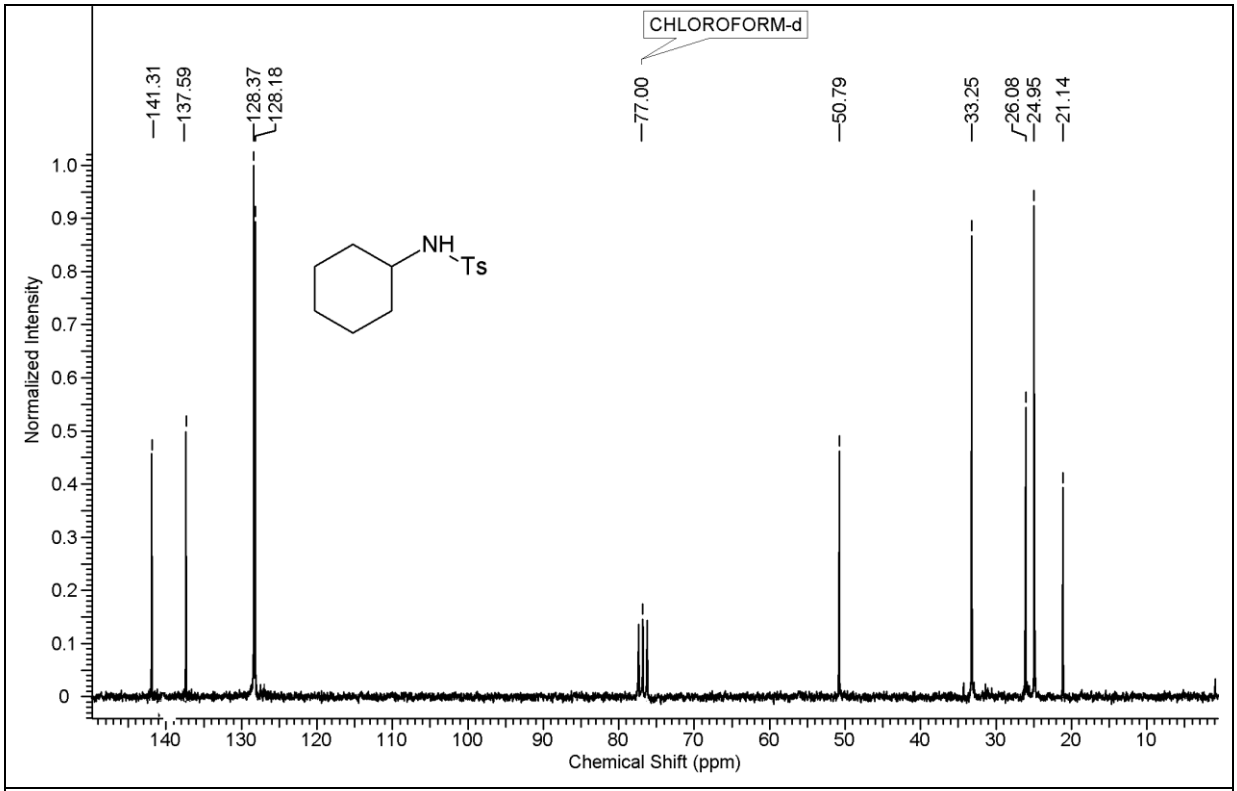
^{1}H-NMR of compound 61 in $CDCl_3$



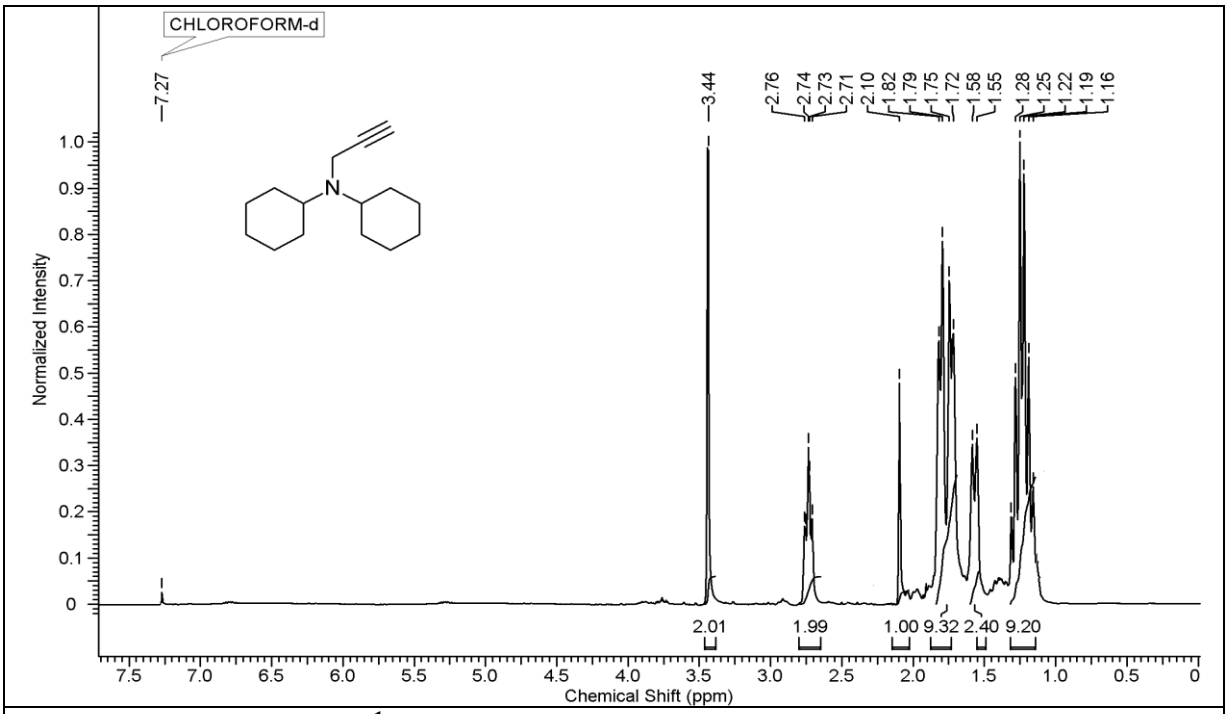
^{13}C-NMR of compound 61 in $CDCl_3$



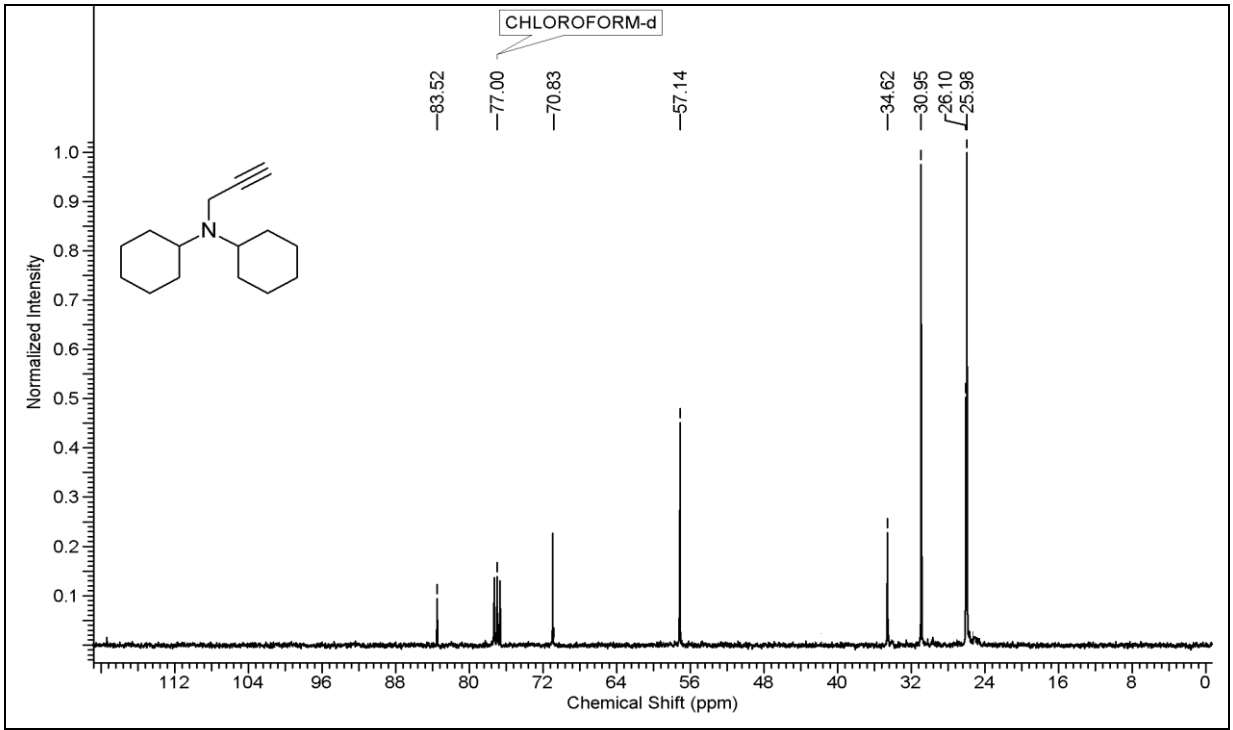
^{1}H-NMR of compound 62 in $CDCl_3$



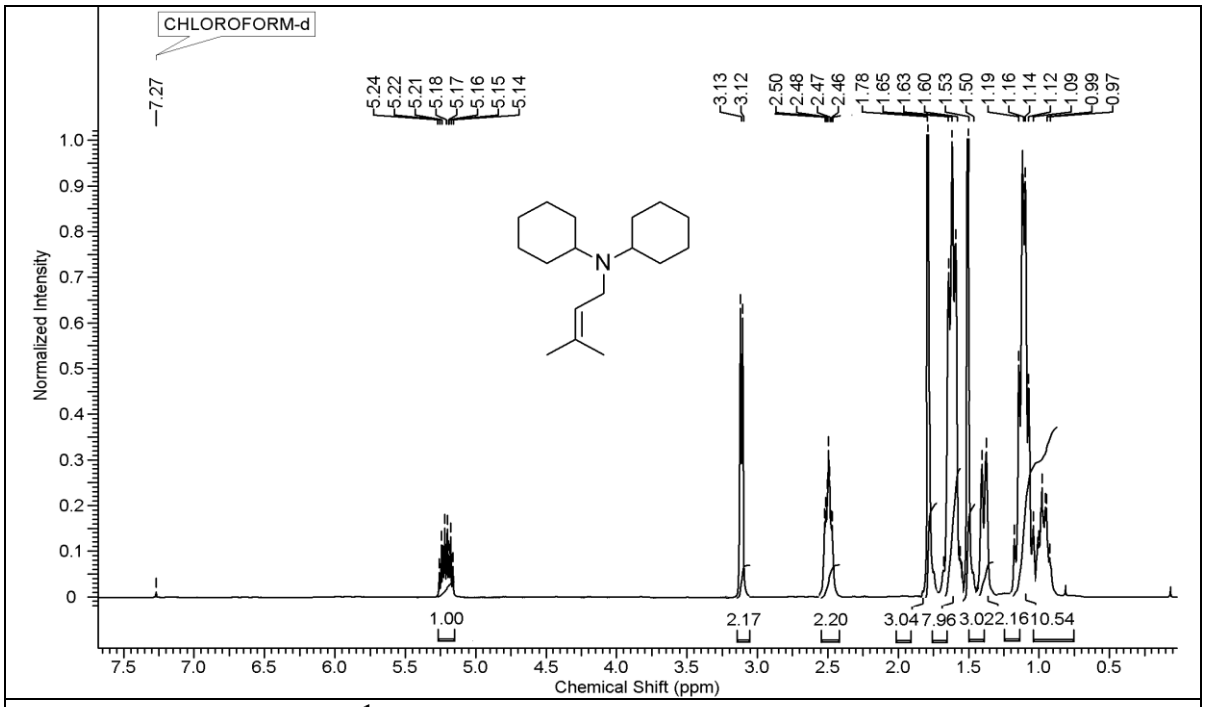
^{13}C-NMR of compound 62 in $CDCl_3$



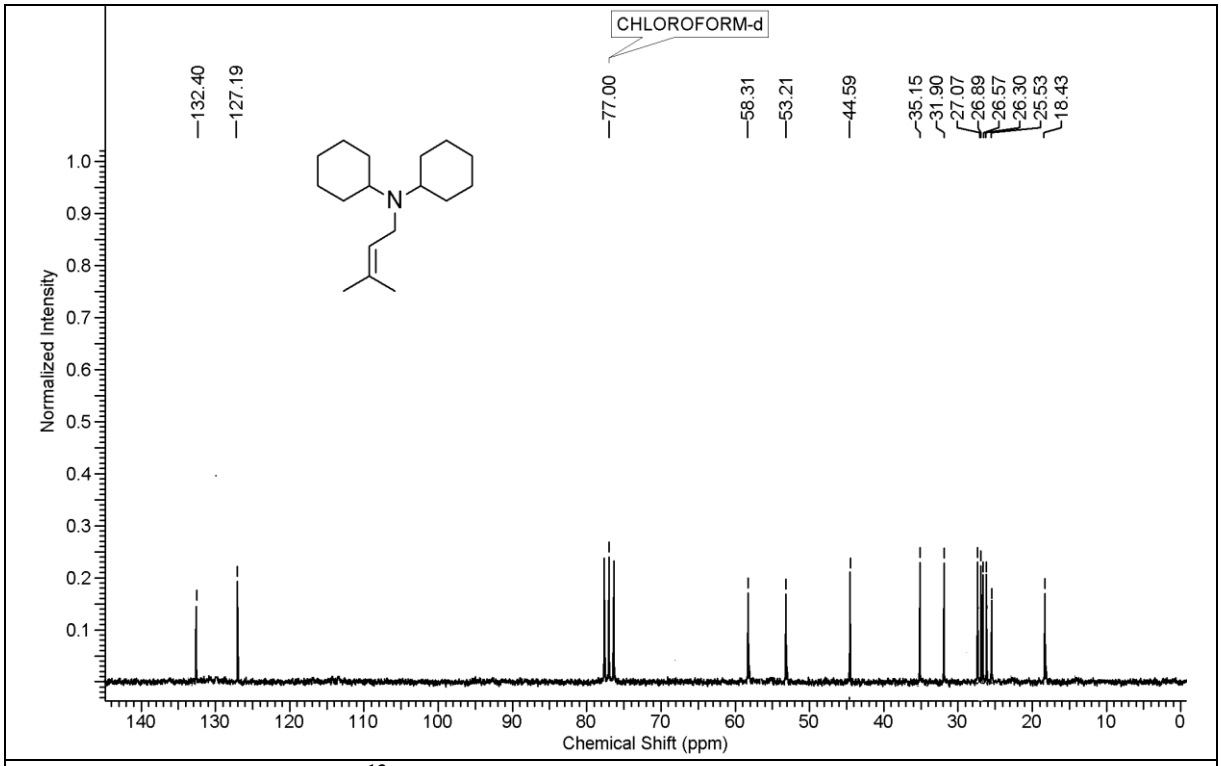
^{1}H-NMR of compound 63 in $CDCl_3$



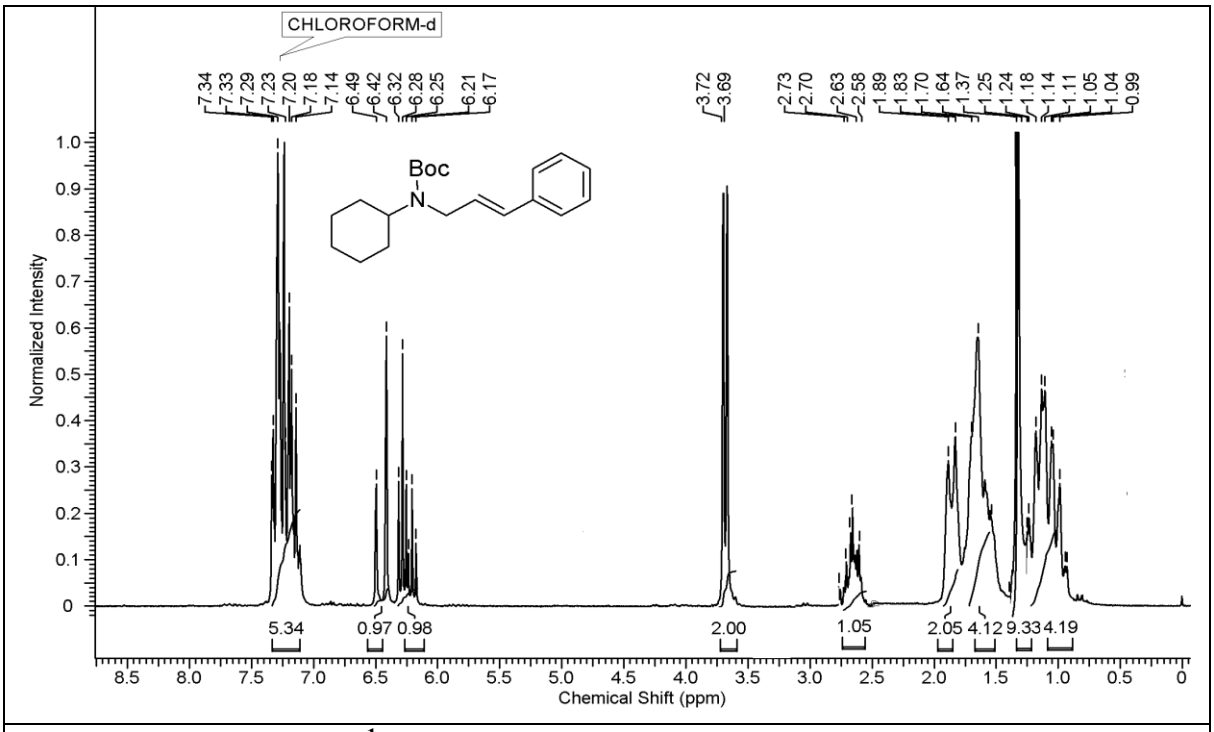
^{13}C-NMR of compound 63 in $CDCl_3$



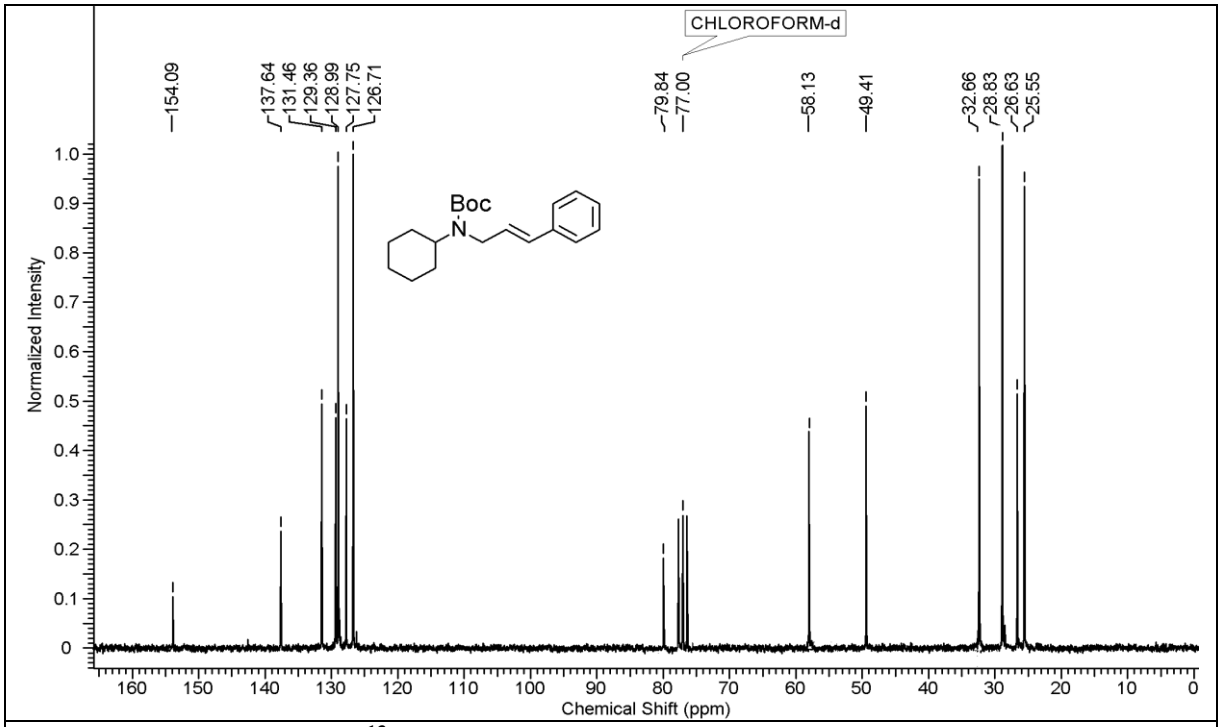
^{1}H-NMR of compound 64 in $CDCl_3$



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



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



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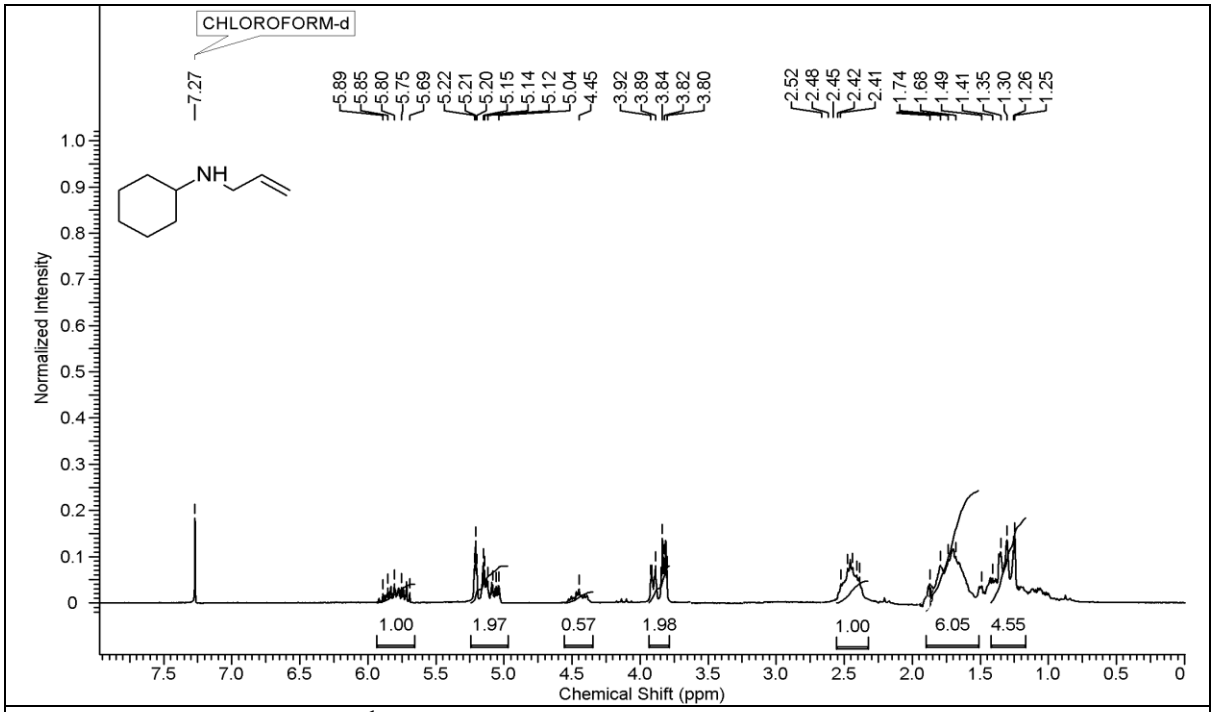
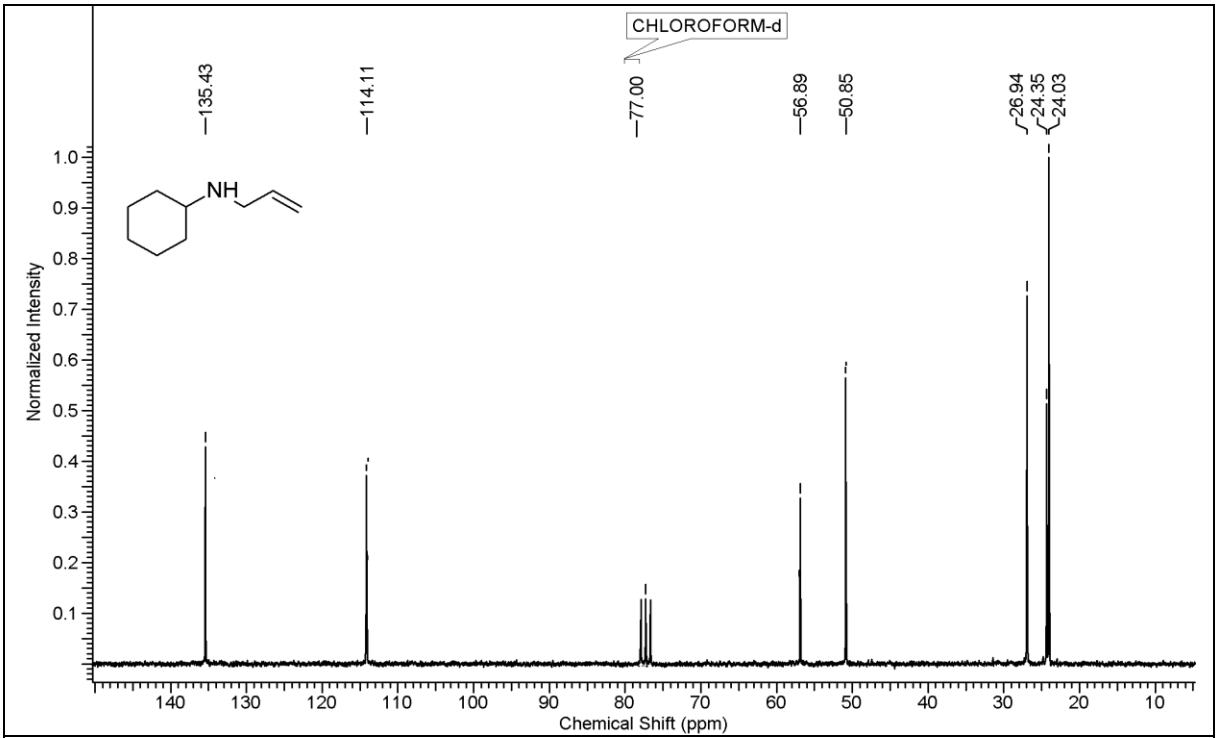
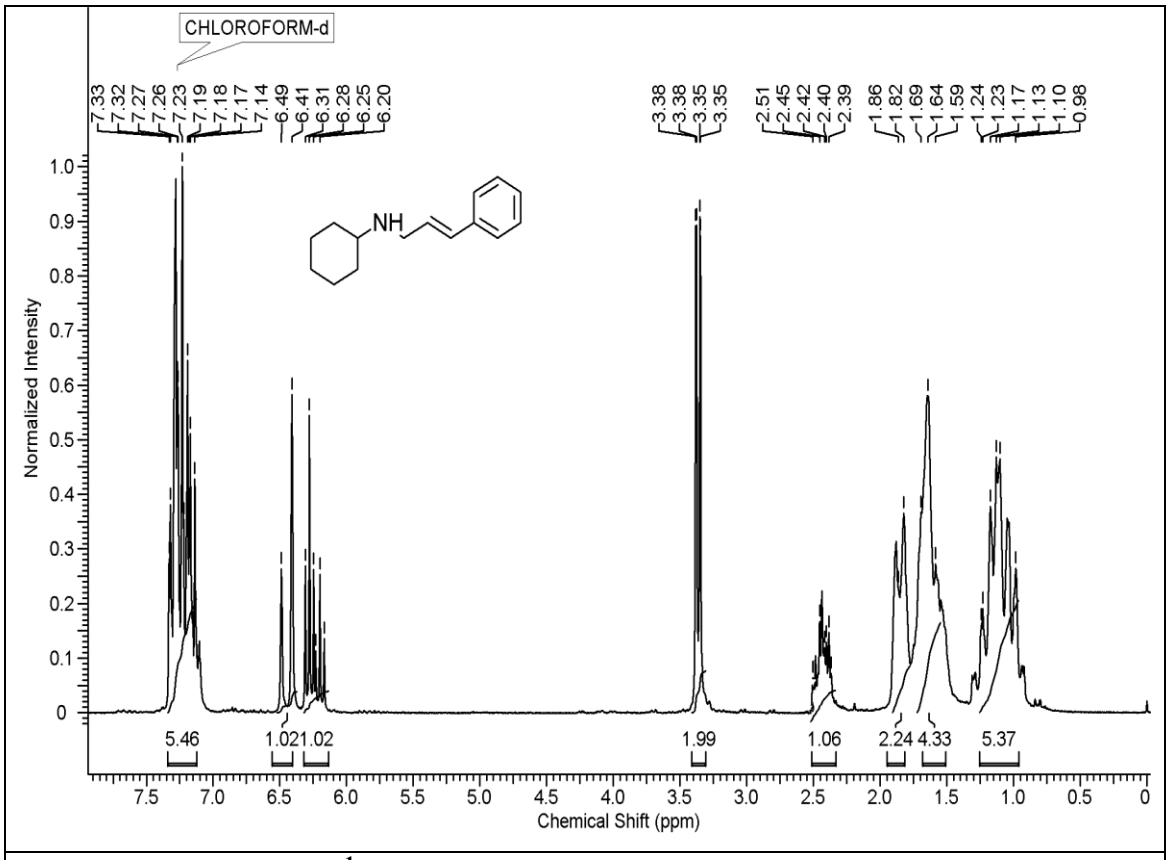


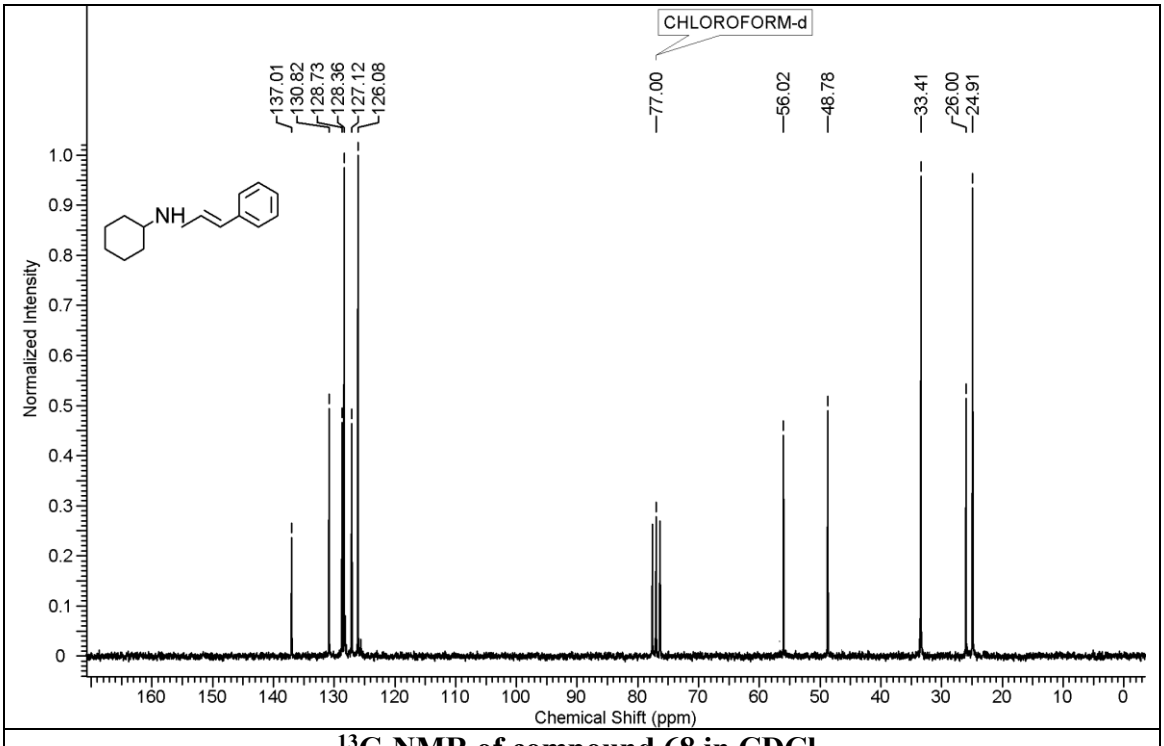
^{1}H-NMR of compound 66 in $CDCl_3$



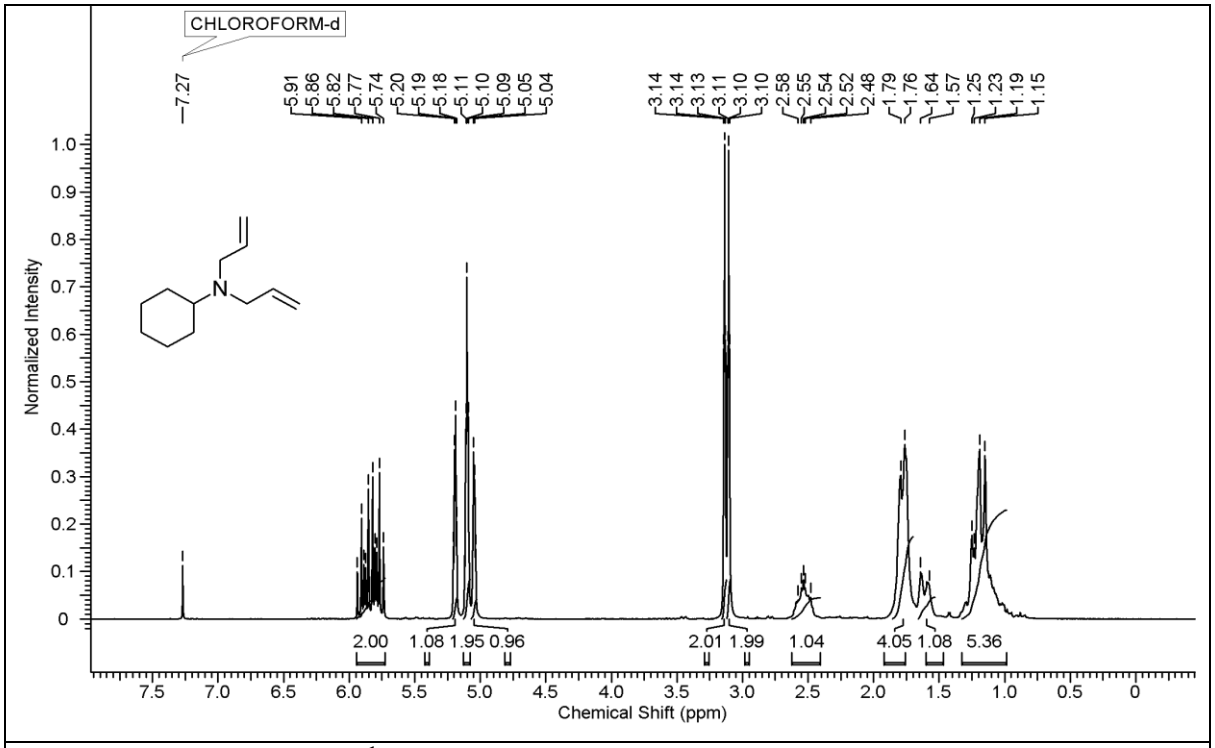
^{13}C-NMR of compound 66 in $CDCl_3$



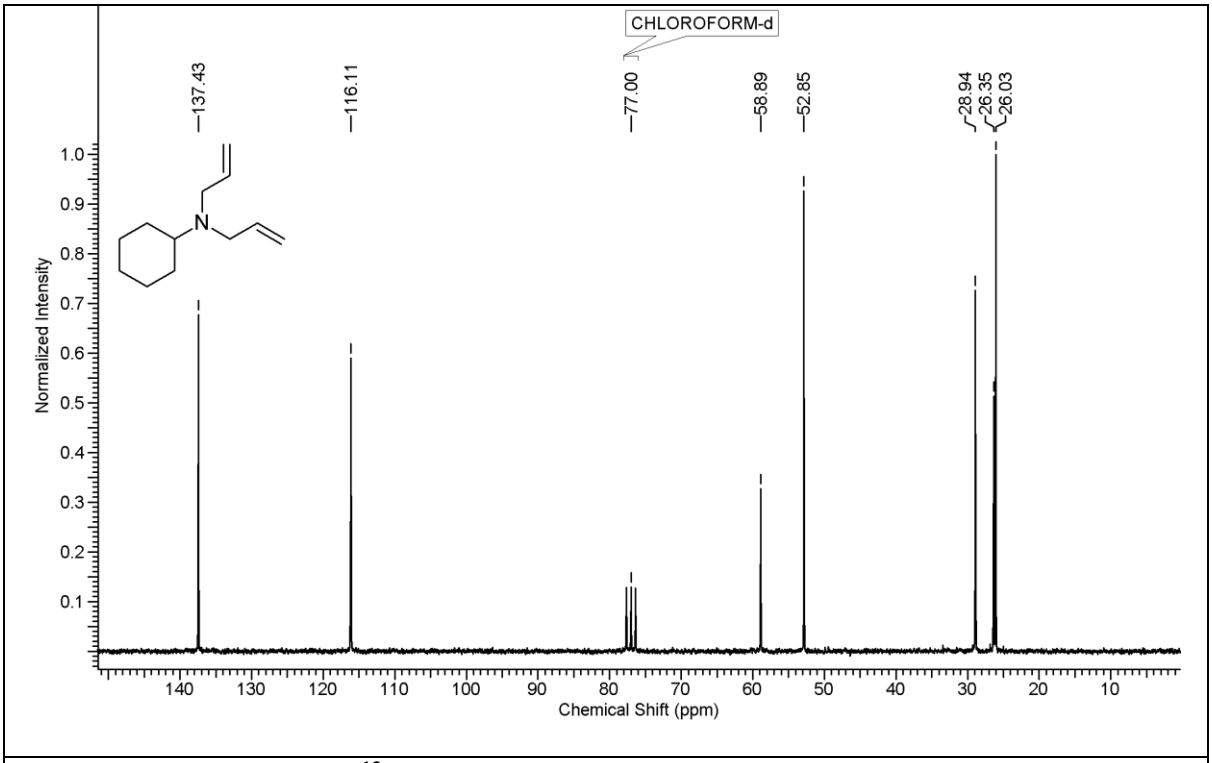
^{1}H-NMR of compound 68 in $CDCl_3$



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



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



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

5.8. References

1. (a) Greene, T.; Wuts, P. G. *Protective Groups in Organic Syntheses*, 3rd ed., Wiley, New York, **1999**; (b) Kocienski, P. J. *Protecting Groups*, Thieme, Stuttgart, **1994**; (c) Guibé, F. *Tetrahedron* **1997**, *53*, 13509.
2. (a) Rivière, M.; Lattes, A. *Bull. Soc. Chim. Fr.* **1968**, 4430; (b) Price, C. C.; Snyder, W. H. *Tetrahedron Lett.* **1962**, 69; (c) Gigg, R.; Conant, R. *Carbohydr. Chem.* **1982**, *100*, C5–C9, and references cited therein.
3. (a) Bertrand, M. P.; Escoubet, S.; Gastaldi, S. *Eur. J. Org. Chem*. **2005**, 3855; (b) Cadierno, V.; Gimeno, J.; Nebra, N. *Chem. Eur. J.* **2007**, *13*, 6590.
4. Du, Y.; Wiemer, D. F. *J. Org. Chem.* **2002**, *67*, 5709.
5. (a) Liu, Q.; Marchington, A. P.; Boden, N.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 511; (b) Carless, H. A. J.; Haywood, D. J. *J. Chem. Soc., Chem. Commun.* **1980**, 980; (c) Boss, R.; Scheffold, R. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 558; (d) Krompiec, S.; Pigulla, M.; Krompiec, M.; Baj, S.; Mrowiec-Bialon, J.; Kasperczyk, J. *Tetrahedron Lett.* **2004**, *45*, 5257.
6. (a) Talukdar,S.; Banerji, A. *J. Indian Chem. Soc.* **1997**, *74*, 842; (b) Rele, S.; Chattopadhyay, S. ; Nayak, S. K. *Tetrahedron Lett.* **2001**, *42*, 9093; (c) Alonso, E.; Ramon, D. J. ; Yus, M. *Tetrahedron* **1997**, *53*, 14355; (d) Merz, A.; Meyer, T. *Synthesis* **1999**, 94; (e) Bertrand, M. P.; Escoubet, S.; Gastaldi, S.; Timokhin, V. I. *Chem. Commun.* **2002**, 216.
7. (a) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Org. Lett.* **2001**, *3*, 3781; (b) Alcaide, B.; Almendros, P.; Alonso, J. M. *Chem. Eur. J.* **2003**, *9*, 5793; (c) Alcaide, B.; Almendros, P.; Alonso, J. M.; Luna, A. *Synthesis* **2005**, 668.
8. Schmitt, L.; Caperelli, C. A. *Nucleosides Nucleotides* **1997**, 2165.
9. Kapnang, H.; Charles, G. *Tetrahedron Lett.* **1983**, *24*, 3233.
10. Garro-Helion, F.; Merzouk, A.; Guibé, F. *J. Org. Chem.* **1993**, *58*, 6109.
11. Prakash, G. K. S.; Mandal, M.; Schweizer, S.; Petasis, N. A.; Olah, G. O. *J. Org. Chem.* **2002**, *67*, 3718.
12. Honda, M.; Morita, H.; Nagakura, I. *J. Org. Chem.* **1997**, *62*, 8932.
13. Chandrasekhar, S.; Reddy, C. R.; Rao, R. J. *Tetrahedron* **2001**, *57*, 3435.
14. Ito, H.; Taguchi, T.; Hauzawa, Y. *J. Org. Chem.* **1993**, *58*, 774.

15. Chippindale, A. M.; Davies, S. G.; Iwamoto, K.; Parkin, R. M.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Tetrahedron* **2003**, *59*, 3253.
16. Moreau, B.; Lavielle, S.; Marquet, A. *Tetrahedron Lett.* **1977**, 2591.
17. Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **1998**, *39*, 4679.
18. Walker, D.; Waugh, T. D. *J. Org. Chem.* **1965**, *30*, 3240.
19. (a) Bharate, S. B. *Synlett* **2006,** 3, 496. (b) Buckle, D. R. *Encyclopaedia of Reagents for Organic Synthesis*, *Vol 3*, Paquette, L. (ed), John Wiley & Sons, Chichester, **1995**, 1699; (c) For a review of oxidation reactions using DDQ, see: Walker, D.; Hiebert, J. D. *Chem. Rev.* **1966**, *66*, 153.
20. (a) Kumar, P.; Gupta, P.; Naidu, S. V. *Chem. Eur. J.* **2006**, *12*, 1397; (b) Gupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 849; (c) Gupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2005**, *46,* 6571; (d) Pandey, S. K.; Kumar, P. *Tetrahedron Lett.* **2005**, *46*, 6625; (e) Kumar, P.; Naidu, S. V. *J. Org. Chem*. **2006**, *71*, 3935; (f) Pandey, S. K.; Kumar, P. *Synlett* **2007**, 2894; (g) Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2007**, *48,* 3793; (h) Gupta, P. Kumar, P. *Eur. J. Org. Chem.* **2008**, 1195; (i) Pandey, S. K.; Pandey, M.; Kumar, P. *Tetrahedron Lett.* **2008**, *49,* 3297; (j) Chowdhury, P. S.; Gupta, P. Kumar, P. *Tetrahedron Lett.* **2004**, *50*, 7188; (k) Chowdhury, P. S.; Gupta, P. Kumar, P. *Tetrahedron Lett.* **2009**, *50*, 7018; (l) Gupta, P. Kumar, P. *Tetrahedron Asymm.* **2007**, *18*, 1688; (m) Kondekar, N. B.; Kumar, P. *Organic Lett.* **2009**, *11*, 2611.
21. Oikawa,Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23,* 885.
22. Bauer, S.M.; Armstrong, R. W. *J. Am. Chem. Soc.*, **1999**, *121*, 6355.
23. Schelhaas, M.; Waldmann, H. *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 2056.
24. Becker, H. In *The Chemistry of the Quinonoid Compounds*; Ed.; Wiley and Sons: Toronto, Patai, S. **1974**, 335.
25. (a) Lee-Ruff, E.; Ablenas, F. J. *Can. J. Chem.* **1989**, *67*, 699; (b) Yadav, J. S.; Chandrasekhar, S.; Sumithra, G.; Kache, R. *Tetrahedron Lett.* **1996**, *37*, 6603; (c) Caputo, R.; Guaragna, A.; Palumbo, G.; Pedatella, S. *J. Org. Chem.* **1997**, *62*, 9369; (d) Paterson, I.; Cowden, C. J.; Rahn, V. S.; Woodrow, M. D. *Synlett* **1998**, 915; (e) Vatele, J-M. *Synlett* **2002**, *3*, 507.
26. M. Bertrand, S. Escoubet, S.Gastaldi, *Eur. J. Org. Chem*. **2005**, 3855.

27. Buckley, D.; Dunstan, S.; Henbest, H. B. D. *J. Chem. Soc*. **1957**, 4880.
28. Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42,* 3021.
29. Lee-Ruff, E.; Ablenas, F. J. *Can. J. Chem.* **1989**, *67*, 699.
30. (a)Foster, R. Organic Charge Transfer Complexes; Academic Press: New York, **1969**; (b) Foster, R.; Foreman. M. L. In *The Chemistry of the Quinonoid Compounds*: Patai, S., Ed.; John Wiley & Sons: New York, **1974**: Part I, 257.
31. (a) Sharma, G. V. M.; Lavanya, B.; Mahalingam, A. K.; Krishna, P. R. *Tetrahedron Lett.* **2000**, *41*, 10323; (b) Sharma, G. V. M.; Rakesh, *Tetrahedron Lett.* **2001**, *42*, 5571.
32. Molander, G.A.; Nichols, P. J. *J. Org. Chem.* **1996**, *61*, 6040.

Educational Qualification

M.Sc. (Master of Science) St. Berchmans' College
Changanacherry, (M.G. University
Kottayam, Kerala)
2001-2003.

B.Sc. (Bachelor of Science) Chemistry, Physics, Mathematics
St. Dominic's College, Kanjirapally,
(M.G. University Kottayam, Kerala)
1998-2001.

Fellowships and Awards

- **2004-2006**: Junior Research Fellowship awarded by Council of Scientific and Industrial Research (CSIR), India (www.csir.res.in)
- **2006-2009**: Senior Research Fellowship awarded by Council of Scientific and Industrial Research (CSIR), India.

Examinations Qualified

- **Feb 2004**, Qualified *Graduate Aptitude Test* in Engineering (GATE) conducted by Indian Institute of Technology (IIT) Delhi India with 89.02% score.
- **December 2003,** Qualified *National Eligibility Test,* Eligibility (NET) test for the lectureship at the University

Research Interests

- Development of new asymmetric synthetic methodologies and its applications to the synthesis of bioactive molecules with special emphasis on organocatalysis.
- Total synthesis of bioactive molecules and their application to the medicinal chemistry and material chemistry.

Publications

1. *Enantioselective synthesis of (+)-L-733,060* Shijo K. Cherian and Pradeep Kumar *Tetrahedron: Asymmetry* **2007**, *18*, 982.
2. *Two diverge Hydrolytic Kinetic Resolution (HKR) approaches to verbalactone and its monomer* Shijo K. Cherian and Pradeep Kumar (to be communicated)
3. *Enantiomeric synthesis of substituted chiral γ-butyrolactones from aldehydes via proline-catalysed sequential lactonization reaction and proline-catalysed enantiomeric synthesis of Bruguierol A and Bruguierol B* Shijo K. Cherian; Nagendra B. Kondekar and Pradeep Kumar (to be communicated)
4. *Chemoselective deprotection of N-Allylic amines using DDQ* Shijo K. Cherian and Pradeep Kumar (Submitted for publication)

Symposia / Conferences/ Workshop attended

1. Participated in ACS International Conference "Building Bridges and Forging Bonds between Biology and Chemistry" held at NCL, Pune, in Jan 2006.

2. Participated in CSIR-NSFC Joint Workshop on Organic Chemistry and Chemical Biology: Bridging Bonds for 21st Century, held at NCL, Pune, in April 2007.

3. Participated in *J-NOST* (Junior National Organic Symposium Trust) held at Madurai Kamaraj University, Tamilnadu, India in Dec 2008.

4. Participated in 4th INSA-KOSEF Symposium in Organic Chemistry, held at NCL, Pune, in Feb 2009.