Enantioselective synthesis of bioactive molecules employing proline catalyzed α-Aminoxylation, Sharpless asymmetric epoxidation and Oxidative aromatization of 1,4-Dihydropyridines

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BY

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FEBRUARY–2015

Dedicated To

MY Parents and Teachers

DECLARATION

The research work embodied in this thesis has been carried out at CSIR-National Chemical Laboratory, Pune under the supervision of **Dr. R. P. Singh**, Polymer Science & Engineering Division, CSIR-National Chemical Laboratory, Pune – 411008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other university.

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CERTIFICATE

The research work presented in the thesis entitled **"Enantioselective synthesis of bioactive molecules employing proline catalyzed α-Aminoxylation, Sharpless asymmetric epoxidation and Oxidative aromatization of 1,4-Dihydropyridines"** has been carried out under my supervision and is a bonafide work of **Mr. Bontha Narasimha Reddy**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune – 411008

February – 2015

Dr. R. P. Singh

(Research Guide)

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-B. Narasimha Reddy

DEFINATIONS AND ABREVIATIONS

Ac	–	Acetyl
Ac_2O	–	Acetic anhydride
AcOH	–	Acetic acid
Boc	–	Tert-Butyl oxy carbonyl
Ms	–	Methanesulphonyl chloride
Ts	–	Toluenesulphonyl chloride
Bu	–	Butyl
^{t}BuOH	–	Tertiary butyl alcohol
Cat.	–	Catalytic/catalyst
DCM	–	Dichloromethane
Conc.	–	Concentrated
DMP	–	2,2'-Dimethoxypropane
DMF	–	*N,N*-Dimethylformamide
DMAP	–	*N,N'*-Dimethylaminopyridine
DMSO	–	Dimethyl sulfoxide
Et	–	Ethyl
EC	–	Effective concentration
HRMS	–	High Resolution Mass Spectroscopy
IBX	–	2-Iodobenzoic acid
Liq.	–	Liquid
Me	–	Methyl
NMR	–	Nuclear Magnetic Resonance
Py	–	Pyridine
p-TSA	–	*para*-Toluenesulfonic acid
Ph	–	Phenyl
i-PrOH	–	*iso*-Propanol
rt	–	Room Temperature
Sat.	–	Saturated
TBAF	–	Tetra-*n*-butylammonium fluoride
THF	–	Tetrahydrofuran

Abbreviations used for NMR spectral informations:

br	Broad	q	Quartet
d	Doublet	s	Singlet
m	Multiplet	t	Triplet

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AV–200 MHz, AV–400 MHz, JEOL AL-400 (400 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 AV–50 MHz, AV–100 MHz, JEOL AL-100 (100 MHz) and DRX–125 MHz spectrometer.
- Mass spectroscopy was carried out on PI QStar Pulsar (Hybrid Quadrupole-TOF LC/MS/MS)
- 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.
- All reactions are monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F–254) with UV light, I_2, and anisaldehyde in ethanol as developing agents.
- 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 45 °C unless otherwise specified.
- Silica gel (60–120), (100–200), and (230–400) mesh were used for column chromatography.

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ABSTRACT

Abstract

The Thesis entitled**, "Enantioselective synthesis of bioactive molecules employing proline catalyzed α-Aminoxylation, Sharpless asymmetric epoxidation and Oxidative aromatization of 1,4-Dihydropyridines"** is divided into five chapters. In **chapter 1,** a brief introduction to our work and key reactions are discussed and in **chapter 2**, the stereoselective total synthesis of synthesis of (*R*)-rugulactone by using Sharpless epoxidation followed by selective hydride reduction of epoxy alcohols and Grubb's cross metathesis as the key reactions is described. In **Chapter 3**, the enantioselective synthesis of (*R*)-Massoialactone and enantioselective synthesis of (*S*)-N-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol by employing Shapless asymmetric epoxidation followed by regioselective opening of epoxy alcohols as the key reactions is discussed. In **chapter 4**, the enantioselective synthesis of (*S*)-Ibuprofen *via* proline catalyzed α-aminoxylation followed by selective catalytic deoxygenation of diols and by Jacobsen's hydrolytic kinetic resolution approaches is discussed. In **chapter 5**, the enantioselective synthesis of *β*-hydroxy Nitriles and *β*-hydroxycarboxylic esters using proline-catalyzed α-aminoxylation and sodium perborate mediated oxidative aromatization of 1,4 –Dihydropyridines is described.

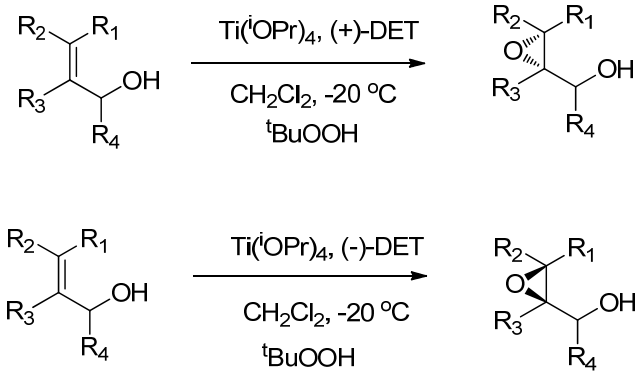
Chapter 1: Introduction to the key reactions

This chapter describes introduction and explains the key reactions used. The enantioselective synthesis of biologically active molecules is essential nowadays because of the differences in biological activities of different enantiomers. Generally either *S* isomer or *R* isomer possesses required biological activity to treat a particular disorder. Therefore, the selective synthesis of required enantiomer is essential, which can be achieved by employing eanantioselective reactions. The key reactions which we employed in our syntheses are discussed below.

Section: 1. Sharpless Asymmetric Epoxidation[1]

Asymmetric epoxidation of allylic alcohols is 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. The Sharpless epoxidation is a popular laboratory and industrial process due to its both enantioselective and catalytic nature. The reaction mixture includes a titanium tetraalkoxide, a chiral tartrate diester, an allylic alcohol substrate, and an alkyl

hydroperoxide as the oxidant. The consistency of the reaction is remarkable, excellent enantiofacial selectivity is realized for allylic alcohol substrates of widely varying structure. In addition to being able to asymmetrically oxidize prochiral substrates to products of predictable absolute configuration, the reaction is extremely sensitive to pre-existing chirality in selected positions of the allylic alcohols. For example, kinetic resolution of racemic secondary allylic alcohols is very efficient since it can be used for generating chiral allylic alcohols as well as *anti*-epoxy alcohols in high enantiomeric excess. Selection of the proper chirality in the starting tartrate esters and proper geometry of the allylic alcohols allows one to establish both the chirality and relative configuration of the product.



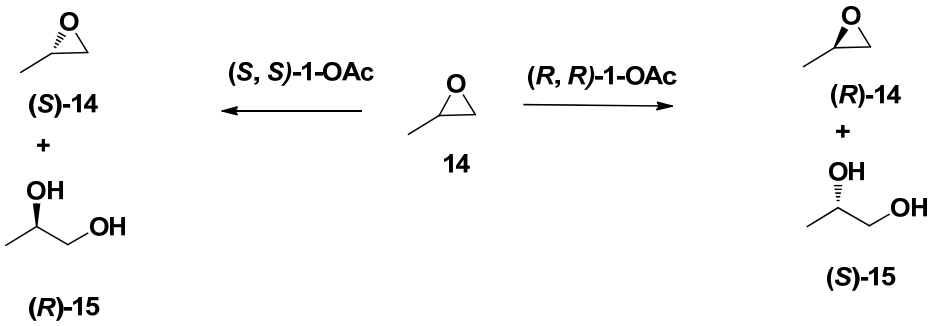
Scheme 1: Sharpless Asymmetric Epoxidation of allylic alcohols.

Since its discovery in 1980, the Sharpless epoxidation of allylic alcohols has become a benchmark classic method in asymmetric synthesis. One factor that simplifies the standard epoxidation reaction is that the active chiral catalyst is generated *in situ*, which means that the pre-preparation of the active catalyst is not required. It is believed that the species containing equal moles of Ti and tartrate is the most active catalyst. It promotes the reaction much faster than Ti(IV) tetraalkoxide alone and exhibits selective ligand-accelerated reaction.

Section: 2. Hydrolytic Kinetic Resolution (HKR) of terminal epoxides[1b]

Recently Jacobsen had discovered the (salen)Co complex which can catalyze hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides efficiently **(Scheme 2).** The HKR also provides useful enantio-enriched 1,2-diols, including many that are otherwise not readily accessible using existing asymmetric

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



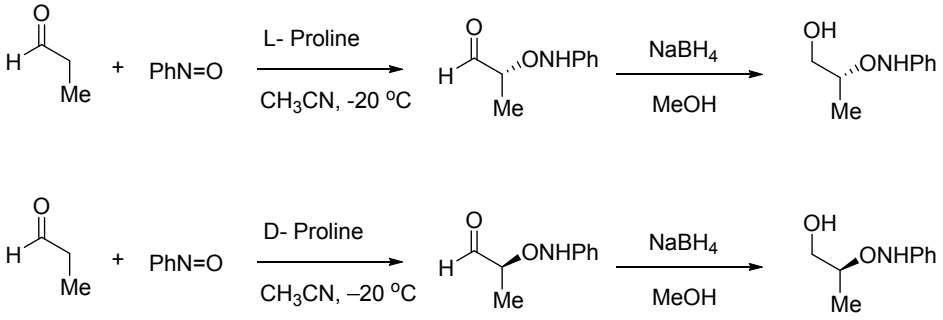
Scheme 2. Hydrolytic kinetic resolution of epoxides

Section: 3. Proline catalyzed α-Aminoxylation[2]

Optically active α-hydroxy aldehydes and ketones are important intermediates inorganic synthesis, and because of these 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-hydroxyacids are widely used. Diastereoselective reactions such as nucleophilic addition to chiral glyoxal derivatives or alkylation of chiral hydrazones are other useful synthetic methods. Asymmetric hydrocyanation and enzymatic resolution have also been employed as a key step in their synthesis. Optically active α-hydroxyketones, on the other hand, can be prepared by several methods such as the electrophilic α-hydroxylation of enolates using chiral oxaziridines as the oxidizing agent. Several methods using asymmetric catalytic reactions are known, including the asymmetric dihydroxylation of enolethers developed by Sharpless et al., the asymmetric epoxidation of silylenol ethers with a chiral dioxirane, and the asymmetric epoxidation of enol ethers with achiral Mn-Salen catalyst. Most of these

preparations, however, require multiple manipulations, and no direct method from the corresponding aldehyde or ketone has been available.

The direct proline-catalyzed asymmetric α-aminoxylation of aldehydes and ketones has been developed using nitrosobenzene as an oxygen source, affording α-anilinoxy-aldehydes and ketones with excellent enantioselectivity. The proline catalyzed α-aminoxylation of aldehydes is shown in **Scheme 3**.



Scheme 3: proline catalyzed α-aminoxylation of aldehydes

<u>Chapter 2</u>: A facile enantioselective synthesis of (*R*)-rugulactone

This chapter describes the enantioselective synthesis of (*R*)-rugulactone by using Sharplessepoxidation followed by selective hydride reduction of epoxy alchols and experimental procedure with complete characterization of compounds.

The 6-alkyl and aryl substituted α-pyrones (6-arylalkyl-5,6-dihydro-2H-pyran-2-ones) possess important biological properties such as antitumor, antiviral, antifungal, and anti-inflammatory[3] etc. These properties arise as a result of Michael acceptor property of α-pyrones towards the amino acid residues of the receptors. The biological assays of 6-arylalkyl-5,6-dihydro-2H-pyran-2-one, (*R*)-Rugulactone **1,** which has been extracted from the evergreen tree *cryptocarya Rugulosa*[4] of Lauraceae family has been found to inhibit the nuclear factor (NF-kB) activation pathway occurring in different types of cancers[5].

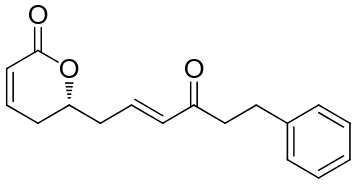
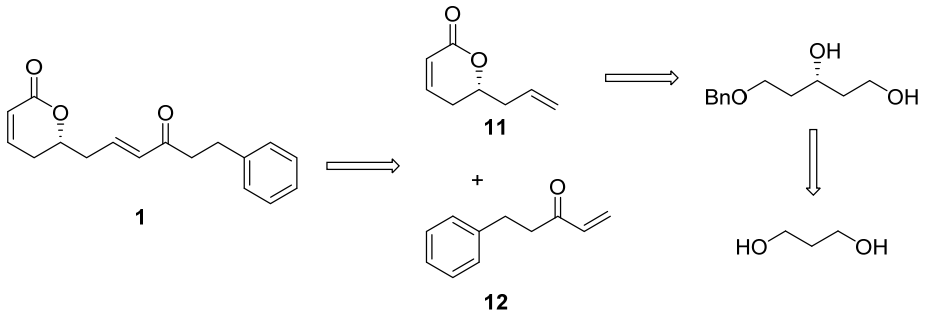


Figure 1: (*R*)-Rugulactone, **1**

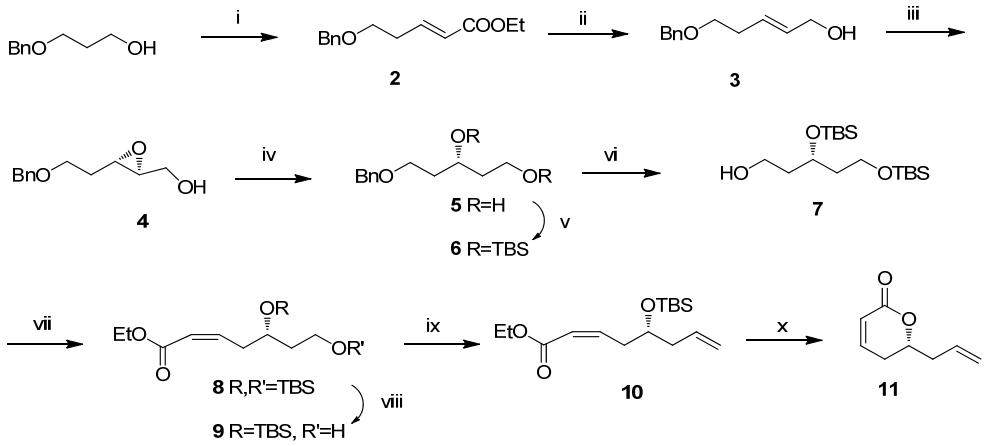
The retrosynthetic disconnections are shown in **Scheme 4**.



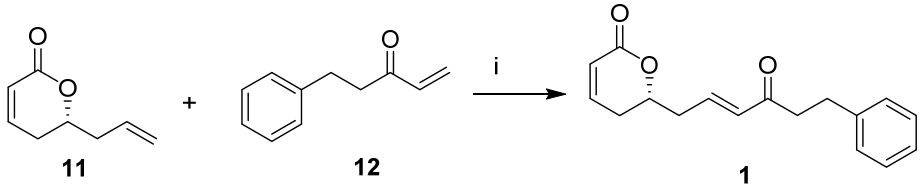
Scheme 4: Retrosynthesis of (*R*)-Rugulactone, **1**

As outlined in **Scheme 5**, our synthetic strategy commenced with 3-benzyloxypropanol. The primary alcohol of 3-benzyloxypropanol was oxidized by using Swern's protocol to the corresponding aldehyde, and then Horner-Wardsworth-Emmons olefination of aldehyde afforded α,β-unsaturated ester **2** in 95% yield. The compound **2** was subsequently reduced to allyl alcohol **3** by employing alane reduction ($LiCl/LiAlH_4$) conditions. The allyl alcohol **3** was then subjected to Sharpless asymmetric epoxidationto produce epoxy alcohol **4** in 85% yields, which on selective hydride reduction with Red-al yielded 1,3- diol **5**. The two hydroxyl groups in **5** were completely protected to its disilyl ether **6**. The subsequent removal of benzyl group was achieved by using Birch debenzylation protocol to afford alcohol **7**, which was further oxidized to aldehyde and Still - Gennari modification of Horner – Emmons olefination of the crude aldehyde produced Z/E 95:5 mixture of α, β-unsaturated ethyl esters in favor of desired isomer **8**. The geometric isomers were easily separated using silica gel column chromatography to get pure Z isomer of ethyl ester in 74% yield. Later the primary silyl ether was selectively cleaved to produce alcohol**9**, which on further oxidation followed by Wittig olefination furnished unsaturated ester **10**. Further α, β-unsaturated ester **10** was stirred in methanol for 2 h in presence of *p*-toluene sulfonic acid to furnish **11** in 91% yield.

The remaining task was to couple the fragment 5-phenyl-pent-1-en-3-one **12** and lactone **11** (3:1 ratio) by cross metathesis, was implemented by refluxing them in CH_2Cl_2 in presence of Grubb's second generation catalyst (5 mol%) to deliver enantiomerically pure (*R*)-rugulactone(**1)** in 74 % yield as colorless oil. $[\alpha]^{25}_D$: -46.2 (*c* 1, $CHCl_3$), Lit $[\alpha]^{25}_D$: - 46.9 (*c* 1, $CHCl_3$).



Scheme 5: *Reagents and conditions: (i) (a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78° C, 1 h. (b) triethylphosphonoacetate, NaH, dry Benzene, 0 ºC- RT, 8 h, 95%; (ii) $LiAlH_4$, $AlCl_3$, THF, 0 °C, 1 h, 82%; (iii) (-)- DET, $Ti(O\text{-}i\text{-}Pr)_4$, TBHP, dry CH_2Cl_2, molecular sieves 4 A°, -15 °C, 87%; (iv) Red-al, THF, -20 °C, 6 h, 96%; (v) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, RT, 8 h., 96%; (vi) Na, Liq. NH_3, dry THF, -78 °C, 15 min., 92%; (vii) (a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78°C, 1h, (b) $EtO_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, dry THF, -78°C, 2 h, 74%; (viii) CSA, MeOH:CH_2Cl_2 (1:1), RT, 85%; (ix) (a)DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78°C, 1 h, (b)$(C_6H_5)_3PCH_3I$, n-BuLi, THF, 0 °C, 82%; (x) PTSA, MeOH, 3 h, 91%.*



Scheme 6: *Reagents and conditions: (i) Grubb's 2nd generation catalyst (5mol %), dry CH_2Cl_2, 45 °C, 12 h, 75%.*

Chapter3: Enantioselective synthesis of (*R*)-Massoialactone and enantioselective synthesis of (*S*)-N-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol

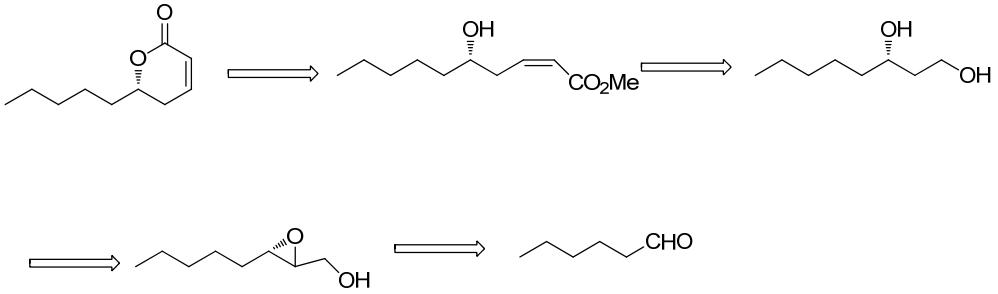
This chapter describes the enantioselective synthesis of (*R*)-Massoialactoneand Enantioselective synthesis of (*S*)-N-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol and experimental procedure with complete characterization of compounds. This chapter is further divided into two sections,

Section 1: Enantioselective synthesis of (*R*)-Massoialactone

Natural δ-lactones containing alkyl side chain have become interesting synthetic targets due to their attractive biological activity[6]. One such lactone, (*R*)-

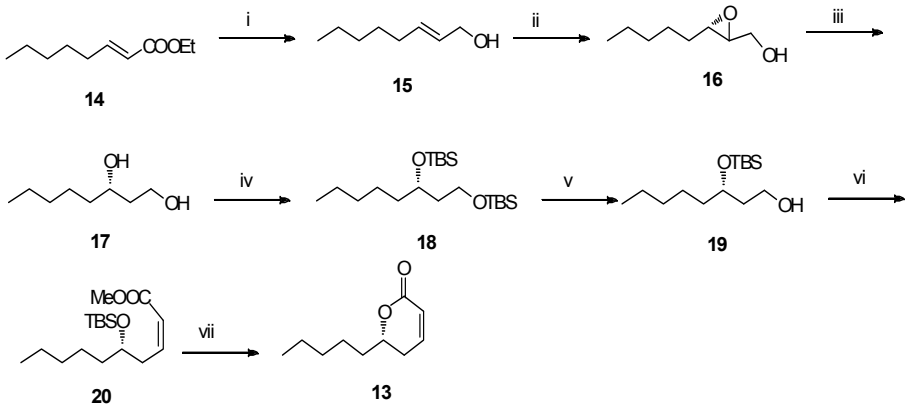
Massoialactone **13** was first isolated from thebark oil of *cryptocarya massoi*[7]in 1937, which had been used for centuries as constituent of native medicine[9]. Later it was also isolated from jasmine flowers as well as from the cane molasses. Compound **13** is widely used in perfume industry, food industry, and in the manufacture of alcoholic drinks, tincures.[8] (*R*)-Massoialactone is also an alarm pheromone in two formicine species of the family *camponotous*[9].

Our synthetic route commenced with α,β-unsaturated ester**14**, which is reduced to α,β-unsaturated alcohol**15** using alane as reducing agent. The compound**15** was then subjected to Sharpless asymmetric epoxidation to obtain epoxy alcohol **16**. The epoxide in compound **16** is regioselectively opened by Red-al to furnish 1, 3-diol **17**, which was then completely protected to its disilyl ether **18**.



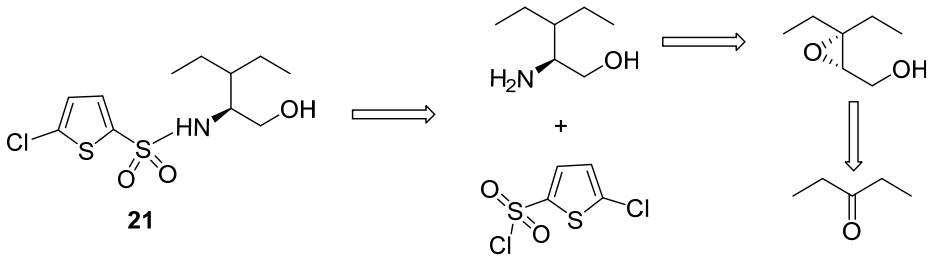
Scheme 7: Retrosynthesis of (*R*)-Massoialactone **13.**

The primary silylether is selectively cleaved with camphor sulfonic acid to afford compound **19**. The primary hydroxyl group in **19** was oxidized to aldehyde with IBX, which further upon Horner-Wordsworth-Emmons reaction gave α,β-unsaturated ester**20** with exclusively Z isomer. Finally the compound **20** on treatment with p-toluene sulfonic acid led to the deprotection of remaining silyl group followed by lactonization provided (*R*)-Massoialactone, **13.**



Scheme 8: *Reagents and conditions: (i) $LiAlH_4$, $AlCl_3$, THF, 0 ^oC, 1 h, 80%; (ii) (-)-DET, $Ti(O\text{-}i\text{-}Pr)_4$, TBHP, dry CH_2Cl_2, molecular sieves 4 A^o, -15 ^oC, 88%; (ii) Red-al, THF, -20 ^oC, 6 h, 94%; (iv) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, RT, 8 h, 95%; (v) CSA, MeOH:CH_2Cl_2 (1:1), RT, 83%; (vi) (a) IBX, DMSO, 1 h, (b) $EtO_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, dry THF, -78$^oC$, 2 h, 76%; (vii) PTSA, MeOH, 3 h, 89%.*

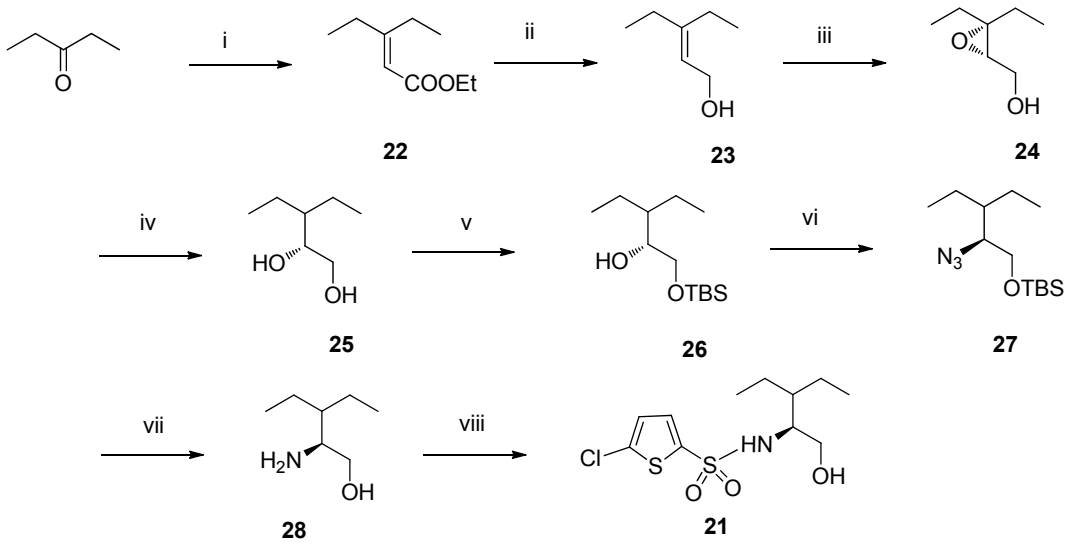
Section 2: A facile Enantioselective synthesis of (S)-N-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol



Scheme 9: Retrosynthesis of **21**

Alzheimer's disease (AD) is a common neurodegenerative disease characterized by progressive deterioration of memory, dementia, severe behavioral abnormalities, ultimately leading to death.[10] The AD is believed to be caused by the accumulation of extracellular senile plaques made primarily by deposits of amyliod-beta (Aβ) peptides on the nerve cells that are produced by the proteolytic cleavage of amyloid precursor protein (APP). (S)-N-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol**21**, a Notch-1-sparing-γ-secretase inhibitor has become an interesting synthetic target due to its promising activity in reducing the production of Aβ in vivo.

As outlined in **Scheme 10**, the synthesis of **21** commences with 2-pentanone, which on Horner-Wardsworth-Emmons olefination yielded α,β–unsaturated ester **22**. The compound **22** was subsequently reduced to allyl alcohol **23**by employing alane reduction conditions. The allyl alcohol **23** was then subjected to Sharpless asymmetric epoxidation to produce epoxy alcohol **24**in 87% yields. Selective hydride reduction of epoxyalcohol **24** with DIBAL-H afforded diol **25**. The primary hydroxyl group was then converted to its TBS ether using TBSCl and Imidazole in dry DCM to yield **26**. Further, the secondary hydroxyl group was converted to its mesylate, which was then treated with NaN_3 in DMF to get azide **27** in 74% yields. Reduction of azide **27** under $LiAlH_4$ reduction conditions afforded corresponding amine **28** with simultaneous



Scheme 10: *Reagents and conditions: (i) triethylphosphonoacetate, NaH, dry THF, 0 ºC-RT, 8 h, 90%; (ii) $LiAlH_4$, $AlCl_3$, THF, 0 °C, 1 h, 78%; (iii) (-)- DET, $Ti(O\text{-}iPr)_4$, TBHP, dry CH_2Cl_2, molecular sieves 4 A°, -15 °C, 87%; (iv) DIBAL-H, benzene, RT, 1 h, 87% ;(v) TBSCl, imid, CH_2Cl_2, 0-25 ºC, 4 h, 82%; (vi) (a) MsCl, Et_3N, 30 min; (b) NaN_3, dry DMF, 60 ºC, 30 h, 74%; (vii) $LiAlH_4$, dry THF, 50 ºC, 12 h, 98%; (viii) 5-chlorothiophene-2-sulfonyl chloride, Et_3N, dry CH_2Cl_2, 0 °C, 30 min, 90%.*

removal TBS group. Then the final task was to condense amino alcohol **28** with commercially available 5-chlorothiophene-2-sulfonyl chloride, which was accomplished in presence of Et_3N in dry DCM to get target molecule **21** in 90% yields.

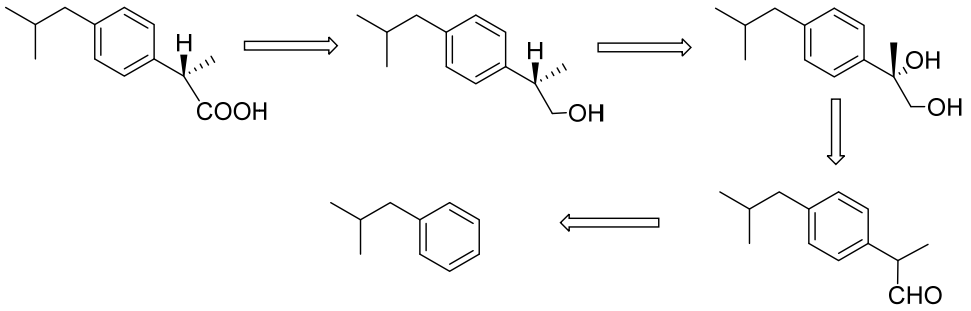
Chapter 4: Enantioselective synthesis of (*S*)-Ibuprofen.

This chapter describes the enantioselective synthesis of (*S*)-Ibuprofen by employing α–aminoxylation and by Jacobsen hydrolytic kinetic resolution reactions and full experimental details with complete characterization of compounds.

Proline catalyzed α–aminoxylation approach:

α-Aryl propanoic acid derivatives are the major class of non-steroidal anti-inflammatory drugs and house hold pain killers. Among these Ibuprofen (2-[4-2-methylpropyl) phenyl] propanoic acid) and naproxen 2-(4-methoxynapthyl) propanoic acid are the best known and are the sold worldwide in large quantities. According to Wetcher, (S)-enantiomer is responsible for the desired therapeutic effect.[11] Despite the fact that, Ibuprofen is currently administered as the racemate, although it has been

demonstrated that its R isomer accumulates in fatty tissue as a glycerol ester, its long terms effects are not known, so there is a need to develop synthetic methods allowing for the preparation of these drugs in an enantiopure form.



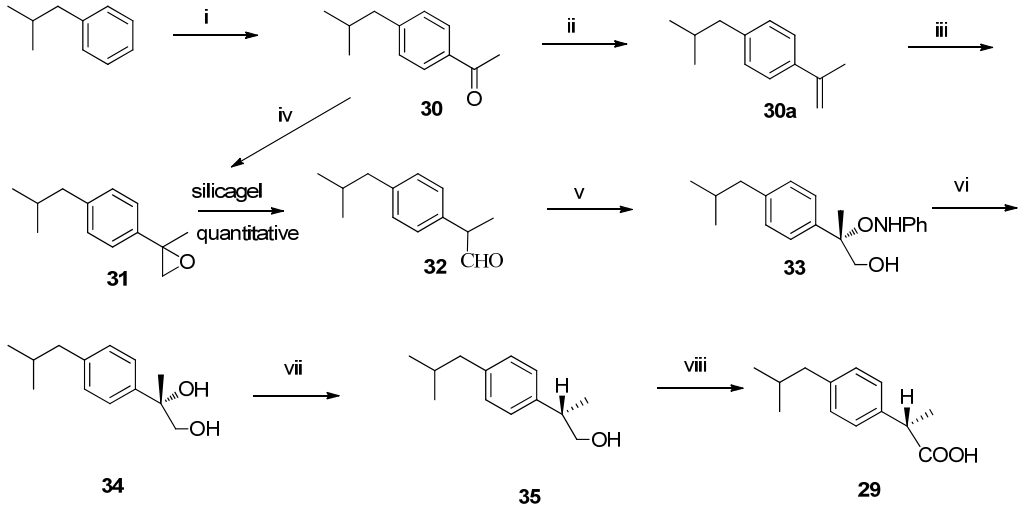
Scheme 11: Retrosynthesis of (*S*)-Ibuprofen, **29.**

So far, several syntheses were reported using organometal catalysis. Since the organometal catalysts are costly and sometimes toxic, so there is a need to synthesize in a cheap and environmentally friendly manner. In recent days enantioselective organocatalysis has emerged as a powerful synthetic tool that is complementary to the organometal catalysis and has been utilized in the synthesis of diverse chiral molecules[12]. The operational simplicity, ready availability of catalysts and low toxicity associated with organocatalysts makes it an attractive method. Herein, we discuss the enantioselective synthesis of (S)-Ibuprofen **29** using D-proline catalyzed α-aminooxylation of aldehydes.

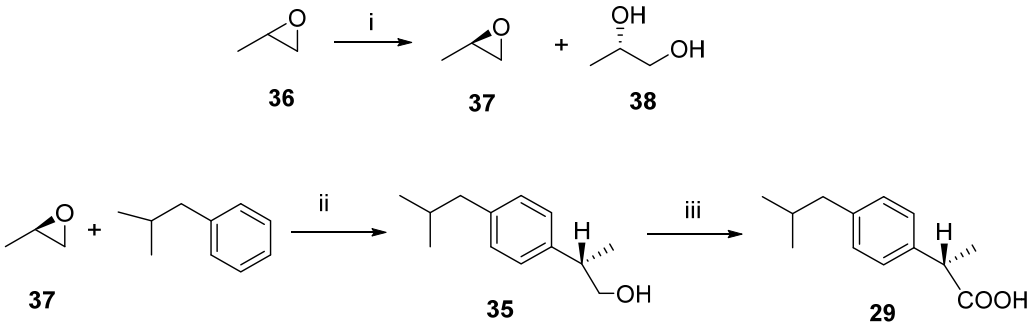
Synthesis commenced with commercially available Isobutyl benzene (**Scheme 12**), which was treated with acetyl chloride in presence of anhydrous aluminum chloride to give ketone **30**, which is then subjected to Corey- Chaykovskyepoxidation to give epoxide **31**. The epoxide then rearranges to aldehyde **32** in presence of silica gel. Thus, obtained aldehyde was subjected to D- proline catalyzed α– aminoxylation[13] followed by reduction gives **33**. The crude product **33** was directly converted into corresponding diol **34** by catalytic hydrogenolysis. Since the enantioselectivity of the alcohol **35** strongly dependent upon the catalyst employed, the best results were obtained with Pearlman's catalyst (palladium hydroxide on carbon). The alcohol **35** on Jones oxidation gives the final product **29** in 79% yields.

As reported in literature, α–aminoxylation of α–branched aldehyes gives corresponding diol with less enantioselectivity, so we made several attempts to improve the yield and enantioselectivity. The maximum yield of the diol is 65% with

an enantioselectivity of 40%. The schematic synthesis of ibuprofen is shown in scheme **9**.



Scheme 12: *Reagents and Conditions: (i) CH_3COCl, anhyd. $AlCl_3$, CH_2Cl_2, 80%; (ii)Ph_3PCH_3I,n-BuLi, THF, 85%; (iii) mCPBA, CH_2Cl_2, aqueous.Na_2CO_3; (iv) $(CH_3)_3SI$,NaH, DMSO, THF, 78%; (v) a) PhNO, D-Proline, CH_3CN,0^oC to RT, b) $NaBH_4$, MeOH; (vi) $CuSO_4$, MeOH, 76% (for three steps); (vii) H_2, $Pd(OH)_2$/C, EtOH, 55%; (viii)$KMnO_4$, H_2SO_4, 79%.*



Scheme 13: *Reagents and condions: (i) (R,R)-Co(salen).OAc, H_2O, 44%; (ii) anhyd. $AlCl_3$, CS_2, 72%; (iii) $KMnO_4$, H_2SO_4, 79%.*

Hydrolytic Kinetic resolution approach:

Since the organoctalytic approach was not satisfactory, so we attempted to synthesize **29** using Jacobsen's Hydrolytic Kinetic resolution of epoxides[14] (**Scheme 13**). The synthesis started with propylene oxide **36** subjected to (R,R)-Co(salen)(III) catalyzed Hydrolytic kinetic resolution with 0.5eq of H_2O to give enantiomerically pure

epoxide**37**in 44% yield. Thus obtained epoxide **37**is then opened with isobutylbenzene in presence of anhyd. $AlCl_3$ to give alcohol **35**. The alcohol **35** is then oxidized with acidic $KMnO_4$ to give **29** in 32% overall yield with 85% ee.

Chapter 5: Eanantioselective synthesis of Enantioselective synthesis of β–Hydroxy Nitriles and β–HydroxyCarboxylic esters and Oxidative aromatization of 1,4-Dihydropyridines

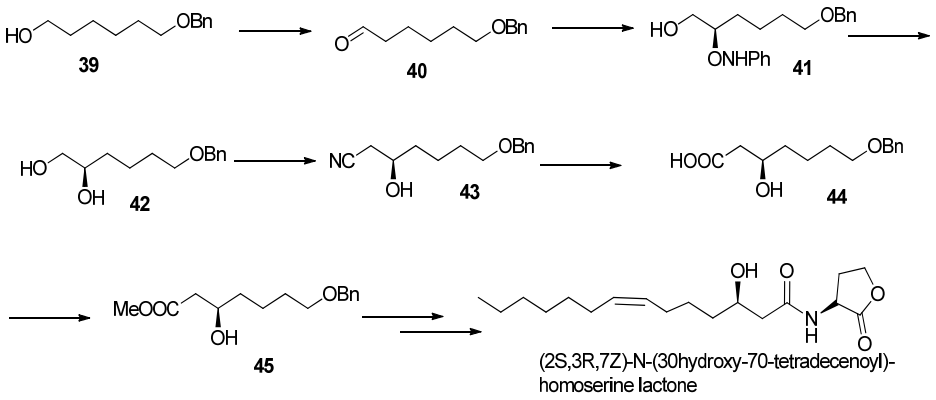
This chapter describes the enantioselective synthesis of β–hydroxy Nitriles and β–hydroxycaroxylic esters and oxidative aromatization of 1,4-Dihydropyridines and full experimental details with complete characterization of compounds.

This chapter is further divided into two sections.

Section 1: Eanantioselective synthesis of Enantioselective synthesis of β–Hydroxy Nitriles and β–HydroxyCaroxylic esters via proline catalyzed α–aminoxylation of aldehydes

Optically active β–hydroxy nitriles and β–hydroxycaroxylic esters are key building blocks for the synthesis of a variety of pharmaceutically important compounds. For example, many biologically active compounds such as β–blocker drugs contain 1,3-amino alcohol moieties, which are often prepared *via* reduction of β–hydroxy nitriles. Chiral β–ydroxy carboxylic acids that can be easily prepared from β–hydroxy nitriles are good precursors for β–aminoacids[15],β–lactams[16], and β–lactones[17]and have been used in the synthesis of pheromones. The β–hydroxycaroxylic ester moiety has often been found in polyketide natural products such as amphotericin B, tylosin, and rosaramicin and the marine natural product hapalosin. Therefore, development of efficient and environmentally benign methodologies for the synthesis of enantiomerically pure β–hydroxy nitriles and β–hydroxycaroxylic esters is of practical importance.

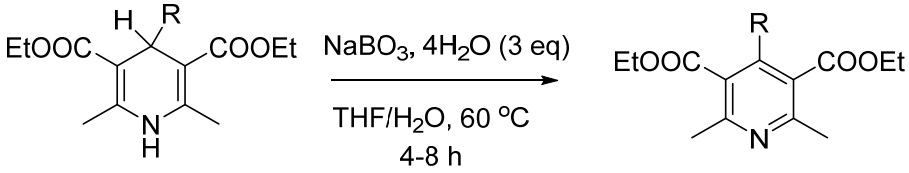
The synthesis started with the monobenzyl protected 1, 6-hexane diol **39**, which upon oxidation gives aldehyde **40** in 95% yield. The aldehyde **40** was then directly subjected to L-proline catalyzed α–aminoxylation and subsequent reduction gives intermediate **41**, which upon hydrogenolysis gave diol**42** in 65% yield for three steps. The diol was selectively tosylated and then subjected to cyanation to give hydroxy cyanide **43**, which was further oxidized to aldehyde and later to acid **44.** The acid **44** was further esterified to hydroxyl ester **45**.



Scheme 14: *Reagents and conditions: (i) PCC, CH_2Cl_2, 95%; (ii) (a) PhNO, L-proline, CH_3CN, -20 ^oC (b) $NaBH_4$, MeOH; (iii) $CuSO_4$, MeOH, 65% (for three steps); (iv) (a) TsCl, Et_3N, Bu_2SnO, DMAP, CH_2Cl_2; (v) NaCN, DMF (1.5 ml/mmol), 60 ^oC, 82%; (vi) (a) DIBAL-H, CH_2Cl_2 (b) $NaClO_2$, NaH_2PO_4, 78%; (vi) Na_2CO_3, MeI, DMF, 90%.*

Section 2: Oxidative aromatization of 1, 4-Dihydropyridines

Oxidative aromatization of 1,4-Hantzsch pyridines is a key step in many biologically important reations[18]. Some of them are oxidation of 1, 4- Dihydropyridine (1,4- DHP) drugs to their pyridine derivative by the action of cytochrome P450 in the liver and calcium channel blockers for the cardiovascular diseases[19].



Scheme 15: Oxidative aromatization of 1, 4–Dihydropyridines by sodium perborate

R	CH_3	H	$CH_2CH_2CH_3$	C_6H_5	p-CH_3 C_6H_5	P-OCH_3 C_6H_5	m-NO_2 C_6H_5
Time	7h	7.5h	6.5h	6h	5.5h	4h	6h
Yield	78	72	70%	78%	82%	86%	80%

Sodium perborate is a very cheap, safe and easily handled oxidizing agent[20] and it is a stable, colorless crystalline solid. Sodium perborate is highly effective and selective oxidizing agent. In our present work we describe the utility of sodium perborate for the oxidative aromatization of 1, 4-dihydropyridines. The oxidation was carried out

with $NaBO_3.4H_2O$ (3 equiv.) in H_2O: THF mixture at 60 ^oC. Various substrates were screened under the same reaction conditions to afford moderate to good yields of the corresponding pyridines as listed in the table.

References:

1. (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc*. **1980**, *102*, 5974; (b) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.
2. Hayashi, Y.; Yamaguchi, J.;Sumiya, T.; Hibino, K.; Shoji, M. *J. Org. Chem*. **2004,** *69*, 5966
3. Drewes, S. E.; Sehlapelo, B. M.; Horn, M. M.; Sandor, O. *Phytochemistry***1995,** *38*, 1427.
4. Meragelman, T. L.; Scudiero, D. A.; Davis, R. E.; Staudt, L. M.; Mc Cloud, T. G; Cardellina, J. H.; Shoemaker R. H. *J. Nat. Prod*. **2009**, *72*, 336.
5. Karin, M. *Nature* **2006**, *441*, 431.
6. Reddy, M. V. R.; Yucel, A. J.; Ramachandran, P. V. *J. Org. Chem*. **2001**, 66, 2512.
7. Takano, S., Setoh, M., and Ogasawara, K., *Tetrahedron: Asymmetry*, **1992**, 3, 533.
8. Abe, S. *J. Chem. Soc. Jpn*. **1987**, 58, 246.
9. Harbindu, A. and Kumar, P., *Synthesis*, **2011**, 1954
10. Schenk, D. B.; Rydel, R. E.; May, P.; Little, S.; Panetta, J.; Lieberburg, I.; Sinha, S.*J. Med.Chem.* **1995**, *38*, 4141.
11. Wetcher, W. J. *J. Clin. Pharmacol.* **1994**, 34, 1036.
12. S. George, A. Sudalai. *Tetrahedron: Asymmetry***2007**, 18, 975.
13. Sung-Gon Kim, Tae-Ho park. *Tetrahedron Letters* **2006**, *47*, 9067
14. Makoto Tokunaga, Jay F. Larrow, Fumitoshi, K; Eric N. Jacobsen. *Science***1997**, 277, 936.
15. Thaisrivongs, S.; Schostarez, H. J.; Pals, D. T.; Turner, S. R. *J. Med.Chem.* **1987,** *30*, 1837.
16. Schostarez, H. J. *J. Org. Chem.* **1988**, *53*, 3628.
17. Capozzi, G.; Roelens, S.; Talami, S. *J. Org. Chem.* **1993**, *58*, 7932
18. Esiner, U.; Kuthan, J. *J. Chem. Rev*. **1972**, *72*, 1.
19. Janis, R. A.; Triggle, D. J. *J. Med. Chem*. **1983**, *25*, 775.
20. Alanxander, M.; William, R. S. *Tetrahedron*, **1995**, *51,* 6145.

CHAPTER I:

Introduction to the key reactions

SECTION: I

Asymmetric Epoxidation of Allylic Alcohols

1.1.1. Introduction

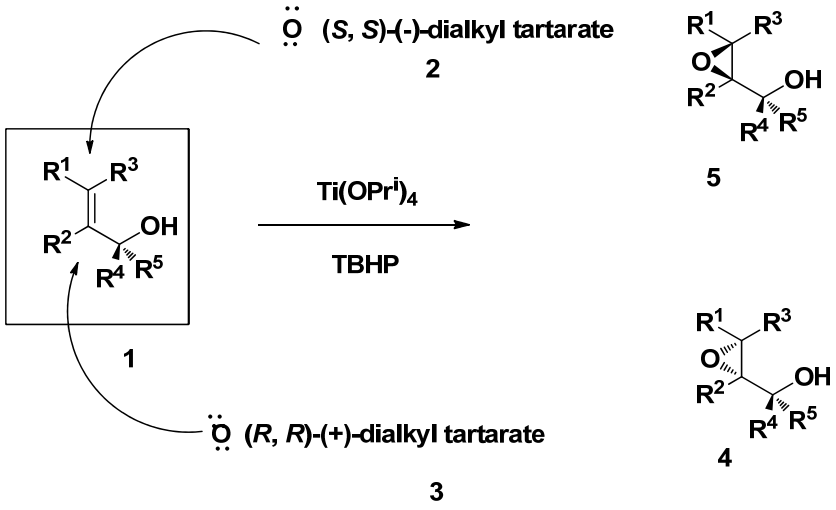
Asymmetric synthesis of bioactive molecules the prominent area of synthetic organic chemistry due to its varied applications in drug and pharmaceutical industries. The aim of asymmetric synthesis is to prepare stereochemically-enriched compounds in the most efficient and practical manner. In the last two decades, many powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds. Catalytic asymmetric reactions provide a practical entry into the chiral world due to their economical use of asymmetric inducing agents.[1] Especially useful is the carbon- heteroatom bond forming reaction, since the resulting functional group can be readily manipulated to produce many important classes of compounds. It is not surprising, therefore, that the oxidative addition of heteroatoms to olefins has been a fruitful area in last three decades. A number of transition metal-mediated methods for the epoxidation,[2] oxidative cyclization,[3] halohydrin formation,[4] dihydroxylation[5] and aminohydroxylation[6] have emerged. A common feature of most of these processes is the phenomenon of ligand acceleration,[7] wherein a metal catalyzed process turns over faster in the presence of a coordinating ligand. Epoxides are versatile and very useful intermediates in organic chemistry. The strain of three membered oxirane ring makes them reactive towards a large variety of reagents.

Sharpless and Katsuki have designed method for the asymmetric epoxidation of primary and secondary allylic alcohols employing titanium tetraisopropoxide, a

diakyl tartrate as a chiral ligand, and *tert*-butyl hydroperoxide as the oxidizing agent.[8] Interestingly, this reaction exhibits higher levels of enantioselectivity. Like other metal catalyzed epoxidations, this reaction also proceeds under mild conditions with good product yield and with high regio-and chemoselectivity.

1.1.2. Asymmetric Epoxidation with the Titanium (IV) Tartrate Catalyst

The combination of $Ti(O^iPr)_4$, t-butyl hydroperoxide and a dialkyl tartarate epoxidizes most allyic alcohols in good chemical yield and with predictably high enantiofacial selectivity according to the empirical rule illustrated in **Scheme 1**. When an allylic alcohol (R^4, R^5 = H) **1** is drawn in a plane with the hydroxymethyl group positioned at the lower right, the delivery of oxygen occurs from the bottom side of the olefin to give the (2*S*)-epoxide **5** if an (*R*,*R*)-dialkyl tartrate **3** is used as the chiral auxiliary.

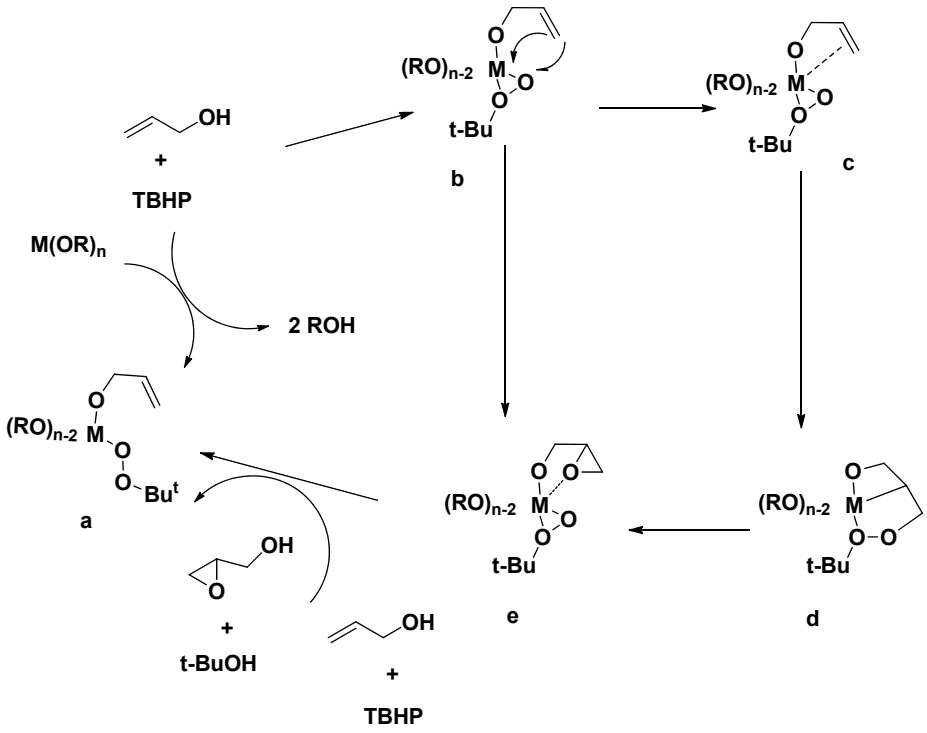


Scheme 1

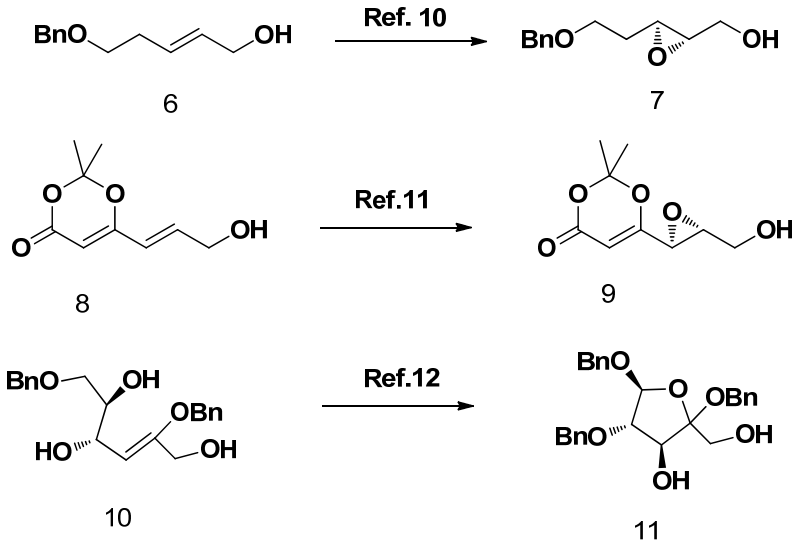
When an (*S*,*S*)-dialkyl **2** tartrate is employed, oxygen is delivered from the top side. The enantiofacial selectivity of the reaction is > 90% ee for substrate without a Z-olefinic substituent (R^3 = H). The degree of facial selectivity for a Z-allylic alcohol depends on the nature of the Z substituent R^3. The enantioselectivity for

substrate with unbranched R^3 substituents ranges from 80 to 94% ee, but that for substrates with branched substituent is lower.[9]

Mechanism

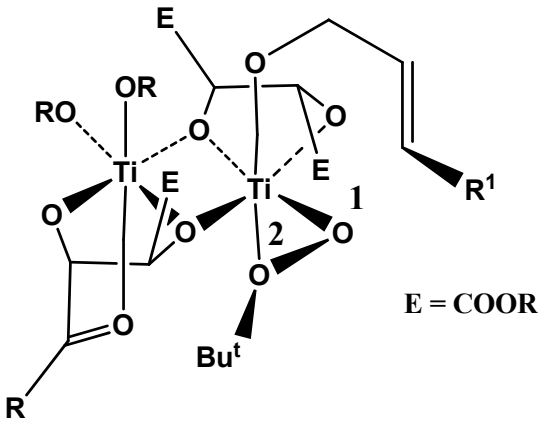


Scheme 2



Scheme 3. Typical examples of epoxidation of allylic alcohols.

The reaction sequence proposed for the metal-catalyzed epoxidation of allylic alcohols is shown in **Scheme 3**.[13] Metal alkoxides generally undergo rapid ligand exchange with alcohols. When a metal alkoxide, an allylic alcohol, and an alkyl hydroperoxide are mixed, ligand exchange occurs to afford a mixture of complexes. Among them, only species such as '**a**', bearing both allylic alkoxide and alkyl hydroperoxide groups, are responsible for the epoxidation. The incorporated alkyl hydroperoxide is thought to be further activated by coordination of the second oxygen atom (O-2) to the metal center. The ensuing transfer of O-1 to the double bond of the allylic alcohol occurs in an intramolecular fashion is supported by comparison of the epoxidation rate of allylic alcohol with that of allyl methyl ether.[14] However controversy still surrounds the oxygen transfer process (**b-e**).



12

Figure. 1

One suggestion is that the double bond first coordinates to the metal center and then inserts into the μ–2-alkyl hydroperoxide ligand to give epoxide via the peroxometallocycle intermediate.[15] An alternative proposal is that the double bond attacks the distal oxygen along the axis of the O-O bond that is broken[9] Frontier

molecular orbital treatment of peroxometal complexes also suggests that d-transition metal complexes of ROO^- exhibit electrophilic behavior.[16] Finally, exchange of *tert*-butoxide and the epoxy alkoxide so formed with allylic alcohol and alkyl hydroperoxide completes the reaction cycle.

The titanium tartarate mediated asymmetric epoxidation of allylic alcohols also follows the same basic reaction pathway of **Scheme 3**. The mechanism of transfer of oxygen to the substrate is found by determing the structures of titanium-dialkyl tartrate complexes,[15,17] as well as those prepared from $Ti(OPr^i)4$ and (*R*,*R*)-*N*,*N*'-dibenzyltartramide and from Ti(OEt)4, (*R*,*R*)-diethyl tartrate, and Ph(CO)-N(OH)Ph.[18] Based on the X-ray analysis of these complexes, the structure of the asymmetric epoxidation catalyst **12** (**Fig. 1**) has been proposed.

SECTION: II

Hydrolytic Kinetic Resolution (HKR) of terminal epoxides

1.2.1. Introduction

Resolutions fall broadly into three classes. Classical resolutions involve the use of a stoichiometric amount of a chiral resolving agent.[18] The resolving agent is associated to the substrate, either covalently or non-covalently, to generate a pair of diastereomers. The diastereomers are separated and, through a separate chemical transformation, the substrate is released from the resolving agent. This approach has proven to be especially useful if salt formation is straightforward, as in the case of amines and carboxylic acids.[19] Chiral chromatography generally relies on the use of a chiral stationary phase to resolve enantiomers contained in a mobile phase, and in principle it can be carried out on analytical or preparative scale. In reality, the large solvent volumes, long separation times, and relatively high costs of chiral chromatography supports often limit the scale at which chromatographic separations can be carried out. Kinetic resolution involves using a chiral catalyst or reagent to promote selective reaction of one enantiomer over the other giving a mixture of enantio-enriched starting material and product, and the desired component is then isolated.[20]

As noted above, the theoretical yields for such resolutions are usually 50%. If the "undesired" resolution byproduct can be racemized or otherwise converted back to the desired enantiomer, then this can improve the yield, and therefore the practicality, of the resolution process, provided the additional cost in time and materials does not eclipse the cost of the initial resolution. In some special circumstances, it is possible to induce substrate racemization under the conditions

of resolution. It then becomes possible in principle to convert essentially 100% of the racemate to the desired product. Such processes constitute a very special subclass of kinetic resolution reactions known as dynamic kinetic resolutions.

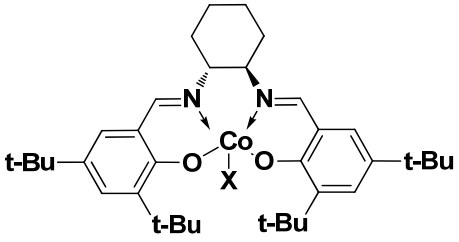
For the most part, however, racemization is not readily affected and the issue of a maximum yield of 50% holds. This applies equally to parallel kinetic resolutions, an additional subclass of kinetic resolution reactions. However, given that racemates can often be much less than half as expensive as their enantiopure counterparts, it is clearly simplistic to consider resolutions as being inherently inelegant or impractical. Indeed, the fact that resolution remains so widely used is probably the best evidence that it can in fact be the most attractive option for accessing enantio- enriched compounds. Catalytic kinetic resolutions are particularly attractive, at least in principle, because of the need for only small amounts of chiral "resolving agent". However, kinetic resolution has been used very little in a commercial context compared to classical or even chromatographic resolution. The racemate is cheap and no good enantioselective, chiral pool, or classical resolution route to the product exists.

1.2.2. Merits of Hydrolytic Kinetic Resolution of epoxides

1. The catalyst is highly selective for one enantiomer and is effective at low loadings.
2. The catalyst is inexpensive or it can be recycled efficiently.
3. The reaction is economical and safe (i. e., inexpensive stoichiometric reagents, no undue dangers associated with the reagents, high volumetric throughput, and a minimum of waste generated).

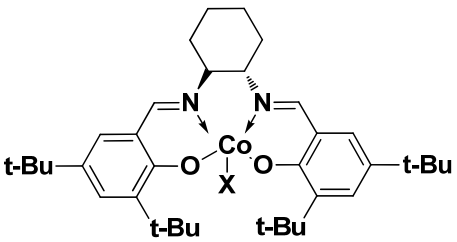
Recently Jacobsen had discovered the (salen)Co complex **13** which can catalyze

hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides efficiently (**Scheme 4**).[21-23] This new method appeared to hold considerable promise with regard to meeting all of the criteria outlined above for kinetic resolution to be practical. Racemic 1,2-epoxides are generally available directly from commercial suppliers at low cost or are obtainable in one step from inexpensive olefins or aldehydes. In fact, certain racemic epoxides, such as propylene oxide, epichlorohydrin, styrene oxide, and butadiene monoepoxide, are commodity chemicals and are no more expensive than common organic solvents. Second, the ligands for catalyst **13** had previously been commercialized and manufactured on a ton scale in the context of (salen)Mn epoxidation catalysts.[24] The cobalt analogues (*R*,*R*)-**13** and (*S*,*S*)-**13** proved equally accessible, and these are also now available in bulk. Third, water is perhaps the ideal reagent for effecting the resolution reaction: it is inexpensive and safe, and the rate of the ring-opening reaction can be controlled simply by modulating the rate of addition of water to the epoxide-catalyst mixture. Fourth, for those examples that were described in the preliminary report, highly enantio-enriched epoxides were recovered from HKR.



X = OAc

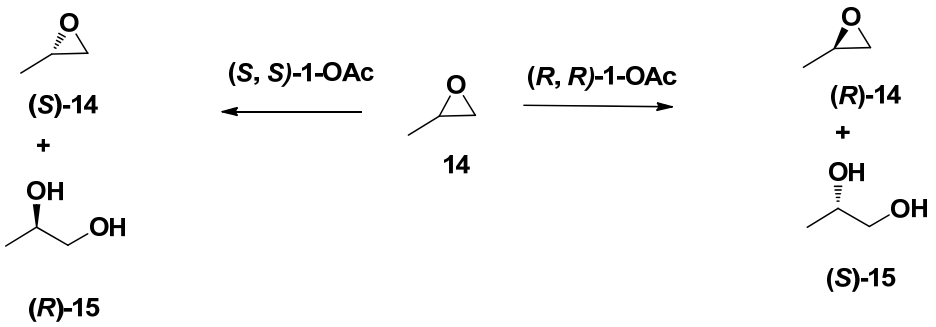
(R, R)-13



X = OAc

(*S, S*)-13

Figure 2. Jacobsen's catalyst



Scheme 4. Hydrolytic kinetic resolution of epoxides

Finally, the HKR provided useful enantio-enriched 1,2-diols, including many that are otherwise not readily accessible using existing asymmetric dihydroxylation methods.[56] The HKR has seen rapid adoption as the method of choice for the preparation of a variety of terminal epoxides in enantio-enriched form, and a number of applications in target oriented synthesis have been reported already.[57] In addition, the commercial manufacture of enantio-enriched propylene oxide, epichlorohydrin, and styrene oxide using HKR methodology has been implemented, thereby reducing the cost of these useful chiral building blocks.[54] Jacobsen has discovered that the HKR is an extraordinarily general reaction, allowing efficient kinetic resolution of virtually any type of terminal epoxide.

1.3. References

1. For reviews, see: *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, **1993.**

2. (a) Katsuki, T.; Martin, V. S. *Org. React*. **1996**, *48*, 1; (b) Katsuki, T. *J. Mol. Catal. A: Chem*. **1996**, *113*, 87; (c) For a review, see: Johnson, R. A.; Sharpless, K. B. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, **1993**, pp. 101.

3. (a) McDonald, F. E.; Towne, T. B. *J. Org. Chem.* **1995**, *60*, 5750; (b)

Kennedy, R. M.; Tang. S. *Tetrahedron Lett.* **1992***, 33*, 3729; (c) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992***, 33*, 5299; (d) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992***, 33*, 5303; (e) Boyce, R. S.; Kennedy, R. M. *Tetrahedron Lett*. **1994**, *35*, 5133.

4. Sharpless, K. B.; Teranishi, A. Y.; Backvall, J. -E. *J. Am. Chem. Soc*. **1977**, *99*, 3120.

5. a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994,** *94*, 2483; (b) Schroder, M. *Chem*. *Rev*. **1980**, *80*, 187.

6. (a) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew*. *Chem*. *Int. Ed*. **1996**, *35*, 451; (b) Rudolph, J.; Sennhenn,P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew*. *Chem*. *Int. Ed.* **1996**, *35*, 2810; (c) Li, G.; Sharpless, K. B. *Acta Chem. Scand*. **1996**, *50*, 649; (d) Angelaud, R.; Landais, Y.; Schenk, K. *Tetrahedron Lett*. **1997**, *38*, 1407.

7. Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1995**, *34*, 1059.

8. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

9. (a) Wood, R. D.; Ganem, B. *Tetrahedron Lett.* **1982**, *23*, 707; (b) Erickson, T. J. *J. Org. Chem.* **1986**, *51*, 934.

10. Hirai, Y.; Chintani, M.; Yamazaki, T.; Momose, T. *Chem. Lett.* **1989**, 1449.

11. Sakai, J.; Sugita, Y.; Sato, M.; Kaneko, C. *J. Chem. Soc., Chem. Commun.* **1991**, 434.

12. (a) Sugita, Y.; Sakai, J.; Sato, M.; Kaneko, C. *J. Chem. Soc., Perkin Trans 1*, **1992**, 2855; (b) Boschetti, A.; Panza, L.; Ronchetti, F.; Russo, G.; Toma, L. *J. Chem. Soc., Perkin Trans*. *1*, **1988**, 3353.

13. (a) Parker, R. E.; Issacs, N. S. *Chem. Rev.* **1959**, *59*, 737; (b) Sharpless, K. B.; Verhoeven, J. R. *Aldrichim*. *Acta.* **1979**, *12*, 63.

14. Sharpless, K. B. Proceedings of the Robert A. *Welch Foundation Conferences on Chemical Reasearch XXVII*, Houston, Texas, **1983**, pp. 59.

15. (a) Chaumette, P.; Mimoun, H.; Sussine, L.; Fischer, J.; Mitschler, A. *J.*

Orgnomet. Chem. **1983**, *250*, 291; (b) Mimoun, H.; Charpentier, R.; Mitschler, A.; Fische, J.; Weiss, R. *J. Am. Chem. Soc*. **1980**, *102*, 1047; (c) Mimoun, H. *Angew Chem Int. Ed. Engl.* **1982**, *21*, 737; (d) Sharpless, K. B.; Woodard, S. S.; Finn, M. G. *Pure & Appl. Chem.* **1983**, *55*, 1823.

16. Bach, R. D.; Wolber, G. J.; Coddens, B. A. *J. Am. Chem. Soc.* **1984**, *106*, 6098.

17. (a) Rossiter, B. E.; Sharpless, K. B. *The Scripps Research Institute*, La Jolla, CA, unpublished results; (b) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353; (c) Woodward, S. S.; Ph.D Dissertation, *Stanford University*, California, **1981**;

18. J. Jacques, A. Collet, S. H. Wilen, Enantiomers, Racemates, and Resolutions, Krieger, Malabar, FL, **1991.**

19. J. F. Larrow, E. N. Jacobsen *Org. Synth*. **1998**, 75, 1.

20. (a) Fumagillin: Tarbell, D. S.; Carman, R. M.; Chapman, D. D.; Cremer, S. E.; Cross, A. D.; Huffman, K. R.; Kuntsmann, M.; McCorkindale, N. J.; McNally, J. G.; Rosowsky, A.; Varino, F. H. L.; West, R. L. *J. Am. Chem. Soc.* **1961**, *83*, 3096; (b) Ovalicin: Sigg, H. P.; Weber, H. P. *Helv. Chim. Acta* **1968**, *51*, 1395; (c) Coriolin: Takeuchi, T.; Iinuma, H.; Iwanaga, J.; Takahashi, S.; Takita, T.; Umezawa, H. *J. Antibiot.* **1969**, *22*, 215; (d) Disparlure: Bierl, B. A.; Beroza, M.; Collier, C. W. *Science* **1970**, *170*, 87; (e) Triptolide: Kupchan, S. M.; Court, W. A.; Dailey, R. G.; Gilmore, C. J.; Bryan, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7194; (f) Periplanone B: Persoons, C. J.; Verwiel, P. E. J.; Ritter, F. J.; Talman, E.; Nooijen, P. J.; Nooijen, W. J. *Tetrahedron Lett.* **1976**, *17*, 2055.

21. (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.

22. For earlier studies involving (salen) metal-catalyzed reactions of epoxides that served as a foundation for the discovery of the HKR, see: (a) Tekeichi, T.; Arihara, M.; Ishimori, M.; Tsuruta, T. *Tetrahedron* **1980**, *36*, 3391. (b) Maruyama, K.; Nakamura, T.; Nakamura, S.; Ogino, A.; Nishinaga, A. *React. Kinet. Catal. Lett.* **1991**, *45*, 165. (c) Larrow, J. F., Schaus, S. E.,

Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420.

23. The HKR is complementary to biocatalytic methods exploiting epoxide hydrolases. For a review, see: Archelas, A.; Furstoss, R. *Trends Biotechnol.* **1998**, *16*, 108.

24. (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.

25. For the most effective catalyst developed thus far for the asymmetric dihydroxylation of terminal olefins, see: Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448.

26. (a) Gurjar, M. K.; Sadalapure, K.; Adhikari, S.; Sarma, B. V. N. B. S.; Talukdar, A.; Chorghade, M. S. *Heterocycles* **1998**, *48*, 1471; (b) Schaus, S. E.; Brånalt, J. E.; Jacobsen, E. N. *J. Org. Chem*. **1998**, *63*, 4876; (c) Gurjar, M. K.; Krishna, L. M.; Sarma, B. V. N. B. S.; Chorghade, M. S. *Org. Proc. Res. Dev.* **1998**, *2*, 422; (d) Savle, P. S.; Lamoreaux, M. J.; Berry, J. F.; Gandour, R. D. *Tetrahedron: Asymmetry* **1998**, *9*, 1843; (e) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092; (f) Hou, X.-L.; Li B.-F.; Dai, L.-X. *Tetrahedron: Asymmetry* **1999**, *10*, 2319; (g) Rodrı´guez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J. *Tetrahedron Lett.* **1999**, *40*, 5161; (h) Kamada, M.; Satoh, T.; Kakuchi, T.; Yokota, K. *Tetrahedron: Asymmetry* **1999**, *10*, 3667.

CHAPTER II:

A facile stereoselective total synthesis of (*R*)-rugulactone

A facile stereoselective total synthesis of (*R*)-rugulactone

2.1. Introduction and pharmacology

The 6-alkyl and aryl substituted α-pyrones (6-arylalkyl-5,6-dihydro-2H-pyran-2-ones) possess important biological properties such as antitumor, antiviral, antifungal anti-inflammatory[1] etc. These properties arise as a result of Michael acceptor property of α-pyrones towards the amino acid residues of the receptors. The biological assays of 6-arylalkyl-5,6-dihydro-2H-pyran-2-one, (*R*)-Rugulactone (**1)**, which has been extracted from the evergreen tree *cryptocarya Rugulosa*[2] of Lauraceae family has been found to inhibit the nuclear factor (NF-kB) activation pathway occurring in different types of cancers[3]. NF-kB is a protein complex that acts as a transcription factor that is found in almost all types of animal cells and has an important role in cellular responses to stimuli such as stress, ultraviolet irradiation, cytokines, oxidized low-density lipoproteins, free radicals and bacterial or viral antigens. NF-kB therefore plays a vital role in regulating the immune response to infections.

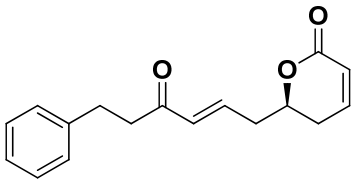


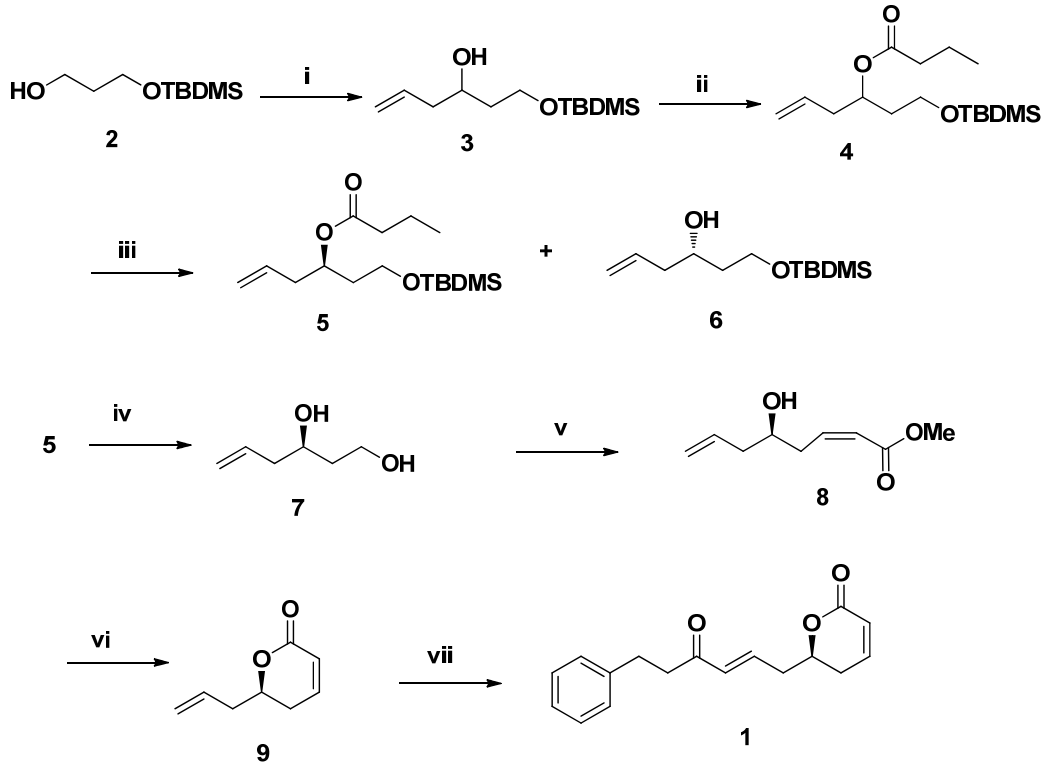
Figure 1. (*R*)-Rugulactone (**1)**

2.2. Review of literature

Various syntheses of (*R*) - rugulactone have been documented in the literature. Some of the interesting and important synthetic routes to (*R*) - rugulactone are described below.

Fadnavis's approach (2010)[4]

Fadnavis *et al.* have reported the synthesis of (*R*)-rugulactone (**1**) starting from 1,3-propane diol. The key steps employed in their approach are selective enzymatic resolution of butyrate esters and Grubb's cross metathesis reactions. Swern oxidation of monosilyl protected diol **2** gave aldehyde, which upon olefination produced homoallylic alcohol **3** which was further esterified with butyric acid to afford **4**.



Scheme 1: *Reagents and conditions;(i) (a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 ^oC, 1 h; (b) Zn, allyl bromide, NH_4Cl in THF, 3h; (ii) DCC, DMAP, Butyric acid in DCM, 2h; (iii) Tris- HCl buffer,0.05M, pH 7.5; candida rugosa lipase, 48h; (iv) PTSA, MeOH, 1h, (v) (a) BIAB, TEMPO, 4h; (b) $EtO_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, dry THF, -78 ^oC: (vi) PTSA, benzene, reflux 1h; (vii) $ArCH_2CH_2COCHCH_2$, Grubb's 2nd generation catalyst (5 mol %), dry CH_2Cl_2, 45 ^oC, 5 h,*

The butyrate ester **4** on lipase catalyzed hydrolysis produces **5** with 99% ee. The chiral ester **5** was further hydrolyzed, and the diol **7** was selectively oxidized to

aldehyde,which further was subjected to olefination to obtain unsaturated ester **8** via Horner-Emmons olefination reaction. The unsaturated laconte **9** on Grubb's cross metathesis with vinyl benzyl ketone produced the required target molecule **9** (**Scheme 1).**

D. K Mahapatra's approach (2009)[5]

D. K. Mahapatra *et al.* have developed a practical route for the synthesis of (*R*)-rugulactone starting with the epoxide **11**, which was prepared by Jacobsen's hydrolytic kinetic resolution (HKR) of the racemate **10** using (*R*,*R*)-(Salen)Co^{III}(OAC) catalyst to obtain chiral epoxide **11**. Opening of epoxide **11**with vinyl Grignard in presence of CuI produced intermediate **12**, which was further converted to acrylate ester by treating with acryloyl chloride in presence of Et_3N. Deprotection of PMB group with DDQ followed by oxidation of primary hydroxyl group with Dess Martin periodinane (DMP) afforded aldehyde, which was immediately subjected to Horner- Wardswoth- Emmons homologation with dimethyl (2-oxo-4-phenylbutyl)phosphonate in presence of sodium bis(trimethylsilyl)-amide gave the α,β- unsaturated ketone **13 (Scheme 2)**.

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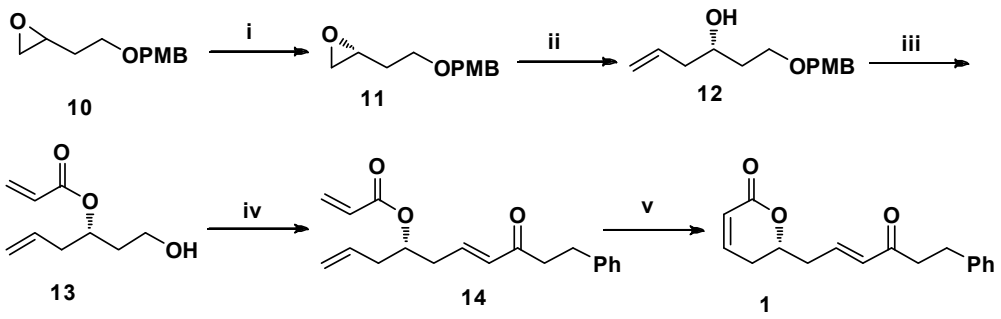
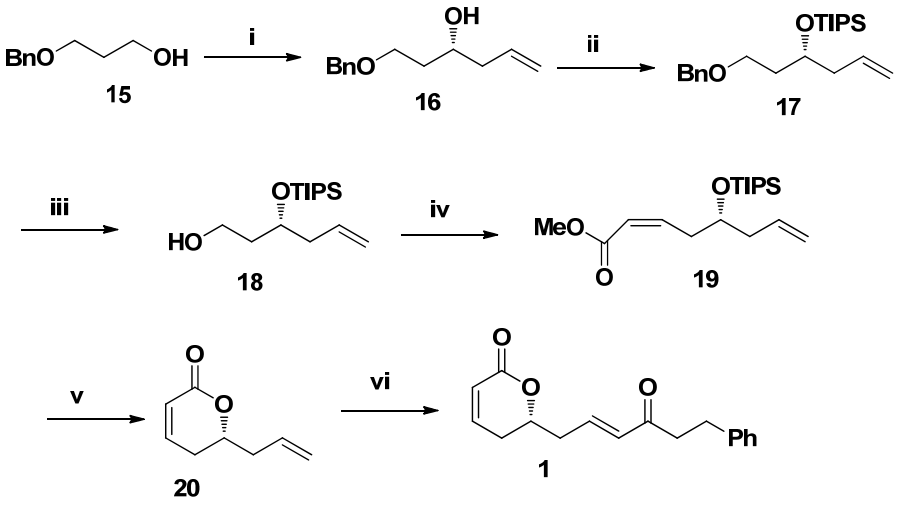


Scheme 2 : *Reagents and conditions; (i) (R,R) – (Salen)Co^{III}(OAC) catalyst, H_2O; (ii) vinyl magnesium bromide, CuI, THF, 0 ^oC, 2 h; (iii) (a) acryloyl chloride, Et_3N, DMAP, CH_2Cl_2, 12 h; (b) DDQ, CH_2Cl_2, H_2O, rt, 1 h; (iv) (a) DMP, CH_2Cl_2, 0 ^oC, 2 h; (b) NaHMDS, phosphonate, 0 ^oC, 12 h; (v) Grubb's catalyst, CH_2Cl_2, reflux, 12 h:*

Finally, the Grubb's ring closing metathesis reaction of ketone **13** with Grubb' first generation catalyst afforded the required target molecule **1**.

Y. Venkateswarlu's approach (2009)[6]

As outlined in **Scheme 3**, the synthesis began with monobenzyl protected 1,3-propanediol **15**, which was oxidized to using iodoxybenzoic acid (IBX) in DMSO to afford the corresponding aldehyde, which was subjected to the catalytic asymmetric allyl stannation to furnish the homoallylic alcohol **16** in 80% yield. The secondary hydroxyl group **16** was protected as its TPS ether using TPSCl and imidazole in dry DCM to yield **17**. Next, the benzyl group in compound **17** was removed to yield primary alcohol **18**. The primary hydroxyl group in compound **18** was oxidized using IBX in DMSO to yield the aldehyde which was further subjected to still-Gennari modification of the olefination reaction to afford unsaturated ester **19** in 80% yield.

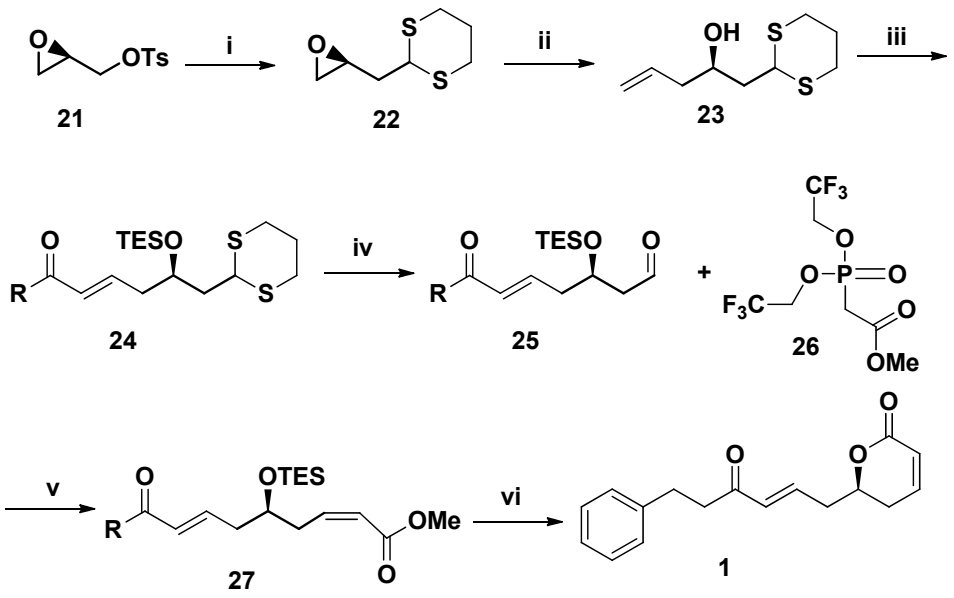


Scheme 3: *Reagents and conditions; (a) IBX, dry DMSO, dry CH_2Cl_2, 5 h; (b) (R)-BINOL, 4 Å MS, $Ti(OiPr)_4$, dry CH_2Cl_2, allyltributylstannane, -78 ^oC to -20 ^oC (ii) TBDPSCl, dry CH_2Cl_2, 4 h; (iii) Li in naphthalene, -20 ^oC, 3h; (iv) (a) IBX, dry DMSO; dry CH_2Cl_2, 5 h; (b) $EtO_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, dry THF, -78 ^oC; (v) 3% HCl in MeOH 30 min; (vi) $ArCH_2CH_2COCHCH_2$, Grubb's 2nd generation catalyst (5 mol %), dry CH_2Cl_2, 40 ^oC, 12h 74%:*

The compound **19** upon treatment with 3% HCl in MeOH afforded 6-allyl-5,6-dihydro-a-pyrone **20** in 78% yield. The fragment 5-phenyl-pent-1-en-3-one was prepared from phenyl-1-propanal to yield allyl alcohol which on oxidation with IBX in DMSO afforded vinyl ketone. Finally, the cross metathesis reaction between vinyl ketone and pyrone **20** fragments using Grubb's second generation catalyst yielded desire (*R*)-rugulactone 1.

Florent Allais's approach (2010)[7]

As outlined in **Scheme 4**, the synthesis of rugulactone began from commercially available (2*S*)-glycidyl tosylate **21**. Compound **24** was easily obtained in three steps from **21**. First, the tosylate moiety in **21** was displaced by using lithiated 1,3-dithiane (n-BuLi, 1,3-dithiane, THF, -78 ^{o}C) to give the corresponding thioacetal **22**. The epoxide ring in **22** was then opened by copper catalyzed Grignard vinylation, which gave the secondary homoallylic alcohol **23**.



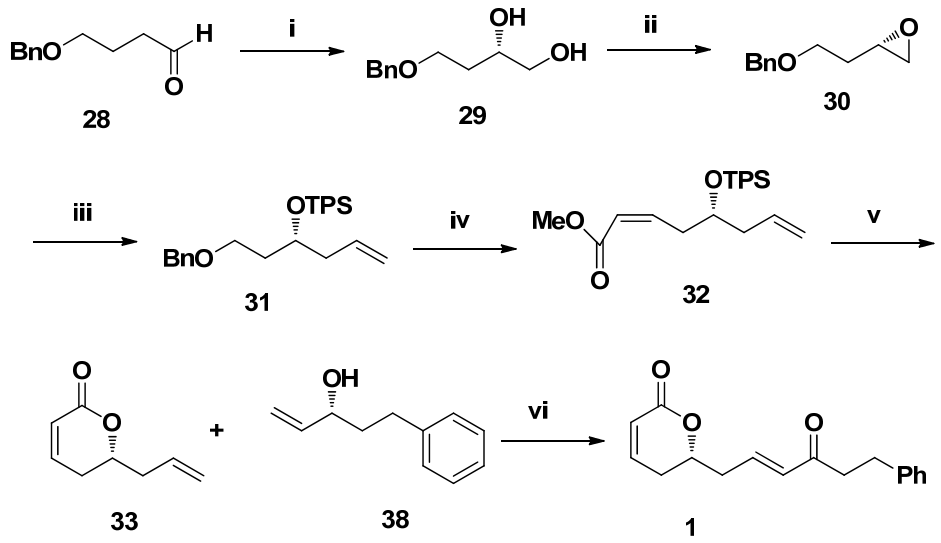
Scheme 4: *Reagents and conditions; (i) n-BuLi, dithiane, THF, -78 ^{o}C; (ii) (a) vinyl magnesium bromide, CuI, THF, -40 ^{o}C (b) TESCl, imidazole, DMAP, DMF; (iii) $ArCH_2CH_2COCHCH_2$, Grubb's 2nd generation catalyst (5 mol %), dry CH_2Cl_2, 40*

^{o}C, 12h 72%: (iv) $CaCO_3$, MeI, CH_3CN-H_2O; (v) KHMDS, 18-crown-6, THF, -78 ^{o}C; (vi) 80% AcOH, heat.

Finally, protection of as its triethylsily ether with tri ethyl silyl chloride using imidazole as base gave the cross-metathesis precursor **23**. The metathesis coupling reaction of **23** and vinyl ketone using Grubb's second generation catalyst in DCM under reflux conditions gave the desire intermediate **24**. Removal of the thioacetal group from dithiane was then performed cleanly(methyl iodied, calcium carbonate, aqueous acetonitrile) to give the crude aldehyde **25**, which was immediately subjected to still-Gennari olefination using potassium hexamethyldisilazide as base and 18-crown-6 as phase transfer catalyst to give Z - α,β-unsaturated ethyl ester. Finally, one pot deprotection and intramolecular lactonization of **27** with 80% AcOH gave (*R*)-rugulactone **1** in 30% overall yield.

D. K. Reddy's approach (2010)[8]

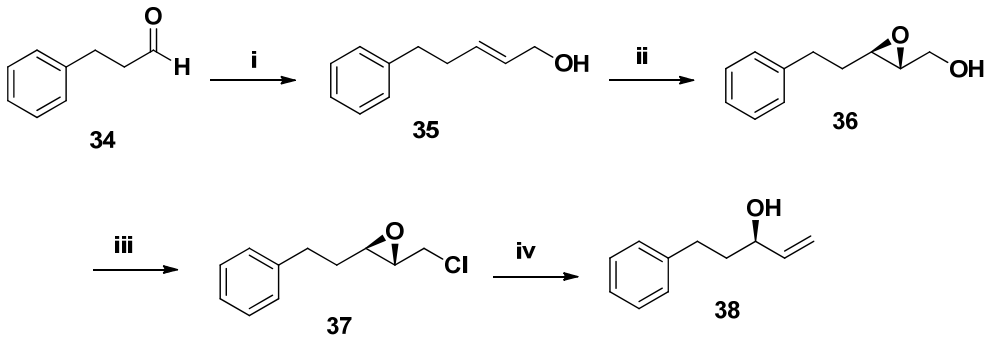
As outlined in **Schemes 5 & 6**, the synthsesis of (*R*)-rugulactone commenced with 4-benzyloxybutanal **28** and 3-phenylpropanol **34**. The 4-benzyloxybutanal was reacted with nitrosobenzene in the presence of D-proline followed by treatment with $NaBH_4$ in MeOH gave the crude aminoxy alcohol, subsequent reduction of the crude aminoxy product with 30 mol% $CuSO_4$ yielded (*R*)- diol **29** in 85% yield. The primary hydroxyl group in **29** was protected with tosyl chloride using triethl amine and catalytic amount of Bu_2SnO to give tosylated compound, which upon reaction with potassium carbonate in methanol gave epoxide **30**. Regioselective opening of epoxide with vinyl magnesium bromide in presence of catalytic amount of CuI furnished homoallylic alcohol. The secondary hydroxyl group was protected as its TPS ether using TPSCl and imidazole in dry DCM to yield **31**. Now the benzyl group was removed using lithium napthanlenide to yield primary alcohol which was oxidized



Scheme 5: *Reagents and conditions;(i) (a) PhNO, D-proline (25 mol %), CH_3CN, -20 ^oC, 24 h then MeOH, $NaBH_4$; (b) $CuSO_4$ (30 mol %), MeOH, 0 ^oC, 10 h, 85%; (ii) (a)TsCl, Bu_2SnO, Et_3N, 0 ^oC to rt, 4 h, 81%; (b) K_2CO_3, MeOH, rt, 1 h, 93%; (iii) (a) vinyl magnesium bromide, CuI, THF, -40 ^oC, 1 h; (b) TBDPSCl, dry CH_2Cl_2, 4 h; (iv) (a) Li in naphthalene, -20 ^oC, 3h; (b) IBX, dry DMSO; dry CH_2Cl_2, 5 h; (c) $EtO_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, dry THF, -78 ^oC, 2h; (v) 3% HCl in MeOH, 30 min, 75%; (vi) (a) Grubb's 2nd generation catalyst (5 mol %), dry CH_2Cl_2, 40 ^oC, 12h; (b) MnO_2, CH_2Cl_2, rt:*

using IBX in DMSO to yield aldehyde which was further undergone Horner-Emmons olefination reaction to afford unsaturated ester **32** with Z/E ratio of 95:05 in 80% yield. Compound **32** on treatment with 3% HCl in MeOH afforded 6-allyl-5,6-dihydro-α-pyrone **33** in 75% yield.

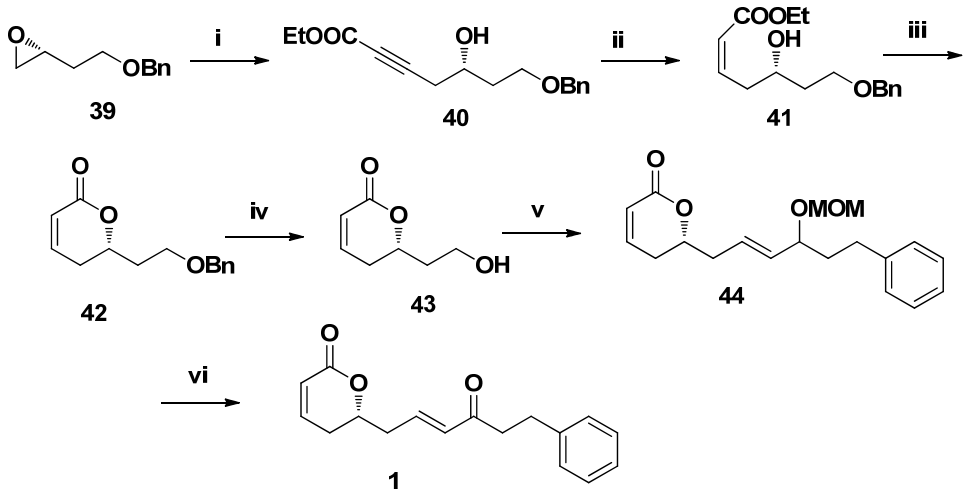
The another important fragment in this synthesis was prepared from 3-phenylpropanol **34**, which on Wittig's olefination gave unsaturated ester, the ester was subsequently reduced to allyl alcohol **35**. Sharpless epoxidation of allyl alchol afforded epoxide **36** in good yield. Regioselective opening of epoxide with triphenyl phosphine in CCl_4 furnished compound **37**, which was then reduced to compound **38** (**Scheme 6).**



Scheme 6: *Reagents and conditions; (i) (a) Ph_3P=CHCOOEt, benzene, reflux, 1 h; (b) DIBAL-H, CH_2Cl_2, -78 ^oC, 30 min; (ii) (-)-DET, $Ti(OPri)_4$, TBHP, molecular sieves 4 A^o, DCM, -20 ^oC,15 h; (iii) PPh_3, CCl_4, 80 ^oC, 2 h; (iv) sodium metal, ether, 6h, 82%.*

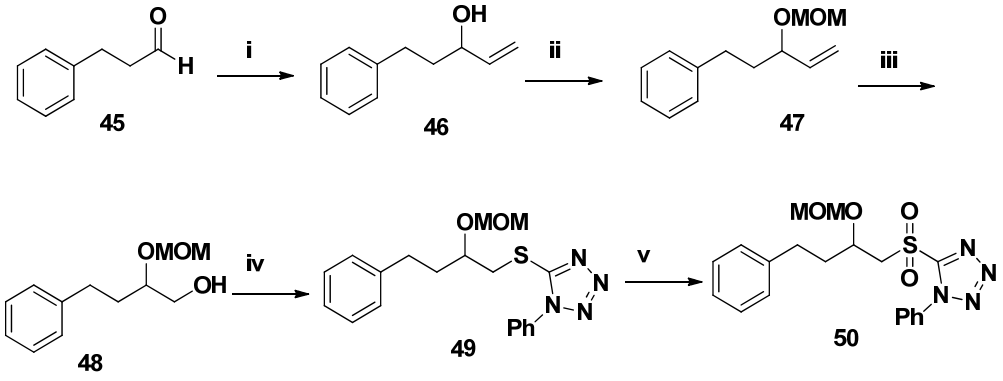
Barua's approach (2010)[9]

The key reaction in their approach was the Julia-Kociensky reaction between aldehyde and sulfone **50** to construct C_8-C_9 trans double bond. Aldehyde was synthesized starting from the epoxide **39**. The synthesis of the sulfone derivative was achieved from commercially available 3-phenyl propionaldehyde, which on treatment with vinyl magnesium bromide in THF yielded alcohol **46**, then the hydroxyl group was protected to its MOM ether to furnish compound **47 (Scheme 8)**.



Scheme 7: *Reagents and conditions (i) Ethyl propionate, n-BuLi, $BF_3.OEt_2$, -78 ^oC; (ii) H_2, Lindlar catalyst, quinoline, EtOAc; (iii) 3% HCl in methanol, 90 %; (iv) DDQ, CH_2Cl_2–H_20;(v) DMP, dry CH_2Cl_2, 0 ^oC to rt; (vi)* ***50****, KHMDS, dry THF, -78 ^oC; (vii) (a) 37% HCl, ethanol, 40 ^oC; (b) IBX, dry DMSO, 92%.*

Oxidative cleavage of **47** with OsO_4/ $NaIO_4$ gave aldehyde, which without further purification was reduced with sodium borohydride in methanol to afford the primary alcohol **48**. The alcohol was then converted to into sulfide **49** by a Mitsunobu reaction employing 1-phenyl-1H-tetrazole- 5-thiol (PT-SH) as the nucleophile. Sulfide **49** was then oxidized to yield the corresponding sulfone **50**.



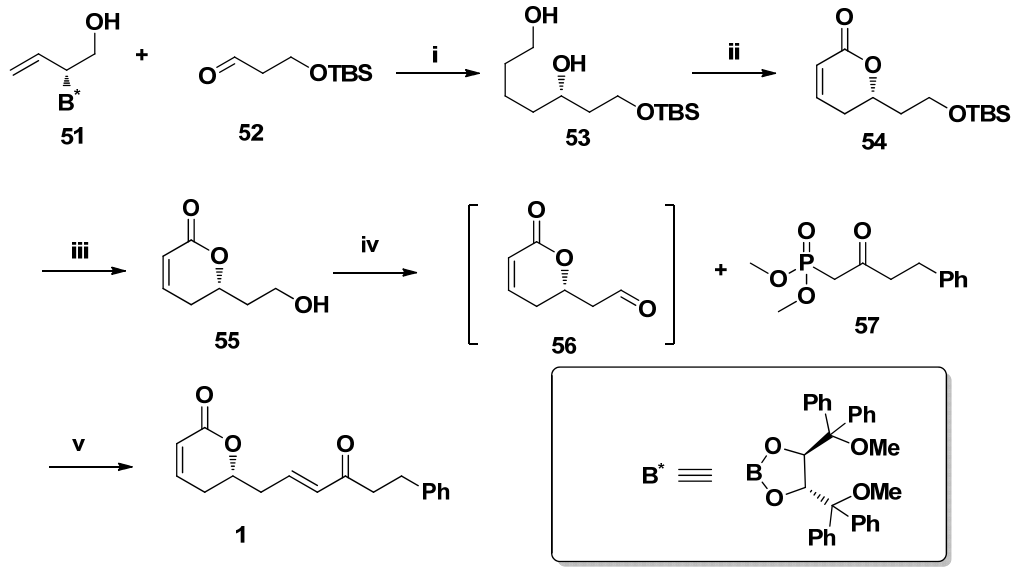
Scheme 8: *Reagents and conditions; (i) vinyl magnesium bromide, THF, -30 ^oC, 90%;(ii) MOMCl, DIPEA, 0 ^oC to rt, 90%; (iii) (a) OsO_4, 2,6-lutidine, NaIO4, dioxane/water; (b) NaBH4, MeOH, 0 ^oC, 95% over two steps; (iv) TPP, PTSH, DIAD, THF, 0 ^oC, to rt, 85%; (v) m-CPBA, CH_2Cl_2, 0 ^oC, 90%.*

The α-pyrone fragment **43** was synthesized starting from known epoxide **39**, which on coupling with ethyl propiolate under Yamaguchi coupling conditions affording the corresponding propargyllic alcohol **40**. Subsequent hydrogenation of compound **40** over Lindlar catalyst furnished unsaturated hydroxy ester **41**. Hydrolysis of the ester proceeded with in situ lactonization to deliver lactone **42**. Removal of the benzyl protecting group with DDQ furnished the α-pyrone fragment **43**. The primary

hydroxy group was oxidized to aldehyde, the crude aldehyde was further coupled with sulfone fragment **50** under Julia-Kociensky reaction conditions to afford compound **44**. The deprotection of MOM group followed by oxidation of hydroxy group gave the final (*R*)-rugulactone **1 (Scheme 7)**.

Pietruszka's approach (2011)[10]

As outlined in **Scheme 9**, the synthesis started with the addition of allyl boronic ester **51** to the aldehyde **52** to yield diol **53** in 92 % yield. The regioselective oxidation of diol with phenyl iodoacetate produced lactone **54**. The TBS group was deprotected with $BF_3.OEt_2$ to obtain lactone **55** in 92% yield. The oxidation of lactone 55 with BIAB led to aldehyde **56**, which was directly subjected to HWE- olefination to afford (*R*)-rugulactone **1** in 38% yield after 5 steps.



Scheme 9: *Reagents and conditions; (i) CH_2Cl_2, 0 ^oC to rt 92%.; (ii) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 92%.;(iii) $BF_3.OEt_2$, CH_2Cl_2, 0 ^oC, 90%; (iv) $PhI(OAc)_2$,TEMPO, CH_2Cl_2; (v) NaHMDS, THF, -78 ^oC to rt, 48% for two steps.*

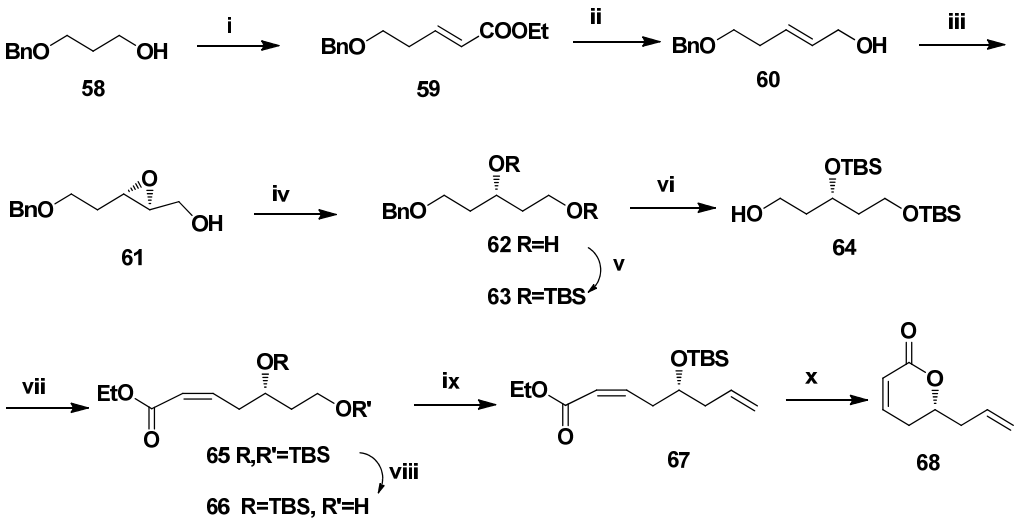
2.3. Present work

2.3.1. Objective

As can be seen from the literature section, most of the reported methods uses expensive catalysts or reagents, which is not industrially viable and some other methods suffer from low atom economical reactions. Hence we planned to synthesize (*R*)-rugulactone in a comparatively less number of simple steps in high overall yield.

2.3.2. Results and discussion

As outlined in **Scheme 10**, our synthetic strategy commenced with 3-benzyloxypropanol **58**. The primary alcohol of 3-benzyloxypropanol was oxidized by using Swern's protocol to the corresponding aldehyde, and then Horner-Wardsworth-Emmons olefination of aldehyde with triethylphosphonoacetate using NaH as base in THF solvent afforded α,β-unsaturated ester **59** in 95% yield. The two peakes at δ 5.84-5.94(d, *J* =15.79 Hz, 1H), 6.91-7.05(m, 1H) in ^{1}H NMR corresponds to two olefinic protons and thus confirms formation of the product. The compound **59** was subsequently reduced to allylic alcohol compound **60** by employing alane reduction ($LiCl/LiAlH_4$) conditions.[11] The disappearance of a peak at δ 166.3 in ^{13}CNMR

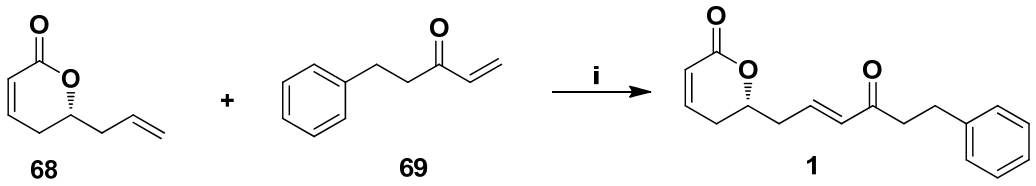


Scheme 10: *Reagents and conditions; (i) (a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78° C, 1 h; (b) triethyl phosphonoacetate, NaH, dry Benzene, 0 ºC- RT, 8 h, 95%; (ii) $LiAlH_4$, $AlCl_3$, THF, 0 °C, 1 h, 82%; (iii) (-)- DET, $Ti(O\text{-}i\text{-}Pr)_4$, TBHP, dry CH_2Cl_2, molecular sieves 4 A°, -15 °C, 87%; (iv) Red-al, THF, -20 °C, 6h, 96%; (v) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, RT, 8 h., 96%; (vi) Na, Liq. NH_3, dry THF, -78 °C, 15 min., 92%; (vii) (a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C, 1h; (b) $EtO_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, dry THF, -78 °C, 2 h, 74%; (viii) CSA, MeOH:CH_2Cl_2 (1:1), RT, 85%; (ix) (a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C, 1 h; (b)$(C_6H_5)_3PCH_3I$, n-BuLi, THF, 0 °C, 82%; (x) PTSA, MeOH, 3 h, 91%.*

Confirms the reduction of keto group in compound **59**.The allyl alcohol **60** was then subjected to Sharpless asymmetric epoxidation[12] to produce epoxy alcohol **61** in 85% yield, which on selective hydride reduction with Red-al[13] yielded 1,3- diol **62**. A peak at δ 4.04-4.16 (m, 1H) in due to (C**H**OH) ^{1}H NMR and a broad at 3447 cm^{-1} due to two hydroxyl groups confirms the diol **62.** The two hydroxyl groups were completely protected to its disilyl ether **63**. The disappearance of a broad band at 3447 cm^{-1} confirms the conversion of hydroxy groups. The subsequent removal of benzyl group was achieved by using Birch debenzylation[14] protocol to afford alcohol **64**. The disappearance of a peak at δ 4.49(br s, 2H) due to benzylic protons (C**H**$_2$Ph) confirms the removal of benzylic group.

Compound **64** was further oxidized to aldehyde and Still - Gennari modified HWE[15] olefination of the crude aldehyde produced Z/E 95:5 mixture of α, β-unsaturated ethyl esters in favor of desired isomer **65**. A peak at δ 168.35 ^{13} CNMR shows the presence of an ester carbonyl group(**C**=O). The geometric isomers were easily separated using silica gel column chromatography to get pure Z isomer of ethyl ester. Later the primary silyl ether was selectively deprotected with camphor sulfonic acid to produce alcohol **66,.** The formation of compound is confirmed by the disappearance of a peak at δ -5.3 in ^{13} CNMR spectrum due to the loss of one silyl carbon. Further, Compound

66 on oxidation followed by Wittig olefination furnished unsaturated ester **67**. Later, α, β-unsaturated ester **67** was stirred in methanol for 2 h in presence of *p*-toluene sulfonic acid to furnish **68** in 91% yield.



Scheme 11: *Reagents and conditions; (a) Grubb's 2nd generation catalyst (5 mol %), dry CH_2Cl_2, 45 ^oC, 12 h, 75%.*

The remaining task was to couple the fragment 5-phenyl-pent-1-en-3-one[16] **69** and lactone **68** (3:1 ratio) by cross metathesis,[17] was implemented by refluxing them in CH_2Cl_2 in presence of Grubb's second generation catalyst[18] (5 mol%) to deliver enantiomerically pure (*R*)-rugulactone**(1)** in 74 % yield as colorless oil (**Scheme 11**) $[\alpha]^{25}_D$: -46.2 (*c* 1, $CHCl_3$), Lit [40] $[\alpha]^{25}_D$: - 46.9 (*c* 1, $CHCl_3$). The formation of product was confirmed by the peaks at δ 198.6 due to lactone carbonyl group, δ 128.5, 133.5, 139.9 due to aromatic carbons in its ^{13}CNMR spectrum**.**

2.4. Conclusion

The stereoselective total synthesis of naturally occuring bioactive compound (*R*)-rugulactone **1** has been successfully achieved employing Sharpless asymmetric epoxidation of allyl alcohol, selective hydride reduction of epoxy alcohol and olefin cross metathesis reactions as the key steps. The synthetic route can conveniently be utilized for the preparation of various analogs of **1** useful for biological evaluation.

2.4. Experimental Section

2.4.1. (E)-ethyl-5-(benzyloxy)pent-2-enoate, 59

DMSO (7.135g, 91.47 mmol) was added drop-wise to a stirred solution of Oxalyl chloride (7.07 g, 60.98 mmol) in CH_2Cl_2 (150 ml) at -78 ^oC. After stirring for 15 min, monoprotected alcohol **58 (**10 g, 30.49 mmol) was added and stirring was continued for additional 45 min. The reaction mixture was finally quenched by the addition of triethylamine (12.31 g, 121.96 mmol) at -78 ^oC and stirring was continued for further 20 min at same temperature and for 30 min at room temperature. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and the contents were washed with water thrice. Organic layer was dried over anhydrous Na_2SO_4, evaporated under reduced pressure and proceded to further reaction with the crude aldehyde.

To a stirred solution of above crude aldehyde in benzene (50 mL) was added (ethoxycarbonylmethylene)triphenylphosphorane (9g, 26mmol) at room temperature. After stirring for 3h, the solvent was evaporated and the residue was chromatographed over silica gel (100-200 mesh, EtOAc/hexane 1:9) yielding pure compound **59** (9.84 g, 95%); IR(neat); ν 3050, 2970, 1630, 1772, 1724, 1650, 1556, 1220, 1097, 745 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.25-1.38(t, *J*=7.0Hz, 3H),2.48-2.58(m, 2H),3.58(m, J=6.44Hz, 2H), 4.13-4.24(m, 2H), 4.5(br s, 2H), 5.84-5.94(d, *J* =15.79 Hz, 1H), 6.91-7.05(m, 1H), 7.25-7.34 (m, 5H);^{13}CNMR (50 MHz, $CDCl_3$): δ 14.2, 32.5, 60.1, 68.2, 72.9, 122.8, 127.6, 128.3, 138.0, 145.5, 166.3; Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.73. Found C, 71.15; H, 7.93.

2.4.2. (E)-ethyl-5-(benzyloxy)pent-2-en-1-ol, 60

To a suspension of Lithium Aluminum hydride (12.8 mmol, 0.486 g) in dry THF at 0^oC under N_2 atmosphere was added a drop wise solution of $AlCl_3$(0.577 g, 4.3 mmol) in THF. The reaction mixture was stirred at same temperature for 30 min. To this stirred suspension, was added the drop wise solution of unsaturated ester **59** (2 g, 8.54 mmol) in THF over a period of 10 min and the contents were stirred at 0^oC for 1h.

The reaction mixture was quenched with water and filtered through Celite and the residue was washed with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure.The residue was chromatographed over silica gel (100-200 mesh, EtOAc/hexane 2:8) yielding pure alcohol **60** (7.96 g, 78%)as colorless oil; IR (neat) ν 3455, 3120, 3095, 2975, 1779,1660, 1557, 1250, 1095, 745cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$): δ 2.35 (m, 2H), 3.48-3.55(t, J=6.7 Hz, 2H), 4.07(br s, 2H), 4.5(br s, 2H), 5.71(m, 1H), 7.25-7.34(m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 32.4, 63.0, 69.4, 72.62, 127.4, 127.5, 128.2, 131.0, 138.0;Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.97.; H, 8.39. Found C, 74.78; H, 8.45.

2.4.3. ((3S)-3-(2-(benzyloxy)ethyl)oxirane-2-yl)methanol, 61

(-)-Diethyl tartarate (0.2 g, 1 mmol), $Ti(O\text{-}iPr)_4$ (0.23 g, 0.8 mmol) were added sequentially to a suspension of 4 A^o molecular sieves (3 g) in CH_2Cl_2 (20 mL) at -20 ^{o}C and the suspension was stirred for 30 min. A solution of compound **60** (0.6 g, 2.6 mmol) in dry CH_2Cl_2 (15 mL) was then added drop wise at the same temperature followed by the addition of tBuOOH (0.45 g, 2 mmol) and the reaction mixture was stirred for 12 h at -10 °C. When the starting material was not observed on the TLC, the reaction was quenched with 20% NaOH solution saturated with NaCl (1 mL) and the reaction mixture was stirred vigorously for another 30 min at RT. The resulting reaction mixture was filtered through celite, the solvent was evaporated and the crude product was purified by column chromatography over silica gel (60-120 mesh, EtOAc/hexane 3:7) to afford pure epoxy alcohol **61** in 87% yield (0.54 g); $[\alpha]_D^{25}$: + 16.9 (*c* 0.6, $CHCl_3$); IR (neat): ν 3478, 3125, 3053, 2920, 1585, 1267, 1250, 1192, 1124, 1094, 845, 790, 744 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.87-1.97 (m, 2H), 2.98(s, 1H), 3.10 (s, 1H), 3.58-3.66 (m, 3H), 3.86-3.94 (dd, J = 2.65, 9.98 Hz, 1H)

4.52 (br s, 2H) 7.25-7.35 (m, 5H); ^{13}C NMR (50 MHz): δ 32.0, 53.7, 58.5, 61.7, 73.0, 127.6, 128.4, 138.1; Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found C, 69.45; H, 7.85.

2.4.4. (R)-5-(benzyloxy)pentane-1,3-diol, 62

To a stirred solution of epoxy alcohol **61** (0.15 g, 0.75 mmol) in THF (5 mL) at -15 °C was added drop wise solution of sodium bis (methoxyethoxy) aluminum hydride (Red-al) (3.5 M solution in toluene, 1.2 mmol). The reaction mixture was stirred for 6 h at the same temperature. When no starting material was observed on TLC, the temperature was raised to 0 ^{o}C, reaction mixture was quenched with citric acid solution and the resultant reaction mixture was stirred for another 10 min. Then contents were decanted leaving behind a residue, which was further dissolved in water and extracted with EtOAc thrice. The combined organic layers were evaporated under reduced pressure, and the residue was chromatographed over silica gel (60-120 mesh, EtOAc/hexane 3:7) yielding pure diol **62** (0.14g, 96 %) as viscous liquid; $[\alpha]_D^{25}$: - 5.8 (*c* 0.6, $CHCl_3$); IR (neat): ν 3447, 3123, 2186, 1769, 1576, 1478, 1267, 1181, 1134, 1096, 748 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.65-1.83 (m, 5H), 3.63-3.75 (m, 2H), 3.81-3.86 (m, 2H), 4.04-4.16 (m, 1H), 4.53 (br s, 2H), 7.25-7.35 (m, 5H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 36.5, 38.4, 61.4, 69.0, 71.7, 73.4, 127.8, 128.5, 137.7 ; Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found C, 69.15; H, 7.95.

2.4.5.(S)-5-(2-(benzyloxy)ethyl)-2,2,3,3,9,9,10,10,-octamethyl-4,8-dioxa-3,9-disilaundecane, 63

To a stirred solution of diol **62** (1 g, 4.8 mmol) in dry CH_2Cl_2 (80 ml), Imidazole (0.68 g, 10 mmol) were added and the reaction mixture was cooled to 0^{o}C, a solution of tertButyldimethylsilyl chloride (1.4 g, 9.6 mmol) indry CH_2Cl_2(20 mL) was added drop wise at 0^{o}Cand the reaction mixture was stirred at room temperature for 12 h.

After completion of the reaction (as monitored by TLC) reaction mixture was diluted with CH_2Cl_2 (40 ml) and washed with water, organic layer was dried and concentrated under reduced pressure. The residue was chromatographed over silica gel (60-120 mesh, EtOAc/hexane 1:9) yielding pure compound **63** (2.1g, 96%) as colorless oil; $[\alpha]_D^{25}$: + 8.9 (*c* 0.5, $CHCl_3$): IR (neat): ν 3121, 3035, 2928, 1767, 1598, 1475, 1267, 1186, 1134, 1092, 746cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$); δ 0.04(br s, 12H), 0.88(br s, 18H), 1.66-1.81(m, 4H), 3.51-3.57(t, J=6.57Hz, 2H), 3.98(m, 1H), 4.49(br s, 2H), 7.25-7.35(m, 5H) ; ^{13}C NMR (200 MHz, $CDCl_3$): δ -5.3, -4.6, 25.9, 37.3, 40.5, 59.8, 67.0, 66.7, 72.9, 127.6, 128.3;Anal. Calcd for$C_{17}H_{40}O_3Si_2$: C, 58.56; H, 11.51. Found C, 59.15; H, 10.95.

2.4.6. (S)-3, 5-bis((tert-butyldimethylsilyloxy)penta-1-ol, 64

To a stirred solution of Na (0.207 g , 9 mmol) in liquid NH_3 at -78 ^{o}C was added compound **63** (1.45 g, 3 mmol) in dry THF (10 mL) and the reaction mixture was stirred for 15 min at the same temperature. Then the reaction was quenched by adding saturated NH_4Cl (5 mL) solution drop wise. The contents were filtered through celite pad and the solvents were evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel (60-120 mesh, EtOAc/hexane 1:9) to yield pure compound **64** (1.13 g, 92%)as colorless viscous liquid;$[\alpha]_D^{25}$: + 18.3 (*c* 0.6, $CHCl_3$); IR (neat): ν 3448, 3023, 2932, 1265, 1252, 1141, 1126, 1042, 996, 915, 756cm^{-1} ;^{1}H NMR (200 MHz, $CDCl_3$): δ 0.09(br s, 12H), 0.89(br s, 18H), 1.64-1.90(m, 4H), 2.60(br s, 1H), 3.63.3.69(t, J=6.44 Hz, 2H0, 3.72-3.87(m, 2H), 4.15 (m, 1H);^{13}C NMR (200 MHz, $CDCl_3$): δ -5.4, -4.6, 18.0, 25.9, 38.0, 39.6, 59.7, 60.1, 69.0;Anal. Calcd for $C_{17}H_{40}O_3Si_2$: C, 58.56; H, 11.51.Found C, 59.15; H, 10.95.

2.4.7. (S, Z)-ethyl 5, 7-bis(tert-butyldimethylsilyl)oxy)hept-2-enoate, 65

BAIB (4.99 g, 15.51 mmol) and TEMPO (0.162 g, 1.04 mmol) were added to a stirred solution of **64** (1.2 g, 10.34 mmol) in CH_2Cl_2 (30 mL) at room temperature and stirred for 4 h, then reaction was quenched with saturated solution of $Na_2S_2O_3$ in water (0.5 mL). Reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with water and dried over anhydrous Na_2SO_4. The organic layer was concentrated under *vacuum* to get crude aldehyde.

NaH (0.448 g, 13.30 mmol) was added to a stirred solution of ethyl P,P bis (2,2,2-trifluoroethyl) phosphonoacetate (3.496 g, 10.52 mmol) in dry THF (50 mL) at 0 ^oC, resulting ylidesolution was stirred for 45 min at the same temperature,then the reaction mixture was cooled to -78 ^oC. The crude aldehyde obtained above dissolved in dry THF (10 mL) was added drop wise and stirring was continued for further 3 h. After completion of the reaction, the reaction was quenched with saturated NH_4Cl solution (2 mL) at 0 ^oC, concentrated under reduced pressure. Residue obtained was dissolved in EtOAc washed with water and brine. Organic layer was driedover Na_2SO_4,evaporated under *vacuum* and the crude product was purified by silica gel column chromatography (100-200 mesh, EtOAc/hexane 2:8) to obtain **65** (1.33 g, 74%) as colorless oily compound; $[\alpha]_D^{25}$: - 12.3 (*c* 1, $CHCl_3$);IR (neat): ν 3116, 3020, 2922, 1724, 1679, 1326, 1243, 1125, 1141, 1047, 1024, 747 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$):δ 0.12, (br s, 12H), 0.91(br s, 18H), 1.29-1.33(t, *J* = 7.08 Hz, 3H), 1.69 (br s, 1H), 1.75-1.80 (m, 2H), 2.88-2.99 (m, 2H), 3.73-3.85 (m, 2H), 4.12 (m, 1H), 4.16-4.21(m, 2H). 5.88 (d, *J* =11.54 Hz, 1H), 6.38 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ -5.4, -4.7, 14.2, 25.7, 40.5, 51.0, 59.2, 60.6, 65.5, 123.4, 145.8, 168.35; Anal. Calcd for $C_{21}H_{44}O_4Si_2$: C, 60.52; H, 10.68. Found C, 61.15;H, 9.98.

2.4.8. (S, Z)-ethyl 5,7-(tert-butyldimethylsilyl)oxy)-7-hydroxyhept-2-enoate, 66

Camphor sulphonic acid (0.074 g, 0.33 mmol) was added to a stirred solution of compound **65** (0.416 g, 1mmol) in 1:1 mixture of MeOH and CH_2Cl_2 at room temperature. The reaction mixture was stirred for 1.5 h and upon completion; the reaction was quenched with saturated $NaHCO_3$ solution. The product was extracted into CH_2Cl_2,the organic layer was evaporated under reduced pressure and the residue was column chromatographed over silica gel (60-120 mesh, EtOAc/hexane 1:9) to yield pure alcohol **66** (0.054 g, 85 %); $[\alpha]_D^{25}$: + 22.1 (*c* 1, $CHCl_3$); IR (neat): ν 3466, 3116, 3023, 2926, 1732, 1679, 1331, 1267, 1224, 1121, 1098, 945, 743 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$): δ 0.12 (br s, 6H), 0.91(br s, 9H), 1.29-1.33 (t, *J* = 7.08 Hz, 3H), 1.69 (br s, 1H), 1.75-1.80 (m, 2H), 2.88-2.99 (m, 2H), 3.73-3.85 (m, 2H), 4.12(m, 1H), 4.16-4.21(m, 2H), 5.88 (d, *J* =11.54 Hz, 1H), 6.38 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ -4.8, 14.2, 25.8, 36.1, 38.5, 59.93, 60.1, 70.6, 121.3, 145.9, 166.4;Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.00.Found C, 58.79;H, 9.05.

2.4.9. (R, Z) –ethyl 5-((tert-butyldimethylsilyl)octa-2,7-dienoate, 67

The precursor aldehyde for compound **67** was prepared from the above obtained alcohol **66** following the procedure described under section **2.4.1**

To a stirred solution of methyltriphenylphosphonium iodide (1.313 g, 3.2 mmol) in THF (10 mL) at 0 ^oC, added n- BuLi (1.6 M solution in hexane, 3.2 mmol) drop wise. After stirring for 15 min, a solution of crude aldehyde (0.75g, 2.5 mmol) in THF (10 mL) was added drop wise. The reaction mixture was stirred at the same temperature for another 2h. Then the reaction was quenched with saturated NH_4Cl, the two layers were separated and the aqueous layer was treated with EtOAc thrice. The combined organic layers were concentrated under reduced pressure to furnish crude product which on further purification by column chromatography over silica gel (60-120 mesh, EtOAc/hexane 1:9) yielded pure compound **67** as color less oil (1.45 g, 85%);

$[\alpha]_D^{25}$: - 15.6 (*c* 1, $CHCl_3$); IR (neat): ν3158, 3024, 2927, 2928, 1737, 1675, 1376, 1279, 1257, 1154, 1136, 1041, 945,743cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$):δ 0.12, (br s, 6H), 0.91(br s, 9H), 1.19-1.27 (m, 3H), 2.26–2.37 (m, 2H), 2.80–2.89 (m, 2H), 3.71-3.74 (m, 1H), 4.07-4.21(m, 2H), 5.12–5.19 (m, 2H), 5.04-5.14 (m, 2H), 5.67-5.88 (m, 2H), 6.83-6.98 (dt, *J* = 3.41, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ -4.6, 14.3, 17.2, 25.9, 36.1, 42.0, 59.7, 71.4, 117.2, 121.0, 134.8, 146.4, 166.1; Anal. Calcd for$C_{16}H_{30}O_3Si$:C, 64.38; H, 10.13.Found C, 63.15;H, 10.95.

2.4.10. (R)-6-Allyl-5,6-dihydro-2H-pyran-2-one, 68

To a stirred solution of compound **67** (0.594 g, 3 mmol) in MeOH was added catalytic amount of PTSA and the contents were stirred for 3h at room temperature. When no starting material was observed on TLC, the reaction mixture was concentrated under reduced pressure, dissolved in EtOAc and washed with Na_2CO_3 solution (5 mL, 10%). Organic layer was separated and dried over anhydrous Na_2SO_4, concentrated under *vacuum* and the obtained residue was chromatographed over silica gel (100-200 mesh, CH_2Cl_2/hexane 1:9) yielding **68** (910 mg, 91%) as a colorless oil; $[\alpha]_D^{25}$: - 114.8 (*c* 1, $CHCl_3$); IR (neat): ν3065, 2921, 2815, 1711, 1615, 1458, 1365, 1241, 1041, 905, 742cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$): δ 2.34-2.37 (m, 2H), 2.44-2.60 (m, 2H), 4.45-4.52 (p, 1H), 5.15 (s, 1H), 5.17-5.19 (d, 1H), 5.79-5.89 (m, 1H), 6.1-6.03 (d, J=7.03 Hz, 1H), 6.85-6.90 (m, 1H); ^{13}NMR (200 MHz, $CDCl_3$): δ 28.7, 39.1, 77.0, 118.9, 121.5, 132.3, 144.7, 164.0;Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found C, 69.48; H, 7.19.

2.4.11.(*R*,*E*)-6-(4-Oxo-6-phenylhex-2-enyl)-5,6-dihydro-2H-pyran-2-one(*R*)-Rugulactone, 1

Grubb's second-generation catalyst (123.1 mg, 0.145 mmol) was added to the stirred solution of lactone **68** (200 mg, 1.45 mmol) and 5-phenylpent-1-ene-3-one **69**

(693.173 mg, 4.347 mmol) in CH_2Cl_2, stirring was continued for 12 h at 45 ^oC, when starting material was completely consumed (checked by TLC), the reaction mixture was concentrated and purified by silica gel (100-200 mesh) chromatography (EtOAc/hexane 3:7) to yield (*R*)-**1** (293 mg, 75%) as a colorless oil. $[\alpha]^{25}_D$ = -46.2 (*c* 1, $CHCl_3$), Lit[5] $[\alpha]^{25}_D$ = -46.9 (*c* 1, $CHCl_3$); IR (neat): ν 3067, 2925, 2818, 1720, 1626, 1038, 992, 928, 845, 756 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.29-2.36 (m, 2H), 2.59-2.68 (m, 2H), 2.87-2.93 (m, 4H), 4.47-4.61 (m, 1H), 6.01-6.07 (dt, *J* = 1.70, 6.50 Hz, 1H), 6.13-6.23(dt, *J* = 1.49, 14.53 Hz, 1H), 6.71-6.92 (m, 2H), 7.16-7.26 (m, 5H); ^{13}C NMR (50 MHz): δ 29.0, 30.0, 37.6, 41.8, 121.6, 128.4, 128.5, 133.5, 139.9, 141.0, 144.4, 163.4, 198.6; Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found C, 75.46; H, 6.69.

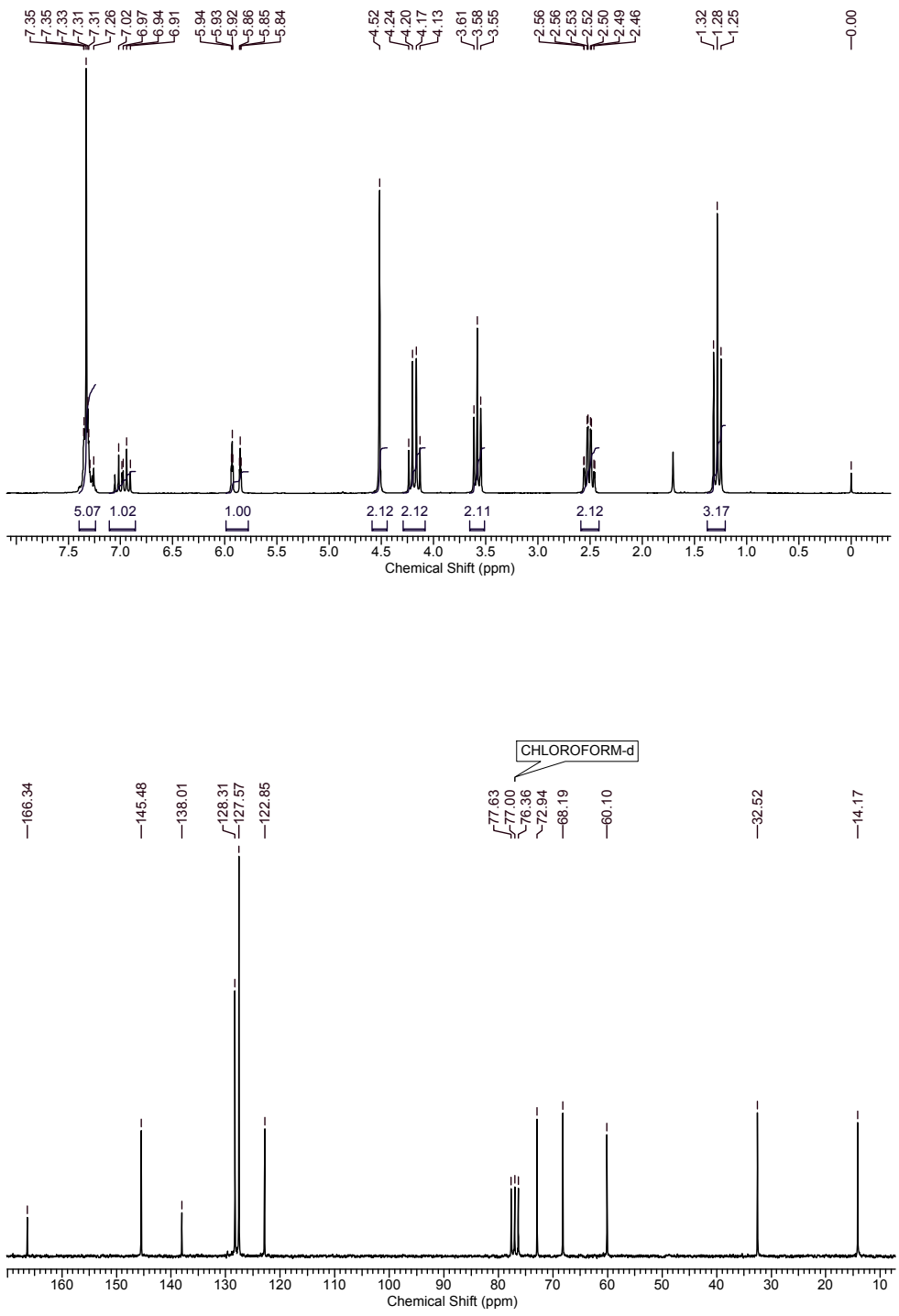


Figure 2. ^{1}H-NMR and ^{13}C-NMR of unsaturated ester **59**

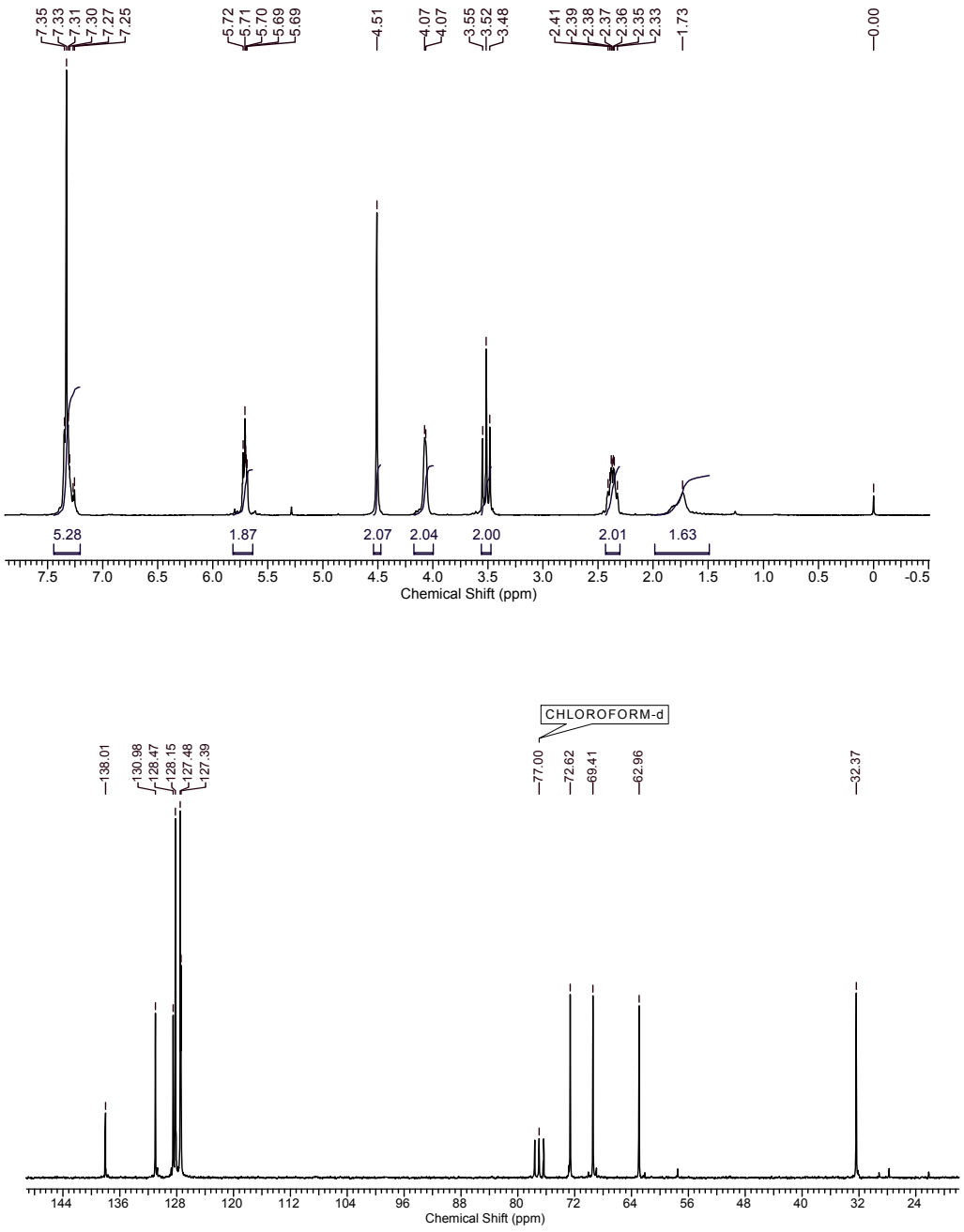


Figure 3. ^{1}H-NMR and ^{13}C-NMR of compound **60**

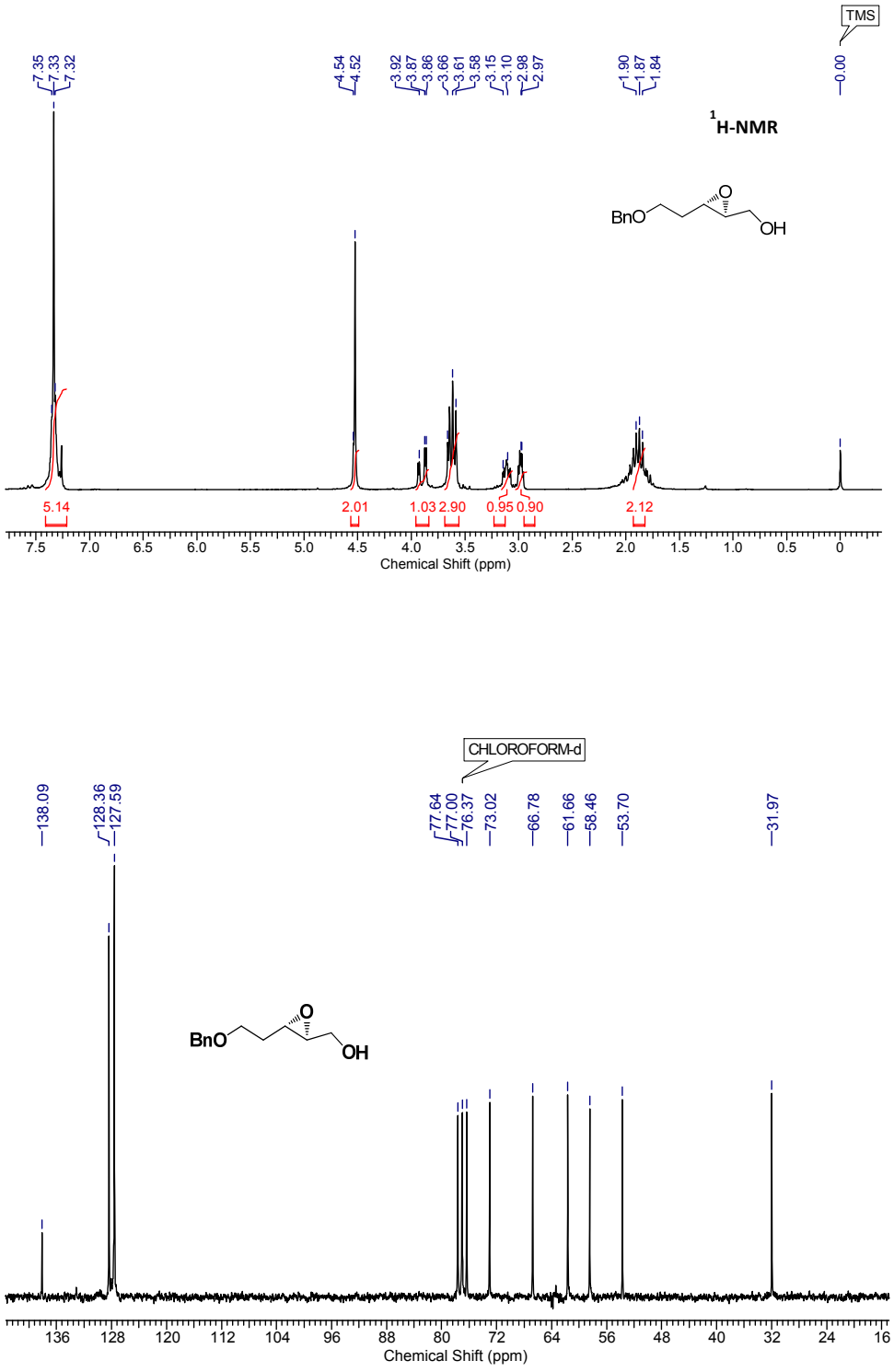


Figure 4. ^{1}H-NMR and ^{13}C-NMR of compound **61**

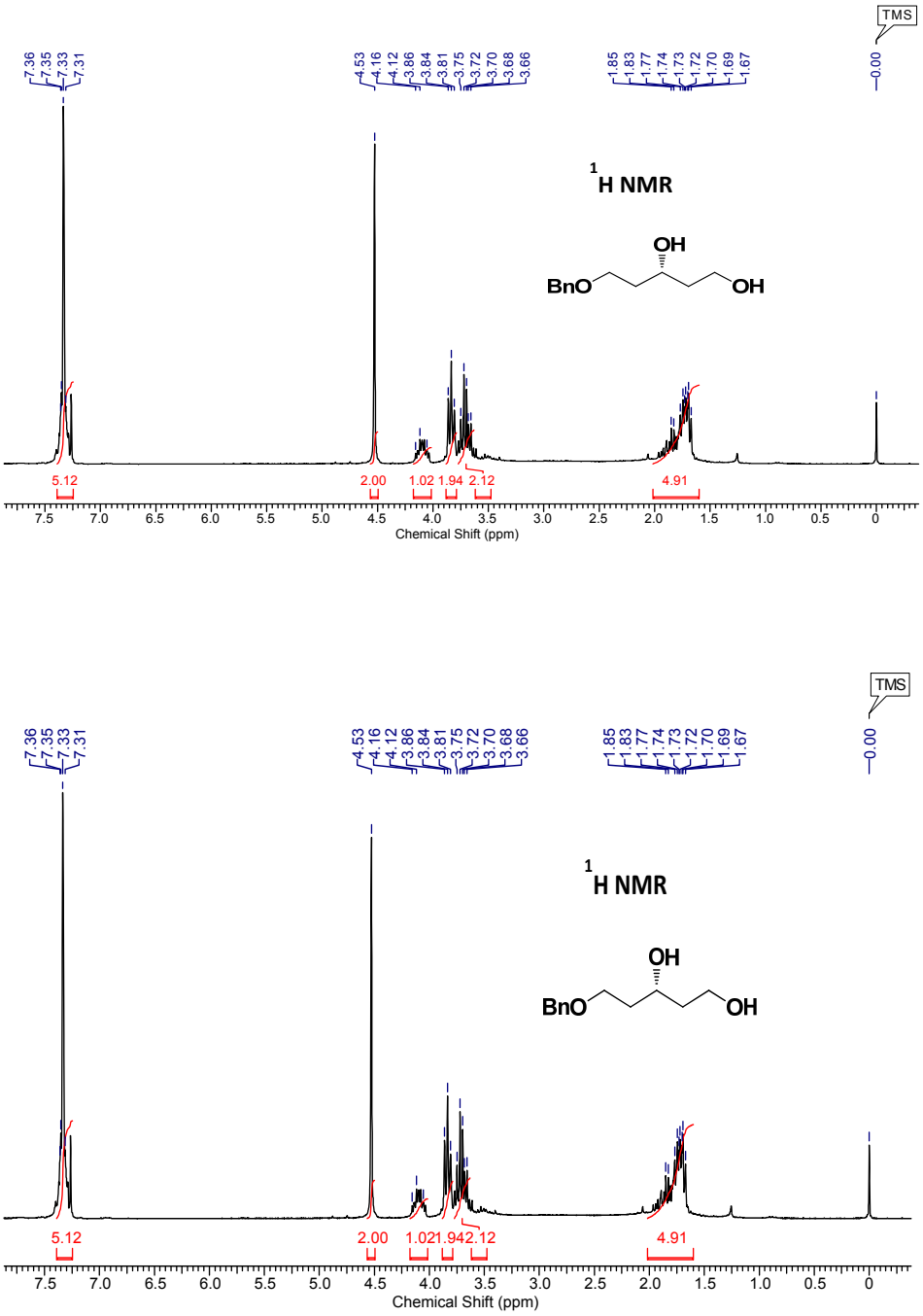


Figure 5. ^{1}H-NMR and ^{13}C-NMR of compound **62**

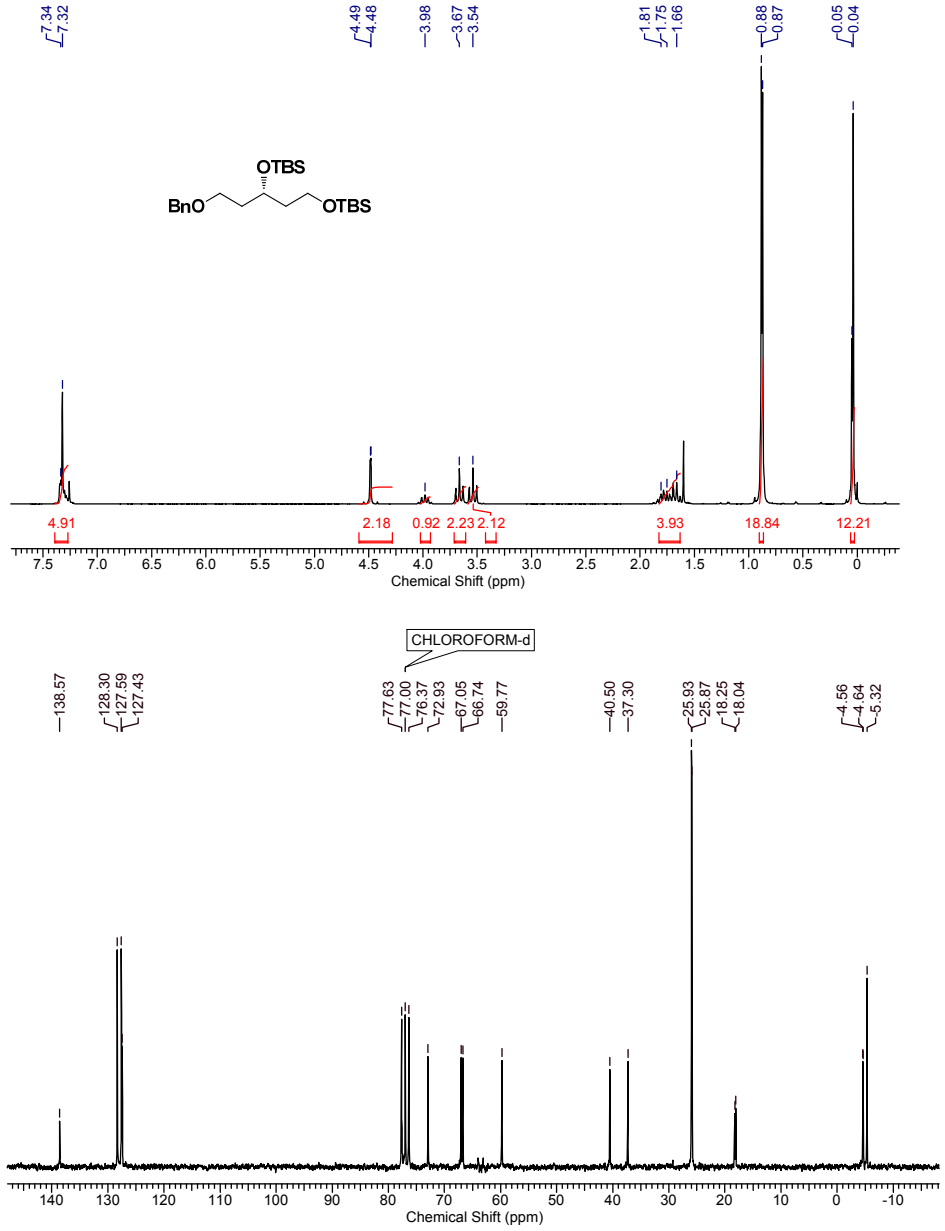


Figure 6. ^{1}H-NMR and ^{13}C-NMR of compound **63**

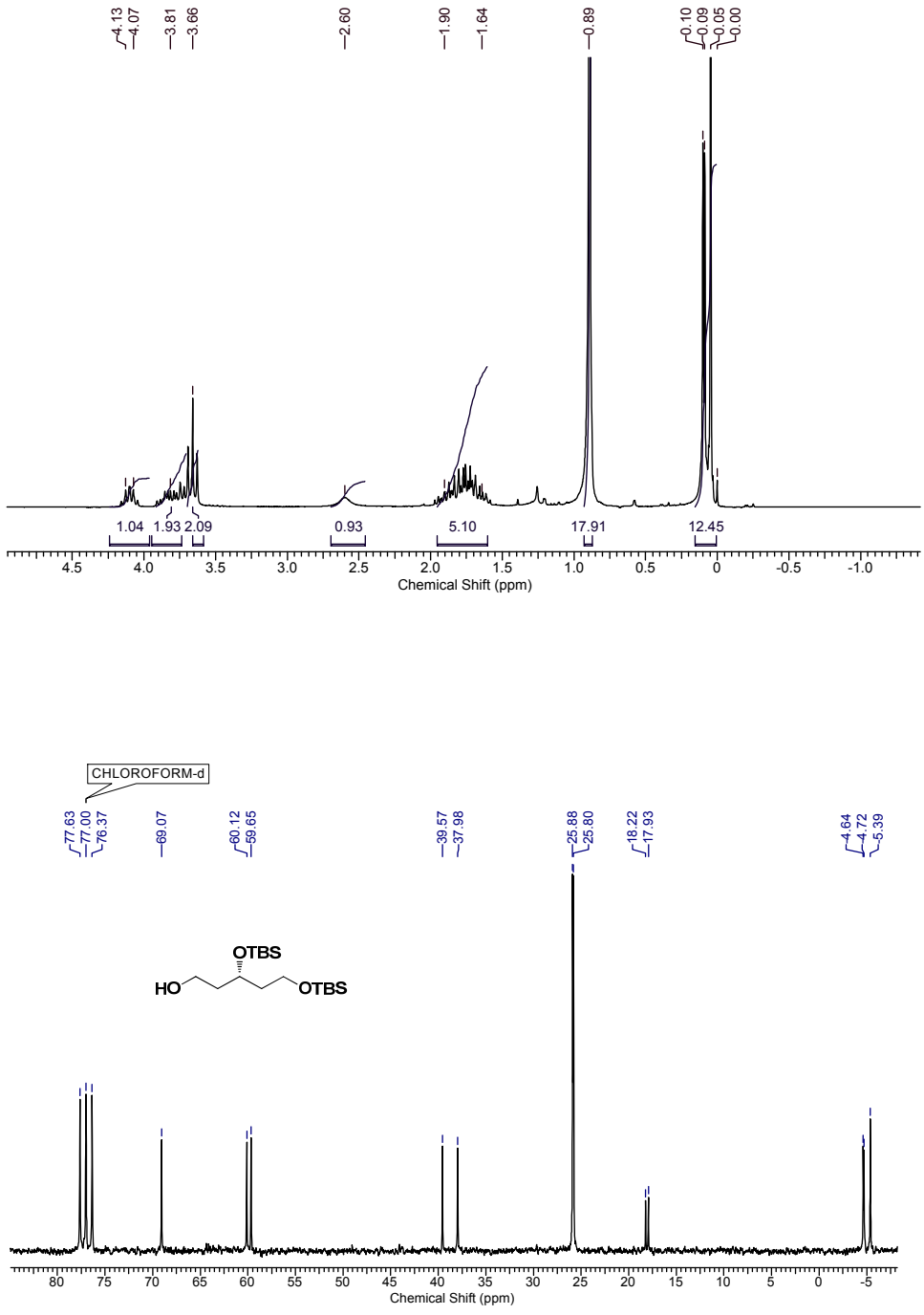


Figure 7. ^{1}H-NMR and ^{13}C-NMR of compound **64**

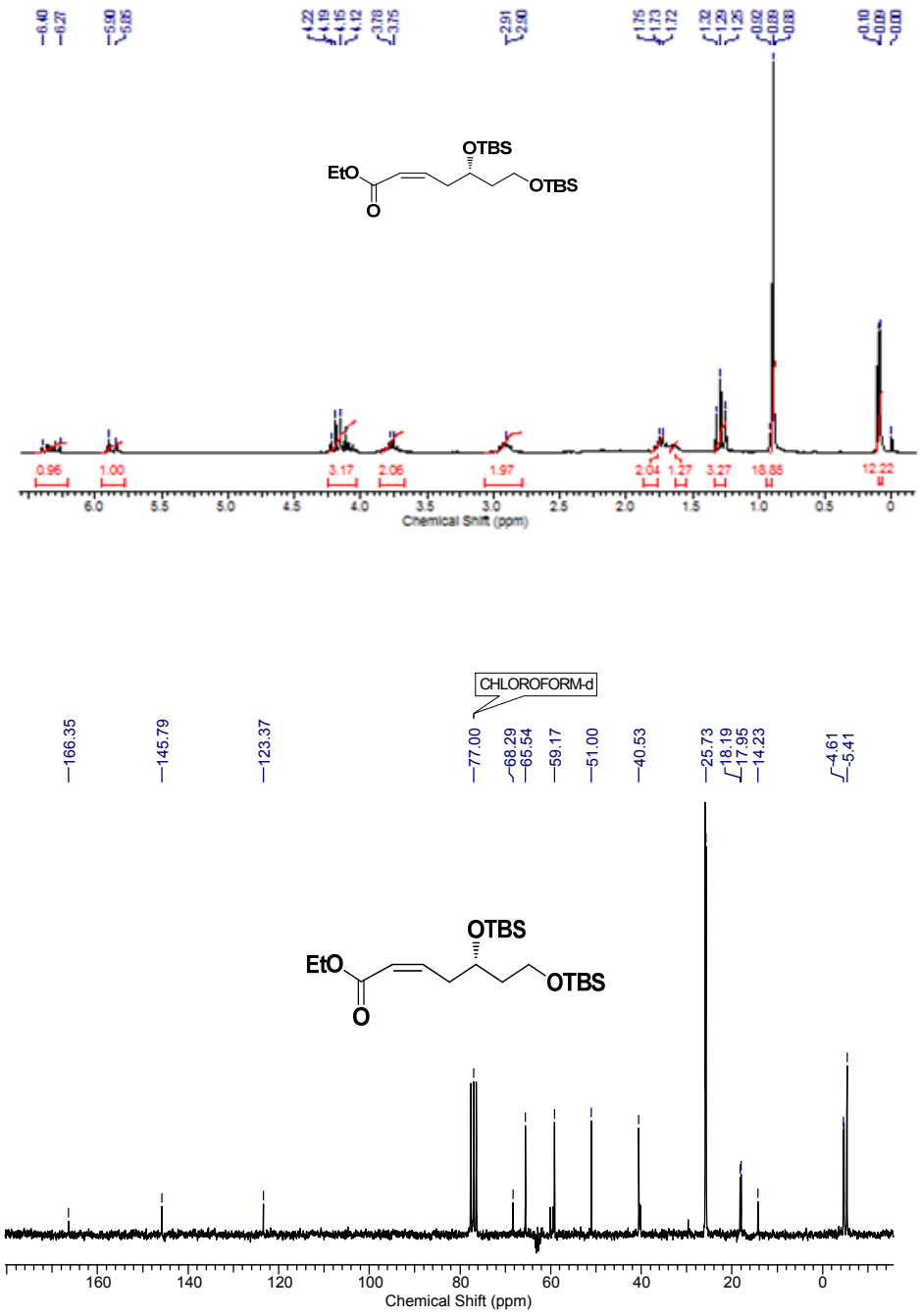


Figure 8. ^{1}H-NMR and ^{13}C-NMR of compound **65**

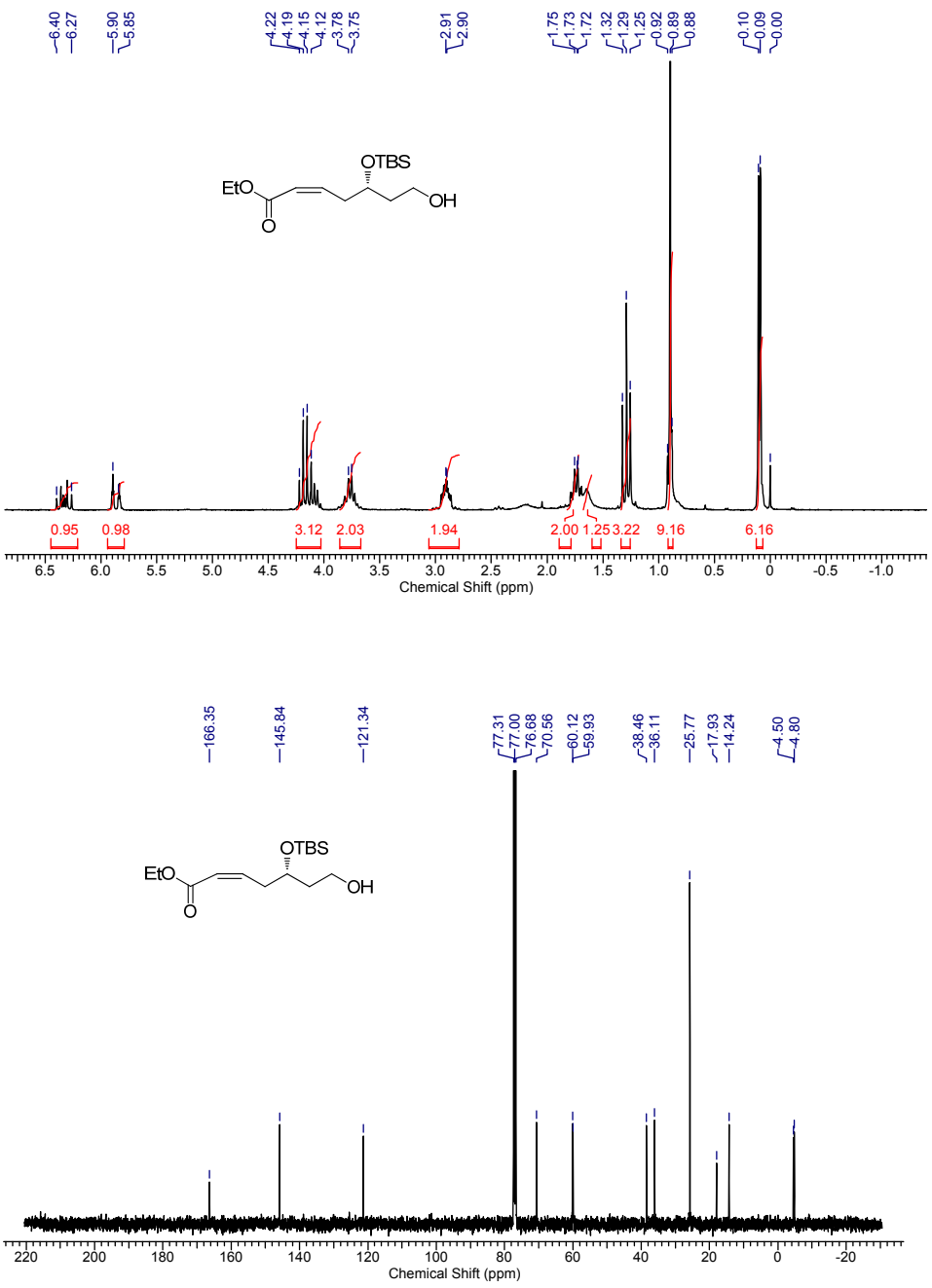


Figure 9. ^{1}H-NMR and ^{13}C-NMR of compound **66**

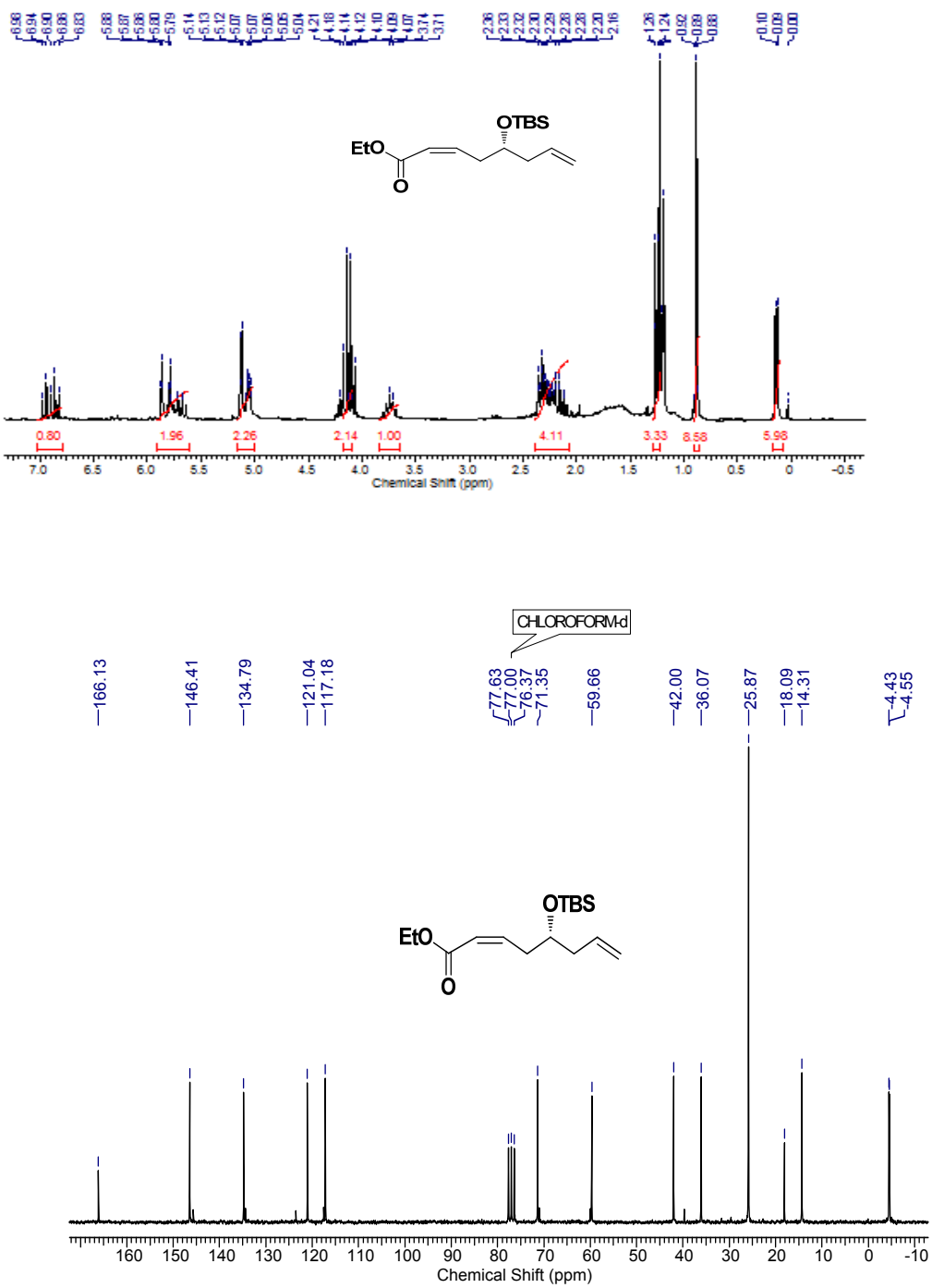


Figure 10. ^{1}H-NMR and ^{13}C-NMR of compound **67**

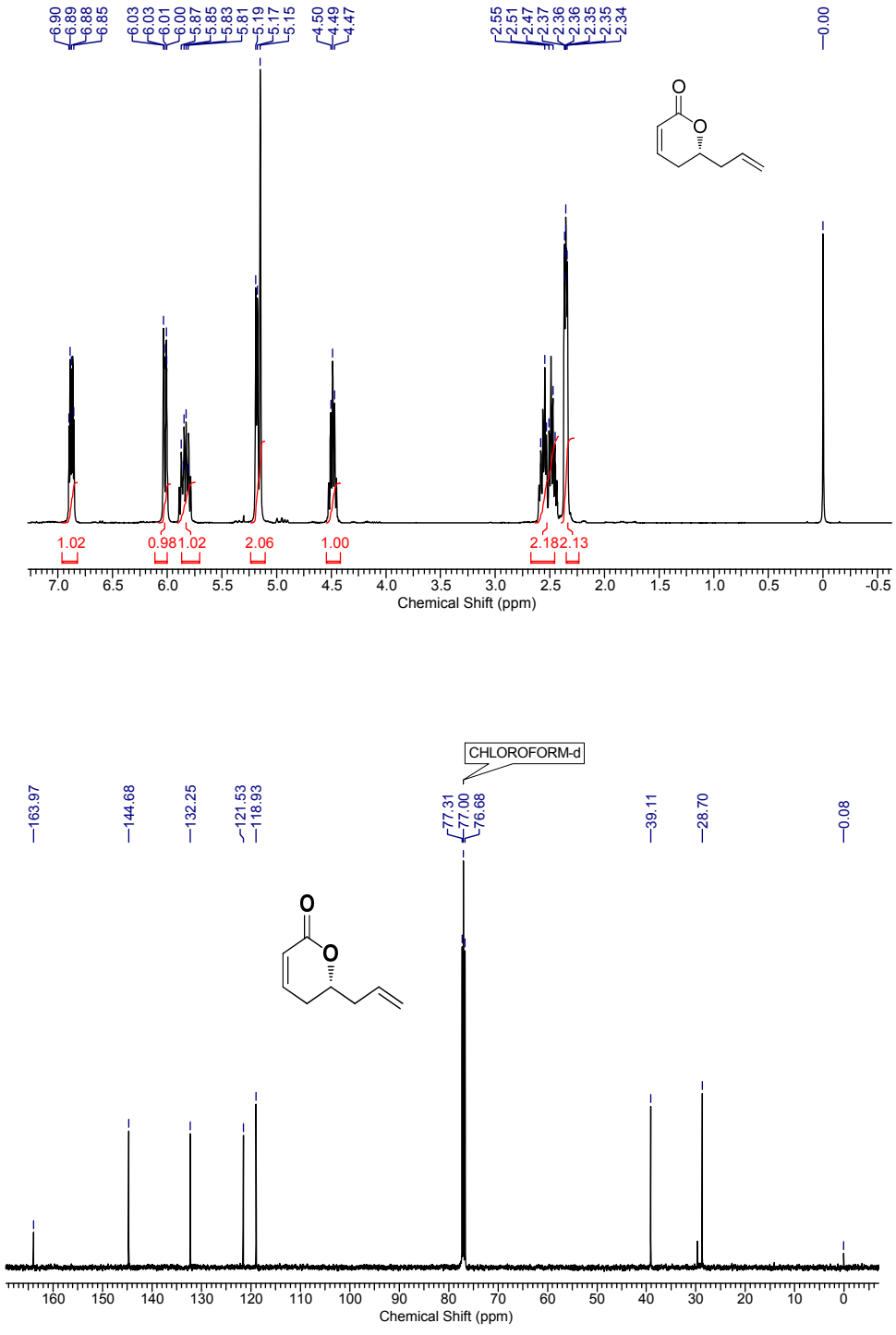


Figure 11. ^{1}H-NMR and ^{13}C-NMR of compound **68**

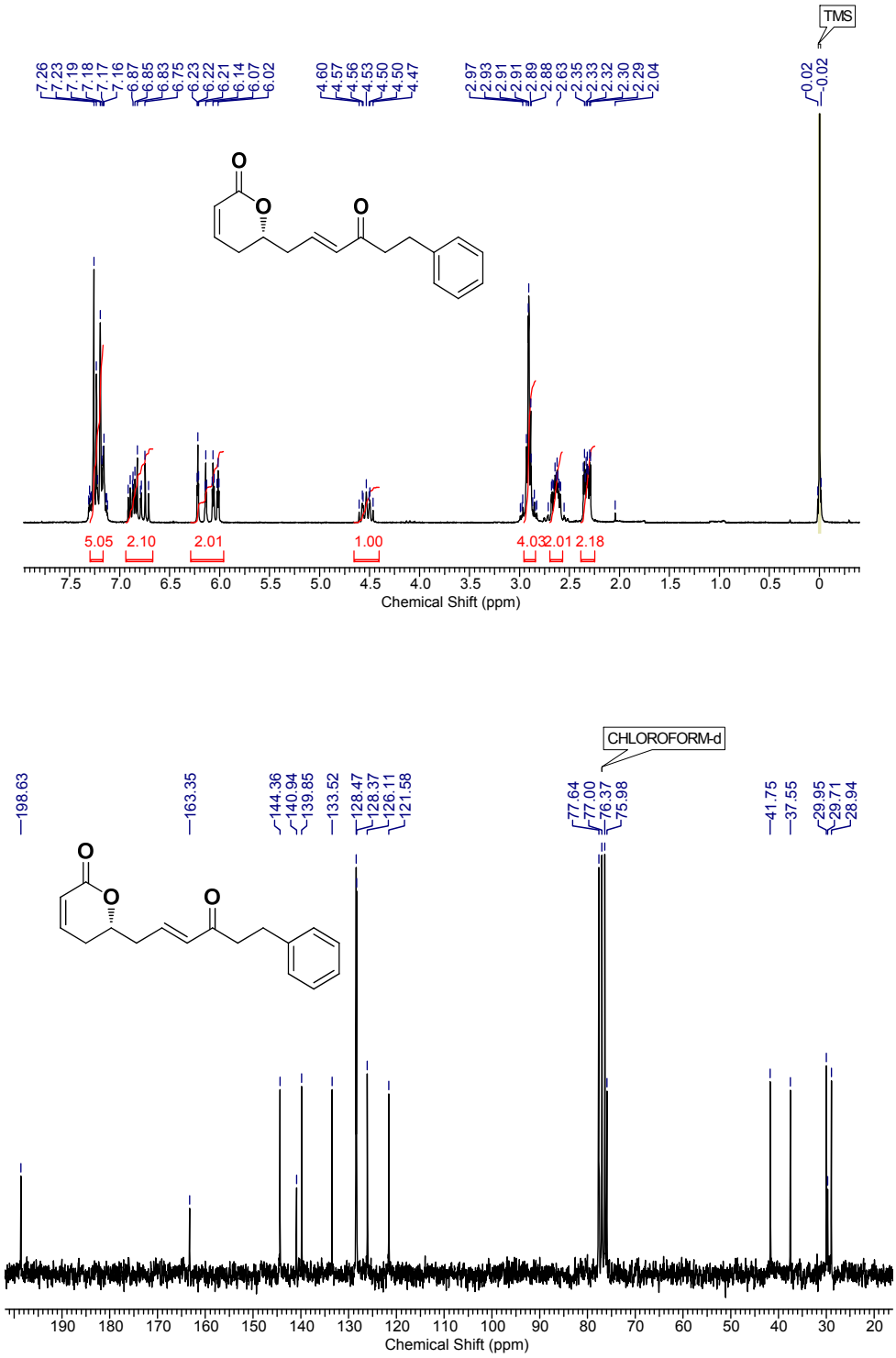


Figure 12. ^{1}H-NMR and ^{13}C-NMR of (*R*)-rugulactone, **1**

1. Drewes, S. E.; Sehlapelo, B. M.; Horn, M. M.; Scott-Shaw, R.; Sandor, O. *Phytochemistry* **1995**, *38*, 1427-1430; (b) Drewes, S. E.; Horn, M. M.; Shaw, R. S. *Phytochemistry* **1995**, *40*, 321; (c) Rychnovsky, S. D. *Chem. Rev*. **1995**, *95,* 2021.; (d) Carda, M.; Rodrguez, S.; Gonzalez, F.; Castillo, E.; Villanueva, A.; Marco, J. A. *Eur. J. Org. Chem.* **2002**, 2649; (e) Kikuchi, H.; Sasaki, K.; Sekiya, J.; Maeda, Y.; Amagai, A.; Kubohara, Y.; Oshima,Y. *Bioorg. Med. Chem*. **2004**, *12*, 3203-3214; (f) Pereda-Mirinda, R.; Fragoso-Serremo, C. M,; Cerda- Garcia-Rojas, *Tetrahdron* **2001**, *57*, 47; (g) de Fatima, A.; Kohn, L. K.; Antonio, M. A.; Carvalho, J E.; Pillia, R. A. *Bioorg. Med. Chem.* **2005**, *13*, 2927; (h) Spencer, G. F.; England, R. E.; Wolf, R. B. *Phytochemistry* **1984**, *23*, 2499; (i) Govindachari, T. R.; Parthasarathy, P.C.; Desai, H. K.; Shanbhag, M. N. *Tetrahedron* **1973**, *29*, 3091-3094; (j) Sam, T.W.; Yeu, C. S.; Jodynis-Liebert, J.; Murias, M.; Bloszyk, E. *Planta Med*. **2000**, *66*, 199; (k) Zschocke, S.; Van Staden, J. *J. Ethnopharmacol* **2000**, *71*, 473; (l) Drewes, S. E.; Horn, M. H.; Mavi, S. *Phytochemistry* **1997**, *44*, 437.

2. Meragelman, T. L.; Scudiero, D. A.; Davis, R. E.; Staudt, L. M.; Mc Cloud, T. G; Cardellina, J. H.; Shoemaker R. H. *J. Nat. Prod*. **2009**, *72*, 336.

3. (a) Karin, M. *Nature* **2006**, *441*, 431; (b) Coussens, L. M.; Werb. Z. *Nature* **2002**, *420*, 860; (c) Sethi, G.; Sung, B.; Aggarwal, B. B. *Exp. Biol. Med*. **2008**, *233*, 21; (d) Luo, J.L.; Kamata, H.; Karin, M. J. *Clin. Invest.* **2005**, *115*, 2625-2632; (e) Greten, F. R.; Karin, M. *Cancer Lett.* **2004**, *206*, 193.

4. Reddipalli, G.; Venkataiah, M.; Fadnavis, N. W. *Tetrahedron: Asymmetry* 21, **2010**, 320.

5. Mohapatra, D. K.; Das, P. P.; Reddy, D. S.; Yadav, J. S. *Tetrahedron Lett.* **2009**, *50*, 5941.

6. Reddy, D. K.; Shekhar, V.; Reddy, T. S.; Reddy, S. P.; Venkateswarlu, Y. *Tetrahedron: Asymmet*ry **2009**, *20*, 2315.

7. Allais, F.; Aouhansou, M.; Majira, A.; Ducrot, P. H. *Synthesis*, **2010**, 2787.

8. Reddy, D. K.; Shekhar, V.; Prabhakar, P.; Chinna Babu, B.; Sidharta, B.; Murthy, U. S. N.; Venkateswarlu, Y. *Eur. J. Org. Chem.* **2010**, *45*, 4657.

9. Cros, F.; Pelotier, B.; Piva, O. *Eur. J. Org. Chem.* **2010**, 5063.

10. Dietrich, B.; Fernandez, E.; Jorg, P. *J. Org. Chem.* **2011**, *76*, 4363.

11. Yadav, J.S.; Reddy, Ch. S. *Org. Lett.* **2009**, *11*, 1705.

12. (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974; (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

13. (a) Katsuki, T.; Lee, P.M.; Martin, V.S.; Masamune, S.; Sharpless, K.B.; Tuddenham, D.; Walker, F.J. *J. Org. Chem*. **1982**, *47*, 1376; (b) James M. Finan,; Yishito Kishi. *Tetrahedron Lett.* **1982**, *23*, 2713.

14. Kerstin, D.; Philips. Zemilicka, J.; Jerome, J. H. *Carbohydrate Research* **1973**, *30*, 281.

15. Still, W. C.; Gennari, C. *Tetrahedron Lett*. **1983**, *24*, 4405.

16. Yadav, J. S.; Reddy, B. V. S.; Vishnumurthy, P. *Tetrahedron Lett*. **2008**, *49*, 4498.

17. (a) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117; (b) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed*. **2003**, *42*, 4592; (c) Furstner, A. *Angew. Chem., Int. Ed.* **2002**, *39*, 3012.

18. Chatterjee, A. K. Choi, T.L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc*. **2003**, *125*, 11360.

CHAPTER III:

A facile enantioselective synthesis of (*R*)-Massoialactone and A facile stereoselective total syntheis of (*S*)-N-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol

SECTION: I

A facile enantioselective synthesis of (*R*)-Massoialactone

3.2.1. Introduction and Pharmacology

Natural products containing 6-subsitituted δ-lactone moiety exhibit interesting biological activities.[1] (*R*)-Massoialactone[2] (1, figure 1), a member of this family, was isolated for the first time in 1937 by Abe[3] from the bark of *Cryptocarya massoia* which grows wild in New Guinea. It is a skin irritant and produces systolic standstill in frog heart muscle. Later, this lactone was also isolated from cane molasses[4] and jasmine blossoms[5] as a flavor substance. It is an alarm pheromone of two species of formicine ants of the genus *Componotus* collected in Western Australia[6]. The absolute configuration of **1** was determined to be (*R*) form by the synthesis of unnatural (*S*)-form. (*R*)-Massoialactone (**1**) is characterized by a pleasant and sweet light coconut odor[7] and is used as aromatizer in perfumery and in the manufacture of alcoholic drinks and tinctures.[8] Synthetic compound[9] of **1** is widely used in food and perfume industry in order to save its natural resources.

1 **2**

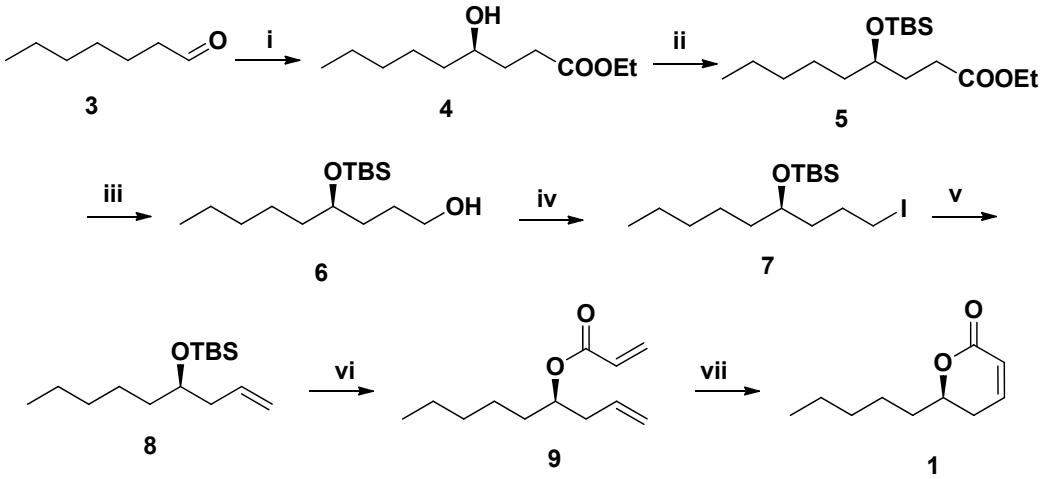
Figure1: Structures of (*R*)-Massoialactone **(1)** and (*S*)-Massoialactones **(2)**

3.2.2. Review of Literature

Various syntheses of (*R*)-Massoialactone (**1)** have been reported in the literature. Some of the interesting and important synthetic routes to (*R*)-Massoialactone (**1**) are described below.

Pradeep Kumar' approach (2011)[10]

Pradeep Kumar *et al.* have reported the synthesis of (*R*)-Massoialactone starting from commercially available n-heptanal **3**. The sequential α-aminoxylation of n-heptanal with nitrosobenzene and L-proline as a catalyst and HWE olefination using triethyl phosphonoacetate, followed by hydrogenolysis using Pd/C to furnish γ-hydroxy ester **4**. The free hydroxy group of **5** was protected as TBS ether using t-butyldimethylsilyl chloride to furnish compound **6**.



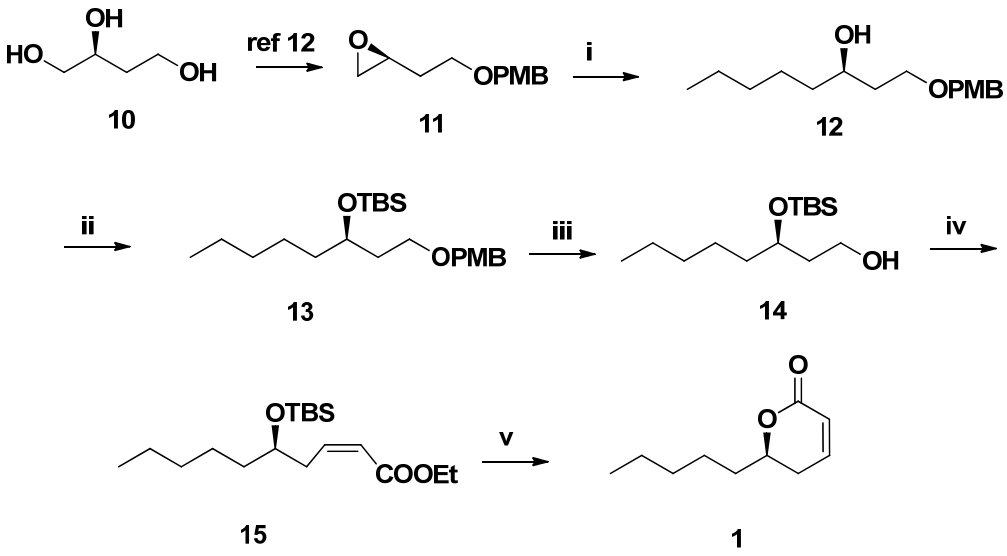
Scheme 1: *Reagents and conditions: (i) (a) nitrosobenzene, L-proline, DMSO,then HWE salt, DBU, LiCl, MeCN; (b) H_2, Pd/C, EtOAC, 68% (over two steps); (ii) TBSCl, imidazole, CH_2Cl_2, 14h, 94% (iii) DIBAL-H, CH_2Cl_2, -78 ^oC, 2 h, 83%; (iv) I_2, PPh_3, imidazole, THF, MeCN, r.t., 2 h, 72%; (v) tBuOK, benzene, r.t., 30 min, 69%; (vi) (a) TBAF, THF, r.t., 2 h, 88%; (b) acryloyl chloride, Et_3N, CH_2Cl_2, 0 ^oC, 6 h, 82%; (vii) $(Cy_3P)_2Ru(Cl)_2$=CHPh (20 mol%), $Ti(O\text{-}i\text{-}Pr)_4$, CH_2Cl_2, reflux, overnight.*

DIBAL-H reduction of ester **5** furnished the alcohol **6** in good yield, which was then converted to iodo derivative **7**. The iodo compound **7** was then treated with potassium

t-butoxide to yield TBS protected homoallylic alcohol **8** in 69% yield. The TBS group in **8** was deprotected and further converted to its acrylate ester **9** using acryloyl chloride and triethyl amine in dichloromethane solvent. Finally, the ring closing metathesis of **9** using Grubb's second generation catalyst in dichlromethane yielded (*R*)-Massoialctone, **1** in 86% yield (**Scheme1**).

G. Sabitha's approach (2007)[11]

As outlined in **Scheme 2**, the synthesis of (*R*)-Massoialctone started with (*S*)- epoxide **11**, which was obtained from (*S*)- butane-1,2,4-triol **10** following the literature report.

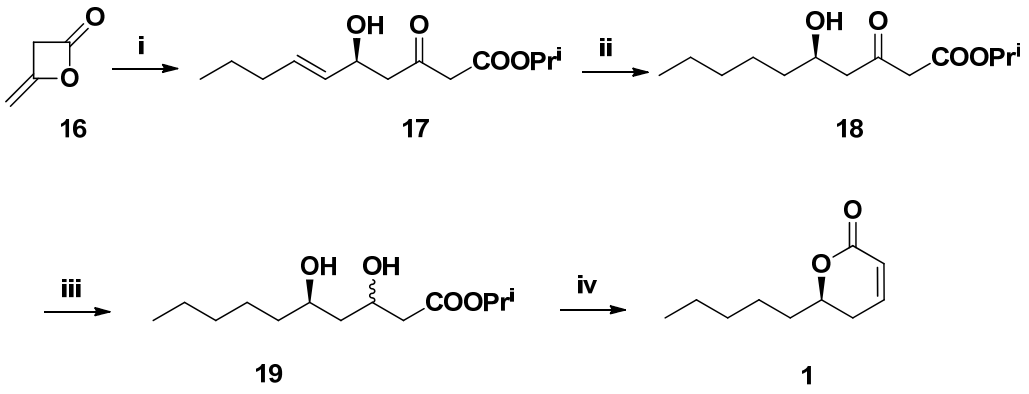


Scheme 2: *Reagents and conditions: (i) CuI, n-BuLi, dry ether, -20 ^{o}C, 1.5 h, 87%; (ii) TBSCl, imidazole, CH_2Cl_2, 0 ^{o}C, 2 h, 74%; (iii) DDQ, CH_2Cl_2:H_2O, r. t., 3 h, 80%;(iv) (a))IBX, DMSO, CH_2Cl_2, 2 h, 68% ; (b) $H_3COOCCH_2P(O)(OCH_2CF_3)_2$, NaH, THF, 1 h, 85%; (v) PTSA/MeOH, 30 min, benzene, 1 h, 76%.*

Selective opening of epoxide **11** with CuI and n-BuLi furnished compound **12** in 87% yield. The secondary hydroxyl group in compound **12** was converted to its TBS ether **13** using TBSCl, imidazole in DCM. Oxidative deprotection of the p-methoxybenzyl (PMB) group using DDQ in aq. DCM gave the primary alcohol **14** in 80% yield,

which on oxidation with iodoxy benzoic acid (IBX) in dimethyl sulphoxide solvent furnished aldehyde, which on further Horner-Wardsworth-Emmons reaction using methyl (bistrifluoroethyl) phosphonoacetate gave Z-unsaturated ester **15**, exclusively. Subsequent cyclization of Z-unsaturated ester and in situ deprotection of TBS group was achieved using catalytic amount of p-TsOH in a mixture of methanol and benzene to furnish the target molecule **1** in76% yield.

K. Yoshikawa's approach (2008)[13]

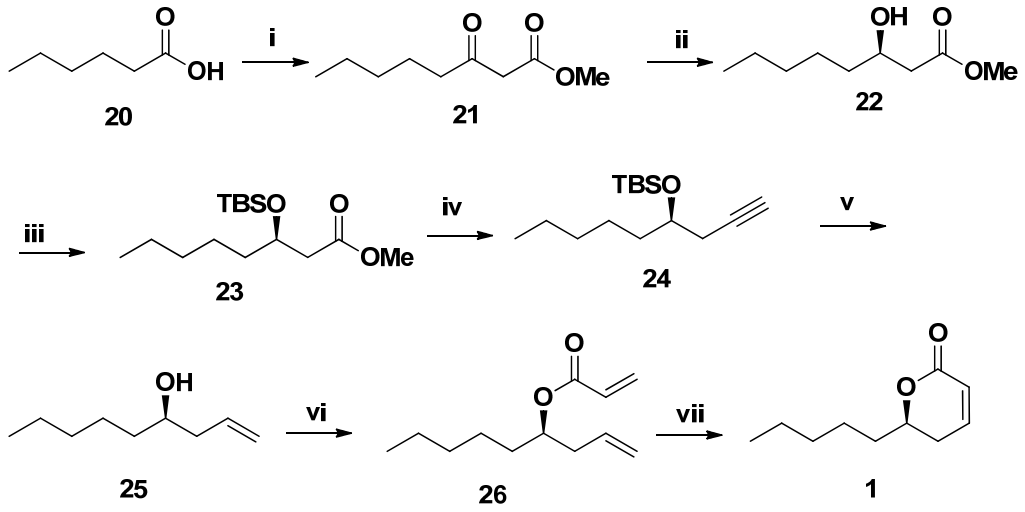


Scheme 3: *Reagents and conditions: (i) (S)-BINOL, $Ti(OPri)_4$, n-hexenal, CH_2Cl_2, r.t., 20 h;(ii) Raney nickel, hexane, H_2 (5 MPa), r.t., 8 h;(iii) $NaBH_4$, EtOH, THF, r.t., 30 min; (iv) TsOH, toluene, reflux, 2 h.*

As outlined in **Scheme 3**, the synthetic route to (*R*)-Massoialctone began with diketene **16** subjected to enantioselective aldol type reaction with n-hexenal in presence of (*S*)-BINOL-$Ti(OPri)_4$ chiral complex to afford compound **17**. Reduction of double bond in **17** was achieved with Raney Ni, H_2 to afford hydroxy ester **18**.Sodium borobydride reduction of compound **18** in a mixture of ethanol and THF yielded dihydroxy ester compound **19**. Paratolunesulfonic acid treatment of compound **18** in toluene at reflux conditions gave the final (*R*)-Massoialactone, **1** in good yield.

Ridha's approach (2006)[14]

As outlined in **Scheme 4**, their synthetic route commenced with commercially available hexanoic acid **20**, which was converted into β-keto ester **21** using Masamune's procedure. Thus, by the addition N,N'-carbonyldiimidazole followed by treatment with magnesium salt of monomethyl malonic acid afforded methy-3-oxooctanoate in 82% yield. The asymmetric hydrogenation of compound was achieved using in situ generated [$RuBr_2$((*R*)-SYNPHOS)] catalyst in methanol solvent

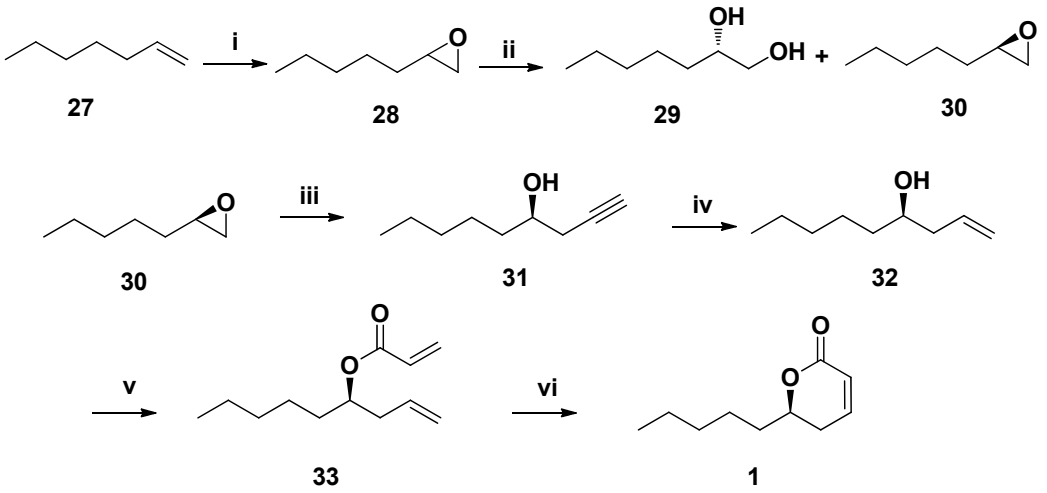


Scheme 4: *Reagents and conditions: (i) N,N'- Carbonyl imidazole, THF, r.t., 6 h then $Mg(O_2CCH_2CO_2Me)_2$, THF, r.t., 16 h, 82%; (ii) H_2, (5 bar), 50 ^oC, [$RuBr_2$((R)-SYNPHOS)], MeOH, 24 h;(iii) 2,6-lutidine, TBDMSOTf, CH_2Cl_2, -25 to -15 ^oC , 45 min, 94%; (iv) (a) DIBAL-H, CH_2Cl_2, -78 ^oC, 4 h, 71%;(b) LDA, $TMSCHN_2$, THF, -78 to -10 ^oC, 87%; (v) (a) Bu_4NF (1 M in THF), 2 h, rt, 95%; (b) Pd/BaSO4, quinoline, EtOAC, H_2(1 bar), r.t., 2 h, 74%; (vi) acryloyl chloride, Et_3N, CH_2Cl_2, 0 ^oC, 8 h, 82%; (vii) $(PCy_3)_2Ru(Cl)_2$=CH–Ph (25 mol %), CH_2Cl_2, $Ti(i\text{-}PrO)_4$, reflux, 6 h, 78%.*

to afford β-hydroxyester **22** in 94% yield. The β-hydroxyester **22** was then converted as its t-butyl dimethylsilyl ether **23**, which was then reduced with DIBAL-H in dichloromethane to afford aldehyde. The aldehyde was immediately transformed into alkyne compound **24** using trimethylsilyl diazomethane (Ohira-Shioiri method) and LDA in 87 % yield. The TBS group in compound was cleaved and then the triple

bond was partially reduced using Lindlar's catalyst in ethyl acetate solvent to afford homoallylic alcohol **25** in good yield. The hydroxy group in **25** was converted to its acrylate ester **26** using acryloyl chloride and triethyl amine as base. Finally, the ring closing metathesis of **26** using Grubb's second generation catalyst in dichloromethane gave target molecule **1** in 78% yield.

Vasudeva Naidu's approach (2004)[15]

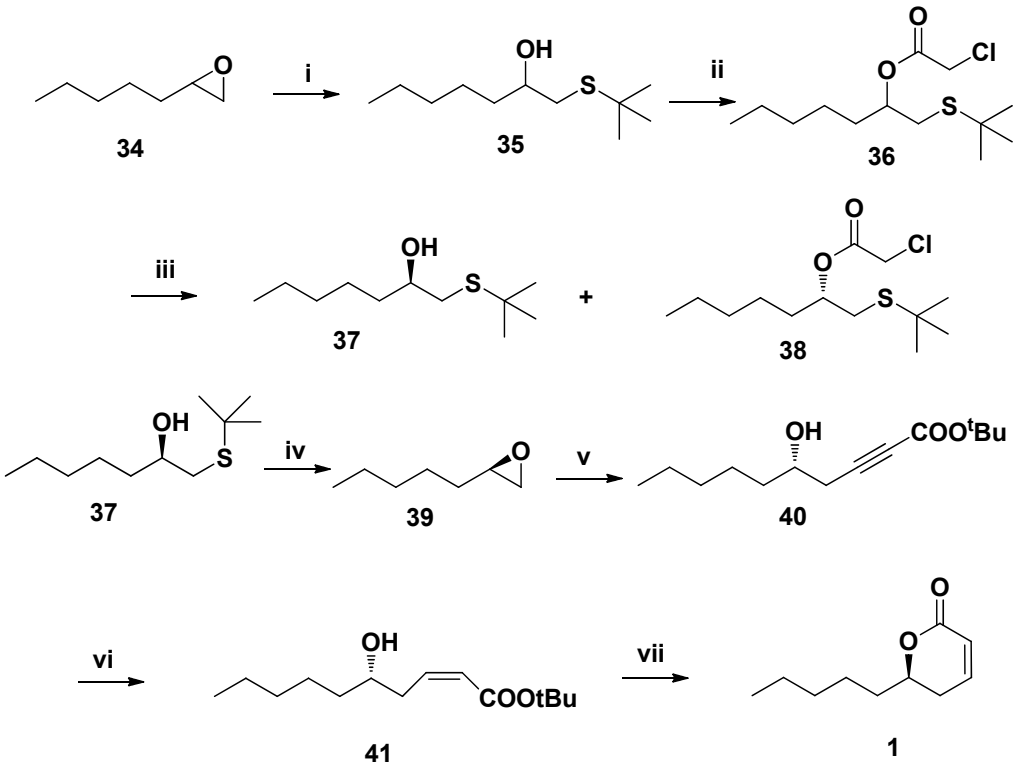


Scheme 5: *Reagents and conditions: (i) m-CPBA, CH_2Cl_2, 0 ^oC to r.t., 10 h, 92 %; (ii) R,R-salen–Co-(OAc) (0.5 mol %), distd. H_2O, (0.55 equiv), 0 ^oC, 16 h; (iii) LiCBCH–ethylene diamine, DMSO, rt, 12 h, 86%; (iv) H_2, Pd/BaSO4, quinoline, benzene, 1 bar, r.t., 0.5 h, 92%; (v) acryloyl chloride, Et_3N, CH_2Cl_2, 0 ^oC, 6 h, 89%; (vi) $(PCy_3)_2Ru(Cl)_2$=CH–Ph (20 mol %), CH_2Cl_2, $Ti(i\text{-}PrO)_4$, reflux, 12 h, 84%.*

As outlined in **Scheme 5**, the synthesis commenced with 1-heptene **27**, which was subjected to m-CPBA mediated epoxidation in dichloromethane to yield racemic heptenoixide **28**. Jacobsen's hydrolytic kinetic resolution (HKR) of the racemate **28** using (*R*,*R*) – (Salen)Co^{III}(OAC) catalyst afford chiral diol **29** and chiral epoxide **30**. The chiral epoxide **30** was separated and treated with excess lithium acetylide to yield compound **31** in 92% yield. The partial hydrogenation of triple bond in **31** using Lindlar's catalyst furnished homallylic alcohol **32** in 92% yield. The compound **32**

was esterified with acryloyl chloride and triethyl amine to afford **33** in 89% yield. The subsequent ring-closing metathesis in dichloromethane under reflux conditions using Grubb's catalyst afforded (*R*)-Massoialctone, **1** in 84% yield.

Manfred's approach (1993)[16]



Scheme 6: *Reagents and conditions: (i) NaH, tBuSH, THF,0 ^oC to reflux, 92%; (ii) $(ClCH_2CO)_2$ O, pyridine, DMAP, CH_2Cl_2, 0 ^oC, 92%; (iii) Lipase from Pseudomonas sp. (SAM II), buffer pH 7; 0 ^oC, 46%, 40%; (iv) Trimethyl oxonium tetra fluoroborate, CH_2Cl_2, r.t., 4.5 h, 74%;(v) t-butyl propiolate, n-BuLi, BF_3, THF, -78 ^oC to r.t., (vi) H_2, Pd/BaSO4, quinoline, EtOAc, r.t., 0.5 h, 93%; (vii) TsOH, toluene:water, reflux, 1.5 h, 97%.*

As outlined in **Scheme 6**, the synthetic route began with racemic heptenoxide **34**, which was regioselectively opened with t-butylthiol to yield compound **35.** Treatment of compound **35** with acrylic anhydride in presence of pyridine and DMAP afforded compound **36**. The enzyme mediated kinetic resolution of **36** using *lipase from Pseudomonas sp.* and phosphate buffer pH-7 gave compounds **37** and **38**. The

compound **37** was then treated with triemethyl oxonium tetrafluoroborate in dichloromethane solvent to afford chiral epoxide **39**. Regioselective opening of epoxide **39** with lithium t-butyl propiolate gave compound **40**. The partial hydrogenation of triple bond in **40** using Lindlar's catalyst gave compound **41**. Finally, cyclization and simultaneous elimination of TBS group yielded target molecule **1**.

3.2.3. Present work

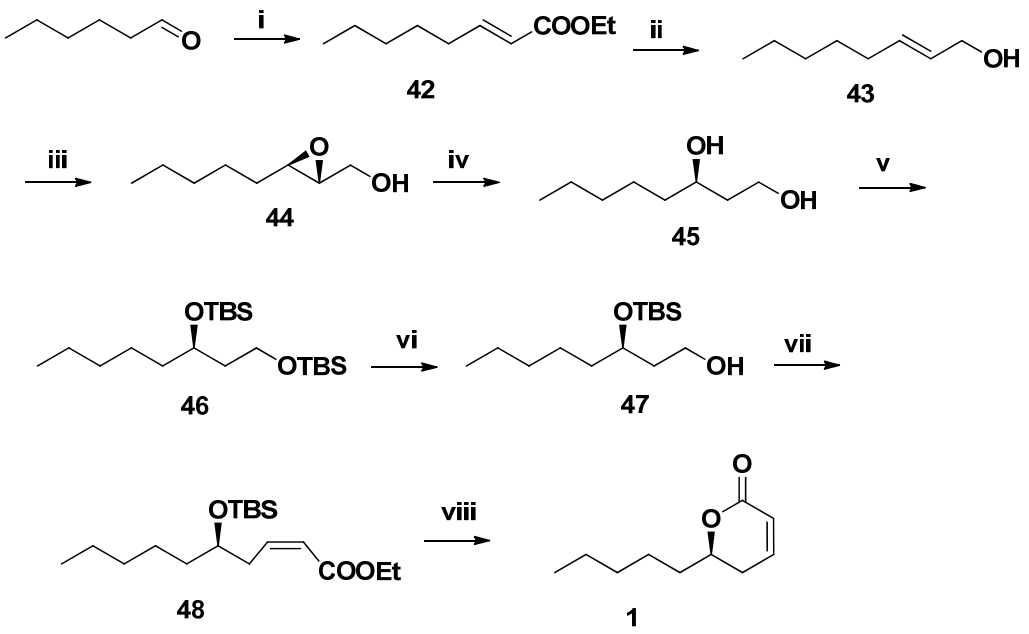
3.2.3.1. Objective

As can be seen from literature section, several synthesis of (*R*) - Massoialactone have been reported. However, many of them suffer from one or more disadvantages, which include low yielding key reactions, use of harsh reaction conditions and the use of costly catalysts. With an aim to synthesize (*R*)- Massoialactone with high overall yield and employing relatively less number of steps, we have chosen the present synthetic route starting from commercially available and cheap n-hexanal.

3.2.3.2. Results and discussion

As outlined in **Scheme 7**, the α,β- unsaturated ester **42** was obtained from commercially available, cheap n-hexanal. The Horner-Wardsworth-Emmons olefination of aldehyde with triethylphosphonoacetate using NaH as base in benzene afforded α,β-unsaturated ester 4**2** in 95% yield. The compound **42** was then reduced to allyl alcohol **43** by employing alane reduction[17] conditions ($LiCl/LiAlH_4$) in THF. At first, alane (AlH_3) is produced in situ by the reaction between LiCl and $LiAlH_4$, which later selectively reduces the ester functionality in α,β-unsaturated ester **42** to yield allyl alcohol **43** in 82 % yield. The formation of two characteristic peaks at

δ 128.69, 133.51 in its ^{13}C NMR spectrum due to two olefinic carbons (**C**H=**C**H) confirms the product. The allyl alcohol compound **43** was then subjected to Sharpless asymmetric epoxidation[18] with Titanium isopropoxide and t-butyl hydroperoxide in presence of (+)- Diethyl tartarate in dichloromethane solvent at -15 ^{o}C afforded epoxy alcohol compound **44** in 85% yield. The formation of two peaks at δ 3.58-3.66 and 3.89-3.96 in its ^{1}H NMR spectrum proves the presence of epoxide ring. The next task was to open the epoxide in **44** regioselectively to get 1, 3- diol compound **45**, which was accomplished by treating the epoxy alcohol **44** with Red-al[19] in THF solvent at -20 ^{o}C for 8 hours. A characteristic peaks at δ 3.76-3.92 in its ^{1}H NMR spectrum due to methylene protons of C**H**OH and C$\mathbf{H_2}$OH confirms the formation of product. The 1, 3- diol is exclusively produced and the other isomer 1, 2-diol was almost not detected in the reaction mixture. The two hydroxy groups in **45** were completely protected as silyl ethers using TBSCl and triethyl ethyl amine (Et_3N) in Presence of dimethyl aminopyridine (DMAP) catalyst to yield **46** in 96% yield. the disappearance of a broad band at 3462 cm^{-1} in its IR spectrum and two characteristic peaks at δ 0.04 (s, 12H) , 1.27 (brs, 8H) due silyl group protons in its ^{1}H NMR spectrum confirms the formation of the product. Further, the primary hydroxy group in compound **46** was selectively deprotected using camphor sulfonic acid (CSA) in methanol and dichloromethane mixture to yield compound **47** in 85% yield. The disappearance of a peak at -4.41due to one of the silyl group carbon in its ^{13}C NMR spectrum confirms its removal.



Scheme 7: *Reagents and conditions:(i) triethyl phosphonoacetate, NaH, CH_2Cl_2, 0 °C- RT, 8 h, 95%; (ii) $LiAlH_4$, $AlCl_3$, THF, 0 °C, 1 h, 82%;(iii) (+)- DET, $Ti(O\text{-}i\text{-}Pr)_4$, TBHP, CH_2Cl_2, molecular sieves 4 A°, -15 °C, 85%; (iv) Red-al, THF, -20 °C, 6h, 96% (v) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, RT, 8 h., 96%. (vi) CSA, MeOH:CH_2Cl_2 (1:1), RT, 85% (vii) (a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C, 1h; (b) $EtO_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, dry THF, -78 °C, 2 h, 74%. (viii) p-TSOH, MeOH, 3 h, 91%.*

The free hydroxy group was then oxidized to aldehyde using Iodoxy benzoic acid (IBX) in dimethyl sulfoxide (DMSO) solvent, thus obtained crude aldehyde was then immediately subjected to Still - Gennari modification of Horner – Emmons olefination[20] using ethyl(bistrifluoroethyl) phosphonoacetate in the presence of NaH in THF to afford Z-ester **48** exclusively. Finally, cylization of Z-ester was accomplished using catalytic amount of p-toluenesulfonic acid (p-TsOH) in methanol to yield (*R*) - Massoialactone, **1** in 91% yield by the in situ deprotection of TBS group.

3.2.4. Conclusion

The stereoselective total synthesis of naturally occurring bioactive compound (*R*)-Massoialactone has been successfully achieved employing Sharpless asymmetric epoxidation of allyl alcohol, selective hydride reduction of epoxy alcohol and olefin cross metathesis reactions as the key steps. The present synthetic route can conveniently be utilized for the preparation of various analogs of (*R*)-Massoialactone useful for biological evaluation.

3.2.5. Experimental Section

3.2.5.1. (E)-ethyl oct-2-enoate, 42

To a stirred solution of above hexanaldehyde in dichloromethane (50 mL) was added Wittig's ylide (9 g, 26 mmol) at room temperature. After stirring for 12h, the solvent was evaporated and the residue was chromatographed over silica gel (100-200 mesh, EtOAc/hexane 1:9) yielding pure compound **42** (9.84 g, 95%) as colorless oil.

3.2.5.2. (E)- oct-2-en-1-ol, 43

To a suspension of Lithium Aluminum hydride (12.8 mmol, 0.486 g) in dry THF at 0^oC under N_2 atmosphere was added a drop wise solution of $AlCl_3$ (0.577 g, 4.3 mmol) in THF. The reaction mixture was stirred at same temperature for 30 min. To this stirred suspension, was added the drop wise solution of unsaturated ester 4**2** (1.4 g, 8.54 mmol) in THF over a period of 10 min and the contents were stirred at 0^oC for 1h. The reaction mixture was quenched with water and filtered through celite and the residue was washed with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was chromatographed over silica gel (100-200 mesh, EtOAc/hexane 2:8) yielding pure alcohol 4**3** (78%)as colorless oil; IR (neat, cm^{-1}): 3352, 3042, 2911,

1642, 1125, 1094; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85-0.92 (t, *J* = 6.32 Hz, 3H), 1.24-1.42 (m, 6H), 1.99-2.17 (m, 3H), 4.07-4.10 (d, *J* = 4.8 Hz, 2H), 5.55-5.78 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.97, 22.46, 28.75, 31.32, 31.12, 63.7, 128.69, 133.51; ESI-MS: *m/z* = 141 (M+Na)

3.2.5.3. ((2R, 3R)-3-pentyloxiran-2-yl) methanol, 44

(+)-Diethyl tartarate (0.2 g, 1 mmol), $Ti(O\text{-}iPr)_4$ (0.23 g, 0.8 mmol) were added sequentially to a suspension of 4 A^{o} molecular sieves (3 g) in CH_2Cl_2 (20 mL) at -20 ^{o}C and the suspension was stirred for 30 min. A solution of compound **43** (0.35 g, 2.6 mmol) in dry CH_2Cl_2 (15 mL) was then added drop wise at the same temperature followed by the addition of tBuOOH (0.45 g, 2 mmol) and the reaction mixture was stirred for 12 h at -10 °C. When the starting material was not observed on the TLC, the reaction was quenched with 20% NaOH solution saturated with NaCl (1 mL) and the reaction mixture was stirred vigorously for another 30 min at RT. The resulting reaction mixture was filtered through celite, the solvent was evaporated and the crude product was purified by column chromatography over silica gel (60-120 mesh, EtOAc/hexane 3:7) to afford pure epoxy alcohol **44** in 87% yield; $[\alpha]_D^{25}$: + 16.9 (*c* 0.6, $CHCl_3$); IR (neat, cm^{-1}): 3402, 2912, 1268, 1112, 894, 764; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87-0.93 (t, *J* = 6.69 Hz, 3H), 1.27-1.63 (m, 8H), 2.92-2.99 (m, 3H), 3.58-3.66 (m, 1H), 3.89-3.96 (dd, *J* =2.4 Hz, 10.23 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.92, 22.50, 25.56, 27.88, 31.47, 56.06, 58.53, 61.72; ESI-MS: *m/z* = 145 (M+1)

3.2.5.4. (R)-Octane-1, 3-diol, 45

To a stirred solution of epoxy alcohol **44** (0.11 g, 0.75 mmol) in THF (5 mL) at -15 °C was added drop wise solution of sodium bis (methoxyethoxy) aluminum hydride (Red-al) (3.5 M solution in toluene, 1.2 mmol). The reaction mixture was stirred for 6

h at the same temperature. When no starting material was observed on TLC, the temperature was raised to 0 ^{o}C, reaction mixture was quenched with citric acid solution and the resultant reaction mixture was stirred for another 10 min. Then contents were decanted leaving behind a residue, which was further dissolved in water and extracted with EtOAc thrice. The combined organic layers were evaporated under reduced pressure, and the residue was chromatographed over silica gel (60-120 mesh, EtOAc/hexane 3:7) yielding pure diol **45** (96 %) as viscous liquid; $[\alpha]_D^{25}$: - 5.8 (*c* 0.6, $CHCl_3$); IR (neat, cm^{-1}): 3462, 2944, 1361, 1124; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86-0.92 (t, *J* =6.06 Hz, 3H), 1.30-1.47 (m, 8H), 1.63-1.74 (m, 2H), 2.73 (brs, 2H), 3.76-3.92 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.99, 22.59, 25.17, 31.79, 37.76, 38.21, 61.80, 72.32; ESI-MS: *m/z* = 147 (M+1).

3.2.5.4. (R)-2,2,3,3,9,9,10,10-octamethyl-5-pentyl-4,8-dioxa-3,9-disilaundecane, 46

To a stirred solution of diol **45** (1g, 4.8mmol) in dry CH_2Cl_2 (80 ml), Imidazole (0.68g, 10 mmol) were added and the reaction mixture was cooled to 0 ^{o}C, a solution of t-Butyldimethylsilyl chloride (1.4 g, 9.6 mmol) in dry CH_2Cl_2 (20 mL) was added drop wise at 0^{o}C and the reaction mixture was stirred at room temperature for 12 h. Upon completion of the reaction (as monitored by TLC) reaction mixture was diluted with CH_2Cl_2 (40 ml) and washed with water, organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed over silica gel (60-120 mesh, EtOAc/hexane 1:9) yielding pure compound **46** (96%) as colorless oil; $[\alpha]_D^{25}$: + 8.9 (*c* 0.5, $CHCl_3$): IR (neat, cm^{-1}): 2924, 1121, 1089, 825; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 12H), 0.88-0.89 (d, *J* = 1.26 Hz, 21H), 1.27 (brs, 8H), 1.59-1.69 (q, *J* = 6.57 Hz, 2H), 3.63-3.82 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ -5.30, -4.41, 14.04, 18.12, 18.28, 22.66, 24.84, 25.94, 32.03, 37.34, 40.11, 60.08, 69.39; ESI-MS: *m/z* = 397 (M+Na).

3.2.5.5. (R)-3-((tert-butyldimethylsilyl) oxy) octan-1-ol, 47

Camphor sulphonic acid (0.074 g, 0.33 mmol) was added to a stirred solution of compound **46** (0.368 g, 1mmol) in 1:1 mixture of MeOH and CH_2Cl_2 at room temperature. The reaction mixture was stirred for 1.5 h and upon completion; the reaction was quenched with saturated $NaHCO_3$ solution. The product was extracted into CH_2Cl_2,the organic layer was evaporated under reduced pressure and the residue was column chromatographed over silica gel (60-120 mesh, EtOAc/hexane 1:9) to yield pure alcohol **47** (0.054 g, 85 %); $[\alpha]_D^{25}$: + 22.1 (*c* 1, $CHCl_3$); IR (neat, cm^{-1}): 3354, 2924, 1121, 1089, 825; ^1H NMR (200 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.82 (s, 12H), 1.17-1.35 (brs, 8H), 1.51-1.59 (q, *J* = 6.17 Hz, 2H), 3.28 (brs, 1H), 3.72-3.82 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ -5.30, 14.04, 18.12, 18.28, 22.66, 25.94, 32.03, 37.34, 40.11, 60.08, 69.39; ESI-MS: *m/z* = 283 (M+Na).

3.2.5.6. (R,Z)-ethyl 5-((tert-butyldimethylsilyl)oxy)dec-2-enoate, 48

To a solution of compound **47** (1.4 g, 5.34 mmol) in DMSO (5 mL) in a round-bottomed flask was added IBX (1.68 g, 6 mmol) in one portion and the reaction mixture was stirred for 1 h at ambient temperature. The reaction mixture was quenched with diethylether (5 mL), H_2O (0.5 mL) and filtered through a pad of celite. The residue was repeatedly washed with diethyl ether. The filtrate was then washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated to give the crude aldehyde, which was pure enough and used in the next step without further purification.

60 % dispersion of NaH (0.448 g, 13.30 mmol) in mineral oil was added to a stirred solution of ethyl P,P bis (2,2,2-trifluoroethyl) phosphonoacetate (3.496 g, 10.52 mmol) in dry THF (50 mL) at 0 ^oC, resulting ylide solution was stirred for 45 min at

the same temperature,then the reaction mixture was cooled to -78 ^{o}C. The crude aldehyde obtained above dissolved in dry THF (10 mL) was added drop wise and stirring was continued for further 3 h. After completion of the reaction, the reaction was quenched with saturated NH_4Cl solution (2 mL) at 0 ^{o}C, concentrated under reduced pressure. Residue obtained was dissolved in EtOAc washed with water and brine. Organic layer was dried over Na_2SO_4, evaporated under *vacuum* and the crude product was purified by silica gel column chromatography (100-200 mesh, EtOAc/hexane 2:8) to obtain **48** (74%) as colorless oily compound; $[\alpha]_D^{25}$: - 12.3 (*c* 1, $CHCl_3$);; IR (neat, cm^{-1}): 1728, 1682, 1080, 820; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.82 (brs,12H), 1.25-1.32 (m, 11H), 2.88-2.99 (m, 2H) 3.73-3.85 (m, 1H), 4.13-4.24 (q, 2H) 5.88 (d, *J* = 11.2 Hz, 1H), 6.38 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ -4.55, 14.31, 18.01, 22.46, 25.17, 31.79, 37.76, 38.21, 59.66, 71.35, 121.04, 146.41, 166.13; ESI-MS: *m/z* = 341 (M+Na).

3.2.5.7. (R)-6-pentyl-5,6-dihydro-2H-pyran-2-one, (R)- Massoialactone, 1

To a stirred solution of compound **48** (0.594 g, 3 mmol) in MeOH was added catalytic amount of PTSA and the contents were stirred for 3h at room temperature. When no starting material was observed on TLC, the reaction mixture was concentrated under reduced pressure, dissolved in EtOAc and washed with Na_2CO_3 solution (5 mL, 10%). Organic layer was separated and dried over anhydrous Na_2SO_4, concentrated under *vacuum* and the obtained residue was chromatographed over silica gel (100-200 mesh, CH_2Cl_2/hexane 1:9) yielding (*R*)-**1** (91%) as a colorless oil; $[\alpha]_D^{25}$: -114.8 (*c* 1, $CHCl_3$); IR (neat, cm^{-1}): 2930, 1716, 1610, 1048, 835; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86-0.91 (t, *J* = 6.4 Hz, 3H), 1.21- 1.30 (m, 5H), 1.62-1.86 (m, 3H), 2.28-2.38 (m, 2H), 4.4-4.45 (m, 1H), 6.1 (d, *J* = 9.8 Hz, 1H), 6.81-6.90 (m, 1H); ^{13}C NMR

(50 MHz, $CDCl_3$): δ 13.91, 22.43, 24.54, 29.42, 31.49, 34.81, 78.02, 121.45, 144.82, 164.43; ESI-MS: *m/z* = 191 (M+Na).

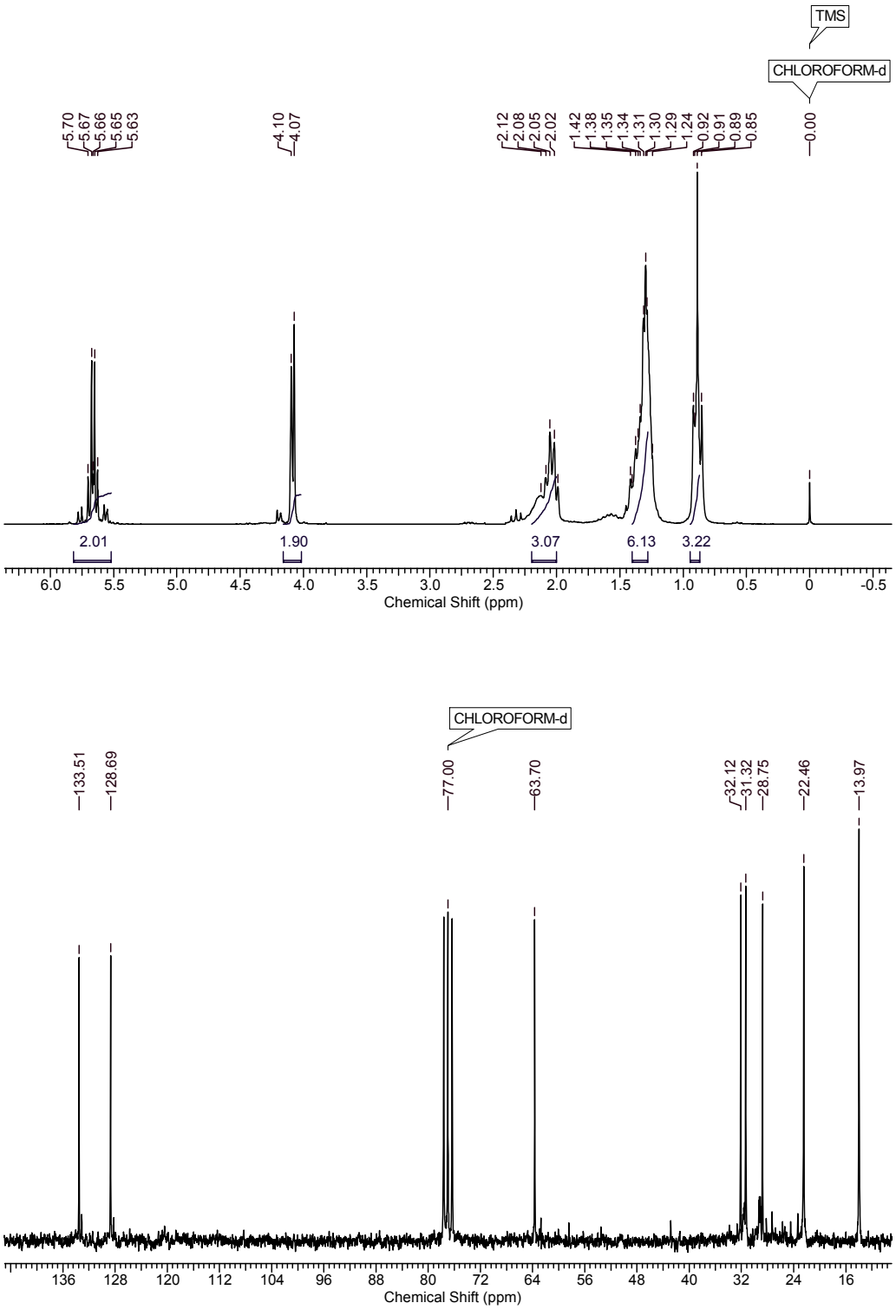


Fig. 2: ^{1}H-NMR and ^{13}C-NMR spectra of compound 43

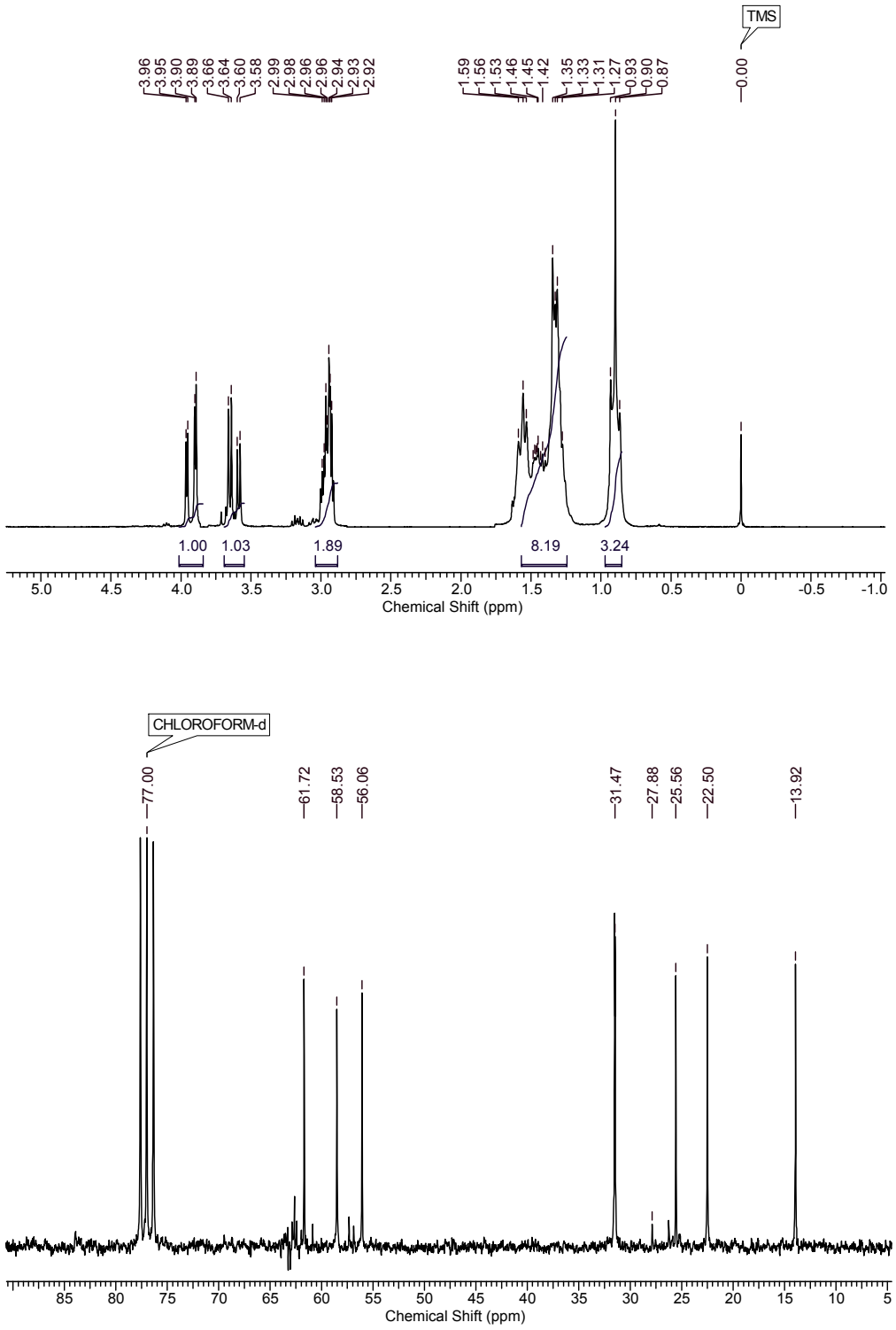


Fig. 3: ^{1}H-NMR and ^{13}C-NMR spectra of compound 44

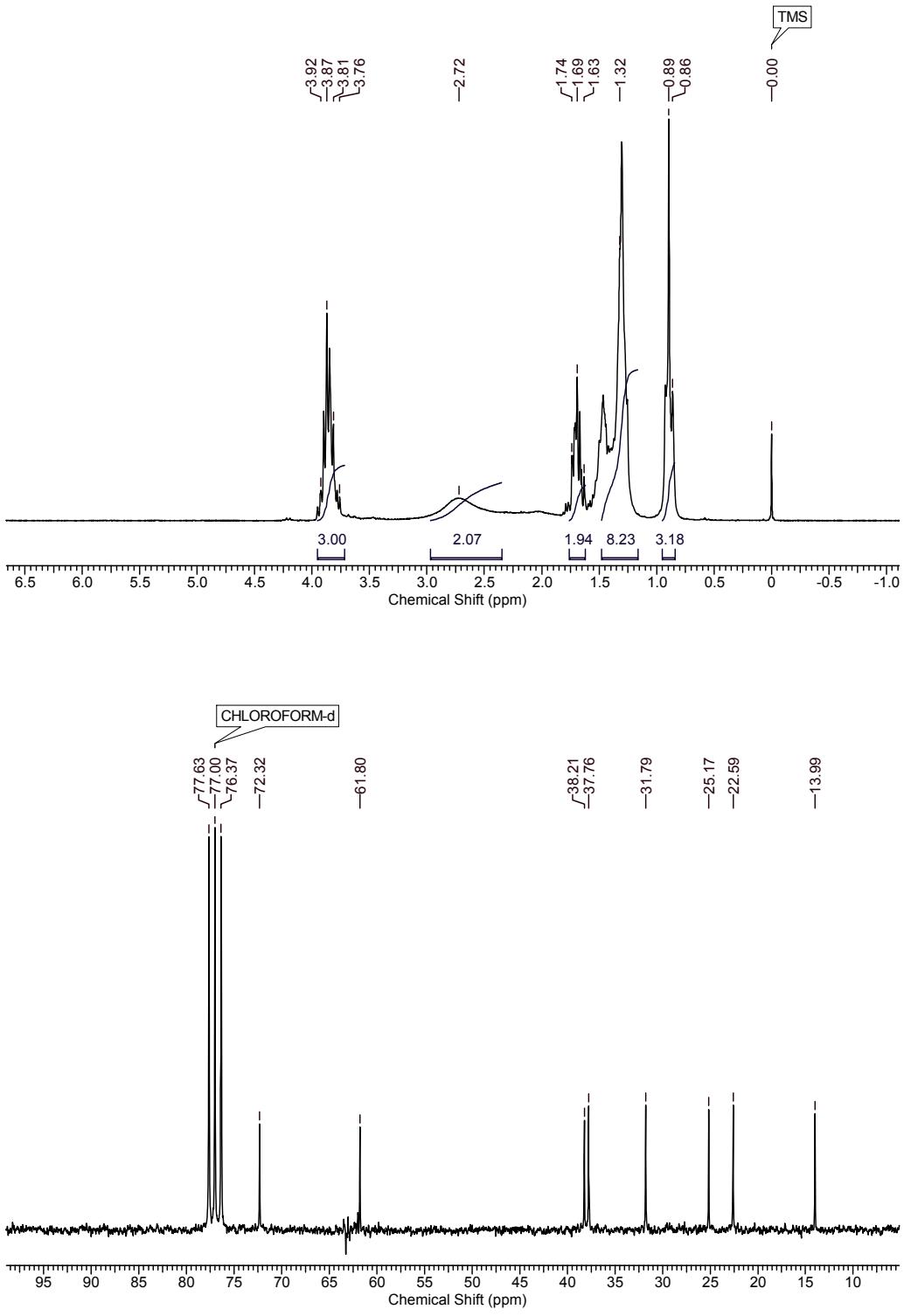


Fig. 4: ^{1}H-NMR and ^{13}C-NMR spectra of compound 45

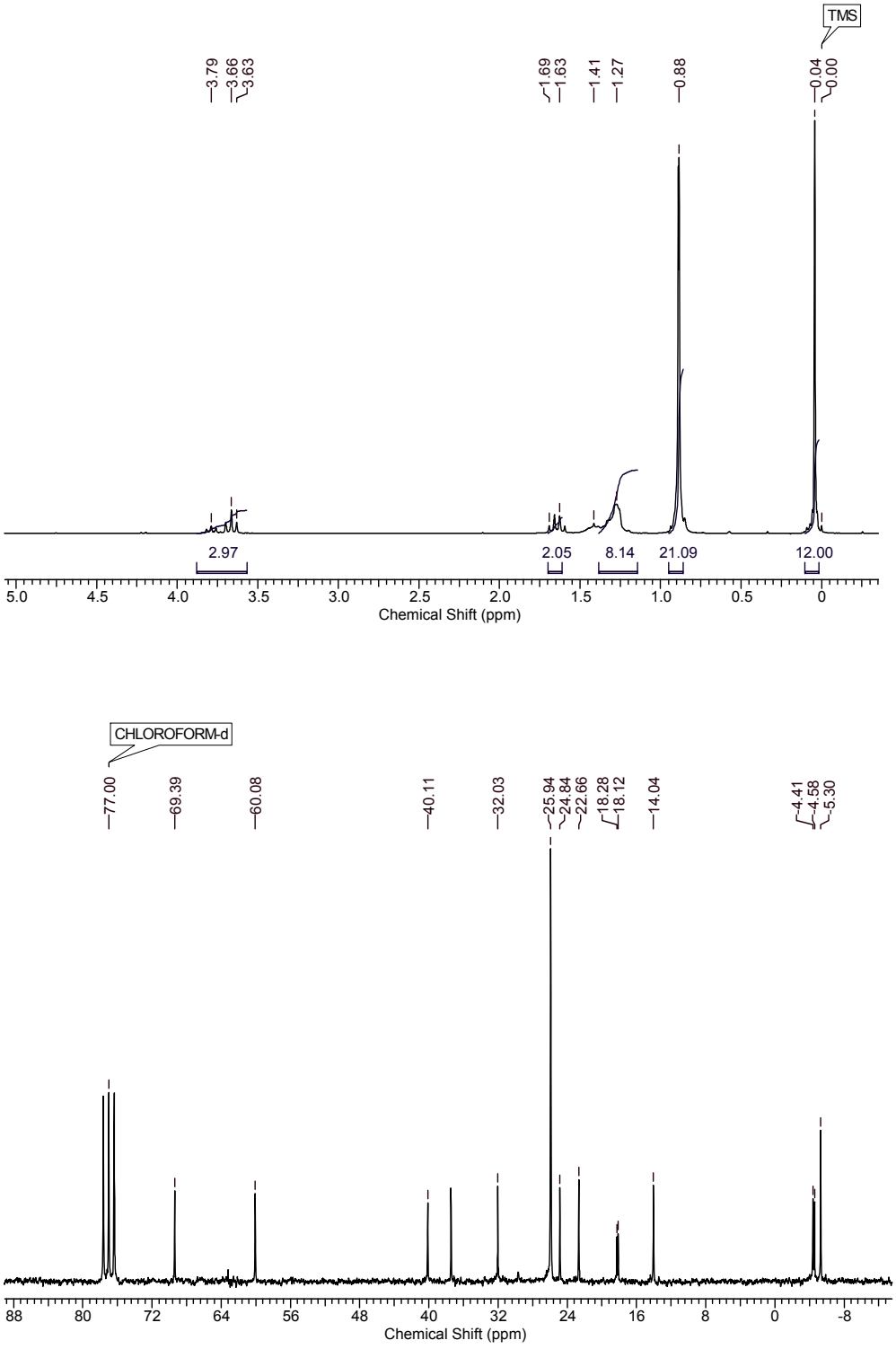


Fig. 5: ^{1}H-NMR and ^{13}C-NMR spectra of compound 46

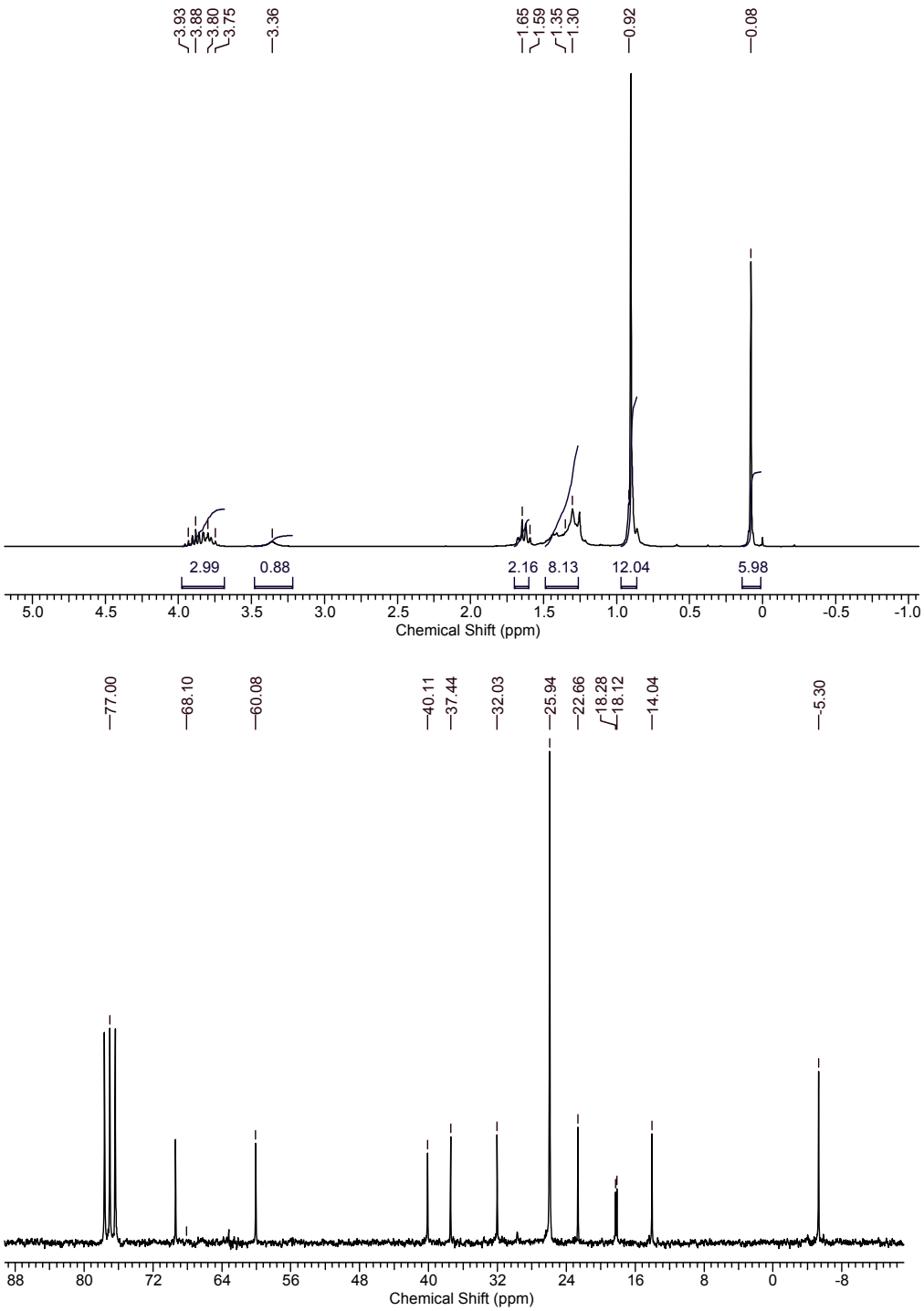


Fig. 6: ^{1}H-NMR and ^{13}C-NMR spectra of compound 47

SECTION: II

A facile stereoselective total synthesis of (*S*)-*N*-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaniol

3.2.1. Introduction and pharmacology

Alzheimer's disease (AD) is a chronic, neurodegenerative disorder which shows characteristics such as loss of cognitive ability, severe abnormalities in behavior.[21] A key event in the pathogenesis of Alzheimer's disease is found to be the deposition of β-amyloid (Aβ) plaques in the brain that are produced by the cleavage of amyloid precursor protein (APP) by β and γ-secretase.[22] Recent studies have further shown that neuritic plaques and neurofibriliary tangles are accepted pathological hallmarks of AD as confirmed at autopsy.[23] γ-Secretase inhibitors like LY-450139, MK-0752 and BMS-299897 are under clinical trials.[24] (*S*)-*N*-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol **1**, a Notch-1-sparing γ-secretase inhibitor (EC_{50}= 28 nM), has been proved to be effective in the reduction of Aβ production *in vivo*.[24] (**Fig. 9**).

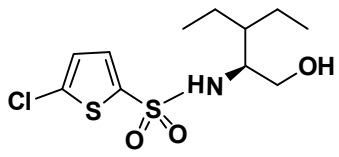


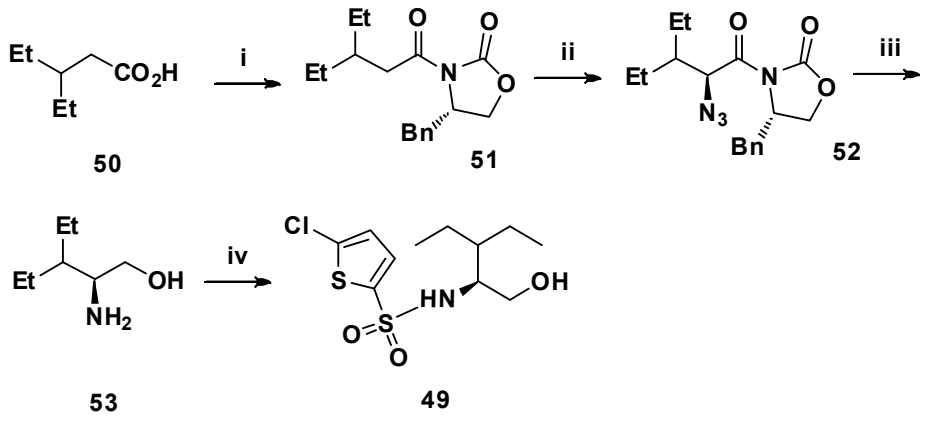
Figure 9: Structure of (*S*)-*N*-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol (**49**)

3.2.2 Review of Literature

Literature search has revealed that only a few synthetic reports are available for the synthesis of target molecule **49**.

Mayer's approach (2008)[25]

Mayer *et al.* have reported the synthesis of (*S*)-*N*-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol **49** starting from pent-2-enoic acid **50** which was coupled with (R)-4-benzyl-2-oxazolidinone to give the alkenoyloxazolidin-2-one products **51**. Chiral α-aziridination was accomplished then by using KHMDS as base and 2,4,6-triisopropylbenzenesulfonyl azide as azide source. Compound was converted to amino alcohol by treatment with lithium aluminum hydride. Amino alcohols **53** was reacted with 5-chlorothiophene-2-sulfonyl chloride to give the desired 5-chlorothiophene-2-sulfonyl amino alcohols **49.**

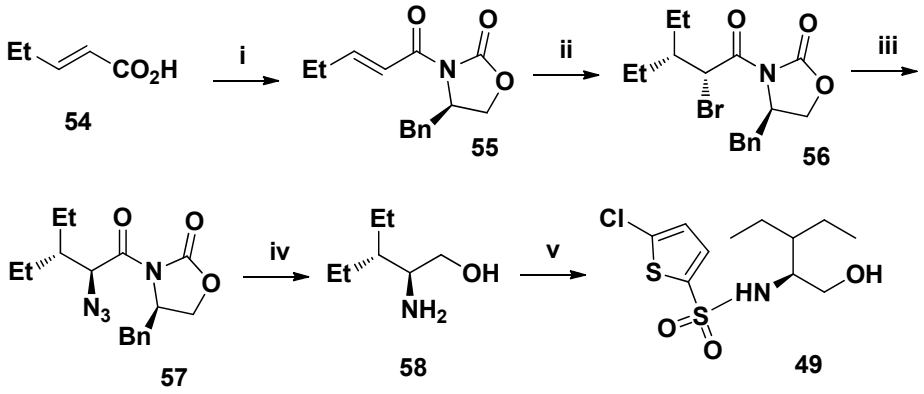


Scheme 8: *(i) (a) (S)-4-benzyl-2-oxazolidinone, $(CH_3)_3CCOCl$, Et_3N, THF, (ii) (a) KHMDS, THF, -78 ^oC, 30 min; (b) 2,4,6-triisopropylbenzenesulfonyl azide, THF -78 ^oC; (iii) $LiAlH_4$, THF, 60 ^oC; (e) 5-chlorothiophene-2-sulfonyl chloride, Et_3N, THF.*

Cole's approach (2009)[24]

Cole *et al.* have reported the synthesis of (*S*)-*N*-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol **49** starting from pent-2-enoic acid **54** which was coupled with (*R*)-4-benzyl-2-oxazolidinone to give the alkenoyloxazolidin-2-one products **55**. Cuprate reagents prepared in situ by addition of Grignard reagents to copper bromide dimethylsulfide under carefully controlled temperature conditions, underwent Michael addition and the anion was trapped with N-bromosuccinimide to give the α-bromo

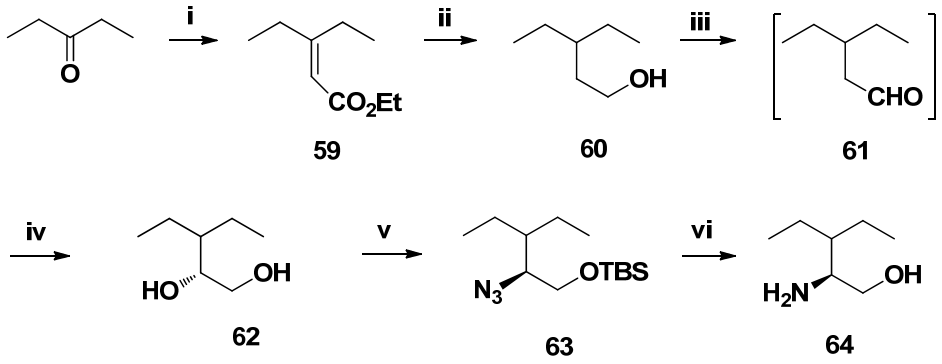
derivatives **56**. Displacement of the bromide with N,N,N',N'-tetramethylguanidinium azide yielded the corresponding azide **57**. Simultaneous reduction of amide and azide moieties by treatment with lithium aluminum hydride yielded the corresponding amino alcohols **58**, which were reacted with 5-chlorothiophene-2-sulfonyl chloride to give the desired 5-chlorothiophene-2-sulfonyl amino alcohols **49** (**Scheme 11**).



Scheme 9: *(i) (R)-4-benzyl-2-oxazolidinone, $(CH_3)_3CCOCl$, Et_3N, THF, (ii) n-BuLi, THF; (iii) (a) EtMgBr, CuBr.DMS, THF -40 to -15 ^oC; (b) NBS, -78 ^oC; (c) N,N,N',N'-tetramethylguanidinium azide, CH_3CN, rt; (iv) $LiAlH_4$, THF, 60 ^oC; (iv) 5-chlorothiophene-2-sulfonyl chloride, Et_3N, THF.*

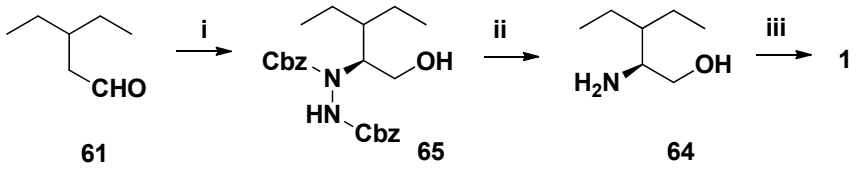
Varun's approach (2010)[26]

In their approach, the synthesis of **49** commenced from 3-pentanone, which on Horner-Wardworth-Emmons olefination, gave the corresponding α, β-unsaturated ester **59** in 93% yield. Hydrogenation of the unsaturated ester **59** produced the crude saturated ester, which was directly subjected to reduction with $LiAlH_4$ affording the saturated primary alcohol **60** in 83% yield over two steps. Oxidation of primary alcohol **60** gave the key precursor aldehyde **61**, which was immediately subjected to proline-catalyzed α-aminooxylation and α-amination respectively (**Schemes 10& 11**).



Scheme 10. *Reagents and conditions (i) triethyl phosphonoacetate, NaH, dry THF, 0-25 ºC, 8 h, 93%; (ii) (a) H_2 (1 atm), 10% Pd/C, MeOH, 12 h, 25 ºC; (b) $LiAlH_4$, dry THF, 25 ^oC, 12 h, 83% (for two steps); (iii) IBX, dry DMSO, 25 ºC. 2 h; (iv) (a) PhNO, L-proline (20 mol %), CH_3CN, -20 ºC, 24 h then MeOH, $NaBH_4$; (b) H_2 (1 atm), 10% Pd/C, MeOH, 12 h, 25 ºC, 77% (over two steps); (c) TBSCl, imid, CH_2Cl_2, 0-25 ºC, 2 h, 81%. (v) (a) MsCl, Et_3N, 45 min; (b) NaN_3, dry DMF, 60 ºC, 30 h, 78%; (vi) $LiAlH_4$, dry THF, 50 ºC, 12 h, 75%.*

Firstly, the L-proline-catalyzed α-aminooxylation of aldehyde **61** was carried out in a two-step reaction sequence: (i) reaction of aldehyde **61** with nitrosobenzene as the oxygen source in the presence of 20 mol% L-proline followed by sodium borohydride reduction gave the crude α-aminooxy alcohol *in situ* and (ii) subsequent reduction of the crude α-aminooxy alcohol with 10% Pd/C over H_2 (1 atm) furnished chiral diol **62**. Selective protection of primary hydroxyl group in diol **62** with TBSCl produced TBS ether in 81% yield, followed by mesylation of the secondary alcohol which gave the corresponding mesylate. This crude mesylate was treated immediately with sodium azide to afford the corresponding azide **63** in 78% yield. The $LiAlH_4$ reduction of TBS azide **63** in THF at 50 °C afforded the key intermediate (*S*)-2-amino-3-ethylpentan-1-ol **64** in 75% yield was accomplished with the simultaneous removal of TBS group (**Scheme 10**).



Scheme 11. *Reagents and conditions:(i) (i) dibenzyl azodicarboxylate, D-proline (10 mol%), CH_3CN, 0-20 ºC, 3 h then MeOH, $NaBH_4$, 92%; (ii) H_2 (11.8 atm), Raney Ni, MeOH, AcOH, 70%; (iii) 5-chlorothiophene-2-sulfonyl chloride, Et_3N, dry CH_2Cl_2, 0 ^oC, 30 min., 91%.*

In another approach, aldehyde **61** was subjected to α-amination with dibenzyl azodicarboxylate in the presence of D-proline (10 mol%) to produce the α-amino aldehyde, which upon *in situ* reduction with $NaBH_4$ afforded the protected amino alcohol **65** in 92% yield and. The amino alcohol was then subjected to hydrogenolysis with hydrogen, Raney Ni to give (*S*)-2-amino-3-ethylpentan-1-ol **64** in 70% yield (**Scheme 11**). Finally, the amino alcohol **64** was condensed with 5-chlorothiophene-2-sulfonyl chloride in the presence of Et_3N to afford the target molecule **49**.

3.2.3. Present Work

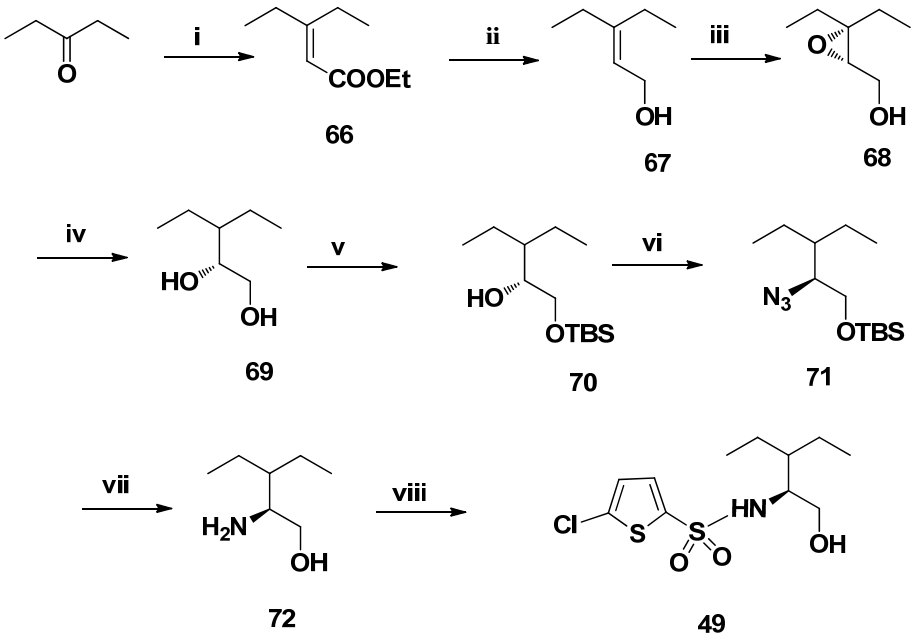
3.2.3.1. Objective

As can be seen from the above discussion, the reported synthetic methods employ either chiral pool approaches (low atom economical reactions) or involve harsh reaction conditions such as H_2, Raney Ni. Therefore, we aimed at developing a synthetic route to **49** employing highly atom economical, operationally simple reactions such as Sharpless epoxidation of allylic alcohol followed by regioselective hydride reduction of epoxy alcohols.

3.2.3.2. Results and discussion

As outlined in scheme 2, the synthesis of **49** began with commercially available 2-pentanone, which on Horner-Wardsworth-Emmons olefination with triethyl

phosphonoacetate in presence of NaH in dry THF yielded α,β–unsaturated ester **66** in 90% yield. A characteristic peak at δ 133.6 in its ^{13}C NMR spectrum due to olefinic carbon (=**C**H-COOEt) confirms the product. The compound **66** was subsequently reduced to allyl alcohol **67** by employing alane reduction conditions[27] *(*$LiAlH_4$, $AlCl_3$, THF, 0°C, 1h, 90%). The two characteristic peaks in its ^1H NMR spectrum at δ 3.39-3.45 due to olefinic proton (C**H**=), and δ 3.64-3.79 due to protons of C$\mathbf{H_2}$OH group confirms the product. The allyl alcohol **67** was then subjected to Sharpless asymmetric epoxidation[28] with titanium tetraisopropoxide and t-butyl hydroperoxide in presence of (-)-DET to produce epoxy alcohol **68** in 87% yields. A peak at δ 2.98-3.03 in its ^1H NMR spectrum due to epoxide protons (C**H**O) and two peaks at δ 63.06, 64.86 in ^{13}C NMR spectrum due to epoxide carbons (**C**O**C**) prove its formation.



Scheme 2: *Reagents and conditions:(i) triethylphosphonoacetate, NaH, dry THF, 0 °C-RT, 8 h, 90%;(ii)* $LiAlH_4$, $AlCl_3$, *THF,0°C, 1h, 78%; (iii) (-)- DET,* $Ti(O\text{-}iPr)_4$, *TBHP, dry* CH_2Cl_2, *molecular sieves 4 A°, -15 °C, 87%; (iv) DIBAL-H, benzene, RT, 1h, 89% ;(v)TBSCl, imid,* CH_2Cl_2, *0-25 °C, 4 h, 82%;(vi)(a) MsCl,* Et_3N, *30 min; (b)* NaN_3, *dry DMF, 60 °C, 30 h, 74%; (vii)* $LiAlH_4$, *dry THF, 50 °C, 12 h, 98%; (viii) 5-chlorothiophene-2-sulfonyl chloride,* Et_3N, *dry* CH_2Cl_2, *0 °C, 30 min., 90%.*

Regioselective hydride reduction[29] of epoxyalcohol **68** with DIBAL-H in benzene at room temperature afforded diol **69** in good yield. The primary hydroxyl group was then selectively protected as its TBS ether using TBSCl and Imidazole in dry DCM to yield **70** in 82% yield. Further, the remaining secondary hydroxyl group was converted to its mesylate (a good leaving group) with methanesulfonyl chloride and triethyl amine as base. As the mesylates are generally unstable, the crude mesylate was immediately treated with NaN_3 in DMF at 60 ^oC to afford azide compound **71** in 74% yields. The azide functionality was then reduced with $LiAlH_4$ in dry THF at 50 ^oC to yield amino alcoholic compound **72** with the simultaneous removal TBS group[30]. Then the final task was to condense amino alcohol **72** with commercially available 5-chlorothiophene-2-sulfonyl chloride, which was accomplished in presence of Et_3N in dry DCM to get target molecule **49** in 90% yield.

3.2.4. Conclusion

In conclusion, we have developed a novel, short synthetic route to **49** employing Sharpless asymmetric epoxidation and regioselective hydride reduction of epoxy alcohol as the key reactions. The operationally simple reactions with less number of steps, high overall yields make this approach an attractive and useful process.

3.2.5. Experimental Section

3.2.5. 1. Ethyl 3-ethylpent-2-enoate, 66

To a stirred suspension of NaH (60 % dispersion in mineral oil,0.96g, 40mmol) in dry THF (50 mL) a solution of triethylphosphonoacetate (5.2 g, 24mmol) in dry THF (10 mL) was added dropwiseat 0 ^oC followed by the addition of a solution of 3-pentanone (1.4 g, 16 mmol) in dry THF (10 mL). The reaction mixture was then stirred at 25 ^oC for 8 h. After completion of the reaction (monitored by TLC), it was quenched with

saturated solution of ammonium chloride and the product with extracted with diethyl ether. The combined organic layer was then washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure and column chromatographic purification (100-200 mesh, EtOAc/hexane, 1:9) gave α,β-unsaturated ester **3** as colorless liquid. Yield: 90%; IR ($CHCl_3$, cm^{-1}) 867, 1147, 1273, 1444, 1634, 1719, 2877, 2972; ^{1}H NMR (200 MHz, $CDCl_3$): 1.07 (t, *J* = 7.8 Hz, 6 H), 1.28 (t, *J* = 7.7 Hz, 3 H), 2.18 (q, *J* = 6.5, 8.1 Hz, 2 H), 2.60 (q, *J* = 8.1, 14.2 Hz, 2 H), 4.12 (q, *J* = 8.1, 16.1 Hz, 2 H), 5.59 (s, 1 H); ^{13}CNMR(50 MHz, $CDCl_3$): δ 11.9, 12.9, 14.2, 25.3, 30.7, 59.3, 113.6, 166.5, 167.2; Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32; found C, 69.29; H, 10.37%.

3.2.5. 2.Ethyl-3-ethylpent-2-en-1-ol, 67

To a suspension of Lithium Aluminium hydride (0.486 g,12.8 mmol) in dry THF at 0^{o}C under N_2 atmosphere was added a drop wise solution of $AlCl_3$ (0.577 g, 4.3 mmol) in THF. The reaction mixture was stirred at the same temperature for 30 min. To this stirred suspension, was added a drop wise solution of unsaturated ester **3** (1 g, 8.54 mmol) in THF over a period of 10 min and stirred at 0^{o}C for 1h. The reaction mixture was then quenched with water and filtered through Celite. The residue was washed with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was chromatographed over silica gel (100-200 mesh, EtOAc/hexane, 2:8) yielding pure allylalcohol**4** as colorless liquid; Yield 78%;IR (neat, cm^{-1}): 906, 995, 1020,1115, 1236, 1409, 1619, 2861, 2983, 3356; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85-1.06 (m, 6H), 1.45 (br s, 1H), 2.1-2.15 (m, 4H), 4.17(d, J = 6.95 Hz, 2H), 5.32-5.39 (t, J = 7.07 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.31, 13.51, 23.42, 28.94, 58.79, 121.52, 148.59;Anal. Calcd for$C_7H_{14}O$: C, 73.63; H, 12.36; found C, 73.96; H, 12.46%.

3.2.5.3. (*S*)-(3,3-diethyloxiran-2-yl)methanol, 68

(-)- Diethyl tartarate (0.2g, 1mmol), $Ti(O\text{-}iPr)_4$ (0.23g,0.8mmol) were added sequentially to a suspension of 4A^o molecular sieves (3 g) in CH_2Cl_2 (20 mL) at -20 ^{o}C and the suspension was stirred for 30 min. A solution of Compound **4**(0.3 g, 2.6 mmol) in dry CH_2Cl_2 (15 mL) was then added drop wise at the same temperature followed by the addition of t-BuOOH (0.45 g, 2 mmol)) and the reaction mixture was stirred for 12 h at -10 ^{o}C.After completion of the reaction (as monitored by TLC), the reaction was quenched with 20% NaOH solution saturated with NaCl(1 mL) and the reaction mixture was stirred vigorously for another 30 min at RT. The resulting reaction mixture was filtered through celite, the solvent was evaporated, and the crude product was purified by column chromatography over silica gel (100-200 mesh, EtOAc/hexane 3:7) to afford pure epoxy alcohol **5**as colorless viscous liquid: Yield 87%; $[\alpha]_D^{25}$ + 17.9 (*c* 0.6, $CHCl_3$);IR (neat, cm^{-1}): 798, 889, 1097, 1257, 1367, 2857, 3365; ^{1}H NMR (200 MHz, $CDCl_3$): δ0.89-1.02 (m, 6H), 1.47-1.69 (m, 4H), 2.09 (br s, 1H), 2.98-3.03 (m, 1H), 3.64-3.73 (m, 1H), 3.82-3.91 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 8.74, 9.95, 23.1, 27.17, 61.87, 63.06, 64.86;Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84; found C, 64.92; H, 10.37%.

3.2.5.4. (*R*)-3-ethylpentane-1,2-diol, 69

To a stirred solution of compound **5** (1.225g, 5mmol) in dry benzene, was added diisobutylaluminium hydride (1M solution in toulene, 5 mL) dropwise at room temperature. The reaction mixture was stirred for 1h at the same temperature and upon completion of the reaction; reaction mixture was diluted with a saturated solution of sodium potassium tartarate and stirred for another 4h. The organic phase was separated and the aqueous phase was treated with EtOAc thrice. The combined organic layer was then washed with water, brine and finally dried over anhydrous

Na_2SO_4. Solvents were removed under reduced pressure to give crude product, which was further purified by column chromatography over silica gel (100-200 mesh, EtOAc/hexane 1:9) to afford pure product**7**as colorless liquid in 87% yield; $[\alpha]_D^{25}$ -4.9 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}): 1073, 1124, 1379, 1461, 2875, 2961, 3387; ^1H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, *J* = 6.4 Hz, 6 H), 1.29-1.52 (m, 5 H), 2.04-2.16 (m, 2 H), 3.44-3.70 (m, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.3, 11.4, 21.2, 21.6, 43.7, 64.9, 73.6. Anal. Calcd for$C_7H_{16}O_2$: C, 63.60; H, 12.20; found C, 63.63; H, 12.25%.

3.2.5.5. (*R*)-1-((tert-butyldimethylsilyl)oxy)-3-ethylpentan-2-ol, 70

To a solution of diol**5** (1.97 g, 15.14 mmol) in dry CH_2Cl_2 (50 mL) at 0 ^oC was added imidazole (1.54 g, 22.70 mmol) and *tert*-butyldimethylsilyl chloride (2.51 g, 16.65 mmol). The reaction mixture was then stirred at 25 ^oC for 4 h. After completion of reaction (monitored by TLC), it was diluted with CH_2Cl_2, washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave the crude product which was then purified by column chromatography over silica gel (100-200 mesh, EtOAc/hexane 2:8)to furnish **6** as colorless liquid.Yield: 82%; $[\alpha]_D^{25}$ -5.0 (*c* 1.6, $CHCl_3$); IR (neat, cm^{-1}): 836, 1097, 1256, 1462, 2858, 2929, 2958, 3437; ^1H NMR (200 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.86-0.98 (m, 15H), 1.33–1.53 (m, 6H), 2.37 (br.s, 1H), 3.46-3.69 (m, 3 H);^{13}C NMR (50 MHz, $CDCl_3$): δ -5.3, -5.2, 11.2, 11.4, 18.3, 21.1, 21.6, 25.9, 43.2, 65.5, 72.9; Anal. Calcd for$C_{13}H_{30}SiO_2$: C, 63.35; H, 12.27; found C, 63.68; H, 12.21%.

3.2.5.6. ((*S*)-2-azido-3-ethylpentyloxy)(tert-butyl)dimethylsilane, 71

Compound **7** (312 mg, 1mmol) and triethylamine (0.3 g, 3 mmol) were dissolved in dry CH_2Cl_2 (15 mL), and the solution cooled to 0 ^oC.Methanesulfonyl chloride (229.2 mg, 2 mmol) was added, and then the resulting solution was stirred at 0 ^oC for 30 min. After TLC showed that the reaction was complete, more CH_2Cl_2 (20 mL) was added.

The organic phase was washed with brine and then dried over anhydrous Na_2SO_4. After the solvent was removed under vaccum, the crude product was dissolved in DMF and NaN_3 (390 mg, 6 mmol) was added. The reaction mixture was then stirred at 60 ^oC for 30 h. After the completion of reaction (monitored by TLC), the reaction mixture is then partitioned between EtOAc and brine. The organic layer is further washed with brine, dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave crude product which on column chromatography over silica gel (100-200 mesh, EtOAc/hexane 1:9) gave the corresponding azide **8**.Yield: 74%; $[\alpha]_D^{25}$:-21.8 (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 837, 964, 1214, 1251, 1459, 1490, 1603, 2113, 2894, 3069; ^1H NMR (200 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.85-0.92 (m, 15H), 1.34-1.38 (m, 5H), 3.39-3.45 (m, 1H), 3.64-3.79 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ -5.7, 11.2, 11.3, 18.2, 21.7, 22.6, 25.8, 41.9, 65.1, 66.2; Anal. Calcd for $C_{13}H_{29}N_3OSi$: C, 57.52; H, 10.77; N, 15.48; found C, 57.51; H, 10.85; N, 15.55%.

3.2.5.7. (*S*)-2-amino-3-ethylpentan-1-ol, 72

To a suspension of $LiAlH_4$ (1.01 g, 26.66 mmol) in dry THF (30 mL), a solution of azido compound **8** (5.0 g, 24.24 mmol) in THF (50 mL) was added dropwise at 0 °C. The reaction mixture was then stirred at 50 ^oC for 12 h. After completion of reaction (monitored by TLC), it was quenched with aq. 20% solution of sodium hydroxide (2 mL) at 0 °C. The reaction mixture was filtered through sintered funnel, dried over anhydrous Na_2SO_4 and concentrated. Purification by column chromatography over silica gel (100-200 mesh, EtOAc/hexane 7:3) gave the amino alcohol **10** as a colorless liquid.Yield: 98%; $[\alpha]_D^{25}$ -12.3 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}): 3020, 2930, 2857, 1722, 1572, 1472, 1215; ^1H NMR (200 MHz, $CDCl_3$): 0.83-0.92 (m, 6H), 1.23-1.42 (m, 5H), 2.34 (br.s, 3H), 2.83 (m, 1H), 3.26-3.35 (m, 1H), 3.57-3.69 (m, 1H); ^{13}C

NMR (50 MHz, $CDCl_3$): δ 11.4, 11.5, 21.4, 21.8, 44.8, 54.9, 64.3; Anal. Calcd for $C_7H_{17}NO$: C, 64.07; H, 13.06; N, 10.67; found C, 64.34; H, 12.86; N, 10.42%.

3.2.5.8. (*S*)-*N*-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol, 49

To a solution of amino alcohol **9** (1.0 g, 11.2 mmol) in dry CH_2Cl_2 (50 mL) at 0 ºC was added imidazole (0.916 g, 13.4 mmol,) after stirring for 10 min.,5-chlorothiophene-2-sulfonyl chloride(1.8 g, 12.3 mmol,) was added and the reaction mixture was stirred at 25 ºC for 3 h. After completion of the reaction, solvent was removed under reduced pressure and the crude product was then purified by column chromatography over neutral Al_2O_3 (pet ether: EtOAc, 70:30).Yield: 90%; Colorless crystalline solid; m.p.114-116^oC (crystallized from heptane:ethylacetate, 4:1) {lit.[3a]m.p. 115-117.6 ^oC}; $[\alpha]_D^{25}$ +10.3 (*c* 0.6, MeOH) {lit.[3a] $[\alpha]_D^{25}$ +10.81 (1% solution,MeOH)}; IR ($CHCl_3$, cm^{-1}) :1093,1133,1339, 1456,1617, 2882,2956,3034, 3065, 3301, 3515; ^1H NMR (200 MHz, $CDCl_3$) δ 0.78-0.87 (m, 6H), 1.17-1.34 (m, 5H), 1.94 (br. s, 1H), 3.30-3.42 (m, 1H), 3.57-3.60 (m, 2H), 4.93 (br. s, 1H), 6.93 (d, *J* = 4.1 Hz, 1H), 7.42 (d, *J* = 4.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.4, 11.7, 22.7, 21.9, 42.7, 57.8, 62.6, 126.6, 131.5, 137.3, 140.1; Anal. Calcd for $C_{11}H_{18}ClNO_3S_2$: C, 42.37; H, 5.82; N, 4.49; found C, 42.26; H, 5.71; N, 4.55%.

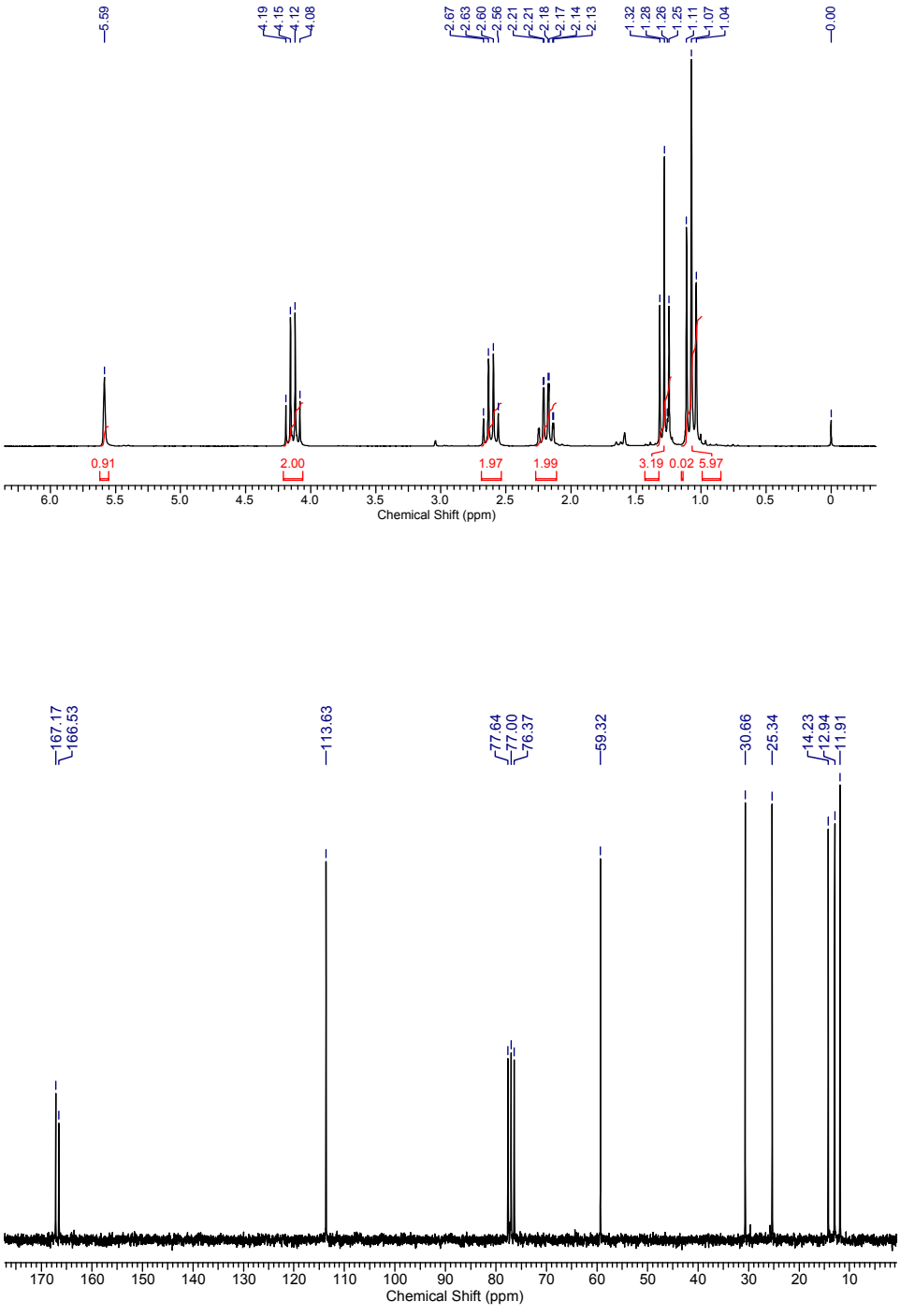
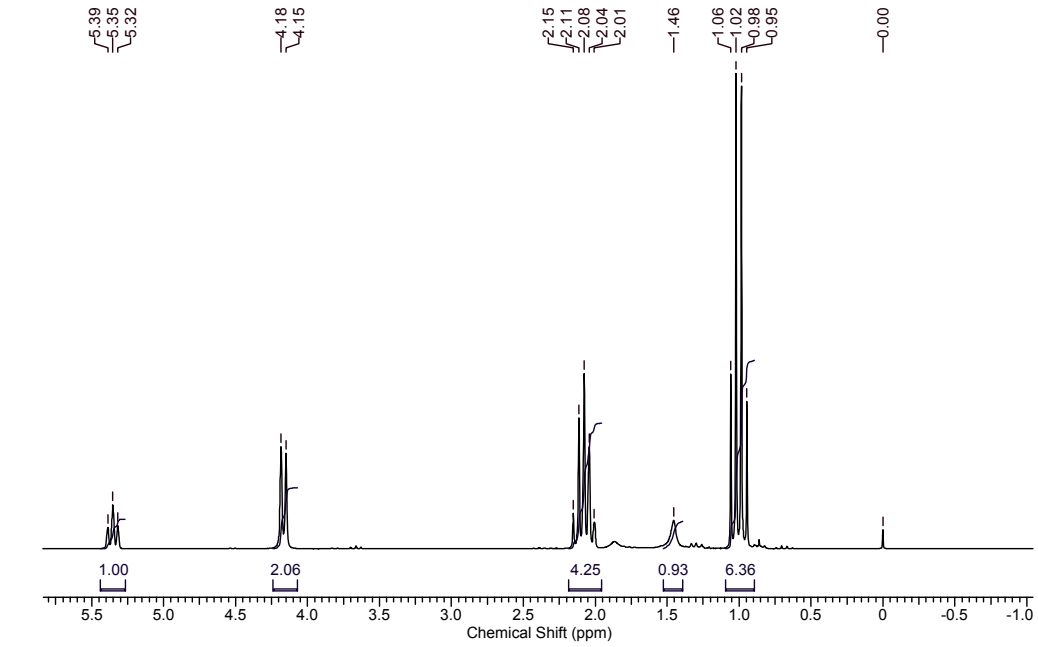


Figure 10. ^{1}H NMR & ^{13}C NMR spectra of compound **66**



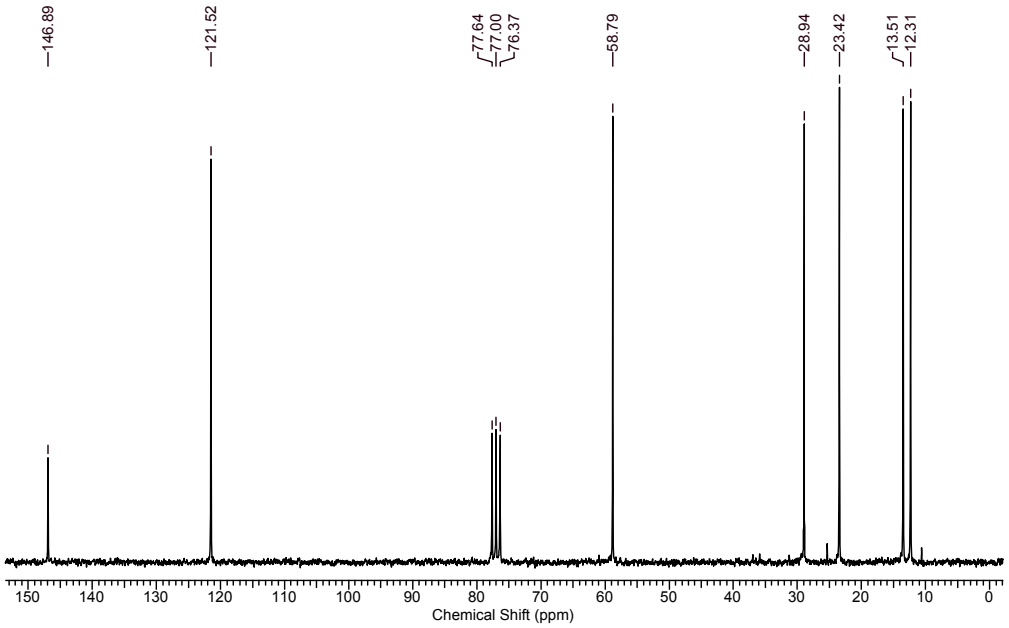


Figure 10. ^{1}H NMR & ^{13}C NMR spectra of compound **67**

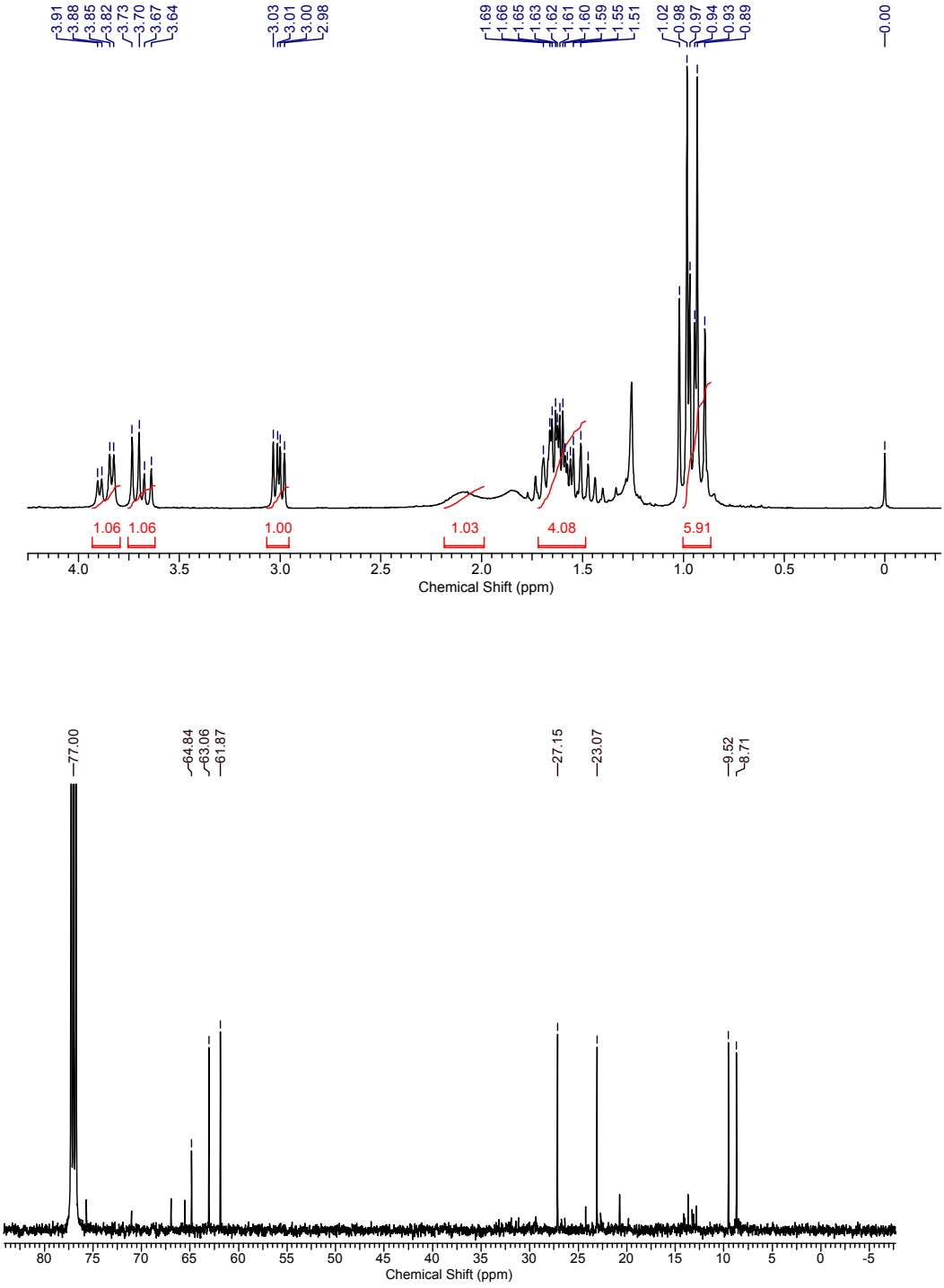


Figure 12. ^{1}H NMR & ^{13}C NMR spectra of compound **68**

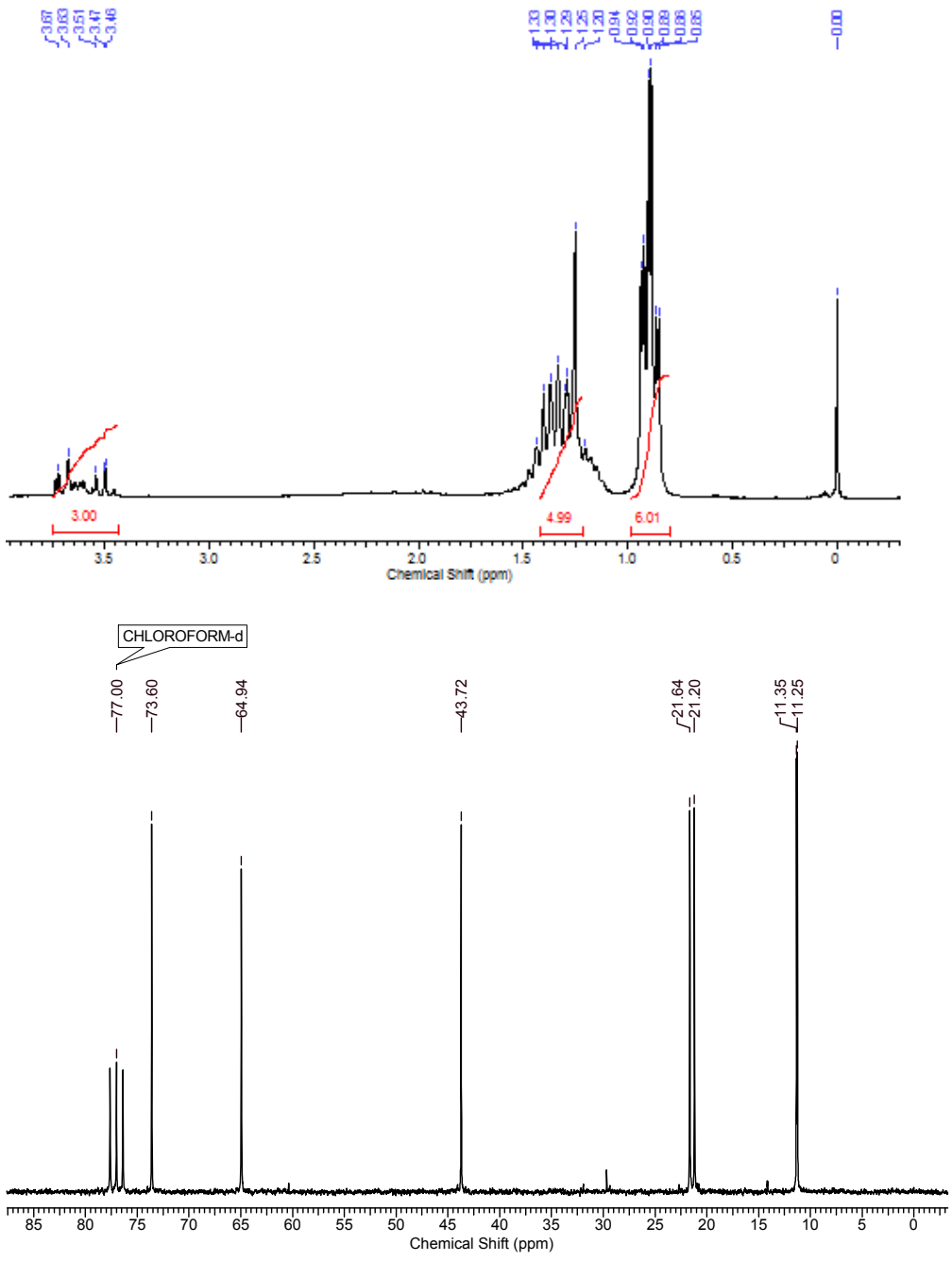


Figure 13. ^{1}H NMR & ^{13}C NMR spectra of compound **69**

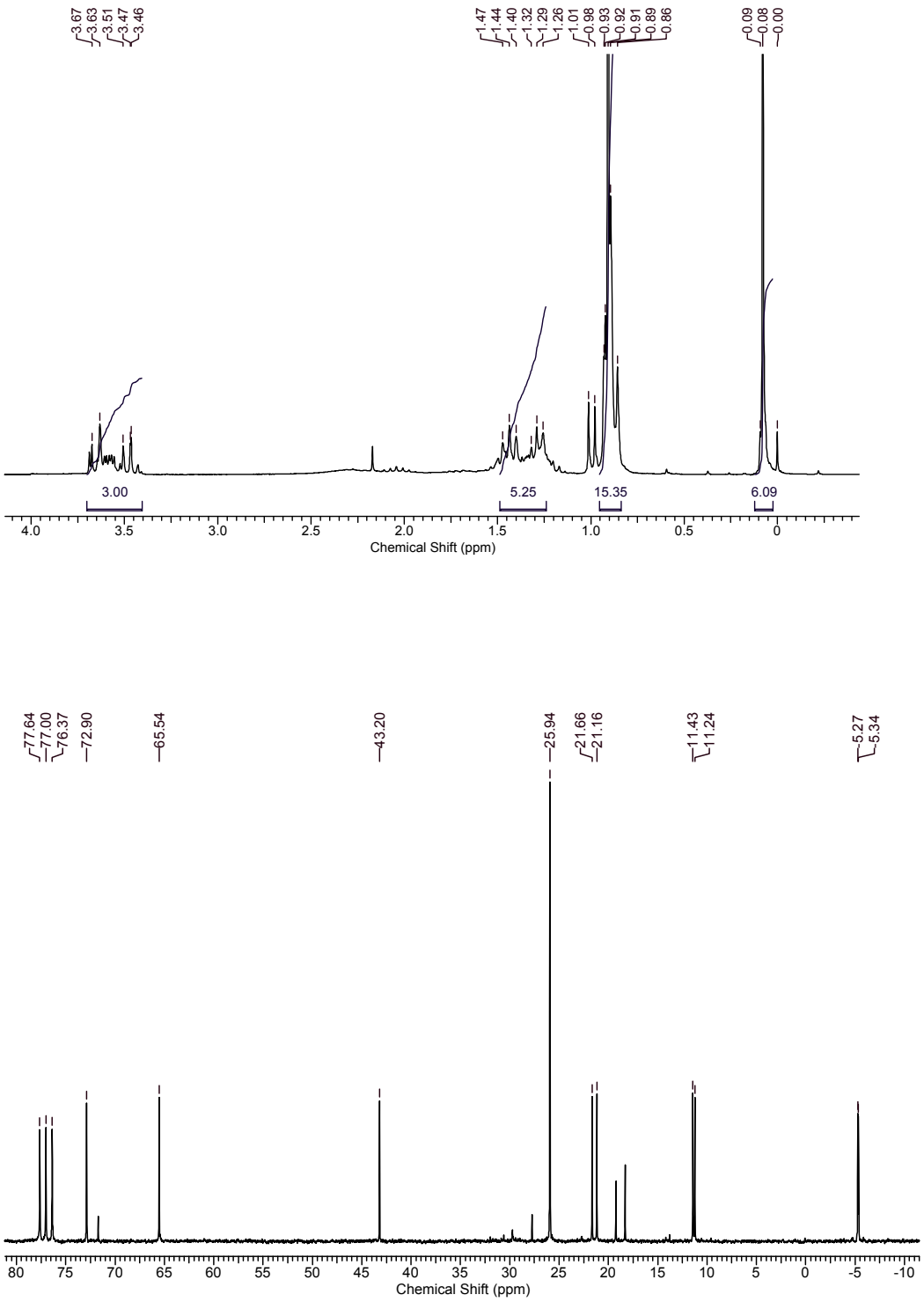


Figure 14. ^{1}H NMR & ^{13}C NMR spectra of compound **70**

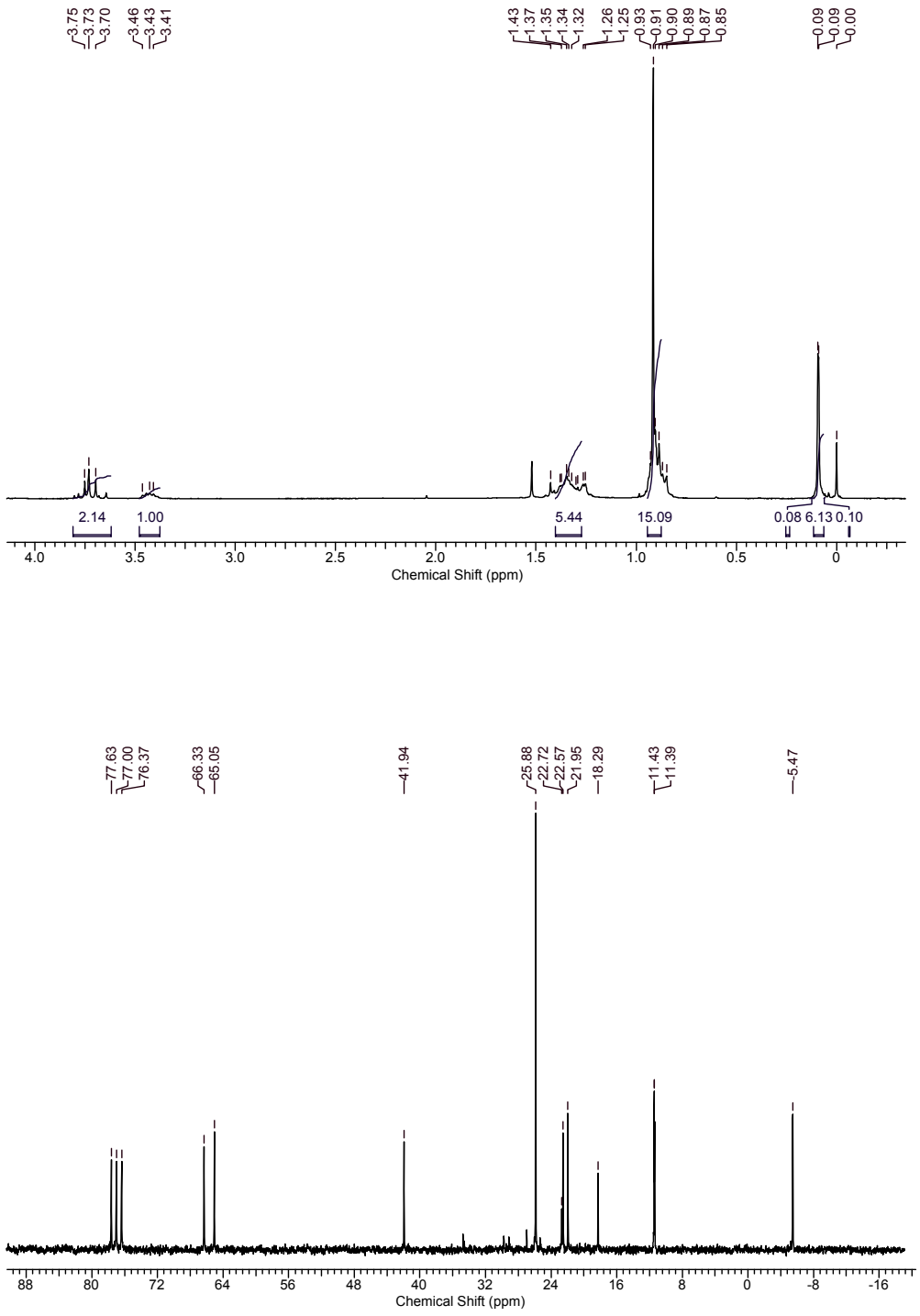


Figure 15. ^{1}H NMR & ^{13}C NMR spectra of compound **71**

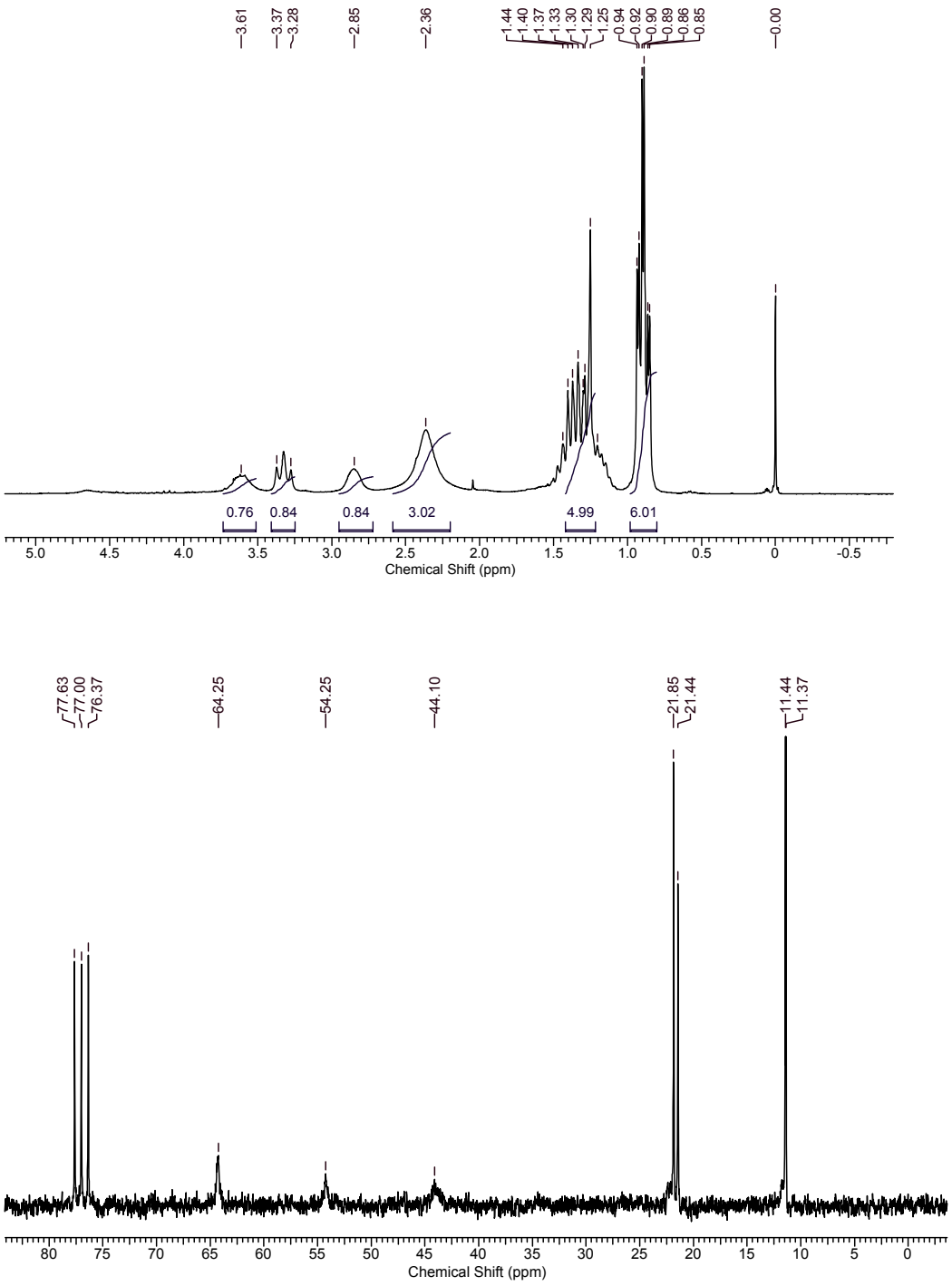


Figure 16. ^{1}H NMR & ^{13}C NMR spectra of compound **72**

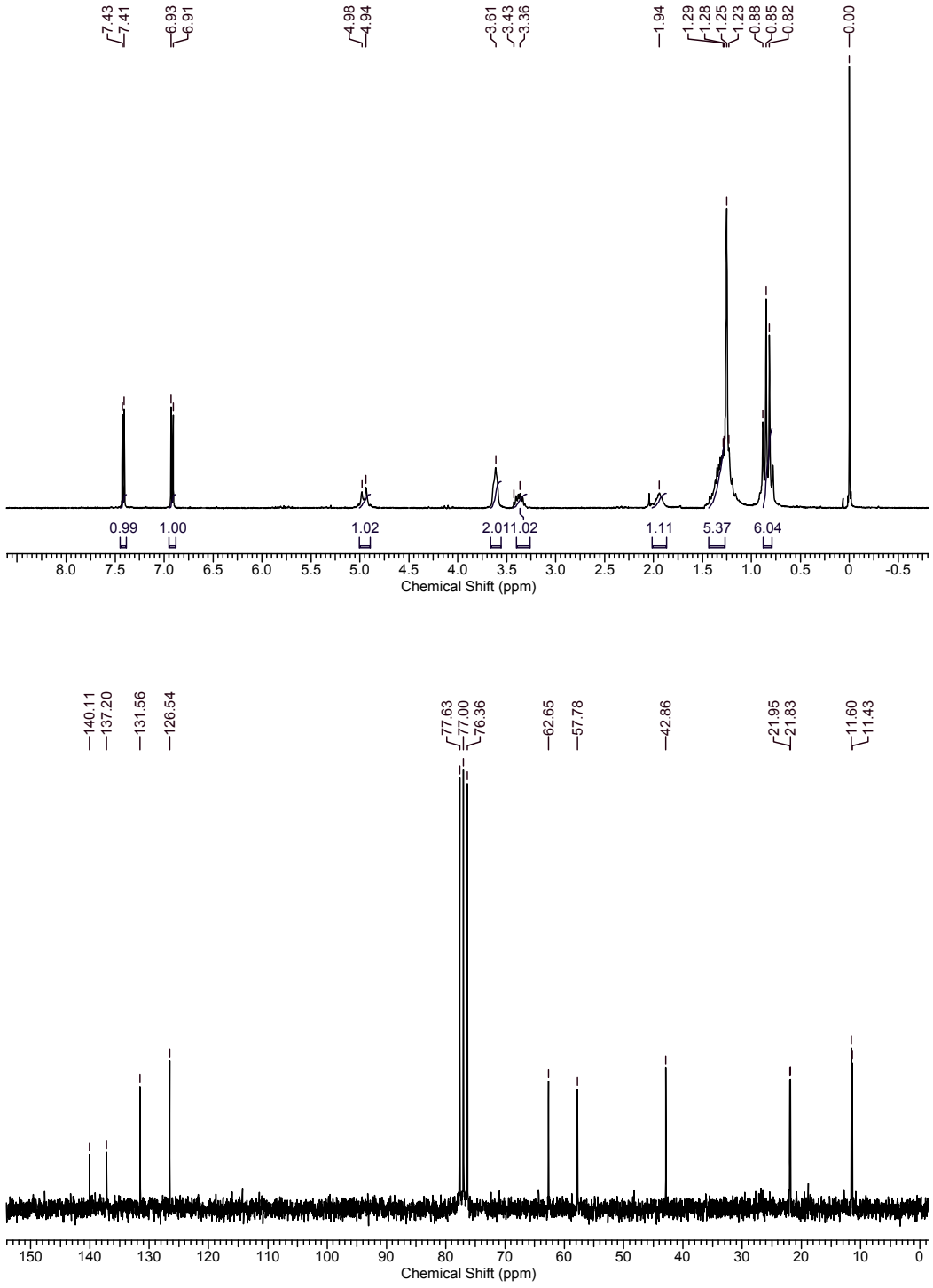


Figure 17. ^{1}H NMR & ^{13}C NMR spectra of compound **49**

3.3. References

1. (a) Reddy, M. V. R.; Yucel, A. J.; Ramachandran, P. V. *J. Org. Chem*. **2001**, *66*, 2512; (b) Reddy, M. V. R.; Rearick, J. P.; Hoch, N.; Ramachandran, P. V. *Org. Lett.* **2001**, *3*, 19; (c) Smith, A. B.; Brandt, B. M. *Org. Lett.* **2001**, *3*, 1685; (d) Boger, D. L.; Ichikawa, L.; Zhong, W. *J. Am. Chem. Soc*. **2001**, *123*, 4161; (e) Gosh, A. K.; Bilcer, G. *Tetrahedron Lett.* **2000**, *41*, 1003.
2. (a) Meijer, M. *Recl. Trav. Chim. Pays-Bas* **1940**, *59*, 191; (b) Crombie, L. *J. Chem. Soc.* **1955**, 2535.
3. Abe, S. *J. Chem. Soc. Jpn.* **1937**, *58*, 246.
4. Hashizumi, T.; Kikuchi, N.; Sasaki, Y.; Sakata, I. *Agric Biol. Chem.* **1968**, *32*, 1306.
5. Kaiser, P.; Lamparsky, D. *Tetrahedron Lett.* **1976**, 1659
6. Cavill, G. W. K.; Clark, D. V.; Whitefield, F. B. *Aust. J. Chem.* **1968**, *21*, 2819.
7. Mori, K., *Agric. Biol. Chem*., **1976**, *40*, 1617.
8. Garg, A.; Singh, V.K., *Tetrahedron*, **2009**, *65*, 8677.
9. Sabitha, G.; Braskar, V.; Yadav, J.S., *Synth. Commun.,* **2008,** *38*, 3129.
10. Harbindu, A.; Kumar, P., *Synthesis*, **2011**, *12,* 1954.
11. Sabitha, G., Gopal, P., Yadav, J.S., *Synth. Commun.,* **2007,** *37*, 1495.
12. Simpson, T. J.; Smith, R. W.; Westaway, S. M.; Willis, C. L. *Tetrahedron Lett*. **1997**, *38*, 5367.
13. Yoshikawa, K.; Takeshi, K. *Flavour Fragr. J.* **2008**, *23*, 441.
14. Ridha, T.; Virginie, R. V.; Ben Hasssine, B.; Jean-Pierre, G. *Tetrahedron: Asymmetry* **2006**, *17*, 3400.
15. Priti, G.; Vasudeva, N.; Pradeep, K. *Tetrahedron Lett*. **2004,** *45*, 849.

16. Bernhard, H.; Manfred, P. S**.** *Tetrahedron: Asymmetry* **1993**, *4*, 1017.

17. Yadav, J.S.; Reddy, Ch. S. *Org. Lett.* **2009**, *11*, 1705.

18. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974; (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

19. Kerstin, D.; Philips. Zemilicka, J.; Jerome, J. H. *Carbohydrate Research* **1973**, *30*, 281.

20. Still, W. C.; Gennari, C. *Tetrahedron Lett*. **1983**, *24*, 4405.

21. (a) Schenk, D. B.; Rydel, R. E.; May, P.; Little, S.; Panetta, J.; Lieberburg, I.; Sinha, S.*J. Med.Chem.***1995**,*38*, 4141; (b) Suzhen, D.;Yale, D.;Yinghe, H.; Zheng, Z. *Translational Neurodegeneration*2012, 1:18; (c) Hardy, J. A.; Higgins, G. A. *Science***1992**, *256*, 184; (d) Katzman, R. N. *Engl. J. Med*. **1986**, *314*, 964.

22. (a) Hardy J,; Higgins G. A.*Science* **1992,***256*, 184;(b) Hardy, J.; Selkoe, D. J. *Science* **2002**, *297*, 353.

23. (a) Walsh, D. M.; Klyubin, I.; Fadeeva, J. V.; Cullen, W. K.; Wolfe, M. S.; Rowan, M. J.; Selkoe, D. J. *Nature* **2002**, *416*, 535; (b) Cai, L.; Liow, J. S.; Zoghbi, S. S.; Baetas, C.; Hong, J.; Shetty, H. U.; Seneca, N. M.; Brown, A. K.; Gladding, R.; Temme, S. S.; Herman, M. M.; Innis, R. B.; Pike, V. W. *J. Med. Chem*. **2008**, *51*, 148

24. Cole, D. C.; Stock, J. R.; Comery, T. A.; Kreft, A. F.; Antane, M.; Aschmies, S. H.; Atchison, K. P.; Casebier, D. S.; Diamantidis, G.; Harrison, B. L.; Hu, Y.; Jin, M.; Kubrak, D. M.; Lu, P.; Mann, C. W.; Martone, R. L.; Moore, W. J.; Oganesian, A.; Sun, S. C.; Riddell, D. R.; Ellingboe, J. W.; Reines, J. S.;

Wagner, E.; Wang, Z.; Woller, K. R.; Xu, Z.; Zhou, H.; Jacobsen, J. S. *Bioorg. Med. Chem. Lett.* **2009,** *19***,** 926;

25. Mayer, S. C.; Kreft, A. F.; Reinhart, P.; Harrison, B.; Aschmies, S.; Atchison, K.; Chlenov, M.; Cole, D. C.; Ellingboe, J.; Fan, K.; Galante, R.; Huryn, D.; Gonzales, C.; Ho, D. M.; Hoke, M. E.; Hu, Y.; .; Zhang, M.; Jain, U.; Jin, M.; Kremer, K.; Kubrak, D.; Lin, M.; Lu, P.; Martone, R.; Moore, W.; Oganesian, A.; Gharbia, M. A.; Pangalos, M. N.; Zaleska, M. M.; Comery, T.; Porte, A.; Resnick, L.; Riddell, D. R.; Reines, J. S.; Sun, S. C.; Wagner, E.; Wang, T.; Woller, K.; Xu, Z.; Zeldis, JZhou, H.; Jacobsen J. S. *J. Med. Chem.* **2008,** *51,* 7348.
26. Varun, R.; Pandurang V. C.; Vilas B. C.; Gurunath S.; Sudalai, A. *Tetrahedron Lett.* **2010**, *51*, 6565.
27. Yadav, J.S.; Suresh Reddy, Ch. *Org. Lett.***2009**, *11*, 1705.
28. (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974 (b) Gao, Y.; Hanson, R.M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**,*109*, 5765.
29. James M. F.; YishitoK. *Tetrahedron Lett.***1982**, *23*, 2713.
30. Erik F. J.; Johannes, B.; Arnevander, G. *J. Org. Chem.* **1994,***59***,** 7133.

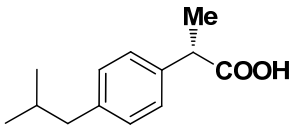
CHAPTER IV

A novel enantioselective syntheses of (*S*)-Ibuprofen

A novel enantioselective syntheses of (*S*)-Ibuprofen

4.1. Introduction and pharmacology

α-Aryl propanoic acids are the major class of non-steroidal anti-inflammatory drugs and house hold pain killers. Among these (*S*)-Ibuprofen (**1**) (2-[4-2-methylpropyl) phenyl] propanoic acid) and (*S*)-naproxen (**2**) (2-(4-methoxynapthyl) propanoic acid) and (*S*)-ketoprofen (**3**) (2-(3-benzoylphenyl) propanoic acid) are the best known and are being marketed in large quantities worldwide. The use of enantiopure drugs in chemotherapy has become almost mandatory in recent years. The specific biological activities of organic compounds are often closely related with their chirality, hence the synthesis of organic compounds in enantiomeriacally pure form has become a hot topic in organic chemistry. According to Wetcher, S enantiomer of Ibuprofen is responsible for the desired therapeutic effect[1], where as R isomer gets accumulated in fatty tissue as a glycerol ester and its long terms effects are not known. Hence there is a need to develop synthetic methods which allow the preparation of these drugs in an enantiopure form.



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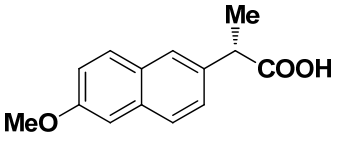

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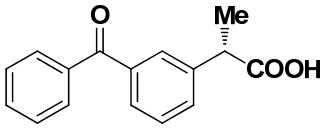

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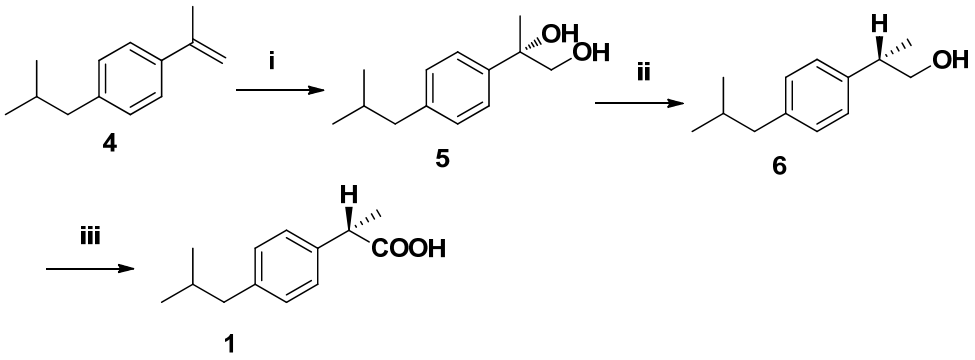
4.2. Review of Literature

Literature search has revealed that several synthetic routes have been reported for the synthesis of (S)-Ibuprofen, the most important of them are described below.

H. Ishibashi's approach (1999)[2]

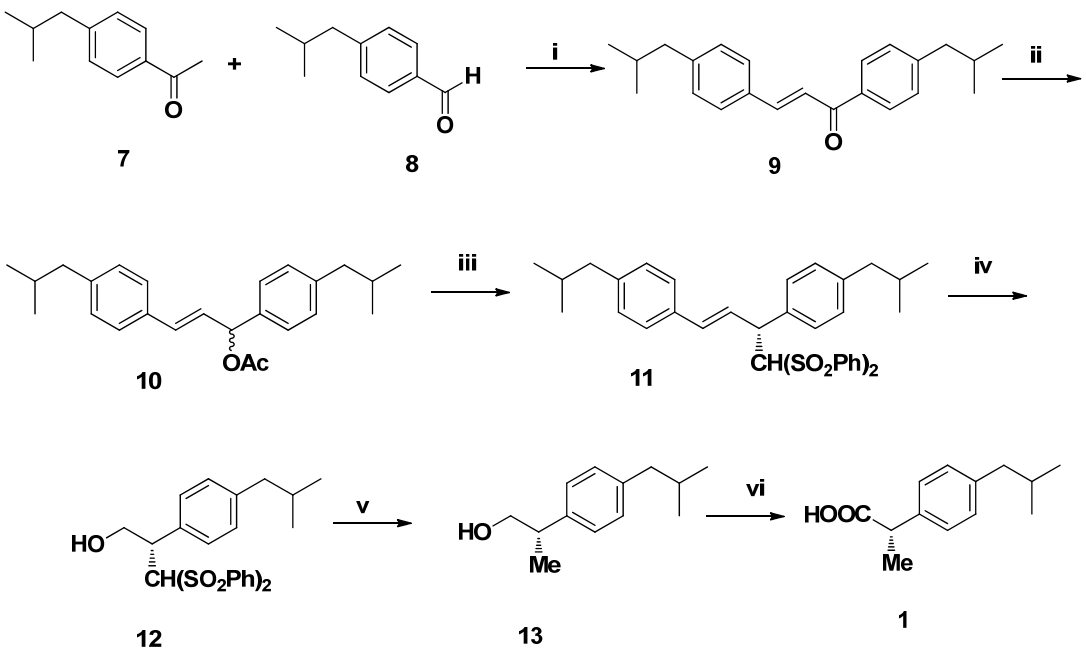
As outlined in **Scheme 1**, the synthesis of (*S*)-Ibuprofen began with the substituted styrene **4**. The Sharpless asymmetric dihydroxyaltion of **4** with AD-mix-α in equal volumes of tert-butanol and water gave diol **5** in quantitative yield. Hydrogenolysis of diol **5** with Pearlman's catalyst (Pd $(OH)_2$) under hydrogen atmosphere in ethanol afforded alcohol compound **6** in 55% yield. Finally, oxidation of **7** using Jones reagent (CrO_3, H_2SO_4) gave (*S*)-Ibuprofen in 83% yield.



Scheme 1: *Reagents and conditions: (i) AD-mix-α,tert-BuOH: H_2O, Na_2SO_3, 6 h, 0 ^oC, 100%; (ii) $BF_3.Et_2O$, Et_3SiH, 2h, RT, 58%; (iii) H_2, $Pd(OH)_2$, EtOH, RT, 2 h, 55%; (iv) CrO_3, H_2SO_4, acetone, RT, 2 h, 83%.*

William's approach (2003)[3]

As described in **Scheme 2**, the synthesis commenced with 4-isobutyl benzaldehyde **8** subjected to aldol condensation with 4-isobutyl acetophenone **7** using sodium hydroxide as base to yield unsaturated keto compound **9** in 60% yield. The Luche reduction ($NaBH_4$, $CeCl_3.7H_2O$) of keto functionality of **9** in methanol to the corresponding alcohol followed by treatment with acetic anhydride in presence of triethyl amine gave acetate compound **10** in 95% yield. Asymmetric allylic substitution of **10** with



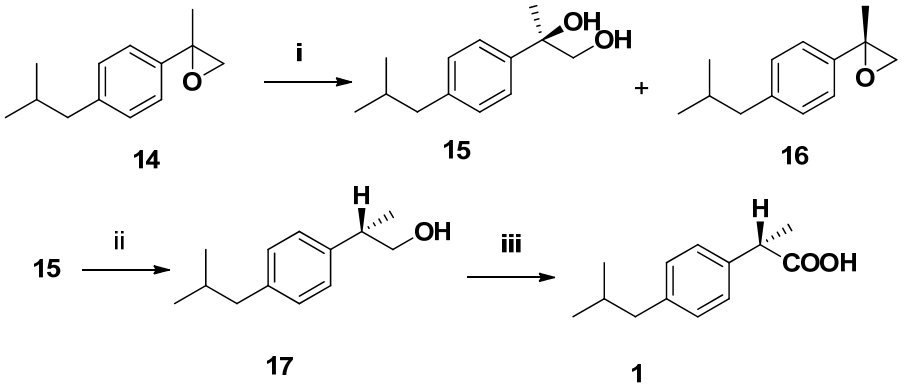
Scheme 2: *Reagents and conditions: (i) NaOH solid, EtOH, rt, 12 h, 60%; (ii)(a) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -10 ^oC; (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 2h, 95%; (iii)$[Pd(allyl)Cl]_2$, $CH_2(SO_2Ph)_2$, chiral catalyst, 1,4-dioxane, 70 ^oC, 90%;(iv) O_3, CH_2Cl_2,MeOH, $NaBH_4$, -78 ^oC, 4 h; (v) Mg, MeOH, rt-50 ^oC, 5h; (vi) PDC, DMF, rt, 12h, 78%;*

bis(phenylsulfonyl)methane catalysed by palladium and oxazoline ligand in 1,4-dioxane afforded compound **11** in 90% yield. Ozonolysis of **11** followed by reductive opening of the corresponding ozonide with sodium borohydride gave compound **12**. The desulfonylation of **12** with magnesium metal in methanol yielded hydroxy compound **13**. Finally, the hydroxy group in **13** was oxidized using pyridinium chlorochromate (PDC) in DMF solvent to afford the required target molecule **1** in 78% yield.

R. Furstoss' approach (1999)[4]

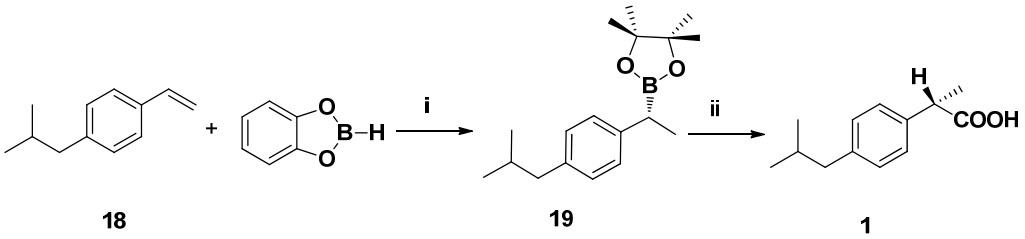
As outlined in **Scheme 3**, the synthetic route to (*S*)-Ibuprofen began with substituted styrene epoxide **14**, which was subjected to enzymatic resolution using *A. niger*

enzyme extract in presence of a buffer (pH: 7) to afford diol **15** and epoxide **16**. The palladium catalyzed hydrogenation of **15** in mono methyl formaamide solvent yielded alcoholic compound **17** in good yield. Finally, the oxidation of compound **17** with acidic potassium permanganate furnished the target molecule **1** in 76% yield.



Scheme 3: *Reagents and conditions: (i)A.niger enzyme extract, buffer(pH-7); (ii) Pd/H_2, MMF, 12 h, 0 ^oC; (iii) $KMnO_4$, H_2SO_4, 1 h, 0 ^oC, 76%.*

M.Crudden's approach (1999)[5]

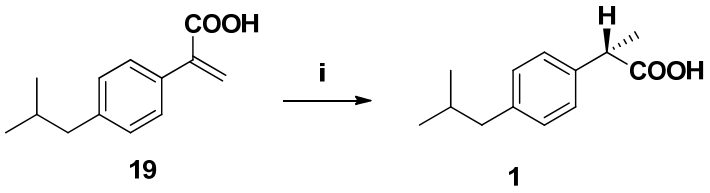


Scheme 4: *Reagents and conditions: (i) $[Rh\ (COD)_2]^+BF_4^-$, (R)-Binap, Pinacol, 97%; (ii) $LiCHCl_2$, $NaOCl_2$, 79%.*

As described in **Scheme 4**, the synthesis commenced with isobutyl styrene**18**, which was subjected to enantioselective hydroboration in presence of cationic rhodium BINAP complex ($[Rh\ (COD)_2]^+BF_4^-$) to afford boronate ester **19** in 97% yield. The subsequent homologation of **18** with $LiCHCl_2$ followed by treatment with sodium chlorite afforded (*S*)-Ibuprofen **1** in 97% yield.

Takaya's approach (1996)[6]

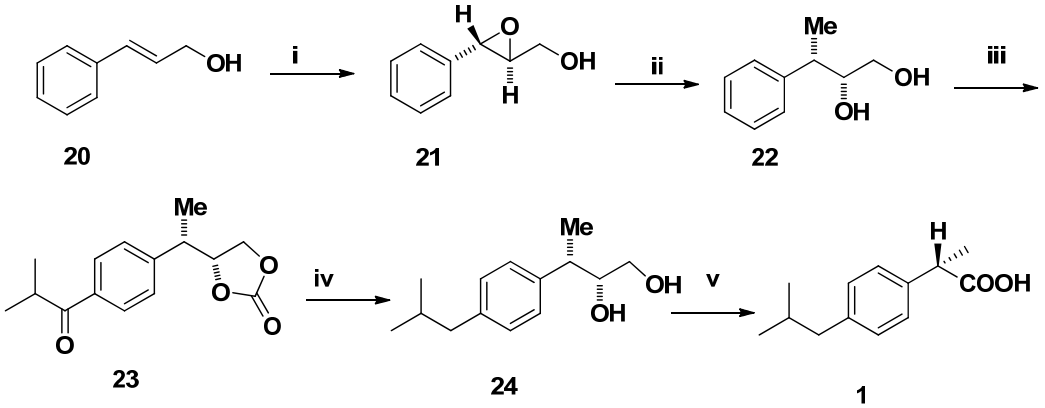
As outlined in **Scheme 5**, the asymmetric hydrogenation of 2-(4-isobutylphenyl) propenoic acid **19** using $Ru(OAc)_2$[(S)- H_8- BINAP] catalyst under hydrogen atmosphere in methanol produced (*S*)-Ibuprofen **1** in 75% yield.



Scheme 5: *Reagents and conditions: (i) $Ru(OAc)_2$[(S)- H_8- BINAP], H_2, MeOH, 75%.*

Takano's approach (1989)[7]

As outlined in **Scheme 6**, the synthesis began with *trans*-cinnamyl alcohol **20**, which was subjected to Sharpless asymmetric epoxidation with t-butyl hydroperoxide in presence of (+)-diethyl tartarate and titanium tetraisopropoxide in dichloromethane solvent to furnish epoxy alcohol **21** in good yield. The regioselective opening of epoxide in **21** with



Scheme 6: *Reagents and conditions: (i) (+)- DET, $Ti(O\text{-}i\text{-}Pr)_4$, TBHP, CH_2Cl_2, molecular sieves 3 A^o, -20 ^oC; (ii) Me_3Al, CH_2Cl_2, -70 ^oC; (iii) (a)$(EtO)_2CO$, K_2CO_3, 80 ^oC; (b) $Me_2CHCOCl$, $AlCl_3$, CS_2; (iv) NH_2NH_2, KOH, H_2O, $O(CH_2CH_2OH)_2$, 180 ^oC;(v) $RuCl_3$. $3H_2O$, $NaIO_4$, $MeCN/CCl_4/H_2O$;*

trimethyl alluminum in dichloromethane gave vicinal diol compound **22**. The two hydroxy groups of **22** were then converted to carbonate by treating with diethyl carbonate and subsequent Friedel-Craft acylation afforded compound **23**. The reduction of keto group and simultaneous cleavage of carbonate was achieved by treating the compound **23** with hydrazine in presence of a base to yield **24**. Finally, the oxidative cleavage of **24** using ruthenium trichloride and sodium meta periodate afforded the required target molecule **1**.

4.3. Present work

4.3.1. Objective

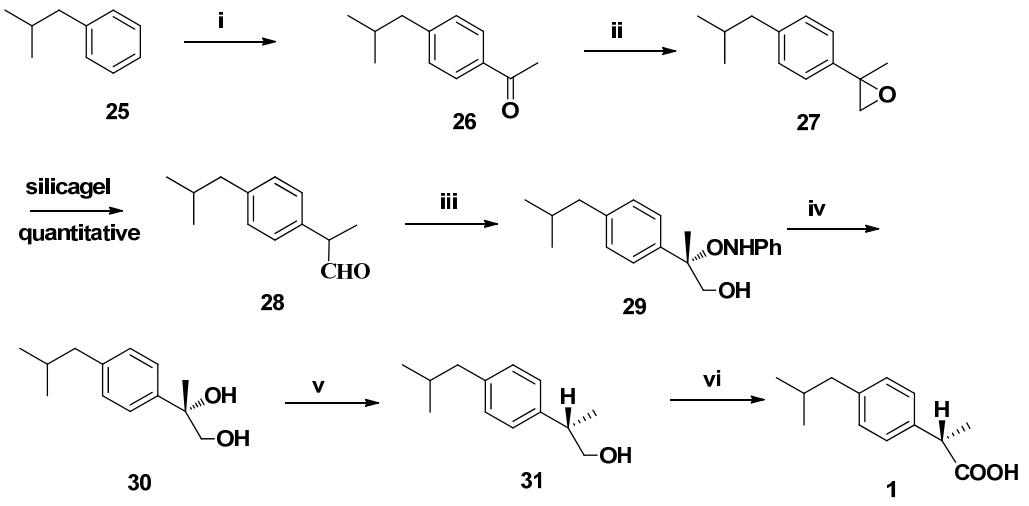
So far, several syntheses of (*S*)-Ibuprofen were reported via organometal catalysis. Since the organometal catalysts are costly and are most of them are toxic, so there is a need to find an alternative method for the synthesis of (*S*)-Ibuprofen in a cheap and environmentally friendly manner. In recent days enantioselective organocatalysis has emerged as a powerful synthetic tool that is complementary to the organometal catalysis and has been utilized in the synthesis of diverse chiral molecules[8]. The simple experimental procedure, ready availability of less toxic organocatalysts such as proline and its derivatives makes it an attractive method. Herein, we discuss the enantioselective synthesis of (*S*)-Ibuprofen **1** using D-proline catalyzed α-aminooxylation of aldehydes.

4.3.2. Results and discussion

Proline catalyzed α-aminooxylation approach

Synthesis commenced with commercially available and cheap Isobutyl benzene **25** (**Scheme 12**), which was subjected to Friedel Crafts acylation with acetyl chloride in

presence of anhydrous aluminum chloride in dichlomethane solvent to give 4-isobutylacetophenone **26** in 80% yield. The Corey- Chakovsky epoxidation of **26** with trimethyl sulfonium iodide and NaH furnished substituted styrene oxide **27** in 78% yield. During the silica gel column purification, the epoxide **27** (which is generally very much prone for rearrangement) undergoes rearrangement to yield aldehyde **28** quantitatively. Since silica gel (SiO_2) is acidic in nature, can easily catalyze the rearrangement. Thus obtained aldehyde was then subjected to D-proline catalyzed α-aminoxylation[9] with nitroso benzene at -20 ^oC followed by reduction of aldehyde functionality with $NaBH_4$ furnished aminoxy alcohol **29** in good yield. Due to its unstability, the crude product **33** was immediately proceeded without any further purification. The hydrogenolysis of **29** was carried out with $CuSO_4$ in methanol to afford diol **30** in 76% yield (for three steps).

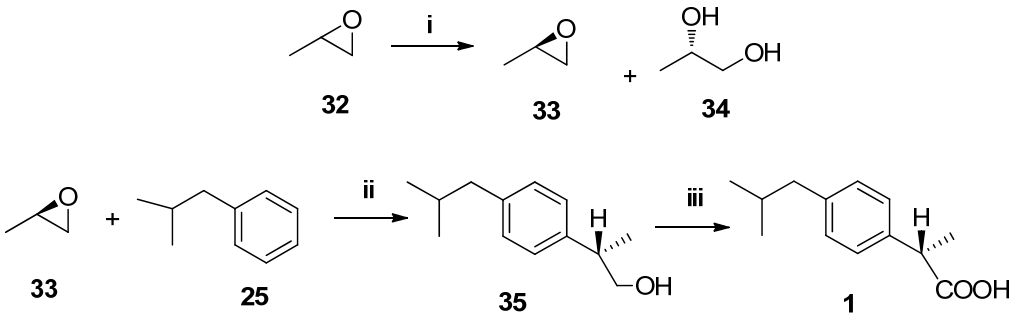


Scheme 7: *Reagents and Conditions: (i) CH_3COCl, anhyd. $AlCl_3$, CH_2Cl_2, 80%; (ii) $(CH_3)_3SI$, NaH, DMSO, THF, 78%;(iii)(a) PhNO, D-Proline, CH_3CN, 0 ^oC to RT; (b) $NaBH_4$, MeOH (iv) $CuSO_4$, MeOH, 76% (for three steps); (v) H_2, $Pd(OH)_2$/C, EtOH, 55%; (vi) $KMnO_4$, H_2SO_4, 79%.*

In order to remove tert-hydroxy group selectively, the diol **30** ($[\alpha]_D^{25}$: -6.5 (*c* 1, $CHCl_3$)was treated with Pearlman's catalyst (palladium hydroxide on carbon) under

hydrogen atmosphere in ethanol to furnish compound[2] **31** ($[\alpha]_D^{25}$: -4.7 (*c* 1, $CHCl_3$)) in 55% yield . Finally, oxidation of **31** with acidic $KMnO_4$ yielded (*S*)-Ibuprofen **1** ($[\alpha]_D^{25}$: +23.1 (*c* 1.5, $CHCl_3$) [Lit[10] ($[\alpha]_D^{20}$: +53.1 (*c* 0.4, EtOH)] in 79% yield. since, α-aminoxylation of α-branched aldehyes gave corresponding diol with less enantioselectivity, hence we made several attempts to improve the yield and enantioselectivity. The maximum yield of the diol **30** is 65% with an enantioselectivity of 40% obtained. The schematic synthesis of (*S*)-Ibuprofen is shown in scheme **7**.

Jacobson's Hydrolytic Kinetic resolution (HKR) approach



Scheme 8: *Reagents and conditions: (i) (R,R)-Co(salen).OAc, H_2O, 44% (ii) anhyd. $AlCl_3$, CS_2, 72%; (iii) $KMnO_4$, H_2SO_4, 79%.*

Since the organoctalytic approach was not satisfactory with respect to enantioselectivity of **1**, so we attempted to synthesize **1** using Jacobsen's Hydrolytic Kinetic resolution of epoxides[11] (**Scheme 8**). The synthesis started with propylene oxide **32** subjected to (*R,R*)-Co(salen)(III) catalyzed Hydrolytic kinetic resolution[12] with 0.5 equiv. of H_2O to give enantiomerically pure epoxide **33** ($[\alpha]_D^{25}$: +11.3 (*c* 1.15, $CHCl_3$) in 44% yield. Thus obtained epoxide **33** was then stereoselectively opened with isobutylbenzene **25** in presence of anhyd. $AlCl_3$ in carbon disulfide solvent[13] to give alcohol **34** ($[\alpha]_D^{25}$: -11.3 (*c* 1.2, $CHCl_3$) in 72% yield. The alcohol **34** was finally oxidized with acidic $KMnO_4$ to furnish **1**($[\alpha]_D^{25}$: +49.1.3 (*c* 1.2, $CHCl_3$)

) [Lit[10] ($[\alpha]_D^{20}$: +53.1 (*c* 0.4, EtOH)] in 32% overall yield with 85% enantioselectivity (ee).

4.4. Conclusion

The eanantioselective synthesis of 2-aryl propanoic acid ((*S*)-Ibuprofen) **1** using D-proline catalyzed α-aminooxylation of aldehydes and selective deoxygenation of vicinal diol is accomplished. The efficacy of Jacobson's hydrolytic kinetic resolution approach to the synthesis of (*S*)-Ibuprofen is also studied.

4.5. Experimental section

4.5.1. 1-(4-isobutylphenyl)ethanone, 26

To a solution of isobutyl benzene **25** (1.34 g, 10 mmol) and $AlCl_3$ (3.32 g, 25 mmol) in DCM (15 mL), added a solution of acetyl chloride (0.7 mL, 9 mmol) in DCM (5 mL) drop-wise at 0 ^oC. After the completion of addition (when the evolution of HCl fumes ceases), the reaction mixture was refluxed for 10 min. The contents were poured on crushed ice and the organic layer was separated and washed with 3 M NaOH (3x20 mL), brine solution, finally dried over anhyd. Na_2SO_4. The solvent was evaporated under reduced pressure and residue was chromatographed over silica gel (100-200 mesh, EtOAc/hexane 1:9) to yield pure **26** as oily substance; IR (neat): ν cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89-0.93 (d, J = 6.69 Hz, 6H), 1.80-2.00 (m, 1H), 2.52-2.55 (d, J = 7.20 Hz, 2H), 2.59 (s, 3H), 7.21-7.26 (d, J = 8.46 Hz, 2H), 7.86 -7.90 (d, J = 8.34, 2H); ^{13}C NMR (50 MHz): δ 22.16, 26.34, 29.94, 45.19, 128.15, 129.11, 134.79, 147.39, 197.63; ESI-MS: *m/z* = 177 (M+H).

4.5.2. 2-(4-isobutylphenyl)-2-methyloxirane, 27

NaH (0.8 g, 20 mmol) was placed in a round bottom flask and dry DMSO (15 mL) was introduced under N_2. The resulting mixture was heated with stirring to 70 ^oC. After 20 min., the reaction mixture was diluted with THF (10 mL) and cooled to 0 ^oC. A solution of trimethyl sulfonium iodide (4 g, 20 mmol) in DMSO (10 mL) was added over a period of 5 min. After the addition of a solution of ketone **26** (2.2 g, 13 mmol) in THF (5 mL) at 0 ^oC, stirring was continued for 30 min. at the same temperature. The contents were warmed gradually to room temperature over 1 h. The reaction was quenched with water (10 mL) and extracted with EtOAc (3x30 mL). The organic layer was separated, washed with water, brine and finally dried over anhyd. Na_2SO_4. The solvent was evaporated under *vacuum* and the residue was chromatographed over neutral alumina (150 mesh, EtOAc/hexane 1:9) to yield pure **27** as oily substance; IR ($CHCl_3$): ν cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.89-0.92 (d, *J* = 6.57 Hz, 6H), 1.79-1.83 (m, 1H), 2.14 (s, 3H), 2.45-2.48 (d, *J* = 7.07 Hz, 2H), 5.03 (s, 1H), 7.08-7.12 (d, *J* = 7.08 Hz, 2H), 7.37-7.47 (d, *J* = 7.41Hz, 2H); ^{13}C NMR (50 MHz): δ 21.08, 22.37, 30.19, 45.06, 115.51, 125.16, 128.95, 138.43, 140.99, 143.05; ESI-MS: *m/z* = 213 (M+Na).

The spectral data of aldehyde **28:** ^1H NMR (200 MHz, $CDCl_3$): δ 0.89-0.92 (d, *J* = 6.57 Hz, 6H), 1.40-1.44 (d, *J* = 7.07 Hz, 3H), 1.79-1.92 (m, 1H), 2.44-2.48 (d, *J* = 7.07 Hz, 2H), 3.53-3.64 (q, 1H), 7.06-7.16 (m, 4H), 9.65 (s, 1H); ^{13}C NMR (50 MHz): δ 14.53, 22.33, 30.17, 44.97, 52.61, 127.99, 129.78, 134.79, 141.01, 201.26.

4.5.3. (S)-2-(4-isobutylphenyl)propane-1,2-diol, 30

To a stirred solution of nitrosobenzene (7.37 g, 68.84 mmol) and D-proline (1.58 g, 20 mol %) in CH_3CN (200 mL) was added precursor aldehyde **28** (which was simply obtained by the silica gel column purification of epoxide **27**) at -20 °C. The reaction

mixture was stirred at the same temperature for 24 h followed by the addition of MeOH (100 mL) and $NaBH_4$ (10.42, 275.36 mmol) and stirring for another 1 h. After completion of reaction (checked by TLC) the reaction mixture was quenched with saturated solution of ammonium chloride. The removal of solvent under *vacuum* followed by extraction with EtOAc gave the crude aminooxy alcohol **29**.

To a solution of the crude aminooxy alcohol in MeOH (50mL) was added $CuSO_4.5H_2O$ (0.64 g, 2.55mmol) at 0 ^oC. The reaction mixture was allowed to stir for 10 h at this temperature. After the addition of the phosphate buffer, the resulting mixture was extracted into $CHCl_3$ (3X30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude diol which was then purified by column chromatography over silica gel (100-200 mesh, EtOAc/hexane 6:4) to give **30** (2.80 g, 85%) as white solid; M.P: =91 ^oC; IR (neat): ν 3405 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.87-0.91 (d, *J* = 6.69 Hz, 6H), 1.47 (s, 3H), 1.77-1.90 (m, 1H), 2.24-2.46 (d, *J* = 7.20 Hz, 2H), 3.51-3.57 (d, *J* = 11.24 Hz, 1H), 3.67-3.73 (d, *J* = 11.24 Hz, 1H), 7.08-7.13 (d, *J* = 8.21 Hz, 2H), 7.29-7.53 (d, *J* = 8.34 Hz, 2H), 2.7-3.7 (brs, 2H); ^{13}C NMR (50 MHz): δ 22.31, 25.83, 30.08, 44.87, 70.80, 74.73, 124.79, 128.95, 140.35, 142.22; ESI-MS: *m/z* = 221 (M+Na).

4.5.4. (*S*)-2-(4-isobutylphenyl)propan-1-ol, 31

A solution of 2 (120 mg, 0.79 mmol) in EtOH (5mL) containing Pearlman's catalyst (120 mg) was stirred at room temperature under hydrogen gas for 2 h. The catalyst was filtered off and washed with hot EtOH (5 mL). The combined organic layers were concentrated, and the residue was chromatographed on silica gel (hexane/AcOEt, 5:1) to give **31**(55%): IR ($CHCl_3$): ν 3380 cm^{-1};^1H NMR (200 MHz, $CDCl_3$): δ 0.88-0.92 (d, *J* = 6.57 Hz, 6H), 1.21-1.27 (d, *J* = 7.03 Hz, 3H), 1..55 (brs, 1H), 1..78-1.91 (m,

1H), 2.43-2.46 (d, *J* = 7.20 Hz, 2H), 2.82-2.99 (m,1H), 3.64-3.68 (d, *J* = 6.82 Hz, 2H), 7.07-7.16 (m, 4H); ^{13}C NMR (50 MHz): δ 17.59, 22.38, 30.16, 41.95, 44.98, 68.67, 127.11, 129.27, 139.93, 140.75; ESI-MS: *m/z* = 231 (M+K).

4.5.5. (*S*)-Ibuprofen, 1

A solution of of (*S*)-**8** (2.76 mmol) in 12 mL acetone/H_2SO_4 (3 N) was cooled in an ice bath under stirring. To this solution was added $KMnO_4$ (5.0 mmol) portion wise at 0 °C. After the solution was stirred for 1 h at the same temperature, the ice bath was removed and the mixture was stirred for 2 more hours at room temperature. Subsequently, solid $NaHSO_3$ was added until the solution became colorless. The mixture was dissolved in 50 mL of water and the aqueous phase was extracted with EtOAc. The collected organic phase was extracted with dil. NaOH solution, and the thus obtained aqueous phase was acidified with dil. HCl. The turbid aqueous phase was extracted with $CHCl_3$, and the collected organic phase fractions were dried and concentrated in *vacuum*. The residue was chromatographed over silica gel (100-200 mesh, DCM/hexane 8:2) yielding pure **1** (79%) as sticky low melting solid. M.P: = 49 °C; IR ($CHCl_3$): ν 3505, 1705 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87-0.91 (d, *J* = 6.57 Hz, 6H), 1.47-1.51 (d, *J* = 7.20 Hz, 3H), 1.71-1.90 (m, 1H), 2.42-2.46 (d, *J* = 7.20 Hz, 2H), 3.65-3.75 (m,1H), 7.07-7.11 (d, *J* = 8.08 Hz, 2H), 7.19-7.24 (d, *J* = 8.21 Hz, 2H); ^{13}C NMR (50 MHz): δ 18.12, 22.42, 30.18, 45.07, 45.01, 127.31, 129.41, 137.00, 140.87, 180.99; ESI-MS: *m/z* = 229 (M+Na).

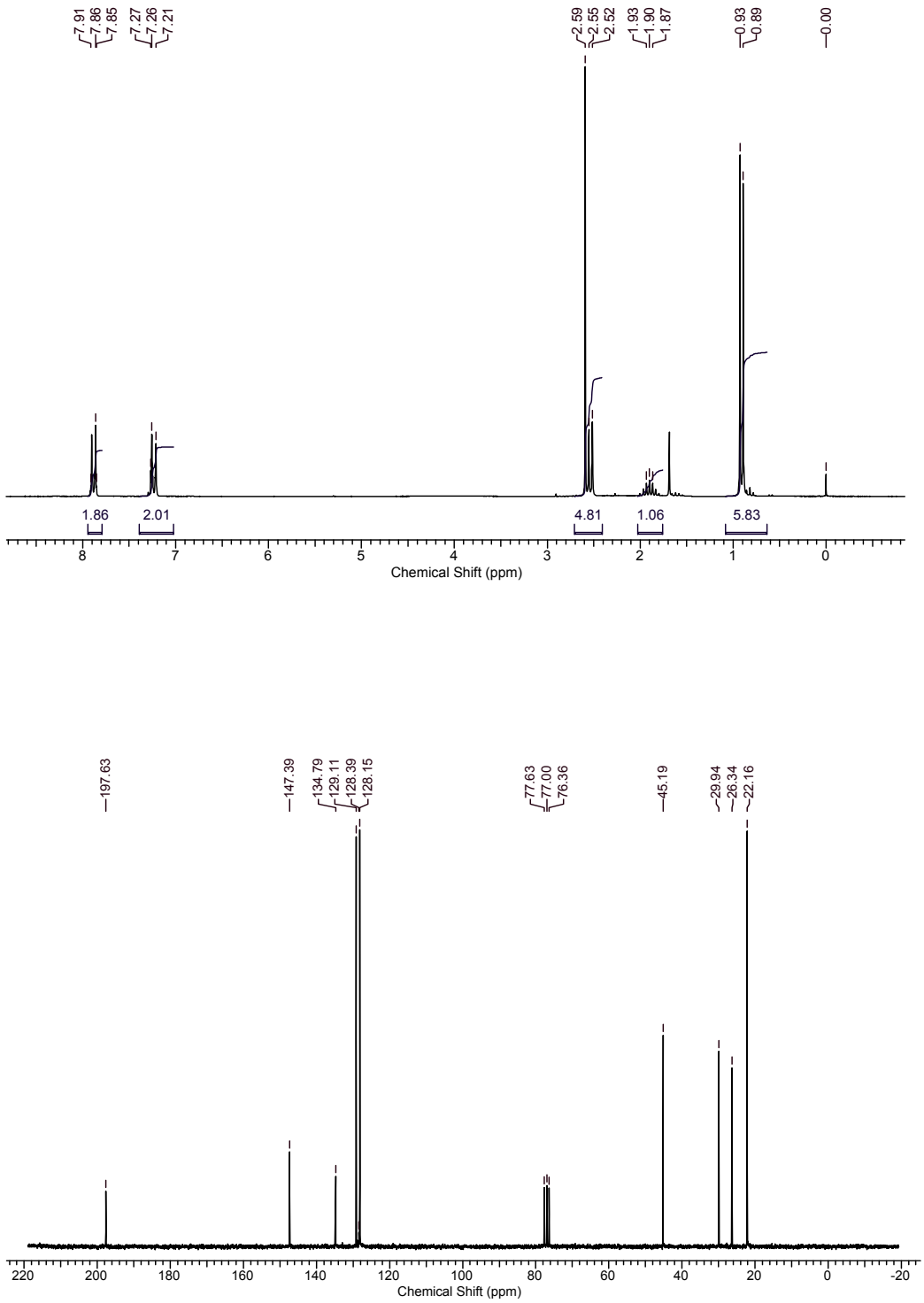


Fig. 1: ^{1}H-NMR & ^{13}C-NMR of acetophenone compound (**26**)

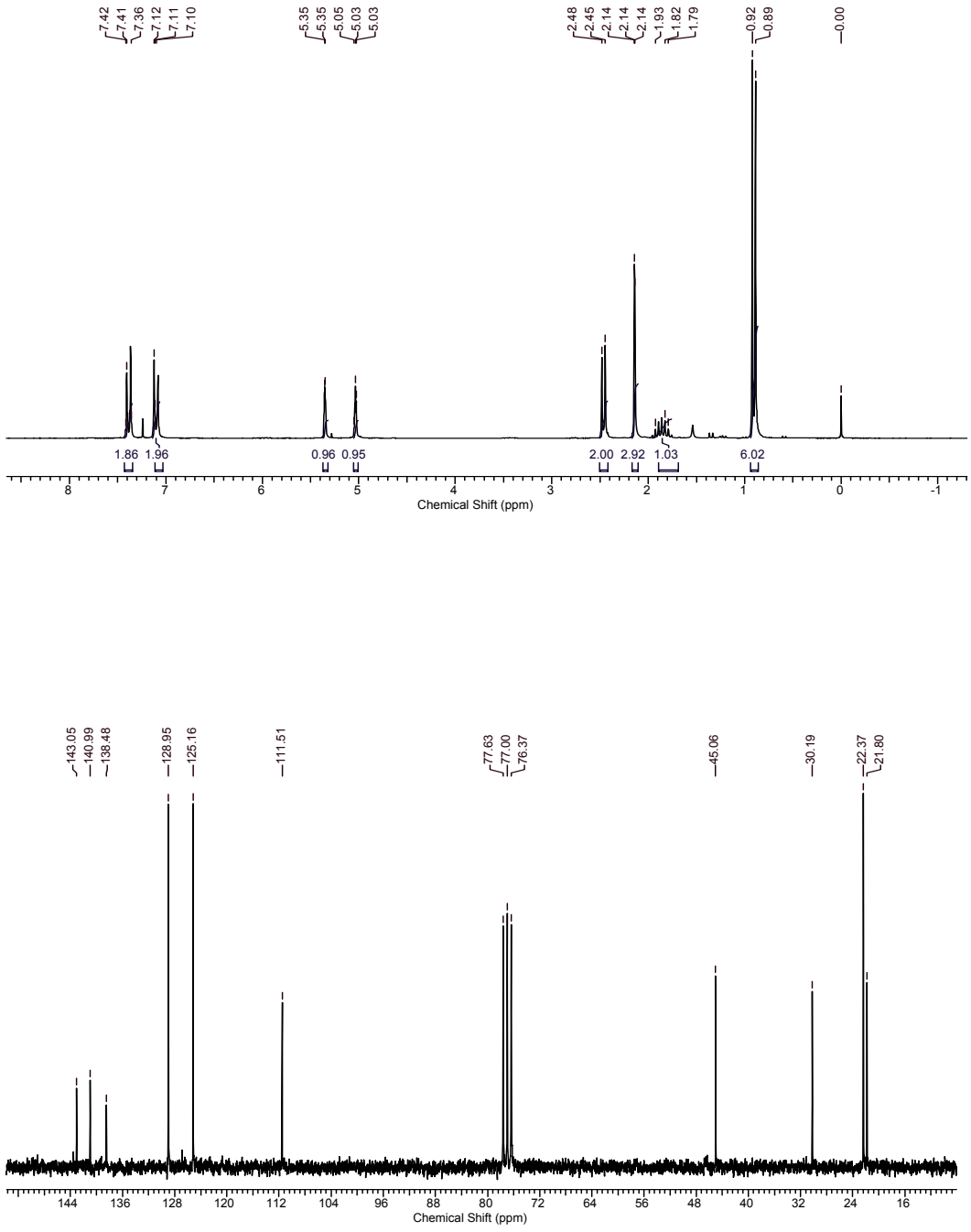


Fig. 2: ^{1}H-NMR & ^{13}C-NMR of epoxide compound (**27**)

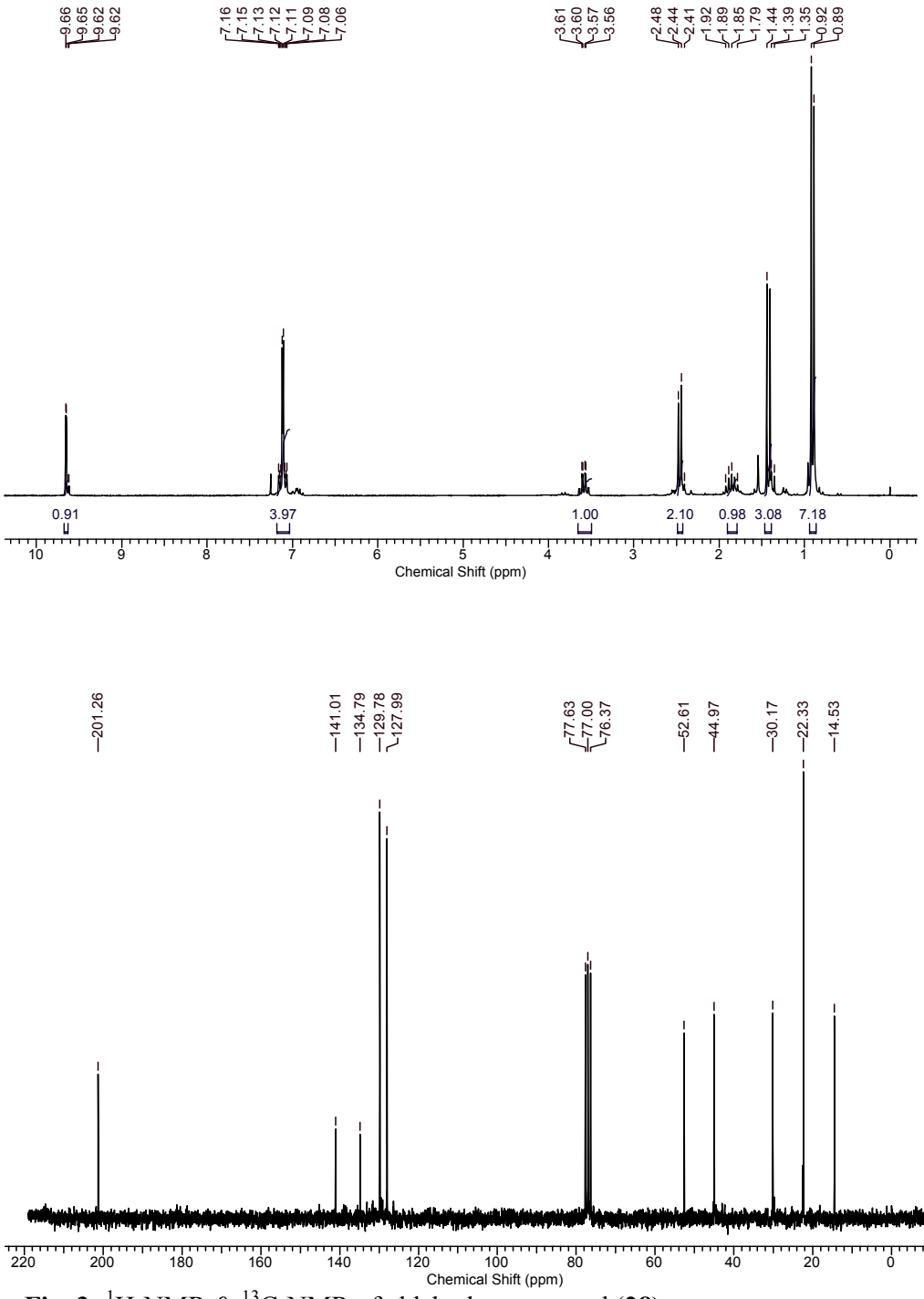


Fig. 3: ^{1}H-NMR & ^{13}C-NMR of aldehyde compound (**28)**

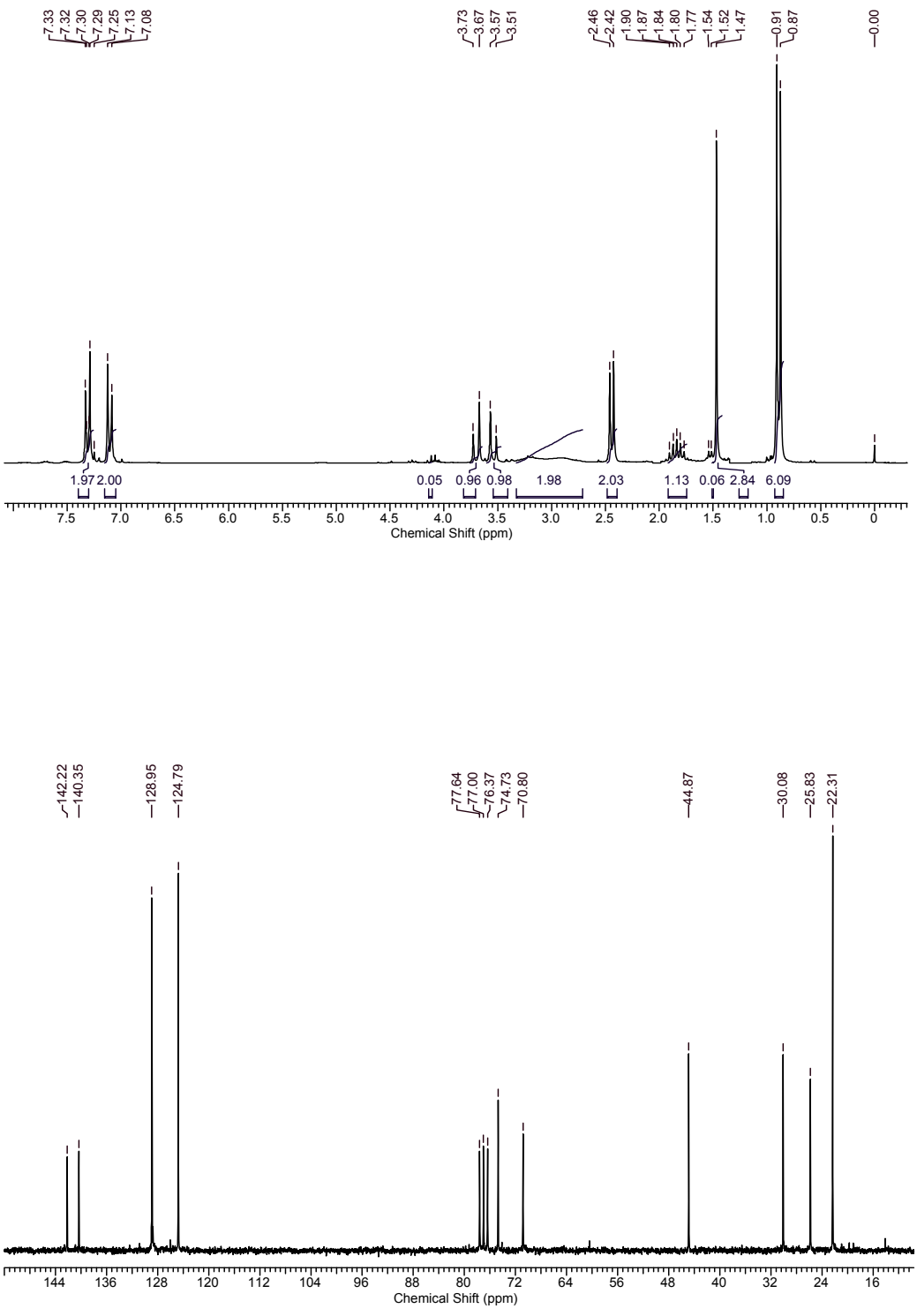


Fig. 4: ^{1}H-NMR & ^{13}C-NMR of diol compound (**30**)

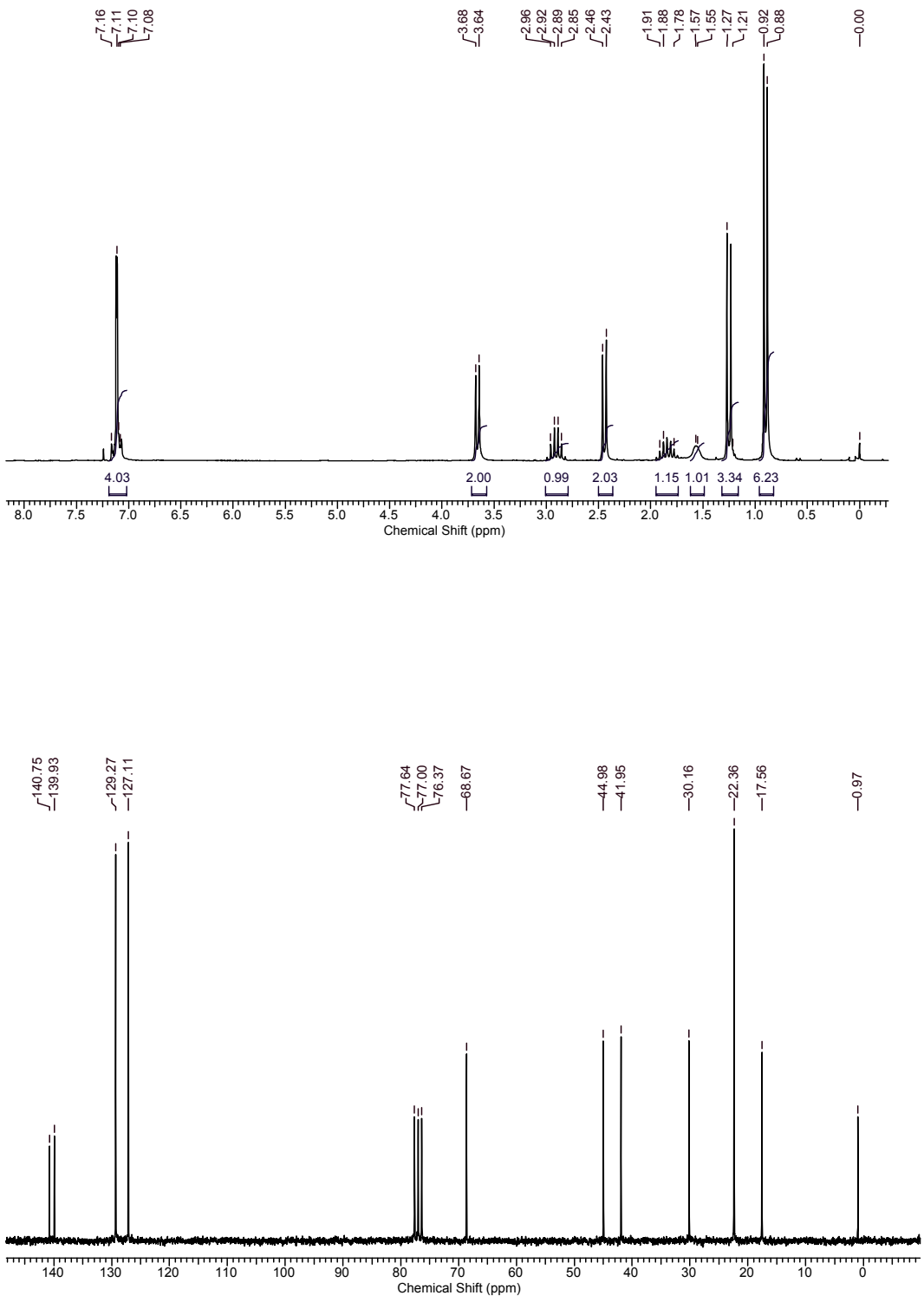


Fig. 5: ^{1}H-NMR & ^{13}C-NMR of alcoholic compound (**31**)

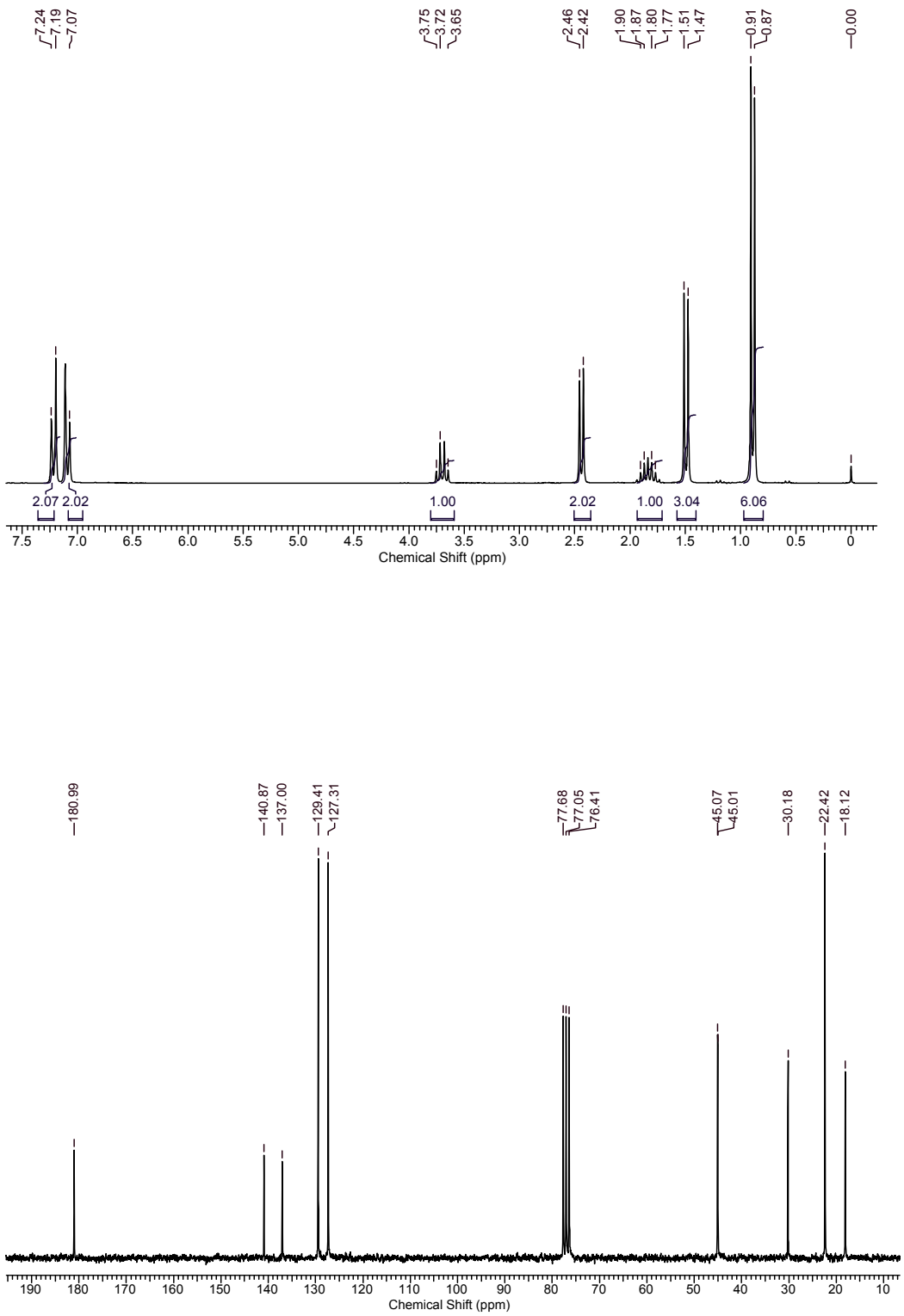


Fig. 6: ^{1}H-NMR & ^{13}C-NMR of (*S*)-Ibuprofen (**1**)

4.6. References

1. Wetcher, W. J. *J. Clin. Pharmacol.* **1994**, *34*, 1036.
2. Ishibashi, H.; Momoe, M.; Junko, Y.; Masashi, O.;Tae, K.; *Tetrahedron* **1999**, *55*, 6075.
3. Lara, A.; Williams, M. J. *Journal of Molecular Catalysis A: Chemical* **2003***, 196,* 3.
4. Cleij, M.; Archelas, A.; Furstoss, R. *J. Org. Chem.* **1999**, *64,* 5029.
5. Austin, C.; Ren, Li.; Crudden, M. C. *J. Org. Chem.* **1999**, *64,* 9704.
6. Toshitsugi, U.; Xiaoyoung, Zhang, K.; Matsumura, A.; Noboru , S.; Hidenori, K.; Tetsuo, O.; Kyoko, N.; Takaya, H. *J. Org. Chem.* **1996**, *61,* 5510.
7. Takano, S.; Yanase, P.; Ogasawara, K. *Heterocylces* **1989**, 1849.
8. S. George, A. Sudalai. *Tetrahedron: Asymmetry* **2007**, *18*, 975.
9. (a) List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc*. **2000**, *122*, 2395; (b) Sung, G. K.; Tae, H. *Tetrahedron Letters* **2006**, *47*, 9067.
10. Bando, T.; Namba, Y.; Shishido, K. *Tetrahedron: Asymmetry* **1997**, *8,* 2159.
11. (a) Makoto T.; Jay F. L.; Fumitoshi, K; Jacobsen, E. N. *Science* **1997**, *277*, 936; (b) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org.Chem*. **1998**, *63*, 6776; (c) Archelas, A.; Furstoss, R. *Trends Biotechnol.* **1998**, *16*, 108.
12. Scott, E. S.; Bridget, D. B.; Jay, F. L.; Makoto, T.; Karl, B. H.; Alexandra, E.; Gould, M.; Furrow, E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124,* 1307.
13. Nakajima, T.; Suga, S. *Tetrahedron* **1969**, 25, 1807.

CHAPTER V

Enantioselective synthesis of β-Hydroxy nitriles and β-Hydroxy esters *via* proline catalyzed α-aminoxylation of aldehydes and Oxidative aromatization of 1,4-Dihydropyridines

SECTION I:

Enantioselective synthesis of β-Hydroxy nitriles and β-Hydroxy esters *via* proline catalyzed α-aminoxylation of aldehydes

5.1.1. Introduction and pharmacology

Optically active *β*-hydroxy nitriles and *β*-hydroxycarboxylic esters are key building blocks for the synthesis of a variety of pharmaceutically important compounds. For example, many biologically active compounds such as *β*-blocker drugs contain 1, 3-amino alcohol moieties, which are often prepared via reduction of *β*-hydroxy nitriles. Chiral *β*-hydroxy carboxylic acids that can be easily prepared from *β*-hydroxy nitriles are good precursors for *β*-aminoacids[1], *β*-lactams[2], and *β*-lactones[3]and have been used in the synthesis of pheromones. The *β*-hydroxycarboxylic ester moiety has often been found in polyketide natural products such as amphotericin B, tylosin, and rosaramicin and the marine natural product hapalosin. Therefore, development of efficient and environmentally benign methodologies for the synthesis of enantiomerically pure *β*-hydroxy nitriles and *β*-hydroxy esters is of practical importance.

5.1.2. Review of Literature

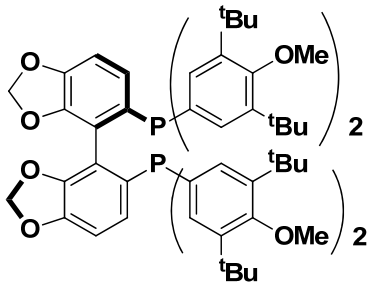
Various methods for the preparation of *β*-hydroxy nitriles and *β*-hydroxy esters have been reported in the literature. Some of the interesting and recent methods are described below.

Shibasaki's approach (2005)[4]

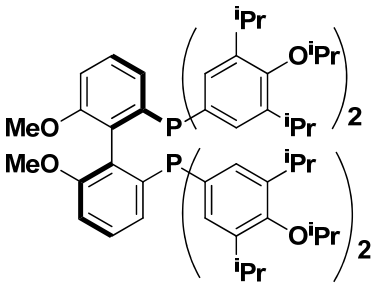
Shibasaki *et al.* have reported the synthesis of enantiopure *β*-hydroxy nitriles by catalytic enantioselective direct nitrile aldol reaction using Cu^{t}OBu-DTBM-

SEGPHOS complex as catalyst in a strongly donating solvent (HMPA). Since the

Scheme 1: *Reagents and conditions; (i) CuO^{t}Bu (10 mol%), Chiral ligand (15 mol%) 1or 2, HMPA, rt, 50-80% yields.*



(***R***)-DTBM-SEGPHOS (**1**)

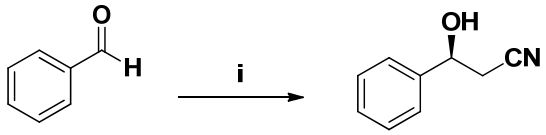


Tuned BIPHEP (**2**)

enantiomeric excess of the product was less, a modified chiral ligand Tuned BIPHEP (**2**) was employed in place of (*R)*-DTBM-SEGPHOS (**1**). The enantiomeric excess was improved up to 78% and yields up to 80% with the new chiral ligand (**Scheme 1**).

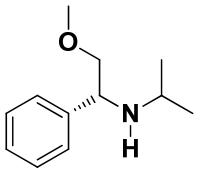
Hilmersson's approach (2006)[5]

Asymmetric 1, 2-addition of organo lithium reagents to aldehydes in presence of chiral lithium amido sulfide and lithium amido esters is studied in their approach. The addition of lithio acetonitrile to benzaldehyde in presence of various chiral amides

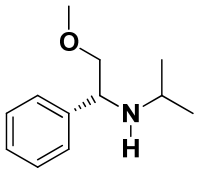


Scheme 2: *Reagents and conditions; (i) Li-amide, LiCH$_2$CN, MeOH, up to 80%.*

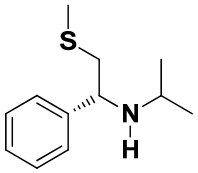
(which are prepared from chiral ligands **3**-**7** shown below) afforded β-hydroxy nitriles in good yields. Amongst them, chiral amido sulfides derived from chiral ligands **5** and **7** are particularly proved to be effective as they could produce hydroxyl ntriles with good enantioselectivities (up to 91%) (**Scheme 2**).



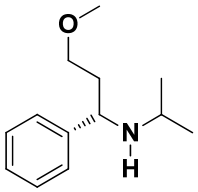
(*S*)-3



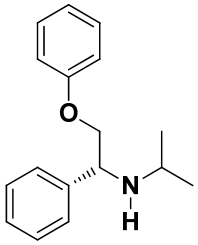
(*R*)-4



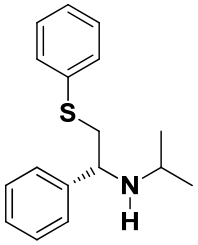
(*R*)-5



(*R*)-6



(*R*)-7



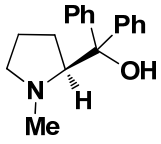
(*R*)-8

Kenso Soai's approach (1992)[6]

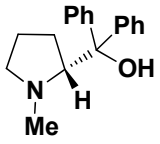
As outlined in **Scheme 3**, the addition of caynomethylzinc bromide to aldehydes in presence of (1-methylpyrrolidin-2-yl)diphenylmethanol (**8** & **9**) chiral ligands yielded corresponding β-hydroxy nitriles in good yields with enantioselectivity up to 93%. This is an enantioselective Reformatsky reaction which employs the proline derivatives **8** and **9** as chiral ligands.

R= Ph, 4-OMe, 2-napthyl, $PhCHCH_2$

Scheme 3: *Reagents and conditions; (i) chiral catalyst 8 or 9, THF, -13 ^{o}C, up to 78%.*



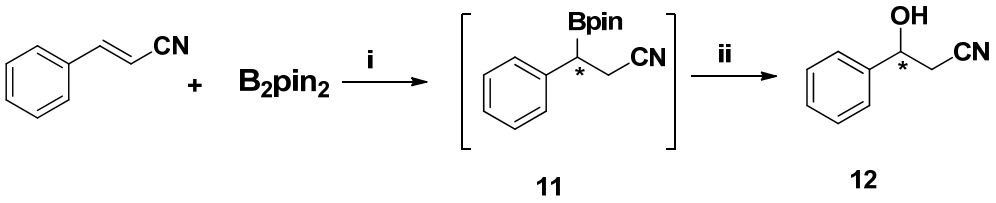
(*S*)- (+)-DPMPM (**8**)



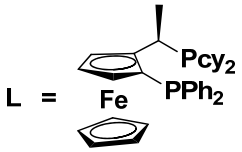
(*R*)-(-)-DPMPM (**9**)

Jaesook Yun's approach (2006)[7]

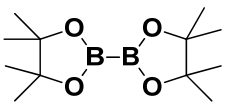
The asymmetric β-boration of cinnamonitrile with bis(pincolato)diboron using Josiphos as chiral ligand yielded intermediate compound **11**. The subsequent oxidation of compound **11** with sodium metaborate in a mixture of THF and water yielded β-hydroxy nitrile **12** up to 83% enantiomeric excess (**Scheme 4**).



Scheme 4: *Reagents and conditions; (i) CuCl, L, NaO^{t}Bu, MeOH, THF, rt; (ii) $NaBO_3$, THF: H_2O, 84%.*



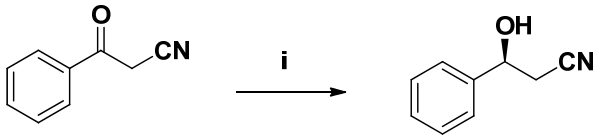
(*R*)-(*S*)-Josiphos



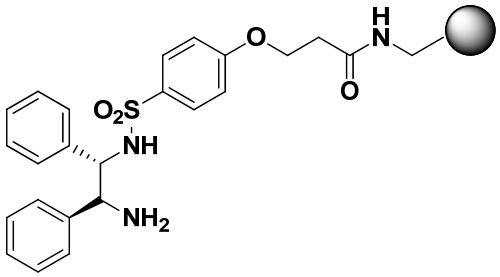
bis(pinacolato)diboron (**B_2pin_2**)

Wang's approach (2005)[8]

As outlined in **Scheme 5**, the asymmetric transfer hydrogenation β-ketonitrile with [$RuCl_2$ (p-cymene)] $_2$ and formic acid-triethyl amine azeotrope in the presence of a chiral ligand **10** gave chiral β-hydroxy nitrile in 98% yield. This was exemplified by the synthesis of fluxotene employing asymmetric transfer hydrogenation to β-ketonitrile as the key reaction.



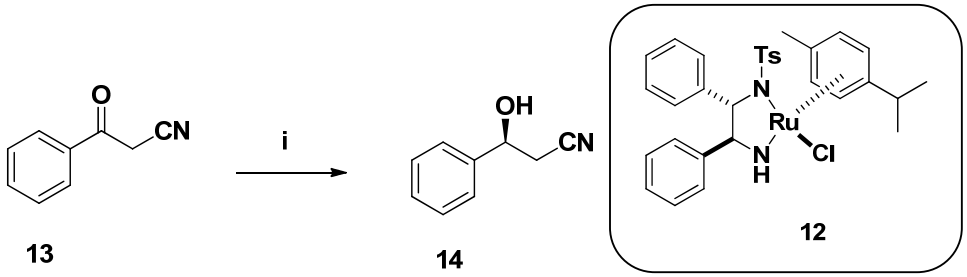
Scheme 5: *Reagents and conditions; (i) Ligand 11, [$RuCl_2$ (p-cymene)]$_2$, HCOOH-Et_3N, CH_2Cl_2, 98%.*



11

Takao Ikaria's approach (2002)[9]

As described in **Scheme 6**, β-hydroxy nitrile **14** were prepared by reducing 2- cyano acetophenones **13** with a mixture of formic acid and triethyl amine containing a chiral Ru-(II) catalyst **12** , RuCl [(*S,S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethy lenedia mine] (*p*-cymene) in good yields with high enantioselectivities.

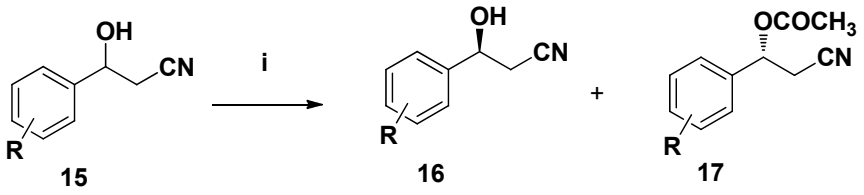


13 14 12

Scheme 6: *Reagents and conditions; (i) Ligand **12**, HCOOH-Et_3N, 30 ^oC, 98%.*

Ahemad Kamal's approach(2002)[10]

As outlined in **Scheme 7**, 3-hydroxy-3-phenyl pronaenitrile (β-hydroxy nitrile) has been prepared from its racemic mixture by enzymatic kinetic resolution. The racemic hydroxyl nitrile **15** on *lipase* mediated transesterification gave (*S*)-β-hydorxy ntirle **16** and *R*-acetate **17** in good yields with high enantioselectivities.

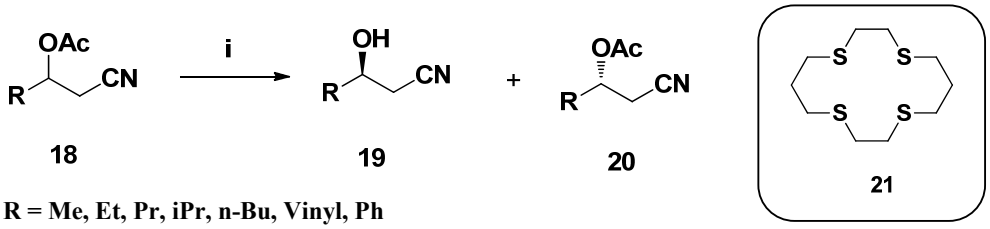


R= H, 3-Cl, 3-CH_3

Scheme 7: *Reagents and conditions; (i) Lipase (PS, PS-C), vinyl acetate, ($^{i}Pr)_2O$, 40 ^{o}C, up to 50 % of* ***16****.*

Hiroshi Tsukube's approach (1997)[11]

As described in **Scheme 8**, the β-hydroxy nitriles have been prepared by the enzymatic hydrolysis of corresponding alkane nitrile acetates. '*Pseudomonas cepacia* lipase' enzyme catalyzed hydrolysis of alkanenitrile acetates **18** in presence of thiacrown ether **21** (1,4,8,11-tetrathiacyclotetradecane) in a mixture of acetone and water at 35 ^{o}C. The obtained yields of **19** and **20** are about 50% each with high percentage of enantioselectivity.



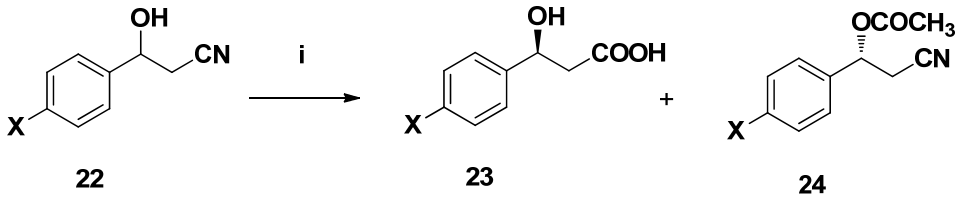
R = Me, Et, Pr, iPr, n-Bu, Vinyl, Ph

Scheme 8: *Reagents and conditions; (i) Lipase PS, Acetone-H_2O, crown ether 21, 35 ^{o}C.*

Ling Hua's approach (2006)[12]

As outlined in **Scheme 9**, the β-hydroxy nitriles were prepared by the enzyme catalyzed enantioselective hydrolysis of racemic β-hydroxy nitriles. Substituted phenyl β-hydroxy nitriles **22** under goes hydrolysis with enzyme '*nitrilase bll6402*' in presence of a buffer (pH: 7) to furnish enantiopure β-hydroxy nitrile acetate **24** and β-

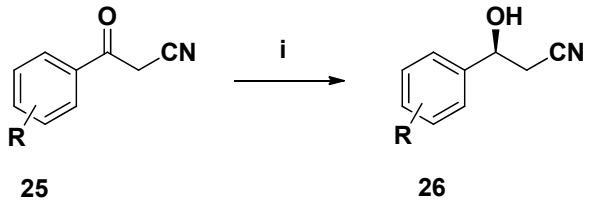
hydroxy carboxylic acid **23** almost in equal yield and with moderate to high enantioselectivities (max. ee for **24** is 75 % and 90% for **23**).



X= H, Cl, F, OCH_3, CH_3

Scheme 9: *Reagents and conditions; (i) Nitrilase bll6402, Potassium phosphate buffer (pH: 7), 12 h, up to 57% yields of **24**.*

Hari babu's approach (2006)[13]



R= H, 4-F, 4-Cl, 4-Br, 4-CH_3, 4-CN, 4-NO_2, 3-NO_2, 3-OCH_3

Scheme 10: *Reagents and conditions; (i) Carbonyl reductase Ymr226c, NADPH, buffer (pH: 7), DMSO, up to 90% yield.*

As outlined in **Scheme 10**, β-hydroxy nitriles were prepared by the chemoenzymatic reduction of β-keto nitriles in good yields with high enantiopurity. Substitiuted phenyl keto nitirles **25** on enzymatic reduction with *carbonyl reductase (*isolated from *Candida magnolia (*CMCR)) or with alcohol dehydrogenase, ymr226c (isolated from *Saccharomyces cerivisae*) gave various aromatic β-hydroxy nitriles **26** bearing either electron-donating or electron-withdrawing groups with high optical purity and in excellent yields (up to 90%).

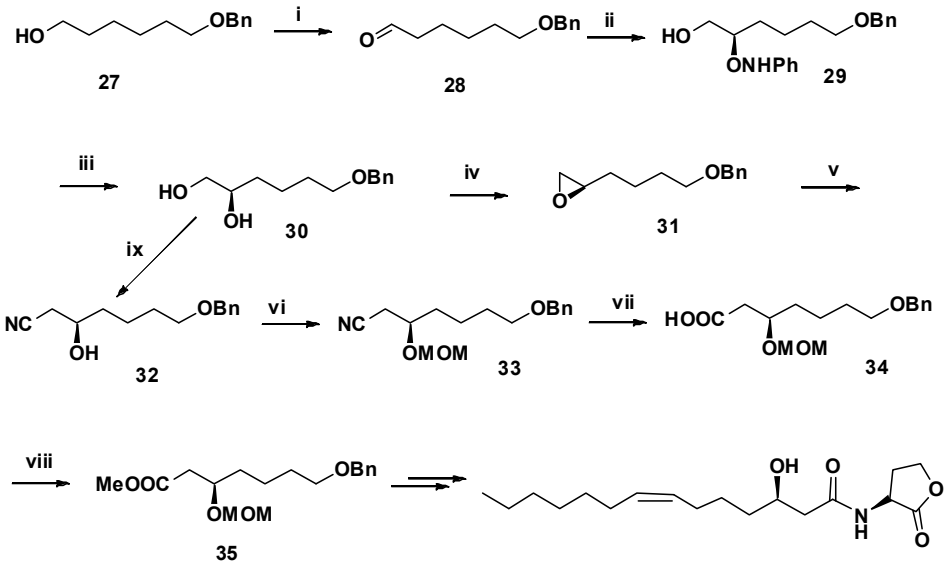
5.1.3. Present work

5.1.3.1. Objective

As can be seen from the literature section, most of the reported methods involve either use of expensive metal catalysts or low yielding resolution approaches. Hence, we thought of developing a methodology to overcome the short falls of existing methods by synthesizing β-hydroxy nitriles *via* proline catalyzed α-aminoxylation of aldehydes.

5.1.3.2. Results and discussion

Our synthetic route started with the monobenzyl protected 1, 6-hexane diol **27**, which was obtained by the selective benzylation of cheap and commercially available 1, 6-hexane diol. Oxidation of **27** with Iodoxy benzoic acid (IBX) in DMSO at room temperature gave corresponding aldehyde **28** in quantitative yield. Owing to the lesser stability of aldehyde, it was proceeded to further reaction with crude product obtained after aqueous work up. Then, the stage was set to carry out the key reaction of the synthetic route i.e α-aminoxylation. The aldehyde **28** on treatment with nitrosobenzene in presence L-proline in CH_3CN solvent at -20 ^oC for 14 h followed by sodium borohydride reduction furnished aminoxy alcohol **29**. Due to its unstability even at lower temperatures, aminoxy alcohol **29** was immediately subjected to hydrogenolysis with $CuSO_4$ in methanol for overnight at room temperature to yield diol **30**. The overall yield for the last three steps is 65%. Further, the selective mono tosylation of diol **30** was carried out with tosyl chloride in presence of dibutyl tin oxide (Bu_2SnO) and triethyl amine to get primary mono tosylate in good yield. Without column chromatographic purification, tosylate was further subjected to nucleophilic substitution with sodium cyanide (NaCN) in DMF solvent (1.5 mL/ each mmol of tosylate) at 60 ^oC for 6 h to yield β-hydroxy nitrile **32** in 82% yield. Alternatively, tosylate was treated with K_2CO_3 in methanol to get



(2S,3R,7Z)-N-(3'hydroxy-7'-tetradecenoyl)-homoserine lactone

Scheme 11: *Reagents and conditions: (i) IBX, DMSO,1h, rt, 95% ;(ii) (a) PhNO, L-proline, CH_3CN, -20 ^oC ;(b) $NaBH_4$, MeOH ;(iii) $CuSO_4$, MeOH, 65% (for three steps) (iv) (a) TsCl, Et_3N, Bu_2SnO, DMAP, CH_2Cl_2; (b) K_2CO_3, MeOH, 95% (v) NaCN, EtOH: H_2O, 6 h, 89%;(vi) MOMCl, NaH, THF, 1 h, 90%; (vii) (a) DIBAL-H, CH_2Cl_2, 3 h; (b) $NaClO_2$, NaH_2PO_4 .H_2O, tBuOH:H_2O, 2 h,78% ;(viii) Na_2CO_3, MeI, DMF, 90%; (ix) NaCN, DMF (1.5 ml/mmol), 60 ^oC, 6h, 82% .*

epoxide **31** which was further regioselectively opened with soium cyanide to afford **32** in 89% yield. Then the hydroxy group in **32** was converted to its MOM-ether by treating with MOMCl in presence of NaH in THF. Further, MOM protected nitrile **33** was subjected to oxidation with DIBAL-H in CH_2Cl_2 to afford aldehyde, which was immediately converted to carboxylic acid **34** by treating with $NaOCl_2$, NaH_2PO_4 in a mixture of tBuOH and water. Finally, carboxylic acid compound **34** was treated with MeI, Na_2CO_3 in DMF to get its methyl ester **35** in 90% yield.

5.1.4. Conclusion

The enantioselective synthesis of β-hydroxy nitrile has been achieved by employing L-proline catalyzed α-aminoxylation. The present synthetic strategy can conveniently be applied for the synthesis of various biological active molecules.

5.1.5. Experimental Section

5.1.5.1. 6-(benzyloxy)hexanal, 28

To a solution of compound **27** (1.4 g, 5.34 mmol) in DMSO (5 mL) in a round-bottom flask was added IBX (1.68 g, 6 mmol) in one portion and the reaction mixture was stirred for 1 h at ambient temperature. The reaction mixture was quenched with diethylether (5 mL), H_2O (0.5 mL) and filtered through a pad of celite. The residue was repeatedly washed with diethyl ether. The filtrate was then washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated to give the crude aldehyde, which was pure enough and used in the next step without further purification.

5.1.5.2. (*R*)- Aminoxy alcohol, 29

To a stirred solution of nitrosobenzene (7.37 g, 68.84 mmol) and D-proline (1.58 g, 20 mol %) in CH_3CN (200 mL) was added precursor aldehyde **28** at -20 °C. The reaction mixture was stirred at the same temperature for 24 h followed by the addition of MeOH (100 mL) and $NaBH_4$ (10.42, 275.36 mmol) and stirring for another 1 h. After completion of reaction (checked by TLC), the reaction mixture was quenched with saturated solution of ammonium chloride. The solvent was evaporated and the residue was dissolved in EtOAc and washed with water followed by brine solution. Organic phase was dried over anhyd. Na_2SO_4 and the solvent was removed under *vacuum* to give crude aminoxy alcohol **29.**

5.1.5.3. (*R*)-6-(benzyloxy)hexane-1,2-diol, 30

To a solution of the crude aminooxy alcohol **29** in MeOH (50mL) was added $CuSO_4.5H_2O$ (0.64 g, 2.55 mmol) at 0 ^oC. The reaction mixture was allowed to stir for 10 h at this temperature. After the addition of the phosphate buffer, the resulting mixture was extracted into $CHCl_3$ (3x30 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude diol which was then purified by column chromatography over silica gel (100-200 mesh, EtOAc/hexane 6:4) to give **30** (65%, for three steps) as white solid; $[\alpha]_D^{25}$: +16.3 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 1150, 1610, 2955, 3017, 3450 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.33 (brs, 3H), 1.47 (brs, 3H), 3.31-3.37 (t, *J* = 6.06 Hz, 2H), 3.71-3.79 (m, 2H), 3.85-3.91 (m, 1H), 4.37 (s, 2H), 7.18-7.22 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.03, 29.43, 32.40, 69.07, 69.90, 127.49, 127.58, 128.03, 138.44; ESI-MS: *m/z* = 247 (M+Na).

5.1.5.4. (*R*)-7-(benzyloxy)-3-hydroxyheptanenitrile, 32

To a solution of diol **30** (4.7 g, 21mmol) in CH_2Cl_2 (45 mL) were added Bu_2SnO (0.105 g, 0.42 mmol), tosyl cholroide and Et_3N (4 g, 21 mmol). The reaction mixture was stirred until TLC indicates the complete consumption of starting material. Then the reaction mixture was filtered and filtrate was concentrated in *vacuum* to get crude tosylate.

To a solution of crude tosylate in DMF (30 mL, 1.5 mL/each mmole of tosylate), was added sodium cyanide (2 g, 40 mmol) at once and then reaction mixture was allowed to stir at 60 ^oC for 6 h. After completion of the reaction (as indicated by TLC), water (200 mL) was added to the reaction mixture and extracted with Et_2O (3x100 mL). The organic phase was washed with water followed by brine solution and finally dried over anhyd. Na_2SO_4. Solvent was evaporated under reduced pressure and thus obtained crude product was purified by column chromatography over silica gel (100-200 mesh, EtOAc/hexane 7:3) gave β-hydroxy nitrile **32** a colorless liquid in 89%

yield; $[\alpha]_D^{25}$: - 14.6 (*c* 1.2, $CHCl_3$); IR (neat): ν 1145, 1620, 2350, 2955, 3017, 3430 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.53-1.68 (m, 6H), 2.41-2.46 (m, 2H), 3.45-3.50 (t, *J* = 5.94,2H), 3.84 (m, 1H), 4.48 (s, 2H), 7.28-7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.12, 25.94, 29.10, 35.99, 67.17, 69.93, 72.90, 117.73, 127.61, 127.68, 128.34, 138.13; ESI-MS: *m/z* = 246 (M+Na).

5.1.5.5. (*R*)-2-(4-(benzyloxy)butyl)oxirane, 31

To a solution of crude tosylate in MeOH (50 mL) was added K_2CO_3 (1.79 g, 13 mmol) and the mixture was stirred at 0 °C for 30 min. After the reaction was complete (monitored by TLC), solvent was evaporated and the residue was extracted with diethyl ether (3 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude product which was then purified by column chromatography over silica gel (100-200 mesh, EtOAc/hexane 7:3) to afford the epoxide **31** as a colorless liquid; $[\alpha]_D^{25}$: - 28.6 (*c* 1.1, $CHCl_3$); IR (neat): ν 790, 850, 1160, 1620, 2955, 3017 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.54-1.68 (brs, 6H), 2.41-2.44 (m,1H), 2.68-2.72 (t, *J* = 4.08 Hz,1H), 2.86 (s,1H), 3.43-3.49 (t, *J* = 5.81 Hz, 2H), 4.48 (3, 2H), 7.29 (brs, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): 22.78, 29.52, 48.51, 51.81, 69.84, 72.78, 127.35, 127.41, 128.20, 138.52; ESI-MS: *m/z* = 229 (M+Na).

To a solution of epoxide **31** (1.8 g, 9 mmol) in ethanol (10 mL) was added water (30 mL). After stirring for 5 min. sodium cyanide (0.9 g, 17 mmol) was added and stirring was continued overnight at room temperature. On completion of the reaction (as indicated by TLC) the reaction mixture was concentrated to about 25% of original volume under reduced pressure. The residue was then extracted with EtOAc and the organic phase was washed with brine, dried over anhydrous Na_2SO_4 and finally evaporated under reduced pressure to give crude product. It was then purified by

column chromatography over silica gel (100-200 mesh, EtOAc/hexane 7:3) to give the β-hydroxy nitrile **32** as a colorless liquid in 95% yield; $[\alpha]_D^{25}$: - 14.4 (*c* 1.2, $CHCl_3$).

5.1.5.5. (*R*)-7-(benzyloxy)-3-(methoxymethoxy)heptanenitrile, 33

To a solution of sodium hydride (593 mg, 24 mmol) in THF (20 mL) at 0 ^oC, was added a solution of β-hydroxy nitrile **32** (4.8 g, 20 mmol) in THF (20 mL) drop-wise. After stirring the reaction mixture for 10 min., MOMCl (2.3 mL, 30 mmol) was added drop-wise and stirring was continued for another 2 h at the same temperature. The reaction was quenched with water, and then EtOAc (50 mL) was added. The aqueous layer was separated and extracted with EtOAc (3x50 mL). the combined organic layers were dried and concentrated under *vacuum* to get crude product, which was finally chromatographed over silica gel (100-200 mesh, EtOAc/hexane 7:3) gave compound **33** as a white solid in 90% yield; $[\alpha]_D^{25}$: +21.4 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 1090, 1145, 1260, 1620, 2955, 3017 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.47-.171 (m, 6H), 2.45-2.70 (m, 2H), 3.40 (s, 3H), 3.44-3.50 (t, *J* = 5.94 Hz, 2H), 3.74-3.80 (m, 1H), 4.49 (s,2H), 4.68 (s, 2H), 7.26-7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.74, 23.53, 29.31, 33.98, 55.69, 69.87, 72.73, 73.12, 95.93, 117.18, 127.35, 127.43, 128.17, 138.36; ESI-MS: *m/z* = 278 (M+H).

5.1.5.6. (*R*)-7-(benzyloxy)-3-(methoxymethoxy)heptanoic acid, 34

To a solution of **33** (1.1 g, 4mmol) in CH_2Cl_2, was added DIBAl-H (1.6 M in toluene, 5 mL) drop-wise at -78 ^oC and the reaction mixture was stirred for 3 h at the same temperature. After completion of the reaction (checked by TLC), reaction was quenched with methanol, sodium potassium tartarate was added and the contents were allowed to stir for another 6 h. Finally, reaction mixture was filtered and the filtrate was evaporated to get crude aldehyde.

To a solution of crude aldehyde in tBuOH: H_2O added solid $NaOCl_2$ and solid $NaH_2PO_4.H_2O$ at room temperature. The contents were allowed to stir for 12 h at the same temperature, solvent was evaporated to 25% of its initial volume and extracted with EtOAc (3x 30 mL) and organic layer was dried and evaporated under reduced pressure and finally on column purification of the crude over silica gel (100-200 mesh, EtOAc/hexane 5:5) gave compound **34** as a white solid in 78% yield; $[\alpha]_D^{25}$: -25.3 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 1090, 1145, 1260, 1620, 1710, 2955, 3030, 3240, cm^{-1} ;^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47-1.83 (m, 6H), 2.41-2.61 (m, 2H), 3.33 (s, 3H), 3.93-4.05 (m, 1H), 4.28-4.35 (t, *J* = 6.57 Hz, 2H), 4.59-4.67(dd, *J* = 7.07 Hz, 3.03 Hz, 2H), 7.38-7.57 (m, 3H), 7.99-8.03 (d, *J* =7.35 Hz, 2H);^{13}C NMR (50 MHz, $CDCl_3$): δ 22.41, 29.34, 30.34, 35.15, 40.67, 52.55, 65.39, 75.13, 96.75, 128.95, 130.18, 133.48, 172.42; ESI-MS: *m/z* = 335 (M+K).

5.1.5.7. (R)-Methyl 7-(benzyloxy)-3-hydroxyheptanoate, 35

Methyl iodide (95 mg, 0.64 mmol) and Na_2CO_3 (34 mg, 0.32 mmol) were added to a solution of carboxylic acid **34** in DMF (2 mL). The resulting mixture was stirred for 4 h at room temperature, then diluted with EtOAc and washed with water. The organic layer was dried and solvent was evaporated under reduced pressure to the crude product. The column chromatographic purification of crude over silica gel (100-200 mesh, EtOAc/hexane 9:1) gave pure methyl ester **35** as a white solid 82% yield; $[\alpha]_D^{25}$: +29.6 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$): ν 1080, 1145, 1260, 1620, 1740, 2955, 3020 cm^{-1} ; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.56-1.80 (m, 6H), 2.41-2.61(m, 2H), 3.33 (s, 3H), 3.96-4.02 (m, 1H), 4.28-4.35 (t, *J* = 6.5 Hz, 2H), 7.38-7.50 (m, 3H) 7.98-8.03 (d, *J* = 8.21 Hz) ; ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.77, 28.70, 29.71, 34.51, 39.50, 51.61, 55.60, 64.75, 74.49, 96.11, 127.61, 128.31, 129.54, 130.36, 132.81, 171.78; ESI-MS: *m/z* = 333 (M+Na).

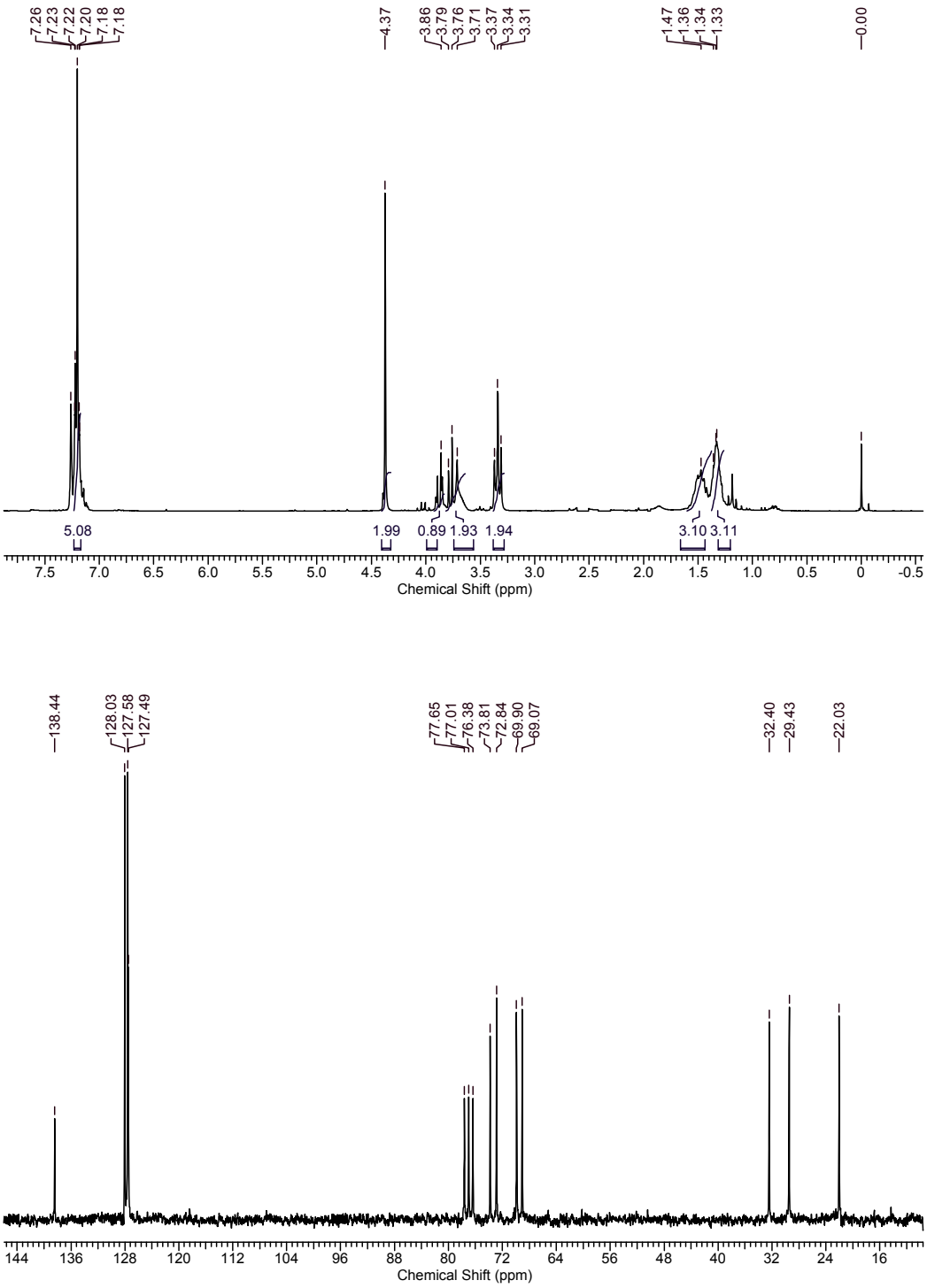


Fig: 6. ^{1}H-NMR and ^{13}C-NMR spectra of compound 30

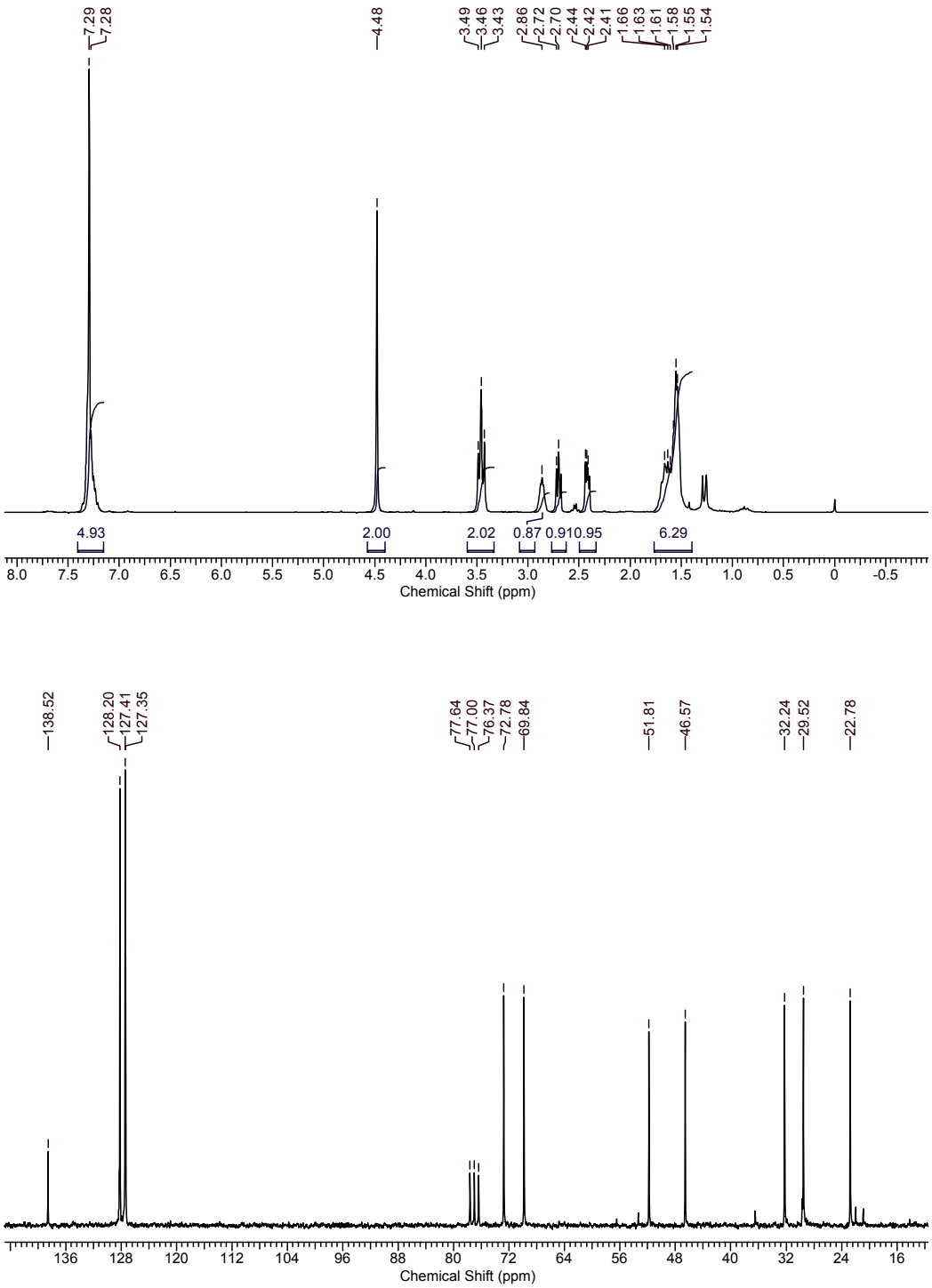


Fig: 6. ^{1}H-NMR and ^{13}C-NMR spectra of compound 31

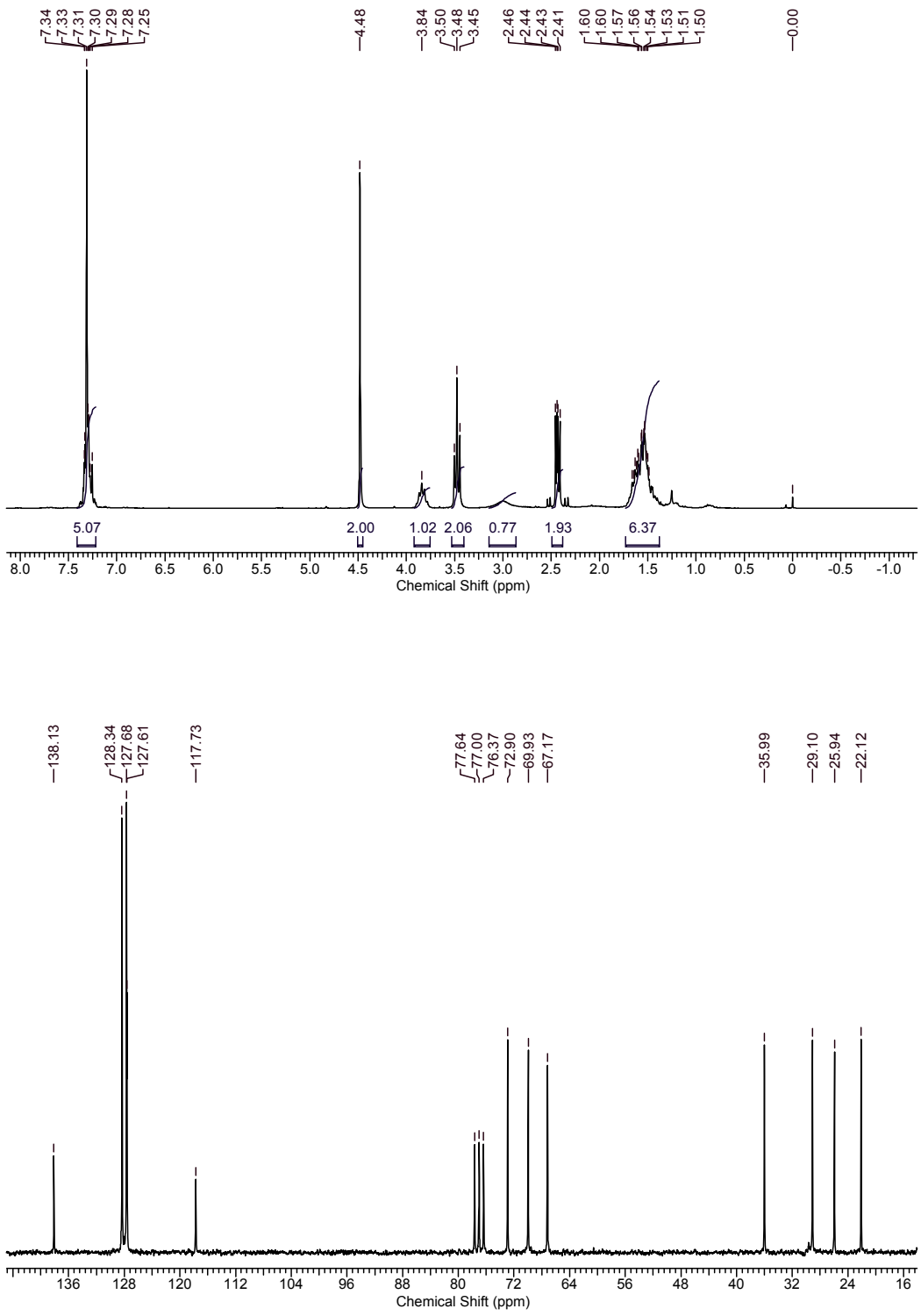


Fig: 6. ^{1}H-NMR and ^{13}C-NMR spectra of compound 32

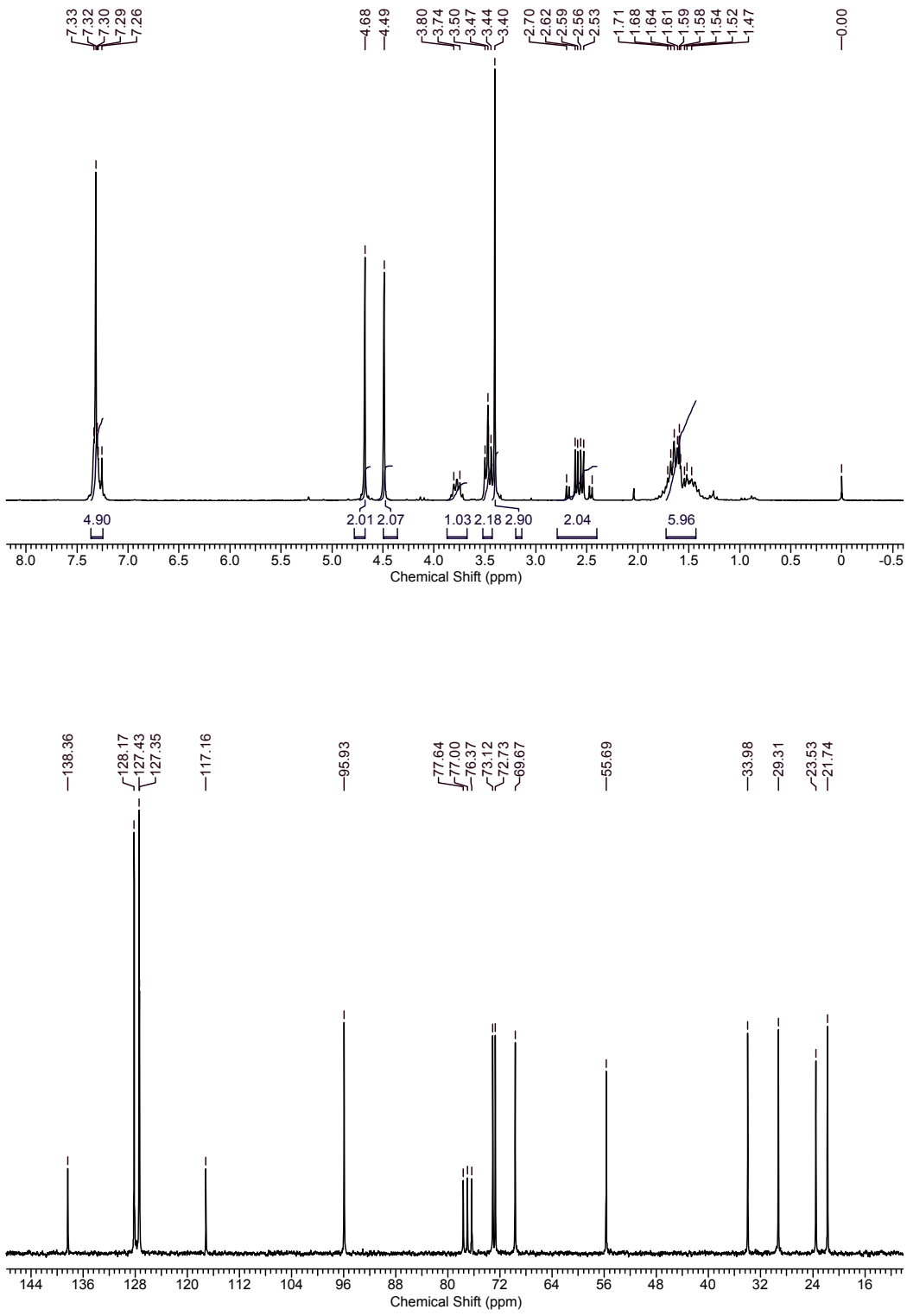


Fig: 6. ^{1}H-NMR and ^{13}C-NMR spectra of compound 33

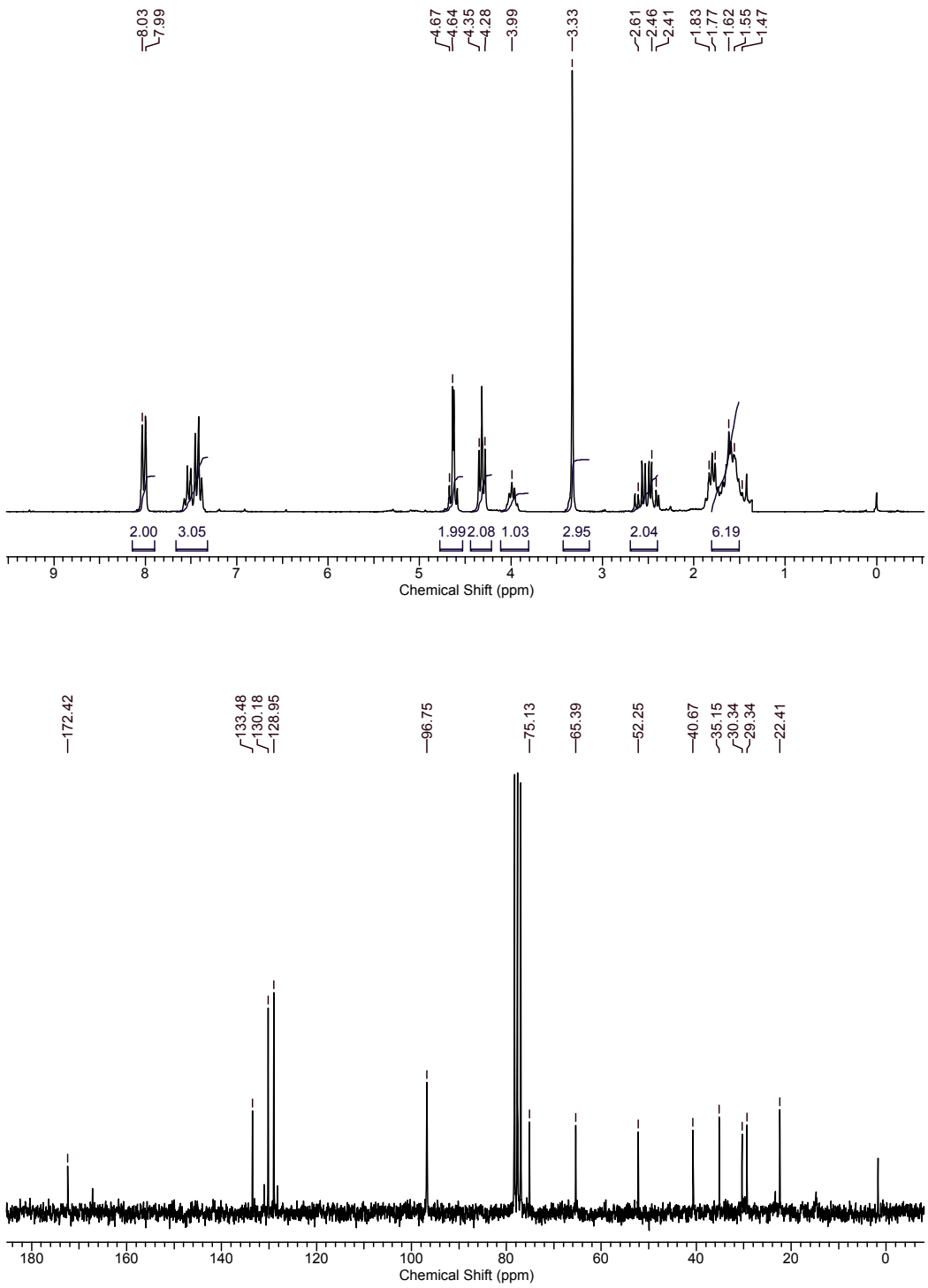


Fig: 5. Fig: 6. ^{1}H-NMR and ^{13}C-NMR spectra of compound 34

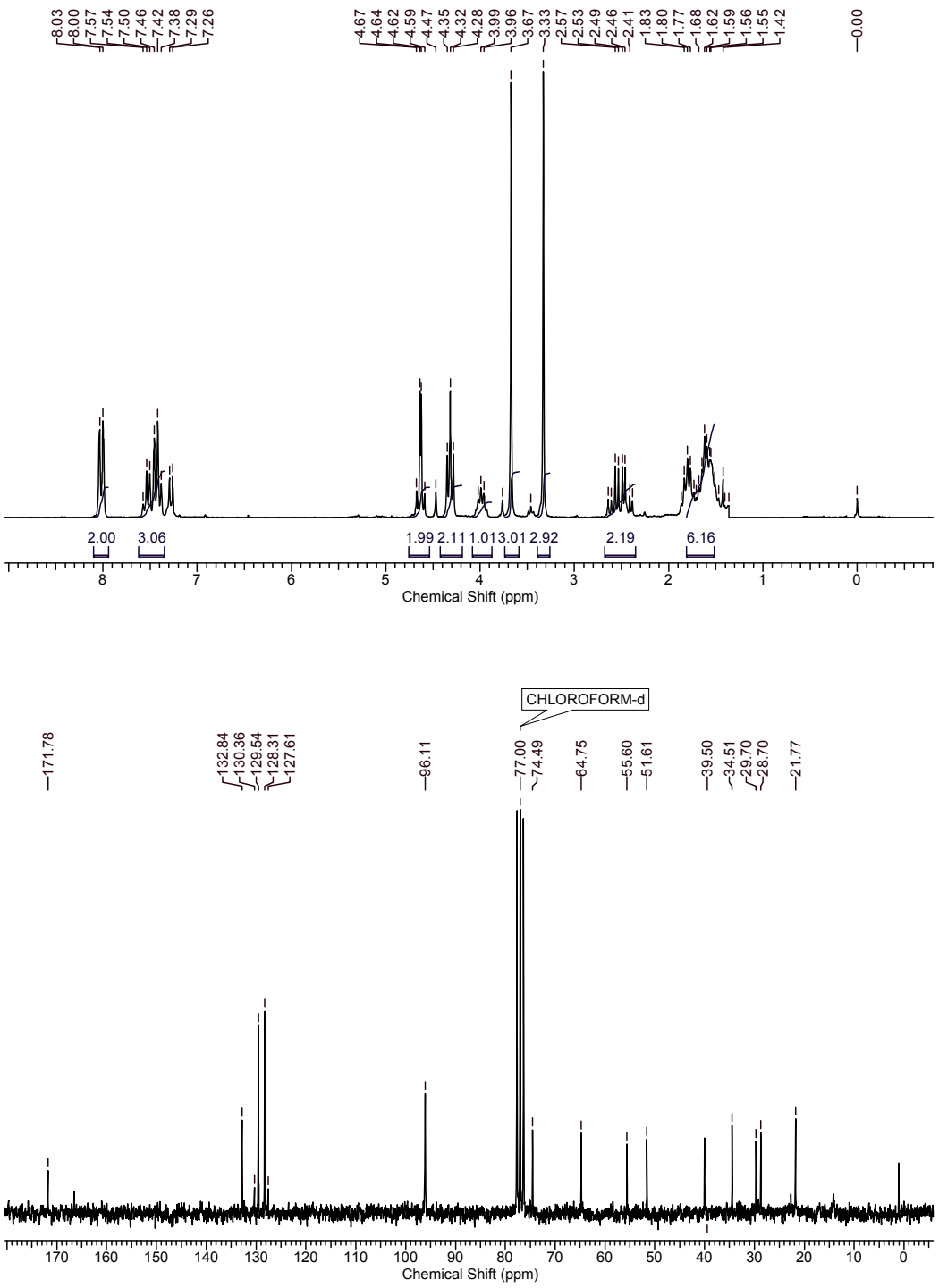


Fig: 6. ^{1}H-NMR and ^{13}C-NMR spectra of compound 35

Section II:

Oxidative aromatization of 1, 4-Dihydropyridines by Sodium perborate

Introduction

1,4-dihydropyridines (1,4-DHPs) are one of the important cardiovascular drugs because of their promising calcium antagonistic effect.[14] The oxidation of 1,4-DHPs into the corresponding pyridine compounds is one of the important metabolic pathways of these drugs. The oxidative metabolism of 1,4-DHPs in the liver by the action of cytochrome P450 (CYP) [15] forms pyridine derivatives. In addition, 1,4-DHPs were also used in modeling the coenzymes NADH in its bio-logical redox processes[16] and 1,4-DHP moieties are found in a number of chemotherapeutic agents used for the treatment of the cardiovascular disease[17] such as angina pectoris and hypertension, *e.g.* amlodipine, felodipine, nifedipine and nimodipine. In order to understand these metabolic processes as well as to develop new synthetic routes for preparing poly-substituted pyridines, a great attention has been paid to the aromatization of 1,4-DHPs.

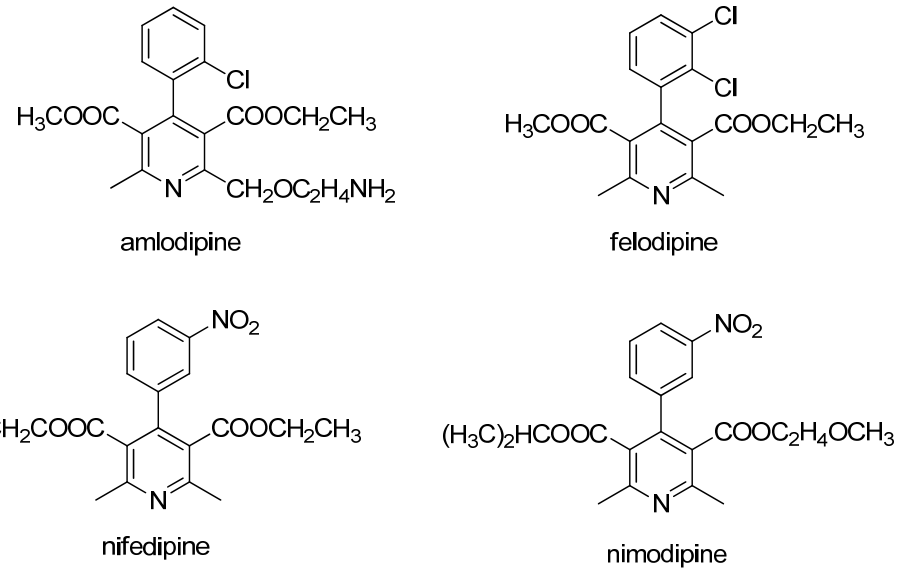


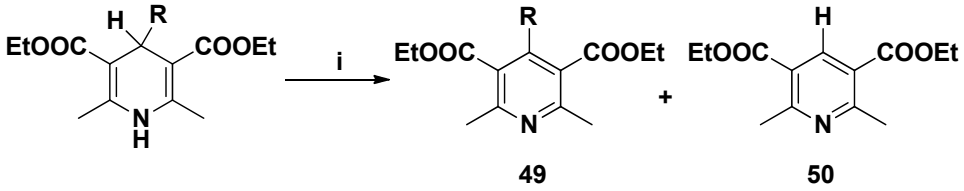
Figure 1: Well known calcium channel blockers.

Review of Literature

Literature search has revealed that there are numerous methods for the oxidation of 1,4-dihydropyridines. Out of which, important and recent synthetic routes are described below.

Zhen-Chu Chen's approach (2002)[18]

In this approach, the oxidation of 1,4-dihydropyridines to the corresponding pyridine derivatives with high yields was achieved by treating with Iodobenzene diacetate (IBD) in dichloromethane at room temperature. A wide variety of substrate containing electron-donating and electron-withdrawing groups were screened and found that all the substrate were oxidized to the respective pyridine derivatives with high yields proving the versatility of the approach (**Scheme 12**).

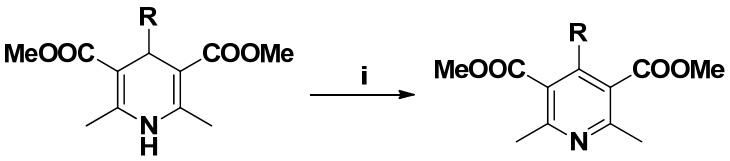


Scheme 12: *Reagents and conditions: (i) IBD, CH_2Cl_2, 20-70 hours, yields up to 90%.*

R	H	C_6H_5	3-$NO_2C_6H_4$	4-CH_3O C_6H_4	4-Cl C_6H_4	n-C_4H_7	4-CH_3 C_6H_4
Product	50	49	50	50	50	49	50

Vladimir Vinkovic's approach (2008)[19]

Vladimir Vinkovic *et al.* have reported the oxidation of 1,4-dihydropyridines catalyzed by Iron(III) pthalocyanine chloride. The reaction took place smoothly at room temperature within an hour to afford products of high optical purity and in excellent yield. The plausible mechanism of this reaction involves the formation of high-valent oxoferryl intermediate as cytochrome P450 itself (**Scheme 13**).

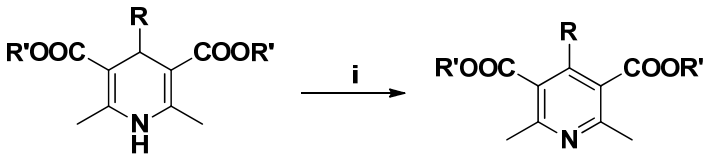


R=H, alkyl, aralkyl, substituted phenyl

Scheme 13: *Reagents and conditions: (i) ^{t}BuOOH, Iron(III) pthalocyanine chloride, AcOH, rt, yields up to 94%.*

Chinpiao Chen's approach (2010)[20]

The efficient oxidation of various 1,4- dihydropyridines employing different metal nitrates, tetrabutyl ammonium periodate (TBAP) and trinitratocerium(IV) bromate as oxidizing agents in acetic acid is reported in this approach. Ceric ammonium nitrate (CAN) and sodium bromate ($NaBrO_3$) are well known as oxidizing agents. The synergistic effect between those two oxidizing agents gives a novel oxidizing agent i.e. $(NO_3)_3CeBrO_3$ (TNCB). The aromatization of 1,4-dihyropyridines with TNCB at 100 ^{o}C in acetic acid was completed in a short time with moderate to good yields of the products. Metal nitrates such as $Ni(NO_3)_3.6H_2O$ was proved to be an another efficient oxidizing agent for the oxidation of 1,4-DHPs. the oxidizing agents such as tetrabutyl ammonium periodate (TBAP), $Cu(NO_3)_3.6H_2O$ and $Mg(NO_3)_3.6H_2O$ were also studied (**Scheme 14**).



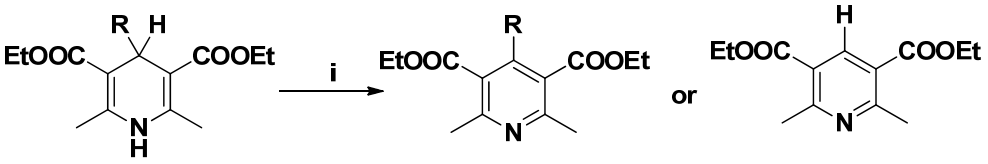
R=H, alkyl, aralkyl substituted phenyl; R'= ethyl, methyl

Scheme 14: *Reagents and conditions: (i) $Ni(NO_3)_3.6H_2O$ or TNCB or TBAP, AcOH, 100 ^{o}C, yields up to 95%.*

Behbhani's approach (2009)[21]

Behbhani *et al.* have reported an efficient protocol for the oxidation of Hantzsch 1,4-

dihydropyridines using a heterogeneous, reusable and green catalysts $Mn(Pbdo)_2Cl_2$/Al-MCM-41 or $Mn(Pbdo)_2Cl_2$/MCM-41 which are obtained by complexing Mn(II) ion with 2.2'-bipyridine, 1,1'-dioxide (bpdo) ligand immobilized with nano reactors of MCM-41. The reaction was reported to be of high yielding in refluxing acetic acid (**Scheme 15**).

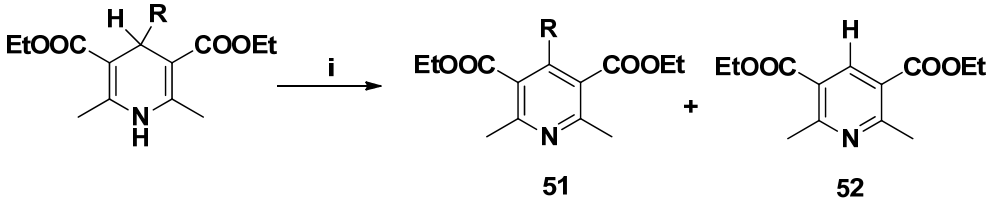


R=H, alkyl, aryl, aralkyl

Scheme 15: *Reagents and conditions: (i) $Mn(Pbdo)_2Cl_2$/Al-MCM-41 (0.5 g) or $Mn(Pbdo)_2Cl_2$/MCM-41, AcOH, reflux, yields up to 97%.*

Parvin's approach (2009)[22]

In their approach, the solid state oxidative dealkylation and oxidative aromatization of 1, 4- dihydropyridines are reported with hypervalent iodine reagents such as Iodobenzene diacetate (IBD) and hydroxy(tosyloxy)iodobenzene (HTIB) (**Scheme 16**). Though the aromatization of 1, 4-dihyropyridines is reported with the same



R=H, alkyl, aralkyl, substituted phenyl

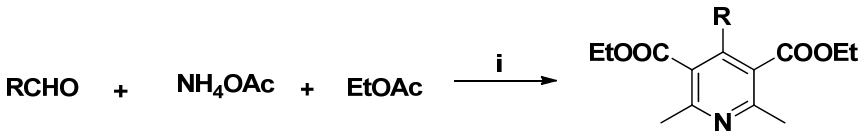
Scheme 16: *Reagents and conditions: (i) IBD or HTIB, grinding 15-20 h, yields up to 97%.*

R	H	C_6H_5	3-$NO_2C_6H_4$	4-CH_3O C_6H_4	4-Cl C_6H_4	n-C_4H_7	4-CH_3 C_6H_4
Product	52	51	51	51	51	51	51

reagents by Zhen-Chu Chen *et al.* in solution state, but the reaction times are longer in solution when compared to that of solid state.

Jing Jing's approach (2009)[23]

Jing Jing *et al.* have reported the synthesis and aromatization of 1,4-dihydropyridines by an environmentally benign method. Firstly, aldehydes were mixed with ammonium acetate, ethyl aceate and refluxed in water to yield 1,4-dihydropyridine. The addition of manganese dioxide (MnO_2) to the same reaction pot afforded oxidized 1,4-DHPs. This reaction is simplified to a two step-one pot process (**Scheme 17**).



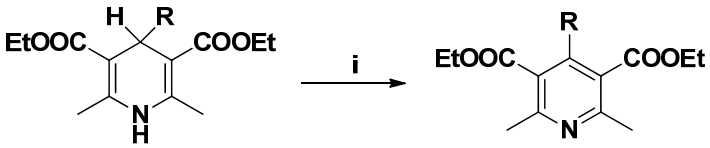
R = H, CH_3, C_6H_4, 4-$CH_3C_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$

Scheme 17: *Reagents and conditions: (i) MnO_2, H_2O, Reflux, yields up to 79%.*

Chun Wang's approach (2010)[24]

Chung wang *et al.* have reported a novel, mild method for the aromatization of 1,4-dihdropyridnes with sodium chlorite($NaClO_2$) at ambient temperatures to afford corresponding pyridines in excellent yield. Several solvents were screened and among them THF, EtOH, CH_2Cl_2, Et_2O are found to be highly suitable for the excellent yields. Various 1,4-dihydropyridines containing phenyl group attached to electron-withdrawing or electron-donating groups were screened and found to be of high yielding. It is well known that sodium chlorite reacts with the hydrochloric acid to liberate chlorine dioxide, which in fact oxidizes the 1,4-DHP's. The merits of this approach are the mild reactions conditions such as ambient temperature and short reactions times (30 min).

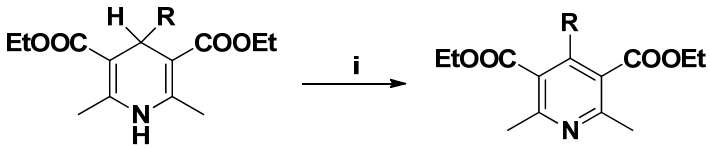
R	Yield (%)
H	99
C_6H_5	96
4-$NO_2C_6H_4$	94
4-CH_3O C_6H_4	89
4-Cl C_6H_4	95
Me	97
4-HOC_6H_4	92
2-$NO_2C_6H_4$	95
2-furyl	95
4-Cl C_6H_4	95



Scheme 18: *Reagents and conditions: (i) $NaClO_2$, con. HCl, 30 min., solvent (THFor CH_2Cl_2 or Et_2O or EtOH), 20 ^oC.*

Hekmatshoar's approach (2009)[25]

Hekmatshoar et al. have reported the aromatization of 1 4-dihydropyridines into pyridines by employing Glycinium chlorochromate (GCC) supported onto silica gel under grind and microwave irradiation conditions. For some substrates the mixture of silica gel supported GCC and 1,4-DHP was ground for some time (10 min.) and for some other substrate the mixture was exposed to microwave radiation in microwave oven to complete the reaction . Shorter reaction times and clean workup procedure are the major advantages of this approach **(Scheme 19**)



Scheme 19: *Reagents and conditions: (i) Silica gel supported GCC, grind or irradiate with microwaves, within 5 min.*

Not only the methods discussed above, but several other methods have also been reported for the conversion of 1,4-DHPs into pyridines. However, most of the reported methods involve strong oxidizing agents, such as CAN,[26] $KMnO_4$,[27] HNO_3,[28] and PCC.[29]Aerobic oxidations of 1,4-dihydropyridines was reported with catalysts such as $RuCl_3$, Pd/C and activated carbon.[30-33]

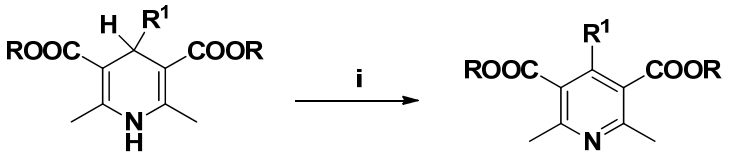
Present work

Objective

Since most of the reported methods have drawbacks such as employing expensive or toxic reagents, harsh reaction conditions, longer reaction times or tedious workup procedures. Hence we made an attempt to develop a simple and mild oxidative method for the oxidation 1,4-dihydropyridines to pyridine derivatives, which is discussed in the following section.

Results and discussion

Sodium perborate tetra hydrate is a very cheap, safe and easily handled oxidizing agent[34] and it is a stable, colorless crystalline solid. Sodium per borate is highly effective and selective oxidizing agent. In our present work we describe the utility of sodium perborate for the oxidative aromatization of 1, 4-dihydropyridines. The oxidation was carried out with $NaBO_3.4H_2O$ (3 equiv.) in H_2O: THF mixture at 60 ^oC



53a-i **54a-i**

Scheme 20: *Reagents and conditions: (i) $NaBO_3.4H_2O$ (3 equiv.), THF: H_2O (1:1), 60 ^oC, 3-7 h.*

for several hours. Various substrates were screened under the same reaction conditions to afford moderate to high yields of the corresponding pyridines (**Table 1**). Of all the substrates screened, 4-methoxyphenyl group containing 1,4-dihydropyridine (3f, entry 6) readily under gone oxidative aromatization with sodium per borate to yield corresponding pyridine derivative in high yield, where as 2-nitro phenyl group containing dihydropyridine do not show much tendency to undergo oxidation.

Table1: Oxidation of different 1, 4-Dihydropyridines to pyridines by $NaBO_3.4H_2O$.

S. No.	R^1	R	Substrate	Product	Time (Hours)	Yield (%)
1	H	Et	53a	54a	5 h	82
2	CH_3	Et	53b	54b	4 .5 h	86
3	n-C_3H_7	Et	53c	54c	4.5 h	89
4	C_6H_5	Et	53d	54d	3.5 h	90
5	4-$CH_3C_6H_5$	Et	53e	54e	3.5 h	92
6	4-$CH_3OC_6H_5$	Et	53f	54f	3 h	95
7	C_6H_5	Me	53g	54g	3.5 h	91
8	4-CH_3OC6H_5	Me	53h	54h	3 h	95
9	2-$NO_2C_6H_5$	Me	53i	54i	7 h	76

The yield of the corresponding pyridine derivative is comparatively less and reaction time is also longer. This trend in the reactivity of various 1,4-dihyropyridines may be due to electronic effects of the groups attached to the benzene ring. Also, the presence of methyl ester or ethyl ester did not make any difference with respect to yield and reaction time. The required starting materials (1, 4-dihydropyridines) are prepared by Hantzsch reaction using ammonium carbonate.[35]

Conlusion

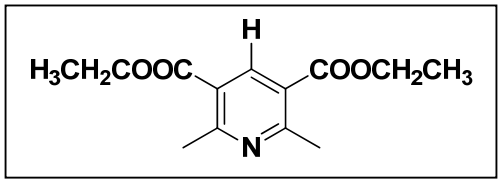
A mild, environmentally benign method for the aromatization of 1,4-dihydropyridines is developed. The reagent used is compatible with many functional groups, thus providing a versatile method for the aromatization of 1,4-DHPs.

Experimental Section

General procedure for the aromatization of the 1,4-dihydropyridines: To a

solution of sodium per borate tetra hydrate (3 mmol) in THF:H_2O (1:1) (4 mL), added 1,4-dihyropryridine compound (1 mmol) and the contents were stirred at 60 ^oC for the duration indicated in Table 1. After the completion of the reaction, solvent was concentrated to minimum volume and dissolved in diethyl ether, washed with water, dried and solvent was removed under vacuum to yield crude product, which was later recrystalized in ethanol to get pure pyridine derivatives **54a-i.**

diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (54a)



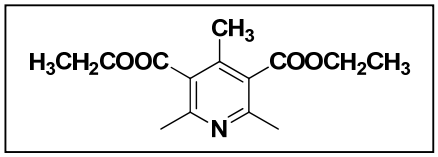
IR ($CHCl_3$): ν_{max} 771, 1123, 1223, 1297, 1590, 1718, 3121 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 1.40 (τ, J = 7.2 Hz, 6H), 2.82 (s, 6H), 4.38 (m, 4H), 8.66 (s, 1H);

^{13}C NMR (100 MHz, $CDCl_3$)**:** δ 14.3, 25.01, 61.4, 123.0, 140.9, 162.2, 165.9.

MS (*m/z*): 251 (M^+, 42), 201 (16), 206 (100), 195 (18), 178 (44), 151 (15)

diethyl 2,4,6-trimethylpyridine-3,5-dicarboxylate (54b)



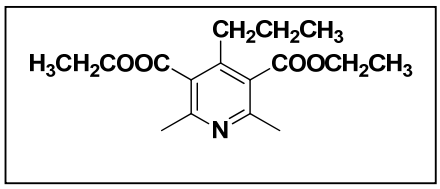
IR ($CHCl_3$): ν_{max} 1041, 1106, 1238, 1567, 1727 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 1.31 (t, J = 7.1 Hz, 6H), 2.22 (s, 3H), 2.45 (s, 6H), 4.34 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$)**:** δ 14.1, 16.9, 22.9, 61.5, 22.9, 61.5, 127.5, 141.9, 154.8, 168.3.

MS (*m/z*): 265 (M^+, 42), 236 (28), 220 (100), 219 (18), 208 (25), 192 (16).

diethyl 2,6-dimethyl-4-propylpyridine-3,5-dicarboxylate (54c)



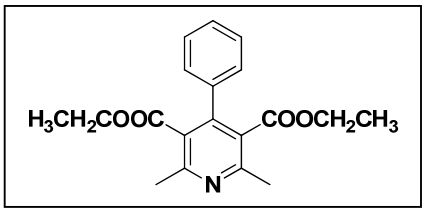
IR ($CHCl_3$): ν_{max} 1040, 1106, 1202, 1237, 1569, 1728 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) **:** δ 0.89 (t, J = 7.3 Hz, 3H), 1.35 (t, J = 7.1 Hz, 6H), 1.54 (m, 2H), 2.46 (s, 6H), 2.50 (m, 2H), 4.37 (m, 4H)

^{13}C NMR (100 MHz, $CDCl_3$)**:** δ 14.1, 14.4, 22.9, 24.1, 33.4, 61.5, 127.2, 146.3, 155.0, 168.5.

MS (*m/z*): 293 (M^+, 12), 265 (16), 264 (100), 248 (81), 139 (29), 115 (15).

diethyl 2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (54d)



IR ($CHCl_3$): ν_{max} 701, 1043, 1105, 1232, 1290, 1558, 1731 cm^{-1}.

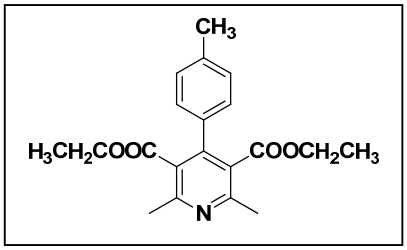
^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 0.84 (t, J = 7.1 Hz, 6H), 2.55 (s, 6H), 3.95 (m, 4H), 7.20

(m, 2H), 7.31 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$)**:** δ 13.5, 22.8, 61.3, 126.8, 128.0, 128.0, 128.4, 136.5, 146.0, 155.3, 167.8.

MS (*m/z*): 327 (M^+, 100), 282(48), 254 (33), 236 (54), 210 (29), 139 (25).

diethyl 2, 6-dimethyl-4-(p-tolyl)pyridine-3,5-dicarboxylate (54e)



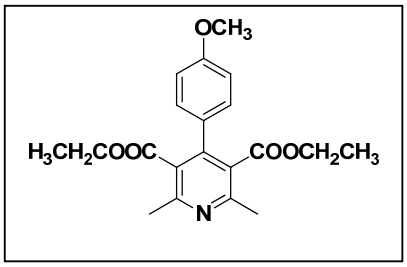
IR ($CHCl_3$): ν_{max} 821, 1104, 1209, 1233, 1290, 1557, 1726 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$)**:** δ 0.90 (t, J = 6.9 Hz, 6H), 2.31 (s, 3H), 2.54 (s, 6H), 3.98 (m, 4H), 7.11 (m, 4H),

^{13}C NMR (100 M Hz, $CDCl_3$)**:** δ 13.5, 21.2, 22.8, 61.2, 127.0, 127.9, 128.7, 133.5, 138.2, 146.1, 155.2, 167.9.

MS (*m/z*): 341 (M^+, 95), 296(30), 265 (34), 250 (100), 223 (24), 152 (17)

diethyl 4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (54f)

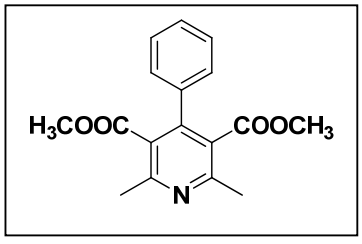


IR ($CHCl_3$): ν_{max} 1040, 1105, 1234, 1249, 1292, 1515, 1725 cm^{-1}

^{1}H NMR (400 M Hz, $CDCl_3$)**:** δ 0.94 (t, J = 7.2 Hz, 6H), 2.53 (s, 6H), 3.77 (s, 3H), 4.01 (m, 4H), 6.85 (m, 2H), 7.14 (m, 2H),

^{13}C NMR (100 M Hz, $CDCl_3$)**:** δ 13.7, 22.8, 55.2, 61.3, 113.5, 127.2, 128.6, 129.3, 145.7, 155.1, 159.7, 168.0.

dimethyl 2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (54g)

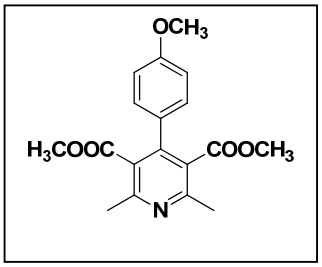


IR ($CHCl_3$): ν_{max} 701, 1043, 1105, 1232, 1290, 1558, 1735 cm^{-1}

^{1}H NMR (400 M Hz, $CDCl_3$)**:** δ 2.82 (s, 6H), 3.54 (s, 6H), 7.18-7.25 (m, 2H), 7.41-7.46 (m, H).

^{13}C NMR (100 M Hz, $CDCl_3$)**:** δ 18.3, 52.8, 126.9, 128.5, 129.9, 130.4, 133.6, 152.7, 153.0, 164.1 ppm.

dimethyl 4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (54h)

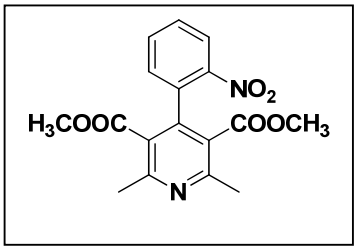


IR ($CHCl_3$): ν_{max} 1048, 1095, 1239, 1256, 1287, 1521, 1719 cm^{-1}

^{1}H NMR (200 M Hz, $CDCl_3$)**:** δ 2.55 (s, 6H), 3.55 (s, 6H), 3.81 (s, 3H), 6.85 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 8.8 Hz, 2H);

^{13}C NMR (50 M Hz, $CDCl_3$) **:** δ 22.8, 52.1, 55.0, 113.6, 126.8, 128.4, 129.0, 145.6,155.2, 159.6, 168.5 ppm.

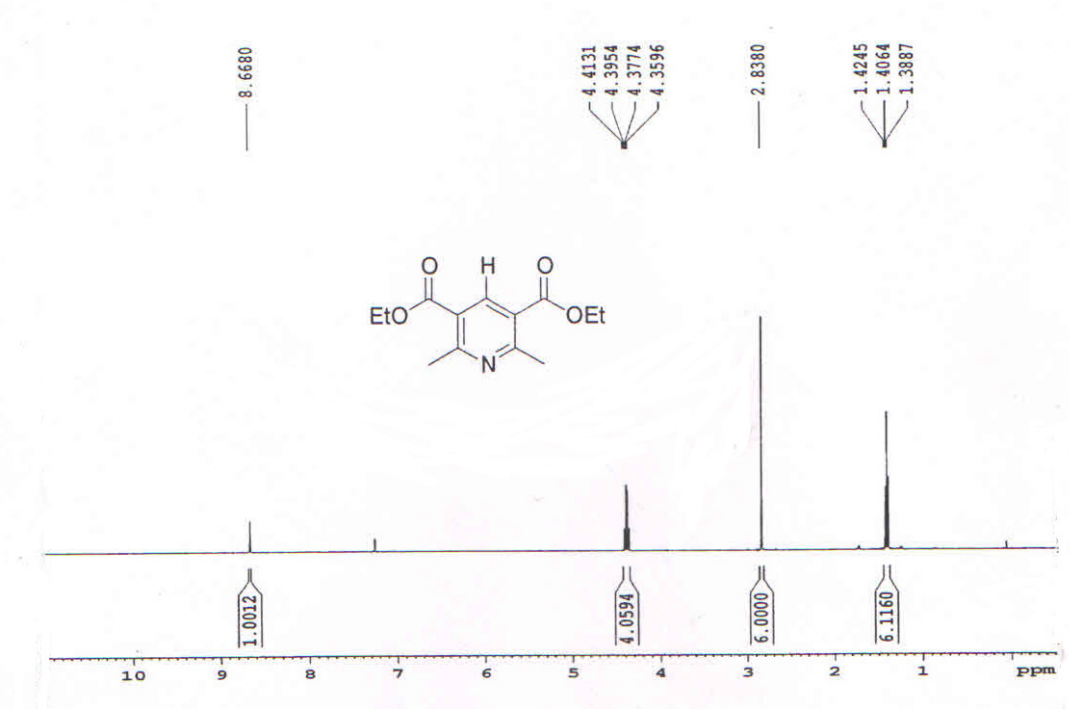
dimethyl 2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate (54i)



IR ($CHCl_3$): ν_{max} 1048, 1095, 1239, 1256, 1287, 1560, 1719 cm^{-1}

^{1}H NMR (200 M Hz, $CDCl_3$)**:** δ 2.62 (s, 6H), 3.48 (s, 6H), 7.15-7.20 (m, 1H), 7.52-7.61 (m, 2H), 8.19-8.22 (m, 1H):

^{13}C NMR (50 M Hz, $CDCl_3$)**:** δ 23.0, 51.6, 125.8, 126.1, 128.7, 129.3, 129.8, 132.3, 135.2, 144.3, 156.2, 167.0 ppm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4.3596
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1.4245
1.4064
1.3887
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O
EtO
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N
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7
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3
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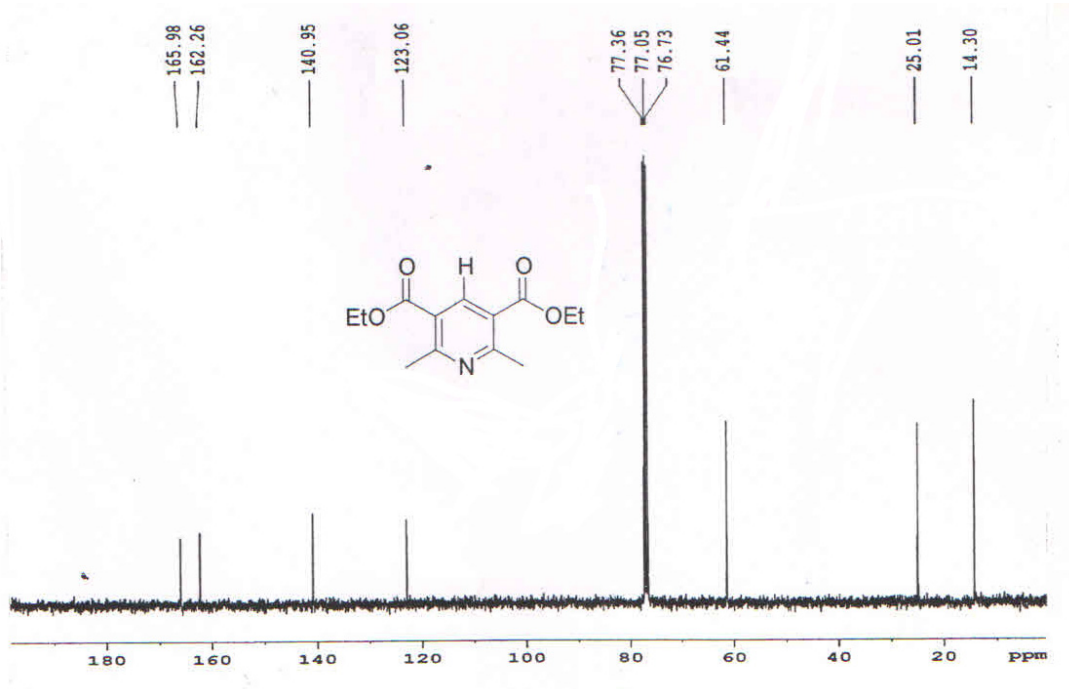
1
ppm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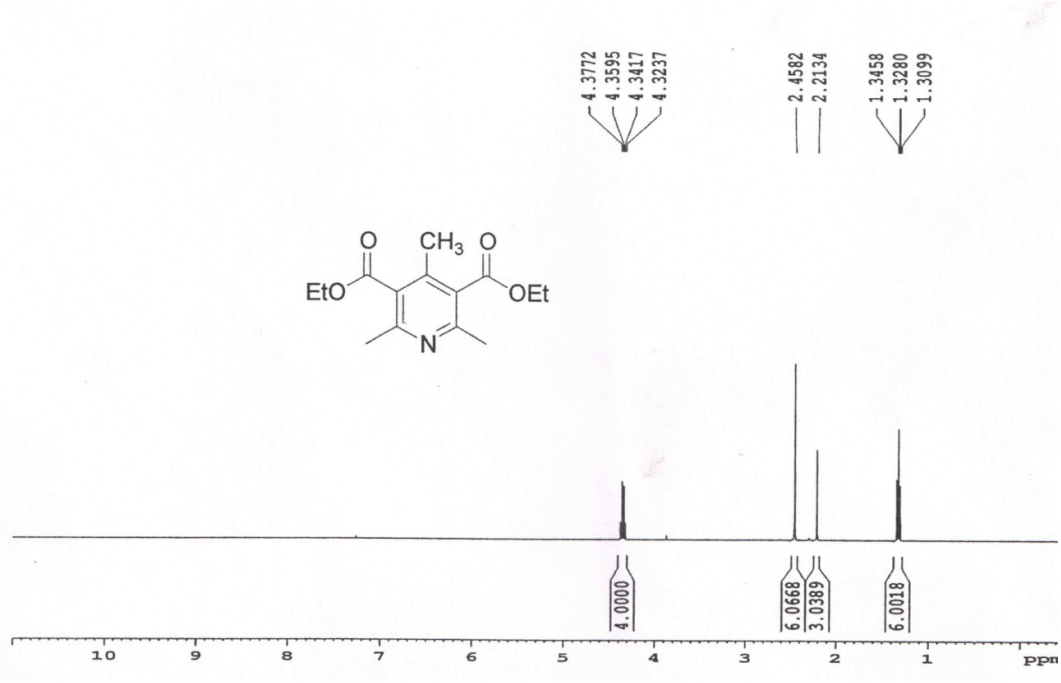
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EtO
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7
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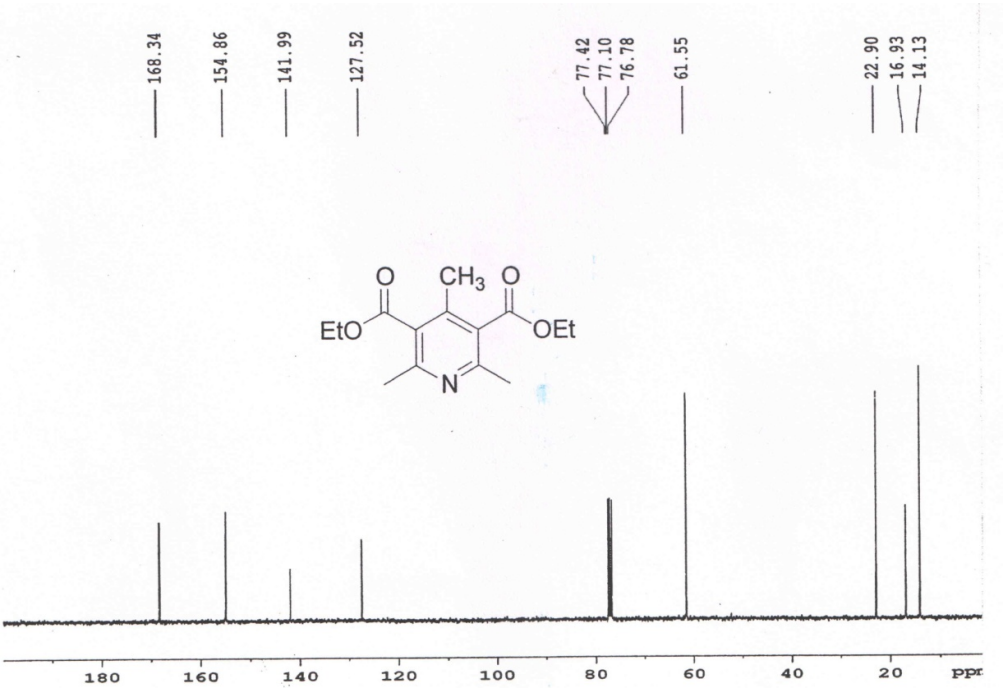
1
ppm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60
40
20
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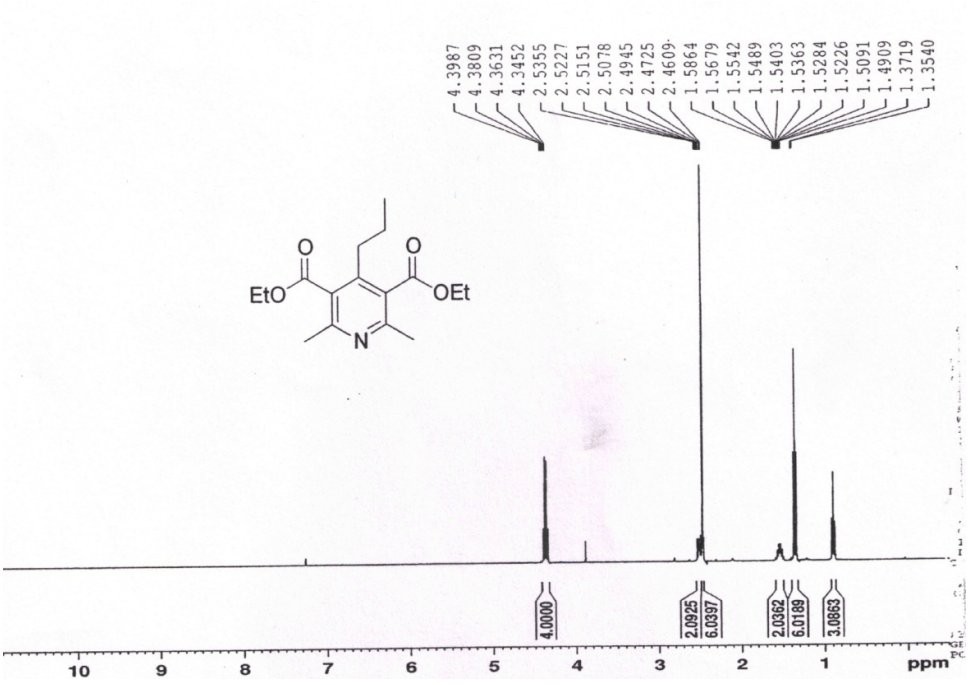
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2.5227
2.5151
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1.5542
1.5489
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1.5284
1.5226
1.5091
1.4909
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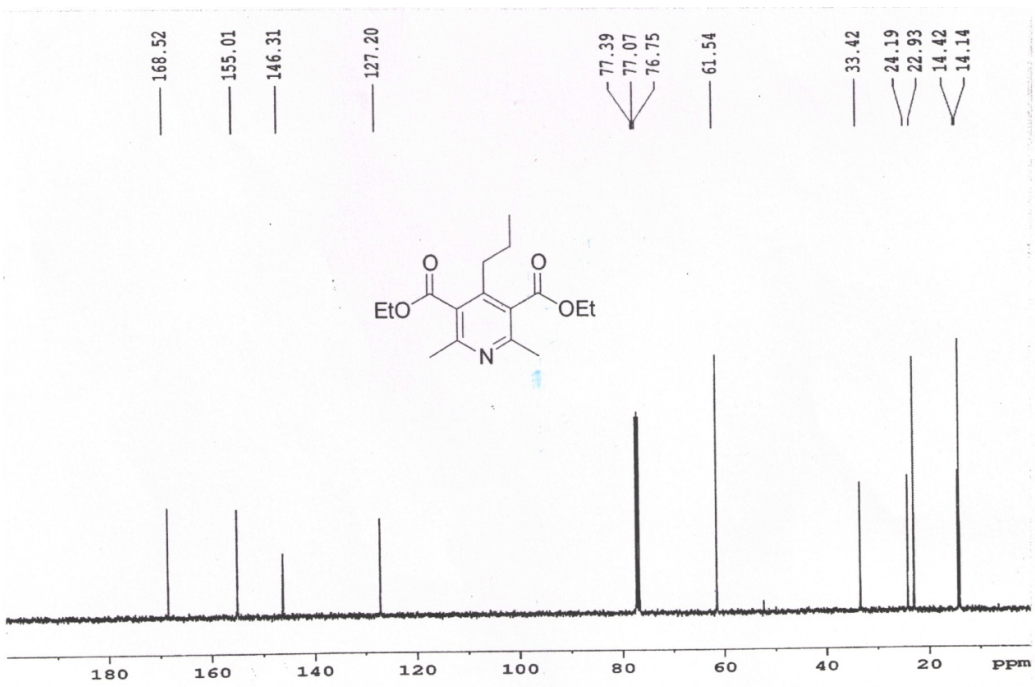
ppm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OEt
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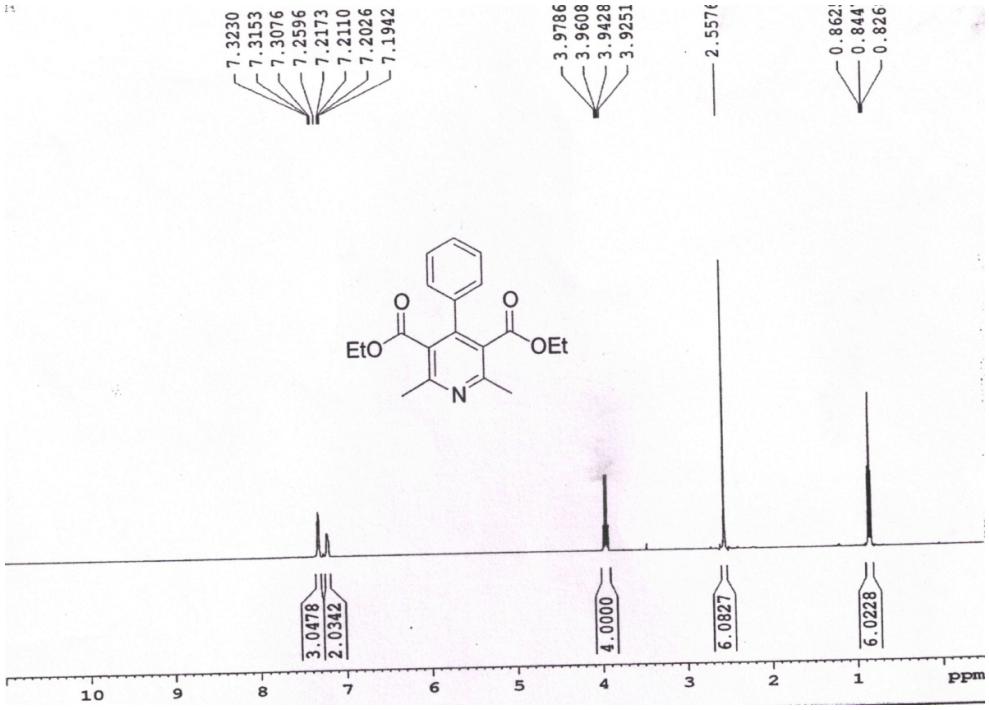
ppm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2.5576
0.8621
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OEt
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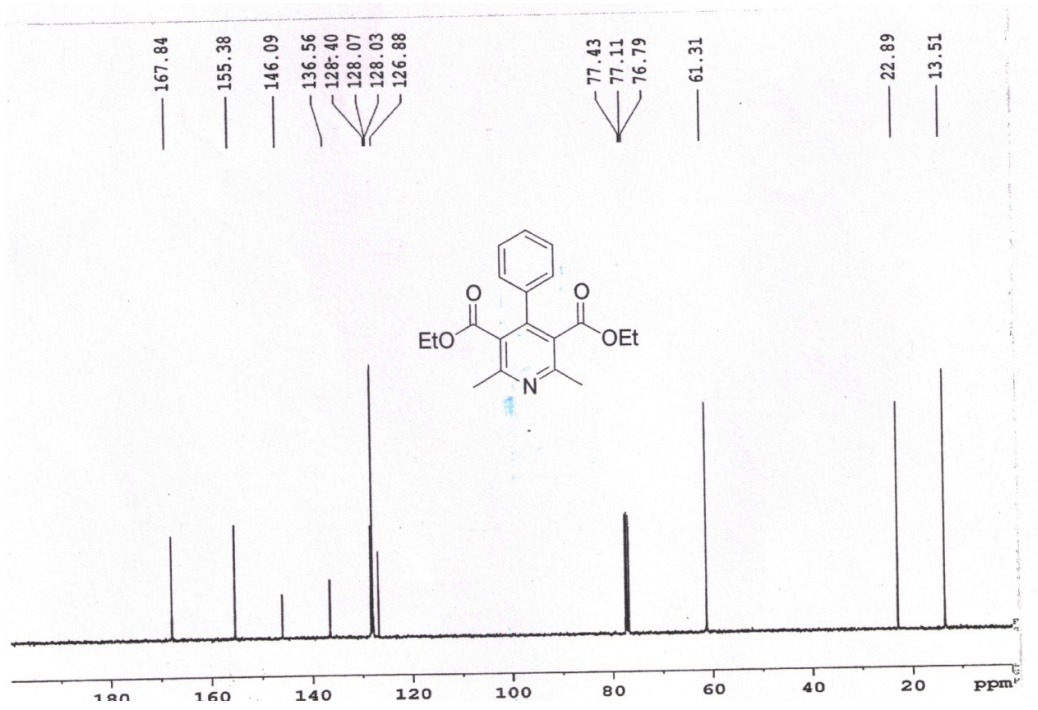
2.0342
4.0000
6.0827
6.0228
10
9
8
7
6
5
4
3
2
1
ppm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128.03
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22.89
13.51
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OEt
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140
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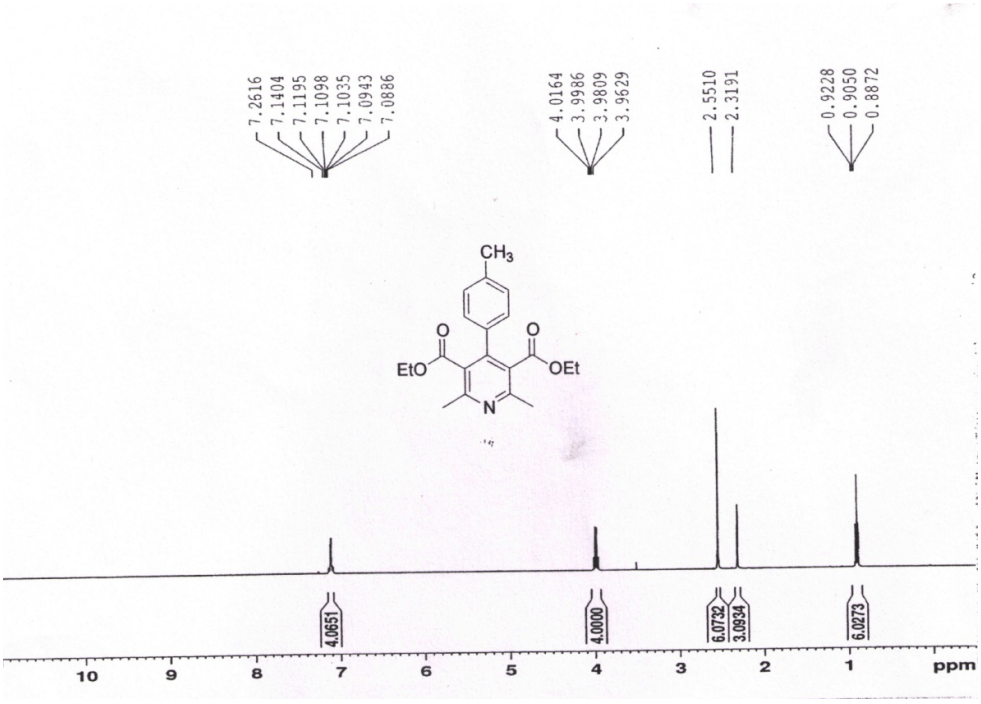
80
60
40
20
ppm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3.9629
2.5510
2.3191
0.9228
0.9050
0.8872
CH3
EtO
OEt
N
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3.0934
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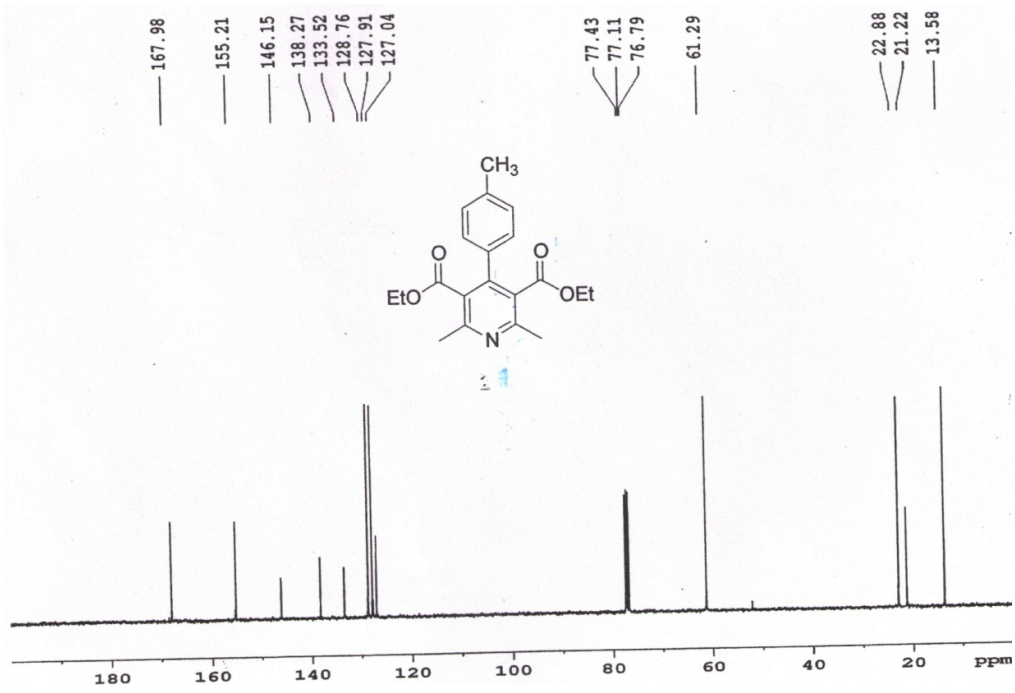
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146.15
138.27
133.52
128.76
127.91
127.04
77.43
77.11
76.79
61.29
22.88
21.22
13.58
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EtO
OEt
N
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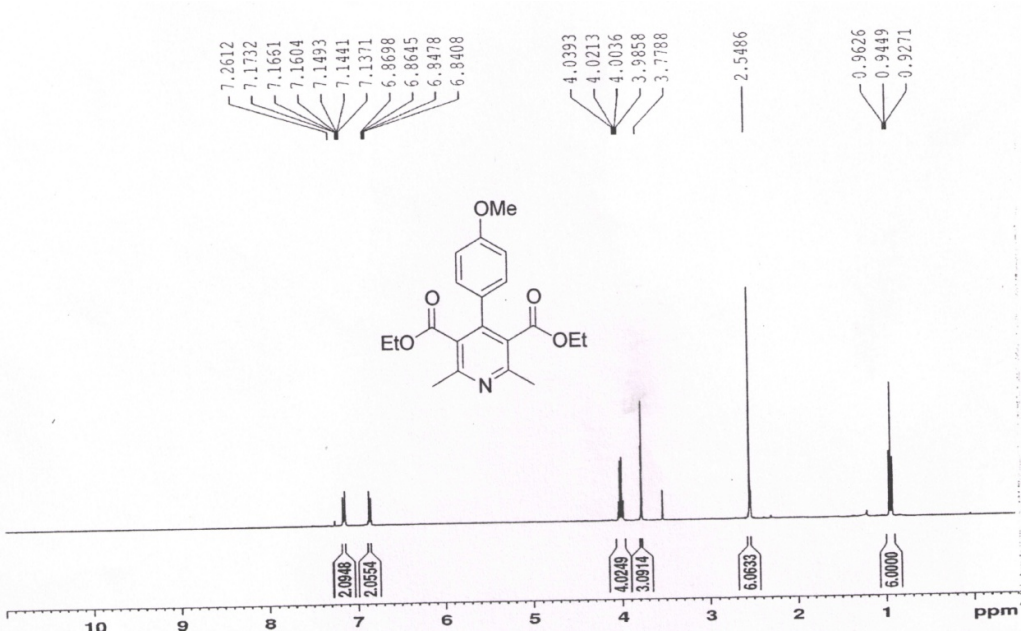
160
140
120
100
80
60
40
20
ppm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7.1493
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7.1371
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6.8645
6.8478
6.8408
4.0393
4.0213
4.0036
3.9858
3.7788
2.5486
0.9626
0.9449
0.9271
OMe
O
O
EtO
OEt
N
2.0948
2.0554
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3.0914
6.0633
6.0000
10
9
8
7
6
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4
3
2
1
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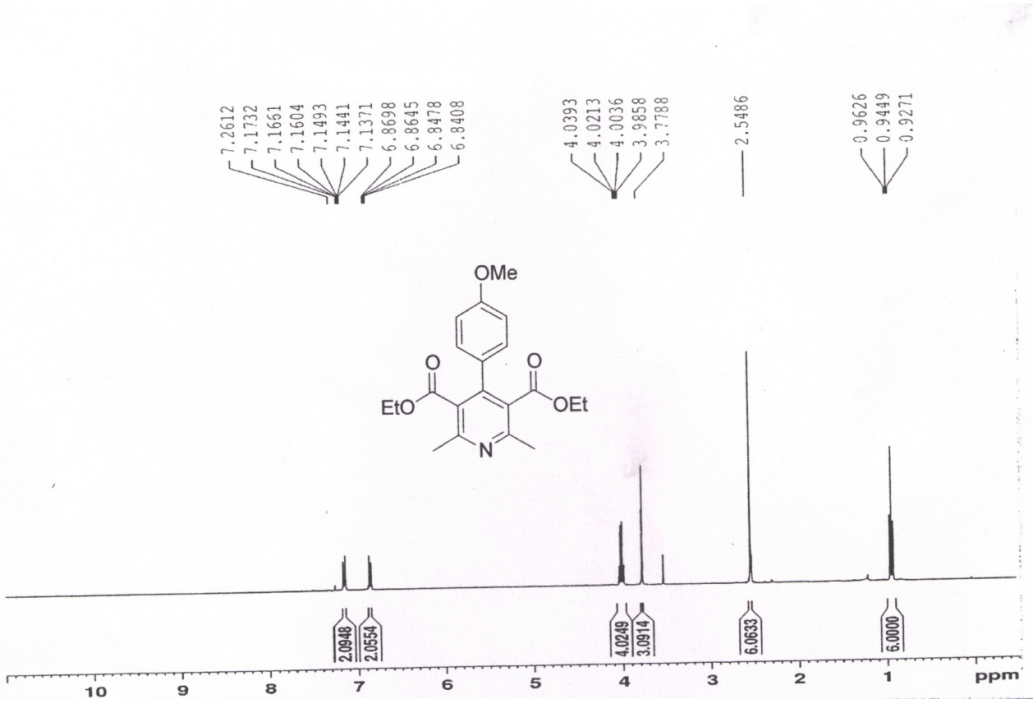
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6.8645
6.8478
6.8408
4.0393
4.0213
4.0036
3.9858
3.7788
2.5486
0.9626
0.9449
0.9271
OMe
O
O
EtO
OEt
N
2.0948
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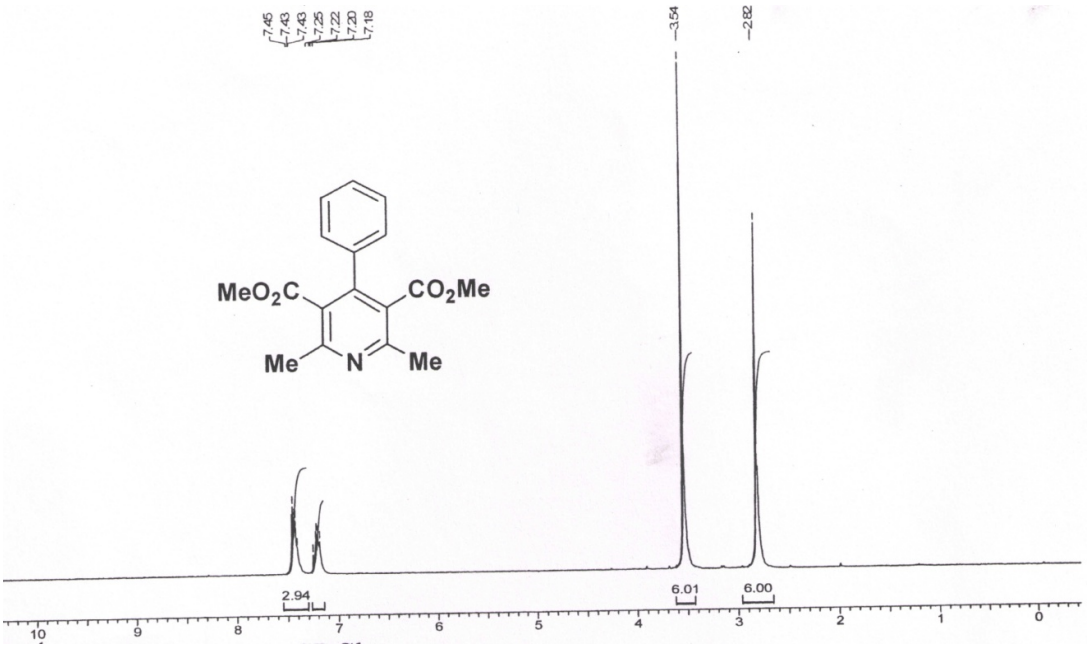
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7.43
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7.20
7.18
3.54
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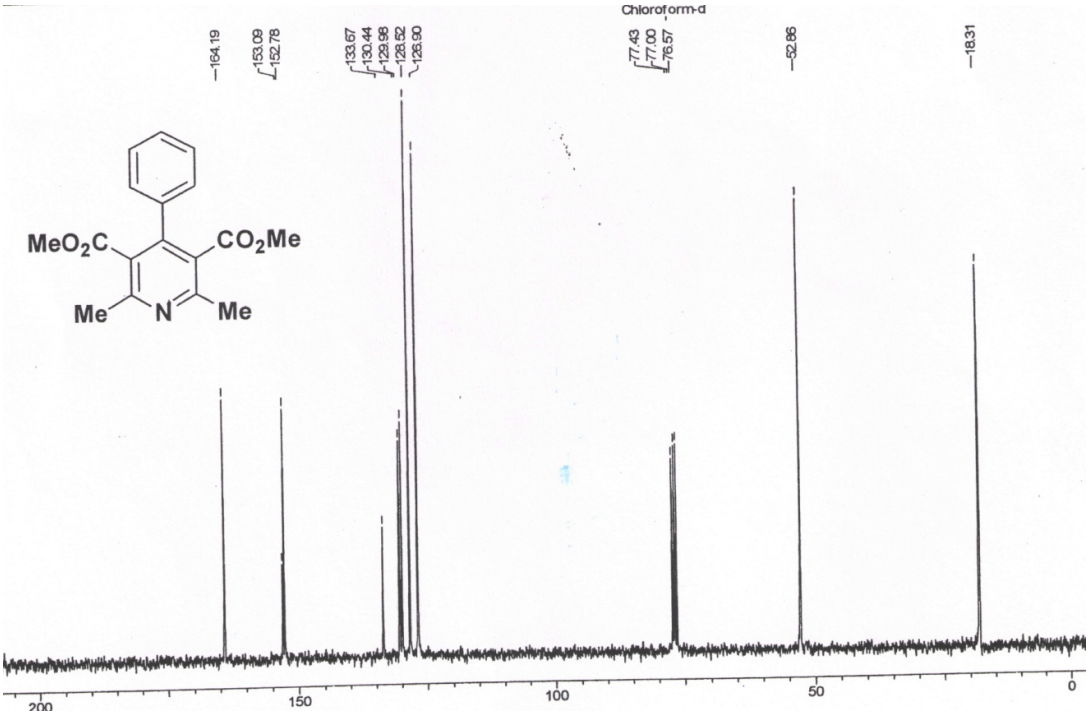
CO2Me
Me
N
Me
2.94
6.01
6.00
10
9
8
7
6
5
4
3
2
1
0


Chloroform-d
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129.98
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128.90
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77.00
76.57
52.86
18.31
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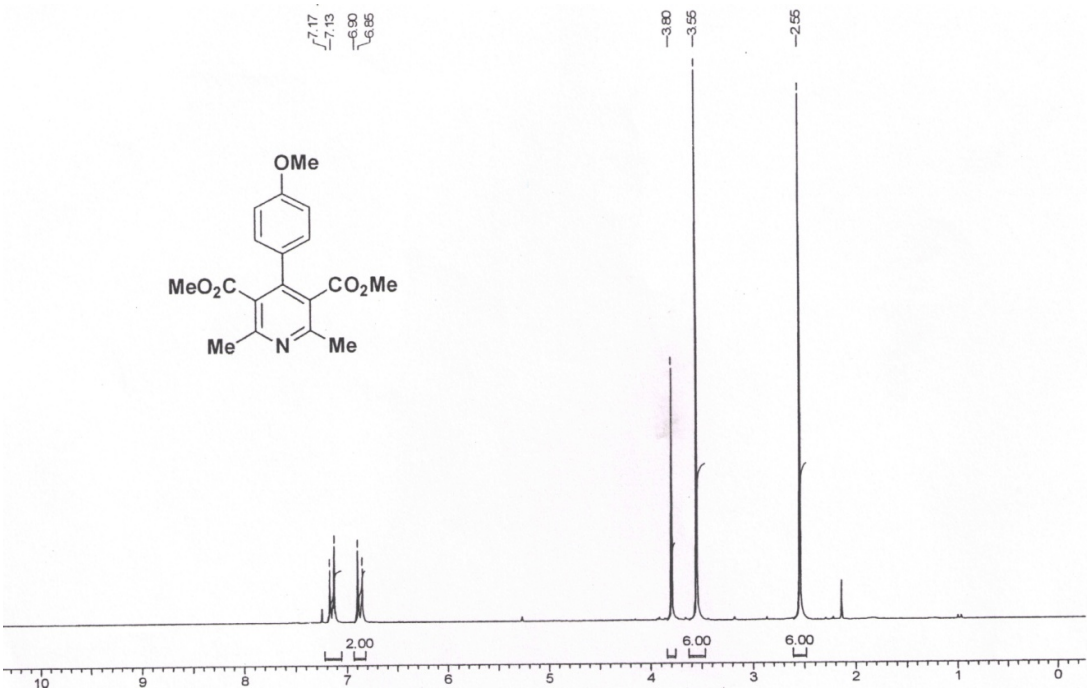
CO2Me
Me
N
Me
200
150
100
50
0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3.80
3.55
2.55
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MeO2C
CO2Me
Me
N
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6.00
6.00
10
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8
7
6
5
4
3
2
1
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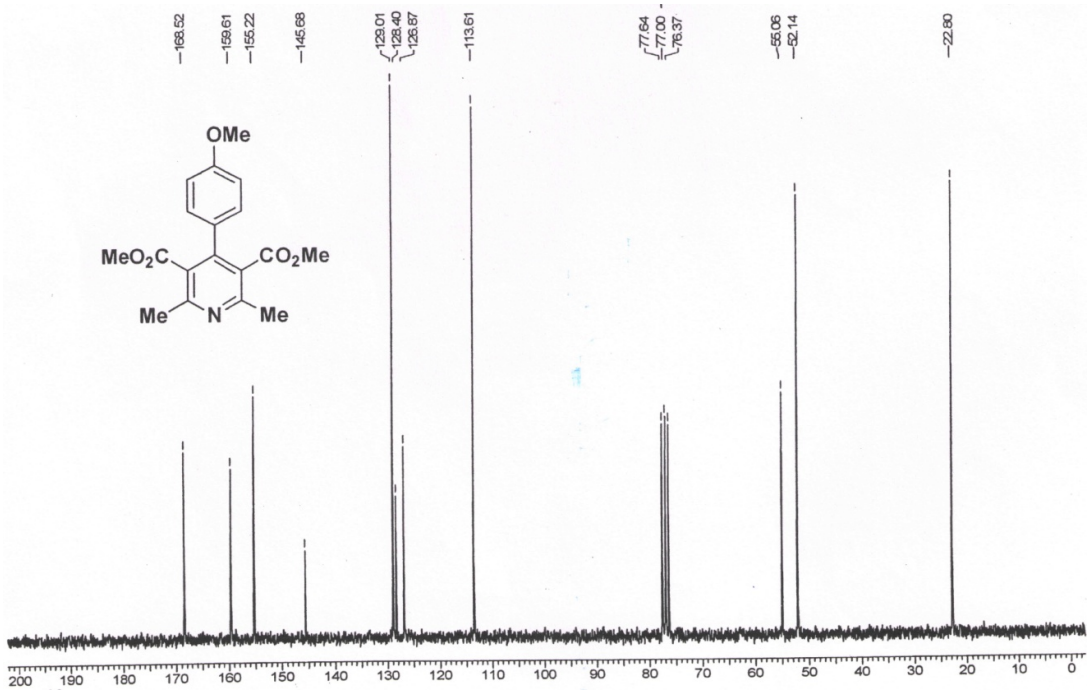
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155.22
145.68
129.01
128.40
126.87
113.61
77.64
77.00
76.37
55.06
52.14
22.80
OMe
MeO2C
CO2Me
Me
N
Me
200
190
180
170
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150
140
130
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110
100
90
80
70
60
50
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30
20
10
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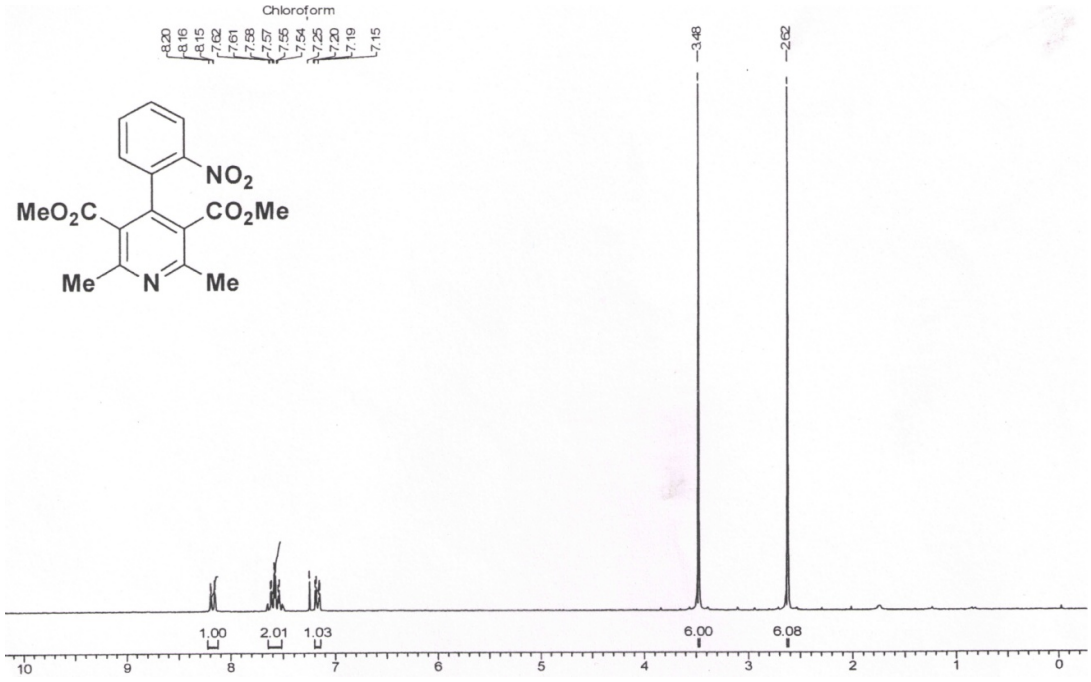
Chloroform
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8.15
7.62
7.61
7.58
7.57
7.55
7.54
7.25
7.20
7.19
7.15
3.48
2.62
NO2
MeO2C
CO2Me
Me
N
Me
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1.03
6.00
6.08
10
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8
7
6
5
4
3
2
1
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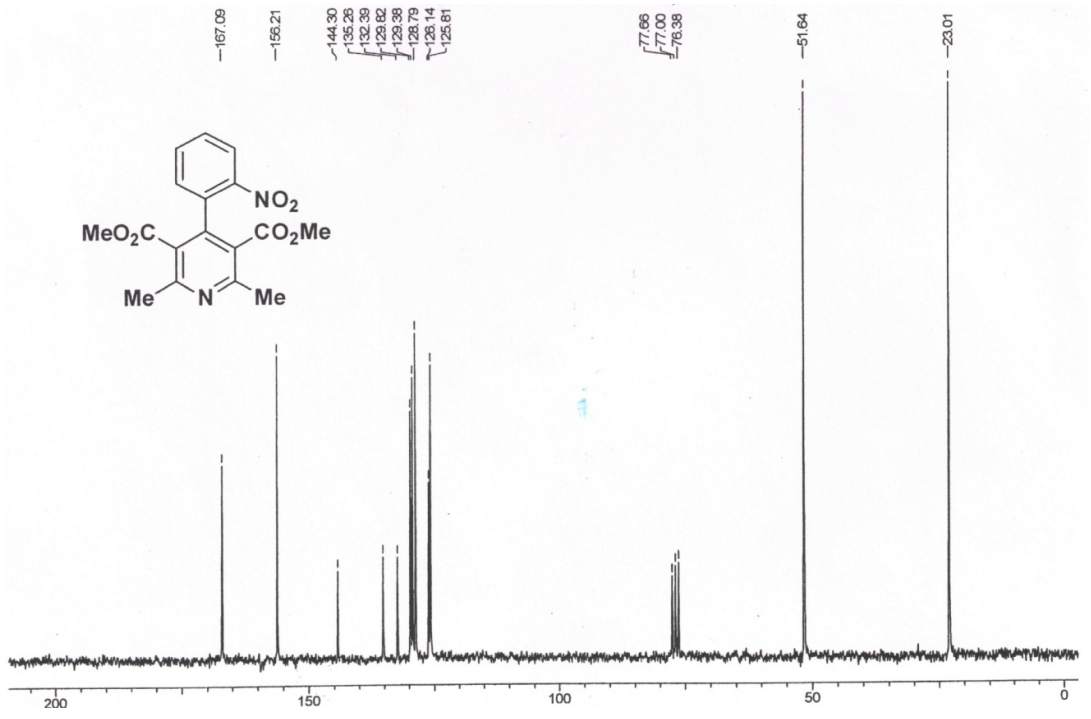
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126.14
125.81
77.66
77.00
76.38
51.64
23.01
NO2
MeO2C
CO2Me
Me
N
Me
200
150
100
50
0

References

1. Thaisrivongs, S.; Schostarez, H. J.; Pals, D. T.; Turner, S. R. *J. Med.Chem.* **1987**, *30*, 1837.
2. Schostarez, H. J. *J. Org. Chem.* **1988**, *53*, 3628.
3. Capozzi, G.; Roelens, S.; Talami, S. *J. Org. Chem.* **1993**, *58*, 7932.
4. Suto, Y.; Tsuji, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 3757.
5. Granander, J.; Erikson, J.; Hilmersson, G. *Tetrahedron: Asymmetry* **2006**, *17*, 2021.
6. Soai, K.; Hirose, Y.; Sakata, S. *Tetrahedron: Asymmetry* **1992**, *3*, 677.
7. Mun, S.; Jaesook, L.; Yun, J. *Org. Lett.* **2006**, *8*, 4887.
8. Li, Y.; Li, F.; Wang, Q.; Tao, F. *Org. Biomol. Chem.* **2005**, *3*, 2513.
9. Watanabe, M.; Murata, K.; Takao, I. *J. Org. Chem.* **2002**, *67*, 1712.
10. Ahemmad, K.; Khanna, G. R.; Ramu, R. *Tetrahedron: Asymmetry* **2002**, *13*, 2039.
11. Itoh, T.; Mitsukura, K.; Takagi, Y.; Kihara, H.; Tsukube, H. *J. Org. Chem.* **1997**, *62*, 9165.
12. Kamila, S.; Biehl, R.; Ling, H. *Org. Lett.* **2006**, *8*, 4429.
13. Haribabu, A.; Dunming, Z.; Yang, Y.; Edward, B.; Hua, L. *J. Org. Chem.* **2009**, *74*, 7932.
14. (a) Miller, R. J.; Freedman, S. B. *Life Sci.* **1984**, *34*, 1205–1221; (b) Freedman, D. D.; Waters, D. *D. Drugs* **1987**, *34*, 578; (c) Catterall, W. A.; Seagar, M. J.; Takahashi, M. *J. Biol. Chem*. **1988**, *263*, 3535; (d) Meredith, P. A.; Elliott, H. L. *J. Hypertens*. **2004**, *22*, 1641.

15. (a) Guengerich, F. P.; Bocher, R. H. *J. Biol. Chem*. **1988**, *263*, 8168; (b) Guengerich, F. P.; Brian, W. R.; Iwasaki, M.; Sari, M.-A.; Baarnhielm, C.; Berntsson, P. *J. Med. Chem*. **1991**, *34*, 1838.

16. (a) Bioorganic Chemistry; Tamelen, E. E.; Academic: New York, **1978**; 4, 239; (b) Bocker, R. H.; Guengerich, F. P. *J. Med. Chem*. **1986**, *29*, 1596.

17. (a) Friedols, F.; Knox, R. *J. Biochem. Pharmacol.* **1992**, *44*, 631; (b) Janis, R. A.; Triggle,D.J. *J. Med. Chem*. **1983**, *25*, 775; (c) Brewster, M. E.; Simay, A.; Czako, K.; Winwood, D.; Fatag, H.; Bodor, N. *J. Org. Chem.* **1989**, *54*, 3721.

18. Dong-Ping, C.; Zhen-Chu, C. *Synth Commun., 2002, 32793.*

19. Mirela, F. L.; Malden, L.; Vinkovic, V. *Tetrahedron Lett*. **2008**, 16, 9276.

20. Ajam, C. S.; Chinpiao, C. *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 3664.

21. Majid, M. H.; Hossien, A. O.; Reihane, M.; Behnoush, A.; Hamideh, A.; Rarahnaz, K.B. *Catalysis Communications* **2009,** *10,* 819.

22. Kumar; Parvin *Chinese Journal of Chemistry*, **2009,** *27*, 1487.

23. Xia; Jingjing, Z.; Kehua, J. J. *Chinese Journal of Organic Chemistry*, **2009,** *29*, 1849.

24. Xiali, L.; Wenbin L.; Jun, L.; Chun W. *Tetrahedron Lett*. **2010**, 51, 3859.

25. Hematshoar, R.; Akram, R.; Masoumeh, H.; Azadeh, J. O.; Sodeh, S. *J. Chin. Chem. Soc.,* **2009***, 56,* 40.

26. Pfister, J. R. *Synthesis* **1990**, 689.

27. Vanden Eynde, J.J.; D Orazio, R.; Haverbeke, Y. V. *Tetrahedron* **1994**, *50*, 2479.

28. Singer, A.; McElvain, S. M. *Org. Synth.* **1934,** *14*, 30.

29. Vanden Eynde, J.-J.; Mayence, A.; Maquestiau, A. *Tetrahedron* **1992**, *48*, 463.

30. Lopez-Alarcon, C.; Nunez-Vergara, L. J.; Squella, J. A. *Electrochim. Acta* **2003**, *48*, 2505.

31. Mashraqui, S. H.; Karnik, M. A. *Tetrahedron Lett*. **1998**, 39, 4895.

32. Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Synthesis* **2004**, 1015.

33. Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett*. **2002**, *4*, 3955.

34. (a) Laurence, H. J. *Chem. Educ.,* **1977**, *54*, 327; (b) Alanxander, M.; William, R. S. *Tetrahedron*, **1995**, *51,* 6145; (c) Victoria, M. G.; Ruben, C.; Ester, V.; Moreno, Antonio, H.; Angel, D. Green Chem., **2007**, *9*, 331; (d) Pilarski, L. T.; Janson, P.G.; Szabo, K. J. , *J. Org. Chem.*, **2011**, *76*, 1503; (e) Hussain, M. M.; Hussain, H. L.; Urena, P. J.; Carroll, P.; Walsh, J. *J. Am. Chem. Soc.*, **2009**, *131*, 6516; (f) McKillop, A.; Kemp, D. *Tetrahedron*, **1989**, *45*, 3299; (g) Firouzabadi, H.; Iranpoor, N.; Amani, K. *Green Chemistry,* **2001**, *3*, 131-132; (h) Muzart, J. *Synthesis*, **1995**, 1325; (i) McKillop, A.; Sanderson, W. R. J.Chem. Soc., *Perkin Transactions 1*, **2000**, 471.

35. Tamaddon, F.; Razmi, Z.; Abbas, A. J. *Tetrahedron Lett*. **2010**, 51, 1187.