Synthetic studies towards biotin, oxybiotin , *α*-lipoic acid and scalable synthesis of 3-ethyl-4-methyl- 1, 5-dihyro-2*H*-pyrrole-2-one and development of synthetic methodologies.

by

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Under the supervision of

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I Mr. Ambaji Agnerao Pawar, a Ph.D. student of the Academy of Scientific and Innovative Research (AcSIR) with Registration No. 10CC14A26006 hereby undertake that, the thesis entitled "Synthetic studies towards biotin, oxybiotin , α-lipoic acid and scalable synthesis of 3-ethyl-4-methyl- 1,5-dihyro-2H-pyrrole-2-one and development of synthetic methodologies" has been prepared by me and that the document reports original work carried out by me and is free of any plagiarism in compliance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* and the CSIR Guidelines for "*Ethics in Research and in Governance (2020)".*

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Date : 27/07/2021
Place : Pune

Dedicated to

....To my beloved parents and teachers

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Section 1: Synthetic study towards the synthesis of 3-ethyl-4-methyl- 1,5- dihyro-2*H*- . pyrrole-2-one.

Chapter 3

Development of the synthetic methodologies.

Section 1: Solvent free, microwave assisted unusual C-alkylation of phenols with PMB using imidazolium ionic liquid as the green and eco-friendly catalyst.

Abbreviations:

- **Units**

°C	Degree centigrade
mg	Milligram
h	Hour
Hz	Hertz
µg	Microgram
mL	Millilitre
min	Minutes
MHz	Megahertz
mmol	Millimole
ppm	Parts per million

- **Chemical Notations**

Ac_2O	Acetic anhydride
AcOH	Acetic acid
AcCl	Acetyl chloride
AIBN	Azobisisobutyronitrile
$AlCl_3$	Aluminium chloride
ALA	Alpha lipoic acid
API	Active pharmaceutical ingredient
AllylMgCl	Allylmagnesium chloride

AllylBr	Allyl bromide
BnBr	Benzyl bromide
n-BuLi	*n*-Butyllithium
n-Bu_3SnH	Tributyltin hydride
t-BuOH	*tert*-Butyl alcohol
$(Boc)_2O$	Di-*tert*-butyl dicarbonate
Cs_2CO_3	Cesium carbonate
CH_2O	Formaldehyde
HCO_2H	Formic acid
CH_3CHO	Acetaldehyde
CH_3CN	Acetonitrile
$CHCl_3$	Chloroform
$COCl_2$	Phosgene
CuI	Copper(I) iodide
CuBr	Copper(I) bromide
CuCN	Copper(I) cyanide
$Cu(OAc)_2$	Cupric acetate
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DABCO	1,4-Diazabicyclo(2.2.2)octane
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulphoxide
DMF	*N*,*N*-Dimethylformamide

DIBAL-H	Diisobutylaluminium hydride
DEPT	Distortionless enhancement by polarization transfer
dr	*Diastereomeric ratio*
CH_2N_2	Diazomethane
Et_2O	Diethyl ether
ee	*Enantiomeric excess*
Et	Ethyl
EtOH	Ethanol
EtOAc	Ethyl acetate
Et_3N	Triethylamine
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HCl	Hydrochloric acid
IR	Infra-red
MeI	Iodomethane
K_3PO_4	Tripotassium posphate
K_2CO_3	Potassium carbonate
$KMnO_4$	Potassium permanganate
$LiAlH_4$	Lithium aluminium hydride
LiOH	Lithium hydroxide
$LiBH_4$	Lithium borohydride
LiBr	Lithium bromide

m-CPBA	*meta*-Chloroperoxybenzoic acid
M+	Molecular ion
Me	Methyl
MeOH	Methanol
Min	Minute
Mg	Magnesium
Mp	Melting point
MS	Molecular sieves
MsCl	Methanesulfonyl chloride
NaH	Sodium hydride
NaI	Sodium iodide
NaCl	Sodium chloride
NaOH	Sodium hydroxide
$NaIO_4$	Sodium periodate
$NaBH_3CN$	Sodium cyanoborohydride
NH_4Cl	Ammonium chloride
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
NaHMDS	Sodium hexamethyldisilazide
$NaBH_4$	Sodium borohydride
NaOMe	Sodium methoxide
OsO_4	Osmium tetroxide
$(COCl)_2$	Oxalyl chloride
Pd/C	Palladium on activated charcoal

PDC	Pyridinium dichromate
KOH	Potassium hydroxide
t-BuOK	Potassium *tert*-butoxide
Ph	Phenyl
PPh_3	Triphenylphosphine
PCC	Pyridinium chlorochromate
$PdCl_2$	Palladium(II) chloride
$POCl_3$	Phosphoryl chloride
Py	Pyridine
Rf	Retention factor
$SOCl_2$	Thionyl chloride
H_2SO_4	Sulfuric acid
$AgSbF_6$	Silver hexafluoroantimonate(V)
Ag_2O	Silver oxide
$NaHCO_3$	Sodium bicarbonate
Na_2SO_4	Sodium sulfate
TBAF	*Tetra-n*-butylammonium fluoride
Et_3SiH	Triethylsilane
TBSCl	*tert*-Butyldimethylsilyl chloride
TMEDA	Tetramethylethylenediamine
TBHP	*tert*-Butyl hydroperoxide
p-TSA	*p*-Toluenesulfonic acid
$TsNHNH_2$	*p*-Toluenesulfonhydrazide
THF	Tetrahydrofuran

$TiCl_4$	Titanium tetrachloride
TLC	Thin layer chromatography
TFA	Trifluoroacetic acid
TMSCl	Trimethylsilyl chloride
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Zn	Zinc
$ZnCl_2$	Zinc chloride

General Remarks:

- Deuterated solvents for NMR spectroscopic analyses were used as received. All ^{1}H NMR and ^{13}C NMR and 2D NMR analysis were obtained using a Bruker or JEOL 200 MHz, 400 MHz or 500 MHz spectrometers. Coupling constants were measured in Hertz. All chemical shifts are quoted in ppm, relative to TMS and $CHCl_3$ in $CDCl_3$, using the residual solvent peak as a reference standard. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br =broad.
- HRMS spectra were recorded at UHPLC-MS (Q-exactive-Orbitrap Mass Spectrometer) using electron spray ionization [(ESI^{+}+/- 5kV), solvent medium: water, acetonitrile, methanol and ammonium acetate] technique and mass values are expressed as m/z. GC-HRMS (EI) was recorded in Agilent 7200 Accurate-mass-Q-TOF.
- Infrared spectra were scanned on Bruker ALPHA spectrometers with sodium chloride optics and are measured in cm^{-1}
- Optical rotations were measured with a JASCO P-2000 digital polarimeter.
- Melting points were recorded on Buchi M-535, M-560 melting point apparatus and are uncorrected and the temperatures are in centigrade scale.
- All reactions are monitored by Thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, Iodine adsorbed on silica gel or by immersion in ethanolic solution of phosphomolybdic acid (PMA), p-anisaldehyde or $KMnO_4$ followed by heating with a heat gun for ~15 sec.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- Column chromatography was performed on silica gel (100-200 or 230-400 mesh size).
- Chemical nomenclature (IUPAC) and structures were generated using Chem Draw Professional 15.1. v
- Reactions were carried out in oven-dried glassware under a positive pressure of argon unless otherwise mentioned with magnetic stirring. Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa.

- The compounds, scheme and reference numbers given in each section of chapter refers to that particular section of the chapter only.
- All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification.

	Synthetic studies towards towards biotin, oxybiotin, *α*-lipoic acid and scalable synthesis of 3-ethyl-4-methyl- 1, 5-dihyro-2*H*-pyrrole-2-one and development of synthetic methodologies.
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Research Supervisor	Dr. Subhash P. Chavan

Introduction:

The medicinally important molecules have always attracted the attention of synthetic chemists. In the present work medicinally important compounds have been synthesized and described. The thesis is divided into three chapters. Chapter **1** deals with the synthetic studies towards biotin, oxybiotin and *epi*-oxybiotin using isosorbide as the starting material. Chapter **2** is divided into two sections. Section **1** deals with synthetic studies towards *α*-lipoic acid and section **2** deals with 3-ethyl-4-methyl-1, 5-dihydro-2*H*-pyrrol-2-one. Chapter **3** is divided into two sections. Section **1** and Section **2** which deals with the study of synthetic methodologies. Section **1** includes the C-alkylation of phenols by using ionic liquid as the catalyst and the section **2** deals with *N*-PMB/benzyl alkylation of amides using ionic liquid as a catalyst.

Statement of problem and objectives:

Chapter 1:

Section A: Synthetic studies towards biotin, oxybiotin and *epi*-oxybiotin by using isosorbide as the starting material.

Introduction:

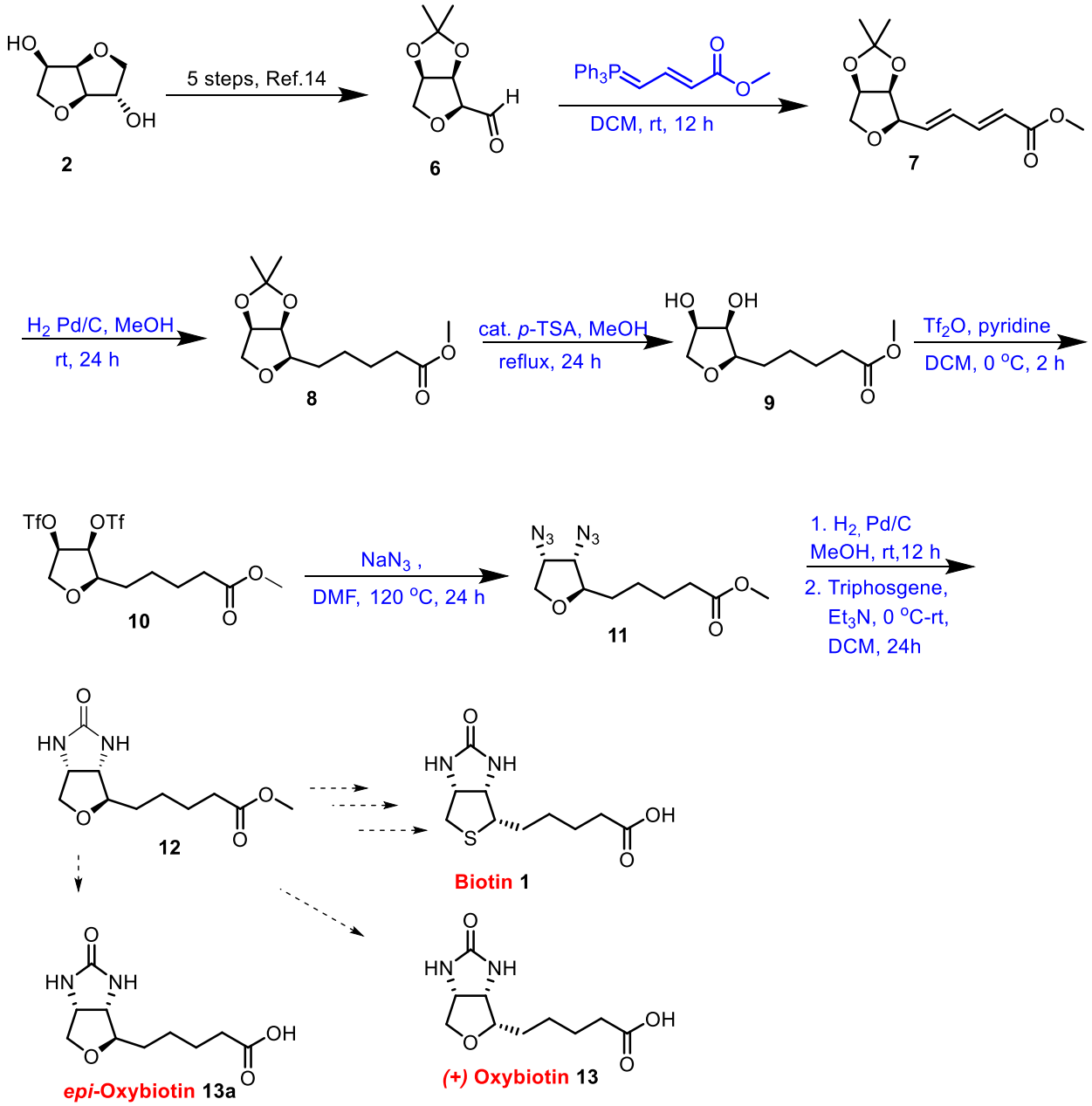
Biotin **1** is the well known vitamin which is dissolvable in water. In addition, the biotin is familiar as the "Vitamin H." Biotin was isolated separately from the three natural raw materials. In the beginning the biotin was characterized by Kong *et al*. as the growth for the yeast in the form of its methyl ester in the year 1936.[1] Further, this was mentioned as the "bios IIb" and later on it was named as the "biotin." The similar substance was also known as the "co-enzyme R" by the Nilssonet and the co-workers.[2] However, in the year 1936 the isolation of the biotin was achieved by West *et al.* from the root nodule bacteria of the genus *Rhizobium trifoli*.[3] Also, the researcher Boas observed that the consumption of the more amount of egg white in rats caused serious disorders which led to death.[4] Owing to the dramatic changes of the illness by the biotin, the substance was also called "protective factor X". Finally, Gyorgyet *et al*.[5] assured the specification of this substance as the biotin and co-enzyme R and dubbing it as the "Vitamin H." Biotin is a co-enzyme for the carboxylation enzyme which has the important role in the fatty acid metabolism.

Oxybiotin is another active analogue of such an important molecule biotin. It is proved that oxybiotin has biotin like activity for many species such as bacteria, yeast and rats and chicken.[6-10] The ability of oxybiotin to replace biotin is inferred to its capacity to carry out few of the functions as like biotin. In addition to this, many oxybiotin analogues have been synthesized and studied e.g. sulphonic acid analogues of oxybiotin and homooxybiotin were synthesized and studied by the Klaus Hoffman *et al.*[11] Also, in the year 1949 the synthesis of *epi*-oxybiotin and the racemic 3, 4-diamino-2-tetrahydrofuran valeric acids was reported by the Klaus Hoffman *et al.*[12] Additionally, the total synthesis of *dl*-oxybiotin was also reported by the Klaus Hoffman *et al*.[13] However, we found that there is only one synthesis named *epi*-oxybiotin was reported in the year 1949 by Klaus Hoffman *et al*.[12] This turned the attention for the synthesis of the *epi*-oxybiotin. Thus the synthesis of *epi*-oxybiotin starting from isosorbide was initiated.

Synthesis of biotin, oxybiotin and *epi*-oxybiotin by using isosorbide:

The synthesis started by using commercially available starting material *viz*- Isosorbide **2**. The isosorbide **2** was converted to the aldehyde **6** by the utilization of the known experimental procedures reported in the literature. In addition, the Wittig reaction of this aldehyde **6** with 4-

carbon Wittig salt in DCM at room temperature for 12 h furnished the unsaturated ester **7** and subsequently this unsaturated ester **7** was then subjected for the hydrogenation reaction by using H_2, Pd/C in MeOH at room temperature for 24 h to get the saturated ester **8**. In addition to this, the saturated ester **8** which is having acetonide functionality was subjected to acetonide deprotection by using cat. *p*-TSA in MeOH at reflux conditions for 24 h to afford the diol ester **9** as depicted in the below **Scheme 1**.



Scheme 1: Synthesis of biotin, oxybiotin and *epi*-oxybiotin.

Further this diol ester **9** was reacted with the triflic anhydride and the pyridine at 0 ^{o}C for 2 h to afford the di O-triflate ester **10**. The ester **10** was then treated with NaN_3 in DMF at 120 ^{o}C for 24 h to get the diazide ester **11**.

Further, the diazide ester **11** was reduced to diamine ester by using H_2, Pd/C in MeOH at room temperature for 12 h and this crude diamine ester was then immediately treated with triphosgene and triethylamine to get the urea ester **12.** In addition, few attempts to covert **12** into the biotin failed. Further, by the proper choice of the reagents and conditions the synthesis of the biotin, oxybiotin and *epi*-oxybiotin can be achieved.

Conclusion:

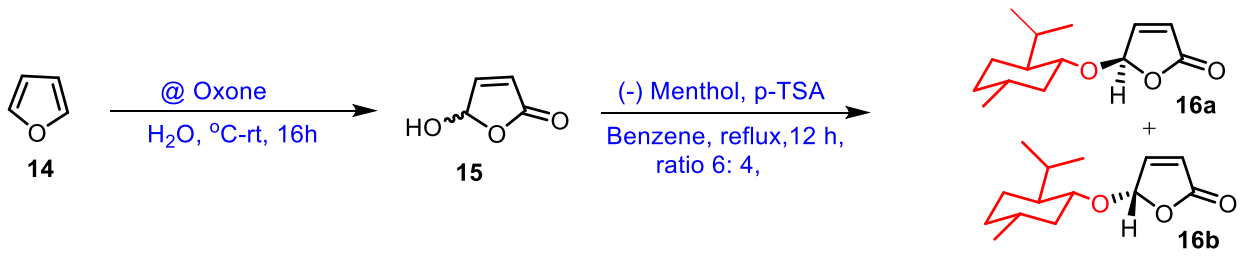
This synthesis utilizes the isosorbide as a starting material which is commercially available. The synthesis is very close to the interim structure of *epi*-oxybiotin. Further, by the use of proper choice of the reagents and conditions the synthesis of the biotin, oxybiotin can be achieved.

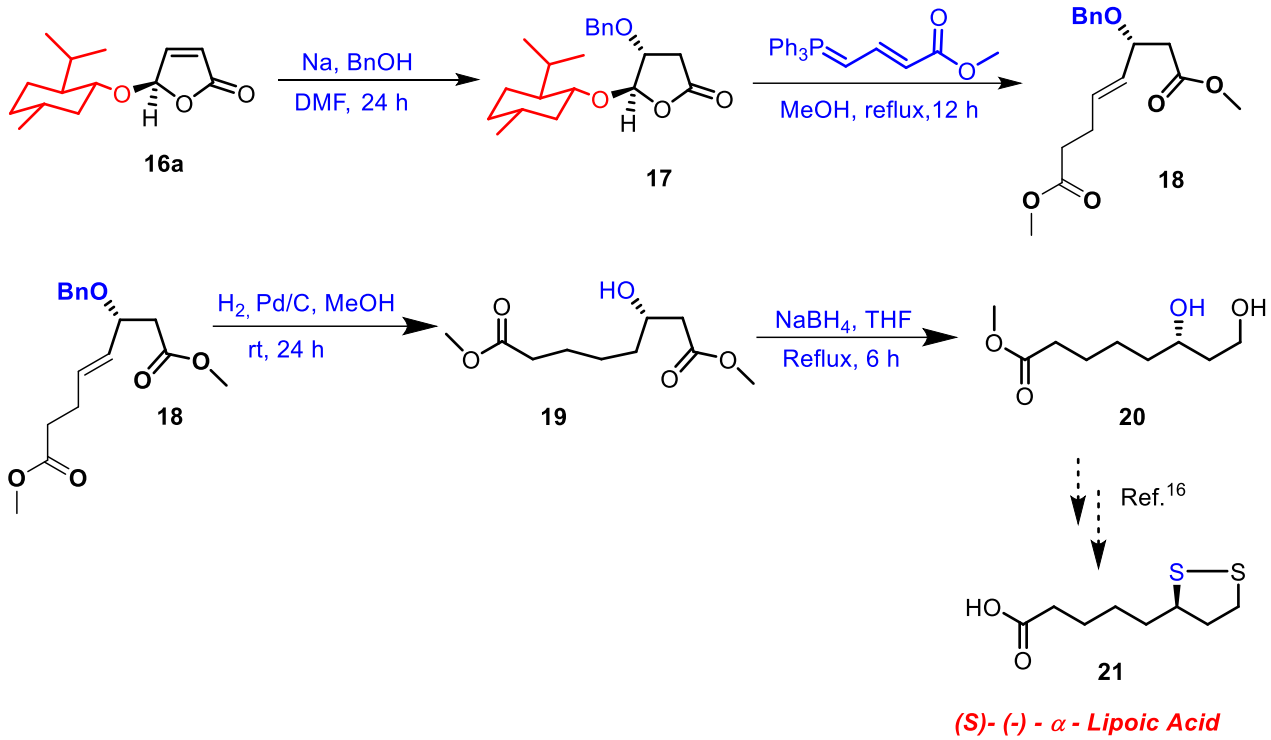
Chapter 2:

Section 1: Synthetic studies towards *α*-lipoic acid using furan as the starting material.

The *α*-lipoic acid or 1, 2-dithiolane-3-pentanoic acid, is a naturally occurring dithiol compound synthesized enzymatically in the mitochondrian from octanoic acid. Lipoic acid is a necessary cofactor for mitochondrial α-ketoacid dehydrogenesis, and thus serves a critical role in mitochondrial energy metabolism. In addition, lipoic acid has been described as a potent biological antioxidant, a detoxification agent and a diabetes medicine. Also, it has been used to improve age associated cardiovascular, cognitive and neuromuscular deficits.[15]

Herein, a different synthetic route for the asymmetric synthesis of *α*- lipoic acid was planned by using modified butenolide approach as shown in the following **Scheme 2**.





Scheme 2: Synthesis of the lipoic acid.

Furan **14** was oxidized to hydroxyl butanolide **15** by using oxone at 0 ^{o}C-rt for 16 h. Further, the protection free hydroxyl group of the butenolide lactone was carried out by treating it with (-) - menthol and cat. *p*-TSA in benzene under reflux conditions by the azeotropic removal of water formed. This led to the formation of the diastereomeric mixture containing the butenolides **16a** and **16b**. In addition, the compound **16a** was recrystalized and was further used in the synthesis. The compound **16a** was subjected for the conjugated addition of the benzyl alcohol by using the cat. sodium metal to afford the lactone **17**. Additionally, the butenolide lactone **17** was treated with 4-carbon Wittig salt in methanol under reflux conditions gave the Wittig reaction product **18**. The olefin **18** was hydrogenated by using the H_2, Pd/C conditions in methanol for 24 h to get the monohydroxy diester compound **19** in good yields. Further, this monohydroxy diester compound **19** was subjected for chemoselctive reduction by using the $NaBH_4$ in the solvent THF under reflux conditions for 6 h to afford the 1,3- diol ester **20** which can be converted to the *S* (-) α- lipoic acid **21** by using the known reactions.[16]

Conclusion:

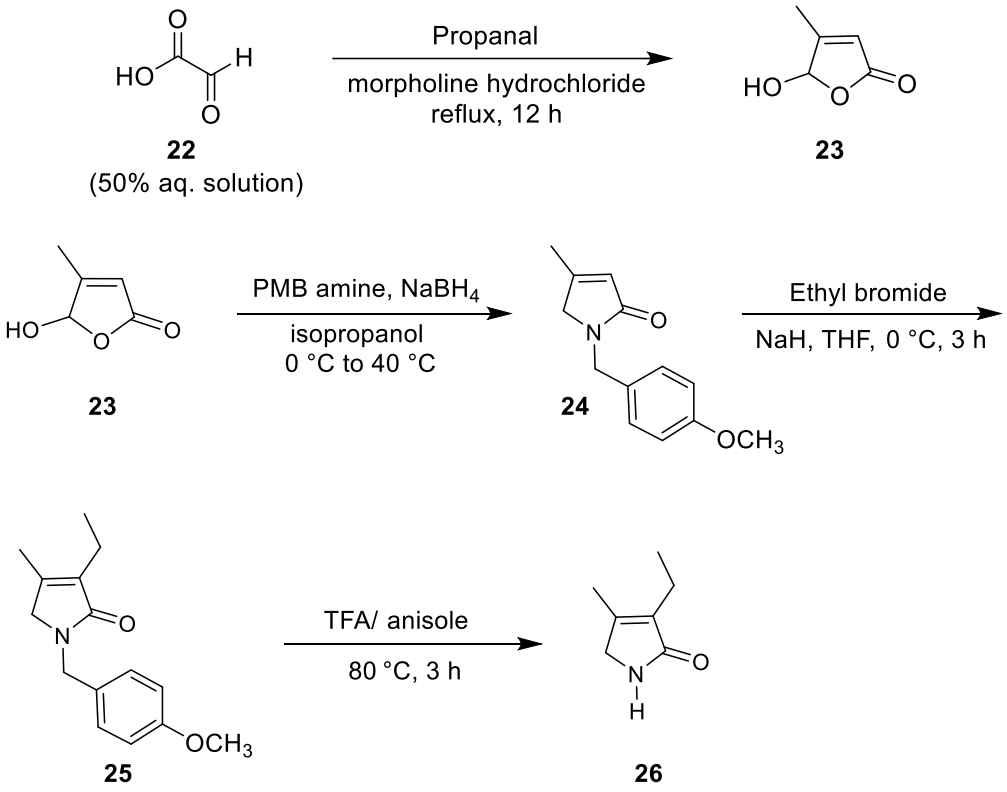
A simple protocol for the synthesis of (*S*) - (-) - α- lipoic acid has been established. The synthesis began by using furan **14** as the starting material which is commercially available and cheap. The

synthesis of (6*S*) - (-) - methyl-6, 8-dihydroxy octanoate **20** has been achieved. The chiral auxiliary alcohol menthol can be recovered. Diol **20** could be converted into (*S*) - (-) -*α*- lipoic acid by known method. Thus it provides a simple route for the synthesis of (*S*) - (-) -*α*-lipoic acid with 94% of ee.

Section 2:

Scalable synthesis of 3-Ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-on: An important building block for antidiabetic drug glimepiride.

The rapid prevalence of diabetes, especially among the middle and low-income countries causes growing concern among the scientific community. In the year 2016, diabetes alone was responsible for the deaths of an estimated 1.6 million people. Herein, the process for the scalable synthesis of 3-ethyl-4-methyl-3-pyrrolin-2-one **26** which is an important component of antidiabetic drug *viz.* glimepiride was initiated **Scheme 3**.



Scheme 3. First-generation approach for the synthesis of **26**.

Our synthesis commenced with the preparation of 3-methyl-4-hydroxy-2-butenolide **23** using glyoxylic acid **22** as the starting material (**Scheme 3**). The glyoxylic acid **22** was reacted with propanal in the presence of the morpholine hydrochloride in water under reflux conditions afforded the compound 3-methyl-4-hydroxy-2-butenolide **23** which was subjected for the reductive lactamization by using PMB amine and the sodium borohydride at 0 ^{o}C - 40 ^{o}C in isopropanal to get the lactam **24**. In addition, this lactam **24** was treated with ethyl bromide in the presence of the sodium hydride at 0 ^{o}C in THF which resulted in the formation of ethylated product **25**. Finally, the debenzylation of the PMB group by using triflic acid in anisole at 80 ^{o}C for 3 h accomplished the synthesis of the 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-on which is an important building block of the antidiabetic drug glimepiride.

Conclusion:

In conclusion, short, cost-effective, and scalable synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-on has been developed. Key features are synthesis of 3-methyl-4-hydroxy-2-butenolide in water, one-pot opening-reductive cyclization of butenolide for the synthesis of five-membered lactam and triflic acid-mediated *N*-benzyl deprotection of lactam.[18]

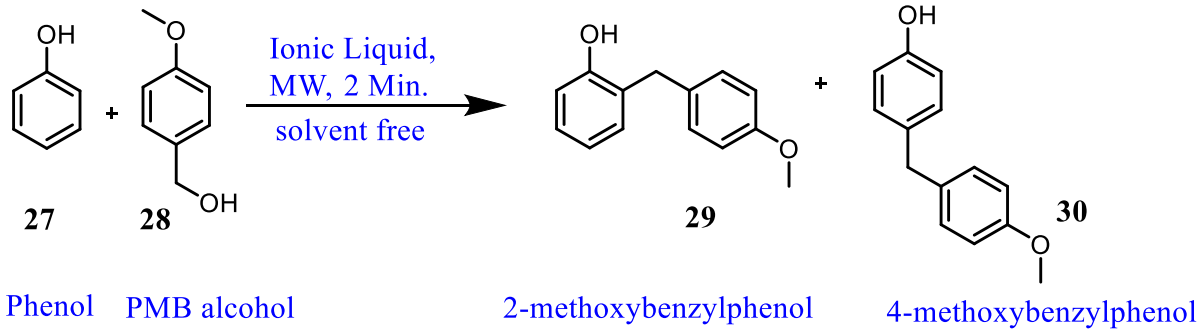
Chapter 3:

Section 1:

C-alkylation of phenols using ionic liquid as a catalyst.

Ionic liquids (ILs) are normally defined as compounds completely composed of ions with melting point below 100 °C. The first IL (ethyl ammonium nitrate) was reported by Paul Walden in 1914, who at that time never realized that ILs would become a major scientific area after almost one century. The imidazolium ionic liquid was synthesized and explored this ionic liquid for PMB alkylation reaction on different substituted phenols. In addition, the same reaction was carried out on different phenols.

When phenol **27** and PMB alcohol **28** were treated with catalytic amount of imidazolium ionic liquid in microwave for 2 minutes, it afforded 2-methoxybenzylphenol **29** and 4-methoxybenzylphenol **30** as shown in the below **Scheme 4**.



Scheme 4: C-alkylation of phenol.

Conclusion:

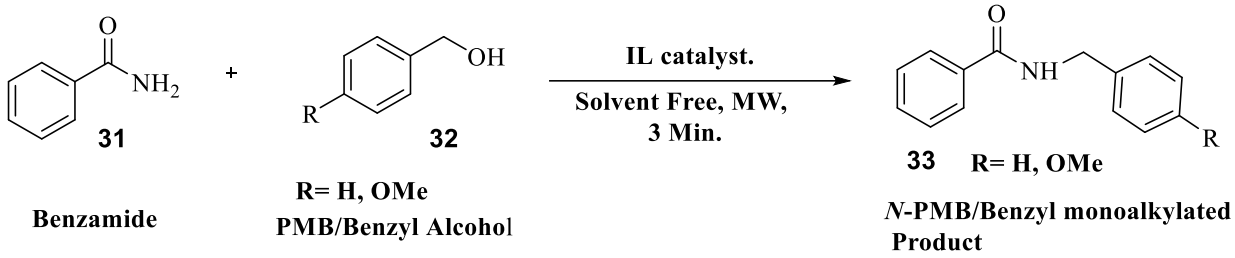
A new methodology for the PMB alkylation of phenols by using imidazolium ionic liquid as a catalyst has been developed. This methodology of PMB alkylation works very efficiently on electron rich phenols. However, with electron deficient phenols the reaction did not work**.**

Section 2:

***N*-PMB/Benzyl alkylation of amides using ionic liquid as a catalyst.**

N-alkylation of amides has extensive demand in the chemical industry, besides this *N*-alkyl amides has potential importance in organic chemistry as many natural products and drugs contain C-N bond linkage in their core structure.[18-21.]

In the present work, microwave assisted ionic liquid catalyzed one pot *N*-alkylation of PMB alcohol and benzyl alcohol with various amides has been described. The initial reaction was carried out on benzamide as a model substrate with PMB alcohol under optimized conditions it afforded mono *N*-PMB-alkyalated product with good yields. Further, the reaction was investigated on the various substrates such as amide, lactam and pyrrolidone. The reaction is as shown in the below **Scheme 5.**



Scheme 5: *N*-PMB/benzyl alkylation of amide.

In conclusion, a novel-one pot, solvent free microwave assisted synthetic rout having short reaction time for the *N*- alkylation of PMB/benzyl alcohol has been developed by using ionic liquid as the catalyst.

Publications:

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Chapter 1

Synthetic studies towards biotin, oxybiotin and epi-oxybiotin by using isosorbide as the starting material

1.1. Introduction:

Biotin **1** is the well known vitamin which is dissolvable in water. In addition, the biotin is familiar as the "Vitamin H." Biotin was isolated separately from the three natural raw materials. In the beginning the biotin was characterized by Kong *et al*. as the growth for the yeast in the form of its methyl ester in the year 1936.[1] Further, this was mentioned as the "bios IIb" and later on it was named as the "biotin." The similar substance was also known as the "co-enzyme R" by the Nilssonet and the co-workers.[2] However, in the year 1936 the isolation of the biotin was achieved by West *et al.* from the root nodule bacteria of the genus *Rhizobium trifoli*.[3] Also, the researcher Boas observed that the consumption of the more amount of egg white in rats caused serious disorders which led to death.[4] Owing to the dramatic changes of the illness by the biotin, the substance was also called "protective factor X". Finally, Gyorgyet *et al*.[5] assured the specification of this substance as the biotin and co-enzyme R and dubbing it as the "Vitamin H." Biotin is a co-enzyme for the carboxylation enzyme which has the important role in the fatty acid metabolism.

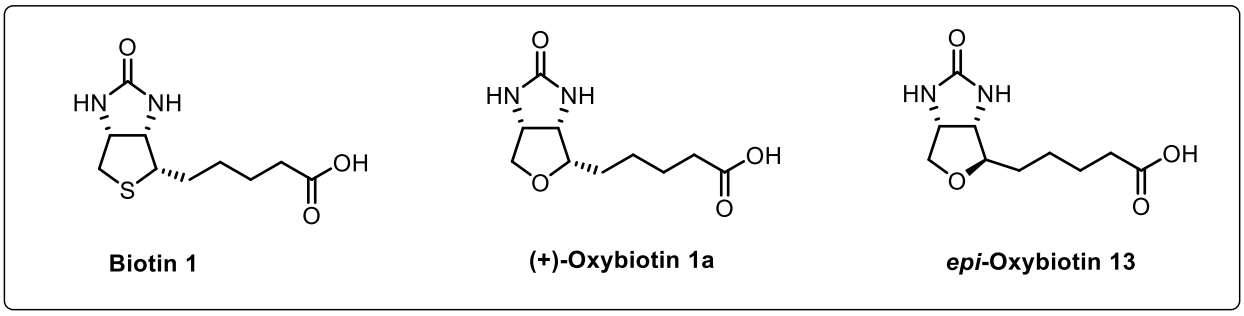


Figure 1: Structure of biotin, (+)-oxybiotin and *epi*-oxybiotin

Oxybiotin **1a** is an active analogue of an important molecule biotin. It is proved that oxybiotin has biotin like activity for many species such as bacteria, yeast and rats and chicken.[6-10] The ability of oxybiotin to replace biotin is inferred to its capacity to carry out few of the functions as like biotin. In addition to this, many oxybiotin analogues have been synthesized and studied e.g. sulphonic acid analogues of oxybiotin and homooxybiotin were synthesized and studied by Klaus Hoffman *et al.*[11] Also, in the year 1949 the synthesis of *epi*-oxybiotin and the racemic 3, 4-diamino-2-tetrahydrofuran valeric acids was reported by Klaus Hoffman *et al.*[12] Additionally, the total synthesis of *dl*-oxybiotin was also reported by Klaus Hoffman *et al*.[13] Furthermore, the activity of the *dl*-oxybiotin for the curing of egg white injury in rats was also studied by Klaus

Hoffman *et al*.[14] This study was carried out by using the growth response as the criteria for the 14 or 28 days therapeutic evaluation procedure. According to this study the *dl*-oxybiotin possessed 4% of activity of the *d*-biotin. Also, it has been stated that the biological activity of few (+)-biotin analogues depends upon the length of the side chain containing the carboxylic group, similar biological activity is anticipated for the (+)-oxybiotin analogues which contain the hetero atom (S or O) in the side chain of carboxylic group.[15] Earlier Hoffman made a conclusion that the biotin and oxybiotin are having similar spacial configurations and both the compounds only differ by the nature of one hetero atom. In terms of desthiobiotin, the yeast could transform it into the biotin. However, this was not happening in the case of oxybiotin. Hoffmann also demonstrated that the yeast utilizes the oxybiotin as it is and it does not transform into biotin. This demonstrative study was based on the fact that the oxidizing agents transform biotin to an inactive sulphone but these oxidizing agents don't attack the oxybiotin. Even though, several biological investigations of biotin analogues reported earlier led to some interesting outcomes, [16, 17, 18] the additional development in this area largely depends on the preparation of the new derivatives of the biotin and oxybiotin. Biotin has got tremendous commercial importance as it is used for treating biotin deficiency associated with different diseases. *e.g*. it is used to treat malnutrition, weight loss, hair loss. It is also used for the brittle nails and skin rash treatment. Additionally, it has been also used to treat the diabetes and depression. As the oxybiotin is having somewhat similar activity as that of biotin, the chemists have taken keen interest in the synthesis of oxybiotin and its analogues. By going through the literature, it was noticed that there is only one synthesis named *epi*-oxybiotin and was reported in the year 1949 by Klaus Hoffman *et al*.[12] This turned the attention for the synthesis of the *epi*-oxybiotin.

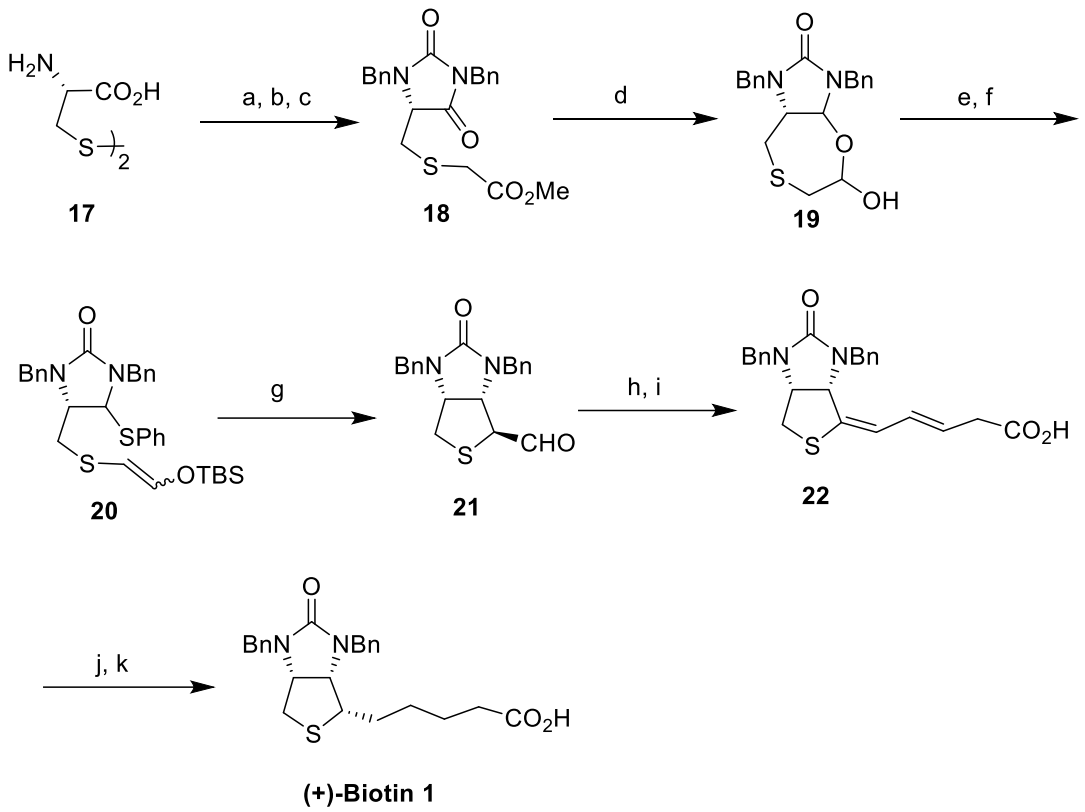
1.2. Literature review:

1. Biotin:

The first time isolation of the biotin from the egg yolk was achieved in the year 1936.[1] Later on it was also isolated from the beef liver as well as the milk concentrates.[19, 20] The biotin molecule is the timeless challenge for the synthetic chemists. The synthesis of biotin has been well reviewed in the year 1997 by the Prof. Pierre J. De Clercq.[21] This group is also actively involved in the synthesis of biotin by using the different strategies for its synthesis. Few of them are described in this literature review section.

Chavan *et al.*[22a] 1st approach

Chavan *et al.* accomplished the synthesis of the (+)-biotin **1** starting from the cystine as shown in the **Scheme 1**.



Scheme 1

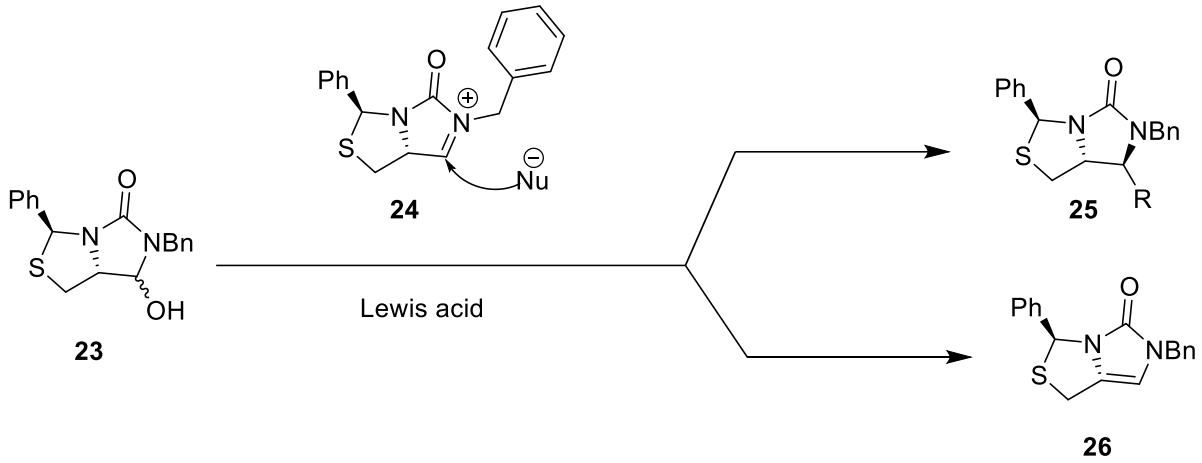
Reagents and conditions: (a) Ref. 22b; (b) (i) BnNCO, DCM, rt, 1 h; (c) p-TSA, rt, 6 h, 90% (two steps); (d) DIBAl-H, Tol, -78 ^{o}C, 2 h, 72 %; (e) PhSH, p-TSA, 0 ^{o}C, 5 min, 70%; (f) DBU, TBSCl, DCM, reflux, 2 h, 92%; (g) p-nitrobenzaldehyde, DCM, TBSOTf, 5 min, 95% (h) Ph_3P=CHCH=CHCOOCH_3, DCM, rt, 12 h, 89 %; (i) 1 M NaOH, MeOH, 0 ^{o}C, 12 h, 97%; (j) 10% Pd-C/H_2 (3 atm.), 8 h, 92 %; (k) 48% HBr, reflux, 2 h, 80%.

The synthesis started with the preparation of the compound **18** which was derived from the cystine. Further, the reduction of the compound **18** was done by the utilization of the DIBAl-H to get the lactol **19**. Additionally, the conversion of the lactol **19** into its thermodynamically more stable aldehyde **21** was achieved by doing reaction with thiophenol and subsequently treating it with TBDMSCl/DBU followed by the reaction of TBDMSOTf in the presence of *p*-

nitrobenzaldehyde which acts the thiophenol scavenger. In addition, the aldehyde **21** was treated with the 4-carbon Wittig reagent with subsequent base promoted deconjugation of the olefinic ester afforded the isomerised acid **22**. Further, the catalytic reduction of the olefin **22** and the debenzylation of the resulting compound by the use of HBr gave the final product D-(+)-biotin **1**.

Chavan *et al.* [23] **2nd approach**

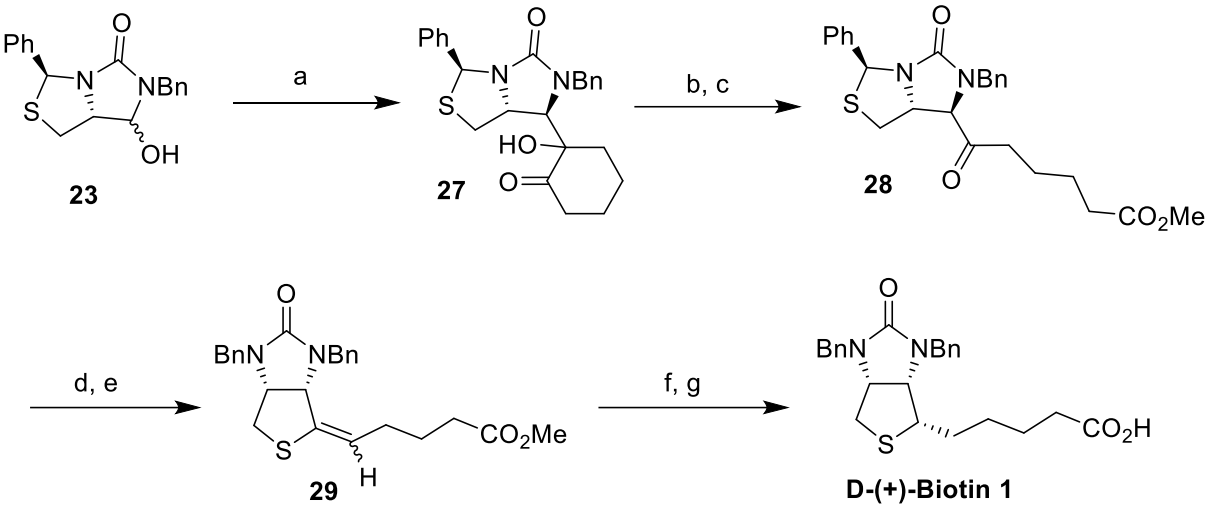
Chavan *et al.* in the year 2005 reported the short and systematic route for the preparation of D-(+)-biotin which consisted stereospecific amidoalkylation reaction of hydroxyl imidazothiazolone methodology. The hydroxyl compound **23** was derived by using the L-cystine hydrochloride salt by the known method. Further, on this compound **23** the stereospecific amidoalkylation reaction with proper nucleophile was used to access the stereospecific *trans* compound **25** in good yields.



Scheme 2

The schematic presentation of the stereo specific nucleophilic reaction is shown in the **Scheme 2**.

Additionally, the ketone **27** was synthesized by the use of proper nucleophile and was further subjected to the famous Bayer-Villiger oxidation reaction to afford the keto acid which on esterification reaction gave the keto ester **28**. Additionally, the olefin ester **29** was prepared from the keto ester **28** by the breaking of C-S bond in Zn /AcOH with subsequent thiol cyclization and the dehydration. Further, the stereospecific hydrogenation and the debenzylation by using HBr led to the synthesis of the D-(+)-biotin **1** which is shown in the **Scheme 3**.



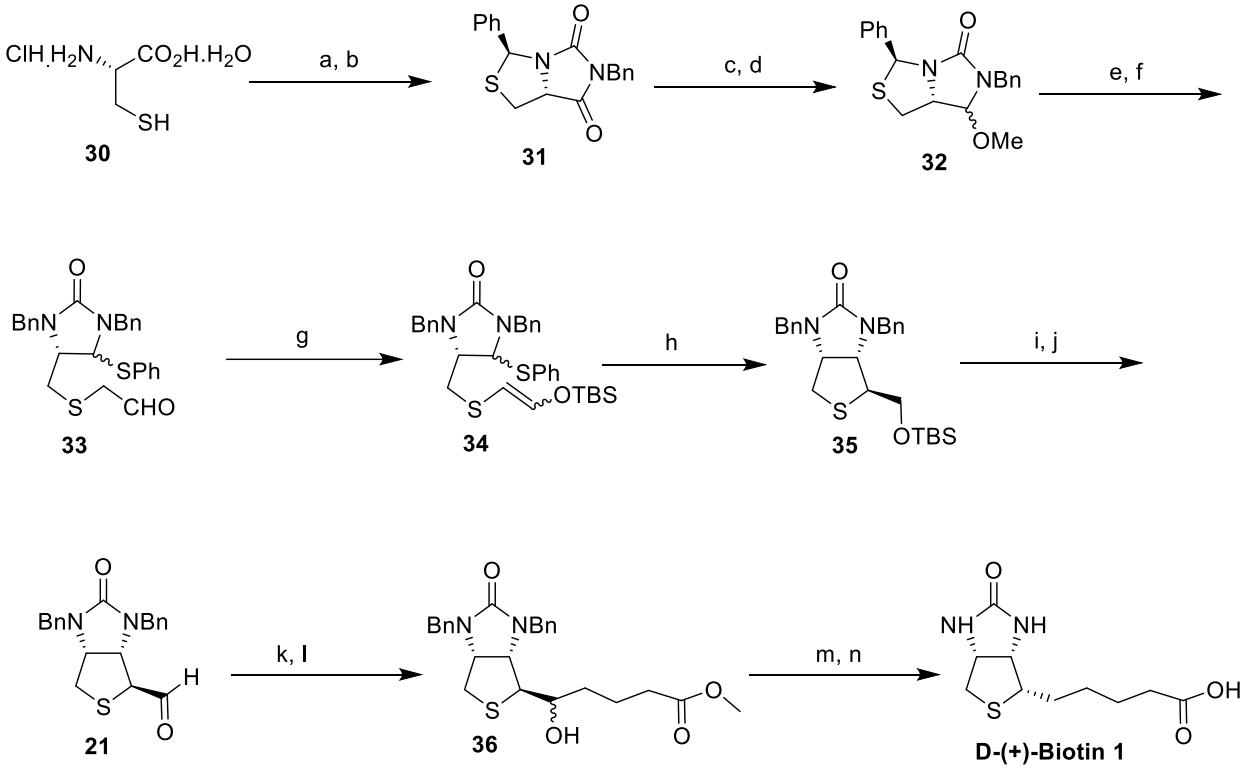
Scheme 3

Reagents and conditions: (a) 1, 2-*Bis* (trimethylsilyloxy) cyclohexene (1.5 equiv), $BF_3.OEt_2$, DCM, 98%; (b) 70% TBHP, KOH-MeOH, 15 min; (c) CH_2N_2, 10 min, 70%; (d) Zn/AcOH, 80 ^oC, 5 h; (e) AcOH/piperidine, 100 ^oC, 90 min, 70%; (f) H_2/Pd-C, MeOH, 200 psi, 100%; (g) 47% HBr, 5 h, 78%.

Chavan *et al*.[24] 3rd approach

Chavan *et al*. in the 2005 communicated another synthesis of biotin using the L-cysteine in which stereo specific radical cyclization reaction was used. The synthesis began by the utilization of the L-cysteine hydrochloride **30** which was then derived to the ketone **31** by known literature procedures. Further the reduction of the ketone was achieved by using the sodium borohydride to its corresponding alcohol which was then treated with methanol and p-TSA leading to the formation of the compound **32**. In addition, this compound **32** was treated with Zn which cleaved the C-S bond. This led to the formation of the crude thiol product which was then alkyalated by the use of ethyl chloroacetate to access the compound **33**. The sulphide **33** was reduced by the utilization of the DIBAL-H to get the aldehyde and resulting crude aldehyde was then converted to the enol **34** by the use of TBSCl/DBU. Additionally, this enol **34** was subjected for the important reaction step of the radical cyclization by the use of tributyltin hydride and the catalytic AIBN to access the cyclised product **35**. Further, the product **35** was derived to its aldehyde **21** by the utilization of the TBS deprotection reaction and then doing the Swern oxidation reaction. In addition, the introduction of the side chain was accomplished by reaction

of the compound **21** with 1,3-propane diamagnesium bromide and subsequently quenching it with CO_2 gas. Further, the resulting acid was esterified by the use of diazomethane to get the ester **36** and finally, converting this ester **36** to D-(+)-biotin **1** as depicted in **Scheme 4**.

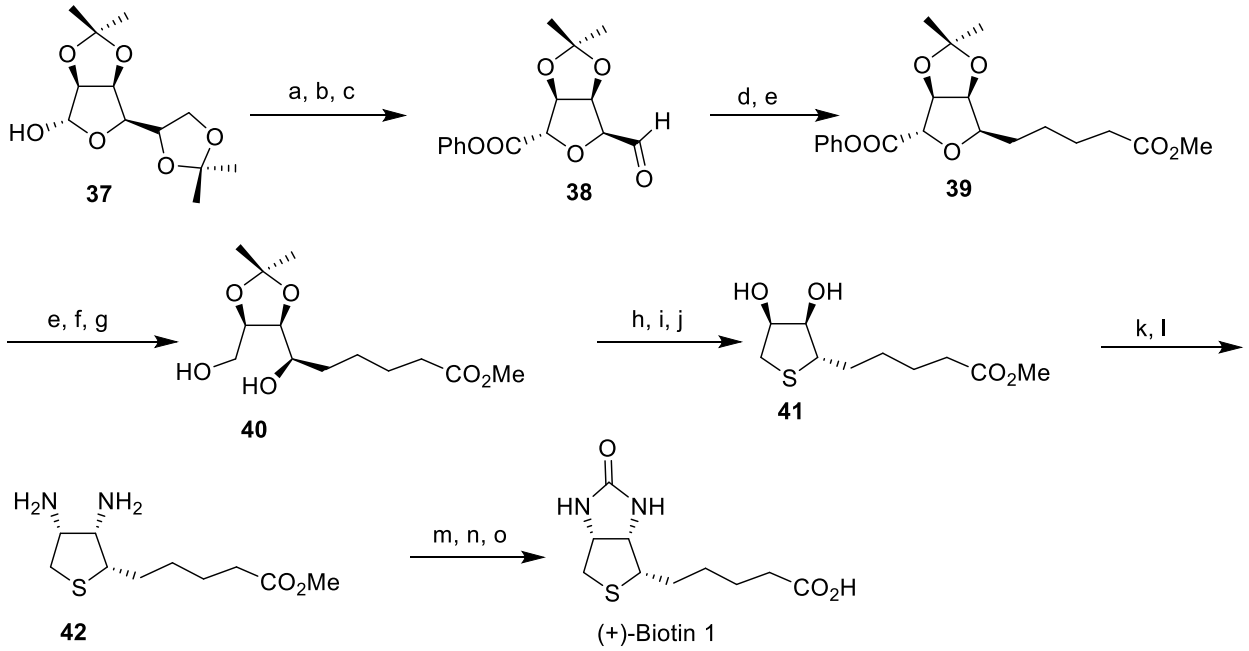


Scheme: 4

Reagents and conditions: (a) PhCHO, KOAc, MeOH:H_2O (1:1), rt, 6 h, 98%; (b) BnNCO, DCM, 60 min, conc. HCl, 60 min, reflux, 90 min, 90%; (c) $NaBH_4$, MeOH, 0 ^oC to rt, 1 h, 99%; (d) MeOH, *p*-TSA (cat.), 15 min, 98%; (e) PhSH, *p*-TSA (cat.), DCM, 10 min, 93%; (f) DIBAL-H, toluene, -78 ^oC, 2 h, 78%; (g) TBSCl, DCM, DBU, reflux, 30 min, 80%; (h) Bu_3SnH, AIBN, benzene, reflux, 4 h, 53%; (i) $BF_3.Et_2O$, $CHCl_3$, rt, 2 h, 75%; (j) $(COCl)_2$, DMSO, DCM, Et_3N, -78 ^oC to rt, 2.5 h, 61%; (k) Mg, $BrCH_2CH_2CH_2Br$, THF, 12 h, then cooled to -15 ^oC, CO_2, 2 h, rt; (*l*) CH_2N_2, 15 min, 76% (two steps); (m) MsCl, TEA, DCM, 0 ^oC to rt, 3h; (n) DBU, 60 ^oC, 12 h, 80% (two steps); (o) 10% Pd/C, H_2, 200 psi, 65 ^oC, 6 h, 99%; (p) HBr (47%), reflux, 5 h, 75%.

Ohrui *et al.* [25]

Ohrui *et al.* reported the synthesis of (+)-biotin **1** which is shown in the **Scheme 5**. The protected R-D-mannofuranose **37** was converted to benzoate of anomeric alcohol. Further, the selective removal of 5,6-isopropylidene functionality and subsequent oxidative cleavage afforded aldehyde **38**. In addition, the aldehyde **38** on Wittig reaction and subsequent catalytic hydrogenation gave the compound **39**. Additionally, the ester **39** was treated with methanol in presence of sodium methoxide as the base which led to formation of hemiacetal, which on reduction led to diol **40**. Further, the thiophane formation and the subsequent hydrolysis of the compound **40** led to formation diol ester **41**, which was again derived to diamine **42**. The diamine **42** was then converted to acid by hydrolysis of the ester by using barium hydroxide which was further treated with phosgene to access the final product (+)-biotin **1**.

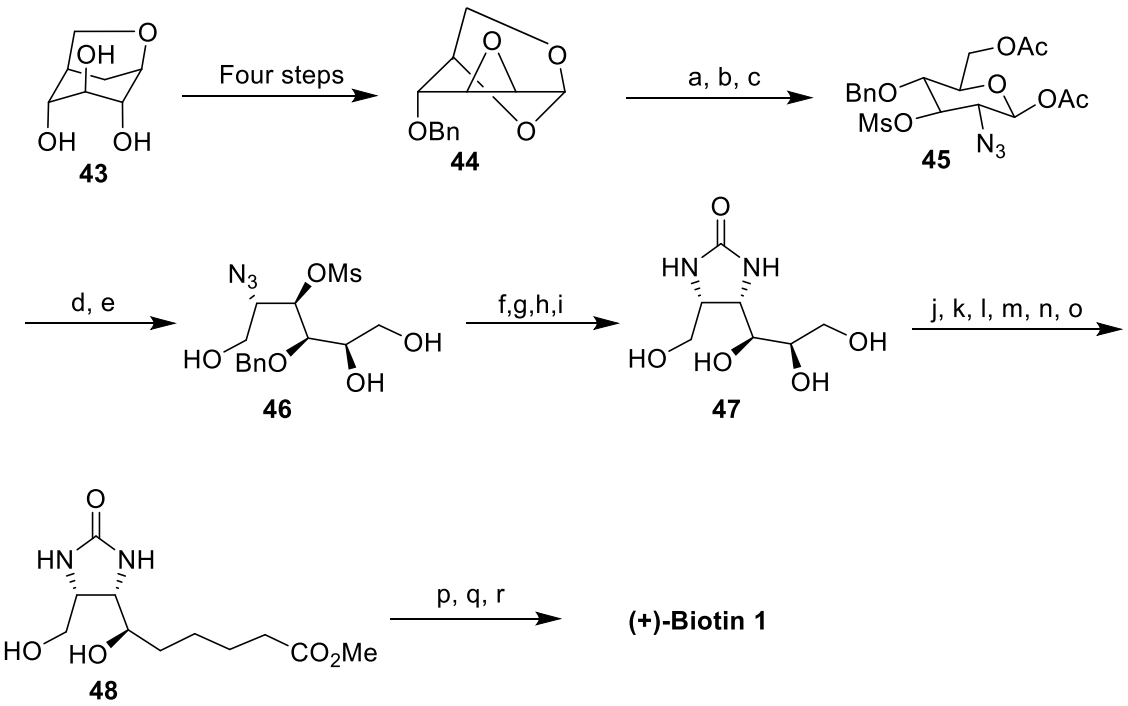


Scheme 5

Reagents and conditions: (a) PhCOCl, pyridine; (b) HOAc, H_2O; (c) $NaIO_4$, CH_3COCH_3/H_2O; (d) Ph_3P=CH-CH=CHCOOCH$_3$, DCM; (e) H_2, Pd/C, MeOH; (f) $NaOCH_3$, MeOH; (g) $NaBH_4$; (h) CH_3SO_2Cl; (i) Na_2S, HMPA, 100 ^oC; (j) 90% HCOOH, 20 ^oC; (k) CH_3SO_2Cl; (*l*) NaN_3, HMPA, 80 ^oC; (m) PtO_2, MeOH/Ac_2O; (n) $Ba(OH)_2$, H_2O, 140 ^oC; (o) $COCl_2$.

Ogawa *et al.*[26]

Ogawa and co-workers developed the route for the synthesis of the biotin by using D-glucose as starting material. Glucose was converted to the compound **43** which is a triol. Further, this triol **43** was derived to the compound **44** by the utilization of the four-step reaction sequence. In addition, the compound **44** was converted to azide followed by subsequent mesylation to get the corresponding mesylate, which was further treated with acetic anhydride and $BF_3.Et_2O$ to afford the azide **45.** Additionally, the azide **45** on acidic hydrolysis and reduction with $NaBH_4$ afforded the compound **46**. Further, for the incorporation of the second nitrogen, the compound **46** was treated with dimethoxypropane and then reacted with LiN_3. Subsequently Lindlar reduction and urea formation resulted in the synthesis of the urea compound **47**. Also, the urea **47** was transformed to diol **48** by using the six-step reaction sequence (**Scheme 6**). Finally, the introduction of the sulphur atom was carried out by mesylation and treating the mesylate with Na_2S and the base resulted in the formation of (+)-biotin **1**.



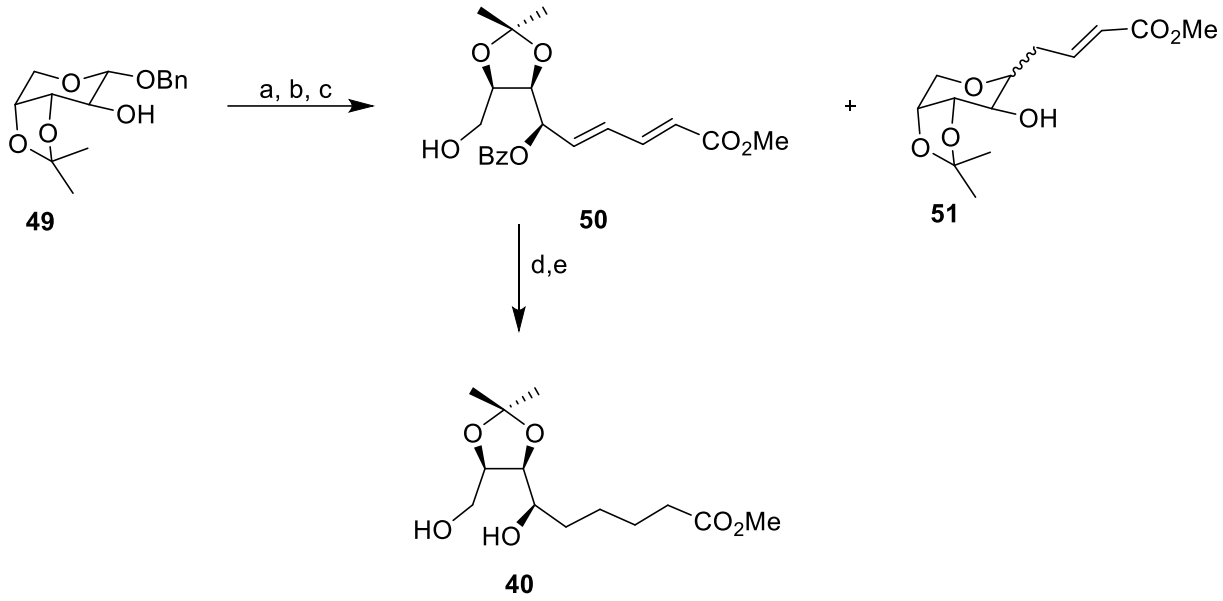
Scheme 6

Reagents and conditions: (a) NaN_3, NH_4Cl, $CH_3OCH_2CH_2OH/H_2O$, 120 ^oC; (b) MsCl; (c) $BF_3.Et_2O$, Ac_2O; (d) HCl, MeOH; (e) $NaBH_4$, $B(OH)_3$, EtOH; (f) $(CH_3)_2C(OCH_3)_2$, DMF, *p*-TsOH; (g) LiN_3, DMF, 80 ^oC; (h) H_2, Lindlar, EtOH; (i) $COCl_2$; (j) Ac_2O, py; (k) $AcOH/H_2O$, 70

^{o}C; (*l*) $NaIO_4$, $EtOH/H_2O$; (m) Ph_3P=CH-CH=CHCOOCH$_3$, DCM; (n) H_2, Pd/C, MeOH; (o) CH_3ONa, MeOH; (p) CH_3SO_2Cl, C_2H_5N, -10 ^{o}C; (q) Na_2S, DMF, 100 ^{o}C; (r) NaOH.

Vogel *et al.*[27]

Vogel and co-workers synthesized (+)-biotin by using the starting material D-arabinose. In this synthesis the hemiacetal **49** was prepared from D-arabinose. The hemiacetal **49** was then subjected for the Wittig reaction, reduction and the benzoate removal which resulted in the formation of diol **40** in low yield because of the formation of tetrahydropyran **51** due to the Michel addition reaction of free hydroxyl group to olefin moiety **50** (**Scheme 7**).



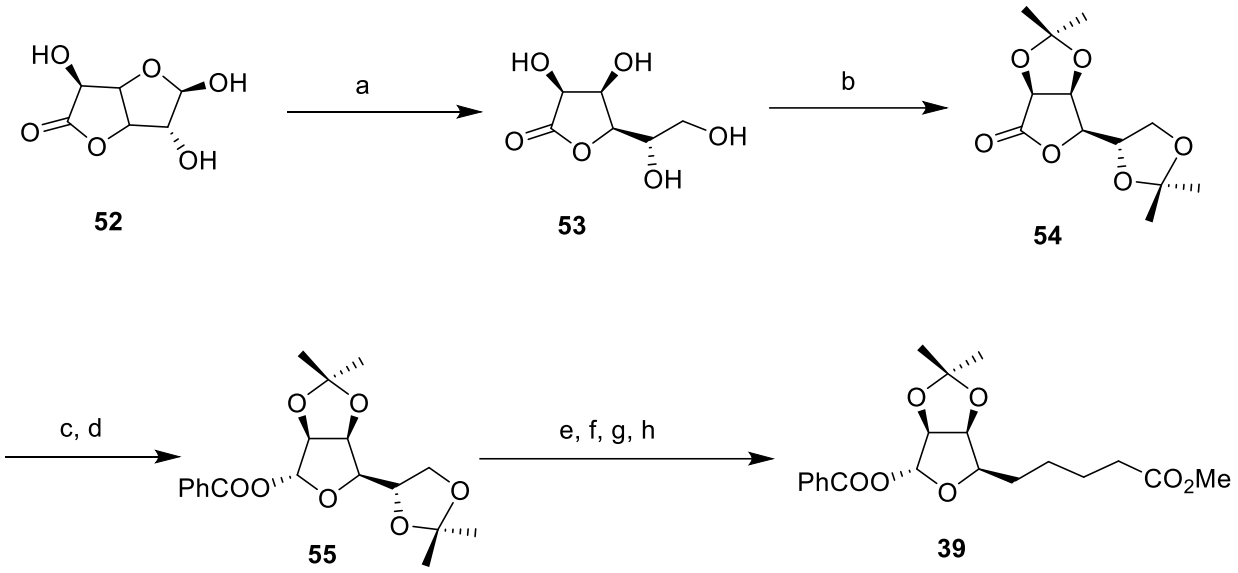
Scheme 7

Reagents and conditions: (a) PhCOCl, pyridine; (b) H_2, Pd/C, dioxane; (c) Ph_3P=CH-CH=CHCOOCH$_3$, DCM; (d) H_2, Pd/C, (e) $NaOCH_3$, MeOH (65%).

Ravindranathan *et al.*[28]

Ravindranathan *et al*. in the year 1984 utilized the modified strategy for the synthesis of D-(+)-biotin from D-glucose. The strategy used is depicted in the following **Scheme 8**. The synthesis began by using the D-glucurono-6,3-lactone **52**, which was converted to L-gulono-1,4-lactone **53** by the reduction. Additionally, the deprotection of acetonide functionality from the lactone **53**

led to the formation of compound **54**. Further, the compound **54** was reduced by using $NaBH_4$ and was treated with benzoyl chloride/pyridine to furnish of diacetonide **55**. Additionally, the compound **55** on four-step conversion led to formation of ester **39** which is an intermediate in Ohrui synthesis of D-(+)-biotin.



Scheme 8

Reagents and conditions: (a) H_2, Raney Ni; (b) $(CH_3)_2C(OCH_3)_2$, DMF, *p*-TsOH; (c) $NaBH_4$, MeOH, 0 ^oC; (d) PhCOCl, C_5H_5N; (e) MeOH, HCl; (f) $NaIO_4$, acetone/H_2O, 0 ^oC; (g) Ph_3P=CH-CH=CHCOOCH$_3$, DCM; (h) H_2, Pd($NaBH_4$).

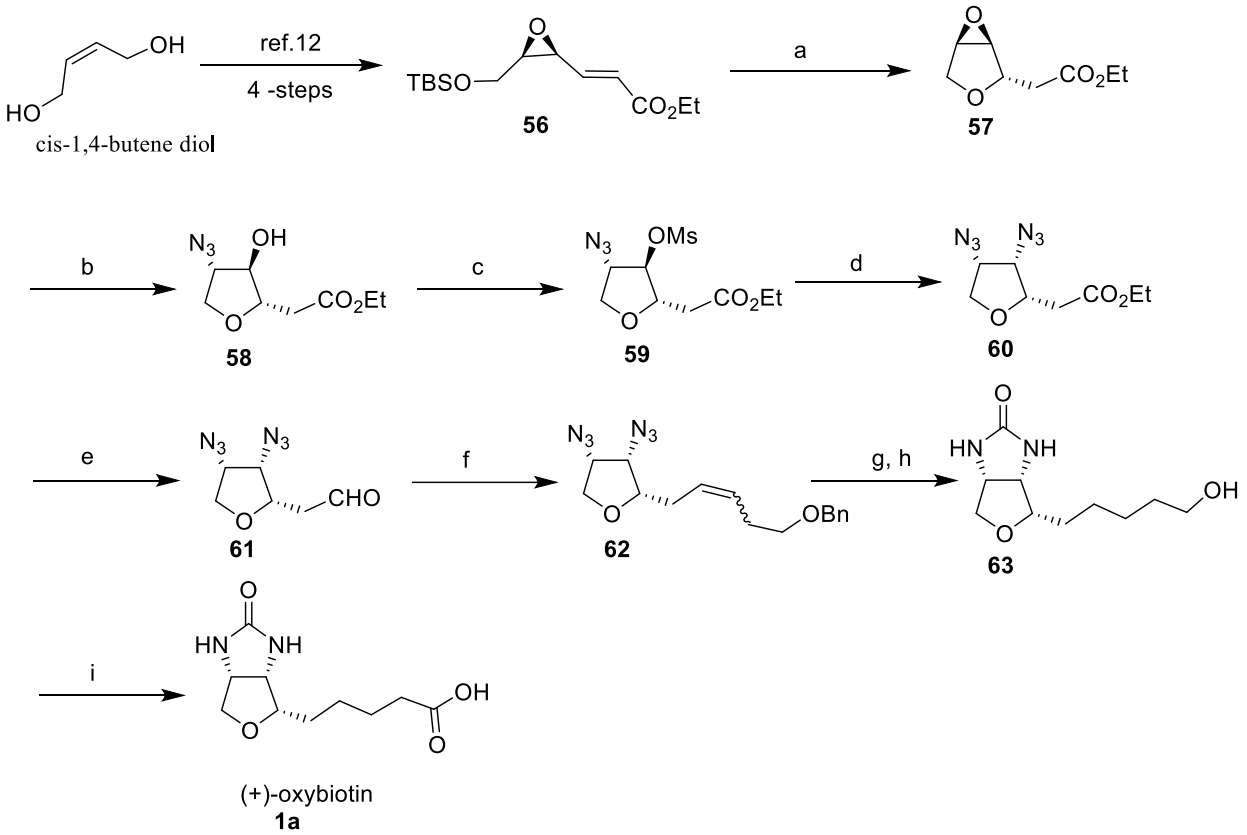
2. Oxybiotin, *dl*-oxybiotin and *epi*-oxybiotin:

Oxybiotin:

The (+)-oxybiotin which is an oxygenated analogue of (+)-biotin is well known to hold on to the growth restoring activity of natural biotin, suggesting that the change from the sulphur atom to the oxygen atom do not affect the bioactivity of biotin and since then considering its biological activity, various synthetic routes including the chiral pool approaches such as D-xylose,[29] D-arabinose,[30] and 3,4,6-tri-O-benzyl-D-glucal[31] *etc* have already been used for the total synthesis of (+)-oxybiotin .

Sudalai *et al.*[32]

Recently, in the year 2014 Sudalai *et al.* have reported one more synthesis of (+)-oxybiotin by using the Sharpless asymmetric epoxide formation reaction and the diastereoselective desilylation oxa-Michael addition reaction as the important steps in the synthesis (**Scheme 9**). The chiral epoxide **56** was prepared according the protocol reported in the literature.[33] Further, the deprotection of the OTBS-group from the epoxide **56** led to the intramolecular cyclization and formation of epoxide **57**. In addition, the opening epoxide **57** by the sodium azide led to formation of the azide compound **58**. Further, the mesylation and the treatment with sodium azide of the compound **58** was carried out in order to get the diazide compound **60**. The reduction of ester group in the diazide **60** was achieved by using the DIBAl-H; this led to the formation of aldehyde **61**. Additionally, the aldehyde **61** on Wittig reaction, reduction and oxidation led to the formation of (+)-oxybiotin **1a**.



Scheme 9

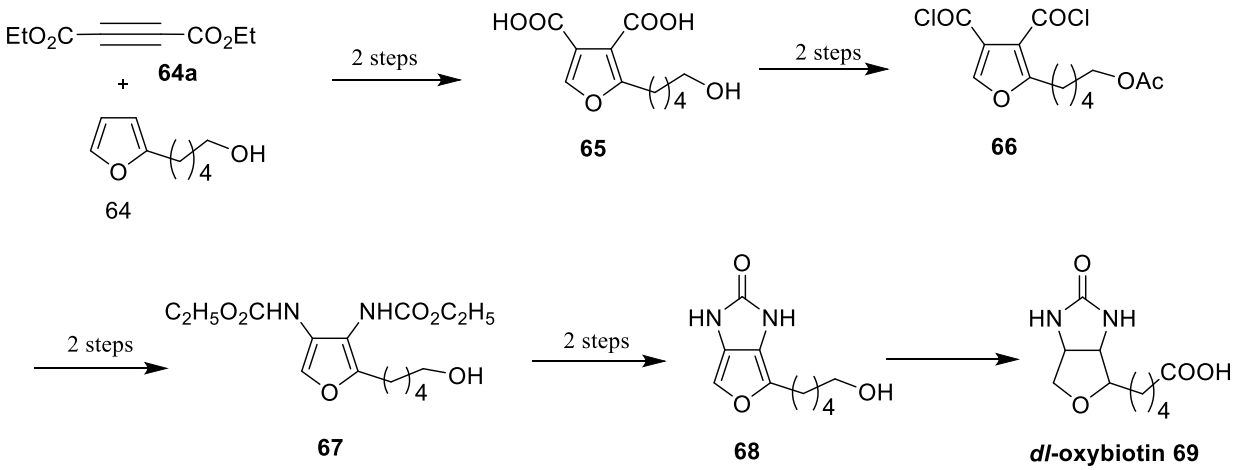
Reagents and conditions: (a) TBAF, THF, 25 ^{o}C, 2 h, 99%; (b) NaN_3, NH_4Cl, EtOH:H_2O (4:1), 80 ^{o}C, 12 h, 91%; (c) MsCl, Et_3N, dry DCM; (d) NaN_3, DMF, 120 ^{o}C, 75%; (e) DIBAL-H,

toluene, -78 ^{o}C, 1 h; (f) $BnO(CH_2)_3P^+Ph_3I^-$, KO^{t}Bu, THF, -78 ^{o}C to 25 ^{o}C, 2 h, 75%; (g) H_2, (1 atm), 10% Pd/C, MeOH, 25 ^{o}C, 24 h; (h) Triphosgene, Et_3N, DCM, ^{o}C 2 h, then 25 ^{o}C, 20 h, 76%; (i) TEMPO, $PhI(OAc)_2$, CH_3CN:H_2O (4:1), 25 ^{o}C, 4 h, 99%.

The total synthesis of *dl*-oxybiotin:

Klaus Hofmann *et al.* [13]

In the year 1945 Klaus Hofmann *et al*. reported the synthesis of *dl*-oxybiotin. In this synthesis 2-furanpentanol was used as raw material, which was synthesized from the furfural by using the conventional methods. The condensation of the compound **64** with the diethyl-acetylene-dicarboxylate **64a** and the saponification of the resulting 3,4-dicarbethoxy-2-furanpentanol afforded the 3,4-dicarboxy-2-furanpentanol **65**. The compound **65** was further acetylated and then converted to the acid chloride **66**. In addition, the acid chloride **66** on modified Curtius degradation reaction gave the 3,4-di-aminocarbethoxy-2-furan-pentanol acetate, which was hydrolyzed to afford the compound **67**. This conversion of compound **66** to **67** was done by using the two-step protocol. Firstly, it was converted to the acetate of the compound **67** and then it was hydrolyzed to the compound **67**.



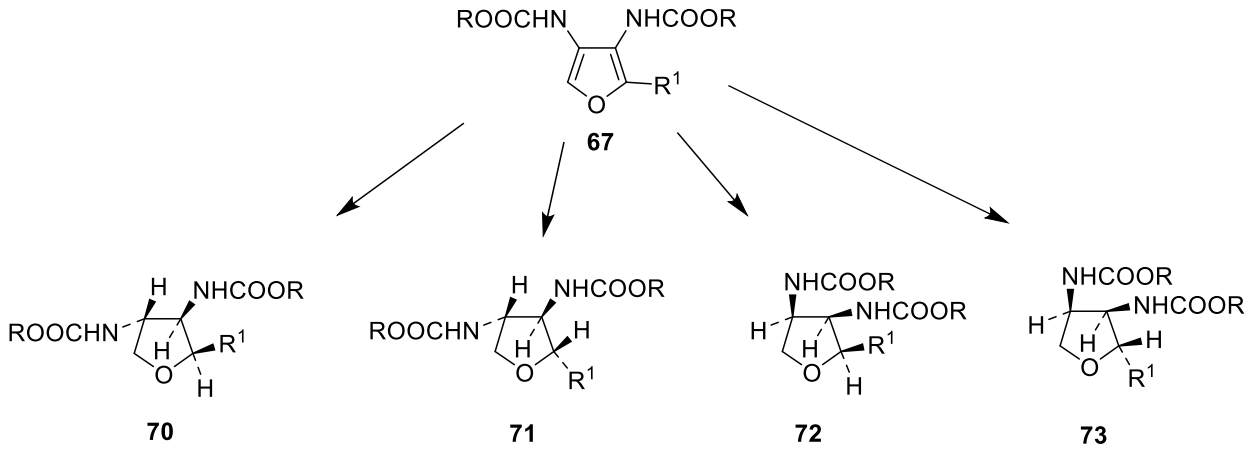
Scheme 10

Additionally, the compound **67** was hydrogenated to get the mixture of stereoisomers of 3,4-diaminocarbethoxy-2-tetrahydrofuranpentanols. In addition, this on treatment with barium hydroxide afforded the compound **68** in good yield. Finally, the oxidation of compound **68** with alkaline $KMnO_4$ led to the syntheses of the *dl*-oxybiotin **69** (**Scheme 10**).

Synthesis of *dl-epi*-oxybiotin:

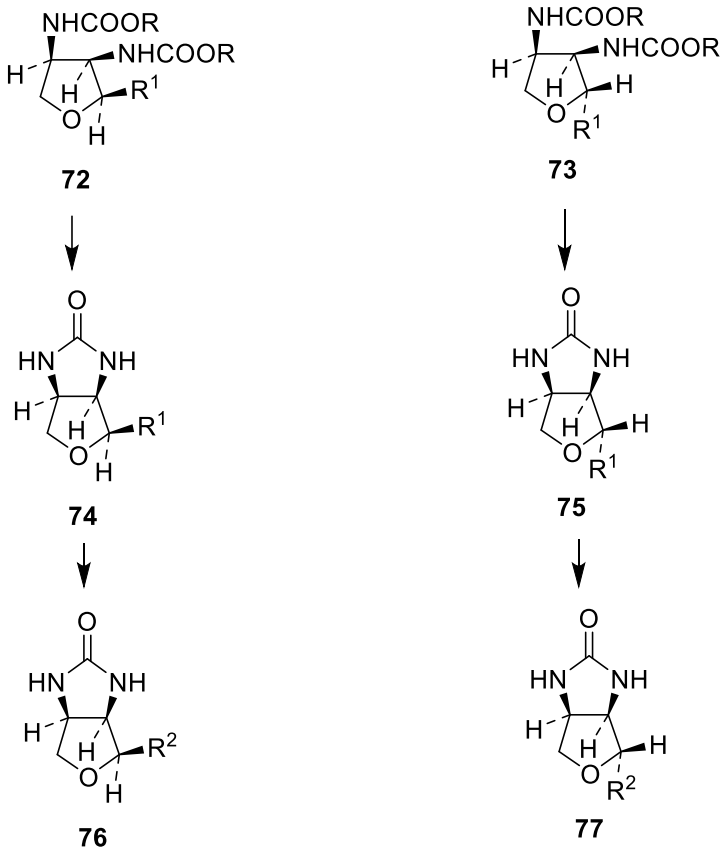
Klaus Hofmann *et al.* [12]

The above first total synthesis of *dl*-oxybiotin was also reported by Klaus Hofmann *et al*. The main features of this synthesis were catalytic hydrogenation of the compound 3,4-dicarbethoxyamino-2-furan-pentanol **67** to its corresponding compound *cis*-3,4-dicarbethoxyamino-2-tetrahydrofuranpentanol. The hydrogenation reaction of the tri-substituted furan **67** leads to the creation of the three asymmetric carbon centers in the structure of this compound and to the four racemic tetrahydrofurans, **70**, **71**,**72**, **73** are expected (**Scheme 11**). Two of them **70** and **71** have *trans* structures and the compounds **72** and **73** possess *cis*-configuration of the carbethoxyamino functional groups. Therefore the structural isomers in every pair differ in their spacial arrangements of the side chain R^1. Further, they can be designed as the *trans*, *cis* **70**, the *trans*, *trans* **71** and *cis*, *cis* **72** and the *cis*, *trans* **73** isomers respectively and Klaus Hofmann synthesized all theoretical compounds of racemic 3,4-diamino-2-tetrahydrofuran valeric acids.



Scheme 11: The four racemic tetrahydrofurans, **70**, **71**, **72**, **73** (R^1 = -$(CH)_4$-CH_2-OH).

Additionally, the cautious study of the hydrogenation reaction products of compound **67** revealed the existence of three isomeric compounds of the 3,4-dicarbethoxyamino-2-tetrahydrofuranpentanols **71**, **72** and **73**. However, in the progress of the oxybiotin synthesis, the hydrogenation reaction products were reacted with the barium hydroxide and these different urethanes were not separated. Although the compounds **72** and **73** were not isolated, the existence of these hydrogenation reaction products was demonstrated by transforming them into the corresponding cyclic urea derivatives. In addition, the oxidation and esterification of compounds **74** and **75** resulted in the formation of *dl-epi*-oxybiotin methyl ester and the subsequent hydrolysis of *dl-epi*-oxybiotin methyl ester resulted in the formation of the *dl-epi*-oxybiotin (**Scheme 12**).



Scheme 12: The synthesis of *dl-epi*-oxybiotin ((R^1 = -$(CH)_4$-CH_2-OH, R^2 = -$(CH)_4$-COOH).

1.3. Present work:

Introduction:

Biotin is a vitamin H which is dissolvable in water. Kong *et al*.[1] separated biotin independently from the three natural deposits. Curative effectiveness of the biotin, which gives a new method to treat diabetes, was checked out in the patients having non-insulin-dependent diabetes mellitus.[1b] The use of biotin is being done in the pharmaceutical industry for the purpose of production of the ointments and tonics, *etc*. Also, it is being used in the poultry for fast growth of chicks and for the healthy hatching of eggs. Besides this biotin is also used in the cosmetic industry.

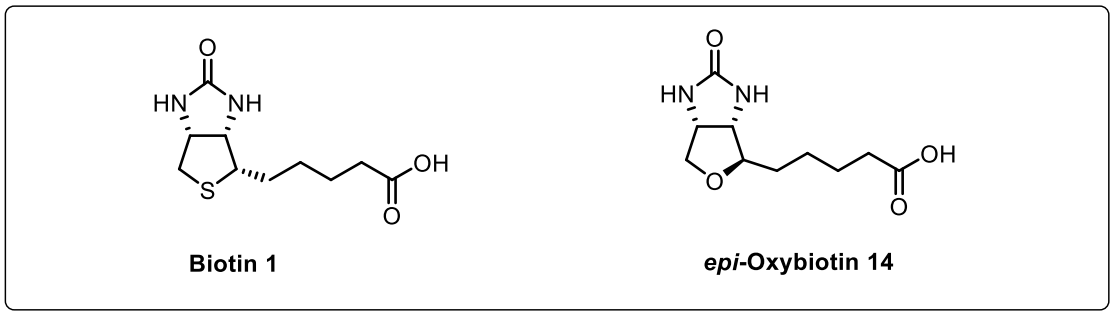


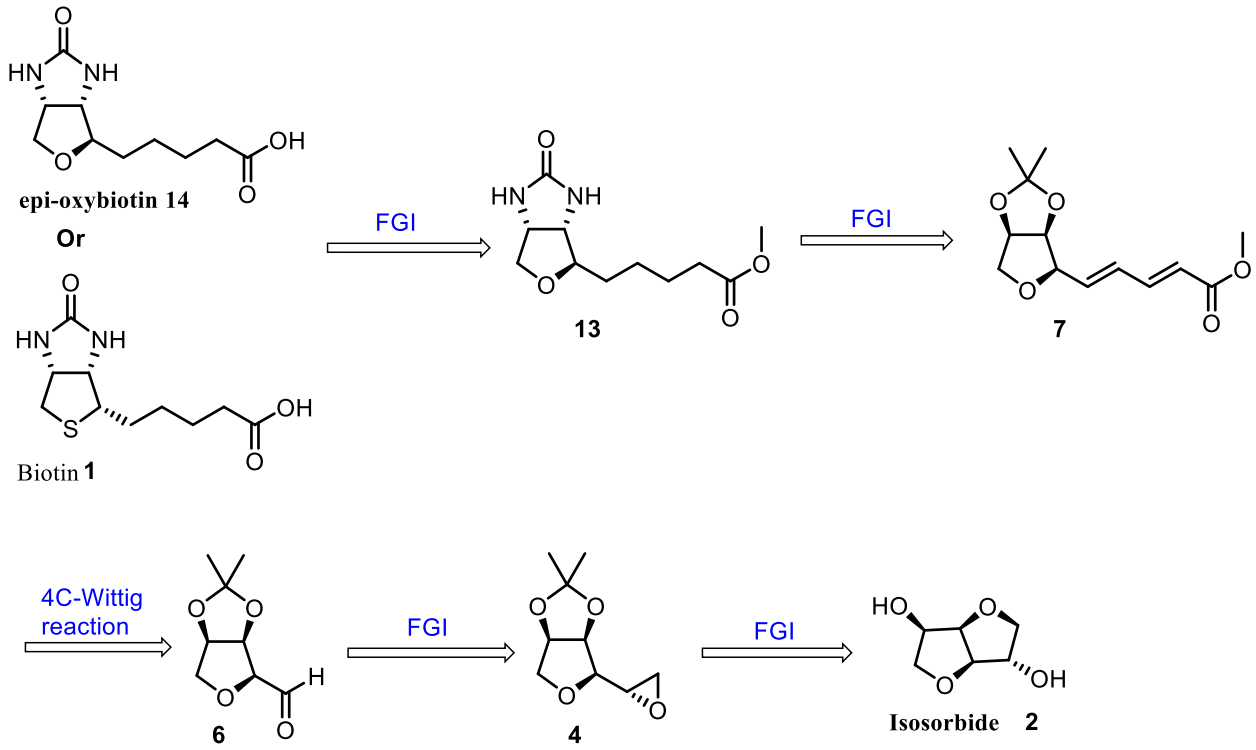
Figure 1: Structure of biotin and *epi*-oxybiotin.

The (+)-oxybiotin is another active analog of biotin whose biological activity is also similar as that of biotin and it is found effective in carrying out few of the functions like biotin. Since the (+)–oxybiotin has its own importance in terms of biological activity; many of its derivatives have been synthesized and studied.[11] Also, in the year 1949 the synthesis of *epi*-oxybiotin and the racemic 3, 4-diamino-2-tetrahydrofuran valeric acids was reported by Klaus Hoffman *et al.*[12] The synthesis of *dl*-oxybiotin was also reported by Klaus Hoffman *et al*.[13] In addition, the literature search revealed that there is only one synthesis of *epi*-oxybiotin which was reported in the year 1949 by Klaus Hoffman *et al*.[12] This turned the attention for the synthesis of the *epi*-oxybiotin.

1.4. Present scheme and retrosynthetic analysis:

It was thought that biotin **1** and *epi*-oxybiotin **14** could be accessed from commercially available isosorbide as the starting material. For this a new retrosynthetic analysis was planned which is shown in the **Scheme 1**. It was thought that biotin **1** could be accessed from ureido ester **13**

which in turn could be prepared from unsaturated ester **7**. The unsaturated ester **7** can be prepared from aldehyde **6** by using a four carbon Wittig reaction on it.



Scheme 1: Retrosynthesis**.**

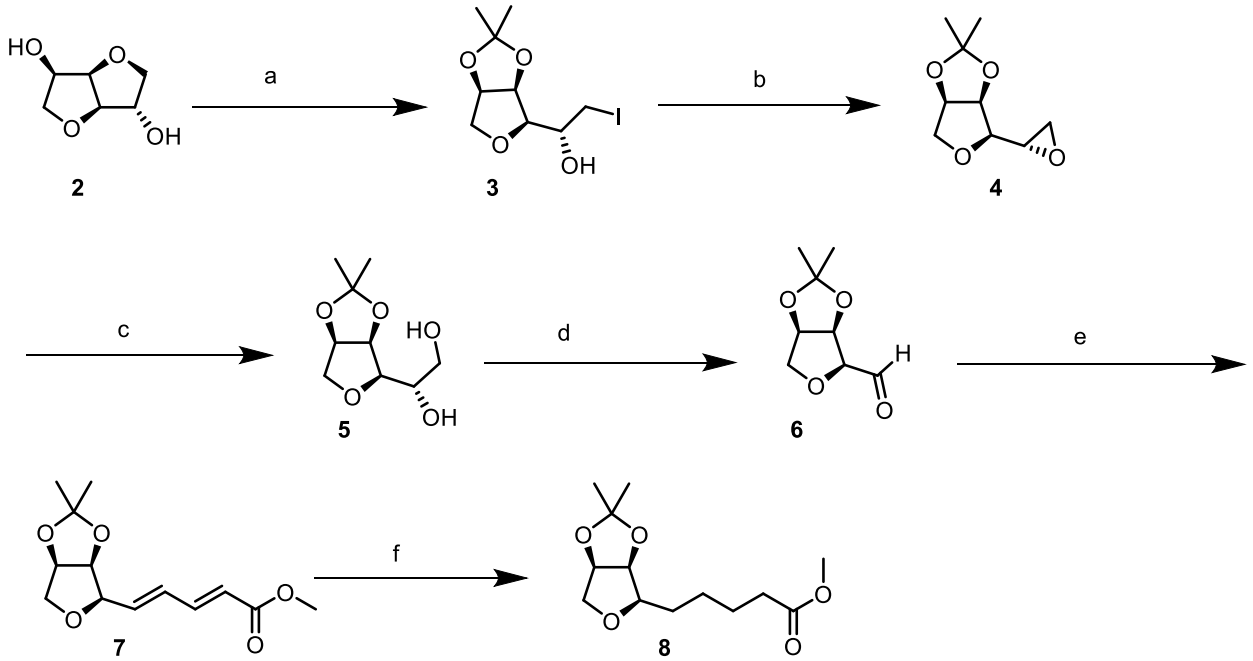
Further the aldehyde **6** can be accessed from epoxide **4** by base catalyzed ring opening of epoxide **5** by aq. NaOH and chopping of the resulting diol by $NaIO_4$. In addition, the epoxide **4** can be synthesized by using isosorbide as a starting material.

Synthesis of *epi*-oxybiotin and biotin by using isosorbide:

The synthesis started by using commercially available starting material *viz*. isosorbide **2**. Thus isosorbide **2** on treatment with TMSCl, NaI and acetone in acetonitrile for 12 h at room temperature afforded iodoalcohol **3** in 99% yield. Further, the compound **3** was treated with NaH in THF at 0 ^{o}C to room temperature for 5 h to afford the epoxide **4** in 72% yields.

In addition to this, the epoxide **4** was refluxed with aqueous NaOH in THF for 48 h to get the diol **5** in 60% yield and further the diol **5** was cleaved to aldehyde **6** in 82% yield by using $NaIO_4/SiO_2$ in DCM for 6 h at room temperature. The synthesis of aldehyde **6** from the isosorbide **2** was carried out according to the reported procedures in the literature.[34] In addition,

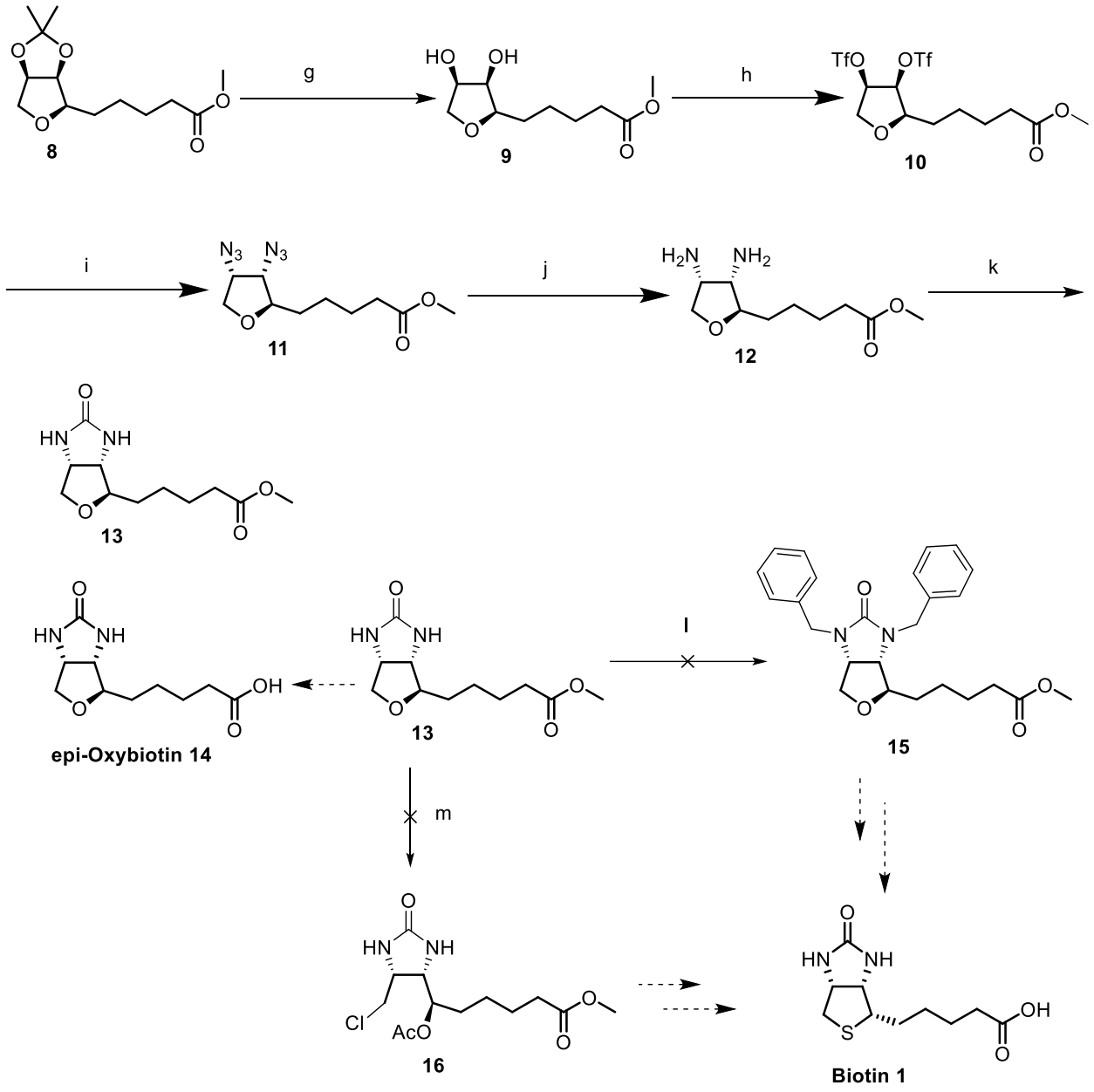
the Wittig reaction of this aldehyde **6** with 4-carbon Wittig salt **6a** in DCM at room temperature for 12 h furnished the unsaturated ester **7** in 59% yield and subsequently this unsaturated ester **7** was subjected for hydrogenation reaction by using H_2, Pd/C in MeOH at room temperature for 24 h to get the saturated ester **8** in 83% yield (**Scheme 2**).



Scheme 2

Reagents and conditions: (a) TMSCl, NaI, Acetone, CH_3CN, rt, 12 h, 99%; (b) NaH, THF, 0-25 oC, rt, 5 h, 72%; (c) aq. NaOH, THF, reflux, 48 h, 60%; (d) $NaIO_4$, SiO_2, DCM, rt, 6 h, 82%; (e) Methyl (*E*)-4-(triphenyl-l5-phosphaneylidene)but-2-enoate (**6a**), DCM, rt, 12 h, 59%, (f) H_2/ Pd/C, in MeOH, 200 psi, rt, 24 h, 83%.

Further, the saturated ester **8** which is having acetonide functionality was subjected to acetonide deprotection by using cat. *p*-TSA in MeOH at reflux conditions for 24 h which afforded the diol ester **9** in 68% yields. Additionally, this diol ester **9** was reacted with triflic anhydride and pyridine at 0^{o}C to room temperature to afford the triflate ester **10** in 87% yields. The triflate ester **10** was treated with NaN_3, in DMF at 80^{o}C to get the diazide ester **11** in good yields (93%). The azide formation was confirmed by taking IR of the synthesized compound **11**, the peak at 2109 cm^{-1} confirmed the presence of azide functional group in the compound **11**.



Scheme 3

Reagents and conditions: (g) cat. *p*-TSA, MeOH, reflux, 24 h, 68%; (h) Tf_2O, pyridine, DCM, 0 ^oC, 2 h, 87%; (*i*) NaN_3, DMF, 80 ^oC, 24 h, 93%, (j) H_2, Pd/C, MeOH, rt, 12 h; (k) Triphosgene, Et_3N, 0 ^oC-rt, DCM, 24 h, 65% for two steps. (*l*) (**i**) NaH, BnBr, THF, 0 ^oC-rt, (**ii**) NaH, BnBr, DMF, 0 ^oC-rt, *no reaction*; (m) AcCl, heat, *no reaction*.

Further, the diazide ester **11** was reduced to diamine ester **12** by using H_2, Pd/C in MeOH at room temperature for 12 h. Additionally, this crude diamine ester **12** was reacted with triethylamine and triphosgene at 0 ^oC to room temperature for 24 h to afford the urea ester **13.**

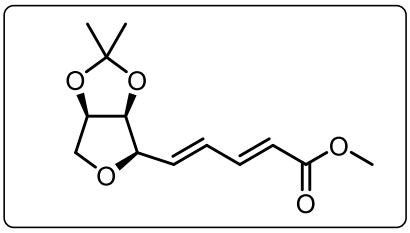
The urea **13** was well characterized by ^{1}HNMR and ^{13}CNMR spectral analysis. Further, this urea ester **13** was reacted with the benzyl bromide and sodium hydride in THF/DMF solvent at 0 ^{o}C to room temperature for 12 h with the hope to get the compound **15**. However, this reaction did not work and the starting material was recovered. In addition, the urea ester **13** was heated in presence of acetyl chloride to access the compound **16**, unfortunately this attempt also failed and the reaction did not work. Thus, few attempts for the conversion of urea ester **13** into the (+)-biotin **1** failed (**Scheme 3**). However, the total synthesis of *epi*-oxybiotin by using the urea ester **13** can be accomplished in one step by the hydrolysis of the ester functional group in compound **13**. Thus, the attempts towards the total synthesis of *epi*-oxybiotin are in progress in the laboratory.

1.5. Conclusion:

This synthesis utilizes the isosorbide as a starting material which is commercially available. The synthesis of methyl 5-((3a*S*, 4*R*, 6a*R*)-2-oxohexahydro-1*H*-furo[3, 4-d]imidazol-4-yl)pentanoate **13** has been successfully accomplished. Due to paucity of time due to COVID-19 pandemic the conversion of 13 to biotin (1) could not be accomplished. However, by proper choice of reagents and conditions the synthesis of biotin and *epi*-oxybiotin can be accomplished from this advanced intermediate.

1.6. Experimental:

Methyl (2*E*, 4*E*)-5-((3a*S*,4*R*,6a*R*)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4yl)penta-2,4-dienoate (7) :



To a stirred solution of crude aldehyde **6** (3.8 g, 14.94 mmol, 1eq.) in 100 ml of DCM was added 4-carbon Wittig salt i.e. methyl (*E*)-4-(triphenyl-l5-phosphaneylidene)but-2-enoate **6a** (11.930 g, 33.10 mmol, 1.5 eq.) at room temperature and the resulting mixture was stirred for 12 h. The progress of the reaction was monitored by the TLC. After complete consumption of the starting materials, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography which afforded 7.91 g of the diene **7** as a colorless liquid.

Colorless liquid.

R_f : 0.6 (EtOAc–PE= 20: 80).

Molecular Formula: $C_{13}H_{18}O_5$.

Yield: 59%.

$[\alpha]_D^{25}$: -37.85 (C = 1, $CHCl_3$).

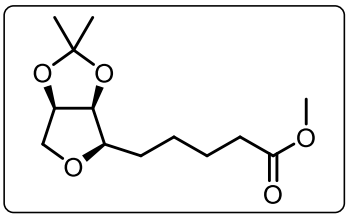
IR: 3022, 1728, 1601, 1216, 771 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.50 (s, 3H), 3.56 (dd, *J* = 10.68, 3.81 Hz, 1H), 3.75 (s, 3H), 4.09 (d, *J* =10.68 Hz, 1H), 4.42 (dd, *J* = 8.01, 3.43 Hz, 1H), 4.69 (dd, *J* = 5.72, 3.81 Hz, 1H), 4.84 (dd, *J* = 5.91, 3.62 Hz, 1H), 5.97 (d, *J* = 15.26 Hz, 1H), 6.02 (dd, *J* = 10.87, 8.20 Hz, 1H), 6.37 (t, *J* = 11.44 Hz, 1H), 7.60 (dd, *J* = 15.26, 11.83 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 24.99, 26.24, 51.91, 73.31, 78.52, 81.60, 82.66, 112.66, 123.61, 129.90, 133.74, 139.19, 167.48.

HRMS (ESI): *m/z* calculated for $C_{13}H_{18}NaO_5$ [M + Na]$^+$ **:** 277.1046, found: 277.1046.

Methyl 5-((3a*S*,4*R*,6a*R*)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)pentanoate (8):



The compound **7** (1 g, 3.87 mmol, 1 eq.) was taken in 10 ml of methanol and was added to the hydrogenation par reactor in which

catalytic amount of Pd/C (100 mg) was also added. Further, the reaction mass was hydrogenated under the pressure of 200 psi for 24 h. After completion of the reaction, the reaction mass was filtered through the cellite pad by giving the excess wash of the methanol and the resulting filtrate was concentrated *in vacuo*. The remaining residue was further purified by using the flash column chromatography. This afforded 0.850 gm of the hydrogenated compound **8** as the colorless oil.

Colorless oil.

R_f : 0.5 (EtOAc–PE= 20: 80).

Molecular Formula: $C_{13}H_{22}O_5$.

Yield: 83%.

$[\alpha]_D^{25}$: -5.62 (C = 1, $CHCl_3$).

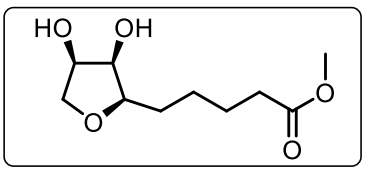
IR: 2940, 1733, 1192, 863 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (s, 3H), 1.43 (s, 3H), 1.40 - 1.54 (m, 2H), 1.57 - 1.85 (m, 4H), 2.30 (t, *J* = 7.33 Hz, 2H), 3.25 - 3.38 (m, 1H), 3.42 (d, *J* = 3.64 Hz, 1H), 3.63 (s, 3H), 3.94 (d, *J* = 10.69 Hz, 1H), 4.41 - 4.61 (m, 1H), 4.71 (dd, *J* = 6.12, 3.69 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 25.11, 25.20, 26.05, 26.24, 28.25, 34.14, 51.67, 72.78, 81.25, 81.33, 82.73, 112.05, 174.32.

HRMS (ESI): *m/z* calculated for $C_{13}H_{23}O_5$ $[M + H]^+$ **:** 259.1540, found: 259.1539.

Methyl 5-((2*R*, 3*R*, 4*R*)-3, 4-dihydroxytetrahydrofuran-2-yl)pentanoate (9):



A solution of compound **8** (0.850 g, 3.89 mmol, 1eq.) was taken in methanol and the catalytic *p*-TSA.H_2O (73 mg, 0.38 mmol, 0.1 eq.) was added and the resulting reaction mass was refluxed for 24 h. The methanol was evaporated by using the rotavapor and to the remaining residue water wash was given and extracted two-three times with ethyl acetate. Further, the ethyl acetate was removed *in vacuo* and the remaining residue was purified by using the flash column chromatography. This gave the compound **9** (492 mg) as the yellow liquid and remaining starting material was recovered.

Yellow liquid.

R_f : 0.2 (EtOAc–PE= 50: 50).

Molecular Formula: $C_{10}H_{18}O_5$.

Yield: 68.52%.

$[\alpha]_D^{25}$: -26.55 (C = 1, $CHCl_3$).

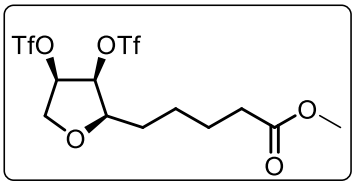
IR: 3415, 1727, 1216, 765 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 - 1.50 (m, 2H), 1.54 - 1.72 (m, 4H), 2.30 (t, J = 7.63 Hz, 2H), 3.54 (br s, 1H), 3.63 (s, 3H), 3.64 - 3.70 (m, 2H), 3.75 (br s, 1H), 3.77 - 3.83 (m, 1H), 3.95 - 4.04 (m, 1H) 4.27 - 4.37 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 25.08, 25.76, 28.74, 34.06, 51.83, 71.90, 72.12, 72.31, 81.99, 174.73.

HRMS (ESI): *m/z* calculated for $C_{10}H_{18}NaO_5$ [M + Na]$^+$ **:** 241.1046, found: 241.1046.

Methyl 5-((2*R*, 3*S*, 4*R*)-3, 4-bis(((trifluoromethyl)sulfonyl)oxy)tetrahydrofuran-2-yl)pentanoate (10).



To a stirred and cooled solution of **9** (0.300 g, 0.62 mmol, 1eq.) at 0 ^oC in dry DCM and pyridine (1.1 ml, 13.76 mmol, 10 eq.) was added dropwise a solution of Tf_2O (1.8 ml, 11.09 mmol, 8 eq.) in dry DCM (5 ml). The mixture was stirred at 0 ^oC for 2 h, then diluted with DCM and washed successively with aq. 5% HCl (25 mL), 1% $NaHCO_3$ (25 mL) and water (25 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and evaporated to afford the compound **10** as yellow oil (0.580 g).

Yellow oil.

R_f : 0.5 (EtOAc–PE= 20: 80).

Molecular Formula: $C_{12}H_{16}F_6O_9S_2$.

Yield: 87%.

$[\alpha]_D^{25}$: +14.75 (C = 1, $CHCl_3$).

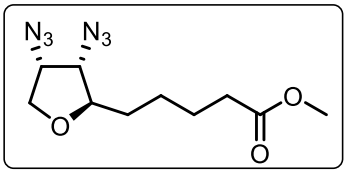
IR: 3022, 1730, 1426, 1216, 767 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 - 1.47 (m, 1H), 1.52 - 1.60 (m, 1H), 1.60 - 1.83 (m, 4H), 2.34 (t, *J* = 7.25 Hz, 2H), 3.68 (s, 3H), 4.02 - 4.14 (m, 2H), 4.19 (dd, *J* = 10.68, 6.87 Hz, 1H), 5.30 (t, *J* = 4.58 Hz, 1H), 5.38 - 5.53 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.38, 25.10, 28.69, 33.67, 51.58, 67.72, 78.69, 81.05, 83.65, 118.33 (2C, quart. *J* = 320.13 Hz), 173.80.

HRMS (ESI): *m/z* calculated for $C_{12}H_{16}F_6NaO_9S_2$ [M + Na]$^+$ **:** 505.0032, found: 505.0008.

Methyl 5-((2*R*, 3*S*, 4*R*)-3, 4-diazidotetrahydrofuran-2-yl)pentanoate (11):



To a solution of **10** (0.580 g, 2.16 mmol, 1 eq.) in dry DMF (3 ml) was added NaN_3 (0.469 g, 7.21 mmol, 6 eq.) and the resulting suspension was heated at 80 ^oC for 12 h. The mixture was poured in water (15 ml) and extracted with ethyl acetate. The organic layer was washed with H_2O and dried over anhydrous sodium sulphate, filtered and the ethyl acetate was evaporated to give the diazide compound **11** as a yellow oil. Flash column chromatography of the residue gave pure diazide ester **11** (0.300 g) as a pale yellow oil.

Pale yellow oil.

R_f : 0.4 (EtOAc–PE= 20: 80).

Molecular Formula: $C_{10}H_{16}N_6O_3$.

Yield: 93.16%.

$[\alpha]_D^{25}$: + 33.10 (C = 1, $CHCl_3$).

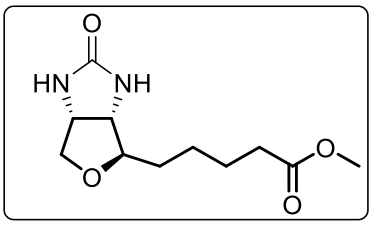
IR: 3022, 2109, 1727, 1216, 765 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 - 1.64 (m, 4H), 1.65 - 1.75 (m, 2H), 2.34 (t, *J* = 7.44 Hz, 2H), 3.61 (dd, *J*=7.44, 6.19 Hz, 1H), 3.68 (s, 3H), 3.71 - 3.78 (m, 2H), 4.10 - 4.18 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 25.06, 25.47, 33.46, 34.14, 51.85, 62.84, 66.95, 70.58, 80.74, 174.21.

HRMS (ESI): *m/z* calculated for $C_{10}H_{16}N_6NaO_3$ [M + Na]$^+$ **:** 291.1176, found : 291.1175.

Methyl 5-((3a*S*, 4*R*, 6a*R*)-2-oxohexahydro-1*H*-furo[3, 4-d]imidazol-4-yl)pentanoate (13):



To a solution of the diazide compound **11** (0.350 g, 1.44 mmol, 1eq.) in methanol was added catalytic Pd/C (0.050 g) and the resulting mixture was hydrogenated by using the hydrogen bladder at room temperature for 24 h. The progress of the reaction was monitored by TLC. After complete hydrogenation of the diazide compound **11**, the reaction mass was filtered through a cellite pad and excess wash of the methanol was given to it. The resulting filtrate was dried over anhydrous sodium sulphate and filtered. Further, the solvent methanol was removed *in vacuo* and thus the crude diamine **12** (0.239 g) was obtained. To a stirred solution of the crude diamine **12** (0.239 g, 1.10 mmol, 1eq.) and triethylamine (0.227 ml, 1.62 mmol, 1.4 eq.) at 0 ^{o}C in DCM under argon atmosphere was added triphosgene (0.052 g, 0.17 mmol, 0.16 eq.) and the resulting mixture was stirred for 24 h at 0 ^{o}C-rt. After completion of the reaction, water wash was given and the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated by removing the DCM *in vacuo*. The residue obtained was purified by flash column chromatography which gave the pure compound urea ester **13** (0.176 g) as a viscous liquid.

Viscous liquid.

R_f : 0.2 (MeOH-EtOAc = 20: 80).

Molecular Formula: $C_{11}H_{18}N_2O_4$.

Yield: 65%.

$[\alpha]_D^{25}$: +146.06 (C = 1, $CHCl_3$).

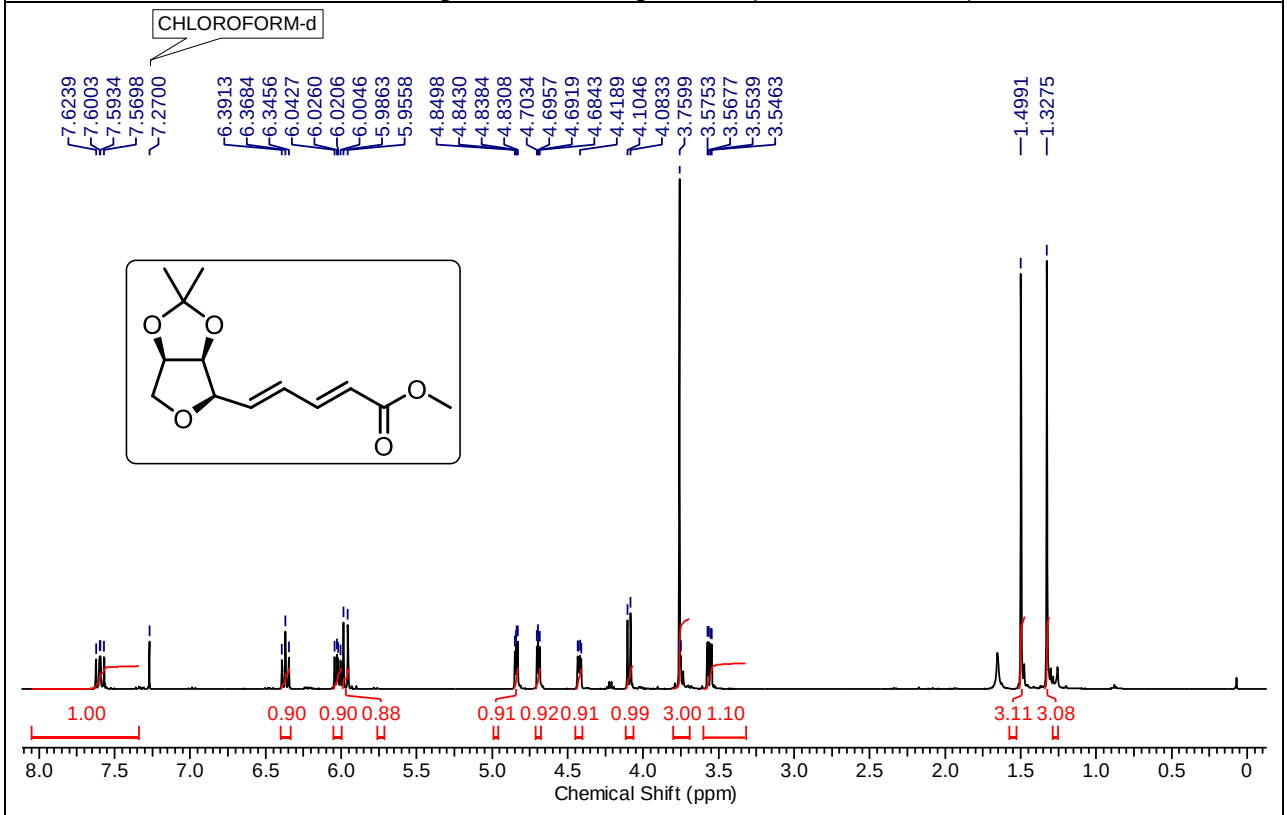
IR: 3410, 3282, 2928, 1722, 1669, 1277 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 - 1.60 (m, 4H), 1.65 (quint, *J* = 7.34 Hz, 2H), 2.32 (t, *J* = 7.25 Hz, 2H), 3.66 (s, 3H), 3.68 (d, *J* = 3.81 Hz, 1H), 3.74 - 3.79 (m, 1H), 3.84 (dd, *J* = 9.16, 3.43 Hz, 1H), 4.03 (dd, *J* = 9.54, 5.72 Hz, 1H), 4.22 - 4.38 (m, 1H), 5.72 (br s, 1H), 5.84 (br s, 1H).

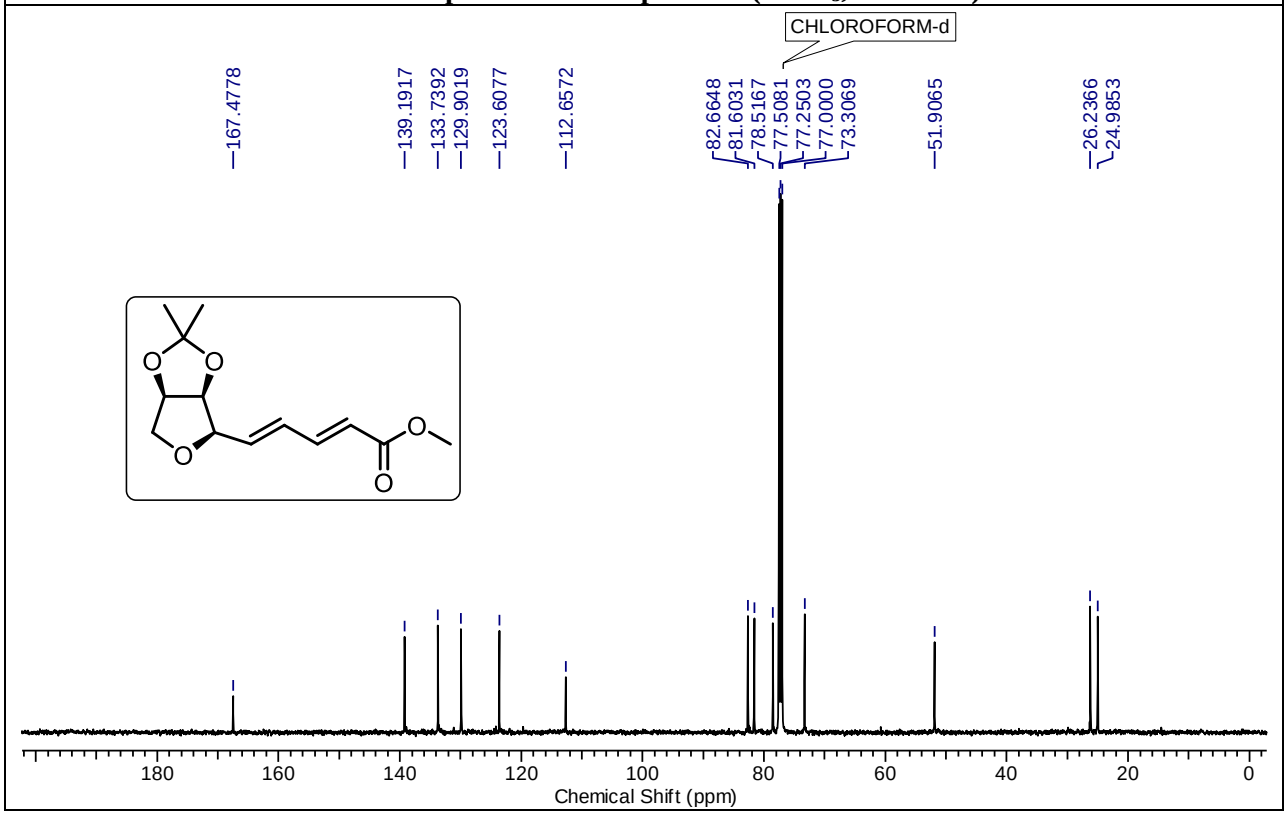
^{13}C NMR (125 MHz, $CDCl_3$): 24.75, 25.47, 31.99, 33.99, 51.79, 57.33, 61.95, 74.03, 86.27, 163.13, 174.28.

HRMS (ESI): *m/z* calculated for $C_{11}H_{19}N_2O_4$ [M + H]$^+$ **:** 243.1339, found: 243.1341.

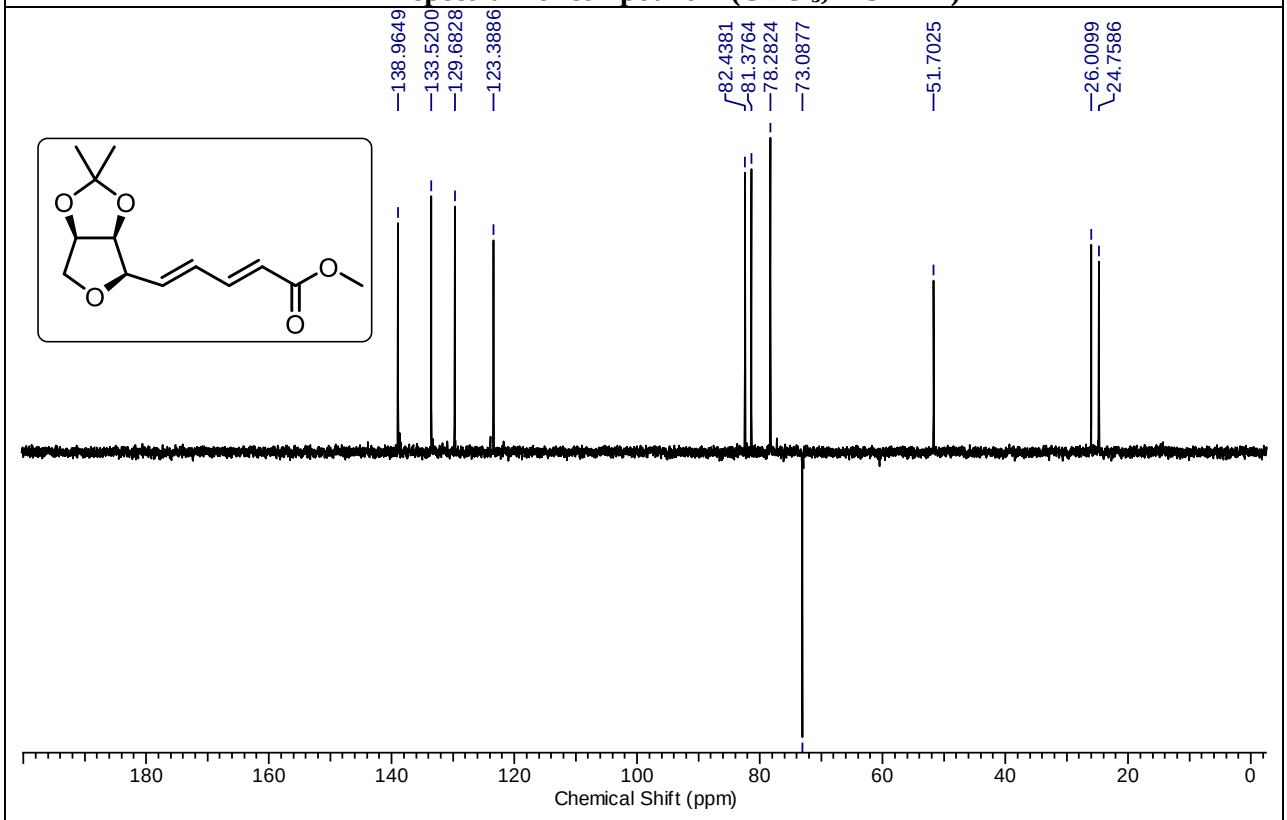
^{1}H-NMR spectrum of compound 7 ($CDCl_3$, 500 MHz)



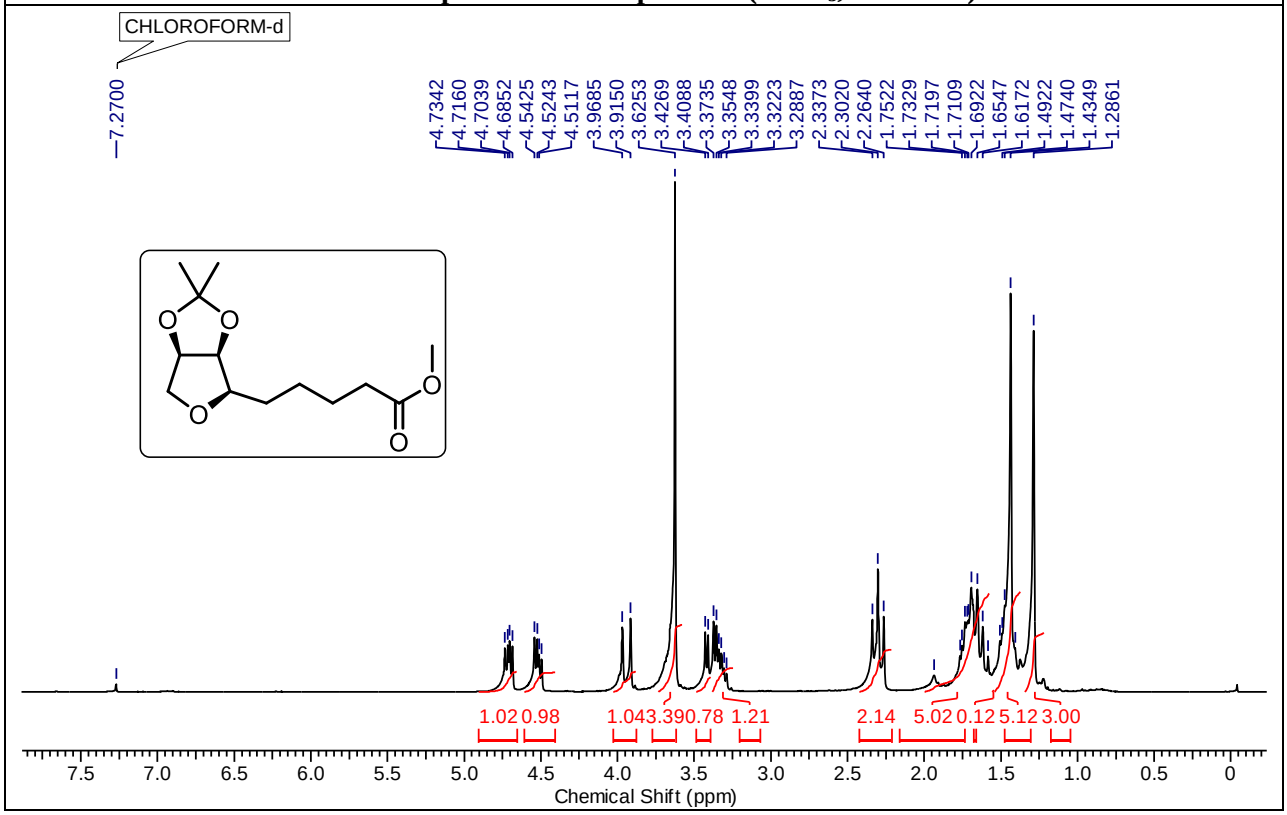
^{13}C-NMR spectrum of compound 7 ($CDCl_3$, 125 MHz)



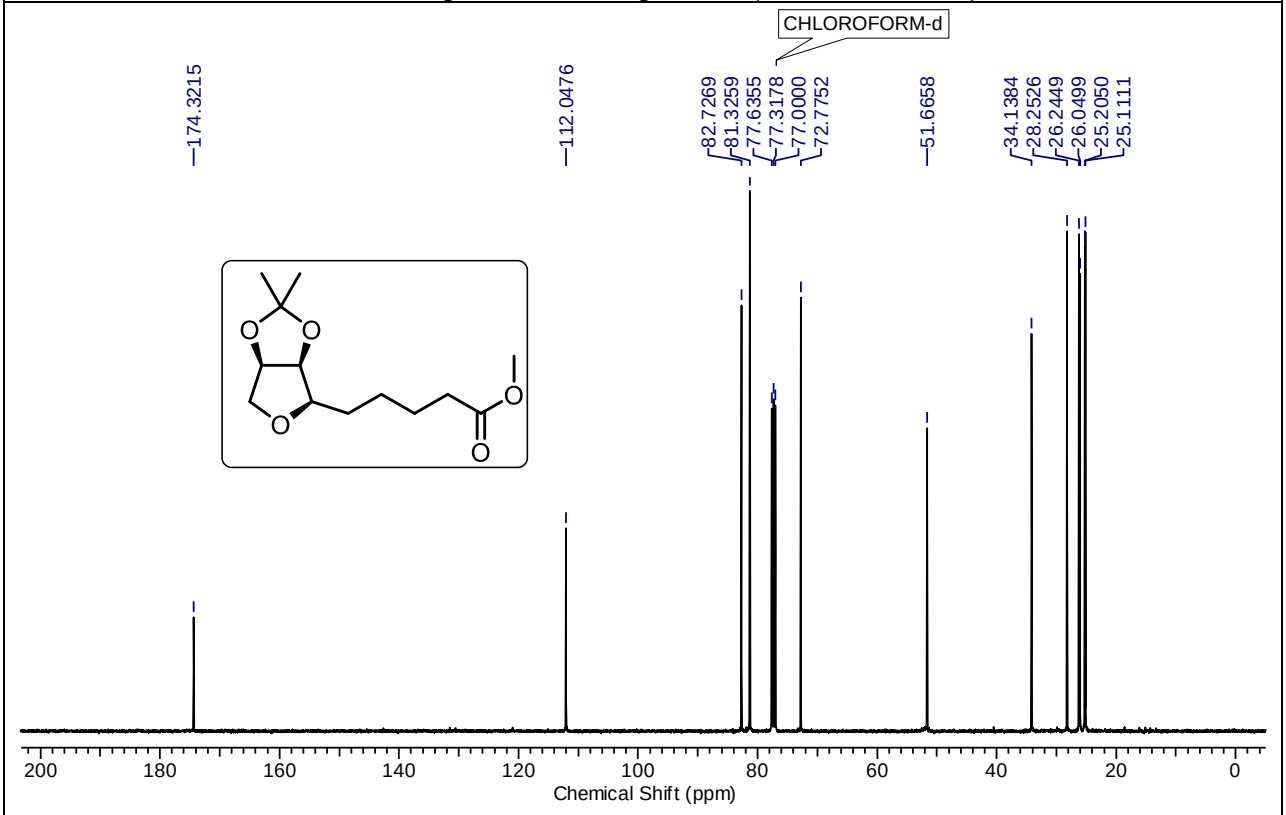
DEPT spectrum of compound 7 ($CDCl_3$, 125 MHz)



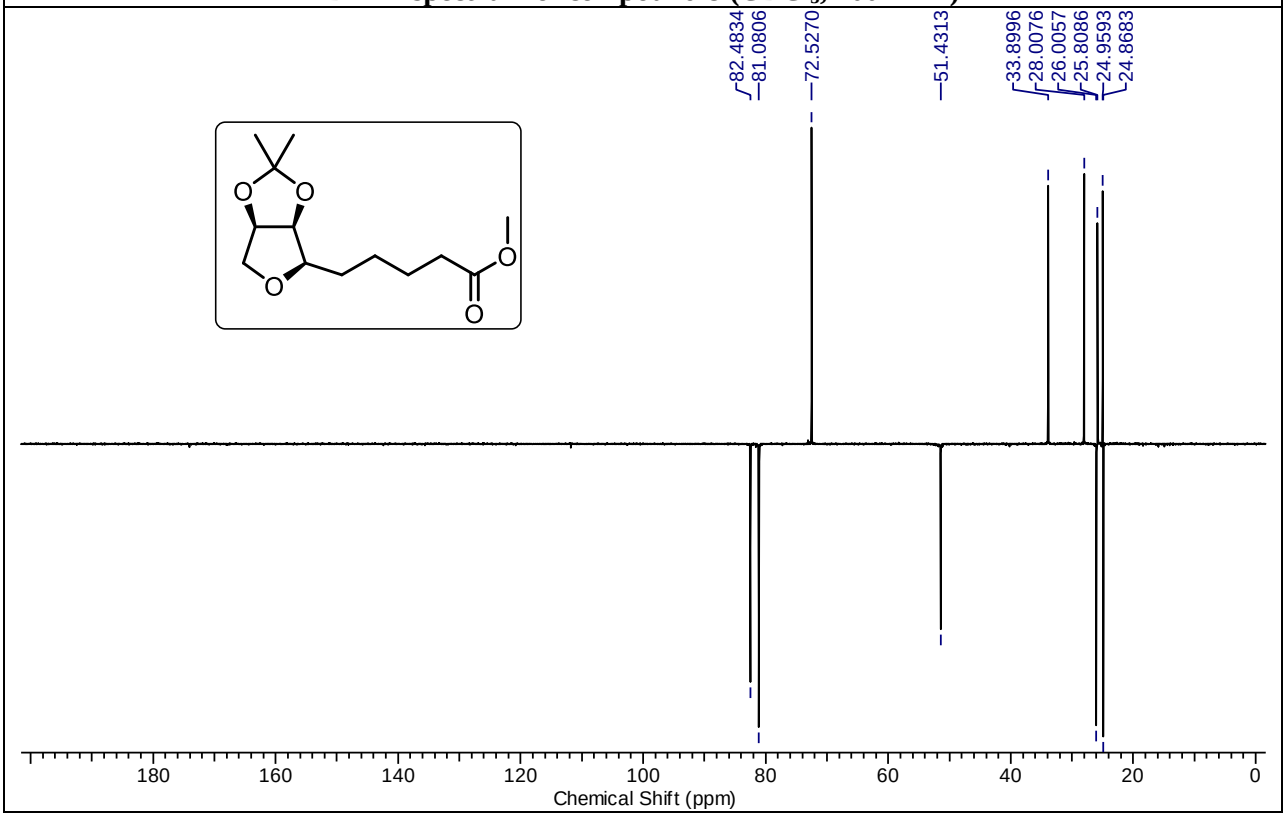
^{1}H-NMR spectrum of compound 8 ($CDCl_3$, 200 MHz)



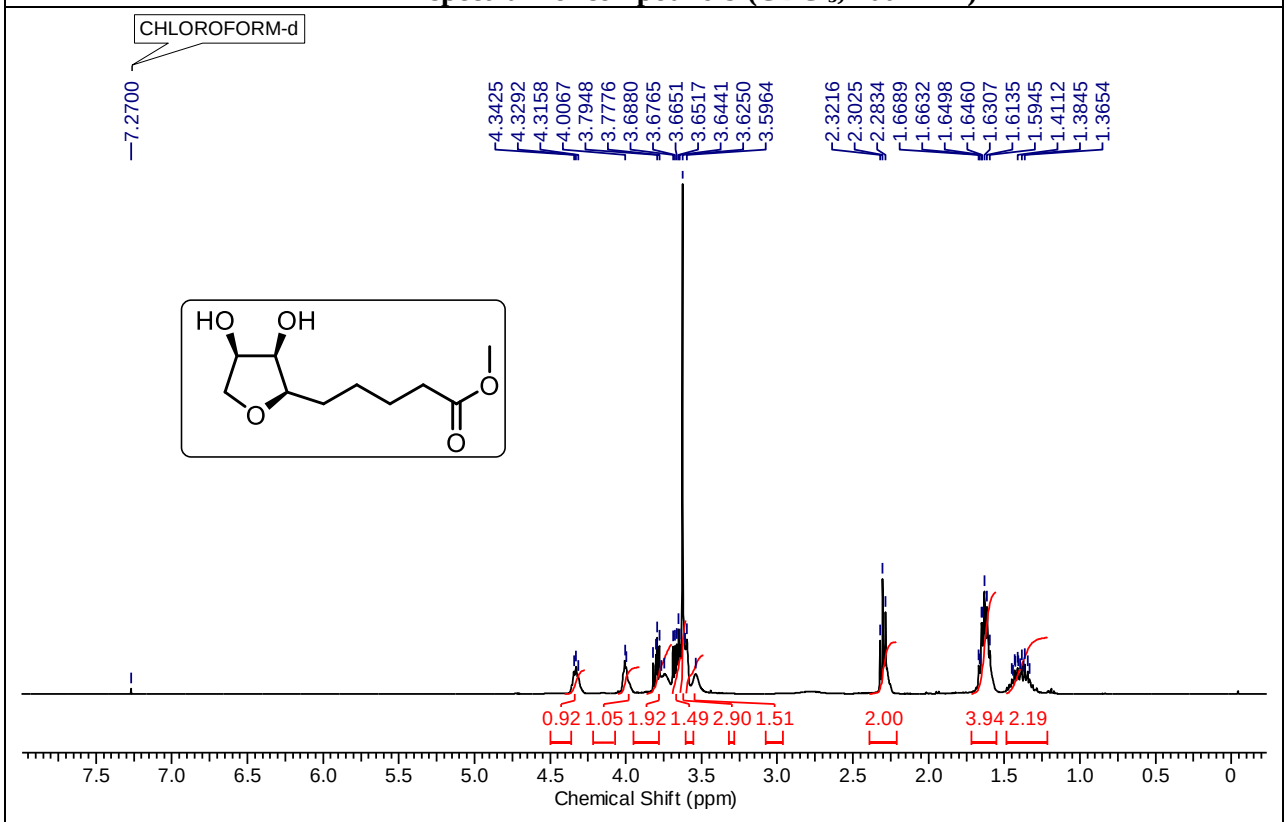
^{13}C-NMR spectrum of compound 8 ($CDCl_3$, 100 MHz)



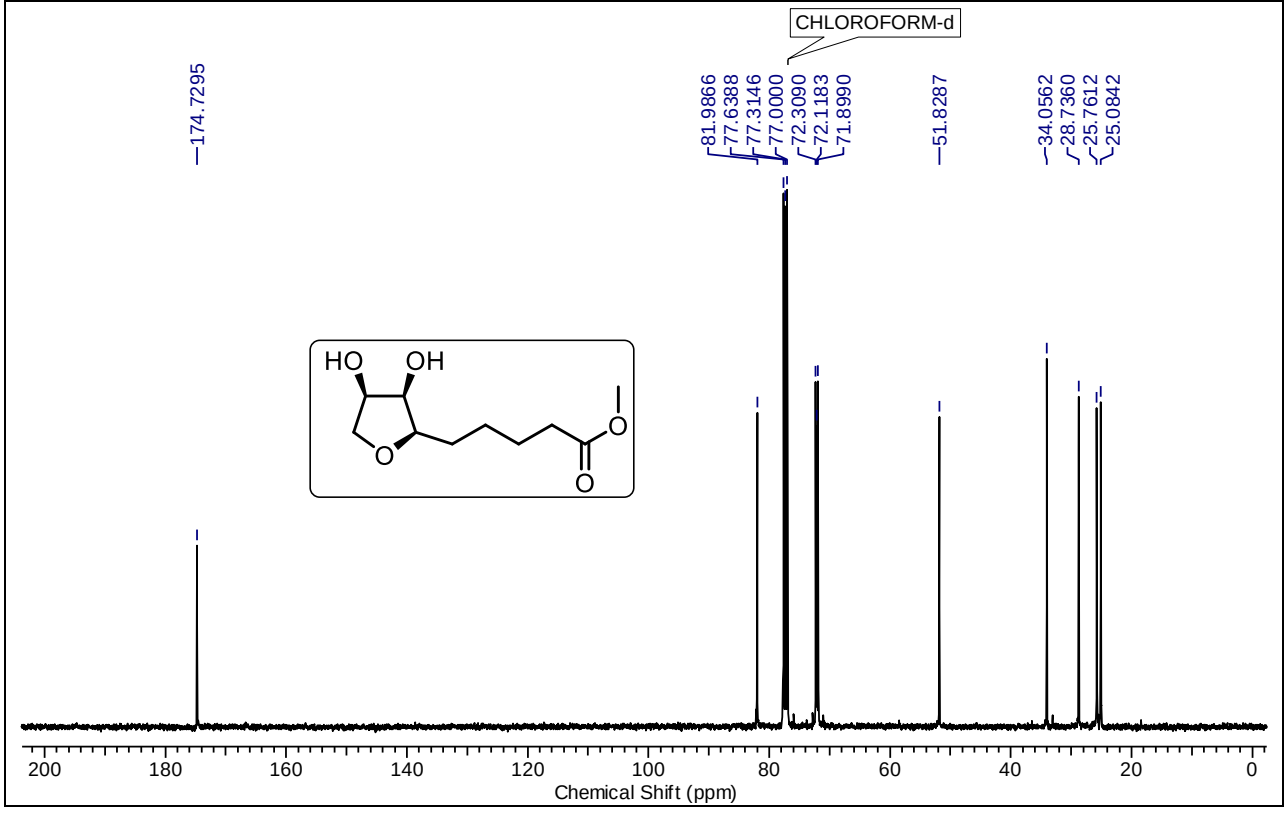
DEPT spectrum of compound 8 ($CDCl_3$, 100 MHz)



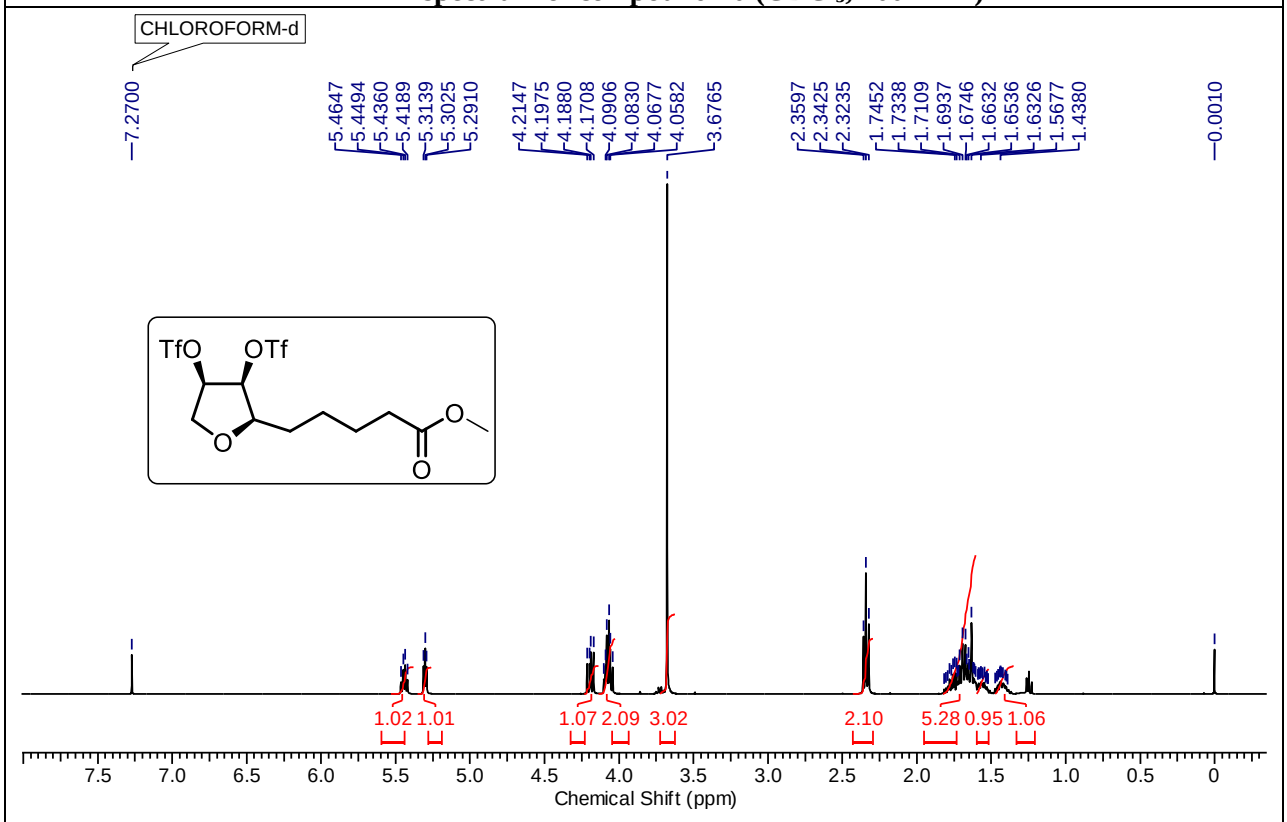
^{1}H-NMR spectrum of compound 9 ($CDCl_3$, 400 MHz)



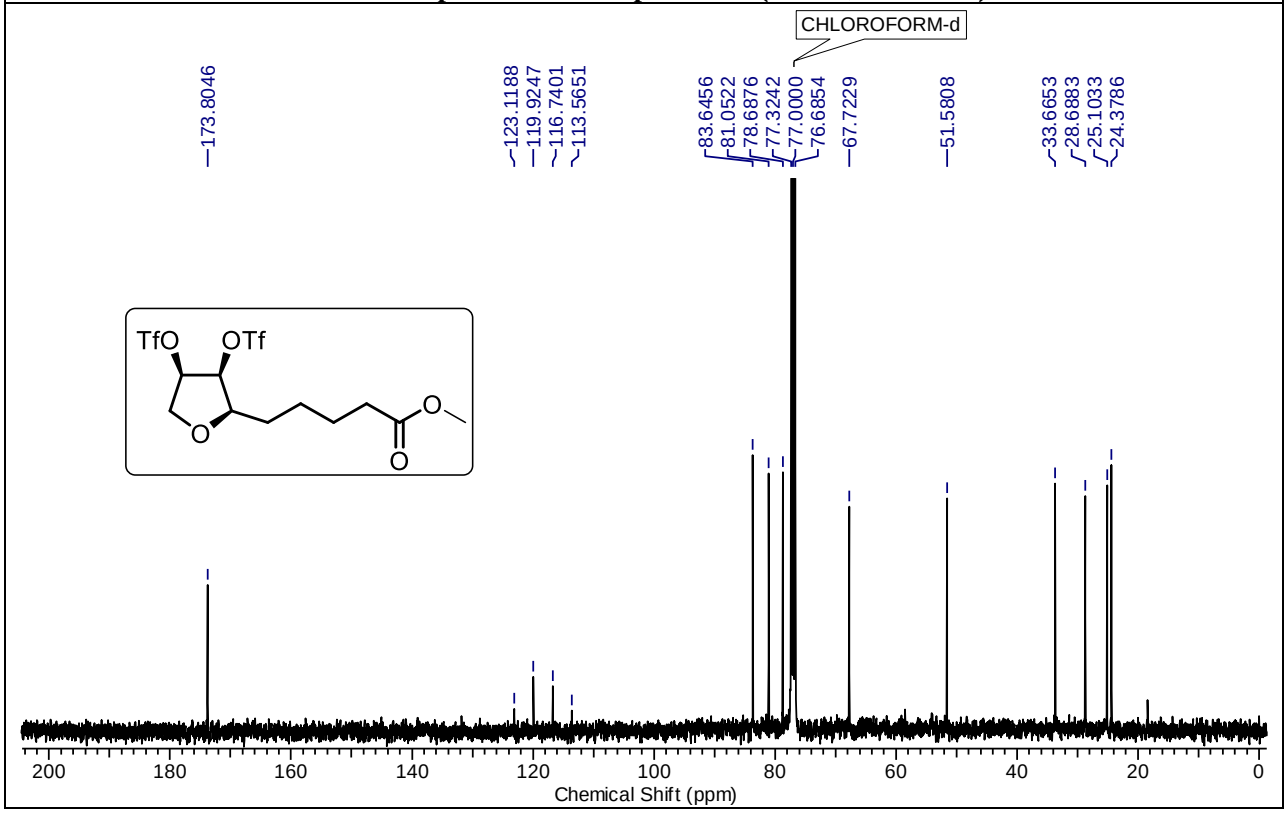
^{13}C-NMR spectrum of compound 9 ($CDCl_3$, 100 MHz)



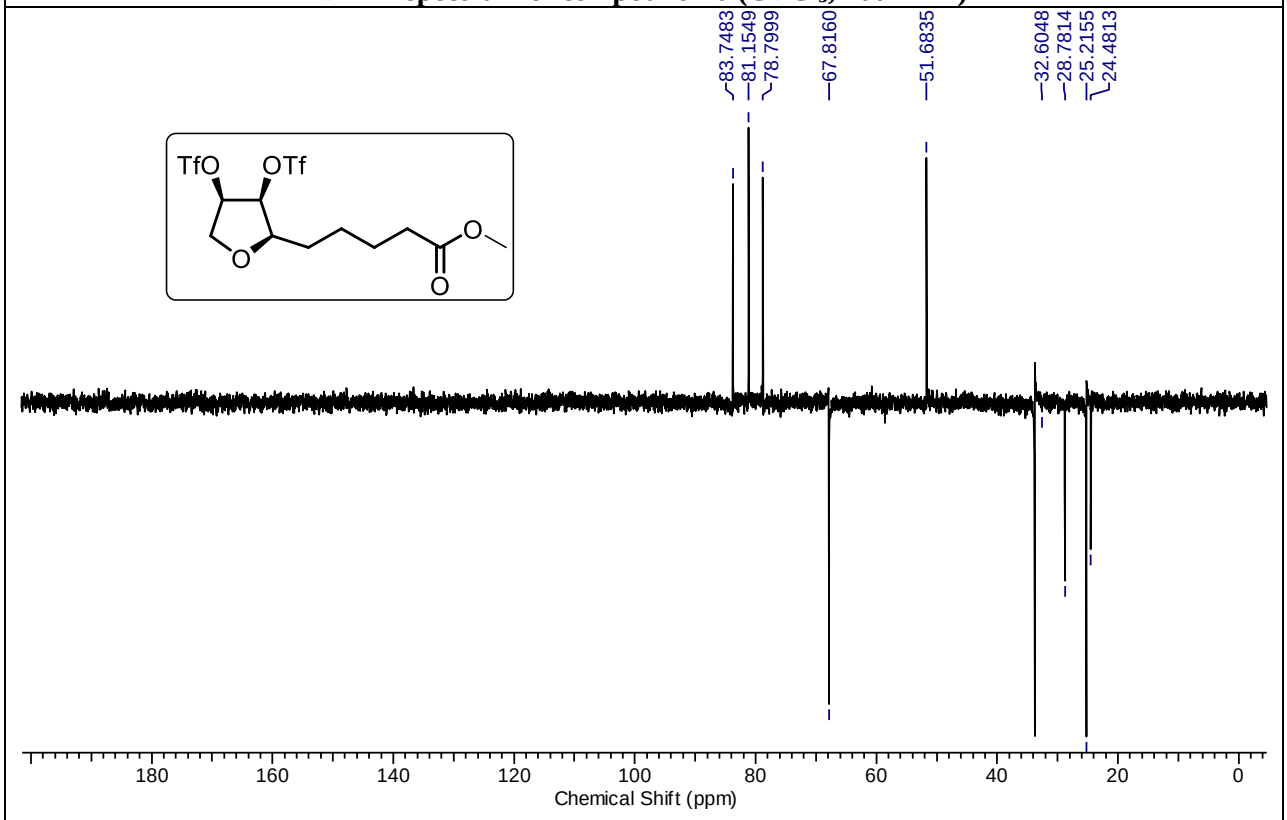
^{1}H-NMR spectrum of compound 10 ($CDCl_3$, 400 MHz)



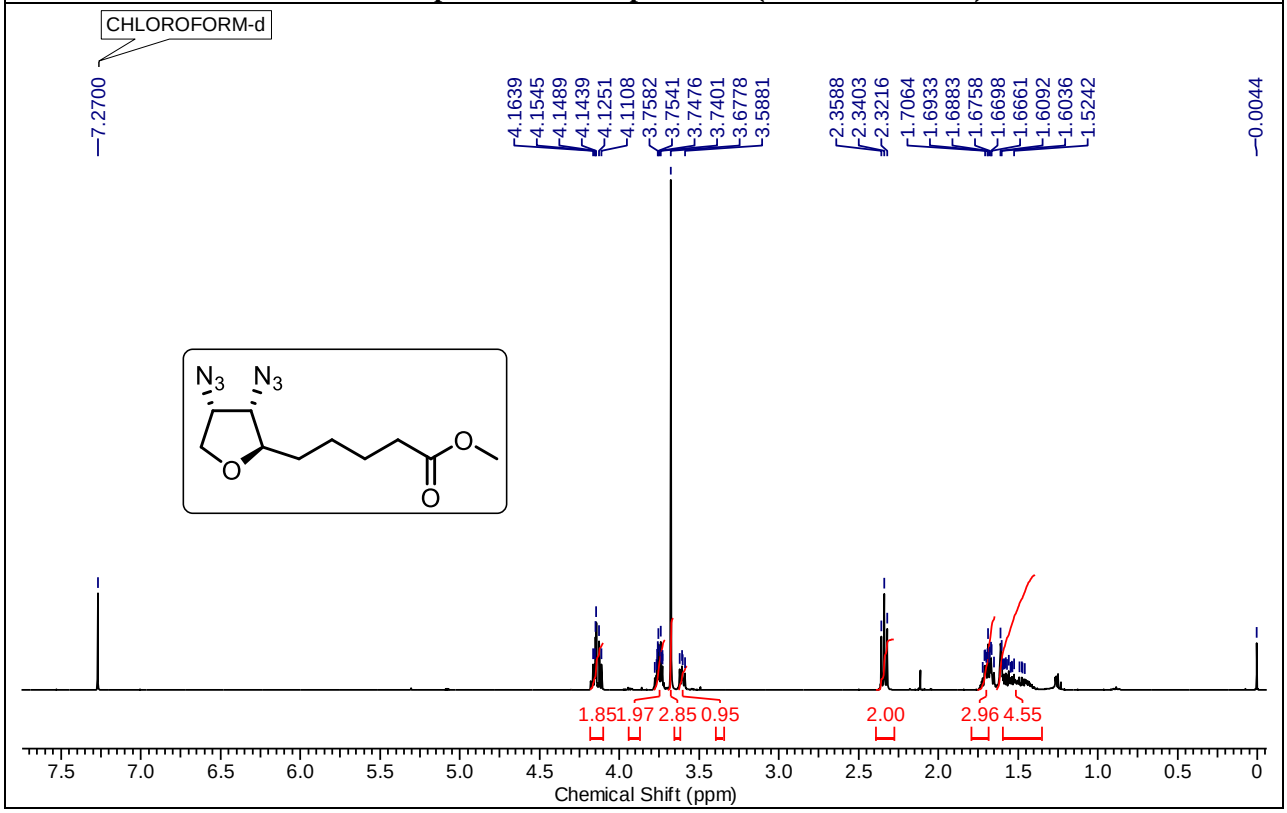
^{13}C-NMR spectrum of compound 10 ($CDCl_3$, 100 MHz)



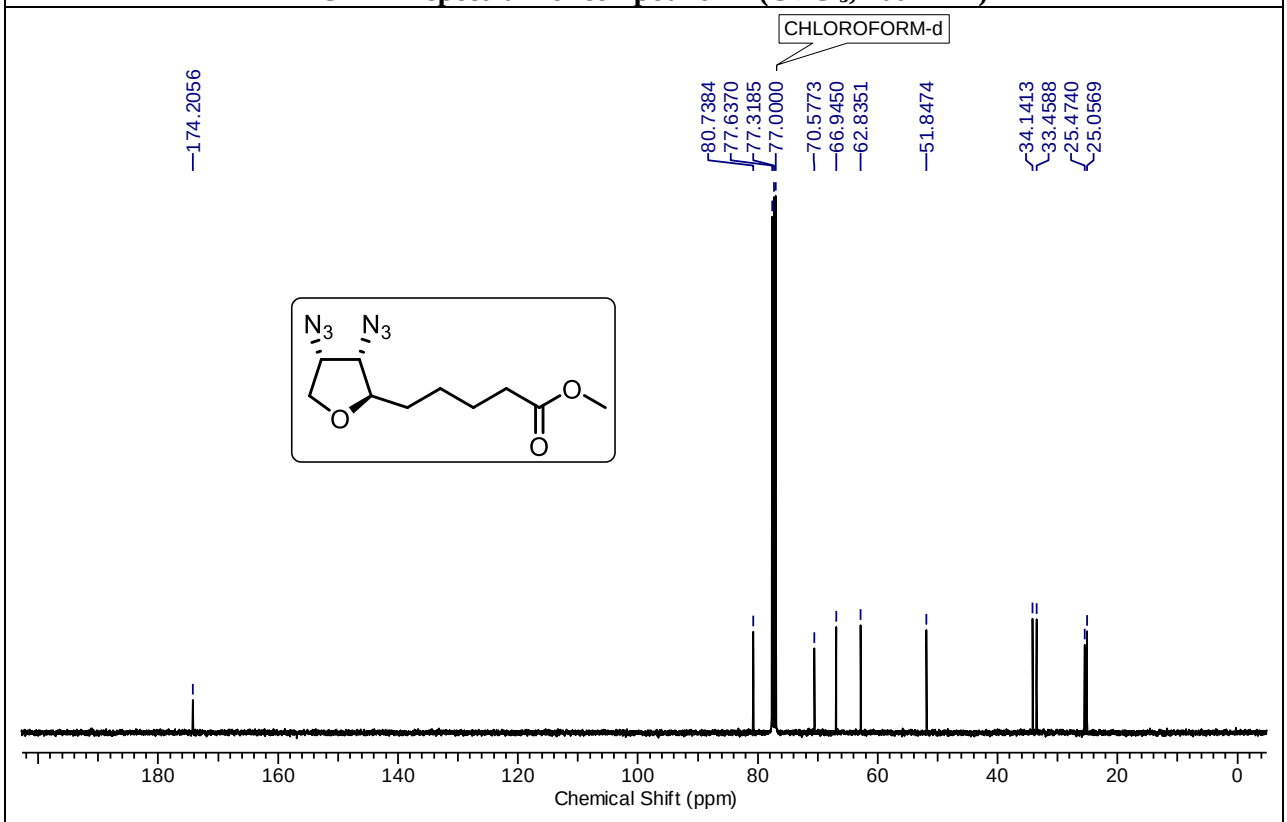
DEPT spectrum of compound 10 ($CDCl_3$, 100 MHz)



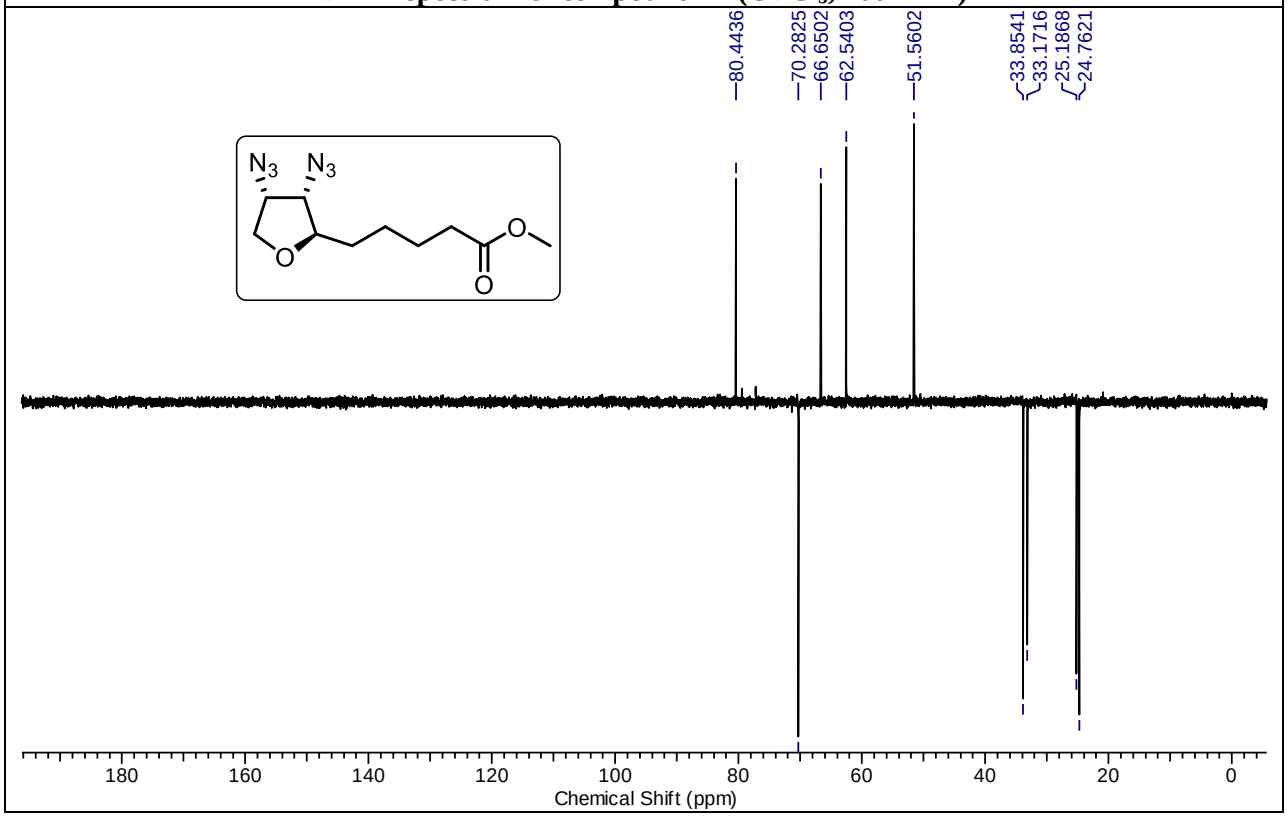
^{1}H-NMR spectrum of compound 11 ($CDCl_3$, 400 MHz)



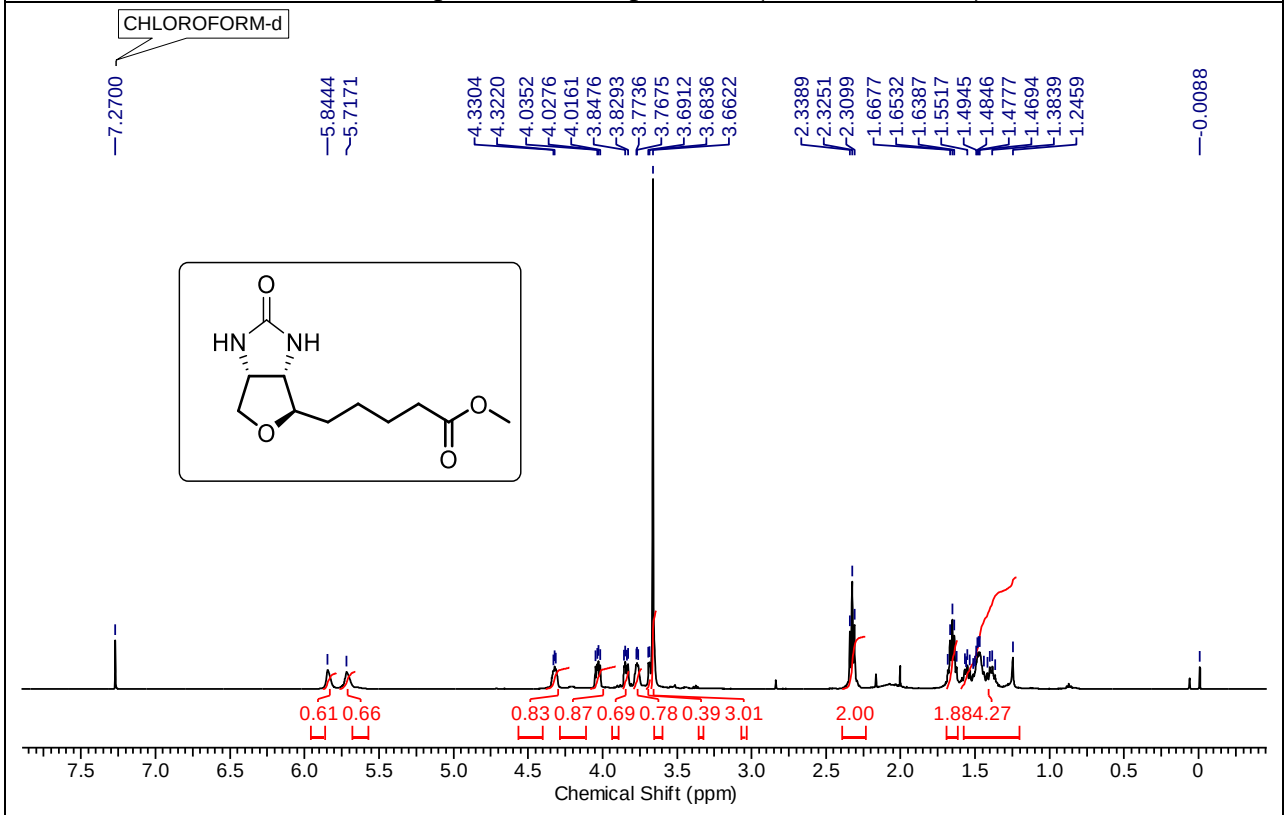
^{13}C-NMR spectrum of compound 11 ($CDCl_3$, 100 MHz)



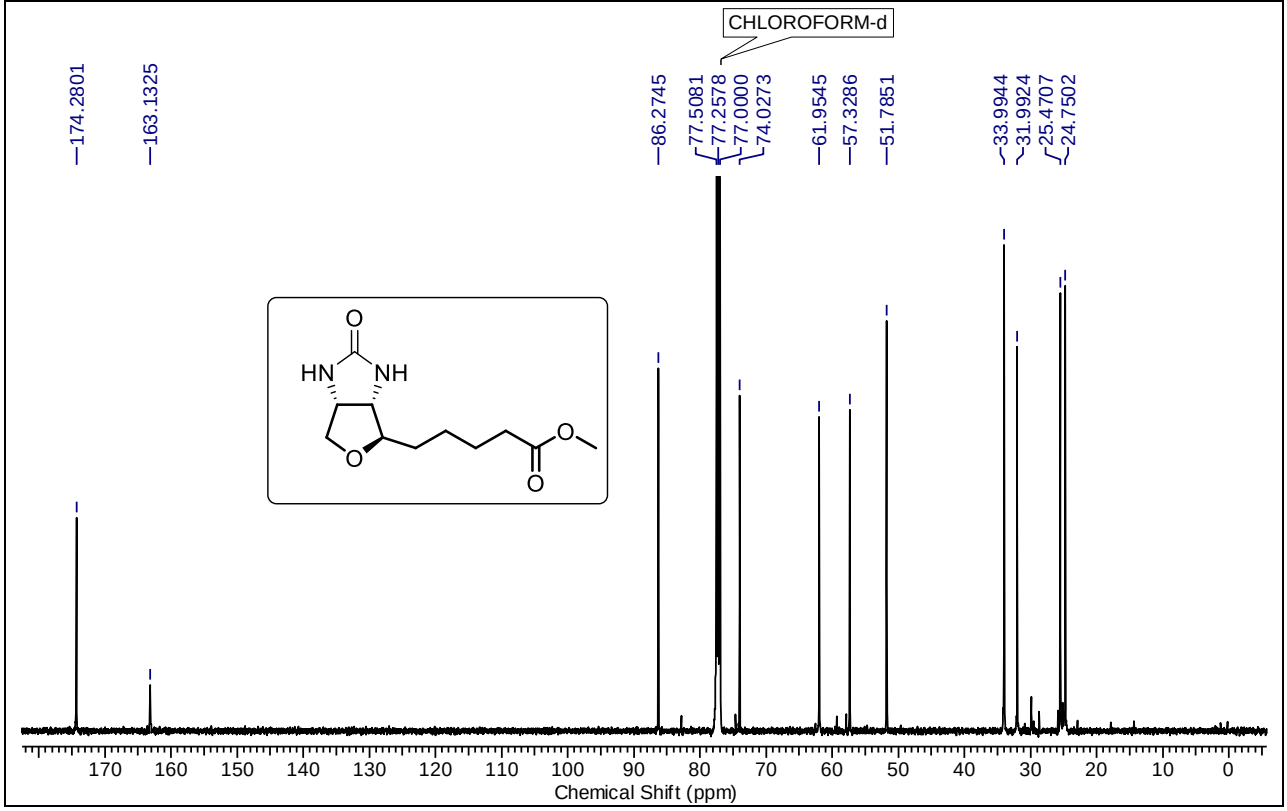
DEPT spectrum of compound 11 ($CDCl_3$, 100 MHz)



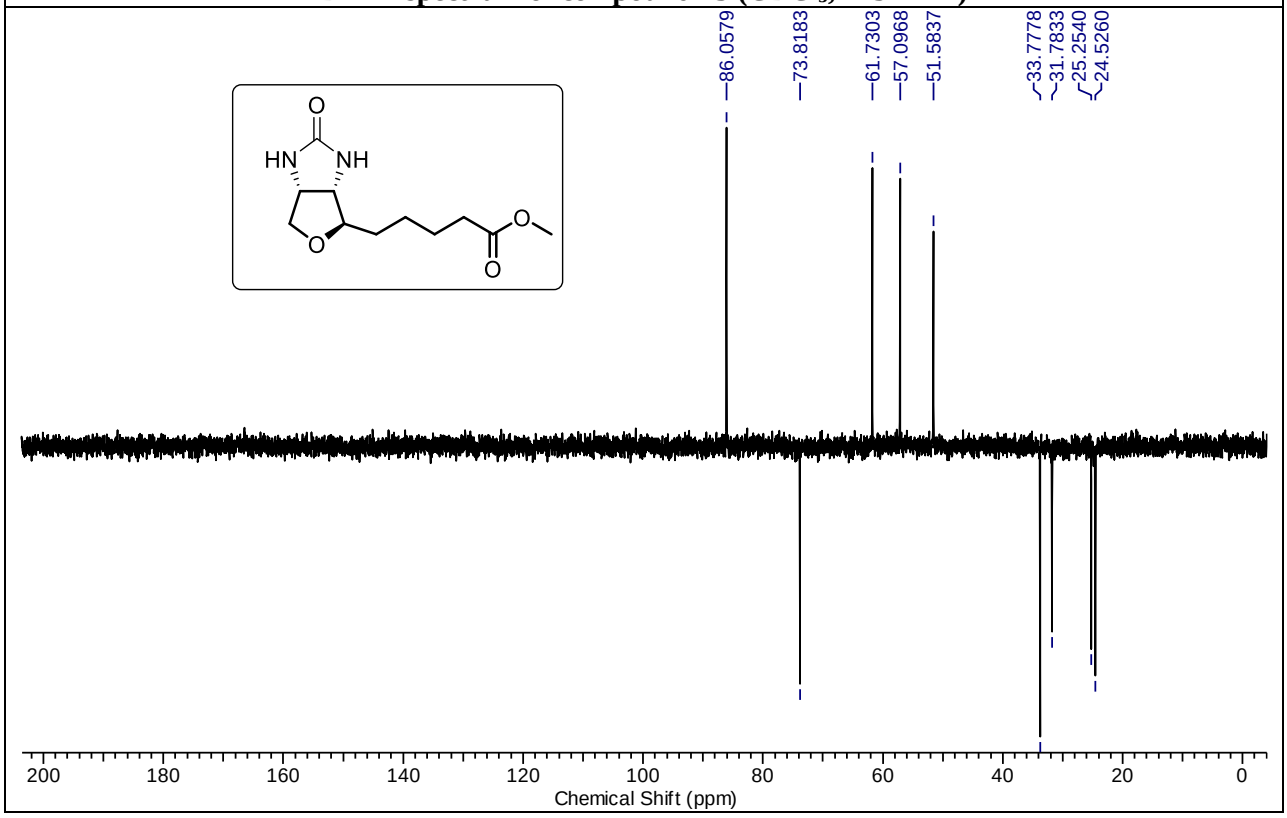
^{1}H-NMR spectrum of compound 13 ($CDCl_3$, 500 MHz)



^{13}C-NMR spectrum of compound 13 ($CDCl_3$, 125 MHz)



DEPT spectrum of compound 13 ($CDCl_3$, 125 MHz)



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Chapter 2, Section I

3-ethyl-4-methyl-1,5-dihydro-2H-pyrrol-2-one: An Important Building Block of Antidiabetes Drug Glimepiride

2.1.1. Introduction to the 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one: An Important Building Block of Antidiabetes Drug Glimepiride:

In the area of the medication, the chemistry has always played a vital role in the design and the synthesis of the multitargeted medicines. Nowadays, chemists are taking the keen interest to develop the multitargeted medicines that can bind to the particular receptors in the targeted area for the specific diseases.[1] In addition, there is a growing use of the combined oral drugs. One of such an example is the combination of the Metformin and Glimepiride which are used in the therapy of the type 2 diabetes mellitus (T2DM). This combination was set up after safeguarding the existing marketed amalgamation of the medicine formulations. Both these medicines are useful in the management of the T2DM either in single form or in combined medication.[2] Glimepiride **1** and its derivatives, which correspond to the class of the sulphonyl urea drugs are nowadays widely used for the treatment of the diabetic patients.

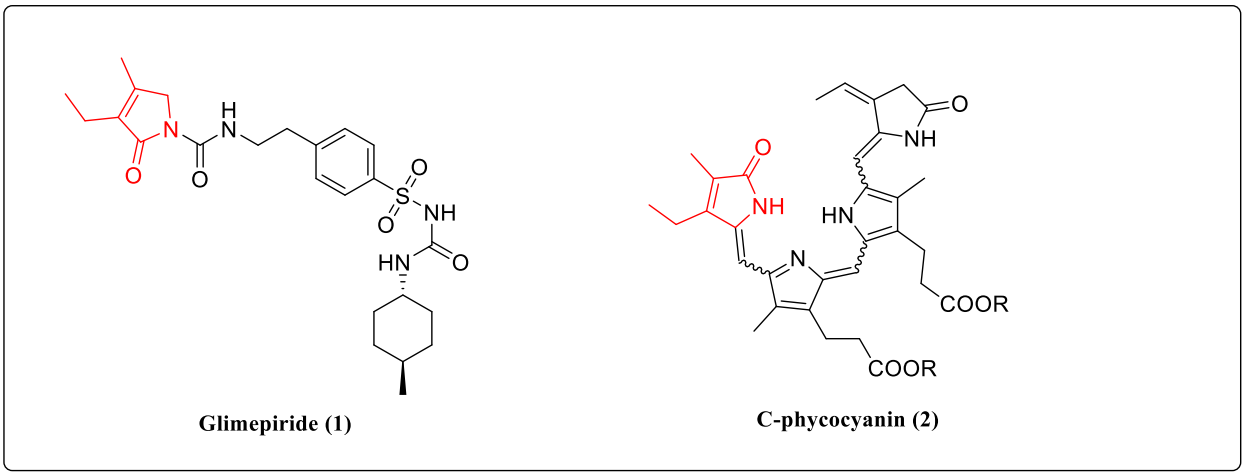


Figure 1: Structures of Glimepiride **1** and C-phycocyanin **2.**

In the year 2003 Gurjar *et al.* have synthesized the *cis*- and *trans*-hydroxyglimepiride which are the active metabolites of the Glimepiride **1**.[3] Glimepiride **1** has several benefits such as it diminishes the high sugar levels in the blood. Hence, it is also called as sugar lowering agent. Glimepiride **1** is also well known for the prevention of the extra insulin release in the body which in turn reduces the risk of the hypoglycemia.

Today, diabetes is increasing worldwide and has become the major health concern. Globally, India is recognized as the 'diabetes capital'. According to the latest report published on January 2021 by the Union Ministry of the Family and Health Welfare of the India, 9.3% adults from the rural India were diagnosed for the diabetes. It has been found that the diabetes also leads to the

other diseases like amputation, blindness and the failure of the kidneys. Also, in the current ongoing Covid-19 pandemic, the diabetic patients are advised to take more precautions as they come under high risk profile and are vulnerable for the corona virus infection, causing serious illness due to Covid-19 disease. Doctors are facing difficulties in treating the diabetic patients due to serious alteration of the glucose levels in the blood of the diabetic patients. Thus, the diabetes is causing several complications in the treatment of the many diseases. Although, the diabetes is common disease, it can lead to fatalities when the patients are having multiple diseases. Thus the eradication of the diabetes from the globe is necessary. Glimepiride **1** and its metabolite drugs are found effective in treating this diabetes disease.

3-Ethyl-4-methyl-1, 5-dihydro-2*H*-pyrrol-2-one (**Figure 2**) is the chief building block of important antidiabetic drug Glimepiride **1** and its other analogues.

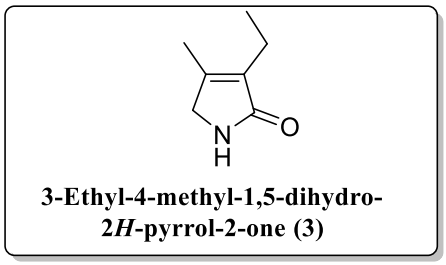


Figure 2.

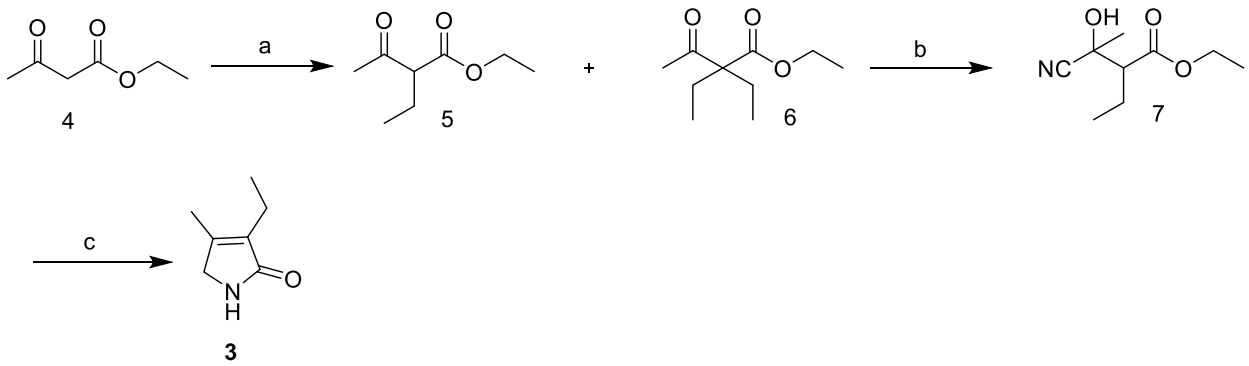
Majority of the natural products having bioactivities contain five and six-membered lactams as the main building blocks in their core structures. Pyrrolidone **3** is also the crucial building block of the bile pigments i.e. C-phycocyanin **2** which is shown in the **Figure 1**. This was separated from blue-green algae whose scientific name is *Synechoccus sp. 6301***.** Besides this, it is an antenna pigment which is composed of three different tetrapyrrole-established chromophores which are linked by the thioether linkage to the proteins.[4] Bile pigments are also known as the biological pigments. These bile pigments participate in the process of the photosynthetic reactions.

2.1.2. Literature Survey

Henry *et al.*[4]

Henry *et al.* accomplished the synthesis of pyrrolidone **3** by using the ethyl acetoacetate **4** as the commercially available staring material. Initially, the ethyl acetoacetate **4** was subjected for the alkylation reaction by using the ethyl iodide and sodium ethoxide in the presence of the ethanol as the solvent under reflux conditions to give the mixture of monoalkylated and dialkylated

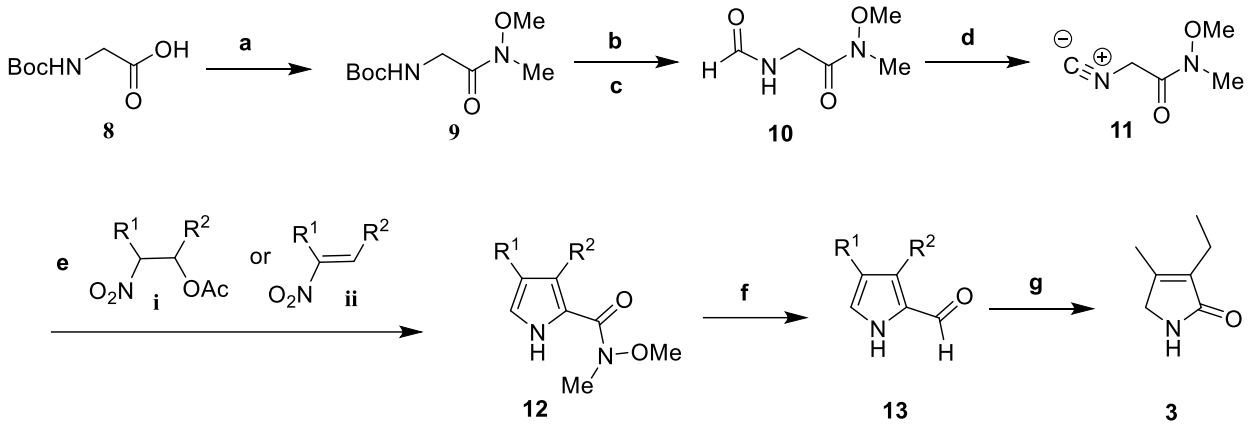
products **5** and **6** in 52% and 20 % yields respectively. The monoalkylated product **5** was then treated with sodium cyanide in the presence of sodium bisulphite which resulted in the formation of the cyanohydrin **7**. This cyanohydrin **7** was further reduced and then subsequently cyclized by using the Raney nickel under the atmosphere of the H_2 gas pressure (50 psi) at 33 ^oC and the dehydration of the resulting compound by sodium carbonate formed the expected pyrrolidone **3** in 29 % yield **(Scheme 1).**



Scheme 1. ***Reagents and conditions*****:** (a) NaOEt (1.0 eq.), EtI (1.0 eq.), EtOH, 80 ^oC, 4 h, 52 % (b) $NaHSO_3$ (1.23 eq.), NaCN (1.05 eq.), H_2O, 0 ^oC, 3 h (c) H_2, T-1 Ra-Ni, Ac_2O, 50 psi, 33 ^oC, 12 h, reflux, 8 h (ii) Na_2CO_3, H_2O, reflux, 4 h, 29%.

Pelkey *et al.* [5]

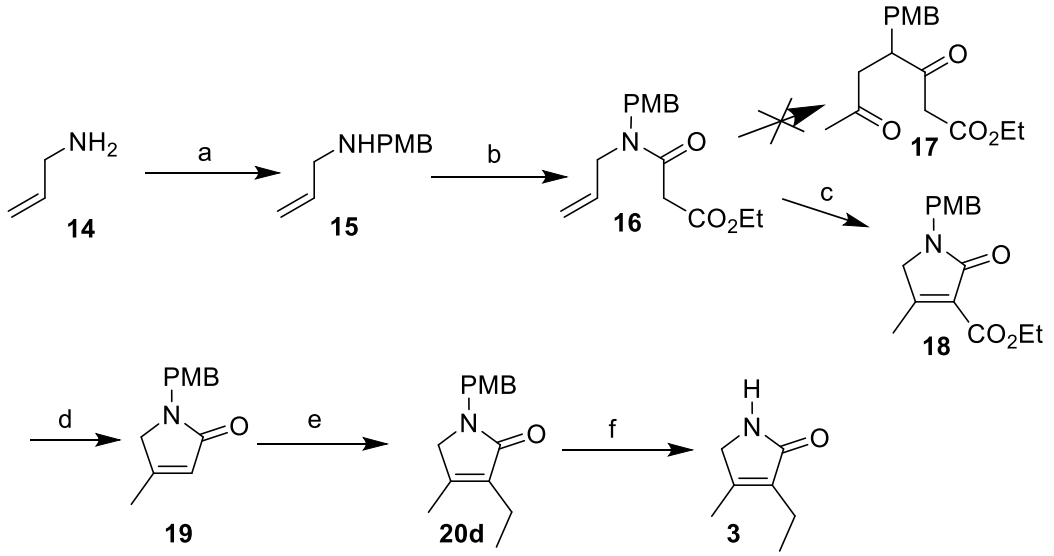
Pelkey *et al*. completed the synthesis of the pyrrolidone **3** in seven steps and the overall yield of the synthesis was 14%. The synthesis was started by using the compound Boc-glycine **8** as the starting material. The compound **8** was coupled with *N, O*- dimethyl hydroxyl amine by the utilization of the DCC coupling reaction to afford the Weinreb amide **9** in 78% yield. In addition, the Boc group from the Weinreb amide **9** was deprotected and subsequently it was formylated to get the aldehyde **10** and the yield for these two steps was 65%. Additionally, the formamide **10** was dehydrated by the utilization of the $POCl_3$ to furnish the intermediate isocyanide **11** in 70% yields. Further, the cycloaddition reaction by using nitroacetate **i** or the α-nitroalkene **ii** in the presence of DBU as the base led to the formation of the Weinreb amide **12** in excellent yields. The amide **12** was then converted into the pyrrole-2-carboxaldehyde **13** by the reduction with $LiAlH_4$ in the THF solvent to give 65% yield. In the final step, the aldehyde **13** was oxidized to its 3-pyrrolidone-3-ones **3** by using H_2O_2 and sodium bicarbonate. Thus, the total synthesis of the pyrrolidone **3** was completed (**Scheme 2)**.



Scheme 2. ***Reagents and conditions*****:** (a) MeONHMe, DCC, CH_2Cl_2, 0 ^oC-rt, 78%; (b) HCO_2H, 80 ^oC; (c) HCO_2Et, Et_3N, heat, (65% for two steps); (d) $POCl_3$, Et_3N, THF, 70%; (e) **i** or **ii**, DBU, THF, 0 ^oC-rt, 90%; (f) $LiAlH_4$, THF, 0 ^oC, 65%; (g) H_2O_2, $NaHCO_3$, MeOH, rt, 67%.

Chavan *et al.*[6]

Chavan *et al*. achieved the synthesis of the pyrrolidone **3** by the utilization of the novel palladium catalyzed cyclization and the ring closing metathesis reaction. The synthesis was started by using the commercially available and cheap allyl amine **14** as the staring material. The amine **14** was converted to PMB protected secondary amine **15** by the utilization of the *p*-anisaldehyde and subsequently reducing the imine formed by the sodium borohydride. The amine **15** was then converted to amide **16** in 86% yields by using ethylmalonyl chloroacetate. Additionally, the amide **16** on the treatment with 10 mol % palladium chloride in the presence of

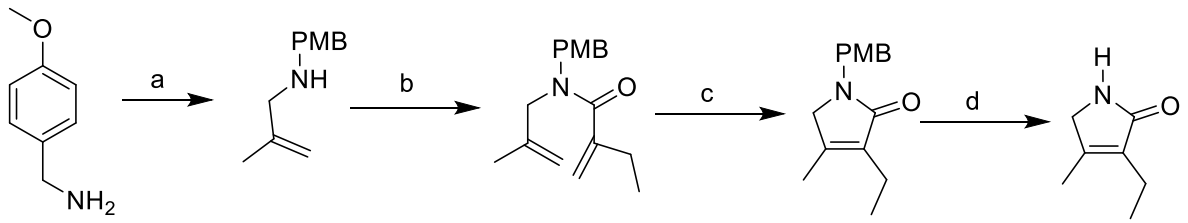


Scheme 3. ***Reagents and conditions*****:** (a) (i) *p*-anisaldehyde (1.1 eq.), MeOH, 0 °C, 1 h; (ii)

$NaBH_4$ (1.0 eq.), MeOH, 0 °C, 1 h, 97%; (b) K_2CO_3 (1.2 eq.), ethyl malonyl chloride (1.2 eq.), CH_2Cl_2, 0 °C, 1 h, 86%; (c) $PdCl_2$ (10 mol%), $CuCl_2$ (2.1 eq.), DMF–H_2O (3:1), 95 °C, 6–8 h, 62%; (d) NaCl (4.0 eq.), DMSO–H_2O (3:1), 120–130 °C, 12 h, 87%; (e) NaH (1.2 eq.), EtI (1.2 eq.), anhydr. THF, 0 °C to r.t., 3 h, 71%; (f) CAN (2.5 eq.), MeCN–H_2O (5:1), r.t., 2 h, 80%.

the copper chloride as the co-oxidant in DMF: H_2O system at 95 °C for 6 h afforded the cyclized lactam **18** in 62%. However, the desired ketone **17** was not formed. The lactam **18** was then transformed into the compound **19** by using the Krapcho decarboxylation reaction. Finally, the regioselective alkylation by using the ethyl iodide and sodium hydride led to the formation of the desired product **20d.** In addition, the PMB group in the lactam **20d** was removed by using CAN in ACN: H_2O system and the expected pyrrolidone **3** was formed in good yield (**Scheme 3**).

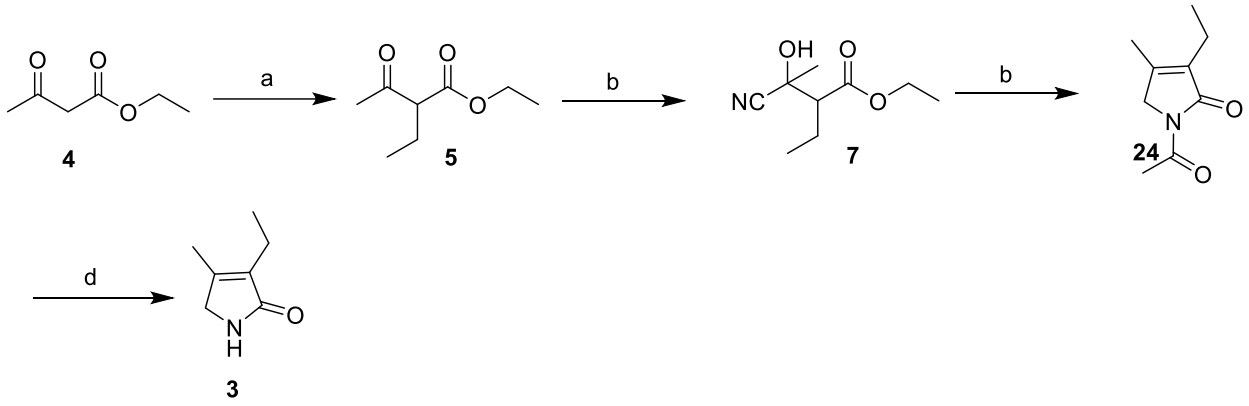
In another method Chavan *et al*. accomplished the synthesis of the compound **3** by the utilization of the ring closing metathesis reaction which is depicted in the **Scheme 4**. In this strategy the synthesis was started by using the readily available 4-methoxy benzylamine **21** as the starting material which was subjected for the alkylation by the use of methallyl chloride, potassium carbonate and potassium iodide in the catalytic amount to give the secondary amine **22**. Further, the amine **22** was *N*-acylated by the use of ethacryloyl chloride which was synthesized from the butyraldehyde by the reported protocol.[7, 8] This furnished the tertiary amine **23** in very good yields. After achieving the precursor amide **23** it was then subjected for the famous ring closing metathesis reaction by the use of the 10 mol % Grubbs' 2nd generation catalyst in dry toluene at 80 °C for 24 h to give the 40 % yield of the unsaturated lactam **20d** and then this lactam **20d** was converted to the desired pyrrolidone **3** by the known method described in the **Scheme 3**.



Scheme 4. ***Reagents and conditions*****:** (a) Methallyl chloride (0.33 eq.), K_2CO_3 (1.2 eq.), KI (cat.), anhydr. CH_2Cl_2, 0 °C to r.t., 12 h, 84%; (b) K_2CO_3 (1.2 eq.), ethacryloyl chloride (1.2 eq.), anhydr. CH_2Cl_2, 0 °C to r.t., 3 h, 91%; (c) Grubbs' II catalyst (10 mol%), Ti(O*i*-Pr)$_4$ (2.0Eq.), anhydr. toluene, 80 °C, 12 h, 90% (based on recovered **23**).

Gurjar *et al.*[3]

Gurjar *et al.* commenced the synthesis of **3** from the ethyl acetoacetate **4** which was alkylated to get the compound **5** by using the dimethylamine and diethyl sulphate at 10-15 ºC. Additionally, the compound **5** was treated with sodium cyanide in dimethyl formamide solvent at 0–5℃ to afford the cyanohydrin **7** in 80% yields. Further, the cyanohydrin **7** was reduced followed by cyclization by the use of hydrogen gas in the presence of Raney nickel catalyst and acetic anhydride to access the lactam **24**. Finally, the removal of the acetate group by using the sodium carbonate in water under reflux conditions resulted in the formation of the expected lactam **3** in 90% yields.

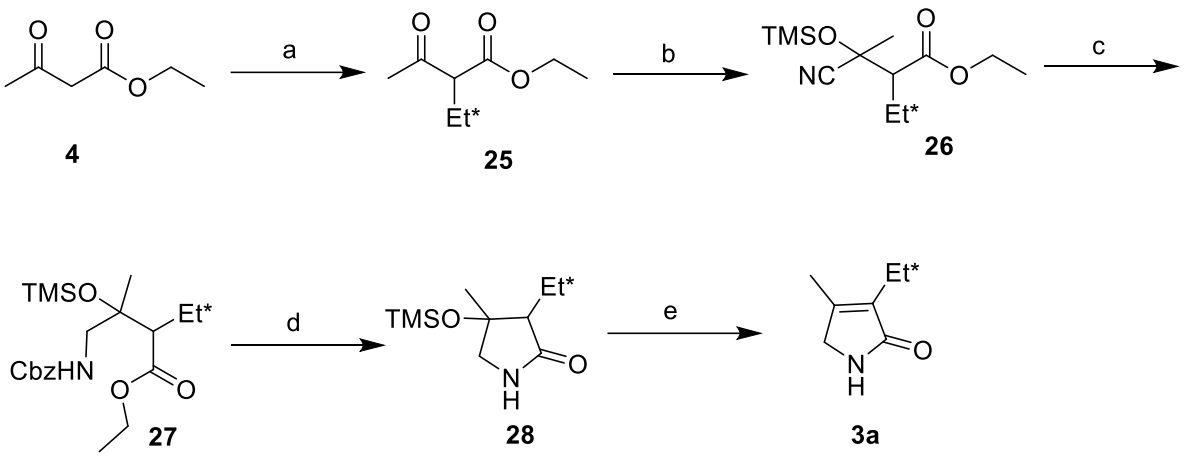


Scheme 5. ***Reagents and conditions*****:** (a) $HNMe_2$, Et_2SO_4, 10–15°C, 70%; (b) NaCN, DMF, 0–5°C, 80%; (c) H_2, Ra–Ni, Ac_2O, 40°C, 5 Kg/cm^2,15%; (d) Na_2CO_3, H_2O, reflux, 90%.

Burton *et al.*[9]

Burton *et al.* reported the synthesis of $^2H_5$-Glimepiride in which they also synthesized the $^2H_5$ labelled pyrrolidone **3**. It is the modification of the synthesis reported by Rapoport.[4] Easily available $^2H_5$-ethyl iodide was chosen as the suitable isotopic labeled initial material for the synthesis. Ethyl acetoacetate **4** was alkylated by using the $^2H_5$-ethyl iodide and the phase transfer catalyst ($BnEt_3N^+Cl^-$) to get the alkylation product β-ketoester **25**. Further, the β-ketoester **25** was then converted to the silyl cyanohydrin **26** by using the TMSCN and catalytic zinc iodide in dichloromethane at 20 ºC for 16 h and the yield of the reaction was 95%. The silyl cyanohydrin was further reduced to amine by the utilization of the nickel hydride under Caddick's conditions.[10] Additionally, the use of the dibenzyl dicarbonate trapped the formation of the primary amine. Further, the protection of amine was carried out using benzyl chloroformate to access the compound **27**. In addition, the compound **27** was cyclized to its lactam **28** by

performing the hydrogenation under high vacuum. The treatment of the lactam **28** with sulphuric acid at 20 ^{o}C resulted in the formation of the $^{2}H_5$ labelled pyrrolidone **3a** in the yield of 95% (**Scheme 6**).



* = position of the $^{2}H_5$ lebell.

Scheme 6. ***Reagents and conditions*****:** (a) 1 eq. EtI, K_2CO_3, 5 mol% $BnEt_3N^+Cl^-$, 20°C, 41 h, 76%; (b) 1.2 eq. Me_3SiCN, 5 mol% ZnI_2, CH_2Cl_2, 20°C, 16 h, 95%; (c) **i.** 2 eq. $NiCl_2.6H_2O$, 2 eq. $(CO_2Bn)_2O$, 8 eq. $NaBH_4$, MeOH, 5-10°C, 1.5 h; 20°C, 17 h; **ii.** 4 eq. $ClCO_2Bn$, pyridine, CH_2Cl_2, 20°C, 45%; (d) **i.** H_2, 10% Pd-C; **ii.** High vacuum, 20°C, EtOH, 94%; (e) H_2SO_4, 20^{o}C, 24 h, 95%.

Thus the above literature survey depicts the utilization of the various reactions for the synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (pyrrolidone **3**).

2.1.3. References:

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2. Thipparaboina, R.; Kumar, D.; Chavan, R. B.; Shastri, N. R. Multidrug co-crystals: Towards the development of effective therapeutic hybrids. *Drug Discov. Today* **2016**, *21*, 481.
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5. (a) Deng, Y.; Zhong, Y. *Huaxi Yaoxue Zalzhi*. **2000**, *15*, 289. (b) Deng, Y.; Zhong, Y.; Tang, W.; Zhong, Z. *Zhongguo yaowu Huaxue Zazhi*, **2000**, *10*, 134. (c) Coffin, A. R.; Roussell, M. A.; Tserlin, E.; Pelkey, E. T. *J. Org. Chem*. **2006**, *71*, 6678 and references cited therein.
6. Chavan, S. P.; Pathak, A. B.; Pawar, K. P.; *Synthesis* **2015,** *47*, 955.
7. Pikh, Z. G.; Fedevich, M. D.; Yatchishin, I. I. *Zh. Org. Khim.* **1978**, *1*, 60.
8. Hon, Y.-S.; Lin, W.-C. *Tetrahedron Lett.* **1995**, *36*, 7693.
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10. Caddick, S.; Haynes, A.; Judd, D. B.; Williams, M. R. V. *Tetrahedron Lett*. **2000**; *41*, 3513.

2.1.4. Introduction:

The rapid prevalence of diabetes, especially among the middle and low-income countries causes growing concern among the scientific community. In the year 2016, diabetes alone was responsible for the deaths of an estimated 1.6 million people. Almost half of all deaths due to high blood glucose occur before the age of 70 years. WHO estimated that diabetes was the seventh leading cause of death in the year 2016.[1]

Currently, many drugs are available in the market for the treatment of diabetics. In that context, in the year 2003, Gurjar *et al*. reported the synthesis of *trans*-hydroxyglimepiride, a metabolite of the antidiabetic drug glimepiride (**1**).[2] The antidiabetic drug glimepiride (**1**) consists of 3-ethyl-4-methyl-1, 5-dihydro-2*H*-pyrrol-2-one (**3**) as an essential heterocyclic building block. Pyrrolinone **3** is also present as the main precursor in bile pigments; the blue protein C-phycocyanin (**2**) (**Figure 1**).

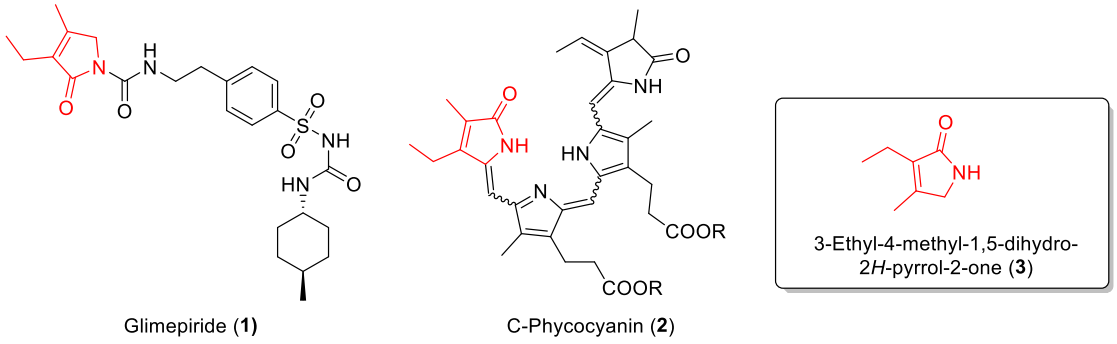


Figure 1. Glimepiride (**1**) and C-phycocyanin (**2**) consist of scaffold 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**).

2.1.5. Present Work:

Due to the ring strain and steric crowding of the substituents present on olefin, the synthesis of pyrrolidone **3** becomes challenging. Though there are only a few practical synthetic routes reported in the literature,[3] its importance in the medicinal chemistry attracted synthetic chemists for the short and industrially scalable synthesis of pyrrolidone **3**. The earlier reported synthetic routes involved the use of hazardous reagents such as NaCN, an expensive catalyst such as $PdCl_2$ and Grubbs' catalyst and harsh conditions such as high temperature and pressure (**Figure 2**). So there is a long-standing need to develop a short, high yielding and industrially scalable method using simple and easily accessible reagents. In continuation of research towards the synthesis of

biologically active natural products and medicinally important drug molecules,[4] development of the scalable process for the synthesis of 3-ethyl-4-methyl-3-pyrrolin-2-one (**3**) was initiated.

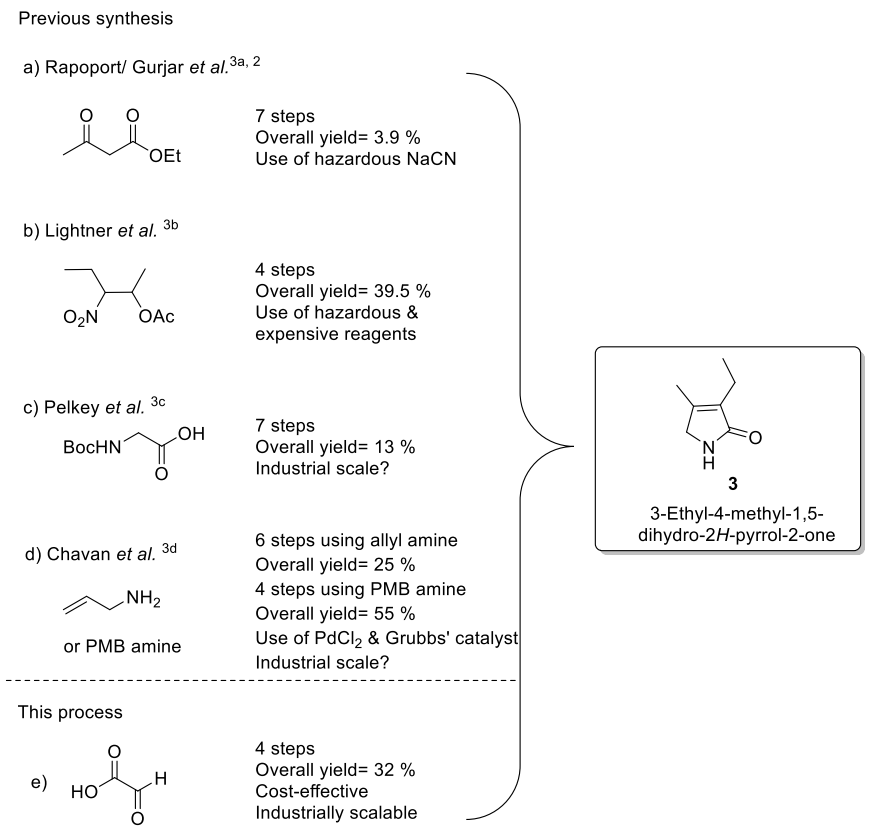
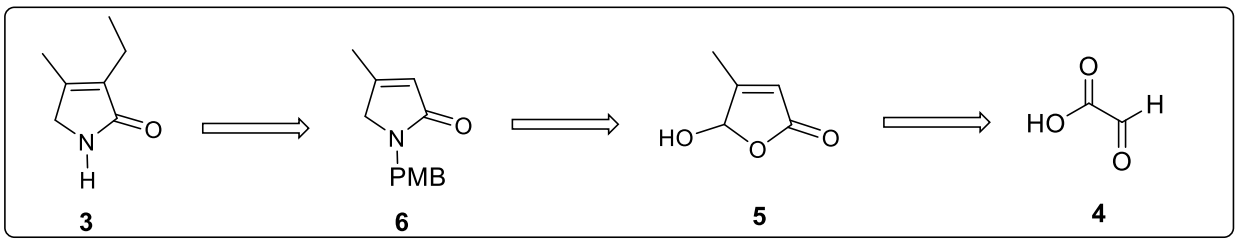


Figure 2. Synthetic approaches to 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**).

Retrosynthetic Analysis:

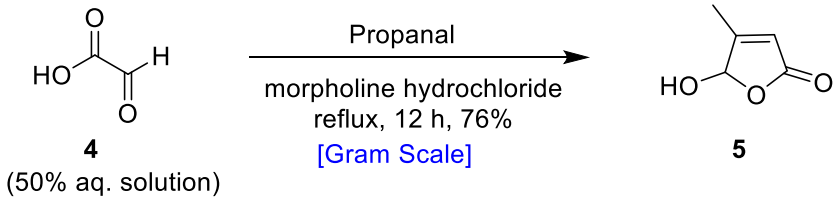
It was thought that the 3-ethyl-4-methyl-3-pyrrolin-2-one (**3**) could be obtained from the unsaturated lactam **6** by using the alkylation reaction and the PMB deprotection and the lactam **6** in turn can be accessed from the hydroxy butenolide **5** by using the reductive cyclization reaction of the PMB amine. In addition, the hydroxy butenolide **5** could be prepared from the glyoxylic acid **4** as shown in the **Scheme 1**. Further, according to the retrosynthetic plan the synthesis was designed.



Scheme 1: Retrosynthesis.

2.1.6. Results and discussion:

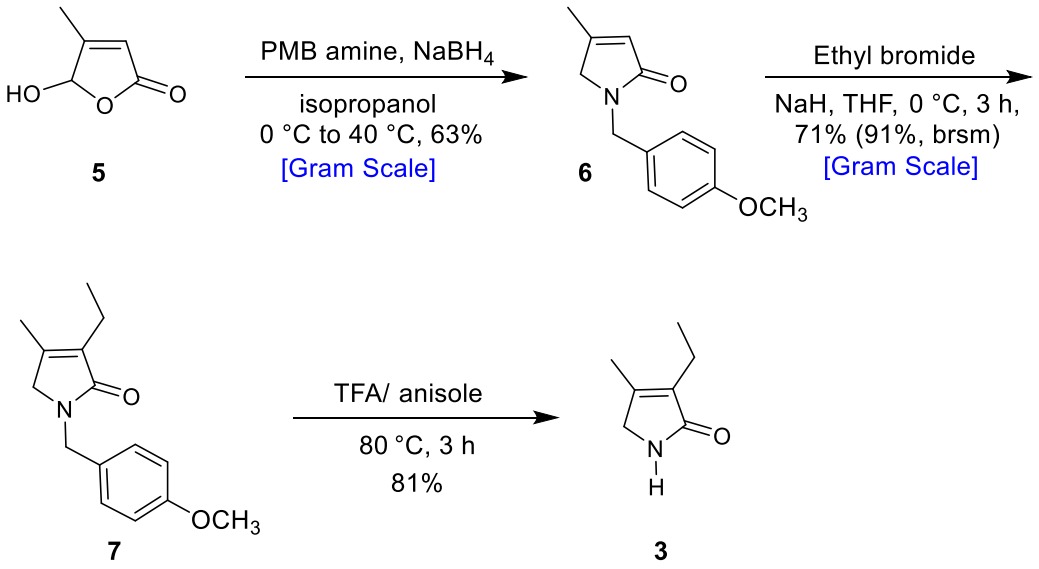
Synthesis commenced with the preparation of 3-methyl-4-hydroxy-2-butenolide **5** using glyoxylic acid **4** as a starting material (**Scheme 2**). Synthesis of 3-methyl-4-hydroxy-2-butenolide **5** from glyoxylic acid and propanal in dioxane as a solvent was reported by Wermuth *et al*.[5] For the large scale synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one **3**, cost of the solvent dioxane contributed significantly in the total cost of API. So it was decided to develop a process using either water as a solvent, which is considered to be a green solvent or solvent-free process. Towards this, when the reaction of glyoxylic acid (50% aqueous solution) with propanal in the presence of morpholine hydrochloride was carried out at reflux temperature, pleasingly, the formation of 3-methyl-4-hydroxy-2-butenolide **5** was observed in 55% yield in 24 h. After slight optimization, 3-methyl-4-hydroxy-2-butenolide **5** was isolated in 76% yield in 12 h reaction time. It is worthy of mentioning that, morpholine hydrochloride was prepared from morpholine and 35% HCl and used as such without isolation. Thus, 3-methyl-4-hydroxy-2-butenolide **5** was successfully synthesized in multigram scale using water as a solvent, which makes this process green, cost-effective, and industrially applicable.



Scheme 2. Synthesis of 3-methyl-4-hydroxy-2-butenolide **5** in water.

Next crucial step was the synthesis of lactam **6** from 3-methyl-4-hydroxy-2-butenolide **5**. To this end, when 3-methyl-4-hydroxy-2-butenolide **5** was treated with PMB amine in isopropyl alcohol followed by treatment with $NaBH_4$ under basic condition, it furnished lactam **6** in 63% yield (**Scheme 2**). Initially, isolation of hydroxy lactam was attempted, and then it was subjected to reduction using $NaBH_4$, but the yield of lactam was severely reduced to ~20% mainly due to unstability of the product in the silica gel purification of hydroxy lactam. To get the required substitution on olefin moiety, lactam **6** was treated with ethyl iodide and NaH at 0 °C to obtain compound **7** in 71% yield (91% brsm). Here it was observed that, the starting material remained even after using excess reagents and stirring the reaction for a longer time at various temperatures. All the efforts to get 100% conversion failed in this case. The final step was the *N*-

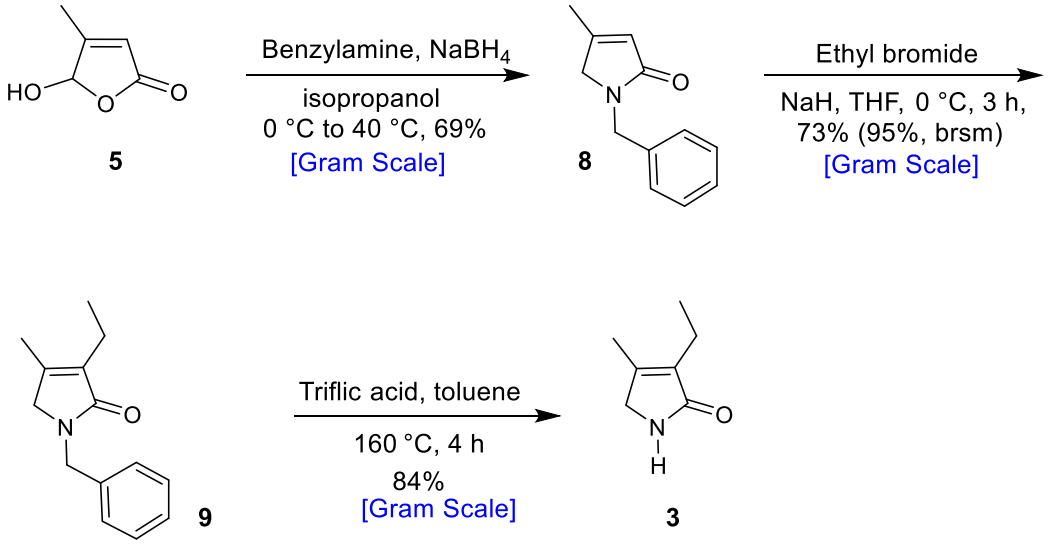
para-methoxybenzyl (PMB) deprotection of the lactam. In literature, PMB deprotection of lactam was carried out using CAN.[3d] But considering the problems associated with the CAN at large scale, the attention was turned towards another method for the deprotection of *N*-PMB of lactam. Towards this, *N*-PMB deprotection of lactam **7** was carried out using TFA in anisole at 80 °C under microwave condition to obtain 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one **3** in 81% yield.[6] The same reaction was reproduced using conventional heating condition for the synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**).



Scheme 3. First-generation approach for the synthesis of **3**.

Though the good overall yield of this process (35 %) was achieved in the less number of steps (4) and the process is scalable at large scale, the main goal was to develop a cost-effective and scalable process for the synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**). Cost calculation of API 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**) synthesized using the above process suggested that PMB amine, TFA, and anisole contributed largely to the overall cost of the process. Here, though PMB amine is mostly accountable for overall cost of the process, it was used for the lactam formation keeping in mind that, in the final step its deprotection was carried out using known and mild reaction condition. So there is a need for the alternative for PMB amine such as benzylamine and also, development of the method for the *N*-debenzylation of lactam, which would make this protocol cost-effective.

Accordingly, following a similar reaction sequence, *N*-benzyl lactam **9** was synthesized using benzylamine in three steps in 50% yield (**Scheme 4**). In the last step, to achieve the *N*-benzyl deprotection of lactam **9**, known reaction conditions were screened. When *N*-benzyl lactam **9** was treated with TFA in anisole, starting material was recovered after 48 h and product formation was not observed. But when *N*-benzyl lactam **9** was subjected to microwave mediated *N*-benzyl deprotection using triflic acid (4 eq.) in toluene, product formation was observed in 86% yield.[7] To avoid microwave condition, when the same reaction was carried out using conventional heating using triflic acid in toluene, delightfully, the formation of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one **3** was observed in 84% yield, which meets the requirements of the scalable process. The spectral and analytical data of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**) were in complete agreement with the reported data.



Scheme 4. Second generation approach for the synthesis of **3**.

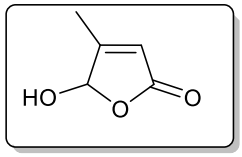
2.1.7. Conclusion:

In conclusion, short, cost-effective, and scalable synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one has been developed. Key features are synthesis of 3-methyl-4-hydroxy-2-butenolide in water, one-pot opening-reductive cyclization of butenolide for the synthesis of five-membered lactam and triflic acid-mediated *N*-benzyl deprotection of lactam **9**. As the synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**) has been achieved in 32 % overall yield in 4 steps, it is believed that this short, cost-effective and scalable synthesis of 3-ethyl-4-methyl-1,5-dihydro-

2*H*-pyrrol-2-one (**3**), an API of antidiabetic drug glimepiride paves the way for its industrial-scale synthesis.

2.1.8. Experimental:

5-Hydroxy-4-methylfuran-2(5*H*)-one (5)[7]:



To a stirred, ice-cold (0 °C) solution of morpholine (58.2 mL, 675 mmol, 1 equiv), conc. HCl (70.4 mL, 675 mmol, 1 equiv) was added dropwise over a 15-min period. The reaction mixture was then stirred for 2 h. To this, glyoxylic acid (100 mL, 50% aqueous solution, 675 mmol, 1 equiv) was added followed by propanal (50.7 mL, 708 mmol, 1.05 equiv), and the reaction mixture was further stirred at rt for 1 h and then refluxed for 12 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was concentrated to dryness and the residue was extracted with EtOAc (3 × 500 mL). The combined organic layer was washed with brine (200 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer *in vacuo* followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 30:70) afforded pure **5** as yellow oil.

Yield: 58.5 g (76%).

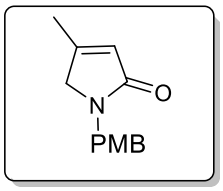
R_f = 0.3 (EtOAc–PE, 50:50).

IR ($CHCl_3$): 3407, 1760, 1216, 766 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.00 (s, 1 H), 5.85 (q, J = 1.5 Hz, 1 H), 5.41 (br s, 1 H), 2.10 (d, J = 1.5 Hz, 3 H).

Spectroscopic data were consistent with the earlier reported analytical information. [7]

1-(4-Methoxybenzyl)-4-methyl-1, 5-dihydro-2*H*-pyrrol-2-one (6)[5d]:



To a stirred solution of *p*-methoxybenzylamine (6.52 mL 49.9 mmol, 1.14 equiv) in isopropyl alcohol (40 mL), compound **5** (5 g, 43.8 mmol, 1 equiv) was added at room temperature. The reaction mixture was stirred at 40 °C for 1 h, then cooled to 0 °C and treated with a freshly prepared solution of $NaBH_4$ (1.06 g, 28 mmol, 0.64 equiv) in water (15 mL) containing NaOH (1 mL, 50% w/w in water) while maintaining the internal temperature below 25 °C. The reaction mixture was stirred for 1.5 h at that temperature. Excess $NaBH_4$ was quenched by addition of acetone to the reaction

mixture while maintaining the internal temperature below 30 °C. The mixture was filtered and AcOH (1 mL) was added to the filtrate to adjust the pH between 7–8 and the reaction mixture was heated at 50 °C for 16 h. The mixture was allowed to cool to rt and the solvent was evaporated under reduced pressure. The obtained residue was extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer *in vacuo* followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 40:60) afforded pure **6** as a pale yellow solid.

Yield: 6.0 g (63%).

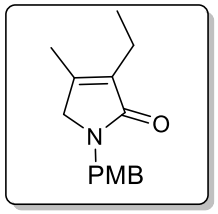
M. P. = 121 °C (Lit.[5d] 122 °C).

R_f = 0.2 (EtOAc–PE, 50:50).

IR ($CHCl_3$): 1674, 1222, 760 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.17 (d, J = 8.4 Hz, 2 H), 6.85 (d, J = 8.4 Hz, 2 H), 5.86 (br s, 1 H), 4.52 (s, 2 H), 3.79 (s, 3 H), 3.69 (s, 2 H), 2.00 (br s, 3 H). Spectroscopic data were consistent with the earlier reported analytical information. [5d]

3-Ethyl-1-(4-methoxybenzyl)-4-methyl-1,5-dihydro-2*H*-pyrrol-2- one (7)[5d] :



To a stirred solution of compound **6** (1 g, 4.6 mmol, 1 equiv) in anhydrous THF (25 mL), NaH (0.121 g, 5.06 mmol, 1.1 equiv) was added slowly at 0 °C. The reaction mixture was stirred for 15 min, ethyl bromide (0.41 mL, 5.52 mmol, 1.2 equiv) in anhydrous THF (5 mL) was added dropwise at 0 °C, and stirring was continued for 3 h at that temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was treated with saturated NH_4Cl solution and extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer *in vacuo* followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 20:80) afforded pure **7** as a yellow solid.

Yield: 0.62 g (55%) alongwith recovery of the starting material (0.3 g).

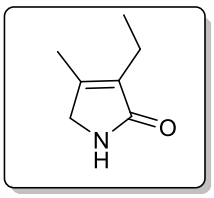
M. P. = 128 °C (Lit.[5d] 127–131 °C).

R_f. = 0.6 (EtOAc–PE, 50:50).

IR ($CHCl_3$): 1674, 1216, 762 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.17 (d, J = 8.6 Hz, 2 H), 6.85 (d, J = 8.6 Hz, 2 H), 4.54 (s, 2 H), 3.79 (s, 3 H), 3.58 (s, 2 H), 2.29 (q, J = 7.5 Hz, 2 H), 1.91 (s, 3 H), 1.08 (t, J = 7.5 Hz, 3 H). Spectroscopic data were consistent with the earlier reported analytical information. [5d]

3-Ethyl-4-methyl-1, 5-dihydro-2*H*-pyrrol-2-one (3)[5d]:



To a stirred solution of compound **7** (0.2 g, 0.816 mmol, 1 equiv) in anisole (2 mL), TFA (2 mL) was added and the reaction mixture was heated at 80 °C for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was allowed to cool to room temperature, quenched with saturated $NaHCO_3$ solution (4 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer *in vacuo* followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 50:50) afforded pure **3** as a pale yellow solid.

Yield: 82 mg (81%).

M. P. = 103 °C (Lit.[5d] 102 °C).

R_f = 0.3 (EtOAc–PE, 70:30).

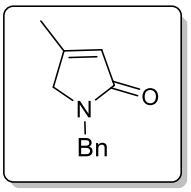
IR ($CHCl_3$): 3440, 1722, 1216, 765 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (br s, 1 H), 3.77 (s, 2 H), 2.24 (q, J = 7.5 Hz, 2 H), 1.96 (s, 3 H), 1.04 (t, J = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 148.6, 133.9, 50.0, 16.5, 13.1, 12.9.

HRMS (ESI): m/z calcd for $C_7H_{12}NO$ $[M + H]^+$: 126.0913; found: 126.0910.

1-Benzyl-4-methyl-1, 5-dihydro-2*H*-pyrrol-2-one (8):



To a stirred solution of benzylamine (5.45 mL, 50 mmol, 1.14 equiv) in isopropyl alcohol (45 mL), compound **5** (5 g, 43.8 mmol, 1 equiv) was added at room temperature. The reaction mixture was stirred at 40 °C for 1 h, then cooled to 0 °C and treated with a freshly prepared solution of $NaBH_4$ (1.06 g, 28 mmol, 0.64 equiv) in water (15 mL) containing NaOH (1 mL, 50% w/w in water) while maintaining the internal temperature below 25 °C. The reaction mixture was stirred for 1.5 h at that temperature. Excess $NaBH_4$ was quenched by addition of acetone to the reaction mixture while maintaining the internal temperature below 30 °C. The mixture was filtered and AcOH (1 mL) was added to the filtrate to adjust the pH between 7–8 and the reaction mixture was heated at 50 °C for 16 h. The mixture was allowed to cool to rt and the solvent was evaporated under reduced pressure. The obtained residue was extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer *in vacuo* followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 50:50) afforded pure **8** as a yellow solid.

Yield: 5.65 g (69%).

M. P. = 96–98 °C.

R_f = 0.3 (EtOAc–PE, 30:70).

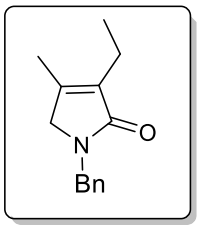
IR ($CHCl_3$): 1674, 1217, 763 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.32–7.09 (m, 5 H), 5.82 (q, J = 1.4 Hz, 1 H), 4.53 (s, 2 H), 3.65 (s, 2 H), 1.95 (d, J = 1.4 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 171.9, 155.2, 137.3, 128.5 (2 C), 127.8 (2C), 127.3, 122.5, 54.9, 45.6, 15.1.

HRMS (ESI): m/z calcd for $C_{12}H_{14}NO$ $[M + H]^+$: 188.1070; found: 188.1062.

1-Benzyl-3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (9):



To a stirred solution of compound **8** (8 g, 42.7 mmol, 1 equiv) in anhydrous THF (200 mL), NaH (1.13 g, 47.0 mmol, 1.1 equiv) was added slowly at 0 °C. The reaction mixture was stirred for 15 min, ethyl bromide (3.83 mL, 51.3 mmol, 1.2 equiv) in anhydrous THF (40 mL) was added dropwise at 0 °C, and stirring was continued for 3 h at that temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was treated with saturated NH_4Cl solution and extracted with EtOAc (3 × 200 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer *in vacuo* followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 35:65) afforded pure **9** as a sticky yellow solid.

Yield: 5.25 g (57%) alongwith recovery of the starting material (1.5 g).

R_f = 0.26 (EtOAc–PE, 50:50).

IR ($CHCl_3$): 1703, 1216, 765 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.15 (m, 5 H), 4.60 (s, 2 H), 3.60 (s, 2 H), 2.31 (q, J = 7.5 Hz, 2 H), 1.62 (s, 3 H), 1.09 (t, J = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 145.4, 137.6, 134.1, 128.6 (2 C), 128.0 (2 C), 127.3, 53.5, 45.9, 17.0, 13.1, 12.7.

HRMS (ESI): m/z calcd for $C_{14}H_{18}NO$ $[M + H]^+$: 216.1383; found: 216.1379.

3-Ethyl-4-methyl-1, 5-dihydro-2*H*-pyrrol-2-one (3) by *N*-debenzylation of lactam 9.

Method A: Microwave Assisted.

To a glass vial, equipped with a Teflon cap, compound **9** (0.2 g, 0.93 mmol, 1 eq.) in toluene (2 mL) was added followed by triflic acid (0.328 mL, 3.72 mmol, 4 eq.). The reaction mixture was kept for 45 min in a microwave reactor (Anton Paar, Monowave 300 microwave synthesis reactor) at 800 W (150 °C). The progress of the reaction was monitored by TLC. After completion, the reaction mixture was allowed to cool to rt, quenched with saturated $NaHCO_3$

solution (5 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer *in vacuo* followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 50:50) afforded pure **3** as a pale yellow solid.

Yield: 0.1 g (86%).

Method B: By Heating.

To a stirred solution of compound **9** (3 g, 13.9 mmol, 1 eq.) in toluene (30 mL) was added triflic acid (4.94 mL 55.8 mmol, 4 eq.). The reaction mixture was heated at 160 °C for 24 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was allowed to cool to rt, quenched with saturated $NaHCO_3$ solution (20 mL), and extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer *in vacuo* followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 50:50) afforded pure **3** as a pale yellow solid.

Yield: 1.47 g (84%).

M. P. = 103 °C (Lit.[5d] 102 °C).

R_f = 0.3 (EtOAc–PE, 70:30).

IR ($CHCl_3$): 3440, 1722, 1216, 765 cm^{-1}.

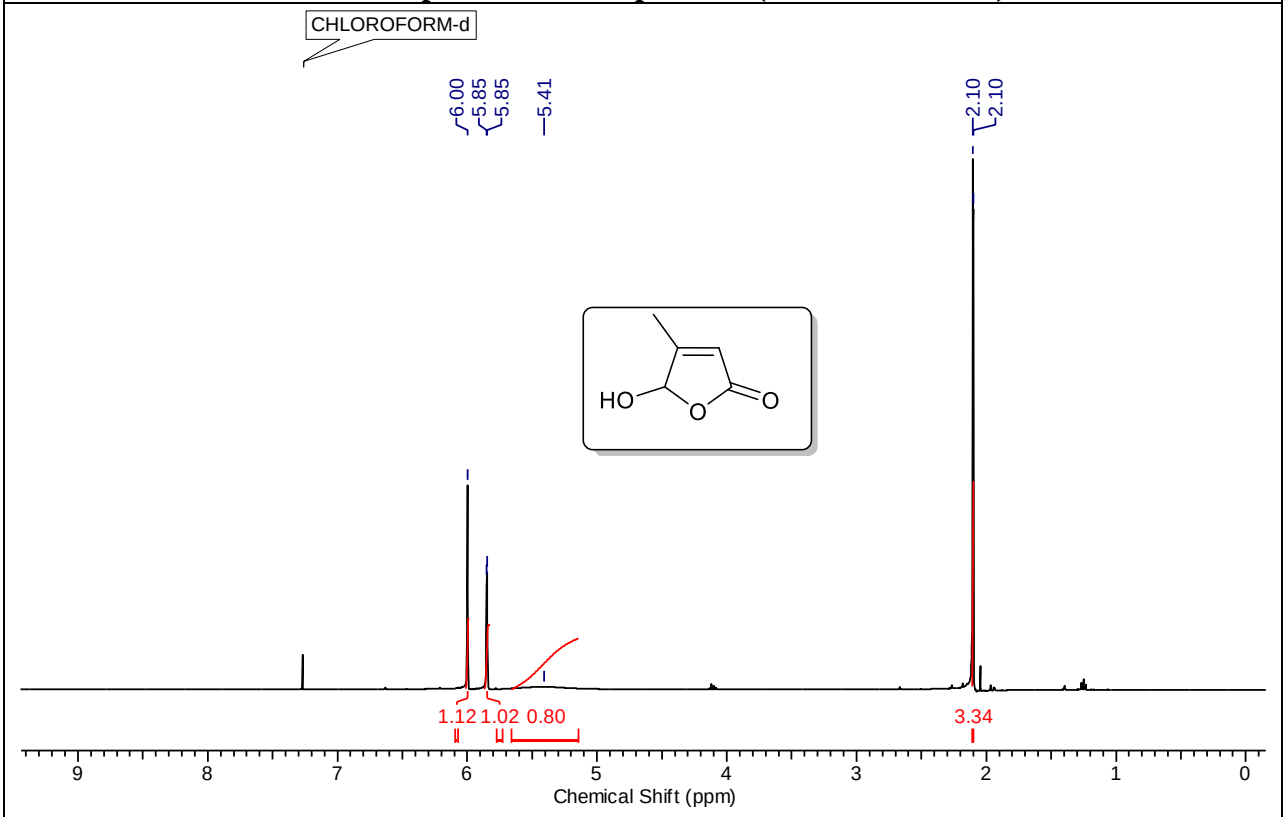
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (br s, 1 H), 3.77 (s, 2 H), 2.24 (q, J = 7.5 Hz, 2 H), 1.96 (s, 3 H), 1.04 (t, J = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 148.6, 133.9, 50.0, 16.5, 13.1, 12.9.

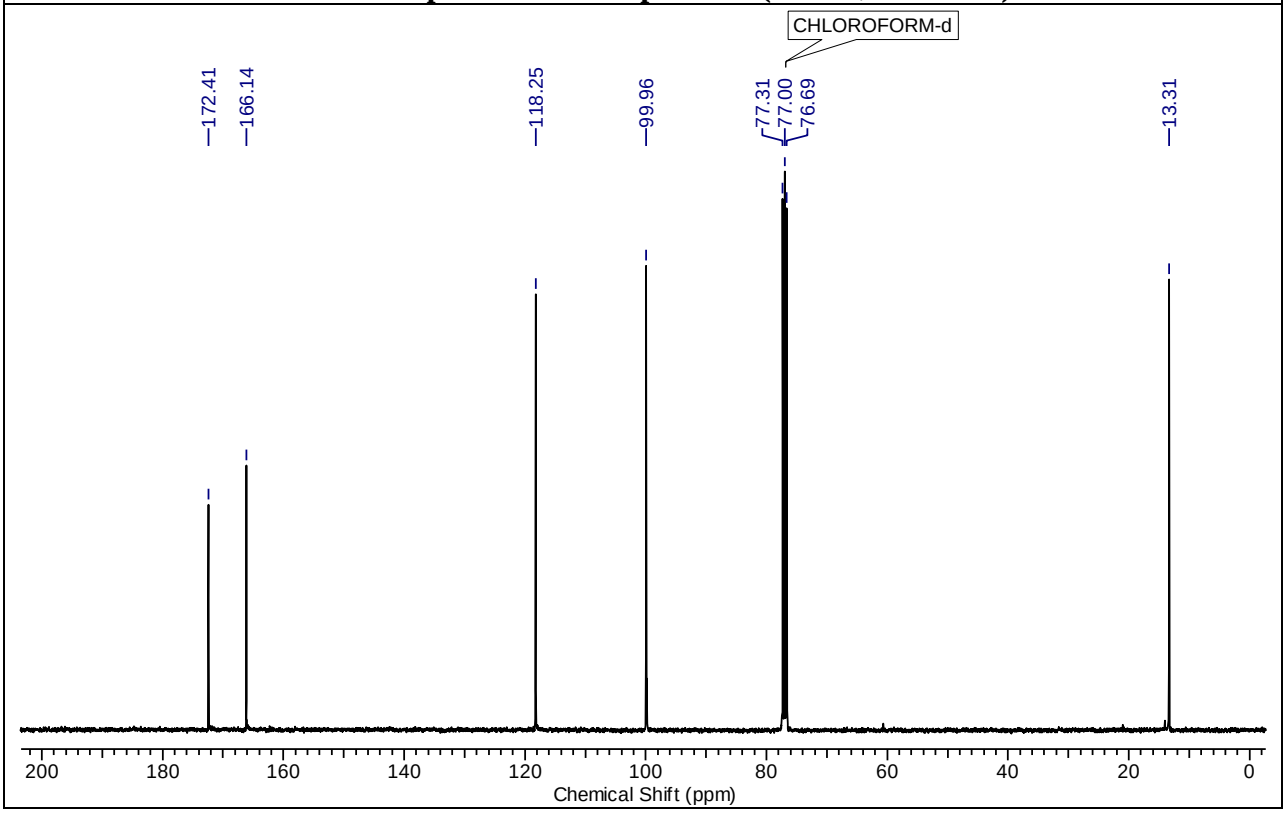
HRMS (ESI): m/z calcd for $C_7H_{12}NO$ $[M + H]^+$: 126.0913; found: 126.0910.

2.1.9. NMR Spectra:

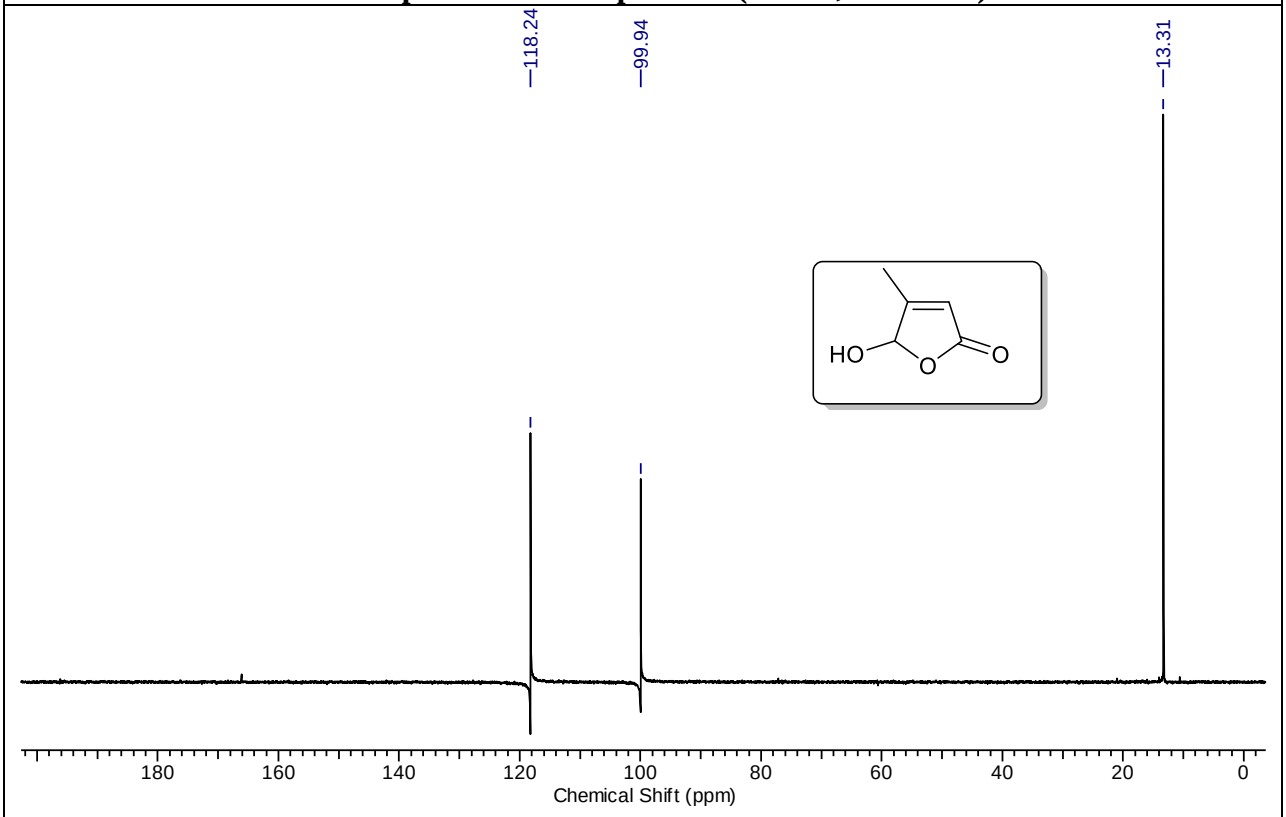
^{1}H-NMR spectrum of compound 5 ($CDCl_3$, 400 MHz)



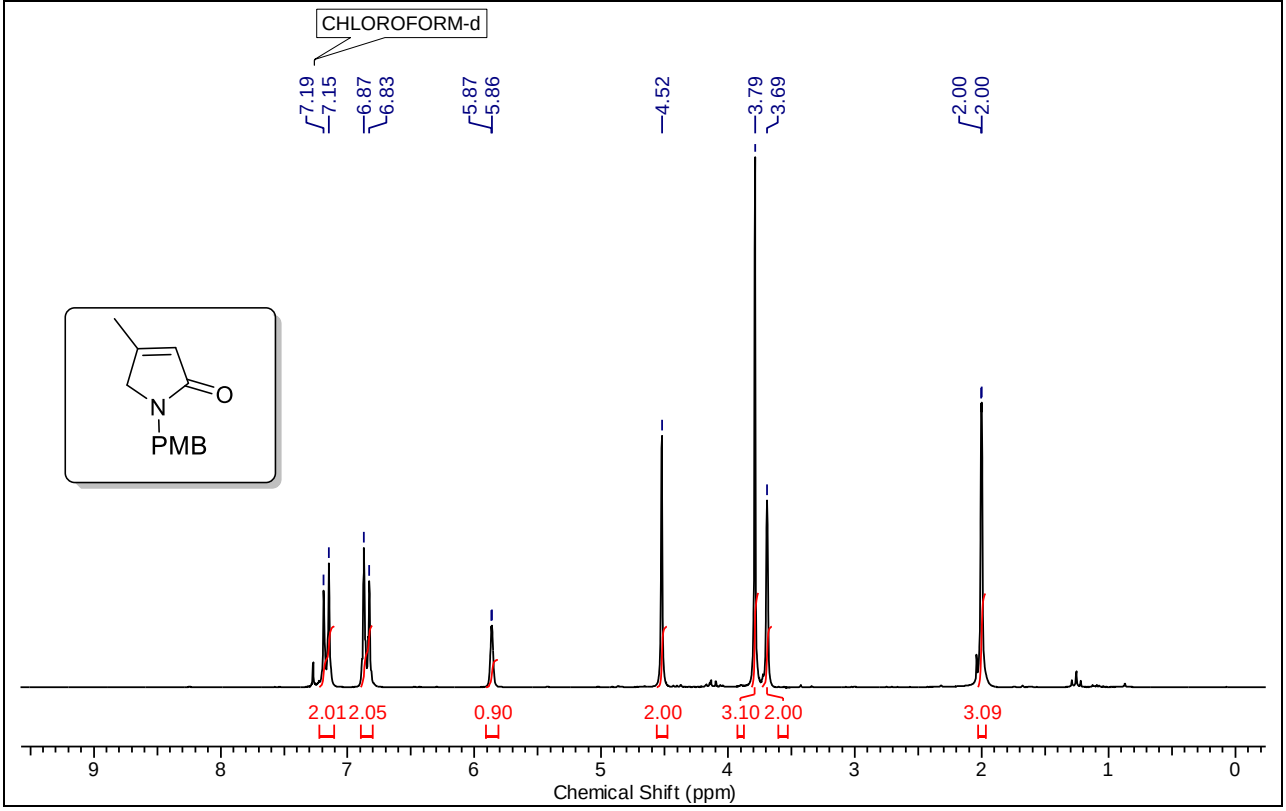
^{13}C-NMR spectrum of compound 5 ($CDCl_3$, 100 MHz)



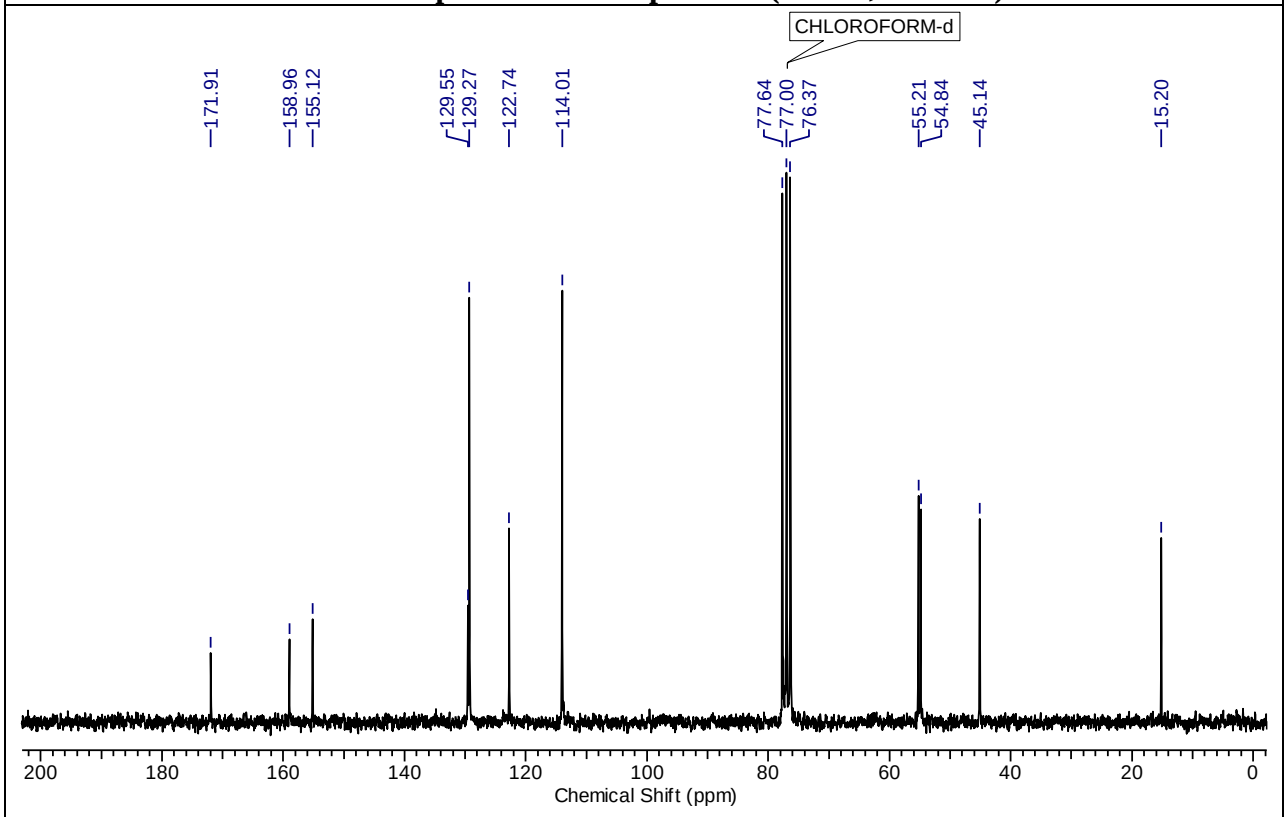
DEPT spectrum of compound 5 ($CDCl_3$, 100 MHz)



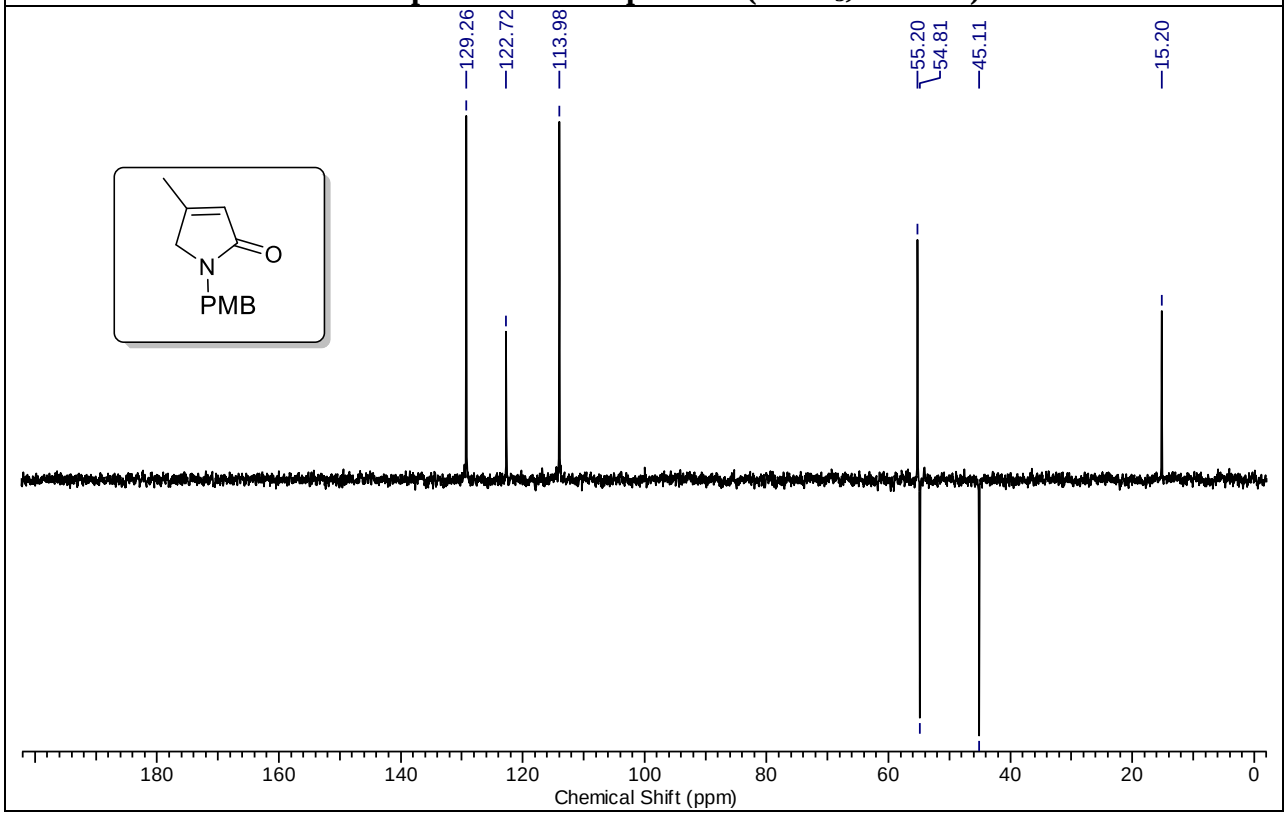
^{1}H-NMR spectrum of compound 6 ($CDCl_3$, 200 MHz)



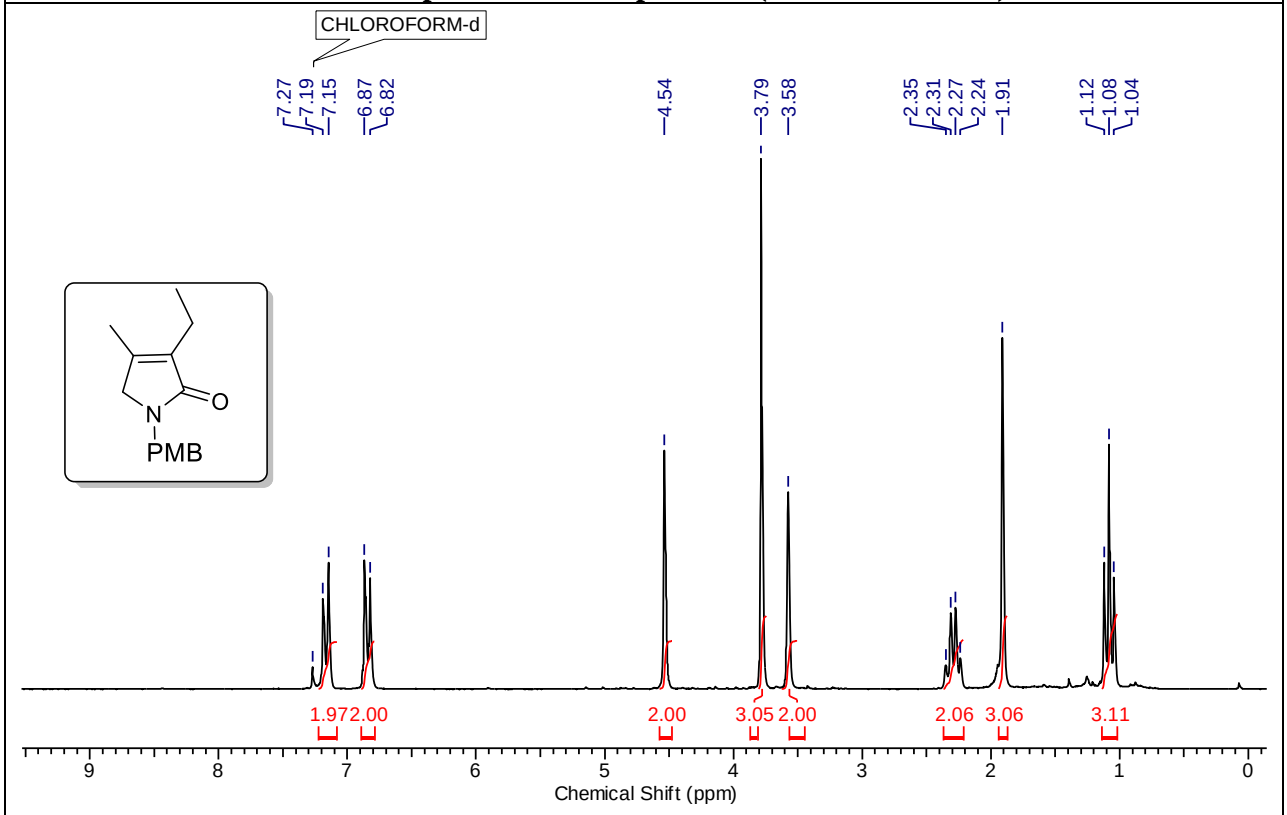
^{13}C-NMR spectrum of compound 6 ($CDCl_3$, 50 MHz)



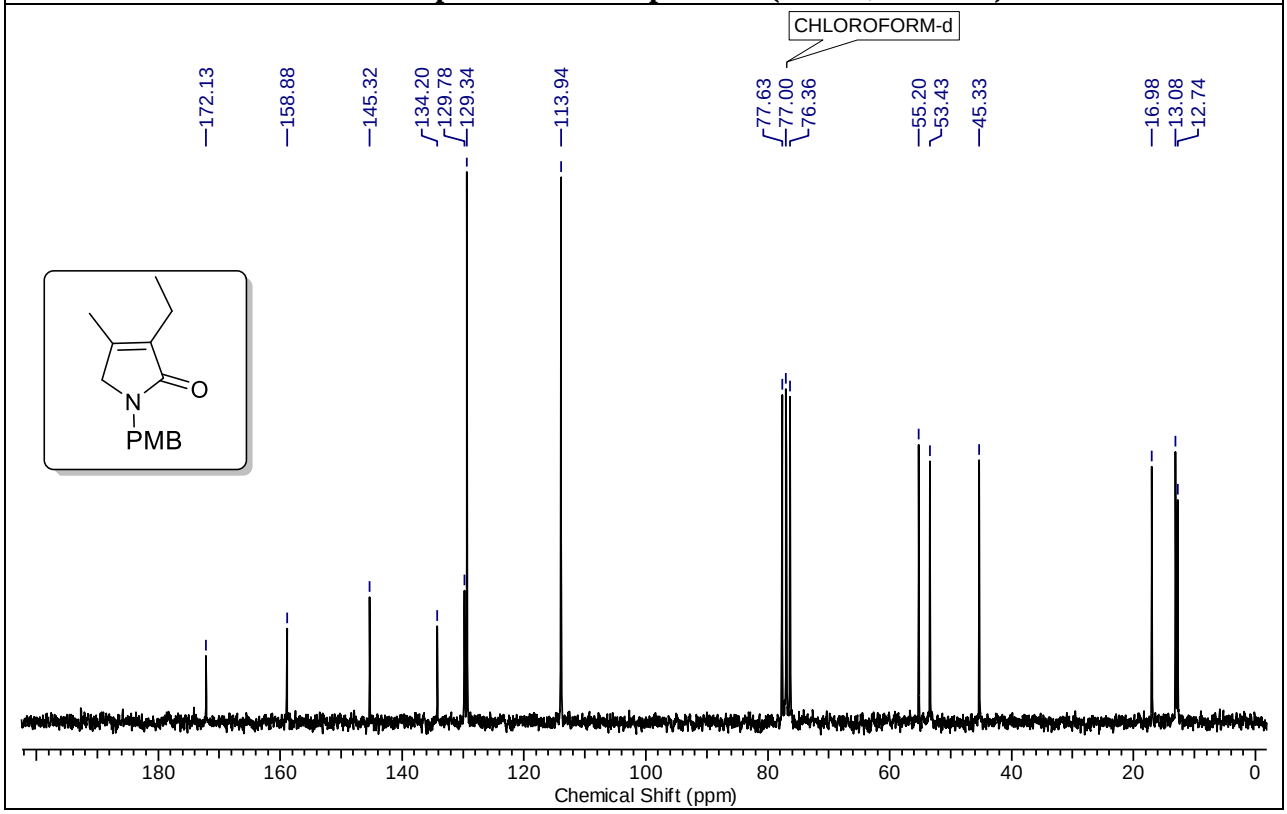
DEPT spectrum of compound 6 ($CDCl_3$, 50 MHz)



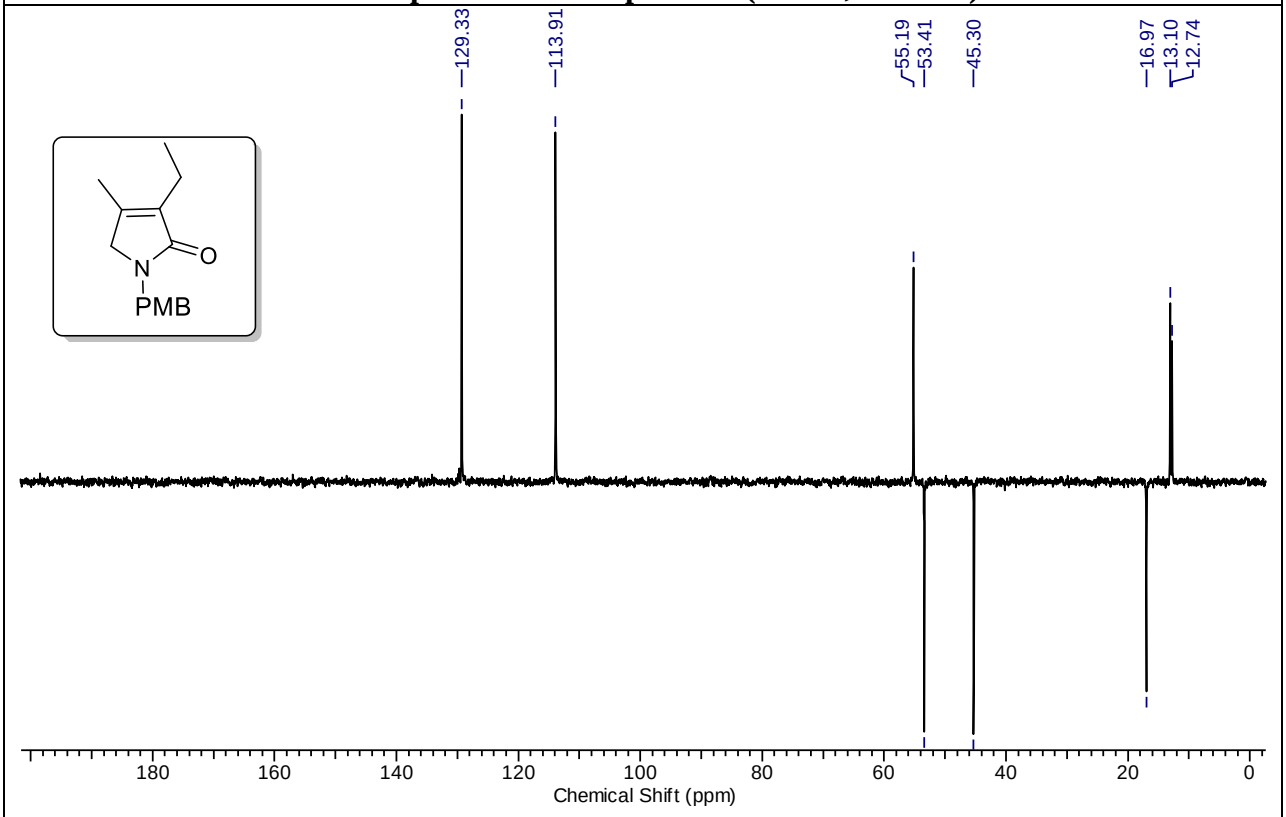
^{1}H-NMR spectrum of compound 7 ($CDCl_3$, 200 MHz)



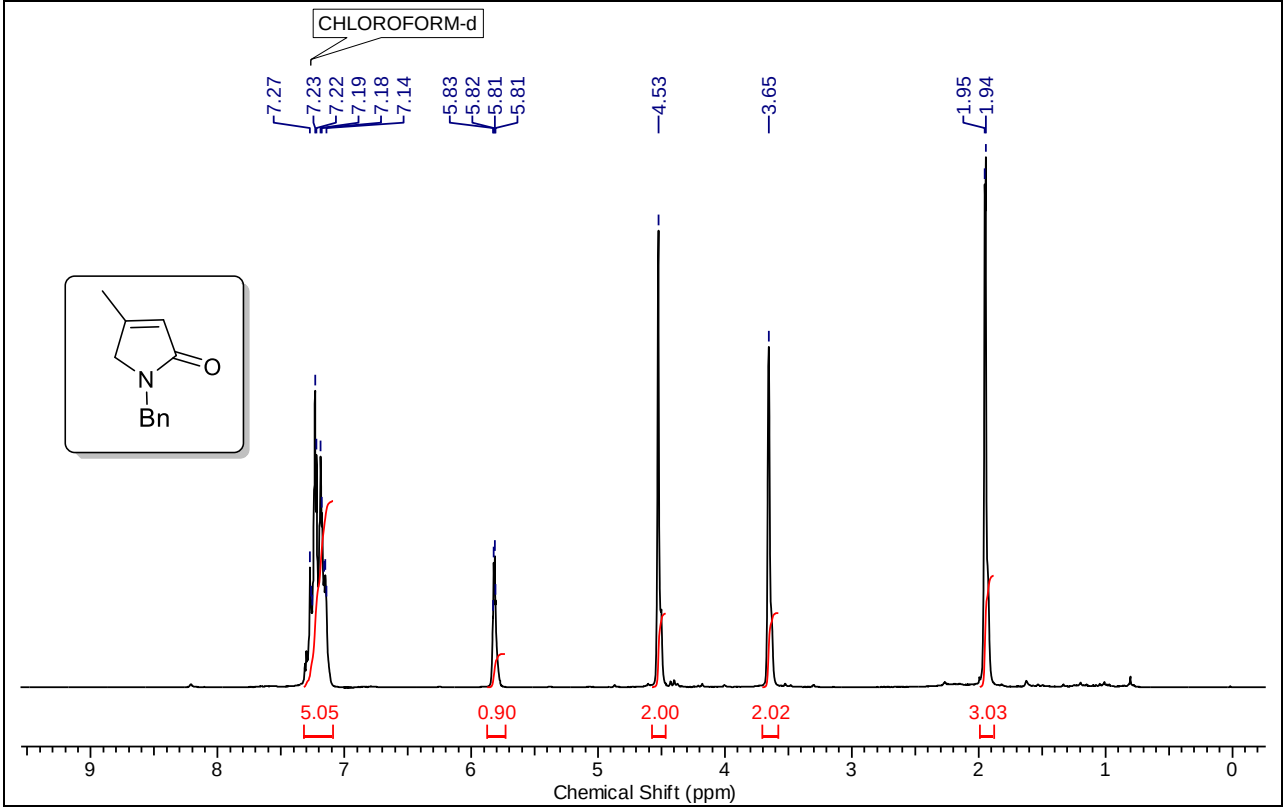
^{13}C-NMR spectrum of compound 7 ($CDCl_3$, 50 MHz)



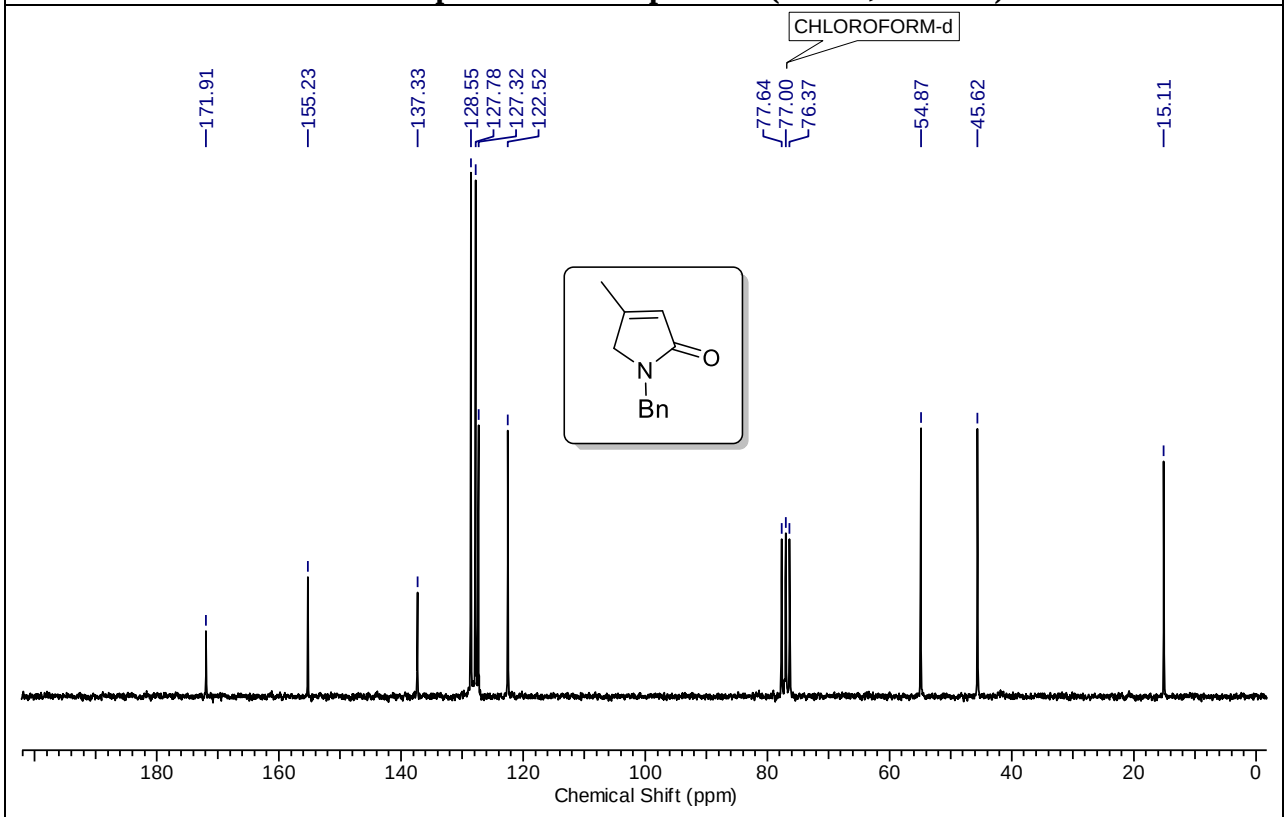
DEPT spectrum of compound 7 ($CDCl_3$, 50 MHz)



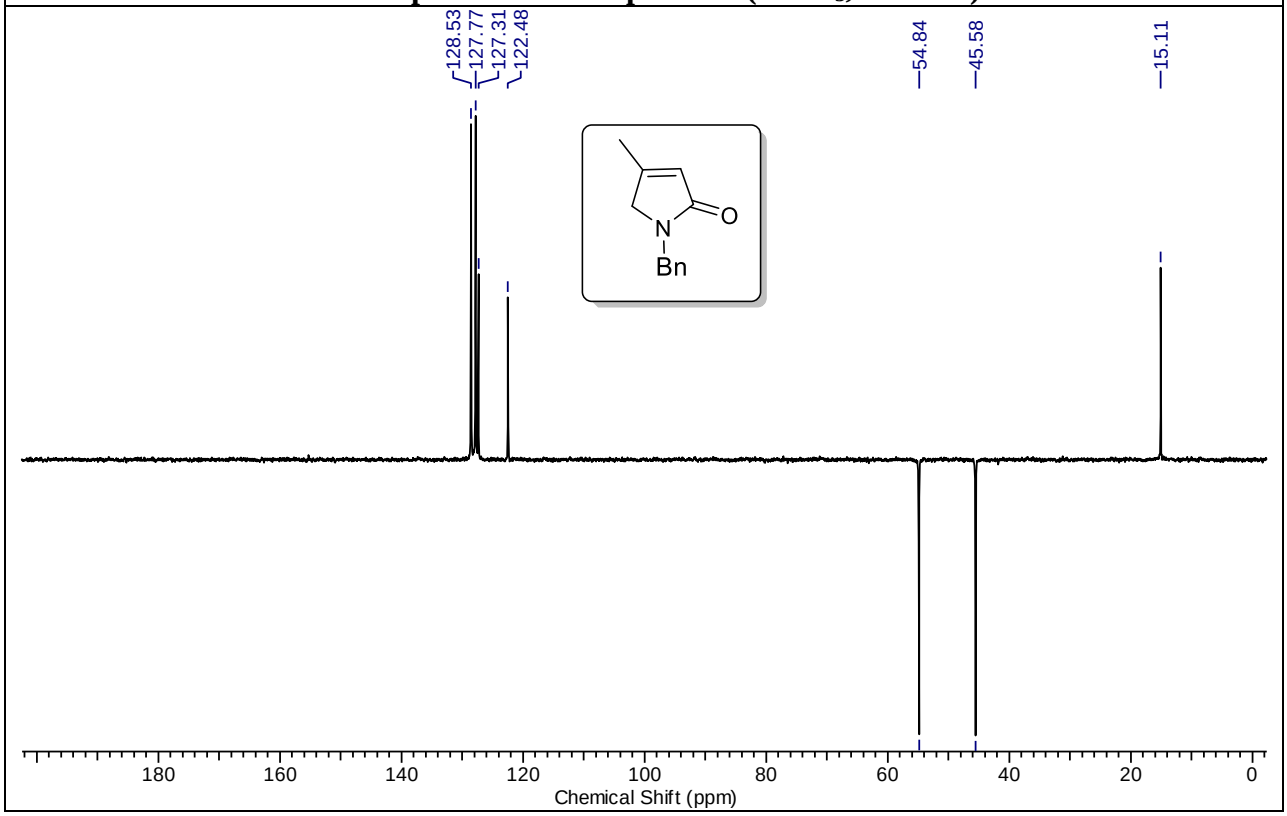
^{1}H-NMR spectrum of compound 8 ($CDCl_3$, 200 MHz)



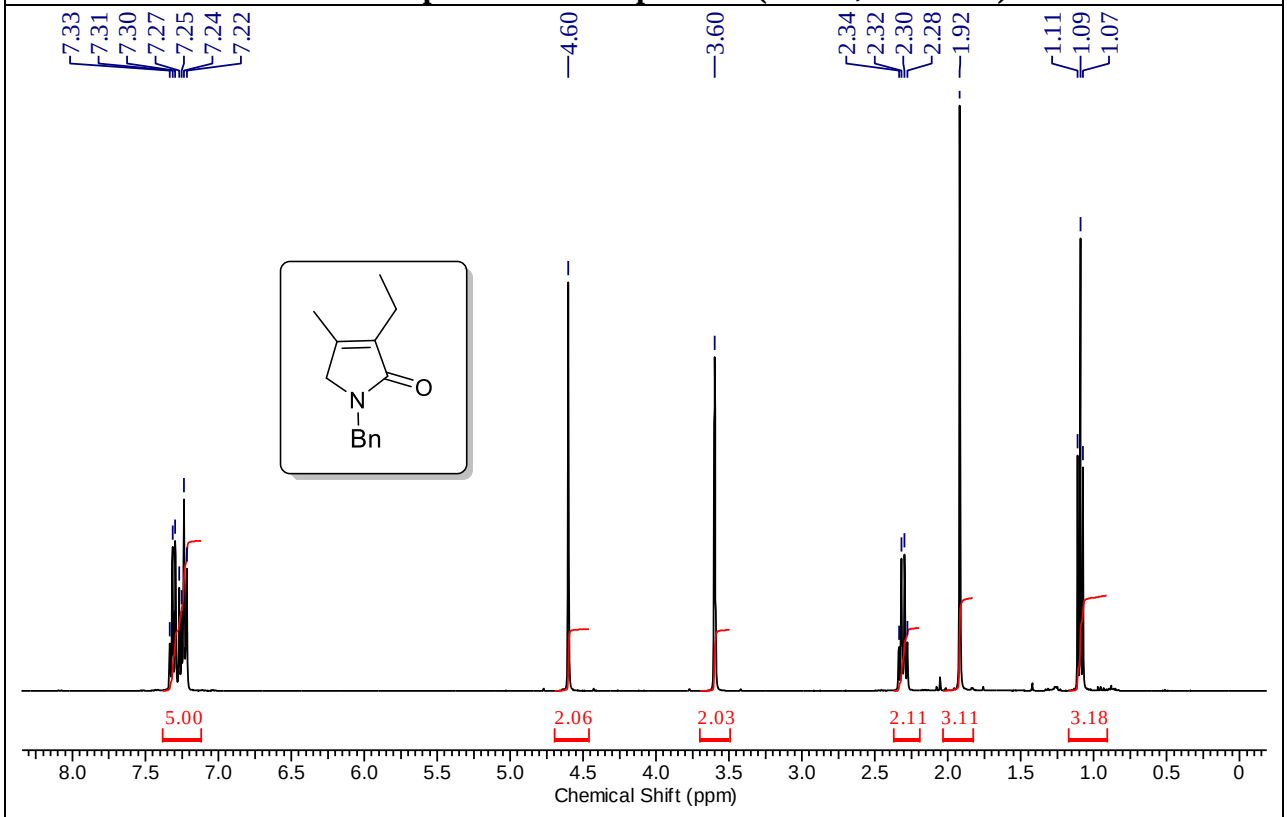
^{13}C-NMR spectrum of compound 8 ($CDCl_3$, 50 MHz)



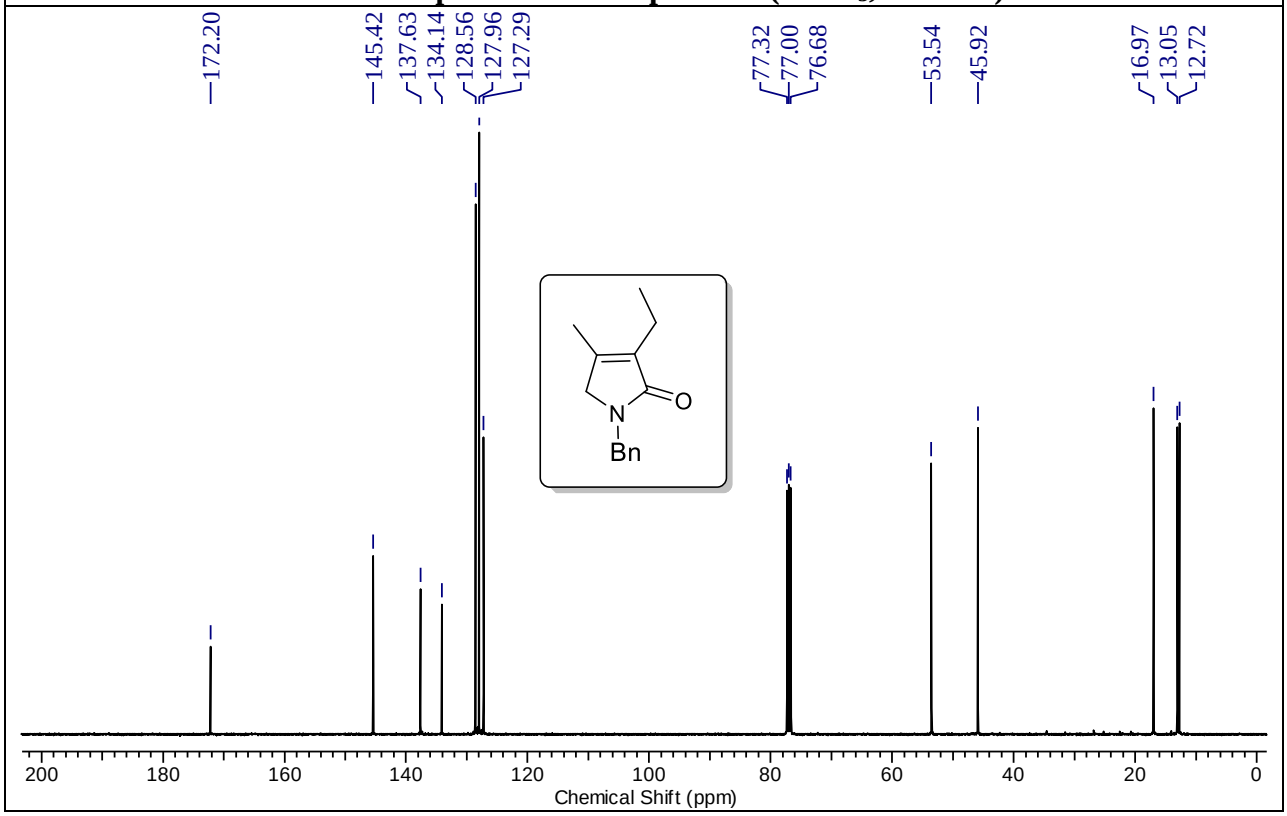
DEPT spectrum of compound 8 ($CDCl_3$, 50 MHz)



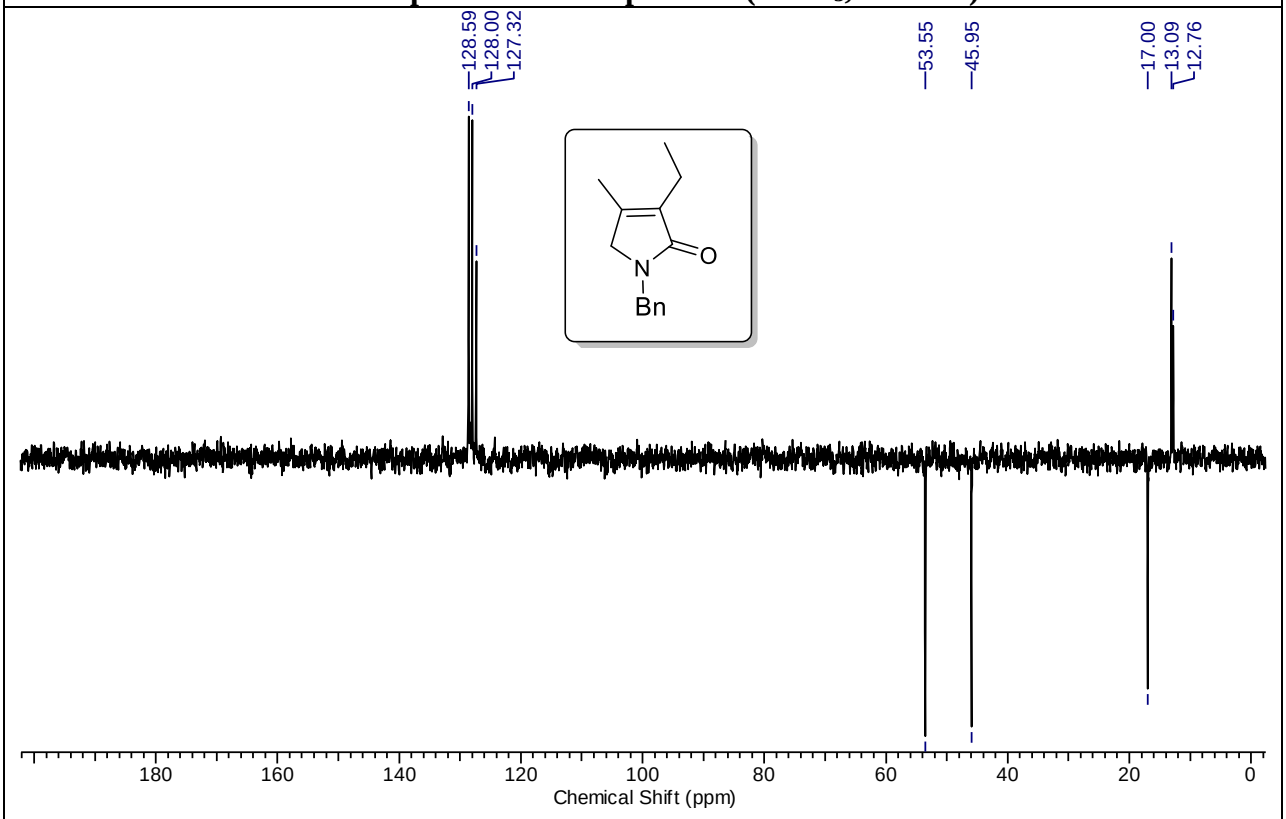
^{1}H-NMR spectrum of compound 9 ($CDCl_3$, 200 MHz)



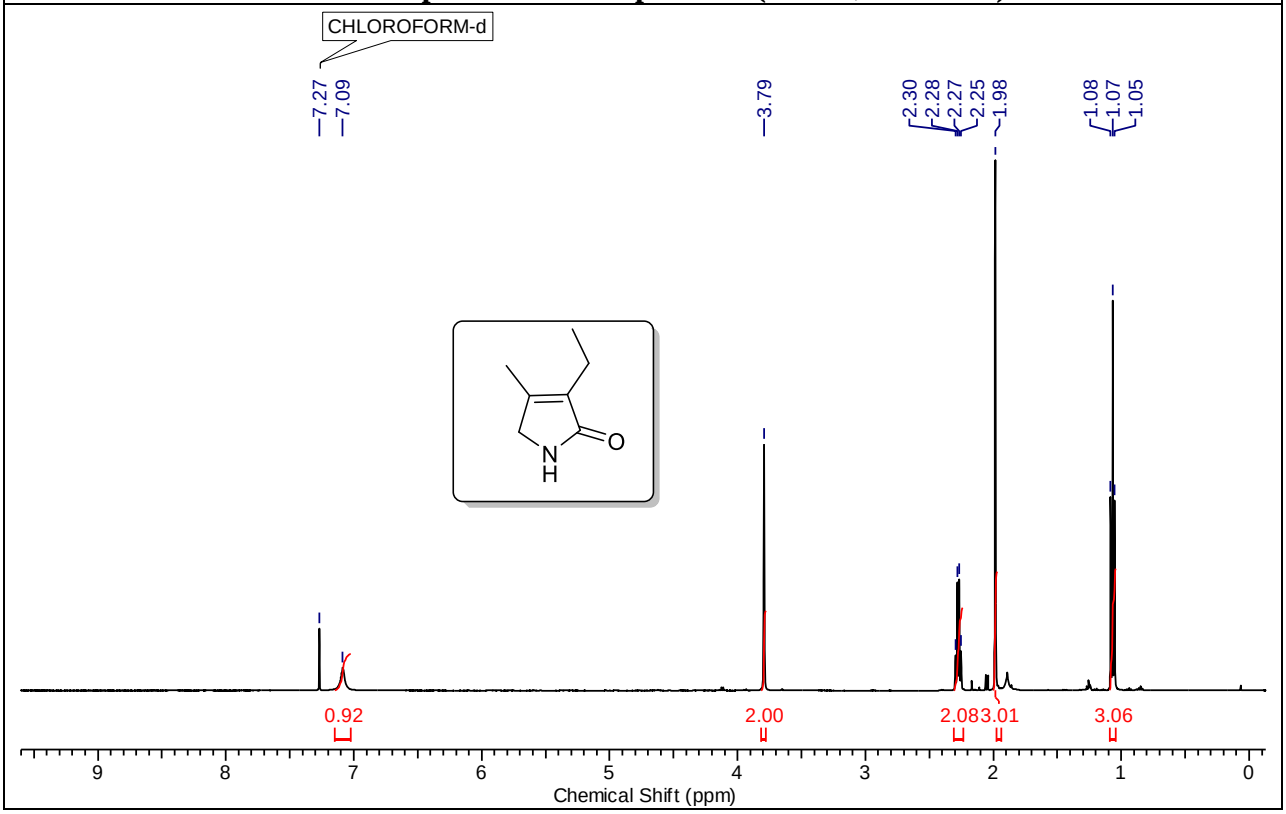
^{13}C-NMR spectrum of compound 9 ($CDCl_3$, 50 MHz)



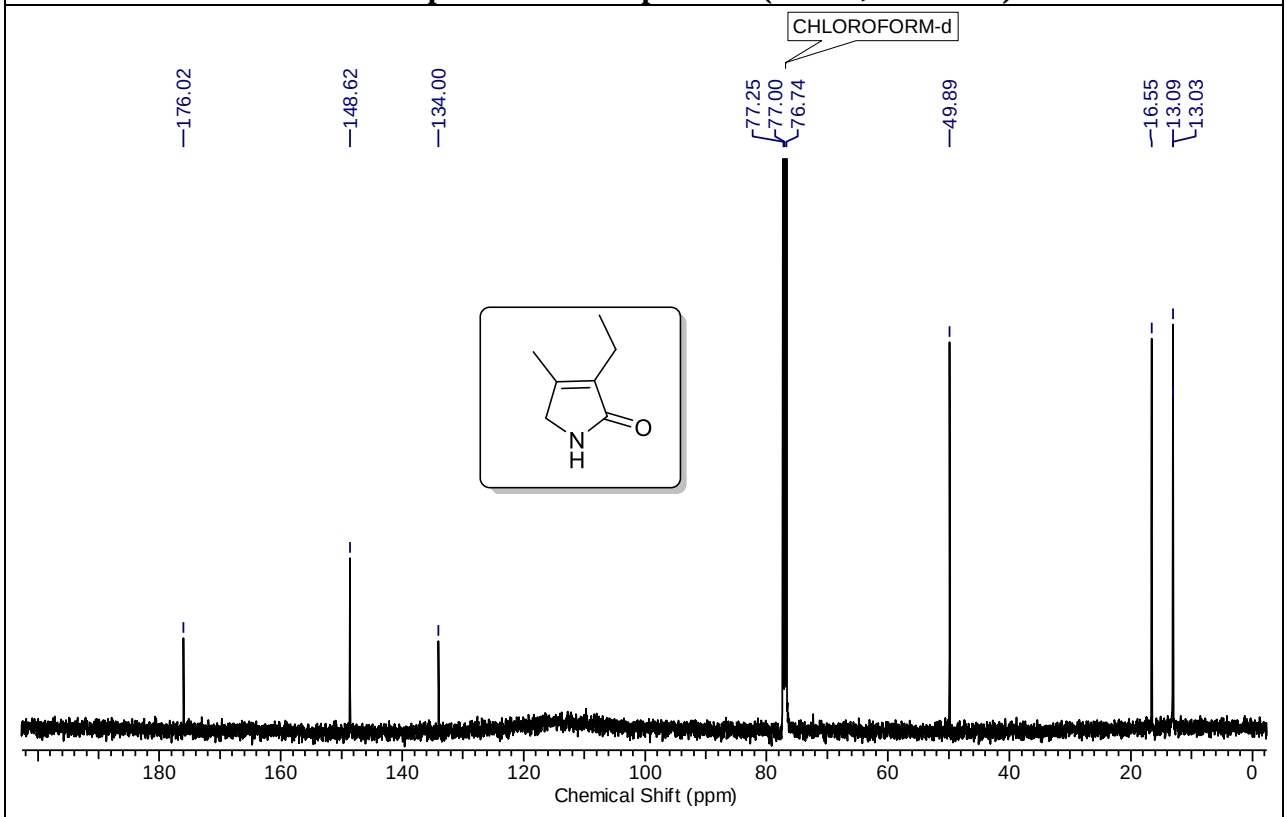
DEPT spectrum of compound 9 ($CDCl_3$, 50 MHz)



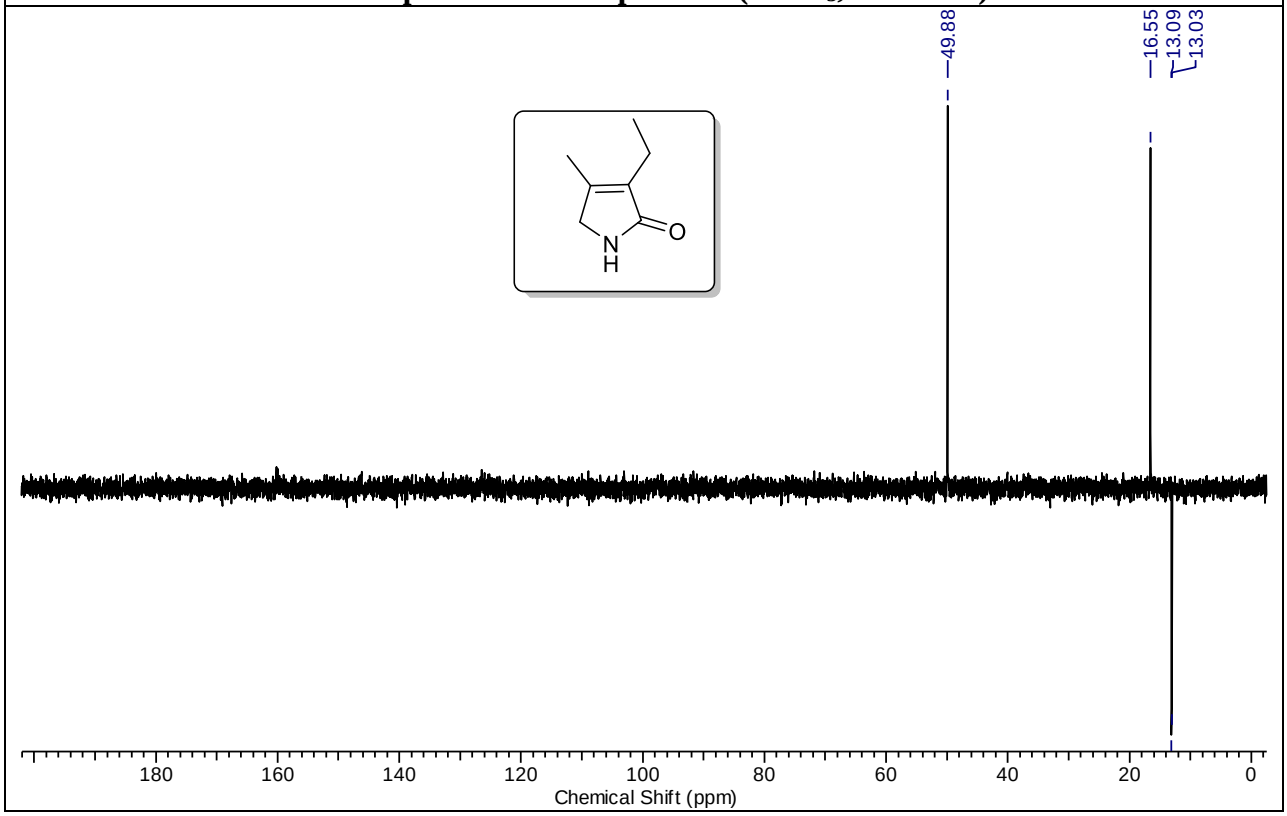
^{1}H-NMR spectrum of compound 3 ($CDCl_3$, 500 MHz)



^{13}C-NMR spectrum of compound 3 ($CDCl_3$, 125 MHz)



DEPT spectrum of compound 3 ($CDCl_3$, 125 MHz)



2.1.10. References:

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4. Selected publications of this research group a) Chavan, S. P.; Tejwani, R. B.; Ravindranathan, T. *J. Org. Chem.* **2001**, *66*, 6197. b) Chavan, S. P; Chittiboyina, A. G.; Ravindranathan. T.; Kamat, S. K.; Kalkote, U. R. *J. Org. Chem.* **2005**, *70*, 1901. c) Chavan, S. P.; Chavan, P. N.; Khairnar, L. B. *RSC Adv.* **2014**, *4*, 11417. d) Chavan, S. P.; Pawar, K. P.; Garai, S. *RSC Adv.* **2014**, *4*, 14468. e) Chavan, S. P.; Kadam, A. L.; Lasonkar, P. B.; Gonnade, R. G. *Org. Lett.* **2018**, *20*, 7011. f) Chavan, S. P.; Kadam, A. L.; Kawale, S. A. *ACS Omega* **2019**, *4*, 8231.
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Chapter 2, Section II

Synthetic studies towards α-lipoic acid by using modified butanolide approach

2.2.1. Introduction to the α-lipoic acid:

The synthetic routes of the chiral molecules have a great demand in the chemical and pharmaceutical industry. The chirality plays important role in the bioactivities of the enantiomers. The particular enantiomer can have the increased bioactivity over the other enantiomer. Addtionally, one of the antipodes may have adverse biological properties. Due to this fact the asymmetric synthesis of the bioactive molecules has gained much attention by the chemists.

The first time isolation of the lipoic acid (**1)** from the liver residue was done by Reeds *et al*.[1] The name lipoic acid was given from its capability to dissolve in lipids. The α-lipoic acid **1** is not a vitamin, the reason behind this is that it can be prepared by the body in less amounts from the vital fatty acids.

The nutrients which straightly or secondarily safeguard the mitochondria from oxidative harm and increase the mitochondrial function are known as the ‘‘mitochondrial nutrients’’. The α-lipoic acid is also one of the mitochondrial nutrients. It is a co-enzyme which is associated with mitochondrial metabolism. It is proven that the lipoic acid **1** and its analogues enhance the age related decline of the memory, enhance the mitochondrial structure and function and reduce the age-associated increase of oxidative destruction. Also, it increases the quantity of antioxidants which restore the activity of key enzymes.[2] It is found that the lipoic acid **1** does not accumulate into the tissues, hence does not have any toxicity in the amounts consumed as it is distributed throughout the tissues. It also protects eyes and the brain from the free radical damage.

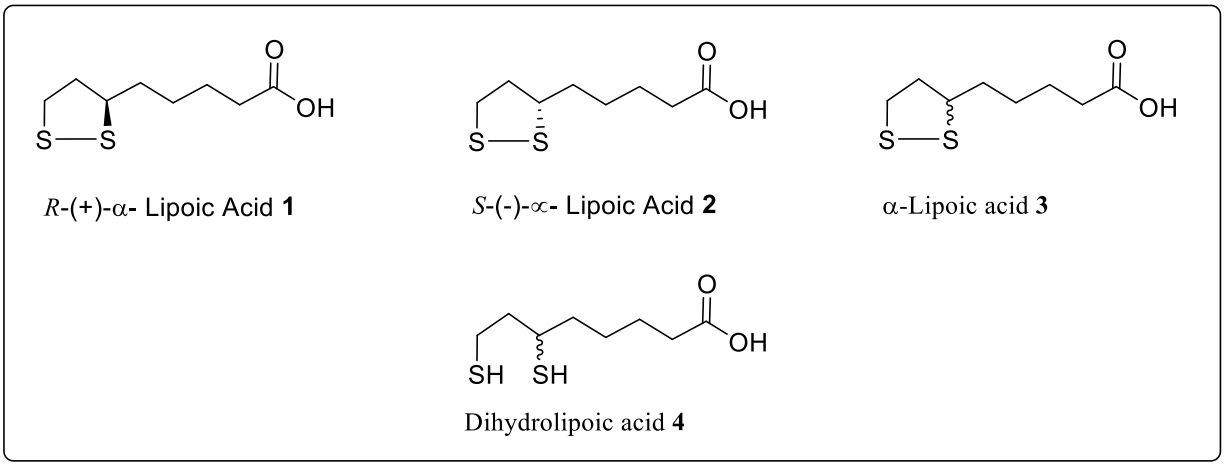


Figure 1: Lipoic acid structures.

Additionally, it is a protein-bound co-enzyme and growth factor observed in the plant and animal tissues and also in micro-organisms.[3, 4] It is predominant in the biology and well known as an important cofactor for the multi-enzyme complex which translates different transformations in the biological system. Besides this, it plays vital role in the photosynthesis and in the tricarboxylic acid cycle.

The naturally found isomer of α-lipoic acid **1** is the *R*-enantiomer, having additional activities than the *S*-enantiomer. However, it was observed that (*S*) - isomer does not affect the activity of the (*R*) - isomer.

Also, α- lipoic acid **1** assists in prevention of the specific cell damage by restoring the levels of vitamin C and vitamin E. It is used to build the energy for the organs into the body by breaking down the carbohydrates. Besides this the α-lipoic acid **1** as well as the dihydrolipoic acid **4** acts as the global anti-oxidant by quenching the free radicals in the lipid and cell membranes of the tissues. Free radicals harm the etiology, causing many chronic health issues. However, the antioxidants such as α-lipoic acid act as the scavenger of the radicals and stop the tissue damage by quenching the free radicals formed.

Additionally, the α-lipoic acid is very useful for the patients with diabetic neuropathy. The oral dose of 600 mg to 1800 mg of the lipoic acid reduces the nerve pain in these patients. However, the low dose of it is ineffective. Also, the consumption of the α-lipoic acid for longer duration (up to 4 years) is found to be effective in the lowering of the cholesterol levels in the body. Nowadays the obesity in humans is the growing concern worldwide. The modern research highlights on the utilization of α-lipoic acid for the treatment of the obesity. The consumption of the α-lipoic acid by the adults for 2-48 weeks moderately reduces the obesity in them. It is also found to be effective in the children to reduce the weight. However, it is not useful for the liver disease for the people who consume alcohol. Although the lipoic acid is synthesized in the body in the less amounts, if the body is healthy no external supply of the lipoic acid is required.

However, many diseased conditions arise due to the low levels of the lipoic acid inside the body. Use of externally synthesized α-lipoic acid in such a time is recommended.

Although the α-lipoic acid **1** was isolated in the 1951, even after almost seven decades it's the molecule of high interest. The lipoate coenzyme is special in all of the mammalian metabolism.

Many synthetic derivatives of the α-lipoic acid have been synthesized and studied for the different applications in the biology. Recently one such derivative α-lipoic ester of alloxanthoxyletin has been synthesized and studied for the anticancer activity by the Wioletta Olejarz and co-workers.[5] This newly synthesized derivative had the promising anticancer activity. Also, the lipoic acid analogs with enhanced pharmacological activity were synthesized and studied by Steven A. Kate *et al.*[6] Lipoic acid is also studied and considered as the supportive therapy for the breast cancer.[7] Many oral diseases are caused by the oral microorganisms and such microorganisms complicate the etiology of the oral diseases. The study related to the antibacterial effects of alpha lipoic acids versus different oral organisms was carried out by Shebi S. *et al.*[8] They found that the α-lipoic acid suppressed the growth of all the microorganisms investigated and they concluded that the alpha lipoic acid can be thought as the additional therapeutic approach to improve oral health. Additionally, the α-lipoic acid attenuates metabolic stress and improves insulin sensitivity in part through activation of the heat shock response (HSR).[9] Also, it has been studied that the combining of lipoic acid to the methylene blue decrease the Warburg effect in the Chinese Hamster Ovary (CHO) cells.[10]

In addition to this, Victor Manuel Mendoza-Nunez *et al.* carried out the research on the result of 600 mg of the lipoic acid boosting on the oxidative stress, inflammation, and receptor for advanced glycosylation end products (RAGE) in the older adults with Type 2 Diabetes Mellitus.[11] Their study revealed that managing the doses of 1200–1800 mg/day of α-lipoic acid can be helpful to reduce the oxidative destress, inflammation and to keep away the making of AGEs (advanced glycosylation end-products) which occur in T2DM (type 2 dibetis mellitus) in older adults. However, the usefulness of such a high dose must be confirmed through the controlled clinical trials. Bone loss is one of the emerging health concerns worldwide. The use of alpha lipoic acid reduces the bone loss. Also, the immunomodulatory effect of the alpha lipoic acid on the autoimmune disease have been reviewed.[12] Additionally, therapeutic use of the α-lipoic acid has also been reviewed.[13]

The lipoic acid is identified by the different names such as 1,2-dithiolane-3-pentanoic acid; 6, 8-thioctic acid; 5-(1,2-dithiolan-3-yl)-valeric acid and 5-3-(1,2-dithiolanyl)-pentanoic acid. The natural isomer is *R*-Lipoic acid and *S*-Lipoic acid is synthetic in nature. There are the two sulphur atoms present in the lipoic acid molecule. These two sulphur atoms in the molecule can

be oxidized or reduced. When the reduction of the sulphur atoms in the molecule occurs the resultant structure is known dihydrolipoic acid whereas when the oxidation of these sulphur atoms takes place the resulting structure from it is called lipoic acid. Both the enantiomers of the lipoic acid can be synthesized in the laboratory.

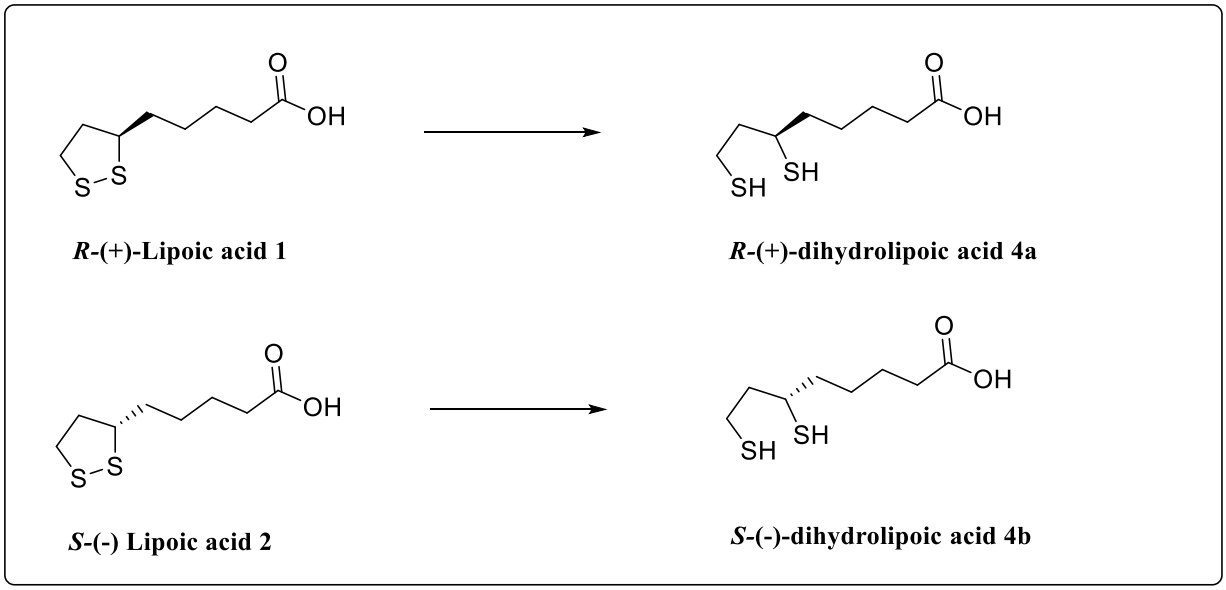


Figure 2: Structures of the *R* and *S* Lipoic acids and their resulting *R* and *S* dihydrolipoic acids.

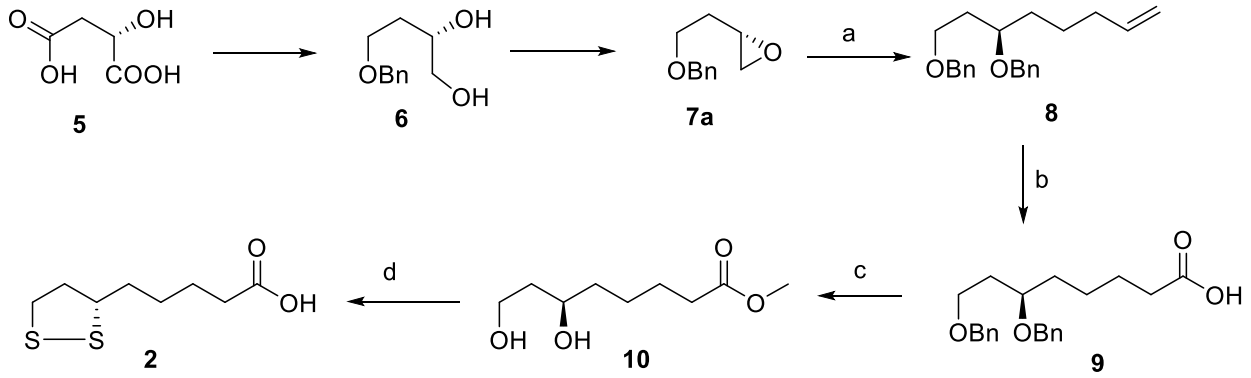
2.2.2. The literature review of the α-lipoic acid.

The lipoic acid **1** has been isolated in the 1950's and its structural configuration was determined to be *R* in the year 1983. In the early days after the isolation of the lipoic acid, researchers thought of lipoic acid as the small molecule. However, after revealing the pharmaceutical importance of the lipoic acid, various researchers got attracted towards its synthesis. This led to the number of syntheses of the (*dl*) -alpha lipoic acid including the chiral preparation of both (*R* & *S*) enantiomers of the α-lipoic acid. Few of the syntheses are described in this literature review section.

Golding *et al.* [14, 15]

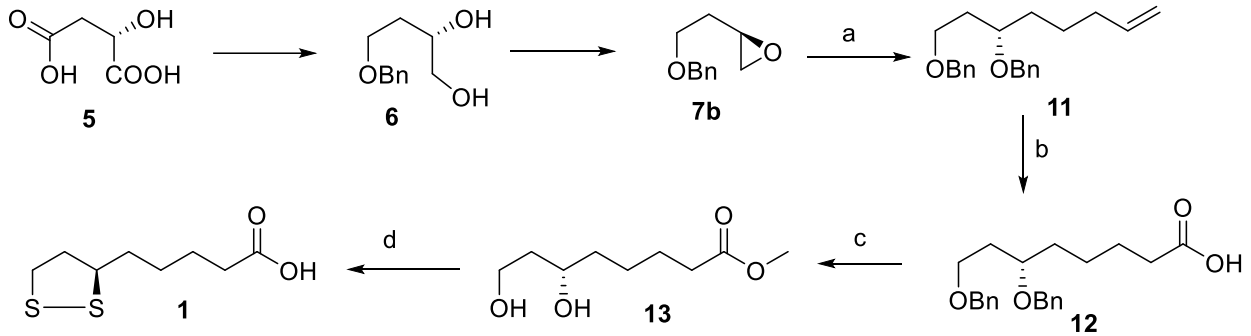
The S-malic acid derived chiral epoxide **7a** was used as the chiral building block by Golding *et al*. The synthesis of this epoxide was achieved from the *S*-malic acid **5** by the known chemistry.[15b] Further, the chiral epoxide was cleaved regioselectively by using but-3-

enylmagnesium bromide and lithium chlorocuprate to get the compound **8**. In addition, the compound **8** was converted to acid **9** by using the hydroboration and PDC oxidation reactions. Additionally, the esterification of acid **9** and debenzylation of the resulting ester produced the compound **10** a diol ester, which was converted to *S*- lipoic acid **2** by using dimesylation reaction and treating the dimesylated compound with Na_2S powder in DMF followed by hydrolysis of the ester (**Scheme 1**).



Scheme1: ***Reagents and conditions*****:** (a) (i) CH_2=$CHCH_2CH_2MgCl$, cat. Li_2CuCl_4, THF; (ii) $PhCH_2Br$, NaH, THF; (b) (i) $HBSia_2$, THF, alkaline H_2O_2; (ii) PDC, DMF; (C) (i) MeOH-HCl; (ii) Pd/C, H_2; (d) (i) $MeSO_2Cl$, Et_3N; (ii) Na_2S, S, DMF; (iii) aq. NaOH.

The similar approach starting from the (*S*)-malic acid **5** has been used by Golding *et al.* to synthesize the *R*-lipoic acid. The only modification was the inversion of the chiral center of the hydroxyl group to synthesize the chiral epoxide **7b**.[15b] Further, by using the epoxide **7b,** the preparation of *R* -lipoic acid **1** was accomplished by using the same reactions which have been used in the above synthesis of *S*-lipoic acid **2** (**Scheme 2**).

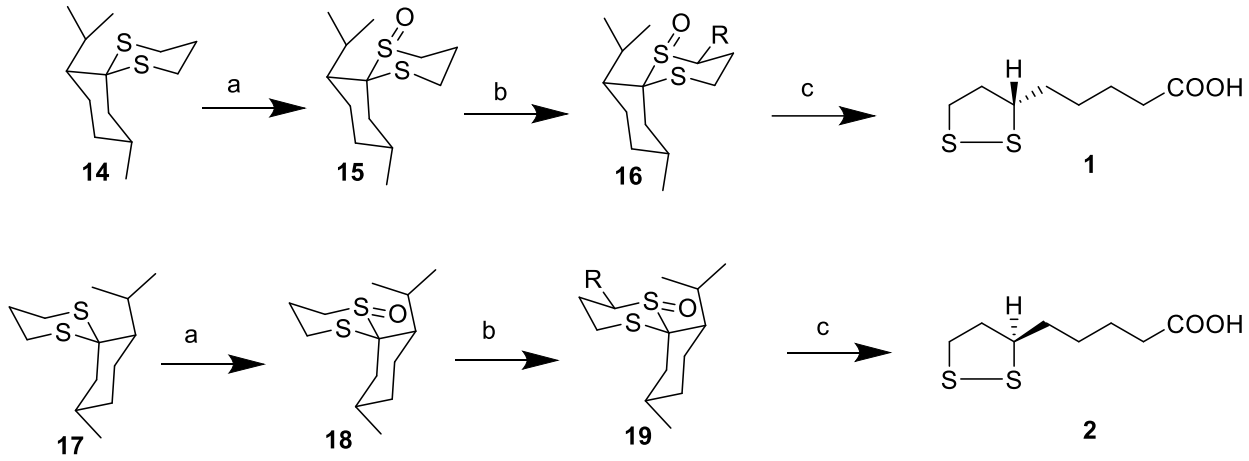


Scheme 2. ***Reagents and conditions*****:** (a) (i) AcOK, Ac_2O; (ii) $MeSO_2Cl$, Et_3N; (iii) K_2CO_3, MeOH; (b) (i) CH_2=CH_2CH_2MgCl, Li_2CuCl_4 (catalytic), THF; (ii) $PhCH_2Br$, NaH, THF; (c) (i)

$HBSia_2$, THF, alkaline H_2O_2; (ii) PDC, DMF; (d) (i) MeOH-HCl; (ii) Pd/C, H_2; (e) (i) $MeSO_2Cl$, Et_3N; (ii) Na_2S, S, DMF; (iii) aq. NaOH.

Ravindranathan *et al.*[16]

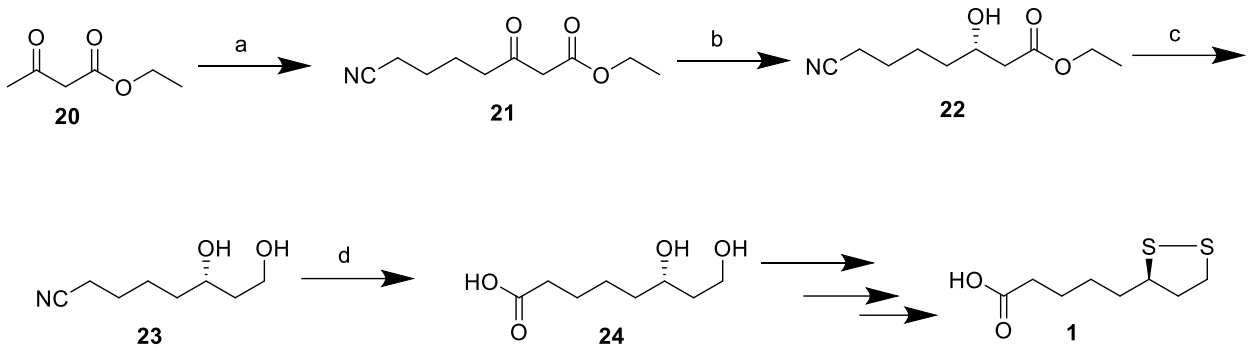
This approach consisted of preparation of 1,3-dithiane **14** from the 1,3-propanedithiol and L-menthone. The regioselective oxidation of the 1,3-dithiane **14** gave the sulfoxide **15**. Stereoselective alkylation of the **15** to afford **16** and subsequent hydrolytic cyclization gave *R*-(+) lipoic acid **1**. In another approach following the similar sequence of the reactions, *S* (-) lipoic acid has been synthesized by using the D-menthone. This synthetic route is short and excellent for the preparation of both enantiomers of α -lipoic acid.



Scheme 3. ***Reagents and conditions*:** (a) $NaIO_4$, MeOH, 0 ^oC; (b) LDA, TMEDA, THF, Br-$(CH_2)_4CO_2Li$, -78 ^oC; (c) aq. HCl, benzene.

Gopalan *et al*. [17]

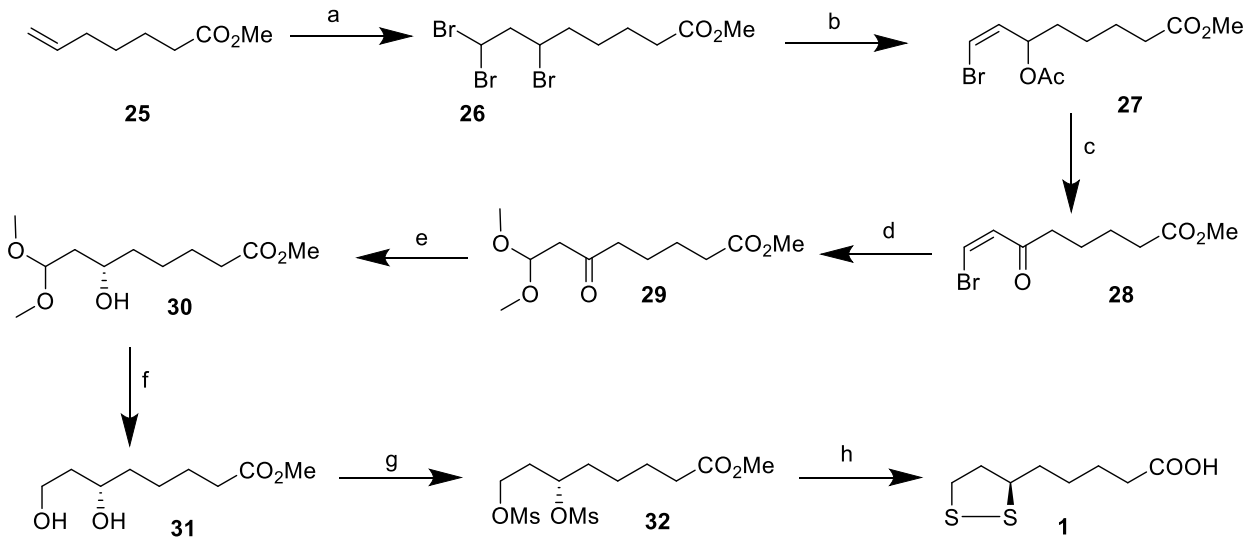
In this synthesis, Gopalan *et al.* used highly enantio-selective yeast reduction of the β- keto ester **20** to get the keto ester **21** which was reduced with Baker's yeast to give hydroxy ester **22**. Further, the reduction of the ester **22** with $LiBH_4$ in the THF at room temperature delivered the diol **23**. Additionally, the –CN group in the compound **23** was transformed to the diol acid **24** by performing the reaction of ethanol under acidic medium. In addition, the *R*-(+)-lipoic acid was synthesized by using the known functional group inter-conversions on the diol ester **24** (**Scheme 4**).



Scheme 4. ***Reagents and conditions*:** (a) (i) NaH, THF, HMPA, 0 ^{o}C; (ii) n-BuLi, I$(CH_2)_3$ CN; (b) Baker's Yeast; (c) $LiBH_4$, THF, 0 ^{o}C; (d) EtOH, H^+, reflux.

Bhalerao *et al*.[18]

In this synthesis, Bhalerao *et al*. utilized copper catalyzed bromoform addition to alkene **25** to get the methyl-6, 8, 8-tribromooctanoate **26** which was further treated with potassium acetate and 18-crown-6 in DMF to give the compound **27**. Addionally, it was subjected for hydrolysis, oxidation and followed by the treatment with triton-B to give the keto acetal **29**. In addition, this keto acetal **29** was subjected for enantioselective reduction by Baker's Yeast to afford the compound **30**, which when treated with H_3PO_4 in acetone and subsequent reduction by $NaBH_4$ resulted in the synthesis of diol **31**. This diol was converted to the *R*-(+)-lipoic acid **1** by using known reactions on it (**Scheme 5**).

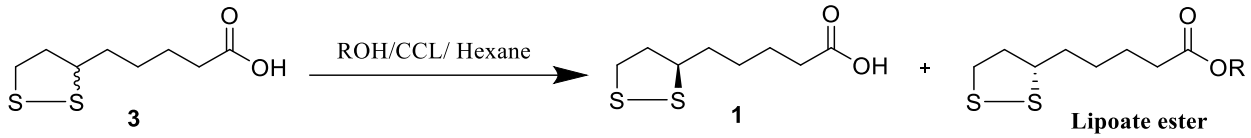


Scheme 5. ***Reagents and conditions*:** (a) Cu, $CHBr_3$, 80%; (b) AcOK, 18-crown-6, DMF; (c)

K_2CO_3, MeOH then PCC, 68%; (d) Triton B, MeOH; (e) Baker's Yeast, pH 4.5-5; (f) (i) H_3PO_4, acetone; (ii) $NaBH_4$, MeOH; (g) $MeSO_2Cl$, TEA, (h) (i) Na_2S, S, DMF, 60 ^oC; (iii) aq. NaOH.

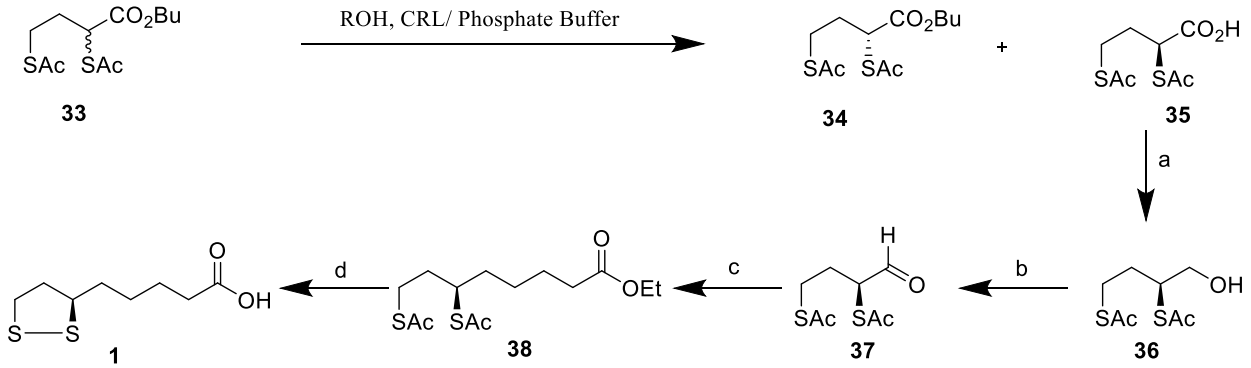
Fadnavis *et al*. [19]

Fadnavis *et al*. reported lipase catalysis for enantioselective ester formation of the racemic α-lipoic acid **3** to furnish the *R*-(+) - lipoic acid **1**.[19a] In this strategy the *S*-isomer was transformed to its lipoate ester by using lipase of *Candida rugosa* (**Scheme 6**).



Scheme 6. *Reagent and conditions***:** ROH/CCL/Hexane.

Also, in another report by Fadanvis *et al. R* and *S* isomers of the lipoic acid were prepared by using the lipase catalyzed regio- and stereo-specific hydrolysis of the n-butyl ester of 2, 4-dithioacetyl butanoic acid **33** to get the compounds **34** and **35**.[19b] Further, by the reduction of the acid **35** by BH_3.DMS followed by the PCC oxidation, the aldehyde **37** was obtained. Addionally, this aldehyde was treated with the four carbon Wittig salt (homologation) followed by the hydrogenation of the resulting compound by the Wilkinson's catalyst to give the ethyl ester **38**. In addition, the hydrolysis of the **38** by using wheat germ lipase and subsequently treating it with oxidative enzyme mushroom tyrosine afforded *R*-(+) -lipoic acid **1**. Also, by using similar reactions, the synthesis of the *S*-(-) lipoic acid **2** was reported from the compound **34** (**Scheme 7**).

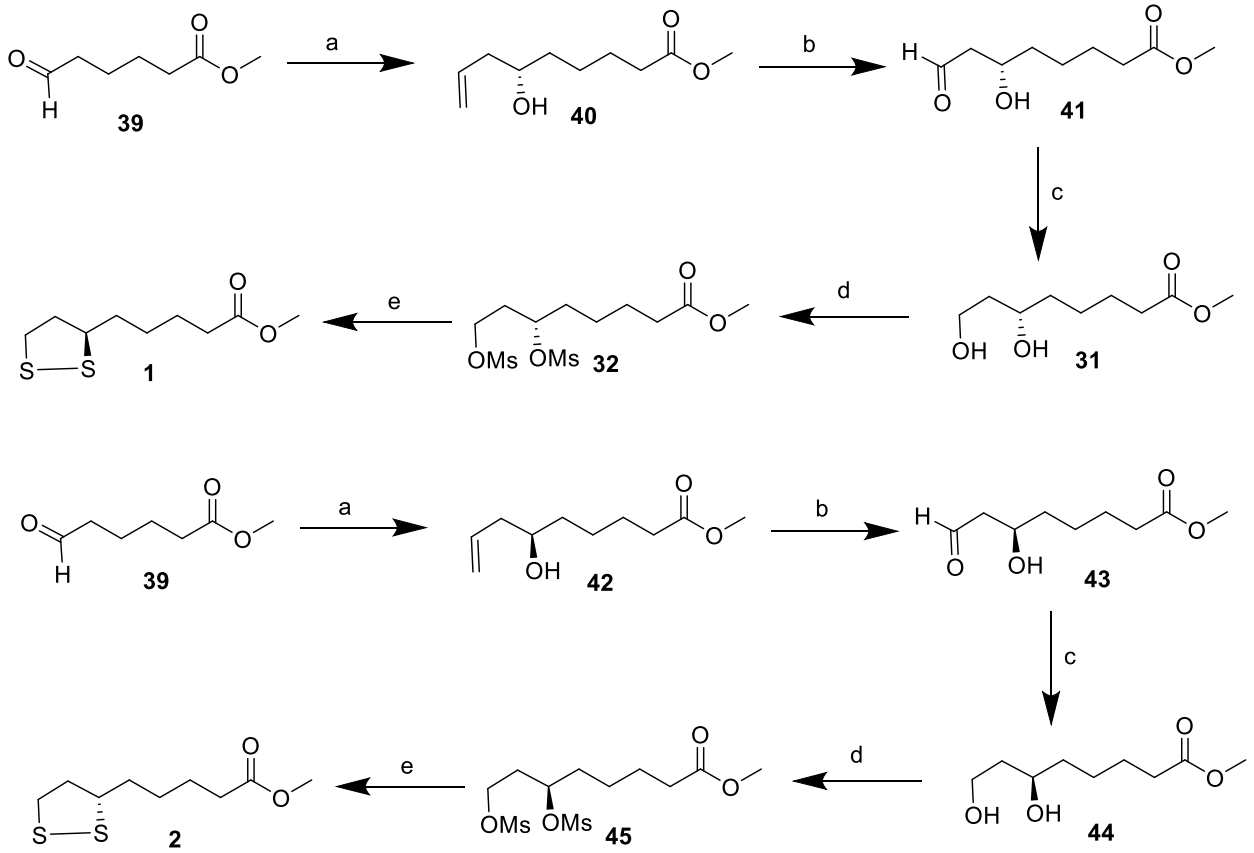


Scheme 7. ***Reagents and conditions*:** (a) (i) BH_3.DMS, 0 ^oC; (b) PCC (c) (i) Br^- $^+PPh_3$-

$CH_2(CH)_2CO_2Et$, NaHMDS, -78 ^oC; (ii) $(PPh_3)_3RhCl$, H_2; (d) (i) Wheat germ Lipase, pH 7.0; (ii) Tyrosinase.

Zimmer *et al*. [20]

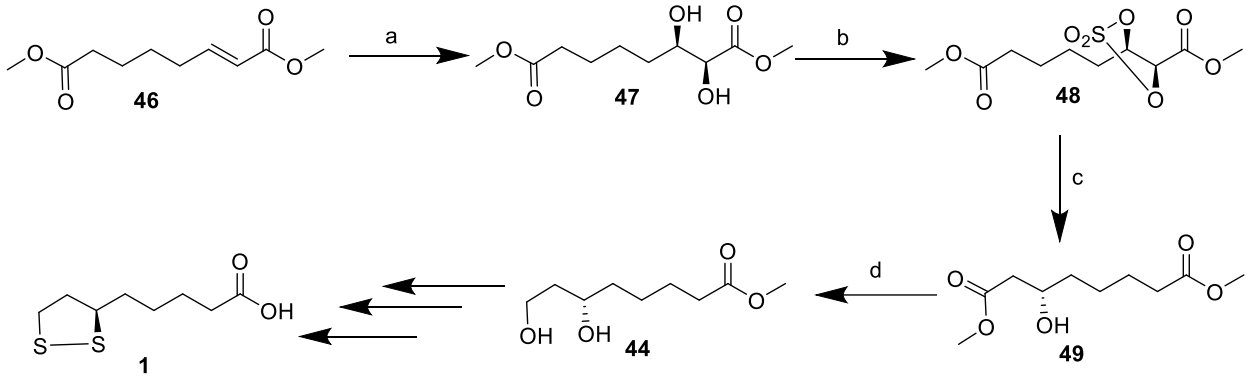
Zimmer and co-workers utilized the catalytic asymmetric allyl stannation as the main reaction to get the essential stereochemistry of the compound **40**. By the use of 0.2 eq. of the (*S*)-BINOL, 0.2 eq. of $Ti(OiPr)_4$ and the 4^oA molecular sieves aldehyde **39** and allyl tributyl stannane afforded the *R*-alcohol **40** having 98% ee. Further, this allylic alcohol compound was synthesized to *R*-(+) - lipoic acid **1** by following the known method (**Scheme 8**). Additionally, Zimmer *et al.* have synthesized *S*-(-)- lipoic acid **2** by following the similar protocol of the reactions as depicted in the following scheme by the utilization of the (*R*)- BINOL as the catalyst.



Scheme 8. ***Reagents and conditions*:** (a) allylBu_3Sn, (*S*)-BINOL (0.2 eq.), $Ti(O^iPr)_4$ (0.2 eq.), CH_2Cl_2, 2 days, 75% ee; (b) O_3, MeOH; (c) $NaBH_4$, MeOH, rt; (d) TEA, MsCl, ^oC; (f) (*R*)-BINOL (0.2 eq.), $Ti(O^iPr)_4$ (0.2 eq.), CH_2Cl_2, 6 days, 89%, 98% ee.

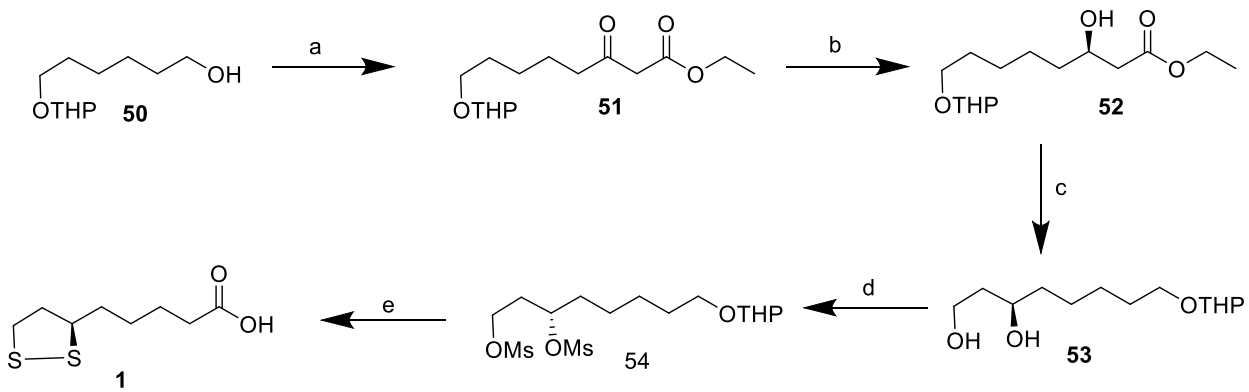
Sudalai *et al*.[21]

Sudalai *et al*. utilized the sharpless asymmetric dihydroxylataion reaction on the unsaturated ester **46** to get the intermediate **47**, which by using sulphone cyclization and the reduction with sodium borohydride underwent sulphone ring opening to afford the product **49**. The compound **49** was reduced by BH_3.DMS to get the intermediate **44**. In addition, this compound **44** was transformed to the *R*-(+)-lipoic acid **1** by using the reported reactions (**Scheme 9**).



Scheme 9. ***Reagents and conditions*:** (a) OsO_4, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, 0 °C, MeCN, 95%; (b) $SOCl_2$, Et_3N, DCM, 0 °C, 9 h; (ii) cat. $RuCl_3$, $NaIO_4$, 85%; (c) $NaBH_4$, DMAC, 20% H_2SO_4, 63%; (d) $NaBH_4$, Et_3N, MeOH:DMF (2:1), AcOH, 0 °C, 5 h.

Also, in the second synthesis ruthenium catalyzed asymmetric hydrogenation reaction was utilized on the keto-intermediate **51** to afford the beta-hydroxyl ester **52**. In addition, this beta-hydroxy ester **52** was reduced and subsequently the protection of the alcohol gave the intermediate **53**. Further, this intermediate was transformed into the *R*-(+)-Lipoic acid **1** by using the known functional group interconversions as shown in the **Scheme 10**.

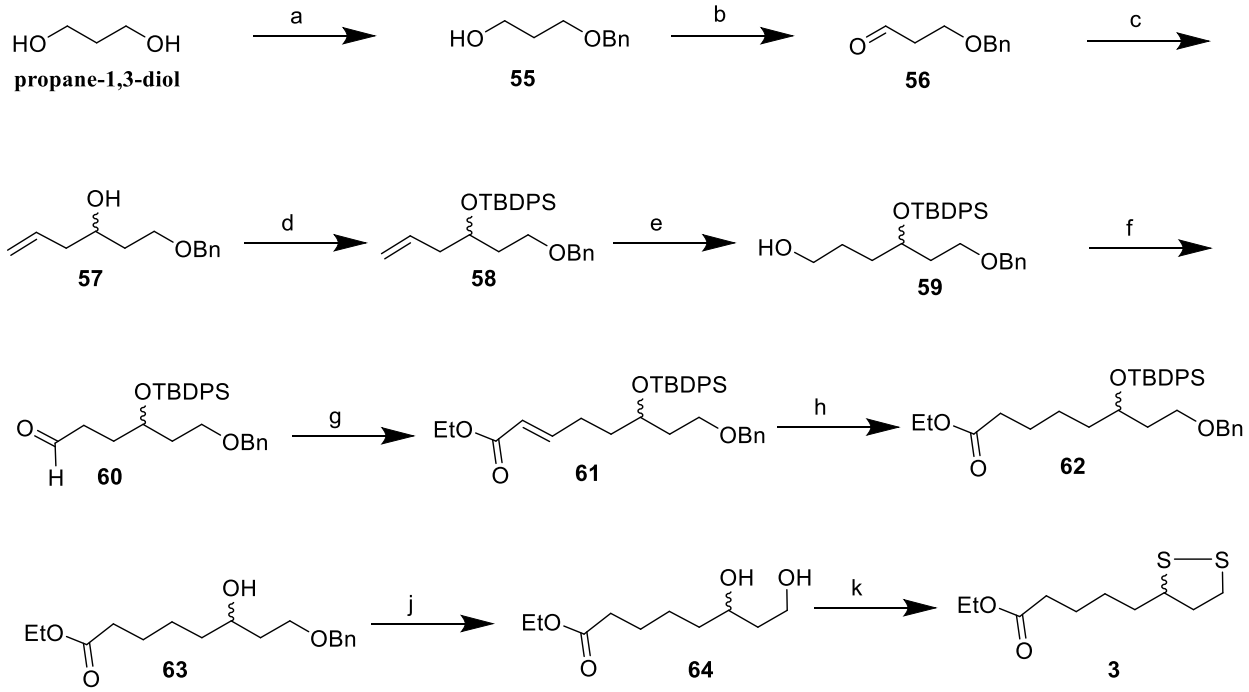


Scheme 10. ***Reagents and conditions*:** (a) (i) $(COCl)_2$, DMSO, DCM, Et_3N, 75%; (ii)

N_2CHCO_2Et, CH_2Cl_2, $SnCl_2$, 1 h, 85%; (or) Zn, $BrCH_2CO_2Et$, benzene, 4 h, then PCC, CH_3CO_2Na, CH_2Cl_2, 4h, 65%; (b) H_2 (400 Psi), MeOH, (*S*)-BINAP-Ru, 6 h, 90%; (c) (i) $NaBH_4$, $CuSO_4$, EtOH, 7 h, (ii) DHP, H^+; (d) (i) $MeSO_2Cl$, Et_3N, DCM, 0 ^oC, 6 h; (ii) *p*-TSA, MeOH, 10 h, (iii) PCC, DCM, 3 h, and then Ag_2O, NaOH, 1 h, 62%; (e) $Na_2S.9H_2O$, DMF, HCl, 28 h, 45%.

Kalkote *et al.*[22]

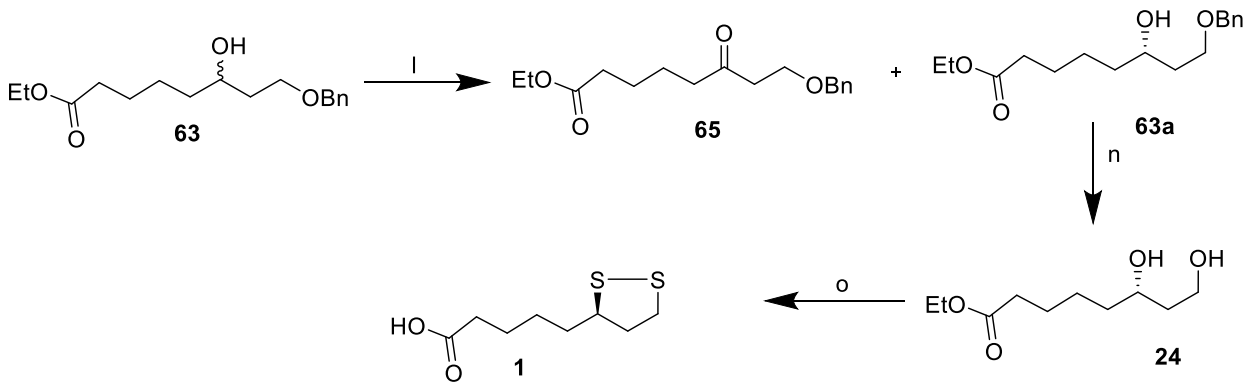
Kalkote and co-workers have synthesized both the enantiomers of the lipoic acid by employing the Mn (III)- salen- catalysed oxidative cyclization reaction as the key step in this report. The preparation of the lipoic acid **1** started with the O-benzyl protection of the readily accessible propan-1,3-diol to get the monobenzyl protected compound **55** and the other hydroxyl group present in the **55** was oxidized to aldehyde **56** by using the PCC oxidation reaction. Subsequently this was treated with allyl bromide and by the use of the activated zinc metal in THF solvent, to afford the compound **57**. Additionally, the hydroxyl group in the **57** was protected as its TBDPS derivative. Further, the hydroboration, oxidation and Wittig reaction of the resulting compound gave unsaturated ester compound **61** in 60% yield for these three steps (**Scheme 11**).



Scheme 11. ***Reagents and conditions*:** (a) NaH, BnBr, THF, 7 h, 91%; (b) PCC, DCM, Celite, rt, 0.5 h ; (c) Allyl bromide, Zn THF, Aq. NH_4Cl, 76%; (d) Im, DCM, TBDPS-Cl, rt, 12 h, 92%; (e) BH_3:DMS, THF, H_2O_2, CH_3COONa, 2 h, 78%; (f) PCC, DCM, 0.5 h, 94%; (g)

Ph_3P=CHCOOEt, THF, 10 h, 89%; (h) H_2, Pd-C, EtOAc, rt, 2 h, 91%; (i) TBAF, THF, rt, 6 h, 87%; (j) H_2, Pd-C, EtOAc, rt, 2 h, 90%; (k) (i)TEA, MsCl, DCM, 0 ^{O}C to rt; ii) Na_2S, S powder, DMF, reflux, 24 h, 85%; (ii) KOH, EtOH, rt, 12 h, 79%.

The unsaturated ester **61** was hydrogenated to reduce the double bond and the subsequent deprotection of the TBDPS afforded the ethyl 8-(benzyloxy)-6-hydroxyoctanoate **63** in 79% yield over two steps. In this synthesis, ethyl 8-(benzyloxy)-6-hydroxyoctanoate **63** is the crucial compound for the *R* or *S* lipoic acid synthesis. However, the racemic preparation of the lipoic acid **3** was accomplished from the ester **63**. Additionally, this ester compound **63** was subjected for asymmetric synthesis of both the enantiomers of the lipoic acid. The oxidative kinetic resolution of racemic compound **63** was done by the utilization of the Mn (III)–salen. Further, the secondary alcohol was resolved to give the chiral compound **63a** resulting in the high ee and in 47% yields. In addition, the ester **63a** was debenzylated by using H_2 gas in the presence of the catalytic Pd/C to afford the diol ester **24** (**Scheme 12**).

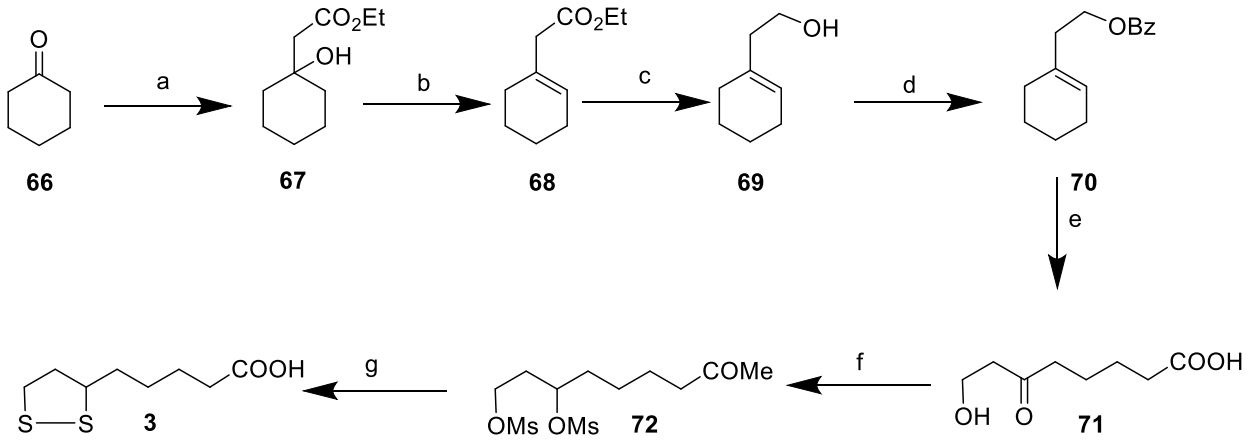


Scheme 12. ***Reagents and conditions*****:** (l) (*S, S*)-Mn (III)-salen, 2 mol% $PhI(OAc)_2$, KBr, DCM, H_2O, rt, 49% ; (m) $NaBH_4$, EtOH, rt, 94%; (n) H_2, Pd-C, EtOAc, rt, 90%; (o) (i) TEA, MsCl, DCM, 0 ^{o}C-rt; (ii) Na_2S, S powder, DMF, reflux, 75%; (iii) KOH, EtOH, rt, 12 h.

Further, five membered core structure containing the sulphur atoms was achieved by doing the mesylation of the diol ester **24** and heating it with sodium sulphide and sulphur in the DMF and subsequently the hydrolysis of the ester led to the formation of the (*R*)- lipoic acid **1**. Also, the other enantiomer was prepared by executing the similar reactions using (*R, R*)-Mn (III)-salen.

Chavan *et al.* [23, 24, 25]

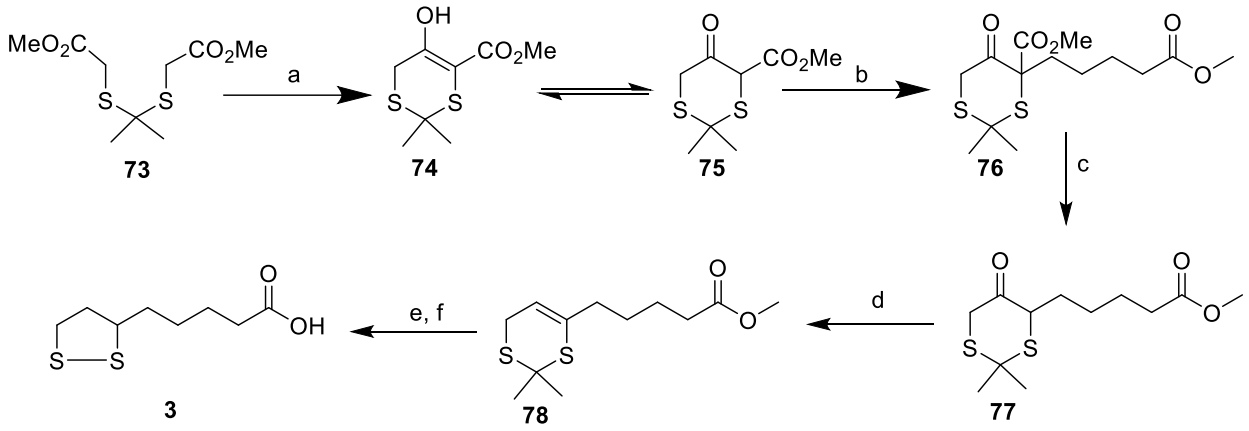
Chavan and co-workers have synthesized the lipoic acid **3** by using the modified Reformatsky reaction.[23] Dehydroxylation of the alcohol to get the β,γ-unsaturated ester is the beauty of this method. The well known Reformatsky reaction was employed by using the chloroester on the cyclohexanone **66** to get the β-hydroxy ester **67** which was subsequently subjected for the elimination reaction of the hydroxyl group by using the thionyl chloride and pyridine. This led to the formation of the β,γ-unsaturated ester **68**. Further, this ester was reduced by using the DIBAL-H to afford the unsaturated alcohol **69**. The alcohol was protected by the utilization of the benzoyl chloride to afford the benzoate ester **70,** subsequently it was ozonolyzed and then it was treated with Jones-oxidation conditions to get the keto-acid **71**. Additionally, the keto-acid was esterified and then mesylated to get the mesylated ester **72** and subsequently it was transformed into the racemic α-lipoic acid **3** by using the known protocol of reactions on it (**Scheme 13**).



Scheme 13. ***Reagents and conditions*:** (a) Zinc, $ClCH_2COOEt$, benzene-ether (1:1), reflux, 65 %; (b) $SOCl_2$, pyridine, DCM; (c) DIBAL-H, DCM, -78 ^oC, 65%; (d) BzCl, Et_3N, DCM, 92%; (e) (i) O_3, DCM; (ii) Jones reagent, 85 %; (f) (i) $NaBH_4$, MeOH, 90%; (ii) CH_2N_2, ether, 91%; (iii) $MeSO_2Cl$, Et_3N; (g) Na_2S, S, DMF, 60% for two steps.

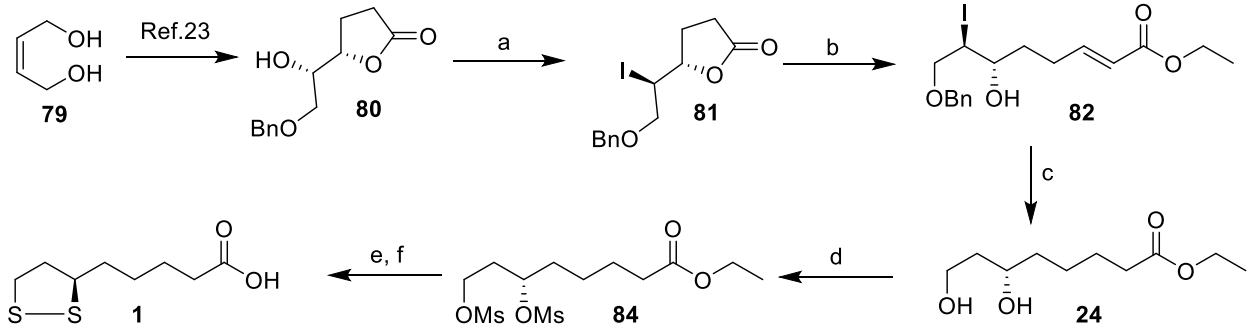
Additionally, Chavan *et al.* [24] in the second report skilled the synthesis of racemic α-lipoic acid **3** by employing the diester **73**, which can be immediately accessed in the two steps starting from the thioglycolic acid. Further, this ester **73** was put through the Dickmann condensation reaction to get the α-keto ester **75**. This α-keto ester **75** exhibits the keto-enol tautomerism. In addition, the alkylation of the ester **75** was accomplished by using the phase transfer catalyst and

subsequently it was decarboxylated to access the ester **77**. The keto ester **77** was treated with tosyl hydrazine and it was again refluxed in the presence of the NaOH as a base to access the olefin **78**. The double bond present in the olefin was reduced by using the Et_3SiH, TFA conditions and the resulting compound was further oxidized to mono sulphoxide. Subsequently the hydrolytic cyclization of the ester was carried out to afford the racemic α-lipoic acid **3** (**Scheme 14**).



Scheme 14. ***Reagents and conditions*:** (a) NaH, THF, 60 °C, 3 h, 86%; (b) (i) K_2CO_3, $Br(CH_2)_4COOCH_3$, Bu_4NHSO_4, THF, rt; (c) DMSO, NaCl, H_2O, 140 °C; (d) (i) $TsNHNH_2$, MeOH, rt, 67%; (ii) NaOH (2 eq.), iPrOH, reflux, 84%; (e) (i) Et_3SiH, TFA, 0 °C; rt, 73%; (ii) $NaIO_4$, MeOH, 0 °C, 2 h, 68%; (f) aq. HCl: Benzene (1:1), 50 °C, 7 h, 69%.

Also, in the third synthesis Chavan *et al*. synthesized the enantiomerically pure lactone **80**, which is the versatile intermediate for the synthesis.[25] This can be prepared in four-step reaction sequence starting from the *cis*-2-butene-1, 4-diol **79**.



Scheme 15. ***Reagents and conditions*:** (a) PPh_3, I_2, imidazole, 70 °C, 3 h, 94%; (b) DIBAL-H, DCM, 78 °C, 1 h, $Ph_3PCHCOOC_2H_5$, 24 h; rt, 96%; (c) W2 Raney nickel, H_2, rt, 24 h, 84%; (d)

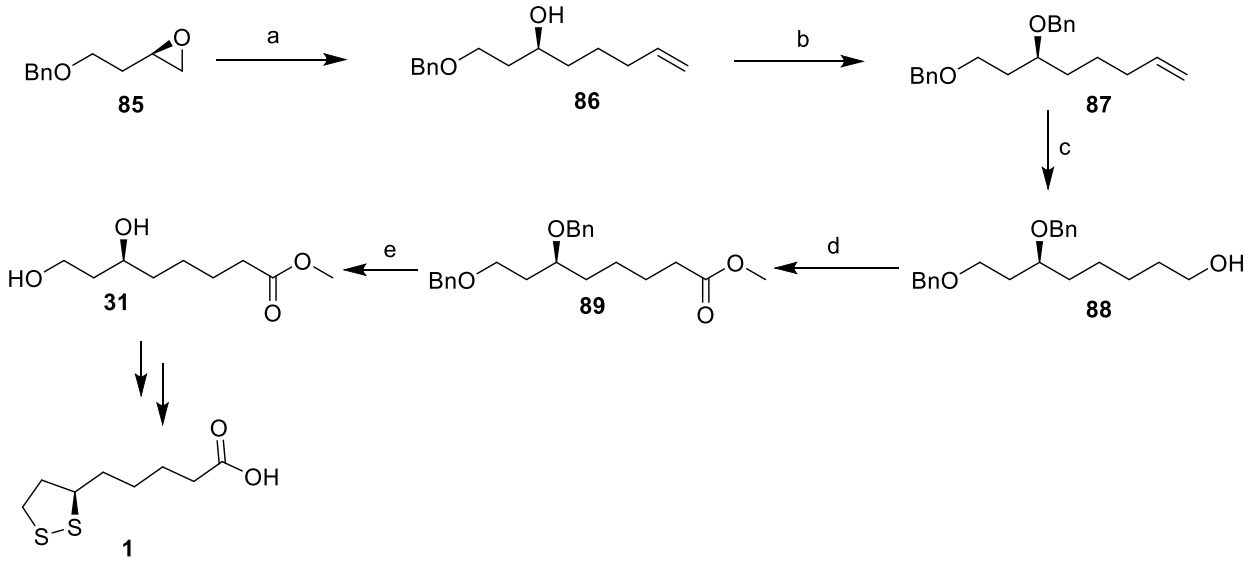
CH_3SO_2Cl, Et_3N, DCM, 0 ^oC, 4 h, 92%; (e) Na_2S, S, DMF, 90 ^oC, 24 h, 72%; (f) 1M ethanolic KOH, rt, 24 h, 75%.

The lactone **80** on the treatment with triphenylphosphine, iodine and imidazole gave the iodo lactone **81**. Further, on reduction with DIBAL-H and subsequent *in-situ* Wittig reaction, the lactone **81** afforded the unsaturated ester **82**. The compound **82** was tranformed to the diol **24** by treating with W2 Raney nickel in the medium of hydrogen gas. The diol **24** is a known intermediate for the synthesis of *R*-(+)-lipoic acid (**Scheme 15**).

In addition, the unnatural *S*-(-)-lipoic acid has also been synthesized by preparing the antipode of hydroxy lactone **80** by using AD-mix-β. Further, the similar sequence of the reactions were utilized in the synthesis of the *R*-(+)-lipoic acid.

Bose *et al*.[26]

Bose and co-workers reported the another method of syntheses for *R*-lipoic acid **1** by employing the regiospecific epoxide ring opening reaction of the epoxide (*R*) - **85** by using the but-3-enylmagnesium bromide as the crucial step in this synthesis. The ring opening of the epoxide afforded the alcohol **86** in 90% yields (**Scheme 16**).



Scheme 16. ***Reagents and conditions*:** (a) CH_2=$CHCH_2CH_2$-MgBr, Li_2CuCl_4 (cat.), THF, -78 ^oC to rt; (b) NaH, BnBr, TBAI, DMF, 85%; (c) BH_3.DMS, $MeCO_2Na$, H_2O_2, THF, 88%; (d) (i) $NaClO_2$, TEMPO, NaOCl; (ii) CH_2N_2, Et_2O; (e) H_2, Pd/C, EtOH.

The protection of the hydroxyl group in the alcohol **86** by BnBr resulted in the formation of the compound **87**. Further the hydroboration, oxidation and esterification by diazomethane of the compound **87** led to the formation of the ester **89**. The debenzylation of the ester **89** by using H_2, Pd/C afforded the diol ester **31** which was then derived to *R* - (+)-lipoic acid **1** by the known chemical transformations.

The above literature survey gives an insight about how the different chemical methods have been used for to access the α-lipoic acid **3** and the lipoic acid enantiomers.

2.2.3. References.

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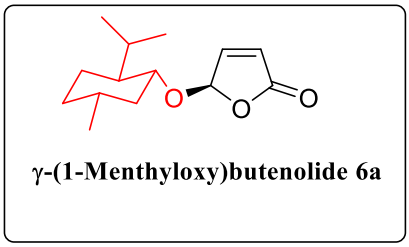
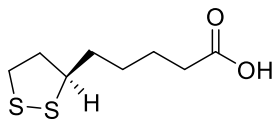
2.2.4. Present Work:

The γ-lactone moiety is present in the many natural products. Several natural products containing this lactone moiety are of medicinal importance.[1] Well known examples of this are the antibiotic PA-147[2] and acetomycin[3]. In addition, the preparation of the γ-substituted butenolides is in the focus due to distinctive carbon skeleton of the 2(*5H)* furanone as it is present in the biologically active compounds. In the asymmetric transformations, chiral auxiliaries have influenced the good results. The chiral butenolides have been used in the synthesis of many natural products.[4] Feringa *et al.* have shown that γ – (1-methyloxy) butenolide (**6a)** is very good chiral synthon for the preparation of enantiomerically pure amino diols.[5] Additionally, **6a** acts as a chiral maleic anhydride analogue in the asymmetric Diels-Alder reactions with a variety of dienes.[6]

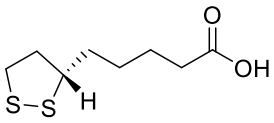


γ-(1-Menthyloxy)butenolide 6a

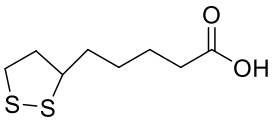
It was thought that this γ – (1-menthyloxy)butenolide (**6a**) can be employed in the synthesis of the lipoic acid by the use of additional chemical transformations on it and accordingly, a different modified synthetic method for the asymmetric synthesis of α- lipoic acid was planned by using butenolide approach.



(*R*)-(-)-α-Lipoic acid 1



(*S*)-(-)-α-Lipoic acid 2



α-Lipoic acid 3

Figure 1. Chiral and the racemic Lipoic acid structures.

The isolation of lipoic acid **1** was achieved in the year 1950 by Reeds *et al.*[7] and is the cyclic disulphide of 6,8-di-mercapto-n-caprylic acid. The separation of both the enantiomers was achieved in 1954.

The separation was carried out by the resolution method and also, it was established that *R*-lipoic acid shows moderate bioactivity than its antipode *S*-lipoic acid.[8] Due to the biological activity of the α-lipoic acid, it has got immense commercial importance. Even after the seven decades of the isolation, today also it is the molecule of the high importance for the synthetic chemists.

Present work and Scheme:

Herein, a different synthetic route for the asymmetric preparation of α- lipoic acid was planned by using modified butenolide approach as shown in the following retrosynthetic analysis scheme.

2.2.5. Retrosynthetic Plan:

It was thought that the (*S*)-(-)-α-lipoic acid **2** could be obtained from 1,3-diol ester **11** which in turn can be synthesized from the (4*R*, 5*R*)-(-)4-benzyloxy-5-[1*R*, 2*S*, 5*R*)-menthyloxy]-γ-butyrolactone **8**. Further, the compound **8** can be obtained from 5-menthyloxy-2(5*H*)-furanone **6a** by conjugate addition of the benzyl alcohol. Additionally, 5-menthyloxy-2(5*H*)-furanone **6a** can be accessed from the 5-hydroxy-2(*5H*)-furanone **5** which in turn can be obtained by oxidation of furan **4**.

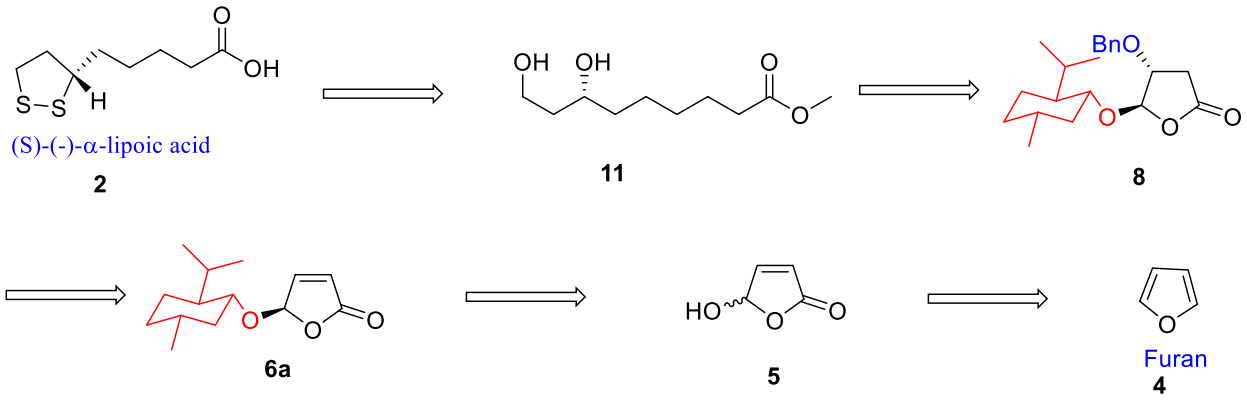


Figure 2. Retrosynthesis.

2.2.6. Results and discussion:

The synthesis began by using furan as a commercially available starting material. The chiral entity, 5-menthyloxy-2-(*5H*)-furanone **6a** was synthesized from the furan **4**. The furan **4** on

oxidation with the oxone by using the water as the solvent by the method developed by this group gave the oxidized product 5-hydroxy-2(*5H*)-furanone **5** in 75% yield.[10] Additionally, 5-hydroxy-2(*5H*)-furanone **5** was then refluxed by using cat. *p*-TSA and with menthol in benzene, the azeotropic removal of the water formed in the reaction afforded the 5-menthyloxy-2-(*5H*)-furanone containing the diastereomeric mixture of the diastereomers **6a** and **6b** in 86% yields. This diastereomeric ratio (60:40) was confirmed from the ^{1}HNMR spectrum of the compound. Further, on the successive recrystallizations of this reaction mixture in the petroleum ether, the major diastereomer **6a** was synthesized as the white crystalline solid in 57% yield. This process of recrystalization is associated with the epimerization of one diastereomer to other (**Figure 3**).

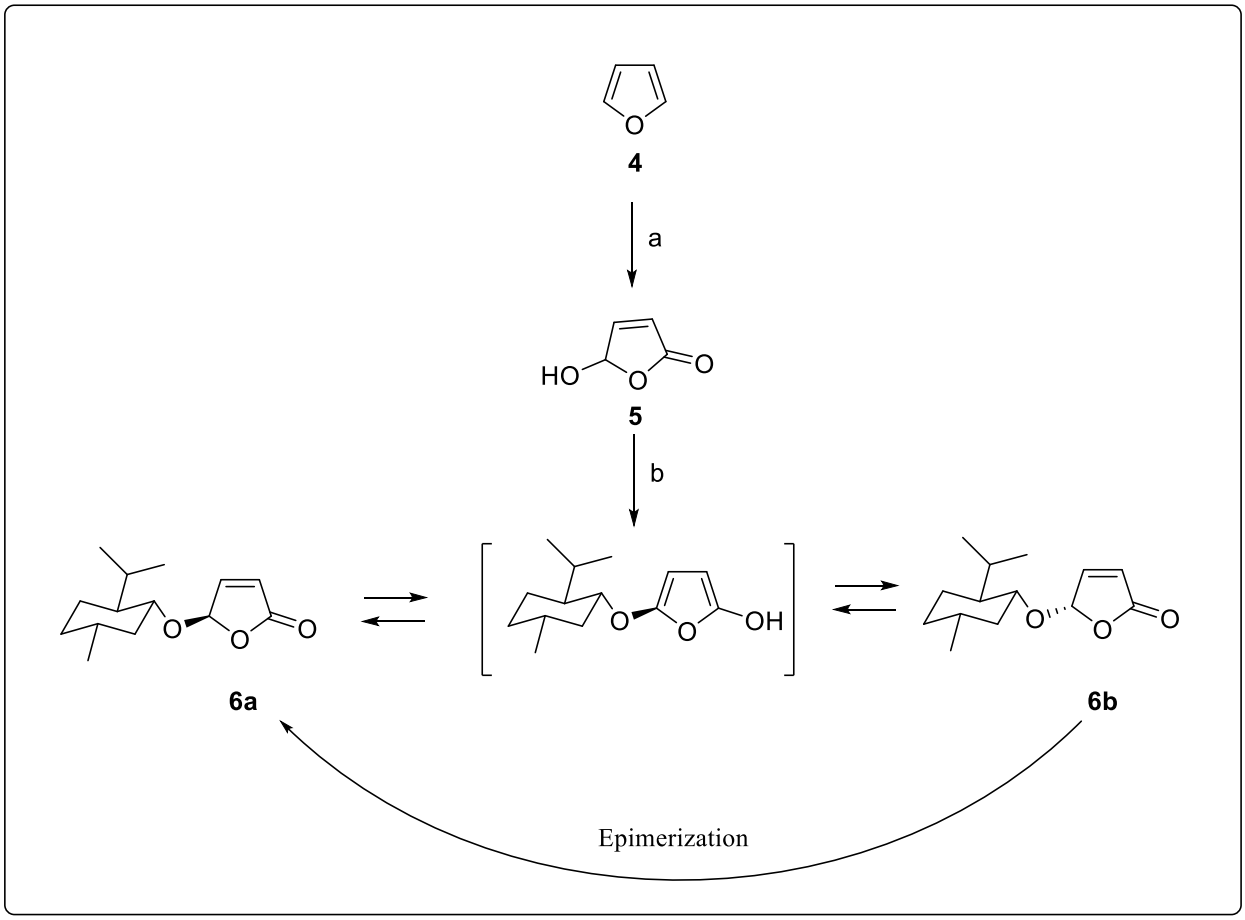
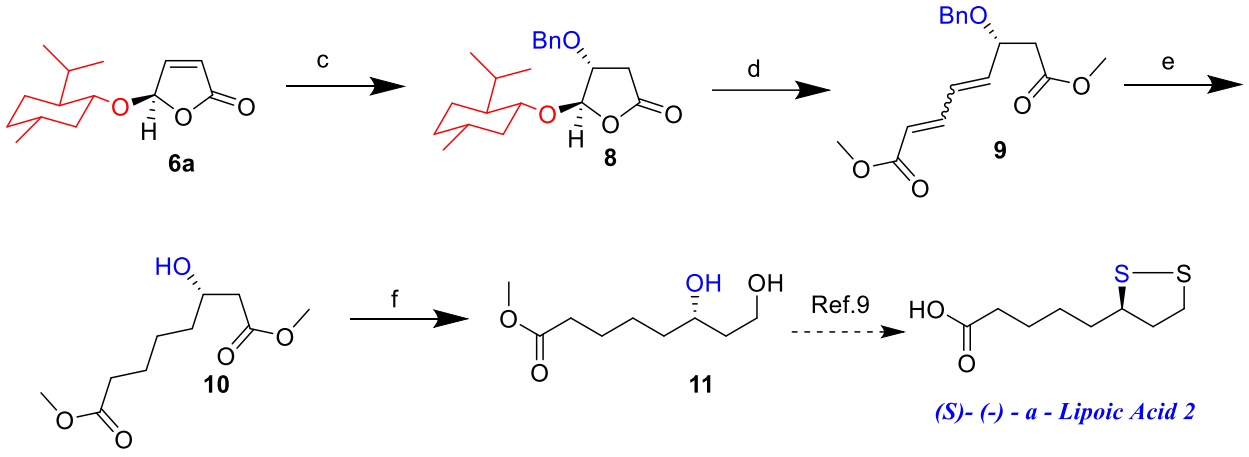


Figure 3. Epimerization of **6b** to **6a**.

Reagents and the conditions: a) oxone, H_2O, ^{o}C-RT, 16 h, 75%; b) *l*-menthol, *p*-TSA, benzene, reflux, 12 h, 86% (**6a + 6b**).

The diastereomer **6a** was then subjected to 1,4-addition with the benzyl alcohol by known method using catalytic sodium in dry DMF at the room temperature to furnish (*4R, 5R*)-(-) 4-benzyloxy-5-[*1R, 2S, 5R*)-menthyloxy]-γ-butyrolactone **8** in 84% yield. Further, the butyrolactone **8** was treated with 4-carbon Wittig salt (methyl (*E*)-4-(triphenyl-l5-phosphaneylidene) but-2-enoate) in methanol under reflux conditions to afford the E/Z mixture of the olefin **9** in 1:1 ratio in 85% yield, which was then subjected for hydrogenation by using Pd/C and H_2 gas in balloon pressure at room temperature to afford diester **10** in 82% yield. Additionally, chiral HPLC of the compound **10** was taken to assure its enantiomeric excess. Further, the diester **10** was then subjected for chemoselective reduction by using the $NaBH_4$ under reflux conditions to afford the diol **11** in 80% yields. Further by using this diol **11**, the synthesis of the *S*-(-)-*α*-lipoic acid is known. Thus, the formal synthesis of the α-lipoic acid has been achieved in 94% of the enantiomeric excess. (All the compounds synthesized in this scheme were characterized by using ^{1}HNMR, ^{13}CNMR, IR and HRMS).



Reagents and conditions: c) cat. sodium metal, BnOH, DMF, RT, 84%; d) Methyl (*E*)-4-(triphenyl-l5-phosphaneylidene) but-2-enoate, MeOH, reflux, 85%; e) H_2, Pd/C, MeOH, RT, 82%; f) $NaBH_4$, THF, reflux, 80%.

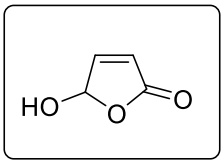
2.2.7. Conclusion:

The synthesis was started by using furan as the starting material which is commercially available and cheap. The synthesis of (6*S*)-(-)-methyl-6,8-dihydroxyoctanoate has been accomplished. The chiral auxiliary alcohol (menthol) can be recovered with 75% yield. The diol **11** can be converted

into (*S*)-α-lipoic acid by known method. Thus it provides a simple route for the synthesis of (*S*)-(-)-α-lipoic acid with 94% ee.

2.2.8. Experimental:

5-Hydroxyfuran-2(5*H*)-one (5)[10]:



Procedure: To a mechanically stirred, cooled (0 °C) solution of furan (50 g, 0.735 mol) in water (1000 mL) was added oxone (564 g, 0.919 mol) portion-wise and stirred at 0 °C for 8 h. The mixture was allowed to warm to room temperature and stirred for the next 8 h. The reaction mixture was filtered off, solid was thoroughly washed with ethyl acetate, and the layers were separated. The aqueous layer was extracted with ethyl acetate (500 mL X 3). Additionally, the aqueous layer was saturated with NaCl and extracted with ethyl acetate (500 mL X 3). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated below 40 °C under reduced pressure to give crude 5-hydroxy-2(5*H*)-furanone as a clear liquid which solidified on cooling. The solid was recrystallized at -78 °C from chloroform (300 mL) to afford 55.3 g (75% yield) of 5-hydroxy-2(5*H*)-furanone (**5**).

Molecular Formula: $C_4H_4O_3$.

Yield: 75%.

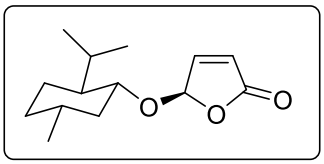
R_f : 0.2 (**EtOAc–PE=** 50:50).

M. p.: 53–55 ºC (lit.[1] M.p. = 54 ºC).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.33 (dd, J = 1.1, 5.6 Hz, 1H), 6.27 (s, 1H), 6.22 (dd, J = 1.1, 5.6 Hz, 1H), 5.32 (br s, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.3, 152.0, 124.6, 98.7.

(*R*)-5-(((*1R, 2S, 5R*)-2-isopropyl-5-methylcyclohexyl) oxy) furan-2(*5H*)-one (6a):



Procedure: The mixture of 5-hydroxy-2(5*H*)-furanone (**5**) (20 g, 0.2 mol), menthol (29.6 g, 0.19 mmol) and catalytic amount of p-TSA (190 mg, 1 mmol) was taken in benzene and refluxed for 20 h with azeotropic removal of water. The reaction mixture was cooled to room temperature and washed with water and brine and dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under vacuum and the residue was purified by column chromatography (Pet. ether: EtOAc = 99: 1) to yield mixture of diastereomers in the ratio 60:40 in 86% yields. After repeated

recrystalizations from the light petroleum ether at -23 ºC, diasteromerically pure **6a** was in obtained 57% yield.

R_f : 0.5 (**EtOAc–PE=** 10:90).

Molecular Formula: $C_{14}H_{22}O_3$.

Yield: 86 % (60:40 mixture, after repeated recrystalizations 57% enantiomerically pure **6a**).

M. P: 70 ºC (lit.[11] Mp = 70.5-70.7 ºC).

$[\alpha]_D^{25}$: -141.7 (c =1, ab. Ethanol). {lit.[11] $[\alpha]_D$ = -136.4, (c =1, ab. Ethanol)}

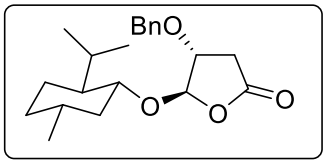
IR: 3022, 2959, 1761, 1216, 767 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (d, *J* = 6.88 Hz, 3H), 0.88 (d, *J* = 7.13 Hz, 3H), 0.95 (d, *J* = 6.63 Hz, 3H), 0.97 - 1.09 (m, 2H), 1.21 - 1.31 (m, 1 H), 1.34 - 1.48 (m, 1H), 1.60 - 1.72 (m, 3H), 2.05 - 2.19 (m, 2H), 3.66 (td, *J* = 10.66, 4.31 Hz, 1H), 6.09 (t, *J* = 1.19 Hz, 1H), 6.20 (dd, *J* = 5.63, 1.25 Hz, 1H), 7.17 (dd, *J* = 5.63, 1.25 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 15.43, 20.51 (2C), 21.88, 22.80, 24.98, 31.13, 33.85, 39.98, 47.43, 100.12, 124.44, 150.55, 170.41.

HRMS (ESI): *m/z* calculated for $C_{14}H_{23}O_3$ [M + H]$^+$ **:** 238.9874**,** found: 238.9874.

(*4R, 5R*)-(-)-4-Benzyloxy-5-[(*1R, 2S, 5R*)-menthyloxy]-γ-butyrolactone (8):



Procedure: To a stirred solution of benzyl alcohol (2 ml) in DMF (5 ml) was added a catalytic amount of metallic sodium (10 mg, 0.42 mmol). As soon as the sodium disappeared, (*5R*)-5(l-menthyloxy)-2 (*5H*)-furanone (**6a**) (1.0 g, 4.2 mmol) was added and the resulting red solution was stirred at room temperature for 24 h, then the reaction mixture was taken in ether and washed with water, brine and dried over anhydrous sodium sulphate. The ether layer was then filtered and the removal of solvent afforded the crude product which was purified by column chromatography (Pet. ether: EtOAc = 98.5:1.5). The product was recrystallized from hexane to yield 1.220 g of (*4R, 5R*)-(-)-4-benzyloxy-5-[(*1R, 2S, 5R*)-menthyloxy]-γ-butyrolactone **8** as a white solid.

R_f : 0.4 (**EtOAc–PE=** 05:95).

Molecular Formula: $C_{21}H_{30}O_4$.

Yield: 84% **.**

M. P.: 86 ºC (white solid).

$[\alpha]_D^{25}$: -129.06 (c=1, hexane). {lit.[12] $[\alpha]_{578}^{20}$ = -230 (c =1, hexane)}.

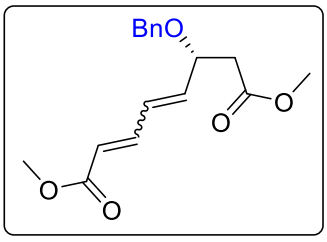
IR: 3021, 2967, 1786, 1216, 769 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (d, *J* = 6.88 Hz, 3H), 0.87 (d, *J* = 7.13 Hz, 3H), 0.95 (d, *J* = 6.63 Hz, 3H), 0.97 - 1.08 (m, 1H), 1.15 - 1.30 (m, 2H), 1.33 - 1.44 (m, 1H), 1.54 - 1.75 (m, 3H), 1.89 - 2.10 (m, 2H), 2.54 (dd, *J* = 17.95, 1.56 Hz, 1H), 2.81 (dd, *J* = 17.89, 6.13 Hz, 1 H), 3.53 (td, *J* = 10.69, 4.25 Hz, 1H), 4.00 - 4.16 (m, 1H) 4.48 - 4.68 (m, 2H), 5.59 (s, 1H), 7.30 - 7.44 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 15.87, 21.14, 22.53, 23.35, 25.83, 31.62, 34.56, 34.61, 39.88, 47.94, 71.99, 77.18, 78.89, 103.20, 128.10 (2C), 128.48, 128.94 (2C), 137.25, 175.21.

HRMS (ESI): *m/z* calculated for $C_{21}H_{30}NaO_4$ [M + Na]$^+$ **:** 369.2041, found: 369.2049.

Dimethyl (*R*)-6-(benzyloxy) octa-2, 4-dienedioate (1:1 *E/Z* mixture) (9):



Procedure: In a round bottom flask having two necks and equipped with a magnetic needle, condenser, argon balloon and a septum, was added 1 eq. (700 mg) of (*4R, 5R*)-(-)-4-benzyloxy-5-[(*1R, 2S, 5R*)-menthyloxy]-γ-butyrolactone (**8**). To this flask was added 1.5 eq. of 4-carbon Wittig salt (methyl (*E*)-4-(triphenyl-l5-phosphanylidene) but-2-enoate) followed by the addition of dry methanol (10 ml) maintaining the dry conditions. This resulting mixture was refluxed at 65 ºC for 12 h, the progress of the reaction was monitored by taking the TLC and dipping it in the $KMnO_4$ solution. After 12 h, the reaction mass was taken into 100 ml round bottom flask. The solvent was evaporated *in vacuo*. Further, the residue was purified by column chromatography. This afforded dimethyl (*R*)-6-(benzyloxy)octa-2,4-dienedioate **9** (1:1 *E/Z* mixture) as a colorless oil in 85% yield alongwith menthol as a byproduct.

R_f : 0.2 (**EtOAc–PE=** 20:80).

Molecular Formula: $C_{17}H_{20}O_5$.

Yield: 85%

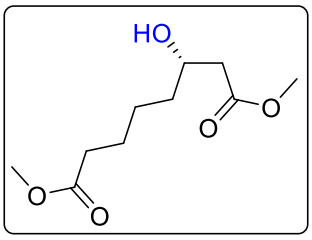
B. P. : Colorless liquid.

IR: 3022, 1724 (b), 1215, 756 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) (1:1 *E/Z* mixture): δ 2.43 - 2.59 (m, 2H), 2.74 (td, *J* = 15.60, 7.82 Hz, 2H), 3.65 - 3.70 (m, 6H), 3.73 - 3.79 (m, 6H), 4.35 - 4.45 (m, 3H), 4.52 - 4.61 (m, 2H), 4.70 (s, 2H), 4.80 - 4.90 (m, 1H), 5.76 (t, *J* = 10.19 Hz, 1H), 5.89 - 6.00 (m, 2H), 6.06 (dd, *J* = 15.32, 7.32 Hz, 1H), 6.28 - 6.48 (m, 2H), 7.28 - 7.36 (m, 11H), 7.36 - 7.39 (m, 4H), 7.56 (ddd, *J* = 15.26, 11.82, 1.06 Hz, 1H).

HRMS (ESI): *m/z* calculated for $C_{17}H_{20}NaO_5$ [M + Na]$^+$**:** 327.1208, found: 327.1204.

Dimethyl (*S*)-3-hydroxyoctanedioate (10):



Procedure: In a round bottom flask equipped with magnetic needle was taken 1 eq. (500 mg) dimethyl (*R*)-6-(benzyloxy)octa-2,4-dienedioate **9** (1:1 *E/Z* mixture), a colorless oil, with the help of micropipette. Then 8 ml of anhydrous methanol was added to the R.B. flask followed by the addition of the catalytic amount (0.1 eq., 50 mg) of Pd/C in it. Further, the hydrogen bladder containing the hydrogen gas (H_2 gas balloon) was attached to it and the resulting reaction mixture was stirred for 24 h under the atmosphere of H_2 gas. The progress of the reaction was monitored by TLC. After completion of the reaction, hydrogen bladder was removed and the reaction mass was filtered through cellite pad. Further, the additional wash of methanol (20 ml) was given to this cellite pad. The filtrate was collected in the R.B. flask and the methanol was evaporated under reduced pressure. The remaining residue in the R.B. flask was purified by column chromatography. This gave dimethyl (*S*)-3-hydroxyoctanedioate **10** as the colorless oil in 82% yield. Additionally, the chiral HPLC was performed of the pure compound dimethyl (*S*)-3-hydroxyoctanedioate **10.** The chiral HPLC showed 94% ee**.**

R_f : 0.2 (**EtOAc–PE=** 30:70).

Molecular Formula: $C_{10}H_{18}O_5$.

Yield: 82%**.**

B. P. : Colorless liquid.

$[\alpha]_D^{25}$: 1.20 (c = 1, $CHCl_3$).

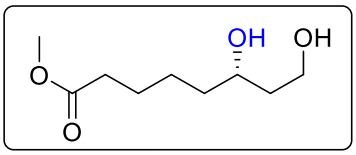
IR: 3620, 3021, 2976, 1748, 1733, 1216, 771 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 - 1.54 (m, 4H), 1.56 - 1.74 (m, 2H), 2.32 (t, *J* = 7.39 Hz, 2H), 2.38 - 2.62 (m, 2H), 2.99 (br s, 1H), 3.66 (s, 3H), 3.71 (s, 3H), 3.90 - 4.11 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.70, 25.00, 33.91, 36.02, 41.03, 51.49, 51.75, 67.69, 173.40, 174.05.

HRMS (ESI): *m/z* calculated for $C_{10}H_{19}O_5$ [M + H]$^+$ **:** 219.1232, found : 219.1233.

Methyl (*S*)-6, 8-dihydroxyoctanoate:



Procedure: To a solution of dimethyl (*S*)-3-hydroxyoctanedioate **10;** (1eq, 450 mg) in dry THF (8 ml), portionwise addition of sodium borohydride ($NaBH_4$) (6 eq; 313 mg**)** was done at room temperature. Then this reaction mixture was refluxed for 6 h under argon atmosphere at 66 ^oC. The progress of the reaction was monitored by taking TLC. After complete consumption of the starting material i.e. after 6 h, the reaction mass was cooled to 0 ^oC and quenched by the addition of saturated ammonium chloride solution. Further, the THF was removed under reduced pressure. The residue was extracted with ethyl acetate two-three times. The solvent was evaporated on a rotary evaporator and the residue was then purified by flash column chromatography to yield the pure product methyl (*S*)-6,8-dihydroxyoctanoate **11** (315 mg) as the viscous oil in 80% yield.

R_f : 0.3 (**EtOAc–PE=** 70:30).

Molecular Formula: $C_9H_{18}O_4$.

Yield: 80%.

B. P. : Viscous liquid.

$[\alpha]_D^{25}$: -4.62 (c = 2, $CHCl_3$); {lit.[13] $[\alpha]_D^{25}$ = -3.9, (c =2.3, $CHCl_3$)}.

IR: 3621, 2942, 1735, 1224, 772 cm^{-1}.

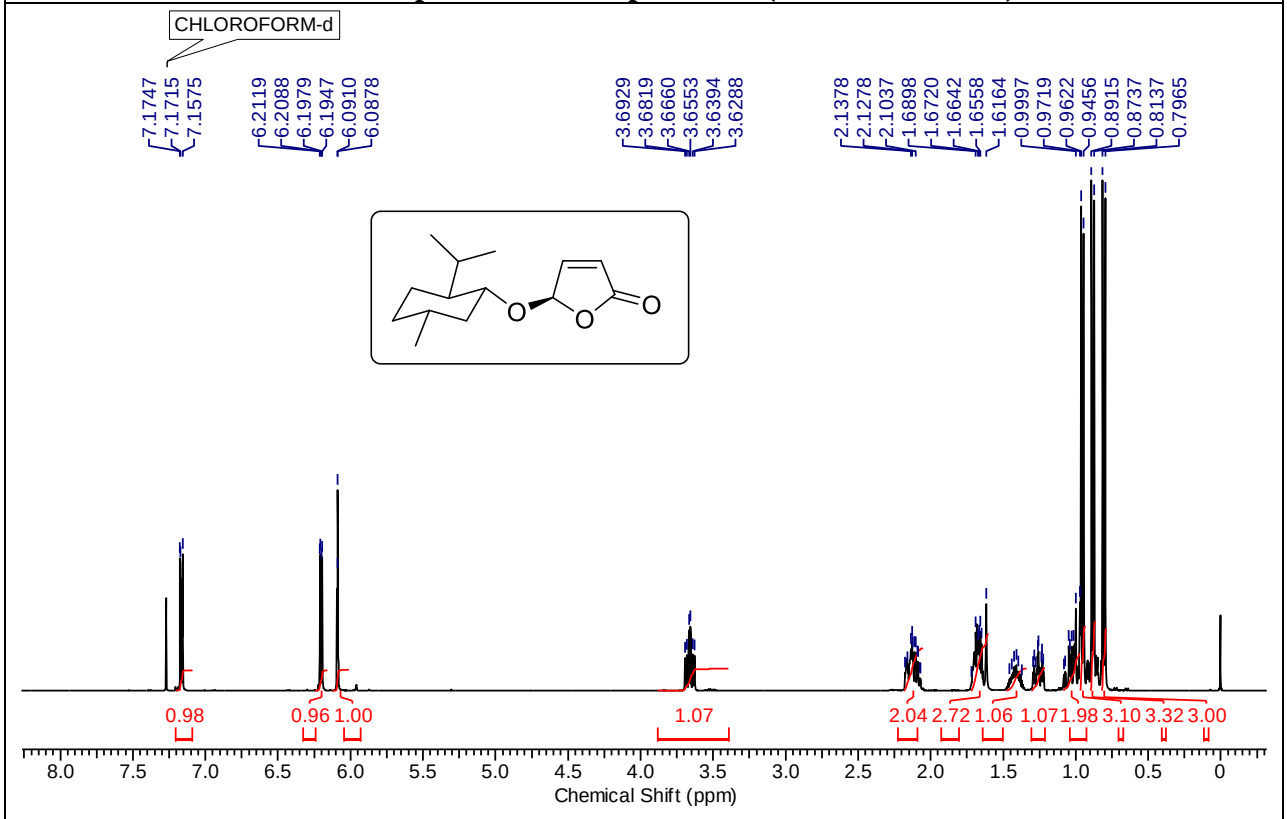
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 -1.42 (m, 2H), 1.43 - 1.54 (m, 2H), 1.56 - 1.73 (m, 4H), 2.33 (t, *J* = 7.44 Hz, 2H), 2.89 (br s, 2H), 3.66 (s, 3H), 3.81-3.83 (m, 1H), 3.84 - 3.91 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 24.94, 25.21, 34.15, 37.50, 38.48, 51.76, 61.92, 71.98, 174.51.

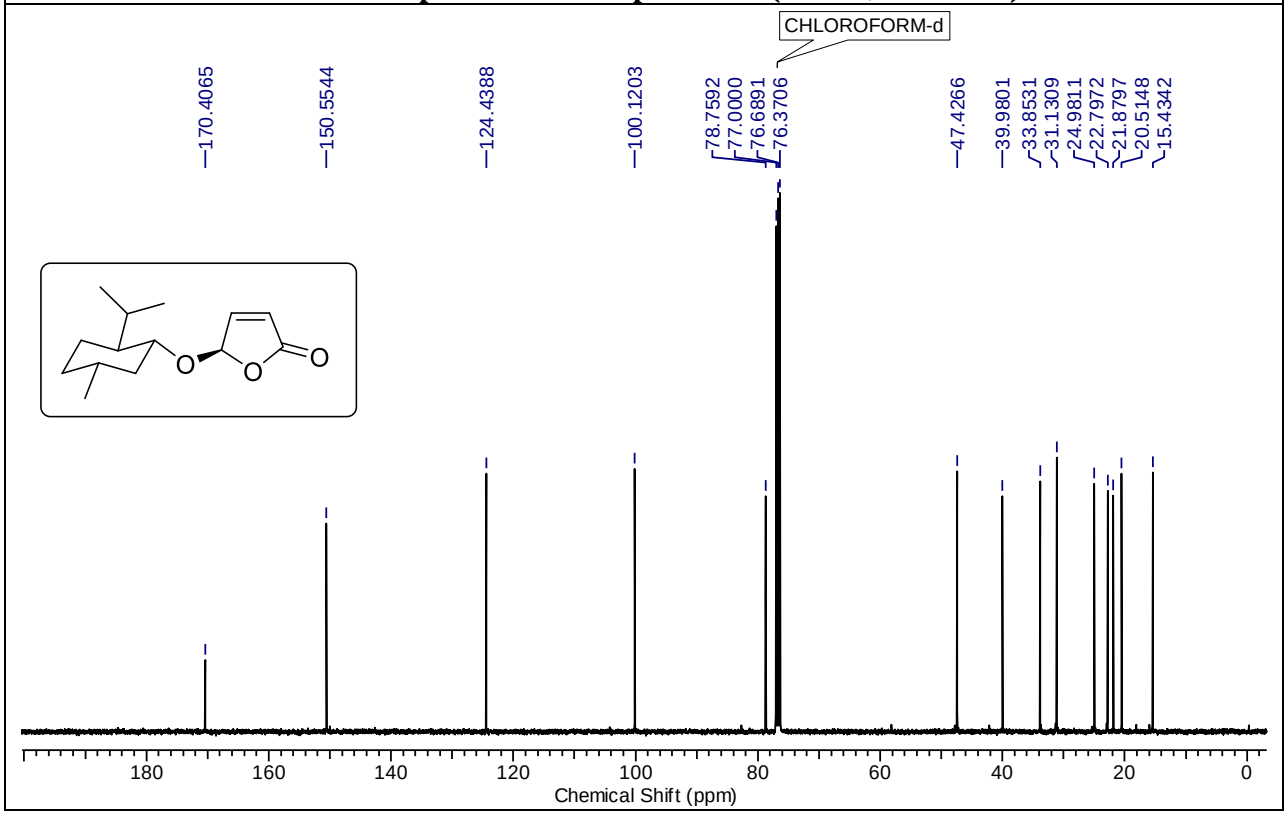
HRMS (ESI): *m/z* calculated for $C_9H_{19}O_5$ $[M + H]^+$ **:** 191.1283, found:191.1277.

2.2.9. NMR Spectra:

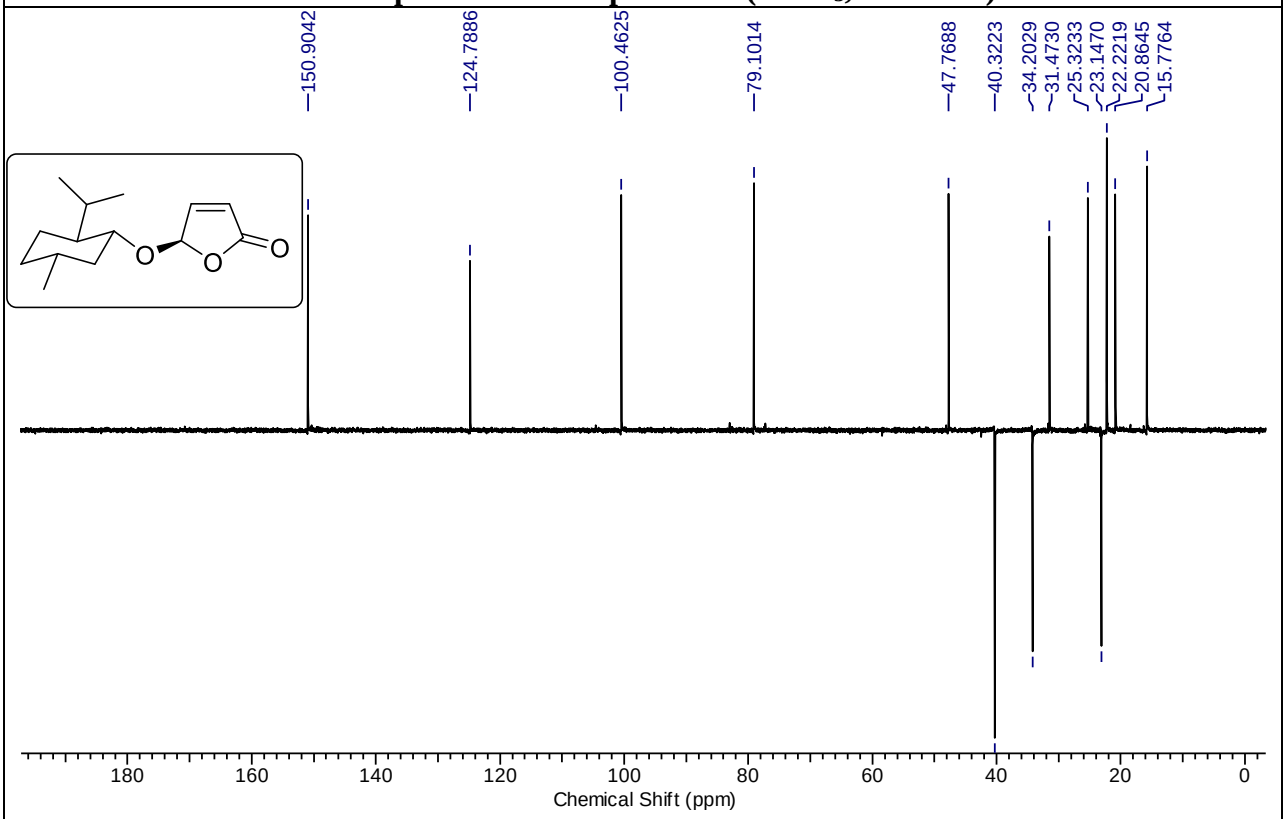
^{1}H-NMR spectrum of compound 6a ($CDCl_3$, 400 MHz)



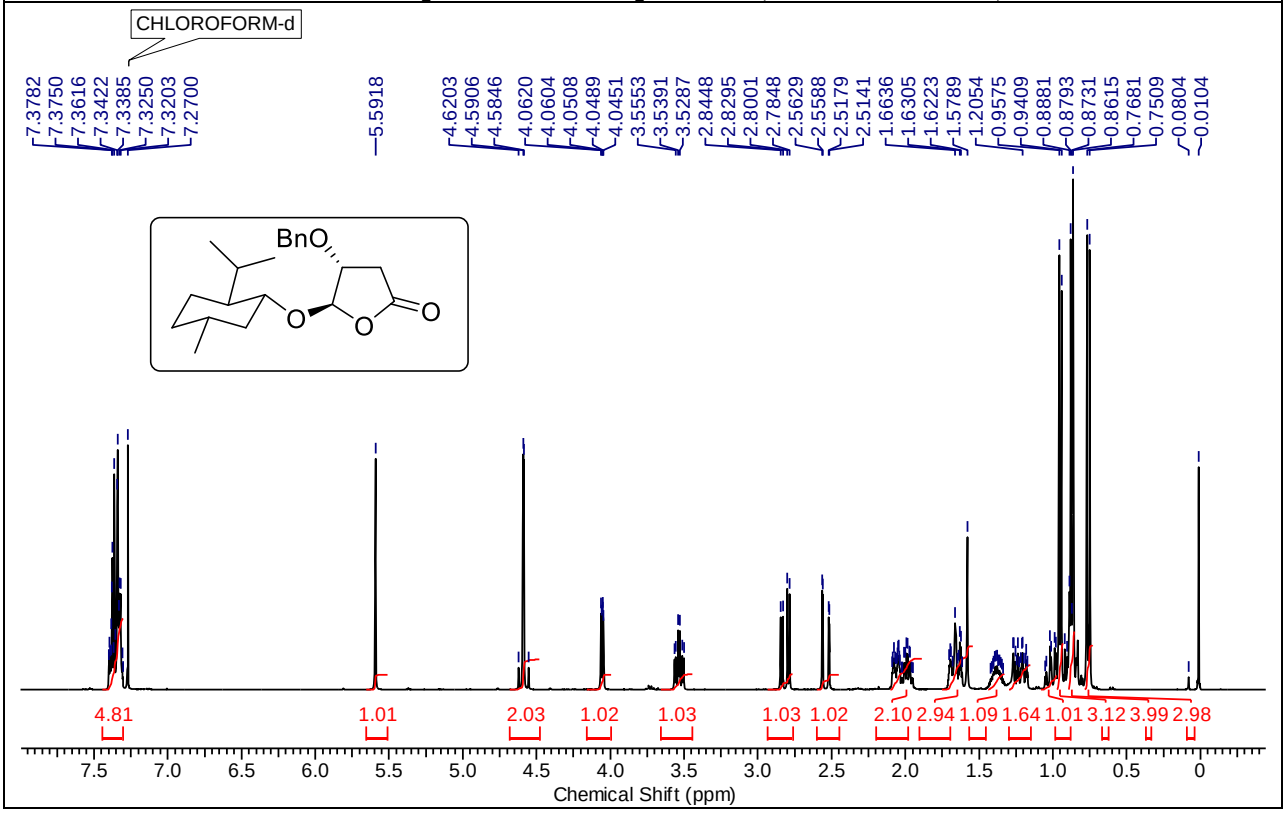
^{13}C-NMR spectrum of compound 6a ($CDCl_3$, 100 MHz)



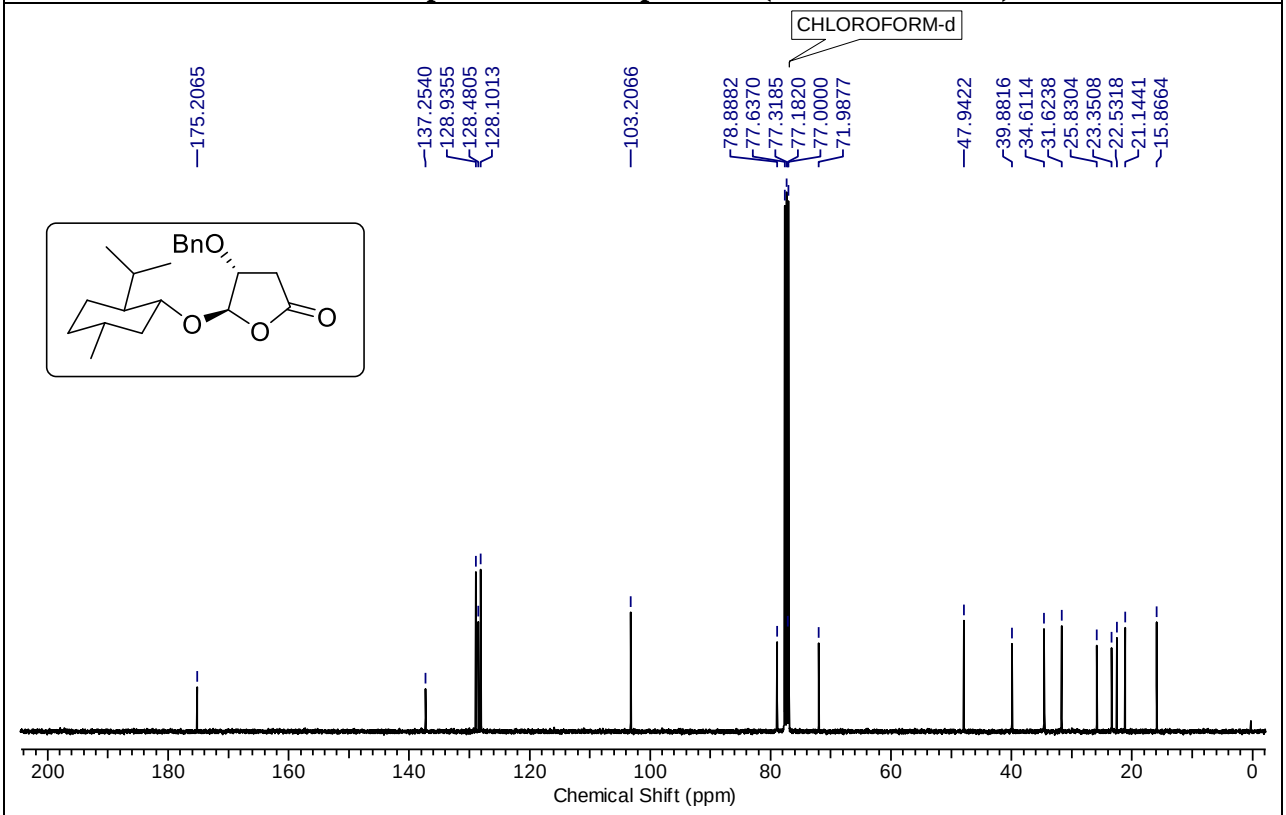
DEPT spectrum of compound 6a ($CDCl_3$, 100 MHz)



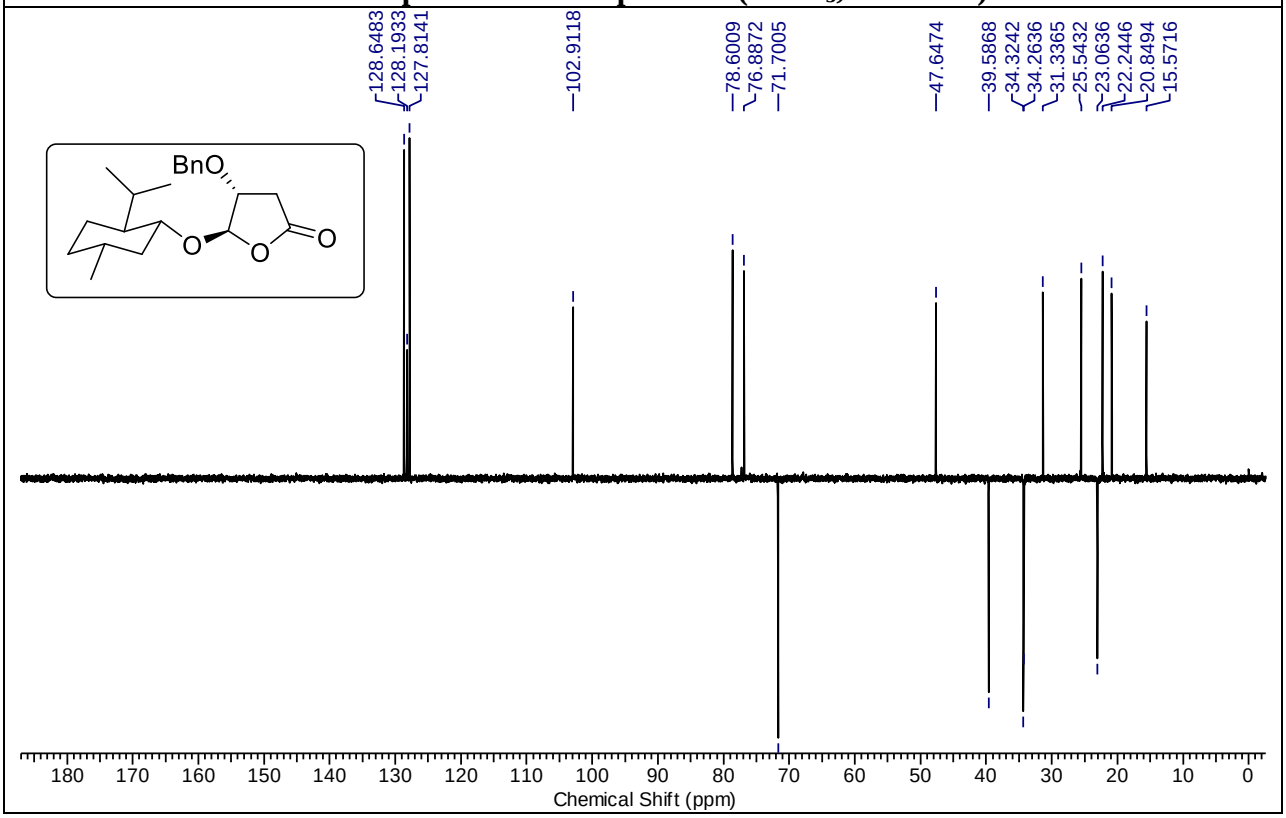
^{1}H-NMR spectrum of compound 8 ($CDCl_3$, 400 MHz)



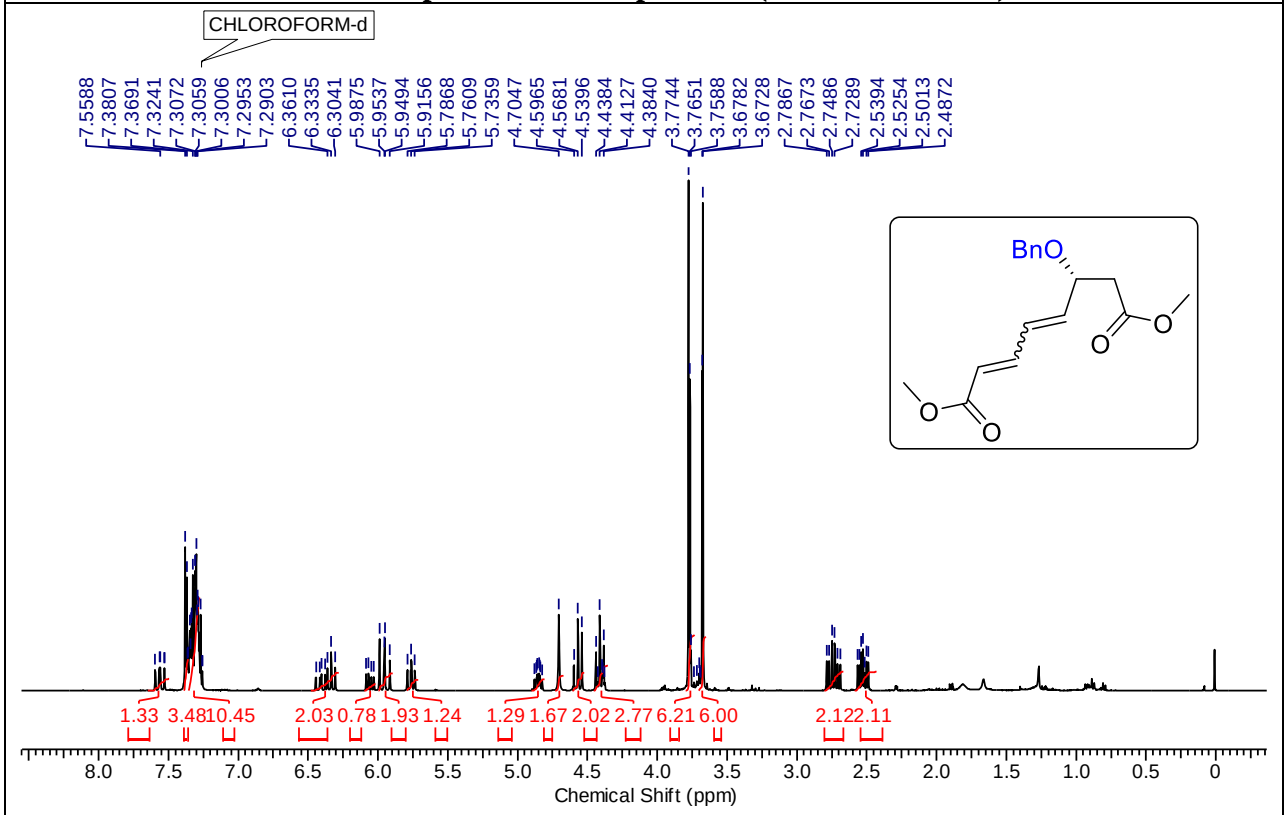
^{13}C-NMR spectrum of compound 8 ($CDCl_3$, 100 MHz)



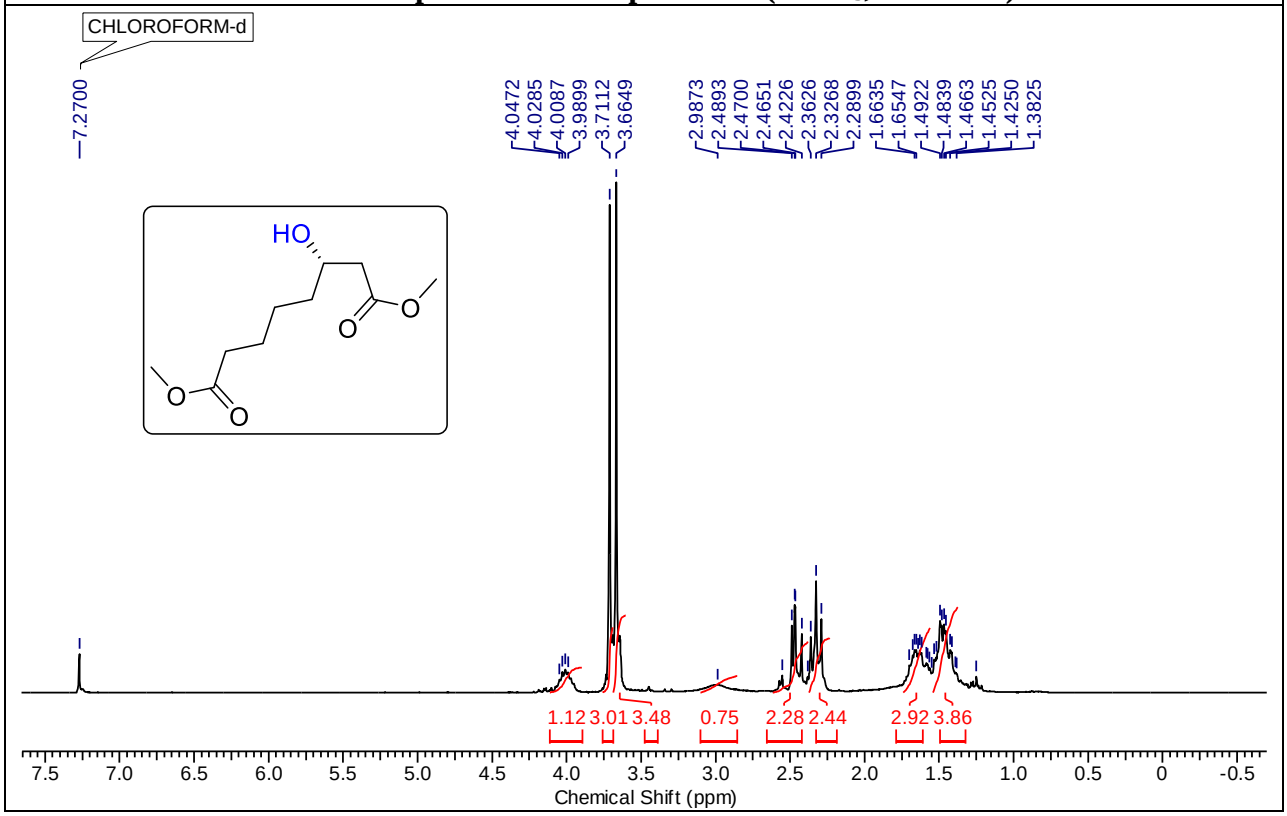
DEPT spectrum of compound 8 ($CDCl_3$, 100 MHz)



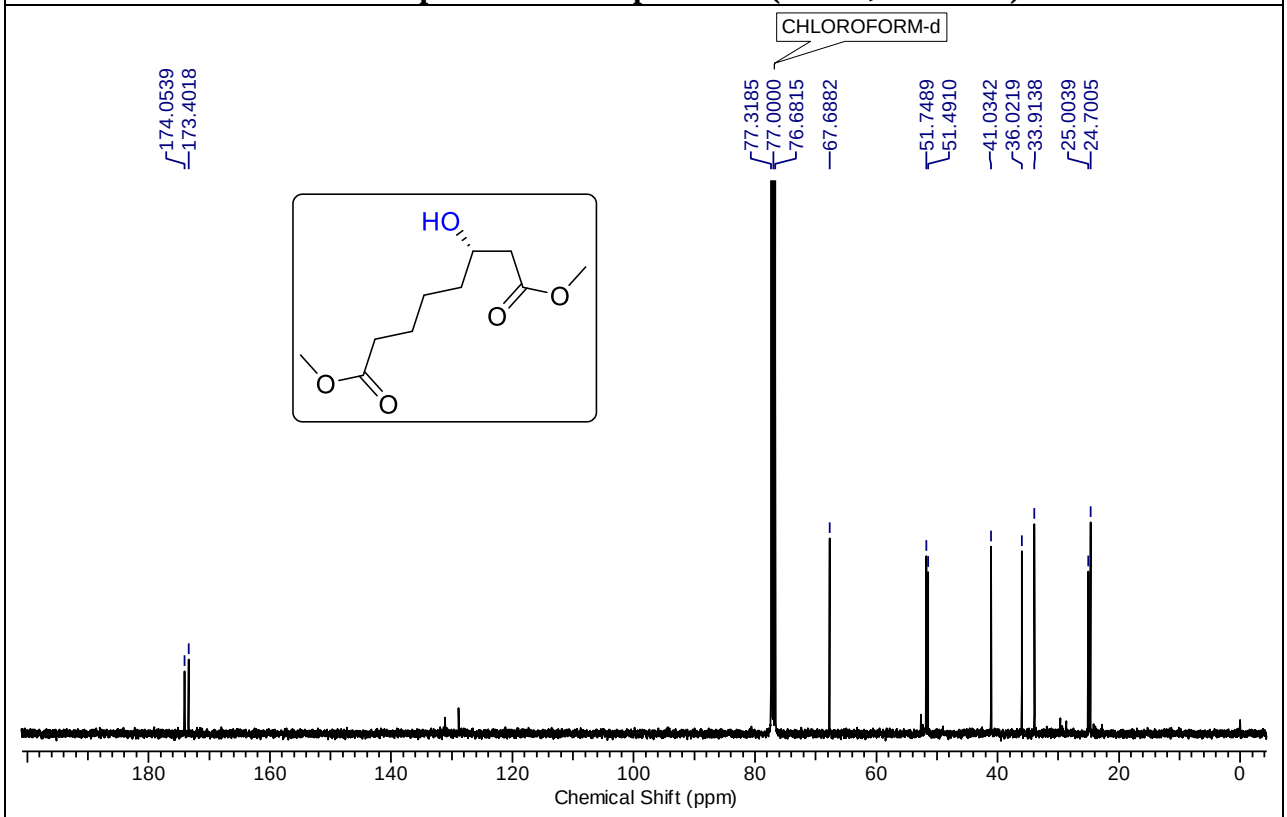
^{1}H-NMR spectrum of compound 9 ($CDCl_3$, 400 MHz)



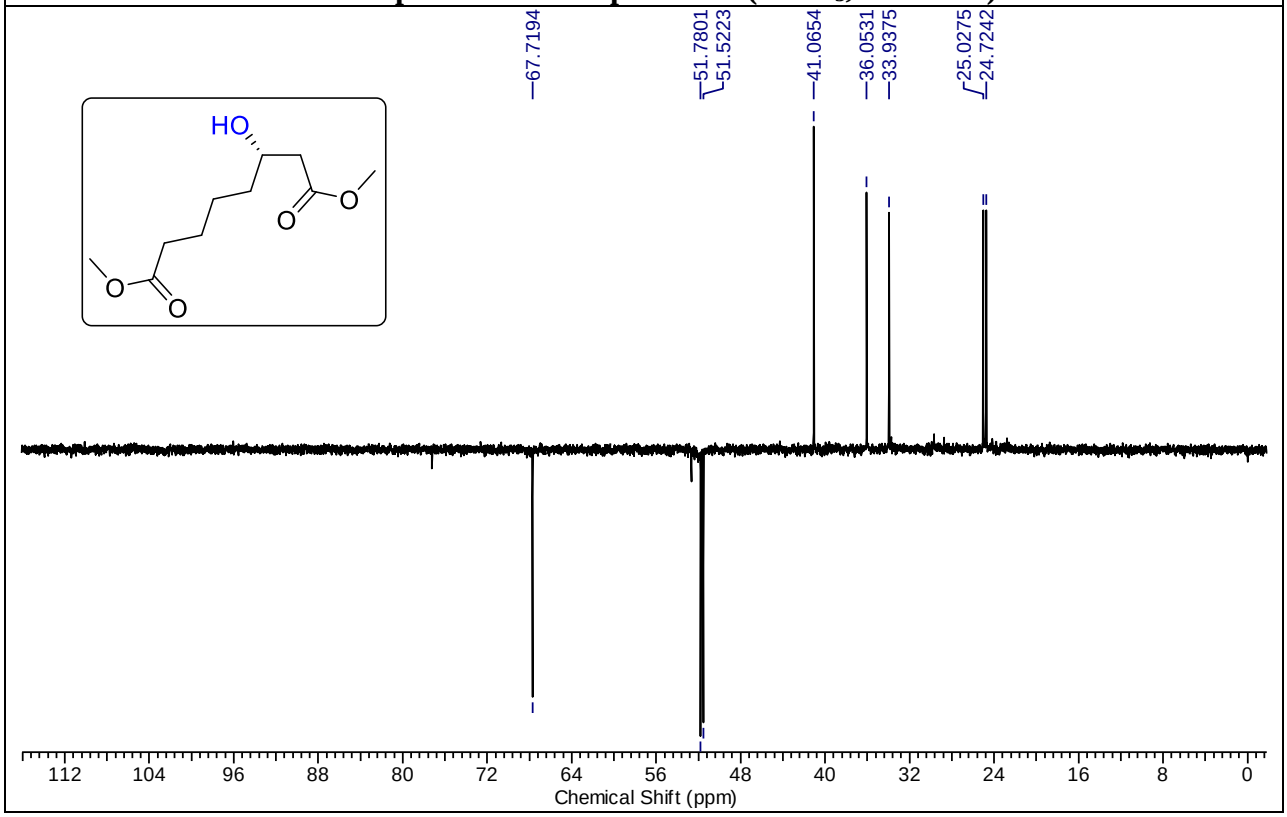
^{1}H-NMR spectrum of compound 10 ($CDCl_3$, 200 MHz)



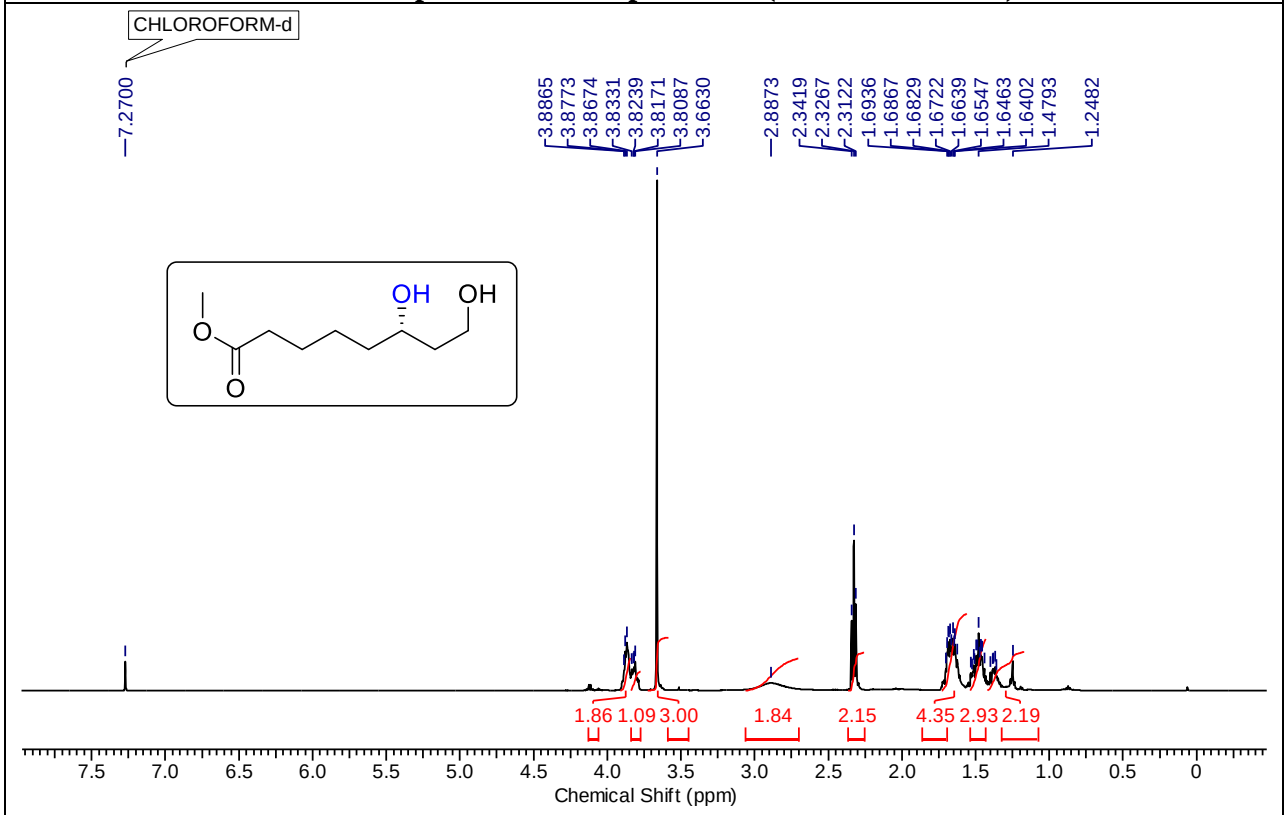
^{13}C-NMR spectrum of compound 10 ($CDCl_3$, 100 MHz)



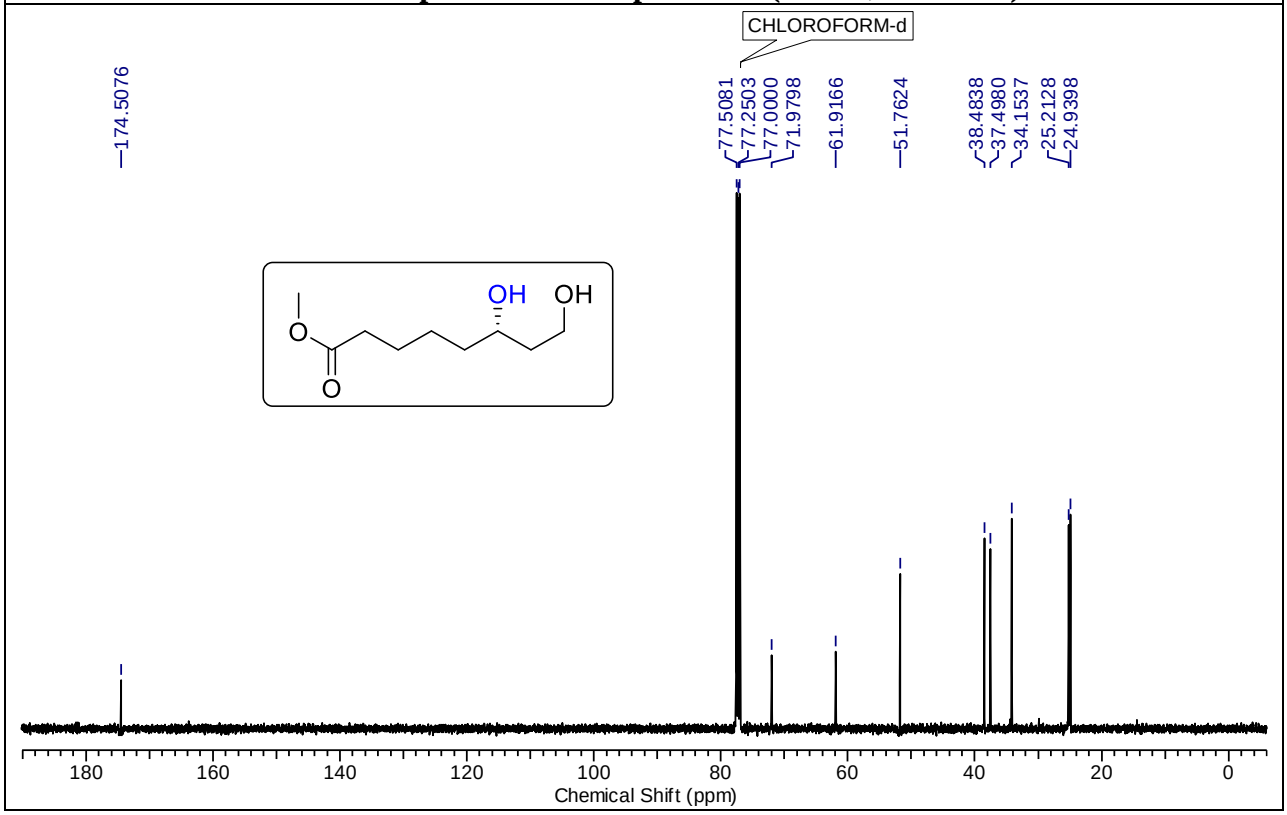
DEPT spectrum of compound 10 ($CDCl_3$, 100 MHz)



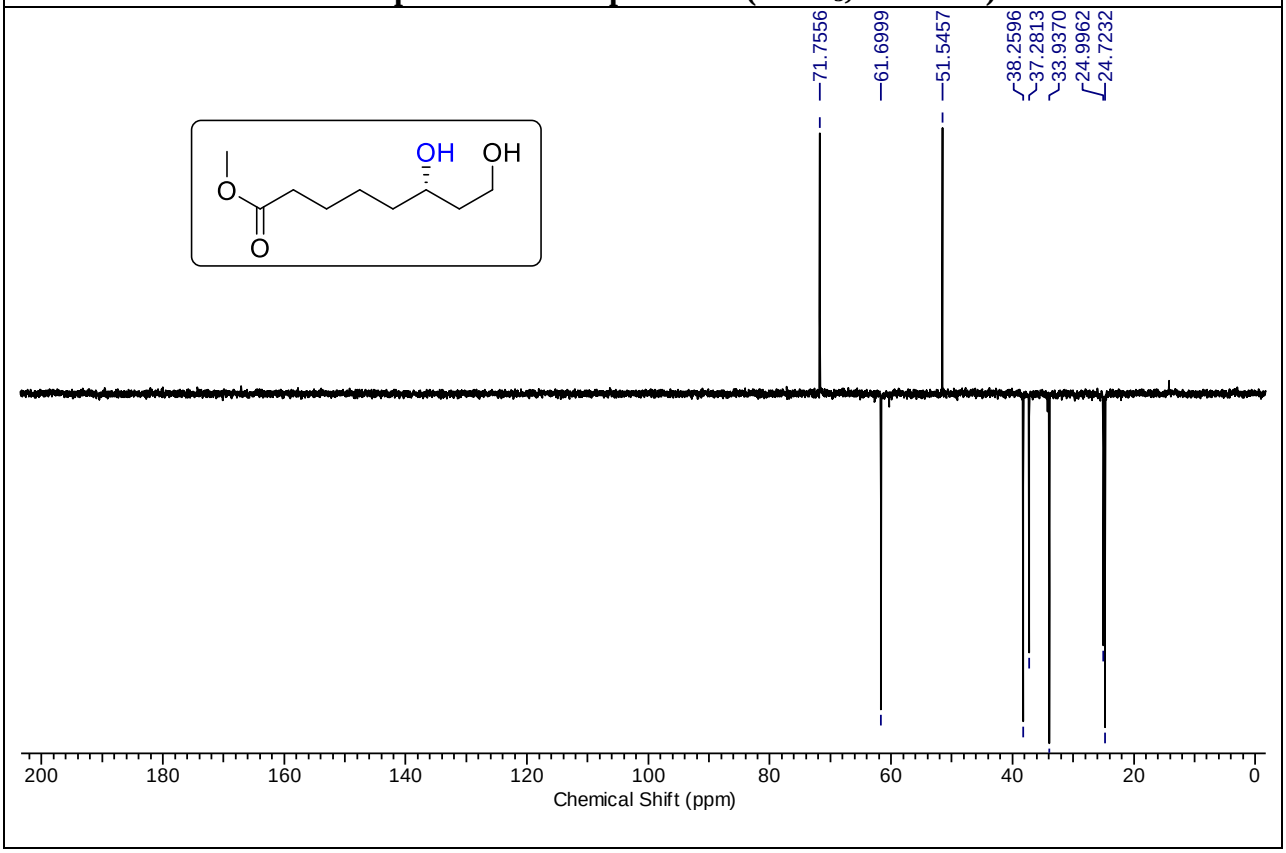
^{1}H-NMR spectrum of compound 11 ($CDCl_3$, 500 MHz)



^{13}C-NMR spectrum of compound 11 ($CDCl_3$, 125 MHz)



DEPT spectrum of compound 11 ($CDCl_3$, 125 MHz)



Area % Report

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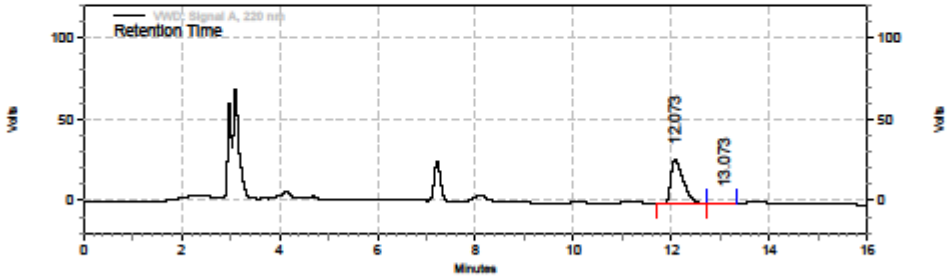

VWD: Signal A, 220 nm Results

Retention Time	Area	Area %
12.073	7969789	97.89
13.073	171428	2.11
Totals	8141217	100.00

Column: CHIRALPAK IB
Eluent System: 85 : 15 (HEXANE:IPA)
Flow rate: 1.0 ml/min Injection
vol.: 10 ul
Wavelength: 220 nm
Sample Conc.: 1.0mg/ml

2.2.10. HPLC of the chiral Compound dimethyl (*S*)-3-hydroxyoctanedioate (10).

Area % Report

Data File: E:\dr.p.maity\AMBAJT\ambaji hplc\racambaji 95 hex 5 ipa ib -5.dat
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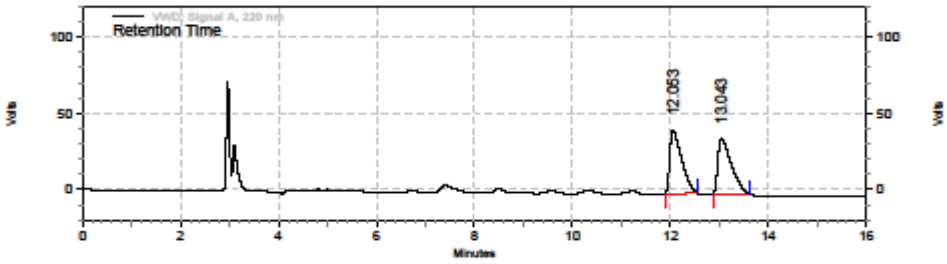

VWD: Signal A, 220 nm Results

Retention Time	Area	Area %
12.053	11831844	50.05
13.043	11807628	49.95
Totals	23639472	100.00

Column: CHIRALPAK IB
Eluent System: 85 : 15 (HEXANE:IPA)
Flow rate: 1.0 ml/min Injection
vol.: 10 ul
Wavelength: 220 nm
Sample Conc.: 1.0mg/ml

2.2.11. HPLC of the racemic compound dimethyl (*S*)-3-hydroxyoctanedioate (10).

Area % Report

Data File: E:\dr.p.maity\soniya\ap chiral 85 hex 15 ipa 1ml min IB 29-3.dat
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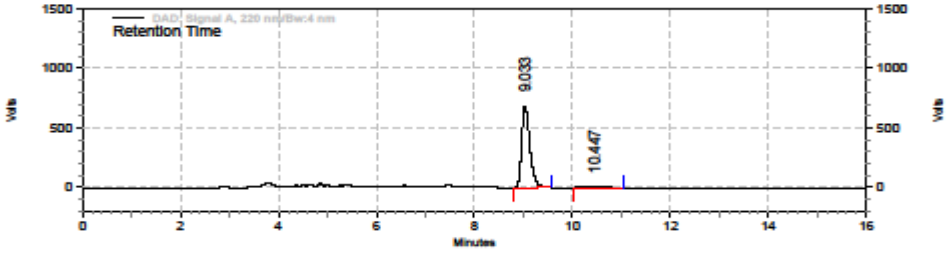

DAD: Signal A, 220 nm/Bw:4 nm
Results

Retention Time	Area	Area %
9.033	16640835	97.33
10.447	455862	2.67
Totals	17096697	100.00

Column: CHIRALPAK IB
Eluent System: 85 : 15 (HEXANE:IPA)
Flow rate: 1.0 ml/min Injection
vol.: 10 ul
Wavelength: 220 nm
Sample Conc.: 1.0mg/ml

HPLC of the pure chiral compound dimethyl (*S*)-3-hydroxyoctanedioate (10) (recorded on another HPLC instrument).

2.2.12. References:

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Chapter 3, Section I

Solvent free, microwave assisted unusual C-alkylation of phenols with PMB alcohol by using imidazolium ionic liquid as the green and eco-friendly catalyst.

3.1.1. Introduction:

The art of alkylation of a phenol and its derivatives is considered as an industrially important reaction as the phenolic compounds have antioxidant, antimicrobial, and coloring properties. Many phenol derivatives are used as chemical intermediates in bulk industries like petrochemicals, fine chemicals, agrochemicals *etc*. Generally, the phenol alkylation is carried out by using Friedel-Crafts alkylation and the catalysts involved in this are many Lewis acids like $AlCl_3$, $ZnCl_2$ *etc*. The other methods include different catalysts that direct the *ortho*- and *para*-selectivity during the course of alkylation reactions of a phenol.[1, 2] Also, there are many patented processes for this purpose.[3] Additionally, there are many research papers published on the alkylation of a phenol, and a few of them have been discussed in the literature review section. However, in some methods catalyst used generates toxic aqueous waste which creates many problems and in order to overcome these problems recently many eco-friendly processes have been developed which use macroporous cation-exchange resins such as amberlyst-15, [4] zeolites [5] and other hetero-polyacids [6] as the catalysts.

The other problem in the alkylation of phenol is the competing reaction of O-alkylation which leads to formation of a phenolic ether. Also, in the phenol alkylation reactions, sometimes the nature of catalyst decides whether the reaction gives O-alkyalated product or the C-alkylated product, *e. g.* O- alkylation of phenol derivatives through the nucleophilic substitution reaction is reported by the catalyst $BF_3.OEt_2$.[7] Due to this, the catalyst giving only C-alkylation product is of high importance. Science has enhanced the quality of human life. In order to have better life, the greener and safe chemical transformation methods are always in demand. Paul Anastas and John Warner have developed the outlines that would make the greener chemical process.[8] Ionic liquid are also the green catalysts. Moreover, there are a very few reported methods which use ionic liquid as a catalyst for the alkylation reaction of a phenol and its derivatives. [9-10] This led to study the ionic liquid catalyzed PMB alkylation of the phenols. The main features of ionic liquids are as follows:

3.1.2. Ionic Liquids:

Ionic liquids (ILs) are the compounds completely composed of the ions having melting point below 100 °C. Paul Walden has reported the first ionic liquid (ethyl ammonium nitrate) in 1914.

Having made the discovery of the first ionic liquid in those days, he never imagined that the ionic liquids would become big scientific area in the 21st century.

Ionic liquids are nonvolatile, non-flammable, and air and water stable compounds. ILs are more suitable compared to conventional solvents/catalysts in several chemical processes. Few of the common ionic liquids are shown below (**Figure 1**).

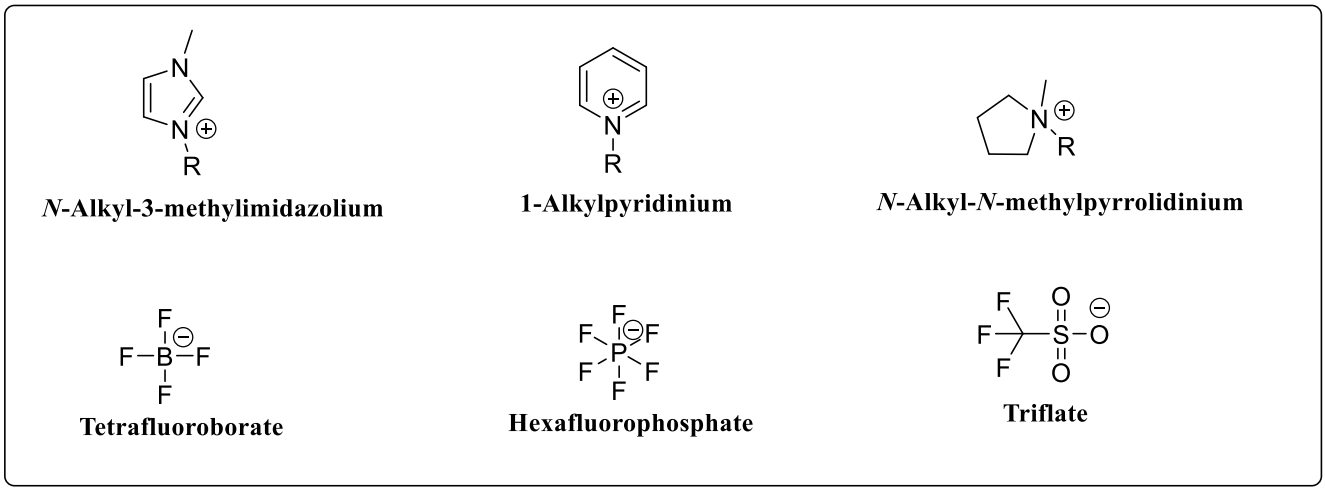


Figure: 1

Types of the ionic liquids:

Recently, as the use of ionic liquid has increased, ILs have been classified into the several types as follows:

1. Room-temperature Ionic Liquids (RTILs).
2. Task-specific Ionic Liquids (TSILs).
3. Polyionic Liquids (PILs).
4. Supported Ionic Liquid membranes (SILMs).

1. Room-temperature Ionic Liquids:

These ionic liquid salts are having broad temperature range. Such ionic liquids are made up of ions which possess delocalized charge and oppose the formation of solid-state structure. Additionally, these ionic liquids include bulky and asymmetric organic cations (**Figure 2**).

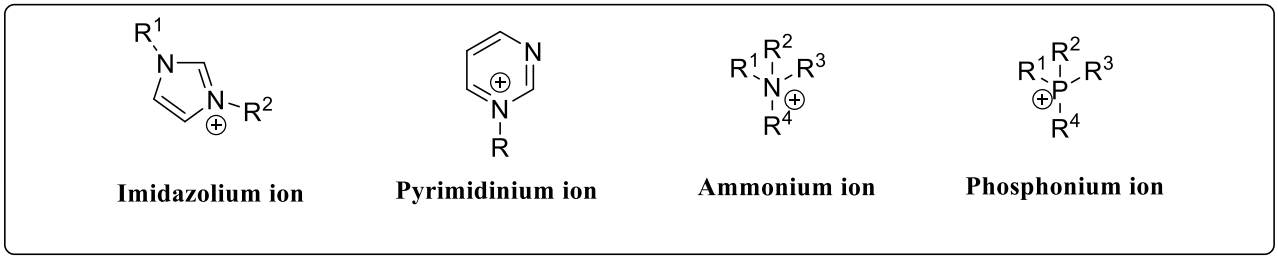


Figure: 2

2. Task-specific Ionic Liquids (TSILs):

These ionic liquids are choosy in liquid/liquid removal of heavy metals from water layer and were first time reported in the year 2001 by Robin D. Rogers *et al.*[11] In these ILs functionalized imidazolium cations having urea, thiourea or thiourea derivatives side chain act as metal ligating moieties, whereas the PF_6^- anions supply the desired water immiscibility (**Figure 3**).

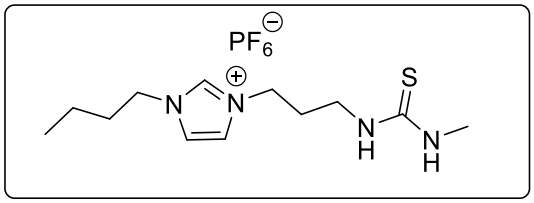


Figure: 3

3. Polyionic Liquids (PILs):

PILs are also known as polymerized ionic liquids. These are subgroup of polyelectrolytes which are characteristic ionic liquid (IL) species containing monomer repeating units and are linked through the polymeric backbone to arrange the macromolecular architecture. The distinctive properties of these ionic liquids include in the polymer chains, generating the new class of polymeric materials. Additionally, these ionic liquids enlarge the scope of properties and applications of ILs (**Figure 4**).

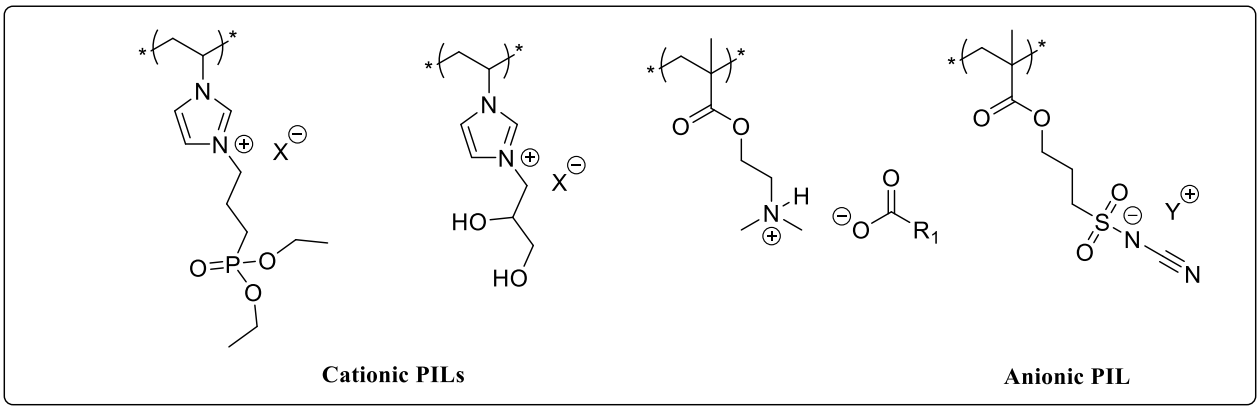


Figure: 4.

4. Supported Ionic Liquid membranes (SILMs):

These are combinations of ionic liquids which are supported on metal–organic frameworks (MOFs).

Advantages of using ILs:

Some of the advantages of ionic liquids are like they act as good solvents for different reactions. They remain intact with glass, polyethylene, or Teflon. ILs can be utilized for different temperature ranges (-40 to +200 ^{0}C) as the reaction medium. ILs are non-volatile, water soluble and near about 10^8 different ILs can be prepared. Another importance of ILs is that they show both acidic and basic properties. ILs are cheap and can be easily prepared.

Applications of Ionic Liquids:

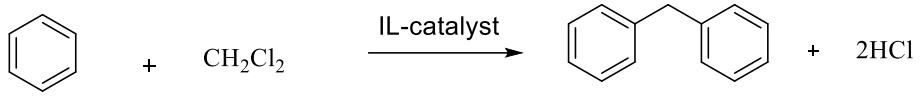
ILs find use in lot of applications. They can be used as antistatic agents, electrolytes, as solvents and as lubricants.

3.1.3. Ionic Liquids in Organic Synthesis:

ILs are nowadays extensively used in organic synthesis as they possess unique physical properties. Besides solvents, ILs are having many functions in the catalytic reactions. ILs can act as the catalyst, co-catalyst and support for the catalytic process.

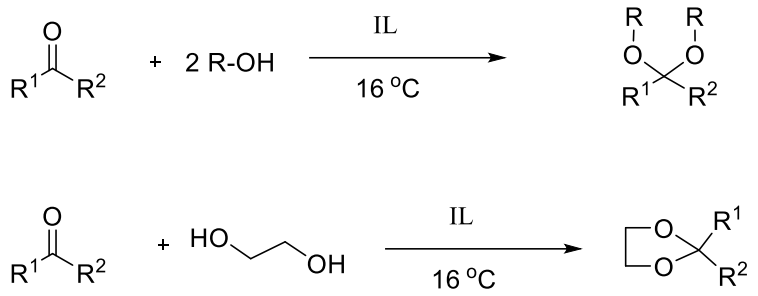
Fischer indole synthesis has been reported by using ILs as the dual catalyst and as the solvent. The reaction was carried out in $BMlmHSO_4$ at 70-110 ^{0}C for 0.5-6 h, wherein 2,3-disubtstituted indoles were observed in the reaction of alkyl methyl unsymmetrical ketones.[12] Esterification reaction of alpha pinene and acetic acid was carried out by using acidic ionic liquid. It was

observed that acidic ILs, (3-sulphonic acid)-propyltriethylamine hydrosulfate [HSO_3–$(CH_2)_3$–NEt_3]HSO_4 and (3-sulphonic acid) propyltriethylaminedihydrogen phosphate [HSO_3–$(CH_2)_3$–NEt_3]H_2PO_4, possessed good catalytic activity. The products obtained were easily separated from the reaction mixture and these ILs had good reusability.[13] Use of acidic IL has been reported in the alkylation reaction of benzene and DCM to yield diphenyl methane (DPM) [14] (**Scheme 1**).



Scheme 1: Alkylation using IL catalyst

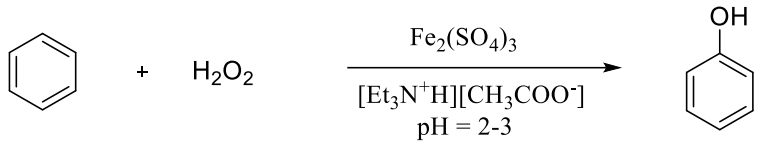
Many acid functional ILs whose cations have two adjacent acidic sites were synthesized and the same ILs were used for the acetalisation of aldehydes with good catalytic activity under mild conditions[15] (**Scheme 2**).



Scheme 2: Acetalisation using IL

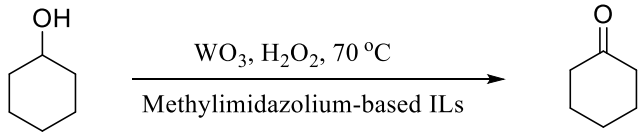
Nitrogen based Bronsted acidic organic ionic liquid catalyst 1-methylimidazole and 1-butyl-3-methylimidazolium which contains inorganic anions of the types BF_4-, PF_6-, and $PTSA^-$ was synthesized and has been used as a catalyst and reaction medium for the Fisher esterification reaction of alcohols with the acids.[16]

The reaction of benzene with hydrogen peroxide in the presence of the IL catalyst [Et_3N^+H][CH_3COO^-] to give phenol is reported. Also, in this reaction the catalyst [Et_3N^+H][CH_3COO^-] retards the decomposition of H_2O_2 by protecting the performance of over oxidation of a phenol[17] (**Scheme 3**).



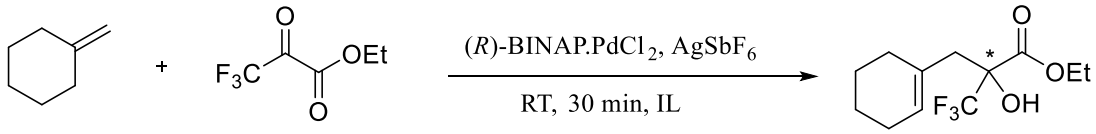
Scheme 3: Benzene and H_2O_2 reaction catalysed by IL catalyst.

In addition to this, the dual role of solvent and a catalyst of Bronsted IL has been reported for the Claisen Schmidt condensation of the acetophenone and benzaldhyde to produce chalcones.[18] The hydrophobic methylimidazolium derived ILs have been used in the oxidation reaction of cyclohexanol with H_2O_2 to produce cyclohexanone [17](**Scheme 4**).



Scheme 4: Oxidation of cyclohexanol to cyclohexanone

The extended application of the ionic liquids as the constructive media in asymmetric Carbonyl-Ene reactions for the reuse of the costly palladium catalyst has been reported by Gathergood, Connon and co-workers. A chiral $[Pd\{(R)\text{-}BINAP\}]^{2+}$ $(SbF_6^-)_2$ catalyst was used to effect the enantioselective reaction. Admirable enantioselectivity and yields (both up to 96%) were achieved and the results were complementary to ordinary volatile solvents, such as DCM[19] (**Scheme 5**).



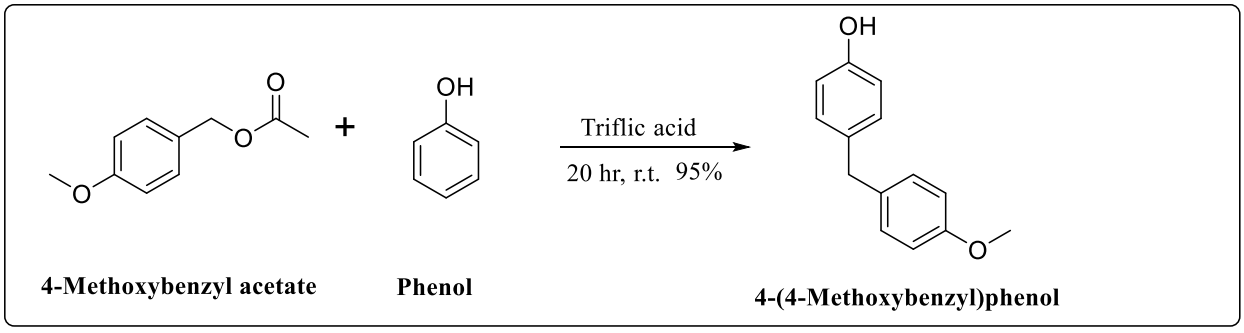
Scheme 5: ILs as a solvent in carbonyl-ene reaction

3.1.4. C-alkylation of phenols, a literature review:

In order to have a comparative view of the different methods for the C-alkylation of phenol or its

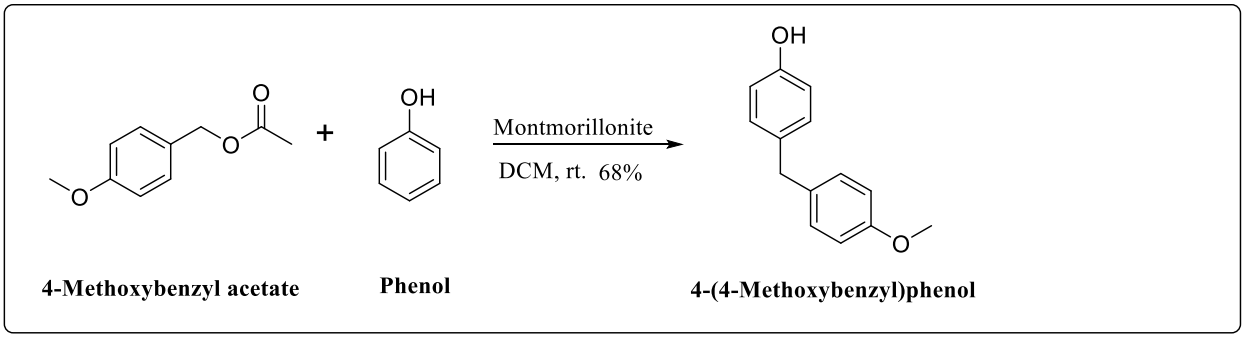
other derivatives developed so far, a short descriptive literature survey of the work reported by different groups is being described below.

Mendoza, Oscar *et al.* [20]



When the phenol was allowed to react with 4-methoxybenzyl acetate in presence of triflic acid for 20 h at room temperature, it formed 4-(4-methoxybenzyl)phenol with over 95% yield.

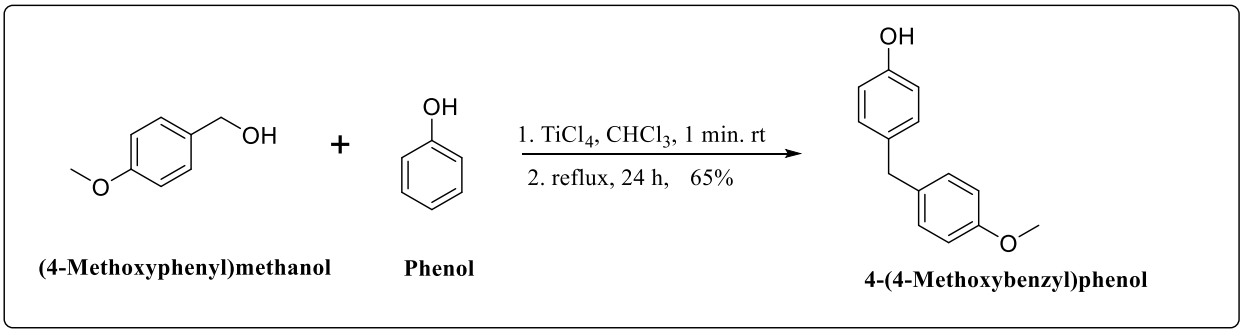
Chen, Dongyin *et al.*[21]



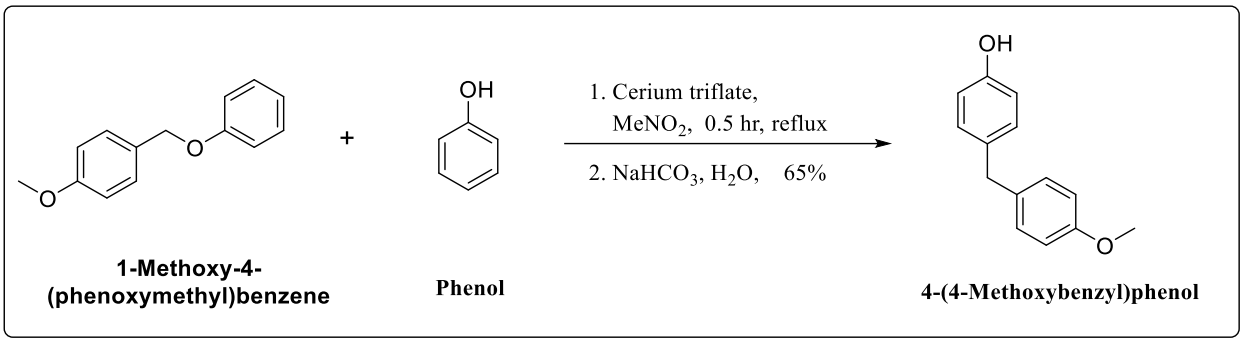
Also, when the phenol was treated with 4-methoxybenzyl acetate catalyzed with Montmorillonite which is a phyllo silicate group of member with molecular formula $(Na, Ca)_{0.33}(Al, Mg)_2(Si_4O_{10})$ at room temperature, it furnished C-alkyalated product of phenol with 68% yield.

Tsai, Chen-Yu *et al.*[22]

When the mixture of phenol and (4-methoxyphenyl) methanol was stirred for 1 min. at room temperature with titanium tetrachloride and chloroform followed by reflux for one day, it formed 4-(4-methoxybenzyl)phenol with over 65% yield.

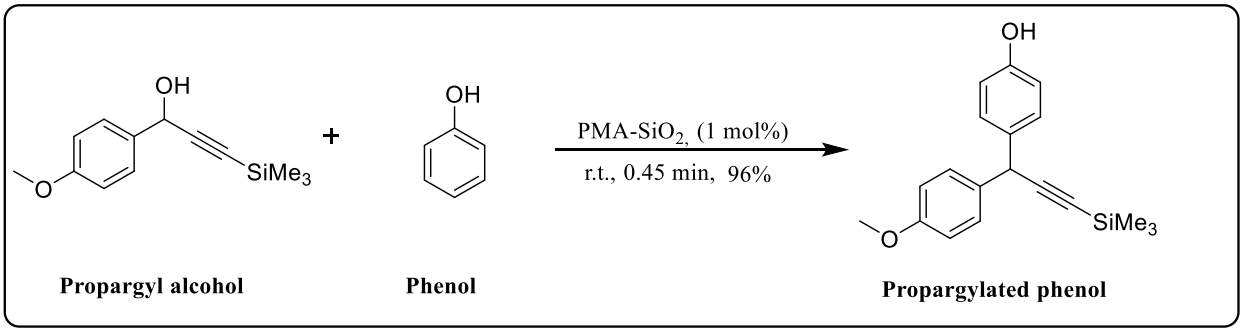


Bartoli, Giuseppe *et al.*[23]



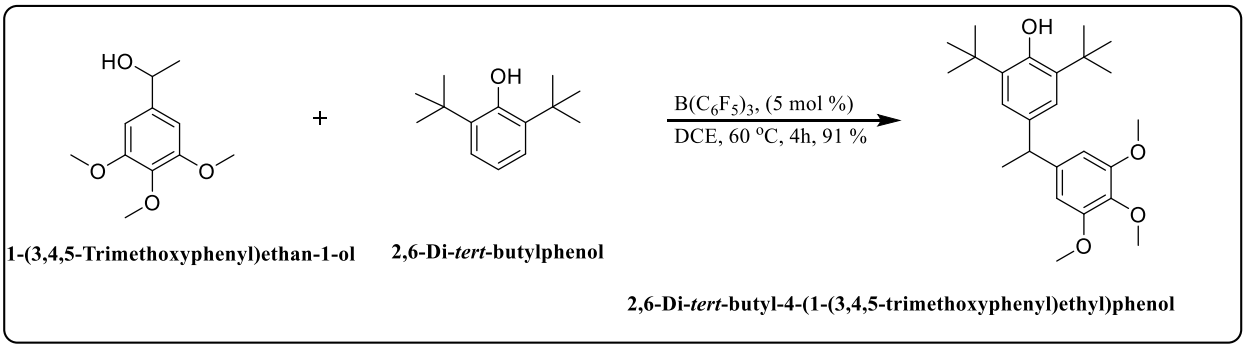
Additionally, when the catalytic amount of cerium(III) trifluoromethanesulfonate is used to react with the phenol and 1-methoxy-4-(phenoxymethyl) benzene under reflux for 0.5 hr using nitromethane as a solvent followed by treating it with sodium bicarbonate in the next step yields 4-(4-methoxybenzyl) phenol in 65% yield.

Prabbaraja Shrihari *et al.*[24]



Similarly, PMA–silica gel catalyzed propargylation of a phenol with arylpropargyl alcohols in the absence of solvent under environmentally benign conditions to afford propargylated phenol in 96 % yield has been reported.

Shan-Shui Meng *et al.*[25]



In addition to this, when the 2, 6-di-tert-butylphenol was treated with 1-(3,4,5-trimethoxyphenyl) ethan-1-ol in presence of catalytic non-metallic Lewis acid $B(C_6F_5)_3$, it gave 2,6-di-tert-butyl-4-(1-(3,4,5-trimethoxyphenyl)ethyl)phenol in 91% yield.

3.1.5. Results and discussion:

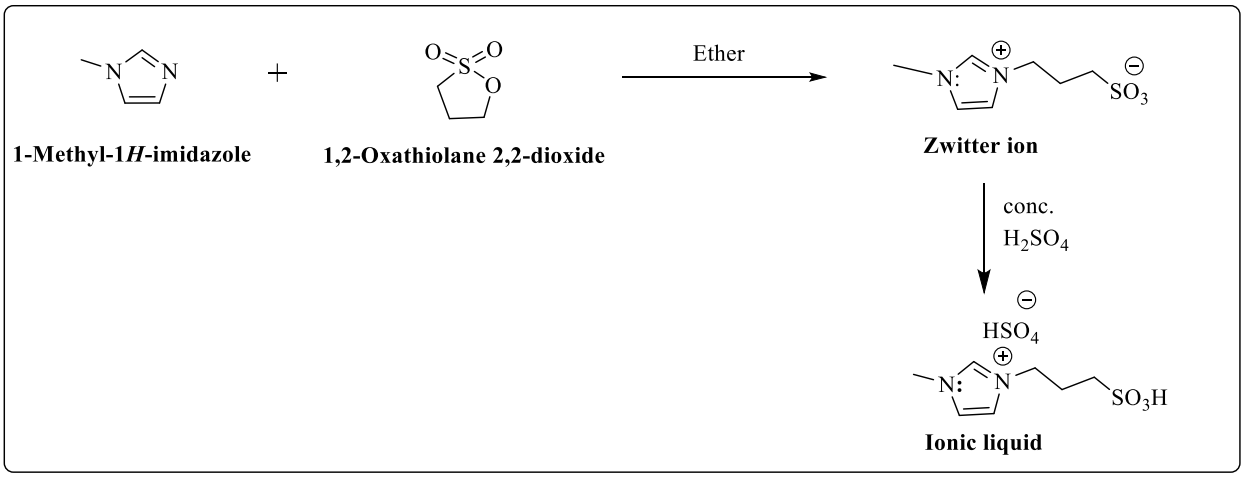
Looking at the literature, although ionic liquids were employed as a solvent to effect alkylation of phenols, an additional activator was required. It was surprised to utilize an acidic ionic liquid which could serve both as a solvent and activator.

In the present work, microwave assisted ionic-liquid catalyzed unusual C-alkylation of PMB alcohol with various substituted phenols has been studied. When the phenol was treated with (4-methoxyphenyl)methanol *i.e.* PMB alcohol, C-alkylation of the phenol was observed. This result was interesting which made us to screen different phenol substrates. Surprisingly, it was working well with electron rich phenols while the reaction did not work with electron deficient phenols.

Further the literature search disclosed that there is no report for the C- alkylation of the PMB alcohol with the phenols by using ionic liquid as the catalyst.

Synthesis of Ionic Liquid:

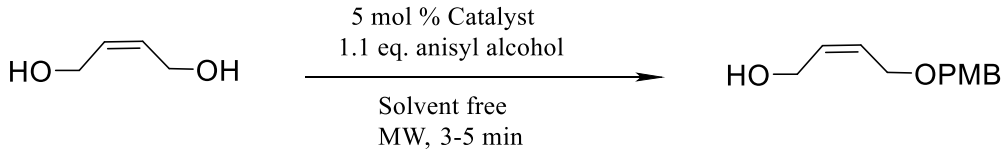
Ionic liquid catalyst was prepared by the literature procedure.[26] 1-Methylimidazole on the reaction with 1,3-propanesultone gave white zwitter ion solid intermediate, which was found to be moisture sensitive and can be turned to liquid when exposed to air. Hence, this solid obtained was immediately reacted with stoichiometric amount of conc. sulphuric acid to give viscous clear liquid (**Scheme 6**). Both the steps in the synthesis were quantitative.



Scheme 6: Synthesis of Ionic Liquid.

3.1.6. Unusual C-Alkylation of Phenols Using IL as the Catalyst:

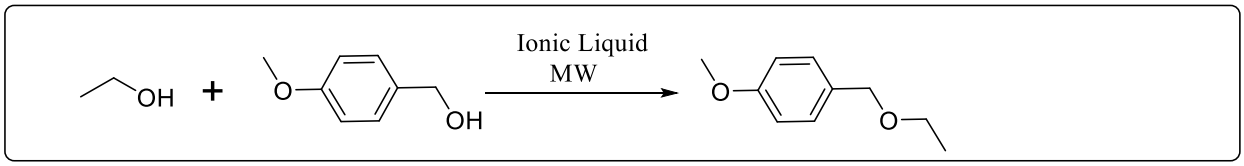
Previously, from this research group work on the synthesis of imidazolium ionic liquid and its application for PMB protection of alcohols was carried out successfully**. Scheme No. 7** illustrates this protection methodology which was performed in microwave (LG: MC-808WAR).



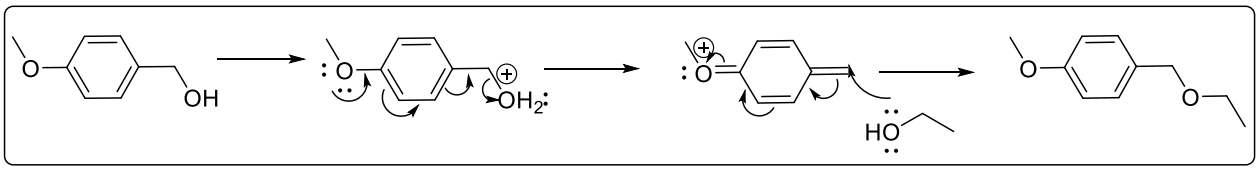
Scheme 7 : PMB protection of alcohols.

Proposed mechanism for the PMB protection of alcohols:

Reaction:



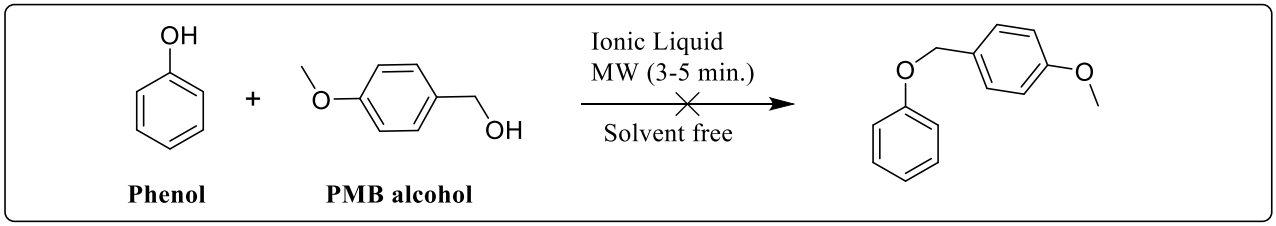
Proposed Mechanism:



Attempt of PMB protection of a phenol:

Furthermore, when the **Scheme No. 7** was tried on the phenols some interesting observations were made. It was observed that instead of the protection of the hydroxyl group of a phenol, C-alkylation was occurring. This might be due to the fact that in phenols the lone pair of oxygen resonates inside the ring making aromatic carbon nucleophilic instead of oxygen to attack on electrophilic centre of the PMB alcohol in line with HSAB principle.

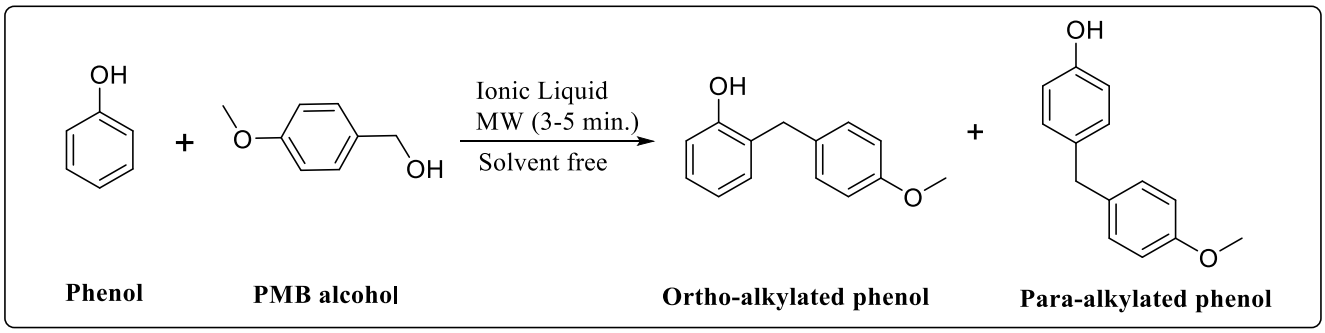
General Reaction:



Scheme 8: O-PMB protection of a phenol.

A phenol and the PMB alcohol were reacted in 1:1 equivalent by loading 10 mol % of the ionic liquid catalyst (IL) in the microwave. The products were separated by silica-gel column chromatography and the compounds obtained were characterized by ^{1}H NMR and ^{13}C NMR analysis.

Observed Reaction:

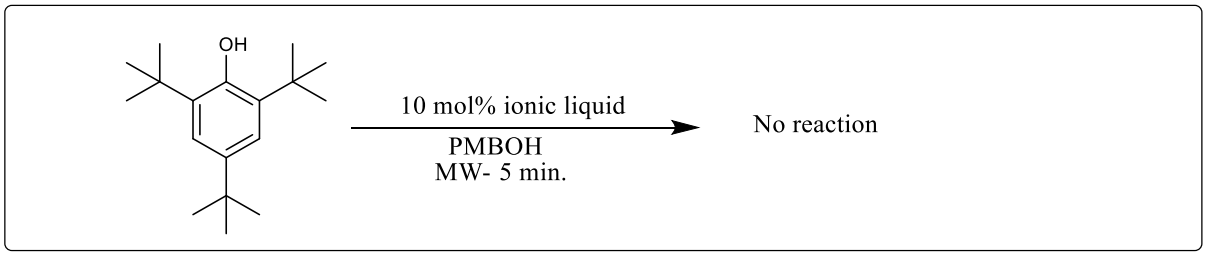


Scheme 9: C-alkylation of a phenol.

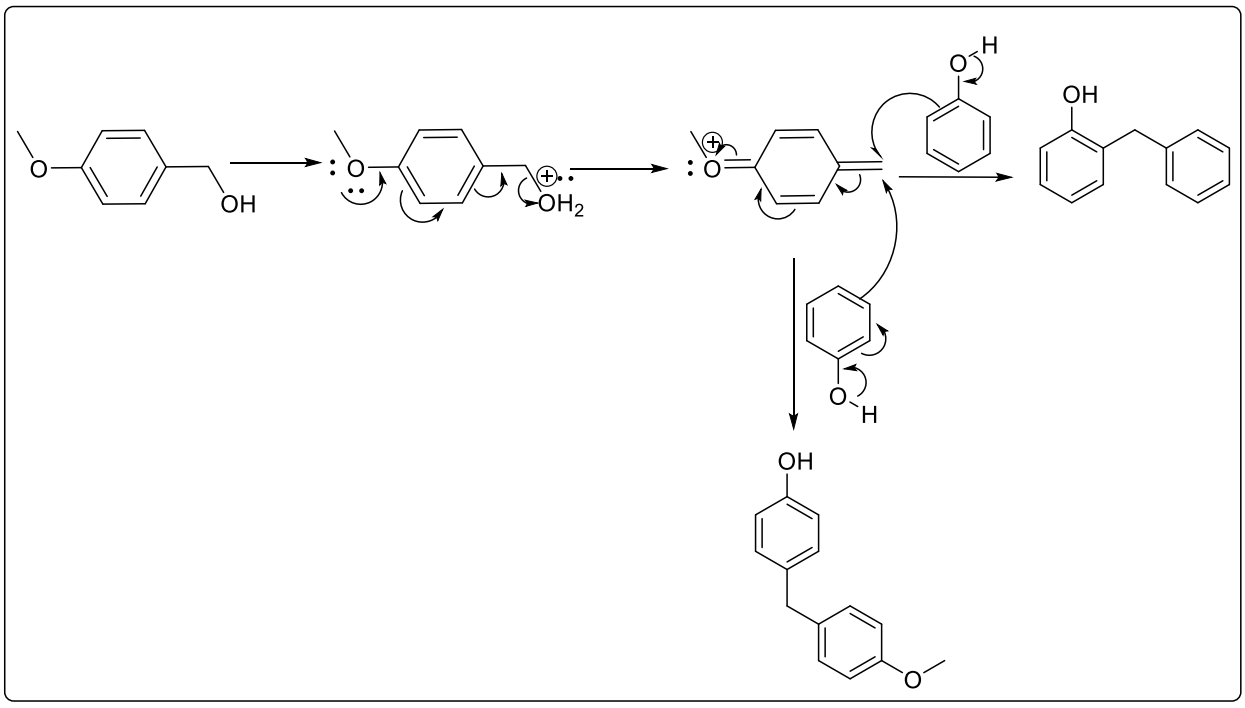
3.1.7. Substrate scope of the reaction:

A variety of phenols were screened for the C-alkylation of phenols using ionic liquid as a catalyst. It has been observed that, good yields were obtained with shorter and acceptable time period. Also, phenols in which electron donating groups were attached (activating group)

participated well in the reaction as compared to those having electron withdrawing groups attached (deactivating group) even though they were irradiated in microwave for longer period of time. 2, 4, 6-Tritertbutylphenol shows no reaction as its *ortho*- and *para*- positions are blocked with respect to hydroxyl group.

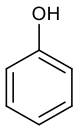
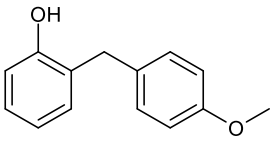
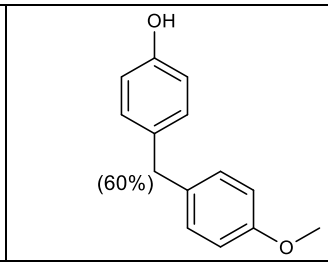
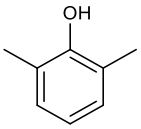
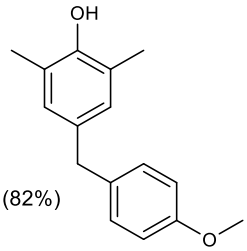
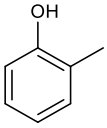
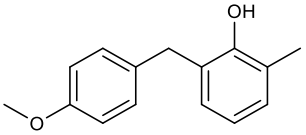
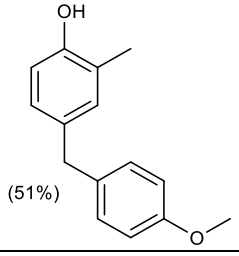
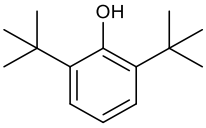
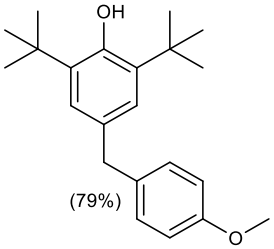
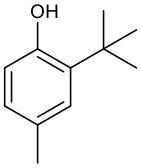
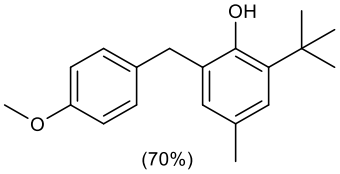
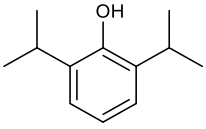
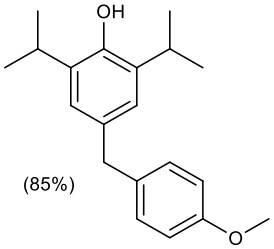


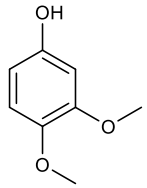
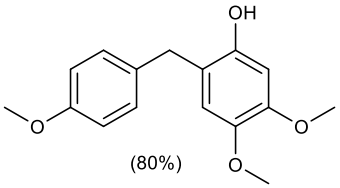
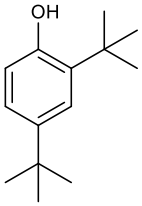
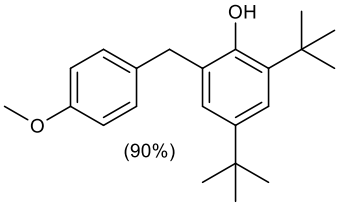
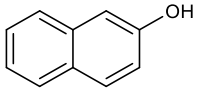
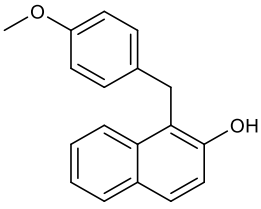
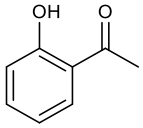
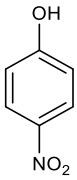
Proposed Mechanism:



We believe that the above shown mechanism is a plausible mechanism. In the first step, the hydroxyl group of a PMB alcohol gets protonated and forms methyl (4-methylenecyclohexa-2, 5-dien-1-ylidene)oxonium by elimination of a water molecule. In the next step, the phenol undergoes electrophilic aromatic substitution i.e. Friedel-Crafts alkylation with the methyl (4-methylenecyclohexa-2, 5-dien-1-ylidene)oxonium resulting in the PMB-alkylation of a phenol at *ortho*- and *para*- positions of a phenol .

Substrate scope of the reaction: Table 1.

Entry	Phenols	PMB alkyalated product with percentage yield	Time in minute
1.		 (40%)  (60%)	2
2.		 (82%)	2
3.		 (49%)  (51%)	2
4.		 (79%)	3
5.		 (70%)	3
6.		 (85%)	3

7.		 (80%)	3
8.		 (90%)	3
9.		 (92%)	3
10		No reaction	4
11.		No reaction	4

All the reactions were performed in Whirlpool Magicook 20G Electronics (Power: 700 watts).

3.1.8. Conclusion:

Thus a Bronsted acidic imidazolium ionic liquid was successfully synthesized. This ionic liquid was efficiently exploited as a catalyst for direct ***one- pot C-alkylation of phenols***. The selectivity was also observed among the electronically rich and poor phenols.

Selectively electronically rich phenols were alkylated whereas electronically poor phenols were found to be unchanged to much extent even after prolonged reaction.

Thus a very simple, mild, useful, eco-friendly and efficient method for direct C-alkylation of phenols using ionic liquid as a catalyst with good yields has been developed.

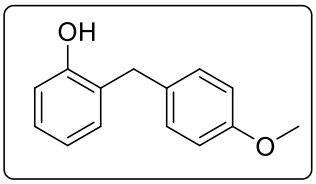
3.1.9. Experimental:

General procedure for the C- alkylation of PMB alcohol with phenols:

Ionic liquid (0.1 eq.), PMB alcohol (1 eq.) and a phenol (1 eq.) were taken in a glass vial and resulting vial containing these three compounds was kept in a LG microwave and heated for 3 minutes. The resulting reaction mass was diluted with ethyl acetate and poured into the separating funnel containing water. The organic layer was extracted by adding more ethyl acetate and dried over sodium sulphate (anhydrous Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel) using petroleum ether/ethyl acetate to furnish the C-PMB alcohol alkylated product (**Scheme 9**).

Spectral Data:

1. 2-(4-Methoxybenzyl)phenol:



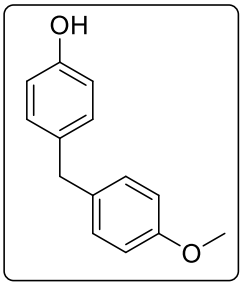
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 3H), 3.95 (s, 2H), 4.85 (s, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 2H), 6.87 - 6.90 (m, 1H), 7.13 (d, *J* = 9.1 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 35.85, 55.57, 114.39 (2C), 116.03, 121.17, 127.58, 128.07, 129.94 (2C), 131.13, 132.04, 154.07, 158.44.

IR ($CHCl_3$): ν_{max} 3421.55, 1640.65, 1511.28, 1462.80, 1245.50, 1176.70, 756.62 cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{14}H_{13}O_2$ [M-1]**:** 213.0910, found: 213.0905.

2. 4-(4-Methoxybenzyl)phenol:



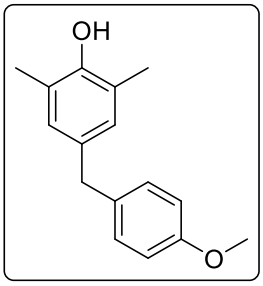
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3H), 3.87 (s, 2H), 5.34 (br s, 1H), 6.77 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 7.05 (d, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 39.72, 54.93, 113.48 (2C), 114.89 (2C), 129.22 (2C), 129.38 (2C), 129.55, 133.38, 153.43, 157.41.

IR ($CHCl_3$): ν_{max} 3419.43, 1638.49, 1507.77, 1454.42, 1240.93, 1173.17, 764.39 cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{14}H_{13}O_2$ [M-1]: 213.0910, found: 213.0906.

3. 4-(4-Methoxybenzyl)-2, 6-dimethylphenol:



^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 6H), 3.81 (s, 3H), 3.82 (s, 2H), 4.56 (s, 1H), 6.82 (s, 2H), 6.85 (d, *J* = 8.3 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H).

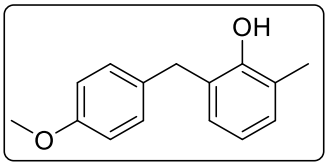
^{13}C NMR (100 MHz, $CDCl_3$): δ 15.88 (2C), 40.15, 55.21, 113.77 (2C), 122.91 (2C), 128.87 (2C), 129.65 (2C), 133.14, 133.93, 150.37, 157.78.

IR ($CHCl_3$): ν_{max} 3415.92, 1590.99, 1416.90, 1217.63, 1117.49, 769.24 cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{16}H_{17}O_2$ [M-1]: 241.1223, found: 241.1217.

4. 2-(4-Methoxybenzyl)-6-methylphenol:

Yellowish solid, **M. P.** = 59-61 ^{o}C.



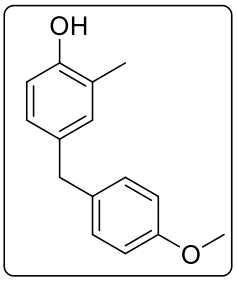
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 3H), 3.79 (s, 3H), 3.94 (s, 2H), 4.65 (s, 1 H), 6.78 - 6.91 (m, 3H), 7.04 (d, *J* = 6.8 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 16.15, 36.28, 55.57, 114.46 (2C), 120.66, 124.23, 126.90, 128.85, 129.59, 129.90 (2C), 131.87, 152.50, 158.56.

IR ($CHCl_3$): ν_{max} 3415.76, 1641.47, 1587.99, 1217.20, 766.10 cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{15}H_{15}O_2$ [M-1]: 227.1067, found: 227.1070.

5. 4-(4-Methoxybenzyl)-2-methylphenol:



^{1}H NMR (400 MHz, $CDCl_3$): δ 2.22 (s, 3H), 3.79 (s, 3H), 3.83 (s, 2H), 4.66 (s, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 6.82 - 6.91 (m, 3H), 6.94 (s, 1H), 7.10 (d, *J* = 8.3 Hz, 2H).

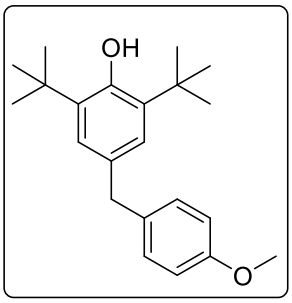
^{13}C NMR (100 MHz, $CDCl_3$): δ 15.85, 40.23, 55.35, 113.92 (2C), 114.92, 123.73, 127.38, 129.79 (2C), 131.48, 133.85, 133.92, 152.11, 157.93.

IR ($CHCl_3$): ν_{max} 3415.58, 3022.39, 1596.93, 1522.93, 1425.60, 1216.08, 768.49 cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{15}H_{15}O_2$ [M-1]: 227.1067, found: 227.1059.

6. 2, 6-di-tert-Butyl-4-(4-methoxybenzyl)phenol:

Solid, M. P. = 135-138 ºC**.**



^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 (s, 18H), 3.80 (s, 3H), 3.85 (s, 2H), 5.05 (s, 1H), 6.84 (d, *J* = 8.4 Hz, 2 H), 6.98 (s, 2 H), 7.12 (d, *J* = 8.8 Hz, 2 H).

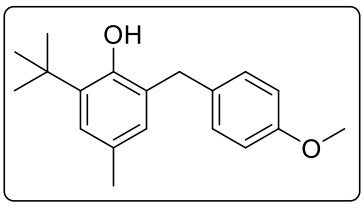
^{13}C NMR (125 MHz, $CDCl_3$): δ 30.32 (6C), 34.30 (2C), 40.90, 55.26, 113.76 (2C), 125.32 (2C), 129.75 (2C), 131.99, 134.00, 135.80 (2C), 152.00, 157.78.

IR ($CHCl_3$): ν_{max} 3449.46, 3022.15, 1216.78, 914.09, 764.20 cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{22}H_{29}O_2$ [M-1]: 325.2162, found: 325.2167.

7. 2-(tert-Butyl)-6-(4-methoxybenzyl)-4-methylphenol:

Solid, M. P. = 83-85 ºC**.**



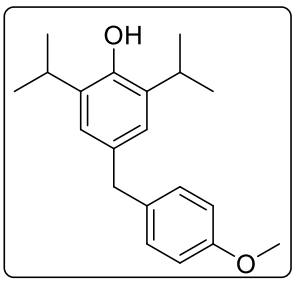
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (s, 9H), 2.30 (s, 3H), 3.84 (s, 3H), 5.02 (s, 2H), 6.82 - 6.97 (m, 3H), 7.00 (br s, 1H), 7.12 (s, 1H), 7.39 (d, *J* = 8.6 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 20.89, 29.93 (3C), 34.82, 55.35, 69.95, 112.45, 113.95 (2C), 127.16, 127.65, 129.00 (2C), 129.43, 129.76, 138.11, 155.59, 159.21.

IR ($CHCl_3$): ν_{max} 3418.45, 3021.47, 1519.21, 1427.06, 1216.54, 765.36 cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{19}H_{24}O_2[M]^+$: 284.1771**,** found: 284.1765.

8. 2, 6-Diisopropyl-4-(4-methoxybenzyl)phenol:



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (d, *J* = 6.8 Hz, 12H), 3.06 - 3.25 (m, 2H), 3.80 (s, 3H), 3.87 (s, 2H), 4.67 (s, 1H), 6.84 (d, *J* = 9.1 Hz, 2H), 6.87 (s, 2H), 7.12 (d, *J* = 9.1 Hz, 2H).

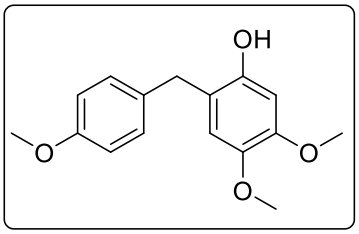
^{13}C NMR (100 MHz, $CDCl_3$): δ 22.41 (4C), 26.91 (2C), 40.38, 54.92, 113.41 (2C), 123.58 (2C), 129.32 (2C), 132.88, 133.23 (2C), 133.64, 147.84, 157.41.

IR ($CHCl_3$): ν_{max} 3449.46, 3021.44, 1216.77, 914.09, 764.66 cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{20}H_{25}O_2$ [M-1]: 297.1843, found: 297.1843.

9. 4, 5-Dimethoxy-2-(4-methoxybenzyl) phenol.

Solid, M. P. = 174-175 ^oC**.**



^{1}H NMR (400 MHz, $CDCl_3$): δ *3.*71 (s, 3H), 3.78 (s, 6H), 3.88 (s, 2H), 5.58 (br s, 1H), 6.42 (s, 1H), 6.64 (s, 1H), 6.84 (d, *J* = 14.5 Hz, 2H), 7.14 (d, *J* = 14.5 Hz, 2H).

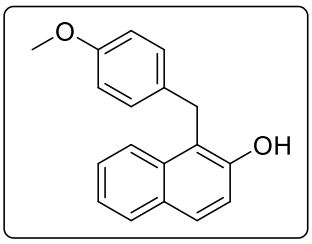
^{13}C NMR (100 MHz, $CDCl_3$): δ 34.42, 54.78, 55.34, 56.15, 100.76, 113.54 (2C), 113.99, 117.94, 129.02 (2C), 131.97, 142.23, 147.35, 147.66, 157.44.

IR ($CHCl_3$): ν_{max} 3598, 3022, 2952, 1215, 772 cm^{-1}.

HRMS (ESI): *m/z* calculated for $C_{16}H_{18}NaO_4$ [M+Na]: 297.1097, found: 297.1089.

10. 1-(4-Methoxybenzyl)naphthalen-2-ol:

White solid, M. P. = 130-132 ^oC**.**



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 3H), 4.41 (s, 2H), 5.08 (s, 1H), 6.76 (d, *J* = 8.8 Hz, 2H), 7.09 - 7.19 (m, 3H), 7.33 - 7.39 (m, 1H), 7.44 - 7.52 (m, 1H), 7.72 (d, *J* = 8.76 Hz, 1H), 7.77 (d, *J* = 8.63 Hz, 1H), 7.95 (d, *J* = 8.63 Hz, 1H).

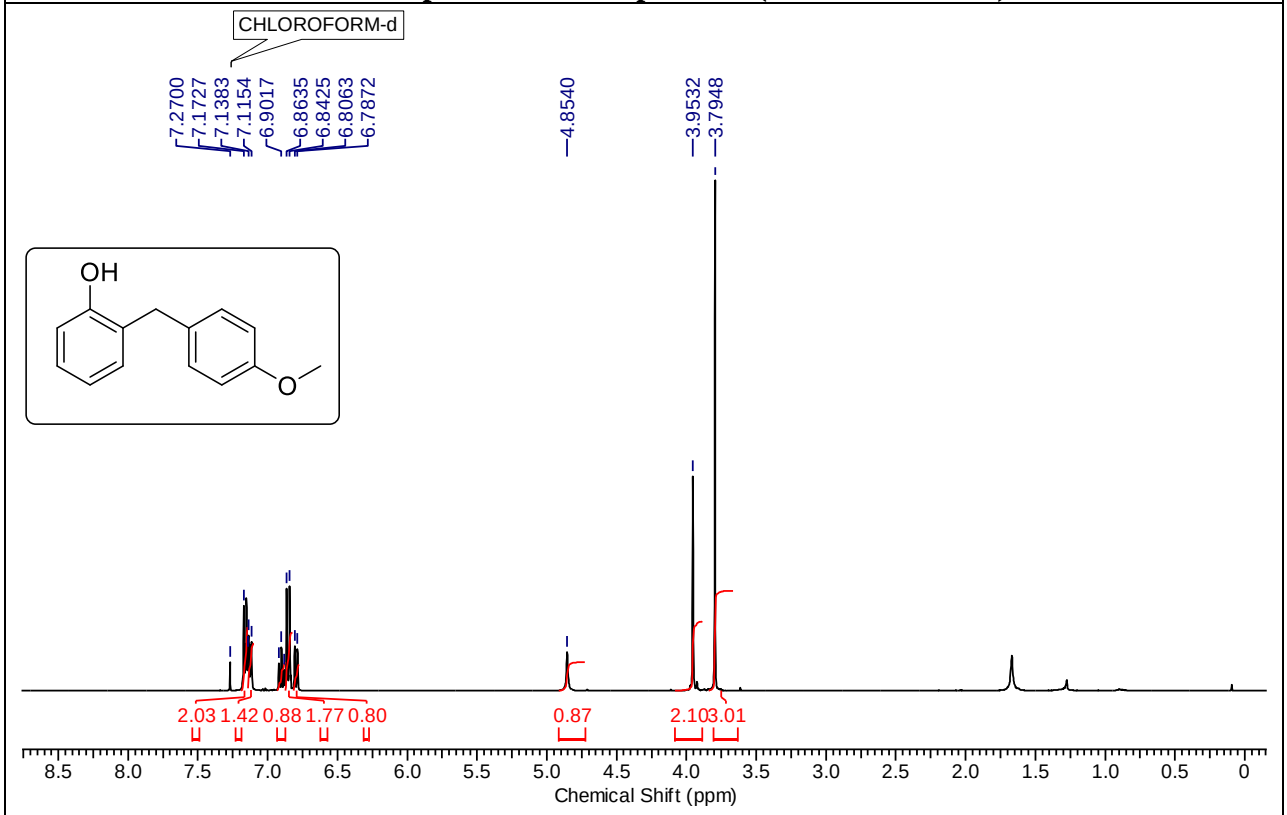
^{13}C NMR (100 MHz, $CDCl_3$): δ 29.75, 55.21, 114.02 (2C), 117.89, 118.44, 123.17, 123.28, 126.62, 128.41, 128.52, 129.11 (2C), 129.44, 131.85, 133.58, 151.13, 157.93.

IR ($CHCl_3$): ν_{max} 3410, 3061, 2933, 1627, 1586, 1456, 1384, 1231, 802, 742 cm^{-1}**.**

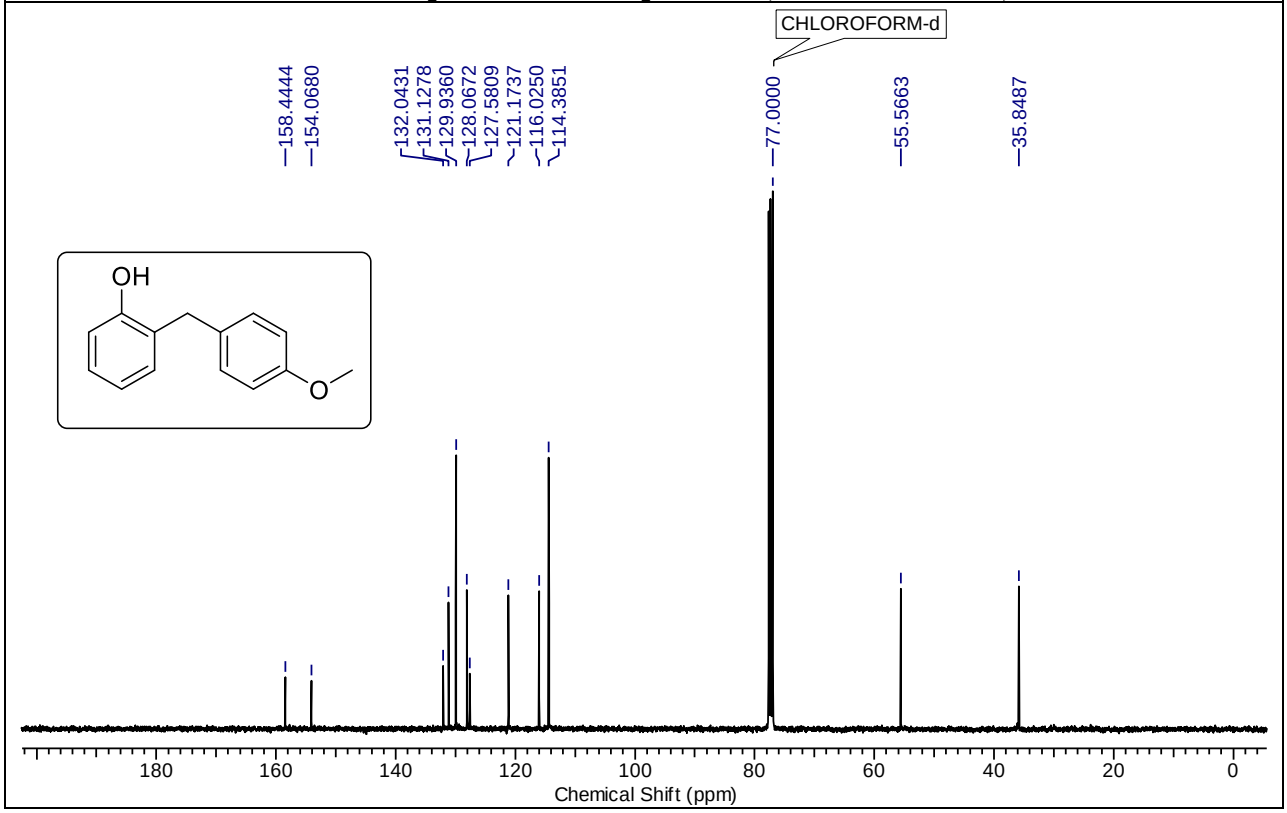
HRMS (ESI): *m/z* calculated for $C_{18}H_{16}O_2[M]^+$**:** 264.1145, found: 264.1146.

3.1.10. NMR Spectra:

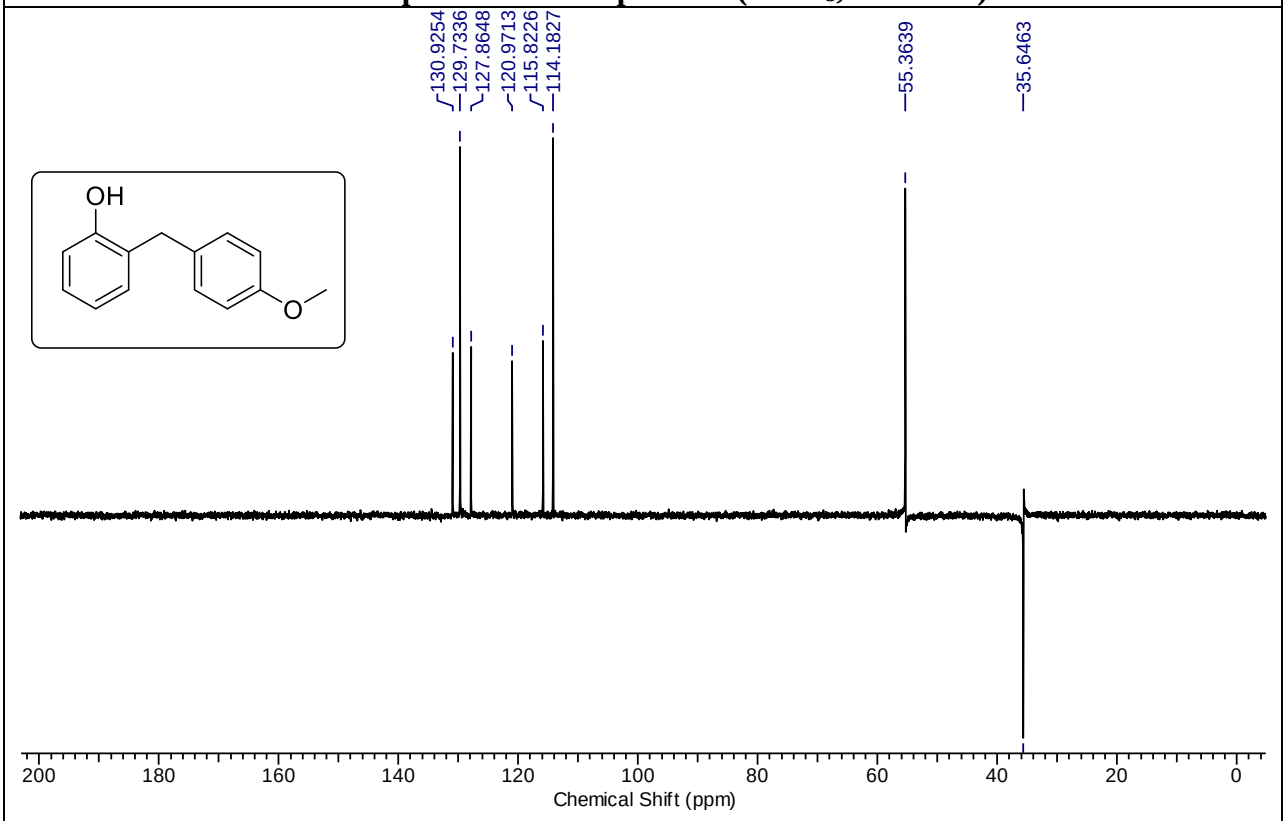
^{1}H-NMR spectrum of compound 1 ($CDCl_3$, 400 MHz)



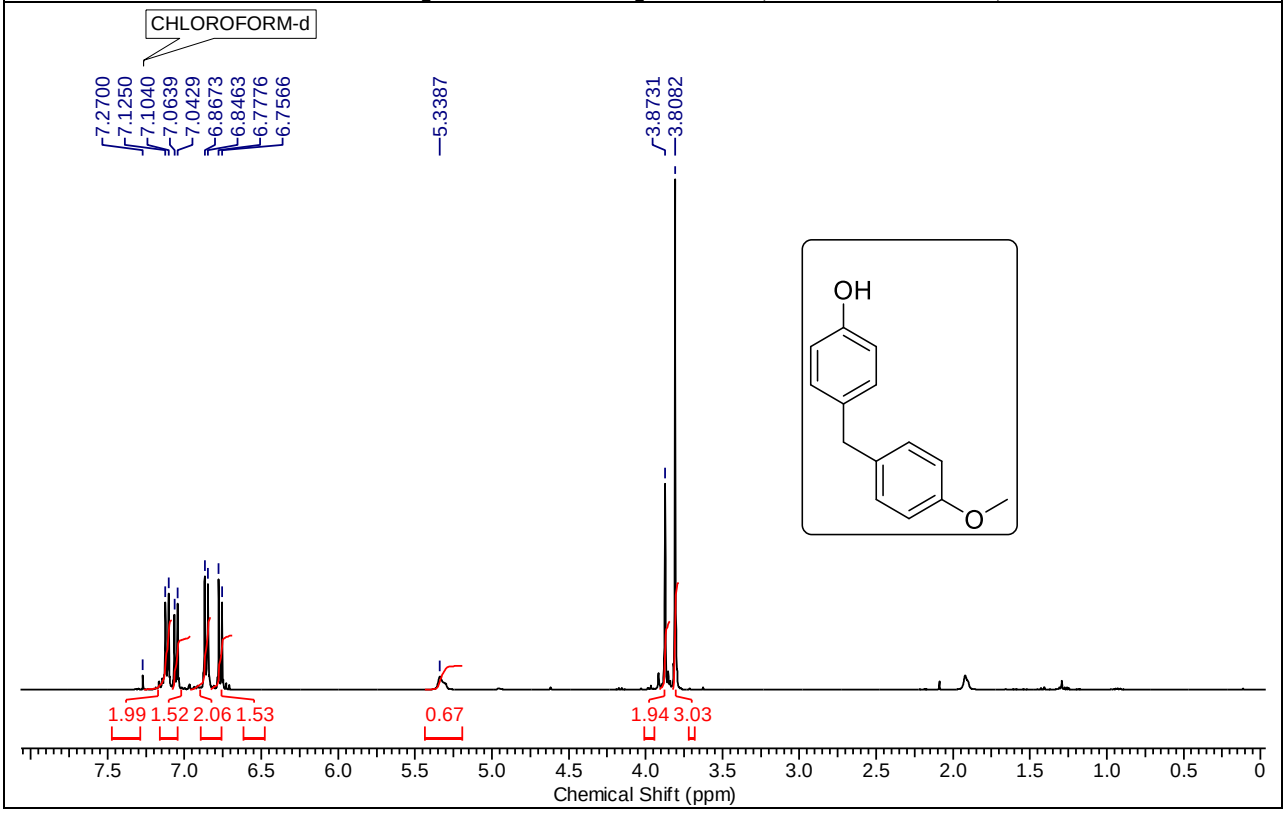
^{13}C-NMR spectrum of compound 1 ($CDCl_3$, 100 MHz)



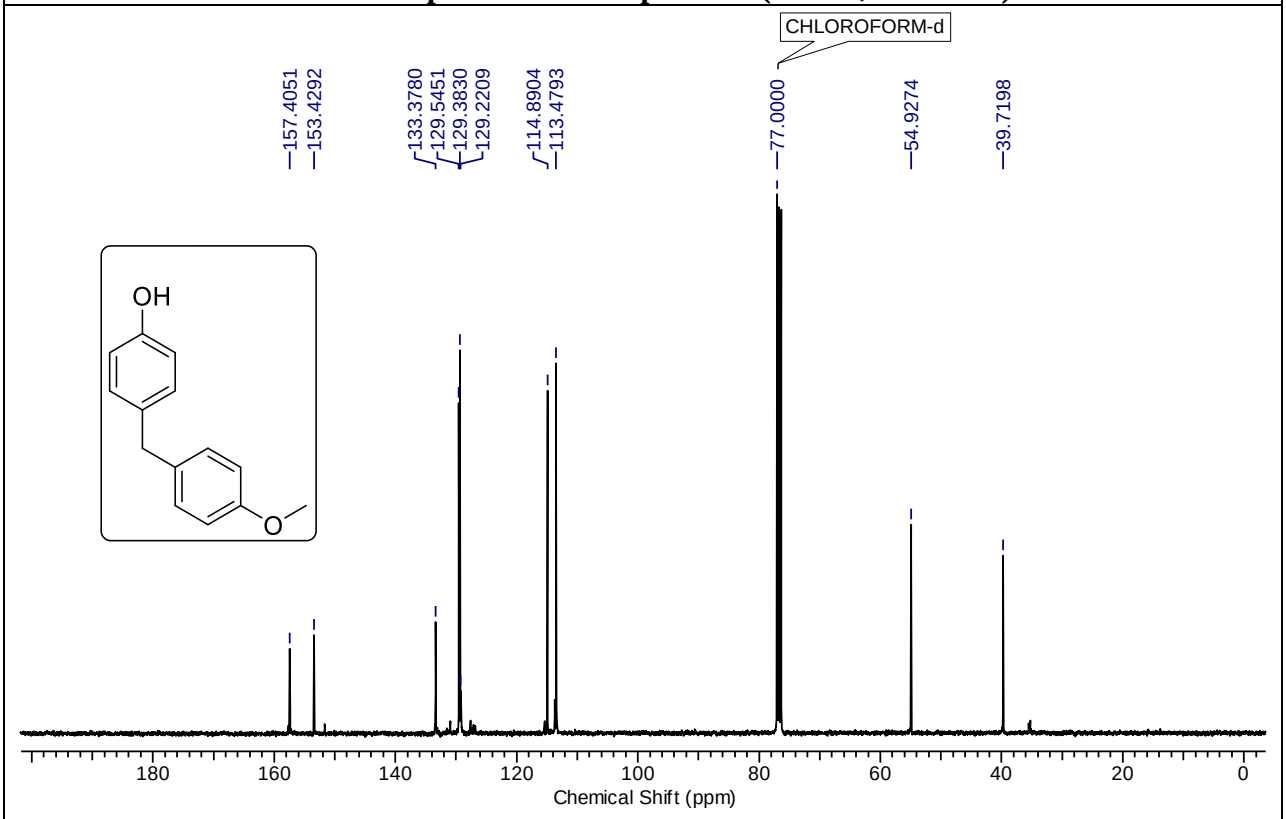
DEPT spectrum of compound 1 ($CDCl_3$, 100 MHz)



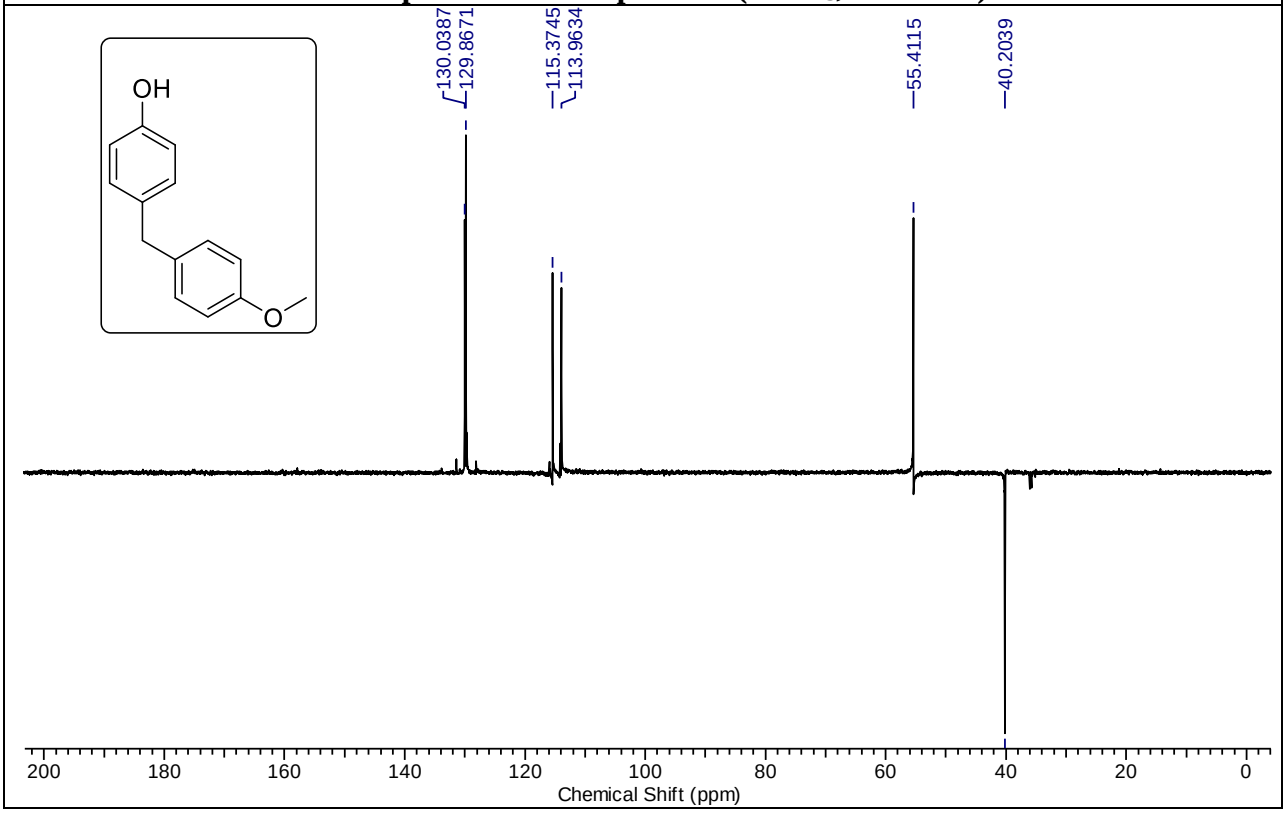
^{1}H-NMR spectrum of compound 2 ($CDCl_3$, 400 MHz)



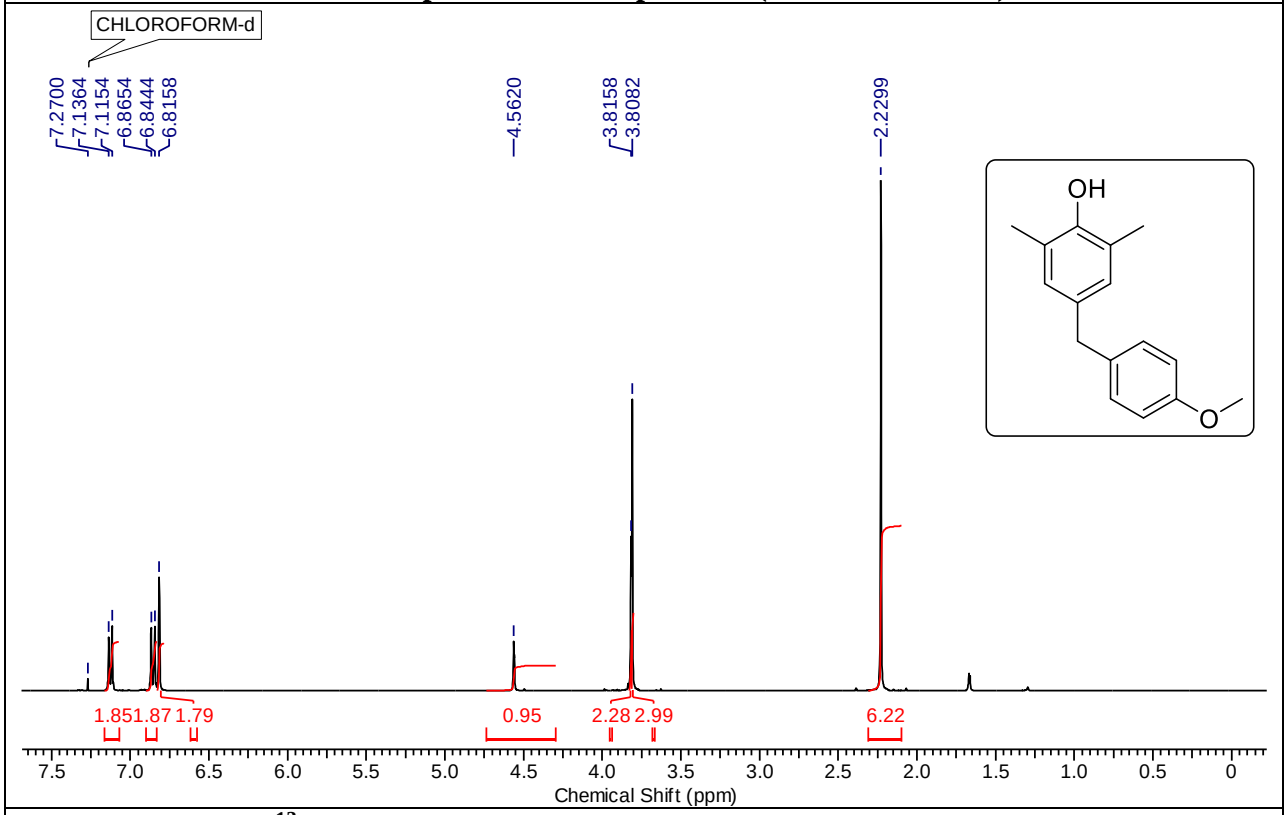
^{13}C-NMR spectrum of compound 2 ($CDCl_3$, 100 MHz)



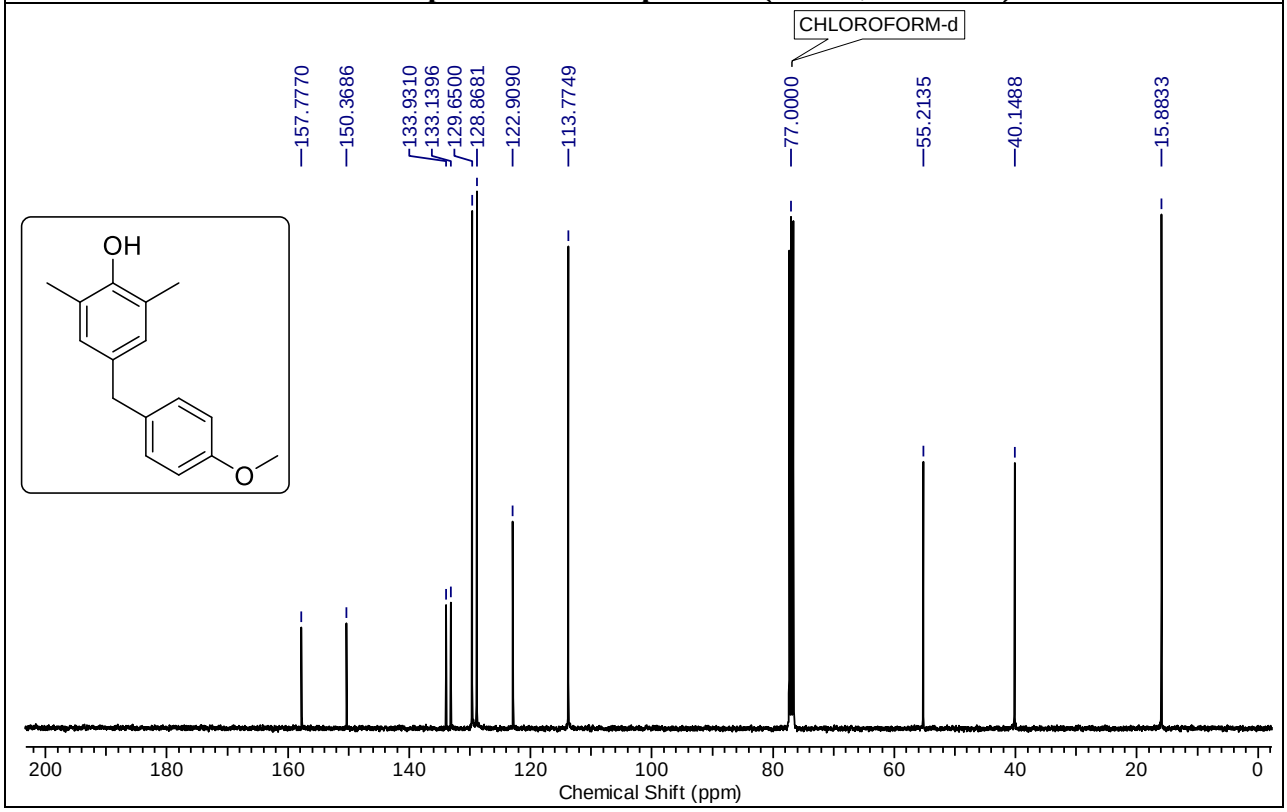
DEPT spectrum of compound 2 ($CDCl_3$, 100 MHz)



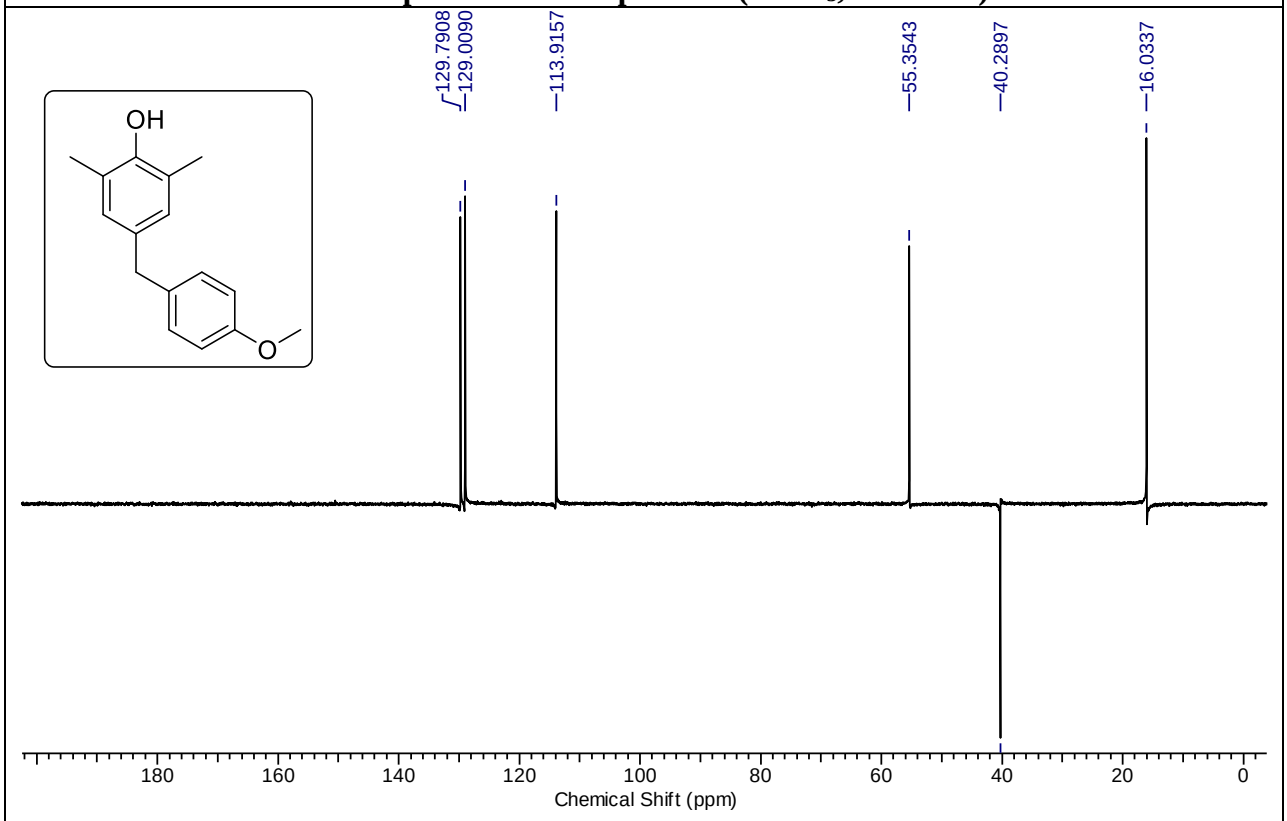
^{1}H-NMR spectrum of compound 3 ($CDCl_3$, 400 MHz)



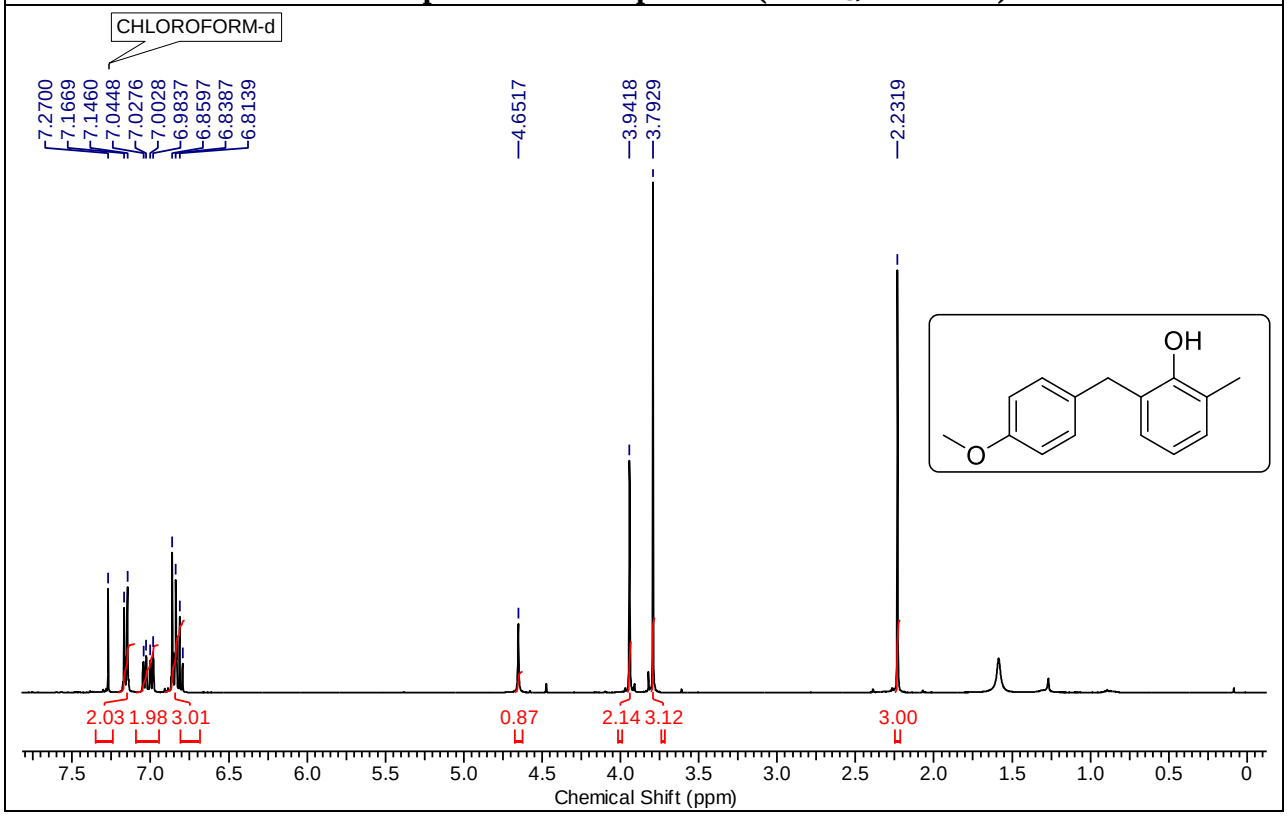
^{13}C-NMR spectrum of compound 3 ($CDCl_3$, 100 MHz)



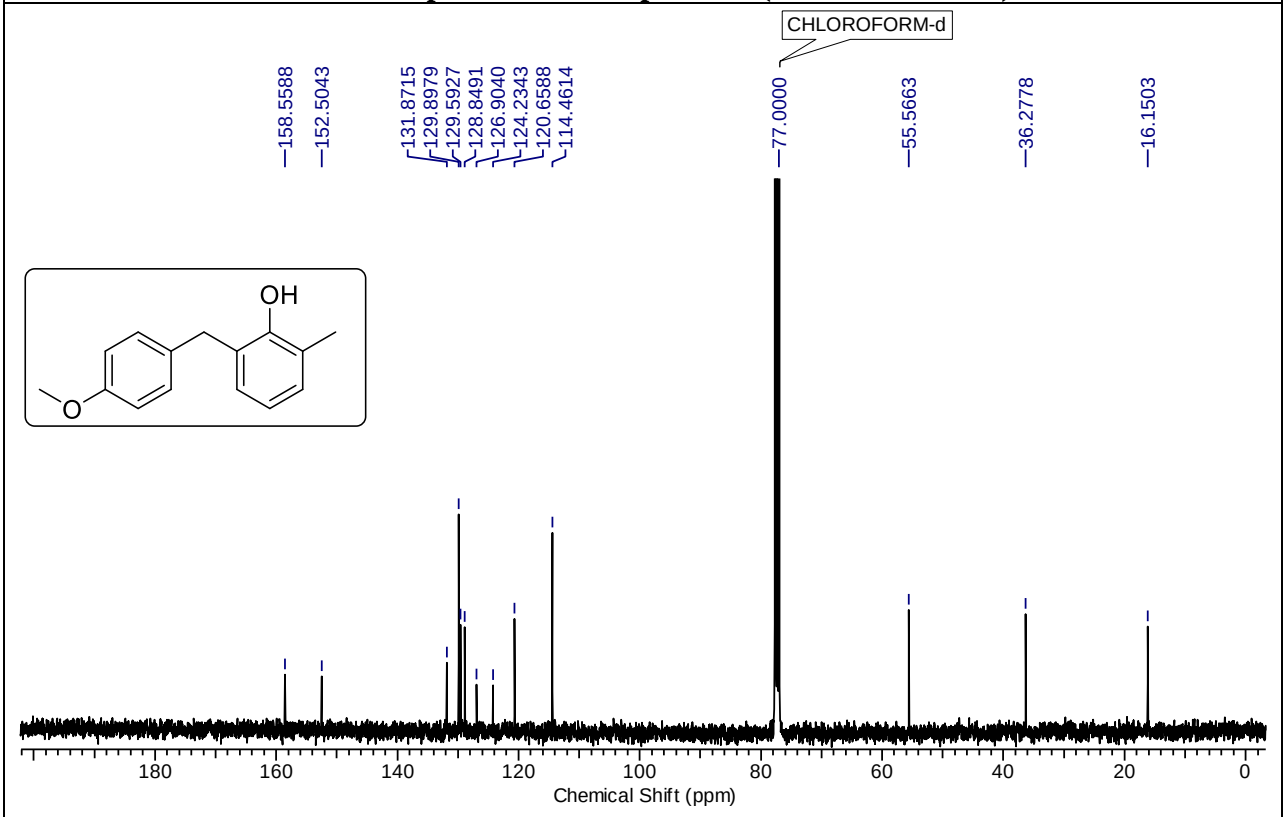
DEPT spectrum of compound 3 ($CDCl_3$, 100 MHz)



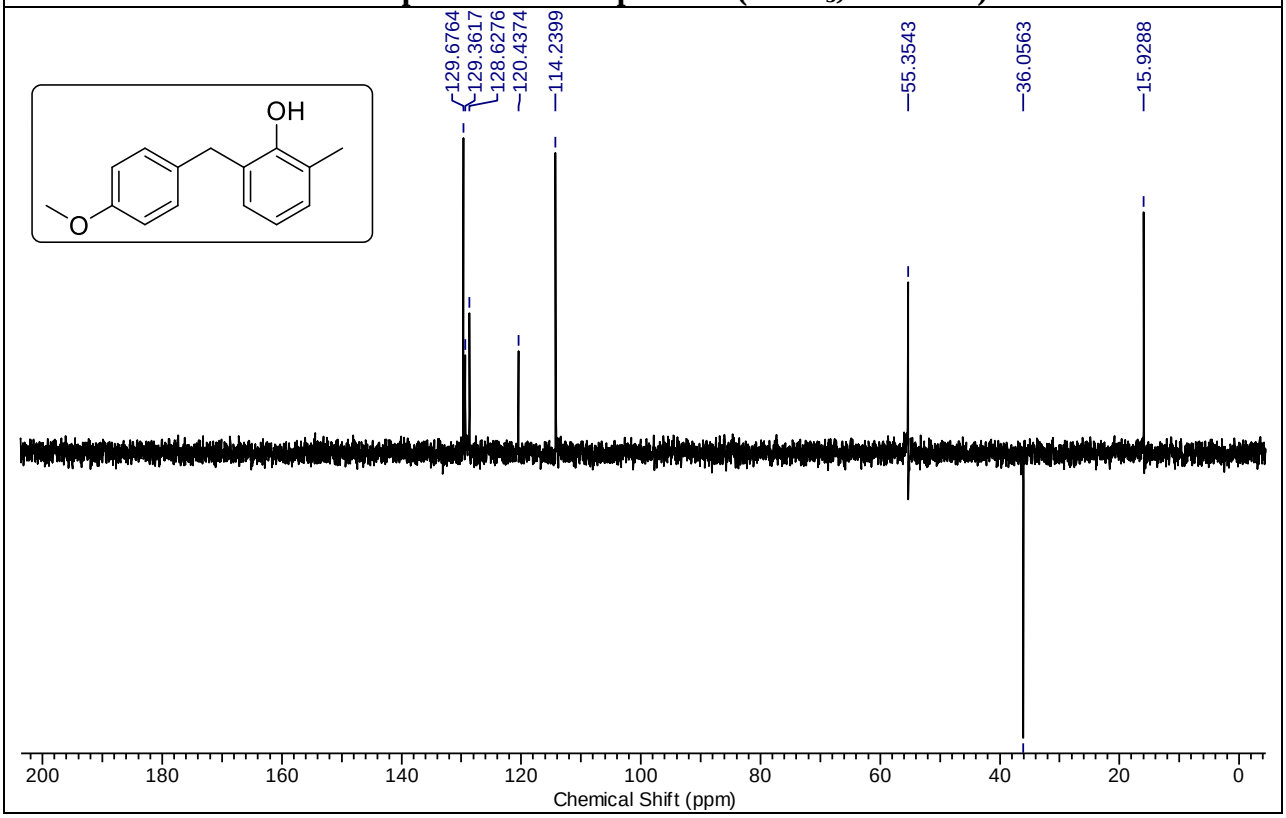
^{1}H-NMR spectrum of compound 4 ($CDCl_3$, 400 MHz)



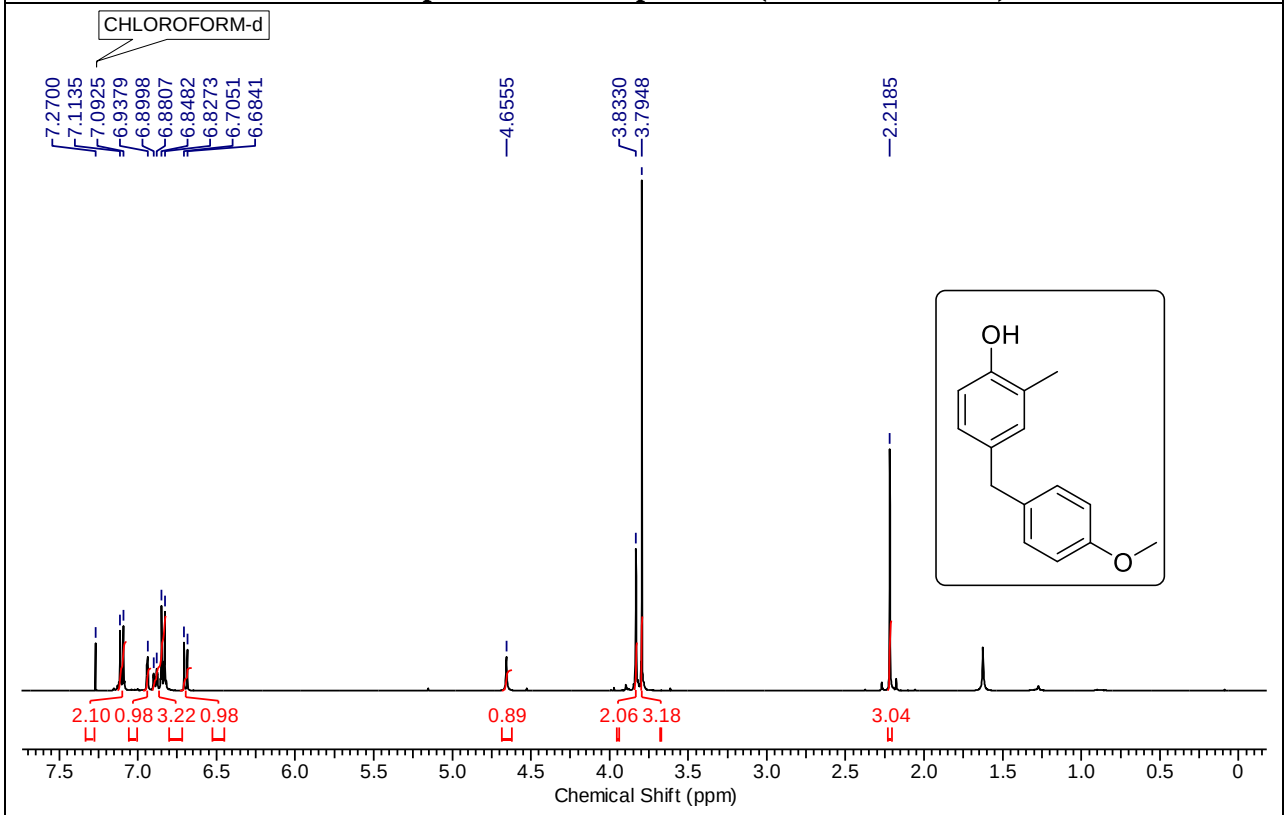
^{13}C-NMR spectrum of compound 4 ($CDCl_3$, 100 MHz)



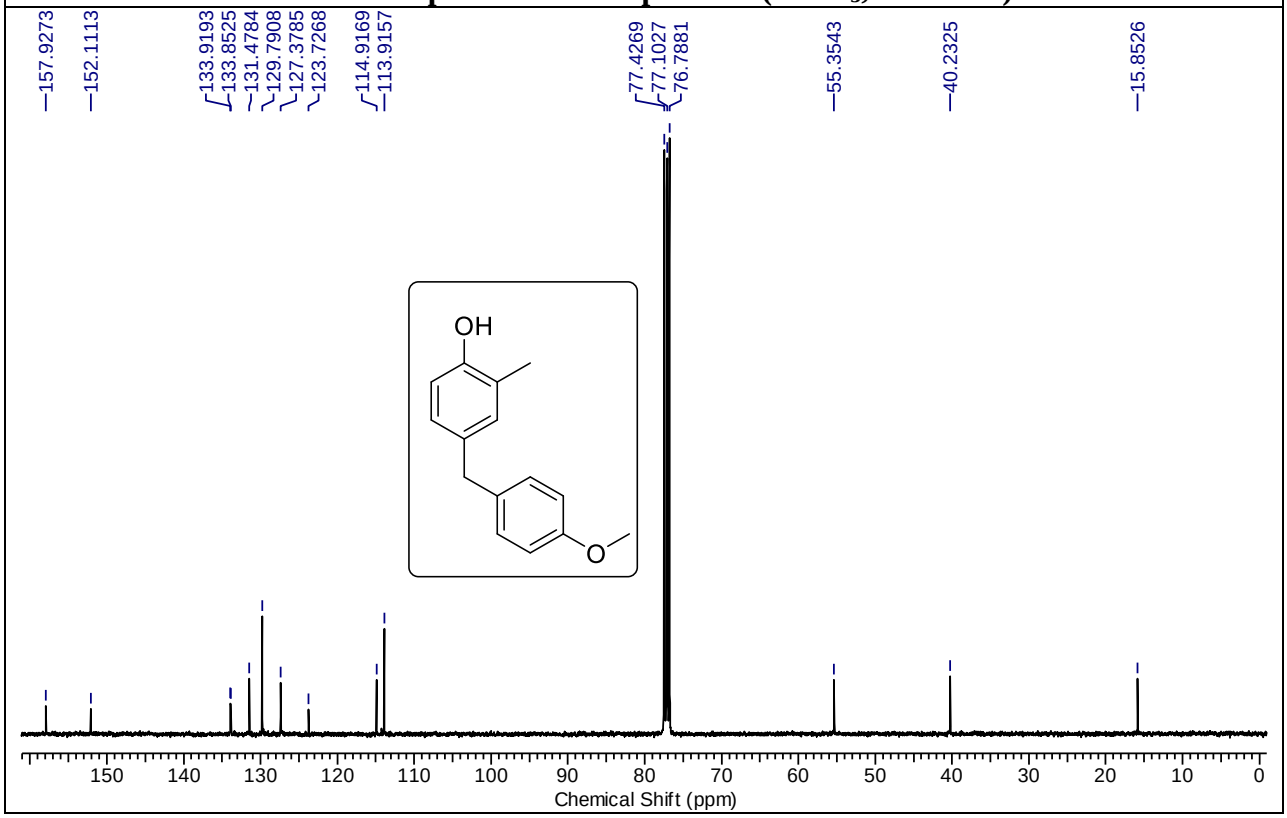
DEPT spectrum of compound 4 ($CDCl_3$, 100 MHz)



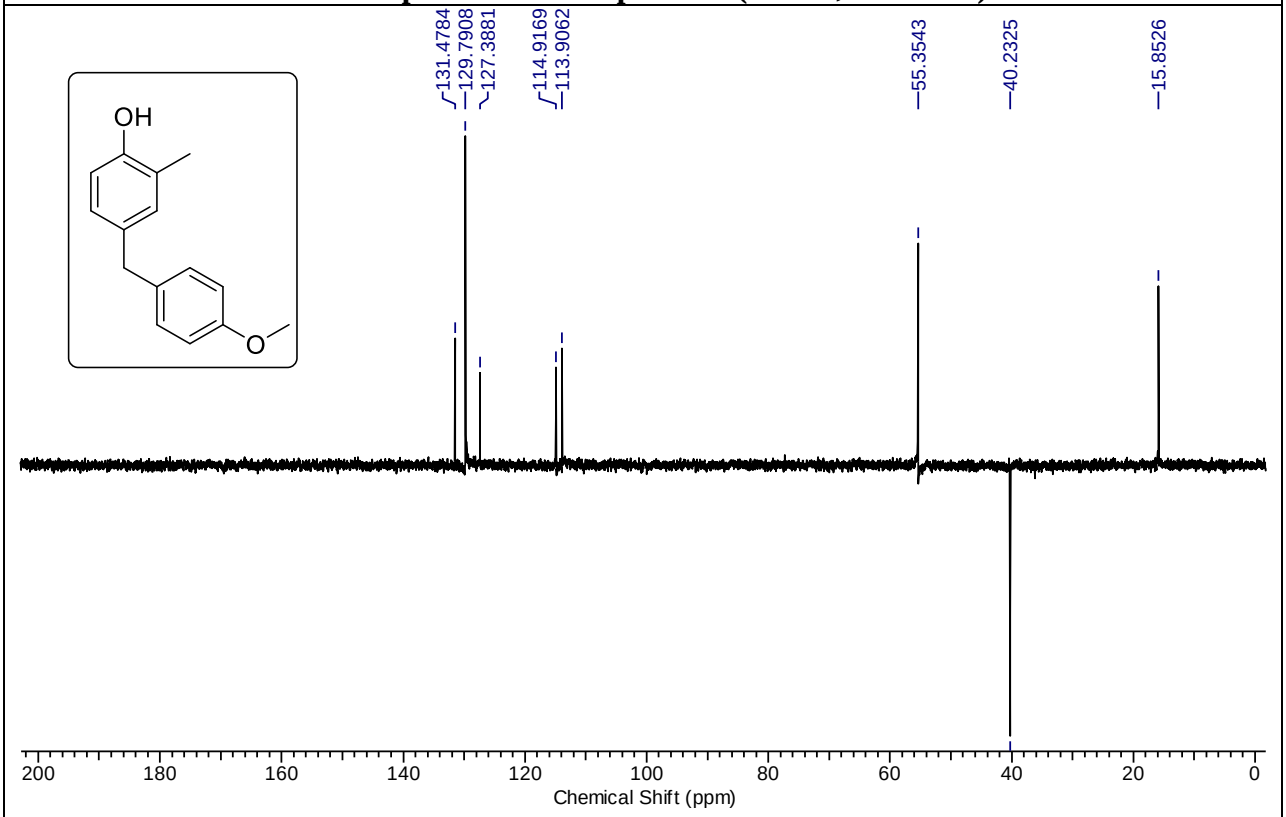
^{1}H-NMR spectrum of compound 5 ($CDCl_3$, 400 MHz)



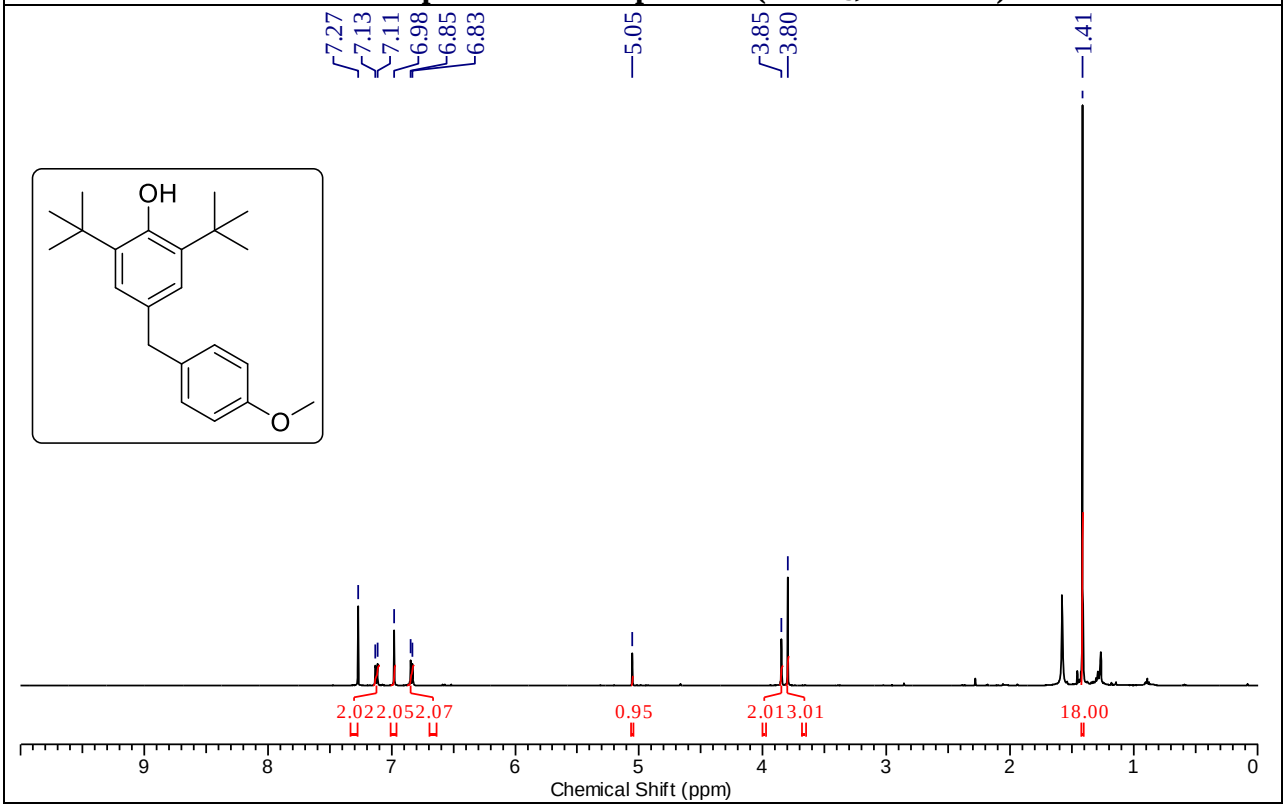
^{13}C-NMR spectrum of compound 5 ($CDCl_3$, 100 MHz)



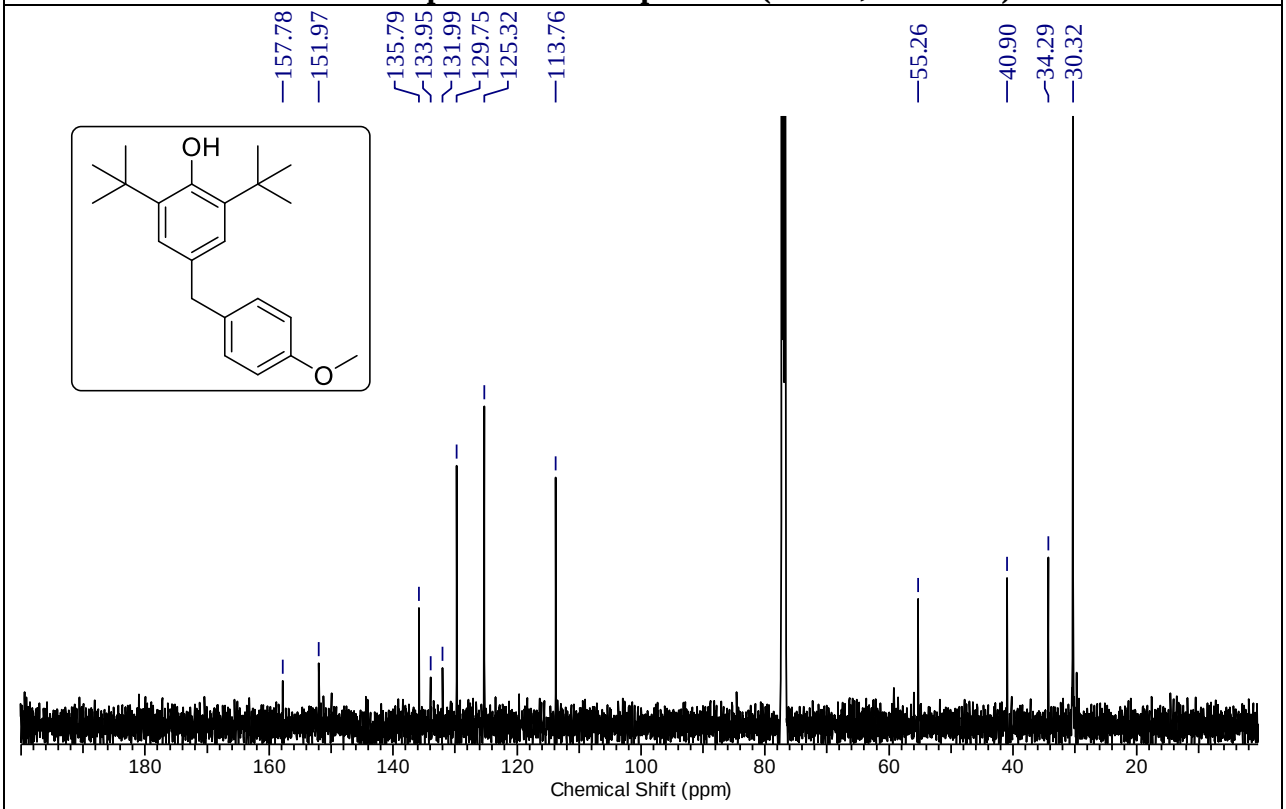
DEPT spectrum of compound 5 ($CDCl_3$, 100 MHz)



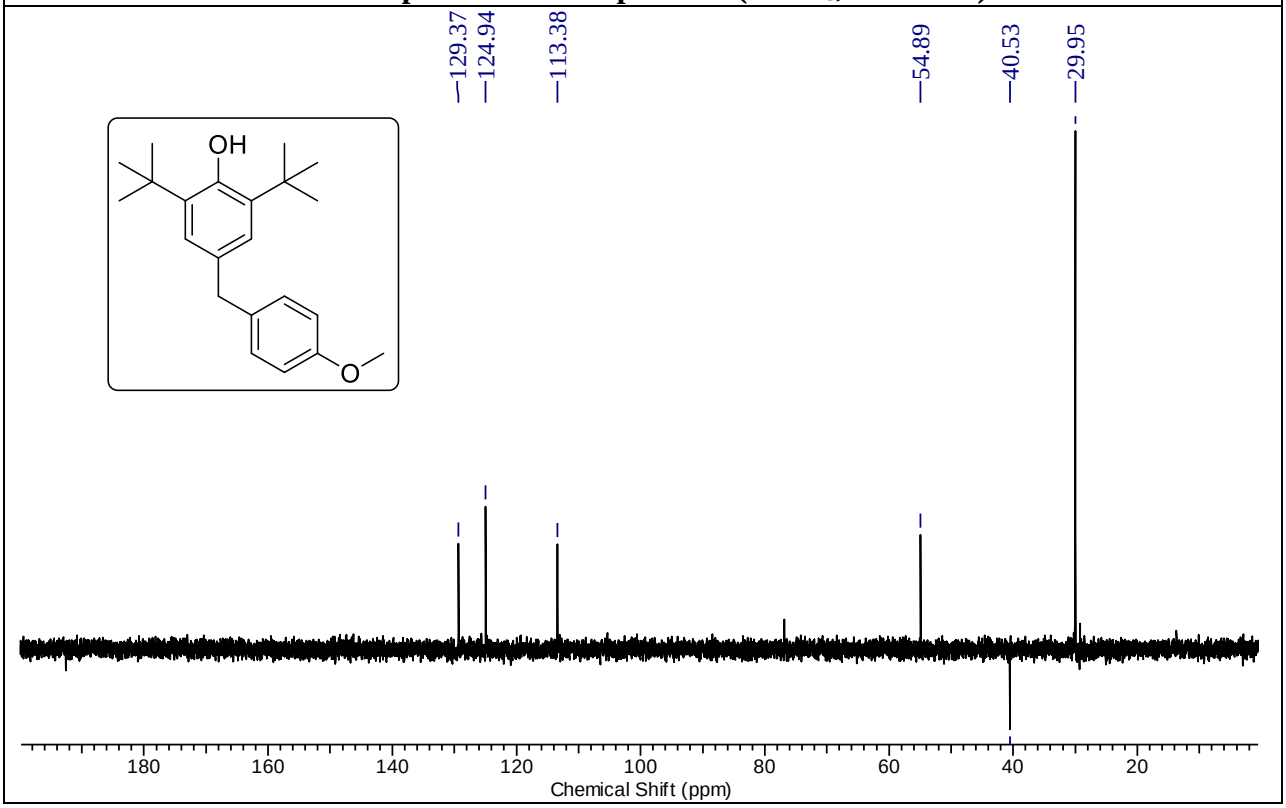
^{1}H-NMR spectrum of compound 6 ($CDCl_3$, 500 MHz)



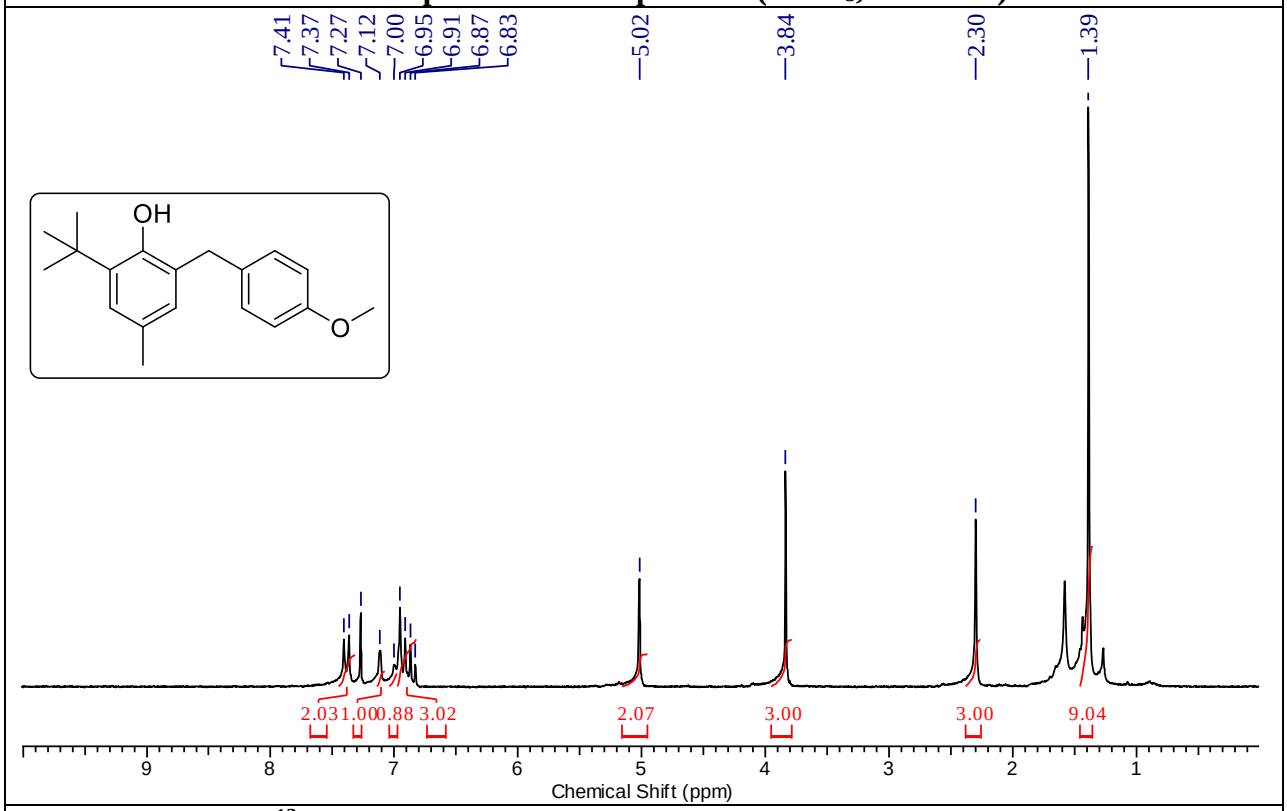
^{13}C-NMR spectrum of compound 6 ($CDCl_3$, 125 MHz)



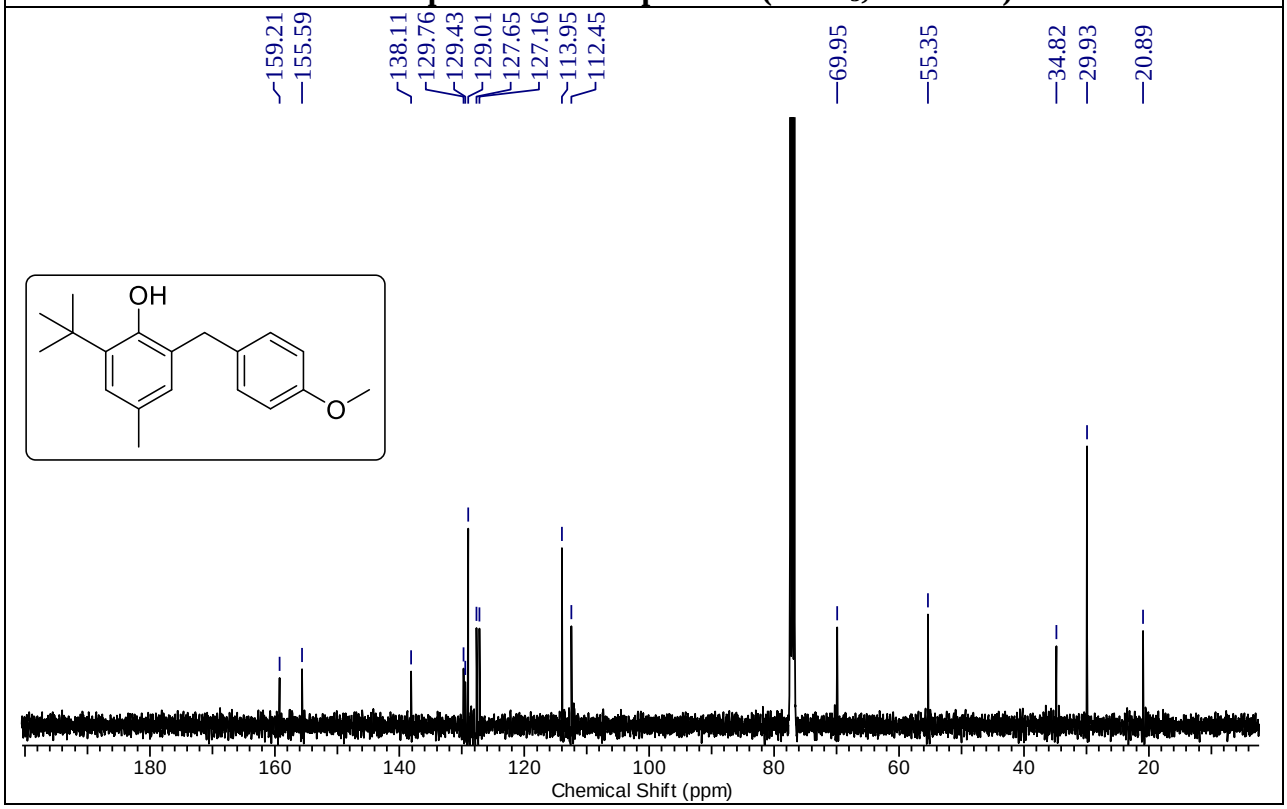
DEPT spectrum of compound 6 ($CDCl_3$, 125 MHz)



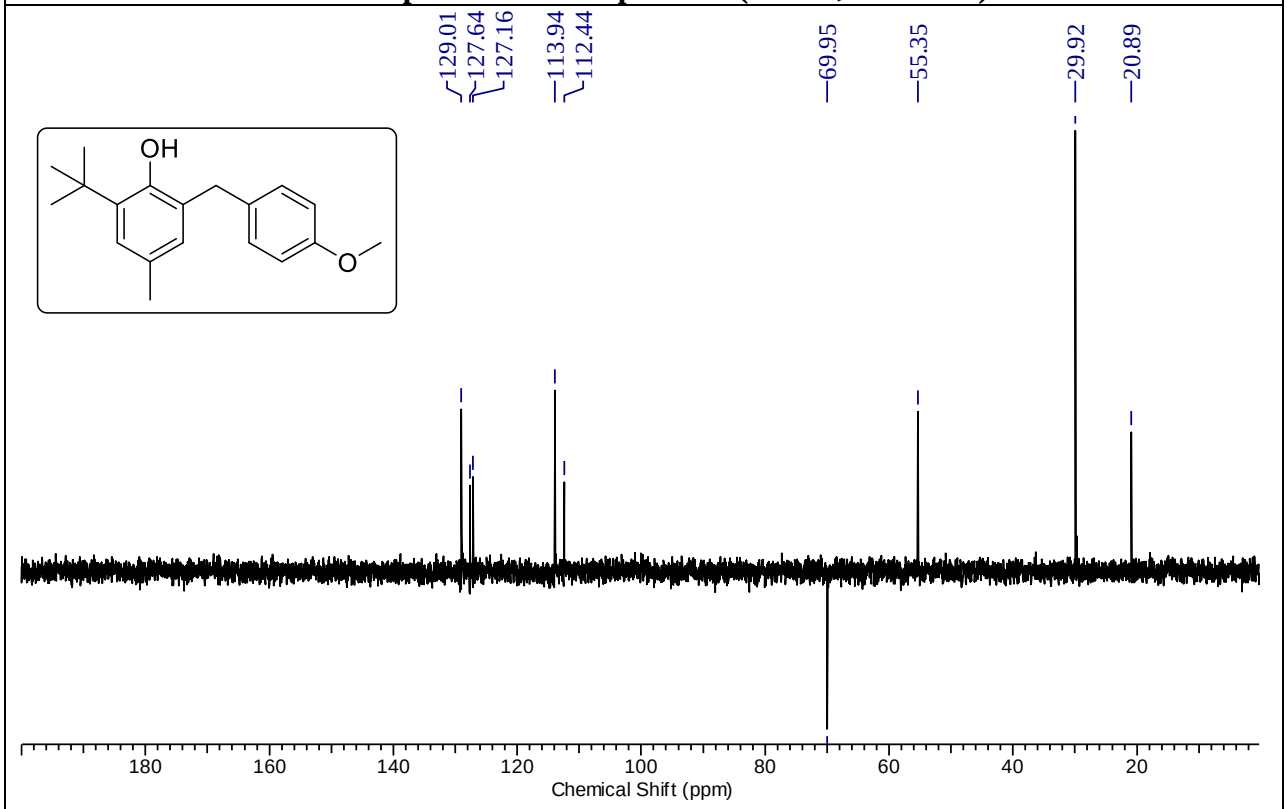
^{1}H-NMR spectrum of compound 7 ($CDCl_3$, 500 MHz)



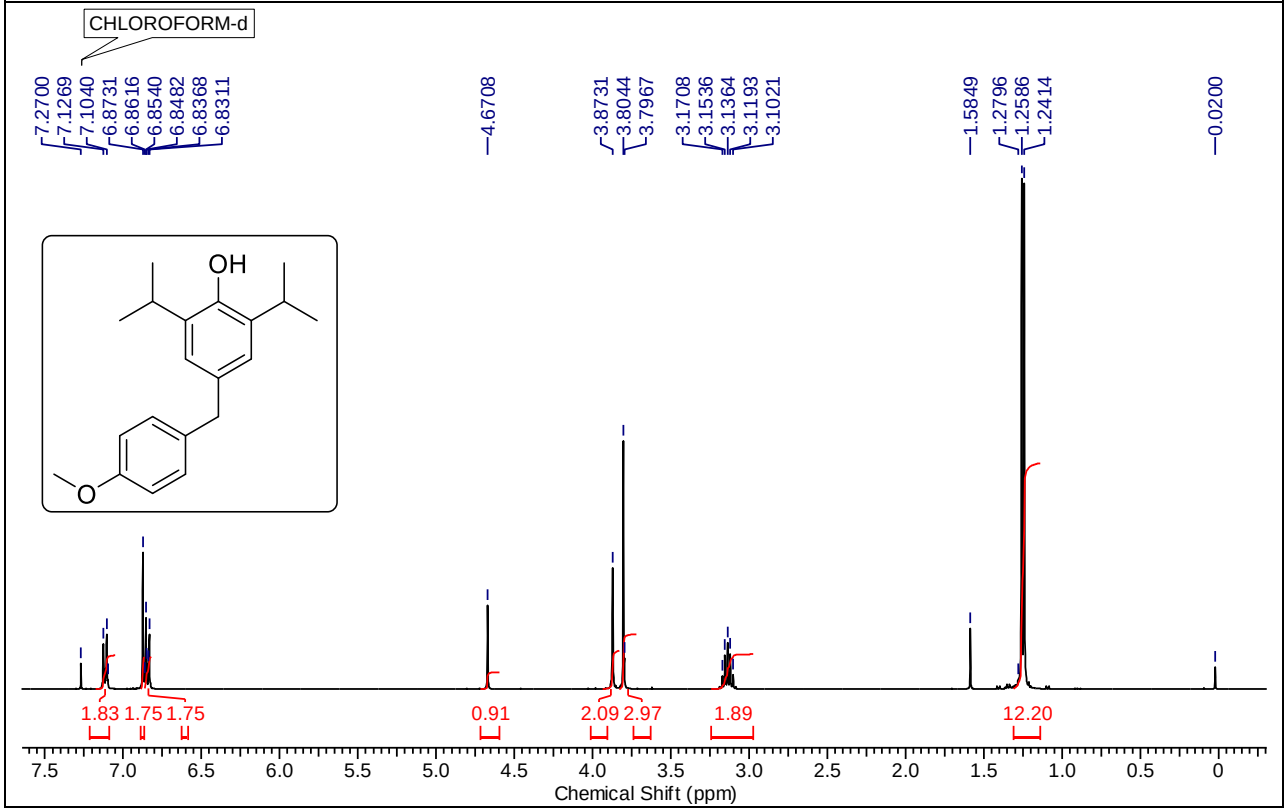
^{13}C-NMR spectrum of compound 7 ($CDCl_3$, 125 MHz)



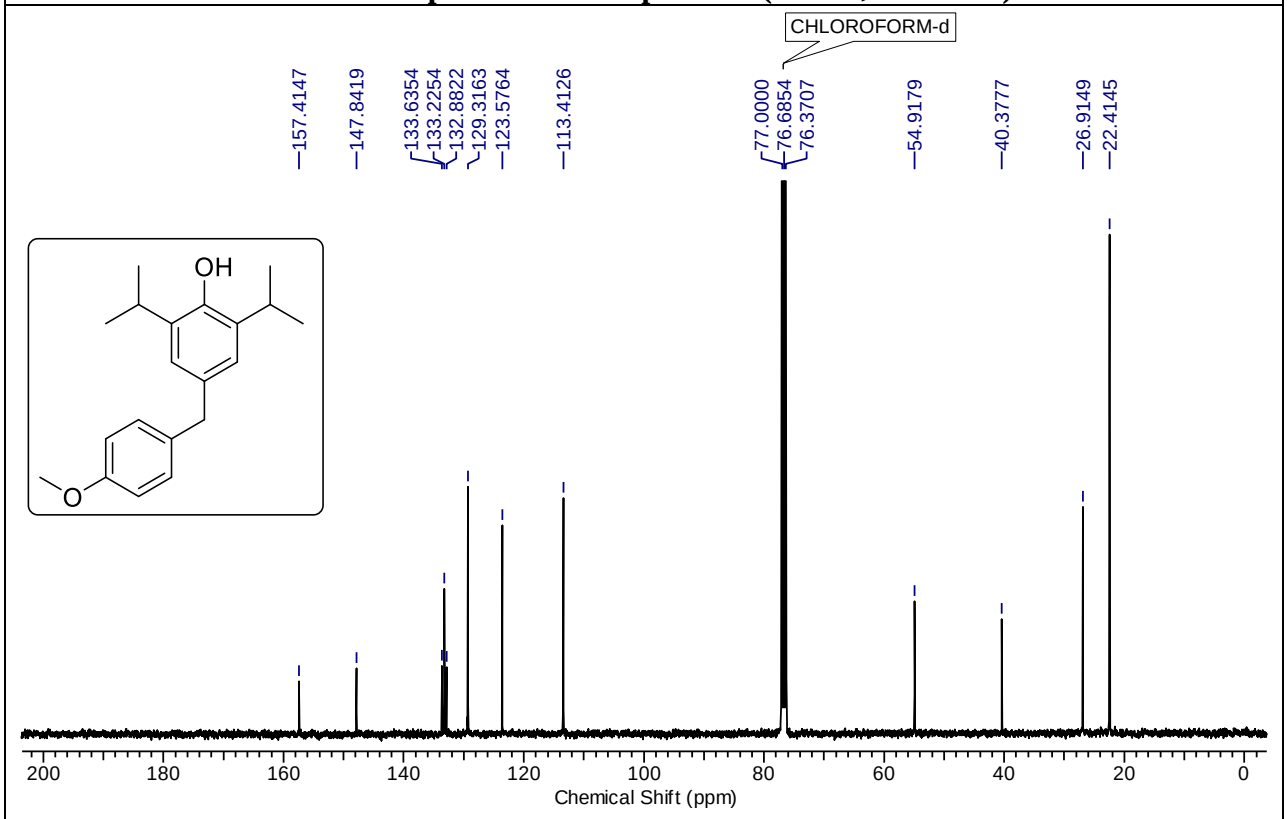
DEPT spectrum of compound 7 ($CDCl_3$, 125 MHz)



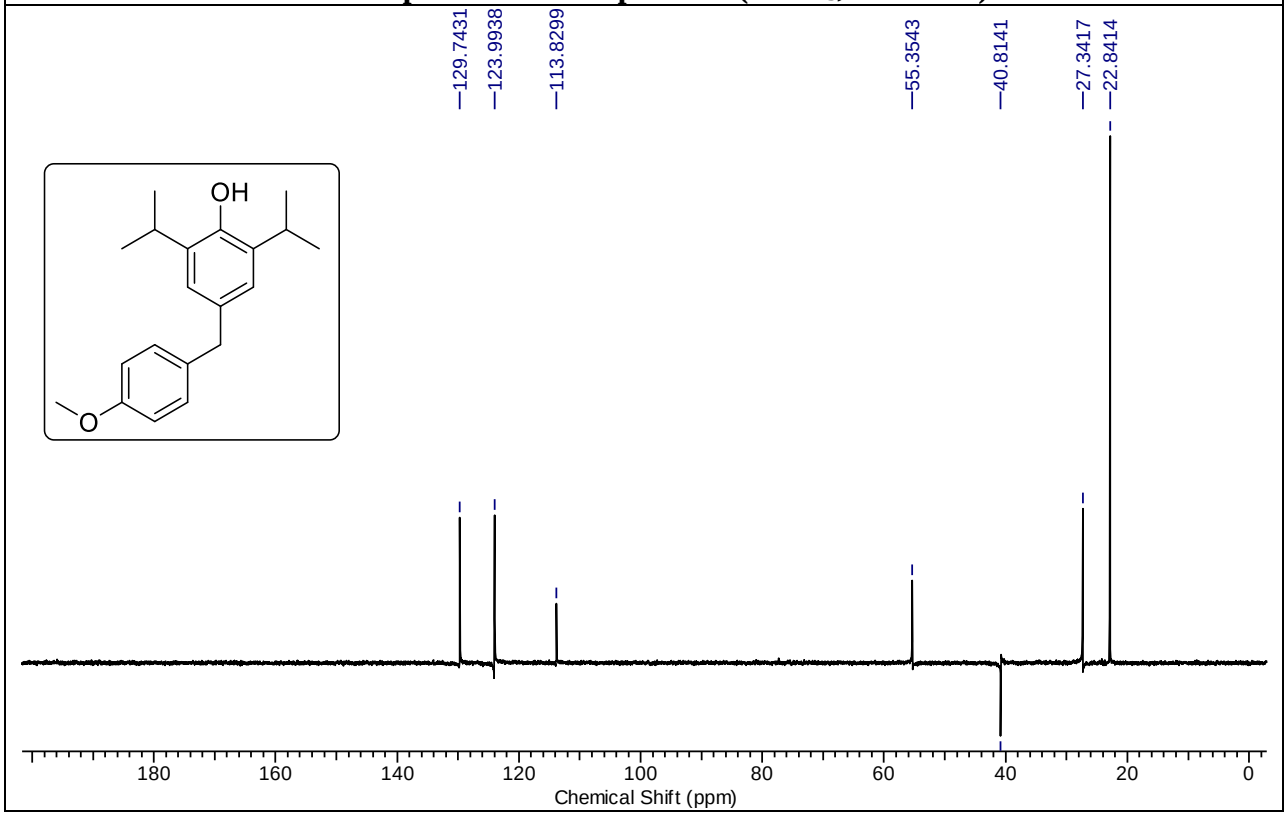
^{1}H-NMR spectrum of compound 8 ($CDCl_3$, 400 MHz)



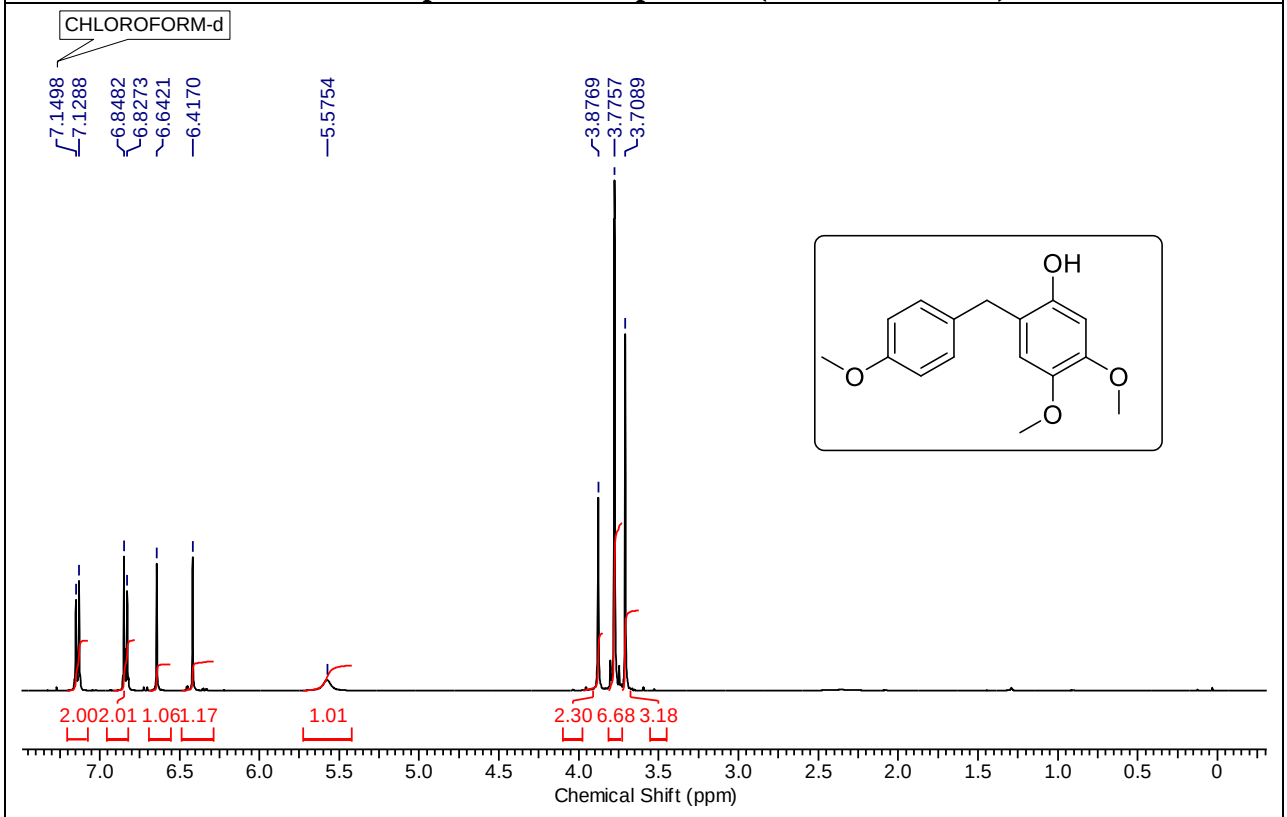
^{13}C-NMR spectrum of compound 8 ($CDCl_3$, 100 MHz)



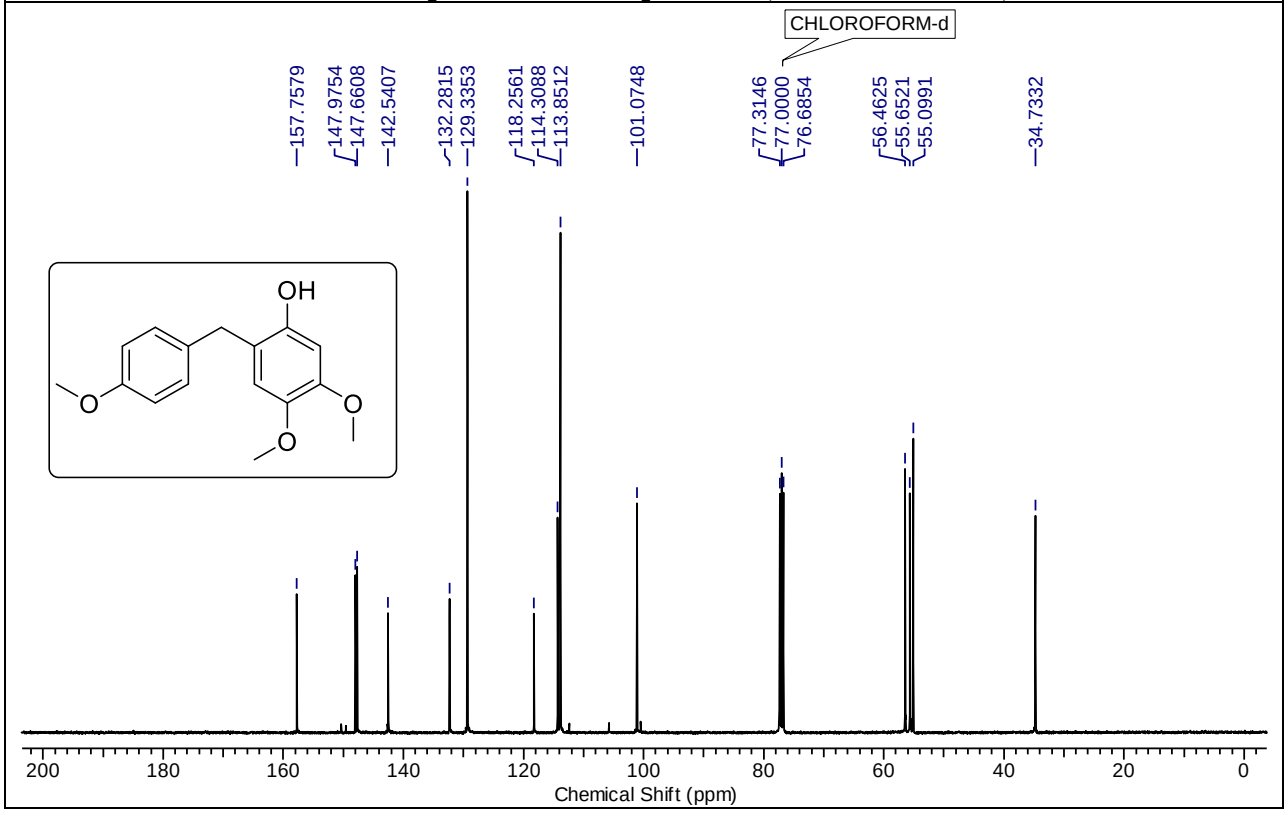
DEPT spectrum of compound 8 ($CDCl_3$, 100 MHz)



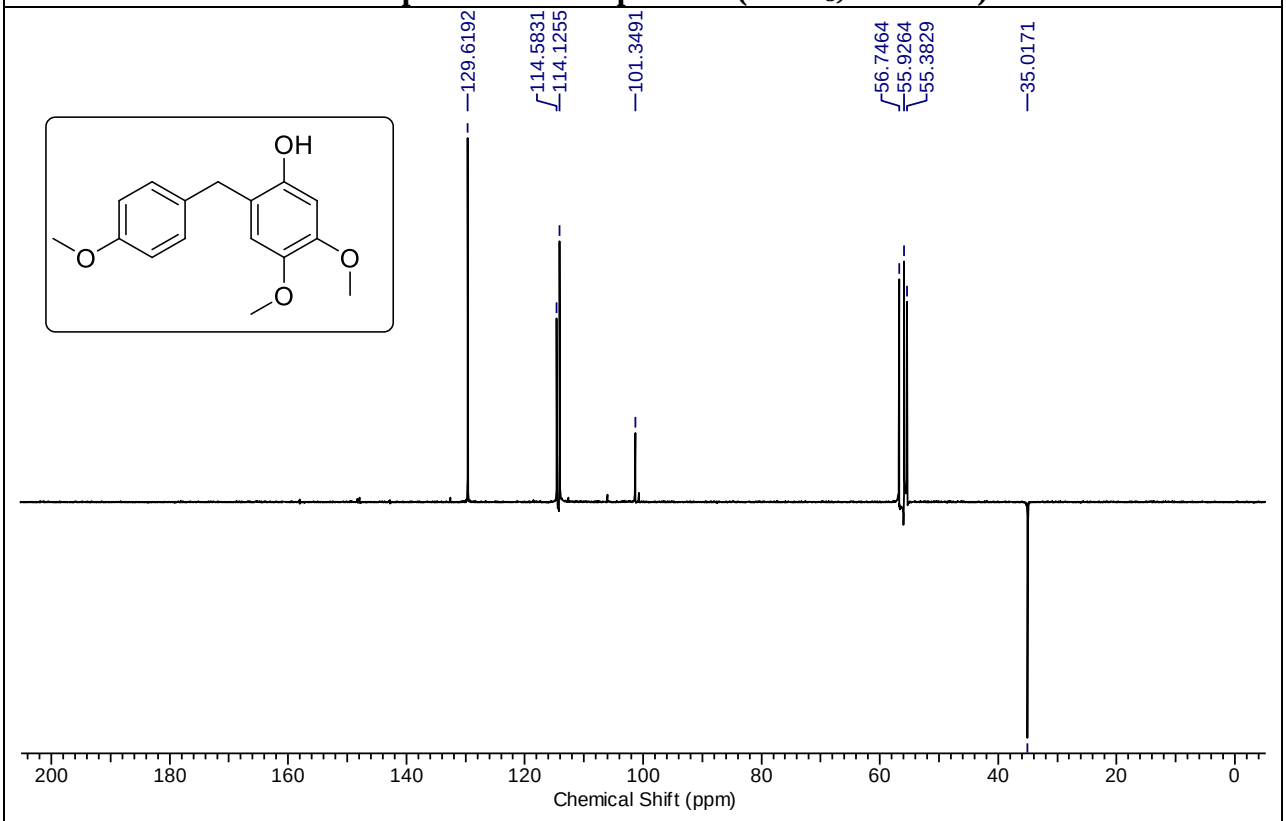
^{1}H-NMR spectrum of compound 9 ($CDCl_3$, 400 MHz)



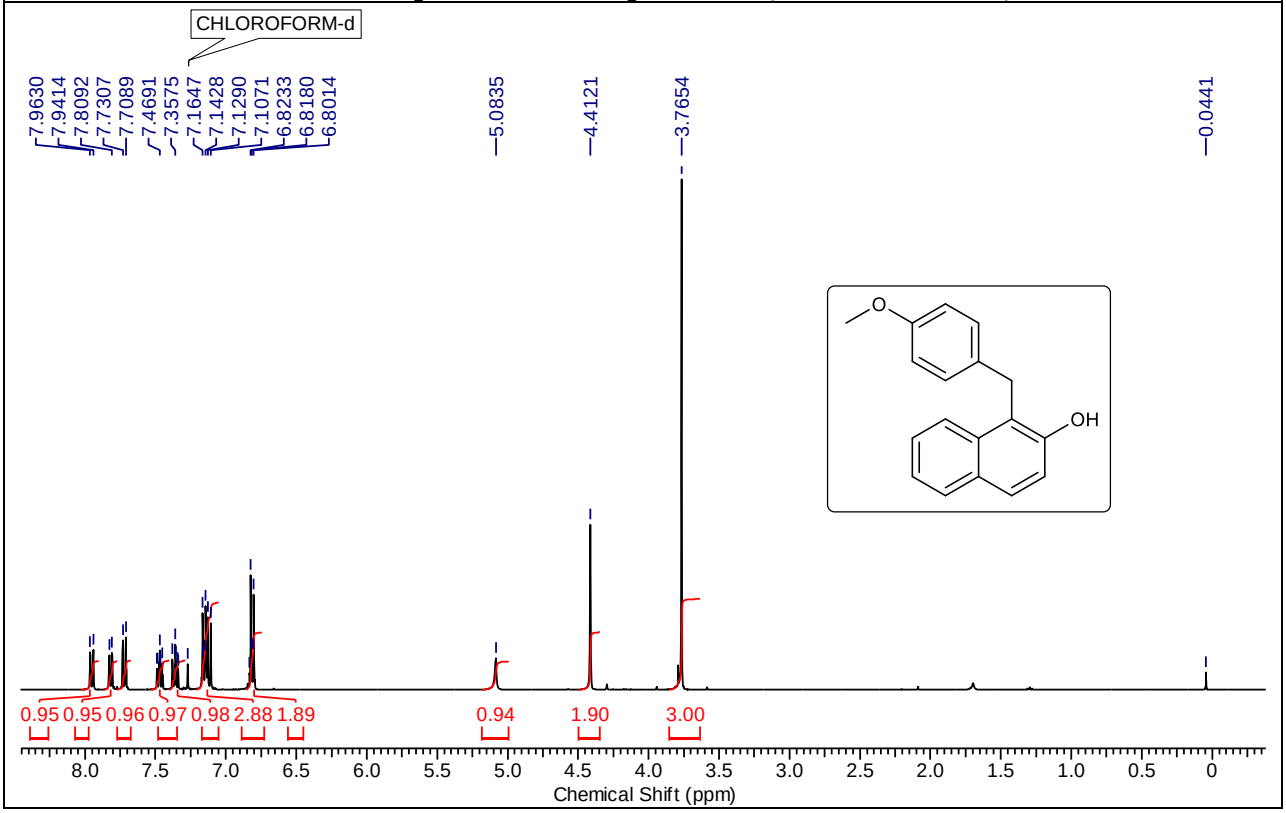
^{13}C-NMR spectrum of compound 9 ($CDCl_3$, 100 MHz)



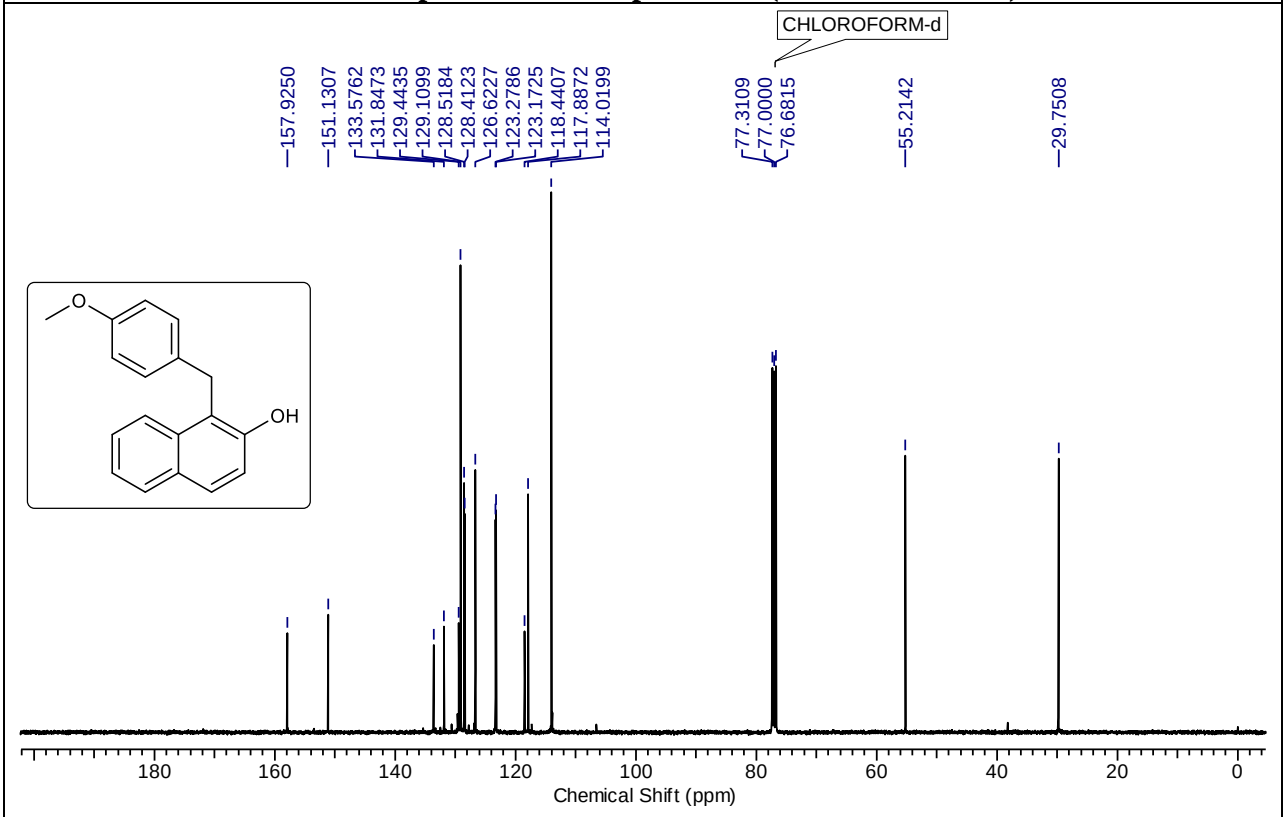
DEPT spectrum of compound 9 ($CDCl_3$, 100 MHz)



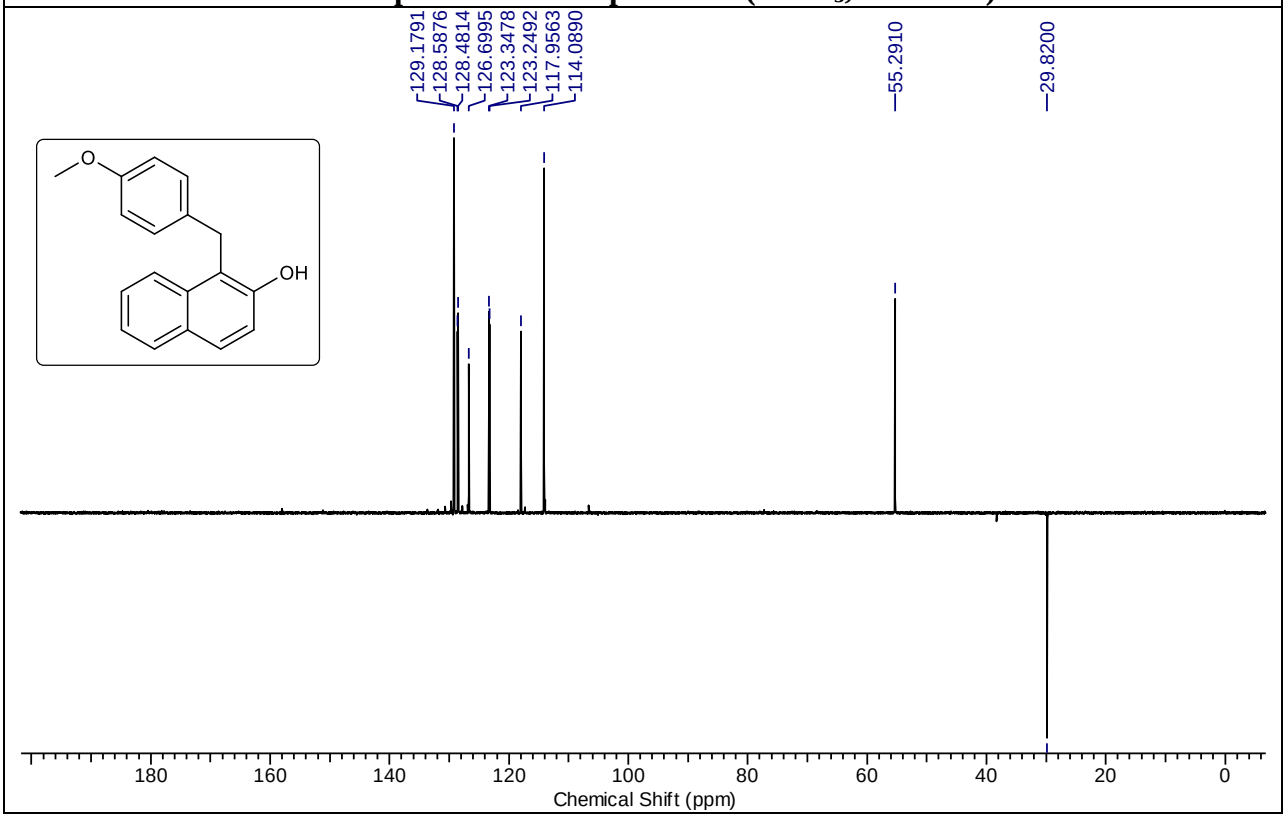
^{1}H-NMR spectrum of compound 10 ($CDCl_3$, 400 MHz)



^{13}C-NMR spectrum of compound 10 ($CDCl_3$, 100 MHz)



DEPT spectrum of compound 10 ($CDCl_3$, 100 MHz)



3.1.11. References:

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Chapter 3, Section II

Solvent free, microwave assisted N-alkylation of amides with PMB/benzyl alcohol by using imidazolium ionic liquid as the green and eco-friendly catalyst.

3.2.1. Introduction:

N-Alkylation of amides has extensive demand in the chemical industry; besides this *N*-alkyl amides have potential importance in organic chemistry as many natural products and drugs contain C-N bond linkage in their core structure.[1-4] There are many reported methods known for the synthesis of the C-N bonds. However, the C-N bond formation by aryl and alkyl halides is one of the conventional methods and for the perspective of green chemistry these methods become less important. So it is very important to develop new methods for the formation of the C-N bonds of the amides by using environment-friendly raw materials in the reaction. Also, it is important to note that alcohols are less toxic, commercially readily available and are cheap. However, the –OH group of an alcohol is a bad leaving group and because of the poor electrophilicity of the alcohols, the harsh reaction conditions are utilized in order to make the reaction work with alcohols. Many metal catalyzed reactions have been employed for the C-N bond formation *i.e. N*-alkylations.[5-8] However, these methods have some drawbacks such as use of metal catalysts is itself an uneconomical process in the organic synthesis and also another drawback is their limited abundance in the nature and harsh reaction conditions.

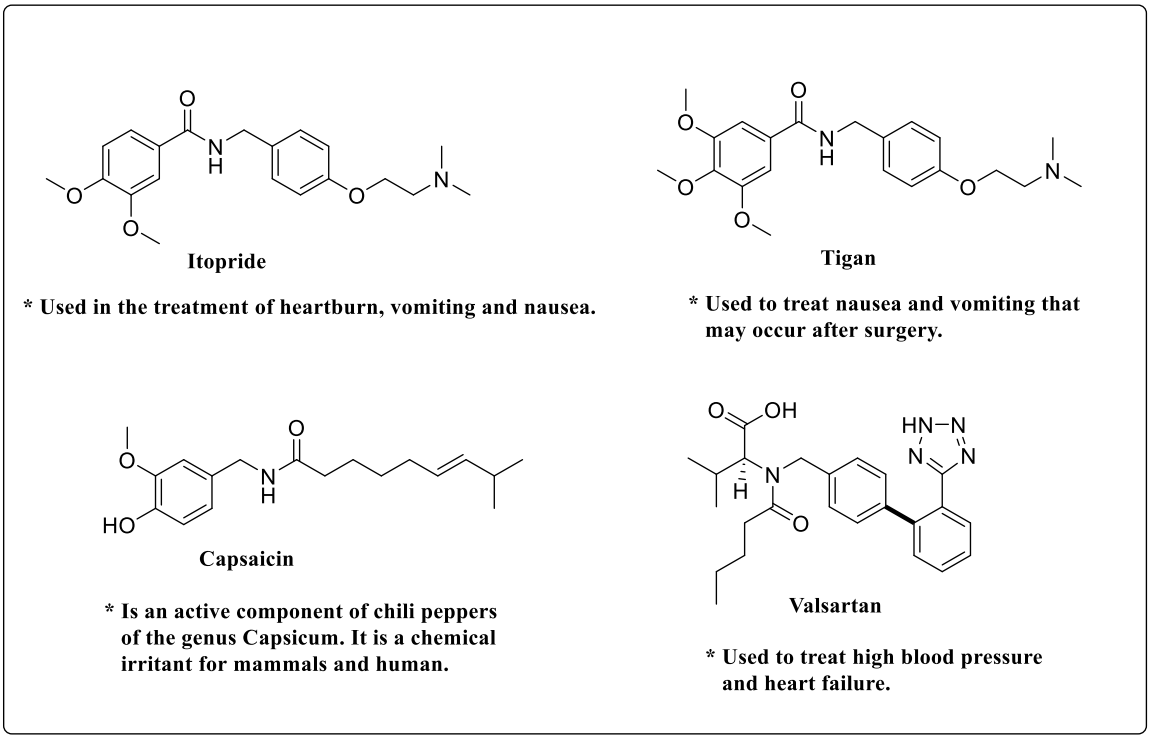


Figure 1: Few important molecules having aryl amide linkage.

Recently, alkylation of amides has been also explored,[9] however, *N*-alkylation of primary amide is restricted due to the less nucleophilicity of amides and large amount of catalysts and higher temperatures are required. In general, the preparation of amides requires the reaction of activated acid chlorides, carboxylic acids and anhydrides or sometimes esters with amines.[10-11] Considering the conventional methods, the straightforward use of an alcohol in the alkylation reaction of an amide is of a great importance as it reduces the cost of the reactions employed in the C-N bond formation and also is environment friendly. Additionally, alcohols are globally abundant and are easily available, but because of the low electrophilicity of alcohols the severe reaction conditions or the more number of the steps are utilized in the synthesis of amides. By considering these facts, it was decided to develop environment-friendly and cost-effective and solvent-free reaction for the making of C-N bonds of the amides. It was thought that ionic liquids (ILs) can be an alternative for this purpose. Nowadays use of ILs in the chemical transformations is growing. This is attributed to their property of non-flammability, non-volatility, highly solvating, non-coordinating and high thermal stability. ILs are used in several catalytic processes.[12-25] Also, the ILs have been used in the C-N bond making reactions. The electrochemical method in the preparation of organic carbamates by using the amines and carbon dioxide was invented by utilization of selective cathodic reduction of the CO_2 gas in CO_2-soaked room-temperature ionic liquid such as BMIm-BF_4 solutions.[26] The recyclable ionic liquid [C_4-DABCO][$N(CN)_2$] has been used in the peptide coupling reaction to develop the new C-N bond.[27] In addition to this, the magnetic nano-Fe_3O_4 supported ionic liquid was used as a phase transfer reactionary for the C-N cross coupling reaction.[28] The DABCO-based ionic liquid catalyst has been used for the Aza- Michael addition reactions by H. L. Hou *et al*.[29] Further, the formation of cyclic urethanes derived from the amino alcohols and carbon dioxide by utilizing ionic liquid catalysts with promoters such as alkali metal is reported by S. Fujata *et al*.[30] More recently, the dimethyl acetal protected benzimidazole 2-carboxaldehydes have been prepared by B. Deb *et al*. by using the task-specific imidazolium ionic liquid (HBIm·TFA) catalyst.[31] However, by going through the literature it was noticed that there is no report for the C-N bond synthesis of amides with PMB/benzyl alcohols by using ionic liquid as the catalyst.

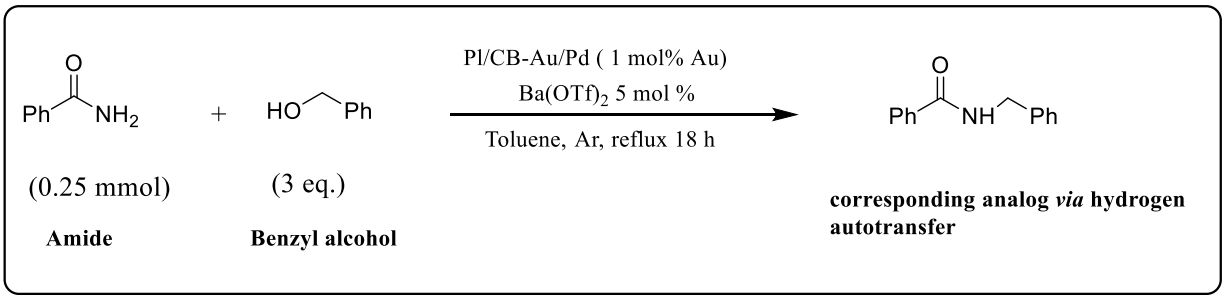
3.2.2. Literature review:

Recently, in the year 2019, Xingchao Dai and Feng Shi have reported a short review on *N*-alkylation of amides by the use of alcohols as the alkylating reagents.[9]

The earliest example of *N*-alkylation of amides by using alcohols as the alkylating compound was reported by Cheeseman and Poller in 1962.[32] Here, the stoichiometric amount of *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) was utilized to carry out the *N*-alkylation of *o*-methoxybenzamide and benzhydrol. Additionally, the reaction mass was heated under reflux conditions to afford 25% of the *N*-benzhydryl-2-methoxybenzamide.

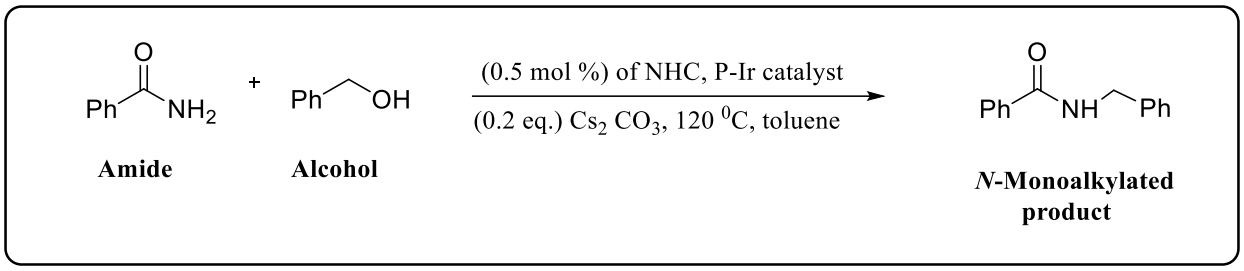
Also, in the year 1996, the catalytic H_2SO_4 was used as the reactionary for the *N*-alkyl amide synthesis and this was reported by Henneuse and co-workers.[33] In this reaction *25 µL* of H_2SO_4 in the solvent acetic acid was utilized at 20 ℃ and the reaction duration was of 18–48 hours. In addition, several amides including primary aromatic and aliphatic amides, lactams and challenging urea reacted with 4,4′-dimethoxybenzhydrol to form the expected *N*-alkylated amides.

Additionally, the use of metal nano-particles and their catalysis has gained much attention in the research.[34] In the year 2015, Kobayashi *et al.* reported a synergetic catalytic system by employing the inactivated Au/Pd nano-particles and the Lewis acids such as $Ca(OTf)_2$/$Ba(OTf)_2$ for the C-N bond making of primary amides with benzyl alcohol analogs *via* hydrogen auto-transfer (**Scheme 1**). Interestingly, it is the first example of a metal nano-particle catalyzed hydrogen auto-transfer operation that employed primary amide substrate.[35]



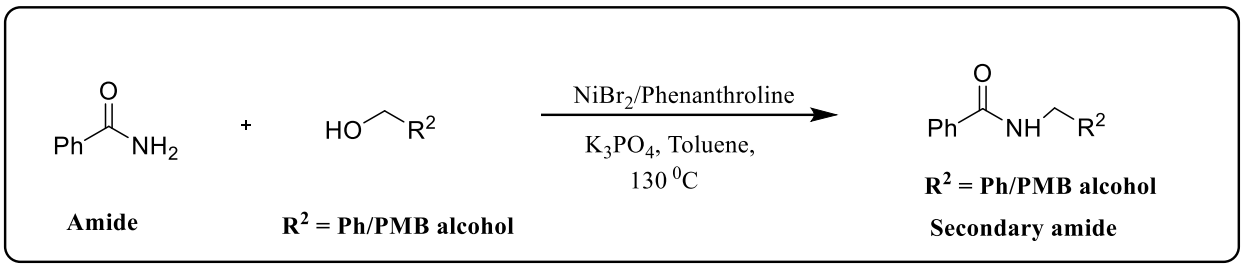
Scheme: 1

In the year 2015, Anderson *et al.* invented a new process for the *N*-monoalkylation of amide with alcohols by means of hydrogen transfer, in which they developed complexes of the *N*-heterocyclic carbene-phosphine iridium. These (NHC-Ir) complexes were found to be very reactive as the catalyst for the preparation of *N*-monoalkyl amides by the use of alcohols. Also, the catalysts developed were successfully employed for the reaction using various substrates with low catalyst loading and shorter duration of reaction resulting in the good yields [36] (**Scheme 2**).



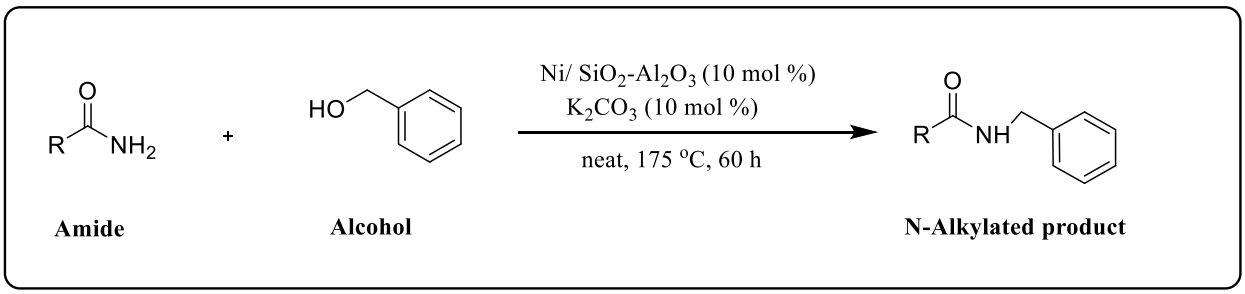
Scheme 2

More recently, in the year 2018, Jagdish Das and Debashish Banerjee reported the nickel-catalyzed phosphine-free reaction for the preparation of *N*-alkyl amides with alcohols.[37] They developed practical and selective nickel promoted formation of secondary amides (**Scheme 3**).



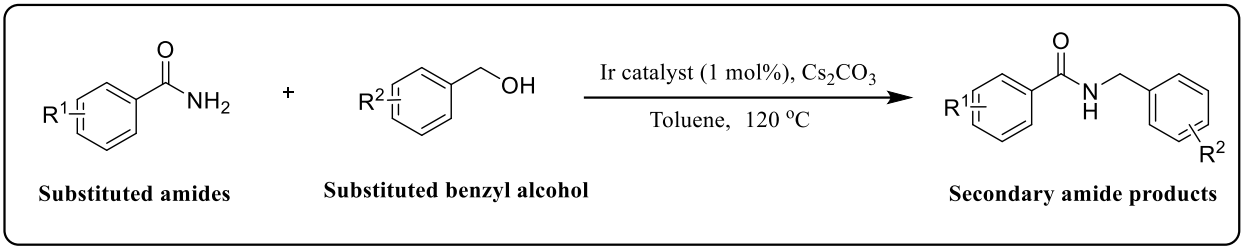
Scheme 3

The solvent-free process for *N*-alkylation of amides with alcohols by the use of nickel on silica-alumina was developed in the year 2019 by Nicolas Duguet *et al*.[38] In this method, the *N*-alkylation of phenylacetamide was carried out by the use of benzyl alcohol and the expected product was produced in an excellent yield. The advantage of this method is neat reaction conditions, surplus use of amide and less quantity of base was used. Additionally, these conditions were used on the various amides and alcohols, to afford the desired compounds. (**Scheme 4**).



Scheme 4

In the year 2020, W. Yao *et al.* synthesized pyridine-oxadiazole iridium complexes and applied these complexes for the C-N bond formation reactions. Here, the prepared iridium complexes disclosed surprisingly very good catalytic reactivity in C -N bond formation of amides and aryl alcohols with the help of non-coordinating anions (**Scheme 5**).[39]



Scheme 5

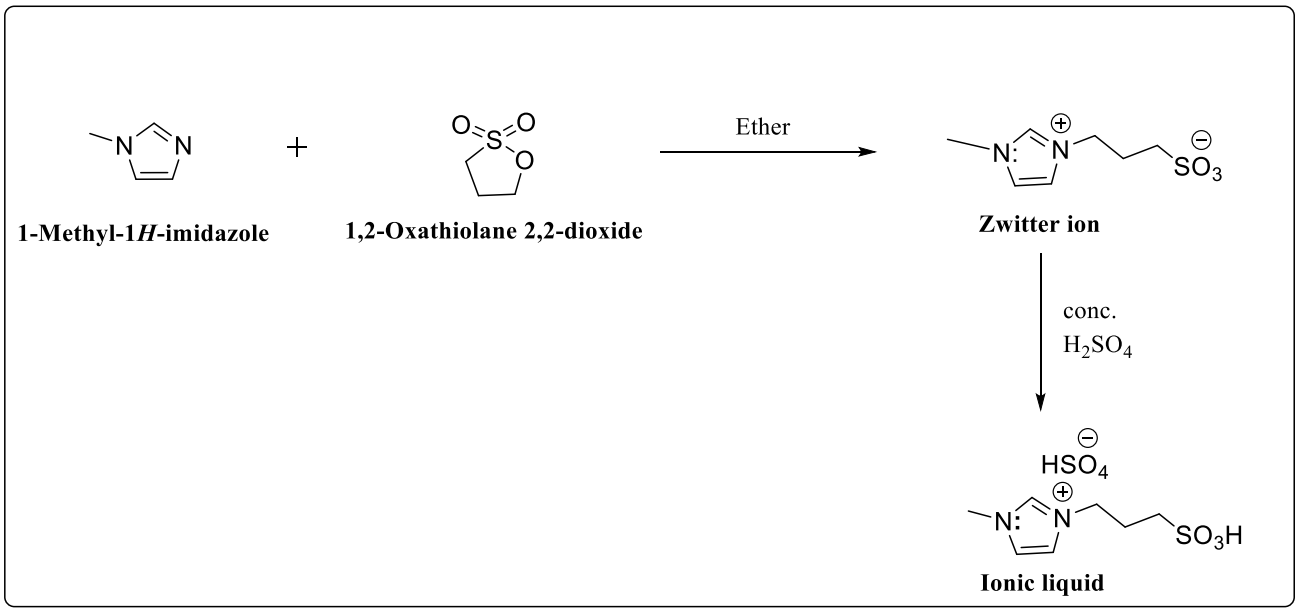
3.2.3. Results and Discussion:

In the present work, microwave assisted ionic liquid catalyzed one-pot *N*-alkylation of PMB alcohol and benzyl alcohol with various amides has been described. When the amide was treated with PMB alcohol or benzyl alcohol in presence of catalytic amount of ionic liquid as a catalyst mono *N*-alkylated product was observed (**Scheme 7**). This led to the screening of the different amide substrates; interestingly it worked well with almost all amides except sulphonamide.

Further, the literature search revealed that there is no report for the N-PMB/benzyl alcohol alkylation of amides by using ionic liquid as the catalyst.

Synthesis of Ionic Liquid:

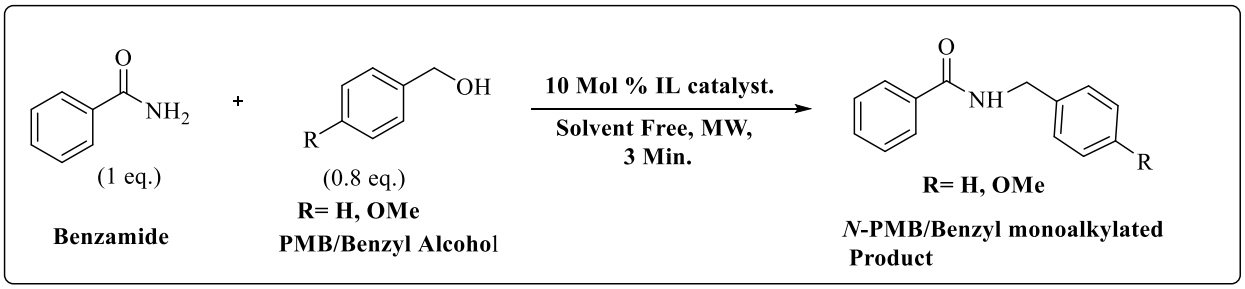
Ionic liquid catalyst was prepared by the literature procedure.[40] 1-Methylimidazole on the reaction with 1,3 -propanesultone gave white zwitter ion solid intermediate, which was found to be moisture sensitive and can be turned to liquid when exposed to air. Hence, this solid obtained was immediately reacted with stoichiometric amount of conc. sulphuric acid to give viscous clear liquid. Both steps in the synthesis were quantitative in yields (**Scheme 6**).



Scheme 6: Synthesis of Ionic Liquid

Optimization of the Reaction Conditions:

The initial reaction was carried out on bezamide (1 eq.) as a model substrate with PMB alcohol (1 eq.) by using 20 mol % ionic liquid as a catalyst in the microwave, the reaction worked but this was leading to mixture of *mono* and *di N*-PMB alkylated products. Further the different parameters (mol % of the catalyst and also of the reactants and the time of the reaction *etc*.) were changed to optimize the reaction conditions for *N*-monoalkylation of amides. After successful optimization of the reaction conditions (**Scheme 7**), the attention was turned to examine the scope of this reaction. Interestingly, this reaction worked on the various amides, lactams and pyrrolidones in good yields.



Scheme 7: N-PMB/Benzyl alkylation of amide

3.2.4. The Proposed Reaction Mechanism:

The reaction mechanism for the *N*-alkylation of amide by using *N*-methyl imidazoliun IL catalyst is shown below (**Figure 2)**. It is assumed that the below shown mechanism is a plausible mechanism. In the first step, the hydroxyl group of a PMB alcohol gets protonated and then forms methyl (4-methylenecyclohexa-2,5-dien-1-ylidene)oxonium ion by elimination of a water molecule. In the very next step, the amide nitrogen atom attacks the methyl (4-methylenecyclohexa-2,5-dien-1-ylidene)oxonium ion and subsequently one of the hydrogen atom attached to nitrogen atom gets deprotonated resulting in the formation of the secondary amide as the reaction product. Also, it is believed that the same sequence of mechanism is followed for the benzyl alcohol reaction with amide in presence of IL catalyst. In the case of benzyl alcohol the resulting benzyl cation (4-methylenecyclohexa-2,5-dien-1-ylium) is resonance stabilized. Hence, the attack of nucleophilic amide takes place on the benzyl cation giving the secondary amide product.

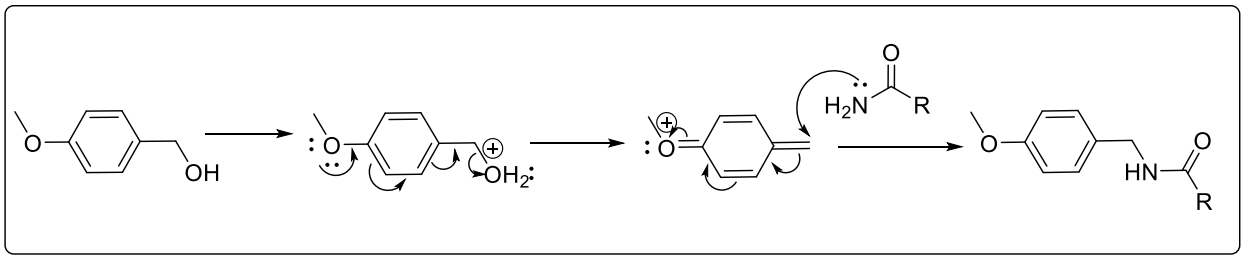
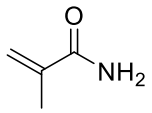
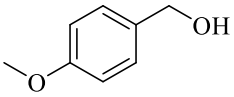
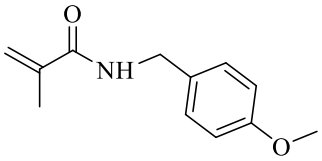
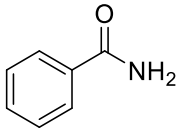
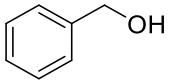
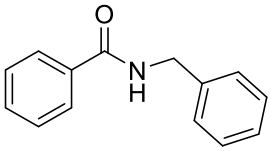
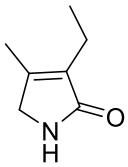
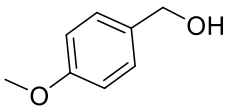
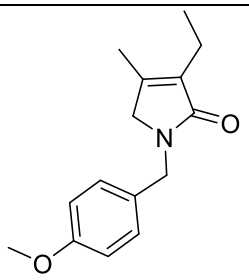
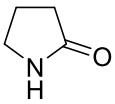
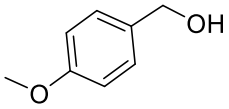
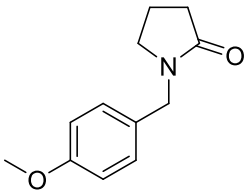
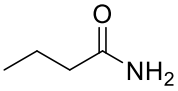
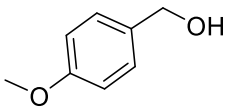
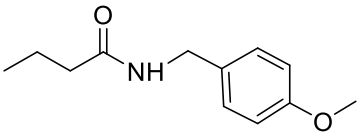
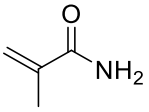
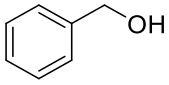
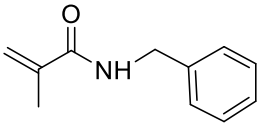


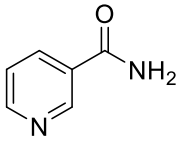
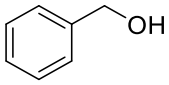
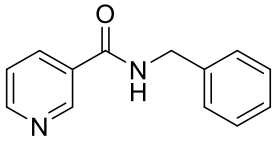
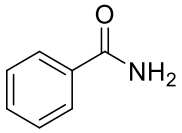
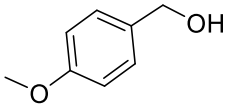
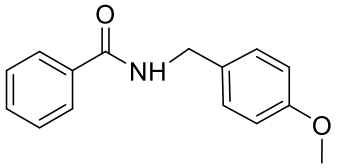
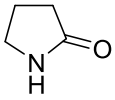
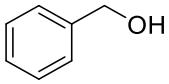
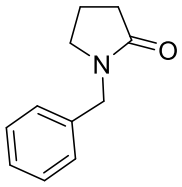
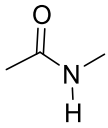
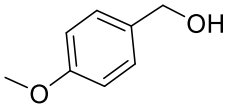
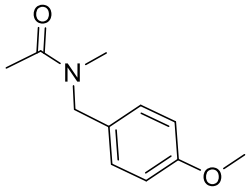
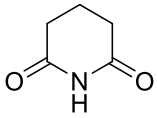
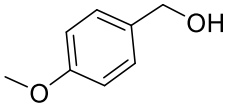
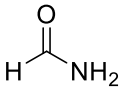
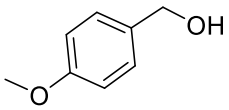
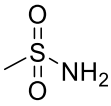
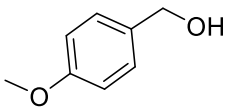
Figure 2

3.2.5. Substrate scope of the reaction:

We observed that by using this IL catalysed microwave assisted methodology, a variety of amides can be *N*-PMB/benzyl alkylated. The reaction is facile with both aliphatic and aromatic amides. The secondary and the tertiary *N*-PMB/ benzyl amide can be synthesized by using this methodology. Successful application of this methodology on different substrates is shown below (**Table 1)**. The *N*-PMB/benzyl alkylation of the double bond containing methacrylamide and 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one was successfully achieved and the double bonds in the both the substrates remained unaffected and intact. Additionally, the cyclic amide substrate pyrrolidin-2-one was also *N*-PMB alkylated. However, when the same reaction was tried on piperidine-2, 6-dione, formamide, methanesulfonamide and tert-butyl carbamate, the reaction did not work and the starting materials were recovered.

Substrate Scope of the Reaction: Table 1

Entry	Amide	PMB/Benzyl alcohol	*N*-PMB/ Benzyl alkylated product	% Yield	Reaction Time (in minutes)
1.				**75**	**3**
2.				**63**	**3**
3.				**82**	**3**
4.				**78**	**3**
5.				**72**	**3**
6.				**66**	**3**

7.				**68**	**3**
8.				**72**	**3**
9.				**64**	**3**
10.				**91**	**3**
11.			No reaction	-	**4**
12.			No reaction	-	**3**
13.			No reaction	-	**3**

3.2.6. Conclusion:

In conclusion, a novel one-pot, solvent-free microwave-assisted synthetic route having short reaction time for the *N*- alkylation of PMB/benzyl alcohol has been developed by using ionic liquid as the catalyst. The yields of the reactions were moderate to good. It is believed that the present methodology would be useful to synthetic organic chemists.

3.2.7. Experimental:

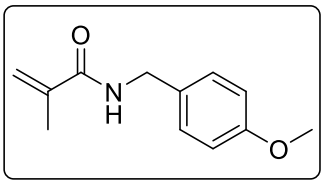
General procedure for *N*- PMB/benzyl alcohol alkylation of amides:

Ionic liquid (0.1 eq.), PMB/benzyl alcohol (0.8 eq.) and amide (1 eq.) were taken in a glass vial and resulting vial containing these three compounds was kept in a LG microwave (LG: MC-808WAR) and heated for 3 minutes. The resulting reaction mass was diluted with ethyl acetate and poured into the separating funnel containing water. The organic layer was extracted by adding more ethyl acetate and dried over sodium sulphate (anhydrous Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel) using petroleum ether/ethyl acetate to furnish the *N*-PMB/benzyl alkylated product (**Table 1**).

3.2.8. Spectral Data:

***N*-(4-Methoxybenzyl) methacrylamide (1):**

Viscous colorless liquid.



^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.98 (s, 3H), 3.80 (s, 3H), 4.44 (d, J = 5.34 Hz, 2H), 5.34 (s, 1H), 5.71 (s, 1H), 6.05 (br s, 1H), 6.88 (d, *J* = 8.39 Hz, 2H), 7.24 (d, *J* = 8.39 Hz, 2H).

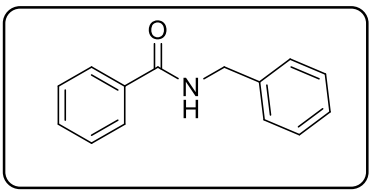
^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.69, 43.25, 55.28, 114.10 (2C), 119.58, 129.22 (2C), 130.26, 139.93, 159.05, 168.15.

IR ($CHCl_3$): ν_{max} 3452, 3014, 2404, 1664, 1217, 769 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{12}H_{16}NO_2$ $[M + H]^+$ **:** 206.1176, found: 206**.**1175.

***N*-Benzylbenzamide (2)[41a]:**

White solid**,** M. P. = 104-105 ^oC **(** lit.[41b] M. P. = 105 ^oC**).**



^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.61 (d, *J* = 6.10 Hz, 2H), 6.64 (br s, 1 H), 7.20 - 7.35 (m, 5H), 7.39 (t, *J*=7.63 Hz, 2 H), 7.43 - 7.51 (m, 1H), 7.72 - 7.81 (m, 2H).

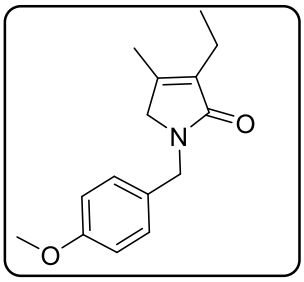
^{13}C NMR ($CDCl_3$, 100 MHz): δ 43.71, 126.62 (2C), 127.19, 127.50 (2C), 128.18 (2C), 128.37 (2C), 131.15, 133.99, 137.85, 167.04.

IR ($CHCl_3$): ν_{max} 3732, 3021, 2402, 1660, 1216, 766 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{14}H_{14}NO$ $[M + H]^+$: 212.1070, found: 212.1070.

3-Ethyl-1-(4-methoxybenzyl)-4-methyl-1, 5-dihydro-2*H*-pyrrol-2-one (3)[42]:

Yellow solid**,** M. P. **=** 128 ºC**.**



^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.06 (t, *J* = 7.57 Hz, 3H), 1.89 (s, 3H), 2.27 (q, *J* = 7.55 Hz, 2H), 3.56 (s, 2H), 3.75 (s, 3H), 4.51 (s, 2H), 6.88 (d, *J* = 8.76 Hz, 2H), 7.14 (d, *J* = 8.63 Hz, 2H).

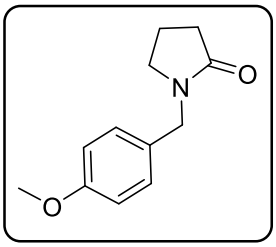
^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.94, 13.30, 17.20, 45.53, 53.66, 55.41, 114.16 (2C), 129.54 (2C), 129.99, 134.37, 145.61, 159.10, 172.34.

IR ($CHCl_3$): ν_{max} 3008, 2406, 1668, 1217, 762 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{15}H_{20}NO_2$ $[M + H]^+$: 246.1494, found: 246.1483.

1-(4-Methoxybenzyl)pyrrolidin-2-one (4)[43]:

Brown liquid.



^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.97 (quint, *J* = 7.70 Hz, 2H), 2.42 (t, *J* = 8.13 Hz, 2H), 3.24 (t, *J* = 7.13 Hz, 2H), 3.79 (s, 3H), 4.38 (s, 2H), 6.85 (d, *J* = 8.75 Hz, 2H), 7.17 (d, *J* = 8.75 Hz, 2H).

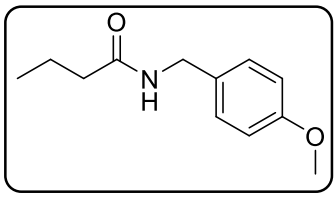
^{13}C NMR ($CDCl_3$, 100 MHz): δ 17.95, 31.30, 46.23, 46.75, 55.54, 114.28 (2C), 128.95, 129.75 (2C), 159.31, 175.07.

IR ($CHCl_3$): ν_{max} 3017, 2403, 1614, 1294, 764 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{12}H_{16}NO_2$ $[M + H]^+$: 206.1181, found: 206.1177.

***N*-(4-Methoxybenzyl)butyramide (5)[44]:**

White solid, M. P. = 88-90 ºC.



^{1}H NMR (CDCl$_3$, 400 MHz): δ 0.96 (t, *J* = 7.38 Hz, 3H), 1.57 - 1.77 (m, 4H), 2.18 (t, *J* = 7.50 Hz, 2H), 3.81 (s, 3H), 4.38 (d, *J* = 5.50 Hz, 2H), 5.65 (br s, 1H), 6.87 (d, *J* = 8.75 Hz, 2H), 7.21 (d, *J* = 8.75 Hz, 2H).

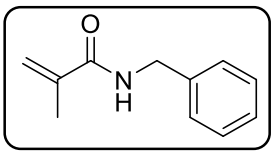
^{13}C NMR (CDCl$_3$, 100 MHz): δ 14.09, 19.48, 39.04, 43.38, 55.62, 114.41 (2C), 129.50 (2C), 130.82, 159.35, 173.01.

IR (CHCl$_3$): ν_{max} 3444, 3009, 2312, 1650, 1247, 759 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{12}H_{18}NO_2$ $[M + H]^+$: 208.1337, found: 208.1334.

***N*-Benzylmethacrylamide (6)[45]:**

Colorless needles, M. P. = 83-84 ºC (lit.[45] M. P. = 82-83 ºC).



^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.97 (s, 3H), 4.49 (d, *J* = 6.10 Hz, 2H), 5.33 (s, 1H), 5.70 (s, 1H), 6.10 (br s, 1H), 7.13 - 7.43 (m, 5H).

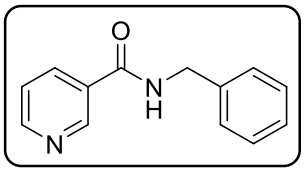
^{13}C NMR (CDCl$_3$, 100 MHz): δ 19.00, 44.07, 119.99, 127.86, 128.14 (2C), 129.04 (2C), 138.50, 140.21, 168.56.

IR (CHCl$_3$): ν_{max} 3416, 1632, 1217, 768 cm^{-1} **.**

HRMS (ESI): *m/z* calcd for $C_{11}H_{14}NO$ $[M + H]^+$: 176.1070, found: 176.1069.

***N*-Benzylnicotinamide (7)[41a]:**

White solid, M. P. = 72-73 ºC (lit. [41c] M. P. = 120 -130 ºC).



^{1}H NMR (CDCl$_3$, 400 MHz): δ 4.66 (d, *J* = 5.34 Hz, 2H), 6.65 (br s, 1H), 7.28 - 7.42 (m, 6 H), 8.15 (dt, *J* = 8.01, 1.72 Hz, 1H), 8.71 (dd, *J* = 4.58, 1.53 Hz, 1H), 8.97 (bs, 1H).

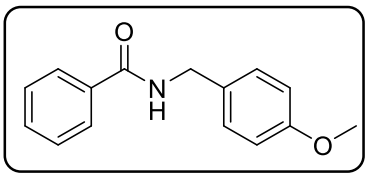
^{13}C NMR (CDCl$_3$, 100 MHz): δ 44.53, 123.86, 128.13, 128.29 (2C), 129.18 (2C), 130.39, 135.55, 137.99, 148.10, 152.56, 165.74.

IR (CHCl$_3$): ν_{max} 3687, 3022, 2402, 1670, 1215, 767 cm^{-1}**.**

HRMS (ESI): *m/z* calcd for $C_{13}H_{13}N_2O$ $[M + H]^+$: 213.1022, found: 213.1022.

***N*-(4-Methoxybenzyl) benzamide (8)**[41a]**:**

White solid, M. P. = 94-95 °C (lit. [41c] M. P. = 92-95 °C).



^{1}H NMR (CDCl$_3$, 400 MHz): δ 3.81 (s, 3H), 4.59 (d, *J* = 5.50 Hz, 2H), 6.36 (br s, 1H), 6.90 (d, J = 8.63 Hz, 2H), 7.30 (d, *J* = 8.50 Hz, 2H), 7.40 - 7.47 (m, 2H), 7.47 - 7.53 (m, 1H), 7.76 - 7.81 (m, 2H).

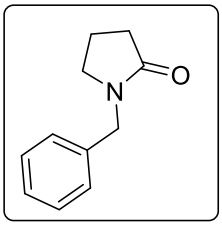
^{13}C NMR (CDCl$_3$, 100 MHz): δ 43.64, 55.31, 114.15 (2C), 126.90 (2C), 128.57 (2C), 129.32 (2C), 130.19, 131.50, 134.42, 159.12, 167.23.

IR (CHCl$_3$): ν_{max} 3444, 3015, 2386, 1648, 1217, 760 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{13}H_{12}NO$ $[M + H]^+$ **:** 242.1181, found: 242.1179.

1-Benzylpyrrolidin-2-one (9)[43]**:**

Yellowish oil.



^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.99 (quint, *J* = 7.75 Hz, 2H), 2.57 (t, *J* = 8.25 Hz, 2H), 3.56 (t, *J* = 7.13 Hz, 2H), 4.57 (s, 2H), 7.29 - 7.57 (m, 5H).

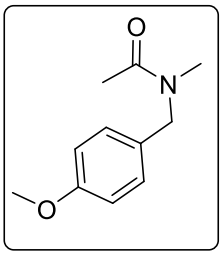
^{13}C NMR (CDCl$_3$, 100 MHz): δ 17.34, 30.55, 46.21, 46.23, 127.15 (2C), 127.73 (2C), 128.28, 136.16, 174.63.

IR (CHCl$_3$): ν_{max} 3017, 1673, 1216, 764 cm^{-1}.

HRMS (ESI): *m/z* calcd for $C_{11}H_{14}NO$ $[M + H]^+$ **:** 176.1075, found: 176.1068.

***N*-(4-Methoxybenzyl)-*N*-methylacetamide (10)**[46]**:**

Colorless oil.



^{1}H NMR (CDCl$_3$, 400 MHz): δ 22.14 (s) & 2.16 (s, 3H combined), 2.90 (s) & 2.91 (s, 3H combined), 3.80 (s) & 3.81 (s, 3H combined), 4.46 (s) & 4.51 (s, 2H combined), 6.86 (d, *J* = 8.63 Hz) & 6.90 (d, *J* = 8.75 Hz, 2H combined), 7.10 (d, *J* = 8.76 Hz) & 7.19 (d, *J* = 8.76 Hz, 2H combined). The doubling of the peaks is due to rotamers.

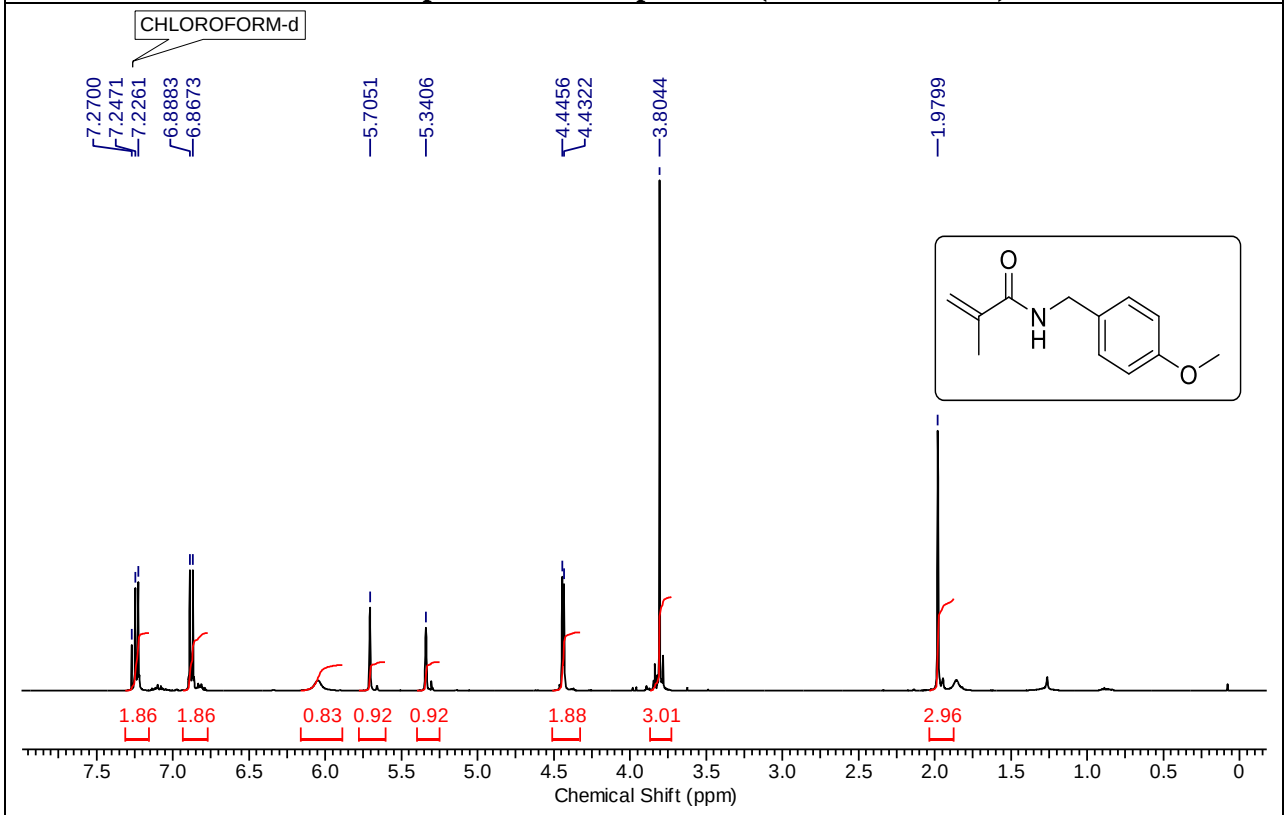
^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.44 & 21.86, 33.45 & 35.27, 49.92 & 53.68, 55.24 & 55.30, 113.92 & 114.29 (2C), 127.61 & 128.43 (2C), 129.40 & 129.49, 158.92 &159.11, 170.58 & 170.87.

IR ($CHCl_3$): ν_{max} 3019, 1631, 1216, 761 cm^{-1}.

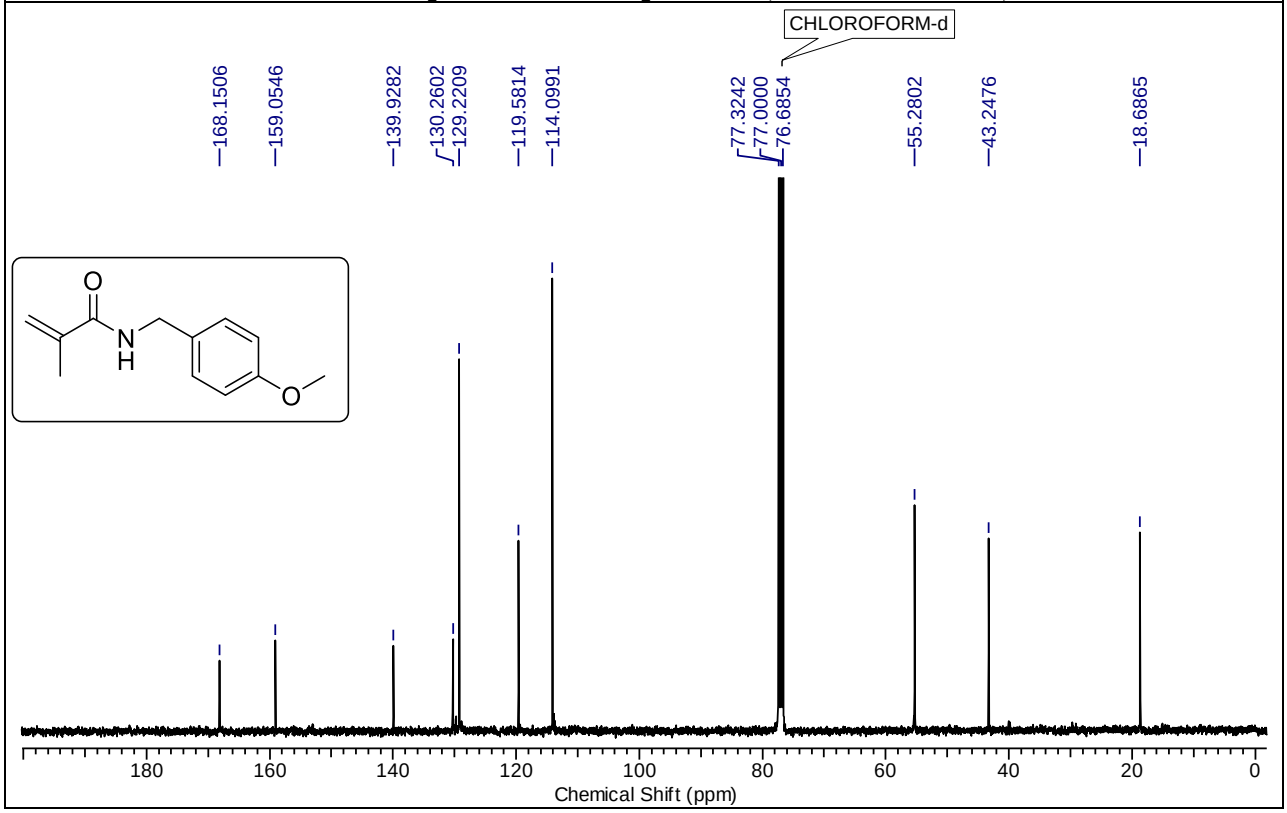
HRMS (ESI): *m/z* calcd for $C_{11}H_{16}NO_2$ $[M + H]^+$ **:** 194.1181, found: 194.1175.

3.2.9. NMR Spectra:

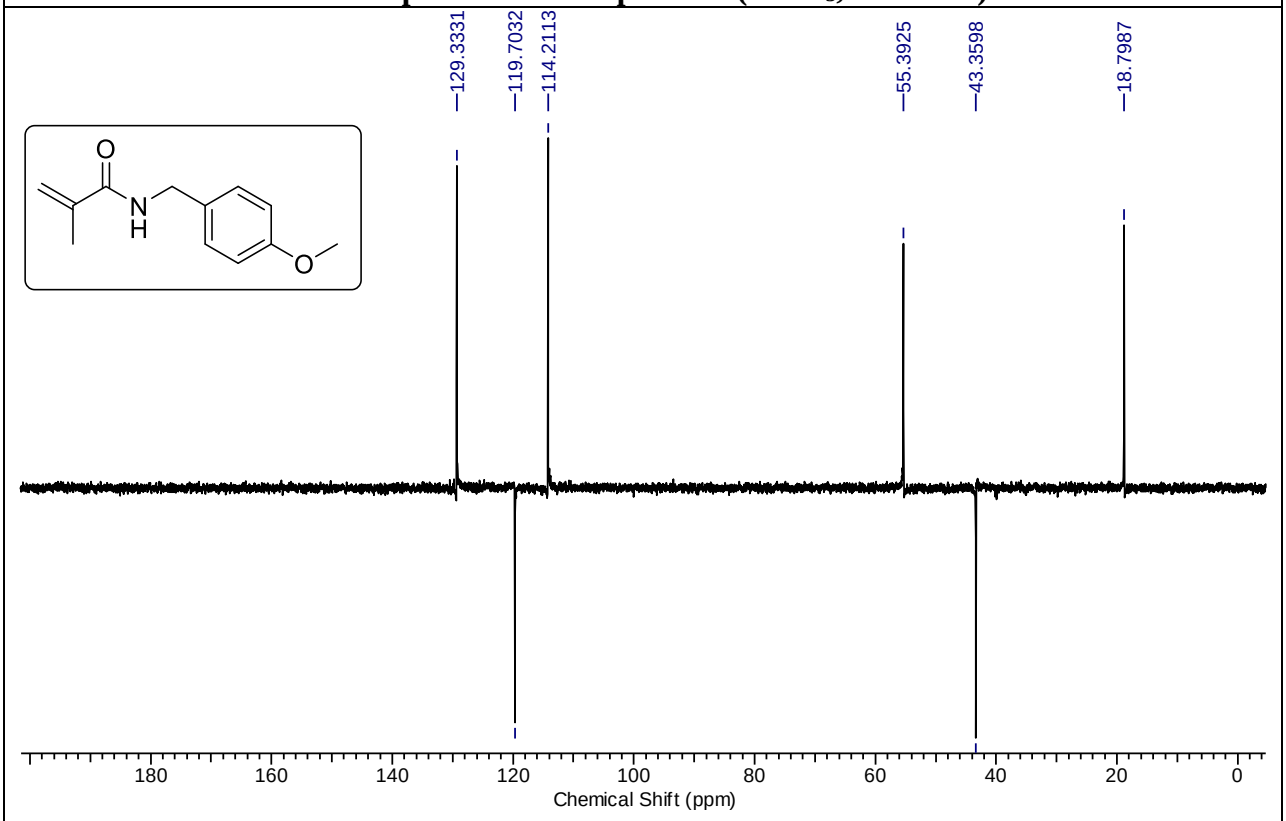
^{1}H-NMR spectrum of compound 1 ($CDCl_3$, 400 MHz)



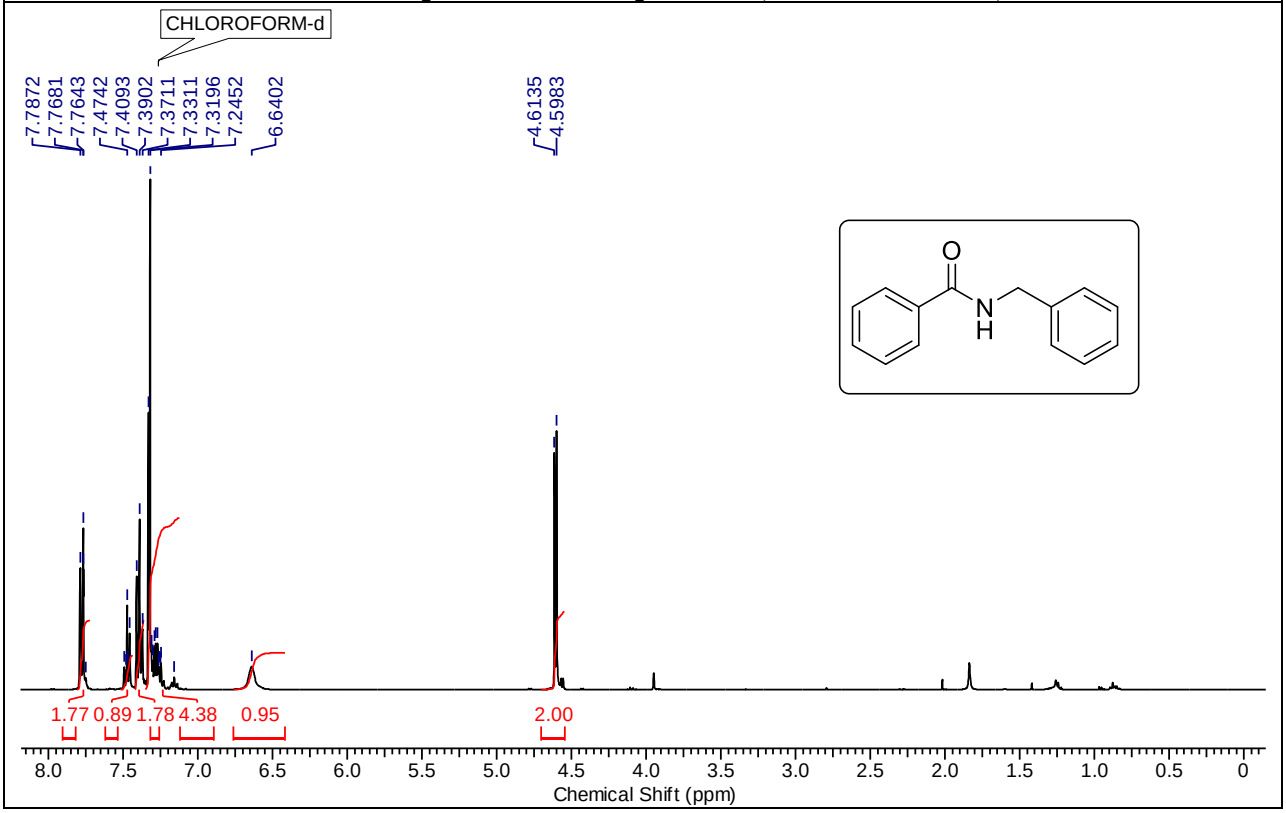
^{13}C-NMR spectrum of compound 1 ($CDCl_3$, 100 MHz)



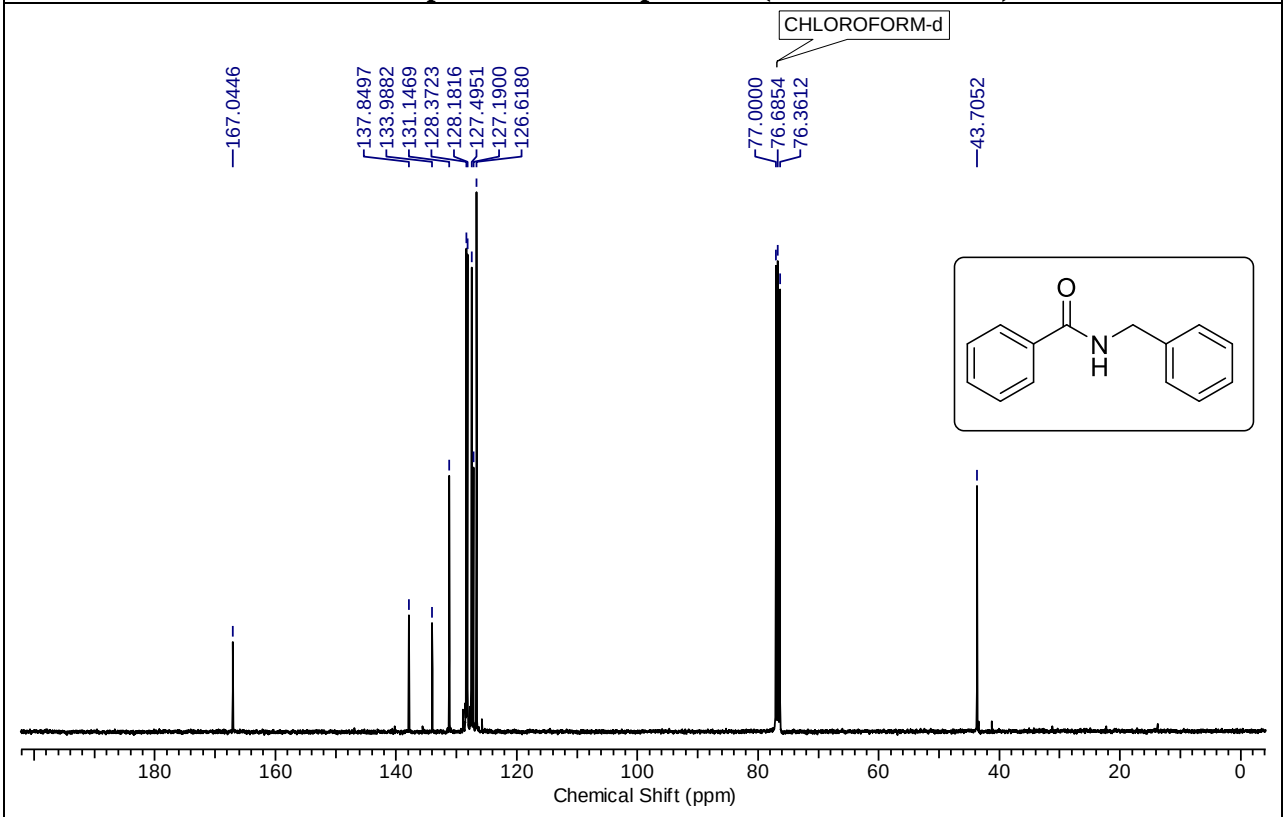
DEPT spectrum of compound 1 ($CDCl_3$, 100 MHz)



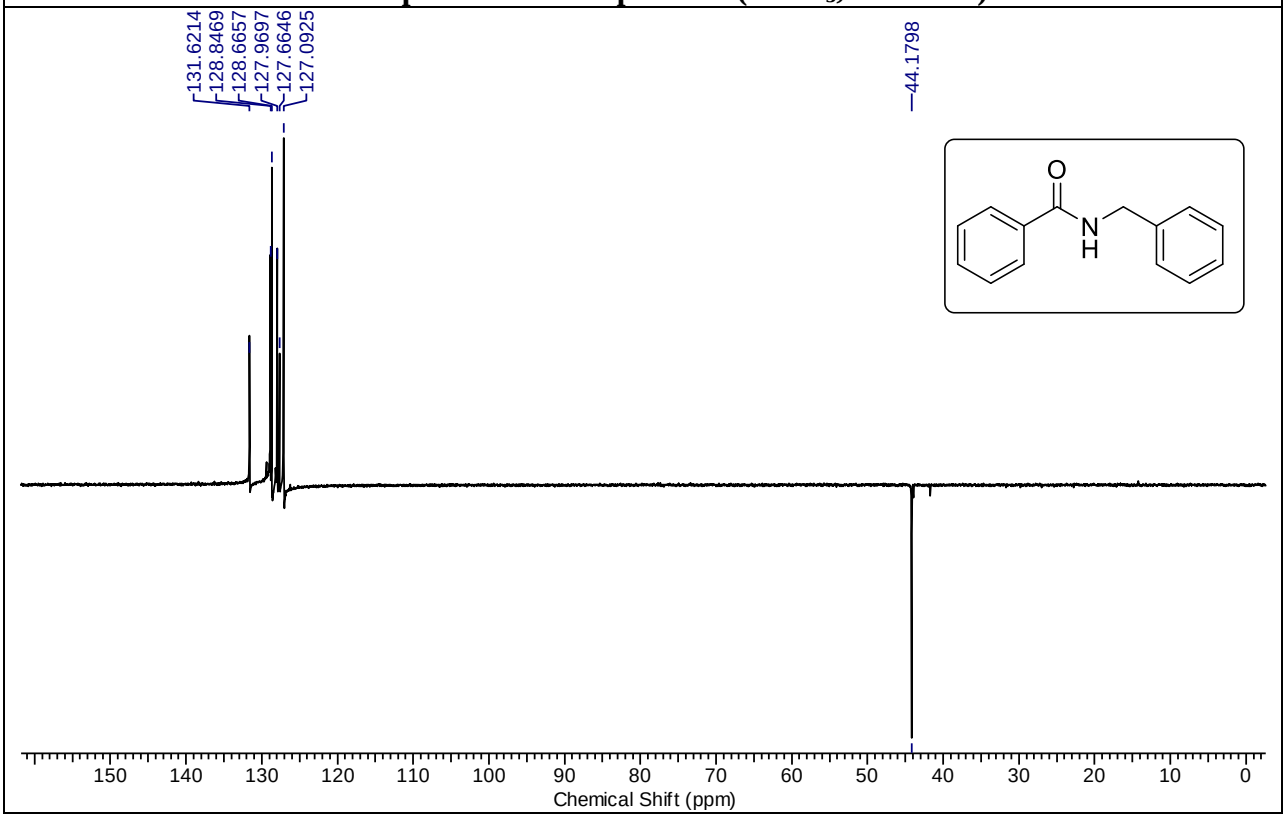
^{1}H-NMR spectrum of compound 2 ($CDCl_3$, 400 MHz)



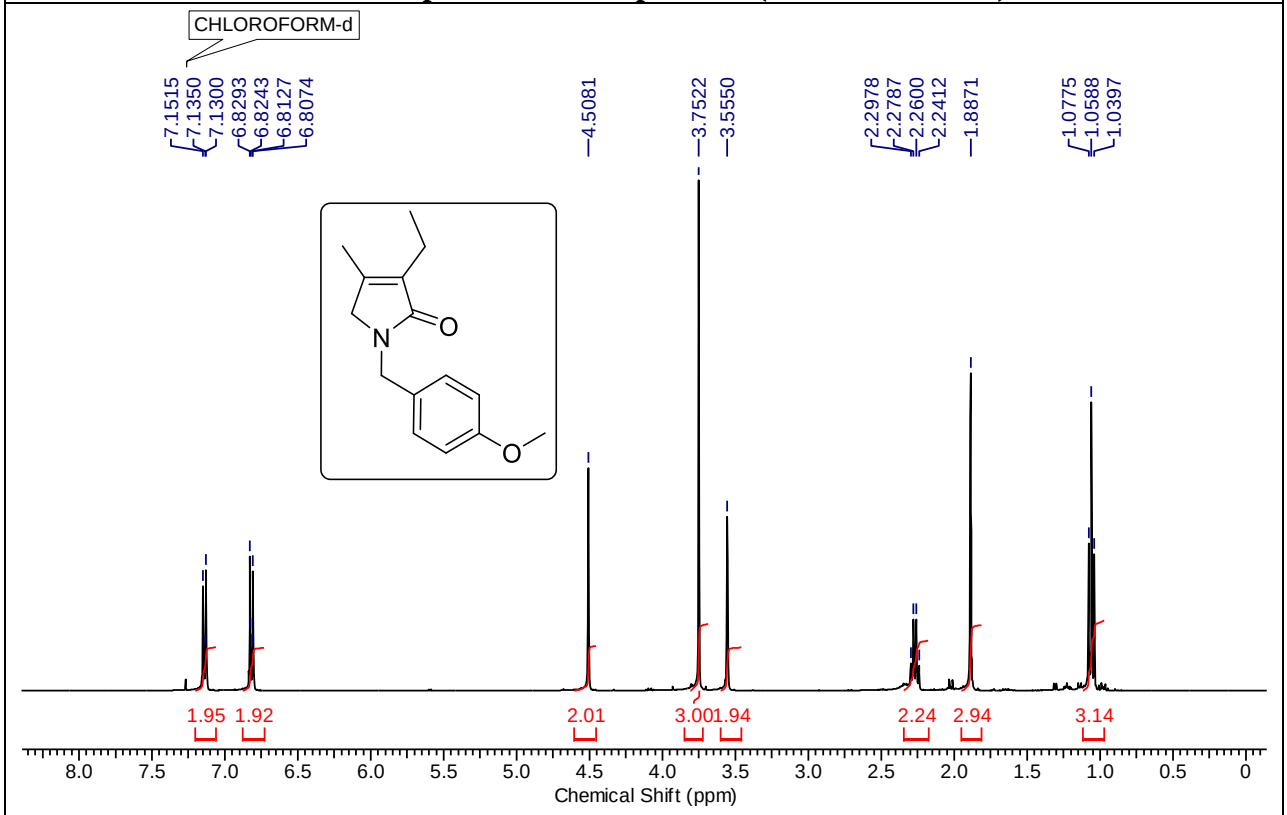
^{13}C-NMR spectrum of compound 2 ($CDCl_3$, 100 MHz)



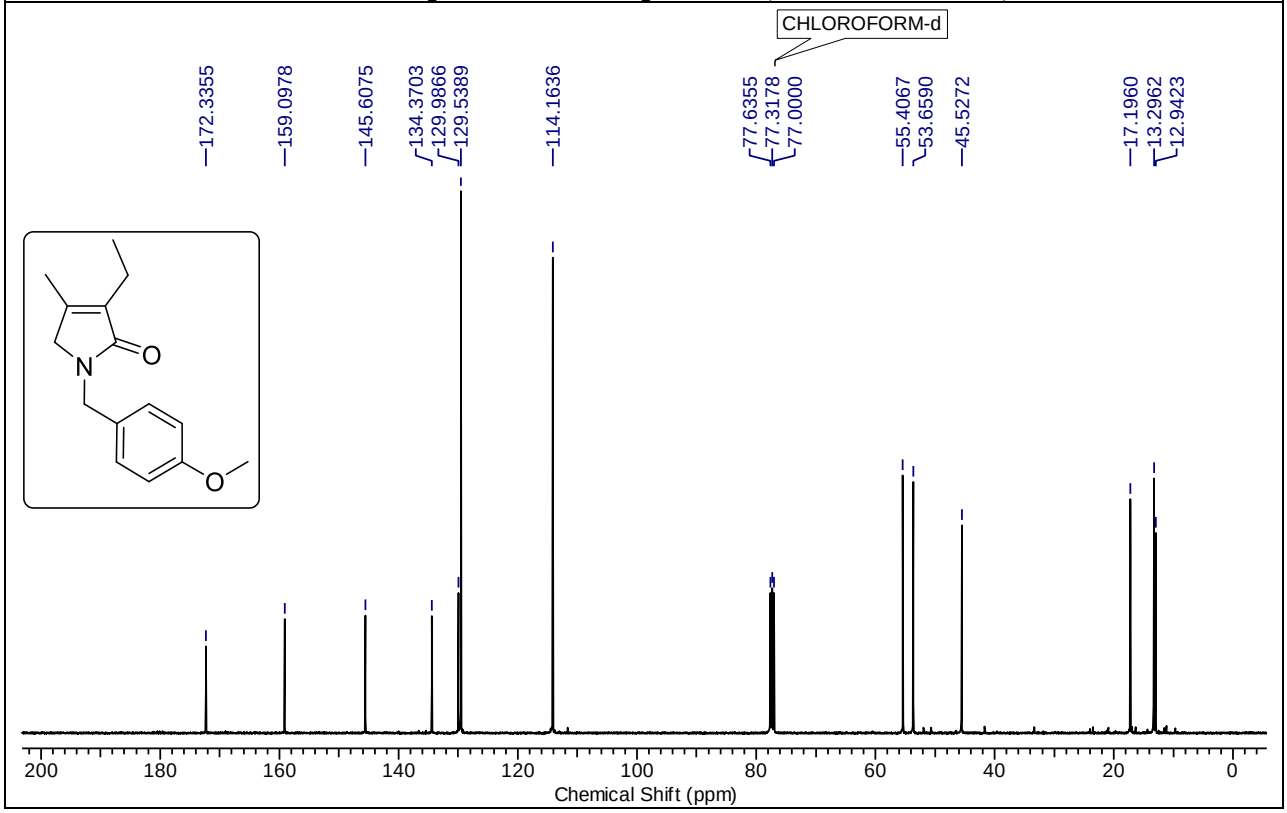
DEPT spectrum of compound 2 ($CDCl_3$, 100 MHz)



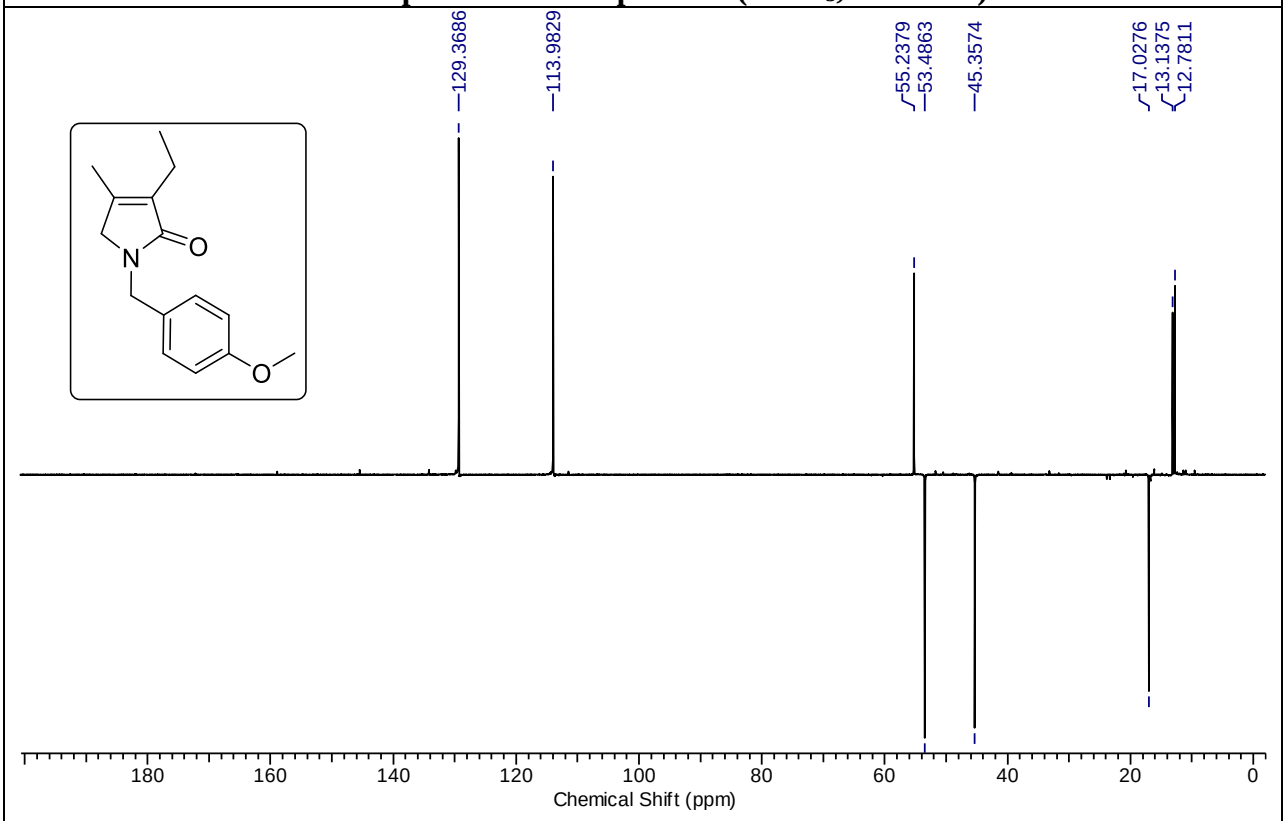
^{1}H-NMR spectrum of compound 3 ($CDCl_3$, 400 MHz)



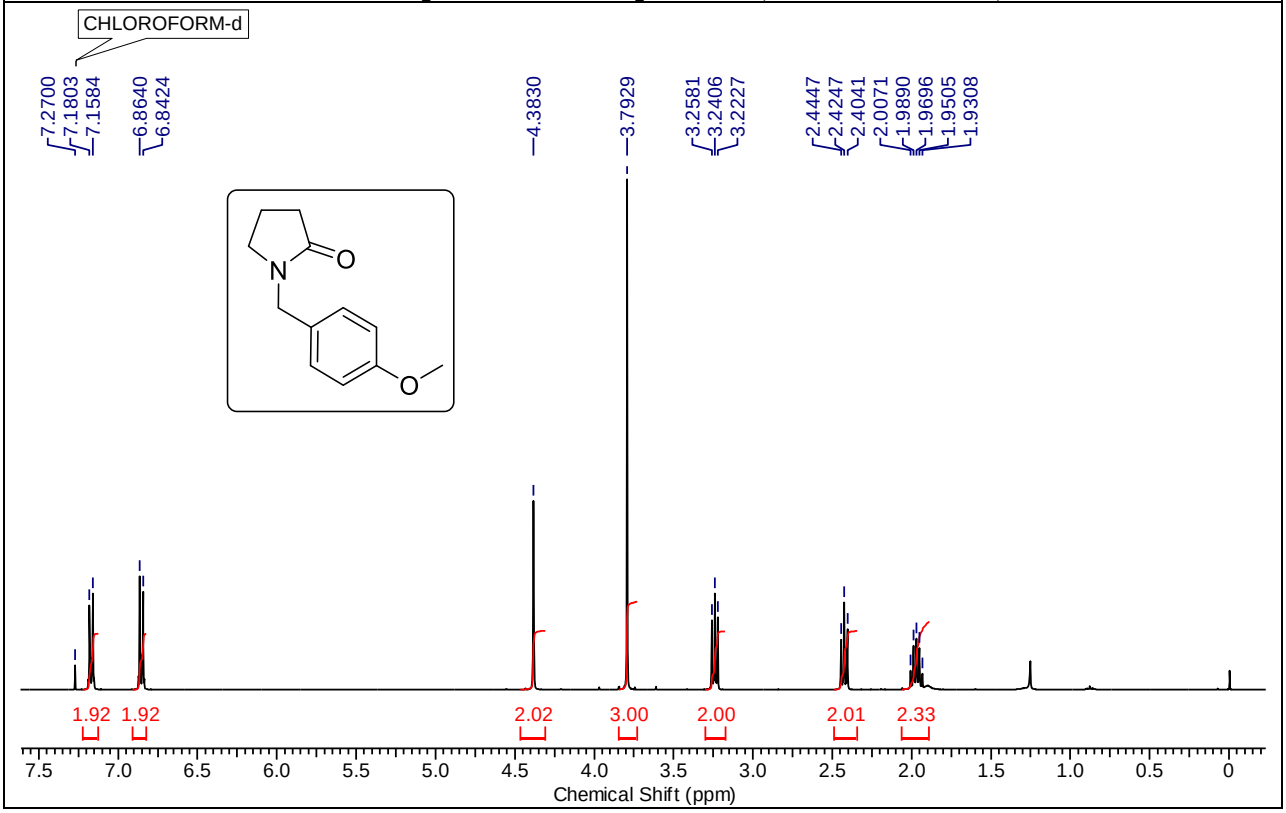
^{13}C-NMR spectrum of compound 3 ($CDCl_3$, 100 MHz)



DEPT spectrum of compound 3 ($CDCl_3$, 100 MHz)



^{1}H-NMR spectrum of compound 4 ($CDCl_3$, 400 MHz)



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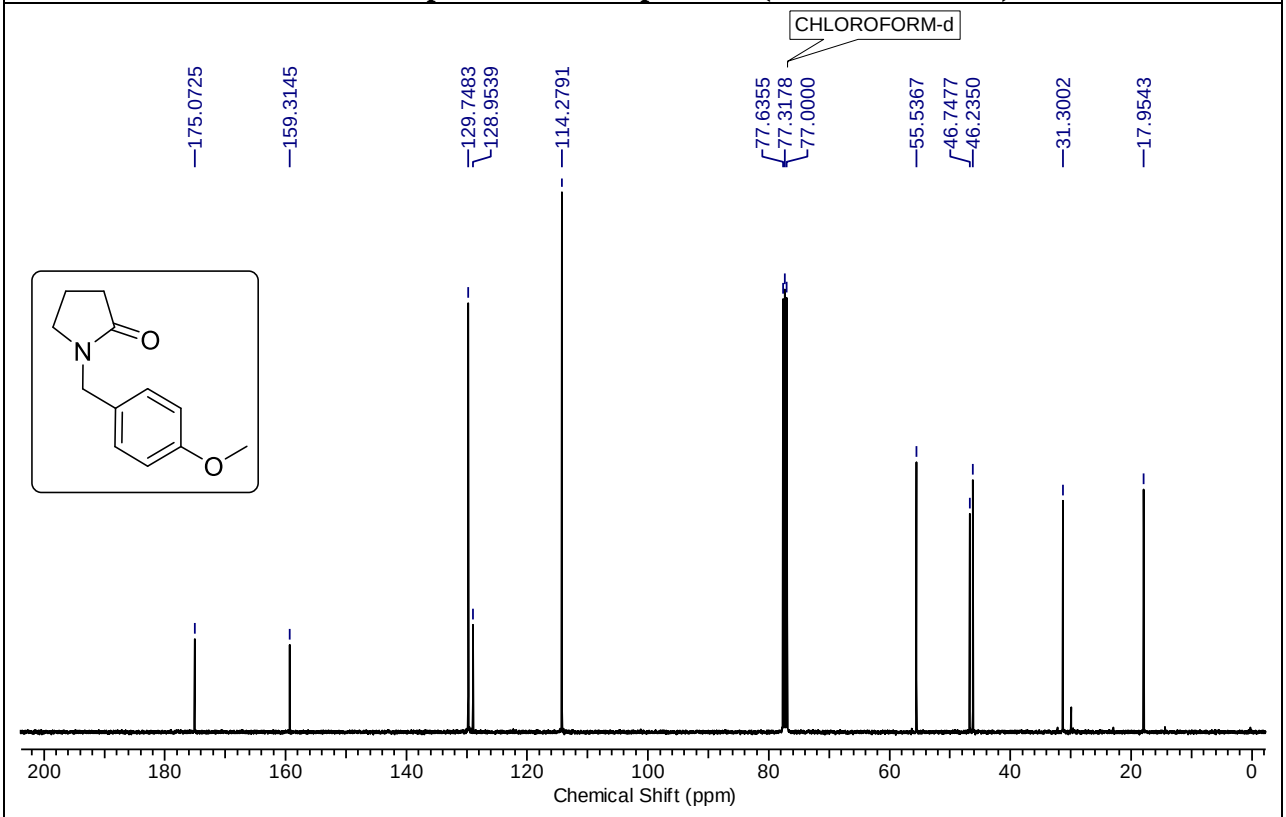

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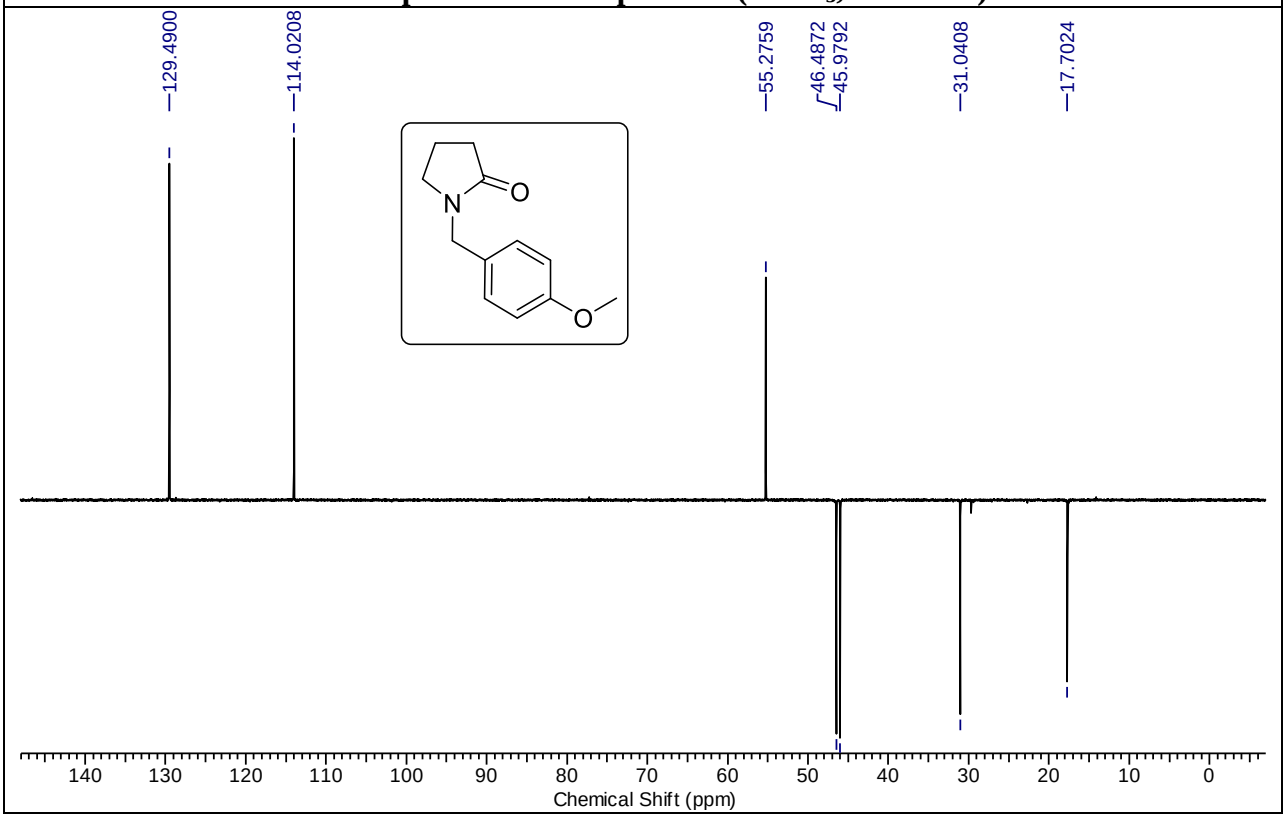

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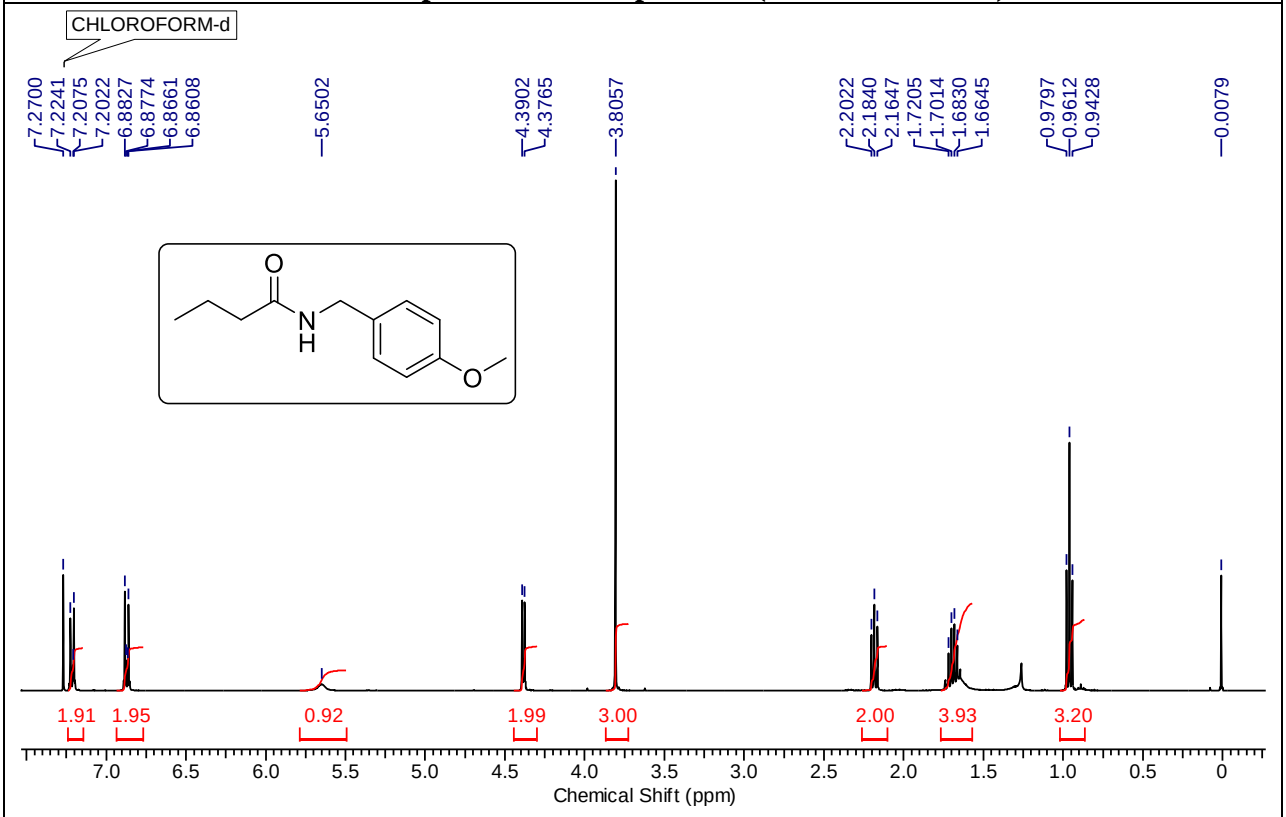

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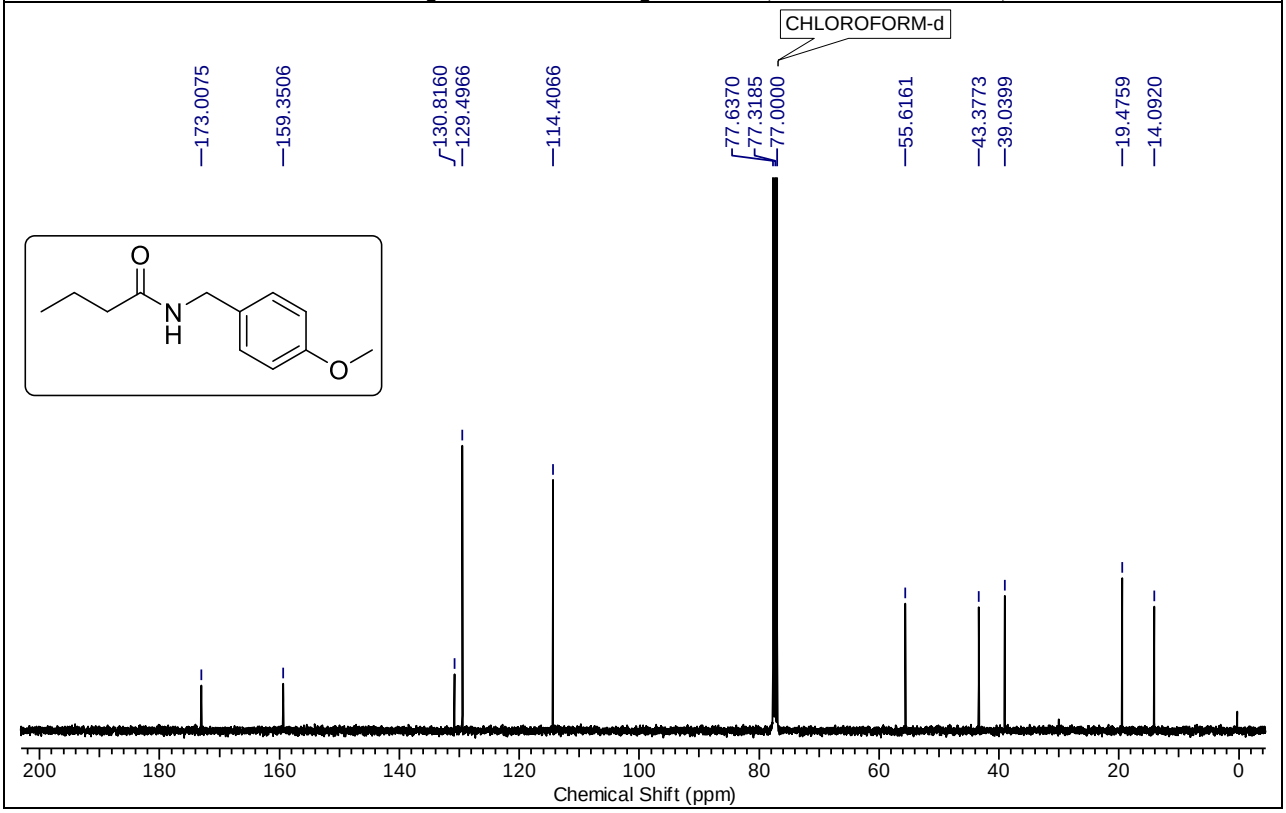

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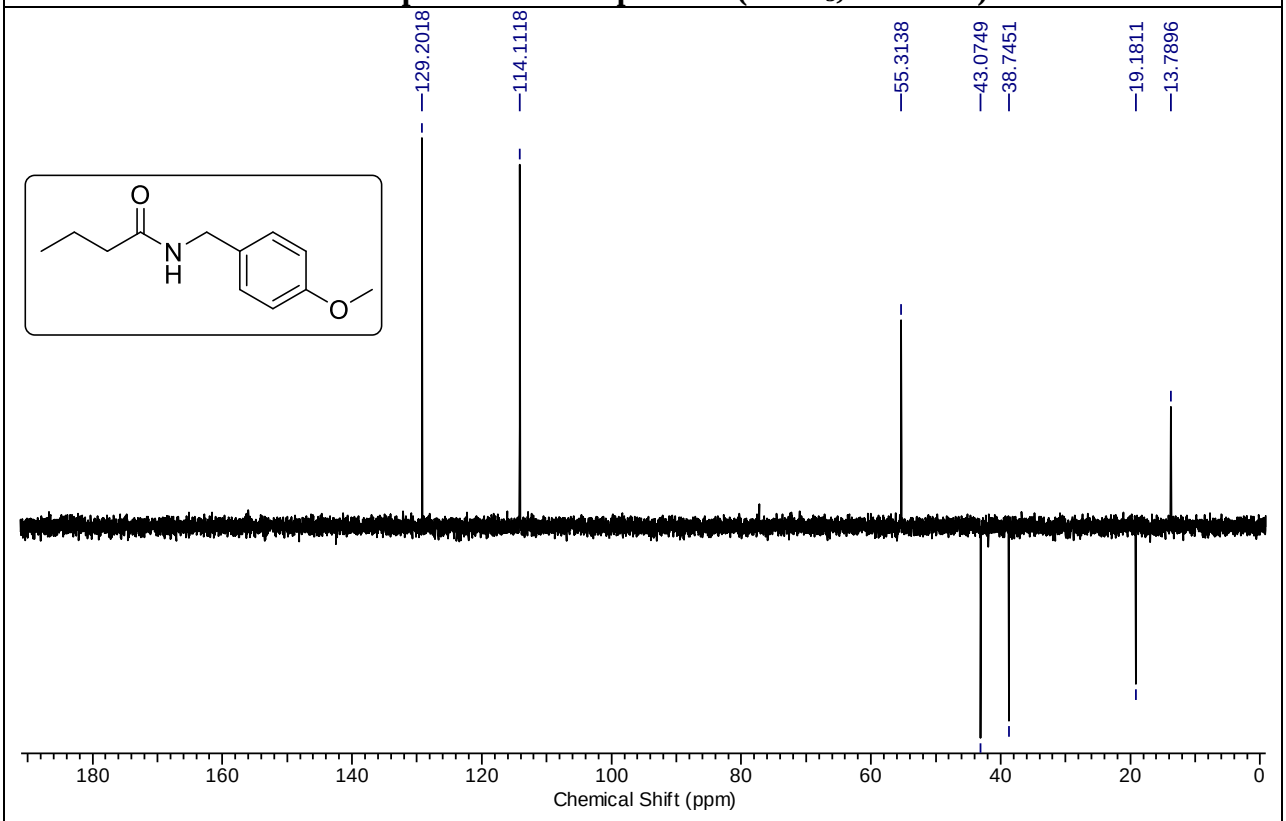

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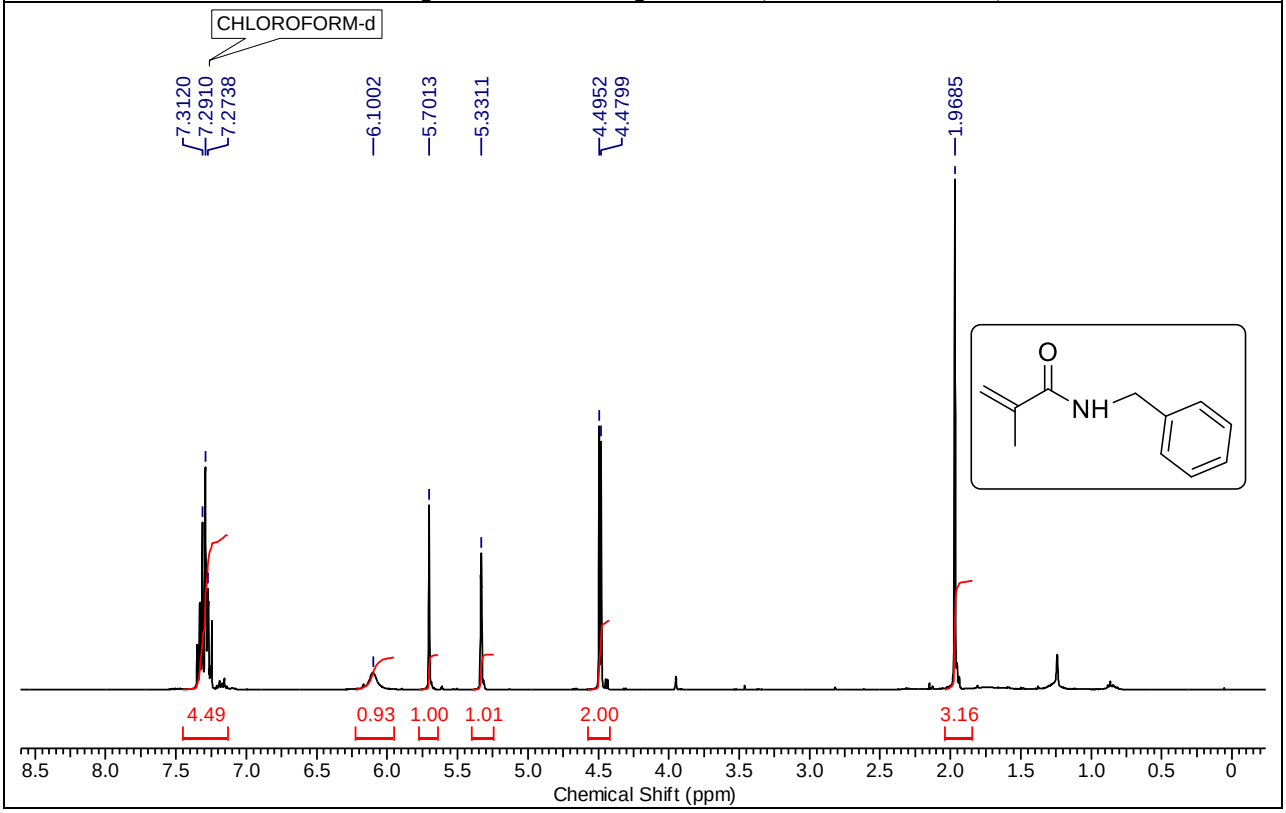

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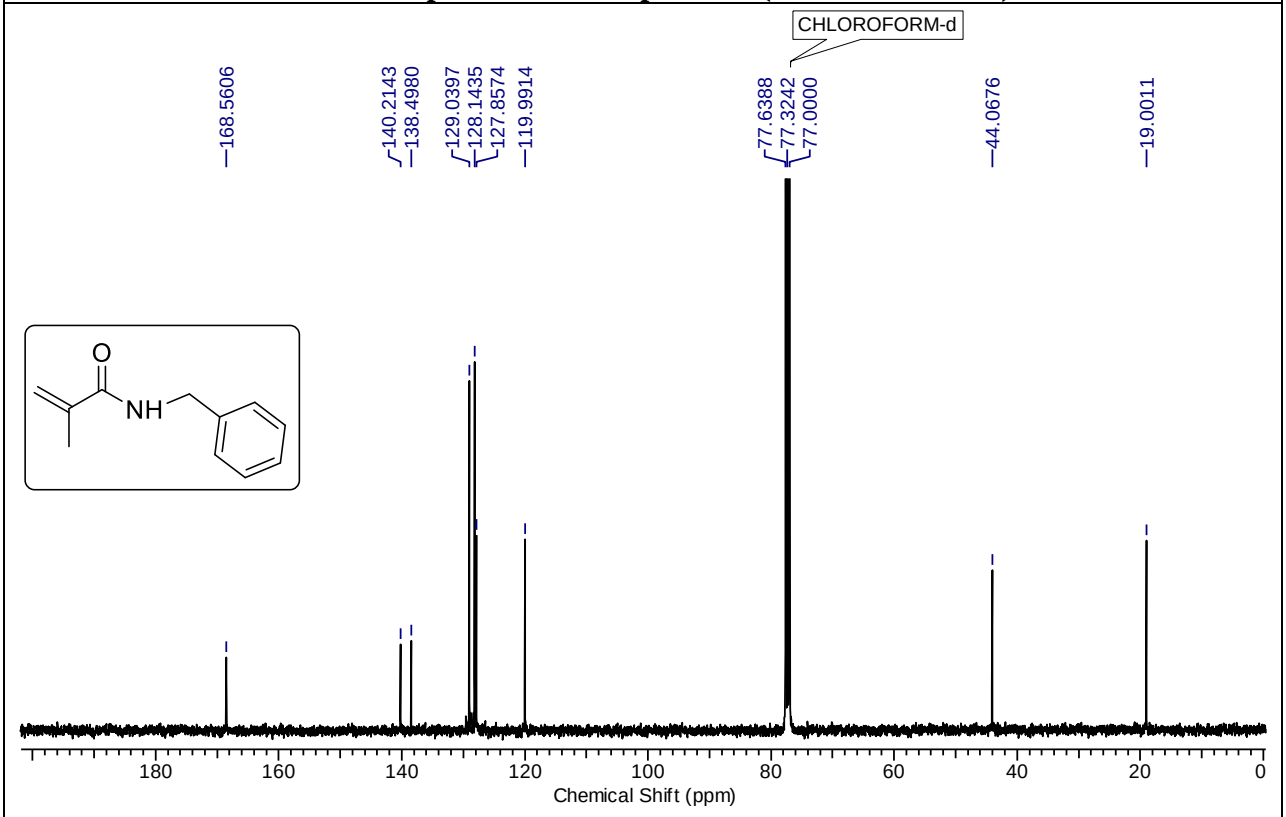

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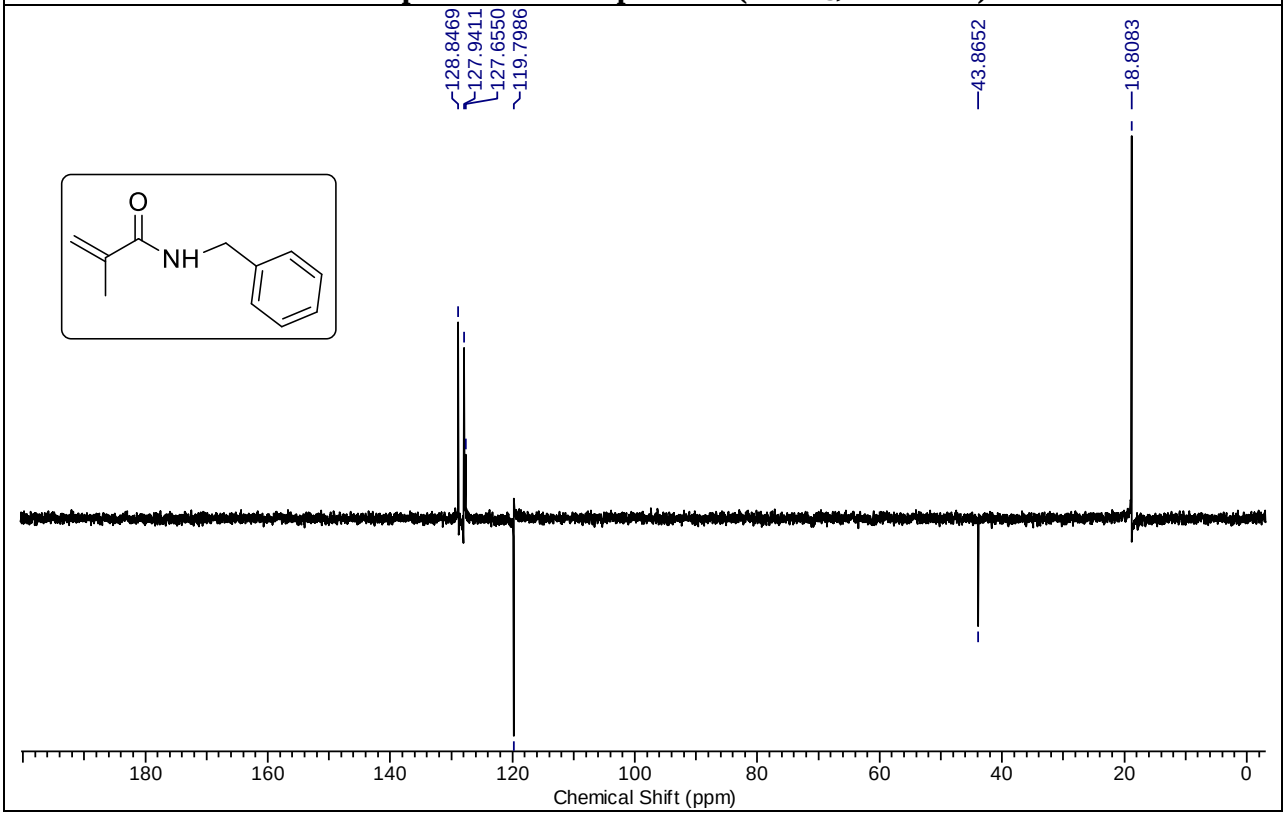

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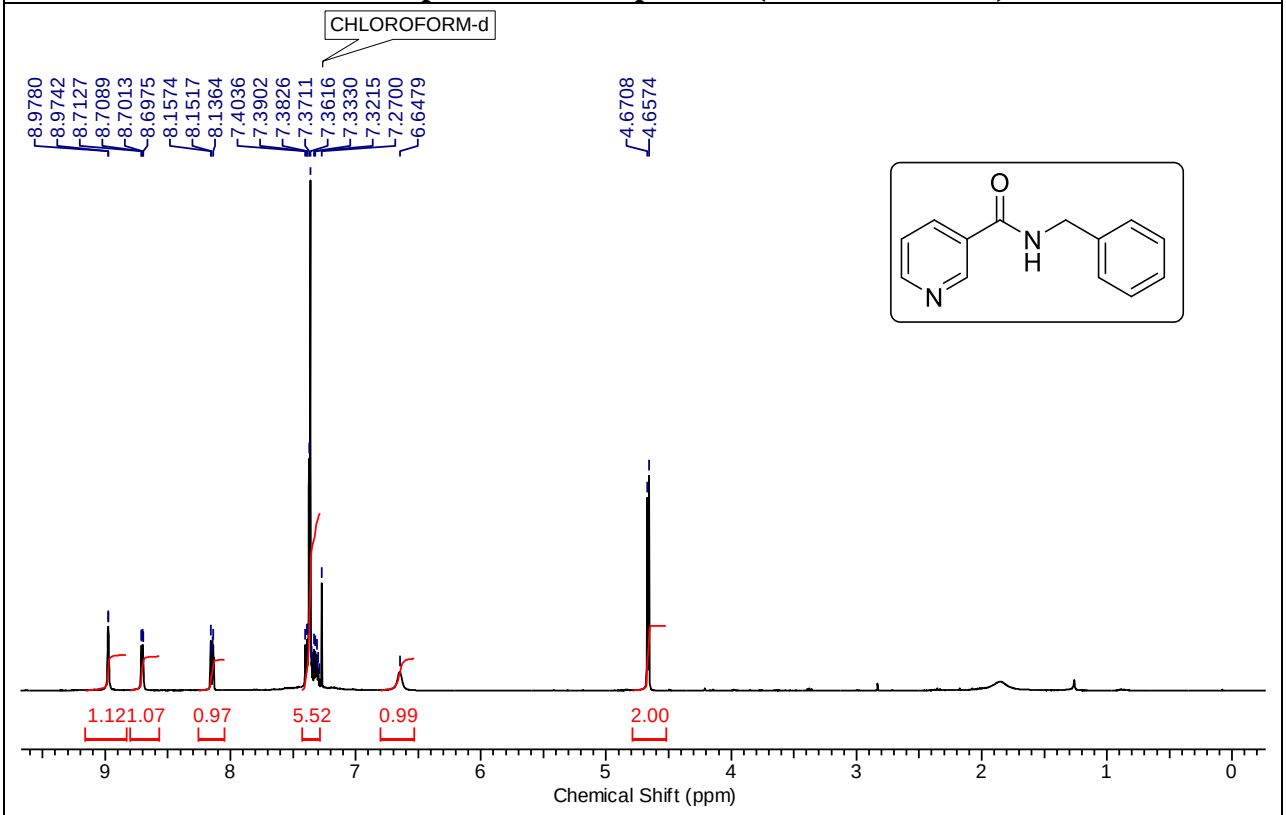

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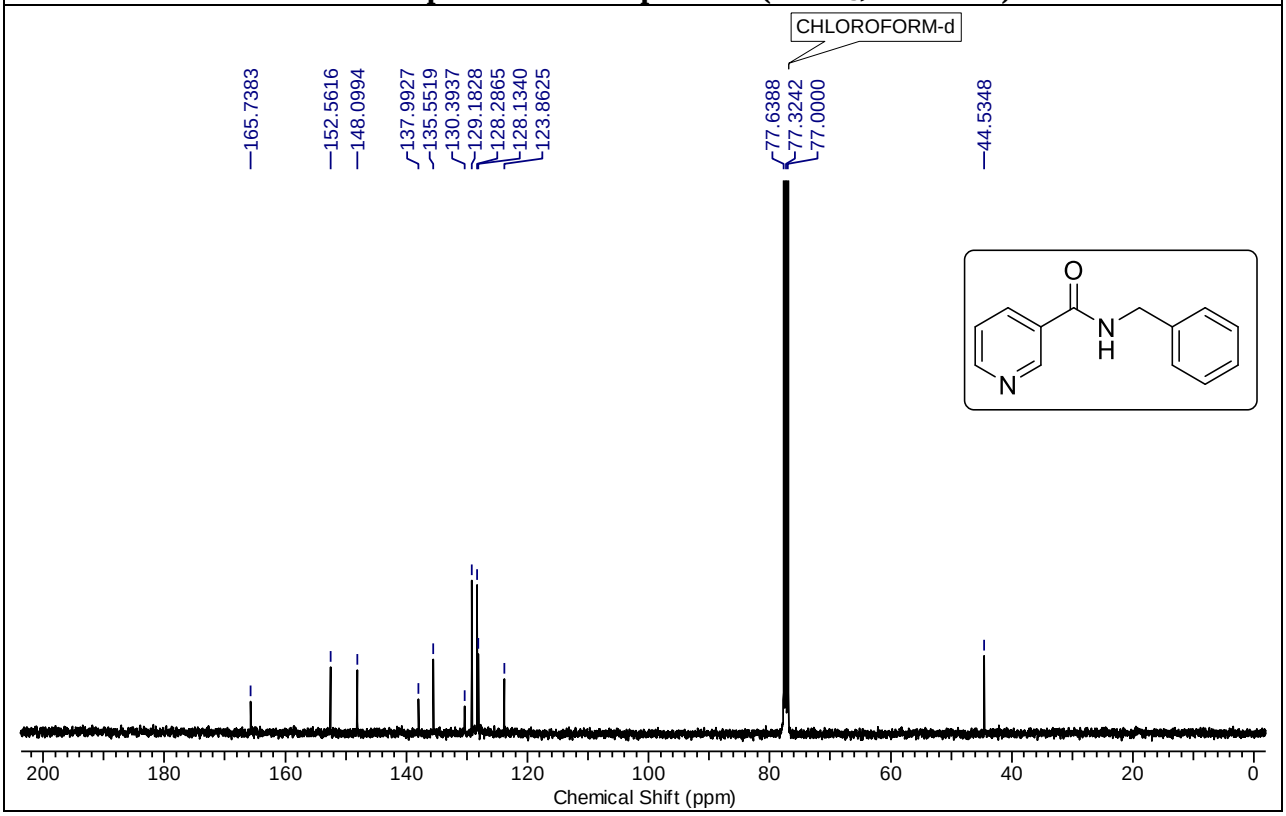

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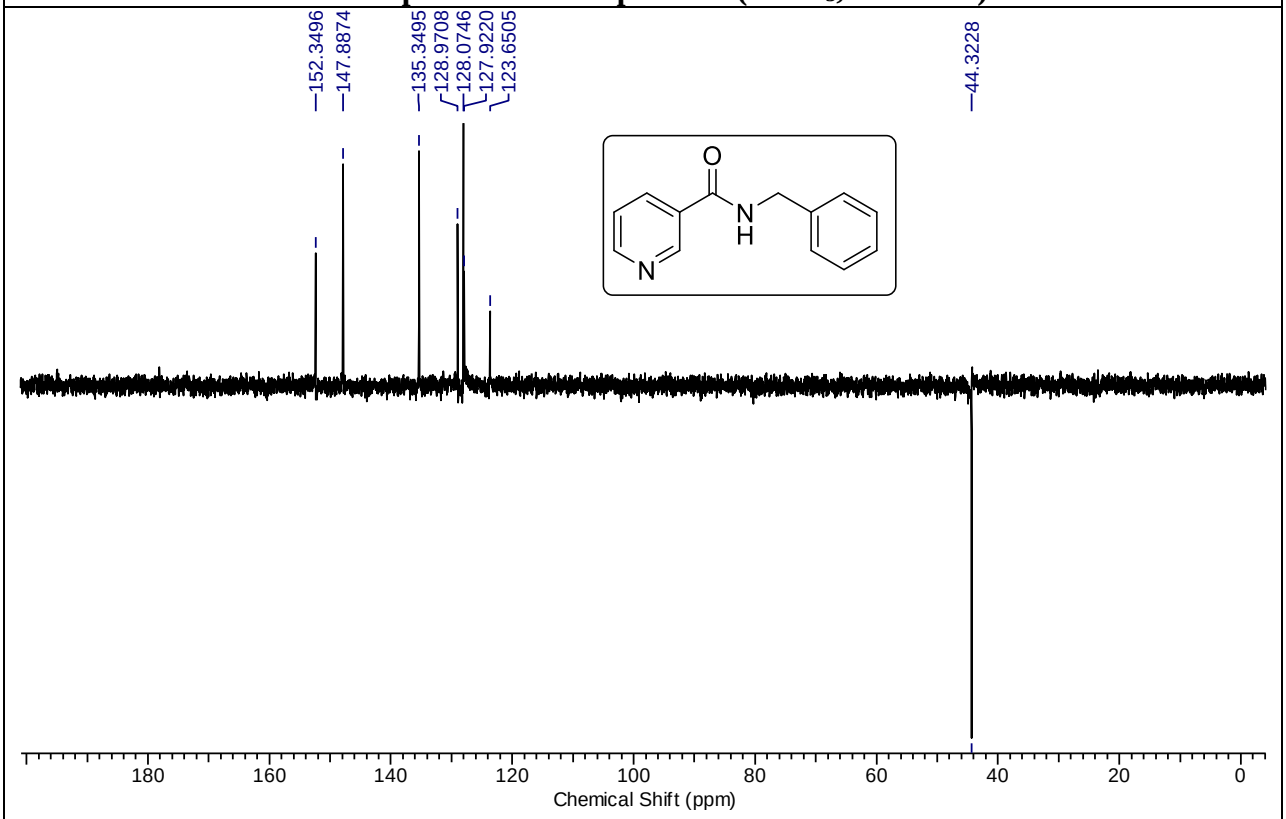

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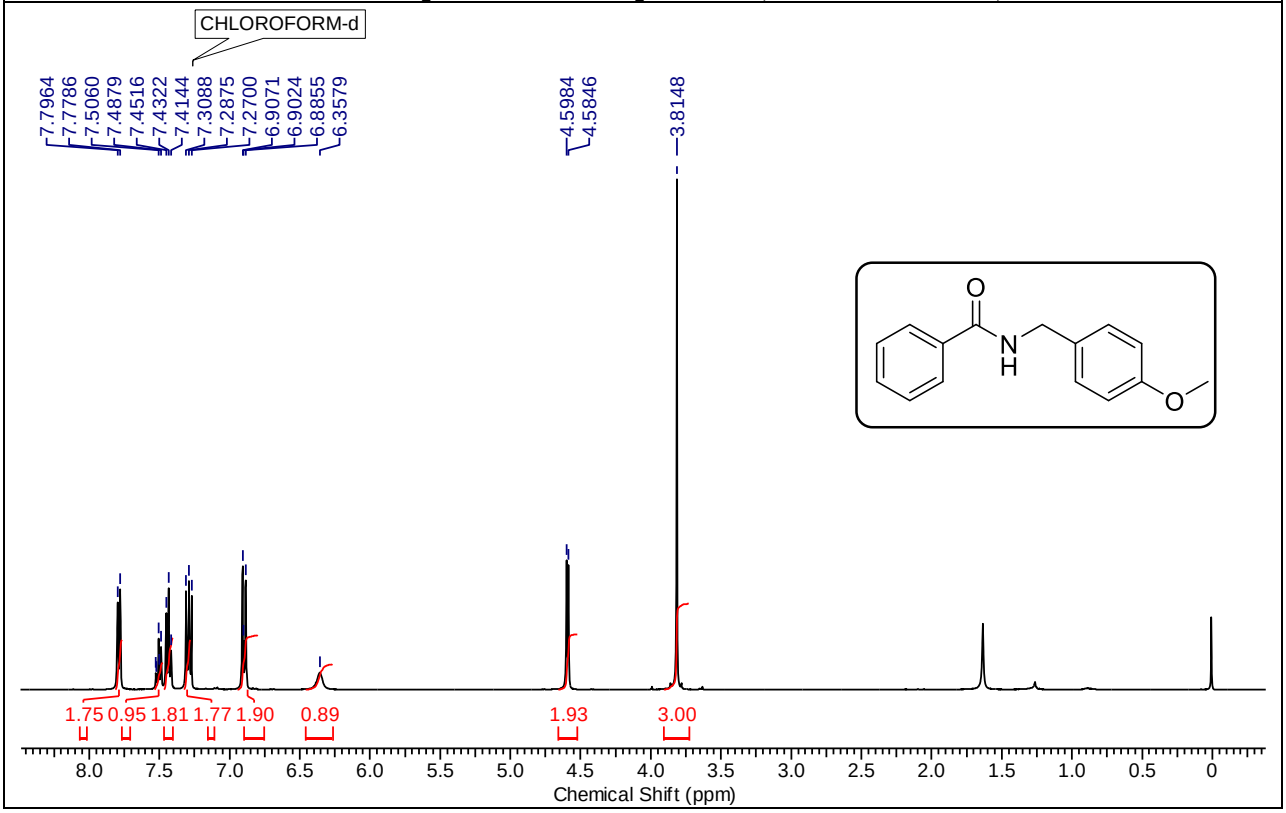

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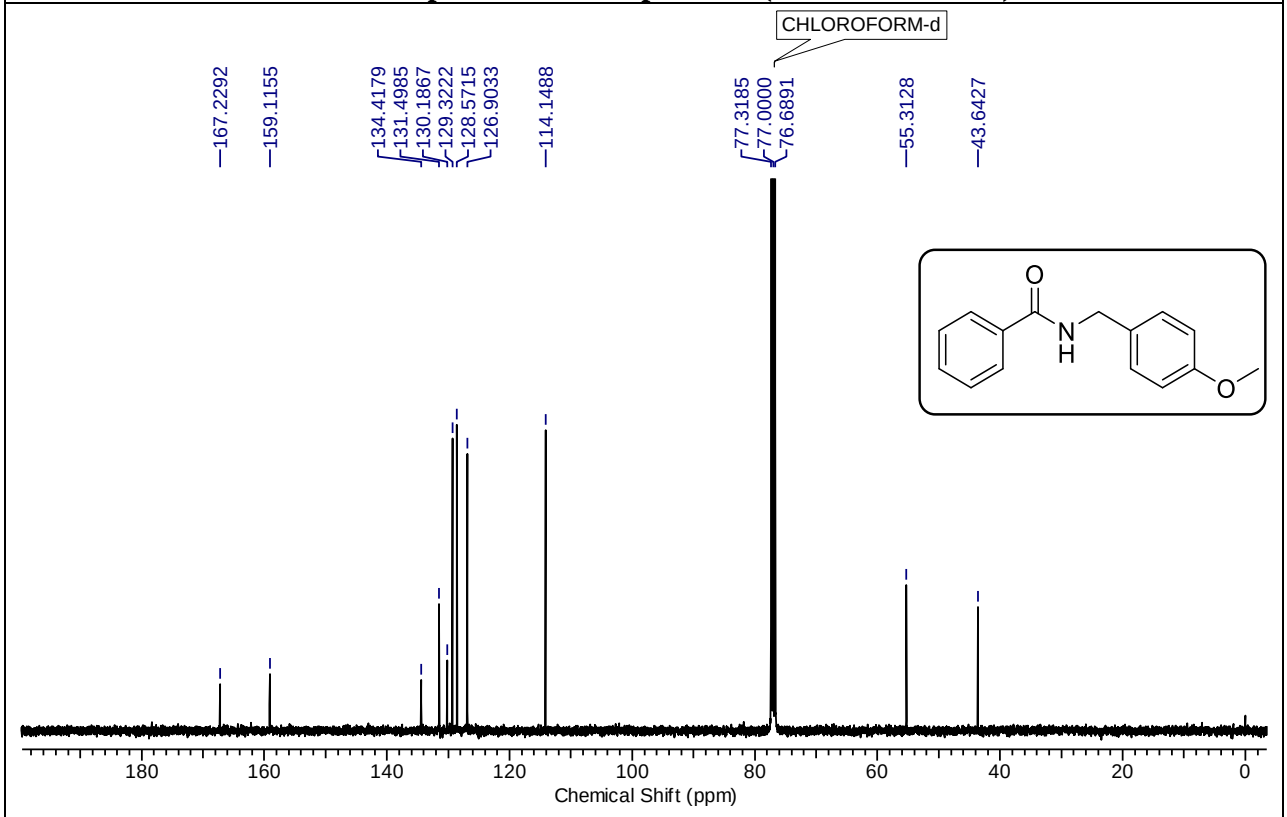

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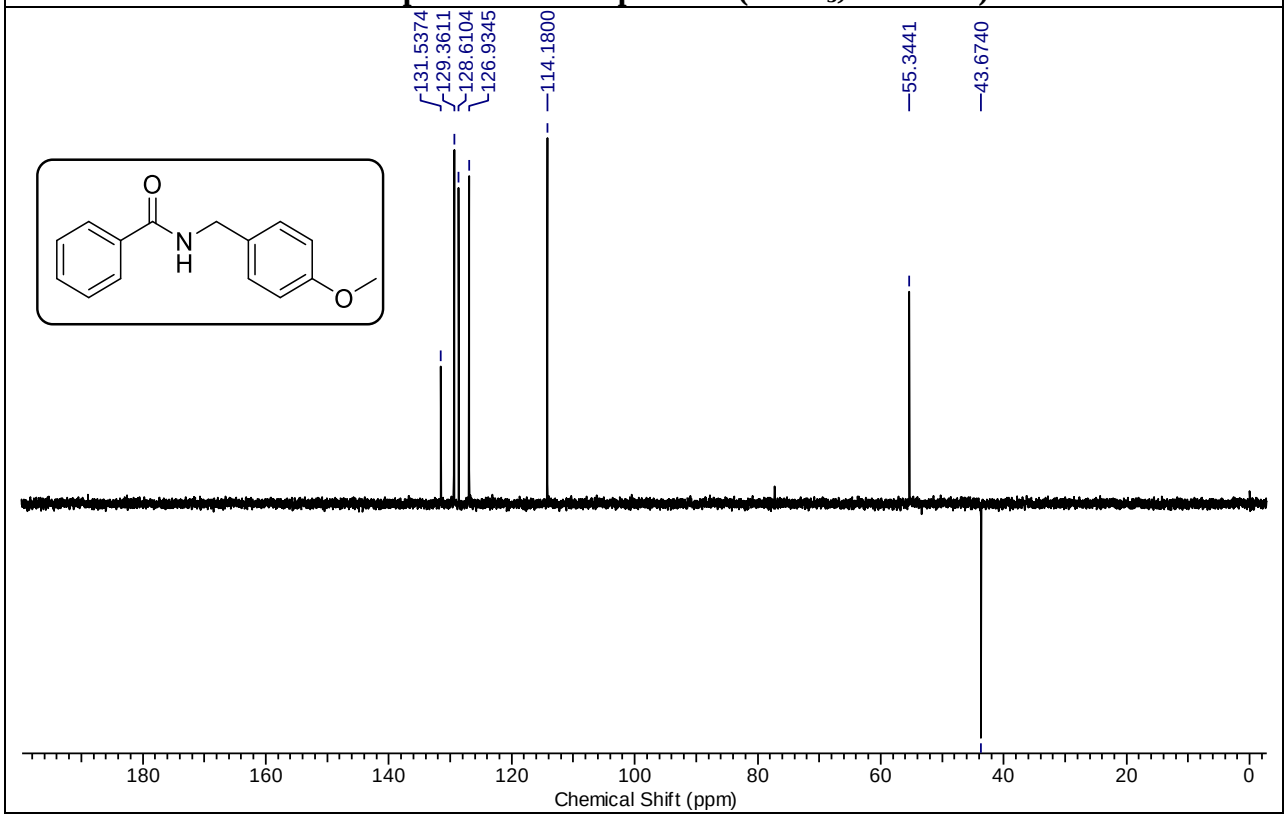

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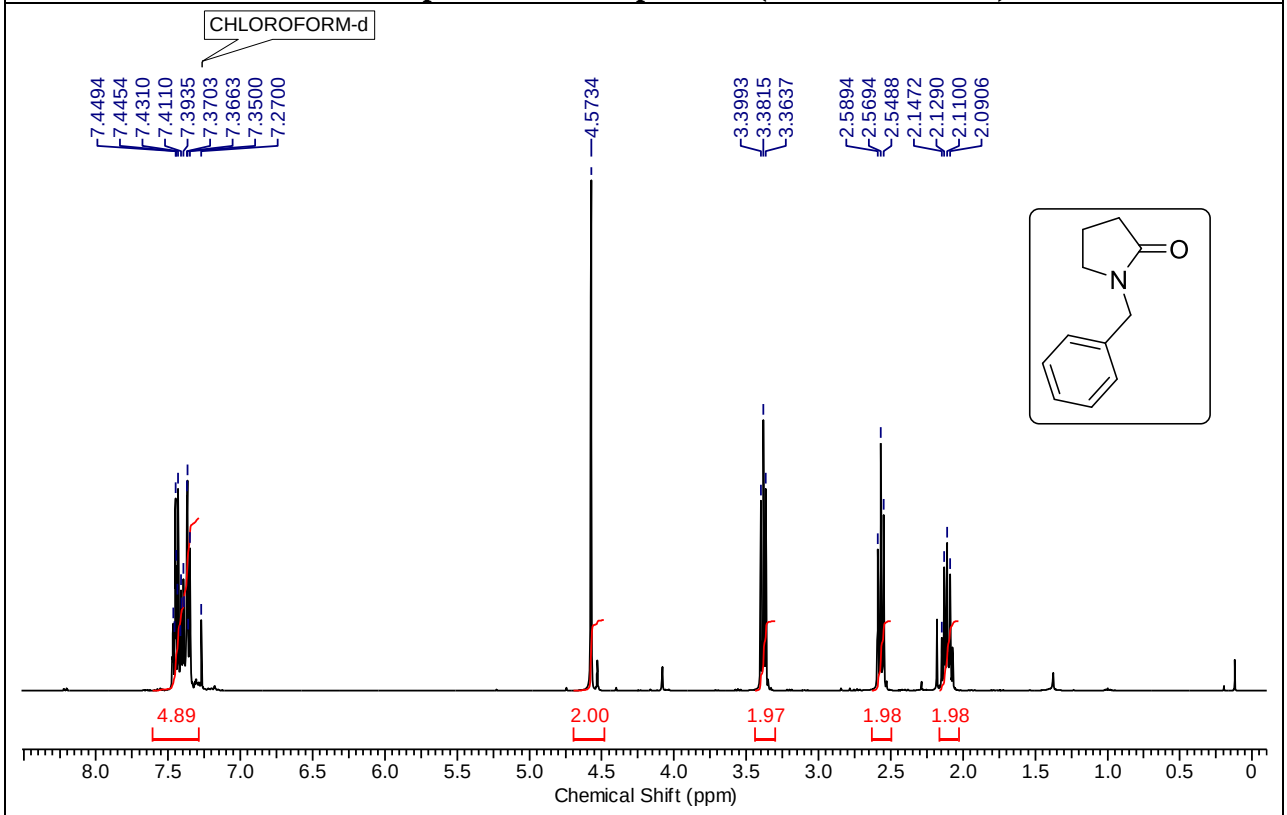

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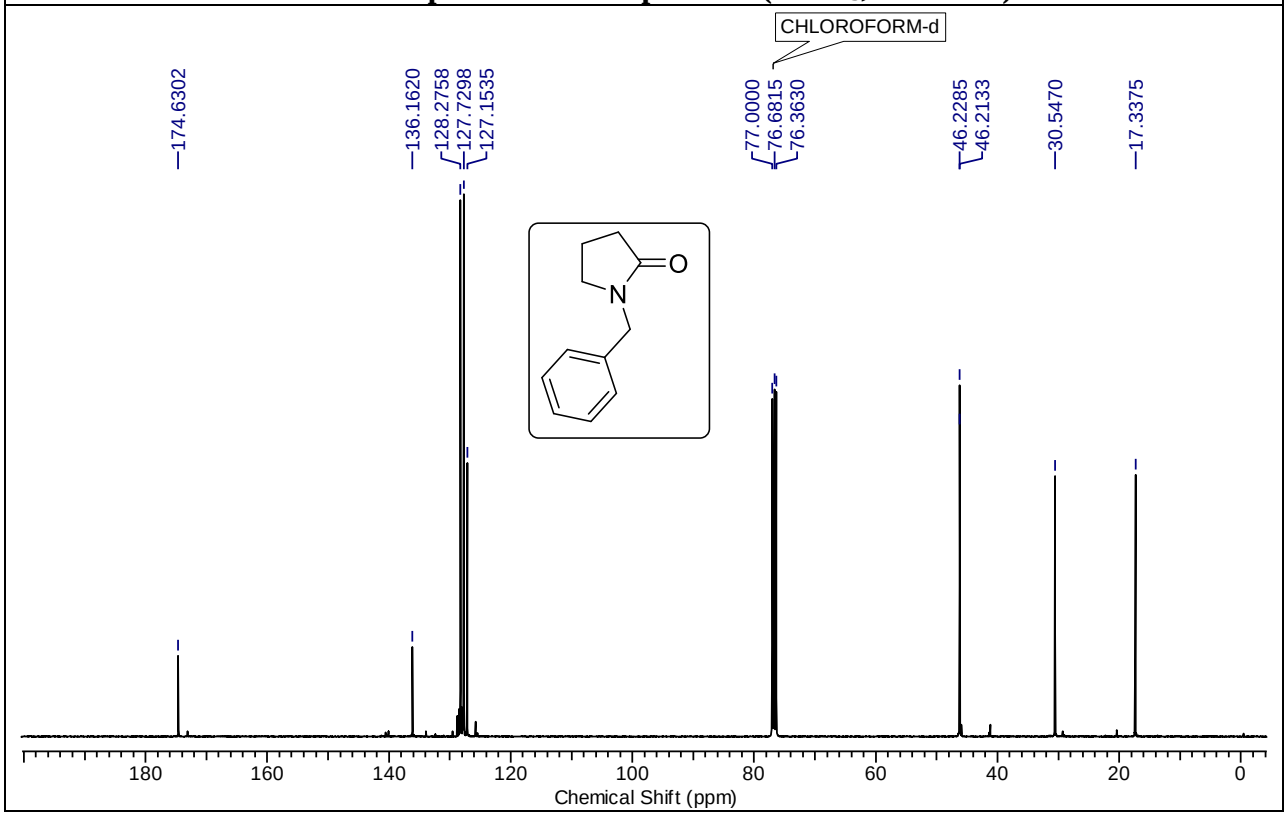

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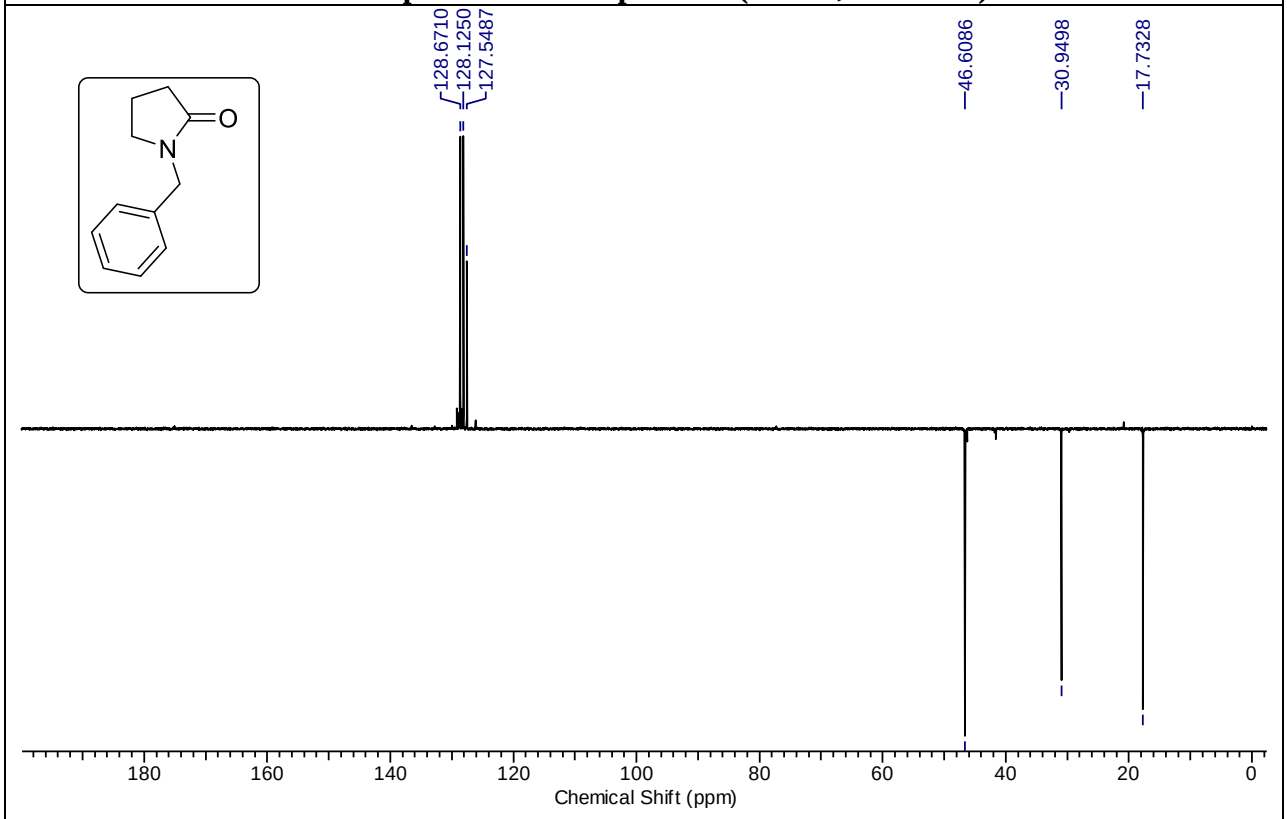

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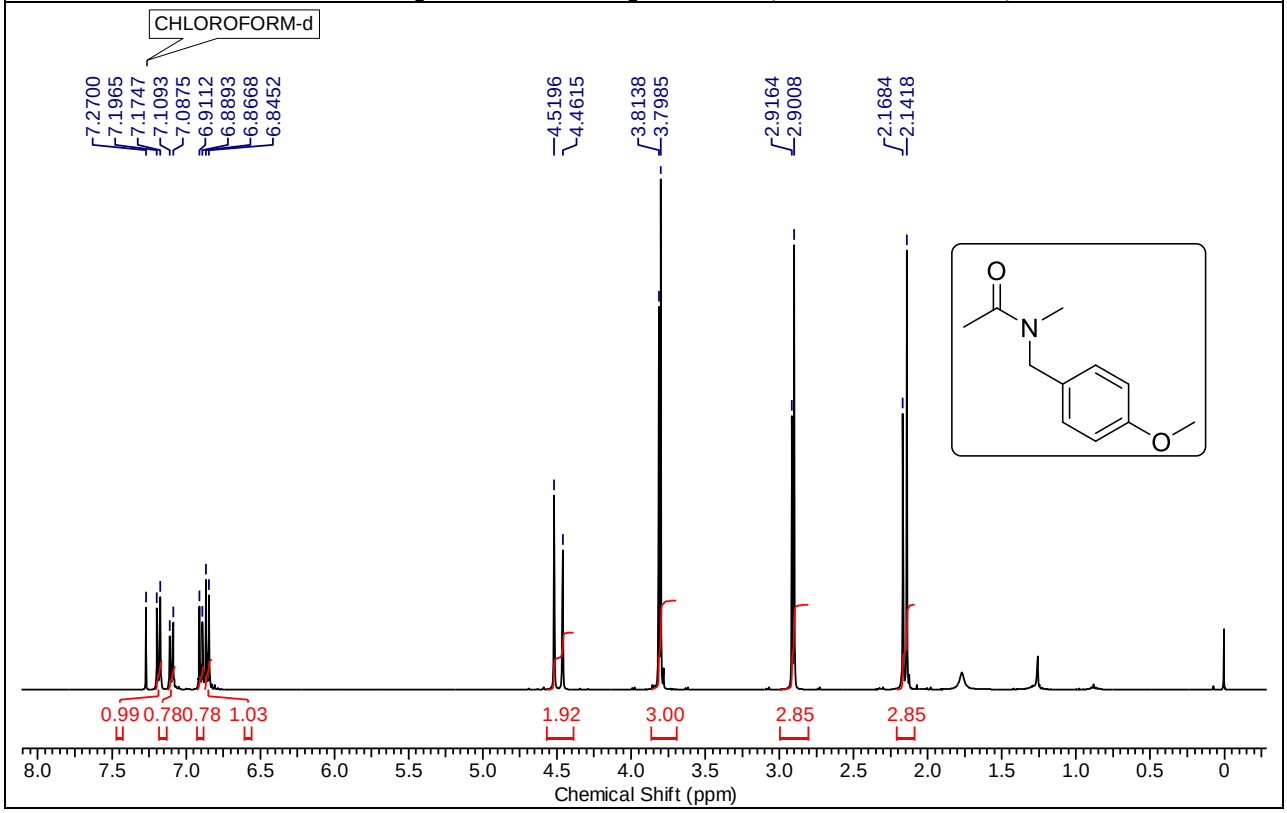

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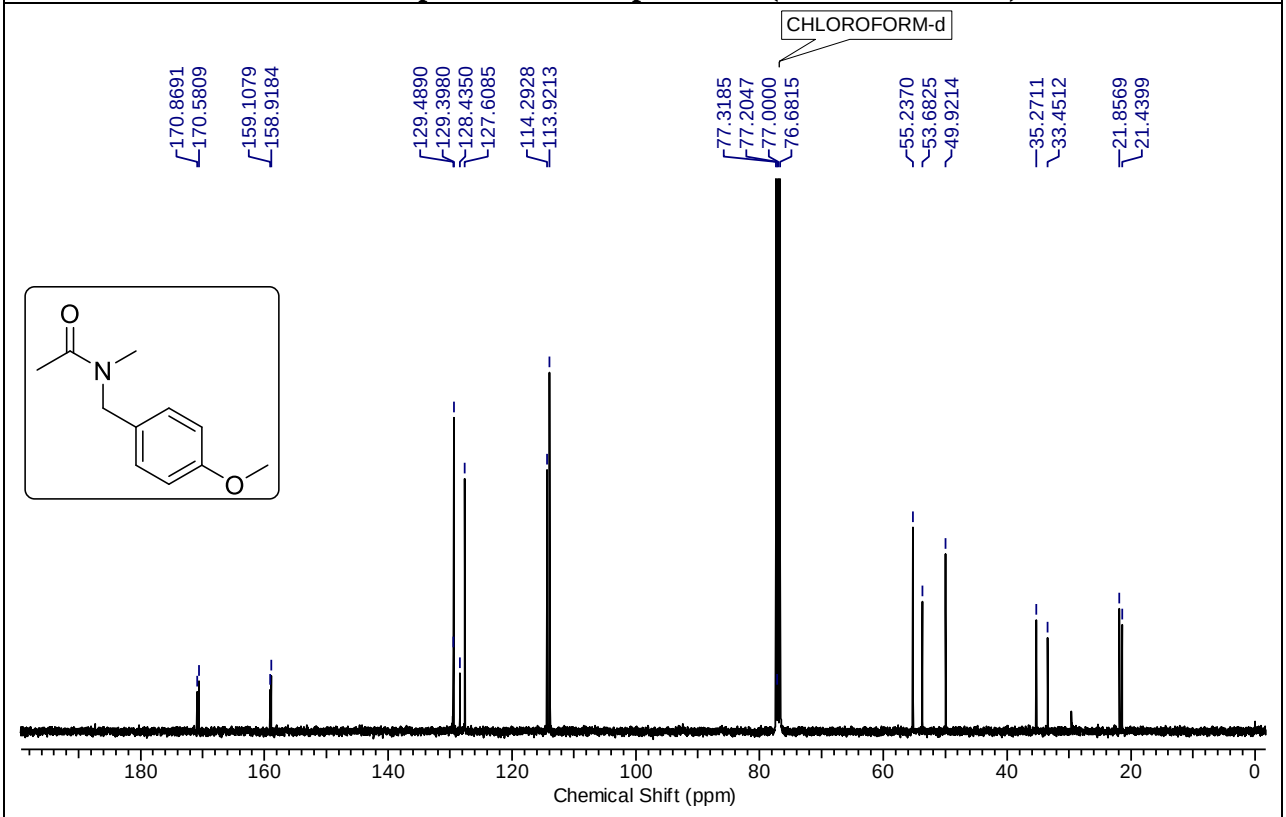

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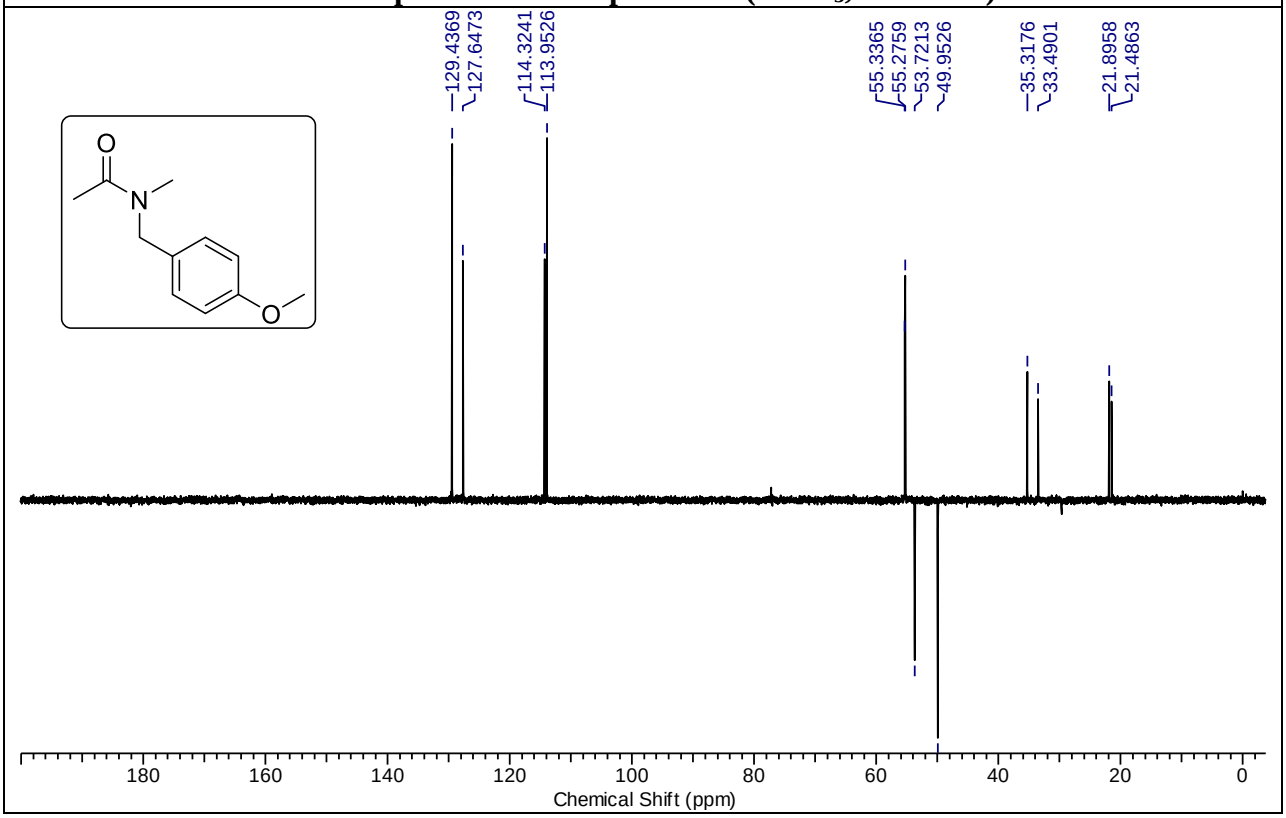

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ABSTRACT

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Faculty of Study: Chemical Science

Year of Submission: 2021

AcSIR academic centre/CSIR Lab:
CSIR-National Chemical Laboratory, Pune

Name of the Supervisor: Dr. Subhash Prataprao Chavan

Title of the thesis: Synthetic studies towards biotin, oxybiotin , *α*-lipoic acid and scalable synthesis of 3-ethyl-4-methyl- 1,5-dihyro-2*H*-pyrrole-2-one and development of synthetic methodologies.

The medicinally important molecules have always attracted the attention of synthetic chemists. In the present work medicinally important compounds have been synthesized and described. The thesis is divided into three chapters. Chapter **1** deals with the synthetic studies towards biotin, oxybiotin and *epi*-oxybiotin using isosorbide as the starting material. Chapter **2** is divided into two sections. Section **1** deals with synthetic studies towards *α*-Lipoic acid and section **2** deals with 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one. Chapter **3** is divided into two sections. Section **1** and Section **2** which deals with the study of synthetic methodologies. Section **1** includes the C-alkylation of phenols by using ionic liquid as the catalyst and the section **2** deals with *N*-PMB/benzyl alkylation of amides using ionic liquid as a catalyst.

List of Publications Emanating from the Thesis Work

Publications:

1. Scalable Synthesis of 3-Ethyl-4-methyl-1,5-dihydro-2H-pyrrol-2-one: An Important Building Block of the Antidiabetic Drug Glimepiride. Chavan, S. P.; **Pawar, A, A**.; Patil, N. B,; Kadam, A.L.; Shinde, S. S.; *Synthesis* **2020,** *52*, 3480.

Patents:

1. Process for the Preparation of Glimepiride intermediate. *Chavan, S. P.; **Pawar, A. A.**; Patil, N. B.; Kadam, A. L.; Shinde, S. S. IN Patent App. 201,911,040,874.

List of Posters Presented with Details

1. National Science Day Poster presentation at CSIR-National Chemical Laboratory, Pune (February 26-27, **2020**):

   Title: Scalable Synthesis of 3-Ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one: An Important Building Block for Antidiabetic drug Glimepiride.

   Abstract: A 4-step, practical, and easily scalable synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one, an important building block of anti-diabetic drug glimepiride has been accomplished. Key features are the synthesis of 3-methyl-4-hydroxy-2-butenolide in water, one-pot opening-reductive cyclization of butenolide with benzyl amine for the synthesis of five-membered lactam and triflic acid-mediated *N*-benzyl deprotection of lactam 9. The triflic acid-mediated *N*-benzyl deprotection of lactam under conventional heating condition is reported for the first time. The main advantages of this process are scalable synthetic route and less number of reaction steps, which paves the way for the industrial-scale synthesis of 3-ethyl-4-methyl-1, 5-dihydro-2*H*-pyrrol-2-one.

List of Conference Attended with Details

1) 17th CRSI National Symposium in Chemistry 2015 held in CSIR-NCL Pune, India (February 2015)

Synthesis S. P. Chavan et al. Paper

Scalable Synthesis of 3-Ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one: An Important Building Block of the Antidiabetic Drug Glimepiride

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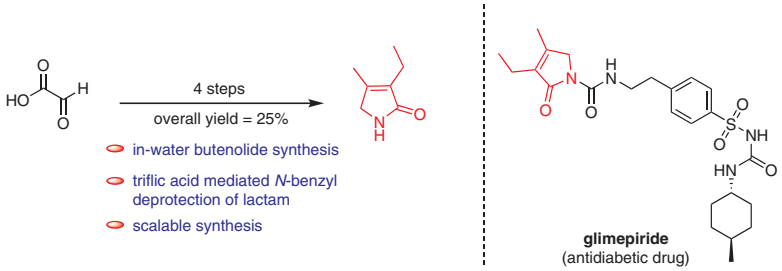

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DOI: 10.1055/s-0040-1707344; Art ID: ss-2020-n0639-op

Abstract A four-step, practical, and easily scalable synthesis of 3-ethyl-4-methyl-1,5-dihydro-2H-pyrrol-2-one, an important building block of the antidiabetic drug glimepiride, has been accomplished. Key features are the synthesis of 3-methyl-4-hydroxy-2-butenolide in water and triflic acid mediated N-benzyl lactam N-deprotection. The main advantages of this process are the scalable synthetic route and decreased number of reaction steps, which paves the way for the industrial-scale synthesis of 3-ethyl-4-methyl-1,5-dihydro-2H-pyrrol-2-one.

Key words glimepiride, antidiabetic drug, scalable synthesis, lactams, butenolide

The rapidly rising prevalence of diabetes, especially among the middle- and low-income countries, has caused growing concern among the scientific community. In 2016, diabetes alone was responsible for the deaths of an estimated 1.6 million people. Also, another 2.2 million deaths were attributable to high blood sugar in 2012. Almost half of all deaths due to high blood glucose occur before the age of 70 years. WHO estimates that diabetes was the seventh leading cause of death in 2016.[1]

Currently, many drugs are available in the market for the treatment of diabetes. In that context, in 2003, Gurjar et al. reported the synthesis of *trans*-hydroxyglimepiride, a metabolite of the antidiabetic drug glimepiride (**1**).[2] Glimepiride is a third-generation sulfonylurea approved in 1995 for the treatment of type 2 diabetes mellitus. It is used in medication as a monotherapy or in combination with metformin or insulin, and is currently used in more than 60 countries worldwide. Glimepiride reduces the blood sugar by stimulating the release of insulin by the pancreas and induces increased activity of intracellular insulin receptors.[3] The antidiabetic drug glimepiride (**1**) consists of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**) as an essential heterocyclic building block. Pyrrolinone **3** is also present as the main precursor in bile pigments, and is in the blue protein C-phycocyanin[4] (**2**) (Figure 1).

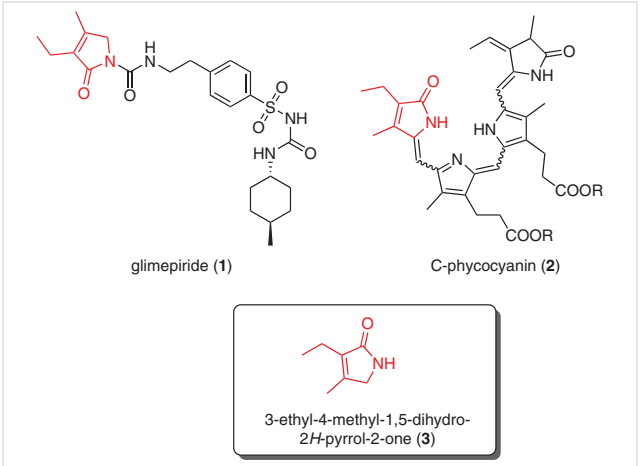


Figure 1 Glimepiride (**1**) and C-phycocyanin (**2**) consist of the scaffold 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**)

The importance in medicinal chemistry and the challenging structural features of pyrrolinone **3** have attracted synthetic chemists for its short and industrially scalable synthesis.[5,6] The reported synthetic routes involve the use of toxic reagents such as NaCN and $Pb(OAc)_4$, and expensive transition-metal catalysts such as $PdCl_2$ and Grubbs' catalyst (Figure 2). So, there is a long-standing need to develop a short, high yielding, and industrially scalable method using simple and easily accessible reagents. In continuation of our research towards the synthesis of biologically active natural products and medicinally important drug molecules, development of a scalable process for the synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**) was initiated.

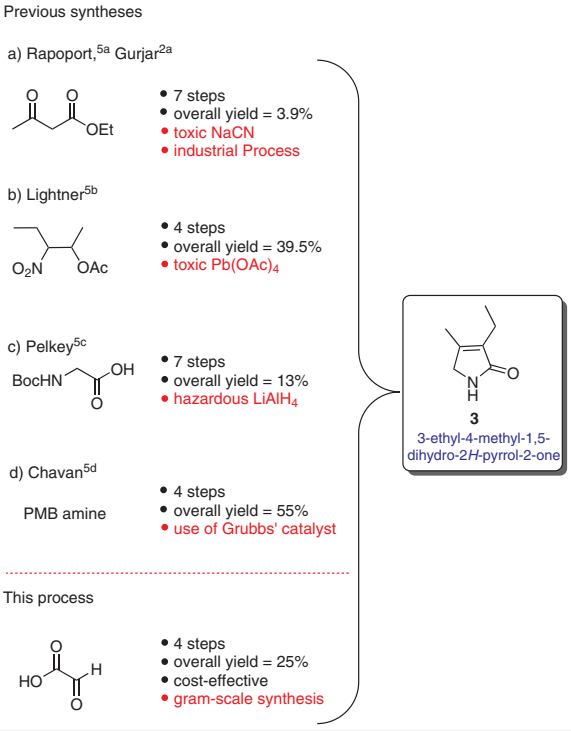
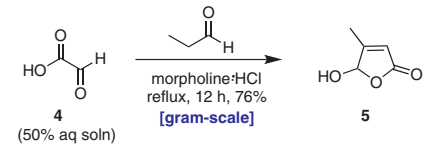


Figure 2 Synthetic approaches to 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**)

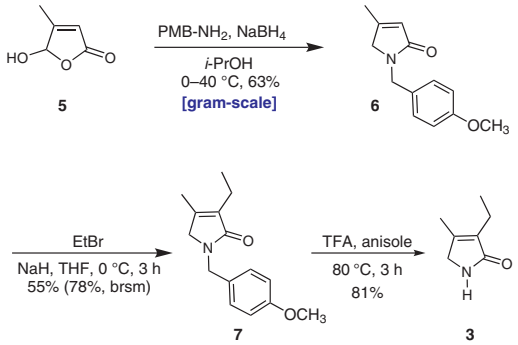
Our synthesis commenced with the preparation of 3-methyl-4-hydroxy-2-butenolide (**5**) using glyoxylic acid (**4**) as starting material (Scheme 1). Synthesis of butenolide **5** from acid **4** and propanal in dioxane as solvent has been reported by Bourguignon and Wermuth.[7] For the large-scale synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**), the cost of the solvent dioxane would contribute significantly to the total cost of compound **3**. So, we decided to develop a process using either water as the solvent, which is considered to be a green solvent, or a solvent-free process. Towards this, when the reaction of glyoxylic acid (50% aqueous solution) with propanal in the presence of morpholine hydrochloride was carried out at reflux temperature, to our delight the formation of 3-methyl-4-hydroxy-2-butenolide (**5**) was observed in 55% yield in 24 hours. After slight optimization of the time, butenolide **5** was isolated in 76% yield in 12 hours. It was observed that longer reaction time (24 h) reduces the yield of the reaction mainly due to decomposition of the product formed. It is noteworthy that morpholine hydrochloride was prepared from morpholine and 35% HCl and used as such without isolation.

Thus, 3-methyl-4-hydroxy-2-butenolide (**5**) was successfully synthesized on a multigram scale using water as solvent, which makes this process green, cost-effective, and industrially applicable.



Scheme 1 Synthesis of 3-methyl-4-hydroxy-2-butenolide (**5**) in water

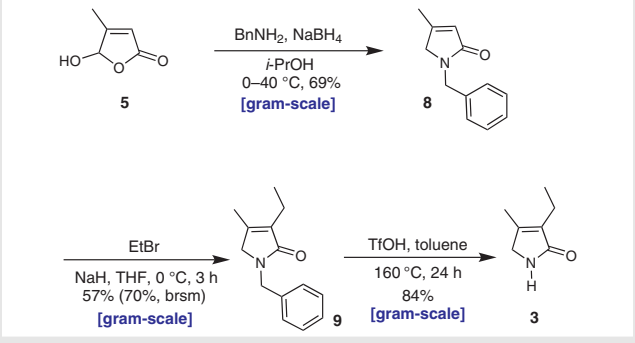
The next crucial step was the synthesis of lactam **6** from butenolide **5**. To this end, when 3-methyl-4-hydroxy-2-butenolide (**5**) was treated with *p*-methoxybenzylamine (PMB amine) in isopropyl alcohol, followed by treatment with $NaBH_4$ under basic conditions, lactam **6** was furnished in 63% yield (Scheme 2). Initially, isolation of hydroxy lactam was attempted, and then it was subjected to reduction using $NaBH_4$, but the yield of lactam was severely reduced to ~20% mainly due to instability of the hydroxy lactam on silica gel purification. For the required substitution on the olefin moiety, lactam **6** was treated with ethyl bromide and NaH at 0 °C to obtain compound **7** in 55% yield (78% brsm).[5d] Here, it was observed that starting material remained even after stirring the reaction mixture for a longer time under a range of temperature conditions. All our efforts to obtain 100% conversion failed in this case. The final step, *N*-PMB deprotection of the lactam, was carried out using CAN, as earlier reported by us.[5d] CAN, a well-known one-electron oxidant, has several disadvantages, one of which is its requirement for excess addition (2 equivalents or more) owing to its high molecular weight. This not only adds to the cost, but also raises disposal and environmental issues. These issues have led to the development of a simple and more convenient method which could be utilized on a large scale. Towards this, *N*-PMB deprotection of lactam **7** was carried out using TFA in anisole at 80 °C under microwave conditions to obtain 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**) in 81% yield.[8] The same reaction was reproduced using conventional heating conditions for the synthesis of pyrrolinone **3**.



Scheme 2 First-generation approach for the synthesis of **3**

Though we achieved a good overall yield for this process (21%) in a decreased number of steps and the process was scalable at large scale, our main goal was to develop a cost-effective and scalable process for the synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**). It was realized that PMB amine, TFA, and anisole contributed largely to the overall cost of the process. This led us to explore commercially, readily available and inexpensive benzylamine and the development of a cost-effective and practical method for the N-debenzylation of lactam.

Accordingly, following a similar reaction sequence, *N*-benzyl lactam **9** was synthesized from **4** in three steps in 30% yield (Scheme 3). To achieve the last step, the *N*-benzyl deprotection of lactam **9**, known reaction conditions were screened. When *N*-benzyl lactam **9** was treated with TFA in anisole, starting material was recovered after 48 hours and product formation was not observed. But, when *N*-benzyl lactam **9** was subjected to microwave-mediated *N*-benzyl deprotection using triflic acid in toluene, product formation was observed in 86% yield.[9] To avoid the microwave conditions, when the same reaction was carried out using conventional heating with triflic acid in toluene, to our delight the formation of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**) was observed in 84% yield, which meets our requirements of a scalable process. The spectroscopic and analytical data of pyrrolinone **3** were in complete agreement with the reported data.[5d]



Scheme 3 Second-generation approach for the synthesis of **3**

In conclusion, a short, cost-effective, and scalable synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**) has been developed. Key features are the synthesis of 3-methyl-4-hydroxy-2-butenolide in water, one-pot opening–reductive cyclization of the butenolide for the synthesis of five-membered lactams, and triflic acid mediated *N*-benzyl deprotection of lactam **9**. As the synthesis of pyrrolinone **3** was achieved in four steps in 25% overall yield, we believe that this short, cost-effective, and scalable synthesis of 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one, a key building block of the antidiabetic drug glimepiride, paves the way for its industrial-scale synthesis.

All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen, unless otherwise mentioned, with magnetic stirring. Air-sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa. All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification. Reactions were monitored by TLC with 0.25 mm precoated silica gel plates (60 F254). Visualization was accomplished with either UV light, iodine adsorbed on silica gel, or by immersion in an ethanolic solution of phosphomolybdic acid, *p*-anisaldehyde, 2,4-DNP, $KMnO_4$, or ninhydrin followed by heating with a heat gun for ~15 sec. Melting points are uncorrected. ^{1}H NMR spectra were recorded on Bruker AV 200, 400, and 500 MHz NMR spectrometers (^{13}C NMR spectra at 50, 100, and 125 MHz, respectively) using solvent residue signal as an internal standard ($CDCl_3$, ^{1}H NMR: 7.27 ppm, ^{13}C NMR: 77.00 ppm). HRMS (ESI) were taken on an Orbitrap (quadrupole plus ion trap) TOF mass analyzer. IR spectra were recorded on a Bruker FT-IR spectrophotometer. Column chromatographic separations were carried out on silica gel (230–400 mesh).

5-Hydroxy-4-methylfuran-2(5*H*)-one (5)[7]

To a stirred, ice-cold (0 °C) solution of morpholine (58.2 mL, 675 mmol, 1 equiv), concd HCl (70.4 mL, 675 mmol, 1 equiv) was added dropwise over a 15-min period. The reaction mixture was then stirred for 2 h. To this, glyoxylic acid (100 mL, 50% aqueous solution, 675 mmol, 1 equiv) was added followed by propanal (50.7 mL, 708 mmol, 1.05 equiv), and the reaction mixture was further stirred at rt for 1 h and then refluxed for 12 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was concentrated to dryness and the residue was extracted with EtOAc (3 × 500 mL). The combined organic layer was washed with brine (200 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 30:70) afforded pure **5** as a yellow oil; yield: 58.5 g (76%).

R_f = 0.3 (EtOAc–PE, 50:50).

IR ($CHCl_3$): 3407, 1760, 1216, 766 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.00 (s, 1 H), 5.85 (q, *J* = 1.5 Hz, 1 H), 5.41 (br s, 1 H), 2.10 (d, *J* = 1.5 Hz, 3 H).

Spectroscopic data were consistent with the earlier reported analytical information.

1-(4-Methoxybenzyl)-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (6)[5d]

To a stirred solution of *p*-methoxybenzylamine (6.52 mL 49.9 mmol, 1.14 equiv) in isopropyl alcohol (40 mL), compound **5** (5 g, 43.8 mmol, 1 equiv) was added at rt. The reaction mixture was stirred at 40 °C for 1 h, then cooled to 0 °C and treated with a freshly prepared solution of $NaBH_4$ (1.06 g, 28 mmol, 0.64 equiv) in water (15 mL) containing NaOH (1 mL, 50% w/w in water) while maintaining the internal temperature below 25 °C. The reaction mixture was stirred for 1.5 h at that temperature. Excess $NaBH_4$ was quenched by addition of acetone to the reaction mixture while maintaining the internal temperature below 30 °C. The mixture was filtered and AcOH (1 mL) was added to the filtrate to adjust the pH between 7–8 and the reaction mixture was heated to 50 °C for 16 h. The mixture was allowed to cool to rt and the solvent was evaporated under reduced pressure. The obtained residue was extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer in vacuo followed by

purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 40:60) afforded pure **6** as a pale yellow solid; yield: 6.0 g (63%).

Mp 121 °C (Lit.[5d] 122 °C); R_f = 0.2 (EtOAc–PE, 50:50).

IR ($CHCl_3$): 1674, 1222, 760 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.4 Hz, 2 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 5.86 (d, *J* = 1.1 Hz, 1 H), 4.52 (s, 2 H), 3.79 (s, 3 H), 3.69 (s, 2 H), 2.00 (d, *J* = 1.1 Hz, 3 H).

Spectroscopic data were consistent with the earlier reported analytical information.

3-Ethyl-1-(4-methoxybenzyl)-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (7)[5d]

To a stirred solution of compound **6** (1 g, 4.6 mmol, 1 equiv) in anhydrous THF (25 mL), NaH (0.121 g, 5.06 mmol, 1.1 equiv) was added slowly at 0 °C. The reaction mixture was stirred for 15 min, ethyl bromide (0.41 mL, 5.52 mmol, 1.2 equiv) in anhydrous THF (5 mL) was added dropwise at 0 °C, and stirring was continued for 3 h at that temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was treated with saturated NH_4Cl solution and extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 20:80) afforded pure **7** as a yellow solid [yield: 0.62 g (55%)] along with recovery of the starting material (0.3 g).

Mp 128 °C (Lit.[5d] 127–131 °C); R_f = 0.6 (EtOAc–PE, 50:50).

IR ($CHCl_3$): 1674, 1216, 762 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 4.54 (s, 2 H), 3.79 (s, 3 H), 3.58 (s, 2 H), 2.29 (q, *J* = 7.5 Hz, 2 H), 1.91 (s, 3 H), 1.08 (t, *J* = 7.5 Hz, 3 H).

Spectroscopic data were consistent with the earlier reported analytical information.

3-Ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (3)[5d]

To a stirred solution of compound **7** (0.2 g, 0.816 mmol, 1 equiv) in anisole (2 mL), TFA (2 mL) was added and the reaction mixture was heated at 80 °C for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was allowed to cool to rt, quenched with saturated $NaHCO_3$ solution (4 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 50:50) afforded pure **3** as a pale yellow solid; yield: 82 mg (81%).

Mp 103 °C (Lit.[5d] 102 °C); R_f = 0.3 (EtOAc–PE, 70:30).

IR ($CHCl_3$): 3440, 1722, 1216, 765 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.74 (br s, 1 H), 3.77 (s, 2 H), 2.24 (q, *J* = 7.5 Hz, 2 H), 1.96 (s, 3 H), 1.04 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.3, 148.6, 133.9, 50.0, 16.5, 13.1, 12.9.

HRMS (ESI): *m*/*z* calcd for $C_7H_{12}NO$ $[M + H]^+$: 126.0913; found: 126.0910.

1-Benzyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (8)

To a stirred solution of benzylamine (5.45 mL, 50 mmol, 1.14 equiv) in isopropyl alcohol (45 mL), compound **5** (5 g, 43.8 mmol, 1 equiv) was added at rt. The reaction mixture was stirred at 40 °C for 1 h, then cooled to 0 °C and treated with a freshly prepared solution of $NaBH_4$ (1.06 g, 28 mmol, 0.64 equiv) in water (15 mL) containing NaOH (1 mL, 50% w/w in water) while maintaining the internal temperature below 25 °C. The reaction mixture was stirred for 1.5 h at that temperature. Excess $NaBH_4$ was quenched by addition of acetone to the reaction mixture while maintaining the internal temperature below 30 °C. The mixture was filtered and AcOH (1 mL) was added to the filtrate to adjust the pH between 7–8 and the reaction mixture was heated to 50 °C for 16 h. The mixture was allowed to cool to rt and the solvent was evaporated under reduced pressure. The obtained residue was extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 50:50) afforded pure **8** as a yellow solid; yield: 5.65 g (69%).

Mp 96–98 °C; R_f = 0.3 (EtOAc–PE, 30:70).

IR ($CHCl_3$): 1674, 1217, 763 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.32–7.09 (m, 5 H), 5.82 (q, *J* = 1.4 Hz, 1 H), 4.53 (s, 2 H), 3.65 (s, 2 H), 1.95 (d, *J* = 1.4 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.9, 155.2, 137.3, 128.5 (2 C), 127.8 (C), 127.3, 122.5, 54.9, 45.6, 15.1.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{14}NO$ $[M + H]^+$: 188.1070; found: 188.1062.

1-Benzyl-3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (9)

To a stirred solution of compound **8** (8 g, 42.7 mmol, 1 equiv) in anhydrous THF (200 mL), NaH (1.13 g, 47.0 mmol, 1.1 equiv) was added slowly at 0 °C. The reaction mixture was stirred for 15 min, ethyl bromide (3.83 mL, 51.3 mmol, 1.2 equiv) in anhydrous THF (40 mL) was added dropwise at 0 °C, and stirring was continued for 3 h at that temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was treated with saturated NH_4Cl solution and extracted with EtOAc (3 × 200 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 35:65) afforded pure **9** as a sticky yellow solid [yield: 5.25 g (57%)] along with recovery of the starting material (1.5 g).

R_f = 0.26 (EtOAc–PE, 50:50).

IR ($CHCl_3$): 1703, 1216, 765 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.15 (m, 5 H), 4.60 (s, 2 H), 3.60 (s, 2 H), 2.31 (q, *J* = 7.5 Hz, 2 H), 1.62 (s, 3 H), 1.09 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 145.4, 137.6, 134.1, 128.6 (2 C), 128.0 (2 C), 127.3, 53.5, 45.9, 17.0, 13.1, 12.7.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{18}NO$ $[M + H]^+$: 216.1383; found: 216.1379.

3-Ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (3) by *N*-Debenzylation of Lactam 9

Method A: Microwave Assisted

To a glass vial, equipped with a Teflon cap, compound **9** (0.2 g, 0.93 mmol, 1 equiv) in toluene (2 mL) followed by triflic acid (0.328 mL, 3.72 mmol, 4 equiv) was added. The reaction mixture was kept for 45 min in a microwave reactor (Anton Paar, Monowave 300 microwave synthesis reactor) at 800 W (150 °C). The progress of the reaction was monitored by TLC. After completion, the reaction mixture was allowed to cool to rt, quenched with saturated $NaHCO_3$ solution (5 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 50:50) afforded pure **3** as a pale yellow solid; yield: 0.1 g (86%).

Method B: By Heating

To a stirred solution of compound **9** (3 g, 13.9 mmol, 1 equiv) in toluene (30 mL) was added triflic acid (4.94 mL 55.8 mmol, 4 equiv). The reaction mixture was heated at 160 °C for 24 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was allowed to cool to rt, quenched with saturated $NaHCO_3$ solution (20 mL), and extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer in vacuo followed by purification of the obtained residue by silica gel column chromatography (EtOAc–PE, 50:50) afforded pure **3** as a pale yellow solid; yield: 1.47 g (84%).

Mp 103 °C (Lit.[5d] 102 °C); R_f = 0.3 (EtOAc–PE, 70:30).

IR ($CHCl_3$): 3440, 1722, 1216, 765 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.74 (br s, 1 H), 3.77 (s, 2 H), 2.24 (q, *J* = 7.5 Hz, 2 H), 1.96 (s, 3 H), 1.04 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.3, 148.6, 133.9, 50.0, 16.5, 13.1, 12.9.

HRMS (ESI): *m*/*z* calcd for $C_7H_{12}NO$ $[M + H]^+$: 126.0913; found: 126.0910.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707344.

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