SYNTHETIC STUDIES TOWARDS STEMOAMIDE, PAROXETINE, FEMOXETINE, 3-HYDROXYPIPECOLIC ACID AND DEVELOPMENT OF SYNTHETIC METHODOLOGY

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Synthetic studies towards Stemoamide, Paroxetine, Femoxetine, 3-Hydroxypipecolic acid and development of synthetic methodology"** submitted by Mr. Kishor R. Harale was carried out by him under my supervision at National Chemical Laboratory, Pune. Material that has been obtained from other sources is duly acknowledged in this thesis.

June, 2012

National Chemical Laboratory

Pune 411 008

Dr. Subhash P. Chavan

Research Supervisor

DECLARATION

I hereby declare that the thesis entitled **"Synthetic studies towards Stemoamide, Paroxetine, Femoxetine, 3-Hydroxypipecolic acid and development of synthetic methodology"** submitted for Ph. D. degree to the University of Pune has been carried out at National Chemical Laboratory, under the supervision of Dr. Subhash P. Chavan. This work is original and has not been submitted in part or full by me for any degree or diploma to this or any other university.

June, 2012 Kishor R. Harale

Division of Organic Chemistry

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Dedicated to

…….my beloved Parents

Acknowledgements

As I complete my journey to the most cherished dream, it gives immense pleasure and sense of satisfaction to record my heartfelt gratitude to all those persons who have made this possible for me. I wish to express my heartfelt gratitude to my teacher and research supervisor ***Dr. Subhash P. Chavan*** *at the first place for believing in my abilities and providing me an incredible opportunity to pursue my career as a Ph. D. student. I thank him for his excellent guidance, constant encouragement, sincere advice, understanding and unstinted support during all the times of my Ph.D. life. My interactions with him have improved my belief towards research as well as real life. I consider very fortunate for my association with him, which has given a decisive turn and a significant boost in my career.*

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Kishor Ramarao Harale

NCL, Pune

Contents

Chapter 3: Synthetic studies towards stemoamide and development of Synthetic methodology for PMB protection of alcohols, selective mono and di-PMB protection of diols.

Section 1: Introduction to (–)-stemoamide

Section 2: Synthetic studies towards (−)-stemoamide

Section 3: Development of methodology for PMB protection of alcohols, selective mono and di-PMB protection of diols.

General Remarks

1. All the melting points are uncorrected and the temperatures are in the centigrade scale.
2. The compound numbers, Scheme numbers and reference numbers given in each section refer to that section only.
3. All the solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80 ºC.
4. Organic layers were dried over anhydrous sodium sulfate.
5. TLC analysis was carried out using thin layer plates pre-coated with silica gel 60 F254 (Merck) and visualized by fluorescence quenching or Iodine or by charring after treatment with *p*-anisaldehyde.
6. In cases where chromatographic purification was done, silica gel (200-400 mesh) was used as the stationary phase or otherwise as stated.
7. IR spectra were recorded on **Perkin-Elmer Infrared Spectrophotometer Model 68B** or on **Perkin-Elmer 1615 FT Infrared Spectrophotometer.**
8. ^{1}H NMR and ^{13}C NMR were recorded on **Bruker AV-200** (50 MHz) or **Bruker AV-400** (100 MHz) or **Bruker DRX-500** (125 MHz). Figures in the parentheses refer to ^{13}C frequencies. Tetramethyl silane was used as the internal standard.
9. Mass spectra were recorded at an ionization energy of 70 eV on **Finnigan MAT-1020**, automated GC/MS instrument and on **API Q STARPULSAR** using electron spray ionization [(ESI), solvent medium: a mixture of water, acetonitrile and ammonium acetate] technique and mass values are expressed as *m/z*. HRMS were recorded on a micromass Q-T of micro with spray source (ESI^{+}) mode.
10. Starting materials were obtained from commercial sources or prepared using known procedures.
11. Microanalysis data were obtained using a **Carlo-Erba CHNS-O EA 1108** elemental analyzer within the limits of accuracy (± 0.4%).

Ac	Acetyl
ADD	(Azodicarbonyl)dipiperidine
AIBN	2,2-Azobis(*iso*-butyronitrile)
Ar	Aryl
Aq.	Aqueous
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BMS	Borane dimethyl sulfide
Bn	Benzyl
Boc	*tert*-butoxy carbonyl
Bu	Butyl
s-Bu	*sec*-butyl
t-Bu	*tert*-butyl
CAN	Cerric ammonium nitrate
Cat.	Catalytic
Cbz	Carbobenzyloxy
m-CPBA	*meta*-chloroperbenzoic acid
CSA	Camphor sulfonic acid
DBDMH	1,3-Dibromo-5,5-dimethylhydantoin
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCB	1,2-Dichlorobenzene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEPT	Distortionless Enhancement by Polarization Transfer
DIAD	Diisopropylazodicarboxylate
DIBAL	Diisobutyl aluminium hydride
DIPT	Diisopropyltartrate

DMAP	4-Dimethylamino pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMS	Dimethy sulfide
DMSO	Dimethyl sulfoxide
dppf	(Bis-diphenylphosphino)ferrocenyl
Et	Ethyl
g	gram(s)
GABA	Gamma-aminobutyric acid
h	hour(s)
IPA	*iso*-propyl alcohol
IR	Infra red
HMPA	hexamethylphosphoramide
Hz	Hertz
KHMDS	Potassium hexamethyl disilazide
LDA	Lithium diisopropyl amide
LHMDS	Lithium hexamethyl disilazide
LICA	Lithium isopropyl cyclohexylamide
MAD	Methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide)
Me	Methyl
min	minute(s)
mL	mililitres
Mp	Melting point
Ms	Methanesulfonyl
MVK	Methyl vinyl ketone
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	*N*-methyl morpholine oxide
NMR	Nuclear magnetic resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PCC	Pyridinium chlorocromate

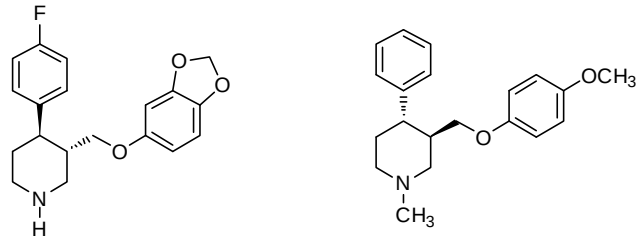
PDC	Pyridinium dichromate
PEG	Polyethylene glycol
PHMS	Poly(hydromethylysiloxane)
PLE	Pig liver esterase
PMB	*para*-methoxybenzyl
PPA	Polyphosphoric acid
PTAB	Phenyl trimethylammonium tribromide
PTC	Phase transfer catalysis
PPTS	Pyridinium *para*-toluene sulfonate
PTSA	*para*-toluene sulfonic acid
rt	Room temperature
TBAB	Tetrabutyl ammonium bromide
$TBAHSO_4$	Tetrabutyl ammonium hydrogen sulfate
TBAI	Tetrabutyl ammonium iodide
TBSOTf	*tert*-butyldimethylsilyl triflate
TBSCl	*tert*-butyldimethylsilyl chloride
TFA	Trifluoroacetic acid
THF	Tetrahydofuran
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMSCl	Trimethylsilyl chloride
Ts	Toluenesulfonyl
Triton-B	Benzyltrimethylammonium hydroxide

The thesis entitled, **"Synthetic studies towards Stemoamide, Paroxetine, Femoxetine, 3-Hydroxypipecolic Acid and development of synthetic methodology"** is divided into three chapters.

Chapter first deals with the introduction and synthesis of (±)-paroxetine and (±)-femoxetine. The second chapter deals with the introduction and synthesis of 3-hydroxypipecolic acid. The synthetic studies towards (–)-stemoamide and a methodology for PMB protection of alcohols described in chapter third.

Chapter 1. Synthetic studies towards (±)-paroxetine and (±)-femoxetine

Section 1: Introduction to paroxetine and femoxetine. The present section includes the details about biological action and comprehensive literature on synthesis of Paroxetine and femoxetine. Both Paroxetine and Femoxetine are the potent antidepressants and these are selective serotonin reuptake inhibitor. Both share a common backbone of 3,4-trans disubstituted piperidine core (Figure 1).

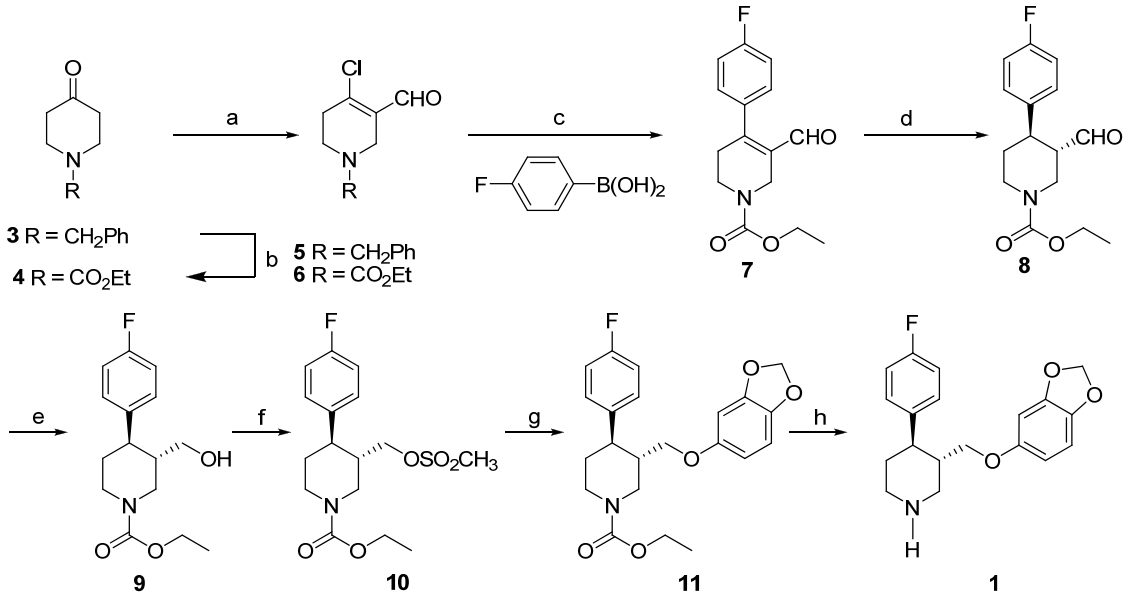


1 (-)-Paroxetine **2** (+)-Femoxetine

Figure 1. Structure of (-)-Paroxetine and (+)-Femoxetine.

Section 2: Total synthesis of (±)-paroxetine

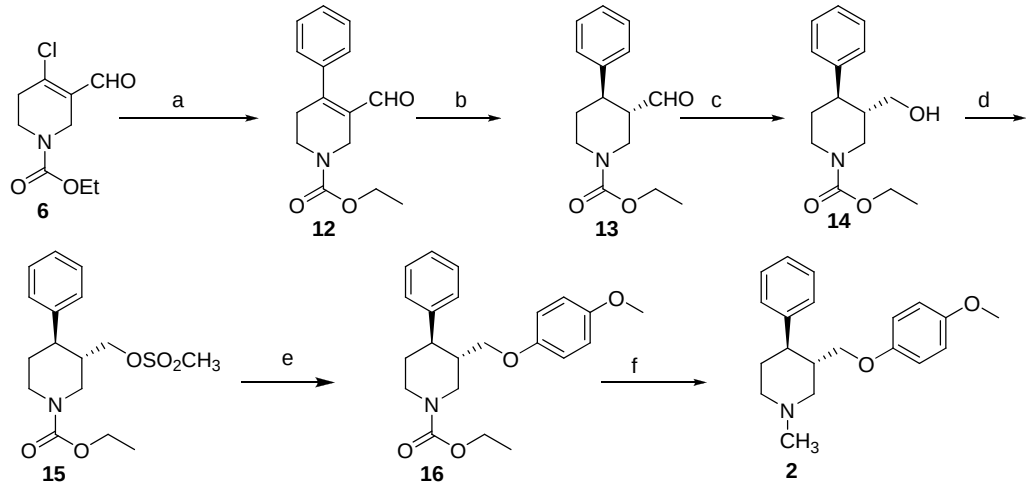
The synthesis started with the commercially available *N*-benzyl-4- piperidone **2** (Scheme 1). *N*-benzyl-4- piperidone on Vilsmeier-Haack formylation provided chloro aldehyde **5** a key intermediate. Suzuki coupling of **5** gave aldehyde **7**, which on reduction provided alcohol **9**. Alcohol **9** on mesylation followed by replacement of mesyl by sesamol moiety provided **11**, which on carbamate deprotection provided (±)-**1**.



Scheme 1: Synthesis of (±)-Paroxetine.

Reagents and conditions: *a) DMF, $POCl_3$, DCM, rt, 90% b) EtOCOCl, Na_2CO_3, DCM, 95% c) p-Fluoro phenylboronicacid, $Pd(OAc)_2$, TBAB, K_2CO_3, H_2O, 50 ^{o} C, 73% d) H_2, Pd/C, MeOH, 50% e) $NaBH_4$, MeOH, 95% f) CH_3SO_2Cl, Et_3N, DCM, quant. g) Sesamol, NaH, DMF, reflux, 61% h) KOH, MeOH, reflux, 70%.*

Section 3: Total synthesis of (±)-femoxetine



Scheme 2: Synthesis of femoxetine

Reagents and conditions: a) phenylboronic acid, TBAB, K_2CO_3, $Pd(OAc)_2$, H_2O, 50°C, 70% b) H_2,Pd-C, MeOH, rt, 56% c) $NaBH_4$, MeOH, quant. d) CH_3SO_2Cl, Et_3N, DCM, quant. e) p-methoxyphenol, NaH, DMF, reflux, 72% f) LAH, THF, rt, 85%.

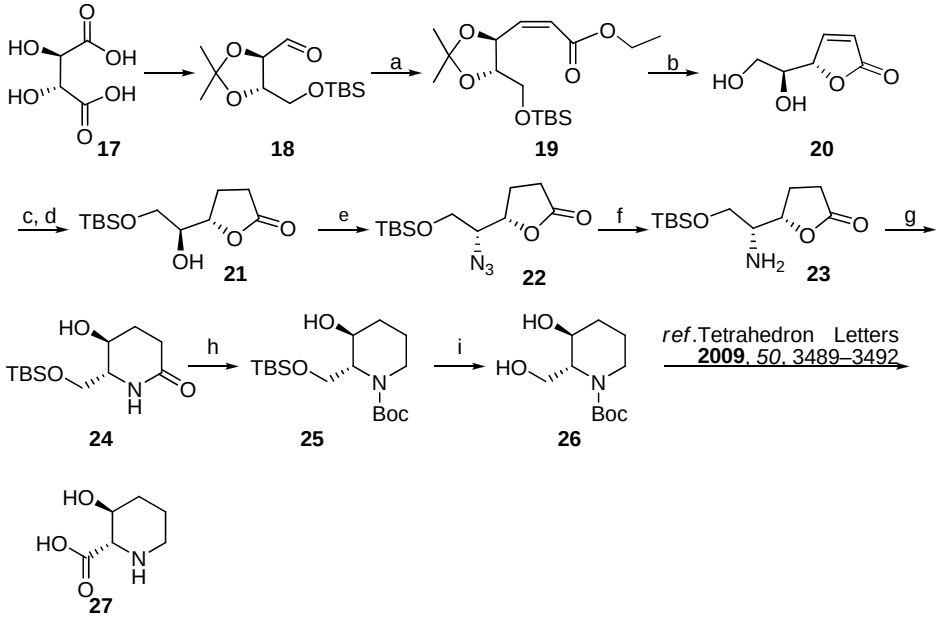
This section describes the synthesis of (±)-femoxetine. The total synthesis of (±) femoxetine started from **6** as described in Scheme 2. The Suzuki coupling followed by catalytic reduction of double bond as well as aldehyde with sodium borohydride provided **14**. The mesylation of **14** followed by replacement with *p*-methoxyphenol and carbamate reduction leads to (±)-**2**.

Chapter 2. Synthetic studies towards (2*S*,3*S*)-3-hydroxypipecolic acid

Section 1: Introduction to (2*S*,3*S*)-3-hydroxypipecolic acid

This section describes the biological activity and reported synthetic routes to (2*S*,3*S*)-3-hydroxypipecolic acid **27**. (2*S*,3*S*)-3-hydroxypipecolic acid **27** belongs to the azasugar family compounds. It is constituent of many biologically active compounds like swainsonine, prosopinene, nojirimycin, febrifugine and tetrazomine.

Section 2: Formal synthesis of (2*S*,3*S*)-3-hydroxy pipecolic acid



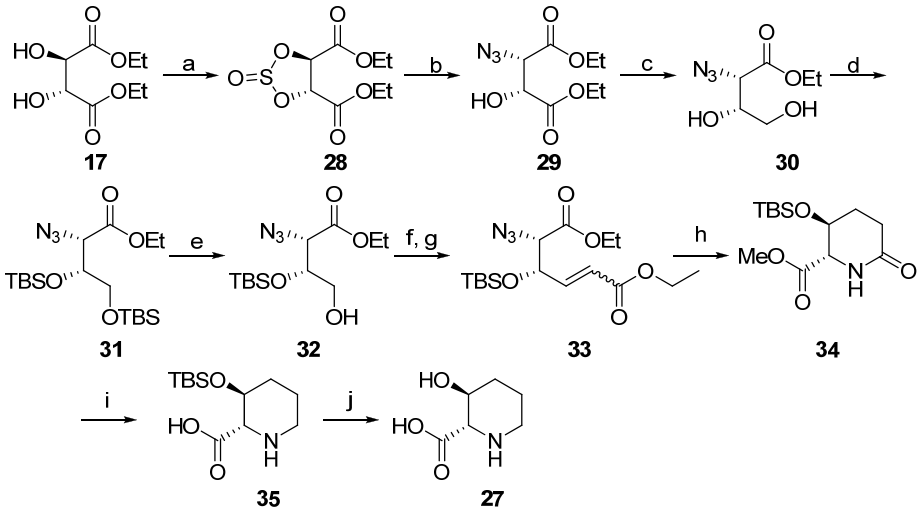
Scheme 3. Synthesis of (2*S*,3*S*)-3-Hydroxy pipecolic acid

Reagnets and conditions: a) $Ph_3PCHCOOEt$, MeOH, –50 ^oC, 70% b) Cat. H_2SO_4, MeOH, 82% c) H_2, Pd/C, MeOH d)TBSCl, Et_3N, DCM, 80 % (over two steps) e) HN_3, PPh_3, DEAD, THF, 92% f) H_2, Pd/C, MeOH, 95% g) MeONa, MeOH, 83% h) BH_3.DMS, THF and then Boc_2O. Et_3N, 73% i) TBAF, THF, 88%.

The synthesis started from L-(+)-tartaric acid (Scheme 3), which was converted to aldehyde **18** by known method. The Wittig reaction on aldehyde followed by acid treatment provided lactone **20.** The amine **23** was obtained by hydrogenation, selective mono TBS protection and Mitsunobu reaction on **20**. Cyclisation of amine **23**, amide reduction followed by Boc protection and TBS deprotection provided piperidine **26**.

Section 3: Total synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid

Another approach for synthesis of 3-hydroxy pipecolic acid started from L(+)-tartaric acid (Scheme 4) is described in the present section.



Scheme 4. Synthesis of Pipecolic acid

Reagents and conditions: a) $SOCl_2$, Cat. DMF, CCl_4, reflux b) NaN_3, DMF, 74% (over two steps) c) BH_3.DMS, Cat. $NaBH_4$, THF, 60% d) TBSOTf, Et_3N, DCM, 85% e) PPTS, MeOH, 78% f) IBX, EtOAc, reflux g) Ph_3PCHCO_2Et, toluene, reflux, 75% (over two steps) h) H_2, Pd/C, EtOH, 90% i) BH_3.DMS, THF, 78% j) 6N, HCl, reflux, 91%

The sulfite **28** was opened with azide followed by selective reduction of ester moiety in **29** provided azido alcohol **30**. The di-TBS protection, selective mono TBS deprotection followed by oxidation and two carbon Wittig reaction provided unsaturated ester **33.**

Azide **33** on hydrogenation followed by selective amide reduction and acid treatment furnished target molecule **27**.

Chapter 3: Synthetic studies towards stemoamide and methodology for PMB protection of alcohols, selective mono PMB protection of diols & di-PMB protection of diols.

Section 1: Introduction to (-)-Stemoamide

The present section describes the isolation and reported synthetic approaches for the synthesis of (–)-Stemoamide **36** (figure 2).

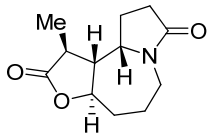


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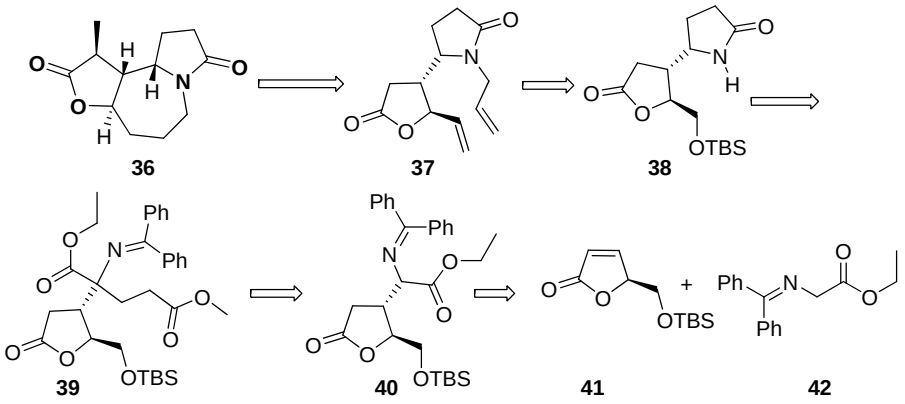
Figure 2: (-)-Stemoamide

Section 2: Synthetic studies towards (–)-stemoamide

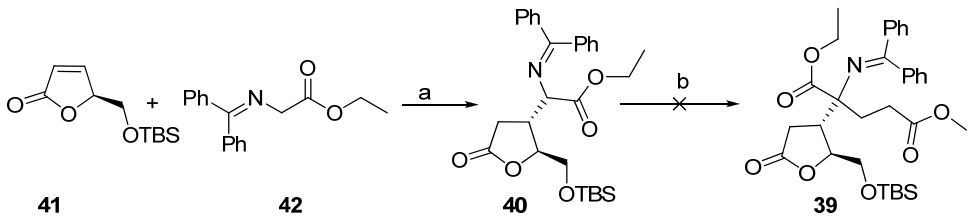
Our retrosynthetic plan is shown in scheme 5.



36 **37** **38** **39** **40** **41** **42**

Scheme 5: Retrosynthesis for (–)-**36**.

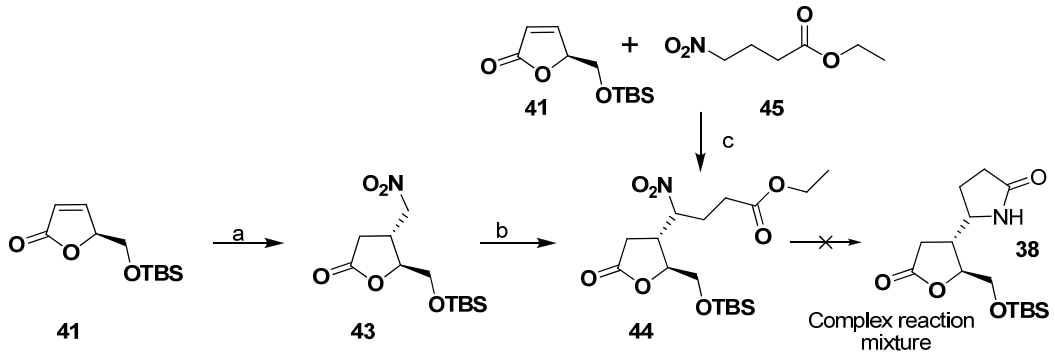
The butenolide fragment **41** was prepared from D-mannitol diacetonide by known method. Conjugate addition of imine **42** on **41** provided butyrolactone **40** (Scheme 6). However subjecting **40** to Michael addition with ethyl acrylate did not furnish the desired ester **39**.



Scheme 6. Synthesis of Stemoamide.

Reagents and conditions: a) LiBr, Et_3N, THF, 80% b) Ethyl acrylate, NaH, THF

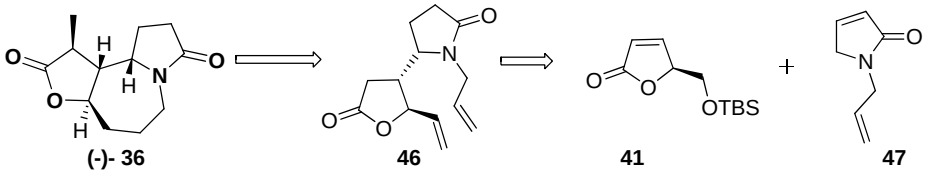
After failure in C-C bond formation the strategy was changed. The nitroester **44** was obtained by two strategies as shown in scheme 7. The attempts to reduce nitro group to the amine to obtain lactam **38** failed in spite of several conditions tried.



Scheme 7. Synthesis of Stemoamide

Reagents and conditions: a) Nitromethane, DBU, 84% b) Ethyl acrylate, DBU, CH_3CN, 75%, c) NaOEt, THF, reflux, 78%

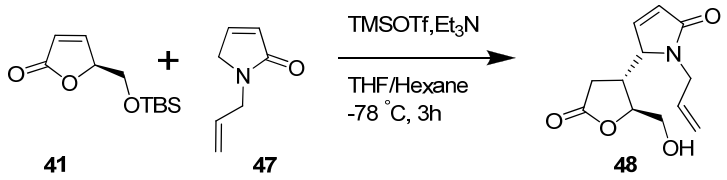
Taking in account failure of the two approaches, the plan was changed. The revised retrosynthetic plan is shown in Scheme 8.



Scheme 8. Retrosynthetic analysis for **43**.

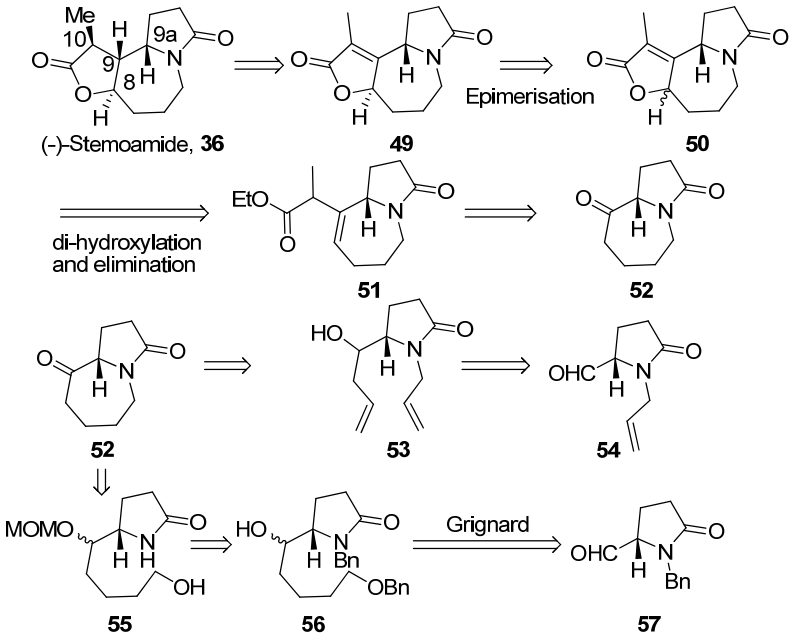
The *N*-allyl pyrrolinone **47** was prepared from methyl crotonate in five steps. According to the plan Vinylogous Mukaiyama Michael reaction was carried out in between

substrates **41** & **47**, which provided **48,** which was confirmed by mass but furnished complex ^{1}H-NMR (Scheme 9).



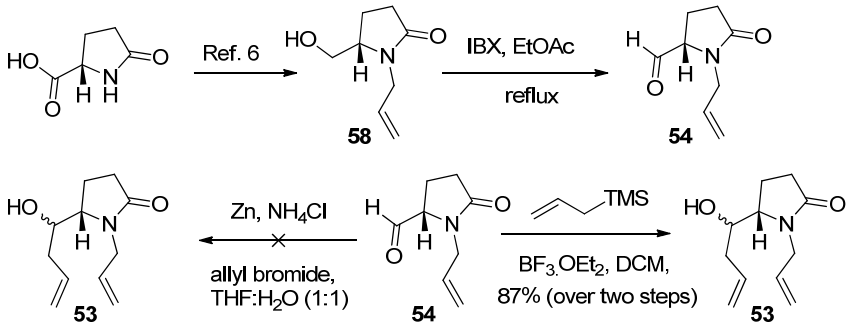
Scheme 9. Vinylogous Mukaiyama Michael reaction

Unfortunately in this case also the required product could not be obtained. Hence again the strategy was changed. It is according to the retrosynthesis shown in Scheme 10.



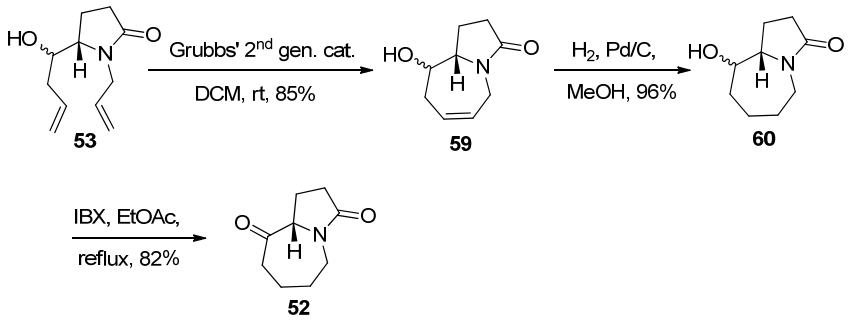
Scheme 10. New retrosynthetic plan to **36**

Synthesis started from L-pyroglutamic acid (Scheme 11). Allylation of **54** using allyltrimethyl silane furnished diallyl alcohol **53**.



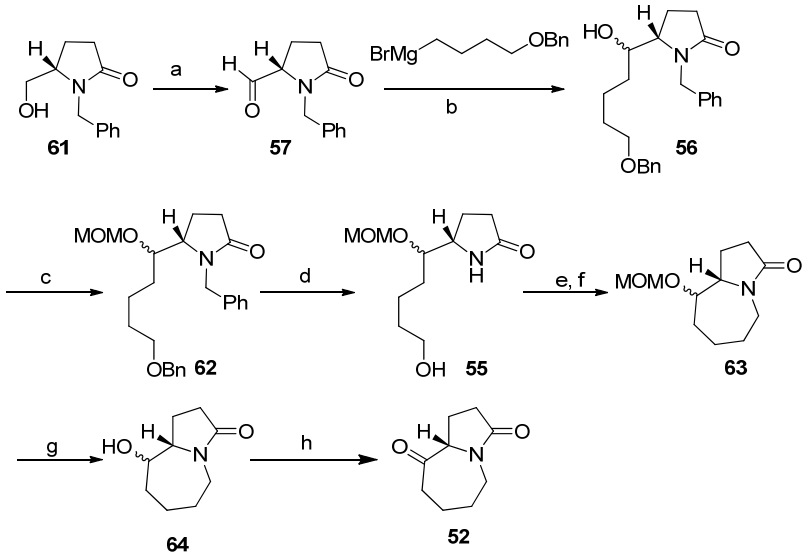
Scheme 11. Synthesis of diallyl alcohol **53** from **57**

The crucial intermediate ketone **52** was prepared by subjecting **53** to RCM followed by hydrogenation and oxidation (Scheme 12).



Scheme 12. Synthesis of ketone **52**

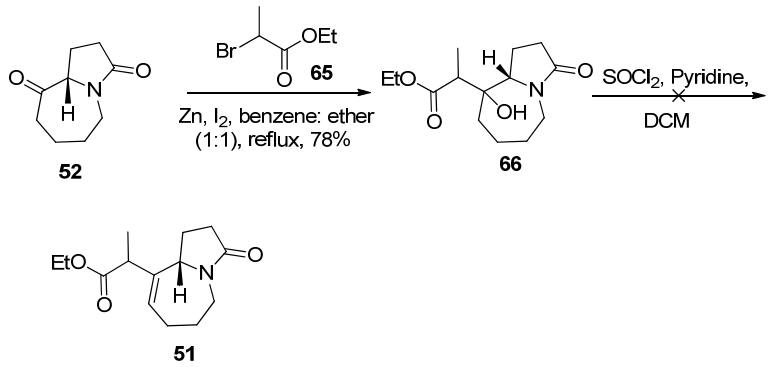
The alternative approach to RCM for the synthesis of **52** is depicted in Scheme 13.



Scheme 13. Synthesis of ketone **21** alternate route to RCM

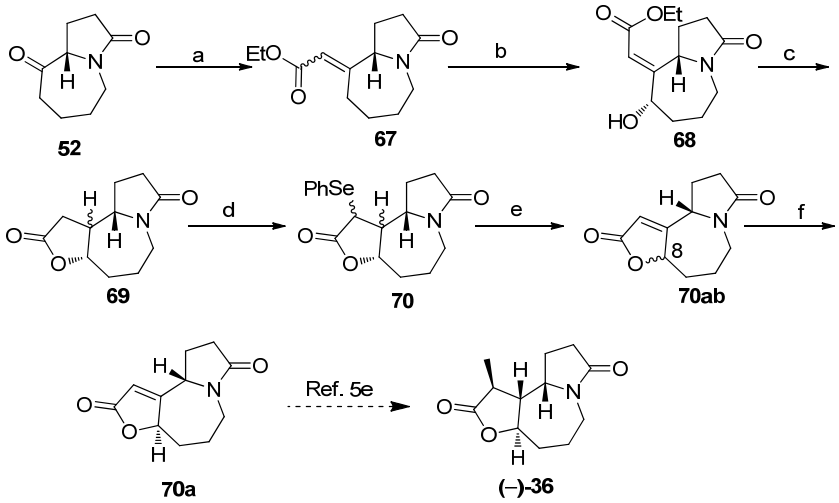
Reagents and conditions: a) IBX, EtOAc, reflux b) THF, –50 ^{o}C (74% over two steps) c) MOMCl, DIPEA, DCM, reflux, 90% d) Na, NH_3, THF, –78 ^{o}C, 87% e) MsCl, Et_3N, DCM f) NaH, THF (86% over two steps) g) trace HCl, MeOH, reflux, 74% h) IBX, EtOAc, reflux, 82%

Accordingly ketone **52** was subjected to Reformatsky reaction using ethyl propionate to provide alcohol **39** (Scheme 14). Elimination of **39** furnished the undesired products.



Scheme 14. Construction of butenolide ring

Since the problem was faced during elimination Wittig Horner reaction on **52** was carried out which furnished **67.** The allylic oxidation of **67** followed by reduction furnished butyrolactone **69**. The selenation of **69** followed by selenoxide formation and elimination to funrnish butenolide **70ab** which on epimerization gave **70a**. This constitutes a formal total synthesis of Stemoamide.

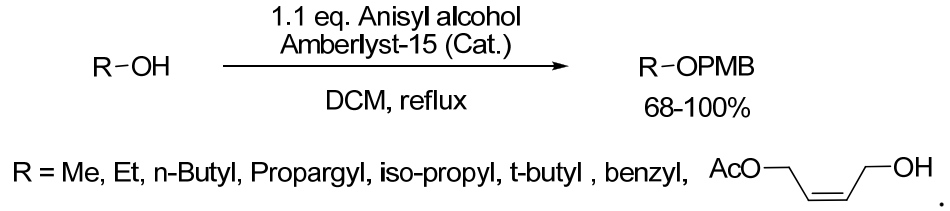


Scheme 15. Alternative route for butenolide ring construction.

Reagents and conditions: a) Triethyl phosphonoacetate, NaH, benzene, 88% b) SeO_2, AcOH, reflux, 45% c) $NiCl_2$, $NaBH_4$, THF, 78% d) LiHMDS, PhSeBr, THF, 95% e) 30% H_2O_2, DCM, 92% f) Et_3N, DCM, 2 days

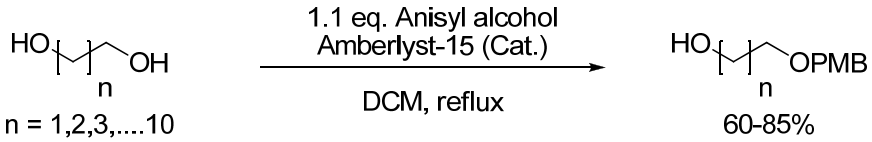
Section 3: Development of methodology for PMB protection of alcohols, selective Mono-PMB protection of diols and di-PMB protection of diols

The present section describes an efficient, practical and catalytic methodology for PMB protection of alcohols, selective mono PMB protection of diols and di-PMB protection of diols. PMB protection of alcohols carried out using anisyl alcohol and cat. Amberlyst-15 in DCM



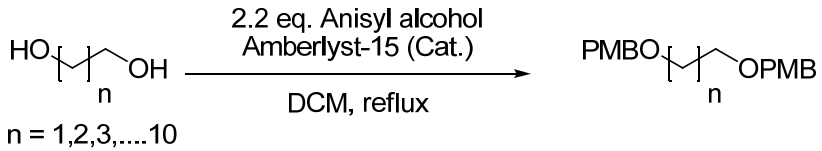
Scheme 16. PMB protection of alcohols.

The catalyst Amberlyst-15 was recycled and reused; up to 3 times it gives good yield without loss in activity. The conventional methods for mono-PMB protection of diols are associated with low yield and di-PMB protected compounds as a common impurity. Thus a mild, highly selective and simple method for mono-PMB protection of diols has been developed.



Scheme 17. Selective mono PMB protection of diols.

The various diols furnished good yields of mono-PMB protected diols. The di-PMB protection of diols was also carried out successfully in yields ranging from 75-92 % (Scheme 18).



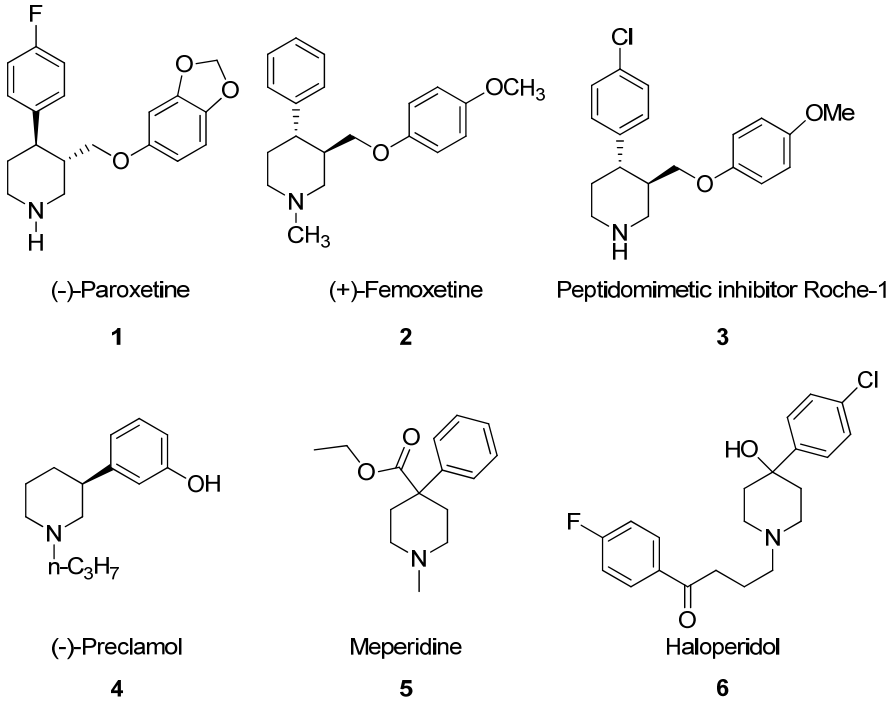
Scheme 18. di-PMB protection of diols

Chapter 1. Synthetic studies towards (±)-Paroxetine and (±)-Femoxetine

Section 1: Introduction to Paroxetine and Femoxetine

1.1.1. Introduction

The class of compounds containing 3, 4-disubstituted piperidine ring as a core structure is of substantial medicinal use. Many biological compounds, which consist the piperidine core have wide range of biological activity.[1] The biological activity of these classes of compounds depends on the position and substitution at the piperidine ring. The two molecules belonging to the 3, 4-disubstituted piperidine class are paroxetine (**1**)[2] and femoxetine (**2**), both are the well known antidepressant drugs.



(-)-Paroxetine **1** | (+)-Femoxetine **2** | Peptidomimetic inhibitor Roche-1 **3**

(-)-Preclamol **4** | Meperidine **5** | Haloperidol **6**

Figure 1

Paroxetine is a selective serotonin reuptake inhibitor (SSRI) introduced in market by a pharmaceutical company, GlaxoSmithKline in 1992. Paroxetine is mainly used for the treatment of major depression, obsessive-compulsive disorder (OCD), panic disorder, social anxiety and generalized anxiety disorder in adult outpatients.[3] Paroxetine is marketed under trade names Paxil, Seroxat and Aropax.

Femoxetine (**2**) and piperidine Roche-1 (**3**) have close proximity in structure with paroxetine (**1**) and also act as a potent SSRI. The piperidine Roche-1 (**3**) is a nonpeptide peptidomimetic type III inhibitor of rennin. The other structurally related piperidine

biologically active compounds include preclamol (**4**) which is a dopamine (DA) autoreceptor agonist at the D_2 receptor,[4] meperidine (**5**)[5] is an opoid analgesic drug and haloperidol (**6**)[6] is an antipsychotic drug. This shows the broad spectrum of biologically active piperidine derivatives.

1.1.2. Pharmacology

The human brain consists of neurotransmitters[7] like serotonin or 5-hydroxy tryptamine (5HT), dopamine, noradrenaline (NA) or norepinephrine (NE), acetylcholine (ACh), glutamate and GABA. These neurotransmitters work as signal transmitters, the imbalance of neurotransmitters results in depression in man. If a person has reduced levels of serotonin and noradrenaline in the part of the brain that controls above said factors, the person is said to be suffering from depression. There are many theories about how depression occurs but present day clinical pharmacology treats depression on the basis of monoamine hypothesis.[8] Paroxetine is a potent and selective inhibitor of the neuronal reuptake of serotonin (5-hydroxytryptamine; 5-HT),[9] which results in increased concentration of serotonin. Paroxetine is also found to be useful in other disorders like obsessive compulsive disorder and panic disorder.[10] The short term clinical trial studies indicated that paroxetine has greater clinical improvements compared to placebo. A similar type of improvement in reduction of depression was observed in case of paroxetine compared to other agents like tricyclic antidepressants, maprotiline, nefazodone and the selective serotonin reuptake inhibitors like fluoxetine, sertraline and fluvoxamine. Up to one year treatment of patients with paroxetine indicated that, this is effective in prevention of relapse or recurrence of depression. In elders the overall efficacy of paroxetine was found to be good compared with other agents.

In conclusion, paroxetine is effective and well tolerated, and suitable as first-line therapy for depression. It also appears to be a useful alternative to other available agents for the treatment of patients with OCD or panic disorder.

1.1.3. Literature review

The piperidine alkaloids have broad spectrum of biological activities. The potent antidepressant properties of both paroxetine and femoxetine attracted attention of many

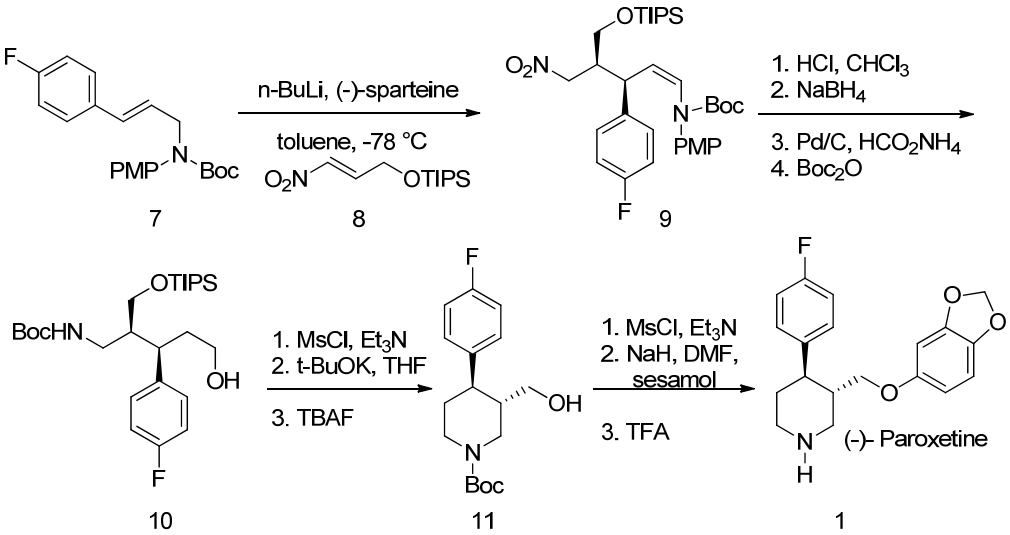
organic chemists. The broad classification of the reported routes based on piperidine ring construction are categorized as (a) asymmetric synthesis using chiral ligands (b) synthesis using chiral auxiliaries (c) using chiral pool approach (d) using resolution strategy and (e) miscellaneous. Some of the important syntheses from each class have been discussed below.

(a) Asymmetric syntheses using chiral ligands

In this section the reported syntheses for paroxetine and femoxetine are mainly based on asymmetric conjugate addition of active methylene compounds on the unsaturated electron withdrawing partners. The other reports are based on asymmetric reduction and asymmetric alkylation as well as arylation.

Beak's Approach (*J. Am. Chem. Soc.* **2001**, *123*, 1004–1005; *J. Am. Chem. Soc*. **2002**, *124*, 11689–11698)

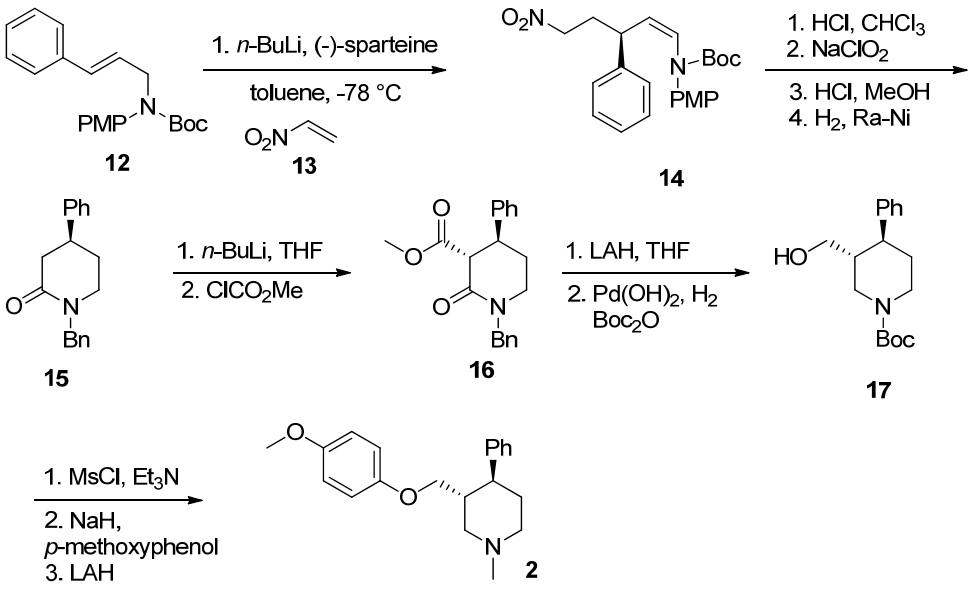
Beak *et al*. developed a novel diastereoselective conjugate addition of allylamines on the nitro alkenes in presence of (–)-sparteine as a chiral ligand. The conjugate addition of allylamines on nitro alkenes was exploited for the synthesis of (–)-paroxetine (**1**) as well as (+)-femoxetine (**2**) (Scheme 1 & 2).[11]



Scheme 1

The protected allylamine **7** was treated with nitro alkene **8** in presence of *n*-BuLi and (–)-sparteine as a ligand to furnish nitro amine **9**. Subsequent acidification of **9** provided aldehyde which was reduced using $NaBH_4$. The nitro group was reduced using palladium/C as the catalyst and ammonium formate as the hydrogen donor and the resultant amine was protected as its Boc derivative to provide carbamate alcohol **10**. Mesylation of amino alcohol **10** and subsequent treatment with base and TBAF provided piperidine **11**. Hydroxy group in **11** was mesylated and replaced by sesamol using base, to provide (–)-paroxetine (**1**).

Beak *et al*. also achieved the synthesis of (+)-femoxetine (**2**) using diastereoselective conjugate addition (Scheme 2).

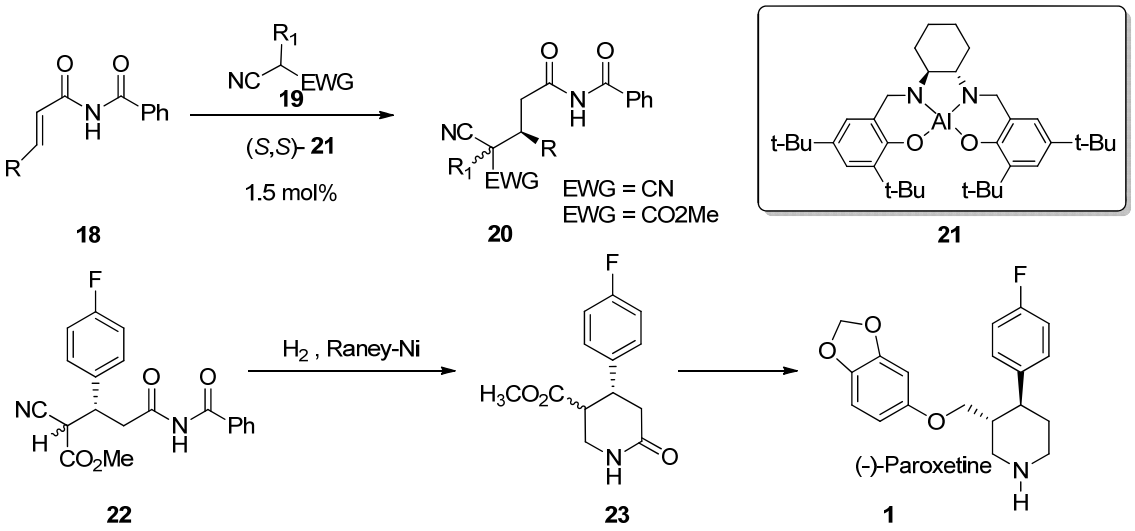


Scheme 2

The conjugate addition of protected allylamine **12** on nitroalkene **13** in presence of *n*-BuLi and (–)-sparteine provided nitro allylamine **14**. The allylamine **14** was converted to aldehyde on acidification which was subsequently oxidized to acid and further converted to ester. The nitro group on reduction was furnished lactam **15,** which was treated with *n*-BuLi and methyl chloroformate to provide lactam ester **16**. The lactam ester **16** was reduced to alcohol **17**, which in turn was converted to its mesyl derivative and replaced with *p*-methoxyphenol which on LAH reduction furnished femoxetine (**2**).

Jacobsen's approach (*J. Am. Chem. Soc.* **2003**, *125*, 11204–11205)

Jacobsen *et al*. demonstrated the use of Al-salen complex for the asymmetric conjugate addition of aryl and heteroaryl cyanoacetates to alkyl and aryl substituted unsaturated imides. The method was further exploited for the synthesis of (–)-paroxetine (**1**) (Scheme 3).[12]



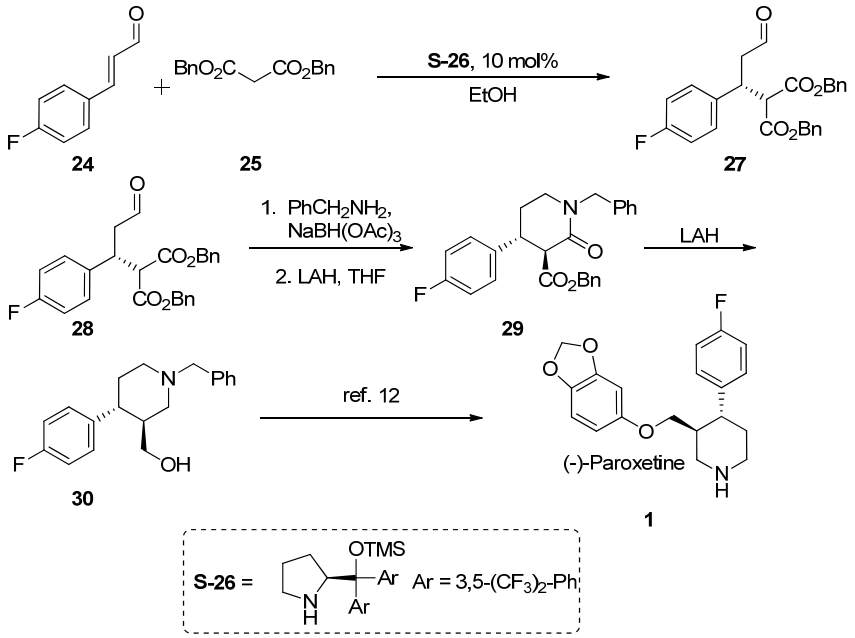
Scheme 3

The conjugate addition of **19** (EWG = CO_2Me) on *p*-fluoroaryl substituted imide **18** gave cyano imide **20**. The cyano group in imide **20** was reduced using Raney-Ni to furnish lactam **23**, which was further transformed to (–)-paroxetine (**1**).

Jørgensen's approach (*Angew. Chem. Int. Ed.* **2006**, *45*, 4305 –4309)

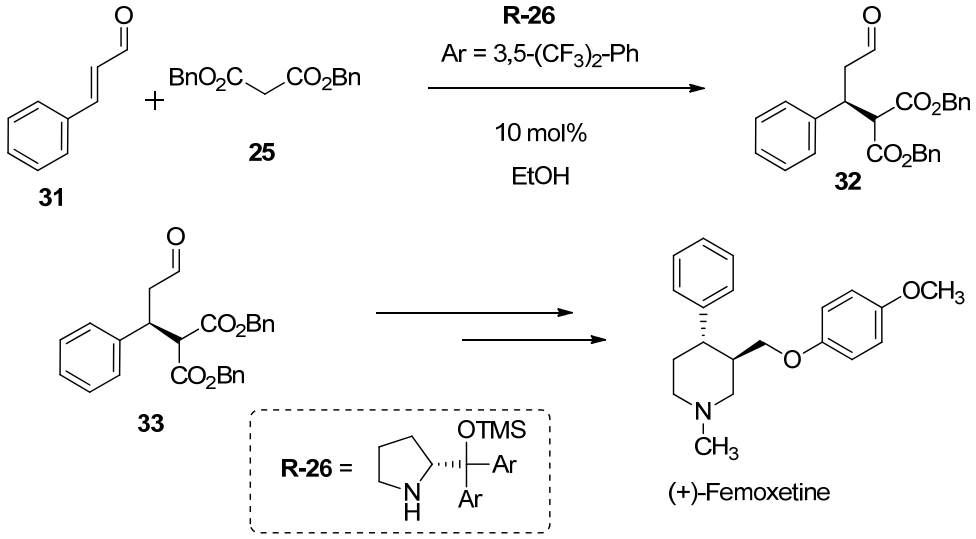
The first organocatalytic approach for the synthesis of (–)-paroxetine (**1**) & (+)-femoxetine (**2**) was reported by Jørgensen *et al*.[13a] An efficient organocatalytic enantioselective conjugate addition of malonates to aromatic α,β-unsaturated aldehydes was developed and exploited for the synthesis of **1** and **2** (Scheme 4). The conjugate addition of di-benzyl malonate (**25**) on unsaturated aldehyde **24** in presence of (*S*)-**26** provided **27** in more than 92% ee. The aldehyde ester **27** was subjected to reductive amination using benzyl amine followed by LAH reduction to provide alcohol **30**, which

has been already reported to be converted to (–)-paroxetine (**1**) thus accomplishing the formal synthesis of (–)-paroxetine (**1**).



Scheme 4

The use of *R*-**26** for conjugate addition (Scheme 5) of di-benzyl malonate (**25**) on cinnamaldehyde **31** provided aldehyde ester **32**, which was exploited for the formal synthesis of (+)-femoxetine (**2**) in two steps. A similar strategy for the synthesis of (–)-paroxetine **1** appeared from Rios *et al*. in 2009 (*Tetrahedron Lett.* **2009**, *50*, 1943–1946).[13b]



Scheme 5

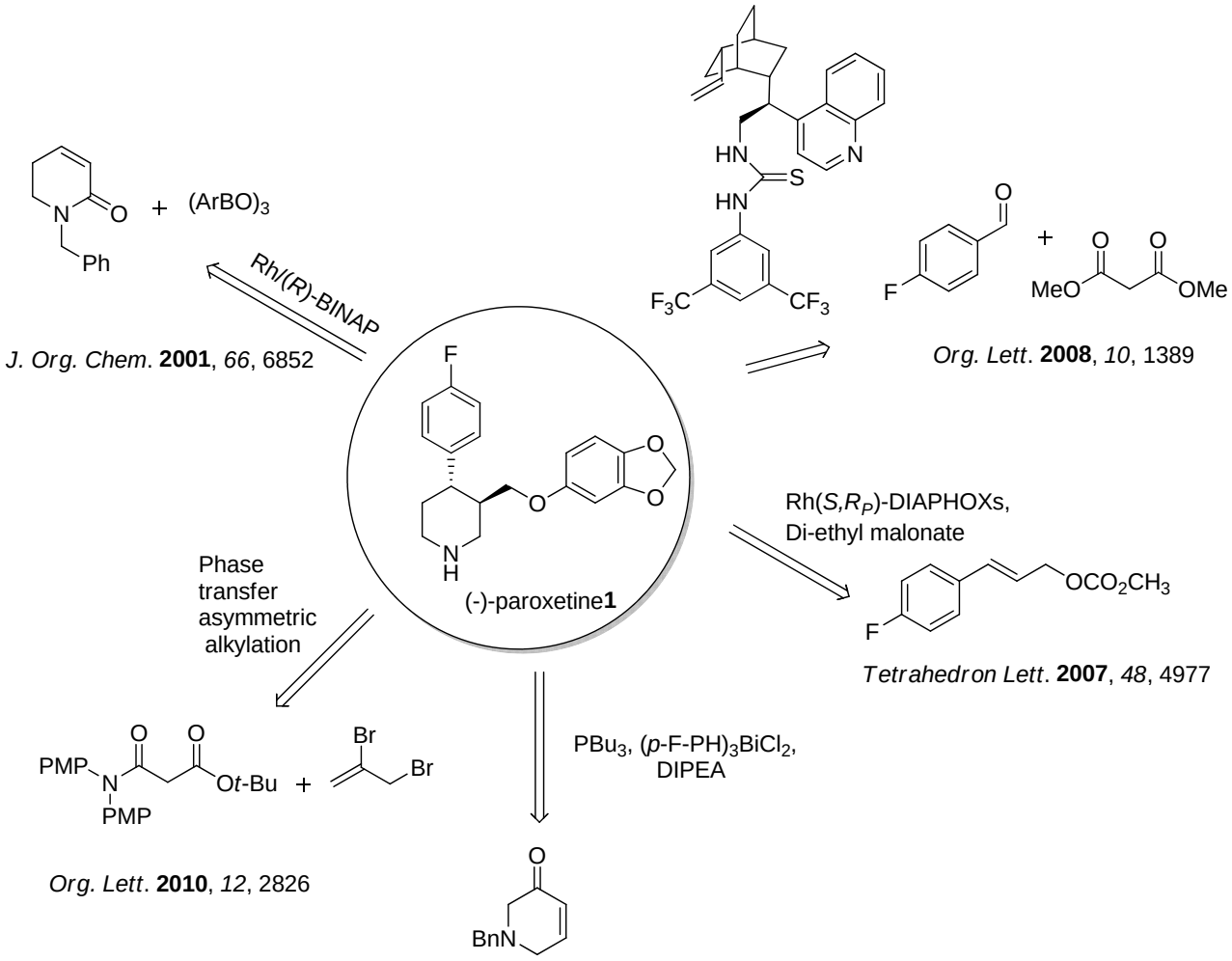


Figure 2

The other syntheses of paroxetine and femoxetine using conjugate addition are by Hayashi *et al*.[14] (*J. Org. Chem.* **2001**, *66,* 6852-6856) and Dixon *et al*. (*Organic Lett.* **2008**, *10*, 1389-1391). Hayashi *et al*. used the stereoselective conjugate addition of substituted aryl boron reagents using BINAP ligands on α,β-unsaturated δ-lactams (Figure 2). Dixon *et al*. reported the synthesis of (–)-paroxetine (**1**) using enantioselective Michael addition of malonates to nitro olefins using quinine derived bi-functionalorganocatalyst (Figure 2).[15] Jew *et al*. (*Organic Letters* **2010**, *12*, 2826-2829) developed stereoselective alkylation of malonamides using phase transfer chiral

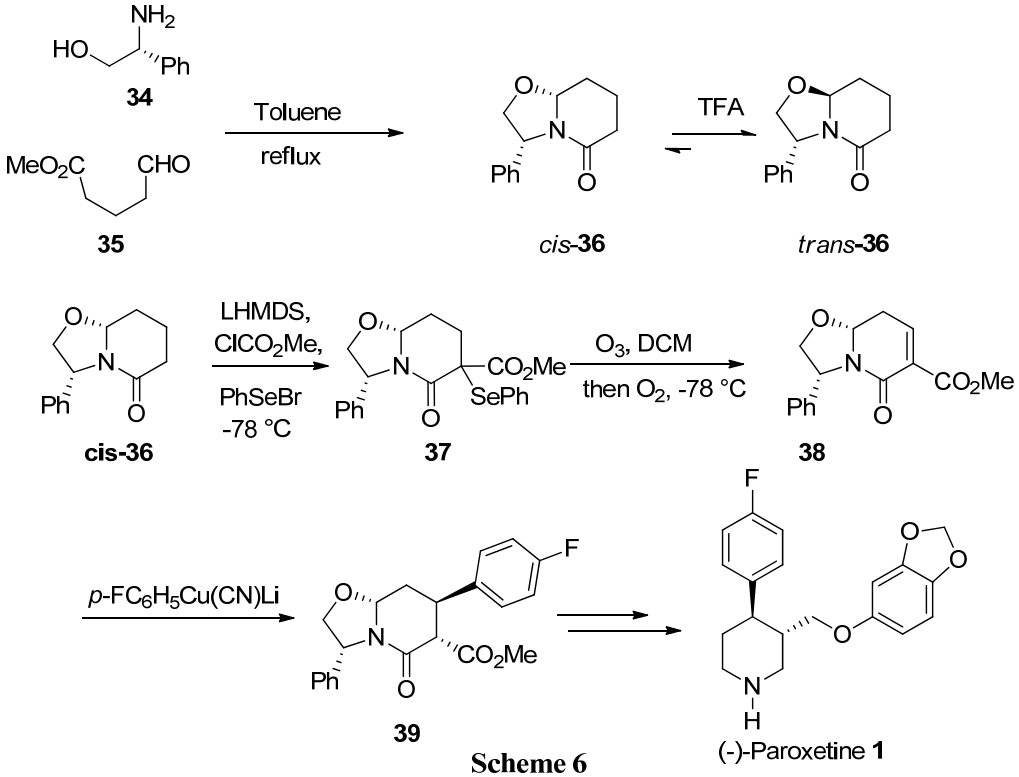
catalyst.[16] The alkylated product was further transformed to (–)-paroxetine (**1**) in 15 steps (Figure 2). Hamada *et al*. (*Tetrahedron Lett*. **2007**, *48*, 4977–4981) carried out the nucleophilic addition to allyl-carbonates using, Ir(DIAPHOX) catalyst and the substituted product obtained was converted to (–)-paroxetine (**1)**.[17] Krische *et al*. (*Tetrahedron* **2006**, *62*, 10594–10602) in 2006 reported synthesis of **1** using Heck arylation strategy (Figure 2).[18]

b) Syntheses using chiral auxiliaries

The majority of reports employed the chiral auxiliaries as ester derivatives for the diastereoselective conjugate addition on α,β-unsaturated-δ-lactams.

Amat's approach (*J. Org. Chem.* **2000**, *65*, 3074–3084); *Tetrahedron: Asymmetry,* **1996**, *7*, 1591-1594)

Amat *et al*. used a phenyl glycinol **34** as a chiral auxiliary in order to prepare the α,β-unsaturated-δ-lactams as a precursor to carry out the diastereoselective conjugate addition



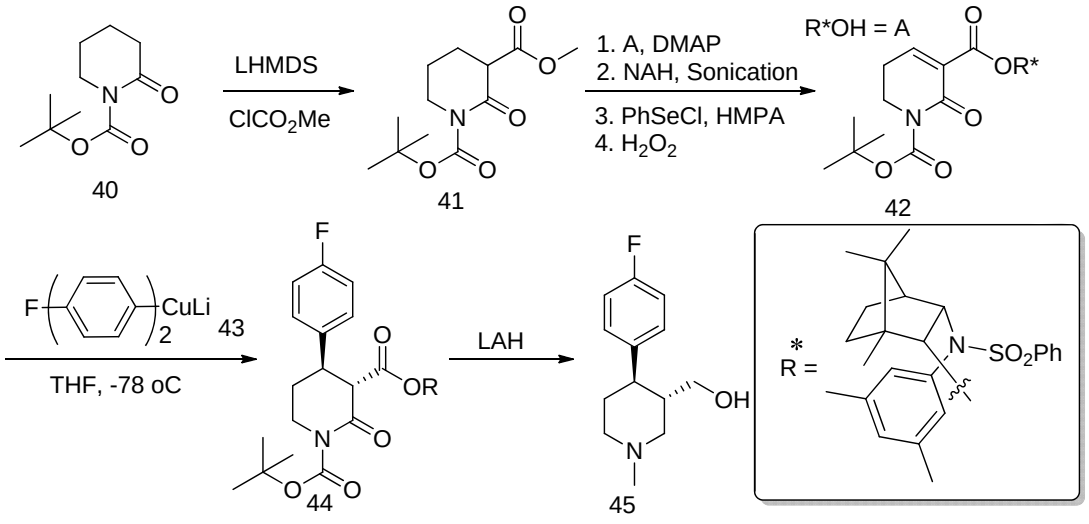
Scheme 6

of organocuprates with good diastereoselectivity (Scheme 6). Reaction of phenyl glycinol **34** with 5-oxopentanoate **35** gave the *cis* and *trans* lactams **36** with equilibrium favored towards *cis*-**36**. The *cis*-bicyclic lactam **36** on one-pot treatment with LHMDS, methylchloroformate and phenylselenyl bromide furnished the seleno ester **37** which was converted to unsaturated lactam **38**. The diastereoselective conjugate addition of *p*-fluorophenyl cuprate reagent was carried on unsaturated lactam **38** to give lactam **39** with a very high diastereoselectivity (97:3). The lactam **39** was further transformed to (–)-paroxetine **1** in 4 steps.[19]

Keshava Murthy *et al*. (*Tetrahedron Lett.* **2003**, *44*, 5355-5358) also reported the similar type of conjugate addition using Oppolzer's (1*S*)-(–)-camphorsultam as a chiral auxiliary and aryl magnesium reagents with good diastereoselectivity for the addition.[20]

Cossy's approach (*New J. Chem.* **2003**, *27*, 475–482*; Tetrahedron Lett.* **2001**, *42*, 7805–7807)

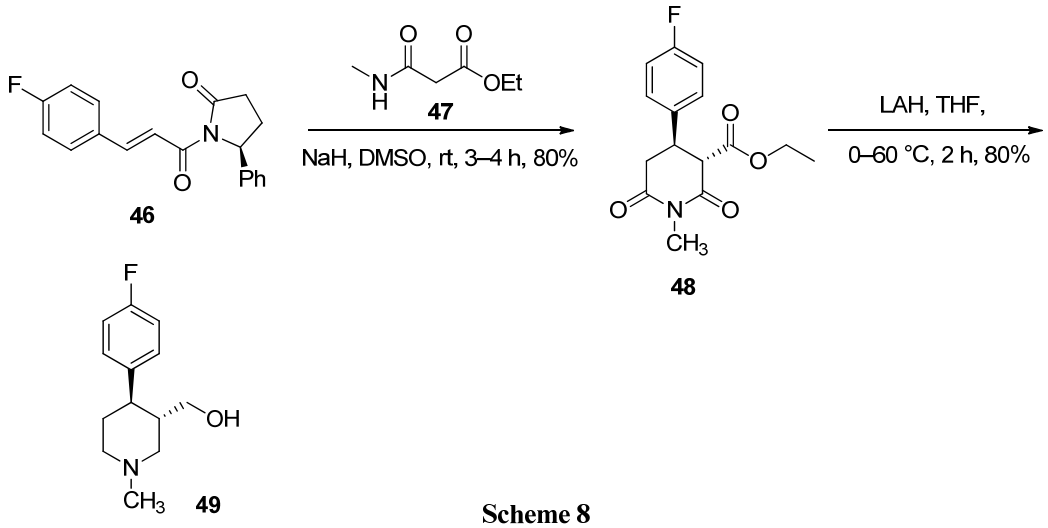
Cossy *et al*. used the δ-valerolactam for the synthesis of paroxetine **1** (Scheme 7). The crucial intermediate α,β-unsaturated ester **42** was prepared by treatment of lactam **40** with strong base LHMDS, methyl chloroformate followed by transesterification with camphor derived chiral auxiliary.[21]



Scheme 7

The diastereoselective conjugate addition of *p*-fluoro phenyl lithium cuprate **43** on α,β-unsaturated ester **42** furnished ester **44** with excellent diastereoselectivity (98: 2). The amido ester **44** was subjected to reduction using LAH, which was further converted to (–)-paroxetine **1**.

Reddy's approach (*Tetrahedron: Asymmetry* **2011**, *22*, 1–3) Reddy *et al*.[22] recently used the diastereoselective conjugate addition on α,β-unsaturated amido ester **46** of ethyl-*N*-methylmalonamide (**47**), by taking the advantage of the Evans chiral auxiliary for the formal synthesis of (–)-paroxetine **1** (Scheme 8).



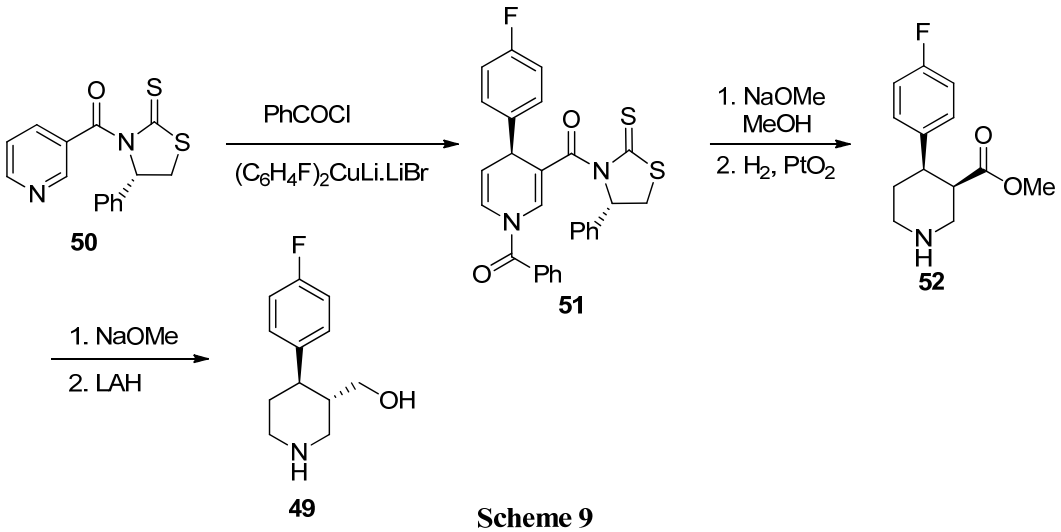
Scheme 8

The conjugate addition of **46** and **47** in the presence of NaH and DMSO furnished imide **48.** The subsequent reduction of imide **48** furnished alcohol **49** which is a crucial intermediate for the synthesis of paroxetine **1**.

Yamada's Approach (*Tetrahedron Lett.* **2005**, *46*, 8673-8676)

Yamada *et al*. used the novel face selective addition of aryl cuprates to chiral pyridinium salt. The face selectivity was attributed to the selective blockage of one face due to the electronic interaction between sulfur and pyridinium salt (Scheme 9). Amide **50** on treatment with benzoyl chloride and diaryl lithiumcuprate at -78 ºC furnished amide **51** in 78% yield and >99% de. The chiral auxiliary was removed using NaOMe, MeOH and reduction using PtO_2/H_2 provided amino ester **52**. The amino ester **52** was epimerized using NaOMe and the resulting ester was reduced using LAH to furnish alcohol **49** in

quantitative yield. Similarly the formal synthesis of (+)-femoxetine (**2**) was achieved by using the other enantiomer of the chiral auxiliary for the conjugate addition.[23]

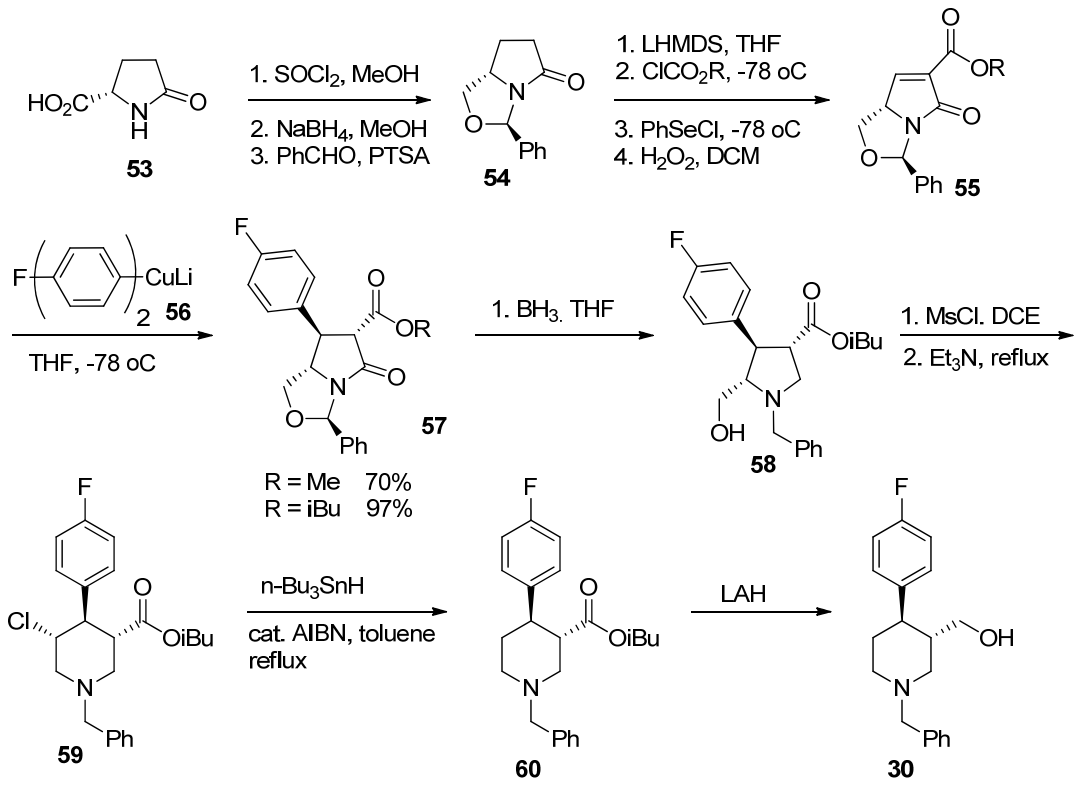


Scheme 9

(c) Syntheses using chiral pool approach

Cossy's Approach (*Eur. J. Org. Chem.* **2002**, 3543-3551; *Tetrahedron Lett*. **2001**, *42*, 5705–5707)

Cossy *et al*. used pyroglutamic acid as a chiral starting material for the formal synthesis of (–)-paroxetine (**1**) (Scheme 10). The key steps used are the ring enlargement from five to six membered ring and diastereoselective conjugate addition. L-pyroglutamic acid was esterified using thionyl chloride in methanol. The resultant ester was reduced with $NaBH_4$ and the alcohol as well as amide was protected using benzaldehyde PTSA to furnish the bicyclic compound **54**. The α,β-unsaturated amido-ester **55** was prepared from **54** by treatment with LHMDS and corresponding chloroformate followed by phenyl selenyl chloride and elimination using hydrogen peroxide. The conjugate addition of **56** was carried out on **55** in THF at –78 ºC followed by reduction using borane THF to furnish amino alcohol **58**. In a key step, amino alcohol **58** on treatment with mesyl chloride and triethylamine furnished amino ester **59**.



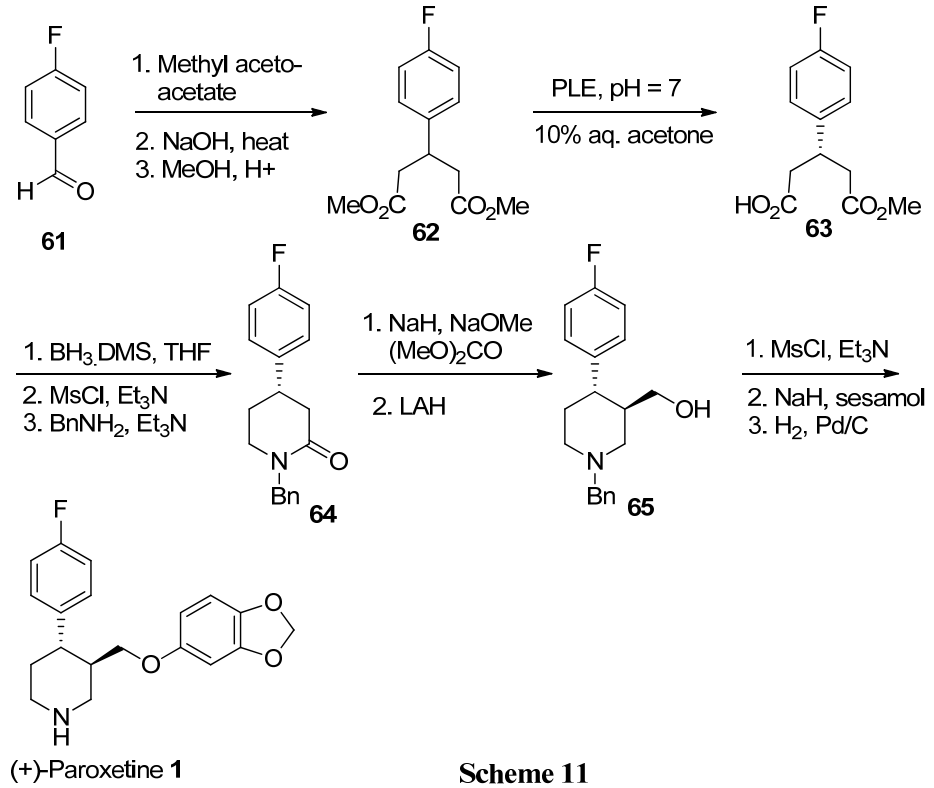
Scheme 10

Dechlorination of **59** was carried out using tributyltin hydride and catalytic AIBN to give amino ester **60**. The ester **60** was reduced using LAH in THF to provide alcohol **30**.[24]

(d) Synthesis using desymmetrisation and resolution strategy

Yu`s Approach (*Tetrahedron Lett.* **2000**, *41*, 5647-5651)

Yu *et al*. used the desymmetrisation of the glutaric ester **62** using pig liver esterase enzyme (PLE) (Scheme 11). *p*-Fluorobenzaldehyde was subjected to reaction with methyl acetoacetate, followed by NaOH and esterification to furnish substituted glutaric acid ester **62**. The substituted glutaric acid diester **62** was subjected to enzymatic desymmetrization using PLE (600U) to provide acid ester **63** in 86% and 94% ee. The acid **63** was reduced to alcohol using borane dimethylsulfide complex and subsequently the alcohol was mesylated and treated with benzylamine to furnish amide **64**. The α-functionalisation of amide **64** was carried out using NaH, dimethyl carbonate and the resultant ester as well as amide were reduced using LAH to give alcohol **65**. The alcohol

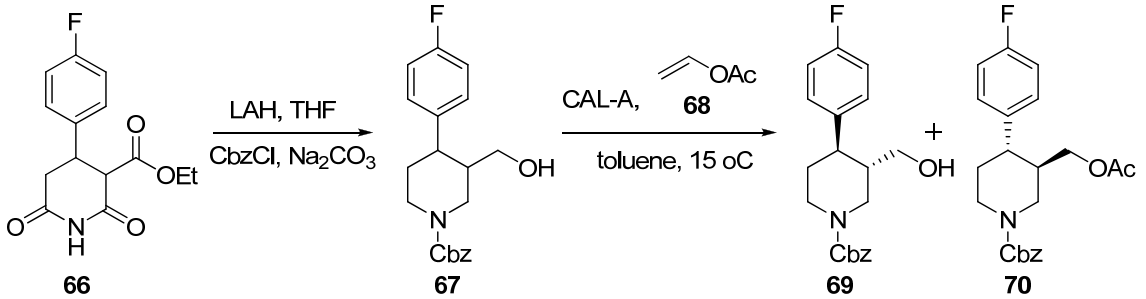


Scheme 11

in amino alcohol **65** was exchanged with sesamol *via* mesylate and the benzyl deprotection on hydrogenation using palladium furnished (+)-paroxetine (**1**).[25]

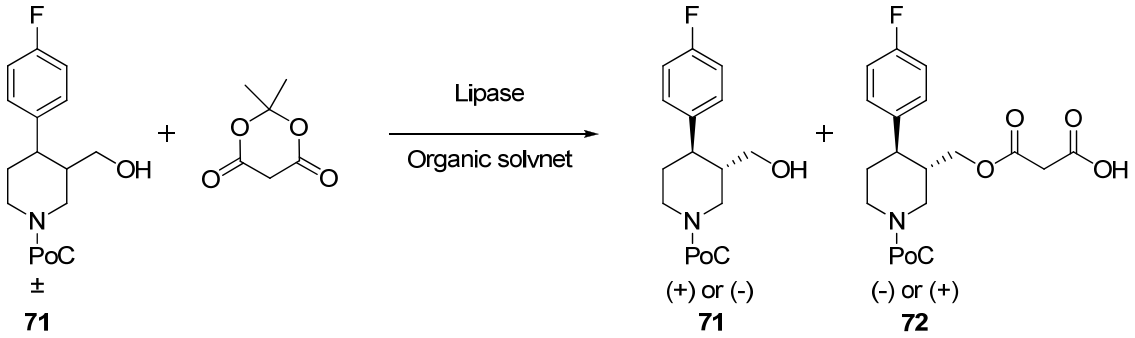
Gotor's Approach (*J. Org. Chem.* **2001,** *66*, 8947-8953, *J. Org. Chem.* **2003**, *68*, 3333-3336)

Gotor *et al*. have done the extensive optimization of the conditions for the resolution of alcohol **67** (Scheme 12). The enzyme CAL-A and vinyl acetate **68** as an acylating agent in toluene at 15 ºC proved to be the ideal conditions.[26]



Scheme 12

Gotor *et al*. (Scheme 13) in 2003 reported the 2nd resolution approach using enzymes CAL-A, CAL-B and cyclic anhydride. CAL-A and CAL-B furnished complementary enantiopreference for opposite enantiomers. The *trans*-alcohol on treatment with CAL-A lipase enzyme in toluene at 30 ºC provided the (3*R*, 4*S*)-**71.** However, the CAL-B lipase provided the enantiomer of **71** under identical conditions.[27]

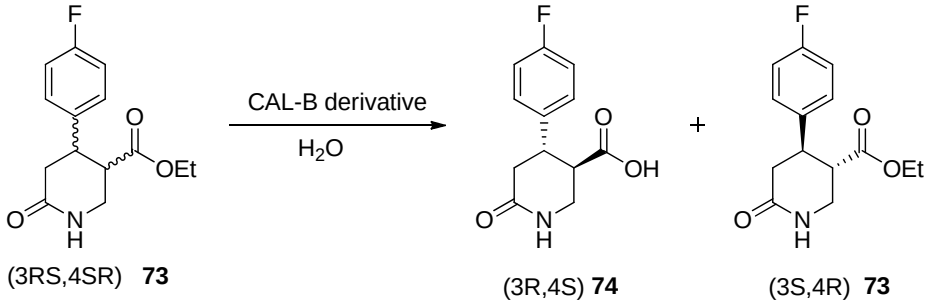


Scheme 13

The present method provides the access to both the enantiomers of the alcohol **71** in efficient manner.

Guisan's approach (Tetrahedron: *Asymmetry* **2002**, *13*, 2375–2381)

Guisan *et al*. (Tetrahedron: *Asymmetry* **2002**, *13*, 2375–2381) (Scheme 14) carried out the enzymatic resolution of amido ester **73** using the CAL-B enzyme in aqueous conditions with >99% ee.[28]

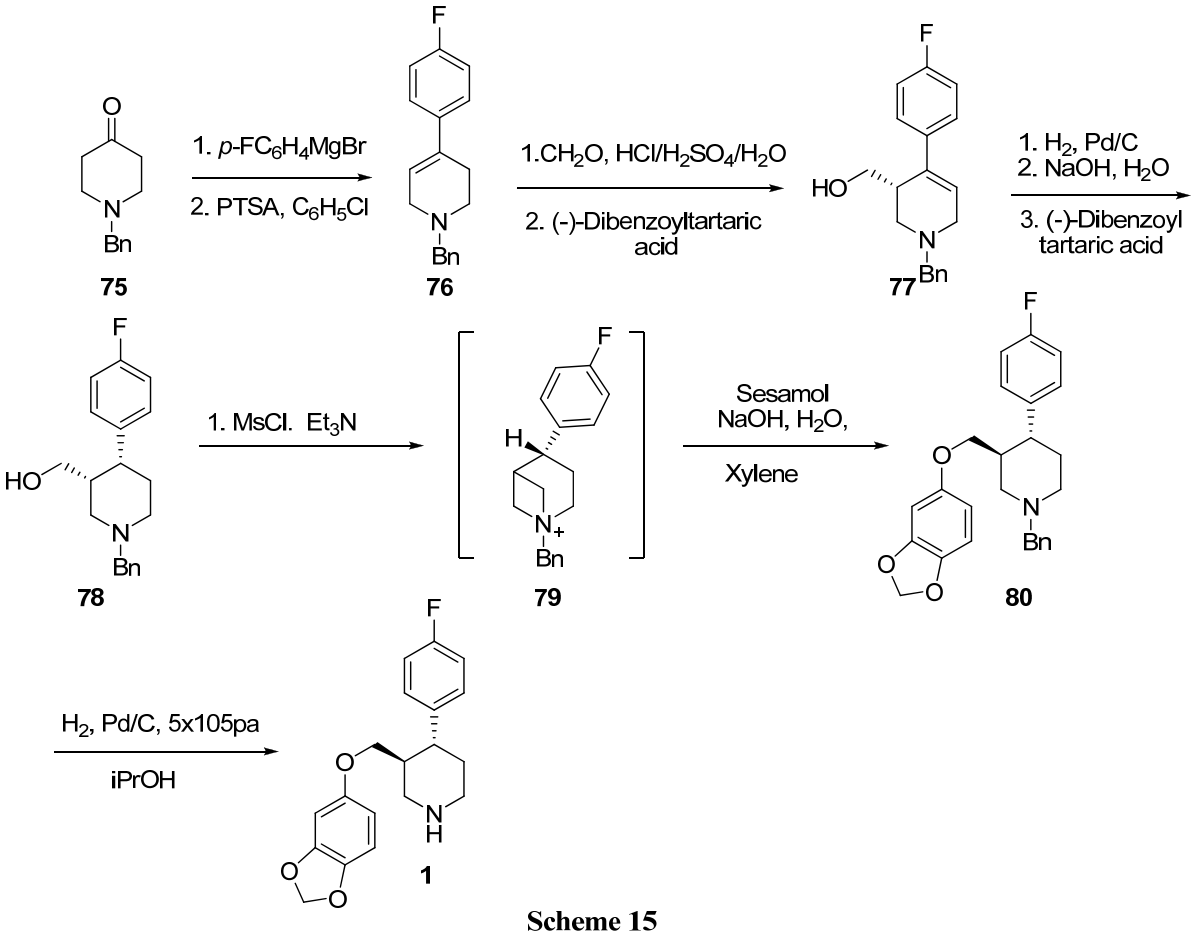


Scheme 14

Nemes's Approach (*Eur. J. Org. Chem.* **2004**, 3336-3339)

Nemes *et al*. (Scheme 15) exploited the *N*-benzyl piperidone **75** for the synthesis of (–)-paroxetine (**1**). The key steps used are Prins reaction on amino alkene **76** using

formaldehyde and acid resolution of and the resulting alcohol **77** using (–)-dibenzoyltartaric acid. Double bond in amino alcohol **77** was hydrogenated using palladium under hydrogen atmosphere to furnish *syn* amino alcohol **78** which on mesylation followed by replacement of mesyl group with sesamol provided **80**. The compound **80** was debenzylated to provide paroxetine **1**.[29]

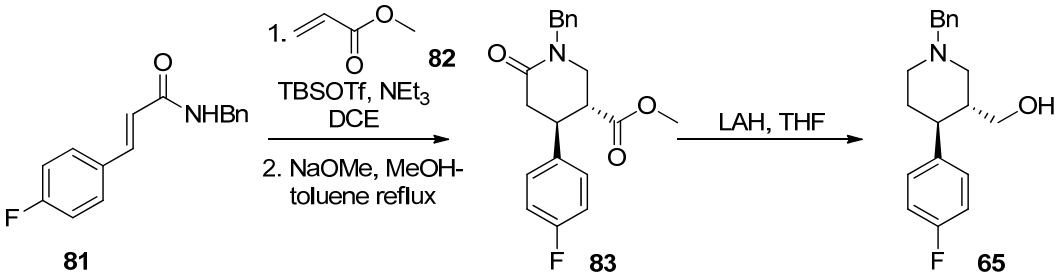


Scheme 15

(e) Miscellaneous Approaches

Ihara's Approach (*J. Org. Chem.* **2005**, *70*, 3957-3962)

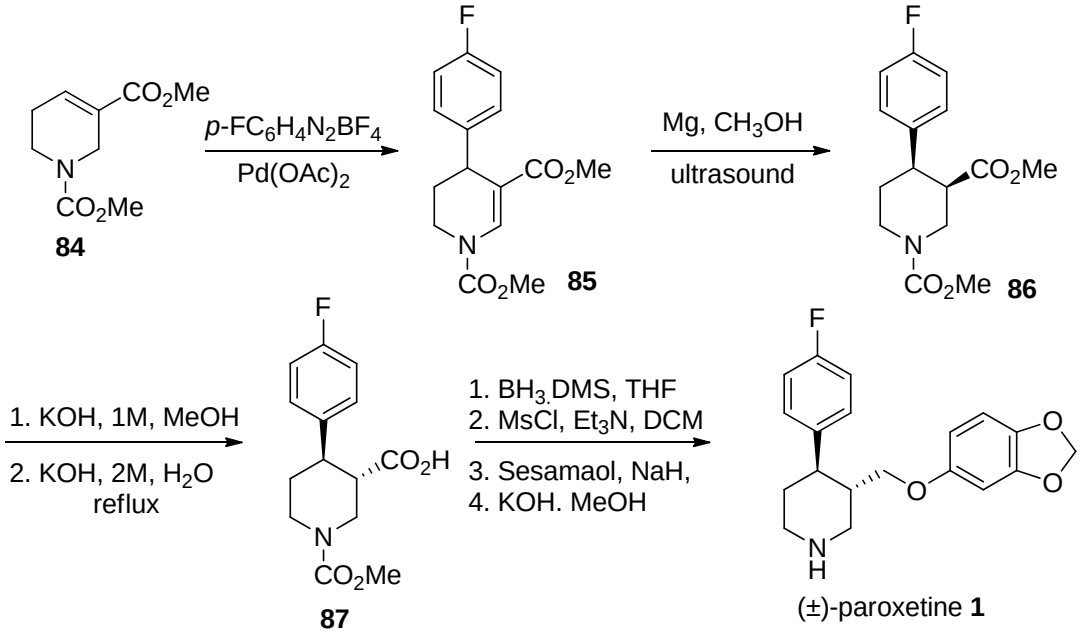
Ihara *et al* (Scheme 16) reported novel racemic formal synthesis of paroxetine using aza-double Michael addition of α,β-unsaturated amides with unsaturated carbonyls.



Scheme 16

The unsaturated amide **81** was treated with methyl acrylate **82** in presence of TBSOTf and triethylamine followed by treatment with sodium methoxide to furnish lactam **83** in 58% yield. The lactam was reduced using LAH in THF to give alcohol **65**.[30]

Correia's Approach (*Org. Lett.* **2006**, *8*, 1657-1660)



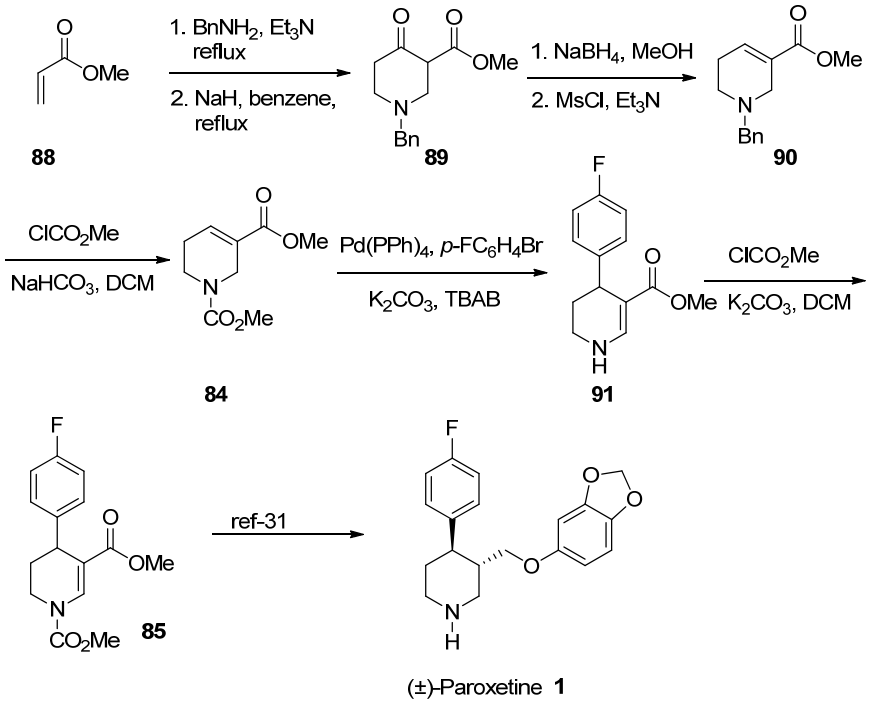
Scheme 17

Correia *et al*. (Scheme 17) developed a Heck arylation of acyclic- and cyclic-substituted acrylates using different substituted tetrafluoroborates**.** The method was exploited for the synthesis of racemic paroxetine. The unsaturated ester **84** was subjected to Heck reaction using *p*-fluorobenzenetetrafluoroborate in presence of palladium acetate to give ester **85** with shifting of double bond. Double bond in **85** was reduced using Mg, methanol to furnish the *cis* product **86**. Ester **86** was transformed to *trans* ester using KOH, methanol and hydrolyzed using KOH in water to acid **87**. Acid **87** was reduced using borane

dimethylsulfide complex and the resulting alcohol was mesylated, replaced with sesamol using NaH in DMF and finally carbamate was deprotected using base to furnish racemic paroxetine **1**.[31]

Chavan's Approach (*Synth. Commun.* **2007**, *37*, 3143-3149)

Concurrent to Correia's approach this group reported the synthesis of racemic paroxetine **1** (Scheme 18) starting from cheap and commercially available starting materials benzylamine and methyl acrylate. The key step used is the Heck reaction using *p*-fluorobromobenzene in presence of palladium catalyst in aqueous conditions. Methyl



Scheme 18

acrylate on refluxing with benzyl amine and triethyl amine gave double Michael adduct of benzyl amine which on treatment with NaH underwent Dieckmann condensation to furnish β-keto ester **89**. β-keto ester **89** on $NaBH_4$ reduction followed by mesylation provided eliminated product α,β-unsaturated ester **90**, which was subjected to Heck arylation using *p*-fluorobromobenzene and palladium catalyst in an attempt to obtain the coupled product but the reaction met with failure. Then the benzyl group in **90** was

replaced with methyl carbamate using methyl chloroformate to form ester carbamate **84**. The ester carbamate **84** was then subjected to Heck arylation using similar conditions as above to furnish the arylated product **91** with migration of double bond as well as carbamate deprotection.[32] Protection of **91** with methyl chloroformate furnished the carbamate **85** which was identical to the one obtained by Correia.

1.1.4 References and notes

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Chapter 1. Synthetic studies towards (±)-Paroxetine and (±)-Femoxetine

Section 2: Total synthesis of (±)-Paroxetine

1.2.1: Present Work

1.2.1.1: Objective

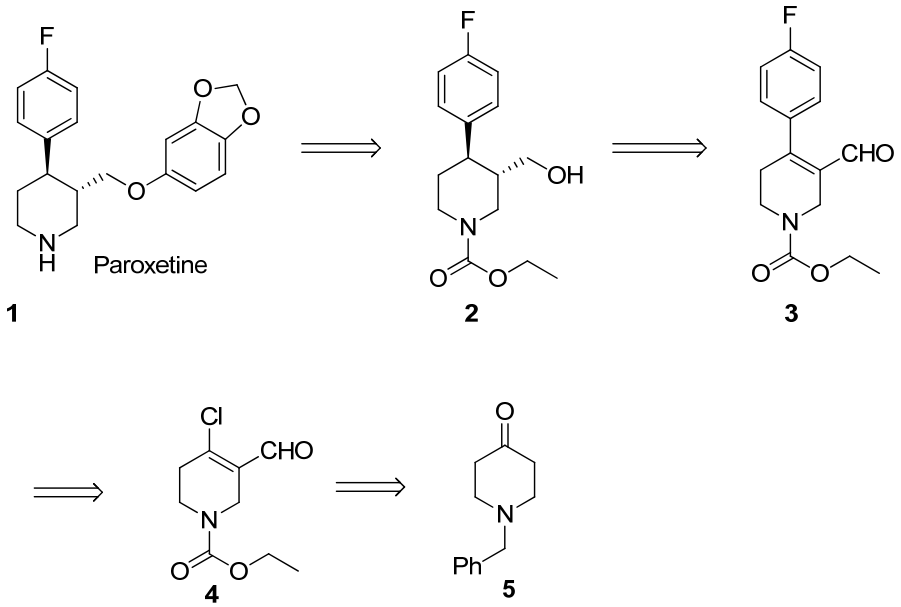
Literature survey revealed that paroxetine as well as femoxetine attracted the attention of many organic chemists towards its synthesis due to their potent antidepressant activities. The literature reports also revealed that the piperidones are less explored for the synthesis of paroxetine and femoxetine. The reported routes based on asymmetric conjugate additions, chiral pool approaches and enzymatic resolutions are associated with lengthy routes and low yields. In this context, there is a need of convenient and efficient route for the synthesis of these compounds from piperidones.

This group is engaged in the synthesis of biologically active compounds and earlier this group developed a technically practical, efficient and economically viable protocol for the synthesis of potent antidepressant drug venlafaxine.[1] In continuation of search for practical routes for such molecules, synthesis of antidepressant drugs paroxetine and femoxetine was undertaken.

3,4-Di-substituted piperidines are the common core structure in many biologically active compounds. Methods for construction of 3,4-di-substituted derivatives of piperidines are limited compared to methods for construction of C-2 and C-6 substituted piperidines. If the construction of 3,4-di-substitution of piperidines is done efficiently, it would be possible to prepare paroxetine and femoxetine in good yields and less number of steps.

1.2.1.2. Retrosynthetic analysis

According to our retrosynthetic plan (Scheme 1), the paroxetine (**1**) could be obtained from alcohol **2**. The alcohol **2** could be obtained by reduction of double bond followed by reduction of aldehyde. The *p*-fluorophenyl group could be introduced by Suzuki coupling[2] on unsaturated chloro aldehyde **4**. The unsaturated chloro aldehyde **4** could be obtained by taking advantage of Vilsmeier-Haack formylation on piperidone **5**.[3]



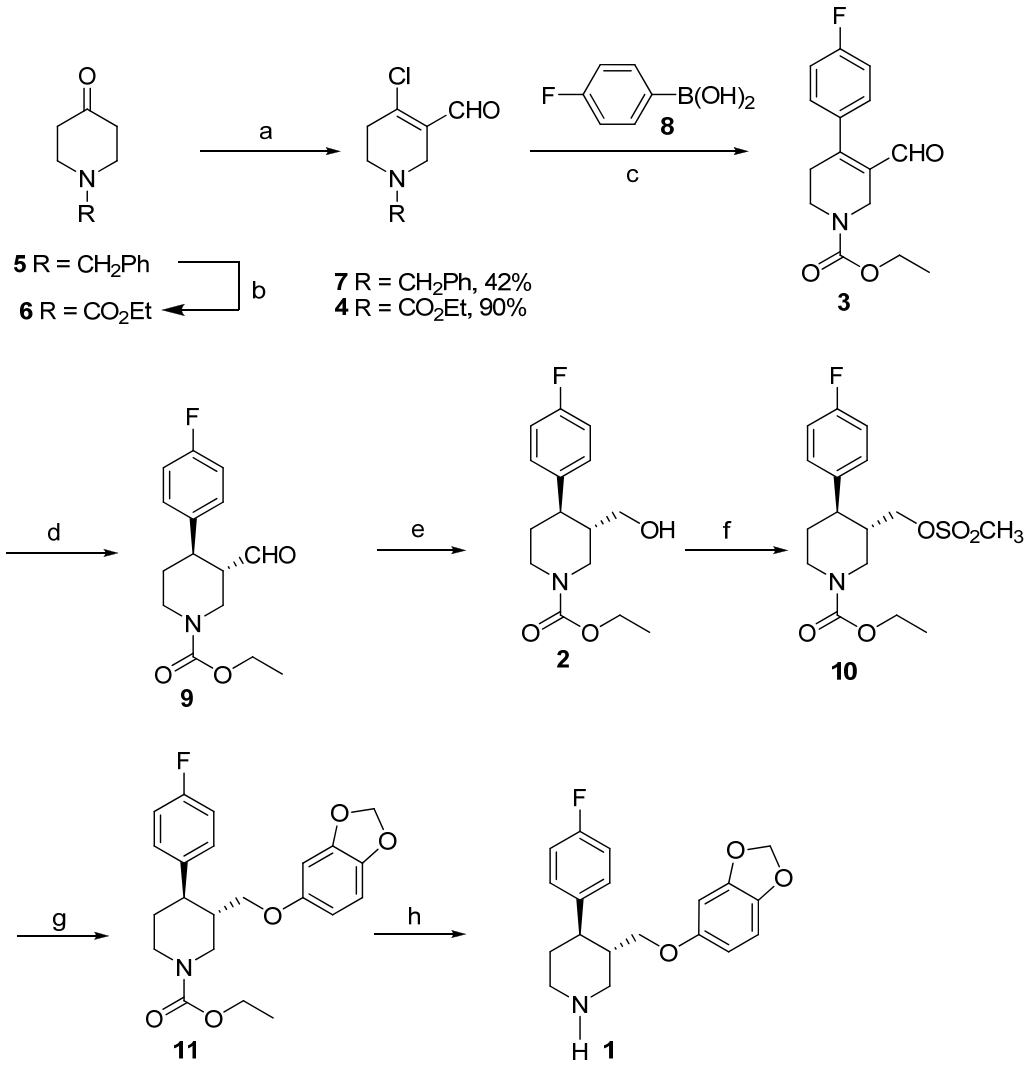
Scheme 1: Retrosynthetic analysis for **1**

1.2.1.3. Results and discussion

The synthetic strategy for (±)-paroxetine (**1**) is shown in **scheme 2**. The exploitation of piperidone in to 3,4-di-substituted piperidines using Vilsmeier-Haack formylation and Suzuki coupling reaction in aqueous medium constitute the key steps.

The α,β-unsaturated chloro aldehyde **7** was prepared by the Vilsmeier-Haack formylation of *N*-benzyl-4-piperidone (**5**) using $POCl_3$, DMF in DCM in poor yield (42%). The lone pair of nitrogen may be interacting with electrophilic adduct during formylation resulting in the low yield of the reaction. Keeping this in mind, the *N*-benzyl group in **5** was removed and replaced with carbamate group to furnish **6**. Then carbamate **6** was subjected to Vilsmeier-Haack formylation, furnishing aldehyde **4** in 90% yield. The IR spectrum of **4** showed strong bands at 1694, 1676 and 1631 cm^{-1} indicating the presence of unsaturated aldehyde, carbamate and olefin functionalities. Its ^{1}H-NMR spectrum showed characteristic singlet at δ 10.14 due to presence of aldehyde functionality (O=CH). The peak at δ 4.18 corresponding to (NCH_2) merged in to the quartet corresponding to ethyl carbamate at δ 4.15 and appearance of triplet at δ 1.28 confirmed the presence of unsaturated aldehyde **4**.

The unsaturated aldehyde **4** was subjected to Suzuki coupling conditions using *p*-fluorophenyl boronic acid in presence of palladium acetate catalyst in water at 50 ºC to



Scheme 2: Synthesis of (±)-Paroxetine.

Reagents and conditions: *a) DMF, $POCl_3$, DCM, rt, 90% b) EtOCOCl, Na_2CO_3, DCM, 95% c) p-Fluoro phenylboronic acid, $Pd(OAc)_2$, TBAB, K_2CO_3, H_2O, 50 ^{o} C, 73% d) H_2, Pd/C, MeOH e) $NaBH_4$, MeOH, 50% f) CH_3SO_2Cl, Et_3N, DCM, 95% g) Sesamol, NaH, DMF, reflux, 61% h) KOH, MeOH, reflux, 70%.*

provide *β*-aryl aldehyde **3** in 73% yield.[2a] The IR spectrum of **3** showed intense bands at 1693 and 1669 cm^{-1} indicating the presence of unsaturated aldehyde and carbamate functionalities. The ^{1}H-NMR of **3** showed peaks in aromatic region at δ 7.05 and δ 7.18 confirming the presence of aromatic ring. Its ^{13}C-NMR spectrum showed peaks at δ 190 for aldehyde carbon and three doublets at δ 115.6 (J = 30 Hz), 130.3 (J = 8 Hz) and 133.3 (J = 3.6 Hz) due to the C-F coupling clearly indicating the presence of *p*-fluorophenyl ring.

The β-aryl aldehyde **3** was subjected to catalytic hydrogenation using palladium catalyst in presence of hydrogen atmosphere to furnish saturated aldehyde **9** which was found to be unstable and was immediately subjected to reduction using sodium borohydride in methanol to provide alcohol **2**. The absence of peaks at 1630 and 1693 cm^{-1} in IR spectrum of **2** confirmed the reduction of double bond as well as aldehyde and presence of strong band at 1675 cm^{-1} indicated the presence of carbamate functionality. Its ^{1}H-NMR spectrum showed a characteristic peak at δ 2.56 which appeared as a dt with coupling constants of 11.6 Hz and 4.5 Hz corresponding to ax-ax (11.6 Hz) coupling further split in to doublet with ax-eq coupling (4.5 Hz) indicating the presence of di-equatorial substitution. The peak at δ 2.76 with coupling constant 11.7 Hz for (Ar-CH) clearly indicated the position of Ar to be equatorial. The ax-ax coupling in case of both protons at C3, as well as C4 clearly indicated the *trans* stereochemistry of substituents at C3 and C4. Its ^{13}C-NMR showed peak at δ 155.4 for carbamate carbonyl while the doublets at δ 115.5, 128.3 and 128.7 clearly indicated the *p*-fluoro aryl substitution. Its mass spectrum showed the molecular ion peak at m/z 304 $(M+Na)^{+}$ confirming the formation of **2**.

Alcohol **2** was treated with mesyl chloride and triethylamine in DCM to provide mesyl compound **10** in 95% yield. Its IR spectrum showed strong band at 1694 cm^{-1} corresponding to carbamate. Its ^{1}H-NMR showed singlet at δ 2.90 for $-SO_2-CH_3$ of mesyl group. Peaks of $–CH_2OH$ were shifted from δ 3.44 and 3.25 to δ 3.99 and 3.81 respectively due to –I effect of mesyl group. The strong peak at δ 36 along with all other required peaks present in ^{13}C-NMR confirmed the mesyl compound **10**.

The mesyl compound **10** was subjected to displacement of mesyl group by sesamol in presence sodium hydride as a base in DMF under refluxing conditions to provide compound **11** in 61% yield. A strong band at 1689 cm^{-1} in its IR spectrum showed the presence of carbamate carbonyl. Its ^{1}H-NMR showed a singlet at δ 5.89, a characteristic peak of sesamol $–O-CH_2-O-$ group and peaks at δ 6.14 (dd), δ 6.37 (d), and 6.61 (d) corresponding to the aromatic protons of sesamol group. Absence of mesyl methyl peak at δ 2.90 suggested that the mesyl group was replaced. ^{13}C-NMR of **11** showed peaks at δ 154.1, 141.6, 138.9, 107.8, 105.5, 101.1 and 98.0 corresponding to the sesamol moiety. Peak at δ 155.5 corresponded to the carbamate carbonyl group. Doublets at δ 128.7 and

115.5 were the characteristic peaks due to fluoro group coupling. The DEPT spectrum showed the presence of 6 CH_2 carbons and total 8 peaks corresponding to CH and CH_3 carbons. Further the mass spectrum of **11** showed the molecular ion peak at m/z 424 $(M+Na)^+$ which confirmed the formation of **11**.

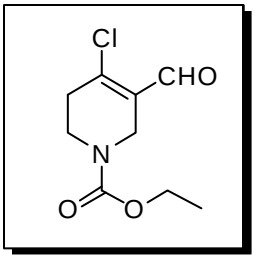
Finally, the carbamate group in **11** was deprotected using 10 eq. of KOH in methanol under reflux conditions to provide the target molecule (±)-paroxetine **1** in 70% yield. Its ^{1}H-NMR showed absence of peaks at δ 4.17 (q) and at δ 1.30 (t) which indicated the deprotection of carbamate. Peak at δ 1.93-2.03 (m, 2H)) corresponding to CH_2-$\underline{CH_2}$-CH protons, multiplet at δ 2.34-2.40 due to the -$\underline{CH_2}$-O and peak at δ 2.69-2.64 (m, 1H) for the Ar-$\underline{CH}$ and peak at δ 2.82-3.14 (m) correspond to the –N-CH_2 protons. Peak at δ 5.88 was assigned to -OCH_2O- group in sesamol and the other peaks included δ 6.08 (dd), δ 6.31 (d), δ 6.59 (d) and δ 6.98 (t), δ 7.20 (m) corresponding to sesamol and *p*-fluorophenyl ring respectively. Its ^{13}C-NMR showed peaks at δ 30 (CH_2), δ 39.3 (CH), δ 41.7 (CH) and 67.5 (CH_2) corresponding to aliphatic region of paroxetine (**1**). Peaks at δ 97.9 (CH), δ 100.5 (CH_2), δ 105.5 (CH), δ 107.9, δ 115.5 (d, J = 21.2 Hz, CH), δ 128.5 (d, J = 7.8 Hz, CH), δ 137.2 (d, J = 3 Hz, C), δ 142.0 (C), δ 148.2 (C), 153.7 (C) and 162.2 (d, J = 246 Hz, C) all correspond to aromatic region in paroxetine (**1**). Presence of a peak at m/z 352 $(M+Na)^+$ in its mass spectrum confirmed the structure of paroxetine (**1**). The spectral data of synthetic paroxetine were in good agreement with the reported one.[4]

1.2.2. Conclusion

Total synthesis of (±)-paroxetine has been accomplished employing Suzuki coupling reaction under aqueous media. The commercially available starting material *N*-benzyl piperidone was employed for synthesis by taking advantage of Vilsmeier-Haack formylation. The present method for construction of 3,4-di-substituted piperidines could be explored for the synthesis of different piperidine derivatives and similar natural products.

1.2.3. Experimental

Ethyl 4-chloro-3-formyl-5,6-dihydropyridine-1(2H)-carboxylate (4)



A mixture of anhydrous DCM (8 mL) and anhydrous DMF (15.2 mL, 197 mmol) was cooled to 0 ºC using ice and to that was added $POCl_3$ (14.7 mL, 158 mmol) dropwise and stirred further for 2 hours at room temperature. Ethyl 4-oxopiperidine-1-carboxylate (**6**) (13.5 g, 79 mmol) in DCM (10 mL) was added dropwise at 0 ºC and stirred further for 3 hours at rt. Reaction mixture was quenched first by using ice followed by careful addition of sat. $NaHCO_3$ solution. Reaction mixture was allowed to separate in separating funnel, organic layer was separated and aqueous layer again extracted twice using DCM (50 mL). The collected organics were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to furnish β-chloro aldehyde **4** (15.4 g, 90%) as a crude product.

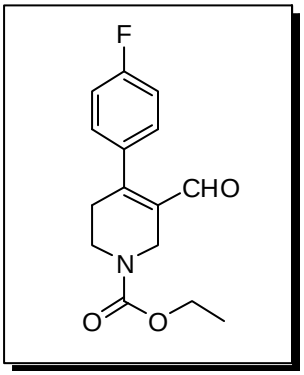
Molecular formula **:** $C_9H_{12}ClNO_3$

Yield **:** 90%

IR ($CHCl_3$) **:** 3019, 2872, 1694, 1676, 1236, 1216, 757 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 10.14 (s, 1H), 4.11-4.22 (m, 4H), 3.67 (t, *J* = 5.8 Hz, 2H), 2.65-2.74 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

Ethyl 4-(4-fluorophenyl)-3-formyl-5,6-dihydropyridine-1(2H)-carboxylate (3)



β-Chloro aldehyde **4** (5 g, 23 mmol), *p*-fluorophenyl boronic acid (3.5 g, 25 mmol), *tetra*-butylammonium bromide (7.4 g, 23 mmol), potassium carbonate (8 g, 57 mmol) and palladium acetate (100 mg, 2 mol %) were taken together and to that was added deionized water (50 mL). The solution was stirred vigorously at 45 ºC for three hours. The dark and nonhomogenous reaction mixture was diluted with water (50 mL) and extracted using ethyl acetate (3 x 100 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated to provide sticky dark brown liquid. Purification

by flash chromatography (pet ether : ethyl acetate 75:25) furnished (4.15 g, 73%) of pure product aldehyde **3** as a colorless dense liquid.

Molecular formula : $C_{15}H_{16}FNO_3$

Yield : 73%

IR ($CHCl_3$) : 3019, 1693, 1669, 1603, 1234, 1215, 757 cm^{-1}

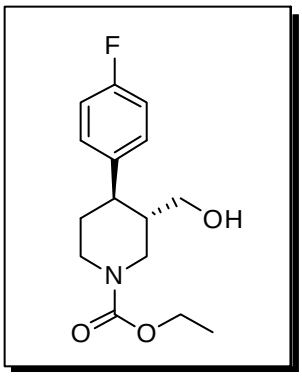
^{1}H NMR (200 MHz, $CDCl_3$) : δ 9.41 (s, 1H), 7.14-7.22 (m, 2H), 7.00-7.10 (m, 2H), 4.07-4.20 (m, 4H), 4.63 (t, *J* = 5.8 Hz, 2H), 2.55-2.63 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 190.5, 162.5 (d, *J* = 250 Hz), 155.3, 133.4 (d, *J* = 3.6 Hz), 132.2, 135.1, 130.5 (d, *J* = 8.1 Hz), 115.8 (d, *J* = 21.9 Hz), 61.6, 41.4, 39.8, 33.0, 14.7.

MS (ESI) (m/z) : 300 $(M+Na)^+$

Elemental analysis : Calculated C, 64.97; H, 5.82; N, 5.05%
Found C, 64.95; H, 5.85; N, 5.01%

Ethyl 4-(4-fluorophenyl)-3-(hydroxymethyl)piperidine-1-carboxylate (2)



To the aldehyde **3** (3 g, 10 mmol) in methanol (30 mL) was added Pd/C (5%, 10 mg) and put under hydrogen atmosphere (60 psi) on shaker for 1 hour. Reaction mixture was filtered from celite and concentrated under reduced pressure to provide crude saturated aldehyde as a dense liquid. The crude aldehyde was subsequently dissolved in methanol and cooled to 0 ºC. $NaBH_4$ (0.4 g, 10 mmol) was added portion wise over 10 min and stirred further for 1 hour. Methanol was removed from reaction mixture and water was added (30 mL) and extracted using ethyl acetate (3 x 30 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide colorless dense liquid. Purification of crude product using flash chromatography (pet ether : ethyl acetate 60:40) furnished alcohol **2** (1.52 g, 50%) as a colorless dense liquid.

Molecular formula : $C_{15}H_{20}FNO_3$

Yield : 50%

IR ($CHCl_3$) : 3436, 2929, 1682, 1509, 1440, 1223, 832, 768 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 7.08-7.18 (m, 2H), 6.94-7.03 (m, 2H) 4.40 (br s,

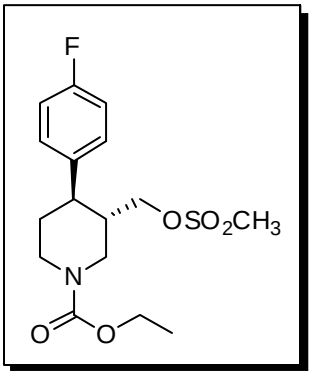
1H), 4.26 (br s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.44 (dd, *J* = 10.8, 2.5 Hz, 1H), 3.26 (dd, *J* = 10.8, 6.5 Hz, 1H), 2.86-2.72 (m, 2H), 2.56 (m, 1H), 1.77 (m, 2H), 1.65 (m, 2H), 1.29 (t, *J* = 7.1, 3H)

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 161.5 (d, *J* = 140 Hz), 155.4, 139.3 (d, *J* = 3.0 Hz), 128.7 (d, *J* = 7.5 Hz), 115.5 (d, *J* = 20.5 Hz), 62.8, 61.3, 47.1, 44.4, 44.0, 43.8, 34.0, 14.8

MS (ESI) (m/z) **:** 304 $(M+Na)^+$

Elemental analysis **:** Calculated C, 64.04; H, 7.17; N, 4.98%
Found C, 64.06; H, 7.13; N, 4.99%

Ethyl 4-(4-fluorophenyl)-3-(((methylsulfonyl)oxy)methyl)piperidine-1-carboxylate (10)



To the alcohol **2** (230 mg, 0.81 mmol) in DCM (5 mL) was added triethylamine (0.4 mL, 2.4 mmol) and mixture was cooled to 0 °C. Methanesulfonyl chloride (0.1 mL, 1 mmol) was added dropwise and reaction mixture was further stirred for 2h at room temperature. Water (15 mL) was added and the aqueous layer was extracted using DCM (10 x 3). Organics were dried over Na_2SO_4, filtered and removal of the solvent furnished a residue which was purified on flash chromatography (pet ether : ethyl acetate 65:35) to furnish mesylate **10** (280 mg, 95%) as a thick oil.

Molecular formula **:** $C_{16}H_{22}FNO_5S$

Yield **: 9**5%

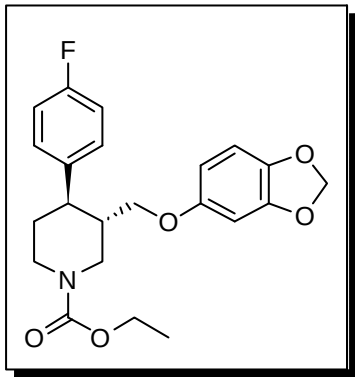
IR ($CHCl_3$) **:** 2983, 2937, 1694, 1510, 1437, 1355 1224, 1174, 962 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 7.27-7.12 (m, 2H), 7.06- 6.98 (m, 2H), 4.45-4.23 (m, 2H), 4.18 (q, *J* = 7.1, 2H), 3.98 (dd, *J* = 10.1, 2.9 Hz, 1H), 3.81 (dd, *J* = 10.1, 6.3 Hz, 1H), 2.90 (s, 3H), 2.69-2.84 (m, 1H), 2.66-2.52 (m, 1H), 2.17-1.95 (m, 1H),1.88-1.77 (m, 1H), 1.73- 1.58 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) : δ 161.2 (d, *J* = 246 Hz), 155.1, 137.8 (d, *J* = 2.5 Hz), 128.6 (d, *J* = 7.7 Hz), 115.7 (d, *J* = 21.2 Hz), 69.3, 61.4, 46.3, 44.0, 43.6, 41.0, 36.9, 33.8, 14.6.

MS (ESI) (m/z) **:** 382 $(M+Na)^+$

Ethyl-((benzo[d][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidine-1-carboxylate (11)



To the solution of sesamol (216 mg, 1.5 mmol) in DMF (5 mL) was added NaH (93 mg, 2.3 mmol, 60%) under nitrogen atmosphere. Mesyl compound **10** (280 mg, 0.78 mmol) dissolved in DMF (2 mL) was added and reaction mixture refluxed for 20 minutes. The reaction mixture was cooled to room temperature and quenched carefully using water (10 mL) and extracted using diethyl ether (3 x 15 mL). The collected organics were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure and the residue was purified using flash chromatography (pet ether : ethyl acetate 75:25) to provide compound **11** (190 mg, 61%) as colorless liquid.

Molecular formula **:** $C_{22}H_{24}FNO_5$

Yield **:** 61%

IR ($CHCl_3$) **:** 2980, 1685, 1432, 1023, 735 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) : δ 7.11-7.18 (m, 2H), 6.94-7.02 (m, 2H), 6.64 (d, *J* = 8.5 Hz, 1H), 6.37 (d, *J* = 2.5 Hz, 1H), 6.15 (dd, *J* = 8.5, 2.4 Hz, 1H), 5.89 (s, 2H), 4.43-4.52 (m, 1H), 4.27-4.34 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.62 (dd, *J* = 9.5, 2.8 Hz, 1H), 3.36 (dd, *J* = 9.4, 6.3 Hz, 1H), 2.80-2.93 (m, 1H), 2.71 (dt, *J* = 11.5, 4.3 Hz, 1H), 1.93-2.11 (m, 1H), 1.63-1.33 (m, 3H), 1.30 (t, *J* = 7.1 Hz, 3H)

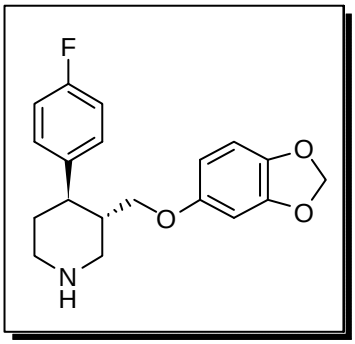
^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 159.5 (d, *J* = 245 Hz), 155.5, 154.2, 148.1, 141.7, 138.9 (d, *J* = 3.3 Hz), 128.7 (d, *J* = 7.7 Hz),

115.5 (d, J = 20.9 Hz), 107.8, 105.6, 101.1, 98.0, 68.7, 61.4, 47.2, 44.3, 43.9, 41.9, 33.8, 14.7.

MS (ESI) (m/z) : 424 $(M+Na)^+$

Elemental analysis : Calculated C, 65.82; H, 6.03; N, 3.49%
Found C, 65.82; H, 6.00; N, 3.48%

(±)-3-((benzo[d][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidine (1)



To the solution of carbamate **11** (190 mg, 0.5 mmol) in methanol (10 mL) was added KOH (265 mg, 4.7 mmol) and reaction mixture refluxed for 5 days. Reaction mixture was then cooled to rt, methanol was evaporated on rotavapour and excess KOH was quenched using 10% HCl solution till pH was neutral and the reaction mixture was extracted using ethyl acetate (3 x 10 mL). The organics were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to furnish (±)-paroxetine (**1**) as a dense liquid.

Molecular formula : $C_{19}H_{20}FNO_3$

Yield : 61%

IR ($CHCl_3$) : 2980, 1430, 1050, 738 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) : δ 7.17-7.24 (m, 2H), 6.94-7.02 (t, J = 8.6 Hz, 2H), 6.59 (d, J = 8.5 Hz, 1H), 6.31 (d, J = 2.3 Hz, 1H), 6.09 (dd, J = 8.5, 2.4 Hz, 1H), 5.88 (s, 2H), 3.56-3.71(m, 2H), 3.41-3.48 (m, 1H), 2.82-3.14 (m, 3H), 2.69-2.64 (m, 1H), 2.34-2.40, (m, 1H), 1.93-2.03 (m, 2H)

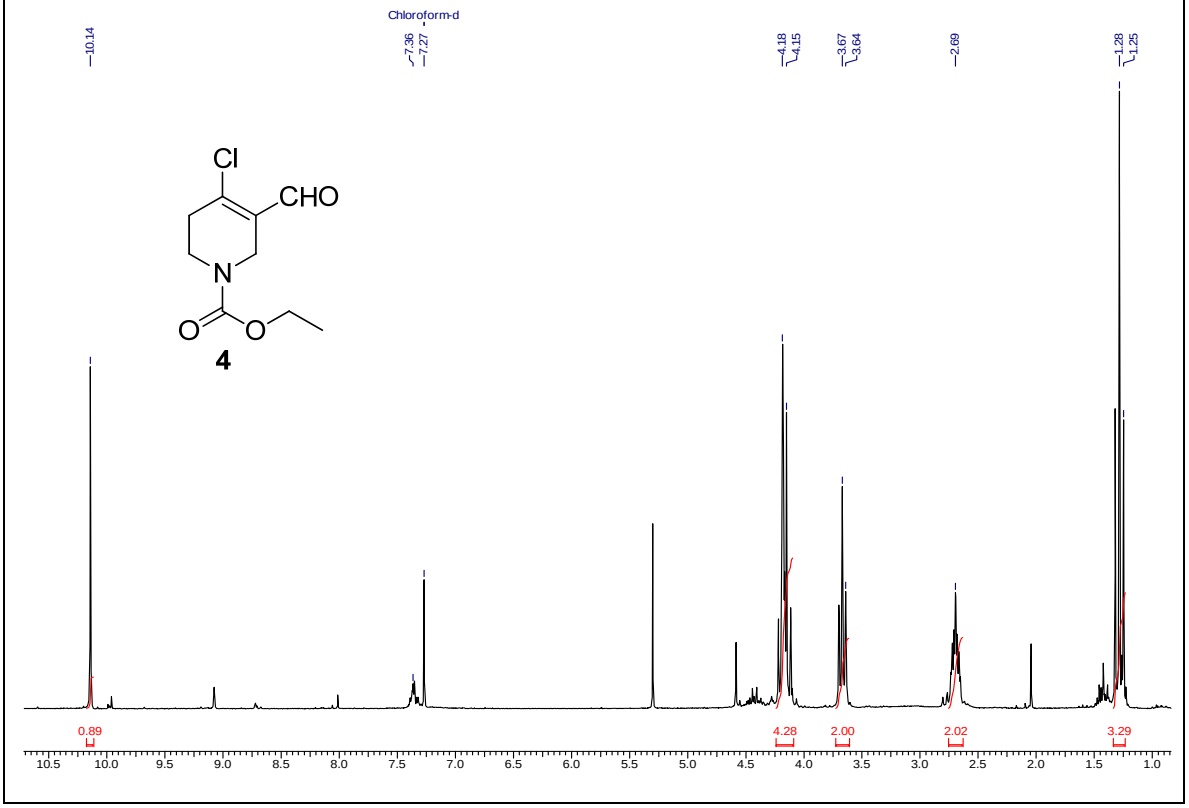
^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 162.2 (d, J = 246 Hz), 153.7, 148.2, 142.0, 137.2, 28.5 (d, J = 7.8 Hz), 115.5 (d, J = 21.2 Hz), 107.9, 105.5, 101.1, 97.9, 67.5, 64.2, 46.7, 44.5, 41.7, 39.3, 30.0

MS (ESI) (*m/z*) : 352 $(M+Na)^+$

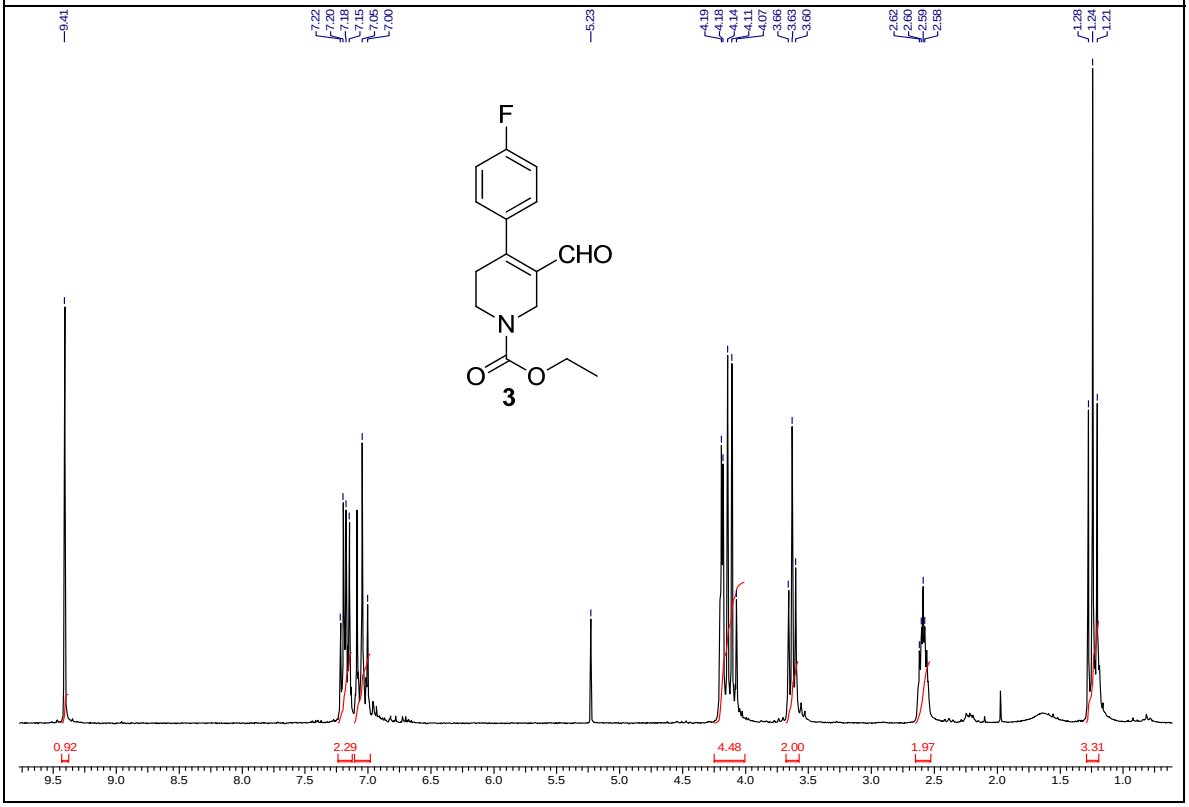
Elemental analysis : Calculated C, 69.29; H, 6.12; N, 4.25%
Found C, 69.28; H, 6.10; N, 4.28%

1.2.4 NMR Spectra

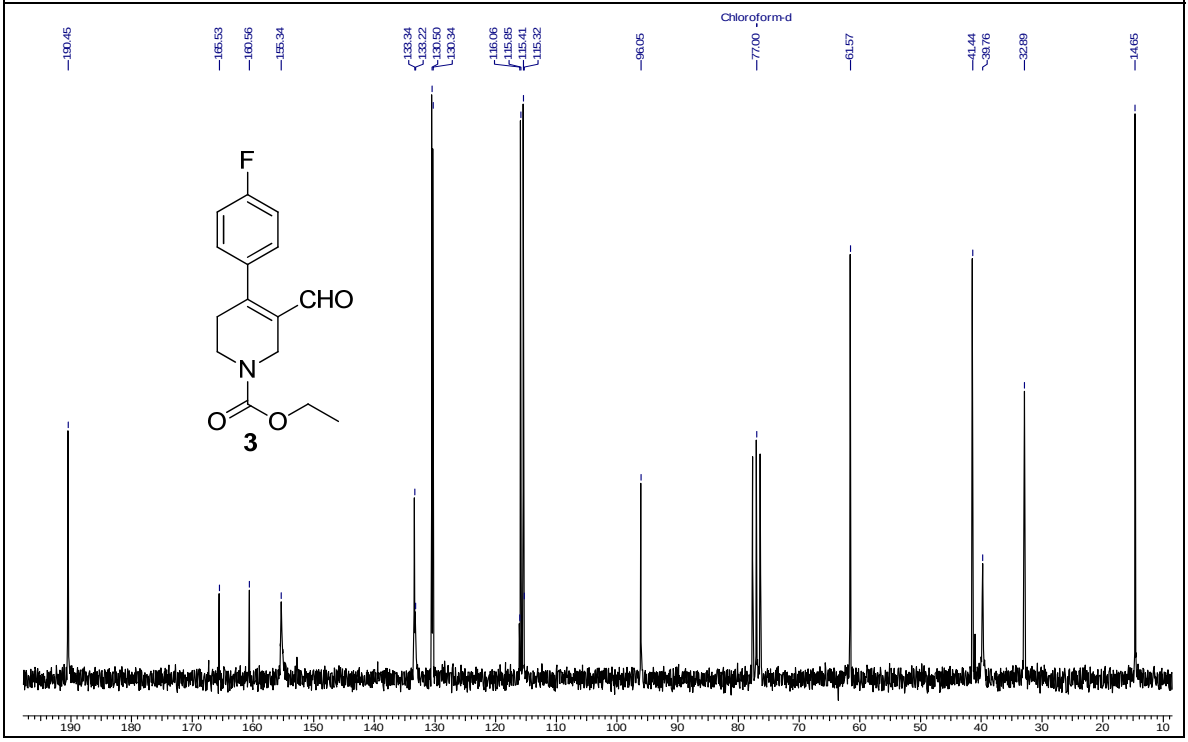
^{1}H NMR spectrum of compound **4** ($CDCl_3$, 200 MHz)



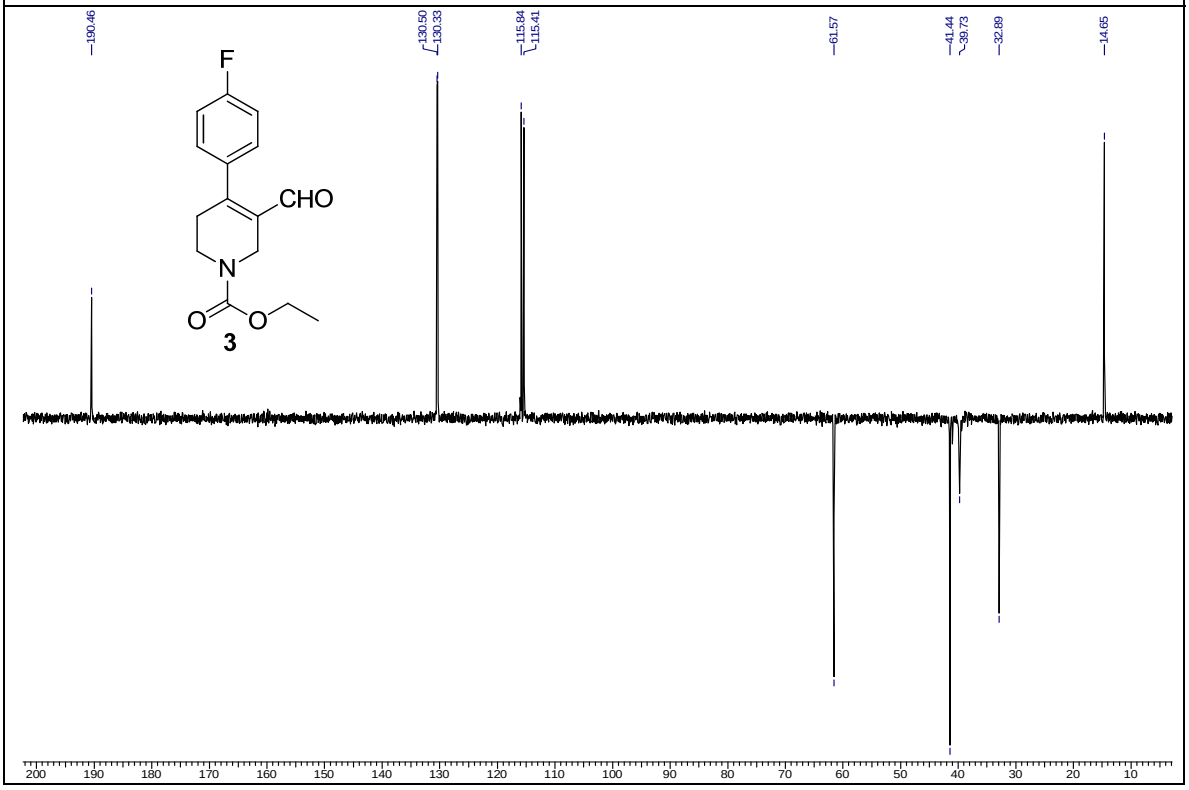
^{1}H NMR spectrum of compound **3** ($CDCl_3$, 200 MHz)



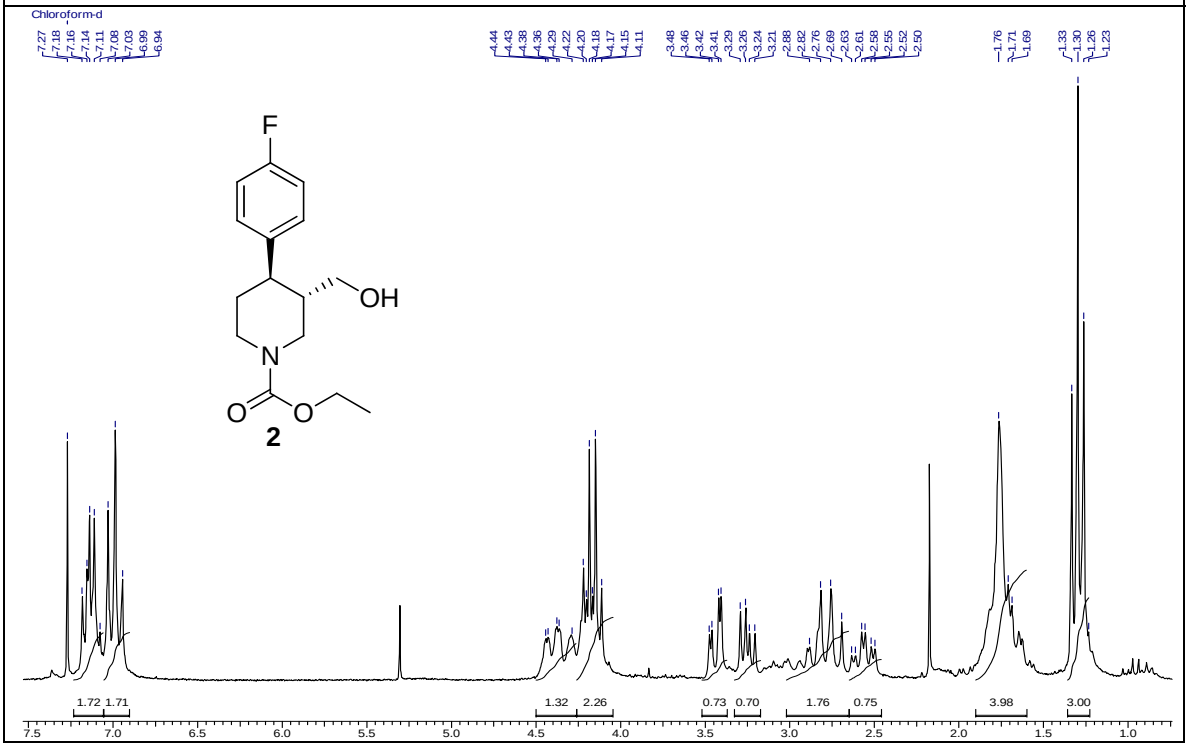
^{13}C NMR spectrum of compound **3** ($CDCl_3$ + CCl_4, 200 MHz)



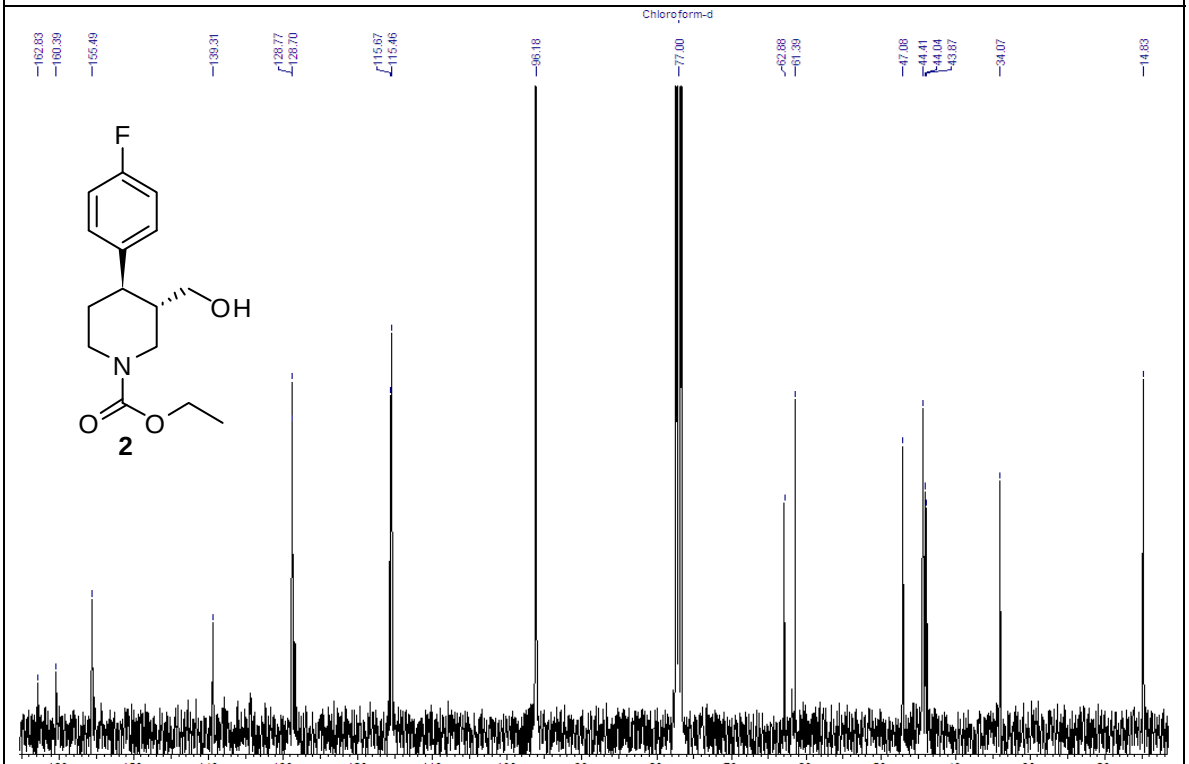
DEPT spectrum of compound **3** ($CDCl_3$ + CCl_4, 200 MHz)



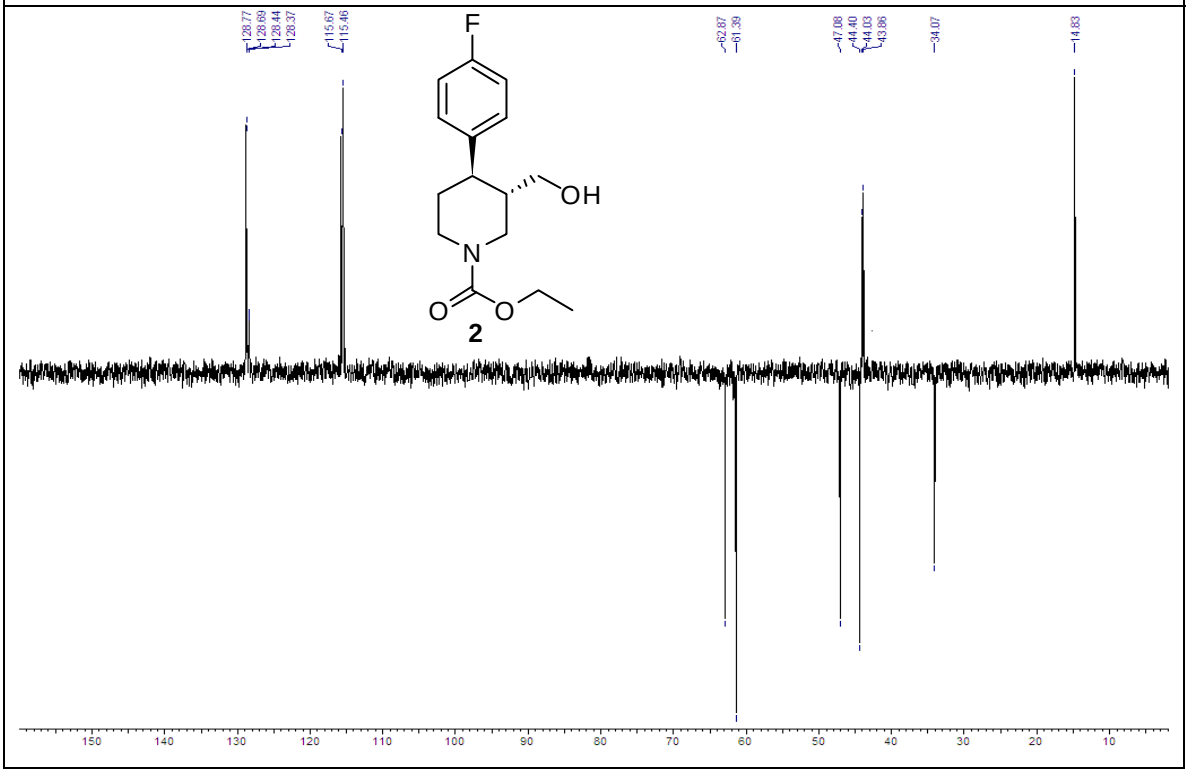
^{1}H NMR spectrum of compound **2** ($CDCl_3$, 200 MHz)



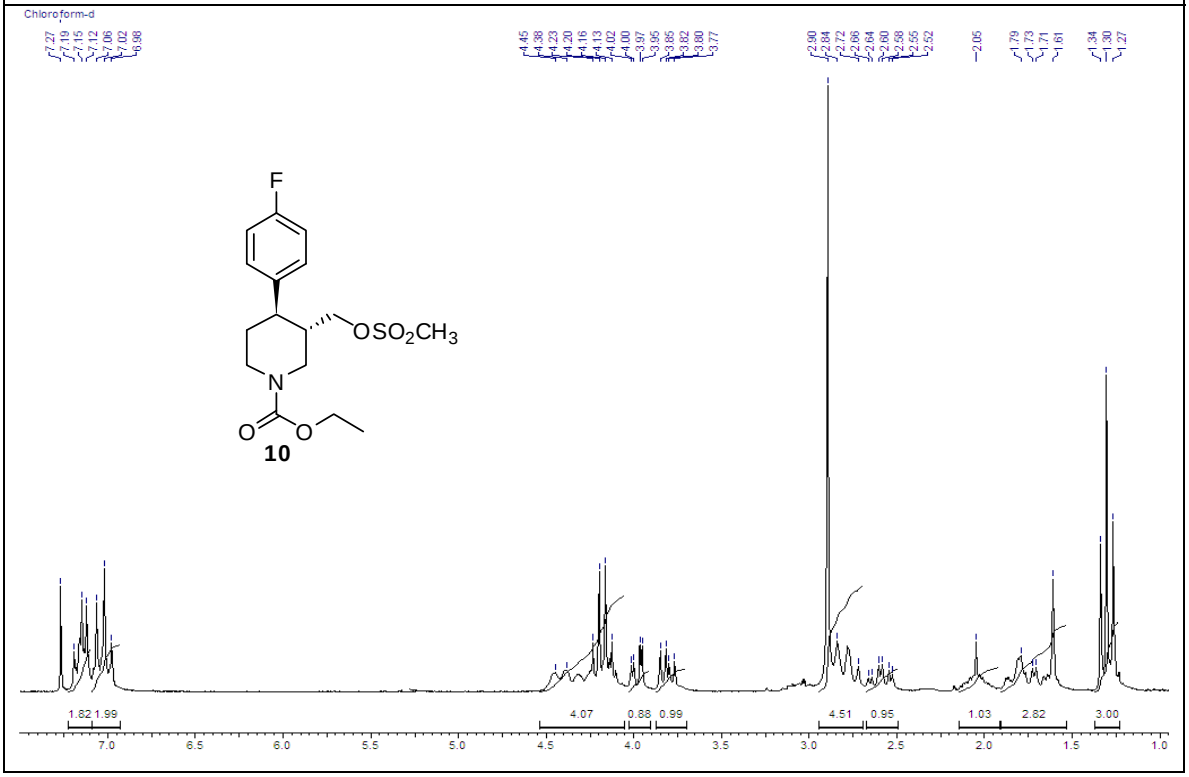
^{13}C NMR spectrum of compound **2** ($CDCl_3$ + CCl_4, 50 MHz)



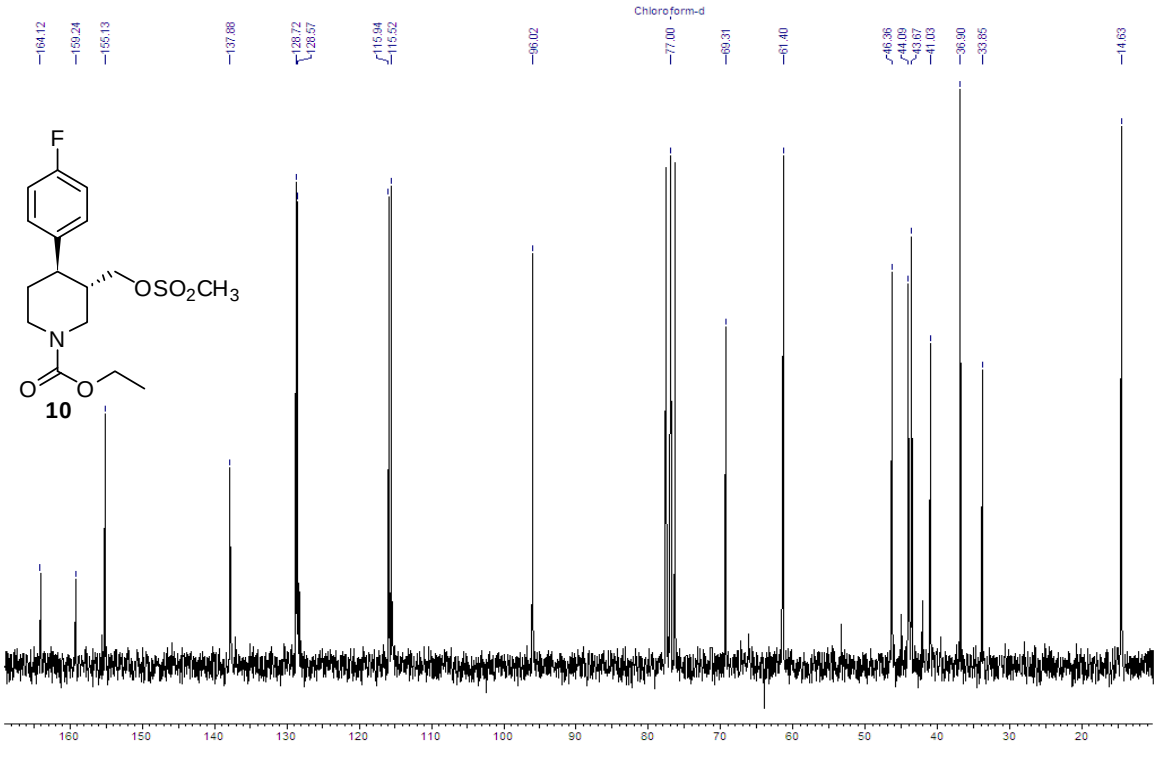
DEPT spectrum of compound **2** ($CDCl_3$ + CCl_4, 50 MHz)



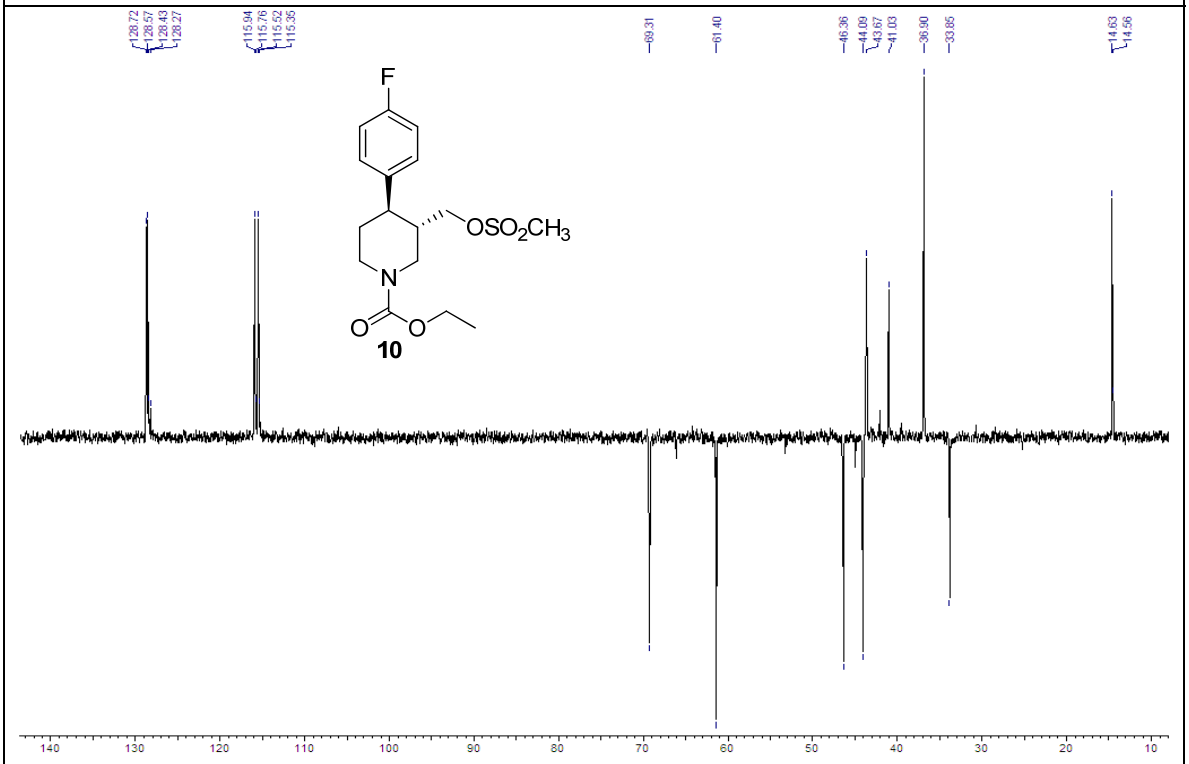
^{1}H NMR spectrum of compound **10** ($CDCl_3$, 200 MHz)



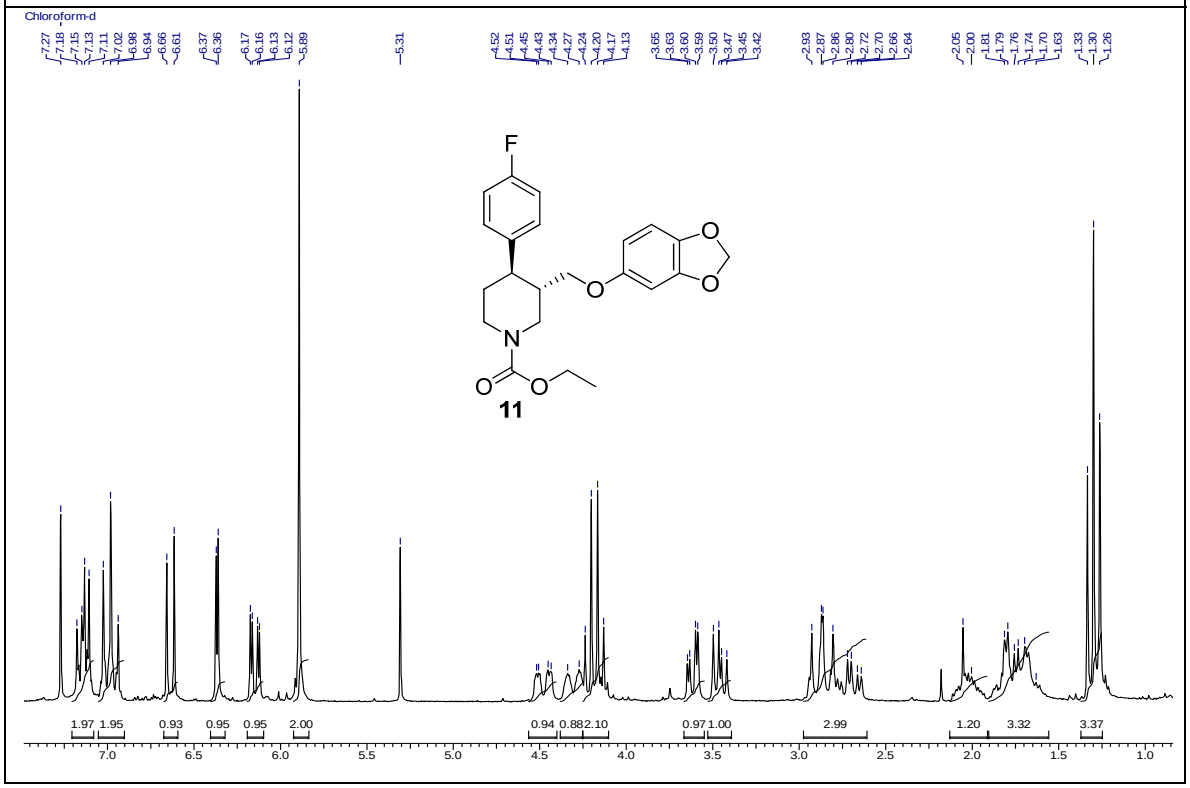
^{13}C NMR spectrum of compound **10** ($CDCl_3$ + CCl_4, 50 MHz)



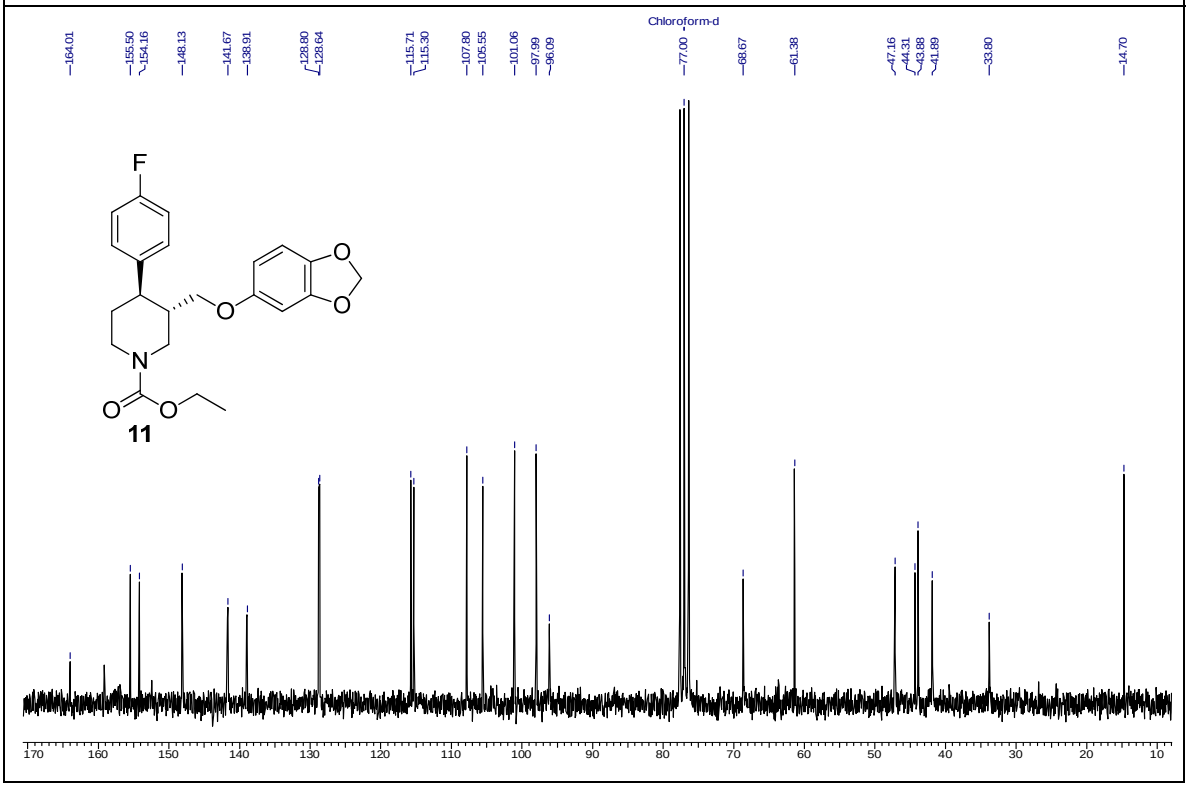
DEPT spectrum of compound **10** ($CDCl_3$ + CCl_4, 50 MHz)



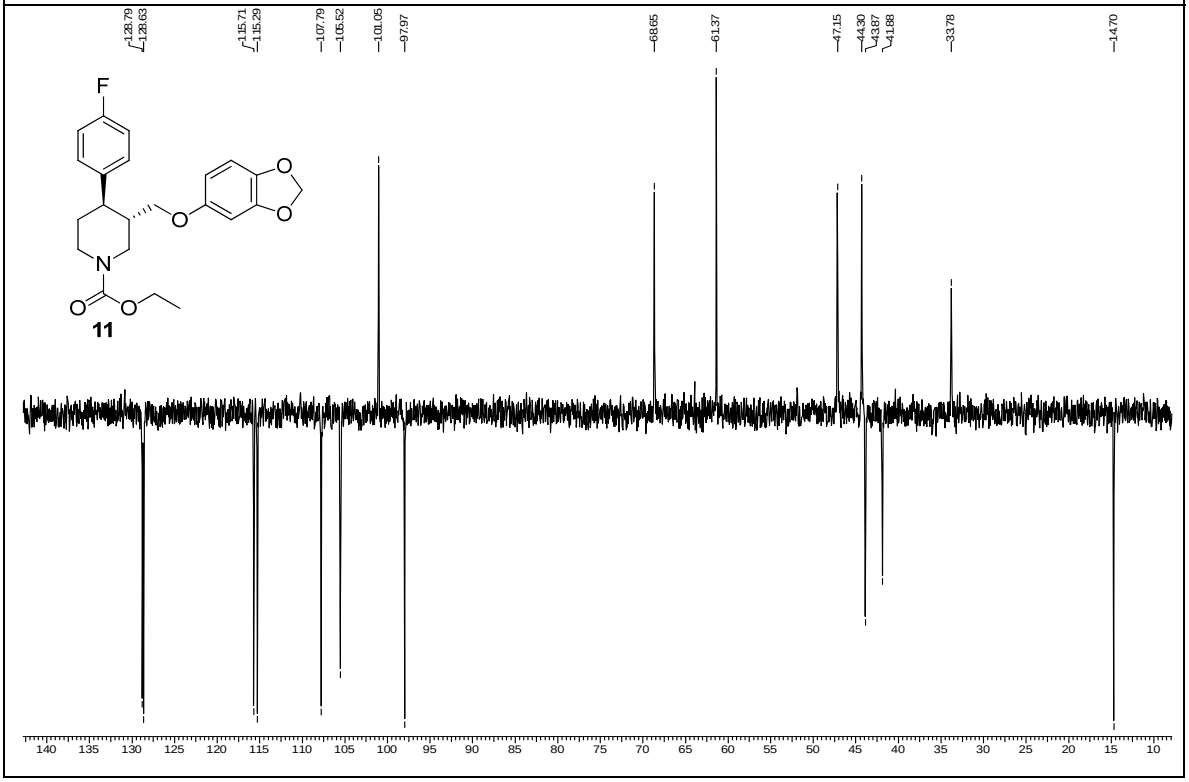
^{1}H NMR spectrum of compound **11** ($CDCl_3$, 200 MHz)



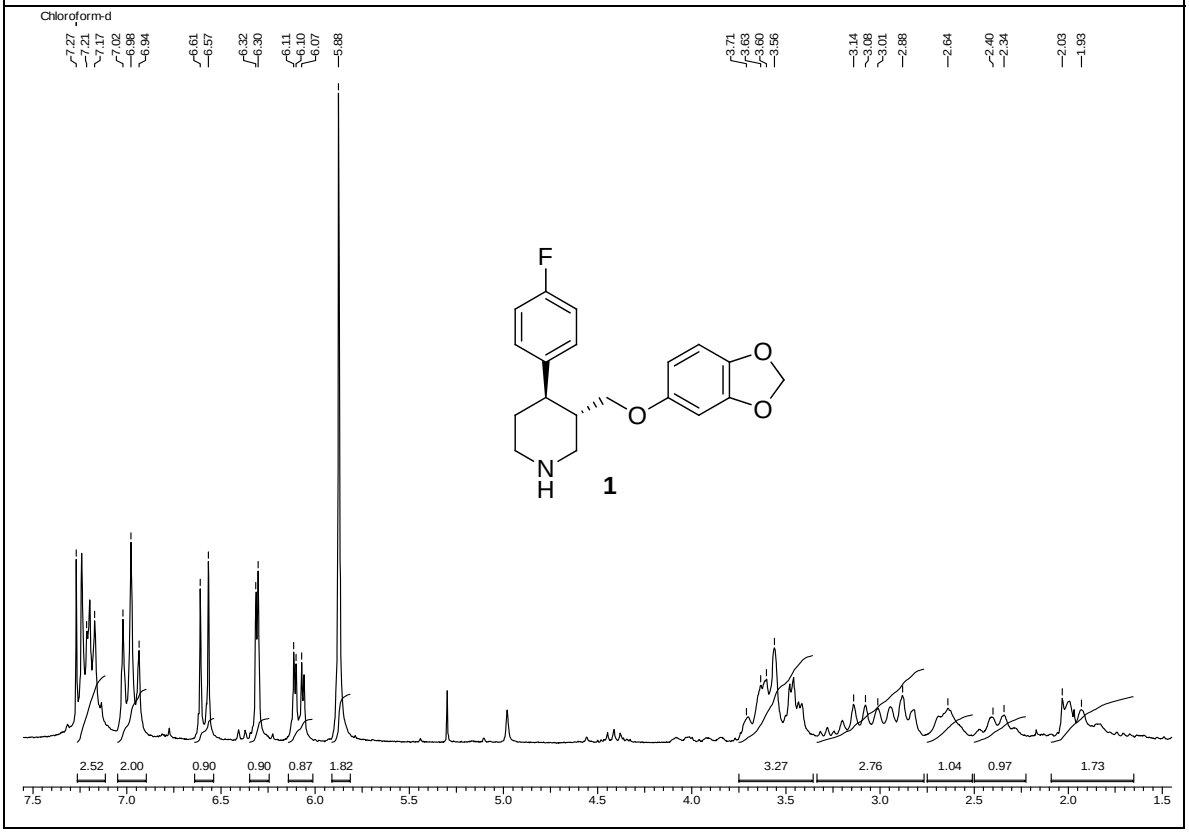
^{13}C NMR spectrum of compound **11** ($CDCl_3$ + CCl_4, 50 MHz)



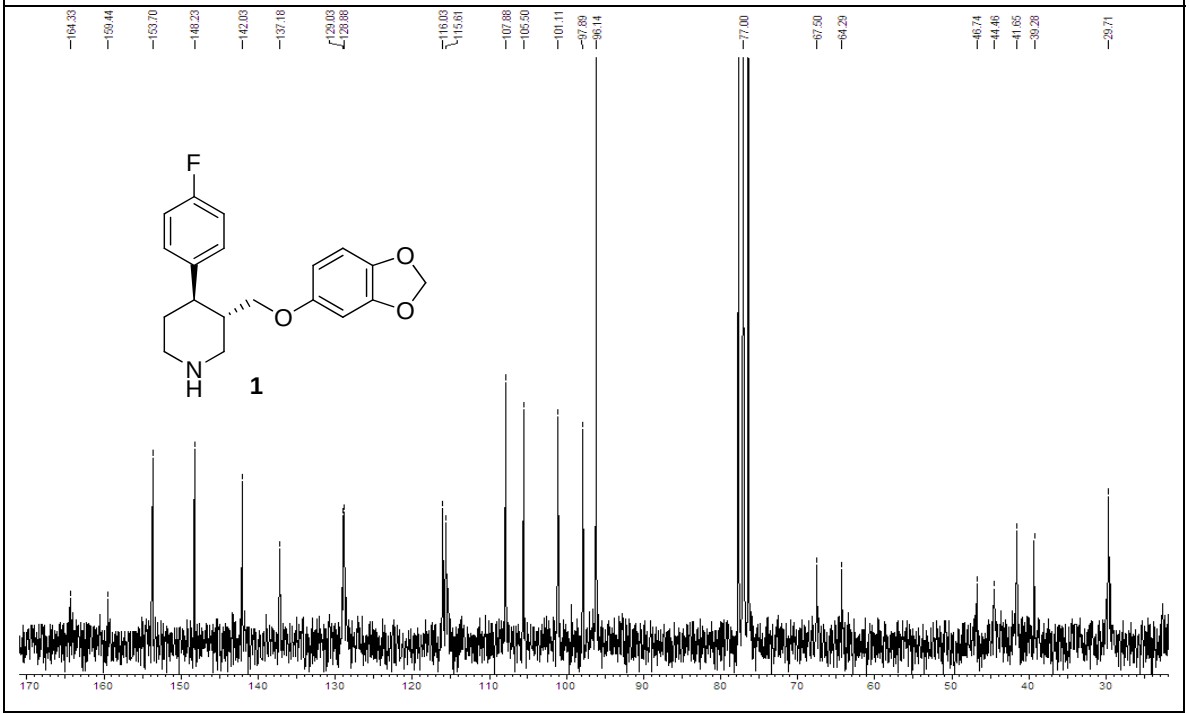
DEPT spectrum of compound **11** ($CDCl_3$ + CCl_4, 50 MHz)



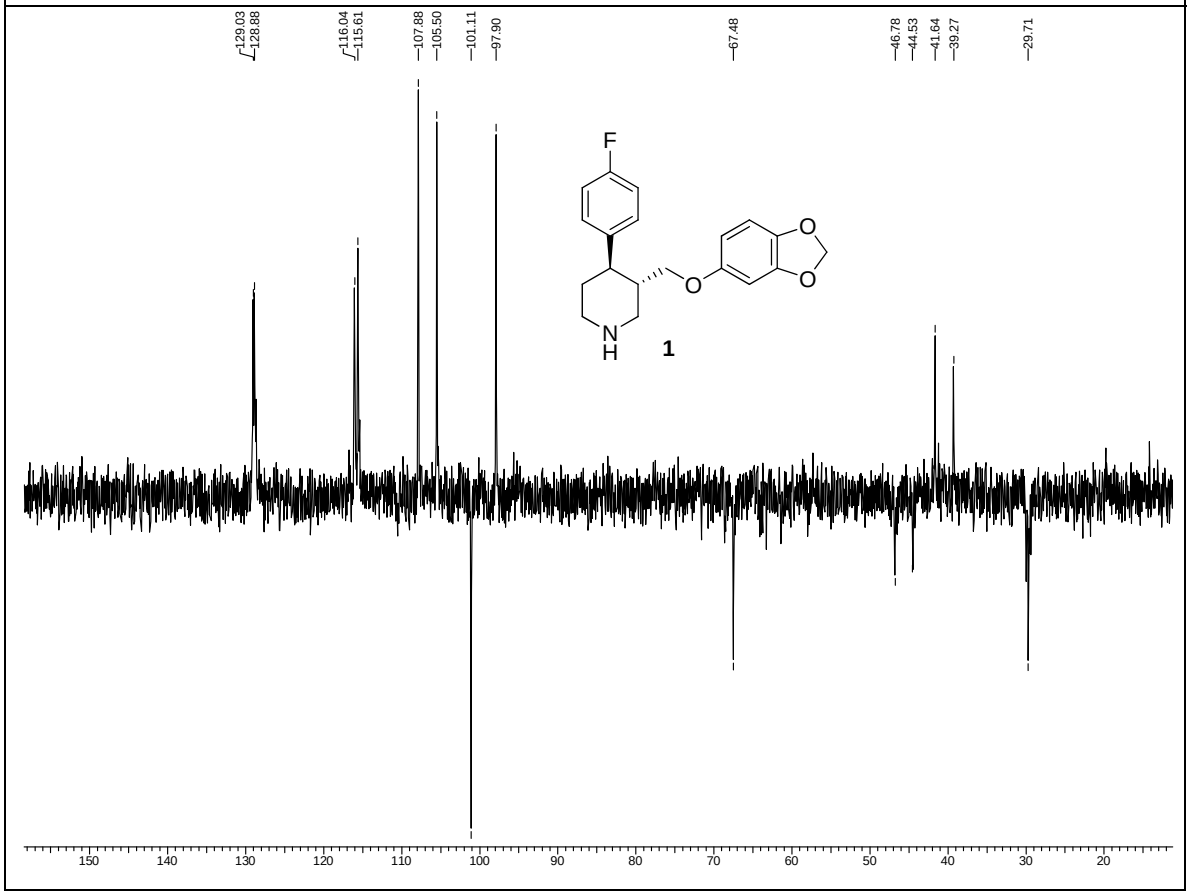
^{1}H NMR spectrum of compound **1** ($CDCl_3$, 200 MHz)



^{13}C NMR spectrum of compound **1** ($CDCl_3$ + CCl_4, 50 MHz)



DEPT spectrum of compound **1** ($CDCl_3$ + CCl_4, 50 MHz)



1.2.5. References

1. (a) Chavan, S. P.; Kamat, S. K.; Sivadasan, L.; Balakrishnan, K.; Khobragade, D. A.; Ravindranathan, T.; Gurjar, M. K.; Kalkote, U. R. US Patent 6,350,912 B1 *Chem. Abstr.* **2002**, *136*, 200009. (b) Chavan, S. P.; Kamat, S. K.; Sivadasan, L.; Balakrishnan, K.; Khobragade, D. A.; Ravindranathan, T.; Gurjar, M. K.; Kalkote, U. R. US Patent 6,504,044 B2, **2003**. (c) Chavan, S. P.; Kamat, S. K.; Sivdasan, L.; Balakrishna, K.; Khobragade, D. A.; Ravindranathan, T.; Gurjar, M. K.; Kalkote, U. R. *Tetrahedron Lett.* **2004**, *45*, 7291.
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Chapter 1. Synthetic studies towards (±)-Paroxetine and (±)-Femoxetine

Section 3: Total synthesis of (±)-Femoxetine

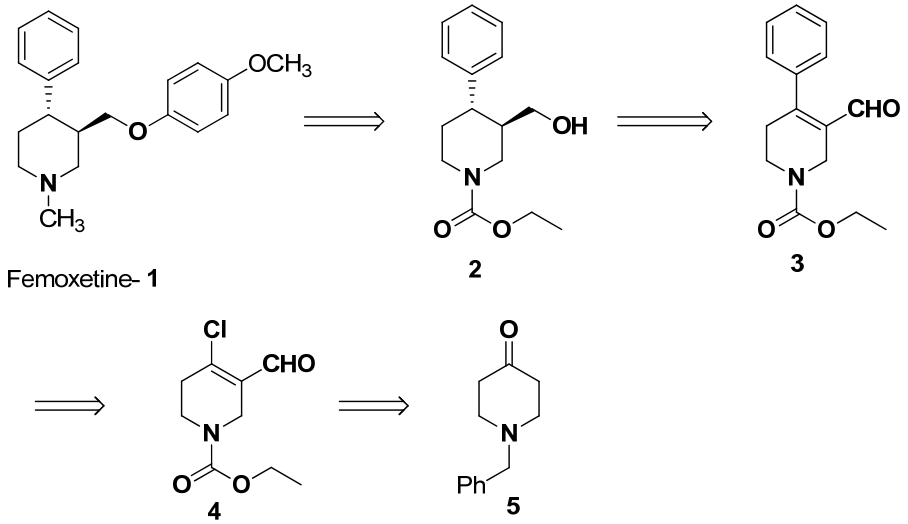
1.3.1: Present Work

1.3.1.1: Objective

The potent serotonin (5-HT)-uptake inhibitory properties of the femoxetine[1] and its structural similarity with paroxetine was the driving force for its synthesis, using 4-piperidone as a commercially available starting material.

1.2.1.2. Retrosynthetic analysis

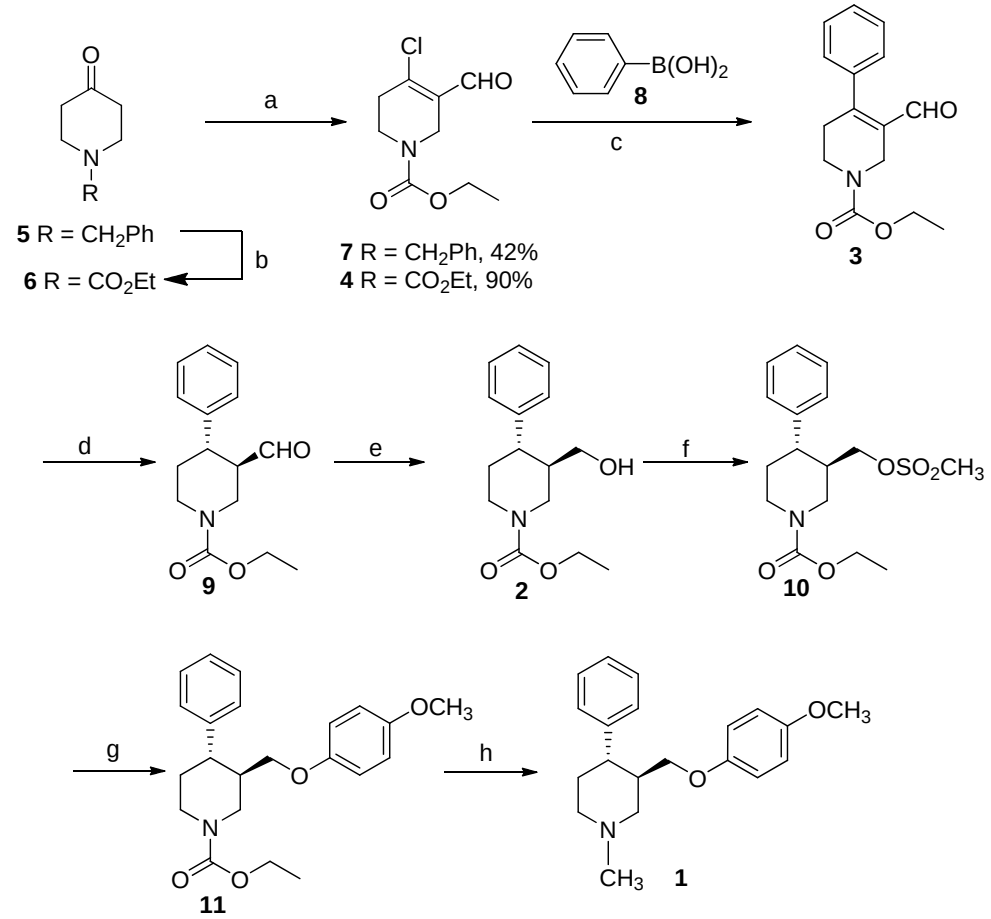
The retrosynthetic analysis for (±)-femoxetine (**1**) is shown in scheme 1.



Scheme 1: Retrosynthetic analysis for **1**

The target molecule **1** could be obtained from carbamate **2** by LAH reduction and attaching side chain via SN^2 displacement of the alcohol with 4-methoxy phenol. The carbamate **2** could be readily obtained from unsaturated aldehyde **3** by hydrogenation, epimerization and aldehyde reduction. The unsaturated aldehyde **3** could be constructed by taking advantage of Suzuki reaction on chloro aldehyde **4** using phenyl boronic acid.[2] The common intermediate used for the synthesis of paroxetine (chapter 1, section 2) chloro aldehyde **4** could be employed for the synthesis of (±)-femoxetine (**1**). The chloro aldehyde **4** could be obtained from 4-piperidone **5** by Vilsmeier-Haack formylation.[3]

1.3.1.3. Results and discussion



Scheme 2: Synthesis of (±)-Femoxetine **1**.

Reagents and conditions: *a) DMF, $POCl_3$, DCM, rt, 90% b) EtOCOCl, Na_2CO_3, DCM, 95% c) Phenylboronic acid (**8**), $Pd(OAc)_2$, TBAB, K_2CO_3, H_2O, 50 ^{o} C, 70% d) H_2,Pd-C, MeOH, rt e) $NaBH_4$, MeOH, 56% (over two steps) f) MsCl, Et_3N, DCM, (g) p-Methoxyphenol, NaH, DMF, reflux, 72% h) LAH, THF, rt, 85%*

The synthesis of (±)-femoxetine (**1**) started from *N*-benzyl piperidone **5** as a commercially available starting material which was also used for the synthesis of (±)-paroxetine. The replacement of *N*-benzyl group in **5** by ethyl carbamate and its Vilsmeier-Haack formylation[3] provided aldehyde **4** as described in detail in chapter-1-section-2. Chloro aldehyde **4** was subjected to Suzuki coupling reaction using phenyl boronic acid **8** in presence of catalytic palladium acetate in water to provide the coupled product *β*-aryl aldehyde **3** in 70% yield.[2] Its IR spectrum showed intense bands at 1690 and 1675 cm^{-1} corresponding to unsaturated aldehyde and carbamate functionality respectively. The ^{1}H-NMR spectrum of **3** showed peak at δ 9.49 indicating the presence of an aldehyde functionality while peaks at δ 7.41 and 7.26

integrating for 3 and 2 protons respectively showed the presence of aromatic ring. Its ^{13}C-NMR spectrum showed peaks at δ 191 and 155 corresponding to aldehyde and carbamate functionalities respectively. Peak at m/z 282 $(M+Na)^+$ in its mass spectrum confirmed the formation of **3**.

β-Aryl aldehyde **3** was subjected to hydrogenation in methanol in the presence of palladium catalyst under hydrogen atmosphere to provide saturated aldehyde **9**, which was observed to be unstable during purification and therefore it was directly subjected to reduction using sodium borohydride to provide alcohol **2** in 56% yield over two steps. Peak at δ 9.49 in the ^{1}H-NMR spectrum of **2** vanished confirming the reduction of aldehyde. Peaks at δ 4.34 and 4.24 were ascribed to protons adjacent to nitrogen. carbamate methylene protons appeared as a quartet at δ 4.45. Peaks appearing at δ 3.41 and 3.25 as dd each were attributed to –$\underline{CH_2}$OH protons. Its ^{13}C NMR spectrum showed peak at δ 155 corresponding to carbamate. Absence of peak at δ 191 showed the absence of aldehyde functionality and appearance of peaks in aliphatic region at δ 43 (CH) and 45 (CH) confirmed the reduction of double bond. Further, the mass spectrum of **2** showed the molecular ion peak at m/z 264 $(M+1)^+$, m/z 286 $(M+Na)^+$ which confirmed the formation of **2**.

Alcohol **2** was subjected to mesylation using mesyl chloride and triethylamine to provide mesyl compound **10**. Mesyl compound **10** without purification was subjected to displacement of mesyl group by *p*-methoxy phenoxy group using sodium hydride as a base in DMF under reflux conditions to provide di-aryl compound **11** in 72% yield. Its IR spectrum showed intense band at 1678 cm^{-1} corresponding to carbamate carbonyl functionality. Peaks in its ^{1}H-NMR spectrum at δ 6.75, 6.68 integrated for 2 protons each and peak at δ 3.73 appearing as a singlet accounted for 3 protons indicating the presence of *p*-methoxy phenyl ring. Peaks corresponding to $\underline{CH_2}$O- appeared at δ 3.65 and δ 3.60, each as a doublet of doublet. Its ^{13}C NMR spectrum showed peaks at δ 115, 114 and δ 153, 152 corresponding to *p*-methoxy phenyl moiety. Peaks that resonated at δ 128, 127, 126 and 143 were due to phenyl ring. The two di-substituted tertiary carbons of piperidine ring appeared at δ 44 and δ 41. The carbamate carbonyl appeared at δ 155. Further, the mass spectrum of **11** showed the peak at m/z 392 $(M+Na)^+$ confirming the formation of **11**.

Finally the di-aryl compound **11** was subjected to reduction using Joshnson's[4] approach by LAH[5] in THF to provide target molecule (±)-femoxetine (**1**) in 85% yield. Absence of peaks

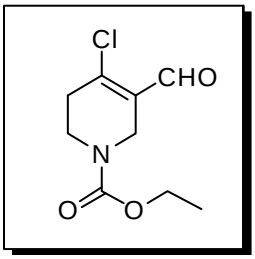
at δ 4.18 (q) and δ 1.29 (t) and appearance of peak at δ 2.46 (s) in its ^{1}HNMR spectrum clearly indicated the conversion of carbamate to methyl group. The aromatic protons appeared at δ 7.33 (m, 2H) and 7.25 (m, 3H) corresponding to aryl group. Doublets at δ 6.79 and δ 6.71 with coupling constant 9 Hz were assigned to *p*-methoxy phenyl group. Peak appearing at δ 3.78 was due to aromatic methoxy group. Two double doublets appeared at δ 3.66 and δ 3.54 corresponding to -CH_2O- protons. Its ^{13}C NMR spectrum showed peak at δ 153.1 corresponding to the aromatic quaternary C-O and peaks at δ 115.4 and δ 114.5 corresponding to aromatic CH in *p*-methoxy phenyl ring. Peak at δ 143.8 corresponded to the quaternary aryl carbon and peaks at δ 128.6, 127.5, and 126.6 were due to aromatic CH. The other peaks appeared at δ 69.2 (CH_2), 59.6 (CH_2), 56.2 (CH_2), 55.6 (CH_3), 46.4 (CH_3), 44.2 (CH), 41.8 (CH) and δ 34.1 (CH_2). Its mass spectrum showed molecular ion peak at 312 $(M+1)^+$ thereby confirming the formation of (±)-femoxetine (**1**). The spectral data of the target molecule **1** was in good agreement with the reported one.[5,6]

1.3.2. Conclusion

Total synthesis of (±)-femoxetine has been accomplished employing Suzuki coupling reaction under aqueous medium and Vilsmeier-Haack formylation was the key steps. The total synthesis of (±)-femoxetine has been accomplished in 8 steps with 17% overall yield starting from commercially available starting material *N*-benzyl piperidone. The presented method for construction of 3,4-di-substituted piperidines can be explored for the synthesis of similar class of compounds.

1.3.3. Experimental

Ethyl 4-chloro-3-formyl-5,6-dihydropyridine-1(2H)-carboxylate (4)



A mixture of anhydrous DCM (8 mL) and anhydrous DMF (15.2 mL, 197 mmol) was cooled to 0 ºC using ice and to that was added $POCl_3$ (14.7 mL, 157 mmol) dropwise and stirred further for 2 hours at room temperature. Ethyl 4-oxopiperidine-1-carboxylate (**6**) (13.5 g, 78 mmol) in DCM (10 mL) was added dropwise at 0 ºC and further stirred for 3 hours at room temperature. Reaction mixture was quenched first by using ice followed by careful addition of sat. $NaHCO_3$ solution. Reaction mixture was allowed to separate in separating funnel, organic layer was separated and aqueous layer was again extracted twice using DCM (50 mL). The collected organics were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to furnish β-chloro aldehyde **4** (15.4 g, 90%) as a crude product.

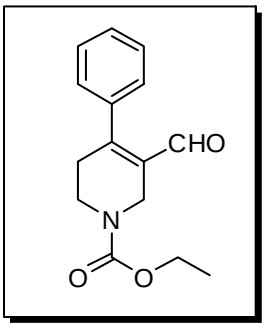
Molecular formula **:** $C_9H_{12}ClNO_3$

Yield **:** 90%

IR ($CHCl_3$) **:** 3019, 2872, 1694, 1676, 1236, 1216, 757 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 10.14 (s, 1H), 4.11-4.22 (m, 4H), 3.65-3.74 (t, *J* = 5.8 Hz, 2H), 2.69 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H)

Ethyl 3-formyl-4-phenyl-5,6-dihydropyridine-1(2H)-carboxylate (3)



β-Chloro aldehyde **4** (5 g, 23 mmol), phenyl boronic acid (3.1 g, 25 mmol), *tetra*-butyl ammonium bromide (7.4 g, 23 mmol), potassium carbonate (8 g, 57 mmol) and palladium acetate (100 mg, 2 mol %) were taken together and to that was added deionized water (50 mL). The mixture was stirred vigorously at 45 ºC for three hours. The dark red nonhomogeneous reaction mixture was diluted with water (50 mL) and extracted using ethyl acetate (3 x 100 mL). The combined organics were dried over anhydrous sodium sulfate, filtered and concentrated to provide sticky dark brown liquid. Purification by flash chromatography (pet ether : ethyl acetate 72:28) furnished 4.2 g (70%) of pure product aldehyde **3** as a colorless dense liquid.

Molecular formula **:** $C_{15}H_{17}NO_3$

Yield **:** 70%

IR ($CHCl_3$) **:** 3017, 1698, 1671, 1603, 1225, 761 cm^{-1}

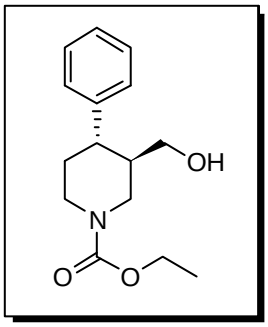
^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 9.49 (s, 1H), 7.41-7.42 (m, 3H), 7.26-7.28 (m, 2H), 4.27 (bs, 2H), 4.20 (q, *J* = 7 Hz, 2H), 3.71 (t, *J* = 5.8 Hz, 2H), 2.69 (bs, 2H), 1.32 (t, *J* = 7 Hz, 3H)

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 190, 157.2, 155.3, 137.5, 132.8, 128.9, 128.5, 128.4, 61.5, 41.4, 39.8, 32.8, 14.6

MS (ESI) (m/z) **:** 282 $(M+Na)^+$

Elemental analysis **:** Calculated C, 69.48; H, 6.61; N, 5.40%
Found C, 69.50; H, 6.57; N, 5.43%

Ethyl 3-(hydroxymethyl)-4-phenylpiperidine-1-carboxylate (2)



Aldehyde **3** (2.5 g, 9.6 mmol) was dissolved in methanol (30 mL) and to it was added Pd over carbon (5%, 10 mg). Reaction mixture was kept under hydrogen atmosphere (60 psi) on shaker for 45 min. Reaction mixture was filtered through celite and the filtrate concentrated under reduced pressure to provide crude saturated aldehyde as a dense liquid. The crude aldehyde was subsequently dissolved in methanol and cooled to 0 ºC. $NaBH_4$ (0.35 g, 9.6 mmol) was added portion wise over 10 min and stirred further for 1 hour. Methanol was removed from reaction mixture and to that water (30 mL) was added and extracted using ethyl acetate (3 x 30 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to provide colorless dense liquid. Purification of crude product using flash chromatography (pet ether : ethyl acetate 60:40) furnished alcohol **2** (1.42 g, 56%) as a sticky liquid.

Molecular formula **:** $C_{15}H_{21}NO_3$

Yield **:** 56%

IR ($CHCl_3$) **:** 3436, 2928, 1685, 1511, 1440, 1225 cm^{-1}.

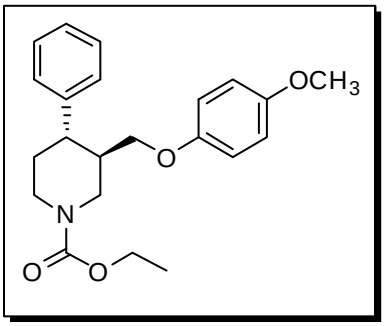
^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 7.14-7.29 (m, 5H), 4.24-4.40 (m, 2H), 4.15 (q, *J* = 7 Hz, 2H), 3.42 (dd, *J* = 11.1, 3.2 Hz, 1H), 3.25 (dd, *J* =11.0, 6.5 Hz, 1H), 2.81 (m, 1H), 2.72 (dd, *J* = 13.3, 11.5 Hz, 1H), 2.48-2.55 (m, 1H), 2.17-2.88 (m, 3H), 1.27 (q, *J* = 7 Hz, 3H)

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 155.5, 143.7, 128.8, 127.4, 126.8, 63.2, 61.4, 47.1, 45.1, 44.5, 43.8, 34.0, 14.9

MS (ESI) (m/z) **:** 264 $(M+H)^+$**,** 286 $(M+Na)^+$

Elemental analysis **:** Calculated C, 68.42; H, 8.04; N, 5.32%
Found C, 68.41; H, 8.08; N, 5.30%

Ethyl 3-((4-methoxyphenoxy)methyl)-4-phenylpiperidine-1-carboxylate (11)



To the solution of *p*-methoxy phenol (750 mg, 6 mmol) in DMF (5 mL) was added NaH (356 mg, 9 mmol, 60%) under nitrogen atmosphere. Mesyl compound **10** (1 g, 3 mmol) dissolved in DMF (10 mL) was added and the reaction mixture was refluxed for 20 minutes. The reaction mixture was cooled to room temperature and quenched carefully using water (50 mL) and extracted using diethyl ether (3 x 50 mL). The collected organics were dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure and the residue was purified using flash chromatography (pet ether : ethyl acetate 70:30) to provide compound **11** (788 mg, 72%) as a colorless liquid.

Molecular formula **:** $C_{22}H_{27}NO_4$

Yield **:** 72%

IR ($CHCl_3$) **:** 3085**,** 2980, 1683, 1025, 731 cm^{-1}.

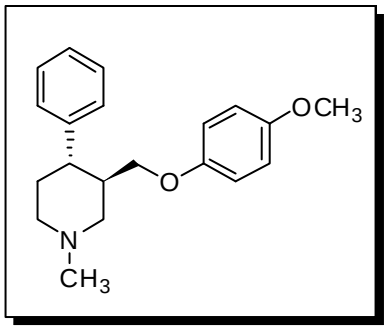
^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 7.26-7.37 (m, 2H), 7.17-7.23 (m, 3H), 6.75 (d, *J* = 9.0 Hz, 2H), 6.68 (d, *J* = 9.0 Hz, 2H), 4.51 (bs, 1H), 4.30 (bs, 1H), 4.18 (t, *J* = 7.0 Hz, 2H), 3.73 (s, 3H), 3.65 (dd, *J* = 9.5, 2.8 Hz, 1H), 3.50 (dd, *J* = 9.4, 6.8 Hz, 1H), 2.83-2.89 (m, 1H), 2.67-2.71 (m, 1H), 2.09-2.11 (m, 1H), 2.04-2.13 (m, 1H), 1.74-1.86 (m, 1H), 1.63 (bs, 1H), 1.29 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 155.6, 153.8, 152.9, 143.4, 128.7, 127.4, 126.7, 115.5, 114.5, 68.7, 61.4, 55.7, 47.3, 44.8, 44.4, 41.7, 33.8, 14.7

MS (ESI) (m/z) **:** 392 $(M+Na)^+$

Elemental analysis **:** Calculated C, 71.52; H, 7.37; N, 3.79%
Found C, 71.49; H, 7.39; N, 3.78%

3-((4-Methoxyphenoxy)methyl)-1-methyl-4-phenylpiperidine (1)



The suspension of LAH (256 mg, 6.7 mmol) in anhydrous THF (20 mL) was cooled to 0 ºC and to that was added carbamate compound **11** (500 mg, 1.3 mmol) in anhydrous THF (10 mL) dropwise. The reaction mixture was further stirred for 4 h at room temperature. The excess LAH was quenched by careful addition of 2N NaOH (0.5 mL) followed by water (5 mL). The aqueous layer was extracted using ethyl acetate (3 × 15 mL), organics were dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure and the residue was purified using flash chromatography (pet ether : ethyl acetate 10:90) to provide (±)-femoxetine (**1**) (357 mg, 85%) as a sticky liquid.

Molecular formula **:** $C_{20}H_{25}NO_2$

Yield **:** 85%

IR ($CHCl_3$) **:** 2935, 1508, 1230 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4) : δ 7.32-7.35 (m, 2H), 7.23-7.27 (m, 3H), 6.79 (d, *J* = 9.1 Hz, 2H), 6.71 (d, *J* = 9.1 Hz, 2H), 3.78 (s, 3H), 3.66 (dd, *J* = 9.3, 2.7 Hz, 1H), 3.54 (dd, *J* = 9.2, 7.1 Hz, 1H), 3.33 (bd, *J* = 11.5 Hz, 1H), 3.08 (bd, *J* = 11.2 Hz, 1H), 3.53 (dt, *J* = 11.7, 4.2 Hz, 1H), 2.46 (s, 3H), 2.37-2.43 (m, 1H), 2.13-2.20 (m, 2H), 2.01-2.09 (m, 1H), 1.90-1.93 (m, 1H)

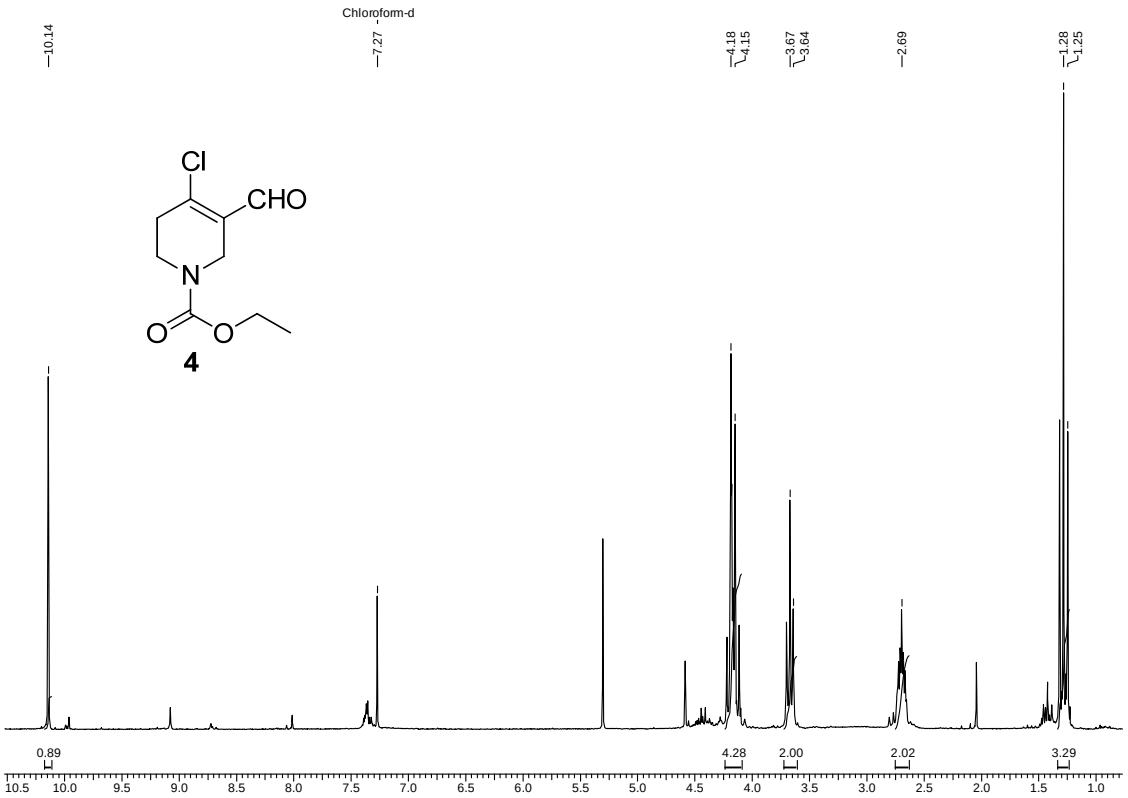
^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4) : δ 153.8, 153.1, 143.0, 128.6, 127.5, 126.6, 115.4, 114.5, 69.2, 59.6, 56.2, 55.6, 46.4, 44.2, 41.8, 34.1

MS (ESI) (m/z) **:** 312 $(M+H)^+$

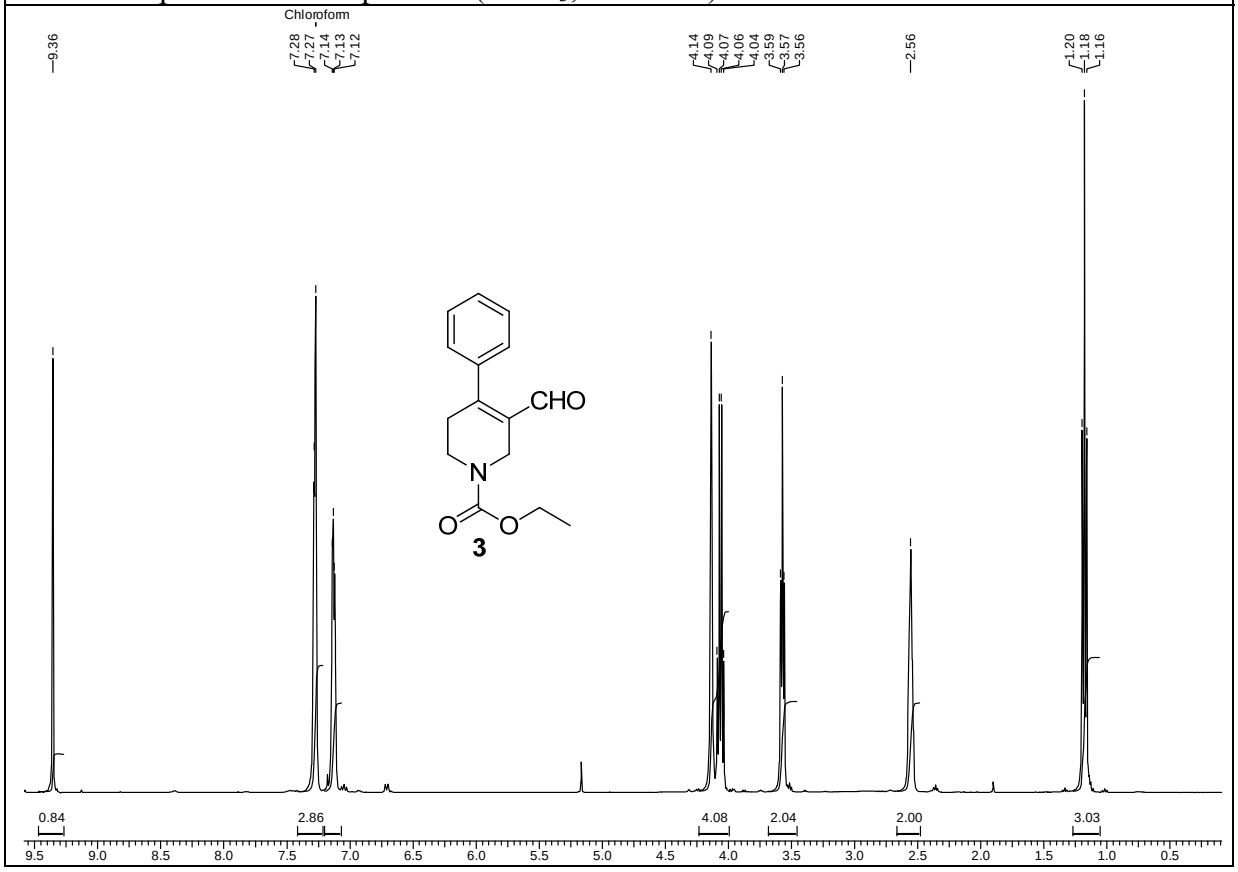
Elemental analysis **:** Calculated C, 77.14; H, 8.09; N, 4.50%
Found C, 77.17; H, 8.08; N, 4.52%

1.3.4 NMR Spectra

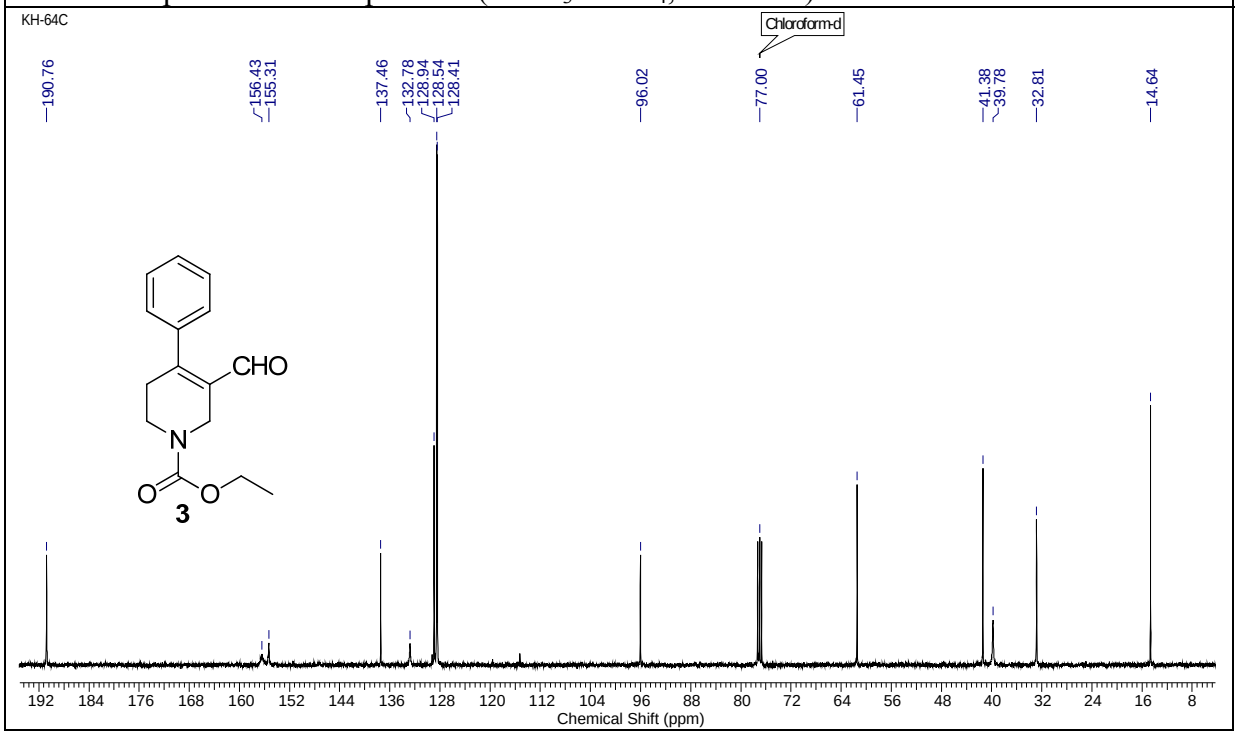
^{1}H NMR Spectrum of compound **4** ($CDCl_3$, 200 MHz)



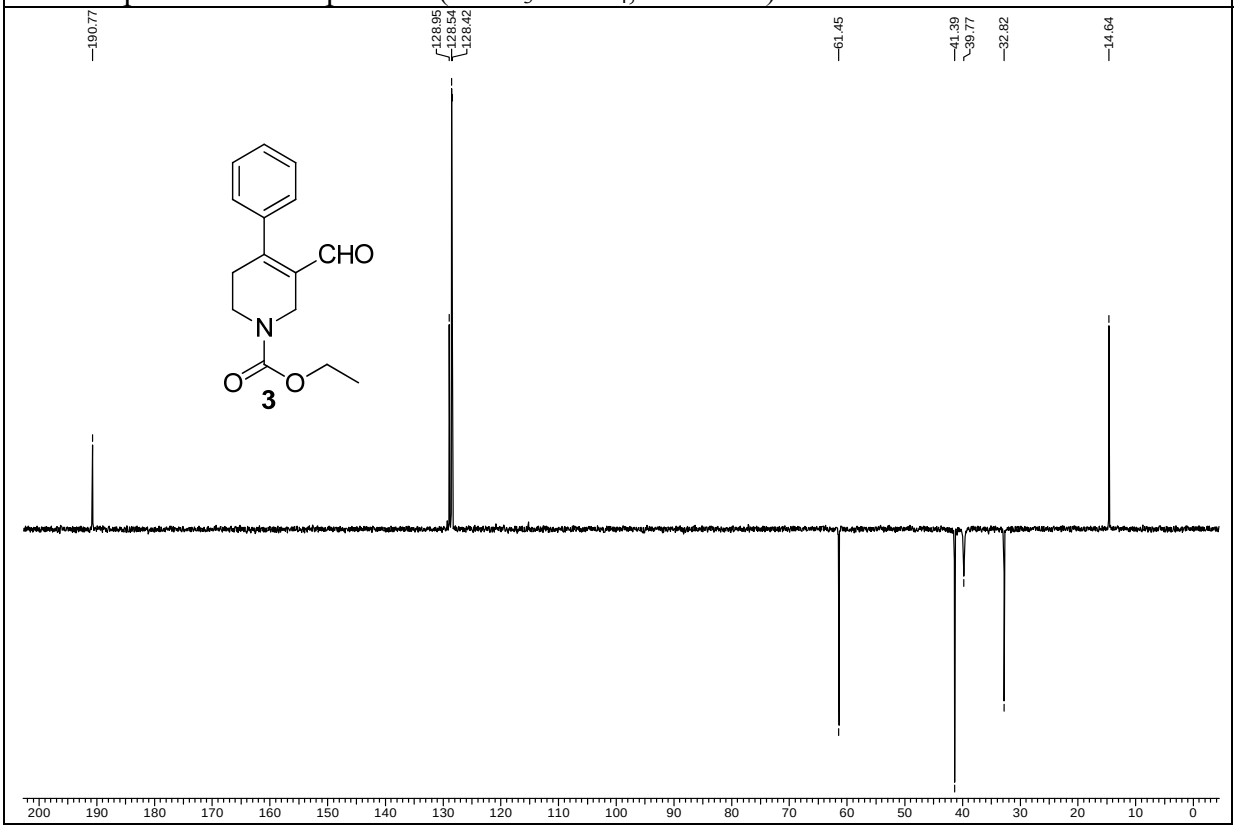
^{1}H NMR Spectrum of compound **3** ($CDCl_3$, 400 MHz)



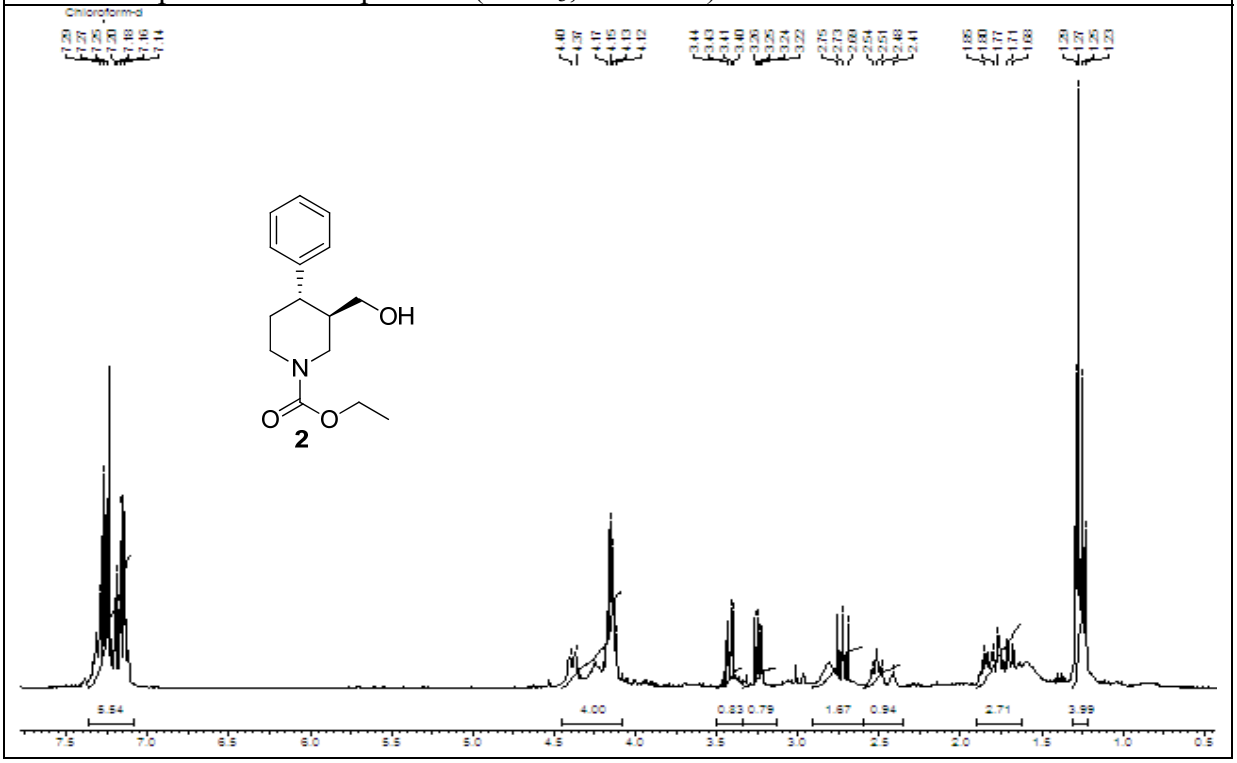
^{13}C NMR spectrum of compound **3** ($CDCl_3$ + CCl_4, 100 MHz)



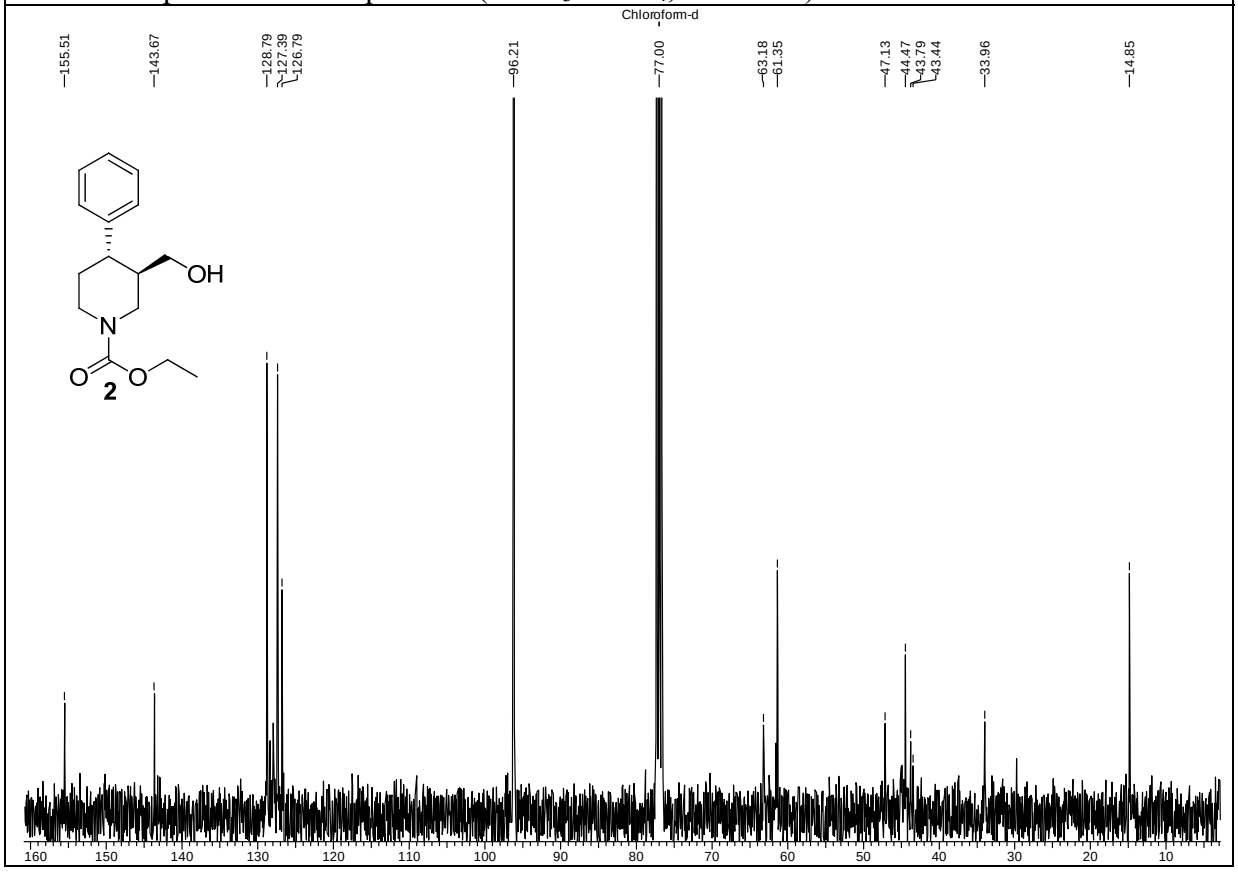
DEPT Spectrum of compound **3** ($CDCl_3$ + CCl_4, 100 MHz)



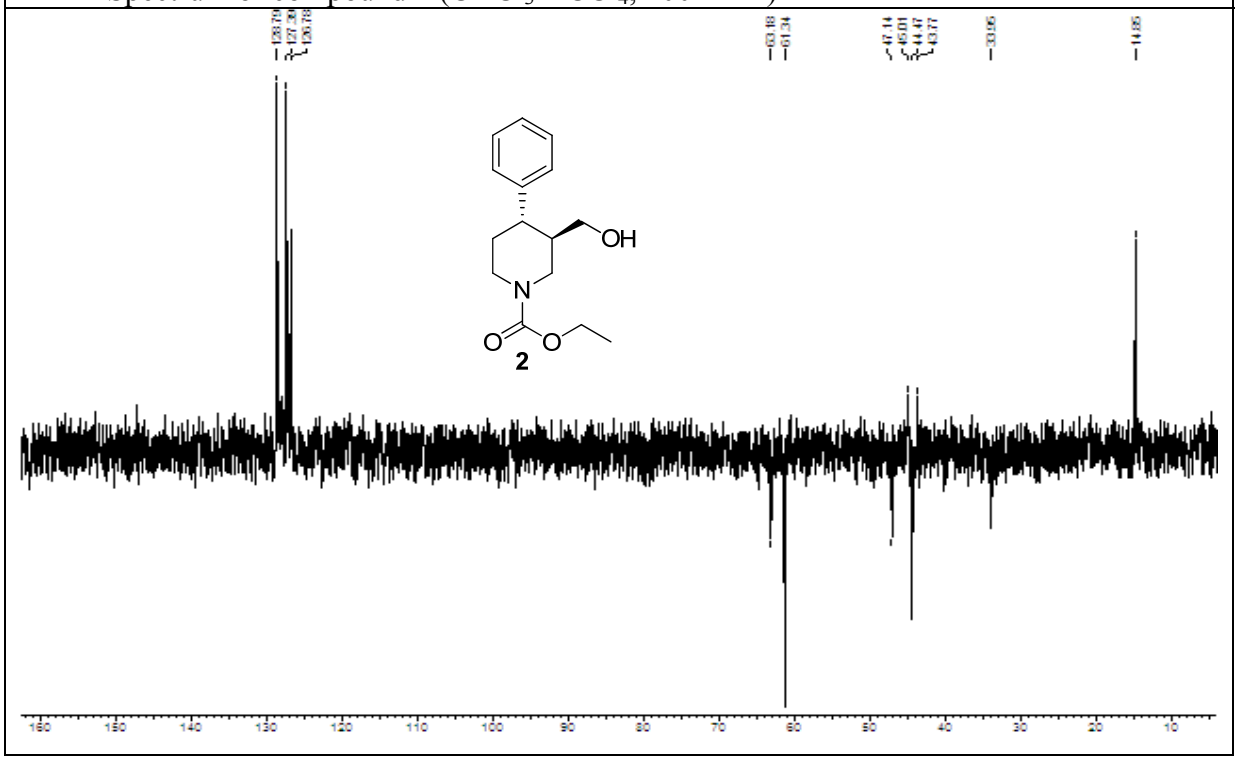
^{1}H NMR Spectrum of compound **2** ($CDCl_3$, 400 MHz)



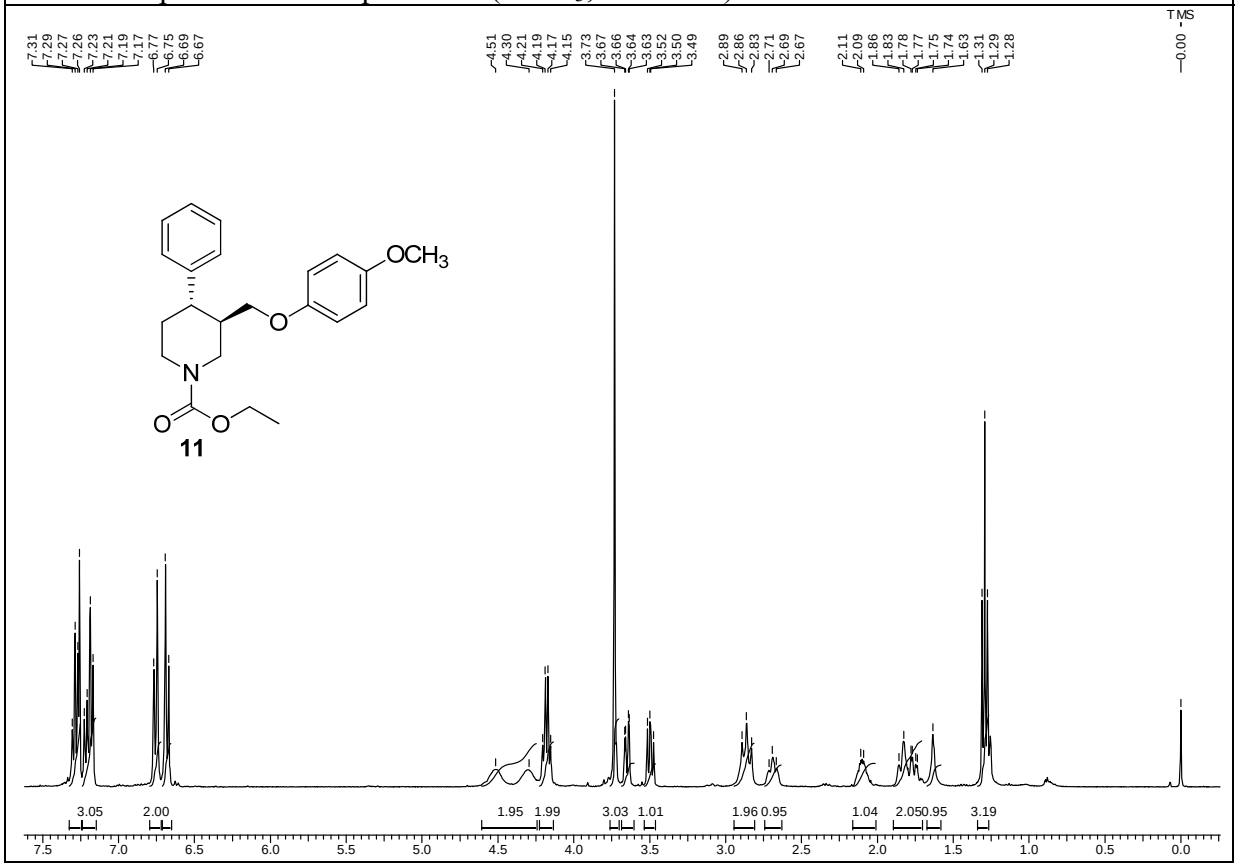
^{13}C NMR spectrum of compound **3** ($CDCl_3$ + CCl_4, 100 MHz)



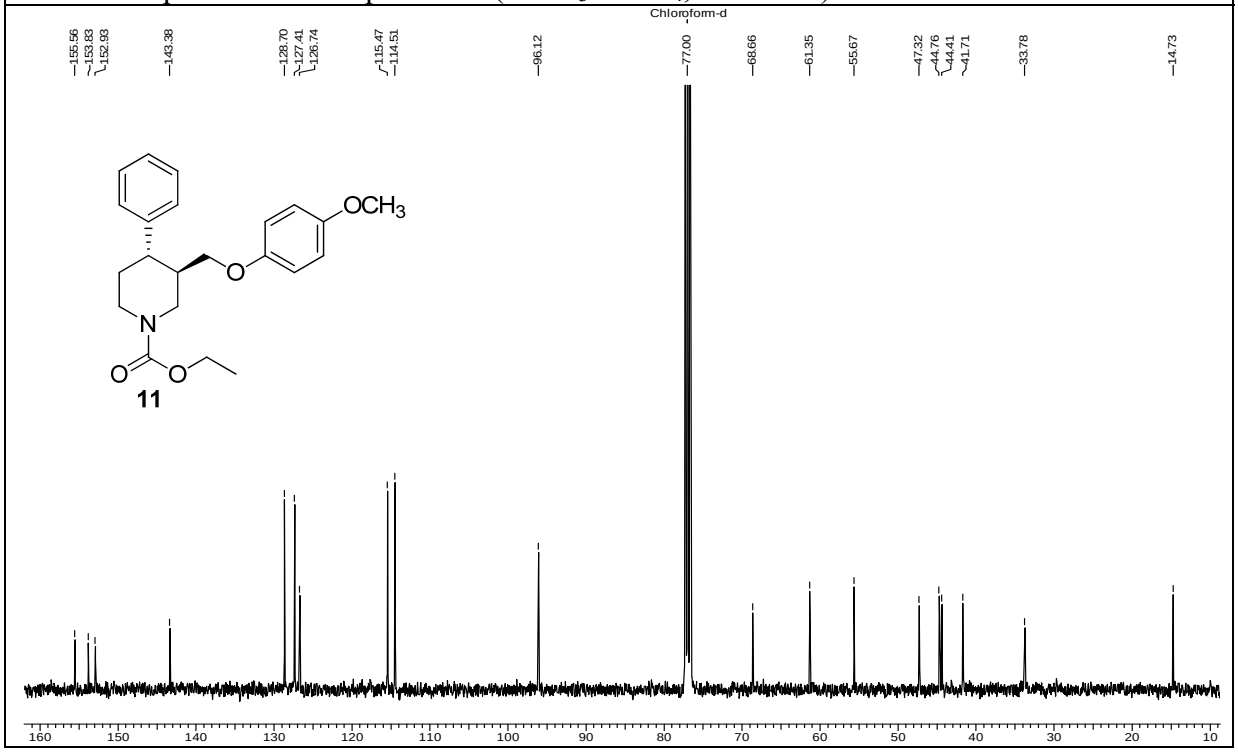
DEPT Spectrum of compound **2** ($CDCl_3$ + CCl_4, 100 MHz)



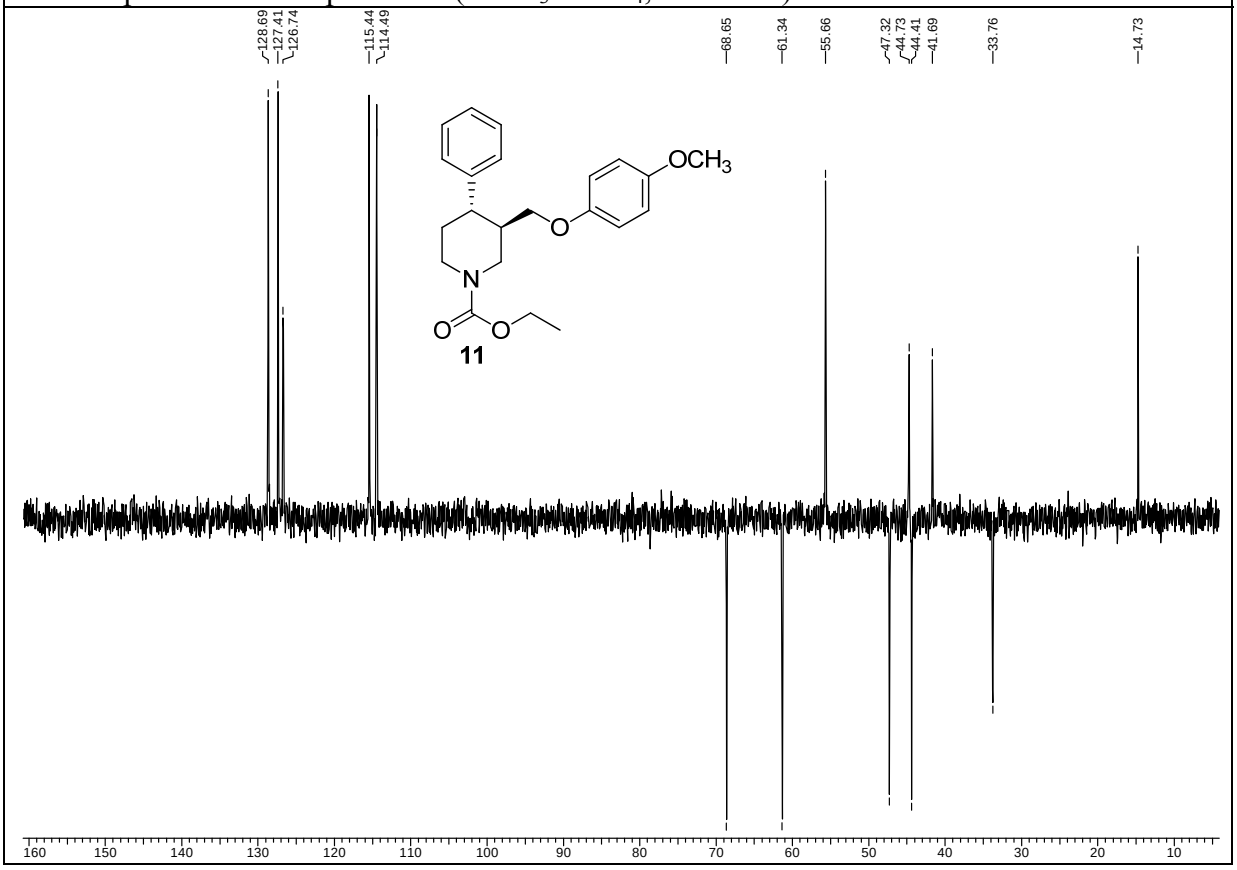
^{1}H NMR Spectrum of compound **11** ($CDCl_3$, 400 MHz)



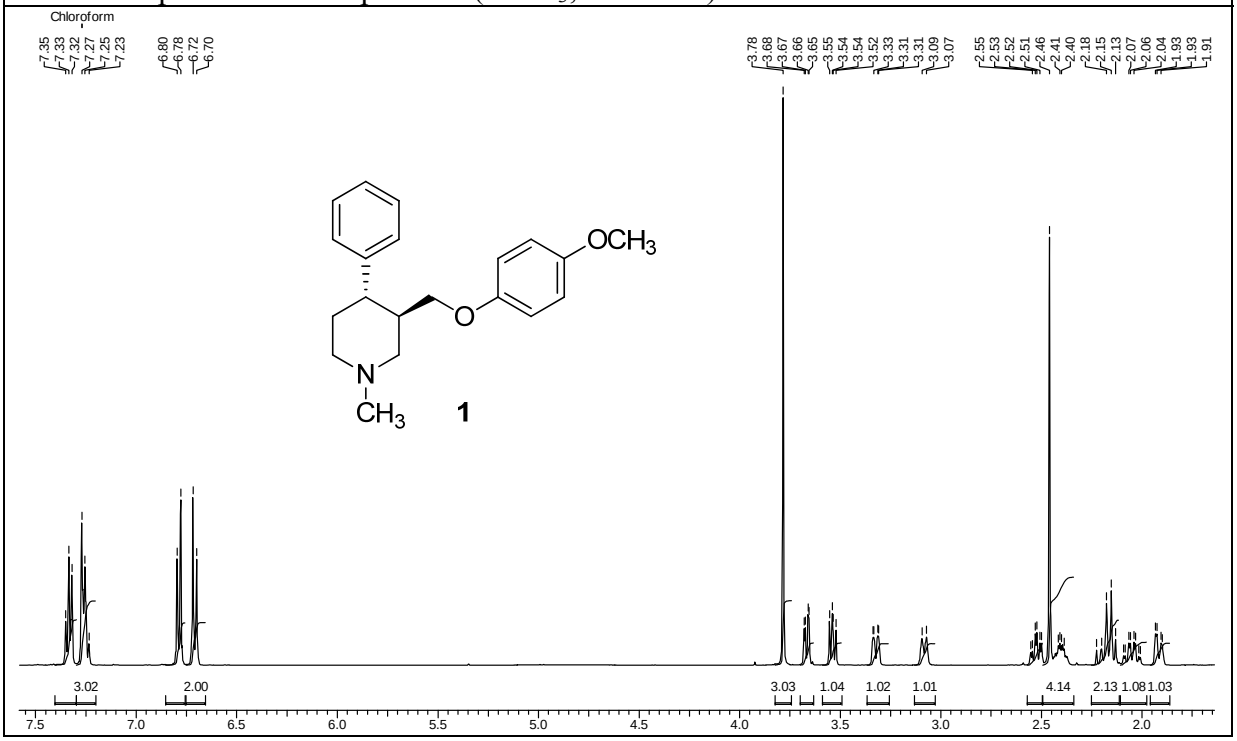
^{13}C NMR spectrum of compound **11** ($CDCl_3$ + CCl_4, 100 MHz)



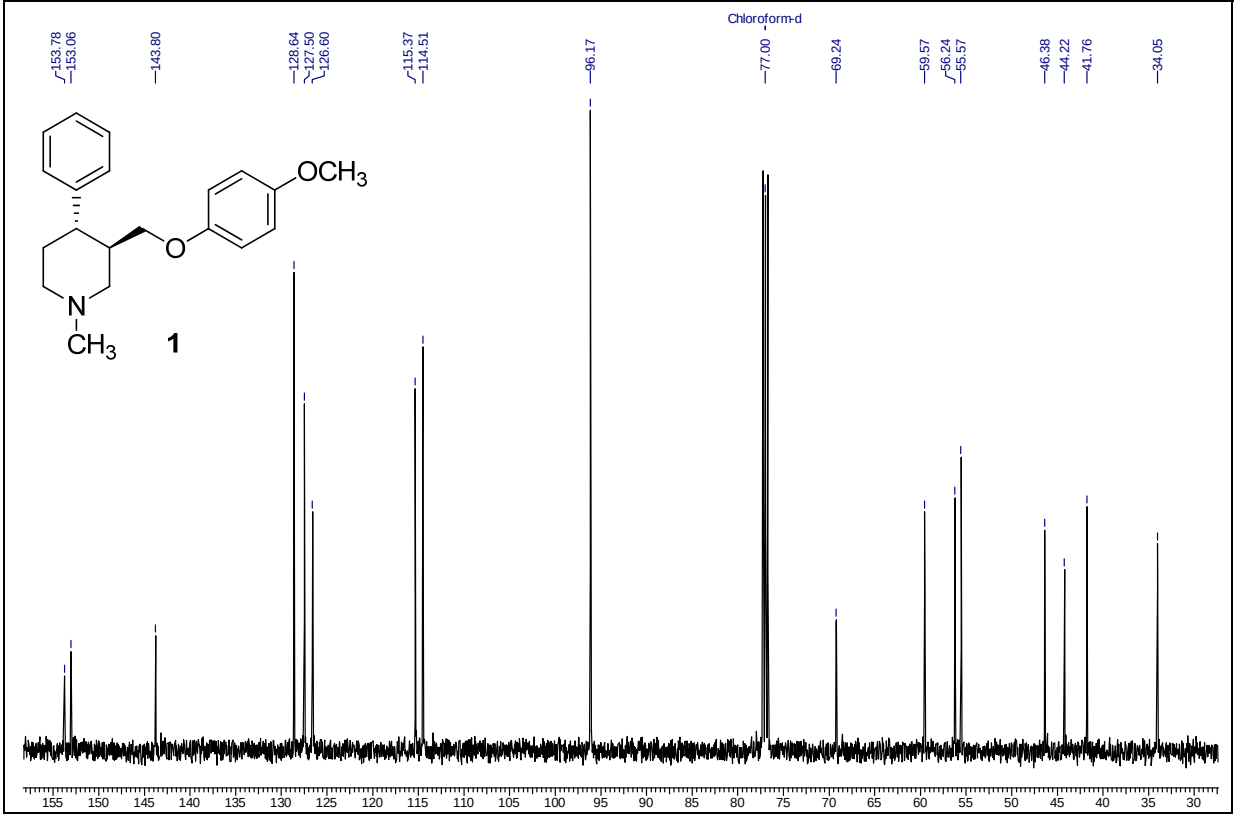
DEPT Spectrum of compound **11** ($CDCl_3$ + CCl_4, 100 MHz)



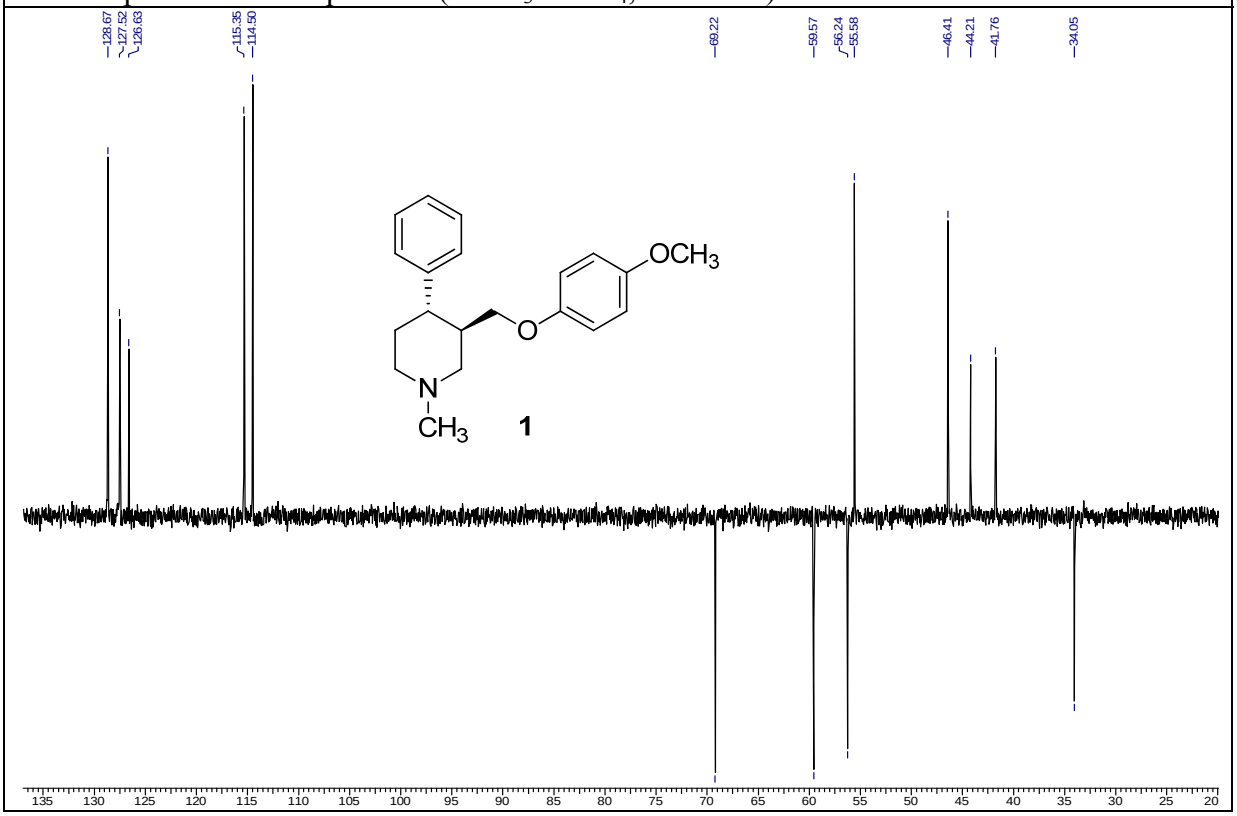
^{1}H NMR Spectrum of compound **1** ($CDCl_3$, 400 MHz)



^{13}C NMR spectrum of compound **1** ($CDCl_3$ + CCl_4, 100 MHz)



DEPT Spectrum of compound 1 ($CDCl_3$ + CCl_4, 100 MHz)



1.3.5. References

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Chapter 2. Synthetic studies towards (2*S*,3*S*)-3-hydroxy pipecolic acid

Section 1: Introduction to (2*S*,3*S*)-3-hydroxy pipecolic acid

2.1.1. Introduction

Pipecolic acid is a naturally occurring cyclic α-amino acid which is found abundantly in different species of plants and animals. It was first detected on paper chromatograms of extracts of *Phaseolus vulgaris* and later on its structure was indentified.[1] Later, presence of pipecolic acid was observed in several legumes, edible mushroom, potato tuber, green pepper, tulip, celery, asparagus,[2] Rhodesian teak,[3] barley[4] and coconut milk.[5, 6] Pipecolic acid is a non-proteinogenic amino acid and it is a component of several secondary metabolites in plants and fungi. Pipecolic acid is a metabolite of lysine[7] and is involved as a metabolite in formation of secondary metabolites like rapamycin, FK-506 and immunomycin which are act as immunosuppressors. Another secondary metabolite of pipecolic acid is a sandramycin which acts as antitumor antibiotic.[8] The peptides of cyclic amino acids like pipecolic acid and analogues have interesting biological properties.[9]

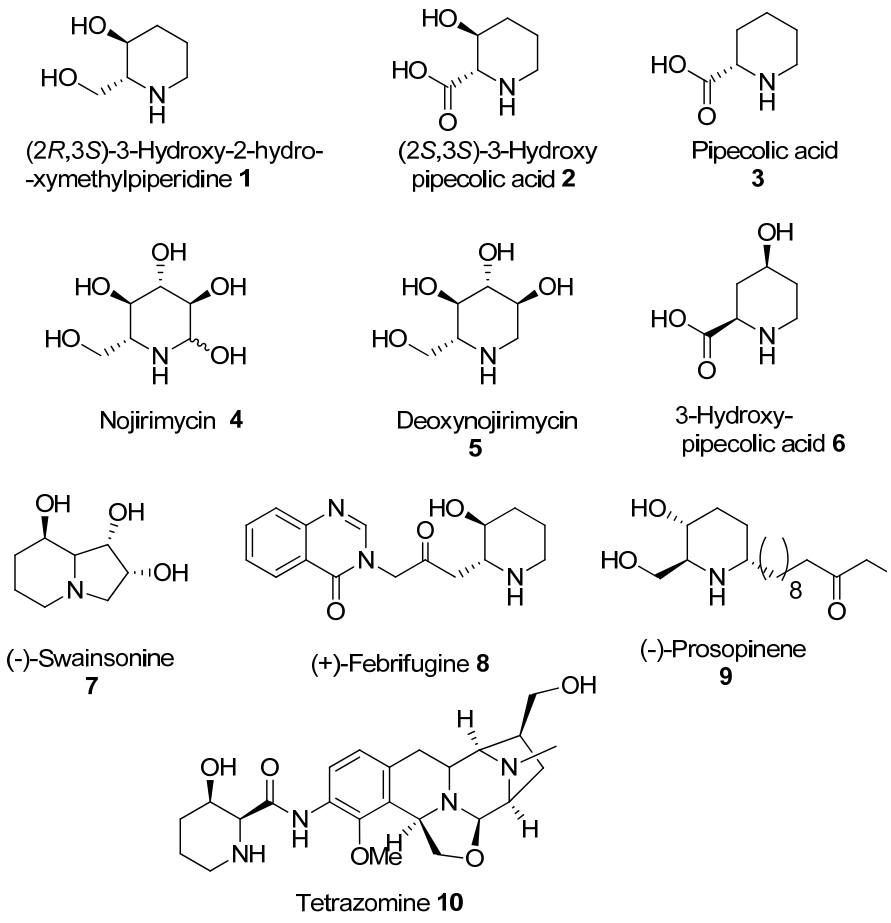


Figure 1

(2*R*, 3*S*)-3-Hydroxy-2-hydroxymethyl piperidine (**1**)[10] (Figure 1) is a constituent of many compounds having potent biological activities[11] like nojirimycin (**4**) which was the first heterose found in nature and has remarkable biological activity against drug resistant strains of *shigella*, *lutea* and *sarcina*.[12] The other analogues of **1** include deoxy-nojirimycin (**5**) which is a potent glycosidase inhibitor[13]and (–)-prosopinene (**9**) which acts as an antibiotic and anaesthetic.[14]

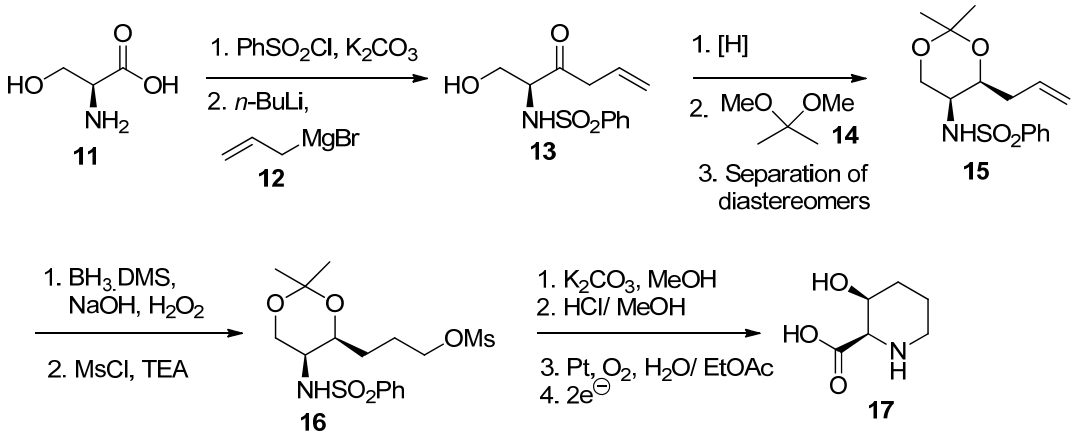
3-Hydroxypipecolic acid (**2**) is a non-proteinogenic cyclic amino acid and is used in the preparation of conformationally restricted peptides and ligand binding studies. (2*S*, 3*S*)-3-Hydroxypipecolic acid is also an important scaffold present in many natural as well as synthetic biologically active molecules. (–)-Swainsonine (**7**), an analogue of **2**, is a potent α-mannosidase inhibitor[15] and (+)-febrifugine (**8**) is a potent antimalarial agent.[16] The *cis*-isomer of **2** is a structural unit of the antitumor antibiotic tetrazomine (**10**).[17]

2.1.2. Literature review

The wide applicability and occurrence of this scaffold attracted attention of many organic chemists towards its synthesis. The reported routes for the synthesis of **1** and **2** are broadly divided in to two groups, (a) Synthesis using chiral pool approach and (b) synthesis using chiral induction. Some of the important syntheses in each class have been described here.

(a) Syntheses using chiral pool approach

Rapoport's Approach (*J. Org. Chem.***1989**, *54*, 1866-1875)

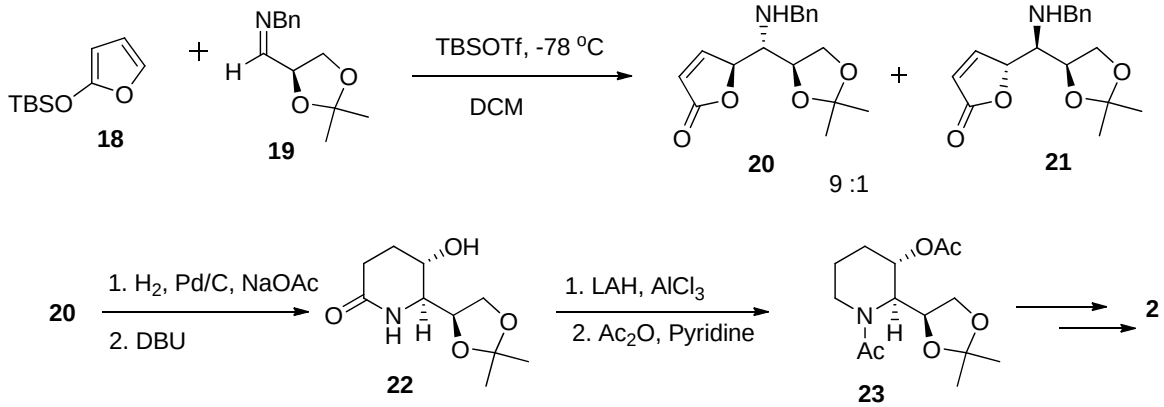


Scheme 1

Raporort *et al*. (Scheme 1) developed a method for alkylation of acids derived from L-serine and exploited for the synthesis of β-hydroxy-α-amino acids.[18] The amine in L-serine **11** was protected as a sulphonamide, and the resultant acid subjected to reaction with allylmagnesium bromide in presence of *n*-butyl lithium to provide keto- sulphonamide **13**. The sulphonamide **13** on reduction furnished 1,3-diol which on protection as its acetonide provided diastereomers which were separated to provide **15**. Compound **15** was then subjected to hydroboration followed by mesylation to provide mesyl sulfonamide **16.** Sulphonamide **16** was treated with base followed by acidification and oxidation to provide *cis*-3-hydroxypipecolic acid (**17**) in good yield.

Casiraghi's Approach (*Tetrahedron: Asymmetry* **1997**, *8*, 2975–2987)

Casiraghi *et al*. (Scheme 2) developed a novel diastereoselective addition of silyloxy furan TBSOF and imines derived from L and D glyceraldehydes with excellent diastereomeric excess and exploited it for the synthesis of both the enantiomers of 3-hydroxypipecolic acid **2**.[19]

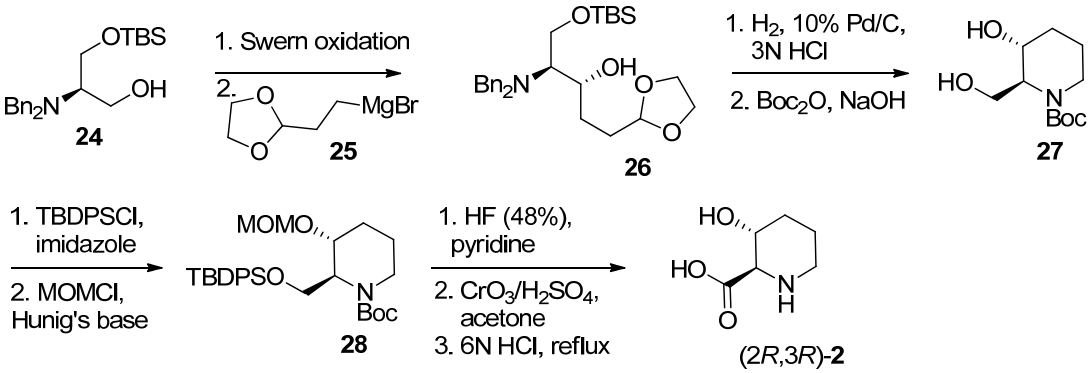


Scheme 2

Thus, the 2-silyloxyfuran **18** and imine **19** were coupled to provide butenolide amine **20** and **21** in the ratio 9:1. Butenolide amine **20** was subjected to hydrogenation followed by treatment with DBU to provide amide **22**. Amide **22** was reduced using LAH, $AlCl_3$ to provide aminol acetate **23** which on subsequent transformations was converted to 3-hydroxypipecolic acid **2**. The enantiomer of **2** was also prepared starting from D-glyceraldehyde.

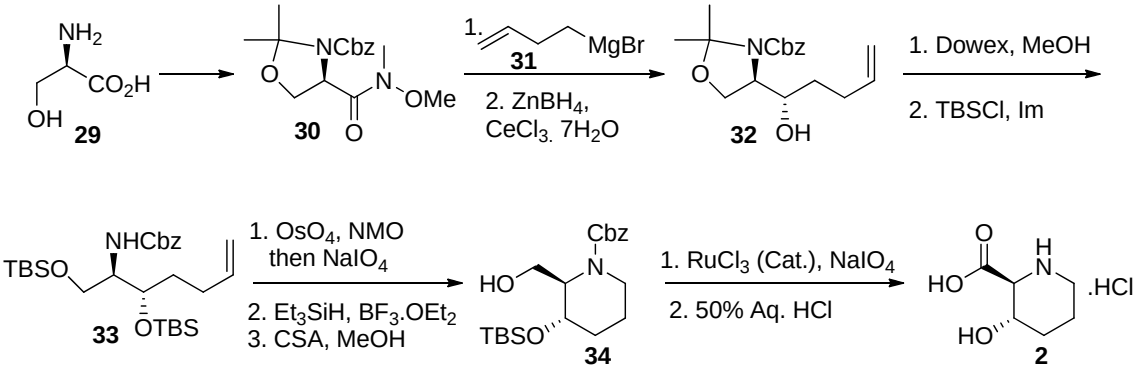
Zhu's Approach (*Tetrahedron Lett*. **2000**, *41*, 7033-7036)

Zhu *et al*. synthesized enantiomer of 3-hydroxypipecolic acid (**2**) starting from amino alcohol **24** derived from serine (Scheme 3). Amino alcohol **24** was oxidized to aldehyde and subjected to reaction with Grignard reagent **25** to obtain anti amino alcohol **26** as a major product which was exploited for the synthesis of (2*R*, 3*R*)-**2**. Protected amino alcohol **26** was subjected to hydrogenation and subsequently for Boc protection to provide diol **27**. The primary alcohol in diol **27** was protected with TBDPS group selectively and then secondary alcohol with MOM, then the TBDPS group was deprotected, and the resulting alcohol was subjected to oxidation and subsequently MOM group was deprotected to provide (2*R*, 3*R*)- 3-hydroxypipecolic acid (**2**).[20]



Scheme 3

Datta's Approach (*J. Org. Chem.* **2005**, *70*, 10182-10185)

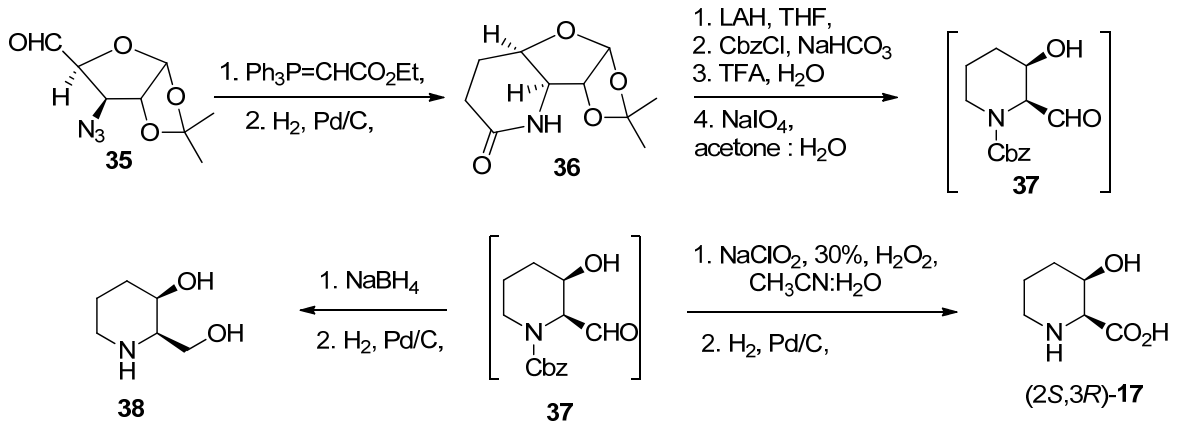


Scheme 4

Datta *et al*. synthesized **2** starting from D-serine (**29**) (Scheme 4), using diastereoselective reduction of ketone and reductive cyclization as the key steps. They prepared Weinreb amide **30** from **29** by known procedure. [21] Weinreb amide **30** on reaction with **31** forms ketone which was reduced using zinc borohydride along with cerium chloride to provide alcohol **32**. The acetonide deprotection of **32** and subsequent protection of diol with TBS provided aminol **33**. Aminol **33** was subjected to dihydroxylation followed by cleavage of diol using $NaIO_4$ followed by reduction and deprotection to furnish **34**. Piperidine derivative **34** upon oxidation and deprotection resulted in to the formation of hydrochloride salt of 3-hydroxypipecolic acid (**2**).

Dhavale's Approach (*J. Org. Chem.* **2008**, *73*, 3619–3622)

Dhavale *et al*. utilized D-glucose as a starting material for the synthesis of **38** and **17** (Scheme 5). The azido aldehyde **35** obtained from D-glucose by reported method was subjected to Wittig reaction followed by azide reduction to furnish amide **36**. Amide **36** was reduced using LAH followed by Cbz protection, acetonide deprotection and cleavage to provide aldehyde **37**.



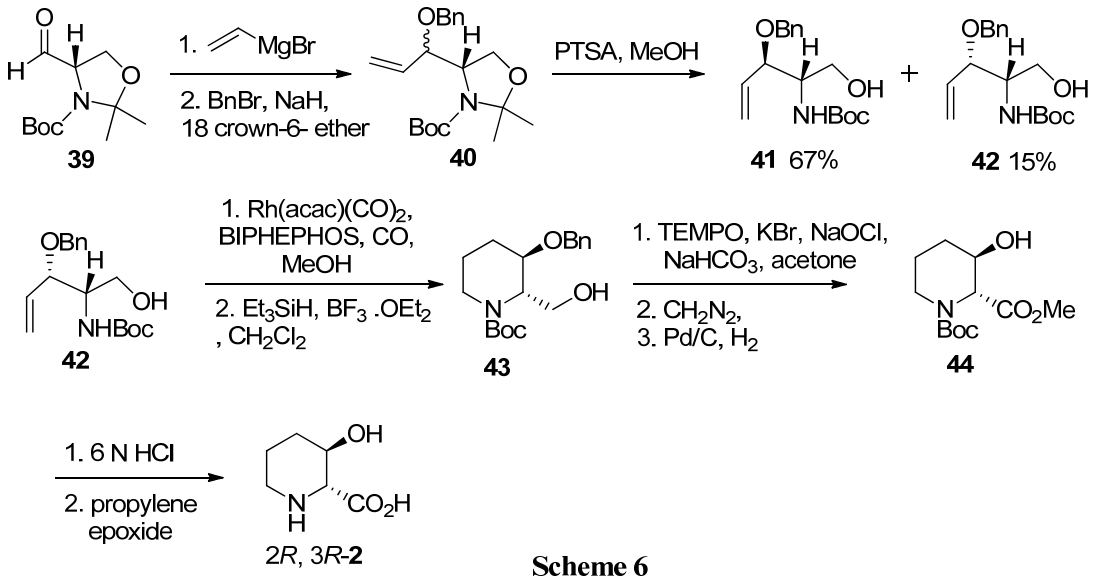
Scheme 5

Aldehyde **37** was converted to 3-hydroxypipecolic acid **17** as well as **38** in two steps each.[22]

Chiou's Approach (*J. Org. Chem*. **2010**, *75*, 1748–1751)

Chiou *et al*. synthesized *cis* and *trans* 3-hydroxypipecolic acid starting from Garner's aldehyde employing diastereoselective Grignard reaction and Rh catalyzed

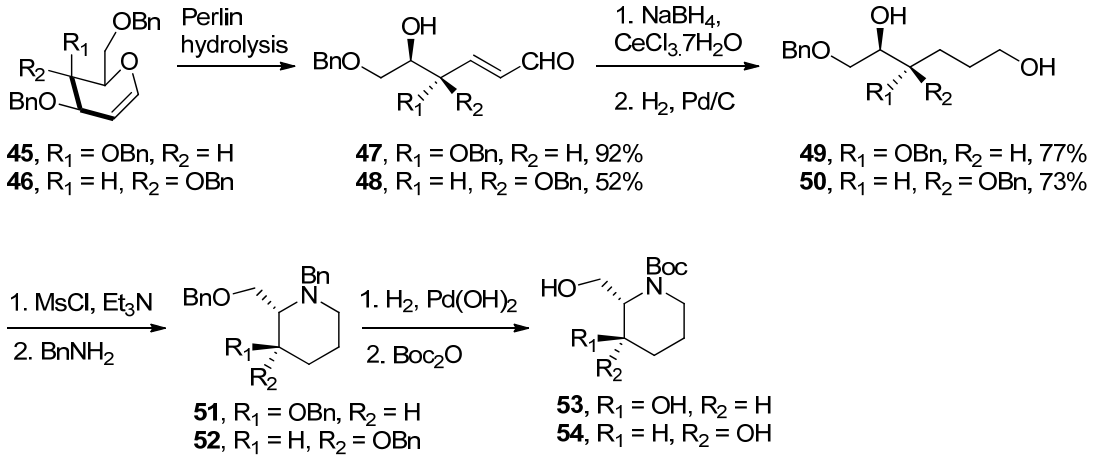
cyclohydrocarbonylation (Scheme 6). Nucleophilic addition of vinyl magnesium bromide on aldehyde **39** furnished diastereomeric mixture of alcohol, which was protected with benzyl bromide to give benzyl ether **40**. Compound **40** was subjected to acetonide deprotection to provide mixture of alcohols **41** and **42**, which were separated. Alcohol **42** was subjected to cyclohydrocarbonylation followed by reduction to provide piperidine alcohol **43**, which was further explored to (2*R*, 3*R***)**-3-hydroxypipecolic acid**.** Similarly the alcohol **41** was explored for the synthesis of *cis* 3-hydroxypipecolic acid.[23]



Scheme 6

Vankar's Approach (*J. Org. Chem*. **2010**, *75*, 4608–4611)

Vankar *et al*. (Scheme 7) completed formal synthesis of pipecolic acid along with



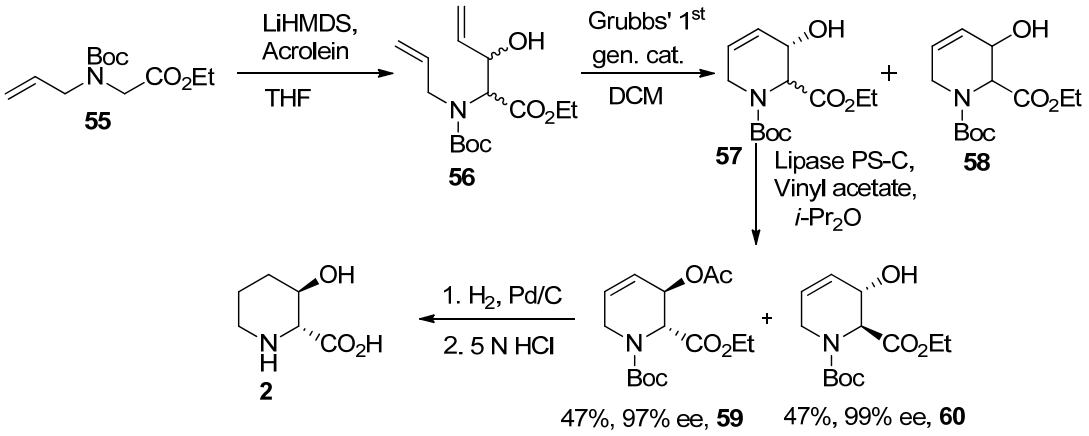
Scheme 7

deoxoprosophylline starting from D-glycal by taking advantage of Perlin hydrolysis, chemoselective saturation of olefins and reductive amination as the key steps.[24] D-Glycals **45** and **46** were subjected to Perlin hydrolysis to provide unsaturated aldehydes **47** and **48** respectively, which were subjected to reduction followed by hydrogenation to furnish diols **49** and **50**. Diols **49** and **50** on mesylation and subsequent treatment with benzyl amine provided piperidines **51** and **52**, which on hydrogenation and Boc protection gave diols **53** and **54** respectively.

(b) Synthesis using chiral induction

Takahata's Approach (*Bioorg. Med. Chem*. **2008**, *16*, 8273–8286)

Takahata *et al*. reported synthesis of **2** using RCM and enzymatic resolution as the key steps (Scheme 8). Ester **55** was treated with LiHMDS and then with acrolein to provide di-allyl compound **56**, which was subsequently subjected to RCM reaction to furnish a mixture of piperidines **57** and **58**. The major piperidine derivative **57** on enzymatic resolution gave acetate **59** and alcohol **60** with excellent ee. The acetate ester **59** on hydrogenation followed by acidic hydrolysis provided 3-hydroxypipecolic acid (**2**).[25]

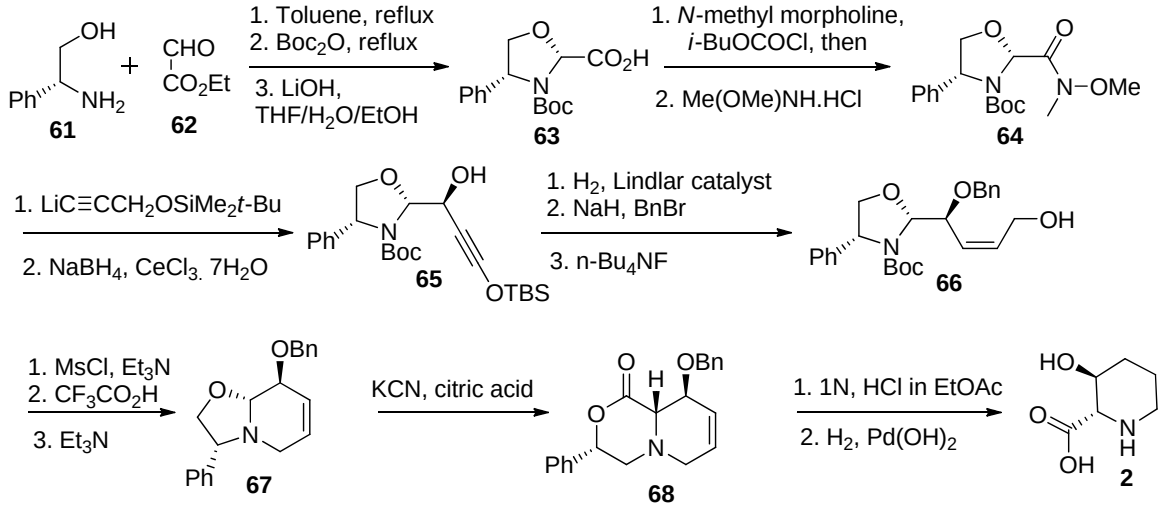


Scheme 8

Couty's Approach (*Tetrahedron Letters*, **1996**. *37*, 4001-4002)

Couty *et al*. used diastereoselective reduction of ketone and stereoselective addition of cyanide as key steps in their route for the synthesis of **2**. Synthesis was carried out according to the sequence of steps shown in Scheme 9. The hemiaminal acid **63** was prepared from **61**

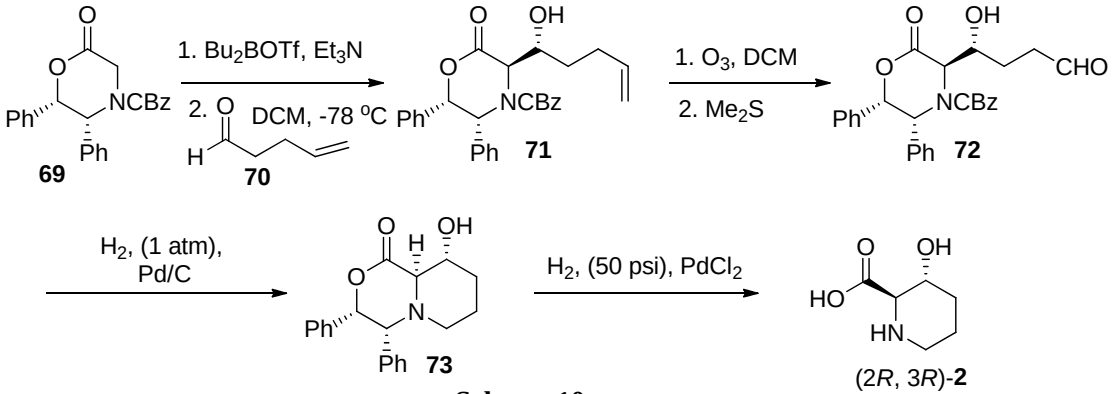
in there steps. Acid **63** was converted to Wienreb amide **64** and subsequently treated with lithium acetalide to provide ketone and the resulting ketone was reduced to furnish alcohol **65**. Alcohol **65** was protected as benzyl ether, the triple bond was reduced using LAH followed by TBS deprotection, mesylation and cyclization to give bicyclic compound **67**. Nucleophilic addition on **67** with cyanide anion followed by hydrolysis and hydrogenation resulted in to formation of 3-hydroxypipecolic acid.



Scheme 9

Williams's Approach (*Tetrahedron Lett*. **1998**, *39*, 3659-3662)

Williams *et al*. utilized commercially available lactone **69** for the synthesis of **2** using diastereoselective aldol condensation between **69** and aldehyde **70** to provide alcohol **71**.

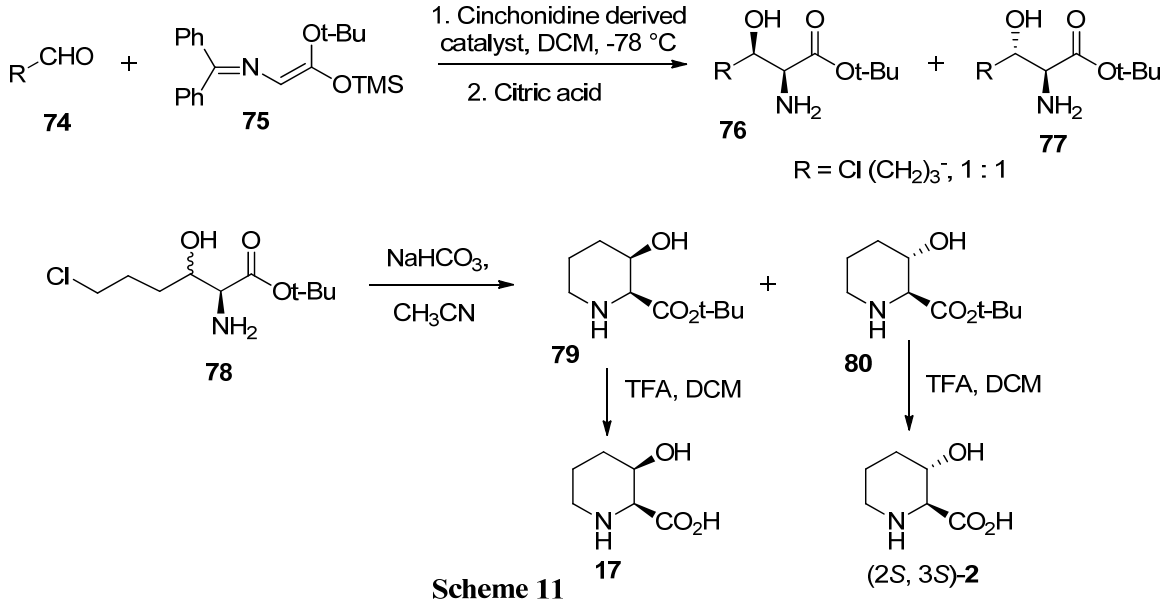


Scheme 10

Ozonolysis of the olefin **71** furnished aldehyde **72**, which on mild catalytic hydrogenation afforded bicyclic compound **73**. Finally **73** on hydrogenation on carbon black furnished (2*R*, 3*R*)-3-hydroxypipecolic acid. Similarly (2*S*, 3*S*)-3-hydroxypipecolic acid was synthesized using enantiomer of **69** as the starting material.[26]

Corey's Approach (*Tetrahedron Lett*. **1999**, *40*, 3843-3846)

Corey *et al*. developed a novel method for preparation β-hydroxy-α-amino acids by aldol condensation between various aldehydes and imine **75** catalyzed by cinchona derived chiral catalyst. Thus, the aldol condensation between aldehyde **74** and silyl enol ether **75** gave a mixture of amino alcohols **76** and **77** in the ratio 1:1. The method was exploited for the synthesis of *cis* as well as *trans* 3-hydroxypipecolic acid (Scheme 11).[27]

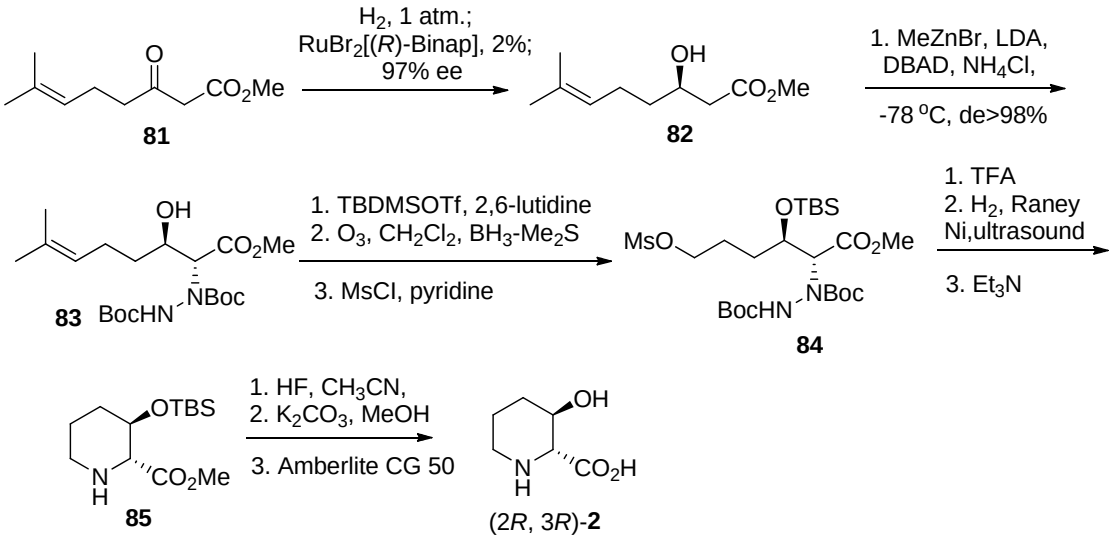


Scheme 11

The amino alcohol **78** was treated with sodium bicarbonate to provide a mixture of piperidine derivatives and separation on column chromatography gave pure diastereomeric piperidine alcohols **79** and **80**. The piperidine derivatives **79** and **80** were treated with TFA to provide (2*S*, 3*R*)- 3-hydroxy pipecolic acid (**17**) and (2*S*, 3*S*)-3-hydroxy pipecolic acid (**2**) respectively.

Genêt's Approach (*Tetrahedron Lett.* **1996**, *37*, 2031-2034)

Genêt *et al*. reported synthesis of 3-hydroxy pipecolic acid starting from keto ester **81**, employing chiral reduction of ketone and chiral amination as the key steps (Scheme 12). Keto ester **81** on reduction using Ru-BINAP catalyst furnished hydroxy ester **82**, which was subjected to α-amination to provide aminol **83**. The aminol **83** was protected with TBS and subsequently subjected to ozonolysis followed by mesylation of resulting alcohol to give **84**. The mesylate **84** on acidification, treatment with Raney Ni and triethylamine provided piperidine derivative **85** which was subjected to TBS deprotection and ester hydrolysis to give (2*R*, 3*R*)-3-hydroxypipecolic acid (**2**).[28]

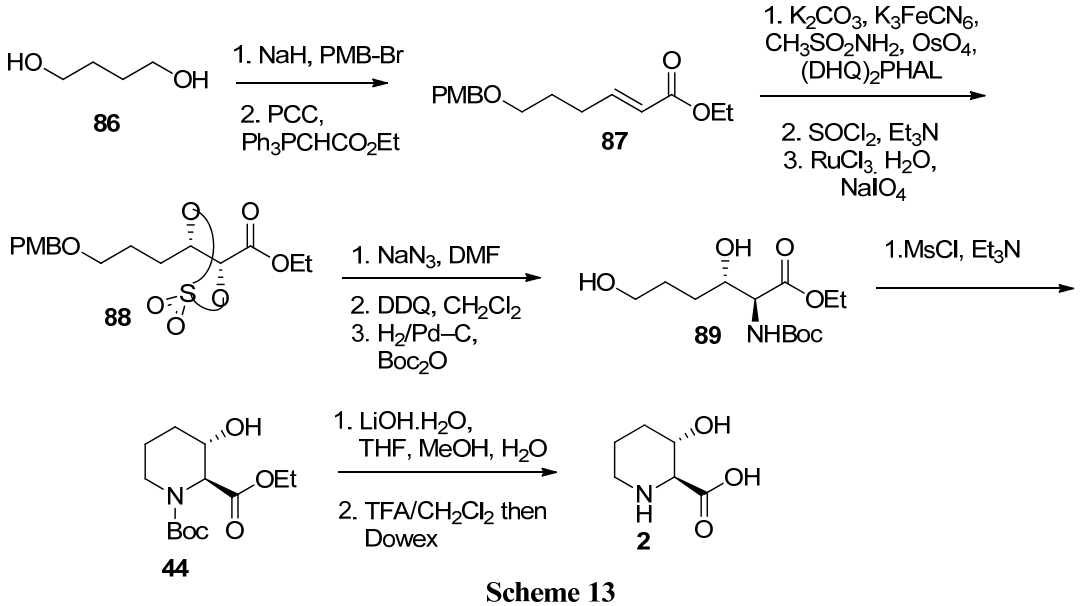


Scheme 12

Pradeep Kumar's Approach (*Tetrahedron Lett.* **2004**, *45*, 8461–8463)

Pradeep Kumar *et al*. used Sharpless chiral dihydroxylation as a key step in the synthesis of 3-hydroxy pipecolic acid (**2**) starting from butane diol **86** (Scheme 13).[29] Diol **86** was protected selectively, oxidized and subsequently subjected to Wittig reaction to give unsaturated ester **87**. Unsaturated ester **87** was subjected to Sharpless di-hydroxylation and resulting diol was protected as a sulfate **88**. Sulfate **88** was opened with sodium azide, which on reduction followed by Boc protection provided amino-diol **89**. The diol **89** on selective

mesylation gave piperidine **44**, which on acid hydrolysis followed by Boc deprotection furnished 3-hydroxy pipecolic acid (**2**).

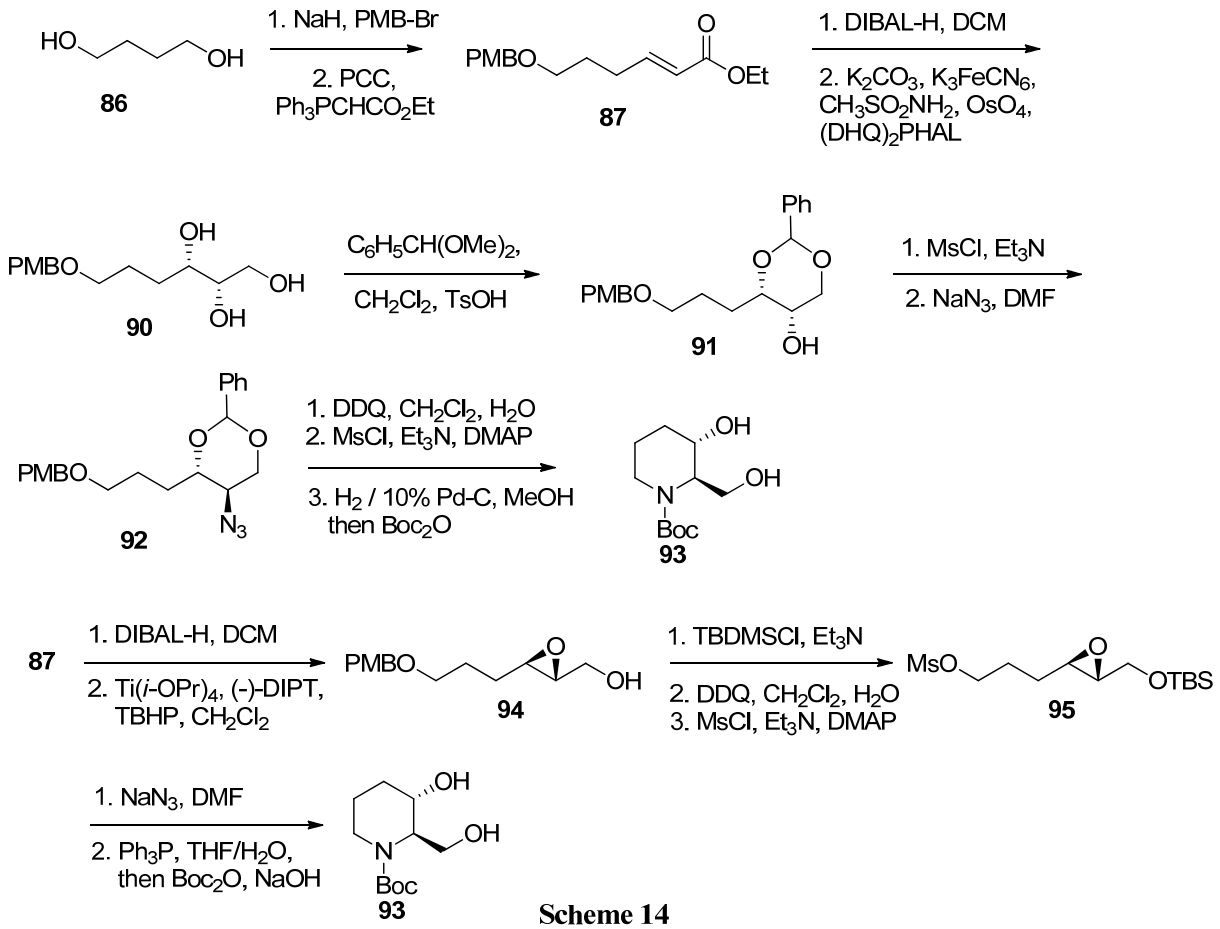


Scheme 13

Pradeep Kumar's Approach (*J. Org. Chem.* **2005**, *70*, 360-363)

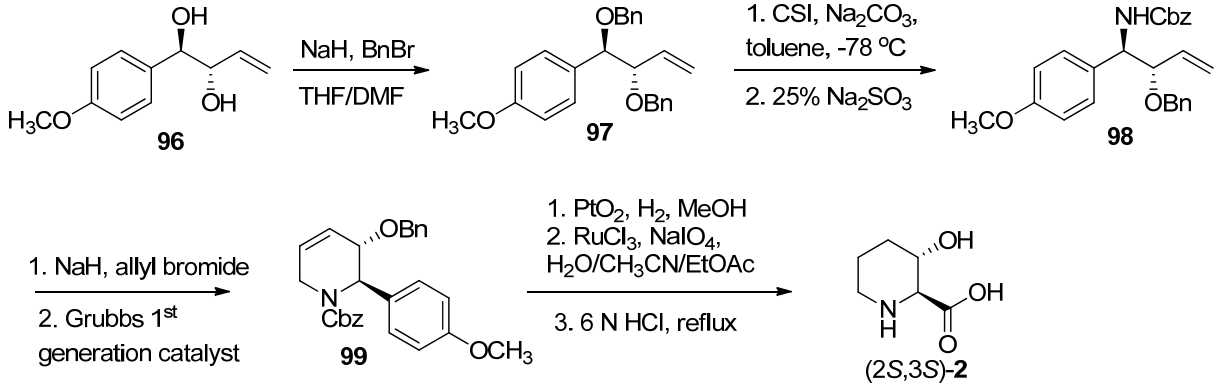
Pradeep Kumar *et al*. (Scheme 14) achieved formal synthesis of **2** starting from same starting material as in **Scheme 13**. The mono-PMB protection of **86**, followed by oxidation of resulting alcohol and Wittig reaction gave unsaturated ester **87**. The ester functionality in **87** was reduced using DIBAL-H, followed by asymmetric dihydroxylation employing Sharpless dihydroxylation to furnish triol **90**. The 1, 3-acetal protection was carried out to provide **91** followed by mesylation and subsequent reaction with sodium azide to provide azide **92**. The compound **92** was subjected to *p*-methoxybenzyl ether deprotection and the resulting hydroxy compound was mesylated and subsequently subjected to hydrogenation to provide piperidine diol **93**.

The authors prepared **93** by an alternate route which involved reduction of ester **87** with DIBAL-H followed by Sharpless epoxidation of the resulting allyl alcohol to provide epoxy alcohol **94**. The alcohol moiety in **94** was protected as its TBS derivative followed by PMB ether deprotection and mesylation to give mesylate **95**. The mesyl group in **95** was replaced with azide followed by reduction of azide to furnish the diol **93**.[30]



Scheme 14

Jung's Approach (*Tetrahedron Lett.* **2006**, *47*, 7289–7293; *Tetrahedron* **2007**, 63, 2622–2633)

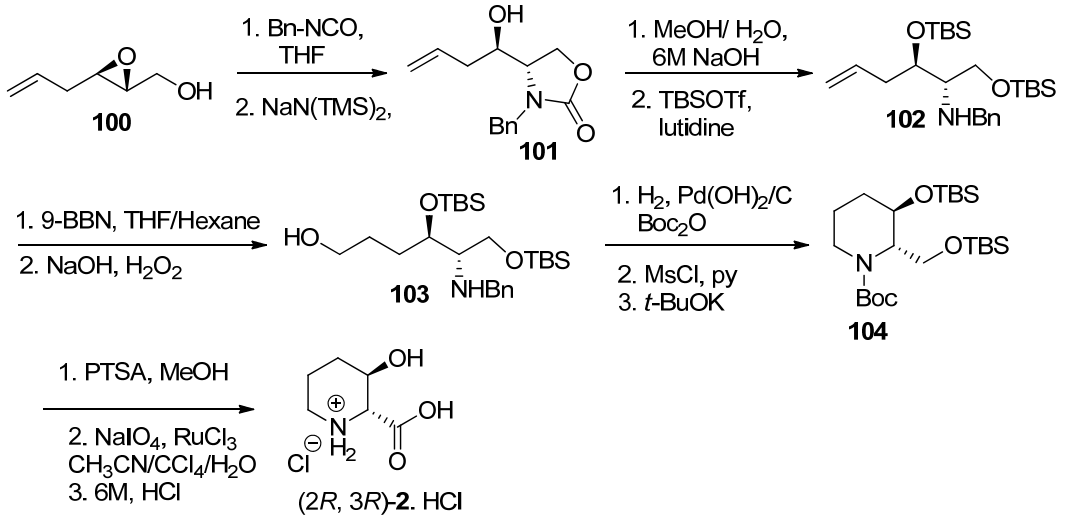


Scheme 15

Jung *et al*. reported synthesis of **2** starting from known diol **96** (Scheme 15). Diol **96** was protected as dibenzyl ether **97** and further reacted with chlorosulfonyl isocyanate (CSI) followed by treatment with base to provide amino alcohol **98**. Amine in **98** was allylated followed by RCM reaction to furnish piperidine derivative **99**. Olefin in **99** was reduced using PtO_2 as the catalyst followed by oxidation of aryl ring by Ru catalyst and acidification to furnish (2*S*, 3*S*)-3-hydroxypipecolic acid (**2**).[31,32]

Riera's Approach (*Eur. J. Org. Chem.* **2008**, 1789–1796)

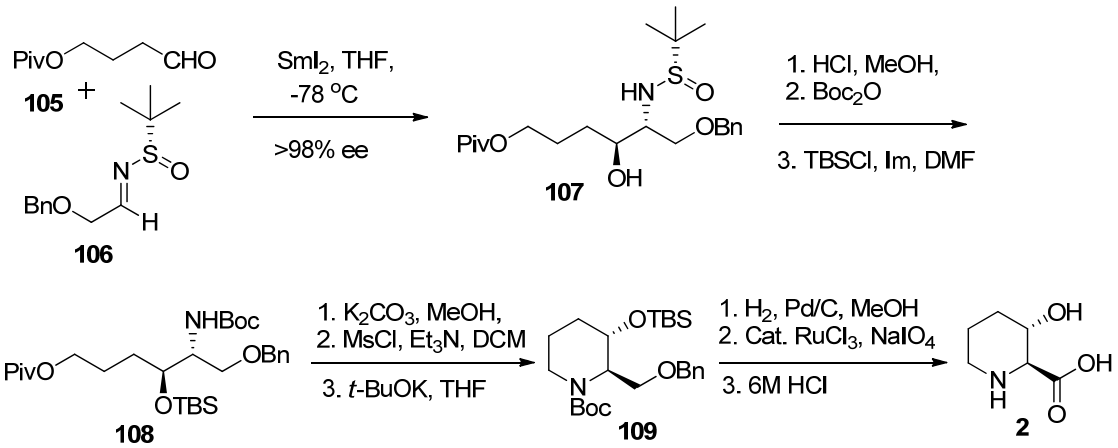
Riera *et al*. started synthesis of (2*R*, 3*R*)- 3-hydroxypipecolic acid from epoxide **100** which in turn was prepared by Sharpless epoxidation (Scheme 16). Epoxide **100** was intramolecularly opened at C-2 by nitrogen using benzyl isocyanate to provide cyclic carbamate **101**. Cyclic carbamate **101** was deprotected under basic condition and the resulting diol was protected as its TBS derivative. The olefin **102** was subjected to hydroboration using 9-BBN followed by oxidation to furnish alcohol **103**. The *N*-benzyl in **103** was deprotected under hydrogenation conditions followed by protection with Boc. Subsequently alcohol was mesylated followed by treatment with base to furnish piperidine derivative **104**. Selective primary OTBS ether deprotection was carried out using PTSA followed by oxidation using Ru catalyst and acidification to give hydrochloride salt of (2*R*, 3*R*)-3-hydroxypipecolic acid (**2**).[33]



Scheme 16

Wang's Approach (*Eur. J. Org. Chem.* **2009**, 2845–2851)

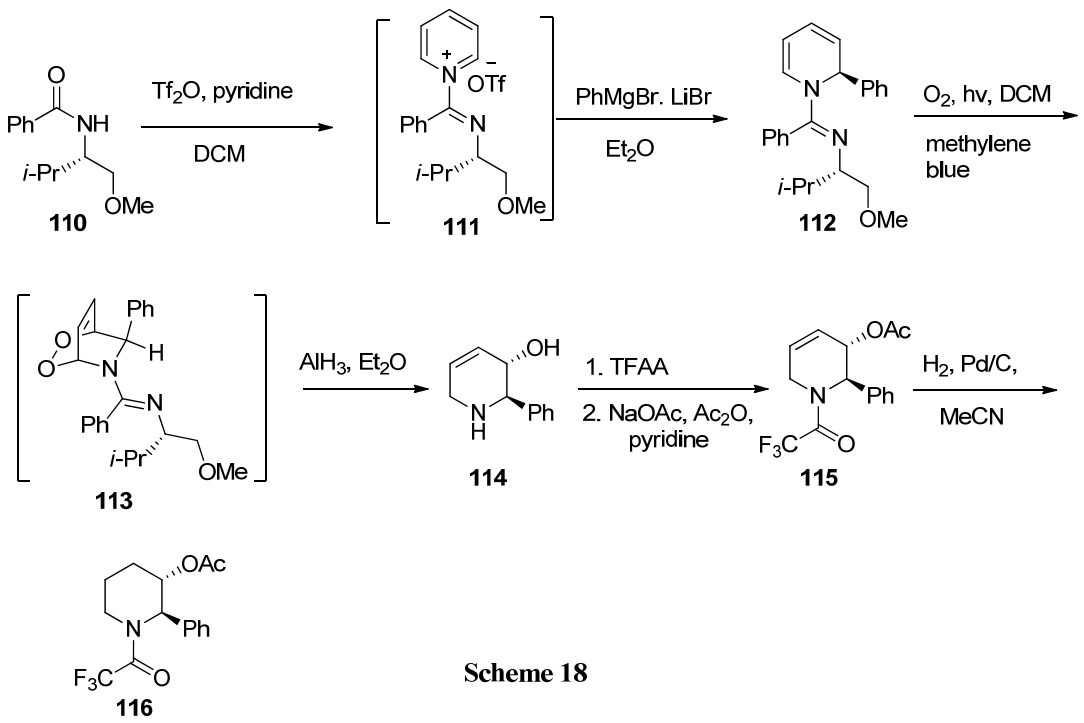
Wang *et al*. (Scheme 17) developed a Pinacol type reductive coupling between aldehyde **105** and sulfinyl imine **106** with excellent ee and exploited it for the synthesis of **2**. The removal of the sulfinyl auxiliary followed by selective *N*-protection with Boc_2O afforded carbamate **108**. The pivalyl group in **108** was deprotected and the resulting alcohol was converted in to its mesyl derivative followed by treatment with base to furnish piperidine derivative **109**. The benzyl group in **109** was deprotected under hydrogenation conditions followed by oxidation of alcohol and acidification to give final product 3-hydroxypipecolic acid (**2**).[34]



Scheme 17

Charette's Approach (*J. Org. Chem*. **2010**, *75*, 2077–2080)

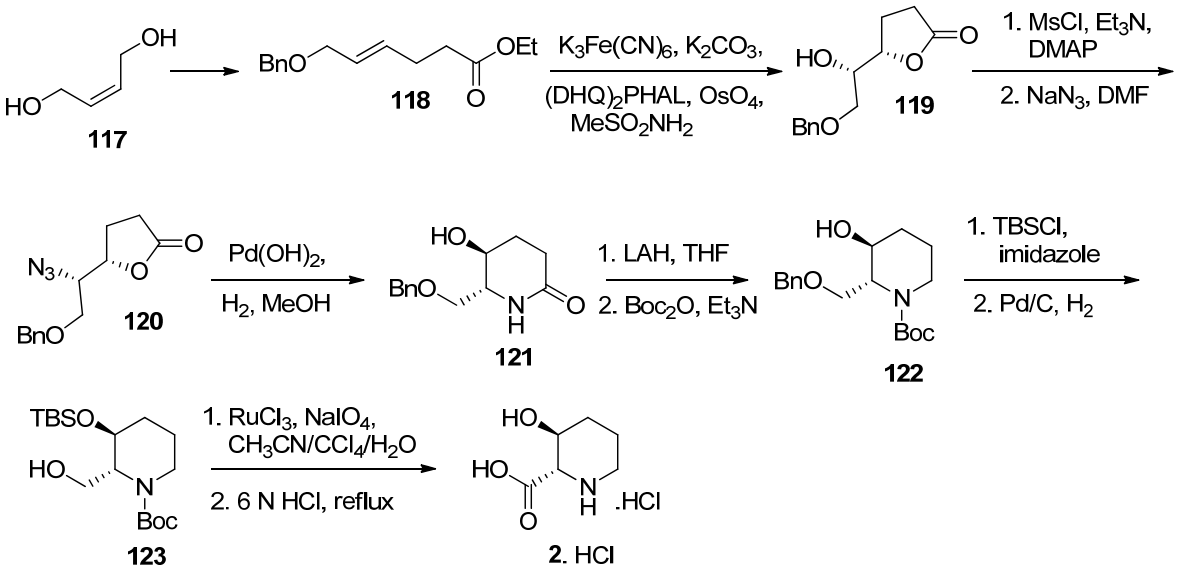
Charette *et al*. reported the formal synthesis of 3-hydroxypipecolic acid (**2**) using a diastereoselective addition of phenyl magnesium bromide on *N*-pyridinium salt **111** (Scheme 18). The dihydropyridine derivative **112** was subjected to 4+2 cycloaddition with oxygen followed by treatment with aluminum hydride to furnish piperidine derivative **114**. The protection of amine as well as alcohol gave **115** which on hydrogenation led to known intermediate **116**.[35]



Scheme 18

Chavan's Approach (*Tetrahedron Lett.* **2011**, *52*, 404–406)

Chavan *et al*. (Scheme 19) recently reported the enantioselective synthesis of 3-hydroxypipecolic acid (**2**) by Sharpless dihydroxylation as a key step starting from



Scheme 19

commercially available starting material *cis*-2-butene-1, 4-diol **117**. The *cis*-2-butene-1,4-diol **117** was converted in to γ,δ-unsaturated ester **118** by known method reported by this group. The ester **118** was subjected to Sharpless asymmetric dihydroxylation to provide lactone **119.** The hydroxy group in lactone **119** was mesylated followed by replacement with azide to give azido lactone **120** which on hydrogenation gave lactam **121**. Lactam **121** was reduced to give amine followed by protection with Boc_2O to furnish hydroxy piperidine **122**. Protection of hydroxy group in **122** as its TBS derivative followed by benzyl deprotection gave piperidine alcohol **123**. Alcohol in **123** was oxidized to acid using Ru catalyst followed by acidification to furnish hydrochloride salt of **2**.[36]

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Chapter 2. Synthetic studies towards (2*S*,3*S*)-3-hydroxypipecolic acid

Section 2: Formal synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid

2.2.1: Present work

2.2.1.1: Objective

The literature survey revealed that (2*S*, 3*S*)-3-hydroxypipecolic acid has attracted the attention of many organic chemists towards its synthesis due to its presence in number of natural as well as synthetic biologically active compounds. The literature reports also revealed that there are a few routes for the synthesis of (2*S*, 3*S*)-3-hydroxypipecolic acid starting from chiral natural starting materials. The reported chiral pool approaches are associated with low yields and lengthy routes. In this context, there is a need of convenient and efficient route for its enantiopure synthesis.

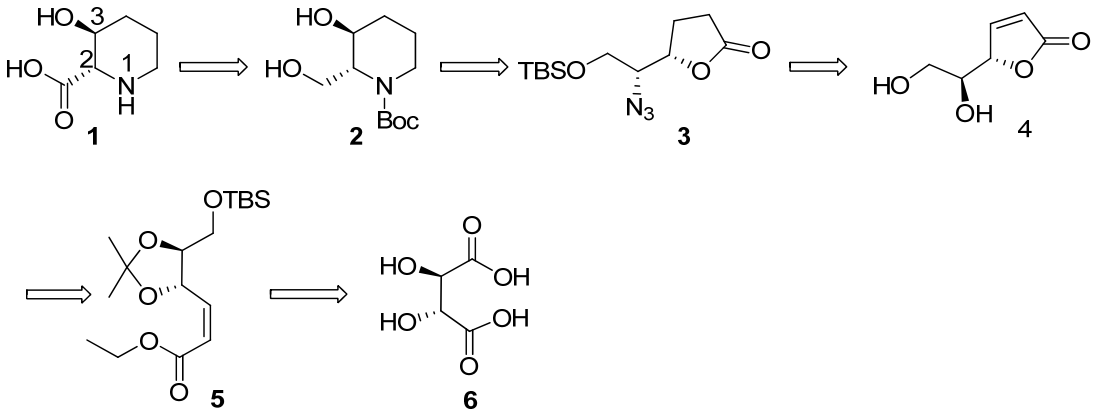
More than half of the present day drugs are chiral compounds because the racemic mixture and enantiomer may have the difference in pharmacology, toxicology, pharmacokinetics, metabolism *etc*.[1] The chiral pool approach for the synthesis of such biologically active compounds is one of the best method to get chirally pure compounds.

Owing to the importance of this scaffold there is a need for an efficient and scalable route for the preparation of (2*S*,3*S*)-3-hydroxypipecolic acid (**1**) in enantiopure form. This group over several years is engaged in the syntheses of biologically active compounds, including piperidine alkaloids. (2*S*,3*S*)-3-Hydroxypipecolic acid with its use in many natural and non-natural biologically active compounds attracted the attention of this group. Recently this group accomplished the synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid employing Sharpless asymmetric dihydroxylation.[2] In present section an alternative approach based on chiral pool strategy is described. The current novel route for its synthesis involved the use of L-(+)-tartaric acid which is abundantly available cheap starting material. However, till date there is not a single report for its synthesis from L-(+)-tartaric acid.

2.2.1.2: Retrosynthetic analysis

According to the retrosynthetic plan shown in **Scheme 1**, the synthesis of (2*S*, 3*S*)-3-hydroxypipecolic acid (**1**) was envisioned from Boc-protected piperidine core **2**. The C-2 and C-3 chiral centers in **1** could be easily fixed using the natural chirality in L-(+)-tartaric acid. The six membered piperidine core **2** could be accessed from protected azido alcohol **3** by

reduction followed by cyclisation. The azido alcohol **3** could be obtained by protection of primary alcohol followed by conversion of secondary alcohol to azide using Mitsunobu reaction on **4**. Taking the advantage of kinetic control of formation of five membered lactone ring over six and seven membered lactone, butyrolactone **4** could be constructed by deprotection of acetonide as well as TBS group in *Z*-alkene **5**. The *Z*-alkene **5** in turn could be readily obtained from L-(+)-tartaric acid by simple functional group transformations.



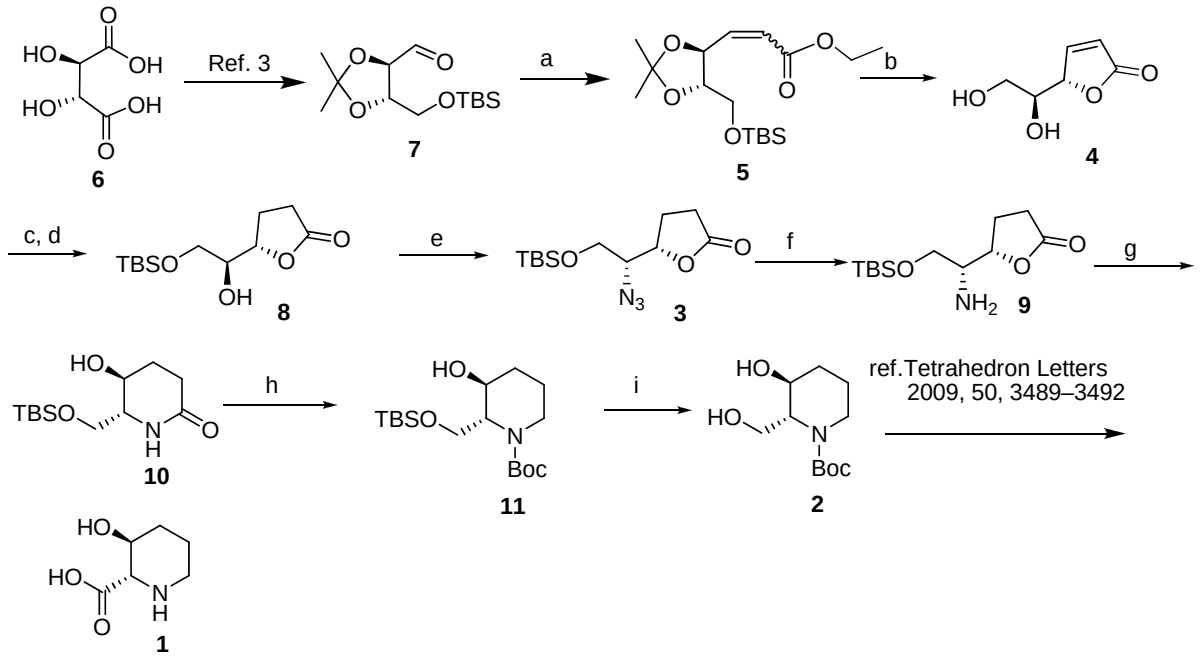
Scheme-1: Retrosynthetic analysis

2.2.1.3: Results and discussion

The synthetic strategy for (2*S*, 3*S*)-3-hydroxypipecolic acid (**1**) is shown in **Scheme 2**. The exploitation of L-(+)-tartaric acid using Mitsunobu reaction and kinetically controlled butenolide formation constitutes the key steps.

Accordingly, the synthesis commenced from naturally occurring L-(+)-tartaric acid **1**. The aldehyde **7** was obtained from tartaric acid in four steps as per procedure described in the literature.[3] The aldehyde **7** was subjected to Wittig reaction using two carbon ylide (PPh_3CHCO_2Et) derived from ethyl bromoacetate in methanol at –50 ^oC to room temperature to give an inseparable mixture of *E* and *Z*-alkenes (30:70) **5** in 93% yield. The IR spectrum of **5** showed strong bands at 1728 cm^{-1} indicating the presence of unsaturated ester. Its ^1H-NMR spectrum showed double peaks in the alkene region. Peak at δ 6.18 corresponding to β-hydrogen in *cis* alkene integrating for 0.70 proton compared with peak at δ 6.96

corresponding to β-hydrogen in *trans* alkene integrating for 0.30 proton clearly indicated the *cis*: *trans* ratio to be 70 : 30.



Scheme 2. Synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid

Reagents and conditions: a) $Ph_3PCHCOOEt$, MeOH, –50 ^oC, 93% b) Cat. H_2SO_4, MeOH, 65% c) H_2, Pd/C, MeOH d)TBSCl, Et_3N, DCM, 80 % (over two steps) e) HN_3, PPh_3, DEAD, THF, 92% f) H_2, Pd/C, MeOH, 95% g) MeONa, MeOH, 83% h) BH_3.DMS, THF and then Boc_2O. Et_3N, 73% i) TBAF, THF, 88%.

According to retrosynthetic plan the simultaneous deprotection of acetonide and TBS groups were carried out using catalytic amount of conc. H_2SO_4 in methanol to provide butyrolactone **4** in 65% yield. Its IR spectrum showed strong bands at 3335, 1740 and 1596 cm^{-1} indicating the presence of diol moiety, butenolide and double bond functionalities respectively. In its ^{1}H-NMR spectrum, a peak at δ 7.37 corresponding to β-proton in butenolide appeared as a dd and the α-proton of butenolide appeared at δ 5.89 as a dd. The multiplet at δ 4.95 corresponded to the γ-proton of butenolide. Its ^{13}C-NMR spectrum showed peaks at δ 172 and 154 corresponding to butenolide carbonyl and β-carbon in **4**. The α-carbon appeared at δ 120. Further, the mass spectrum of **4** showed the molecular ion peak at m/z 145 $(M+H)^+$, 167 $(M+Na)^+$ which confirmed the formation of **4**.

Selective protection of primary alcohol using TBSCl and imidazole in DCM of butyrolactone **4** resulted in racemisation at C-4 in protected compound. To avoid racemisation at C-4 in **4**, first the double bond was hydrogenated using palladium catalyst under hydrogen atmosphere and then protection of primary alcohol was carried out to give butyrolactone **8** in 80% yield over two steps. Strong band at 1773 cm^{-1} in its IR spectrum indicated the presence of butenolide carbonyl and broad band at 3448 cm^{-1} corresponded to hydroxyl group in **8**. The disappearance of peaks at δ 7.37 and 5.89 in its ^{1}H-NMR spectrum and appearance of peaks at δ 2.27 to 2.67 corresponding to aliphatic protons clearly indicated the reduction of double bond. Further, appearance of characteristic peaks at δ 0.90 and 0.09 corresponding to TBS group confirmed the selective TBS protection of a primary alcohol. Its ^{13}C-NMR showed a peak at δ 177 corresponding to carbonyl carbon of butenolide. Its DEPT spectrum showed four peaks for CH and CH_3 carbons and two peaks indicating two CH_2 carbons. Further, its mass spectrum showed peak at m/z 283 $(M+Na)^+$ which confirmed the formation of **8**.

The single step protocol was utilized in order to convert the hydroxyl group in **8** to azide compound **3**. Accordingly, the compound **8** was subjected to Mitsunobu reaction conditions using hydrazoic acid as a nucleophile as well as a source of azide along with DEAD and PPh_3 in THF to render azide **3** with inversion of configuration in 92% yield. Its IR spectrum showed the characteristic strong bands at 2123 and 1781 cm^{-1} which indicated the presence of azide and γ-lactone moiety respectively. Peaks at δ 0.92 and 0.11 in its ^{1}H-NMR spectrum indicated the presence of TBS group, while the γ-proton of lactone appeared at δ 4.50. The peaks that appeared as multiplets at δ 3.84 and 3.64 corresponded to the protons adjacent to hydroxy and azide functionalities respectively. The characteristic peaks at δ 175 and 77 in its ^{13}C-NMR spectrum indicated the presence of a lactone ring. Its DEPT spectrum showed presence of four peaks for CH and CH_3 carbons and three peaks corresponding to CH_2 carbons. Molecular ion peak at m/z 308 $(M+Na)^+$ confirmed the formation of azido lactone **3**.

The azido lactone **3** was subjected to hydrogenation using Pd/C in methanol to provide amine **9**. It was anticipated that the amine **9** would undergo cyclisation to furnish lactam **10**. Unfortunately, the amine **9** didn't undergo cyclisation to the desired lactone **10**. The absence of band at 2123 cm^{-1} in its IR spectrum indicated the reduction of azide. The strong band at 1774 cm^{-1} showed presence of lactone and confirmed that the amine didn't undergo

cyclisation to lactam **10**. The ^{1}H-NMR spectrum of **9** revealed peak at δ 4.45 corresponding to γ-proton of lactone ring and peak at δ 3.01 corresponding to proton adjacent to amine. Its ^{13}C-NMR showed peak at δ 177 indicating the presence of carbonyl in γ-lactone. Its DEPT spectrum showed three CH_2 carbons and four CH and CH_3 carbons. Peak at m/z 260 $(M+1)^+$ confirmed the reduction of azide to amine **9**.

Amine **9** was treated with DBU in toluene with a hope to provide lactam **10** but the starting amine **9** was recovered. Cyclisation of **9** to lactam **10** was readily accomplished using sodium methoxide in methanol at room temperature in 83% yield. A characteristic strong band at 1630 cm^{-1} in its IR spectrum clearly indicated the formation of amide. Its ^{1}H-NMR spectrum showed broad singlet at δ 6.18 corresponding to a characteristic peak of lactam proton. Four protons appeared in the range δ 3.85 to 3.34 corresponding to protons adjacent to hydroxy and amine functionalities. Peaks at δ 0.89 and 0.08 indicated the presence of TBS protecting group. Its ^{13}C-NMR showed a peak at δ 171 indicating the presence of lactam carbonyl. Further, the lactam formation was confirmed by its mass spectrum which showed molecular ion peak at (m/z) 260 $(M+H)^+$ and 282 $(M+Na)^+$.

The lactam reduction as well as the Boc protection were carried out using BH_3.DMS in THF and Boc anhydride to provide urethane **11** in 73% yield. Strong bands in its IR spectrum at 3443 and 1676 cm^{-1} indicated the presence of the free hydroxy and Boc groups. Its ^{1}H-NMR spectrum showed a peak at δ 1.46 that integrated for nine protons corresponding to protons of Boc group. Two singlets at δ 0.89 and 0.06 corresponded to the protons of TBS group. Its DEPT spectrum showed presence of five CH and CH_3 carbons and four CH_2 carbons and provided strong support for the formation of urethane **11**. Its mass spectrum showed molecular ion peak at m/z 368 $(M+Na)^+$ which confirmed the formation of **11**.

The TBS deprotection in **11** was carried out using TBAF in THF at room temperature to give compound **2** in 88% yield. Its IR spectrum showed strong band at 1674 cm^{-1} corresponding to the Boc group. Absence of peaks at δ 0.89 and 0.06 in its ^{1}H-NMR spectrum indicated the deprotection of TBS group and peak at δ 1.39 integrating for nine protons was assigned to protons of Boc group. Its ^{13}C-NMR spectrum showed peak at δ 155.9 corresponding to Boc carbonyl group. The other peaks appeared at δ 79.1 (C), 63.8 (CH), 59.9 (CH), 59.1 (CH_2), 39.8 (CH_2), 28.1 (CH_3), 26.6 (CH_2) and 18.9 (CH_2). Finally, the molecular formula was

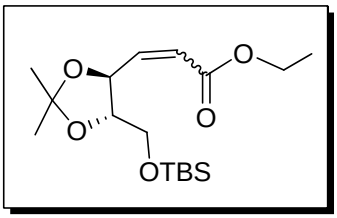
confirmed by HRMS, which showed peak at m/z 231.1470 which is in good agreement with calculated value 231.1484 for $C_{11}H_{21}NO_4$. The enantiomeric purity of compound **2** was established using chiral HPLC (99% ee). The synthesis of pipecolic acid from intermediate **2** is well documented in the literature.[4] Thus the present work constitutes a formal synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid.

2.2.2. Conclusion

In conclusion, we have described the convenient formal synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid (**1**) starting from cheap and abundant chiral building block L-(+)-tartaric acid. The synthesis of **2** was achieved in 23% overall yield.

2.2.3. Experimental

(*Z*)-Ethyl3-((4*S*,5*S*)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (5)



To the aldehyde **7** (7.1 g, 23.3 mmol) in methanol (40 mL), was added $Ph_3PCHCO_2C_2H_5$ (8.5 g, 25 mmol) in methanol (30 mL) dropwise at –50 ºC and the resultant reaction mixture was further stirred at same temperature for 5 hours. Reaction mixture was allowed to come to room temperature, methanol was removed under reduced pressure and to the residue was added pet ether (3 x 50 mL) and filtered through filter paper. Combined filtrates were concentrated under reduced pressure and the residue was purified on flash chromatography (pet ether/ethyl acetate = 95:5) to render the mixture of alkenes **5** (6.2 g, 93%) as a colorless oil.

Molecular formula **:** $C_{17}H_{32}O_5Si$

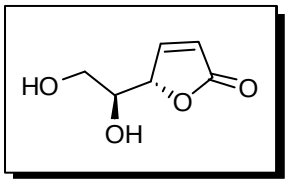
Yield **:** 93%

IR ($CHCl_3$) υ_{max} **:** 2932, 1728, 1590, 1464, 1230 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.13-6.19 (m, 1H), 5.88-5.94 (m, 1H), 5.36-5.41 (m, 1H),

(For major isomer) 4.26-4.12 (m, 2H), 3.72-3.80 (m, 3H), 1.44 (s, 6H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H)

(*S*)-5-((*S*)-1,2-Dihydroxyethyl)furan-2(5H)-one (4)



A solution of the *cis*-alkene **5** (2 g, 5.81 mmol) in methanol (20 mL) was treated with conc. sulphuric acid (ca. 0.2 mL of 100%), and the resulting reaction mixture was stirred at room temperature for 4 hours. The solution was passed through a small bed of silica gel. Evaporation of the solvent and recrystallisation of the obtained solid compound from ethyl acetate furnished pure product diol **4** as a crystalline solid (82%).

Molecular formula **:** $C_6H_8O_4$

Yield **:** 65%

MP **:** 77–79 ºC

$[\alpha]_D^{25}$: +39 (c 1.0, $CHCl_3$)

IR ($CHCl_3$) υ_{max} **:** 3335, 2924, 1740, 1596, 1464, 1377 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$+ DMSO-d_6): δ 7.37 (dd, *J* = 5.8, 1.5 Hz, 1H), 5.89 (dd, *J* = 5.8 Hz, 1H), 4.93-4.97 (m, 1H) 3.84, (br s, 2H), 3.56 -3.64 (m, 1H), 3.40-3.43 (m, 2H)

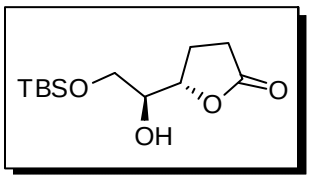
^{13}C NMR (50 MHz, $CDCl_3$+ DMSO-d_6): δ 172.2, 154.3, 120.5, 83.3, 70.5, 61.9.

ESIMS (m/z) **:** 145 $(M+1)^+$, 167 $(M+Na)^+$.

Elemental analysis **:** Calculated C, 50.00; H, 5.59%

Found C, 50.01; H, 5.56%

(*S*)-5-((*S*)-2-(*tert*-butyldimethylsilyloxy)-1-hydroxyethyl)dihydrofuran-2(3*H*)-one (8)



To the butenolide **4** (1 g, 6.94 mmol) in methanol (20 mL), was added catalytic amount of palladium hydroxide (10 mg, 20% over carbon). The resulting reaction mixture was kept on a shaker at 60 psi under a hydrogen atmosphere for 2 h. The reaction mixture was filtered on Celite. Methanol was evaporated on a rotavapour under reduced pressure. The crude product obtained (1 g, 99%, 6.84 mmol) was dissolved in anhydrous DCM (15 mL). Imidazole (0.967 g, 10.2 mmol) was added to the above solution followed by the addition of TBS chloride (1.12 g, 7.52 mmol) in DCM (5 mL) at 0 ºC, and the reaction mixture was stirred at room temperature (3 h). Water (10 mL) was added to the reaction mixture and extracted using DCM (3 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered. Evaporation of the organic layer under reduced pressure furnished a residue. The residue on flash chromatography using silica gel afforded **8** (1.42 g, 80%) as a clear colorless liquid.

Molecular formula **:** $C_{12}H_{24}O_4Si$

Yield **:** 80%

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

IR ($CHCl_3$) υ_{max} **:** 3448, 2930, 1773, 1119, 838 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.55–4.61 (m, 1H), 3.70–3.72 (m, 3H), 2.27–2.67 (m, 4H), 0.90 (s, 9H), 0.09 (s, 6H).

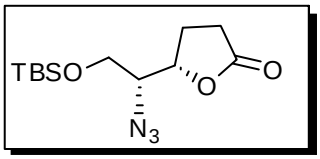
^{13}C NMR (50 MHz, $CDCl_3$) : δ 177.6, 79.4, 73.4, 63.6, 28.3, 25.8, 23.8, 18.2, 5.5.

ESIMS (m/z) **:** 283 $(M+Na)^+$.

Elemental analysis **:** Calculated C, 55.35; H, 9.29%

Found C, 55.32; H, 9.31%

(*S*)-5-((*S*)-1-Azido-2-((*tert*-butyldimethylsilyl)oxy)ethyl)dihydrofuran-2(3*H*)-one (3)



To the alcohol **8** (0.5 g, 2 mmol) in THF (8 mL) the following reactants were added in the given order; PPh_3 (1 g, 3.8 mmol), HN_3 (1.8 mL 1 M soln in benzene) and DEAD (0.768 g, 4.41 mmol) drop wise at 0 ºC. The reaction mixture was stirred (15–20 min) at 0 ºC and then stirred at room temperature (16 h). THF was removed under reduced pressure and pet ether was added to the reaction mixture and filtered on Celite. The organic layer was concentrated under reduced pressure. The crude reaction mixture on flash chromatography (pet. ether–ethyl acetate 90:10) afforded the azide **3** (0.504 g, 92%) as a colorless liquid.

Molecular formula **:** $C_{12}H_{23}N_3O_3Si$

Yield **:** 92%

$[\alpha]_D^{25}$ **:** –8 (c 1.0, $CHCl_3$)

IR ($CHCl_3$) υ_{max} **:** 3021, 2956, 2931, 2859, 2123, 1781, 1463, 1258, 1216, 838, 757 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.47–4.57 (m, 1H), 3.74–3.92 (m, 2H), 3.58–3.67 (m, 1H) 2.52-2.63 (m, 2H), 2.05–2.33 (m, 2H), 0.92 (s, 9H), 0.11 (s, 6H).

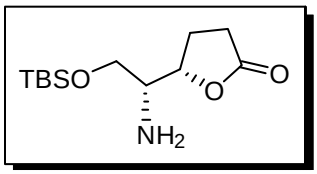
^{13}C NMR (50 MHz, $CDCl_3$) : δ 175.9, 77.5, 65.1, 63.1, 27.9, 25.3, 23.8, 18.2, –5.6.

ESIMS (m/z) **:** 308 $(M+Na)^+$

Elemental analysis **:** Calculated C, 50.50; H, 8.12; N, 14.72%

Found C, 50.49; H, 8.13; N, 14.75%

(*S*)-5-((*R*)-1-Amino-2-((*tert*-butyldimethylsilyl)oxy)ethyl)dihydrofuran-2(3H)-one (9)



To the azide compound **3** (0.45 g, 1.73 mmol) in methanol (100 mL) was added a catalytic amount of palladium hydroxide (5 mg, 20% over carbon). The reaction mixture was put on a shaker at 65 psi for 2 h. The reaction mixture was filtered on Celite and the filtrate concentrated under reduced pressure. The crude reaction mixture on purification by flash chromatography over silica gel (ethyl acetate) afforded amine **9** (0.38 g, 95%) as a colorless liquid.

Molecular formula **:** $C_{12}H_{25}NO_3Si$

Yield **:** 95%

$[\alpha]_D^{25}$ **:** +22 (c 1.0, $CHCl_3$)

IR ($CHCl_3$) υ_{max} **:** 3277, 3020, 2955, 2930, 2858, 1774, 1471, 1256, 1216, 757, 668 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 3.38–3.49 (m, 1H), 3.58–3.73 (m, 2H), 2.99–3.07 (m, 1H), 2.51–2.59 (m, 2H), 2.09–2.32 (m, 2H), 1.78 (br s, 2H), 0.89 (s, 9H), 0.06 (s, 6H).

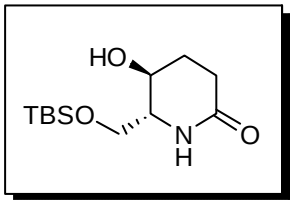
^{13}C NMR (50 MHz, $CDCl_3$) : δ 177.2, 80.9, 64.2, 55.2, 28.6, 25.8, 23.9, 18.2, –5.5.

ESIMS (m/z) **:** 260 $(M+H)^+$

Elemental analysis **:** Calculated C, 55.56; H, 9.71; N, 5.40%

Found C, 55.57; H, 9.73; N, 5.37%

(5*S*,6*R*)-6-(((*tert*-butyldimethylsilyl)oxy)-methyl)-5-hydroxypiperidin-2-one (10)



To amine **9** (0.35 g, 1.35 mmol) in methanol (5 mL), catalytic amount of sodium methoxide was added. The reaction mixture was stirred at room temperature for 2 hours. Reaction was quenched with saturated aq. ammonium chloride solution (5 mL) followed by removal of methanol under reduced pressure. The aqueous layer was extracted using excess ethyl acetate (3 x 25 mL) and the combined organics were dried over anhydrous Na_2SO_4 and filtered. Removal of the organic solvent under reduced pressure furnished a residue. Purification of the residue by flash chromatography over silica gel (pet ether-ethyl acetate 10:90) afforded amide **10** (0.29 g, 83%).

Molecular formula **:** $C_{12}H_{25}NO_3Si$

Yield **:** 83%

$[\alpha]_D^{25}$: +21 (c 1.0, $CHCl_3$)

IR ($CHCl_3$) υ_{max} **:** 3019, 2929, 2856, 2400, 1630, 1524, 1221, 780, 669 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.18 (s, 1H), 3.81–3.85 (dd, *J* = 9.8, 5.2 Hz, 1H), 3.73–3.78 (m, 1H), 3.54–3.59 (m, 1H), 3.34–3.39 (m, 1H), 2.48–2.54 (m, 1H), 2.29–2.39 (m, 1H), 2.00–2.08 (m, 1H), 1.85–1.90 (m, 1H) 0.89 (s, 9H), 0.08 (s, 6H).

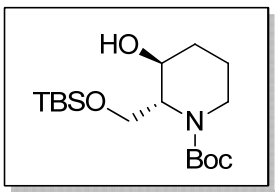
^{13}C NMR (50 MHz, $CDCl_3$) : δ 171.5, 67.2, 65.5, 59.5, 28.6, 28.3, 25.8, 18.1, –5.5.

ESIMS (m/z) **:** 260 $(M+H)^+$, 282 $(M+Na)^+$.

Elemental analysis **:** Calculated C, 55.56; H, 9.71; N, 5.40%

Found C, 55.53; H, 9.72; N, 5.36%

(2*R*,3*S*)- tert-Butyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-hydroxypiperidine-1-carboxylate (11)



To the amide **10** (300 mg, 1.1 mmol) in anhydrous THF (5 mL), BH_3.DMS (3.4 mmol, 1 M in THF) was added dropwise at 0 ºC. The reaction mixture was stirred further overnight (16 h). Ethanol (20 mL) was added and evaporated under reduced pressure on a

rotavapour. To the residue, ethanol (20 mL) was added, and the reaction mixture was refluxed for 5 h. The solvent was evaporated under reduced pressure and THF was added to the crude reaction mixture. Triethylamine (3.4 mmol) and Boc anhydride (1.2 mmol) were added to reaction mixture and stirred for 5 h. Water (30 mL) was added to reaction mixture and extracted using ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and was filtered. The organic layer was concentrated under reduced pressure and the reaction mass purified by flash chromatography using silica gel (pet ether–ethyl acetate 80:20) to afford product **11** (248 mg, 73%).

Molecular formula : $C_{17}H_{35}NO_4Si$

Yield : 73%

$[\alpha]_D^{25}$: –39.2º (c 1.0, $CHCl_3$)

IR ($CHCl_3$) υ_{max} : 3443, 3018, 2931, 2858, 2400, 1676, 1215, 752 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 3.96–4.13 (m, 3H), 3.65–3.75 (m, 2H), 2.71–2.86 (m, 1H), 1.74–1.77 (m, 2H), 1.46 (s, 9H), 1.23–1.30 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H).

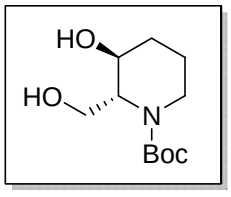
^{13}C NMR (50 MHz, $CDCl_3$) : δ 155.9, 79.7, 64.9, 61.2, 58.7, 39.7, 28.4, 26.3, 25.8, 18.8, 18.1, –5.5.

ESIMS (m/z) : 368 $(M+Na)^+$

Elemental analysis : Calculated C, 59.09; H, 10.21; N, 4.05%

Found C, 59.10; H, 10.21; N, 4.03%

(2*R*,3*S*)-*tert*-Butyl 3-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate (2)



To the TBS protected alcohol **11** (240 mg, 0.7 mmol) in anhydrous THF (5 mL) TBAF (1 M solution in THF, 0.8 mL, 0.8 mmol) was added and the reaction mixture was stirred for 4 hours at room temperature. Water (10 mL) was added to the reaction mixture and extracted in ethyl acetate (3 x 25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue thus obtained was purified by flash chromatography (pet ether–ethyl acetate 10:90) to afford diol **2** (141 mg 88 %) as a white crystalline solid.

Molecular formula : $C_{11}H_{21}NO_4$

Yield : 88%

MP : 133–135 ºC

$[\alpha]_D^{25}$: –27º (c 1.0, MeOH), lit.[5] (enantiomer of **2**) $[\alpha]_D^{25}$= +29.8° (*c*: 0.99, MeOH)

IR ($CHCl_3$) υ_{max} : 3448, 3025, 2945, 1674, 1215, 1120, 838 cm^{-1}.

^{1}H NMR (200 MHz, CD_3OD): δ 4.08-4.16 (m, 1H), 3.89-3.92 (m, 2H), 3.45-3.61 (m, 2H), 2.69-2.82 (m, 1H), 1.61-1.82 (m, 3H), 1.39 (s, 9H), 1.15-1.29 (m, 1H).

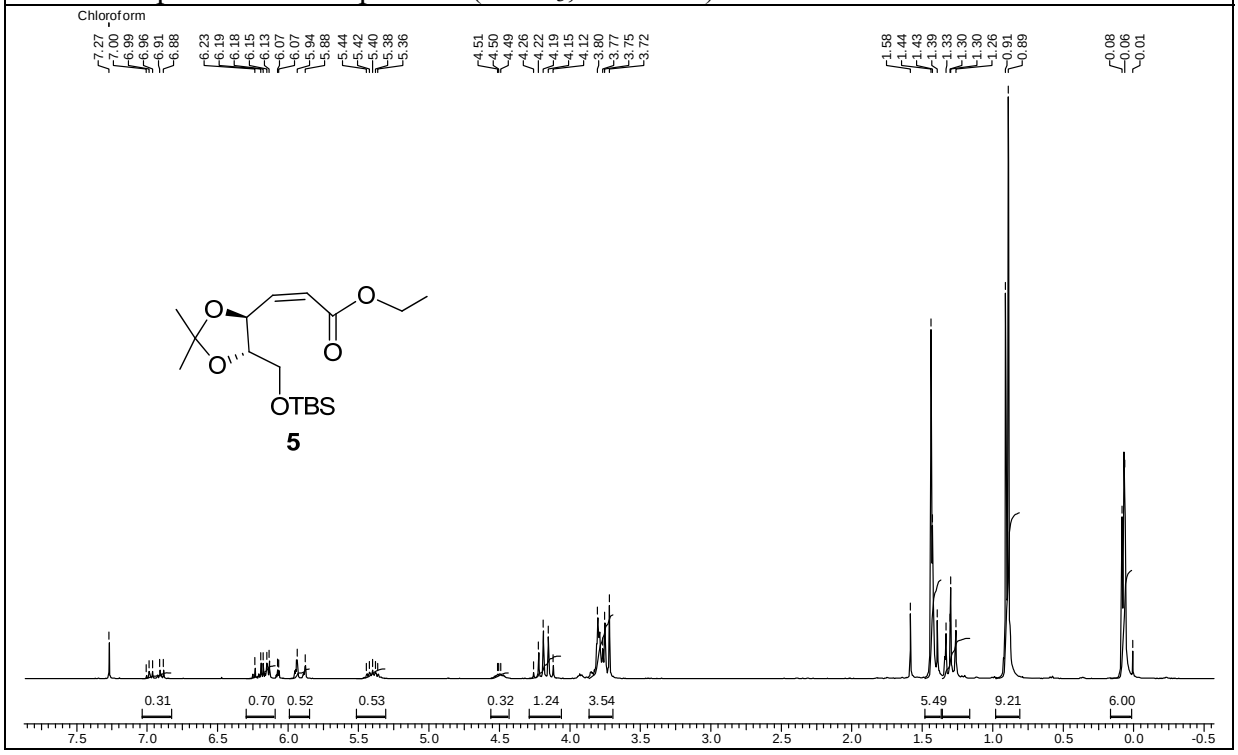
^{13}C (125 MHz, C_2D_6SO+ $CDCl_3$): δ 155.9, 79.1, 63.8, 59.9, 59.1, 39.8, 28.2, 26.6, 18.9.

HRMS (CI+) : Calcd For $C_{11}H_{21}NO_4$: 231.1484; found: 231.1470;

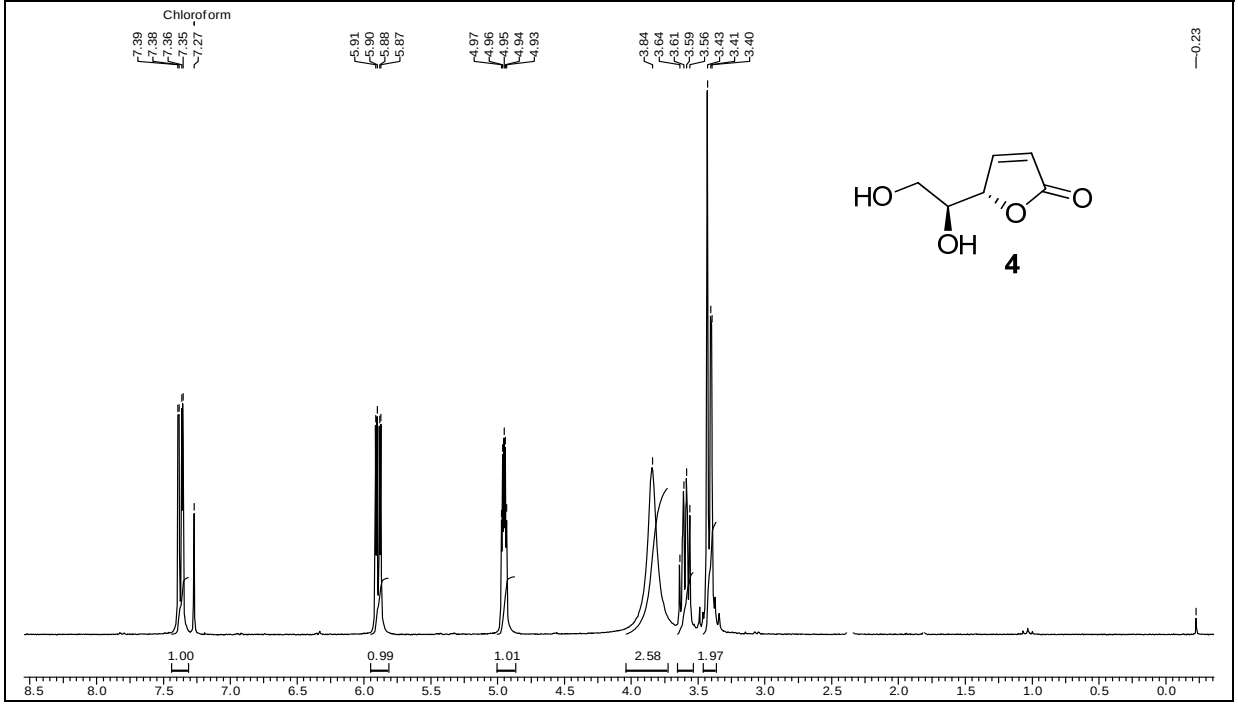
ESIMS (m/z) : 232 $(M+H)^+$, 254 $(M+Na)^+$.

2.2.4 NMR Spectra

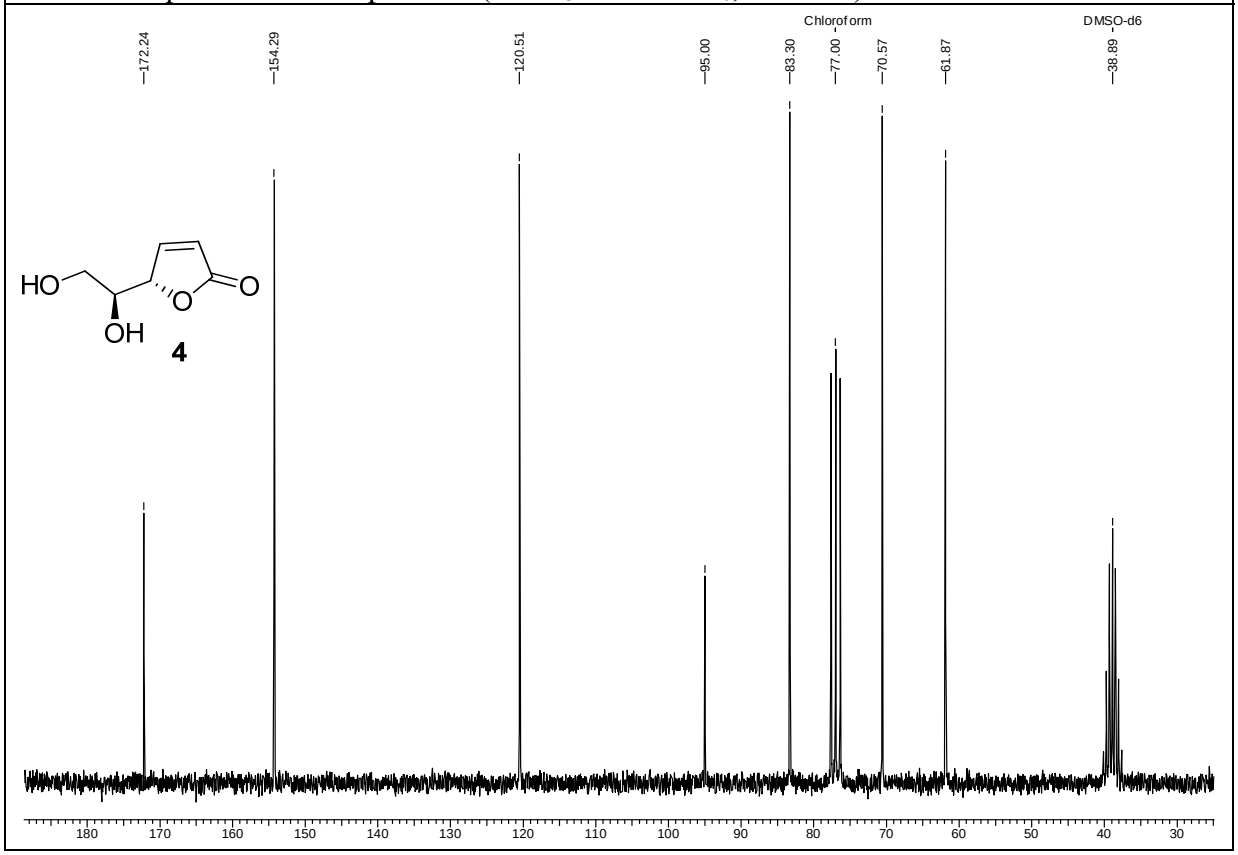
^{1}H-NMR spectrum of compound **5** ($CDCl_3$, 200 MHz)



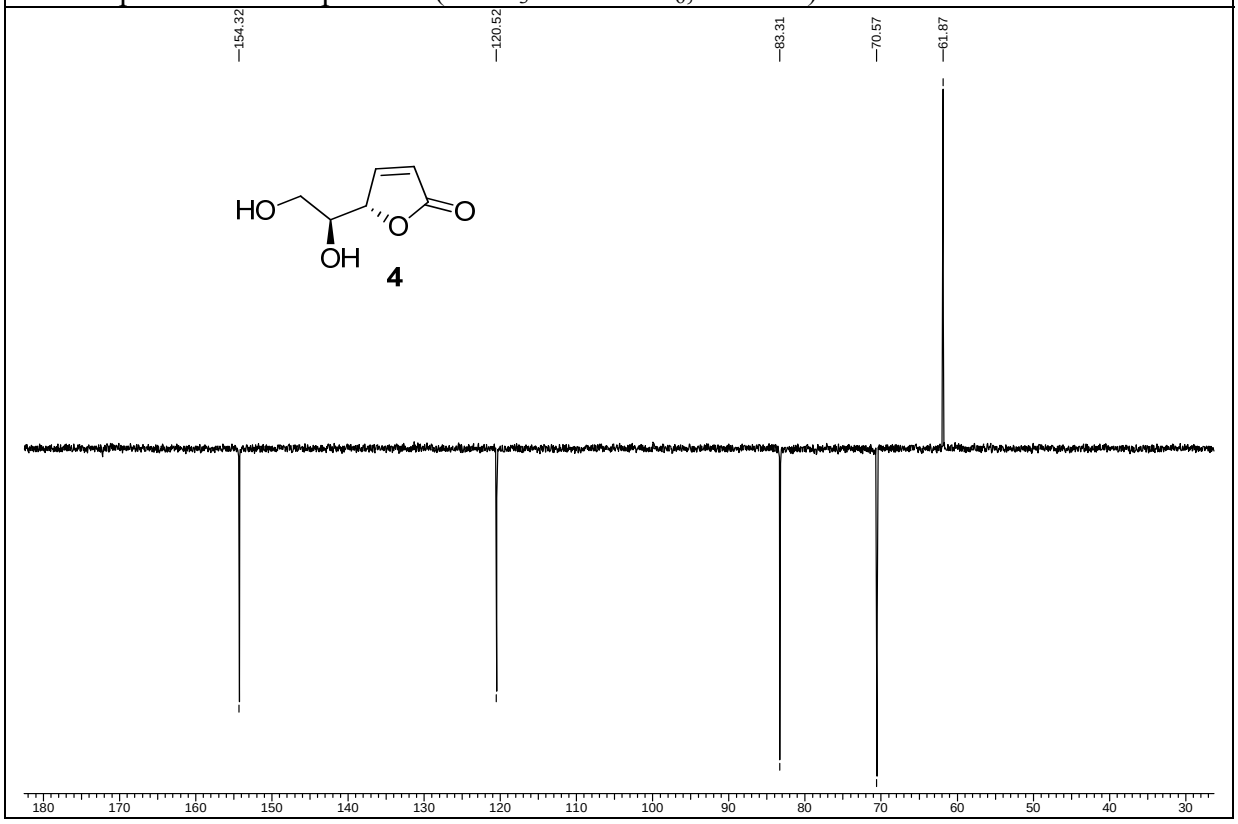
^{1}H-NMR spectrum of compound **4** ($CDCl_3$+ DMSO-d_6, 200 MHz)



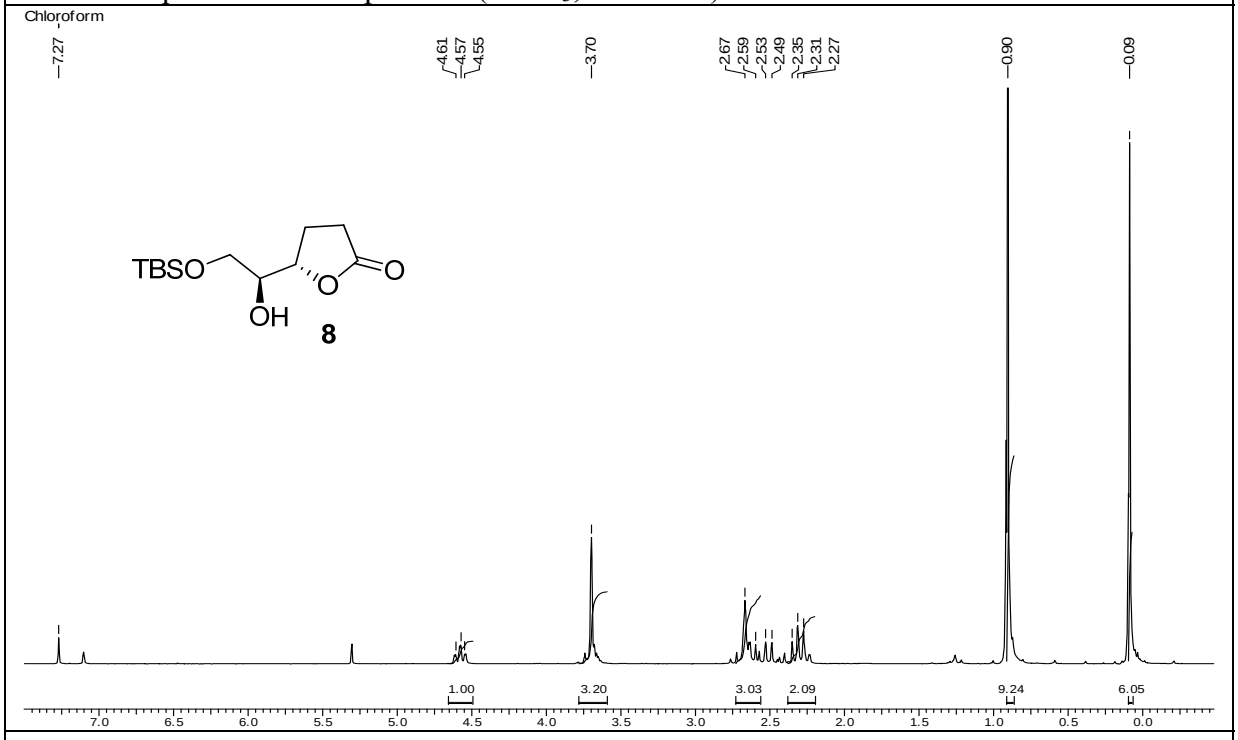
^{13}C-NMR spectrum of compound **4** ($CDCl_3$+ DMSO-d_6, 50 MHz)



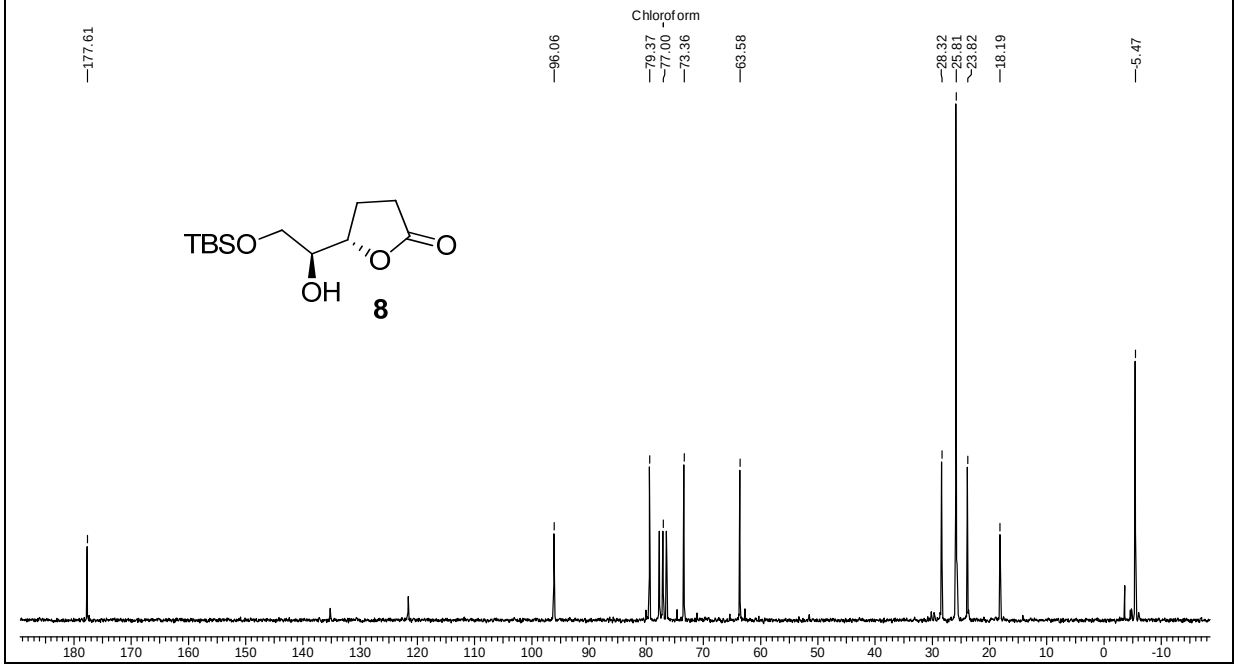
DEPT spectrum of compound **4** ($CDCl_3$+ DMSO-d_6, 50 MHz)



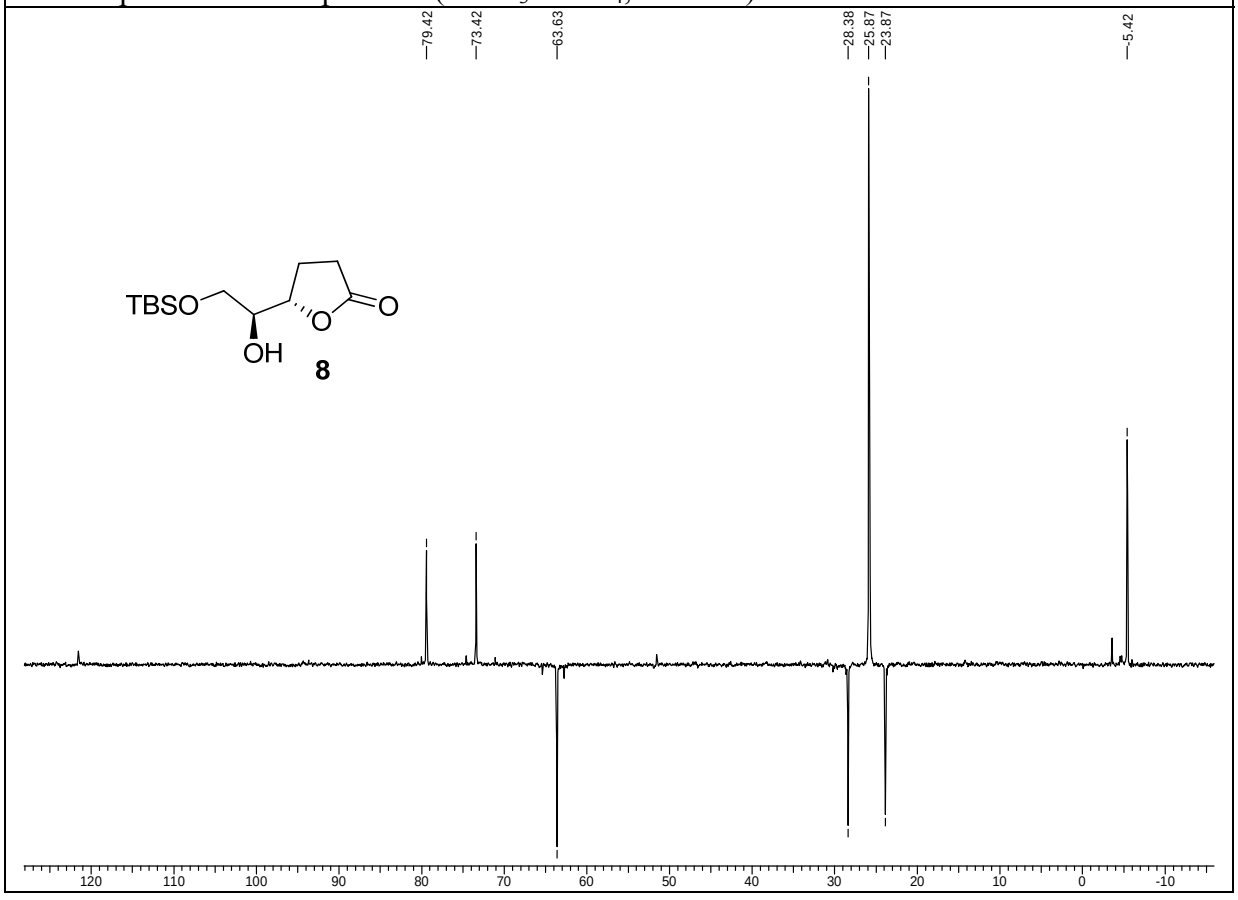
^{1}H-NMR Spectrum of compound **8** ($CDCl_3$, 200 MHz)



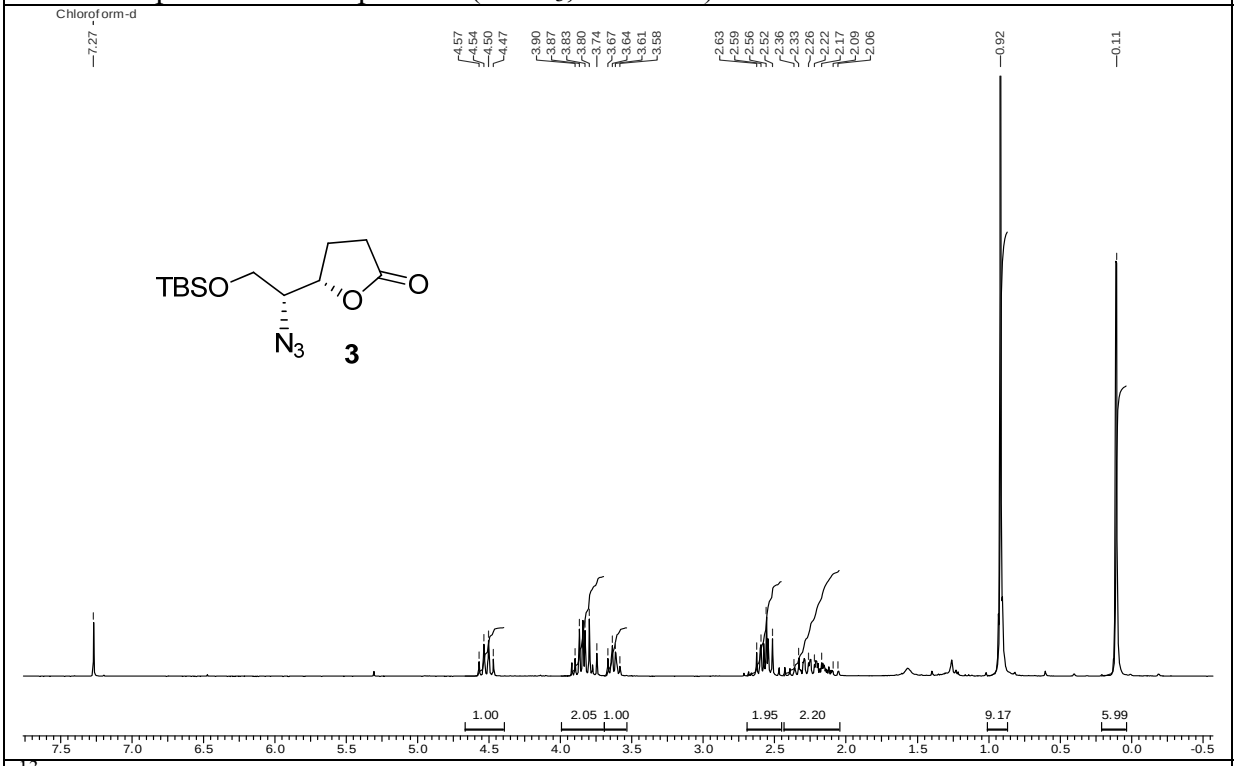
^{13}C-NMR spectrum of compound **8** ($CDCl_3$ + CCl_4, 50 MHz)



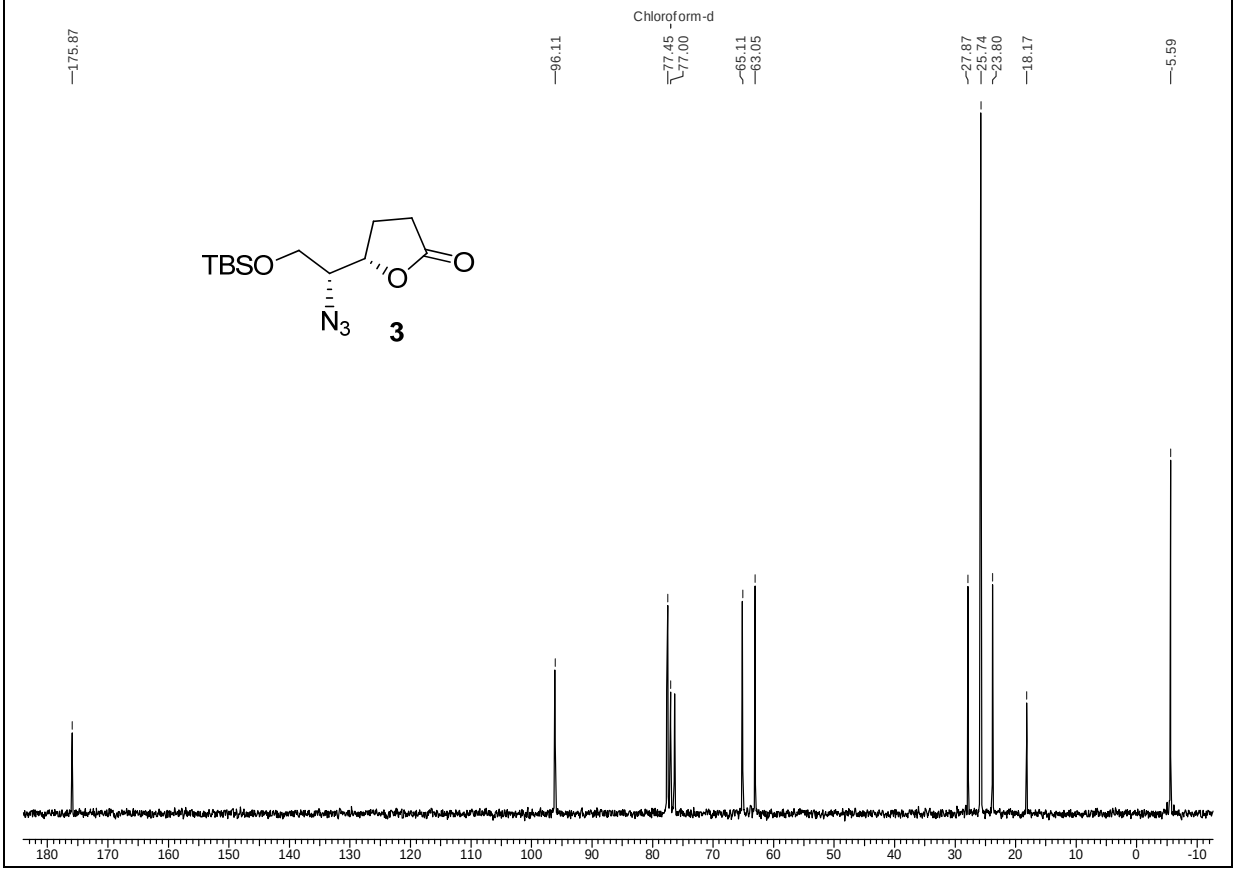
DEPT spectrum of compound **8** ($CDCl_3$ + CCl_4, 50 MHz)



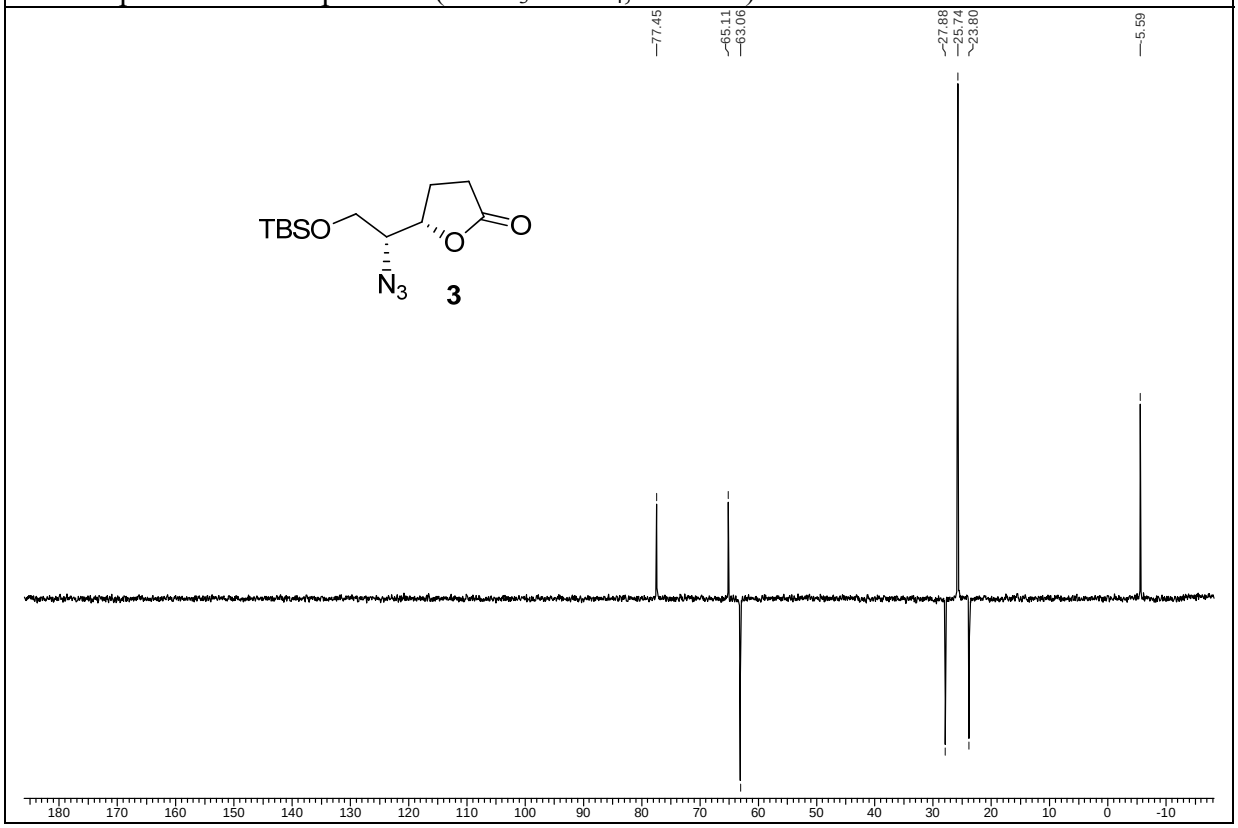
^{1}H-NMR spectrum of compound **3** ($CDCl_3$, 200 MHz)



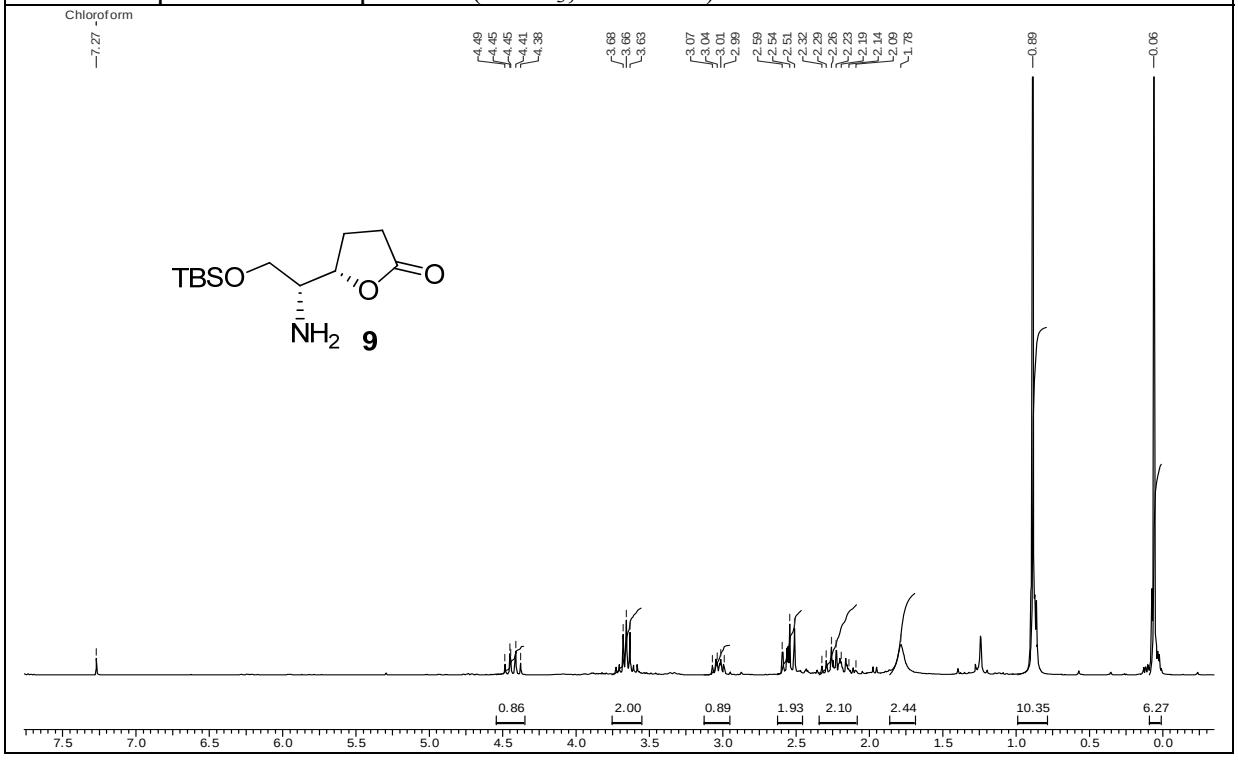
^{13}C-NMR spectrum of compound **3** ($CDCl_3$ + CCl_4, 50 MHz)



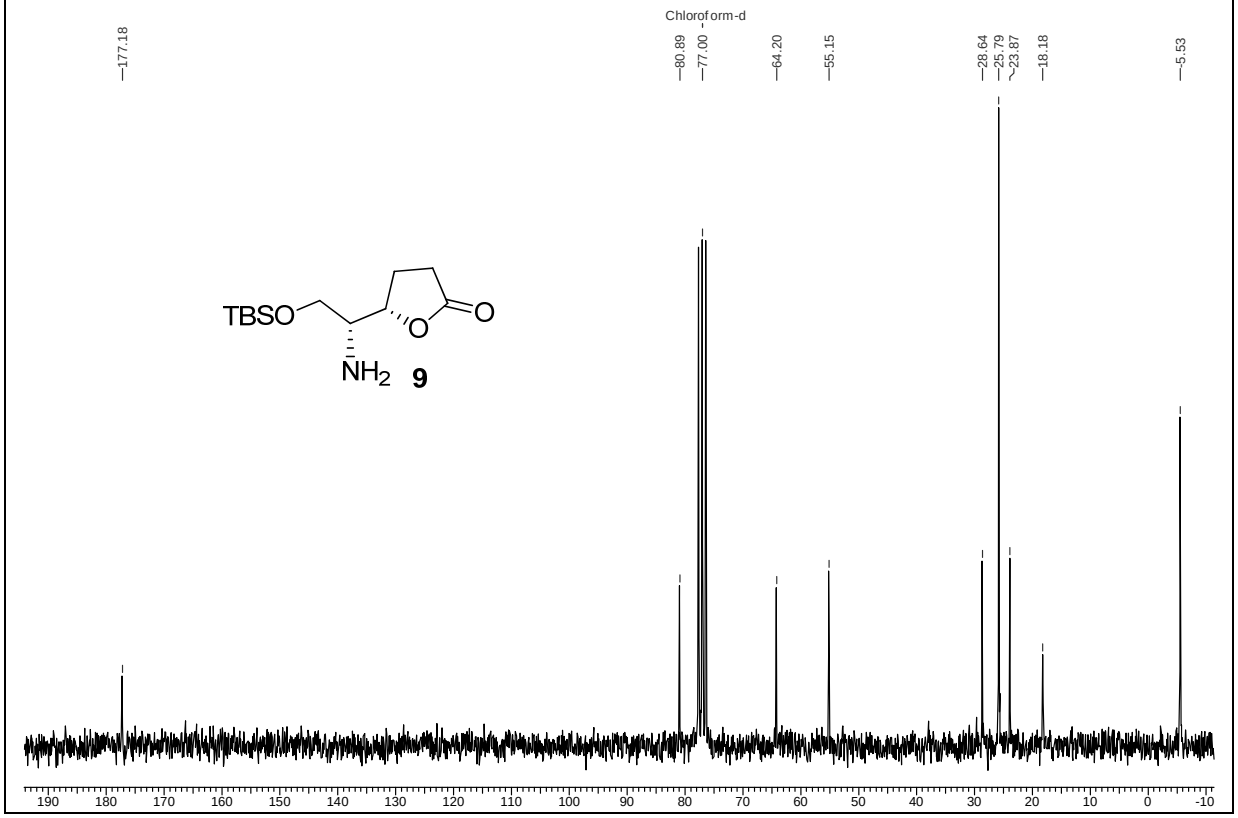
DEPT spectrum of compound **3** ($CDCl_3$ + CCl_4, 50 MHz)



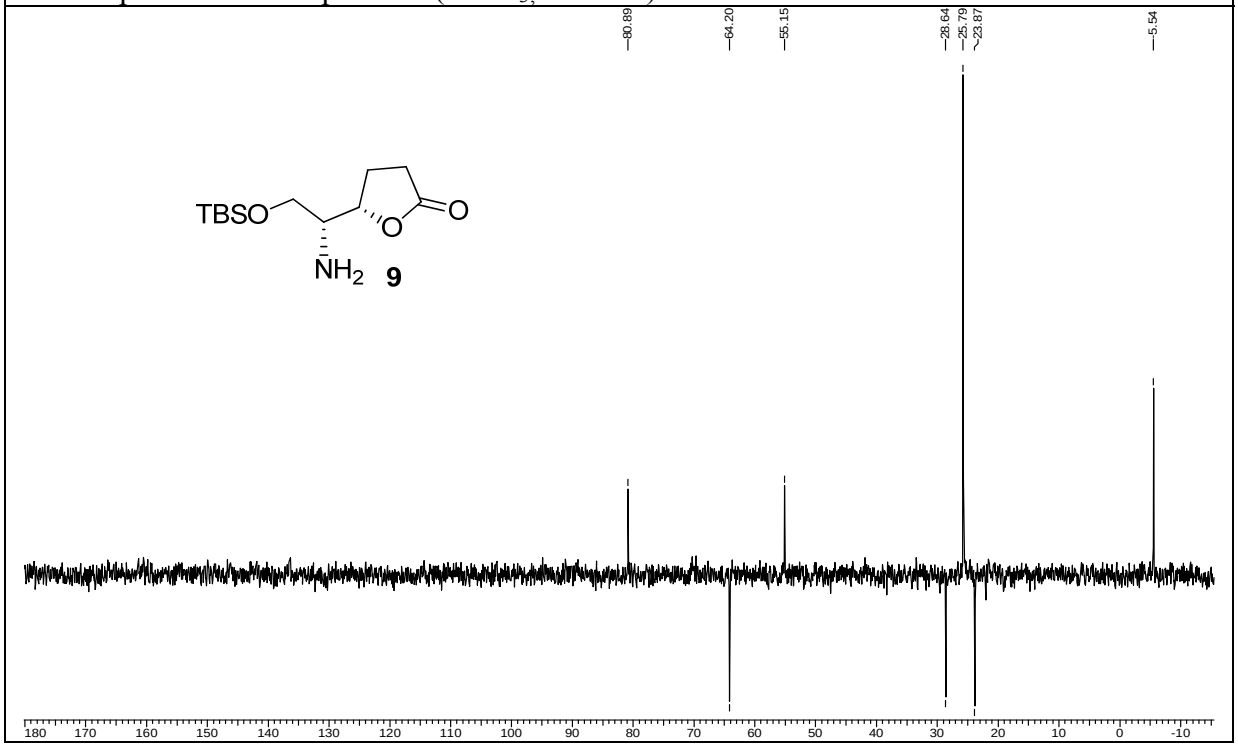
^{1}H-NMR spectrum of compound **9** ($CDCl_3$, 200 MHz)



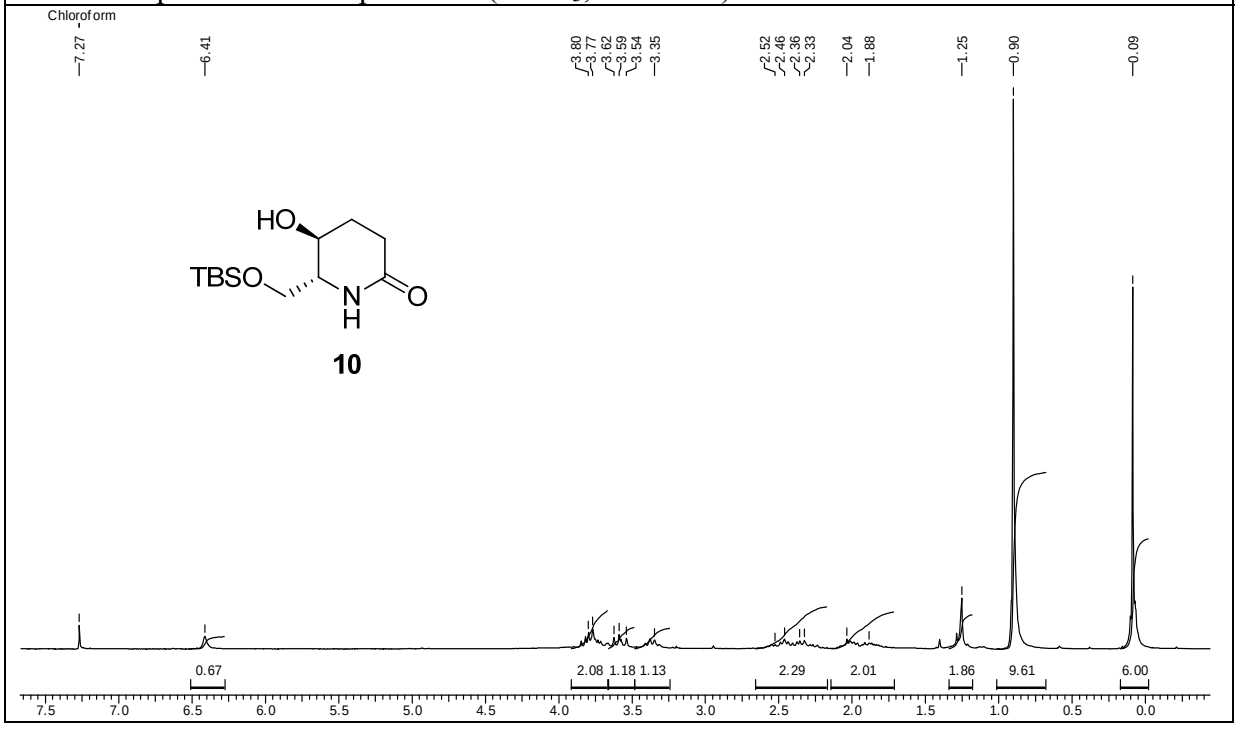
^{13}C-NMR spectrum of compound **9** ($CDCl_3$, 50 MHz)



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

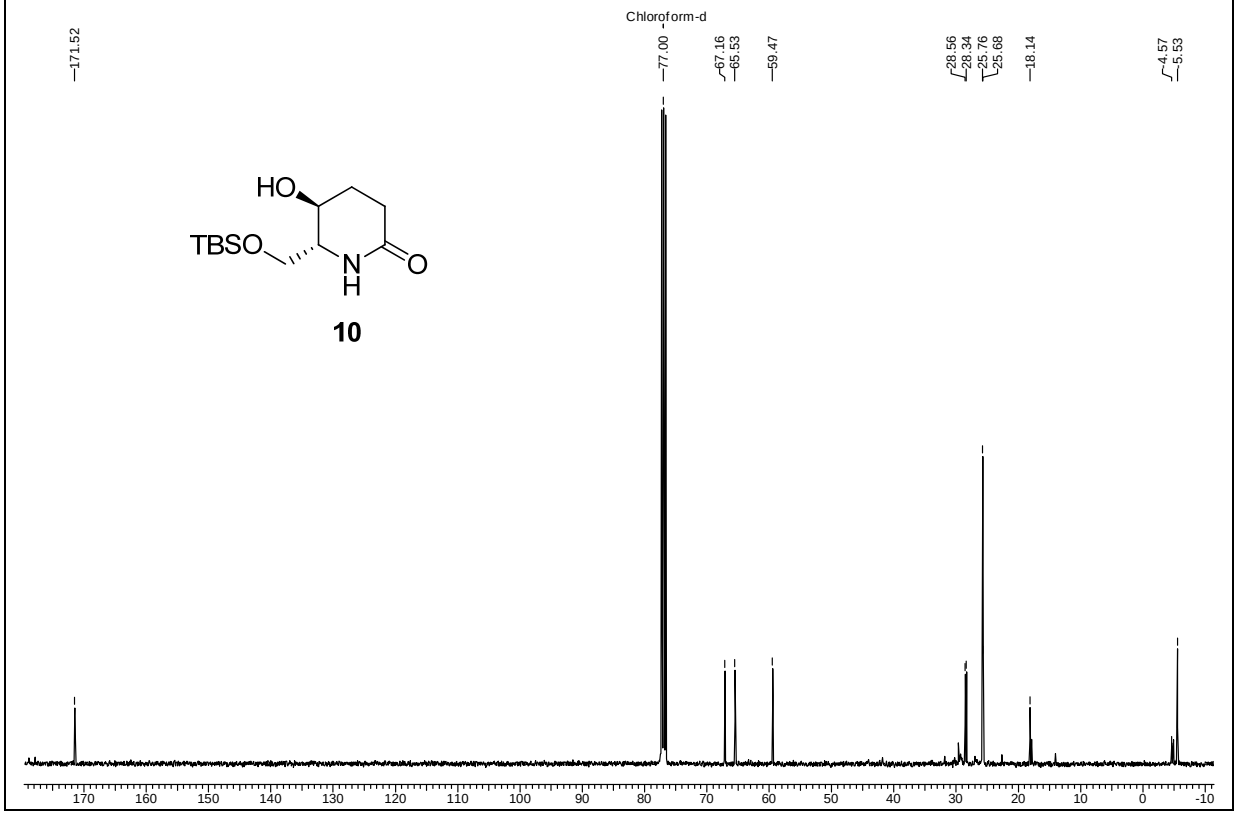


^{1}H-NMR spectrum of compound **10** ($CDCl_3$, 200 MHz)



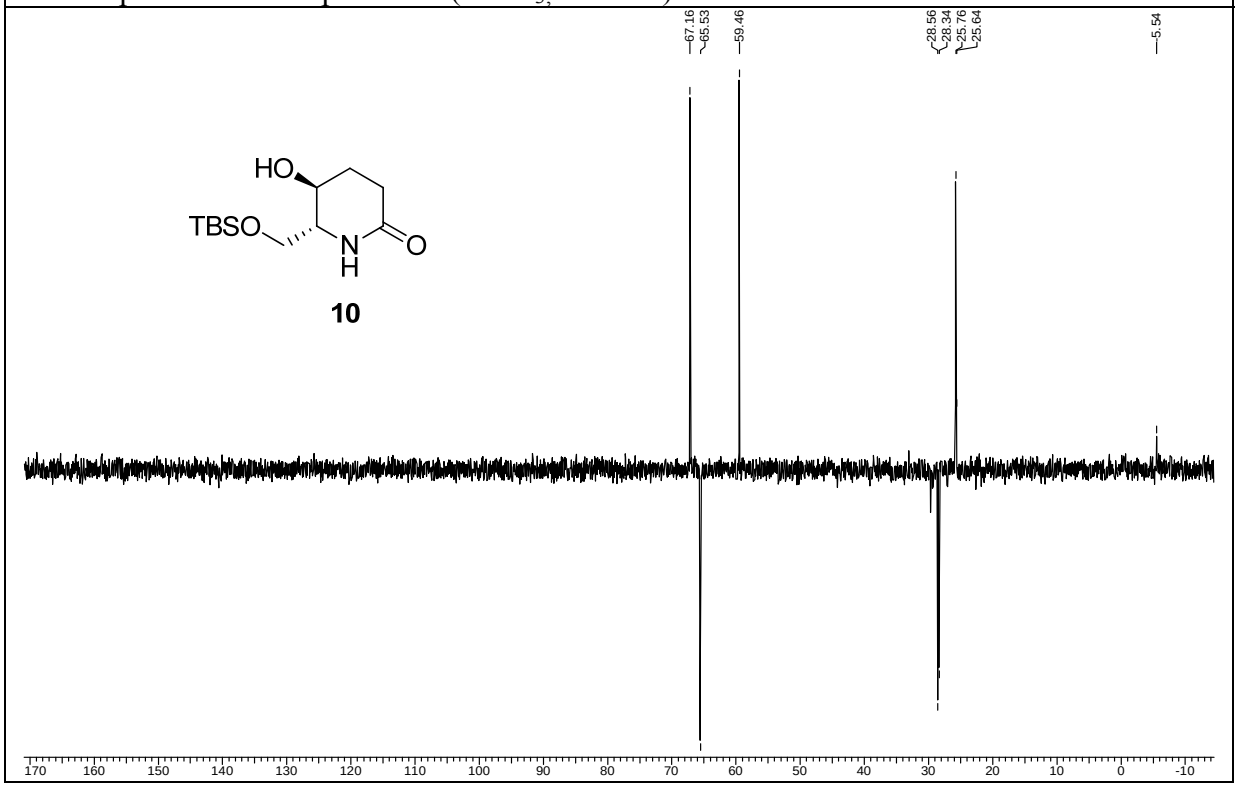
10

^{13}C-NMR spectrum of compound **10** ($CDCl_3$, 50 MHz)

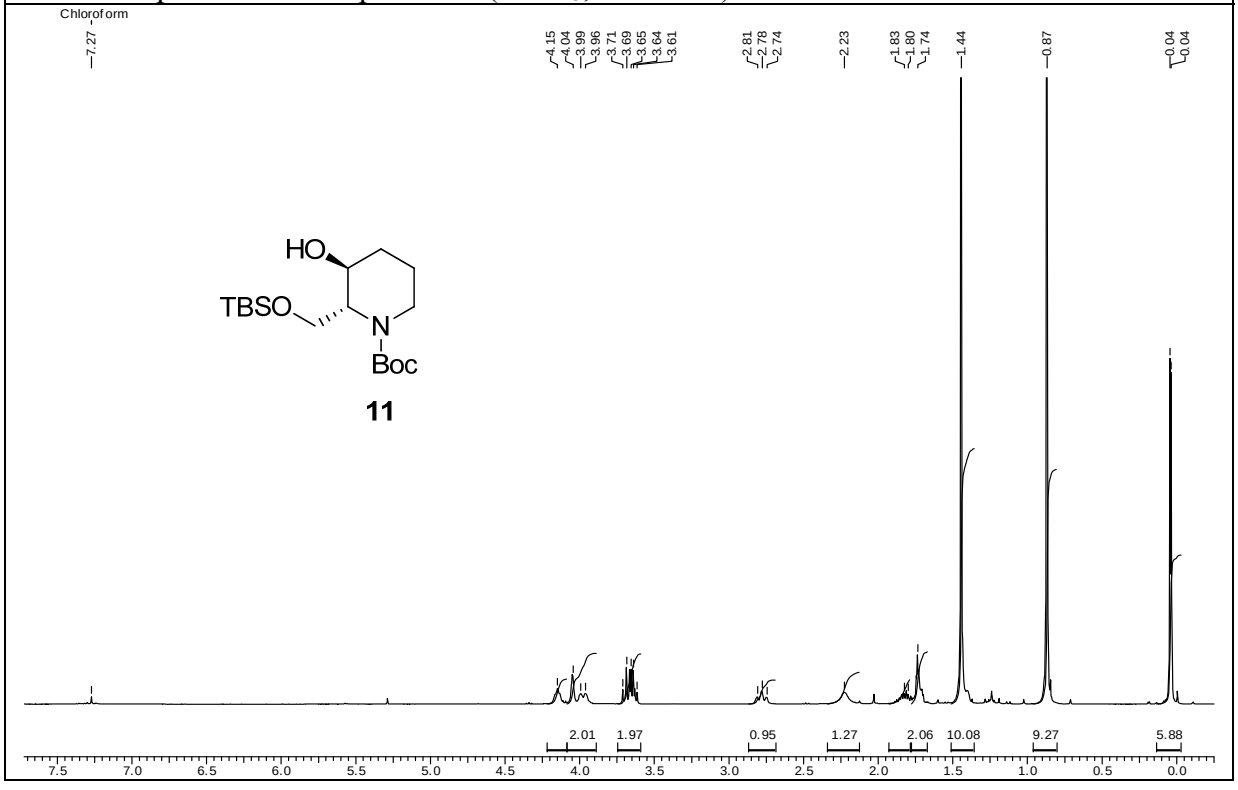


10

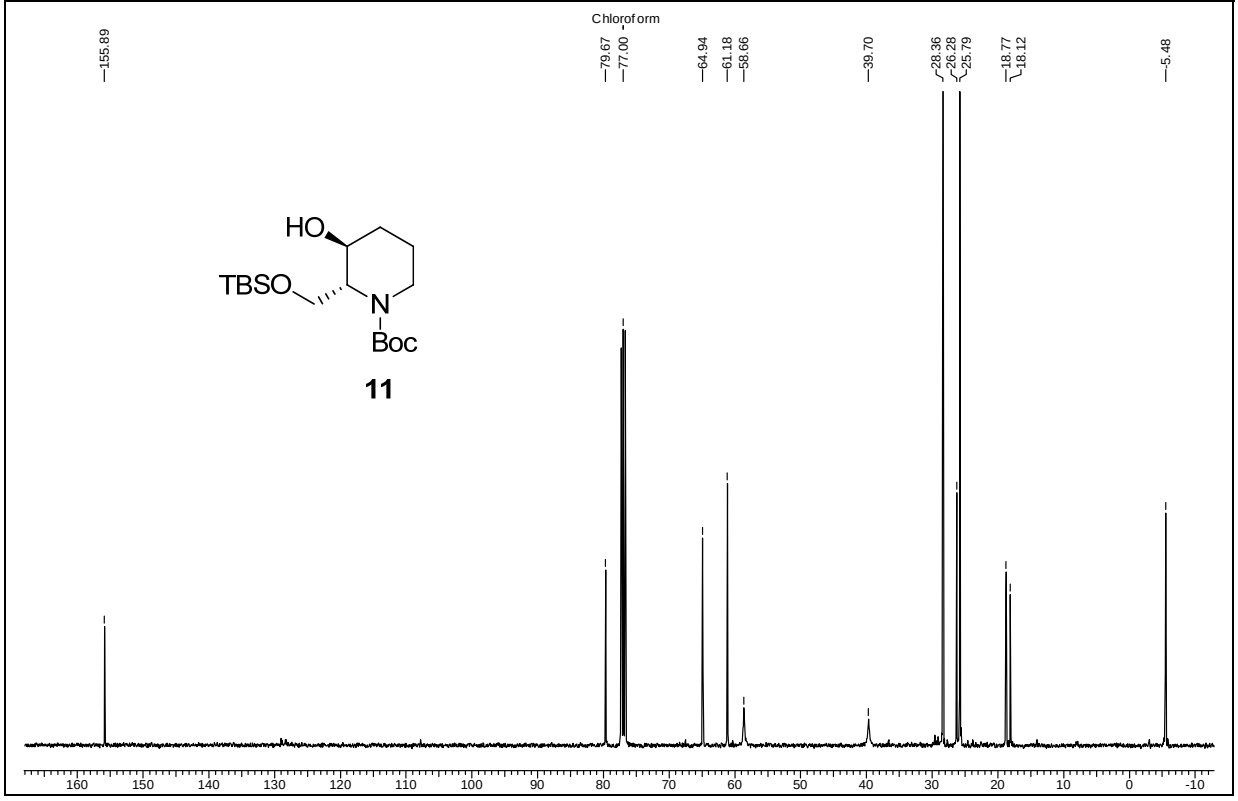
DEPT spectrum of compound **10** ($CDCl_3$, 50 MHz)



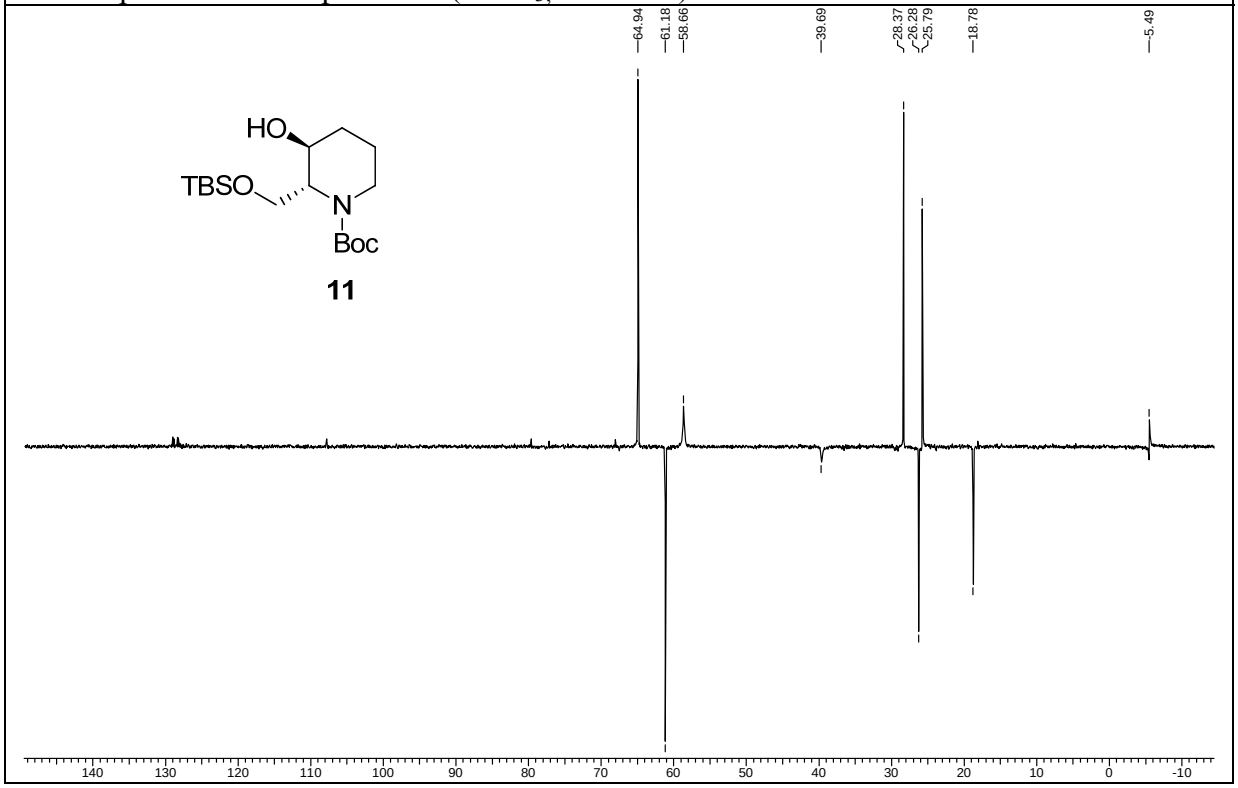
^{1}H-NMR spectrum of compound **11** ($CDCl_3$, 400 MHz)



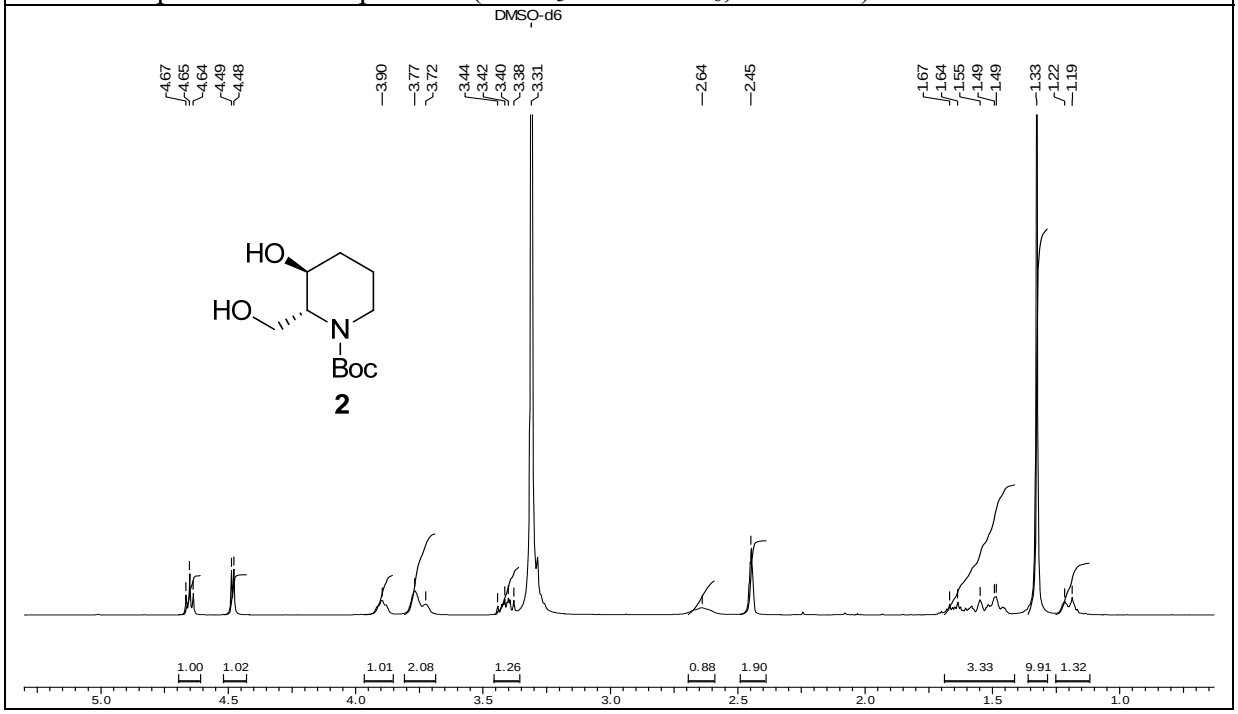
^{13}C-NMR spectrum of compound **11** ($CDCl_3$, 100 MHz)



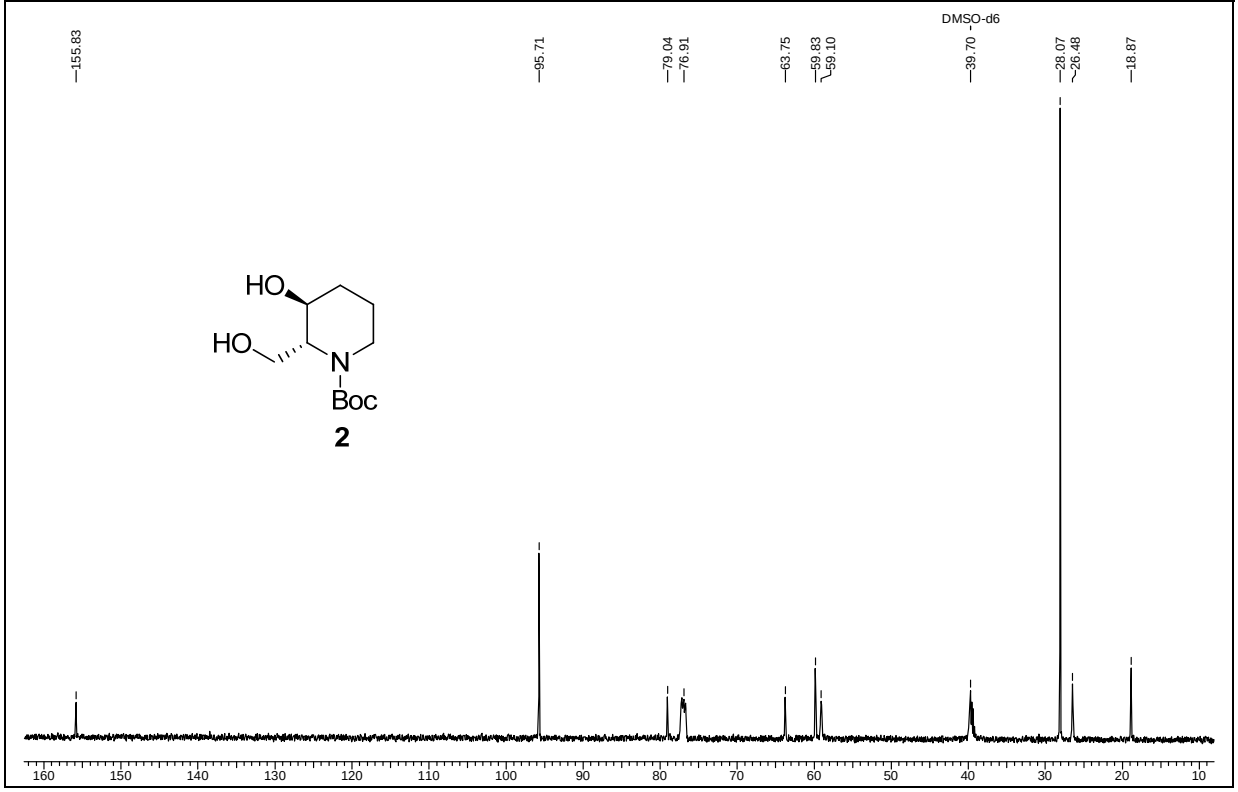
DEPT spectrum of compound **11** ($CDCl_3$, 100 MHz)



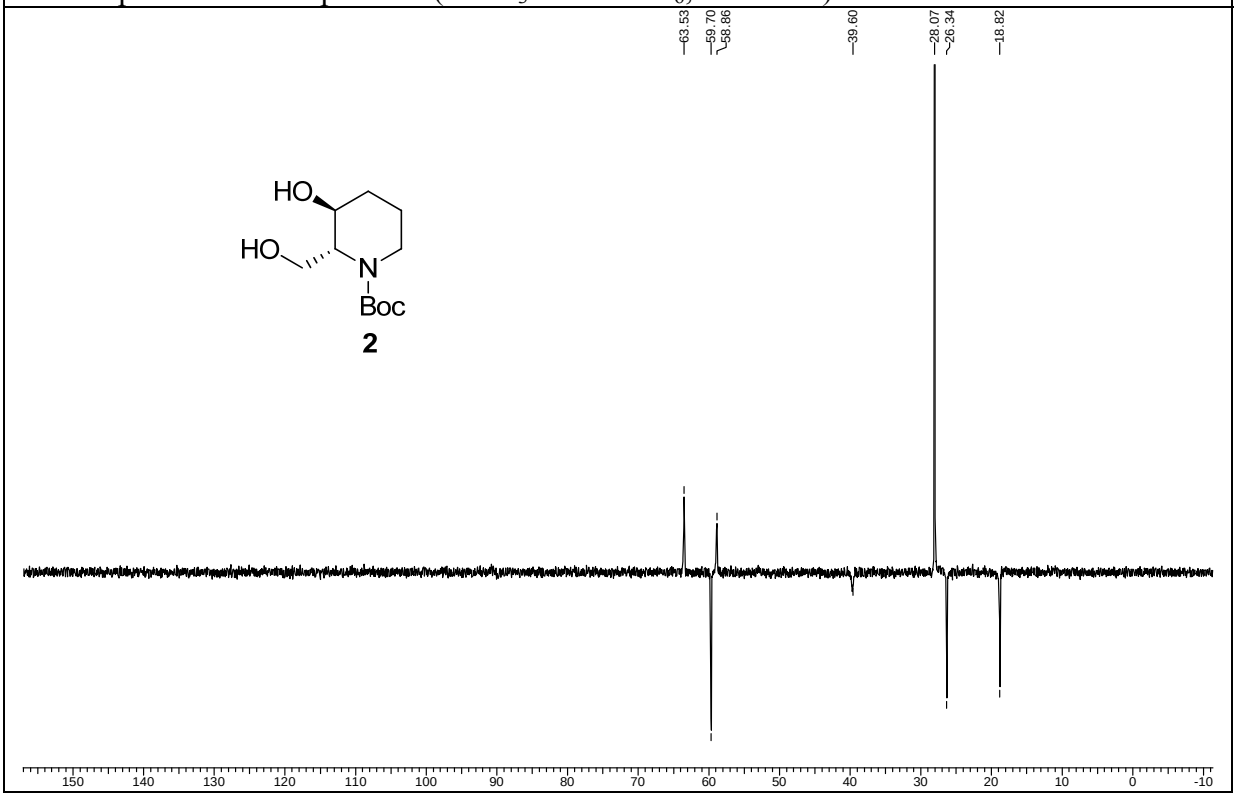
^{1}H-NMR spectrum of compound **2** ($CDCl_3$+ DMSO-d_6, 200 MHz)



^{13}C NMR spectrum of compound **2** ($CDCl_3$+ DMSO-d_6, 125 MHz)



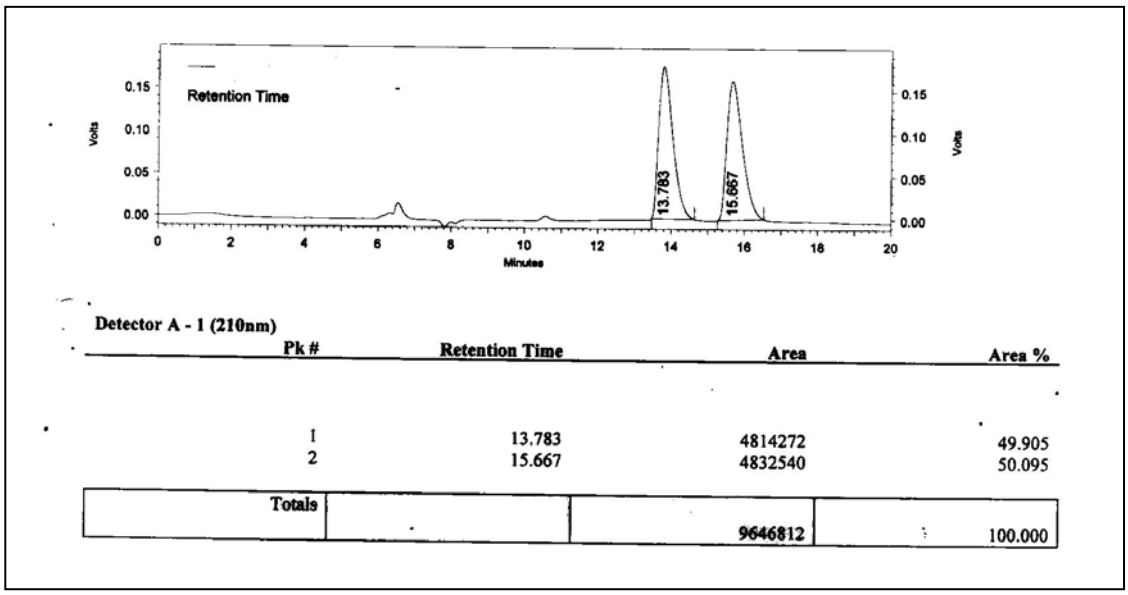
DEPT spectrum of compound **2** ($CDCl_3$+ DMSO-d_6, 125 MHz)



Chiral HPLC analysis of compound 2:

Column: Chiralcel OJ-H (4.6 x 25mm)

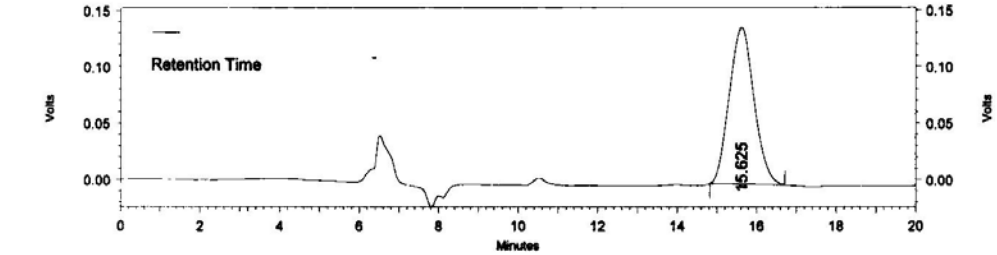
Mobile phase: IPA : PE (95 : 5); wavelength: 210 nm; flow rate: 0.5 mL/min



Detector A - 1 (210nm)

Pk #	Retention Time	Area	Area %
1	13.783	4814272	49.905
2	15.667	4832540	50.095
Totals		9646812	100.000

(Racemic)



Detector A - 1 (210nm)

Pk #	Retention Time	Area	Area %
1	15.625	6032099	100.000
Totals		6032099	100.000

(Optically active)

2.2.5 References

1 . Nguyen, L. A.; He, H.; Pham-Huy, C. *Int. J. Biomed. Sci.* **2006**, *2*, 85.

2 . Chavan, S. P.; Dumare, N. B.; Harale, K. R.; Kalkote, U. R. *Tetrahedron Lett*. **2011**, *52*, 404.

3 . Iida, H.; Yamazaki, N.; Kibayashi. C. ***J. Org. Chem***. **1987**, *52*, 3337.

4 . Pham, V. T.; Joo, J. E.; Tian, Y. S.; Chung, Y. S.; Lee, K. Y.; Oh, C. Y.; Ham, W. H. *Tetrahedron: Asymmetry* **2008**, *19*, 318.

5 . Chiou, W. H.; Lin, G. H.; Liang, C. W. *J. Org. Chem*. **2010**, *75*, 1748.

Chapter 2. Synthetic studies towards (2*S*, 3*S*)-3-hydroxypipecolic acid

Section 3: Total synthesis of (2*S*, 3*S*)-3-hydroxypipecolic acid

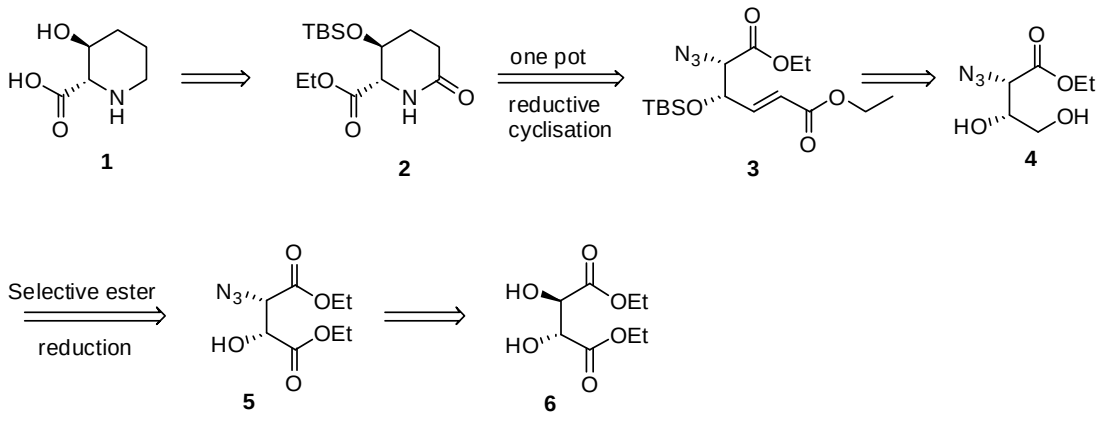
2.3.1: Present work

2.3.1.1: Objective

As described before, we accomplished the formal synthesis of 3-hydroxypipecolic acid starting from L(+)-tartaric acid (Chapter-2, section-2).[1] Total synthesis of 3-hydroxypipecolic acid starting from *cis*-butene diol using Sharpless asymmetric di-hydroxylation as the key step to install chirality was developed in our group, which is described in an introductory section (Chapter-2, section-1).[2] The work described in the present section was undertaken to achieve the synthesis of 3-hydroxypipecolic acid from L(+)-tartaric acid in less steps and using milder reagents.

2.3.1.2: Retrosynthetic analysis

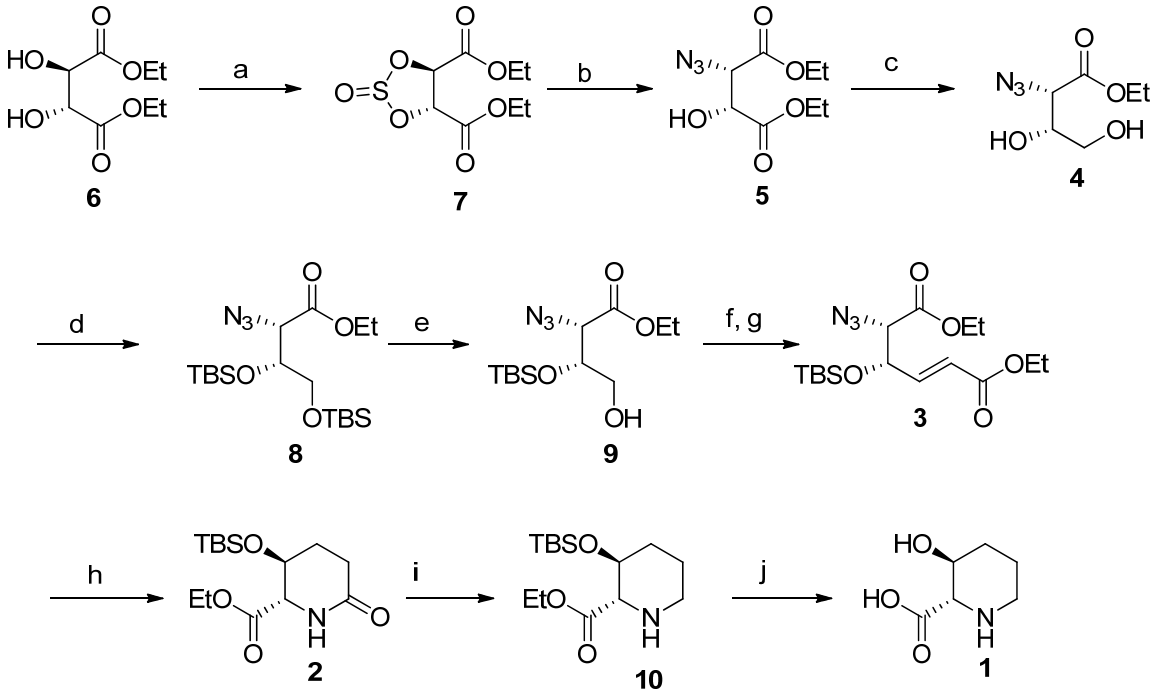
From our retrosynthetic plan (Scheme 1) it was envisioned that the 3-hydroxypipecolic acid **1** could be obtained from the corresponding amide **2**. The amide **2** could be obtained from azide **3** by one-pot reduction of azide and double bond followed by cyclization. The intermediate azido alkene **3** could be obtained from the oxidation of corresponding alcohol followed by two carbon Wittig reaction. The diol **4** was envisioned to be synthesized by selective reduction of hydroxyl ester **5**. One of the ester groups in **5** should be retained in order to get the acid in 3-hydroxypipecolic acid **1**. The azido alcohol **5** could be obtained from tartaric acid by reported method.[3]



Scheme 1. Retrosynthetic analysis for **1**

2.3.1.3: Results and discussion

The synthesis started from cheap and abundant starting material viz. L-(+)-tartaric acid (Scheme 2). The diethyl tartrate **6** was prepared from tartaric acid by esterification using reported method[4] in quantitative yield. The diethyl tartrate **6** was treated with thionyl chloride in the presence of catalytic amount of DMF in refluxing CCl_4 to furnish sulfite **7**. The sulfite **7** was subsequently opened with azide using sodium azide to provide azido alcohol **5** in 74% yield over two steps.



Scheme 2. Synthesos of (2*S*, 3*S*)-3-hydroxypipecolic acid

Reagents and conditions: a) $SOCl_2$, Cat. DMF, CCl_4, reflux b) NaN_3, DMF, 74% (over two steps) c) BH_3.DMS, Cat. $NaBH_4$, THF, 60% d) TBSOTf, Et_3N, DCM, 85% e) PPTS, MeOH, 78% f) IBX, EtOAc, reflux g) Ph_3PCHCO_2Et, toluene, reflux, 75% (over two steps) h) H_2, Pd/C, EtOH, 90% i) BH_3.DMS, THF, 78% j) 6N, HCl, reflux, 91%

The IR spectrum of azido alcohol **5** showed strong band at 2141 and 1728 cm^{-1} indicating the presence of azide and ester functionalities respectively. Presence of broad band at 3276 cm^{-1} showed the presence of hydroxy group. Peak at δ 4.62 in its ^{1}H-NMR spectrum appeared as a doublet accounting for one proton adjacent to hydroxy group. The proton adjacent to azide merged in to the methylene protons of ester which showed multiplet at δ 4.23-4.35

integrating for five protons. Its ^{13}C-NMR spectrum showed characteristic peaks at δ 170 and 166 which were assigned to two carbonyl carbons. Its DEPT spectrum showed presence two CH carbons that appeared at δ 71 and 64, while two CH_2 carbons appeared at δ 62.3 and 62.1 in accordance with the structure of **5**. Formation of **5** was further supported by its mass spectrum which showed the molecular ion peak at m/z 254 $(M+Na)^+$.

One of the ester groups in di-ester **5** was selectively reduced by taking advantage of the free hydroxy group. The azido alcohol **5** was subjected to reduction using BH_3.DMS and catalytic amount of $NaBH_4$ in anhydrous THF to furnish diol **4** in 60% yield. Its IR spectrum showed broad band at 3479 cm^{-1} indicating the presence of hydroxy functionality and peaks at 2121 and 1747 cm^{-1} clearly indicated the presence of azide and ester functionalities respectively. The broad peak at δ 2.57 in its ^{1}H-NMR spectrum was assigned to –OH protons. Four protons at δ 3.68 to 4.12 were corresponding to protons adjacent to hydroxy and azide functionalities. Peaks appearing as a quartet at δ 4.30 and triplet at δ 1.36 were assigned to the ethyl protons of ester group. Its ^{13}C-NMR spectrum showed the peak at δ 169 corresponding to the ester carbonyl functionality. Its DEPT spectrum showed presence of two peaks corresponding to CH_2 carbons and three peaks corresponding to CH_3 and CH carbons, which is in accordance with the structure of **4**. Further, the formation of **4** was also confirmed by mass spectroscopy which showed a molecular ion peak at m/z 190 $(M+H)^+$.

The diol **4** was subjected to TBS protection using TBSOTf and triethyl amine in DCM at 0 ºC to furnish di-TBS compound **8** in 85% yield. Strong bands at 2111 and 1744 cm^{-1} in its IR spectrum indicated the presence of azide as well as ester functionalities respectively. Its ^{1}H-NMR spectrum showed peaks at δ 0.90 and 0.10 clearly showing the presence of two TBS groups, while peaks at δ 4.21 (q) and 1.32 (t) corresponded to the ester functionality. Peak at δ 167 in its ^{13}C-NMR spectrum corresponded to ester carbonyl. Its DEPT spectrum showed appearance of two CH_2 carbons and eight CH and CH_3 carbons supporting the formation of **8**. Finally, molecular ion peak at m/z 418$(M+H)^+$, 440$(M+Na)^+$ in its mass spectrum confirmed the formation of **8**.

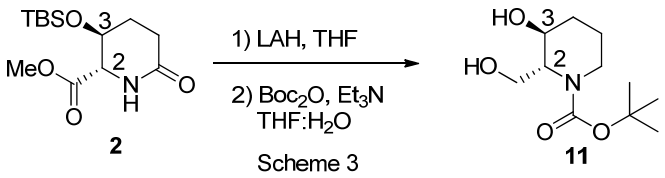
The deprotection of primary OTBS ether was tried using acid catalysts like PTSA (cat.) and CSA (cat.) which resulted in to formation of lactone instead of the desired compound **9**. The desired TBS deprotection was then successfully achieved using equimolar amount of PPTS

in anhydrous methanol to provide mono TBS deprotected compound **9** in 78% yield. The characteristic peaks at 2112 and 1730 cm^{-1} in its IR spectrum indicated the presence of azide and ester functionalities respectively. Peaks at δ 0.89 and 0.11 in its ^{1}H-NMR spectrum integrating for 9 and 6 protons respectively provided strong evidence for mono-TBS deprotection. Its ^{13}C-NMR spectrum showed peak at δ 168 corresponding to carbonyl carbon. Its DEPT spectrum showed six peaks for CH and CH_3 carbons and two peaks for CH_2 carbons. Further, the mono-TBS deprotection was confirmed by its mass spectrum which showed a molecular ion peak at m/z 304 $(M+H)^+$.

The oxidation of azido alcohol **9** was carried out using IBX in refluxing ethyl acetate and the resultant crude aldehyde was subjected to Wittig reaction using two carbon ylide Ph_3PCHCO_2Et in toluene under reflux conditions to render the α,β-unsaturated ester **3** in 75% yield over two steps. The strong bands at 2113, 1739 and 1726 cm^{-1} in its IR spectrum showed the presence of azide, ester and unsaturated ester functionalities respectively. The appearance of doublet of doublets at δ 6.87 with coupling constants 15.7 and 5.7 Hz and δ 6.06 with coupling constants 15.7 and 1.4 Hz in its ^{1}H-NMR spectrum clearly indicated the presence α,β-unsaturated ester moiety. Peaks at δ 4.17-4.31 (m), and 1.33 (t), corresponded to the ethyl ester while those at 0.92 (s), 0.12 (s) and 0.08 (s) corresponded to TBS protecting group. Peaks at δ 167 and 165 in its ^{13}C-NMR spectrum showed the presence of two carbonyl functionalities and peaks at δ 144 and 123 corresponded to double bond carbons. Its DEPT spectrum showed 8 CH and CH_3 carbons and 2 CH_2 carbons wherein peaks corresponding to both ethyl carbons appeared at same chemical shift. Its mass spectrum showed molecular ion peak at m/z 394 $(M+Na)^+$ which confirmed the formation of **3**.

The crucial step *viz* reductive of **3** cyclization was carried out under hydrogenation conditions using hydrogen and palladium over carbon in methanol to provide amide **2** in 80% yield. Absence of peaks at 2113 and 1726 cm^{-1}in its IR spectrum strongly supported the reduction of azide as well as double bond and appearance of peaks at 1643 and 1732 cm^{-1} clearly showed the presence of amide and ester functionalities respectively. Disappearance of characteristic peaks of protons on double bond at δ 6.87 and 6.06 in its ^{1}H-NMR spectrum indicated the double bond reduction. The broad singlet at δ 5.96 was assigned to the proton on amide nitrogen. The quartet at δ 4.23 and triplet at δ 1.30 integrating for two and three

protons respectively were assigned to ethyl ester protons. Its ^{13}C-NMR spectrum showed peaks at δ 171 and 170 corresponding to ester and amide carbonyl carbons. Peak at δ 65 was assigned to methylene carbon in ethyl ester and peaks at δ 62 and 61 were assigned to two tertiary carbons. Its DEPT spectrum showed presence of three CH_2 carbons and six CH and CH_3 carbons which is in accordance with structure of amide **2**. Further, the formation of amide **2** was confirmed by its mass spectrum which showed a molecular ion peak at m/z 302 $(M+H)^+$.



Scheme 3

In order to check the chiral purity at C2 and C3 the amide **2** was subjected to reduction using lithium aluminum hydride in anhydrous THF. Gratifyingly the ester, amide reduction as well as TBS deprotection was observed in a single step. The LAH reduction of **2** followed by *N*-Boc protection provided *N*-Boc amine **11**. The chiral HPLC analysis of the **11** revealed that the chiral purity of **11** is ~100%.[5]

Amido ester **2** was subjected to selective reduction of amide functionality using borane dimethyl sulfide complex in anhydrous THF to furnish the amino ester **10** in 78% yield. The presence of strong band at 1731 cm^{-1} and disappearance of band at 1643 cm^{-1} in its IR spectrum strongly supported the reduction of amide. In its ^{1}H-NMR spectrum the CH_2 protons of ethyl ester split in to two multiplets, appeared at δ 4.31-4.39 and 4.10-4.18 and the triplet appearing at δ 1.36 was assigned to the methyl protons of ester. Multiplet at δ 3.98 and doublet of triplet at δ 3.78 are corresponding to the two –CH- protons. The characteristic peaks of TBS group appeared at δ 0.86, 0.06 and 0.00. Peak at δ 170 in its ^{13}C-NMR spectrum corresponded to ester carbonyl and the two tertiary carbons appeared at δ 70.5 and 70.2. Further, the CH_3 carbons appeared at δ 25.5, 13.9, –4.5, –5.3 and CH_2 carbons appeared at δ 61.8, 52.2, 32.2 and 23.1. Further, peaks at m/z 288 $(M+H)^+$, 310 $(M+Na)^+$ in its mass spectrum confirmed the formation of **10**.

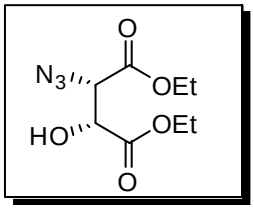
The ester hydrolysis as well as OTBS deprotection was carried out in a single step using 6N HCl to provide 3-hydroxy pipecolic acid **1** in 91% yield. Its ^{1}H-NMR spectrum showed multiplet at δ 4.13-4.17 and doublet at δ 3.83 corresponding to –CH- protons. Other peaks included multiplets at δ 3.36-3.40, 3.07-3.12 and 1.64-1.80 and singlet at δ 2.22. Peak at δ 170.1 in its ^{13}C-NMR was attributed to the acid carbonyl carbon and the peaks at δ 65.5 and 61.0 were due to the tertiary carbons. The three carbons appearing at δ 42.5, 28.8 and 18.6 all corresponded to the CH_2 carbons. Its DEPT spectrum showed two carbons corresponding to -CH- carbons and three carbons due to the $–CH_2$- carbons. Molecular ion peak at m/z 146 $(M+H)^+$ in its mass spectrum confirmed the formation of **1**. The spectral data and optical rotation values were in good agreement with the reported one.[6]

2.3.2. Conclusion

In conclusion, a total synthesis of 3-hydroxypipecolic acid was achieved starting from cheap and abundant starting material L(+)-tartaric acid in 10 steps and in 12.5% overall yield. The main steps used are the selective ester group reduction, reductive cyclization and selective amide reduction. The intermediate **3** could be further explored for the synthesis of other imino sugars.

2.3.3. Experimental

(2*S*,3*R*)-Diethyl 2-azido-3-hydroxysuccinate (5)



To the di-ethyl tartrate **6** (10 gm, 48 mmol) in CCl_4 (100 mL) was added thionyl chloride (7.2 mL, 97 mmol) dropwise followed by catalytic amount of DMF (0.2 mL). The resulting reaction mixture was heated to 50 ºC for two hours, cooled to rt and concentrated under reduced pressure to obtain the sulfite **7** as a thick oil. The crude sulfite **7** was dissolved in DMF (100 mL) and to this solution was added sodium azide (7 gm, 60 mmol) and stirred overnight. The reaction mixture was quenched using water (200 mL) and was extracted in ethyl acetate (3 x 200 mL). The combined organics were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* carefully. The crude reaction mixture on flash chromatography using silica gel (pet ether/ethyl acetate 70/30) afforded **5** (8.3 g, 74%) as a gummy liquid.

Molecular formula : $C_8H_{13}N_3O_5$

Yield : 74%

$[\alpha]_D^{25}$: +31º (c 1.0, MeOH)

IR ($CHCl_3$) υ_{max} : 3276, 2985, 2141, 1728, 1621, 1268 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.62 (d, *J* = 2.8 Hz, 1H), 4.35-4.23 (m, 5H), 1.35-1.27 (m, 6H).

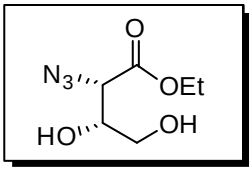
^{13}C-NMR (50 MHz, $CDCl_3$): δ 170.6, 166.8, 71.9, 64.2, 62.3, 62.1, 13.83, 13.81.

ESIMS (m/z) : 254 $(M+Na)^+$.

Elemental analysis : Calculated C, 41.56; H, 5.67; N, 18.17 %

Found C, 41.54; H, 5.69; N, 18.19%

(2*S*,3*R*)-Ethyl 2-azido-3,4-dihydroxybutanoate (4)



To the solution of azido alcohol **5** (5 gm, 21 mmol) in THF (60 mL) was added BH_3.DMS (2.2 mL, 20 mmol) dropwise at room

temperature. The reaction mixture was stirred further for half an hour (until the bubbles stop). Catalytic amount of $NaBH_4$ (5 mol%, 38 mg) was added at 0 ºC (exothermic reaction) and further stirred for 4 hours at room temperature. Reaction mixture was quenched by adding ethanol (100 mL) and PTSA (300 mg) and after being stirred for 30 min at room temperature the reaction mixture was concentrated *in vacuo*. The resulting gum was dissolved in ethanol-benzene solution (1:1) and concentrated repeatedly in order to remove the $B(OEt)_3$ to get the colorless compound. The crude product on flash chromatography using silica gel (pet ether /ethyl acetate 6.5 / 3.5) provided the diol **4** as a colorless thick liquid (2.45 gm, 60%).

Molecular formula **:** $C_6H_{11}N_3O_4$

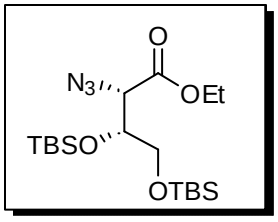
Yield **:** 60%

IR ($CHCl_3$) υ_{max} **:** 3479, 2986, 2941, 2121, 1747, 1207, 1028 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.30 (q, *J* = 7.2 Hz, 2H), 4.05 (d, *J* = 7 Hz, 1H), 3.68-4.12 (m, 2H), 3.99-3.94 (m, 1H), 3.77-3.68 (m, 2H), 2.57 (bs, 2H), 1.36 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 169.2, 71.7, 63.1, 62.6, 62.3, 13.9.

(2*S*,3*R*)-Ethyl 2-azido-3,4-bis((*tert*-butyldimethylsilyl)oxy)butanoate (8)



To the solution of diol **4** (2 gm, 10 mmol) dissolved in DCM (25 mL) was added tri-ethylamine (7.3 mL, 50 mmol) and was cooled to 0 ºC. To the reaction mixture was added TBDMSOTf (5.7 mL, 25 mmol) dropwise and the reaction mixture was further stirred for 10 min at 0 ºC. Water (20 mL) was added and the organic and aqueous layers were allowed to separate. The aqueous layer was extracted twice using DCM (2 x 20 mL). The collected organics were dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified using flash chromatography (SiO_2) (5:95 EtOAc: pet ether) to furnish di-TBS compound **16** as a colorless liquid (3.75 gm, 85%).

Molecular formula **:** $C_{18}H_{39}N_3O_4Si_2$

Yield **:** 85%

$[\alpha]_D^{25}$ **:** +20º (c 1.0, $CHCl_3$)

IR ($CHCl_3$) υ_{max} **:** 3020, 2931, 2859, 2111, 1744, 1215 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.21 (q, *J* = 7.1 Hz, 2H), 4.09-4.06 (m, 2H), 3.77-3.62 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.07 (s, 6H)

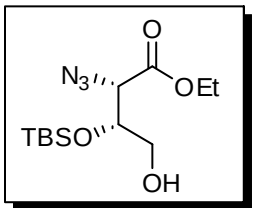
^{13}C-NMR (50 MHz, $CDCl_3$) : δ 167.9, 74.4, 64.3, 63.8, 61.4, 25.9, 25.7, 18.4, 18.0, 14.2, –4.4, –5.1, –5.4, –5.5.

ESIMS (m/z) **:** 418 $(M+H)^+$, 440 $(M+Na)^+$.

Elemental analysis **:** Calculated C, 51.76; H, 9.41; N, 10.06%

Found C, 51.73; H, 9.42; N, 10.08%

(2*S*,3*R*)-Ethyl 2-azido-3-((*tert*-butyldimethylsilyl)oxy)-4-hydroxybutanoate (9)



To the di-TBS compound **8** (2 gm, 5 mmol) in anhydrous methanol (30 mL) was added PPTS (4.8 gm, 19 mmol) at once at room temperature. The reaction mixture was further stirred for 20 h at room temperature. Methanol was removed under reduced pressure and water (20 mL) was added to residue and extracted using DCM (3 x 20 mL). The collected organics were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified using flash column chromatography (SiO_2) (30:70 EtOAc: pet ether) to furnish azido alcohol **9** (1.13 gm, 78 %) as a colorless liquid.

Molecular formula **:** $C_{12}H_{25}N_3O_4Si$

Yield **:** 78%

$[\alpha]_D^{25}$ **:** +12º (c 1.0, $CHCl_3$)

IR ($CHCl_3$) υ_{max} **:** 3514, 3020, 2956, 2858, 2112, 1730, 1216 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.25 (t, *J* = 7.2 Hz, 3H), 4.12-4.08 (m, 1H), 3.74-3.67 (m, 2H), 1.96 (bs, 1H), 1.34 (t, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.11

(s, 6H).

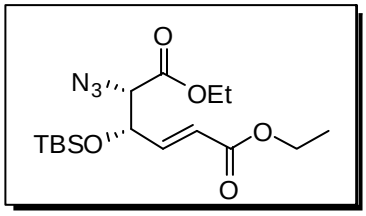
^{13}C-NMR (50 MHz, $CDCl_3$) : δ 168.5, 73.3, 63.9, 62.9, 61.8, 25.6, 17.8, 14.1, –4.6, –5.1.

ESIMS (m/z) **:** 304 $(M+H)^+$.

Elemental analysis **:** Calculated C, 47.50; H, 8.30; N, 13.85%

Found C, 47.51; H, 8.34; N, 13.84%

(4*S*,5*S*)-Diethyl 5-azido-4-((*tert*-butyldimethylsilyl)oxy)hex-2-enedioate (3)



To the azido alcohol **9** (1 gm, 3.3 mmol) in ethyl acetate (15 mL) was added IBX (1.8 gm, 6.6 mmol) and the reaction mixture was heated at reflux for 3.5 h. The reaction mixture was allowed to cool to room temperature and then filtered through Whatman filter paper. The filtrate was concentrated under reduced pressure to get the crude aldehyde as a colorless sticky liquid. The crude aldehyde was dissolved in toluene (20 mL) and to that was added Ph_3PCHCO_2Et (2.3 gm, 6.6 mmol). The reaction mixture was heated at reflux for 4h and cooled to room temperature. Pet ether (10 mL) was added and filtered, this was repeated for 3 times. The collected organics were concentrated *in vacuo* and the crude product was purified using flash chromatography (SiO_2) (05:95 EtOAc: pet ether) to furnish the α,β-unsaturated ester **3** (0.92 gm, 75% over two steps) as a colorless liquid.

Molecular formula **:** $C_{16}H_{29}N_3O_5Si$

Yield **:** 75%

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

IR ($CHCl_3$) υ_{max} **:** 2932, 2859, 2113, 1739, 1726, 1662, 1261 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.87 (dd, *J* = 15.7, 5.7 Hz, 1H), 6.06 (dd, *J* = 15.7, 1.4 Hz, 1H), 4.69 (t, 6.8, 1H), 4.31-4.17 (m, 4H), 3.95 (d, *J* = 5.3 Hz, 1H), 1.36-1.29 (m, 6H), 0.92 (s, 9H), 0.12 (s, 3H), 0.08, (s, 3H).

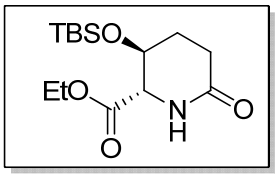
^{13}C-NMR (50 MHz, $CDCl_3$): δ 167.3, 165.5, 144.9, 123.5, 73.1, 66.1, 62.0, 60.6, 25.7, 18.1, 14.3, 14.2, –4.4, –5.1.

ESIMS (m/z) **:** 394 $(M+Na)^+$

Elemental analysis **:** Calculated C, 51.73; H, 7.87; N, 11.31%

Found C, 51.70; H, 7.88; N, 11.35%

(2*S*,3*S*)-Methyl 3-((*tert*-butyldimethylsilyl)oxy)-6-oxopiperidine-2-carboxylate (2)



The azido ester **3** (0.8 gm, 2.2 mmol) was dissolved in ethanol (10 mL) and to that was added catalytic amount of palladium hydroxide over carbon (20%, 10 mg) under argon atmosphere. The resulting reaction mixture was stirred under hydrogen atmosphere using balloon for 2 hours. The reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography using silica gel (30:70 EtOAc: pet ether) to provide amide **2** (0.52 g, 80%) as a colorless thick oil.

Molecular formula **:** $C_{14}H_{27}NO_4Si$

Yield **:** 90%

$[\alpha]_D^{25}$ **:** +26º (c 1.5, $CHCl_3$)

IR ($CHCl_3$) υ_{max} **:** 3399, 2955, 2857, 1732, 1643, 1215 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 5.96 (bs, 1H), 4.39-4.35 (m, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.02-3.99 (m, 1H), 2.72-2.54 (m, 1H), 2.40-2.26 (m, 1H), 1.88-1.79 (m, 2H), 1.68 (bs, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.90 (s, 9H), 0.12 (s, 6H).

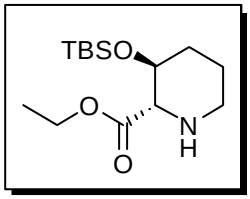
^{13}C-NMR (50 MHz, $CDCl_3$): δ 171.4, 170.1, 65.4, 62.3, 61.8, 26.5, 26.4, 25.6, 17.9, 14.1, –4.90, –5.1.

ESIMS (m/z) **:** 302 $(M+H)^+$

Elemental analysis **:** Calculated C, 55.78; H, 9.03; N, 4.65%

Found C, 55.79; H, 9.01; N, 4.68%

(2*S*, 3*S*)-Ethyl 3-((*tert*-butyldimethylsilyl)oxy)piperidine-2-carboxylate (10)



To the amide **2** (200 mg, 0.7 mmol) in anhydrous THF (5 mL) was added BH_3.DMS (0.2 mL, 2 mmol) dropwise at 0 ºC. The resulting reaction mixture was further stirred at 5 ºC for 20 h. Methanol (excess) was added to the reaction mixture, stirred for 4 hours and concentrated under reduced pressure. Water (10 mL) was added and the reaction mixture was extracted using DCM (3 x 10 mL). The collected organics were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude product which was purified using flash chromatography over silica gel (70:30 EtOAc: pet ether) to furnish amine **10** (147 mg, 78%) as a colorless dense liquid.

Molecular formula **:** $C_{14}H_{29}NO_3Si$

Yield **:** 78%

$[\alpha]_D^{25}$ **:** +27º (c 1.0, $CHCl_3$)

IR ($CHCl_3$) υ_{max} **:** 3436, 3020, 2931, 2400, 1731, 1215 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.39-4.31 (m, 1H), 4.18-4.10 (m, 1H), 3.98 (m, 1H), 3.78 (dt, *J* = 10.5, 5.4 Hz, 1H), 3.32 (d, *J* = 13.5 Hz, 1H), 3.11 (dd, *J* = 10.1, 1.1 Hz, 1H), 2.53-2.64 (m, 1H), 2.01-2.05 (m, 1H), 1.87-1.84 (m, 1H), 1.68-1.58 (m, 2H), 1.51-1.41 (m, 2H), 1.36 (t, *J* = 7.3 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0 (s, 3H)

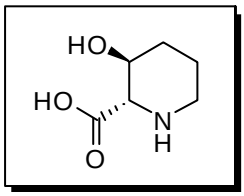
^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.8, 70.5, 70.2, 61.8, 52.2, 32.2, 25.5, 23.1, 17.8, 13.9, –4.2, –5.3.

ESIMS (m/z) **:** 288 $(M+H)^+$, 310 $(M+Na)^+$.

Elemental analysis **:** Calculated C, 58.49; H, 10.17; N, 4.87%

Found C, 58.52; H, 10.16; N, 4.89%

(2*S*,3*S*)-3-Hydroxypiperidine-2-carboxylic acid (1)



A mixture of amine **10** (100 mg, 0.35 mmol) and 5 N HCl (10 mL) was kept at 120 ºC for 3 h. The solvent was removed under reduced pressure and the residue was dissolved in H_2O (50 mL). The mixture was loaded on an ion-exchange column (DOWEX 50W X8) and eluted with H_2O and then with aq. NH_3 solution. The eluate of aq. NH_3 was concentrated to dryness under reduced pressure to give **1** (46 mg, 91%) as a crystalline solid.

Molecular formula **:** $C_6H_{11}NO_3$

Yield **:** 91%

mp **:** 238–243 ºC (dec), lit.[7] 230-238 °C

$[\alpha]_D^{25}$ **:** +13.8 º (c 1.0, HCl 10% aq.) lit. +13º (*c* 0.49, HCl 10% aq.)[6c]

IR ($CHCl_3$) υ_{max} **:** 3287, 2920, 1625, 1405 cm^{-1}.

^{1}H NMR (400 MHz, D_2O) : δ 4.17- 4.13 (m, 1H), 3.83 (d, *J* = 7.8 Hz, 1H), 3.40-3.36 (m, 1H), 3.07-3.12 (m, 1H), 2.22 (s, 1H), 2.02-2.08 (m, 2H), 1.80-1.64 (m, 2H).

^{13}C-NMR (100 MHz, D_2O): δ 170.1, 65.5, 61.0, 42.5, 28.8, 18.6.

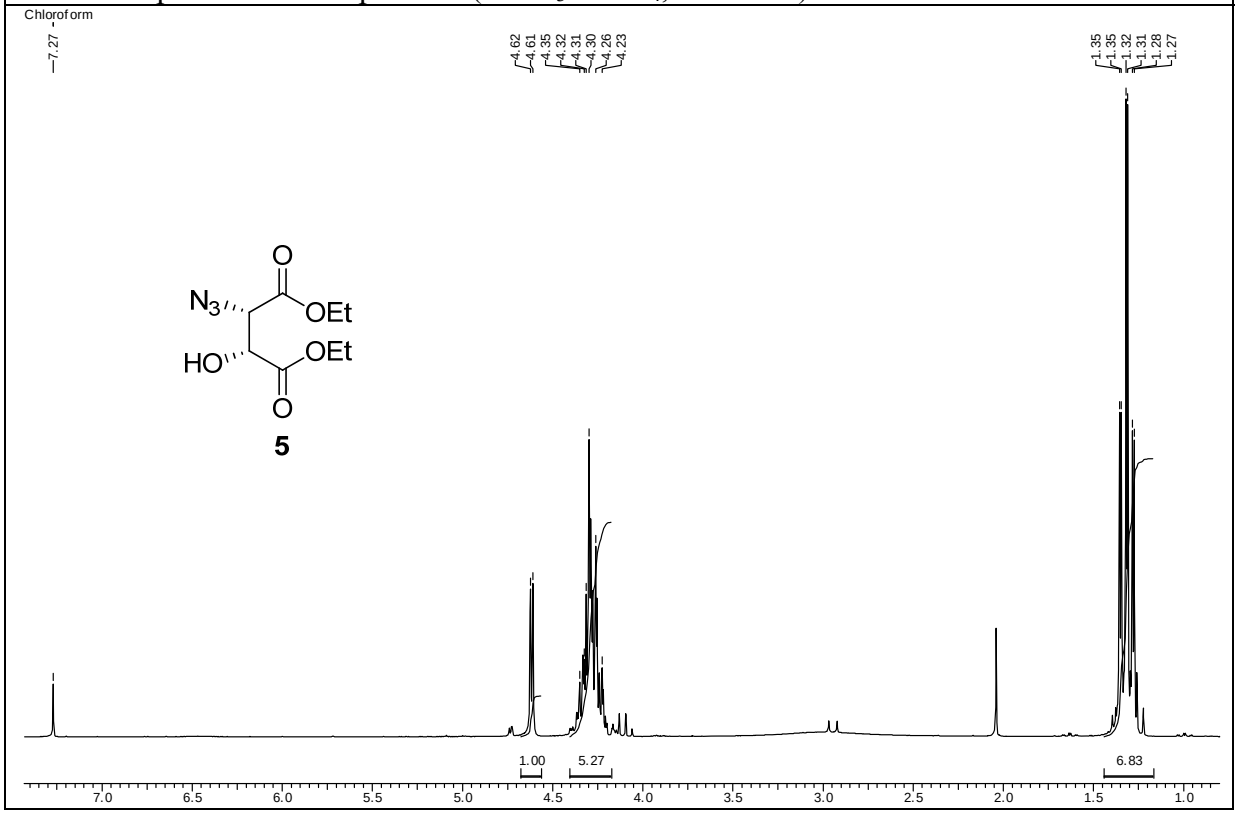
ESIMS (m/z) **:** m/z 146 (M+H)+

Elemental analysis **:** Calculated C, 49.65; H, 7.64; N, 9.65%

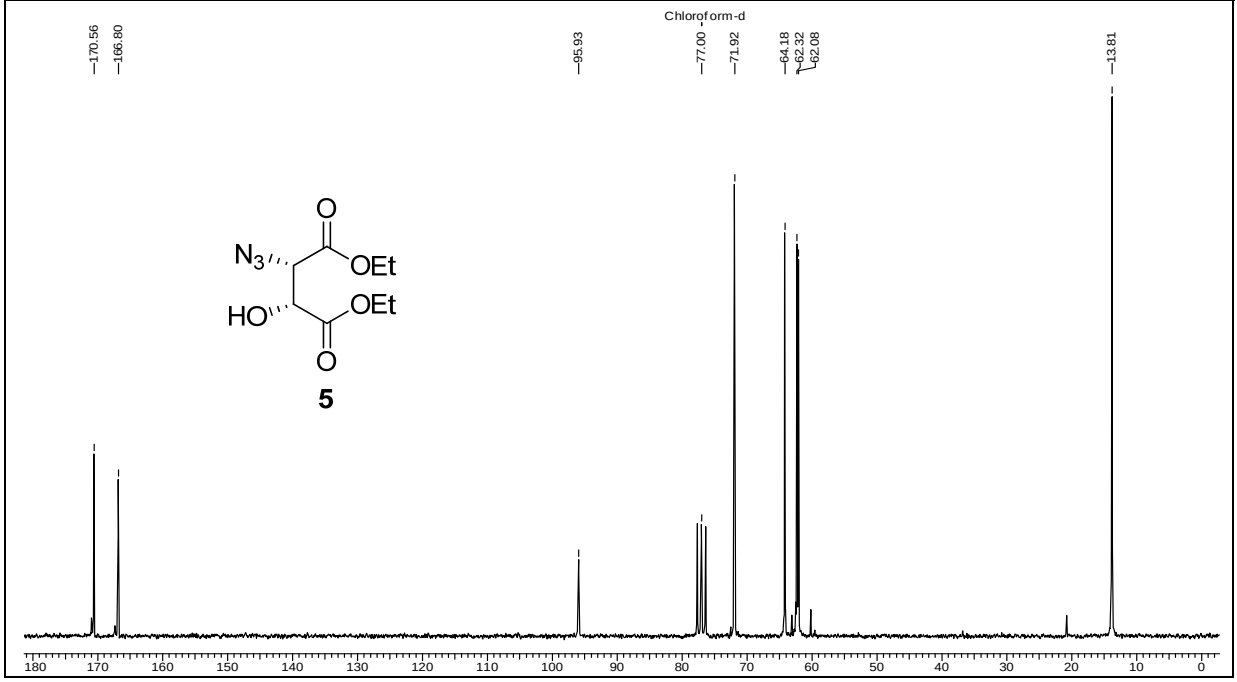
Found C, 49.63; H, 7.65; N, 9.64%

2.2.4 NMR Spectra

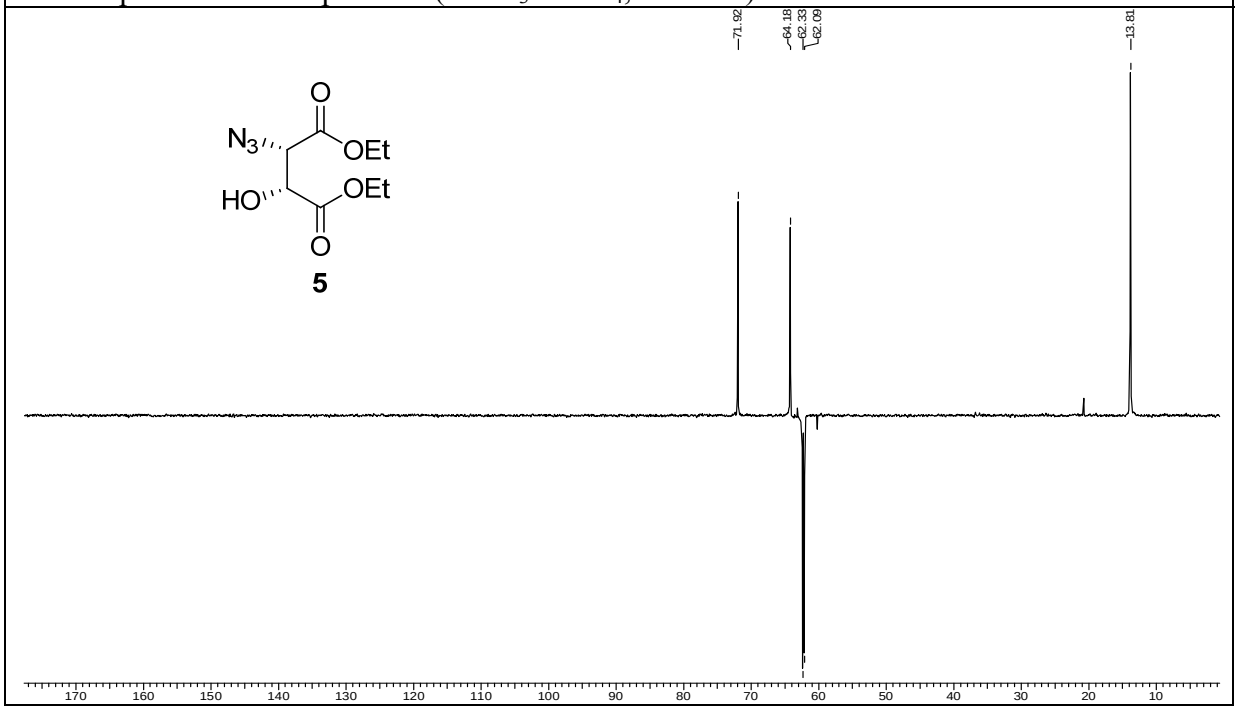
^{1}H-NMR spectrum of compound **5** ($CDCl_3$ + CCl_4, 200 MHz)



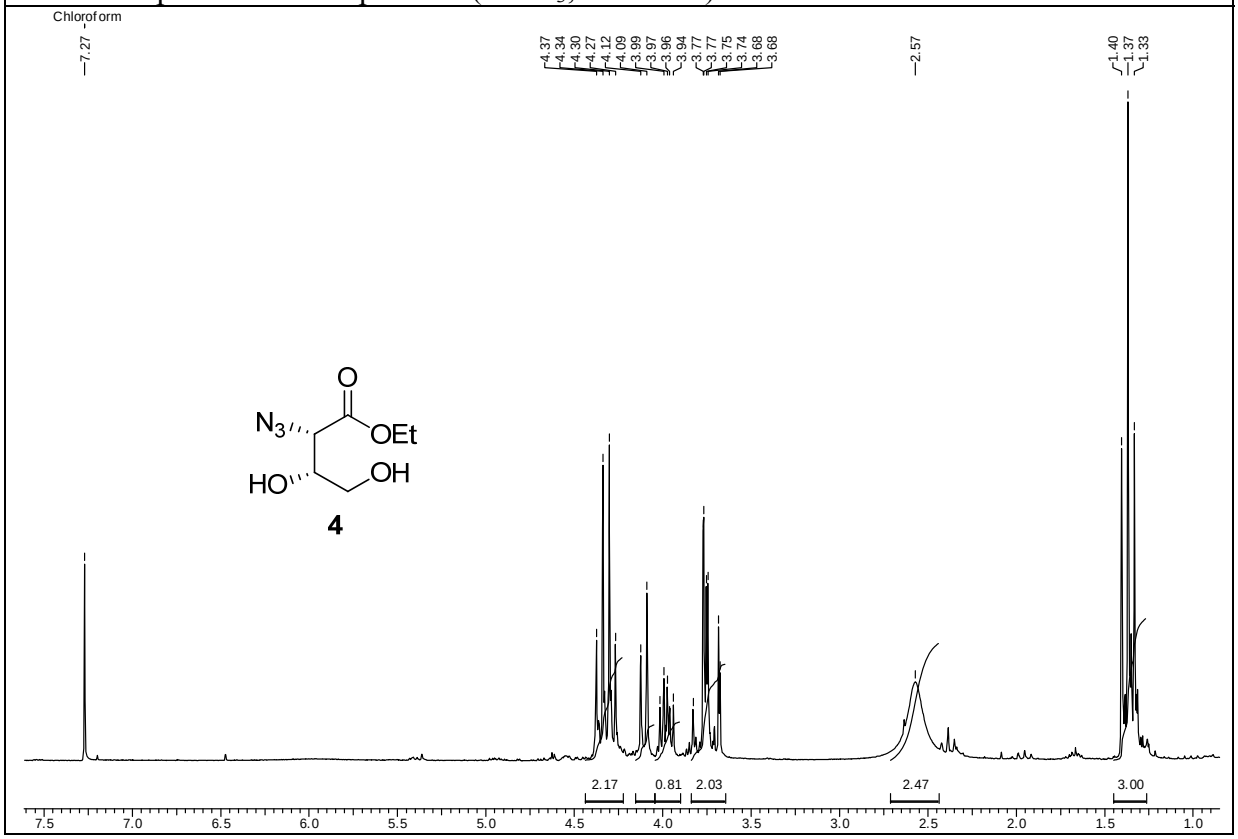
^{13}C-NMR spectrum of compound **5** ($CDCl_3$ + CCl_4, 50 MHz)



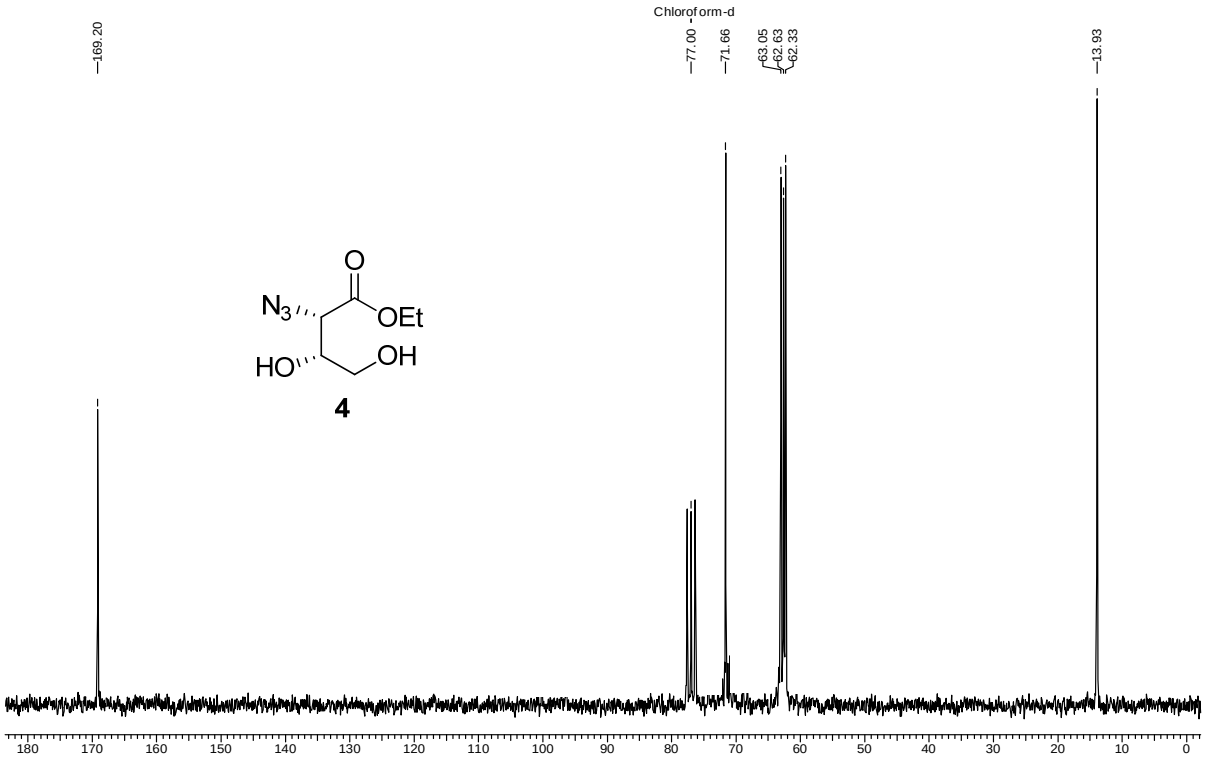
DEPT spectrum of compound **5** ($CDCl_3$ + CCl_4, 50 MHz)



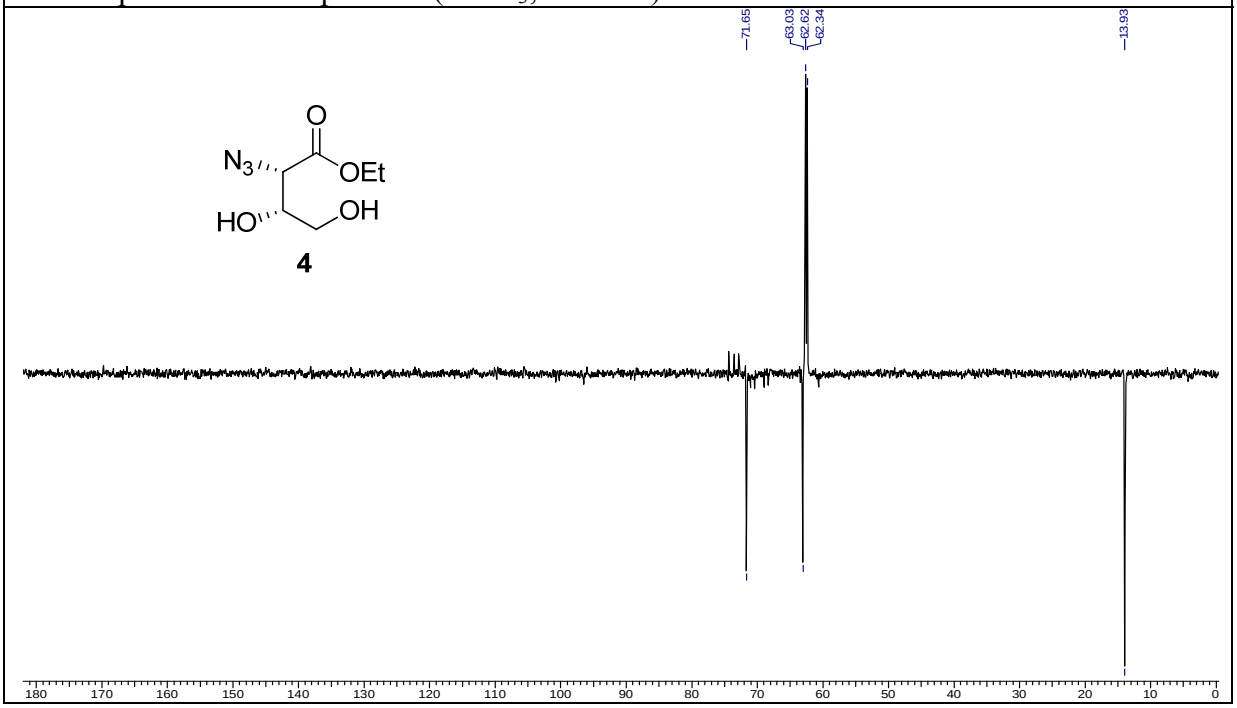
^{1}H-NMR spectrum of compound **4** ($CDCl_3$, 200 MHz)



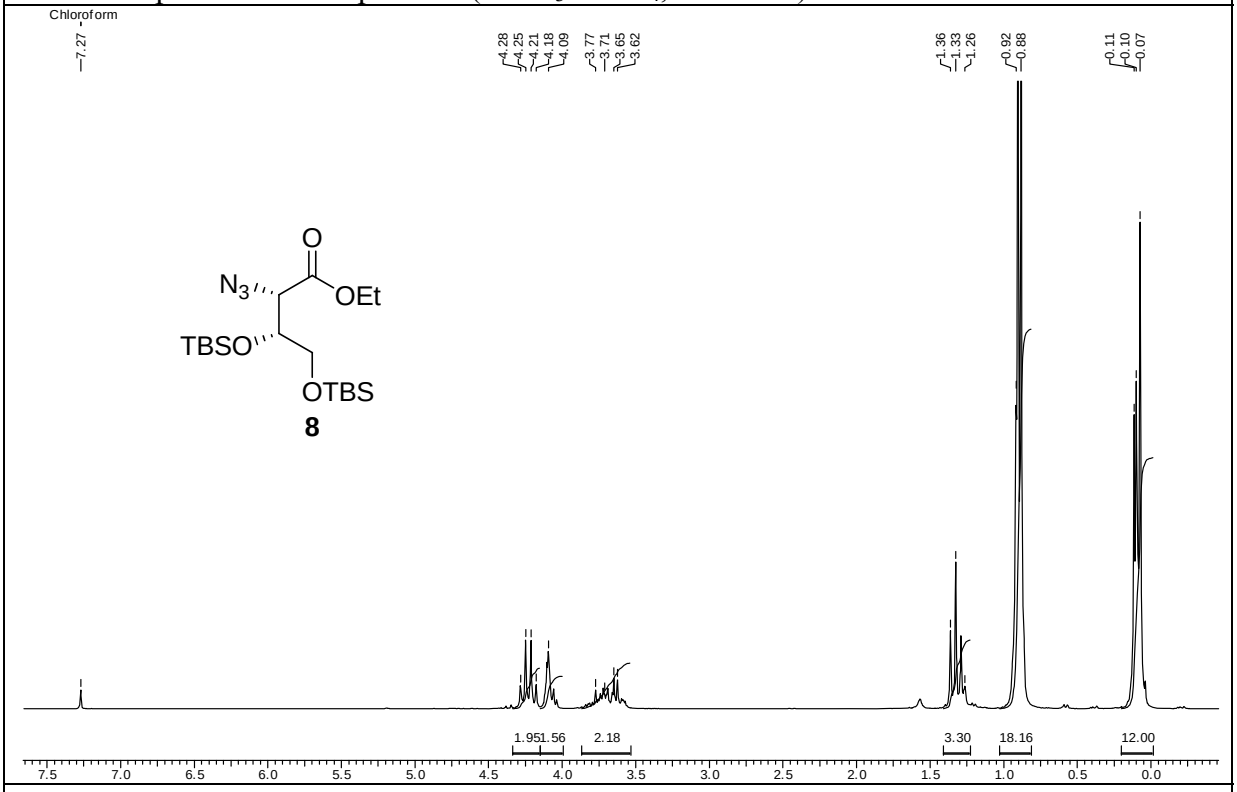
^{13}C-NMR spectrum of compound **4** ($CDCl_3$, 50 MHz)



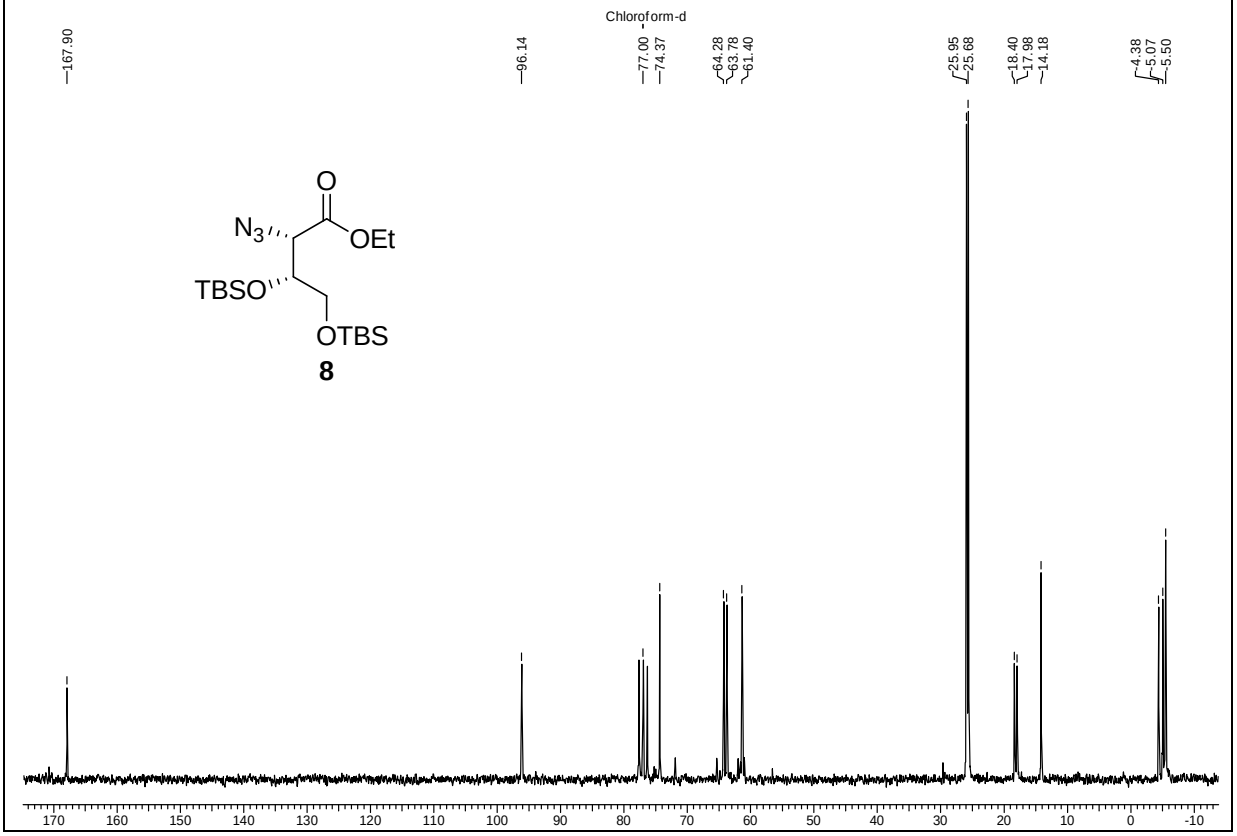
DEPT spectrum of compound **4** ($CDCl_3$, 50 MHz)



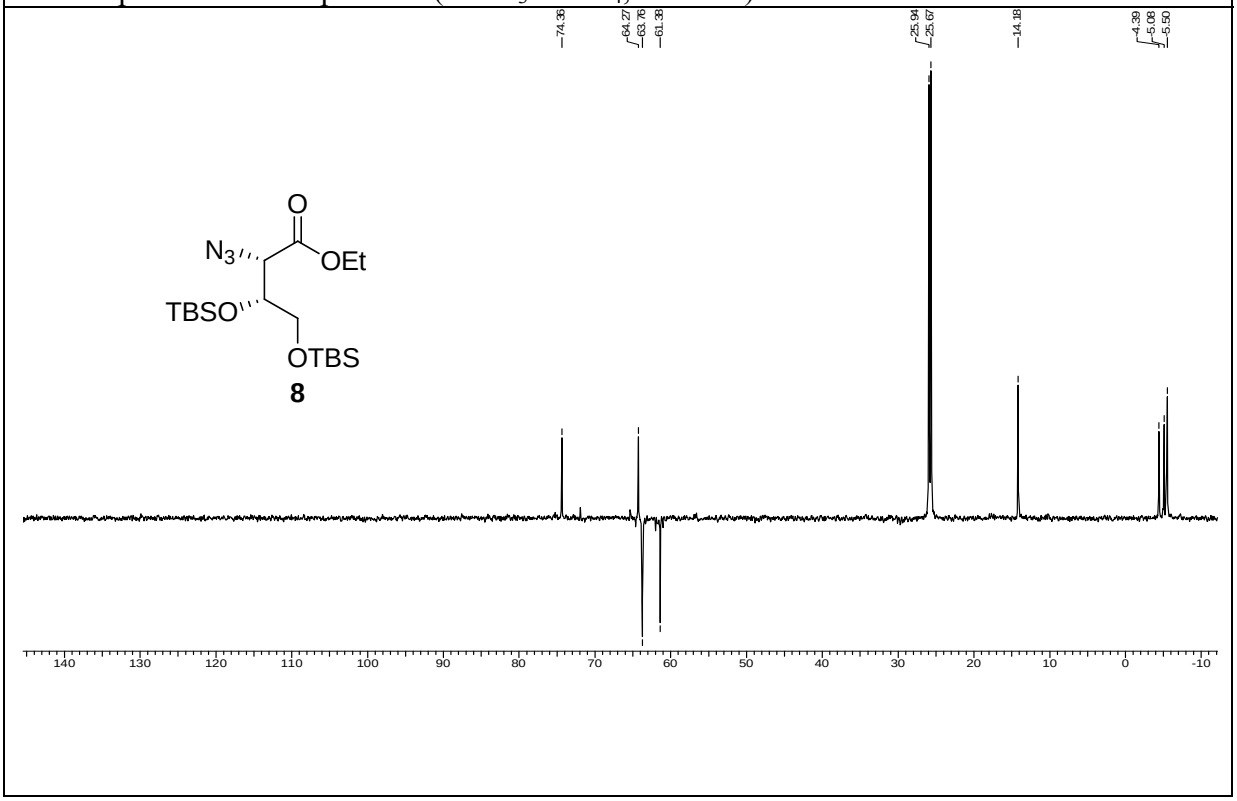
^{1}H-NMR spectrum of compound **8** ($CDCl_3$ + CCl_4, 200 MHz)



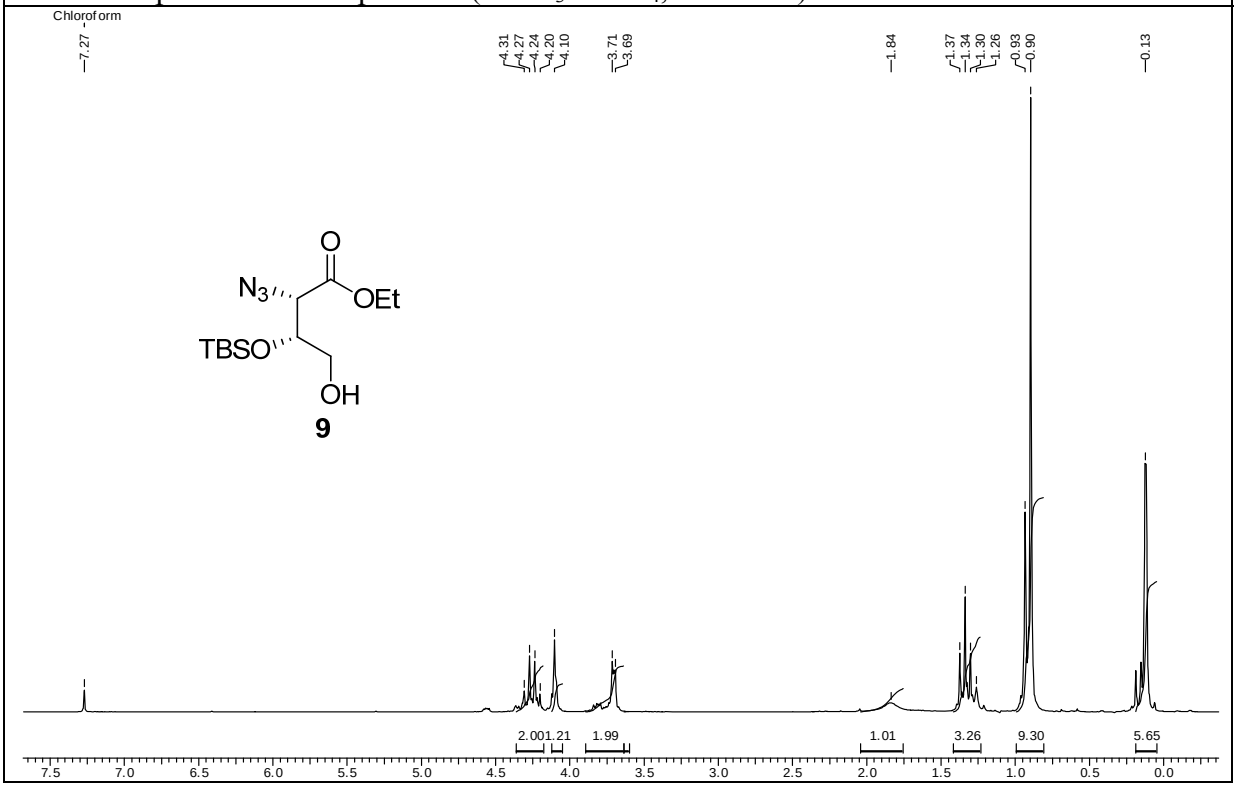
^{13}C-NMR spectrum of compound **8** ($CDCl_3$ + CCl_4, 50 MHz)



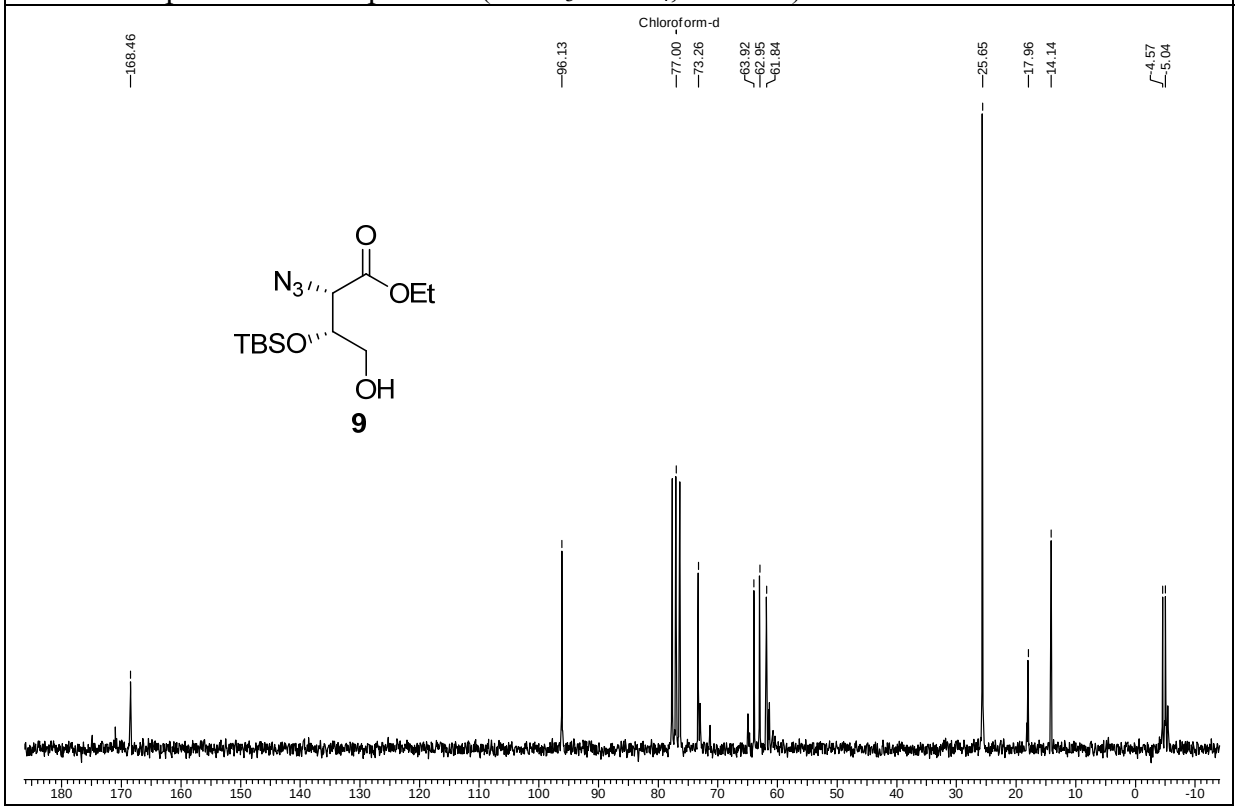
DEPT spectrum of compound **8** ($CDCl_3$ + CCl_4, 50 MHz)



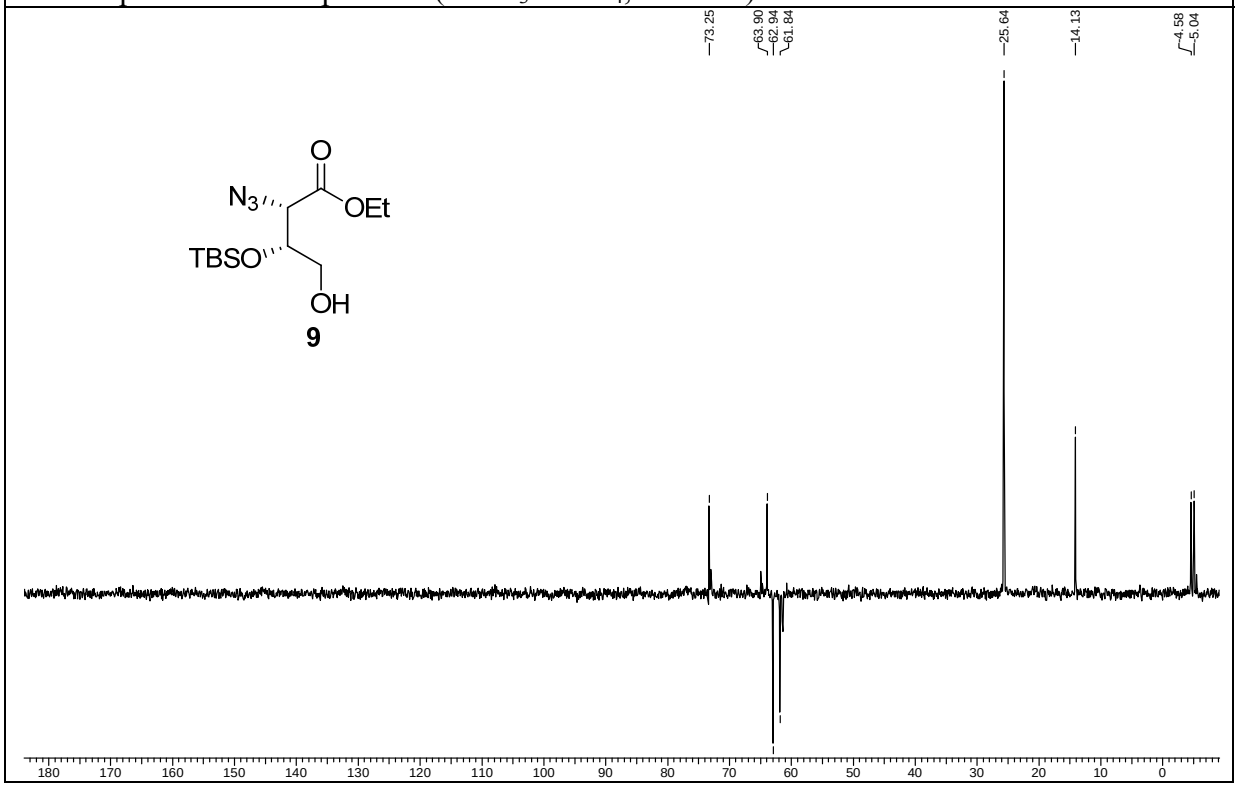
^{1}H-NMR spectrum of compound **9** ($CDCl_3$ + CCl_4, 200 MHz)



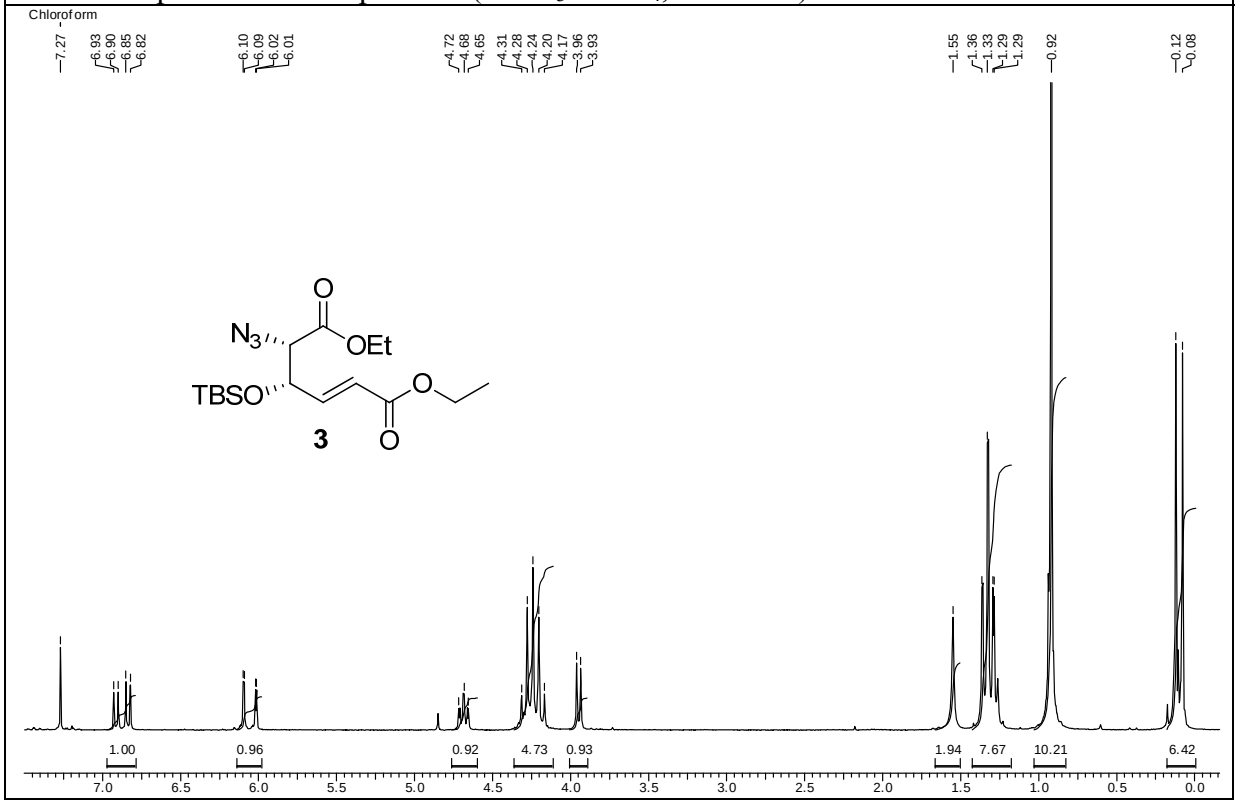
^{13}C-NMR spectrum of compound **9** ($CDCl_3$ + CCl_4, 50 MHz)



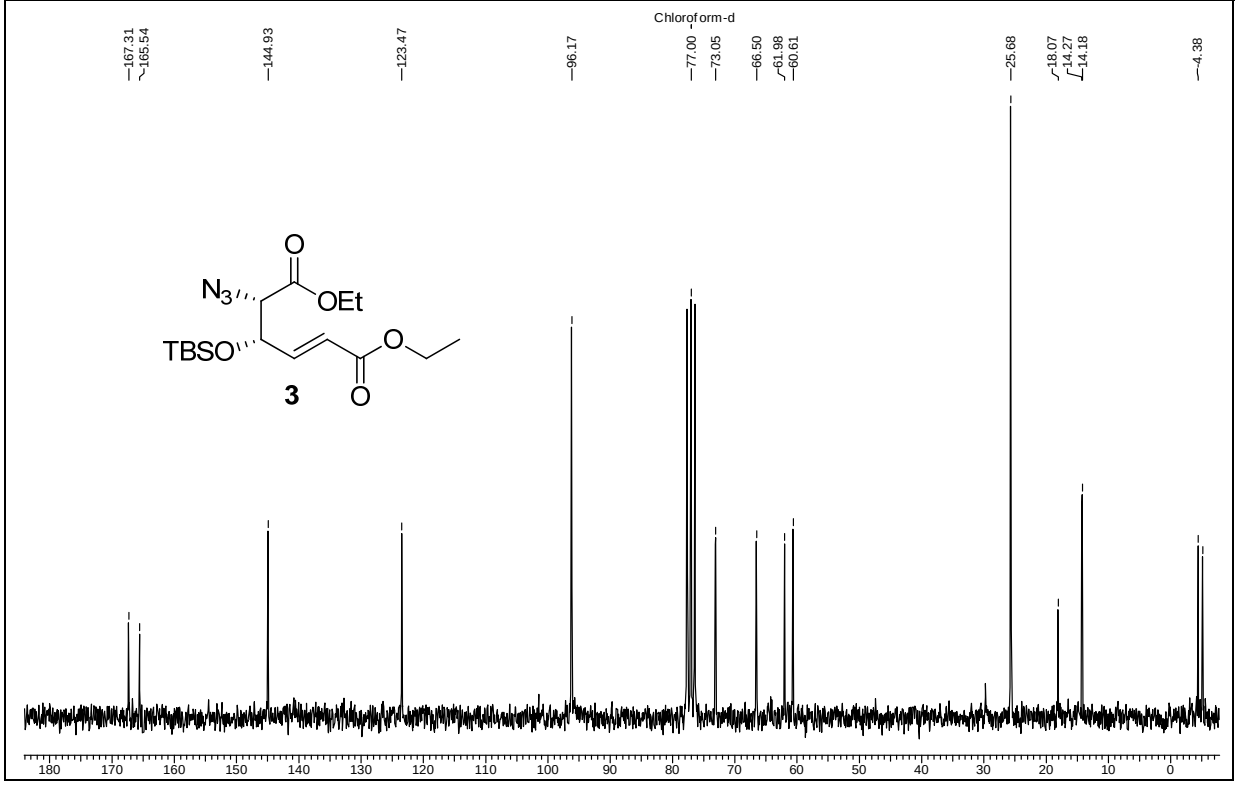
DEPT spectrum of compound **9** ($CDCl_3$ + CCl_4, 50 MHz)



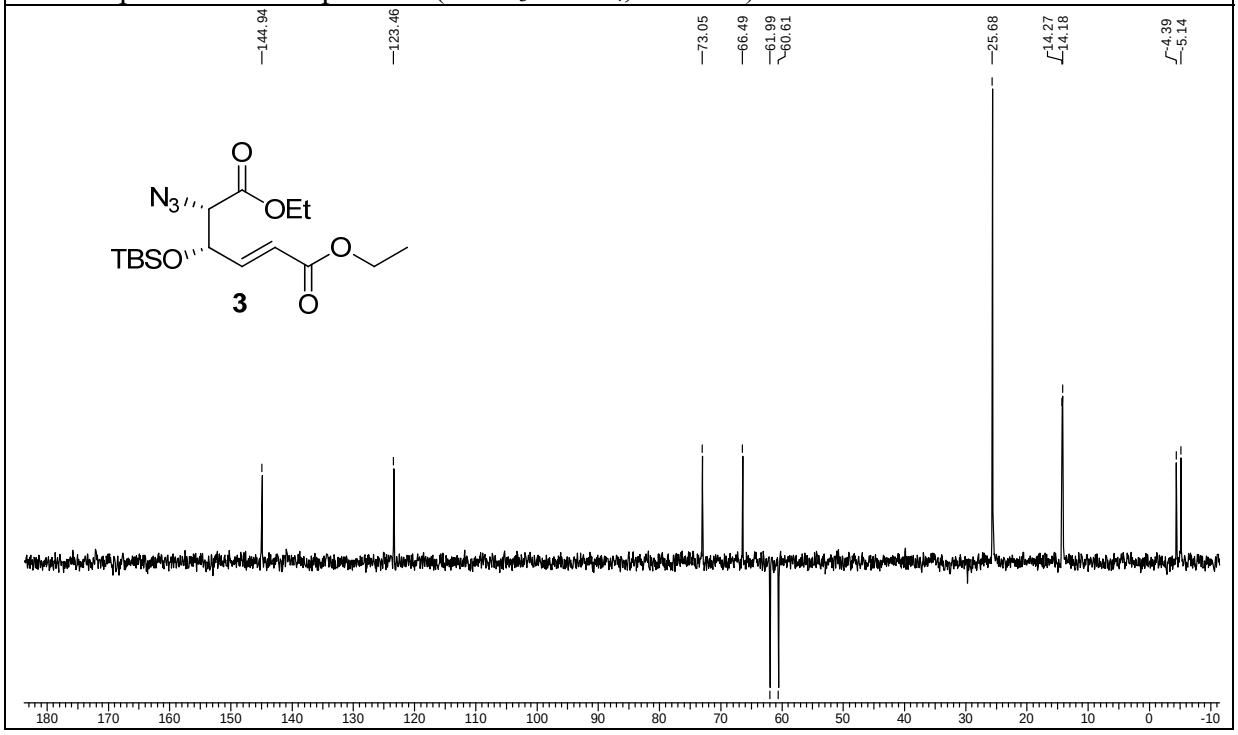
^{1}H-NMR spectrum of compound **3** ($CDCl_3$ + CCl_4, 200 MHz)



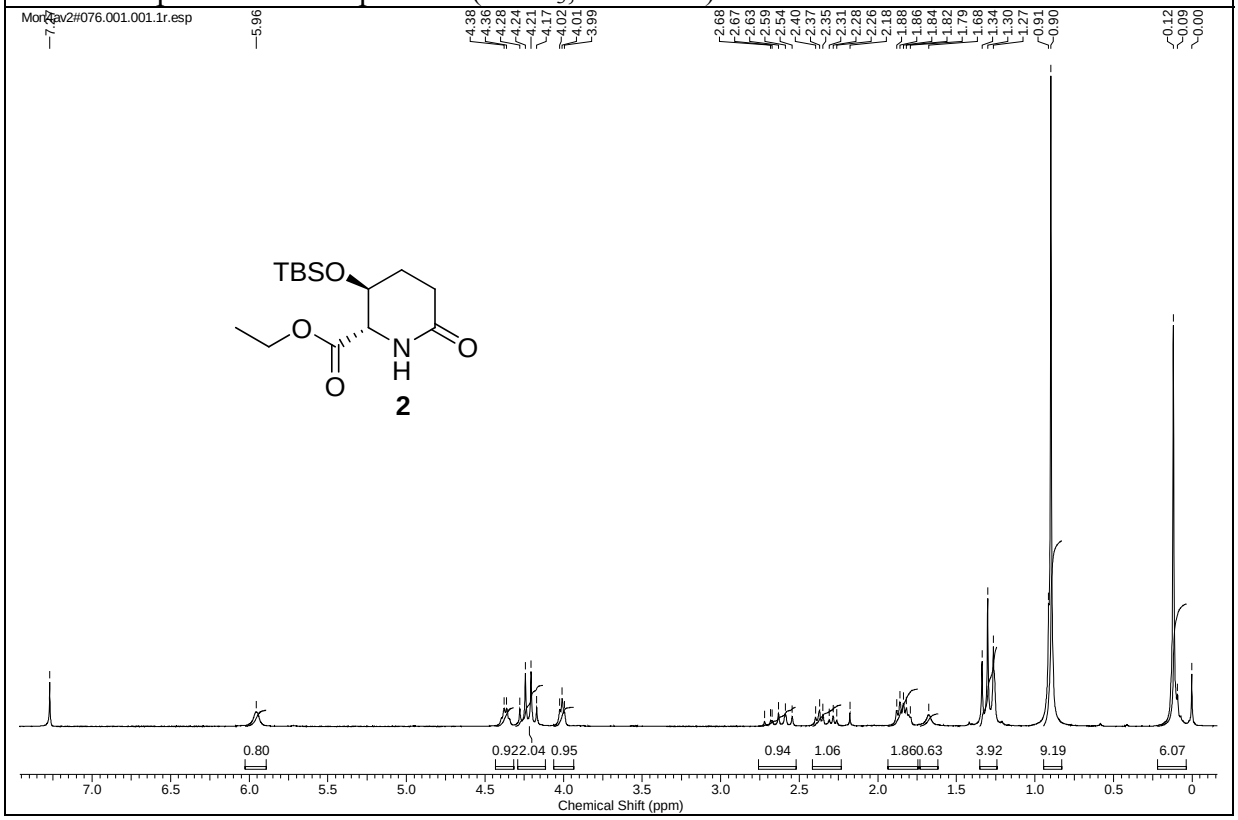
^{13}C-NMR spectrum of compound **3** ($CDCl_3$ + CCl_4, 50 MHz)



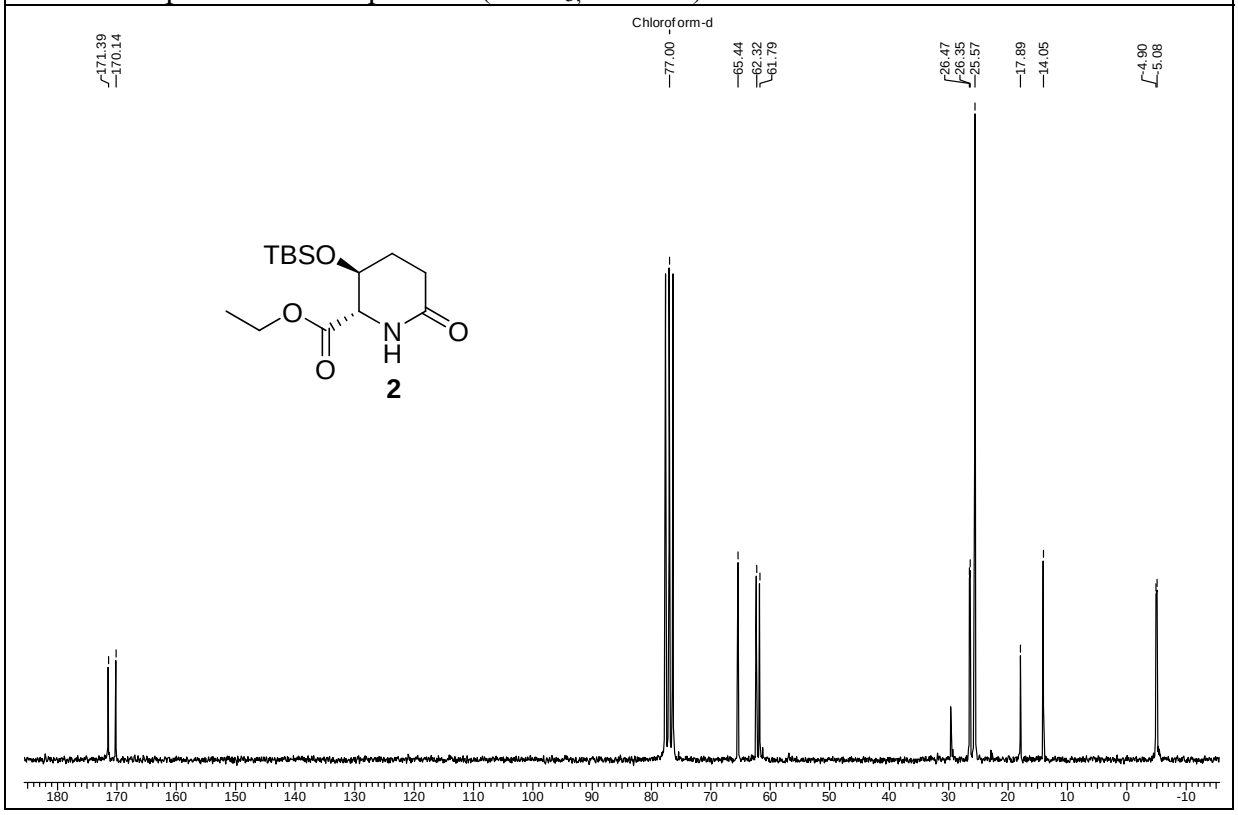
DEPT spectrum of compound **3** ($CDCl_3$ + CCl_4, 50 MHz)



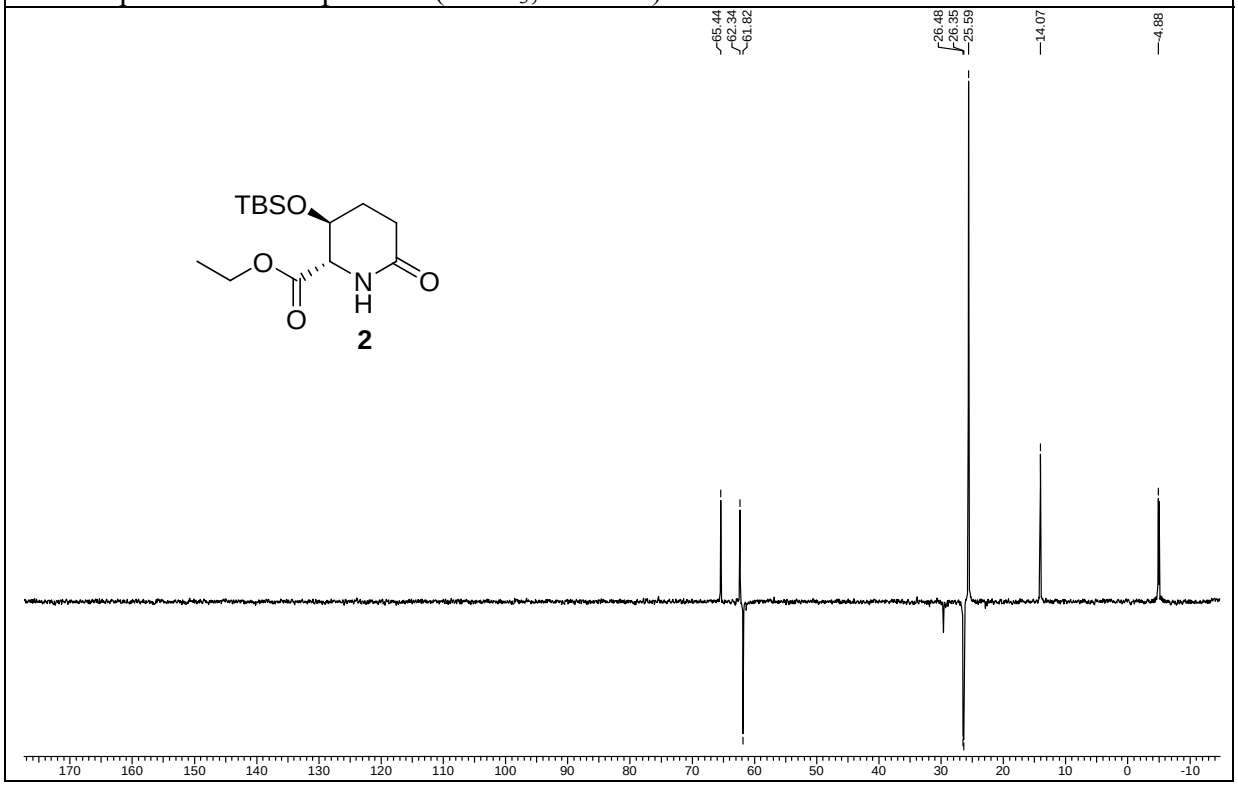
^{1}H-NMR spectrum of compound **2** ($CDCl_3$, 200 MHz)



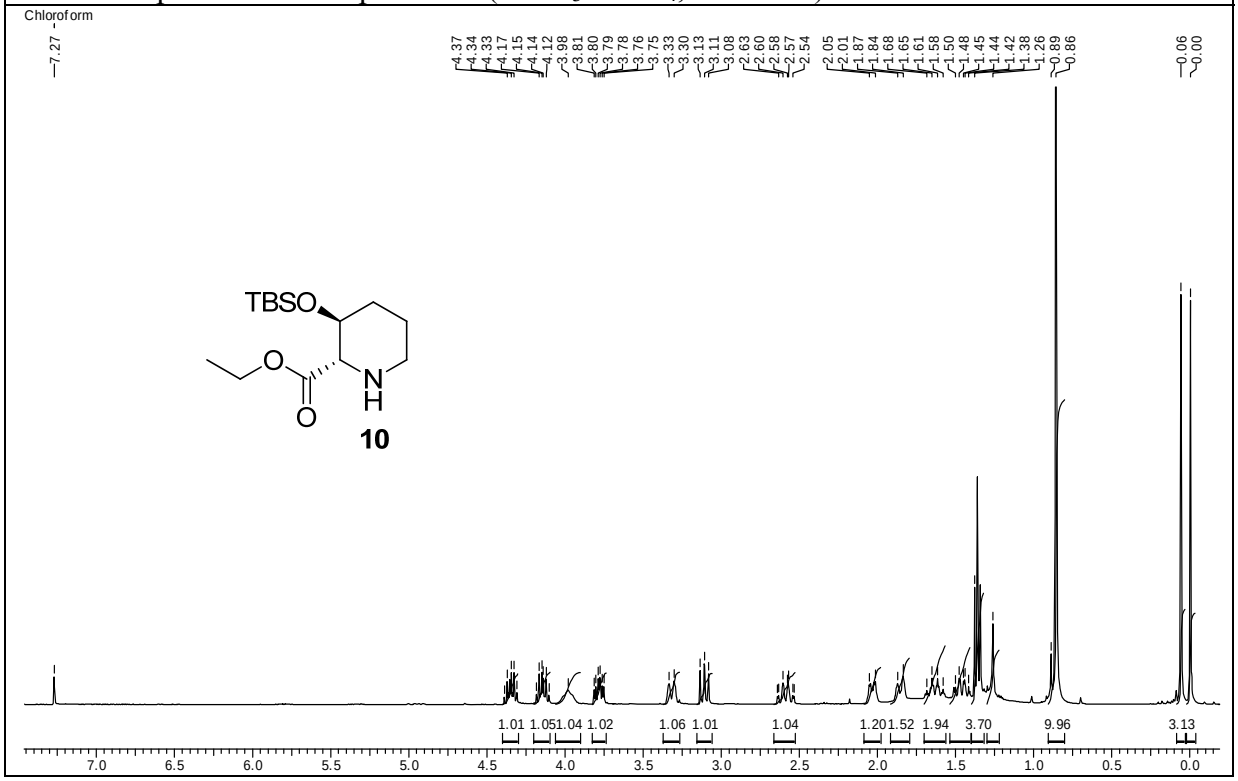
^{13}C-NMR spectrum of compound **2** ($CDCl_3$, 50 MHz)



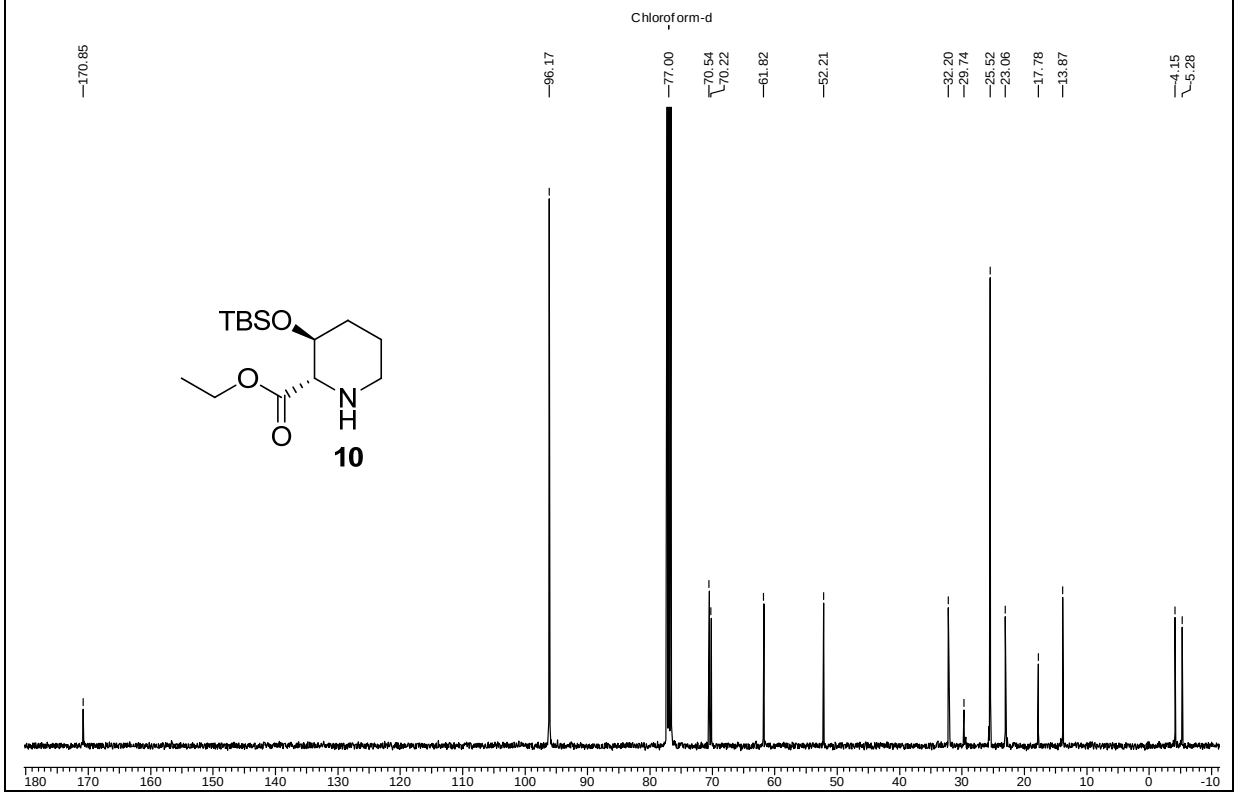
DEPT spectrum of compound **2** ($CDCl_3$, 50 MHz)



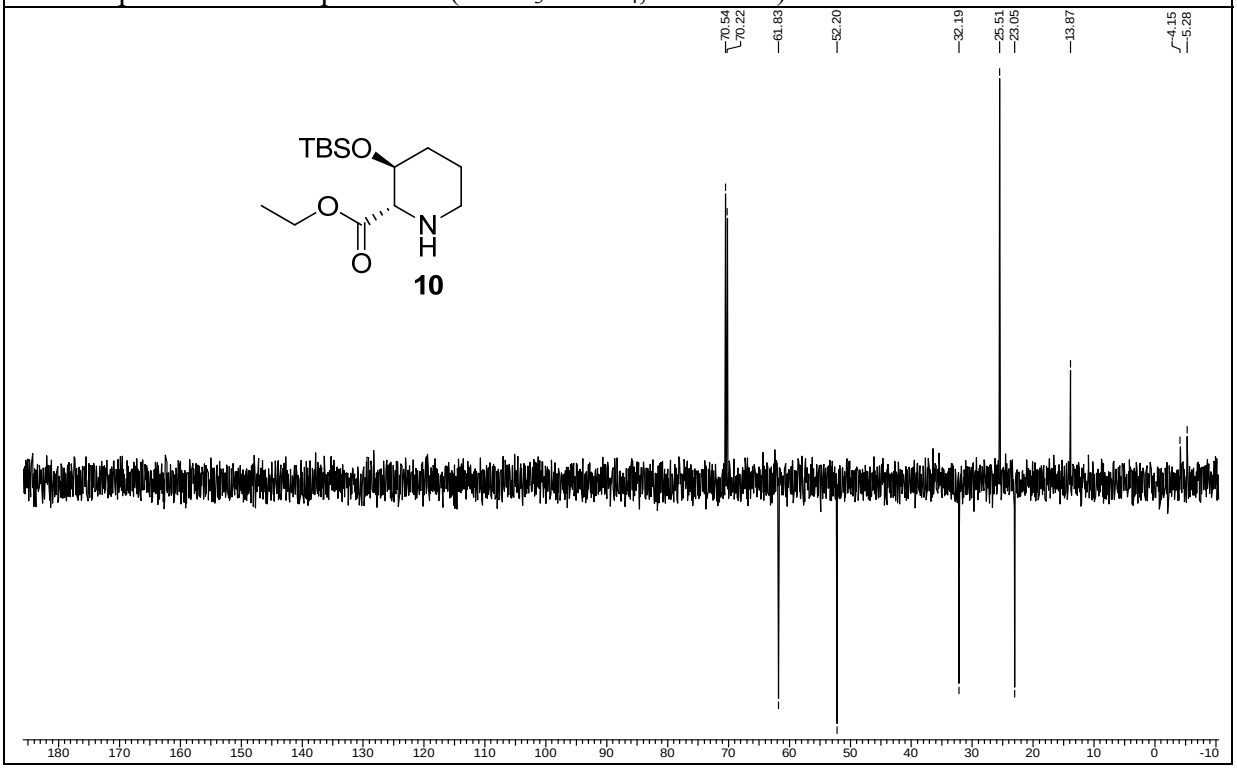
^{1}H-NMR spectrum of compound **10** ($CDCl_3$ + CCl_4, 200 MHz)



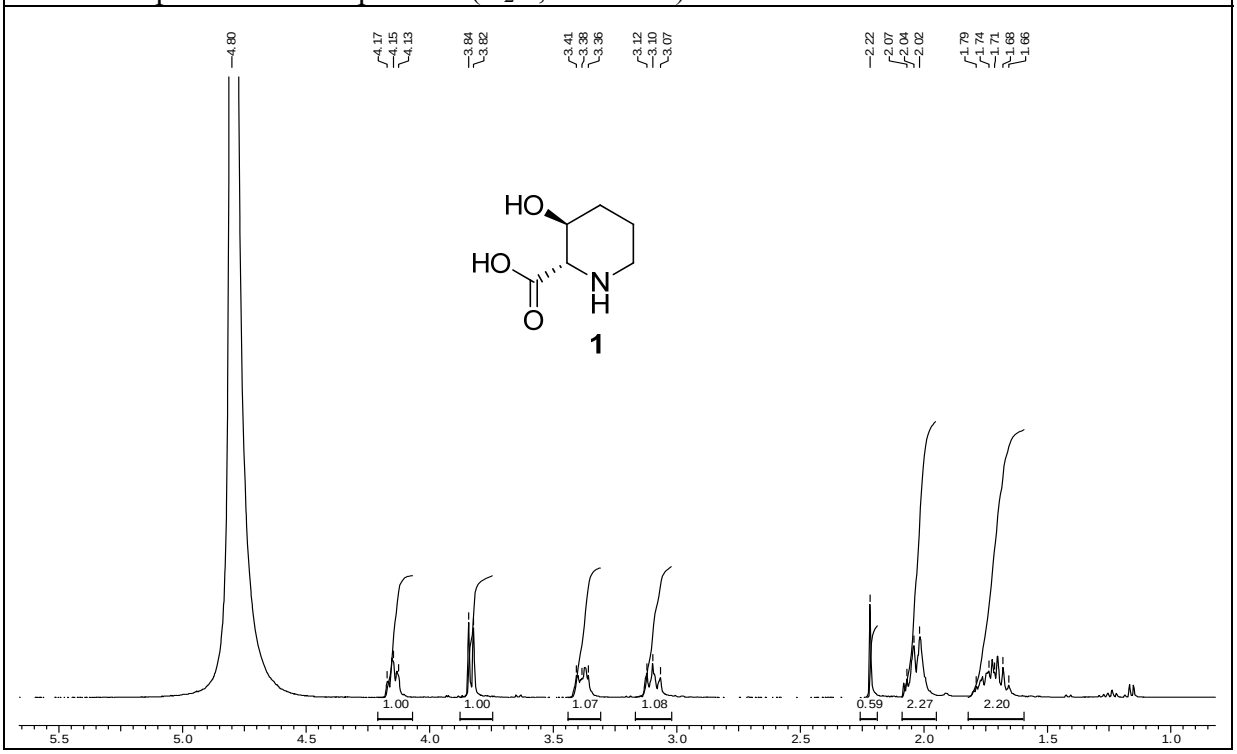
^{13}C-NMR spectrum of compound **10** ($CDCl_3$ + CCl_4, 100 MHz)



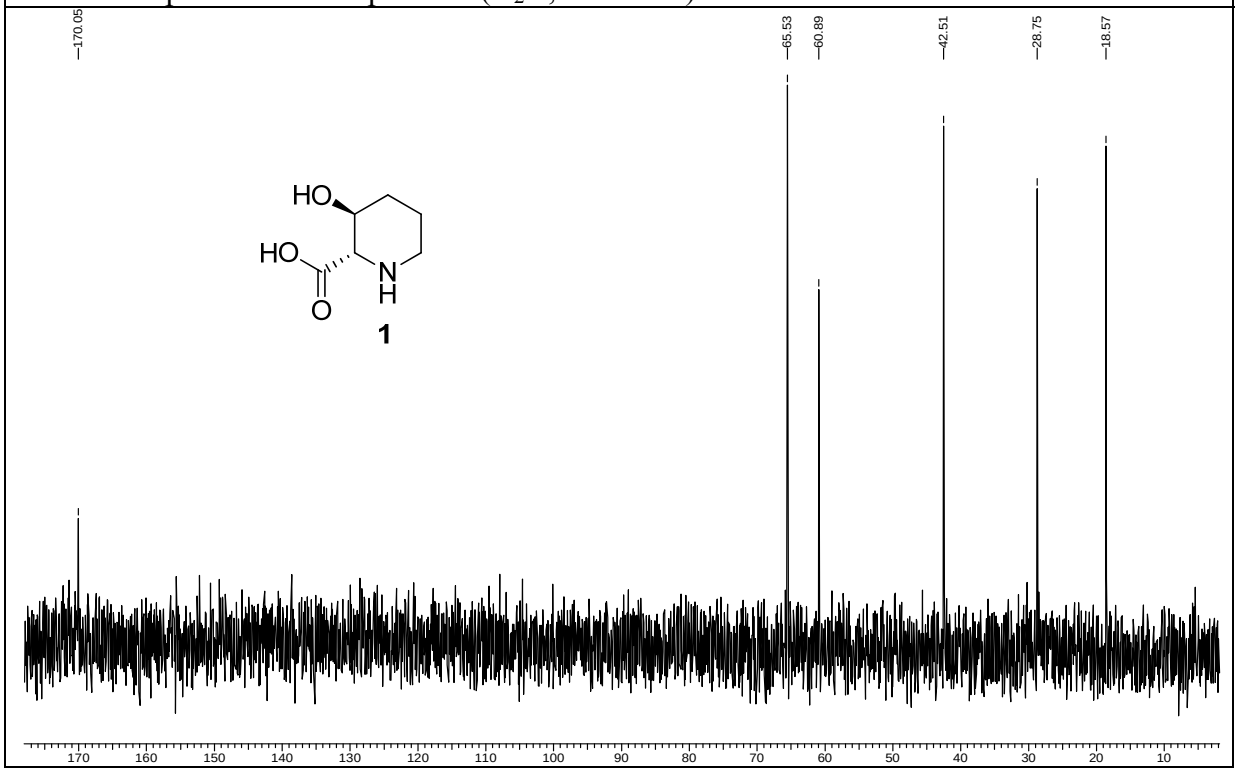
DEPT spectrum of compound **10** ($CDCl_3$ + CCl_4, 100 MHz)



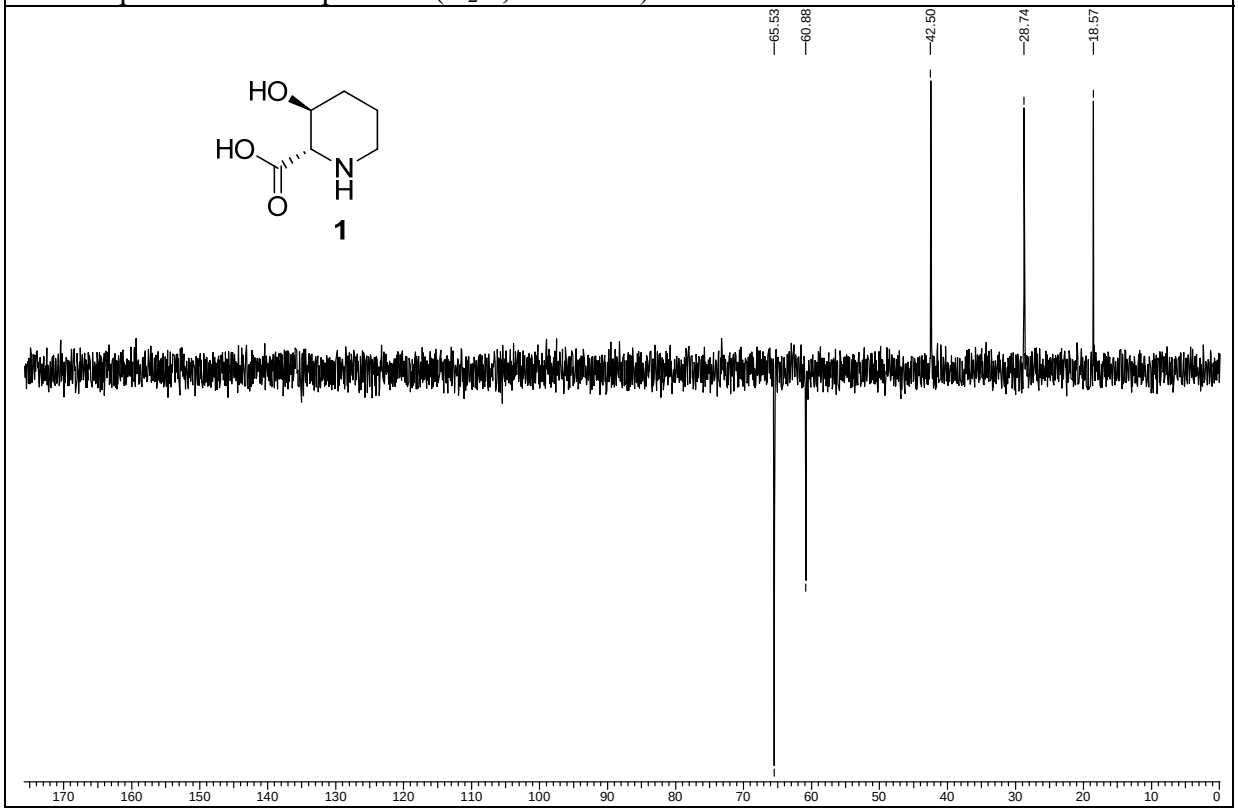
^{1}H-NMR spectrum of compound **1** (D_2O, 400 MHz)



^{13}C-NMR spectrum of compound **1** (D_2O, 100 MHz)



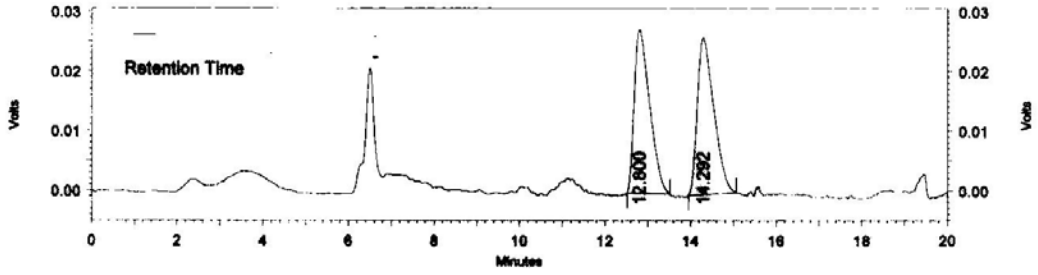
DEPT spectrum of compound **1** (D_2O, 100 MHz)



Chiral HPLC analysis of compound 11:

Column: Chiralcel OJ-H (4.6 x 25 mm)

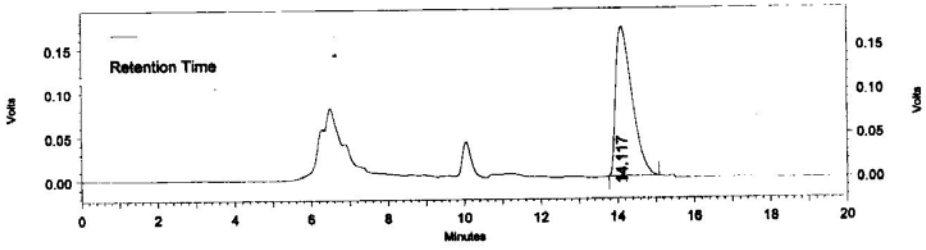
Mobile phase: IPA : PE (95 : 5); wavelength: 210 nm; flow rate: 0.5 mL/min



Detector A - 1 (210nm)

Retention Time	C Area	Area %
12.800	687637	49.324
14.292	706486	50.676
Totals	1394123	100.000

(Racemic)



Detector A - 1 (210nm)

Retention Time	C Area	Area %
14.117	5027015	100.000
Totals	5027015	100.000

(Optically active)

2.3.5 References

1. Chavan, S. P.; Harale, K. R.; Dumare, N. B.; Kalkote, U. R. *Tetrahedron: Asymmetry* **2011,** *22*, 587.
2. Chavan, S. P.; Dumare, N. B.; Harale, K. R.; Kalkote, U. R. *Tetrahedron Lett.* **2011**, *52*, 404.
3. Becker, M. H.; Chua, P.; Downham, R.; Douglas, C. J.; Garg, N. K.; Hiebert, S.; Jaroch, S.; Matsuoka, R. T.; Middleton, J. A.; Ng, F. W.; Overman, L. E. *J. Am. Chem. Soc.* **2007**, *129*, 11987.
4. Kim, K. I.; Lill-Elghanian, D. A.; Hollingsworth, R. I. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1691.
5. For racemic dihydroxy compound (**11**) HPLC chiracel OJ-H column (250 x 4.6 mm). Isopropanol/pet ether = 5:95 flow rate 0.5 ml/min, λ = 210 nm) retention time (min): Rt1 = 12.80; Rt2 = 14.29 (1:1). Enantiomerically pure dihydroxy compound (**11**) HPLC chiracel OJ-H column (250 x 4.6 mm) isopropanol/pet ether = 5:95 flow rate 0.5 ml/min, λ = 210 nm) retention time (min): 14.20 (exclusive).
6. (a) Kim, I. S.; Oh, J. S.; Zee, O. P.; Jung, Y. H. *Tetrahedron* **2007**, *63*, 2622. (b) Chiou, W. H.; Lin, G. H.; Liang, C. W. *J. Org. Chem*. **2010**, *75*, 1748. (c) Lemire, A.; Charette, A. B. *J. Org. Chem.* **2010**, *75*, 2077.
7. Battistini, L.; Zanardi, F.; Rassu, G.; Spanu, P.; Pelosi, G.; Fava, G. G.; Ferrari, M. B.; Casiraghi, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2975.

Chapter 3. Synthetic studies towards stemoamide and development of synthetic methodology for PMB protection of alcohols, selective mono-PMB protection of diols and di-PMB protection of diols

Section 1: Introduction to (–)-stemoamide

3.1.1. Introduction

The stemona class of polycyclic alkaloids represents alkaloids with relatively complex structures (Figure 1).[1]The common feature encountered in this class of alkaloids is the presence of a central pyrrolo[1,2-*a*]azepine core as a characteristic feature.[2] Also the presence of butenolide ring is encountered in a number of stemona alkaloids. More than hundred and thirty stemona alkaloids have been isolated from root extracts of *Stemonaceae* family.[3] The root extracts of *Stemonaceae* family have been used in the traditional Chinese and Japanese folk medicine in the treatment of respiratory diseases and as anthelmintics. The water extracts obtained from the roots of some *Stemonaceae* species were widely used in China against human and cattle parasites, agricultural pests and as domestic insecticides.[1]

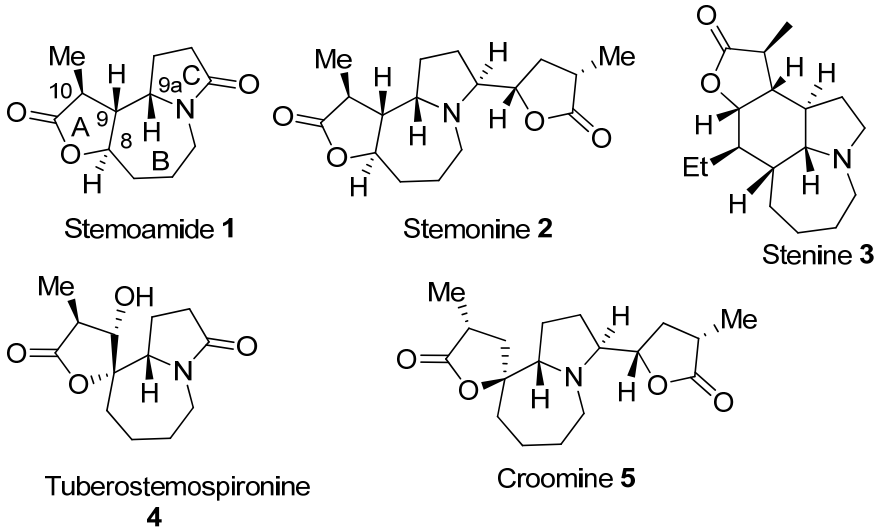


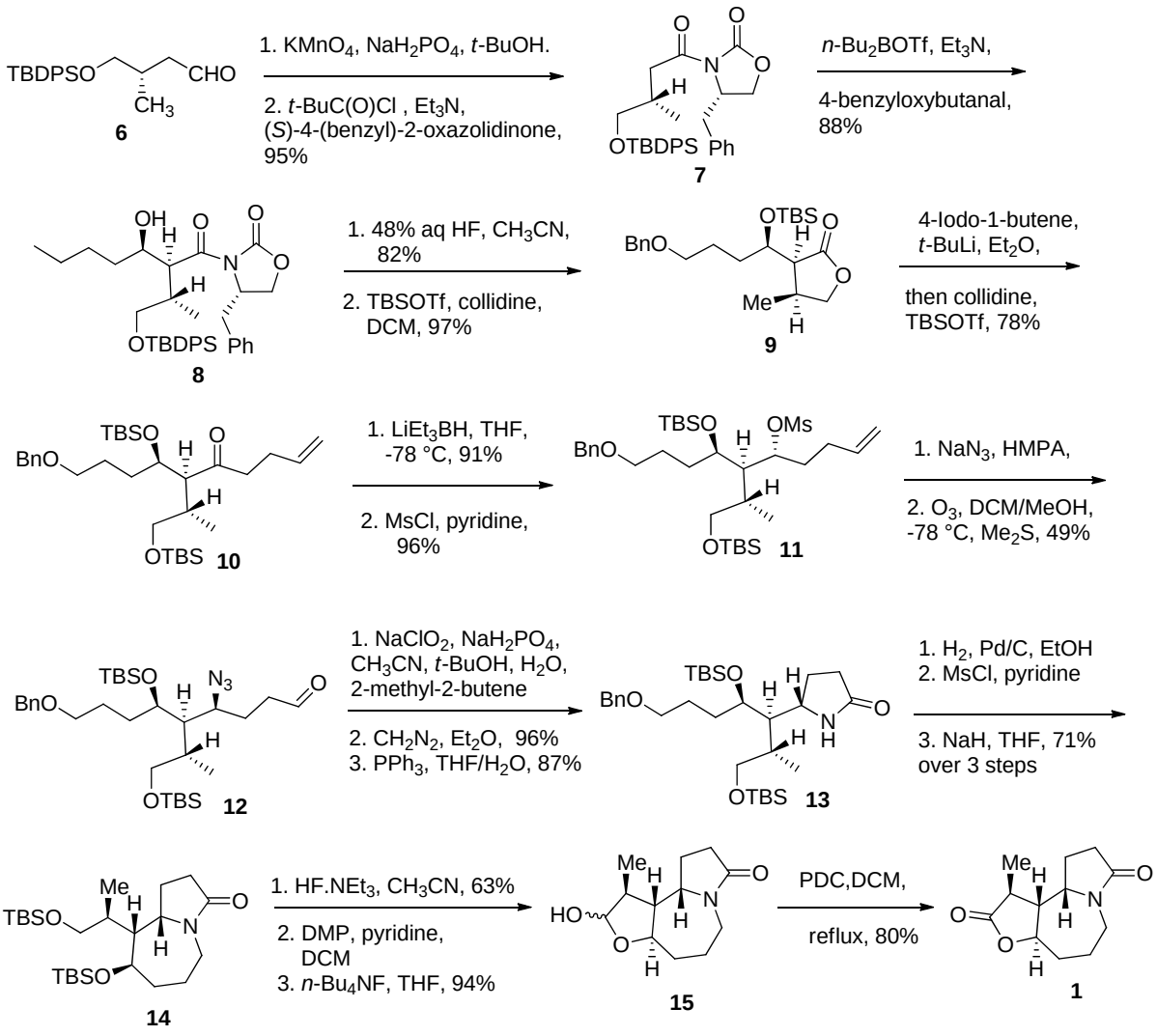
Figure 1. Stemona alkaloids

Among the stemona alkaloids, (–)-stemoamide is the simplest stemona alkaloid. The interesting structural feature of stemoamide along with other stemona alkaloids has resulted in the continuous flow of reports for their synthesis. Various synthetic routes reported towards the synthesis of (–)-stemoamide have been discussed here.

3.1.2. Literature review

Williams' approach (*Tetrahedron Lett.* **1994**,*35*, 6417-4420)

The first enantiocontrolled total synthesis of (–)-stemoamide (**1**) was reported by Williams *et al* in1994 starting from aldehyde **6** in 25 steps and 5.6% overall yield (Scheme 1).[4]



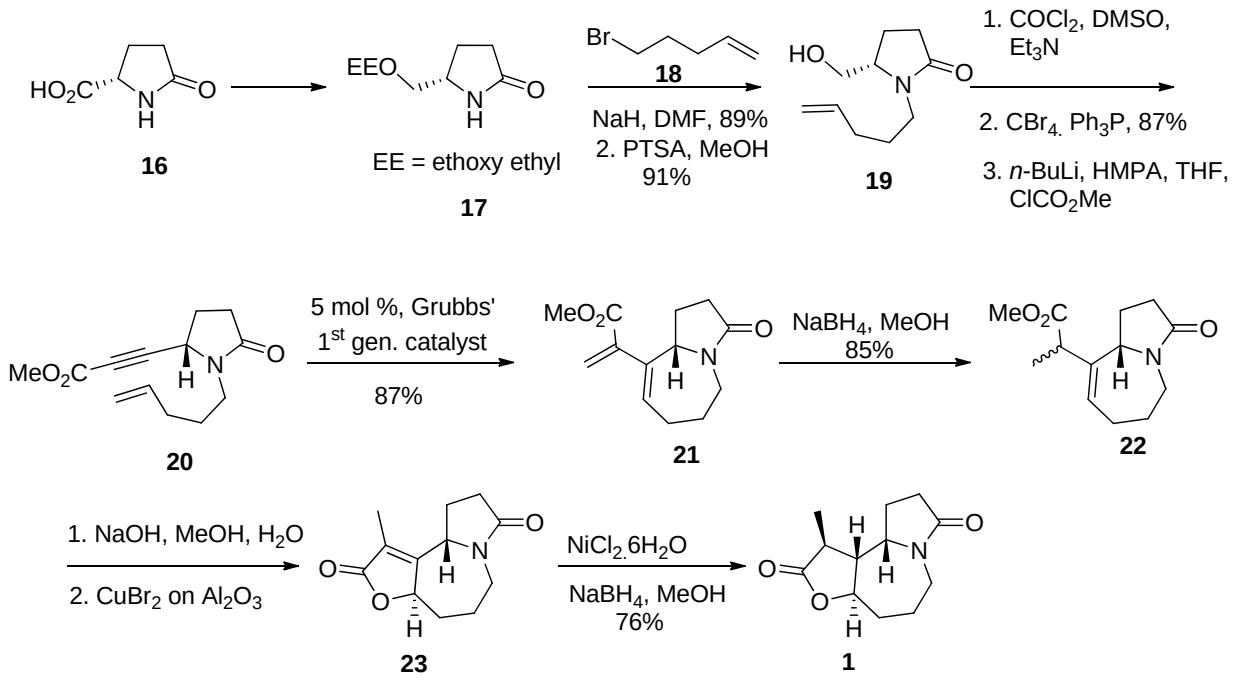
Scheme 1

The synthesis started from aldehyde **6**, which on oxidation to acid followed by acid chloride formation and treatment with (*S*)-4-(benzyl)-2-oxazolidinone furnished imide **7**. The asymmetric Evans aldol reaction of **7** with 4-benzyloxybutanal followed by TBS deprotection with acid and protection of secondary hydroxyl group furnished lactone **9**.

Opening of lactone **9** with alkyllithium followed by protection of resulting alcohol as its TBS derivative rendered ketone **10**. Reduction of **10** with $LiEt_3BH$ (exclusively from the carbonyl *si*-face) and mesylation followed by methanesulfonate displacement with sodium azide proceeded with inversion of configuration. At this point all the carbons and the stereogenic centers of (–)-stemoamide (**1**) were in place and the remaining steps were dedicated to the formation of rings A, B and C and functional group interconversions.

Mori's Appraoch (*J. Org. Chem*. **1996**, *61*, 8356-8357; *Heterocycles***1997**,*46*, 287-299)

Mori *et al*. reported synthesis of **1** starting from L-pyroglutamic acid, using enyne metatheis as a key reaction.[5]Amide **17** was prepared according to the method reported in the literature. Alkylation of **17** with bromo compound **18** followed by deprotection of ethoxy ethyl group using PTSA furnished alcohol **19**.Alcohol **19** was converted to enyne **20** using two step sequence, oxidation of alcohol followed by treatment with PPh_3, CBr_4 and then with *n*-BuLi.



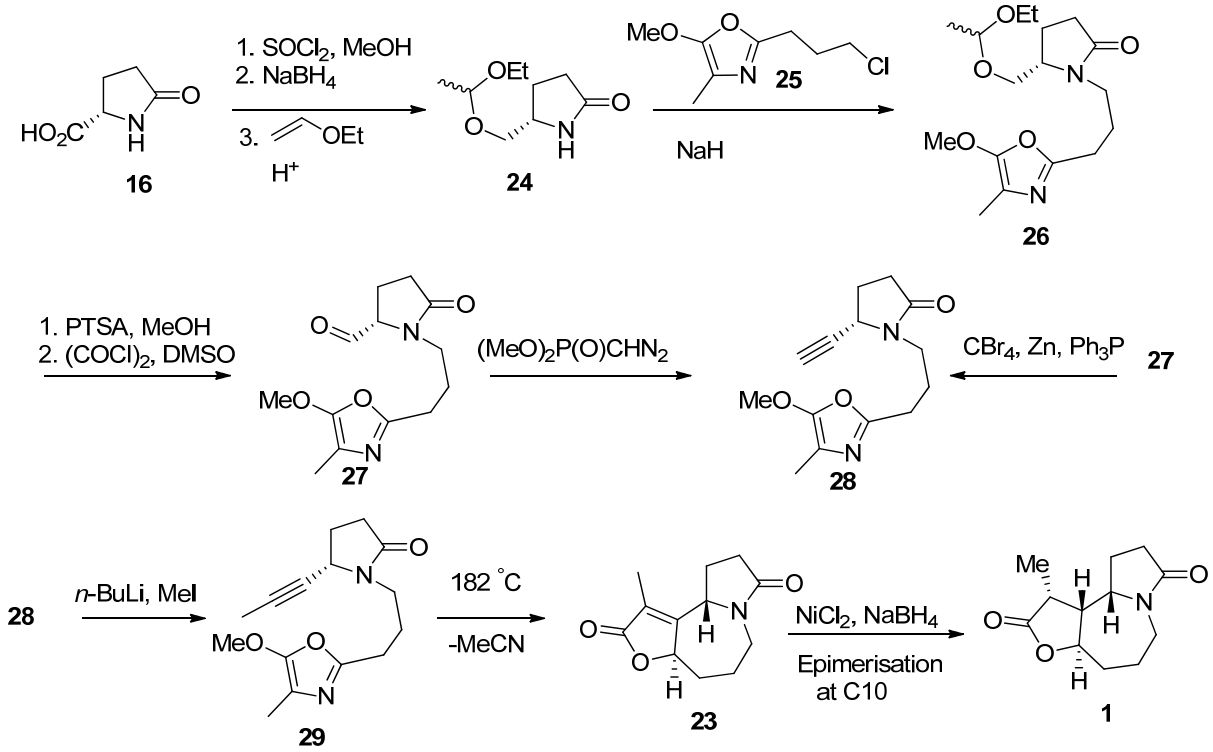
Scheme 2

Enyne metathesis proceeded smoothly, when a benzene solution of enyne **20** and a catalytic amount of ruthenium catalyst was stirred. The ring C was constructed by sequence of reactions which included chemoselective double bond reduction, hydrolysis of resulting ester

followed by $CuBr_2$ induced cyclization. Reduction of enone **23** with $NaBH_4$ in the presence of $NiCl_2.6H_2O$ in MeOH gave (–)-stemoamide (**1**).

Jacobi's Approach (*J. Am. Chem. Soc.* **2000,** *122*, 4295-4303)

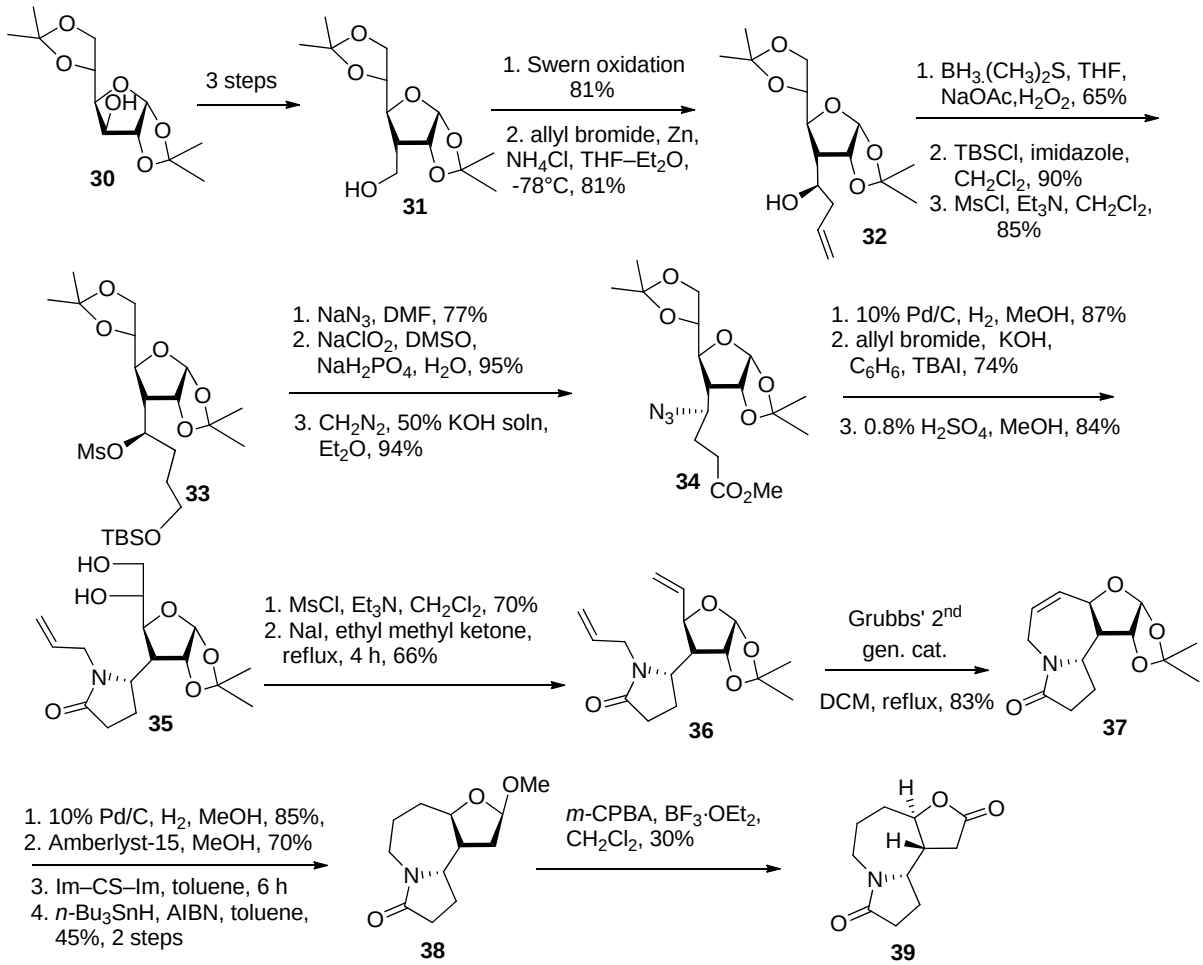
Enantioselective synthesis of **1** was achieved starting from γ-chlorobutyryl chloride and pyroglutamic acid **16** (Scheme 3). Esterification of **16** followed by $NaBH_4$ reduction and protection of resulting alcohol furnished amide **24**. Base induced alkylation of **24** with oxazole derivative **25** gave oxazole amide **26**. Precursor for Diels-Alder reaction **29** was prepared by a 4-step sequence which included deprotection of alcohol followed by oxidation to aldehyde and subsequent conversion of aldehyde to acetylene followed by methylation on acetylene. Intramolecular (Diels-Alder)-(retro-Diels-Alder) reaction of **29** gave butenolide **23** directly upon aqueous workup. The remaining two stereocentres in **1** were established in a single step by a highly selective reduction of **23** ($NaBH_4/NiCl_2$), followed by equilibration to the thermodynamically favored natural configuration.[6]



Scheme 3

Gurjar's Approach (*Tetrahedron Lett.* **2002**, *43*, 295–298)

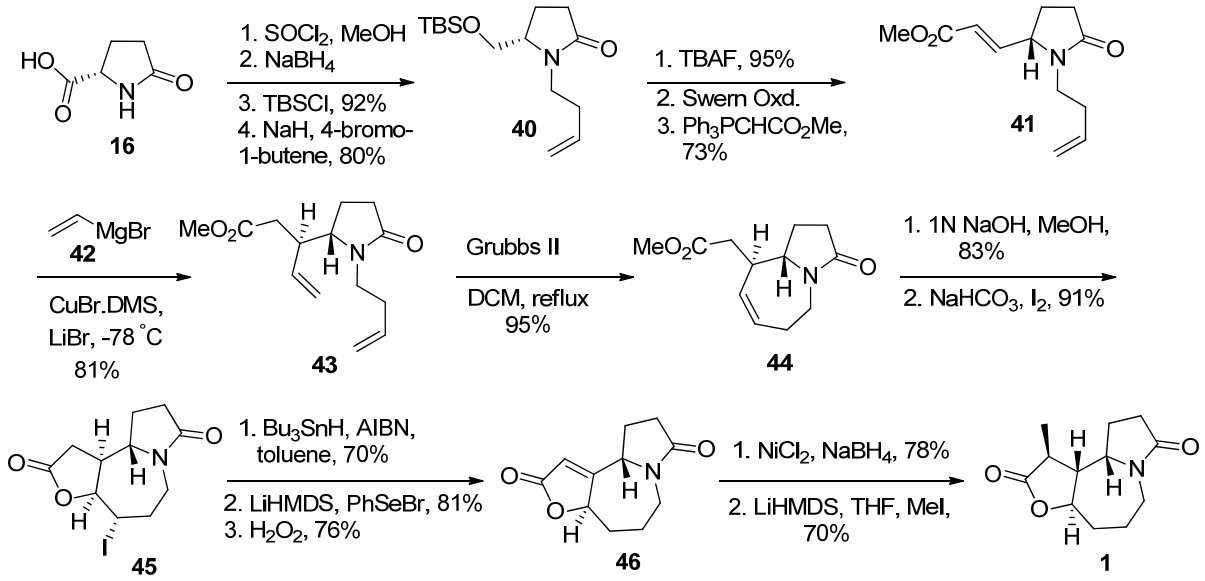
A formal synthesis of **1** was achieved by Gurjar *et al*. starting from D-glucose employing stereoselective allylation and RCM as the key steps (Scheme 4). Allylic alcohol **32** was obtained from alcohol **31** by oxidation followed by diastereoselective allylation of resulting aldehyde. Hydroboration of the allyl group followed by selective protection of the primary alcohol as its TBS derivative and mesylation of secondary alcohol furnished **33** in which mesyl group was replaced with azide. Azido ester **34** was obtained from **33** in three steps. Hydrogenation of azide led to the cyclization to 2-pyrrolidinone derivative which on allylation gave **35**. The diene precursor **36** for RCM reaction was prepared in two steps from **35**, which on RCM reaction rendered cyclized product **37**. Further, the cyclized product was transformed to **39** from which synthesis of (–)-**1** is known in literature in one step.[7]



Scheme 4

Sibi'sAppraoch (*Synlett***2004**, 1211)

Sibi *et al*. reported the enantioselective synthesis of (–)-stemoamide (**1**) in 14 steps starting from pyroglutamic acid (**16**) (Scheme 5). The key steps used in the strategy are conjugate addition of a vinyl copper reagent and a ring closing metathesis (RCM) reaction. Esterification of **16** followed by reduction of resulting ester to alcohol, which in turn was protected as its TBS derivative and subsequent alkylation of amide, resulted in to formation of **40**. Precursor for conjugate addition **41** was prepared from olefin **40** in three steps. The conjugate addition of vinyl magnesium bromide from re-face furnished **43** with opposite stereochemistry at newly formed centre as that of **1**. Ring closure of **43** using either Grubbs' 1st or 2nd generation catalyst gave the bicyclic lactam **44** in 95% yield.

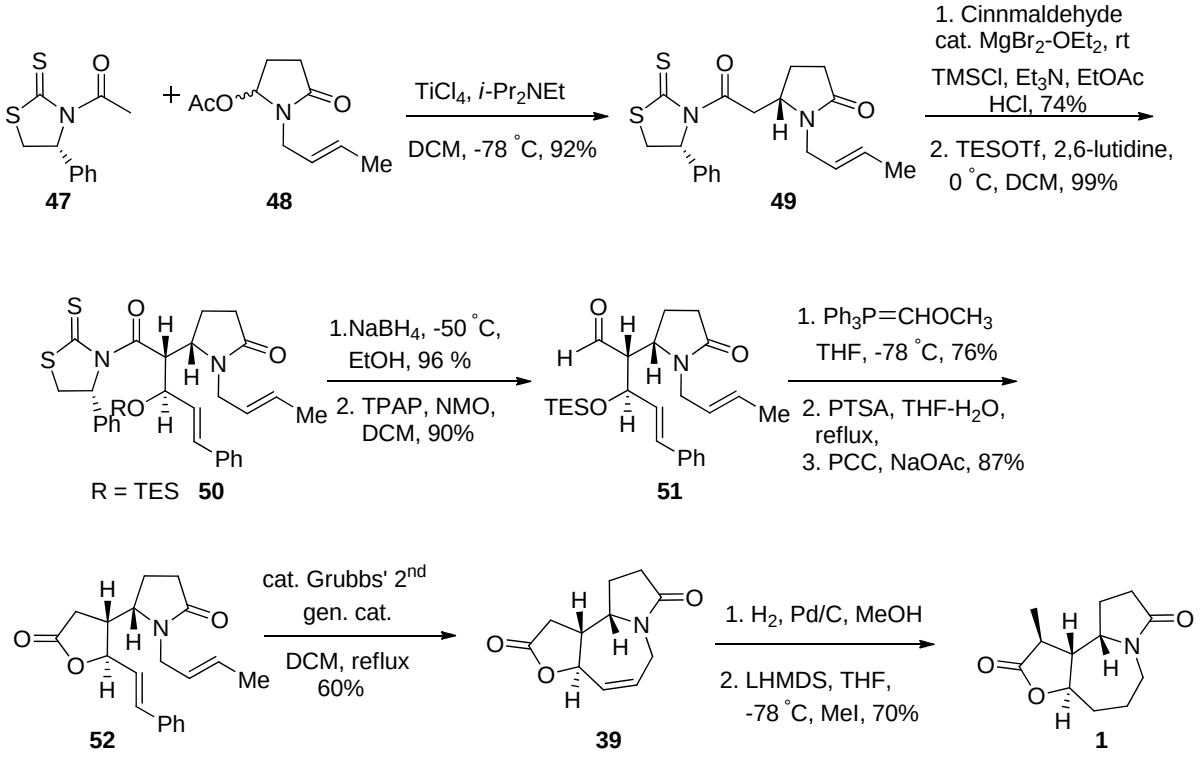


Scheme 5

The iodolactone **45** was obtained from γ,δ-unsaturated ester **44** on ester hydrolysis followed by iodolactonisation. Tricyclic compound **46** was obtained by three-step sequence from iodo lactone **45**. Face selective reduction of double bond in **46** followed by diastereoselective methylation gave **1**.[8]

Olivo's Approach (*J. Org. Chem*. **2006**, *71*, 3287-3290)

Olivo *et al*. achieved the synthesis of (–)-stemoamide in 11 steps from 5-acetoxy-*N*-crotyl pyrrolidinone**48** (Scheme 6). The stereochemistry at C9a carbon was established by the method developed by this group which includes the addition of the titanium(IV) enolate of 4*S*-phenylthiazolidinethione **47** to cyclic *N*-acyl iminium ion derived from **48** to furnish desired stereoisomer **49.**A highly diastereoselective *anti*-aldol reaction employing chiral

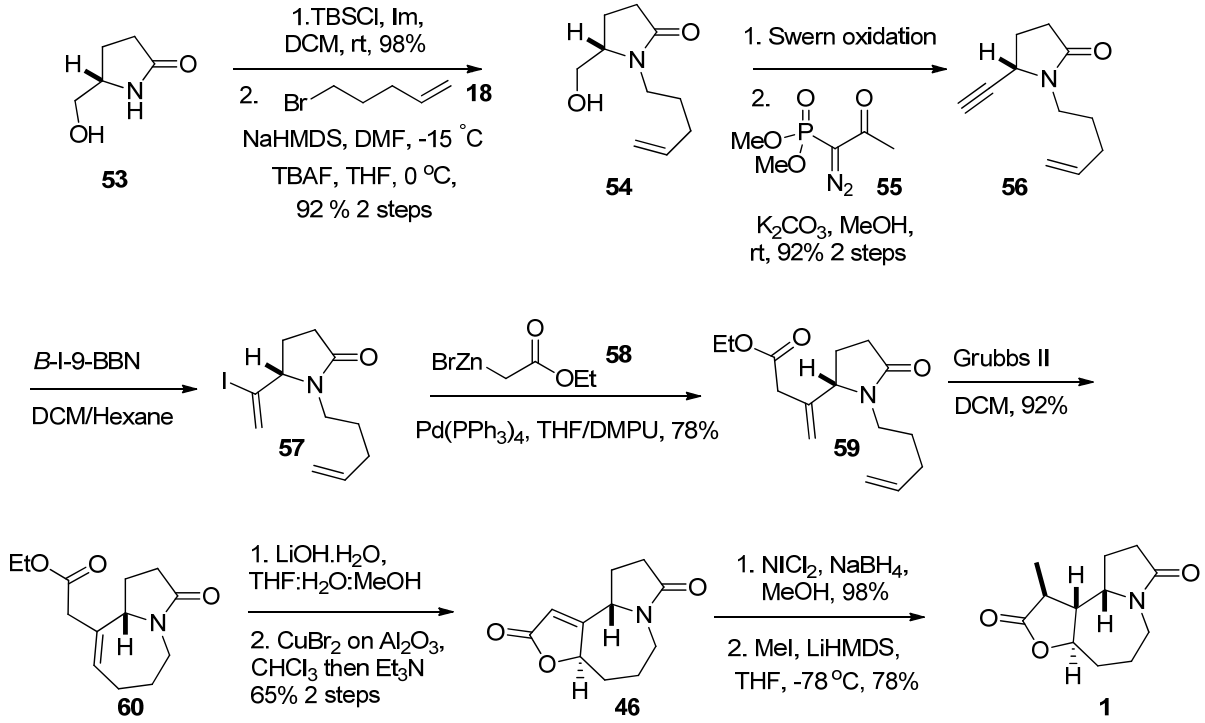


Scheme 6

thiazolidinethione **49** and cinnamaldehyde catalyzed by $MgBr_2$, followed by TES protection of resulting alcohol furnished **50**. Reduction of thiazolidinethione **50** with sodium borohydride followed by oxidation of the resulting alcoholtoaldehyde **51** occurred in 90% yield. Aldehyde **51** was reacted with the ylide derived from methoxymethyl chloride to give an inseparable *E,Z*-mixture of methylvinyl ethers; under acidic conditions, the silyl ether was removed and the methylvinyl ether was hydrolyzed to deliver a diastereomeric mixture of lactols, which on oxidation using PCC gave the desired lactone **52**. Diene **52** on treatment with Grubbs' 2nd gen. catalyst furnished tricyclic compound **39**, which on hydrogenation followed by methylation gave **1**.[9]

Somfai's Appraoch (*J. Org. Chem*. **2007**, *72*, 4246-4249)

Somfai *et al*. reported the stereocontrolled total synthesis of (–)-stemoamide (**1**) starting from (*S*)-pyroglutaminol (**53**) (Scheme 7). Synthesis began with protection of alcohol **53** as the corresponding TBS-ether followed by *N*-alkylation of the resulting lactam with halide **18** and subsequent removal of the TBS group to give alcohol **54**. Conversion of alcohol **54** into alkyne **56** was realized by Swern oxidation followed by treatment of resulting aldehyde with

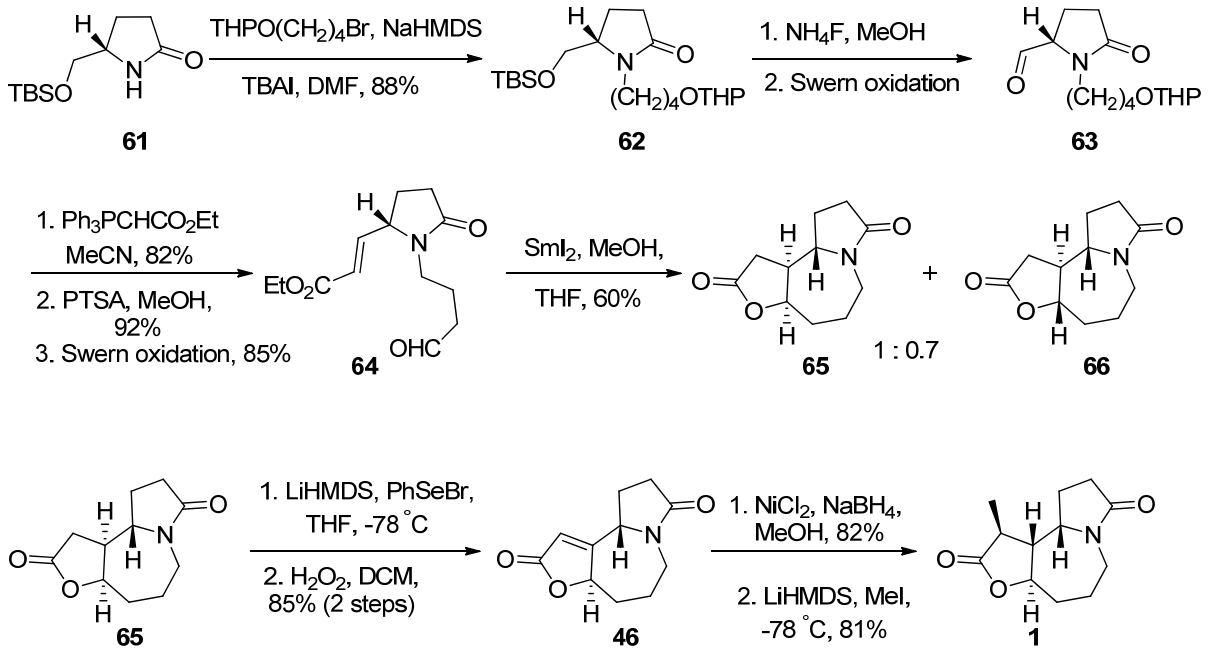


Scheme 7

Ohira-Bestmann diazophosphonate **55**. Iodoboration of the alkyne functionality in **56** furnished vinyliodide moiety **57**. Subjecting a mixture of vinyliodide **57** with Reformatsky reagent **58** in presence of $Pd(PPh_3)_4$ gave β, γ-unsaturated ester **59** in high yield. The ring closed product **60** was realized by treatment of diene **59** with Grubbs' 2nd gen. catalyst in DCM. Installation of butyrolactone moiety using a bromolactonization reaction, a strategy that was successfully used by Mori and co-workers, completed the synthesis of **1**.[10]

Honda's Approach (*Org. Biomol. Chem*. **2011**, *9*, 673–675)

Honda *et al*. accomplished the diastereoselective synthesis of (–)-stemoamide (**1**) starting from pyroglutamic acid derivative in eight steps and 24% overall yield (Scheme 8). The key step involved in their synthesis is a samarium diiodide-promoted 7-*exo*-*trig* cyclization to construct the tricyclic core. Aldehyde **63** was prepared starting from the known lactam **61** in a three-step sequence which includes the alkylation of the lactam **61** with 2-(4-bromobutoxy)tetrahydro-2*H*-pyran followed by removal of the silyl group of **62** upon treatment with ammonium fluoride and the subsequent Swern oxidation of the resulting primary alcohol.



Scheme 8

Aldehyde **64** the precursor for the key cyclization reaction was prepared from **63** in three steps, which include the Wittig reaction of aldehyde **63** followed by THP deprotection and the Swern oxidation of the resulting alcohol. A samarium diiodide-promoted carbon–carbon bond forming reaction was realized by treatment of **64** with 5.0 equivalents of samarium diiodide in THF in the presence of 5.0 equivalents of MeOH as the proton source to give an inseparable diastereoisomeric mixture **65** and **66** in 60% yield. The desired compound **65** was further converted to **1** in four steps which included the treatment of **65** with PhSeBr in

presence of LiHMDS followed by elimination of resulting selenide to furnish butenolide **46** which was further converted to **1** in two steps by method reported in literature.[11]

Other approaches for the racemic and non-natural isomers of the stemoamide (**1**) are summarized in figure 2. Narasaka *et al*. (*Bull. Chem. Soc. Jpn.* **1996**, *69*, 2063) utilized the oxidative coupling reactions of stannyl compounds with silylenol ethers to construct the tricyclic skeleton of (±)-**1**.[12] Jacobi *et al*. (*J. Am. Chem. Soc.* **1997**, *119*, 3409) used intramolecular (Diels-Alder)-(retro-Diels-Alder) reaction of **29** for the construction of tricyclic core of (±)-**1**.[13]Khim *et al*. (*J. Org. Chem.* **2004**, *69*, 7734) took advantage of the intramolecular 7-*exo*-*trig* radical cyclization of **68** as a key step and completed the synthesis of (-)-9,10-*epi*-stemoamide in nine steps and 13% overall yield.[14]

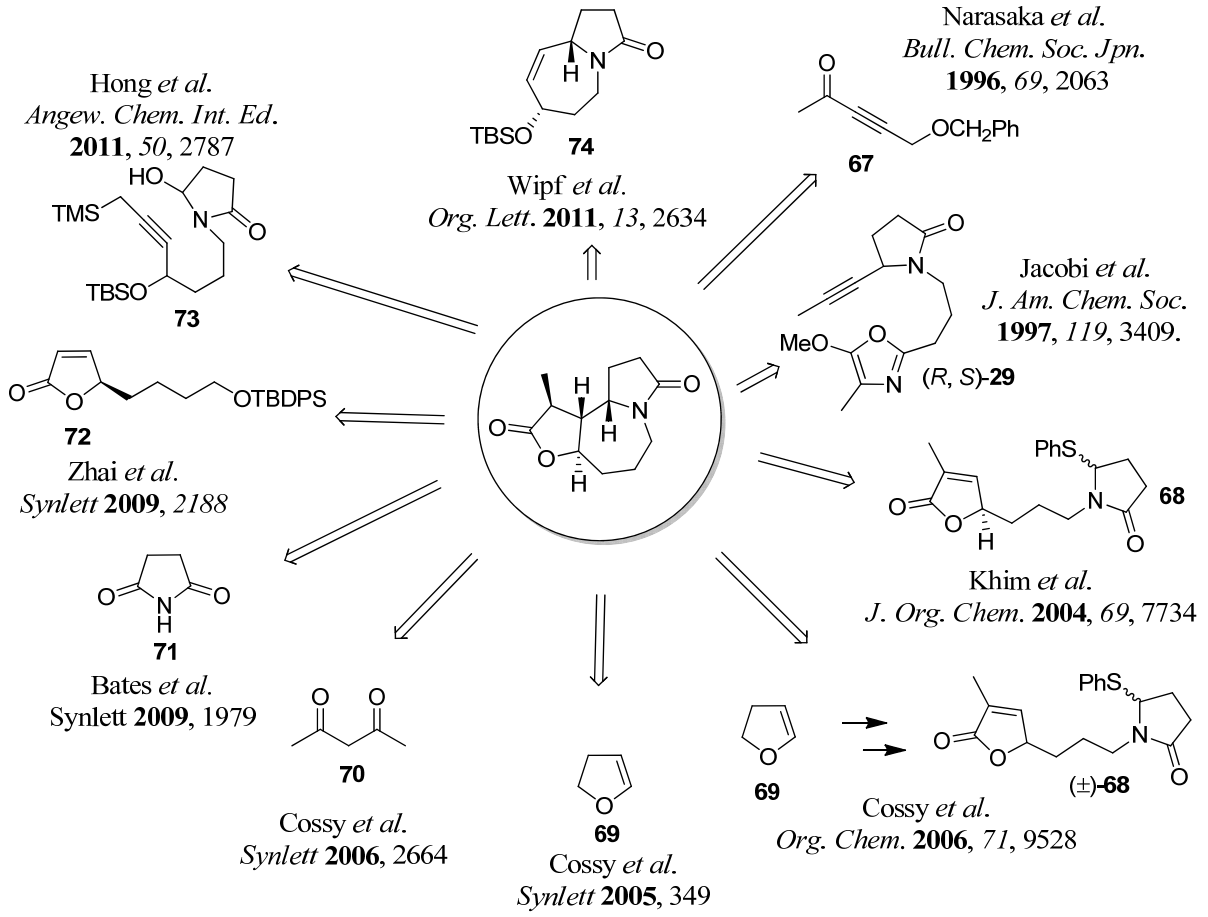


Figure 2

Cossy *et al*. realized the synthesis of (±)-9,10-bis-*epi*-stemoamide using diastereoselective radical 7-*exo*-trig cyclization as a key step. Starting from **69** synthesis of (±)-9,10-bis-*epi*-stemoamide achieved in 10 steps.[15] Again Cossy *et al*. (*J. Org. Chem.* **2006**, *71*, 9528) in **2006** reported the formal synthesis of (±)-stemoamide (**1**) starting from **69**.[16] Cossy *et al*. (*Synlett* **2006**, 2664) in their third approach used 1,3-diketone **70** as a starting material for the synthesis of (+)-stemoamide.[17] Bates *et al*. (*Synlett* **2009**, 1979) reported diastereoselective synthesis of (±)-stemoamide using succinimide as a starting material.[18]

Zhai *et al*. (*Synlett **2009***, 2188) described the synthesis of (+)-9a-*epi*-stemoamide, which has been achieved in six steps from α,β-unsaturated-γ-butyrolactone **72**.[19] Recently Hong*et al*. (*Angew. Chem. Int. Ed*. **2011**, *50*, 2787) reported synthesis of (±)-stemoamide by bioinspired iminium ioncyclization of **73** in combination with the ruthenium-catalyzed cyclocarbonylation of the resulting allenic alcohol. The synthesis of racemic stemoamide was completed in eight steps.[20] Wipf *et al*. (*Org. Lett.* **2011**, *13*, 2634) used 3, 3 sigmatropic reaction i.e. Ireland-Claisen rearrangement of **74** for the stereoselective installation of C8 and completed synthesis of (–)-8-*epi*-Stemoamide starting from pyroglutamic acid.[21]

3.1.3 References:

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Chapter 3: Synthetic studies towards (–)-stemoamide and methodology for PMB protection of alcohols, selective mono PMB protection of diols and di-PMB protection of diols

Section 2: Synthetic studies towards (−)-stemoamide

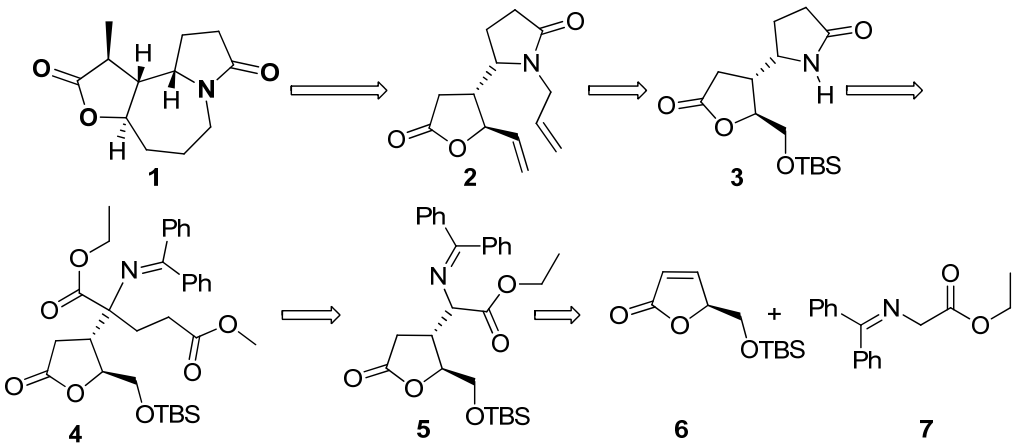
3.2.1: Present work

3.2.1.1: Objective

The intriguing structure of stemoamide (**1**) and its use in the Chinese and Japanese folk medicine in the treatment of respiratory diseases and as anthelmintics was the impetus to develop a flexible strategy for its synthesis. A distinguishing feature of this group of alkaloids is the presence of a perhydroazaazulene ring, and the most members also contain a α-methyl-γ-butyrolactone functionality. A modern synthetic design demands better yielding sequences coupled with mild reaction conditions, high stereoselectivity and readily available starting materials. Keeping these features in mind, a convergent route to **1** has been chosen from D-mannitol diacetonide as a starting material for the synthetic endeavor because of its ready availability in enantiopure form.

2.2.1.2: Retrosynthetic analysis

The basic strategy for the synthesis of stemoamide (**1**) is shown in the retrosynthetic analysis (Scheme 1).



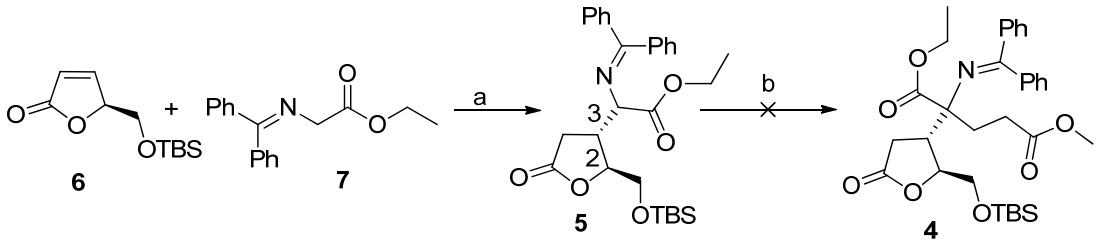
Scheme 1. Retrosynthetic analysis for **1.**

An appealing strategy for the convergent synthesis of stemoamide can be envisaged by the installation of azepine ring structure using ring closing metathesis approach followed by appropriate fictionalization. Synthesis of the diene **2**, precursor for ring closing metathesis was envisioned by allyaltion at pyrrolidinone moiety. In turn the pyrrolidinone ring could be constructed from **4** by imine hydrolysis followed by decarboxylation. The diastereoselective

conjugate addition of **7** on butyrolactone **6** would lead to the imine **5** with the desired stereochemistry at C2 and C3 as in **1**.

3.2.1.3: Results and discussion

The first step of the synthesis is the conjugate addition between butenolide **6** and imine **7**. Among the starting materials for conjugate addition, the butenolide **6** was prepared according to the method reported by Wilson *et al*.[1] while diphenylamine Schiff's base **7** was prepared by O'Donnells' procedure from diphenylimine and glycine ester hydrochloride.[2] Thus, treating the equimolar mixture of the butenolide **6** and diphenylamine Schiff's base **7** in THF with LiBr and Et_3N furnished the imine **5** in 80% yield (Scheme 2).

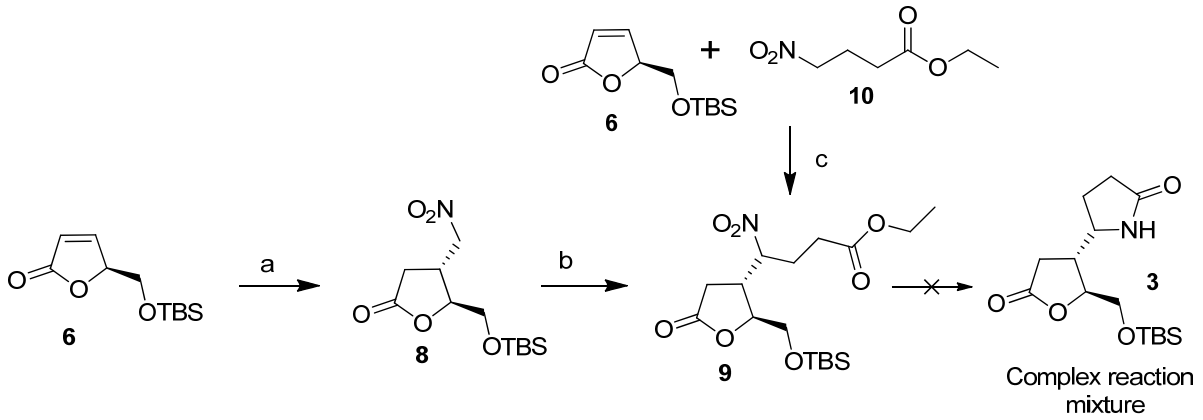


Scheme 2. Synthesis of **1**

Reagents and conditions: a) LiBr, Et_3N, THF, 80% b) Ethyl acrylate, NaH, THF

Strong bands at 1782 and 1735 cm^{-1} in its IR spectrum showed the presence of five membered lactone and ester functionalities respectively. ^1H NMR spectrum of **5** revealed the presence of multiplets at δ 7.74-7.14 integrating for 10 protons, thereby, confirming the incorporation of diphenyl moiety. Three singlets at δ 0.81, 0.00 and 0.01 integrating for 9, 3 and 3 protons respectively indicated the presence of TBS group. Its mass spectrum showed molecular ion peak at m/z 496 $(M + H)^+$ thus confirming the formation of **5**.

Imine **5** was then subjected to reaction with sodium hydride and ethyl acrylate in THF with the hope to obtain addition product **4**, but unfortunately a complex reaction mixture was observed. Instead of sodium hydride use of bases like Cs_2CO_3, Et_3N, DBU and LDA under identical reaction conditions failed to furnish product **4**. So alternatively, it was thought to prepare **3** by condensation with nitromethane and the nitro ester **10** with butenolide **6**.



Scheme 3. Alternate route to synthesis of **1**

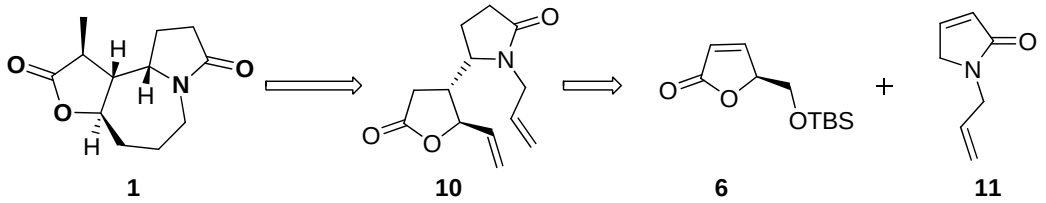
Reagents and conditions: a) Nitromethane, DBU, 84% b) Ethyl acrylate, DBU, CH_3CN, 75%, c) NaOEt, THF, reflux, 78%

Nitrocompound **9** was prepared by two routes which include the Michael addition of nitromethane on butenolide **6** and the Michael addition of nitro compound **10** on **6** (Scheme 3). Butenolide **6** was subjected to reaction with excess nitromethane and catalytic DBU to provide nitro compound **8**. Presence of a strong band at 1782 cm^{-1} and disappearance of band at 1756 cm^{-1} in its IR spectrum indicated the presence of five memebered lactone. Disappearance of peak at δ 7.49 and 6.16 in its ^{1}H-NMR spectrum and appearance of peak at δ 4.52 integrating for two protons clearly indicated the formation of **8**. Three peaks for CH_2 and four peaks for CH_3 and CH carbons in its DEPT spectrum were in accordance with the structure **8**. Finally, its mass spectrum showed molecular ion peak at 280 $(M+H)^+$ which confirmed the formation of **8**.

The formation of **9** was realized by two ways. In the first case, equimolar amounts of **8** and ethyl acrylate reacted with DBU to furnish **9** in 75% yield, while in second case addition of **10** with **6** was carried out in presence of sodium ethoxide in THF to give **9** in 78% yield. Strong bands at 1785, 1735 and 1552 cm^{-1} in its IR spectrum indicated the presence of five membered lactone, ester and nitro functionalities respectively. Its ^{1}H-NMR spectrum showed quartet at δ 4.16 and triplet at δ 1.26 which revealed the presence of ethyl ester moiety. Peaks at δ 0.89 and 0.07 were assigned to the TBS group. Peaks at δ 174 and 171 in its ^{13}C-NMR spectrum indicated the presence of lactone carbonyl and ester carbonyl respectively. Peak at δ 93 was attributed to the carbon adjacent to nitro group. Finally the formation of **9** was confirmed by its mass spectrum which showed molecular ion peak at m/z 412 $(M+Na)^+$.

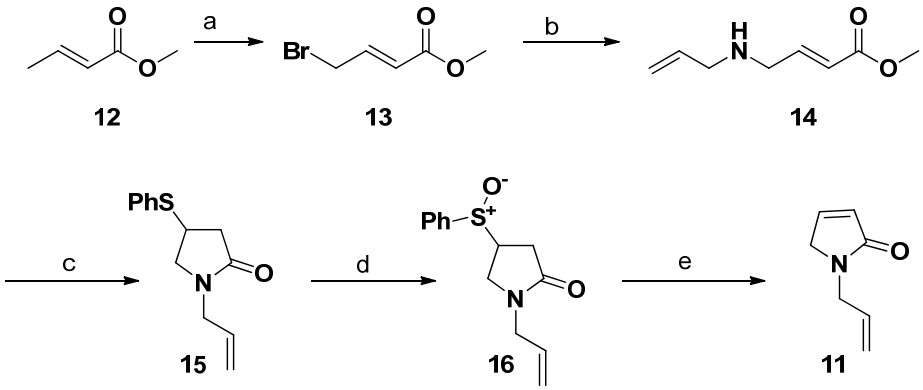
During the efforts to prepare pyrrolidinone **3** by reduction of nitro group a report appeared by Zhai *et al*.[3] which described the synthesis of **1** utilizing a similar type of strategy as proposed in the present work. Hence, it was decided not to proceed with the above mentioned approach for the synthesis of **1** and was proposed an alternative retrosynthetic route (Scheme 4).

Here it was surmised that the construction of tricyclic core of **1** could be realized by RCM reaction of diene **10**. In turn, the diene could be constructed by Vinylogous Mukaiyama Michael addition between butenolide **6** and *N*-allyl pyrrolinone **11**.



Scheme 4. Revised retrosynthesis for **1**

According to the revised convergent retrosynthetic plan, the synthesis of **1** started from **11** which was prepared from methyl crotonate in five steps (Scheme 5).



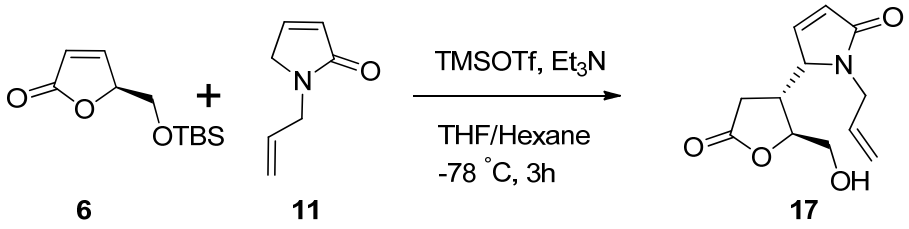
Scheme 5. Synthesis of **11.**

Reagents and conditions: a) NBS, Cat. AIBN, CCl_4, reflux, quant. b) Allylamine, THF, 73% c) PhSH, Et_3N, reflux, 91% d) $NaIO_4$, $MeOH/H_2O$, 74% e) $NaHCO_3$, Toluene, reflux, 60%.

A mixture of equimolar amounts of methyl crotonate and NBS in CCl_4 was refluxed in presence of catalytic amount of AIBN to provide bromomethyl crotonate **13** in quantitative yield. Reaction of bromomethyl crotonate **13** with allylamine in THF furnished allylamine crotonate **14**. The formation of cyclic pyrrolidinone **15** was realized by conjugate addition of

thiophenol on **14**. Sulfide **14** was oxidized to sulfoxide **16** on treatment with $NaIO_4$ in methanol-water in 74% yield. The next task was the elimination of the sulfoxide to *N*-allyl pyrrolinone which was effected by heating of **16** in toluene in presence of sodium bicarbonate in 60% yield. Starting from methyl crotonate *N*-allyl pyrrolinone **11** was prepared in 30% overall yield.

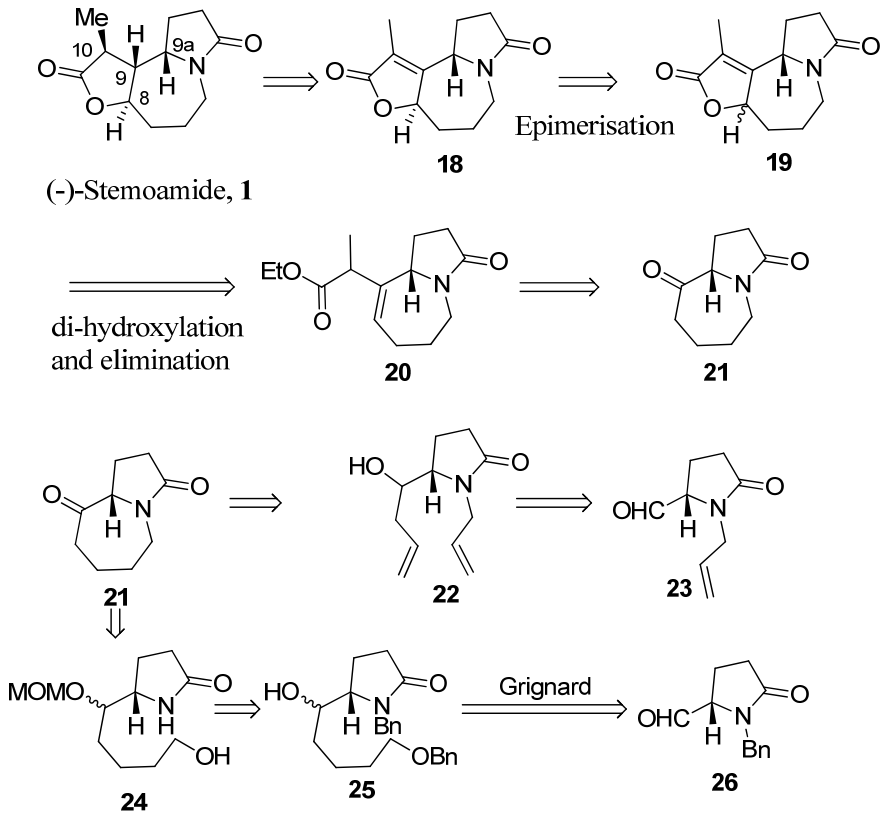
The key step of Vinylogous Mukaiyama Michael reaction was carried out using equimolar amounts of butenolide **6**, pyrrolinone **11** and TMSOTf in presence of triethyamine in THF-hexane system to provide addition product **17** (Scheme 6). Its mass spectrum showed the molecular ion peak at m/z 238 $(M + H)^+$ indicating presence of **17**. But unfortunately ^{1}H-NMR of this compound was not in accordance with **17**.



6 **11** **17**

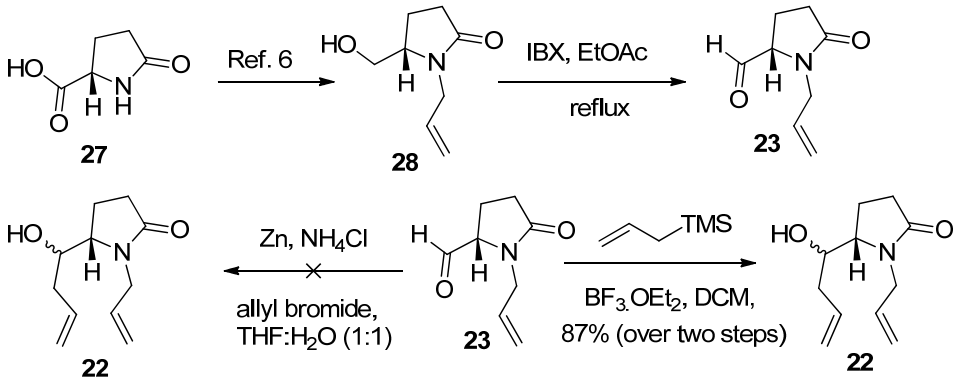
Scheme 6

Failures in all the above approaches to stemoamide, led to the design of a different strategy for its synthesis. New retrosynthetic plan starting from commercially available chiral starting material L-pyroglutamic acid is shown in Scheme 7. According to the proposed plan, the key intermediate is butenolide **18**. Elaboration of the intermediate **18** to **1** is well documented in the literature.[4] In turn the focus was the construction of butenolide ring in **18** based on our previously reported strategy for butenolide synthesis,[5] which includes the Reformatsky reaction on ketone **21** to furnish the corresponding hydroxy ester which on dehydration would furnish β,γ-unsaturated ester which on dihydroxylation and treatment with acid would provide butenolide. The ketone **21** could be constructed by two routes, one by taking advantage of RCM strategy and another route by taking advantage of Grignard reaction on aldehyde **26**. The di-allylated precursor **22** could be constructed from L-pyroglutamic acid **27**.



Scheme 7. New retrosynthetic plan to **1**

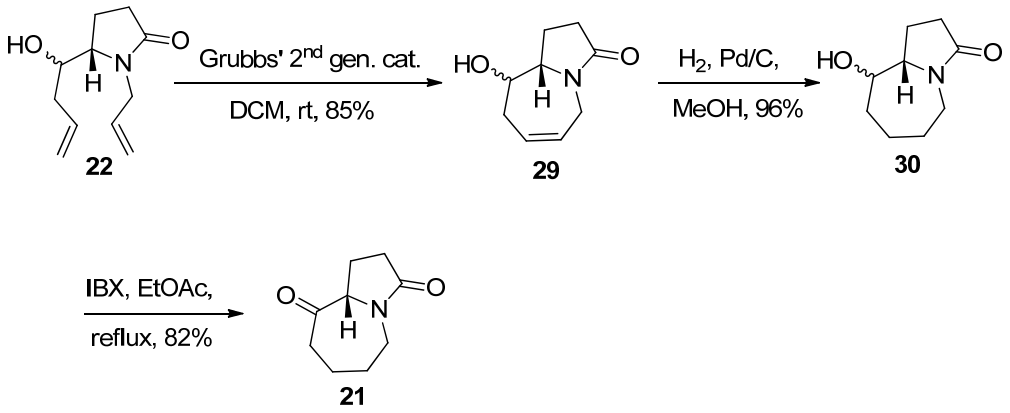
The synthesis started from L-pyroglutamic acid **27** (Scheme 8) wherein the *N*-allyl alcohol **28** was prepared using reported method with no loss in chirality.[6]



Scheme 8. Synthesis of diallyl alcohol **22** from **27**

The *N*-allyl alcohol **28** was oxidized to aldehyde **23** using IBX in refluxing ethyl acetate. The crude aldehyde **23**, as such, was subjected to equimolar quantities of Zn and allyl bromide in

presence of ammonium chloride to give two undesired products which could not be well characterized. Allylation of **23** using allyltrimethylsilane and TBAF in THF gave **22** but it was not possible to get di-allylated product **22** in good yields despite modifications in the amounts of allyltrimethylsilane and of TBAF. However, by performing the reaction under Lewis acidic conditions employing $BF_3.OEt_2$ as the catalyst in DCM, the di-allylated product **22** was obtained in 87% yield. Its IR spectrum showed strong band at 3390 and 1675 cm^{-1} indicating the presence of hydroxy and amide functionalities respectively. The ^{1}H-NMR spectrum of di-allylated compound **22** showed it to be a mixture of diastereomers. Multiplets at δ 5.88-5.71 and 5.25-5.00 corresponded to the allyl group. Multiplet at δ 4.35-4.24 integrated for one proton which represented the proton adjacent to hydroxy group. The double peaks in its ^{13}C-NMR indicated the presence of diastereomeric mixture of di-allylated compound **22**, which did not matter as the alcohol functionality in **22** was to be oxidized at a later stage. Presence of five peaks corresponding to CH_2 carbons and four peaks corresponding to CH and CH_3 carbons in its DEPT spectrum indicated the formation of **22**. Further, formation of **22** was confirmed by its mass spectrum which showed molecular ion peak at m/z 196 $(M+H)^+$.



Scheme 9. Synthesis of ketone **21**

The di-allylated product **22** was subjected to RCM reaction (Scheme 9) using Grubbs' 1st generation catalyst (2 mol%) in DCM, which resulted in cyclic olefin product but low yields (34%) were obtained at room temperature as well as under reflux conditions. Varying the amount of Grubbs' catalyst up to 8 mol% also resulted in unsatisfactory yield, up to a maximum of 40%. However, switching over to the use of Grubbs' 2nd generation catalyst (2

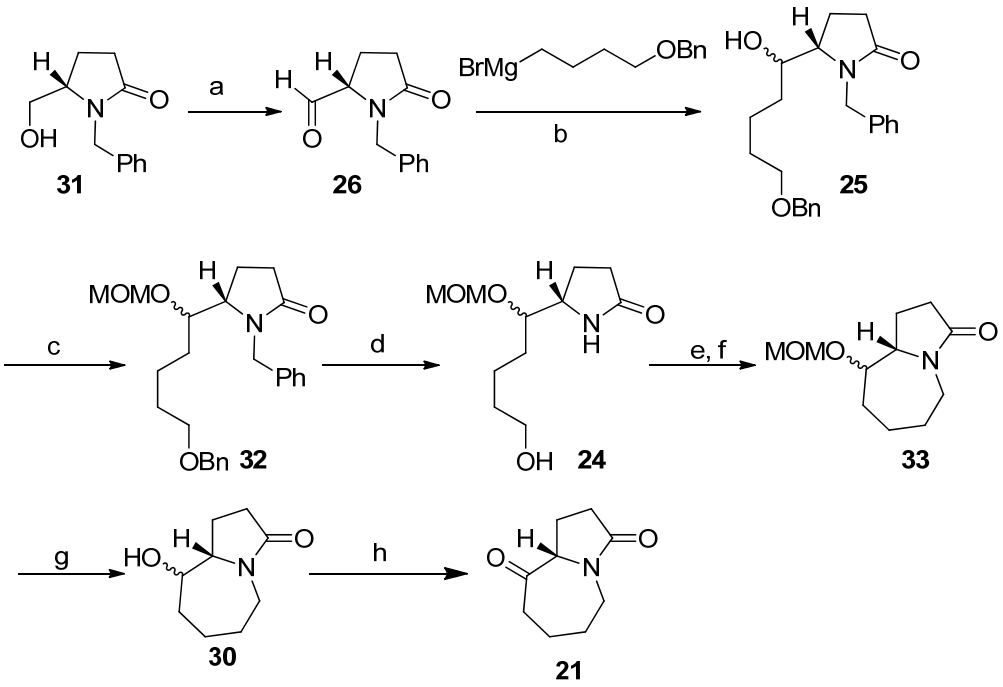
mol%) in DCM at room temperature furnished good yield (85%) of ring closed product **29**.[7] Strong bands at 3393 and 1674 cm^{-1} in its IR spectrum indicated the presence of hydroxy and five membered lactam functionalities respectively. From its ^{1}H-NMR spectrum it was evident that it is a diastereomeric mixture. Multiplets at δ 6.07-5.87 and 5.73-5.57 in its ^{1}H-NMR spectrum accounted for one proton each clearly pointing to the formation of cyclized product. Proton adjacent to hydroxy group appeared at δ 4.67-4.49 as a multiplet. Its ^{13}C-NMR spectrum showed peaks at δ 174, 129 and 127 corresponding to lactam carbonyl and double bond carbons respectively. Its DEPT spectrum showed presence of four CH_2 carbons and four CH carbons. Finally, the formation of **29** was confirmed by its mass spectrum which showed molecular ion peak at m/z 168 $(M+H)^+$, 190 $(M+Na)^+$.

Homoallylic alcohol **29** was subjected to hydrogenation using catalytic palladium over carbon under hydrogen atmosphere to provide bicyclic alcohol **30** in 96% yield. Strong band at 1693 cm^{-1} in its IR spectrum indicated the presence of five membered lactam carbonyl. Absence of multiplets at δ 6.07-5.87 and 5.73-5.57 in its ^{1}H-NMR spectrum clearly indicated the reduction of double bond. Further, multiplet at δ 3.95-3.88 integrating for two protons corresponded to protons adjacent to hydroxy and nitrogen (CH). Two multiplets at δ 3.58-3.53 and 3.32-3.29 corresponded to *N*-CH_2 protons. Its ^{13}C-NMR spectrum showed peak at δ 176 which was assigned to lactam carbonyl carbon and peak at δ 73 was assigned to CHOH carbon. Its DEPT spectrum showed presence of two CH carbons and six CH_2 carbons. Its mass spectrum showed molecular ion peak at m/z 192 $(M+Na)^+$ which confirmed the formation of **30**.

Oxidation of alcohol **30** to ketone **21** was realized by using IBX in refluxing ethyl acetate in 82% yield. Its IR spectrum showed strong bands at 1720 and 1692 cm^{-1} clearly indicating the presence of ketone and five membered lactam carbonyl functionalities respectively. Its ^{1}H-NMR spectrum showed the multiplets at δ 4.31-4.20 and 4.02-3.94 corresponding to protons adjacent to carbonyl and adjacent to nitrogen respectively. The remaining peaks accounted for 11 protons. Peaks at δ 212 and 174 in its ^{13}C-NMR spectrum were assigned to ketone and lactam carbonyls respectively. Peak at δ 68 was assigned to the CH flanked by nitrogen and ketone. Its DEPT spectrum showed presence of one CH carbon and six CH_2 carbons

confirming the formation of ketone **21**. Further, the formation of **21** was supported by its mass spectrum which showed molecular ion peak at m/z 168 $(M+H)^+$, 190 $(M+Na)^+$.

The alternative route to RCM strategy to construct the seven membered ring started from the common starting material *viz* L-pyroglutamic acid (Scheme 10).



Scheme 10. Synthesis of ketone **21** alternate route to RCM

Reagents and conditions: a) IBX, EtOAc, reflux b) THF, –50 ^oC (74% over two steps) c) MOMCl, DIPEA, DCM, reflux, 90% d) Na, NH_3, THF, –78 ^oC, 87% e) MsCl, Et_3N, DCM f) NaH, THF (86% over two steps) g) trace HCl, MeOH, reflux, 74% h) IBX, EtOAc, reflux, 82%

Alcohol **31** was prepared according to the reported procedure from L-pyroglutamic acid.[8] Alcohol **31** was oxidized using IBX in ethyl acetate under reflux conditions to provide aldehyde **26** with no loss in chirality and was subjected to Grignard reaction without further purification. The required Grignard reagent was prepared from 4-benzyloxybutyl bromide and activated Mg in THF. The crude aldehyde **10** was initially treated with 2 eq. of Grignard reagent at room temperature in THF which resulted in complex reaction mixture. After optimization of reaction conditions, the Grignard reaction was carried out at –50 ºC in THF

as the solvent to furnish alcohol **25** in 74% yield (over two steps). Strong bands at 3401 and 1666 cm^{-1} in its IR spectrum indicated the presence of hydroxy and γ-lactam carbonyl functionalities respectively. Appearance of multiplet in aromatic region at δ 7.34-7.20 in its ^{1}H-NMR spectrum integrating for ten protons provided the strong evidence for formation of alcohol **25**. Singlet at δ 4.48 integrating for 2 protons and doublets at 4.88 and 4.26 integrating for one proton each were assigned to *O*-benzyl and *N*-benzyl protons respectively. Four protons appearing at δ 3.41-3.65 were assigned to protons adjacent to oxygen and nitrogen. Its ^{13}C-NMR spectrum showed peak at δ 176 corresponding to the lactam carbonyl carbon. Two peaks appeared at δ 138 and 137 which were assigned to the substituted aromatic carbons and peaks that appeared at δ 128.6, 128.3, 128.0, 127.6, 127.5 and 127.4 were assigned to remaining aromatic carbons. Carbons that resonated at δ 73, 72.9, 70.1 and 61.6 were assigned to carbons adjacent to hydroxy and nitrogen respectively. Its DEPT spectrum showed appearance of 8 CH carbons and 8 CH_2 carbons. Finally, its mass spectrum showed molecular ion peak at m/z 368 $(M+H)^+$ and thus confirmed the formation of alcohol **25**.

The MOM protection of alcohol **25** was effected by reaction with MOMCl in presence of Hunig's base in DCM under reflux conditions in 90% yield. Strong band at 1681 cm^{-1} in its IR spectrum indicated the presence of lactam carbonyl functionality. Appearance of characteristic peaks of MOM group in its ^{1}H-NMR spectrum at δ 4.51 and 3.28 integrated for two and three protons respectively indicating the presence of OMOM group. Multiplet at δ 7.34-7.24 integrating for 10 protons was assigned to the two aromatic rings. Its ^{13}C-NMR spectrum showed peak at δ 175 corresponding to the lactam carbonyl carbon and peaks corresponding to aromatic carbons appeared at δ 138, 136, 128.6, 128.3, 127.6, and 127.5. Peaks at δ 96.7 and 55.7 were assigned to CH_2 and CH_3 carbons in MOM group. Its DEPT spectrum showed presence of 9 CH_2 carbons indicating the formation of **32**. Further, the formation of **32** was confirmed by its mass spectrum which showed the molecular ion peak at m/z 412 $(M+H)^+$.

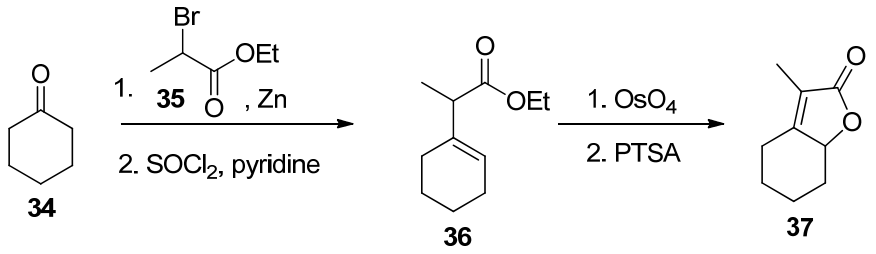
The next task was the deprotection of both benzyl groups. In order to effect the deprotection, the di-benzyl compound **32** was subjected to hydrogenation conditions using Pd/C catalyst under hydrogen in methanol to furnish the only *O*-debenzylated product. Then the di-

debenzylation was realized by treatment of **32** under Birch reduction conditions using Na in ammonia in THF at –78 ˚C which resulted in to formation of deprotected compound **24** in 87% yield. Strong bands at 3433 and 1679 cm^{-1} in its IR spectrum indicated the presence of hydroxy and amide functionalities respectively. Absence of peaks in aromatic region and appearance of characteristic peak of amide proton at δ 7.42 in its ^{1}H-NMR spectrum provided the strong evidence for deprotection of both benzyl groups. Peaks at δ 4.70-4.62 (m) and 3.39 (s) integrating for two and three protons respectively were assigned to MOM group. Peaks at δ 178 and 97 in its ^{13}C-NMR spectrum were assigned to lactam carbonyl carbon and CH_2 carbon in MOM respectively. Its DEPT spectrum showed presence of three CH and CH_3 carbons and seven CH_2 carbons supporting the formation of desired product. Finally the formation of alcohol **24** was confirmed by its mass spectrum which showed molecular ion peak at m/z 254 $(M+Na)^+$.

The formation of seven membered compound **33** was realized by subjecting the alcohol **24** to mesylation to provide mesyl compound which without further purification was subjected to treatment with sodium hydride in THF to provide the cyclized product **33** in 86% yield over two steps. Its IR spectrum showed a strong band at 1687 cm^{-1} and was assigned to lactam carbonyl carbon. Its ^{1}H-NMR spectrum showed peaks at δ 4.73-4.57 (m) and 3.38 (s) integrating for two and three protons and were assigned to CH_2 and CH_3 protons respectively of MOM group. Its ^{13}C-NMR spectrum showed peaks at δ 176 and 95 which were attributed to the carbonyl carbon and methylene carbons of MOM group respectively. Peaks at δ 78 and 62 were assigned to carbons adjacent to oxygen and nitrogen (CH) respectively. Peaks at δ 55 and 43 corresponded to the methyl of MOM group and CH_2 carbon adjacent to nitrogen. Its DEPT spectrum showed presence of three CH and CH_3 carbons and seven CH_2 carbons. Further its mass spectrum showed molecular ion peak at δ 214 $(M+H)^+$ thereby confirming the formation of **33**.

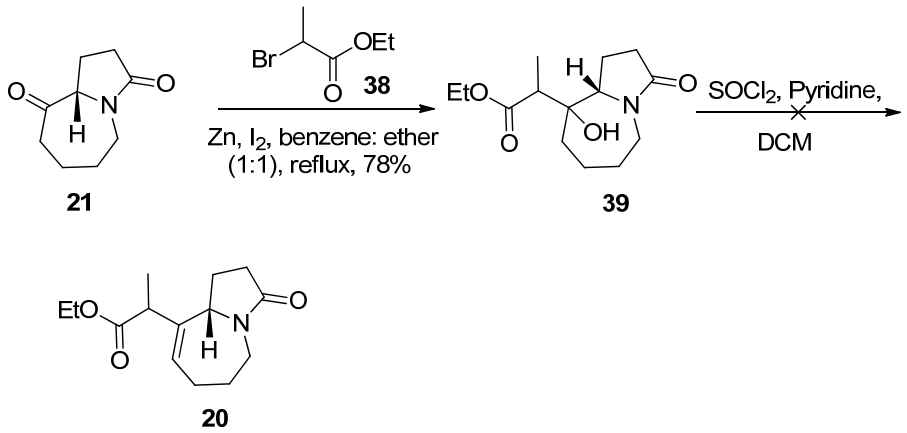
The MOM deprotection in **33** was carried out by treating this compound with trace amount of conc. HCl in methanol to provide alcohol **30** in 74% yield. The spectral data of alcohol **30** was in complete agreement with the alcohol prepared by RCM approach, which on oxidation furnished ketone **21** (Scheme 9).

According to the retrosynthetic plan (Scheme 7), the next task was the construction of butenolide ring, based on previous method developed by this group for butenolide construction (Scheme 11). Accordingly, the ketone **21** was subjected to the reaction with ethyl bromoacetate and activated zinc in benzene: ether (1:1) to provide alcohol **39** in 78% yield (Scheme 12). Strong bands at 1732 and 1676 cm^{-1} in its IR spectrum indicated the presence of ketone and five membered lactam functionalities respectively. Strong broad band at 3345 cm^{-1} showed the presence of hydroxy group. The appearance of characteristic peaks



Scheme 11. Reported method for butenolide construction

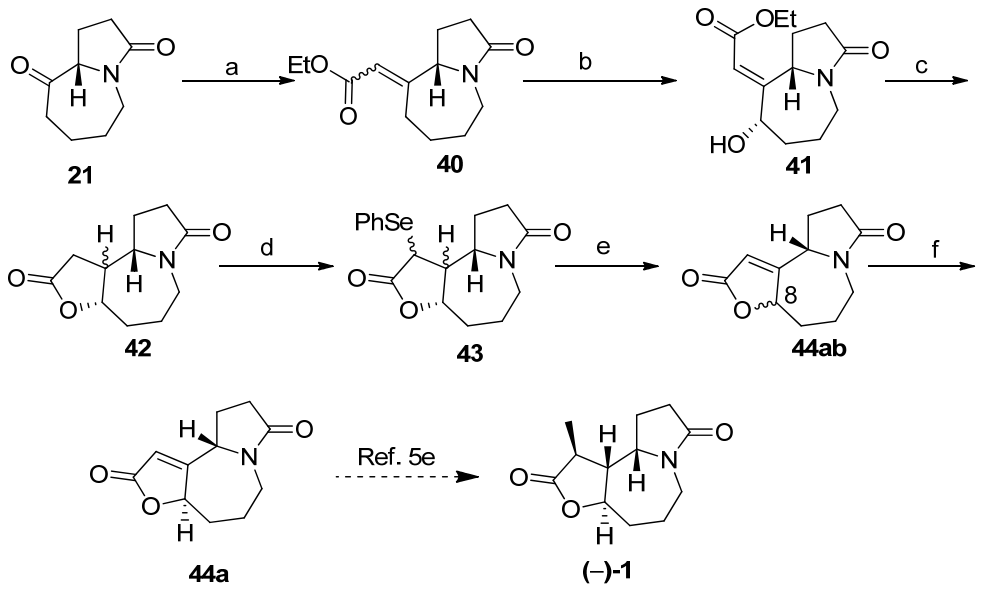
at δ 4.20 (q), 1.31 (t) and 1.20 (t) of ethyl propionate side chain in its ^{1}H-NMR spectrum provided strong evidence for the formation of **39**. Quartet at δ 2.79 and doublet of doublet at 3.60 integrating for one proton each was assigned to the α-proton of ester and proton adjacent to nitrogen (-CH-) respectively. Peaks at δ 176 and 175 in its ^{13}C-NMR spectrum were assigned to the ester carbonyl and lactam carbonyl respectively. The other peaks at δ 66 and 61 were assigned to the quaternary carbon adjacent to hydroxy and CH_2 carbon in ethyl ester. Peaks at δ 47 and 43 corresponded to the carbons adjacent to nitrogen –*C*H-*N*- and –



Scheme 12. Construction of butenolide ring

CH_2-*N*- respectively. Its DEPT spectrum showed presence of four CH and CH_3 carbons and seven CH_2 carbons in accordance with the proposed structure **39**. Finally its mass spectrum showed molecular ion peak at m/z 270 $(M+H)^+$ thus confirming the formation of **39**.

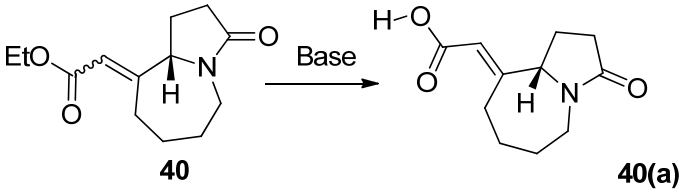
According to the methodology developed by this group (Scheme 11), alcohol **39** was subjected to reaction with thionyl chloride and pyridine in DCM to provide the expected product β,γ-unsaturated ester **20** but the formation of a mixture of isomeric olefins of **20** was observed. The ^{1}H-NMR spectrum of the mixture was complex but the LCMS showed three peaks with equal integration and same mass from which it can be predicted that the **20** may be the mixture of three isomeric olefins, in equal amounts, although the exact identity of the olefins could not be rigorously established. In spite of several modifications, it was not possible to obtain the required alkene **20** exclusively and it was very difficult to proceed with the mixture.



Scheme 17. Alternative route for butenolide ring construction.

Reagents and conditions: a) Triethyl phosphonoacetate, NaH, benzene, 88% b) SeO_2, AcOH, reflux, 45% c) $NiCl_2$, $NaBH_4$, THF, 78% d) LiHMDS, PhSeBr, THF, 95% e) 30% H_2O_2, DCM, 92% f) Et_3N, DCM, 2 days

The undesired results obtained during elimination led to change the route to (–)-stemoamide (**1**). Thus, the ketone **21** was subjected to Horner-Wadsworth-Emmons reaction (Scheme 17) using triethyl phosphonoacetate, to furnish α,β-unsaturated ester **40** in 88% yield. The strong bands at 1711 and 1690 cm^{-1} in its IR spectrum indicated the presence of the α,β-unsaturated ester carbonyl and five membered lactam carbonyl respectively. In its ^{1}H-NMR spectrum peaks at δ 5.78 and 5.77 corresponding to alkenyl proton integrated for 0.2 and 0.8 protons respectively, which indicated that the ratio of diastereomeric olefins should be 1:4. Four protons appeared at δ 4.25-4.05 as a multiplet and were assigned to methylene of ethyl ester and two protons on seven membered ring. Peak at δ 3.58 integrated for one proton which was assigned to proton at the ring junction.



40 **40(a)**

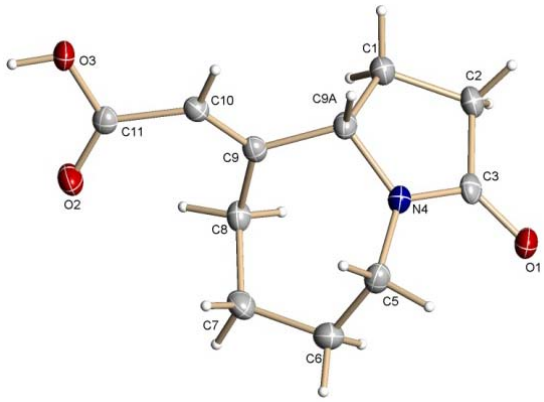
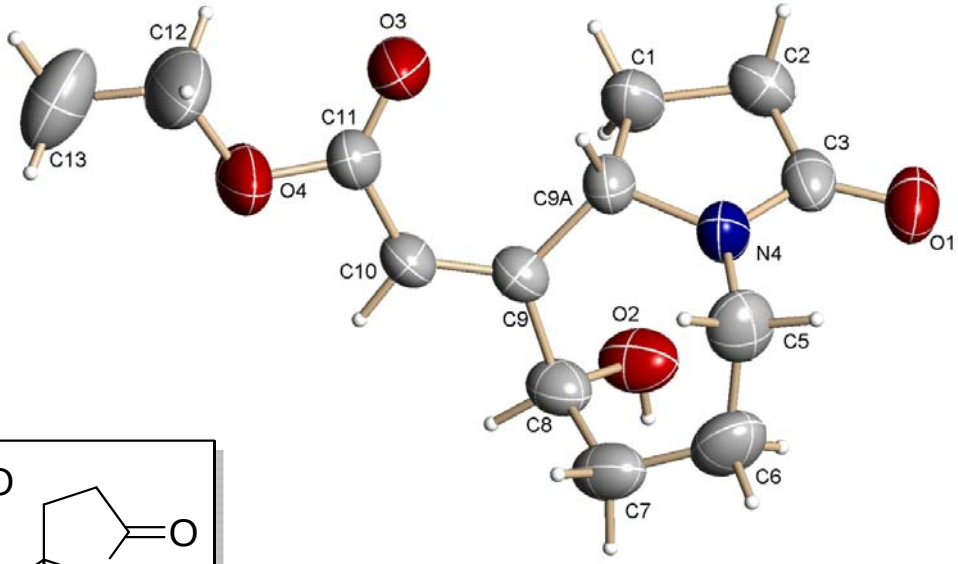


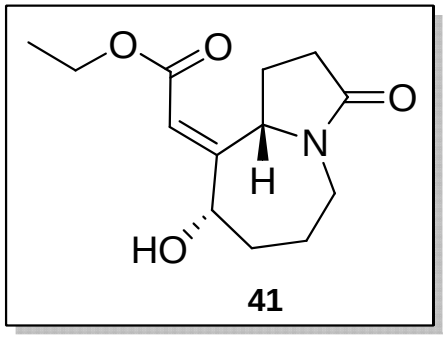
Figure 1. ORTEP view of compound **40(a)**

In order to confirm the formation of **40** as well as configuration of major isomer the ester was hydrolyzed by using LiOH to provide corresponding acid **40(a)**. Acid **40(a)** was recrystalized from ethyl acetate with 76% yield of the recrystalized acid whose single crystal X-ray analysis revealed that the predominating isomer was *E* (Figure **1**).[9]

It was surmised that the butenolide **44(a, b)** could be readily obtained by performing allylic oxidation on ester **40** according to the literature report.[10] Accordingly, the allylic oxidation was carried out using selenium dioxide under reflux conditions in acetic acid, but unfortunately instead of butenolide **44(a, b)**, the uncyclized hydroxy ester **41** was obtained as a single diastereomer. Failure to obtain butenolide was attributed to the *Z* configuration at double bond in hydroxy olefin **41**, in which ester is away from hydroxy group, which indeed

was later confirmed by single crystal X-ray analysis of **41** which clearly indicated that the *E* double bond converted in to *Z* configuration by rotation of α,β-bond during allylic oxidation (Figure 2).[11,12] It may be pointed out that the hydroxy group installed had the opposite stereochemistry than what is required for (–)-stemoamide.





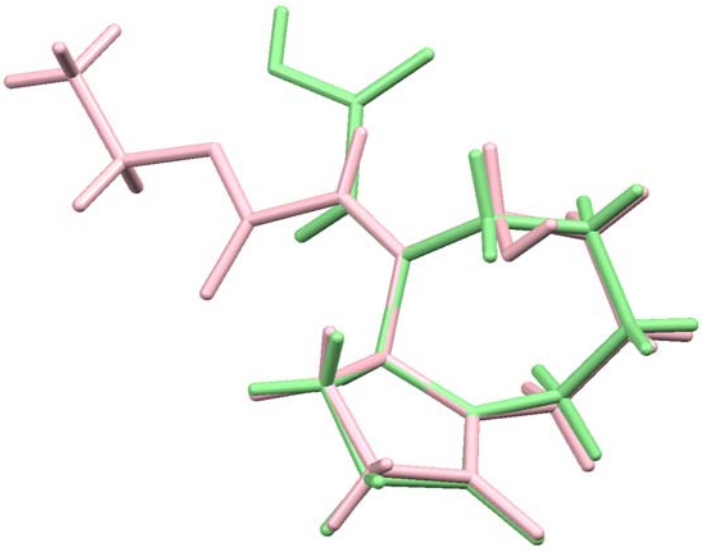


Figure 2: ORTEP diagram of **41** and rotation of double bond during allylic oxidation.

Hydroxy olefin **41** was treated with various reagents like PTSA, H_2SO_4, HCl, thiophenol-triethylamine, thiophenol-sodium hydride but none of the conditions resulted in the formation of butenolide **42**. As it was not possible to transform the hydroxy ester **41** directly to butenolide **44**, one had to take a circuitous route. After the unsuccessful attempts to cyclize the hydroxy olefin **41**, the double bond was reduced using $NiCl_2$:$NaBH_4$ in THF which furnished cyclized butyrolactone product **42** in 78% yield. But the stereochemistry of cyclized product was disappointing because the ^{1}H-NMR spectrum showed it to be a diastereomeric mixture in which stereochemistry at C8 and C9 was not the desired one.

In order to fix these two centres, the cyclized product was converted to α-phenyl selenolactone derivative using LiHMDS and PhSeBr in THF to give selenyl compound **43** in 95% yield (crude), according to Sibi's protocol.[13] The selenolactone **43** was subsequently subjected to elimination using hydrogen peroxide in DCM at 0 ºC, to furnish butenolide **44 (ab)** in 92% yield. Strong bands at 1753 and 1665 cm^{-1} in its IR spectrum indicated the presence of butenolide and five membered lactam carbonyl functionalities respectively. Two peaks at δ 5.98 and 5.84 in its ^{1}H-NMR spectrum corresponding to alkenyl proton integrated for 0.30 and 0.70 protons respectively indicating the 30:70 mixture of diastereomers, with desired isomer in minor amount.

Careful observation revealed that these two diastereomers of **44(a, b)** have a very small difference in Rf values (TLC). This diastereomeric mixture was treated with triethylamine in DCM and delightfully it was observed that the concentration of the faster moving (less polar) spot increased with time when the reaction was monitored by TLC. After prolonging this reaction by stirring the reaction mixture for almost two days, it was observed that the mixture was completely transformed in to the desired butenolide **44(a)**. The disappearance of peak at δ 5.84 and increased integration of peak at δ 5.98 in its ^{1}H-NMR spectrum clearly indicated the conversion of major isomer in to the desired isomer **44(a)**. Multiplet at δ 5.0-5.03 integrated for one proton which was assigned to γ-proton of butenolide. Its ^{13}C-NMR spectrum showed peaks at δ 174.5, 174.2 and 171.7 which were assigned to butenolide carbonyl, lactam carbonyl and β-carbon of butenolide respectively. Peaks at δ 116 and 82.9 corresponded to α and γ-carbons of butenolide respectively. Peaks at δ 58 and 43 were assigned to carbons adjacent to nitrogen. The remaining four carbons appeared at δ 34, 30, 27 and 25. Its mass spectrum showed molecular ion peaks at m/z 208 $(M+H)^+$, 230 $(M+Na)^+$

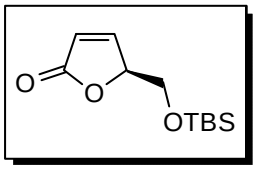
confirming the formation of **44(a)**. The spectral data, rotation value and melting point of **44(a)** were in good agreement with the reported one.[14] The conversion of butenolide **44(a)** to (–)-stemoamide (**1**) is well documented in the literature in two steps,[15] hence this constitutes the formal total synthesis of (–)-stemoamide.

3.2.2. Conclusion:

The formal total synthesis of (–)-stemoamide was achieved by taking advantage of RCM rection and allylic oxidation in 11 steps in 15% overall yield. The alternate route to seven membered ring construction was also developed using Grignard reaction and base induced cyclization to furnish butenolide **44(a)** in 14 steps in 11% overall yield. Complete novel epimerization of **44(a, b)** to expected isomer **44(a)** was achieved successfully.

3.2.3. Experimental

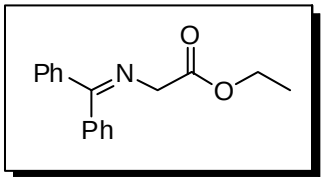
(*S*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)furan-2(5*H*)-one (6): Was prepared from tartaric acid according to reported procedure.[1]



Molecular Formula : $C_{11}H_{20}O_3Si$

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.49 (dd, *J* = 5.8, 1.5 Hz, 1H), 6.16 (dd, J = 5.8, 2.0 Hz, 1H), 5.07-5.01 (m, 1H), 3.98-3.77 (m, 2H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H)

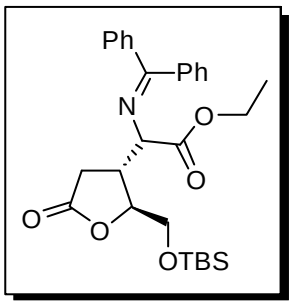
Ethyl 2-((diphenylmethylene)amino)acetate (7): Was prepared from glycine and diphenylimine hydrochloride according to the reported procedure.[2]



Molecular Formula: $C_{17}H_{17}NO_2$

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.67-7.65 (m, 2H), 7.50-7.41 (m, 4H), 7.35-7.32 (m, 2H), 7.21-7.19 (m, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.19 (s, 2H), 1.29 (t, *J* = 7.2 Hz, 3H)

(*R*)-Ethyl 2-((2*S*,3*R*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-oxotetrahydrofuran-3-yl)-2-((diphenylmethylene)amino)acetate (5)



To the well stirred solution of butenolide **6** (3.2 g, 14 mmol) and diphenylamine ethyl glycinate **7** (3.7 g, 14 mmol) in anhydrous THF (30 mL) was added LiBr (1.7 g, 19.4 mmol) at once. Triethylamine (2.4 mL, 17.3 mmol) was added to above reaction mixture dropwise at room temperature and stirred for 4 h at same temperature. After completion of the reaction, the reaction mixture was poured into saturated ammonium chloride solution and the organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give crude addition product **5**. Purification by flash column chromatography over silica gel (ethyl acetate–pet ether 20/80) afforded Michael adduct **5** (5.5 g, 80%) as a pale yellow dense liquid.

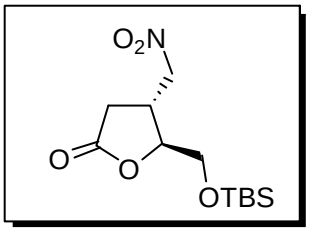
Molecular formula : $C_{28}H_{37}NO_5Si$

Yield **:** 80%

IR ($CHCl_3$) υ_{max} **:** 2932, 1782, 1735, 1464, 1230 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.74-7.70 (m, 2H), 7.62-7.14 (m, 8H), 4.81-4.80 (m, 1H), 4.14-4.04 (m, 3H), 3.94-3.84 (m, 1H), 3.73-3.66 (m, 1H), 3.13-3.03 (m, 1H), 2.65 (dd, *J* = 17.6, 11.1 Hz, 1H), 1.89 (dd, *J* = 17.6, 3.2 Hz, 1H), 1.20 (t, *J* = 7.2 Hz, 3H), 0.81 (s, 9H), 0.00 (s, 3H), –0.01 (s, 3H)

(4*R*,5*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-4-(nitromethyl)dihydrofuran-2(3*H*)-one (8)



To the well stirred solution of butenolide **6** (0.5 g, 2.2 mmol) in nitromethane (5 mL) was added DBU (0.1 mol%, 0.03 mL). The resulting reaction mixture was stirred for 4 h at room temperature. The excess of nitromethane was removed under reduced pressure to provide crude addition product **8**, which on flash column chromatography using silica gel (ethyl acetate–pet ether 20/80) rendered pure nitro compound **8** (0.53 g, 84%) as a colorless dense liquid.

Molecular formula **:** $C_{12}H_{23}NO_5Si$

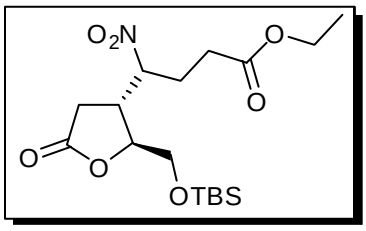
Yield **:** 84%

IR ($CHCl_3$) υ_{max} **:** 2945, 1782, 1556, 1464, 1228 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.63-4.44 (m, 2H), 4.40-4.34 (m, 1H), 3.94-3.77 (m, 2H), 3.35-3.21 (m, 1H), 2.95 (dd, *J* = 17.8, 9.7 Hz, 1H), 2.30 (dd, *J* = 17.8, 4.8 Hz, 1H), 0.89 (s, 9H), 0.09 (s, 3H), 0.10 (s, 3H)

^{13}C-NMR (200 MHz, $CDCl_3$): δ 174.3, 81.4, 76.8, 64.3, 35.4, 32.5, 25.8, 18.2, –5.5, –5.6

(*S*)-Ethyl 4-((2*S*,3*R*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-oxotetrahydrofuran-3-yl)-4-nitrobutanoate (9)



Method 1: To the stirred solution of nitro compound **8** (150 mg, 0.5 mmol) in acetonitrile (2 mL) was added ethyl acrylate (0.1 mL, 1 mmol) and the resulting reaction mixture was stirred for 10 min. Catalytic DBU (5 mol%, 0.07 mL) was added and the resulting reaction mixture was stirred further for 4 h at room temperature. Solvent was removed under reduced pressure to provide crude **9,**

which on flash column chromatography using silica gel (ethyl acetate–pet ether 15/85) rendered pure nitro compound **9** (150 mg, 75%) as a colorless dense liquid.

Method 2: To the stirred solution of butenolide **6** (100 mg, 0.43 mmol) and γ-nitro butyrate **10** (70 mg, 0.43 mmol) in THF (5 mL) was added sodium methoxide (23 mg, 0.43 mmol) at once at room temperature. The resulting reaction mixture was refluxed for 5 h and then cooled to room temperature. Reaction was quenched using sat. aq. ammonium chloride solution (10 mL) and extracted using ethyl acetate (3 x 10 mL). The combined organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to provide crude product which on flash column chromatography using silica gel (ethyl acetate–pet ether 15/85) rendered pure nitro compound **9** (133 mg, 78%) as a colorless dense liquid.

Molecular formula : $C_{17}H_{31}NO_7Si$

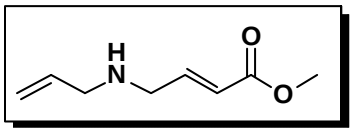
Yield : 78%

IR ($CHCl_3$) υ_{max} : 2955, 2931, 2858, 1785, 1735, 1552, 1184, 758 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.73-4.49 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.95-3.88 (m, 1H), 3.77-3.58 (m, 1H), 3.51-3.40 (m, 1H), 3.26-3.17 (m, 1H), 2.93-2.79 (m, 1H), 2.49-2.30 (m, 5H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H).

ESIMS (m/z) : 412 $(M+Na)^+$.

(*E*)-Methyl 4-(allylamino)but-2-enoate (14)



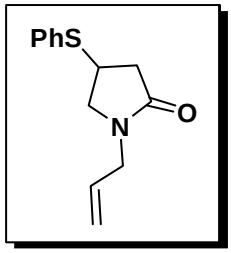
To the methyl 4-bromocrotonate (**13**) (1 gm, 5.6 mmol) in anhydrous THF (10 mL) was added allylamine (0.44 ml, 1.2 mmol) dropwise at 0 ^oC. The reaction mixture was allowed to warm to room temperature and was stirred for 4 hours. Water was then added to the reaction mixture and extraction was carried out in ethyl acetate (50 ml x 3). The ethyl acetate layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Purification of the crude product by flash column chromatography using silica gel (ethyl acetate–pet ether 45/55) furnished pure amine compound **14** (0.6 g, 73%) as a colorless dense liquid.

Molecular formula : $C_8H_{13}NO_2$

Yield : 73%

^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.09-6.95 (m, 1H), 6.13-5.86 (m, 2H), 5.37-5.25 (m, 3H), 4.23-3.97 (m, 1H), 3.78-3.67 (m, 4H), 3.55 (dd, *J* = 5.8, 1.2 Hz, 2H), 3.40 (d, *J*= 6.7 Hz, 2H).

1-Allyl-4-(phenylthio)pyrrolidin-2-one (15)



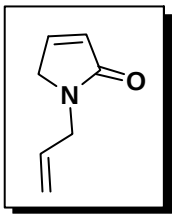
To the amine **14** (1.4 g, 9 mmol) in anhydrous THF (15 mL), was added triethylamine (3.8 ml, 27 mmol). The reaction mixture was cooled to 0 ^oC with stirring. Thiophenol (1.09 ml, 9.9 moles) was added drop wise at this temperature. The reaction mixture was then refluxed for 4 hrs. Water (20 mL) was then added to the reaction mixture and it was extracted with ethyl acetate (3 x 30 ml). Organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain the crude product. Purification of the crude product by flash column chromatography using silica gel (ethyl acetate–pet ether 40/60) furnished pure amide compound **14** (2 g, 95%) as a colorless dense liquid.

Molecular formula : $C_{13}H_{15}NOS$

Yield : 95%

^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.41-7.27 (m, 5H), 5.80-5.61 (m, 1H), 5.25- 5.17 (m, 2H), 3.96-3.83 (m, 3H), 3.73-3.64 (m, 1H), 3.36-3.28 (m, 1H), 2.86 (dd, *J* = 17.3, 8.3 Hz, 1H), 2.47 (dd, *J* = 5.4, 17.3 Hz, 1H).

1-Allyl-1*H*-pyrrol-2(5*H*)-one (11)



To the sulfide **14** (1 g, 4.3 mmole) in methanol (15 ml), was added solution of $NaIO_4$ (0.914 g, 4.3 mmol) in water (18 mL) dropwise at 0 ^oC. The reaction mixture was stirred at room temperature till the completion of reaction (5 h). The reaction mixture was filtered on celite. Methanol was evaporated under reduced pressure and extraction was carried out with ethyl acetate (3 x 30 mL). The collected organics were dried over anhydrous sodium sulphate, filtered and concentrated on rotavapor to furnish the sulfoxide **28** (0.96 g, 74%). The crude **28** as such was dissolved in toluene (20 mL) and to it was added $NaHCO_3$ (356 mg, 4.3 mmol). The resulting reaction mixture was refluxed for 3 h and then cooled to room

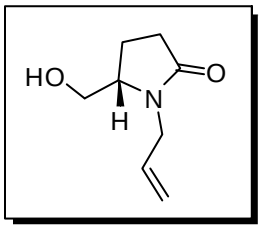
temperature. Water (20 mL) was added to reaction mixture and it was extracted using ethyl acetate (3 x 20 mL). The combined organics were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide crude **11**. Purification of the crude product by flash column chromatography using silica gel (ethyl acetate–pet ether 70/30) furnished pure pyrrolinone **11** (0.316 mg, 60%) as a colorless dense liquid.

Molecular formula : C_7H_9NO

Yield : 60%

^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.11-7.06 (m, 1H), 6.22-6.17 (m, 1H), 5.89-5.70 (m, 1H), 5.20-5.11 (m, 2H), 4.06 (d, *J* = 5.8 Hz, 2H), 3.97-3.96 (m, 2H).

(*S*)-1-Allyl-5-(hydroxymethyl)pyrrolidin-2-one (28)



Molecular formula : $C_8H_{13}NO_2$

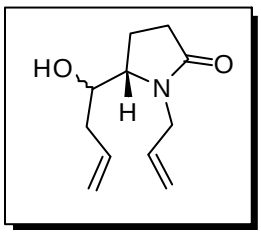
IR ($CHCl_3$) υ_{max} : 3410, 3018, 1672, 1417, 1215, 756, 667 cm^{-1}

^{1}H-NMR (200 MHz, $CDCl_3$): δ 5.65-5.85 (m, 1H), 5.17-5.25 (m, 2H), 4.24 (dd, *J* = 16.2, 4.3 Hz, 1H), 3.65 (bs, 2H), 3.52 (m, 2H), 2.85 (s, 1H), 2.01-2.61 (m, 4H)

^{13}CNMR (50 MHz, $CDCl_3$): δ 174, 132, 118, 62.3, 59.2, 58.8, 44.5, 30.5

ESIMS (m/z) : 156 $(M+H)^+$, 178 $(M+Na)^+$.

(5*S*)-1-Allyl-5-(1-hydroxybut-3-en-1-yl)pyrrolidin-2-one (22)



To the alcohol **28** (5 gm, 32 mmol) in ethyl acetate (70 mL), was added IBX (13.5 gm, 48 mmol) and heated at reflux for 3-4 hours. Reaction mixture was filtered through Whatman filter paper and concentrated *in vacuo*. The crude aldehyde was dissolved in anhydrous DCM (60 mL) and to it was added allyltrimethylsilane (10.2 mL, 64 mmol) at 0 ºC and subsequently $BF_3.OEt_2$ (9.2 mL, 64 mmol) was added dropwise. Reaction mixture was stirred for 2-2.5 h at 0 ºC and quenched using saturated ammonium chloride solution (20 mL). Water (50 mL) was added and DCM layer was separated and the aqueous layer was extracted using DCM (2 x 50 mL). The combined

organics were dried over anhydrous sodium sulfate, filterd and concentrated under reduced pressure. The crude product was purified using flash column chromatography (30:70 Pet ether:EtOAc) to afford the diallylated product **22** (5.5 gm, 87%) as a colorless sticky liquid.

Molecular formula : $C_{11}H_{17}NO_2$

Yield : 87%

IR ($CHCl_3$) υ_{max} : 3390, 3998, 2851, 1675, 1250, 924, 624 cm^{-1}.

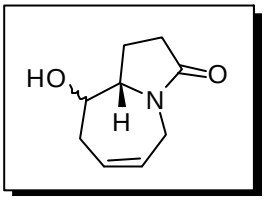
^{1}H-NMR (200 MHz, $CDCl_3$): δ 5.88-5.71 (m, 2H), 5.25-5.09 (m, 4H), 4.35-4.24 (m, 1H), 3.99-3.92 (m, 1H), 3.84-3.58 (m, 3H), 2.85 (bs, 1H), 2.50-2.25 (m, 3H), 2.19-1.86 (m, 3H).

^{13}CNMR (50 MHz, $CDCl_3$): δ 175.7, 133.9, 132.8, 118.6, 117.5, 72.1, 61.3, 44.8, 36.8, 30.1, 20.5.

ESIMS (m/z) : 196 $(M+H)^+$, 218 $(M+Na)^+$.

Elemental analysis : Calculated C, 67.66; H, 8.78; N, 7.17%
Found C, 67.61; H, 8.75; N, 7.20%

(9a*S*)-9-Hydroxy-5,8,9,9a-tetrahydro-1*H*-pyrrolo[1,2-a]azepin-3(2*H*)-one (29)



Diallylated compound **22** (1 gm, 5 mmol) and Grubbs' 2nd generation catalyst (82 mg, 2 mol %) in anhydrous DCM (500 mL) was stirred at room temperature for 5 hours. The reaction mixture was filtered through celite and concentrated *in vacuo* to provide crude **29**. The crude product was purified using flash chromatography (SiO_2) (Ethyl acetate) to provide the ring closed product **29** (0.73 gm, 85%) as a colorless sticky liquid.

Molecular formula : $C_9H_{13}NO_2$

Yield : 85%

IR ($CHCl_3$) υ_{max} : 3393, 3019, 1674, 1421, 1216, 1076, 756 cm^{-1}.

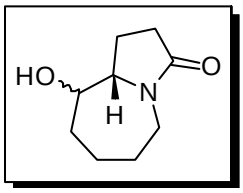
^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.07-5.87 (m, 1H), 5.73-5.57 (m, 1H), 4.61 (dd, J = 16.3, 7.5 Hz, 1H) 3.95-3.91 (m, 1H), 3.84-3.77 (m, 1H), 3.72-3.58 (m, 1H), 3.44-3.29 (m, 1H), 2.71-2.29 (m, 3H), 2.23-1.80 (m, 3H)

^{13}CNMR (50 MHz, $CDCl_3$) : δ 174.2, 129.6, 127.7, 71.5, 67.2, 40.1, 33.5, 29.9, 22.3.

ESIMS (m/z) **:** 168 $(M+H)^+$, 190 $(M+Na)^+$.

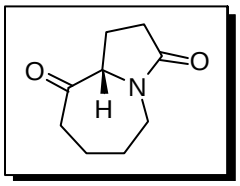
Elemental analysis **:** Calculated C, 64.65; H, 7.84; N, 8.38%
Found C, 64.61; H, 7.87; N, 8.36%

(9a*S*)-9-Hydroxyhexahydro-1*H*-pyrrolo[1,2-a]azepin-3(2*H*)-one (30)



To the solution of alcohol **29** (0.5 gm, 3 mmol) in methanol (30 mL) was added catalytic amount of palladium hydroxide (20% over charcoal) and subjected to 60 psi hydrogen pressure for 1 h in a Paar Shaker. The solution was filtered through celite and the filtrate concentrated *in vacuo*. The crude product (0.48 gm, 96%) was obtained as a colorless sticky liquid and was used as such for subsequent reactions. The alcohol thus obtained had identical physical and spectral properties to the one obtained by Grignard reaction route (Scheme 10).

(*S*)-Tetrahydro-1*H*-pyrrolo[1,2-a]azepine-3,9(2*H*,9a*H*)-dione (21)



The alcohol **30** (1 gm, 6 mmol) and IBX (5 gm, 18 mmol) in ethyl acetate (30 mL) were heated at reflux for 4 hours. The reaction mixture was filtered through Whatman filter paper and the residue was washed with ethyl acetate (30 mL). The filtrate was concentrated *in vacuo* to provide crude product as sticky liquid. The crude product was purified using flash chromatography (SiO_2) (Ethyl acetate/ pet ether 80/20) to provide ketone **21** (0.8 g, 82%) as a colorless sticky liquid.

Molecular formula **:** $C_9H_{13}NO_2$

Yield **:** 82%

IR ($CHCl_3$) υ_{max} **:** 3018, 2923, 2820, 1720, 1692, 1413, 1230, 1120, 750 cm^{-1}.

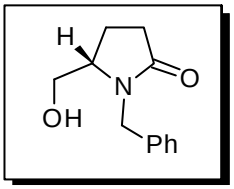
^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.31-4.27 (m, 1H)), 4.03-4.00 (m, 1H), 2.70-2.66 (m, 2H), 2.48-2.31 (m, 4H), 2.06-2.01 (m, 1H), 1.91-1.83 (m, 2H), 1.77-1.68 (m, 1H), 1.54-1.45 (m, 1H).

^{13}CNMR (50 MHz, $CDCl_3$): δ 211.9, 174.7, 68.2, 43.8, 40.7, 29.8, 28.9, 24.4, 22.3.

ESIMS (m/z) **:** 168 $(M+H)^+$, 190 $(M+Na)^+$.

Elemental analysis **:** Calculated C, 64.65; H, 7.84; N, 8.38%
Found C, 64.62; H, 7.85; N, 8.35%

(*S*)-1-Benzyl-5-(hydroxymethyl)pyrrolidin-2-one (31)



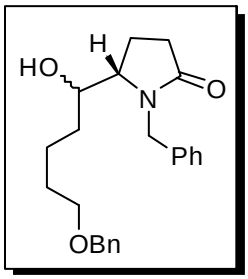
Molecular formula : $C_{12}H_{15}NO_2$

IR ($CHCl_3$) υ_{max} : 3395, 1672, 1219, 1056, 746 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.35-7.21 (m, 5H), 4.95-4.86 (m, 2H), 4.42 (d, *J* = 15.1 Hz, 1H), 3.85-3.78 (m, 1H), 3.54-3.43 (m, 2H), 3.02 (bs, 1H), 2.67-2.30 (m, 2H), 2.08-1.97 (m, 2H).

^{13}CNMR (50 MHz, $CDCl_3$): δ 176.2, 136.4, 128.6, 127.9, 127.5, 61.7, 58.5, 44.2, 30.5, 20.9.

(5*S*)-1-Benzyl-5-(5-(benzyloxy)-1-hydroxypentyl)pyrrolidin-2-one (25)



The mixture of alcohol **31** (2 gm, 9.7 mmol) and IBX (5.4 gm, 19 mmol) in ethyl acetate (30 mL) was heated at reflux for 4 hours. The reaction mixture was filtered through Whatman filter paper and the residue was washed with ethyl acetate (30 mL). The filtrate was concentrated *in vacuo* to provide crude aldehyde **26** as a sticky liquid. Aldehyde **26** was dissolved in anhydrous THF (20 mL) and the mixture was cooled to –50 ºC. The preformed Grignard reagent generated from 4-benzyloxybutyl bromide (5.8 g, 24 mmol) and activated Mg (0.7 g, 29 mmol) in THF (30 mL) was added dropwise (30 min) at – 50 ºC with vigorous stirring. Reaction mixture was allowed to warm to room temperature and then quenched with sat. ammonium chloride solution (20 mL). The organic layer was separated and the aqueous layer was extracted using ethyl acetate (2 x 40 mL). The combined organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to provide crude product. The crude product was purified using flash chromatography over SiO_2 (Ethyl acetate/ pet ether 80/20) to provide alcohol **25** (2.5 g, 74%) as a colorless dense liquid.

Molecular formula : $C_{23}H_{29}NO_3$

Yield **:** 74%

IR ($CHCl_3$) υ_{max} **:** 3401, 2929, 2835, 1666, 1250, 1145, 751 cm^{-1}.

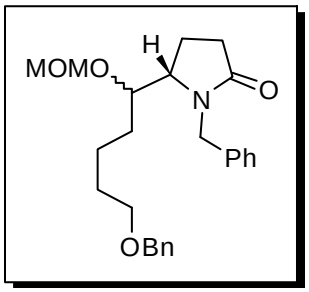
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.33-7.20 (m, 10H), 4.88 (d, *J* = 14.9 Hz, 1H), 4.48 (s, 2H), 4.27 (d, *J* = 14.9 Hz, 1H), 3.65 (bs, 1H), 3.53-3.41 (m, 3H), 2.48-2.35 (m, 2H), 2.08-1.93 (m, 2H), 1.93-1.78 (m, 1H), 1.69-1.54 (m, 4H), 1.38-1.23 (m, 4H).

^{13}CNMR (50 MHz, $CDCl_3$): δ 175.9, 138.3, 137.1, 128.8, 128.6, 128.3, 128.0, 127.6, 124.4, 73.0, 72.9, 70.1, 61.6, 46.0, 31.6, 30.2, 29.3, 22.6, 20.4.

ESIMS (m/z) **:** 368 $(M+H)^+$

Elemental analysis **:** Calculated C, 75.17; H, 7.95; N, 3.81%
Found C, 75.20; H, 7.93; N, 3.80%

(5*S*)-1-Benzyl-5-(5-(benzyloxy)-1-(methoxymethoxy)pentyl)pyrrolidin-2-one (32)



To the alcohol 25 (1.5 g, 4.1 mmol) in anhydrous DCM (20 mL) was added di-isopropylethyl amine (0.4 mL, 5.3 mmol) and the reaction mixture was cooled to 0 ºC using ice. Methoxymethyl chloride (1.8 mL, 6.1 mmol) was added dropwise at 0 ºC and the resulting reaction mixture was refluxed for 3 hours. Reaction mixture was cooled to room temperature, quenched using water (20 mL) and the organic and aqueous layers were separated. The aqueous layer was extracted using DCM (2 x 20 mL). The combined organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to provide crude product. The crude product was purified using flash chromatography over SiO_2 (Ethyl acetate/ pet ether 60/40) to provide MOM protected compound **32** (1.5 g, 90%) as a colorless dense liquid.

Molecular formula **:** $C_{25}H_{33}NO_4$

Yield **:** 90%

IR ($CHCl_3$) υ_{max} **:** 2925, 2842, 1671, 1245 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.34-7.21 (m, 10H), 4.88 (d, *J* = 14.7 Hz, 1H), 4.51 (s, 2H), 4.48 (s, 2H), 4.08 (d, *J* = 14.7, 1H), 3.72-3.59 (m, 2H), 3.44-

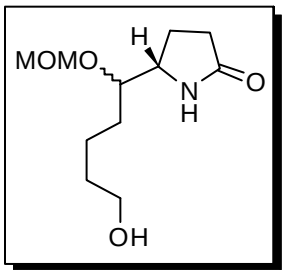
3.38 (m, 2H), 3.28 (s, 3H), 2.46-2.35 (m, 2H), 1.66-1.12 (m, 8H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 175.5, 138.5, 136.7, 128.6, 128.3, 128.2, 127.6, 127.5, 96.7 77.9, 72.6, 70.0, 60.0, 55.6, 45.5, 30.3, 29.7, 28.5, 22.5, 18.9.

ESIMS (m/z) **:** 412 $(M+H)^+$

Elemental analysis **:** Calculated C, 72.96; H, 8.08; N, 3.40%
Found C, 72.99; H, 8.05; N, 3.42%

(5*S*)-5-(5-Hydroxy-1-(methoxymethoxy)pentyl)pyrrolidin-2-one (24)



A solution of *t*-butanol (1.5 mL) and THF (15 mL) was cooled to –78 ºC, to that was passed ammonia gas till the total volume became 20 mL approximately. Small pieces of sodium (120 mg, 5 mmol) were added portion wise and the resultant reaction mixture was stirred vigorously for 15-20 minutes (solution became deep blue in color). Dibenzyl compound **32** (500 mg, 1.2 mmol) in THF (15 mL) was added dropwise and the resultant reaction mixture was stirred for 45 minutes at –78 ºC. The reaction mixture was quenched using sat. aqueous ammonium chloride solution (5 mL) at –78 ºC and was allowed to come to room temperature. Reaction mixture was extracted with ethyl acetate (3 x 20 mL). The collected organics were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide crude alcohol **24**. The crude product was purified using flash chromatography over SiO_2 (Ethyl acetate/ MeOH 98/02) to provide alcohol **24** (244 mg, 87%) as a colorless dense liquid.

Molecular formula **:** $C_{11}H_{21}NO_4$

Yield **:** 87%

IR ($CHCl_3$) υ_{max} **:** 3433, 2929, 2841, 1679, 1240 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.36 (bs, 1H), 4.70-4.64 (m, 2H), 3.74-3.58 (m, 3H), 3.39 (s, 3H), 3.37-3.34 (m, 1H), 2.43-2.27 (m, 2H), 2.22-2.06 (m, 1H), 1.86-1.77 (m, 1H), 1.66-1.47 (m, 6H).

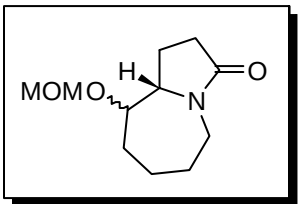
^{13}C-NMR (50 MHz, $CDCl_3$): δ 178.8, 96.7, 82.4, 61.4, 57.1, 55.8, 32.6, 30.6, 30.2, 23.7, 20.1.

ESIMS (m/z) **:** 254 $(M+Na)^+$.

Elemental analysis **:** Calculated C, 57.12; H, 9.15; N, 6.06%

Found C, 57.09; H, 9.16; N, 6.03%

(9a*S*)-9-(Methoxymethoxy)hexahydro-1*H*-pyrrolo[1,2-a]azepin-3(2*H*)-one (33)



Alcohol **24** (200 mg, 0.86 mmol) was dissolved in DCM (5 mL) and to it was added triethylamine (0.25 mL, 1.7 mmol) and the resultant reaction mixture was cooled to 0 ºC. Methanesulfonyl chloride (0.08 mL, 1 mmol) was added dropwise at 0 ºC and stirred further for 6 hours at room temperature. Reaction mixture was quenched with water (5 mL) and extracted with DCM (3 x 5 mL). The collected organics were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide crude mesylate. The crude mesylate in THF (2 mL) was added dropwise to the suspension of sodium hydride (41 mg, 1 mmol) in THF (2 mL) at 0 ºC and the resulting reaction mixture was further stirred for 3 hours at room temperature. Reaction mixture was quenched using sat. aqueous ammonium chloride solution (2 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide crude product. The crude product was purified using flash chromatography over SiO_2 (Ethyl acetate) to provide alcohol **24** (158 mg, 86%) as a colorless sticky liquid.

Molecular formula : $C_{11}H_{19}NO_3$

Yield : 86%

IR ($CHCl_3$) υ_{max} : 2926, 2848, 1687, 1235 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.72-4.58 (m, 2H), 3.89-3.81 (m, 2H), 3.63-3.56 (m, 1H), 3.39 (s, 3H), 3.20-3.14 (m, 1H), 2.52-2.44 (m, 1H), 2.35-2.28 (m, 1H), 2.16-1.98 (m, 2H), 1.94-1.76 (m, 3H), 1.70.-1.56 (m, 3H).

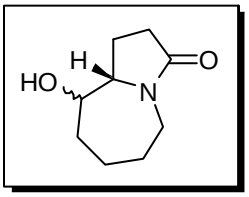
^{13}C-NMR (50 MHz, $CDCl_3$): δ 175.6, 95.2, 78.2, 61.5, 55.9, 43.2, 31.3, 30.7, 27.0, 24.1, 13.1.

ESIMS (m/z) : 214 $(M+H)^+$.

Elemental analysis : Calculated C, 61.95; H, 8.98; N, 6.57%

Found C, 61.96; H, 8.94; N, 6.59%

(*S*)-9-Hydroxyhexahydro-1*H*-pyrrolo[1,2-a]azepin-3(2*H*)-one (30)



MOM protected bicyclic amide **33** (150 mg, 0.7 mmol) was dissolved in methanol (5 mL) and to it was added trace amount of conc. HCl. The resulting reaction mixture was refluxed for 15 minutes and then the methanol was removed under reduced pressure to provide crude alcohol. The crude product was purified using flash chromatography over SiO_2 (Ethyl acetate) to provide alcohol **30** (88 mg, 74%) as a colorless dense liquid.

Molecular formula : $C_9H_{15}NO_2$

Yield : 96%

IR ($CHCl_3$) υ_{max} : 3395, 3017, 1693, 1210, 1068, 750 cm^{-1}.

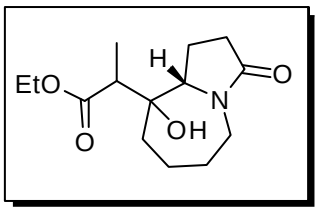
^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.95-3.88 (m, 2H), 3.58-3.53 (m, 1H), 3.32-3.29 (m, 1H), 2.61 (bs, 1H), 2.36-2.18 (m, 4H), 2.00-1.89 (m, 2H), 1.74-1.43 (m, 4H).

^{13}CNMR (50 MHz, $CDCl_3$) : δ 176.9, 73.2, 62.1, 44.0, 35.5, 31.0, 29.7, 23.6, 22.9.

ESIMS (m/z) : 192 $(M+Na)^+$.

Elemental analysis : Calculated C, 63.88; H, 8.93; N, 8.28%
Found C, 63.91; H, 8.91; N, 8.30%

Ethyl 2-((9a*S*)-9-hydroxy-3-oxooctahydro-1*H*-pyrrolo[1,2-a]azepin-9-yl)propanoate (39)



To the ketone **21** (200 mg, 1.2 mmol) in benzene: ether (1:1, 2 mL) was added zinc (226 mg, 3.6 mmol) and catalytic amount of iodine and the reaction was stirred for 15 minutes. Ethyl 2-bromopropionate in benzene: ether (1:1, 2 mL) was added dropwise and stirred under reflux at 70 ºC. Reaction was quenched using 10% HCl (2 mL), filtered from simple filter paper and extracted using ethyl acetate (3 x 20 mL). The collected organics were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified using flash chromatography (4:6 Pet ether:EtOAc) to afford the ester **39** (280 mg, 87%) as a yellowish solid (Mp.94-95 ºC).

Molecular formula : $C_{14}H_{23}NO_4$

Yield **:** 87%

Melting point **:** 94-95 ºC

IR ($CHCl_3$) υ_{max} **:** 3433, 3018, 2952, 1734, 1670, 1412, 1250, 910 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.20 (q, *J* = 7.1 Hz, 2H), 3.95-3.83 (m, 1H), 3.60 (dd, 8.3, 4.2 Hz, 1H), 3.05-2.91 (m, 1H), 2.79 (q, *J* = 7.4 Hz, 1H), 2.67-2.50 (m, 1H), 2.32-2.21 (m, 1H), 2.18-2.02 (m, 2H), 1.98-1.80 (m, 2H), 1.75-1.70 (m, 2H), 1.66-1.51 (m, 2H), 1.31 (t, *J* = 7.1, 3H), 1.20 (d, *J* = 7.4 Hz, 3H).

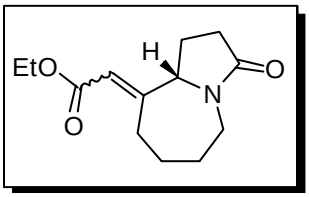
^{13}CNMR (50 MHz, $CDCl_3$): δ 176.0, 175.4, 76.4, 65.9, 61.2, 46.7, 42.5, 33.5, 30.5, 26.1, 21.1, 20.3, 14.1, 12.1.

ESIMS (m/z) **:** 270 $(M+H)^+$.

Elemental analysis **:** Calculated C, 62.43; H, 8.61; N, 5.20%

Found C, 62.40; H, 8.62; N, 5.23%

(*S*)-Ethyl 2-(3-oxohexahydro-1*H*-pyrrolo[1,2-a]azepin-9(9a*H*)-ylidene)acetate (40)



To the suspension of NaH (60% in mineral oil, 95 mg, 2.4 mmol) in benzene (5 mL) was added triethyl phosphonoacetate (0.5 ml, 2.4 mmol) dropwise at room temperature and stirred for one hour. Ketone **21** (400 mg, 2.4 mmol) in benzene (5 mL) was added dropwise and stirred for further 24 hours. Reaction was quenched using water (20 mL) and extracted using ethyl acetate (3 x 20 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure and crude product was purified using flash chromatography over SiO_2 (Pet ether/EtOAc 40/60) to afford α, β-unsaturated ester **40** (500 mg, 88%) as a colorless liquid.

Molecular formula **:** $C_{13}H_{19}NO_3$

Yield **:** 88%

(Data given for methyl ester as a pure major *E* isomer: This was prepared by hydrolyzing ester **40** to acid. The acid was then recrystallized and esterified using diazomethane to methyl ester)

IR ($CHCl_3$) υ_{max} **:** 2983, 2935, 1711, 1690, 1156, 754 cm^{-1}.

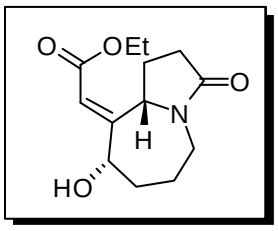
^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.77 (s, 1H), 4.18 (t, *J* = 8.2 Hz, 1H), 4.10-4.07 (m, 1H), 3.72 (s, 3H), 3.67-3.57 (m, 1H), 2.48-2.40 (m, 3H), 2.22-

2.07 (m, 2H), 1.84-1.25 (m, 5H).

^{13}CNMR (100 MHz, $CDCl_3$): δ 174.2, 165.9, 163.1, 117.1, 66.9, 51.2, 42.1, 30.6, 28.9, 28.7, 26.5, 25.7.

ESIMS (m/z) **:** 224 $(M+H)^+$.

(*E*)-Ethyl 2-((8*S*,9a*S*)-8-hydroxy-3-oxohexahydro-1*H*-pyrrolo[1,2-a]azepin-9(9a*H*)-ylidene)acetate (41)



To the α, β-unsaturated ester **40** (400 mg, 1.7 mmol) in acetic acid (10 mL), was added selenium dioxide (284 mg, 2.5 mmol) and heated at reflux for 5 hours. The reaction mixture was filtered from celite and washed with ethyl acetate (50 mL). The collected filtrate was concentrated *in vacuo* and purified using flash chromatography (EtOAc) to provide hydroxyl compound **41** (192 mg, 45%) as a crystalline solid.

Molecular formula **:** $C_{13}H_{19}NO_4$

Yield **:** 45%

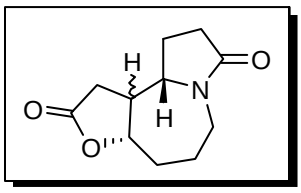
Melting point **:** 104-105 ºC

IR ($CHCl_3$) υ_{max} **:** 3367, 2925, 2800, 1706, 1663, 1402, 1223, 1175 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.80 (s, 1H), 5.41 (t, *J* = 7.2 Hz, 1H), 4.60 (d, *J* = 6.2 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.13-4.09 (m, 1H), 2.65-2.34 (m, 4H), 2.25-2.20 (m, 1H), 2.09-1.88 (m, 2H), 1.61-1.54 (m, 2H), 1.30 (t, *J* = 7.2, 3H).

^{13}CNMR (100 MHz, $CDCl_3$): δ 175.7, 165.6, 163.9, 117.5, 77.2, 60.4, 60.2, 42.8, 35.3, 30.3, 25.6, 21.9, 14.2.

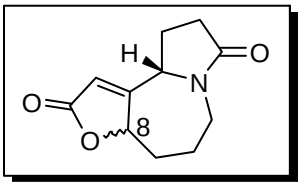
(3a*S*,10a*S*)-Hexahydro-1*H*-furo[3,2-c]pyrrolo[1,2-a]azepine-2,8(9*H*,10b*H*)-dione (42)



To a solution of hydroxyl compound **41** (100 mg, 0.4 mmol) in MeOH (2.0 mL) was added $NiCl_2.6H_2O$ (23 mg, 0.1 mmol) followed by $NaBH_4$ (60 mg, 1.6 mmol) at –30 °C. After 3 h, the solution was quenched with HCl (1.0 mL, 1 M) and diluted with CH_2Cl_2 (3 mL). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced

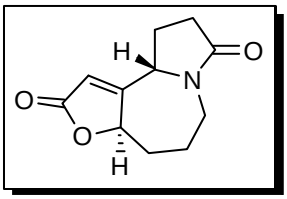
pressure. Flash chromatography over SiO_2 (MeOH/ EtOAc, 5/95) of the residue gave tricycliclactone **42** (64 mg, 78%) as a clear oil.

(10a*S*)-3a,4,5,6,10,10a-Hexahydro-2*H*-furo[3,2-c]pyrrolo[1,2-a]azepine-2,8(9*H*)-dione (44ab)



To a stirred solution of **42** (50 mg, 0.24 mmol) in THF (4 mL) was added LiHMDS (1 M in THF solution, 0.26 mL, 0.95 mmol) at -78 °C. After being stirred at the same temperature for 30 min, phenylselenenyl bromide (112 mg, 0.48 mmol) was added, and the resulting mixture was stirred for 1 h. After the reaction mixture was quenched by addition of 1 M HCl, the aqueous phase was extracted with ethyl acetate (3 x 5 mL). The extract was washed with brine and dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to provide the crude selenide **43** (82 mg, 95%) which was then dissolved in CH_2Cl_2 (5 mL). The solution was cooled to 0 °C and treated with 30% hydrogen peroxide (1 mL). After the mixture was vigorously stirred for 1 h at the same temperature, the aqueous layer was extracted with DCM (3 x 5 mL) and then washed with sat. aqueous $NaHCO_3$ solution followed by water. The combined organics were dried over Na2SO4, filtered and concentrated under reduced pressure to leave a residue, which was subjected to column chromatography on silica gel. Elution with MeOH-EtOAc (2:98, v/v) afforded **44ab** (44 mg, 92%) as a white solid.

(3a*R*,10a*S*)-3a,4,5,6,10,10a-Hexahydro-2*H*-furo[3,2-c]pyrrolo[1,2-a]azepine-2,8(9*H*)-dione (44a)



To the diastereomeric mixture of butenolide **44ab** (30 mg, 0.15 mmol) in anhydrous DCM (5 mL) was added triethylamine (0.04 ml, 2.9 mmol) and stirred further for 2 days. The reaction mixture was concentrated *in vacuo* and purified using flash chromatography (SiO_2) (MeOH: EtOAc 2:98) to afford enantiomerically pure **44a** (24 mg, 80%) as a white solid.

Molecular formula : $C_{11}H_{13}NO_3$

Yield : 80%

$[\alpha]_D^{25}$: – 227 (c, 0.4 $CHCl_3$), lit[5h]-$[\alpha]^{20}{}_D$ – 224 (c, 0.4 $CHCl_3$)

Melting point : 158-159 ºC, lit[5k] mp-157-159 ºC

IR ($CHCl_3$) υ_{max} : 2928, 2850, 1753, 1665, 1454, 1223, 911, 750 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.98 (s, 1H), 5.03-5.00 (m, 1H), 4.81-4.77 (m, 1H), 4.32-4.29 (m, 1H), 2.58-2.49 (m, 5H), 1.94-1.84 (m, 2H), 1.76-1.68 (m, 1H), 1.48-1.40 (m, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 174.5, 174.1, 171.7, 115.9, 82.9, 58.1, 43.4, 34.5, 30.2, 27.7, 25.7

ESIMS (m/z) : 208 $(M+H)^+$, 230 $(M+Na)^+$.

Crystal data for $C_{11}H_{15}NO_3$ compound 40(a):

Single crystals of the complex were grown by slow evaporation of the solution of ethyl acetate. Data was collected on SMART APEX-II CCD using Mo-Kα radiation to a maximum θ range of 25.00°. Colourless plate like crystal of approximate size 0.34 x 0.32 x 0.20 mm^3, was used for data collection. Exposure / frame = 10.0 sec / frame, completeness to θ of 25.00 º, is 99.9 %. C11 H15 N O3, M = 209.24. Crystals belong to Monoclinic, space group C2/c, a = 15.271(2), b = 7.2304(7), c = 19.654(2) Å, V = 2090.0(4) $Å^3$, Z = 8, D_c = 1.330 g /cc, 9773 reflections measured, 1836 unique [I>2σ(I)], R value 0.0323, wR2 = 0.0816. SHELX-97 (ShelxTL)[ref] was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. Data collection and refinement parameters are listed in table 1.

The conformation of the molecule was established by single crystal X-ray analysis shows C9a to have S configuration.

Table 1. Crystal data and structure refinement for C11H15NO3compound **40a**.

Empirical formula	C11 H15 N O3	
Formula weight	209.24	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 15.271(2) Å	α= 90°.
	b = 7.2304(7) Å	β= 105.609(5)°.

	c = 19.654(2) Å γ = 90°.
Volume	2090.0(4) $Å^3$
Z	8
Density (calculated)	1.330 g/cc
Crystal size	0.34 x 0.32 x 0.20 mm^3
Theta range for data collection	2.77 to 25.00°.
Reflections collected	9773
Independent reflections	1836 [R(int) = 0.0303]
Completeness to theta = 25.00°	99.9 %
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.065
Final R indices [I>2sigma(I)]	R1 = 0.0323, wR2 = 0.0816
R indices (all data)	R1 = 0.0360, wR2 = 0.0844

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for kh645_0m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	8906(1)	7591(1)	5288(1)	25(1)
O(2)	8615(1)	5455(1)	1561(1)	27(1)
O(3)	8883(1)	2399(1)	1605(1)	23(1)
C(1)	7968(1)	3950(2)	4055(1)	24(1)
C(2)	8058(1)	4780(2)	4786(1)	22(1)
C(3)	8725(1)	6346(2)	4836(1)	20(1)
N(4)	9123(1)	6201(1)	4309(1)	19(1)
C(5)	9786(1)	7540(2)	4192(1)	23(1)
C(6)	9330(1)	9093(2)	3699(1)	26(1)
C(7)	8899(1)	8488(2)	2938(1)	26(1)
C(8)	8220(1)	6880(2)	2857(1)	21(1)
C(9)	8679(1)	5057(2)	3086(1)	18(1)
C(9A)	8838(1)	4572(2)	3858(1)	20(1)
C(10)	8942(1)	3848(2)	2668(1)	18(1)
C(11)	8792(1)	4031(2)	1897(1)	19(1)

Table 3. Bond lengths [Å] and angles [°] for kh645_0m.

O(1)-C(3)	1.2431(15)
O(2)-C(11)	1.2139(15)
O(3)-C(11)	1.3352(15)
O(3)-H(3)	0.8400
C(1)-C(2)	1.5290(17)
C(1)-C(9A)	1.5468(18)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-C(3)	1.5087(18)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-N(4)	1.3374(16)
N(4)-C(5)	1.4634(16)
N(4)-C(9A)	1.4677(16)
C(5)-C(6)	1.5226(19)
C(5)-H(4A)	0.9900
C(5)-H(4B)	0.9900
C(6)-C(7)	1.5273(19)
C(6)-H(5A)	0.9900
C(6)-H(5B)	0.9900
C(7)-C(8)	1.5373(18)
C(7)-H(6A)	0.9900
C(7)-H(6B)	0.9900
C(8)-C(9)	1.5039(17)
C(8)-H(7A)	0.9900
C(8)-H(7B)	0.9900
C(9)-C(10)	1.3331(18)
C(9)-C(9A)	1.5113(17)
C(9A)-H(11)	1.0000
C(10)-C(11)	1.4772(17)
C(10)-H(9)	0.9500
C(11)-O(3)-H(3)	109.5

C(2)-C(1)-C(9A)	104.76(10)
C(2)-C(1)-H(1A)	110.8
C(9A)-C(1)-H(1A)	110.8
C(2)-C(1)-H(1B)	110.8
C(9A)-C(1)-H(1B)	110.8
H(1A)-C(1)-H(1B)	108.9
C(3)-C(2)-C(1)	104.11(10)
C(3)-C(2)-H(2A)	110.9
C(1)-C(2)-H(2A)	110.9
C(3)-C(2)-H(2B)	110.9
C(1)-C(2)-H(2B)	110.9
H(2A)-C(2)-H(2B)	109.0
O(1)-C(3)-N(4)	123.44(12)
O(1)-C(3)-C(2)	127.28(11)
N(4)-C(3)-C(2)	109.27(10)
C(3)-N(4)-C(5)	123.20(11)
C(3)-N(4)-C(9A)	114.08(10)
C(5)-N(4)-C(9A)	122.72(10)
N(4)-C(5)-C(6)	111.77(11)
N(4)-C(5)-H(4A)	109.3
C(6)-C(5)-H(4A)	109.3
N(4)-C(5)-H(4B)	109.3
C(6)-C(5)-H(4B)	109.3
H(4A)-C(5)-H(4B)	107.9
C(5)-C(6)-C(7)	114.47(11)
C(5)-C(6)-H(5A)	108.6
C(7)-C(6)-H(5A)	108.6
C(5)-C(6)-H(5B)	108.6
C(7)-C(6)-H(5B)	108.6
H(5A)-C(6)-H(5B)	107.6
C(6)-C(7)-C(8)	114.77(11)
C(6)-C(7)-H(6A)	108.6
C(8)-C(7)-H(6A)	108.6
C(6)-C(7)-H(6B)	108.6
C(8)-C(7)-H(6B)	108.6
H(6A)-C(7)-H(6B)	107.6

C(9)-C(8)-C(7)	112.68(10)
C(9)-C(8)-H(7A)	109.1
C(7)-C(8)-H(7A)	109.1
C(9)-C(8)-H(7B)	109.1
C(7)-C(8)-H(7B)	109.1
H(7A)-C(8)-H(7B)	107.8
C(10)-C(9)-C(8)	125.64(11)
C(10)-C(9)-C(9A)	118.20(11)
C(8)-C(9)-C(9A)	116.16(10)
N(4)-C(9A)-C(9)	111.21(10)
N(4)-C(9A)-C(1)	102.54(10)
C(9)-C(9A)-C(1)	113.65(10)
N(4)-C(9A)-H(11)	109.7
C(9)-C(9A)-H(11)	109.7
C(1)-C(9A)-H(11)	109.7
C(9)-C(10)-C(11)	125.80(12)
C(9)-C(10)-H(9)	117.1
C(11)-C(10)-H(9)	117.1
O(2)-C(11)-O(3)	123.33(11)
O(2)-C(11)-C(10)	125.76(11)
O(3)-C(11)-C(10)	110.91(10)

Table 6. Torsion angles [°] for kh645_0m.

C(9A)-C(1)-C(2)-C(3)	21.18(13)
C(1)-C(2)-C(3)-O(1)	168.28(12)
C(1)-C(2)-C(3)-N(4)	-12.47(13)
O(1)-C(3)-N(4)-C(5)	-2.73(19)
C(2)-C(3)-N(4)-C(5)	177.99(11)
O(1)-C(3)-N(4)-C(9A)	177.09(11)
C(2)-C(3)-N(4)-C(9A)	-2.19(14)
C(3)-N(4)-C(5)-C(6)	-90.42(14)
C(9A)-N(4)-C(5)-C(6)	89.78(14)
N(4)-C(5)-C(6)-C(7)	-67.60(14)
C(5)-C(6)-C(7)-C(8)	54.06(16)
C(6)-C(7)-C(8)-C(9)	-72.79(14)

C(7)-C(8)-C(9)-C(10)	-92.21(15)
C(7)-C(8)-C(9)-C(9A)	88.54(13)
C(3)-N(4)-C(9A)-C(9)	137.42(11)
C(5)-N(4)-C(9A)-C(9)	-42.76(15)
C(3)-N(4)-C(9A)-C(1)	15.61(13)
C(5)-N(4)-C(9A)-C(1)	-164.57(11)
C(10)-C(9)-C(9A)-N(4)	140.93(11)
C(8)-C(9)-C(9A)-N(4)	-39.76(14)
C(10)-C(9)-C(9A)-C(1)	-103.97(13)
C(8)-C(9)-C(9A)-C(1)	75.34(14)
C(2)-C(1)-C(9A)-N(4)	-22.03(12)
C(2)-C(1)-C(9A)-C(9)	-142.16(11)
C(8)-C(9)-C(10)-C(11)	-3.2(2)
C(9A)-C(9)-C(10)-C(11)	176.06(11)
C(9)-C(10)-C(11)-O(2)	18.9(2)
C(9)-C(10)-C(11)-O(3)	-161.51(12)

Crystal Data for $C_{13}H_{19}NO_4$ compound 41: Single crystals of the compound were grown by slow evaporation of the solution in ethyl acetate. Colorless plate crystal of approximate size 0.46 x 0.44 x 0.05 mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo K_α radiation. exposure / frame = 5.0 sec / frame, θ range = 2.30 to 24.99 º, completeness to θ of 24.99 º is 100.0 %. C13 H19 N O4, M = 253.29. Crystals belong to Orthorhombic, space group $Pna2_1$, a = 8.696(1), b = 17.732(3), c = 8.557(1) Å, V = 1319.4(3) $Å^3$, Z = 4, D_c = 1.275 g /cc, T = 90(2) K, 6328 reflections measured, 2284 unique [I>2σ(I)], R value 0.0442, wR2 = 0.0940. SHELX-97 (ShelxTL)[ref] was used for structure solution and full matrix least squares refinement on F^2. Data collection and refinement parameters are listed in table 2.

The conformation of the molecule was established by single crystal X-ray analysis shows that C8 and C9a to have S configuration.

Table 2. Crystal data and structure refinement for $C_{13}H_{19}NO_4$compound **41**.

Empirical formula	C_{13} H_{19} N O_4
Formula weight	253.29

Temperature	90(2) K	
Crystal system	Orthorhombic	
Space group	Pna2(1)	
Unit cell dimensions	a = 8.696(1) Å	α= 90°.
	b = 17.732(3) Å	β= 90°.
	c = 8.557(1) Å	γ = 90°.
Volume	1319.4(3) $Å^3$	
Z	4	
Density (calculated)	1.275 g/cc	
Crystal size	0.46 x 0.44 x 0.05 mm^3	
Theta range for data collection	2.30 to 24.99°.	
Reflections collected	6328	
Independent reflections	2284 [R(int) = 0.0291]	
Completeness to theta = 24.99°	100.0 %	
Refinement method	Full-matrix least-squares on F^2	
Goodness-of-fit on F^2	1.039	
Final R indices [I>2sigma(I)]	R1 = 0.0442, wR2 = 0.0940	
R indices (all data)	R1 = 0.0629, wR2 = 0.1044	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for KH2461. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	8757(2)	5964(1)	-3640(2)	72(1)
O(2)	8783(2)	4939(1)	588(3)	72(1)
O(3)	4236(2)	6739(2)	1803(3)	88(1)
O(4)	4647(2)	6712(1)	4351(2)	86(1)
C(1)	5761(3)	5577(2)	-882(4)	73(1)
C(2)	6337(3)	5538(2)	-2538(3)	66(1)
C(3)	7840(3)	5941(2)	-2533(3)	54(1)
N(4)	8030(2)	6286(1)	-1174(2)	53(1)
C(5)	9360(3)	6747(2)	-801(4)	70(1)
C(6)	10606(3)	6304(2)	33(4)	78(1)
C(7)	10175(3)	6034(2)	1649(4)	69(1)

C(8)	8755(3)	5528(2)	1735(3)	57(1)
C(9)	7261(3)	5955(1)	1538(3)	47(1)
C(9A)	6754(3)	6184(2)	-76(3)	51(1)
C(10)	6460(3)	6120(2)	2823(3)	53(1)
C(11)	5024(3)	6554(2)	2891(3)	56(1)
C(12)	3244(5)	7144(3)	4621(5)	119(2)
C(13)	2644(4)	6969(2)	6135(6)	116(2)

Table 3. Bond lengths [Å] and angles [°] for **41.**

O(1)-C(3)	1.239(3)
O(2)-C(8)	1.434(3)
O(2)-H(2)	0.8200
O(3)-C(11)	1.201(3)
O(4)-C(11)	1.321(3)
O(4)-C(12)	1.458(4)
C(1)-C(2)	1.505(4)
C(1)-C(9A)	1.542(4)
C(1)-H(1A)	0.9700
C(1)-H(1B)	0.9700
C(2)-C(3)	1.490(4)
C(2)-H(2A)	0.9700
C(2)-H(2B)	0.9700
C(3)-N(4)	1.324(3)
N(4)-C(5)	1.452(3)
N(4)-C(9A)	1.465(3)
C(5)-C(6)	1.517(4)
C(5)-H(5A)	0.9700
C(5)-H(5B)	0.9700
C(6)-C(7)	1.510(4)
C(6)-H(6A)	0.9700
C(6)-H(6B)	0.9700
C(7)-C(8)	1.529(4)
C(7)-H(7A)	0.9700
C(7)-H(7B)	0.9700
C(8)-C(9)	1.514(3)

C(8)-H(8)	0.9800
C(9)-C(10)	1.335(4)
C(9)-C(9A)	1.505(3)
C(9A)-H(9A)	0.9800
C(10)-C(11)	1.468(4)
C(10)-H(10)	0.9300
C(12)-C(13)	1.431(5)
C(12)-H(12A)	0.9700
C(12)-H(12B)	0.9700
C(13)-H(13A)	0.9600
C(13)-H(13B)	0.9600
C(13)-H(13C)	0.9600

C(8)-O(2)-H(2)	109.5
C(11)-O(4)-C(12)	117.9(3)
C(2)-C(1)-C(9A)	105.5(2)
C(2)-C(1)-H(1A)	110.6
C(9A)-C(1)-H(1A)	110.6
C(2)-C(1)-H(1B)	110.6
C(9A)-C(1)-H(1B)	110.6
H(1A)-C(1)-H(1B)	108.8
C(3)-C(2)-C(1)	105.5(2)
C(3)-C(2)-H(2A)	110.6
C(1)-C(2)-H(2A)	110.6
C(3)-C(2)-H(2B)	110.6
C(1)-C(2)-H(2B)	110.6
H(2A)-C(2)-H(2B)	108.8
O(1)-C(3)-N(4)	125.1(3)
O(1)-C(3)-C(2)	125.4(3)
N(4)-C(3)-C(2)	109.5(2)
C(3)-N(4)-C(5)	123.6(2)
C(3)-N(4)-C(9A)	114.3(2)
C(5)-N(4)-C(9A)	122.1(2)
N(4)-C(5)-C(6)	112.3(2)
N(4)-C(5)-H(5A)	109.1
C(6)-C(5)-H(5A)	109.1

N(4)-C(5)-H(5B)	109.1
C(6)-C(5)-H(5B)	109.1
H(5A)-C(5)-H(5B)	107.9
C(7)-C(6)-C(5)	114.7(3)
C(7)-C(6)-H(6A)	108.6
C(5)-C(6)-H(6A)	108.6
C(7)-C(6)-H(6B)	108.6
C(5)-C(6)-H(6B)	108.6
H(6A)-C(6)-H(6B)	107.6
C(6)-C(7)-C(8)	115.5(2)
C(6)-C(7)-H(7A)	108.4
C(8)-C(7)-H(7A)	108.4
C(6)-C(7)-H(7B)	108.4
C(8)-C(7)-H(7B)	108.4
H(7A)-C(7)-H(7B)	107.5
O(2)-C(8)-C(9)	107.6(2)
O(2)-C(8)-C(7)	112.4(2)
C(9)-C(8)-C(7)	113.2(2)
O(2)-C(8)-H(8)	107.8
C(9)-C(8)-H(8)	107.8
C(7)-C(8)-H(8)	107.8
C(10)-C(9)-C(9A)	123.0(2)
C(10)-C(9)-C(8)	117.8(2)
C(9A)-C(9)-C(8)	119.2(2)
N(4)-C(9A)-C(9)	113.6(2)
N(4)-C(9A)-C(1)	103.0(2)
C(9)-C(9A)-C(1)	112.7(2)
N(4)-C(9A)-H(9A)	109.1
C(9)-C(9A)-H(9A)	109.1
C(1)-C(9A)-H(9A)	109.1
C(9)-C(10)-C(11)	126.3(2)
C(9)-C(10)-H(10)	116.8
C(11)-C(10)-H(10)	116.8
O(3)-C(11)-O(4)	122.3(3)
O(3)-C(11)-C(10)	126.6(3)
O(4)-C(11)-C(10)	111.1(2)

C(13)-C(12)-O(4)	109.6(3)
C(13)-C(12)-H(12A)	109.8
O(4)-C(12)-H(12A)	109.8
C(13)-C(12)-H(12B)	109.8
O(4)-C(12)-H(12B)	109.8
H(12A)-C(12)-H(12B)	108.2
C(12)-C(13)-H(13A)	109.5
C(12)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
C(12)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5

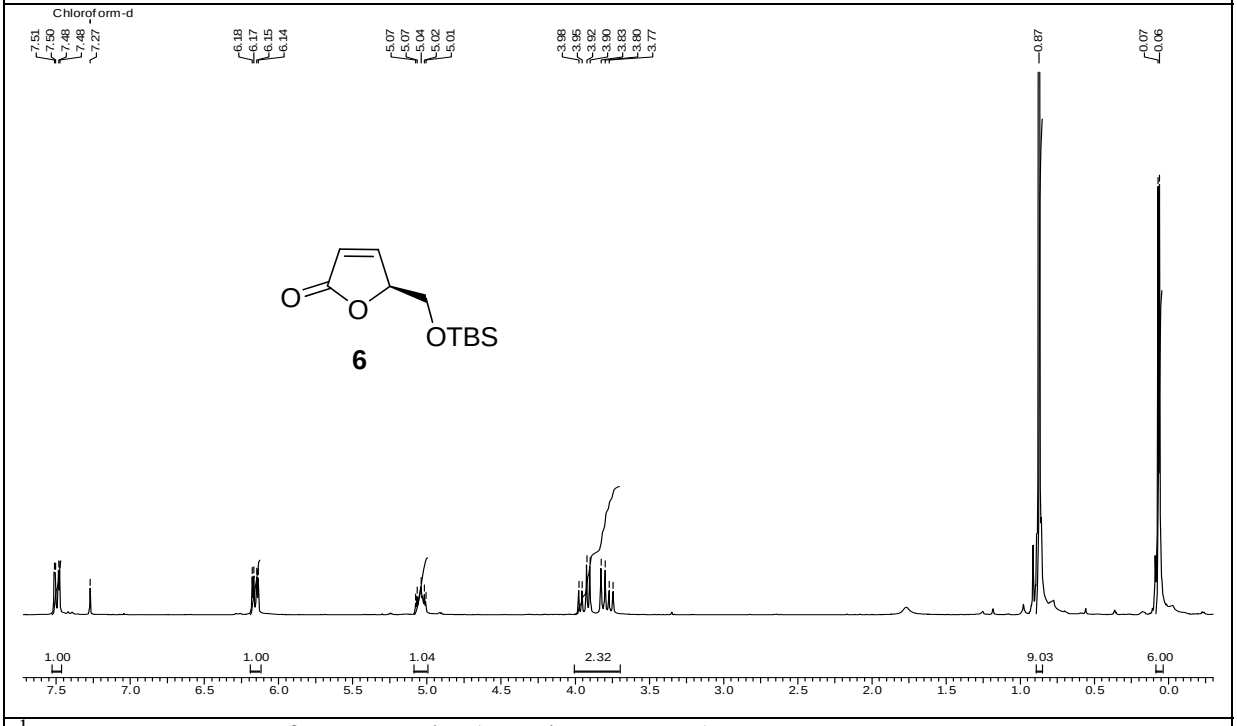
Table 6. Torsion angles [°] for **41**.

C(9A)-C(1)-C(2)-C(3)	14.6(3)
C(1)-C(2)-C(3)-O(1)	172.0(3)
C(1)-C(2)-C(3)-N(4)	-9.5(3)
O(1)-C(3)-N(4)-C(5)	0.2(4)
C(2)-C(3)-N(4)-C(5)	-178.3(2)
O(1)-C(3)-N(4)-C(9A)	178.5(2)
C(2)-C(3)-N(4)-C(9A)	-0.1(3)
C(3)-N(4)-C(5)-C(6)	-93.9(3)
C(9A)-N(4)-C(5)-C(6)	88.0(3)
N(4)-C(5)-C(6)-C(7)	-66.7(3)
C(5)-C(6)-C(7)-C(8)	58.5(4)
C(6)-C(7)-C(8)-O(2)	47.4(3)
C(6)-C(7)-C(8)-C(9)	-74.8(3)
O(2)-C(8)-C(9)-C(10)	134.6(3)
C(7)-C(8)-C(9)-C(10)	-100.6(3)
O(2)-C(8)-C(9)-C(9A)	-46.3(3)
C(7)-C(8)-C(9)-C(9A)	78.6(3)
C(3)-N(4)-C(9A)-C(9)	131.5(2)
C(5)-N(4)-C(9A)-C(9)	-50.3(3)
C(3)-N(4)-C(9A)-C(1)	9.3(3)
C(5)-N(4)-C(9A)-C(1)	-172.5(2)

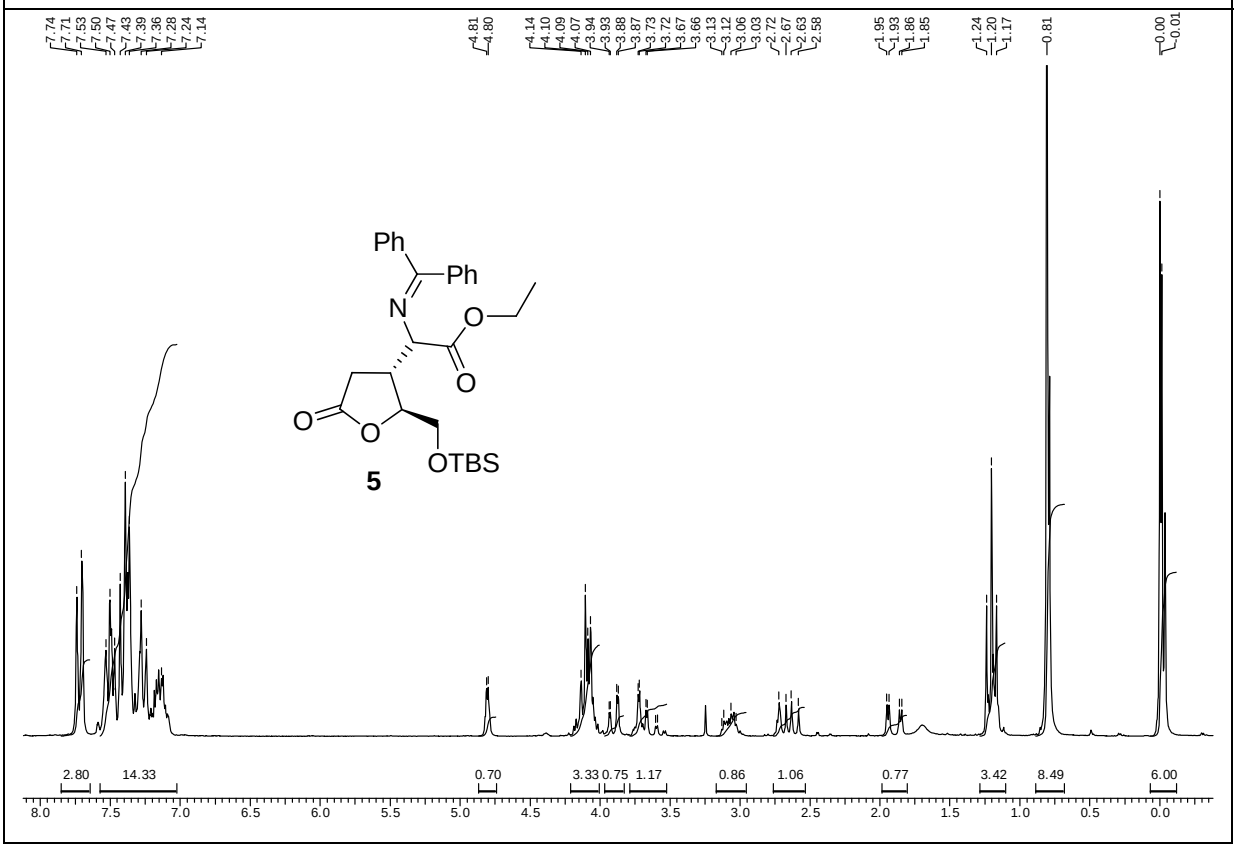
C(10)-C(9)-C(9A)-N(4)	152.0(3)
C(8)-C(9)-C(9A)-N(4)	-27.1(3)
C(10)-C(9)-C(9A)-C(1)	-91.4(3)
C(8)-C(9)-C(9A)-C(1)	89.5(3)
C(2)-C(1)-C(9A)-N(4)	-14.3(3)
C(2)-C(1)-C(9A)-C(9)	-137.1(2)
C(9A)-C(9)-C(10)-C(11)	-1.8(4)
C(8)-C(9)-C(10)-C(11)	177.4(3)
C(12)-O(4)-C(11)-O(3)	-1.7(5)
C(12)-O(4)-C(11)-C(10)	179.9(3)
C(9)-C(10)-C(11)-O(3)	11.0(5)
C(9)-C(10)-C(11)-O(4) C(11)-O(4)-C(12)-C(13)	-170.7(3)

3.2.4 NMR Spectra

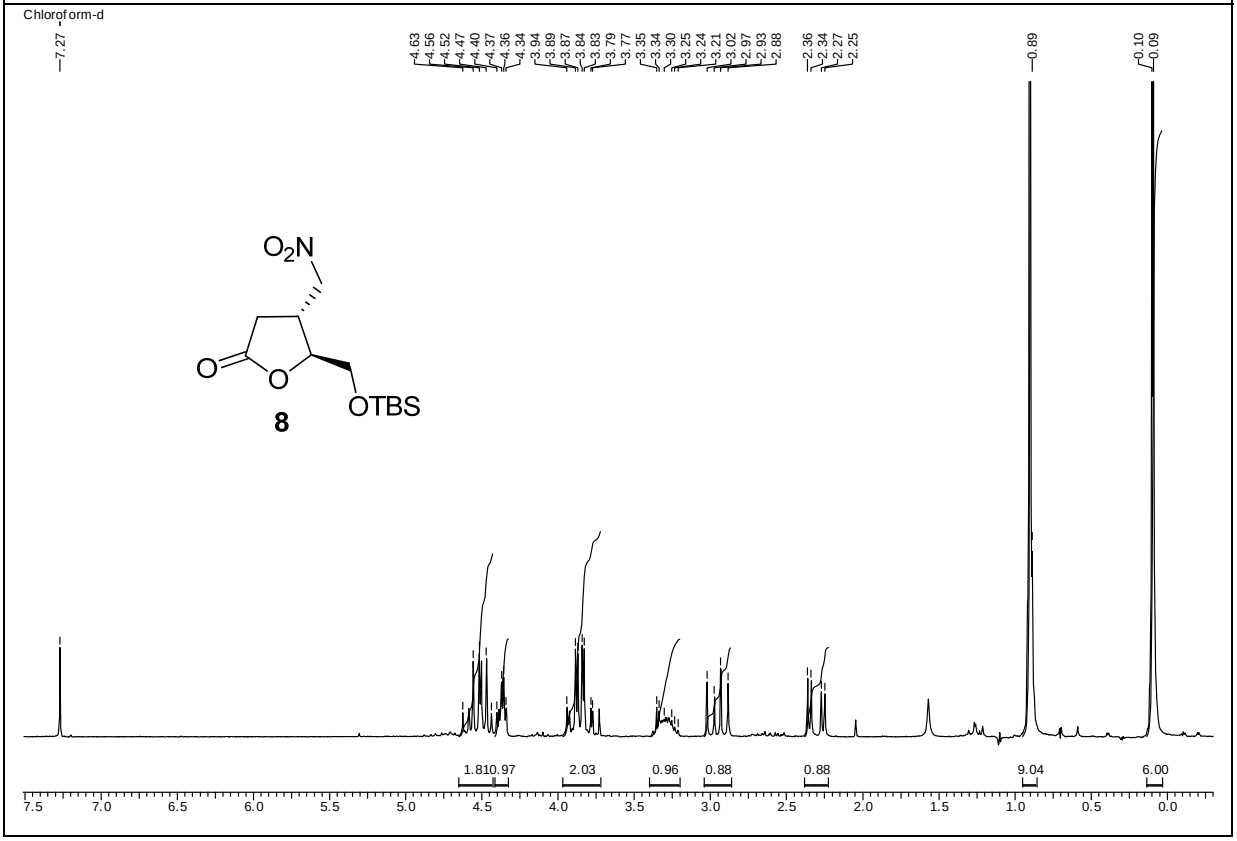
^{1}H-NMR spectrum of compound **6** ($CDCl_3$, 200 MHz)



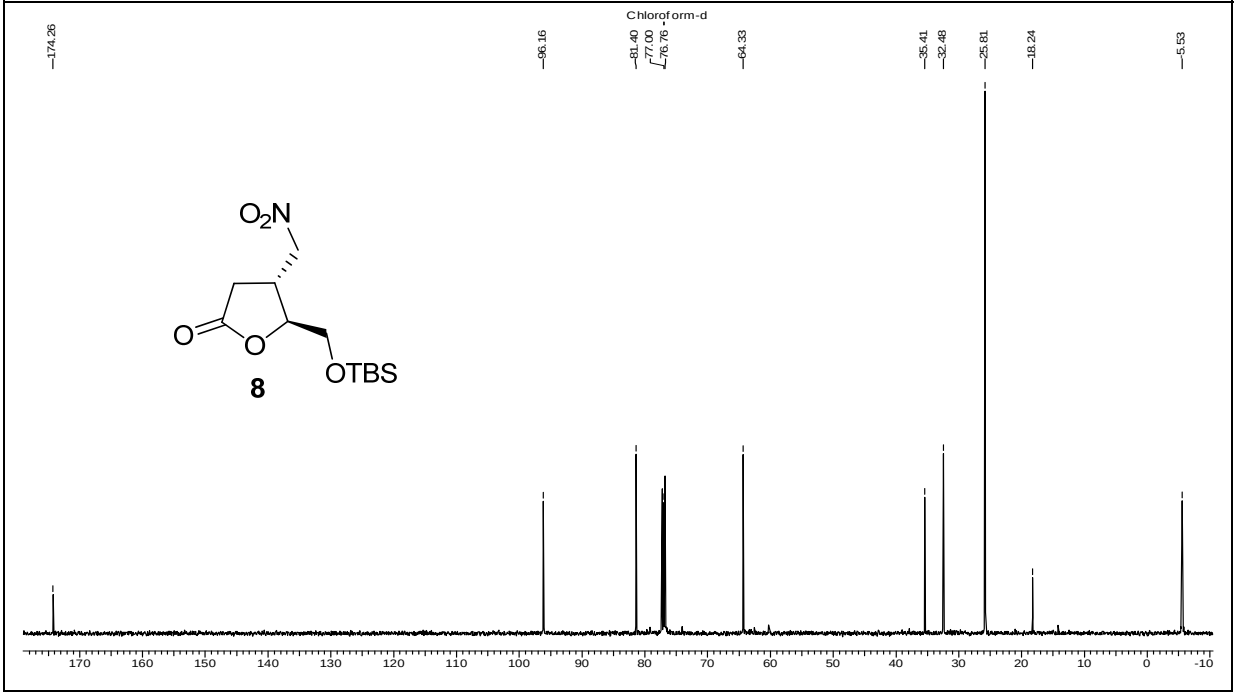
^{1}H-NMR spectrum of compound **5** ($CDCl_3$, 200 MHz)



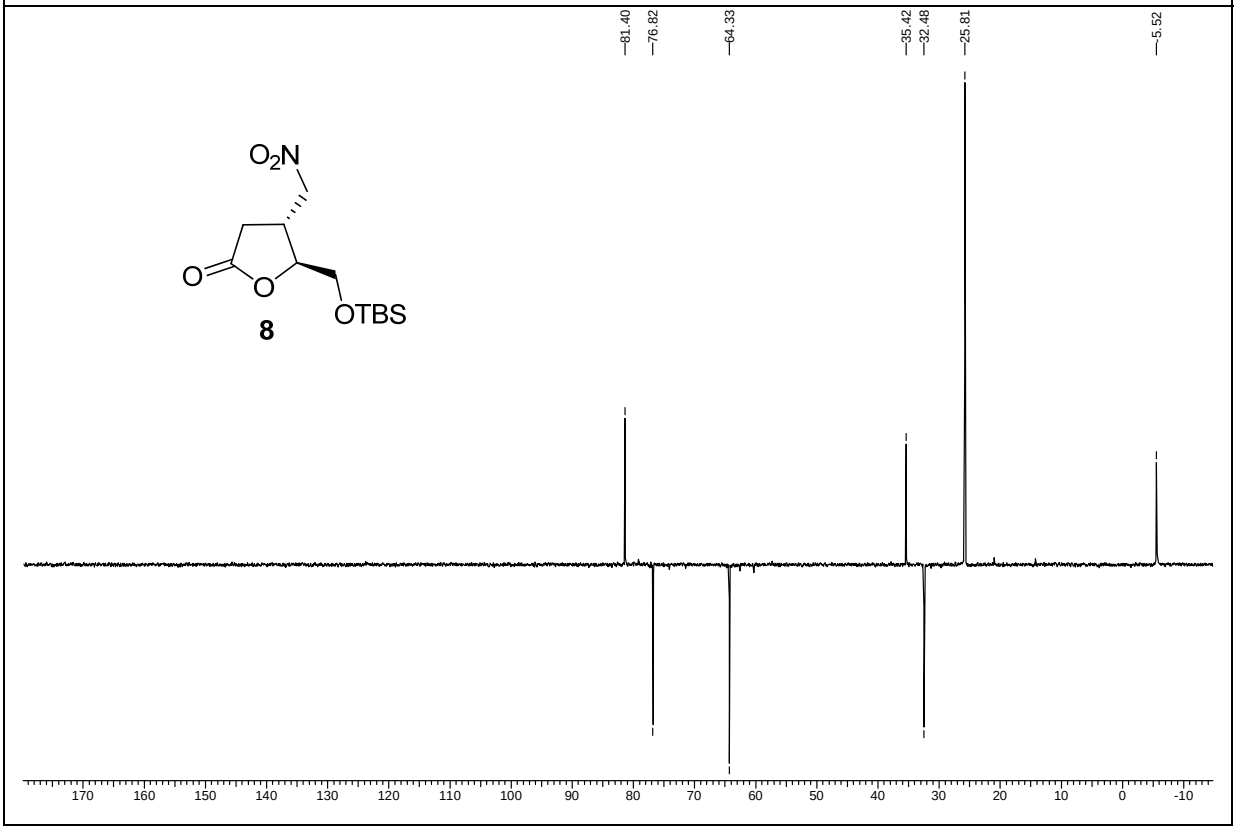
^{1}H-NMR spectrum of compound **8** ($CDCl_3$+ CCl_4, 200 MHz)



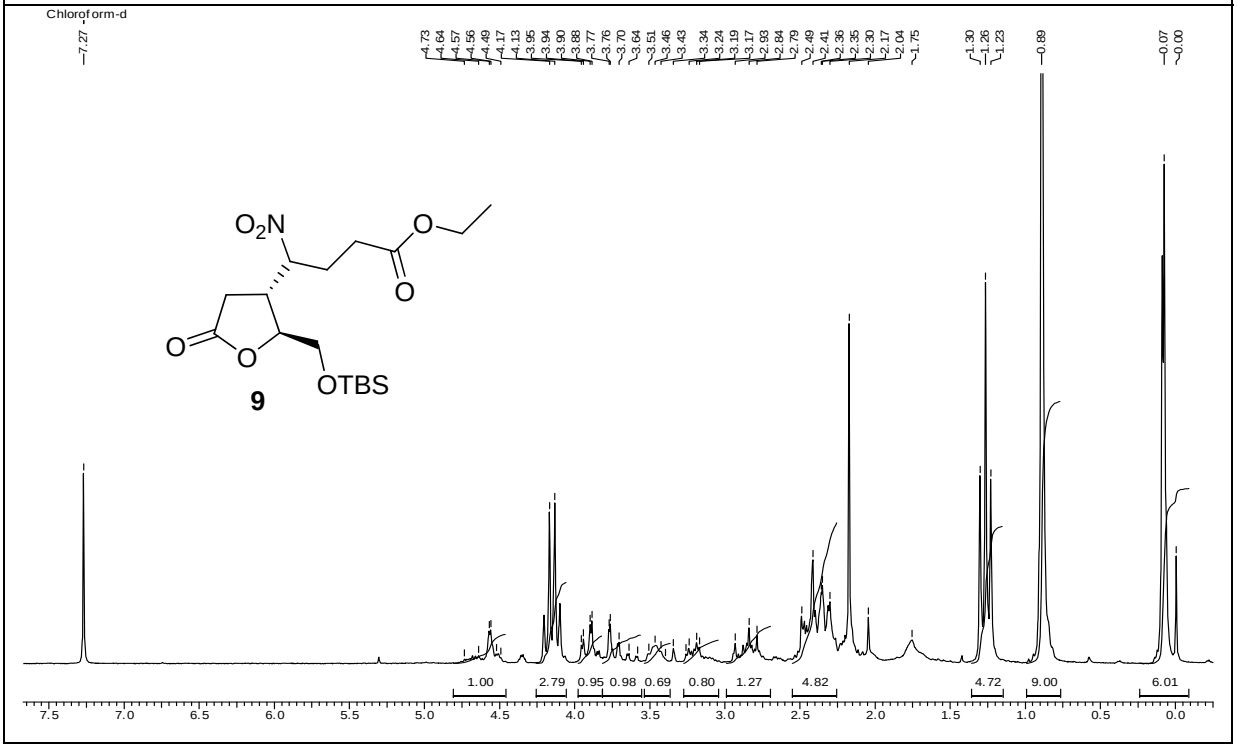
^{13}C-NMR spectrum of compound **8** ($CDCl_3$ + CCl_4, 50 MHz)



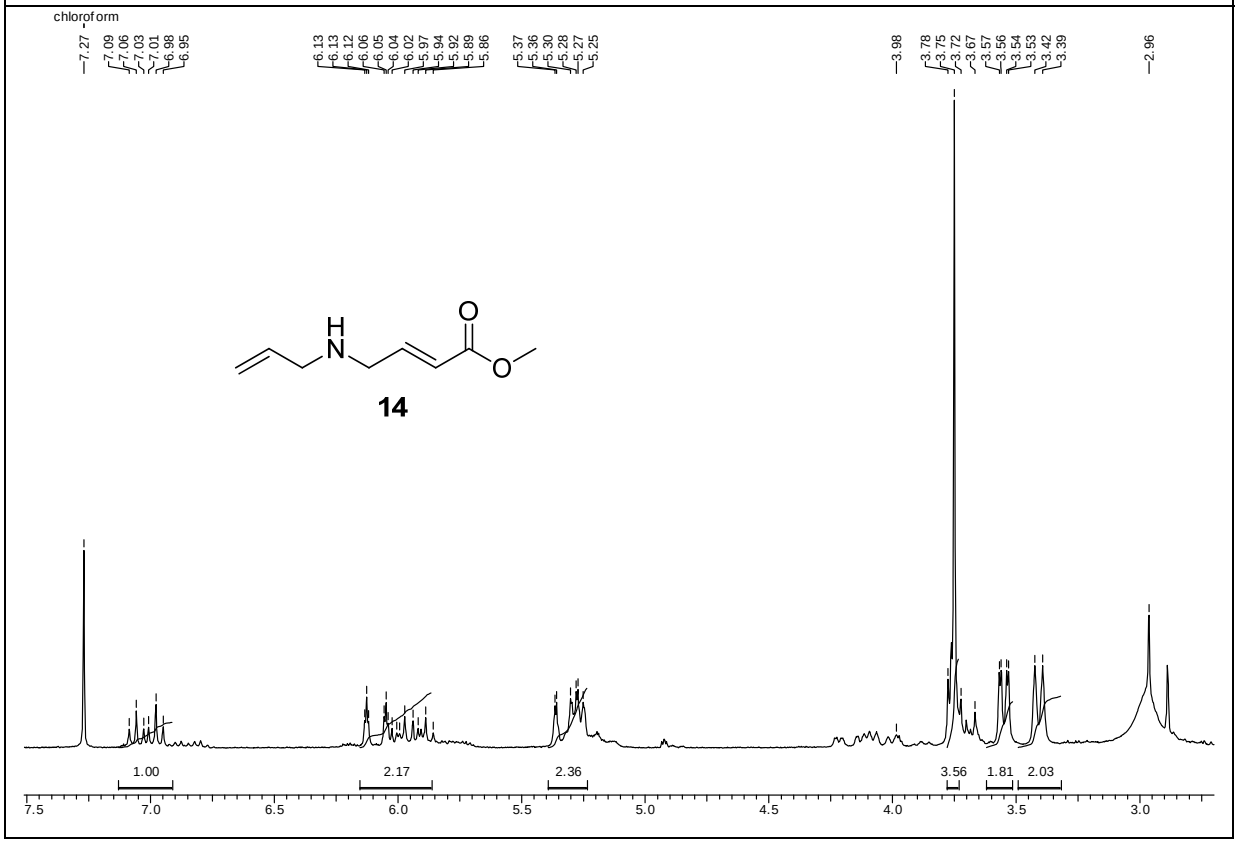
DEPT spectrum of compound **8** ($CDCl_3$ + CCl_4, 50 MHz)



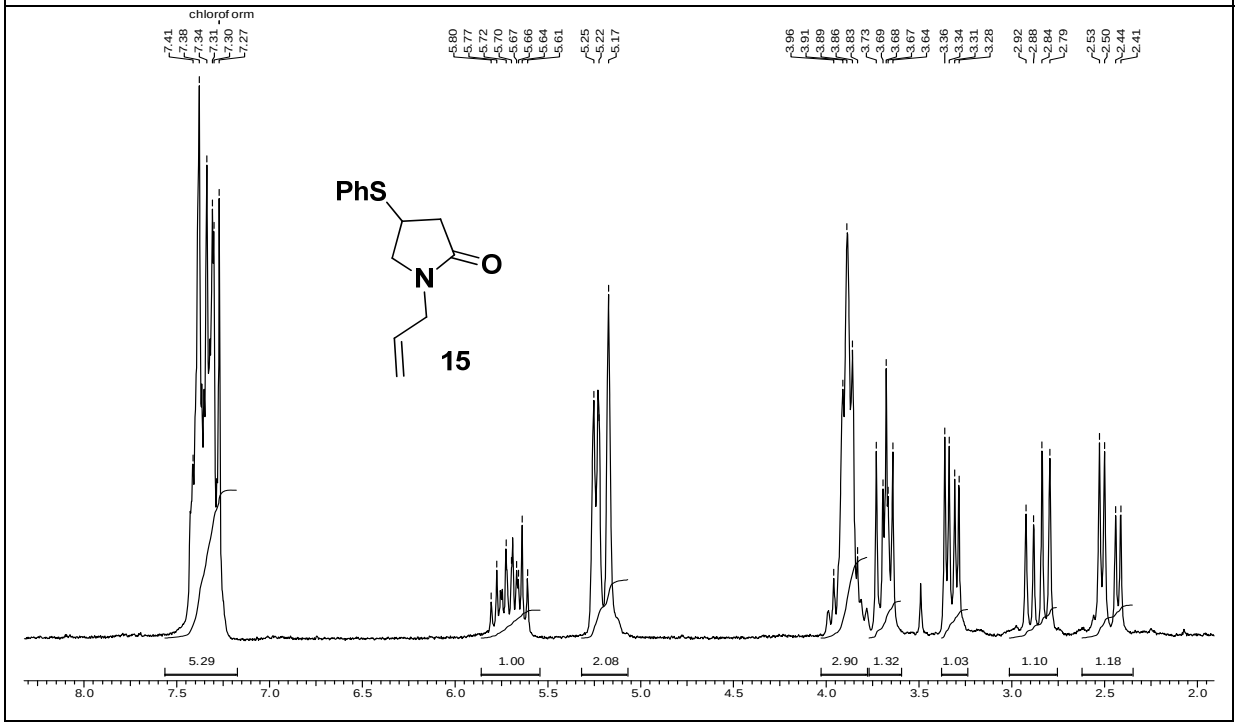
^{1}H-NMR spectrum of compound **9** ($CDCl_3$, 200 MHz)



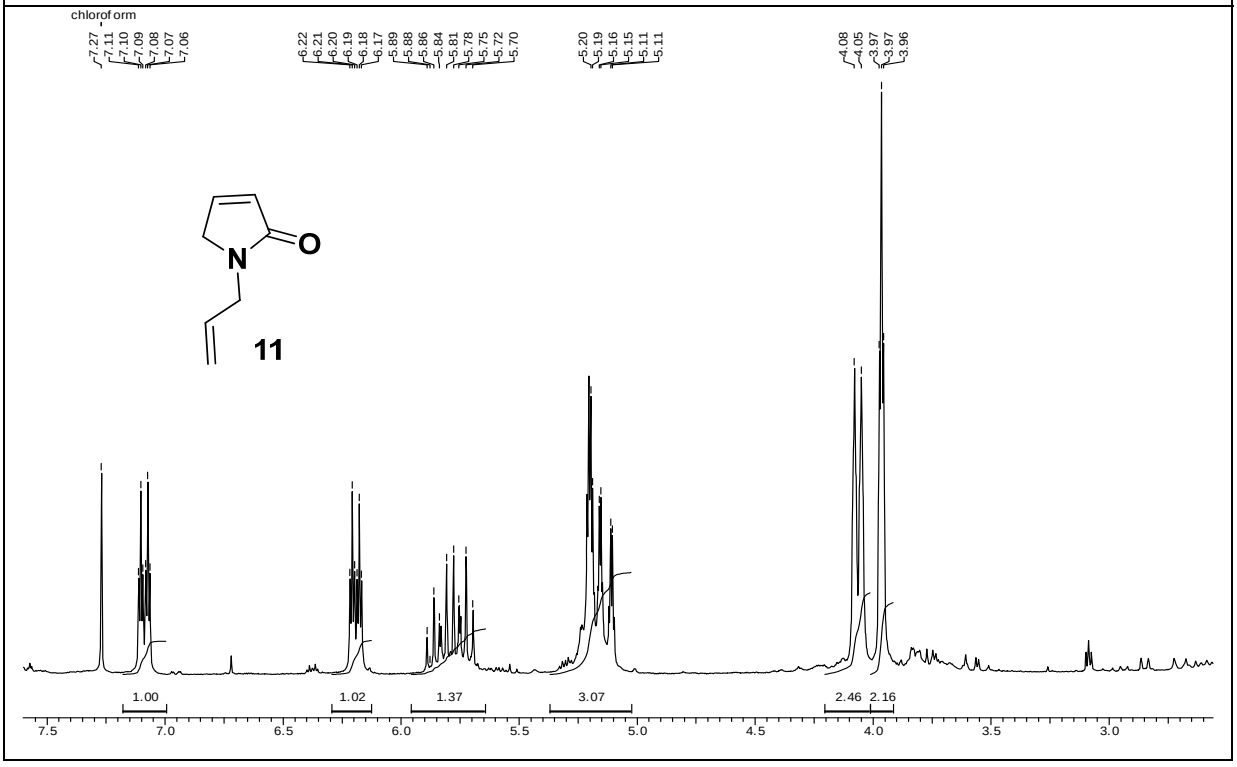
^{1}H-NMR spectrum of compound **14** ($CDCl_3$, 200 MHz)



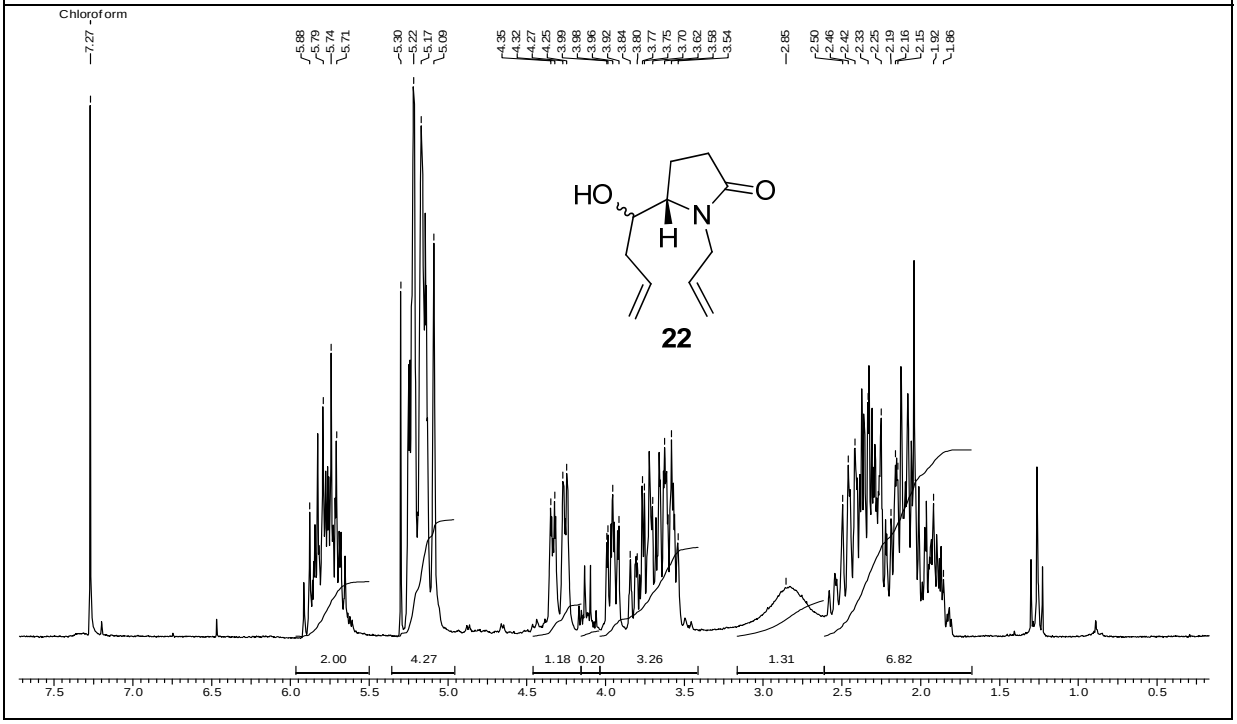
^{1}H-NMR spectrum of compound **15** ($CDCl_3$, 200 MHz)



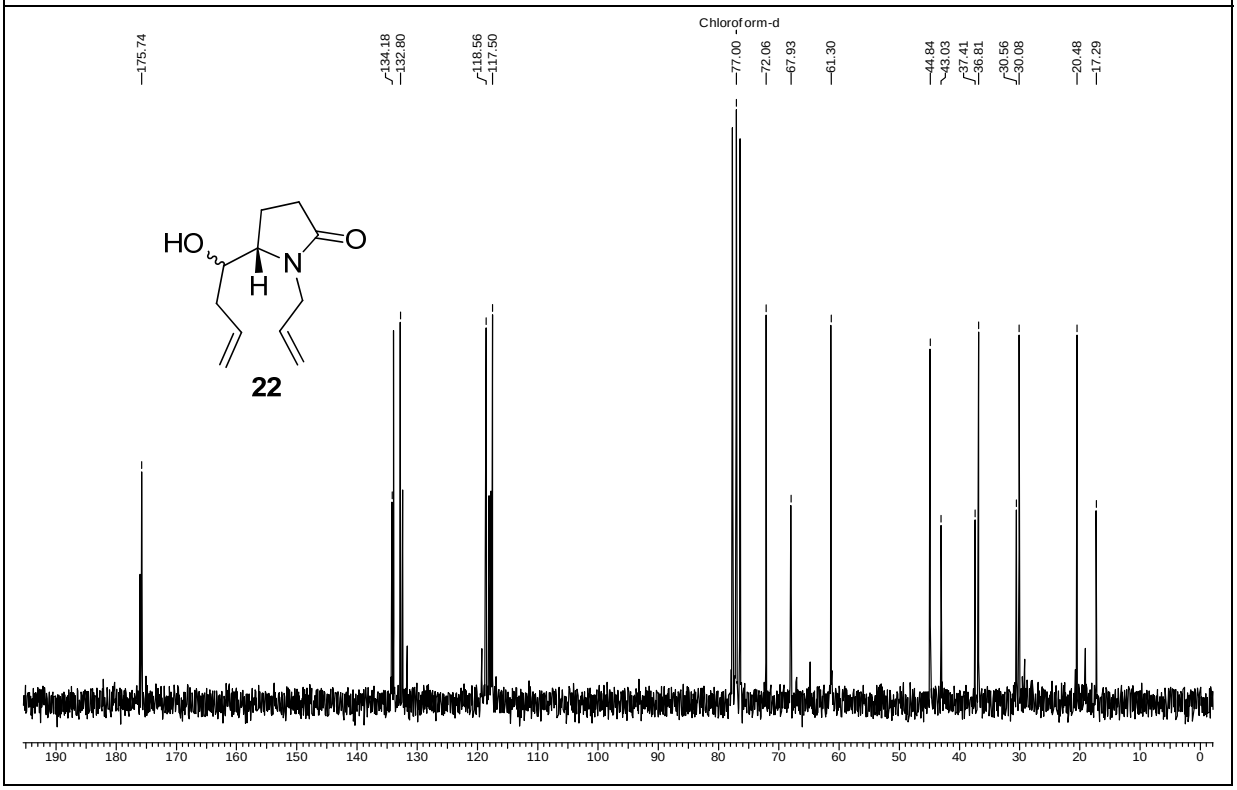
^{1}H-NMR spectrum of compound **11** ($CDCl_3$, 200 MHz)



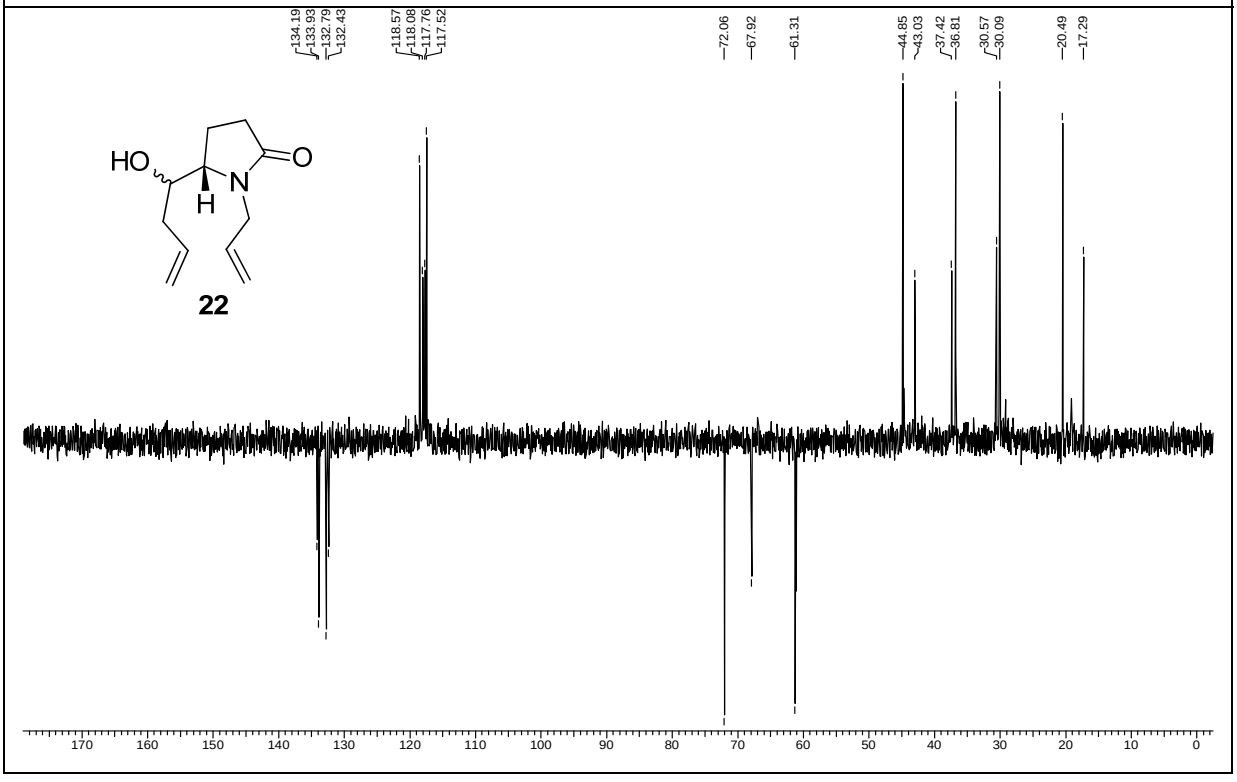
^{1}H-NMR spectrum of compound **22** ($CDCl_3$, 200 MHz)



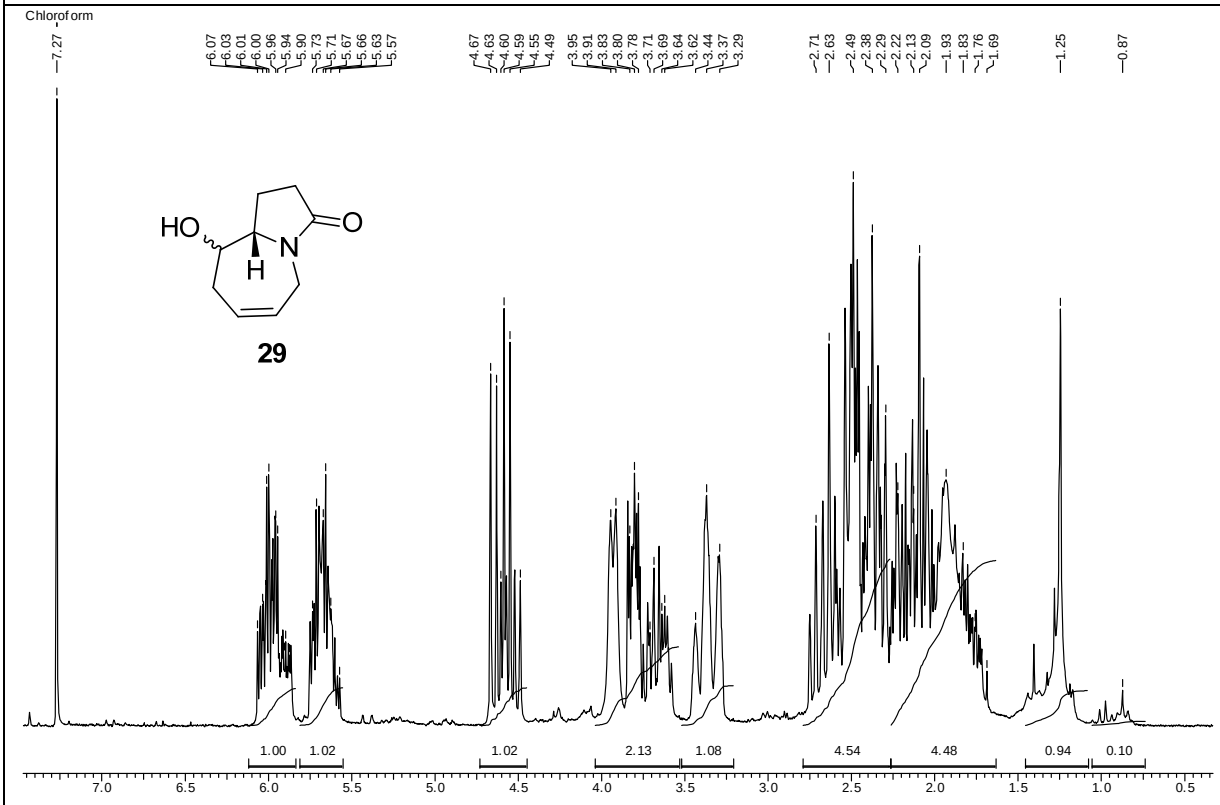
^{13}C-NMR spectrum of compound **22** ($CDCl_3$, 50 MHz)



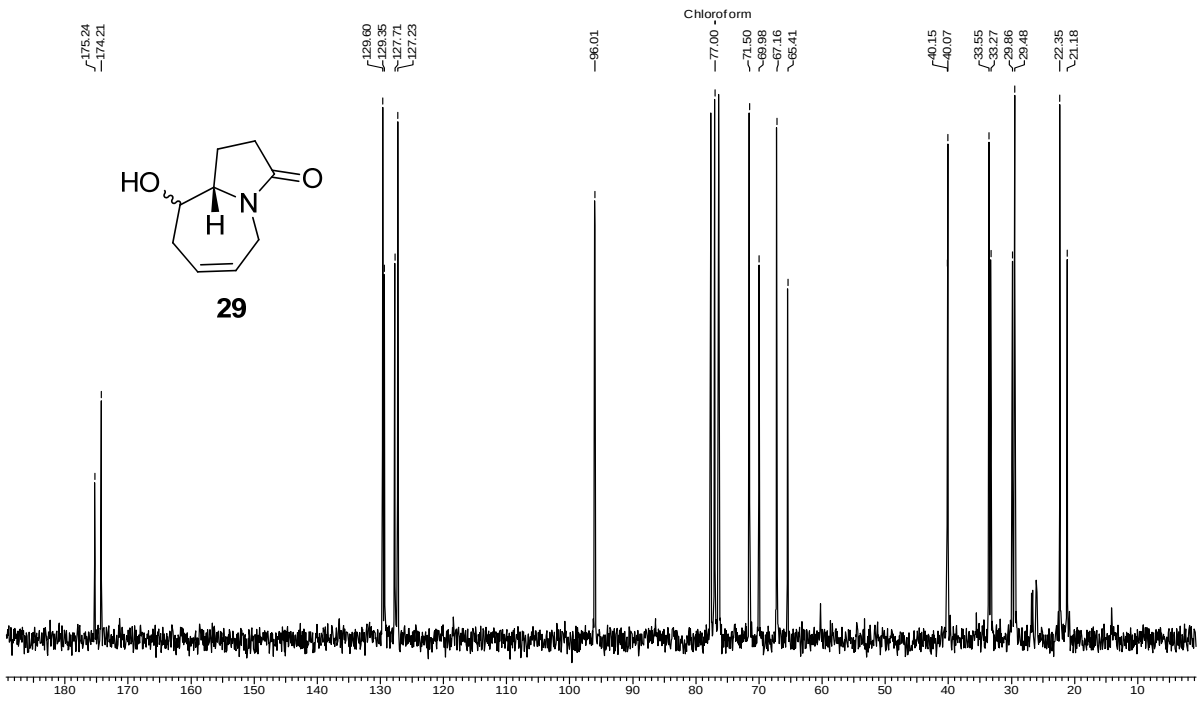
DEPT spectrum of compound **22** ($CDCl_3$, 50 MHz)



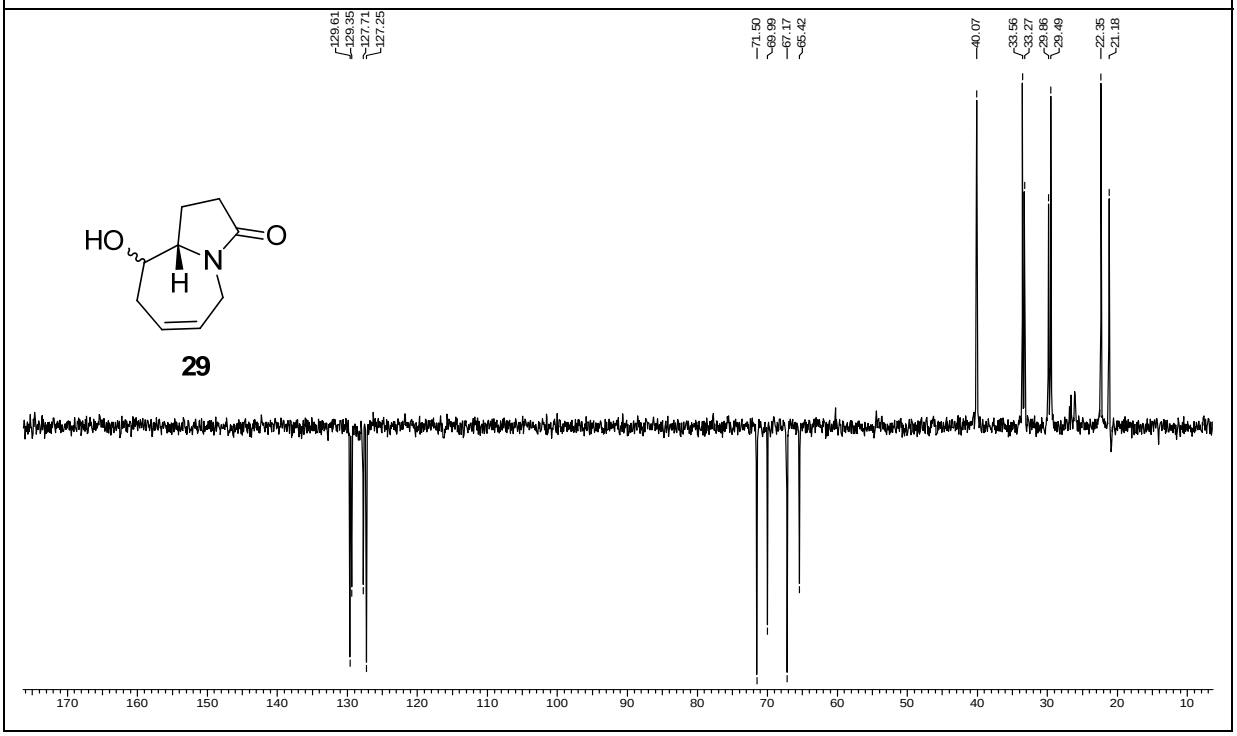
^{1}H-NMR spectrum of compound **29** ($CDCl_3$+CCl_4, 200 MHz)



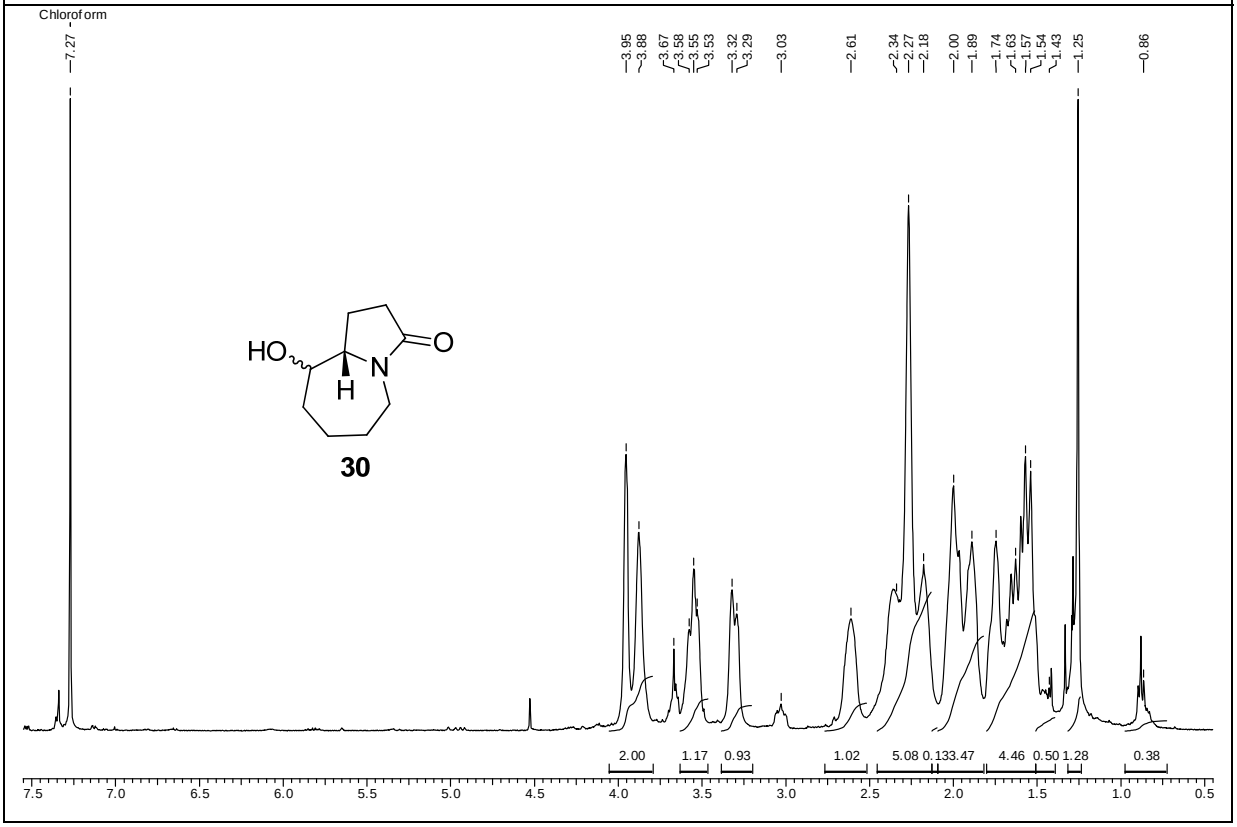
^{13}C-NMR spectrum of compound **29** ($CDCl_3$ + CCl_4, 50 MHz)



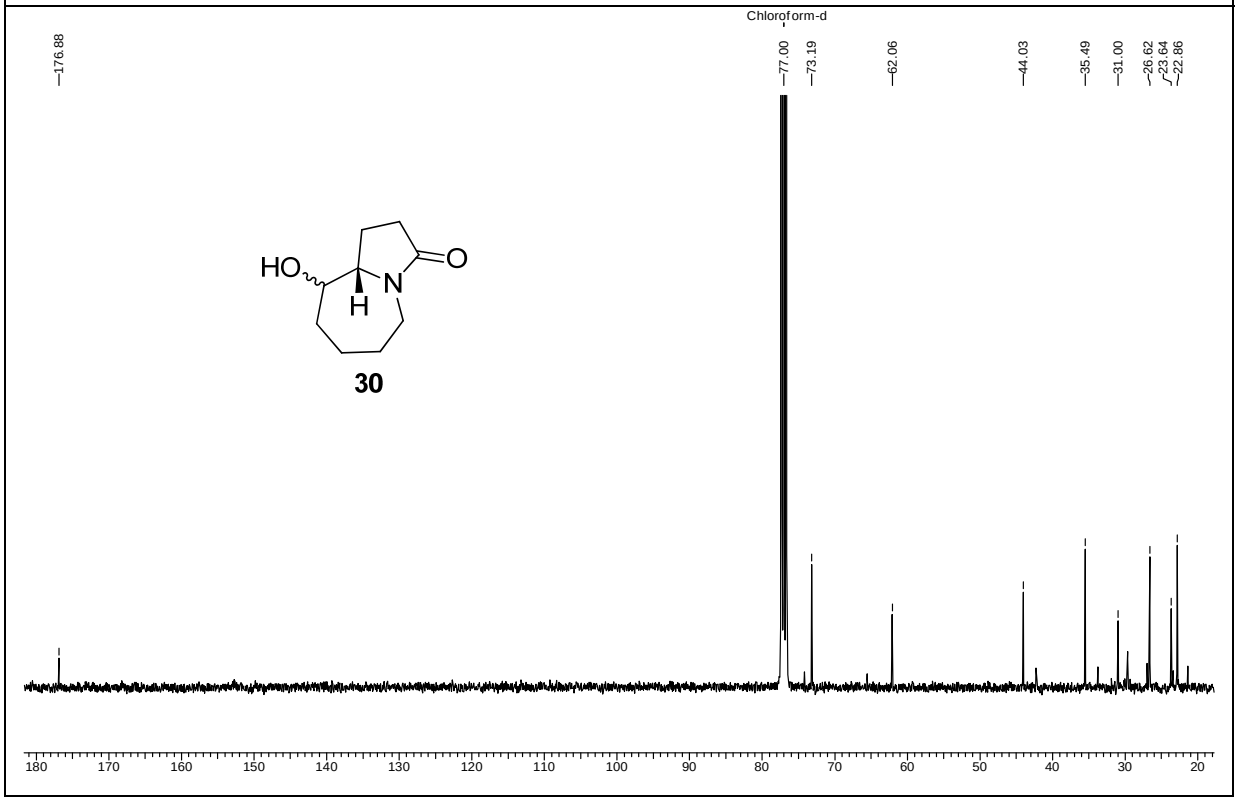
DEPT spectrum of compound **29** ($CDCl_3$ + CCl_4, 50 MHz)



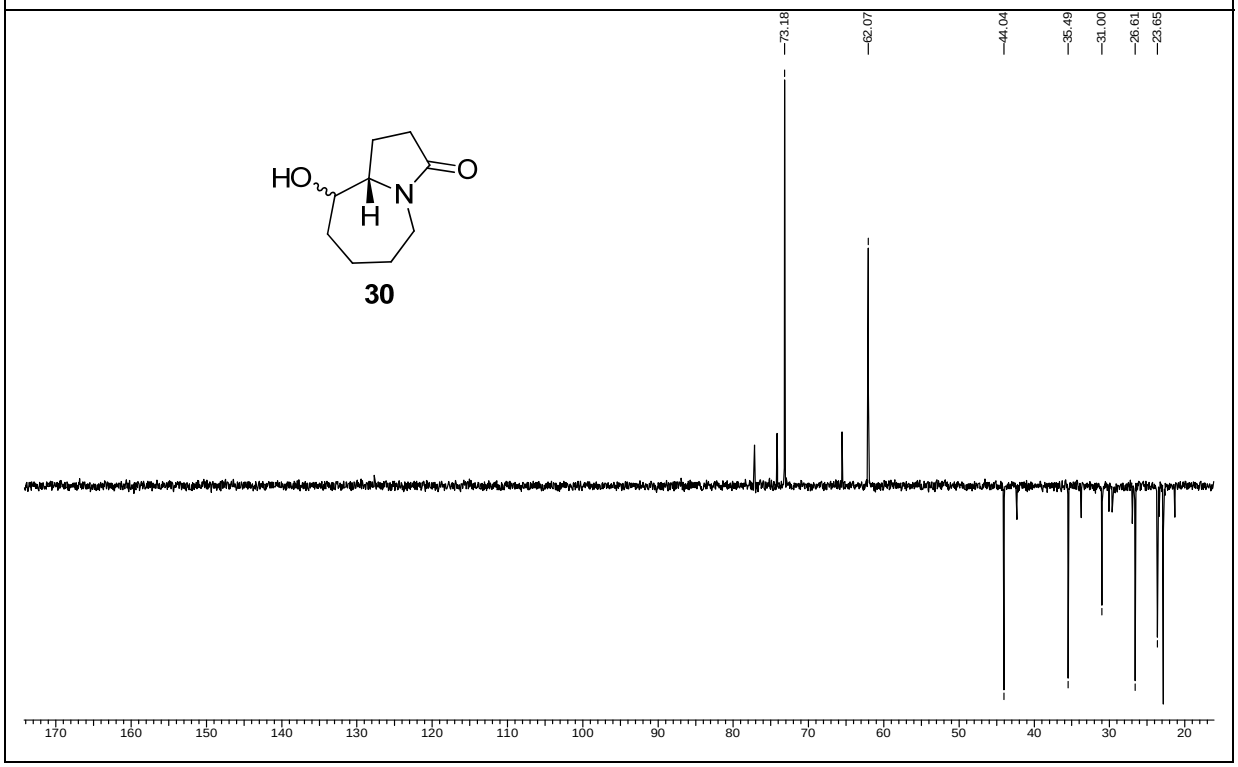
^{1}H-NMR spectrum of compound **30** ($CDCl_3$, 200 MHz)



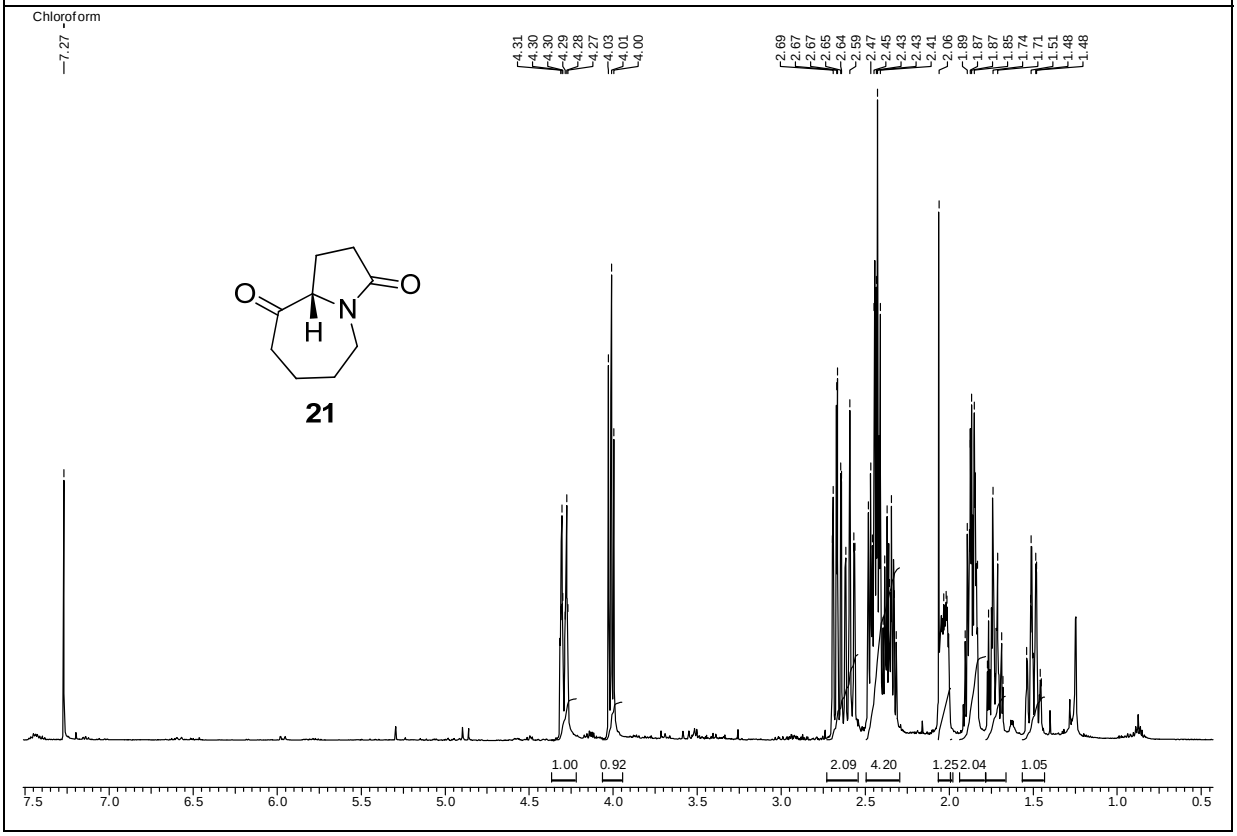
^{13}C-NMR spectrum of compound **30** ($CDCl_3$, 50 MHz)



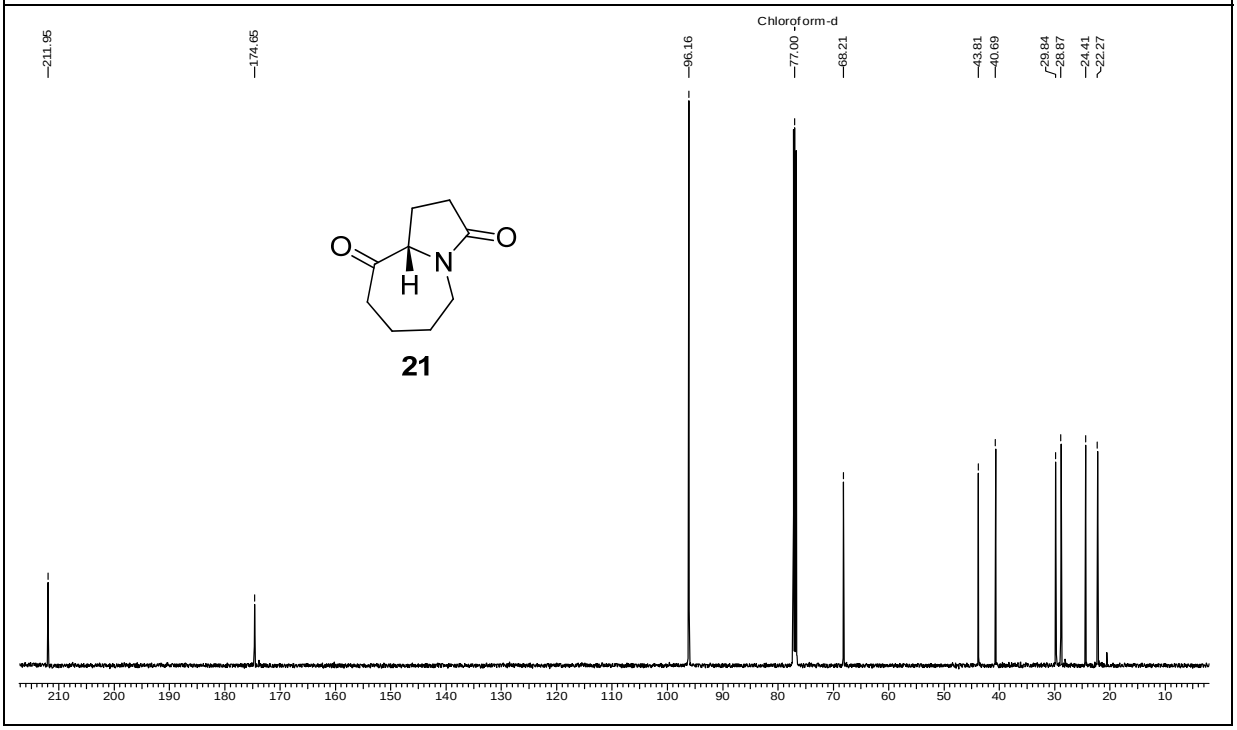
DEPT spectrum of compound **30** ($CDCl_3$, 50 MHz)



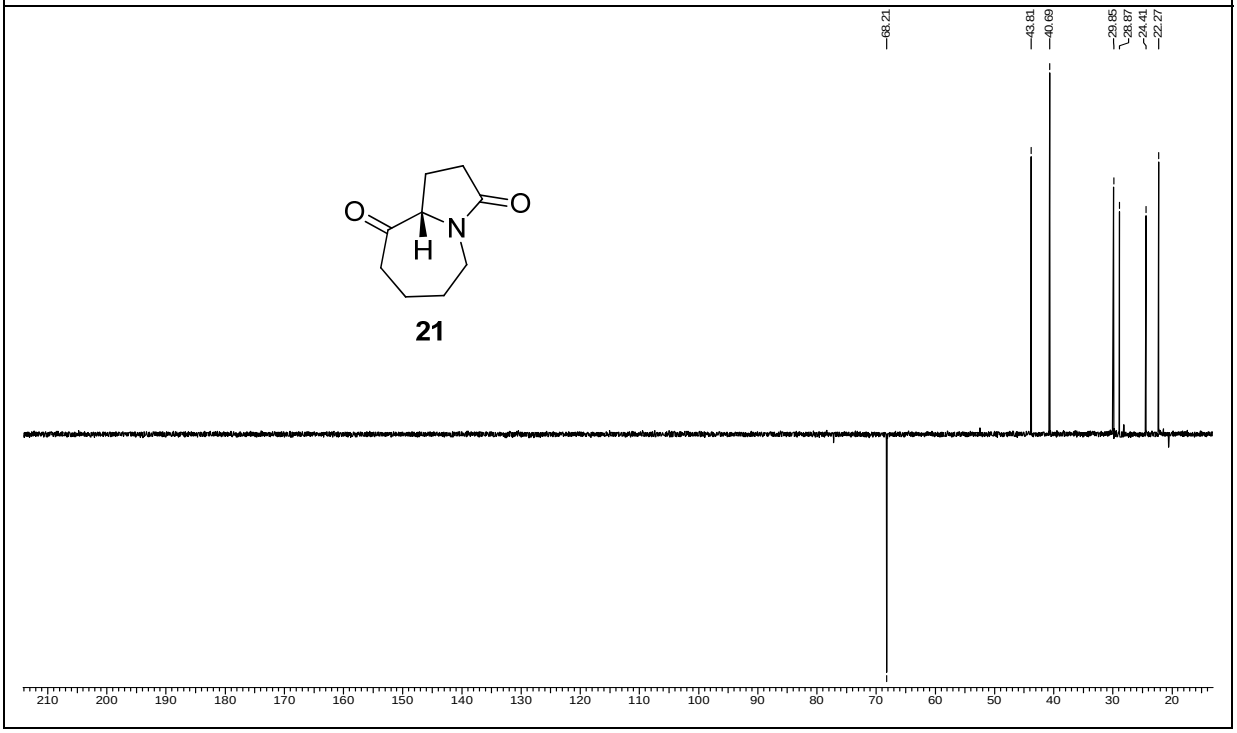
^{1}H-NMR spectrum of compound **21** ($CDCl_3$+ CCl_4, 200 MHz)



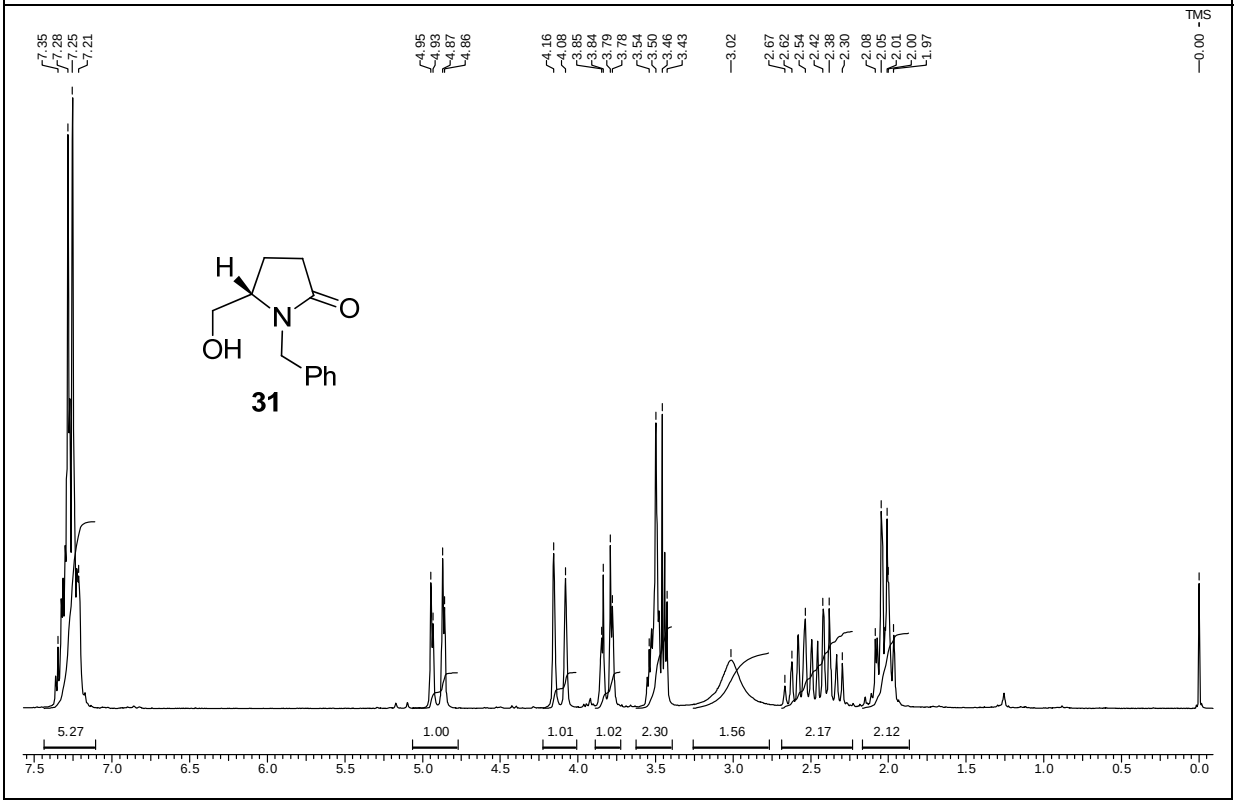
^{13}C-NMR spectrum of compound **21** ($CDCl_3$ + CCl_4, 50 MHz)



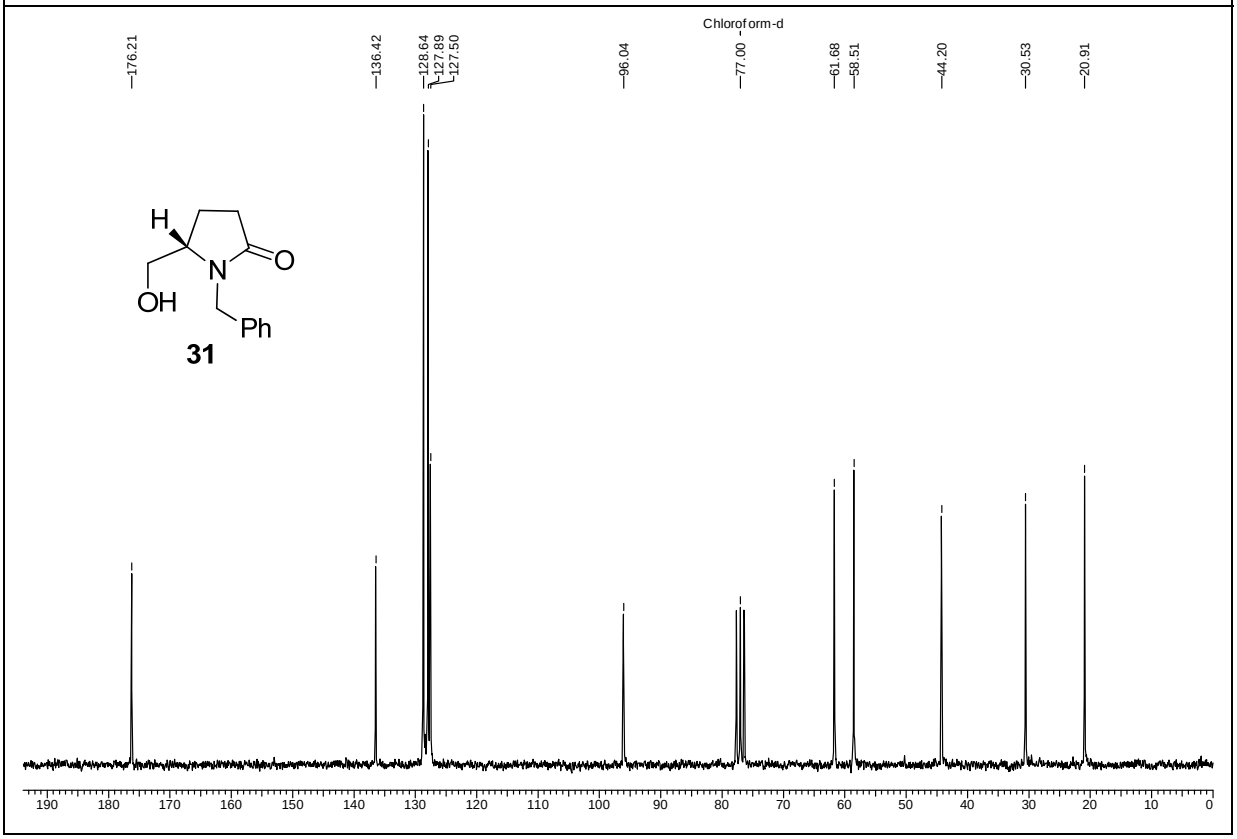
DEPT spectrum of compound **21** ($CDCl_3$ + CCl_4, 50 MHz)



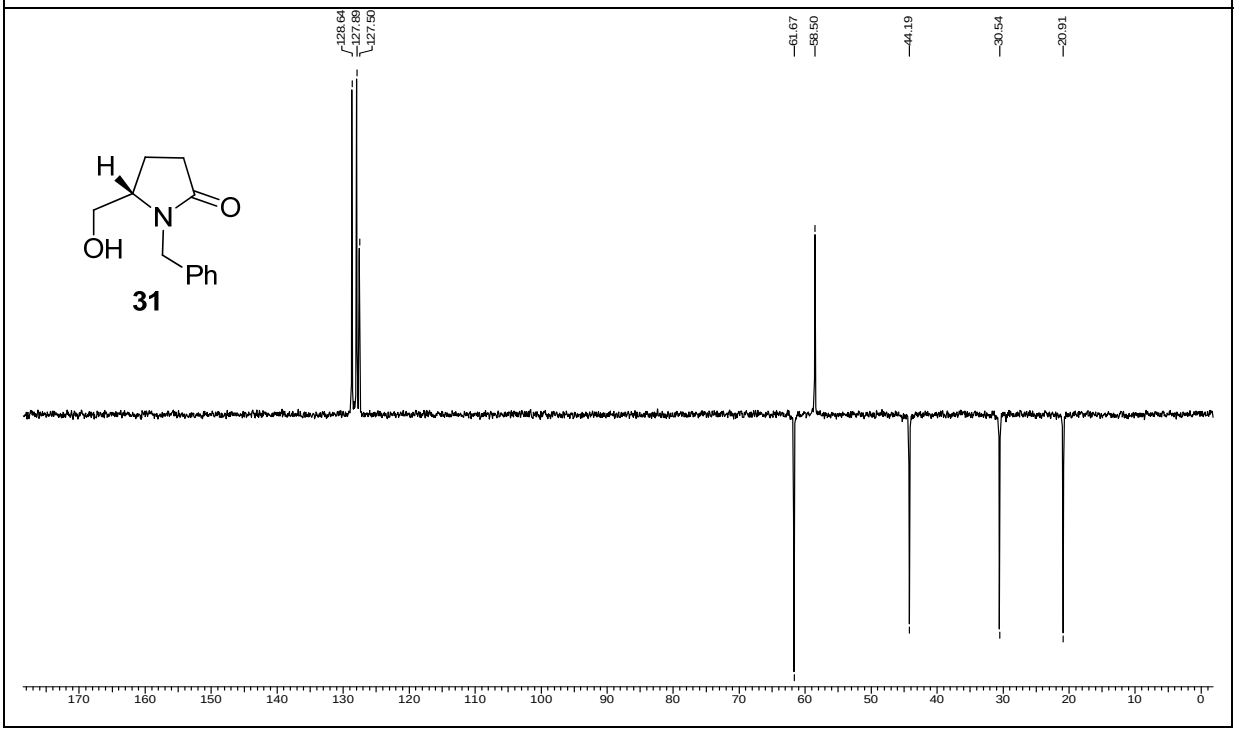
^{1}H-NMR spectrum of compound **31** ($CDCl_3$ + CCl_4, 200 MHz)



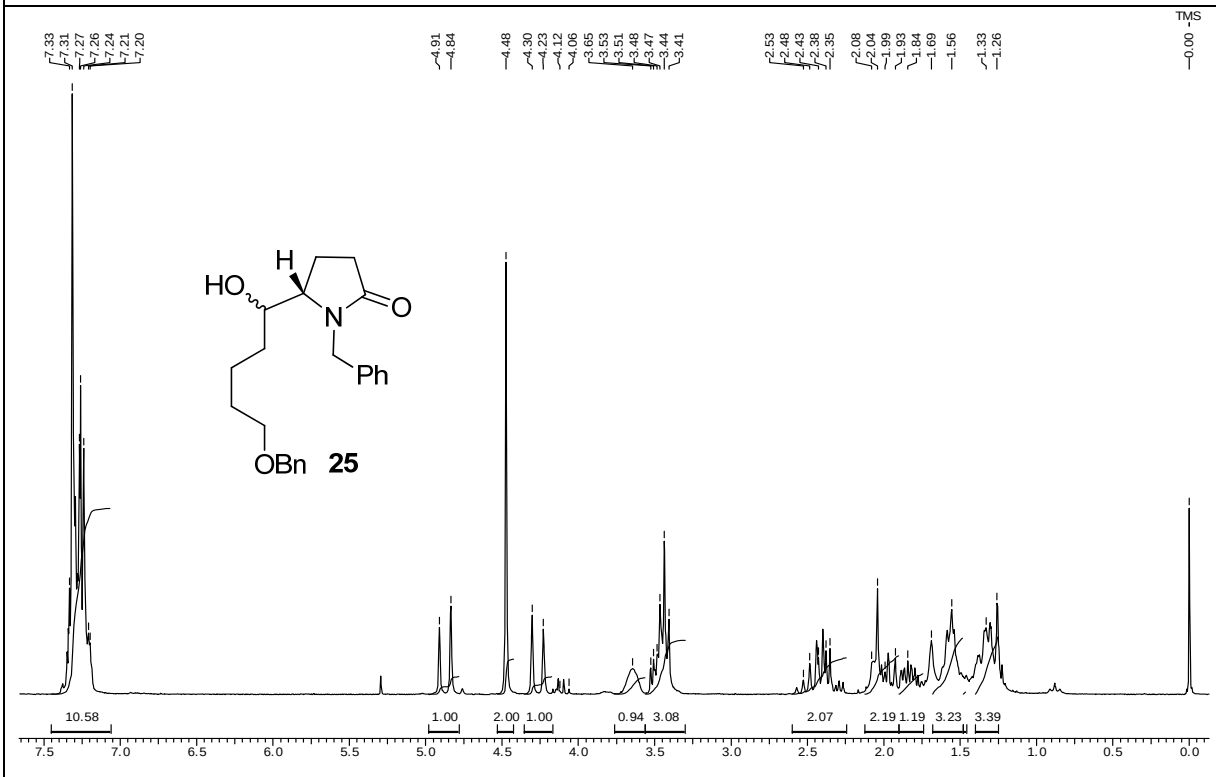
^{13}C-NMR spectrum of compound **31** ($CDCl_3$ + CCl_4, 50 MHz)



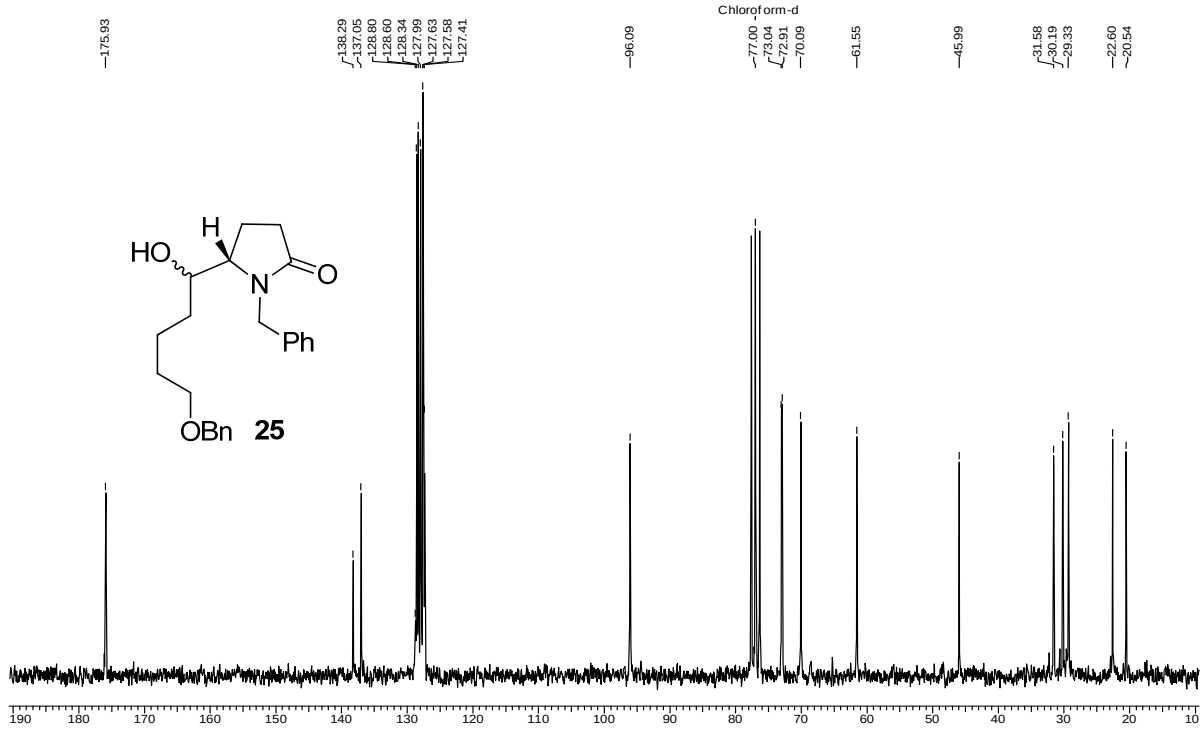
DEPT spectrum of compound **31** ($CDCl_3$ + CCl_4, 50 MHz)



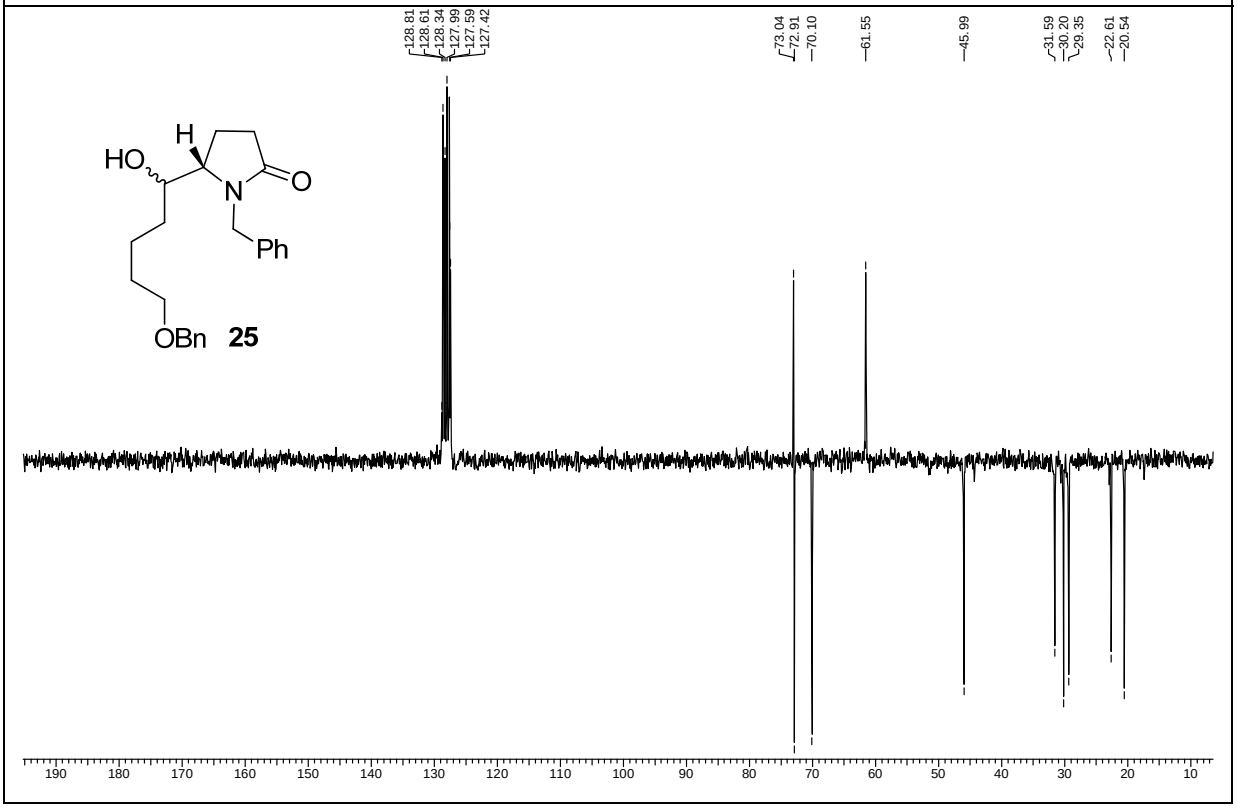
^{1}H-NMR spectrum of compound **25** ($CDCl_3$ + CCl_4, 200 MHz)



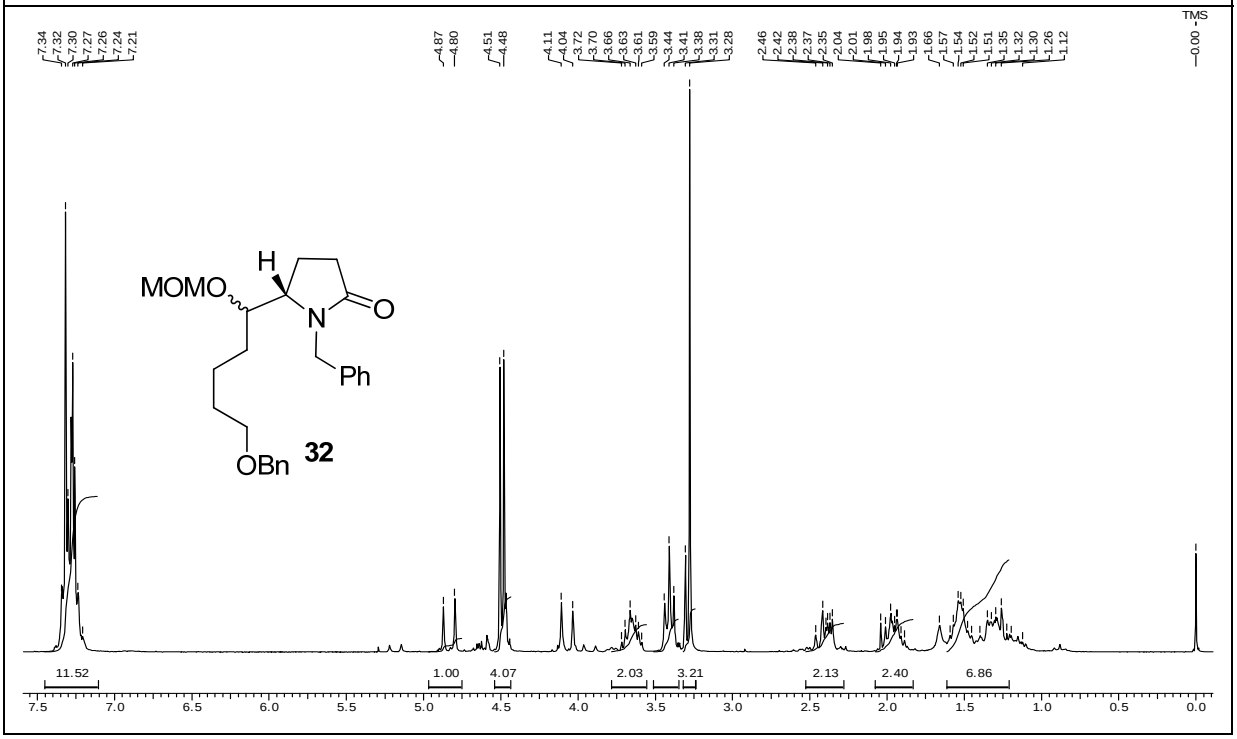
^{13}C-NMR spectrum of compound **25** ($CDCl_3$ + CCl_4, 50 MHz)



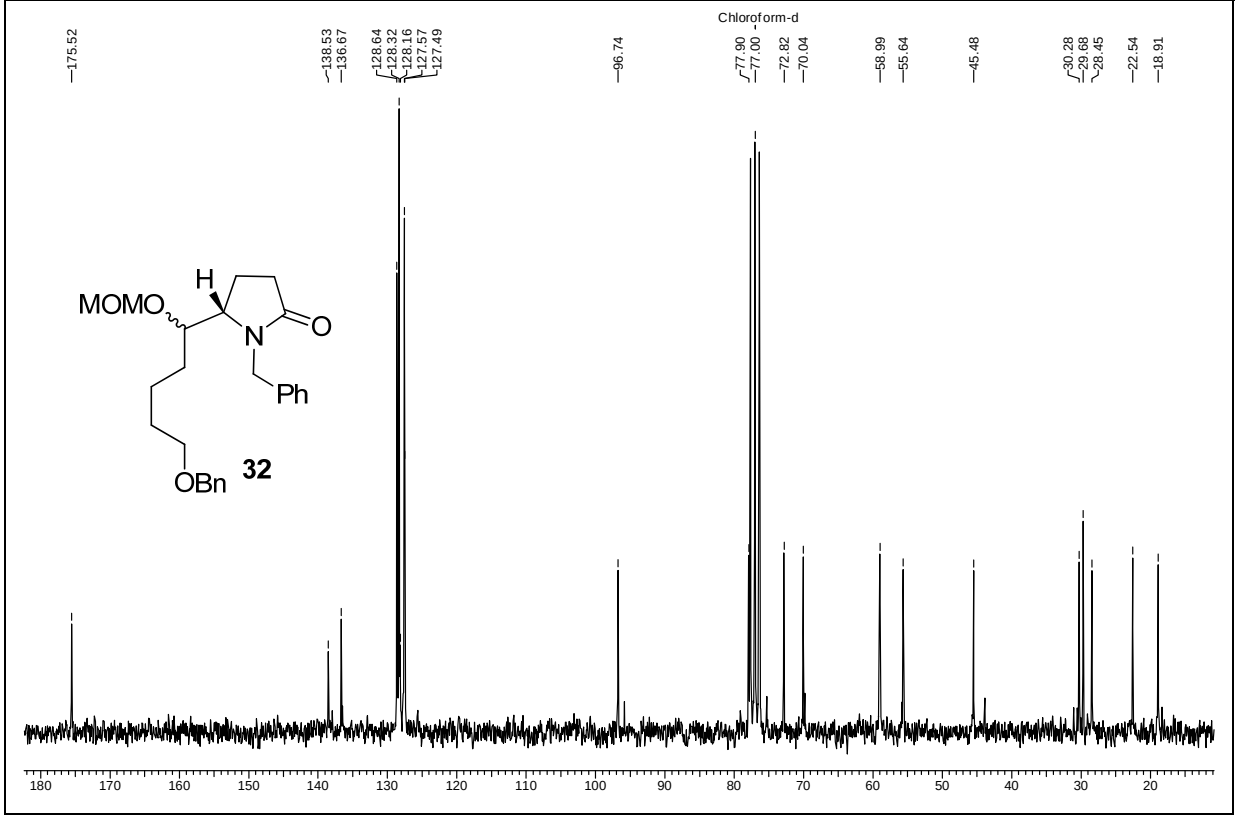
DEPT spectrum of compound **25** ($CDCl_3$ + CCl_4, 50 MHz)



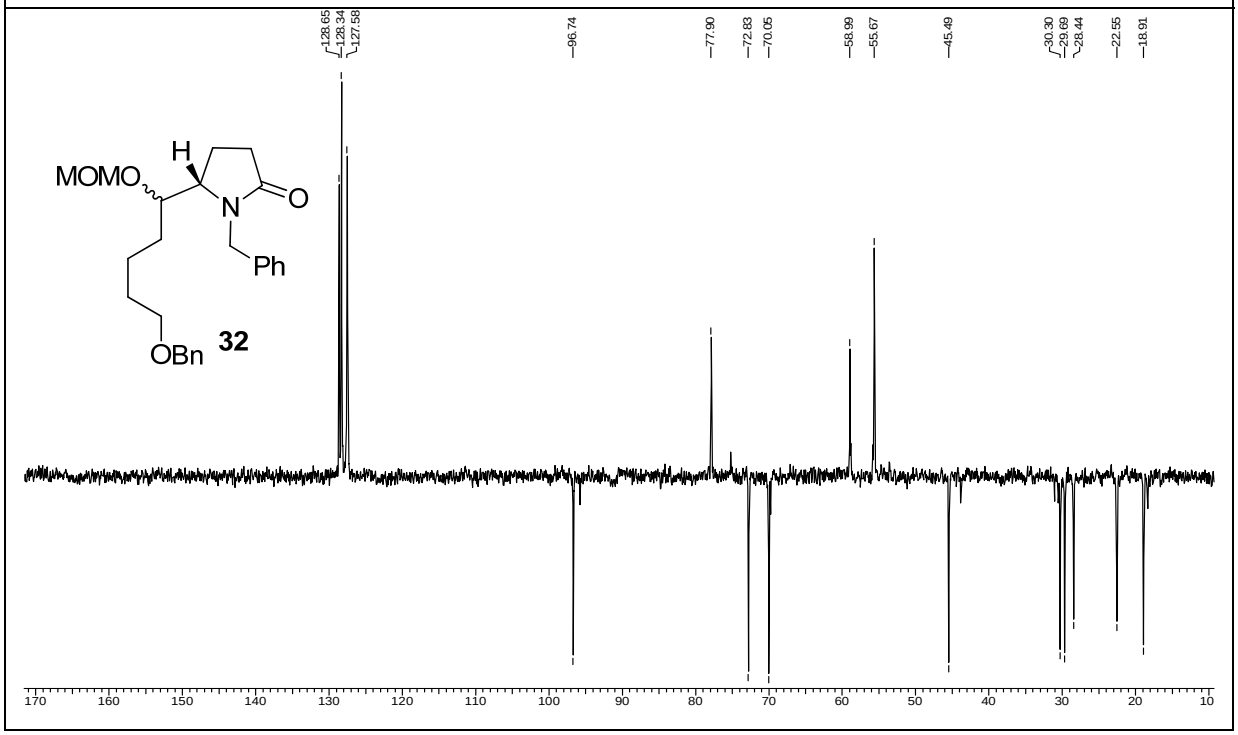
^{1}H-NMR spectrum of compound **32** ($CDCl_3$ + CCl_4, 200 MHz)



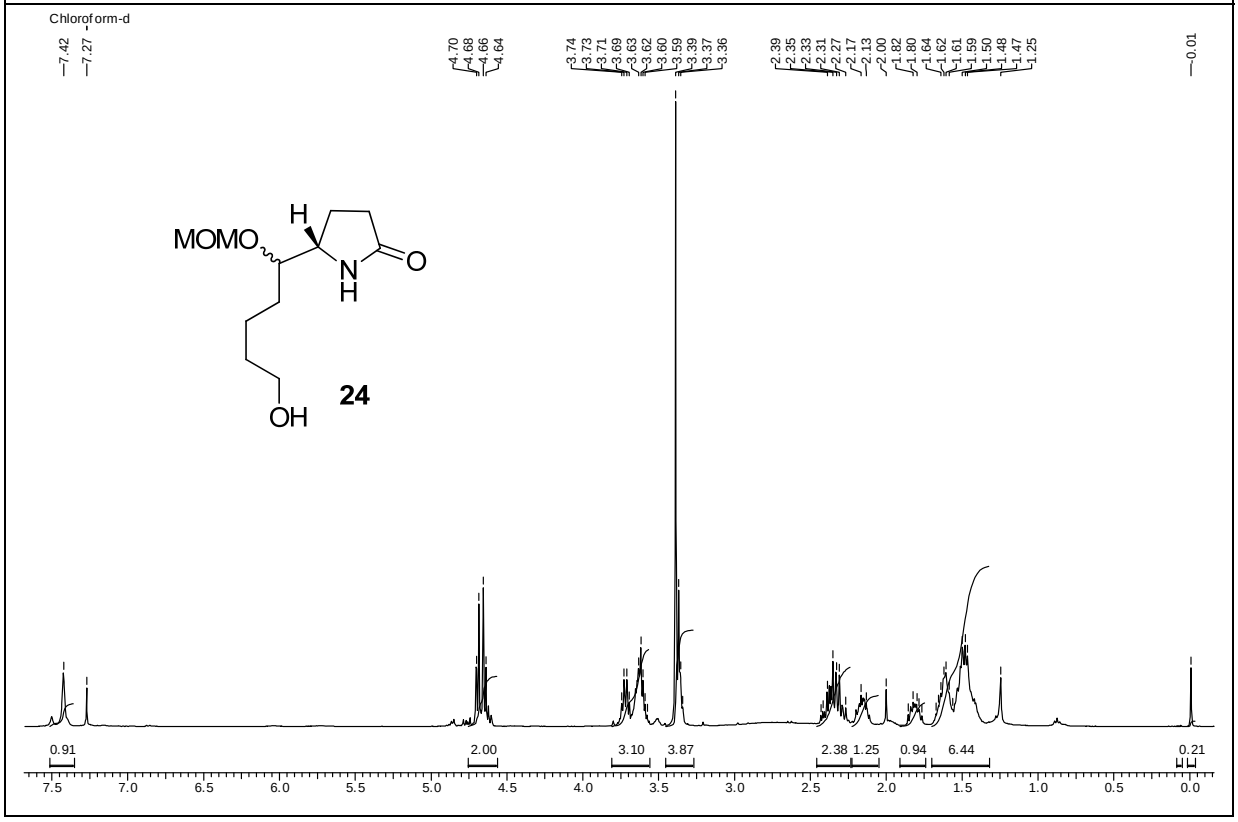
^{13}C-NMR spectrum of compound **32** ($CDCl_3$ + CCl_4, 50 MHz)



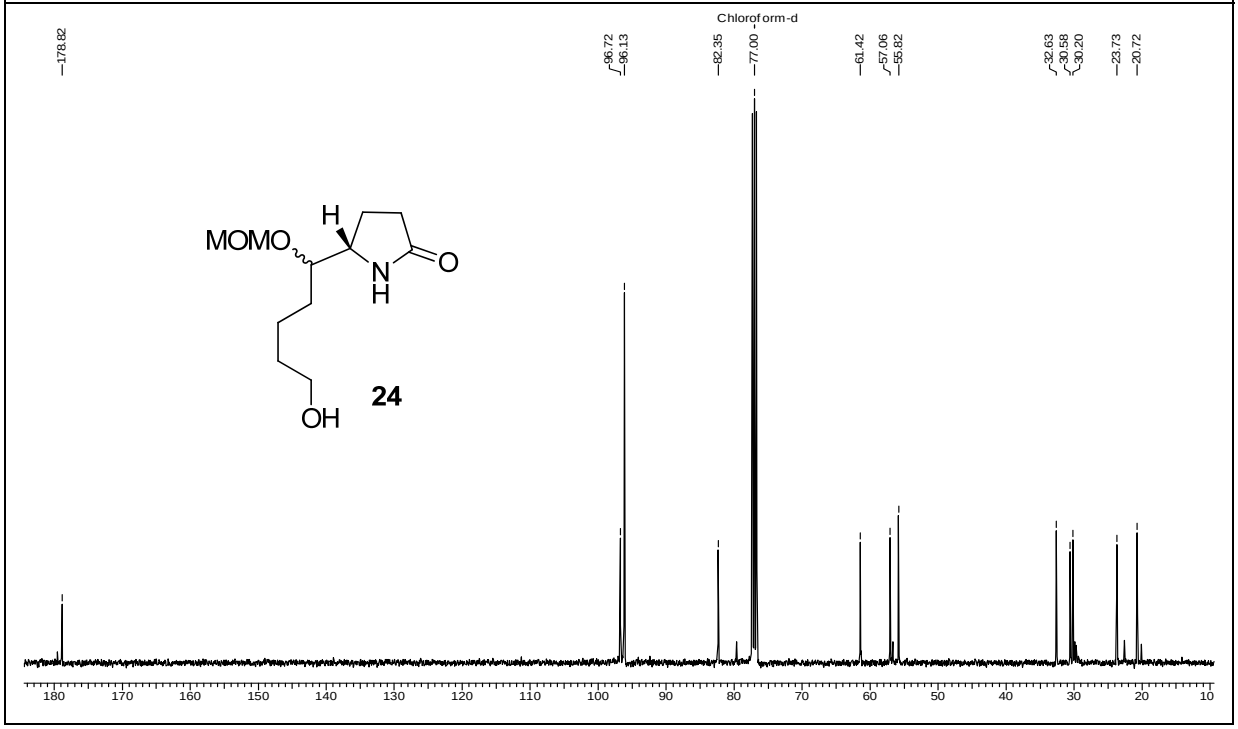
DEPT spectrum of compound **32** ($CDCl_3$ + CCl_4, 50 MHz)



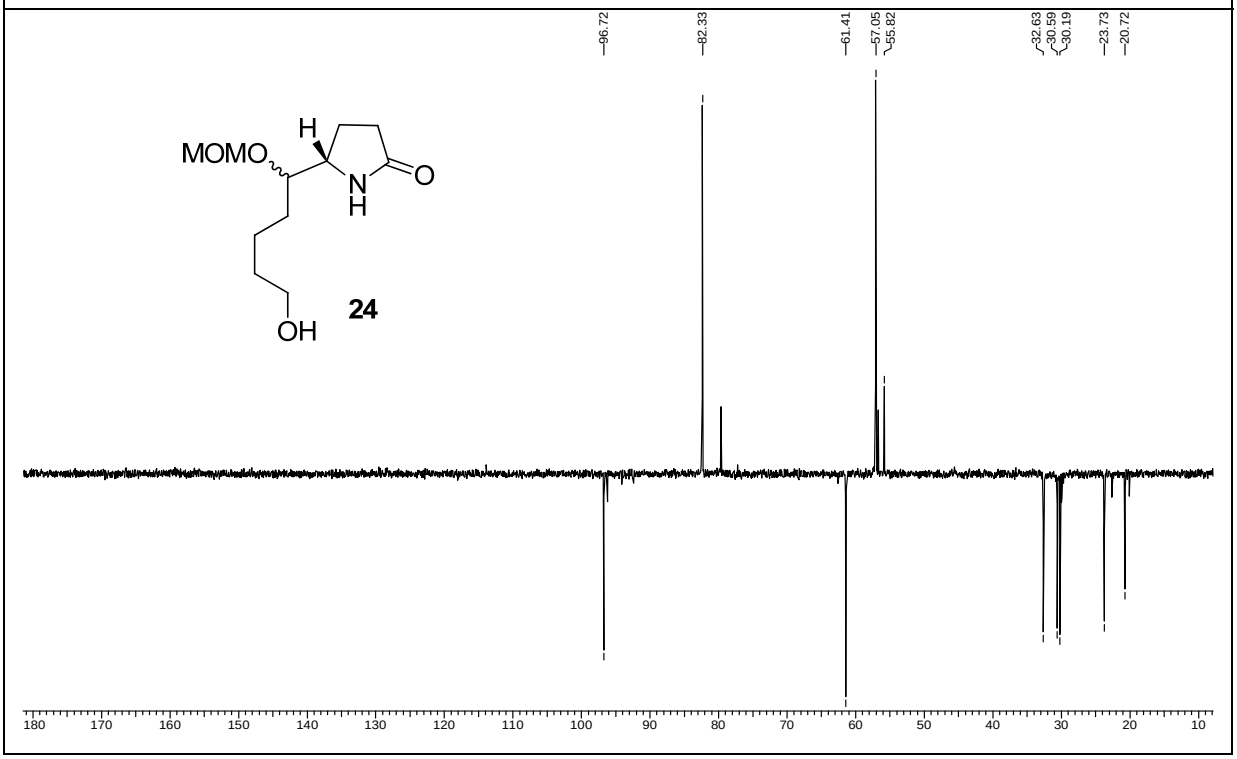
^{1}H-NMR spectrum of compound **24** ($CDCl_3$ + CCl_4, 200 MHz)



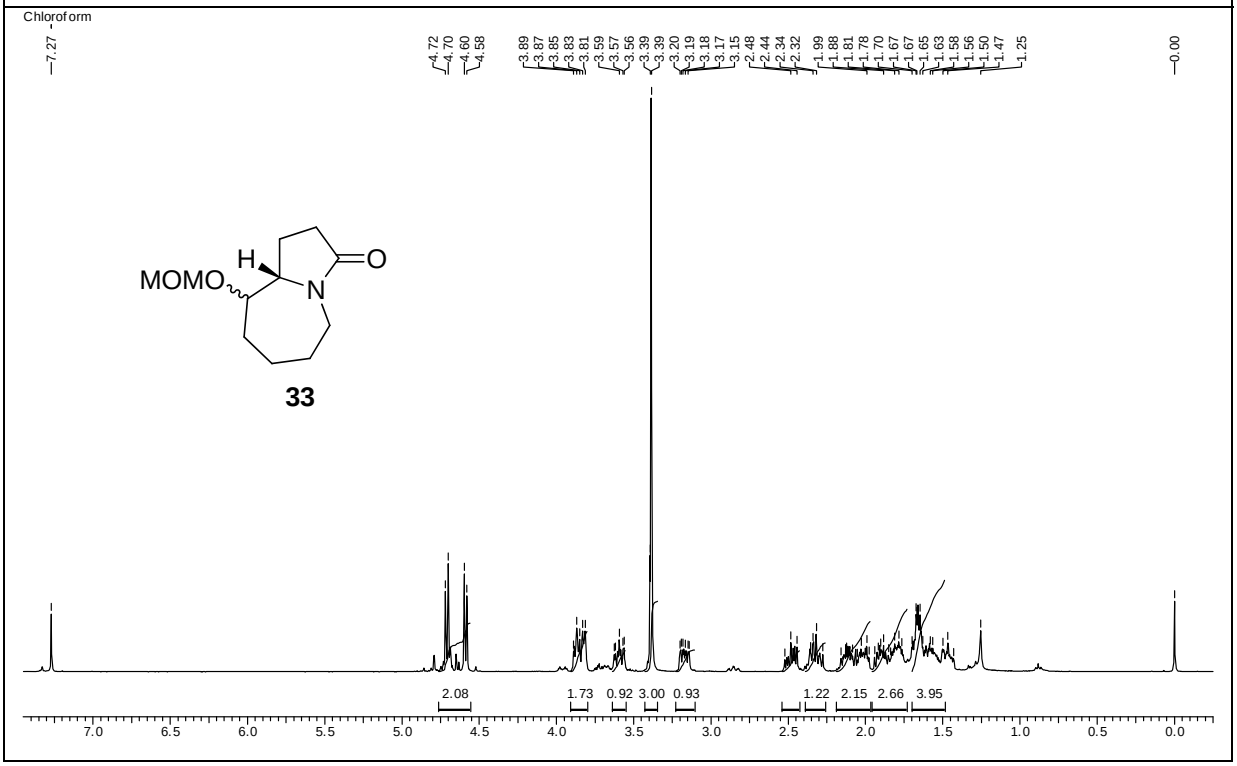
^{13}C-NMR spectrum of compound **24** ($CDCl_3$ + CCl_4, 50 MHz)



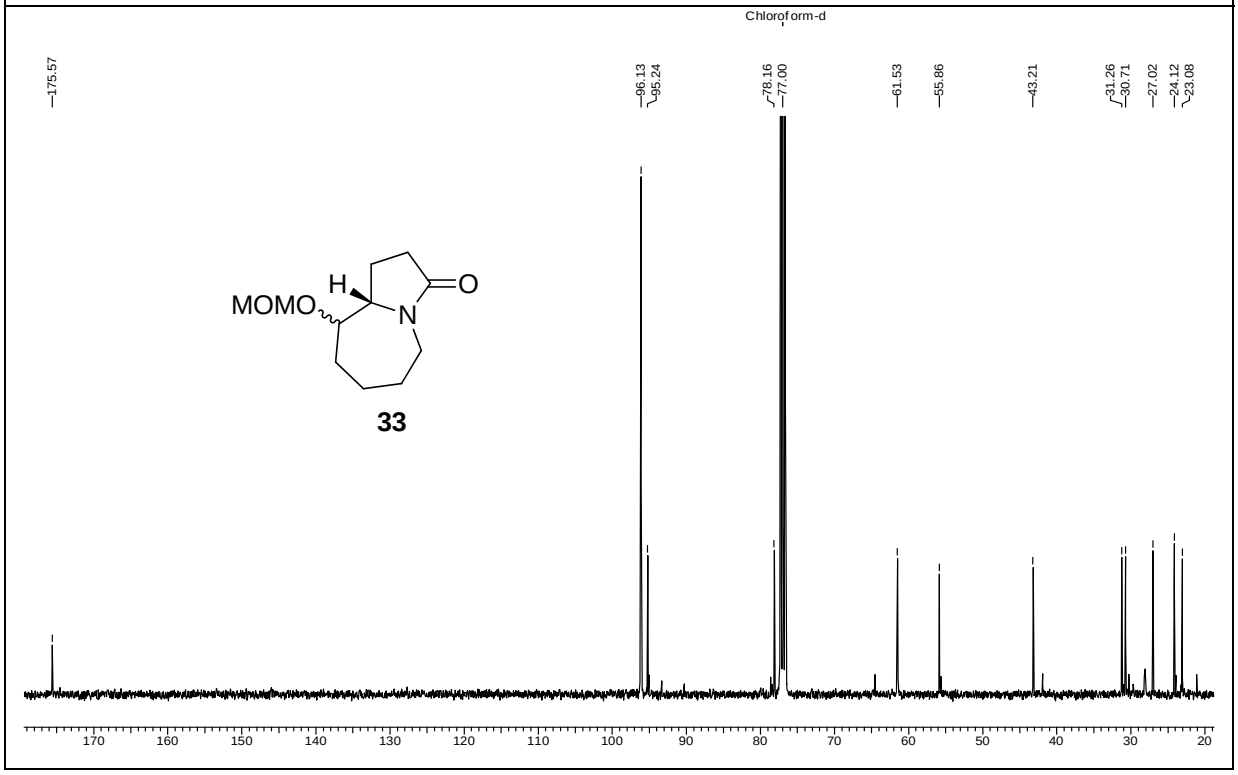
DEPT spectrum of compound **24** ($CDCl_3$ + CCl_4, 50 MHz)



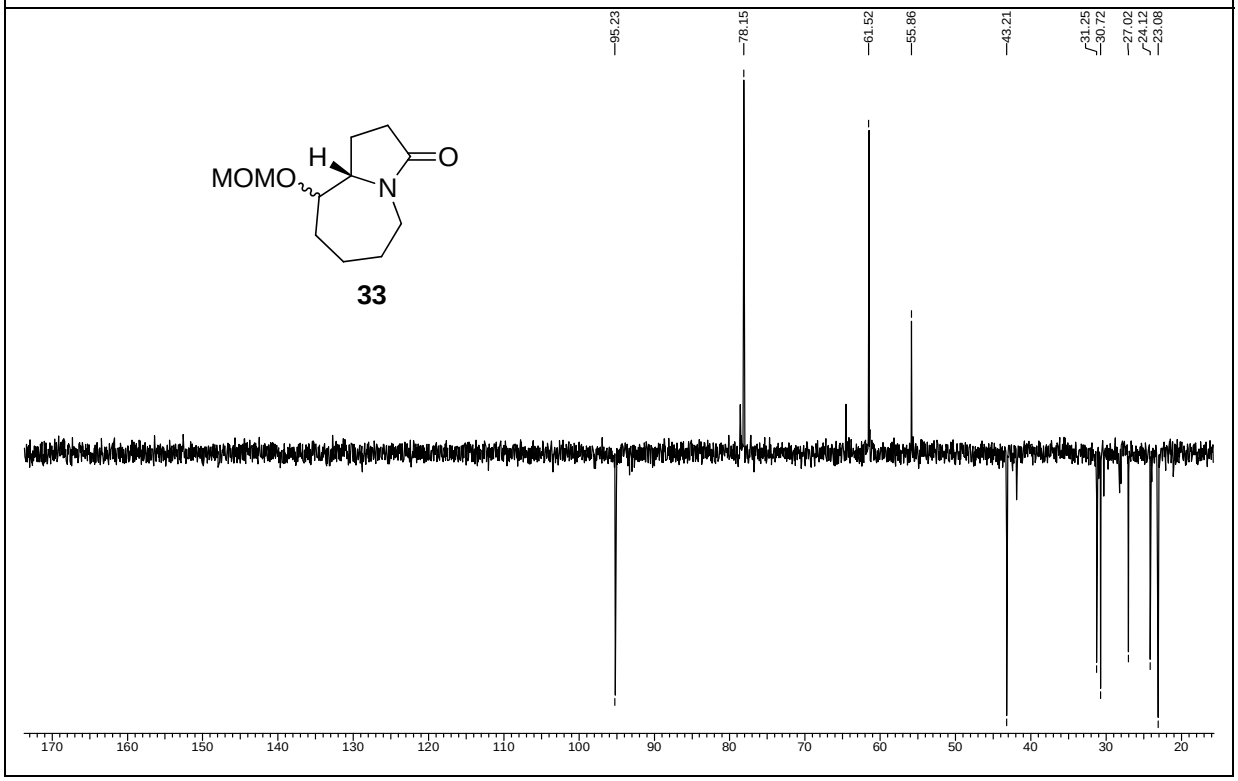
^{1}H-NMR spectrum of compound **33** ($CDCl_3$ + CCl_4, 200 MHz)



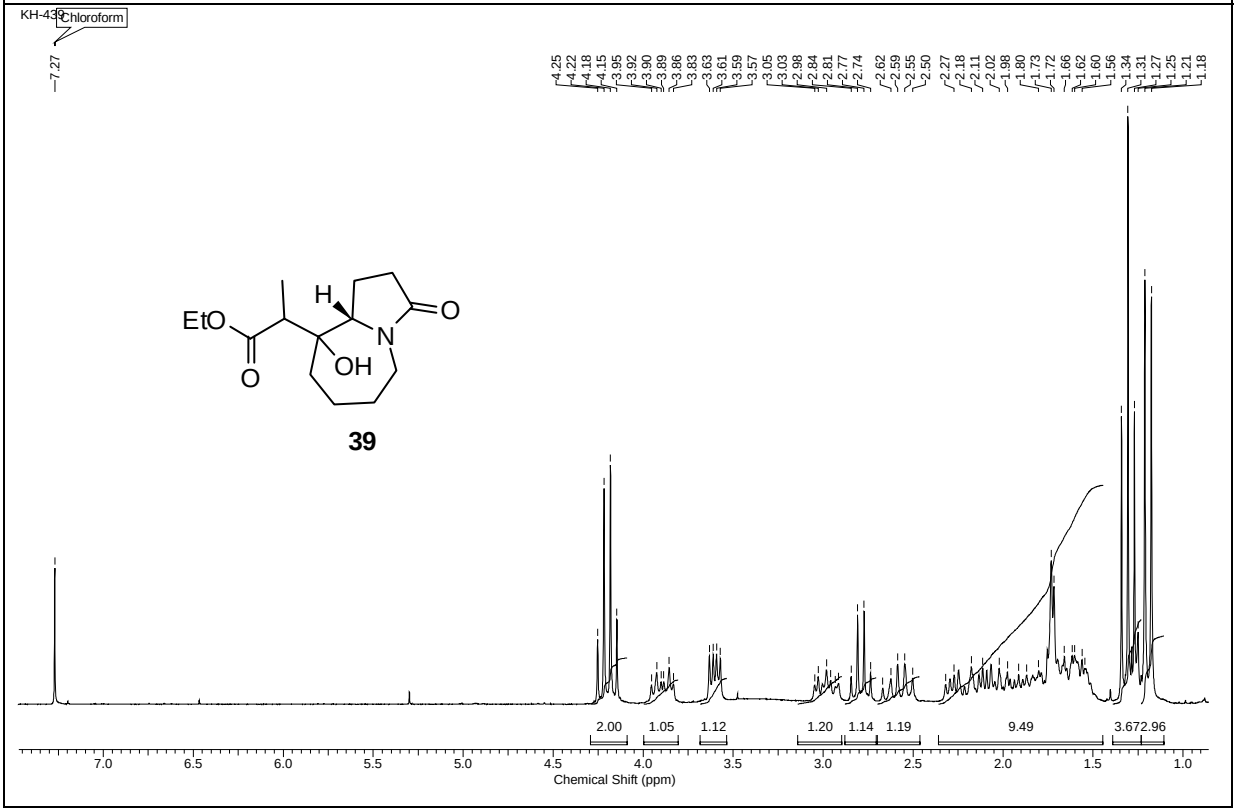
^{13}C-NMR spectrum of compound **33** ($CDCl_3$ + CCl_4, 50 MHz)



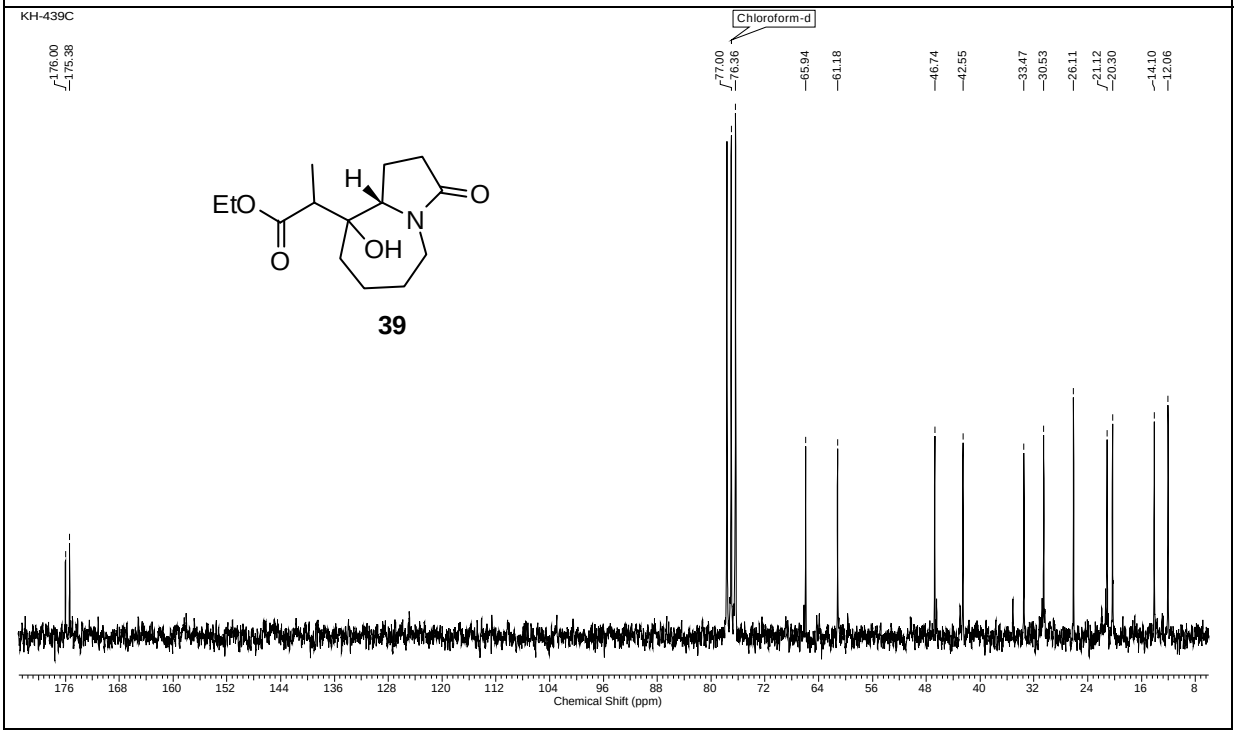
DEPT spectrum of compound **33** ($CDCl_3$ + CCl_4, 50 MHz)



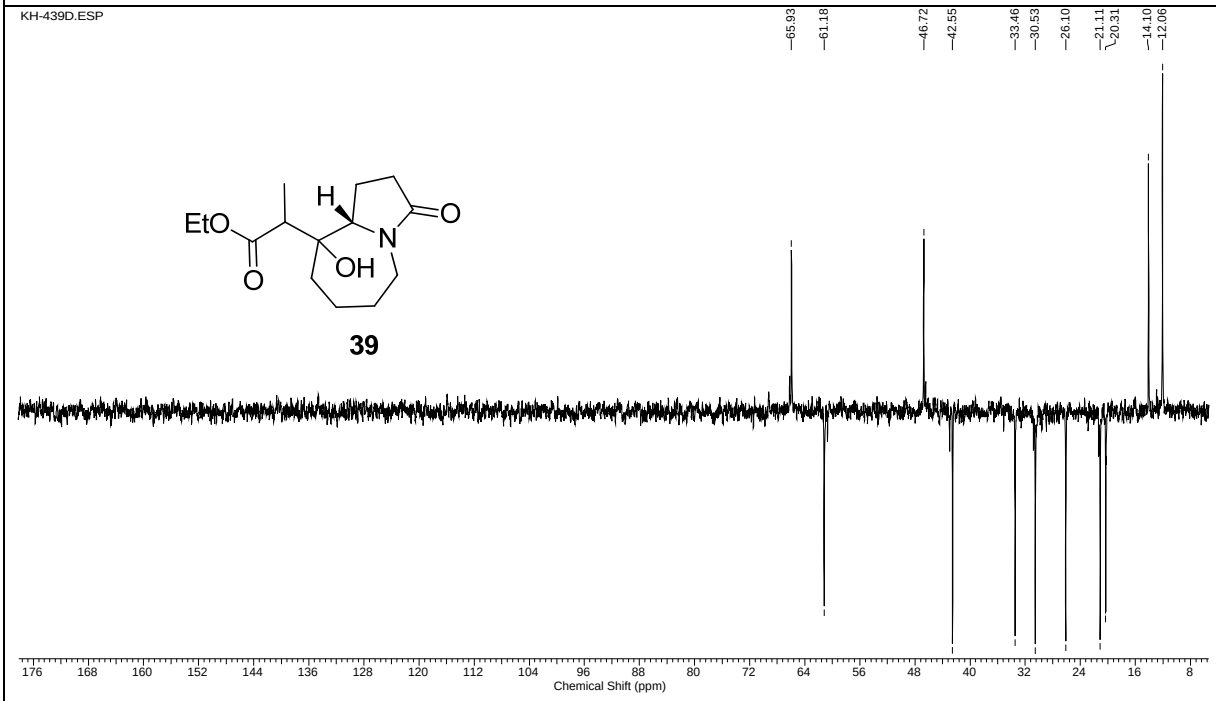
^{1}H-NMR spectrum of compound **39** ($CDCl_3$, 200 MHz)



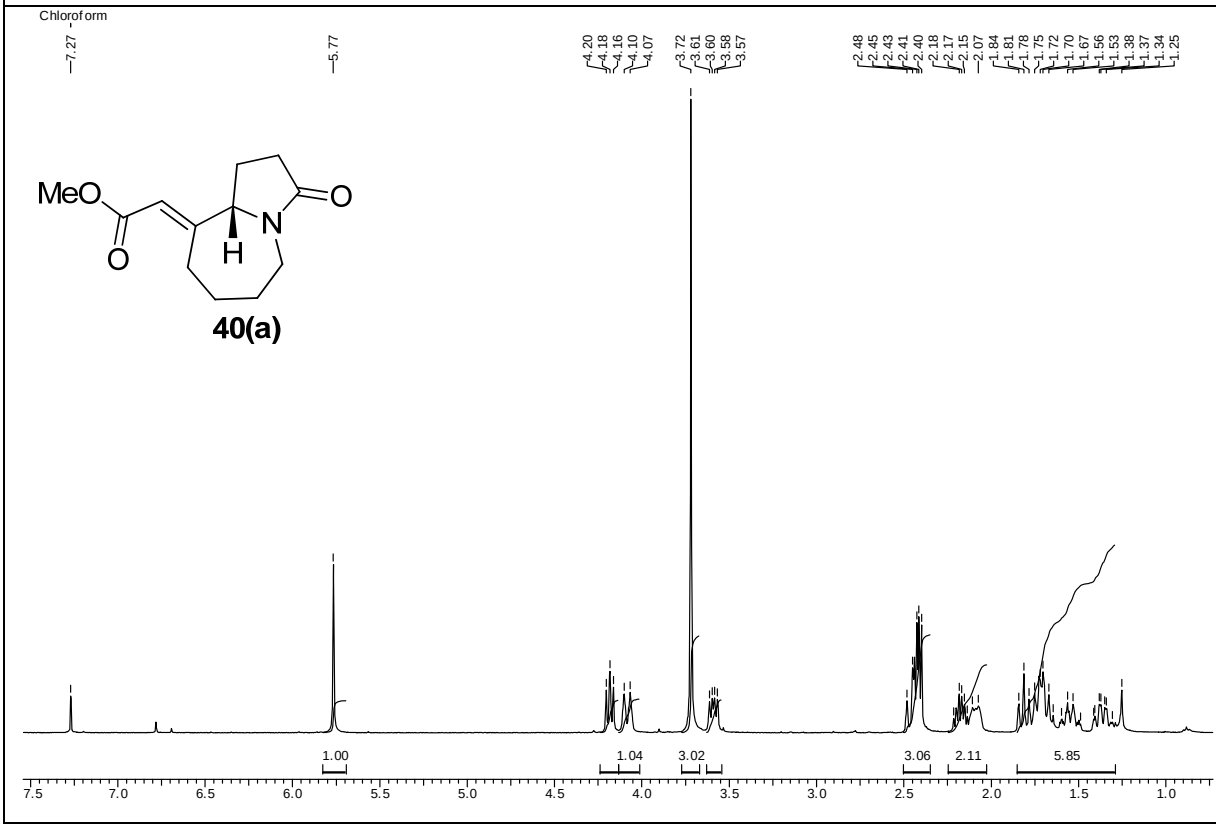
^{13}C-NMR spectrum of compound **39** ($CDCl_3$, 50 MHz)



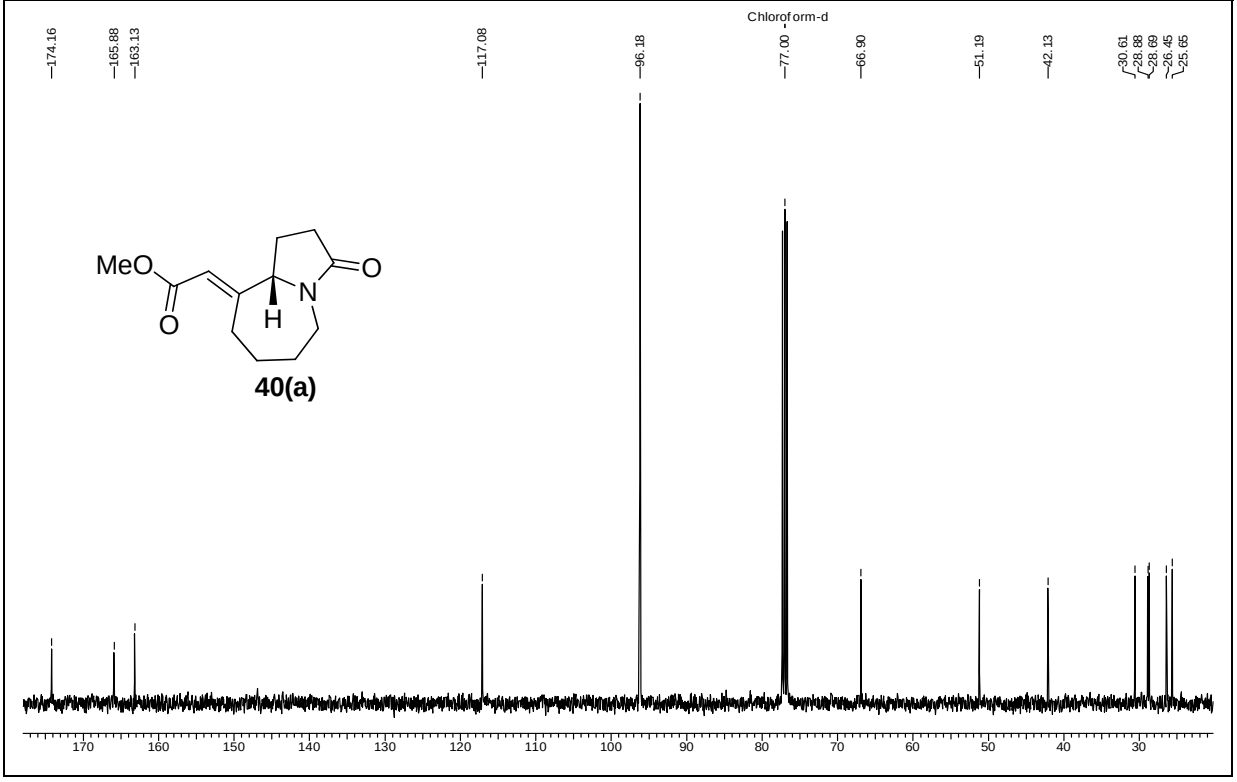
DEPT spectrum of compound **39** ($CDCl_3$ + CCl_4, 50 MHz)



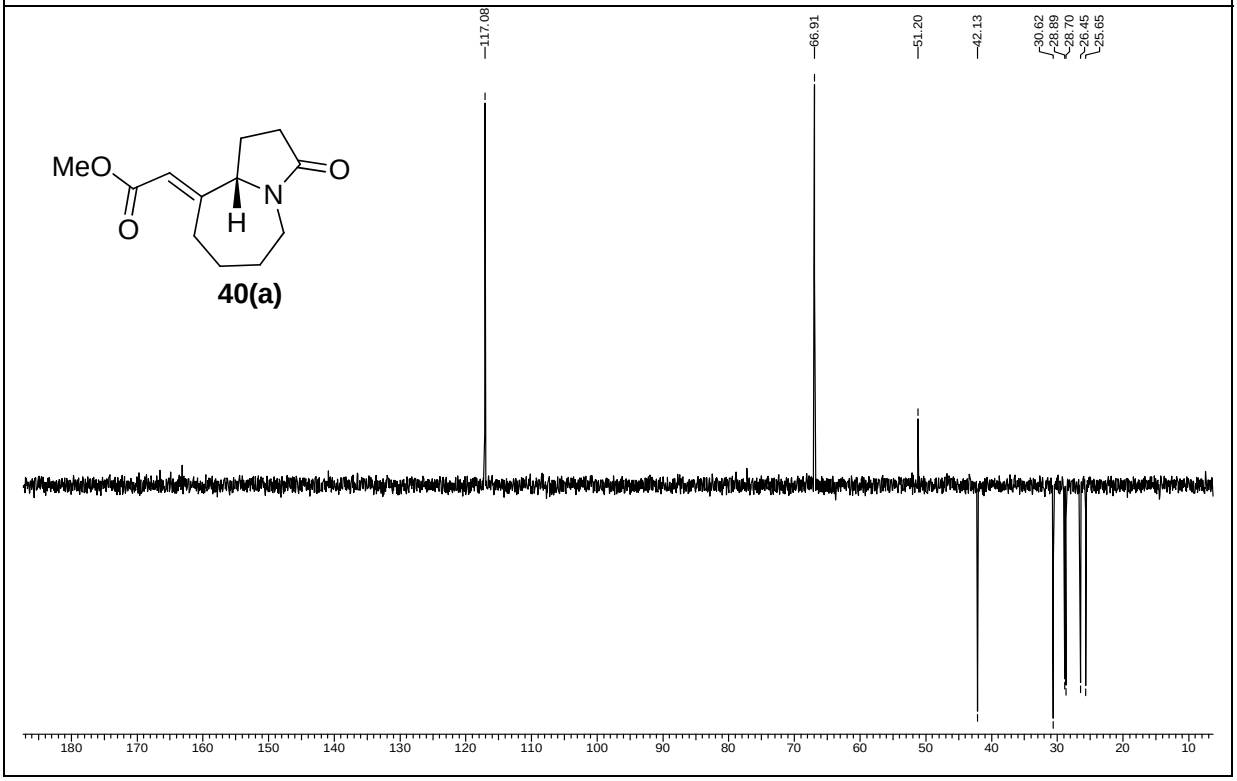
^{1}H-NMR spectrum of compound **40(a)** ($CDCl_3$ + CCl_4, 400 MHz)



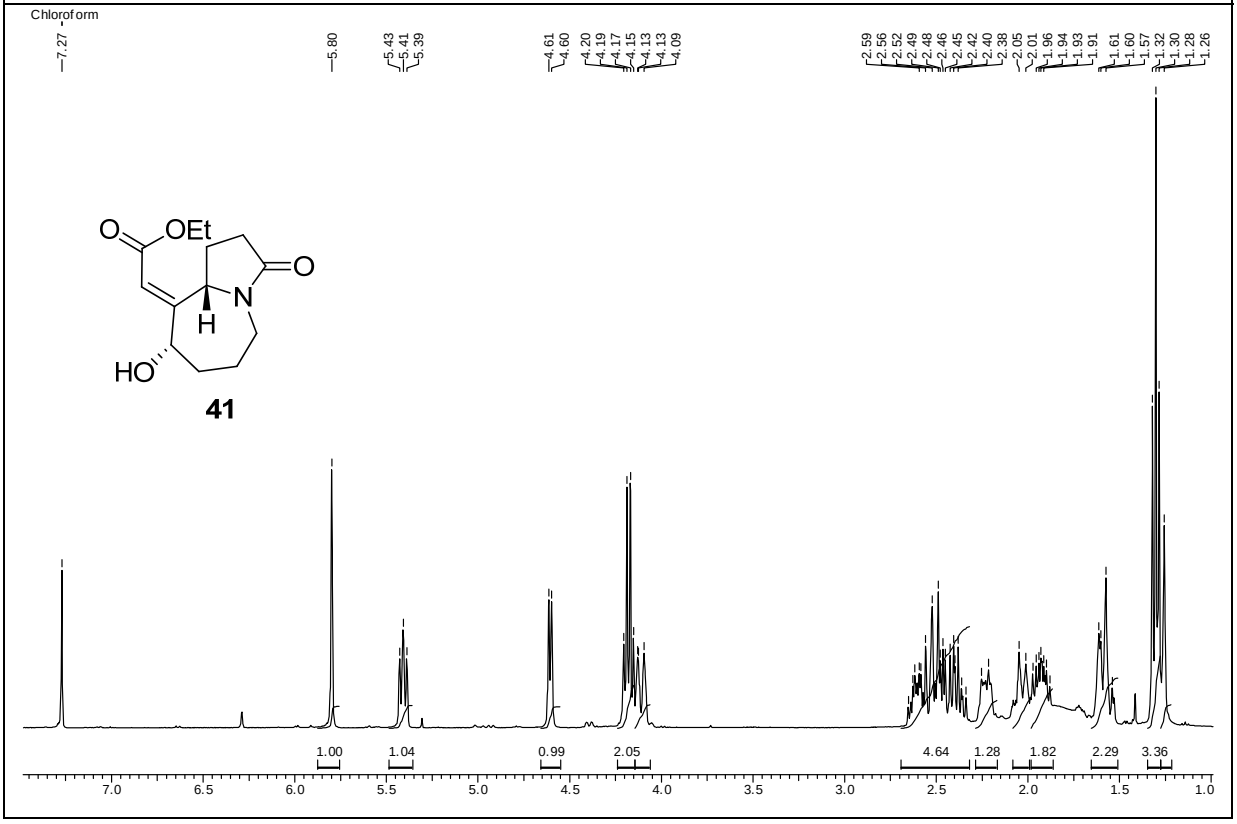
^{13}C-NMR spectrum of compound **40(a)** ($CDCl_3$ + CCl_4, 50 MHz)



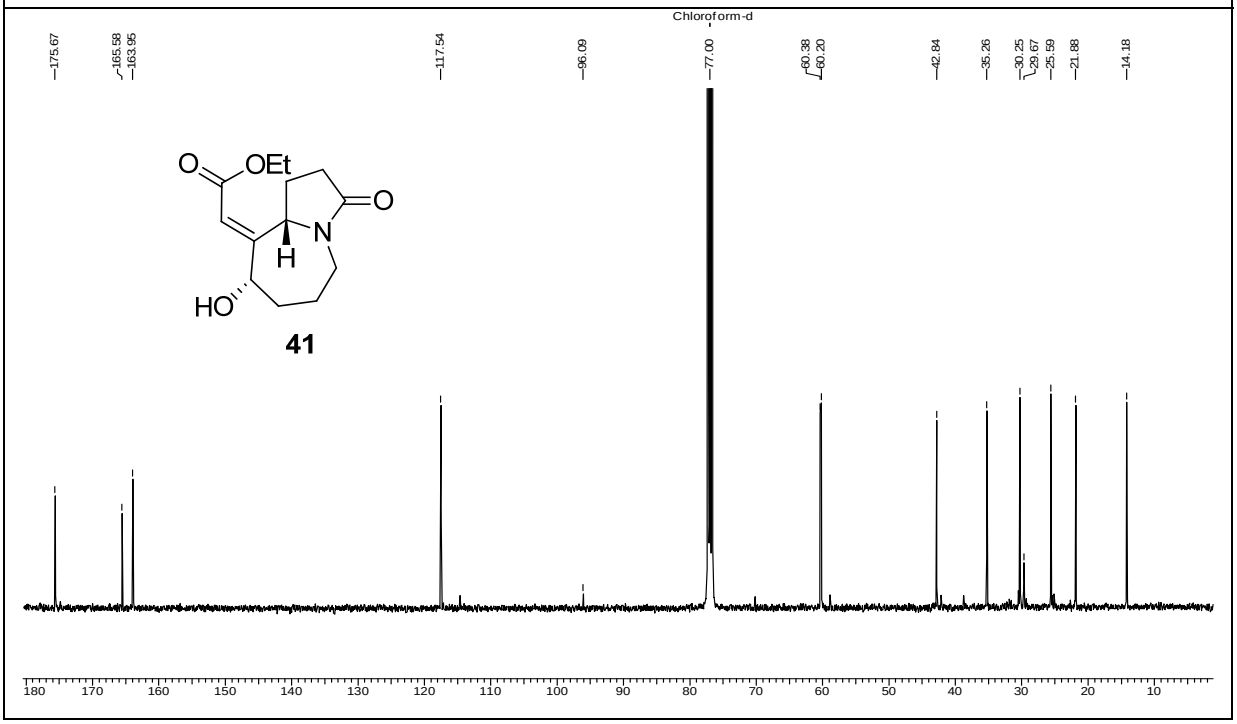
DEPT spectrum of compound **40(a)** ($CDCl_3$ + CCl_4, 50 MHz)



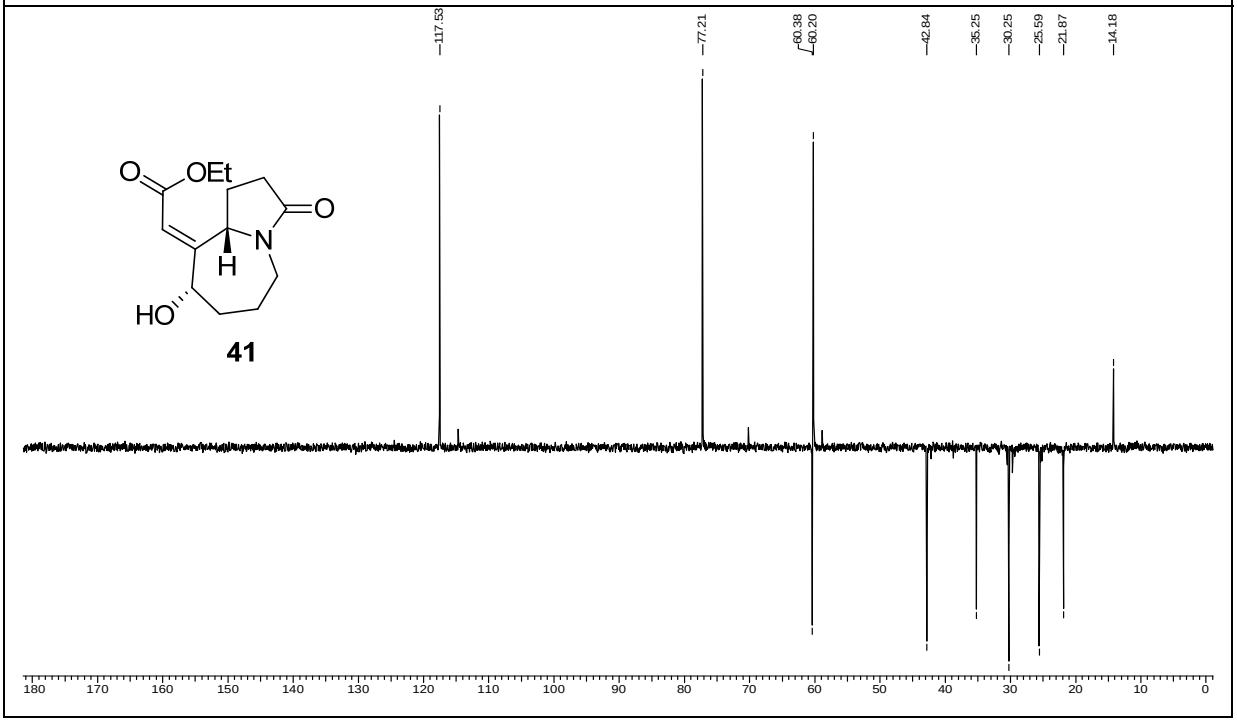
^{1}H-NMR spectrum of compound **41** ($CDCl_3$ + CCl_4, 400 MHz)



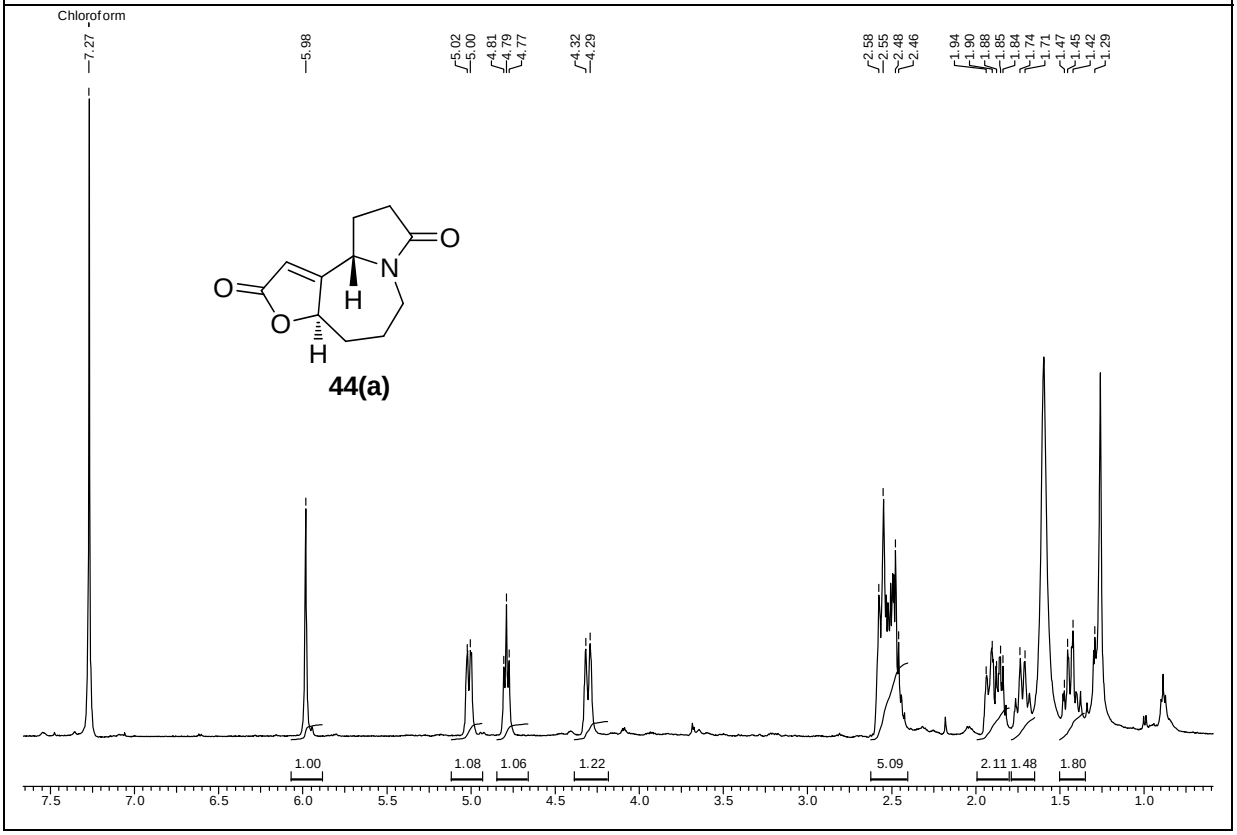
^{13}C-NMR spectrum of compound **41** ($CDCl_3$ + CCl_4, 100 MHz)



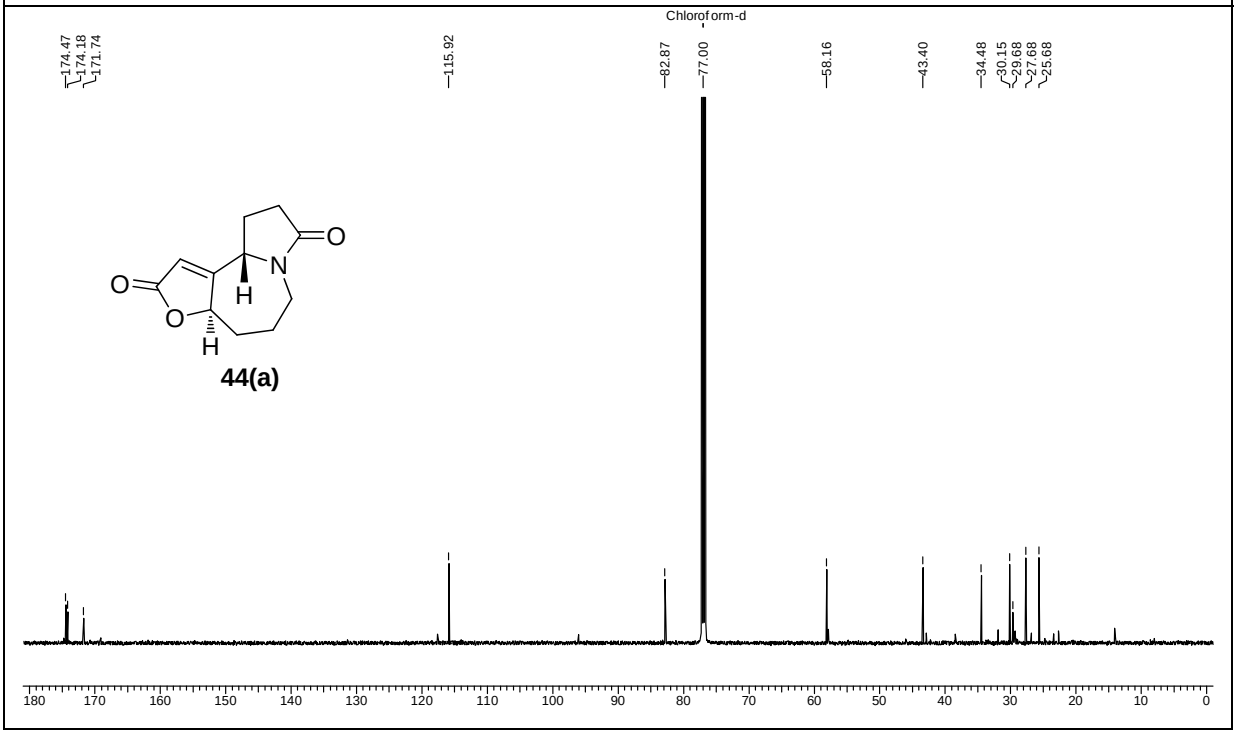
DEPT spectrum of compound **41** ($CDCl_3$ + CCl_4, 100 MHz)



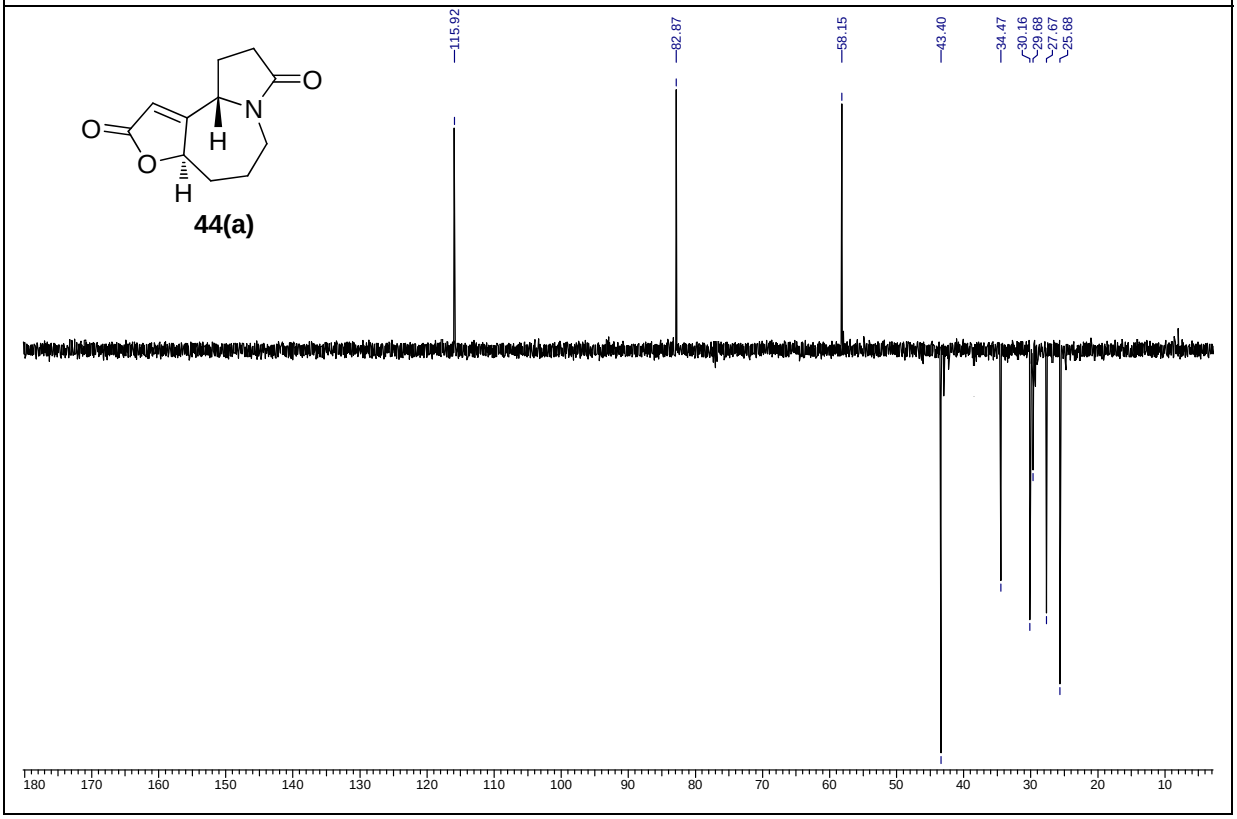
^{1}H-NMR spectrum of compound **44(a)** ($CDCl_3$, 400 MHz)



^{13}C-NMR spectrum of compound **44(a)** ($CDCl_3$, 100 MHz)



DEPT spectrum of compound **44(a)** ($CDCl_3$ + CCl_4, 100 MHz)



3.2.5 References

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9. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 866111. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).
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11. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 866112. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).
12. Patel, R. M.; Puranik, V. G.; Argade, N. P. *Org. Biomol. Chem.* **2011**, *9*, 6312.
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Chapter 3: Synthetic studies towards (–)-stemoamide and methodology for PMB protection of alcohols, selective mono and di-PMB protection of diols

Section 3: Development of methodology for PMB protection of alcohols, selective Mono and di-PMB protection of diols

3.3.1. Introduction:

Protection and deprotection chemistry is one of the inherent parts of the organic synthesis of complex and multifunctional organic molecules. The main role of protecting groups to play is the temporary masking of reactive sites when the chemical reaction is being carreid out at the other reactive sites. The ideal protective group must fulfill a number of requirements. It must react at selective sites and give good yields for protection. The protective group must be stable and unreactive towards the projected reaction conditions. As like good yields for protection the protecting group must be deprotected in good yields using easily available non toxic reagents wich are in turn neutral towards deprotected functional groups and the byproducts must not react with the deprotected functional groups. The protecting groups should not form a chiral centre like tetrahydropyarn after protection which is problematic with substrates having chiral centre as it results in to diastereomeric mixture formation after protection. The protecting groups should not have the additonal functional groups which can lead to the additonal complexities during multistep synthesis. Although no ideal protecting group exists, but the continous efforts by the organic chemists to improve and develop new protecting groups towards ideality continues.

Organic chemistry has made profound advancement in the methods of protection-deprotection strategy,[1] in case of handling of more than one functional groups. The main role of protecting groups is to selectively mask one functional group in order to perform transformation on the other non-compatible groups.[2]

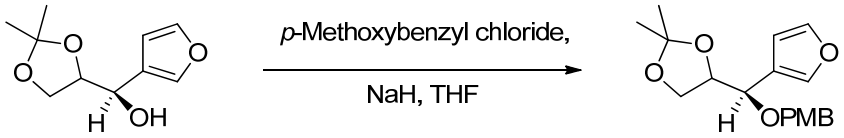
Hydroxy group is one of the most common functional groups. Over the years, number of protecting groups for hydroxy moiety has been developed.[3] The most important one of them is 4-methoxybenzyl (PMB) group.[4] The PMB group has an additional advantage over the benzyl group due to its ease of deprotection under mild and neutral conditions in the presence of double bonds, benzyl ethers, carboxybenzyl (CBZ) groups, methoxy methyl (MOM), methoxyethoxymethyl ether (MEM), tetrahydropyranyl (THP) and *tert*-butyldimethylsilyl (TBDMS) ethers *etc*.[5]

3.3.2 PMB protection of alcohols: A review

A short descriptive presentation of the work reported by different groups is being presented to give a better and comparative view of the different methods for PMB protection employed so far.

Marco *et al.* (*Tetrahedron Lett*. **1988**, *29*, 2459-2462)

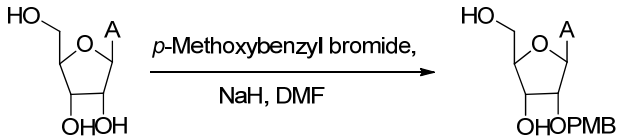
The most employed method for PMB protection of alcohols involves the fresh preparation of the *p*-methoxybenzyl chloride by treatment of equimolar quantities of *p*-anisyl alcohol and con. hydrochloric acid and then treatment with alcohol in presence of strong bases like NaH, *n*-BuLi *etc*. Marco *et al*. used *p*-methoxybenzyl chloride for PMB protection using NaH as a base (Scheme 1).[6]



Scheme 1

Takaku *et al.* (*Chem. Lett*. **1982**, 189-192)

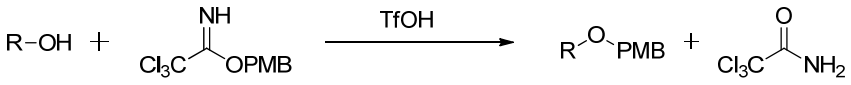
Takaku *et al*. used the *p*-methoxybenzyl bromide along with NaH as a base for the selective PMB protection of alcohols (Scheme 2).[7]



Scheme 2

Nakajima *et al.* (*Tetrahedron Lett.* **1988**, *29*, 4139-4142)

Nakajima *et al*. have reported a convenient acid catalyzed method for the PMB protection of alcohols using corresponding PMB-trichloroacetimidate.[8] Various alcohols were protected as their PMB ethers by treatment with PMB-trichloroacetimidate and 0.3 mol % of trifluoromethane sulfonic acid in good yields (Scheme 3).

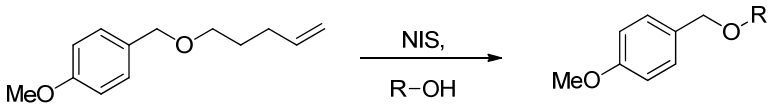


Scheme 3

Takeo *et al.* (*Tetrahedron* **1996**, *52,* 8135-8142)

Takeo *et al*. developed method for PMB protection of alcohols by generation of *p*-methoxybenzyl cation through NIS-mediated activation of *p*-methoxybenzyl 4-pentenyl ether (Scheme 4). Treatment of the various alcohols with *p*-methoxybenzyl 4-

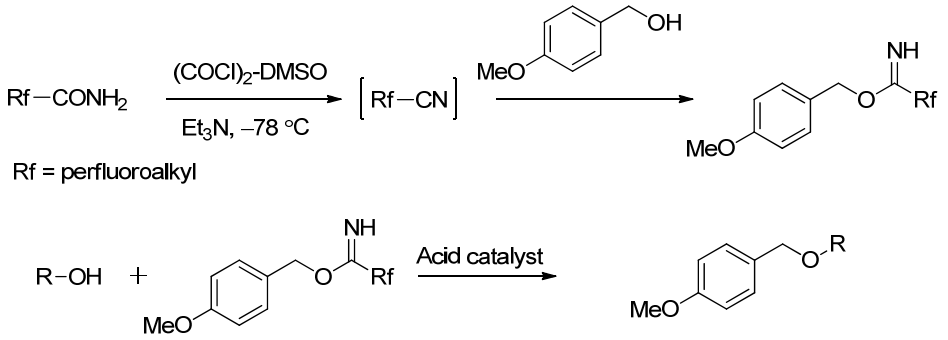
pentenyl ether and NIS in acetonitrile gave the PMB protected alcohols with moderate yields.[9]



Scheme 4

Nakajima *et al*. (*Tetrahedron Lett*. **1998**, *39*, 5565-5568)

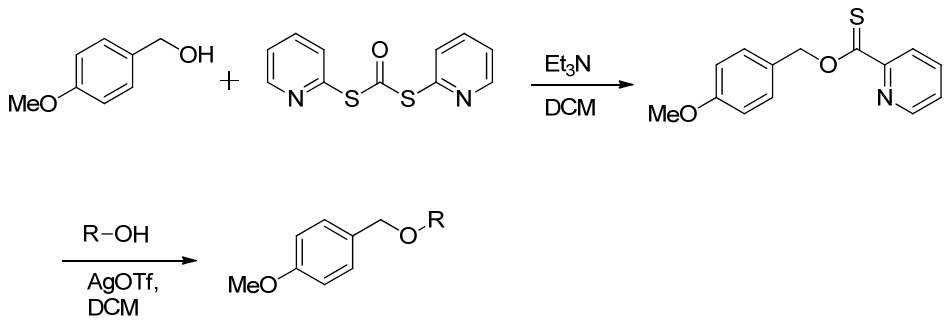
Nakajima *et al*. in their second approach used PMB-perfluoroacetimidate for PMB protection of alcohols under mild acidic conditions in good yields. The motif behind using PMB-perfluoroacetamidates for protection is due to its better stability compared with the PMB-trichloroacetimidates. The PMB-perfluoroacetimidate was prepared in two steps starting from perfluoroamide and *p*-anisyl alcohol and employed for the PMB protection of alcohols in presence of PPTS catalyst in DCM in good yields (Scheme 5).[10]



Scheme 5

Hanessian *et al*. (*Tetrahedron Lett*. **1999**, *40*, 671-674)

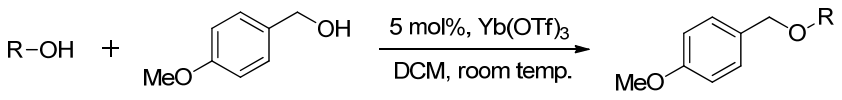
Hanessian *et al*. reported the use of the 4-methoxybenzyl-2-pyridylthio carbonate (PMB-TOPCAT) as a new reagent to convert alcohols into the corresponding PMB ethers in solution and on solid phase (Scheme 6). The primary, secondary and tertiary alcohols were protected under neutral conditions using silver triflate catalyst in DCM in good yields.[11]



Scheme 6

Sharma *et al*. (*J. Org. Chem.* **1999,** *64,* 8943-8944)

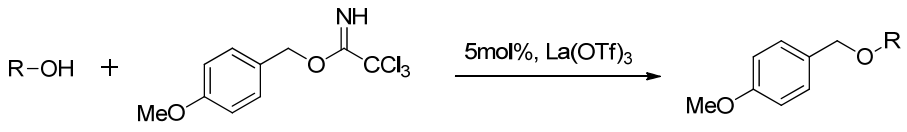
Sharma *et al.* developed a method for PMB protection of alcohols using *p*-anisyl alcohol and $Yb(OTf)_3$ as a catalyst in good yields. The optimized reaction conditions for the PMB protection were the treatment of alcohol with 2 eq. of *p*-anisyl alcohol and $Yb(OTf)_3$ (10 mol%) in DCM (Scheme 7).[12] The main merit of this method was the compatibility with both acid and base labile groups.



Scheme 7

Basu *et al*. (*Tetrahedron Lett*. **2003**, *44*, 2267–2269)

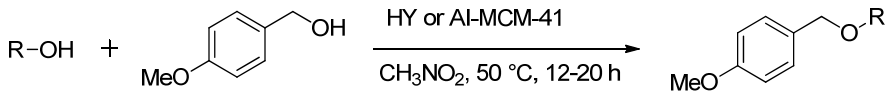
Basu *et al*. developed a method for PMB protection of alcohols using the trichloroacetimidate of PMB alcohol and lanthanum triflate, a neutral catalyst (Scheme 8). The main advantage of this method was the PMB protection of alcohols in presence of acid sensitive groups.[13]



Scheme 8

Sharma *et al*. (*Org. Prep. Proced. Int.* **2004**, *36*, 581-586)

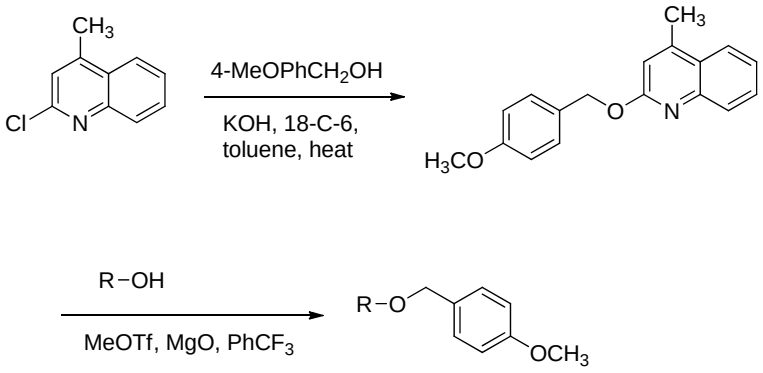
Sharma *et al*. developed a novel method for PMB protection of alcohols by using *p*-anisyl alcohol and zeolite as a catalyst (Scheme 9). Treatment of various alcohols with *p*-anisyl alcohol and zeolite catalyst furnished PMB protected alcohols in good yields.[14]



Scheme 9

Dudley *et al.* (*Chem. Commun*. **2007**, 1436–1437)

Dudley *et al*. developed a method for PMB protection of alcohols under neutral

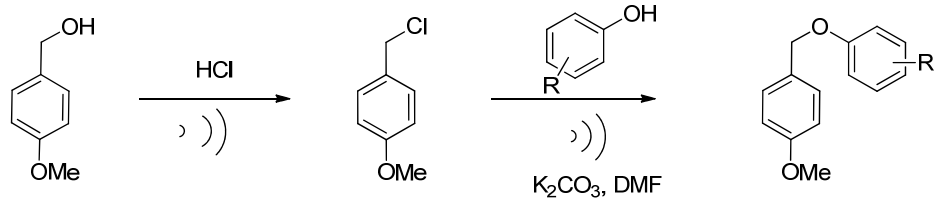


Scheme 10

conditions (Scheme 10). 2-(4-Methoxybenzyloxy)-4-methylquinoline reacts with methyl triflate in the presence of alcohols to generate a neutral organic salt that transfers the *p*-methoxybenzyl (PMB) protecting group onto alcohols in high yield and under mild conditions.[15]

Luzzio *et al.* (*J. Org. Chem.* **2008**, *73*, 5621–5624)

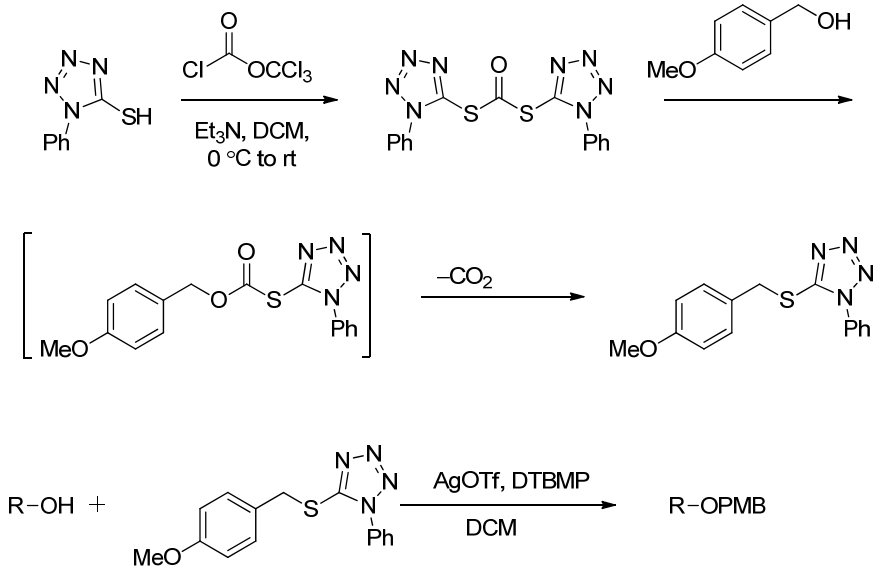
Luzzio *et al*. developed a method for protection of substituted phenols using *p*-methoxybenzyl chloride under ultrasound conditions (Scheme 11). This method involves the treatment of various phenols with PMB-Cl in presence of K_2CO_3 in DMF under ultrasound conditions to furnish the PMB-protected phenols in good yields.[16]



Scheme 11

Lear *et al.* (*Tetrahedron Lett.* **2009**, *50,* 5267–5269)

Lear *et al.* achieved PMB protection of the alcohols by using the silver triflate (AgOTf) mediated activation of 5-(*p*-ethoxybenzylthio)-1-phenyl-1*H*-tetrazole (PMB-ST) in the presence of 2,6-di-tert-butyl-4-methylpyridine (DTBMP) (Scheme 12).[17]



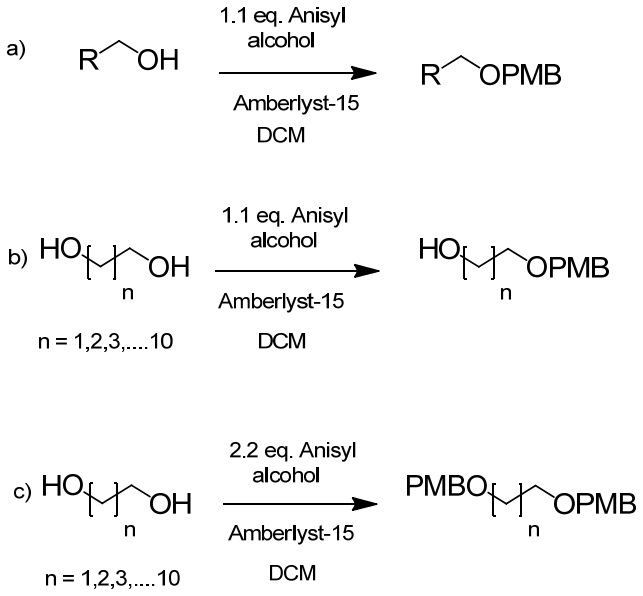
Scheme 12

3.3.3 Results and discussion:

Since hydroxy compounds are the important starting materials, easy and selective protection of the hydroxy functionality as its PMB group is highly desirable. The most commonly employed methods for PMB protection of alcohols involve usage of *p*-methoxybenzyl chloride (PMBCl) or *p*-methoxybenzyl bromide (PMBBr) in the presence of strong base like NaH. The main problem associated with this method is handling and storage of PMBCl and PMBBr which are very prone to decomposition. Additionally, this protocol requires anhydrous conditions and use of hazardous bases like NaH, *n*-BuLi *etc*. The other *p*-methoxybenzylation methods involve use of methoxybenzyl iodides,[18a] trichloroacetamidates,[13] perfluoroacetamidates[10] and *p*-methoxybenzyl azide[17b] depending upon degree of mildness required. Amongst the two available methods for PMB protection using anisyl alcohols, one involves the use of expensive $Yb(OTf)_3$[12] catalyst and the other requires zeolite, which requires extended time of action.[14]

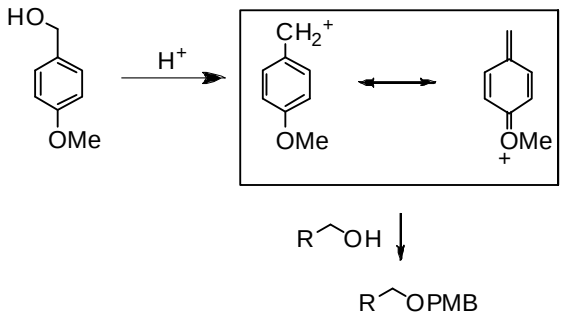
To avoid drawbacks in the synthesis and handling of PMBCl or PMBBr, it is highly desirable to look for an alternate protocol for PMB protection. Current protocol described herein totally avoids these issues by using stable, easy to handle *para*-anisyl alcohol (PMBOH), directly for protection. It was surmised that the direct use of PMBOH would be highly desirable as it is readily available, easy to synthesize, safe to store and handle. It was premised that under acidic conditions PMBOH would easily form a good electrophile which could be trapped by nucleophile. This section details our efforts in this regard.

A highly practical and very simple method for PMB protection has been developed (Scheme 13). Alcohols can be protected directly using anisyl alcohol in presence of acidic resin *viz*. Amberlyst-15. Just heating of alcohol and anisyl alcohol in a low boiling solvent in the presence of heterogeneous acid catalyst provides excellent yield of the corresponding protected alcohol. A noteworthy feature of this protocol is the high regioselectivity observed in mono-PMB protection of diols. This method is logically based on formation of benzylic cation by protonation of anisyl alcohol (Scheme 14).



Scheme 13. a) PMB protection of alcohols, b) Selective mono-PMB protection of diols and c) Di-PMB protection of diols.

The resultant benzylic cation is additionally stabilized by *p*-OMe group by mesomeric donation. This cation can be trapped by alcohol leading to PMB protection.

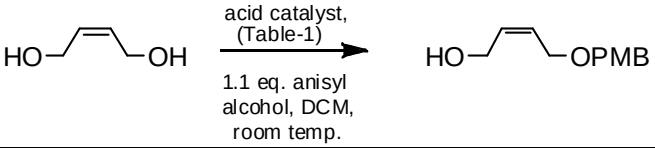


Scheme 14. Proposed mechanism for PMB protection.

The different acid catalysts were screened for the PMB protection of *cis*-2-butene-1,4- diol in a constant time period of 4 hours in DCM at room temperature. The PMB protection of *cis*-2-butene-1,4-diol was carried out using Bronsted acids like HCl,

Table 1. Optimisation for mono-PMB protection of *cis*-2-butene-1,4-diol using different acid catalysts.

.



Entry[a]	Acid (catalytic)	Time (h)	Yield[b] %
1	Conc. HCl	4	79
2	Conc. H_2SO_4	4	55[c]
3	$HClO_4$	4	51[c]
4	PTSA	4	80
5	$BF_3.OEt_2$	4	70
6	Amberlyst-15	4	85

[a] All reactions were carried out in DCM at room temperature using 10% w/v or w/w acid catalyst . [b] Isolated yields. Unreacted alcohol was fully recovered. [c] Formation of 4-methoxy benzyl ether was observed.

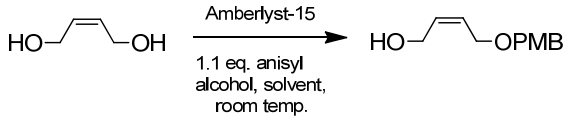
H_2SO_4, $HClO_4$ and PTSA in DCM as the solvent which gave good to excellent yields of PMB protected alcohol (Table 1).

Since the employed conditions were very harsh, other milder conditions involving Lewis acid *viz.* $BF_3.OEt_2$ and acidic resin *viz.* Amberlyst-15 were explored. It was

observed that the acidic resin Amberlyst-15 (entry 6) proved to be an excellent choice of all the acids tried. However, further reduction of time period from 4 hours to 3 hours for completion of the reaction was observed under reflux conditions. The optimized conditions for selective PMB protection of *cis*-2-butene-1,4-diol involved the use of 1.1 eq. of anisyl alcohol and catalytic amounts of resin (10% w/w) under reflux conditions in DCM as a solvent. One of the main advantages of this method is simplicity of the work-up which involves just filtration of reaction mixture to provide products with fairly good purity.

In this study, *cis*-2-butene-1,4-diol was reacted with *p*-anisyl alcohol in the presence of Amberlyst-15 in toluene at room temperature for 4.5 hours when a mono-PMB-

Table 2. PMB protection of *cis*-2-butene-1,4-diol in the presence of Amberlyst-15 under various conditions



Entry[a]	Solvent	Time (hours)	Yield (%)[b]
1	Toluene	4.5	63
2	DCM	4	85
3	THF	5	78
4	CH_3CN	6	67
5	DMF	14	52
6	Acetone	8	56

[a] All reactions were carried out using alcohol (1 eq), anisyl alcohol (1.1 eq) and 10% w/w of Amberlyst-15 catalyst at room temperature. [b] Isolated yields. Unreacted alcohol was fully recovered

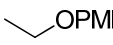
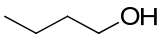
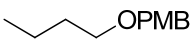
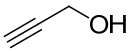
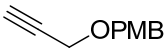
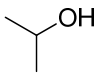
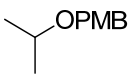
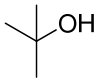
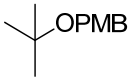
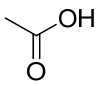
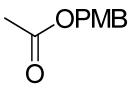
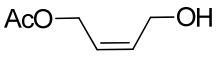
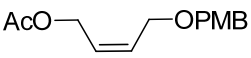
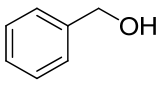
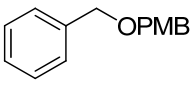
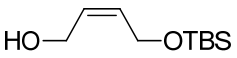
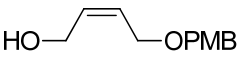
-protected product was obtained in a 63% yield (Table 2). In order to study the role of solvent on the outcome of this reaction the protection of alcohols in solvents of varying polarity was performed, whose results are summarized in table 2.

Reaction in dichloromethane (DCM) was completed in 4 hours with 85% yield and proved to be the best solvent for protection. Reaction in tetrahydrofuran (THF) took 5

hours for the completion with 78% yield. However use of the polar solvents like acetonitrile (ACN), dimethyl formamide (DMF) and acetone took longer times for the completion of reaction and were found to be less effective.

A wide variety of alcohols were subjected to PMB protection using anisyl alcohol (1.1 eq.), resin as a catalyst (10% w/w) and DCM as a solvent under reflux conditions to furnish the corresponding PMB protected alcohols in excellent yields (Table 3). The primary and secondary alcohols gave excellent yield of protection (entry 1-5) in a short period of time whereas *tert*-alcohol (entry 6) gave moderate yield. However, acetic acid (entry 7) did not show any product formation under standard protection conditions. The (*Z*)-4-hydroxybut-2-en-1-yl acetate, containing base sensitive acetate group, gave excellent yield of the corresponding ether (entry 8). In case of mono-TBS protected *cis*-2-butene-1,4-diol as a starting material, PMB protection was observed, with simultaneous deprotection of TBS group (entry 10).

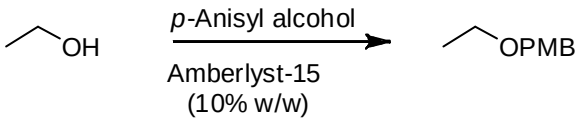
Table 3. PMB protection of alcohols

Entry[a]	Alcohol	product	time (h)	yield %	Ref. No
1			2.5	Quantitative	19
2			2	96	13
3			2.5	95	20
4			1.5	96	16
5			3	90	
6			3	73	19
7				No product formation	-
8			5	92	-
9			1.5	88	19
10			3.5	68	21

[a] Alcohol as a starting material (1 eq), anisyl alcohol (1.1 eq) and Amberlyst-15 10% w/w in DCM under reflux conditions.

In order to establish the reusability and recyclability of the resin, the used resin in reaction was recovered and reused. It was found that the resin can be used up to 3 cycles without any appreciable loss in activity (Table 4).

Table 4. Recycling of the catalyst

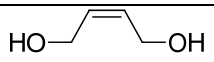
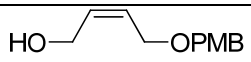
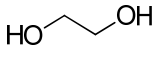
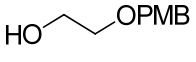
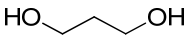
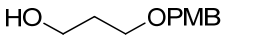
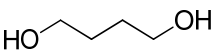
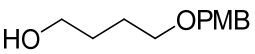
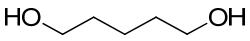
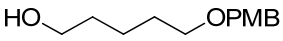
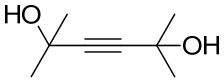
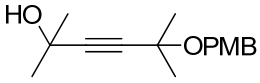
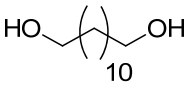
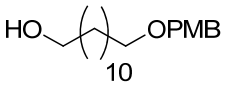
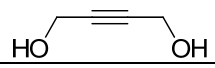
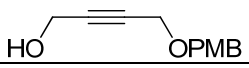


Use of resin[a]	Time (h)	Yield %
1st run	2	96
2nd run	2.5	92
3rd run	3	87

[a] Reactions were carried out in refluxing DCM. Amberlyst-15 was recovered by filtration from first reaction and used for 2nd run, again recovered and used for 3rd run.

Having established the generality and efficiency of this catalytic protocol for protection of alcohols, the attention was turned to selective protection of diols.

Table 5. Selective mono-PMB protection of diols.

Entry[a]	Diol	Product	Time (h)	Yield[b] %	Ref. No
1			3	85	20
2			3.5	78	22
3			4	75	23
4			4.5	83	24
5			4	79	22
6			4	63	-
7			2.5	70	25
8			3.5	65	26

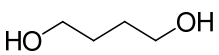
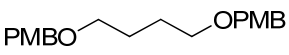
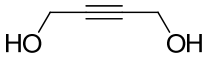
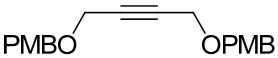
[a] Corresponding diol as a starting material (1 eq), anisyl alcohol (1.1 eq) and Amberlyst-15 (10% w/w) in DCM under reflux conditions. [b] Isolated yields.

Gratifyingly, the selective mono-PMB protection of diols was also achieved in good yields (Table 5). A variety of diols on treatment with 1.1 eq. anisyl alcohol in presence of resin (10% w/w) in DCM as a solvent under reflux conditions provided excellent yields of mono-PMB protected diols.

The saturated diols (Table 5, entry 2-5) furnished mono protected PMB ether in good yields. The diol with tertiary hydroxyl groups (entry 6) was also protected successfully in fairly good yield. The di-protected compound was observed in minor amount (18%) in case of but-2-yne-1,4-diol (entry 8).

Having established conditions for selective protection of diols, the bis-protection of diols was undertaken. The di-PMB protection of diols was carried out in good yields (Table 6) wherein the same method of protection as in mono-PMB protection was employed except, 2.2 equivalents of anisyl alcohol was used.

Table 6. Di-PMB protection of diols

Entry[a]	Diol	Product	Time (h)	Yield	Ref. No
1			8	75	27
2[b]			9.5	70	-
3			7	92	-

[a] The corresponding diol was used as a starting material. All reactions were carried out using DCM as a solvent under reflux condtion. [b] 3 eq. of anisyl alcohol used.

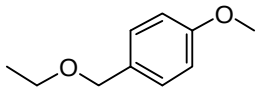
The *cis*-2-butene-1,4-diol on treatment with anisyl alcohol (2.2 eq.) in DCM using catalytic amount of resin (10% w/w) provided 75 % of di-PMB protected compound (entry 1). Similarly, butane diol and but-2-yne-1,4-diol gave very good yields (entry 2 & 3) of corresponding di-protected compounds.

In conclusion, a very simple, mild, useful and efficient method for PMB protection of alcohols under heterogeneous conditions in excellent yields has been developed. The ease of performing the reactions under heterogeneous conditions makes the work-up operationally extremely simple involving mere filtration to get the corresponding ether.

The present method should find widespread usage amongst organic chemists. The unprecedented method for mono-PMB protection of diols in very high yields and simplicity has been developed. Di-PMB protection of diols has been carried out in good yields.

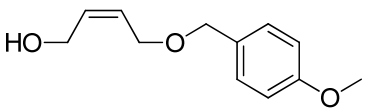
3.3.4 Experimental:

General procedure for PMB protection of alcohols: 1-(Ethoxymethyl)-4-methoxybenzene (Table 3, entry 2):



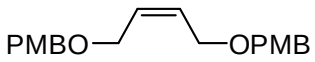
A mixture of ethanol (200 mg, 4.3 mmol), *p*-anisyl alcohol (660 mg, 4.8 mmol) and catalytic amount (10% w/w, 20 mg) of Amberlyst- 15 resin in anhydrous CH_2Cl_2 (10 mL) was refluxed. After 2 h, the crude reaction mixture was filtered through a Whatman filter paper and the residue washed with CH_2Cl_2, dried (over anhydrous Na_2SO_4), filtered and concentrated *in vacuo* and purified using flash chromatography over silica gel (pet ether : ethyl acetate 95:5) to provide 690 mg (96%) of pure product as a colorless liquid. **^{1}H NMR (200 MHz, $CDCl_3$+CCl_4):** δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.50 (q, *J* = 6.9 Hz, 2H), 1.23 (t, *J* = 6.9 Hz, 3H**). ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4):** δ 158.9, 130.4, 128.9, 113.5, 72.1, 65.1, 54.8, 15.0. **ESIMS** (m/z): 166 $(M+H)^+$, 189 $(M+Na)^+$.

General procedure for selective mono PMB protection of diols: (*Z*)-4-((4-Methoxybenzyl)oxy)but-2-en-1-ol (Table 5, entry 1):



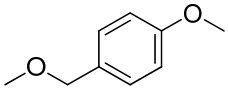
A mixture of *cis*-2-butene-1,4-diol (200 mg, 2.3 mmol), *p*-anisyl alcohol (345 mg, 2.5 mmol) and catalytic amount (10% w/w, 20 mg) of Amberlyst-15 resin in anhydrous CH_2Cl_2 (10 mL) was refluxed. After 3 h, the crude reaction mixture was filtered through a Whatman filter paper and the residue washed with CH_2Cl_2, dried (over anhydrous Na_2SO_4), filtered and concentrated *in vacuo* and purified using flash chromatography over silica gel (pet ether : ethyl acetate 70:30) to provide 401 mg (85 %) of pure product as a colorless dense liquid. **^{1}H NMR (200 MHz, $CDCl_3$+CCl_4)** δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.85-5.66 (m, 1H), 4.45 (s, 2H), 4.16 (d, *J* = 6.1 Hz, 2H), 4.06 (d, *J* = 6 Hz, 2H), 3.80 (s, 3H), 1.80 (br s, 1H). **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4):** δ 159.2, 132.4, 129.8, 129.4, 128.0, 113.8, 72.0, 65.2, 58.4, 55.1. **ESIMS (m/z):** 231 $(M+Na)^+$.

General procedure for di-PMB protection of diols: (*Z*)-1,4-Bis((4-methoxybenzyl)oxy)but-2-ene (Table 6, entry 1):



A mixture of *cis*-2-butene-1,4-diol (500 mg, 5.7 mmol), *p*-anisyl alcohol (1.73 g, 12.5 mmol) and catalytic amount (10% w/w, 50 mg) of Amberlyst-15 resin in anhydrous CH_2Cl_2 (20 mL) was refluxed. After 8 h, the crude reaction mixture was filtered through a Whatman filter paper and the residue washed with CH_2Cl_2, dried (over anhydrous Na_2SO_4), filtered and concentrated *in vacuo* and purified using flash chromatography over silica gel (pet ether : ethyl acetate 90:10) to provide 1.4 g (75 %) of pure product as a colorless dense liquid. **^{1}H NMR (200 MHz, $CDCl_3$+CCl_4):** δ 7.28 (d, *J* = 8.7 Hz, 4H), 6.90 (d, *J* = 8.7 Hz, 4H), 5.82-5.78 (m, 2H), 4.46 (s, 4H), 4.07-4.05 (m, 4H), 3.85 (s, 6H). **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4):** δ 159.1, 130.1, 129.4, 129.2, 113.6, 71.7, 65.3, 54.6. **ESIMS (m/z):** 351 $(M+Na)^+$

Data for 1-methoxy-4-(methoxymethyl)benzene.

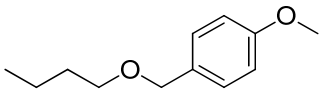


^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.39 (s, 2H), 3.81 (s, 3H), 3.35 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 159.1, 130.1, 129.2, 113.6, 74.2, 57.6, 55.0.

ESIMS (m/z): 153 $(M+H)^+$, 175 (M+Na)+.

Data for 1-(butoxymethyl)-4-methoxybenzene.

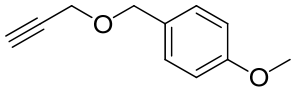


^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.47 (s, 2H), 3.85 (s, 3H), 3.48 (t, *J* = 6.3 Hz, 2H), 1.67-1.57 (m, 2H), 1.49-1.35 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 158.9, 130.6, 128.9, 113.5, 72.3, 69.7, 54.9, 31.8, 19.3, 13.9.

ESIMS (m/z): 217$(M+Na)^+$.

Data for 1-methoxy-4-((prop-2-yn-1-yloxy)methyl)benzene.

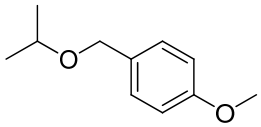


^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.29 (d, *J* = 8.1 Hz, 2H), 6.88 (d, *J* = 8.1 Hz, 2H), 4.56 (s, 2H), 4.15 (d, *J* = 2.4 Hz, 2H), 3.83 (s, 3H), 2.45 (t, *J* = 2.4 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 159.3, 129.6, 129.1, 113.7, 79.7, 74.5, 70.8, 56.4, 54.9.

ESIMS (m/z): 199 $(M+Na)^+$.

Data for 1-isopropoxy-4-methoxybenzene

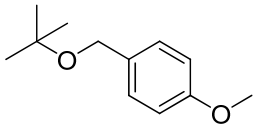


^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.43 (s, 2H), 3.79 (s, 3H), 3.68-3.62 (m, 1H), 1.20 (d, *J* = 7.2 Hz, 6H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 158.9, 131.1, 129.6, 128.9, 113.6, 70.4, 69.5, 55.0, 22.1.

ESIMS (m/z): 203 $(M+Na)^+$.

Data for 1-(*tert*-butoxy)-4-methoxybenzene

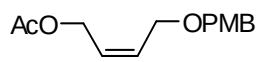


^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.37 (s, 2H), 3.80 (s, 3H), 1.29 (s, 9H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 158.8, 129.7, 128.8, 113.7, 73.2, 63.7, 55.1, 27.8.

ESIMS (m/z): 217$(M+Na)^+$.

Data for (*Z*)-4-((4-methoxybenzyl)oxy)but-2-en-1-yl acetate.



^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.86-5.61 (m, 1H), 4.61 (d, *J* = 6.3 Hz, 2H), 4.43 (s, 2H), 4.00 (d, *J* = 5.7 Hz, 2H), 3.80 (s, 3H), 2.06 (s, 3H).

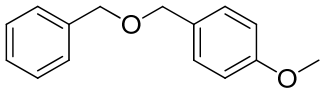
^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 170.3, 159.1, 130.8, 130.1, 129.6, 126.3, 113.6,

71.9, 65.1, 60.1, 54.9, 20.7.

ESIMS (m/z): 273 $(M+Na)^+$.

HR-MS calcd for $C_{14}H_{18}O_4Na$ (M^+ + Na): 273.1103; Found: 273.10973

Dat for 1-((benzyloxy)methyl)-4-methoxybenzene

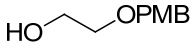


^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.34-7.25 (m, 7H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.52 (s, 2H), 4.48 (s, 2H), 3.80 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 159.1, 138.3, 130.2, 129.6, 129.3, 128.3, 127.7, 127.5, 113.7, 71.7, 71.6, 55.1.

ESIMS (m/z): 251$(M+Na)^+$.

Data for 2-((4-methoxybenzyl)oxy)ethanol

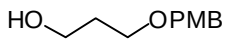


^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.48 (s, 2H), 3.80 (s, 3H), 3.74-3.70 (m, 2H), 3.57-3.53 (m, 2H), 2.13 (bs, 1H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 159.1, 129.9, 129.3, 113.6, 72.7, 71.1, 61.5, 55.0.

ESIMS (m/z): 205 $(M+Na)^+$, 221 $(M+K)^+$.

Data for 3-((4-methoxybenzyl)oxy)propan-1-ol

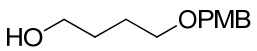


^{1}H NMR (200 MHz, CDCl3+CCl_4): δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.44 (s, 2H), 3.80 (s, 3H), 3.75 (t, *J* = 5.7 Hz, 2H), 3.62 (t, *J* = 5.7 Hz, 2H), 2.21 (bs, 1H), 1.84 (p, *J* = 5.7 Hz, 2H).

^{13}C NMR (50 MHz, CDCl3+CCl_4): δ 159.1, 130.0, 129.2, 113.7, 72.7, 68.5, 61.2, 55.1, 32.0.

ESIMS (m/z): 219 $(M+Na)^+$.

Data for 4-((4-methoxybenzyl)oxy)butan-1-ol

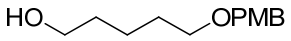


^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.43 (s, 2H), 3.79 (s, 3H), 3.59 (t, *J* = 6 Hz, 2H), 3.47 (t, *J* = 6 Hz, 2H), 2.54 (bs, 1H), 1.71-1.60 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 159.2, 130.1, 129.4, 113.8, 72.8, 70.0, 62.6, 55.1, 30.3, 26.9.

ESIMS (m/z): 233 $(M+Na)^+$, 249$(M+K)^+$.

Data for 5-((4-methoxybenzyl)oxy)pentan-1-ol

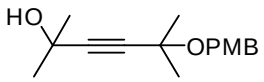


^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.42 (s, 2H), 3.80 (s, 3H), 3.62 (t, *J* = 6.2 Hz, 2H), 3.44 (t, *J* = 6.2 Hz, 2H), 1.67-1.43 (m, 6H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 159.1, 130.5, 129.2, 113.7, 72.5, 69.9, 62.4, 55.1, 32.4, 29.4, 22.4.

ESIMS (m/z): 225 $(M+1)^+$, 247 $(M+Na)^+$.

Data for 5-((4-methoxybenzyl)oxy)-2,5-dimethylhex-3-yn-2-ol



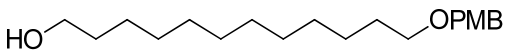
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 4.54 (s, 2H), 3.80 (s, 3H), 1.24 (s, 6H), 1.52 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 158.9, 131.1, 129.8, 129.2, 128.5, 113.7, 88.9, 84.1, 70.3, 66.0, 65.0, 55.2, 31.5, 28.9.

ESIMS (m/z): 285 $(M+Na)^+$.

HR-MS calcd for $C_{16}H_{22}O_3Na$ (M^+ + Na): 285.1467. Found: 285.1461

Data for 12-((4-methoxybenzyl)oxy)dodecan-1-ol

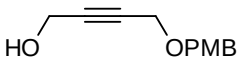


^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.41 (t, *J* = 6.4 Hz, 2H), 1.61-1.52 (m, 4H), 1.40-1.20 (bs, 16H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 159.0, 130.7, 129.1, 113.6, 72.4, 70.1, 62.8, 55.1, 32.7, 29.7, 29.6, 29.4, 26.2, 25.7.

ESIMS (m/z): 345 $(M+Na)^+$.

Data for but-2-yne-1,4-diol.

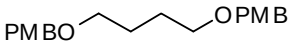


^{1}H NMR (200 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.51 (s, 2H), 4.30 (t, *J* = 1.8 Hz, 2H), 4.16 (t, *J* = 1.9 Hz, 2H), 3.80 (s, 3H), 1.93 (bs, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 159.2, 129.7, 129.0, 113.7, 85.0, 81.1, 71.1, 56.8, 55.0, 50.5.

ESIMS (m/z): 229 $(M+Na)^+$, 245$(M+K)^+$.

Data for 1,4-bis((4-methoxybenzyl)oxy)butane



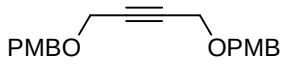
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.27 (d, *J* = 8.7 Hz, 4H), 6.89 (d, *J* = 8.7 Hz, 4H), 4.45 (s, 4H), 3.84 (s. 6H), 3.51-3.45 (m, 4H), 1.75-1.69 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 159.0, 130.6, 129.0, 113.6, 72.3, 69.6, 54.9, 26.4.

ESIMS (m/z): 353 $(M+Na)^+$.

HR-MS calcd for $C_{20}H_{26}O_4Na$ (M^+ + Na): 353.1729. Found: 353.1723

Data for di-PMB protection of but-2-yne-1,4-diol



^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.26 (d, *J* = 8.7 Hz, 4H), 6.86 (d, *J* = 8.7 Hz, 4H), 4.54 (s, 4H), 4.19 (s, 4H), 3.80 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 159.4, 129.7, 129.4, 113.8, 82.5, 71.2, 57.0, 55.2.

ESIMS (m/z): 349 $(M+Na)^+$.

HR-MS calcd for $C_{20}H_{22}O_4Na$ (M^+ + Na): 349.1416. Found: 349.1410.

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