Synthetic Studies Towards (-)-Venlafaxine, (+)-Deoxoprosophylline, 3-Hydroxy pipecolic acid, 1-Deoxynojirimycin, α-Lipoic acid and Development of Synthetic Methodology

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BY

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CERTIFICATE

This is to certify that the work presented in the thesis entitled **"Synthetic Studies Towards (-)-Venlafaxine, (+)-Deoxoprosophylline, 3-Hydroxy pipecolic acid, 1-Deoxynojirimycin, *α*-Lipoic acid and Development of Synthetic Methodology"** submitted by **Mr. Kailash P. Pawar** was carried out by the candidate at National Chemical Laboratory, Pune under my supervision. Such materials as obtained from other sources have been duly acknowledged in the thesis.

(Dr. Subhash P. Chavan)
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CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled **"Synthetic Studies Towards (-)-Venlafaxine, (+)-Deoxoprosophylline, 3-Hydroxy pipecolic acid, 1-Deoxynojirimycin, α-Lipoic acid and Development of Synthetic Methodology"** submitted for the degree of Doctor of Philosophy in Chemistry to the Savitribai Phule Pune University has not been submitted by me to any other university or Institution. This work was carried out at National Chemical Laboratory, Pune, India.

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Senior Research Fellow
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Dedicated to

My Parents and beloved wife

Vaishali

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Kailash P. Pawar

NCL, Pune

Contents

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/ninhydrine/PMA solutions.
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. Tetramethylsilane/residual $CHCl_3$ 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%).

Abbreviations

Ac	Acetyl
ACCN	1,10-Azobis(cyclohexanecarbonitrile)
acac	acetylacetonates
AIBN	2,2-Azobis(*iso*-butyronitrile)
Ar	Aryl
Aq.	Aqueous
9-BBN	9-Borabicyclo[3.3.1]nonane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BIPHEPHOS	6,6′-[(3,3′-Di-*tert*-butyl-5,5′-dimethoxy-1,1′-biphenyl-2,2′-diyl)bis(oxy)]bis(dibenzo[*d,f*][1,3,2]dioxaphosphepin)
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
CSA	Camphorsulfonic acid
m-CPBA	*meta*-Chloroperbenzoic acid
CSA	Camphor sulfonic acid
DBAD	Di-*tert*-butyl azodicarboxylate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DEPT	Distortionless Enhancement by Polarization Transfer
DET	Diethyl tartrate
$(DHQ)_2PHAL$	Hydroquinine 1,4-phthalazinediyl diether
$(DHQD)_2PHAL$	Hydroquinidine 1,4-phthalazinediyl diether
DIPT	Diisopropyl tartrate
DIAD	Diisopropylazodicarboxylate

DIBAL	Diisobutylaluminium hydride
DIPEA	Diisopropylehtyl amine
DIPT	Diisopropyltartrate
DMAP	4-Dimethylamino pyridine
DMP	2,2-Dimethoxypropane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMS	Dimethy sulfide
DMSO	Dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
Et	Ethyl
g	gram(s)
h	hour(s)
IBX	2-Iodoxybenzoic acid
IPA	*iso*-Propyl alcohol
Im	Imidazole
IR	Infra red
HMPA	Hexamethylphosphoramide
HPLC	High-performance liquid chromatography
Hz	Hertz
KHMDS	Potassium hexamethyl disilazide
LAH	Lithium aluminium hydride
LDA	Lithium diisopropyl amide
LHMDS	Lithium hexamethyl disilazide
Me	Methyl
min	minute(s)
mL	millilitres
mmol	millimole
MOM	Methoxymethyl
MP	Melting point
Ms	Methanesulfonyl
MW	Molecular weight

NaHMDS	Sodium hexamethyl disilazide
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
PMA	Phosphomolybdic acid
PMB	*para*-Methoxybenzyl
PTC	Phase transfer catalysis
PPTS	Pyridinium *para*-toluene sulfonate
PTSA	*para*-Toluene sulfonic acid
Py	Pyridine
rt	Room temperature
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TBSOTf	*tert*-Butyldimethylsilyl trifluoromethanesulfonate
TBTH	Tributyltinhydride
TEA	Triethylamine
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy, free radical, 2,2,6,6-Tetramethylpiperidine 1-oxyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydofuran
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	Toluenesulfonyl

Abstract

The thesis entitled, **"Synthetic Studies Towards (-)-Venlafaxine, (+)-Deoxoprosophylline, 3-Hydroxy pipecolic acid, 1-Deoxynojirimycin, α-Lipoic acid and Development of Synthetic Methodology"** is divided into three chapters.

Chapter one deals with the introduction and synthesis of (-)-Venlafaxine and 3-Hydroxy pipecolic acid. The second chapter deals with the introduction and synthesis of (+)-Deoxoprosophylline and deoxynojirimycin. The synthetic studies towards α-Lipoic acid and a methodology for PMB protection of alcohols described in third chapter.

Chapter 1. Synthetic studies towards (-)-venlafaxine and (2*R*,3*S*)-3-hydroxypipecolic acid

Section 1: Introduction of (-)-venlafaxine.

The present section includes the details about biological action and comprehensive literature on synthesis of (-)-venlafaxine. It is a potent antidepressant[1] and selective serotonin norepinephrine reuptake inhibitor. (Figure 1).

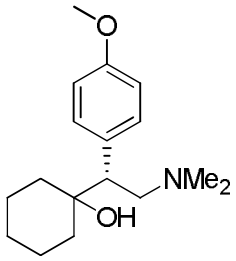
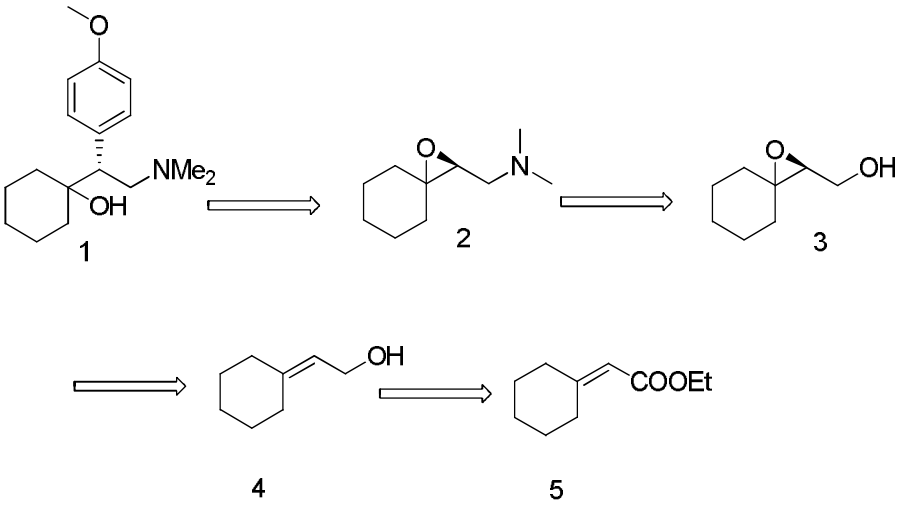


Figure 1. Structure of (-)-venlafaxine **1**.

Section 2: A protecting group free and scalable approach towards total synthesis of (-)-venlafaxine

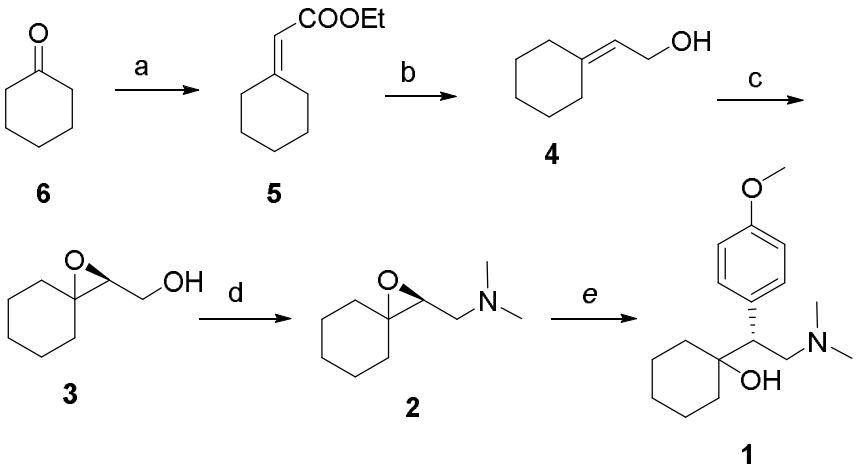
The retrosynthetic disconnections for (-)-venlafaxine is outlined in Scheme-1. The synthesis commenced with the commercially available cyclohexanone. Wittig reaction with cyclohexanone followed by chemoselective ester reduction was carried out. The synthesis of (-)-venlafaxine **1** began from commercially available, inexpensive cyclohexanone **6**. Accordingly, carbonyl of cyclohexanone **6** was homologated with two carbons to convert it in to *α, β*-unsaturated ester **5** in 98% yield. This ester was subjected for the selective ester reduction. The reduction of unsaturated ester to allyl alcohol **4** was carried out by treatment with Red-Al

(commercially known as vitride) in 97% yield. The crude allyl alcohol **4** obtained as very pure, was directly subjected for Sharpless asymmetric epoxidation



Scheme 1. Retrosynthesis

reaction at -50 ^{o}C. The asymmetric epoxidation gave 83% yield of epoxide and 85% ee, determined by chiral GC.The epoxide **3** obtained was treated with methanesulphonyl chloride and triethyl amine at 0 ^{o}C for 15 min to obtain crude mesylate, which was subsequently subjected for amination in 40% aqueous dimethyl amine solution for 10 h at room temperature. The epoxy amine 2 was obtained in 95% yield over two steps and was subjected to nucleophilic epoxide opening. This

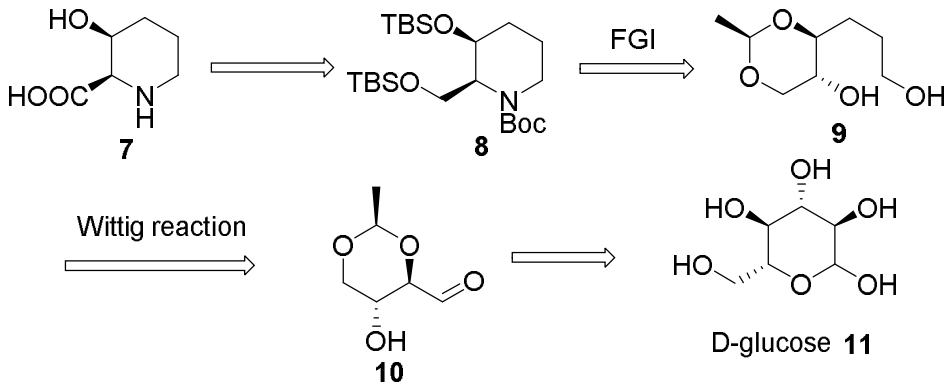


Scheme 2. *Reagents and conditions:* a) $Ph_3PCHCOOEt$, 24 h, Toluene, reflux, 98%; b) Red-Al, 30 min, Toluene, 97%; c) (+) DET, $Ti(OiPr)_4$, MS 4 Å, *t*-BuOOH, DCM, 6 h, -50 ^{o}C, 83%, d) i) MsCl, Et_3N, DCM, 15 min, ii) Dimethylamine 40% aq. solution, 10 h, 95%, *p*-methoxyphenylmagnesium bromide, CuI, THF, -40 ^{o}C, 8 h, 71%.

conversion was carried out by treatment with *p*-methoxyphenylmagnesium bromide in the presence of catalytic copper iodide at -40 ^{o}C for 8 h to afford (-)-venlafaxine **1** in 71% yield with ≥99% *ee* after recrystallization in ethyl acetate. Spectral data and optical rotation for (-)-venlafaxine 1 were in good agreement with the data reported in literature.

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

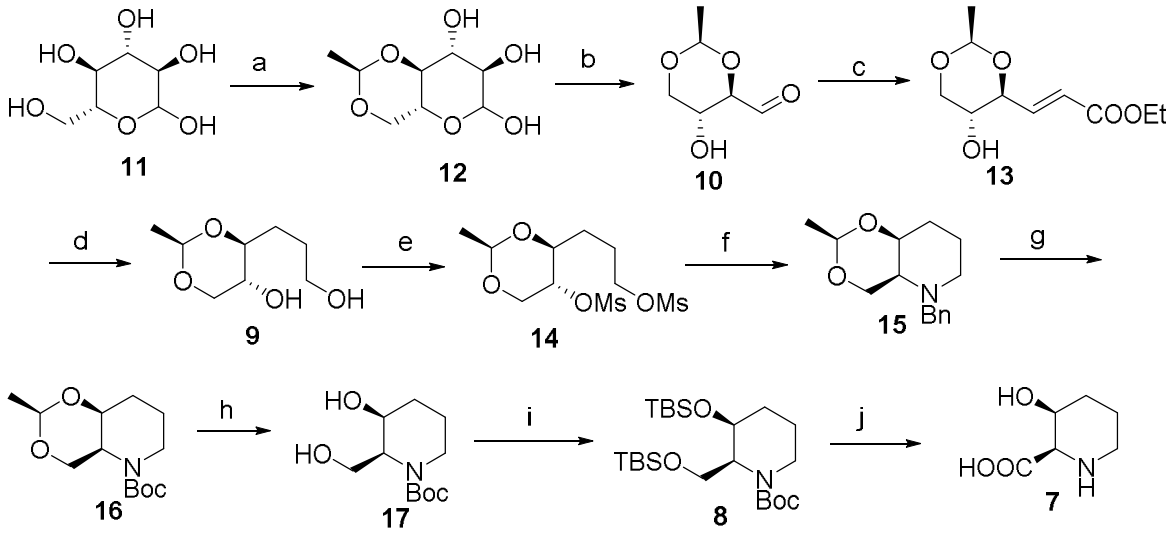
This section describes the biological activity and reported synthetic routes to (2*R*,3*S*)-3-hydroxy pipecolic acid. (2*R*,3*S*)-3-Hydroxy pipecolic acid



Scheme 3. Retrosynthetic analysis.

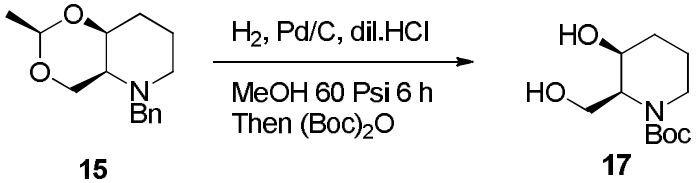
Thus, as shown in the retrosynthetic analysis, our synthesis 3-hydroxy pipecolic acid **7** began with mono acetal protection of glucose **11** to obtain (1'*R*)-(−)-4,6-O-Ethylidene-D-glucose **12** in 65% yield after recrystalization from ethanol. The acetal protected D-glucose was used as such without characterization for further reaction. The compound was subjected for cleavage with $NaIO_4$ to afford (−)-2,4-O-Ethylidene-D-erythrose **10** in almost quantitative yield.[8] This was subsequently subjected for the two-carbon Wittig homologation with $Ph_3PCHCOOEt$ by stirring in DCM which afforded *α,β*-unsaturated hydroxy ester **13** in 7:3 *trans*/*cis* ratio in good yield. The major unsaturated ester **13** was reduced by treatment with LiCl and $NaBH_4$ in THF:Water (1:1) at ambient temperature provided 1,5diol **9** along with traces of allyl alcohol. The Allyl alcohol formed during reduction was hydrogenated with Pd/C in methanol in hydrogen atmosphere which gave the saturated compound 1,5 diol **9** in 97% yield. This 1,5 diol compound was subjected for mesylation by treating it with methanesulphonyl chloride and triethyl amine in DCM at 0 ^{o}C for 0.5 h to obtain

dimesylate compound. This mesylate derivative **14** was used for further cycloamination without purification. Cyclization was carried out by heating dimesylate compound in neat benzyl amine at 90 ^{o}C for 2 h to afford cyclized product **15** in 90% yield. This cyclized benzylated



Scheme 4. *Reagents and conditions:* a) Paraldehyde, Cat.H_2SO_4, 3 days, rt, 65%; b) $NaIO_4$, Water, 3 h, 97%; c) $Ph_3PCHCOOEt$, DCM, rt, 6 h, 87%, d) $NaBH_4$, LiCl, THF:Water (1:1), 12 h, 96%; e) MsCl, TEA, DCM, 0 ^{o}C, 30 min; f) $BnNH_2$, Heat, 2 h, 90%; g) H_2, Pd/C, Boc_2O, MeOH, 60 Psi, 6 h; h) *p*-TSA, MeOH, 3 h, rt, 91%; i) TBSCl, TEA, DMAP, DCM, 12 h, 86%; j) *Ref.*2

piperidine **15** was hydrogenated with Pd/C in methanol at 60 *psi* and concomitant boc protection was carried out to provide one-pot *N*-debenzylated-*N*-Boc **16**. The *N*-boc piperidine **10** was obtained in almost quantitative yield and acetal group present in **10** was deprotected with *p*-TSA in methanol and purified by recrystalization to get the intermediate **17** in quantitative yield. The diol **17** was also synthesized from benzylated piperidine under hydrogenation under acidic environment followed by Boc protection directly.



Also we obtained this intermediate in one pot form *N*-benzylated compound by carrying hydrogenation reaction in presence of dil.HCl followed by addition of boc anhydride addition to get this inter medate **17** in good yields.

The compound **17** was treated with TBSCl in the presence of triethylamine as the base to transform it into Di-TBS compound **8.** From this compound **8** synthesis of **7** is wel documented.[5c]

Chapter 2. Synthetic studies towards (+)-doxoprosophylline and 1-deoxynojirimycin.

Section 1: Introduction of (+)-doxoprosophylline

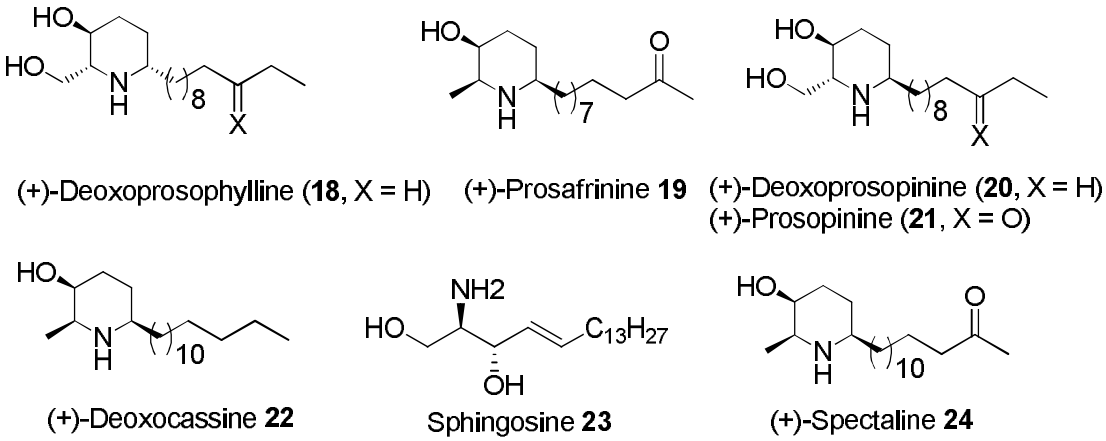


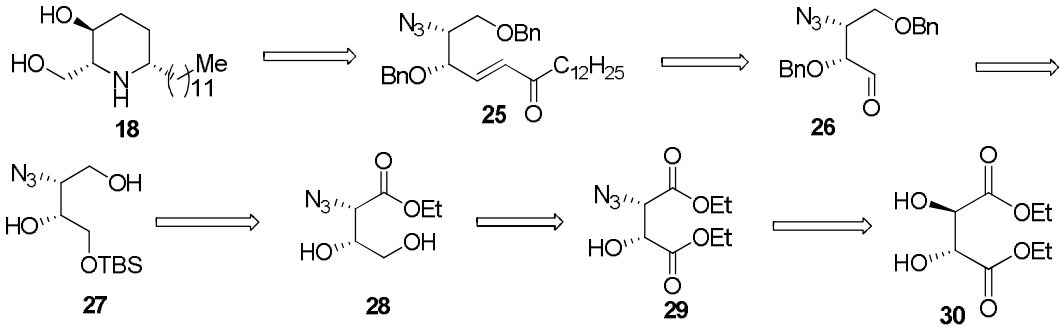
Figure 2. Prosopis alkaloids and analogues**.**

The deoxoprosophylline **17** has been isolated from the African mimosa *Prosopis African taub*[3] found in Africa. 2,6 Disubstituted piperidine-3-ols isolated from genera *Prosopis* and *Cassia* are called Prosopis alkaloids and Cassia alkaloids respectively. Prosopis alkaloid family includes members like (+)-deoxoprosophylline **18**, prosopinine **21**, deoxoprosopinine **20** and related compounds; while Cassia alkaloids contain members like prosafrinine **19**, spectaline **24**, deoxocasssine **22** and related compounds (Figure 1). Although, piperidine ring is present in many alkaloids, Prosopis alkaloids and Cassia alkaloids have special structural characteristics. These contain a polar hydrophilic head group which is constituted by 2,6 disubstituted piperidine-3-ol and hydrophobic group which contains long hydrocarbon chain.

Section 2: Total synthesis of (+)-deoxoprosophylline from L-(+)-tartrate ester.

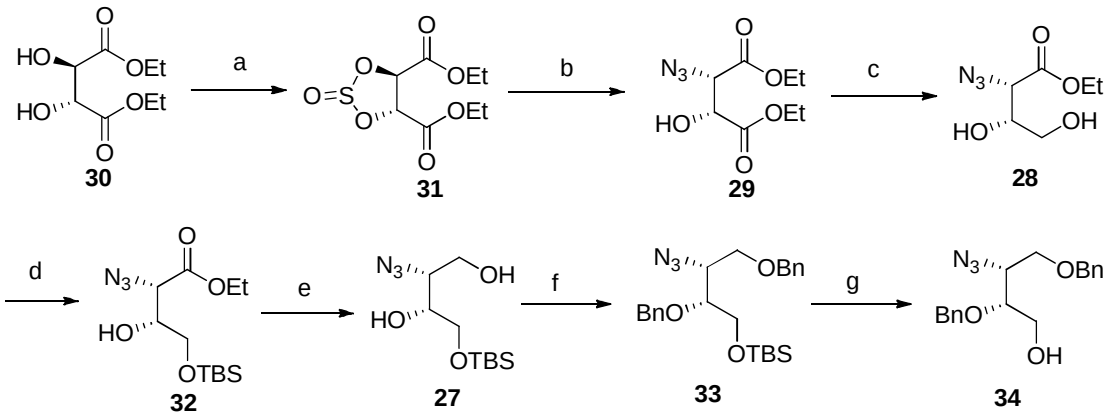
As outlined in Scheme 1, we envisaged that stereochemistry required for (+)-deoxoprosophylline **18** is hidden in tartarate ester **30** and planned our retrosynthesis

accordingly. We envisioned that (+)-deoxoprosophylline **17** can be synthesized from *α,β*-unsaturated keto compound **25** by reductive amination. This azido keto compound **25** in turn can easily be accessed from aldehyde **26** by 14-carbon Horner-Wadsworth-Emmons reaction. Aldehyde **26** could be obtained from tartarate ester **30** derived diol **28** through azido diester compound **29** by various transformations.



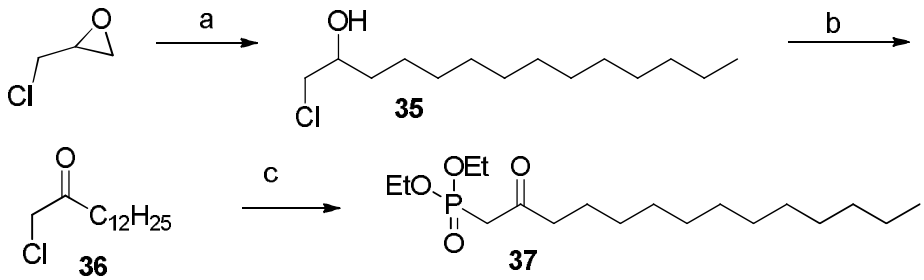
Scheme 5. Retrosynthetic analysis.

Synthesis of (+)-deoxoprosophylline **17** commenced with commercially available tartarate ester **30**, which on treatment with thionyl chloride in CCl_4 under reflux for 4 h affordedsulphite **31**. The crude sulfite **31** thus obtained was subjected to nucleophilic opening. Accordingly, sulphite opening was carried out using NaN_3 in DMF at room temperature (24 h) to obtain 74% yield of the corresponding azido



Scheme 6. *Reagents and conditions:* a) $SOCl_2$, DMF (cat.), CCl_4, reflux, 4 h; b) NaN_3, DMF, rt, 24 h, 74% over two steps; c) BH_3:DMS, $NaBH_4$ (cat.), THF, rt, 8 h, 60%; d) TBSCl, Et_3N, DCM, 2 h, 85%; e) $NaBH_4$, LiCl, THF:Water (1:1), 12 h, 83%; f) NaH, BnBr, THF, rt, 12 h, 94%; g) PTSA, MeOH, 2 h, 91%.

diester **29** over two steps. Azido diester **29** was then subjected to selective ester reduction using α-hydroxyl group of the ester as a handle to reduce it to alcohol **28**. The reduction was carried out using borane-dimethylsulfide complex (1.05 equivalent) and catalytic sodium borohydride in THF to obtain 1,2-diol **28** in 60% yield.[4] The 1,2-diol **28** was treated with TBSCl in DCM as the solvent in the presence of TEA as the base to protect primary hydroxyl group selectively in the presence of secondary hydroxyl group. MonoTBS ether **32** was obtained in 85% yield. Once this monoTBS compound **32** was in hand, we reduced the remaining ester group with LiCl/LiBr and $NaBH_4$ in THF,Water (1:1) system to obtain 1,3-diol compound **27** in 83% yield. The 1,3-diol **27** was dibenzylated using benzyl bromide and NaH (60% suspension in oil) to afford corresponding dibenzyl protected compound **33** in 94% yield. The TBS ether was deprotected using PTSA in methanol to obtain free primary alcohol **34** in 91% yield.

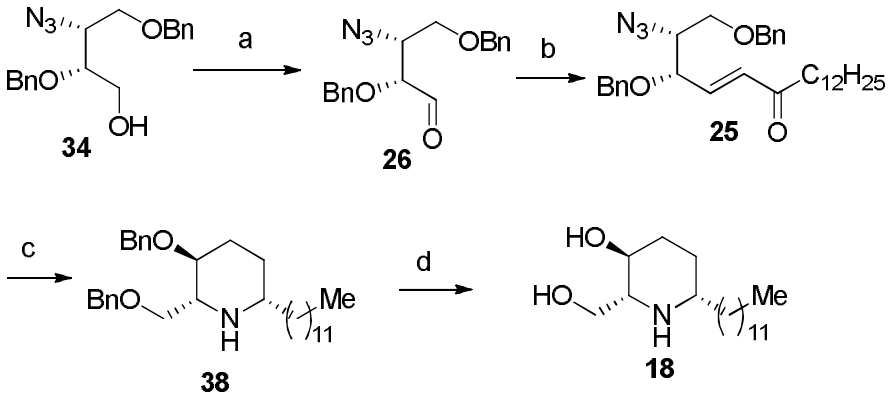


Scheme 7. *Reagents and conditions:* a) 1-Bromoundecane, Mg, CuI, THF, -30 ^{o}C, 3 h, 60%; b) DMSO, $(COCl)_2$, TEA, DCM, -78 ^{o}C, 1 h, 84%; c) $P(OEt)_3$, reflux, acetone, 12 h, 73%.

This primary hydroxyl group was oxidised to aldehyde **26** under Swern reaction condition. The aldehyde **26** thus obtained was used as such without purification for further reaction.

The α-chloroketone **36** was prepared by Swern oxidation[5] of 1-chlorotetradecan-2-ol **35** which was in turn prepared by ringopening of epichlorohydrin with undecylmagnesium bromide in THF.[6] Treatment of chloroketone to Arbuzov reaction with triethyl phosphite afforded β-keto phosphonate **37** in 73% yield.[7] The β-keto phosphonate **37** on treatment with aldehyde **26** with LiCl and Hunig's base in acetonitrile afforded α,β-unsaturated keto compound **25** in 95% yield. Exclusive formation of *trans* product **25** was observed in the process which was confirmed by

coupling constant (J = 16.2Hz). This *α,β*-unsaturated keto compound **25** thus obtained was subjected for one pot azide reduction and diastereoselective intramolecular reductive cyclization by treatment with Pd/C in methanol under hydrogenation.[12f] We expected to get completely debenzylated product along with



Scheme 8. *Reagents and condtions:* a) DMSO, $(COCl)_2$, TEA, DCM, -78 ^oC, 1 h; b) DIPEA, phosphonate **21**, LiCl, MeCN, 0 ^oC to rt, 10 h, 95%; c) H_2, Pd/C, 60 psi, MeOH; d) Na/NH_3, -78 ^oC, 1 h, (93% over two steps).

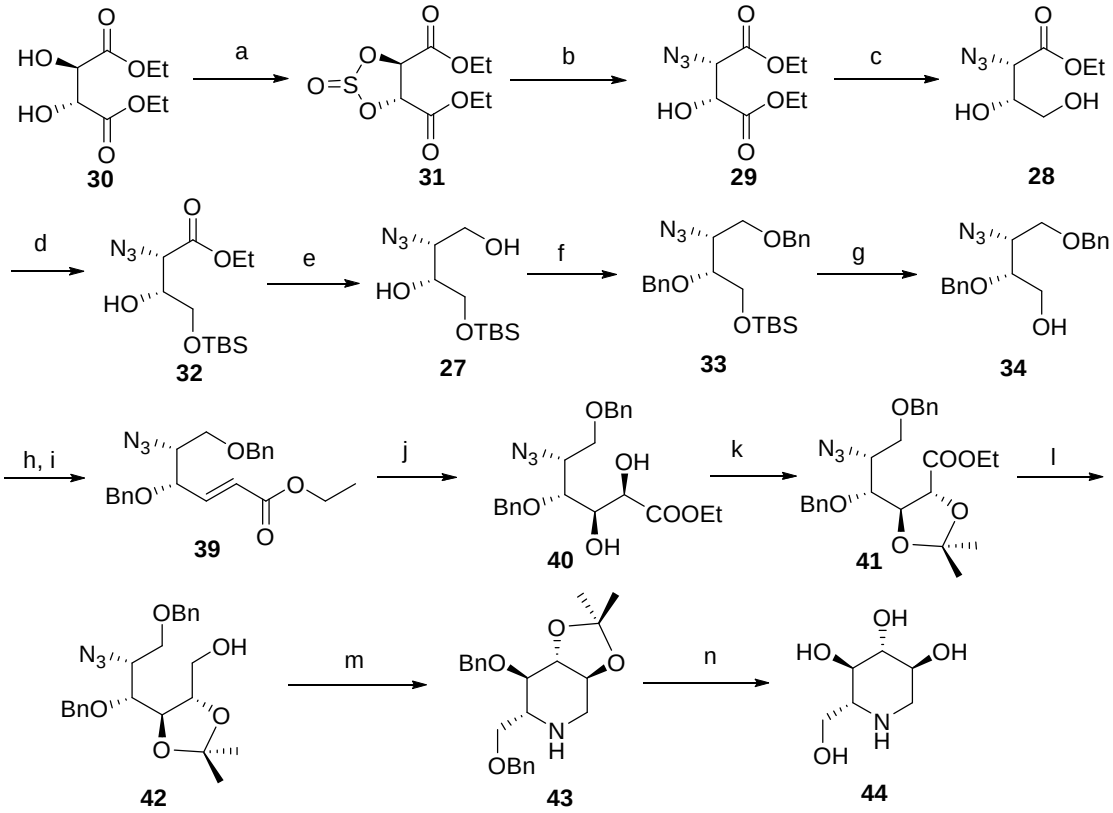
cyclization *i.e.* target compound **18**. Instead, we got a mixture of (+)-deoxoprosophylline **18** along with monobenzyl and dibenzyl cyclized compounds, which was confirmed by mass-spectroscopy. So, we subjected this mixture as such under Birch reduction condition to obtain (+)-deoxoprosophylline **18** in 93% yield. The spectral data of **18** thus obtained was in good agreement with reported data.[12f]

In conclusion, a novel, short and efficient route for synthesis of (+)-deoxoprosophylline **18** has been developed from L-(+)-diethyl tartrate as the source of chirality by two different routes.

Section 3: Formal synthesis of 1-deoxynojirimycin.

After synthesizing primary alcohol **34** it was oxidized to aldehyde, which was subsequently subjected for two carbon homologation to get *trans* isomer **39** as the major product. This *trans* ester **39** was treated with catalytic OsO_4 and stochiometric NMO to get s*yn* dihydroxy ester **40**. This ester **40** was obtanied as the single diastereomer. The free 1,2 diols in **40** were acetonide protected using 2,2-dimethoxy propane in the presence of catalytic *p*-TSA to afford **41**. Then the ester functionality in **41** was reduced to alcohol **42**.This free primary alcohol **42** was mesylated with mesyl chloride and was subsequently subjected for Staudinger reaction. After complete conversion of azide to amine monitored on TLC, the reaction mixture was

heated to obtained cyclized compound **43**. From this **43** the synthesis of deoxynojirimycin is well documented.[8]



Scheme 9. *Reagents and conditions:* a) $SOCl_2$, DMF (cat.), CCl_4, reflux, 4 h; b) NaN_3, DMF, rt, 24 h, 74% over two steps; c) BH_3:DMS, $NaBH_4$ (cat.), THF, rt, 8 h, 60%; d) TBSCl, Et_3N, DCM, 2 h, 85%; e) $NaBH_4$, LiCl, THF:Water (1:1), 12 h, 83%; f) NaH, BnBr, THF, rt, 12 h, 94%; g) *p*-TSA, MeOH, 2 h, 91%; h) DMSO, $(COCl)_2$, TEA, DCM, -78 ^oC, 1 h; i) Ph_3PCHCO_2Et, toluene, reflux, 3 h, 76%; j) OsO_4, NMO, MeCN:H_2O (9:1), 4 h, 88%; k) 2,2-DMP, cat. *p*-TSA, DCM, 18 h, 93%; l) $NaBH_4$, LiCl, THF:Water (1:1), 12 h, 97%; m) i. MsCl, TEA, DCM, 0 ^oC, 30 min, ii. PPh_3, THF:Water (1:1), reflux, 4 h, 70%; n) *Ref. 7.*

Chapter 3: Synthetic studies towards *R*-(+)-lipoic acid and development of synthetic methodology.

Section 1: Introduction of *α*-lipoic acid..

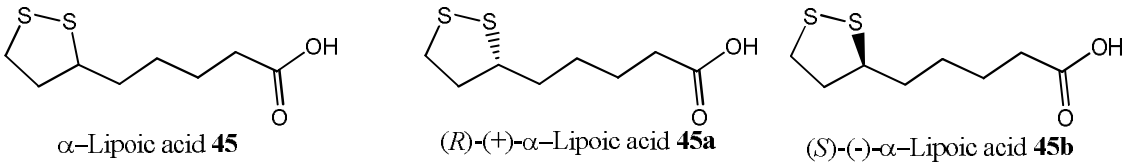
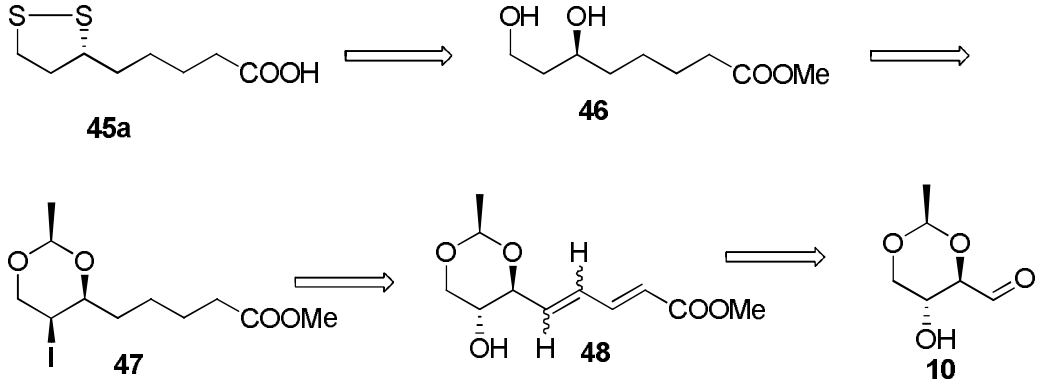


Figure3. Structures of racemic and chiral lipoic acid.

α-Lipoic acid **45** was first isolated by Reed *et al.* in 1950.[9] It is the cyclic disulfide of di-mercapto-n-caprylic acid. Both the antipodes of lipoic acid were obtained by resolution method in 1954, where it was also established that (*R*)-(+)-*α*-lipoic acid **45a** shows more bioactivity than (*S*)-(-)-*α*-lipoic acid **45b**.[10] Golding *et al.* determined the absolute configuration by synthesizing complementary enantiomer from *S*-malic acid.[11] (*R*)-(+)-*α*-Lipoic acid **45a** is vital cofactor widely distributed in many plants and animals. It shows various biological and

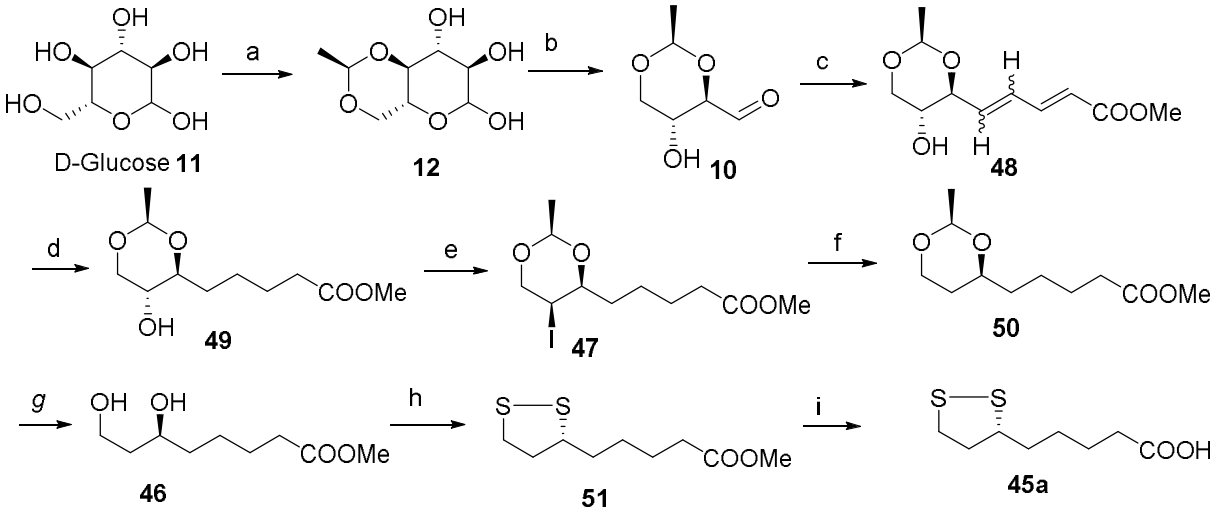
These significant biological activities of (+)-*α*-lipoic acid **45a** are of great commercial importance which has made it an attractive target



Scheme 10. Retrosynthesis of *R*-(+)-lipoic acid.

Synthesis of (+)-*α*-lipoic acid **45a** as outlined in retrosynthetic analysis (Scheme 1), began with 4-carbon Wittig reaction of hydroxy aldehyde **10** by which it was converted to unsaturated hydroxy ester **48** in 87% yield,[12] as an inseparable mixture of *cis* and *trans* isomers. Saturation of double bonds in **48** was carried out using catalytic Pd/C in methanol under hydrogen atmosphere to afford **49** 97% yield of hydroxy

ester.[13] The hydroxyl group in this compound **49** was converted to iodo derivative **47** by treatment with I_2, PPh_3 and imidazole in xylene at 80 ^oC for 3 h in 73% yield. The iodine in this iodoester **49** was removed using Raney Ni in methanol under hydrogen atmosphere to provide deiodinated ester **50** in 94% yield. The acetal group in ester **50** was subsequently deprotected with *p*-TSA in methanol to obtain 1,3-diol **46** in 90% yield.[14] The 1,3-diol **46** was mesylated using methanesulphonyl chloride, triethylamine in DCM. The dimesylate obtained was directly treated with disodium sulphide in DMF at 80 ^oC to convert it into lipoate ester **51** in 81% yield. The lipoate ester thus obtained was hydrolyzed using KOH in ethanol to afford (+)-α-lipoic acid **45a** in 77% yield. The spectral data of (*R*)-(α)-lipoic acid was in good agreement with reported one.



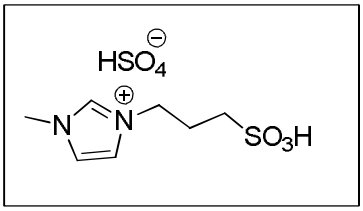
Scheme 11. *Reagents and conditions:* a) Ph_3P=CH-CH=CHCOOMe, DCM, 5 h, 87%; b) H_2, Pd/C, MeOH, 2 h, 97%; c) Ph_3P, I_2, Im, xylene, 70 ^oC, 6 h, 73%; d) TEA, H_2, Raney Ni, MeOH, 5 h 94%; e) PTSA, MeOH 90%; f) i) MsCl, TEA, DCM; ii) $Na_2S.7H_2O$, DMF, 80 ^oC, 12 h, 81% over two steps; g) KOH, EtOH, 24 h, 77%.

In conclusion, a new synthetic route for the total synthesis of (+)-α-lipoic acid **45a** from hydroxy aldehyde **10** was developed..

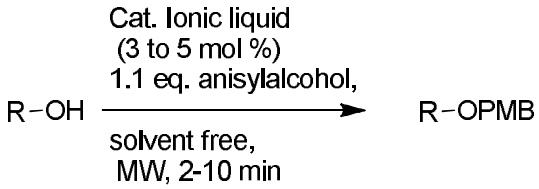
Section 3: Ionic liquid catalyzed methodology for PMB protection of alcohols and selective mono PMB protection of diols.

The present section describes an efficient, practical and catalytic methodology for PMB protection of alcohols and selective mono PMB protection of diols.

The most commonly employed method of the available methods for PMB protection[15] is the two step protocol and include the use of hazardous and expensive chemicals.[16]

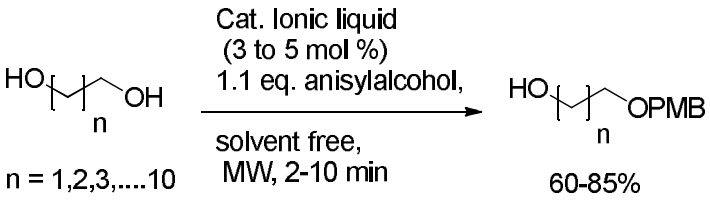


A very simple one step protocol for PMB protection of alcohols has been developed. The ionic liquid was recycled and reused; up to 4 times it gives good yield without loss in activity. Primary alcohols were successfully protected under solvent free conditions (Scheme 12).



Scheme 12. PMB protection of alcohols.

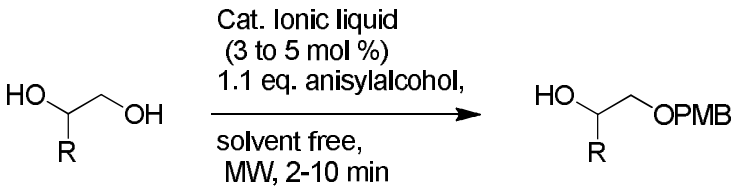
The conventional methods for mono-PMB protection of diols are associated with low yield and mono-PMB protected compounds as a common impurity. Thus a mild,



Scheme 13. Selective mono PMB protection of diols.

highly selective and simple method for mono-PMB protection of diols has been developed. The various diols furnished good yields of mono-PMB protected diols.

The mono-PMB protection of diols was also carried out successfully in yields ranging from 75-92 % (Scheme 14).



Scheme 14. Mono-PMB protection of mixed diols

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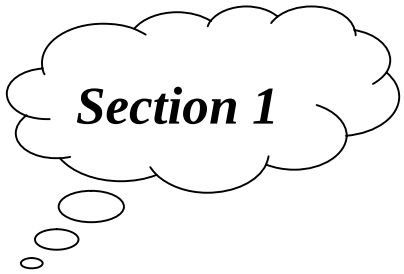
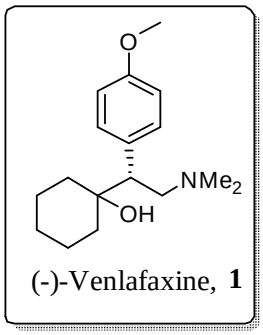
Chapter 1

Synthetic studies towards (-)-venlafaxine and (2*R*,3*S*)-3-hydroxypipecolic acid



Introduction of venlafaxine

2.1.1. Introduction



(-)-Venlafaxine, **1**

Development of a number of nontricyclic antidepressants with reduced or completely diminished cardiovascular or anticholinergic liability has been reported[1] and they have provided impetus to treat depression. Among those one of the most prescribed antidepressants is venlafaxine 1, which is a unique drug with well documented efficacy and safety in the acute treatment of major depressive disorder.[2] It was first time released for clinical trials in 1994 by Wyeth, now part of Pfizer and is globally marketed as Effexor R®. It has now become widely recognised as an effective first line agent in the treatment of major depressive disorder (MDD),[3] generalised anxiety disorders and comorbid indications in certain anxiety disorders for depression. It was a top selling drug from 2006 to 2008 and sixth most prescribed antidepressant in US in the year 2007. In 2010 it was 25th in top 200 brand name drugs by total US prescriptions.

Venlafaxine (**1**) is marketed in recemic form, although both *R* and *S* enantiomers show different bioactivities i.e. *S*-enantiomer is a selective serotonin reuptake inhibitor, while *R*-enantiomer is more selective towards the norepinephrine transporter.[3] Also, it has no or little activity on a variety of neuroreceptors.[4] Recently, generic version of venlafaxine has been approved by USFDA. It is a white to off-white crystalline solid phenylethylamine compound, which exhibits a unique pharmacological profile with antidepression properties. Venlafaxine is structurally and pharmacologically related to the atypical opioid analgesic tramadol, and more distantly to the newly released opioid tapentadol, but not to any of the conventional antidepressant drugs. (–)-Venlafaxine (**1**) is a more potent inhibitor of norepinephrine synaptosomal uptake while (+)-venlafaxine is more selective in serotonin uptake. It is different from other antidepressants in that it has no or little activity on a variety of neuroreceptors (e. g. α or β-adrenergic receptors, muscarinic receptors, cholinergic

receptors, histaminic receptors). Like TCAs it has no activity at the fast sodium channels of cardiac cells, therefore devoid of cardiotoxicity. It does not inhibit MAO activity. It is unique among other antidepressants in that it down regulates β-receptors after a single dose and causes rapid onset of clinical antidepressant activity. It inhibits dopamine reuptake at high dosage. The absence of other significant sites of pharmacological action gives it a wide therapeutic window. Co-administration of two drugs, which inhibit individually either serotonin or norepinephrine uptake, has been shown to shorten the treatment time. Likewise, combination of two drugs inhibiting both serotonin and norepinephrine uptake appears to produce a more rapid onset of clinical antidepressant activity than either drug alone.

2.1.2 Mechanism of Action

Venlafaxine (**1**), a bicyclic antidepressant, is known as a serotonin-norepinephrine reuptake inhibitor (SNRI), but it has been usually referred to as a serotonin-norepinephrine-dopamine reuptake inhibitor (SNDRI).[4] The mode of action is by ihibiting the transporter "reuptake" proteins for key neurotransmitters which are related to affecting mood and hence leaving more active neurotransmitters in the synapse of neurons. If adminestered in high doses it weakly inhibits the reuptake of dopamine[5] also referred as biogenic monoamine, with recent evidence showing that the norepinephrine transporter also transports some dopamine as well. Since dopamine is inactivated by norepinephrine reuptake in the frontal cortex, which largely lacks dopamine transporters, venlafaxine can increase dopamine neurotransmission in this part of the brain.[6,7] Venlafaxine interacts with opioid receptors (mu-, kappa1- kappa3- and delta-opioid receptor subtypes) as well as alpha2-adrenergic receptor and has shown to increase pain level in mice. When mice were tested with a hotplate analgesia meter, both venlafaxine and mirtazapine induced a dose-dependent, naloxone-reversible antinociceptive effect following intraperitoneal injection. These findings suggest venlafaxine's seemingly superior efficacy in severe depression.[8]

Reduced levels of serotonin or noradrenaline lowers the activity of nervous system and it will lead to show the symptoms of depression. In such condition if venlafaxine is administered, it increases the levels of serotonin or noradrenaline which reduces the symptoms of deperession. This is done by blocking the reuptake

(recycling) of neuro-transmitters. The antidepressants like venlafaxine block recycling of serotonin and noradrenaline, so the next time an impulse is to be transmitted, it is transmitted smoothly. A stronger message is passed and activity in respective part of the brain is enhanced. *i. e.* symptoms of depression are either reduced or vanished completely.[9]

Pharmacology

A. Clinical profile

An antidepressant qualifies criteria of a perfect antidepressant if it can start action rapidly. Venlafaxine with its unique structure is representative of phenylethylamine class of antidepressants. Various trials have shown that venlafaxine is much more effective than placebo.[10] Venlafaxine is rapidly absobed in body when administered orally. It is having average half life of 5 h in humans. It is actually prodrug of an O-desvenlfaxine, an active ingredient for action, which is metabolized in liver by the cy to chrome P-450 IID6 isoenzyme. It shows minimum protein binding property compared to other antidepressants. The excretions of antibolites generated after metabolism of this drug are excreted through renal system. SNRIs shows more serotonin reuptake than venlafaxine and the tricyclic antidepressants also show potent inhibition for norepinephrin reuptake but availability of both serotonin and norepinephrin synapse and within central nervous system that is secondary to reuptake blockade is believed to be responsible for venlafaxine's uniqueness in antidepressant activity. Venlafaxine and ODV have no MAO inhibitory activity. It is available in extended-release as well as immediate-release dosings. Extended-release dosing simplifies dosing, single dose a day is sufficient.[11]

B. Safety and Tolerance

Like SNRIs, venlafaxine does not have significant effects on the sodium fast channels, which gives it a upper hand in therapeutic use. Treatment for acute overdoses does not require specific or unusual intervention beyond general nursing care and observation. Overdose causes frequent vomitting and nausea, which further limits its toxicity. The most common adverse side effects are nausea, dizziness and somnolence. It may cause sexual dysfunction after a prolonged treatment. At higher doses common side effects observed are hypertension, sweating and tremor. There is no specific antidote for venlafaxine available. In case seizures are observed, then it can be managed with benzodiazepines or other anticonvulsants. The removal of

venlafaxine by forced diuresis, hemodialysis, exchange transfusion, or hemoperfusion is not helpful significantly.[12]

C. Cost effectiveness

Venlafaxine is a potent drug which offers potential pharmacological benefits including early onset of action, dose flexibility, broad range of activities, improved tolerance and efficacy proves its cost-effectiveness. An earlier response can be much more beneficial in case of more severely depressed patients.[13]

2.1.6. Literature review on synthesis of venlafaxine

Since development of venlafaxine in 1993, number of racemic syntheses has been reported by others and this group. In literature there are only three asymmetric syntheses reported in true sense as resolution of venlfaxine is also reported by Kochetkov *et al*. but it cannot be considered as asymmetric synthesis. Recently Nanda *et al*[14] utilized enzymatic resolution as the key step for asymmetric synthesis of both enantiomers of venlafaxine but its biggest disadvantage is that one can not avoid formation of the other unwanted enantiomer and it is a lengthy synthesis. Davies *et al.*[15] reported asymmetric synthesis of (+)-venlafaxine. In this synthesis Rh-catalysed Mannich reaction was used as the key step where the authors used environmentally hazardous, expensive, costly metal catalyst and tedious reaction conditions. Also this group has reported synthesis of (-)-venlafaxine using organocatalysis as the chirality inducing tool, but this synthesis requires a lengthy route. More number of steps reduced overall yield and hence the efficiency of total synthesis.

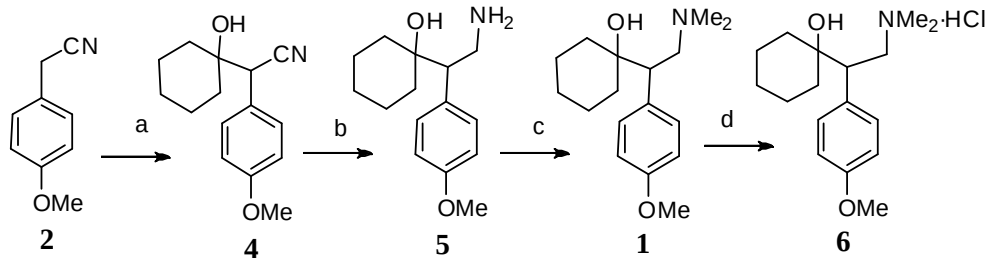
a) Racemic synthesis

Though in literature there are number of racemic syntheses of venlafaxine, here few selected racemic syntheses for (±) venlafaxine are described.

Yardley's Approach[16]

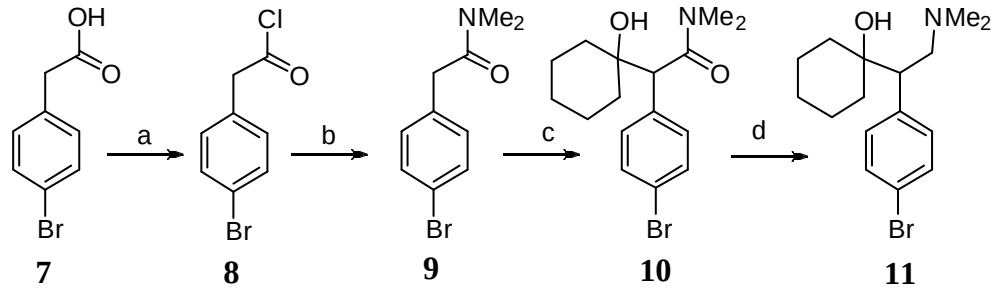
p-Methoxyphenylacetonitrile **2** was nucleophilically added on carbonyl carbon of cyclohexanone **3** using LDA as the base at –78 ^{o}C to provide cyanoalcohol **4** in 83% yield. This cyanoalcohol **4** on hydrogenation reaction with 5% Rh/Al_2O_3 in NH_3/EtOH afforded aminoalcohol **5**. The primary amine on *N,N*-dimethylation, which was carried out by modified Eschweiler-Clarke reaction, afforded venlafaxine **1**.

Hydrochloride salt of venlafaxine, **6** was prepared using 20% HCl in isopropanol (Scheme 6).



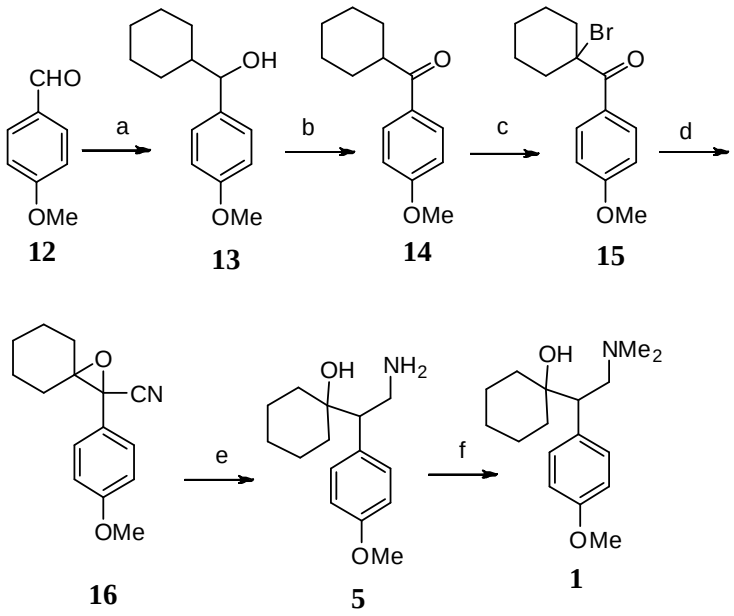
Scheme 6. Reagents and conditions: *a) LDA, THF, –78 °C then cyclohexanone **3**, 2 h, 83%; b) H_2, 5% Rh/Al_2O_3, NH_3-EtOH (2:8), 57%; c) HCHO, HCO_2H, H_2O reflux, overnight; d) HCl (20% in iPrOH) 80% (over 2 steps).*

During the Eschweiler-Clarke reaction, tetrahydroisoquinolines and trace amount of oxazines were formed. This problem was solved in a modified route (Scheme 7), where *p*-bromophenylacetic acid **7** was subjected to $(COCl)_2$ in DMF condition to afford corresponding acid chloride **8**. This acid chloride **8** was converted to its tertiary amide derivative by treatting it with dimethylamine. This tertiary amide **9** was added nucleophilically on cyclohexanone **3** at –78 °C using LDA as the base to furnish amidoalcohol **10**, which was further reduced using $LilH_4$ to provide venlafaxine analogue **11**. By these methods small library of several analogues of venlafaxine have been prepared.



Scheme 7. Reagents and conditions: *a) $(COCl)_2$, DMF, DCM, r t, 4 h; b) Me_2NH, DCM, r t, overnight, 97% (2 steps); c) LDA, THF, –78 °C, then cyclohexanone **3**, 50 min, 44%; d) $LiAlH_4$, conc. H_2SO_4, THF, 0 °C, 1 h, 40%.*

Rathod's approach[17]



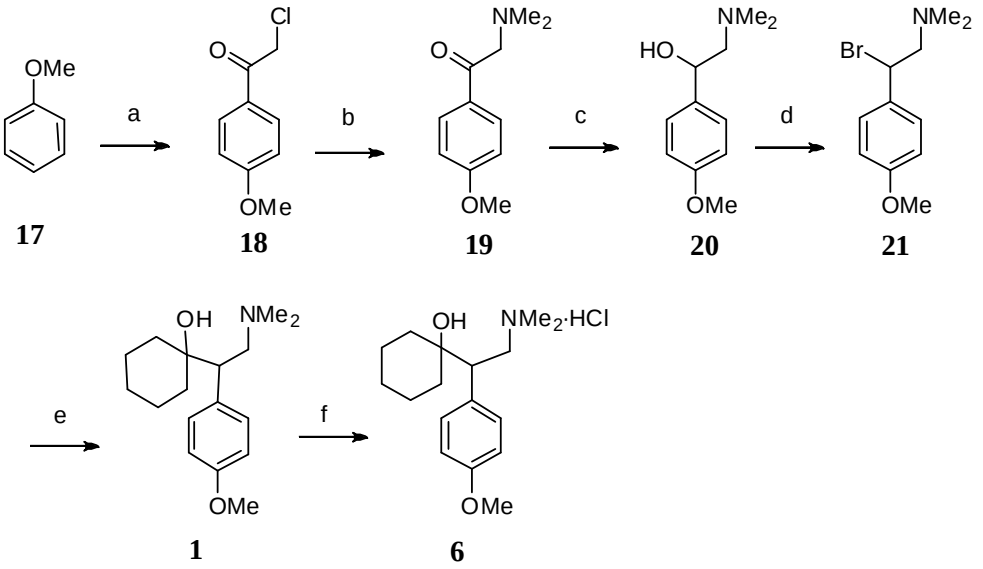
Scheme 8. Reagents and conditions: *a) Cyclohexyl magnesium bromide, THF, 10 ^{o}C to r t, 6 h, 80%; b) CrO_3, H_2O, r t, 3 h, 76%; c) PTAB, THF, reflux, 3 h, 82%; d) NaCN, MeOH, r t, 2 h, 64%; e) H_2, Raney Ni, NH_3-EtOH, 500 kPa, r t, 7 h, 78%; f) HCHO, HCO_2H, H_2O, reflux, 6 h, 75%.*

A patent by Rathod *et al.* reports a new protocol for the synthesis of venlafaxine **1** using Grignard reaction of cyclohexyl magnesium bromide with *p*-anisaldehyde **12** to afford alcohol **13**. The oxidation of alcohol with CrO_3 afforded corresponding ketone **14**, which on treatment with PTAB provided α-bromoketone **15**. *α*-Bromoketone **15** was treated with sodium cyanide to afford spiro epoxide **16** in moderate yield. Opening of epoxide ring and reduction of cyanide was carried out in one pot with Raney nickel to afford aminoalcohol **5**, which was transformed into venlafaxine **1** by a well known methylation procedure (Scheme 8).

Jinpei's approach[18]

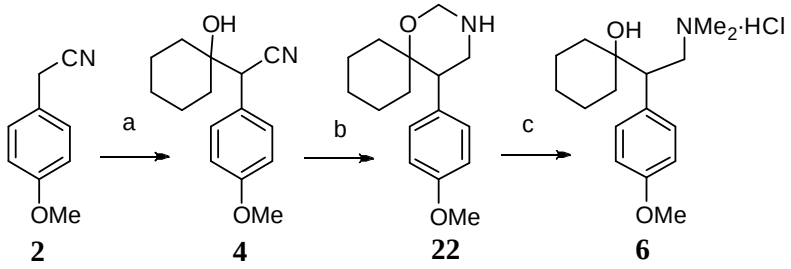
Chloroketone **18** was obtained by Friedel-Crafts acylation of chloroacetyl chloride on anisole **17**, in which chlorine was displaced with dimethylamine to afford aminoketone **19**. Ketone functionality of compound **19** was reduced with KBH_4 which afforded aminoalcohol **20**, which was further converted into the corresponding bromide **21** by using PBr_3 and this bromide was transformed to correspnding Grignard reagent. This Grignard reagent on treatment with cyclohexanone **3** provided

venlafaxine (**1**) which was further converted to its hydrochloride salt **6** by treatment with conc. HCl (Scheme 9).



Scheme 9. Reagents and conditions: *a) $ClCOCH_2Cl$, $AlCl_3$, PhH, reflux, 4 h, 70%; b) 33% aq. Me_2NH, EtOH, r t, 15 h; c) KBH_4, EtOH, r t, 8 h, 64%; d) PBr_3, $CHCl_3$, 0 ^oC then reflux, 15 h, 53%; e) Mg, THF, reflux, then 0 ^oC, cyclohexanone **3** then reflux, 1 h; f) conc. HCl, 47% (over 2 steps).*

Rangappa's approach[19]



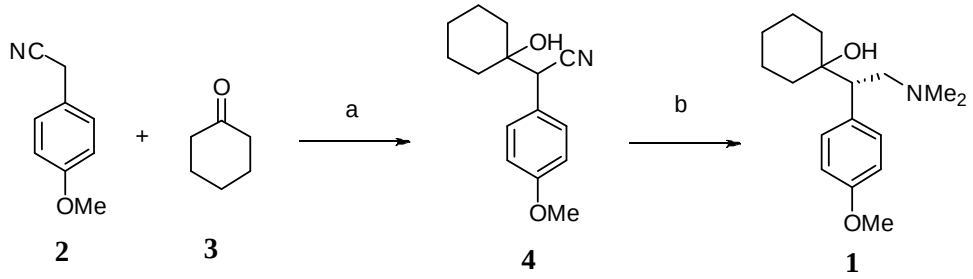
Scheme 10. Reagents and conditions: *a) Cyclohexanone **3**, NaOH, Bu_4NBr, H_2O-MeOH, r t, 15 h, 96%; b) Raney Ni, H_2 (10 atm), anhydrous NH_3-MeOH, 35-40 ^oC, then formalin, 25-30 ^oC, 3 h, 83%; c) HCO_2H, HCHO, reflux, 25-30 h, then HCl in iPrOH (pH = 2), 85%.*

As soon as a US patent was granted to Chavan *et al.*,[20] from this group Rangappa *et al.* published their work, where they nucleophilically added *p*-methoxyphenylacetonitrile **2** on carbonyl of cyclohexanone **3**, using NaOH as the base and MeOH-H_2O (1:1) as the solvent medium to provide caynoalcohol. This

cyanoalcohol **4** was hydrogenated with Raney nickel followed by methylation by reaction with formalin which provided oxazine **22**, which on further subjecting to Eschweiler-Clarke reaction conditions afforded venlafaxine free base **1**. Treatment of **1** with ^{i}PrOH/HCl gave its hydrochloride salt **6** (Scheme 10).

Chavan's approach[20]

A green, novel and mild method for condensation of phenylacetonitrile **2** with cyclohexanone **3** was reported by Chavan *et al.* The condensation afforded cycloalkanol **4**. By utilizing this approach Chavan *et al.* reported the practical synthesis of venlafaxine **1** (Scheme 11).

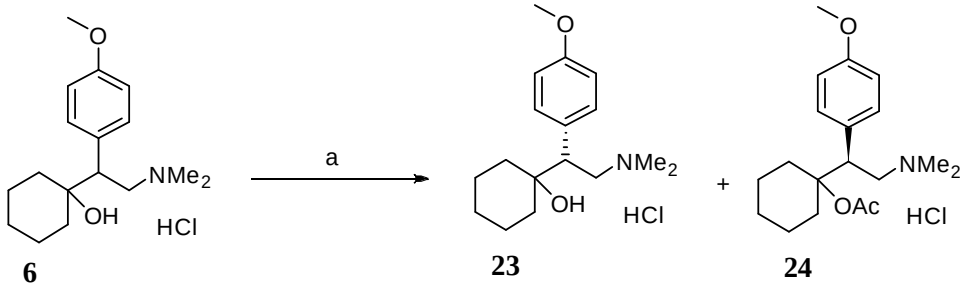


Scheme 11. Reagents and conditions: *a)10% aqueous NaOH, TBAHSO$_4$, 0-15 °C, 30 min-1 h, quantitative yield; (b) H$_2$, 280 psi, formalin, MeOH, 100 °C, 30% (60% cycloalkanol is recovered).*

b) Resolution method

Kochetkov's approach[21]

Resolution of venlafaxine was reported first time by Kochetkev *et al.* Separation of both the enantiomers from racemic mixture of venlafaxine was carried out using enzymatic kinetic resolution. The racemic venlafaxine (**6**) was subjected for acylation with vinyl acetate in the presence of porcine pancreatic lipase (PPL) in chloroform as

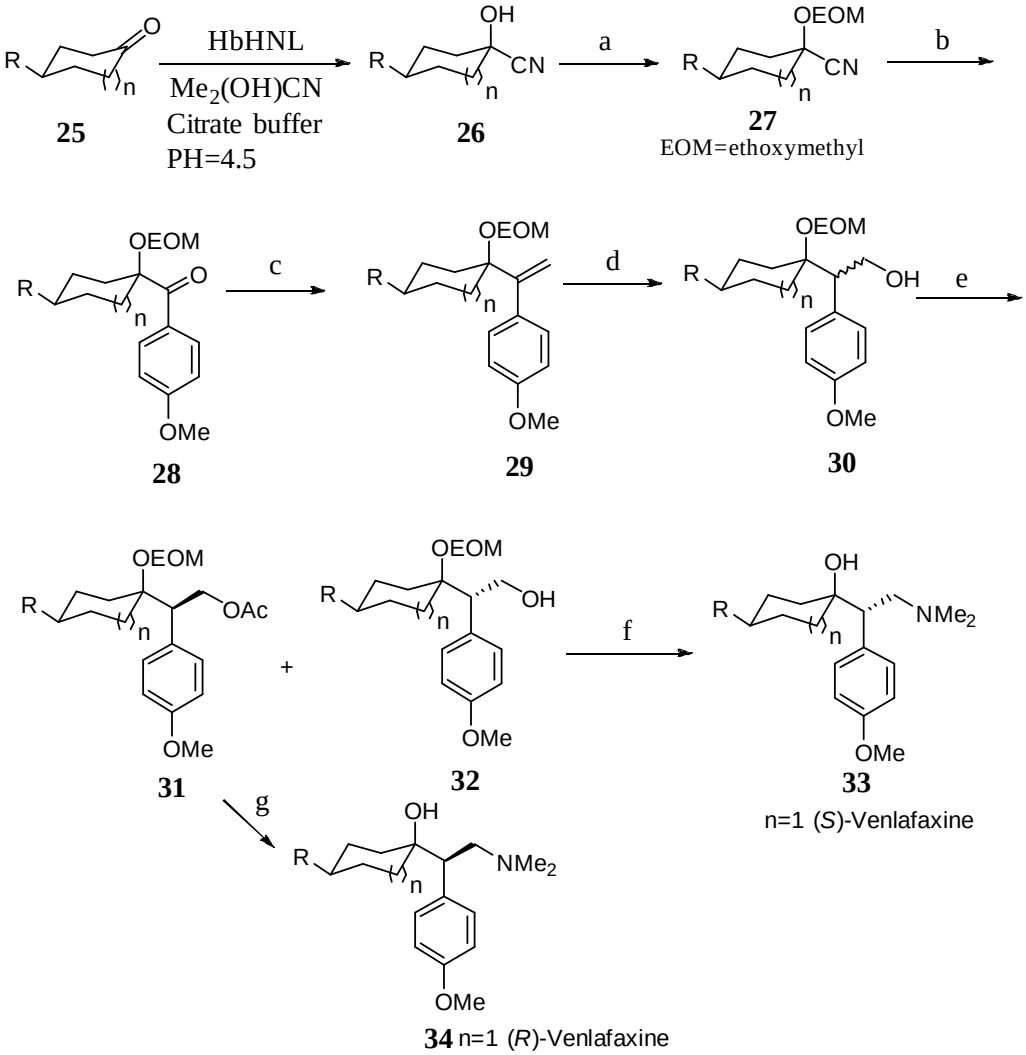


Scheme 12. Reagents and conditions: *a) Vinyl acetate, PPL, CHCl$_3$.*

the solvent at 20 °C which provided its (*R*)-enantiomer **23** and (*S*)-enantiomer as acetate **24** wherein the enantiomeric excess of (*S*)-venlafaxine acetate **24** was > 99% (Scheme 12).

Nanda's Approach[14]

Synthesis of both the enantiomers of venlafaxine (**1**) and some of its analogues was carried out by Nanda *et al.* using chemoenzymatic kinetic resolution as a key step. Cyclohexanone **25** was transformed to cyanohydrin **26** by an enzymatic transcyanation reaction with acetonecyanohydrin and in the presence of HbHNL



Scheme 13. Reagents and conditions: *(a) EOM-Cl, DIPEA, 90%; (b) p-$MeOC_6H_4MgBr$, 85%; (c) Ph_3P^+MeI, KO^tBu, 82%; (d) $BH_3.SMe_2$, KOH, H_2O_2, 84%; (e) CH_2=CHOAc, Lipase PS-D, MS 4 Å, 48%; (f) (i) p-TSCl, Et_3N, DMAP, 88%; (ii) Me_2NH, 80 °C, 48 h; (iii) PTSA, MeOH, 65% (over two steps); (g) (i) K_2CO_3, MeOH; then same reaction sequences as in f.*

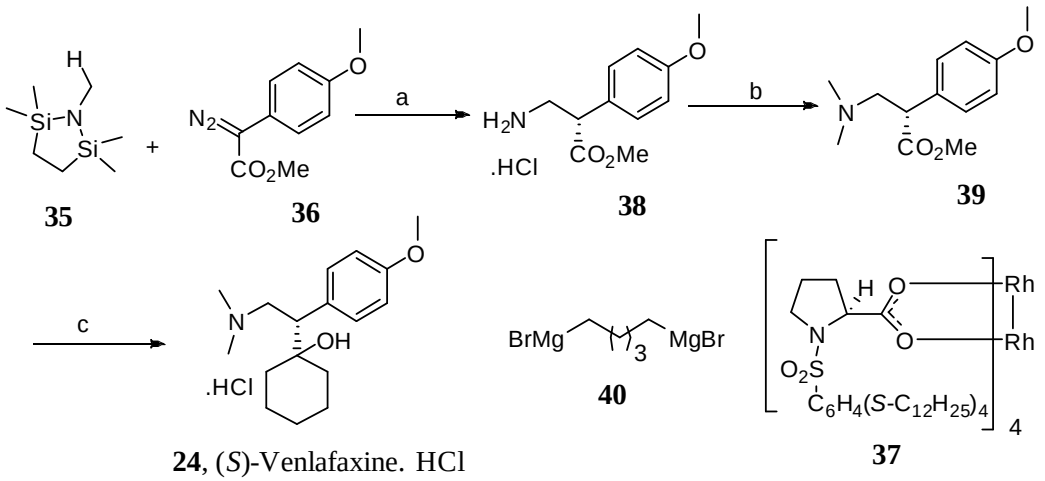
enzyme. Conversion of free hydroxyl group present in compound **26** was carried out by EOM-Cl to afford EOM-protected cyanohydrin **27**. Nucleophilic addition of Grignard reagent generated from 4-bromoanisole on compound **27** followed by acidic work-up provided ketone **28**. The one carbon homologation of ketone **28** was carried out by treatment with methyltriphenylphosphonium iodide in the presence of KO^tBu as the base to afford olefin **29**. The double bond of compound **29** was transformed to racemic hydroxymethylated alcohol **30** on treatment with $BH_3.SMe_2$.. The racemic hydroxymethylated alcohol **30** was subjected for lipase catalyzed enzymatic kinetic resolution with vinyl acetate to afford optically pure acylated compound **31** and free hydroxyl group containing compound **32**. The hydroxyl in compound **32** was converted to its tosylate derivative followed by displacement with dimethyl amine and then deprotection of EOM protecting group by treatment with *p*-TSA to afford (*S*)-venlafaxine **33**. Acetate group in compound **31** was hydrolysed with K_2CO_3–MeOH to afford alcohol and by following the similar reaction sequence as described above (*R*)-venlafaxine **34** was synthesized (Scheme 13).

b) Asymmetric synthesis

In literature only three reports for asymmetric syntheses are available.

Davies' approach[22]

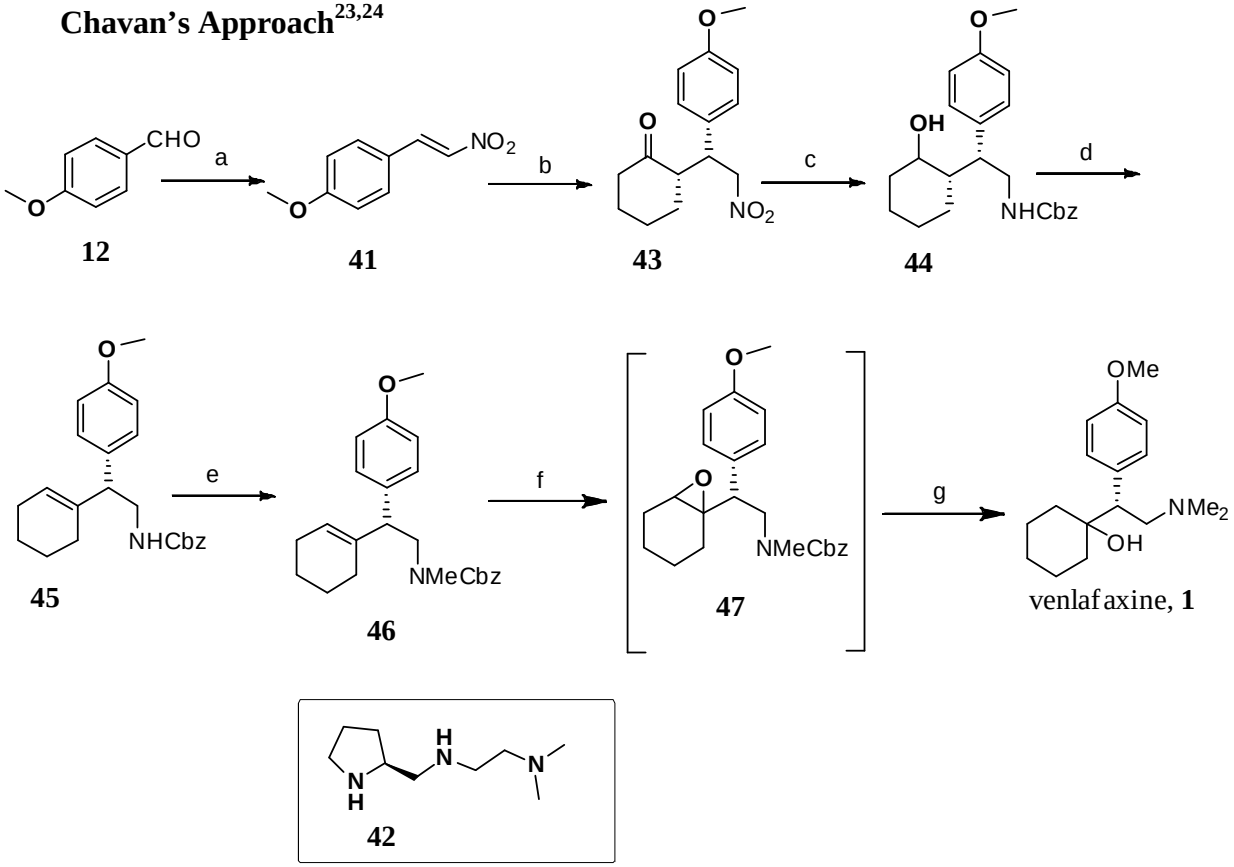
Davies *et al*. utilized rhodium(II) prolinate **37** catalyzed intermolecular C–H insertion between methyl aryldiazoacetates **36** and a bis-silyl protected methylamine **35** to develop a method for the synthesis of chiral *β*-amino esters **38**. This conversion was carried out by using their own methodology to obtain chiral amino ester **38** in moderate yield with 93% *ee*. Primary amine functionality of compound **38** was converted to corresponding tertiary *N,N*-dimethylamine to provide amine **39** under reduction condition in the presence of formaldehyde and $NaBH(OAc)_3$ as the reducing agent. Double Grignard reaction of the **40** with ester **39** provided venlafaxine **1** which was further treated with conc. HCl to convert it in to its hydrochloride salt **24** (Scheme 14).



24, (*S*)-Venlafaxine. HCl

Scheme 14. Reagents and conditions: *a) i)* ***37****, -40 °C; ii) HCl/ether; b) HCHO/NaBH(OAc)*$_3$*, DCM ; c) i)* ***40****; ii) HCl/ether.*

Chavan's Approach[23,24]



Scheme 15. Reagents and conditions: *a)* CH_3NO_2*, AcOH,* NH_4OAc*, sonication, 4 h; b) Cyclohexanone,* ***42****, DMF, PTSA, 48 h, rt, 99% ee, 80%; c) i)* $NaBH_4$*, THF:* H_2O *(9:1); ii)* $NiCl_2$*,* $6H_2O$*,* $NaBH_4$*, MeOH, CbzCl,* Et_3N*, 60%; d) i) MsCl,* Et_3N*, DCM, rt then reflux; ii) DBU,* CH_3CN*, reflux, 90%; e) NaH, MeI, overnight, rt, 90%; f) m-CPBA,* $NaHCO_3$*, 30 min, rt, 75%;) LiAlH*$_4$*, THF, reflux, 80%, ≥ 99% ee.*

Anisaldehyde **12** was converted to nitrostyrene **41** under Henri reaction condition (Scheme 15). Nitrostyrene **41** was subjected for asymmetric Michael addition of cyclohexanone **3** by using proline derived catalyst **42** to afford nitro keto compound **43**. Nitro keto compound **43** was then reduced to *N*-Cbz protected amino alcohol **44** using $NaBH_4$, $NiCl_2$:$6H_2O$ and *in citu* Cbz protection. The hydroxy group was elminated to afford olefin **45**. Free amine in the olefin **45** was methylated with Methyl iodide and epoxidation of olefin was carried out by using *m*-CPBA. This epoxide **47** was regioselectively opened with $LiAlH_4$ to afford (-)-venlafaxine **1**.

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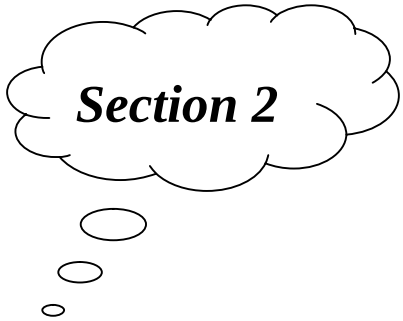
Chapter 1
Synthetic studies towards (-)-venlafaxine and (2*R*,3*S*)-3-hydroxypipecolic acid



A protecting group free and scalable approach towards total synthesis of (–)-Venlafaxine

1.2. Present work

1.2.1 Objective

In literature there are a number of syntheses of venlafaxine (**1**) reported[1] including few reports from this group.[2] But for asymmetric total synthesis of either *R* or *S* venlafaxine there are only three reports available. Davies *et al*.[3] have reported an asymmetric synthesis of (+)-venlafaxine by efficient use of Rh-catalysed Mannich reaction as a key chirality inducing step

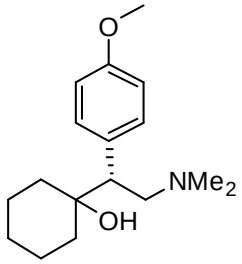


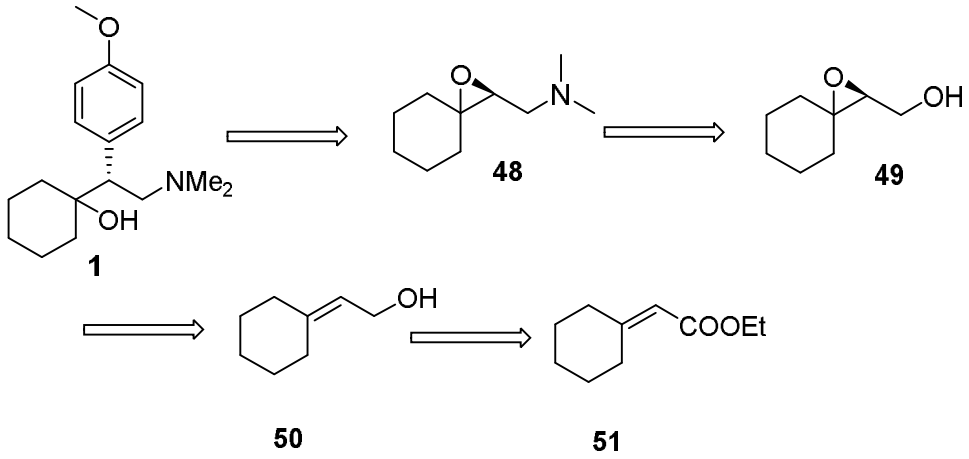
Figure 1. Structure of (-)-Venlafaxine (**1**)

while Nanda *et al*[4] used enzymatic resolution as the key step for the synthesis of both *R* and *S* venlafaxine along with some of its analogs. Also Kochetkov *et al.*[5] have reported resolution of (±)-venlafaxine. Recently, this group has reported a concise and novel route for asymmetric synthesis of (–)-venlafaxine (**1**) using environment friendly organocatalyst.[6]

To overcome problems associated with the reported syntheses and as both the enantiomers have different biological activity, as a part of our continued interest in antidepressant agents, it was thought to develop an efficient, simple and practical strategy for the asymmetric synthesis of (–)-venlafaxine (**1**) by using practical, simple reaction conditions and asymmetric Sharpless epoxidation as the chirality inducing tool. Herein by switching the stereocenter of the catalyst *viz.* tartarate ester one could synthesize both the antipodes of venlafaxine enantioselectively.

Literature survey also led to think that there is a need of more concise and viable asymmetric route for (–)-venlafaxine (**1**). The use of Sharpless asymmetric epoxidation reaction was at advantage as both *R*-Venlafaxine (**1**) as well as *S*-Venlafaxine could be accessed by just switching tartarate ester ligands from D to L. More importantly, in the present work the use of protection-deprotection sequence has been successfully avoided, making the approach more efficient with significant improvement in overall yield.

1.2.2. Retrosynthetic analysis



Scheme 1. Retrosynthetic analysis of (-)-venlafaxine (**1**).

In view of potential use of venlafaxine in medicinal chemistry, a novel synthetic route for the total synthesis of (+) and (–)-venlafaxine (**1**) was devised. As outlined in retrosynthetic scheme 1, it was envisioned that required stereochemistry for target molecule (**1**) can be generated by Sharpless asymmetric epoxidation reaction, followed by opening epoxide **48** with Grignard reagent and hence inversion of stereogenic center to obtain target molecule (**1**). The required epoxy alcohol **49** could be accessed from allyl alcohol **50**, which in turn can be obtained from commercially available *α*, *β*-unsaturated ester **51** or two carbon Wittig product of cyclohexanone **42** by selective ester reduction. Though unsaturated ester **51** is commercially available, the synthesis of (-)-venlafaxine **1** began from commercially available, inexpensive cyclohexanone **42**.

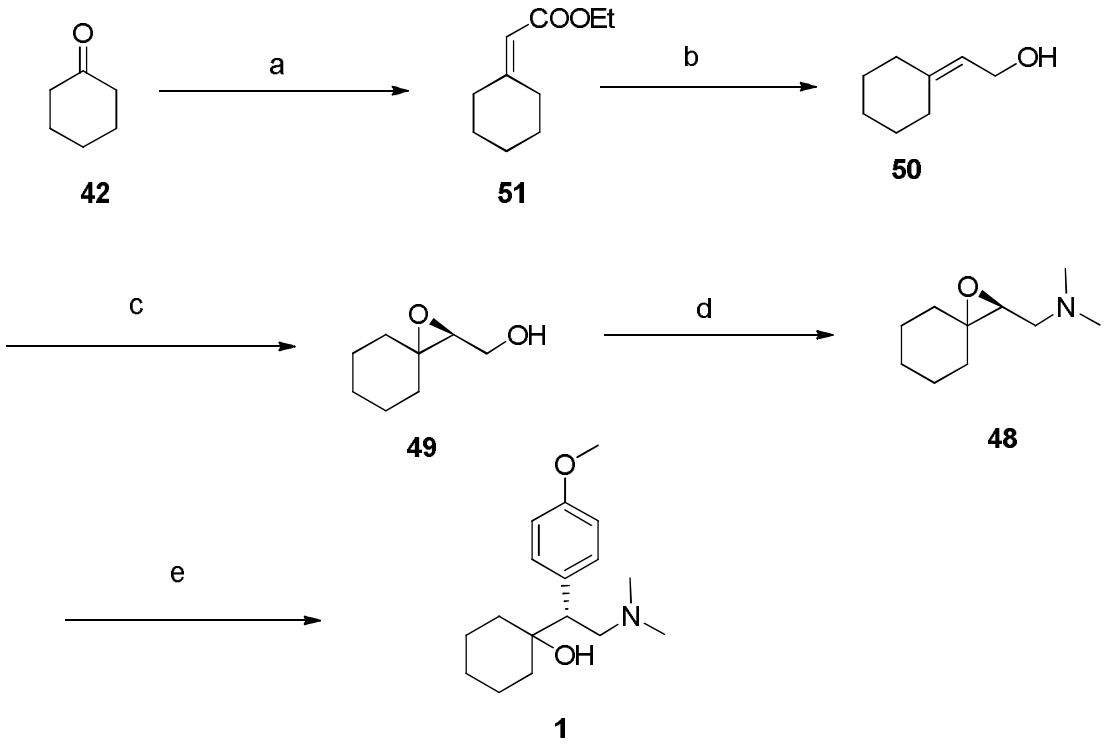
1.2.3. Results and discussion

Accordingly, the synthesis of (–)-Venlafaxine (**1**) began with the Wittig reaction of inexpensive and easily available starting material *viz*. cyclohexanone (**42**) with two carbon ylide in toluene under reflux at 120 ^{o}C to furnish the unsaturated ester **51**[7] in 95% yield (Scheme 2). IR spectrum of compound **51** showed absence of band at 1715 cm^{-1} for corresponding carbonyl functional group of cyclohexanone **42** and appearance of new band at 1705 cm^{-1} which was attributed to carbonyl frequency of ester functionality in **51**. The ^{1}H NMR spectrum showed triplet at δ 1.28 (J = 7.1 Hz) for three protons and quartet at δ 4.13 for two protons characteristic peaks of ethyl of COOEt functional group.This confirmed the presence ethyl ester functionality. The CH present in ester **51** at *α* position was confirmed by

^{1}H NMR, where its corresponding peak appeared δ 5.58. This was further confirmed by its ^{13}C and DEPT NMR spectra, which showed peak at δ 112.96 of CH and it also showed a peak at δ 162.89 corresponding to β carbon of unsaturated ester **51**.

Selective ester reduction of unsaturated ester **51** with Red-Al to allyl alcohol **50** was carried out in 30 min in toluene (or DCM) as the solvent to furnish allyl alcohol **50** in 97% yield. The IR spectrum showed absence of IR peak at 1705 cm^{-1} corresponding to ester group and appearance of broad absorption at 3421 cm^{-1} indicating the presence of a hydroxyl group. In ^{1}H NMR spectrum of compound **50** disappearance of typical quartet at δ 4.13 and triplet at δ 1.28 for ethyl group (OCH_2CH_3) was observed. The ^{13}C NMR spectrum showed absence of peak at δ 162.89 corresponding to quaternary carbon of carbonyl group and ^{13}C and DEPT NMR spectrum showed peaks for CH_2 group at δ 58.21 which confirmed the presence of CH_2OH group. This allyl alcohol **50** was converted to epoxide under asymmetric Sharpless epoxidation conditions. Here L-(+)-isomer of tartrate ester was used as the chiral ligand for

Scheme 2 Total Synthesis of (–)-Venlafaxine (**1**).



Scheme 2. *Reagents and conditions:* a) $Ph_3PCHCOOEt$, toluene, reflux, 24 h, 98%; b) Red-Al, 30 min, toluene, 97%; c) (+)DET, $Ti(OiPr)_4$, MS 4Å, t-BuOOH, DCM, 6 h, -50 ^{o}C, 83%; d) i) MsCl, Et_3N, DCM, 15 min; ii) Dimethylamine (40% aq. Solution), 10 h, 95%; e) *p*-Methoxyphenylmagnesium bromide, CuI, THF, -40 ^{o}C, 8 h, 71%.

chirality induction. The product **49** was obtained in 83% yield and 85% ee. The enantiomeric purity of chiral epoxy alcohol **49** was calculated by chiral GC (Supelco *β*-Dex 120 column, oven temp. 140 ^{o}C for 60 min (isothermal), injection temp. 220 ^{o}C, detection temp. 300 ^{o}C, $t_{(-)}$ = 23.38, $t_{(+)}$ = 24.57 showed 85% ee). The epoxide product was confirmed by ^{1}HNMR where olefinic CH was shifted at δ 2.94 as doublet of doublet with coupling constant (*J* = 6.63, 4.48 Hz) for 1 H from δ 5.36 of allyl alcohol **50** and in ^{13}C NMR the same sp^2 carbon of allyl alcohol **50** was observed at δ 64.33 in epoxy alcohol **49**. The qyternary carbon shifted to δ 60.29 from δ 143.76 and its respective peak was disappeared in DEPT, which confirmed the presence of epoxide ring.

The primary hydroxyl group of compound **49** was converted into the corresponding mesyl derivative by using mesyl chloride (MsCl) in the presence of Et_3N as a base in DCM as the solvent at 0^{o}C in 10 min. The mesylate of epoxide was used as such in further amination reaction without purification, as it was single spot product with no impurity generated in reaction. Mesyl group in mesylate epoxide was displaced with dimethyl amine to get dimethyl amine epoxy compound **48** in more than 95% yield. Displacement was carried out by simply adding 4 equivalent of dimethyl amine (40% aq. solution) to the mesylate and stirring the reaction mixture for 10 h. IR spectrum showd the absence of band at 3421 cm^{-1} corresponding to primary hydroxyl group. This observation suggested its displacement with dimethyl amine. This epoxy dimethyl amine **48** formation was further confirmed by appearance of singlet for 6 protons (CH_3-N-CH_3) at δ 2.1 in ^{1}H NMR and in ^{13}C NMR peak at δ 45.54 corresponding to methyl carbon of (CH_3-N-CH_3). Also the peak at δ 64.33 corresponding to CH_2OH was shifted to δ 57.80 suggesteing that new C-N bond formation to form CH_2N funtionality.

The epoxy amine **48** was subjected for epoxide ring opening. This key step in the synthesis of target compound (**1**) was carried out in THF at -40 ^{o}C, with *p*-methoxyphenylmagnesium bromide and copper iodide by *in situ* genarating Gilman reagents. The formation of final compound (**1**) was confirmed as (–)-Venlafaxine (**1**) by comparing ^{1}H and ^{13}C NMR spectra with the reported data and the optical rotation was also matched with reported one.

The product formation was confirmed by appearance of a broad band at 3464 cm^{-1} in its IR spectrum indicated the presence of free tertiary hydroxyl functional group in the structure. The appearance of two doublets of doublet in aromatic region at δ 6.76 to 7.08 for four protons and singlet for three protons of methoxy group in its ^{1}H NMR spectrum confirmed the addition of aromatic part in epoxide to form the target molecule (**1**). The ^{1}H

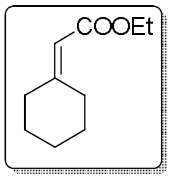
NMR spectrum of compound (**1**) showed a new peak at δ 3.41 (t, *J* = 11.9 Hz, 1 H) and ^{13}C NMR and DEPT spectra showed peak at δ 51.72 which attributed to benzylic CH group, clearly indicating that the epoxide was selectively opened from less hindered side to furnish target compound venlafaxine (**1**). The HRMS of compound (**1**) showed peak at m/z 278.2115 corresponding to $[M+H]^+$. The characterization data was in good agreement with the reported data.[6]

1.2.4 Conclusion:

In conclusion, we have achieved a short, practical and scalable asymmetric total synthesis of (-)-venlafaxine (**1**) in a very efficient manner from commercially easily available, cheap starting material. In present synthesis column chromatographic purification can be avoided in all steps except at epoxidation and can be carried out at gram scale. By using different enantiomers of tartarate ester in Sharpless asymmetric epoxidation reaction both the enantiomers of venlafaxine are accessible in a very concise manner.

1.2.5. Experimental:-

Ethyl 2-cyclohexylideneacetate (51)



A clean, dry 250 ml round bottom flask was charged with cyclohexanone **42** (5g, .051 mmol) and two-carbons Wittig ylide (19.537 g, .0561mmol). Then, temperature of reaction mixture was raised to 120 ^oC. The reaction mixture was refluxed for 24 h. After completion of reaction, toluene was removed *in vacuo*. After removal of toluene, it was suspended in 5 % EA: PE system and filtered through 3 cm thick celite bed to remove triphenyl phosphine oxide. Filtrate was concentrated under reduced pressure and purification of the residue on a silica gel column using EA: PE (2:98) gave unsaturated ester **51** (24.7 g, 98%) as a clear liquid. R_f (5% EA: PE): 0.7.

Yield: 98%

Chemical Formula: $C_{10}H_{16}O_2$

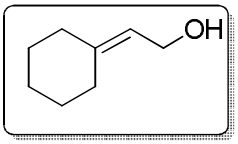
Molecular Weight: 168.23

IR ($CHCl_3$): 3020, 1705, 1646, 1215 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.28 (t, *J* = 7.1 Hz, 3 H), 1.50 - 1.76 (m, 7 H), 2.10 - 2.27 (m, 2 H), 2.64 - 3.01 (m, 2 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 5.58 (t, *J* = 1.0 Hz, 1 H);

^{13}C NMR ($CDCl_3$+CCl_4): δ 14.15, 26.14, 27.61, 28.46, 29.55, 37.80, 59.05, 112.96, 162.89, 166.28.

2-cyclohexylideneethan-1-ol (50)



To a solution of the Red-Al in toluene at 0 ^{o}C (115 mg, 1.5 eq), unsaturated ester **51** in toluene was added in drop wise manner, and the solution was stirred at same temperature for 30 min. The reaction was then quenched with saturated sodium potassium tartarate salt by stirring for 3 h.The solution was extracted with ethyl acetate (3 × 100 mL), washed with water followed by brine, dried over anhydrous Na_2SO_4 and filtered. Removal of the ethyl acetate under reduced pressure furnished pure compound **50** as a clear liquid and it wascharacterized without any purification method (6.1 g, 97%). R_f (40% EA:PE): 0.4.

Yield: 97%

Chemical Formula: $C_8H_{14}O$

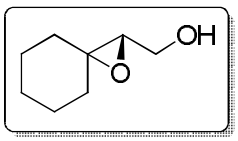
Molecular Weight: 126.12

IR ($CHCl_3$): 3421, 2934, 1647, 1265 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.48 - 1.69 (m, 6 H), 2.01 - 2.29 (m, 4 H), 3.50 (s, 1 H), 4.15 (d, *J* = 7.1 Hz, 2 H), 5.36 (t, *J* = 7.1 Hz, 1 H);

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 26.66, 27.76, 28.32, 28.77, 36.98, 58.21, 120.47, 143.76.

(*S*)-(1-oxaspiro[2.5]octan-2-yl)methanol(49)



To a stirred solution of Ti(O-iPr)$_4$ (7.88 g, 55.5 mmol) and molecular sieves 4Å in dry DCM (40 mL) was added L(+)-diethyl tartarate (11.46 g, 55.5 mmol) at -10 ^{o}C. After stirring for 10 min, TBHP (4 M in tolune, 10 g, 111.08 mmol) was added drop wise to the mixture. After 30 minutes, temperature of the reaction mixture was lowered to -50 ^{o}C. A solution of allyl alcohol **50** (3.5 g, 27.77 mmol) in DCM was added drop wise to the reaction mixture under nitrogen atmosphere. Reaction mixture was stirred for 6 h. The progress of reaction was monitored by TLC. After completion of reaction, reaction was quenched by adding aqueous NaOH solution and stirring for 2 hours at room temperature. Then organic and aqueous layers

were separated. Aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness under reduced pressure. Purification of the residue on a silica gel column using EA: PE (30:70) as eluent furnished the epoxy alcohol **49** (83%) as a colorless liquid. R_f (40%, EA: PE): 0.3.

Yield: 83%

Chemical Formula: $C_8H_{14}O_2$

Molecular Weight: 142.12

Optical rotation: $[\alpha]_D^{25}$ -17.02 (c = 1.03, $CHCl_3$); Lit. $[\alpha]_D^{25}$ -16.01 (c = 1.0, $CHCl_3$)

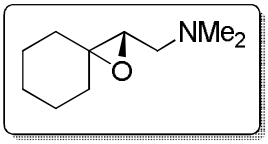
Chiral GC (Supelco β-Dex 120 column, oven temp. 140 ^oC for 60 min (isothermal), injection temp. 220 ^oC, Detection temp. 300 ^oC, $t_{(-)}$ = 23.38, $t_{(+)}$ = 24.57 showed 85% ee.

IR ($CHCl_3$): 3420, 2937, 1264, 735 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.44 - 1.90 (m, 11 H), 2.94 (dd, *J* = 6.63, 4.48 Hz, 1 H), 3.53 - 3.98 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 24.68, 25.45, 29.31, 35.22, 60.52, 63.29, 64.33. **HRMS:** Calculated for $C_8H_{14}O_2Na$:165.0891 found 165.0887 $[M+Na]^+$.

(*S*)-*N, N*-dimethyl-1-(1-oxaspiro[2.5]octan-2-yl)methanamine(48)



To a solution of ethyl epoxy alcohol **49** (2.5 gm, 17.6 mmol) in anhydous CH_2Cl_2 (5 mL) was added Et_3N (5.3 g, 7.32 mL, 52.81 mmol) at 0 °C and methane sulphonyl chloride (3.0 g, 2.15 mL, 26.4 mmol) sequentially in dropwise manner. Progress of the reaction was monitored by TLC. After completion, the reaction was quenched with water (5 mL) and the organic layer was washed with aq $NaHCO_3$ (2 %, 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude compound was used directly in the next reaction. To crude mesylate epoxide (4 g, 18.18 mmol) was added 40% aqueous solution of *N, N*- dimethyl amine (72.72 mmol) and stirred at room temperature for 10 h. The reaction mixture was directly concentrated under reduced pressure at 60 ^oC to furnish crude residue. The crude residue was purified by silica gel column chromatography to get 95 % of **48** as yellow oil.

Yield: 95%

Chemical Formula: $C_{10}H_{19}NO$

Molecular Weight: 169.26

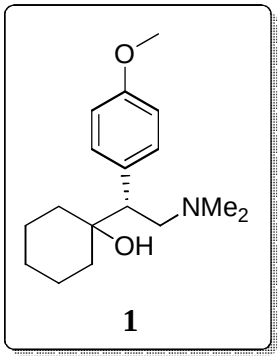
Optical rotation: $[\alpha]_D^{25}$ = - 18.41 (c = 1.4, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.40 - 1.80 (m, 10 H), 2.20 - 2.39 (m, 7 H), 2.56 - 2.73 (m, 1 H), 2.84(dd, *J* = 6.25, 3.98 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 24.42, 24.49, 25.42, 29.26, 35.11, 45.54, 57.80, 61.06, 62.43.

HRMS: Calculated for $C_{10}H_{20}NO$ 170.1545 **found**170.1539 $[M+H]^+$.

Synthesis of (-)- venlafaxine (1)



1

4-Bromoanisole (1.66 g, 8.86 mmol) was added to the suspension of Mg metal turnings (425 mg, 17.7 mmol) in dry THF (30mL) and the resulting mixture was allowed to stir under heating until all magnesium metal disappeared. To this solution was added a mixture of copper iodide (112 mg, 0.59 mmol) and allowed to stir for 15 min. This suspension was cooled to -40 ^oC. A solution of (-)-epoxyamine **48** (1 g, 5.9 mmol) in THF (40 mL) was added slowly to the above reagent and the mixture was stirred at -40 ^oC for 8 h The reaction mixture was quenched with a saturated solution of NH_4Cl. The organic layer and aqueous layers were separated. Aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness under reduced pressure. Purification of the residue on a silica gel column using ethyl acetate as eluent furnished the (−)-venlafaxine **1** (71% over two steps after recrystalization in ethyl acetate) as white solid.

R_f (100% EtOAc): 0.2 (long tail)

Yield: 71%.

Chemical Formula: $C_{17}H_{27}NO_2$

Molecular Weight: 277.40

M.P. 286-287 ^oC

Optical rotation: $[\alpha]_D^{25}$: −24.285 (*c* = 1.04, EtOH) Lit.[6]; *R*-(-)-venlafaxine $[\alpha]_D^{25}$ = - 29.9 (c = 1.04, EtOH).

IR ($CHCl_3$): 3164, 2982, 2938, 2860, 2782, 1610 cm^{-1}.

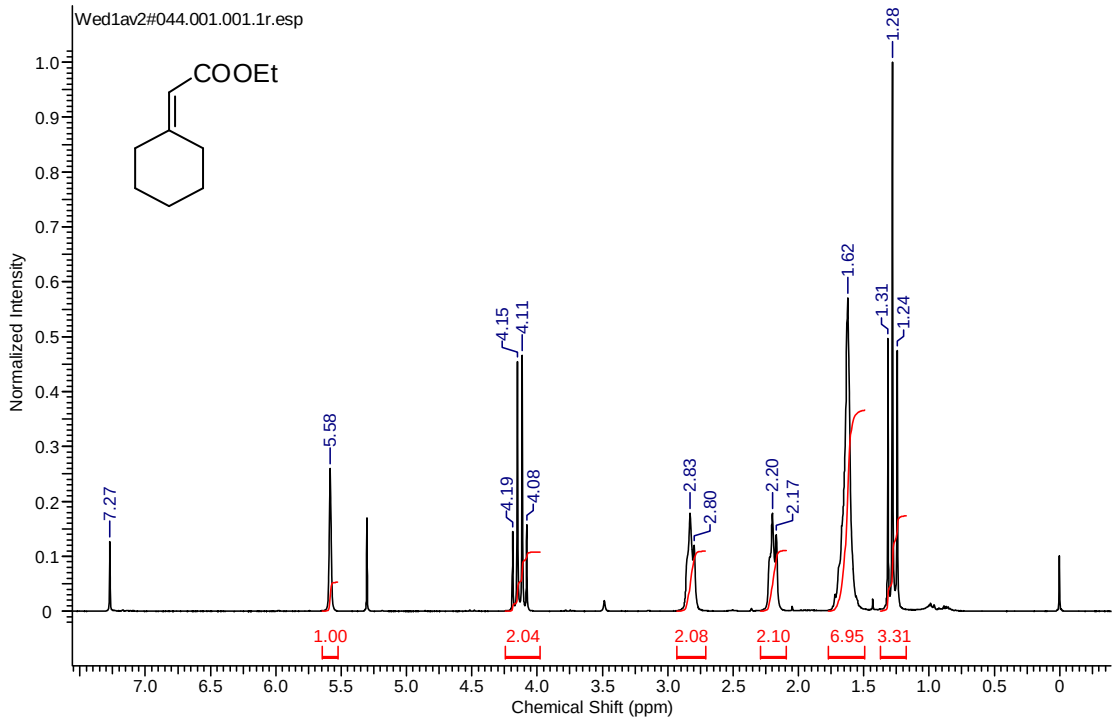
^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 0.73 - 1.11 (m, 2 H) 1.33 - 1.74 (m, 8 H) 2.35 - 2.51 (m, 7 H) 3.01 (d, 1 H) 3.00 (dd, *J* = 11.9, 2.9 Hz, 1 H) 3.41 (t, *J* = 11.9 Hz, 1 H) 3.79 (s, 3 H) 5.49 (bs, 1 H) 6.79 (d, *J* = 8.8 Hz, 2 H) 7.04 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 21.36, 21.54, 25.90, 31.29, 37.84, 45.35, 51.74, 55.06, 61.15, 74.22, 76.68, 77.31, 113.49, 130.08, 132.32, 158.44.

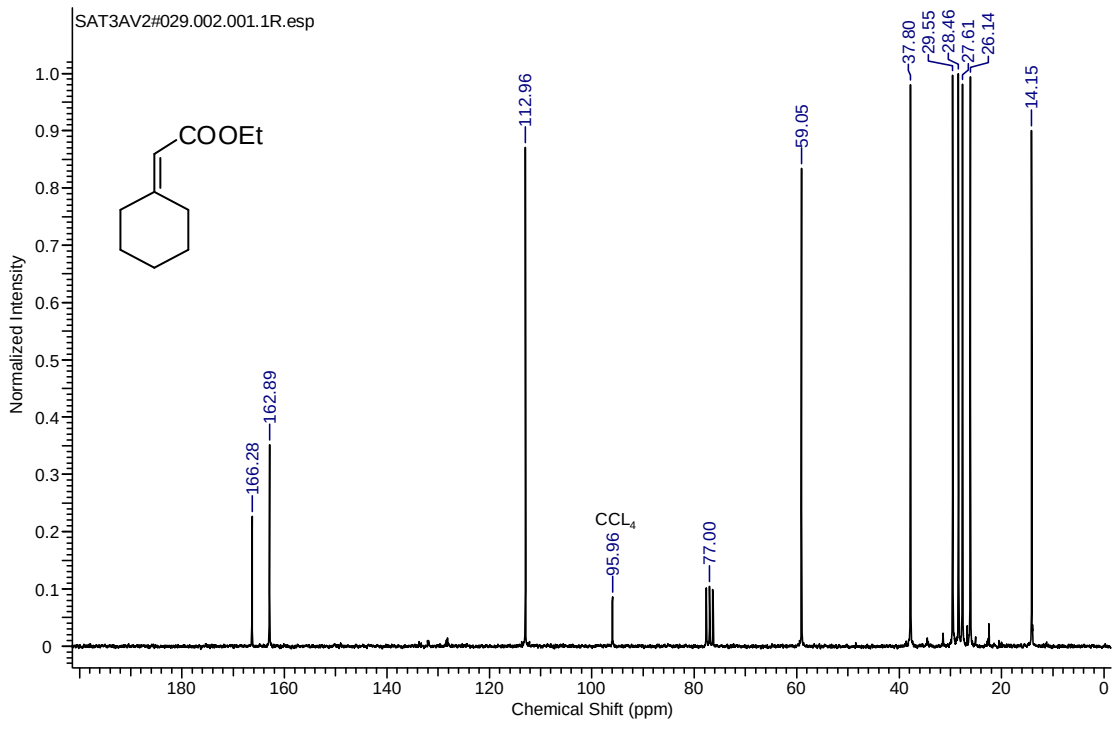
HRMS: Calculated for $C_{17}H_{28}NO_2$ 278.2120 found 278.2115 $[M+H]^+$.

1.2.6. Spectra

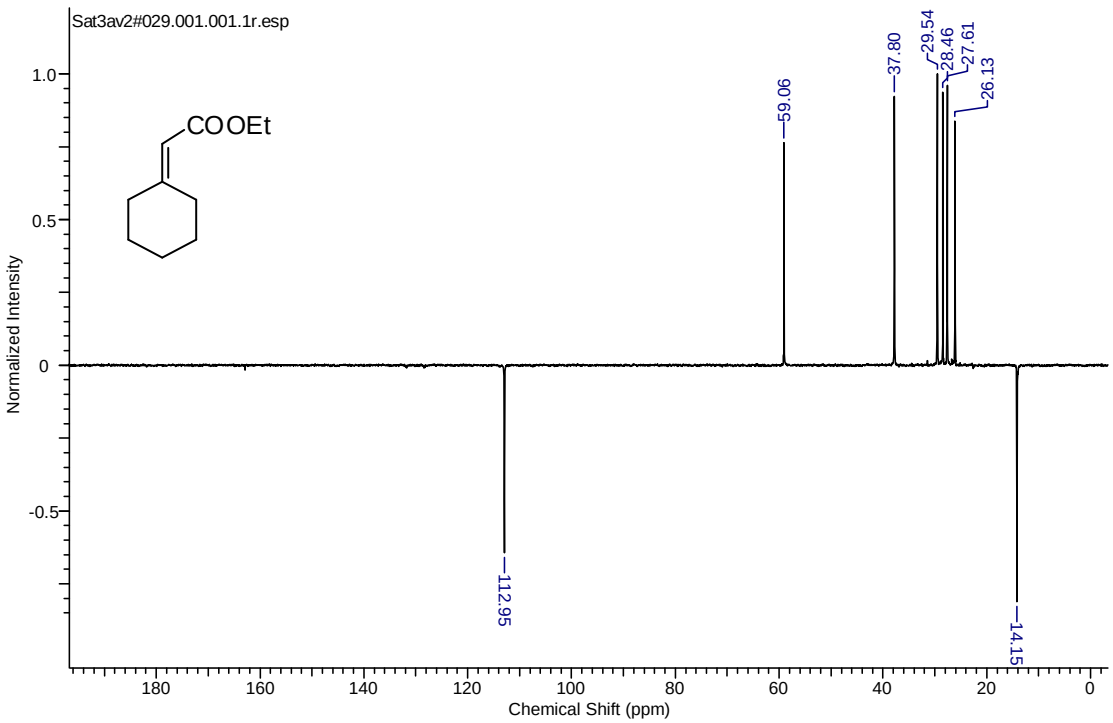
^{1}H NMR spectrum of compound **51** ($CDCl_3$+CCl_4, 200 MHz)



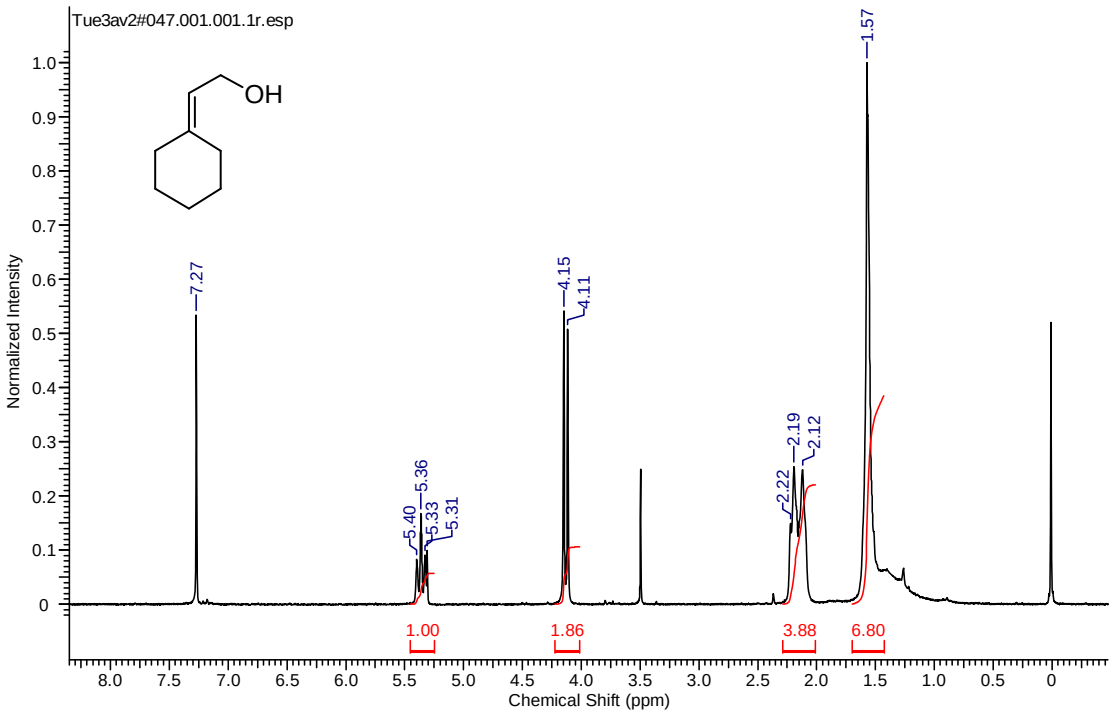
^{13}C NMR spectrum of compound **51** ($CDCl_3$ + CCl_4, 50 MHz)



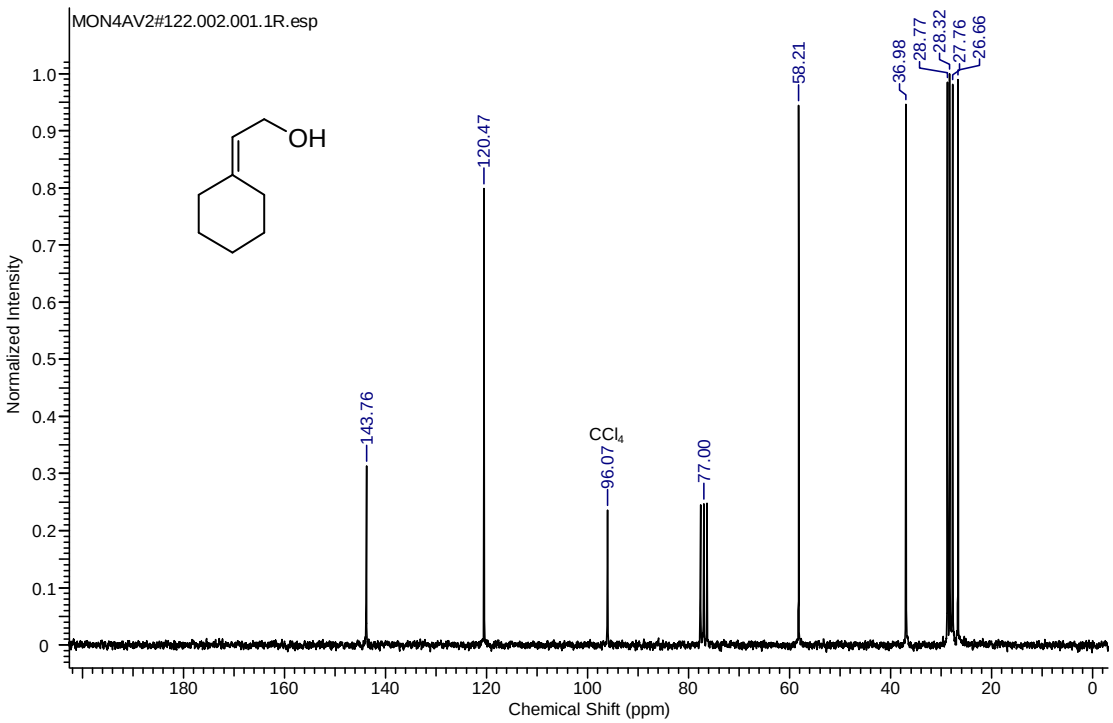
DEPT spectrum of compound **51** ($CDCl_3$ + CCl_4, 50 MHz)



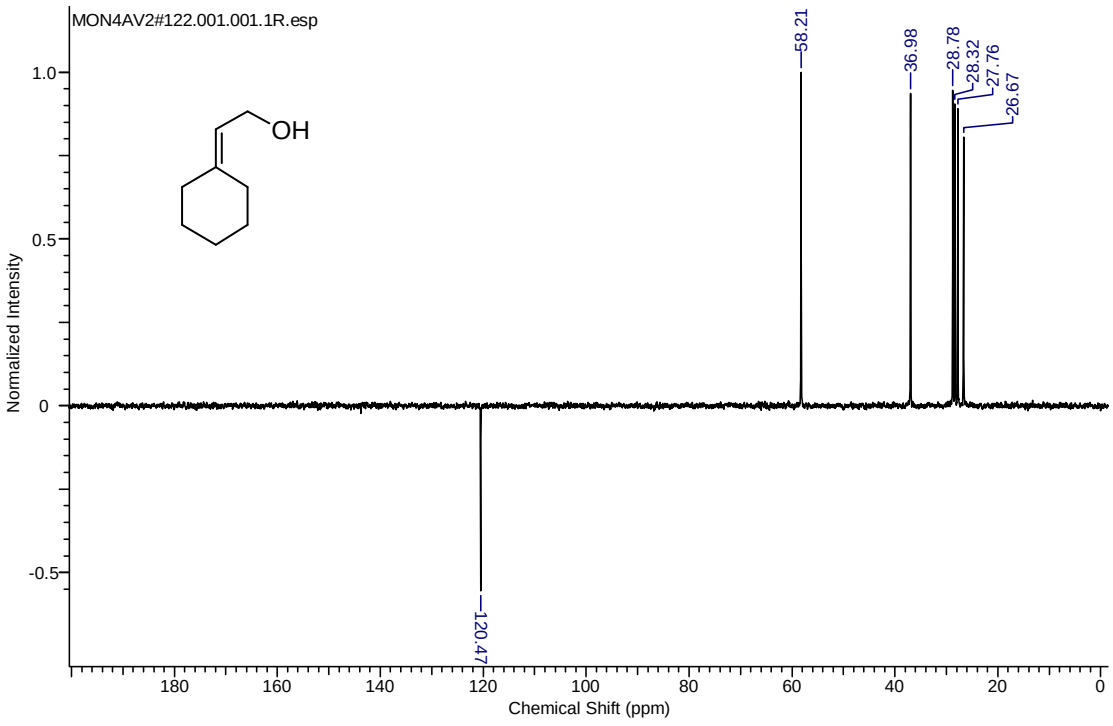
^{1}H NMR spectrum of compound **50** ($CDCl_3$+CCl_4, 200 MHz)



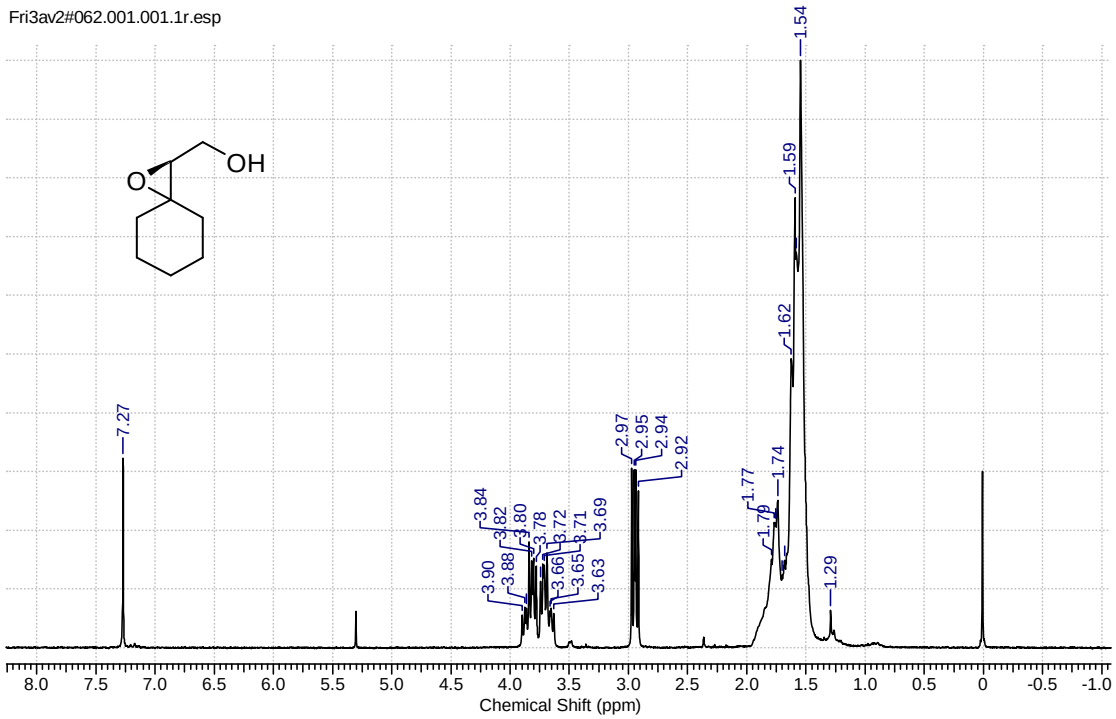
^{13}C NMR spectrum of compound **50** ($CDCl_3$ + CCl_4, 50 MHz)



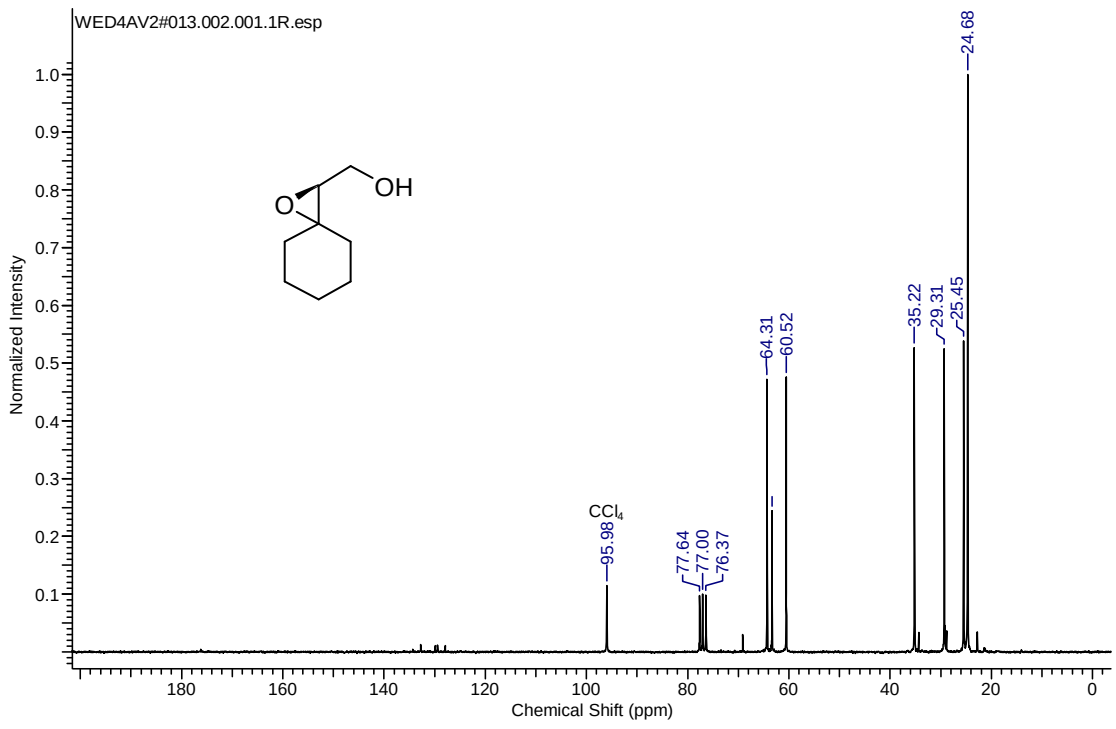
DEPT spectrum of compound **50** ($CDCl_3$ + CCl_4, 50 MHz)



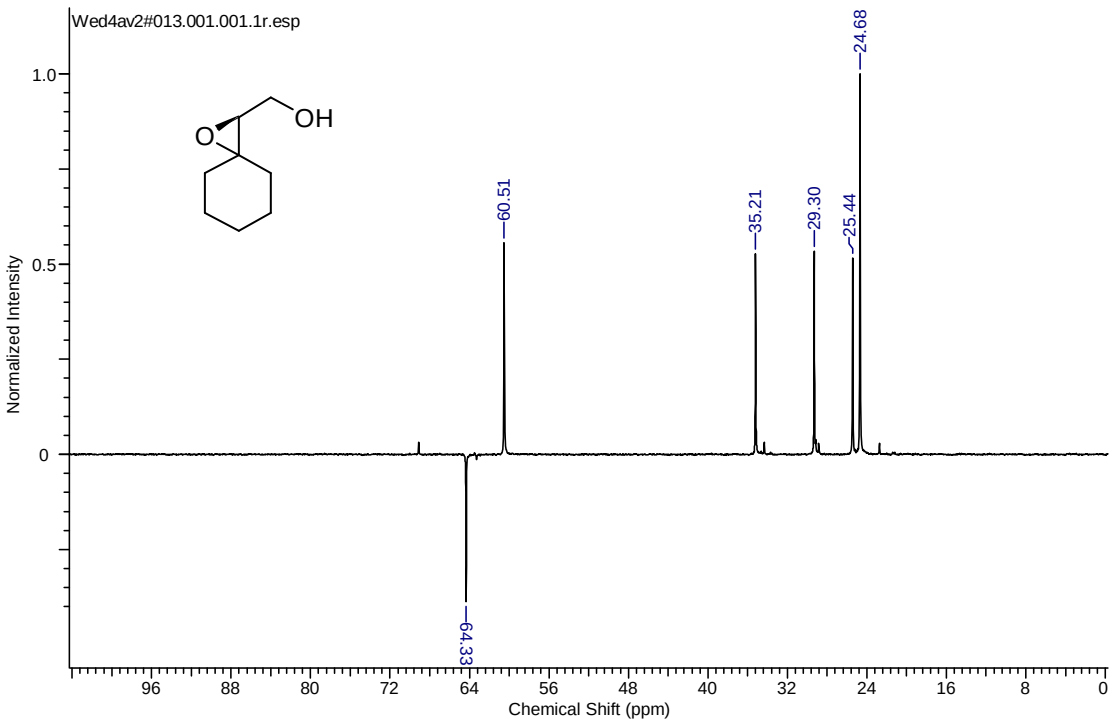
^{1}H NMR spectrum of compound **49** ($CDCl_3$ + CCl_4, 200 MHz)



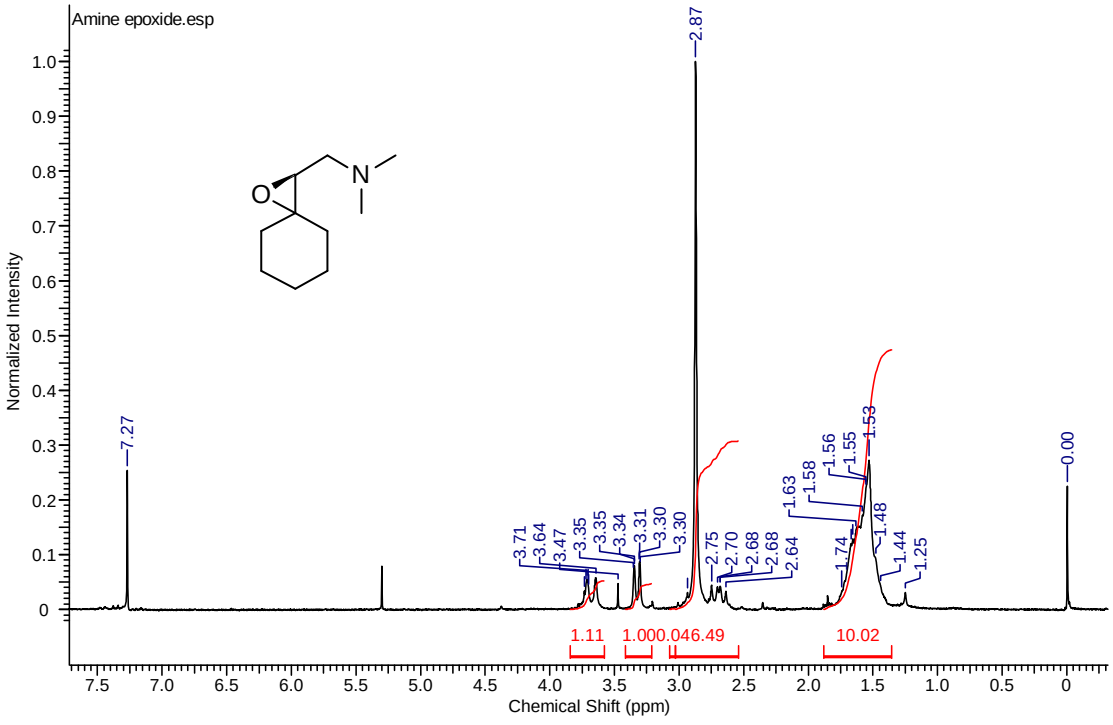
^{13}C NMR spectrum of compound **49** ($CDCl_3$ + CCl_4, 50 MHz)



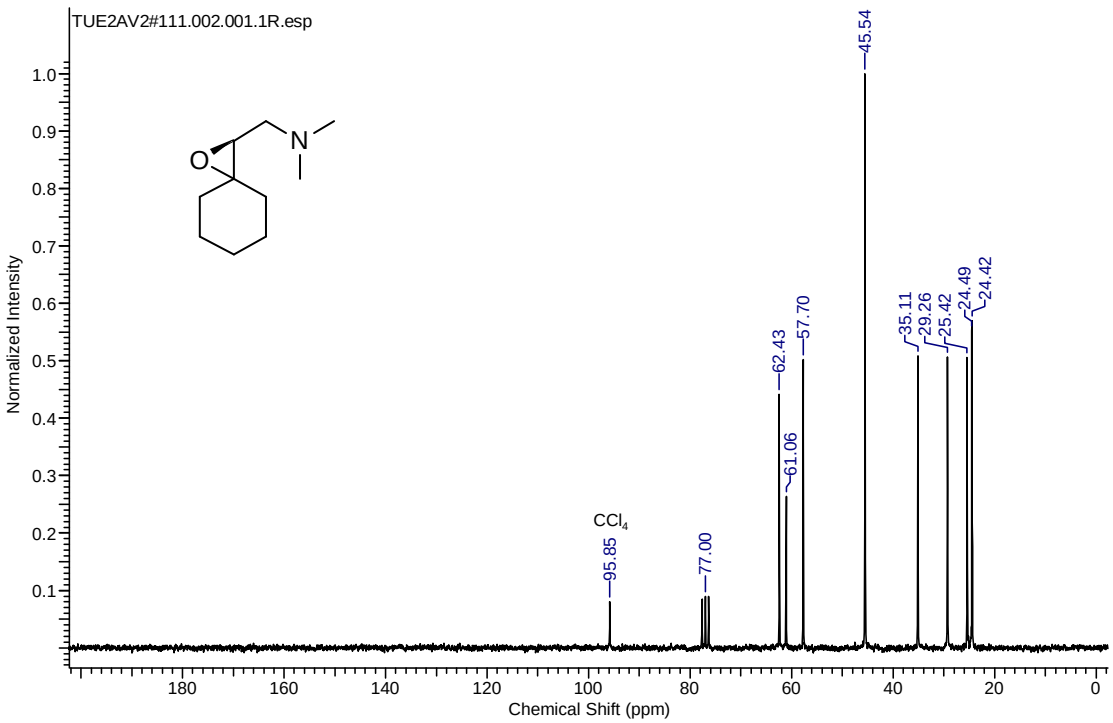
DEPT spectrum of compound **49** ($CDCl_3$ + CCl_4, 50 MHz)



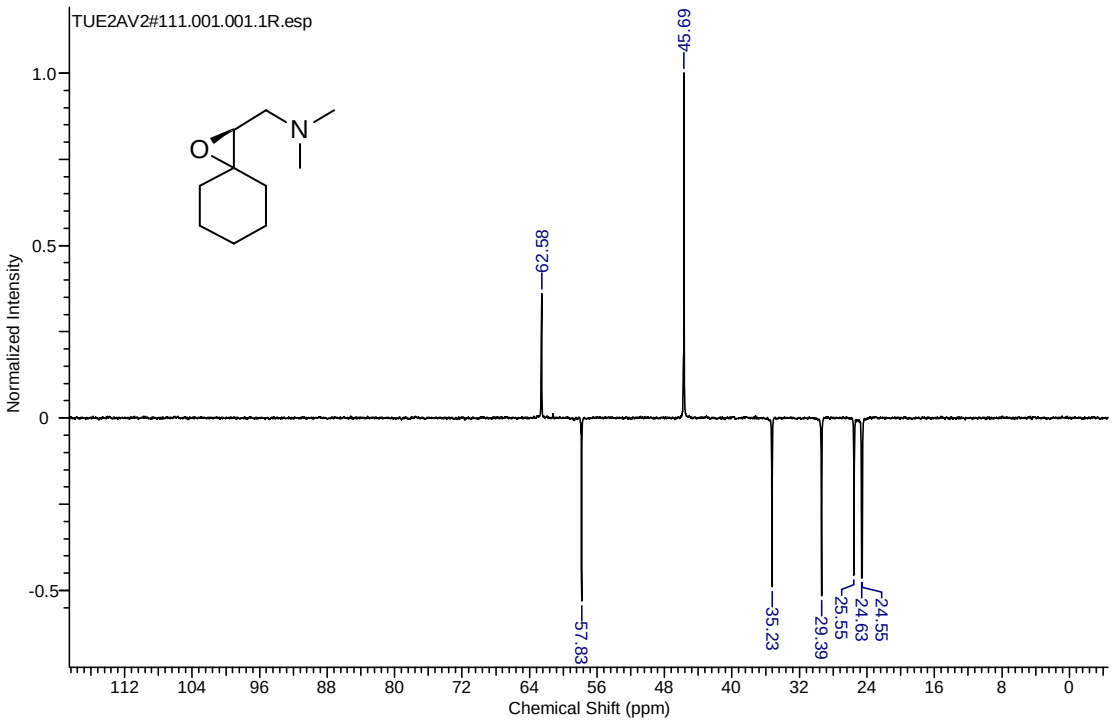
^{1}H NMR spectrum of compound **48** ($CDCl_3$+CCl_4, 200 MHz)



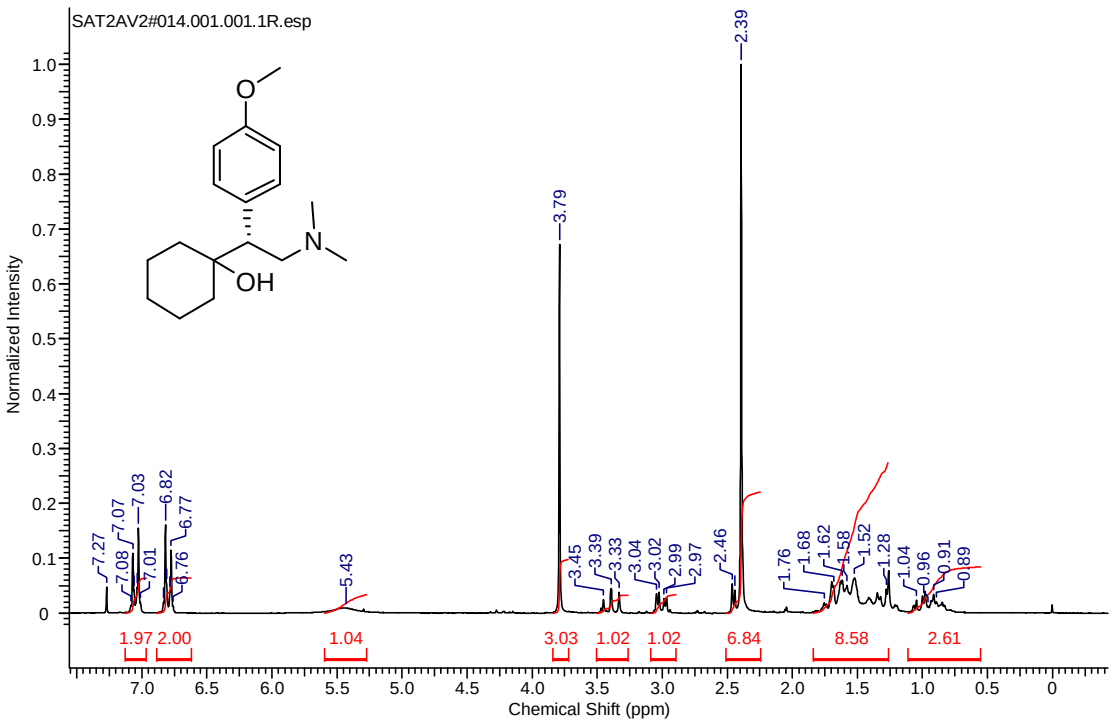
^{13}C NMR spectrum of compound **48** ($CDCl_3$ + CCl_4, 50 MHz)



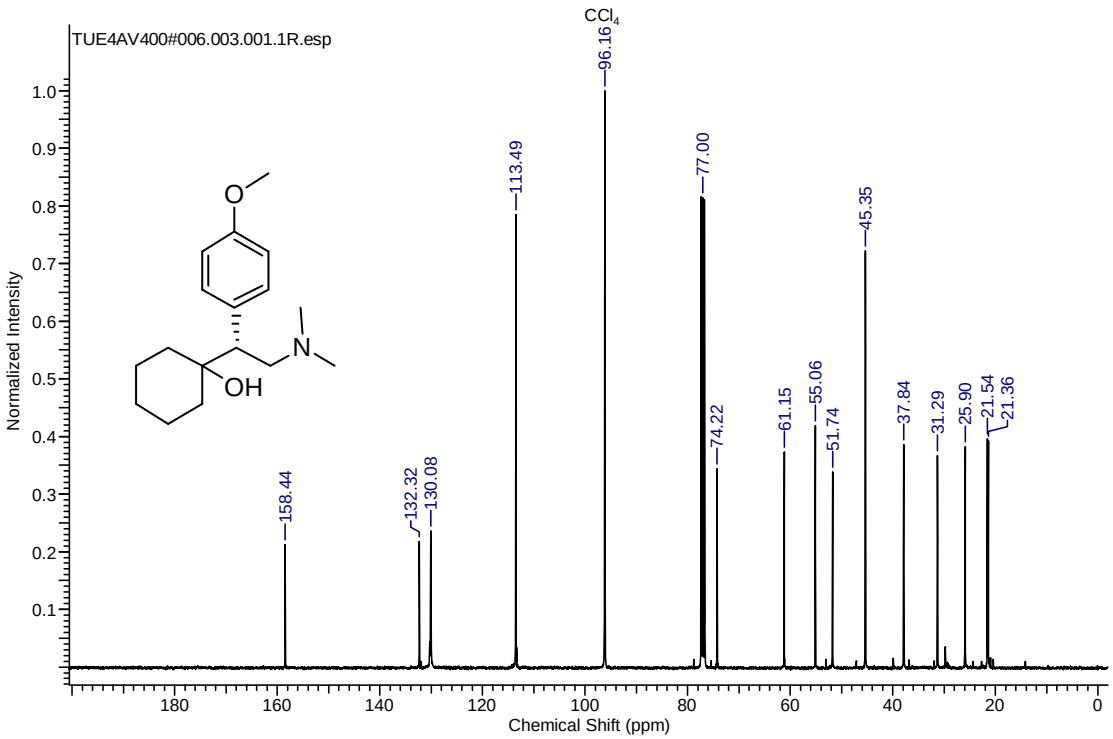
DEPT spectrum of compound **48** ($CDCl_3$ + CCl_4, 50 MHz)



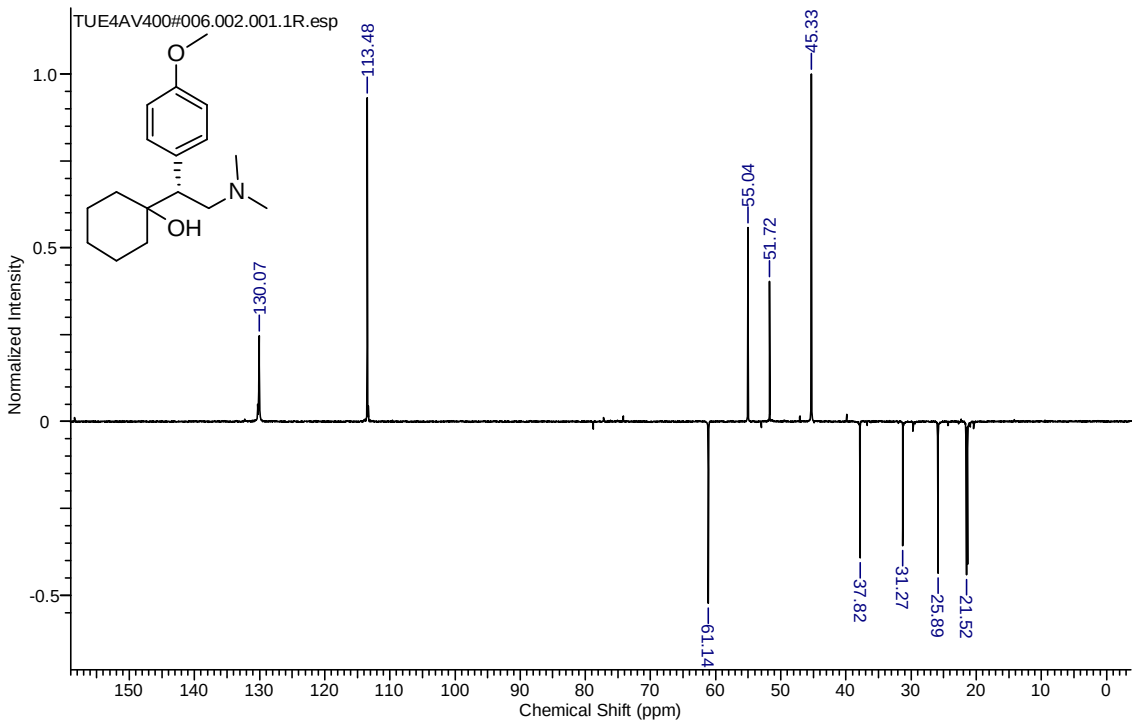
^{1}H NMR spectrum of compound **1** ($CDCl_3$ + CCl_4, 50 MHz)



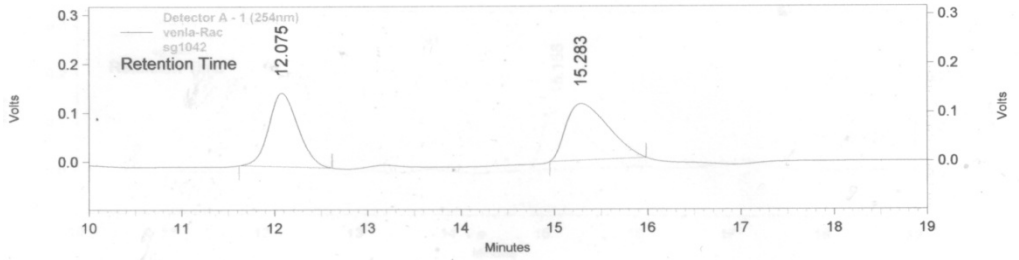
^{13}C NMR spectrum of compound **1** ($CDCl_3$ + CCl_4, 100 MHz)

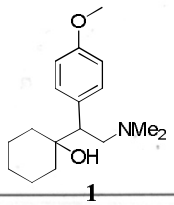


DEPT spectrum of compound **1** ($CDCl_3$+CCl_4, 50 MHz)



HPLC chromatogram of racemic venlafaxine **1**





1

Detector A - 1 (254nm)

Retention Time	C Area	Area %
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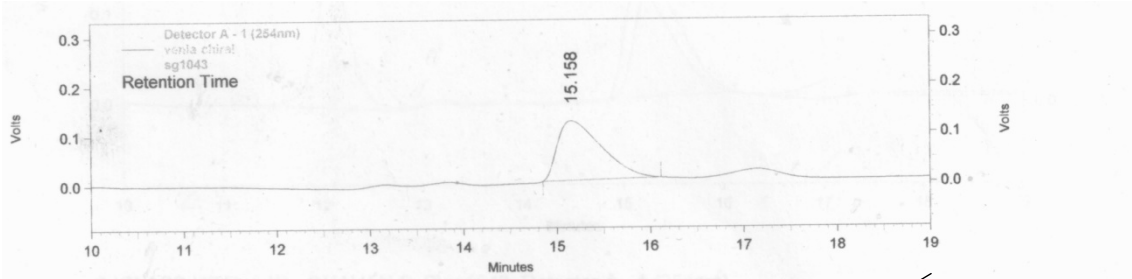
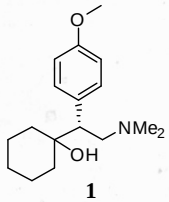
Totals	6917628	100.000

Project Leader : Dr. S. P. Chavan
Column :Kromasil 5-Amy Coat (250x4.6 mm)
Mobile Phase :EtOH: pet ether:DEA (05:95:0.5)
Wavelength :254nm
Flow Rate :0.5ml/min (25Kgf)
conc. :1 mg/1mL
Inj vol- :10 ul

Scanned HPLC chromatogram of chiral (−)-venlafaxine **1**





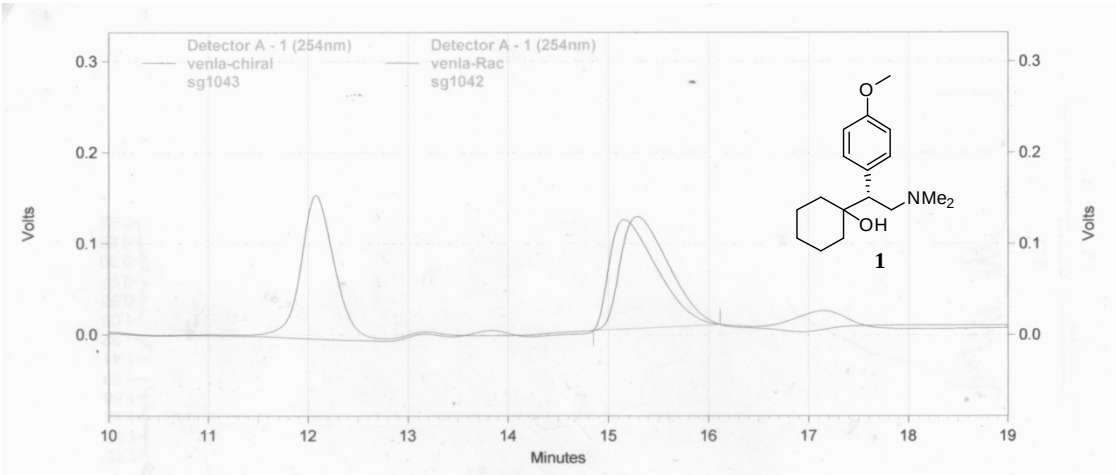
1

Detector A - 1 (254nm)

Retention Time	C Area	Area %
15.158	3923335	100.000
Totals	3923335	100.000

Project Leader : Dr. S. P. Chavan
Column :Kromasil 5-Amy Coat (250x4.6 mm)
Mobile Phase :EtOH: pet ether:DEA (05:95:0.5)
Wavelength :254nm
Flow Rate :0.5ml/min (25Kgf)
conc. :1 mg/1mL
Inj vol- :10 ul

Scanned HPLC overlapping chromatogram of both racemic venlafaxine **1** and chiral (−)-venlafaxine **1**



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Chromatogram racemic:-

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Data Name: C:\CLASS-VP\Data\Dr. CHAVAN S. P\KP 1005
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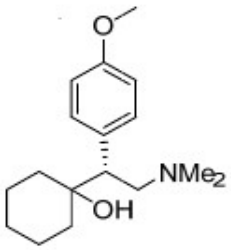
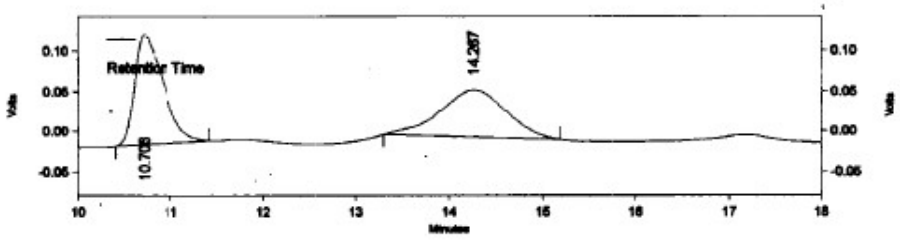
Printed: 8/8/13 6:06:06 PM
Sample Name KP-Rac





Detector A - 1 (254nm)

Retention Time	C Area	Area %
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Project Leader : Dr. S P Chavan
Column :Kromasil 5-AmyCoat (250 x4.6mm)
Mobile Phase :ETOH:PET ETHER:DEA (5:95:0.5)
Wavelength : 254 nm
Flow Rate :0.5/min
Conc. :1 mg/ 1.0 ml
Inj vol- :20ul.

Chromatogram Chiral:-

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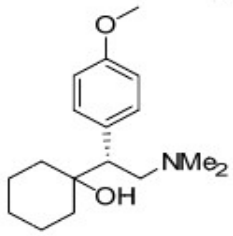
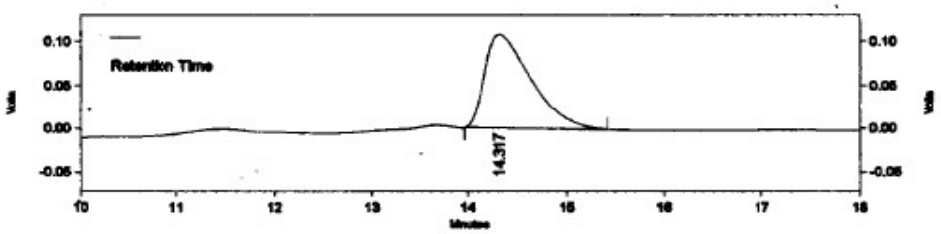
Sample Name KP-Chi





Detector A - 1 (254nm)

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Totals		
	3514022	100.000

Project Leader : Dr. S P Chavan
Column :Kromasil 5-AmyCoat (250 x4.6mm)
Mobile Phase :ETOH:PET ETHER:DEA (5:95:0.5)
Wavelength : 254 nm
Flow Rate :0.5/min
Conc. :1 mg/ 1.0 ml
Inj vol- :20ul.

Racemic GC:-

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COL: supelco beta dex120 flow: 1.5
Sample is Dissolved in DCM

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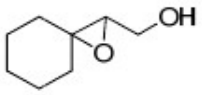
Sample Name : 2-8-13 R
Acq. Operator : BORIKAR
Location : Vial 2
Inj : 1
Inj Volume : Manually



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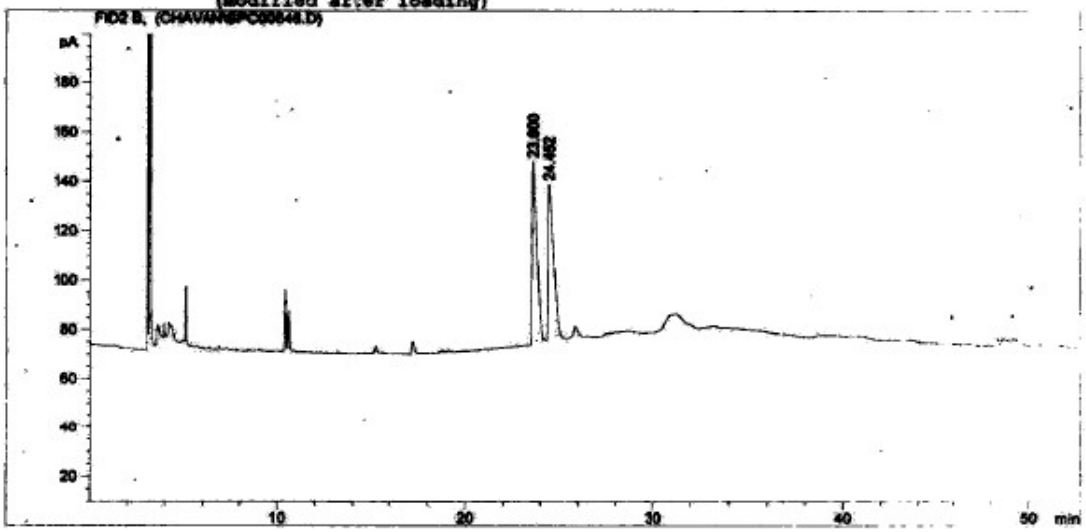

Area Percent Report

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Dilution : 1.0000

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2	24.452	PB	0.2233	1173.92395	49.39620	?

Totals : 2376.54724

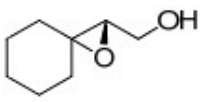
Results obtained with enhanced integrator!

GC ECD 8/12/2013 12:19:03 PM BORIKAR Page 1 of 2

Chiral GC:-

Data File C:\HPCHEM\1\DATA\CHAVAN\SPC00647.D Sample Name: 2-8-13 chi

140Deg(60min);ON 5890N Agilent DET-300 DEG INJ.220 DEG.
COL: supelco beta dex120 flow: 1.5
Sample is Diasolved in DCM



Injection Date : 8/2/2013 12:20:21 PM
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Inj Volume : Manually

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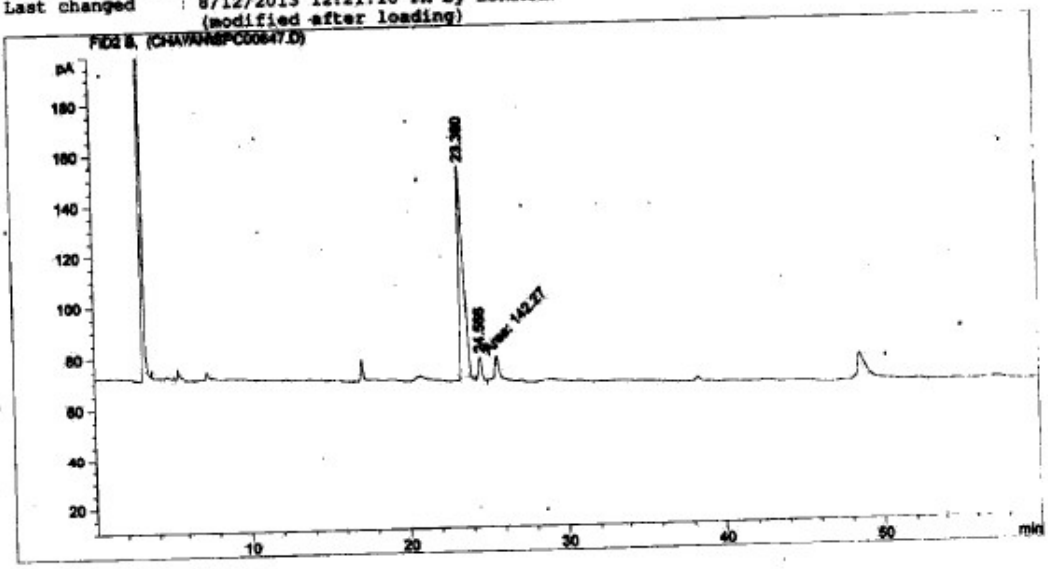

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Signal 1: FID2 B,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Area %	Name
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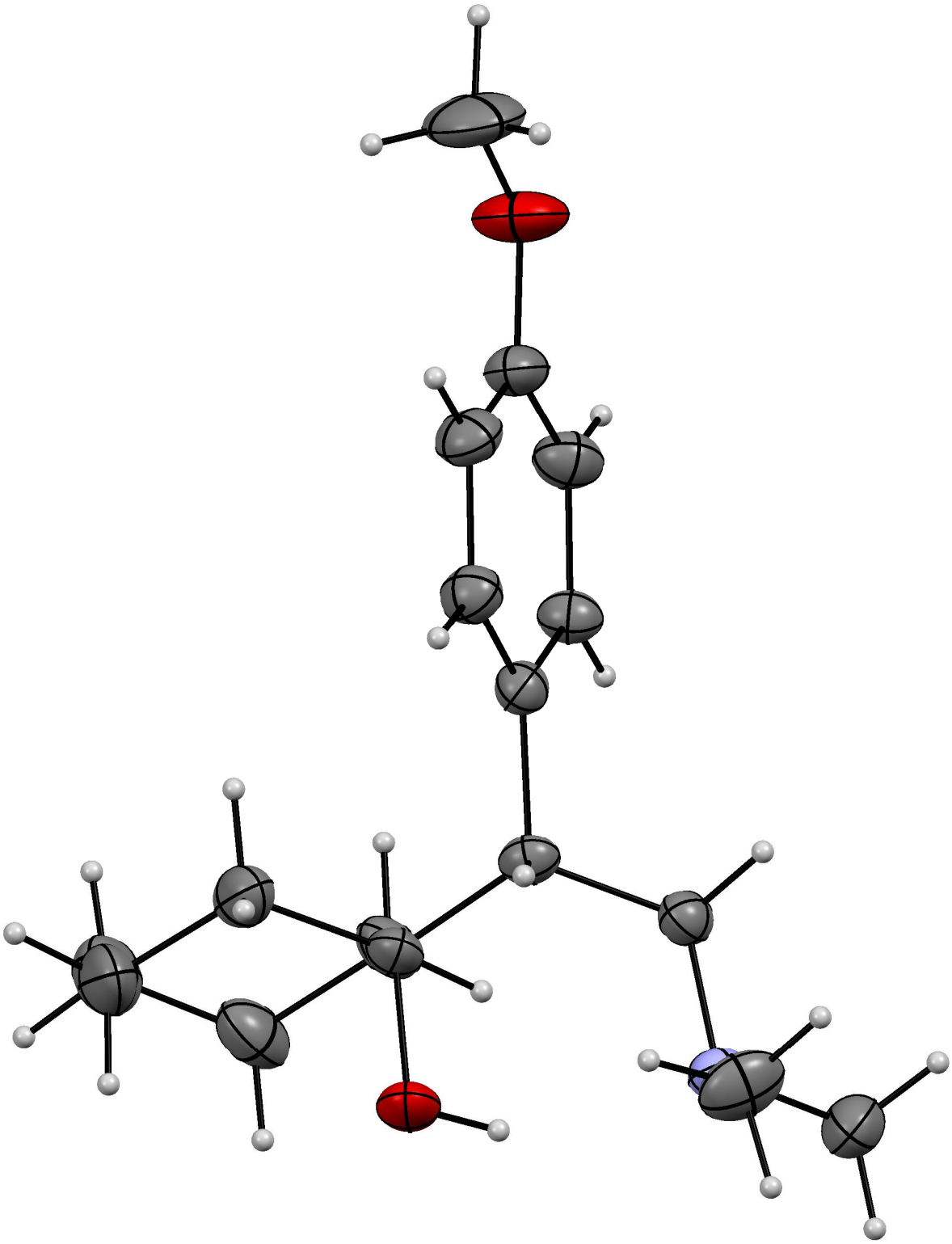
2	24.566	MM	0.2617	142.26976	8.21956	?

Totals : 1730.86803

Results obtained with enhanced integrator!

GC ECD 8/12/2013 12:21:33 PM BORIKAR



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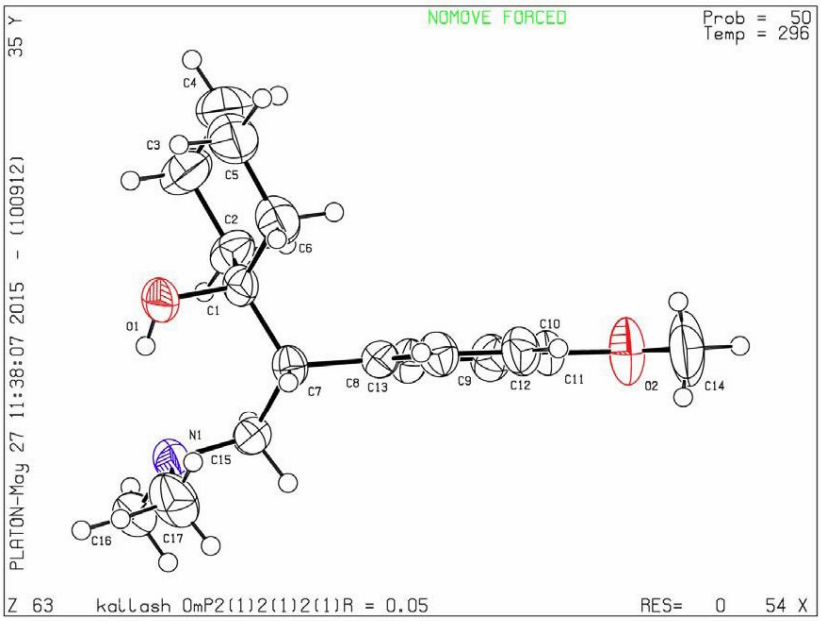

checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

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Bond precision:  C-C = 0.0038 A          Wavelength=0.71073

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Temperature:      296 K

                 Calculated                Reported
Volume           1649.0(3)                 1649.0(3)
Space group      P 21 21 21                P2(1)2(1)2(
Hall group       P 2ac 2ab                 ?
Moiety formula   C17 H27 N O2              C17 H27 N O2
Sum formula      C17 H27 N O2              C17 H27 N O2
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Dx,g cm-3        1.117                     1.117
Z                4                         4
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F000'            608.25
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Nref             2902[ 1693]               2741
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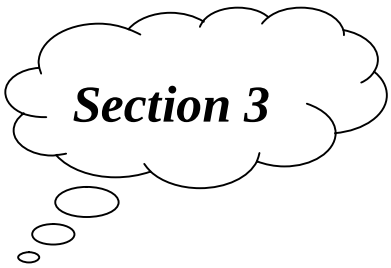
1.2.6. References

1. a) For selected examples, see a) Jinpei, Z.; Huibin, Z.; Xuezhen, H.; Wenlong, H. J. China Pharm. Univ. **1999**, *30*, 249; b) Yardley, J. P. ; Husbands, G. E. M.; Stack, G.; Butch, J.; Moywe, J. A.; Muth, E. A.; Andree, T.; Fletcher, H.; James, N. M. G.; Sielecki, A. R.; *J. Med. Chem.* **1986**, *33*, 2899; c) Husbands, G. E. M.; Yardley, J. P.; Mills, G.; Muth, E. A. US Patent No. 4, 535, 186, **1985**; d) Rathod, D. M.; Rangaraju, S. G.; Moreshwar, M.; Patel, N.; Deodhar, M.; Mandar, M.; EP 1249447, **2001**; e) Basappa; Kavitha, C. V.; Rangappa, K. S.; *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3279; f) Saigal, J.; Gupta, R.; Pandit, V. V.; Desai, A. J.; Mehta, N. V.; Rane, S. H. US Patent No. 7, 026, 513, **2006**; g) Dolitzky, B. Z.; Aronhime, J.; Wizel, S.; Nisnevich, G. A. US Patent No. 6, 924, 393, **2005**.
2. Chavan, S. P.; Kamat, S. K.; Sivadasan, L.; Balakrishnan, K.; Khobragade, D. A.; Ravindranathan, T. ; Gurjar, M. K.; Kalkote, U. R. U.S. Patent US 6, 350, 912B1, *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. U.S. Patent US 6,504,044B2, **2003** c) Chavan, S. P.; Khobragade, D. A.; Kamat, S. K.; Sivadasan, L.; Balakrishnan, K. ; Ravindranathan, T.; Gurjar, M. K. U. R. Kalkote, *Tetrahedron Lett.*. **2004**, *45*, 7291. d) Chavan, S. P.; Khobragade, D. A.; Thakkar, M. ; Kalkote, U. R. *Synthetic Commun.* **2007**, *37*, 2007.
3. Davies, H. M. L.; Ni, A. *Chem. Comm.* **2006**, 3110.
4. Bhuniya, R.; Nanda, S. *Tetrahedron Lett.* **2012**, *53*, 1990.
5. Kochetkov, K. A.; Galkina, M. A.; Galkin, O. M. *Mendeleev Commun.* **2010**, *20*, 314.
6. Chavan, S. P.; Garai, S.; Pawar, K. P. *Tetrahedron lett.* **2013**, *54*, 2137.
7. McNulty, J.; Steere, J. A.; Wolf, S. *Tetrahedron Lett.* **1998**, *39*, 8013.

Chapter 1

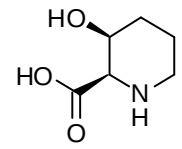
Synthetic studies towards (-)-venlafaxine and (2*R*,3*S*)-3-hydroxypipecolic acid



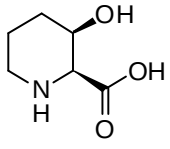
Introduction to *cis*-3-hydroxypipecolic acid and Formal synthesis of (2*R*,3*S*)-3-hydroxypipecolic acid

1.3.1. Introduction

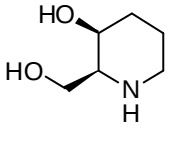
The 3-hydroxypipecolic acid is a non-proteinogenic cyclic α-amino acid. It is used in the preparation of conformationally restricted peptides and ligand binding studies. It is a constituent of many natural as well as synthetic biologically active compounds. The biological activities of piperidines vary with the position and nature of substituent on the ring. Both *cis* as well as *trans* isomers are structural units found in diverse natural products. The hydroxypipecolic acid framework is target of several synthetic efforts. Synthetic chemists are interested in this structural motif because of its presence in compounds with diverse biological activities. They are of pivotal importance to medicinal chemistry and organic synthesis.



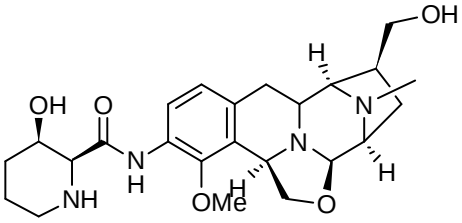
(2*R*,3*S*)-3-Hydroxypipecolic acid
1



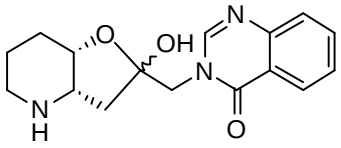
(2*S*,3*R*)-3-Hydroxypipecolic acid
***ent*-1**



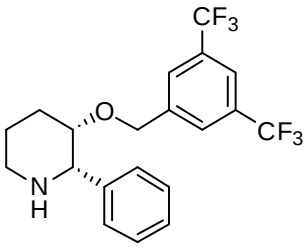
(2*S*,3*S*)-2-(Hydroxymethyl) piperidin-3-ol
2



Tetrazomine **3**



(+)-Isofebrifugine **4**



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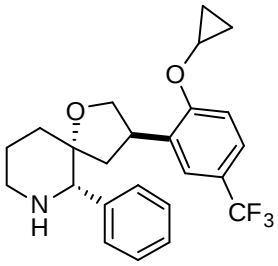


6

Figure-1

In view of their great significance, a number of synthetic strategies have been devoted to the stereoselective synthesis of these chiral piperidines. These syntheses utilized both chiral pool and asymmetric routes. In chiral pool approaches, carbohydrates and non-carbohydrate sources are used for their syntheses. Carbohydrates are ideally suited to the preparation of single isomer of piperidines.

The 3-hydroxypipecolic acid motifs are considered as homologated forms of hydroxy proline moiety or constrained analogues of serine. *cis*-Isomer of 3-hydroxypipecolic acid is present in tetrazomine **3**, which was isolated by the Yamanouchi pharmaceutical co. in 1991, whereas the *trans*-isomer is a precursor to potent α-D-mannosidase inhibitor (-)-swainsonine.

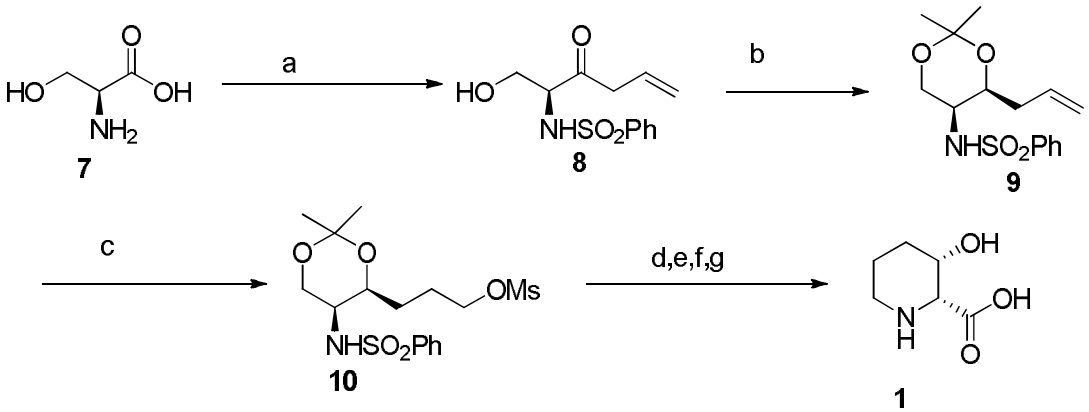
Pipecolic acid and its derivatives are found abundantly in different species of plants and animals and possess a wide range of biological activities.[1] *cis*-Derivatives of 3-substituted-pipecolic acid, *viz.* **1**[2] and *ent*-**1** (Figure 1) are a constituent of many compounds having potent biological activities[3]and used in the preparation of conformationally restricted peptides and ligand binding studies. The *cis*-isomer **1** is a structural unit of the antitumor antibiotic tetrazomine **3**,[4] while reduced analogue of **1** *viz.* **2** is component of isofebrifugine, an antimalarial agent.[5] 2-Phenylpiperidin-3-ols, which are precursors of non-peptidic NK-1 receptor antagonists such as **5**[6] and **6**,[7] have a *cis*-relationship between the phenyl and the ether group on the piperidine ring, and are important for high-affinity binding to the human NK-1 receptor (Figure 1).[8]

1.3.2 Literature review

The variety of applications of 3-hydroxypipecolic acid and its derivatives have attracted organic synthetic community towards its synthesis. The reported methods for the synthesis of **1** and **2** can be broadly classified in to two types, (a) Chiral pool approach and (b) chirality induction approach. In literature many syntheses are reported. Some of the important syntheses in each class have been described here.

(a) Chiral pool approach

Rapoport's approach[9]

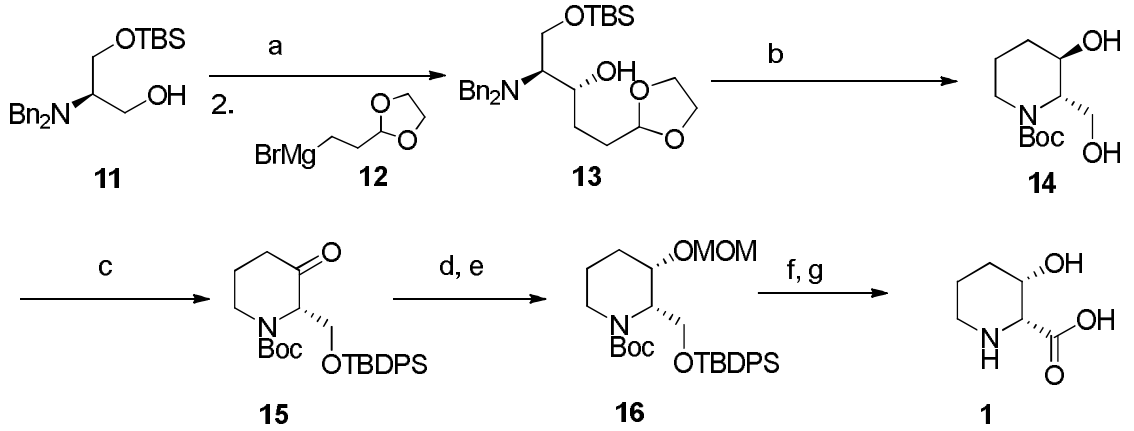


Scheme 1. *Reagents and conditions* a) i) $PhSO_2Cl$, K_2CO_3; ii) *n*-BuLi, allylmagnesium bromide, THF; b) i) $NaBH_4$, ii) 2,2-DMP; c) i) BH_3·DMS, THF, NaOH, H_2O_2, ii) MsCl, TEA, DCM; d) K_2CO_3, MeOH; e) HCl/MeOH; f) Pt, O_2, H_2O/EtOH; g) Na, NH_3, THF.

Raporort *et al.* (Scheme 1) carried out alkylation of acid group in L-serine to its ketone and explored the alkylated product for the synthesis of *β*-hydroxy-*α*-amino acids. The amine group in L-serine **7** was protected with sulphonyl chloride to obtain a sulphonamide, and the resultant acid was subjected to the nucleophilic reaction with Grignard reagent derived from allyl bromide in the presence of *n*-butyl lithium to provide the keto-compound **8**. This keto compound **8** on reduction followed by 1,3-diol protection as its acetonide afforded separable diastereomers and major diastereomer was compound **9**. Compound **9** was treated with borane followed hydrogen peroxide to afford primary hydroxy group which was subsequently mesylated to provide mesylate **10.** Mesylate **10** was cyclized under basic condition followed by acidification, oxidation and removal of sulphonyl group to afford *cis*-(2*R*,3*S*)-3-hydroxypipecolic acid **1** in good yield.

Zhu's approach[10]

Zhu *et al.* reported synthesis of (2*R*,3*S*)-3-hydroxypipecolic acid **1** using serine derived amino alcohol **11** (Scheme 2). Chiral amino alcohol **11** was oxidized to aldehyde and subjected to Grignard reaction with reagent **12** to provide homologated amino alcohol **13**



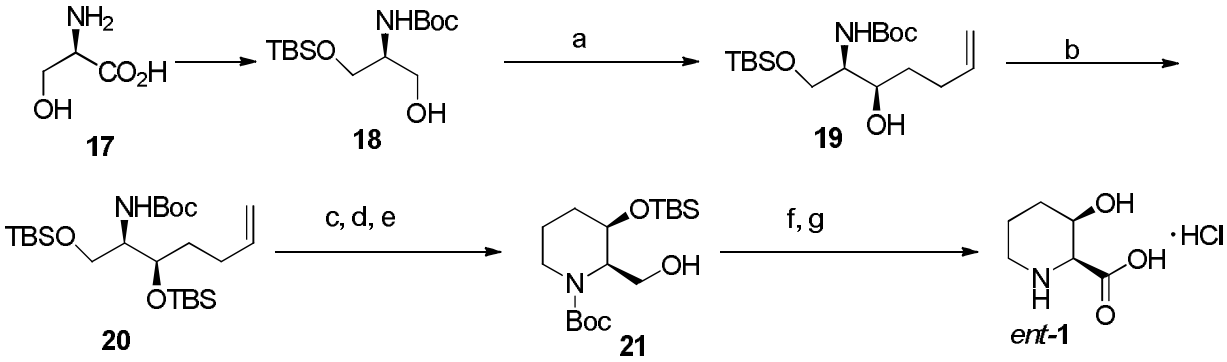
Scheme 2. *Reagents and conditions* a) i) Swern oxidation; ii) **12**, THF; b) H_2, Pd/C, 3N HCl, $(Boc)_2O$, 1N NaOH; c) i) TBDPSCl, Im., DCM, ii) Swern oxidation; d) $NaBH_4$, MeOH, 88%; e) MOMCl, DIPEA, 92%; f) HF, Py; g) i) CrO_3/H_2SO_4 ii) 6N HCl.

as a major constituent. Protected compound **13** was hydrogenated under acidic condition and subsequently Boc protected to obtain diol **14**. The selective TBDPS protection of primary alcohol in diol **14** was carried out using TBDPSCl and secondary alcohol was oxidized to ketone. Again this ketone **15** was reduced with $NaBH_4$ in a highly stereoselective manner

which afforded a *cis* 2,3-disubstituted piperidine. Secondary alcohol was MOM protected followed by TBDPS deprotection. The resulting free primary alcohol was oxidized to carboxylic acid and subsequent MOM deprotection provided 3-hydroxypipecolic acid **1**.

Datta's approach[11]

Datta *et al*. reported synthesis of **1** from D-serine **17** (Scheme 3), by utilizing Grignard reaction on aldehyde in a diastereoselective manner (Scheme 3). They prepared alcohol **18** from **17** by known procedure. Alcohol **18** on Swern oxidation followed by reaction with Grignard reagent (homoallylmagnesium bromide) provided alcohol **19**. The subsequent protection of alcohol **19** with TBS provided compound **20**. Di-OTBS compound **20** was subjected to dihydroxylation followed by cleavage of diol using $NaIO_4$ followed by reduction and deprotection to furnish piperidine alcohol **21**. Piperidine derivative **21** upon oxidation and deprotection resulted in to the formation of hydrochloride salt of **(**2*S*,3*R*)-3-hydroxypipecolic acid *ent*-**1**.

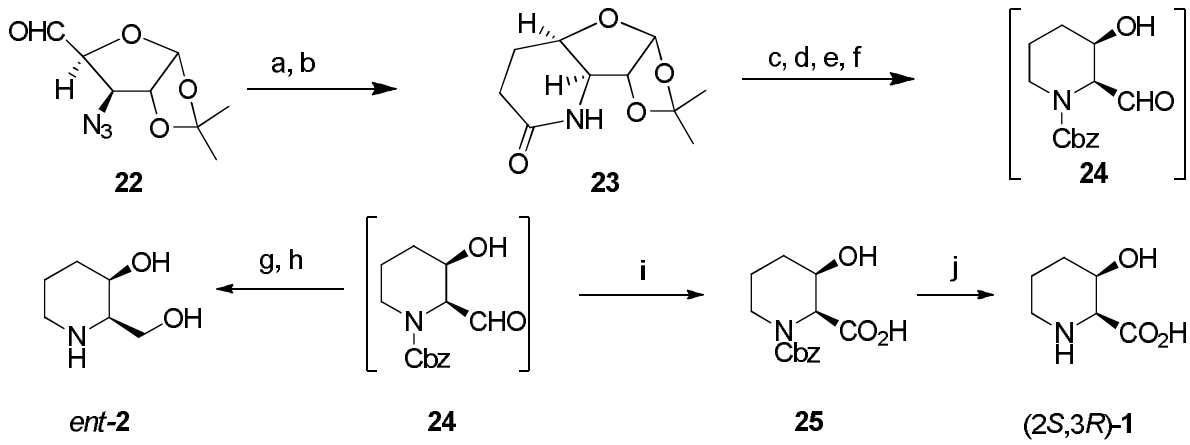


Scheme 3. *Reagents and conditions* a) i) Swern oxidation, ii) Homoallylmagnesium bromide; b) TBSCl, Im, DCM; c) OsO_4, NMO then $NaIO_4$; d) Et_3SiH, $BF_3.OEt_2$; e) CSA, MeOH; f) $RuCl_3$ (Cat.), $NaIO_4$; g) 50% Aq. HCl.

Dhavale's approach[12]

Dhavale *et al*. utilized D-glucose as the starting material for the synthesis of *ent*-**1** and *ent*-**2** (Scheme 4). The azido aldehyde **22** obtained from D-glucose by reported method was subjected to Wittig reaction followed by azide reduction to furnish amide **23**. Amide **23** was reduced using LAH followed by Cbz protection, acetonide deprotection and cleavage to pro-

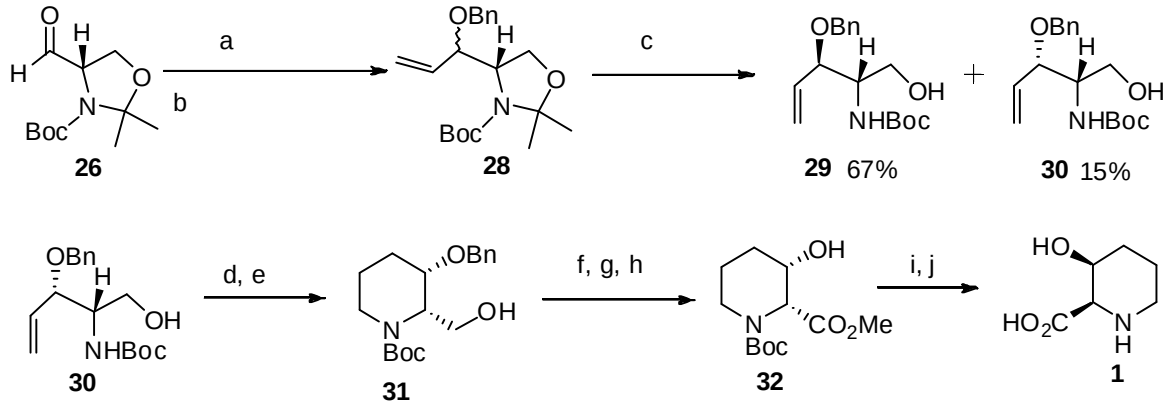
vide aldehyde **24**. Aldehyde **24** was converted to 3-hydroxypipecolic acid *ent*-**1** as well as *ent*-**2** in two steps each.



Scheme 4. *Reagents and conditions* a) $Ph_3P{=}CHCO_2Et$, b) H_2, Pd/C, c) LAH, THF; d) CbzCl, $NaHCO_3$; e) TFA, H_2O f) $NaIO_4$, acetone : H_2O g) $NaBH_4$ h) H_2, Pd/C, i) $NaClO_2$, 30%, H_2O_2, CH_3CN:H_2O; j) H_2, Pd/C, MeOH.

Chiou's approach[13]

Chiou *et al.* reported *cis* and *trans* 3-hydroxypipecolic acid syntheses from Garner's aldehyde **26** using diastereoselective Grignard reaction and Rh catalyzed cyclohydrocarbony

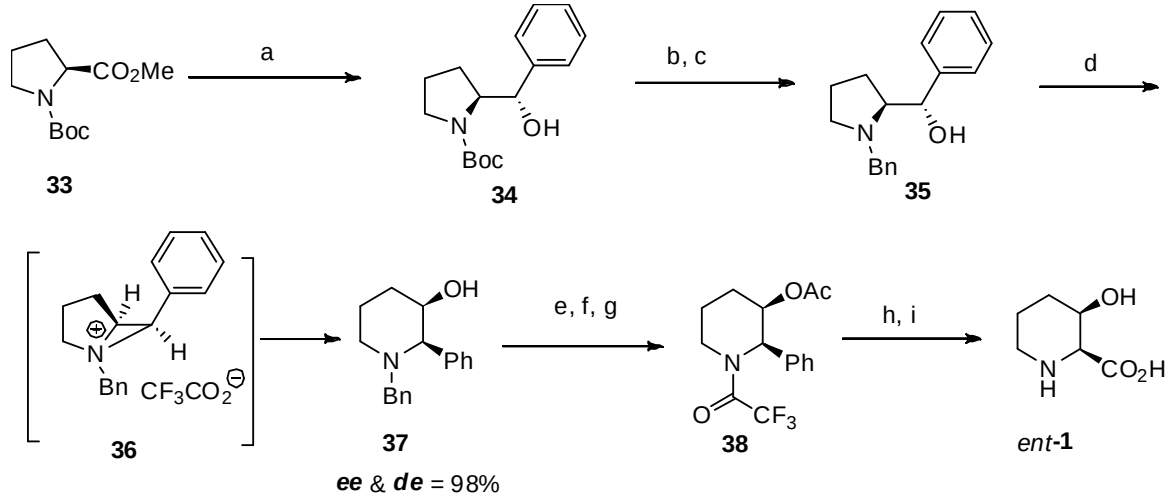


Scheme 5. *Reagents and conditions* a) Vinylmagnesium bromide **27**, THF; b) BnBr, NaH, 18-crown-6-ether; c) PTSA, MeOH; d) $Rh(acac)(CO)_2$,BIPHEPHOS, CO, MeOH; e) Et_3SiH, BF_3 .OEt_2, CH_2Cl_2; f) 1. TEMPO, KBr, NaOCl, $NaHCO_3$, acetone; g) CH_2N_2,; h) Pd/C, H_2; i) 6 N HCl; j) propylene epoxide.

lation (Scheme 5) as the key steps. Vinylmagnesium bromide **27** on treatment with aldehyde **26** provided diastereomeric mixture of alcohol. This mixture of diastereomers was directly subjected for benzyl protection with benzyl bromide to afford benzyl protected alcohol **28**. This benzyl ether **28** was treated with mild acid to carry out deprotection to provide separable mixture of alcohols **29** and **30.** Cyclohydrocarbonylation and subsequent reduction of alcohol **30** afforded piperidine alcohol **31**, which on oxidation and deprotection provided *cis* 3-hydroxypipecolic acid **1**.

Cossy's approach[14]

Cossy *et al.* reported synthesis of 3-hydroxypipecolic acid from proline ester **33** where they used one-pot DIBAL-H reduction / diastereoselective Grignard addition sequence and ring expansion as the key steps (Scheme 6). *N*-Boc prolinate **33** on reduction followed by Grignard reaction afforded compound **34** with excellent diastereoselectivity (99:1). This compound **34** was subjected for ring expansion after changing protecting group from boc to



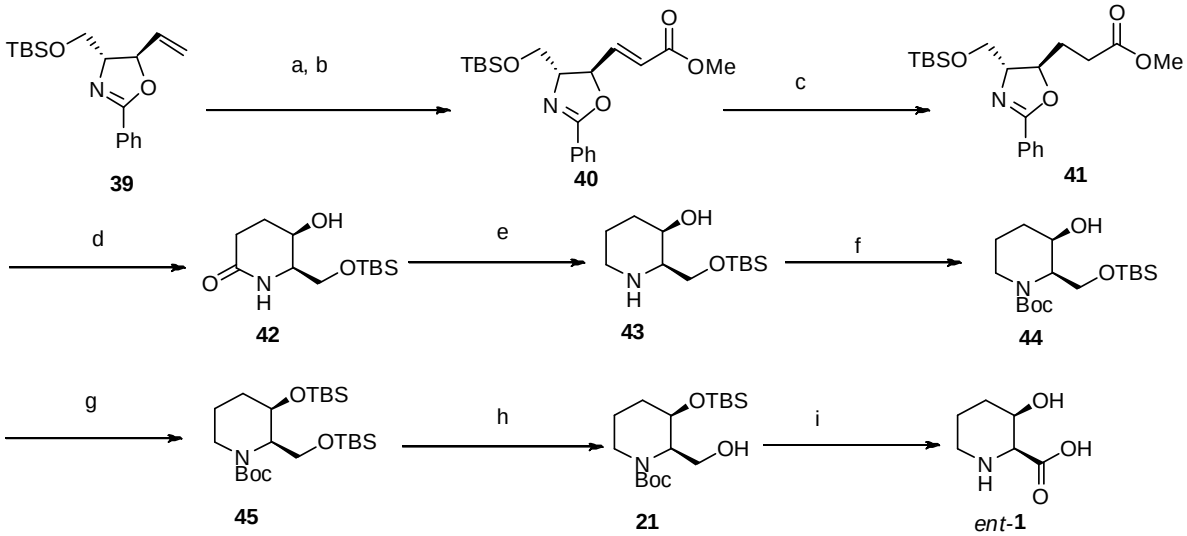
Scheme 6. *Reagents and conditions* a) DIBAL-H, CH_2Cl_2, -78 °C, 30 min. then PhMgBr, -78 °C, rt, 57%; b) TFA, CH_2Cl_2, 87%; c) BnCl, K_2CO_3, CH_2Cl_2, reflux, 73%; d) TFAA, TEA then NaOH, quantitative; e) Ac_2O, TEA, DMAP, 98%; f) H_2, $Pd(OH)_2$, EtOH, H-Cube, 77%; g) TFAA, TEA, DMAP, 98%; h) $RuCl_3$, $NaIO_4$; i) K_2CO_3, MeOH, 67%.

benzyl which provided piperidine compound **37**. The free hydroxyl group in **37** was acetylated and, after hydrogenation, a trifluoroamidation was carried out to obtain compound **38.** The compound **38** was subjected for chopping of phenyl ring under strong oxidizing condi-

tions with $RuCl_3 \cdot 3H_2O/NaIO_4$ followed by hydrolysis to provide the desired 3-hydroxypipecolic acid *ent*-**1** (Scheme 6).

Ham's approach[15]

A concise, stereocontrolled synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid **1** from oxazoline **39** is reported by Ham *et al.* The synthesis of *ent*-**1** began with chopping of oxazoline **39** by ozonolysis to provide the required aldehyde, which on treatment with trimethylphosphonoacetate provided *α*,*β*-unsaturated methyl ester **40** (Scheme 7). Chemoselective reduction of unsaturated double bond in this compound **40** with L-Selectride afforded saturated methyl ester **41**. Hydrogenation of **41**, followed by reduction with $BH_3 \cdot DMS$ provided

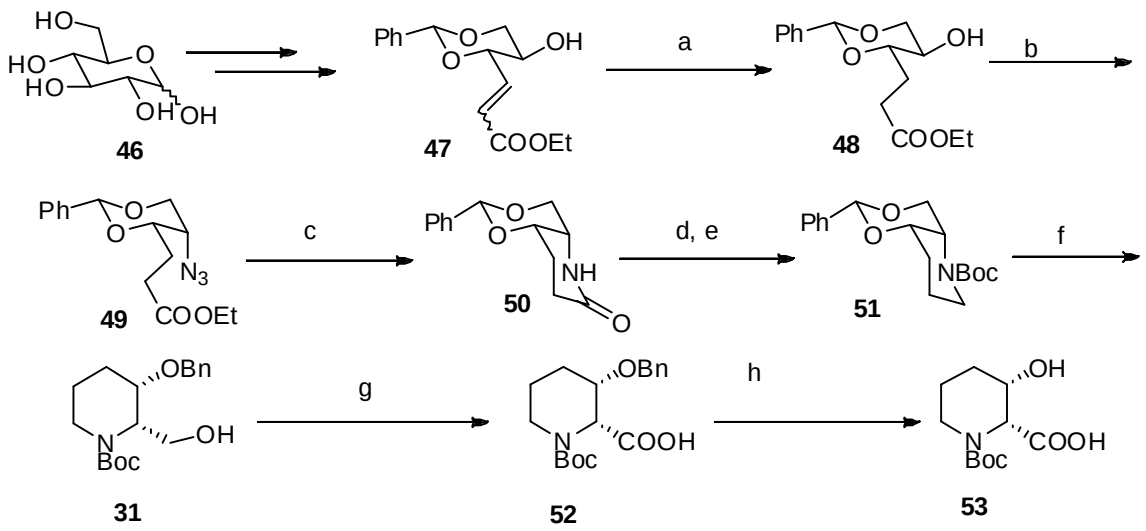


Scheme 7. *Reagents and conditions* a) O_3, MeOH, -78 °C then DMS; b) $(MeO)_2POCH_2CO_2Me$, LiCl, DIPEA, CH_3CN, 95% for 2 steps; c) L-Selectride, t-BuOH, THF, -78 °C, 86%; d) $Pd(OH)_2/C$, H_2, MeOH:AcOH, 80%; e) $BH_3.SMe_2$, MeOH:THF, 83%; f) $(Boc)_2O$, TEA, CH_2Cl_2, 91%; g) TBSCl, Im, DMF, 93%; h) AcOH:H_2O:THF, 94%; i) *Ref.* 11.

cyclized piperidine **43**. The compound **43** was Boc protected with Boc anhydride and secondary alcohol was protected with TBSCl to obtain disilyl *N*-Boc compound **45**, which was subjected for monoTBS deprotection with acetic acid to furnish the free primary alcohol **21** in excellent yield. The primary hydroxyl group on oxidation with $RuCl_3$ and $NaIO_4$ followed by deprotection of the secondary silyl ether provided the corresponding carboxylic acid; Boc group was removed by acidic hydrolysis of the carbamate to furnish the desired (2*S*,3*R*)-3-hydroxypipecolic acid *ent*-**1**.

Baskaran's approach[16]

Baskaran and co-workers described a stereoselective synthesis of *N*-Boc-protected *cis*-(2*R*,3*S*)-3-hydroxypipecolic acid **53**, commencing with D-glucose **46** employing a highly regioselective reductive cleavage of benzylidene acetal **51** as the key step (Scheme 8). D-glucose **46** was readily converted to the corresponding azido ester **49** in a few steps by known method. Lactam **50** was obtained by catalytic hydrogenation of azido ester **49** over Pd/C followed by *in situ* cyclization. The amide in **50** was reduced to amine by $LiAlH_4$ followed by *N*-Boc protection of the amine in the reduced product with Boc anhydride to furnish corresponding *N*-Boc-protected benzylidene acetal **51**. The key step of regioselective reductive cleavage of benzylidene acetal **51** was carried out using $EtAlCl_2/Et_3SiH$ to afford the desired compound **31** in good yield with very high regioselectivity. The oxidation of free primary alcohol followed by catalytic hydrogenation with $Pd(OH)_2$ furnished the corresponding *N*-Boc-protected *cis*-(2*R*,3*S*)-3-hydroxypipecolic acid **53**.

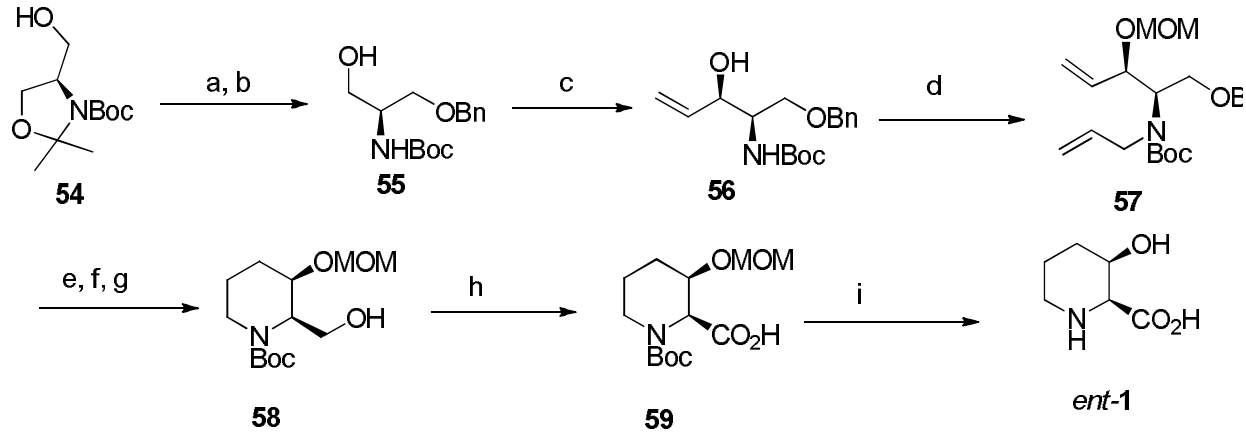


Scheme 8. *Reagents and conditions* a) H_2, Pd/C, EtOH, 95%; b) DPPA, DEAD, Ph_3P, THF, 71%; c) H_2, Pd/C, EtOH, 95%; d) $LiAlH_4$, Et_2O, 88%; e) Boc_2O, CH_3CN, 88%; f) $EtAlCl_2$, Et_3SiH, -78°C, 99%; g) $RuCl_3$, $NaIO_4$, $CH_3CN:CCl_4:H_2O$, 64%; h) H_2, $Pd(OH)_2$, EtOH, 70%.

Chattopadhyay's approach[17]

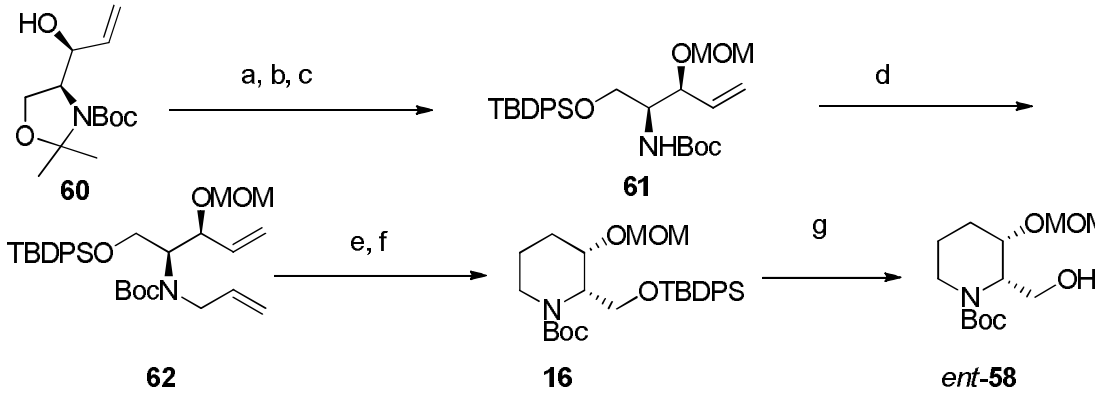
Chattopadhyay *et al.* reported stereoselective synthesis of *cis*-(2*S*,3*R*)-3-hydroxypipecolic acid **1** and two enantiomeric *cis*-2-hydroxymethyl-3-hydroxypiperidine derivatives from a common precursor, which described the use of stereocontrolled vinylation of a chiral aldehyde and ring-closing metathesis as the key steps. Synthesis started from the

serinol derivative **54** (Scheme 9), which was benzyl protected followed by the oxazolidine ring deprotection and oxidation to furnish the aldehyde, which was treated with vinylmagnesium bromide in one-pot wherein the requisite *syn*-allyl alcohol **56** was obtained as the major isomer (dr: 87:13 by HPLC). The free secondary hydroxyl group was then protected with MOM-Cl followed by *N*-allylation with allyl bromide and separation to furnish pure *syn*-isomer **57**. Cyclization by ring closing metathesis of **57** using Grubbs' Ist generation catalyst and subsquent debenzylation and concomitant reduction of the double bond provided the primary alcohol **58** which on oxidation furnished protected acid **59**. This **59** on acidic deprotection of *N*-Boc and *O*-MOM groups then yielded the 3-hydroxypipecolic acid *ent*-**1.**



Scheme 9. *Reagents and conditions* a) NaH, BnBr, 83%; b) aq 5% HCl, MeOH, 86%; c) Swern oxidation, then vinylmagnesium bomide, 62%; d) MOMCl, DIPEA, CH_2Cl_2, 82%; e).NaH, allyl bromide, DMF, 90%; f) Grubbs' Ist gen. cat., CH_2Cl_2, 84%; g) Pd/C-H_2, EtOAc, 94%; h) DMP, then $NaClO_2$; 56%; i) aq. 6 N HCl, 90 °C, 74%.

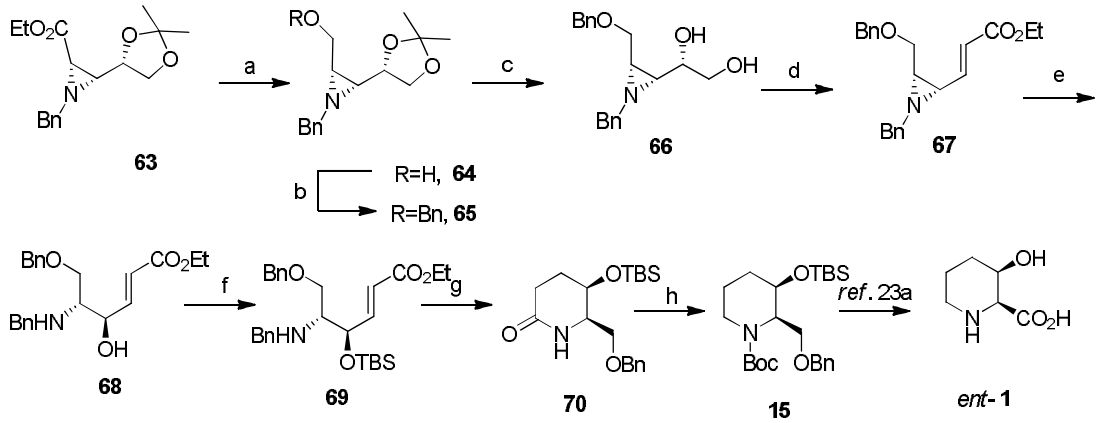
L-Serine, was transformed into the piperidine *ent*-**58** in a seven step reaction sequence from allyl alcohol **60.** The allyl alcohol **60** was converted to its corresponding MOM-ether followed by oxazolidine ring opening to obtain primary alcohol then its subsequent conversion to the silyl ether **61.** The *N*-allylation of silyl ether **61** into the *N*-tethered diene **62** followed by a subsequent RCM and saturation of the double bond under hydrogenation furnished compound **16** which on deprotection of the *O*-silyl group provided the desired piperidine *ent*-**58** (Scheme 10).



Scheme 10. *Reagents and conditions* a) MOMCl, DIPEA, 80%; b) PTSA, MeOH, 78%; c) TBDPSCl, Et_3N, 82%; d) NaH, allyl bromide, DMF, 78%; e) Grubbs' Ist gen. cat. CH_2Cl_2, 83%; f) Pd/C-H_2, EtOAc, 85%; g) TBAF, THF, 82%.

Chavan's approach[18]

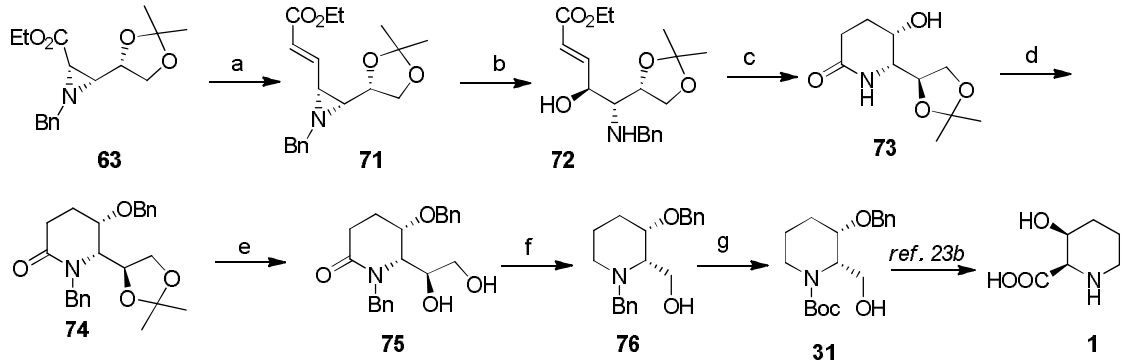
Chavan *et al.* reported synthesis of both the antipdoes of *cis*-3-hydroxypipecolic acid **1** using *cis* aziridine-2-carboxylate **63** which was prepared from D-mannitol diacetonide using known literature procedure (Scheme 11).[19] The *cis* aziridine-2-carboxylate **63** was reduced with



Scheme 11. *Reagents and conditions* (a) LAH, THF, 0 °C, 1h, 90%; (b) BnBr, NaH, cat. TBAI, DMF, 95%; (c) PTSA, CH_3OH, 85%; (d) 1) $NaIO_4$, $(CH_3)_2CO$:H_2O (2:1); 2) Ph_3PCHCO_2Et, cat. $PhCO_2H$, PhMe, reflux, 85% (over two steps); (e) TFA, CH_3CN:H_2O (9:1), 85%; (f) TBSCl, Im, cat. DMAP, CH_2Cl_2, reflux, 90%; (g) H_2, 10% $Pd(OH)_2$/C, EtOH, 88%; (h) 1) BH_3·DMS, THF; 2) $(Boc)_2O$, CH_2Cl_2, Et_3N, 80% (over two steps); i) *Ref.-23a*

LAH to furnish alcohol **64**. The hydroxyl group of **64** was benzyl protected by using benzyl bromide and NaH in DMF to compound **65** in 95% yield. The acetonide group in compound

65 was deprotected using PTSA in methanol to provide diol **66** in 85% yield. Diol **66** was subjected for cleavage using sodium metaperiodate wich provided aldehyde. The crude aldehyde obtained after cleavage was used as such for 2-carbon Witting homologation with Ph_3PCHCO_2Et in the presence of cat. benzoic acid under reflux (a method used for the formation of *E* as major isomer)[20] to furnish homologated product **67** in 85% yield over two steps. Thus obtained α,β-unsaturated ester aziridine **67** was subjected to regio and stereoselective aziridine ring opening with water as the nucleophile in acidic conditions[21] (TFA, 2 eq.) to obtain vicinal aminol **68.** The hydroxyl group of aminol **68** was TBS protected using TBSCl, imidazole and cat. DMAP under reflux in dichloromethane to furnish silyl ether compound **69** with 90% yield. Compound **69** on hydrogenation using 10% $Pd(OH)_2$[22] underwent one pot double bond reduction, selective *N*-debenzylation and cyclization to furnish lactam **70** in 88% yield with requisite piperidine skeleton. Further, amide group in lactam **70** was reduced to amine using borane-dimethyl sulfide complex to obtain crude amine which *N*-Boc protected to get *N*-Boc derivative using Boc-anhydride and triethylamine as the base to give intermediate **15** in 80% yield. Synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid *ent*-**1** in three steps in 73% yield from intermediate **15** is well documented in the literature.[23a] Thus, this constitutes the formal synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid *ent*-**1.**



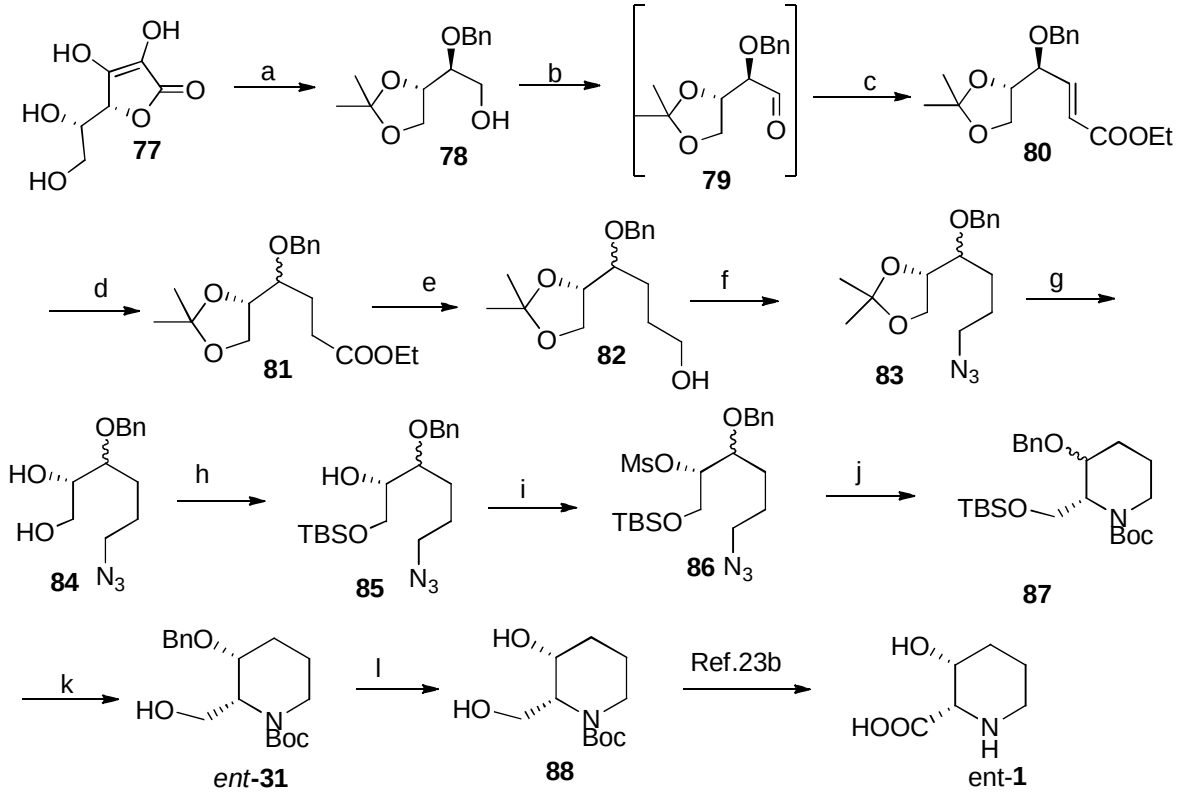
Scheme 12. *Reagents and conditions***:** (a) 1) DIBAL-H, CH_2Cl_2, –78 °C; 2) Ph_3PCHCO_2Et, cat. $PhCO_2H$, PhMe, reflux, 82%, (over two steps); (b) TFA, CH_3CN:H_2O, (9:1), 75%; (c) 10% Pd/C, HCO_2NH_4, MeOH, 60 °C, 90%; (d) BnBr, NaH, cat. TBAI, DMF, 85%; (e) 80% aq. AcOH; (f) 1) $NaIO_4$, $(CH_3)_2CO$:H_2O, (2:1); 2) BH_3·DMS, THF, 65%, over 3 steps; (g) 1) H_2, 10 % $Pd(OH)_2$/C, EtOH; 2) $(Boc)_2O$, Et_3N, CH_2Cl_2, 80% over 2 steps; h) *Ref.*23b.

The other enantiomer (2*R*,3*S*)-3-hydroxypipecolic acid **1** (scheme 12) was also synthesiszed from the same common synthetic precursor *viz.* c*is*-aziridine-2-ester **63** which on ester reduction using DIBAL-H followed by 2-carbon Wittig homologation to provide *α,β*-unsaturated aziridine-ester **71.** Aziridine ester **71** on treatment with trifluoroacetic acid in CH_3CN-H_2O[18] underwent regio and stereoselective aziridine ring opening reaction to provide *δ*-hydroxy,*γ*-amino,*α,β*-unsaturated ester **72** with desired stereochemistry**.** Compound **72** under transfer hydrogenation condition[24] using cat. Pd/C (10%) and ammonium formate underwent one pot double bond reduction, *N*-debenzylation and cyclization to afford 3-hydroxy substituted *δ*-lactam **73** in 90% yield. The free hydroxyl group in **73** was benzyl protected followed by acetonide group deprotection to ofbtain diol **75**. This diol 75 was chopped and reduced to afford alcohol **76**. The selective *N*-debnzylation and subsequent *N*-boc protection provided key intermediate **31** from this synthesis of **1** is reported in literature.[23b]

Chavan's approach [25]

Chavan *et al.* reported formal synthesis of both *cis* and *trans* of 3-hdroxypipecolic acid from L-ascorbic acid **77**. Ascorbic acid **77** was transformed to alcohol **78** by known protocol[26]. Alcohol **78** was oxidised to aldehyde **79** which was used as such for Wittig homologation to furnish *α,β*- unsaturated ester **80**. Exclusive *trans* olefin **80** was obtained using Wittig Horner reaction conditions.[27] Under hydrogenation double bond of *α,β*- unsaturated ester **80** was reduced using cat. $Pd(OH)_2$ and $HCOONH_4$ in methanol under reflux to furnish ester **81** in 92% yield. The epimerization of the allylic center observed in this reaction was exploited to synthesize both the isomers of 3-hydroxy pipecolic acid. The inseparable diastereomeric mixture of **8** was carried foeward for further steps andseparated them at the later stage. Thus, ester in **81** was reduced by using LiBr and $NaBH_4$ to furnish alcohol **82** in 88% yield.[28] Alcohol **82** was mesylated which was followed by the displacement of mesylate with azide using NaN_3 in DMF at 80 ^oC to provide azide **83** in 70% yield (over two steps).[29] The acetonide group of compound **83** was deprotected using AcOH: H_2O (8:2) at room temperature to furnish diol **84** in 85% yield which was converted to its TBS derivative **85** by using TBSOTf, TEA in DCM at 0 ^oC to provide *O*-TBS derivative **85** in 90% yield.[6c] Secondary hydroxy group of compound **85** was converted to its mesylate to afford *O*-mesylate compound **7** in 92% yield. The mesylate **86** was cyzlized under Staudinger reaction conditions[30] followed by treatment with $(Boc)_2O$ to furnish cyclic carbamte **87** in 50% yield. The *O*-TBS functionality

in compound **87** was removed using TBAF in THF solvent to obtain the column separable hydroxy methyl compounds *ent*-**31** and the *trans* isomer in 80% (*dr* 6:4) yield (Scheme 13).



Scheme 13. *Reagents and conditions*: a) *Ref.* 31; b) IBX, EA, reflux, 3 h; c) $(EtO)_2P(O)CH_2COOEt$, NaH, benzene, 80% (over two steps**);** d) Pd $(OH)_2/C$, $HCOONH_4$, MeOH, reflux, 2 h, 92%; e) LiBr, $NaBH_4$, MeOH:H_2O, 3 h, 88%; f) i) MsCl, TEA, DCM, 0 ^oC, 30 min; ii) NaN_3, DMF, 90 ^oC, 6 h, 70% (over two steps); g) AcOH:H_2O (8:2), rt, 85%; h) TBSOTf, TEA, DCM, 0 ^oC, 30 min, 90%; i) MsCl, TEA, DCM, 0 ^oC, 30 min, 92 %; j) PPh_3, Benzene:H_2O (9:1), reflux; k) $(Boc)_2O$, TEA, DMAP (Cat.), THF, rt, 50% (over two steps); l) TBAF, THF, 0 ^oC- rt, 80%.

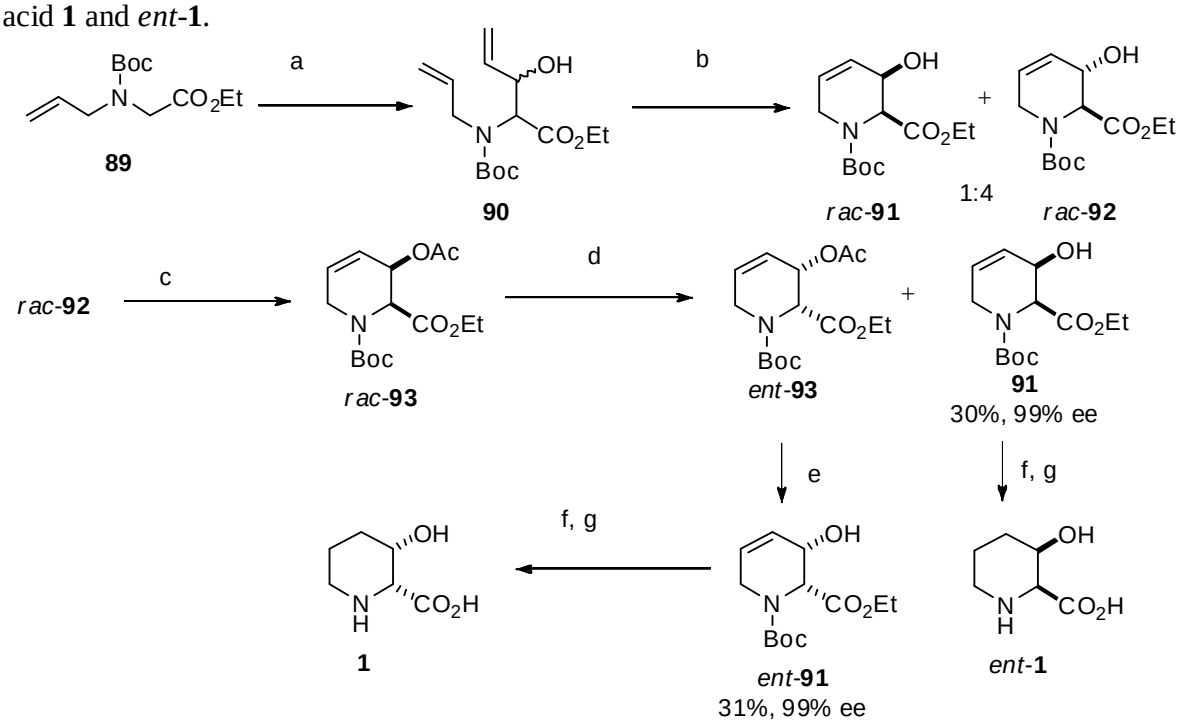
The column separated benzyl ether compounds *ent*-**31** and *trans* isomers were separately hydrogenated to furnish the diol **88** in 85% yields. Diols **88** were further elaborated to the *cis* 3-hydroxy pipecolic acids **1** by known literature protocol.[6,32]

(b) Synthesis using chiral induction

Takahata's approach[33]

Takahata*et al*. used RCM and enzymatic resolution as the key steps (Scheme 14) for synthesis of *ent*-**1**. In this allyl ester **89** was treated with LiHMDS and acrolein to provide diallyl derivative **90**, which was subsequently subjected to ring closing metathesis reaction

catalyzed by Grubb's I[st] generation catalyst to obtain a mixture of cyclized compounds **91** and **92**. The major isomer **92** on inversion of 3-hydroxy group followed by enzymatic resolution furnished acetate *ent*-**93** and alcohol **91** with excellent enantiomeric purity. The resolved acetate ester *ent*-**93** and **91** after hydrogenation and hydrolysis provided 3-hydroxypipecolic acid **1** and *ent*-**1**.

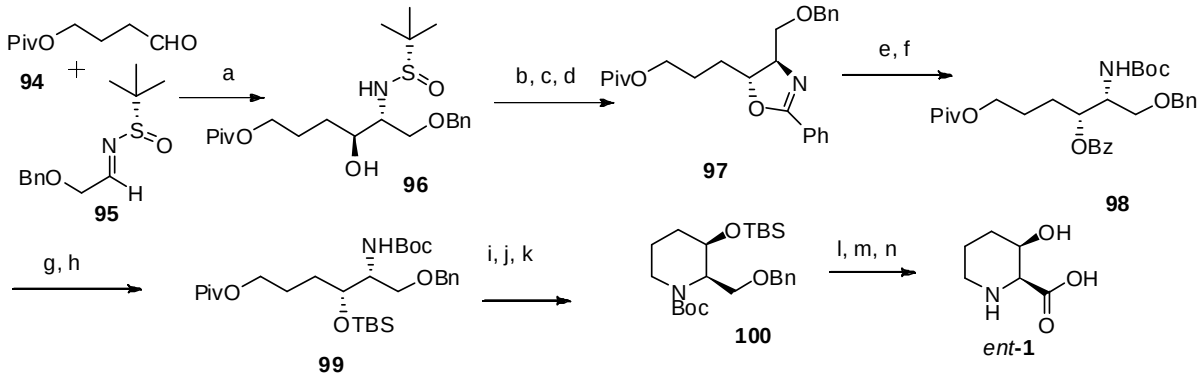


Scheme 14. *Reagents and conditions* a) LiHMDS, Acrolein, THF; b) Grubbs' I[st] gen. cat. CH_2Cl_2; c) PPh_3, DEAD, AcOH; d) Lipase PS-C acetone:buffer; e)LiOH; f) H_2, Pd/C; g). 5N HCl.

Wang's approach[34]

Wang *et al*. (Scheme 15) reported synthesis of *ent*-**1** by using Pinacol type reductive coupling between aldehyde **94** and sulfinyl imine **95** with excellent enantiomeric purity. The sulfinyl auxiliary was removed and subsequently selective *N*-protection with Bz_2O was carried out to obtain benzoyl derivative which on treatment with MsCl, TEA underwent the stereospecific inversion at C-3 position to form an oxazoline derivative **97**. Oxazoline **97** was hydrolyzed under acidic condition and amine was protected as *N*-Boc to furnish compound **98**. The benzoyl group in 75 was changed to TBS after carrying out a two step protocol to obtain **99**. The pivaloyl group in **99** was deprotected to furnish free alcohol which was mesylated and treated with base to provide cyclized piperidine **100**. The benzyl group deprotection

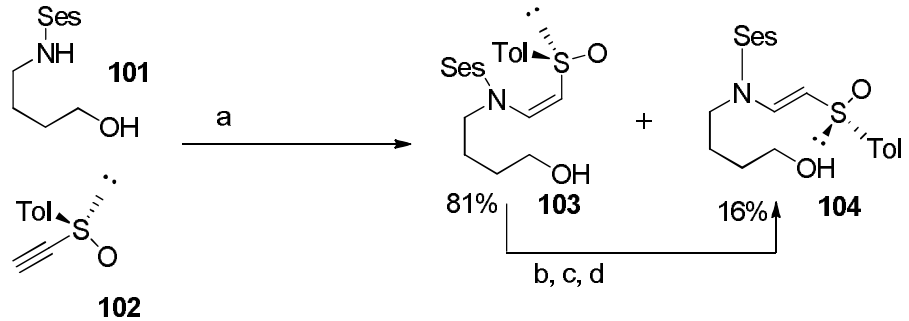
was carried out by treatment of **100** with Pd/C under hydrogenation conditions followed by oxidation of alcohol and TBS deprotection to furnish 3-hydroxypipecolic acid *ent*-**1**.



Scheme 15. *Reagents and conditions* a) SmI_2, THF, -78 ^oC, >98% ee; b) HCl, MeOH; c) Bz_2O, Et_3N; d) MsCl, Et_3N; e) aq. HCl, THF; f) $(Boc)_2O$, $NaHCO_3$; g) K_2CO_3, MeOH; h) TBSCl, Im; i) K_2CO_3, MeOH; j) MsCl, Et_3N, DCM; k) *t*-BuOK, THF; l) H_2, Pd/C, MeOH; m) Cat. $RuCl_3$, $NaIO_4$; n) 6M HCl

Lee's approach[35]

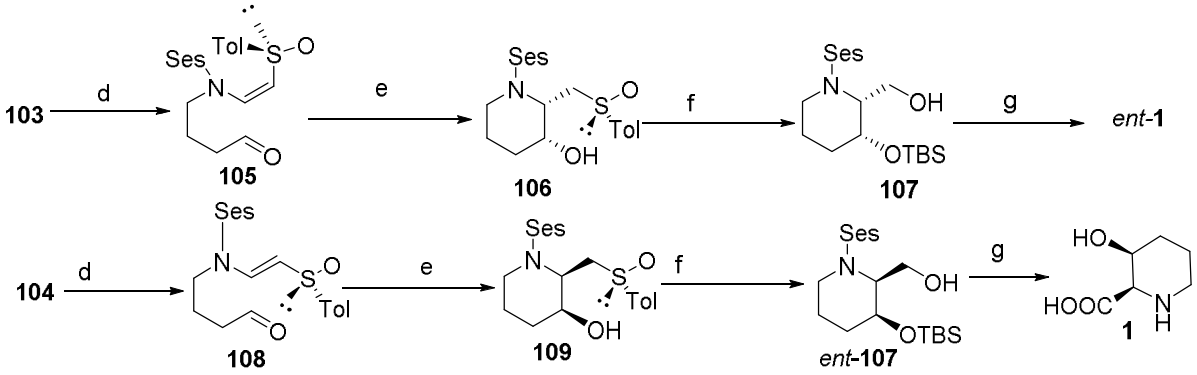
Lee *et al*. reported stereoselective synthesis of *cis*-3-hydroxypipecolic acid **1** using chirality transfer by the SmI_2-mediated cyclization reactions of aldehydo-*β*-aminovinyl sulfoxides. Treatment of **101** with alkynyl sulfoxide **102** in the presence of TEA and DMAP furnished a mixture of the (*Z*)-(*S*)- and (*E*)-(*S*)-*β*-aminovinylsulfoxides **103** in 81% and **104** in 16% yields. The *cis* isomer **103** was converted to *trans* isomer **104** by aetylation followed by treatment with iodine and basic hydrolysis (Scheme 16).



Scheme 16. *Reagents and conditions* a) Et_3N, DMAP; b) Ac_2O, Et_3N, DMAP; c) I_2; d) K_2CO_3, 75%

Also, the **103** and **104** were used to obtain corresponding enantiomers by IBX oxidation of **103** and **104** which furnished the corresponding aldehydes **105** and **108**, respectively. SmI_2

mediated cyclization provided 3-hydroxypiperidine product **106** from the (*Z*)-(*S*)-aldehyde **105** and reaction of the (*E*)-(*S*)-isomer **108** furnished product **109** after it readily underwent cyclization (Scheme 14). TBS derivatives of the products **106** and **109** on Pummerer rearrangement followed by sodium borohydride reduction yielded enantiomeric pair of primary alcohols **107** and *ent*-**107** respectively. Further conversion to (2*S*,3*R*)-3-hydroxypipecolic acid *ent*-**1** was carried out using Dess–Martin oxidation, Pinnick oxidation and cesium fluoride deprotection (Scheme 17).



Scheme 17. *Reagents and conditions* d) IBX, EtOAc, reflux, 98%; e) SmI_2, MeOH; f) i) TBSCl, Im, DMAP, ii) TFAA, Py, $NaBH_4$,65%; g) i) DMP, ii) $NaClO_2$, iii) CsF, 51%.

1.3.3 Present work:

1.3.3.1. Objective:

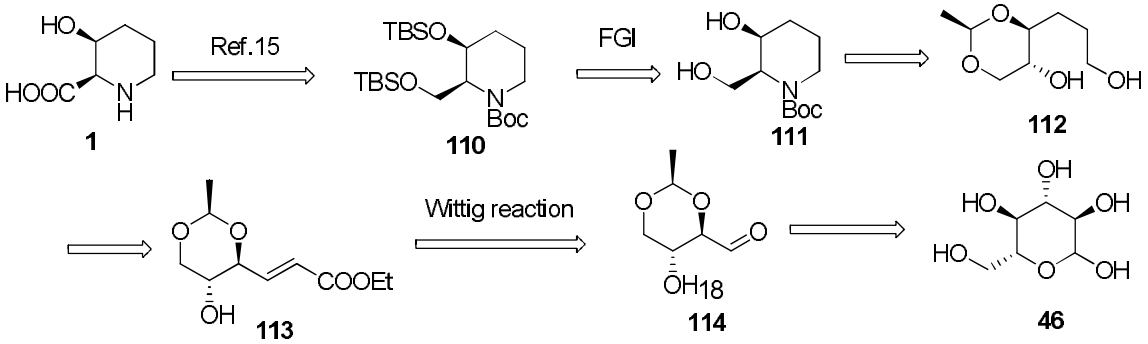
3-Hydroxy pipecolic acid **1** is a non proteinogenic cyclic α-amino acid. It is used in the preparation of conformationally restricted peptides and ligand binding studies. It is a constituent of many natural as well as synthetic biologically active compounds.[1] The biological activities of piperidines varies with the position and nature of substituent on the ring. Both *cis* as well as *trans* isomers are structural units found in diverse natural products. The hydroxy pipecolic acid framework is a target of several synthetic efforts. Synthetic chemists are interested in this structural motif because of its presence in compounds with diverse biological activities.[3] They are of pivotal importance to medicinal chemistry and organic synthesis.[4]

In view of their great significance, a number of synthetic strategies have been devoted to the stereoselective synthesis of these chiral piperidines. These syntheses utilized both chiral pool and asymmetric routes. In chiral pool approaches, carbohydrates and non-carbohydrate sources are used for their syntheses. Carbohydrates are ideally suited to the

preparation of single isomer of piperidines. In general, the asymmetric methodologies are prevalent for *trans* 3-hydroxy piperidines due to the easy out come of *trans* stereochemistry. Literature scrutiny indicates that only few methods for synthesis of *cis* isomer are reported.

1.3.3.2. Retrosynthetic analysis:

In continuation of interest in the chiral template assisted synthesis of biologically



Scheme 18. Retrosynthetic analysis.

active compounds, a practical and scalable route for *cis* (2*S*, 3*R*)-3hydroxy pipecolic acid **1** from D-glucose **46**, has been developed in enantiomerically pure form. Accordingly, the strategy was planned from D-glucose **46** (Scheme 18). It was envisioned that required stereochemistry of the target compound is embedded in D-glucose **46**, which can be used to synthesize the key intermediate piperidine **110**. This piperdine intermediate could be easily accessed from 1,5-diol **112** *via* compound **111** by cycloamination. The compound 1,5-diol **112** in turn could be obtained from *α,β*-unsaturated hydroxy ester **113** by reduction and *α,β*-unsaturated hydroxy ester **113** can be easily prepared from D-glucose **46** by reported protocol.

1.3.3.3. Results and discussion

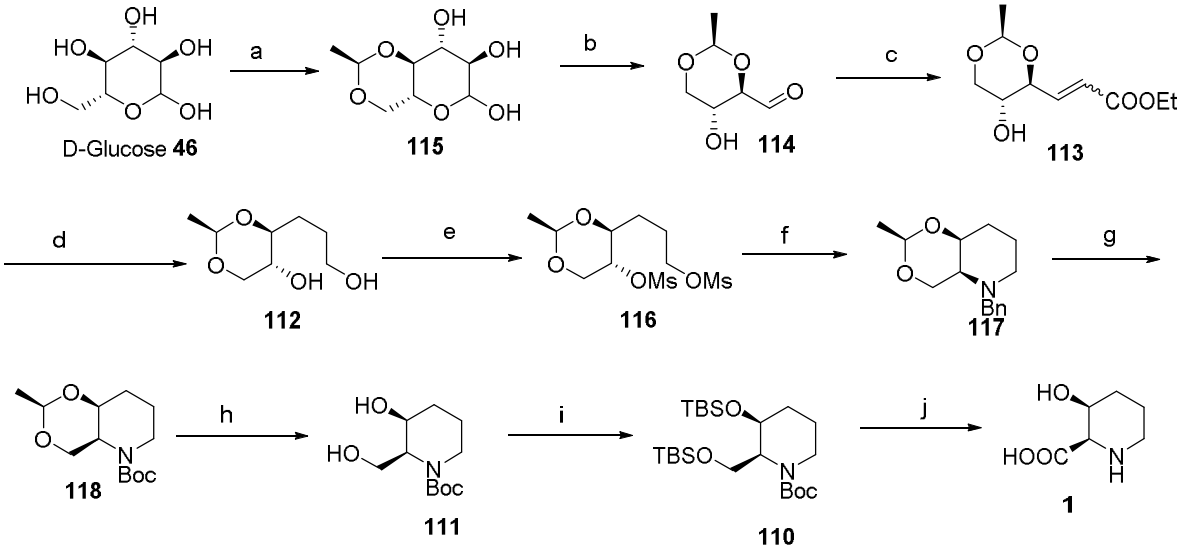
Thus, as shown in the retrosynthetic analysis, the synthesis of 3 hydroxy pipecolic acid **1** began with mono acetal protection of glucose to obtain (1'*R*)-(−)-4,6-O-ethylidene-D-glucose **115** in 65% yield after recrystalization from ethanol (Scheme 19). The acetal protected D-glucose **115** was used as such without characterization for further reaction. The compound **115** was subjected for cleavage with $NaIO_4$ to afford (−)-2,4-O-ethylidene-D-erythrose **114** in almost quantitative yield.[8] This was subsequently subjected for the two-carbon Wittig homologation with $Ph_3PCHCOOEt$ by stirring the reaction mixture at room temperature in DCM which afforded *α,β*-unsaturated hydroxy ester **113** in 7:3 *trans*/*cis* ratio

in good yield.[9] The major unsaturated ester **113** was confirmed by ^{1}H NMR in which two protons corresponding to α and β positions were observed at δ 6.14 and δ 7 respectively and coupling constant observed was J = 15.8 which suggetsed trans double bond. Characteristic ethyl group showed peaks at δ 1.31 as triplet for CH_3 and δ 4.21 as quartet for CH_2 with J value (J = 7.2) which clearly indicated presence of OCH_2CH_3 group in the compound. In ^{13}C NMR ester carbonyl was observed at δ 166.5 and two carbons in olefinic region (at δ122.19 and 143.68) which indicated the presence of α,β-unsaturated double bond. IR spectrum showed peak at 1718 cm^{-1} which further supported the presence of ester carbonyl functionality.

The reduction of α,β-unsaturated hydroxy ester by treatment with LiBr or LiCl and $NaBH_4$ in THF:Water (1:1) at ambient temperature provided 1,5diol **112** along with traces of allyl alcohol. The Allyl alcohol formed during reduction was hydrogenated with Pd/C in methanol under hydrogen atmosphere which gave the saturated compound 1,5 diol **112** in 96% yield.[10] The diol **112** in its IR spectrum showed the disappearance of peak at 1718 cm^{-1} and appearance of new band at 3390 cm^{-1} corresponding to hydroxyl groups. ^{1}H spectrum also showed the disappearance of ethyl group where characteristic triplet and quartet. ^{13}C NMR showed disappearance of carbonyl carbon at δ 166.5 and appearance of two extra CH_2 in ^{13}CNMR at δ 28.03 and 62.18 typicallly corresponding to CH_2-CH_2-OH. The peaks in olefinic region were diminished confirming the saturation of double bond. The all peaks were in good agreement with the structure of **112**.

This 1,5 diol **112** was subjected for mesylation by treating it with methanesulphonyl chloride and triethyl amine in DCM at 0 ^{o}C for 0.5 h to obtain dimesylate **116**. This mesylate derivative **116** was used for further cycloamination without purification.[11] Cyclization was carried out by heating dimesylate **116** in neat benzyl amine at 90 ^{o}C for 2 h to afford cyclized product **117** in 90% yield. Its IR spectrum showed disappearance of peak at 3453 cm^{-1} indicating displacement of hydroxy functinality. Its ^{1}H NMR spectrum showed peak in aromatic region as multuplet at δ 7.15-7.44 for 5 protons suggesting the presence of phenyl ring in the compond. which was further confirmed by ^{13}C NMR where 3 peaks corresponding to aromatic carbons were observed. The benzylic CH_2 appeared at δ 57.05 in ^{13}C NMR comfirmed the presence of *N*-benzylic CH_2 in the **117**.

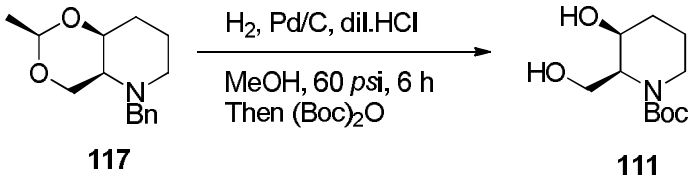
This cyclized benzylated piperidine was hydrogenated with Pd/C in methanol at 60 *psi* and concomitant *N*-Boc protection was carried out to provide one-pot *N*-debenzylation-*N*-boc protection to afford compound **118**.[12] A characteristic strong band at 1671 cm^{-1} in its IR spectrum clearly indicated the formation of carbamate. Its ^{1}H NMR spectrum showed singlet at δ 1.44 corresponding to a characteristic peak of *tert*-butyl of boc group and absence of peaks corresponding to aromatic protons in aromatic region and benzylic CH_2 in ^{1}HNMR and ^{13}CNMR suggested debenzylation. Also, CH_2 adjacent to *N*-boc group showed a broad singlet for two protons at δ 3.36. Its ^{13}C NMR spectrum showed a peak at δ 154.93 indicating the presence of carbamate carbonyl of *N*-Boc group. The *N*-boc piperidine was obtained in almost quantitative yield.



Scheme 19. *Reagents and conditions* a) *Ref*.36 ; b) $NaIO_4$, Water, 3 h, 97%; c) $Ph_3PCHCOOEt$ DCM, rt, 6 h, 87%; d) i) $NaBH_4$, LiCl, THF:water (1:1), 12 h, ii) H_2, Pd/C, MeOH, 60 *psi*, 3 h, 96%; e) MsCl,TEA, DCM, 0 ^{o}C, 30 min; f) $BnNH_2$, heat, 2 h, 90%; g) H_2, Pd/C, Boc_2O, MeOH, 60 *Psi*, 6 h; h) PTSA, MeOH, 3 h, rt, 91%; i) TBSCl, TEA, DMAP, DCM, 12 h, 86%; j) *Ref*.15.

The acetal group present in this **118** was deprotected with *p*-TSA in methanol and purified by recrystalization from pet. ether to obtain an intermediate **111** in excellent yield. The diol **111** was also synthesized from benzylated piperidine under hydrogenation and acidic environment followed by *N*-Boc protection directly. Its IR spectrum showed peak at 3453 cm^{-1} indicating hydroxy functinality. Its ^{1}H NMR spectrum showed disappearance of doublet at δ 1.31 for three protons and quartet at δ 4.01 for 1 proton showed deprotection of acetal group which was further confirmed by ^{13}CNMR where at typical peak at δ 98.36 for CH and

at δ 21.35 for CH_3 disappeared. Aslo, appearance of broad singlet at at δ 2.82 (br. s, 1 H) and 3.79 (br. s, 1 H) indicated presence of hydroxy functionality, which was again confirmed by IR value at frequency 3407 cm^{-1}.



117 **111**

Scheme 20: one pot boc protection.

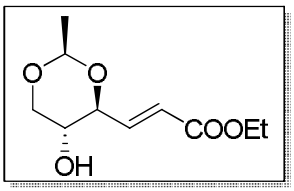
Also, this intermediate **111** was obtained in one pot from *N*-benzylated compound by carrying hydrogenation reaction in the presence of dil.HCl followed by addition of boc anhydride to get this inter medate in good yields. The *N*-boc diol **111** was protected as its silyl ether using TBSCl, triethyl amine and catalytic DMAP in DCM to convert it in to the key diTBS intermediate **110**. The formation of silyl ether in intermediate **110** was confirmed by disappearance of band at IR frequency 3407 cm^{-1} and appearance of multiplet in upfield region at δ 0.02 - 0.17 in ^{1}HNMR, for twelve protons and multiplet in the range of δ 0.79 - 1.00 confirmed the presence of TBS groups, which was further confirmed by their corresponding peaks observed in ^{13}CNMR. The data of this key di-TBS intermediate was in good agreement with the reported data.[15]

3.1.4. Conclusion

The formal synthesis of 3-hydroxy pipecolic acid **1** was completed in 8 steps. By carrying out one pot debenzylation and *N*-boc protection this intermediate was also obtained in 7 steps. A formal synthesis of 3-hydroxy pipecolic acid **1** in a short, practical, scalable and in a very efficient manner from commercially easily available, inexpensive starting material *viz.* D-glucose has been developed. In present synthesis column chromatographic purifications can be avoided in 6 steps during scale up of this synthesis.

1.3.5. Experimental:

Ethyl (*E*)-3-((2*R*,4*S*,5*R*)-5-hydroxy-2-methyl-1,3-dioxan-4-yl)acrylate (113):



The crude aldehyde **114** (1.12 g, 7.87 mmol) was dissolved in DCM (100 mL) and to this solution Ph_3PCHCO_2Et (3 g, 8.66 mmol) was added. The reaction mixture was stirred at room temperature for 4 h. Completion of reaction was monitored on TLC. After completion of reaction, solvent was removed under reduced pressure and the crude product was purified using silica gel coloumn chromatography to furnish the *α,β*-unsaturated ester **113** (1.7 g, 87%) as a colorless solid. R_f(ethyl acetate: pet. ether/2:3): 0.3

Yield: 87%

Molecular formula: $C_{10}H_{16}O_5$;

Molecular weight: 216.2310

IR: 3453, 2988, 2932, 1718, 1662, 1447 cm^{-1}

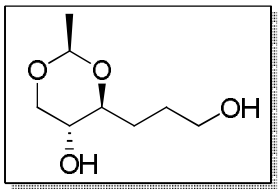
Optical rotation: $[\alpha]_D^{25}$: -41.45 (*c* = 0.5, chloroform)

^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 1.31 (t, *J* = 7.2 Hz, 3 H), 1.36 (d, *J* = 5.0 Hz, 3 H), 2.68 (br. s., 1 H), 3.44 (q, *J* = 10.5 Hz, 1 H), 3.48 - 3.55 (m, 1 H), 3.98 (ddd, *J* = 9.0, 4.6, 1.5 Hz, 1 H), 4.13 (dd, *J* = 10.4, 4.6 Hz, 1 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 4.73 (q, *J* = 5.0 Hz, 1 H), 6.14 (dd, *J* = 15.8, 1.6 Hz, 1 H), 7.08 (dd, *J* = 15.8, 4.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 14.29, 20.45, 60.62, 65.23, 70.71, 80.04, 98.78, 122.19, 143.68, 166.50.

HRMS: calcd for $C_{10}H_{16}O_5Na$ 239.0895 found 239.0890 $[M+Na]^+$.

(2*R*,4*S*,5*R*)-4-(3-hydroxypropyl)-2-methyl-1,3-dioxan-5-ol (112):



To a cold magnetically stirred solution of *α,β*-unsaturated ester **113** (1 g, 4.62 mmol) in THF: H_2O (1:1) (10 mL), LiCl (0.392 g, 9.25 mmol) $NaBH_4$ (0.352 g, 9.25 mmol) was added portion wise at 0 $^oC$and stirred for 12 h at that temperature. The reaction was quenched by addition by saturated NH_4Cl solution at 0 ^oC and again stirred for 10 min. Evaporation of the solvent furnished a residue which was extracted with ethyl acetate (3×8 mL). The combined organic layer was washed with brine (7 mL) and dried over anhydrous

Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was dissolved in methanol. To this solution catalytic Pd/C was added. This reaction mixture was stirred under hydrogen gas pressure. After 3 h, catalyst was filtered off. Methanol was eavaporated under reduced pressure. The residue was purified by a silica gel column chromatography using ethyl acetate/hexane (1:1) as eluent furnished the reduced 1,5-diol compound **112** (790 mg, 97%) as a colorless liquid. R_f (ethyl acetate: pet. ether/3:2): 0.2.

Molecular formula: Formula: $C_8H_{16}O_4$

Molecular Weight: 176.21

Yield: 94%.

Optical rotation: $[\alpha]_D^{25}$: -45.45 (*c* = 1.02, chloroform).

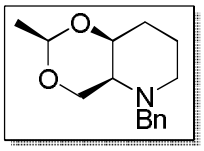
IR ($CHCl_3$): 3390, 2992; 1652 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (d, *J* = 5.0 Hz, 3 H), 1.47 - 1.68 (m, 2 H), 1.69 - 1.83 (m, 1 H), 1.89 - 2.06 (m, 1 H), 3.26 - 3.48 (m, 3 H), 3.57 - 3.76 (m, 3 H), 4.05 (dd, *J* = 10.5, 5.0 Hz, 1 H), 4.29 (br. s., 1 H), 4.65 (q, *J* = 5.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.39, 27.70, 28.03, 62.18, 65.12, 70.71, 81.15, 98.88.

HRMS: calcd for $C_8H_{16}O_4Na$: 199.0946; found 199.0942 $[M+Na]^+$.

(2*R*,4a*S*,8a*S*)-5-Benzyl-2-methylhexahydro-4H-[1,3]dioxino[5,4-b]pyridine(117)



A solution of 1,5-diol **112** (400 mg, 2.27 mmol) in dry CH_2Cl_2 (5 mL), and Et_3N (1.37g, 13.63 mmol) was cooled to 0 ^oC. Subsequently mesyl chloride (780 mg, 6.81 mmol) was added and the mixture was stirred for 30 min at the same temperature. Progress of reaction was monitored by TLC. After completion of the reaction, it was quenched by addition of 5 mL of aqueous solution of $NaHCO_3$ and the organic layer was washed with water (2 x 5 mL), followed by brine (5 mL). The organic layer was dried over $NaSO_4$, filtered and concentrated *in vacuo*. The residue of **116** was used as such for further reaction witout purification.

The dimesylate **116** (300 mg, 0.617 mmol) was dissolved in benzylamine (5 mL) and stirred at 90 ^0C for 2 h. After completion of reaction (monitored by TLC), 10 mL of 1N HCl was added and extracted with DCM (3 x 10 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (10 mL), dried over $NaSO_4$, concentrated *in vacuo*

and the crude product purified by silica gel column chromatography (Hexane-EtOAc = 9:1) to yield **117** (215 mg, 90%) as a colorless oil. R_f(ethyl acetate: pet. ether/2:3): 0.5.

Chemical Formula: $C_{15}H_{21}NO_2$

Molecular Weight: 247.33

Yield: 90%.

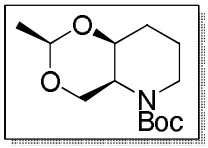
Optical rotation: $[\alpha]_D^{25}$: -37 (c=1.036, chloroform)

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.40 - 1.44 (m, 3 H), 1.88 - 2.23 (m, 6 H), 2.95 (dd, *J* = 10.6, 2.1 Hz, 1 H), 3.59 (d, *J* = 14.1 Hz, 1 H), 3.68 (dd, *J* = 12.8, 2.3 Hz, 1 H), 3.79 - 3.90 (m, 1 H), 4.05 (d, *J* = 14.1 Hz, 1 H), 4.58 (dt, *J* = 12.8, 0.7 Hz, 1 H), 4.80 (q, *J* = 5.1 Hz, 1 H), 7.15 - 7.44 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 19.66, 20.91, 29.93, 51.84, 56.20, 57.05, 67.25, 73.44, 99.41, 126.96, 127.99, 129.30, 136.65.

HRMS: calcd for $C_{15}H_{22}NO_2$: 248.1651**;** found: 248.1645 $[M+Na]^+$.

***tert*-Butyl (2*R*,4a*S*,8a*S*)-2-methylhexahydro-5*H*-[1,3]dioxino[5,4-b]pyridine-5-carboxylate (118):**



To the solution of *N*-benzyl piperidine **117** (0.250 g, 0.546 mmol) in methanol (20 mL, 9:1) was added boc anhydride (0.17 g, 0.65 mmol) and catalytic Pd/C. The reaction mixture was stirred under hydrogen gas atmosphere at 60 psi pressure for 8 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered on celite. The solvent was removed under reduced pressure to afford crude *N*-boc protected compound **118.** The residue was purified by flash silica gel column chromatography in 10% ethyl acetate in pet. ether to give compound **118** (0.118 g, 94%) as colorless thick syrup. R_f(ethyl acetate: pet. ether/1:3): 0.5.

Molecular formula: $C_{13}H_{23}NO_4$

Molecular weight: 257.32

Yield: 94%.

Optical rotation: $[\alpha]_D^{25}$: -32 (*c* = 1.05, chloroform)

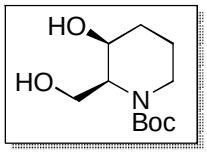
IR ($CHCl_3$): 2979, 1671, 757 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): δ 1.31 (d, *J* = 4.9 Hz, 3 H), 1.44 (s, 9 H), 1.51 - 2.08 (m, 4 H), 3.36 (br. s., 1 H), 3.48 (td, *J* = 12.5, 6.1 Hz, 1 H), 3.72 (dd, *J* = 12.4, 2.3 Hz, 1 H), 3.94 (dd, *J* = 13.1, 7.9 Hz, 1 H), 4.01 (q, *J* = 3.4 Hz, 1 H), 4.25 (d, *J* = 12.2 Hz, 1 H), 4.67 (q, *J* = 5.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 18.75, 21.35, 24.17, 28.52, 38.10, 49.12, 70.50, 71.13, 79.37, 79.40, 98.36, 154.93.

HRMS: calcd for $C_{13}H_{23}NO_4Na$: 280.1519; found: 280.1525 $[M+Na]^+$.

***tert*-butyl (2*S*,3*S*)-3-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate(111)**[32,37]



To a solution of *tert*-butyl (2*R*,4a*S*,8a*S*)-2-methylhexahydro-5*H*-[1,3]dioxino[5,4-b]pyridine-5-carboxylate **118** (1.7 g, 6.88 mmol) in MeOH (20 mL) was added *p*-TSA (130 mg, 0.69 mmol) at 0 °C and the mixture stirred for 2 h at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was neutralized with $NaHCO_3$ and the organic layer and aqueous layers were separated. Aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness under reduced pressure. Purification by column chromatography using petroleum ether: ethyl acetate (1:1) as eluent afforded 1.55 g compound as a white solid in 96% yield. Purification can also be carried out by recrystalizing the compound **111** from pet ether by dissolving in it by addition of minimum amount of ethyl actetate. R_f (ethyl acetate: Pet. ether/2:3): 0.4.

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

Molecular weight: 231.29

Yield: 96%.

MP: 115-117 ^oC Lit.[32] 114-116 ^oC

Optical rotation: $[\alpha]_D^{25}$: +24.2 (*c*: 1, MeOH); Lit.[37] $[\alpha]_D^{25}$: (*c*: 1.03, MeOH), $[\alpha]_D^{25}$: +33.6 (*c* = 1.04, $CHCl_3$); Lit.[37] $[\alpha]_D^{25}$: +23.4 (*c* = 1, $CHCl_3$)

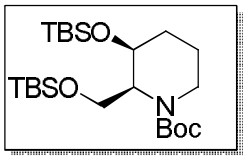
IR ($CHCl_3$): IR: 3407, 2935, 1668, 1423 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 1.45 (s, 10 H), 1.55 - 1.77 (m, 2 H), 1.85 (d, *J* = 12.3 Hz, 1 H), 2.82 (br. s., 1 H), 3.36 (br. s, 2 H), 3.73 (dd, *J* = 11.2, 6.9 Hz, 1 H), 3.79 (br. s., 1 H), 3.87 - 3.96 (m, 1 H), 4.10 (dd, *J* = 11.2, 6.5 Hz, 1 H), 4.42 (q, *J* = 6.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 23.80, 28.34, 28.45, 39.76, 56.08, 59.26, 69.39, 80.26, 155.62.

HRMS: calcd for $C_{11}H_{21}NO_4Na$: 254.1368; found:254.1363 $[M+Na]^+$.

(2*S*,3*S*)-*tert*-Butyl 3-((*tert*-butyldimethylsilyl)oxy)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)piperidine-1-carboxylate (117)[15]



To the solution of diol **111** (40 mg, 0.173 mmol) in DCM (1 mL) TBDMSCl (79 mg, 0.52 mmol), imidazole (71 mg, 0.10 mmol) and DMAP (0.0173 mmol) was added under nitrogen. The mixture was stirred at room temperature for 12 h and diluted with DCM (3.0 mL). An aqueous solution saturated of $NaHCO_3$ (3.0 mL) was added and the product was extracted four times with DCM (3 mL). The organic layer was, dried over $NaSO_4$, filtered and concentrated in *vacuo* and the crude product purified by silica gel column chromatography (Hexane-EtOAc = 9:1) to yield **110** (69 mg, 86%) as a colorless oil. R_f (ethyl acetate: Pet. ether/1:8): 0.3.

Molecular formula: $C_{23}H_{49}NO_4Si_2$

Molecular weight: 459.81

Yield: 86%

Optical rotation: +14 (c 0.5, $CHCl_3$); *ent*-1: Lit.[15] -13:6 (c 0.5, $CHCl_3$);

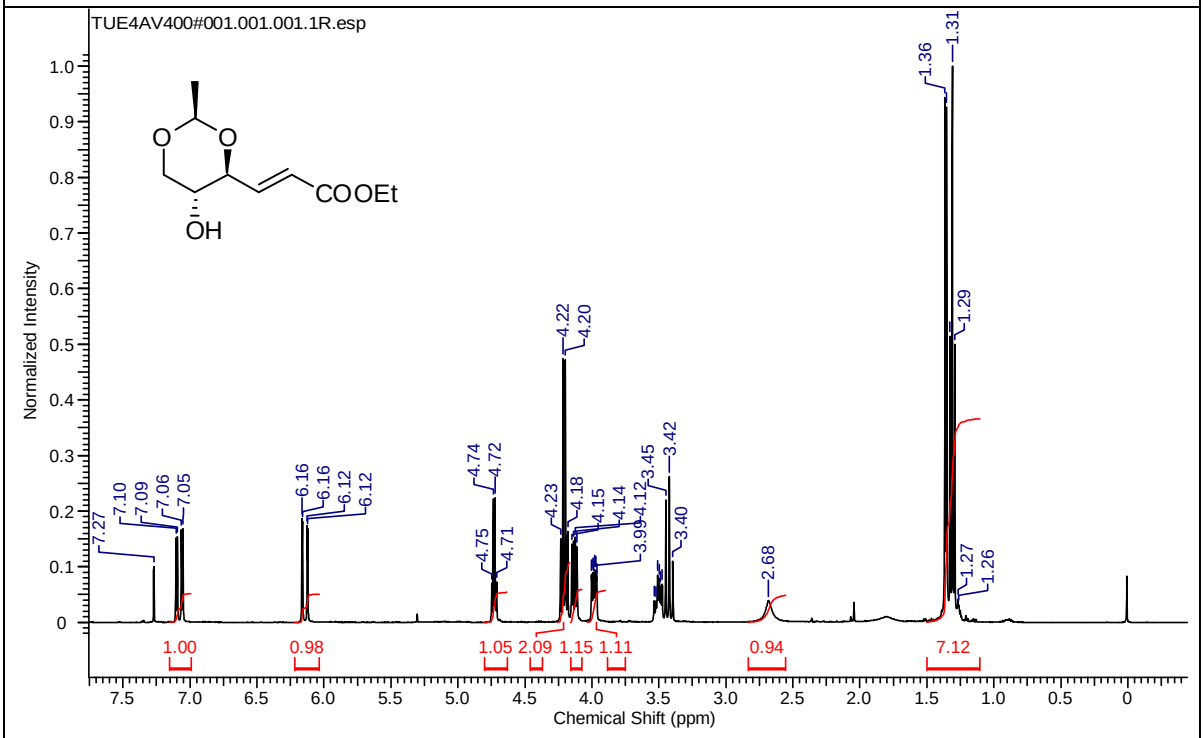
IR ($CDCl_3$): 2930, 1693, 756 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.02 - 0.17 (m, 12 H), 0.79 - 1.00 (m, 18 H), 1.46 (s, 9 H), 1.53 - 1.86 (m, 4 H), 2.71 - 3.06 (m, 1 H), 3.58 - 4.09 (m, 4 H), 4.19 - 4.46 (m, 1 H).

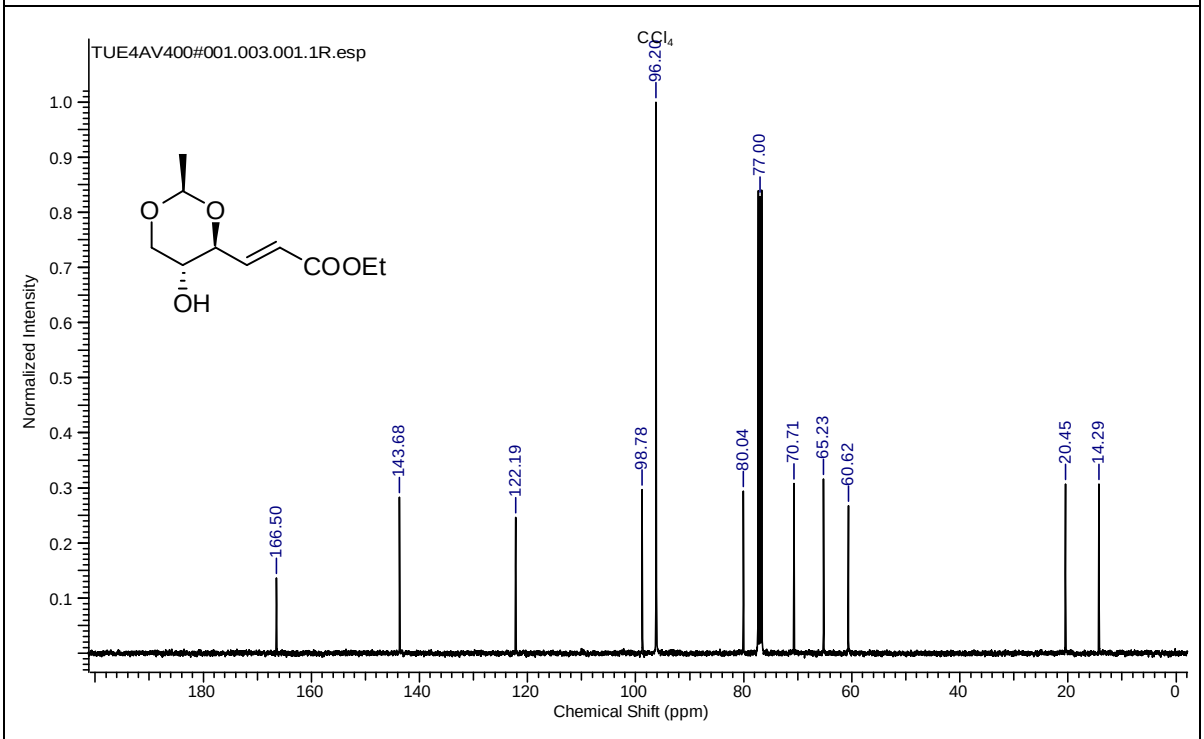
^{13}C NMR (100 MHz, $CDCl_3$): δ -5.4, -5.4, -5.0, -4.8, 18.1, 18.2, 24.2, 25.8, 25.9, 28.4, 29.6, 29.7, 37.3, 39.2, 55.8, 57.8, 58.1, 69.6, 79.1, 155.2.

1.3.6. Spectra

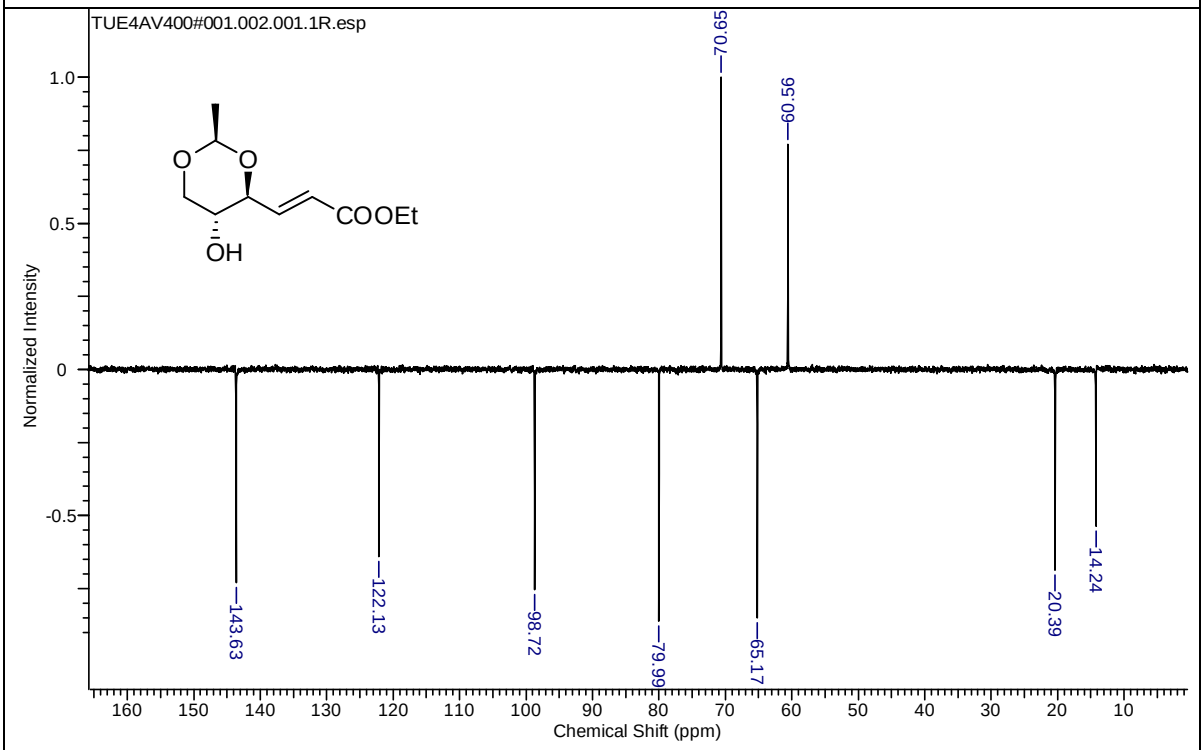
^{1}H NMR spectrum of compound **113** ($CDCl_3$+CCl_4, 200 MHz)



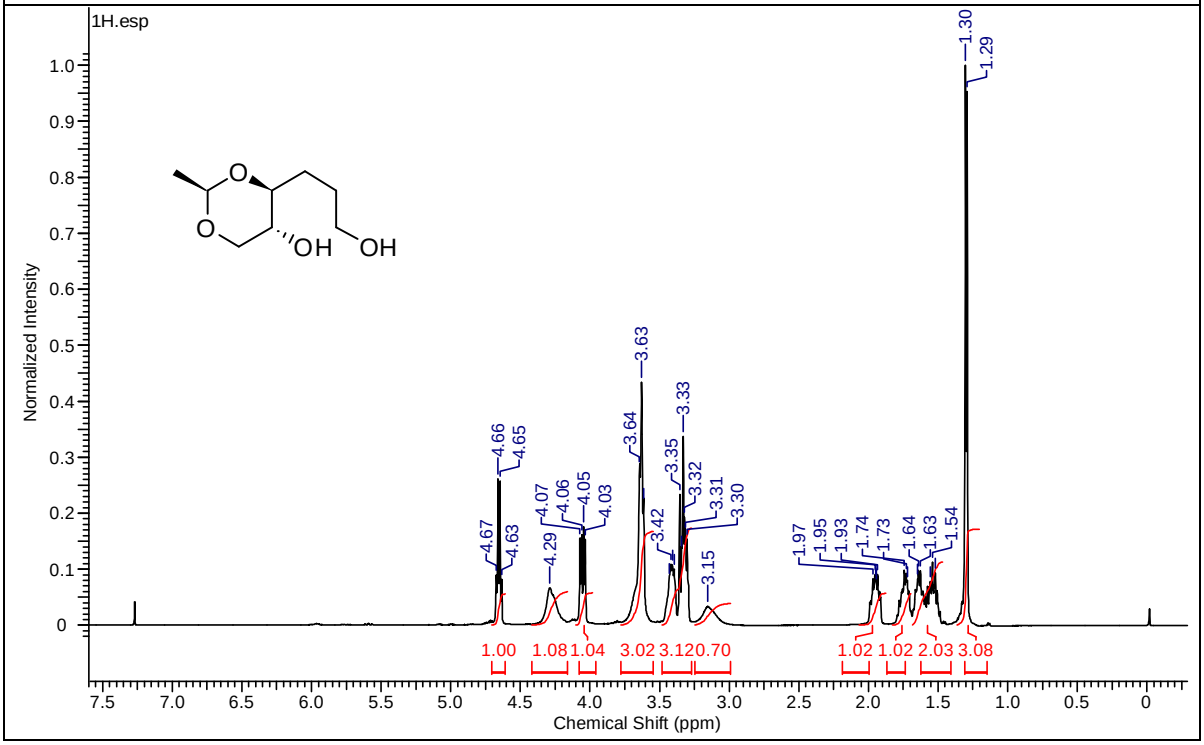
^{13}C NMR spectrum of compound **113** ($CDCl_3$ + CCl_4, 50 MHz)



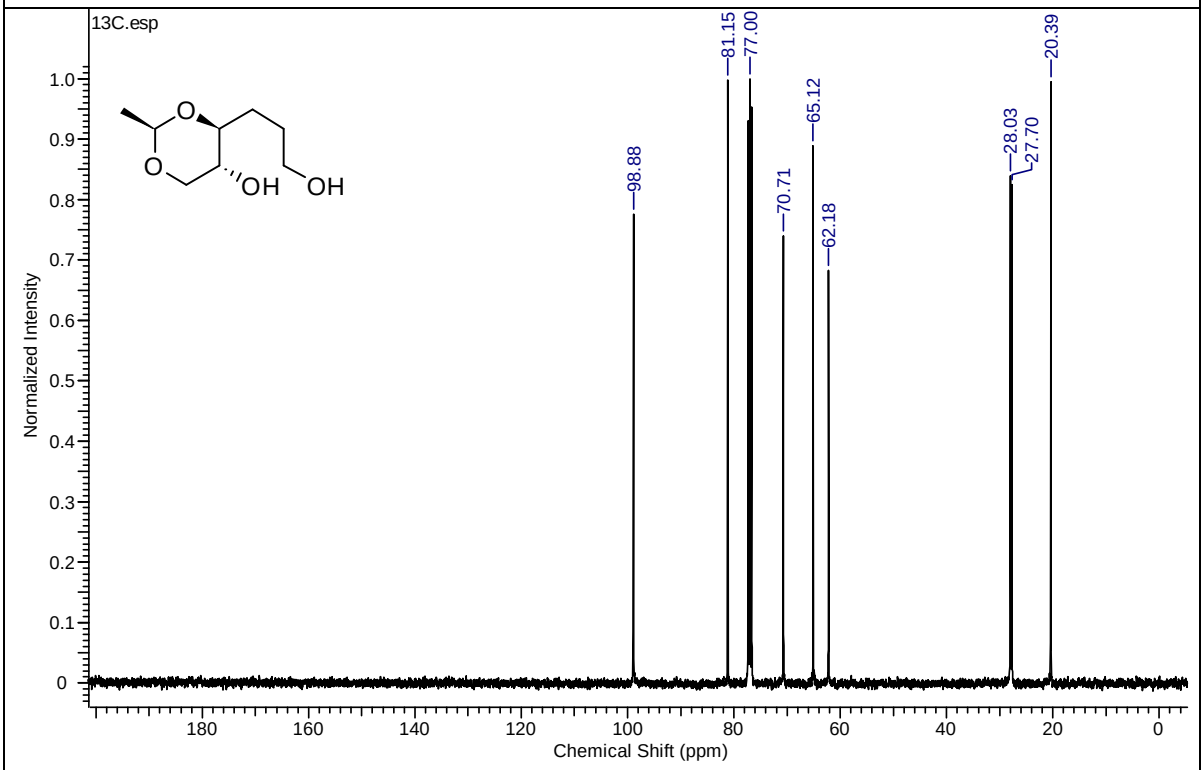
DEPT spectrum of compound **113** ($CDCl_3$ + CCl_4, 50 MHz)



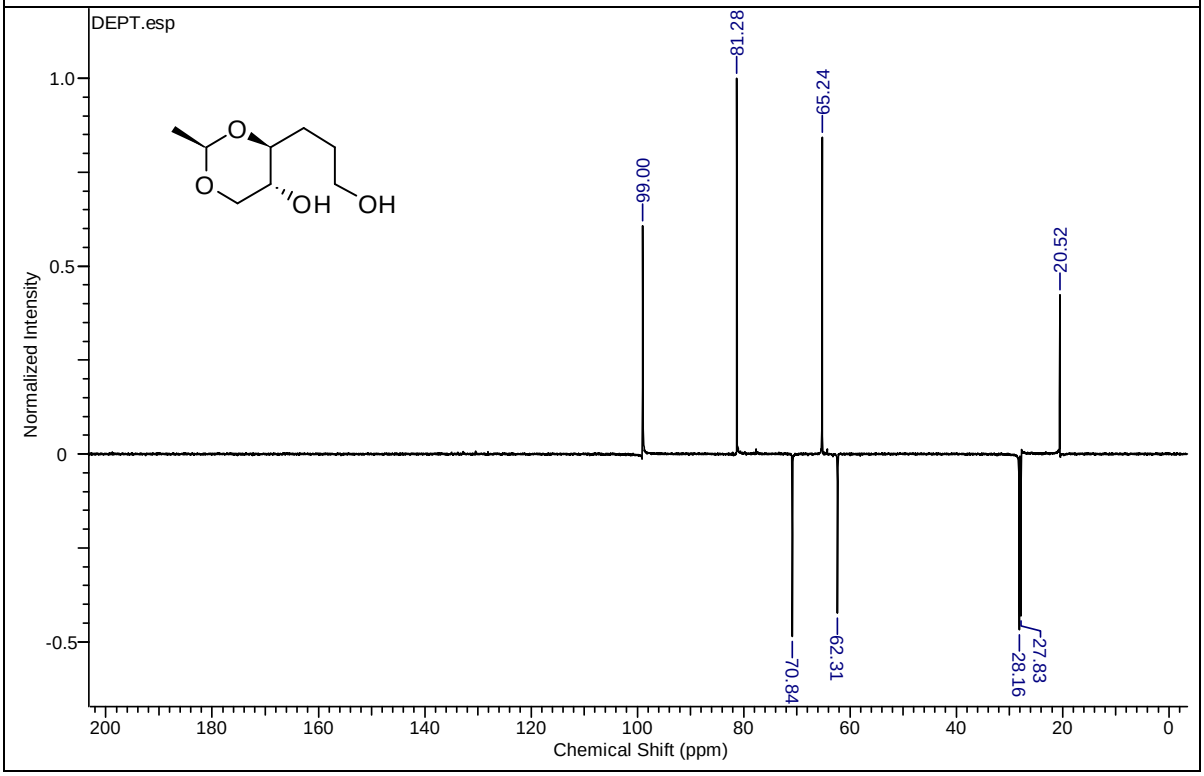
^{1}H NMR spectrum of compound **112** ($CDCl_3$, 200 MHz)



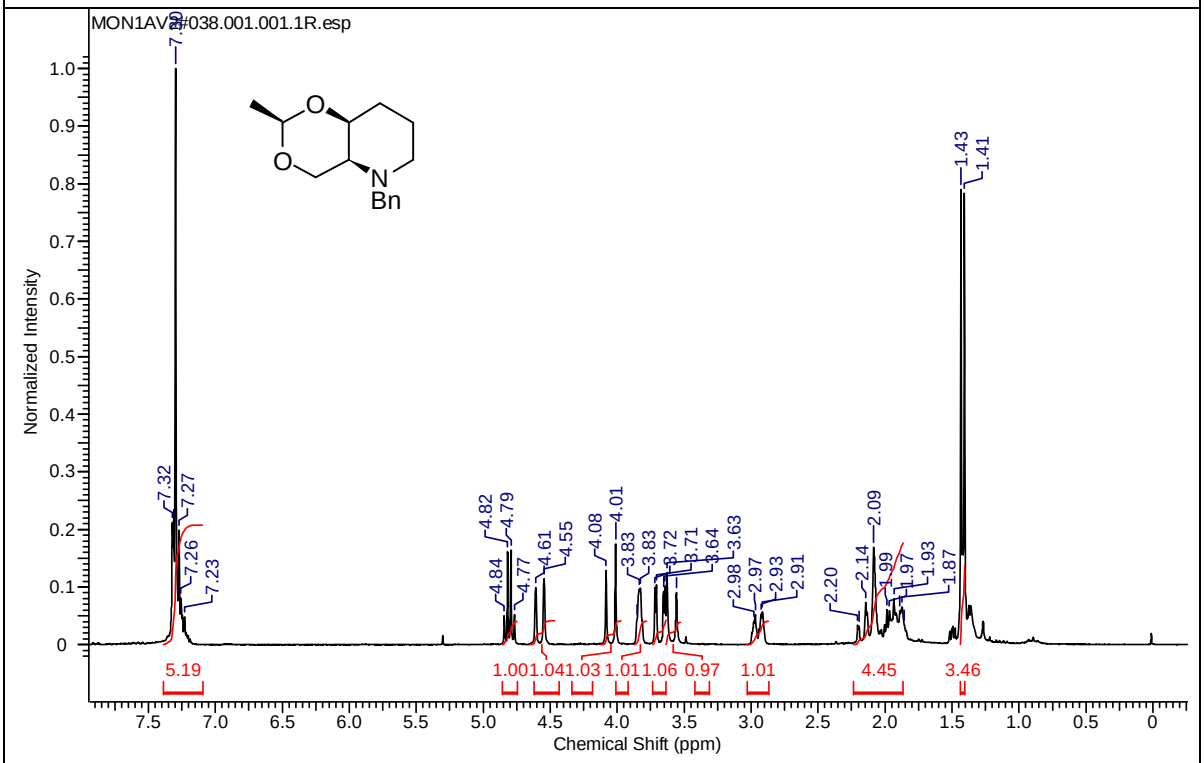
^{13}C NMR spectrum of compound **112** ($CDCl_3$, 100 MHz)



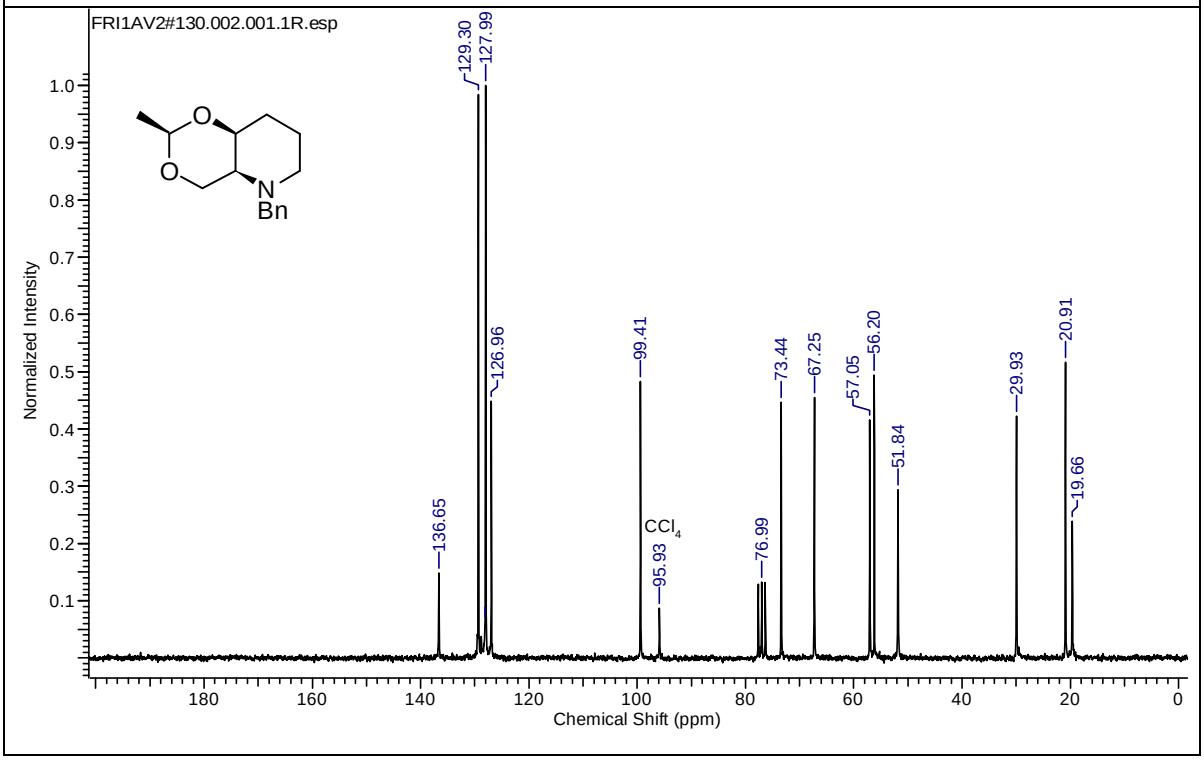
DEPT spectrum of compound **112** ($CDCl_3$, 100 MHz)



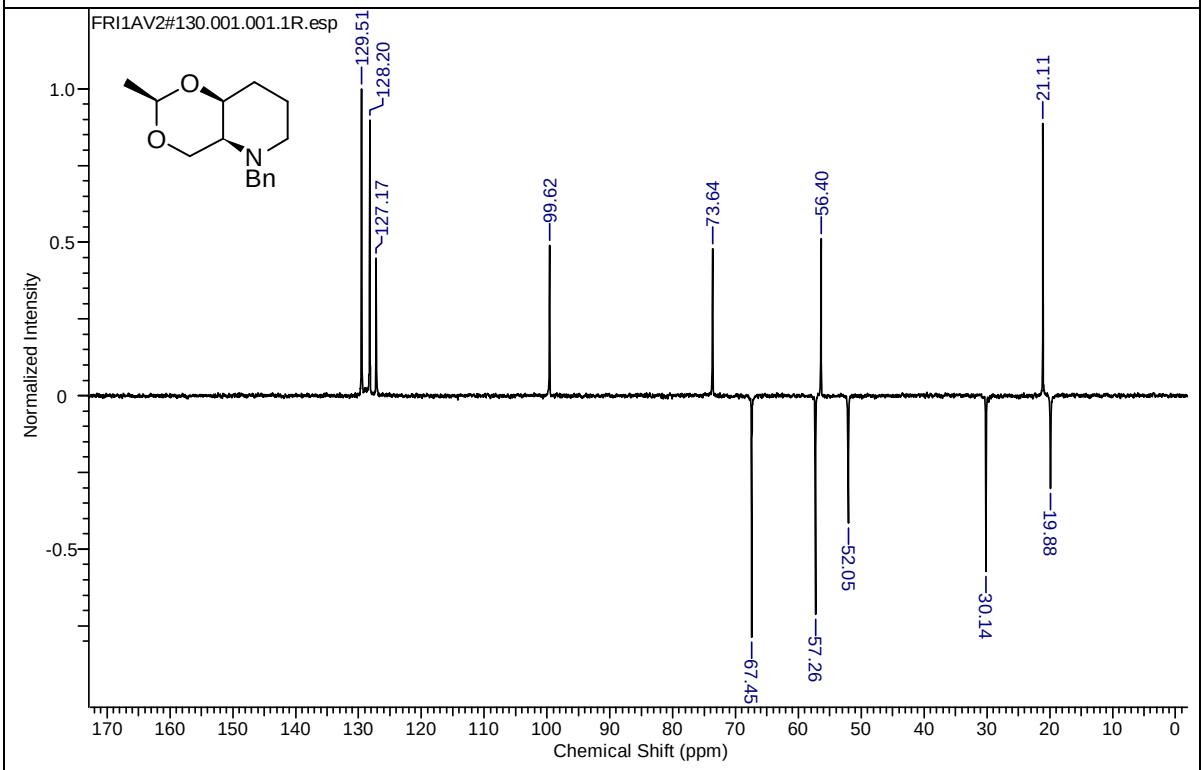
^{1}H NMR spectrum of compound **117** ($CDCl_3$+CCl_4, 200 MHz)



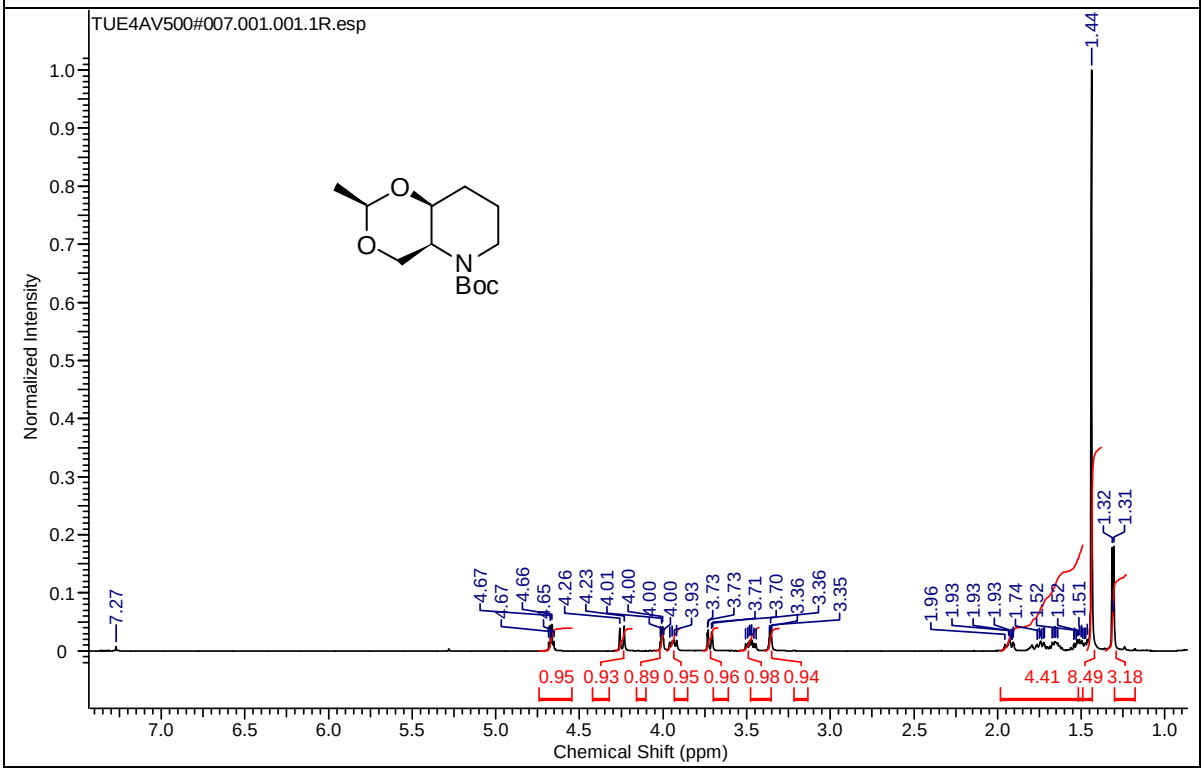
^{13}C NMR spectrum of compound **117** ($CDCl_3$ + CCl_4, 50 MHz)



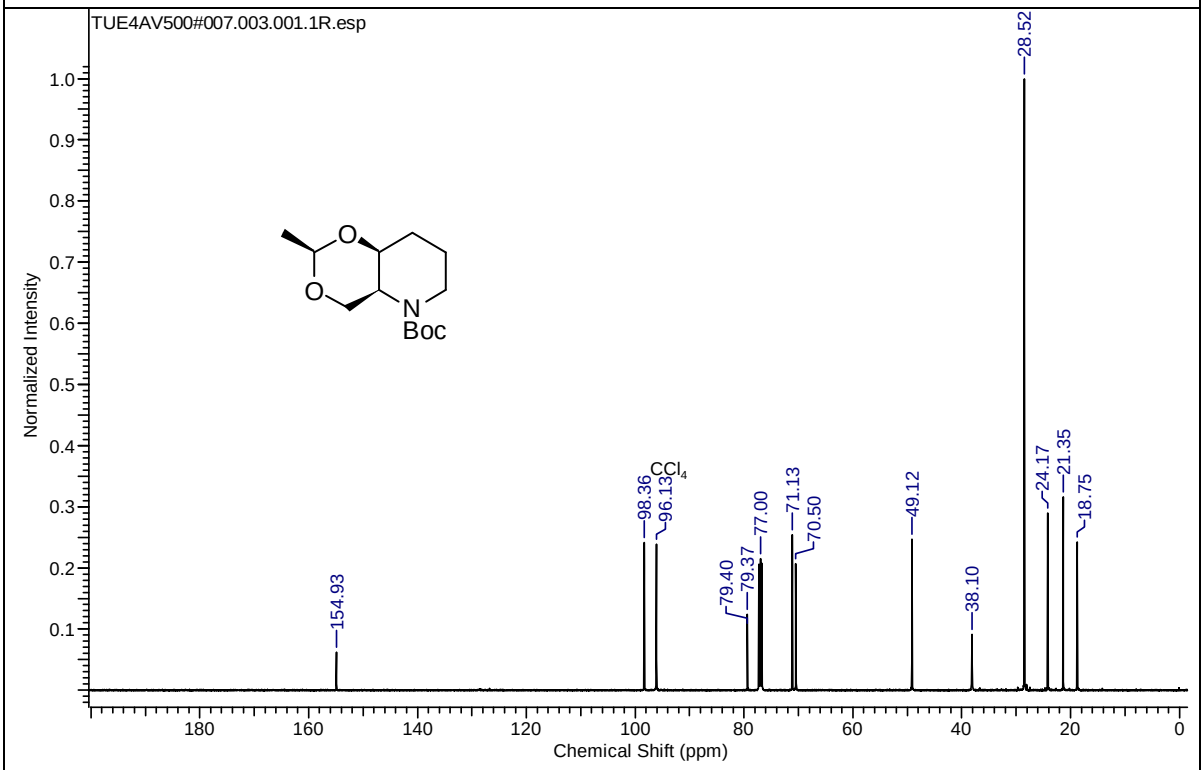
DEPT spectrum of compound **3** ($CDCl_3$ + CCl_4, 50 MHz)



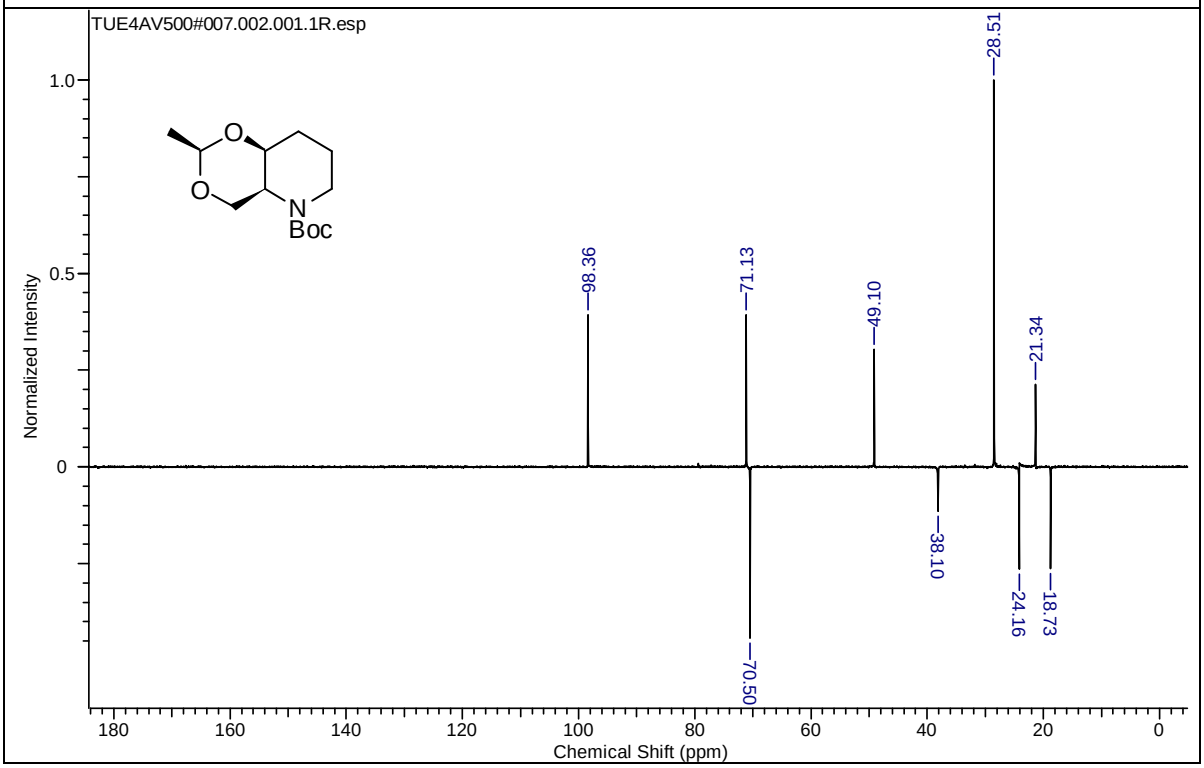
^{1}H NMR spectrum of compound **118** ($CDCl_3$+CCl_4, 500 MHz)



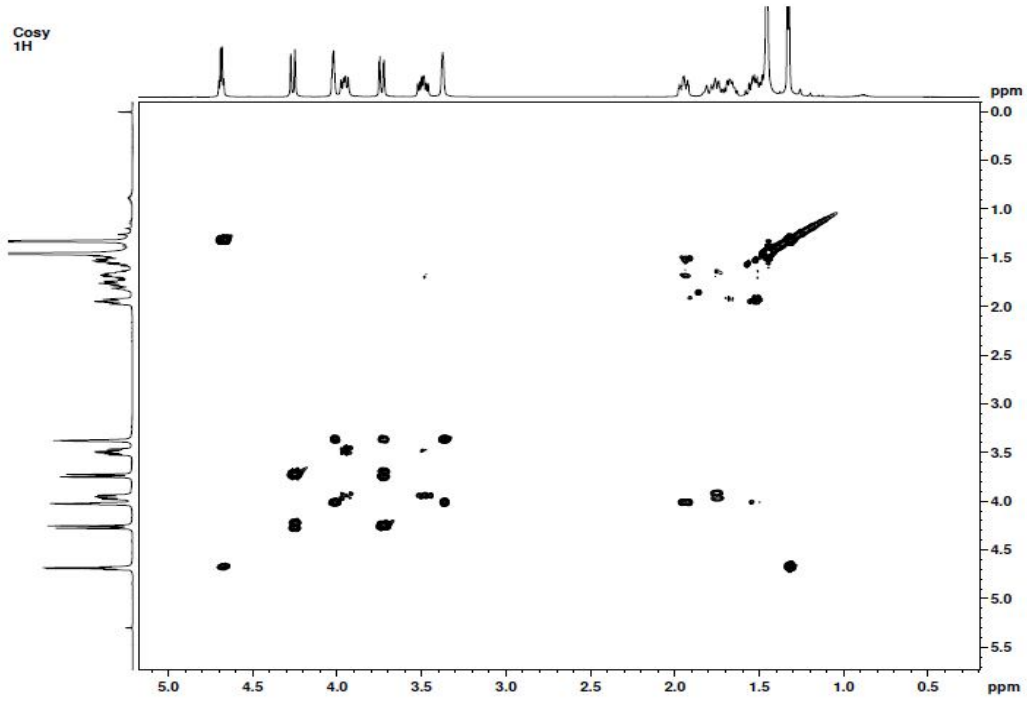
^{13}C NMR spectrum of compound **118** ($CDCl_3$+CCl_4, 125 MHz)



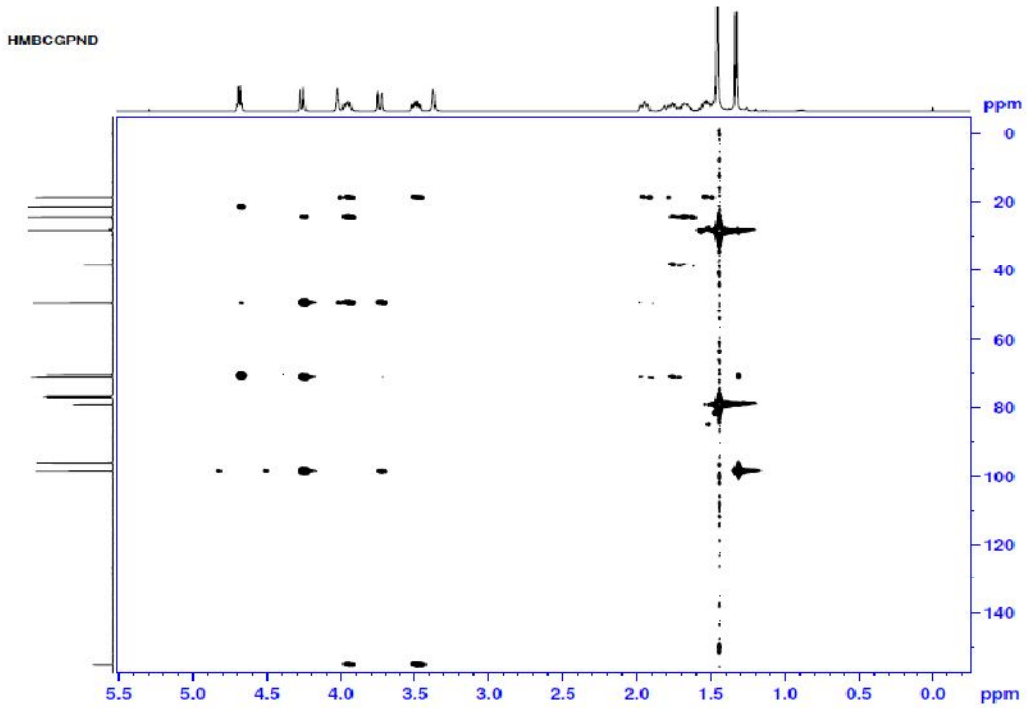
DEPT NMR spectrum of compound **118** ($CDCl_3$+CCl_4, 125 MHz)



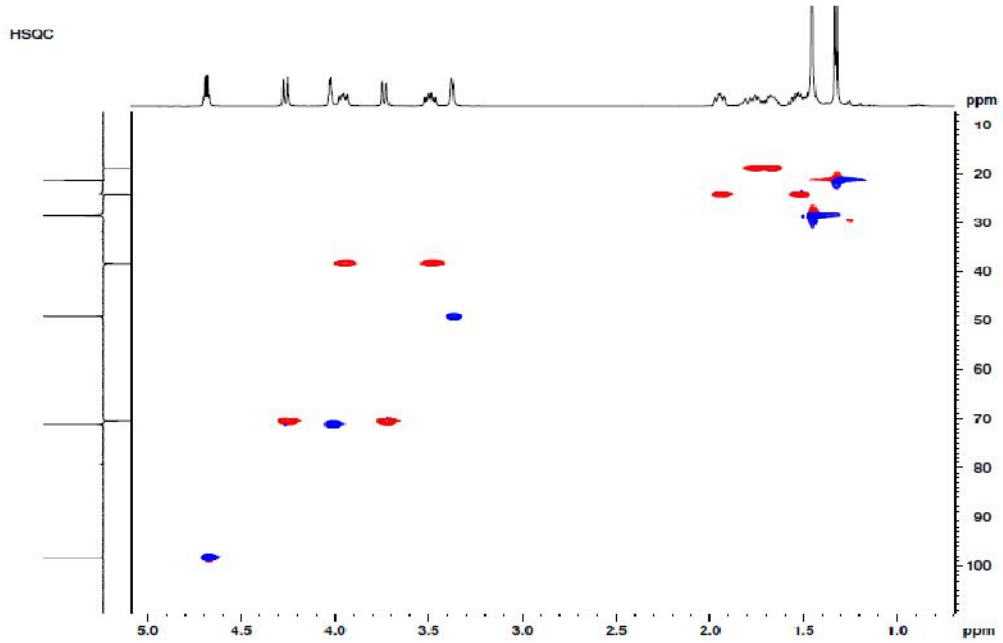
COSY of compound **118** ($CDCl_3$+CCl_4, 125 MHz)



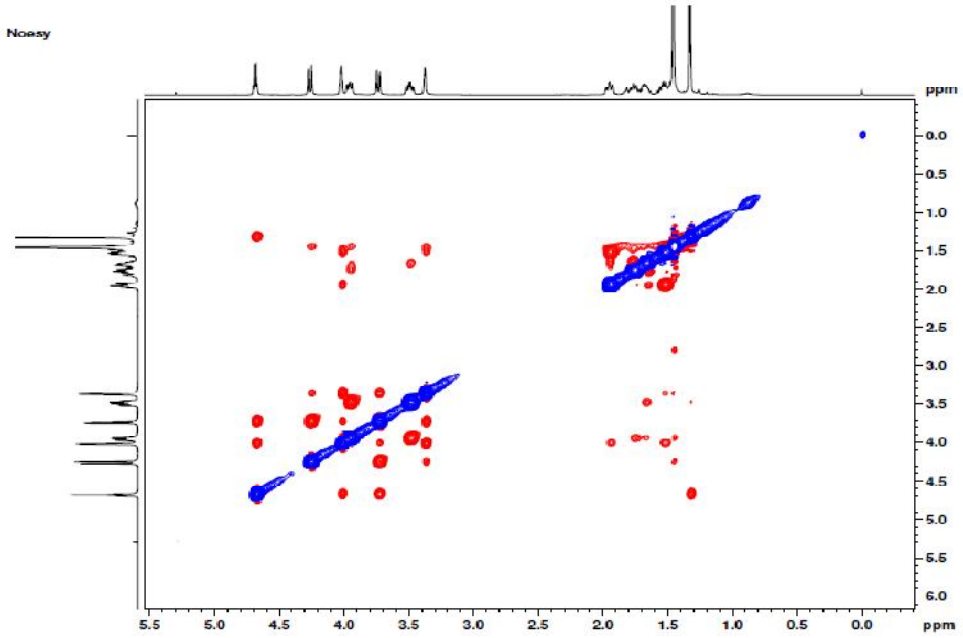
HMBCof compound **118** ($CDCl_3$+CCl_4, 125 MHz)



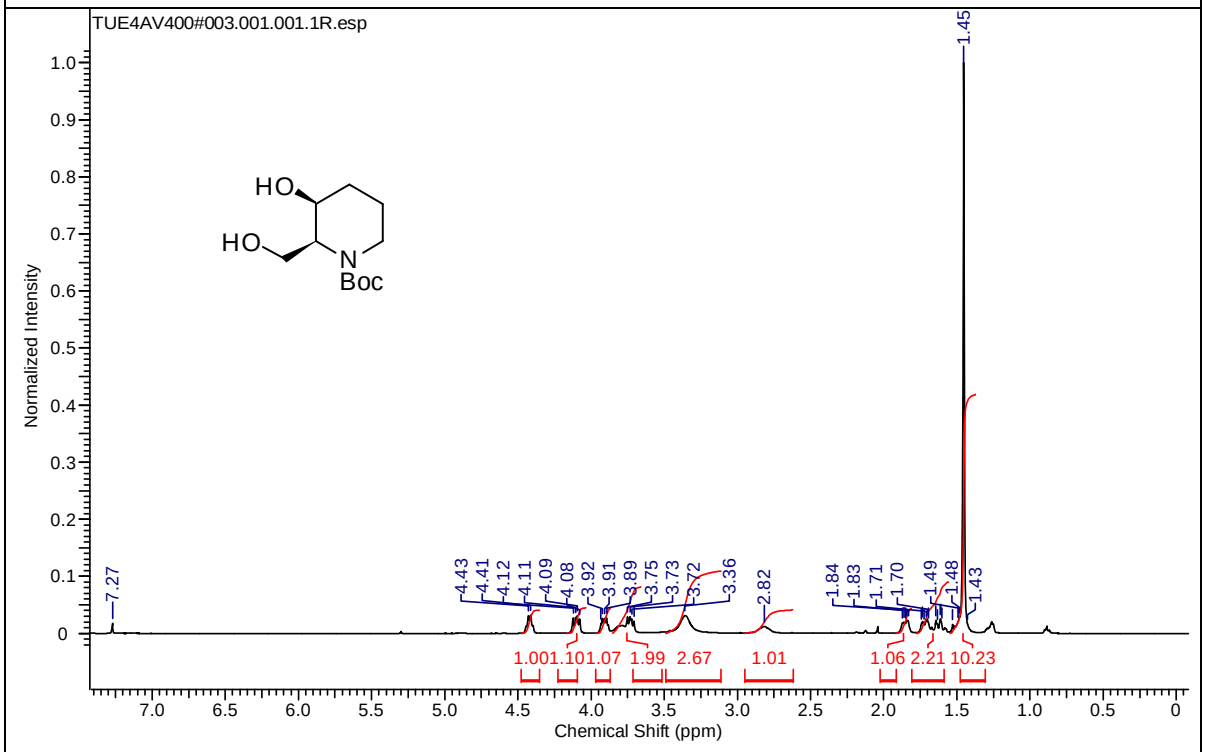
HSQC of compound **118** ($CDCl_3$+CCl_4, 125 MHz)



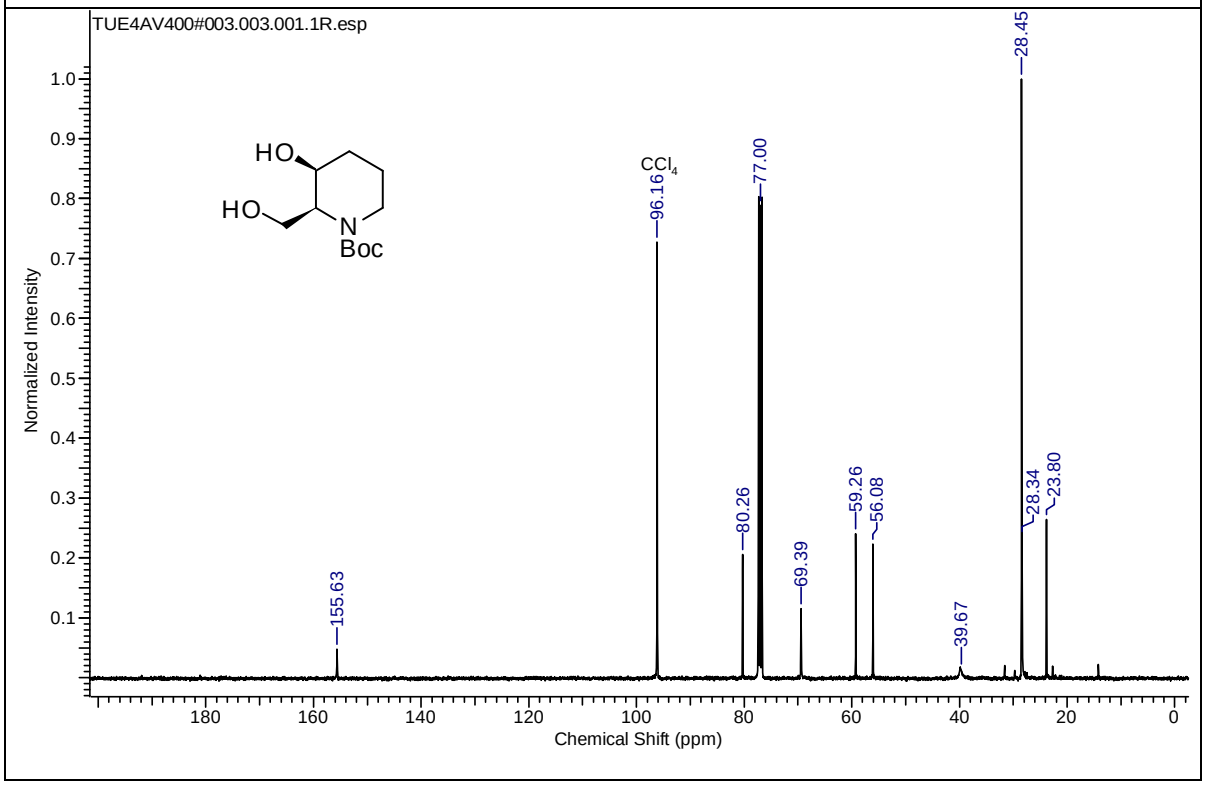
NOSEYof compound **118** ($CDCl_3$+CCl_4, 125 MHz)



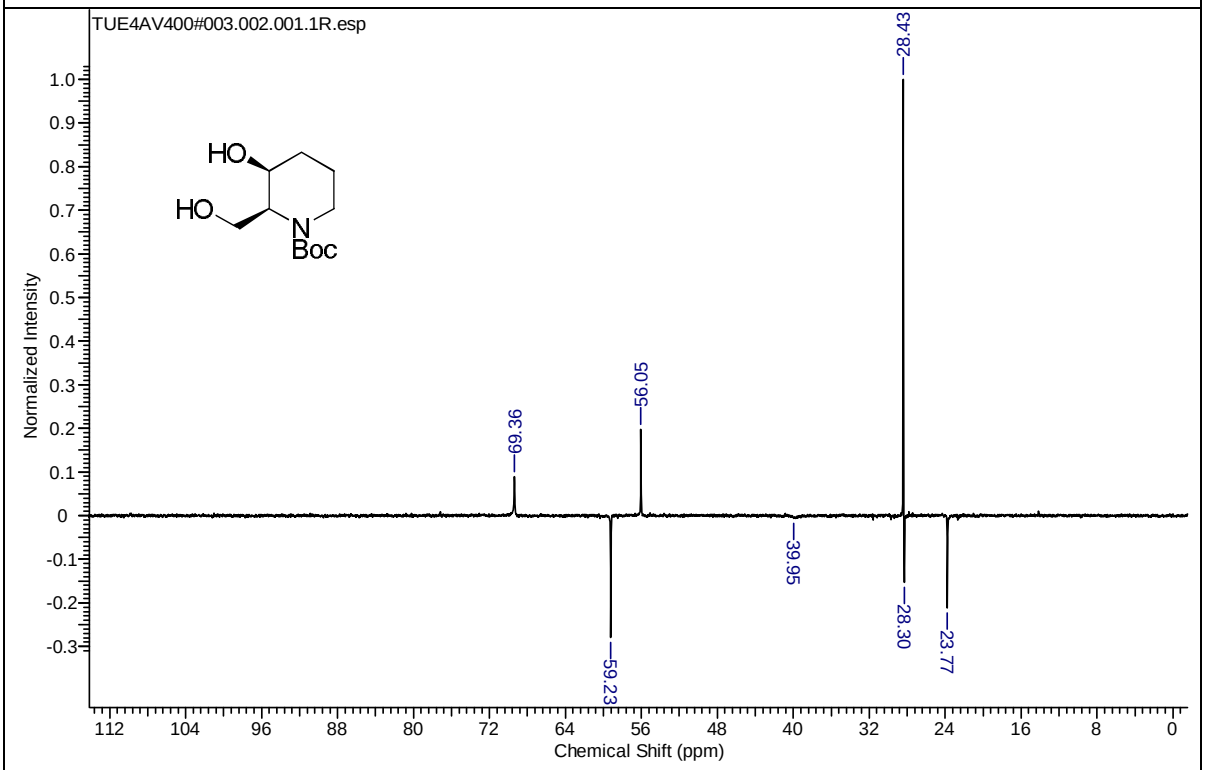
^{1}H NMR spectrum of compound **111** ($CDCl_3$+CCl_4, 400 MHz)



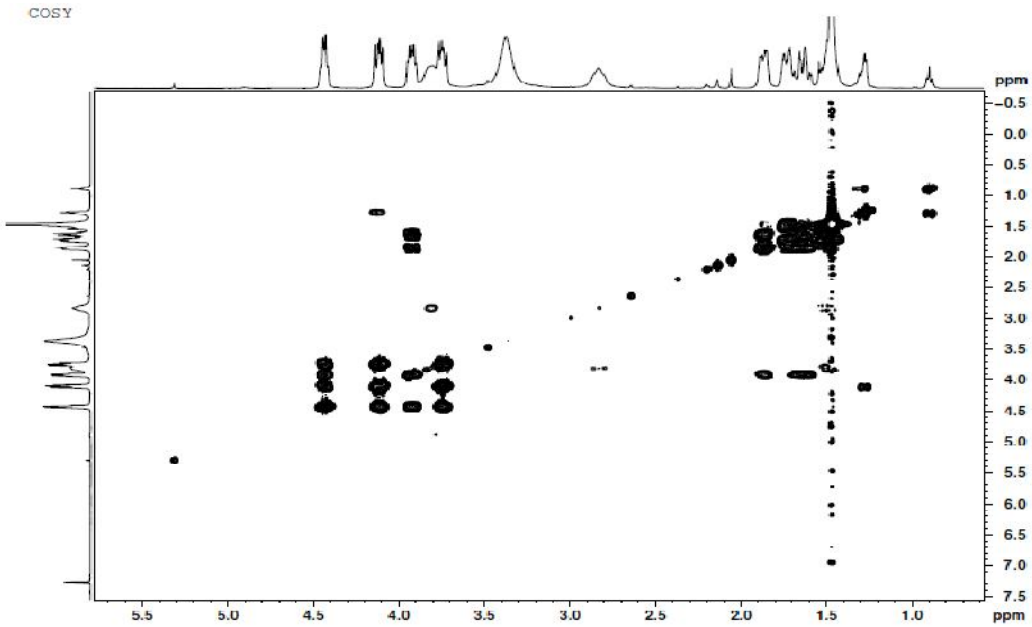
^{13}C NMR spectrum of compound **111** ($CDCl_3$+CCl_4, 100 MHz)



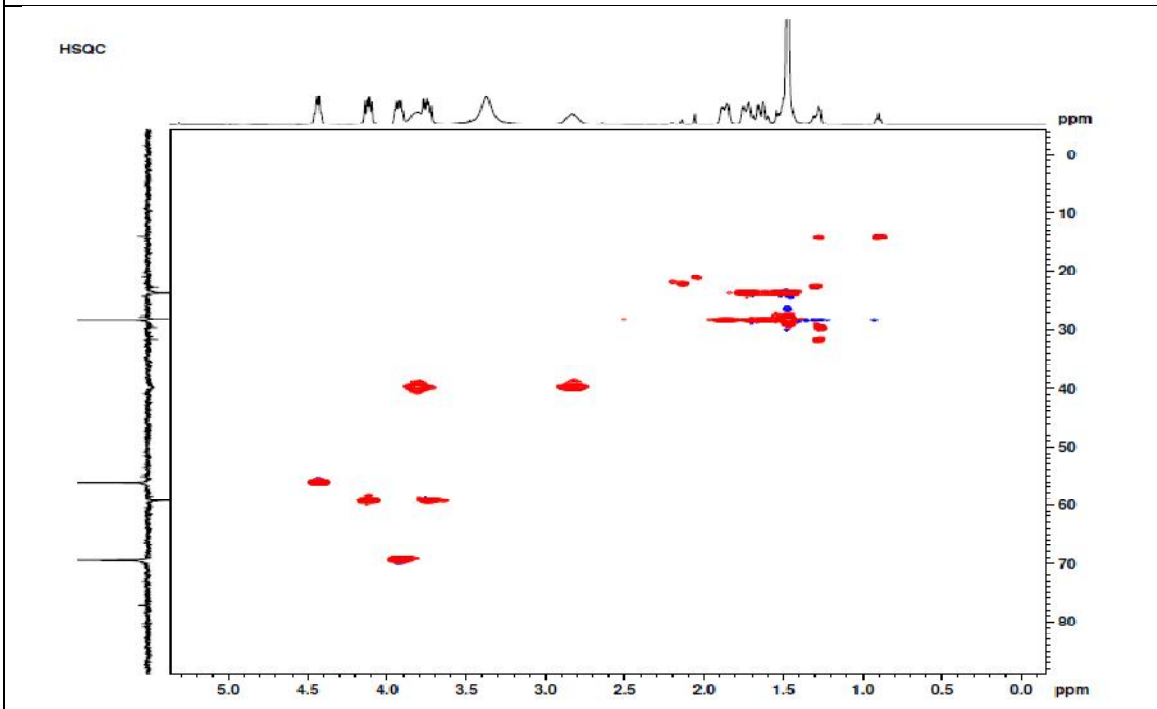
DEPT spectrum of compound **111** ($CDCl_3$+CCl_4, 100 MHz)



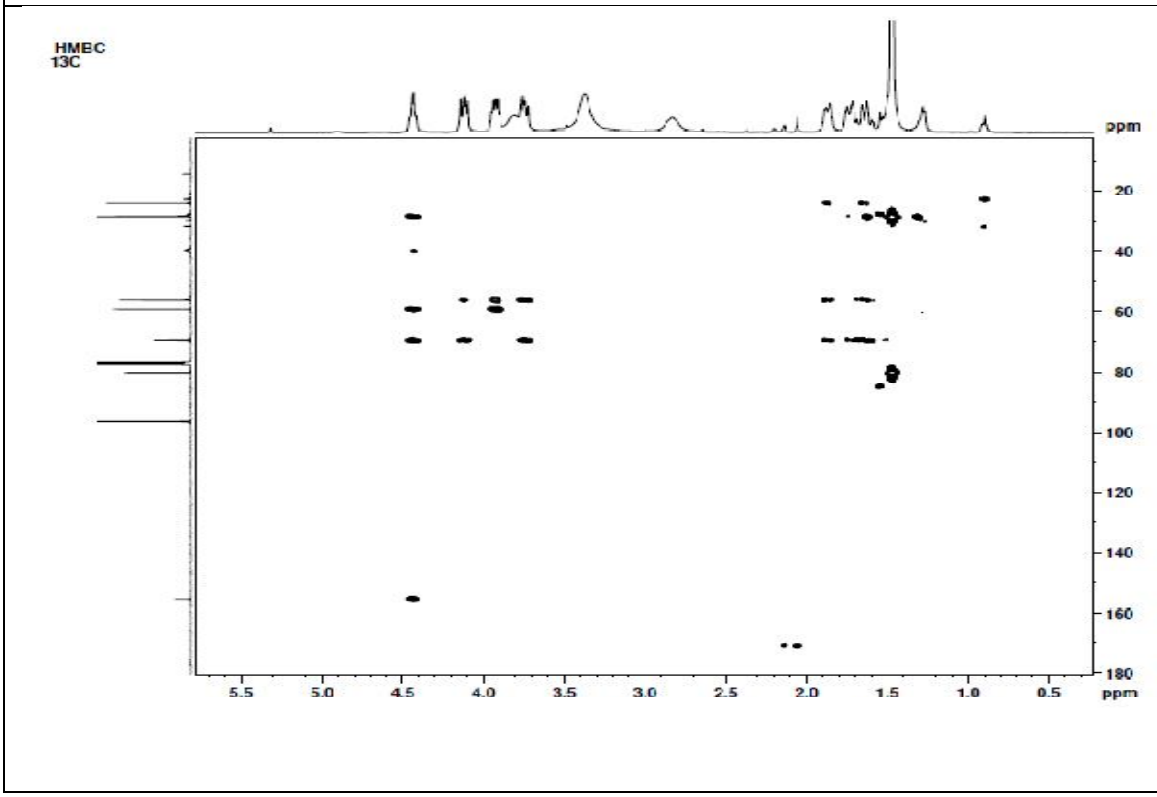
COSEY of compound **111** ($CDCl_3$+CCl_4, 100 MHz)



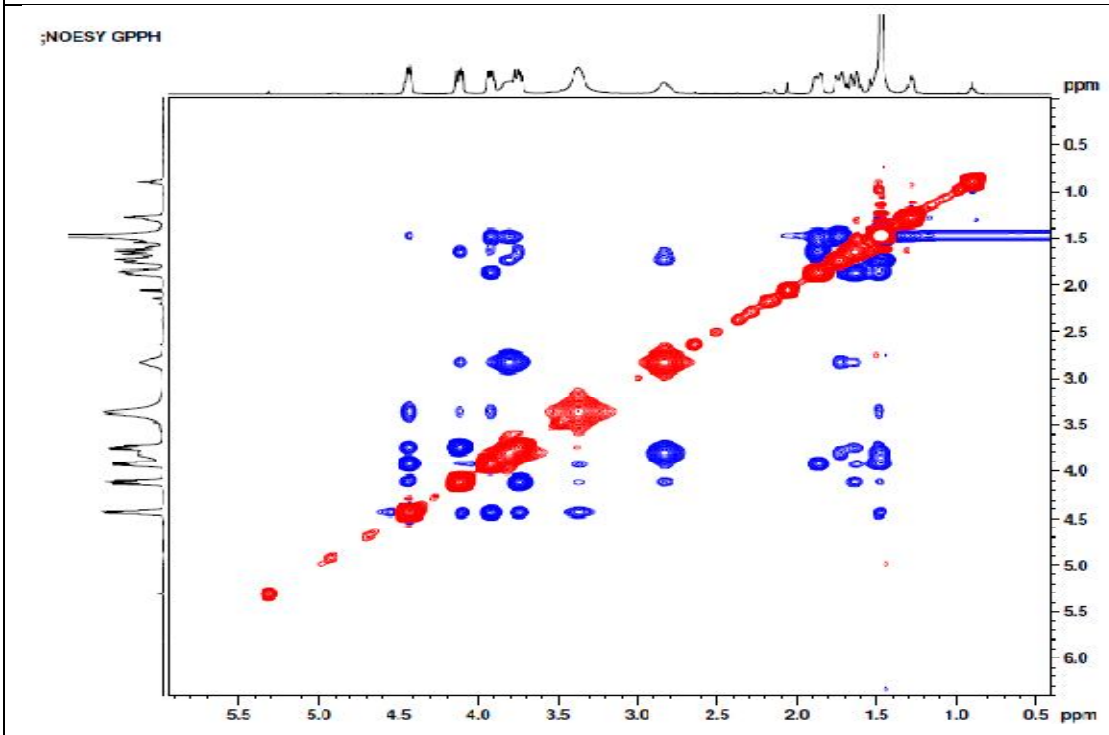
HSQC of compound **111** ($CDCl_3$+CCl_4, 100 MHz)



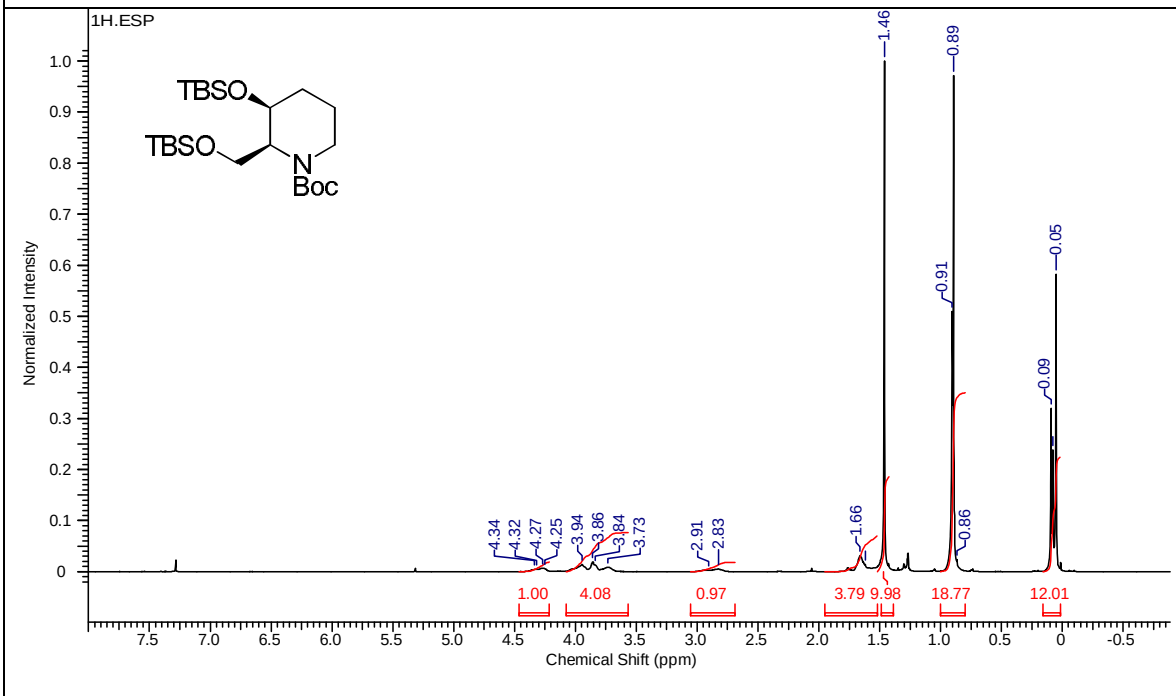
HMBC of compound **111** ($CDCl_3$+CCl_4, 100 MHz)



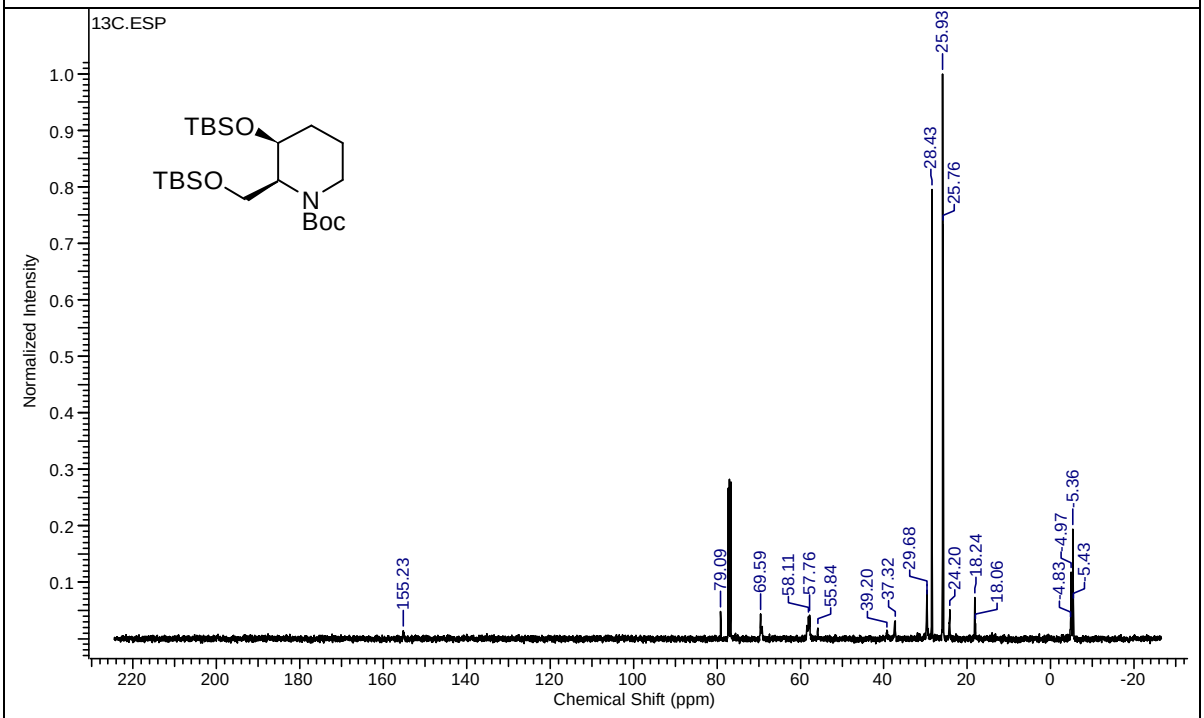
NOSEY of compound **111** ($CDCl_3$+CCl_4, 100 MHz)



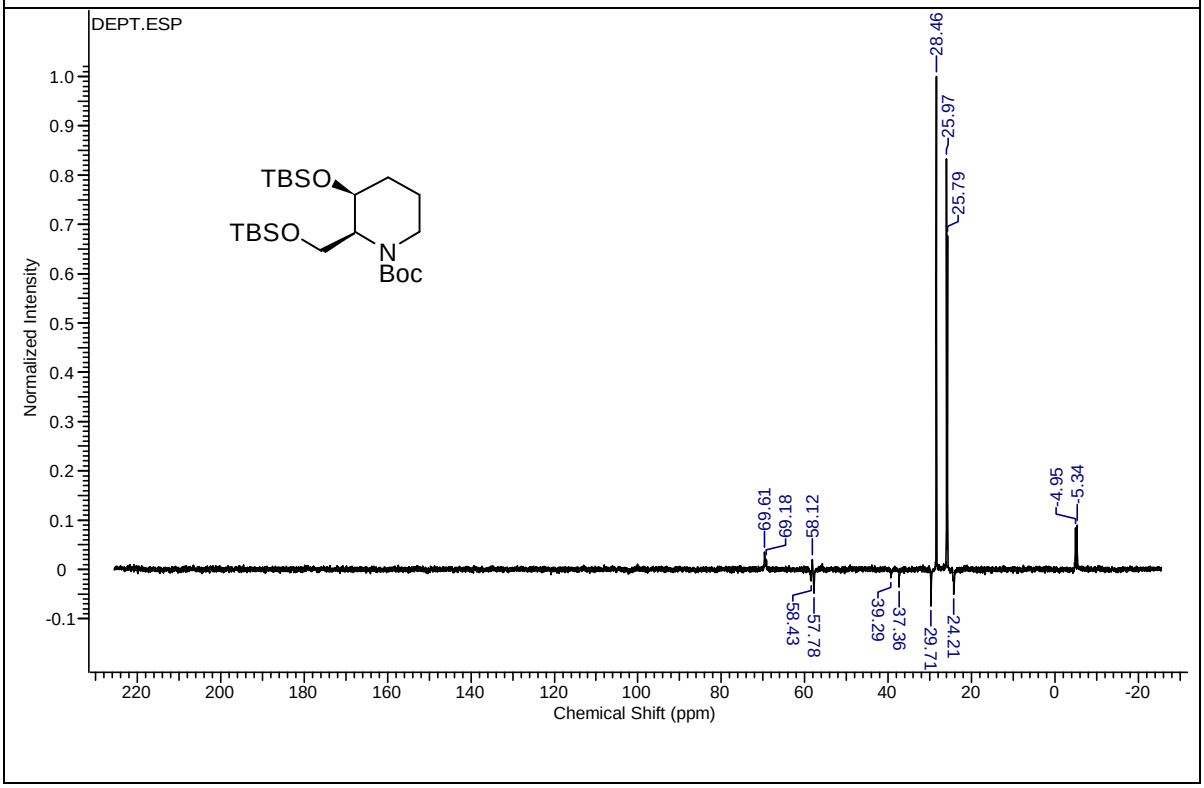
^{1}HNMR of compound **110** ($CDCl_3$, 400 MHz)



^{13}CNMR of compound **110** ($CDCl_3$, 100 MHz)



DEPT of compound **110** ($CDCl_3$, 100 MHz)



1.3.7. References

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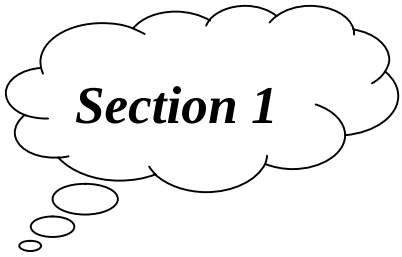
Chapter 2

Synthetic studies towards total synthesis of (+)-deoxoprosophylline and 1-deoxynojirimycin



Introduction to (+)-deoxoprosophylline

2.1.1Introduction

The 2,6-piperidine ring system is one of the most common structural unit found in number of natural and unnatural molecules. Watson *et al*.[1] in year 2000 has reported that the piperidinic structure was mentioned in over 12000 compounds in clinical or pre-clinical studies from July 1988 through December 1998. This observation showed that this motif as been an attractive target of synthetic organic chemists with considerable amount of work done in this regards, in particular with respect to enantiopure syntheses. Multifunctionalized piperidine alkaloids, like polyhydroxylated piperidines and their synthetic analogs are the focus of great interest in the pharmaceutical industry due to their range of biological activities.

The deoxoprosophylline has been isolated from the African mimosa *Prosopis African taub*[2] found in Africa. 2,6-Disubstituted piperidine-3-ols isolated from genera *Prosopis* and *Cassia* are called Prosopis alkaloids and Cassia alkaloids respectively. Prosopis alkaloid family includes members like (+)-deoxoprosophylline **1**, prosophylline **2**, prosopinine **5**, deoxoprosopinine **4** and related compounds; while Cassia alkaloids contain members like prosafrinine **3**, spectaline **8**, deoxocasssine **6** and related compounds. Although, piperidine ring is present in many alkaloids, Prosopis alkaloids and Cassia alkaloids have special structural characteristics. These contain a polar hydrophilic head group which is constituted by 2,6 disubstituted piperidine-3-ol and hydrophobic group which contains long hydrocarbon chain. This hydrophobic part facilitates penetration through lipid membrane present in cell

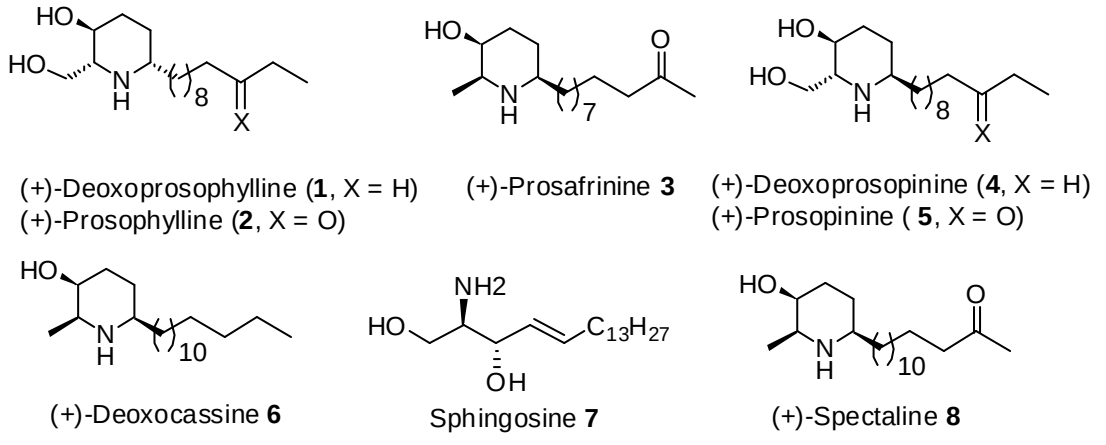


Figure 1. Structures of Prosopis, Cassia alkaloids and their synthetic analogues.

wall.[3] These alkaloids can mimic carbohydrate substrates in number of enzymatic processes.[4] On the other hand, polar head group displays selective inhibition of various enzymes such as

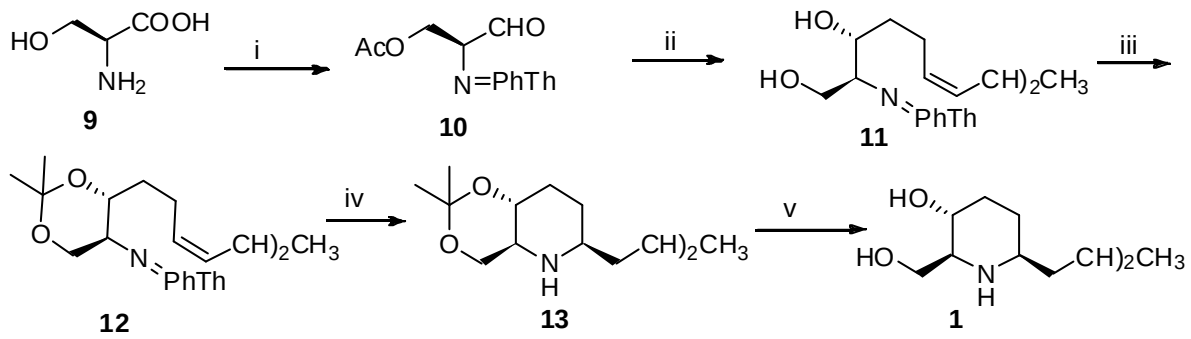
glycosidase, involved in processing glycoproteins. These alkaloids also display acetylcholine esterase inhibition,[5] cytotoxicity,[3b] antibacterial,[3c-f] antimycotic,[3c,e] DNA binding,[3g] anesthetic and analgesic activities.[3h,i] (+)-Deoxoprosophylline is nothing but a reduced scaffold of (+)-prosophylline. It is pharmaceutically important alkaloid as it can be useful for the treatment of viral infection, diabetes and cancer.[6] Its structure and inhibitory activity relationships are not fully understood.[7] Deoxoprosophylline can be assumed as cyclic analogue of lipid sphingosine.[8] (+)-Deoxoprosophylline **1** has attracted many synthetic organic chemists due to its therapeutic potential, interesting structural characteristics and various biological activities to newer synthetic approaches and has been a popular synthetic target. There are several reports in literature available for the enantioselective syntheses of deoxoprosophylline starting from amino acids,[2b,9] carbohydrates,[10] vitamin C,[11] malic acid,[12] or compounds of synthetic origin.[13]

2.1.2. Literature review

Along with the interesting structural features, these piperidine alkaloids and their synthetic analogs show significant biological activities. These various attractive features of piperidine alkaloids have attracted many synthetic organic chemists. A great deal of effort has been devoted to the synthesis of these alkaloids.[14] Among the synthetic routes reported for deoxoprosophylline, the strategy often used is to employ either sugars or amino acids as the chiral pool starting materials. Some of the important literature syntheses are given below.

Takahashi's approach (1980)[15]

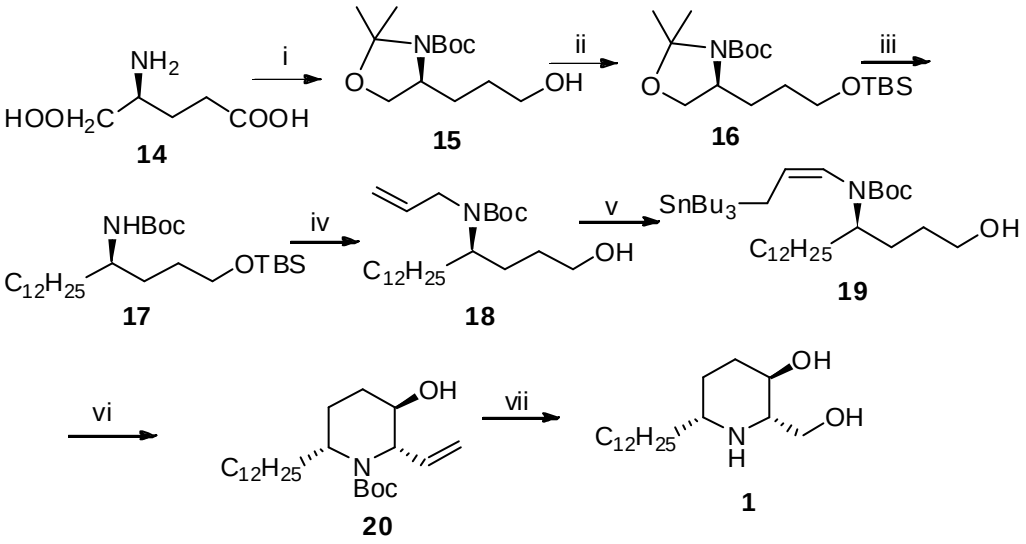
Takahashi *et al.* reported synthesis of (-)-deoxoprosophylline using L-serine **9** as starting material. They synthesized 2*S*-3-acetoxy-2-pthalimido propanal from L-serine **9** by reported method. Grignard reaction of **10** with (*Z*)-3-pentadecenyl bromide gave mixture of diastereomers, in which the major isomer was hydrolyzed and protected as acetonide derivative **11**. Phthaloyl (PhTh) deprotection and aminomercuration of compound **11** with $Hg(OAc)_2$ followed by demercuration with $NaBH_4$ giving two diastereomeric piperidine acetonides **12** and its C-6 epimer. Finally acid hydrolysis of acetonide **13** afforded (-)-deoxoprosophylline (Scheme 1).



Scheme 1. *Reagents and conditions:* (i) *Ref.* 16; (ii) (*Z*)-$CH_3(CH_2)_{10}CH{=}CHCH_2CH_2Br$, Mg, THF: Ether (2:1), -70 ^oC to -40 ^oC; (iii) (a) HCl, MeOH, reflux; (b) 2,2-dimethoxy propane, *p*-TSA (iv) (a) $NH_2.NH_2.H_2O$; (b) $Hg(OAc)_2$, MeOH, rt; (c) $NaBH_4$; (v) HCl, MeOH, reflux.

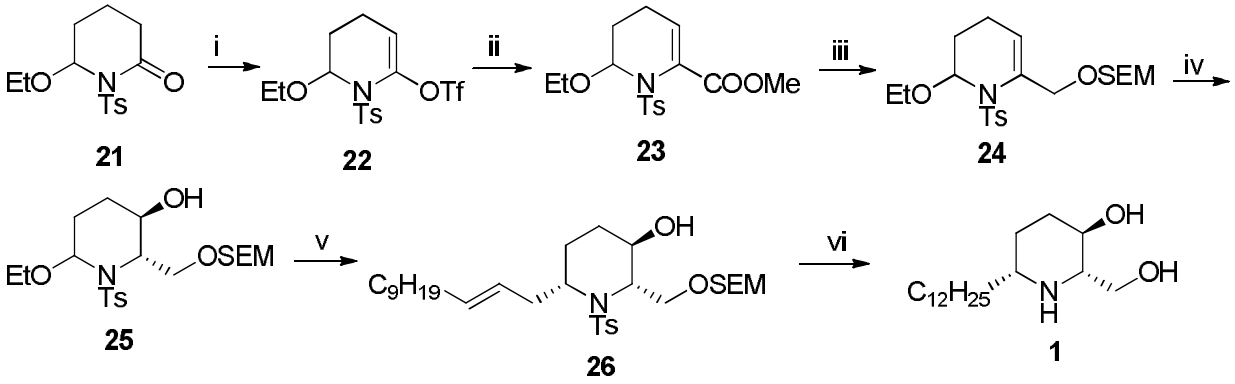
Yamamoto's approach (1997)[17]

Yamamoto *et al*. used L-glutamic acid which was converted to alcohol by wel documented method. Glutamic acid **14** derived compound **15** after protection of its free hydroxyl as TBS ether and selective deprotection of *N*, *O*-acetal gave compound **16**. Tosylation of **16** followed by alkylation with $C_{11}H_{23}Li$/CuI furnished the compound **17**. Allylation and subsequent desilylation of **17** gave **18**, which on treatment with sec-BuLi/TMEDA followed by the reaction of corresponding allylic anion with n-Bu_3SnCl afforded the allyl stannane derivative **19**. Oxidation of **19** followed by Lewis acid catalyzed cyclization gave **20** and it's C-2 epimer. Ozonolysis of **20** followed by $NaBH_4$ reduction and N-Boc deprotection furnished (-)-deoxoprosophylline (Scheme 2).



Scheme 2. *Reagents and conditions:* (i) *Ref*. 18; (ii) (a) TBSCl, imidazole, CH_2Cl_2, rt, 100%; (b) $PdCl_2(CH_3CN)_2$, CH_3CN, reflux, 98%; (iii) (a) TsCl, Et_3N, DMAP, CH_2Cl_2, 98%; (b) $C_{11}H_{23}Li$, CuI, Et_2O, -35 ^oC, 82%; (iv) (a) Allyl bromide, KH, THF, 0 ^oC-rt, 92%; (b) TBAF, THF, RT, 74%; (v) *Sec*. BuLi, TMEDA, THF, -78 ^oC then n-Bu_3SnCl, -78 ^oC-rt, 61%; (vi) (a) SO_3, Pyridine, DMSO, Et_3N, CH_2Cl_2, 0 ^oC, 92%; (b) $MgBr_2.OEt_2$, CH_2Cl_2, 0 ^oC, 72%; (vii) (a) O_3, MeOH, -78 ^oC then $NaBH_4$, -78 ^oC-rt; (b) 6 N HCl, Dioxane, reflux.

Speckamp's approach (1997)[19]



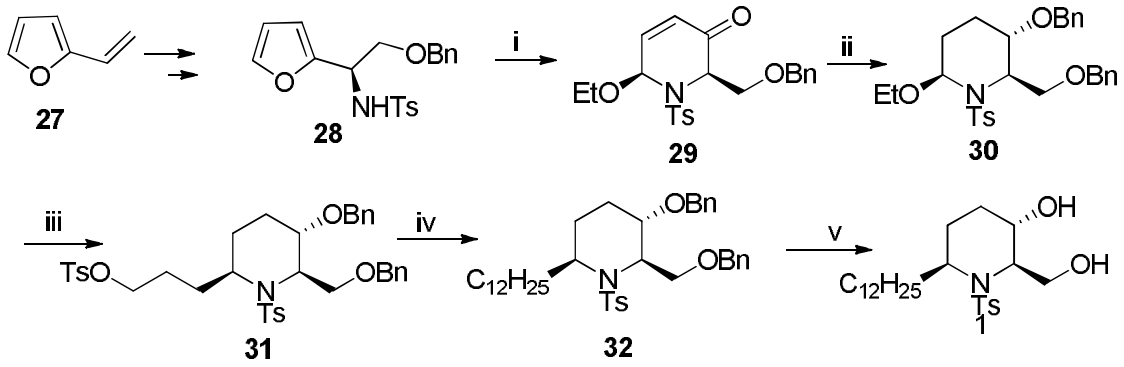
Scheme 3. *Reagents and conditions:* (i) Comin's procedure, *Ref*. 20; (ii) $Pd(AsPh_3)_4$, CO, MeOH, DMF; (iii) (a) DIBAL-H, THF, 70%; (b) SEMCl, DIPEA, CH_2Cl_2, 80%; (iv) (a) BH_3.THF, -78 ^oC then Me_3NO, 85%; (b) TBSOTf, 2,6-Lutidine, CH_2Cl_2, 92%; (v) $C_9H_{19}CH(SiMe_3)CH{=}CH_2$, $BF_3.OEt_2$, -78 ^oC, 55%; (vi) (a) Pd/C, H_2, MeOH; (b) HCl (0.4 M in MeOH), 75% (two steps) (c) Na/NH_3, 75%.

Speckamp *et al* synthesized enol triflate **22** derived from tosyl amide **21**, on methoxy carbonylation yielded ester **23**. Selective 1,2-reduction of ester **23** gave an alcohol, which was

protected as SEM ether **24**. Hydroboration of **24** followed by oxidative work up with trimethylamine *N*oxide afforded alcohol, which was protected as TBS ether **25**. Introduction of 12-carbon chain in one step was straightforward reaction by the generation of *N*-tosyliminium ion. Hydrogenation of olefin **26**, followed by deprotection of the hydroxy and amino groups gave (-)-deoxoprosophylline (Scheme 3).

Zou's approach (1998)[21]

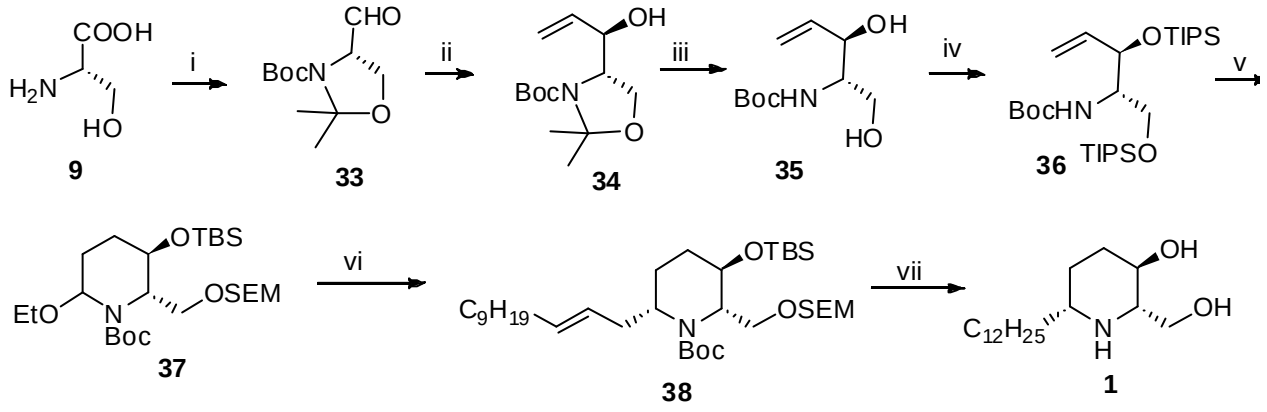
Zhou *et al.* have reported synthesis of (-)-deoxoprosophylline from α-furyl amine derivative **28**. α-furyl amine derivative **28** was obtained from α-furyl ethylene **27** after five steps.This compound **28** was treated with *m*-CPBA and the resultant hydropyridone was protected to give the compound **29**. Reduction of keto group followed by protection of the hydroxyl group as benzyl ether gave compound **30**. Treatment of **30** with allyl trimethyl silane followed by hydroboration and tosylation delivered **31**. Treatment of **31** with Grignard reagent afforded compound **32**. Deprotection of hydroxyl and amino groups delivered (+)-deoxoprosophylline (Scheme 4).



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

Ojima's approach (1998)[22]

Ojima *et al.* used *S*-Garner aldehyde **33** for synthesis of (-)-deoxoprosophylline. *S*-Garner aldehyde **33** was subjected for Grignard reaction with vinylmagnesium bromide afforded mixture of alcohols (6:1 ratio), which were separated to give the desired allyl alcohol **34**. Removal of the acetonide group to get dihydroxy compound **35** followed by protection of

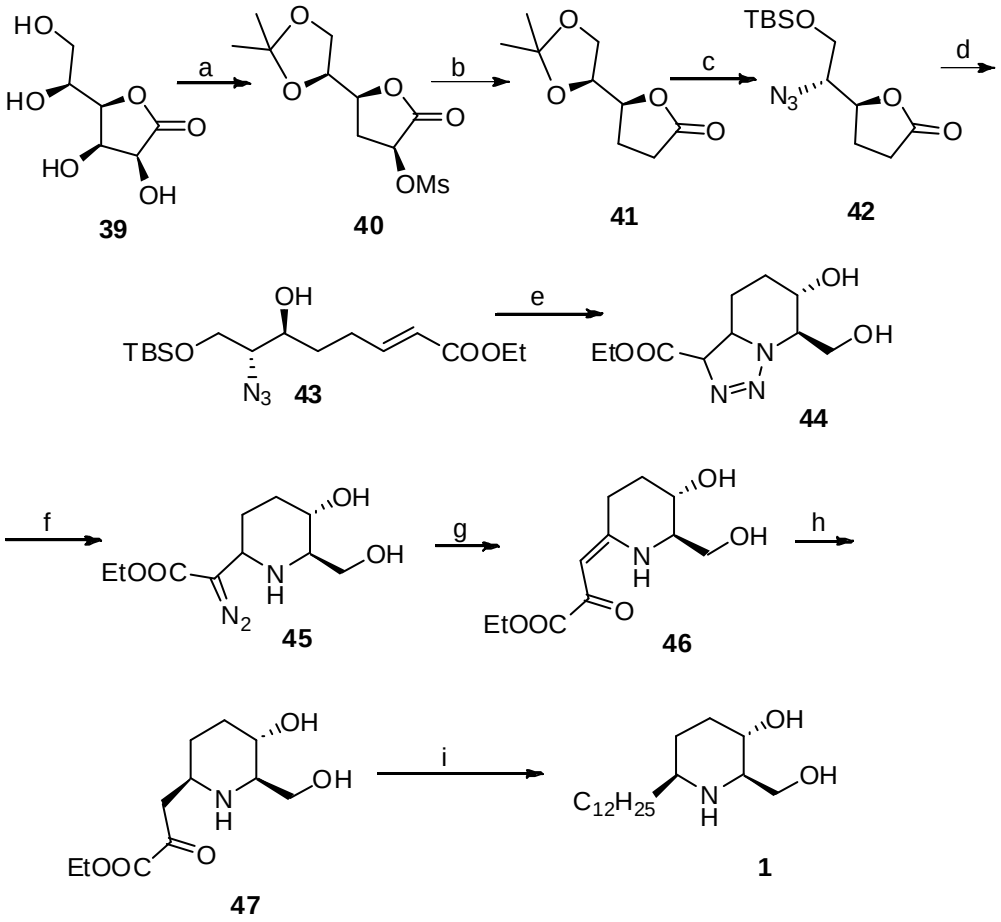


Scheme 5. *Reagents and conditions:* (i) *Ref*. 23; (ii) Vinylmagnesium bromide, 77%; (iii) *p*-TSA, MeOH, 95%; (iv) TIPSCl, imidazole, DMF, 83%; (v) $Rh(acac)(CO)_2$ (1 mol%), BIPHEPHOS (2 mol%), H_2/CO (1/1, 4 atm), EtOH, 65 ^oC, 96%; (vi) $C_9H_{19}CH(SiMe_3)CH=CH_2$, $BF_3.Et_2O$, -78 ^oC, (vii) (a) TBAF, THF; (b) Pd/C, H_2; (c) CF_3COOH, CH_2Cl_2.

hydroxyl groups in **35** as TIPS ether gave compound **36**. Rh-BIPHEPHOS complex catalyzed cyclo hydrocarbonylation of **36** at 65 ^oC and 4 atm CO and H_2 (1:1) in ethanol afforded the key intermediate **37**, which on reaction with allyl silane in the presence of $BF_3.OEt_2$ at –78 ^oC gave compound **38**. Compound **38** on Sequential hydroxyl group deprotection, hydrogenation and *N*-Boc deprtection delivered (-)-deoxoprosophylline. They have also synthesized (+)-Prosopinine starting from *R*-Garner's aldehyde using almost the same reaction sequence (Scheme 5).

Herdeis's approach (1999)[24]

Herdeis *et al*. synthesized (+)-deoxoprosophylline from L-gulanolactone **39**. They synthesized α-mesylated lactone **40** from L-gulanolactone **39**. Conversion of mesyl to Iodo followed by sequential halogenation, acetonide deprotection and selective protection of resultant diol as its TBS derivative delievered the lactone **41**. Conversion of hydroxy compound to azide **42** followed by DIBAL-H reduction and 2-carbon Wittig homologation delivered the α,β-unsaturated ester **43**, which on keeping at room temperature gave the triazole **44** as a diastereomeric mixture. Triazole **44** was converted into urethane derivative **46**, which on hydrogenation gave the piperidine **47** with the required stereochemistry. Sequential hydroxy protection, DIBAL-H reduction, Wittig homologation, hydrogenation and final hydrolysis delivered the (+)-deoxoprosophylline (Scheme 6).

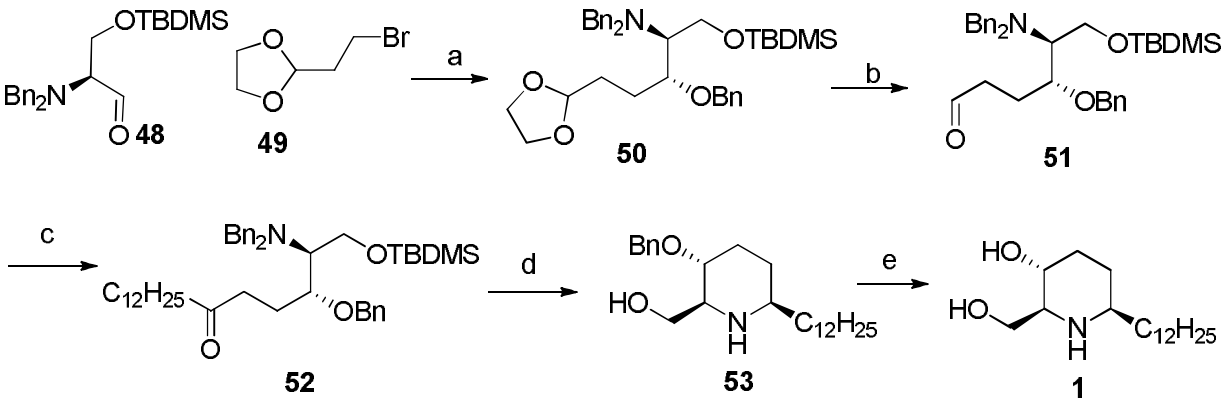


Scheme 6. *Reagents and conditions:* a) *Ref*. 25; b) i. NaI, Acetone, reflux, 92%; ii. H_2, Et_3N, 10% Pd/C, 82%; iii. Conc HCl, *i*-PrOH, 96%; iv. TBSCl, Et_3N, DMAP, DMF, 99%; c) i. MsCl, Et_3N, CH_2Cl_2, 79%; ii. NaN_3, DMPU, 70 ^oC, 65%; d) i. DIBAL-H, THF, -78 ^oC, 69%; ii. Ph_3P=CHCOOEt, Toluene, rt; e) Toluene, rt, 4 days, 98%; f) Et_3N, CH_2Cl_2, 96%; g) i. $Rh_2(OAc)_4$, 97%; ii. H_2, 10% Pd/C, EtOH, 71%; g) i. TBSCl, Im, DMF, 84%; ii. DIBAL-H, *n*-Pentane, -78 ^oC, 66%; h) i. $Ph_3P^+(CH_2)_4CH_3Br^-$, LiHMDS, THF, 79%; ii. H_2, 10% Pd/C, EtOH, 93%; i) HCl, EtOH, 15 min, 6 N KOH, 87%.

Zhu's approach 2001)[26]

Zhu and Jourdnt have synthesized (-)-deoxoprosophylline using L-serine **9** as starting material. Nucleophilic addition of Grignard reagent **49** (Buchi Grignard reagent), on serine aldehyde **48** provided **50**. Protection of the secondary alcohol as its benzyl ether followed by acidic hydrolysis of dioxolane gave the aldehyde **51**. Reaction of aldehyde **51** with dodecyl magnesium bromide afforded alcohol **52**. Swern oxidation and catalytic transfer

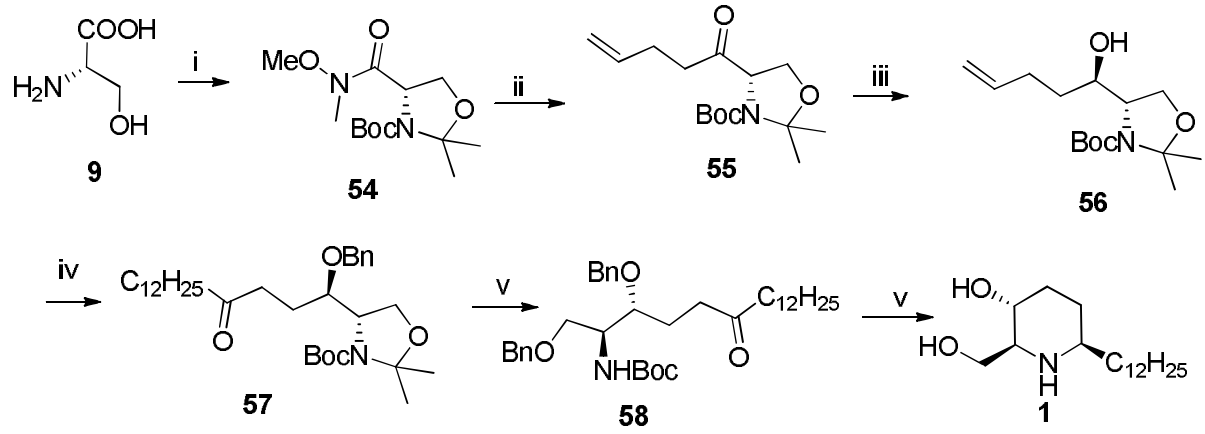
hydrogenolysis provided O-benzyl deoxoprosophylline **53**, which on debenzylation gave the (-)-deoxoprosophylline **7** (Scheme 7).



Scheme 7. *Reagents and conditions:* a) **49**, Mg, THF, rt, 86%; b) i. NaH, BnBr, TBAI, THF, 0 ^{o}C to rt, 85%; ii. 3N HCl, THF; iii. TBSCl, Im, DMF, rt, 90%; c) $C_{12}H_{25}MgBr$, THF, 70 ^{o}C, 80%; d) i. DMSO, $(COCl)_2$ then Et_3N, 84%; ii. $Pd(OH)_2$, Cyclohexene, EtOH, reflux; e) Pd/C, MeOH, 73%.

Apurba Datta's approach (2001)[27]

Weinreb amide was utilized by Datta *et al*. for synthesis of (-)-deoxoprosophylline. In this approach Weinreb amide **54** was subjected for Grignard reaction with 3-butenyl magnesium



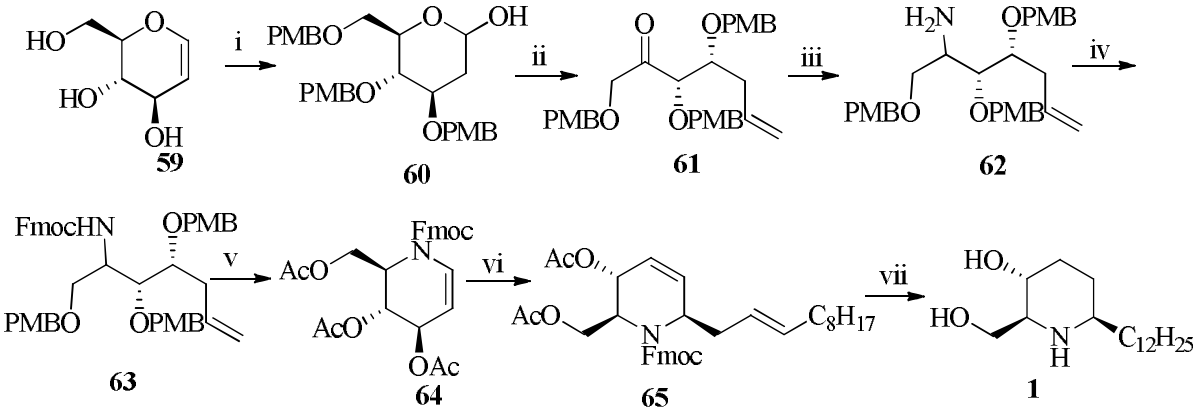
Scheme 8. *Reagents and conditions:* (i) *Ref.* 26 b; (ii) $CH_2=CH(CH_2)_2MgBr$, THF, 0 ^{o}C, 76%; (iii) $Zn(BH_4)_2$, Et_2O, Benzene, 70%; (iv) (a) NaH, BnBr; (b) OsO_4, $NaIO_4$; (c) $C_{12}H_{25}MgBr$; (d) 2-Iodoxybenzoic acid; (v) (a) 80% AcOH in H_2O; (b) BnBr, Ag_2O; (vi) (a) HCOOH; (b) $Pd(OH)_2$, H_2, EtOH, dil. HCl.

bromide which afforded the ketone **55**. $ZnBH_4$ mediated chelation controlled reduction of ketone **54** gave the *anti* amino alcohol **56**. Protection of the free hydroxyl group as its benzyl

ether followed by oxidative cleavage of double bond afforded the aldehyde, which on Grignard reaction with dodecyl magnesium bromide and subsequent oxidation gave ketone **57**. Selective hydrolysis of acetonide and protection of hydroxyl as benzyl ether gave ketone **58**. Treatment of ketone **58** with formic acid followed by hydrogenation delivered (-)-deoxoprosophylline (Scheme 8).

Shipman's approach (2002) [28]

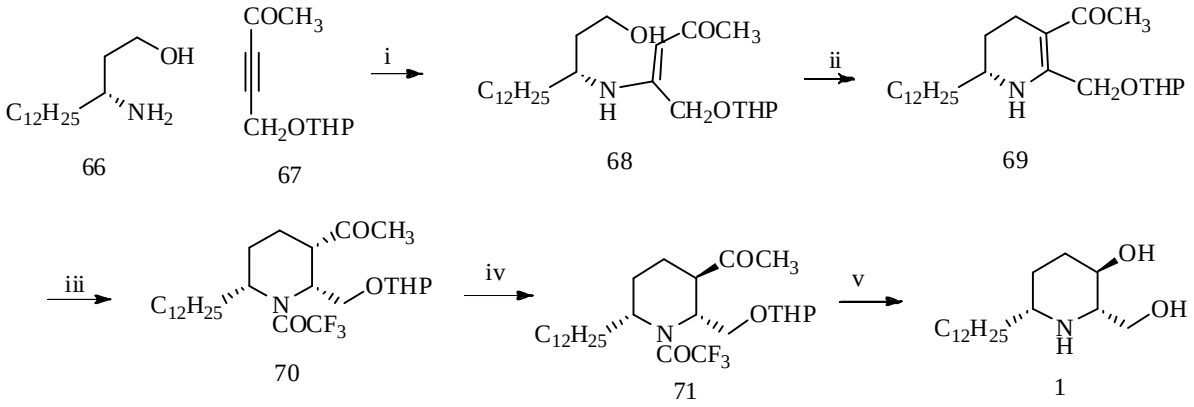
Shipman *et al* utilized D-glucal to synthesize (-)-deoxoprosophylline. Protection of the hydroxyl groups in glucal **59** followed by hydration of double bond gave hemiacetal **60**. Wittig olefination of **60** followed by TPAP oxidation of the resulting secondary alcohol gave ketone **61**, which was converted in to amine **62**. This **62** after masking of amine to obtain **63**, then ozonolytic cleavage of the terminal double bond, followed by dehydration of the hemiacetal gave 3, 4, 6-tri-O-acetylimino glucal **64**. Addition of 3-(trimethyl silyl) dodecec-1-ene to 6 smoothly gave piperidine **65** after Fmoc deprotection. Hydrogenation of **65** followed by removal of the acetate groups delivered (+)-deoxoprosophylline (Scheme 9).



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

Dawei Ma's approach (2003)[29]

Dawei *et al.* used Davies procedure[30] for preparation of chiral amino acid which was utilized for the synthesis of (-)-deoxoprosophylline. Michael addition of **66** to the alkynone **67** gave the enamine **68**, which on treatment with PPh_3 and CCl_4 followed by refluxing in acetonitrile afforded cyclic enamine **69**. Hydrogenation of **69** gave the corresponding piperidine, which was protected with trifluoro acetic anhydride to provide the amide **70**. Epimerization of the 3-acetyl group of **70** was achieved by treating with DBU to deliver compound **71**. Treatment of **71** with trifluoroperacetic acid afforded the Baeyer-Villiger product, which was hydrolysed to deliver the (-)-deoxoprosophylline (Scheme 10).

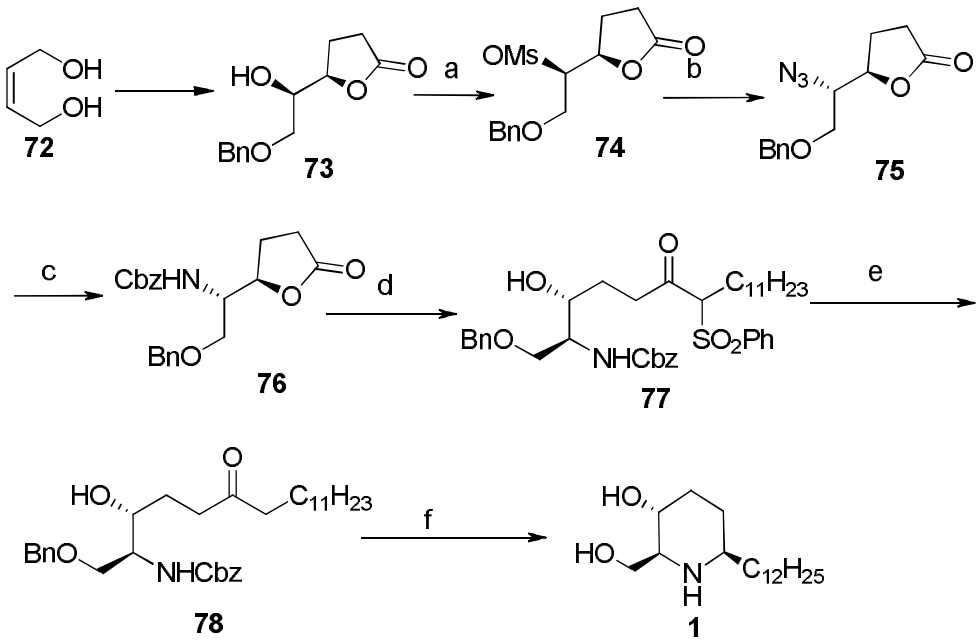


Scheme 10. *Reagents and conditions:* (i) DMF, rt, 82%; (ii) (a) PPh_3, CBr_4, Et_3N, CH_2Cl_2; (b) Et_3N, CH_3CN, Reflux, 76%; (iii) (a) PtO_2, H_2, AcOH; (b) $(CF_3CO)_2O$, Et_3N, DMAP; (iv) DBU, THF, rt, 87%; (v) (a) 95% H_2O_2, $(CF_3CO)_2O$, NaH_2PO_4, CH_2Cl_2; (b) HCl-MeOH, 45 %.

Chavan's approach (2004)[31,32]

Chavan *et al.* reported total synthesis fo both the antipodes of deoxoprosophylline from *cis*-butene-1,4-diol derived lactone synthon. The key synthon **73** was synthesized by known protocol. This lactone **73** was converted into azido lactone **75**. This conversion was carried out by mesylation of hydroxy lactone **73** with mesyl chloride and Et_3N in anhydrous CH_2Cl_2 at 0 ^oC to furnish mesylate **74** in 92% yield. The mesyl in 104 was nucleophilically displaced with NaN_3 in anhydrous DMF to deliver the azido lactone **75** in 89% yield. The azidolactone **75** was converted into Cbz lactone **76**. Thus the azide was reduced to amine using triphenylphosphine and water and the resulting amine was protected as its cbz derivative using CbzCl, TEA and cat. DMAP to yield compound **76**. Next the Cbz lactone was opened by using $C_{12}H_{25}SO_2Ph$ and *n*-BuLi at – 78 ^oC to furnish the compound **77** in 94% yield as a

1:1 mixture of two diastereomers at the C-7 position. The desulphonylation of **77** was rcarried out with 6% Na-Hg and Na_2HPO_4 in MeOH at - 10 ^oC to give **78** in 95 %



Scheme 11. *Reagents and conditions:* a) CH_3SO_2Cl, Et_3N, CH_2Cl_2, DMAP, 0 ^oC, 92%; b) NaN_3, DMF, 90 ^oC, 12 h, 89%; c) i) PPh_3, Benzene:Water (1:1), 8 h, ii) CbzCl, Et_3N,Cat. DMAP, DCM, 75%,; d) $C_{12}H_{25}SO_2Ph$, *n*-BuLi, THF, - 78 ^oC, 94%; e) 6% Na-Hg, Na_2HPO_4, MeOH, -10 ^oC, 95%; f) $Pd(OH)_2/C$, H_2, MeOH, rt, 24 h, 76%.

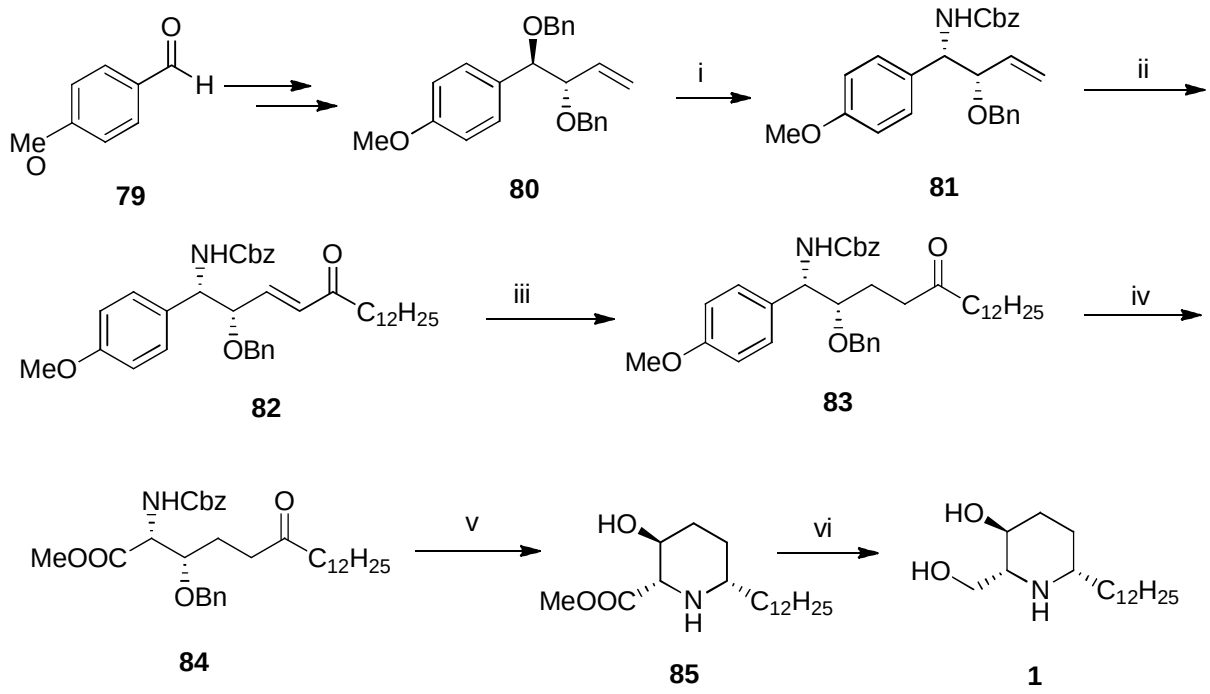
yield. The protecting groups and cyclization of the ketone **78** was achieved in one pot reaction by using $Pd(OH)_2$ and H_2 to provide the (+)-deoxoprosophylline **5** in 76% yield (Scheme 11).

Having accomplished the synthesis of (+)-deoxoprosophylline **1**, the synthesis of its enantiomer *i.e* (-)- deoxoprosophylline **1** was also achieved. Accordingly *cis*-2-butene-1, 4-diol **72** was transformed in a similar fashion to afford (-)- deoxoprosophylline following a similar reaction sequence however, using AD-mix-β in the crucial Sharpless asymmetric dihydroxylation of β, γ-unsaturated ester.

Jung's approach (2007)[33]

Jung and co-workers reported synthesis of (-)-deoxoprosophylline by chirality induction method. In this they carried stereoselective amination of *anti*-1,2-dibenzyl ether using chlorosulfonyl isocyanate (CSI) as key step. Synthesis began with *anti*-1,2-dibenzyl ether **80** obtained from *p*-anisaldehyde **79**. The regioselective and diastereoselective amination of *anti*-

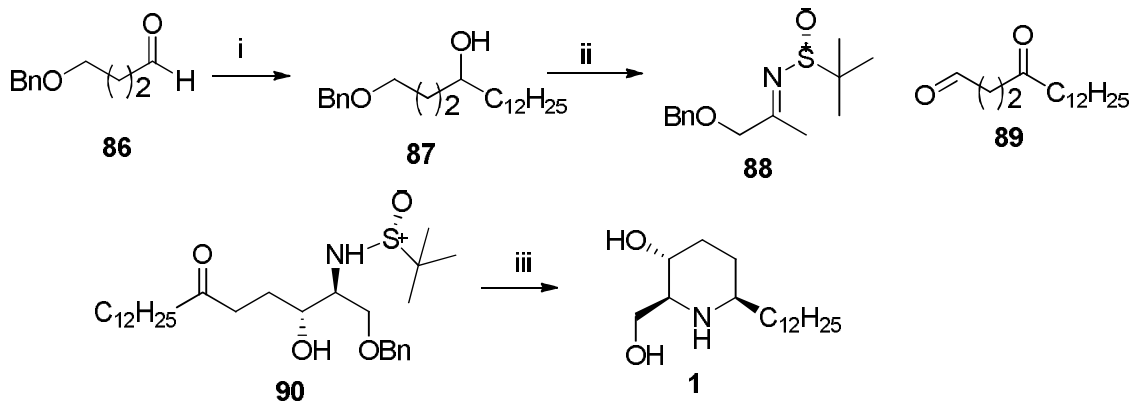
1,2-dibenzyl ether **80** using chlorosulfonyl isocyanate gave *anti*-1,2-amino alcohol **81**. Further *anti*-1,2-amino alcohol **81** was then converted into *α,β*-unsatrated keto compound **82** using cross-metathesis. This **82** on Pt catalyzed hydrogenolysis yielded saturated keto compound **83**. Further, aromatic part was chopped of using cat. $RuCl_3$ and $NaIO_4$ followed by esterification by diazomethane to afford ester **84.** Pd-catalyzed intramolecular cyclization of **84** provided compound **85,** which on reduction provided (-)-deoxoprosophylline (Scheme 12).



Scheme 12: (i) (a) CSI, Na_2CO_3, toluene, -78 ^oC, 24 h; (b) 25% Na_2SO_3, 24 h; (ii) pentadec-1-en-3-one, Hoveyda 2nd Grubb's catalyst, toluene, 80 ^oC, 48 h; (iii) PtO_2, H_2, EtOAc, 2 h; (iv) (a) cat. $RuCl_3$, $NaIO_4$, H_2O/CH_3CN/EtOAc (2:1:1), 4 h; (b) CH_2N_2, Et_2O, 0 ^oC, 1 h; (v) 10% Pd/C, H_2, MeOH, 24 h; (vi) (a) $LiAlH_4$, THF, 12 h; (b) 8 N KOH, MeOH, reflux, 10 h.

Liu's approach (2008)[34]

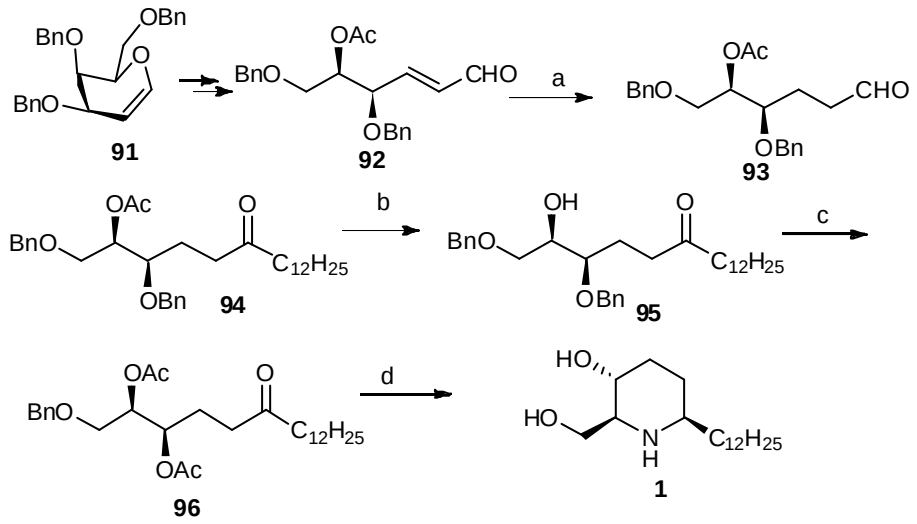
Liu *et al.* have reported the synthesis of (-)-deoxoprosophylline using SmI2-mediated cross-coupling of chiral *N-tert*-butanesulfinyl imine **88** with 4-oxohexadecanal **89**. The imine **88** was generated from aldehyde **86** by Grignard reaction of dodecylmagnesium bromide on **86**. Removal of the chiral auxiliary in **90** followed by acidic hydrogenation gave (-)-deoxoprosophylline **2** (Scheme 13).



Scheme 13: (i) $C_{12}H_{25}MgBr$, THF, 88%; (ii) (b) Pd/C, H_2, MeOH, 25 ^oC, 12 h; (b) PCC, CH_2C_{l2}, 5 h, two steps 81%; (iii) SmI_2, *t*-BuOH, THF, 83%; (iv) (a) HCl/MeOH, MeOH; (b) $Pd(OH)_2/C$, H_2, EtOH, 4 h, then conc. HCl, 33 h, two steps 58%.

Vankar's approach (2010)[35]

Vankar *et al.* have described the synthesis of (-)-deoxoprosophylline starting from chiral staring material, 3,4,6-*tri*-*O*-benzyl glycol **91**. Thus, 3,4,6-*tri*-O-benzylated glycals **91** was subjected to Perlin hydrolysis followed by acetylation to afford *trans*-enals **92**. Chemoselective saturation of double bond in **92** was carried out under H_2/Pd-C conditions to give **93**. The obtained aldehyde **93** was subjected to Grignard reaction using dodecylmagnesium bromide and further oxidation of the free hydroxyl gave ketones **94**. Methanolysis of acetate **94** gave the hydroxy ketone **95**. Conversion of the hydroxyl group of **95** as mesylate followed by an SN^2 displacement with sodium azide gave the azido derivative **96**. These azido ketone **96** underwent reductive ring closure followed by debenzylation gave single isomer of (-)-deoxoprosophylline **2** (Scheme 14).



Scheme 14: (a) H_2/Pd-C, EtOAc, 30 min, 92%; (b) i. $C_{12}H_{25}MgBr$, Et_2O, -78 ^oC; ii. CrO_3, Py, Ac_2O, CH_2Cl_2, 0 ^oC, 71% for two steps; (c) NaOMe (cat.), MeOH, 2 h, 86%; (d) i. MsCl, Et_3N, 0 ^oC, CH_2Cl_2, 20 min, 96%; ii. NaN_3, DMF, 110 ^oC, 6 h, 85%; (e) i. H_2/$Pd(OH)_2$; ii. MeOH, 82%.

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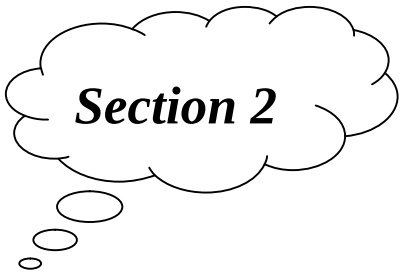
Chapter 2

Synthetic studies towards total synthesis of (+)-deoxoprosophylline and 1-deoxynojirimycin



Total synthesis of (+)-deoxoprosophylline from L-(+)-diethyl tartrate

2.2.1. Objective:

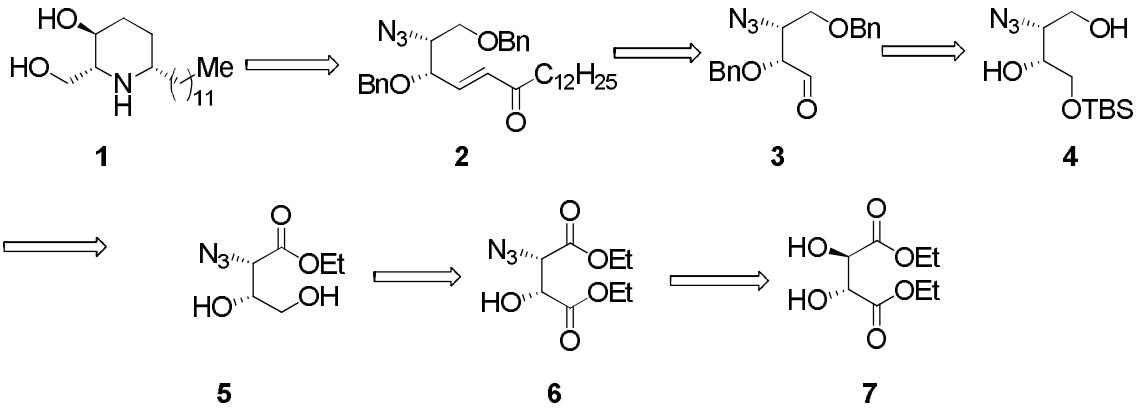
As a part of ongoing programme on the synthesis of piperidine alkaloids of biological relevance[1] the synthesis of (+)-deoxoprosophylline **1** was undertaken by this group. Earlier asymmetric synthesis of (-)-deoxoprosophylline**1** was reported using asymmetric dihydroxylation as the key step to install chirality. This section describes efforts towards the synthesis of (+)-deoxoprosophylline **1** starting from L(+)-tartrate ester as the source of chirality. Literature scrutiny suggested that there are several methods available for the enantioselective syntheses of deoxoprosophylline starting from amino acids,[2] carbohydrates,[3] vitamin C,[4] malic acid,[5] or compounds of synthetic origin.[6] The study of literature revealed that there is no report available for the synthesis of either antipode of deoxoprosophylline using tartrate ester.

Although several synthesis of both (+)- and (-)-deoxoprosophylline are reported in the literature through varied synthetic routes, most of them suffer certain limitations such as use of transition metals like samarium (II) iodide, exotic reagents, low overall yields, lengthy synthetic routes, expensive starting material. However, it is still desirable to develop a general strategy that provides a common pivotal intermediate from which 2,3,6-trisubstituted piperidines with desired stereochemistry can be readily derived. With this in mind, it was envisaged to establish a versatile methodology for the synthesis of an enantio pure 2,6-disubstituted piperidine-3-ol framework starting from commercially available, inexpensive starting material *viz*. L-(+)-tartrate ester, which is abundantly available in nature. This route allows the synthesis of the target compounds in enantiopure form as starting material is optically pure enantiomer and hence reduces the possibility other enantiomer formation even in trace amounts. This section describes an enantioselective synthesis of (+)-deoxoprosophylline and *epi*-(+)-2-deoxoprosopinine synthesis employing simple reaction conditions and with enhanced yields.

2.2.2. Retrosynthesis

As outlined in Scheme 1, it was envisaged that stereochemistry required for (+)-deoxoprosophylline **1** is hidden in tartrate ester **7** and the retrosynthesis was planned accordingly. It was envisioned that (+)-deoxoprosophylline **1** can be synthesized from α,β-unsaturated keto compound **2** by reductive amination. This azido keto compound **2** in turn can easily be accessed from aldehyde **3** by 14-carbon Wittig reaction. Aldehyde **3** could be

obtained from tartrate ester **7** derived diol **5** through azido diester compound **6** by standard functional group transformations.



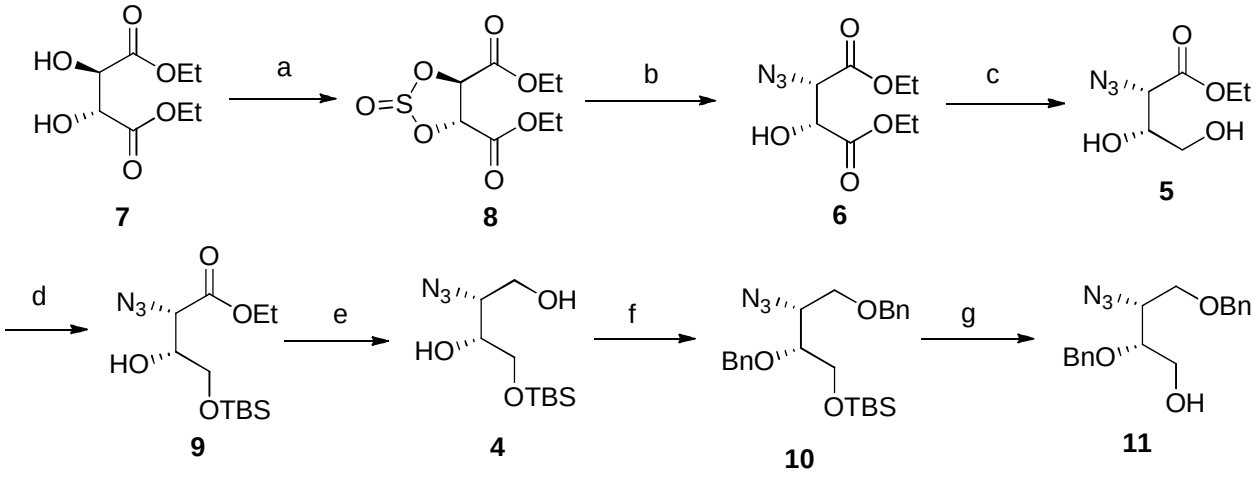
Scheme 1. Retrosynthetic analysis.

2.2.3. Result and discussion:

Synthesis of (+)-deoxoprosophylline **1** commenced with commercially available tartrate ester **7**, which on treatment with thionyl chloride in CCl_4 under reflux for 4 h afforded sulphite **8**. The crude sulfite **8**, thus obtained was subjected to nucleophilic opening. Accordingly, sulphite opening was carried out using NaN_3 in DMF at room temperature (24 h) to obtain 74% yield of the corresponding azido diester **6** over two steps. The IR spectrum of azido alcohol **6** 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 170.6 and 166.8 which were assigned to two carbonyl carbons. Its DEPT spectrum showed presence two CH carbons that appeared at δ 71.9 and 64.2, while two CH_2 carbons appeared at δ 62.3 and 62.1 in accordance with the structure of **6**. Formation of **6** was further supported by its mass spectrum which showed the molecular ion peak at m/z 254 $(M+Na)^+$.

Azido diester **6** was then subjected for selective ester reduction using *α*-hydroxyl group of the ester **6** as a handle to reduce it to alcohol. The reduction was carried out using borane-dimethylsulfide complex (1.05 equivalent) and catalytic sodium borohydride in THF to obtain 1,2-diol **5** in 60% yield.[7] Its IR spectrum showed broad

band at 3490 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 two –

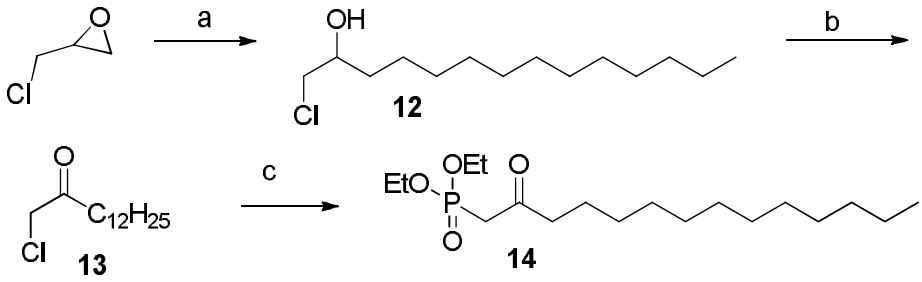


Scheme 2. a) $SOCl_2$, DMF (cat.), CCl_4, reflux, 4 h; b) NaN_3, DMF, rt, 24 h, 74% over two steps; c) BH_3:DMS, $NaBH_4$ (cat.), THF, rt, 8 h, 60%; d) TBSCl, Et_3N, DCM, 2 h, 85%; e) $NaBH_4$, LiCl, THF:Water (1:1), 12 h, 83%; f) NaH, BnBr, THF, rt, 12 h, 94%; g) PTSA, MeOH, 2 h 91%

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 for CH_2 and triplet at δ 1.36 for CH_3 were assigned to the ethyl protons of ester group. Its ^{13}C-NMR spectrum showed the peak at δ 169.2 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 **5**. Further, the formation of **5** was also confirmed by mass spectroscopy which showed a molecular ion peak at m/z 190 $(M+H)^+$.

The 1,2-diol **5** was treated with TBSCl in DCM as the solvent in the presence of TEA as the base to protect primary hydroxyl group selectively in the presence of secondary hydroxyl group. MonoTBS ether **9** was obtained in 85% yield. Its IR spectrum showed broad band at 3435 cm^{-1} indicating the presence of hydroxy functionality and peaks at 2112 and 1741 cm^{-1} clearly indicated the presence of azide and ester functionalities respectively. In ^{1}H-NMR, singlet peaks at δ 0.11 for two CH_3 and 0.92 for three CH_3 of *t*-butyl and corresponding carbons in ^{13}C at δ -5.43 and 25.92 respectively indicated the presence of OTBS group. 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 168.82 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 **9**. Further, the formation of **9** was also confirmed by HRMS which showed a molecular ion peak at m/z 326.1507 $(M+Na)^+$.



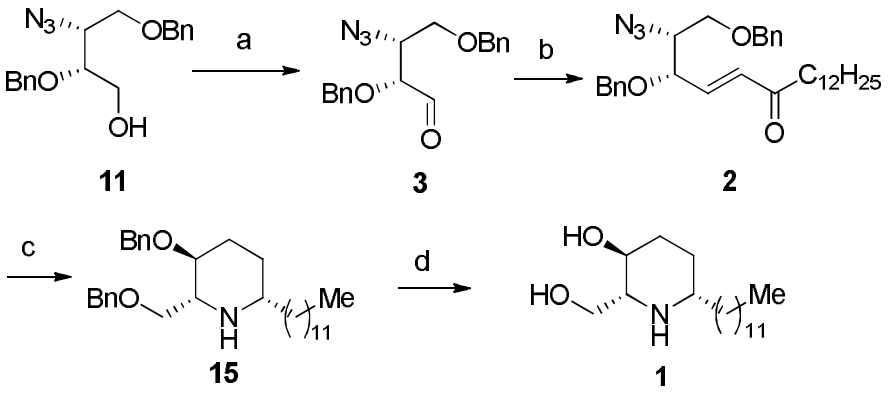
Scheme 3. Preparation of phosphonate: a) 1-Bromoundecane, Mg, CuI, THF, -30 ^oC, 3 h, 60%; b) DMSO, $(COCl)_2$, TEA, DCM, -78 ^oC, 1 h, 84%; c) $P(OEt)_3$, reflux, acetone, 12 h, 73%.

Once this monoTBS compound **9** was in hand, the ester group was reduced with LiCl/LiBr and $NaBH_4$ in THF, water (1:1) system to obtain 1,3-diol compound 4 in 83% yield. Its IR spectrum showed broad band at 3412 cm^{-1} indicating the presence of hydroxy functionality and peaks at 2104 clearly indicated the presence of azide and disappearance of peak at 1741 cm^{-1} suggested the reduction of ester functionality. The typical signals for ethyl protons, quartet at δ 4.30 and triplet at δ 1.36 were disappeared in ^{1}H spectrum. Further absence of their respective carbons in ^{13}C at δ 61.92 and δ 14.21 confirmed the reduction of ester functionality. Its ^{13}C-NMR spectrum showed the peak at δ 169 corresponding to the ester carbonyl functionality had disappeared. Its DEPT spectrum showed presence of two peaks corresponding to CH_2 carbons and absence of CH_3 corresponding to methyl of ethoxy group, which is in accordance with the structure of **4**. Further, the formation of **4** was also confirmed by HRMS which showed a molecular ion peak at m/z 284.1401 $(M+Na)^+$. The 1,3-diol **4** was dibenzylated using benzyl bromide and NaH (60% suspension in oil) to afford corresponding dibenzyl ether **10** in 94% yield. Its IR spectrum showed disappearance of broad band at 3412 cm^{-1} indicating the absence of hydroxy functionalities and peaks at 2121 cm^{-1} indicated the presence of azide group. The multiplet peak aromatic region at δ 7.17-7.50 indicated the presence of phenyl ring in the compound. Its ^{13}C-NMR spectrum showed the peak in olefinic range at δ 127.48 to 137.45 corresponding to two phenyl rings. Appearance

of four protons at δ 3.59-4.05 in ^{1}HNMR, a benzylic protons region and appearance of two CH_2 carbons at 72.82 and 73.41, confirmed by DEPT NMR suggested the presence of two benzylic CH_2 carbons. This is in accordance with the structure of **10**. Further, the formation of **10** was also confirmed by HRMS which showed a molecular ion peak at m/z 350.1474 $(M+Na)^+$.

The TBS ether was deprotected using PTSA in methanol to obtain free primary alcohol **11** in 91% yield. Its IR spectrum showed broad band at 3479 cm^{-1} indicating the presence of hydroxy functionality and peaks at 2121 cm^{-1} clearly indicated the presence of azide functionality. The disappearance of singlets at δ -0.12 and 0.93 confirmed the absence of TBS. Its ^{13}C-NMR spectrum showed absence of respective TBS carbon peaks at δ -5.41, 18.32, 25.90 corresponding to the dimethyl, *tert*-butyl groups present on the TBS functionality. Further, the formation of **11** was also confirmed by mass spectroscopy which showed a molecular ion peak at m/z 349.91 $(M+Na)^+$ and HRMS value was found to be 350.1481 $(M+Na)^+$. This primary hydroxyl group was oxidised to aldehyde **3** under Swern reaction condition.[15] The aldehyde **3** thus obtained was used as such without purification for further reaction.

The *α*-chloroketone **12** was prepared by Swern oxidation[8] of 1-chlorotetradecan-2-ol **13** which was in turn prepared by ringopening of epichlorohydrin with undecylmagnesium bromide in THF.[9] Treatment of chloroketone with triethyl phosphite afforded *β*-keto phosphonate **14** in 73% yield.[10]



Scheme 4. a) DMSO, $(COCl)_2$, TEA, DCM, -78 ^{o}C, 1 h; b) DIPEA, phosphonate **21**, LiCl, MeCN, 0 ^{o}C to rt, 10 h, 95%; c) H_2, Pd/C, 60 psi, MeOH; d) Na/NH_3, -78 ^{o}C, 1 h, (93% over two steps).

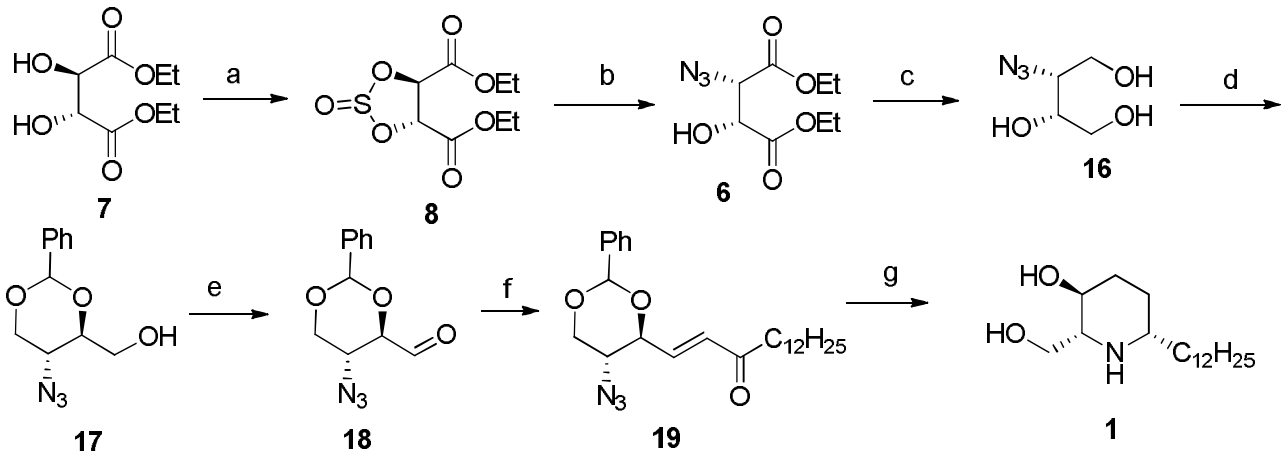
The *β*-keto phosphonate **14** on treatment with aldehyde 10 with LiCl and Hunigs base in acetonitrile afforded *α,β*-unsaturated keto compound **2** in 95% yield. Its IR spectrum showed broad band at 1714 cm^{-1} indicating the presence of ketone functionality and peaks at 2103 clearly indicated the presence of azide functionality. Appearance of triplet for CH_3 at δ 0.90 and multiplet for 18 H at δ 1.09-1.42 in ^{1}H-NMR spectrum suggested presence of linear hydrocarbon chain. Also, the presence of dd for 1H at δ 6.28 and dd for 1H at δ 6.68 corresponding to *α,β*-unsaturated ketone with coupling constant J = 16.2 confirmed the presence of unsaturated ketone functionality. This was further verified by its ^{13}C-NMR spectrum which showed the peak at δ 199.68 corresponding to ketone carbonyl carbon and δ 132.81 and 141.02 corresponding to olefinic *α,β*-unsaturated ketone functionality. It was further confirmed by DEPT spectrum. Further, the formation of **2** was also confirmed by mass spectroscopy which showed a molecular ion peak at m/z 542.23 $(M+Na)^+$ as its HRMS value was observed at 542.3359 $(M+Na)^+$. Exclusive formation of *trans* product was observed which was confirmed by coupling constant (J = 16.2Hz).

This *α,β*-unsaturated keto compound **2** was subjected for one pot azide reduction and diastereoselective intramolecular reductive cyclization by treatment with Pd/C in methanol under hydrogenation.[6] It was expected to get completely debenzylated product along with cyclization *i.e.* target compound **1**. Instead, mixture of (+)-deoxoprosophylline **1** along with monobenzyl and dibenzyl cyclized compounds was obtained, which was confirmed by mass-spectroscopy. This mixture was subjected to Birch reduction condition to obtain (+)-deoxoprosophylline **1** in 93% yield. The spectral data was in good agreement with reported data.[6]

After synthesizing (+)-deoxoprosphylline **1** from tartrate ester, efforts were made to improve overall yield and reduce no of steps to make the synthesis more practical. In the process a shorter route was developed.

The synthesis comenced with reduction of both the ester groups present in the compound **6** to obtain triol **16** which is water soluble compound. This **16** was used directly for further reaction, where it was subjected for 1,3-benzilidine protection with benzyl dimethyl acetal in the presence of catalytic *p*TSA to provide 67% yield of protected compound **17** over two steps. Its IR spectrum showed broad band at 3445 cm^{-1} indicating the presence of hydroxy functionality and peaks at 2111 cm^{-1} clearly indicated the presence of azide functionality. The singlet peak at δ 5.51 in its ^{1}H-NMR spectrum was assigned

benzylidine CH proton which was confirmed by its ^{13}C NMR peak at δ 101.2. Appearance of five protons in aromatic region at δ 7.34 - 7.59 as a multiplet further confirmed the presence of phenyl ring in the compound. Further, the formation of **17** was also confirmed by mass spectroscopy which showed a molecular ion peak at m/z 236.29 $(M+H)^+$.



Scheme 5. *Reagents and conditions:* a) $SOCl_2$, DMF (cat.), CCl_4, reflux, 4 h; b) NaN_3, DMF, rt, 24 h, 74% over two steps; c) $NaBH_4$, LiCl, EtOH, 8 h; d) Benzyl dimethyl acetal, MeCN, reflux, 12 h, 67 % over 2 steps;e) DMSO, $(COCl)_2$, TEA, DCM, -78 ^oC, 1 h; f) DIPEA, phosphonate **14**, LiCl,, MeCN, 0 oC-rt, 3 h, 92%; g) i) H_2, $Pd(OH)_2$, 60 *psi*, MeOH, 24 h, ii) dil. HCl MeOH, 2 h, 97%;

The 1,3-protected benzylidine **17** was oxidized to aldehyde under Swern reaction conditions. This aldehyde **18** was used as such for further reaction without purification and characterization. The Horner-Emmons-Wittig reatcion was carried out on this **18** with 14-carbon *β*-keto phosphonate **14** to provide exclusively *trans* product **19** was confirmed by coupling constant J = 15.87 Hz. Its IR spectrum showed disappearance of broad band at 3445 cm^{-1} indicating the absence of hydroxy functionality. Appearance of two peaks at δ 6.51 and 6.92 as dd (J = 15.87 Hz) showed *α,β*-unsaturated ketone protons respectively. A triplet at δ 0.89 for a CH_3, multiplet for 20 protons at δ 1.12-1.44 in aliphatic region suggested presence of long linear hydrocarobon chain which was confirmed by ^{13}C NMR by assigning respective carbons. Further, the formation of **19** was also confirmed by mass spectroscopy which showed a molecular ion peak in HRMS 450.2727 $(M+Na)^+$.

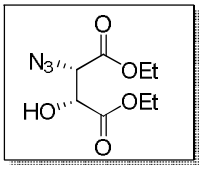
The unsaturated ketone compound **19** was hydrogenated to carry out intramolecular diastereoselective cyclization with Pd/C in MeOH hydrogen gas pressure 60 *psi*. The reaction

provided a benzidine protected deoxoprosophylline along with (+)-deoxoprosophylline This was confirmed by TLC matching with authentic sample. To obtain single diasteriomer I.e. (+)-deoxoprosophylline **1**, the reaction mixture was further treated with dil HCl. The target compound **1** was obtained as HCl salt which was treated with aq. K_2CO_3 to provide (+)-deoxoprosophylline **1**. The spectral data and optical rotation of the (+)-deoxoprosophylline **1** was in good agreement with the reported data.[11] The target compound (+)-deoxoprosophylline **1** was confirmed by the disappearance of aromatic peaks corresponding to Ph group, in its ^{1}H and ^{13}C NMR spectra. In these spectra also, peak corresponding to benzylic CH was missing which further confirmed complete deprotection of benzyl group. The characteristic *α,β*-unsaturated ketone protons peaks were diminished. The multiplets at δ 3.69 - 3.97 (m, 2 H) corresponding to methylene protons bonded to oxygen and a signal at δ 3.52 for 1 proton suggesting it to be a methine proton. This was further confirmied by their repective peaks appeared ^{13}C NMR spectrum at δ 63.76 and 69.69 due to methylene and methine carbons respectively

In conclusion, a novel, short and efficient route for synthesis of (+)-deoxoprosophylline **1** from tartrate ester as the source of chirality with an overall 23.67% yield has been developed. Total synthesis of (+)-deoxoprosophylline **1** is achieved using operationally simple reaction sequence. The key steps involved in the reaction sequence are selective ester reduction, Wittig reaction and diastereoselective intramolecular reductive cyclization. This synthetic strategy could be a general one suitable for the synthesis of several related polyhydroxylated piperidine alkaloids of biological importance by varying side chain in Wittig reaction.

2.2.4. Experimental

(2*S*,3*R*)-Diethyl-2-azido-3-hydroxysuccinate (6)[12]



To the solution of di-ethyl tartrate **7** (10 gm, 48 mmol) in CCl_4 (100 mL) thionyl chloride (7.2 mL, 97 mmol) was added dropwise. The resulting reaction mixture was heated to 50 ºC for 4 hours, cooled to room temperature and concentrated under reduced pressure to obtain the sulfite **8** as thick oil. The crude sulfite **8** was dissolved in DMF (100 mL) and to this solution was added sodium azide (7 gm, 60 mmol) and stirred overnight. After completion of reaction (monitored by TLC), the reaction mixture was quenched using water (200 mL) and was extracted with 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 was eluted on flash chromatography using silica gel with petroleum ether/ethyl acetate (7:3) as eluent to afford **6** (8.3 g, 74%) as a gummy liquid.

Chemical Formula: $C_8H_{13}N_3O_5$
Molecular Weight: : 231
Yield: 74%

Optical rotation: $[\alpha]_D^{25}$: +31º (c 1.0, MeOH).

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

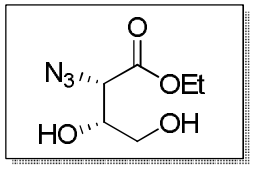
^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.35-1.27(m, 6H), 4.35-4.23 (m, 5H), 4.62 (d, *J* = 2.8 Hz, 1H).

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

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 (5)



To the solution of azido diester **6** (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. After completion of reaction (monitored by TLC), 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 was purified on flash chromatography using silica gel petroleum ether/ethyl acetate (6.5:3.5) to provide diol **5** as a colorless thick liquid (2.45 gm, 60%).

Chemical Formula: $C_6H_{11}N_3O_4$

Molecular Weight: 189

Yield: 60%; colorless thik liquid.

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

IR ($CHCl_3$) υ_{max}: 3490, 2949, 2121, 1747, 1029 cm^{-1}.

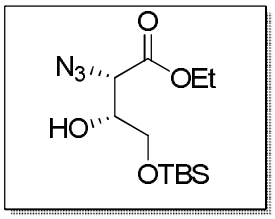
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.2 Hz, 3H), 3.77-3.68 (m, 2H), 2.57 (bs, 2H), 3.99-3.94 (m, 1H), 3.68- 4.12 (m, 2H), 4.05 (d, *J* = 7 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H).

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

ESI-MS (m/z): 212 $(M+Na)^+$.

Elemental Analysis: Calculated: C, 38.10; H, 5.86; N, 22.21; O, 33.83 Found C, 38.09; H, 5.88; N, 22.20; O, 33.84.

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



To the solution of diol **5** (2 gm, 10 mmol) dissolved in DCM (25 mL) was added imidazole (1.44 gm, 20 mmol) and was cooled to 0 ºC. To this reaction mixture was added TBDMSCl (1.8 gm, 11 mmol) and the reaction mixture was further stirred for 2 h at 0 ºC. After completion of reaction (monitored by TLC), 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 30 mL). The collected organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified using flash chromatography using silica gel petroleum ether/ethyl acetate (19:1) to furnish TBS compound **9** as a colorless liquid (2.75 gm, 85%).

Chemical Formula: $C_{12}H_{25}N_3O_4Si$

Molecular Weight: 303

Yield: 85%.

Optical rotation: $[\alpha]_D^{25}$: 5.8 (c 1.0, $CHCl_3$).

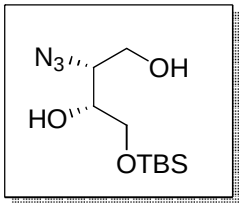
IR ($CHCl_3$) υ_{max}: 3435, 2931, 2859, 2254, 2112, 1741 cm^{-1}.

^{1}H NMR (200 MHz, choroform-*d*+CCl_4): δ 0.11 (s, 6 H), 0.92 (s, 9 H), 1.36 (t, *J* = 7.1 Hz, 3 H), 1.53 (s, 1 H), 2.69 (d, *J* = 6.6 Hz, 1 H), 3.68 - 3.81 (m, 2 H), 3.89 - 4.02 (m, 2 H), 4.30 (q, *J* = 7.1 Hz, 2 H).

^{13}C NMR (50 MHz, chloroform-*d*+ CCl_4): δ -5.43, 14.21, 18.38, 25.92, 61.92, 62.70, 63.06, 71.78, 168.82; **ESIMS (m/z):** 304.08 $[M+H]^+$.

HRMS Calculated: $C_{12}H_{25}N_3NaO_4Si$ 326.1512, found 326.1507 $[M+Na]^+$.

(2*R*, 3*R*)-2-azido-4-((*tert*-butyl-dimethyl-silyl) oxy) butane-1, 3-diol (4)



To the solution of hydroxyl ester **9** (1 gm, 3.3 mmol) dissolved in THF: water (1:1) (200 mL) was added lithium chloride (0.277 gm, 6.6 mmol) and was cooled to 0 ºC. To the reaction mixture was added sodium borohydride (0.251 gm, 6.6 mmol) and the reaction mixture was further stirred for 12 h at 0 ºC. After completion of reaction (monitored by TLC), unreacted sodium borohydride was quenched with saturated ammonium chloride solution. Then ethyl acetate was added and the organic and aqueous layers were allowed to separate. The aqueous layer was extracted twice using ethyl acetate (2 x 100 mL). The collected organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified using flash chromatography using silica gel petroleum ether/ethyl acetate (2:1) to furnish 1,3-diol compound **4** as a colorless gummy liquid (0.75 gm, 87%).

Chemical Formula: $C_{10}H_{23}N_3O_3Si$

Molecular Weight: 261

Yield: 87%.

Optical rotation: $[\alpha]_D^{25}$: - 23.2 (c = 1, chloroform).

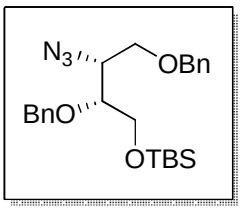
IR ($CHCl_3$) υ_{max}: 3412, 2986, 2941, 2254, 2104, 1207, 1028 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 0.12 (s, 6 H), 0.93 (s, 9 H), 2.41 (br. s., 1 H), 2.68 (d, *J* = 4.9 Hz, 4 H), 3.40 - 3.55 (m, 1 H), 3.59 - 4.03 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ -5.41, 18.32, 25.90, 62.60, 63.58, 63.87, 71.37; **ESIMS (m/z):** 283.95 $[M+Na]^+$.

HRMS: Calculated for $C_{10}H_{23}N_3NaO_3Si$: 284.1406 found 284.1401 $[M+Na]^+$.

((2*R*, 3*R*)-3-azido-2,4-bis(benzyloxy)butoxy)(*tert*-butyl)dimethylsilane (10)



To a solution of sodium hydride (60% suspension in oil, 1.4 gm, 58.23 mmol) in dry THF (100 mL), azido 1,3-diol **4** (3.8 gm, 14.56 mmol) was added at 0 °C. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 °C. To this was added slowly benzyl bromide (7.5 gm, 43.68 mmol) with further stirring for 12 h at room temperature. After completion of reaction (monitored by TLC), the reaction mixture was quenched by addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residual oil was purified by silica gel column chromatography petroleum ether/ethyl acetate (97:3) to furnish 6.1 gm dibenzyl protected alcohol **10**.

Chemical Formula: $C_{24}H_{35}N_3O_3Si$

Molecular Weight: 441

Yield: 94%.

Optical rotation: $[\alpha]_D^{25}$: - 20.7 (c = 0.8, chloroform).

IR ($CHCl_3$) υ_{max}: 2986, 2940, 2121, 1207, 1030, 757 cm^{-1}.

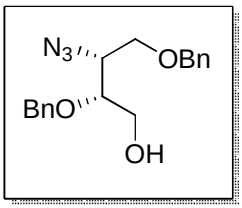
^{1}H NMR (200 MHz, $CDCl_3$): δ -0.00 (s, 6 H), 0.84 (s, 9 H), 3.34 - 3.93 (m, 6 H), 4.37 - 4.73 (m, 4 H), 7.11 - 7.40 (m, 10 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.5, 18.3, 25.9, 61.7, 62.3, 69.7, 72.7, 73.3, 79.0, 127.6, 127.7, 128.3, 137.9, 138.1.

ESIMS (m/z): 464.18 $(M+Na)^+$.

HRMS: Calculated for $C_{24}H_{35}N_3NaO_3Si$ 464.2345, found 464.2342 $[M+Na]^+$.

(2*R*, 3*R*)-3-azido-2, 4-*bis*(benzyl-oxy)butan-1-ol (11)



To a solution of TBS ether **10** (5 g, 11.34 mmol) in MeOH (100 mL) was added *p*-toluene sulphonic acid (0.216 g, 1.1 mmol) at 0 °C and the mixture was stirred for 1 h. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography petroleum ether/ethyl acetate (7:3) to furnish TBS-deprotected azido alcohol **11** as a colorless liquid (3.6 gm).

Chemical Formula: $C_{18}H_{21}N_3O_3$

Molecular Weight: 327

Yield: 97%.

Optical rotation: $[\alpha]_D^{25}$: -15.44 (c = 0.98, chloroform).

IR ($CHCl_3$) υ_{max}: 3479, 2945, 2122, 1211, 1028 cm^{-1}.

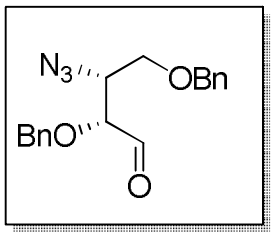
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.93 (t, *J* = 6.3 Hz, 1 H), 3.51 - 3.90 (m, 6 H), 4.59 (d, *J* = 6.7 Hz, 4 H), 7.17 - 7.50 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 60.68, 60.88, 69.24, 72.33,73.17, 78.21, 127.48, 127.61, 127.68, 127.76, 128.25, 128.30, 137.41, 137.45.

ESIMS (m/z): 349.91 $[M+Na]^+$.

HRMS: calculated for $C_{18}H_{21}N_3NaO_3$ 350.1481, found 350.1474 $[M+Na]^+$.

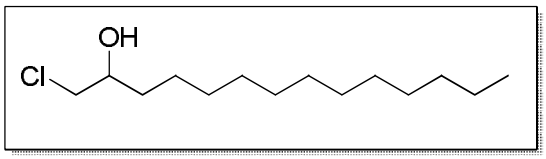
(2*R*, 3*R*)-3-azido-2,4-*bis*(benzyloxy)butanal (3)



To a stirred solution of oxalyl chloride (4.22 mL, 48.92 mmol) in DCM at -78 ^oC was added DMSO (3.82 g, 48.92 mmol) drop wise. After 30 min, a solution of compound **11** (4 g, 12.23 mmol) in DCM was added dropwise to the above mixture at the same temperature. After 1 h, Et_3N (10.21 ml, 12.67 mmol) was added drop wise at-78 ^oC. After the completion of the reaction (monitored by TLC), the reaction was quenched with water and then extracted with dichloromethane (15 mL). The organic layer was dried over

anhydrous Na_2SO_4 filtered and evaporated to afford the crude aldehyde **3,** which was used for next reaction without purification.

1-Chlorotetradecane-2-ol (12)[13]



1-Bromoundecane (5 gm, 21.3 mmol) was added to the suspension of Mg metal (536 mg, 22.3 mmol) in dry THF and the resulting mixture was allowed to stir under heating until all magnesium metal disappears. To this solution was added a mixture of CuI and epichlorohydrin (2.94 gm, 31.9 mmol) in THF at -30 ^oC. The resulting solution was allowed to stir for 30 min and then quenched with a saturated solution of ammonium chloride. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 15 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and solvent was removed under reduced pressure. Residue was purified on silica gel column chromatography petroleum ether/ethyl acetate (19:1) to furnish chlorohydrin **12**.

Chemical Formula: $C_{14}H_{29}ClO$

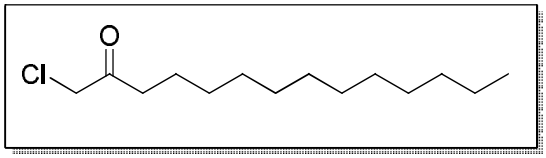
Molecular Weight: 248.1

Yield: 60%

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.8 Hz, 3 H), 1.17 - 1.39 (m, 18 H), 1.40 - 1.70 (m, 4 H), 2.18 (br. s., 1 H), 3.42 - 3.69 (m, 2 H), 3.73 - 3.88 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.10, 22.67, 25.51, 29.33, 29.49, 29.55, 29.62(4C), 31.91, 34.22, 50.57, 71.46.

1-Chlorotetradecane-2-one (13)[2]



To a stirred solution of oxalyl chloride (1.54 gm, 1.21 mmol) in DCM at -78 ^oC was added DMSO (1.89 gm, 2.42 mmol) in DCM in dropwise manner. After 30 min, a solution of chlorohydrin **12** (1.5 gm, 6.05 mmol) in dichloromethane was added dropwise to the above mixture at the same temperature. After 1 h, Et_3N (3.7 gm, 36.3 mmol) was added drop wise at -78 ^oC. Upon completion, the reaction was quenched with water and then extracted with dichloromethane

(2 x15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to get a crude product which was further purified by column chromatography petroleum ether/ethyl acetate (97:3) to furnish 1-chlorotetradecan-2-one **13** as yellow solid.

M.P.: 45-46 ^oC

Chemical Formula: $C_{14}H_{27}ClO$

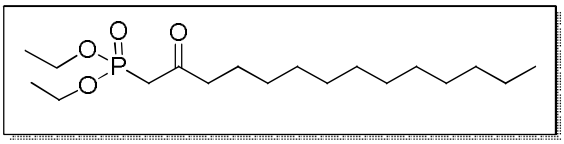
Molecular Weight: 246.81

Yield: 84%

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.79 - 1.00 (m, 3 H), 1.27 (s, 16 H), 1.47 - 1.76 (m, 4 H), 2.60 (t, *J* = 7.3 Hz, 2 H), 4.05 (s, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.18, 22.73, 23.61, 29.12, 29.39, 29.47, 29.48, 29.63, 29.68(2C), 31.96, 39.62, 48.03, 202.55.

***β*-Ketophosphonate (14)[14]**



A solution of chloroketone **13** (1.3gm, 5.28 mmol) and KI (877 mg, 5.28 mmol) in dry acetone20 mL was stirred at room temperature for 2 h, then triethyl phosphite (877.0 mg, 5.28 mmol) in 20 mL of dry diethyl ether was added, and the solution was refluxed for 12 h. The mixture was cooled to room temperature and the precipitate was filtered off. After evaporation of the solvent under reduced pressure the crude phosphonate was obtained. This crude product was directly purified by column chromatography petroleum ether/ethyl acetate (7:3) to furnish *β*-keto phosphonate **14** as a colorless liquid in 73% yield.

Chemical Formula: $C_{18}H_{37}O_4P$

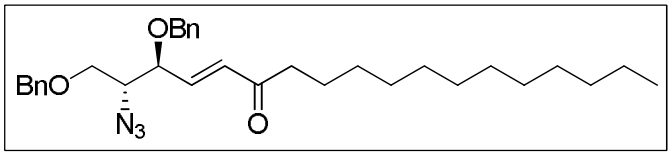
Molecular Weight: 348

Yield: 73%.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.81 - 0.96 (m, 3 H), 1.17 - 1.42 (m, 23 H), 1.48 - 1.71 (m, 3 H), 2.62 (t, *J* = 7.3 Hz, 2 H), 2.97 - 3.20 (m, 2 H), 4.03 - 4.28 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.91, 16.07, 16.19, 22.50, 23.29, 28.82, 29.16, 29.21, 29.28, 29.42, 29.46, 31.74, 40.93, 43.46, 43.92, 62.25, 62.38, 201.91, 202.03.

(2*R*,3*S*,*E*)-2-azido-1,3-bis(benzyloxy)octadec-4-en-6-one (2)



To a well stirred solution of $(EtO)_2P(O)CH_2COC_{12}H_{25}$ **14** (0.976 g, 2.8 mmol), LiCl (0.2 g, 4.7 mmol) in acetonitrile *i*-Pr_2NEt (0.36 g, 2.8 mmol) was added at 0 ^{O}C. Then a solution of azido aldehyde **3** (0.9g, 2.3 mmol) in acetonitrile (10 mL) was added at 0 ^{o}C and reaction mixture was stirred at room temperature for 12 h. After completion of reaction (monitored by TLC), it was quenched with water (5 mL). The product was extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using petroleum ether: ethyl acetate (9:1) to furnish 1.4 g (*E*)-*α,β*-unsaturated azido ketone **2** as a colorless oil.

Chemical Formula: $C_{32}H_{45}N_3O_3$

Molecular Weight: 519

Yield: 95%

Optical rotation: $[\alpha]_D^{25}$: +11.74 (c = 1.1, chloroform).

IR ($CHCl_3$) υ_{max}: 2251, 2102, 1714, 1633, cm^{-1}

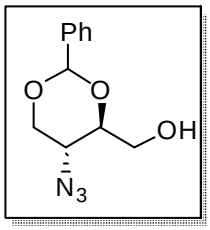
^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 0.90 (t, *J* = 6.9 Hz, 3 H), 1.09 - 1.42 (m, 18 H), 1.53 - 1.80 (m, 2 H), 2.55 (t, *J* = 7.4 Hz, 2 H), 3.61 (dd, *J* = 5.6, 2.9 Hz, 2 H), 3.72 (q, *J* = 5.5 Hz, 1 H), 4.10 - 4.22 (m, 1 H), 4.38 - 4.69 (m, 4 H), 6.28 (dd, *J* = 16.1, 1.0 Hz, 1 H), 6.68 (dd, *J* = 16.2, 6.9 Hz, 1 H), 7.07 - 7.58 (m, 10 H)

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 14.21, 22.74, 24.03, 29.30, 29.40, 29.50, 29.56, 29.68(8C), 31.96, 40.47, 63.83, 68.86, 71.64, 73.48, 77.94, 127.71, 127.74, 127.90, 127.98, 128.49, 132.81, 137.24, 137.46, 141.02, 199.68.

ESIMS (m/z): 542.23

HRMS: calculated for $C_{32}H_{45}N_3NaO_3$ 542.3359, found 542.3351 $(M+Na)^+$.

((4*R*,5*R*)-5-azido-2-phenyl-1,3-dioxan-4-yl)methanol (17):



To a solution of azide **7** (3.1 g, 13.42 mmol) in EtOH (40 mL) was added sodium borohydride (1.53 g, 40.26 mmol) and lithium chloride (1.69 g, 40.26 mmol) were added portion wise at 0ºC. The reaction mixture was stirred at this temperature for 1 h and 8 h at room temperature. After completion of the reaction (monitored by TLC), reaction mixture was quenched by addition of dil. HCl (1M) at 0 ºC until pH 4. The solvent was evaporated and the product **16** was used as such without purification for further reaction.

To a solution of **16** (1.42 g, 9.66 mmol) and benzaldehyde dimethylacetal (4.4 g, 28.98 mmol) in anhydrous acetonitrile (40 mL), p-TsOH was added (5% w/w). The solution was then refluxed under inert atmosphere for 12 h. After completion of the reaction monitored by TLC, reaction was quenched by addition of saturated $NaHCO_3$ solution and extracted with ethyl acetate (3 x 50 mL). Combined organic layers were dried over anhydrous Na_2SO_4, filtered and solvent was evaporated under reduced pressure the crude product was purified by column chromatography (ethyl acetate/pet. ether, 1:4) yielding **17** (2.15 g, 67%) as a yellow oil.

Chemical Formula: $C_{11}H_{13}N_3O_3$

Molecular Weight: 235

Yield: 67%

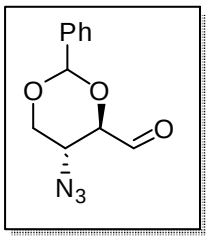
Optical rotation: $[\alpha]_D^{25}$: -37.88(c = 1.1, chloroform).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.07 - 2.22 (m, 1 H), 3.55 - 4.05 (m, 5 H), 4.34 - 4.51 (m, 1 H), 5.51 (s, 1 H), 7.34 - 7.59 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 52.6, 62.1, 68.7, 80.2, 101.2, 126.1, 128.3, 129.3, 137.0.

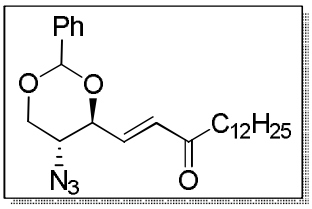
HRMS: calculated for $C_{11}H_{14}N_3O_3$ 236.1035, found 236.1029

(4*R*,5*R*)-5-azido-2-phenyl-1,3-dioxane-4-carbaldehyde (18):



To a stirred solution of oxalyl chloride (0.73 mL, 8.51 mmol) in DCM at -78 ^{o}C was added DMSO (0.66 mL, 8.51 mmol) drop wise. After 30 min, a solution of compound **17** (0.5 g, 2.13 mmol) in DCM was added dropwise to the above mixture at the same temperature. After 1 h, Et_3N (10.21 ml, 12.67 mmol) was added drop wise at -78 ^{o}C. After the completion of the reaction (monitored by TLC), the reaction was quenched with water and then extracted with dichloromethane (15 mL). The organic layer was dried over anhydrous Na_2SO_4 filtered and evaporated to afford the crude aldehyde **18**, which was used for next reaction without purification.

(*E*)-1-((4*S*,5*R*)-5-azido-2-phenyl-1,3-dioxan-4-yl)pentadec-1-en-3-one (19):



To a well stirred solution of $(EtO)_2P(O)CH_2COC_{12}H_{25}$ **14** (0.986 g, 2.83 mmol), LiCl (0.22g, 5.14 mmol) in acetonitrile *i*-Pr_2NEt (0.37 g, 2.83 mmol) was added at 0 ^{o}C. Then a solution of azido aldehyde **18** (0.6 g, 2.3 mmol) in acetonitrile (10 mL) was added at 0 ^{o}C and reaction mixture was stirred at room temperature for 12 h. After completion of reaction (monitored by TLC), it was quenched with water (5 mL). The product was extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using petroleum ether: ethyl acetate (9:1) to furnish 870 mg g (*E*)-*α,β*-unsaturated azido ketone **19** as a colorless oil.

Chemical Formula: $C_{25}H_{37}N_3O_3$

Molecular Weight: 427

Yield: 95%;

Optical rotation: $[\alpha]_D^{25}$: -61.67 (c = 0.9, chloroform)

IR ($CHCl_3$) υ_{max}: 2927, 2253, 2103, 1714, 1635, cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.87 Hz, 3 H), 1.12 - 1.44 (m, 20 H), 1.64 (t, *J* = 7.02 Hz, 2 H), 2.60 (t, *J* = 7.48 Hz, 2 H), 3.52 (td, *J* = 10.07, 5.19 Hz, 1 H), 3.75 (t, *J* = 10.83 Hz, 1 H), 4.26 (dd, *J* = 10.83, 5.19 Hz, 1 H), 4.44 (dd, *J* = 10.99, 5.19 Hz, 1 H), 5.56 (s, 1 H),

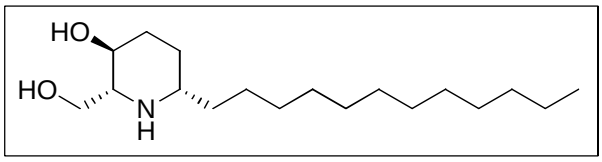
6.51 (dd, *J* = 15.87, 1.22 Hz, 1 H), 6.92 (dd, *J* = 15.87, 4.88 Hz, 1 H), 7.33 - 7.46 (m, 3 H), 7.46 - 7.58 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 22.6, 23.9, 29.2, 29.3, 29.4, 29.4, 29.6, 29.6, 29.6, 31.9, 40.9, 57.0, 69.0, 78.8, 101.1, 126.1, 128.3, 129.3, 131.1, 136.8, 139.2, 200.0

HRMS: calculated for $C_{25}H_{37}N_3NaO_3$ 450.2733, found 450.2727.

(+)-Deoxoprosophylline (1)

Method A: To a solution of **19** (0.680 mg) in dry MeOH (10 mL) was added Pd/C (0.05 g) and the reaction mixture was stirred under an atmosphere of H_2 (60 psi) for 24 h at room temperature. After the completion of the reaction (monitored by TLC), the reaction mixture was filtered over celite. To this filtrate, dil. HCl was added and the mixture was stirred at room temperature for 2 h. The reaction mixture concentrated under reduced pressure to provide deoxoprosophylline salt, which was treated with aq. K_2CO_3 and exctracted in DCM to provide (+)-deoxoprosophylline **1**.



Method B: To a solution of **2** (0.8 g, 1.48 mmol) in dry MeOH was added $Pd(OH)_2$ (0.05 g) and the reaction mixture was stirred under an atmosphere of H_2 (60 psi) for 24 h at room temperature. After the completion of the reaction (monitored by TLC), the reaction mixture was filtered over celite and the filtrate was concentrated under reduced pressure to provide the mixture of deoxoprosophylline along with mono and dibenzylated deoxoprosophylline. This mixture of compounds was used as such for Birch reduction.

To a stirred solution of ammonia (5 mL) at -78 ^oC, freshly cut pieces of sodium (0.4 g) were added under nitrogen atmosphere. To this, a solution of crude mixture (obtained after hydrogenation, 0.6 g, 2.06 mmol) in dry THF (5 ml) was added drop wise and the stirring continued for 1 h at -78 ^oC. The mixture was then quenched with dry solid ammonium chloride and ammonia gas was allowed to evaporate by keeping reaction mixture at room temperature for 1 h. The residue was washed with brine and extracted with chloroform (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude product, which was purified by recrystalization in acetone to afford 0.43 g of (+)-deoxoprosophylline **1** as colorless solid.

Chemical Formula: $C_{18}H_{37}NO_2$

Molecular Weight: 299

Yield: 93%, colorless solid, mp 86-87 ^{o}C {lit.[3] mp. 85-86 ^{o}C}

Optical rotation: $[\alpha]_D^{25}$: +13.4 (c 1, $CHCl_3$) {lit.[3] $[\alpha]_D^{25}$: +13.5 (c 1, $CHCl_3$)}.

IR ($CHCl_3$) υ_{max}: 3450, 3170, 2930.

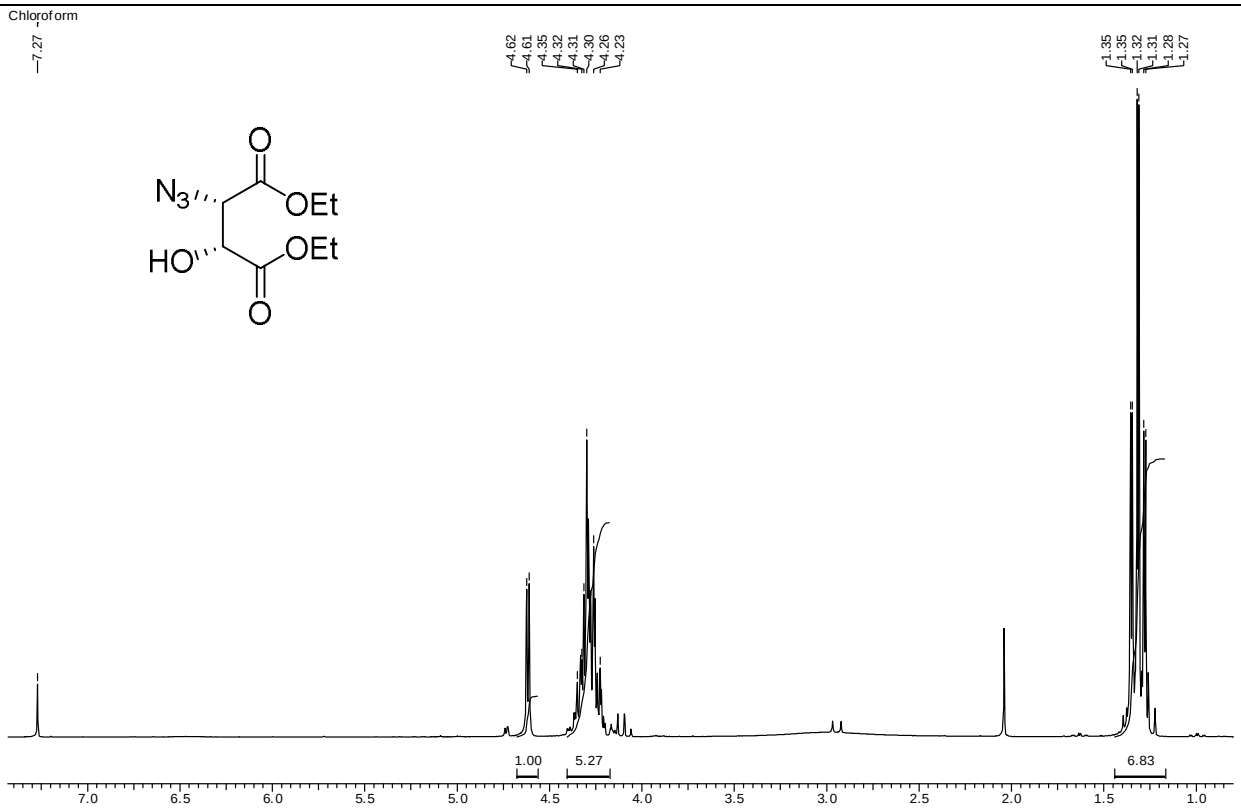
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 3 H), 1.07 - 1.55 (m, 25 H), 1.78 (d, *J* = 11.7 Hz, 1 H), 2.06 (d, *J* = 9.5 Hz, 1 H), 2.60 (br. s., 2 H), 3.00 (br. s., 3 H), 3.52 (br. s., 1 H), 3.69 - 3.97 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.10, 22.67, 26.16, 29.33, 29.58, 29.63(5C), 29.72, 30.58, 31.90, 33.59, 36.07, 56.33, 63.36, 69.69.

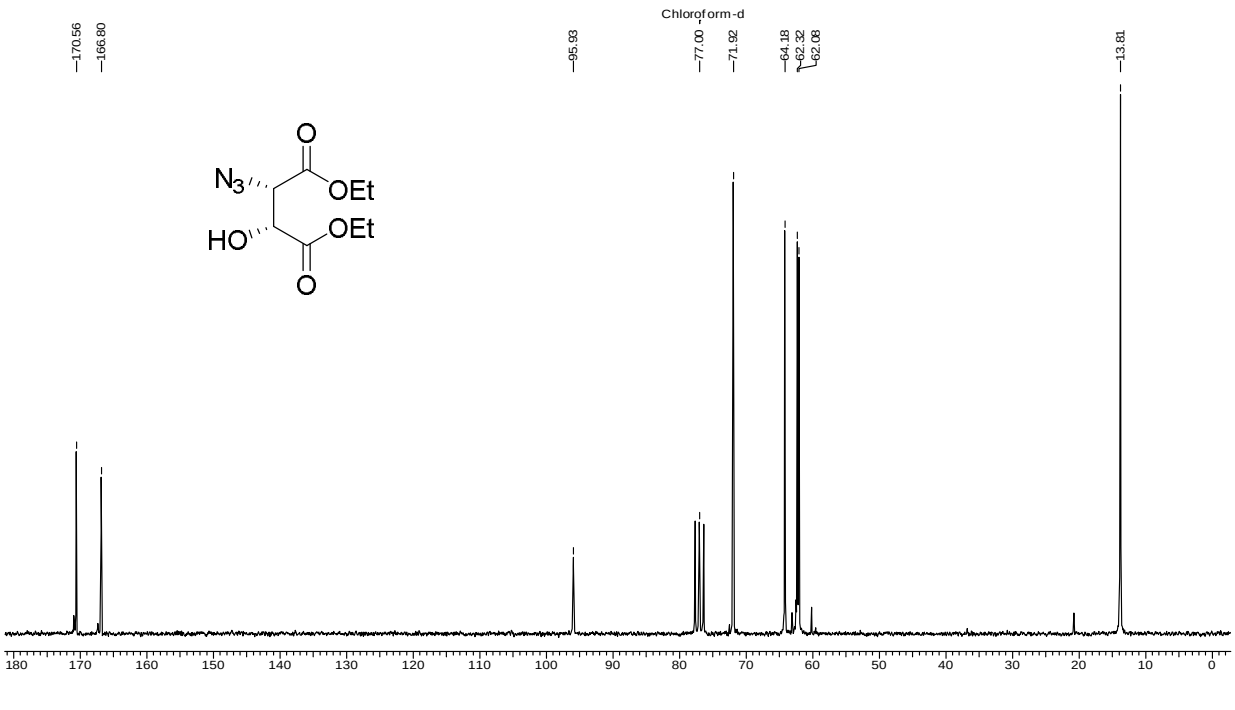
ESIMS (m/z): 300.08 $[M+H]^+$.

2.2.5 Spectra

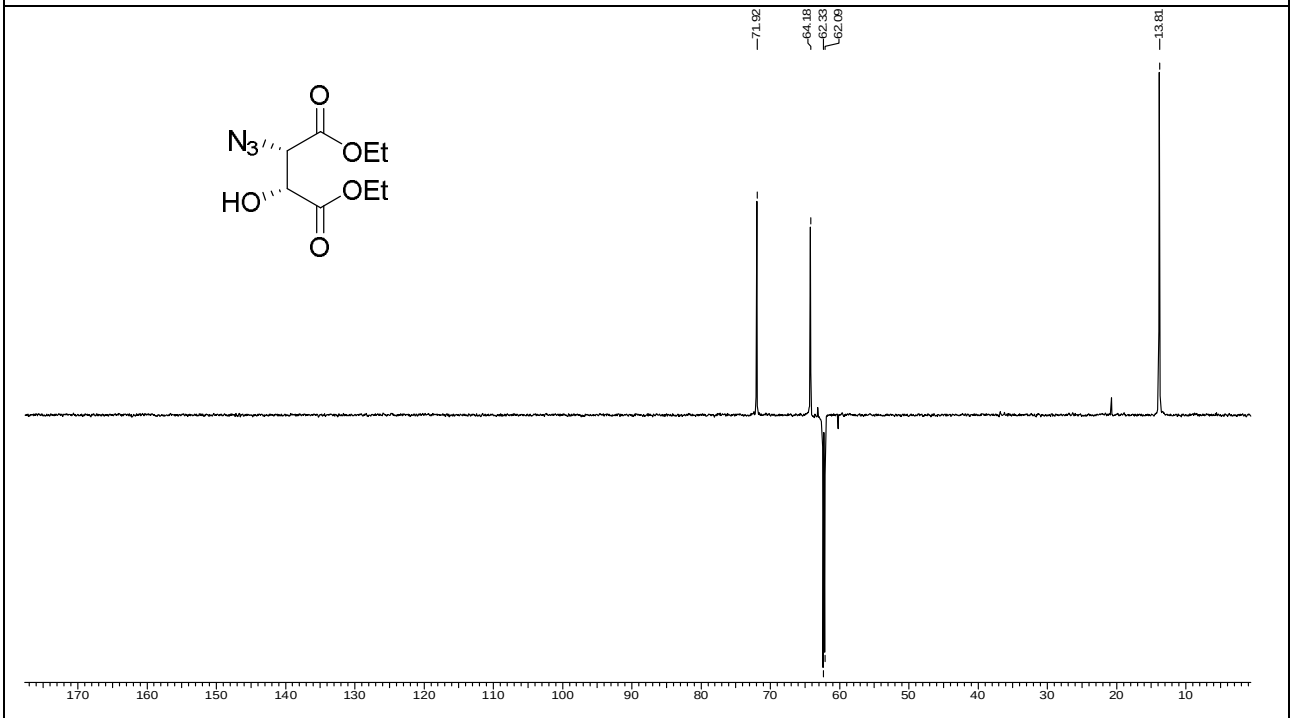
^{1}H-NMR spectrum of compound **7** ($CDCl_3$ + CCl_4, 200 MHz)



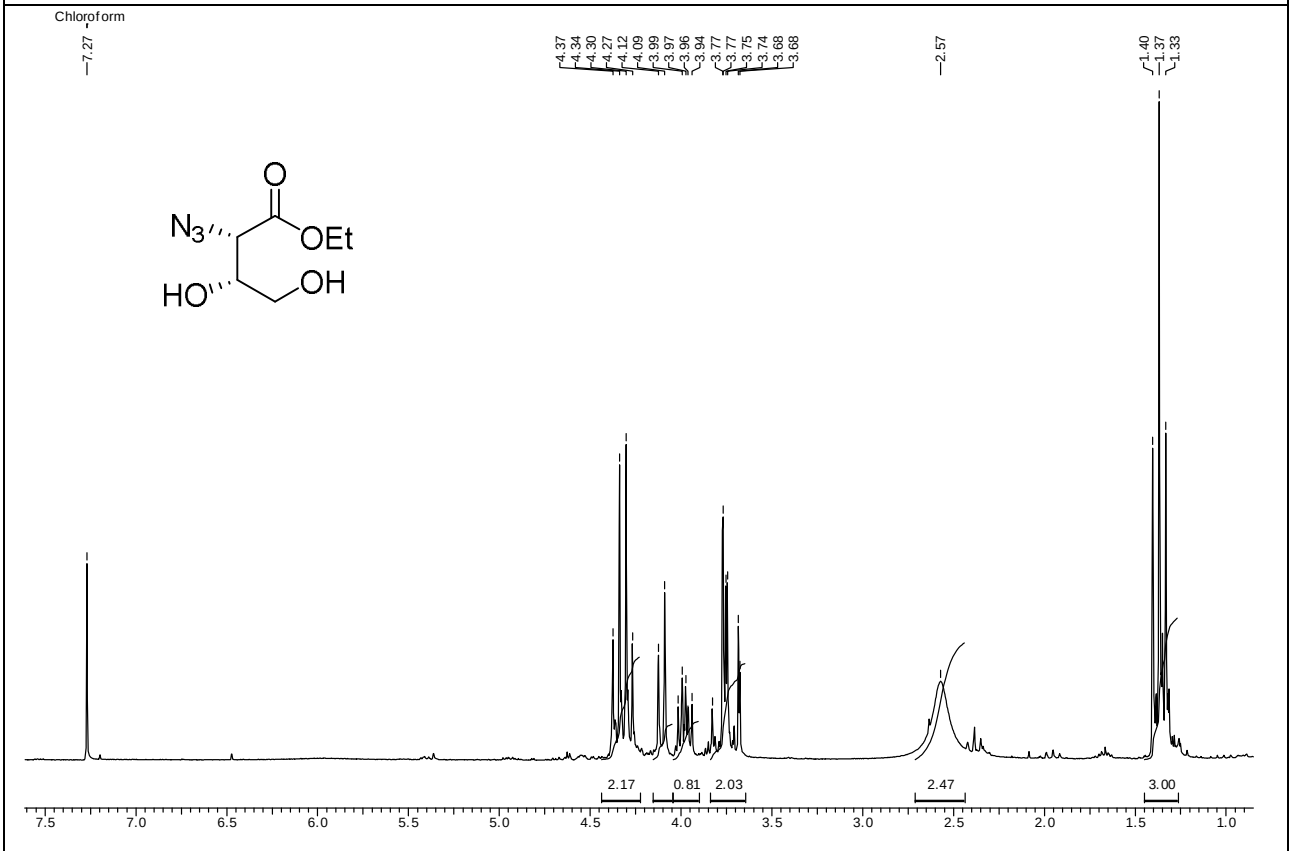
^{13}C-NMR spectrum of compound **7** ($CDCl_3$ + CCl_4, 50 MHz)



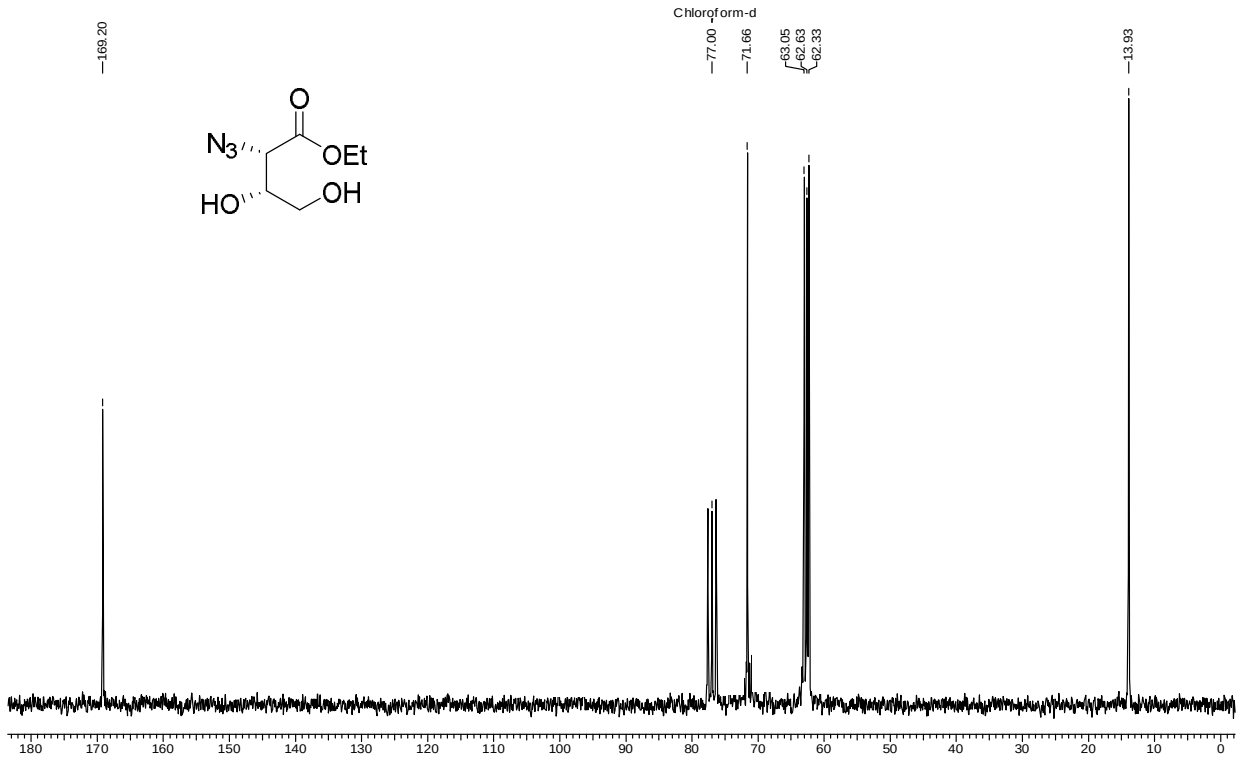
DEPT spectrum of compound **7** ($CDCl_3$ + CCl_4, 50 MHz)



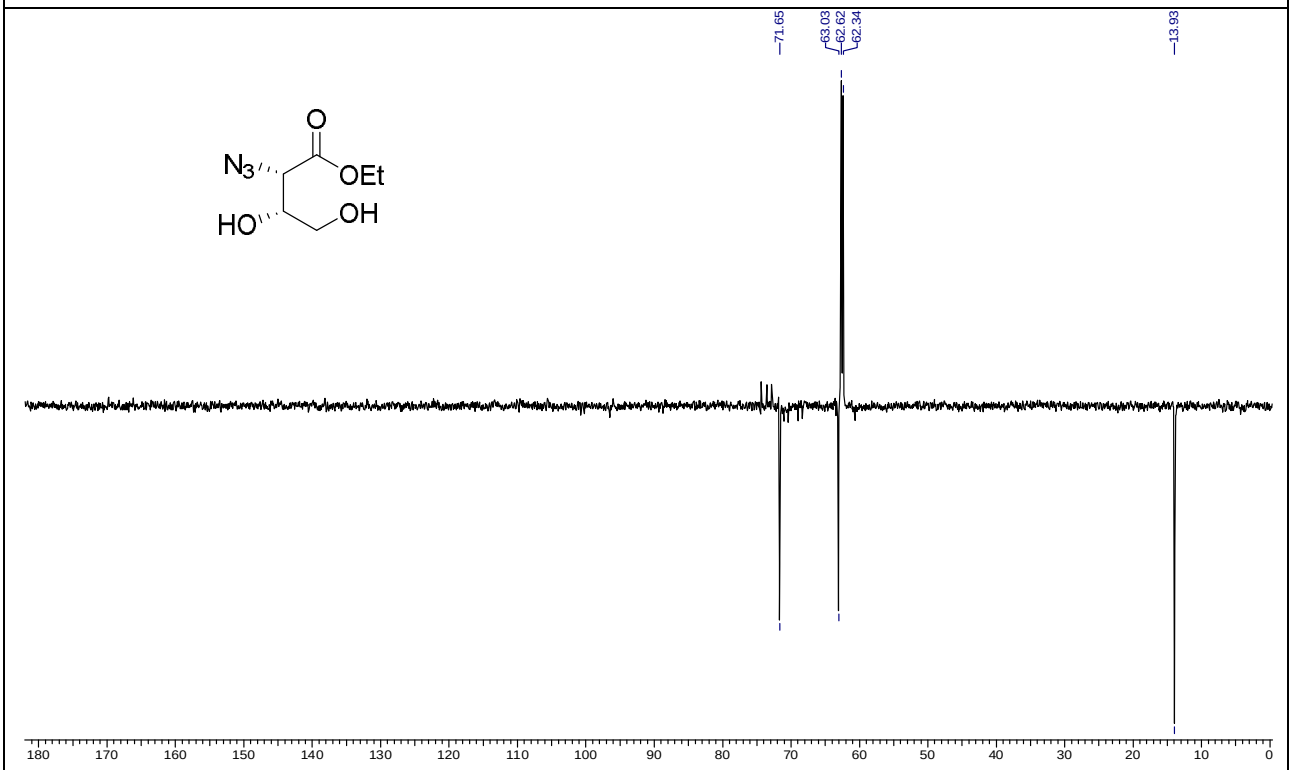
^{1}H-NMR spectrum of compound **5** ($CDCl_3$, 200 MHz)



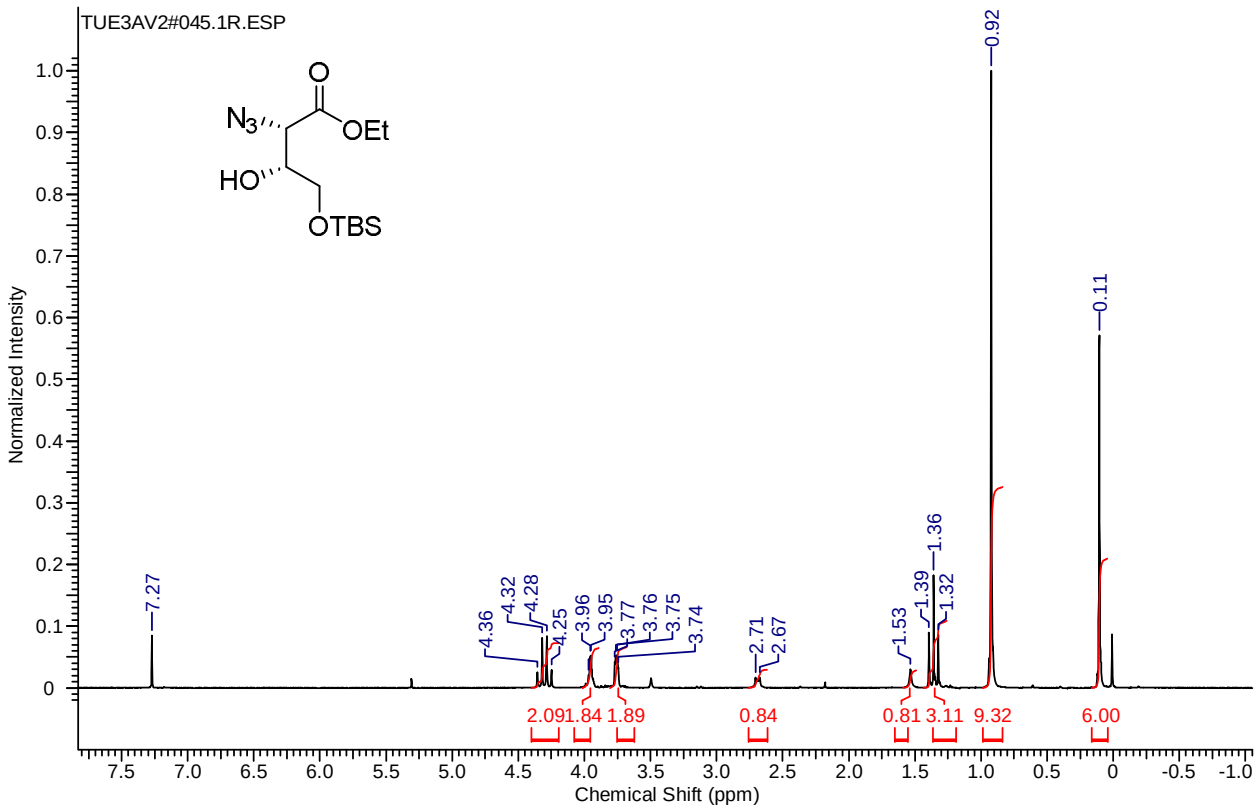
^{13}C-NMR spectrum of compound **5** ($CDCl_3$, 50 MHz)



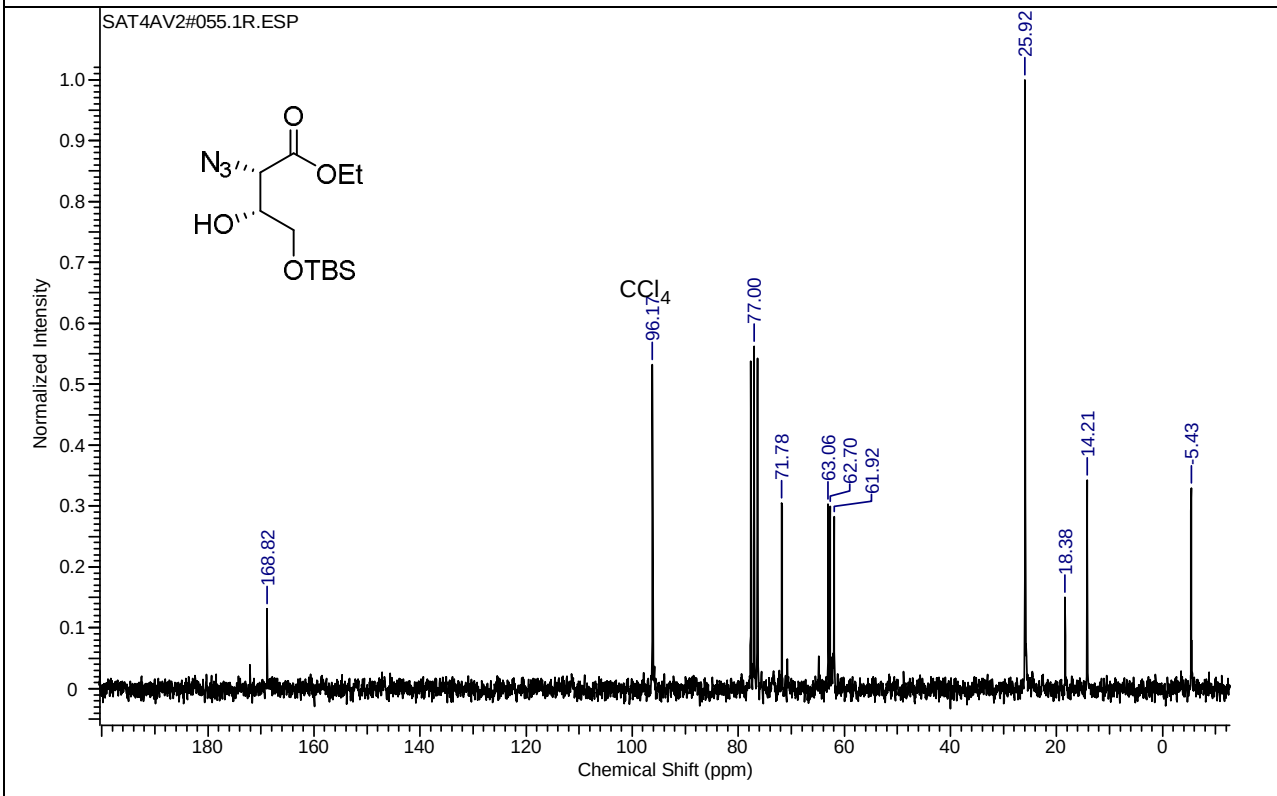
DEPT spectrum of compound **5** ($CDCl_3$, 50 MHz)



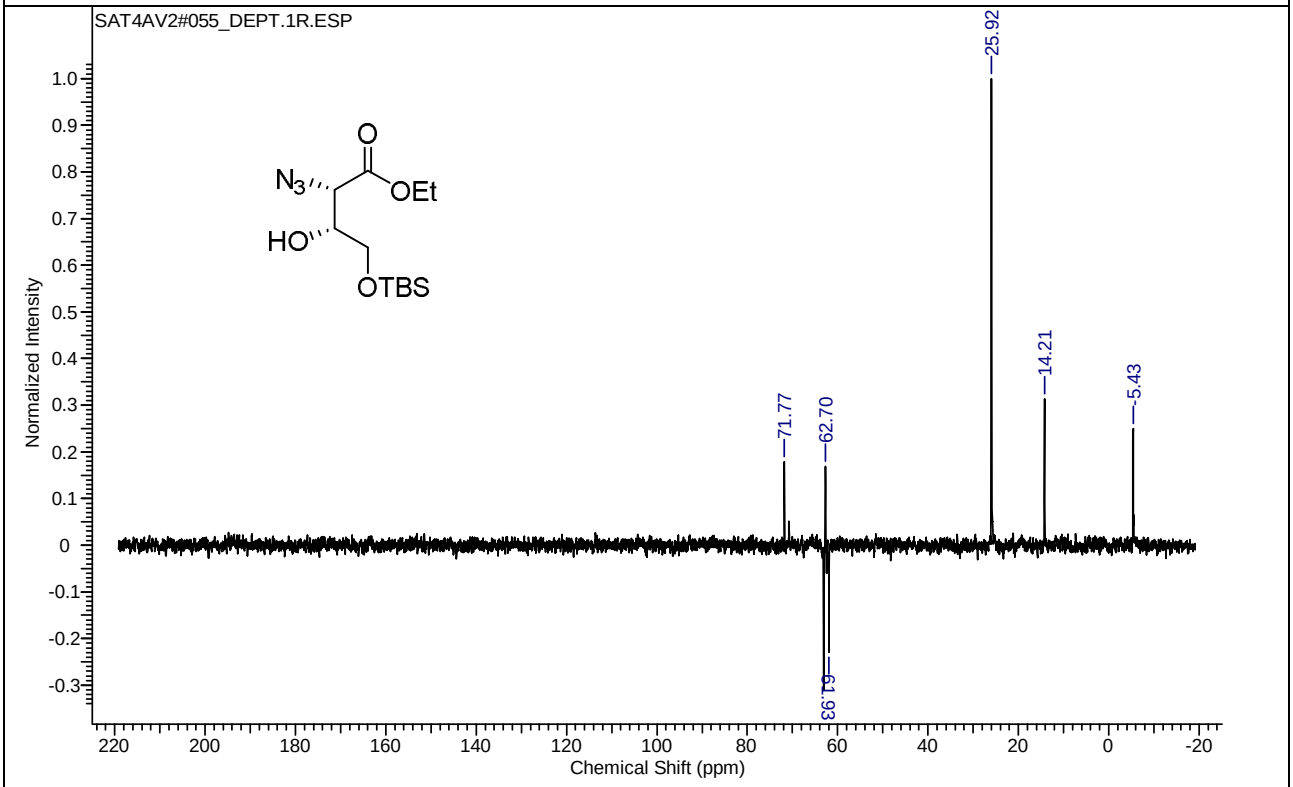
^{1}H-NMR spectrum of compound **9** ($CDCl_3$ + CCl_4, 200 MHz)



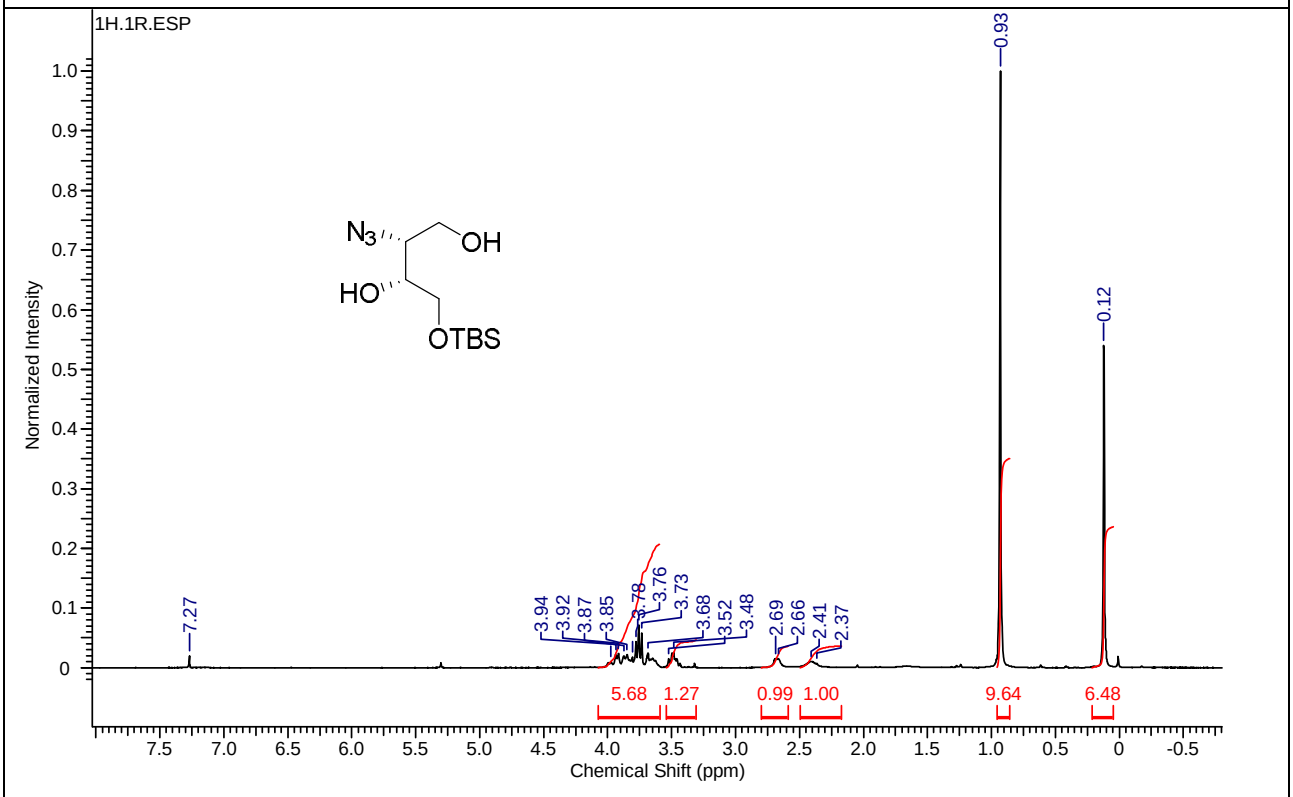
^{13}C-NMR spectrum of compound **9** ($CDCl_3$ + CCl_4, 50 MHz)



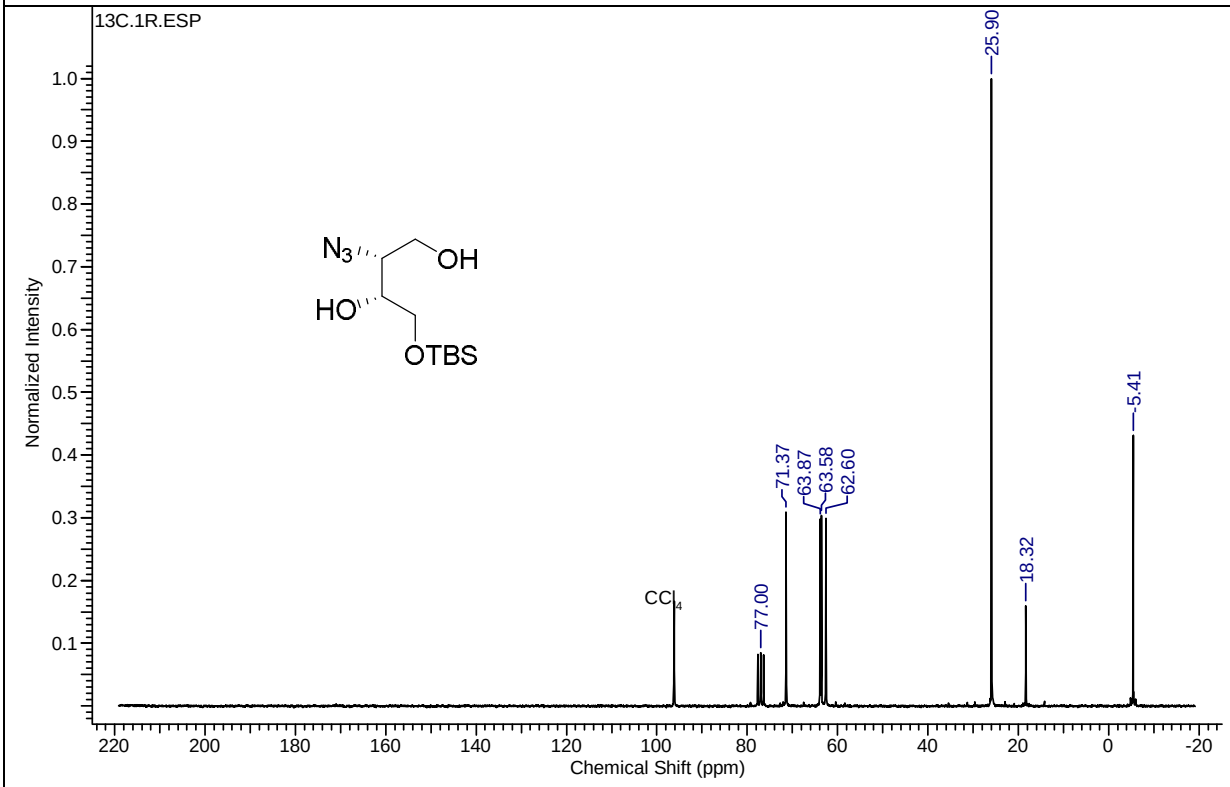
^{13}C-NMR spectrum of compound **9** ($CDCl_3$ + CCl_4, 50 MHz) DEPT



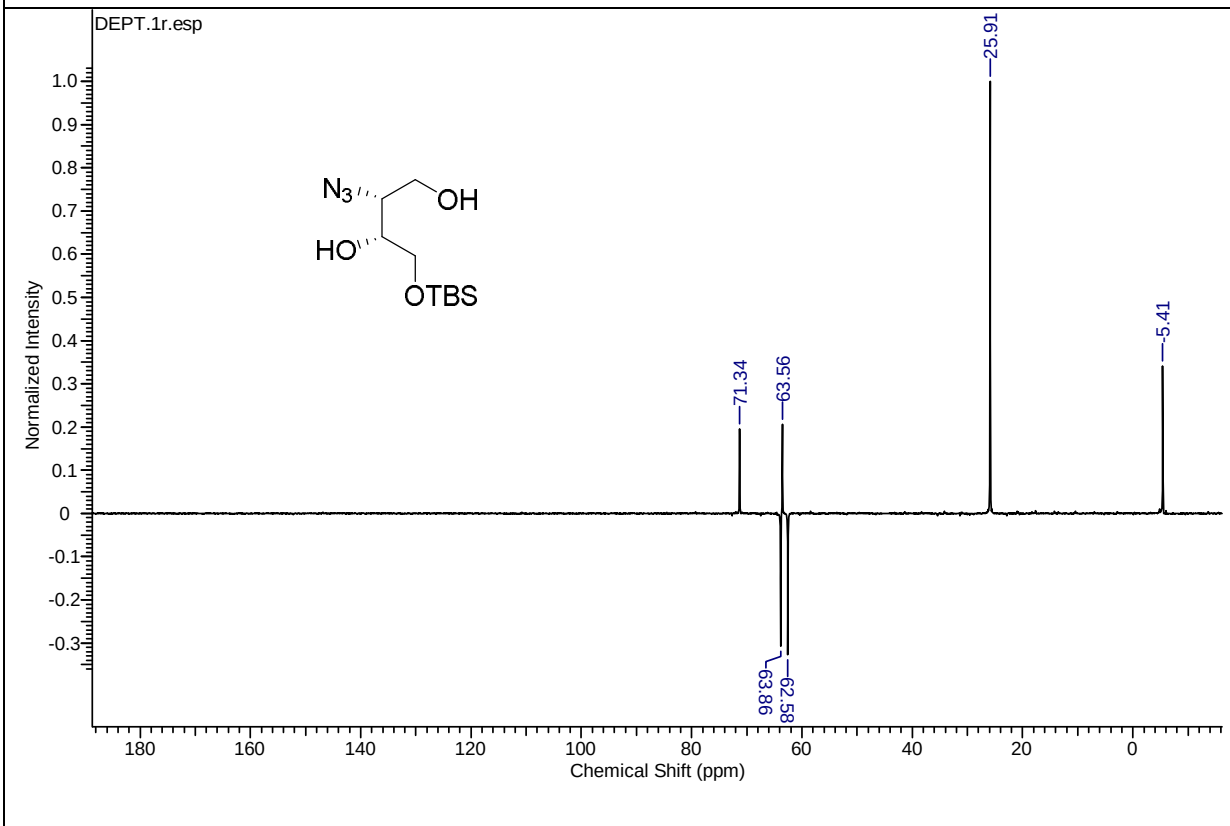
^{1}H-NMR spectrum of compound **4** ($CDCl_3$ + CCl_4, 200 MHz)



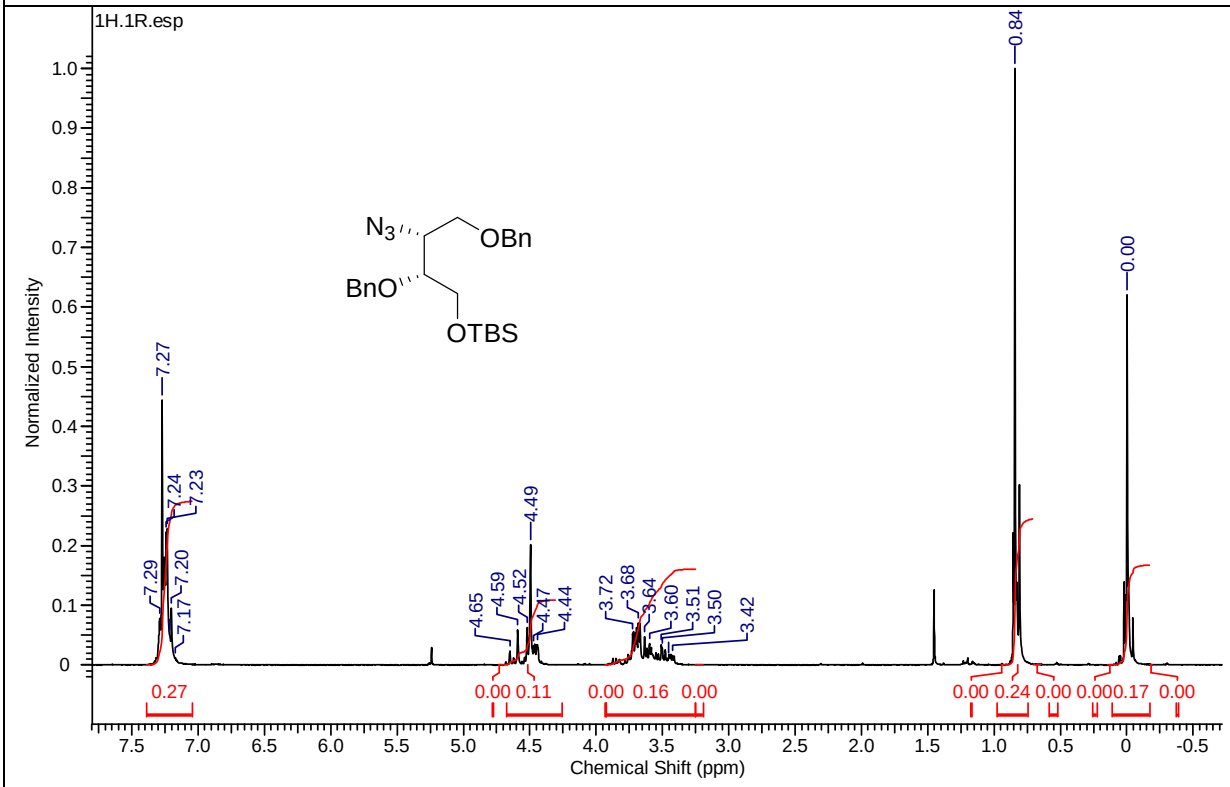
^{13}C-NMR spectrum of compound **4** ($CDCl_3$ + CCl_4, 200 MHz)



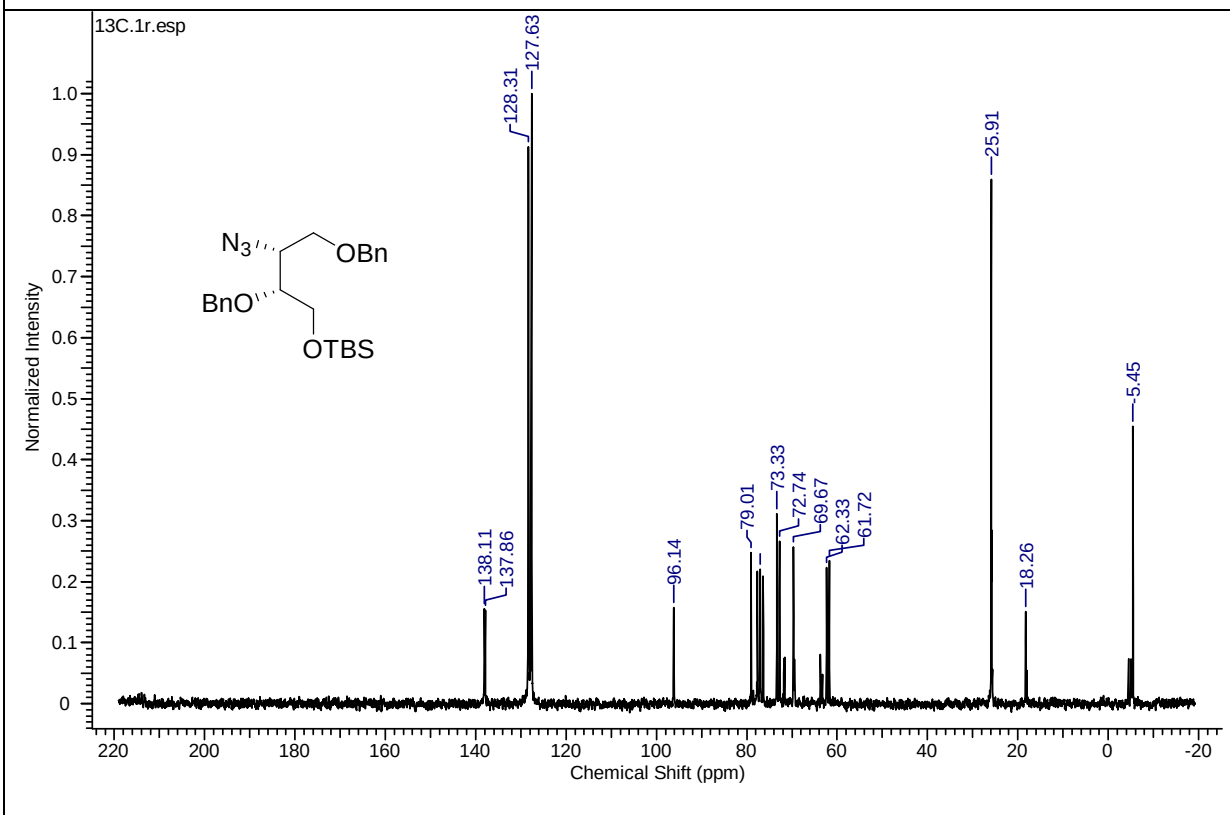
DEPT-NMR spectrum of compound **4** ($CDCl_3$ + CCl_4, 200 MHz)



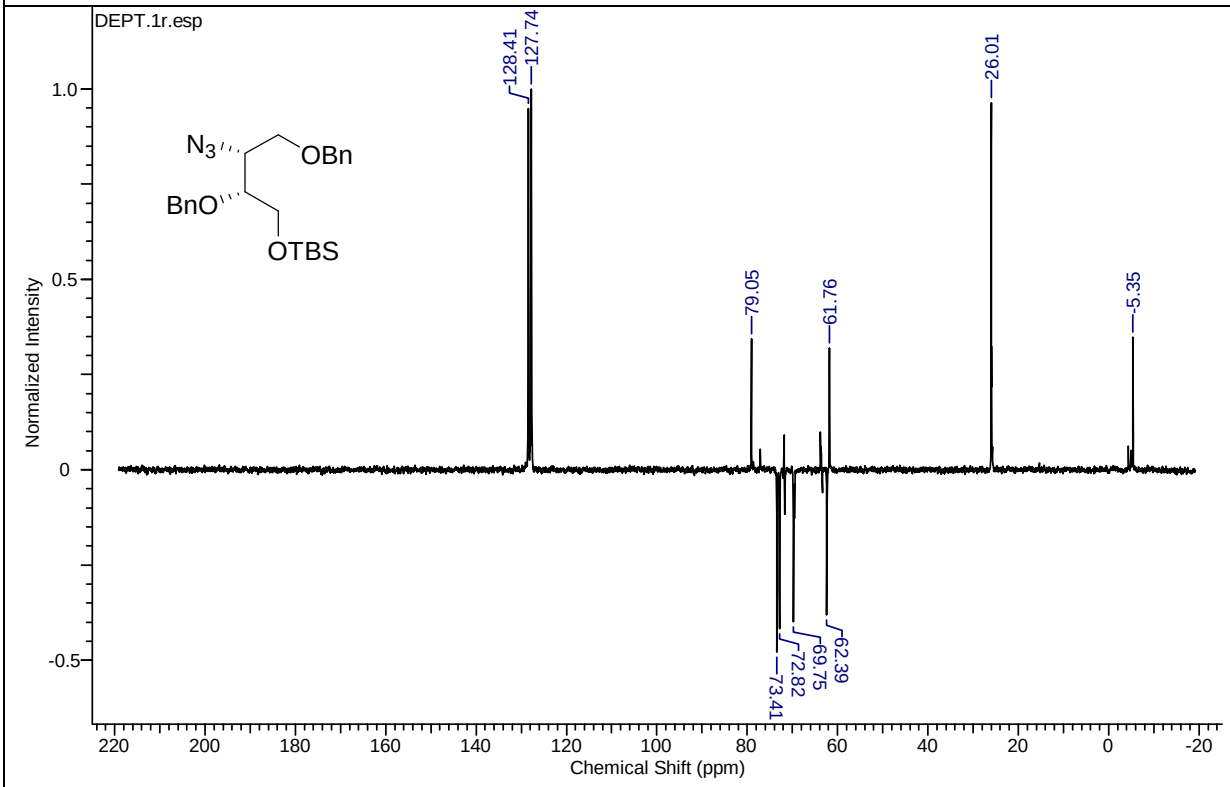
^{1}H-NMR spectrum of compound **10** ($CDCl_3$ + CCl_4, 200 MHz)



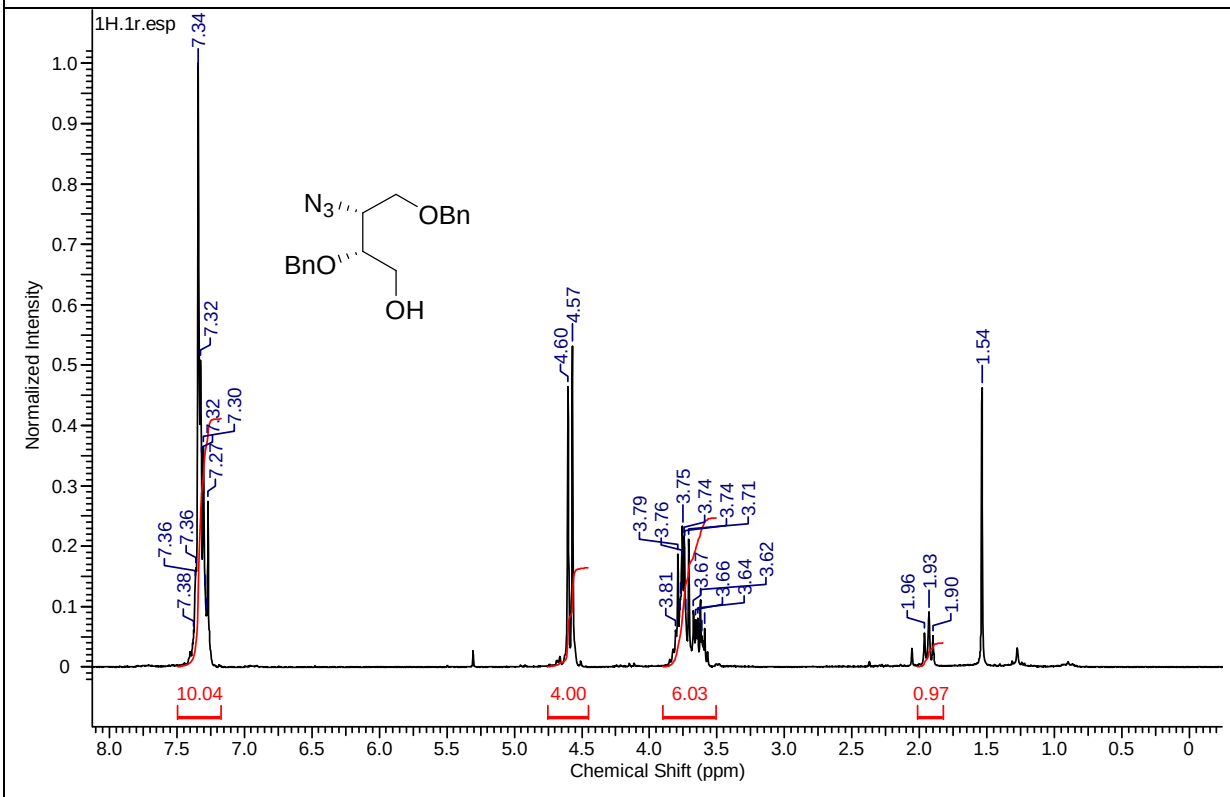
^{13}C-NMR spectrum of compound **10** ($CDCl_3$ + CCl_4, 50 MHz)



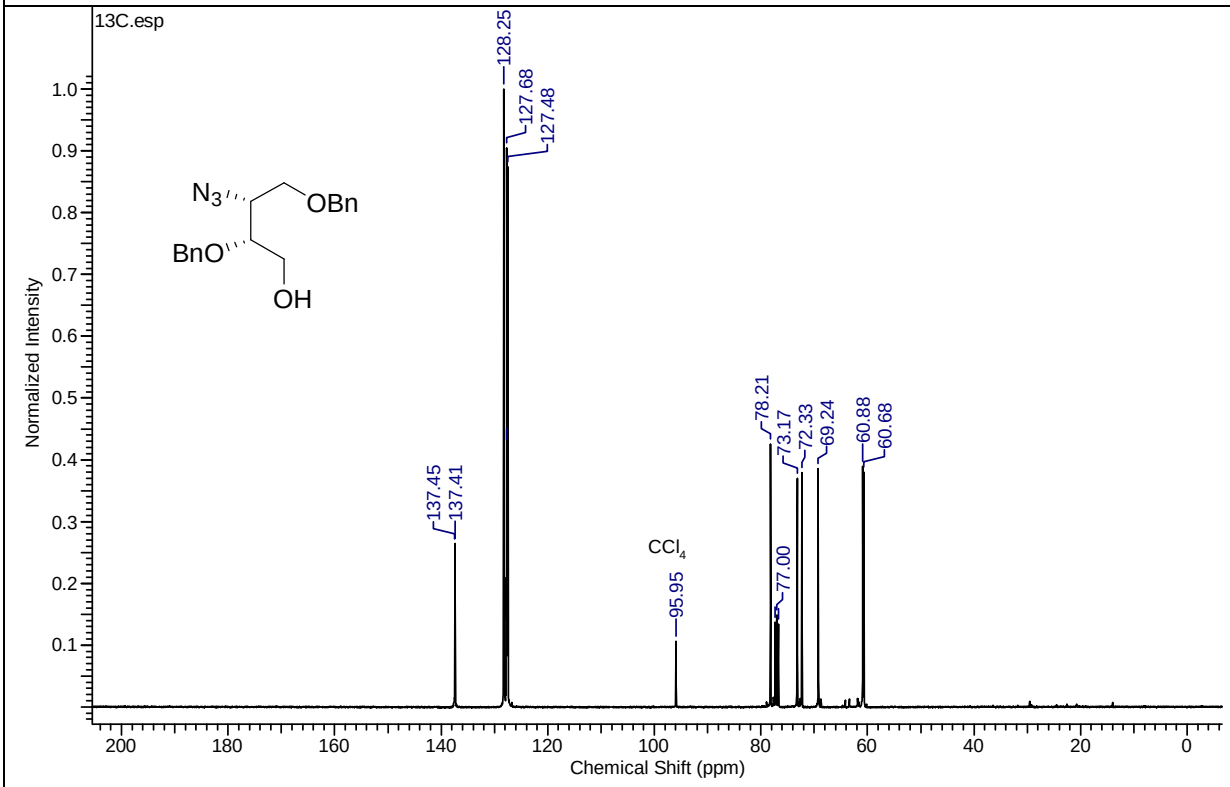
DEPT-NMR spectrum of compound **10** ($CDCl_3$ + CCl_4, 50 MHz)



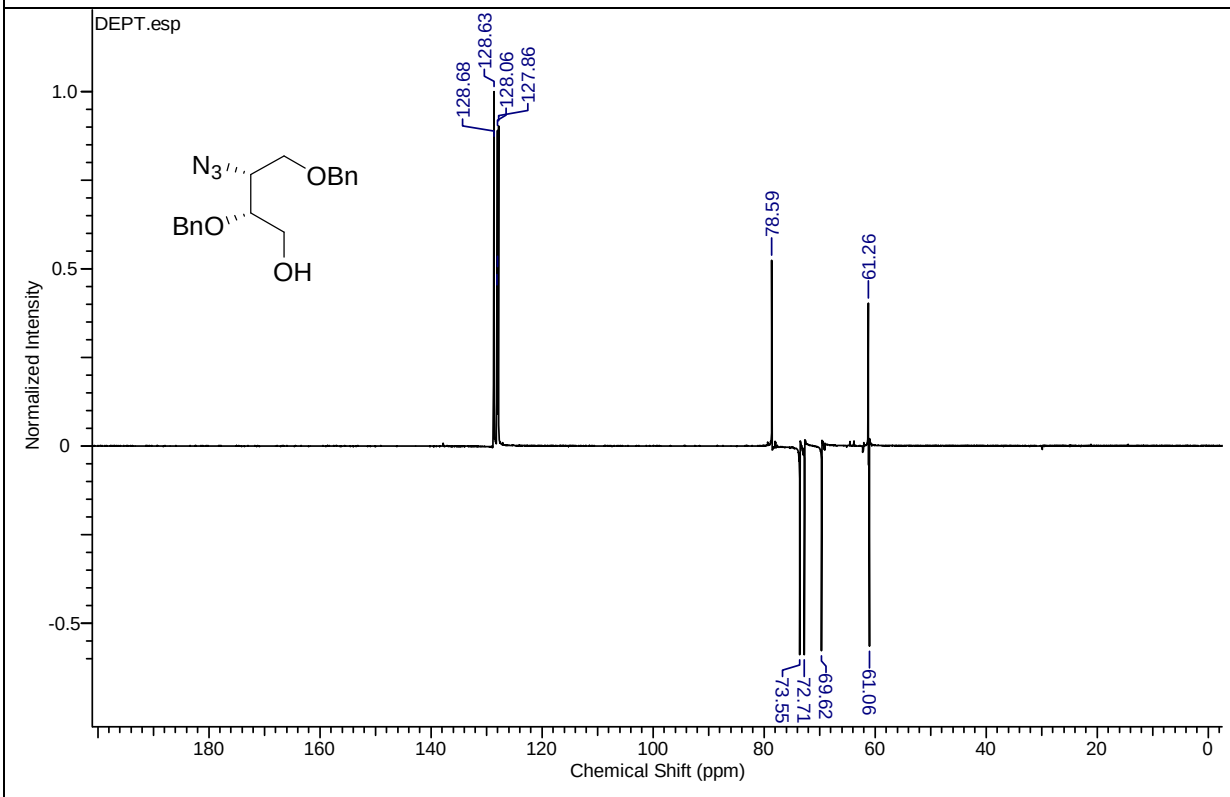
^{1}H-NMR spectrum of compound **11** ($CDCl_3$ + CCl_4, 200 MHz)



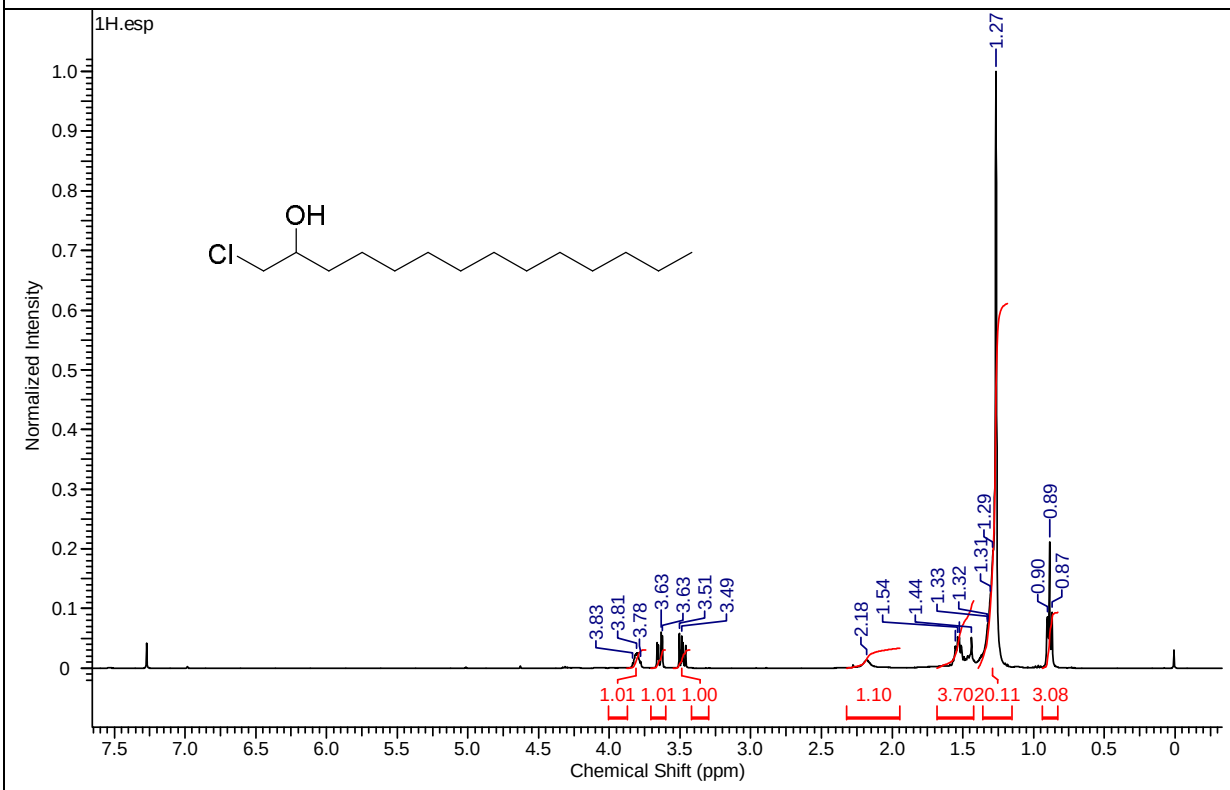
^{13}C-NMR spectrum of compound **11** ($CDCl_3$ + CCl_4, 50 MHz)



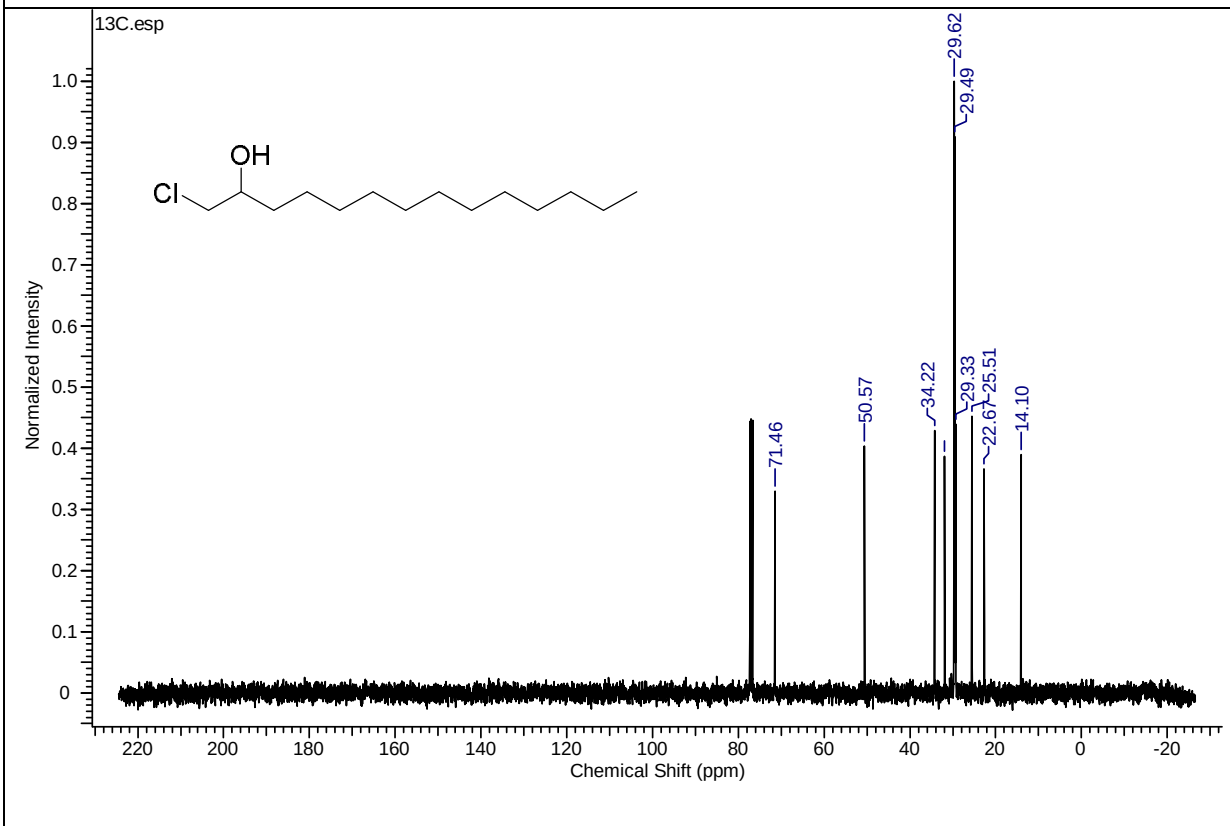
DEPT-NMR spectrum of compound **11** ($CDCl_3$ + CCl_4, 50 MHz)



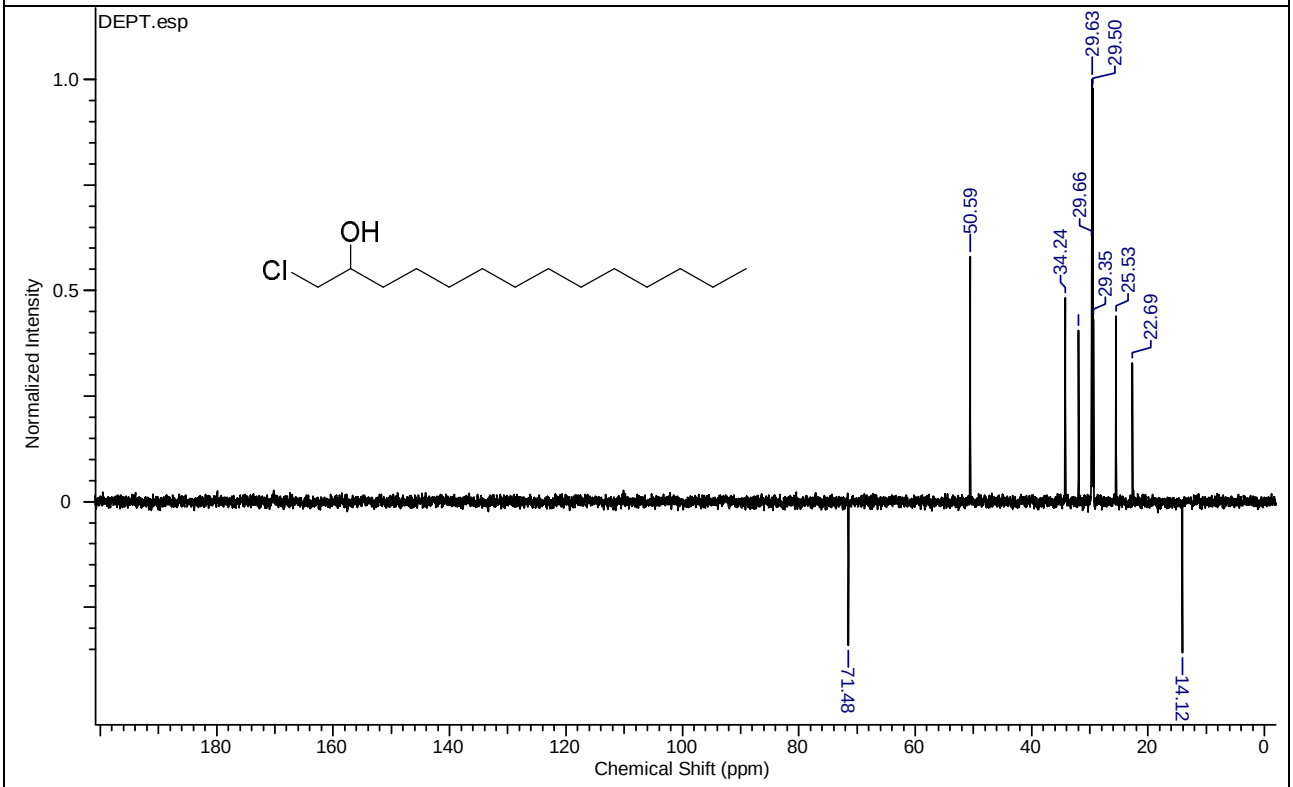
^{1}H-NMR spectrum of compound **12** ($CDCl_3$, 400 MHz)



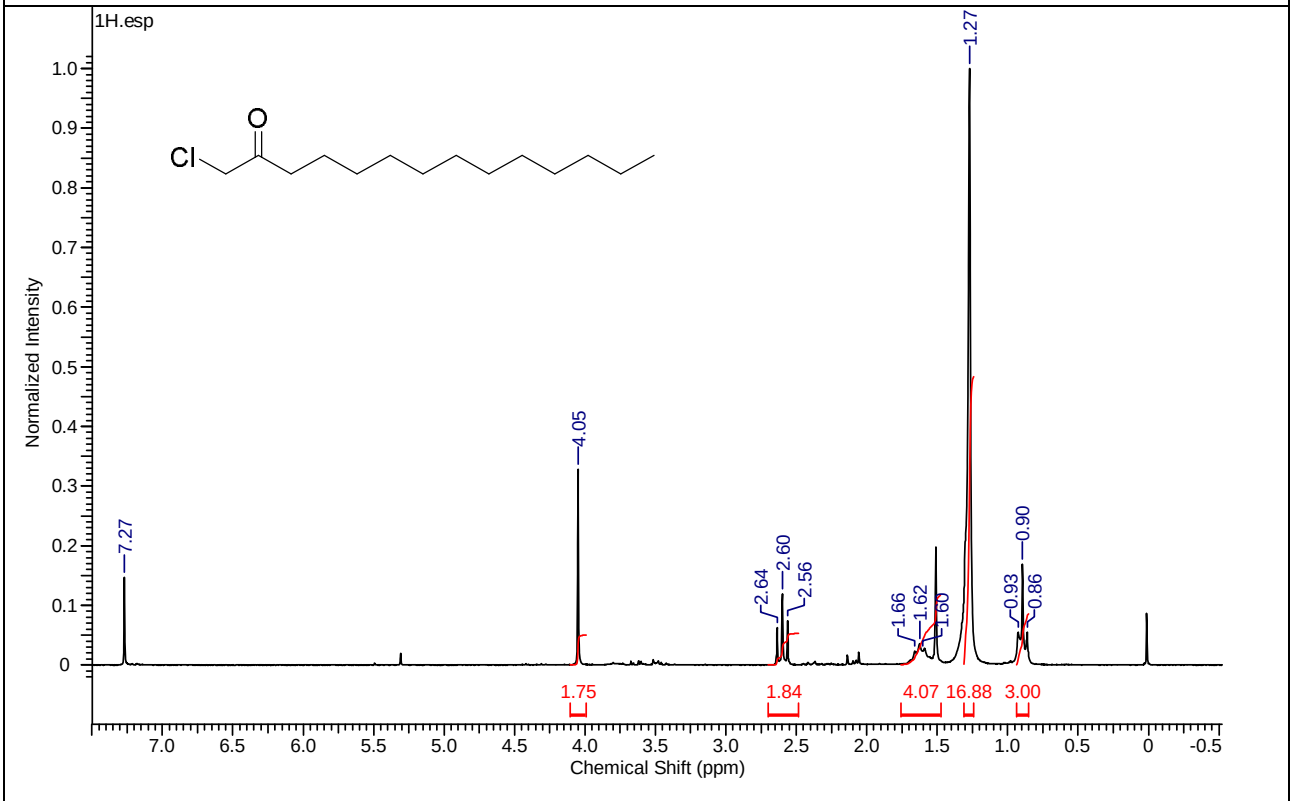
^{13}C-NMR spectrum of compound **12** ($CDCl_3$, 100 MHz)



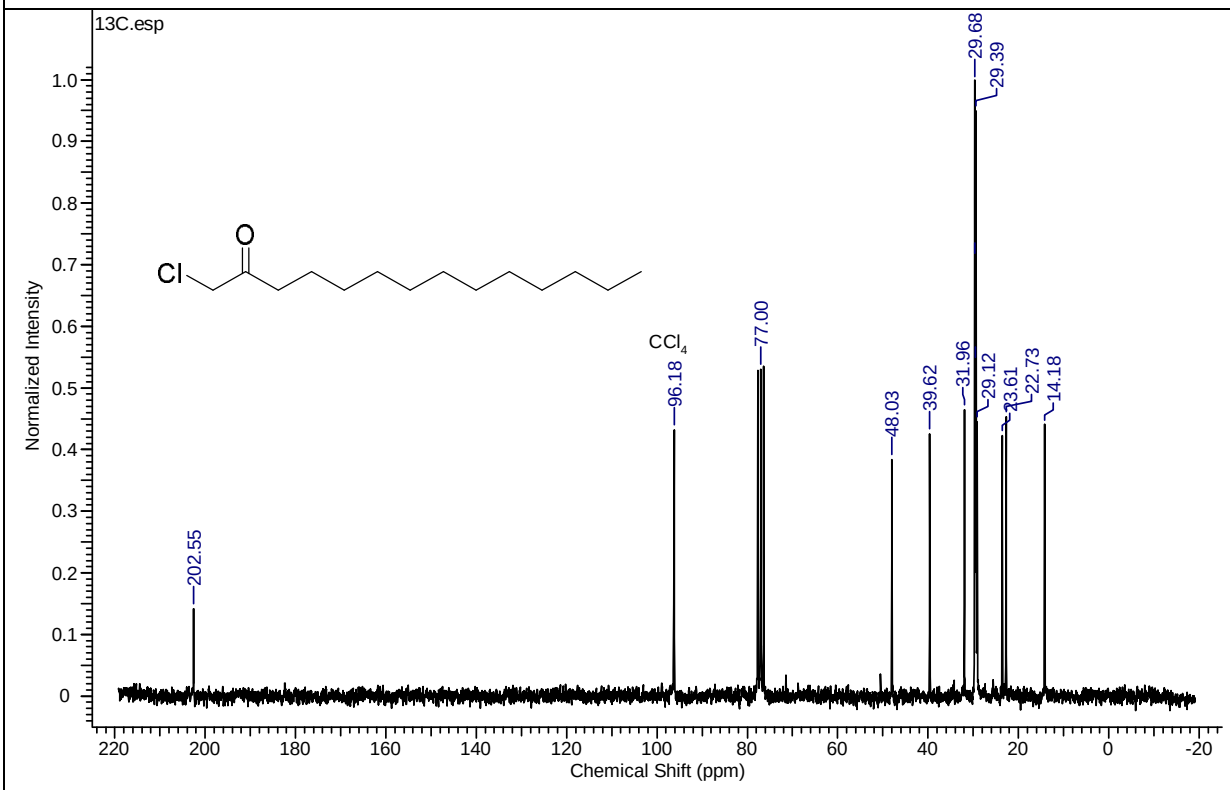
DEPT-NMR spectrum of compound **12** ($CDCl_3$, 100 MHz)



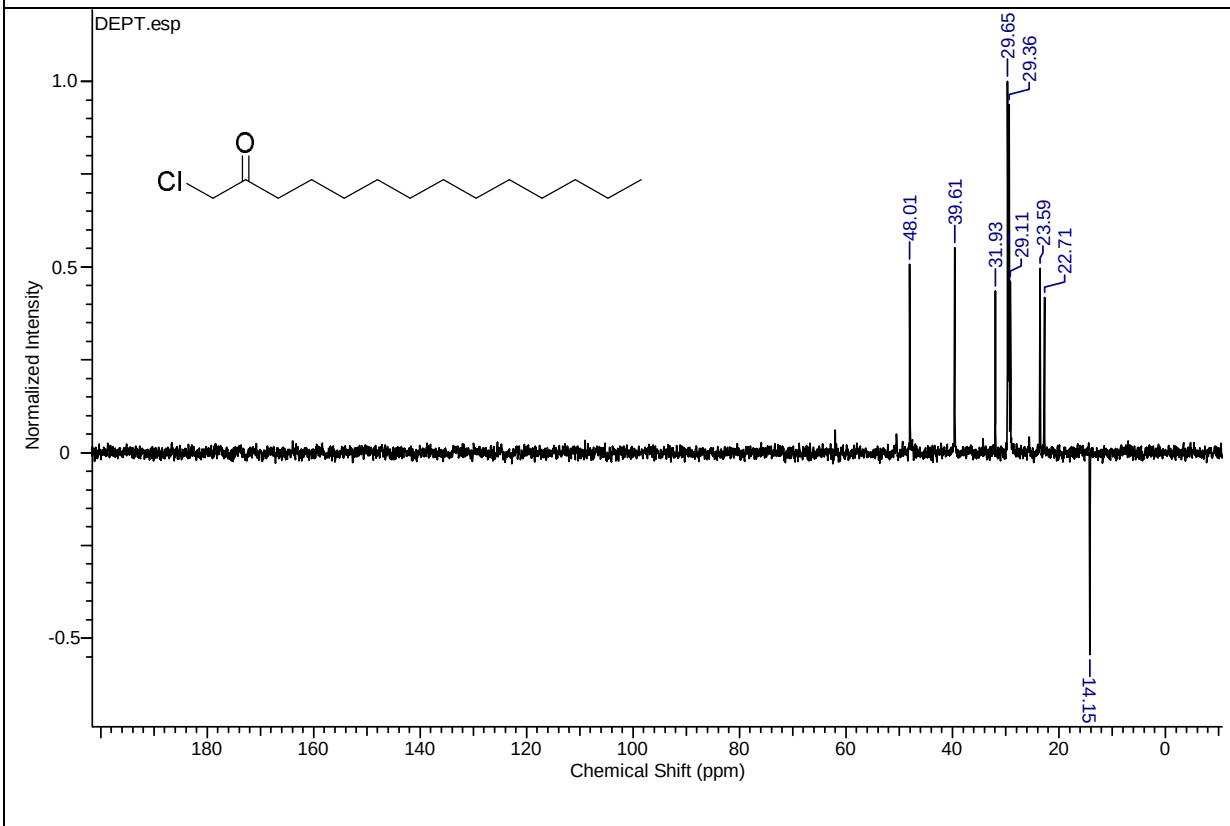
^{1}H-NMR spectrum of compound **13** ($CDCl_3$ + CCl_4, 200 MHz)



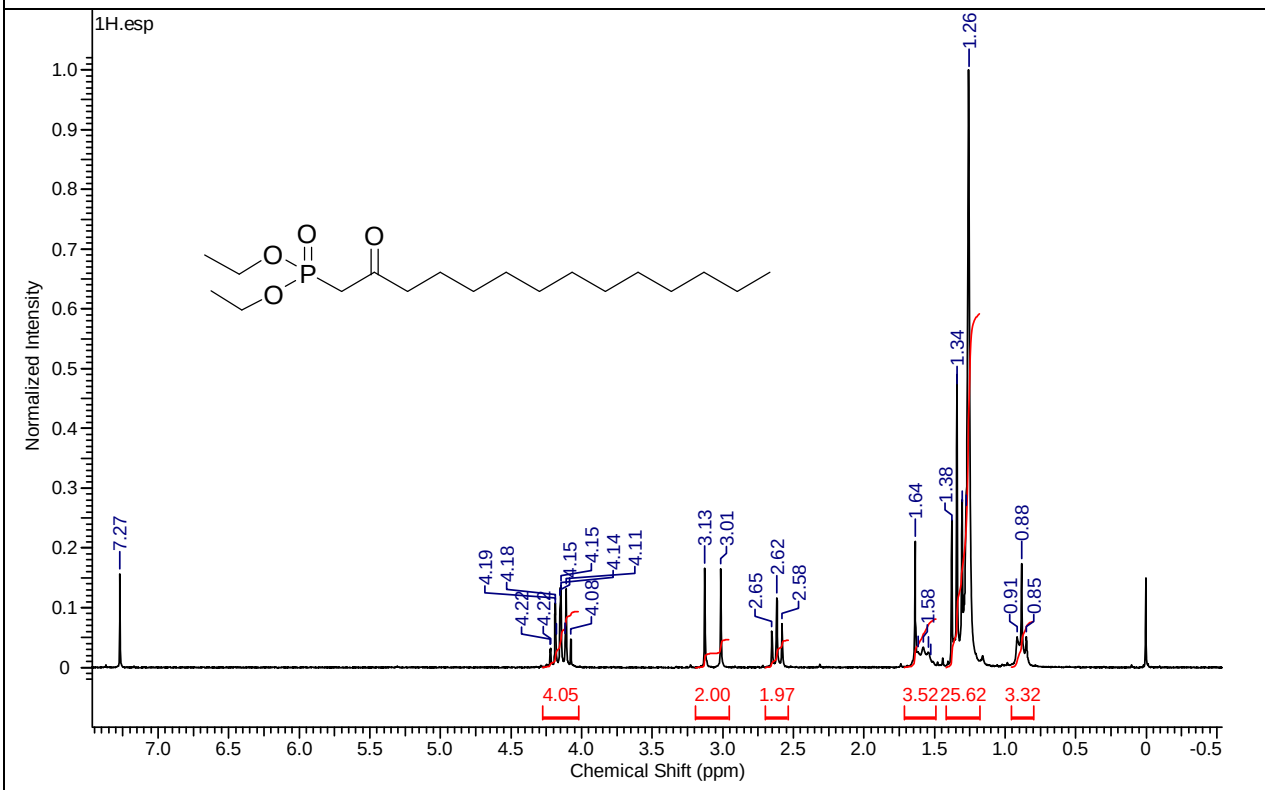
^{13}C-NMR spectrum of compound **13** ($CDCl_3$ + CCl_4, 50 MHz)



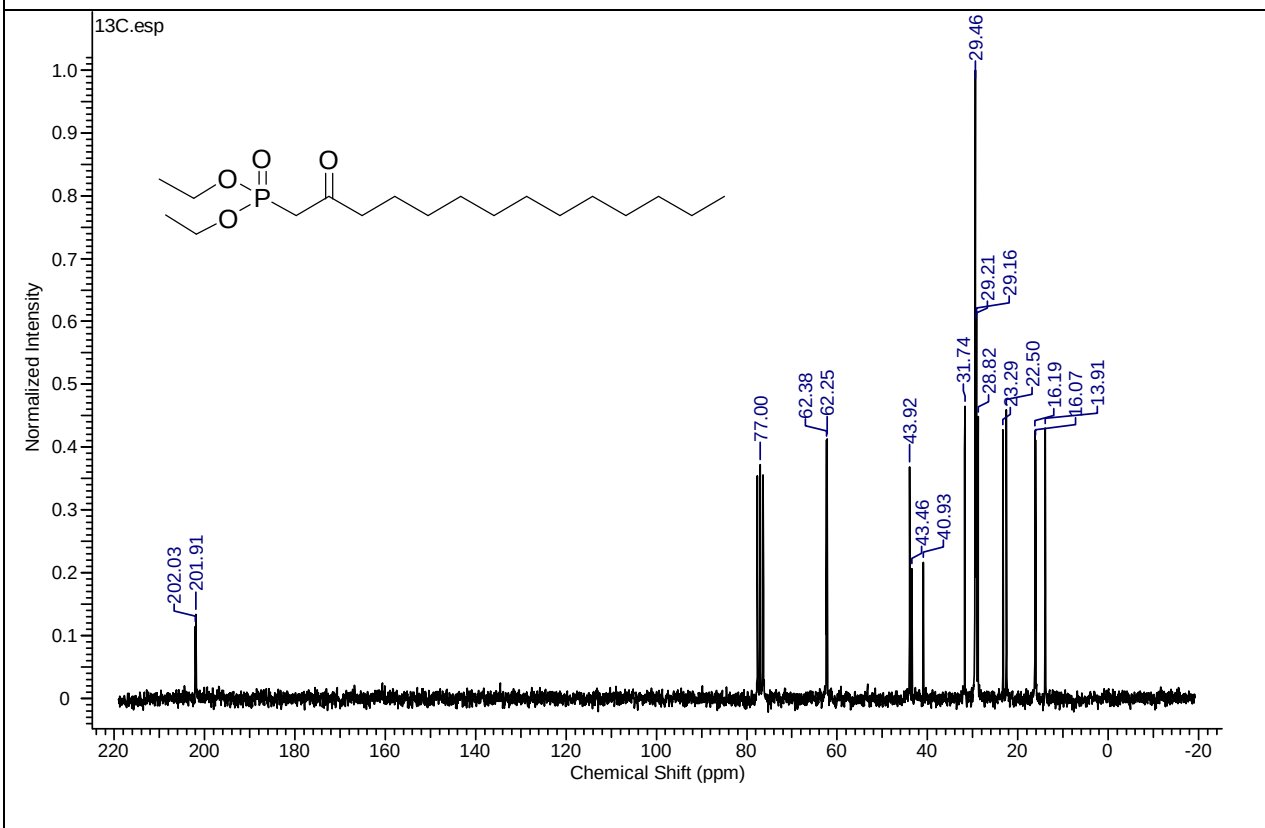
DEPT-NMR spectrum of compound **13** ($CDCl_3$ + CCl_4, 50 MHz)



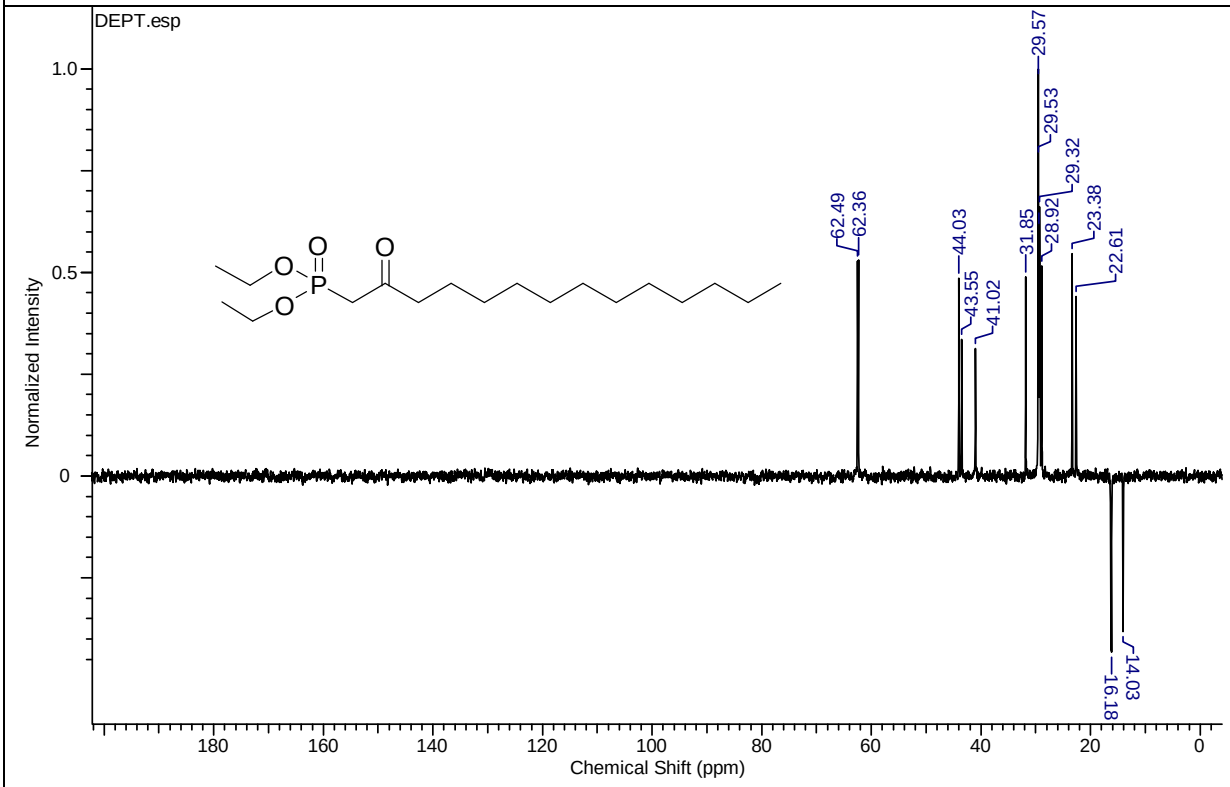
^{1}H-NMR spectrum of compound **14** (CDCl, 200 MHz)



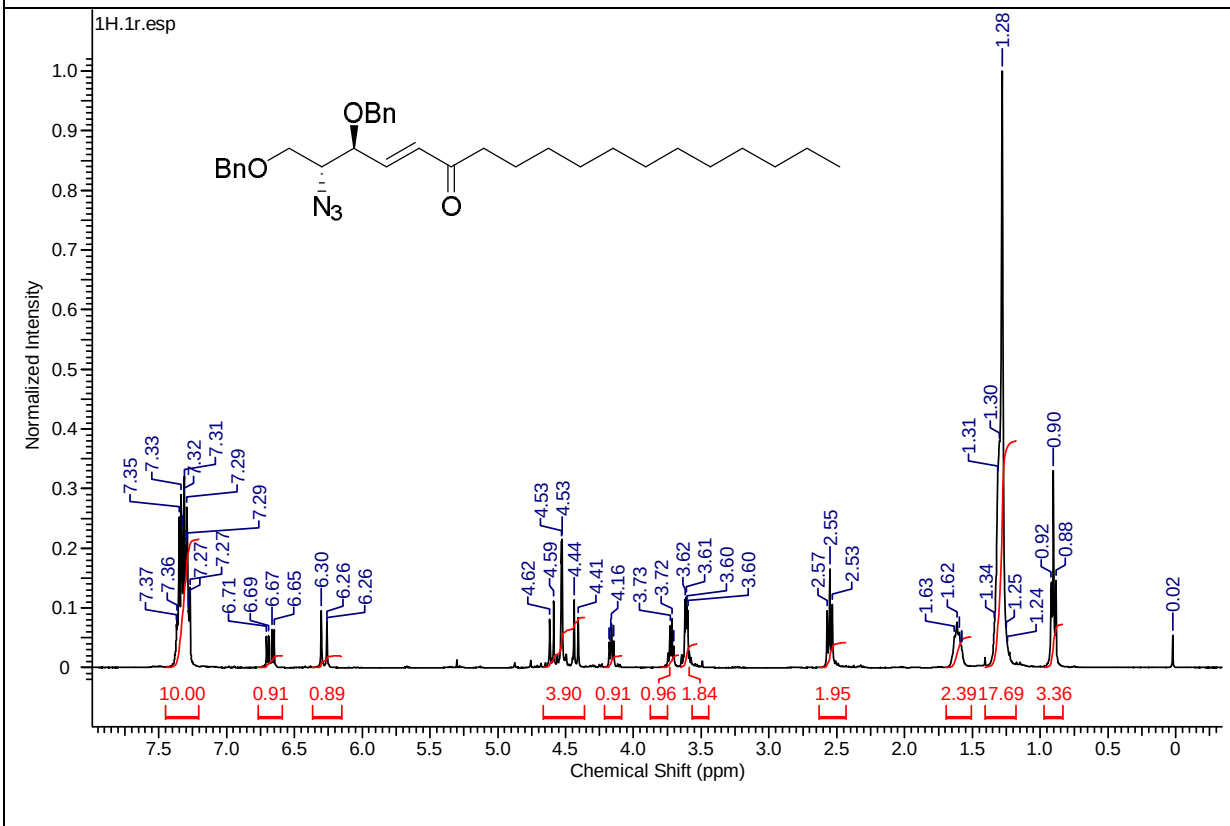
^{13}C-NMR spectrum of compound **14** ($CDCl_3$, 50 MHz)



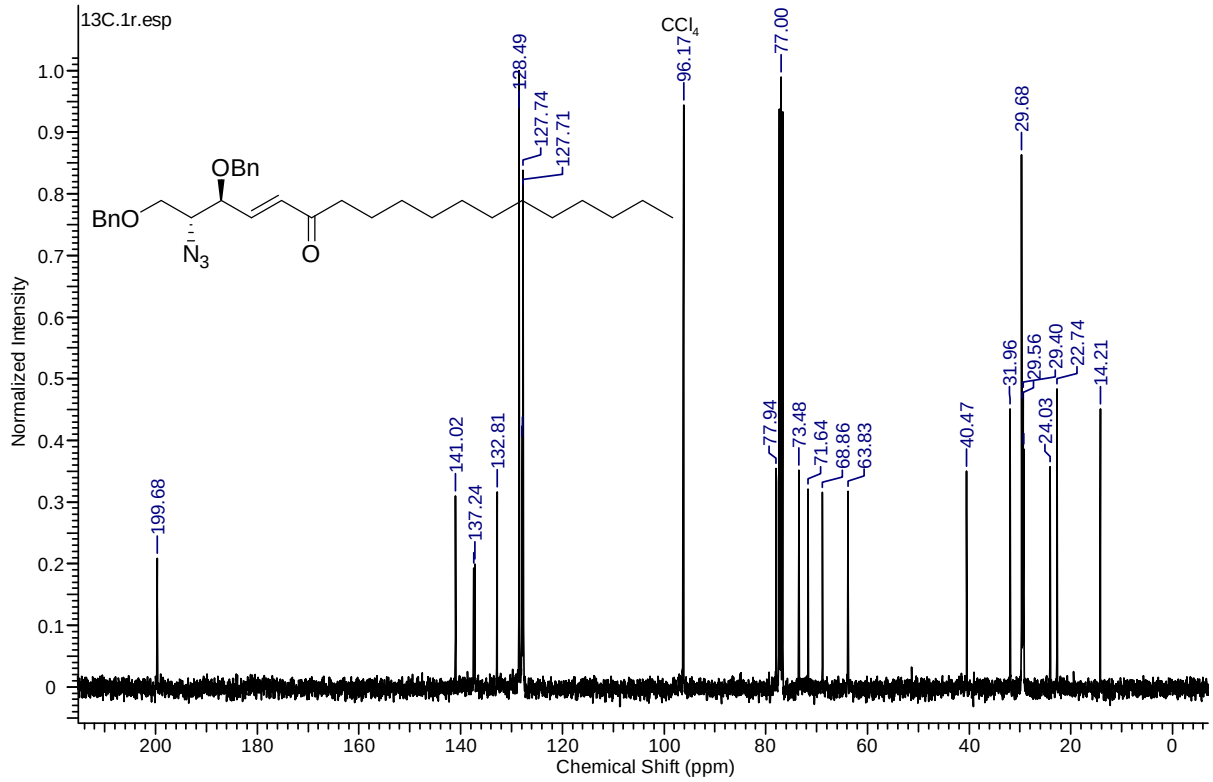
DEPT-NMR spectrum of compound **14** ($CDCl_3$, 50 MHz)



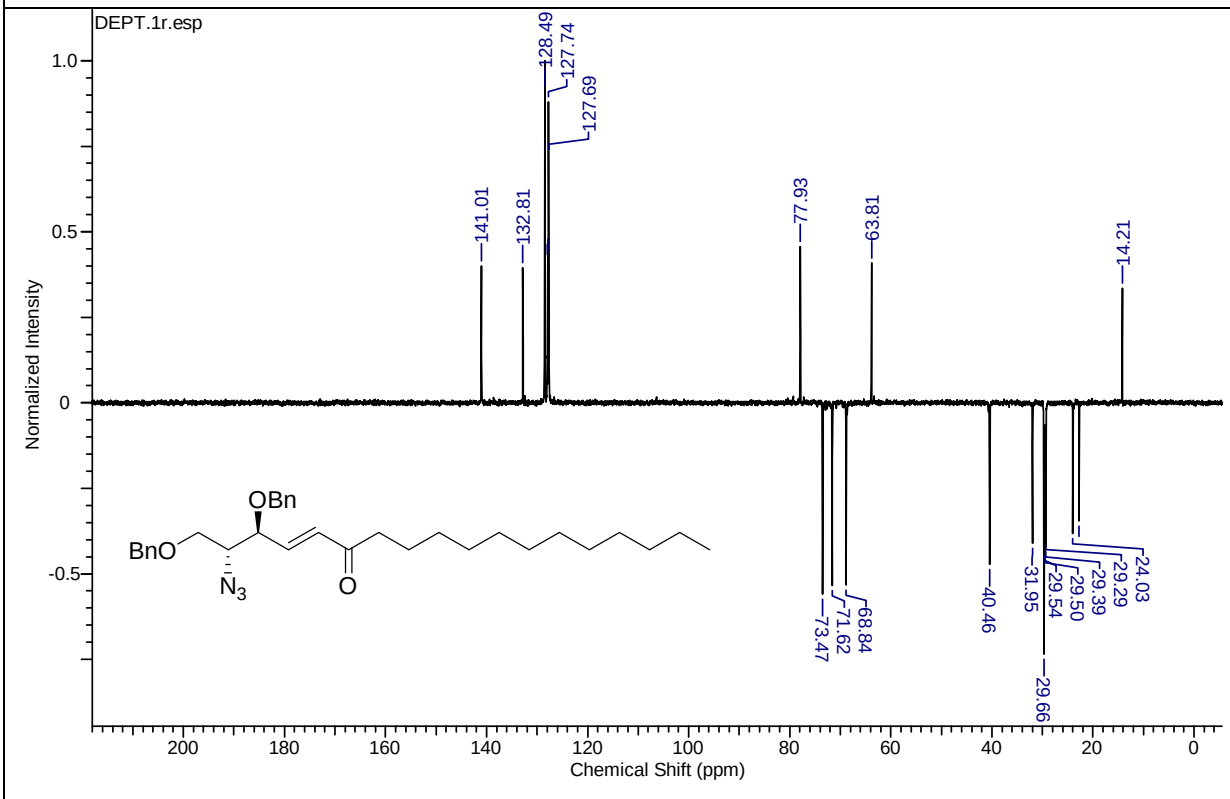
^{1}H-NMR spectrum of compound **2** ($CDCl_3$ + CCl_4, 200 MHz)



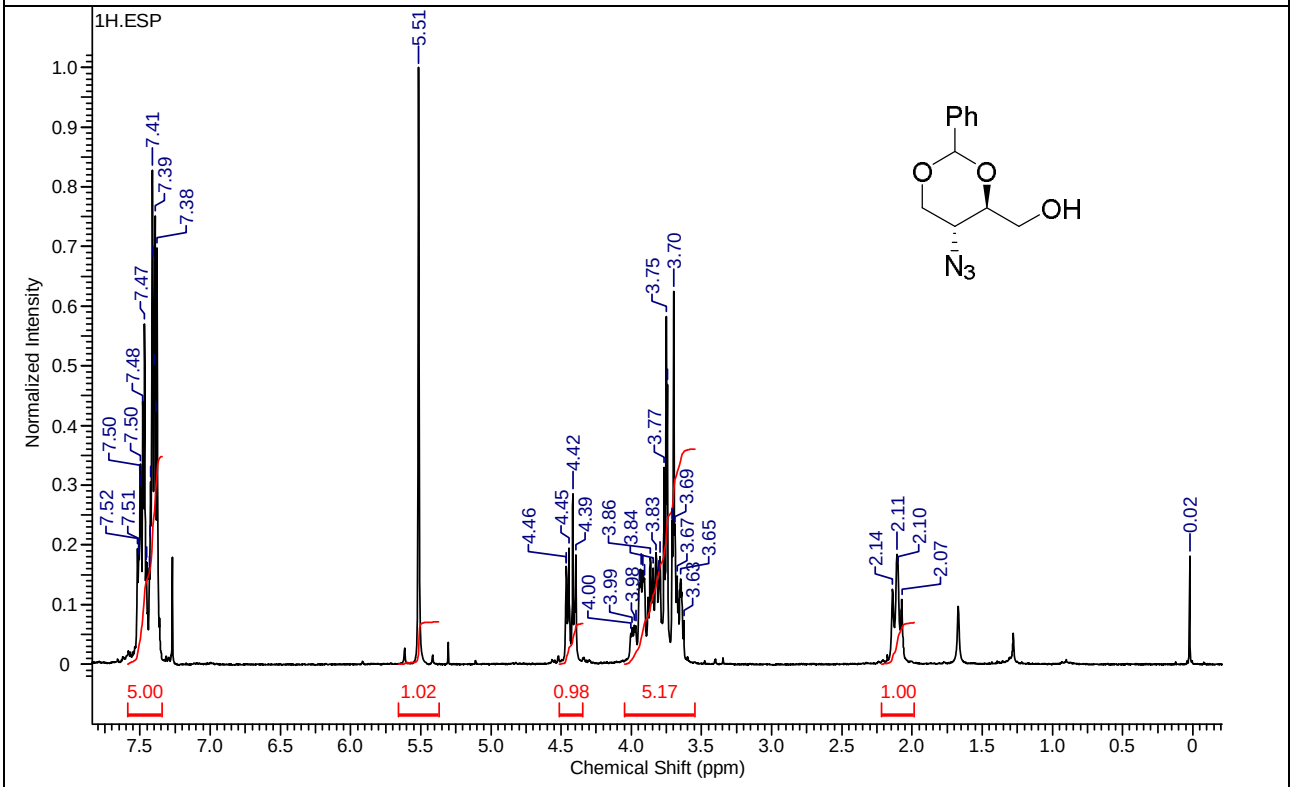
^{13}C-NMR spectrum of compound **2** ($CDCl_3$ + CCl_4, 200 MHz)



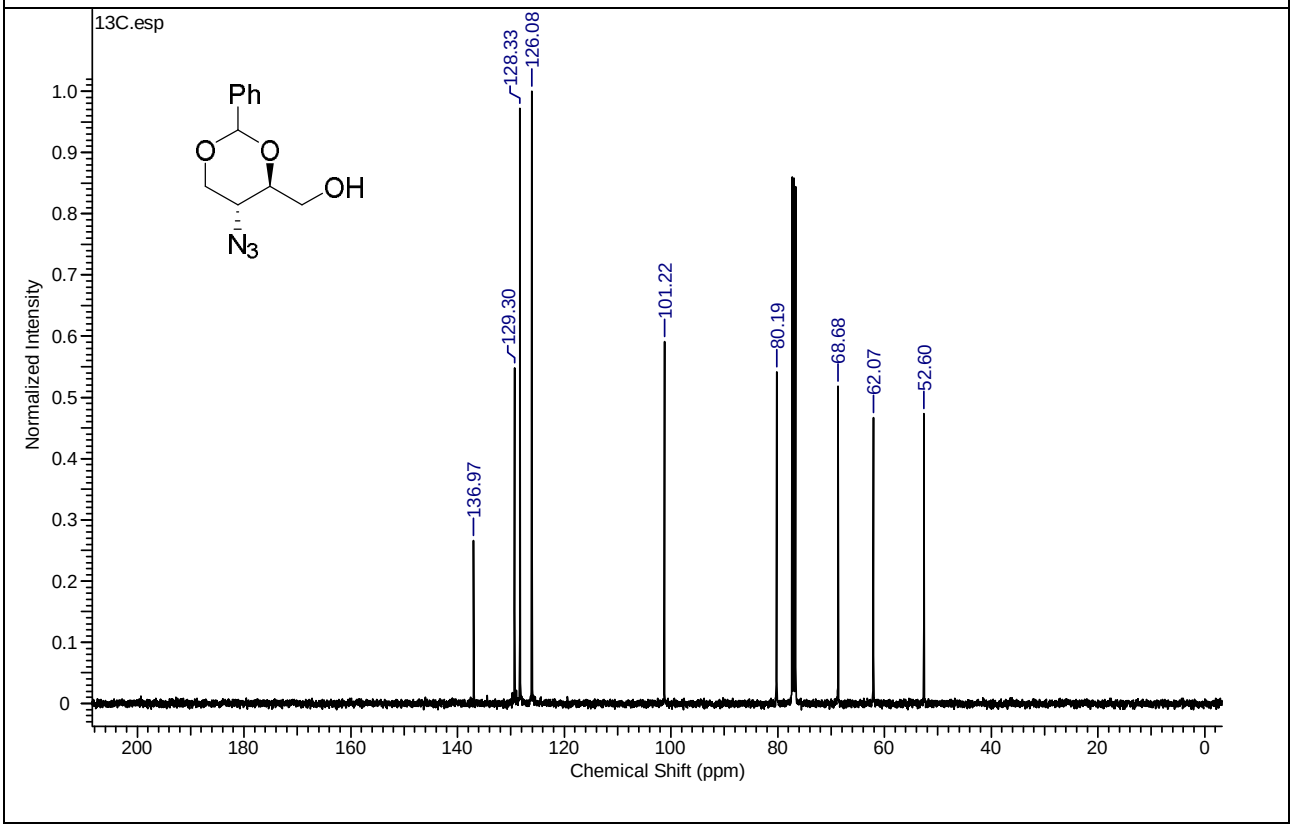
DEPT-NMR spectrum of compound **2** ($CDCl_3$ + CCl_4, 200 MHz)



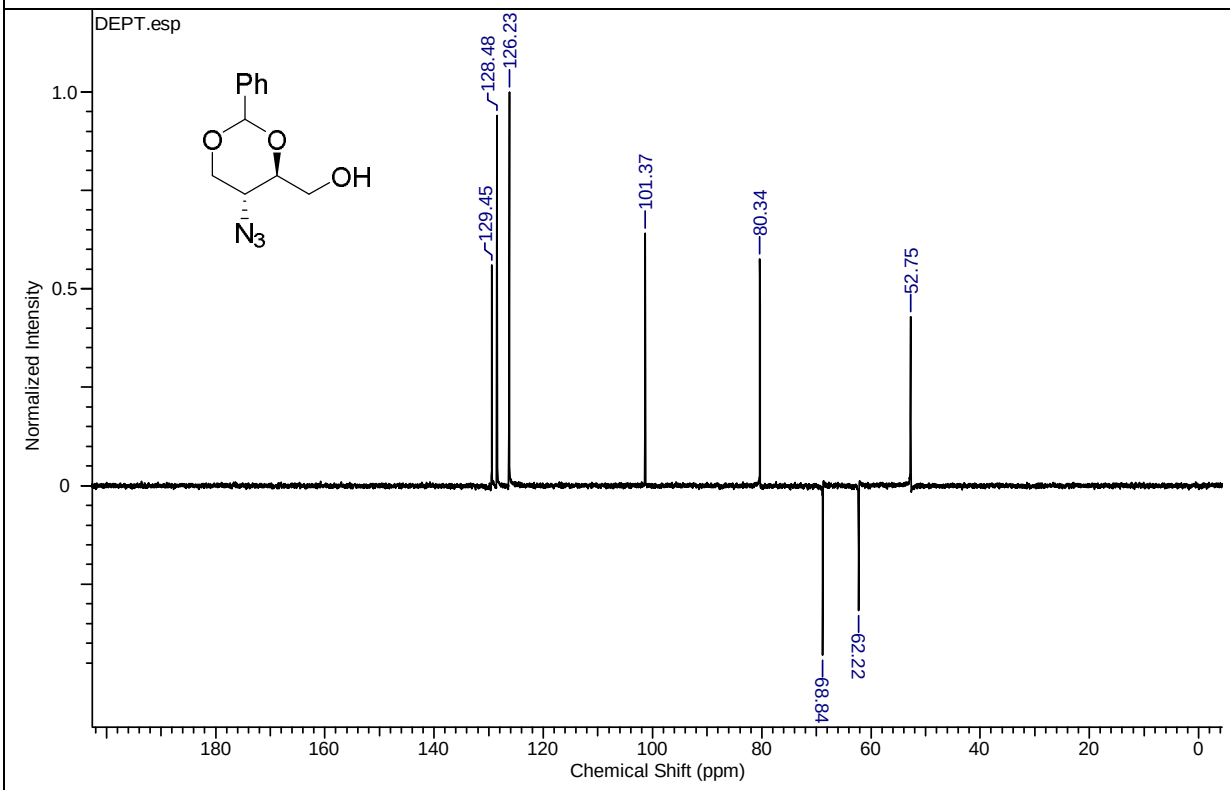
^{1}H-NMR spectrum of compound **17** ($CDCl_3$, 400 MHz)



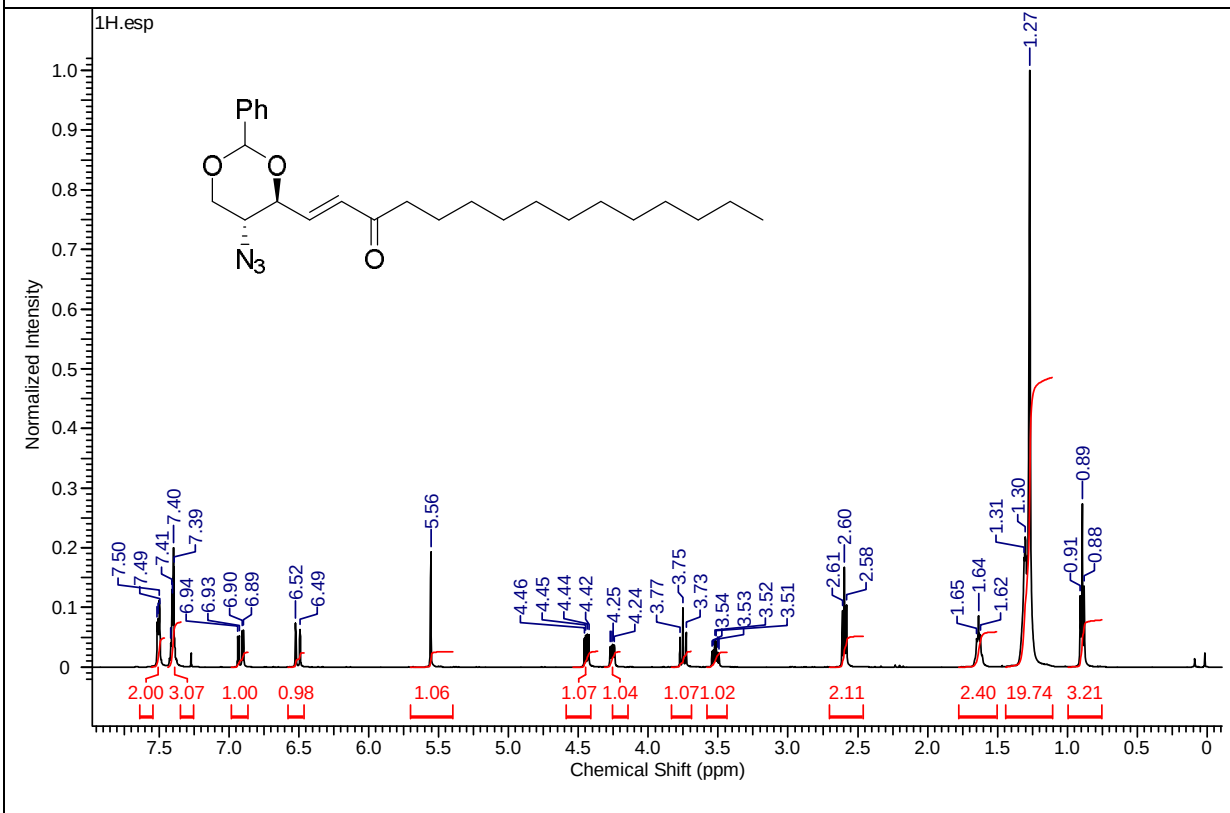
^{1}H-NMR spectrum of compound **17** ($CDCl_3$, 400 MHz)



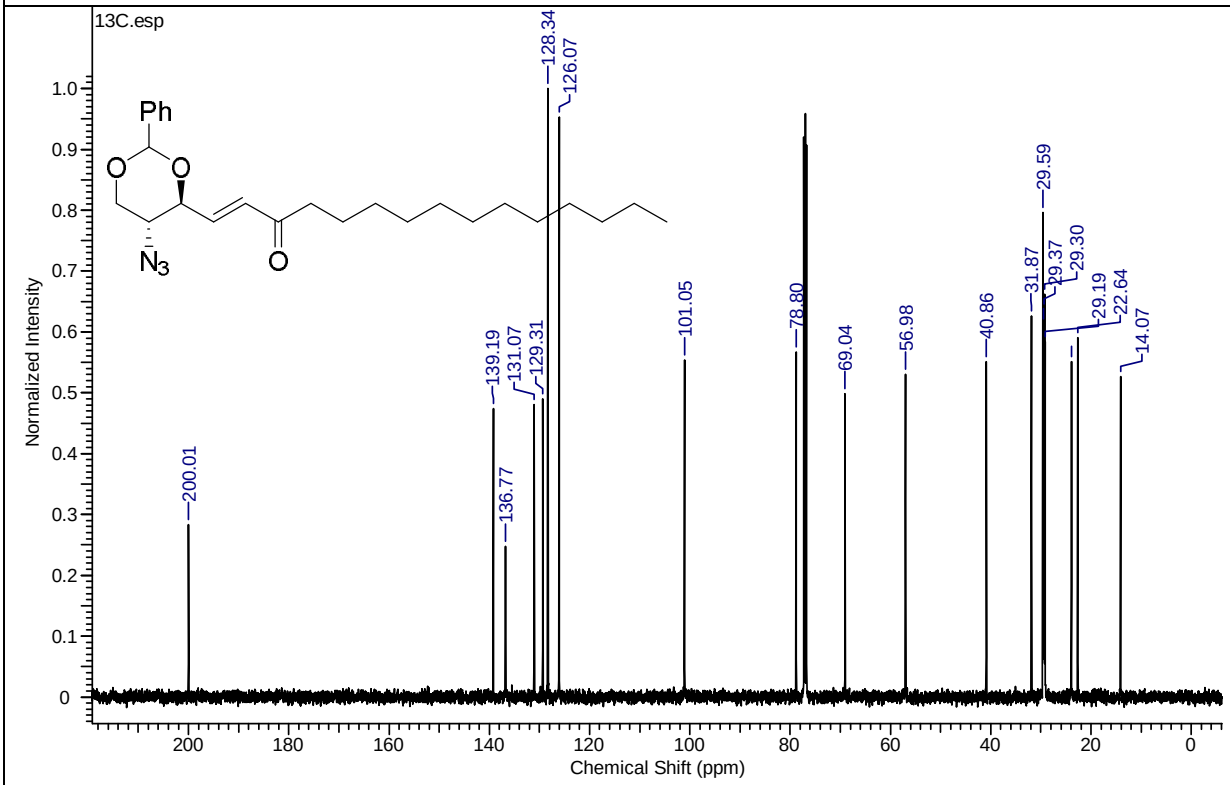
DEPT-NMR spectrum of compound **17** ($CDCl_3$, 100 MHz)



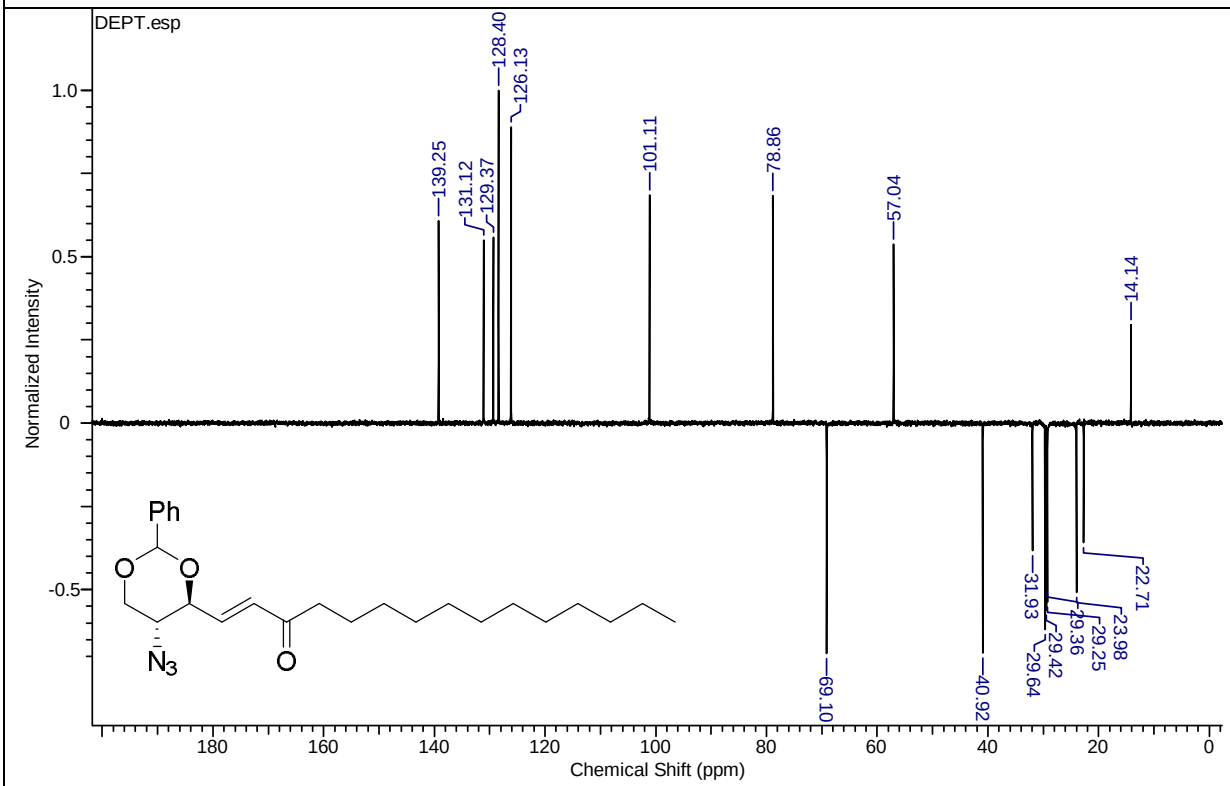
^{1}H-NMR spectrum of compound **19** ($CDCl_3$, 400 MHz)



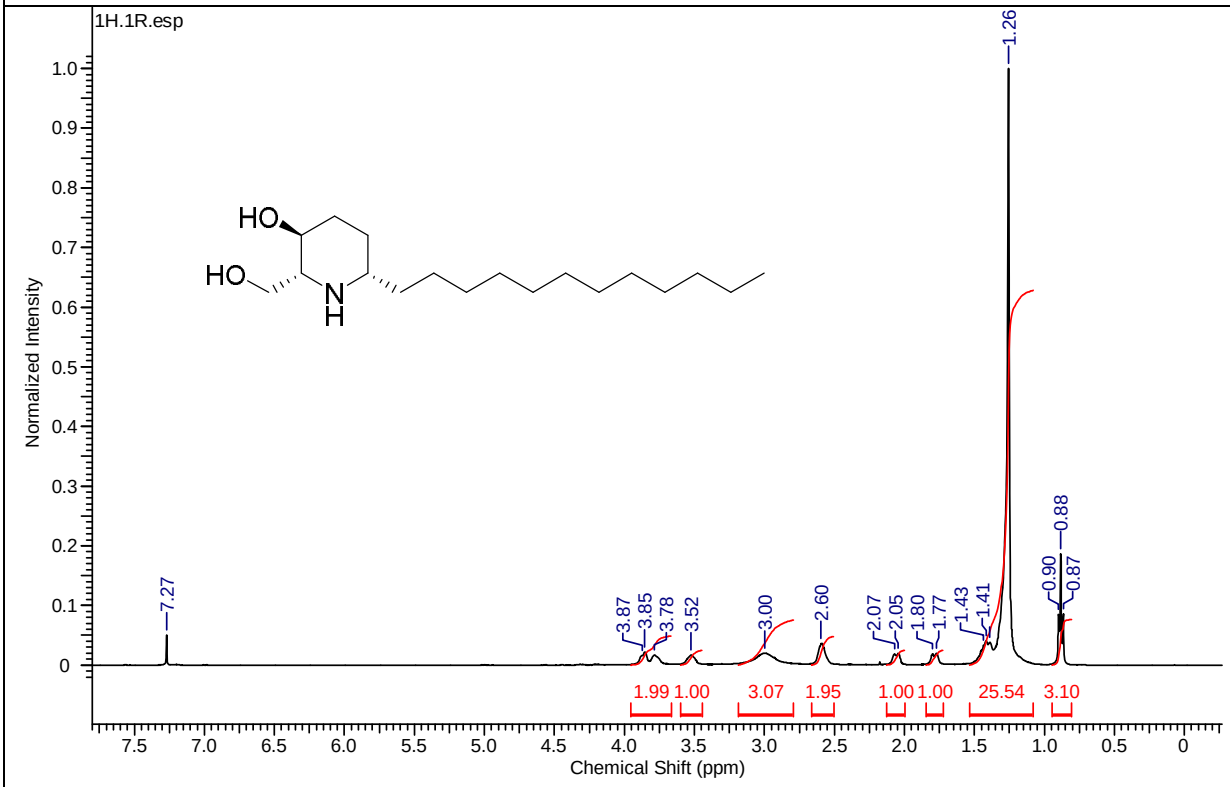
^{1}H-NMR spectrum of compound **19** ($CDCl_3$, 400 MHz)



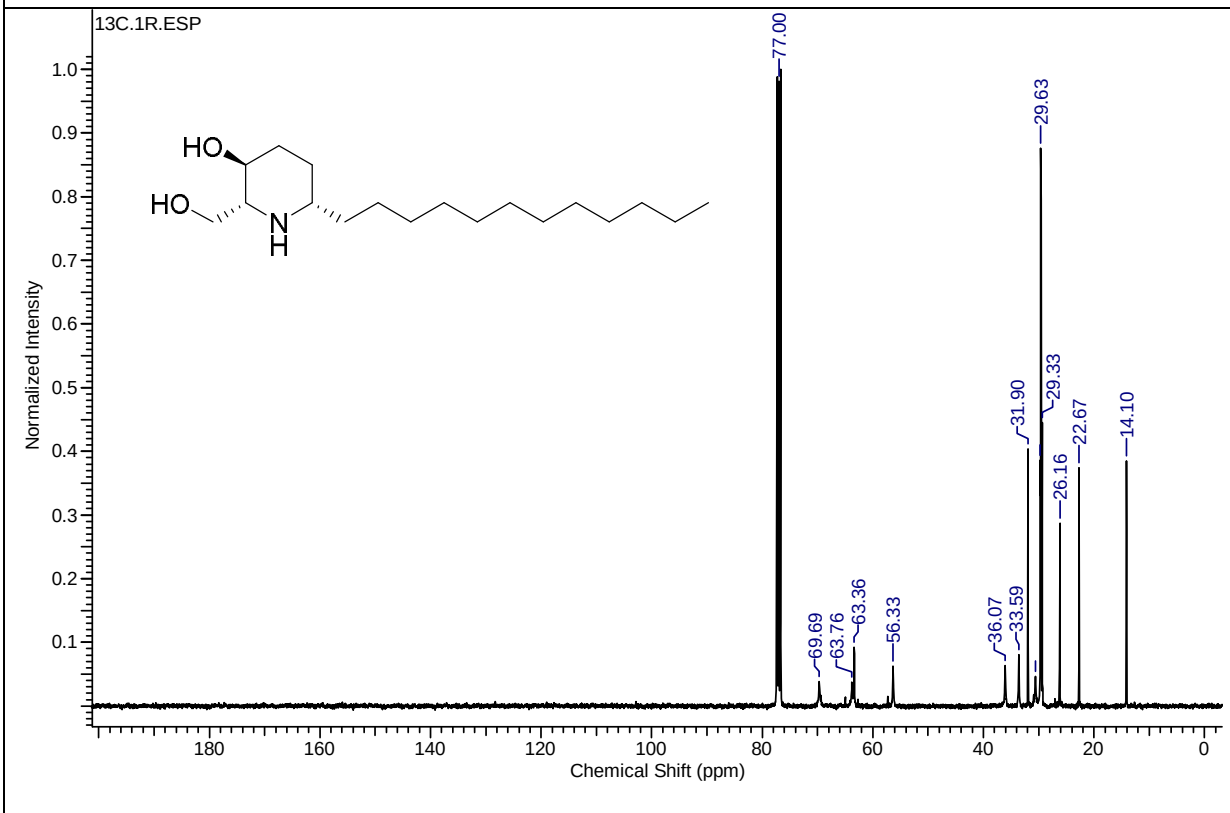
DEPT-NMR spectrum of compound **19** ($CDCl_3$, 400 MHz)



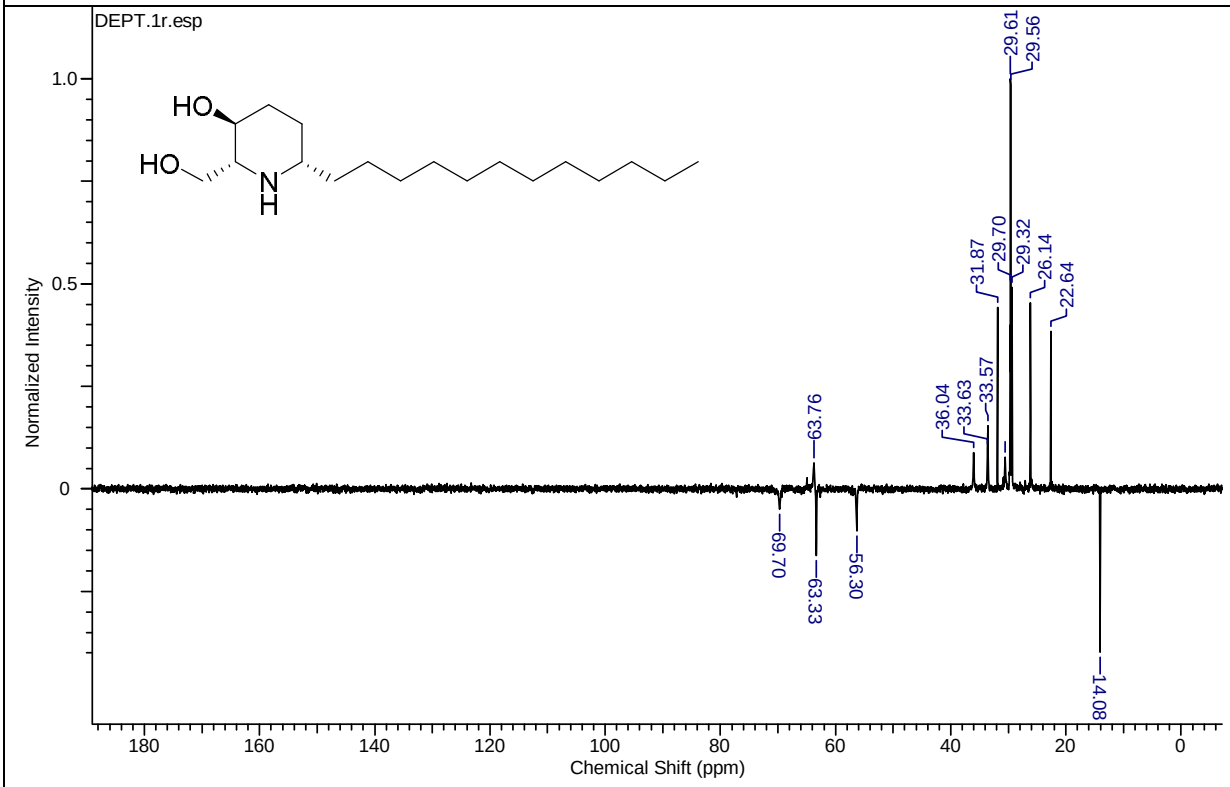
^{1}H-NMR spectrum of compound **1** ($CDCl_3$, 400 MHz)



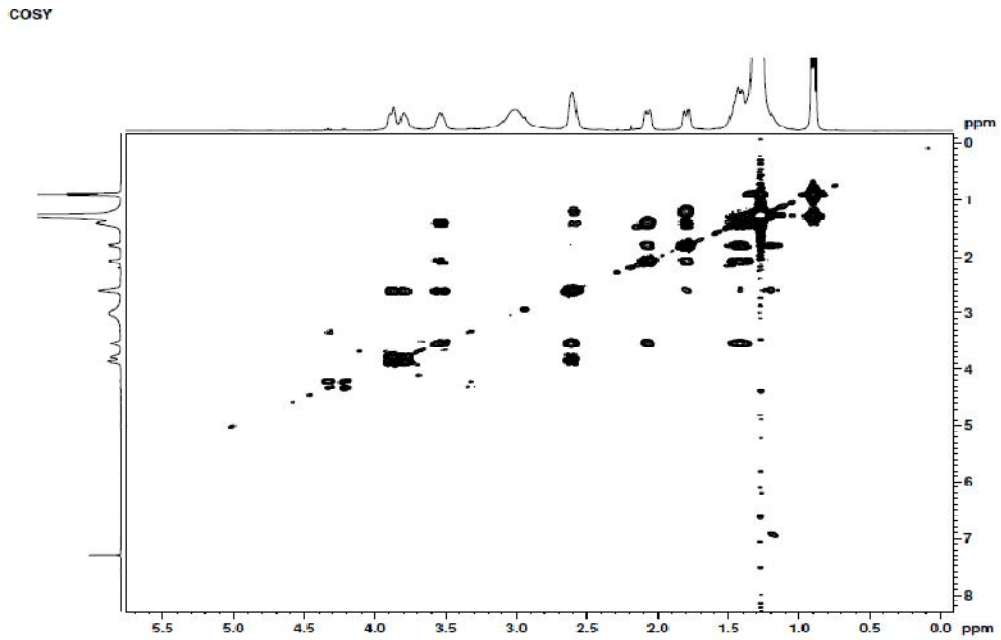
^{13}C-NMR spectrum of compound **1** ($CDCl_3$, 100 MHz)



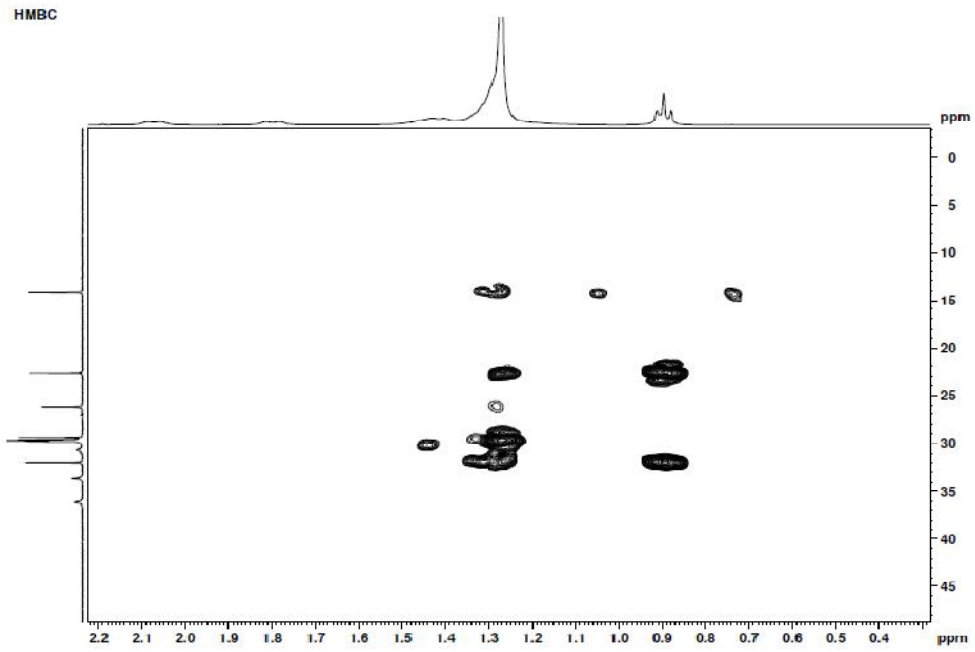
DEPT-NMR spectrum of compound **1** ($CDCl_3$, 100 MHz)



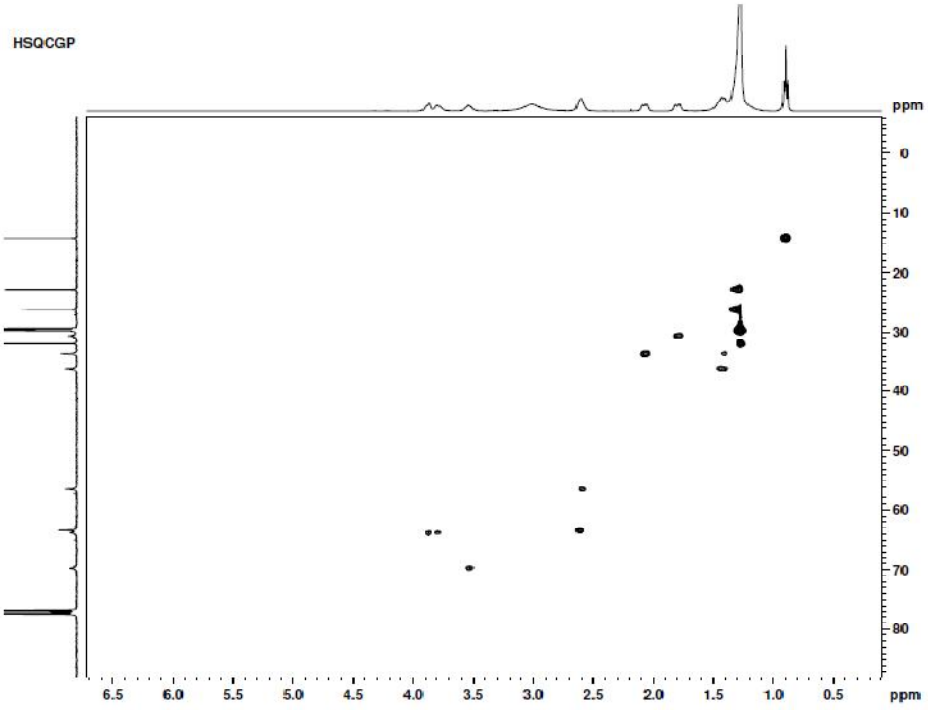
COSY of compound **1** ($CDCl_3$, 100 MHz)



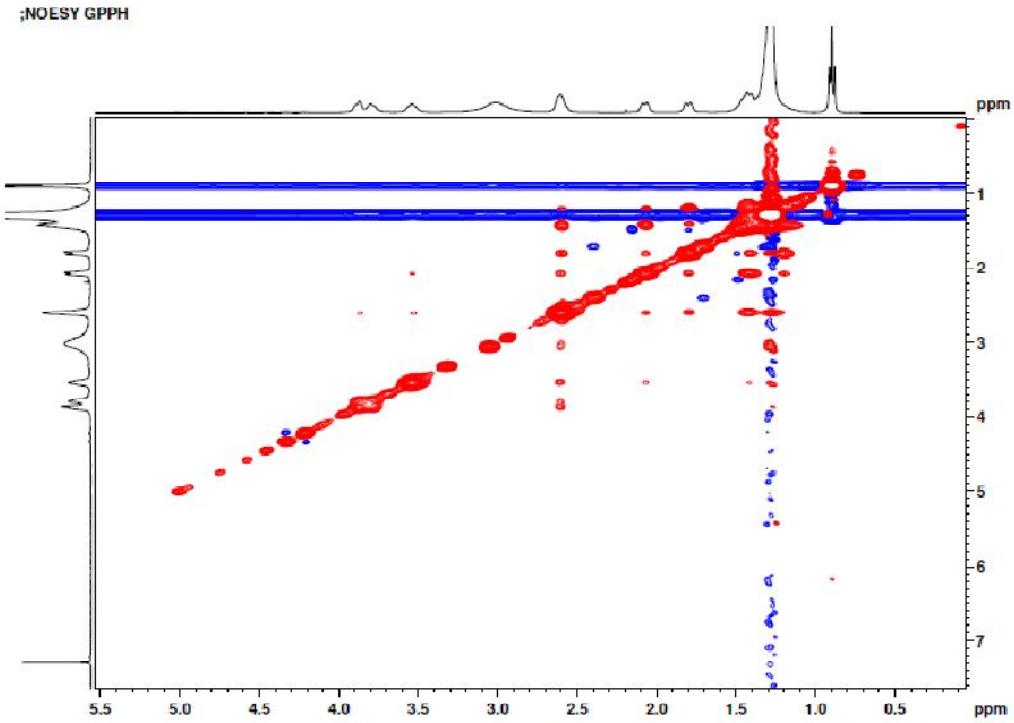
HMBC of compound **1** ($CDCl_3$, 100 MHz)



HSQC spectrum of compound **1** ($CDCl_3$, 100 MHz)



NOESY of compound **1** ($CDCl_3$, 100 MHz)



2.2.6. References:

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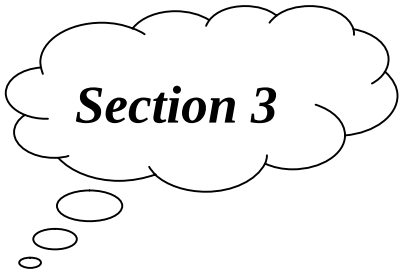
Chapter 2
Synthetic studies towards total synthesis of (+)-deoxoprosophylline and 1-deoxynojirimycin



Formal synthesis of 1-deoxynojirimycin from L-(+)-diethyl tartrate

2.3.1. Introduction:-

1-deoxynojirimycin (1-DNJ **1**) is α-glycosidase inhibitor.[1] It is found to show inhibition of glucose absorption in normal mices and accelarates glucose metabolism in diabetic mices.[2] Naturally and non-naturally occurring polyhydroxy piperidine compounds have shown variety of bioactivites such as antidiabetic,[3] antimalaria,[4] glycosidase inhibitors, anticancer agents[5] and antiviral agents.[6] Deoxynojirimycin **1** (Figure 1) has inhibitory activity towards mammalian α-glucosidase and β-galactosidase.[7] D-1-Deoxynojirimycin **1** was isolated from leaves of a plant scientifically named as *Morus alba* in 1976.[8]

In literature, there are various protocols used for synthesis of piperidine alkaloids (Figure 1).[9,10,11] These alkaloids form an important structural core for many alkaloids[12] and bicyclic alkaloids.[13] Literature survey also, revealed that L-isomer of 1-DNJ *ent*-**1** also possesses inhibitory activity against various glycosidases.[14] 1-DNJ **1** is a reduced analogue of nojirimycin **3**. The nojirimycin **3** was isolated in 1966 by Inouye *et al.* It was isolated from a filtrate of *Streptomyces* culture and this isolated azsugar **3** was found to be active inhibitor of α- and β-glucosidase, therefore, it is also considered as natural mimic of glucose.[15] This sugar closely resembles glucose sugar in stereochemical outcome except at anomeric carbon where oxygen in ring is replaced by nitrogen atom. This is responsible for the significant biological acivities of azasugars. Enzymes catalyzing the cleavage of α-glycosidic bonds are termed as α-glycosidases while those cleaving β-glycosidic bond are termed as β-glycosidases. L-1-Deoxyallonojirimycin (L-*allo*-1-DNJ) **4** has been reported to have more inhibitor activity against α-mannosidase than the D-*manno*-DNJ **5** (Figure 1).

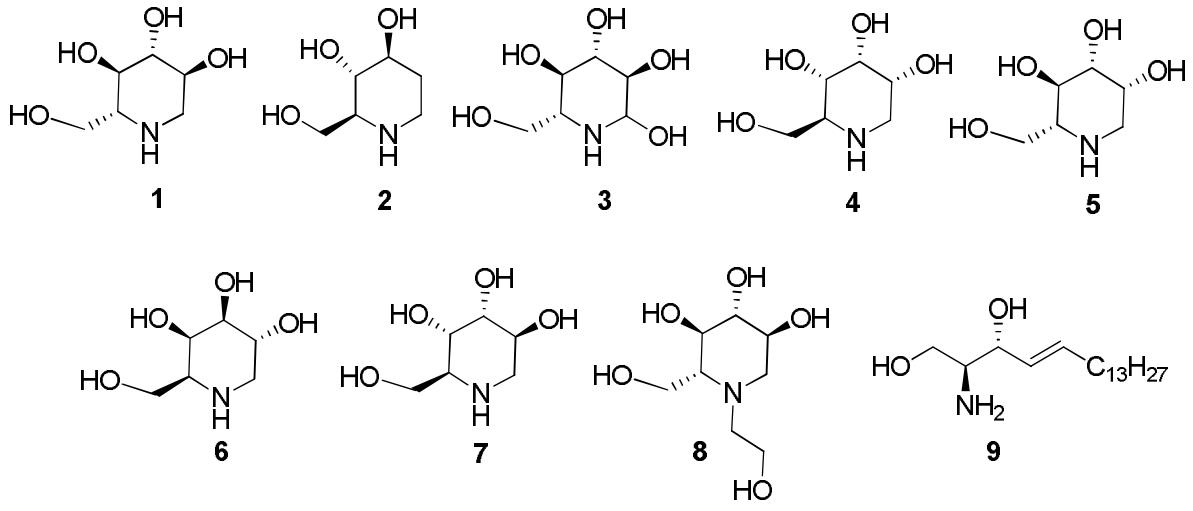


Figure 1. Piperidine alkaloids

The enzymes which carry out metabolic degradation of carbohydrates or sugars can be interferred by azasugars. These kinds of bioactivities shown by azasugars are because of their

interference with the function of enzymes metabolizing carbohydrate and carbohydrate recognizing receptors.[16] These enzymes, which are responsible for the biosynthesis and maintenance of the glycolipid and glycoprotein units, are called as glycosyltransferases and glycosidases.[17] The inhibition shown by them can significantly modulate the function or response of the cell and therefore, they make excellent targets for medicinal research.[18] This has shown good outcome, particularly in the treatment of cancer, viral, diabetes mellitus and bacterial infections and neurological diseases arised due to malfunctioning of sphingolipid storage in the body.

Glycosidase mechanism:

Glycosidase and glycosyl transferases are found everywhere in the biological systems, which catalyzes metabolic glycosyl group-transfer reactions, which are responsible to assemble, break and shaping bioactive glycoprotein and glycolipid conjugates. Overall, these enzymes catalyze cleavage of the glycosidic bond linking anomeric carbon of the sugar with an oligo- or polysaccharide or a nucleoside diphosphate group.

Glycosidases are classified based on the stereochemistry of the anomeric glycosidic bond that they cleave during metabolism. The main differences between α and β-glycosidases are positioning of the catalytic nucleophile and the catalytic proton donor. Typical glycosidase reaction mechanism is depicted in **Figure 2.**[19]

***α*-Glycosidases mechanism:**

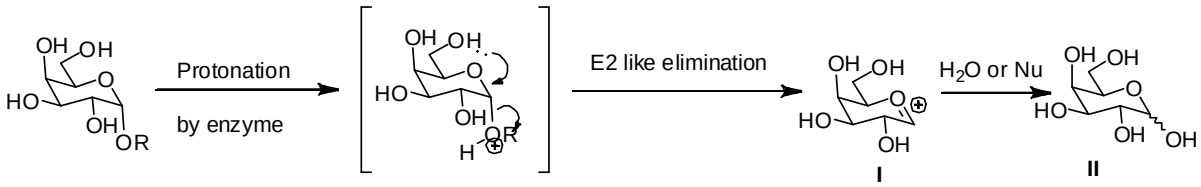


Figure 2. E2 like elimination mechanism by α-Glycosidases.

α-Glycosidases are believed to work through an E2 like elimination mechanism during which enzyme ctalyzed protonation of carbohydrate takes place. A positively charged leaving group (OR) and the lone pair of electrons present on the ring oxygen are positioned antiperiplanar, synergistically facilitating the glycosidic bond cleavage.

***β*-glycosidase Mechanism:**

The β-glycosidase can show two types of mechanisms. One is E1 type of elimination and other E2 type elimination. If the enzyme catalyzed glycosidase activity takes place *via* an E2 type mechanism, similar to that of the α-glycosidases, the protonated intermediate has to go

through a highly strained boat confirmation **V** and this is not a favorable situation for further reaction. Therefore, in the *β*-glycosidase reaction, the positively charged moiety (aglycon) leaves *via* an E1 like mechanism, this involves the glycosyl cation **III**, further stabilized by the lone pair of electrons present on the ring oxygen to give **II**. Although the final reaction intermediate in both the reaction mechanisms is the same flattened, half chair *oxocarbenium ion* **II**, the first intermediate in the case of *β*-glycosidase reaction differs with respect to the position of charge formation.

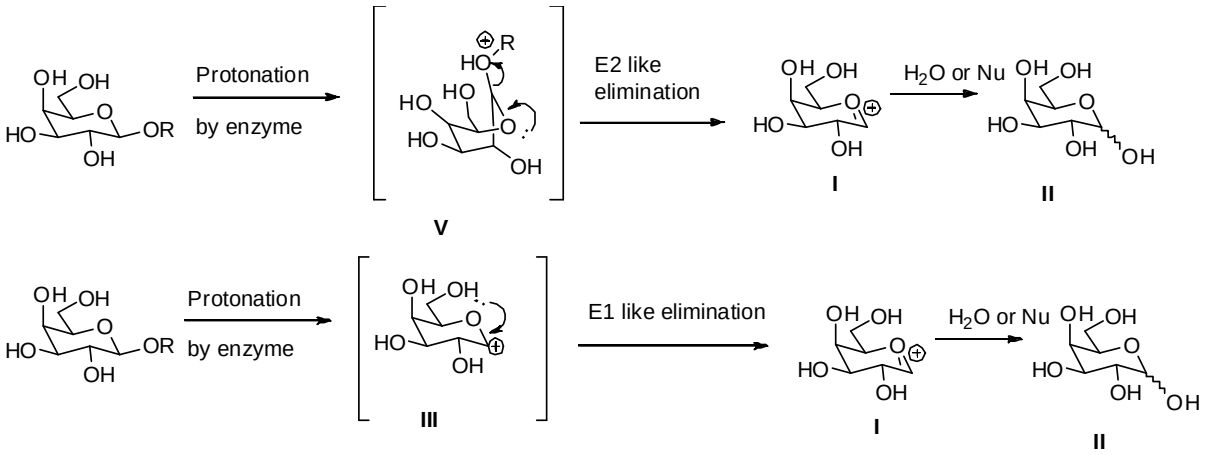


Figure 2. E1 like elimination mechanism as by *β*-Glycosidases.

Glycosidase inhibitors:

Glycosidase enzymes are also classified on the basis of the stereochemical outcome of the newly formed anomeric bond. The enzymatic cleavage of the glycosidic bond liberates a sugar hemiacetal with either the retention or the inversion of hydroxyl group stereochemistry. Based on these results, glycosidases are termed as retaining or inverting glycosidases. Any chemical moiety that is capable of mimicking either the charge or shape or both of the substrate or that of any of the transition states, can act as a reversible inhibitor of that particular glycosidase. These moieties are called as *glycosidase inhibitors*.

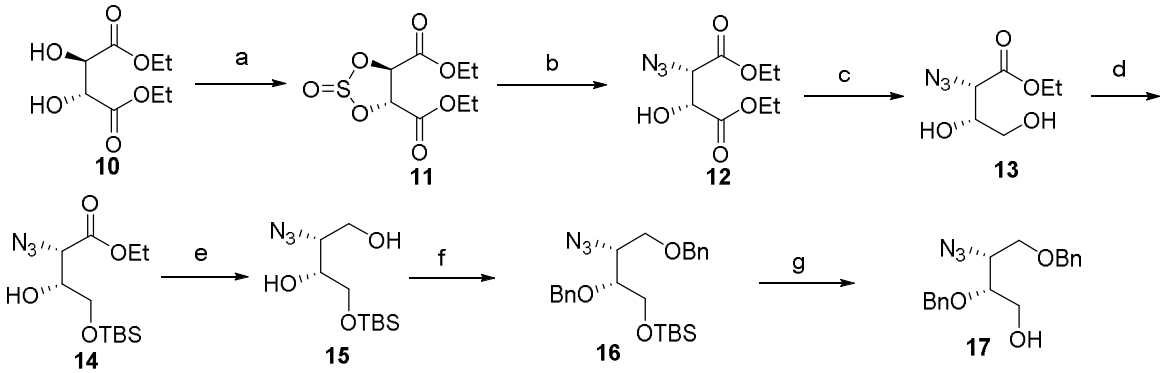
The azasugars show various glycomimetics acivities which comes from their conformational resemblance to natural sugars. 1-Deoxynojirimycin (1-DNJ **1**) acts as protonated intermediate **I** during the *α*-glycosidase catalyzed reaction. During glycosidic bond cleavage, the protonation of the ring nitrogen in the iminosugars at physiological pH mimics the developing charge of an intermediate oxocarbenium ion **III** and not a carbocation **II.** Thus, the presence of azasugar molecule inhibits the process of glycosyl bond cleavage and this special capability of azasugars makes them potential therapeutic moeties for the

treatment of various human diseases. A search for selective and effective inhibitors of oligosaccharide processing enzymes has promoted intense research over the last 20 years in the synthesis and isolation of stereochemically well-defined polyhydroxylated piperidine and pyrrolidine alkaloids and this has led to a number of review articles in the literature.[20] Some of these polyhydroxylated piperidine and pyrrolidine alkaloids are endowed with interesting therapeutic potential due to their action as glycosidase inhibitors. These studies have resulted in the development of a new era of structure-activity relationship at the interface of glycobiology and synthetic organic chemistry.

This group has reported asymmetric syntheses of piperidine alkaloids and polyhydroxy piperidine alkaloids *viz.* L-Fagomine **2**, its isomers, L-*allo*-1-DNJ **4**,[21] L-*galacto*-1-deoxynojirimycin (L-*galacto*-1-DNJ) **6**[22] and L-*altro*-1-deoxynojirimycin (L-*altro*-1-DNJ **7**).[23]

2.3.2. Present work

The synthesis of 1-DNJ **1** commenced with commercially available tartrate ester **10**, which on treatment with thionyl chloride in CCl_4 under reflux condition for 4 h afforded sulphite **11**. The crude sulfite **11** thus obtained was subjected to nucleophilic opening. Accordingly, sulphite opening was carried out using NaN_3 in DMF at room temperature to obtain 74% yield of the corresponding azido diester **12** over two steps. Azido diester **12** was then subjected to selective ester reduction using α-hydroxyl group of the ester as a handle to



Scheme 2. a) $SOCl_2$, DMF (cat.), CCl_4, reflux, 4 h; b) NaN_3, DMF, rt, 24 h, 74% over two steps; c) BH_3:DMS, $NaBH_4$ (cat.), THF, rt, 8 h, 60%; d) TBSCl, Et_3N, DCM, 2 h, 85%; e) $NaBH_4$, LiCl, THF:Water (1:1), 12 h, 83%; f) NaH, BnBr, THF, rt, 12 h, 94%; g) PTSA, MeOH, 2 h, 91%.

reduce it to alcohol **13**. The reduction was carried out using borane-dimethylsulfide complex (1.05 equivalent) and catalytic sodium borohydride in THF to obtain 1,2-diol **13** in 60% yield.[24] The 1,2-diol **13** was treated with TBSCl in DCM as the solvent in the presence of TEA as the base to protect primary hydroxyl group selectively in the presence of secondary hydroxyl group. MonoTBS ether **14** was obtained in 85% yield. Once this monoTBS compound **14** was in hand, the ester group was reduced with LiCl/LiBr and $NaBH_4$ in THF, water (1:1) system to obtain 1,3-diol compound **15** in 83% yield. The 1,3-diol **15** was dibenzylated using benzyl bromide and NaH (60% suspension in oil) to afford corresponding dibenzyl protected compound **16** in 94% yield. The TBS ether was deprotected using *p*-TSA in methanol to obtain free primary alcohol **17** in 91% yield. This primary hydroxyl group was oxidised to aldehyde.

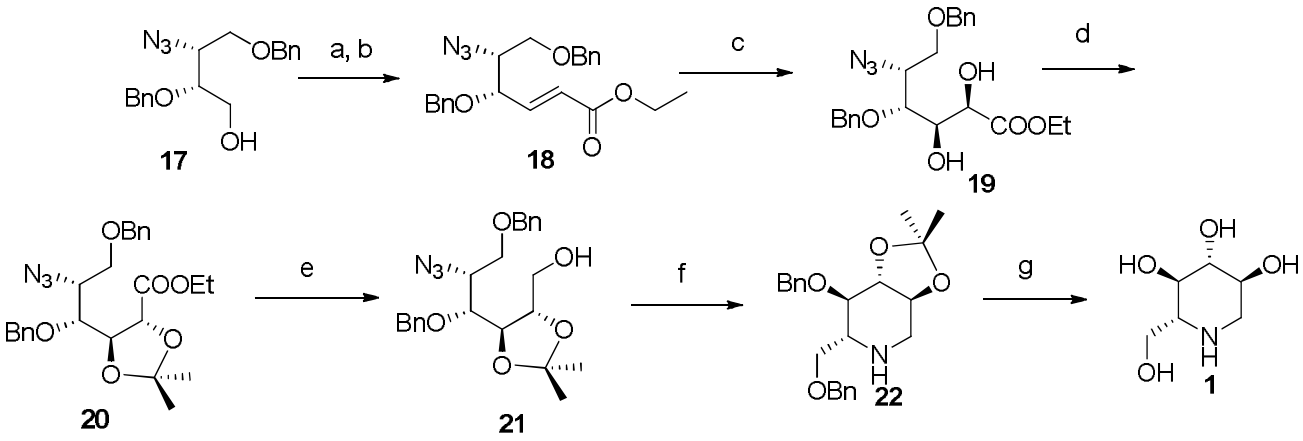
This aldehyde **17** was subjected for two carbon homologation under Wittig reaction conditions. The *trans* olefin **18** compound was obtained as the major product. The IR spectrum showed a new band at 1730 cm^{-1} indicating presence of ester functionality. ^{1}H NMR spectrum of **18** showed disappearance of peak corresponding to CH_2OH and appearance of typical peaks at δ 1.33 (t, 3H) and δ 4.25 (q, 2H) corresponding to ethoxy part of ester confirmed the presence of ester functionality. The peaks at δ 6.11 (d, J = 15.9 Hz, 1H) and δ 6.89 (dd, J = 15.89, 6.85 Hz, 1H) corresponding to *α,β*-unsaturated protons were observed in ^{1}HNMR, their respective peaks in ^{13}CNMR were observed at δ 124.9 aand δ 143.5 respectvely. The peak corresponding to carbonyl carbon was observed at δ 165.5. Also, the *α,β*-unsaturated CH peaks were further confirmed by DEPT NMR.

The compound **18** was subjected for dihydroxylation. The dihydroxylation was carried out using catalytic OsO_4 and NMO as the co-oxidant. Exclusively a single diastereomer of dihydroxylated compound **19** was isolated.[25] The IR spectrum showed a broad at IR 3350 cm^{-1} indicating presence of OH functionality. ^{1}H NMR spectrum of **19** showed disappearance of peak corresponding to *α,β*-unsaturated protons and respective carbons peaks in ^{13}CNMR and The new peaks were observed as the multiplets in aliphatic region. Their corresponding carbon peaks were observed at δ 71.6 and 70.3 respectively. This was confirmed by DEPT NMR, where these new peaks were observed.

This dihydroxy compound **19** was the treated with 2,2-dimethoxy propane in the presence of catalytic *p*-TSA to afford acetonide protected compound **20**. The IR spectrum showed absence of broad band at IR 3350 cm^{-1} indicating that there is no free OH group in the product. This was further confirmed by ^{1}HNMR spectrum. In ^{1}HNMR spectrum, new peaks

at δ 1.45 (s, 3 H) and δ 1.48 (s, 3 H), corresponding to two CH_3 groups of acetonide were observed. In ^{13}CNMR peaks corresponding to these methyl carbons were observed at δ 25.3 and 26.7. The peak of acetonide quaternary carbon was observed at δ 111.1. The remaining data was in good agreement with the assigned structure.

The ester functionality in the acetonide compound **20** was then reduced with LiCl/$NaBH_4$ to obtain alcohol **21**. The IR spectrum showed a new band at IR 3423 cm^{-1} indicating presence of OH functionality. ^{1}H NMR spectrum of **21** showed disappearance of typical triplet and quartet peaks corresponding to ethoxy group (OCH_2CH_3) and in ^{13}NMR the new peak for CH_2OH carbon was observed at δ 63.2 which was confirmed by DEPT NMR. The data matched with the assigned structure of compound **21**.



Scheme 3: *Reagents and conditions:* a) DMSO, $(COCl)_2$, TEA, DCM, -78 ^oC, 1 h; b) Ph_3PCHCO_2Et, toluene, reflux, 3 h, 76%; c) OsO_4, NMO, MeCN:H_2O (9:1), 4 h, 88%; d) 2,2-DMP, cat. *p*-TSA, DCM, 18 h, 93%; e) $NaBH_4$, LiCl, THF:water (1:1) 12 h, 97%; f) i) MsCl, TEA, DCM, 0 ^oC 30 min, ii) PPh_3, THF:Water (1:1), reflux, 4 h, 70%; g) *Ref*. 26.

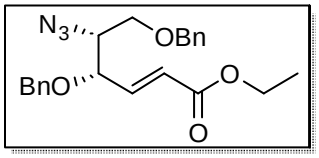
This alcohol **21** was mesylated with mesyl chloride and subsequently it was subjected for Staudinger reaction conditions to reduce azide to amine and its *in situ* cyclization was observed under elevated temperature. The cyclized product **22** was characterized. The data of **22** was in well agreement with the reported data.[26] The IR spectrum showed band at IR 3444 cm^{-1} indicating presence of NH functionality. ^{1}H NMR spectrum of **22** showed peak corresponding to NCH proton as triplet at δ 2.79 (t, *J* = 11.74 Hz 1H) and peaks corresponding to diastereotopic CH_2 adjacent to nitrogen atom (CH_2N) were observed at δ 3.35 – 3.64 as multiplet. The remaining data was in good agreement with the structure assigned.

2.3.3. Conclusion:

The formal synthesis of 1-DNJ 1 was achieved from diethyl tartrate ester in 14 chemical steps. The synthesis involved selective ester reduction, Wittig olefination, selective dihydroxylation and cyclization as the key steps.

2.3.4. Experimental section:

Ethyl (4*S*,5*R*,*E*)-5-azido-4,6-bis(benzyloxy)hex-2-enoate (18):



To a stirred solution of oxalyl chloride (4.19 mL, 48.86 mmol) in DCM at -78 ^{o}C was added DMSO (3.47 mL, 48.85 mmol) drop wise. After 30 min, a solution of compound **17** (4 g, 12.22 mmol) in DCM was added dropwise to the above mixture at the same temperature. After 1 h, Et_3N (10.23 mL, 73.31 mmol) was added drop wise at-78 ^{o}C. After the completion of the reaction (monitored by TLC), the reaction was quenched with water and then extracted with dichloromethane (3x80 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to afford the crude aldehyde**,** which was used for next reaction without purification.

To a well stirred solution of the above crude aldehyde (4.5 g, 13.83 mmol) in toluene (60 mL) Wittig ylide (5.78 g, 16.60 mmol) was added. The reaction mixture was refluxed for 3 h. After completion of reaction (monitored by TLC), the solvent was removed under reduced pressure. The product was directly subjected for purification. The crude residue thus obtained was purified by column chromatography on 10% silver nitrate in silica gel using ethyl acetate/ pet. ether (1:19) to furnish 4.2 g (*E*)-*α,β*-unsaturated compound **18** as a colorless oil.

Rf = 0.6 (EtOAc/pet. ether, 1:4)

Chemical Formula: $C_{22}H_{25}N_3O_4$

Molecular Weight: 395.4516

Yield: 75%

IR ($CHCl_3$) υ_{max}: 2927, 2253, 2103, 1730, 1633, cm^{-1}.

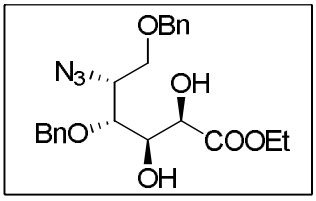
Optical rotation: $[\alpha]_D^{25}$: +24 (c = 1.05, chloroform).

^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 1.33 (t, *J* = 7.09 Hz, 3 H), 33.65 (d, *J* = 5.6 Hz, 2 H), 3.74 (q, *J* = 5.6 Hz, 1 H), 4.12 - 4.20 (m, 1 H), 4.25 (q, *J* = 7.09 Hz, 2 H), 4.42 (d, *J* = 11.74 Hz, 1 H), 4.54 (s, 2 H), 4.63 (d, *J* = 11.74 Hz, 1 H), 6.11 (d, *J* = 15.89 Hz, 1 H), 6.89 (dd, *J* = 15.89, 6.85 Hz, 1 H), 7.28 - 7.42 (m, 10 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 60.7, 63.7, 68.9, 71.6, 73.4, 77.5, 124.9, 127.7, 127.8, 127.9, 128.4, 137.2, 137.5, 143.5, 165.6.

HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{22}H_{25}N_3NaO_4$: 418.1743, found: 418.1737.

Ethyl (2*S*,3*S*,4*R*,5*R*)-5-azido-4,6-bis(benzyloxy)-2,3-dihydroxyhexanoate (19).



To a cooled (0 ^oC) solution of ester compound **18** (1.58 g, 4.83mmol) and NMO (848.06 mg, 7.24 mmol) in acetone:H_2O (20 mL, 9:1) was added 0.04 M toluene solution of OsO_4 (5 mol%). The solution was stirred until the reaction was completed at 0 ^oC. The completion of the reaction was monitored on TLC. After completion of the reaction, it was quenched by saturated aq. Na_2SO_3 (8 mL) and the organic solvent was removed *in vacuo.* The residue was diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue obtained was purified by coloumn chromatography on silica gel using ethyl acetate/pet. ether (1:4) as eluent to give pure compound **19** (1.68 g, 88%) as colorless oil; *Rf* = 0.3 (EtOAc/pet. ether, 3:7).

Chemical Formula: $C_{22}H_{27}N_3O_6$

Molecular Weight: 429.46

Yield: 88%

IR ($CHCl_3$) υ_{max}: 3350, 2930, 2247, 1731, 1603, 1020 cm^{-1}.

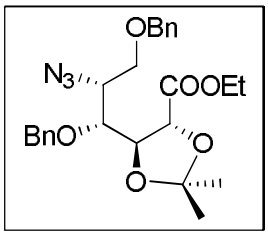
Optical rotation: $[\alpha]_D^{25}$: = -17.3 (c 0.5, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): δ 1.30 (t, *J* = 7.17 Hz, 3 H), 2.74 (dd, *J* = 7.93, 0.61 Hz, 1 H), 3.13 - 3.33 (m, 1 H), 3.64 - 3.92 (m, 3 H), 3.98 - 4.15 (m, 2 H), 4.18 - 4.36 (m, 2 H), 4.39 - 4.85 (m, 5 H), 7.29 - 7.42 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 14.2, 62.2, 62.6, 69.3, 70.3, 71.6, 73.5, 74.2, 78.9, 127.7, 127.9, 128.0, 128.1, 128.5, 137.5, 137.6, 173.5

HRMS: $C_{22}H_{27}O_6N_3Na$ = 452.1792

(4*R*,5*S*)-ethyl 5-((1*R*,2*R*)-2-azido-1,3-bis(benzyloxy)propyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (20): To a solution of ester **19** (1.15 g, 3.38 mmol) and PTSA (30 mg, 0.05 eq.) in 2,2-dimethoxypropane (1.76 mL, 13.51 mmol) and dry DCM (8 mL) was stirred at room temperature for 18 h. The progress of the reaction was monitored on TLC. After



completion of the reaction, it was quenched by adding 1 mL saturated aq. $NaHCO_3$ solution. The excess of 2,2-DMP and DCM was removed under reduced pressure. The residue was dissolved in water and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with brine (30 mL) and dried over anhydrous Na_2SO_4, filtered aand concentrated in *vacuo.* The crude product was purified by column chromatography using silica gel and EtOAc/pet. ether (1:9) as eluent to get compound **20** (1.48 g, 93%) as a colorless oil (*Rf* = 0.4 (EtOAc/pet. ether, 1:9).

Chemical Formula: $C_{25}H_{31}N_3O_6$

Molecular Weight: 469.53

Yield: 93%.

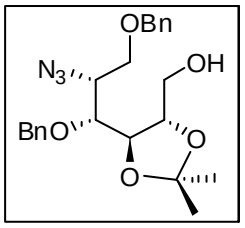
IR ($CHCl_3$) υ_{max}: 3021, 2107, 1731, 1476, 756 cm^{-1}.

Optical rotation: $[\alpha]_D^{25}$:= -36 (*c* 0.95, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.07 Hz, 3 H), 1.43 (s, 3 H), 1.48 (s, 3 H), 3.57 - 3.89 (m, 5 H), 4.23 (q, *J* = 7.07 Hz, 2 H), 4.47 - 4.70 (m, 4 H), 4.71 - 4.88 (m, 1 H), 7.14 - 7.46 (m, 10 H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 25.3, 26.7, 61.4, 61.5, 69.7, 73.3, 74.5, 75.3, 79.3, 111.1, 127.5, 128.4, 137.6, 171.3

((4*S*,5*S*)-5-((1*R*,2*R*)-2-azido-1,3-bis(benzyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (21)



To a cold magnetically stirred solution of compound **20** (1.05 g, 2.24 mmol) in THF: H_2O (1:1, 10 mL), LiCl (0.19 g, 4.47 mmol) $NaBH_4$ (0.17 g, 4.47 mmol) was added portion wise at 0 ^oC. The temperature of the reaction mixture was allowed to rise gradually up to room temperature. Then this reaction mixture was stirred for 12 h at room temperature. The progress of reaction mixture was monitored on TLC. After completion of the reaction, it was quenched by saturated aq. NH_4Cl solution at 0 ^oC and further stirred for 10 min. This solution was exctracted with ethyl acetate (3×50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

The residue was purified by a silica gel column chromatography using ethyl acetate/pet. ether (3:7) as eluent furnished the reduced compound **21** (930 mg, 97%) as a colorless liquid.

R_f(EA: PE/1:3): 0.3.

Chemical Formula: $C_{23}H_{29}N_3O_5$

Molecular Weight: 427.49

Yield: 97%.

IR ($CHCl_3$) υ_{max}: 3423, 2960, 2110, 1694, 1176, cm^{-1}.

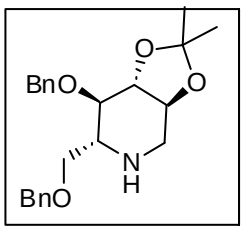
Optical rotation: $[\alpha]_D^{25}$: -24.5 (*c* = 0.5, chloroform).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.37 (s, 3 H), δ 1.40 (s, 3 H), 1.91 (br. s., 1 H), 3.61 - 3.83 (m, 5 H), 3.91 - 4.10 (m, 3 H), 4.49 - 4.65 (m, 3 H), 4.76 (d, *J* = 11.29 Hz, 1 H), 7.26 - 7.42 (m, 10 H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 27.0, 62.3, 63.2, 69.5, 73.4, 73.7, 76.1, 79.6, 80.1, 109.4, 127.6, 128.2, 128.6, 137.0, 137.7

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{23}H_{29}N_3O_5Na$**:** 450.2005, found: 450.1998.

(3a*S*,6*R*,7*R*,7a*R*)-7-(benzyloxy)-6-((benzyloxy)methyl)-2,2-dimethylhexahydro-[1,3]dioxolo[4,5-*c*]pyridine (22):



To a solution alcohol **21** (0.8 g, 1.87 mmol) in anhydous CH_2Cl_2 (5 mL) was added Et_3N (0.523 mL, 3.74 mmol) at 0 °C and methane sulphonyl chloride (0.183 mL, 2.25 mmol) sequentially in dropwise manner. Progress of the reaction was monitored by TLC. After completion, the reaction was quenched with water (2 mL) and the organic layer was washed with aq $NaHCO_3$ (2%, 5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude compound was used directly in the next reaction. To crude mesylate (0.85 g, 1.68 mmol) was dissolved in THF:H_2O (1:1) then triphenyl phosphine (2.02 mmol) was added. The reaction mixture was refluxed for 4 h. The progress of reaction was monitored on TLC. After completion of the reaction, reaction mixture was excrcted with ethyl acetate (3x25 mL). The combined organic layers were dried over anhydrous Na_2SO_3, filtered and conentrated under reduced pressure. The residue was purified by silica gel column chromatography to get 0.4 g of cyclised compound **22** as clear liquid.

Chemical Formula: $C_{23}H_{29}NO_4$

Molecular Weight: 383.4807

IR ($CHCl_3$) υ_{max}: 3444, 2935, 1673, 1612, 757 cm^{-1}.

Optical rotation: $[\alpha]_D^{25}$:+64.0 (*c* 0.5, $CHCl_3$)

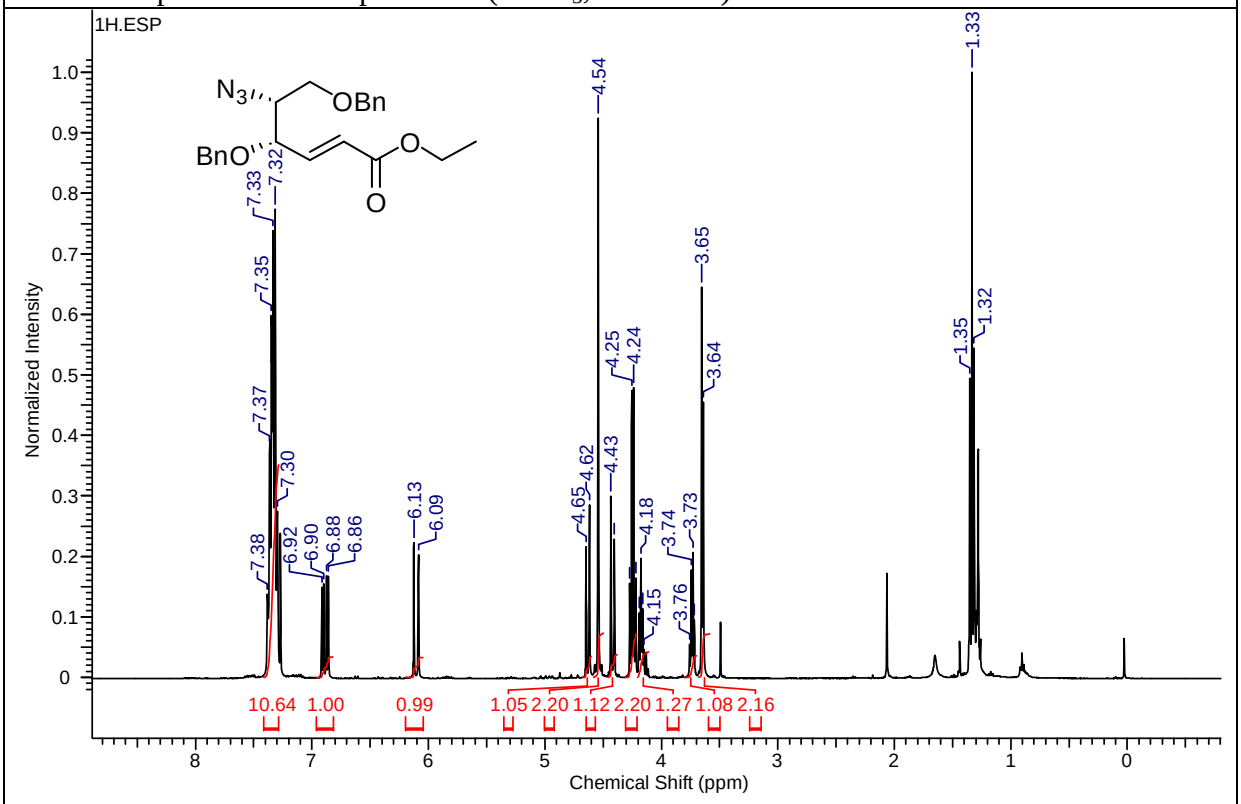
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 3 H), 1.49 (s, 3 H), 2.32 (br. s., 1 H), 2.79 (t, *J* = 11.74 Hz, 1 H), 3.27 (dd, *J* = 12.35, 4.52 Hz, 1 H), 3.35 - 3.64 (m, 4 H), 4.00 (td, *J* = 10.21, 4.52 Hz, 1 H), 4.22 (s, 1 H), 4.47 - 4.58 (m, 2 H), 4.64 (d, *J* = 11.74 Hz, 1 H), 4.90 (d, *J* = 11.74 Hz, 1 H), 7.10 - 7.53 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 26.7, 26.8, 45.3, 57.8, 69.2, 71.7, 73.0, 73.2, 75.3, 79.4, 84.8, 108.7, 127.5, 127.6, 127.7, 127.8, 127.9, 128.3, 128.4, 137.9, 138.6.

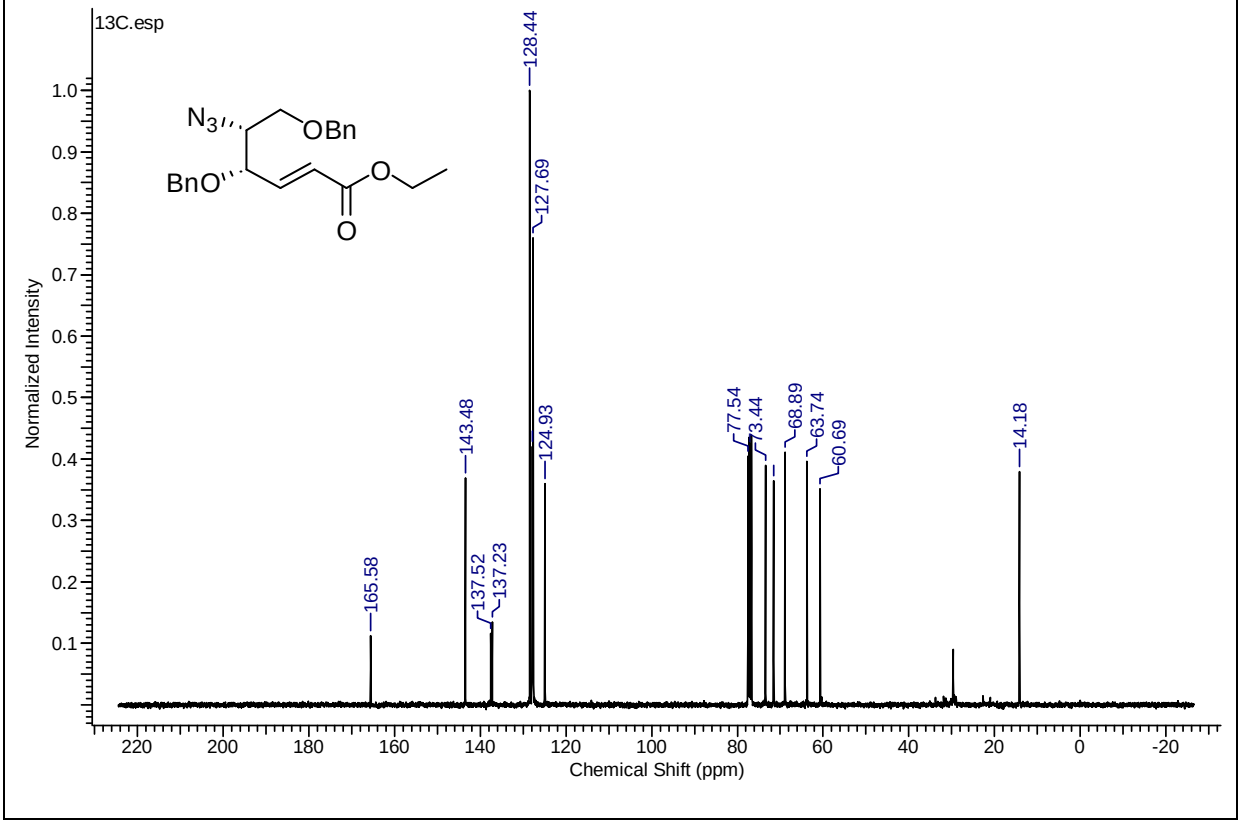
HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{30}NO_4$: 384.1742, found: 384.1745.

2.3.4. Spectra

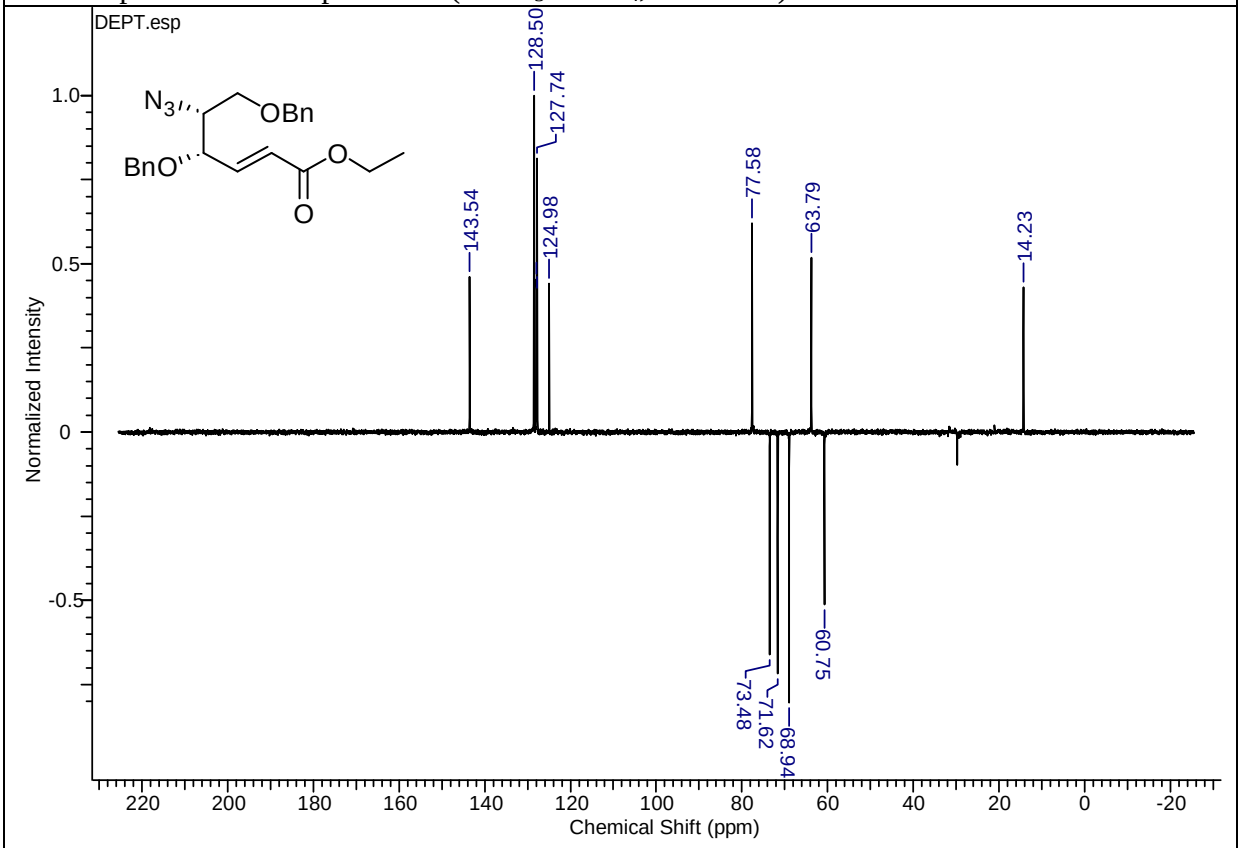
^{1}H-NMR spectrum of compound **18** ($CDCl_3$, 400 MHz)



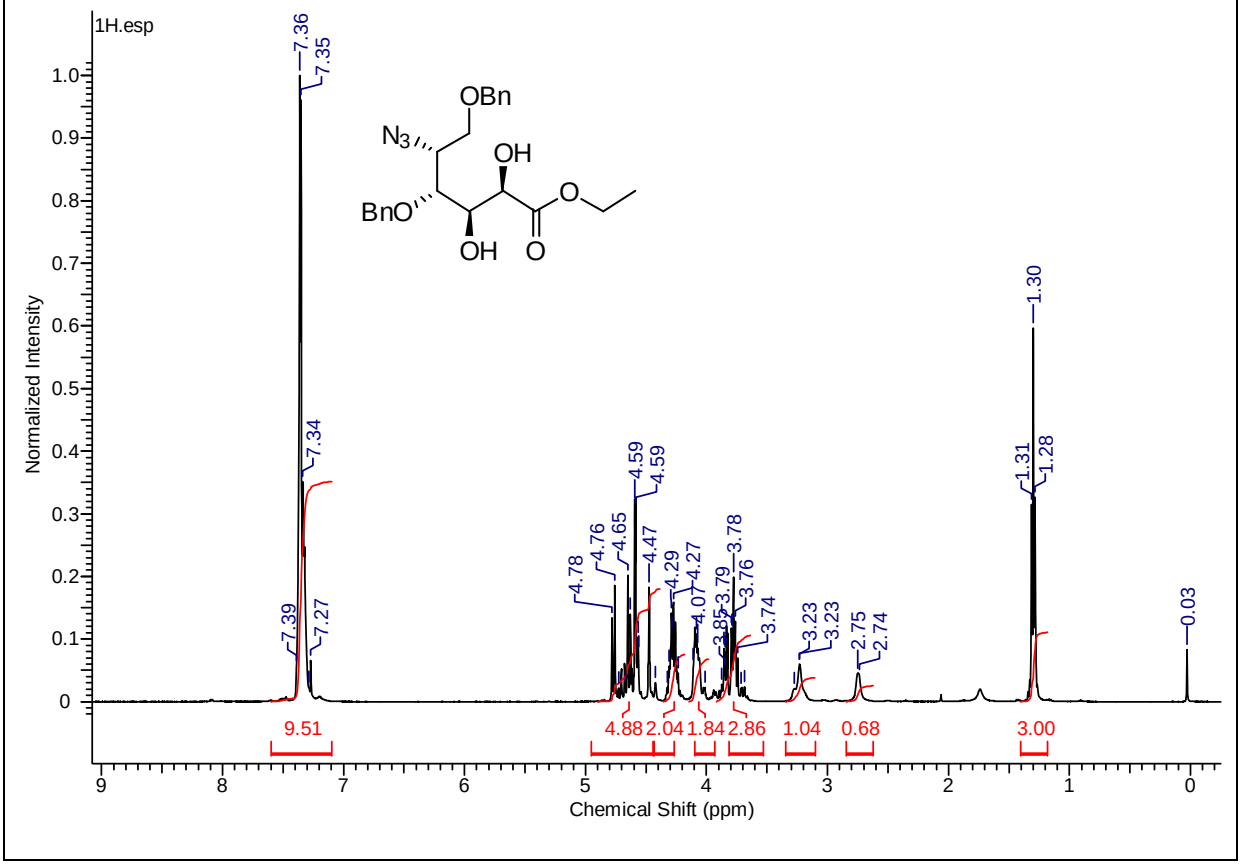
^{13}C-NMR spectrum of compound **18** ($CDCl_3$, 100 MHz)



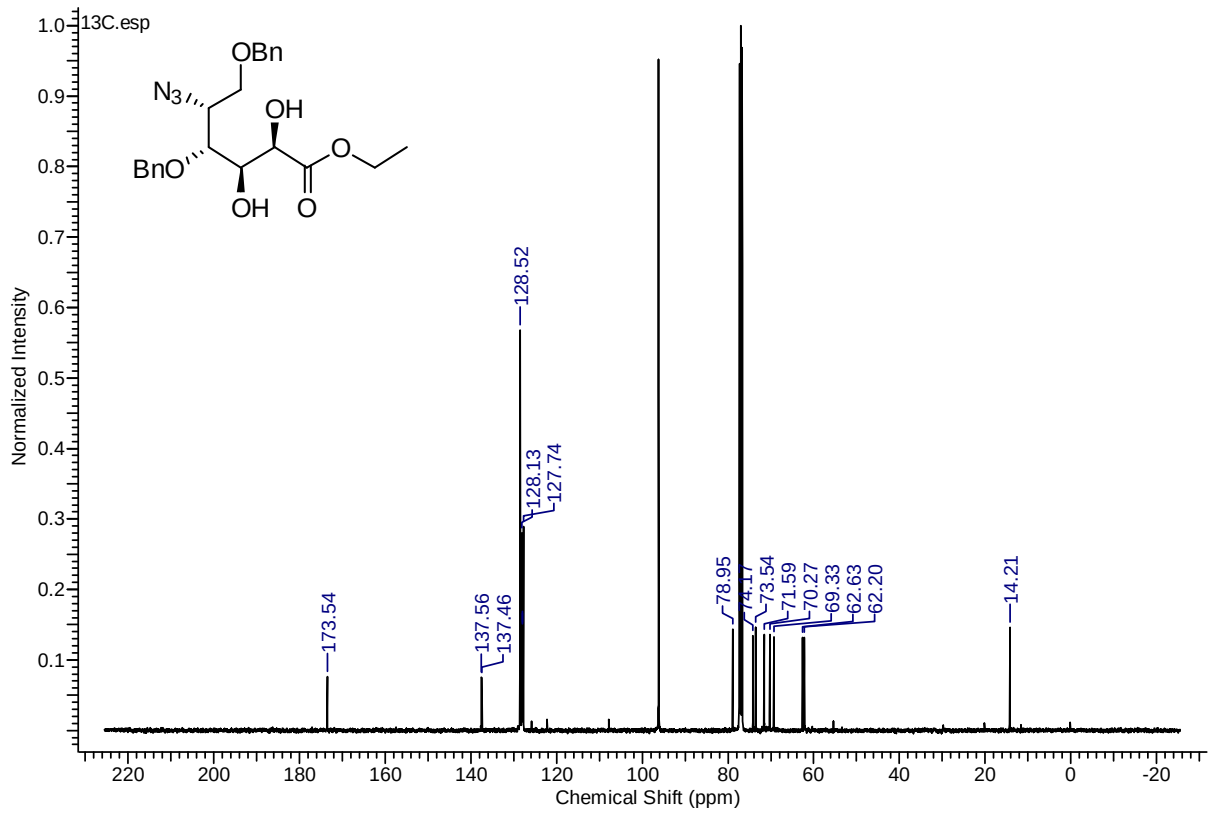
DEPT spectrum of compound **18** ($CDCl_3$ + CCl_4, 200 MHz)



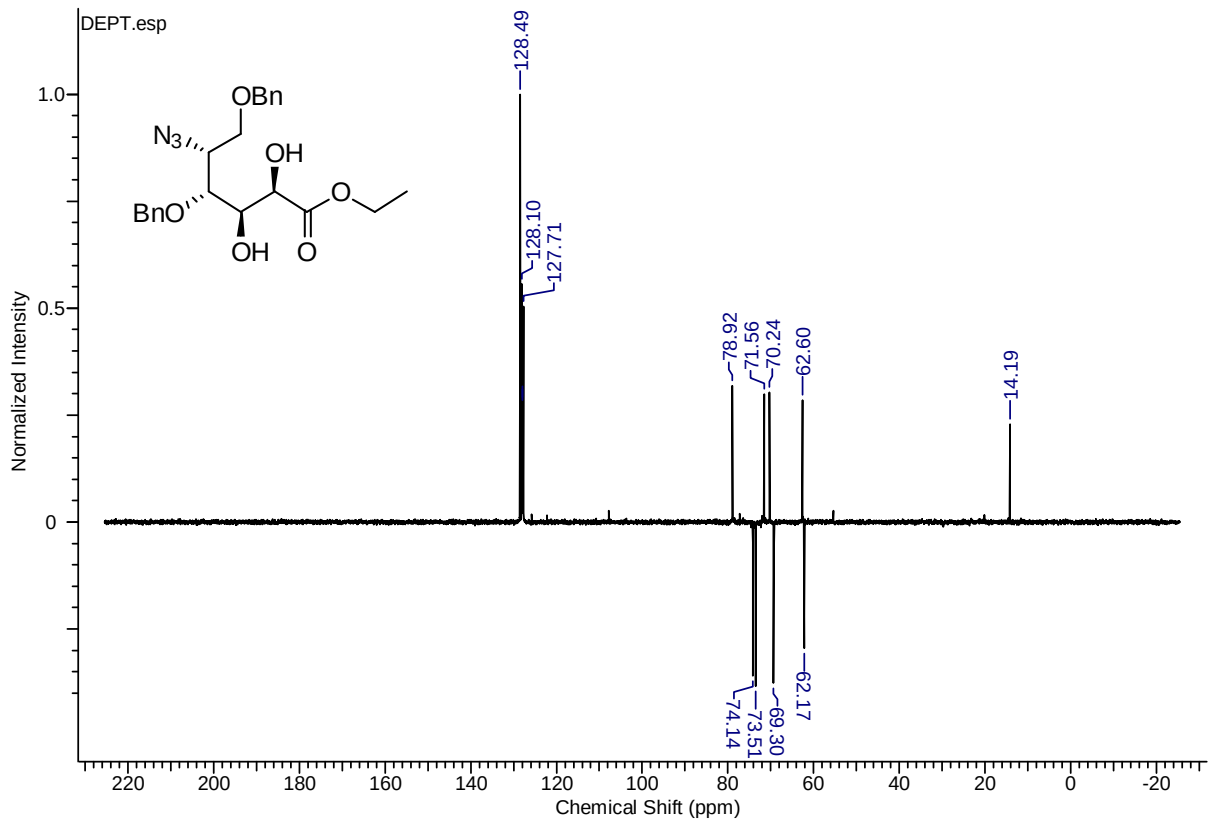
^{1}H-NMR spectrum of compound **19** ($CDCl_3$, 500 MHz)



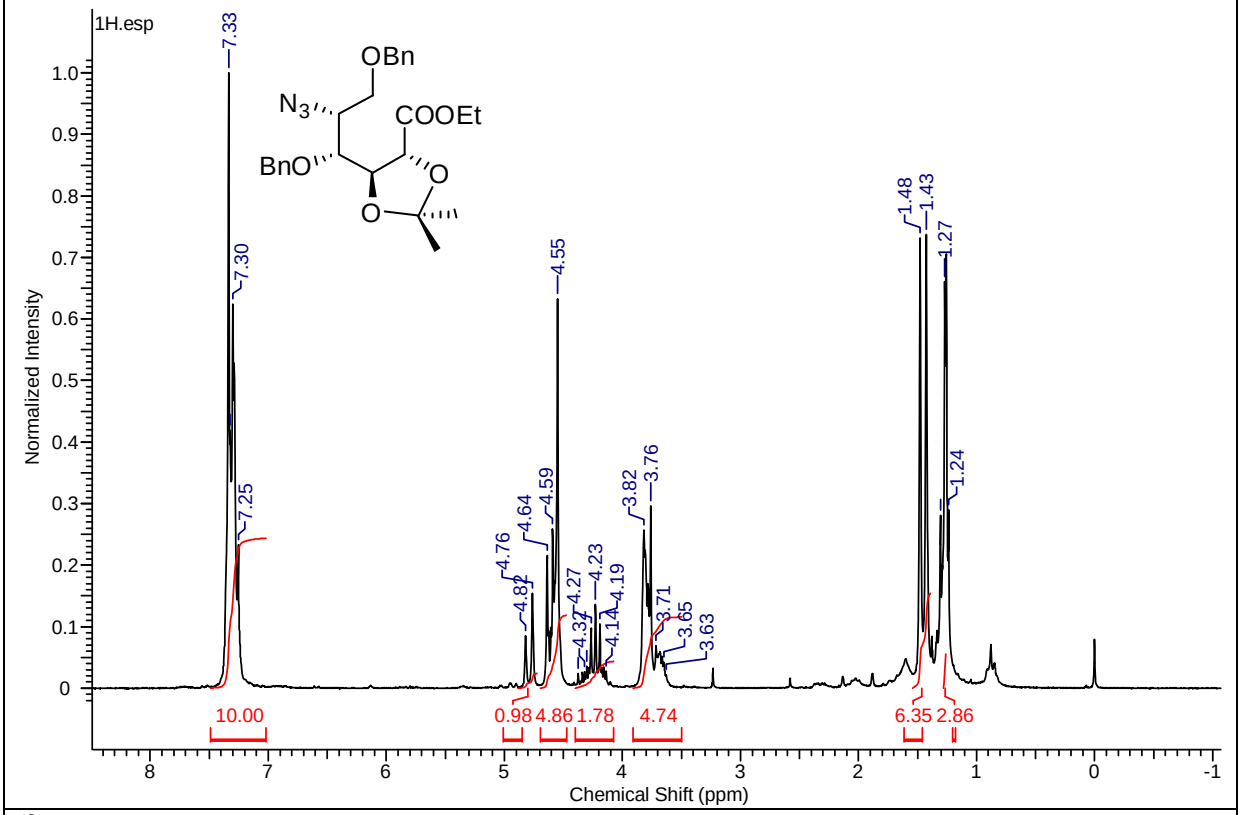
^{13}C-NMR spectrum of compound **19** ($CDCl_3$, 125 MHz)



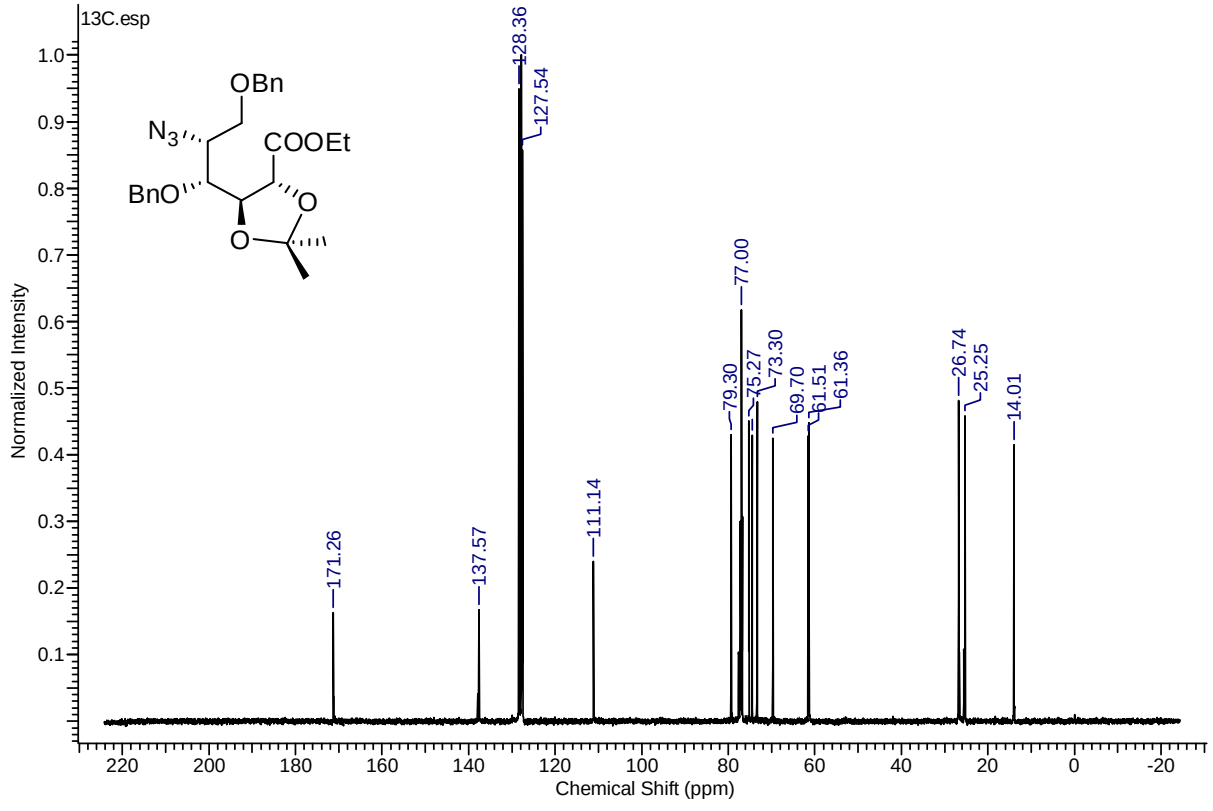
DEPT spectrum of compound **19** ($CDCl_3$, 125 MHz)



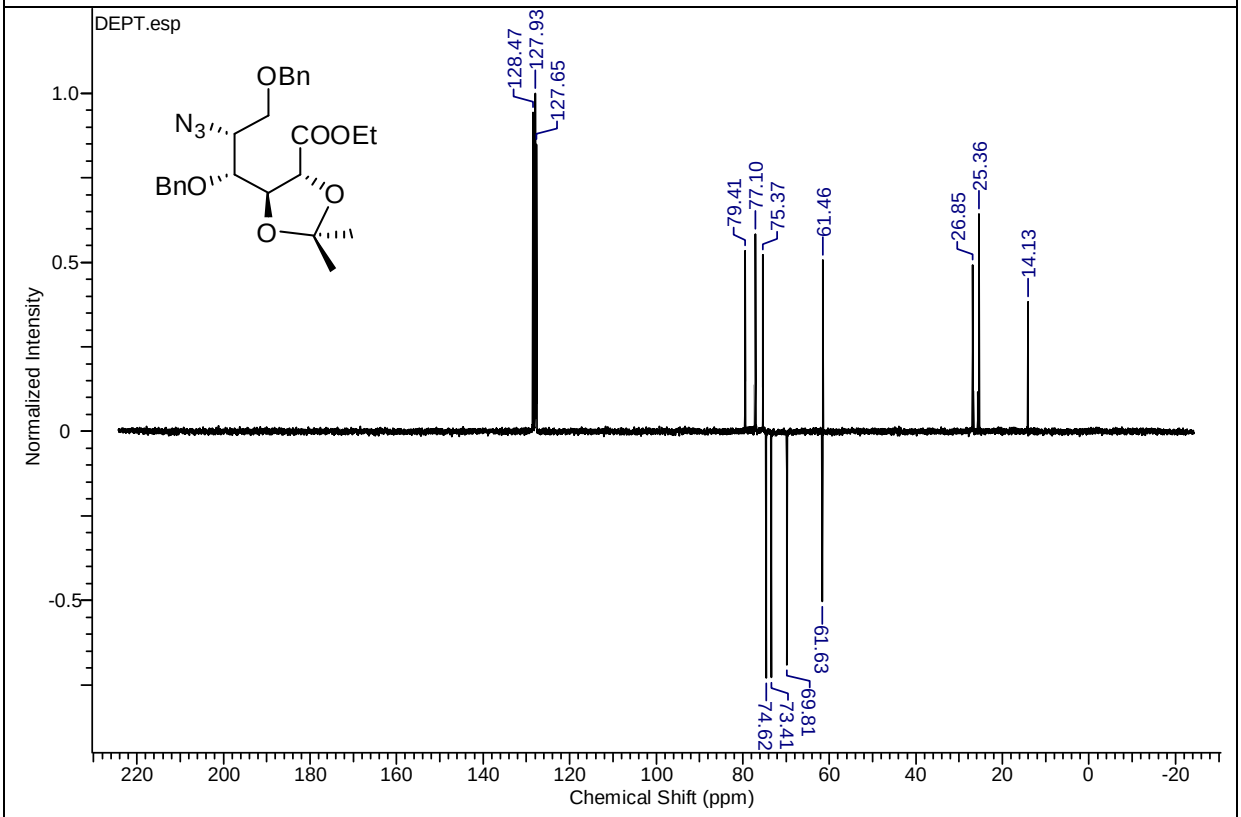
^{1}H-NMR spectrum of compound **20** ($CDCl_3$, 500 MHz)



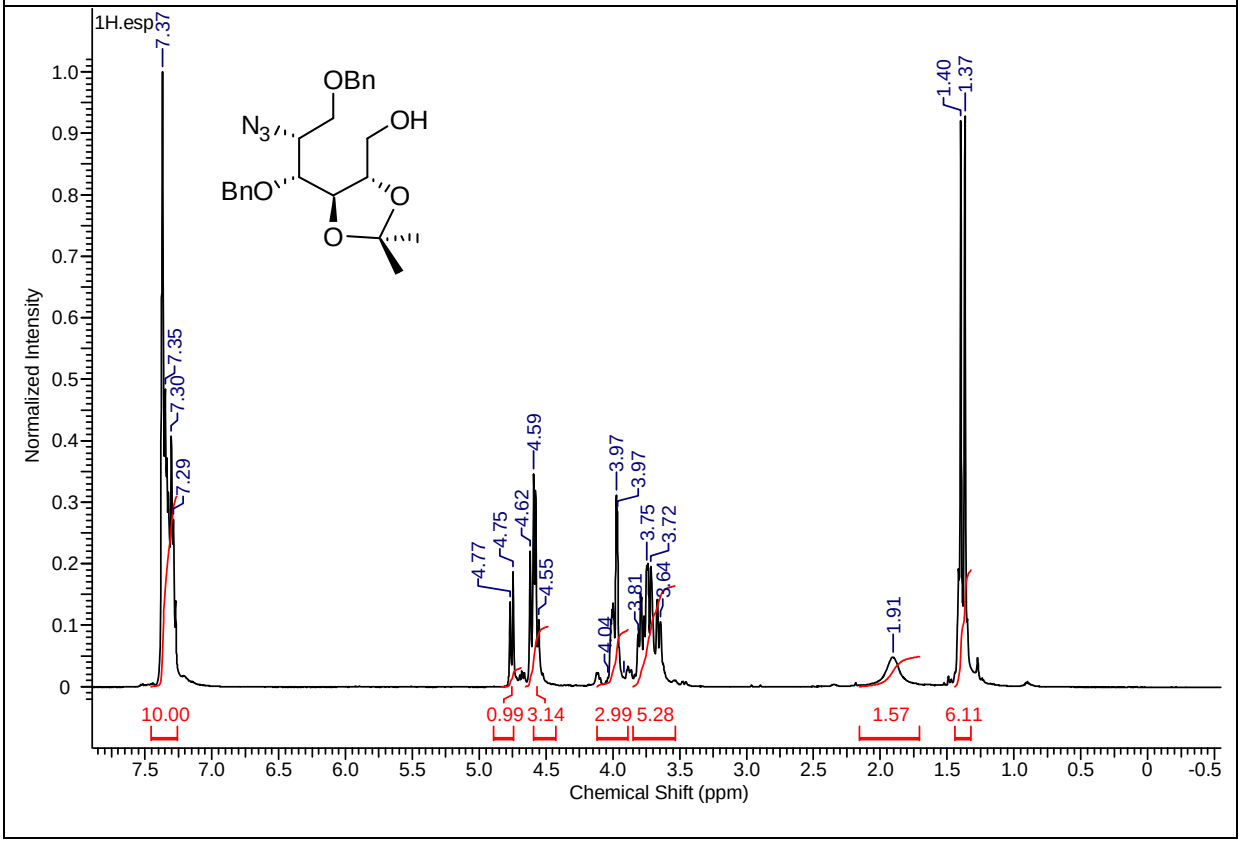
^{13}C-NMR spectrum of compound **19** ($CDCl_3$, 125 MHz)



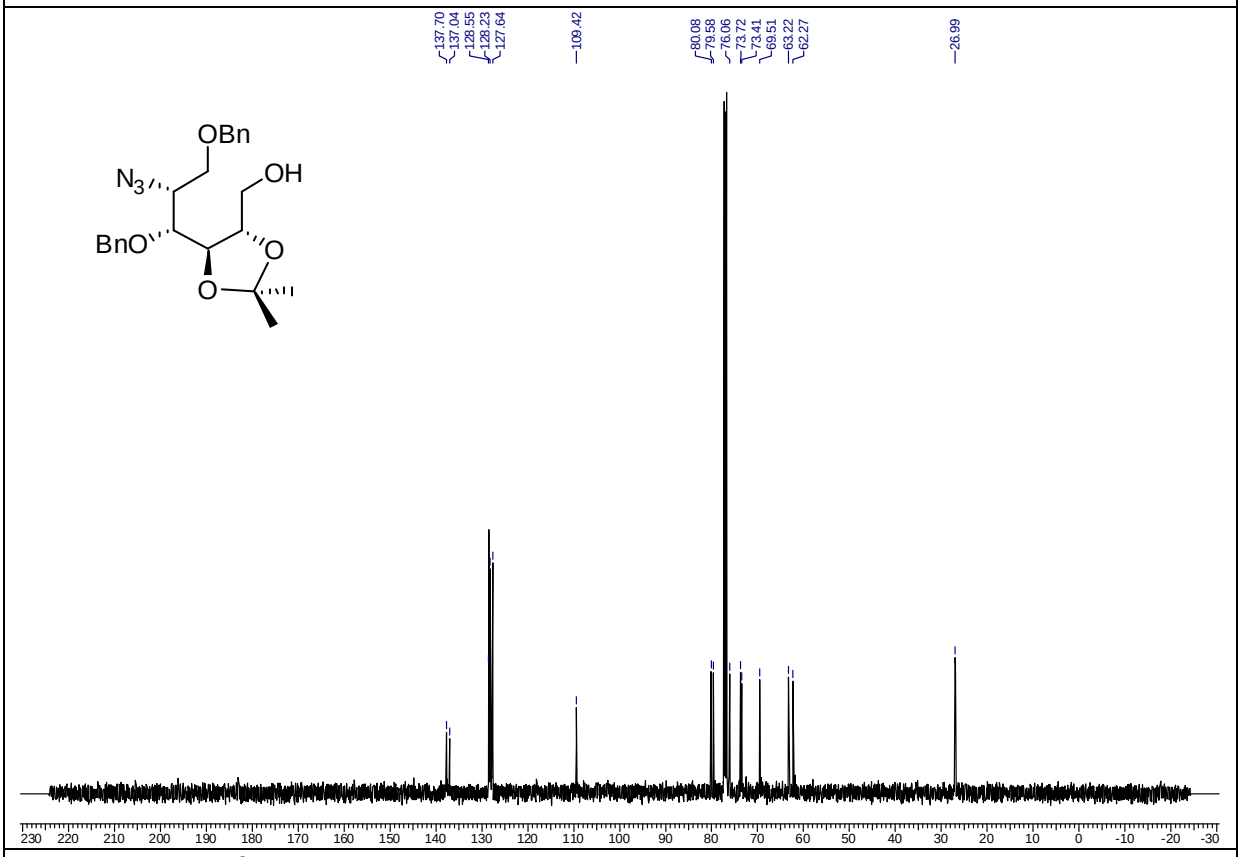
^{13}C-NMR spectrum of compound **20** ($CDCl_3$, 125 MHz)



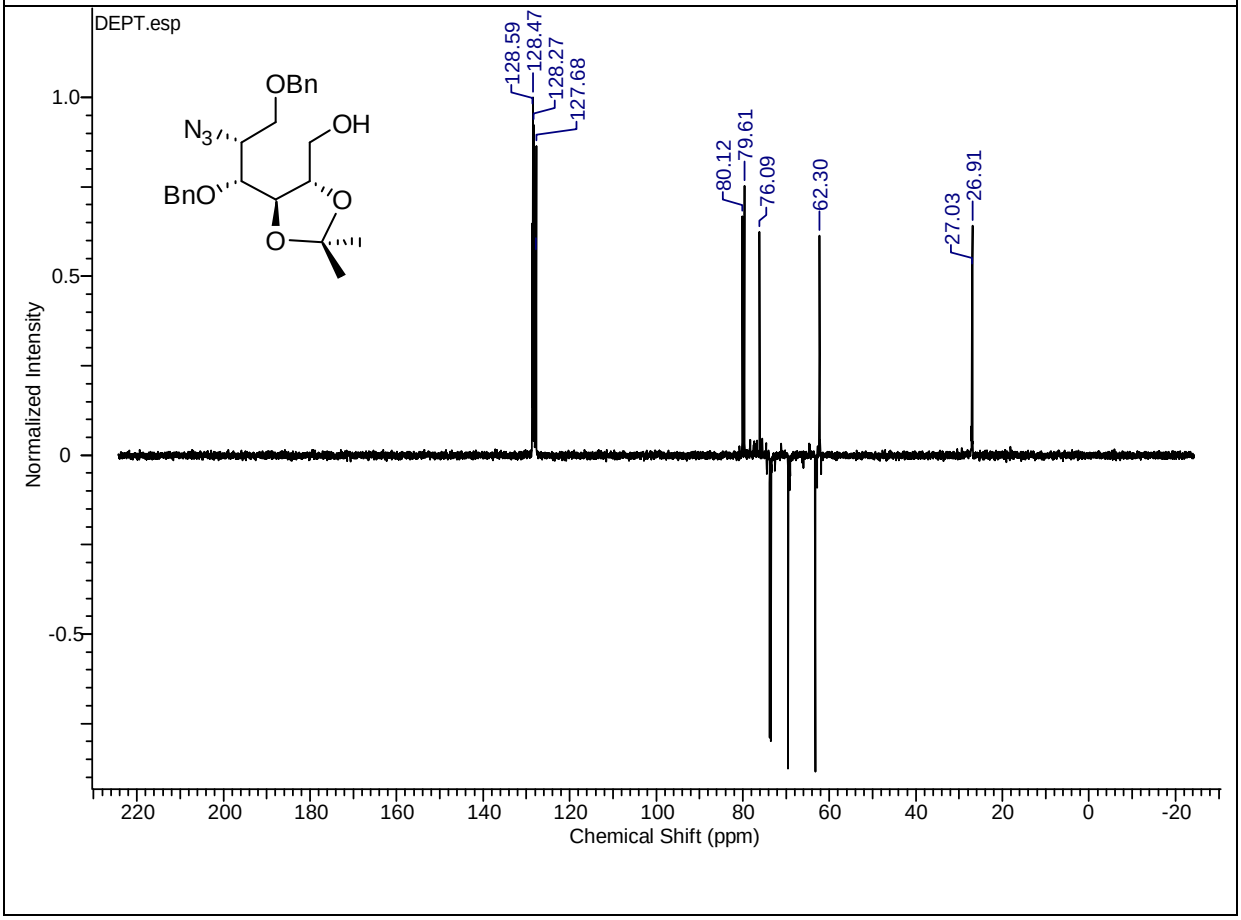
^{1}H-NMR spectrum of compound **21** ($CDCl_3$, 500 MHz)



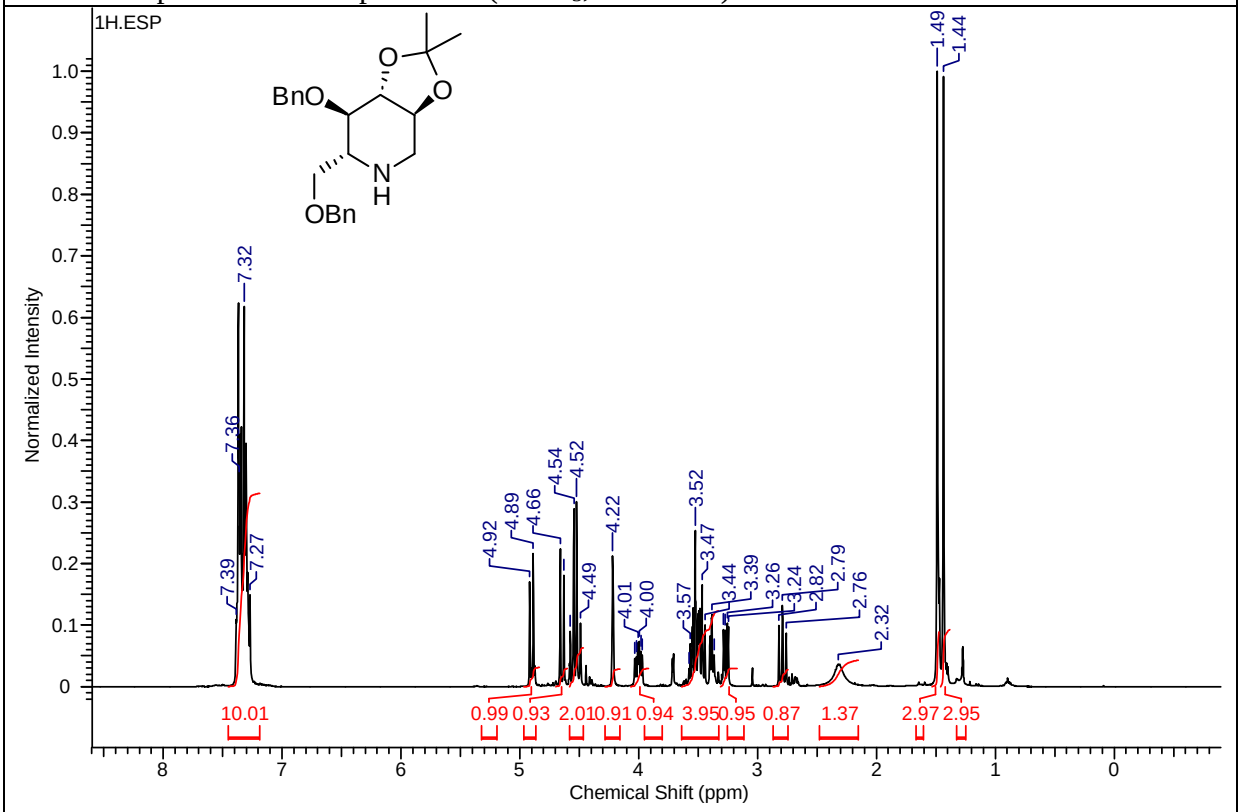
^{13}C-NMR spectrum of compound **21** ($CDCl_3$, 125 MHz)



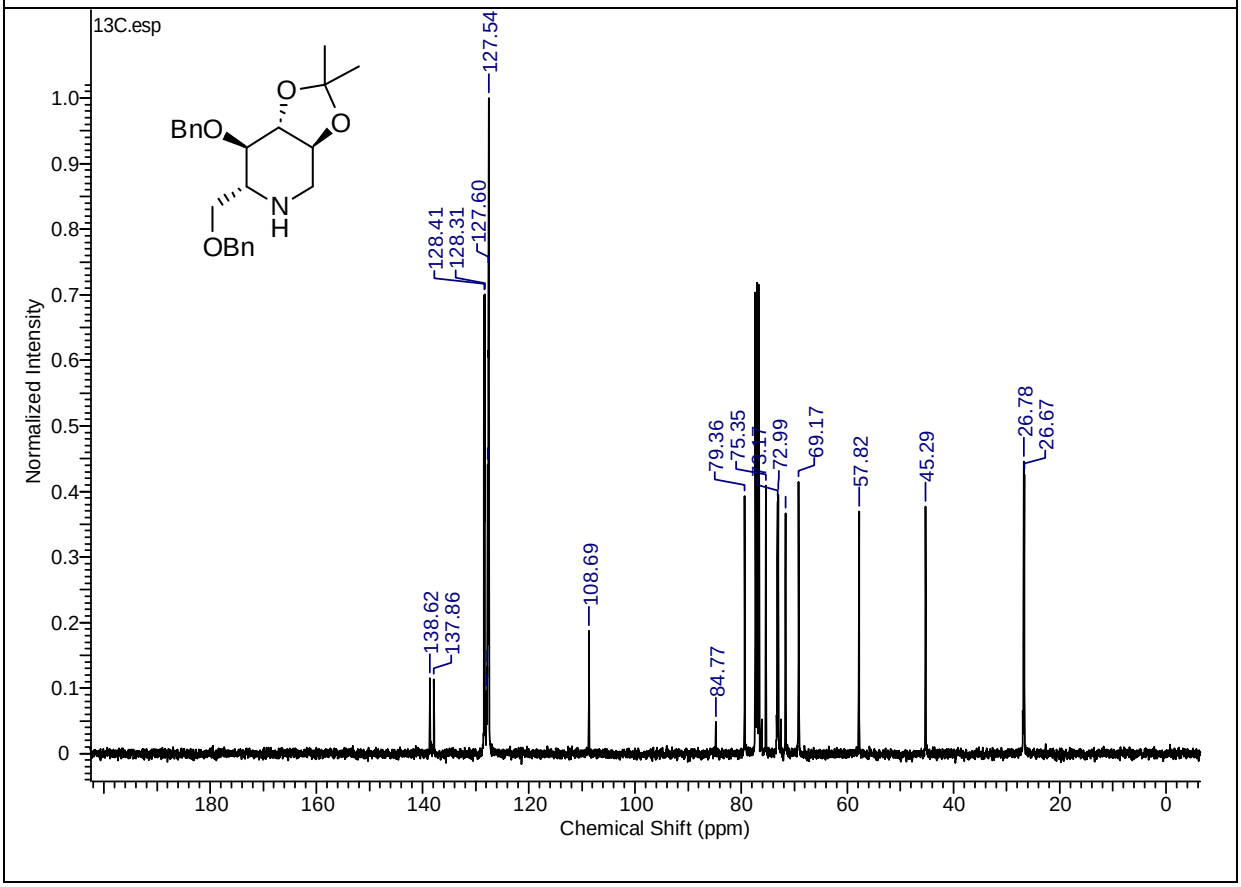
DEPT spectrum of compound **21** ($CDCl_3$, 125 MHz)



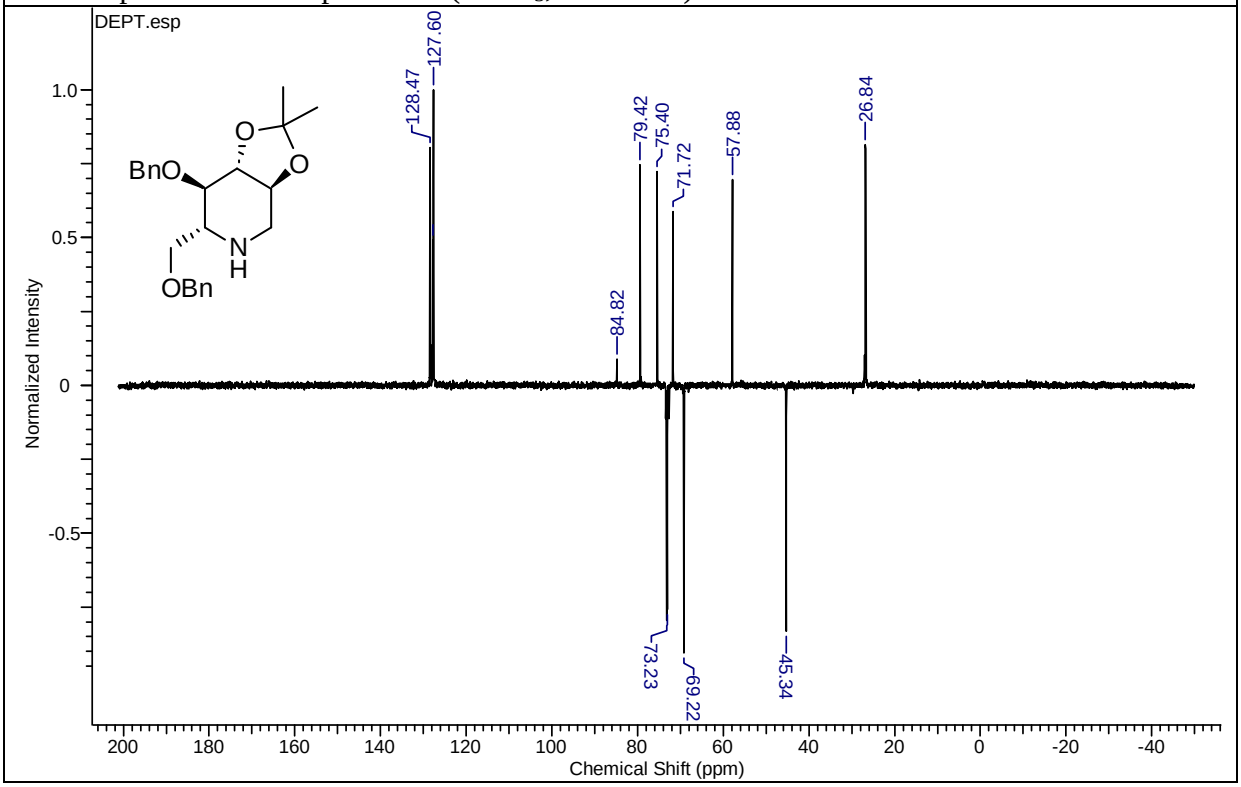
^{1}H-NMR spectrum of compound **22** ($CDCl_3$, 400 MHz)



^{13}CNMRspectrum of compound **22** ($CDCl_3$, 100 MHz)



DEPT spectrum of compound **22** ($CDCl_3$, 100 MHz)



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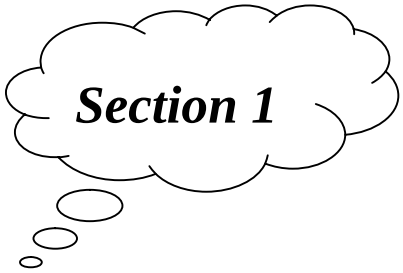
Chapter 3
Total synthesis of *α*-lipoic acid and development of synthetic methodology



Introduction to *α*-lipoic acid

3.1.1 Introduction

The synthesis of chiral molecules is important in pharmaceutical industry due to the different bioactivities shown by enantiomers. One enantiomer may show enhanced therapeutic properties over the other enantiomer, and an understanding *in vivo* activity of both enantiomers is frequently a prerequisite for regulatory approval, the provision of a single enantiomer is often required and essential part. Considering this fact, asymmetric synthesis of α-lipoic-acid is of immense importance.

Lipoic acid **1** was first isolated in 1951 by Reed *et al.*[1] at the university of Texas. The first purified sample of α-lipoic acid **1** was 30 mg of yellow crystals that was extracted from 100 kg of liver residue. Some believed that substance should be named thioctic acid because it contained two sulfur atoms (theion in Greek) and eight carbon atoms (octo in Greek). Finally, the substance was named as lipoic acid because of its ability to dissolve in lipids. α-Lipoic acid is not considered to be a vitamin because it is assumed that it can be synthesized by the body in small amounts from essential fatty acids.

Lipoic acid **1** works at the cellular level to help essential substances for metabolism to enter the mitochondria. Lipoic acid **1** is a powerful and well-known antioxidant. An increase in the amount of lipoic acid **1** increases the amount of cellular fuel that is burned. This generates a greater energy reserve for the body that is available for growth, tissue repair and muscle development.

α-Lipoic acid **1** does not accumulate in tissues and therefore does not have any toxicity in the amounts usually taken because it is distributed through the tissues. It is paticularly useful in protection of the eye and brain, the most sensitive of organs to free radical damage.

α-Lipoic-acid is a protein-bound coenzyme and growth factor found in plant and animal tissues and in microorganisms.[2,3] It is an important part in many biological activities and it has been recognized as an essential cofactor for the multi-enzyme complexes which catalyzes various transformastions in biological system *e.g.* the oxidative decarboxylation of α-ketoacids such as pyruvate, α-ketoglutarate.[4] It also is known to have an important role in photosynthesis and in tricarboxylic acid cycle.

The natural isomer of lipoic acid is *R*-enantiomer and it shows pharmacologically more activity than its *S*-isomer. Moreover, racemic (±)-α-lipoic acid **3** can be important for pharmaceutical purpose using it as such without resolution, since it was observed that (*S*)-enantiomer neither inhibit or effect the activity of the (*R*)-enantiomer **1**.

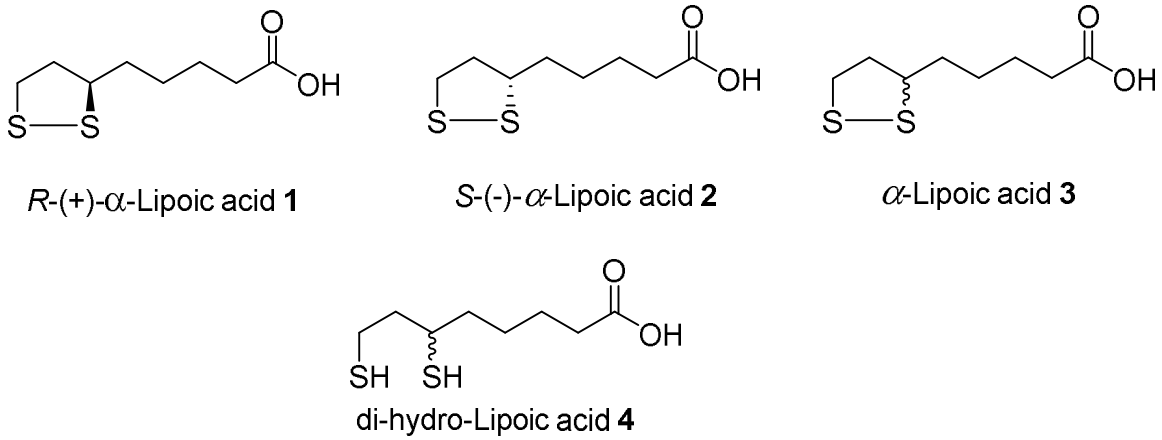


Figure 1: Lipoic acid structure.

α-Lipoic acid **1** is synthesized in the human body in small amounts from essential fatty acids due to this fact it cannot be considered as a vitamin. It is also found in variety of foods, particularly, in kidney, heart and liver meats as well as in vegetables such as spinach, broccoli and potatoes. At cellular level it helps essential substances required for metabolism to enter the mitochondria present in the cells. It also acts as an antioxidant. Its increased concentration increases the amount of cellular fuel that is burned or utilized as energy source. This creates an energy reserve for the body that is required for growth, tissue repair and muscle development. Lipoic acid has been proposed as preventive agent against a variety of disease including aging, diabetes, cancer and cardiovascular disease.

The *α*-Lipoic-acid (**1**) is reduced into dihydrolipoic acid (**4**) in body. Also, it plays a role in the production of glutathione, which appears to be a normal function in the body. *α*-Lipoic acid **1** is unique as it can show vitamins like physiologic functions. Like vitamin C, it is effective as an antioxidant in water based tissues such as the blood, and as dihydro lipoic acid it is also effective in protecting non-water based tissues like fatty tissues and membranes, a role it shares with vitamin E.

The *α*-lipoic-acid **1** and dihydrolipoic acid **4** together function as a universal anti oxidants, i.e., quenches free radicals in both lipid and water-soluble positions of tissues and cells. *α*-lipoic-acid **1** and dihydrolipoic acid **4** are extremely powerful quenchers of hydroxyl, singlet-oxygen, peroxy nitrite and other free radicals. We could also call *α*-lipoic-acid **1** a "broad spectrum" antioxidant because of its activity in aqueous and lipid phases.

Free radicals are associated with the development of artherosclerosis, lung disease and neurological disorders as well as being implicated in chronic inflammation, such as that found with rheumatoid arthritis and inflammatory bowel disease. Some and many other

sources of environmental toxins either are themselves (or) lead to the creation of free radicals in the body.

A healthy body makes enough lipoic acid to supply its requirements; external sources are not necessary. However, several medical conditions appear to be accompanied by low level of lipoic acid, such as specific diabetes, liver cirrhosis and atherosclerosis.

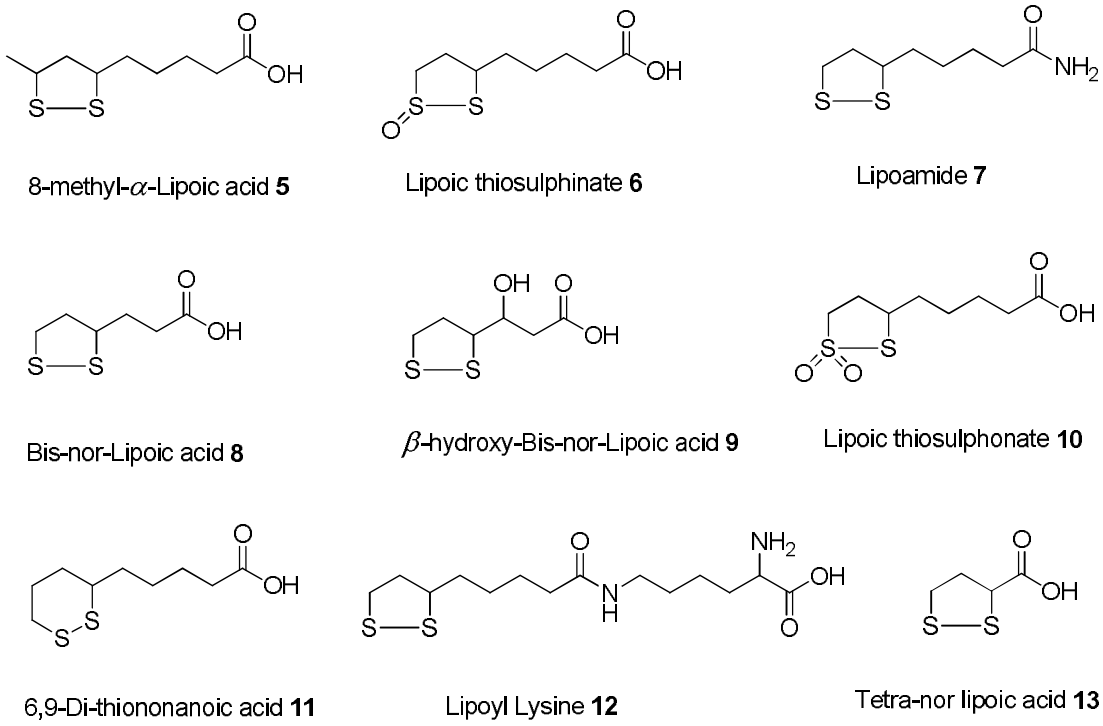
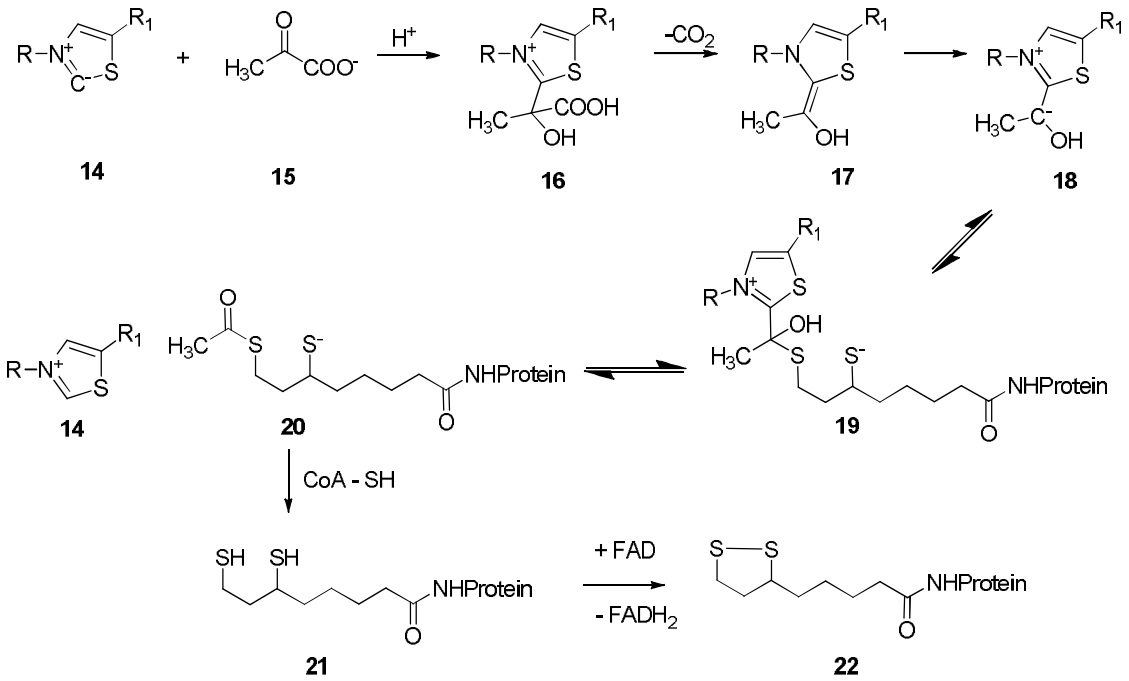


Figure 3. The structure of products related to α-Lipoic acid.

3.1.2 Biological Action of α-Lipoic Acid:

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

The coenzymes required for the overall oxidative decarboxylation of pyruvate are thiamine pyrophosphate (TPP), nicotinamide adenine dinucleotide (NAD), α-lipoic acid **1**, coenzyme A and flavin adenine dinucleotide (FAD).[5] The stages involved in this complex process are shown in scheme-1.



Scheme 1. Biological action of lipoic acid.

Thiamine pyrophosphate interacts with lipoic acid to form an addition complex which subsequently gets cleaved to form acyl lipoic acid complex and TPP is regenerated. The acetyl group, now present as a thioester, is then transferred from acyl lipoic acid to coenzyme-A to form acyl-CoA by the acetyl-transfer enzyme system. Finally, the reduced lipoic acid moiety is reoxidised by the interaction with FAD and the cycle is completed. The acyl-CoA then enters the TCA cycle. FAD is regenerated by interaction with NAD+ in the electron transport system.

The hydrophobic interaction and the metal ion coordinating ability[6] of the molecule for the free passage of the compound in various tissues are the factors responsible for the high biological activity of α-lipoic acid **1**. α-Lipoic acid **1** offers metal ions two different binding sites, the carboxylate group and the disulfide linkage. The carboxylate group dominates the coordinating properties of this ligand towards metal ions but a disulfide-metal ion interaction is still possible, and under stearically favoured conditions, may become very important. This could be true under enzymic conditions when the carbonyl group is no longer free but in the form of amide-linked to the protein. Further, the lipoyl moiety is ideally suited to undergo hydrophobic ligand-ligand interaction in the mixed ligand complexes due to the presence of valeric acid side chain.

3.1.3 Role *α*-lipoic acid in Human Health

α-lipoic acid **1** has been shown to have significant physiological as well as pharmacological properties.[5] There is no doubt that *α*-lipoic acid **1** have an important role in Human Health.[6]

- Alpha lipoic acid functions as a universal antioxidant and free radical scavenger.[7]
- Recycles both Fat and Water-soluble antioxidant vitamins.[8]
- Improves sugar metabolism and energy production. (i. e. controls diabetes).[9]
- *α*-lipoic acid is a co-enzyme associated with α-keto acid dehydrogenation.[10]
- *α*-lipoic acid acid has been used as a therapeutic agent in a number of conditions related to liver.[11]
- *α*-lipoic acid appears to have the potential to slow the process of aging.[12]
- *α*-lipoic acid significantly reduces inflammation and it also acts as an antitumour agent.[13]
- *α*-lipoic acid is an effective inhibitor of human immuno deficiency virus (HIV) replication.[14]
- *α*-lipoic acid has been found beneficial against radiation injury, smoking, heavy metal poisoning and chagas disease.[15]

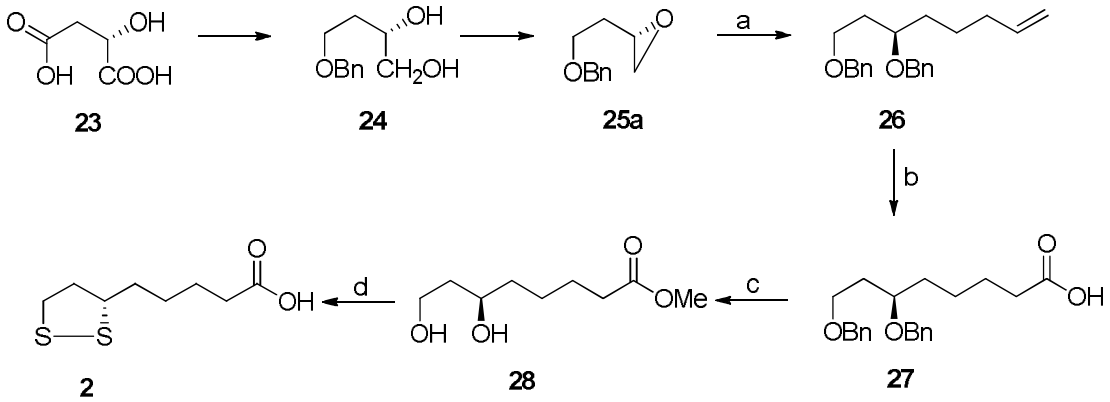
3.1.4 Literature review of α-lipoic acid:

The chemical structure of *α*-lipoic-acid **1** was determined in the early 1950's and its absolute configuration was confirmed to be *R* in 1983, when Golding synthesized the complementary enantiomer from *S*-malic acid. It clearly indicates that scientists considered *α*-lipoic-acid as small molecule and after knowing the pharmaceutical importance the scientific community was attracted by its synthesis as a result a number of synthses over (dl)-*α*-lipoic acid and optically active *R*-(+)-*α*-lipoic acid **1** have been documented in the literature.[16]

Golding *et al.* [16, 17]

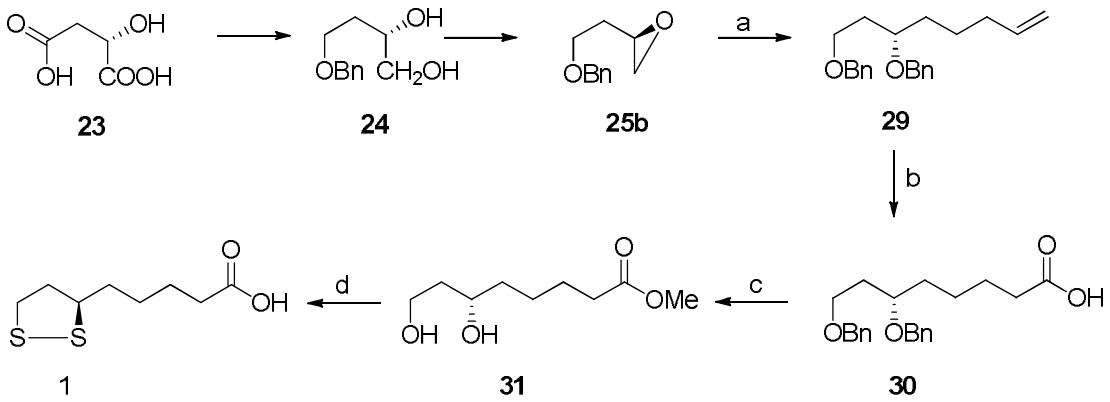
Golding *et al.* have utilized (*S)*-malic acid generated epoxide **25a** as the chiral building block, which was prepared by known protocol from (*S)*-malic acid **23** (Scheme 2). Epoxide ring was opened regioselectvely with but-3-enylmagnesium chloride catalysed by lithium chloro cuprate to furnish the compound **26**. The primary hydroxyl group in 27 was protected

as benzyl ether, followed by hydroboration and oxidation to afford acid **27**. Esterification of acid **27** and debenzylation furnished diol ester **28**, which was dimesylated and converted to methyl lipoate by treatment with sulphur and Na_2S, in DMF and finally, (*S*)-*α*-Lipoic acid **2** was obtained on hydrolysis of ester.



Scheme 2. *Reagents and conditions:* (a) (i) CH_2=$CHCH_2CH_2MgCl$, cat. Li_2CuCl_4, THF; (ii) $PhCH_2Br$, NaH, THF; b) (i) $HBSia_2$, THF, alkaline H_2O_2; (ii) PDC, DMF; (c) (i) MeOH-HCl; (ii) Pd/C, H_2; (d) (i) $MeSO_2Cl$, Et_3N; (ii) Na_2S, S, DMF; (iii) aq. NaOH

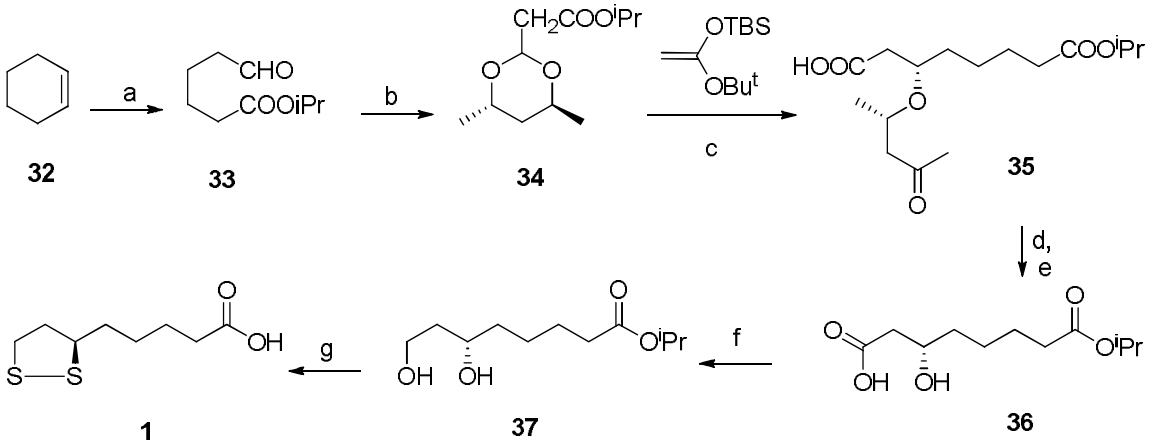
In another approach Golding and Brookes used the same starting material i.e., (*S*)-malic acid **23** but inverted the configuration of hydroxyl group to synthesize the epoxide **25a** (Scheme 3). Epoxide **25b** was converted in to (*R*)-Lipoic acid **1** following the similar sequence of reactions used in the earlier approach.



Scheme 3. *Reagents and conditions:* (a) (i) AcOK, Ac_2O; (ii) $MeSO_2Cl$, Et_3N; (iii) K_2CO_3, MeOH; (b) (i) CH_2=$CHCH_2CH_2MgCl$, Li_2CuCl_4 (catalytic), THF; (ii) $PhCH_2Br$, NaH, THF; (c) (i) $HBSia_2$, THF, alkaline H_2O_2; (ii) PDC, DMF; (d) (i) MeOH-HCl; (ii) Pd/C, H_2; (e) (i) $MeSO_2Cl$, Et_3N; (ii) Na_2S, S, DMF; (iii) aq. NaOH.

Elliott *et al.* [18]

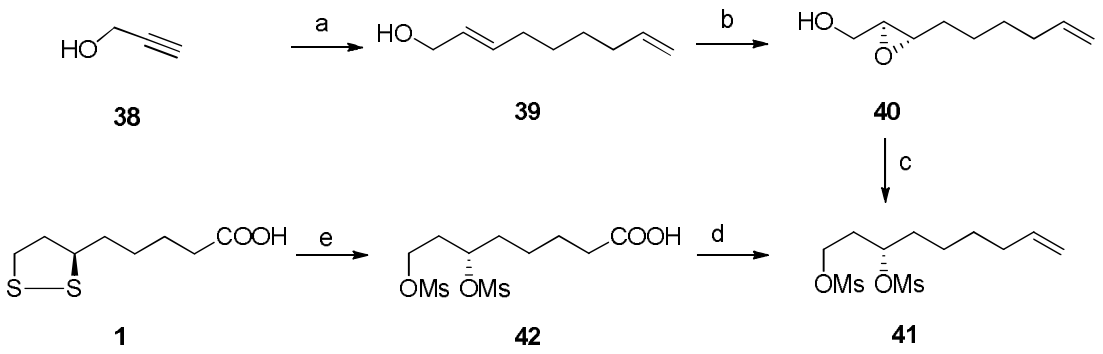
Elliott and co-workers have reported the synthesis of *R*-(+)-lipoic acid using highly diastereoselective $TiCl_4$ catalyzed aldol-type coupling of chiral acetal **34** with 1-*t*-butyldimethyl silyloxy ethane (Scheme 4). The coupling product on hydrolysis followed by oxidation with Jones reagent gave acid **35**. Removal of the chiral auxiliary by β-elimination followed by hydroboration delivered the diol ester **37**. The diol ester **37** was converted to *R*-(+)-lipoic acid **1** by using Golding's Procedure.



Scheme 4. *Reagents and conditions:* (a) O_3, *i*-PrOH, -78 ^oC, Ac_2O, Et_3N; (b) (2*S*, 4*S*)-pentane-2, 4-diol, *p*-TSA, Benzene; (c) (i) $TiCl_4$, CH_2Cl_2, -78 ^oC; (ii) TFA, H_2O; (d) Piperidinium acetate, benzene, reflux, 97%; (e) Jones oxidation; (f) BH_3.THF, 4 M aq. KOH, 82%.; (g) (i) $MeSO_2Cl$, TEA, (ii) Na_2S, S, DMF, 60^oC, (iii) aq NaOH

Sutherland *et al.* [19]

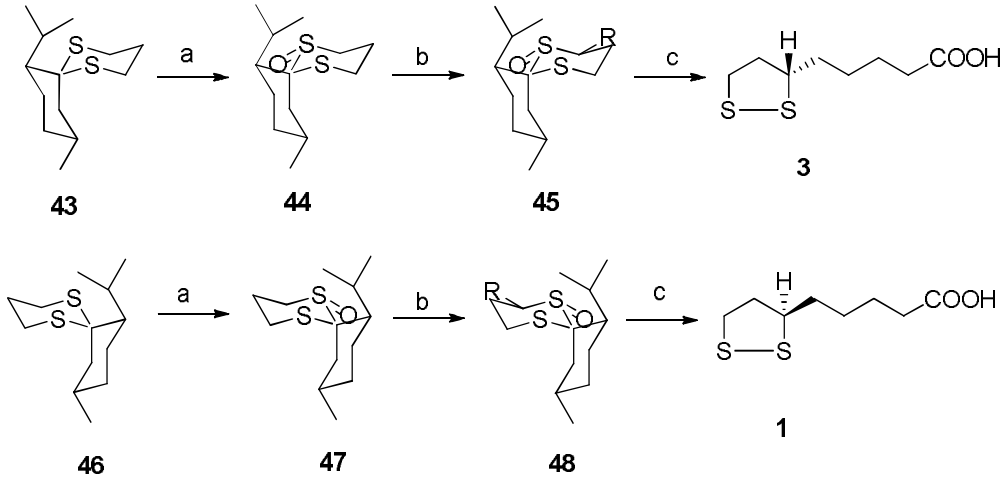
Sutherland *et al.* employed the alkylation of lithio dianion of propargyl alcohol **38** in liquid ammonia solution with 6-bromohex-1-ene followed by dissolving metal reduction to deliver the allyl alcohol **39** (Scheme 5). Sharpless asymmetric epoxidation of allyl alcohol **39** gave the (2*S*, 3*S*)-epoxy alcohol **40**. Reduction of **40** with Red-Al and mesylation of the diol provided the dimesylate **41**. Ruthenium tetroxide oxidation of the terminal double bond gave acid **42** which is converted into *R*-(+)-lipoic acid **1** by known sequence of reactions.



Scheme 5. *Reagents and conditions:* (a) Na, liq. NH_3, $Br(CH_2)_4CH=CH_2$; (b) L-(+)-diisopropyl tartarate, $Ti(OPr^i)_4$, TBHP, CH_2Cl_2, -20 ^oC; (c) (i) Red-Al, THF; (ii) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (d) RuO_4; (e) (i) Na_2S, S, DMF, (ii) 4 M aq. KOH.

Ravindranathan *et al.* [20]

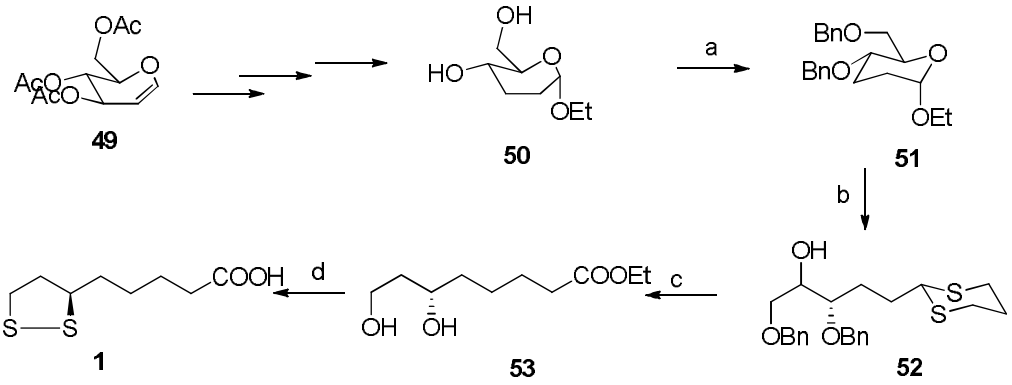
Ravindranathan's approach involves the formation of 1, 3-dithiane **43** from 1, 3-propane dithiol and L-menthone. Regioselective oxidation of dithiane **43** afforded sulfoxide **44**. Stereo selective alkylation of **44** to give **45** followed by hydrolytic cyclization afforded *R*-(+)-lipoic acid **1**. In the similar manner *S*-(-)-lipoic acid prepared by using D-menthone. This approach they recovered the L-menthone in almost quantitative yield. This is the shortest and probably the best synthesis for both the enantiomers of lipoic acid (Scheme 6).



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

Rama Rao *et al.*[21-24]

Rama Rao *et al.* have reported four different routes for the synthesis of lipoic acid. Rama Rao's first synthesized from D-glucose, which was converted to 4,[21] 6-di-o-benzyl derivative **51** through 3, 4, 6-tri-o-acetyl-D-glucal **49** by known procedure. Treatment of **51** with propane dithiol followed by xanthate formation and *n*-Bu_3SnH mediated reductive removal afforded dithiane derivative **52**. Sequential dithiane deprotection, two-carbon Wittig olefination, hydrogenation using Raney nickel delivered the diol **53**. The diol **53** was converted to *R*-(+)-lipoic acid **1** by the known procedure.

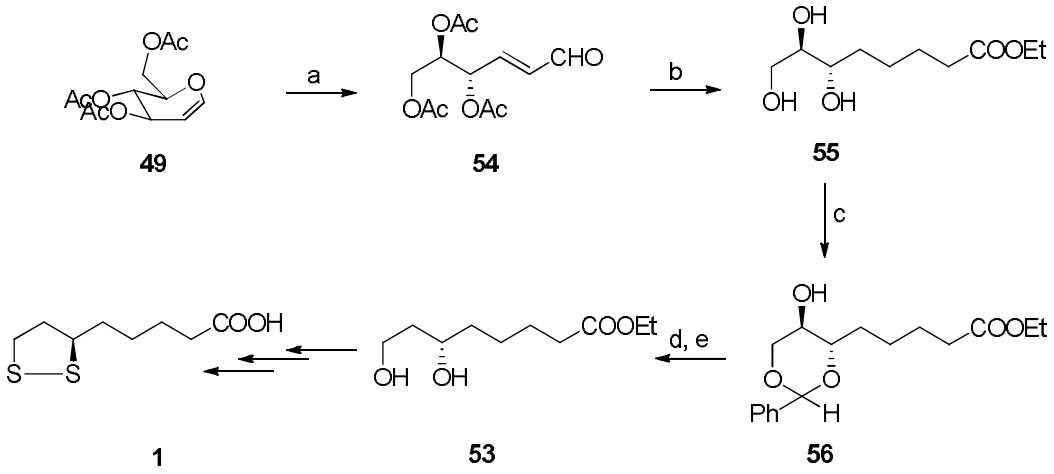


Scheme 7. *Reagents and conditions:* (a) NaH, BnBr; (b) (i) 1, 3-propane dithiol, $BF_3.Et_2O$, CH_2Cl_2; (ii) NaH, CS_2, MeI; (iii) *n*-Bu_3SnH, AIBN; (b) (i) HgO, $BF_3.OEt_2$; (ii) Ph_3P=CHCOOEt (c) H_2, Raney Ni; (d) (i) $MeSO_2Cl$, TEA, (ii) Na_2S, S, DMF, 60^oC, (iii) aq NaOH

In Rama Rao's second approach: tri-o-acetyl-D-glucal **49** was converted to unsaturated aldehyde **54** using mercurous ion catalyzed ring opening.[22] Sequential hydroxyl group protection, two carbon Wittig homologation and hydrogenation gave the tri-acetate **54**. Deacetylation and protection of 6, 8-hydroxyl groups with benzaldehyde dimethyl acetal gave the benzylidene protected compound **56**. Deoxygenation of the free hydroxyl group followed by removal of benzylidene protection gave the diol **53**, which was converted to *R*-(+)-lipoic acid **1** (Scheme-8).

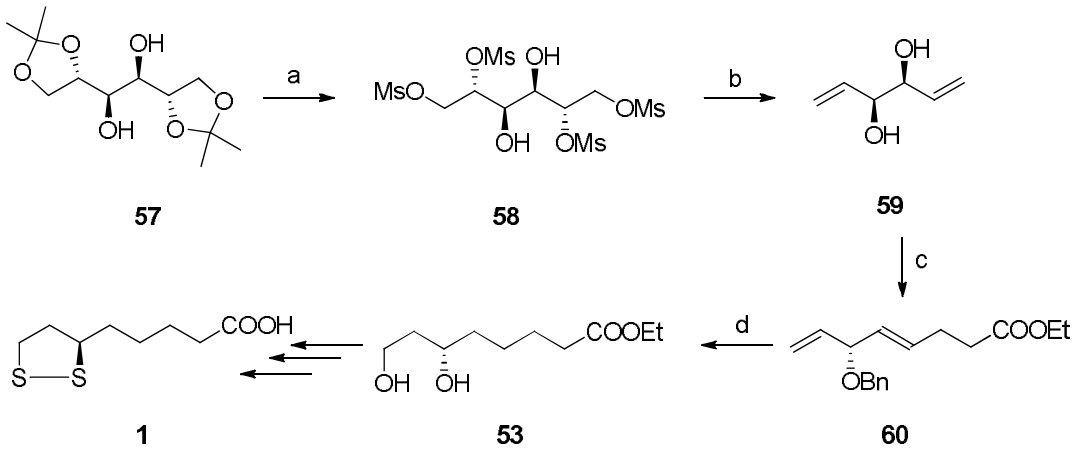
Third approach involves the utilization of mannitol diacetonide **57** as a chiral starting material. Benzoyl protection of the free hydroxyl groups followed by isopropylidene deprotection and mesylation gave the tetra mesylate **58.**[23] Treatment of **58** with sodium iodide and zinc dust followed by debenzoylation gave (3*R*, 4*R*)-1,2-divinyl glycol **59**. Selective protection of hydroxyl group and claisen-ester rearrangement of the resultant monoprotected

benzyl ether delivered the compound **60**. Sequential hydroboration, oxidation and reduction of the double



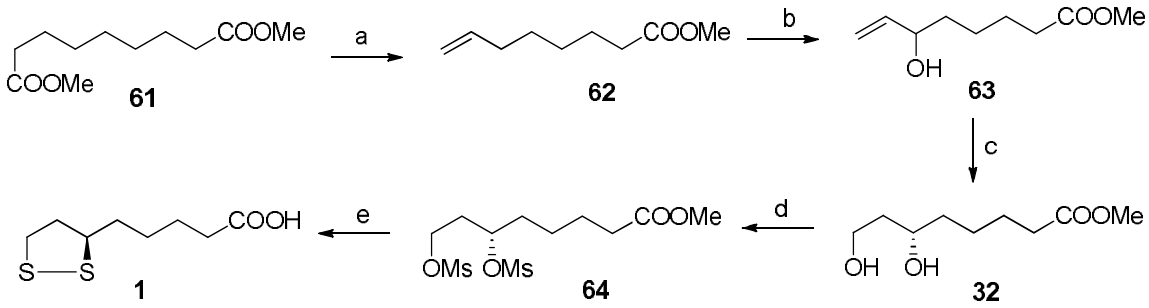
Scheme 8. *Reagents and conditions:* (a) (i) $HgSO_4$, H^+, dioxane; (ii) Ac_2O, pyridine; (b) (i) Ph_3P=CHCOOEt; (ii) H_2, Raney Ni; (iii) NaOEt, EtOH; (c) $PhCH(OMe)_2$, H^+; (d) (i) Thiocarbonyl diimidazole, THF; (ii) n-Bu_3SnH, AIBN; (e) H_2, Pd/C.

bond gave the known diol **53** which was converted in to *R*-(+)-lipoic acid **1** (Scheme 9). Fourth approach of Rama Rao *et al.*[24] employed highly regioselective Sharpless allylic oxidation



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

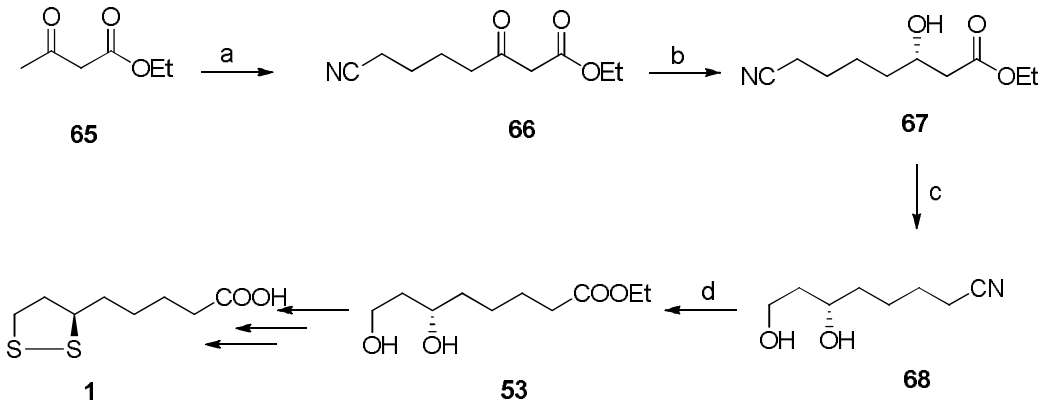
of the olefin **62** with TBHP and SeO_2 to deliver the compound **63** Hydroboration, oxidation of olefinic compound **63** delivered the known diol **64** which was converted to (*R*)- α -lipoic acid **1** by a series of known reactions (Scheme-10).



Scheme 10. *Reagents and conditions:* (a) $Pb(OAc)_4$, $CuSO_4$, benzene; (b) TBHP, SeO_2, CH_2Cl_2; (c) B_2H_6-THF, NaOOH., (d) TEA, MsCl, DCM (e) Na_2S, S, DMF, 60 ^oC.

Gopalan *et al.* [25]

Gopalan and Jacobs have utilized highly enantio-selective yeast reduction of α-keto ester **66** as the key step to deliver the compound **67** (Scheme 11). Reduction of ester **67** with $LiBH_4$ in THF at room temperature furnished the diol **68**. The cyano group in diol **68** was converted in to diol ester **53** by using ethanol in presence of acid. Diol ester **53** was converted to *R*-(+)-lipoic acid by a series of known reactions.

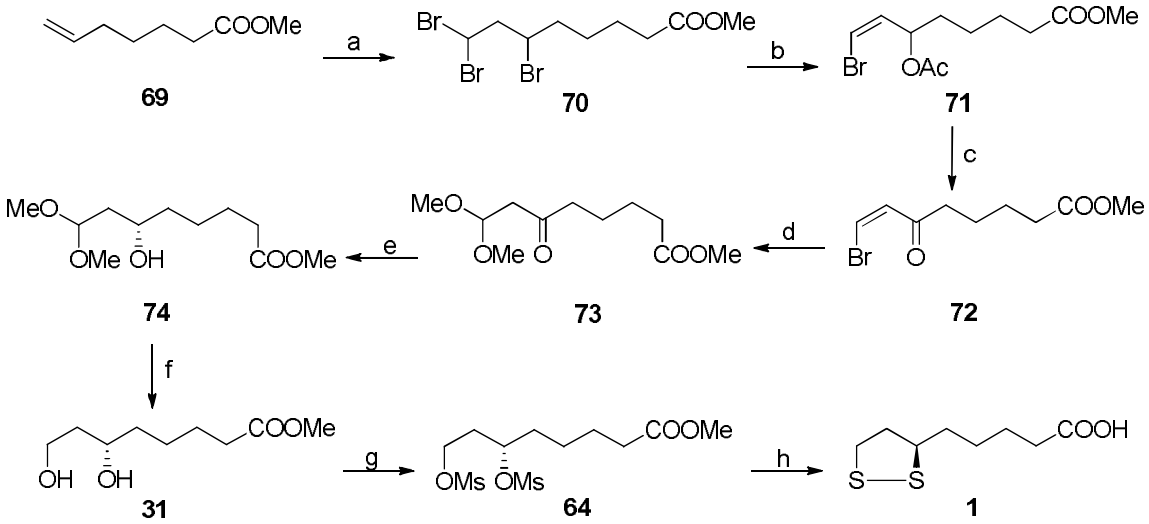


Scheme 11. *Reagents and conditions:* (a) (i) NaH, THF, HMPA, 0 ^oC; (ii) *n*-BuLi, $I(CH_2)_3CN$; (b) Baker's Yeast (c) $LiBH_4$, THF, 0 ^oC; (d) EtOH, H^+, reflux.

Bhalerao *et al* [26]

Bhalerao *et al.* have used copper catalyzed bromoform addition to alkene **69** to give methyl-6,8,8-tribromooctanoate **70**, which on treatment with potassium acetate and 18-

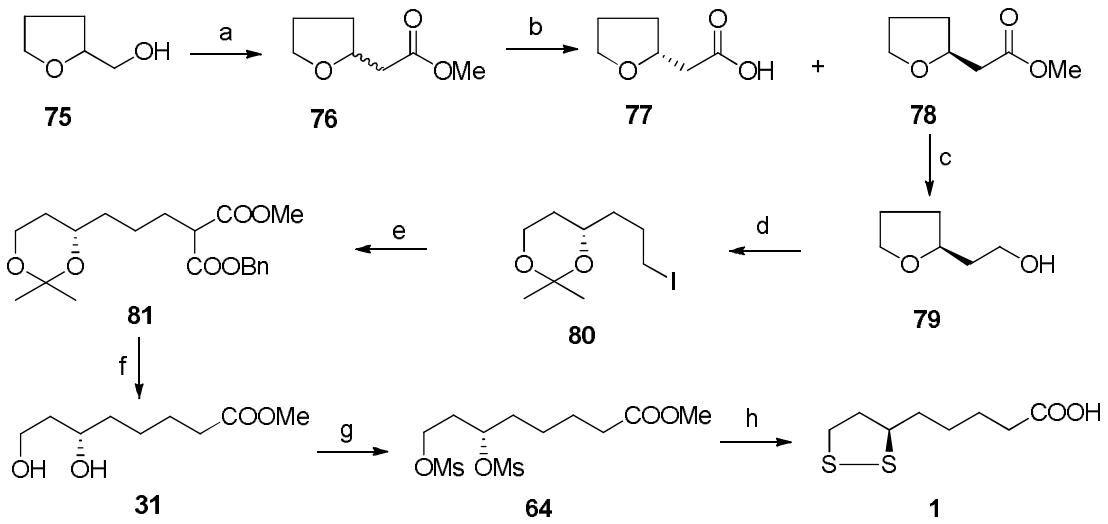
crown-6 in DMF furnished compound **71** (Scheme 12). Hydrolysis, Oxidation and followed by treatment with triton-B to provide the keto acetal **72**. The keto acetal **72** was reduced enantioselectively by Baker's yeast to give compound **73**, which on treatment with H_3PO_4 in acetone followed by $NaBH_4$ reduction resulted in the formation of diol **31**. The diol was converted to *R*-(+)-lipoic acid **1** in a similar fashion reported earlier.



Scheme 12. *Reagents and conditions:* (a) Cu, $CHBr_3$, 80%; (b) AcOK, 18-crown-6, DMF; (c) K_2CO_3, MeOH then PCC, 68%; (d) Triton B, MeOH; (e) Baker's Yeast, pH 4.5-5; (f) (i) H_3PO_4, Acetone; (ii) $NaBH_4$, MeOH; (g) $MeSO_2Cl$, TEA, (h) (i) Na_2S, S, DMF, 60 ^oC, (iii) aq NaOH

Iyengar's *et al.*[27]

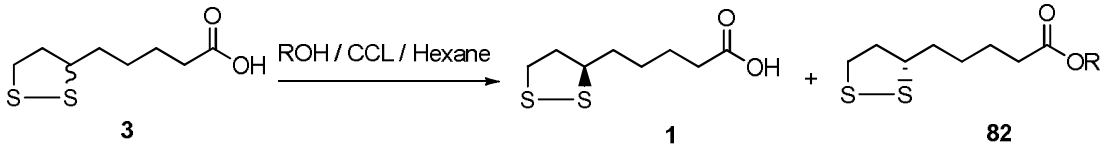
Iyengar *et al.* employed selective lipase hydrolysis of methyl 2-(tetrahydro-2- furyl) acetate **75** during which *R*-isomer undergoes hydrolysis but *S*-isomer remains intact (Scheme 13). *S*-ester **78** was then reduced with $LiAlH_4$ to give the compound **79**. Regioselective opening of **79** with TMSCl, NaI in acetone gave iodo acetonide **80**. Alkylation of **80** followed by debenzylation and decarboxylation furnished the diol ester **31** which was converted to *R*-(+)-lipoic acid **1**.



Scheme 13. *Reagents and conditions:* (a) (i) TsCl, KOH, 93%; (ii) KCN, 74%; (iii) KOH, 93%; (iv) MeOH, H^+; (b) Liphase/ Phosphate buffer (c) $LiAlH_4$, ether, 84% (d) TMS-Cl, NaI, acetone; (e) Benzyl methyl malonate, NaH, THF, 25%; (f) (i) Pd/C, H_2, 98% (ii) MeOH, H^+, 98%.; (g) TEA, MsCl, DCM (h) Na_2S, S, DMF, Heat 60 ^oC

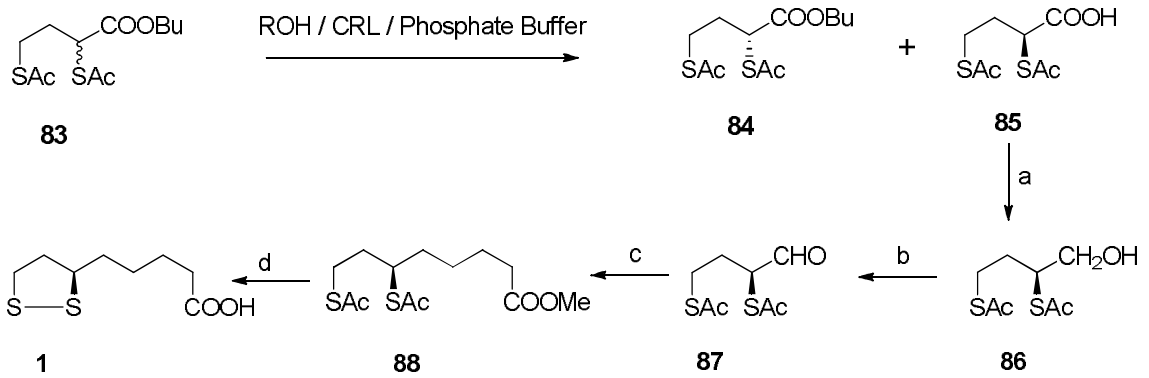
Fadnavis *et al.*[28]

Fadnavis *et al.* utilized lipase catalyzed enantioselective esterification of racemic *α*-lipoic acid **3** to deliver the *R*-(+)-lipoic acid **1**.[28a] In the presence of lipase of candida rugosa *S*-isomer which was converted to its corresponding ester **82** (Scheme 14).



Scheme-14

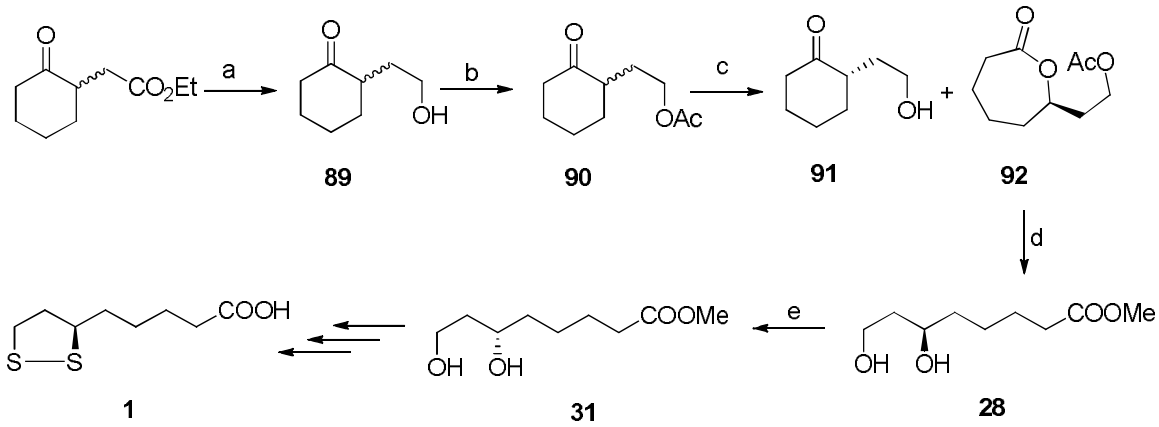
In an another approach Fadnavis *et al.* have synthesized *R* and *S* isomers of lipoic acid using lipase catalyzed regio and stereospecific hydrolysis of *n*-butyl ester of 2,4- dithioacetyl butanoic acid **83** to afford **84** and **85.**[28b] Hydroboration of **85** followed by PCC oxidation resulted in the formation of aldehyde **87**. Aldehyde **87** on four carbon Wittig homologation and subsequent hydrogenation with Wilkinson's catalyst furnished the ethyl ester **88**. Hydrolysis of **88** with wheat germ lipase followed by treatment with oxidative enzyme mushroom tyrosinase gave *R*-(+)-lipoic acid **1**. Similarly *S*-(-)-lipoic acid **2** was prepared from **84** (Scheme 15).



Scheme- 15. *Reagents and conditions:*(a) (i) BH_3.DMS, 0 ^oC; (b) PCC (c) (i) $Br^- {}^+PPh_3$-$CH_2(CH_2)_2COOEt$, NaHMDS, -78 ^oC; (ii) $(PPh_3)_3RhCl$, H_2; (d) (i) Wheat germ Lipase, pH 7.0; (ii) Tyrosinase.

Adger *et al.*[29]

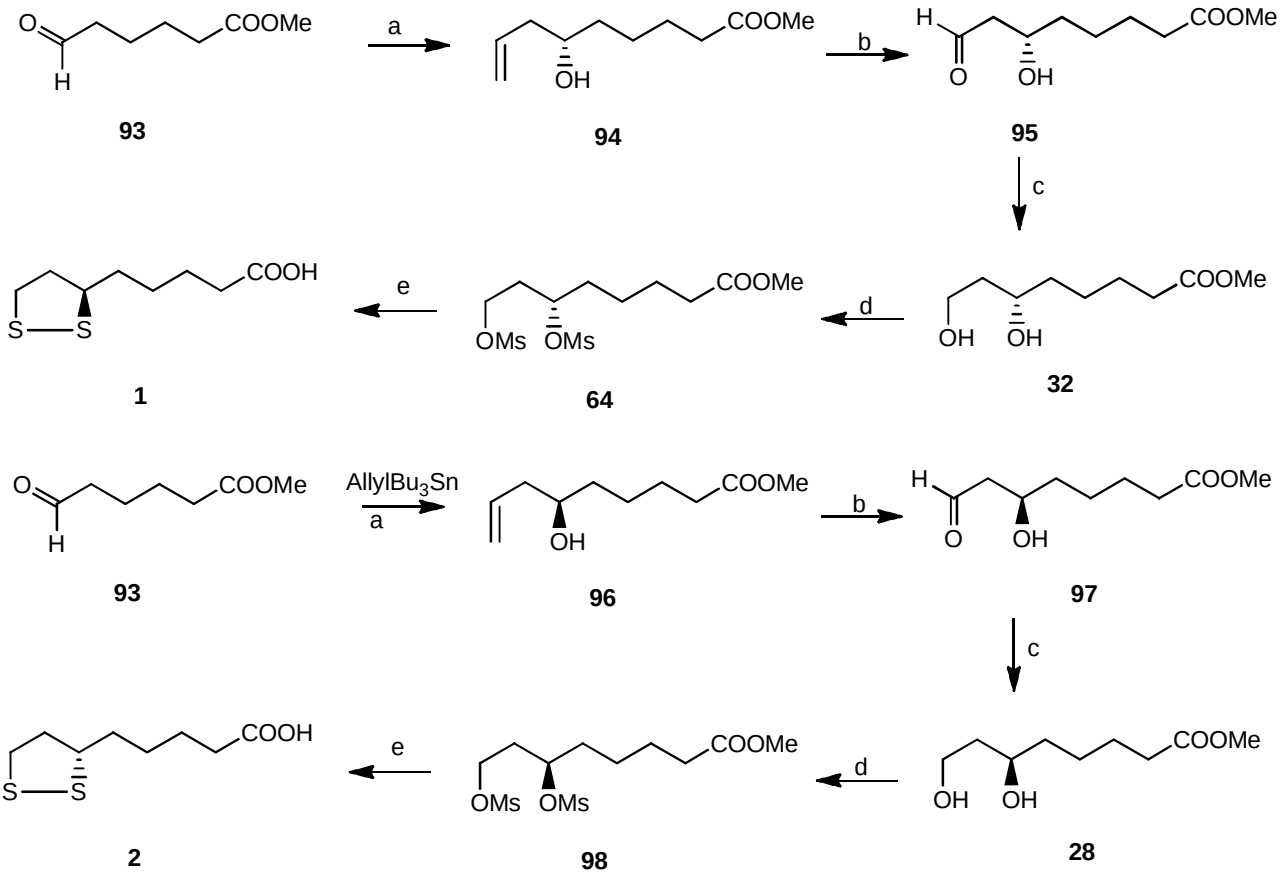
Adger *et al.*, regio and enantioselectively converted 2-(2-acetoxy ethyl) cyclohexanone **90** in to the lactone **92**, using monooxygenase enzyme (Scheme 16). The lactone **92** was converted to diol **28** using sodium methoxide in methanol. The stereochemistry at C-6 was inverted by using Mitsunobu reaction. Hydrolysis of benzoate ester delivered the known diol ester **31,** which was converted to *R*-(+)-lipoic acid **1** by a series of known reactions.



Scheme 16. *Reagents and conditions:* (a) (i) Ethylene glycol, *p*-TSA, toluene; (ii) $LiAlH_4$, ether, 0 to 25 ^oC; (b) Ac_2O, pyridine, DMAP then HCl, MeOH; (c) 2-Oxo-3-4, 5, 5-trimethyl cyclopentenyl acetyl-CoA Monooxegenase, NADPH, G-6-P, G-6-PDH; (d) NaOMe, MeOH; (e) (i) p-$NO_2C_6H_4COOH$, PPh_3, DEAD, THF; (ii) K_2CO_3, MeOH.

Zimmer *et al.*[30]

Zimmer *et al.* have employed catalytic asymmetric allyl stannation reaction as the key step to deliver the required stereochemistry of **94** (Scheme 17). In the presence of 0.2 equivalents of (*S*)-BINOL, 0.2 eq. of $Ti(OiPr)_4$ and 4 Å molecular sieves the aldehyde **93** and allyl tributyl stannane provided *R*-alcohol **94** with 98% enantiomeric excess. This homoallylic alcohol converted to corresponding *R*-(+)-lipoic **1** by known sequence of reactions as shown below. Similarly, Zimmer and co-workers has prepared *R*-(+)-lipoic **1** by same sequence of the reaction as shown below by using (*R*)-BINOL as catalyst for chiral induction.

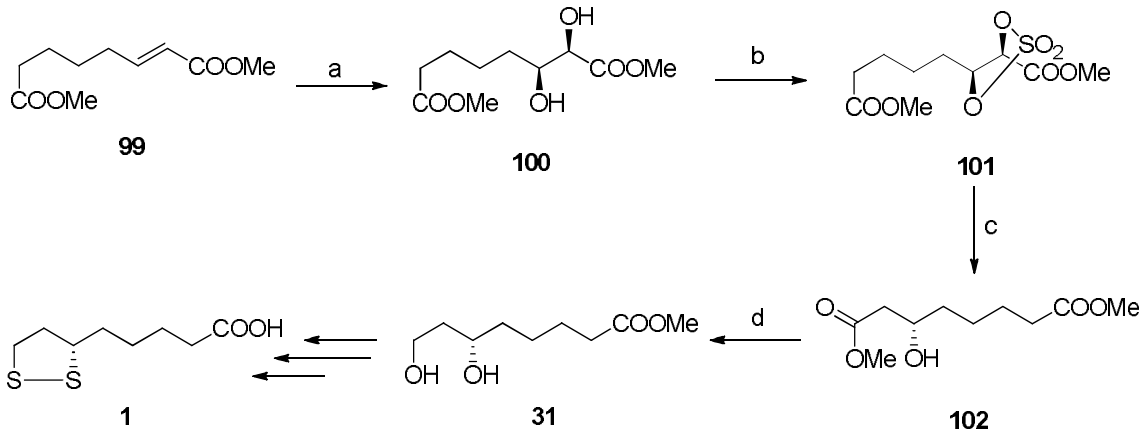


Scheme 17. *Reagents and conditions:* (a) (*S*)-BINOL (0.2 eq), $Ti(O^iPr)_4$ (0.2 eq), CH_2Cl_2, 2 days, 75%, 98% ee. (b) O_3, MeOH ; (c) $NaBH_4$, MeOH, rt; d) TEA, MsCl, DCM (e) Na_2S, S, DMF, Heat 60 ^oC; (f) (*R*)-BINOL (0.2 eq), $Ti(OPr^i)_4$ (0.1 eq), CH_2Cl_2, 6 days, 89%, 98% ee.

Sudalai *et al.*[31]

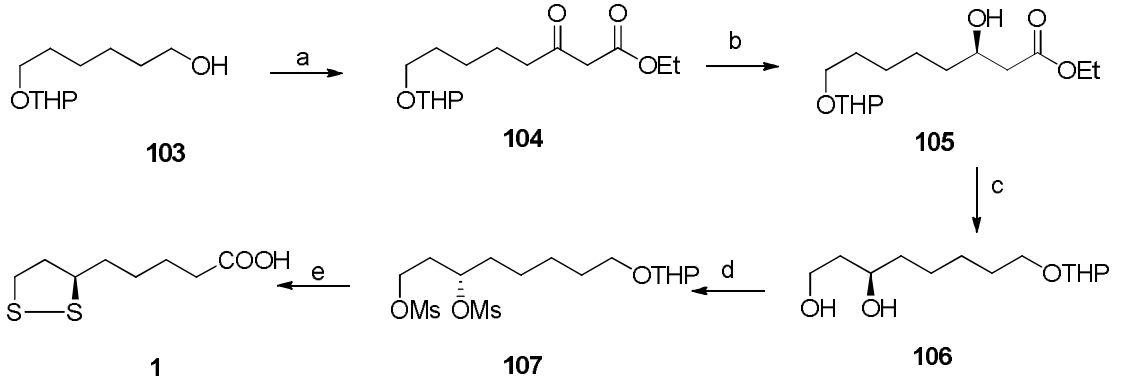
Sudalai *et al.* employed Sharpless asymmetric dihydroxylation over **99** to afford intermediate **100** which on sulphone cyclisation and reduction with $NaBH_4$ undergoes

sulphone ring opening to give deoxygenated product **102**. This intermediate **102** on reduction with borane.Me_2S furnishes intermediate **31**. This intermediate **31** converted into *R*-(+)-lipoic acid **1** by a series of known reactions (Scheme 18).



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

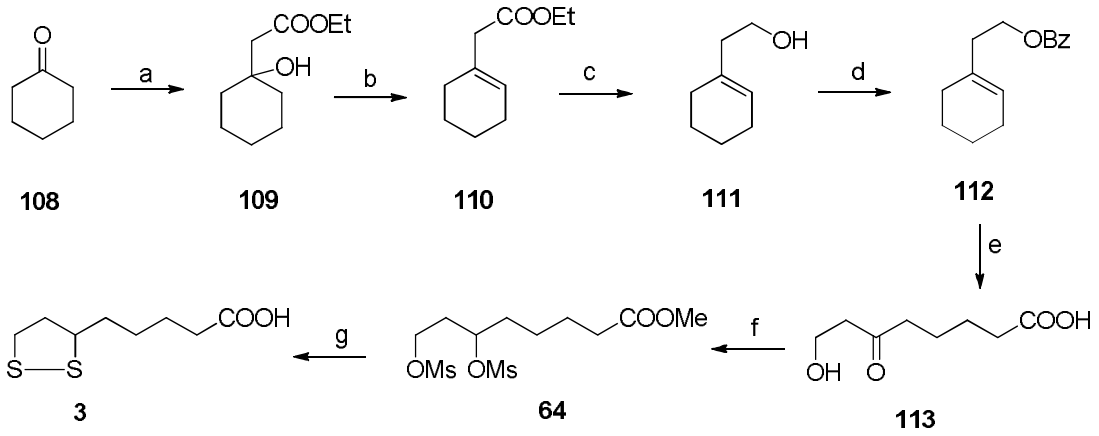
In another approach Ruthenium catalyzed asymmetric hydrogenation reactions had been implemented over keto intermediate **104** to get the *β*-hydroxy ester **105.** This *β*-hydroxy ester **105** on ester reduction followed by protection of alcohol, furnishes intermediate **106** respectively. This intermediate **106** was converted into *R*-(+)-lipoic acid **1** by a series of known reactions as shown in scheme 18.



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

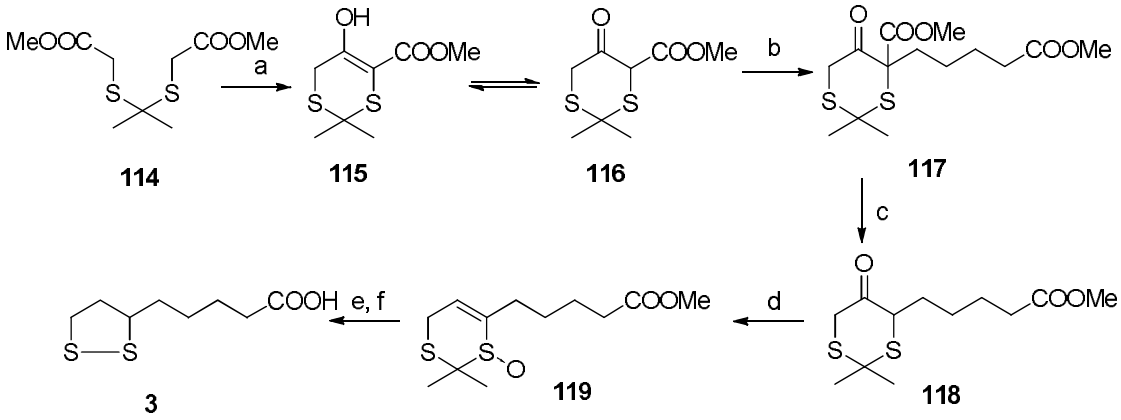
Chavan *et al.* [32,33,34]

Chavan *et al.* reported the synthesis of lipoic acid **3** has been achieved by using modified Reformatsky reaction.[32] In this protocol, β-elimination of the alcohol to furnish selectively the β,γ-unsaturated ester is the another feature of this synthesis. Reformatsky reaction with chloroester was carried out on cyclohexanone **108** to furnish alcohol ester **109**, which was then set for elimination using thionyl chloride and pyridine. The β,γ-ester **110** thus obtained was then reduced using DIBAL-H to furnish **111**. The alcohol **111** formed, was then protected using benzoyl chloride to give benzoate ester **112**, which was then subjected to ozonolysis followed by Jones oxidation to furnish ketoacid **113**. The reduction of ketoacid **113**, followed by esterification, furnished diol ester **64.** The diol ester **64** was then converted to racemic α-lipoic acid **3** by known protocol as shown below (Scheme 20).



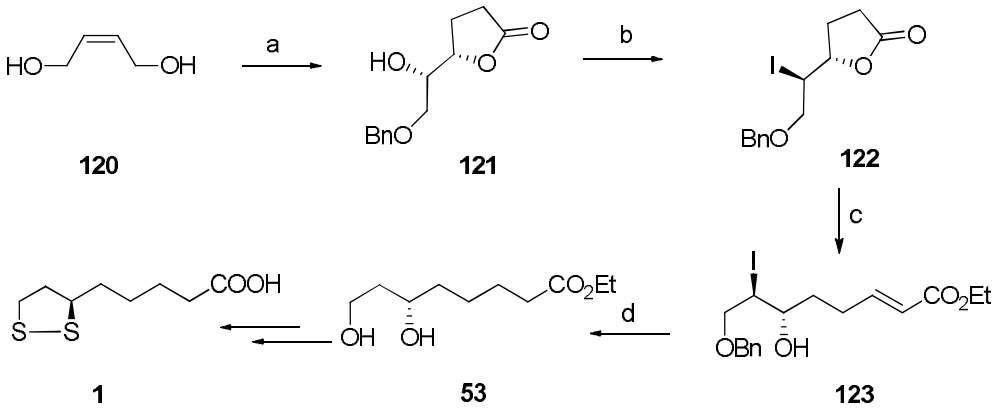
Scheme 20. *Reagents and conditions:* (a) Zinc, $ClCH_2COOEt$, benzene-ether (1:1), reflux, 65%; (b) $SOCl_2$, pyridine, DCM, 86%; (c) DIBAL-H, DCM, -78 ^oC, 65% ; (d) BzCl, Et_3N, DCM, 92%; (e) (i) O_3, DCM; (ii) Jones reagent, 85%; (f) (i) $NaBH_4$, MeOH, 90%; (ii) CH_2N_2, ether; 91%; (iii) $MeSO_2Cl$,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

In another approach Chavan *et al.*[33] accomplished the synthesis of racemic α-lipoic acid **3** by using diester **114**, which was readily prepared in two steps from thioglycolic acid. This diester **114** was subjected to Dieckmann condensation to furnish the α-keto ester **116**, which exists in enolic form. Phase transfer catalyzed alkylation of **116** followed by decarboxylation gave the ester **117**. The keto ester **117** was converted into olefin **119** by treating with tosyl hydrazone followed by refluxing in presence of NaOH. The sequential reduction of double bond, oxidation to mono sulfoxide and final hydrolytic cyclization of **119** afforded racemic α-lipoic acid **3** (Scheme 21).



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

In third approach enantiomerically pure hydroxy lactone **121**, the versatile intermediate for synthesis,.[34] obtained in four steps from cis-2-butene-1,4-diol **120**, was treated with triphenylphosphine, iodine and imidazole to furnish the iodo lactone **122**. Reduction of the lactone **122** using DIBAL-H at -78 ^{o}C followed by an *in-situ* two-carbon Wittig reaction gave the unsaturated ester **123**. Intermediate **123** was converted to diol **53** by using W2 Raney nickel in the presence of hydrogen. The diol **53** is a well known intermediate for the synthesis of (+)-lipoic acid (Scheme 22).

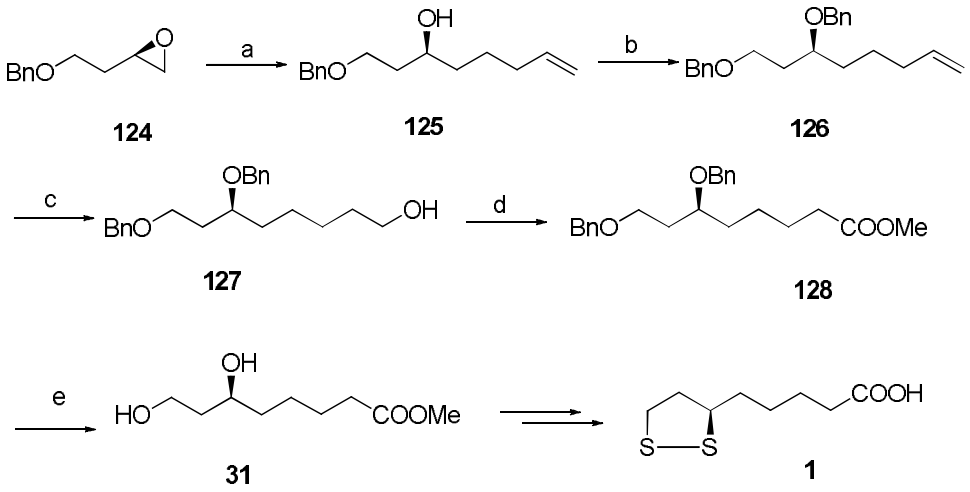


Scheme 22. *Reagents and conditions:* (a) PPh_3, I_2, imidazole, 70 ^{o}C, 3 h, 94%; (b) DIBAL-H, DCM, 78 ^{o}C, 1 h, $Ph_3PCHCOOC_2H_5$, 24 h; rt, 96%; (c) W_2 Raney nickel, H_2, rt., 24 h, 84%.

Bose *et al.*[35]

Bose *et al.* reported synthesis of *R*-lipoic acid **1** using regiospecific opening of epoxide (*R*)-**124** with but-3-enylmagnesium bromide (3 equiv) –78 °C as the key step. The epoxide ringopening furnished 1-enzyloxyoct-7-en-3-ol **125** in 90% yield (Scheme 23). The hydroxy

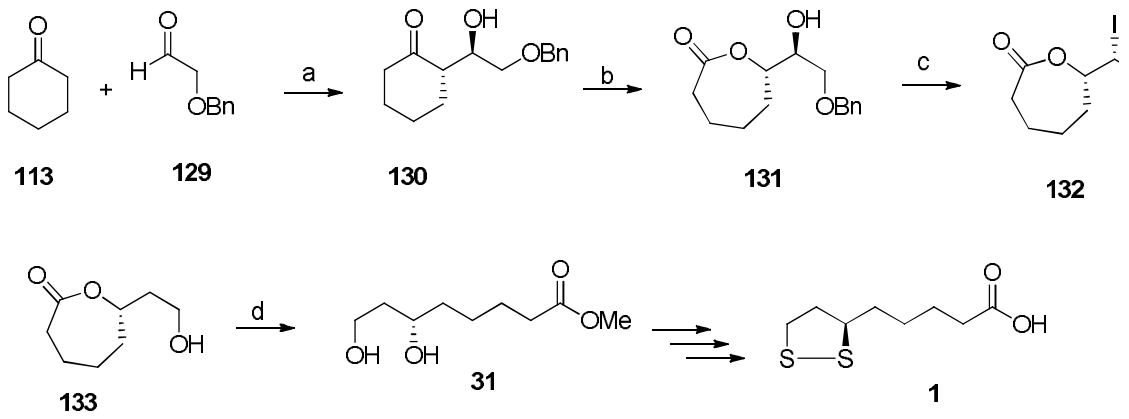
group in **125** was protected to yield **126** followed by elaboration of the terminal olefin into the corresponding acid functionality. This was followed by esterification with diazomethane to afford the ester **128**. Removal of the benzyl group by hydrogenolysis furnished the diol **31**, which was converted to (*R*)-*α*-lipoic acid **1**, by the standard sequence of reactions.



Scheme 23. *Reagents and conditions:* (a) CH_2=$CHCH_2CH_2$-MgBr, Li_2CuCl_4 (cat.), THF, –78 °C to rt; (b) NaH, BnBr, DBAI, DMF, 85%; (c) BH_3·DMS, $MeCO_2Na$, H_2O_2, THF, 88%; (d) (i) $NaClO_2$, TEMPO, NaOCl; (ii) CH_2N_2, Et_2O; (e) H_2, Pd/C, EtOH.

Duan *et al.*[36]

Duan *et al.* accomplished asymmetric synthesis of *R*-(+)-lipoic acid **1** using L-proline catalyzed diastereoselective cross-aldol reaction as the key step. Cyclohexanone **113** on L-proline catalyzed aldol reaction with aldehyde **129** afforded hydroxy ketone **130**. Ketone **130** on Baeyer-Villiger oxidation followed by iodination and hydrogenation afforded lactone **133**. Lactone **133** on treatment with sodium methoxide afforded known diol **31** was which converted to *R*-(+)-lipoic acid **1** using known reaction sequence (Scheme 24).



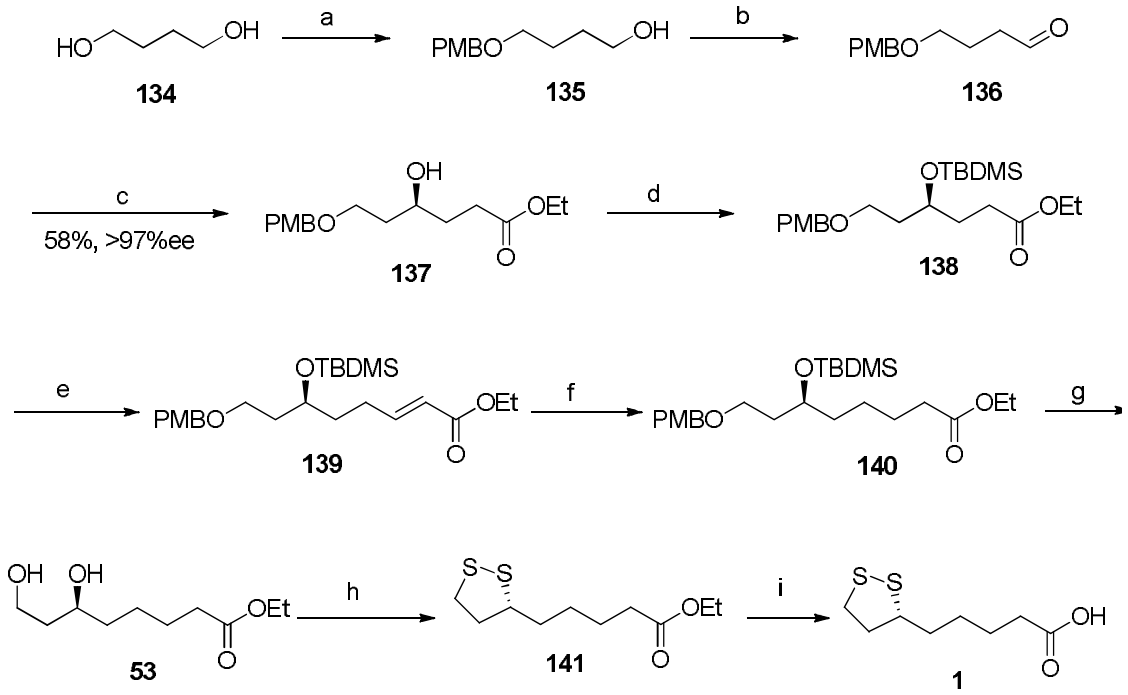
Scheme 24. *Reagents and conditions*: (a) L-proline, DMF, rt.; (b) *m*-CPBA, DCM, rt; (c) PPh_3, I_2, Im, toluene, reflux; (d) W_2 Raney Ni, H_2, MeOH ; (e) MeONa, MeOH, rt.

Kalkote *et al.*[37]:

Kalkote *et al.* accomplished the synthesis of (*R*)-(+)-*α*-lipoic acid **1**, starting from prochiral substrates using organo catalytic enantioselective aminoxylaiton has been achived. Organocatalyst utilised in this aspect is L-proline (Scheme 25).

The synthesis starts from commercially available 1,4-butanediol, which on mono-protection of 4-methoxy benzyl chloride followed by oxidation afforded aldehyde **136**. The aldehyde **136** was subjected to L-proline (20 mol%) catalyzed *α*-aminoxylation followed by Wittig olefination at 0 ^oC. Thus formed *γ*-aminoxy *α,β*-unsaturated ester**,** was then subjected to Pd/C catalyzed hydrogenolysis to yield γ-hydroxy ester **137**. The *γ*-hydroxy ester **137** converted to its silyl ether **137** with TBDMSCl and imidazole in 89% yield.

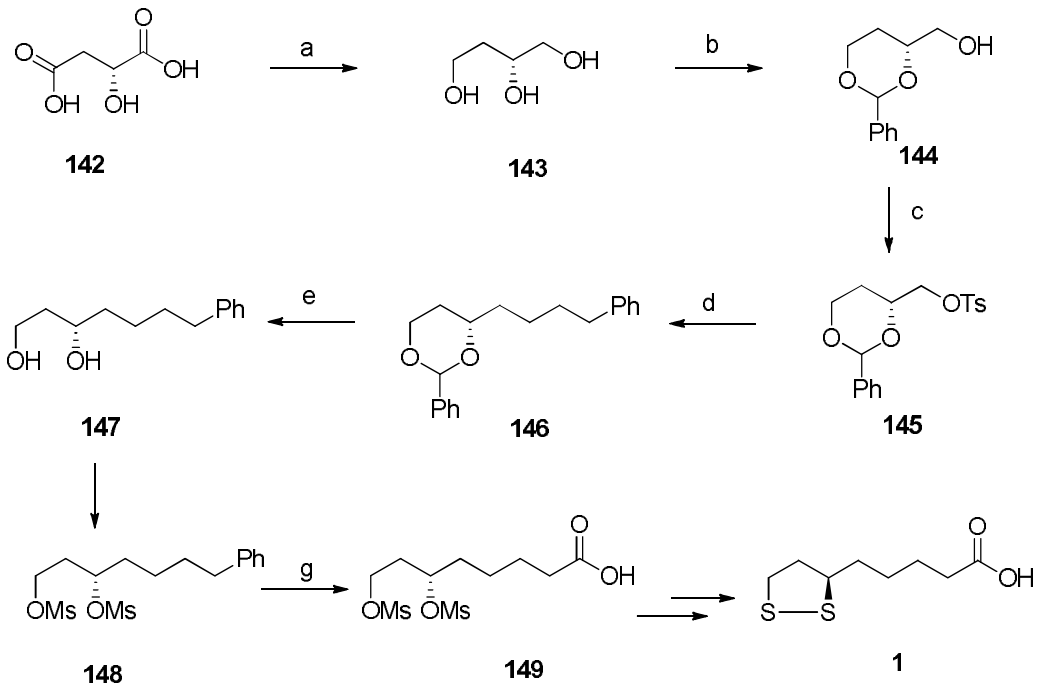
This six carbon unit was extended to eight carbon unit by sequence of ester reduction to aldehyde, 2-carbon Wittig homologation followed by reduction of *α,β* unsaturated double bond to obtain **140.** The ester **140** was treated with $TiCl_4$ to furnish diol **53** which on tratment with MsCl in the presence of Et_3N at 0 ^oC provided dimesylate. The dimesylate on treatment with Na_2S and sulfur in DMF at 80 ^oC for 24 h afforded ethyl lipoate **141**. Finally hydrolysis of ethyl lipoate **141** with 0.1 M KOH aqueous solution in methanol at room temperature for 24 h afforded *R*-(+)-lipoic acid **1.**



Scheme 25. *Reagents and reaction conditions*: (a) NaH, PMB-Cl, DMF, 79%; (b) IBX, DMSO, 94%; (c) (i) L-Proline, PhNO, DMSO, rt, 15 h, (ii) $(EtO)_2P(O)CH_2COOEt$, LiCl, DBU, CH_3CN, 0 ^oC; (iii) EtOAc, Pd/C, H_2, 58%; d) TBDMS-Cl, Im, DCM, 89%; (e) DIBAL-H, DCM, -78^oC, 82%; (f) (i) $(EtO)_2P(O)CH_2COOEt$, LiCl, DBU, Acetinitrile, 0 ^oC; (ii) EtOAc, Pd/C, H_2, 94%; (g) $TiCl_4$, DCM, rt, 87%; (h) (i) TEA, MsCl, DCM (ii) Na_2S, S , DMF heat 80 ^oC, 85%; (I) KOH, EtOH, RT, 24 h, 76%..

Huang *et al.*[38]

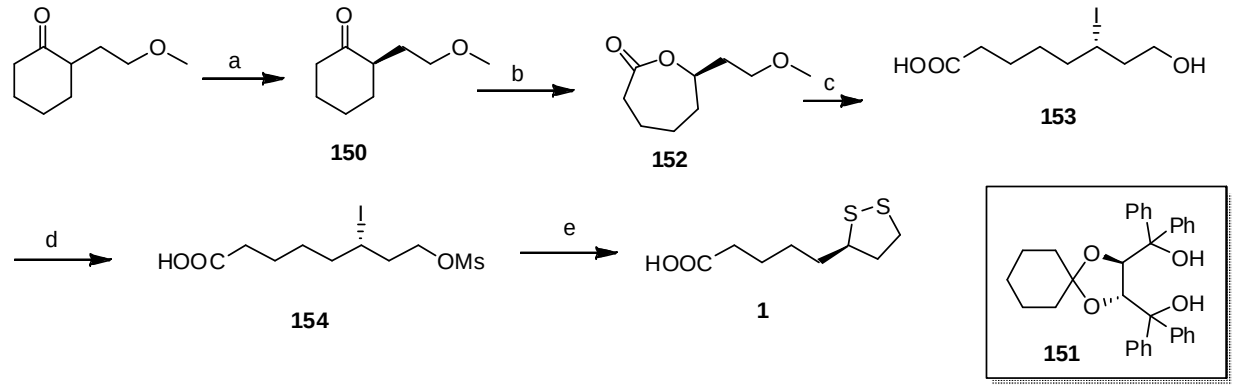
Huang *et al*. reported asymmeric synthesis of *R*-(+)-lipoic acid **1** using (*R*)-malic acid as the starting material (Scheme 26). It was converted to triol **143** by known method. Triol **143** on treatment with benzaldehyde under acidic conditions afforded acetal **144** which was converted to its tosyl derivative **145**. Tosyl derivative **145** on treatment with Grignard reagent afforded **146**. Acetal **146** on iodine treatment furnished diol **147** which was converted to **148** on mesylation. Compound **148** on treatment with Ruthenium chloride and sodium periodate afforded acid **149** which was converted to *R*-(+)-lipoic acid **1** by known reaction sequence.



Scheme 26. *Reagents and conditions*: (a) Ref. 39 (b) PhCHO, TFA, DCM; (c)TsCl, Py, DCM, 0 ^{o}C; (d) $Ph(CH_2)_3MgBr$, CuI, THF, -78 ^{o}C; (e) I_2, MeOH; (f) MsCl, Et_3N, DCM; (g) $RuCl_3.xH_2O$, $NaIO_4$, CH_3CN: EtOAc: H_2O, (2:2:3), rt.

Kaku *et al*[40]

Kaku *et al.* reported synthesis of *R*-lipoic acid **1** using deracemization as the key step. racemic



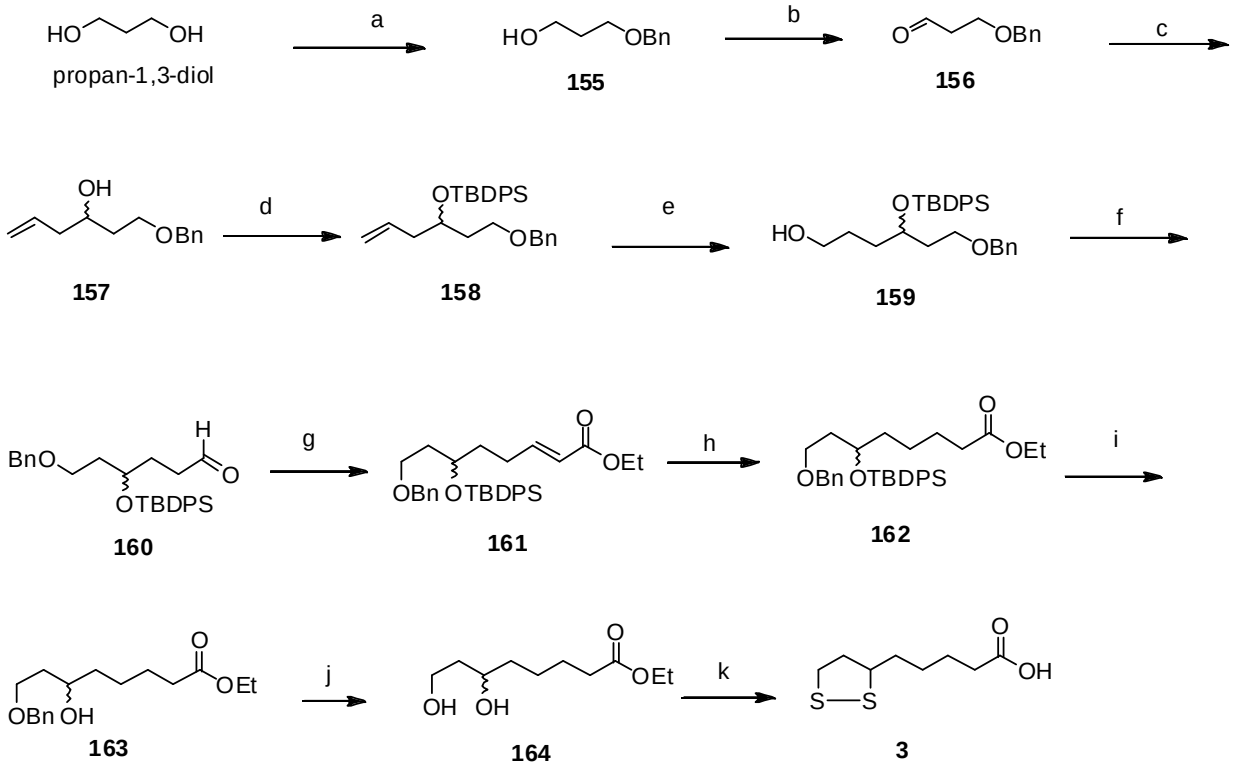
Scheme 27. *Reagents and conditions*:.a) **151** (2 equiv), NaOH (4 equivH_2O–MeOH (2:1), rt, 7 d, 93%; b) MCPBA (1.2 equiv) NaH_2PO_4 (3.0 equiv) DCM; c) SiH_2I_2 (6 equiv), DCM, 24 h, reflux; d) MsCl (5 equiv), Et_3N (5.5 equiv.), DCM, -30 ^{o}C, 10 min, 67%; e) $Na_2S{\cdot}9H_2O$ (1.15 equi, DMF, 80 ^{o}C, 79%.

2-(2-methoxyethyl)cyclohexanone was transformed into the *R*-isomer **150** (99% ee) in 90% yield using **151** as the host molecule under basic conditions. This *R* isomer **150** was then

subjected for Baeyr -Villiger reaction to obtain lactone moiety **152**. This ester **152** on treatment with diiodosilane underwent cleavage of methyl ether linkage with concomitant ringopening iodination of the lactone *via* a SN2-type mechanism at C6. This iodo **153** acid was conerted into target compound **1** by mesylation followed by treatment with sodium sulfide (Scheme 27).

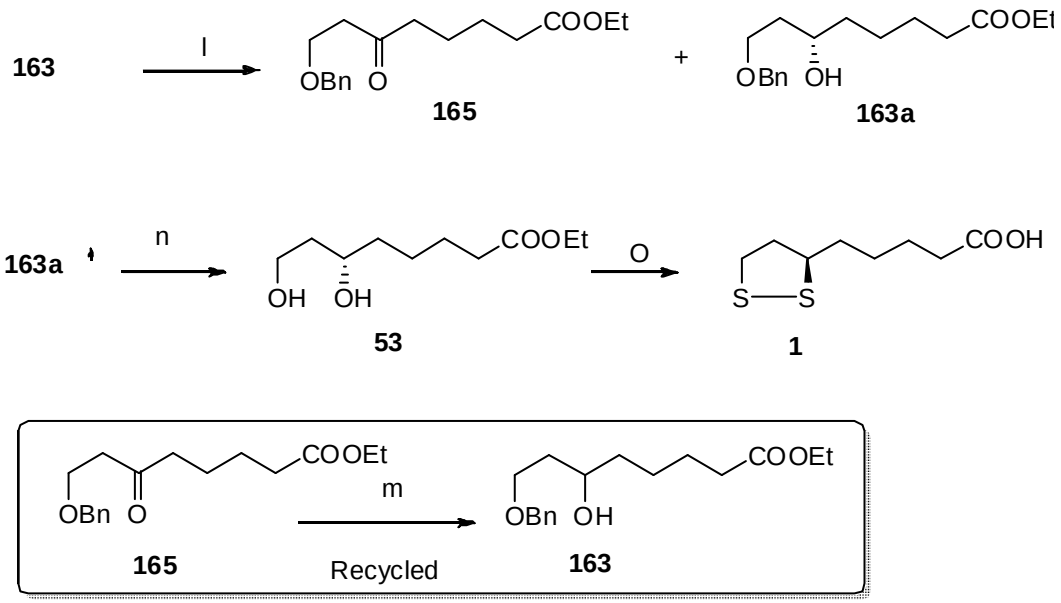
Purude *et al.*[41]

Kalkote and coworkers reported synthesis of both the enantiomers of lipoic acid using Mn (III)- salen-catalyzed oxidative kinetic resolution as the key step (Scheme 28). The synthesis of lipoic acid **1** began with benzyl protection of commercially available propan-1,3-



Scheme 28: *Reagents and conditions:* (a) NaH, BnBr, THF, 7 h, 91%; (b) PCC, DCM, Celite, rt,, 0.5 h ; (c) Allyl bromide, Zn, THF, Aq. NH_4Cl, 76%; (d) Im, DCM, TBDPS-Cl, rt, 12 h, 92%; (e) BH_3:DMS, THF, H_2O_2, CH_3COONa, 2 h, 78%; (f) PCC, DCM, 0.5 h, 94%; (g) Ph3P=CHCOOEt, THF, 10 h, 89%; (h) H_2, Pd-C, EtOAc, rt, 2 h, 91%; (i) TBAF, THF, rt, 6 h, 87%; (j) H_2, Pd-C, EtOAc, rt, 2 h, 90%; (k) i) TEA, MsCl, DCM, 0 ^oC to rt; ii) Na_2S, S Powder, DMF, Reflux, 24 h, 85%; (ii) KOH, EtOH, rt, 12 h, 79%.

diol to afford monobenzyl protected propan-1,3-diol **155**. The free hydroxyl group in **155** was subsequently oxidised to aldehyde **156** followed by treatment with allyl bromide in the presence of zinc in THF yielded 1-(benzyloxy)hex-5-en-3-ol **157**. This alcohol **157** on TBDPS protection, hydroboration, oxidation and Wittig reaction gave unsaturated ester **161** in 60% yield in four steps. This ester **161** was treated under hydrogenation condition to reduce double bond selectively and then deprotection afforded ethyl 8-benzyloxy)-6-hydroxyoctanoate **163** in 79% in two steps. Here the hydrogenation was carried out simply by H_2/Pd-C, a heterogeneous catalysis and deprotection was carried out by treatment with



Scheme 29. *Reagents and conditions:* (l) (*S, S*)-Mn (III)-salen, 2 mole%, $PhI(OAc)_2$, KBr, DCM, H_2O, rt, 49%; (m) $NaBH_4$, EtOH, rt, 94%; (n) H_2, Pd-C, EtOAc, rt, 90%; (o) (i) TEA, MsCl, DCM, 0 ^oC-rt; (ii) Na_2S, S Powder, DMF, reflux, 75%, (iii) KOH, EtOH, rt,12 h.

TBAF. Ethyl 8-(benzyloxy)-6-hydroxyoctan-oate **163** is an important key intermediate of *R* or *S*-lipoic acid synthesis. The racemic synthesis of lipoic acid **3** was completed from **163**. Compound **163** was explored for asymmetric synthesis of both the antipodes of lipoic acid. The oxidative kinetic resolution of racemic ethyl 8-(benzyloxy)-6-hydroxyoctanoate **163** was carried out on Mn (III)-salen. The oxidative resolution of secondary alcohol afforded (*S*)-ethyl 8-(benzyloxy)-6-hydroxy-octanoate **163a** in high enantiomeric excess and in 47% yield and ethyl 8-(benzyloxy)-6-oxooctanoate **165**. The compound **163a** was deprotected by hydrogenation with the catalytic amount of Pd-C.

Then construction of five membered ring containing sulphide linkage was carried out by mesylation and refluxing with sodium sulphide, sulphur in DMF followed by ester hydrolysis to obtain lipoic acid **1**. The other enantiomer **2** was also synthesized by carring out similar reaction sequence using (*R*, *R*)-Mn (III)-salen.

3.1.5 References

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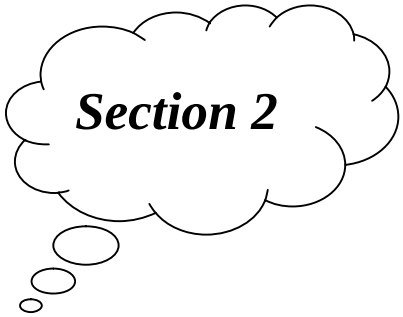
Chapter 3
Total synthesis of *α*-lipoic acid and development of synthetic methodology



Total synthesis of *α*-lipoic acid *via* chiron approach

3.2.1. Present work

3.2.1.1. Objective

α-Lipoic acid **1** is the cyclic disulfide of 6,8-di-mercapto-n-caprylic acid. It was first isolated by Reed *et al.* in 1950.[1] Both the antipodes of lipoic acid were obtained by resolution method in 1954, wherein it was also established that (*R*)-(+)-α-lipoic acid **1a** shows more bioactivity than (*S*)-(-)-α-lipoic acid **1b**.[2] Golding *et al*. determined the absolute configuration by synthesizing complementary enantiomer from *S*-malic acid.[3] (*R*)-(+)-α-Lipoic acid **1a** is vital cofactor widely distributed in many plants and animals. It exhibits wide variety of various biological and pharmaceutical activities. It has been reported to show inhibition of HIV-I replication in T-cells and HeLa-CD^+ at 37-70 µg/mL concentration.[4] Recently, it is also observed that lipoic acid glycol-conjugates show control on nonspecific adsorption of

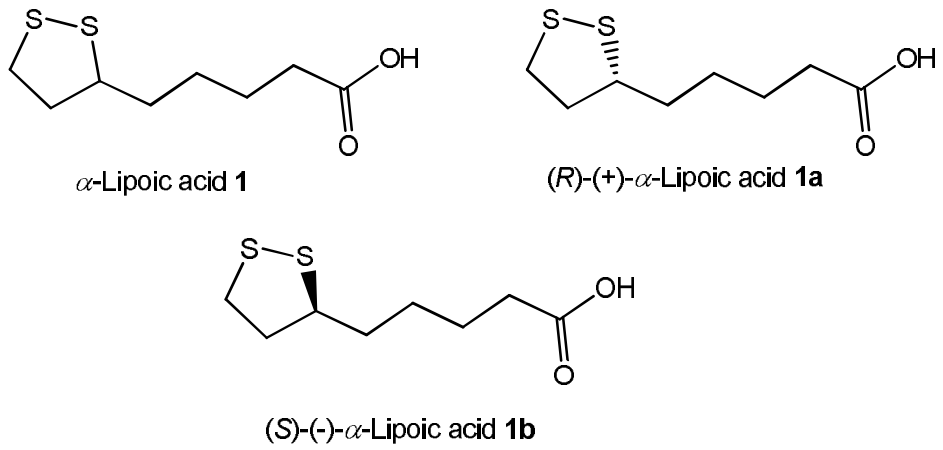


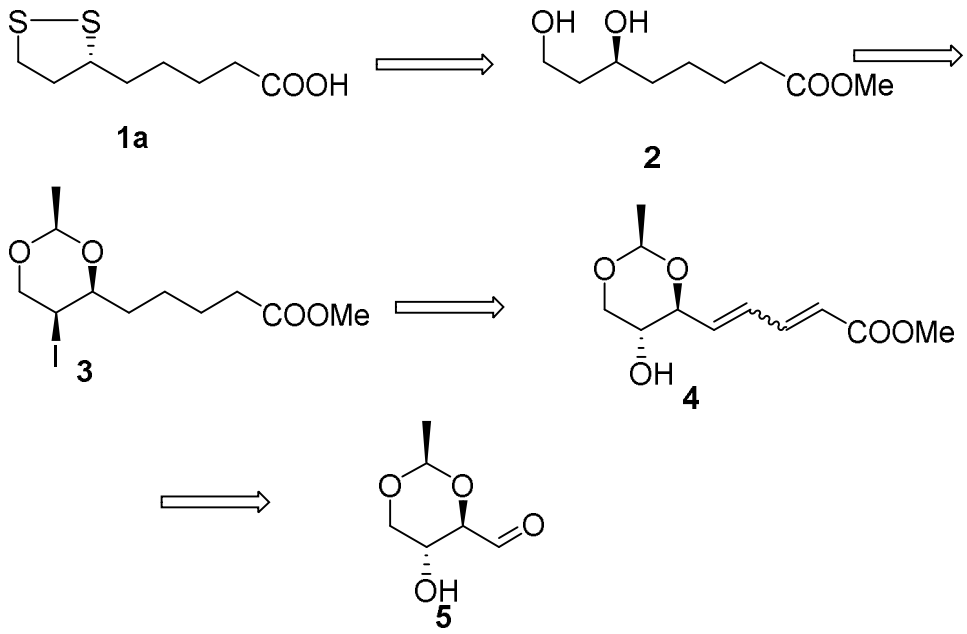
Figure1. Structures of racemic and chiral lipoic acid.

blood serum at biointerface for biosensors and biological applications.[5] It is a biological antioxidant which can scavenge free radicals and protect cells from oxidative damage.[6] It can act as antitumour agent.[7] It is an important growth factor and also a cofactor for the multi enzyme complex that catalyses decarboxylation of β-keto acids.[8] It is useful in treatment of cancer, inflammation, ischemia-reperfusion injury and as an antiaging agent.[9] Moreover, α-lipoic acid is used in treatment of alcoholic liver diseases,[10] mushroom poisoning,[11] metal poisoning,[12] diabetes and neurodegenerative disorders.[13]

These significant biological activities of (+)-α-lipoic acid **1a** are of great commercial importance which has made it an attractive target for synthetic organic chemists for decades and in the process many synthetic endeavours have been reported.[14] The synthesis of racemic

lipoic acid from cyclohexanone required 11 steps[14y] while the other route required 9 steps.[14z] Though these syntheses involved interesting chemistry and are novel synthetic routes, it was realised that there is scope for improvement and some of the critical reaction conditions which may not be viable at higher scale, should be avoided by devising alternate routes using chiral pool approach and chirality induction approach[15] where emphasis was on the use of simple, practical and environmentally benign reaction conditions.

3.2.1.2.. Retrosynthesis



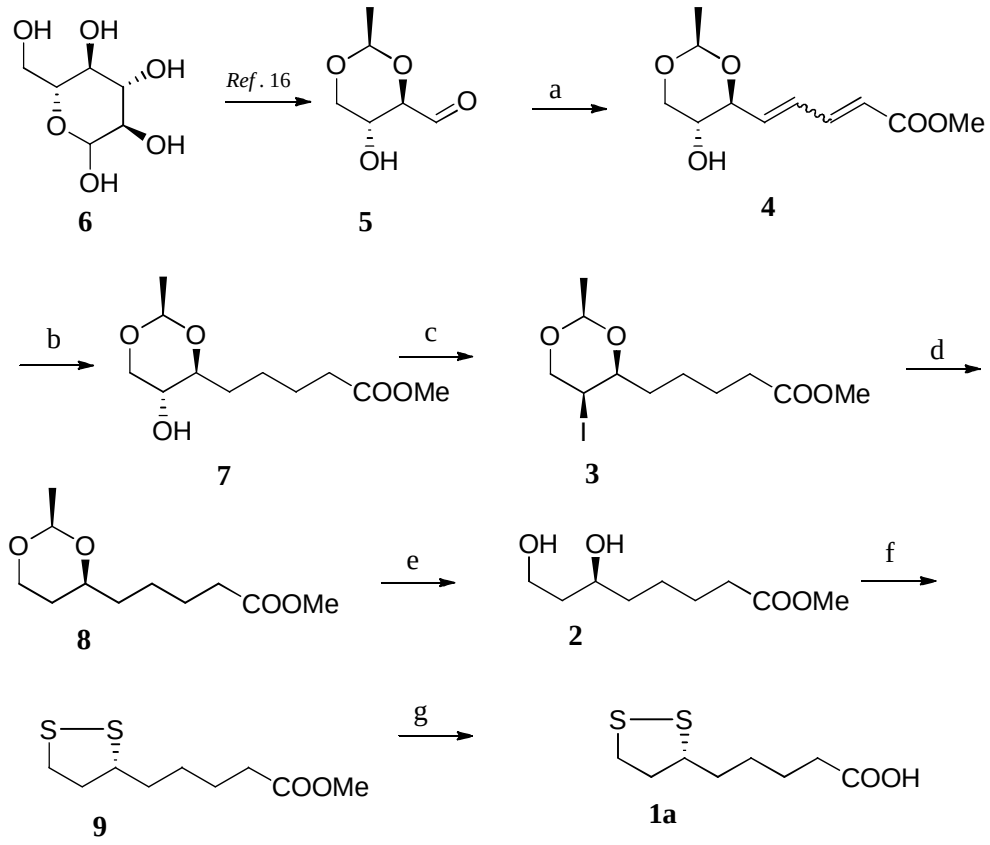
Scheme 4. Retrosynthetic analysis.

Retrosynthetic analysis for (+)-*α*-Lipoic acid **1a** is outlined in retrosynthetic analysis (Scheme 1). It was envisioned that (+)-*α*-lipoic acid **1a** can be accessed from 1,3-diol **2** by straight forward chemical transformations, which in turn can be obtained from iodo compound **3** by deiodination followed by deprotection. The iodo compound **3** can be easily accessed from unsaturated hydroxy ester **4** by saturation of double bonds followed by iodination. Unsaturated hydroxy ester **4** could be synthesized from chiral template of hydroxy aldehyde **5** by Wittig reaction. Synthesis of hydroxy aldehyde **5** from D-glucose is well documented.[16]

3.2.1.3. Results and discussion

In continuation of work on lipoic acid, enantiospecific synthesis of (+)-*α*-lipoic acid **1a** by chiron approach using inexpensive reagents, renewable raw materials and environmentally benign reaction conditions was acheived.

Synthesis of (+)-α-lipoic acid **1a** commenced with 4-carbon Wittig reaction of hydroxy aldehyde **5** by which it was converted to unsaturated hydroxy ester **4**, in 87% yield,[17] as an inseparable mixture of *cis* and *trans* isomers (Scheme 2). The IR spectrum showed a



Scheme 2. *Reagents and conditions:* a) Ph_3P=CH-CH=CHCOOMe, DCM, 5 h, 87%; b) H_2, Pd/C, MeOH, 2 h, 97%; c) Ph_3P, I_2, Im, xylene, 70 ^oC, 6 h, 73%; d) TEA, H_2, Raney Ni, MeOH, 5 h 94%; e) PTSA, MeOH 90%; f) i) MsCl, TEA, DCM; ii) $Na_2S.7H_2O$, DMF, 80 ^oC, 12 h, 81% over two steps; g) KOH, EtOH, 24 h, 77%.

characteristic band at 1732 cm^{-1} confirming presence of ester functionality. The ester methyl was further confirmed by appearance of singlet at δ 3.76 for three protons and its respective peak was observed at δ 51.61 in ^{13}C NMR. The olefinic protons were observed at δ 5.64 - 6.04 (m, 2 H), 6.13 - 6.64 (m, 1 H), 7.09 - 7.77 (m, 2 H) as multiplet including one proton adjacent to hydroxyl group, the respective carbons were also confirmed by their cooresponding peaks in ^{13}C NMR spectra in sp^2 region. The peaks were double in ^{13}C NMR due to *cis*/*trans* mixture. This mixture was subjected for saturation of the double bonds in **4**. This transformation was carried out using catalytic Pd/C in methanol under hydrogen

atmosphere to afford 97% yield of hydroxy ester **7**.[18] The product **7** formation was confirmed by ^{1}H NMR, where the peaks corresponding to olefinic protons were at δ 5.64 - 6.04 (m, 2 H), 6.13 - 6.64 (m, 1 H), 7.09 - 7.77 (m, 2 H) in compound **4**, were disappeared and new peaks at δ 1.37 - 1.73 (m, 5 H) and 1.77 - 1.94 (m, 2 H) corresponding to one OH proton and six protons as multiplates. The triplet for two protons in allylic region *i.e.* δ 2.34 (t, *J* = 7.3 Hz, 2 H) confirmed the presence of CH_2 group adjacent to ester functionality. The ^{13}C NMR also confirmed the absence of peaks in the sp^2 region and appearance of new peaks at δ 24.49 (CH_2), 24.82 (CH_2), 31.19 (CH_2), 33.88 (CH_2) for four CH_2 groups. The HRMS value for this compound was found to be 255.1204 (M+Na).

Hydroxy ester **7** was converted to iodo derivative **3** by treatment with I_2, PPh_3 and imidazole in xylene at 80 ^{o}C for 3 h in 73% yield. The IR spectrum showed the absence of band at 3467 cm^{-1} corresponding to hydroxyl group in **7**. ^{1}H NMR confirmed the there is shift in δ value of CH proton adjacent to hydroxyl group from δ 3.39 – 3.50 to 2.53- 2.82 in **3** as multiplet for one proton. This was further confirmed by ^{13}C NMR where same trend of shifting in the value of this corresponding carbon peak was observed from δ 65.47 to 37.64. The HRMS was observed at m/z: 365.0226 $(M+Na)^{+}$.

The next immediate concern was the transformation of iodo ester **3** into the corresponding ester **8**. Accordingly, the iodo group in this iodoester **3** was removed using Raney Ni in methanol under hydrogen atmosphere to provide deiodinated ester **8** in 94% yield. The ^{1}H NMR spectrum showed one proton corresponding to ICH was shifted from δ 2.53-2.82 in the range at δ 1.34-1.76 for 8 protons as multiplet and and one new peak for an extra CH_2 was observed in ^{13}C NMR which was confirmed by DEPT and hence removal of iodine from the compound. The HRMS value was observed at m/z: m/z: 239.1254 $(M+Na)^{+}$.

The acetal group in ester **8** was subsequently deprotected with PTSA in methanol to obtain 1,3-diol **2** in 90% yield.[19] The IR spectrum of **2** revealed the presence of band at 3469 cm^{-1}and carbonyl absorption at 1731 cm^{-1}. The ^{1}H NMR spectrum showed the disappearance of doublet for methyl protons at δ 1.31 (*J* = 5.1 Hz) and quartet for one proton at δ 4.67 (*J* = 5.1 Hz). Their respective peaks in the ^{13}C NMR at δ 21.21 and 98.92 were also disappeared confirming deprotection of acetal group. The HRMS value was found to be 213.1097 $(M+Na)^{+}$.

The diol **2** is the well known intermediate for the synthesis of *R*-(+)-Lipoic acid and was converted in to the final target molecule by a series of reactions. The 1,3-diol **2** was mesylated using methanesulphonyl chloride and triethylamine in DCM. The dimesylate derivative thus obtained was directly treated with sodium sulphide in DMF at 80 ^{o}C to

convert it into lipoate ester **9** in 81% yield. The lipoate ester **9** thus obtained was hydrolyzed using KOH in ethanol to afford (+)-*α*-lipoic acid **1a** in 77% yield. The spectral data of (+)-*α*-lipoic acid **1a** was in good agreement with reported one.[14]

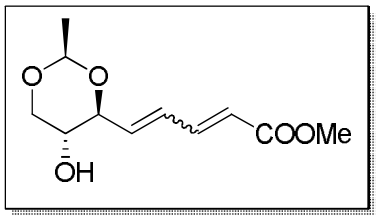
3.2.3. Conclusion

In conclusion, short synthetic route for the total synthesis of (+)-*α*-lipoic acid **1a** from hydroxy aldehyde **5** in 7 steps is developed. The key reactions involved in synthesis are Wittig reaction, iodination and hydrogenation which are simple, requiring inexpensive reagents. Also, the synthesis decribes use of inexpensive reagents and renewable raw materials which have merits over previous reports from this group and provides scope for scale up and minimization of number of purification steps which is highly desirable while performing reactions at a higher scale.

3.2.6. Experimental section

Methyl (2*E*,4*E*)-5-((2*R*,4*S*,5*R*)-5-hydroxy-2-methyl-1,3-dioxan-4-yl)penta-2,4-dienoate (4)

In a single necked, round-bottomed flask, fitted with a nitrogen inlet, aldehyde **5** (8.03 gm, 55 mmol) was taken in DCM (80 mL). To this solution, Wittig ylide (Ph_3P=CH-CH=CHCOOMe) (18 gm, 60.5 mmol) was added. The reaction mixture was stirred for 5 h at room temperature. After completion of reaction (monitored by TLC), solvent was removed under reduced pressure. The crude product was purified by column chromatography over silica with ethyl acetate/ petroleum ether (1:4) as eluent to yield 10.9 g inseparable mixture of *cis, trans* isomers of unsaturated ester **4** as a colourless liquid in 87% yield. R_f(EA: PE/2:3): 0.3.



Yield: 87%

Chemical Formula: $C_{11}H_{16}O_5$

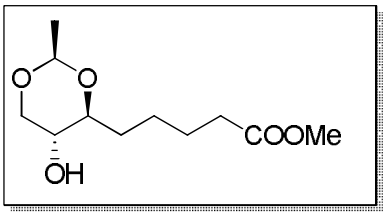
Molecular Weight: 228.24

IR ($CHCl_3$) ν_{max}: 3431, 3019, 1732, 757 cm^{-1}

(for *cis-trans* mixture) ^{1}H NMR (200 MHz, $CDCl_3$+ CCl_4): δ 1.18 - 1.52 (m, 3 H), 2.11 - 2.40 (m, 1 H), 3.32 - 3.60 (m, 2 H), 3.76 (s, 3 H), 3.87 - 4.47 (m, 2 H), 4.03 - 4.51 (m, 2 H), 4.63 - 4.85 (m, 1 H), 5.64 - 6.04 (m, 1 H), 6.13 - 6.64 (m, 1 H), 7.09 - 7.77 (m, 2 H)

(for *cis-trans* mixture) ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 20.34, 51.48, 51.61, 64.94, 65.25, 70.40, 70.61, 77.97, 80.74, 98.55, 98.63, 121.34, 122.85, 128.68, 129.18, 130.05, 131.82, 132.02, 135.87, 138.65, 139.75, 144.03, 167.33, 167.38.

Methyl 5-((2*R*,4*S*,5*R*)-5-hydroxy-2-methyl-1,3-dioxan-4-yl)pentanoate (7)



To a solution of **4** (4 g, 17.5 mmol) in dry methanol (40 mL) was added Pd/C (0.05 g) and the reaction mixture was stirred under hydrogen atmosphere (60 *psi*) for 2 h at 25 ^{o}C. After the completion of the reaction (monitored by TLC), the reaction mixture was filtered over celite and the filtrate was concentrated under reduced pressure to provide the reduced compound, which was purified by column chromatography using ethyl acetate/ petroleum ether (1:4) to obtain 3.95 g pure compound **7** as a colourless liquid. R_f (EA: PE/2:3): 0.3.

Yield: 97%

Chemical Formula: $C_{11}H_{20}O_5$

Molecular Weight: 232.28

Optical rotation: $[\alpha]_D^{25}$: -27.6 (c 1.02, Chloroform)

IR ($CHCl_3$) ν_{max}: 3467, 3010, 1733, 754 cm^{-1}

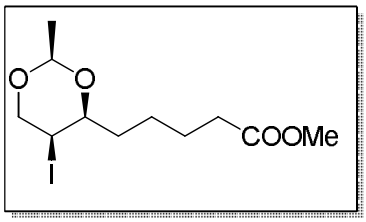
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (d, *J* = 5.0 Hz, 3 H), 1.37 - 1.73 (m, 5 H), 1.77 - 1.94 (m, 2 H), 2.34 (t, *J* = 7.3 Hz, 2 H), 3.24 - 3.37 (m, 2 H), 3.39 - 3.50 (m, 1 H), 3.67 (s, 3 H), 4.07 (dd, *J* = 10.5, 5.0 Hz, 1 H), 4.63 (q, *J* = 5 Hz, 1 H)

^{13}C NMR (100 MHz $CDCl_3$): δ 20.50, 24.49, 24.82, 31.19, 33.88, 51.49, 65.47, 70.82, 81.15, 98.82, 174.34

ESIMS (m/z): 254.88 $(M+Na)^+$

HRMS calculated for $C_{11}H_{20}O_5$:255.1208; found 255.1204 $(M+Na)^+$.

Methyl 5-((2*R*,4*S*,5*S*)-5-iodo-2-methyl-1,3-dioxan-4-yl)pentanoate (3)



A mixture of alcohol **7** (2 g, 8.61 mmol), PPh_3 (3.40 g, 12.9 mmol), imidazole (1.2 g, 17.23 mmol) and I_2 (2.63 g, 10.35 mmol) was stirred under nitrogen in anhydrous xylene (40 mL) at 70 ^{o}C for 6 h. After completion of the

reaction (monitored by TLC), the reaction mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified on silica gel by eluting with light ethyl acetate/ petroleum ether (1:9) to afford iodo ester compound **3** (2.16 g, 73%) as a colourless syrup. R_f (EA: PE/1:4): 0.7.

Yield: 73%

Chemical Formula: $C_{11}H_{19}IO_4$

Molecular Weight: 342.17

IR ($CHCl_3$) ν_{max}: 2955, 1735, 763 cm^{-1}

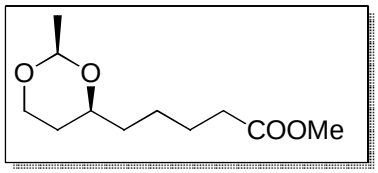
Optical rotation: $[\alpha]_D^{25}$: +51.6 (c 1.1, chloroform);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.09 - 1.89 (m, 9 H), 2.33 (t, *J* = 1.0 Hz, 2 H), 2.53 - 2.82 (m, 1 H), 3.67 (s, 3 H), 3.89 - 4.40 (m, 3 H), 4.75 (q, *J* = 5.1 Hz, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.87, 23.66, 24.55, 33.48, 33.79, 37.64, 51.51, 74.01, 78.07, 100.01, 173.93

HRMS calculated for $C_{11}H_{19}IO_4$: 365.0226, found 365.0220 $[M+Na]^+$.

Methyl 5-((2*R*,4*S*)-2-methyl-1,3-dioxan-4-yl)pentanoate (8)



To a solution of iodo compound **3** (1 g, 29.2 mmol) and triethylamine (590 mg, 58.4 mmol) in dry methanol was added freshly prepared Raney nickel (0.05 g) and the reaction mixture was stirred under an atmosphere of H_2 (60 psi) for 5 h at 25°C. After the completion of the reaction (monitored by TLC), the reaction mixture was filtered over celite and the filtrate was concentrated under reduced pressure to provide the reduced compound, which was purified by column chromatography using ethyl acetate/ petroleum ether (1:9) to obtain 0.6 g pure dehalogenated compound **8** in 94% yield as colourless liquid. R_f (EA: PE/1:4): 0.5.

Yield: 94%

Chemical Formula: $C_{11}H_{20}O_4$

Molecular Weight: 216.28

Optical rotation: $[\alpha]_D^{25}$: -19.7 (c 1.02, chloroform)

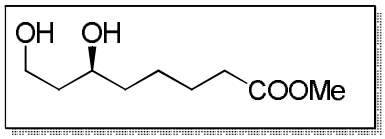
IR ($CHCl_3$) ν_{max}: 3009, 1734, 754 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (d, *J* = 5.1 Hz, 3 H), 1.34 - 1.76 (m, 8 H), 2.22 - 2.40 (m, 2 H), 3.51 - 3.64 (m, 1 H, OC*Ha*H), 3.67 (s, 3 H), 3.76 (dd, 1 H, OCH*Hb*), 3.98 - 4.17 (m, 1 H), 4.67 (q, *J* = 5.1 Hz, 1 H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.21, 24.53, 24.83, 31.09, 33.95, 35.60, 51.45, 66.50, 76.36, 98.92, 174.09

HRMS calculated for $C_{11}H_{20}O_4$: 239.1259; found: 239.1254 $(M+Na)^+$.

Methyl (*S*)-6,8-dihydroxyoctanoate (2)



To a cold stirring solution of acetal ester **8** (500 mg, 2.31 mmol) in methanol (10 mL) was added PTSA (44 mg, 0.23 mmol) and stirred at room temperature for 2 h. After completion of reaction (monitored by TLC), reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of crude material by flash column chromatography using ethyl acetate/ petroleum ether (2:3) afforded 0.4 g of diol **2** as colorless viscous liquid. R_f(EA: PE/2:3): 0.2

Yield: 90%

Chemical Formula: $C_9H_{18}O_4$

Molecular Weight: 190.24

Optical rotation: $[\alpha]_D^{25}$ = -4.2 (*c* = 1, $CHCl_3$) {Lit.[20] $[\alpha]_D^{25}$: -3.8 (*c* 1.0, $CHCl_3$)}

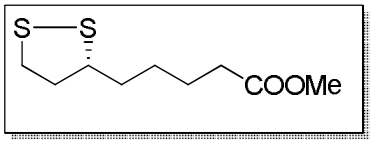
IR ($CHCl_3$) ν_{max}: 3469, 3020, 2400, 1731, 757 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24 - 1.82 (m, 8 H), 2.32 (t, *J* = 1.0 Hz, 2 H), 2.99 (br. s., 2 H), 3.64 (s, 3 H), 3.70 - 3.99 (m, 3 H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.69, 24.95, 33.89, 37.20, 38.24, 51.48, 61.45, 71.50, 174.28

HRMS calculated for $C_9H_{18}O_4$: 213.1103, found: 213.1097 $(M+Na)^+$.

(*5R*)-Methyl 5-(1,2-dithiolan-3-yl)pentanoate or (*R*)-methyl lipoate (9)



To a solution of methyl 6,8-dihydroxyoctanoate **2** (100 mg, 0.49 mmol) in anhydous CH_2Cl_2 (5 mL) was added Et_3N (319 mg, 0.98 mmol) at 0 °C followed by $MeSO_2Cl$ (463 mg, 0.98 mmol) dropwise. After completion of reaction (monitored by TLC), reaction was quenched with water (5 mL) and the organic layer was washed with aq. $NaHCO_3$ (2%, 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude compound was used directly in the next reaction. The solution of crude mesylate, finely ground $Na_2S{\cdot}H_2O$ (410 mg, 0.6 mmol) and sulfur (54 mg, 0.6 mmol) in anhyd DMF (5 mL) was heated at 80 °C for 24 h and then stirred at room temperature for 1h. The reaction mixture was poured into ice-cold water (15 mL) and was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure to furnish 94 mg (81%) of **9** as yellow oil. R_f (EA: PE/1:4): 0.6.

Yield: 81%

Chemical Formula: $C_9H_{16}O_2S_2$

Molecular Weight: 220.35

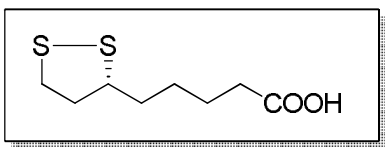
Optical rotation: $[\alpha]_D^{25}$: +63 (*c* = 0.22, $CHCl_3$) {Lit.[21] $[\alpha]_D^{25}$ = +64 (*c* 0.23, $CHCl_3$)}

IR ($CHCl_3$) ν_{max}: 2960, 1735, 757 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 - 1.57 (m, 2 H), 1.58 - 1.78 (m, 4 H), 1.85 - 1.98 (m, 1 H), 2.33 (t, *J* = 7.3 Hz, 2 H), 2.42 - 2.53 (m, 1 H), 3.06 - 3.25 (m, 2 H), 3.53 - 3.62 (m, 1 H), 3.68 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.64, 28.73, 33.82, 34.57, 38.46, 40.19, 51.51, 56.30, 173.92.

(*R*)-5-(1,2-Dithiolan-3-yl)pentanoic acid or (*R*)-α-Lipoic acid (1a)[2]



To a solution of **9** (80 mg, 0.341 mmol) in MeOH (5 mL) was added aqueous KOH (0.1 M, 4 mL) and stirred at room temperature for 24 h. MeOH was evaporated under reduced pressure and the reaction mixture was washed with Et_2O (2 x 10 mL) and the aqueous layer was acidified carefully with 6N HCl to pH 2.

The product was extracted with Et_2O (2 x 10 mL) and the combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated on a rotary evaporator under reduced pressure to afford crude lipoic acid. The resulting residue was purified by flash column chromatography (silica gel) using ethyl acetate/petroleum ether (15:85) as an eluent, to afford **1a** as yellow solid. R_f (EA: PE/1:2): 0.3.

Yield: 77%

Chemical Formula: $C_8H_{14}O_2S_2$

Molecular Weight: 206.32

mp: 48 -49 ^oC°C, Lit.[14x] 48 ^oC.

Optical rotation: 1a: $[\alpha]_D^{25}$: +103.18 (*c* 0.9, Benzene); {Lit.[2] $[\alpha]_D^{25}$ = +106 (*c* 1, Benzene)}

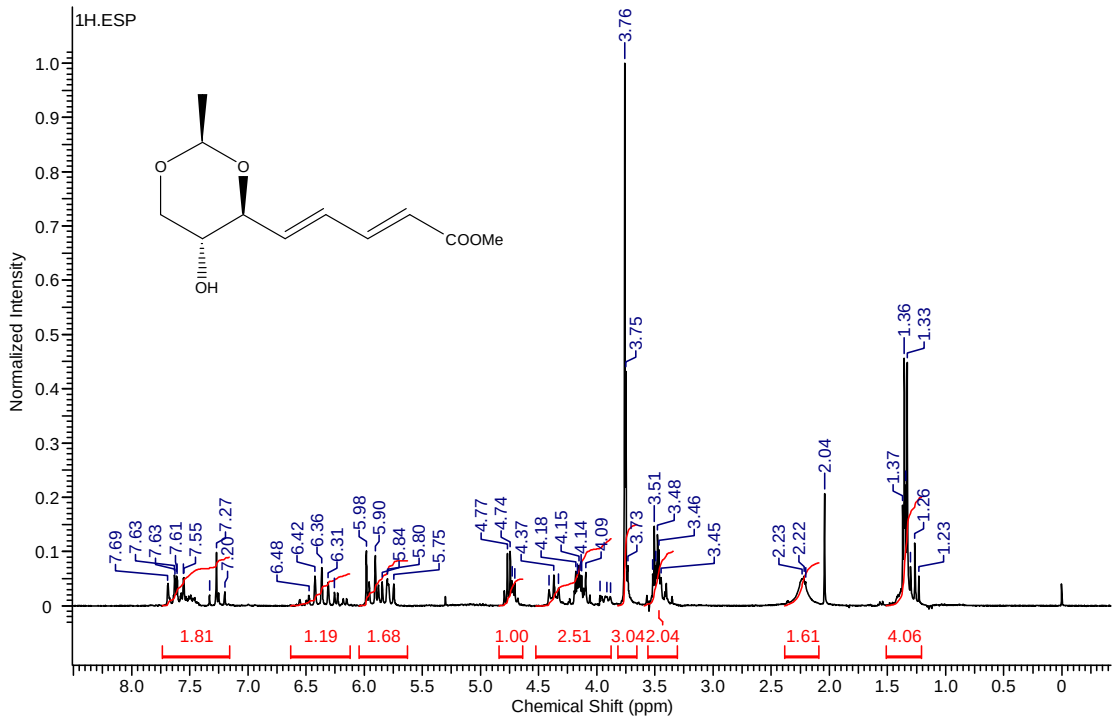
IR ($CHCl_3$) ν_{max}: 3021, 2928, 1709, 1409, 1216, 758 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 - 1.59 (m, 2 H), 1.62 - 1.79 (m, 4 H), 1.86 - 1.99 (m, 1 H), 2.38 (t, *J* = 7.4 Hz, 2 H), 2.43 - 2.53 (m, 1 H), 3.06 - 3.27 (m, 2 H), 3.51 - 3.67 (m, 1 H)

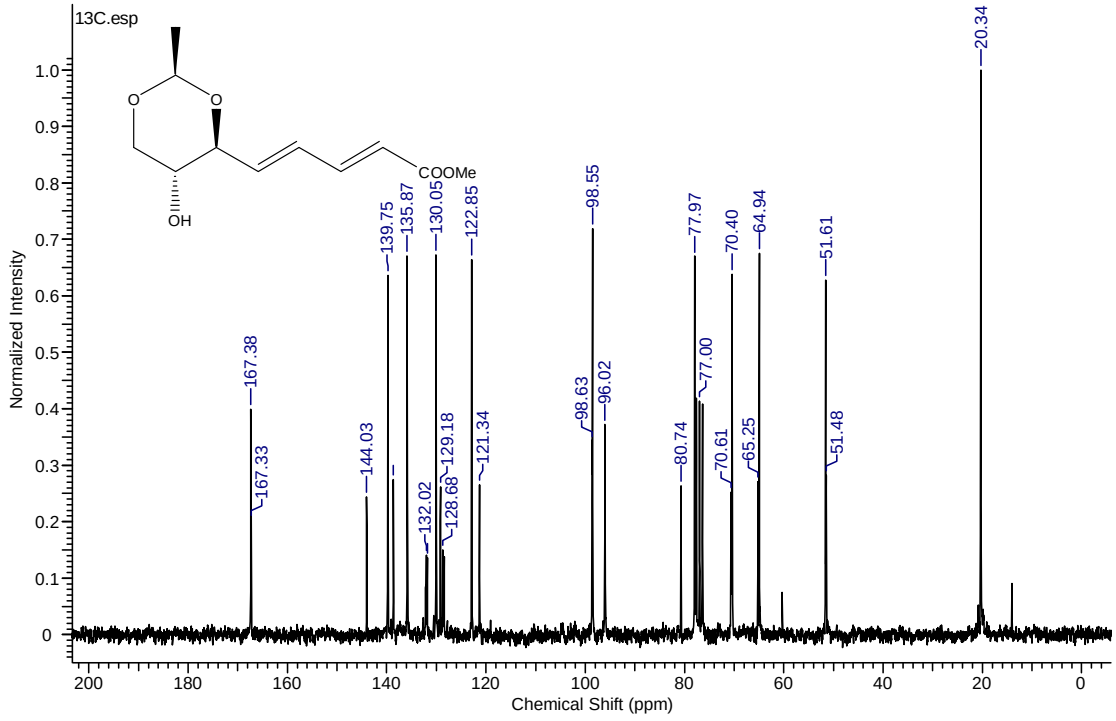
^{13}C NMR (100 MHz, $CDCl_3$): δ 24.34, 28.64, 33.74, 34.55, 38.47, 40.19, 56.25, 179.50; **ESIMS (m/z):** 204.95 $(m-1)^+$.

3.2.4. Spectra

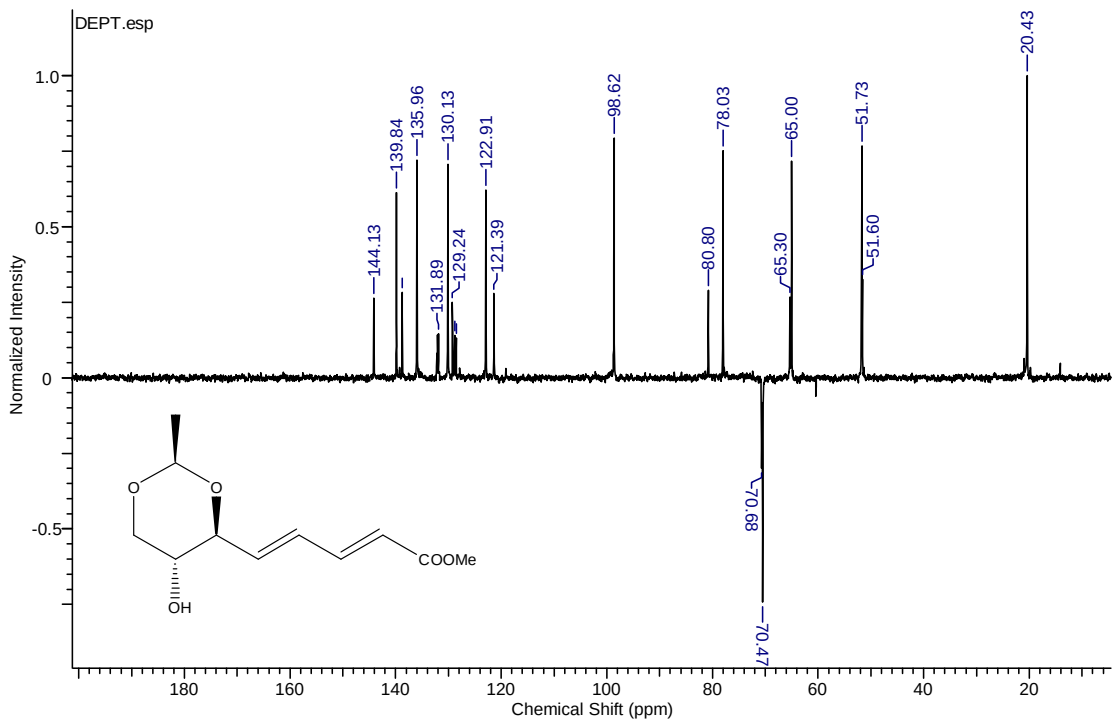
^{1}H-NMR spectrum of compound **4** ($CDCl_3$ + CCl_4, 200 MHz)



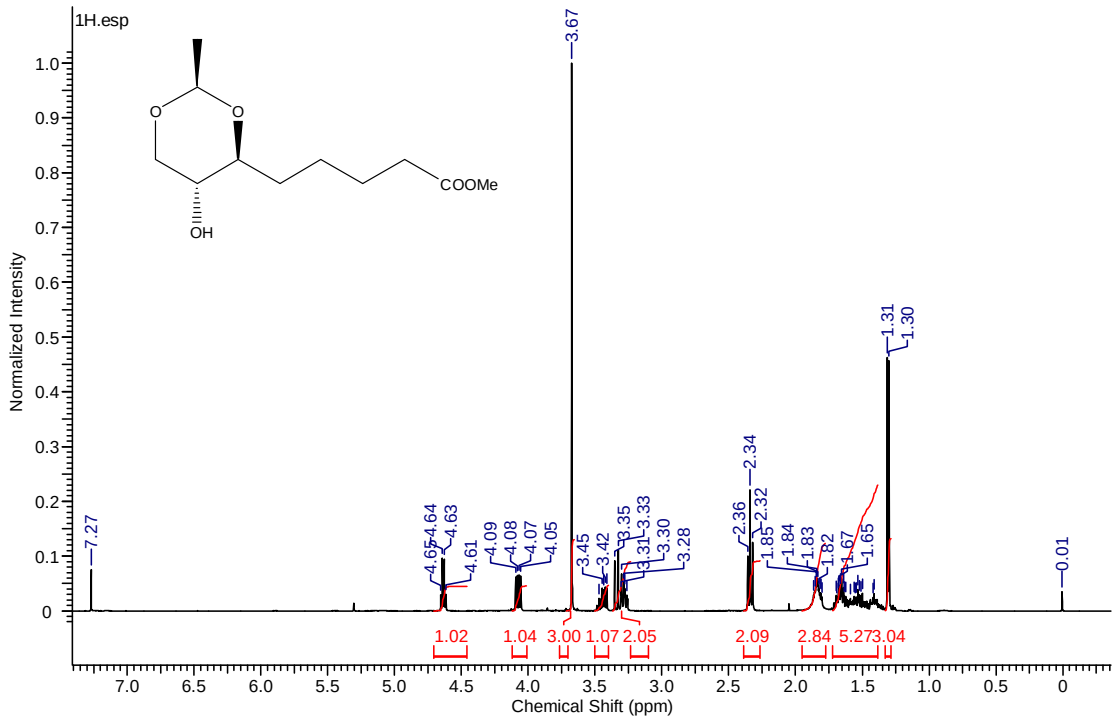
^{13}C-NMR spectrum of compound **4** ($CDCl_3$ + CCl_4, 50 MHz)



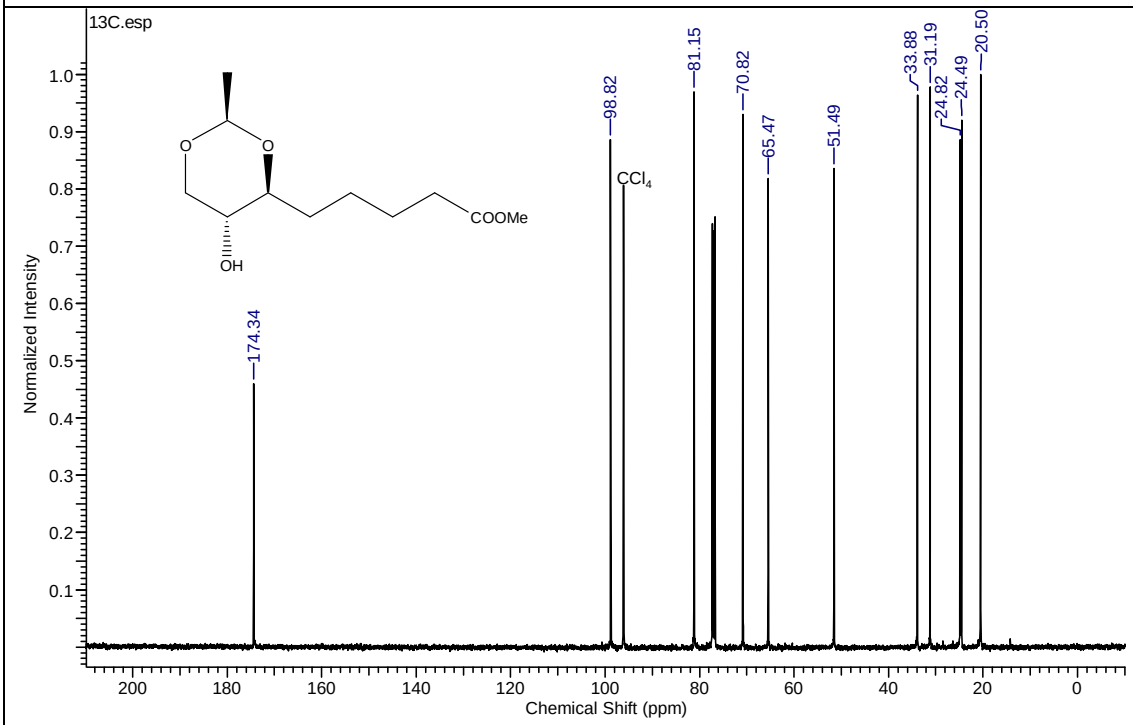
DEPT spectrum of compound **4** ($CDCl_3$ + CCl_4, 50 MHz)



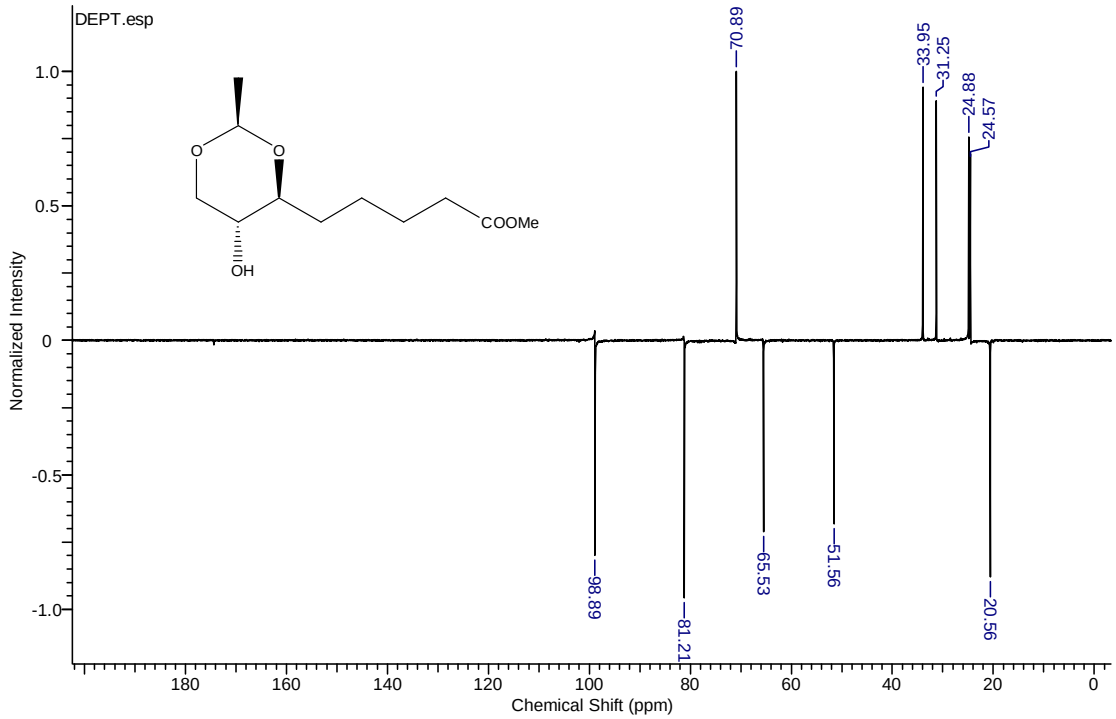
^1H spectrum of compound **7** ($CDCl_3$ + CCl_4, 50 MHz)



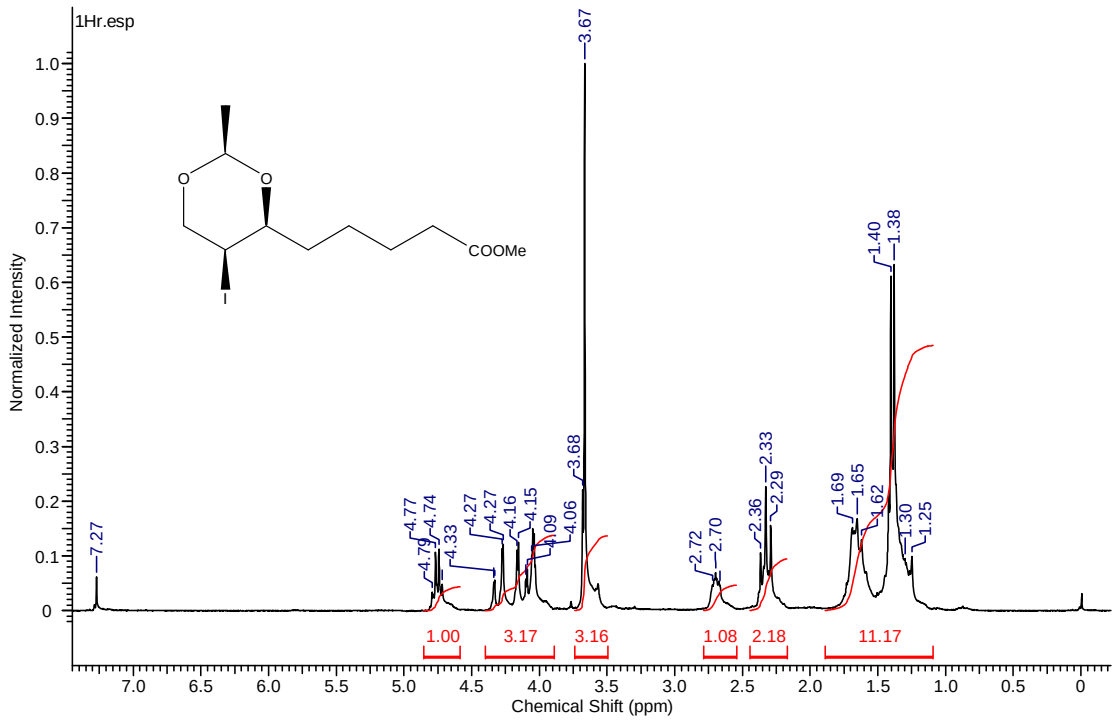
^{13}CNMR spectrum of compound **7** ($CDCl_3$ + CCl_4, 200 MHz)



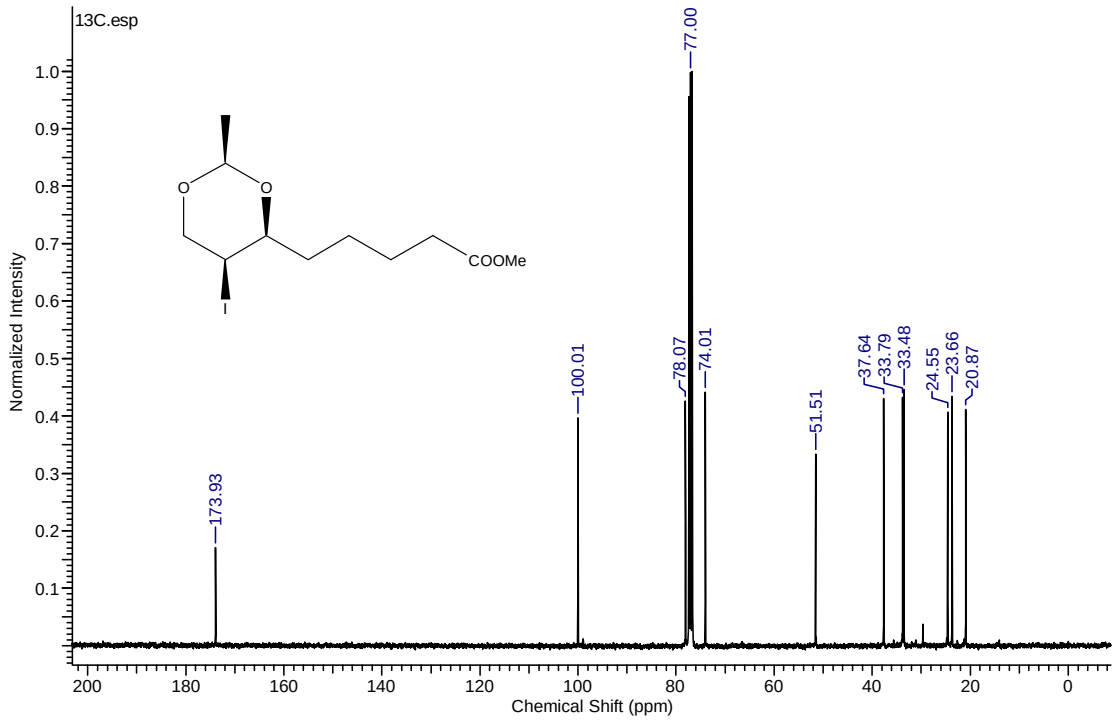
DEPT-NMR spectrum of compound **7** ($CDCl_3$ + CCl_4, 200 MHz)



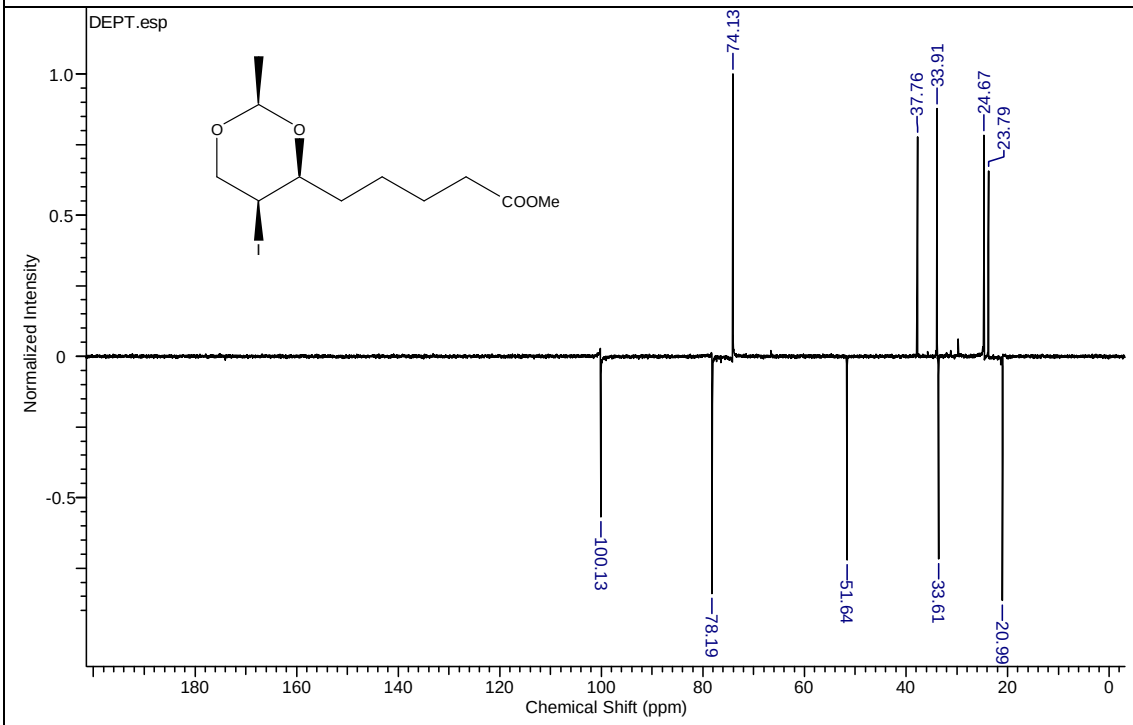
^{1}H spectrum of compound **3** ($CDCl_3$, 50 MHz)



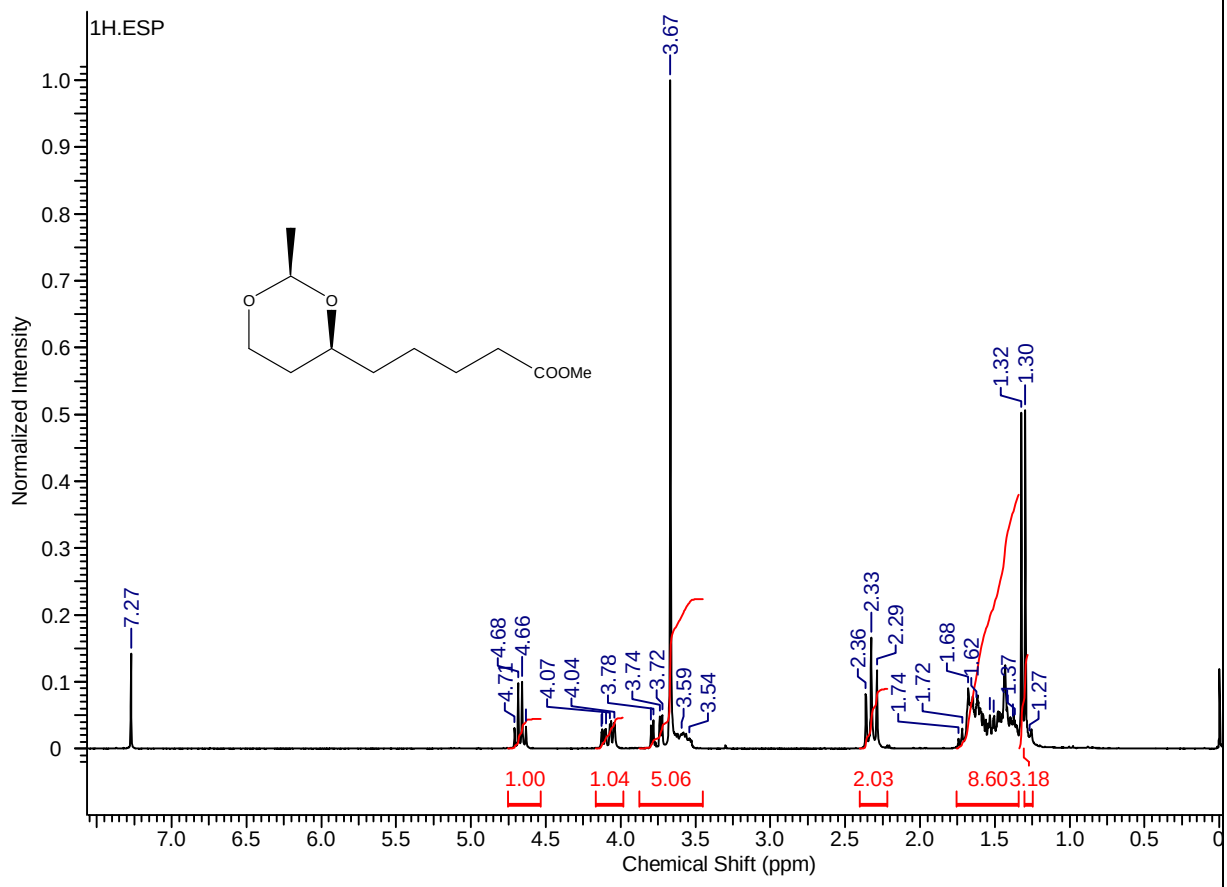
^{13}C-NMR spectrum of compound **3** ($CDCl_3$, 200 MHz)



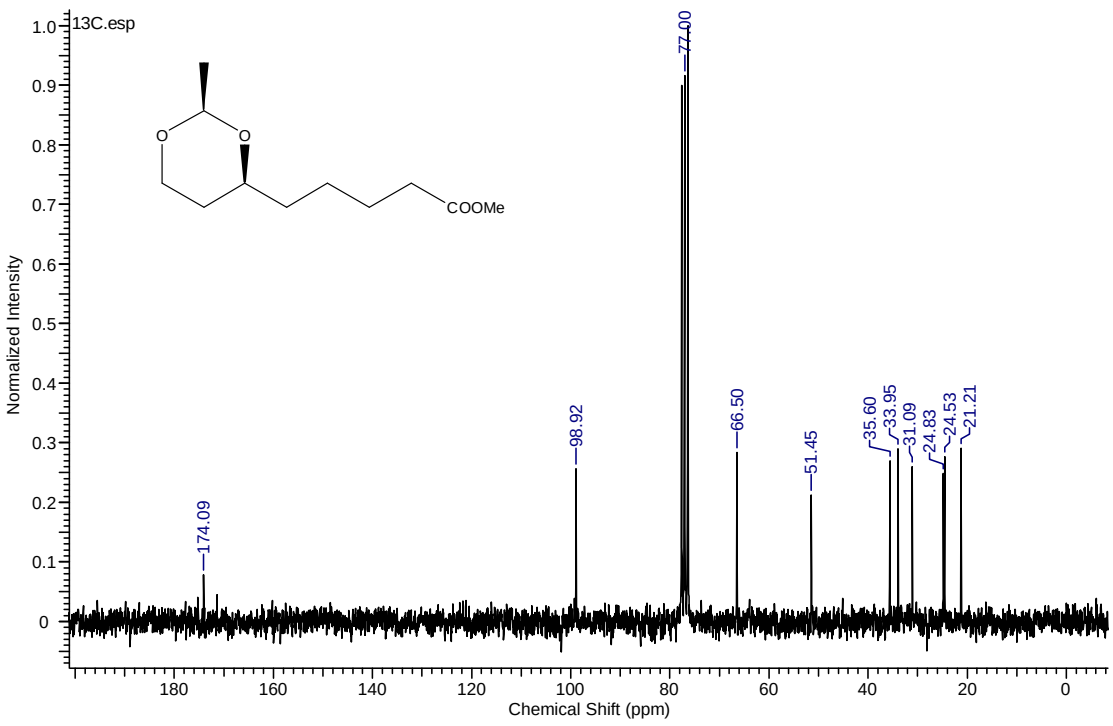
DEPT-NMR spectrum of compound **3** ($CDCl_3$, 200 MHz)



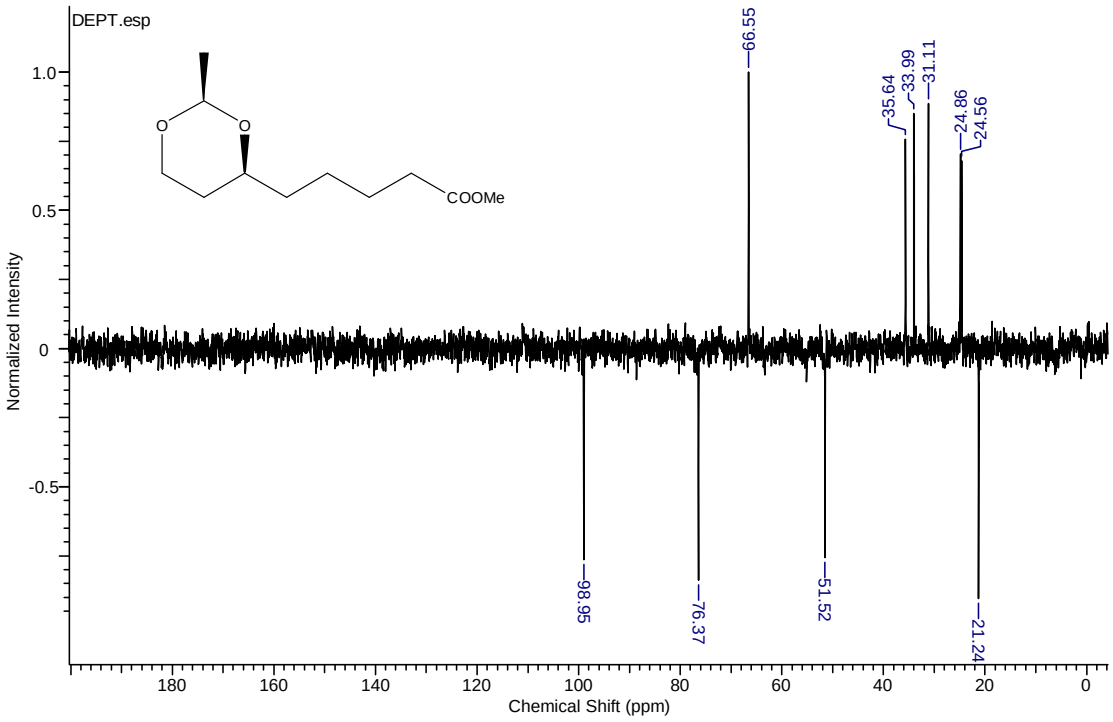
^{1}H-NMR spectrum of compound **8** ($CDCl_3$, 200 MHz)



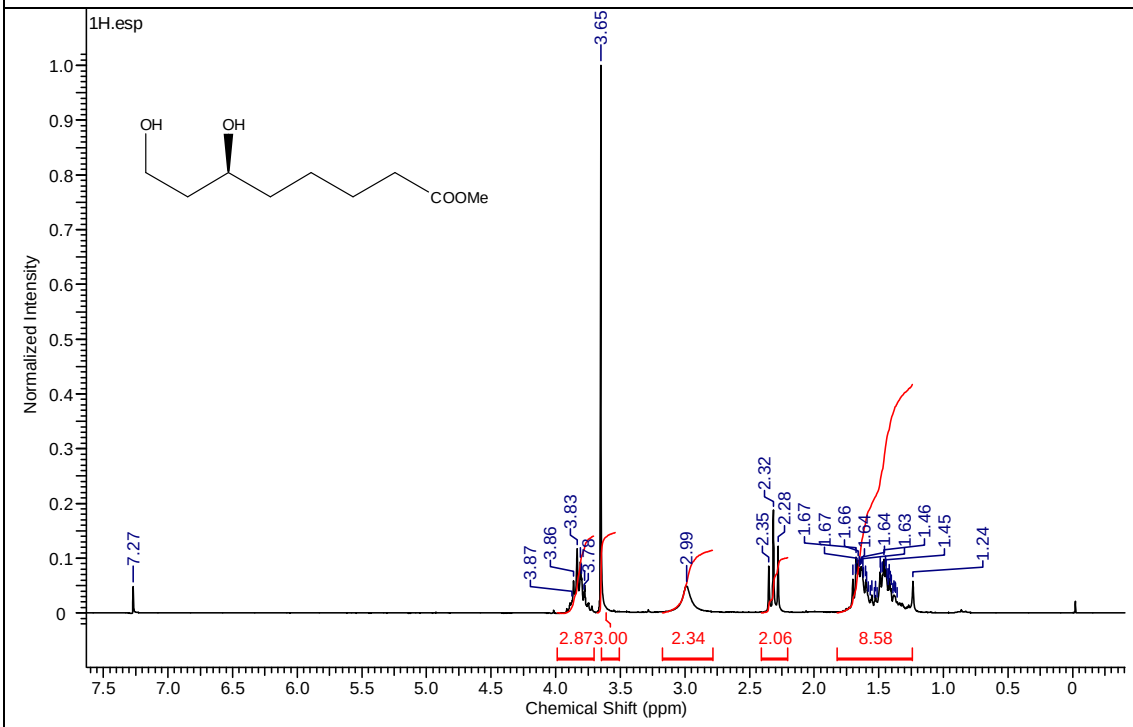
^{13}C-NMR spectrum of compound **8** ($CDCl_3$, 200 MHz)



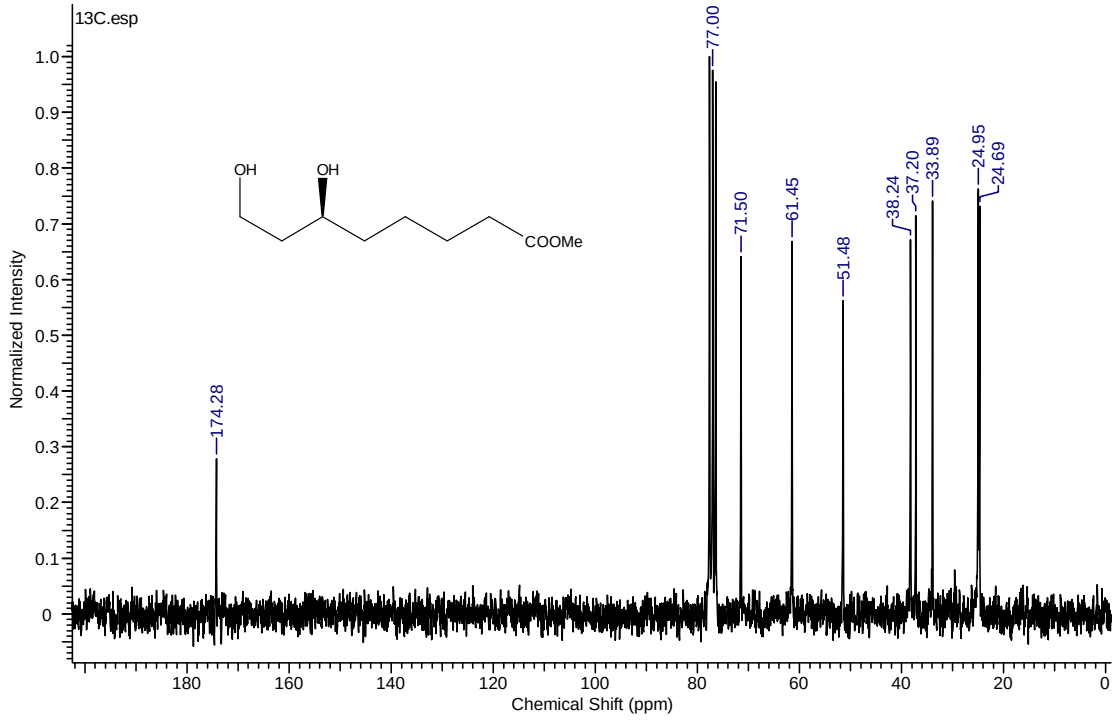
DEPT-NMR spectrum of compound **8** ($CDCl_3$, 200 MHz)



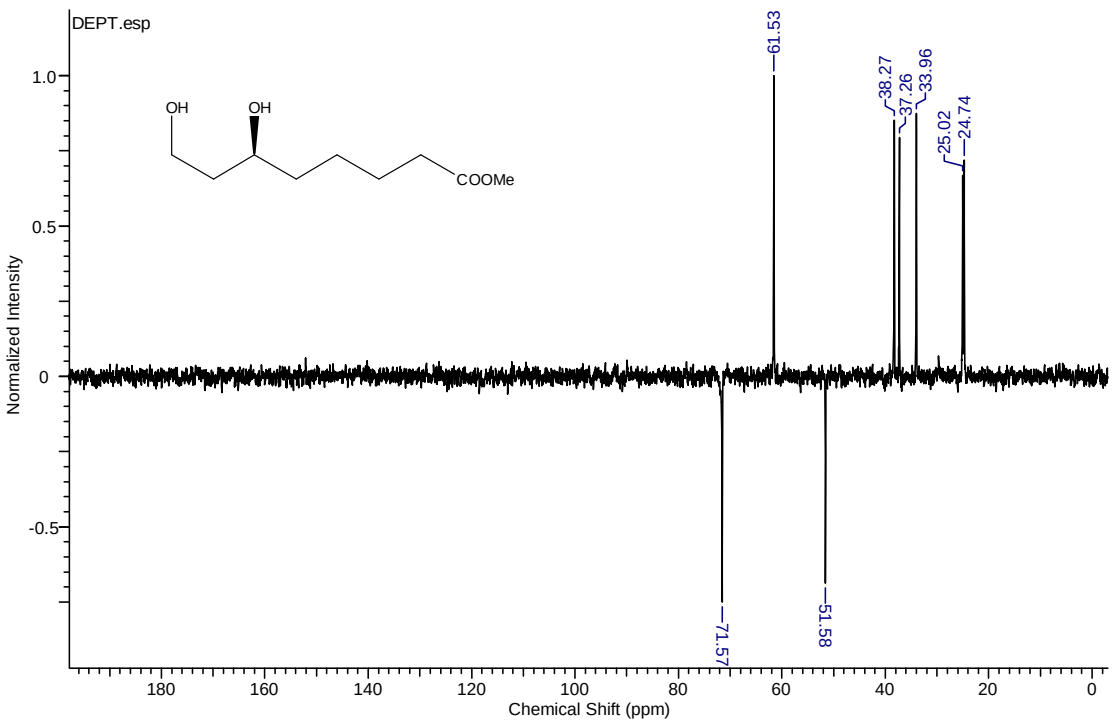
^{1}H-NMR spectrum of compound **2** ($CDCl_3$, 200 MHz)



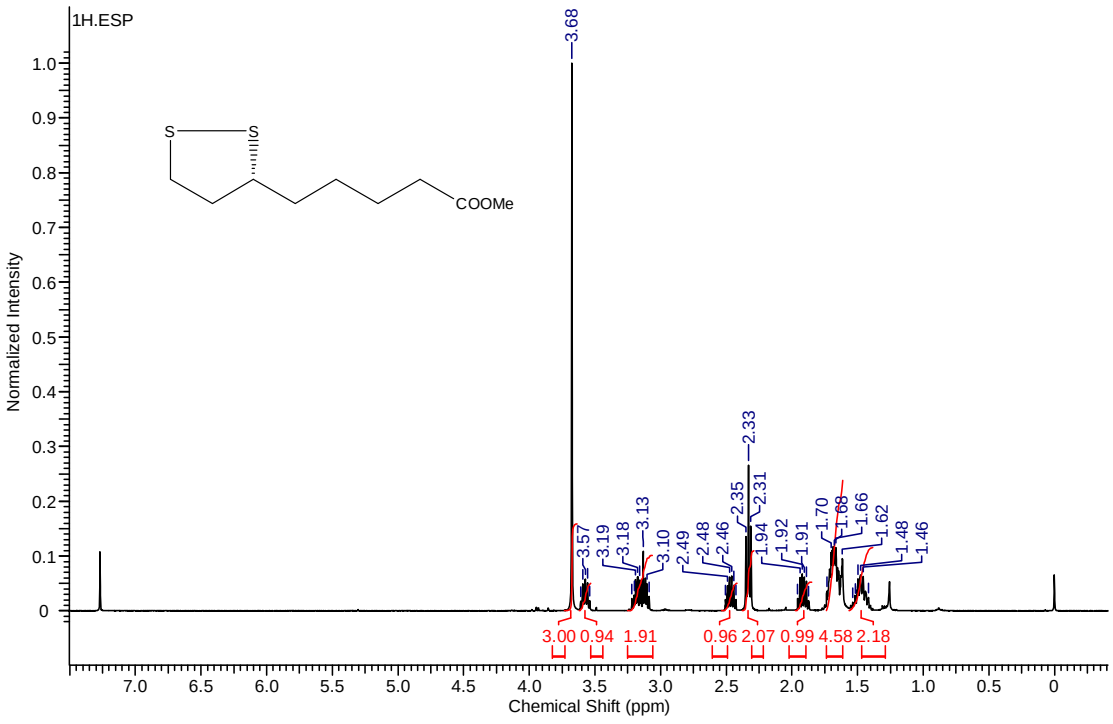
^{13}C-NMR spectrum of compound **2** ($CDCl_3$, 200 MHz)



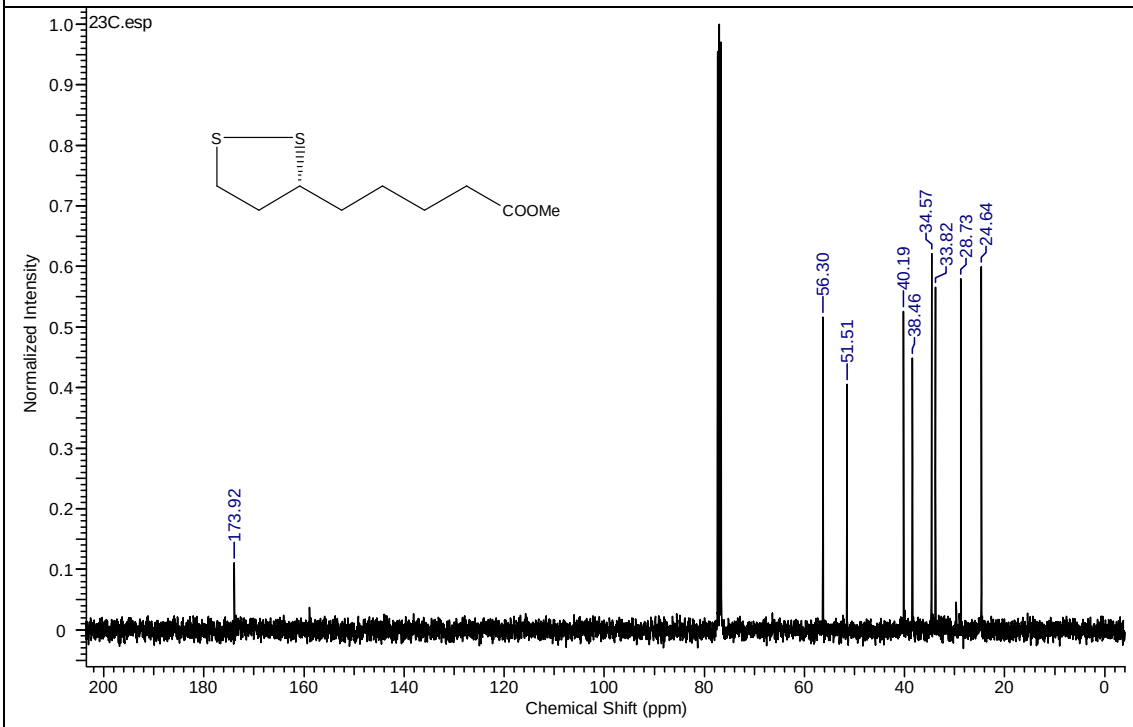
DEPT-NMR spectrum of compound **2** ($CDCl_3$, 200 MHz)



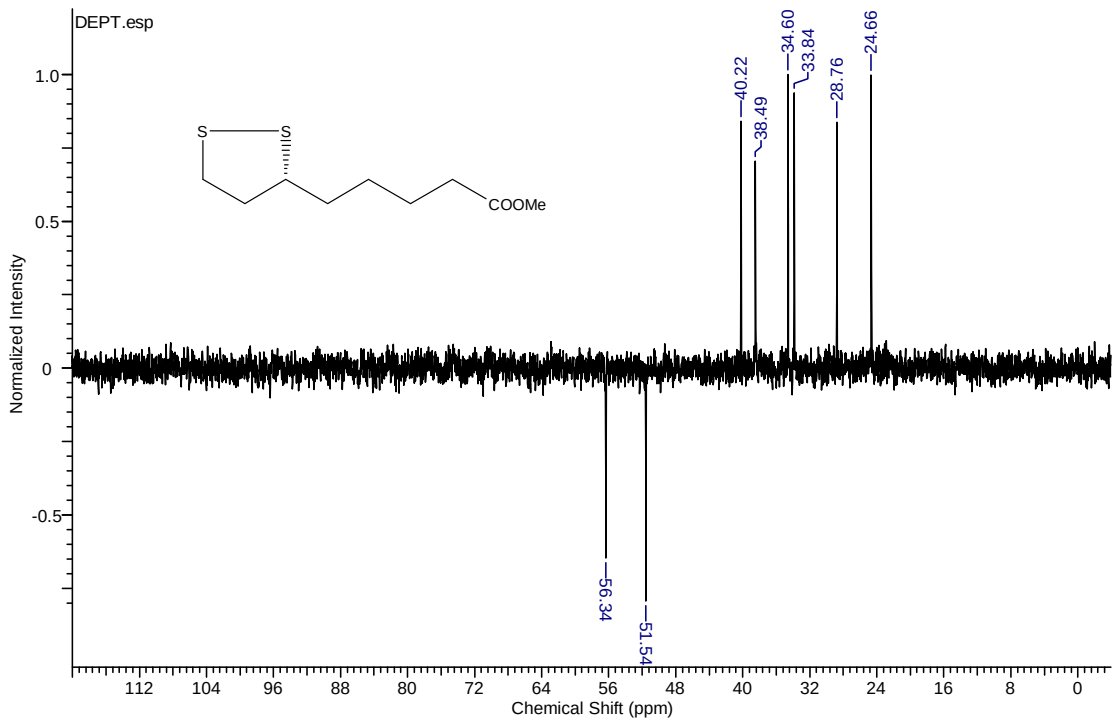
^{1}H-NMR spectrum of compound **9** ($CDCl_3$, 200 MHz)



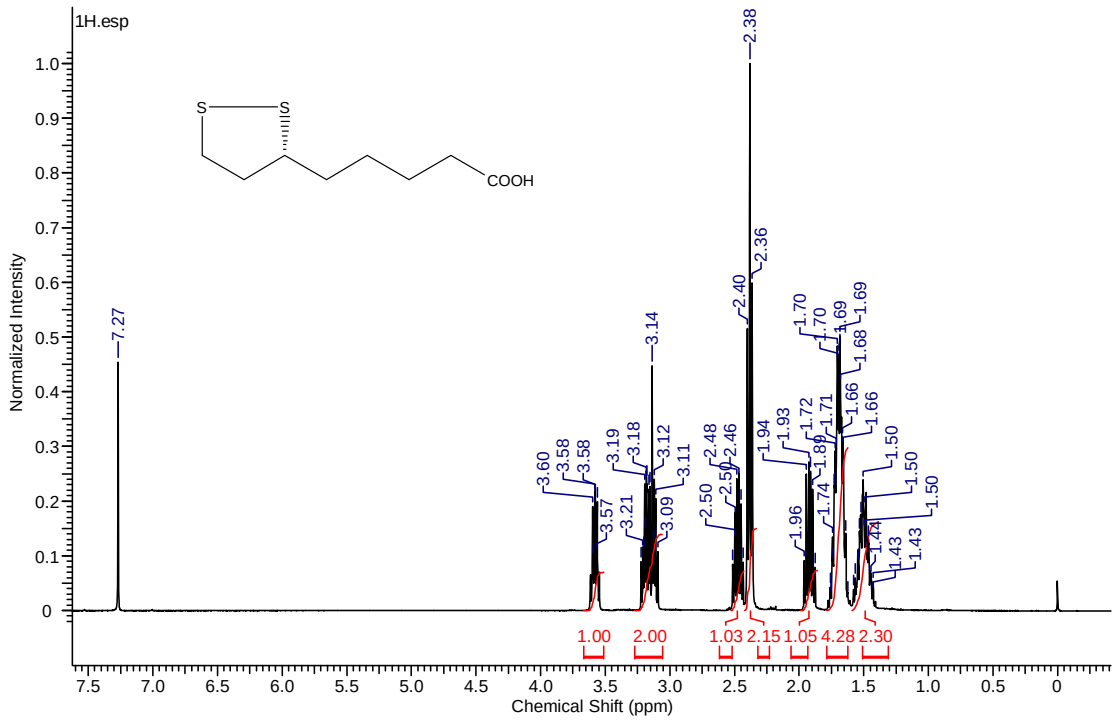
^{13}C-NMR spectrum of compound **9** ($CDCl_3$, 200 MHz)



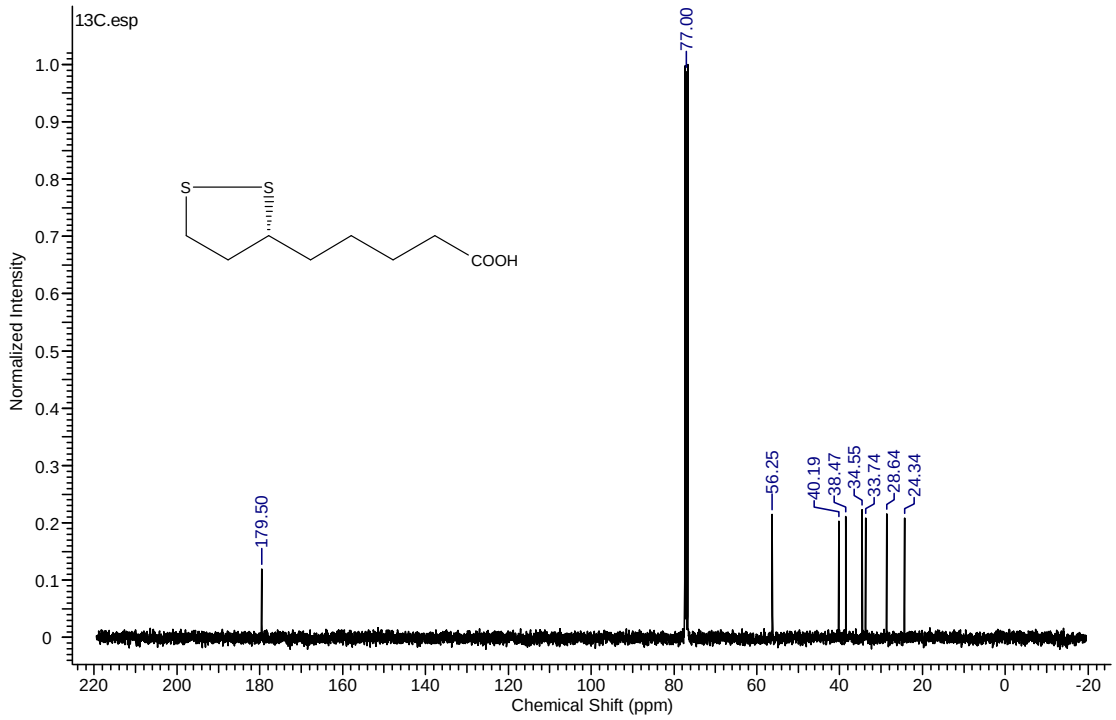
DEPT-NMR spectrum of compound **9** ($CDCl_3$, 200 MHz)



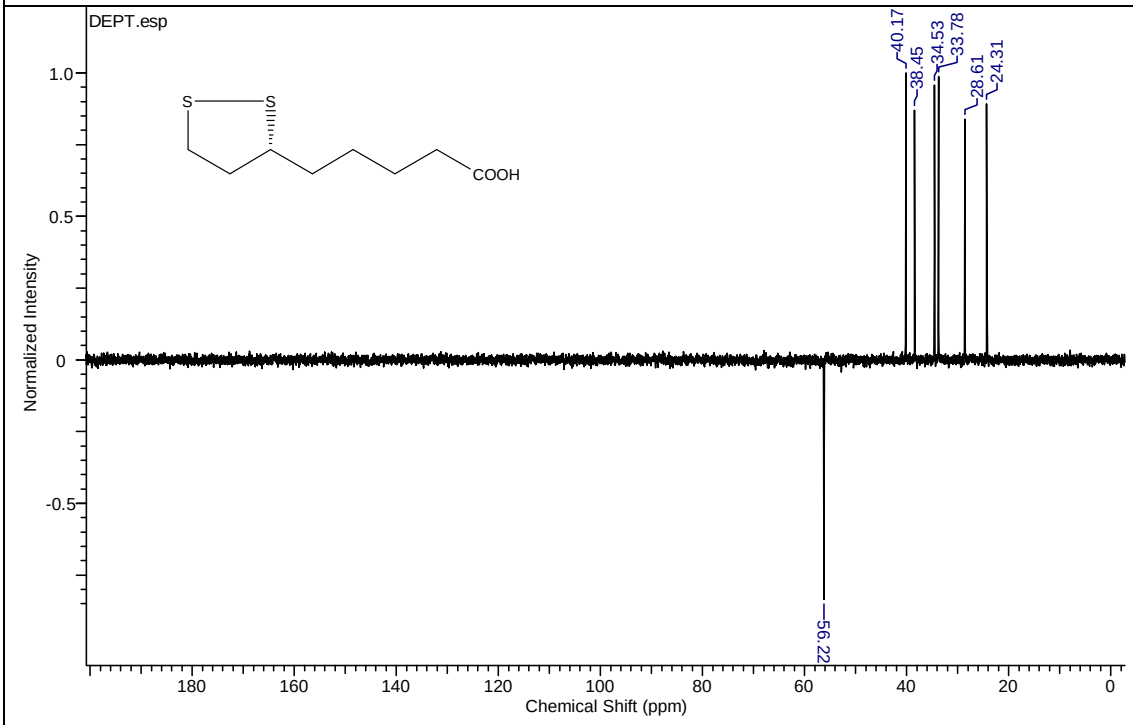
^{1}H-NMR spectrum of compound **1** ($CDCl_3$, 200 MHz)



^{13}C-NMR spectrum of compound **1** ($CDCl_3$, 200 MHz)



DEPT-NMR spectrum of compound **1** ($CDCl_3$, 200 MHz)



3.2.5. References

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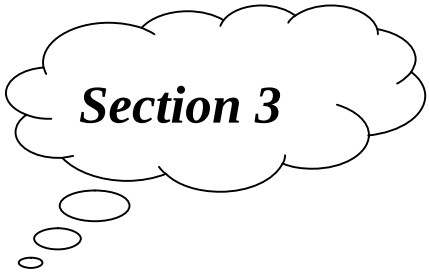
Chapter 3

Total synthesis of *α*-lipoic acid and development of synthetic methodology



Ionic liquid catalyzed methodology for *p*-methoxy benzyl (PMB) protection of alcohols and selective mono-PMB protection of diols.

3.3.1. Introduction:

Protection and deprotection reaction sequence is one of the inherent parts of the total synthesis of multifunctional complex molecules. The important role of a protecting group is to temporarily mask a reactive site when the chemical reaction is being carreid out at the other reactive site. An ideal protective group must fulfill a number of requirements. It must protect a particular site and the protection should proceed in excellent yield. It must be stable and should not interfare in the projected reaction conditions. Also, the deprotection should be in good yields as like protection. The deprotection should not require drastic conditions but should happen under mild, ecofriendly conditions. The non toxic reagents used in deprotection should be neutral towards deprotected functional groups and the byproducts must not react with the deprotected compound or any reactive site of deprotected compound. The protecting groups should not form a chiral centre like THP which forms a new chiral center after THP protection of alcohol, which may create complexity with substrates having asymmetric 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 extra problems during multistep synthesis and affect efficiency of the synthesis. Although, no perfect protecting group exists, but the continous efforts by the organic chemists to improve and develop new protecting groups towards ideality continues.

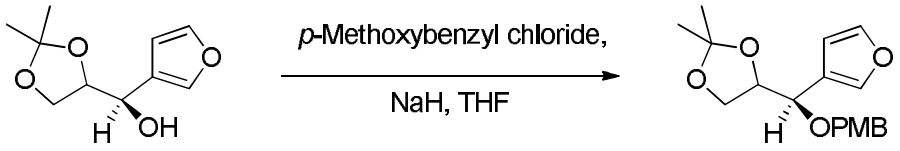
Organic chemists have made profound advancement in the development of methods of protection-deprotection strategies[1] and when one need to manipulate a funtional group in the presence of more than one functional groups the protection-deprotection srategy becomes necessity. The role of protecting group is to mask one functional group so that chemical transformation can be easily carried out on other functional groups of interest.[2] Hydroxy group is one of the most common functional groups found in most of the scaffolds. There are a number of protecting groups and corresponding deprotection conditions for hydroxy functionality have been developed.[3] The protection using 4-methoxybenzyl group (PMB),[1a] which is relatively preferable over benzyl group, has found great significance. This preference is due to its additional advantage of its easy deprotection over the simple benzyl group. as the deprotection of PMB is easy under mild and neutral conditions in the presence of many labile reactive sites such as double bonds, benzyl ethers, tetrahydropyranyl (THP), carboxybenzyl (CBZ) groups, methoxyethoxymethyl ether (MEM), and *tert*-butyldimethylsilyl (TBDMS) ethers, methoxy methyl (MOM) *etc*.[4]

3.3.2 PMB protection of alcohols: A literature review

To have a comparative view of the different methods for PMB protection developed so far, a short descriptive literature survey of the work reported by different groups is being described below:

Marco *et al.*[5]

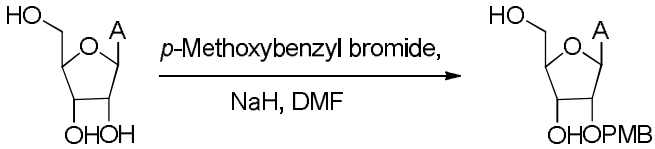
This is one of the most utilized methods for PMB protection of alcohols, which involves the use of freshly prepared *p*-methoxybenzyl chloride by treatment of equimolar quantities of *p*-anisyl alcohol and con. HCl and then its treatment with alcohol in presence of strong bases like NaH, *n*-BuLi *etc*. Marco *et al*. used *p*-methoxybenzyl chloride for PMB protection using NaH as a base (Scheme 1).



Scheme 1

Takaku *et al.*[6]

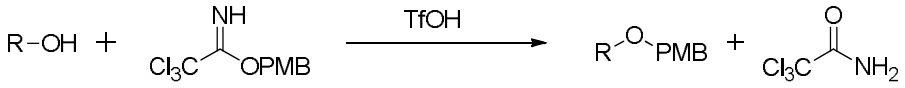
Takaku *et al*. used the *p*-methoxybenzyl bromide (PMB-Br) along with NaH as the base in DMF as solvent for the selective PMB protection of alcohols (Scheme 2).



Scheme 2

Nakajima *et al.*[7]

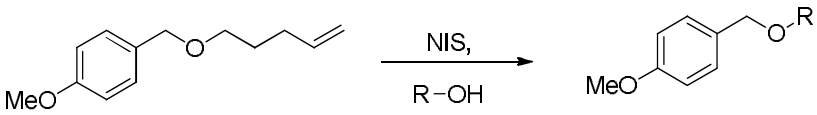
Nakajima *et al*. have reported a convenient acid catalyzed method for the PMB protection of alcohols using corresponding PMB-trichloroacetimidate; this method is preferable when base sensitive sites are present in the target compound. Various alcohols were protected as their PMB ethers by treatment with PMB-trichloroacetimidate and catalytic amount of trifluoromethane sulfonic acid in good yields (Scheme 3).



Scheme 3

Takeo *et al.* [8]

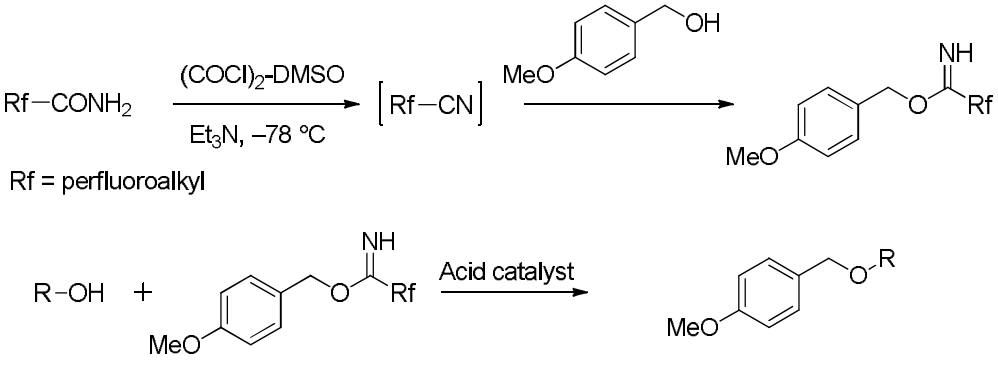
Takeo *et al.* developed a new method for PMB protection of alcohols by generating *p*-methoxybenzyl cation through NIS-mediated activation of *p*-methoxybenzyl 4-pentenyl ether (Scheme 4). Treatment of the various alcohols with *p*-methoxybenzyl 4-pentenyl ether and NIS in acetonitrile gave the PMB protected alcohols with moderate yields.



Scheme 4

Nakajima *et al.* [9]

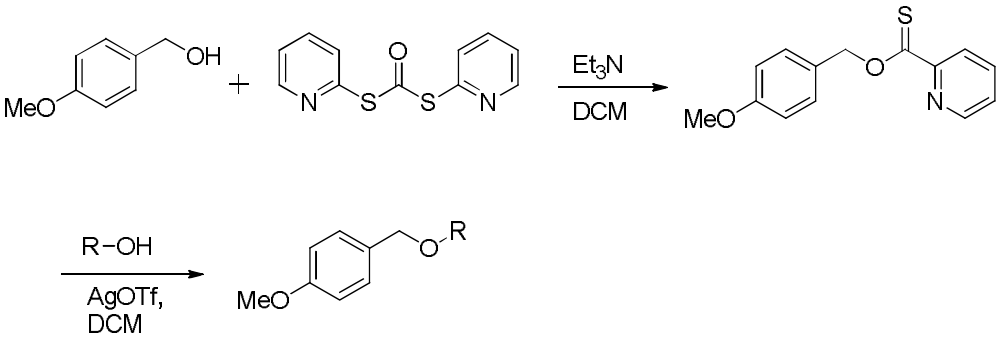
Nakajima *et al.* in their second approach used PMB-perfluoroacetimidate for PMB protection of alcohols under mild acidic conditions in excellent yields. The PMB-perfluoroacetamidate was utilized for protection is due to its better stability compared with the PMB-trichloroacetimidate. The PMB-perfluoroacetimidate was prepared in two step protocol, starting from perfluoroamide and *p*-anisyl alcohol and employed for the PMB protection of alcohols in presence of catalytic PPTS in DCM in good yields (Scheme 5).



Scheme 5

Hanessian *et al.*[10]

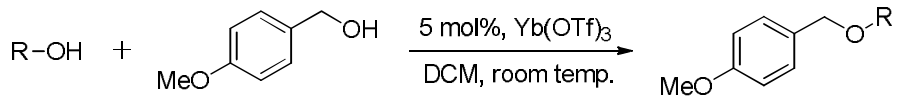
Hanessian *et al*. reported the use of the 4-methoxybenzyl-2-pyridylthio carbonate (PMB-TOPCAT) as a new reagent to convert alcohols into the corresponding PMB ethers in solution and on solid phase under neutral conditions (Scheme 6). The primary, secondary and tertiary alcohols were successfully protected under neutral conditions using silver triflate catalyst in DCM in good yields.



Scheme 6

Sharma *et al.*[11]

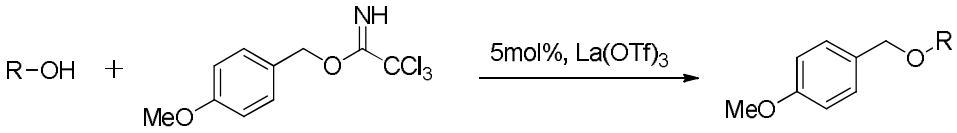
Sharma *et al*. developed a new method for PMB protection of alcohols using PMB-alcohol and $Yb(OTf)_3$ as a catalyst. The optimized reaction conditions for the PMB protection required the treatment of alcohol with 2 eq. of *p*-anisyl alcohol and $Yb(OTf)_3$ (10 mol%) in DCM (Scheme 7). The main merit of this method was the compatibility with both acid and base labile functional groups.



Scheme 7

Basu *et al.* [12]

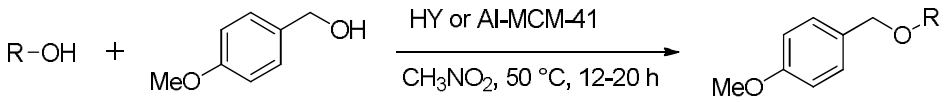
Basu *et al*. developed a method for PMB protection of alcohols using the trichloroacetimidate of PMB alcohol and lanthanum triflate, a neutral catalyst (Scheme 8). The main advantage of this method was the PMB protection of alcohols in presence of acid sensitive functional groups.



Scheme 8

Sharma *et al.* [13]

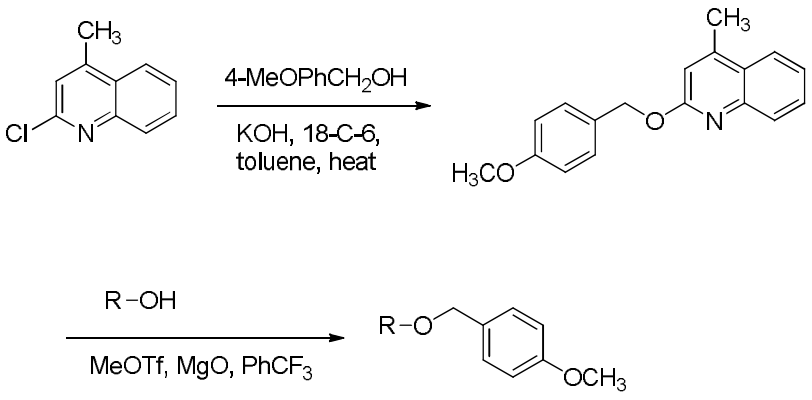
Sharma *et al*. developed a new method for PMB protection of alcohols by using PMB-alcohol and zeolite as the catalyst (Scheme 9). Treatment of various alcohols with PMB-alcohol and zeolite catalyst furnished PMB protected alcohols in good yields.



Scheme 9

Dudley *et al.* [14]

Dudley *et al*. developed a method for PMB protection of alcohols under neutral conditions

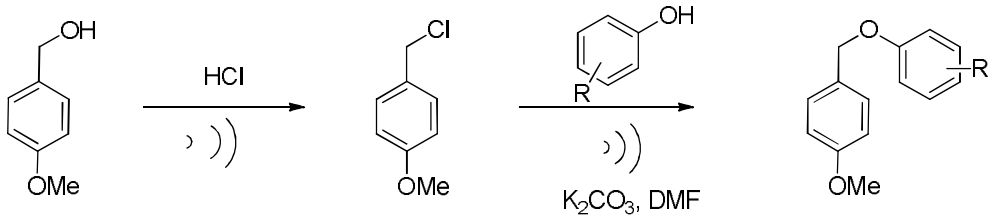


Scheme 10

(Scheme 10). 2-(4-Methoxybenzyloxy)-4-methylquinoline on reaction with methyl triflate to generate a neutral organic salt in the presence of alcohols that transfers the P-methoxybenzyl (PMB) protecting group on correspnding alcoholss in excellent yields under simple reaction condition.

Luzzio *et al.*[15]

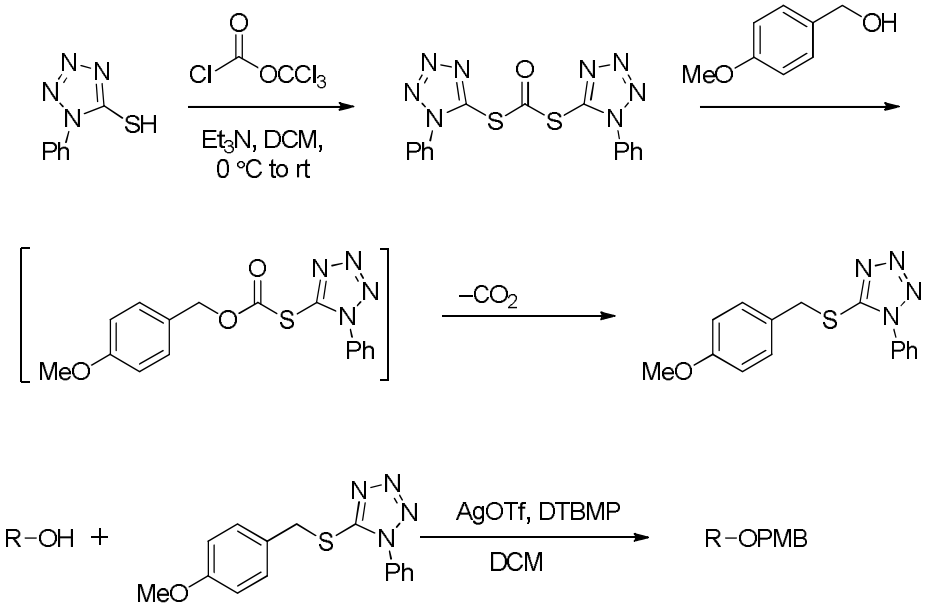
Luzzio *et al*. developed a method for protection of substituted phenols using PMB-chloride under ultrasonic conditions (Scheme 11). This method involves the treatment of various phenols with PMB-Cl in presence of K_2CO_3 in DMF under utrasonic waves to furnish the PMB-protected phenols in good yields.



Scheme 11

Lear *et al.*[16]

Lear *et al*. achieved PMB protection of the alcohols by utilizing the silver triflate 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).

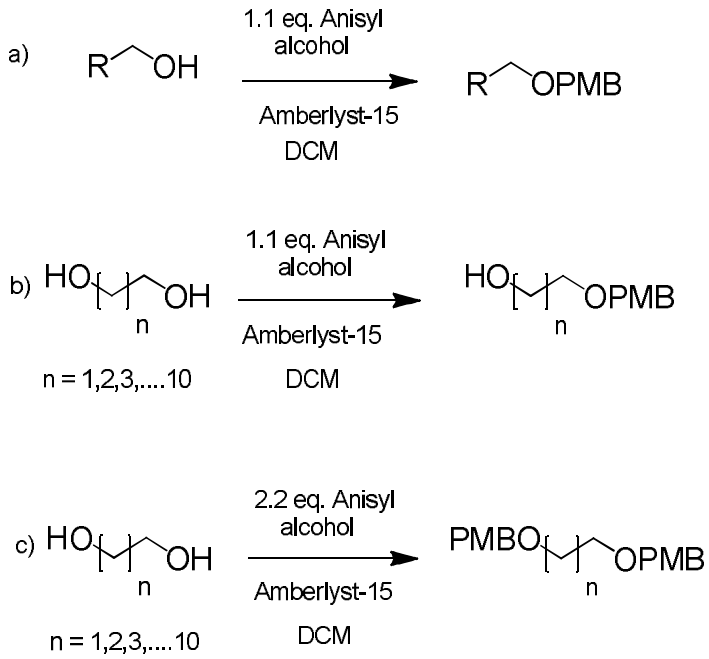


Scheme 12

Chavan *et al*[17].

This group has reported PMB protection of symmetric diols and monoalcohols using Amberlyst-15 as the heterogenous catalyst and DCM as the solvent. This was a one step

protocol involving *in situ* generation of benzyllic cation followed by PMB protection of alcohols.



Scheme 13. a) PMB protection of alcohols, b) Selective mono-PMB protection of diols and c) Di-PMB protection of diols.

3.3.3 Results and discussion:

In the nature there are millions of compounds containing hydroxy group. These compounds are very often utilized as starting materials in the total synthesis of many biologically active compounds. The simple and selective protection of the hydroxy functional groups as its *p*-methoxybenzyl ether (PMB) group is highly desirable when it comes to the multistep synthesis of complex molecules. Genrally uitilzed methods for PMB protection of alcohols requires two step protocol where PMB- chloride or PMB-bromide is treated with various alcohols, in the presence of strong bases like NaH, BuLi, KOH. The problem with this method is requirement of safe handling and storage of PMB halides, which are moisture sensitive and get decomposed on longer storage. Most of the *p*-methoxybenzylation methods involve use of methoxybenzyl iodides,[18a] trichloroacetamidates,[13] perfluoroacetamidates[10] and *p*-methoxybenzyl azide[17b] depending upon substrate sensitivity and stability. Amongst all these, three available methods for PMB protection utilize PMB-alcohol. The first protocol involves the use of expensive f-block element derived $Yb(OTf)_3$[12] catalyst, the second requires zeolite and required comparatively longer time for completion of the reaction,[14] third one is reported by this group in 2011, where Amberlyst-15 was used as the heterogeneous

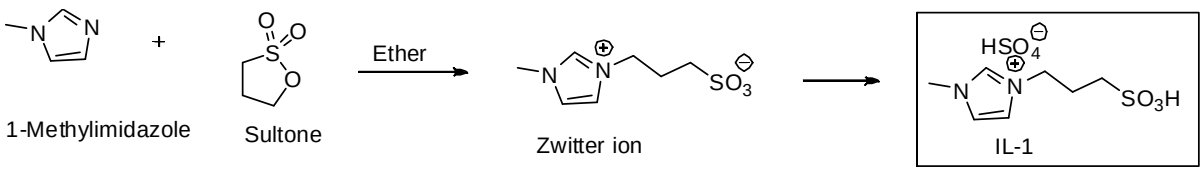
catalyst and this reaction was carried out in DCM. DCM is highly undesired solvent according to green chemistry fundamental rules.

To overcome drawbacks in the previous method by this group and to avoid use of hazardous solvent, synthesis and use of PMB halides, it is highly desired to devise an alternate, simple and practical protocol for PMB protection. Present methodology described herein completely avoids the problems by using stable, easy to handle *p*-methoxy benzylalcohol, directly for PMB protection. It was thought that direct use of PMB-alcohol would be highly attractive and useful, as PMB-alcohol is inexpensive, readily available, can be synthesized easily, there is no storage issue, easy to handle and no any storage issues are related with its storage for long time. It was premised that under acidic conditions PMB-alcohol, the benzylic cation generated from PMB-alcohol would form a good electrophile, which could be trapped by an approprate nucleophile *i.e.* hydroxyl group.

A very simple, solvent free, microwave assisted and highly practical method for PMB protection has been developed. Alcohols can easily be protected directly using P-mthoxy benzyl alcohol in the presence of catalytic amount sultone derived ionic liquid. Microwave treatment of alcohol and anisyl alcohol in the presence of ionic liquid catalyst provides good to excellent yields of the corresponding protected alcohol in a very short time. A noteworthy feature of this protocol is the high regioselectivity observed in mono-PMB protection of diols, where primary alcohols were protected in the presence of secondary and selective mono PMB protection was observed in case of symmetric diols.

Synthesis of ionic liquid catalyst

Ionic liquid catalyst (IL-1) was prepared by literature procedure.[19] Accordingly, 1-methylimidazole on reaction with 1,3-propanesultone gave white zwitter ion solid intermediate which was found to be moisture sensitive and can turn to liquid when exposed to

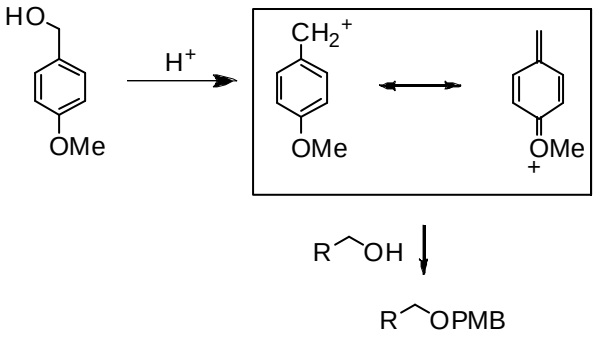


Scheme 14: Synthesis of Ionic Liquid.

air. Hence this solid obtained was immediately reacted with stoichiometric amount of conc. sulfuric acid to give viscous clear liquid **1** (Scheme 14). Both steps in synthesis were quantitative.

Proposed mechanism:

This method is logically based on formation of benzylic cation under acidic condition by protonation of anisyl alcohol. This results in elimination of one H_2O molecule and formation of benzylic cation. The resultant benzylic cation is additionally stabilized by *p*-methoxy group by mesomeric effect. Thus formed carbo-cation can be trapped by alcohol leading to PMB protection (Scheme 15).



Scheme 15. Proposed mechanism for PMB protection.

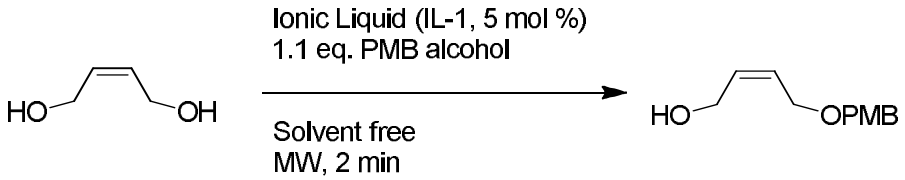
Screening of catalyst:

The ionic liquid (IL-1) synthesized, was subjected to the study of protection of alcohols as their ethers by using it in catalytic amounts. It was found that this acidic ionic liquid could efficiently catalyse the reaction of PMB alcohols and other alcohols to their corresponding PMB ethers.. After successful protection of alcohols, the activity of this catalyst was compared with other acids. It was found after screening various acidic catalysts, this acidic ionic liquid catalyst (IL-1) is much more efficient as compared to the acidic catalysts and acids in catalytic amounts (Table 1). The study was carried out on *cis*-2-butene-1,4-diol, using different types of catalysts under microwave assisted solvent free conditions.

Initially 10% w/w catalyst (IL-1) was used in these reactions. When reactions were performed at room temperature, it was observed that the time required for the completion of reactions was about 24 to 48 h. To reduce the time required for completion of the reaction, the reaction mixture was treated with microwaves. The reaction time was reduced

significantly. Microwave (MW) assisted reactions have been known to reduce the time required for the reaction. ILs has already known to be useful in MW assisted reactions.[20] Protection of *cis*-2-butene-1,4-diol under MW

Table 1. Optimisation for mono-PMB protection of *cis*-2-butene-1,4-diol by screening against different acid catalysts.



Scheme 16. Screening of the catalysts.

Entry	Acid (catalyst)	Time (min)[a]	Yield (%)[b]
1	$H_3PW_{12}O_{40}$(mw=2880g/m)	5	40[c]
2	Conc. H_2SO_4	3	55[c]
3	$H_4[W_{12}SiO_{40}]$ (mw=2878 g/m)	5	31[c]
4	PTSA	2.5	70
5	20% on silica $H_3PW_{12}O_{40}$ (mw=2800g/m)	4	45[c]
6	Amberlyst-15	5	0[d]
7	IL1	2	83

[a] All reactions have been performed in domestic microwave (LG: MC-808WAR); [b] isolated yields; [c] Formation of 4-methoxy benzyl ether was observed; [d]starting material recovered.

conditions provided excellent results, in short period of time and with clean reactions. The reaction catalyzed by phosphotungustic acid ($H_3[PW_{12}O_{40}]$) gave 40% yield in 5 minutes, where as conc. sulfuric acid provided improved (55%) yield. When Silicotungustic acid ($H_4[W_{12}SiO_{40}]$) was used in this screening, it gave only 31% yield in 5 minutes. PTSA was found to catalyze the reaction giving, moderate (70%) yield in 2.5 minutes, but the catalyst failed to exhibit recyclability, which is shown by the IL-1 catalyst. Similar, not so promising results were observed in the case of 20% $H_3PW_{12}O_{40}$ on silica and by using Amberlyst-15.

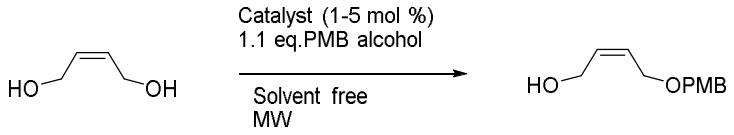
Amberlyst-15 failed to give product. Interestingly IL-**1** has given excellent yield in comparison with all other catalysts (Table1).

On screening the reaction condition *i.e.* solvent free microwave assisted PMB protection with various catalysts, entry no. 7 (Table 1) provided good results as compared to other entries. This suggested that acidic ionic liquid (entry 7) should be a good choice out of all the acids screened. 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 ionic liquid (5 mol%) under microwave and a solvent free condition. One of the main advantages of this method is simplicity of the work-up which involves dilution of reaction mixture with diethyl ether and decantation to provide products. In this study, *cis*-2-butene-1,4-diol was reacted with *p*-anisyl alcohol in the presence of catalyst. Having established the generality and efficiency of this catalytic protocol for protection of alcohols, the attention was turned to selective protection of diols.

Catalyst Loading:

To study the effect of catalyst loading on the PMB protection of cis-2-butene-1, 4-diol, a number of reactions were performed using 1 to 5 mol% of the catalyst (Table 2). These studies have shown that on decreasing the amount of catalyst loading in the reaction required enhanced time duration for the completion and led to decrease in the yield of the product. 4-5 mol% IL-**1** catalyst loading in the PMB protection of *cis*-2-butene-1,4-diol under optimmzied condition has been found to be best choice for further exploration of this catalyst in the application for PMB protection of alcohols.

Table2: Screening of catalyst loading in the PMB protection of *cis*-2-butene-1,4-diol



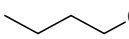
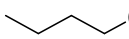
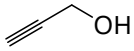
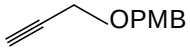
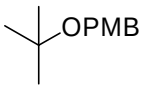
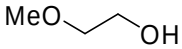
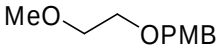
Sr. No.	Catalyst 1 (mol %)	Time (min)	Yield (%)
1.	1	8	57
2.	2	7	60
3.	3	6	63

4.	4	4	78
5.	5	2	84

Protection of primary alcohols:

A wide variety of alcohols were subjected to optimized reaction condition, *i.e.* PMB protection using anisyl alcohol (1.1 eq.), catalyst (5 mol %), solvent free microwave assistance to furnish the corresponding PMB protected alcohols in good to excellent yields (Table 2). The primary alcohols reacted with anisyl alcohol under optimized reaction

Table 3. PMB protection of alcohols.

Entry	Alcohol	Product	Time (min)	Yield (%)
1	MeOH	MeO-PMB	2.5	89%
2			3	84%
3			4	78%
4			2	83%
5			10	16%
6			2.5	87%

condition to provide excellent yields of respectively protected alcohols (entry 1-4 and 6) in a short period of time where as *tert*-alcohol (entry 5) provided low yield. In case of volatile alcohols the starting material was taken in excess to achieve maximum conversion to protected alcohol.

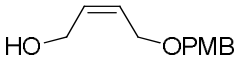
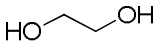
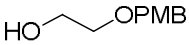
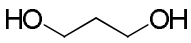
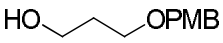
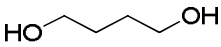
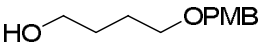
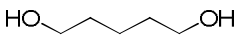
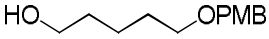
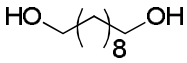
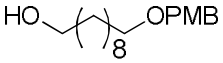
Protection of symmetric diols:

After successful application of optimized condtions for primary alcohols attention was turned towards symmetric diol. Here, selective mono PMB protection of diols was observed when anisyl alcohol was taken in stochiometric amount. Most of the diols were protected in comparable yields (about 80-86%) except1,10-decanediol. Due to the solid nature of the

substrate there was lack of homogeneity with the IL-1 catalyst thereby resulting in low yield. The 50% of the substrate was recovered after the column chromatography. Selectivity in the mono-PMB protection was observed in all substrates.

Gratifyingly, the selective mono-PMB protection of diols was also achieved in good yields (Table 4). A variety of diols on treatment with 1.1 eq. anisyl alcohol in presence of IL-1 (5

Table 4. Selective mono-PMB protection of diols.

Entry	Diol	Product	Time(min)	Yield (%)[b]
1			2	83
2			2.5	80
3			3.5	86
4			3	88
5			2	79
6			5	50

[a] Corresponding diol as a starting material (1. eq.), anisyl alcohol (1.1 eq.) and IL-1 (5% mol%) under solvent free microwave conditions. [b] Isolated yields.

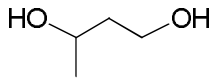
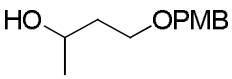
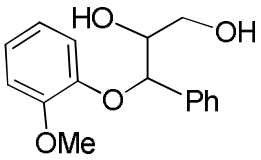
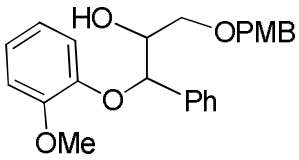
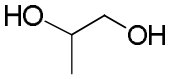
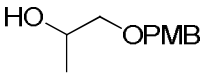
mol%) under solvent free microwave conditions provided excellent yields of mono-PMB protected diols.

Selectivity in mono-PMB protection:

Having established conditions for selective protection of diols, the mixed alcohols were screened against optimized conditions. The results were found promising (Table 4), where the 1,3 diol and 1,2 diols (entries 1-3) were selectvely protected.

The selectivity in the PMB-protection has been tested on a number of diols having primary and secondary alcohol functionalities. The 1,3-butanediol was selectively protected in 89% yield within 3.5 minutes. Further, 1,2-diol (Table 5, entry 2) furnished 83% yield of the mono protected PMB derivatives within 4 minutes time. Lastly, 1,2-propanediol has shown 75% yield in 2.5 minutes time (see Table 5). It was observed that, the primary alcohols were protected selectively in presence of secondary alcohols. The saturated diols (Table 5, entry 1-3) furnished mono protected PMB ether in good yields. The primary alcohols were successfully protected as PMB ethers in the presnce of secondary alcohols.

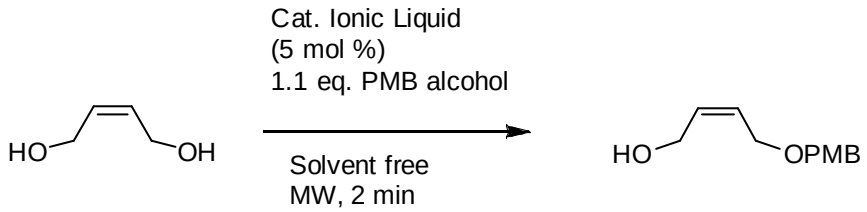
Table 5: Selectivity of primary alcohols over secondary in IL catalyzed PMB protections

Entry	Diol	Product	Time (min)	Yield (%)
1			3.5	89
2			4	83
3			2.5	75

Recyclability of IL Catalyst:

In order to establish the reusability and recyclability of the catalyst, the used IL-**1** in reaction was recovered and reused. After extensive exploitation of IL-**1**, this catalyst was tested for its recyclability. It was found that the IL-**1** can be used up to 5 cycles without any appreciable loss in activity (Table 4). This study was done with the *cis*-2-butene-1,4-diol as a substrate. In the first run with the catalyst yield was 83% yield. The catalyst has been recycled and reused for five times in the reaction. It is observed that, appreciable yields are obtained up to 3rd cycle. Subsequent drop in the yields were observed in further cycles. Along with this the time required for the reaction increased with the number of recycles. Such decrease in yields was attributed to the loss of IL-1 with every workup.

Table 6: Recyclability of IL-**1**



Sr. No.	Cycle	Time(min)	Yield (%)
1	1st Cycle	2	83
2	2ndCycle	2	80
3	3rdCycle	2.5	76
4	4thCycle	5	68
5	5thCycle	6	53

3.3.4 Conclusion:

In conclusion, a successful synthesis of Brønsted acidic imidazolium ionic liquid in solvent free condition and its application in the PMB protection was achieved. The IL-**1** was efficiently exploited as a catalyst for selective protection of a variety of alcohols. The selectivity was also observed among the primary and secondary alcohols. Primary alcohols were protected selectively in the presence of secondary alcohols. All these reactions were carried out under solvent free and microwave condition with high yields. The catalyst was recycled successfully for upto four times. This method is very simple, mild, useful and efficient for PMB protection of alcohols with excellent yields.

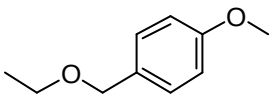
The present method should find widespread usage amongst organic chemists. The unprecedented method for mono-PMB protection of diols in very high yields and simplicity has been developed. PMB protection of diols has been carried out in good yields.

3.3.5 Experimental:

General procedure for PMB protection of alcohols: 1-(Ethoxymethyl)-4-methoxybenzene (Table 3, entry 2):

A mixture of ethanol (200 mg, 4.34 mmol), *p*-anisyl alcohol (150 mg, 1.09 mmol) and 5 mol% IL-**1** (11 mg) were taken in a round bottom flask (5 mL). The mixture was subjected for microwave treatment two minutes. The progress of the reaction was monitored by TLC after every 10 seconds. After completion of the reaction, the reaction mixture was diluted with diethyl ether. The supernatant diethyl ether was decanted in another round bottom flask. This process was repeated thrice (3 x 5 mL). The combined organic layer was centrated *in vacuo* and purified using flash chromatography over silica gel (pet ether : ethyl acetate 95:5) to provide 152 mg (84%) of pure product as a colorless liquid.

1-(Ethoxymethyl)-4-methoxybenzene[21] (Table 3, entry 2)

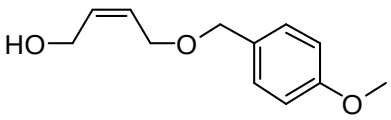


^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.0 Hz, 3 H), 3.51 (q, *J* = 7.0 Hz, 2 H), 3.80 (s, 3 H), 4.43 (s, 2 H), 6.84 - 6.94 (m, 2 H), 7.21 - 7.34 (m, 2 H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 15.21, 55.23, 65.39, 72.33, 113.73, 129.25, 130.68, 159.10

General procedure for selective mono PMB protection of diols:

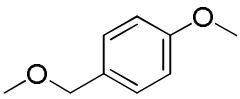
(*Z*)-4-((4-Methoxybenzyl)oxy)but-2-en-1-ol (Table 4, entry 1):



A mixture of *cis*-butene1,4-diol (100 mg, 1.14 mmol), *p*-anisyl alcohol (172 mg, 1.25 mmol) and 5 mol% IL-1 (12 mg, 0.05 mmol) were taken in 5 mL round bottom flask. The mixture was subjected to microwave treatment for two minutes. The progress of the reaction was monitored by TLC after every 10 seconds. After completion of the reaction, the reaction mixture was diluted with diethyl ether. The supernatant diethyl ether was decanted in another round bottom flask. the process was repeated thrice (3 x 5 mL). The combined organic layer was concentrated *in vacuo* and purified using flash chromatography over silica gel (pet ether : ethyl acetate 70:30) to provide 196 mg (85%) of pure product as a colorless dense liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (br. s, 1 H), 3.80 (s, 3 H), 4.06 (d, *J* = 6.41 Hz, 2 H), 4.16 (d, *J* = 6.41 Hz, 2 H), 4.45 (s, 2 H), 5.67 - 5.76 (m, 1 H), 5.77 - 5.87 (m, 1 H), 6.88 (d, *J* = 8.24 Hz, 2 H), 7.18 - 7.31 (m, 2 H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 55.2, 58.7, 65.3, 72.1, 113.8, 128.3, 129.5, 129.9, 132.3, 159.3.

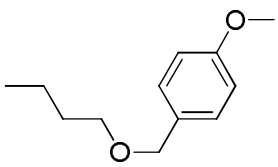
1-Methoxy-4-(methoxymethyl)benzene[21] (Table 3, entry 1)



^{1}H NMR δ (200 MHz, $CDCl_3$): δ 3.36 (s, 3 H), 3.81 (s, 3 H), 4.39 (s, 2 H), 6.80 - 6.97 (m, 2 H), 7.19 - 7.38 (m, 2 H)

^{13}C NMR δ (50 MHz, $CDCl_3$): δ 55.26, 57.77, 74.34, 113.78, 129.34, 130.29, 159.22

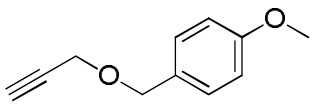
1-(Butoxymethyl)-4-methoxybenzene[21] (Table 3, entry 3)



^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85 - 1.08 (m, 3 H), 1.28 - 1.76 (m, 4 H), 3.47 (t, *J* = 6.44 Hz, 2 H), 3.85 (s, 3 H), 4.46 (s, 2 H), 6.90 (d, *J* = 8.72 Hz, 2 H), 7.29 (d, *J* = 8.84 Hz, 2 H);

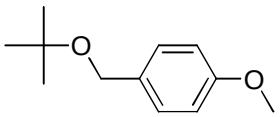
^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 19.3, 31.8, 54.9, 69.7, 72.4, 113.5, 129.0, 129.6, 130.7, 159.0

1-Methoxy-4-((prop-2-yn-1-yloxy)methyl)benzene[22] (Table 3, entry 4)



^{1}H NMR (200 MHz, $CDCl_3$): δ 2.46 (t, *J* = 2.3 Hz, 1 H), 3.84 (s, 3 H), 4.16 (d, *J* = 2.3 Hz, 2 H), 4.57 (s, 2 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 7.30 (d, *J* = 8.7 Hz, 2 H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 54.95, 56.41, 70.85, 74.47, 79.71, 113.66, 129.15, 129.61, 159.25

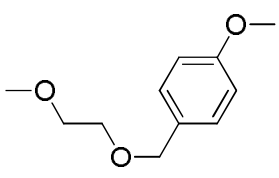
1-(*t*-Butoxymethyl)-4-methoxybenzene[21] (Table 3, entry 5)



^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (s, 9 H), 3.78 (s, 3 H), 4.36 (s, 2 H), 6.83 (d, *J* = 8.72 Hz, 2 H), 7.23 (d, *J* = 8.72 Hz, 2 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.8, 55.1, 63.8, 73.2, 113.7, 128.8, 129.7, 131.9, 158.8

1-Methoxy-4-((2-methoxyethoxy)methyl)benzene[23] (Table 3, entry 6)

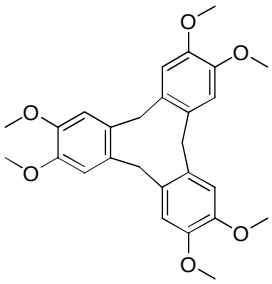


^{1}H NMR (200 MHz, $CDCl_3$): δ 3.38 (s, 3 H), 3.47 - 3.66 (m, 4 H), 3.80 (s, 3 H), 4.50 (s, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 7.27 (d, *J* = 8.7

Hz, 2 H; **^{13}C NMR (50 MHz, $CDCl_3$):**

δ 55.19, 58.98, 68.89, 72.89, 77.00, 113.70, 129.35, 159.15.

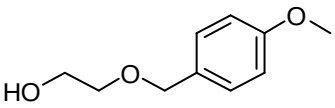
Cyclotrivertrylene [24]



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.55 (d, *J* = 13.69 Hz, 3 H), 3.85 (s, 18 H), 4.77 (d, *J* = 13.94 Hz, 3 H), 6.84 (s, 6 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 36.4, 56.0, 113.1, 131.7, 147.7; m/z: 473.5$(M+Na)^+$.

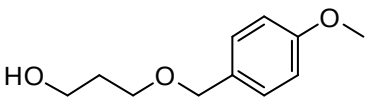
2-(4-Methoxybenzyloxy)ethanol[25] **(Table 4, entry 2)**



^{1}H NMR (200 MHz,$CDCl_3$+CCl_4): δ 2.18 (br. s., 1 H), 3.53 - 3.64 (m, 2 H), 3.72 - 3.80 (m, 2 H), 3.84 (s, 2 H), 4.52 (s, 2 H), 6.91 (d, *J* = 8.72 Hz, 2 H), 7.29 (d, *J* = 8.72 Hz, 2 H);

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 55.0, 61.5, 71.0, 72.7, 113.6, 129.3, 129.9, 159.1

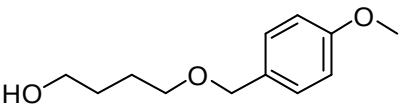
3-(4-Methoxybenzyloxy)propan-1-ol[26] **(Table 4, entry 3)**



^{1}H NMR (200 MHz,$CDCl_3$): δ 1.74 - 2.00 (m, 2 H), 2.26 (br. s., 1 H), 3.67 (t, *J* = 5.7 Hz, 2 H), 3.76 - 3.83 (m, 2 H), 3.84 (s, 3 H), 4.49 (s, 2 H), 6.91 (d, *J*=8.7 Hz, 2 H), 7.28 (d, *J* = 8.8 Hz, 2 H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 32.01, 55.03, 61.18, 68.54, 72.71, 113.68, 129.15, 130.02, 159.09

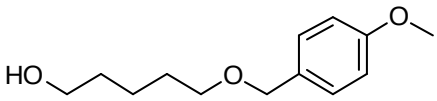
4-(4-Methoxybenzyloxy)but-1-ol[25] **(Table 4, entry 4)**



^{1}H NMR (200 MHz, $CDCl_3$): δ 1.55 - 1.82 (m, 4 H), 2.59 (s, 1 H), 3.52 (t, *J* = 5.81 Hz, 2 H), 3.64 (t, *J* = 5.94 Hz, 2 H), 3.84 (s, 3 H), 4.48 (s, 2 H), 6.90 (d, *J* = 8.72 Hz, 2 H), 7.28 (d, *J* = 8.72 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.9, 30.3, 55.1, 62.6, 70.0, 72.8, 113.8, 129.4, 130.1, 159.2

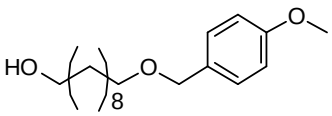
5-(4-Methoxybenzyloxy)pentan-1-ol[5] **(Table 4, entry 5)**



^{1}H NMR (200 MHz, $CDCl_3$): δ 0.55 - 0.77 (m, 7 H), 2.55 (t, *J* = 6.32 Hz, 2 H), 2.68 - 2.82 (m, 2 H), 2.92 (s, 3 H), 3.53 (s, 2 H), 5.97 (d, *J* = 8.72 Hz, 2 H), 6.35 (d, *J* = 9.35 Hz, 2 H);

^{13}C NMR (50 MHz,$CDCl_3$): δ 22.4, 29.4, 32.4, 55.1, 62.4, 69.9, 72.5, 113.7, 129.2, 130.5, 159.1

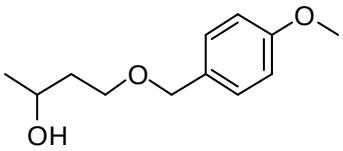
10-(4-Methoxybenxyloxy)decan-1-ol[27] **(Table 4, entry 6)**



^{1}H NMR (200 MHz,$CDCl_3$): δ 1.31 (br. s., 12 H), 1.54 - 1.68 (m, 5 H), 3.46 (t, *J* = 6.57 Hz, 2 H), 3.59 - 3.75 (m, 2 H), 3.84 (s, 3 H), 4.46 (s, 2 H), 6.89 (d, *J* = 8.72 Hz, 2 H), 7.28 (d, *J* = 8.97 Hz, 2 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.8, 26.2, 29.4, 29.6 (4C), 29.7, 32.8, 55.1, 62.8, 70.1, 72.4, 113.6, 129.1, 130.7, 159.0

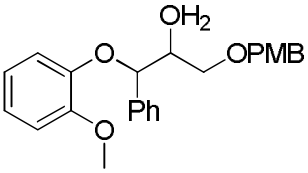
4-(4-Methoxybenzyloxy)butan-2-ol[28] **(Table 5, entry 1)**



^{1}H NMR (200 MHz, $CDCl_3$): δ 1.19 (d, *J* = 6.2 Hz, 3 H), 1.60 - 1.83 (m, 2 H), 2.24 (br. s., 1 H), 3.50 - 3.72 (m, 2 H), 3.80 (s, 3 H), 3.89 - 4.14 (m, 1 H), 4.45 (s, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 7.25 (d, *J* = 8.8 Hz, 2 H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 23.3, 38.1, 55.3, 67.6, 68.8, 72.9, 113.9, 129.3, 130.1, 159.3

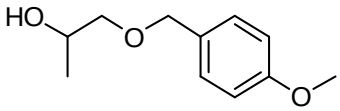
3-(4-Methoxybenzyloxy)-1-(2-methoxyphenyl)-1-phenylpropan-2-ol (Table 5, entry 2)



^{1}H NMR (200 MHz, $CDCl_3$): δ 2.66 (br. s., 1 H), 3.23 (dd, *J* = 10.2, 4.0 Hz, 1 H), 3.54 (dd, *J* = 10.2, 3.0 Hz, 1 H), 3.81 (s, 3 H), 3.90 (s, 3 H), 4.08 (dt, *J* = 7.5, 3.6 Hz, 1 H), 4.28 - 4.54 (m, 2 H), 6.57 - 7.01 (m, 6 H), 7.10 - 7.54 (m, 8 H); m/z: 395.5 $(m+H)^+$

^{13}C NMR (50 MHz, $CDCl_3$): δ 29.74, 55.16, 55.75, 69.34, 73.20, 75.14, 85.19, 111.82, 113.71, 118.40, 120.90, 122.80, 127.20, 128.48, 129.46, 130.15, 138.66, 148.01, 159.21

1-(4-Methoxybenzyloxy)propan-2-ol[29] (Table 5, entry 3)

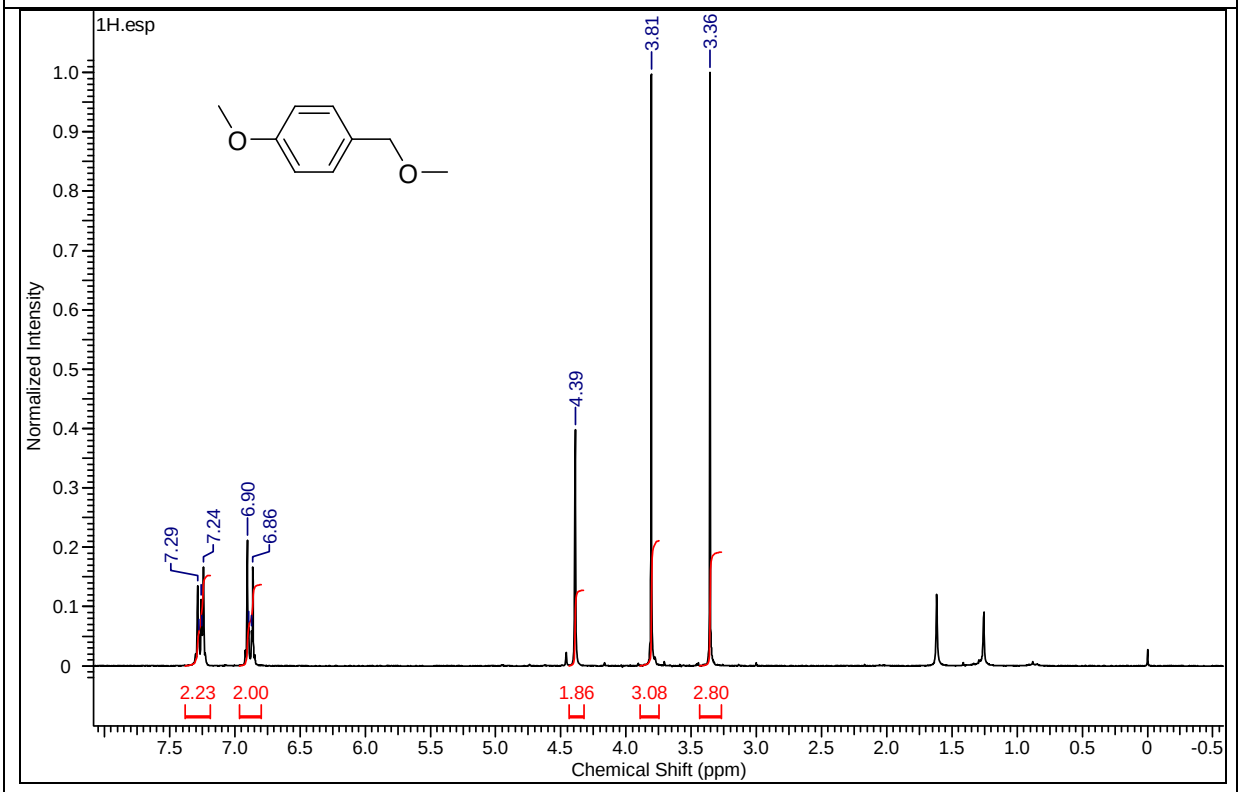


^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13 (d, *J* = 6.4 Hz, 2 H), 2.31 (br. s., 1 H), 3.25 (dd, *J*= 9.5, 8.2 Hz, 1 H), 3.42 (dd, *J* = 9.5, 3.1 Hz, 1 H), 3.79 (s, 2 H), 3.92 - 4.01 (m, 1 H), 4.47 (s, 2 H), 6.88 (d, *J*=8.5 Hz, 2 H), 7.25 (d, *J* = 8.5 Hz, 2 H)

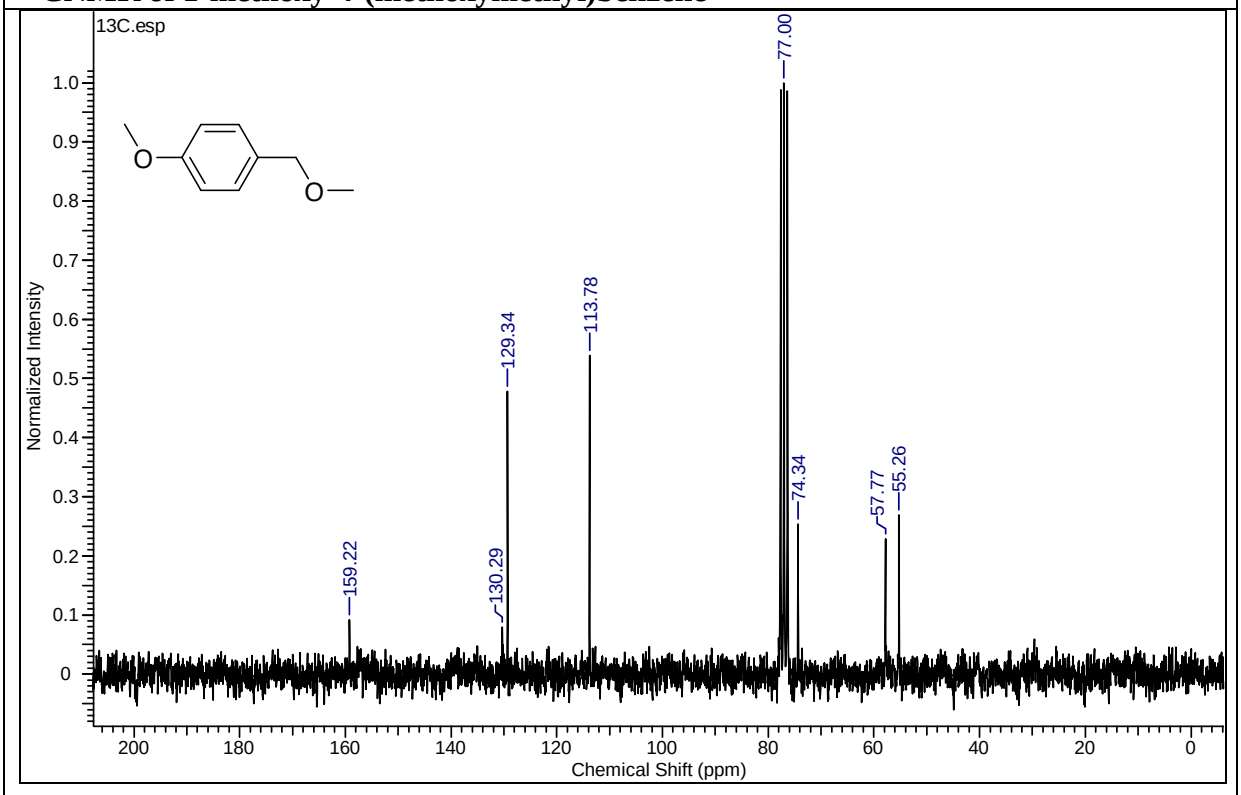
^{13}C NMR (125 MHz, $CDCl_3$): δ 18.58, 55.16, 66.36, 72.86, 75.46, 113.75, 129.31, 129.98, 159.20

3.3.6 Spectra

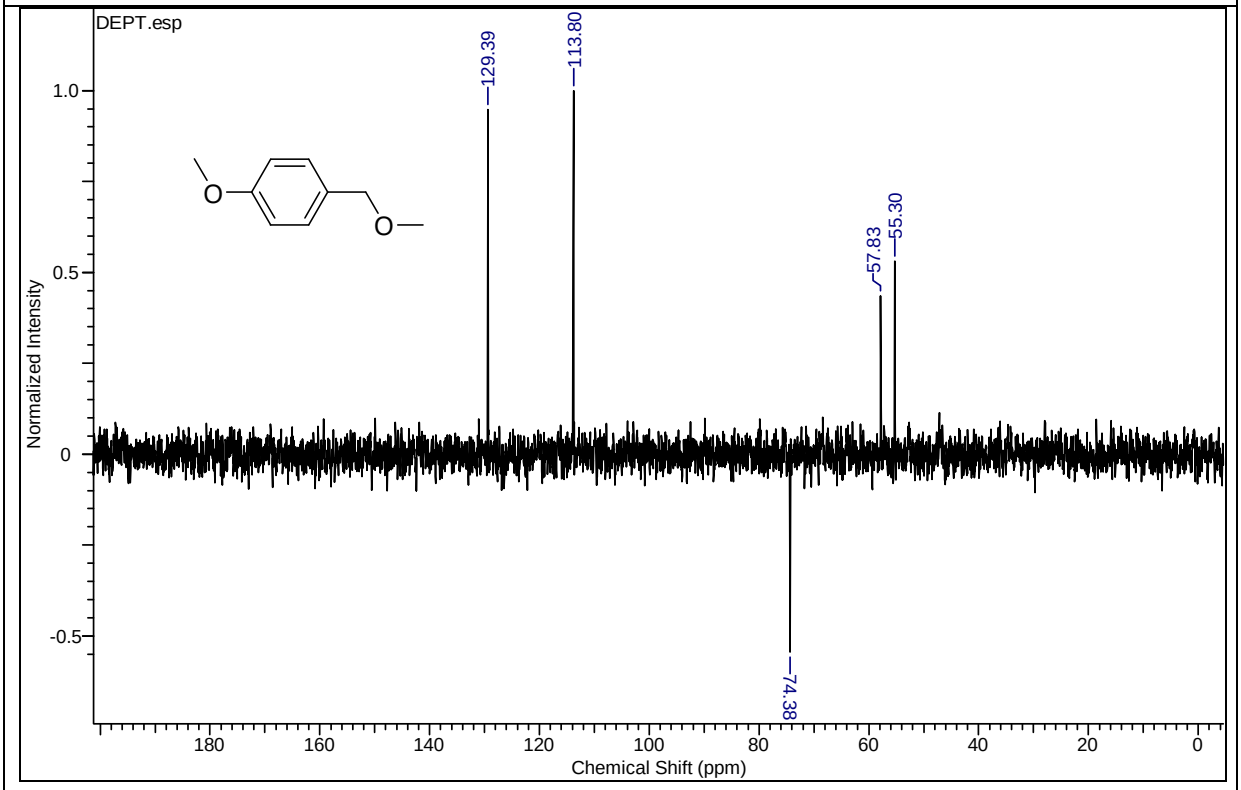
^{1}HNMR of 1-methoxy-4-(methoxymethyl)benzene



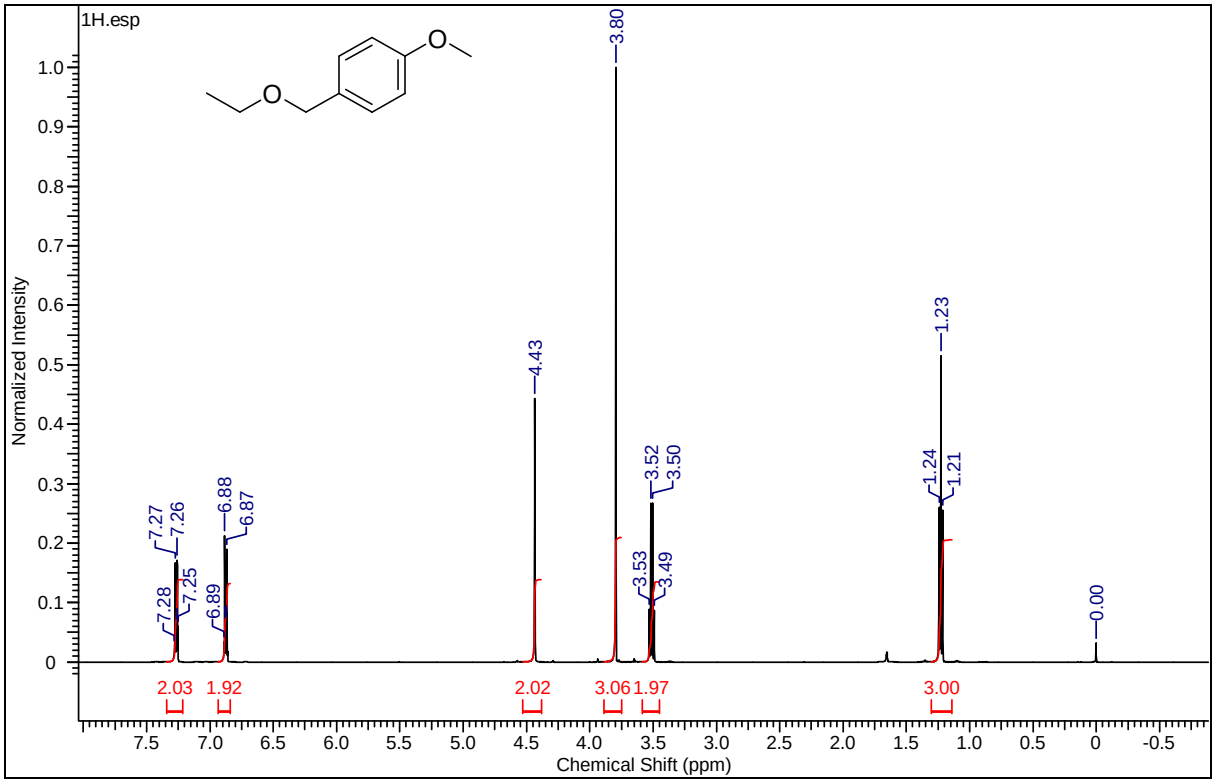
^{13}CNMR of 1-methoxy-4-(methoxymethyl)benzene



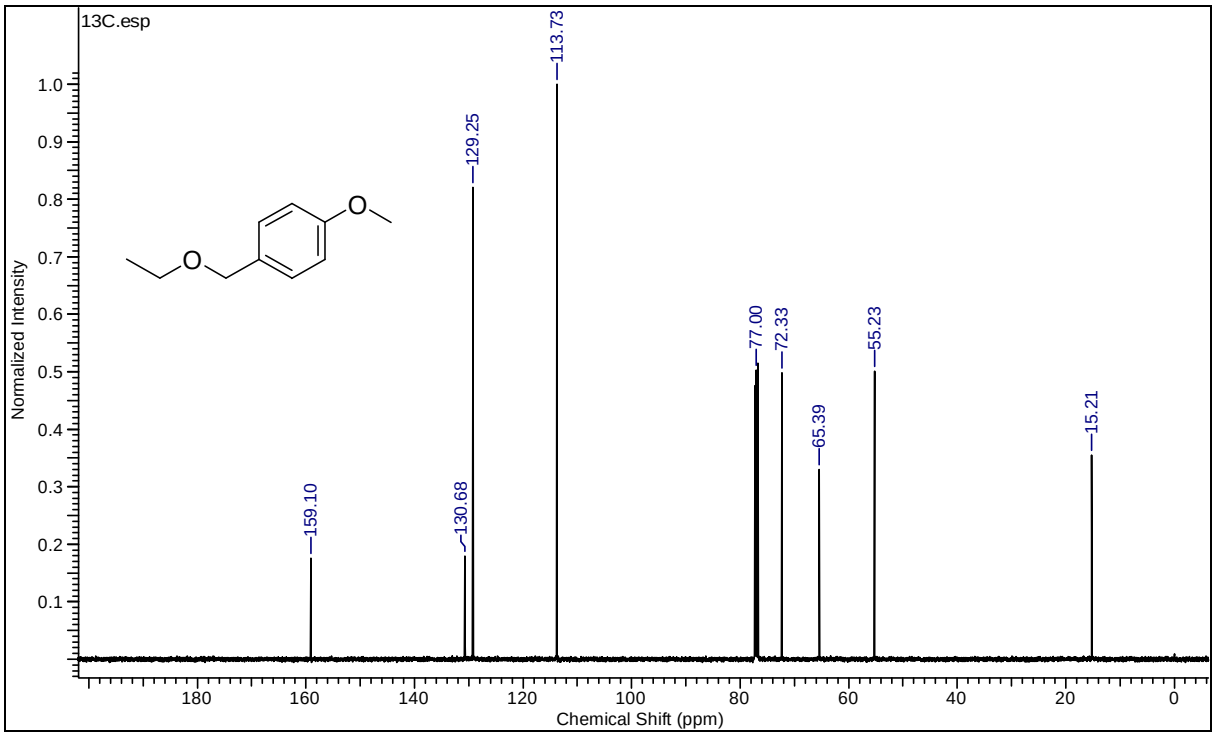
DEPT of 1-methoxy-4-(methoxymethyl)benzene



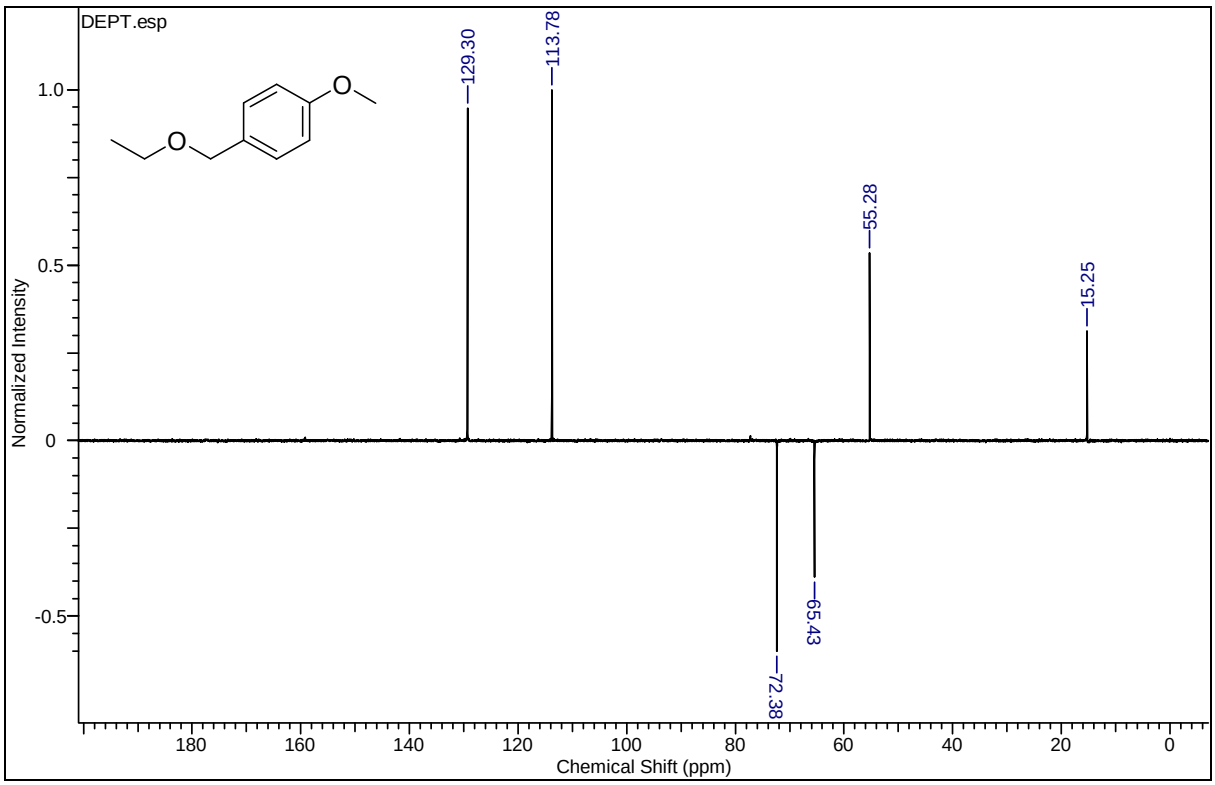
^{1}H NMR of 1-(ethoxymethyl)-4-methoxybenzene



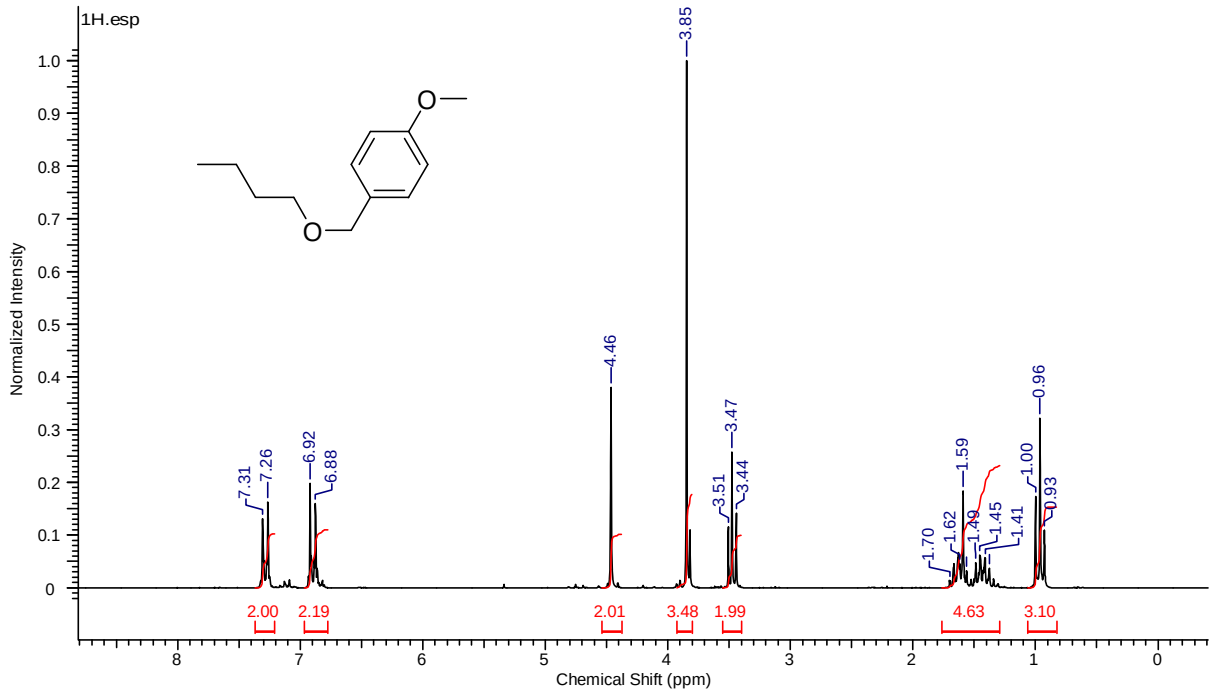
^{13}C NMR of 1-(ethoxymethyl)-4-methoxybenzene



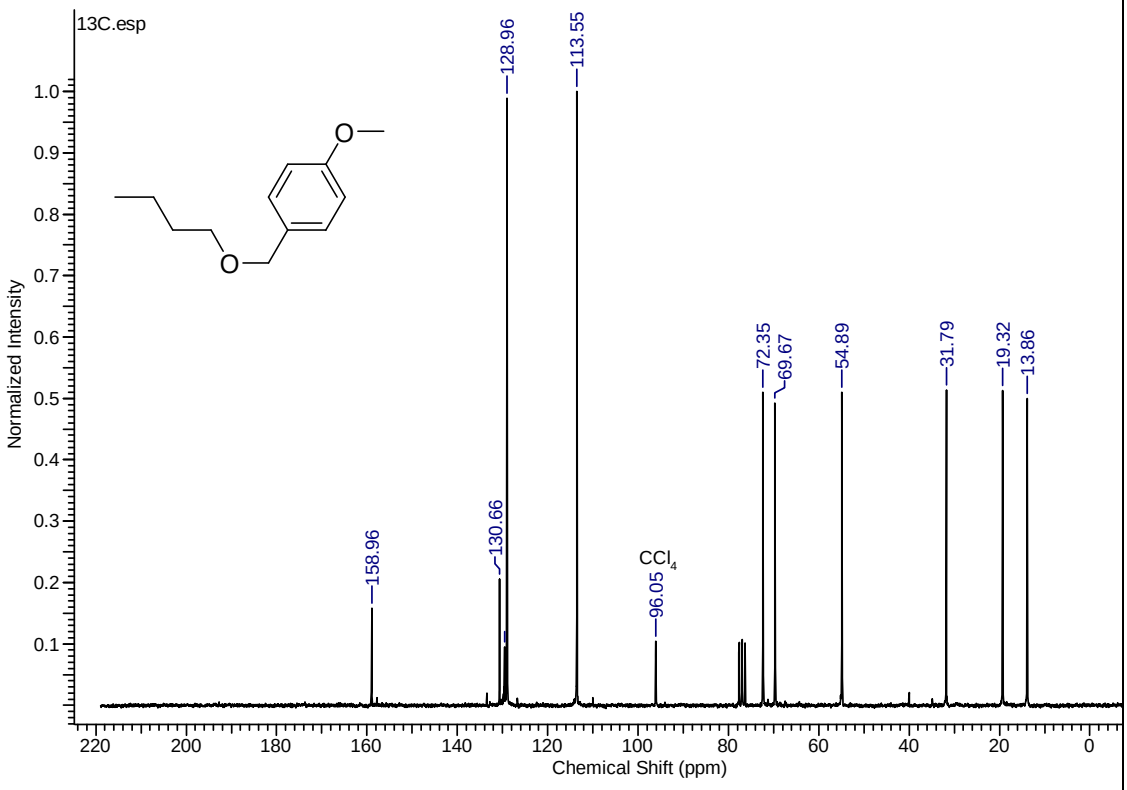
DEPT of 1-(ethoxymethyl)-4-methoxybenzene



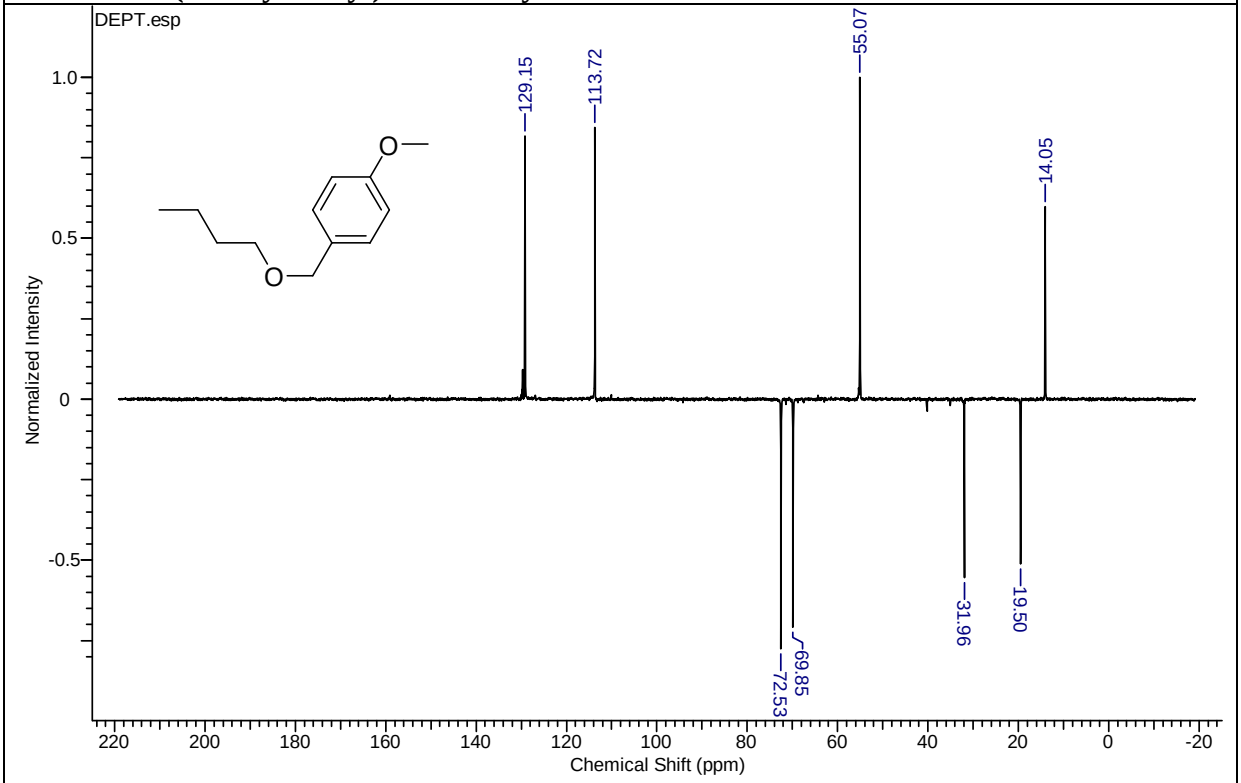
^{1}HNMR of 1-(butoxymethyl)-4-methoxybenzene



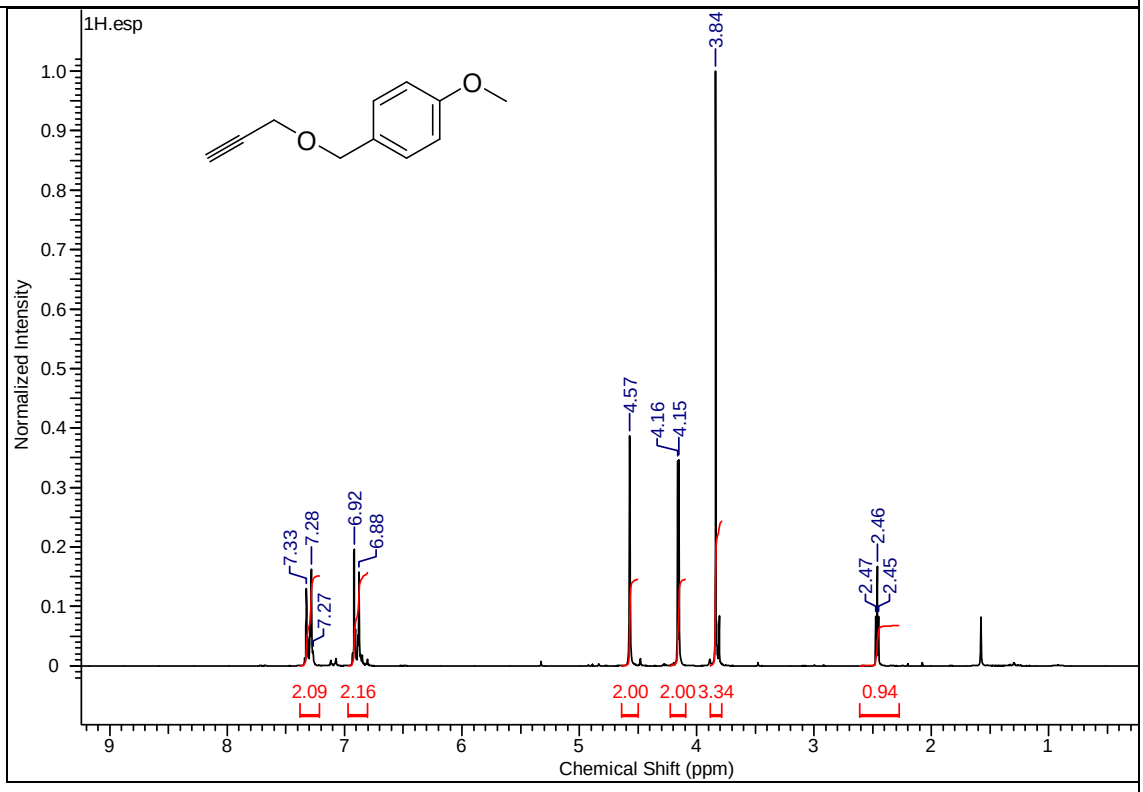
^{13}CNMR of 1-(butoxymethyl)-4-methoxybenzene



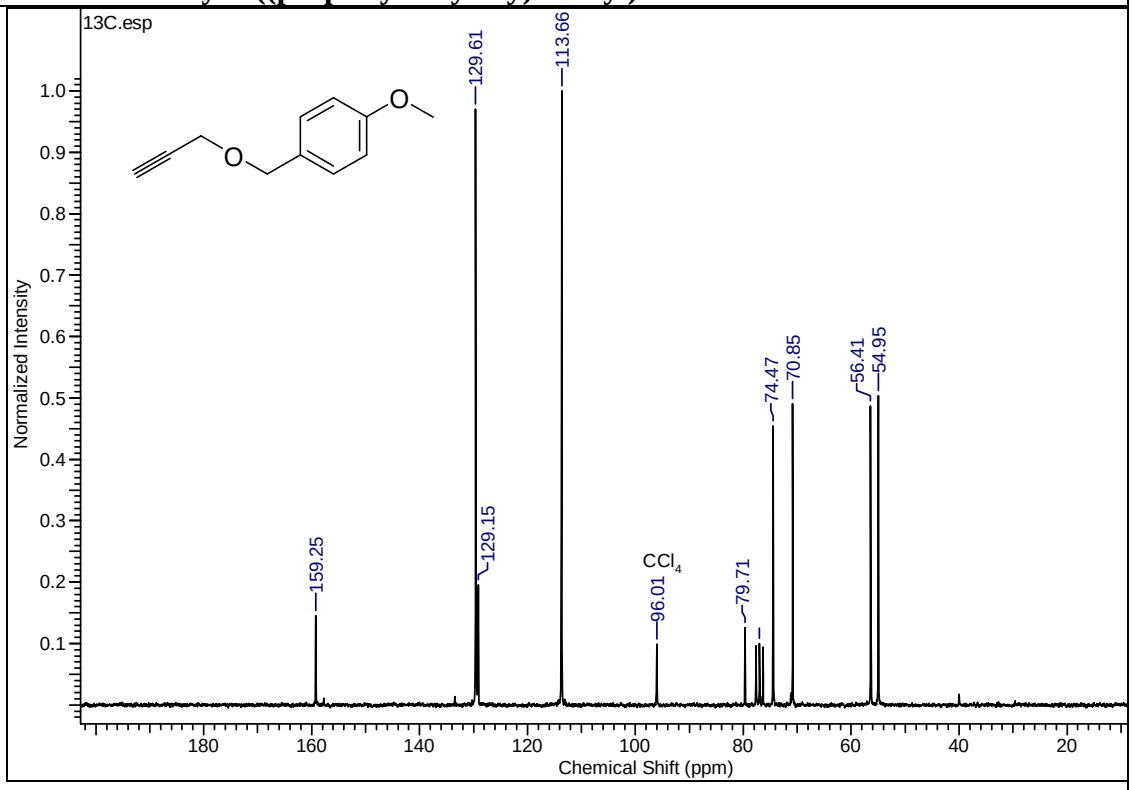
DEPT of 1-(butoxymethyl)-4-methoxybenzene



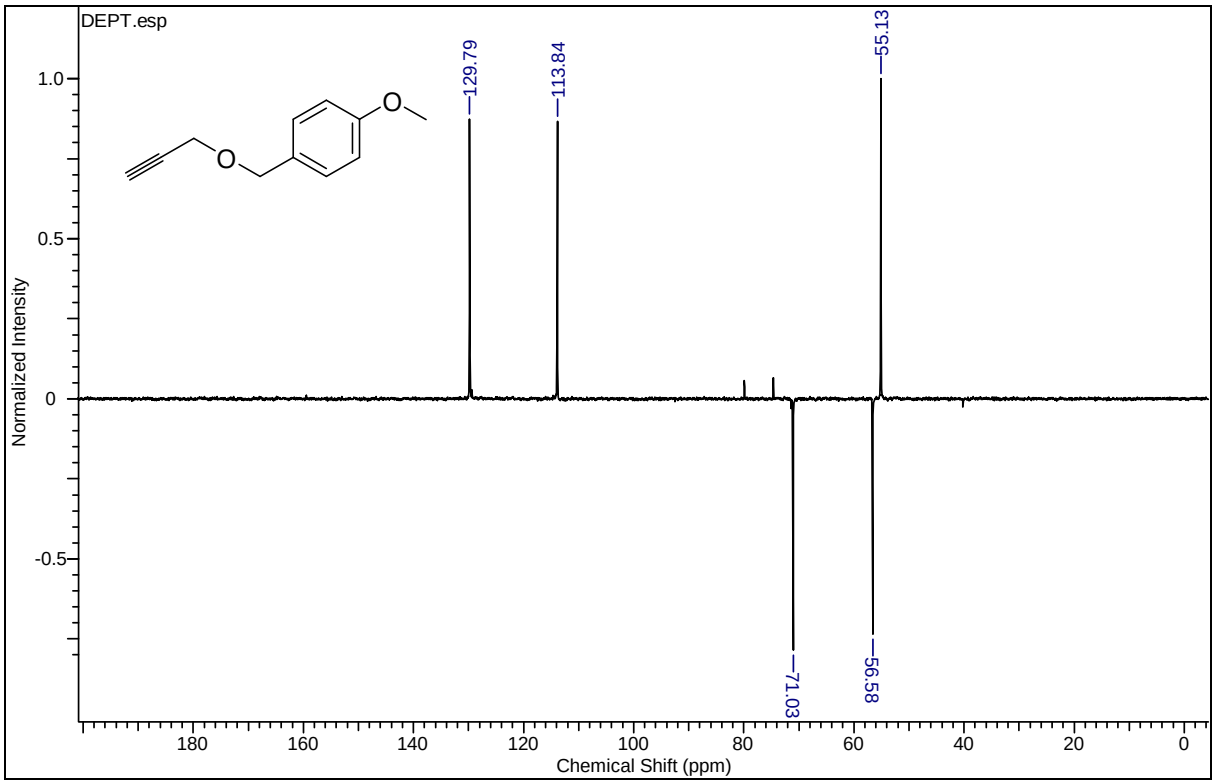
^{1}HNMR of 1-methoxy-4-((prop-2-yn-1-yloxy)methyl)benzene



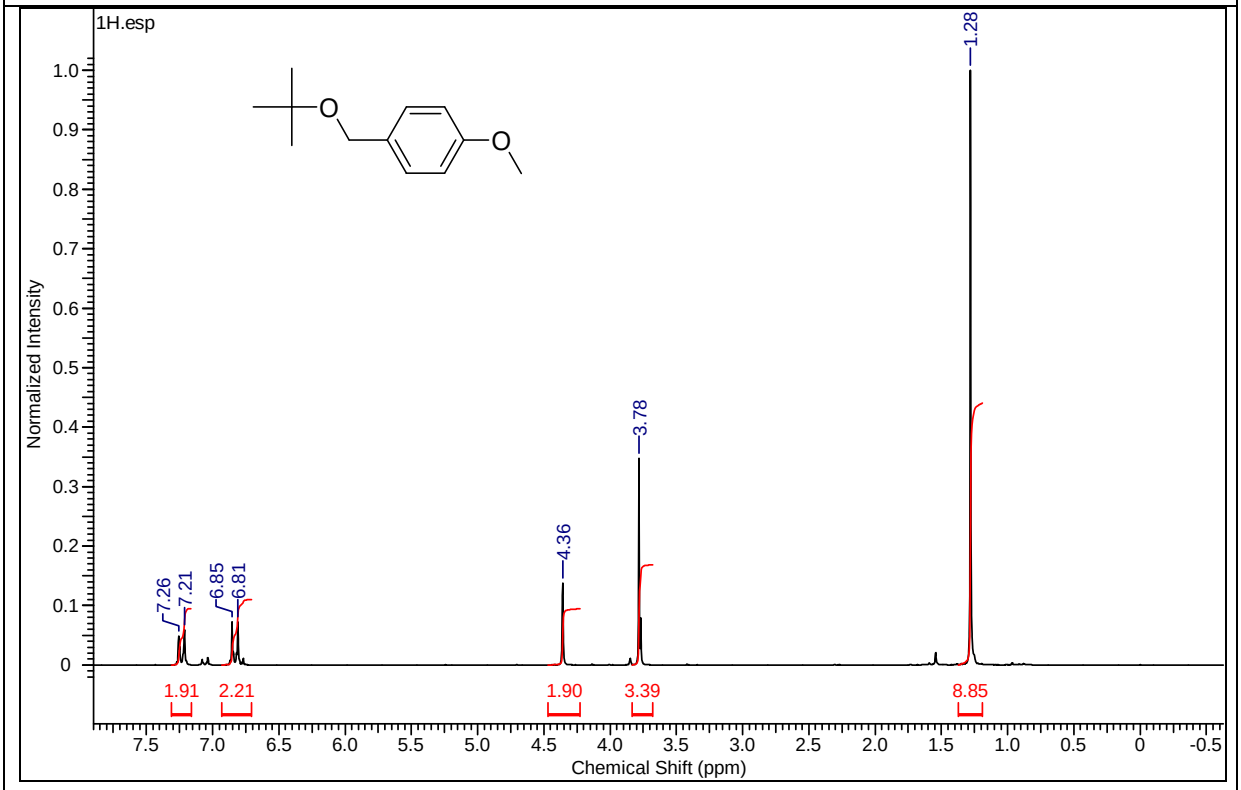
^{13}CNMR of 1-methoxy-4-((prop-2-yn-1-yloxy)methyl)benzene



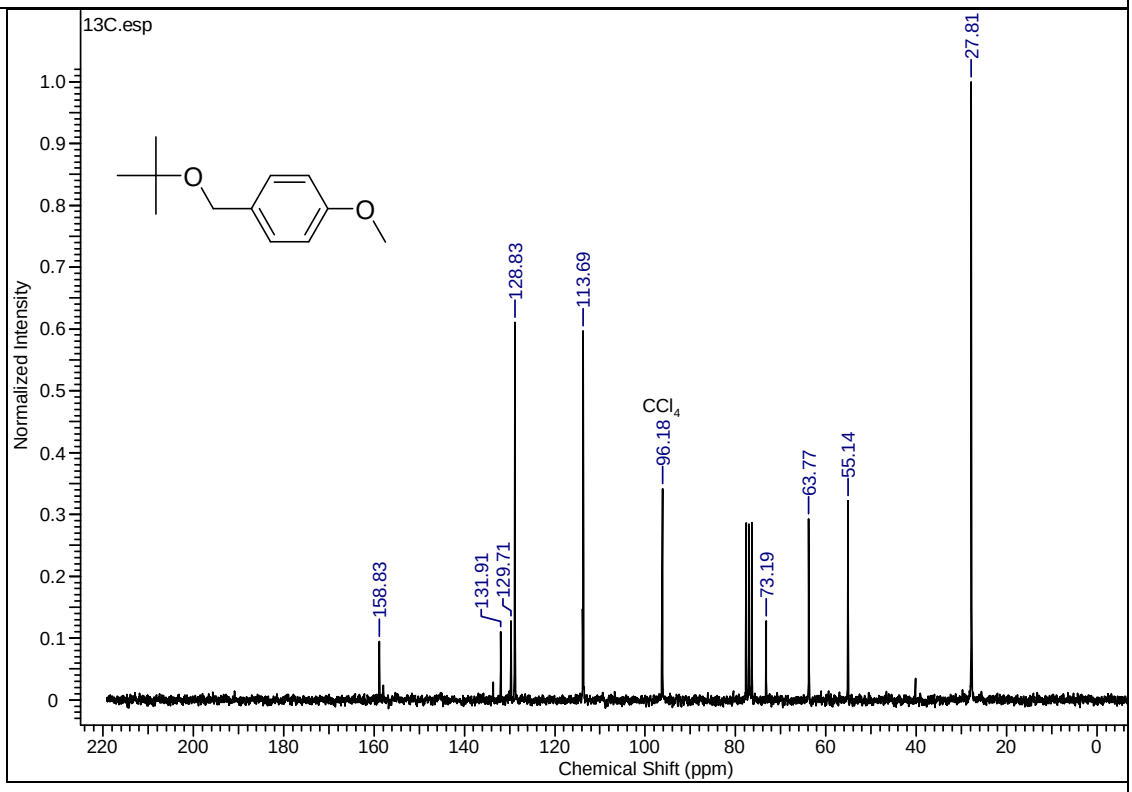
DEPT of 1-methoxy-4-((prop-2-yn-1-yloxy)methyl)benzene



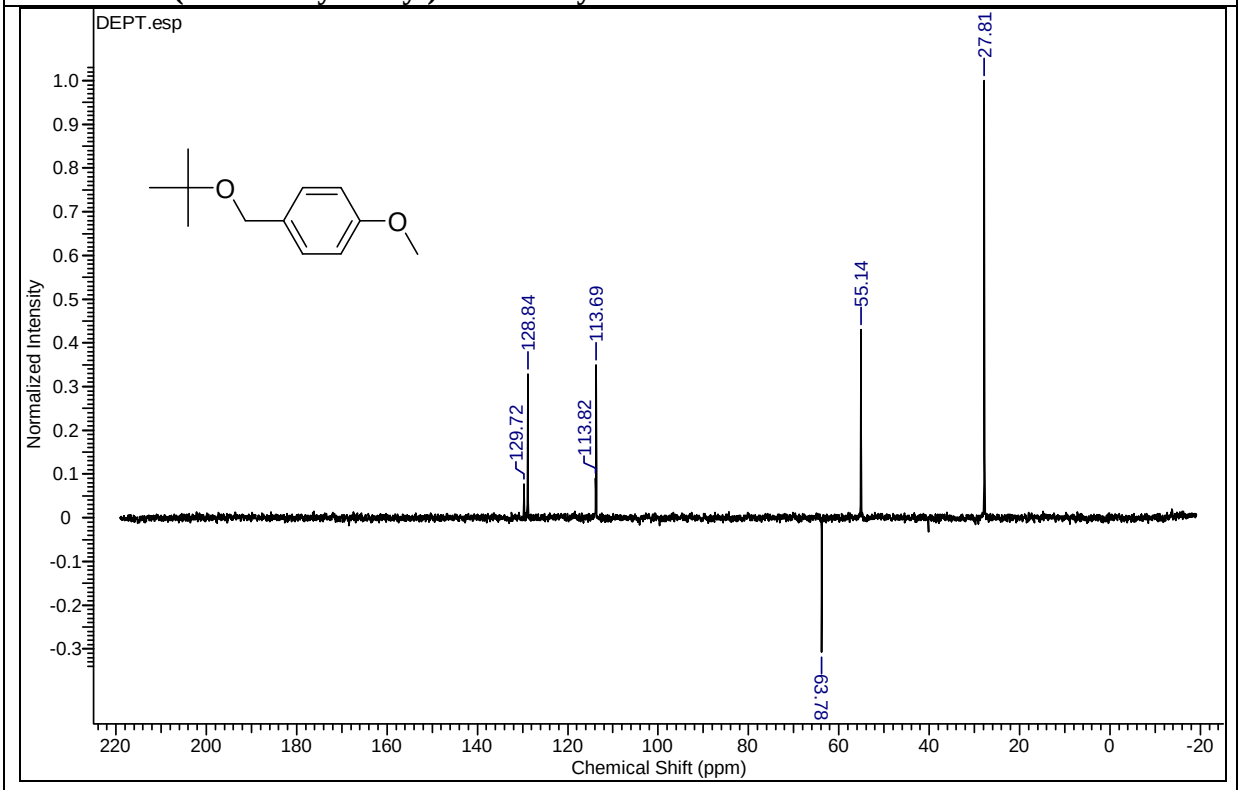
^{1}HNMR of 1-(*tert*-butoxymethyl)-4-methoxybenzene



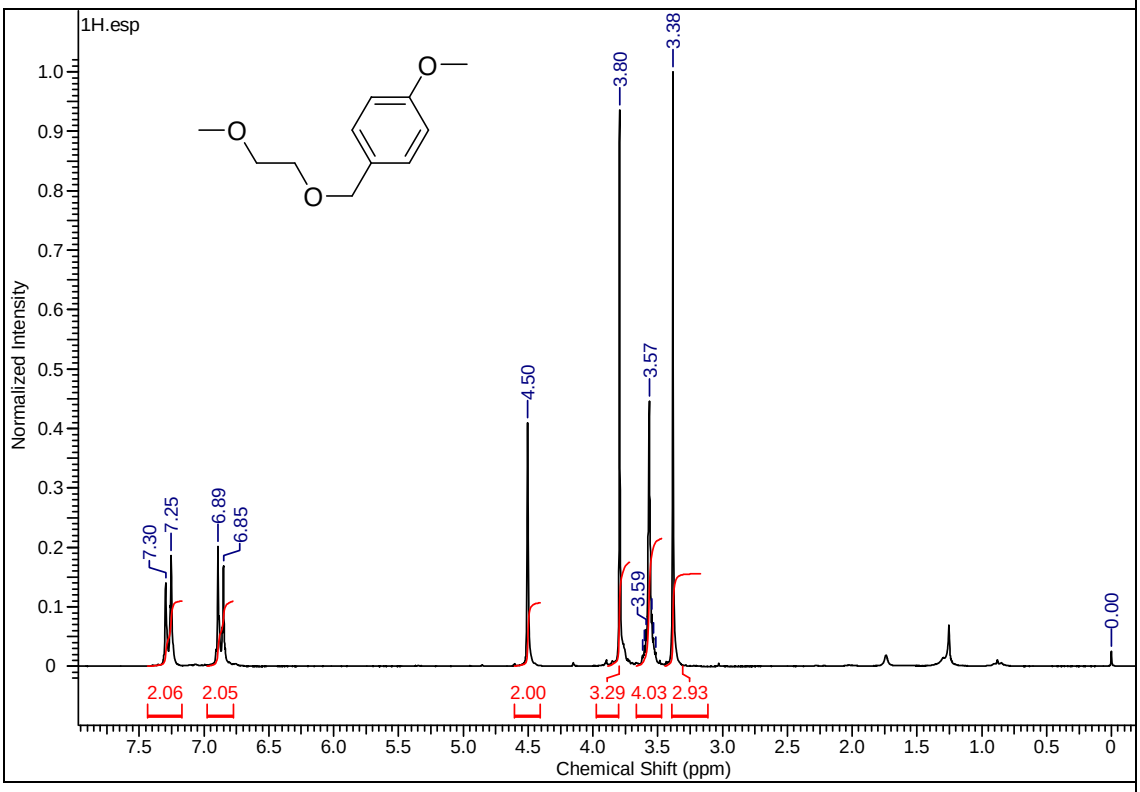
^{13}CNMR of 1-(*tert*-butoxymethyl)-4-methoxybenzene



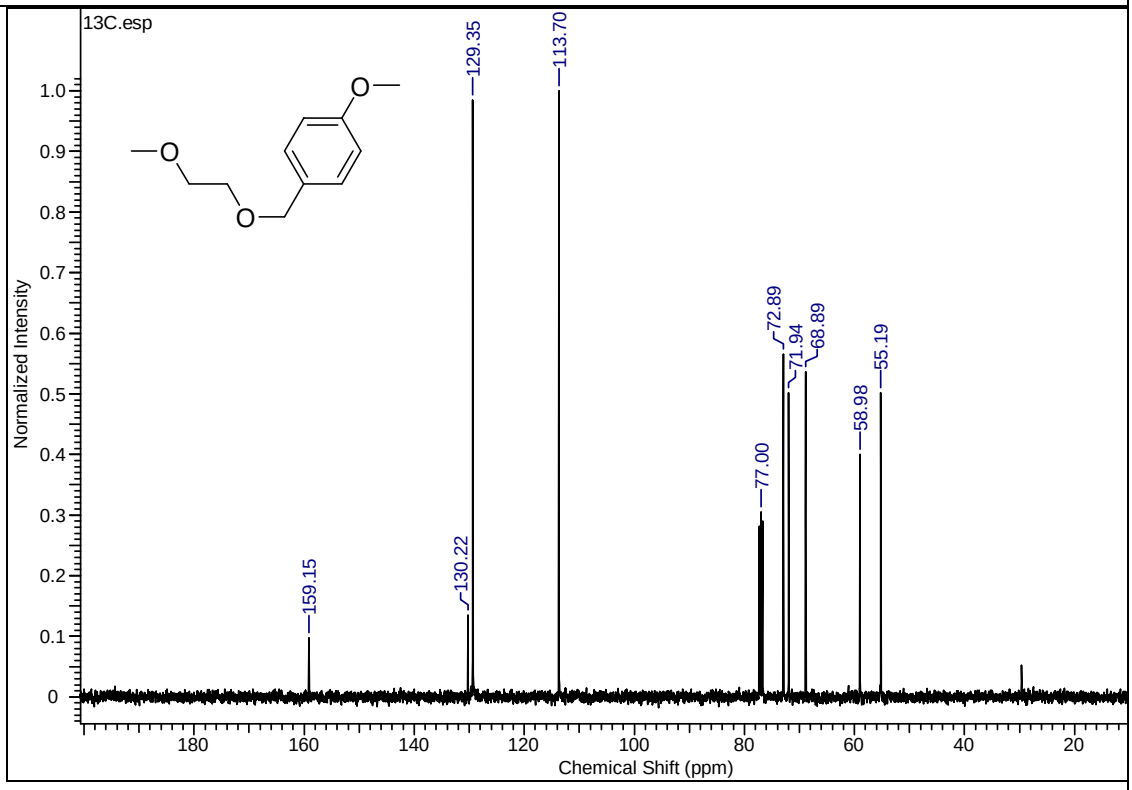
DEPT of 1-(*tert*-butoxymethyl)-4-methoxybenzene



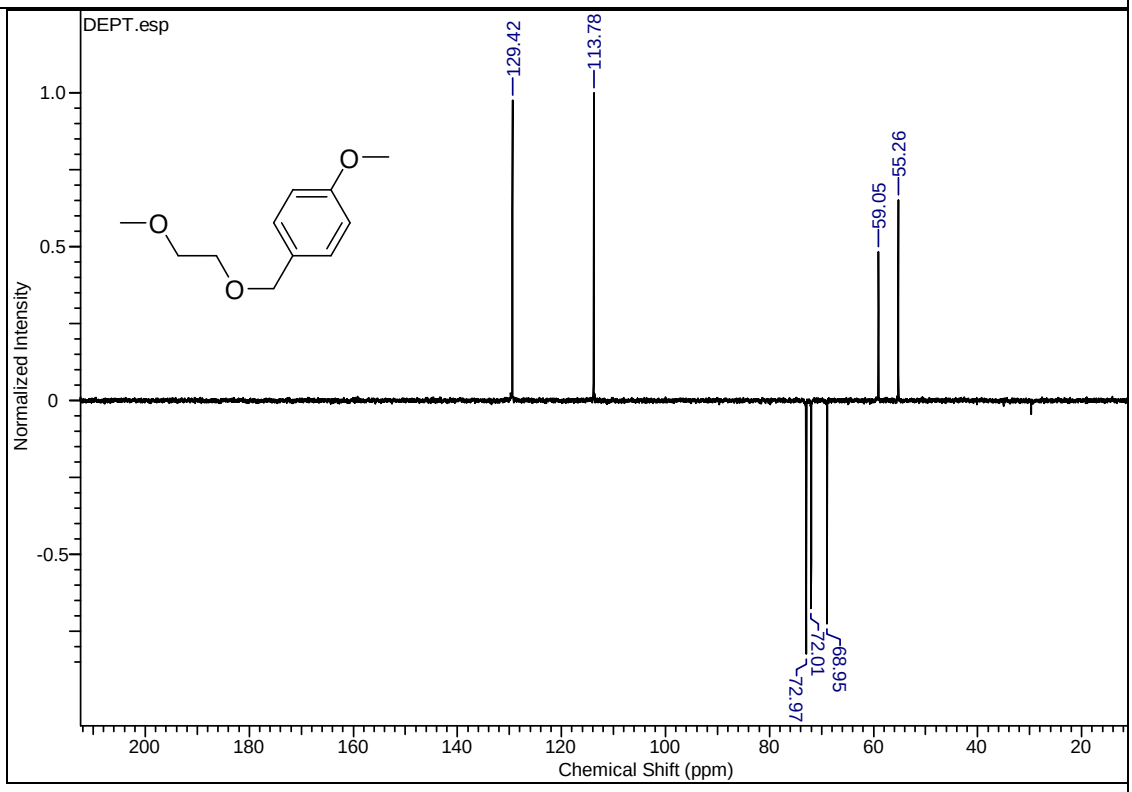
^{1}HNMR of 1-methoxy-4-((2-methoxyethoxy)methyl)benzene



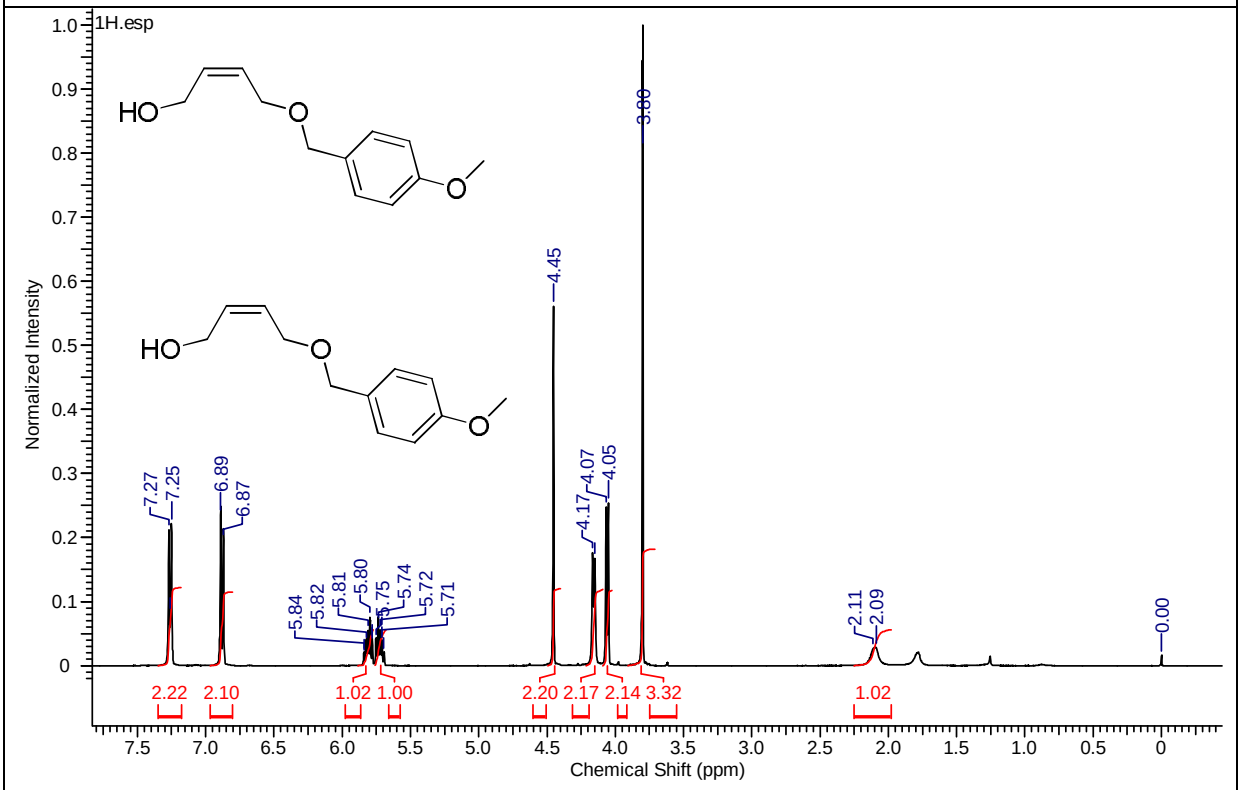
^{13}CNMR of 1-methoxy-4-((2-methoxyethoxy)methyl)benzene



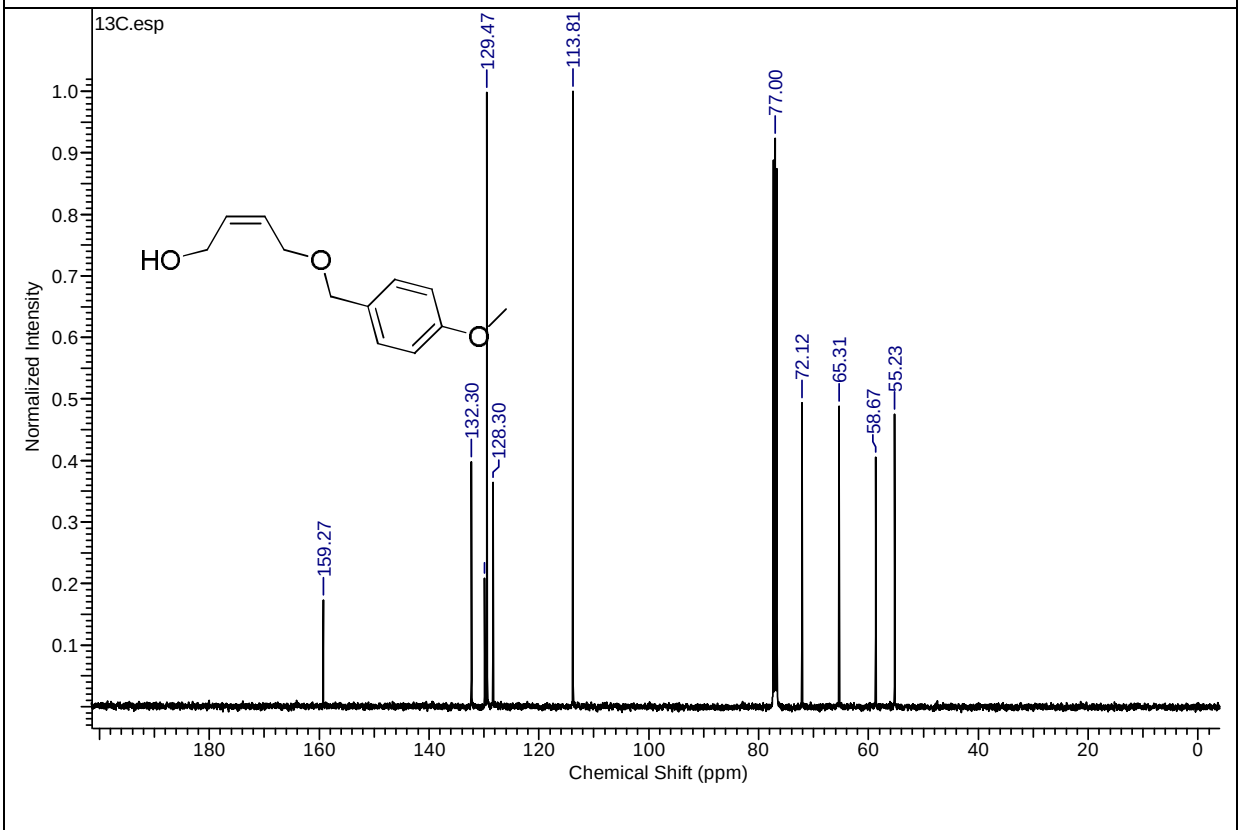
DEPT of 1-methoxy-4-((2-methoxyethoxy)methyl)benzene



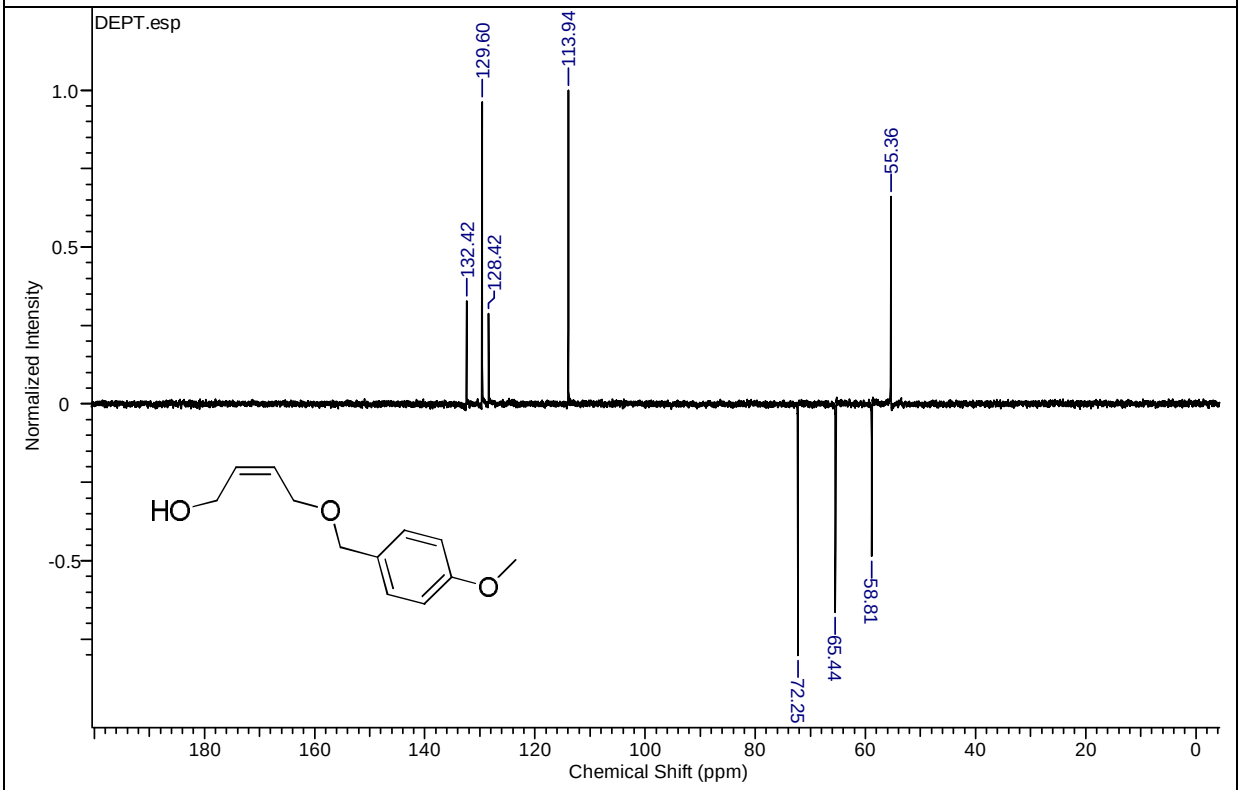
^{1}HNMR of (*Z*)-4-(4-methoxybenzyloxy)but-2-en-1-ol



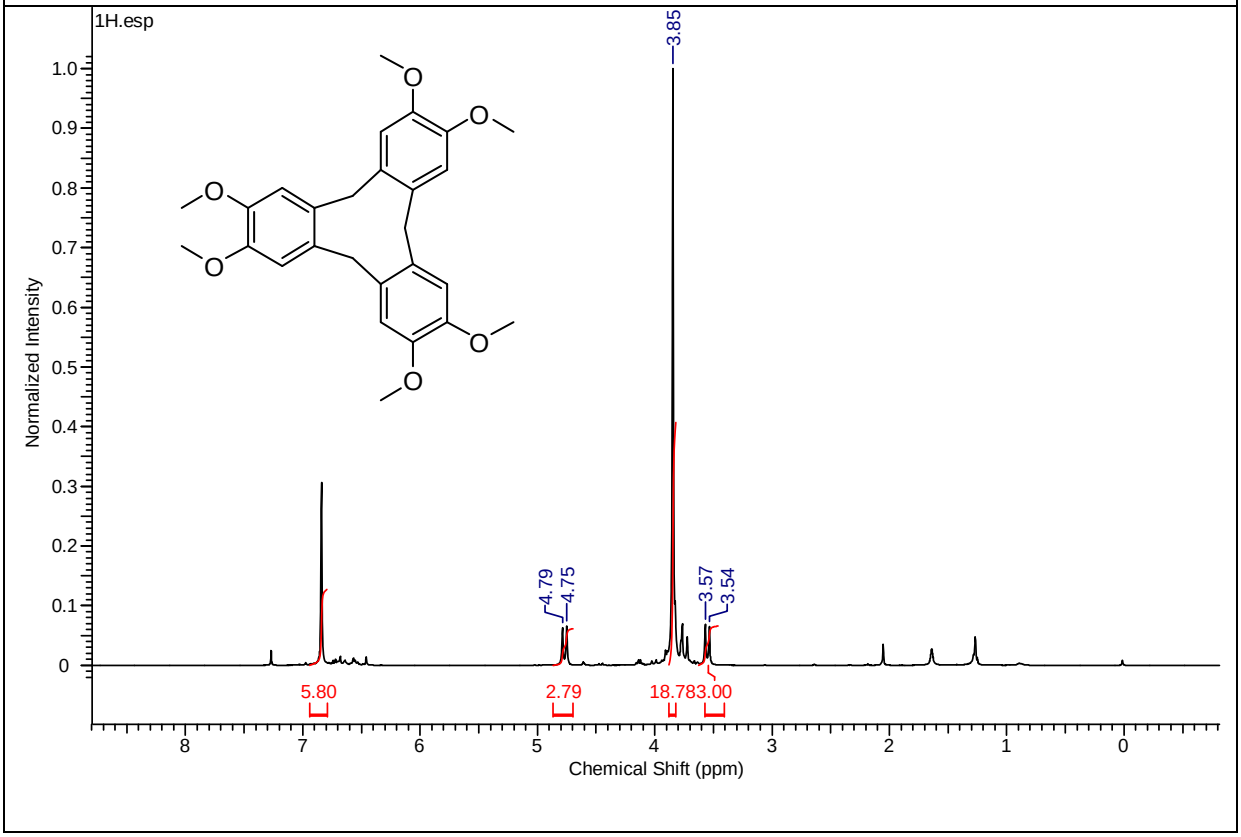
^{13}CNMR of (*Z*)-4-(4-methoxybenzyloxy)but-2-en-1-ol



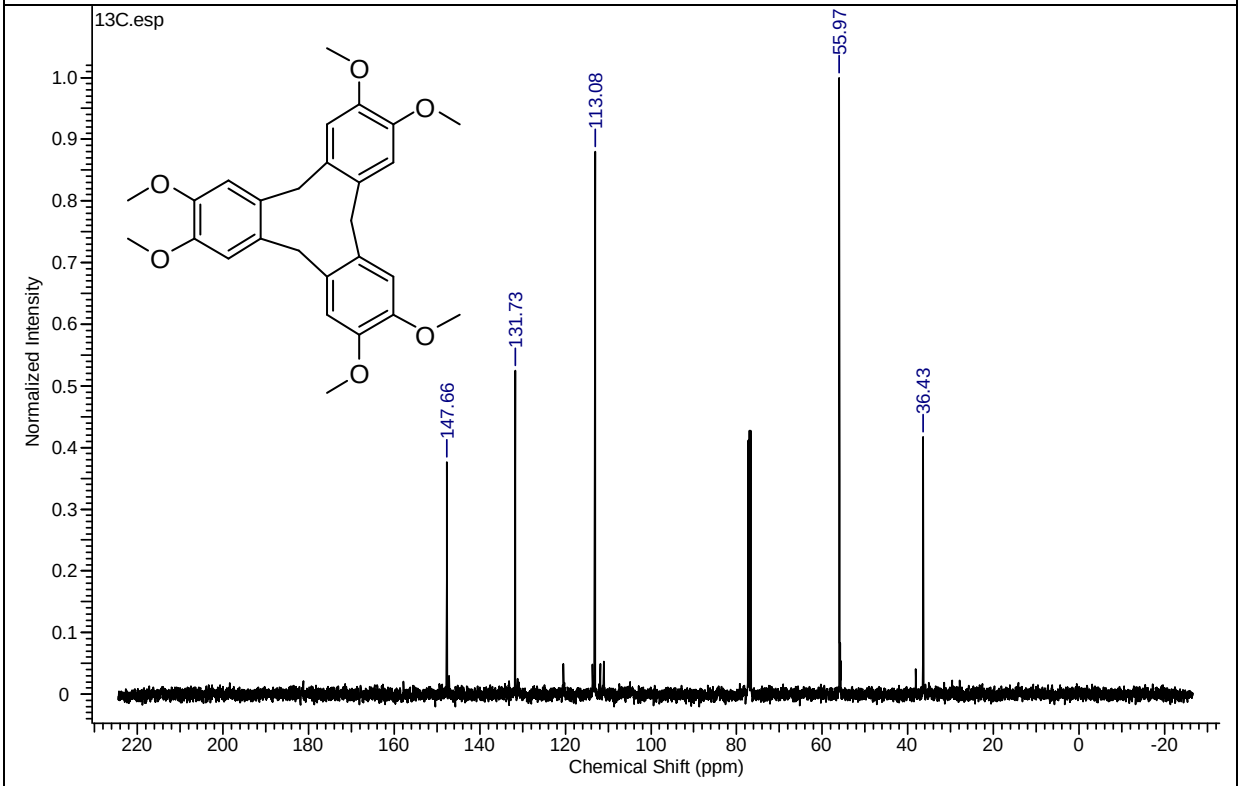
DEPT of (*Z*)-4-(4-methoxybenzyloxy)but-2-en-1-ol



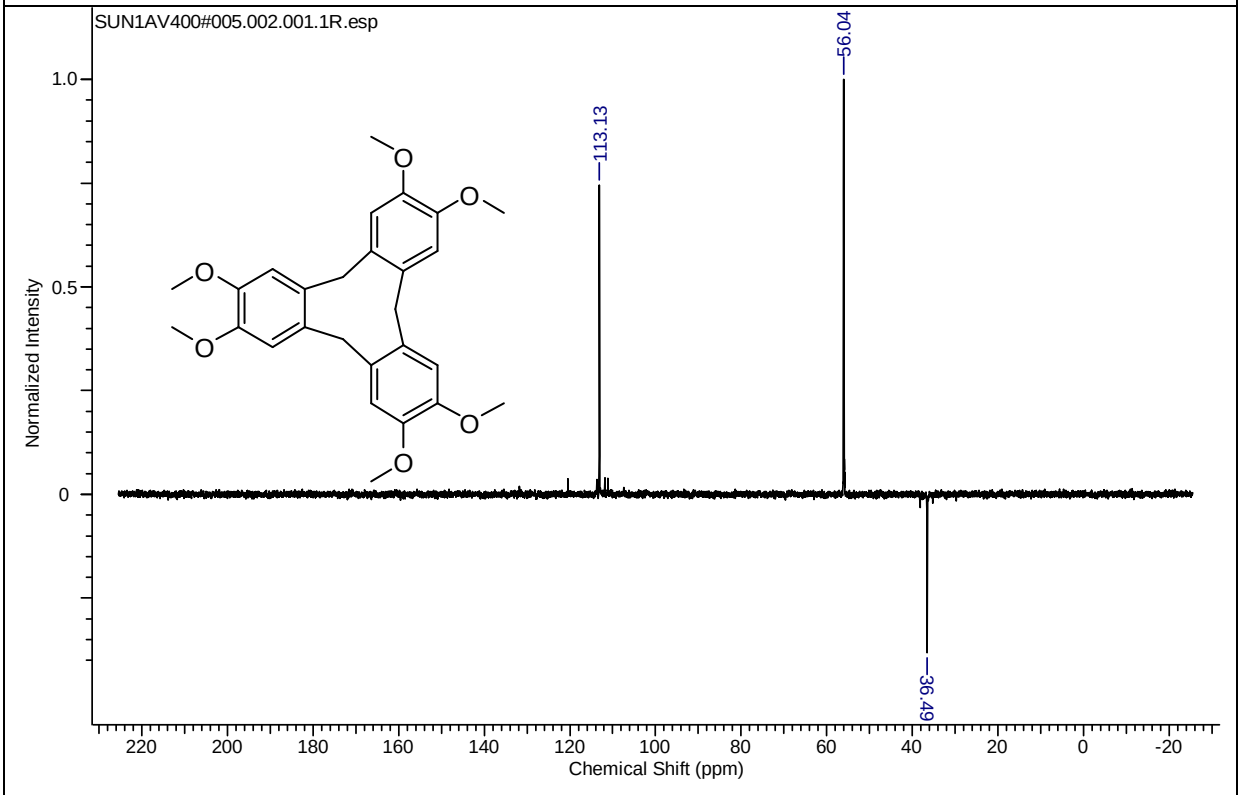
^{1}HNMR of cyclotriveratrilene



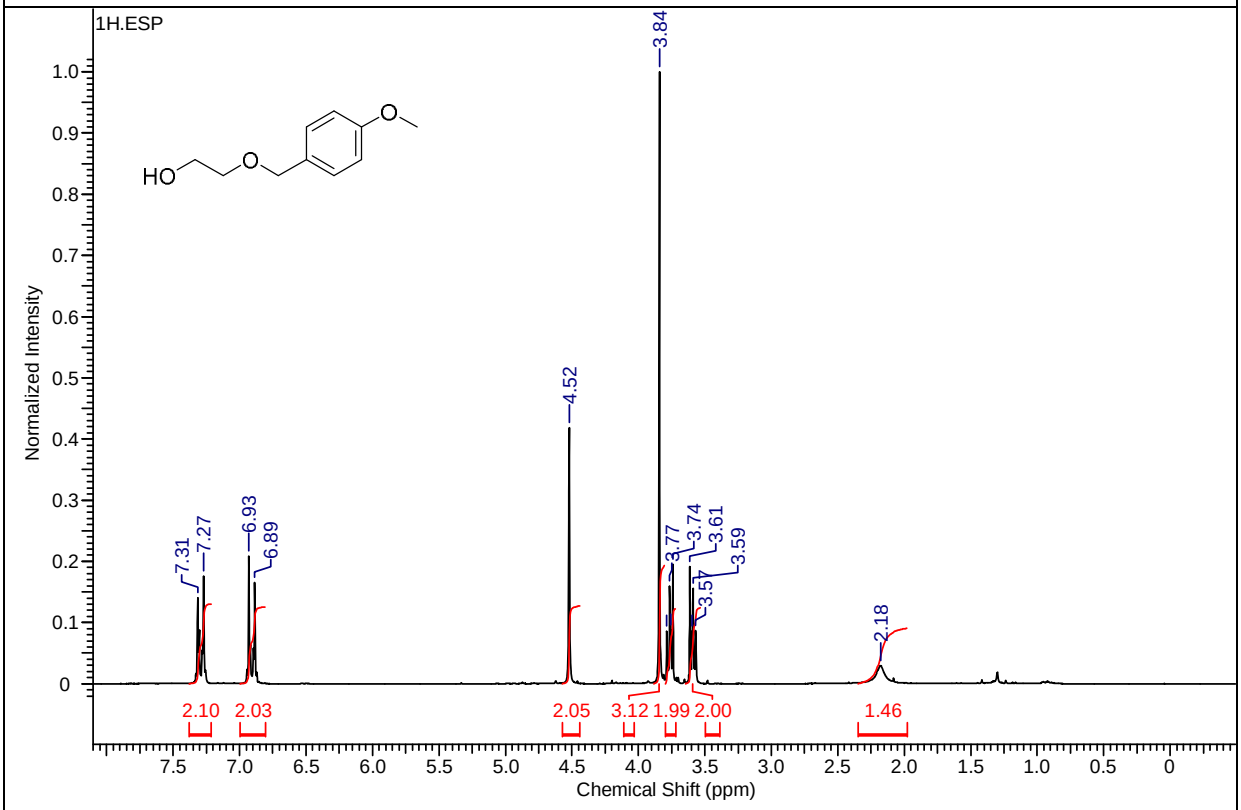
^{13}CNMR of cyclotriveratrilene



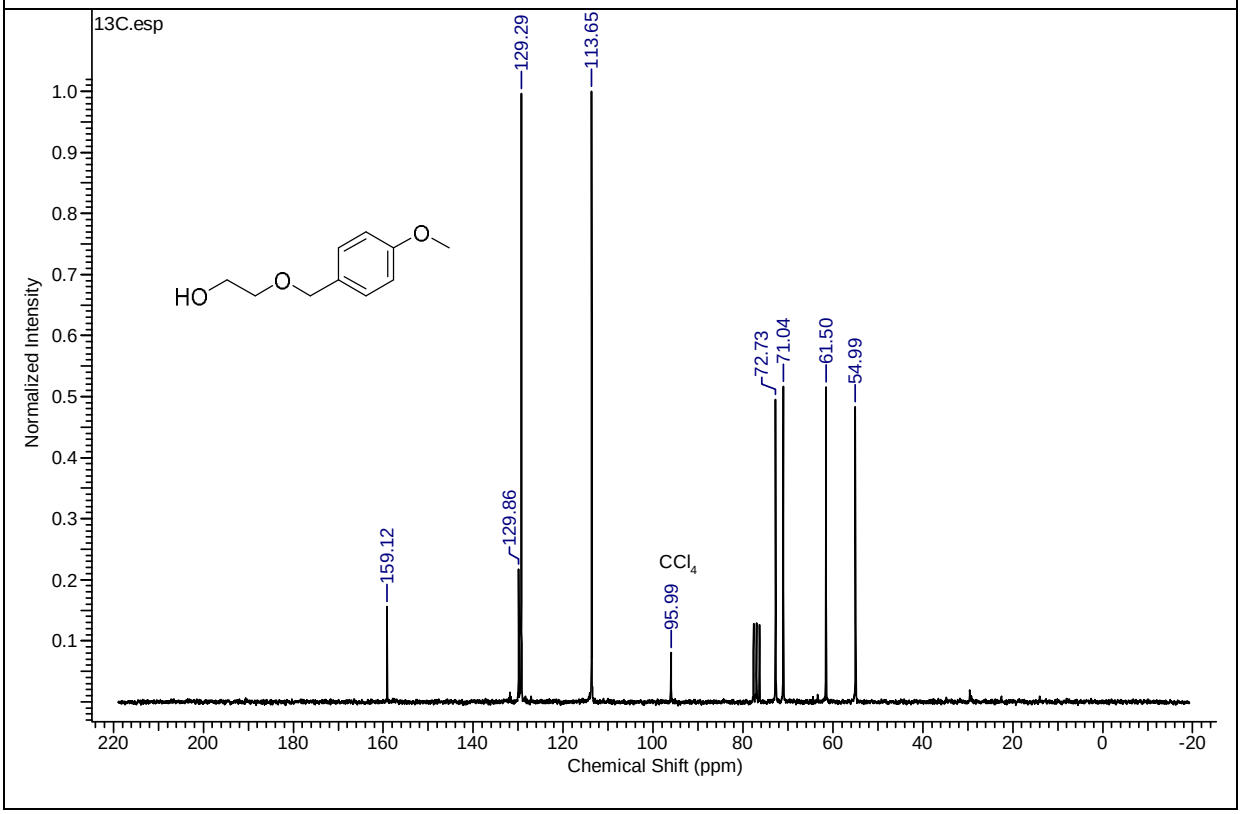
DEPT of cyclotriveratrilene



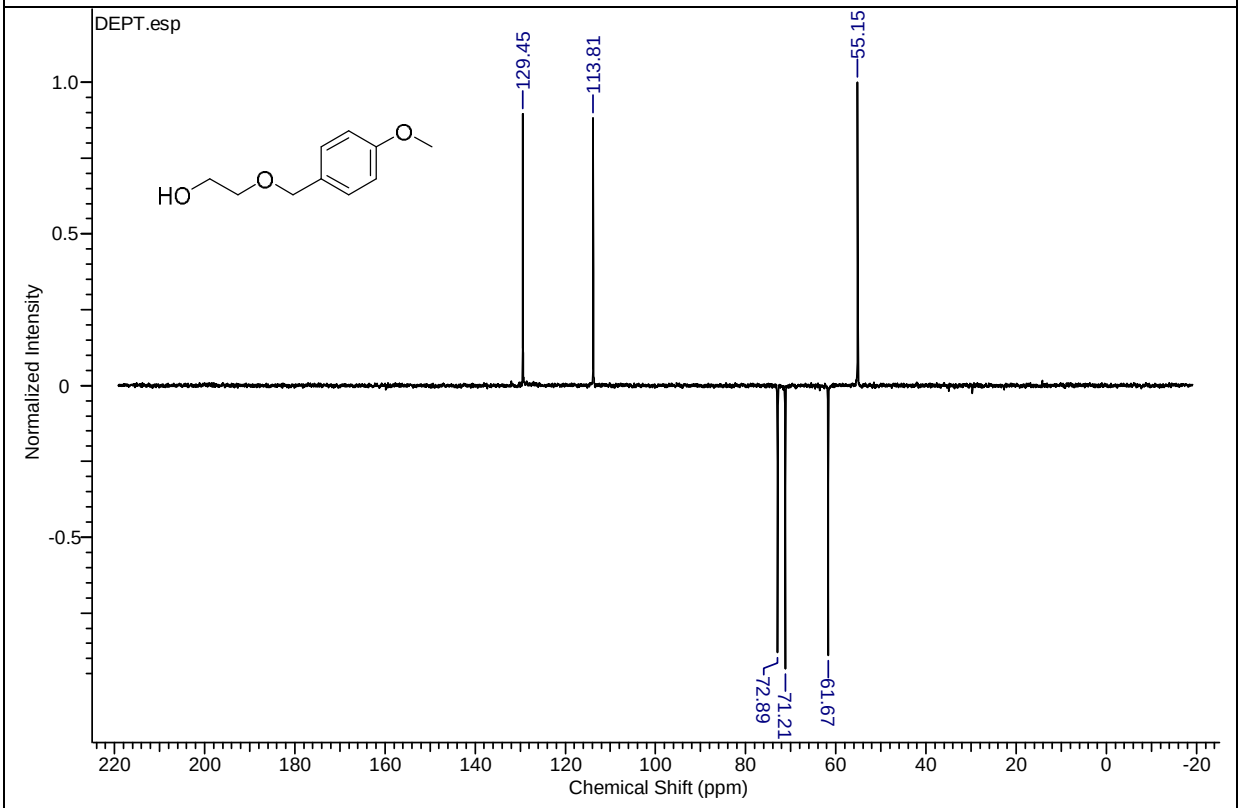
^{1}HNMR of 2-((4-methoxybenzyl)oxy)ethan-1-ol



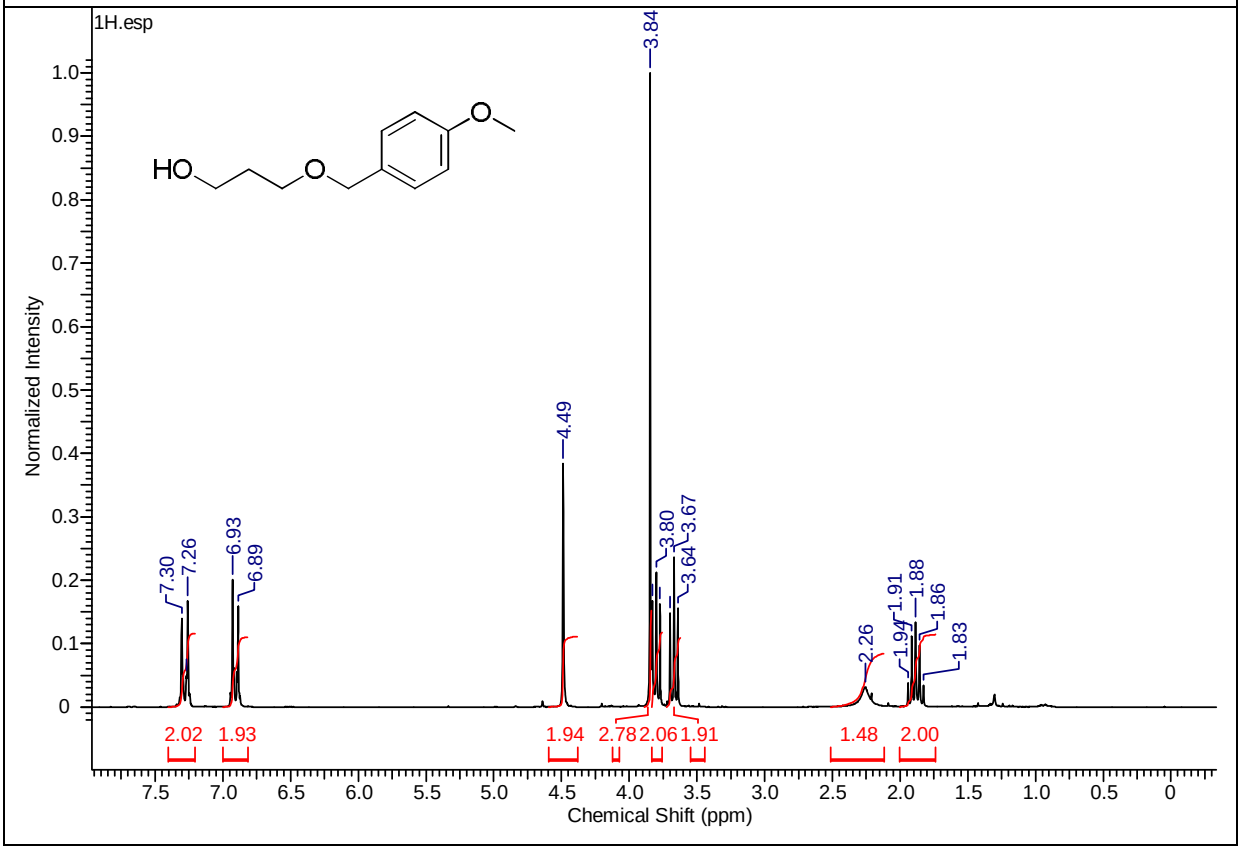
^{13}CNMR of 2-((4-methoxybenzyl)oxy)ethan-1-ol



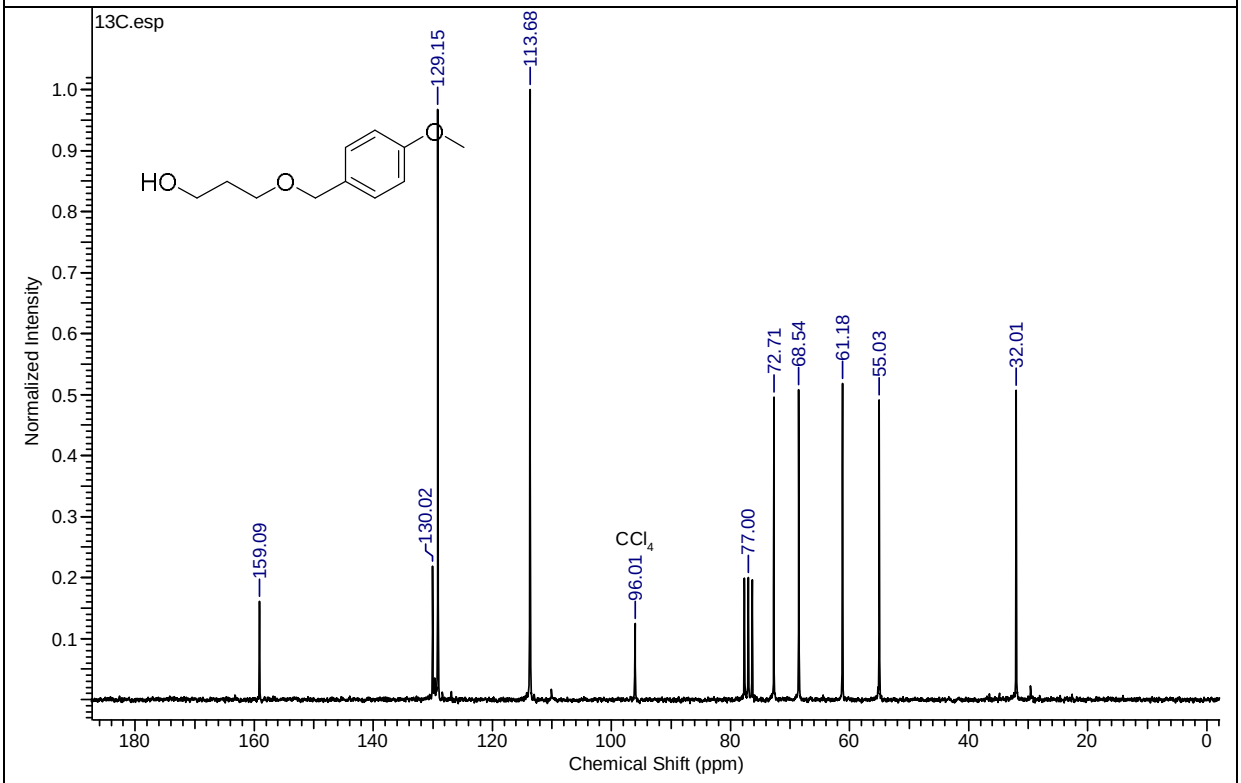
DEPT of 2-((4-methoxybenzyl)oxy)ethan-1-ol



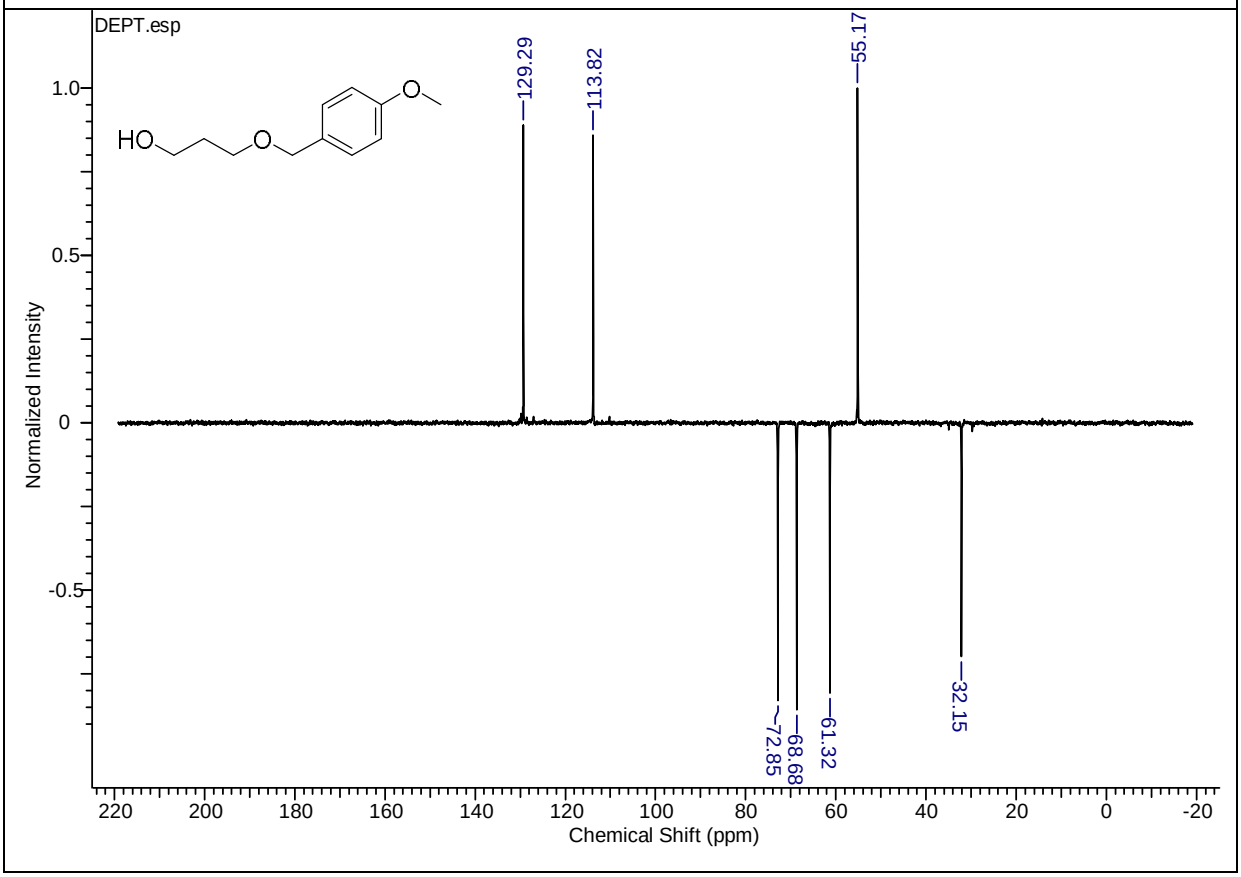
^{1}HNMR of 3-((4-methoxybenzyl)oxy)propan-1-ol



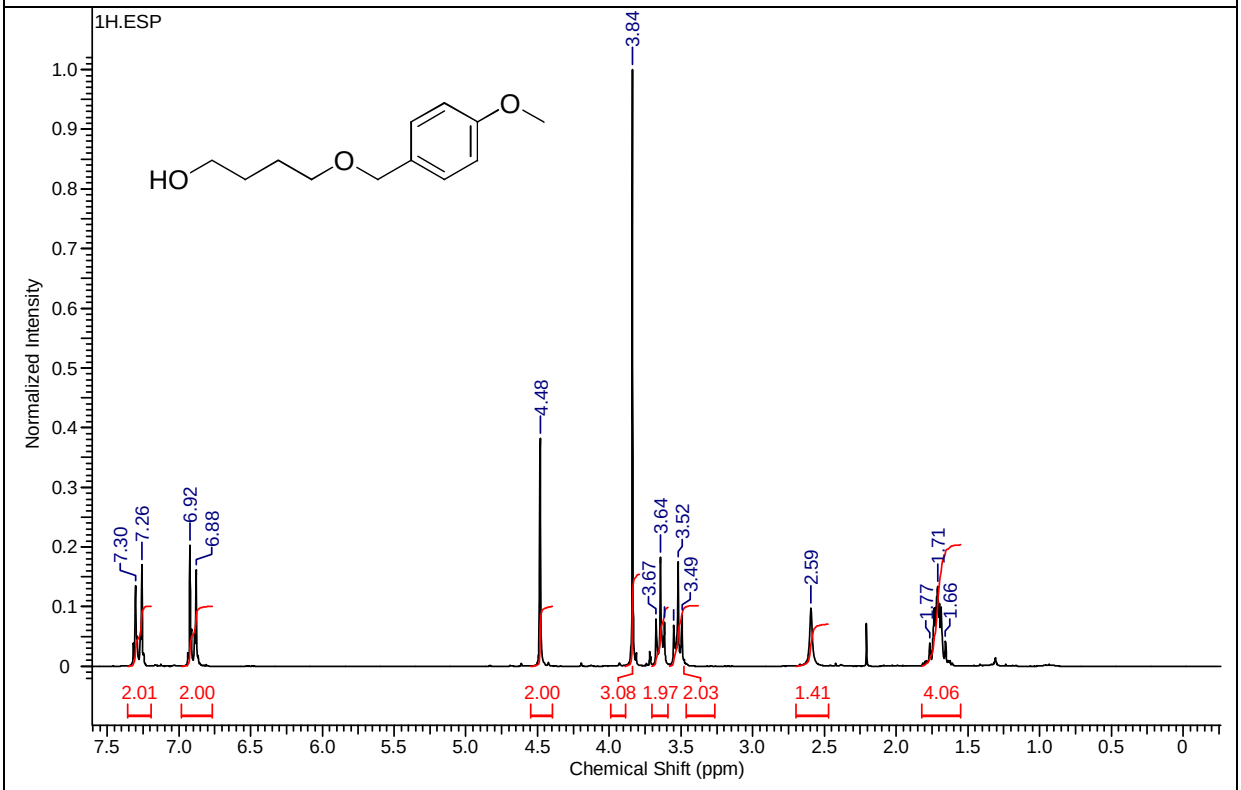
^{13}CNMR of 3-((4-methoxybenzyl)oxy)propan-1-ol



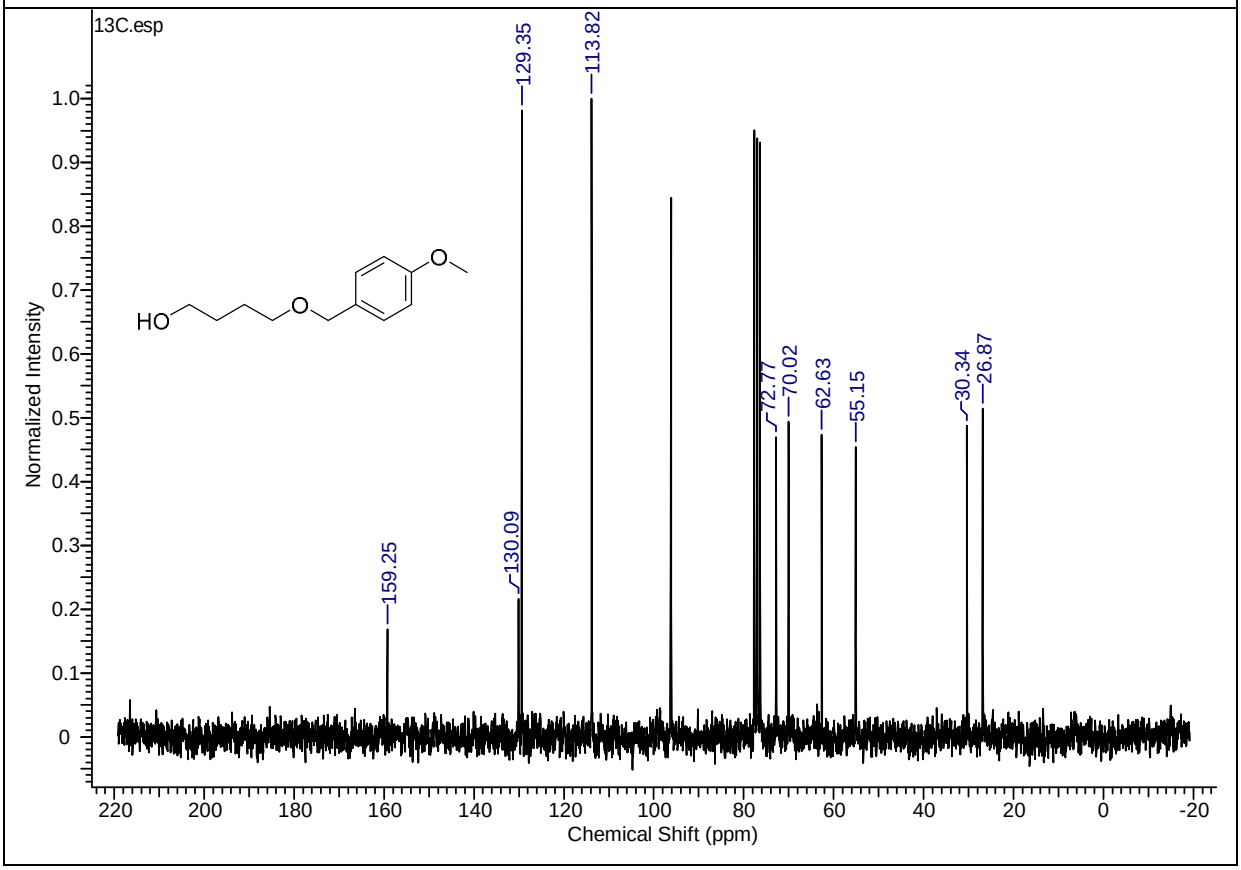
DEPT of 3-((4-methoxybenzyl)oxy)propan-1-ol



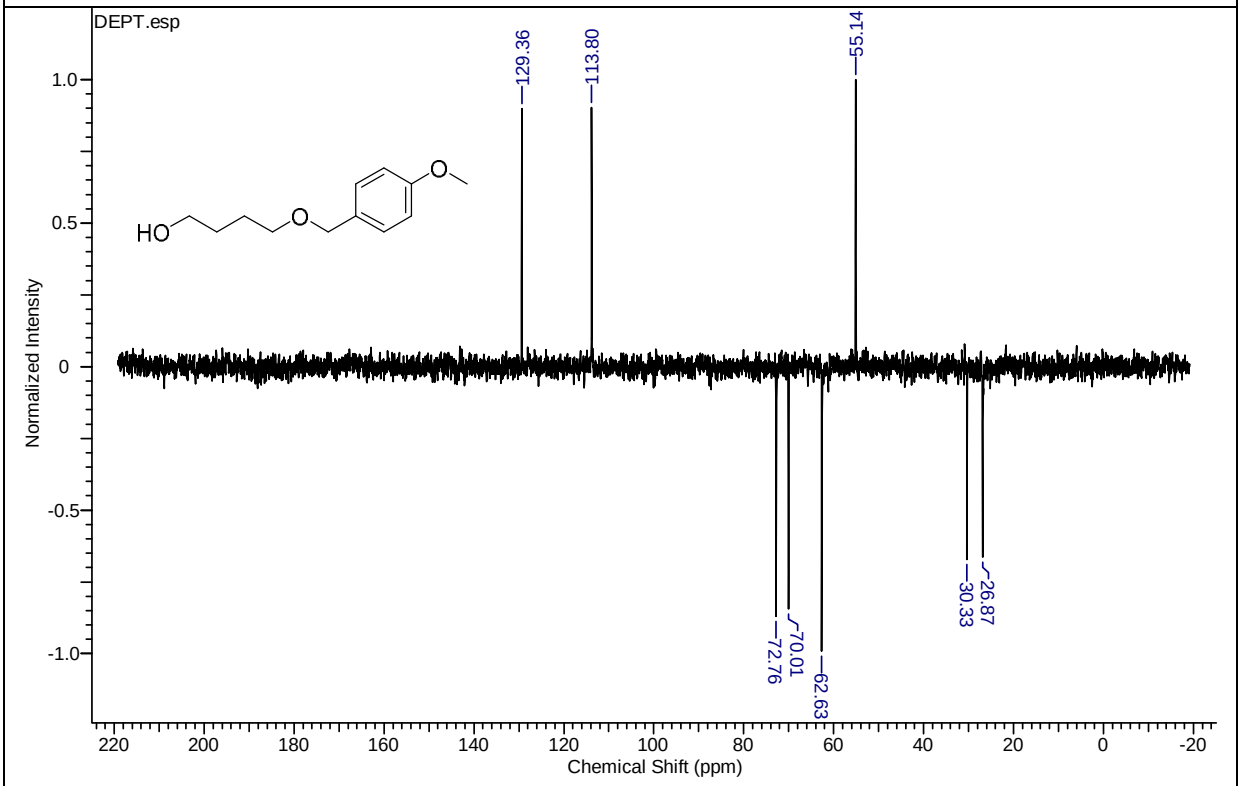
^{1}HNMR of 4-((4-methoxybenzyl)oxy)butan-1-ol



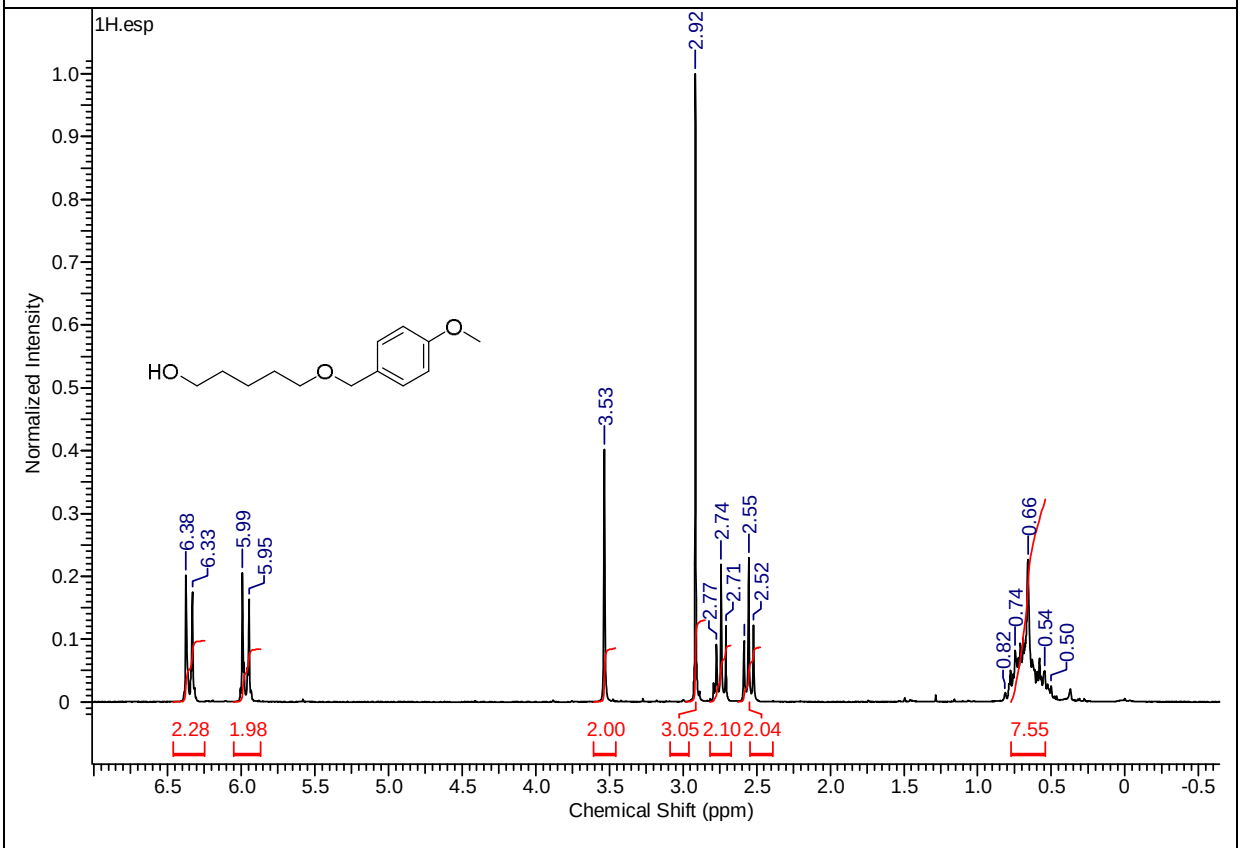
^{13}CNMR of 4-((4-methoxybenzyl)oxy)butan-1-ol



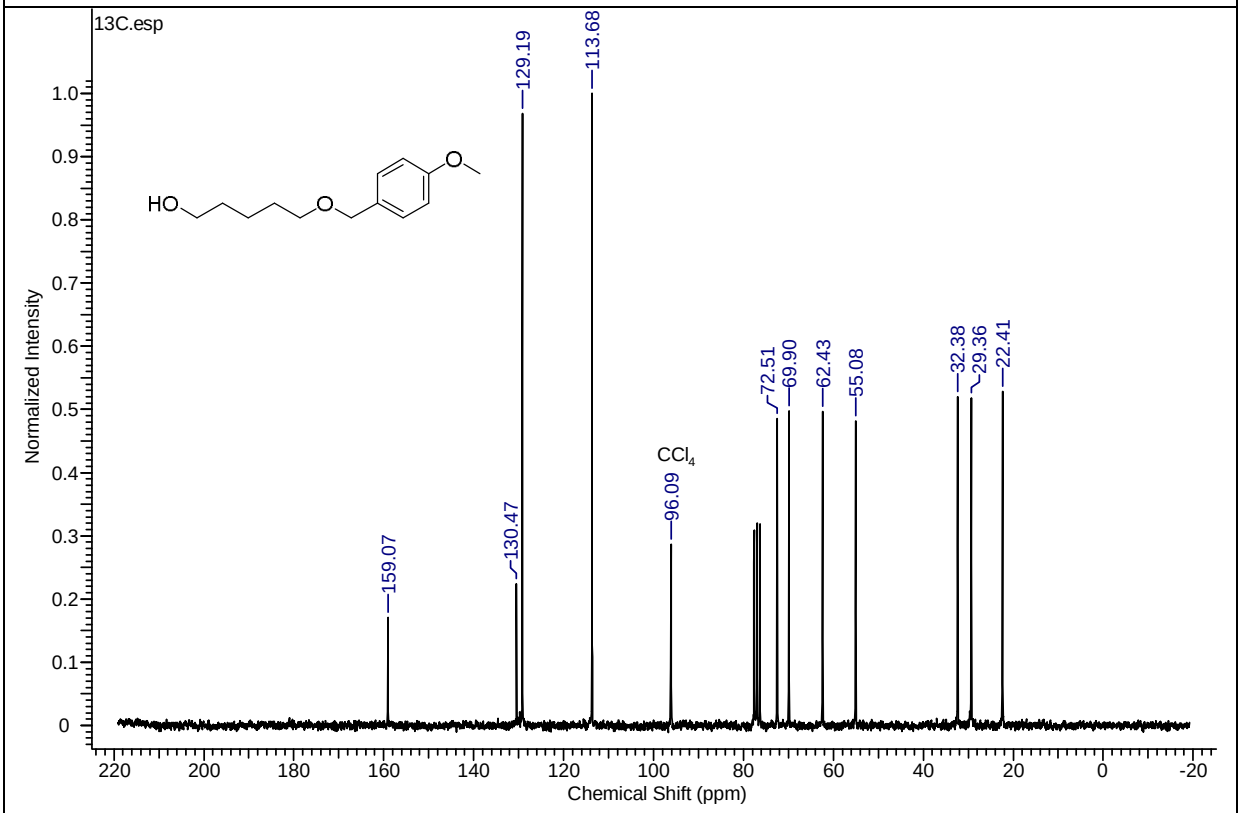
DEPT of 4-((4-methoxybenzyl)oxy)butan-1-ol



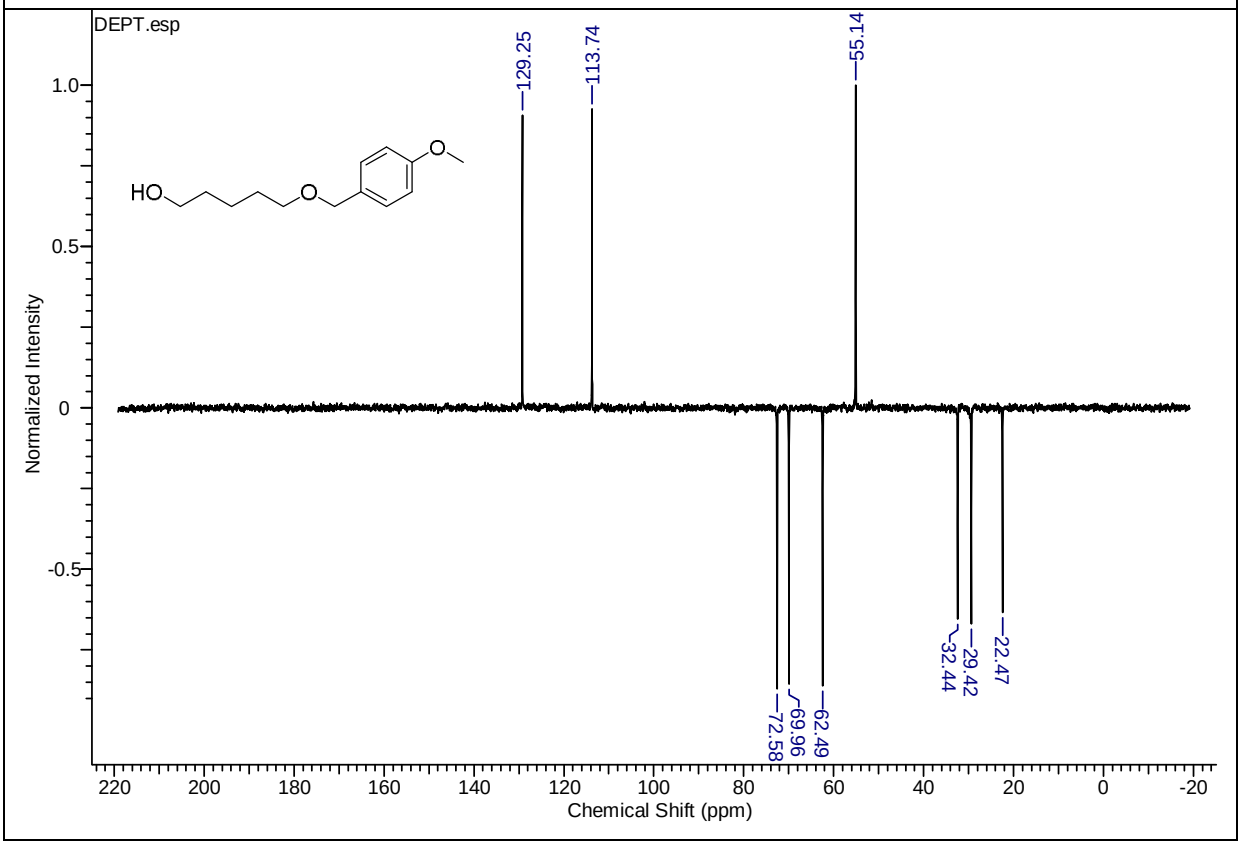
^{1}HNMR of 4-((4-methoxybenzyl)oxy)pentan-1-ol



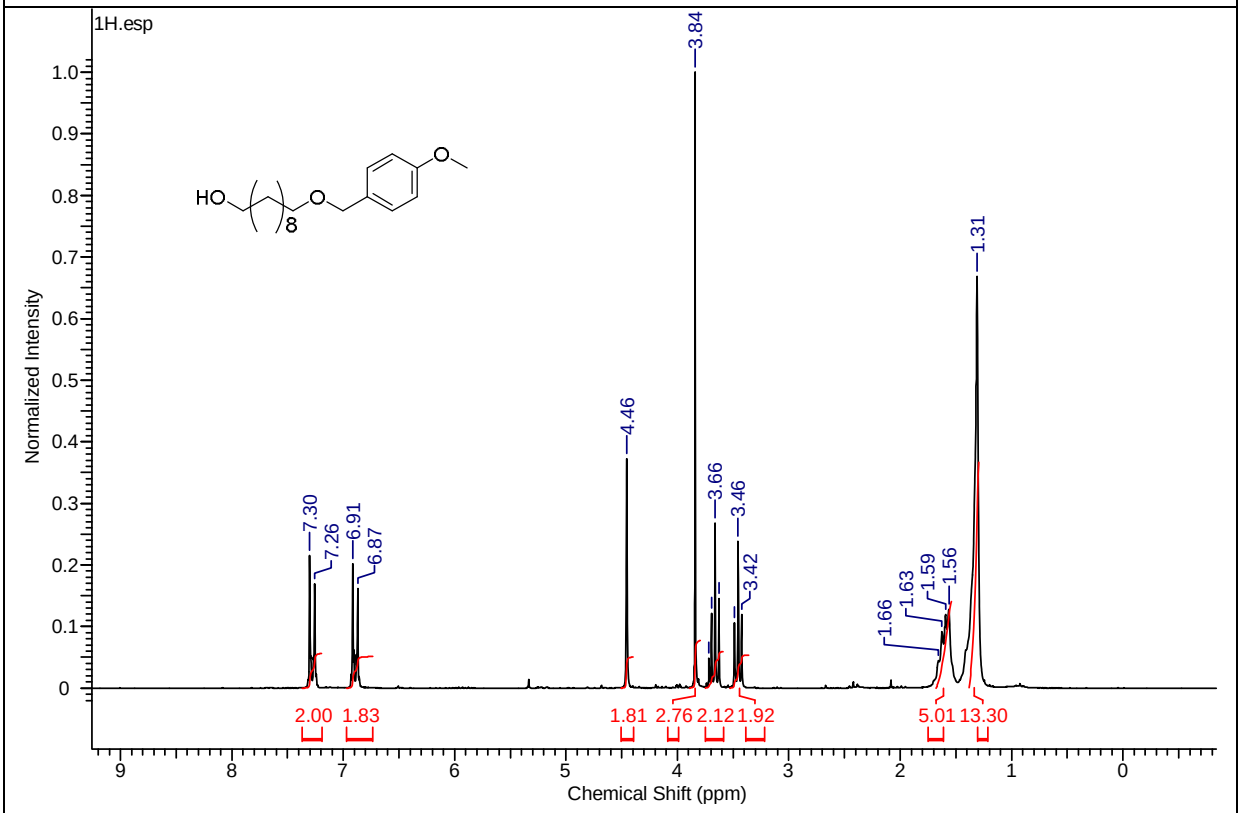
^{13}CNMR of 4-((4-methoxybenzyl)oxy)pentan-1-ol



DEPT of 4-((4-methoxybenzyl)oxy)pentan-1-ol



^{1}HNMR of 4-((4-methoxybenzyl)oxy)decan-1-ol



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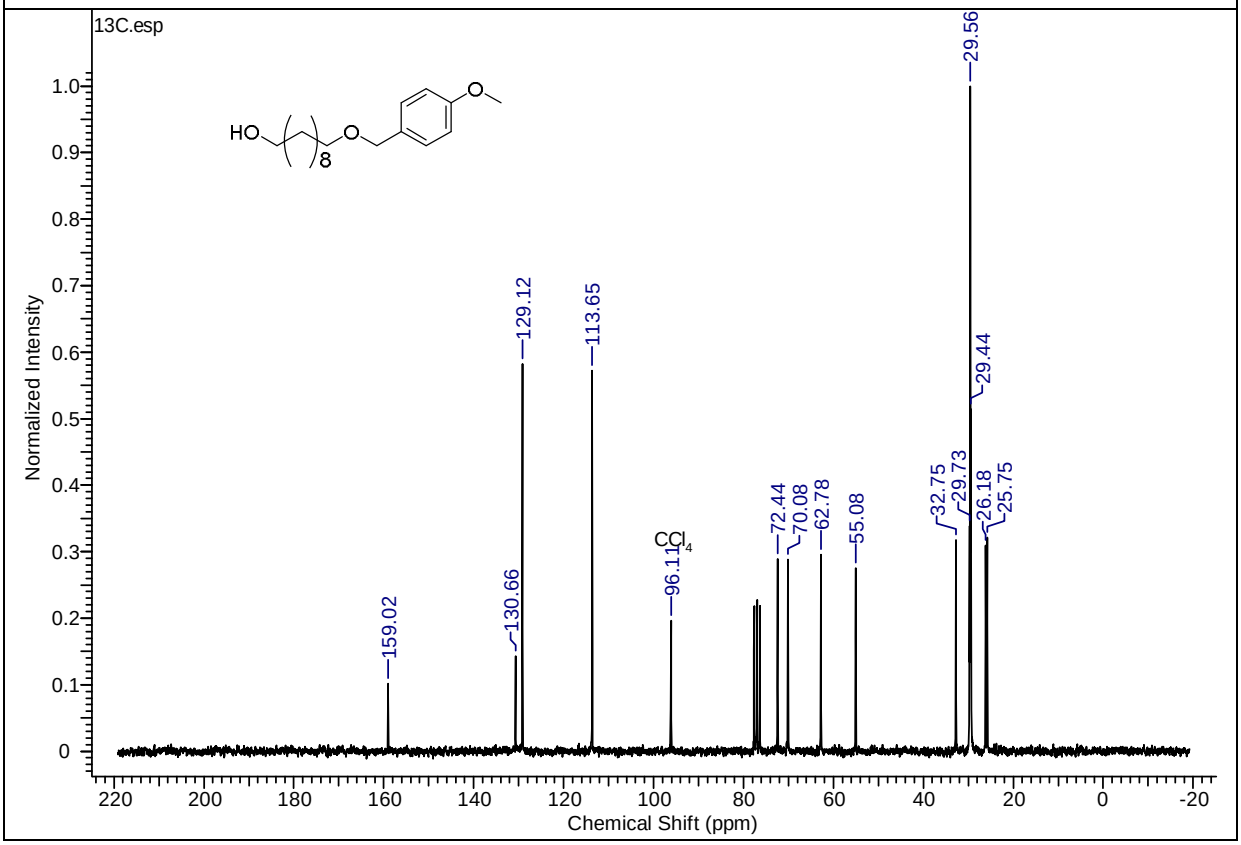

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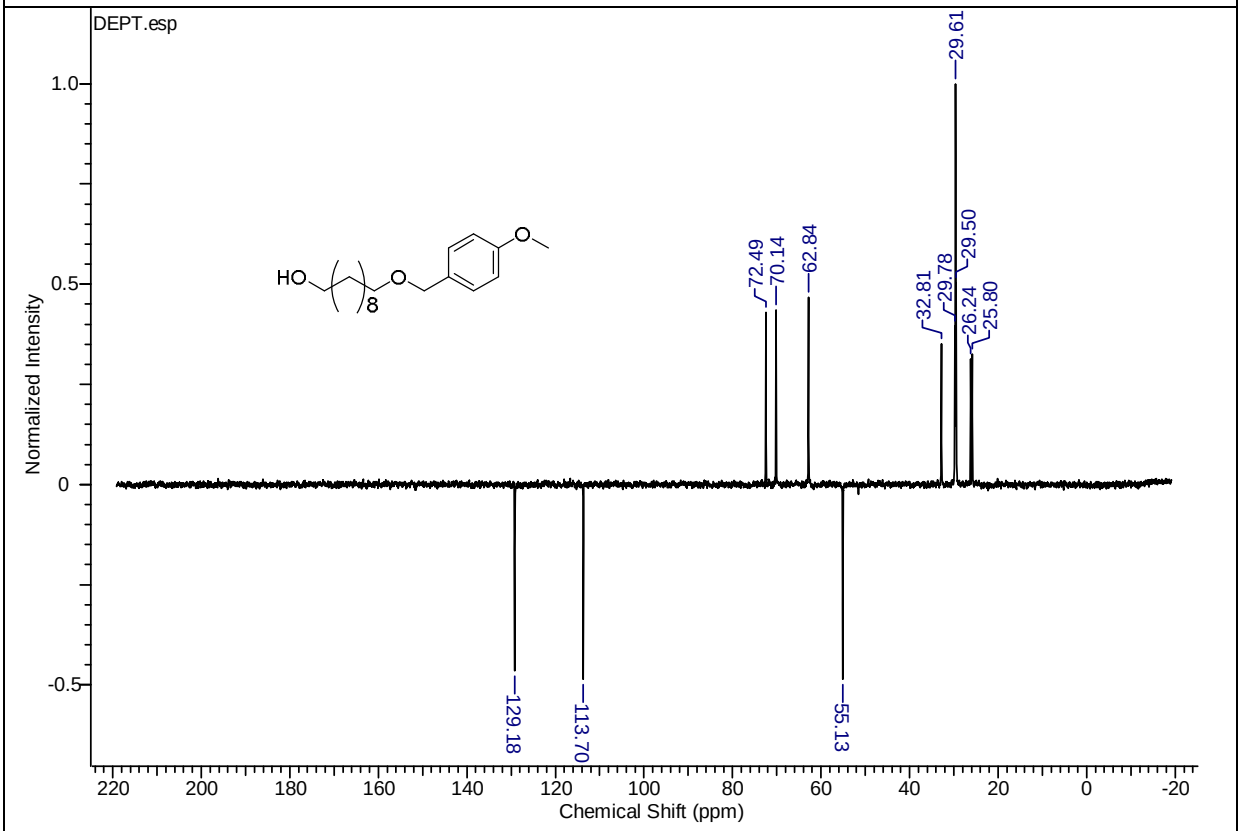

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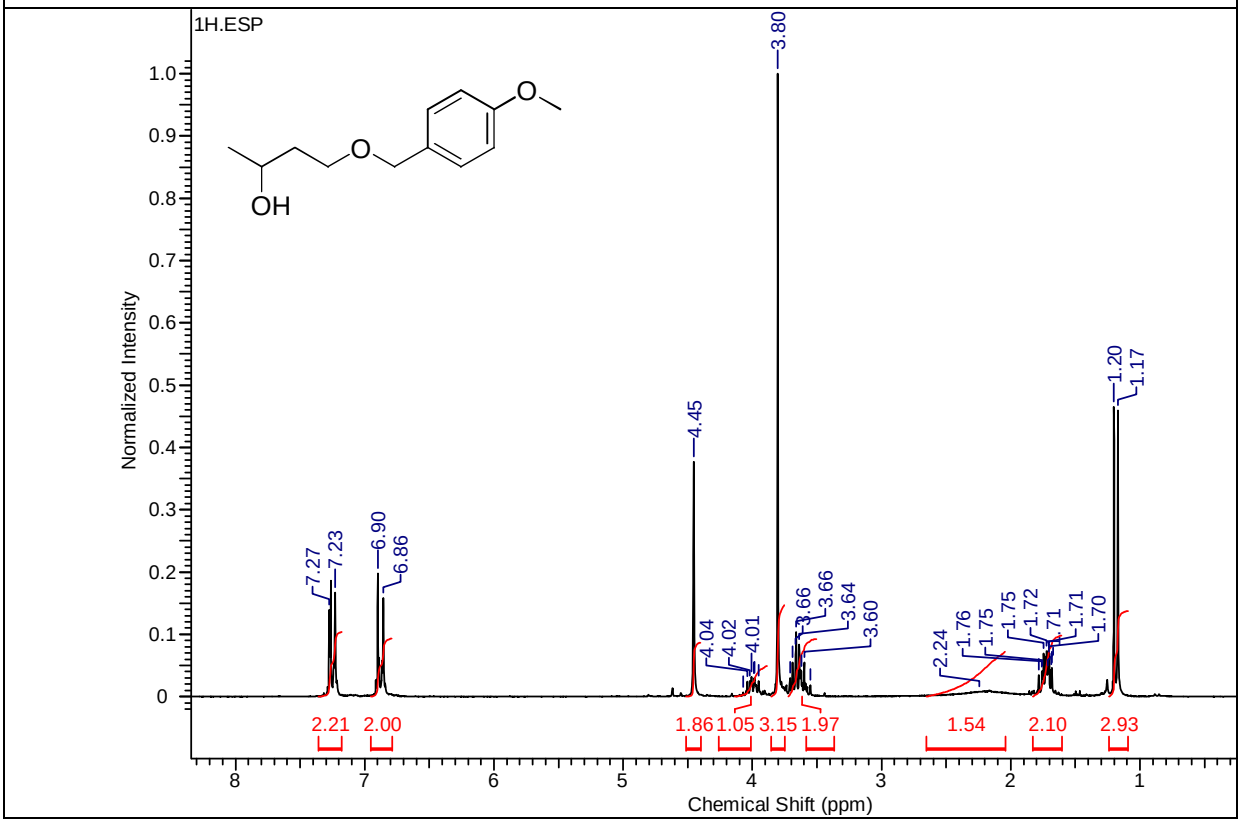

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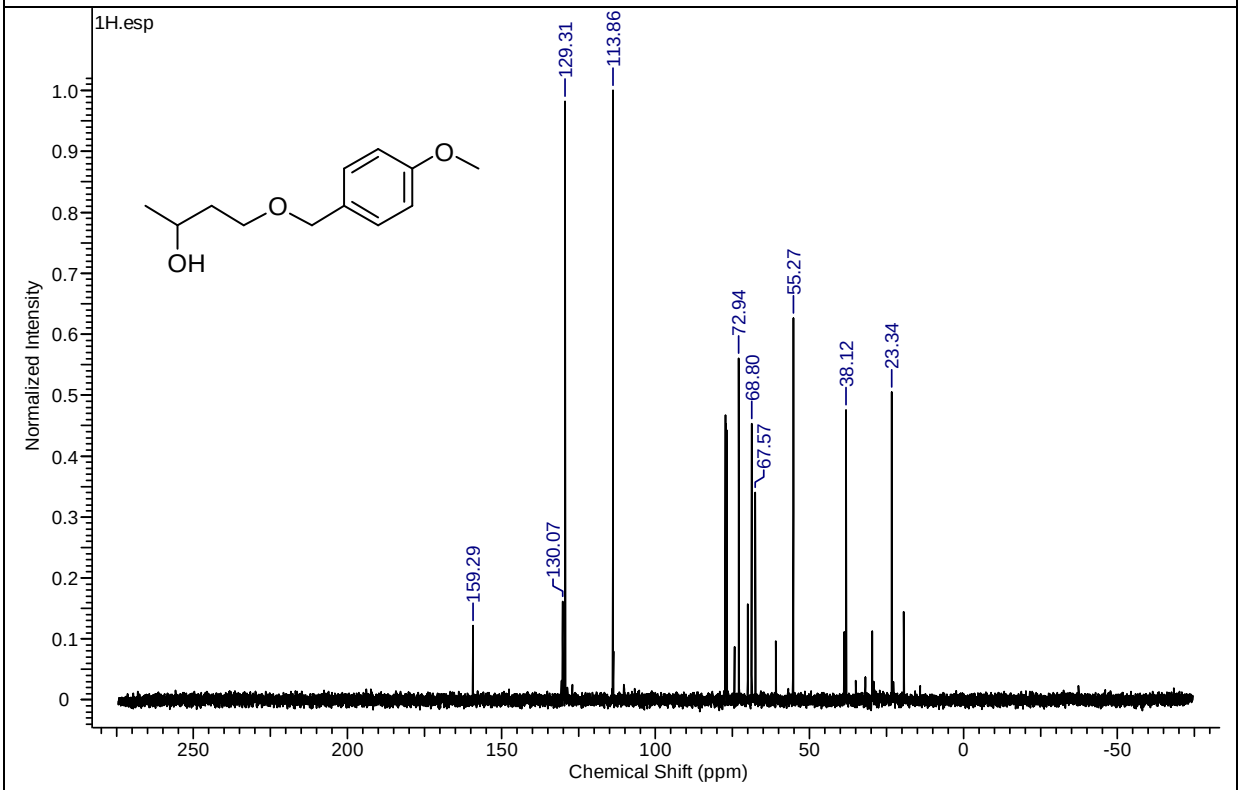

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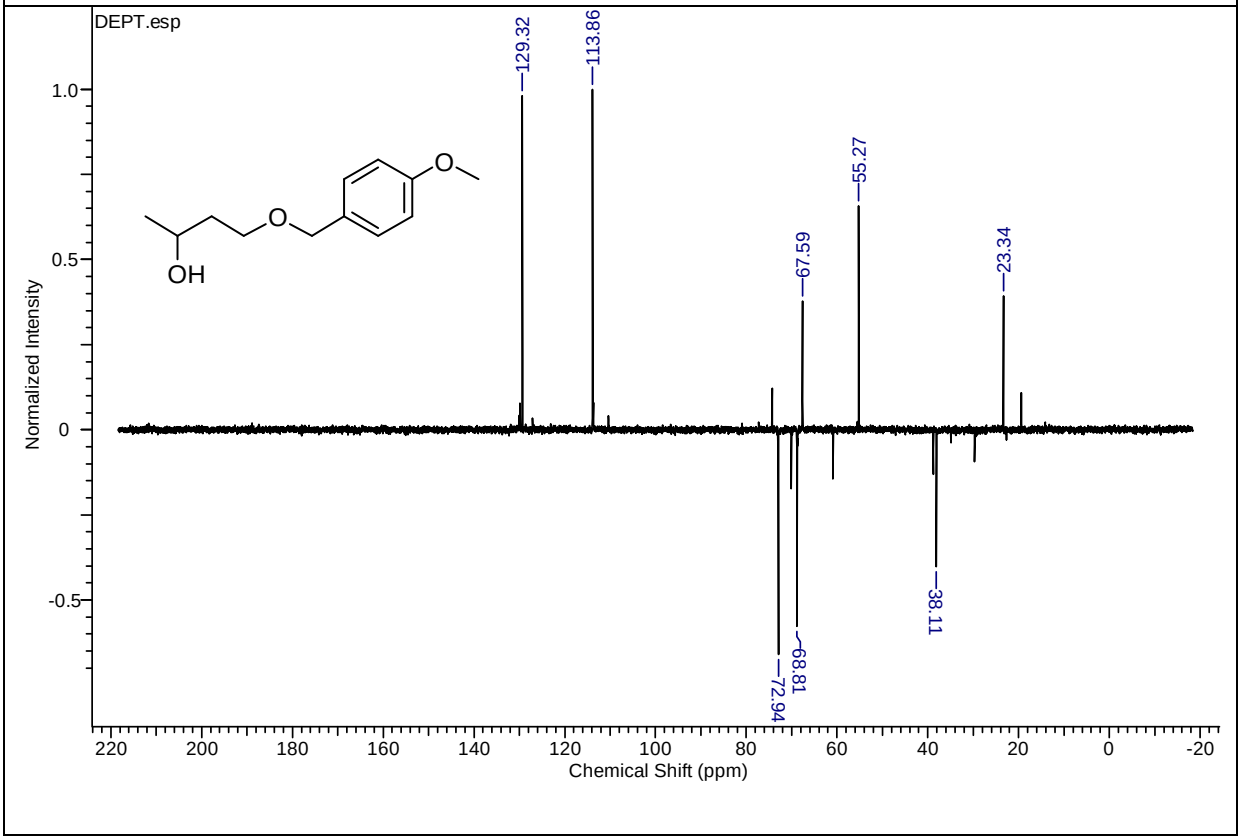

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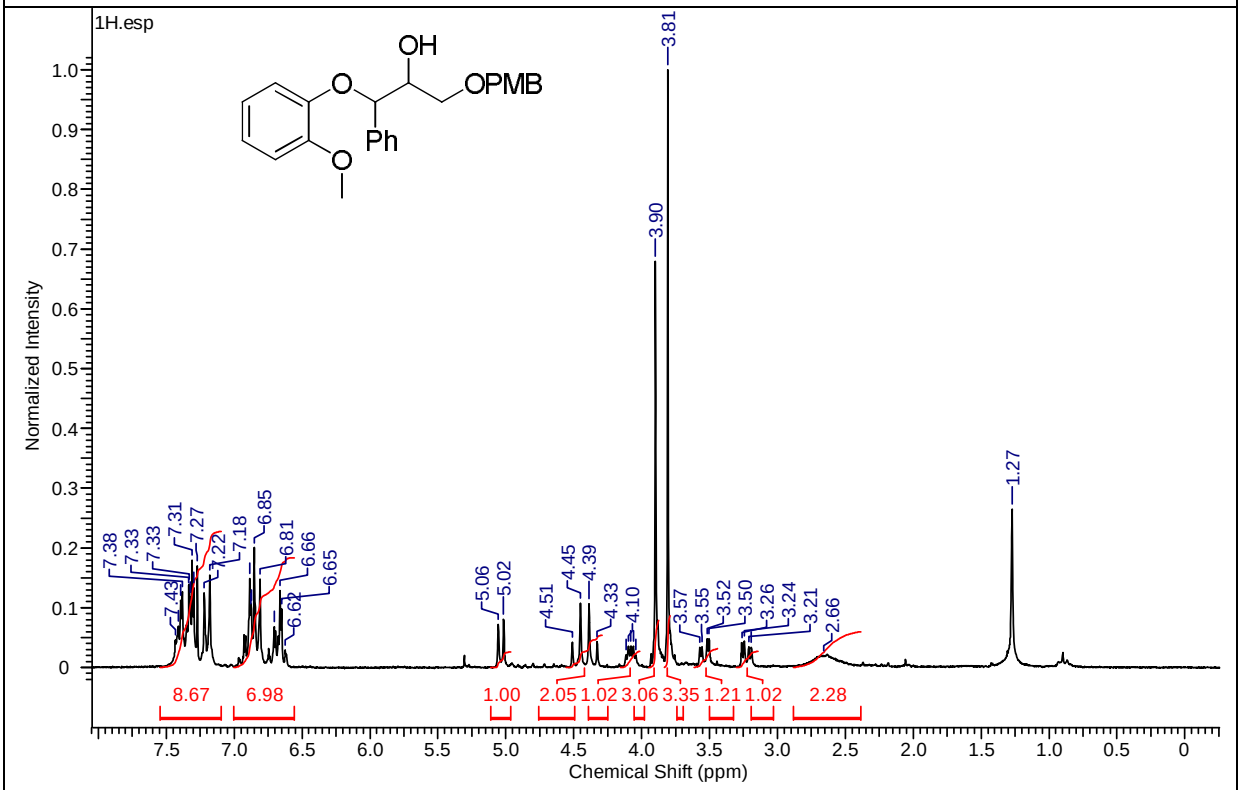

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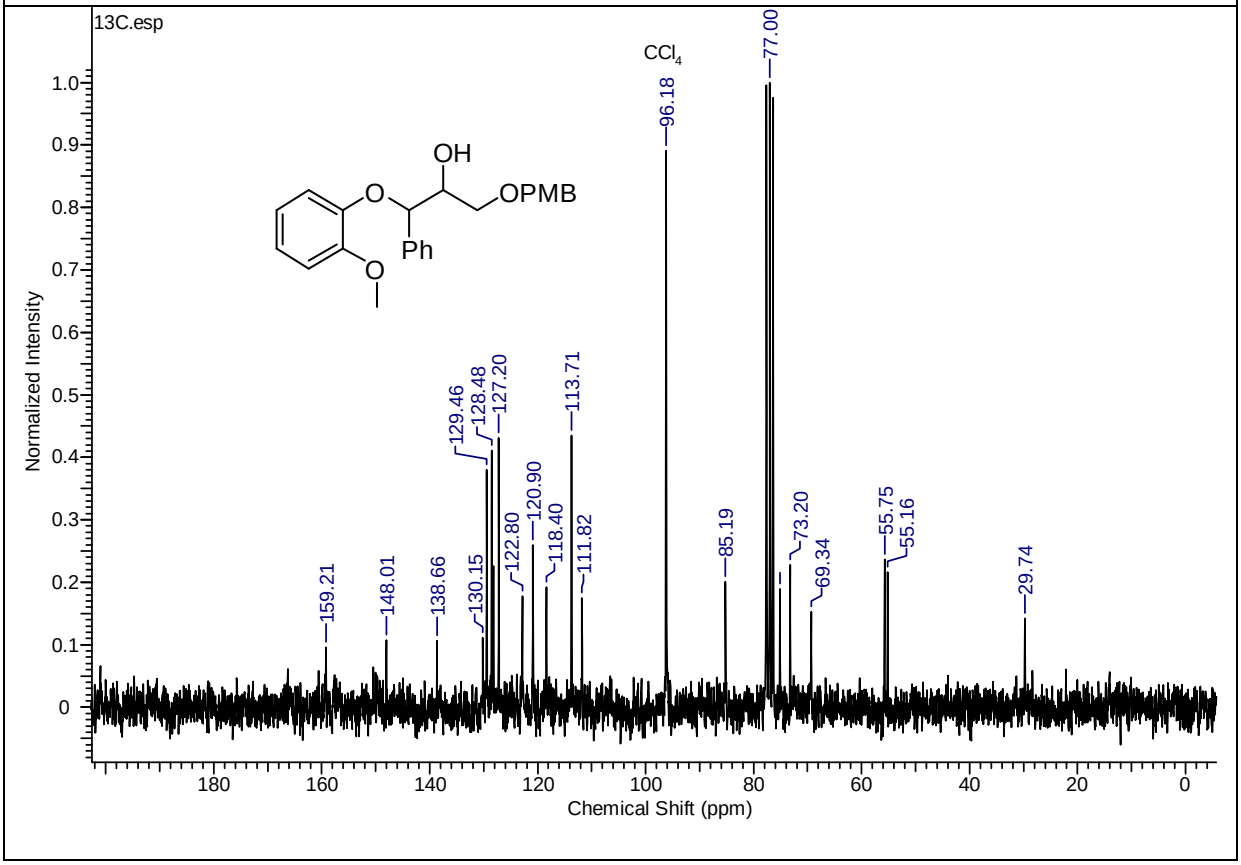

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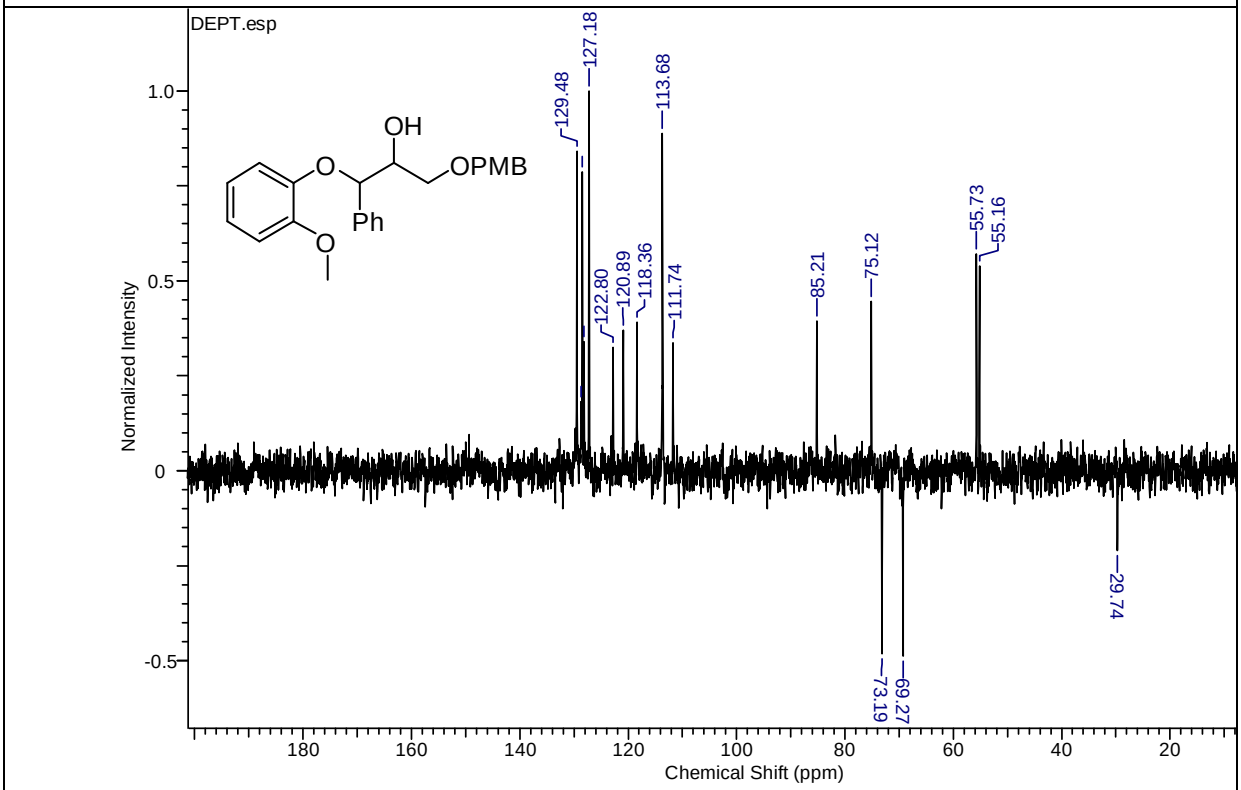

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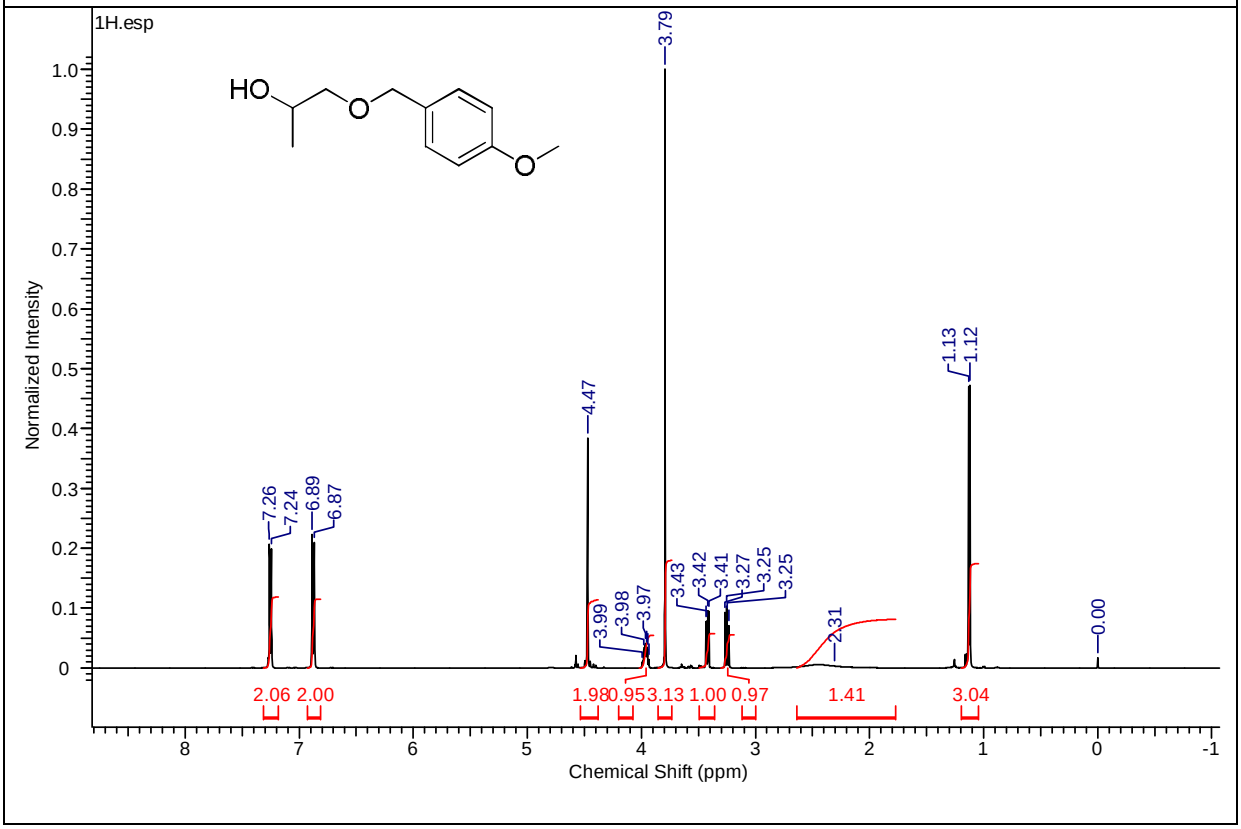

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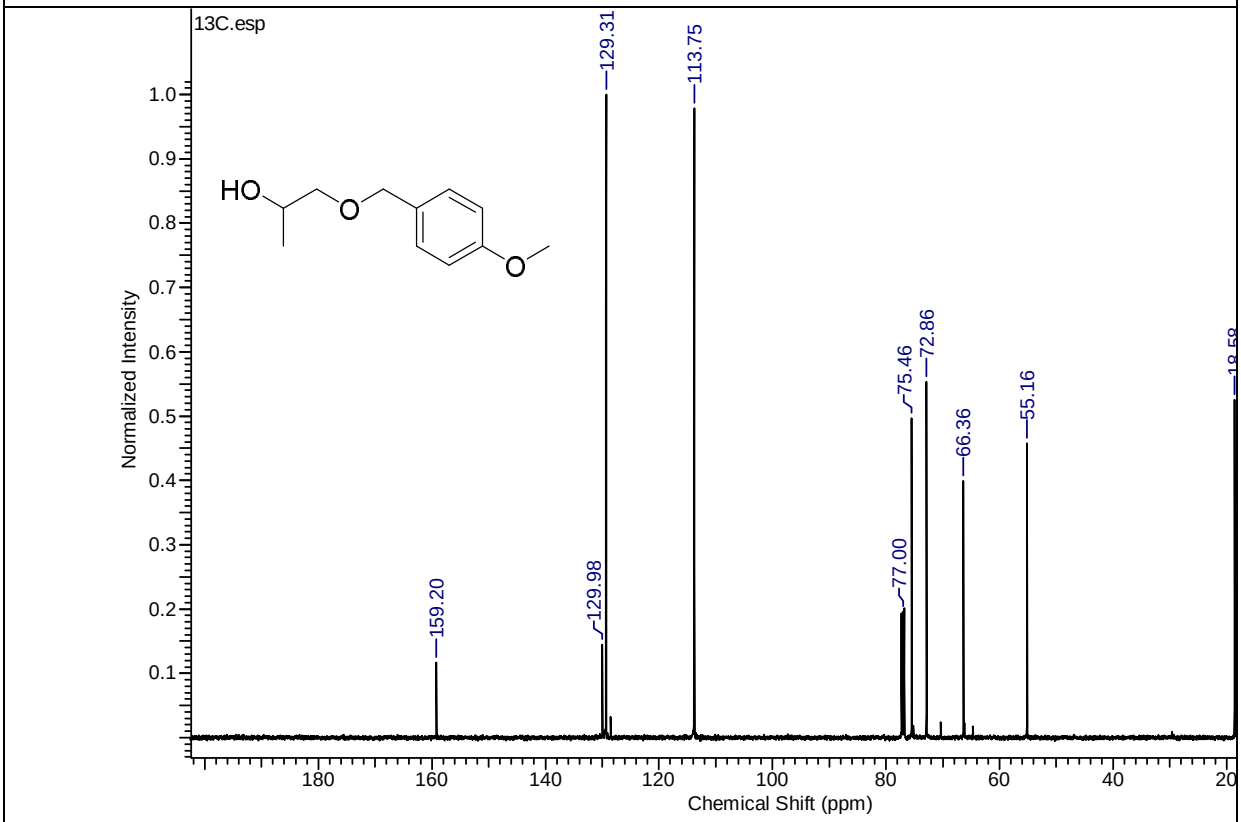

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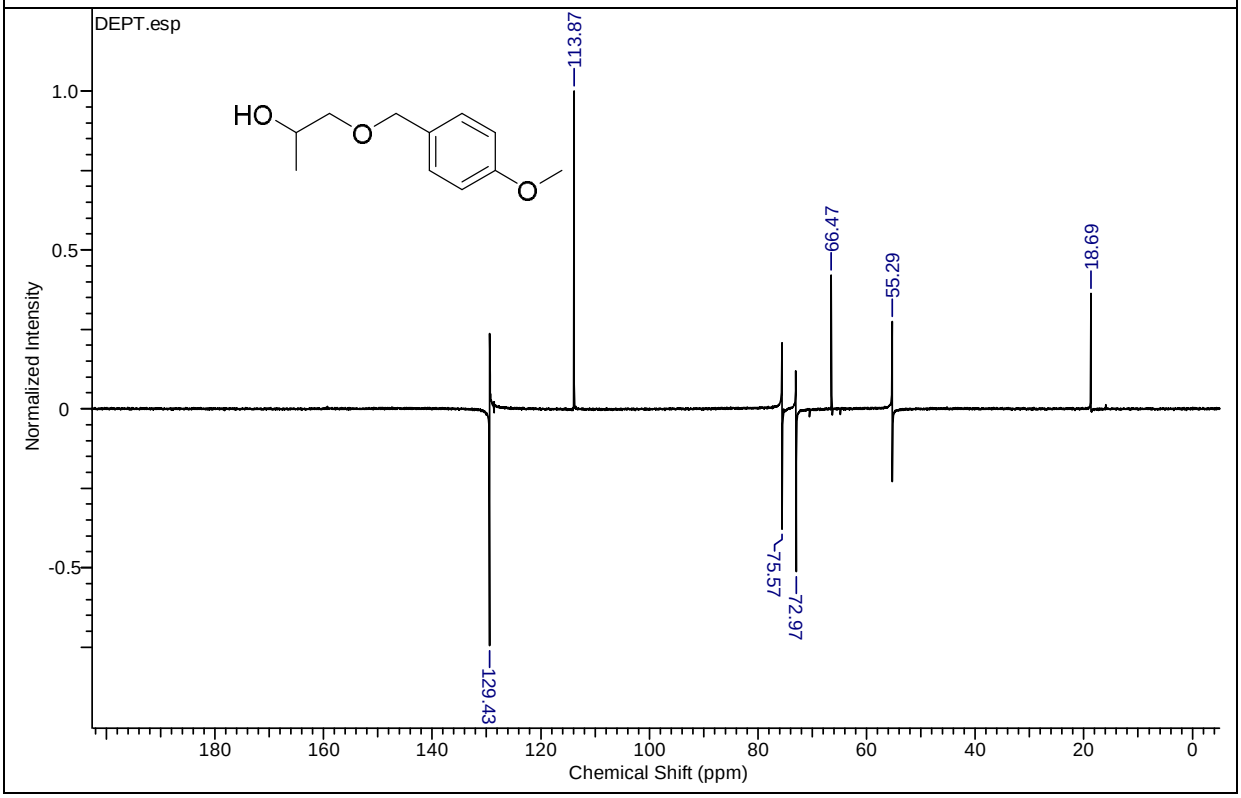

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List of publications:

1. A protecting group free and scalable approach towards total synthesis of (−)-venlafaxine
   Subhash P Chavan,* **Kailash P Pawar** and Sumanta Garai *RSC Adv*. **2014**, *4*, 14468-14470
   Highlighted in ChemInform 12/2014; 45(48). DOI: 10.1002/chin.201448208..
2. Chirality induction and chiron aproaches to enantioselective total synthesis of α-lipoic acid
   Subhash P. Chavan,* **Kailash P. Pawar**, Ch. Praveen and Niteen B. Patil *Tetrahedron* **2015**, *71,* 4213-4218.
3. Chiron approach towards total synthesis of (+)–deoxoprosophylline from L-(+)-tartrate ester
   Subhash P. Chavan*, **Kailash P. Pawar** and Nilesh B. Dumare **2015**, *communicated*.
4. Formal synthesis of (2*R*, 3*S*)-3-hydroxypipecolic acid from D-glucose
   Subhash P. Chavan,* **Kailash P. Pawar** (*Manuscript under preparation*)
5. A short total synthesis of (+)–deoxoprosophylline and formal synthesis of 1-deoxynojirimycin.
   Subhash P. Chavan,* **Kailash P. Pawar,** and Niteen B. Patil (*Manuscript under preparation*)
6. Ionic liquid catalyzed methodology for PMB protection of alcohols and selective mono PMB protection of diols.
   Subhash P. Chavan,* **Kailash P. Pawar,** and Rohit Kumar Gore (*Manuscript under preparation*)

Patents:

1. "Novel Process for total synthesis of Venlafaxine." Provisional patent filing date: 10/29/2013; patent No: APP_NO **3197/DEL/2013**
   Subhash P Chavan* and **Kailash P Pawar**
2. "Process for synthesis of (2*R*, 3*S*)-3-hydroxypipecolic acid." Provisional patent filing date: 8/26/2014, patent No: APP_NO **2867/DEL/2014**
   Subhash P Chavan* and **Kailash P Pawar**

Erratum

Erratum

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Erratum