SYNTHETIC STUDIES TOWARDS 1-DEOXYTHIONOJIRIMYCIN, 1,4-ANHYDRO-4-THIO-D-ARABINITOL AND RELATED THIOSUGARS AND DEVELOPMENT OF IONIC LIQUID MEDIATED ORGANIC TRANSFORMATIONS

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BY
MAHESH H. BHURE

DR. THOMAS DANIEL
(RESEARCH GUIDE)

DIVISION OF ORGANIC CHEMISTRY
NATIONAL CHEMICAL LABORATORY
PUNE 411008, INDIA

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सीएसआयआर-राष्ट्रीय रासायनिक प्रयोगशाला
(वैज्ञानिक तथा औद्योगिक अनुसंधान परिषद)
डॉ. होमी भाभा मार्ग, पुणे - 411 008. भारत
CSIR-NATIONAL CHEMICAL LABORATORY
(Council of Scientific & Industrial Research)
Dr. Homi Bhabha Road, Pune - 411 008. India.

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Synthetic studies towards 1-Deoxythionojirimycin, 1,4-anhydro-4-thio-D-arabinitol and related thiosugars and development of ionic liquid mediated organic transformations"** submitted by Mr. Mahesh H. Bhure was carried out by him under my supervision at National Chemical Laboratory, Pune. Material that has been obtained from other sources is duly acknowledged in this thesis.

Date:

Dr. Thomas Daniel
(Research Supervisor)

National Chemical Laboratory
Pune 411 008

Communication Channels
NCL Level DID : 2590
NCL Board No. : +91-20-25902000
EPABX : +91-20-25893300
+91-20-25893400
FAX
Director's Office : +91-20-25902601
COA's Office : +91-20-25902660
COS&P's Office : +91-20-25902664
WEBSITE
www.ncl-india.org

DECLARATION BY THE CANDIDATE

I hereby declare that the thesis entitled **"Synthetic studies towards 1-Deoxythionojirimycin, 1,4-anhydro-4-thio-D-arabinitol and related thiosugars and development of ionic liquid mediated organic transformations"** submitted for Ph. D. degree to the University of Pune has been carried out at National Chemical Laboratory, under the supervision of Dr. Thomas Daniel. This work is original and has not been submitted in part or full by me for any degree or diploma to this or any other university.

Date**:** Mahesh H. Bhure

Division of Organic Chemistry
National Chemical Laboratory
Pune 411 008.

Dedicated to……..

my beloved Parents, brother, sisters and my adorable wife

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NCL, Pune ***Mahesh H. Bhure***

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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 F_{254} (Merck) and visualized by fluorescence quenching or Iodine or by charring after treatment with *p*-anisaldehyde.
6. In cases where chromatographic purification was done, silica gel (200-400 mesh) was used as the stationary phase or otherwise as stated.
7. IR spectra were recorded on **Perkin-Elmer Infrared Spectrophotometer Model 68B** or on **Perkin-Elmer 1615 FT Infrared Spectrophotometer.**
8. ^{1}H NMR and ^{13}C NMR were recorded on **Bruker AV-200** (50 MHz) or **Bruker AV-400** (100 MHz) or **Bruker DRX-500** (125 MHz). Figures in the parentheses refer to ^{13}C frequencies. Tetramethyl silane was used as the internal standard. NMR values are expressed in δ (ppm).
9. Mass spectra were recorded at an ionization energy of 70 eV on **Finnigan MAT-1020**, automated GC/MS instrument and on **API-QSTAR PULSAR** 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
ADD	(Azodicarbonyl)dipiperidine
AIBN	2,2-Azobis(*iso*-butyronitrile)
Ar	Aryl
Aq.	Aqueous
[Bbim]Br	1,3-di-n-butylimidazolium bromide
[Bbim]Cl	1,3-di-n-butylimidazolium chloride
[Bbim]BF_4	1,3-di-n-butylimidazolium tetrafluoroborate
[Bbim]ClO_4	1,3-di-n-butylimidazolium perchlorate
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BMS	Borane dimethyl sulfide
Bn	Benzyl
Boc	*tert*-butoxy carbonyl
Bu	Butyl
s-Bu	*sec*-butyl
t-Bu	*tert*-butyl
CAN	Cerric ammonium nitrate
Cat.	Catalytic
Cbz	Carbobenzyloxy
m-CPBA	*meta*-chloroperbenzoic acid
CSA	Camphor sulfonic acid
DBDMH	1,3-Dibromo-5,5-dimethylhydantoin
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCB	1,2-Dichlorobenzene
DCC	*N,N′*-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyanoquinone

DET	Diethyl tartrate
DEPT	Distortionless Enhancement by Polarization Transfer
$(DHQ)_2PHAL$	Hydroquinine 1,4-phthalazinediyl diether
$(DHQD)_2PHAL$	Hydroquinidine 1,4-phthalazinediyl diether
DIAD	Diisopropylazodicarboxylate
DIBAL	Diisobutyl aluminium hydride
DIPEA	Diisopropylethyl amine
DIPT	Diisopropyltartrate
DMAP	4-Dimethylamino pyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMS	Dimethy sulfide
DMSO	Dimethyl sulfoxide
dppf	(Bis-diphenylphosphino)ferrocenyl
Et	Ethyl
G	gram(s)
GABA	Gamma-aminobutyric acid
h	hour(s)
IPA	*iso*-propyl alcohol
IR	Infra red
HMPA	hexamethylphosphoramide
Hz	Hertz
KHMDS	Potassium hexamethyl disilazide
LAH	Lithium aluminium hydride
LDA	Lithium diisopropyl amide
LHMDS	Lithium hexamethyl disilazide
LICA	Lithium isopropyl cyclohexylamide
MAD	Methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide)
Me	Methyl
min	minute(s)
mL	mililitres
MOMCl	Methoxy methylene chloride
Mp	Melting point

Ms	Methanesulfonyl
MVK	Methyl vinyl ketone
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	*N*-methyl morpholine oxide
NMR	Nuclear magnetic resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PCC	Pyridinium chlorocromate
PDC	Pyridinium dichromate
PEG	Polyethylene glycol
PHMS	Poly(hydromethylysiloxane)
PLE	Pig liver esterase
PMB	*para*-methoxybenzyl
PPA	Polyphosphoric acid
PTAB	Phenyl trimethylammonium tribromide
PTC	Phase transfer catalysis
PPTS	Pyridinium *para*-toluene sulfonate
PTSA	*para*-toluene sulfonic acid
rt	Room temperature
TBAB	Tetrabutyl ammonium bromide
$TBAHSO_4$	Tetrabutyl ammonium hydrogen sulfate
TBAI	Tetrabutyl ammonium iodide
TBSOTf	*tert*-butyldimethylsilyl triflate
TBSCl	*tert*-butyldimethylsilyl chloride
TEA	Triethyl amine
TFA	Trifluoroacetic acid
THF	Tetrahydofuran
TLC	Thin layer chromatography
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
TMSCl	Trimethylsilyl chloride
Ts	Toluenesulfonyl
Triton-B	Benzyltrimethylammonium hydroxide

Thesis Abstract

The thesis entitled, **"Synthetic studies towards 1-Deoxythionojirimycin, 1,4-anhydro-4-thio-D-arabinitol and related thiosugars and development of ionic liquid mediated organic transformations"** is divided into four chapters.

Chapter 1 deals with introduction to aldol reaction and synthetic studies towards 1-Deoxythionojirimycin. **Chapter 2** deals with synthetic studies towards 1,4-anhydro-4-thio-D-arabinitol and formal synthesis of Salacinol, Salaprinol and Neosalaprinol. **Chapter 3** deals with synthetic studies towards seven membered thiosugars and thio-mimic of Isofagomine. **Chapter 4** deals with introduction to ionic liquids, synthesis of crown ether and imidazolium based novel ionic liquids and development of ionic liquid mediated organic transformations.

Chapter 1. Introduction to aldol reaction and synthetic studies towards 1-Deoxythionojirimycin

Section 1: Introduction to aldol reaction

This chapter gives an overview on the 'direct catalysis of aldol reaction' through biocatalysis, metal catalysis and organo-catalysis. In particular, organocatalysis is very fast growing area for enantioselective transformations especially through 'enamine and iminium ion' catalysis. The mechanistic concept of enamine-catalysis for aldol reaction using proline as an organocatalysts has been described in detail.

Section 2: Synthetic studies towards 1-Deoxythionojirimycin

Thiosugars are carbohydrate analogues in which one or more oxygen atoms are substituted by a sulfur atom. In recent years, these compounds have attracted considerable interest from chemists and biochemists because of their biological activity. For example, both mono and oligosaccharide thiosugars have become increasingly important targets due to their potential value as enzyme inhibitors and therapeutic agents for diabetes, antiviral and antineoplastic treatments. Few of such notable thiosugars are Salacinol **1**, Kotalanol **2**, 5-thio-D-glucose **3**, 5-thio-D-mannose **4** and 1-Deoxythionojirimycin (1-DTNJ) **5** (Figure 1). This section describes a novel synthetic approach towards 1-DTNJ **5**.

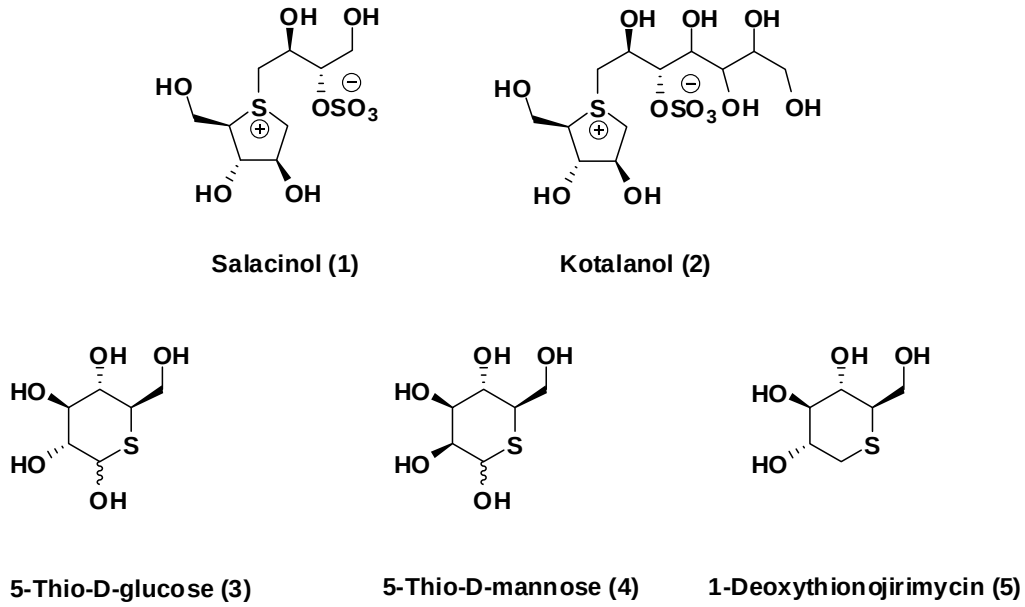


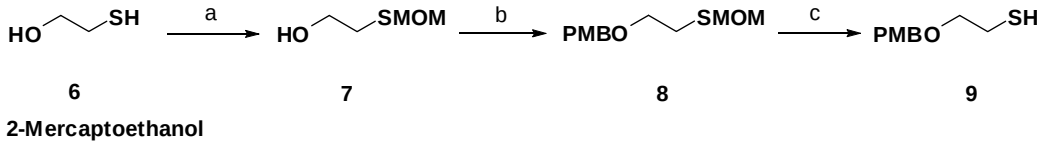
Figure 1. Some notable natural/unnatural thiosugars.

The synthesis of 1-DTNJ **5** actually began with the preparation of starting materials thiol intermediate **9** and iodo intermediate **18**.

Synthesis of thiol intermediate 9

Approach I

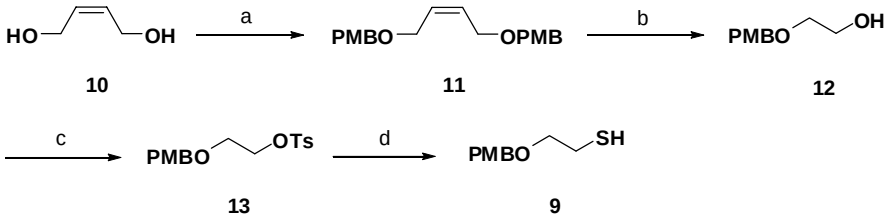
The synthesis of thiol intermediate **9** was started with 2-Mercaptoethanol **6**, which was protected under MOMCl/DIPEA condition to offer MOM-ether **7**. The MOM-ether **7** was further converted to its PMB-ether **8**, which on treatment with TFA underwent MOM deprotection to give thiol intermediate **9** with poor yield 15% (Scheme 1).



Scheme 1. *Reagents and conditions*: *a) DIPEA, MOMCl, DCM, 0 °C, 95%; b) NaH, PMBCl, THF, 0 °C, 97%; c) TFA, DCM, rt, 15%.*

Approach II

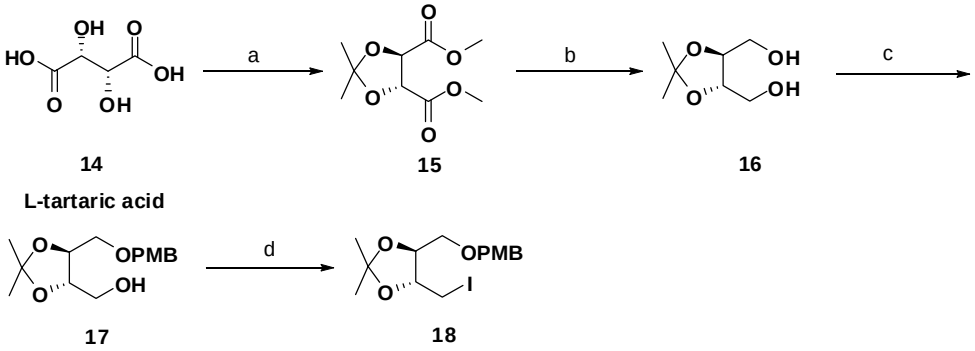
Due to the poor yield of thiol intermediate **9** in approach I, we changed our strategy. We started with *cis*-1,4-butenediol **10**, which was protected to offer diether **11**. Compound **11** was subjected for oxidative cleavage followed by $NaBH_4$ reduction gave alcohol **12**. Compound **12** was further converted to its tosyl-derivative **13**. The tosyl-derivative **13** was further treated with thiourea followed by basic hydrolysis offered thiol **9** with 95% yield (Scheme 2).



Scheme 2. *Reagents and conditions*: *a) NaH, PMBCl, THF, 0 ^oC, 96%; b) (i) OsO_4, $NaIO_4$, DEE: H_2O (1:1), rt, 94%; (ii) $NaBH_4$, MeOH, rt, 97%; c) TEA, TsCl, DCM, 0 ^oC , 96%; d) (i) Thiourea, absolute ethanol, reflux, 3.5 h; (ii) aq.NaOH, reflux, 3.5 h, 95%.*

Synthesis of intermediate 18

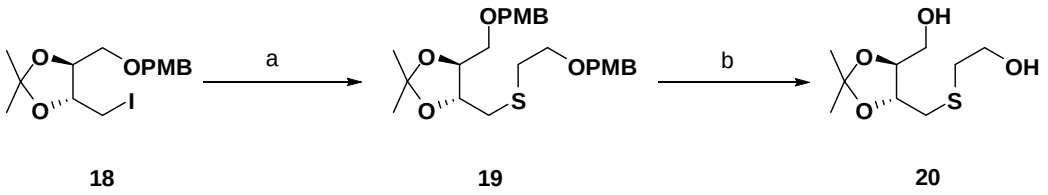
The synthesis of iodo intermediate **18** started with chiral auxiliary L-(+)-tartaric acid **14**. L-(+)-tartaric acid **14** on one pot acetonide protection and esterification gave **15** which on LAH reduction afforded C_2-symmetric diol **16**. The C_2-symmetric diol **16** was mono-protected to **17** which under Appel reaction condition afforded iodo intermediate **18** with 90% yield (Scheme 3).



Scheme 3. *Reagents and conditions*: *a) p-TSA, 2,2-DMP, MeOH, Cyclohexane, 90 ^oC, 95%; b) LAH, THF, reflux, 6 h, 60%; c) NaH, PMBCl, THF:DMF, 0 ^oC, 78%; d) Imidazole, PPh_3, I_2, toluene, reflux, 90%.*

Synthesis of diol 20

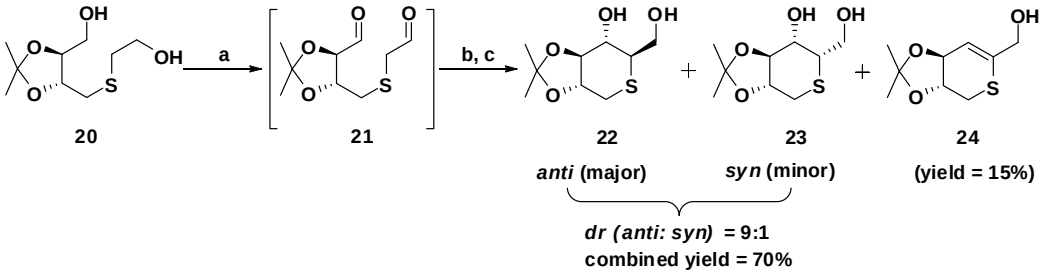
The intermediates **9** and **18** were further coupled to offer thioether **19** which on oxidative cleavage gave diol **20** with 88% yield (Scheme 4).



Scheme 4. *Reagents and conditions*: *a) NaH, THF,* PMBO–SH ***(9)****, 0 °C, 95%; b) DDQ, DCM: H_2O (17:1), rt, 88%.*

L-proline catalyzed 6-*enolexo* aldolization

The diol **20,** the key starting material for the *enolexo* aldolization was further oxidized under IBX/EtOAc condition to afford a dialdehyde **21**, which was directly used for L-proline catalyzed 6-*enolexo* aldolization reaction. The key step of direct 6-*enolexo* aldolization reaction of dialdehyde was carried out using L-proline (30 mol %) as an organocatalyst followed by *in situ* reduction with $NaBH_4$ to afford a mixture of *anti* and *syn* diastereomer **22** and **23** respectively {combined 70% yield, *dr (anti: syn*) = 9:1} and dehydrated by-product **24** with 15% yield (Scheme 5).



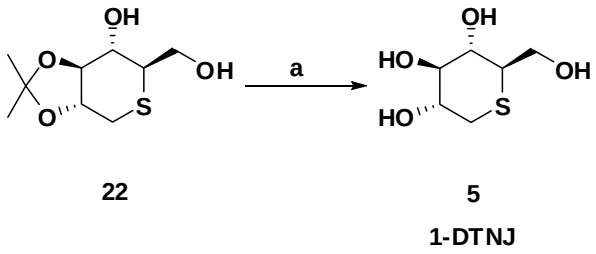
Scheme 5. *Reagents and conditions*: *a) IBX, ethyl acetate, reflux, 95%; b) L-proline (30 mol %), DCM, rt, 45 min.; c) $NaBH_4$, MeOH, rt, (collectively 85%).*

Throughout this synthetic approach, the key synthetic step of direct 6-*enolexo* aldolization offered a mixture of chromatographically separable *anti* and *syn* diastereomer **22** and **23** respectively with combined 70% yield and *dr (anti: syn*) = 9:1 along with dehydrated by-product **24** (15% yield). The structural elucidation of both

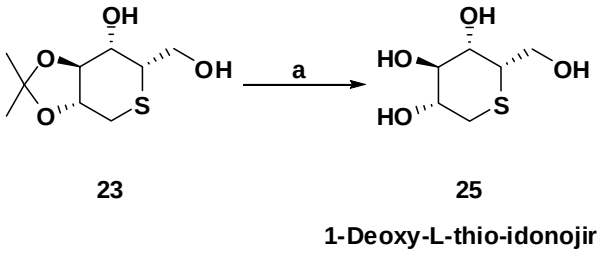
the diastereomers and dehydrated by-product was done by ^{1}H and ^{13}C NMR spectral studies. Further, the stereochemistry of both the diastereomers was determined by 2D-NMR (COSY and NOSEY) studies and it was observed that the diastereomer **22** is an *anti*-isomer whereas **23** is *syn*. Hence, in this synthetic approach *enolexo* aldolization is highly *anti*-selective. Further, the relative stereochemistry of only solid diastereomer **23** was also confirmed by its single crystal X-ray studies.

Synthesis of 1-DTNJ and 1-Deoxy-L-thio-idonojirimycin

After confirming the stereochemistry and assigned structures for both diastereomers **22** and **23**, both of them were further subjected for acetonide deprotection reaction. The *anti*-diastereomer **22** on treatment with Conc. HCl in MeOH offered 1-DTNJ **5** in 85% yield (Scheme 6). Similarly, *syn*-diastereomer **23** was also deprotected with Conc. HCl in MeOH afforded 1-Deoxy-L-thio-idonojirimycin **25** in 80% yield (Scheme 7).



Scheme 6. *Reagents and conditions*: *a) Conc. HCl, MeOH, rt, 85%.*



Scheme 7. *Reagents and conditions*: *a) Conc. HCl, MeOH, rt, 80%.*

Chapter 2. Synthetic studies towards 1,4-anhydro-4-thio-D-arabinitol and formal synthesis of Salacinol, Salaprinol and Neosalaprinol

Salacinol **1** and kotalanol **2** (Figure 2) are α-glucosidase inhibitors isolated from the *Hippocrateaceae* plant *Salacia reticulata* a large woody climbing plant widespread in

SriLanka and South India. Extracts of this plant have been traditionally used in the ayurvedic system of Indian medicine as a treatment for non-insulin-dependent diabetes. Recently, Salaprinol **26**, Ponkoranol **27** and Neosalaprinol **28**, Neoponkoranol **29** (Figure 2) are also isolated separately from extract of roots and stems of the Indian plants *Salacia prinoides* and *Salacia chinensis* respectively which are also used as an Ayurvedic Indian medicine for the treatment of diabetes. 1,4-anhydro-4-thio-D-arabinitol (D-ATA) **30** (Figure 2) is an important thiosugar and major building block for the synthesis of Salacinol **1**, Salaprinol **26** and Neosalaprinol **28**. This chapter describes the synthetic studies towards D-ATA **31** and formal synthesis of Salacinol **1**, Salaprinol **26** and Neosalaprinol **28**.

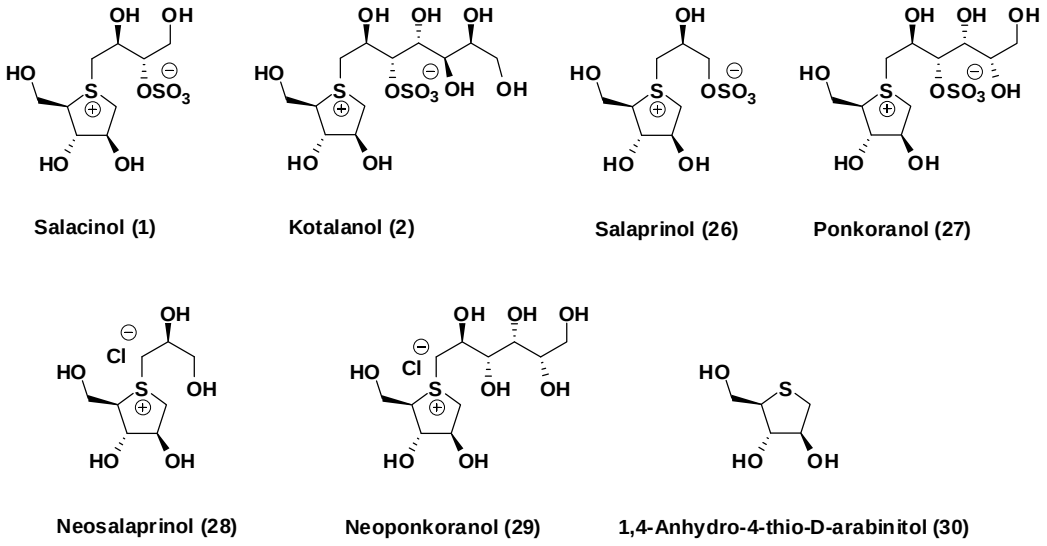


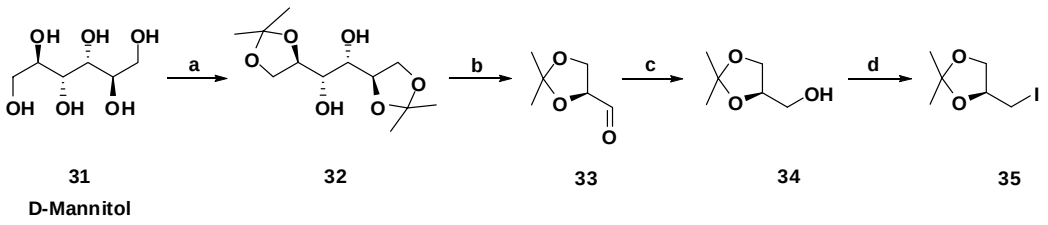
Figure 2. Some notable sulfated natural 4-thiosugars and 1,4-anhydro-4-thio-D-arabinitol.

The synthesis of D-ATA **30** actually began with the preparation of starting material iodo intermediate **35**.

Synthesis of intermediate 35

The preparation of iodo intermediate **35** was started with a cheap and easily available material D-mannitol **31**. D-mannitol **31** was easily converted to its diacetonide derivative **32**. The diacetonide derivative **32** on treatment with $NaIO_4$ underwent oxidative cleavage to afford (*R*)-glyceraldehyde **33**. The (*R*)-glyceraldehyde **33** was

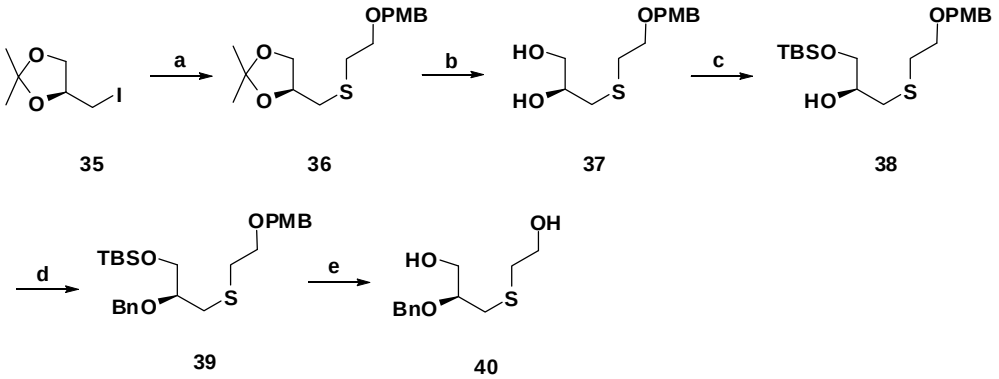
further reduced using $NaBH_4$ to give alcohol **34** which further under Appel reaction condition afforded compound **35** with 92% yield (Scheme 8).



Scheme 8. *Reagents and conditions*: *a) p-TSA, 2,2-DMP, DMSO, rt; b) $NaIO_4$, aq.$NaHCO_3$, DCM, rt, 85%; c) $NaBH_4$, MeOH, rt, 96%; d) Imidazole, PPh_3, I_2, toluene, reflux, 92%.*

Synthesis of diol 40

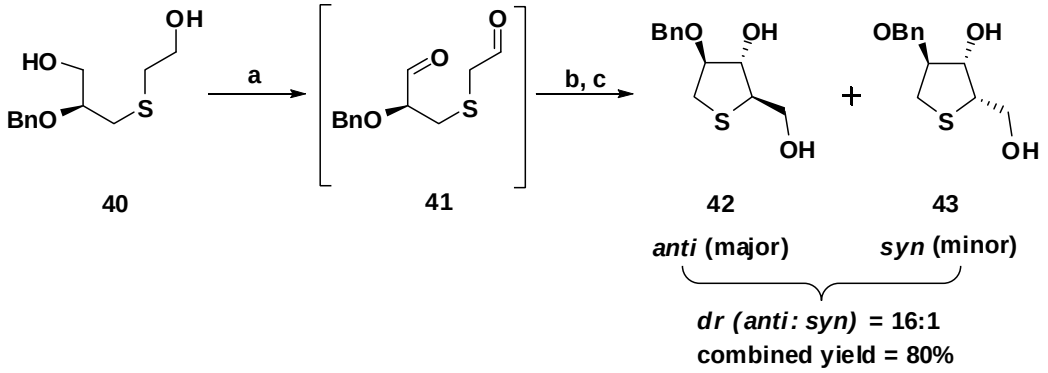
The iodo intermediate **35** and thiol intermediate **9** (Scheme 2, Chapter 1: Section 2) were further coupled to offer thioether **36**. The thioether **36** under *p*-TSA in MeOH condition deprotected to give diol **37**. The TBS protection of diol **37** afforded TBS-ether **38** which subsequently benzylated to give compound **39.** Compound **39** was then subjected for TBS-deprotection with catalytic Phosphotungstic acid followed by oxidative cleavage of PMB group to give diol **40** in 90% yield (Scheme 9).



Scheme 9. *Reagents and conditions*: *a) NaH, THF,* PMBO SH ***(9)****, 0 °C, 95%; b) p-TSA, MeOH, rt, 92%; c) Imidazole, TBSCl, DMAP, DCM, 0 °C, 95%; d) NaH, BnBr, THF, 0 °C, 96%; e) (i) Phosphotungstic acid, MeOH, rt, 95%; (ii) DDQ, DCM: H_2O (17:1), rt, 90%.*

L-proline catalyzed 5-*enolexo* aldolization

The diol **40** the key starting material for the 5-*enolexo* aldolization was further oxidized under IBX/EtOAc condition to afford a dialdehyde **41**, which was directly used for the L-proline catalyzed 5-*enolexo* aldolization reaction. The key step of direct 5-*enolexo* aldolization reaction of dialdehyde **41** was carried out using L-proline (30 mol %) as an organocatalyst followed by *in situ* reduction with $NaBH_4$/MeOH to give a mixture of chromatographically separable *anti* and *syn* diastereomers **42** and **43** respectively with combined 80% yield and a high *dr (anti: syn)* = 16:1 (Scheme 10). Surprisingly no dehydrated by-product was produced throughout the course of 5-*enolexo* aldolization reaction of dialdehyde **41**.

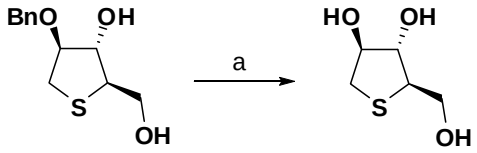


Scheme 10. *Reagents and conditions*: *a) IBX, ethyl acetate, reflux, 96%; b) L-proline (30 mol%), DCM, rt, 4 min.; c) $NaBH_4$, MeOH, rt, (combined 80%).*

The structural elucidation of both the diastereomers was done by ^{1}H and ^{13}C NMR spectral studies. Further, the stereochemistry of both the diastereomers was determined by 2D-NMR (COSY and NOSEY) studies. It was seen that the diastereomer **42** is an *anti*-isomer whereas **43** is *syn*. Hence, in this synthetic approach 5-*enolexo* aldolization is highly *anti*-selective.

Synthesis of 1,4-anhydro-4-thio-D-arabinitol (D-ATA) 30

The *anti*-isomer **42** further on treatment with BCl_3 in DCM at -78 ^{o}C underwent benzyl deprotection to furnish D-ATA **30** in 60% yield (Scheme 11).



42 30

D-ATA

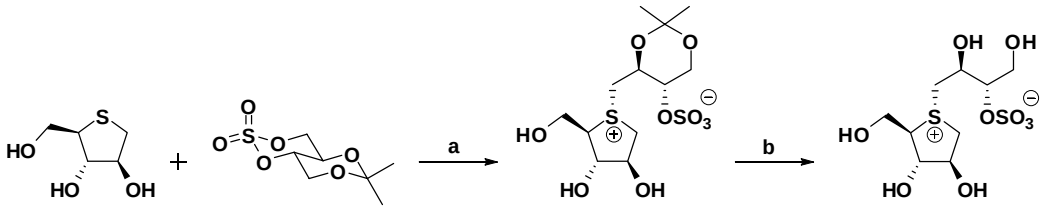
Scheme 11. *Reagents and conditions*: *a) BCl_3, DCM, -78 °C, 1 h, 60%.*

Formal Synthesis of Salacinol, Salaprinol and Neosalaprinol

Being a core important part of the *salacia* family thiosugars, Salacinol **1**, Salaprinol **27** and Neosalaprinol **29**, the synthesized D-ATA **30** also establishes their formal synthesis.

Formal Synthesis of Salacinol 1

The synthesis of Salacinol **1** can be achieved by the reaction of D-ATA **30** and cyclic sulfate **44** by employing the synthetic protocol reported by Yuasa and coworkers (Scheme 12).



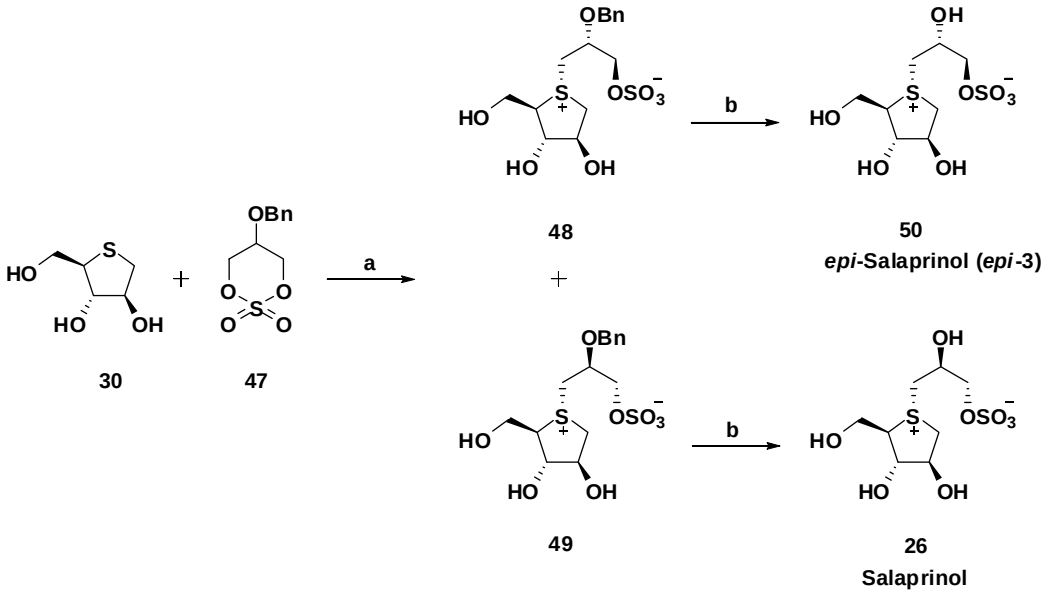
30 44 45 46

D-ATA Cyclic sulfate Salacinol

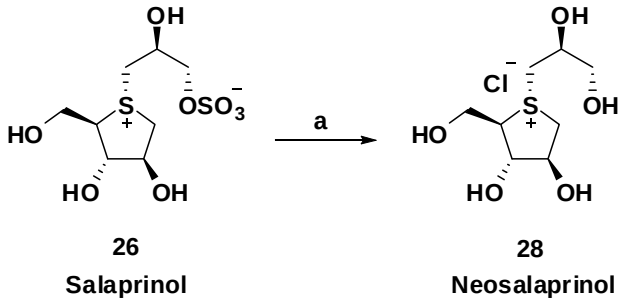
Scheme 12. *Reagents and conditions: a) DMF, 45 ºC, 13 h, 61%; b) 0.01% HCl, 40 ºC, 4 h, 75%.*

Formal Synthesis of Salaprinol 26 and Neosalaprinol 28

The synthesis of Salaprinol **26** and Neosalaprinol **28** can be accomplished by using the synthetic approach reported by Genzoh Tanabe (Scheme 13 and 14).



Scheme 13. *Reagents and conditions: a) K_2CO_3, HFIP, 65-70 ^oC; b) H_2, Pd/C, 80% AcOH, 50 ^oC.*

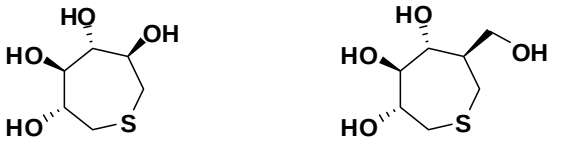


Scheme 14. *Reagents and conditions: a) (i) 5% methanolic HCl, 50 ^oC; ii) IRA 400J (Cl^-form), CH_3OH, rt.*

Chapter 3. Synthetic studies towards seven membered thiosugar and thio-mimic of Isofagomine

Section 1: Synthetic studies towards seven membered thiosugar

Seven membered thiosugars are not available in nature. Myrielle Fuzier and group first reported the synthesis of an unnatural seven membered thiosugar C_2-symmetric L-ido-thiepane **51** as a α-D-glucosidase inhibitor. This section describes the synthetic studies towards the novel seven membered thiosugar **52** which is actually an analogue of unnatural C_2-symmetric L-ido-thiepane **51** (Figure 3).



C_2-symmetric L-ido-thiepane **51**

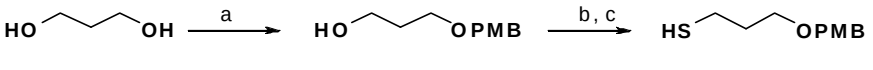
Proposed Seven membered thiosugar **52**

Figure 3. C_2-symmetric L-ido-thiepane and proposed seven membered thiosugar.

The synthesis of proposed seven membered thiosugar **51** actually began with the preparation of starting material thiol intermediate **55**.

Synthesis of thiol intermediate 55

The synthesis of thiol intermediate **55** started with cheap and easily available 1,3-propanediol **53** as a starting material. 1,3-propanediol **53** was mono-protected with PMBCl to give alcohol **54**. The alcohol **54** was then subjected for tosylation followed by treatment with thiourea in absolute ethanol and subsequent *in situ* hydrolysis with aq. NaOH afforded thiol **55** in 95% yield (Scheme 15).

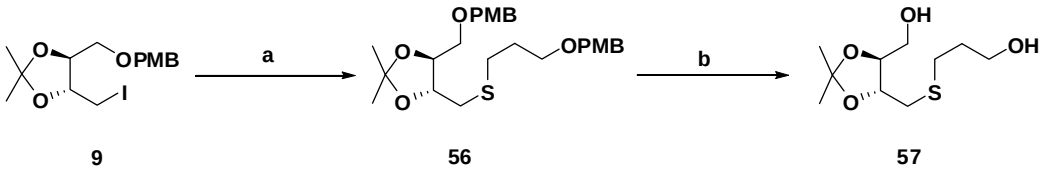


53 **54** **55**

Scheme 15. *Reagents and conditions*: *a) NaH, PMBCl, THF:DMF(1:1), 0 ^oC, 75%; b) TEA, TsCl, DCM, 0 ^oC, 95%; c) (i) Thiourea, absolute ethanol, reflux, 3.5 h; (ii) NaOH, H_2O, reflux, 3.5 h, 95%.*

Synthesis of diol 57

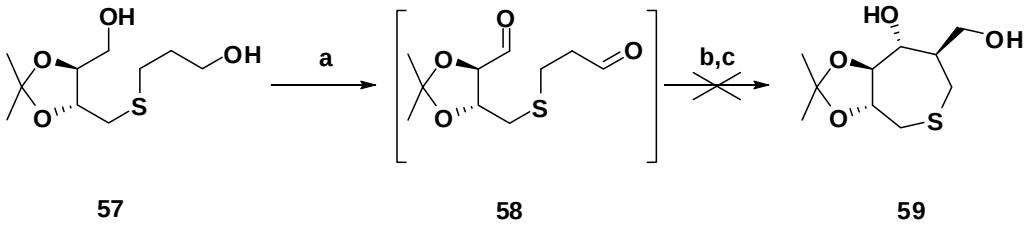
The thiol intermediate **55** and known iodo intermediate **9** (Scheme 3, Chapter 1: Section 2) were further coupled to offer thioether **56** in 96% yield (Scheme 16). Thioether **56** further on oxidative cleavage afforded diol **57** in 85% yield (Scheme 16).



Scheme 16. *Reagents and conditions*: *a) NaH,* HS OPMB ***(55****), THF, 0 °C, 96%; b) DDQ, DCM: H_2O (17:1), rt, 85%.*

L-proline catalyzed 7-*enolexo* aldolization

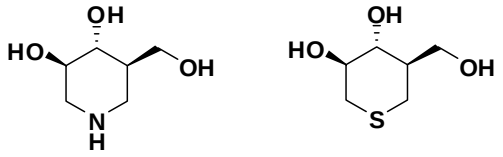
The diol **57,** the key starting material for the 7-*enolexo* aldolization was further oxidized with IBX in refluxing EtOAc to afford a dialdehyde **58** which without any further purification was directly used for the L-proline catalyzed 7-*enolexo* aldolization reaction.[10] The key step of direct 7-*enolexo* aldolization reaction of dialdehyde was carried out using L-proline (30 mol %) as an organocatalyst in solvent DCM at room temperature for 45 min and the reaction progress was monitored by TLC. No reaction progress was observed after 45 min so the reaction was kept for a prolonged time period (45 min-20 h). The reaction was not progressed even after prolonged reaction time period and no aldolization was observed, therefore the reaction mixture was reduced *in situ* with $NaBH_4$ in MeOH and starting material diol **57** was recovered (Scheme 17).



Scheme 17. *Reagents and conditions*: *a) (i) IBX, ethyl acetate, reflux, 96%; (ii) L-Proline (30 mol%), DCM, rt, 45 min-20 h; (iii) $NaBH_4$, MeOH, rt, (starting material **57** recovered 85%).*

Section 2: Synthetic studies towards thio-mimic of Isofagomine

Glucomimetic azasugars such as isofagomine have been shown to exhibit strong inhibitory action towards β-glucosidase. This section describes synthetic studies towards the thio-mimic of isofagomine **61** (Figure 4).



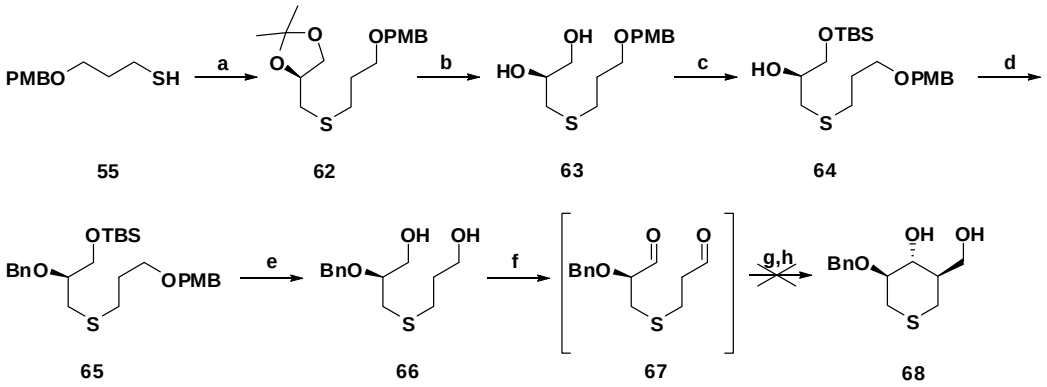
Isofagomine **60**

Thio-mimic of Isofagomine **61**

Figure 4. Structures of Isofagomine and thio-mimic of Isofagomine.

Synthesis of diol and L-proline catalyzed 6-*enolexo* aldolization

The intermediates **35** (Scheme 8, Chapter 2) and **55** (Scheme 15, Chapter 3: section 1) were coupled to offer thioether **62**. The thioether **62** under *p*-TSA in MeOH condition deprotected to diol **63**. The TBS protection of diol **63** afforded TBS-ether **64** which subsequently benzylated to give compound **65.** Compound **65** was then subjected for TBS-deprotection with catalytic Phosphotungstic acid followed by oxidative cleavage of PMB group to give diol **66** in 90% yield (Scheme 18). The diol **66,** the key starting material for the 6-*enolexo* aldolization was further oxidized under IBX in EtOAc condition to afford the dialdehyde **67**, which was directly used for the L-proline catalyzed 6-*enolexo* aldolization reaction. The key step of direct 6-*enolexo* aldolization reaction of dialdehyde **67** was carried out using L-proline (30 mol %) as an organocatalyst. No reaction progress was observed after 45 min therefore the reaction was kept for a prolonged time period (45 min-20 h). The reaction was not progressed even after prolonged reaction time period and no aldolization was observed, so the reaction mixture was reduced *in situ* with $NaBH_4$ in MeOH and starting material diol **66** was recovered (Scheme 18).



Scheme 18. *Reagents and conditions*: *a) NaH,* ***(35****), THF, 0 °C, 96%; b) p-TSA, MeOH, rt, 90%; c) Imidazole, TBSCl, DMAP, DCM, 0 °C, 95%; d) NaH, BnBr*, *THF, 0 °C, 96%; e) (i)Phosphotungstic acid, MeOH, rt, 97%; (ii) DDQ, DCM:H_2O (17:1), rt, 83%; f) IBX, Ethyl acetate, reflux, 92%; h) L-proline (30 mol%), DCM, rt, 45 min-20 h; g) $NaBH_4$, MeOH, rt, (starting material recovered 78%).*

Chapter 4. Introduction to ionic liquids, synthesis of crown ether and imidazolium based novel ionic liquids and development of ionic liquid mediated organic transformations

Section 1: Introduction to ionic liquids

The past few years has witnessed the evolution of a new era in chemical research by the entry of ionic liquids as potential 'Green Designer Solvents' as novel replacements for volatile organic compounds traditionally used as industrial solvents. Ionic liquids (ILs) are systems consisting of salts that are liquid at ambient conditions. A brief history of ionic liquids and their emergence as environmentally benign solvents have been discussed in this section. Various types of ILs and their nomenclature are covered. The unique property of this ionic species, which gives liquid character to it, has been discussed in detail. Among the various ILs, imidazolium based ILs have attracted great deal of attention as a novel reaction media in organic synthesis due to their negligible vapor pressure, low melting point with high thermal and chemical stability.

Section 2: Synthesis of crown ether and imidazolium based novel ionic liquids

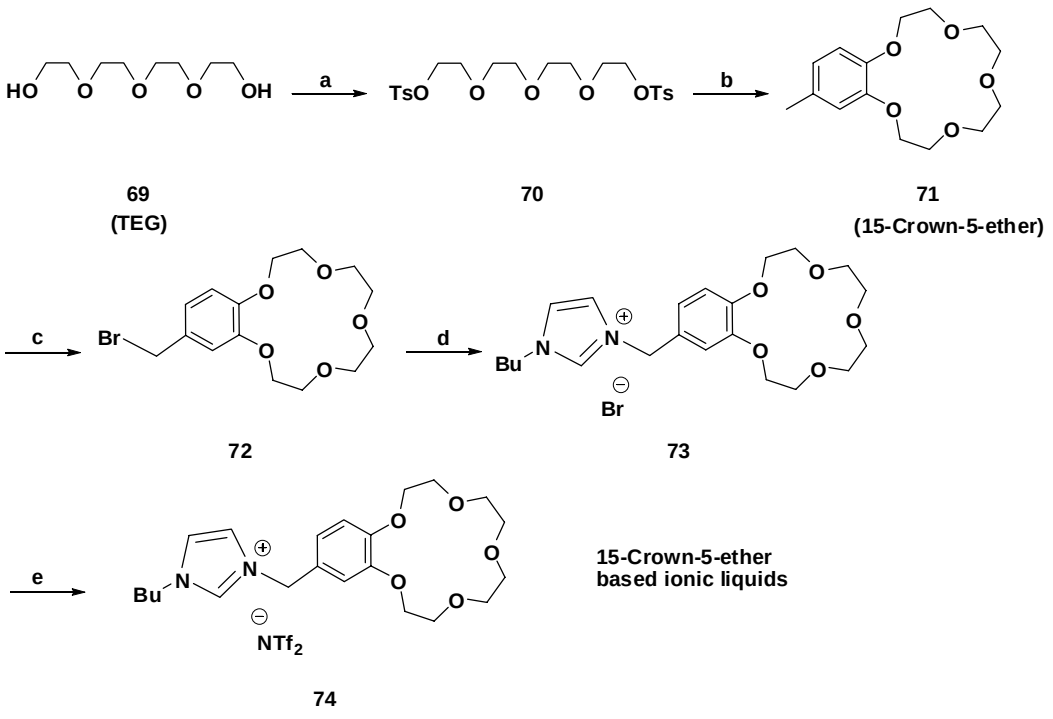
Introduction of an ether group on the N-position of the cation has resulted in some novel properties of ionic liquids (ILs) among which the report on using crown ether as

a functional group is still rare. Till date very few reports are available on crown ether-involving ILs. Crown ether's macrocyclic cavity, chelate ring, macrocycle rigidity, and number and type of donor atoms can be tuned to provide a high degree of metal ion selectivity, so they are arguably the most versatile type of ion-specific extractants. Incorporating these excellent properties into ILs may significantly improve the coordination of ILs with metal ions, and may therefore provide both ILs and crown ethers some promising features for the use in extraction, molecule recognition, chemical sensing, and phase-transfer catalysis or transition metal catalysis.

This section describes the synthesis of 15-crown-5-ether; 18-crown-6-ether and imidazolium based novel ionic liquids with Br and NTf_2 as anions respectively.

Synthesis of 15-Crown-5-ether and imidazolium based ILs

The synthesis started with tetraethylene glycol (TEG) **69**, which was converted to its ditosyl-derivative **70**. The tosyl-derivative **70** was further treated with 4-methylcatechol to give 15-Crown-5-ether **71**. The crown ether **71** was brominated to

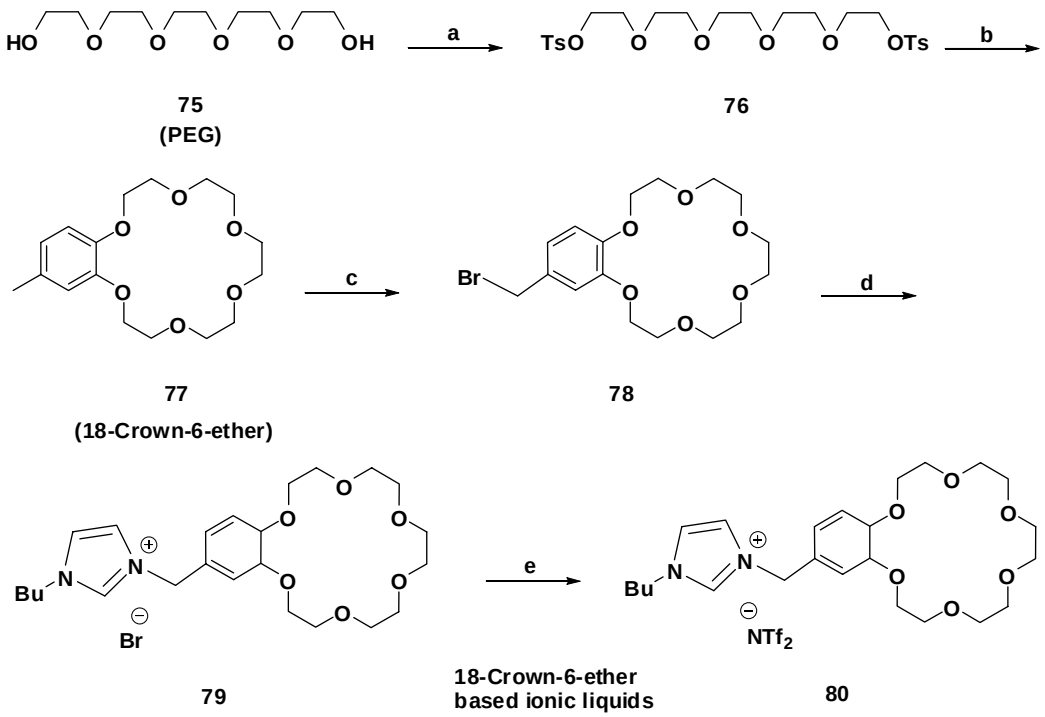


Scheme 19. *Reagents and conditions*: *a) TEA, TsCl, DMAP, DCM, 0 ^oC, 90%; b) K_2CO_3, acetone, 4-methylcatechol, reflux, 44%; c) NBS, CCl_4, 500W light, reflux, 77%; d) N-Butylimidazole, CH_3CN, reflux, 68%; e) $LiNTf_2$, water, rt, 75%.*

offer bromo compound **72**. The bromo compound **72** on treatment with N-butylimidazole afforded 15-crown-5-ether ionic liquid **73**. The 15-crown-5-ether ionic liquid **73** further on treatment with $LiNTf_2$ converted to its NTf_2 counterpart **74** (Scheme 19).

Synthesis of 18-Crown-6-ether and imidazolium based ILs

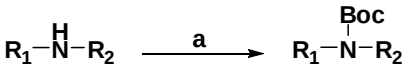
The synthesis started with pentaethylene glycol (PEG) **75**, which was converted to its ditosyl-derivative **76**. The tosyl-derivative **76** was further treated with 4-methylcatechol to offer 18-Crown-6-ether **77**. The crown ether **77** was brominated to give bromo compound **78**. The bromo compound **78** on treatment with N-butylimidazole afforded 18-crown-6-ether ionic liquid **79**. The 18-crown-6-ether ionic liquid **79** further on treatment with $LiNTf_2$ converted to its NTf_2 counterpart **80** (Scheme 20).



Scheme 20. *Reagents and conditions*: *a) Pyridine, TsCl, -10 ^oC, 85%; b) K_2CO_3, acetone, 4-methylcatechol, reflux, 45%; c) NBS, CCl_4, 500W light, reflux, 70%; d) N-Butylimidazole, CH_3CN, reflux, 65%; e) $LiNTf_2$, water, rt, 75%.*

Section 3: [Bbim]Br mediated *N*-Boc protection of alkyl/aryl amines

Organic synthesis has not yet matured to the point where protective groups are not needed for the synthesis of natural and unnatural products; thus, the development of new methods for functional group protection and deprotection continues. Since the introduction of *tert*-butyl carbamate (Boc) group in synthetic organic chemistry it has been extensively used as a protecting group for amine functionality in peptide, heterocyclic synthesis and various organic transformations. Among the several reagents used, Boc-anhydride {$(Boc)_2O$} is safe, cheap and easily available reagent which most often used for the Boc-protection of amines. This section describes [bbim]X mediated highly efficient and chemo-selective *N*-Boc-protection of various structurally varied alkyl/aryl amines at room temperature and under sonication (Scheme 21).



Scheme 21. *Reagents and Conditions: a) [bbim]X, $(Boc)_2O$, silent or sonication, rt. X = Br, Cl, BF_4, ClO_4; $R_1 = R_2 = H$ or alkyl or aryl.*

Table 1. Comparative study of *N*-Boc-protection of benzyl amine **(4a)** in various RTILs at room temperature.

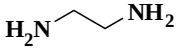
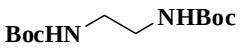
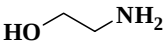
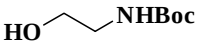
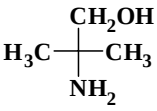
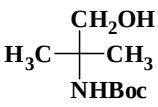
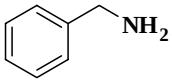
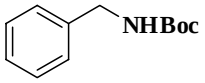
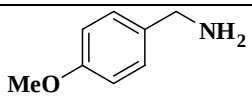
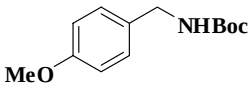
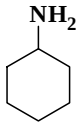
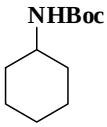
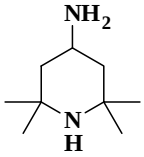
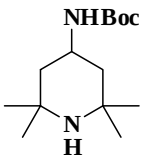
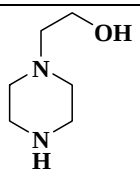
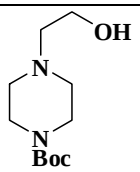
Entry	Ionic liquid	Time (min)		%Yield [a]	
		Silent	(((((	Silent	(((((
1	**[bbim]Br**	**30**	**5**	**95**	**98**
2	**[bbim]Cl**	**35**	**10**	**93**	**96**
3	**[bbim]ClO_4**	**50**	**20**	**87**	**90**
4	**[bbim]BF_4**	**70**	**25**	**85**	**88**

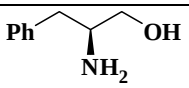
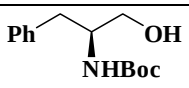
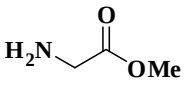
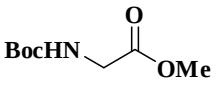
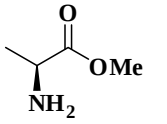
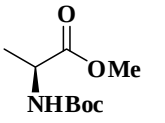
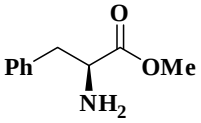
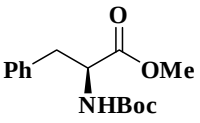
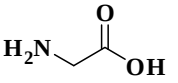
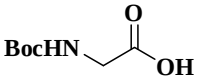
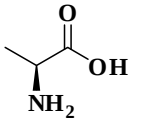
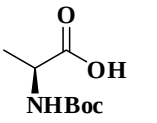
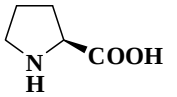
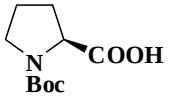
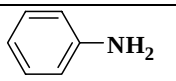
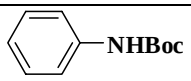
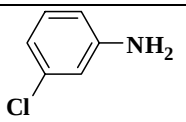
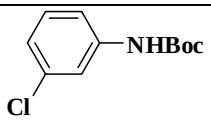
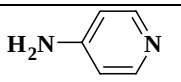
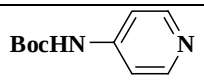
[a] Isolated yield of *N*-Boc product **4b.**

Initially separate experiments using [bbim]Br, [bbim]Cl, [bbim]ClO_4 and [bbim]BF_4 RTILs were carried out for the *N*-Boc protection of benzyl amine **4a** at room

temperature under ultrasound and stirring without ultrasound (silent) condition (Table 1). Among all ILs tested, [bbim]Br IL was found superior with highest yield and lower reaction time period under both silent and ultrasound conditions. Further, [bbim]Br was also tested for *N*-Boc protection of several structurally varied alkyl/aryl amines, amino acids and esters of amino acids and the results are summarized in Table 2.

Table 2. *N*-Boc-protection of various alkyl/aryl amines in [bbim]Br at room temperature.

Entry	Substrate [a]	Product [b]	Time (min)		%Yield[c]	
			Silent	(((((	Silent	(((((
1			**30**	**5**	**95**	**98**
2			**35**	**5**	**92**	**96**
3			**35**	**5**	**94**	**96**
4			**30**	**5**	**95**	**98**
5			**30**	**5**	**94**	**98**
6			**25**	**5**	**95**	**97**
7			**30**	**5**	**93**	**95**
8			**90**	**40**	**93**	**95**

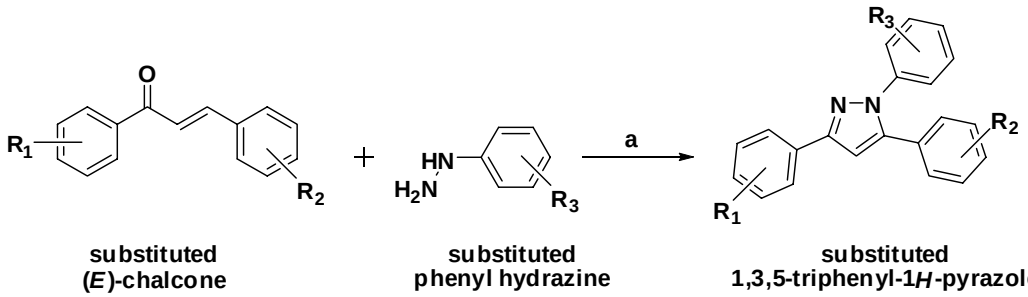
9			**40**	**10**	**92**	**95**
10			**35**	**10**	**94**	**98**
11			**40**	**10**	**95**	**97**
12			**30**	**5**	**95**	**98**
13			**60**	**25**	**88**	**90**
14			**60**	**25**	**90**	**92**
15			**120**	**45**	**85**	**90**
16			**25**	**5**	**94**	**98**
17			**25**	**5**	**95**	**97**
18			**35**	**10**	**92**	**94**

[a] Substrate; [b] *N*-Boc product; [c] Isolated yield for *N*-Boc product.

Section 4: [bbim]Br mediated synthesis of 1,3,5-triphenyl-1*H*-pyrazoles

Aryl pyrazoles are ubiquitous substructures with important biological activity and pharmacological properties, including anti-microbial, anti-inflammatory, hypoglycemic, anti-hypertensive and analgesic properties.[2] However, in spite of their potential utility, many of the reported method for the synthesis of aryl pyrazoles suffer from drawbacks such as lower yields, expensive transition metal oxidant, use of toxic

organic solvent and complexity of work-up. This section describes a simple, efficient and ecofriendly method for one pot synthesis of 1,3,5-triphenyl-1*H*-pyrazoles from (*E*)- chalcones and substituted phenyl hydrazines using [bbim]X as a promoter and reaction media (Scheme 22).



Scheme 22. *Reagents and Conditions:* (a) [bbim]X, silent or sonication, rt. X = Br, Cl, BF_4, ClO_4.

Table 1. Comparative study of synthesis of 1,3,5-triphenyl-1*H*-pyrazole **1c** in various RTILs at room temperature.

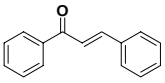
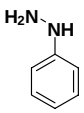
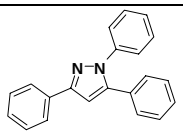
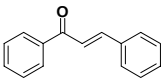
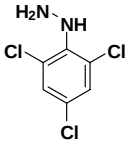
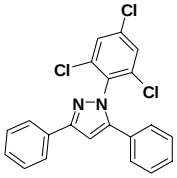
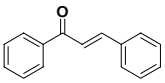
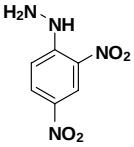
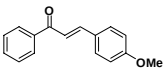
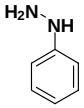
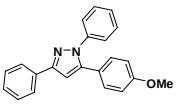
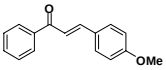
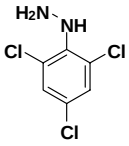
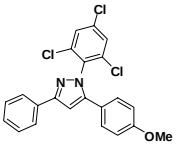
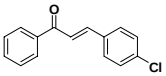
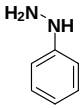
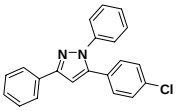
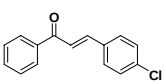
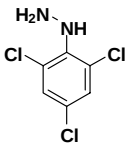
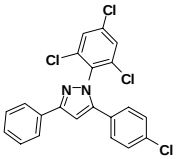
Entry	Ionic liquid	Time (min)[a]		%Yield[b]	
		Silent	(((((	Silent	(((((
1	[bbim]Br	2 h	30	90	95
2	[bbim]Cl	3 h	45	90	94
3	[bbim]ClO_4	6 h	1.5 h	85	92
4	[bbim]BF_4	6 h	1.5 h	85	90

[a] Reaction time in hours if not defined; [b] Isolated yield of 1,3,5-triphenyl-1*H*-pyrazole 1c.

Initially one pot synthesis of 1,3,5-triphenyl-1*H*-pyrazole **1c** from (*E*)-chalcone and phenyl hydrazine was carried out using various RTILs like [bbim]Br, [bbim]Cl, [bbim]ClO_4 and [bbim]BF_4 RTILs at room temperature under ultrasound or stirring without ultrasound (silent) condition (Table 3). Among all ILs tested, [bbim]Br IL was found superior with highest yield and lower reaction time period under both silent and ultrasound conditions. Inspiring with these attractive results, the RTIL [bbim]Br was further used as promoter and reaction media for the synthesis of several other

substituted 1,3,5-triphenyl-1*H*-pyrazoles and the results of the same are summarized in Table 4.

Table 4. Synthesis of 1,3,5-triphenyl-1*H*-pyrazoles in [bbim]Br at room temperature.

Entry	Substrates		Product [c]	Time (min) [d]		%Yield [e]	
	Chalcone [a]	Phenyl hydrazine [b]		Silent	(((((	Silent	(((((
1				**2 h**	**30**	**90**	**95**
2				**2 h**	**20**	**91**	**96**
\3			**No reaction**	**24 h**	**6 h**	**----**	**----**
4				**1.5 h**	**20**	**92**	**97**
5				**1.5 h**	**20**	**94**	**97**
6				**2 h**	**30**	**90**	**94**
7				**2 h**	**25**	**89**	**95**

[a] Chalcone; [b] phenyl hydrazine; [c] product 1,3,5-triphenyl-1*H*-pyrazoles; [d] Reaction time in hours if not defined; [e] Isolated yield of 1,3,5-triphenyl-1*H*-pyrazoles.

Chapter 1

Introduction to aldol reaction and synthetic studies towards 1-Deoxythionojirimycin

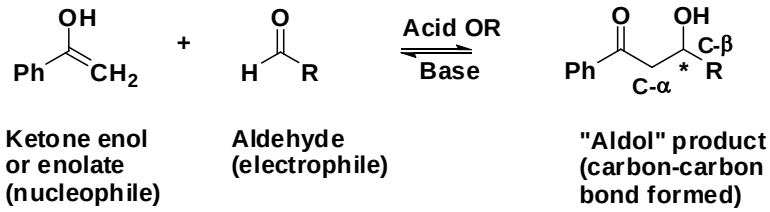
Section 1

Introduction to aldol reaction

Introduction to aldol reaction

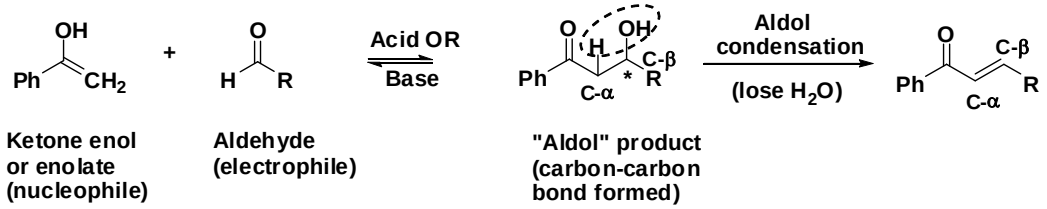
1.1.1 Aldol reaction

The formation of carbon-carbon bonds with complete control of stereochemical outcome of a reaction is one of the important aspects of modern organic synthesis. Aldol reaction is generally regarded as one of the most powerful and efficient method for carbon-carbon bond formation.[1] In general, this reaction involves the nucleophilic addition of *enol* or *enolate* from the enolizable carbonyl group to an aldehyde, which results into the formation of new carbon-carbon bond between the *enol* α-carbon and aldehyde giving a β-hydroxy carbonyl or **aldol** (**ald**ehyde + alcoh**ol**). The name aldol is derived from "**ald**ehyde" and "alcoh**ol**". The carbonyl group should have at least one acidic proton at α-position to exist in to its corresponding *enol* or *enolate* by tautomerisation, which is catalyzed by a base or an acid. Since *enol* or *enolate* possess π- electron system, this can act as a nucleophile, while the carbonyl carbon of aldehyde behaves as an electrophile (Scheme 1).

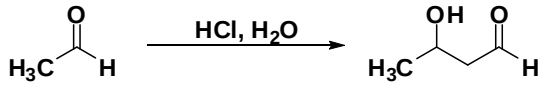


Scheme 1. A typical aldol reaction.

The primary products of aldol reaction are always β-hydroxy carbonyl compound but sometime the aldol addition product loses a molecule of water during the reaction to form α, β-unsaturated carbonyl called as aldol condensation as shown in scheme 2. The aldol reaction was discovered independently by *Charles-Adolphe Wurtz*[2] and by *Alexander*



Scheme 2. Aldol reaction and aldol Condensation.



Scheme 3. Acid induced aldol reaction of acetaldehyde.

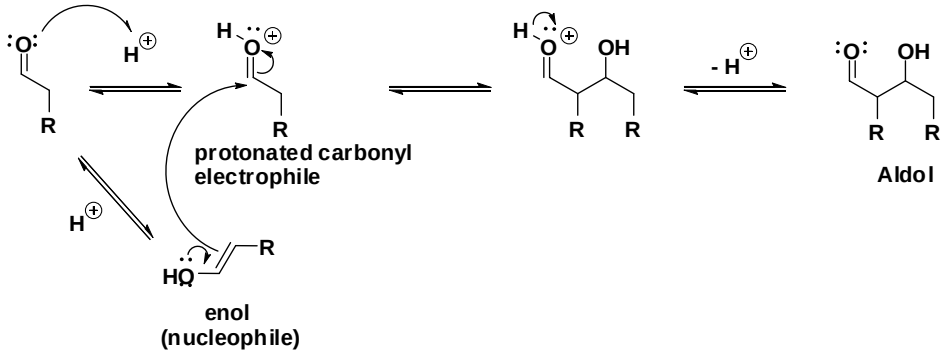
Porfyrevich Borodin in 1872 and observed simultaneous presence of aldehyde and alcohol moieties (an aldol) in 3-hydroxylbutanal resulting from the acid-induced reaction of acetaldehyde (Scheme 3).

1.1.1.1 Catalysis of traditional aldol reaction

The 'traditional' aldol reaction is a reversible reaction, which is catalyzed by either acid or base in the protic solvents proceeds under thermodynamic control.[3] A variety of nucleophiles may be employed in the aldol reaction, including the enols, enolates, and enol ethers of enolizable carbonyl compounds such as aldehydes or ketones but the electrophilic reactant is usually an aldehyde. When the nucleophile and electrophile are different (usual case), the reaction is called as crossed aldol reaction. The aldol reactions proceeds via two fundamentally different mechanisms.[3]

1.1.1.1.1 Enol mechanism

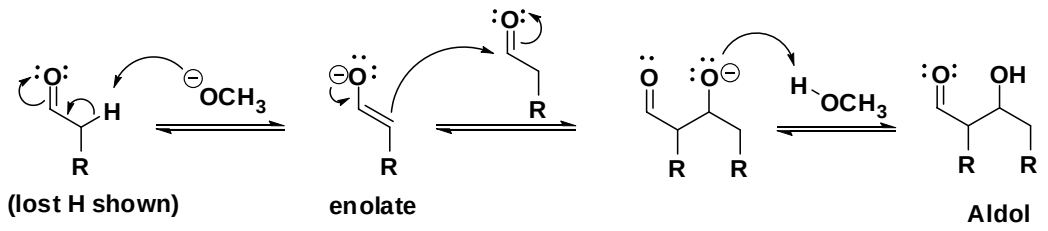
When an acid catalyst is used, the initial step in the reaction mechanism involves acid-catalyzed *tautomerization* of the carbonyl compound having active methylene proton to give an enol. The acid also serves as an activator of carbonyl group of *another molecule* by protonation to make it more electrophilic and can be attacked by even weak nucleophile. The enol, acts as a nucleophile at the α-position attack at the activated carbonyl group to give aldol product after deprotonation (Scheme 4).



Scheme 4. Acid catalyzed aldol mechanism.

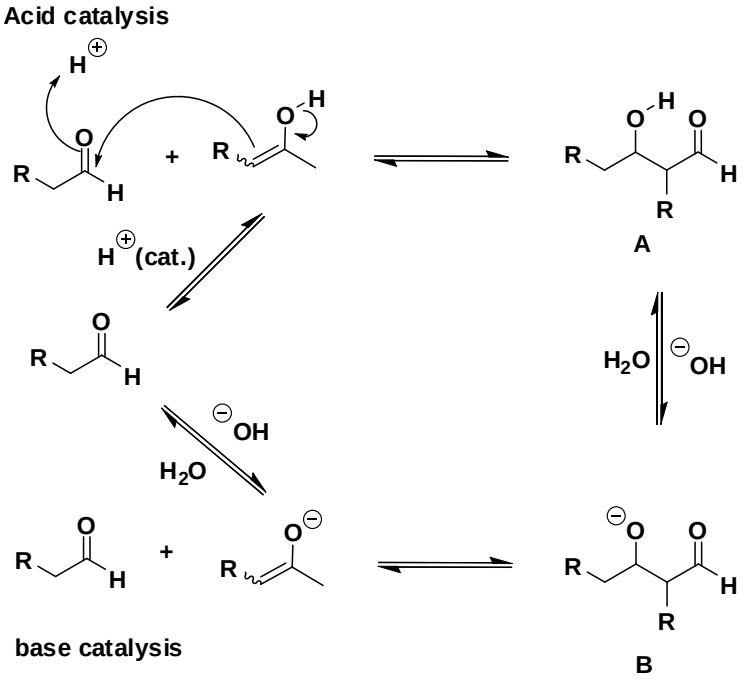
1.1.1.1.2 Enolate mechanism

When this reaction is catalyzed by a moderate base such as hydroxide ion or an alkoxide ion, the carbonyl compound (carbonic acid) gets deprotonated to form resonance-stabilized enolate that is more nucleophilic then enol or enol ethers. This enolate can attack on carbonyl group directly without any kind of the activation of carbonyl group, which is generally required in case of acid catalyzed reaction. Thus this reaction proceeds through the nucleophilic attack of enolate ion on the carbonyl group of another molecule to give aldol product after protonation. (Scheme 5)



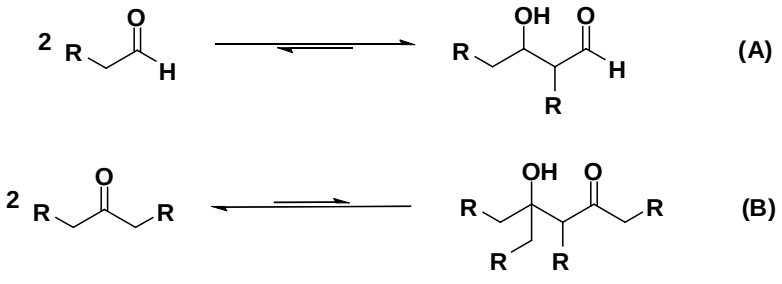
Scheme 5. Base catalyzed aldol reaction (showing $^{-}OCH_3$ as base).

Some of the typical features of 'traditional' aldol reactions are: the reaction is carried out in protic solvents, catalyzed by acid or base, the reaction is reversible particularly under these conditions. Thus this reaction is classified as *retrograde* aldol reaction. The reversibility of the aldol reaction can cause substantial problems from a synthetic point of view. Extensive studies have been carried out in order to determine the relative energies of an enolate and an aldehyde on one hand and the aldolate on the other hand showed the outcome of the aldol reaction to be slightly exergonic.[4] The aldol formed either by acid or base catalyzed reaction is significantly stabilized by a strong OH bond in aldol **A**, which arises either directly from acid-mediated addition or on protonation of the aldolate **B** in the base catalyzed variant as shown in scheme 6.



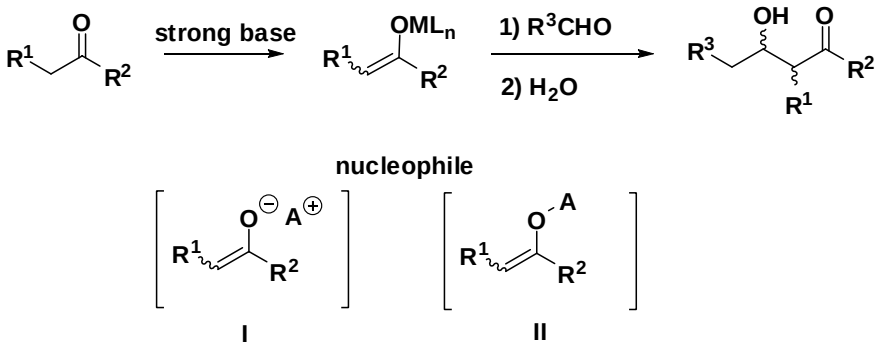
Scheme 6. General acid and base catalysis.

Alternatively, chelation of the counter-ion in aldolates resulting from preformed enolates in non-protic media serves as a driving force.[5] Since the 'traditional' aldol is a reversible reaction, so the yield of the reaction depends upon the position of the equilibrium. As a general rule, in the presence of protic solvents, the equilibrium in an aldol addition is located on the product side when aldehydes react with each other (Scheme 7, **A**), while it is on the side of starting material for the ketones (Scheme 7, B) because the self condensation of the ketones is endothermic as shown in scheme 7.



Scheme 7. Equilibrium for self aldol reaction of aldehyde and a ketone in protic solvents.

The self aldolization of the enolizable carbonyls proceeds much more efficiently in the combination with aldehydes rather then with ketones. This is due to the +I effect of the additional alkyl substituent and carbonyl carbon electrophilicity of ketones is lower than that of an aldehydes carbonyl carbon. Furthermore, a kinetic inhibition is possible due to the presence of the additional steric of an alkyl substituent. Mixed aldol reactions between different aldehydes or ketones usually result in the formation of a mixture of products, because each component can function as a C-H acidic and carbonyl-active compound. Thus, the traditional aldol reaction of non-identical carbonyl compounds is only successful when applied within the framework of a limited substituent pattern. For example, a fruitful combination in case of mixed aldol reaction is that of an aldehyde with enolizable ketone. The classical aldol reaction is highly atom-economic and despite of its undoubted versatility, this reaction suffers from problems of reversibility, dehydration reaction, selectivity notably chemo-, regio-, and stereoselectivity and a further challenge is to perform this reaction asymmetrically.[6]



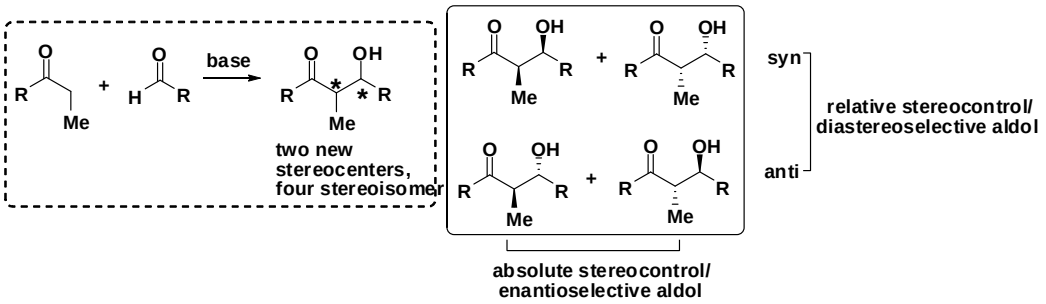
Scheme 8. Directed aldol reaction by stepwise enolization-aldolization sequence and the nucleophilic species involved.

In order to overcome these problems and to control the aldol reaction for making it more practical, new technique of "directed" stepwise aldol methodologies based on the use of preformed species **I** and **II** have been developed.[1,7] The general principle involves a stepwise enolization-aldolization sequence under aprotic conditions as represented in scheme 8.

Such reactions are normally carried out by converting a carbonyl compound to an enolate by using stoichiometric amount of a strong base such as LDA (Lithium

diisopropylamide) or LiHMDS (Lithium-*hexa*-methyldisilylamide), to act as a nucleophile. In this case, the enolate formation is irreversible and this enolate is then allowed to react with a second carbonyl compound. The aldol product is not formed until the metal alkoxide of the aldol product is protonated in a separate work-up step.

Modern synthetic reactions in organic chemistry aim at the synthesis of compounds in enantiopure form. Since the aldol reaction creates two new stereocenters, up to four stereoisomers may result (Scheme 9). Because of the presence of this structural pattern in many molecules of interest, the aldol reaction has been one of the most widely used synthetic methods for designing complex natural and non-natural products.[8]



Scheme 9. Stereochemical outcome of the aldol reaction.

The ability to control the absolute configuration of newly formed stereogenic center is of supreme importance for the synthesis of natural products. By utilizing the directed aldol reaction approach, control of stereochemistry has been accomplished diastereomerically by either using chiral aldehyde as starting material[9] or using chiral auxiliaries attached to the donor enolate.[1,10] However, *the more elegant and economically most attractive way to introduce asymmetry is undoubtedly through by using a catalytic amount of chiral controller.*[6]

1.1.2 Catalytic Asymmetric Aldol Reaction

The development of catalytic enantioselective reactions is one of the most challenging tasks of organic synthesis. The *β*-hydroxy carbonyl (aldol) and 1,3-diol units are frequently found in complex natural products and have attracted a great deal of attention from synthetic organic chemists. The asymmetric aldol reaction is one of the useful and concise methods for the preparation of complex chiral polyol architectures.[11] One of the major areas being studied extensively in synthetic organic

chemistry is the catalytic asymmetric aldol reaction, which can effectively and efficiently brings about the chiral transformation. A number of methods have been developed in recent years for the catalytic asymmetric aldol reaction with both high efficiency and selectivity.[6] In general; the catalytic asymmetric aldol reaction methodologies are classified in to two main types as shown in figure 1.

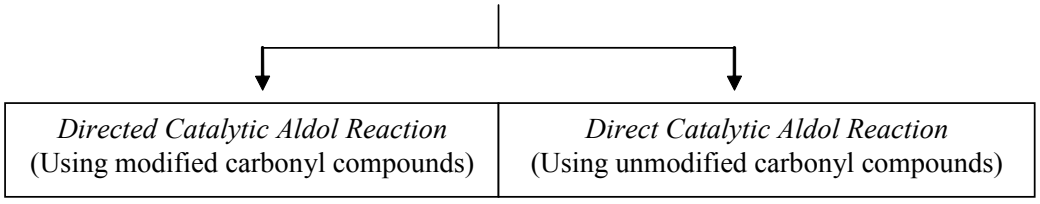
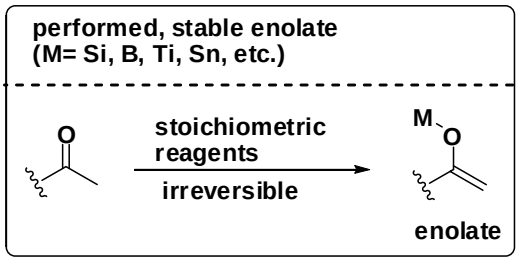


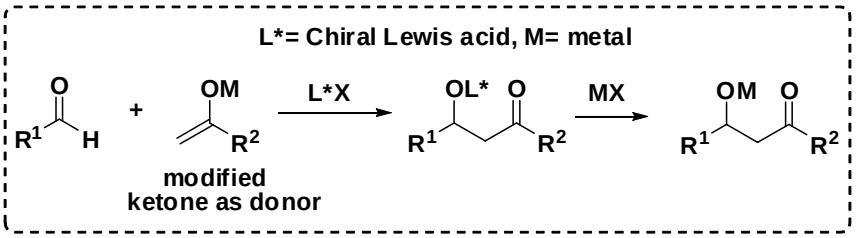
Figure 1. Types of catalytic asymmetric aldol reaction.

1.1.2.1 Directed catalytic asymmetric aldol reaction

This type of aldol reactions requires the preconversion of carbonyl compounds into a more active aldol donor, such as an enol ether or metal enolates by the use of chiral Lewis acid or Lewis base as a catalyst.[12] Thus, the utilization of irreversibly generated *"preformed and stereodefined stable"* metal enolates such as silyl, borane, titanium, and tin enolates in the presence of chiral Lewis acid or Lewis base catalyst is known as directed catalytic aldol reaction. (Scheme 10) In these cases, stoichiometric amount of base and/or adjunct reagents (such as silylating agents to form silyl enol ethers) are required, decreasing the atom efficiency of the process.



Scheme 10. Preformed and stereodefined stable enolate for directed aldol reaction.



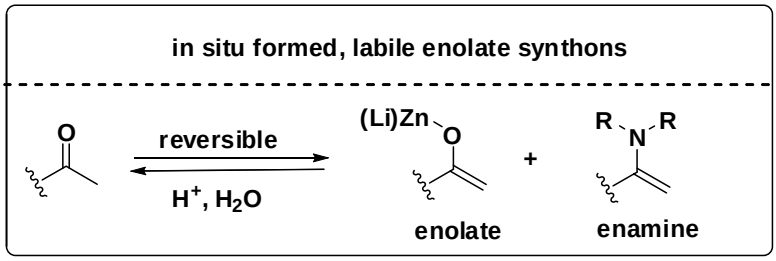
Scheme 11. The Mukaiyama aldol reaction.

The activation of the acceptor aldehyde by Lewis acid towards the addition of silyl enol ether to yield an aldol is commonly referred as the Mukaiyama aldol reaction.[13] This reaction has been rapidly improved from using stoichiometric amount of the (chiral) Lewis acid promoter to the substoichiometric/catalytic versions.[7,14] Since stoichiometric generation of metal enolate/enol ether is involved in a separate step, Mukaiyama aldol reaction is only catalytic at Lewis acid (metal) promoter stage. (Scheme 11)

In this regards, a number of Lewis acids which consist of a metal, including early and late transition elements, and chiral ligands bearing nitrogen, oxygen, and phosphorous donor have been developed.[15] An exciting challenge in enhancing the efficiency of the aldol reaction is to develop a catalytic route for direct aldol addition without prior to the stoichiometric formation of a nucleophile from carbonyl compounds.

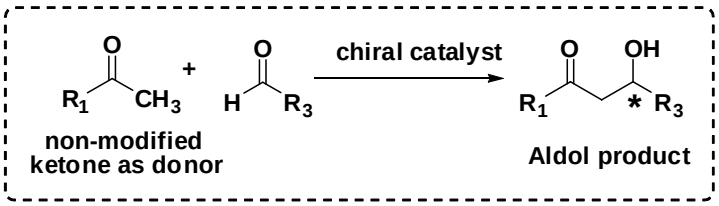
1.1.2.2 Direct catalytic asymmetric aldol reaction

Another type aldol reaction, in which the preconversion of carbonyl compounds is not required and the nucleophile (enol or enolate, carbanion equivalent) can be generated *insitu* reversibly and catalytically is known as '*direct process'*.[16] In this process, carbanion equivalents (nucleophile) of unmodified carbonyl compound are the 'insitu formed labile enolate synthons', which form a mixture of two reversible species, e.g., *keto-enolate* or *keto-enamine* (Scheme 12).



Scheme 12. Insitu formed reversible, labile enolate for direct catalytic aldol reaction.

A major challenge of these direct *catalytic* strategies is that the carbanion generation has to be compatible in the presence of an electrophile. The utilization of unmodified carbonyl compound as a nucleophile (aldol donor) for catalytic asymmetric aldol reaction is highly atom economic (Scheme 13). The development of an efficient route that combines unmodified, hence commercially important carbonyl substrates as nucleophiles, and chiral catalytic system for direct asymmetric catalytic aldol reaction is a worthwhile attempt.



Scheme 13. Direct catalytic asymmetric aldol reaction.

In recent years, the exciting developments have been made in the field of asymmetric aldol reaction, utilizing unmodified carbonyl compound as a labile aldol donor in the presence of catalytic chiral controller to induce chirality in the reaction. An important challenge of aldol reaction is the simultaneous control of the regio -, diastereo-, and enantioselectivity when unsymmetrical ketones are used. The three different approaches can be attempted for the direct asymmetric aldol reaction; (i) using biocatalysis such as aldolases and catalytic antibody and (ii) using metal catalysis and (iii) Organocatalysts (Figure 1).[1,6]

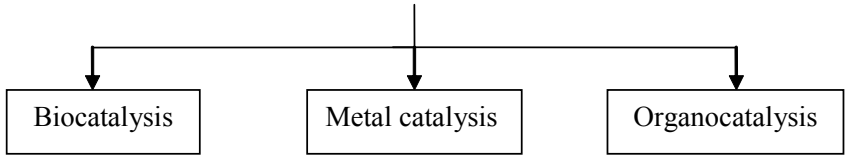


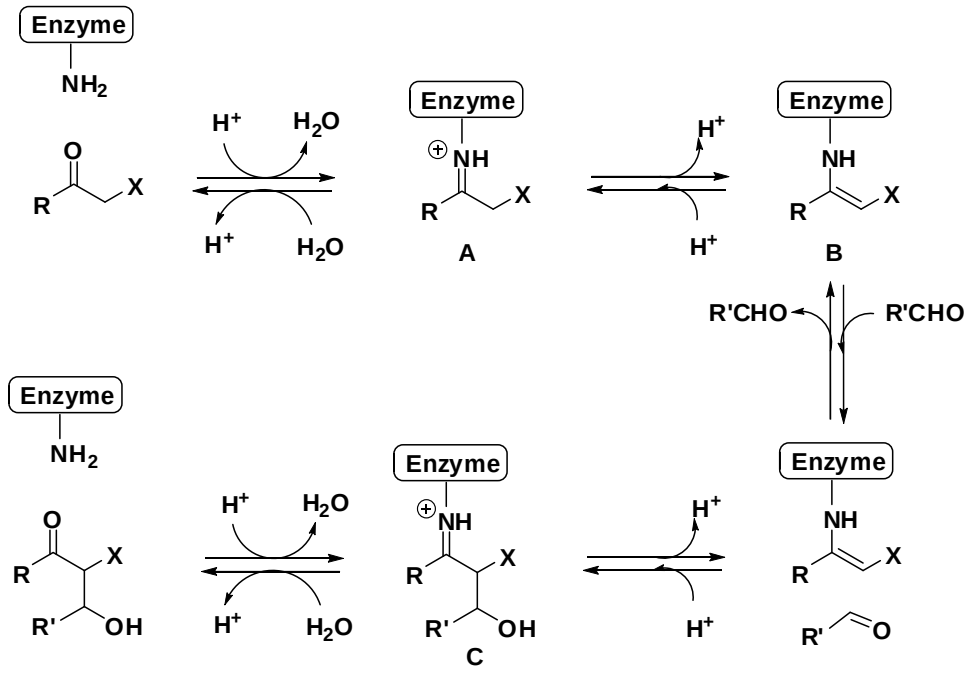
Figure 2. Direct catalysis of aldol reaction.

1.1.2.2.1 Biocatalysis

Enzymes are increasingly recognized as useful catalysts for organic synthesis.[17] Most enzymes used by Nature for C-C bond formation and cleavage ("lyases") catalyze a crossed aldol reaction in the form of a reversible, chemo-, regio-, diastereo-, and enantioselective addition of nucleophilic ketone donor to an aldehyde acceptor. As a result of high selectivity under mild conditions in aqueous solution at or near neutral pH values makes enzymes synthetically useful though in certain cases, the reaction is limited to a narrow range of substrates and the isolation of the products from water could be a problem. There are two type of enzymatic catalysis that effect the aldol reaction: the aldolases, a group of naturally occurring enzymes that catalyze in *vivo* aldol condensation; and catalytic antibodies that have been developed in recent years to mimic the aldolases but with improved substrate specificity.[1d]

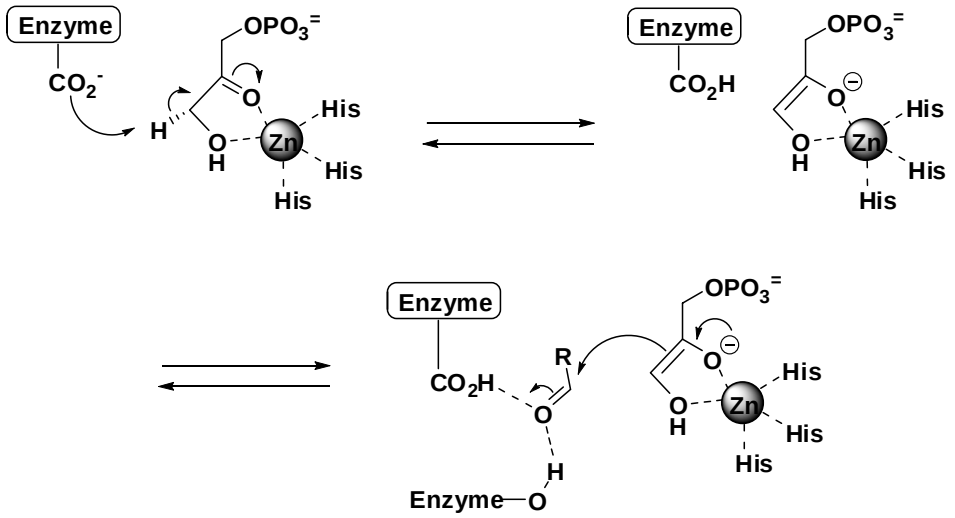
1.1.2.2.1.1 Aldolases

Two different types of aldolases have been identified and classified according to their mechanisms.[1d, 18]



Scheme 14. Schematic mechanism for class I aldolases.

Class I aldolases bind the substrate covalently and activate the donor by forming an *imine-enamine* as an intermediate with the active site Lysine to initiate bond cleavage or formation. This activated donor then adds stereoselectively to the acceptor aldehyde (Scheme 14). Class II aldolases; on the other hand, utilize transition metal ion (Zn^{2+}) Lewis acid cofactor in the active site, which facilitates deprotonation by bidentate coordination of the donor to give the enediolate nucleophile[19] (Scheme 15). In the both type of aldolases the formation of the enolate (that is, the deprotonation step) is rate determining. With only a few exceptions, the stereochemistry in both types of aldolases in controlled by enzyme and do not depend on the structure or the stereochemistry of the substrate, which allows highly predictable product formation. These enzymes generally tolerate a broad range of acceptor substrate but have stringent requirement for donor substrates.

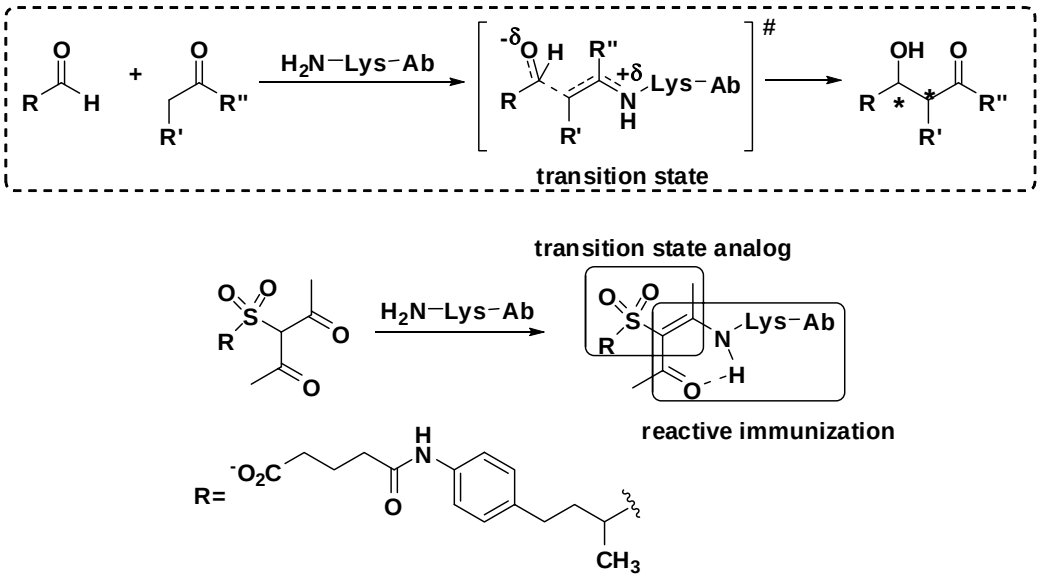


Scheme 15. Schematic mechanism for DHAP-dependent class II aldolases.

1.1.2.2.1.2 Antibodies

In the recent years, catalytic antibody technology has been designed to process a wide range reaction, in particular aldol reaction.[20] Aldolases catalytic antibodies developed recently have the ability to match the efficiency of natural aldolases while accepting a more diverse range of substrate. Although many type of antibody catalyst have been generated, selection of antibody catalyst has typically been based on binding to transition state analogs of the reactants or charged compounds designed using information from the reaction coordinate of a given chemical transformation.[21]

Further progress was made in this field with the development of catalytic function and residue-based selections by using 1,3-diketones for the concept of reactive immunization. Reactive immunization provides a means of selecting antibody catalyst in *vivo* on the basis of their capability to perform a chemical reaction.[22,23] In order to improve the concept of reactive immunization and to develop antibodies with complementary enantioselectivity, a *β*-diketone sulfone was used as hapten[24] (Scheme 16). Unlike natural aldolases, the catalytic antibodies were found to accept a wide range of ketone donor substrates. Antibodies catalyze the direct aldol reaction similar to aldolases class I.



Scheme 16. Aldolases antibodies used for conceptual elements derived from reactive immunization and transition state analog design.

It is clear that Nature's aldolases and antibodies use the combination of acids and bases in their active site to accomplish direct asymmetric aldolization of unmodified carbonyl compounds. These aldolases are distinguished by their different strategy of enolization mode for direct aldolization of two unmodified carbonyl compounds. Class I aldolases use the Lewis base catalysis of a primary amino group and proceed through enamine

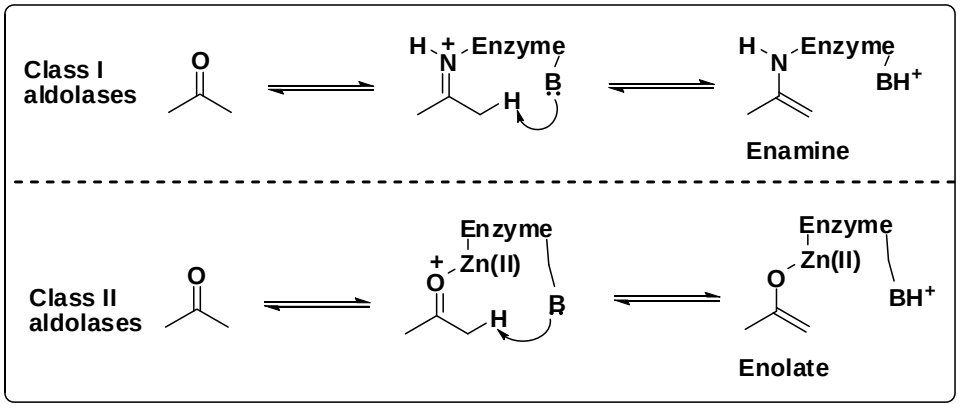
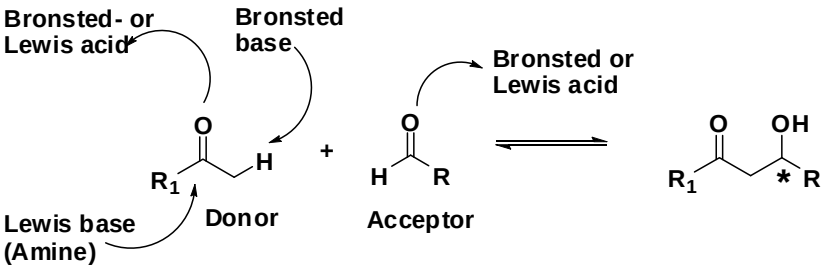


Figure 3. Two enzymatic strategies for enolization of carbonyl compounds.

based mechanism, while Class II aldolases use the Lewis acid catalysis of a Zn (II) cofactor and proceed through zinc enolate mechanism as shown in figure 3. Although chemists also use acids and bases to catalyze aldolization reaction but the aldolases-like direct catalytic asymmetric aldol reaction remained a challenge for a long time. In the recent years, remarkable progress has been made in direction of direct catalytic asymmetric aldol reaction using metal catalysis and organocatalysis.[16]

1.1.2.2.1.2 Metal catalysis

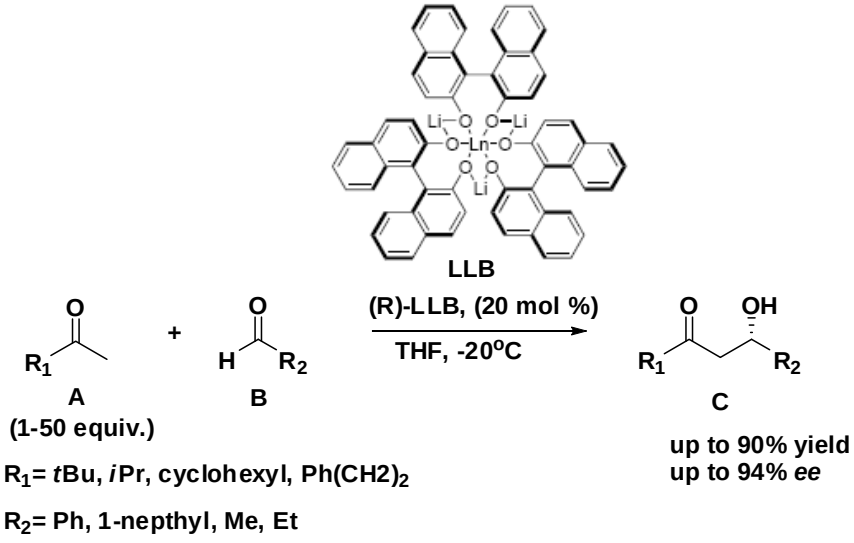
Enantioselective reactions catalyzed by metals have had the most significant impact on the development of synthetic organic chemistry.[25] Since the aldol reaction catalyzed by both Lewis and Brønsted acids and bases.[1] This catalytic diversity is possible because the aldol reaction combine a nucleophilic addition, which is acid-catalyzed, with an enolization, which is catalyzed by both acids and bases as shown in scheme 17.



Scheme 17. Bronsted/Lewis acid and Bronsted/Lewis base catalysis of the aldol reaction.

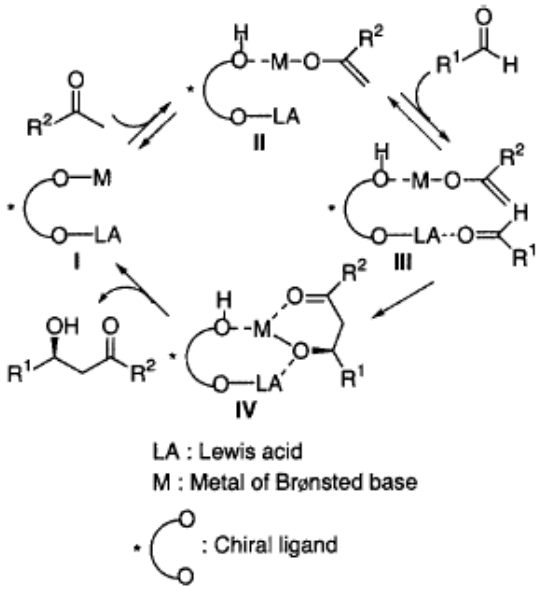
The catalytic activation of aldehyde acceptor by using chiral Lewis acid, using preformed enol/enolate as a nucleophile has achieved a great success but provides a viable strategy for catalytic asymmetric aldol reaction.[16, 26]

An exciting challenge in enhancing the efficiency of the aldol reaction is to find a simple compound that will catalyze direct aldol addition without prior stoichiometric formation of a nucleophile and to do so asymmetrically similar to the enzymes. In the recent years, extensive study has been carried out to provide the synthetic alternatives of enzymatic strategy for direct asymmetric aldol reactions. The first direct catalytic asymmetric aldol reaction has been developed in 1997 by Prof. Shibasaki group, using bifunctional Lewis acid-Bronsted base metal complex which catalyze the direct aldol reaction similar to the class II aldolases.[27] This concept is based on the use of bifunctional catalysts such as the heterobimetallic catalyst $LaLi_3$tris(binaphthoxide) (LLB), which bears both a Lewis acid site and a Brønsted basic site, and is capable of simultaneously activating the nucleophilic ketone and the electrophilic aldehyde. This catalyst can be regarded as enzyme mimics of the metal containing type II aldolases. The reaction of methyl ketones **A** with aldehydes **B** under the presence of a 20 mol% of LLB in THF provides aldol adduct **C** in good yield and high enantioselectivity (Scheme 18).

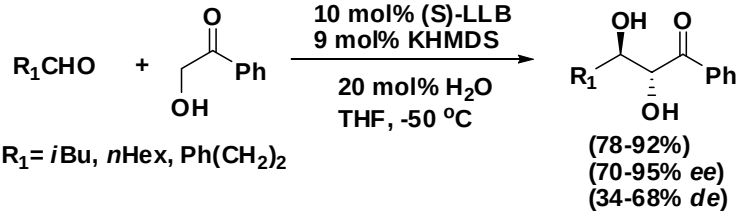


Scheme 18. Direct catalytic asymmetric aldol reaction between aldehyde and unmodified ketones catalyzed by (R)-LLB.

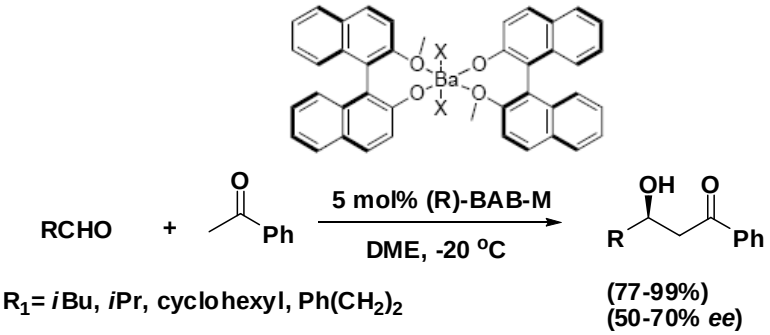
Anhydrous LLB was more efficient then hydrated LLB, the higher yield and *ee* were obtained when excess of ketone was used. The catalyst incorporates a central lanthanum atom, which acts as a Lewis acid and a lithium binaphthoxide moiety, which act as a Brønsted base. The synergistic effect of both functionalities allows the reaction to proceed without the need for any other activation of the starting materials. A proposed mechanism for this transformation is outlined in scheme 19. The Brønsted acid unit **(OM)** of catalyst **I** could deprotonate an α-proton of a ketone to generate the metal enolate **II**, while at the same time a Lewis acid unit **(LA)** could activate an aldehyde to give **III**. These reaction partners might react in the chelation-controlled, asymmetric environment to afford a metal β-oxoalkoxide **IV.** Proton exchange between the metal alkoxide moiety and a hydroxy proton of the aryl unit or an α-proton of a ketone could then generate an optically active aldol product with regeneration of catalyst **I**. A major shortcoming of this catalyst is the need for excess ketone and long reaction time. The catalytic activity of LLB can be enhanced by the incorporation of KOH (insitu generated from $KN(SiMe_3)_2$ and H_2O), into a heteropolymetallic complex that rapidly promotes the aldol reaction with lower catalyst loading (3-8 mo %).[28] The LLB·KOH complex was able to catalyze an enantio- and diastereoselective direct aldol reaction with 2-hydroxyacetophenone, which provides the *anti*-α-β-dihydroxy ketones (Scheme 20).[29]



Scheme 19. Catalytic cycle for direct asymmetric aldol reaction with (R)-LLB.

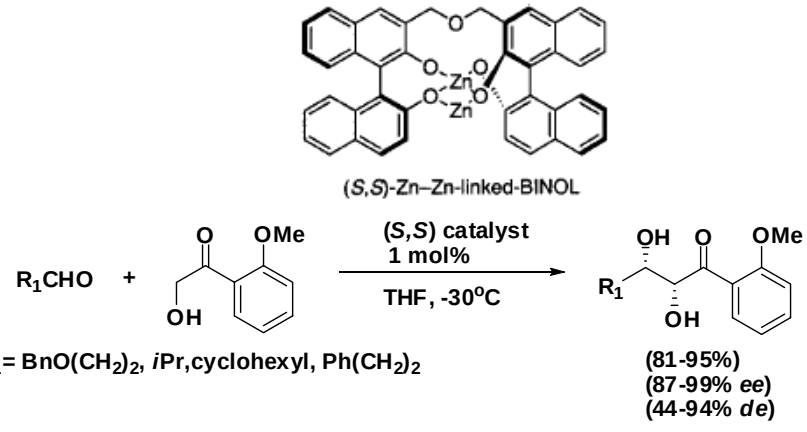


Scheme 20. LLB promoted direct catalytic asymmetric aldol reaction between 2-hydroxyacetophenone and aldehydes.



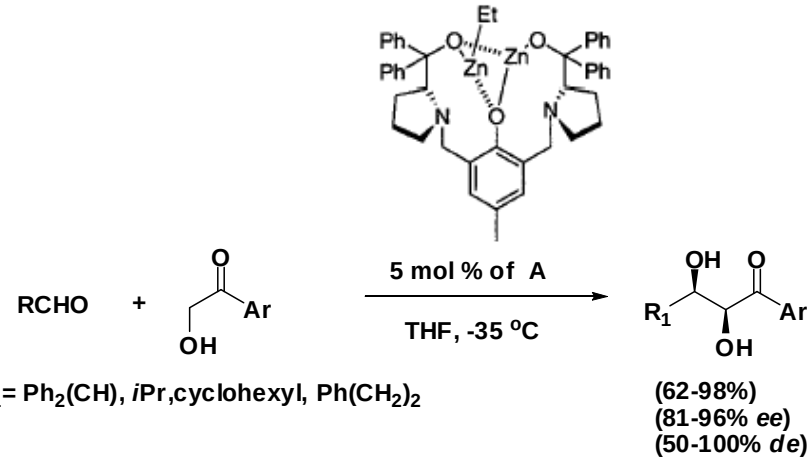
Scheme 21. Direct catalytic asymmetric aldol reaction between aldehyde and unmodified acetophenone, catalyzed by (R)-BaB-M.

A similar catalyst BAB-M, derived from barium phenoxide was developed by Shibasaki group in order to eliminate the shortcomings of the LLB catalyst (long reaction time and excess ketone).[30] The catalyst BAB-M prepared from Ba(O*i*Pr)$_2$ and BINOL-Me, effects the asymmetric aldol reaction between any aldehyde and 2 mol-equiv. of unmodified acetophenone in the presence of 5 mol% of BAB-M much more faster than 20 mol% of LLB at 5 mol-equiv. of ketone. (Scheme 21)

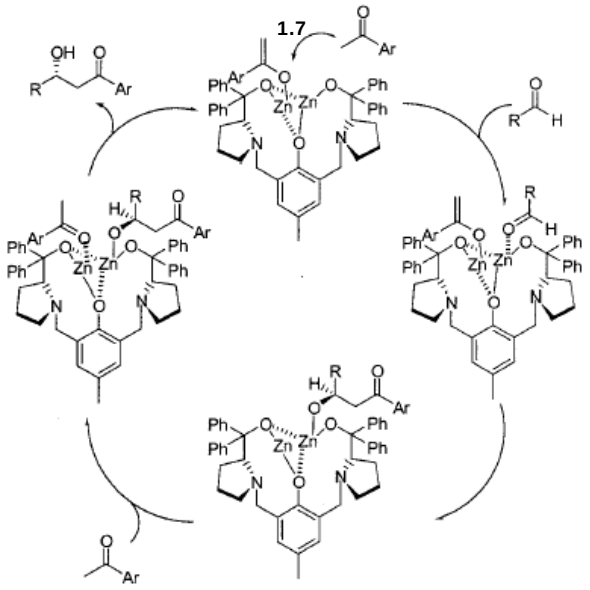


Scheme 22. Zn-Zn-linked BINOL catalyst for direct aldol asymmetric reaction.

Recently, a highly enantio-, diastereoselective aldol reaction of different aldehydes and 2-hydroxy-2'methoxyacetophenone proceeded smoothly with as little as 1 mol% of a dinuclear zinc catalyst, Zn-Zn-linked BINOL, to afford *α*-*β*-dihydroxy ketone in high syn-selective manner and excellent yield. [31] Which is found to be best in terms of catalytic loading (1 mol% for direct asymmetric aldol reactions (Scheme 22).



Scheme 23. Direct catalytic aldol reaction of a-hydroxy ketones mediated by **A**.



Scheme 24. Catalytic cycle of Trost catalyst **A**.

Prof. Trost and co-workers designed a novel catalyst **A** for direct asymmetric aldol reaction of *α*-hydroxy ketones as a donor[32] (Scheme 23). The effectiveness of this catalyst permits the use of nearly molar equivalents amounts of both partners. This catalytic system is very close to reaching the ideal atom-economical version of the

asymmetric aldol addition. In this binuclear organometallic catalyst, the role of one of the two-zinc atoms is to form the requisite enolate and another zinc atom acts as a Lewis acid to coordinate the aldehyde. The mechanism of the catalyst is shown in scheme 24. Thus, one important advantage of using chemically designed catalyst is that their structure can be modified to improve their efficiency.

1.1.2.2.3 Organocatalysis

Enzymes are highly efficient and enantioselective catalysts. While chemists use mostly metal-based catalysts, about half of known enzymes do not contain metals in their active sites. Catalytic asymmetric reactions provide the new and powerful tools for the efficient synthesis of complex molecules.[33] Although for a long time, the field of asymmetric catalysis was dominated by the use of transition metal catalysis[25] and biocatalysis[17]. Synthetic chemists have hardly used small organic molecules as catalysts throughout the last century, even though some of the very first asymmetric catalysts were purely organic molecules. In the recent years, between the extremes of both metal catalysis and enzymatic catalysis; a third approach for the production of enantiomerically pure compounds using metal-free catalysis has emerged, which is termed as *Organocatalysis*.[34] The term "organic catalysts" was introduced by Ostwald (1900), in order to differentiate the small organic molecules as catalytic principles from enzymes or inorganic catalysts.[35] Although the concept of organic catalysis was first introduced by the German chemist Langenbeck back in 1928,[36] and the expression "organische Katalyse" first appeared in the literature in 1931.[37] Generally, Organocatalysis is the catalysis of chemical transformations using a purely *"organic molecules"* which are composed of mainly carbon, hydrogen, nitrogen, sulfur and phosphorus. These small organic molecules are providing synthetic alternative of enzymes to many established asymmetric transformations.[38] Recently, it was proposed to define an organic catalyst as: "an organic compound of relatively low molecular weight and simple structure capable of promoting a given transformation in substoichiometric quantity".[39] This definition is broad enough to cover the varying structural diversity of organic catalyst.

Nature is the principle practitioner of asymmetric synthesis and uses enzymes to catalyze stereoselective reactions with high fidelity. Enzymes generally uses hydrogen bonding between the active sites and the substrates, together with nonbonding dipole-

dipole, electrostatic, and steric interactions, to orient the substrates and stabilize the transition state, leading to high level of stereoselectivity.

Recently, the biocatalytic and metal catalytic processes are facing serious competition, mainly as a result of the blooming of organocatalysis in asymmetric catalysis and the 'organocatalysis' has become the catchword for this field of research. [34,39,40,41] Figure 4 illustrates the increase in publications containing the words "organocatalysis" or "organocatalytic".

The organocatalysts are low molecular weight, metal free, usually non-toxic, readily available, and easily separable from the reaction product without any kind of racemization. Because of the absence of transition metals, organocatalytic methods seem to be especially attractive for the preparation of compounds that do not tolerate metal contamination such as pharmaceutical products. Organic molecules not only have ease of manipulation and a "green" advantage but also can be very efficient catalysts.

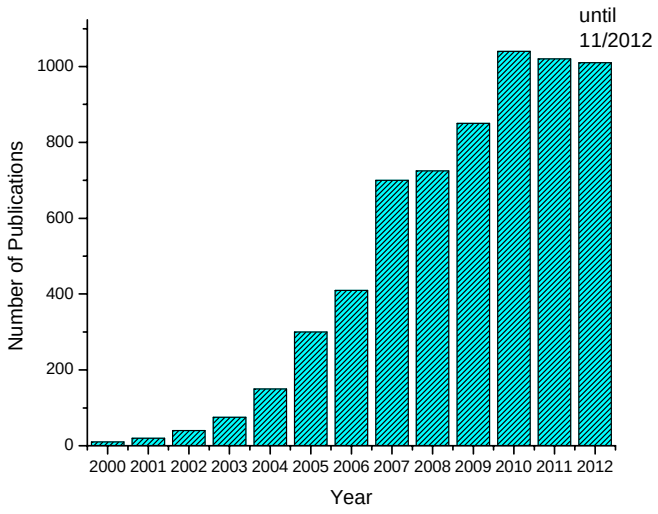
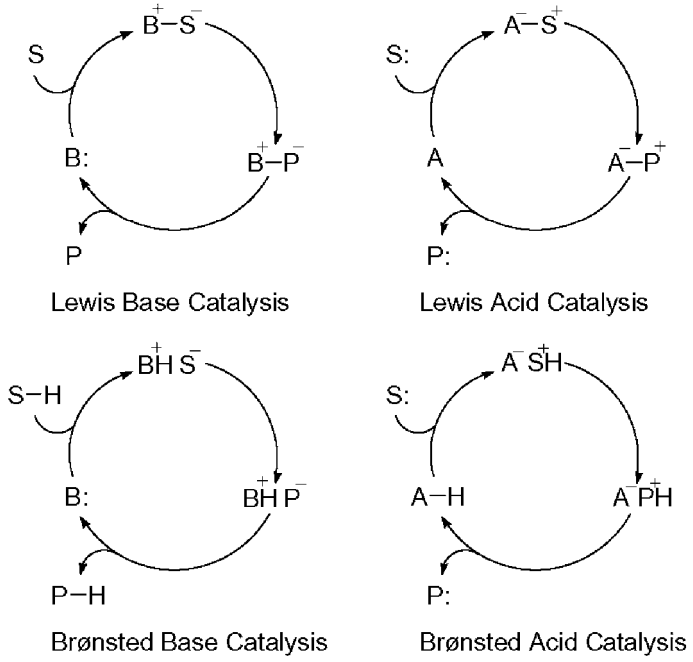


Figure 4. Publication on organocatalysis (SciFinder®).



Scheme 25. Catacycle Lewis base and Brønsted base catalysis.

A significant advantage of many organocatalysts is the capability of promoting several types of reactions through different activation mode proposed by Prof. List.[42] Most of the organocatalyst can be classified in the main category of Lewis acids, Lewis bases, Brønsted acids, and Brønsted bases. Their corresponding catalytic cycle is shown in scheme 25. Accordingly, Lewis base catalysts (B:) initiate the catalytic cycle *via* nucleophilic addition to the substrate (S). The resulting complex undergoes a reaction and then releases the product (P) and regenerates the catalyst to further catalyze the reaction. Lewis acid catalysts (A) activate nucleophilic substrates (S:) in a similar manner. Brønsted base and acid catalytic cycles are initiated *via* a (partial) deprotonation or protonation, respectively. Recently, significant efforts have been made to develop chiral Brønsted acids[43] and bifunctional chiral Brønsted acid/base[44] catalysts in this direction.

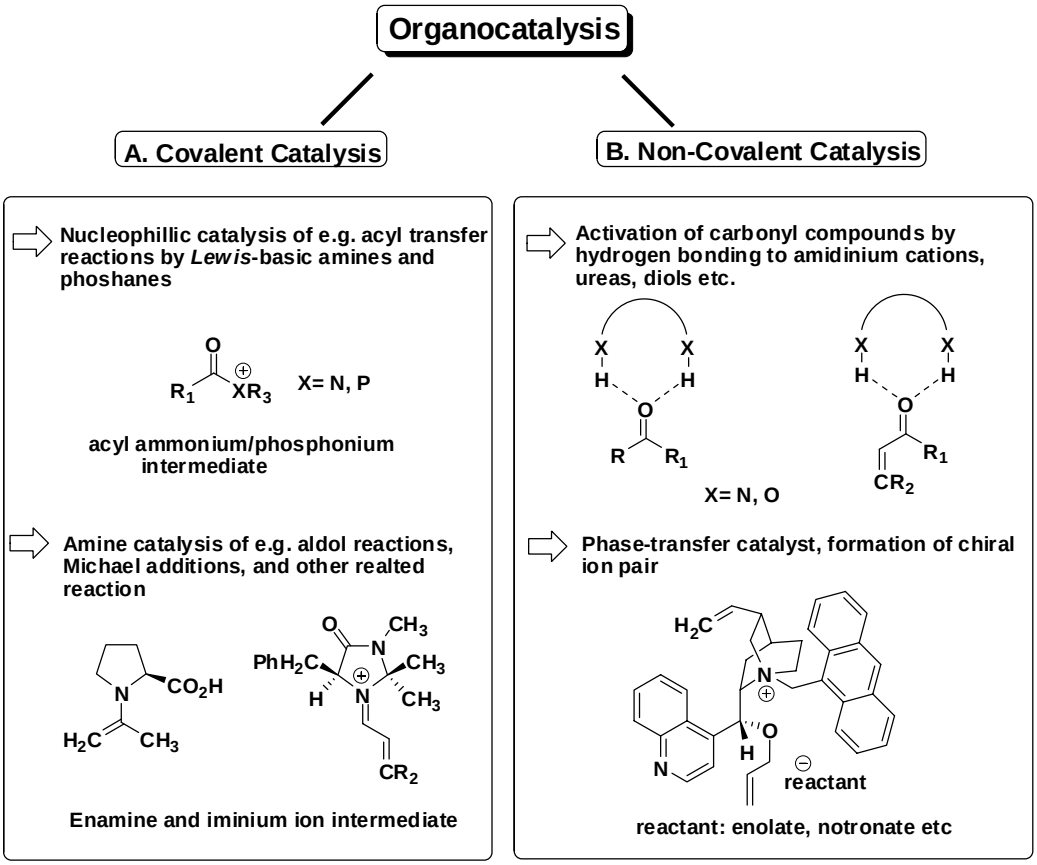


Figure 5. Covalent and non-covalent organo-catalysis.

In many cases, organocatalysts can be considered as "minimum version" of the metal free enzymes catalysis because of their similarity between mechanistic and catalytic actions. In both cases the rate acceleration observed depend on typical interaction between the catalyst and organic molecules. A typical distinction can be made between the processes that involve the *formation of covalent adduct* between catalyst and substrate within the catalytic cycle and the other processes, which involves the non-covalent interactions such as hydrogen bonding or ion pair between the substrate and catalysts. The former interaction has termed as "covalent catalysis" and the later situation is denoted as "non-covalent catalysis". The catalysis of aldol reaction with the formation of *'enamine donor'* represents the category of covalent catalysis having a common mechanism for enzymatic and organo-catalytic processes.

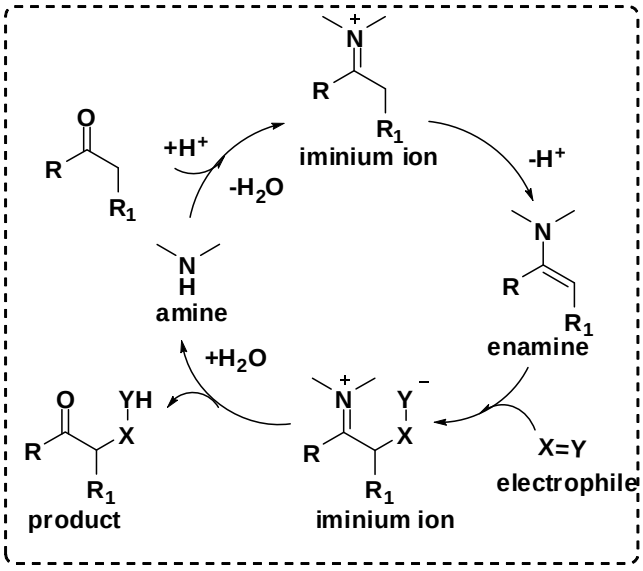
Whereas the non-covalent catalysis relies on the formation of hydrogen-bonded adducts between substrates and catalysts or on protonation/deprotonation processes. Phase-transfer catalysis (PTC) by organic phase-transfer catalyst falls into the category of "non-covalent catalysis" (Figure 5).[34a]

Organocatalysis is an emerging area in asymmetric synthesis, which is growing very rapidly and applied successfully to the several different enantioselective transformation in the recent years.[39,40,41,45] Generally there are five different modes of catalysis to detail the scope of organocatalysis and how it can be applied successfully for the synthesis of pharmaceutically relevant compounds:[45,46]

(i) Secondary amine catalysis via enamines (ii) secondary amine catalysis via iminium ion (iii) phase transfer catalysis (iv) nucleophilic and Brønsted base catalysis; and (v) hydrogen bonding catalysis.

Since organocatalysis is a fast moving field and hundreds of papers have been appeared in last couple of years from different distinguished research group worldwide. Thus, it is not possible here to cover all the development of last six years in different aspects of organocatalysis and its utility in asymmetric synthesis.[46]

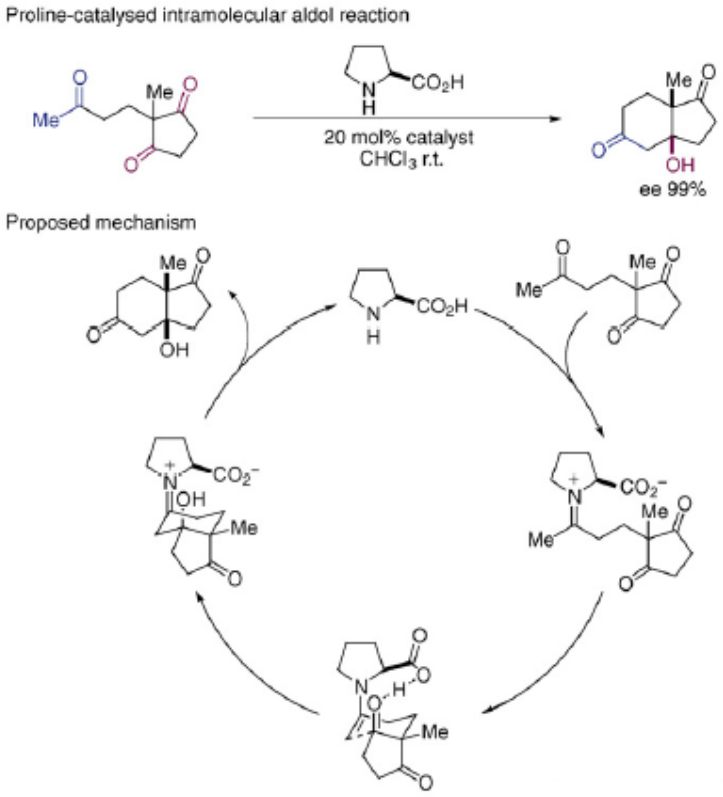
Here we are giving a brief report on the progress in the direction of amine catalysis via enamines intermediates for direct catalytic asymmetric aldol reaction in the recent year's.



Scheme 26. Enamine catalysis.

Amino-catalysis is a biomimetic strategy for aldol reaction via enamine intermediates used by enzymes such as class I aldolases for the application in preparative organic synthesis, particularly in intermolecular aldol addition reaction.[38a,38c] It is believed that the basis of *enamine catalysis* is reversible and catalytic generation of enamine from amines and carbonyl compounds (Scheme 26). Enamine formation is facilitated

by the dramatic increase in C-H acidity upon initial conversion of carbonyl compound in to an iminium ion. The catalytically generated enamine should be able to undergo addition reaction with various electrophiles (X = Y), similarly to the well-studied chemistry of preformed enolates.[47,38c] The resulting new iminium ion furnishes, after hydrolysis with *insitu* generated water, the α-substituted carbonyl product.



Scheme 27. First proline catalyzed intramolecular aldol reaction (1971).

First organocatalysis was a proline catalyzed intramolecular aldol reaction that was reported during 1970s and termed as Hajos-Parrish-Eder-Sauer-Wiechert reaction as shown in scheme 27.[48] The success of this aldol reaction is due to the proposed hydrogen bonding between the carboxylic acid group of proline and the carbonyl electrophile.[48,49] This reaction provides a simple method for the formation highly enantiopure progesterone intermediate that are useful in synthesis.[50]

L-proline a "Universal Organocatalyst"

L-proline has been defined as a "universal catalyst" because of its high utility in variety of asymmetric organic transformations. Proline is the only natural amino acid with a secondary amine functionality, which raises the *p*Ka value and better

nucleophilicity as compared to other amino acids. It can be regarded as a bifunctional catalyst with the secondary amine acts as Lewis base and the acid group acts as Bronsted acid (Figure 6).

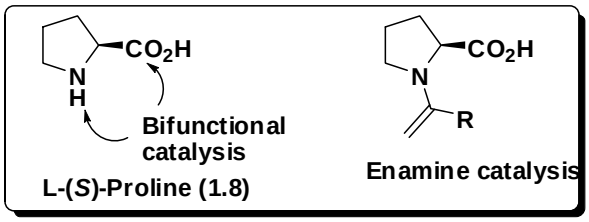
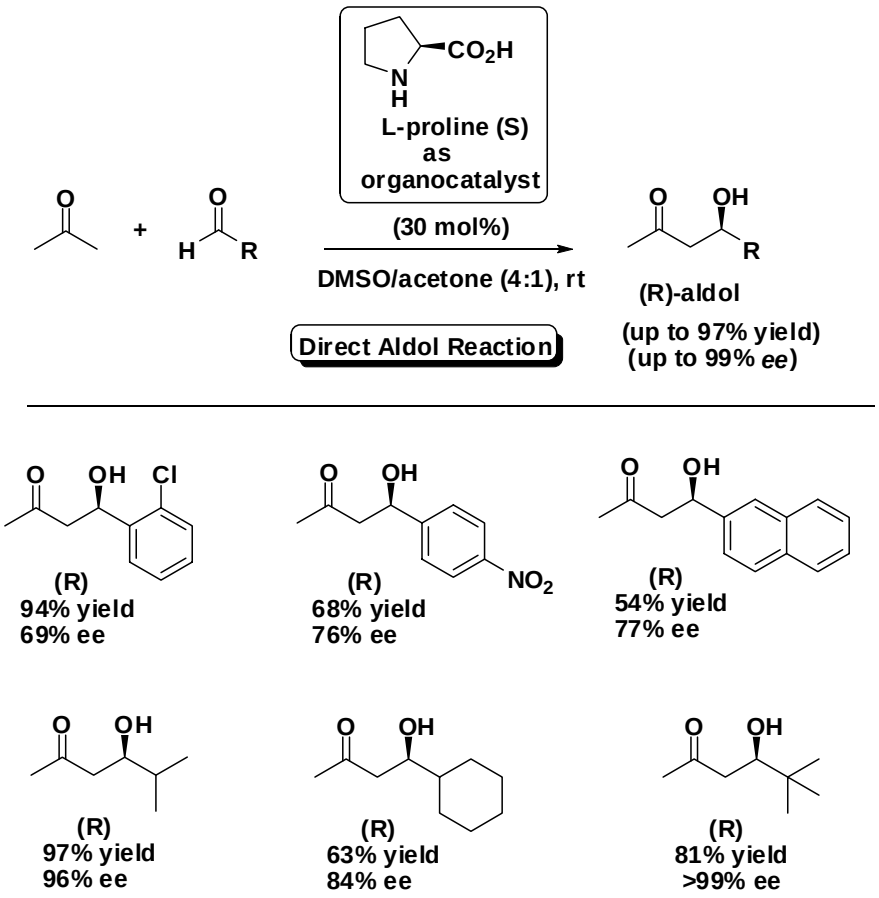


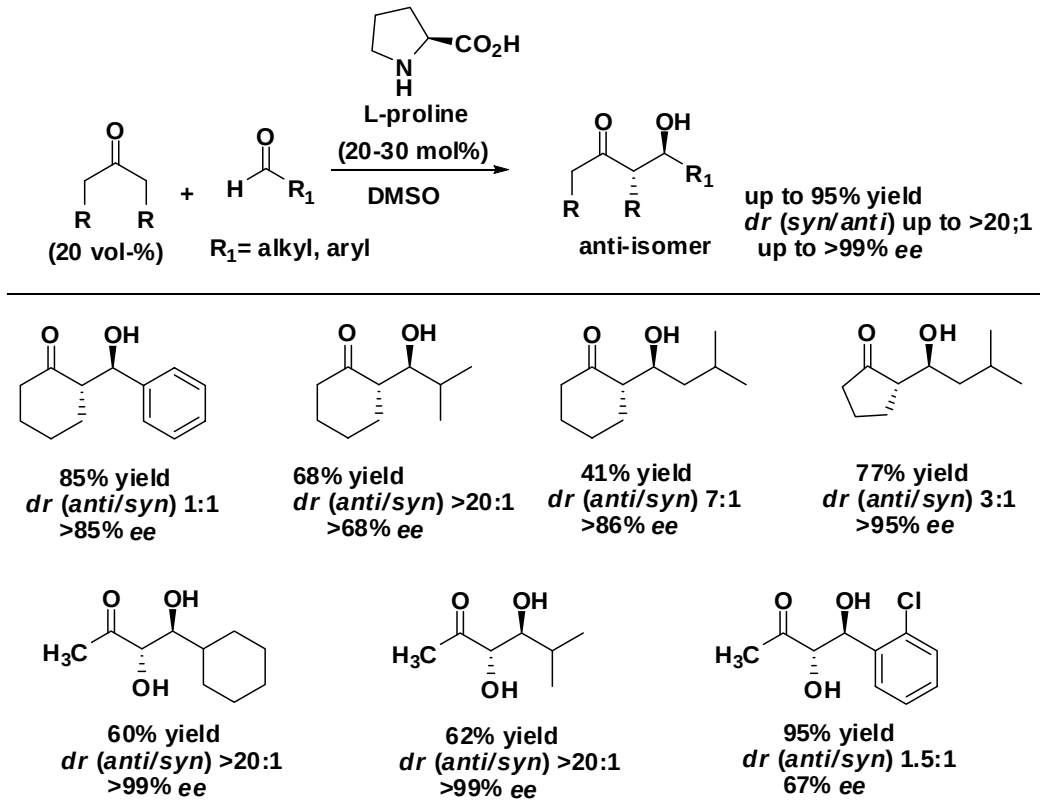
Figure 6. L-proline as organocatalyst.

The high stereoselectivity in the proline-catalyzed reactions is possibly due to its formation of organized transition states with hydrogen bonding frameworks.[47,38c] The historic roots of the use of amino acids as organocatalysis (amino-catalysis) for the aldol reactions was reported first time in 1931.[37,51] Although, the breakthroughs in asymmetric organocatalysis was achieved in 1970s by two industrial groups, [51] the proline catalyzed intramolecular aldol reaction remained little more than a laboratory curiosity and it took around thirty years for a revival of this chemistry, which was initiated by Prof. List, Barbas and Lerner with the discovery of the proline-catalyzed direct asymmetric aldol reaction in intermolecular fashion,[52] which proceed tough the similar manner as enzymatic conversion with class I aldolases. The reaction of acetone with different aldehydes proceeds nicely with good yield and high enantioselectivity. (Scheme 28) This rediscovery has initiated an explosive growth of research activities in the area of organocatalysis both in industry and in academia. Organic molecules not only show a "green" advantage but also ease for functional manipulation to act as very efficient catalysts.



Scheme 28. The first proline catalyzed asymmetric aldol reaction (selected examples).

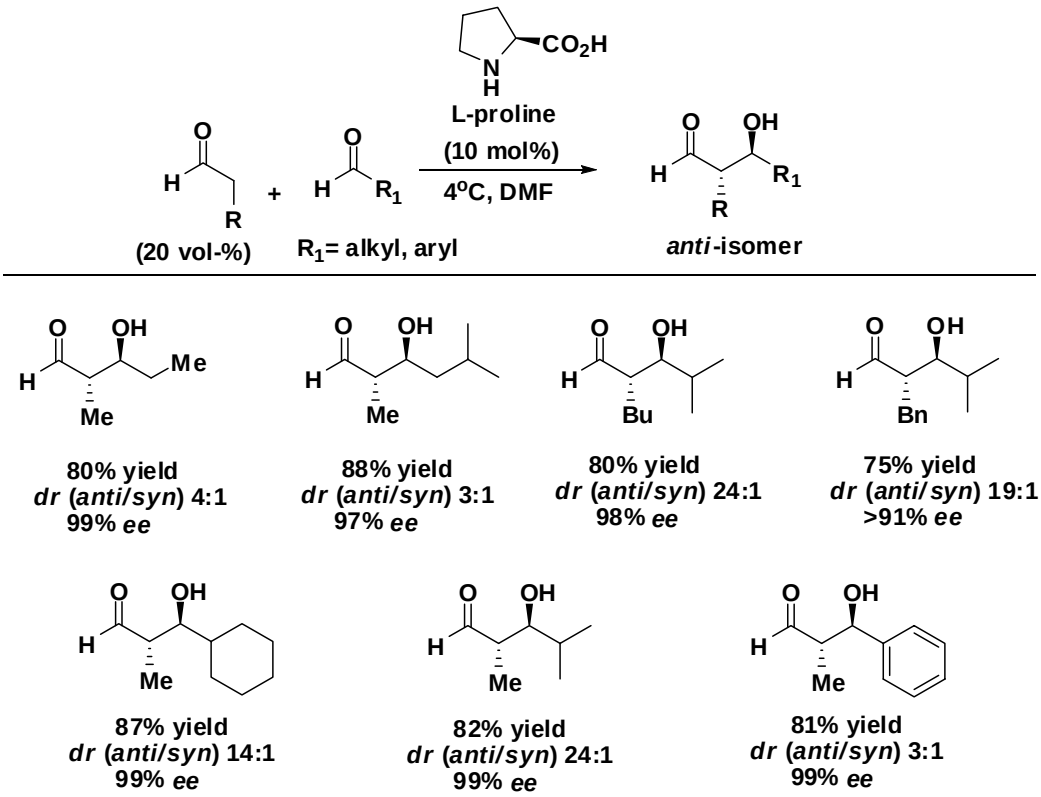
Direct and indirect asymmetric aldol reaction with acetone (or equivalents) as donor are generally considered to be very challenging. This report not only provides a remarkable solution to one of the most intensively studied problems in catalysis, but also marked as a new beginning for the study of proline catalyzed enantioselective reactions. The potential of this proline catalysis direct aldol reaction was also investigated with ketones other than acetone. The use of inexpensive and smaller ketones such as butanone, cyclopentanone, cyclohexanone, and hydroxy acetone, higher enantio and diastereoselectivity (anti), can be achieved depends on the aldehyde used. (Scheme 29).[53]



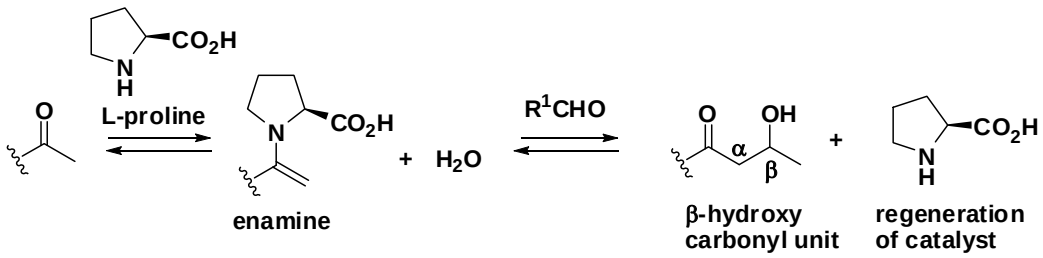
Scheme 29. Direct aldol reaction with hydroxy acetone as a donor (selected examples).

In addition to ketones, aldehydes can be used as aldol donor in proline catalyzed aldol reactions.[54] Recently Prof. McMillan group found that proline also catalyzed cross aldolization of two different aldehydes under carefully developed conditions.[55] These reactions furnish *anti*-aldols in good yield with excellent enantio- and diastereoselectivity (Scheme 30).

There have been numerous reports on small-molecule-catalyzed aldol reaction using the "*later enolate equivalents*" (enamine catalysis). In particular, '*the discovery of versatile catalytic nature of proline occurring via enamine intermediates*' has been the biggest breakthrough in this field of research (Scheme 31).[38-47]

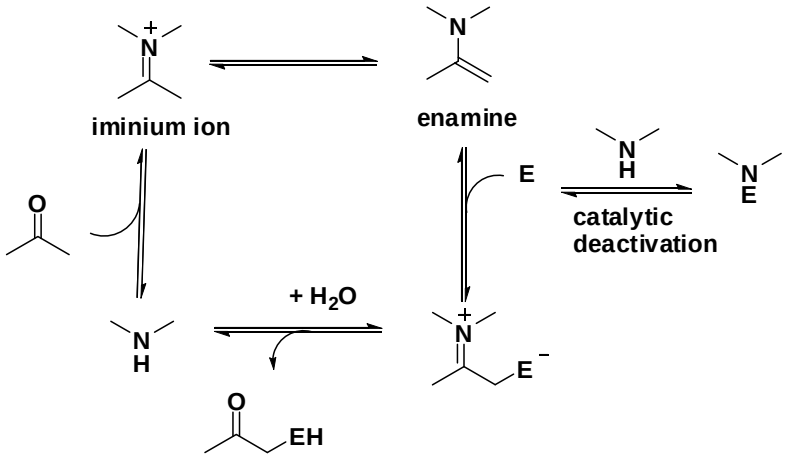


Scheme 30. Direct asymmetric aldolization of aldehydes (selected examples).



Scheme 31. Summary of proline catalyzed intermolecular aldol reaction.

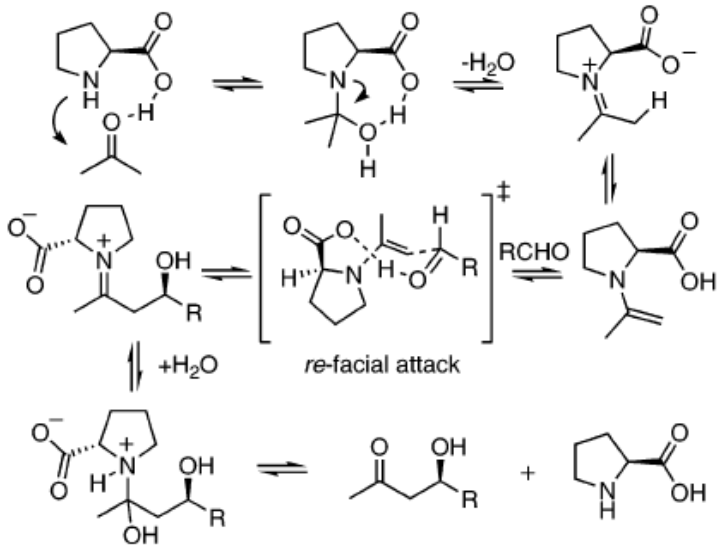
The generalized catalytic cycle for enamine as a carbanion equivalent that describes amine-catalyzed reaction of carbonyl compounds with electrophiles is shown in scheme 32. According to this Scheme, a secondary (or primary) amine reacts with a ketone to furnish key intermediates as iminium ion and the enamine. Iminium ion formation lowers the LUMO energy of the system.



Scheme 32. The enamine catalytic cycle.

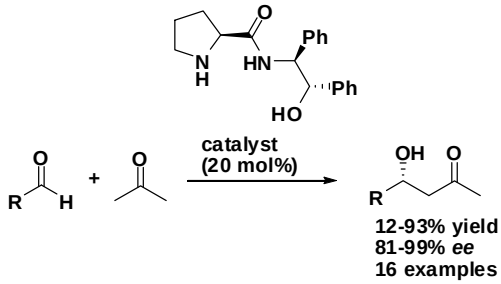
As a result, both nucleophilic addition and α-deprotonation become more facile. Deprotonation leads to the generation of enamine, which is the actual nucleophilic carbanion equivalent. This enamine reacts with an electrophile to give a modified iminium ion that upon hydrolysis furnishes the addition product with the regeneration of catalyst. A potential limitation of this cycle would be the irreversible deactivation of the nucleophilic amino-catalysis by the electrophile.

The mechanism of proline catalyzed intermolecular aldol reaction was proposed through enamine catalysis involving iminium ion, and enamine intermediates,[52,56] which is essentially identical to the accepted mechanism of class I aldolases. According to the fundamental nature of amino-acid catalysis, the acidic part of amine-acid catalyst seems to be largely responsible for the rapidly promoting the step of enamine and carbon-carbon bond formation. The carboxylic acid was proposed to act as a general-purpose Brønsted cocatalyst, replacing the several acid/base functional groups involving in the aldolase mechanism. In this mechanism, Proline functions as a "micro-aldolase" that provide both the nucleophilic amino group and an acid/base cocatalyst in the form of the carboxylate.



Scheme 33. L-proline catalyzed enamine mechanism of the direct catalytic asymmetric aldol reaction.

This cocatalyst may facilitate each individual step of the mechanism including (i) the nucleophilic attack of the amino group, (ii) dehydration of the carbinol amine intermediate, (iii) the deprotonation of the iminium ion (iv) the carbon-carbon bond formation and (v) the step of hydrolysis of the iminium-aldol intermediate. (Scheme 33) Recently, the computational studies carried out by Prof. Houk and coworkers' confirme[57] that this transition state is energetically the most favorable and predicting the stereochemistry correctly. This Houk-List model for proline catalyzed aldol reaction rationalize the selectivity of both intramolecular[49] and intermolecular[52,55,56] variants. According to the Houk-List model, the role of carboxyl group is to activate the carbonyl acceptor by hydrogen bonding, which was further supported by the results of Gong, Wu, and co-workers using proline-derivative (Scheme 34), having two hydrogen bonding sites. This catalyst is significantly more enantioselective than proline, even the reaction can be performed at lower temperature. For the reaction between acetone and benzaldehyde catalyzed by (Scheme 34), author could locate a double-hydrogen-bonded transition state by a initial calculations. Both the amide and hydroxy group were hydrogen bonded to the aldehyde in transition state as shown in scheme 34 and figure 7.[58]



Scheme 34. Double hydrogen-bonding catalyst for the direct enantioselective aldol reaction.

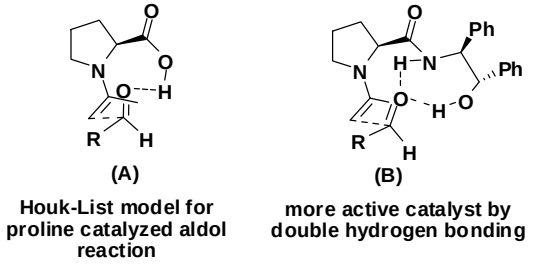
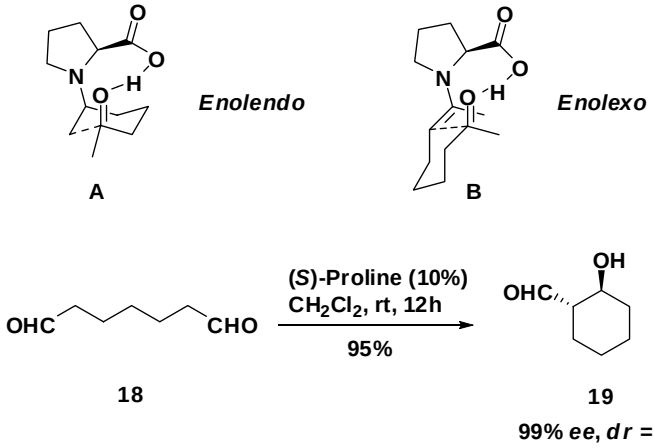


Figure 7. The Houk-List model for the proline catalyzed aldol reaction and the rational behind the success of the Gong-Wu aldol catalyst.

Several study in this direction to make modified proline catalysts have been carried out by different research group, but the concept of the enamine catalysis remain same for both inter- and intramolecular aldol reactions. Although, the catalytic asymmetric *enolendo* aldolization is known from 1970s,[48] the first catalytic asymmetric *enolexo* aldolization was developed recently by Prof. List and co-workers[59] and it was observed that a variety of achiral heptanedials on treatment with a catalytic amount of L-proline furnished *anti*-aldols with excellent enantioselectivity. A selected example of this 6-*enolexo* aldolization is given in scheme 35; in which the desired *trans*-1, 2-disubstituted cyclohexane product is obtained with a diastereomeric ratio of *dr* = 10:1 and a highest enantioselectivity of 99% *ee*.



Scheme 35. Proline catalyzed first enantioselective 6-*enolexo* aldolization.

The catalytic generation of asymmetric enolate equivalents is an area for which there is no general solution and, perhaps, the most surprising factor in the growth of organocatalysis. Since 2000, research by a number of groups has demonstrated the tremendous generality of proline catalysis for the generation of carbon-carbon, carbon-nitrogen, carbon-oxygen, and carbon halogen bonds to ketone or aldehyde substrates and summarized very recently by Gaunt M. J. and co-workers.[45b] Enamine catalysis using proline or related catalyst has now been applied to both intermolecular and intramolecular addition reactions with a variety of electrophiles such as, addition to carbonyl compounds (C=O) for direct aldol reactions, to imines (C=N) in Mannich reactions,[60] azodicarboxylates (N=N) for direct amination reactions,[61] nitrosobenzene (O=N) for direct oxygenation reactions,[62] and Michael acceptor (C=C) for 1,4-conjugate addition reactions,[63] along with that direct intramolecular alkylation reactions of aldehydes using enamine catalysis also have been established by Prof. List[64] recently. The recent achievements of enamine catalysis using proline as an organocatalyst have been summarized in figure 8.

Several other different synthetically important methods such as, fluorination,[65] chlorination,[66] brmonation,[67] sulfenylation,[68] have been developed for the α-functionalization of aldehydes and ketones with high stereoselectivity. In extension of earlier work done on proline catalyzed reaction up to 2004, proline and its derivatives have been used extensively for the development of several other carbon-carbon bond forming methodologies[69] and synthesis of many natural/unnatural organic molecules of biological importance[70] in the recent years. The catalysis for these reactions are carried out by the versatile enamine mechanism using chiral secondary amines derived from proline and imidazolidinones as an organocatalyst. Organocatalytic processes recently used for the synthesis of important drugs and bioactive compounds to further enhance it synthetic application, which has been reviewed very recently.[47] We strongly believe that asymmetric aminocatalytic have great potential in academic and industrial synthesis, the further development and utility of these methods can be expected. We have presented a brief account on the "direct catalysis" of aldol reactions using biocatalysis, metal catalysis, and organocatalysis (small organic molecule catalysts or metal free catalysts).

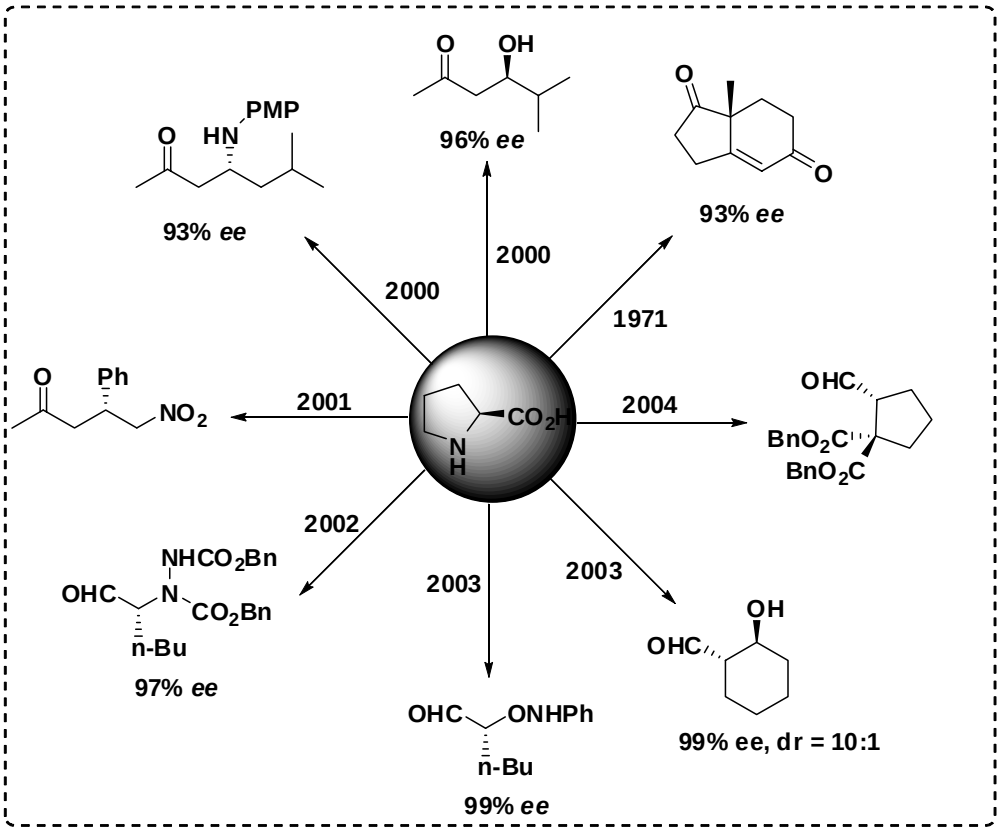


Figure 8. Recent achievement of enamine catalysis using L-proline as organocatalyst.

In particular, organocatalysis is very the fast growing area of the current research in organic chemistry and recently applied in several different enantioselective transformations. Particularly, the detailed mechanistic concept of enamine-catalysis e.g. amino-catalysis for aldol reaction using L-proline as an organocatalyst has been presented here. Tremendous progress has been made in the recent years so it is very difficult to cover all the reports, thus only selected L-proline catalyzed direct intermolecular and intramolecular aldol reactions have been presented here. All the information collected and presented here has been well supported by providing about 100 latest references from various monograph and international journals.

1.1.3 Aim of the Thesis and survey of the contents

The first aim is to make a clear understanding of the original concept of the direct catalytic asymmetric aldol reactions using different catalytic processes like-biocatalysis, metal catalysis and organocatalysis. Critical literature search has been carried out and presented here on the direct aldol reaction, which pointing out that the

discovery of direct enantioselective aldol reaction using enamine catalysis can be viewed as a major breakthrough in the field of aldolization reaction.

However, further need to explore the applications of organocatalysis for the asymmetric synthesis of biological activities compounds and the enamine catalysis for direct asymmetric aldol reaction provides an excellent starting point for further investigation. Thus, the second aim of the thesis is to explore the scope of the direct organocatalytic aldol reactions and to provide the new organocatalytic route to the synthesis of some of the important biologically active compounds using L-proline as an organocatalyst.

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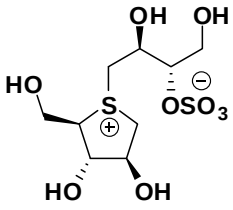
Section 2

Synthetic studies towards 1-Deoxythionojirimycin

Synthetic studies towards 1-Deoxythionojirimycin

1.2.1 Introduction

Thiosugars are sugar equivalents in which one or more oxygen atoms are replaced by a sulfur atom. Both monosaccharide and disaccharide thiosugars own distinctive physicochemical properties such as water solubility, which varies from conventional functionalized monosaccharides.[1,2] Thiosugars and their oxygen equivalents have different geometry, conformation, and flexibility. They also differ electronically; the sulfide function is less electronegative and more polarizable than the ethereal moiety. The **S** atom has dispersed electron density; longer **C-S** bond (1.8 Å) and smaller **C-S-C** bond angle (95-100^{o}) than its oxygen-containing equivalent. The biological activities differences between thiosugars and their oxygen counterparts are governed by physical and electronic differences of the sulfur and oxygen groups.[3]



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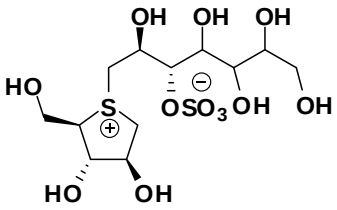
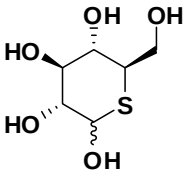
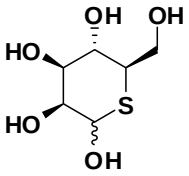


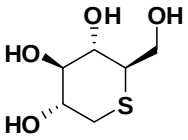
Kotalanol (2)



5-Thio-D-glucose (3)



5-Thio-D-mannose (4)



1-Deoxythionojirimycin (5)

Figure 1. Some notable natural/unnatural thiosugars.

In recent years, the interesting biological properties and activities of these compounds fascinated many chemists and biochemists. Many mono and oligosaccharide thiosugars recognized as potential enzyme inhibitors and could be used as therapeutic agents for diabetes, antiviral and antineoplastic treatments.[4-7] Many naturally

occurring thiosugars containing intracyclic sulfur atom showed remarkable biological activity and can be used as potential sugar-based therapeutics. Salacinol **1** and Kotalanol **2** are few of such examples and both show potential inhibitory activity against α-glucosidase. Among those salacinol is isolated from the ***Hippocrateaceae*** plant ***Salacia reticulata*** extensively found in Srilankan and South Indian forests and used as traditional *Ayurvedic* medicine for diabetes in both the countries.[7]

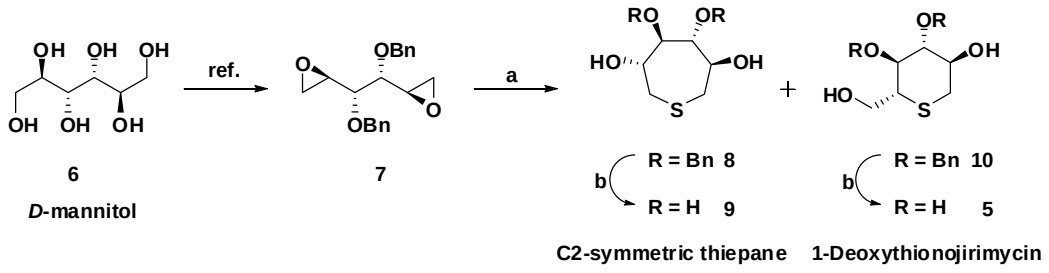
Sugars such as, 5-thio-D-glucose **3** impedes the insulin release[1a], 5-Thio-D-mannose **4** isolated from the marine sponge ***Clathriapyramida*** inhibits mannosidase enzymes[4], 1-deoxythiomannojirimycin **5** is a weak competitive inhibitor of yeast α-D-glucosidase[5] and 1-deoxythionojirimycin (DTNJ) is a synthetic thiosugar, a weak inhibitor of α and β-glucosidases[6b] (Figure 1).

1.2.2 Literature review for 1-Deoxythionojirimycin

Very few reports are available in the literature for the synthesis of 1-deoxythionojirimycin and they are discussed below.

1.2.2.1 Myrielle Fuzier and coworkers approach[6a]

F. Myrielle and co-workers synthesized 1-deoxythionojirimycin from a dibenzyl protected flexible bis-epoxide **7** as a starting material. The nucleophilic ring opening of this bis-epoxide goes through 6-exo-tet process to facilitate the tetrahydrothiopyran core structure. The bis-epoxide 1,2:5,6-dianhydto-3,4-di-*O*-benzyl-*L*-iditol **7** was prepared from D-mannitol **6** by the known procedure.[9] The reaction of bis-epoxide with two equivalents of sodium sulfide nonahydrate in refluxing ethanol afforded a mixture of two chromatographically separable compounds, a benzylated thiepane **8**



Scheme 1. *Reagents & Conditions: a) $Na_2S.9H_2O$, EtOH, Reflux; b) BBr_3, CH_2Cl_2. -50 °C, 85%.*

(seven membered) and tetrahydrothiopyran **10** (six membered). The benzylated thiepane and tetrahydrothiopyran individually on treatment with BBr_3 underwent debenzylation to offer crystalline thiepane **9** and 1-DTNJ **5** respectively (Scheme 1).

1.2.2.2 Gunasundari and Chandrasekaran approach[8]

Gunasundari and Chandrasekaran synthesized 1-Deoxythionojirimycin by employing a protecting group-free protocol and using easily available carbohydrate molecule as starting material, benzyltriethylammonium tetrathiomolybdate ($[BnEt_3N]_2MoS_4$), as a sulfur transfer reagent and borohydride exchange resin (BER) as reducing agent.

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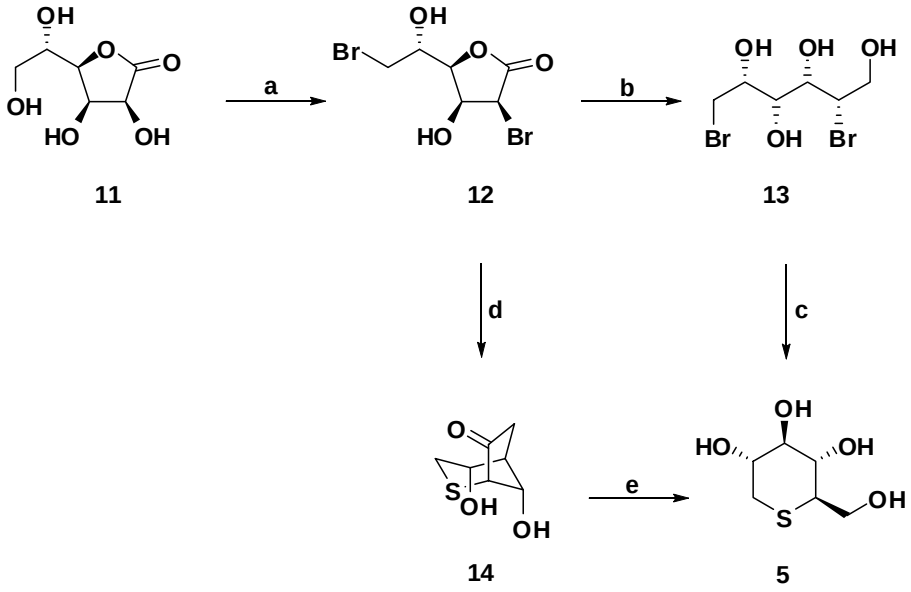


Scheme 2. *Reagents & Conditions: a) HBr/AcOH, 30 ^oC, 4.5 h, 86%; b) $NaBH_4$, MeOH, Amberlite 120 H^+, 20%; (c) $[BnEt_3N]_2MoS_4$, CH_3CN:EtOH (1:1), rt, 30 min, 38%; d) $[BnEt_3N]_2MoS_4$, DMSO, rt, 30 min, 56%; e) BER, MeOH, 0 ^oC-rt, 18 h, 62%.*

Synthesis of 1-deoxythionojirimycin was visualized from commercially available L-gulonic acid-γ-lactone **11**. Bromination of **11** with HBr in acetic acid offered 2,6-dibromo-2,6-dideoxy-D-idono-1,4-lactone **12** which further reduced with sodium borohydride in the presence of Amberlite 120 H^+ resin to give key intermediate dibromide **13** in 20% yield. The subsequent reaction of **13** with tetrathiomolybdate in acetonitrile/ethanol (1:1) mixture furnished in the desired 1-deoxythionojirimycin **5** in 38% yield but in overall poor yield. In order to improve the overall yield, the

precursor 12 was subjected to the sulfur transfer reaction under $[BnEt_3N]_2MoS_4$/ DMSO condition to offer intermediate **14**. The intermediate **14** on treatment with BER in MeOH underwent reduction to give 1-deoxythionojirimycin **5** in 62% yield (Scheme 2).

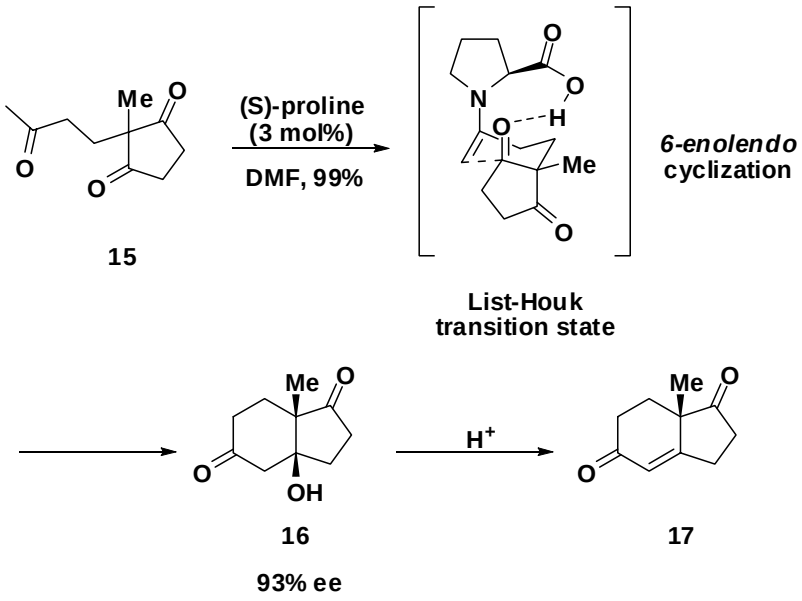
1.2.3 Present work

Over the last several years, substantial work has been done on the synthesis and biological evaluation of viable enzyme inhibitors. These compounds helped in investigating the detailed actual catalytic mechanism and targeted for many promising therapeutic applications such as antiviral, anticancer and AIDS agents.[9]

In connection with a programme on the development of synthetic strategies for thiosugars, we investigated a detailed literature search on organocatalytic aldolization reaction for finding out the possibilities of using it in the synthesis of thiosugars.

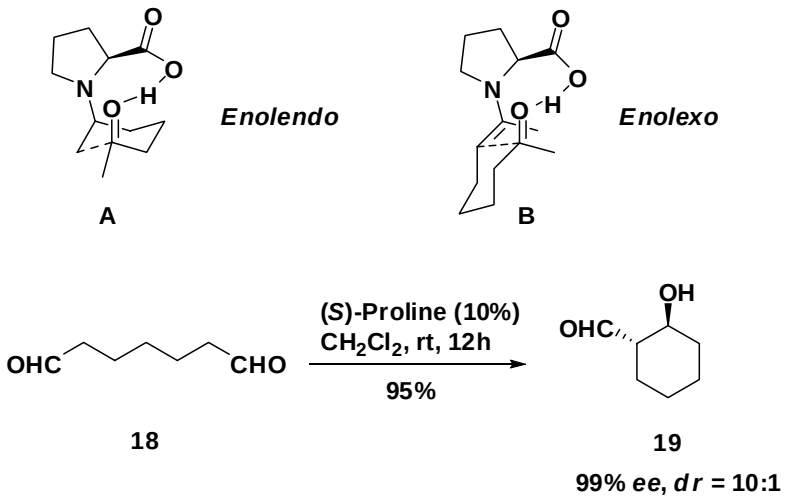
Any reaction which forms a newer **C-C** bond plays a key role in synthetic organic chemistry and aldol reaction is one such extremely useful **C-C** bond-forming reaction which can be used for the stereoselective construction of cyclic and acyclic molecules.[10] After the discovery of first proline catalyzed intermolecular direct asymmetric aldol reaction by List and co-workers[11] in the year 2000, this reaction has been studied most extensively in last few years. Several other proline derived organocatalysts have been also studied for this reaction and used them in the synthetic strategies of many bioactive natural products.[12] While, 30 years before the discovery of first proline catalyzed intermolecular direct asymmetric aldol reaction, in early 1970s, two industrial groups, Hajos and Parrish at Hoffmann-La Roche[13] and Eder, Sauer and Wiechert at Schering[14] independently developed the first proline catalyzed intramolecular aldol reaction of triketones **15** (Scheme 3). This reaction offered a high yield with an excellent enantioselectivity for the synthesis of bicyclic compounds. The carbocyclic intermediate **16** and product **17** are also used as key building blocks for the synthesis of several bioactive products particularly the steroids (Scheme 3).[15] However, this intramolecular aldol reaction has not been explored well as the intermolecular aldol reaction has been explored in the recent years. The mechanism of this intramolecular aldol reaction was unclear and remained the subject of research.[16] However, transition state studies by List and Houk[17] further elucidated the plausible mechanism of intramolecular aldol reaction (Scheme 3). The enamine C-C bond in

intramolecular 6-*enolendo* aldol reaction constitutes the part of the newly formed carbocycle.



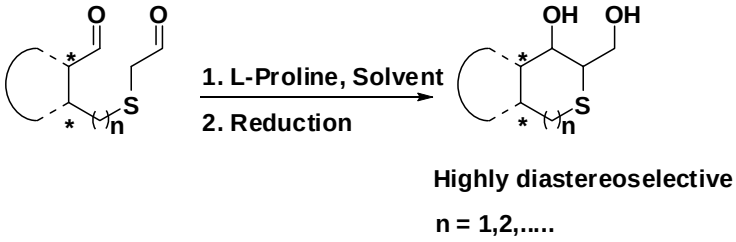
Scheme 3. Intramolecular *enolendo* aldolization reaction.

In 2003, Prof. List and coworkers developed the first proline catalyzed intramolecular asymmetric 6-*enolexo* aldol reaction.[18] A variety of dienal systems (dialdehydes) were screened for proline catalyzed intramolecular *enolexo* aldolization which provided chiral cyclohexanecarbaldehydes (*β*-hydroxy cyclohexane carbonyl derivatives) with excellent enantio- and diastereoselectivities (Scheme 4). The enamine C-C bond in intramolecular *enolexo* aldol reaction does not constitute the part of the newly formed carbocycle (Scheme 4). Further, both enantiomeric products can be accessed simply by using either (*S*) - or (*R*)-proline which give a definite advantage to aldolization methodology over the biocatalysis route which is limited to products of a single absolute configuration.



Scheme 4. Proline catalyzed first enantioselective 6-*enolexo* aldolization.

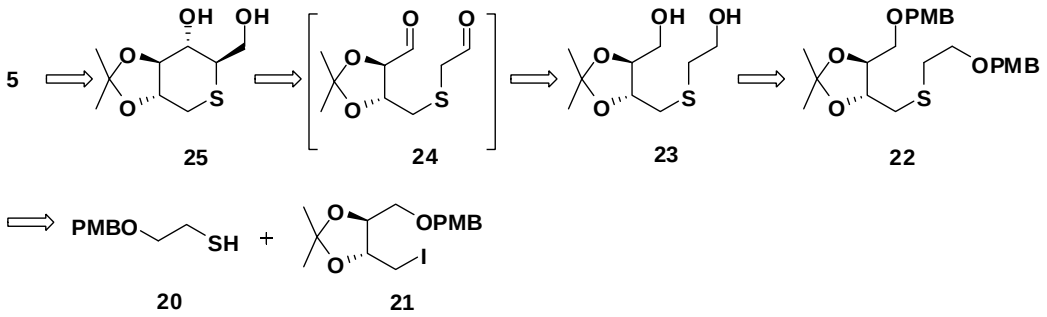
A well defined stereocenter at active methylene position of one of the aldehyde group would help in discriminating two aldehydic groups from the dialdehyde. Due to this the another aldehydic group with unsubstituted active methylene group should definitely get an advantage of enamine formation in presence of the earlier aldehydic group which would also help in defining the acceptor carbonyl and donor methylene group in dialdehyde system. In conjugation with these speculative facts, the interesting result of proline catalyzed *enolexo* aldolization reaction could lead us in designing a novel general approach towards synthesis of thiosugars.



Scheme 5: Our general approach towards thiosugars using 6-*enolexo* aldolization as a key step.

We herewith, proposed an entirely new organocatalytic *enolexo* aldolization route for the synthesis of 1-thiosugars (Scheme 5). An organocatalytic *enolexo* aldolization of a dialdehyde (with well discriminated two aldehydic groups) could form a new C-C bond between acceptor carbonyl carbon and donor methylene carbon β to another

carbonyl group and consecutively generate two new chiral centers, one as an hydroxy group at acceptor carbonyl carbon and another as an aldehyde (could be further *in situ* reduced to hydroxy methylene group) at donor methylene carbon β to another carbonyl group. Further, the stereochemistry of two newly formed chiral centers should be decisively controlled by the already existing chiral center on the α-carbon of acceptor carbonyl group which could produce a highly diastereoselective outcome in 1-thiosugar synthesis (Scheme 5).



Scheme 6. Retrosynthetic disconnections for 1-deoxythionojirimycin.

Accordingly, we decided to use this approach for the synthesis of 1-deoxythionojirimycin **5**. Based on this proposed new organocatalytic general approach towards thiosugars, the retrosynthetic analysis for the diastereoselective synthesis of 1-deoxythionojirimycin **5** is showed in Scheme 6. It was seen that 1-DTNJ **5** could be easily achieved from an acid catalyzed damasking of acetonide of cyclic diol **25**. The cyclic diol **25** could come out as an 6-*enolexo* aldolization product of dialdehyde **24** which in turn could be obtained by the oxidation of diol **23**. The diol **23** could be easily obtained by the deprotection of thioether **22** which could be accessed as coupling product of synthons, thiol **20** and iodo intermediate **21**.

1.2.4 Result and discussion

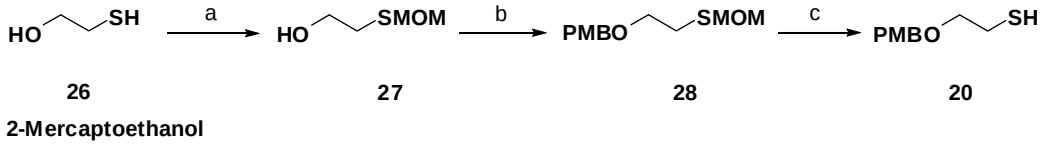
The synthesis starts with the preparation of two synthons, thiol **20** and iodo intermediate **21**.

1.2.4.1 Synthesis of thiol intermediate 20

Approach I

The synthesis of thiol intermediate **24** was started with relatively cheap starting material 2-mercaptoethanol **26.** The commercially available 2-Mercaptoethanol **26**

under MOMCl/ DIPEA in DCM at 0 ^{o}C conditions resulted in selective S-MOM-protection to offer MOM-ether **27** in 95% yield. The MOM-ether **27** was converted to its PMB-ether derivative **28** in 97% yield with PMBCl in presence of sodium hydride in dry THF at 0 ^{o}C, which on further treatment with TFA in DCM at room temperature underwent SMOM deprotection to give thiol **20** in 15% yield (Scheme 7).



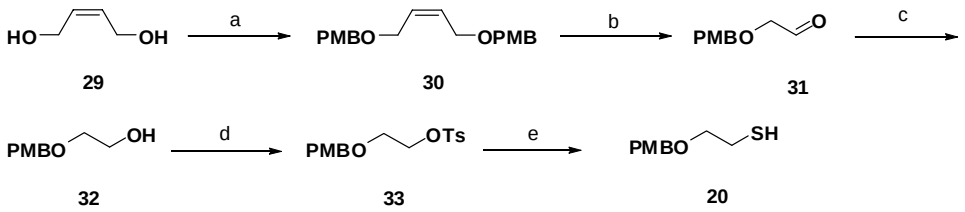
Scheme 7. *Reagents and conditions*: *a) DIPEA, MOMCl, DCM, 0 ^{o}C, 95%; b) NaH, PMBCl, THF, 0 ^{o}C, 97%; c) TFA, DCM, rt, 15%.*

In the ^{1}H NMR spectrum of thiol **20** the methylene protons adjacent to –SH coupled with –SH and neighboring methylene group and appeared up field at δ 2.67 to 2.78 ppm as multiplate whereas being a part of ether linkage (-CH_2-OPMB) its neighboring methylene group appeared down field at δ 3.60 as triplet (J = 6.4 Hz). The characteristic -SH proton resonated in up field as triplet (J = 8.2 Hz) at δ 1.61. In ^{13}C NMR and DEPT, the methylene carbon adjacent to –SH appeared up field at δ 24.0 (DEPT) whereas methylene carbon adjoined to ethereal linkage (-CH_2-OPMB) observed downfield at δ 71.13 (DEPT). The rest of the ^{1}H and ^{13}C spectrum values and mass (ESI-TOF) m/z at 221.61 accounting for $[M+Na]^{+}$ were in complete conformity with the assigned structure of thiol **20**.

Approach II

Due to the poor yield of thiol **20** in approach I, we changed our synthetic strategy. In this approach, we started with commercially available *cis*-1,4-butenediol **29**, which was protected with PMBCl and sodium hydride in dry THF at 0 ^{o}C to give diPMB-ether **30** in 96% yield. The diPMB-ether **30** on oxidative cleavage with OsO_4 in presence of $NaIO_4$ in DEE: H_2O (1:1) at room temperature gave aldehyde **31** in 94% yield**,** which was further reduced with $NaBH_4$ in methanol room temperature to alcohol **32** in almost quantitative yield.[19] The alcohol **32** was further converted to its tosyl-derivative **33** using TsCl in presence of TEA in dry DCM at 0 ^{o}C conditions in 96% yield. The next job was to convert this tosylate into its thiol counterpart; for this

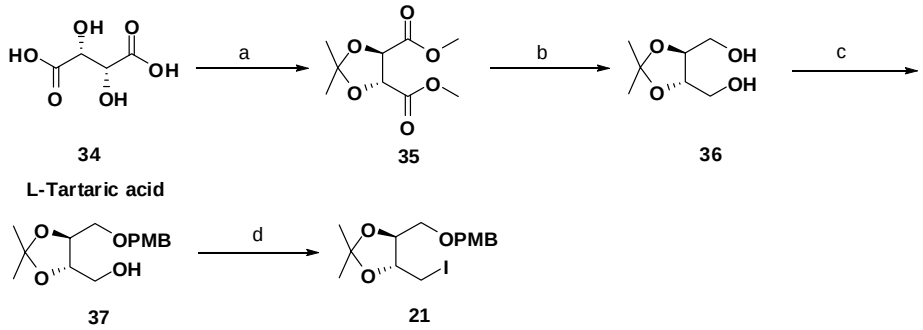
purpose the tosyl-derivative **33** was refluxed with thiourea in absolute ethanol to give a salt which was further in situ hydrolyzed with aq. NaOH under similar reflux conditions to offer thiol **20** in 95% yield (Scheme 8).[20]



Scheme 8. *Reagents and conditions*: *a) NaH, PMBCl, THF, 0 ^{o}C, 96%; b) OsO_4, $NaIO_4$, DEE: H_2O (1:1), rt, 94%; c) $NaBH_4$, MeOH, rt, 97%; d) TEA, TsCl, DCM, 0 ^{o}C , 96%; e) (i) Thiourea, absolute ethanol, reflux, 3.5 h; (ii) aq.NaOH, reflux, 3.5 h, 95%.*

1.2.4.2 Synthesis of iodo intermediate 21

Being a cheap, commercially available material with high enantiomeric purity L-(+)-tartaric acid was a worth starting material for the synthesis of iodo intermediate **21.** L-(+)-tartaric acid **34** on one pot acetonide protection and esterification gave C_2-symmetric L-(+)-dimethyl tartarate **35** in almost quantitative yield.[21,22] The C_2-symmetric L-(+)-dimethyl tartarate **35** further on refluxing with LAH in dry THF reduced to C_2-symmetric diol **36** in 60% yield.[21,22] The C_2-symmetric diol **36** was mono-protected with PMBCl in presence of sodium hydride in THF: DMF (1:1) at 0 ^{o}C to provide **37** in 78% yield, which was further subjected for iodination with iodine, TPP and imidazole in refluxing toluene (Appel reaction) conditions to offer desired iodo intermediate **21** in 90% yield (Scheme 9).[22]



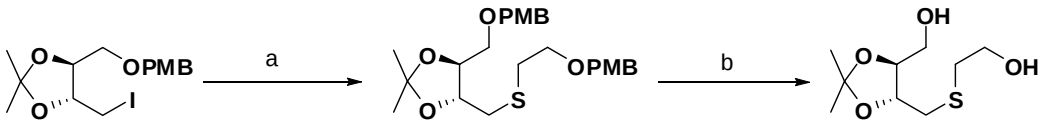
Scheme 9. *Reagents and conditions*: *a) p-TSA, 2,2-DMP, MeOH, Cyclohexane, 90 ^{o}C, 95%; b) LAH, THF, reflux, 6h, 60%; c) NaH, PMBCl, THF:DMF, 0 ^{o}C, 78%; d) Imidazole, PPh_3, I_2, toluene, reflux, 90%.*

In the ^{1}H NMR spectrum of iodo intermediate **21,** the characteristic acetonide protons resonated at δ 1.42, 1.47. The protons of neighboring methylene group to iodo appeared distinctively at δ 3.26 (*J* = 10.6, 5.3 Hz) and δ 3.36 (*J* = 10.5, 5.0 Hz) as doublet of doublet whereas another methylene group being a part of ethereal linkage (-CH_2-OPMB) resonated slightly downfield at δ 3.62 (*J* = 10.1, 5.0 Hz) as doublet of doublet. In ^{13}C spectrum of iodo intermediate **21**, the methylene carbon attached to iodo was observed up field at δ 6.36 (DEPT) whereas methylene carbon connected to ethereal linkage (-CH_2-OPMB) appeared downfield at δ 69.92 (DEPT). The rest of the ^{1}H and ^{13}C spectrum values were in good agreement with the spectral values of assigned structure reported in the literature.

1.2.4.3 Synthesis of diol 23

The thiol **20** and iodo intermediate **21** were further coupled using sodium hydride as base in dry THF at 0 ^{o}C to give thioether **22** in almost quantitative yield (Scheme 10). In the ^{1}H NMR spectrum of thioether **22**, the acetonide protons resonated closely at δ 1.41, 1.42. The protons on two methylene groups adjoined to sulfur atom appeared in up field at δ 2.76 to 2.83 as multiplate whereas being a part of ethereal linkage (-CH_2-OPMB), the protons on another two methylene groups resonated downfield at 3.58 to 3.65 as multiplate. Two methoxy groups from the *p*-methoxybenzyl ethereal linkage represented as two closed singlets at δ 3.80 whereas their benzylic protons appeared as two distinctive singlets at δ 4.46 and 4.50 respectively. The protons from two neighboring stereocenter to acetonide group resonated downfield as multiplate at δ 3.97 to 4.01 where as the two distinct doublets at δ 6.88 (*J* = 8.5 Hz) and δ 7.26 (*J* = 8.2 Hz) represented the rest of the equivalent aromatic protons. In ^{13}C NMR and DEPT, carbons of two methylene adjoined to sulfur atom resonated distinctively up field at δ 32.13 and 34.81 (DEPT) respectively whereas carbons of two methylene adjacent to ethereal linkage (-CH_2-OPMB) and two benzylic carbons were observed downfield at δ 69.25, 70.03 and δ 72.41, 72.94 (DEPT) respectively. Rest of the ^{13}C spectral values were in complete conformity with the assigned structure of thioether **22**. The thioether **22** synthesized and characterized thus was then subjected for PMB-deprotection. Thioether **22** further on treatment with DDQ[23] in DCM: H_2O (17:1) at room temperature underwent oxidative cleavage of PMB groups to offer diol **23** in 88% yield (Scheme 10). In ^{1}H NMR, the acetonide protons as usually sighted closely

at δ 1.43, 1.44 ppm. The protons on two methylene groups adjacent to sulfur atom appeared up field at δ 2.77 to 2.83 ppm as multiplate whereas the methylene protons of terminal hydroxy methylene groups resonated downfield at δ 3.73 to 3.83 as multiplate. A multiplate sighted at δ 3.97 to 4.01 downfield correspond to the protons from two neighboring stereocenter to acetonide group where as two terminal hydroxyl group resonated as two broad singlets at δ 1.88 and δ 2.32. In ^{13}C NMR, the carbons of two methylene adjoined to sulfur atom as usually resonated in up field at δ 34.08 and 35.52 (DEPT) respectively while hydroxy methylene carbons sighted in downfield at δ 60.86 and 61.86 (DEPT) and rest of the ^{13}C spectral values and mass (ESI-TOF) m/z at 245.04 accounting for $[M+Na]^+$ along with its HRMS (TOF) m/z (calculated for $C_9H_{18}NaO_4S$ ($[M+Na]^+$) 245.0783, found 245.0790) were in complete accordance with the assigned structure of diol **23**.



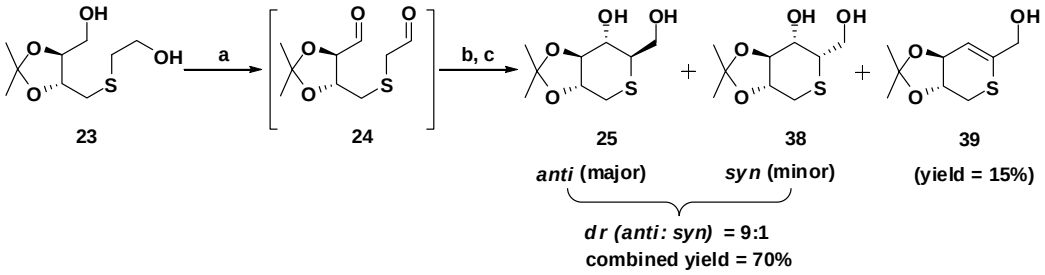
21 **22** **23**

Scheme 10. *Reagents and conditions*: *a) NaH, THF,* PMBO SH ***(20)***, *0 °C, 95%; b) DDQ, DCM: H_2O (17:1), rt, 88%.*

1.2.4.4 L-proline catalyzed 6-*enolexo* aldolization

The diol **23** was further oxidized with IBX in refluxing EtOAc to afford dialdehyde **21** in 95% yield (Scheme 11). The dialdehyde **24** was the key starting material which further without any purification was directly used for L-proline catalyzed *enolexo* aldolization reaction.[24] The key step of direct 6-*enolexo* aldolization reaction of dialdehyde **24** was carried out in presence of L-proline (30 mol %) as an organocatalyst in solvent DCM at room temperature (Scheme 11). The reaction progress was monitored by TLC and it was observed that the starting material dialdehyde was totally consumed and the 6-*enolexo* aldolization reaction was completed within 45 min. As per the earlier observations the cyclic aldol products of such *enolexo* aldolization reactions are unstable over extended time periods at room temperature, but stable diol can be obtained by the in situ reduction of aldol product.[18]

So the *enolexo* aldolization reaction mixture was further in situ reduced with $NaBH_4$ in MeOH at room temperature to afford a mixture of two diastereomers **25** and **38** respectively with a combined 70% yield and a dehydrated by-product **39** with 15% yield after three consecutive steps (Scheme 11). The ^1H and ^{13}C NMR spectral data of diastereomeric mixture was in good agreement with formation of two cyclized products **25** and **38** with a high diastereomeric ratio (*dr*) of 9:1 respectively. Further, we could successfully and quantitatively separate both the diastereomers using flash column chromatography and in order to find out and justify their correct structure and stereochemistry characterized them with all possible spectral techniques.



Scheme 11. *Reagents and conditions*: *a) IBX, ethyl acetate, reflux, 95%; b) L-proline (30 mol %), DCM, rt, 45 min.; c) $NaBH_4$, MeOH, rt, (collectively 85%).*

In ^1H NMR spectrum of diastereomer **25,** two extremely close singlets at δ 1.44 and 1.45 ppm corresponded to acetonide group protons. Apparently looked as an hump but actually a pair of very close broad singlets of two protons were sited at δ 1.84 and 1.88 ppm represented two newly formed hydroxyl groups of the cyclic diol whereas the methylene protons adjacent to sulfur atom appeared in up field as a doublet (J = 6.7 Hz) at δ 2.85. The proton on newly formed center at donor methylene, due to neighboring sulfur influence appeared in up field as a quintet (J = 5.9, 9.5 Hz) at δ 3.03 ppm, whereas the proton on new center formed at acceptor aldehyde resonated in downfield as a triplet (J = 9.5 Hz) at δ 4.01. Among the two neighboring stereocenter to acetonide group, the proton on the stereocenter which is also adjacent to the newly formed stereocenter at acceptor aldehyde, appeared as a triplet (J = 9.5 Hz) at δ 3.29 ppm, while the proton of another stereocenter next to it resonated as doublet of doublet (J = 8.5, 15.0 Hz) at δ 3.80. The two close multiplates sited at δ 3.88 and 3.95 corresponded to the methylene protons from hydroxy methyl group adjoined to

newly formed center at donor methylene. In ^{13}C NMR and DEPT, the acetonide group appeared as a pair of close signal at δ 26.72, 26.91. The signal sited at δ 30.38 (DEPT) in up field represented the methylene carbon adjoined to sulfur whereas the hydroxy methylene carbon resonated at δ 62.45 (DEPT) in downfield. Among two newly formed stereocenters, the carbon of stereocenter formed at donor methylene appeared at δ 48.10 while the carbon of stereocenter formed at acceptor δ 74.03. The signals at δ 76.53, 83.65 corresponded to two neighboring stereocenters to acetonide group whereas the quaternary carbon of acetonide group resonated at δ 110.06. Further a broad absorption at 3450 cm^{-1} in Infrared spectrum indicating the presence of hydroxyl functionality and mass (ESI-TOF) m/z at 243.05 accounting for $[M+Na]^+$ along with its HRMS (TOF) m/z (calculated for $C_9H_{16}NaO_4S$ ($[M+Na]^+$) 243.0662, found 243.0671) also supported the assigned cyclized product **25**.

The ^1H NMR spectrum of **38** showed more resolved and dissimilar pattern of signals than **20**. The acetonide group protons as usually sited as close singlets at δ 1.44 and 1.45, where as a doublet of doublet (*J* = 3.9, 12.0 Hz) at δ 2.71 and a triplet (*J* =12.0 Hz) at δ 2.82 corresponded to methylene protons adjoined to sulfur. Two broad singlets appeared at δ 2.99 and 3.47 indicated the presence of hydroxyl functionality from newly formed cyclized diol. A doublet of doublet (*J* = 5.5, 8.0 Hz) situated at δ 3.16 corresponded to the proton on newly formed center at donor methylene while the proton on newly formed center at acceptor aldehyde resonated as a doublet of doublet (*J* = 5.6, 10.1 Hz) at δ 4.29 in downfield. The doublet of doublet (*J* = 6.9, 12.6 Hz) signal located at δ 3.52 corresponded to the proton of stereocenter adjoined to both acetonide and newly formed stereocenter at acceptor aldehyde while the another acetonide neighboring stereocenter resonated as doublet of doublet of doublet (*J* = 4.0, 8.8, 11.2 Hz) at δ 3.76. Two multiplate signals sited at δ 3.79-3.83 and 4.13-4.17 corresponded to the methylene protons from hydroxy methyl group adjoined to newly formed center at donor methylene group. In ^{13}C NMR and DEPT, a pair of close signals appeared at δ 26.69, 26.91 attributed to the acetonide group. Both the sulfur and hydroxy adjoined methylene carbons were located in up field at δ 28.17 (DEPT) and downfield at δ 61.98 (DEPT) respectively. The signal appeared at δ 46.09 corresponded to the carbon of newly formed stereocenter at donor methylene while the carbon of newly formed stereocenter at acceptor aldehyde resonated in down field at δ 74.01. Two neighboring stereocenters to acetonide group sited downfield at δ

77.40 and 79.41 whereas a signal appeared downfield at δ 109.42 attributed to the quaternary carbon of acetonide group. Presence of a broad absorption band at 3450 cm^{-1} in Infrared spectrum signified the hydroxyl group existence. Moreover the mass (ESI-TOF) m/z at 243.05 accounting for $[M+Na]^+$ and its HRMS (TOF) m/z (calculated for $C_9H_{16}NaO_4S$ ($[M+Na]^+$) 243.0662, found 243.0671) also validated the assigned cyclized product **38**.

In ^1H NMR spectrum of dehydrated by-product **39**, two extremely close singlets located at δ 1.46 corresponded to an acetonide group while a broad singlet at δ 2.24 indicated the presence of hydroxyl group proton. The methylene protons adjacent to sulfur appeared at δ 3.08-3.24, whereas the hydroxy methylene protons resonated as a singlet at δ 4.11 downfield. Methine protons of two stereocenters adjacent to an acetonide group attributed as two distinct signals, one as a doublet of doublet of doublet (J = 5.4, 8.2, 10.9 Hz) at δ 3.94 while another as a multiplate at δ 4.14-4.20. A characteristic singlet sited at δ 6.00 downfield regions corresponded to an alkene proton. In ^{13}C NMR and DEPT, a pair of close singlet at δ 26.74, 26.91 represented the acetonide methyl carbons. The sulfur adjoined methylene carbon resonated in up field at δ 27.95 (DEPT) while hydroxy methylene carbon appeared downfield at δ 64.61 (DEPT). The signals sited downfield at δ 75.65 and 77.22 corresponded to the acetonide adjoined stereo centers whereas an alkene carbon resonated in downfield at δ 116.17. Rest of the acetonide and alkene quaternary carbons appeared downfield at δ 111.45 and 135.72 respectively. Further, the mass (ESI-TOF) m/z at 225.07 accounting for $[M+Na]^+$ and its HRMS (TOF) m/z (calculated for $C_9H_{14}NaO_3S$ ($[M+Na]^+$) 225.0575, found 225.0582) also supported the assigned structure of cyclized dehydrated by-product **39**.

The exact structure and stereochemical outcome of both the diastereomer **25** and **38** could be determined and explained by their 2D-NMR studies. In ^1H NMR analysis, the peak assignments were done using the ^1H-^1H COSY experiments whereas ^{13}C NMR peak assignments were made using the HSQC experiments. In COSY experiment of **25**, the proton on C_5 showed a strong correlation with protons on both the neighboring stereocenters C_4 and C_6. The coupling constant observed for these protons suggested an *anti* relationship for C_5 -proton (J = 9.5 Hz) with both C_4 – proton (J = 9.5 Hz) and C_6 – proton (J = 5.9, 9.5 Hz) indicating an *anti*-diol structure for **25** Further, in NOESY experiment **25** a strong NOE correlation was observed

between protons on C_4 and C_6 but no such correlation was experienced for proton on C_5 with protons on C_4 and C_6 respectively. It denoted that the protons on C_4 and C_6 were on the same side but both of them are *anti* to the proton on C_5, which again supported the assigned *anti*-diol structure for **25** (Figure 2).

In COSY experiment of **38**, a strong correlation was seen for the proton on C_5 with the neighboring C_4 and C_6 protons. The observed coupling constant for C_5 -proton (J = 5.6, 10.1 Hz, C_4 – proton (J = 6.9, 12.6 Hz) and C_6 – proton (J = 5.5, 8.0 Hz) suggested an *anti* relationship between C_4 and C_5 – protons but *syn*-relationship between C_5 and C_6 – protons which indicated a *syn*-diol structure for **38**. The NOESY experiment of **38** experienced a strong NOE correlation between C_5 and C_6 - protons whereas no such correlation was found between C_4 and C_5 – proton which once more signified the anti relationship of C_4 and C_5 - protons and *syn*-relationship of C_5 and C_6 – protons and again supported the assigned *syn*-diol structure for **38** (Figure 2).

The two different transition states with the fixed stereochemistry at C_3 and C_4 can be used to elucidate the observed stereochemical outcome of the 6-*enolexo* aldolization reaction. The enamine attack on acceptor aldehyde in the *Re*-facial manner and proceeds through a more favored *syn*-enamine intermediate which ultimately offers a *anti*-diol as a major product, whereas the formation of *syn*-diol as a minor product can be well explained through a *si*-facial attack on acceptor aldehyde by enamine and formation of less favored *anti*-enamine intermediate (Figure 2).

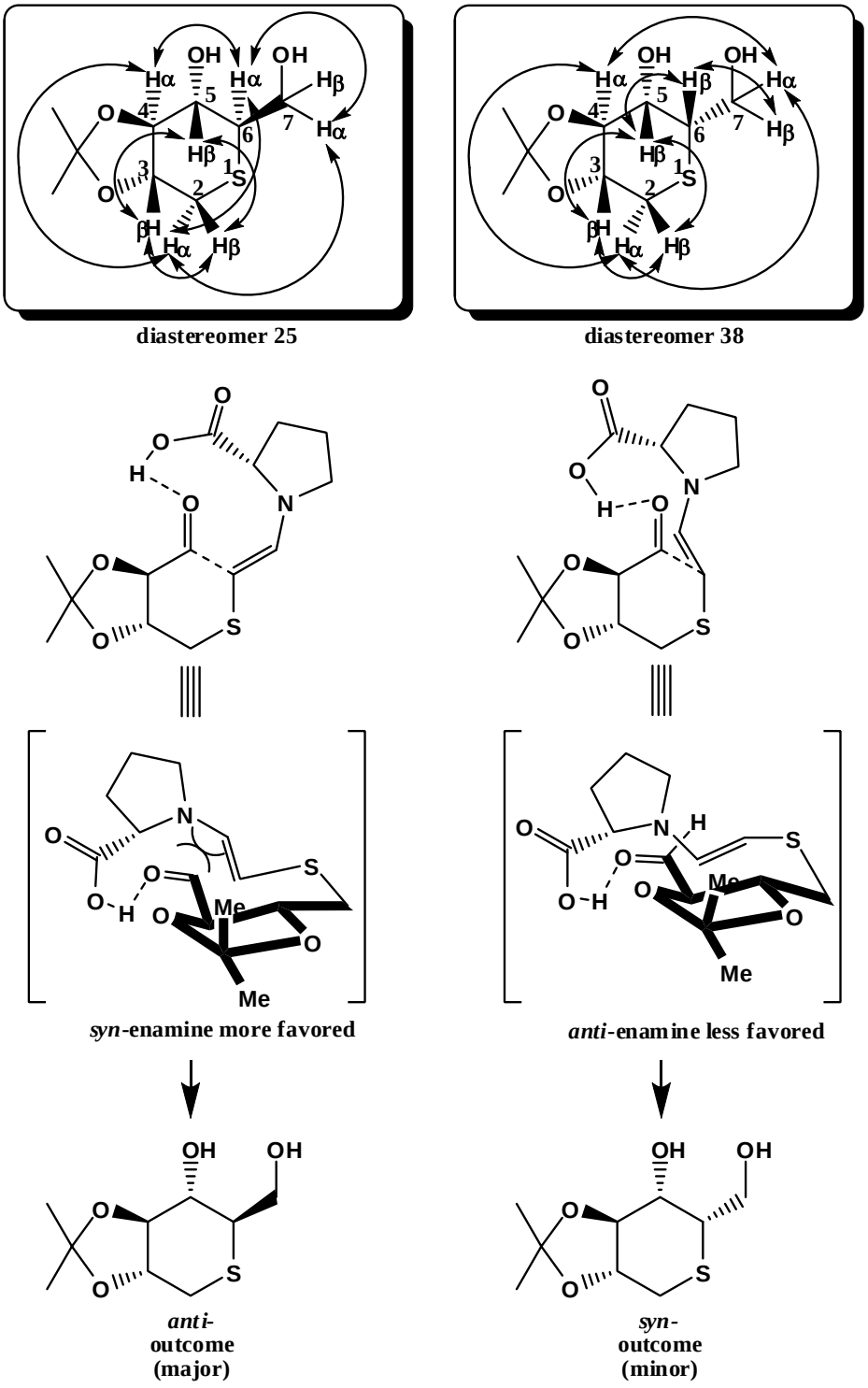


Figure 2. Stereochemical elucidation of **25** and **38** by NOE correlation and transition states.

The only solid product **38** was subjected for crystallization. The single crystals were grown by slowly evaporating the solution of compound **38** in ethyl acetate and pet ether. The crystallization produced colorless crystals among which crystal size of 0.420 x 0.180 x 0.090 mm, was selected and used for collecting data on *Bruker SMART APEX* CCD diffractometer. The crystal was irradiated with the graphite-monochromatized Mo K_α radiation (0.71073 Å) with a fine focus tube at 50 kV and 30 mA. All the data was corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS software programs by Bruker. SHELX-97 program was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. The collected crystal data and refinement parameters are listed in table 1.

The single crystal X-ray crystallography analysis of **38** showed that the hydrogen atom on both newly formed stereocenters were *syn* to each other and *β*-oriented (Figure 3 & 4). These results also supported the relative stereochemistry of these stereocenters determined earlier by COSY and NOESY and were in complete conformity with the stereochemistry and assigned structure of *syn*-diol **38**. Eventually, with this the stereochemistry and assigned structure of *anti*-diol **25** was also established**.** Hence, with a *dr* of 9:1 (*anti: syn*), the synthetic approach 6-*enolexo* aldolization was highly *anti*-selective.

Table 1. Crystal data and structure refinement for **38**.

Empirical formula	$C_9H_{16}O_4S$
Formula weight	220.29
Temperature (*T*)	273(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	a = 6.2315(10) Å $\alpha = 90^{o}$ b = 10.6223(17) Å $\beta = 90^{o}$ c = 16.568(3) Å $\gamma = 90^{o}$
Volume (*V*)	1096.7(3) $Å^3$
Z, Calculated density (ρ)	4, 2.456 mg/m^3
Absorption coefficient (μ)	1.001 mm^{-1}
F(000)	846
Crystal size	0.420 X 0.180 X 0.090
θ range for data collection	2.28 to 24.99 ^{o}
Limiting indices	-3<=h<=7, -12<=k<=12, -18<=l<=19
Reflections collected / unique	5526 / 1937 [R(int) = 0.0293]
Completeness to θ	24.99 ^{o}, 100.0 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1937 / 0 / 131
Goodness-of-fit on F^2 (*S*)	1.188
Final R indices [I>2σ(I)]	$R_1 = 0.0383$, $wR_2 = 0.0938$
R indices (all data)	$R_1 = 0.0390$, $wR_2 = 0.0943$
Absolute structure parameter	0.02(10)
Largest diff. peak and hole	0.246 and -0.223 e $Å^{-3}$

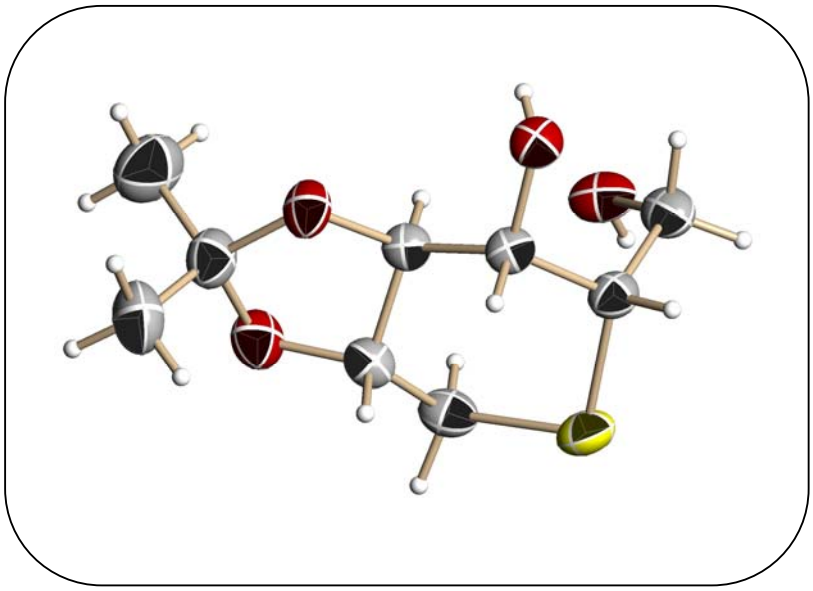


Figure 3. ORTEP diagram of *syn*-diastereomer **38**.

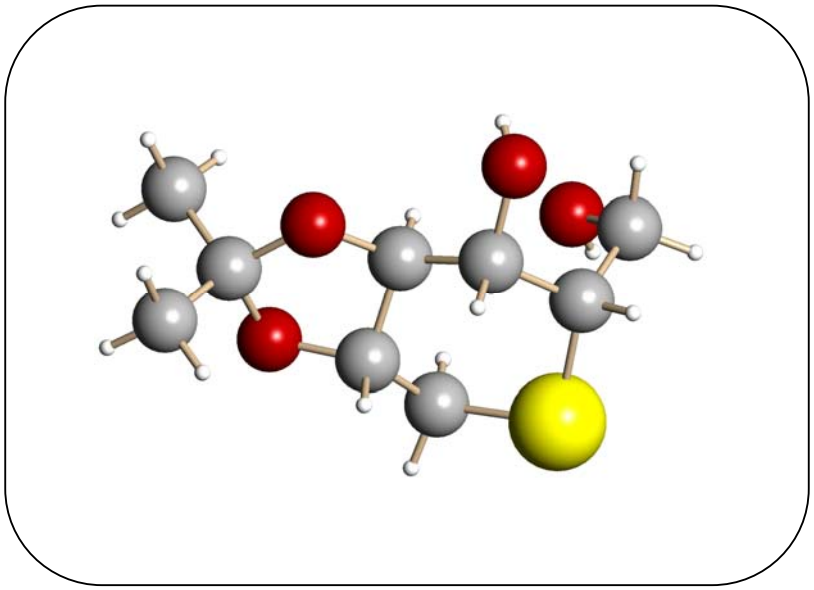
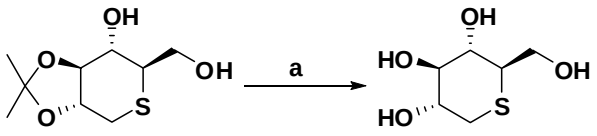


Figure 4. Crystal structure of *syn*-diastereomer **38** (sticks & ball model).

1.2.4.5 Synthesis of 1-DTNJ and 1-Deoxy-L-thio-idonojirimycin

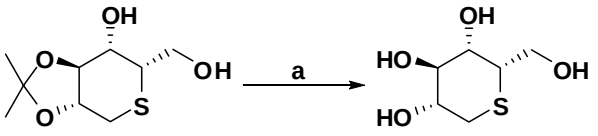
After confirming the stereochemistry and assigned structures for both diastereomers **25** and **38**, both of them were further subjected for acetonide deprotection reaction. The *anti*-diastereomer **25** on treatment with Conc. HCl in MeOH at room temperature underwent acetonide deprotection to offer 1-DTNJ **5** in 85% yield (Scheme 12). Similarly, *syn*-diastereomer **38** was also deprotected with Conc. HCl in MeOH at room temperature to give 1-Deoxy-L-thio-idonojirimycin **40** in 80% yield (Scheme 13).



25 **5**

1-DTNJ

Scheme 12. *Reagents and conditions*: *a) Conc. HCl, MeOH, rt, 85%.*



38 **40**

1-Deoxy-L-thio-idonojirimycin

Scheme 13. *Reagents and conditions*: *a) Conc. HCl, MeOH, rt, 80%.*

The ^{1}H NMR spectrum of **5** was taken in D_2O. A doublet of doublet at δ 2.46 (*J* = 11.0, 13.0 Hz) and a doublet of doublet of doublet at δ 2.55 (*J* = 4.2, 8.3, 13.0 Hz) integrating one proton for each sighted in up field corresponded to methylene protons adjoined to sulfur. Next to it, a multiplate signal integrating for one proton at δ 2.70-2.75 signified the proton on sulfur adjoined stereocenter. Two distinct triplets at δ 3.03 (*J* = 9.2 Hz), 3.32 (*J* = 9.5 Hz) and three separate doublet of doublet of doublet at δ 3.48 (*J* = 4.5, 9.5, 14.0 Hz), δ 3.61 (*J* = 6.2, 12.0, 15.0 Hz), δ 3.61 (*J* = 3.2, 12.4, 15.5 Hz) accounted for rest of the protons from three stereocenters and two hydroxy

methylene group. In ^{13}C NMR the signal appeared at δ 31.18 (DEPT) in up field corresponded to sulfur adjoined methylene carbon while the hydroxy adjoined methylene carbon sighted at δ 60.52 (DEPT) in downfield. The sulfur adjoined stereocenter resonated at δ 48.16 whereas rest of the carbon signals were in good accordance and conformity of the assigned structure of 1-deoxythionojirimycin **5**. Further, the presence of a broad absorption band at 3450 cm^{-1} in IR spectrum also signified the hydroxyl group existence. The optical rotation for **5** ($[\alpha]_D^{25}$ +49.68°, *c* 1.4, H_2O) was also found to be in good agreement with that reported in literature.[6a,8]

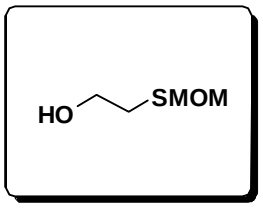
In ^1H NMR spectrum of **40** in D_2O, the sulfur adjacent methylene protons distinctively appeared as doublet at δ 2.44 (*J* = 13.1 Hz) and doublet of doublet at δ 2.56 (*J* = 10.7, 13.4 Hz) in up field while a triplet at δ 3.22 (*J* = 9.2 Hz) signified the proton on sulfur adjoined stereocenter. In ^{13}C NMR the sulfur adjoined methylene carbon appeared at δ 27.29 (DEPT) in up field while the signal at δ 57.13 (DEPT) in downfield corresponded to the hydroxy adjoined methylene carbon. A signal at δ 45.94 denoted the sulfur adjoined stereocenter carbon. Rest of the ^1H and ^{13}C signal values were in good accordance of the assigned structure of 1-deoxy-L-thio-idonojirimycin **40**.

1.2.5 Conclusion

In conclusion, the synthesis of 1-Deoxythionojirimycin and 1-Deoxy-*L*-thio-idonojirimycin was successfully achieved by a novel synthetic route starting with commercially available L-(+)-tartaric acid and using highly diastereoselective L-proline catalyzed 6-*enolexo* aldolization reaction as a key step. In this synthetic approach the 6-*enolexo* aldolization reaction was found highly *anti*-selective [*dr* = 9:1 *(anti: syn)*]. The structures and the relative stereochemistry of both the diastereomers formed in the *enolexo* aldolization reaction were determined by their 2D-NMR (COSY, NOESY and HSQC) studies. The *anti*-selectivity observed for 6-*enolexo* aldolization reaction could be also explained using two different transition states for the formation of both diastereomers. Further, the relative stereochemistry for *syn*-diastereomer was also confirmed by its single crystal X-ray studies. The L-proline catalyzed 6-*enolexo* aldolization protocol is the first organocatalytic protocol of its kind used for the synthesis of thiosugars and can also provide a lead for the synthesis of other isomers of 1-Deoxythionojirimycin as well as its analogues substituted α-to sulfur in 5-thiosugars skeleton.

1.2.6 Experimental

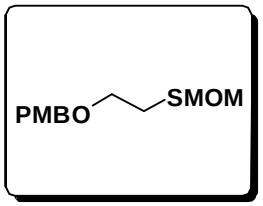
2-[(Methoxymethyl) thio] ethanol (27)



To a stirred solution of 2-Mercaptoethanol **26** (1.56 g, 20 mmol) and *i*-Pr_2EtN (2.84 g, 3.83 mL, 22 mmol) in dry CH_2Cl_2 (25 mL), was added MOMCl (1.77 g, 1.67 mL, 22 mmol) at 0 ^oC. The resulting mixture was stirred further for 5 h at room temperature. The reaction mixture was quenched by 20% aqueous solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted again with dichloromethane (2 x 10 mL). The combined extracts were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure on rotary evaporator. The residue thus obtained was purified by chromatography on silica-gel eluting with petroleum ether: ethyl acetate (7:3) to give **27** (2.33 g, 95% yield) as a colorless dense liquid.

Molecular Formula	: $C_4H_{10}O_2S$.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 2.78 (t, *J* = 5.5 Hz, 2H) , 3.37 (s, 3H), 3.69-3.78 (dd, *J* = 11 Hz, 2H), 4.61 (s, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 34.38, 55.29, 61.58, 75.37.
IR (Neat) cm^{-1}	: 3417 (broad), 2937, 2838, 1244, 1114, 1060, 1047, and 920 (C-O-C and C-S-C).
MS (ESI-TOF) m/z	: 145.03 ($[M+Na]^+$).

(2-(4-Methoxybenzyloxy)ethyl)(methoxymethyl) sulfane (28)

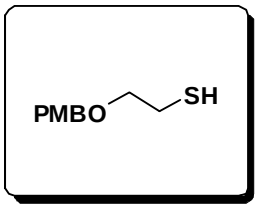


To a solution of **27** (1.22 g, 10 mmol) in dry THF (20 mL) was added sodium hydride (0.288 g, 12 mmol) at 0 °C and then stirred at same temperature for 20 min. To this was added slowly *p*-methoxybenzyl chloride (1.88 g, 1.63 mL, 12 mmol) with further stirring for 6 h at the same temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with water (2 x 10 mL), brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual oil was purified by silica gel

column chromatography using petroleum ether: ethyl acetate (8:2) as eluent to furnish the **28** (2.34 g, 97%) as colorless oil.

Molecular Formula	: $C_{12}H_{18}O_3S$.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 2.81 (t, *J* = 6.7 Hz, 2H), 3.35 (s, 3H), 3.65 (t, *J* = 6.8 Hz, 2H), 3.81 (s, 3H), 4.49 (s, 2H), 4.66 (s, 2H), 7.88 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 30.19, 54.92, 55.33, 69.36, 72.32, 75.52, 113.49, 129.01, 129.97, 158.94.
IR (Neat) cm^{-1}	: 3074, 3050, and 3035 (C-H, aromatic), 2960, 2934, 2895, and 2860 (C-H), 1601, 1585, 1510, 1455 (benzyl), 1369, 1244, 1113 and 1054 (C-O-C and C-S-C), 735 and 702 (aromatic).
MS (ESI-TOF) m/z	: 265.09 ($[M+Na]^+$).

2-(4-Methoxybenzyloxy) ethanethiol (20)



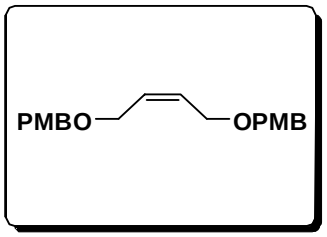
To a solution of **28** (1.21 g, 5 mmol) in dichloromethane (15 mL) was added TFA (20%, 0.114 g, 1 mmol) and stirred at room temperature. The reaction progress was monitored by TLC. After being stirred at room temperature for 24 h, the reaction mixture was neutralized by 20% aqueous solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x15 mL). The combined extracts were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure on rotary evaporator. The residue such obtained was further purified by column chromatography on silica-gel eluting with petroleum ether: ethyl acetate (9:1) to give **20** (0.156 g, 15% yield) as a colorless dense liquid.

Molecular Formula	: $C_{10}H_{14}O_2S$.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 1.61 (t, *J* = 8.2 Hz, 1H), 2.67-2.78 (m, 2H), 3.60 (t, *J* = 6.4 Hz, 2H), 3.82 (s, 3H), 4.49 (s, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H),
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 24.0, 54.75, 71.13, 72.11, 113.37, 128.89, 129.73, 158.82.
IR (Neat) cm^{-1}	: 3018, 2930, 2849, 2560 (S–H), 1609, 1513, 1439,

1224, 1110, 831, 790.

MS (ESI-TOF) m/z : 221.61 ($[M+Na]^+$).

***(Z)*-1,4-Bis(4-methoxybenzyloxy)but-2-ene (30)**



To the solution of *cis*-1,4-butenediol **29** (5.0 g, 56.82 mmol) in dry THF (100 mL), NaH (60% dispersion in oil, 5.68 g, 142.04 mmol) was added 0 ^oC. After 30 min, PMBCl (18.4 mL, 130.68 mmol) was added at the same temperature and stirred for an additional 4 h at room temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with water (2 x 10 mL), brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The dark yellow residual oil was further purified silica gel (60-120 mesh) column chromatography using petroleum ether: EtOAc (9:1) as an eluent to afford diPMB ether **30** as yellow colour liquid (17.99 g).

Molecular Formula : $C_{20}H_{24}O_4$.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 3.84 (s, 6H), 4.07 (d, *J* = 4.8 Hz, 4H), 4.46 (s, 4H), 5.81 (t, *J* = 3.8 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 4H), 7.29 (d, *J* = 8.7 Hz, 4H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 54.85, 65.15, 71.53, 113.47, 129.07, 129.22, 129.94, 158.93.

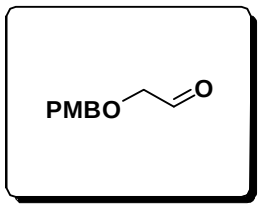
IR (Neat) cm^{-1} : 3008, 2931, 1684, 1035, 759.

MS (ESI-TOF) m/z : 329.17 ($[M+H]^+$), 351.16 ($[M+Na]^+$).

Elemental analysis Calculated: C, 73.15; H, 7.37; O, 19.49%

Found: C, 73.02; H, 7.16; O, 19.30%.

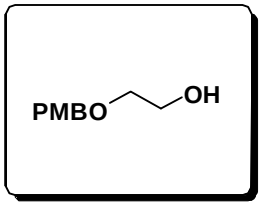
2-(4-Methoxybenzyloxy)acetaldehyde (31)



To a stirred solution of **30** (10.0 g, 30.45 mmol) in DEE-H_2O (1:1, 100 mL) at room temperature, was added OsO_4 (0.33 mL, 0.61 mmol, 2 M solution in toluene). The reaction mixture was stirred for 30 min and $NaIO_4$ (16.28 g, 76.12 mmol) was added to the reaction mixture. The mixture was stirred at room temperature for 12 h and then quenched with aqueous Na_2SO_4 and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give dark brownish liquid**.** The residual liquid was further purified by silica gel column chromatography using petroleum ether: EtOAc (4:1) to give aldehyde **31** (11.4 g, 94%) as colorless dense liquid.

Molecular Formula	: $C_{10}H_{12}O_3$.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) δ 3.82 (s, 3H), 4.08 (s, 2H), 4.57 (s, 2H), 6.90 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 9.71 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 55.1, 73.1, 74.8, 113.8 ,128.7, 129.6, 159.4, 200.4.
IR (Neat) cm^{-1}	: 3010, 2730, 1702, 1684, 763.
MS (ESI-TOF) m/z	: 181.08 ($[M+H]^+$).

2-(4-Methoxybenzyloxy) ethanol (32)



To the ice-cooled solution of aldehyde **31** (9.0 g, 50 mmol) in methanol (100 mL) was slowly added $NaBH_4$ (2.09 g, 55 mmol, slight excess) in portions. The resulting solution was then stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure and residue was dissolved in water (25 mL) followed by the extraction with EtOAc (3 x 25 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated on rotary evaporator to give crude dark brownish liquid. The residual liquid was further purified by silica gel column chromatography using petroleum ether: ethyl acetate (7:3) as eluent, to offer alcohol **32** (8.8 g, 97%) as a pale yellowish dense liquid.

Molecular Formula : $C_{10}H_{14}O_3$.

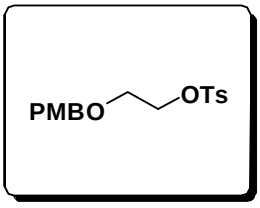
^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 2.26 (bs, 1H), 3.57 (t, *J* = 4.5 Hz, 2H), 3.74 (t, *J* = 4.4 Hz, 2H), 3.81 (s, 3H), 4.50 (s, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 54.75, 61.16, 70.87, 72.40, 113.37, 129.05, 129.73, 158.83.

IR (Neat) cm^{-1} : 3421 (broad), 3001, 2927, 2819, 1615, 1587, 1527, 1445, 1215, 1090, 792, 767.

MS (ESI-TOF) m/z : 205.07 ($[M+Na]^+$).

2-(4-Methoxybenzyloxy) ethyl-4-methylbenzenesulfonate (33)



To a stirred solution of alcohol **32** (3.64 g, 20 mmol) and Et_3N (3.03 g, 4.17 mL, 30 mmol) in dry CH_2Cl_2 (40 mL) tosyl chloride (4.19 g, 22 mmol) was added in portions at 0^{o}C. The reaction mixture was then stirred further for 4 h at the same temperature. Then the reaction mixture was warmed to room temperature and solvent was evaporated under reduced pressure to give crude reaction mass. The crude mass was then taken in EtOAc (50 mL) and stirred with 3% aq. $NaHCO_3$. The organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated on rotary evaporator resulting a dark yellowish liquid which upon silica-gel column chromatography using petroleum ether: ethyl acetate (8:2) as eluent afforded pure tosylate **33** (6.42 g, 96 %) as a pale yellowish oil.

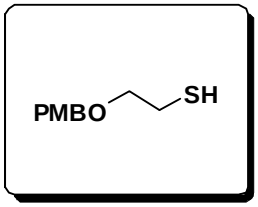
Molecular Formula : $C_{17}H_{20}O_5S$.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 2.44 (s, 3H), 3.63 (t, *J* = 11 Hz, 2H), 3.80 (s, 3H), 4.18 (t, *J* = 11 Hz, 2H), 4.42 (s, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 21.36, 55.0, 66.92, 69.19, 72.56, 113.54, 127.68, 129.09, 129.42, 129.61, 132.72, 144.60, 159.06.

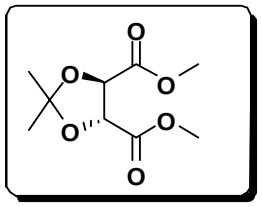
MS (ESI-TOF) m/z : 337.08 ($[M+H]^+$).

2-(4-Methoxybenzyloxy)ethanethiol (20)



To the solution of tosylate **33** (3.36 g, 10 mmol) in absolute ethanol (8 mL) was added thiourea (0.76 g 10 mmol) and the reaction mixture was refluxed for 3.5 h. Then a solution of sodium hydroxide (0.6 g, 15 mmol) in distilled water (6 mL) was added, and the reaction mixture was refluxed for further 3.5 h. The reaction mixture was allowed to cool to room temperature, concentrated and extracted with dichloromethane (2 × 20 mL). The organic layer was separated, dried over Na_2SO_4 and solvent was removed under diminished pressure to give a crude brownish liquid. The residual brownish liquid was further purified by column chromatography on silica-gel eluting with petroleum ether: ethyl acetate (9:1) to give **24** (1.8 g, 95% yield) as a colorless oil.

(4*R*, 5*R*)-Dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (35)

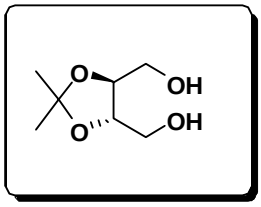


To a 250 mL single-necked round-bottomed flask well equipped with a reflux condenser, magnetic spinning bar and argon atmosphere, was added L-(+)-tartaric acid (10.1 g, 67.3 mmol), dry methanol (4.0 mL), 2,2-dimethoxypropane (19.0 mL, 16.1 g, 154 mmol) and *p*-toluene sulfonic acid (0.04 g, 0.21 mmol) and the resulting mixture was warmed in an oil bath at 50-70 ^{o}C until a dark-red homogeneous solution obtained. The reaction mixture was cooled to room temperature and an additional quantity of 2,2-dimethoxypropane (9.5 mL, 8.05 g, 77 mmol) and dry cyclohexane (45.0 mL) were added. The reflux condenser was replaced with a long distillation head and the resulting two-layered reaction mixture was refluxed to afford a slow removal of cyclohexane-methanol and cyclohexane-acetone azeotropes over a period of 24 h. Once the vapor temperature fell below 50 ºC additional 2,2-dimethoxypropane (0.6 mL, 0.51 g, 4.9 mmol) was added and the reaction mixture was refluxed for further 15 min. Then the reaction mixture was cooled to room temperature and anhydrous potassium carbonate (0.1 g, 0.72 mmol) was added and stirred until the reddish color abated. The reaction mixture was filtered and residual material was washed with ethyl acetate. The filtrate and washings were combined and concentrated under reduced pressure to give a thick dark yellow liquid,

which further upon vacuum distillation (bp = 94 ºC/ 0.5 mm) afforded **35** (13.90 g, 95 %) as a pale yellowish liquid.

Molecular Formula	: $C_9H_{14}O_6$.
Optical rotation	: $[\alpha]_D^{25}$ -42.8°, *c* 5.1, $CHCl_3$ (Lit. $[\alpha]_D^{24}$ -42.6°, *c* 5.1, $CHCl_3$)[21]
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 1.44 (s, 6H), 3.77 (s, 6H), 4.76 (s, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 25.78, 52.15, 76.51, 113.26, 169.56.
IR (Neat) cm^{-1}	: 2990, 2954, 1753, 1435, 1382, 1211, 1109, 1014, 855, 744.
MS (ESI-TOF) m/z	: 241.05 ($[M+Na]^+$).

((4*S*,5*S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)dimethanol (36)

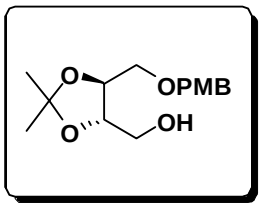


A solution of **35** (10 g, 46 mmol) in dry THF (90 mL) was added to a stirring suspension of lithium aluminium hydride (1.85 g, 48.7 mmol) in dry THF (45 mL) at 0 ºC, over a period of 15 min. After stirring for about an hour at room temperature, the reaction mixture was further refluxed for 6h. The reaction mixture was cooled to 0 ºC and quenched with aq. NaOH (20 %) to give a white suspension which was added anhydrous Na_2SO_4 and the resulting slurry was filtered at the suction pump. The solid residue remained was washed with distilled THF (10 mL). The filtrate and washings were combined and concentrated under reduced pressure to give a crude syrupy mass which further upon silica-gel column chromatography using petroleum ether-ethyl acetate (2:3) as eluent to afford C_2-symmetric diol **36** (4.41 g, 60 %) as a dense colorless oil.

Molecular Formula	: $C_7H_{14}O_4$.
Optical rotation	: $[\alpha]_D^{25}$ +2.82°, *c* 4.7, $CHCl_3$ (Lit. $[\alpha]_D^{24}$ +2.78°, *c* 4.67, $CHCl_3$)[21,22]
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 1.39 (s, 6H), 3.23 (bs, 2H, D_2O exchangeable), 3.70 (m, 4H), 3.92 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 26.67, 62.05, 78.31, 109.02.
IR (Neat) cm^{-1}	: 3415 (broad), 2985, 2932, 1453, 1374, 1216, 1167, 1054, 986, 880, 845, 800, 758.
MS (ESI-TOF) m/z	: 185.02 ($[M+Na]^+$).

((4*R*,5*R*)-4-Hydroxymethyl5-((4-methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (37)

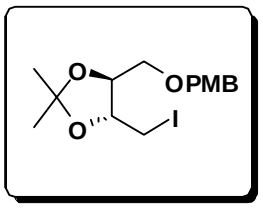


To a solution of **36** (3.24 g, 20 mmol) in dry DMF: THF (1:1) (60 mL) was added sodium hydride (60%, 0.88 g, 22 mmol) at 0 °C and was then stirred at same temperature for 30 min. To this was added slowly *p*-methoxybenzyl chloride (3.44 g, 2.98 mL, 22 mmol) at the same temperature and stirred for an additional 5h at room temperature. The reaction mixture was then quenched with cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water (3 x 30 mL), brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual dark yellowish oil was further purified by silica gel column chromatography using petroleum ether: ethyl acetate (7:3) as eluent to offer the mono-PMB protected alcohol **37** (4.38 g, 78%) as colorless dense oil.

Molecular Formula	: $C_{15}H_{22}O_5$.
Optical rotation	: $[\alpha]_D^{25}$ -8.12 °, *c* 1.00, $CHCl_3$ (Lit. $[\alpha]_D^{23}$ -8.44 °, *c* 1.08, $CHCl_3$).[22]
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 1.45 (s, 3H), 2.43 (bs, 1H, D_2O exchangeable), 3.56 (dd, *J* = 5.7, 9.8 Hz, 1H), 3.70 (dd, 1H, *J* = 6.0, 9.9 Hz, 1H), 3.74 (dd, *J* = 4.3, 8.5 Hz, 2H), 3.84 (s, 3H), 3.95 (m, 1H), 4.02-4.09 (m, 1H), 4.56 (s, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 26.70, 54.93, 62.15, 69.81, 73.0, 76.40, 79.36, 109.05, 113.55, 129.16, 129.40, 159.02.
IR (Neat) cm^{-1}	: 3460 (broad), 2983, 2934, 2869, 1610, 1514, 1245.
MS (ESI-TOF) m/z	: 305.12 ($[M+Na]^+$).

HRMS (TOF) m/z : calculated for $C_{15}H_{22}O_5Na$ [M+Na^+] 305.1365, found 305.1360.

(4*S*,5*R*)-4-(Iodomethyl)-5-((4-methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxolane (21)



A solution of alcohol **37** (4.23 g, 15 mmol), triphenylphosphine (4.72 g, 18 mmol) and imidazole (3.06 g, 45 mmol) in toluene (100 mL) was refluxed under argon atmosphere till clear homogenous solution obtained. The reflux was stopped and iodine (4.95 g, 19.5 mmol) was carefully added and the reaction mixture was further refluxed for 30 min. After 30 min of reflux, the reaction mixture was cooled to room temperature and poured in a separatory funnel containing water (200 mL) and a 10% $Na_2S_2O_3$ aqueous solution (50 mL) and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give dark reddish crude oil. The residual dark reddish crude oil was further purified by silica gel column chromatography using petroleum ether: ethyl acetate (9:1) as eluent to offer the iodo intermediate **21** (5.28 g, 90%) as colorless oil.

Molecular Formula : $C_{15}H_{21}IO_4$

Optical rotation : $[\alpha]_D^{25}$ + 10.91 °, *c* 2.0, $CHCl_3$ (Lit. $[\alpha]_D^{23}$ + 10.96 °, *c* 1.8, $CHCl_3$).[22]

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 1.42 (s, 3H), 1.47 (s, 3H), 3.26 (dd, *J* = 10.6, 5.3 Hz, 1H), 3.36 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.62 (dd, *J* = 10.1, 5.0 Hz, 2H), 3.81 (s, 3H), 3.83-3.97 (m, 2H), 4.52 (s, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 8.7 Hz, 2H).

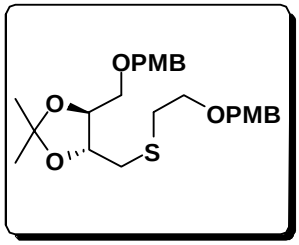
^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 6.36, 27.11, 27.17, 55.05, 69.92, 73.01, 76.47, 79.83, 109.51, 113.62, 129.12, 129.64, 159.07.

IR (Neat) cm^{-1} : 2982, 2931, 2863, 1612, 1510, 1370, 1245.

MS (ESI-TOF) m/z : 415.10 ([M+$Na]^+$).

HRMS (TOF) m/z : calculated for $C_{15}H_{21}O_4NaI$ ([M+$Na]^+$) 415.0382, found 415.0393.

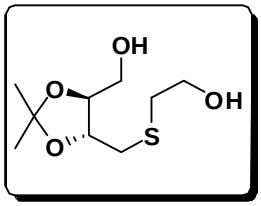
(4*R*, 5*S*)-4-((2-(4-Methoxybenzyloxy) ethylthio) methyl)-5-((4-methoxybenzyloxy) methyl)-2,2-dimethyl-1,3-dioxolane (22)



To a solution of thiol **20** (3.96 g, 20 mmol) in dry THF (40 mL) was added sodium hydride (60%, 1.2 g, 30 mmol) at 0 °C and was then stirred at same temperature for 30 min. To this was added the solution of iodo intermediate **21** (8.62 g, 22 mmol) in dry THF (60 mL) at the same temperature and stirred for an additional 5 h at room temperature. The reaction mixture was then quenched with cold water at 0 °C and the two phases were separated. The aqueous phase was extracted with EtOAc (2 x 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give dark yellowish dense oil which was further purified by silica gel column chromatography using petroleum ether: ethyl acetate (9:1) as eluent to offer the desired thioether **22** (8.71 g, 95%) as dense pale yellowish oil.

Molecular Formula	: $C_{25}H_{34}O_6S$.
Optical rotation	: $[\alpha]_D^{25}$ -6.05 ^{o}, *c* 1, $CHCl_3$.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 1.41 (s, 3H), 1.42 (s, 3H), 2.76-2.83 (m, 4H), 3.58-3.65 (m, 4H), 3.80 (s, 3H), 3.80 (s, 3H), 3.97-4.01 (m, 2H), 4.46 (s, 2H), 4.50 (s, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 26.84, 26.96, 32.13, 34.81, 54.99, 69.25, 70.03, 72.41, 72.94, 78.10, 79.06, 109.16, 113.55, 129.09, 129.76, 129.94, 159.0.
IR (Neat) cm^{-1}	: 3065, 3013, 2926, 2895, 1611, 1585, 1459, 1375, 1234, 1102 and 1034 (C-O-C and C-S-C), 765 and 719 (aromatic).
MS (ESI-TOF) m/z	: 485.22 ($[M+Na]^+$).
HRMS (TOF) m/z	: calculated for $C_{25}H_{34}NaO_6S$ ($[M+Na]^+$) 485.1978, found 485.1971.

2-(((4*R*,5*S*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methylthio)ethanol (23)



To a stirred solution of thioether **22** (4.62 g, 10 mmol) in CH_2Cl_2 (102 mL) and water (6 mL) was added DDQ (6.81 g, 30 mmol) and stirred for 30 min at room temperature. After 30 min the precipitated DDQH was removed by mere filtration and the residue was washed with CH_2Cl_2. The combined organic layers were then washed with saturated $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and concentrated under diminished pressure to give dark brownish oil, which was further purified by silica-gel column chromatography using petroleum ether: ethyl acetate (3:7) as eluent to offer the desired diol **23** (1.94 g, 88%) as a dense pale yellowish oil.

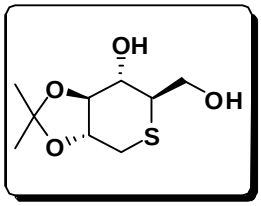
Molecular Formula	: $C_9H_{18}O_4S$.
Optical rotation	: $[\alpha]_D^{25}$ -12.92 ^{o}, *c* 2.00, MeOH.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 1.43 (s, 3H), 1.44 (s, 3H), 1.88 (bs, 1H, D_2O exchangeable), 2.32 (bs, 1H, D_2O exchangeable), 2.77-2.83 (m, 4H), 3.73-3.83 (m, 4H), 3.85-3.93 (m, 1H), 4.07-4.16 (m, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 26.80, 26.85, 34.08, 35.52, 60.86, 61.86, 76.65, 80.61, 109.0.
IR (Neat)	: 3445 (broad), 2926, 2895, 1234, 1097, 984 (C-S-C).
MS (ESI-TOF) m/z	: 245.04 ($[M+Na]^+$).
HRMS (TOF) m/z	: calculated for $C_9H_{18}NaO_4S$ ($[M+Na]^+$) 245.0783, found 245.0790.

L-proline catalyzed 6-*enolexo* aldolization reaction

To the solution of diol **23** (0.222 g, 1 mmol) in EtOAc (15 mL) was added IBX (1.68 g, 6 mmol) and refluxed for 3.5 h at 80^{o}C. After reaction completion (as checked by 2,4-DNP TLC test)[23], reaction mixture was cooled to room temperature and filtered and the filtrate was washed with 20% aqueous $NaHCO_3$ (2 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under diminished pressure to give pale yellowish syrupy crude dialdehyde **24** (0.206 g). The crude dialdehyde was immediately used as a starting material for an *enolexo* aldolization reaction without any further purification. To the solution of crude dialdehyde **24** (0.206 g) in dry DCM

(10 mL) was added L-proline (0.033 g, 30 mol %) and stirred at room temperature for 45 min (reaction completion time as checked by TLC). After 45 min the reaction mixture was reduced *in situ* by adding 5 mL of MeOH and $NaBH_4$ (0.043 g, 1.1 mmol, slight excess) at room temperature for 1 h. The reaction mixture was concentrated on rotary evaporator, treated with cold water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give syrupy mass which was further purified by flash silica-gel (230-400 mesh) column chromatography using petroleum ether: ethyl acetate (7:3, 4:6) to afford cyclized diol **25** (0.139 g, 63%), **38** (0.015 g, 7%) and dehydrated by-product **39** (0.030 g, 15%) with a combined 85% yield after three consecutive steps.

(3a*R*,6*R*,7*S*,7a*S*)-6-(Hydroxymethyl)-2,2-dimethyltetrahydro-3a*H*-thiopyrano[3,4-*d*][1,3]dioxol-7-ol (25)



Physical appearance : Pale yellowish dense liquid.

Molecular Formula : $C_9H_{16}O_4S$.

Optical rotation : $[\alpha]_D^{25}$ -2.15 °, *c* 1, $CHCl_3$.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ (ppm) 1.44 (s, 3H), 1.45 (s, 3H), 1.84 (bs, 1H, D_2O exchangeable), 1.88 (bs, 1H, D_2O exchangeable), 2.85 (d, *J* = 6.77 Hz, 2H), 3.03 (quintet, *J* = 5.9, 9.5 Hz, 1H), 3.29 (t, *J* = 9.5 Hz, 1H), 3.80 (dd, *J* = 8.5, 15.0 Hz, 1H), 3.88 (m, 1H), 3.95 (m, 1H), 4.01 (t, *J* = 9.5 Hz, 1H).

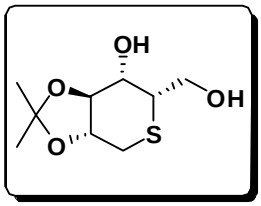
^{13}C NMR ($CDCl_3$, 100 MHz) : δ (ppm) 26.72, 26.91, 30.38, 48.10, 62.45, 74.03, 76.53, 83.65, 110.06.

IR (Neat) : 3445 (broad), 2937, 2881, 1239, 1109, 995 (C-S-C).

Mass (ESI-TOF) m/z : 243.05 ($[M+Na]^+$)

HRMS (TOF) m/z : calculated for $C_9H_{16}NaO_4S$ ($[M+Na]^+$) 243.0662, found 243.0671.

(3a*R*,6*S*,7*S*,7a*S*)-6-(Hydroxymethyl)-2,2-dimethyltetrahydro-3a*H*-thiopyrano[3,4-*d*][1,3]dioxol-7-ol (38)



Molecular Formula : $C_9H_{16}O_4S$.

Physical appearance : White solid.

Mp : 195 ^{o}C.

Optical rotation : $[\alpha]_D^{25}$ +30.17 ^{o}, *c* 1, $CHCl_3$.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ (ppm) 1.44 (s, 3H), 1.45 (s, 3H), 2.71 (dd, *J* = 3.9, 12.0 Hz, 1H), 2.82 (t, *J* =12.0 Hz, 1H), 2.99 (bs, 1H, D_2O exchangeable), 3.16 (dd, *J* =5.5, 8.0 Hz, 1H), 3.47 (bs, 1H, D_2O exchangeable), 3.52 (dd, *J* = 6.9, 12.6 Hz, 1H), 3.76 (ddd, *J* = 4.0, 8.8, 11.2 Hz, 1H), 3.79-3.83 (m, 1H), 4.13-4.17 (m, 1H), 4.29 (dd, *J* = 5.6, 10.1 Hz, 1H).

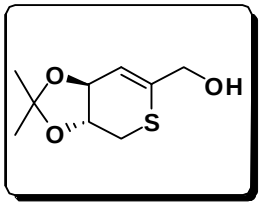
^{13}C NMR ($CDCl_3$, 100 MHz) : δ (ppm) 26.69, 26.91, 28.17, 46.09, 61.98, 74.01, 77.40, 79.41, 109.42.

IR (Neat) : 3430 (broad), 2950, 2875, 1245, 1123, 1005 (C-S-C).

Mass (ESI-TOF) m/z : 243.05 ($[M+Na]^+$)

HRMS (TOF) m/z : calculated for $C_9H_{16}NaO_4S$ ($[M+Na]^+$) 243.0662, found 243.0669.

((3a*R*,7a*S*)-2,2-Dimethyl-4,7a-dihydro-3a*H*-thiopyrano[3,4-*d*][1,3]dioxol-6-yl)methanol (39)



Physical appearance : Pale yellowish dense liquid.

Molecular Formula : $C_9H_{14}O_3S$.

Optical rotation : $[\alpha]_D^{25}$ +150.25 ^{o}, *c* 1, $CHCl_3$.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ (ppm) 1.46 (s, 3H), 1.46 (s, 3H), 2.24 (bs, 1H, D_2O exchangeable), 3.08-3.24(m, 2H), 3.94 (ddd, J = 5.4, 8.2, 10.9 Hz, 1H), 4.11 (s, 2H), 4.14-4.20 (m, 1H), 6.00 (d, *J* = 1.3 Hz, 1H).

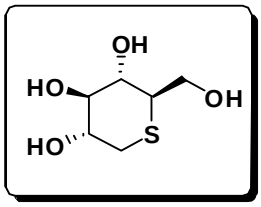
^{13}C NMR ($CDCl_3$, 100 MHz) : δ (ppm) 26.74, 26.91, 27.95, 64.61, 75.65, 77.22, 111.45, 116.17, 135.72.

IR (Neat) : 3410 (broad), 2928, 2871, 1633 (allylic C=C), 1070, and 1035 (C-O-C and C-S-C).

Mass (ESI-TOF) m/z : 225.07 ($[M+Na]^+$).

HRMS (TOF) m/z : calculated for $C_9H_{14}NaO_3S$ ($[M+Na]^+$) 225.0575, found 225.0582.

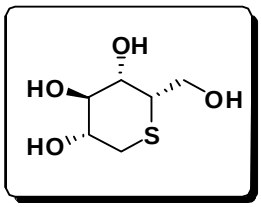
(2*R*,3*S*,4*R*,5*R*)-2-(Hydroxymethyl)tetrahydro-2*H*-thiopyran-3,4,5-triol or 1-(Deoxythionojirimycin) (5)



To a solution of **25** (0.055 g, 0.25 mmol) in distilled methanol (2 mL) was added conc. HCl (0.2 mL) and the reaction mixture was stirred at room temperature for 3 h. After 3 h the solvent methanol and traces of water were removed under diminished pressure to give crude product. The traces of organic impurities were washed off with ethyl acetate (3 x 2 mL) and resulting mass was dried under high vaccum to afford 1-Deoxythionojirimycin **5** (0.038 g, 85 %) as a brownish gum.

Molecular Formula	: $C_6H_{12}O_4S$.
Optical rotation	: $[\alpha]_D^{25}$ +49.68 ^{o}, *c* 1.4, H_2O (Lit. [α]D +50.0, *c* 1.39, H_2O).[6a,8]
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 2.46 (dd, *J* = 11.0, 13.0 Hz, 1H), 2.55 (ddd, *J* = 4.2, 8.3, 13.0 Hz, 1H), 2.70-2.75 (m, 1H), 3.03 (t, *J* = 9.2 Hz, 1H), 3.32 (t, *J* = 9.5 Hz, 1H), 3.48 (ddd, *J* = 4.5, 9.5, 14.0 Hz, 1H), 3.61 (ddd, *J* = 6.2, 12.0, 15.0 Hz, 1H), 3.61 (ddd, *J* = 3.2, 12.4, 15.5 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 31.18, 48.16, 60.52, 72.89, 73.46, 78.44.
IR (neat) cm^{-1}	: 3368 (broad), 2925, 1430, 1103, 1043.
HRMS (TOF) m/z	: calculated for $C_6H_{12}O_4S$+1 ($[M+H]^+$) 181.0535, found 181.0526.

(2*S*,3*S*,4*R*,5*R*)-2-(Hydroxymethyl)tetrahydro-2*H*-thiopyran-3,4,5-triol or 1-Deoxy-L-thio-idonojirimycin) (40)

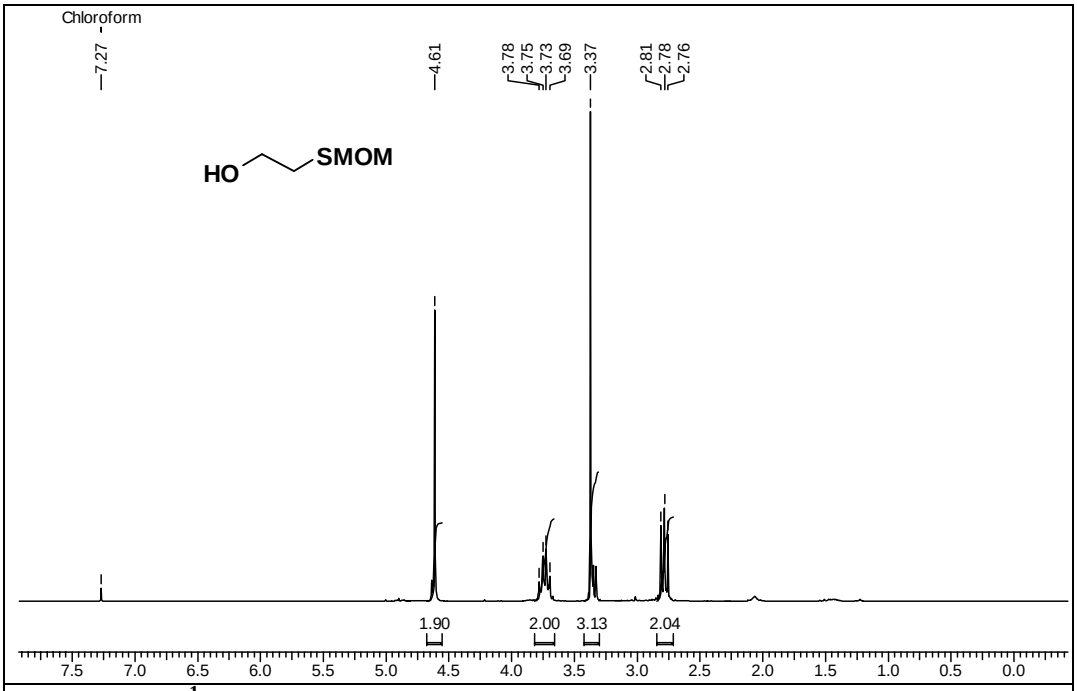


To a solution of **38** (0.011 g, 0.05 mmol) in distilled methanol (1 mL) was added conc. HCl (0.05 mL) and the reaction mixture was stirred at room temperature for 3 h. After 3 h solvent methanol and traces of water was removed under diminished pressure to give crude product. The traces of organic impurities were

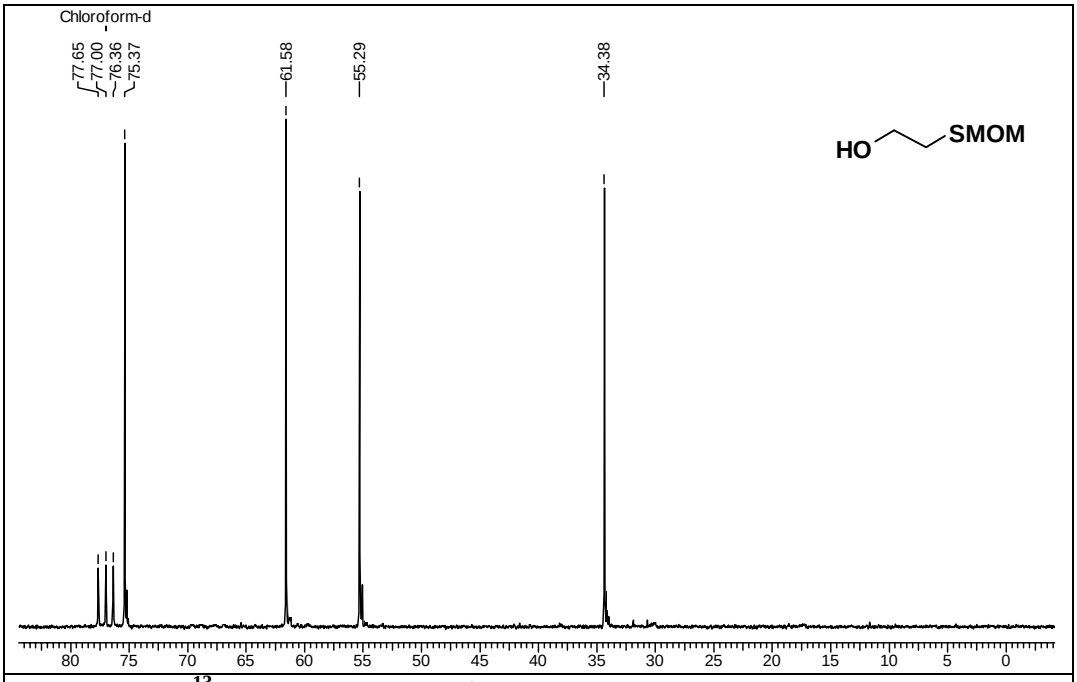
washed off with ethyl acetate (3 x 1 mL) and resulting mass was dried under high vaccum to afford 1-Deoxy-L-thio-idonojirimycin **40** (0.007 g, 80 %) as a brownish gummy product.

Molecular Formula	: $C_6H_{12}O_4S$.
Optical rotation	: $[\alpha]_D^{25}$ -249.26 ^{o}, *c* 1.00, H_2O .
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 2.44 (d, *J* = 13.1 Hz, 1H), 2.56 (dd, *J* = 10.7, 13.4 Hz, 1H), 3.22 (t, *J* = 9.2 Hz, 1H), 3.50-3.55 (m, 1H), 3.59 (t, *J* = 10.7 Hz, 1H), 3.79 (t, *J* = 4.5 Hz, 1H), 3.83 (dd, *J* = 4.0, 11.5 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 27.29, 45.94, 57.13, 72.95, 73.59, 73.76.
IR (neat) cm^{-1}	: 3370 (broad), 2935, 1427, 1117, 1039.
HRMS (TOF) m/z	: calculated for $C_6H_{12}O_4S$ +1 ($[M+H]^+$) 181.0535, found 181.0526.

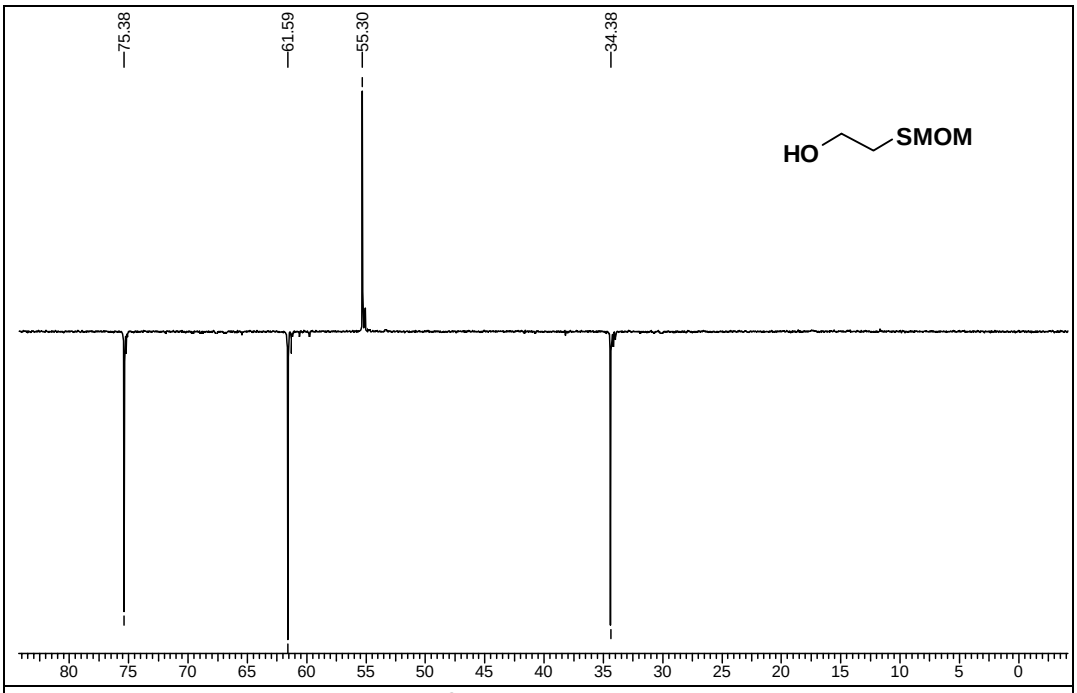
1.2.7 Analytical data



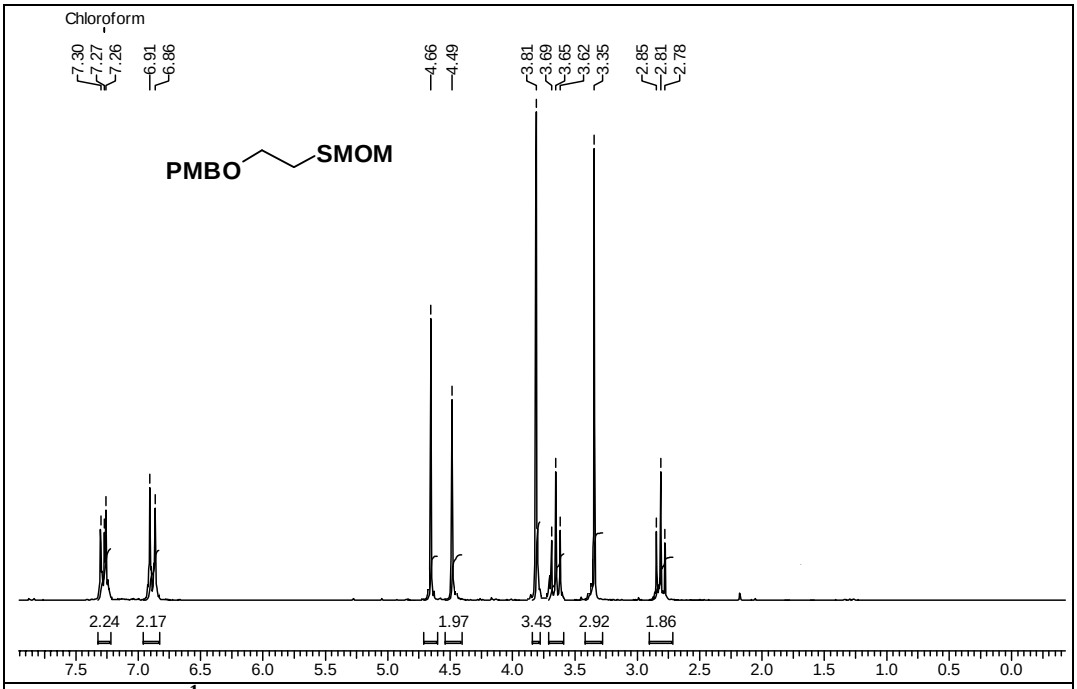
^{1}H NMR spectrum of compound 27 ($CDCl_3$, 200 MHz)



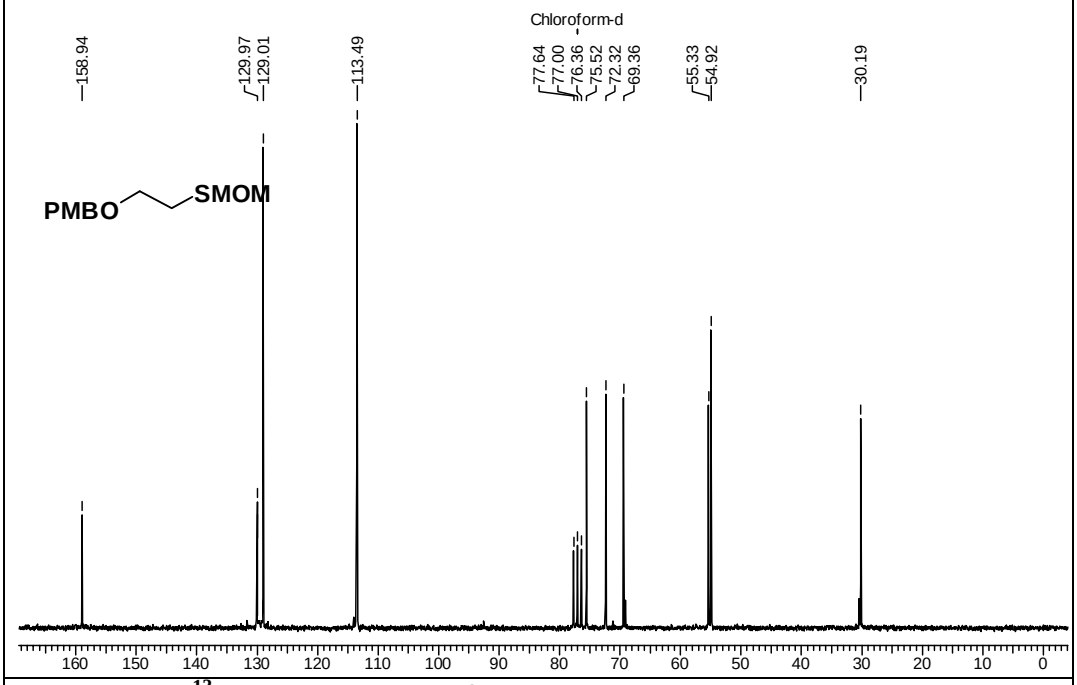
^{13}C NMR spectrum of compound 27 ($CDCl_3$, 50 MHz)



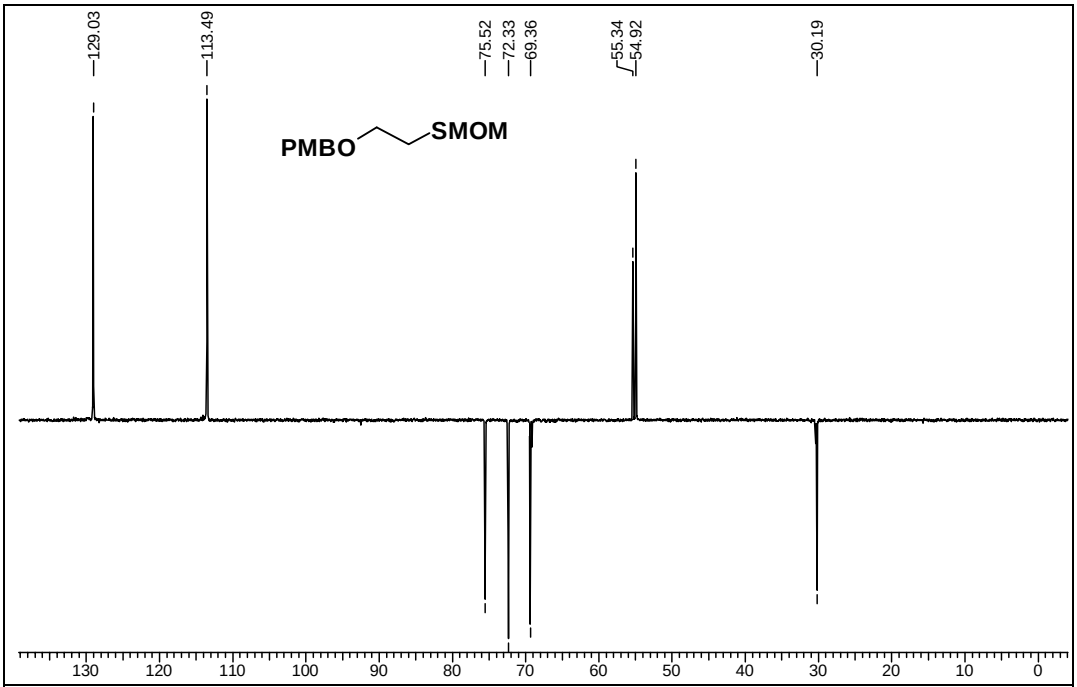
DEPT spectrum of compound 27 ($CDCl_3$, 50 MHz)



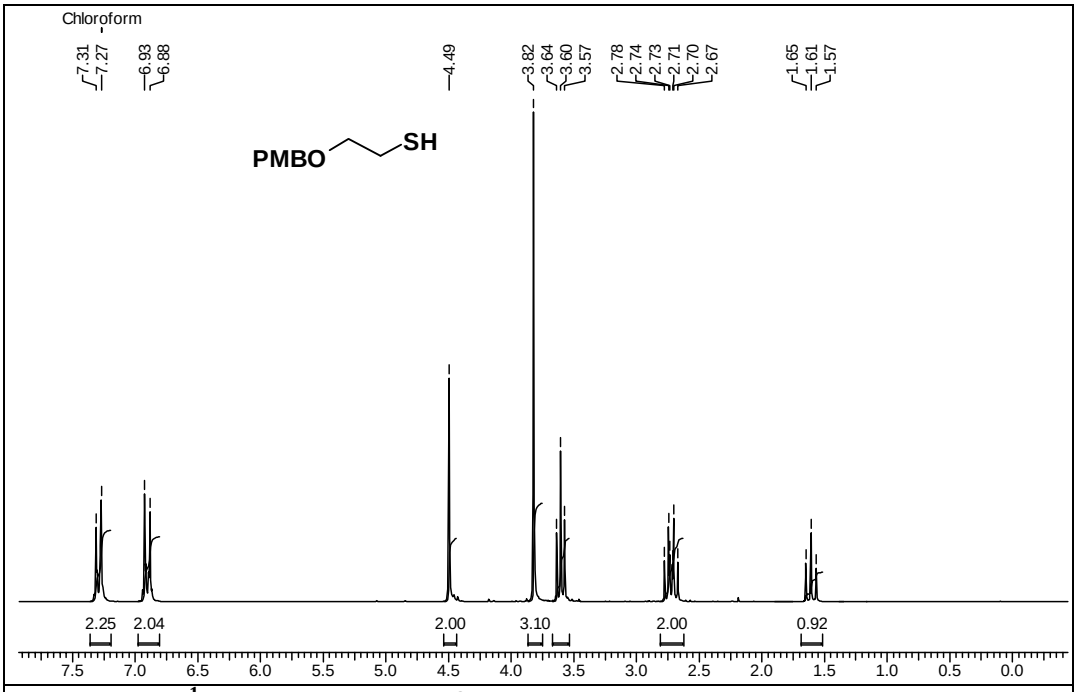
^{1}H NMR spectrum of compound 28 ($CDCl_3$, 200 MHz)



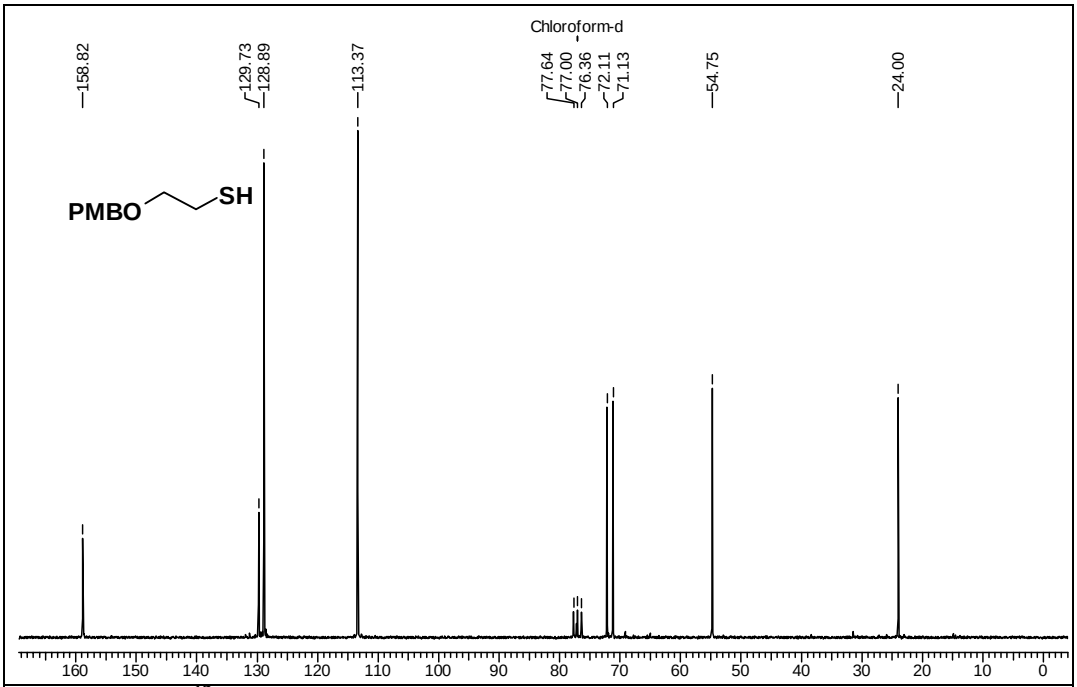
^{13}C NMR spectrum of compound 28 ($CDCl_3$, 50 MHz)



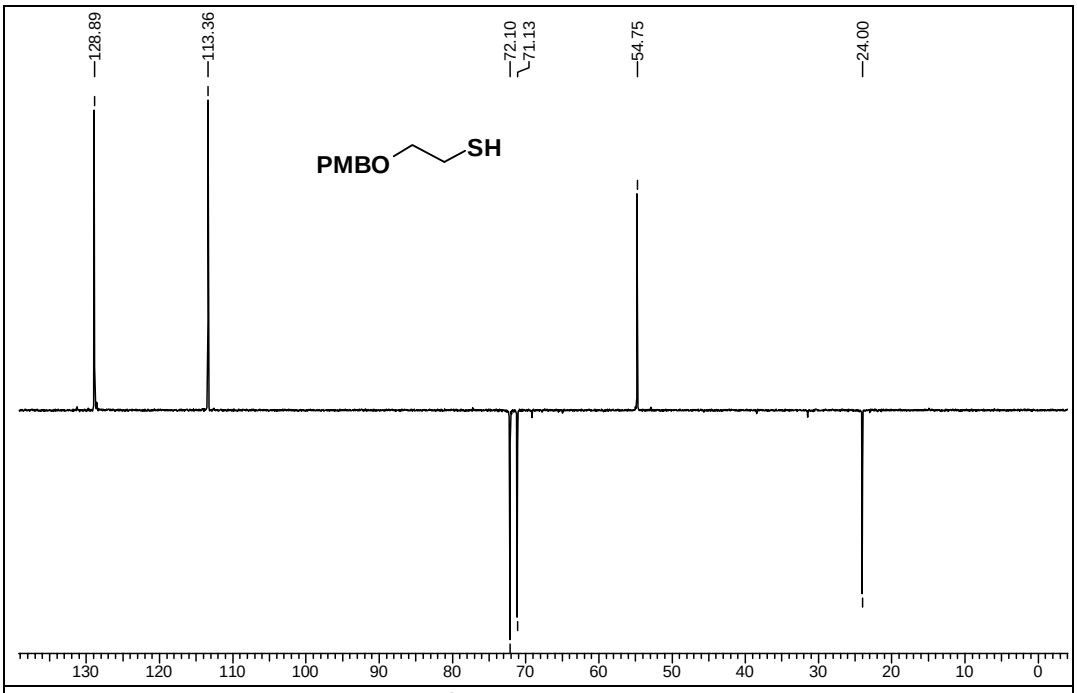
DEPT spectrum of compound 28 ($CDCl_3$, 50 MHz)



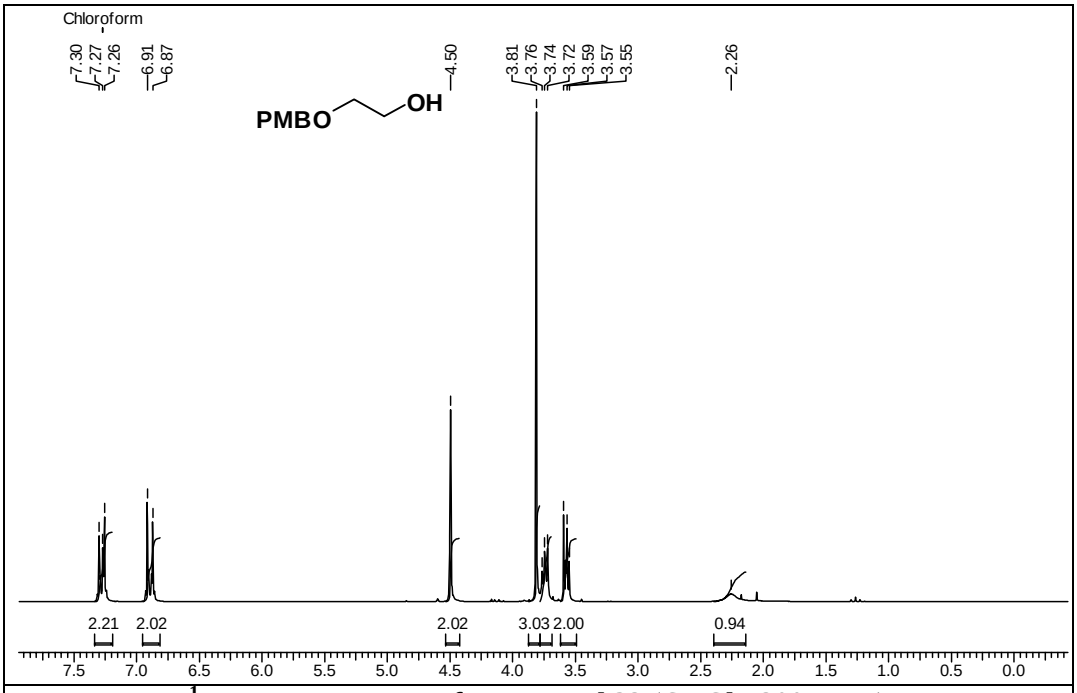
^{1}H NMR spectrum of compound 20 ($CDCl_3$, 200 MHz)



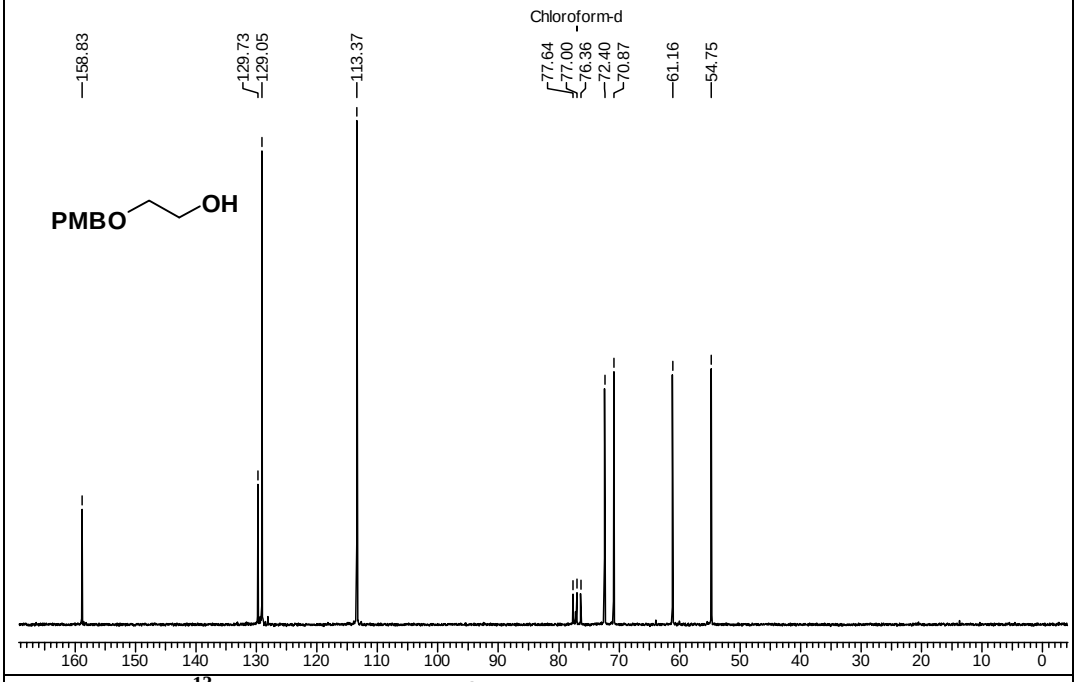
^{13}C NMR spectrum of compound 20 ($CDCl_3$, 50 MHz)



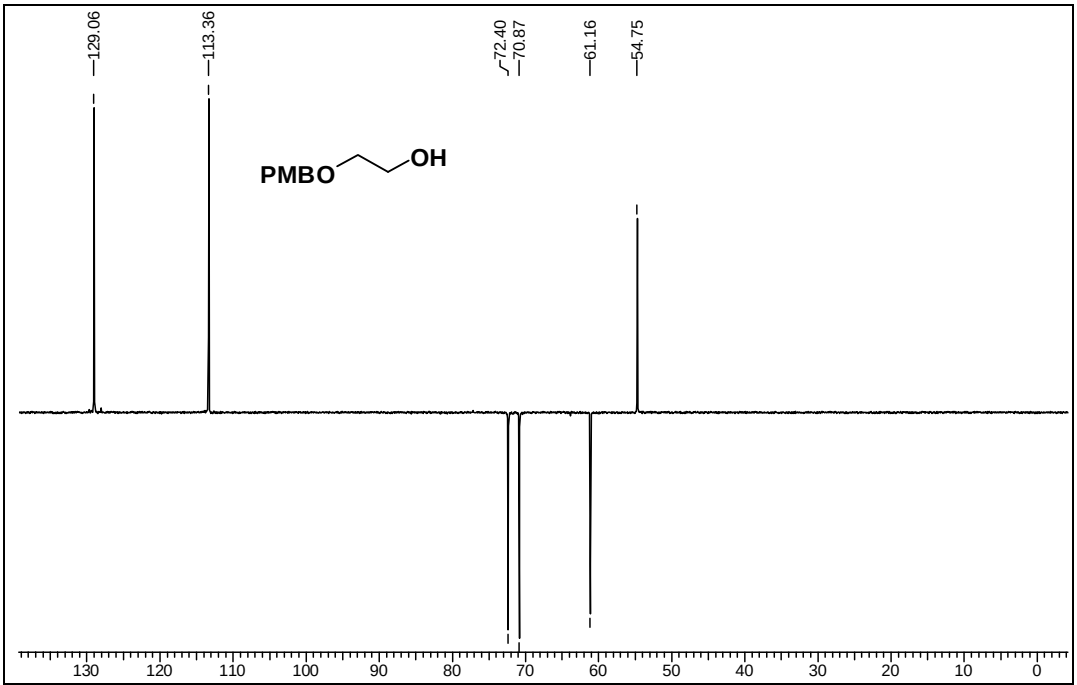
DEPT spectrum of compound 20 ($CDCl_3$, 50 MHz)



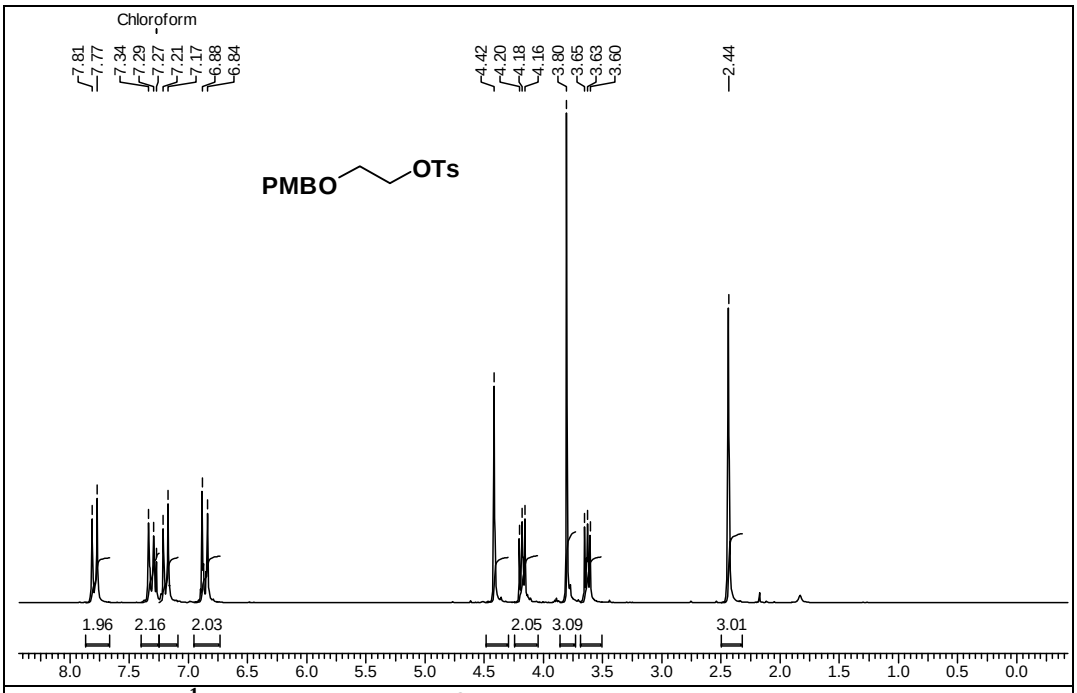
^{1}H NMR spectrum of compound 32 ($CDCl_3$, 200 MHz)



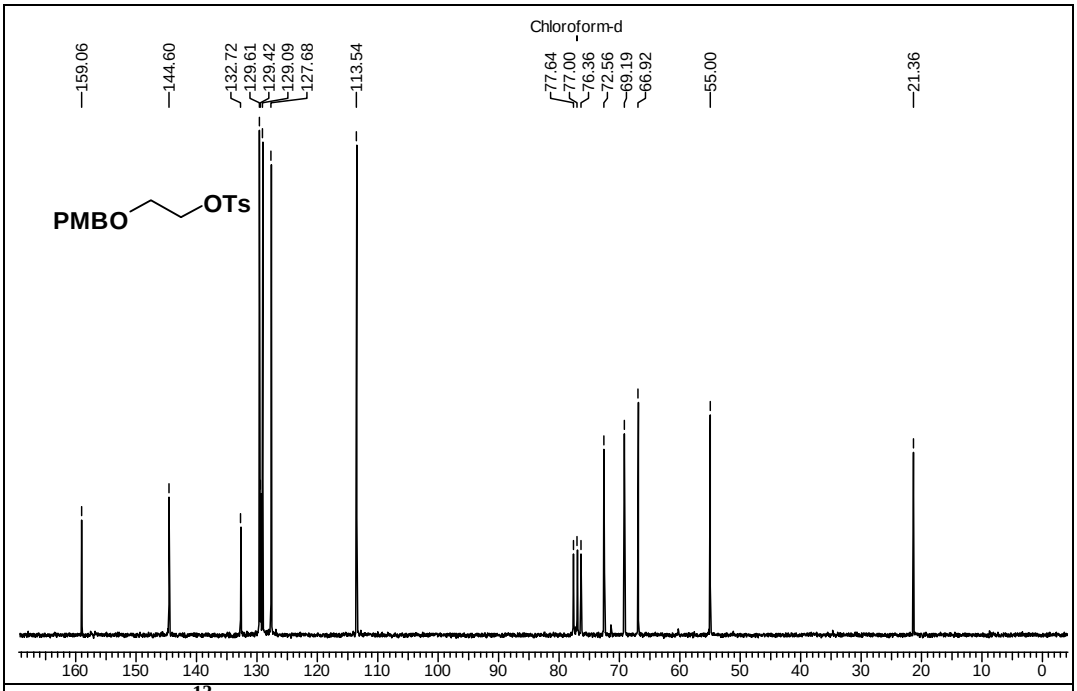
^{13}C NMR spectrum of compound 32 ($CDCl_3$, 50 MHz)



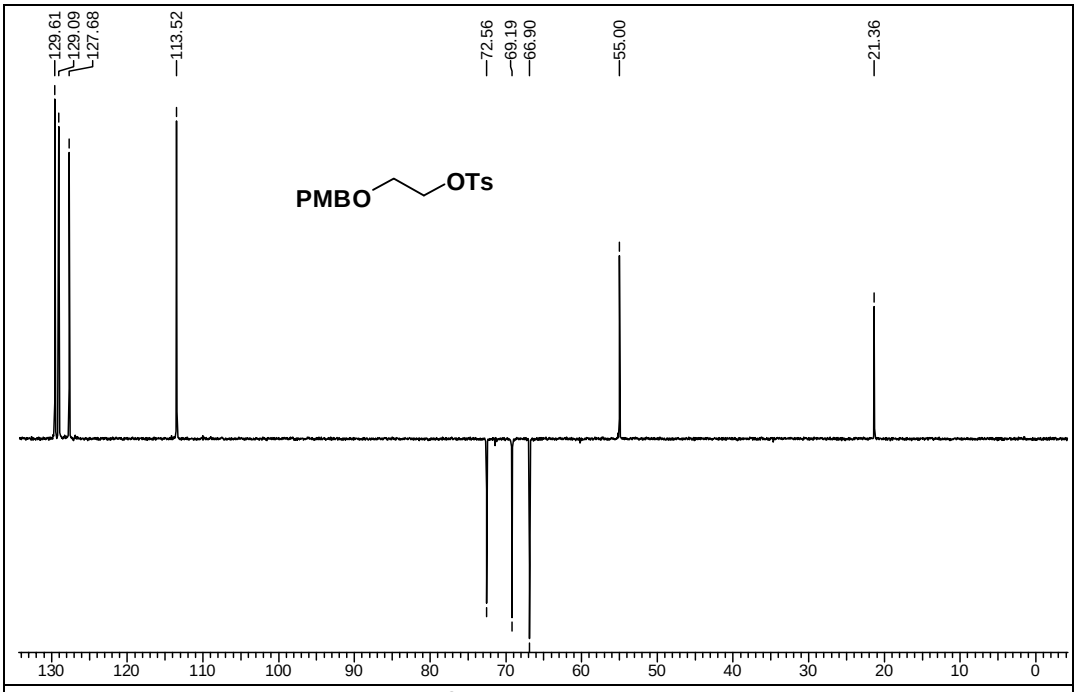
DEPT spectrum of compound 32 ($CDCl_3$, 50 MHz)



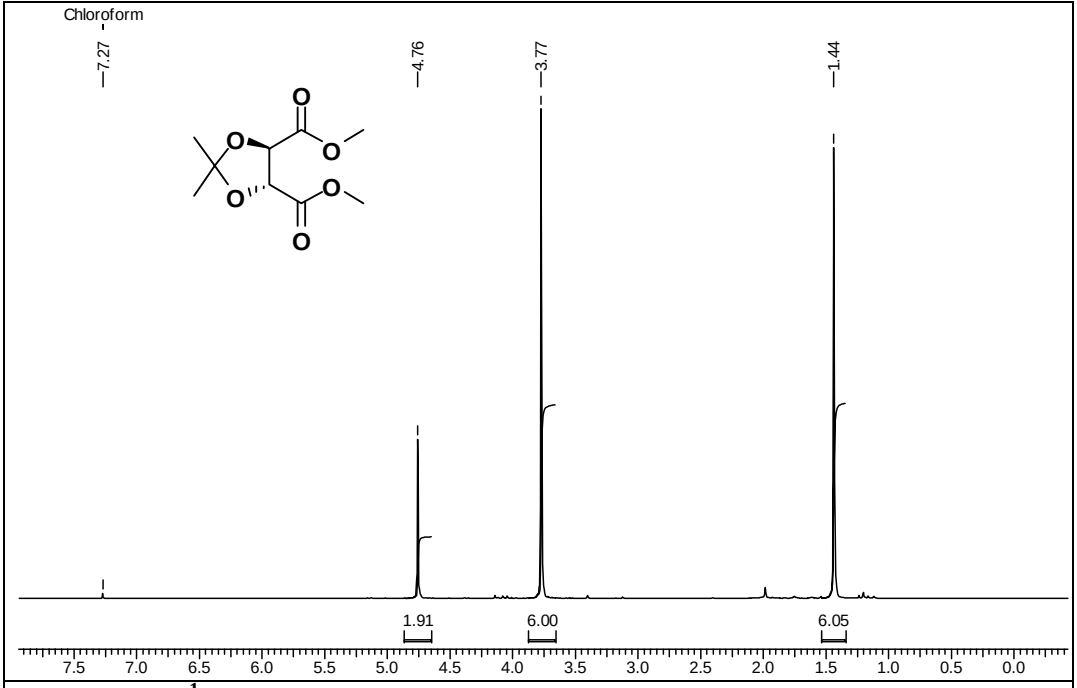
^{1}H NMR spectrum of compound 33 ($CDCl_3$, 200 MHz)



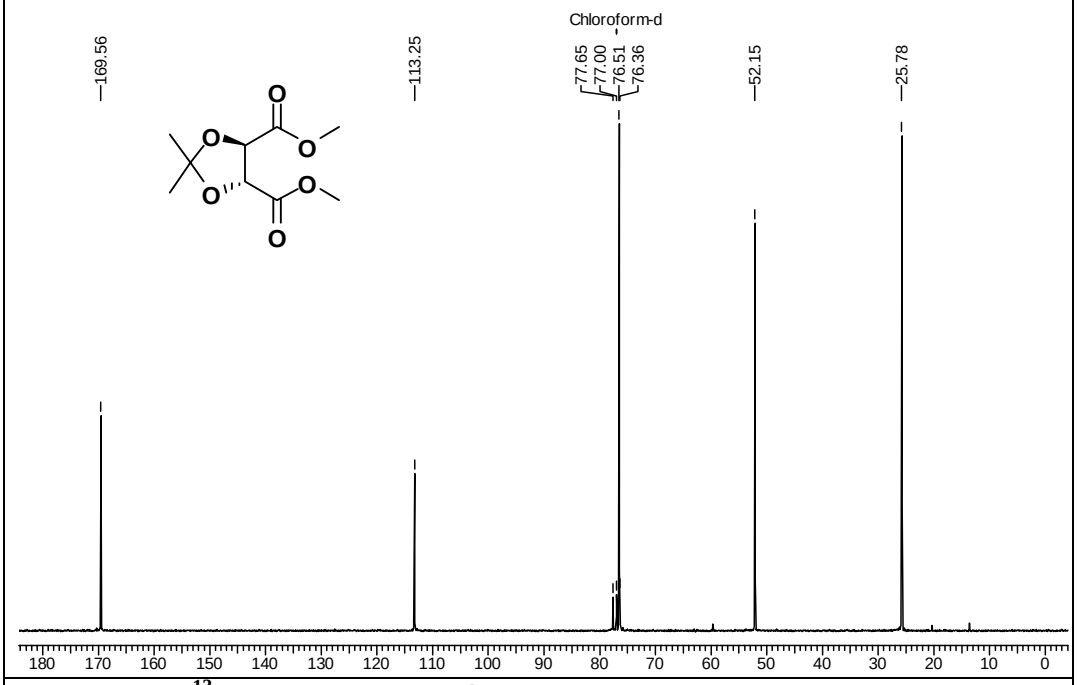
^{13}C NMR spectrum of compound 33 ($CDCl_3$, 50 MHz)



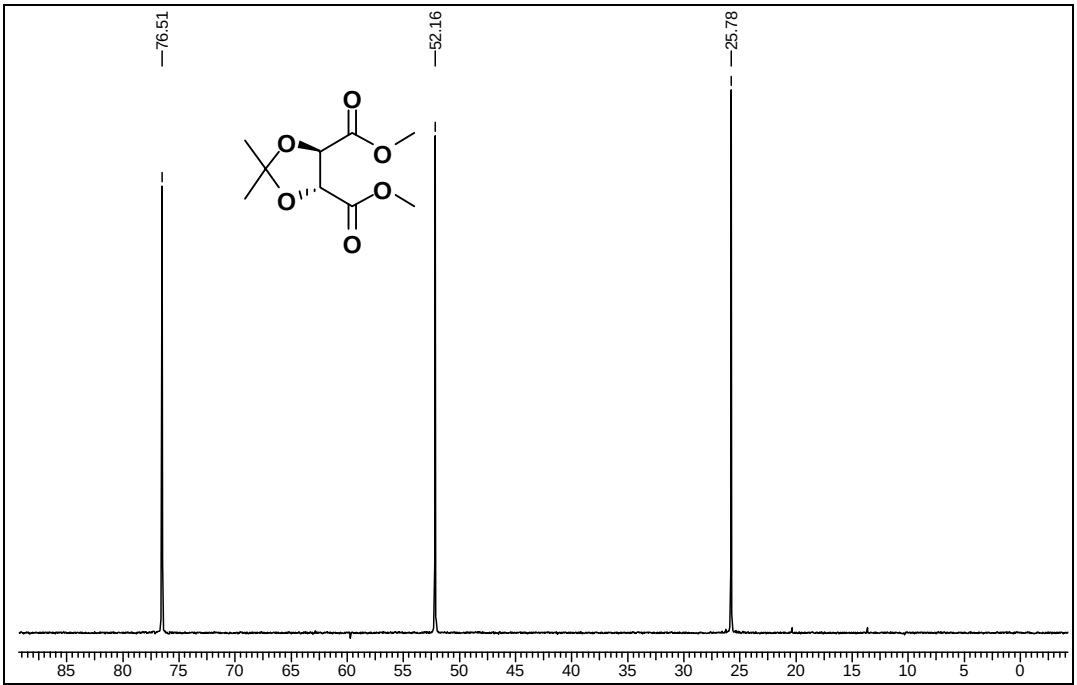
DEPT spectrum of compound 33 ($CDCl_3$, 50 MHz)



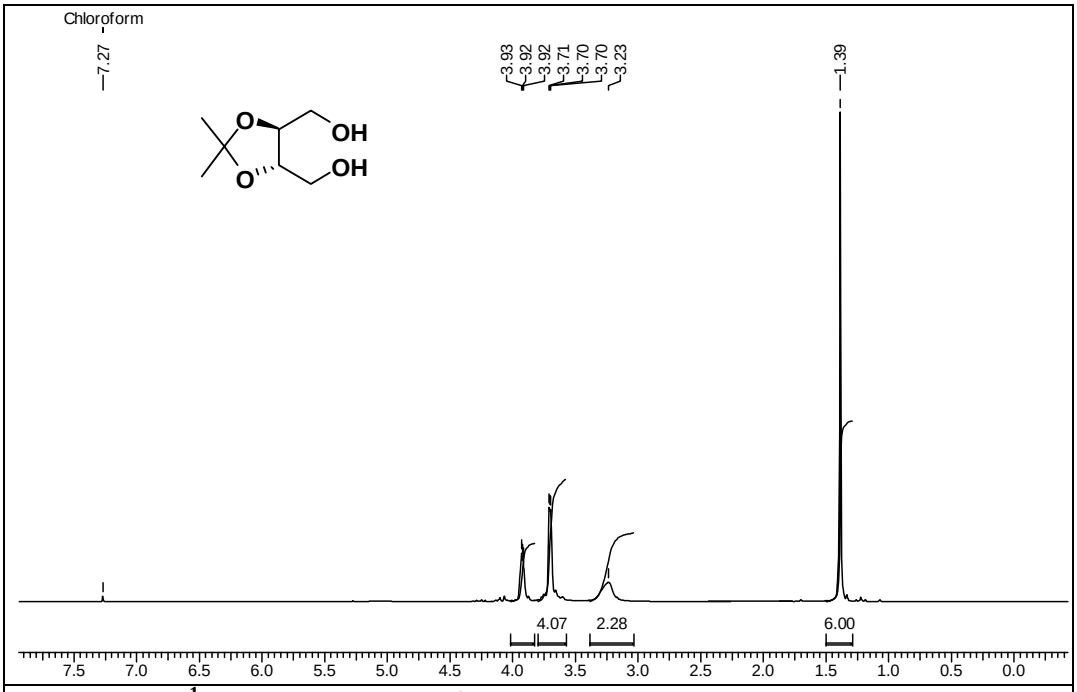
^{1}H NMR spectrum of compound 35 ($CDCl_3$, 200 MHz)



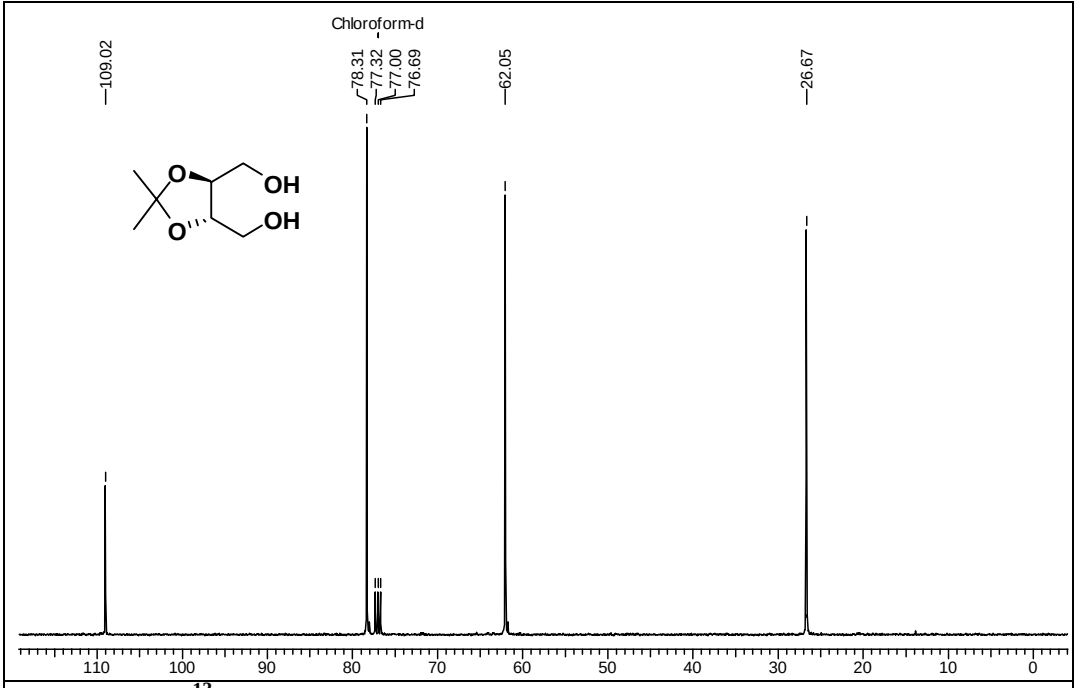
^{13}C NMR spectrum of compound 35 ($CDCl_3$, 50 MHz)



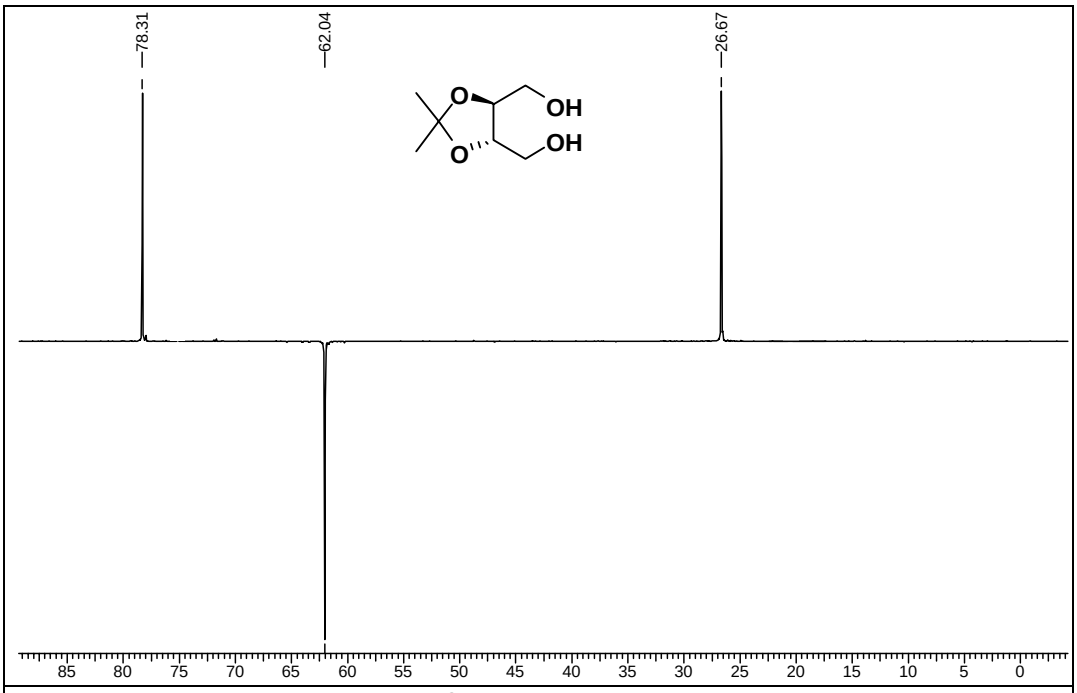
DEPT spectrum of compound 35 ($CDCl_3$, 50 MHz)



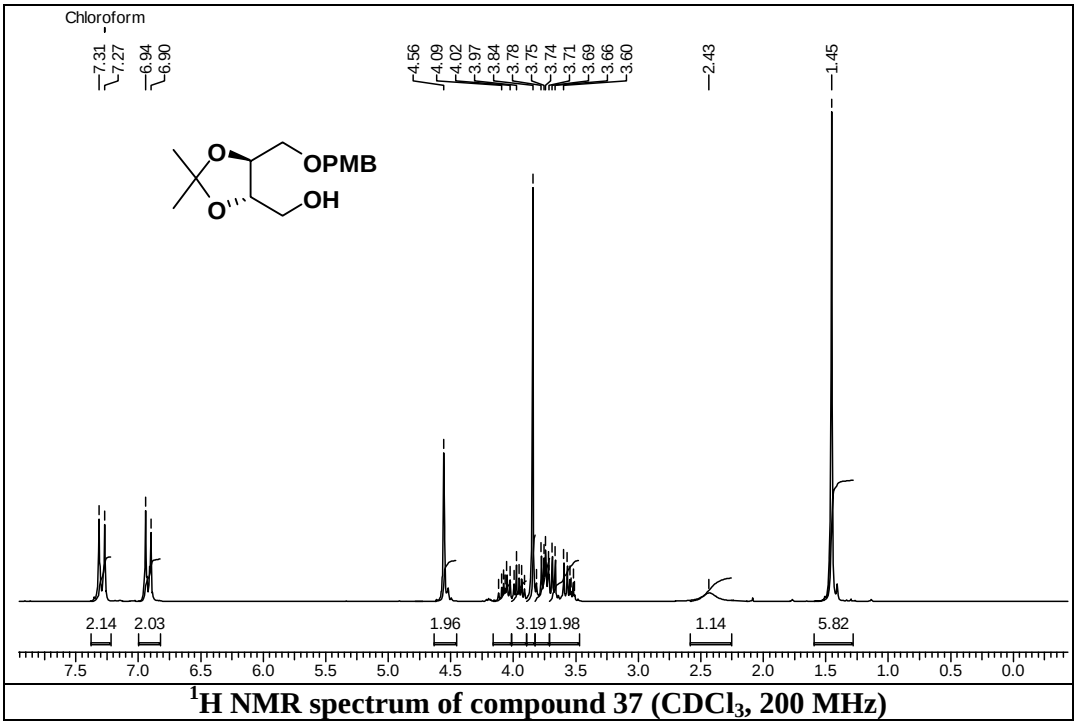
^{1}H NMR spectrum of compound 36 ($CDCl_3$, 200 MHz)



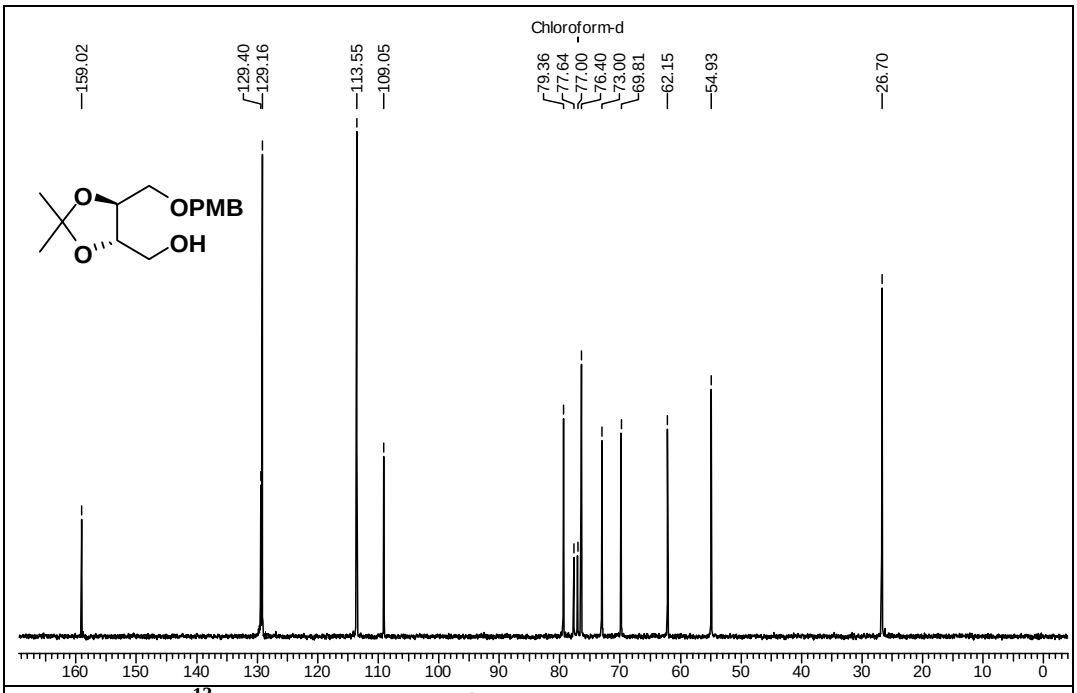
^{13}C NMR spectrum of compound 36 ($CDCl_3$, 50 MHz)



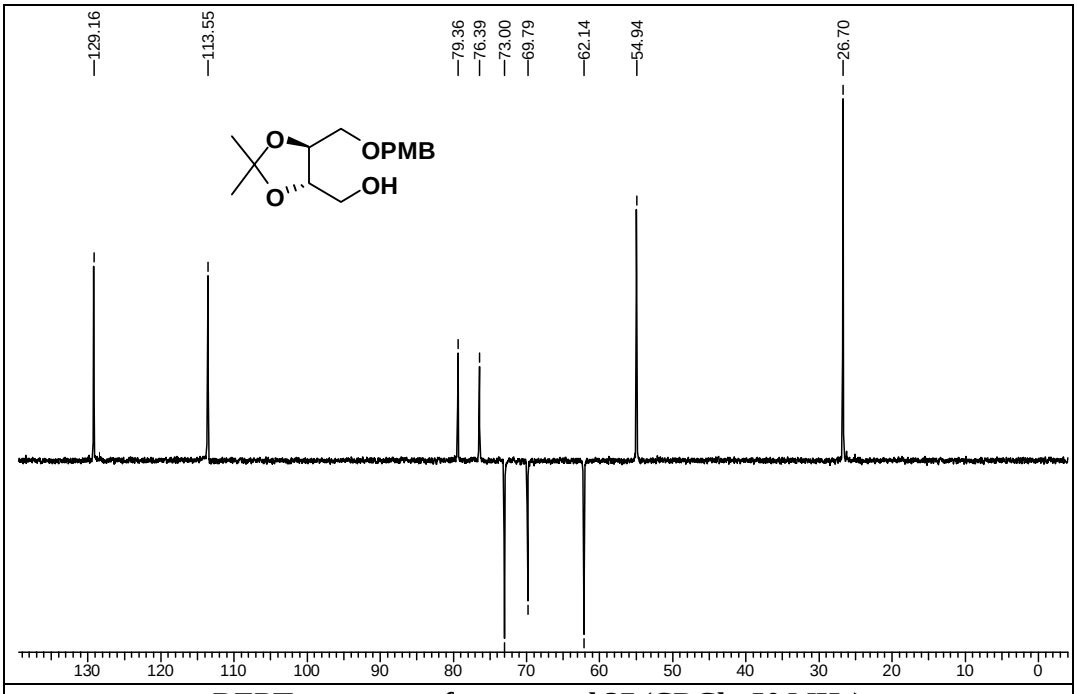
DEPT spectrum of compound 36 ($CDCl_3$, 50 MHz)



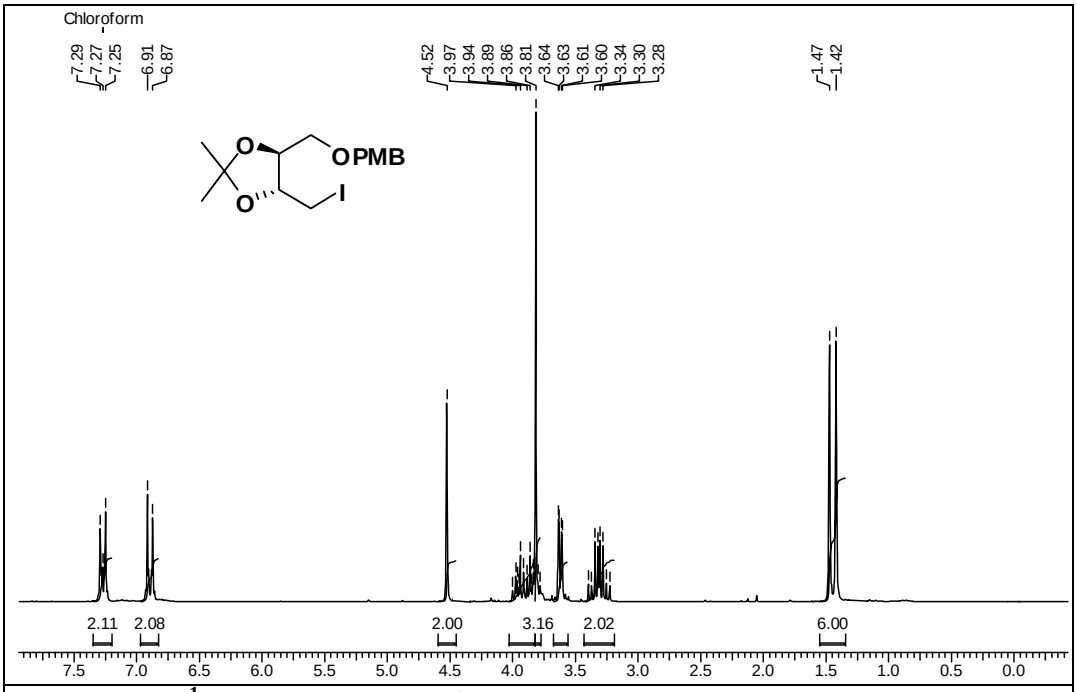
^{1}H NMR spectrum of compound 37 ($CDCl_3$, 200 MHz)



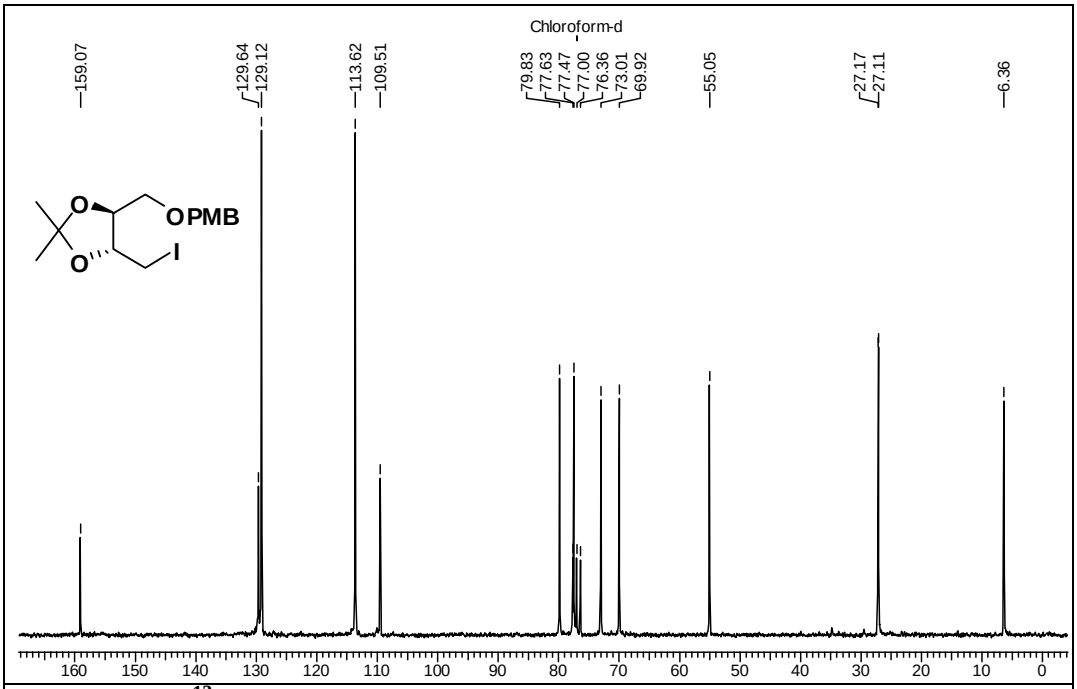
^{13}C NMR spectrum of compound 37 ($CDCl_3$, 50 MHz)



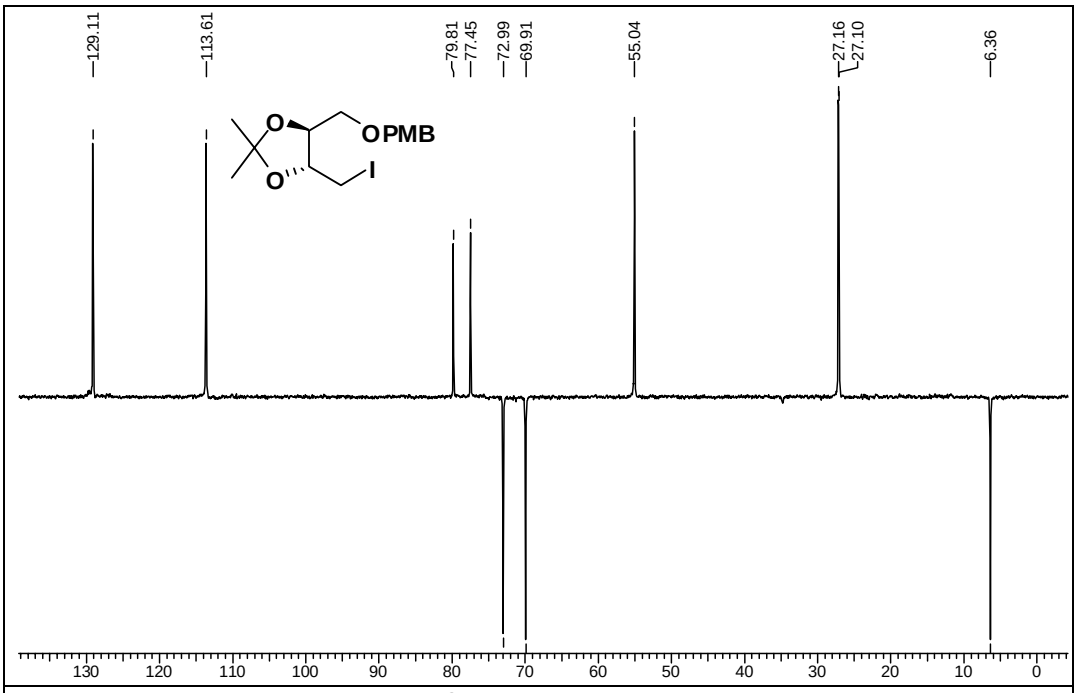
DEPT spectrum of compound 37 ($CDCl_3$, 50 MHz)



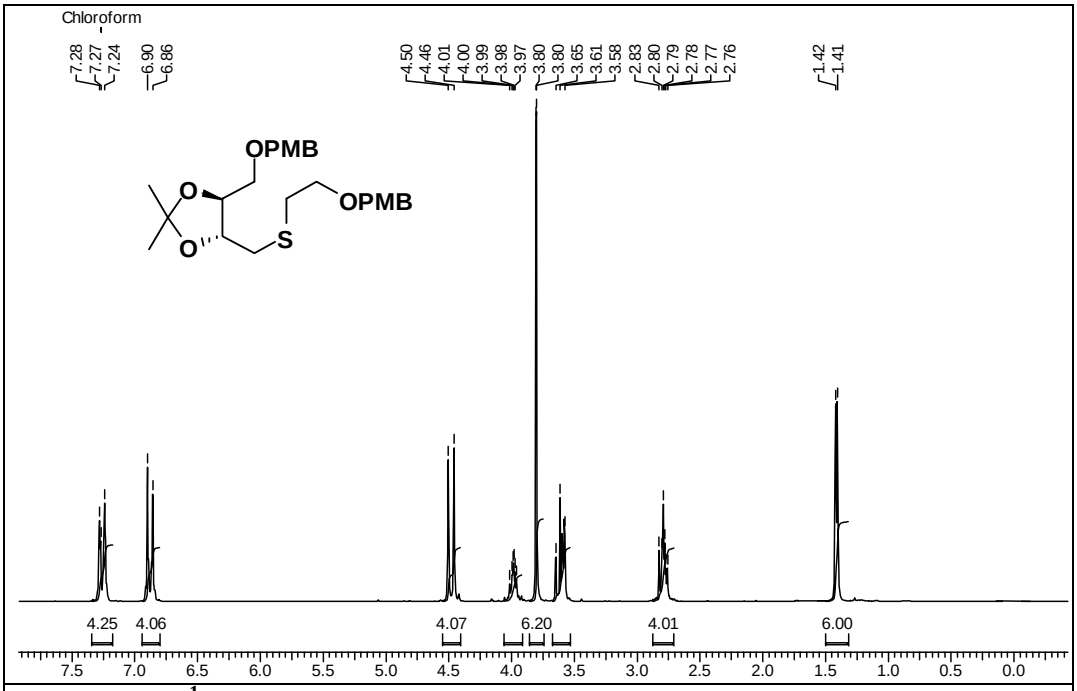
^{1}H NMR spectrum of compound 21 ($CDCl_3$, 200 MHz)



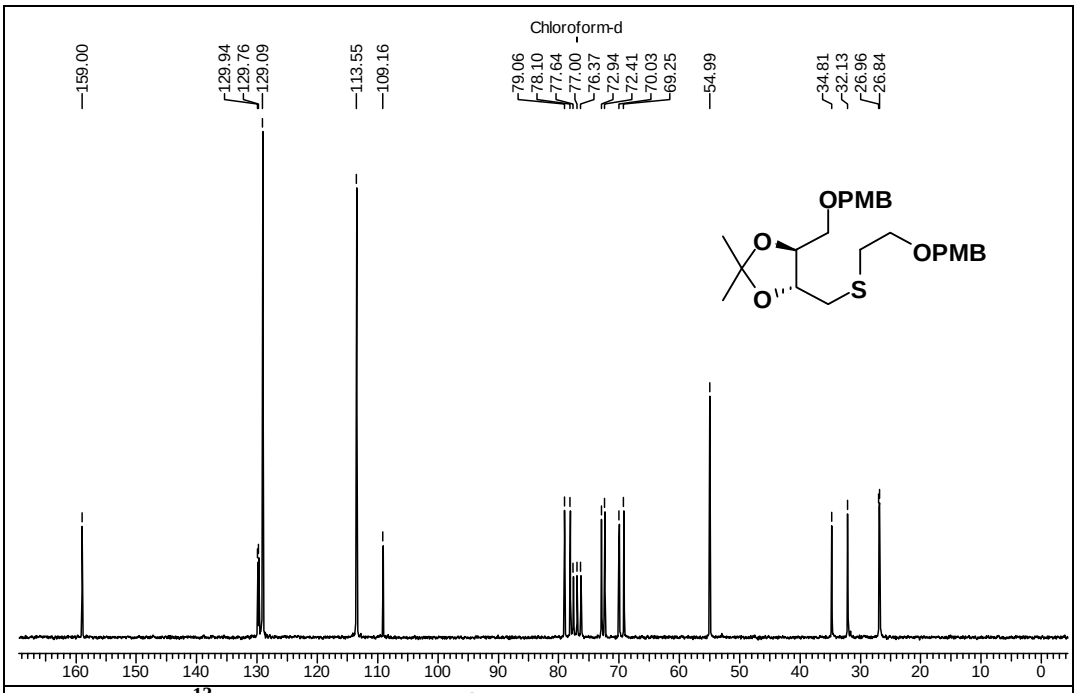
^{13}C NMR spectrum of compound 25 ($CDCl_3$, 50 MHz)



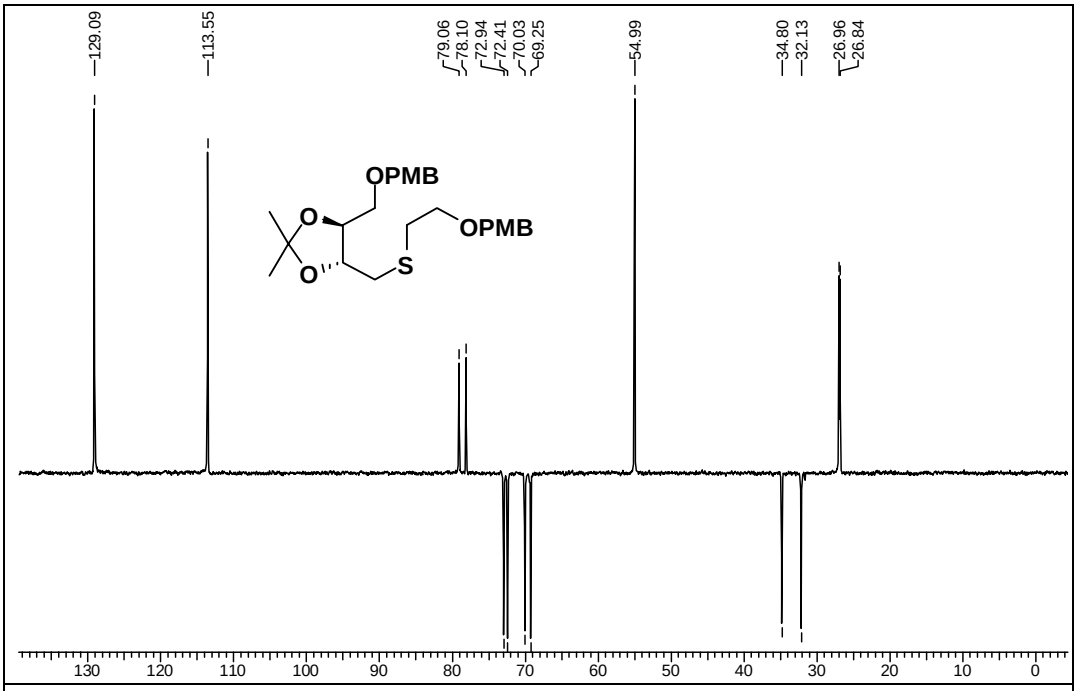
DEPT spectrum of compound 21 ($CDCl_3$, 50 MHz)



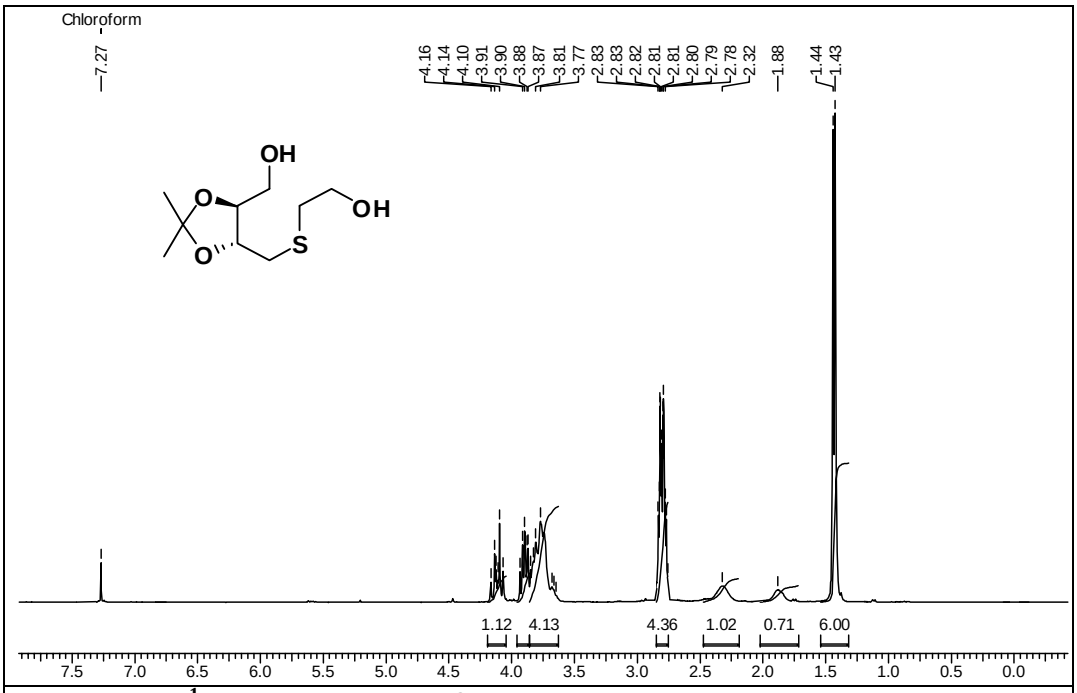
^{1}H NMR spectrum of compound 22 ($CDCl_3$, 200 MHz)



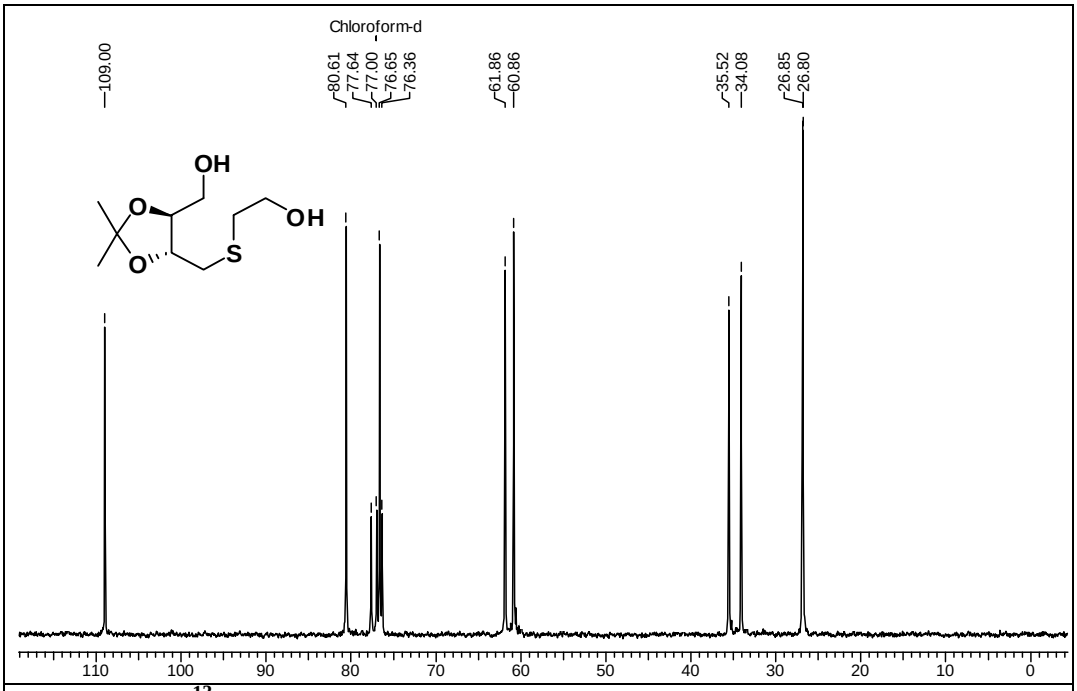
^{13}C NMR spectrum of compound 22 ($CDCl_3$, 50 MHz)



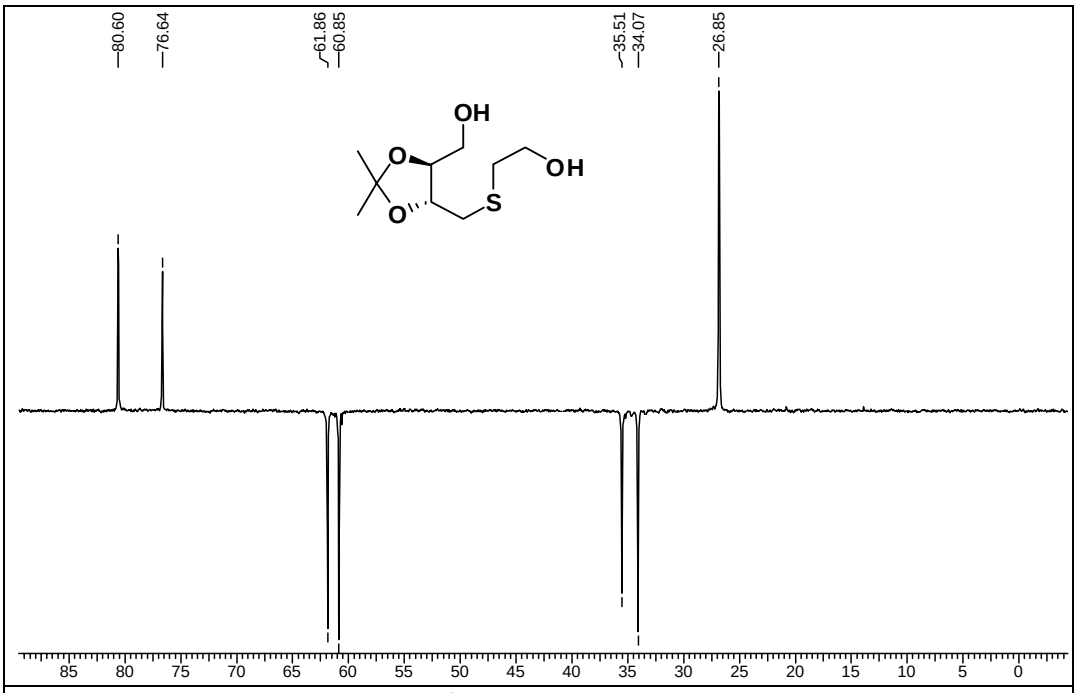
DEPT spectrum of compound 22 ($CDCl_3$, 50 MHz)



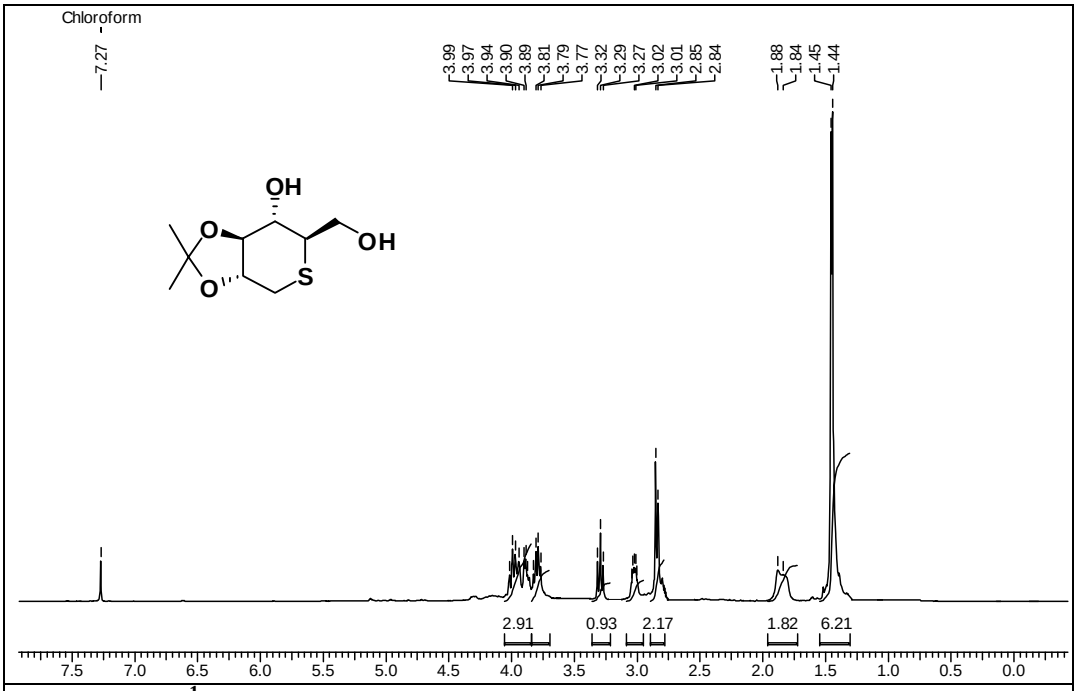
^{1}H NMR spectrum of compound 23 ($CDCl_3$, 200 MHz)



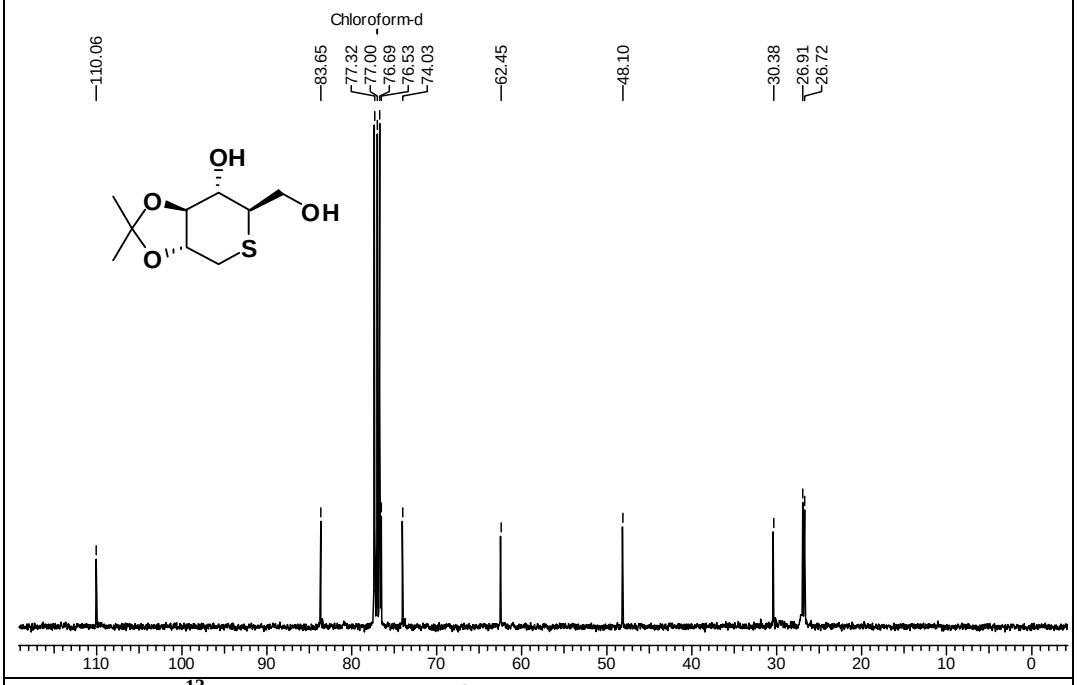
^{13}C NMR spectrum of compound 23 ($CDCl_3$, 50 MHz)



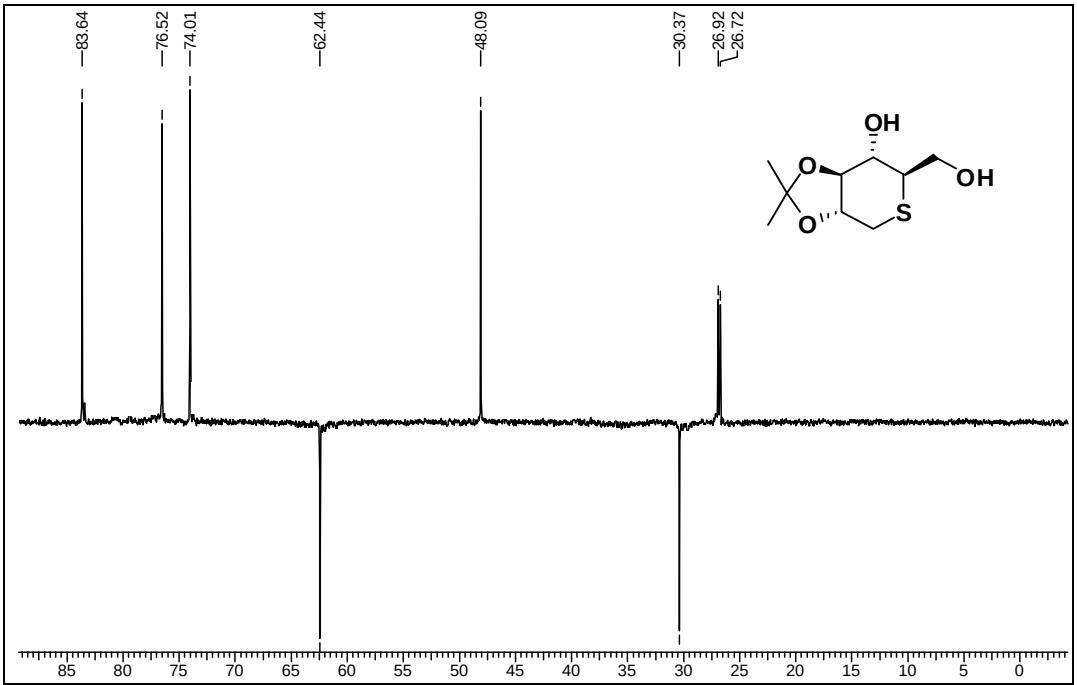
DEPT spectrum of compound 23 ($CDCl_3$, 50 MHz)



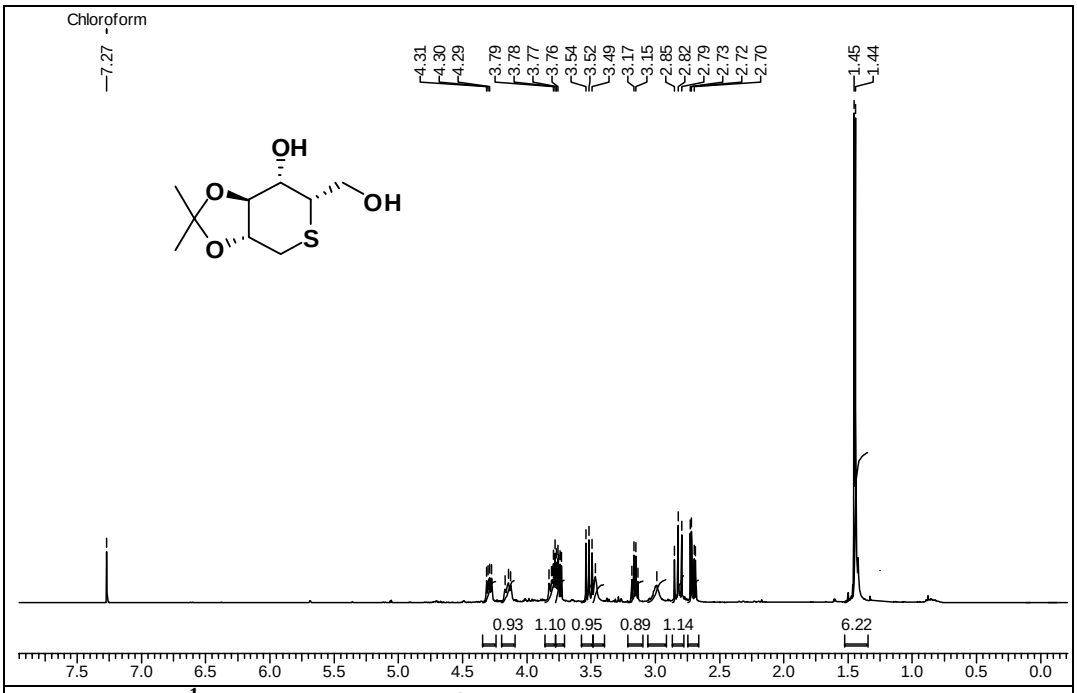
^{1}H NMR spectrum of compound 25 ($CDCl_3$, 400 MHz)



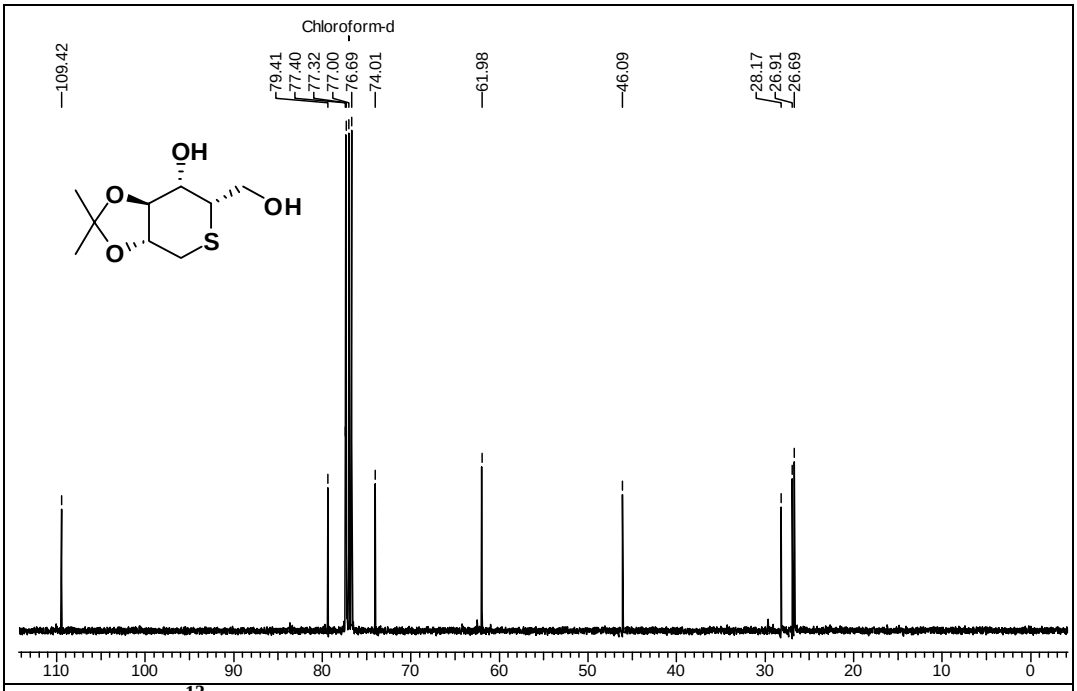
^{13}C NMR spectrum of compound 25 ($CDCl_3$, 100 MHz)



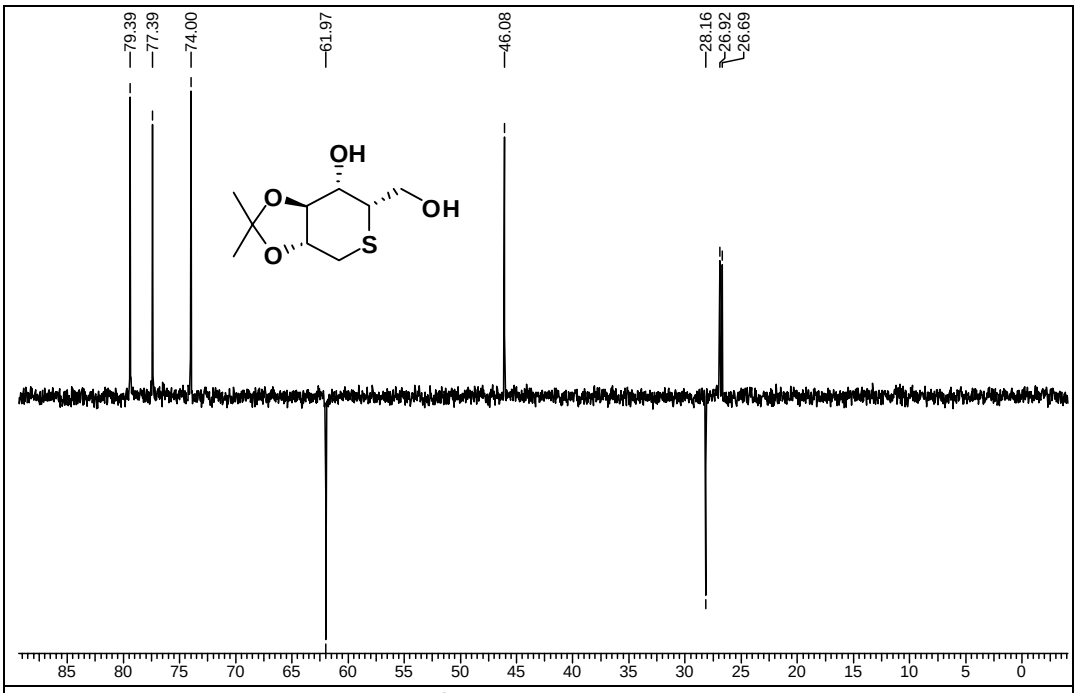
DEPT spectrum of compound 25 ($CDCl_3$, 100 MHz)



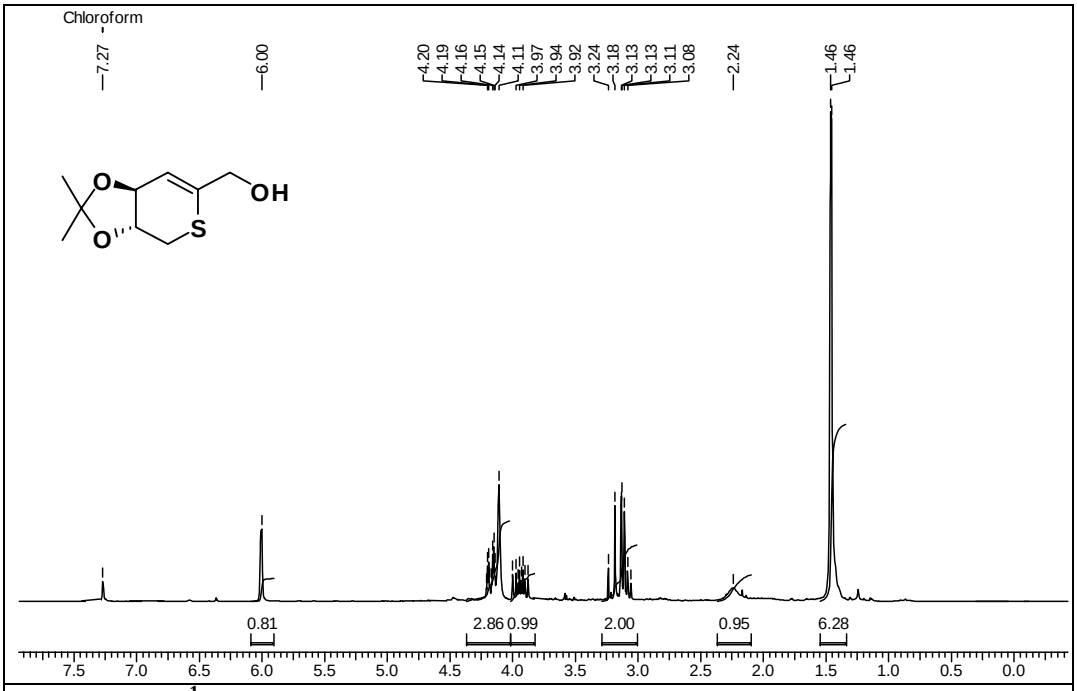
^{1}H NMR spectrum of compound 38 ($CDCl_3$, 400 MHz)



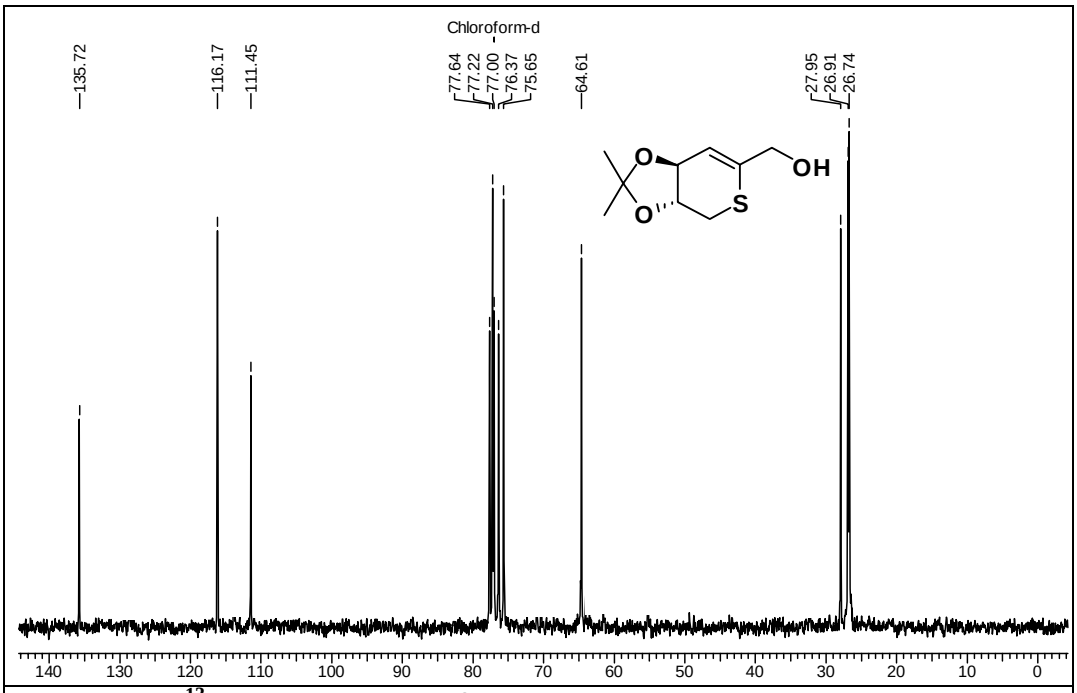
^{13}C NMR spectrum of compound 38 ($CDCl_3$, 100 MHz)



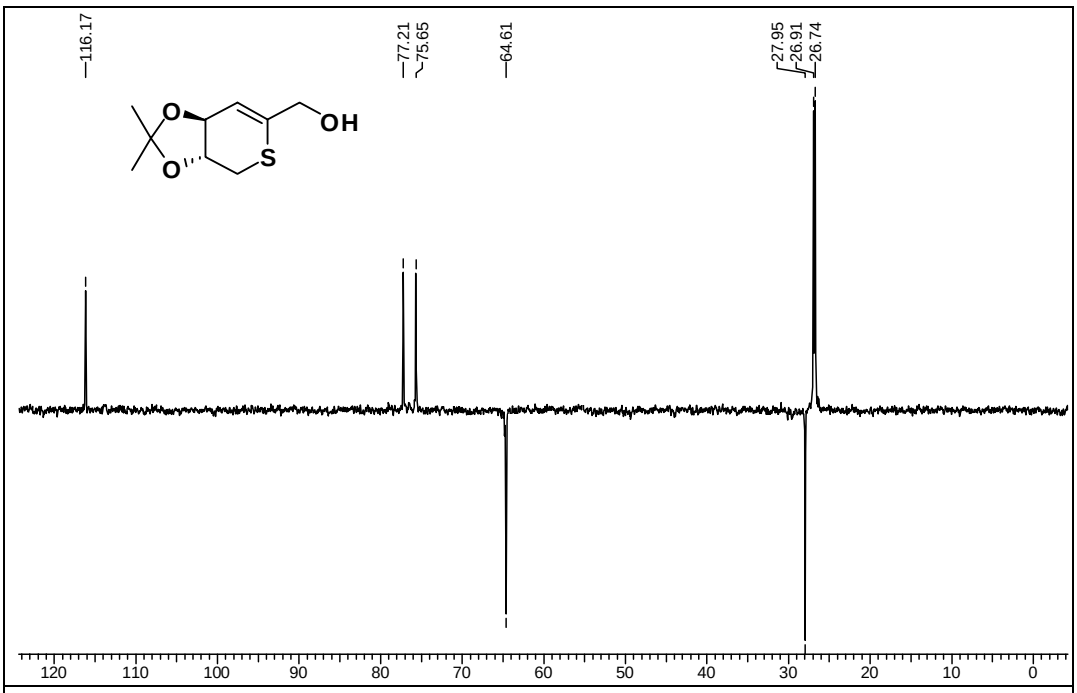
DEPT spectrum of compound 38 ($CDCl_3$, 100 MHz)



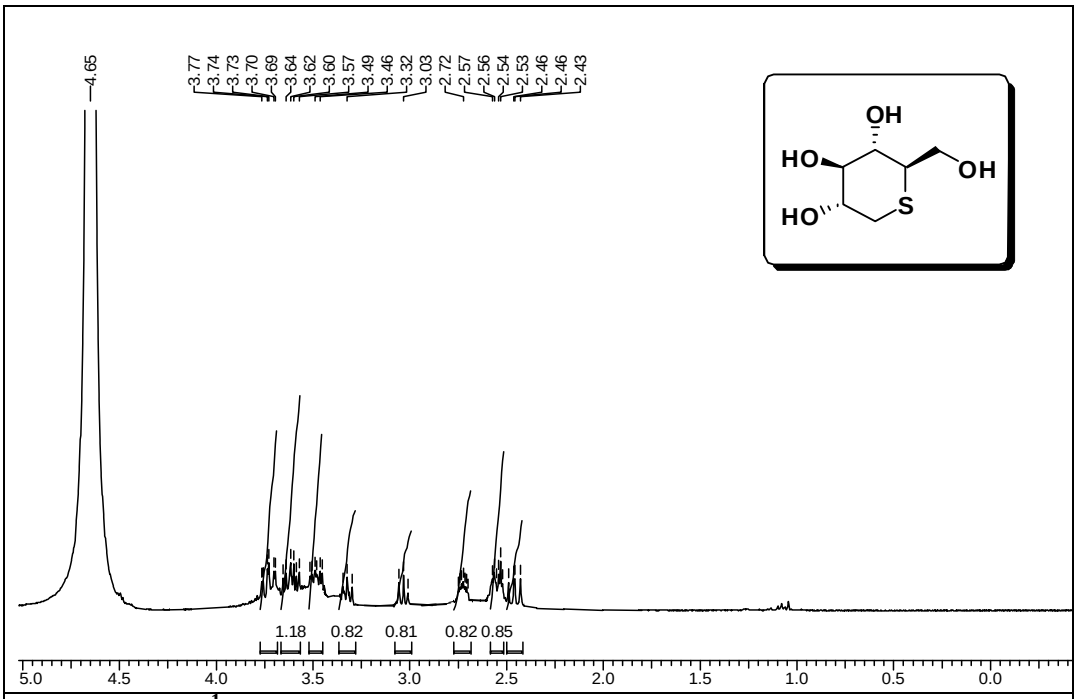
^{1}H NMR spectrum of compound 39 ($CDCl_3$, 400 MHz)



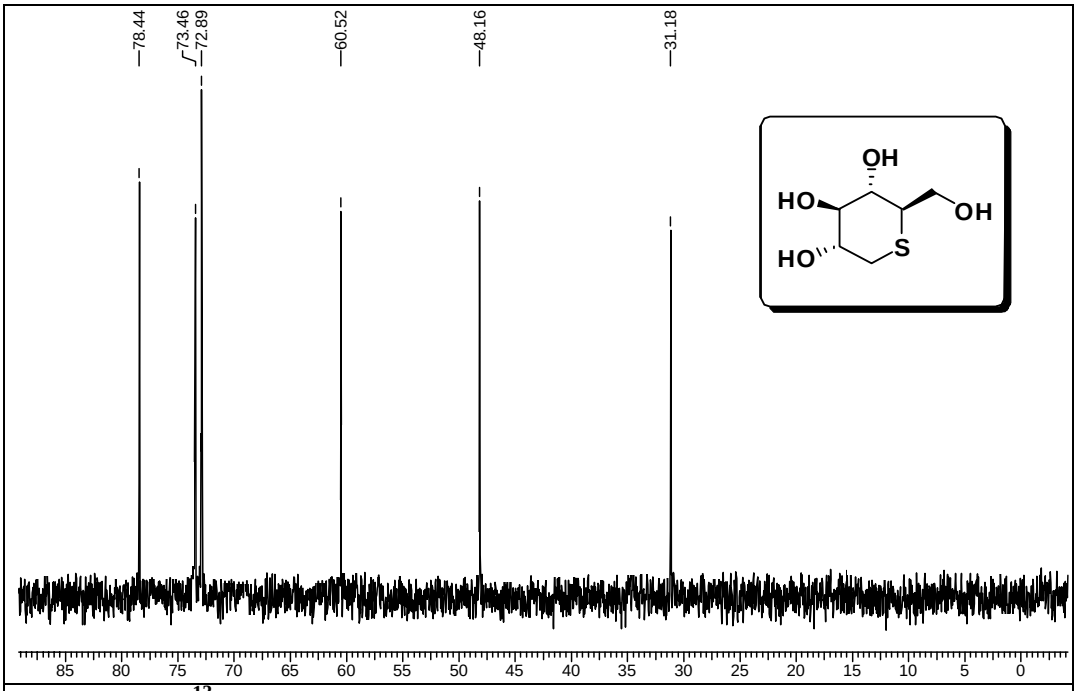
^{13}C NMR spectrum of compound 39 ($CDCl_3$, 100 MHz)



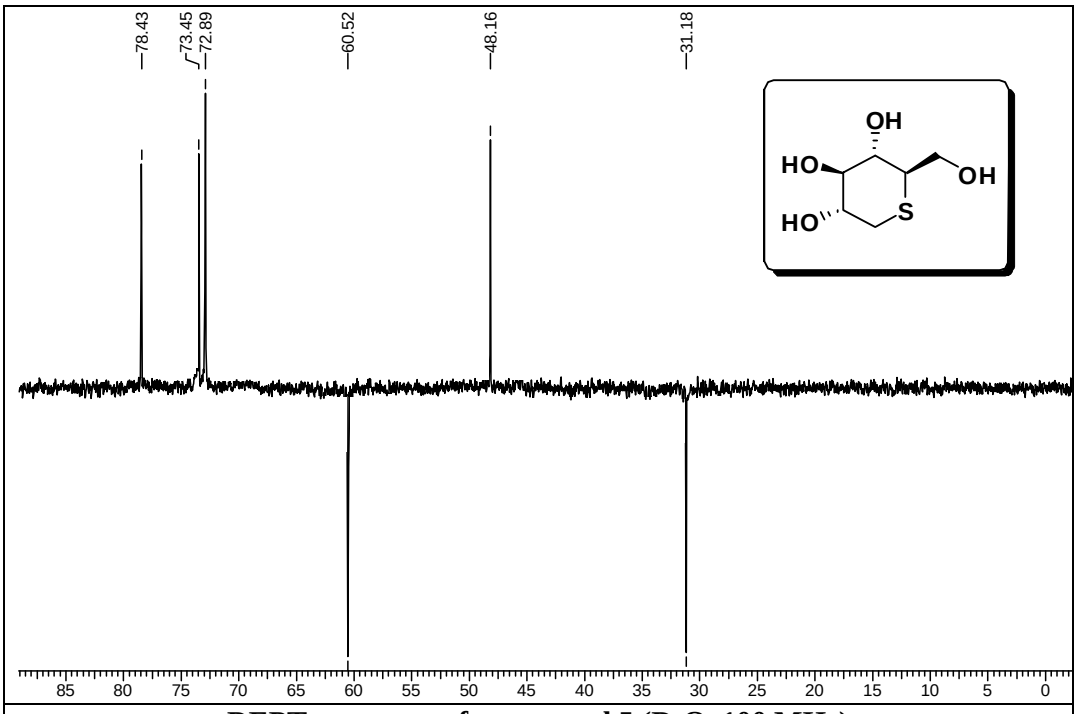
DEPT spectrum of compound 39 ($CDCl_3$, 100 MHz)



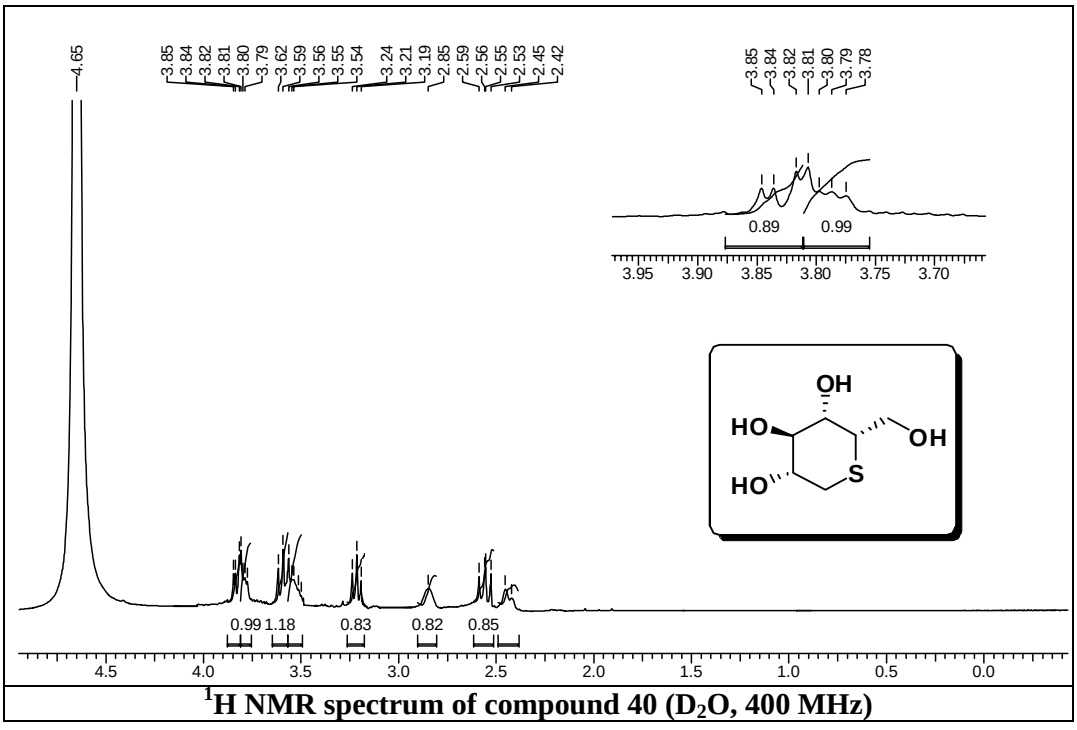
^{1}H NMR spectrum of compound 5 (D_2O, 400 MHz)



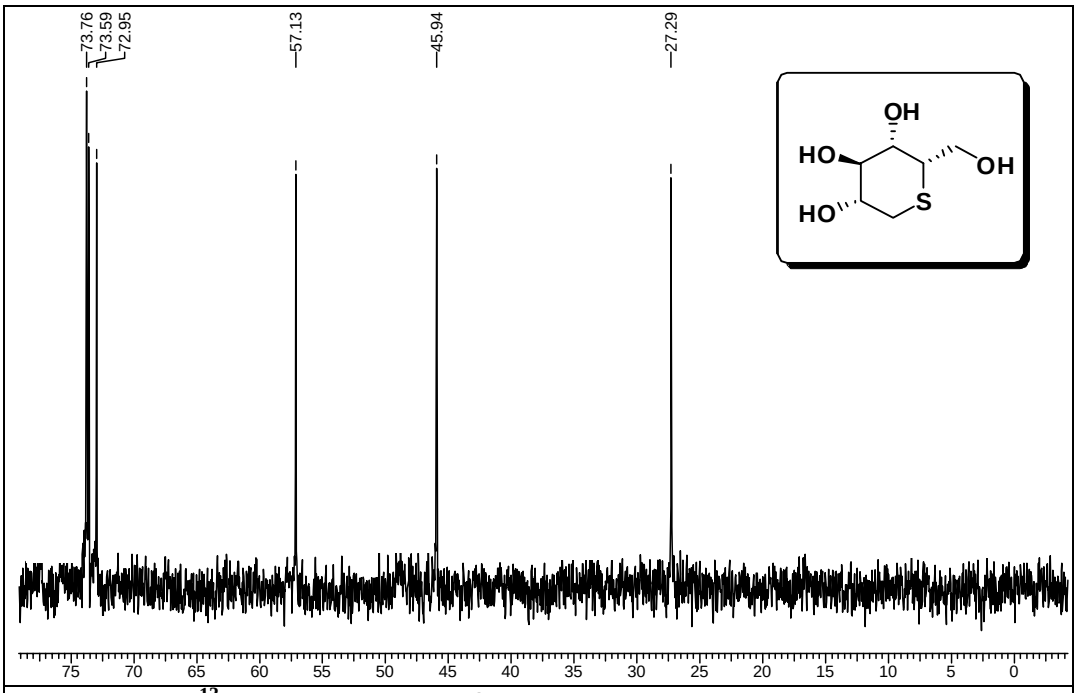
^{13}C NMR spectrum of compound 5 ($CDCl_3$, 100 MHz)



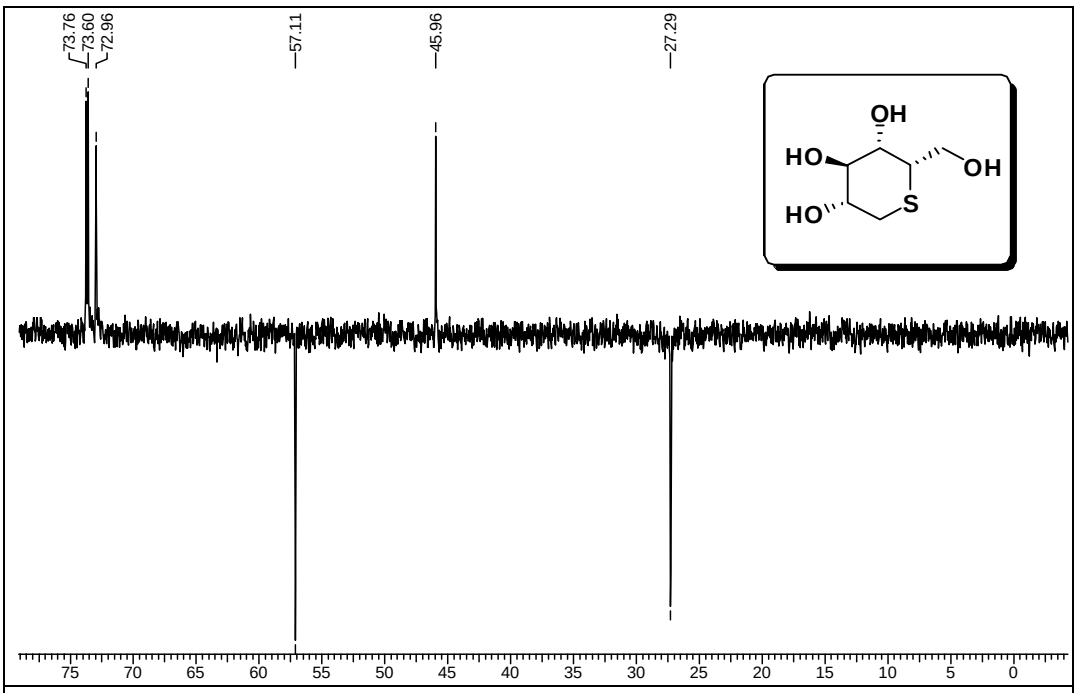
DEPT spectrum of compound 5 (D_2O, 100 MHz)



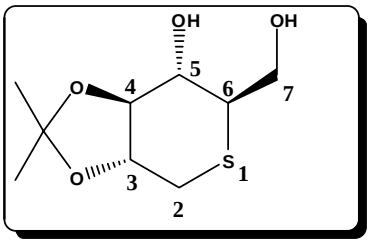
^{1}H NMR spectrum of compound 40 (D_2O, 400 MHz)



^{13}C NMR spectrum of compound 40 (D_2O, 100 MHz)



DEPT spectrum of compound 40 (D_2O, 100 MHz)



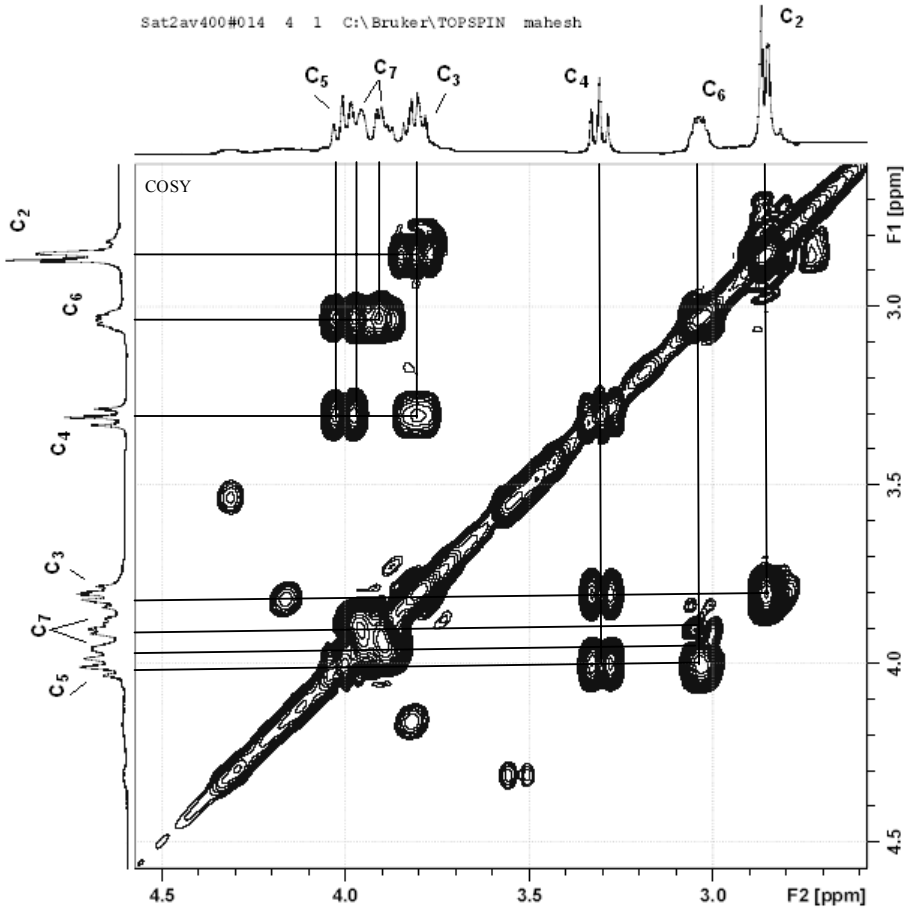
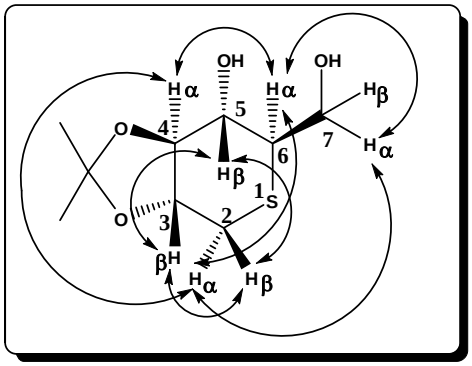


Figure 5. COSY spectrum of diastereomer **25**.



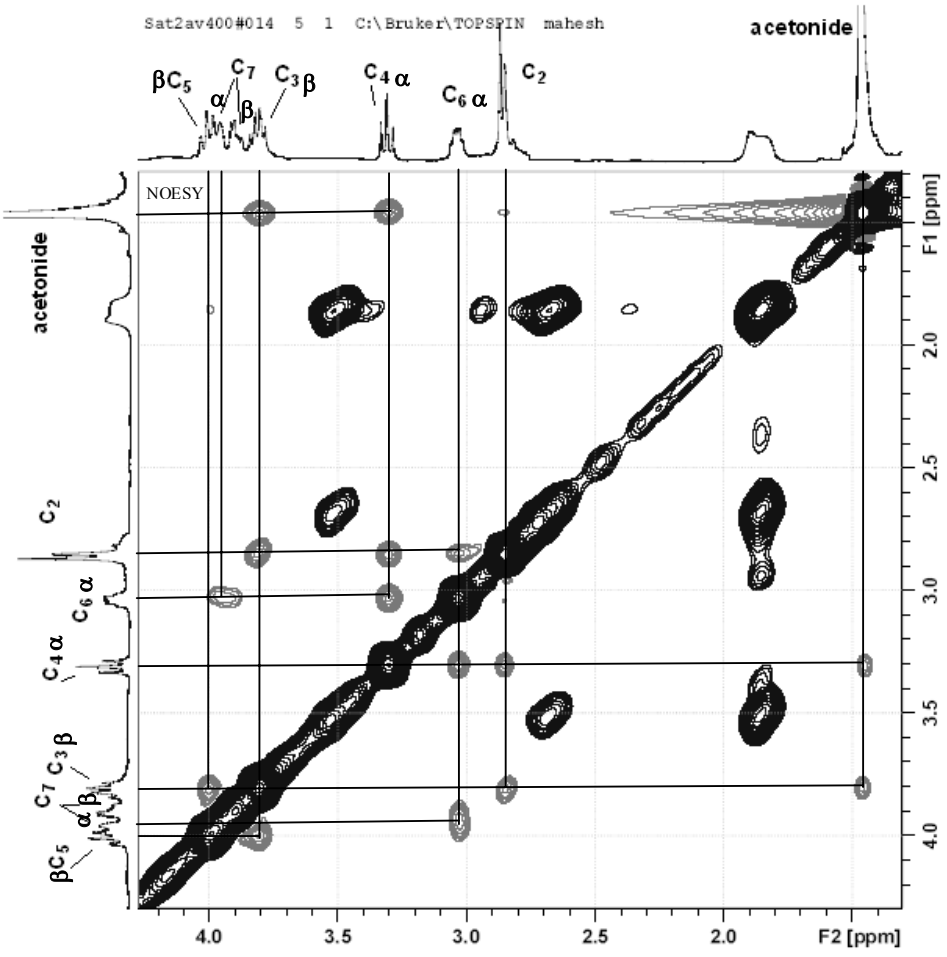
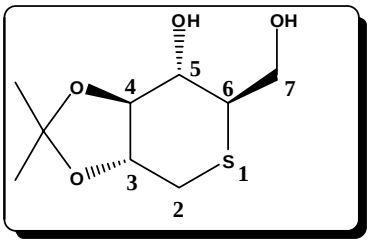


Figure 6. NOESY spectrum of diastereomer **25**.



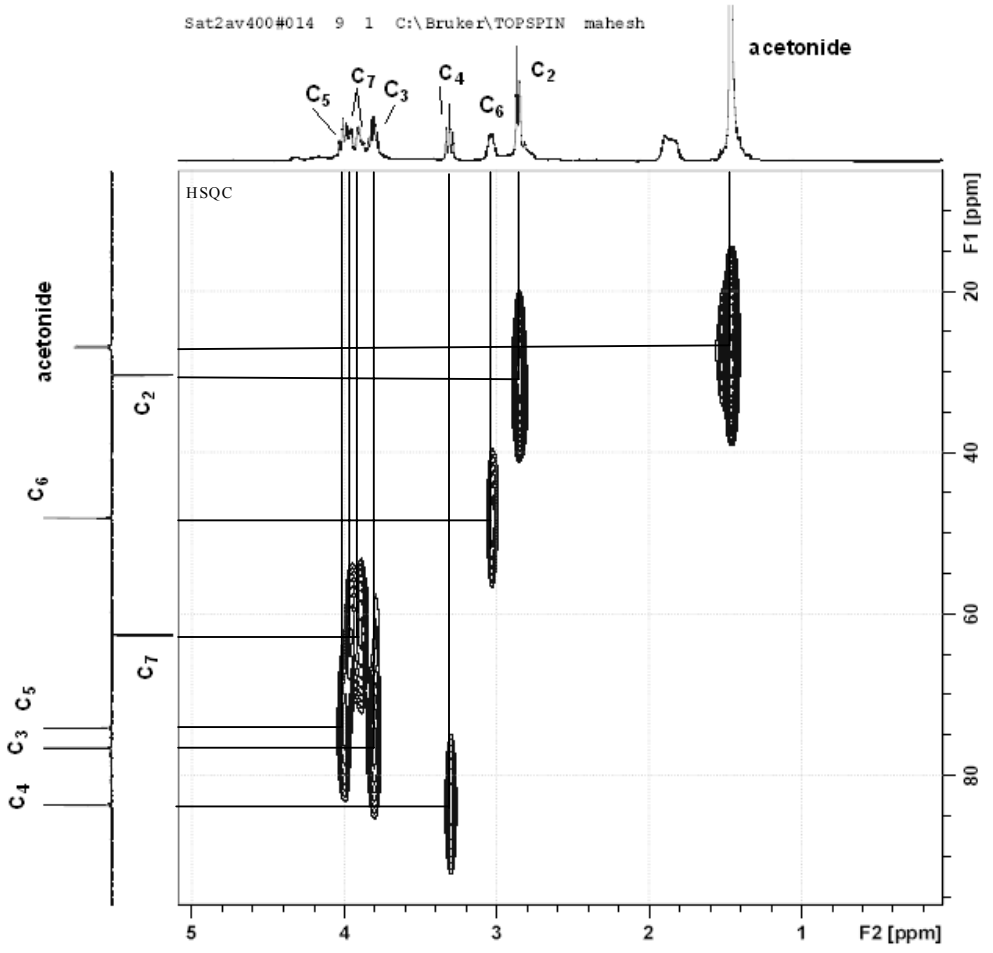
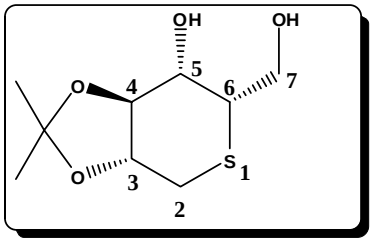


Figure7. HSQC spectrum of diastereomer **25**.



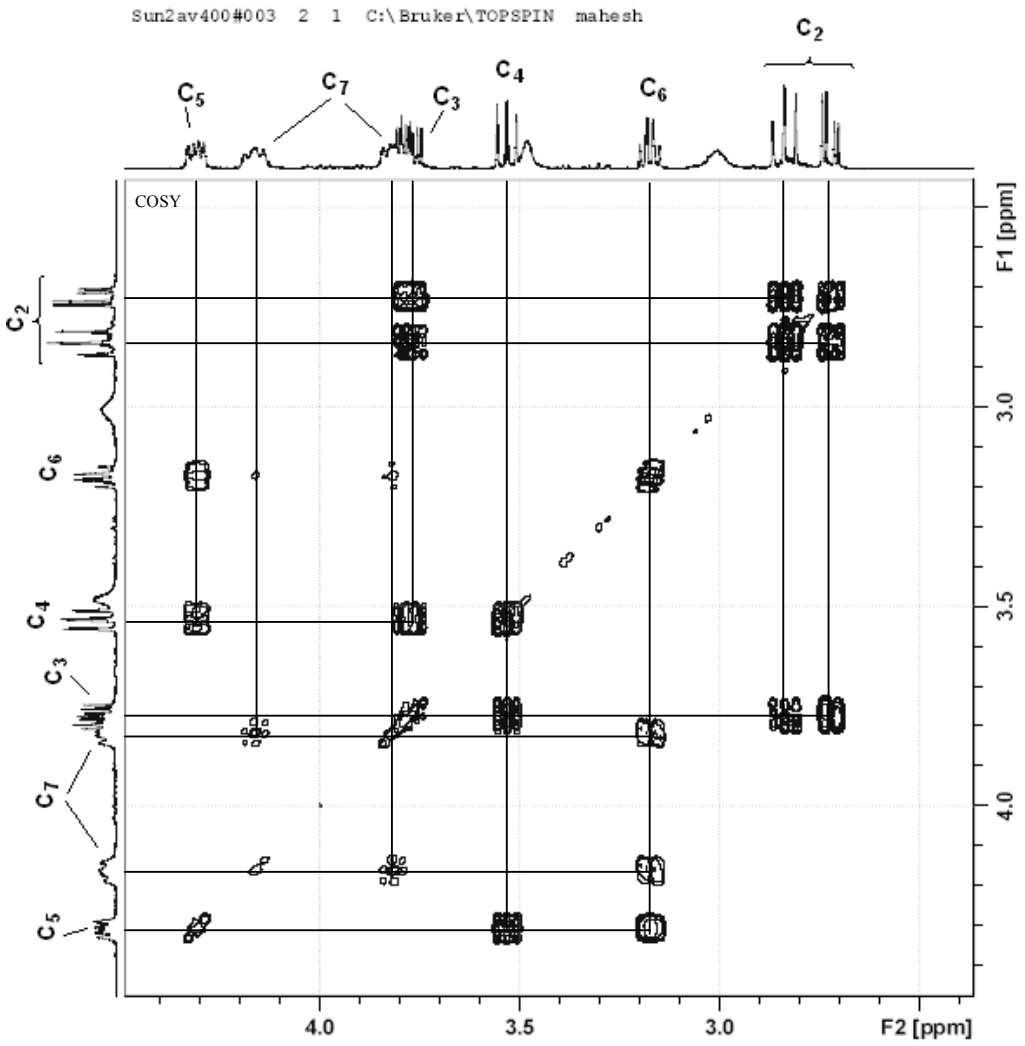
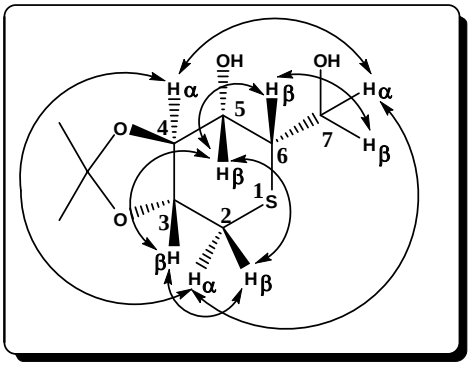


Figure 8. COSY spectrum of diastereomer **38**.



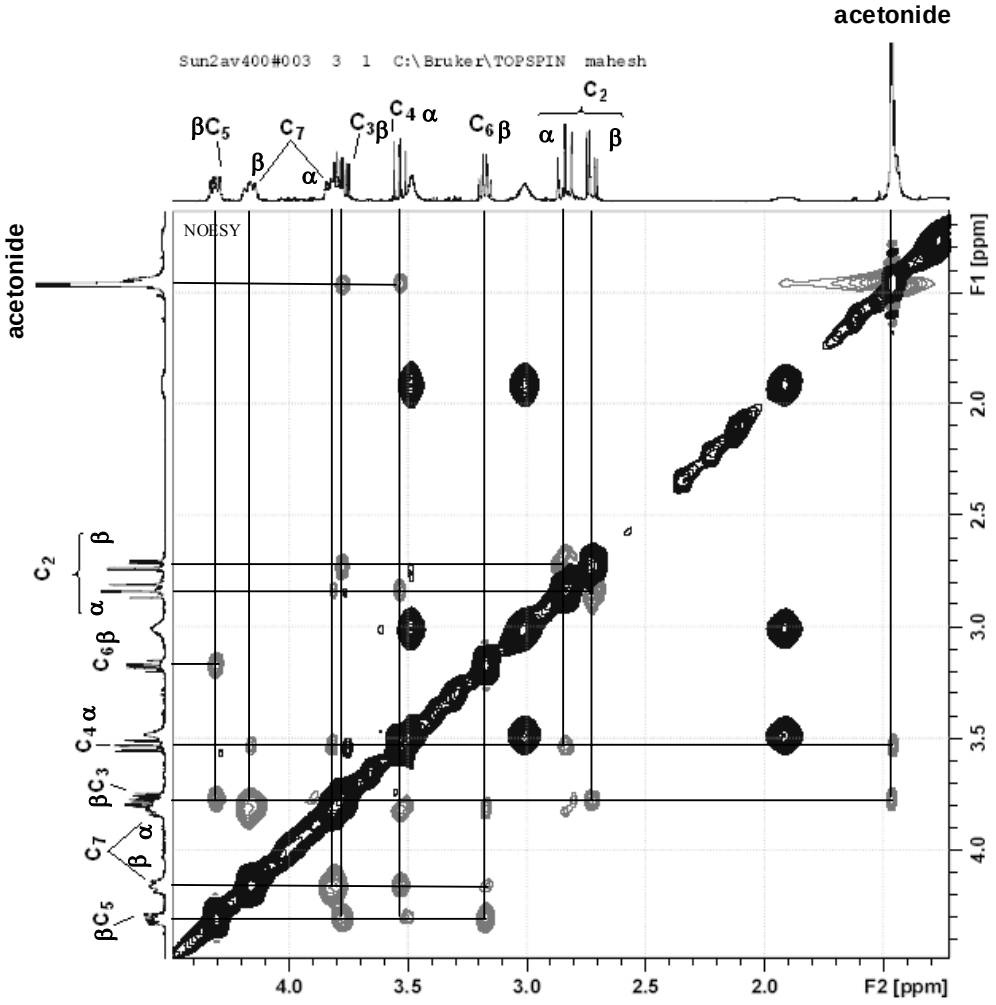
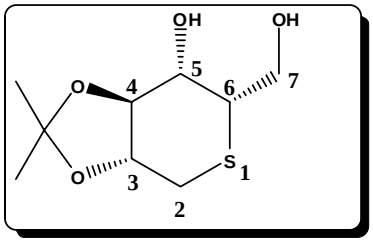


Figure 9. NOSEY spectrum of diastereomer **38**.



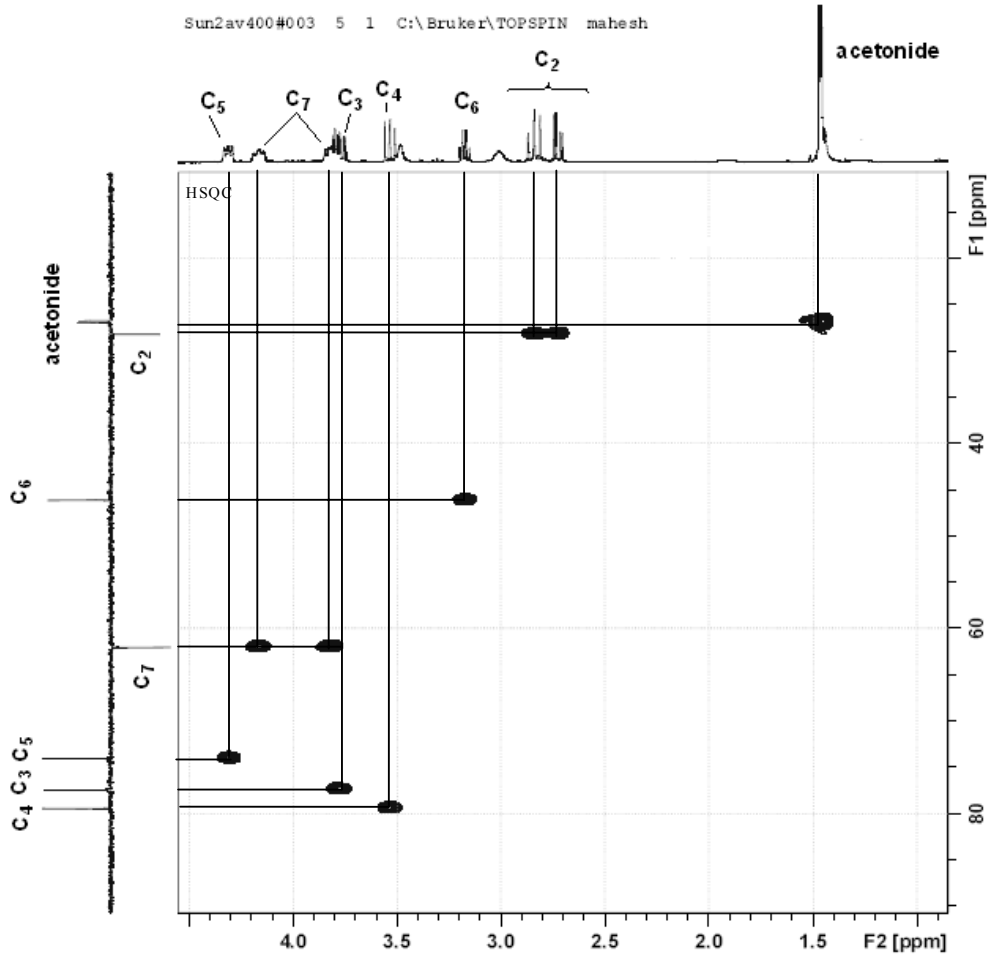


Figure10. HSQC spectrum of diastereomer **38**.

1.2.8 References

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24. In the oxidation reaction of diol **23** with IBX in EtOAc, the total consumption of diol **23** was confirmed by charring its TLC with *p*-anisaldehyde solution. The characteristic greenish spot of diol **23** [R_f = 0.20, Petroleum ether: EtOAc (3:7)] was totally disappeared which indicated the completion of reaction. But no spot was visualized for the dialdehyde **24** in the same TLC. Similar TLC dipped in 2,4-DNP solution in ethanol produced an orange colored characteristic spot of Schiff's base [R_f = 0.7, Petroleum ether: EtOAc (3:7)] on TLC which confirmed the formation of dialdehyde **24**.

Chapter 2

Synthetic studies towards 1,4-anhydro-4-thio-D-arabinitol and formal synthesis of Salacinol, Salaprinol and Neosalaprinol

Synthetic studies towards 1,4-anhydro-4-thio-D-arabinitol and formal synthesis of Salacinol, Salaprinol and Neosalaprinol

2.1 Introduction

After the isolation and discovery of conventional glycosidase inhibitor Nojirimycin from the fermentation broths of several strains of *Streptomyces* such as *S. roseochromogenes* R-468. *S. lavendulae* SF-425 and *S. nojiriensis n. sp.* SF-426 in the year 1967, several other glycosidase inhibitors have been isolated from wide range of plants and microbes species.[1] The diverse functionality of glycosidase enzymes significantly contribute in the biochemical processing of biopolymers containing carbohydrates.[2] An important class of these enzymes is responsible for the release of glucose from its higher oligomers or polymers and disruption in the function and regulation of these enzymes can escort to disease states such as diabetes. Managing the glucose levels in case of Type II noninsulin dependent diabetes (NIDD) is a critical job. However, postprandial blood glucose concentration can be lowered by delaying digestion of ingested carbohydrates which can help in the treatment of NIDD. The α-glucosidase enzymes mediate the hydrolysis of complex starches to oligosaccharides in the small intestine. Therefore α-glucosidase inhibitors were assumed to be powerful therapeutic agents in such carbohydrate metabolic disorders and diabetes as well. The inhibition of poly and oligosaccharides also help in the cure of postprandial hyperglycemia and hyperinsulinemia.

Carbohydrate analogue acarbose, an α-glucosidase inhibitor of microbial origin is an excellent example which is currently used for the oral treatment of diabetes.[3,4] The vital functions of glycosidases in the living systems are revealed by their role in modifying or blocking biological processes. Enzyme mediated carbohydrate hydrolysis is a prevalent biological process due to which glycosidase inhibitors have various potential applications in therapeutics and agrochemicals. They also efficiently contributed in the biosynthesis of the oligosaccharide chains and endoplasmic reticulum (ER) quality control mechanisms of the *N*-linked glycoprotein. The processes like quality control, maturation, transport, secretion of glycoprotein and cell-cell or cell-virus recognition can be intensively affected by the inhibition

glycosidase enzymes.[5] This principle is the basis for the potential use of glycosidase inhibitors for viral infection, cancer and genetic disorders.

In early 1990s, two potent α-glucosidase inhibitors Salacinol **1** and Kotalanol **2**, with an unique thiosugar sulfonium sulfate inner salt structure are isolated from roots, stems, and leaves of plants like *Salacia reticulata* ('kothala himbutu' in Singhalese), *Salacia oblonga*, and *Salacia chinensis* and traditionally used for the treatment of diabetes in Sri Lanka, India, and Thailand. The aqueous extracts of these plants have been traditionally used as the Ayurvedic Indian medicine in the treatment for non-insulin-dependent diabetes.[6] The α-glucosidase inhibitory activities of Salacinol **1** and Kotalanol **2** have been revealed to be as high as those of voglibose and acarbose, which are extensively used in the treatment of diabetes these days.[6a-b]

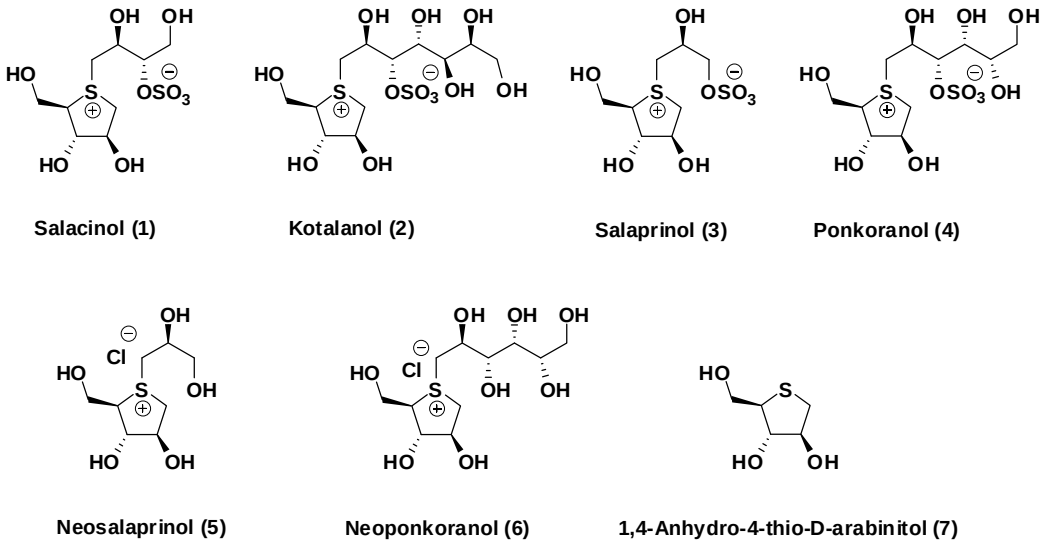


Figure 1. Some notable sulfated natural 4-thiosugars and 1,4-anhydro-4-thio-D-arabinitol.

Salacinol **1** has colorless prisms crystals in pure form with an optical rotation $[\alpha]_D^{28}$ +4.9 (c = 0.35, MeOH).[6b] In the infra red spectrum of Salacinol, the absorption bands at 3417, 1073, 1019 cm^{-1} showed the presence of hydroxyl functionality whereas 1262, 1238, 801 cm^{-1} indicated a sulfate group. The high resolution FAB-MS and SIMS analysis of Salacinol showed $C_9H_{18}O_9S_2$ as it molecular formula and NMR spectral data confirmed the assigned structure of Salacinol. Salacinol **1** is composed of two fragments 1-deoxy-4-thiopentafuranose (1-5-C) and 1-deoxyhexitol-3-sulfate

moieties (1'-4' C). The sulfonium moiety connection was confirmed by HMBC studies while its stereochemistry was elucidated by X-ray crystallographic studies of Salacinol **1**.[6b]

Recently, four more novel thiosugar derivatives, namely Salaprinol **3,** Ponkoranol **4** and Neosalaprinol **5**, Neoponkoranol **6** are also isolated separately from extract of roots and stems of the Indian plants *Salacia prinoides* and *Salacia chinensis* respectively which are also used as an Ayurvedic Indian medicine for the treatment of diabetes.[7]

The general structure of this class of thiosugars constitutes a 1,4-anhydro-4-thio-D-arabinitol (D-ATA) **7** core and a polyhydroxylated acyclic side chain. In all these thiosugars isolated so far, the core part (D-ATA) **7** is retained, and the length of the polyhydroxylated acyclic side chain differed. The absolute stereochemistry for kotalanol **2**, Salaprinol **3** and Ponkoranol **4** were not determined at the time of their isolation from the respective *Salacia* species whereas the reported stereochemistry for Salacinol **1** at the time of its isolation was corrected and assigned explicitly by its total synthesis.[8,6b]

All these thiosugars exist in zwitterionic structural form, where sulfonium cation is stabilized by sulfate anion. The incremental positive charge formed at both the ring oxygen and the anomeric carbon of the glycoside during hydrolysis in the active site of a glycosidase was assumed to impersonate permanently by the sulfonium cation consequently blocking glycosidase activity on the glycoside. The unique sulfonium–sulfate inner salt structure and their potential in the treatment of type-II (NIDD) diabetes made this class of thiosugars an attractive target.[6-8]

2.2 Inhibitory activities of thiosugars isolated from *Salacia* species

The inhibitory activities of five isolated thiosugars Salacinol, Kotalanol, Salaprinol, Neosalaprinol and Ponkoranol were tested for rat small intestinal α-glucosidases in vitro and compared with clinically used antidiabetics Voglibose and Acarbose (Table 1). Maltase and Isomaltase were more efficiently inhibited by Salacinol **1** than Kotalanol **2** and Salaprinol **3** while Kotalanol **2** exhibited potential inhibition of sucrase. The two newly isolated thiosugar Ponkoranol **4** and Neoponkoranol **6** showed potent inhibitory activity against three enzymes tested, whereas Neosalaprinol **5** inhibited both sucrase and Isomaltase more effectively than its sulfate counterpart

Salaprinol **3**. The Ponkoranol series thiosugars **4** and **6** showed potent inhibitory activities irrespective of existence of the sulfate moiety within the molecule and observed them as the most potent inhibitors in this class of thiosugars isolated from *Salacia* species till date.[7b]

Table 1. IC50 Values (μM) of thiosugar sulfonium salts and related compounds against disaccharidases

Compound	Maltase	Sucrase	Isomaltase
Salacinol **1**	5.2[a]	1.6[a]/1.5[b]	1.3[a]/1.5[b]
Kotalanol **2**	7.2[a]	0.75[a]	5.7[a]
Salaprinol **3**	>329 (23)[c]	>329(42)[c]	15
Ponkoranol **4**	3.2[a]	0.29[a]	2.6[a]
Neosalaprinol **5**	>384(35)[c]	90	6.5
Neoponkoranol **6**	5.1	1.0	1.4
Voglibose	1.2[a]	0.2[a]	2.1[a]
Acarbose	2.01	1.7[a]	155[a]

[a] Ref. 9.
[b] Inhibitory activities of **1** against Sucrase and Isomaltase were re-examined in this study as references.
[c] Values in parentheses indicate inhibition (%) at the corresponding concentrations (μM).

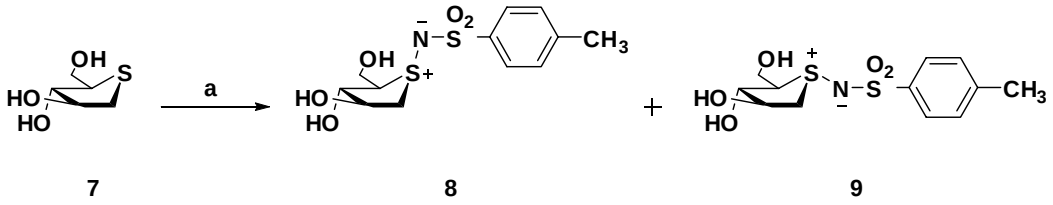
The inhibitory activities of all isolated *Salacia* species thiosugars (**1-6**) against the maltase, sucrase and isomaltase were either nearly equal or much more potent than those of clinically used antidiabetics Voglibose and Acarbose (Table 1). Consequently, all isolated *Salacia* species thiosugars (**1-6**) are potent glucosidase inhibitors and liable component of traditional Ayurvedic medicine used in the treatment of diabetes.

2.3 Literature review for 1,4-anhydro-4-thio-D-arabinitol, Salacinol, Salaprinol and Neosalaprinol

The literature reports for the synthesis of 1,4-anhydro-4-thio-D-arabinitol, Salacinol, Salaprinol and Neosalaprinol are discussed below.

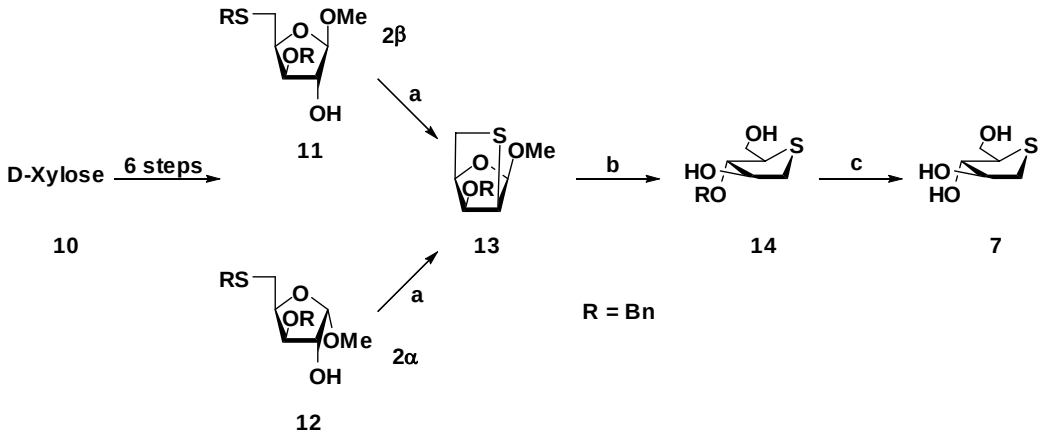
2.3.1 Yuasa and coworkers approach towards 1,4-anhydro-4-thio-D-arabinitol (D-ATA) and Salacinol [6d,8a]

Before the isolation of Salacinol **1**, a new class of glucosidase inhibitors, thiacyclopentane derivatives **8** and **9** with trivalent sulfur atom were synthesized by Yuasa and coworkers.[6d] This type of thiacyclopentane derivatives were synthesized as sulfimide derivatives of (D-ATA) **7** which have exhibited weak inhibitory activity towards *β*-glucosidase (Scheme 1).



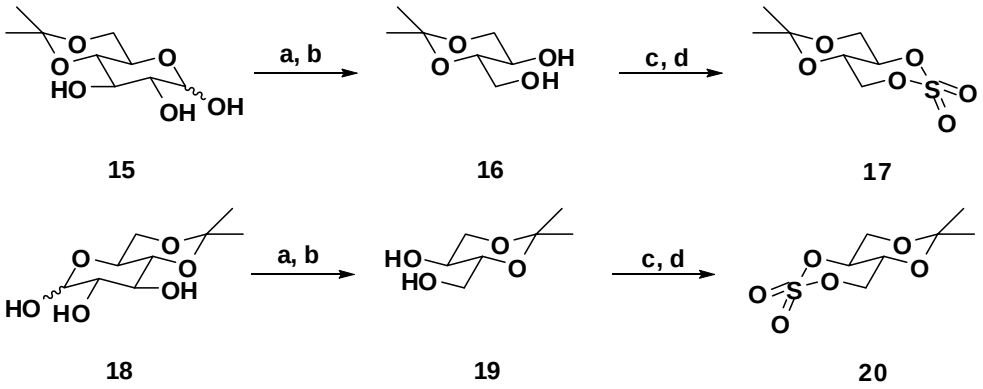
Scheme 1. *Reagents and conditions: a) Chloramine T, 14% for 1S and 53% for 1R.*

The synthesis of (D-ATA) **7** was achieved in 10 steps by using D-xylose **10** as a starting material (Scheme 2).[6d] D-xylose **10** after 6 consecutive chemical trasformations gave two derivatives 3,5-di-*O*-benzyl-5-thio-*α* **11** and *β*-D-xylofuranoside **12** (2*β* and 2*α*) which were further on treatment with triphenylphosphine, iodine and imidazole (Appel reaction conditions) at 110 ^{o}C underwent iodination of free hydroxyl followed by intramolecular cyclization between 5-S and C-2 to offer exclusively compound **13** with *β*-configuration at anomeric carbon in 57% from **11** (2*β*) and 21% from **12 (**2*α*). The compound **13**, on simultaneous hydrolysis and *in situ* reduction with Na(CN)BH_3 in aqueous acetic acid afforded **14** which was further deprotected under Birch reaction condition to give 1,4-anhydro-4-thio-D-arabinitol **7** in 97% yield. This is the first synthetic route reported in the literature for the synthesis of (D-ATA) **7**.

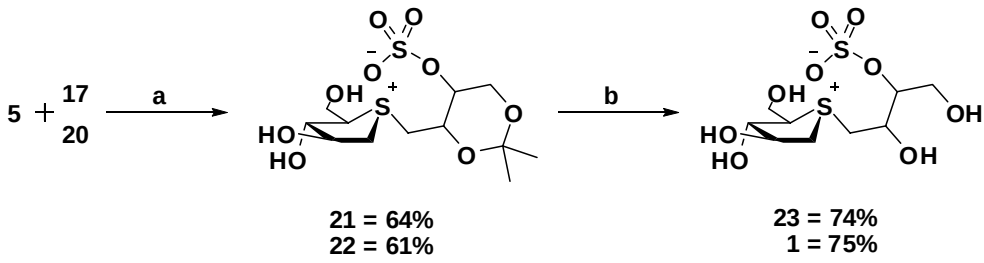


Scheme 2. *Reagents and conditions: a) PPh_3, I_2, Imidazole, 110 ºC, 57% from 2β and 21% from 2α ; b) Na(CN)BH_3, 90% AcOH, 40 ºC, 71%; c) Na/ liq. NH_3, 97%.*

The similar group, Yuasa and coworkers reported the first total synthesis of Salacinol **1** and its diastereoisomer in the year 2000.[8a] The tethering arm of Salacinol **1** is a derivative of erythritol. Depending on the protecting groups for the hydroxyl groups, the cyclic sulfate precursor was derived from either D or L glucose. The periodate oxidation of 4,6-*O*-isopropylidene-D **15** or L-glucose **18** followed by $NaBH_4$ reduction of the resulting aldehyde afforded 2,4 or 1,3-*O*-isopropylidine erythritol **16** (82%) or **19** (62%) respectively. The compounds **16** or **19** were further treated with thionyl chloride in presence of triethyl amine followed by oxidation with catalytic $RuCl_3$ in the presence of $NaIO_4$ to deliver the cyclic sulfates **17** (79%) or **20** (70%) respectively (Scheme 3). Further (D-ATA) **7** was coupled with cyclic sulfate **17** or **20** in solvent DMF at 45 ^oC to give coupling products **21** (64%) and **22** (61%). The coupling products **21** and **22** on treatment with 0.01% HCl at 40 ^oC underwent acetonide cleavage to furnish Salacinol **1** (74%) and its diastereomer **23** (75%) respectively (Scheme 4).



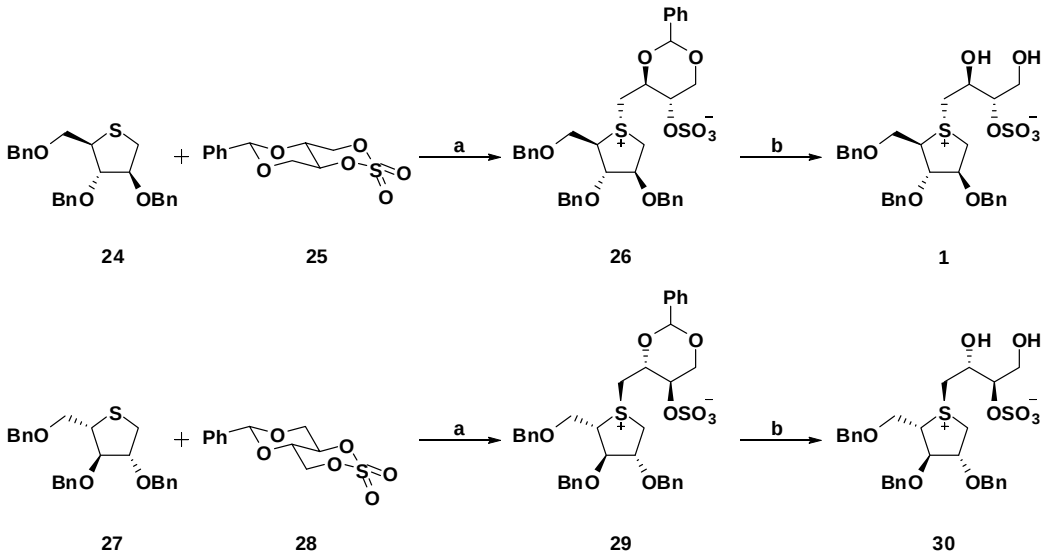
Scheme 3. *Reagents and conditions: a) $NaIO_4$ (2 equiv.), $NaHCO_3$, H_2O, bromocresol green, 5 h; b) $NaBH_4$, CH_3OH, 10 min; c) $SOCl_2$ (1.2 equiv.), TEA (2.5 equiv.), CH_2Cl_2, 0 °C, 10 min; d) $RuCl_3$ (cat.), $NaIO_4$ (2 equiv.), CH_3CN, CCl_4, H_2O, 30 min.*



Scheme 4. *Reagents and conditions: a) DMF, 45 °C, 13 h; b) 0.01% HCl, 40 °C, 4 h.*

2.3.2 Ghavami's approach towards Salacinol [8b]

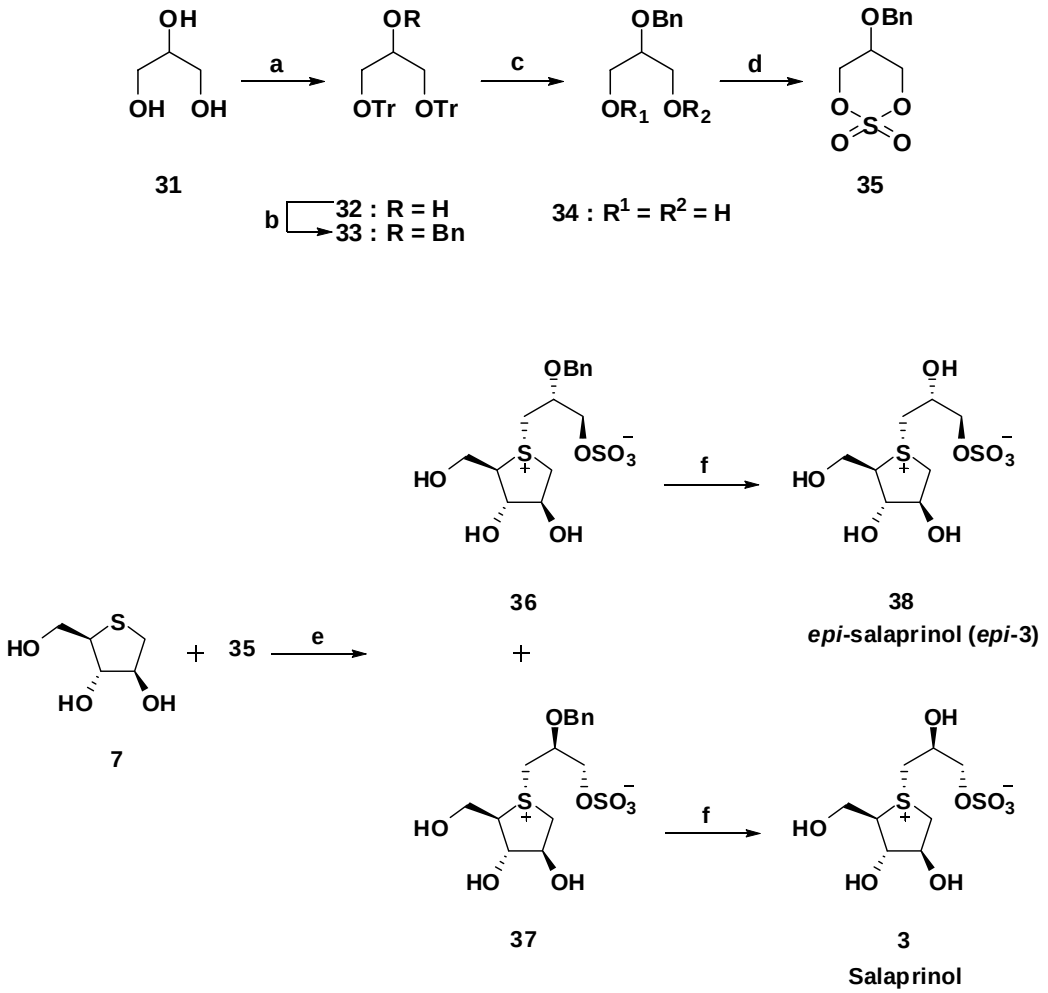
Ghavami and coworkers replaced the protecting group acetonide with benzylidine in the cyclic sulfate. The thio-arabinitols **24** and **27** were synthesized from D-xylose and D-glucose respectively by using Yoshimura's approach[10] while the benzylidine protected cyclic sulfates **25** and **28** were synthesized by Calvo-Flores's approach.[11] The thio-arabinitols **24** and **27** were further coupled with cyclic sulfates **25** and **28** respectively under K_2CO_3 in dry acetone condition to give **26** (33%) and **29** (40%) respectively. The coupling products **26** and **29** further on Pd/C catalyzed hydrogenation in acetic acid underwent benzyl deprotection to furnish Salacinol **1** (67%) and its isomer **30** (80%) respectively (Scheme 5).



Scheme 5. *Reagents & Conditions: a) K_2CO_3, acetone rt; b) Pd/C, H_2, AcOH.*

2.3.3 Genzoh Tanabe's approach towards Salaprinol and Neosalaprinol [7]

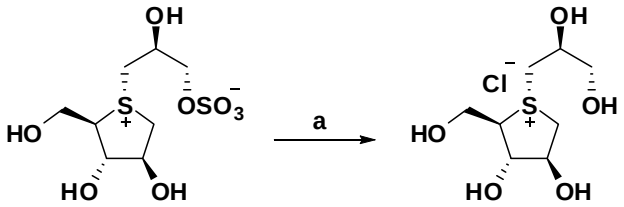
Genozoh Tanabe and coworkers first isolated Salaprinol from the methanolic extract of roots and stems of Indian *Salacia prinoides.* Similar group also reported the first synthetic approach for the synthesis of Salaprinol **3**.[7a] The synthesis of Salaprinol was achieved by the coupling of 2-benzyloxy cyclic sulfate **35** with 1,4-anhydro-4-thio-D-arabinitol **7**. The synthesis of 2-benzyloxy cyclic sulfate **35** was started with cheap starting material glycerol **31**. The selective tritylation of the primary hydroxyl groups of **31** was performed in presence of pyridine at room temperature for 24 h to give 1,3-di-*O*-tritylglycerol **32**. The carbinol moiety of **32** was further protected with BnBr in the presence of sodium hydride to offer 2-*O*-benzyl-1,3-di-*O*-tritylglycerol **33**. The compound **33** was hydrolyzed by refluxing with 10% aqueous H_2SO_4 in dioxane to offer compound **34** in 95% yield. The compound **34** was further on treatment with $SOCl_2$ and Et_3N in DCM followed by oxidation with catalytic $RuCl_3$ in presence of $NaIO_4$ afforded the desired 2- benzyloxy cyclic sulfate **35** (Scheme 6).



Scheme 6. *Reagents and conditions: a) TrCl, pyridine, rt; b) BnBr, NaH, DMF, 0 °C to rt or BnCl, KOH, toluene, reflux; c) 10% aq. H_2SO_4, 1,4-dioxane, reflux; d) (i) $SOCl_2$, TEA, CH_2Cl_2, 0 °C, then (ii) $NaIO_4$, $RuCl_3$, $NaHCO_3$, CCl_4, CH_3CN, H_2O, 0 °C to rt; (e) thiosugar* **7**, *K_2CO_3, HFIP, 65-70 °C; (f) H_2, Pd/C, 80% AcOH, 50 °C.*

The cyclic sulfate **35** was subjected for the coupling reaction with a thiosugar (D-ATA) 7 in presence of K_2CO_3 in HFIP at 65-70 °C to give epimers **36** and **37**. When the reaction was carried out in relatively large scale (4 mmol), one of the epimers **36** deposited fortunately in the reaction mixture and pure **36** was obtained in 16% yield after recrystallization. Although these two epimers were hardly separable by TLC analysis, the careful column chromatography of the condensed filtrate afforded a fraction composed of 10:1 epimeric mixture of **37** and **36**. The hydrogenolysis of **36** with Pd/C in 80% aqueous acetic acid offered *epi*-salaprinol (epi-3) **38** in good yield.

The 10:1 epimeric mixture of **37** and **36** was also hydrogenated under similar conditions to furnish a mixture of Salaprinol **3** and **38** (*epi*-3). Further, exclusive crystallization of the major product Salaprinol **3** from the mixture was successfully conducted by the use of methanol as the solvent, offering pure Salaprinol **3** as colorless crystals (Scheme 6).



3
salaprinol

5
Neosalaprinol

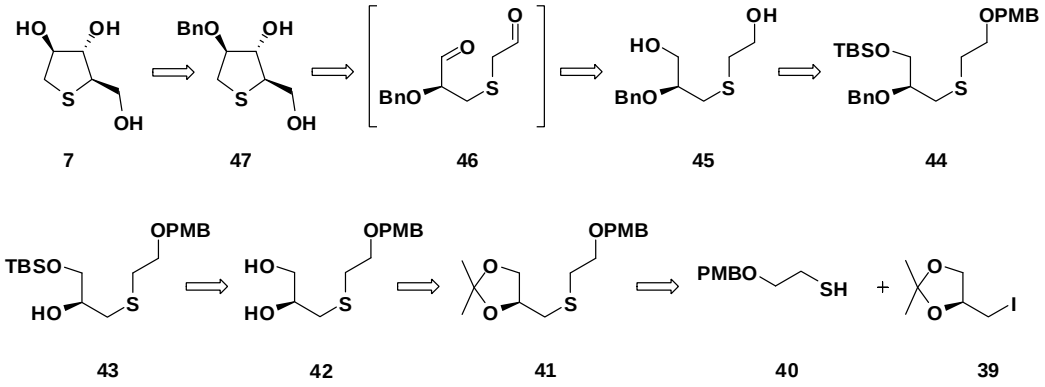
Scheme 7. *Reagents and conditions: a) (i) 5% methanolic HCl, 50 ^{o}C; ii) IRA 400J (Cl^{-}form), CH_3OH, rt.*

The similar group, Weijia Xie, Genozoh Tanabe and coworkers recently isolated Neosalaprinol **5** from the species *Salacia chinensis* and also established its first synthesis from Salaprinol **3** itself.[7b] Salaprinol **3** was treated with 5% methanolic HCl at 50 ^{o}C followed by ion exchange with IRA 400J (Cl^{-} form) in methanol at room temperature to furnish Neosalaprinol **5** (Scheme 7).

2.4 Present Work

Literature survey showed that synthetic strategies for (D-ATA) **7**, Salacinol **1**, Salaprinol **3** and Neosalaprinol **5** utilized naturally occurring chiral pool starting materials (sugar scaffolds). Moreover, a lack of generality was found in the synthesis of (D-ATA) **7** and its isomers, which escort complexity in accessing several other analogues of Salacinol **1**, Salaprinol **3** and Neosalaprinol **5**. Hence, there is still need to develop a common synthetic approach for the synthesis of (D-ATA) **7** and its isomers. In extension of our programme on the synthetic strategies for thiosugars we decided to attempt the synthesis of (D-ATA) **7** which is also a core part of the general structure of thiosugars isolated from *Salacia* species and can be used further for the synthesis of *Salacia* species thiosugars. In this regard, we herewith propose a novel route for the synthesis of 1,4-anhydro-4-thio-D-arabinitol **7** using 5-*enolexo*

aldolization as a key step. The retrosynthetic analysis for the diastereoselective synthesis (D-ATA) **7** is showed in Scheme 8.



Scheme 8. The retrosynthetic disconnections for 1,4-anhydro-4-thio-D-arabinitol (D-ATA).

It was seen that D-ATA **7** could be easily achieved from the benzyl deprotection of cyclic diol **47**. The cyclic diol **47** could come out as 5-*enolexo* aldolization product of dialdehyde **46** which in turn could be accessed by the oxidation of diol **45**. The diol **45** could be easily obtained by the sequential acid catalyzed TBS-deprotection followed by oxidative cleavage of PMB group from thioether **44**. The thioether **44** could be accessed by the benzyl protection of secondary hydroxyl group of alcohol **43** which could be synthesized by the TBS-protection of primary hydroxyl group of diol **42**. The diol **42** could be obtained by the acid catalyzed cleavage of acetonide group of thioether **41** which could be synthesized by the coupling synthons, thiol **40** and iodo intermediate **39** (Scheme 2).

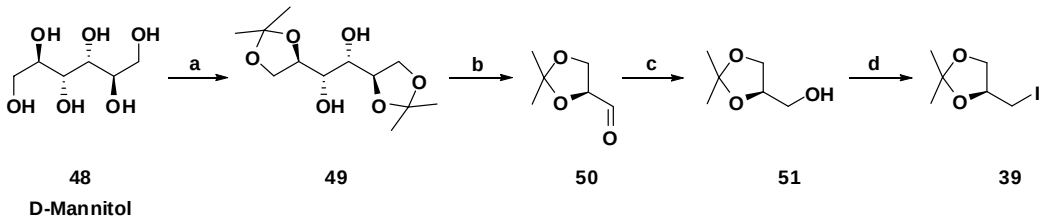
2.5 Result and discussion

The synthesis and characterization of thiol intermediate **40** was previously attempted in chapter 1, hence our synthesis starts with the preparation of iodo intermediate **39**.

2.5.1 Synthesis of iodo intermediate 39

The preparation of iodo intermediate **39** was started with a cheap and easily available material D-mannitol **48**. The starting material D-mannitol **48** was derived into its diacetonide form **49**, which on treatment with $NaIO_4$ in DCM underwent oxidative

cleavage to afford (*R*)-glyceraldehyde **50**.[12] The (*R*)-glyceraldehyde **50** was then reduced with $NaBH_4$ in methanol to give alcohol **51** which further treated with imidazole, triphenylphosphine and iodine in refluxing toluene (Appel reaction condition) afforded desired iodo intermediate **39** with 92% yield (Scheme 9).[13]



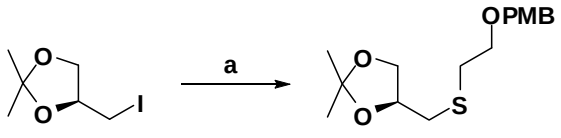
Scheme 9. *Reagents and conditions*: *a) p-TSA, 2,2-DMP, DMSO, rt; b) $NaIO_4$, aq.$NaHCO_3$, DCM, rt, 85%; c)$NaBH_4$, MeOH, rt, 96%; d) Imidazole, PPh_3, I_2, toluene, reflux, 92%.*

In the ^{1}H NMR of iodo intermediate **39**, due the electronic influence of iodine the protons of methylene group connected to it resonated slight up field as a triplet (J = 8.3 Hz) at δ 3.13 and a multiplate at δ 3.21 to 3.28 while in ^{13}C NMR similar methylene noticed much up field at δ 6.65 (DEPT) which is in accordance with the characteristic chemical shift range for the methylene group attached to iodine atom. Rest of the ^{1}H and ^{13}C NMR spectral values were in good agreement with the spectral values of assigned structure of iodo intermediate **39** reported in the literature.

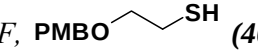
2.5.2 Synthesis of thioether 41

The iodo intermediate **39** and thiol intermediate **40** were further coupled using sodium hydride as a base in dry THF at 0 ^{o}C to furnish thioether **41** in 95% yield (Scheme 10). In ^{1}H NMR spectrum of thioether **41**, the terminal acetonide group protons sighted as two singlets at δ 1.35 and 1.42. A doublet of doublet (J = 7.0, 13.4Hz) at δ 2.66 for one proton, doublet (J = 5.5 Hz) at δ 2.76 for two protons and a doublet of doublet signal (J = 7.0, 5.5 Hz) at δ 2.80 for one proton corresponds to the protons of two methylene groups connected to sulfur atom. The methylene group in ethereal linkage -CH_2-OPMB appeared as a triplet (J = 6.7 Hz) at δ 3.62 while two doublet of doublet signals at δ 3.70 (J = 8.2, 6.4 Hz) and at δ 4.08 (J = 8.2, 6.1 Hz) corresponds to the two protons of another methylene group situated in acetonide ring. The methoxy protons of –OPMB group and benzylic protons as usually sighted as two

singlets at δ 3.79 and δ 4.47 whereas the proton on the only stereocenter in thioether **41** noticed as quintet (J = 12.6, 6.4 Hz) at δ 4.24 ppm. In ^{13}C NMR and DEPT, the two methylene adjoined to sulfur atom appeared distinctively in up field at δ 32.06 and 35.41 (DEPT) respectively while the methylene groups in ethereal linkage -CH_2-OPMB and in acetonide ring noticed closely at δ 68.61 and 69.30 (DEPT) respectively. The *p*-methoxy benzylic carbon sighted at δ 72.48 (DEPT) whereas downfield signal at δ 75.39 corresponds to the carbon of single stereocenter present in thioether **41**. Rest of the ^1H and ^{13}C NMR values were in complete agreement with the assigned structure of thioether **41**.



39 **41**

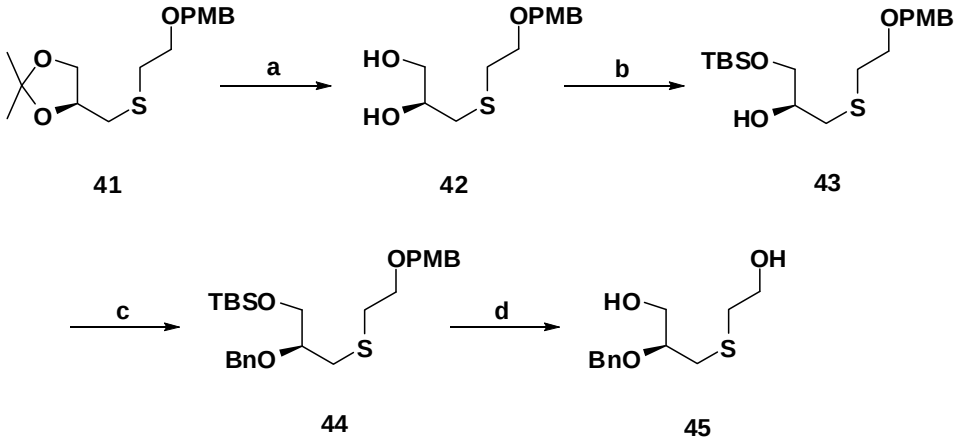
Scheme 10. *Reagents and conditions*: *a) NaH, THF,* 

***(40)**, 0 °C, 95%.*

2.5.3 Synthesis of diol 45

The thioether **41** on treatment with *p*-TSA in MeOH at room temperature underwent acetonide deprotection to give diol **42** in 92% yield. The primary hydroxyl group of diol **42** was then selectively protected with TBSCl (1.1 equivalent) and imidazole in dry CH_2Cl_2 at 0 °C to afford corresponding TBS-protected alcohol **43** with 95% yield (Scheme 11). The two singlets noticed at δ 0.10 and 0.92 accounted for 6 and 9 protons respectively in ^1H NMR and three signals at δ -5.51, 18.13 and 25.74 in ^{13}C NMR authenticated the formation of TBS-protected alcohol **43**. Further benzylation of TBS-protected alcohol **43** with sodium hydride and BnBr in dry THF at 0 °C afforded thioether **44** in almost quantitative yield. In ^1H NMR spectrum of thioether **44**, TBS group noticed as two characteristic singlets at δ 0.09 and 0.93. The two methylene groups linked to sulfur atom resonated as a multiplate at δ 2.72 to 2.87 while two methylene groups in ethereal linkages -CH_2-OPMB and –CH_2-OTBS sighted jointly at δ 3.61 to 3.68 as a multiplate. A doublet (J = 4.9 Hz) noticed at δ 3.74 corresponds to the proton on the only stereocenter in thioether **44** whereas the methoxy protons of –OPMB group sighted as singlet at δ 3.81. Two benzylic groups

from -OPMB and -OBn viewed as two singlets at δ 4.47 and δ 4.67 in up field while two doublets at δ 6.89 (J = 8.5 Hz), δ 7.28 (J = 8.5 Hz) and a multiplate at δ 7.31 to 7.39 signify the rest of aromatic protons. In ^{13}C NMR, signals at δ -5.46, 18.19 and 25.83 denote the presence of TBS group. The carbons of two methylene adjoined to sulfur atom as usually noticed distinctively in up field at δ 32.42 and 33.78 (DEPT) respectively while the carbons of two methylene associated to ethereal linkages -CH_2-OTBS and -CH_2-OPMB appeared at δ 64.03 and 69.50 (DEPT) respectively. Two signals viewed downfield at δ 72.16 and 72.56 (DEPT) correspond to the two benzylic carbons from –OBn and -OPMB respectively whereas a signal at δ 79.63 imply the carbon of only stereocenter present in thioether **44**. Rest of the ^{13}C spectral values were in total accordance of assigned structure of thioether **44**.



Scheme 11. *Reagents and conditions*: *a) p-TSA, MeOH, rt, 92%; b) TEA, TBSCl, DCM, 0 °C, 95%; c) NaH, BnBr, THF, 0 °C, 96%; d) (i) Phosphotungstic acid, MeOH, rt, 95%; (ii) DDQ, DCM: H_2O (17:1), rt, 90%.*

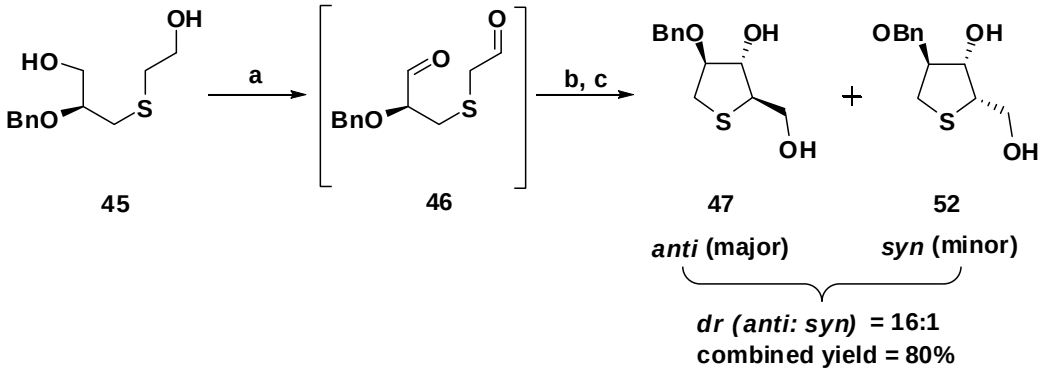
The thioether **44** was then subjected for TBS-deprotection with catalytic Phosphotungstic acid[14] in MeOH at room temperature followed by oxidative cleavage of PMB group with DDQ[15] in DCM: H_2O (17:1) at room temperature to give diol **45** in 90% yield (Scheme 11). In ^{1}H NMR spectrum of diol **45**, two methylene groups connected to sulfur atom resonated as a triplet (J = 6.0 Hz) at δ 2.72 and a doublet of doublet (J = 6.0, 2.5 Hz) at δ 2.78 whereas a triplet (J = 4.5 Hz) at δ 3.64 accounted for one proton and a multiplate at δ 3.67 to 3.73 accounted for three protons represent

the two terminal hydroxy methylene groups. A doublet of doublet (J = 11.5, 4.0 Hz) at δ 3.80 corresponds to the proton on the only stereocenter in diol **45** while benzylic protons noticed as quartet (J = 24.6, 11.5 Hz) at δ 4.64. Rest of the aromatic protons noticed as a multiplate at δ 7.30 to 7.37 whereas the two primary hydroxyl groups of diol **45** sighted as two distinct broad singlets at δ 2.35 and 2.70. In ^{13}C NMR, the two methylene connected to sulfur atom resonated distinctively at δ 32.35 and 35.75 (DEPT) respectively while the remaining two terminal hydroxy methylene groups noticed downfield at δ 60.81 and 62.75 (DEPT). The benzylic carbon appeared at δ 71.88 whereas the signal at δ 78.94 signifies the carbon of only stereocenter present in diol **45**. Further a broad absorption at 3480 cm^{-1} in IR spectrum indicating the presence of hydroxyl functionality and mass (ESI-TOF) m/z at 265.1 accounting for $[M+Na]^+$ along with its HRMS (TOF) m/z (calculated for $C_{12}H_{18}NaO_3S$ ($[M+Na]^+$) 265.0874, found 265.0869.) also supported the assigned structure diol **45**.

2.5.4 L-proline catalyzed 5-*enolexo* aldolization

The diol **45** was further oxidized with IBX in refluxing EtOAc to give dialdehyde **46** in almost quantitative yield. The diol **46,** without any purification was directly used for L-proline catalyzed 5-*enolexo* aldolization reaction.[16] The key step of direct 5-*enolexo* aldolization reaction of dialdehyde **46** was carried out in presence of L-proline (30 mol %) as an organocatalyst in DCM at room temperature. The TLC monitoring of reaction showed that the starting material dialdehyde was totally consumed and the 5-*enolexo* aldolization reaction was completed within 45 minutes. The cyclic aldol products of such *enolexo* aldolization reactions are unstable over extended time periods at room temperature, however stable diol can be obtained by the *in situ* reduction of aldol product.[17] Hence the *enolexo* aldolization reaction mixture was further *in situ* reduced with $NaBH_4$ in MeOH at room temperature to afford a mixture of two diastereomers **47** and **52** respectively with a combined 80% yield after three consecutive steps (Scheme 12). Surprisingly no dehydrated by-product was produced throughout the course of 5-*enolexo* aldolization reaction of dialdehyde **46**. Further, we could successfully and quantitatively separate both the diastereomers using flash column chromatography which afforded diastereomers **47** and **52** with a high diastereomeric ratio (*dr*) of 16:1 respectively. The structure and

relative stereochemistry of both the diastereomers **47** and **52** was confirmed by spectral techniques such as ^{1}H, ^{13}C, COSY and NOESY.



Scheme 12. *Reagents and conditions*: *a) IBX, ethyl acetate, reflux, 96%; b) L-proline (30 mol%), DCM, rt, 45 min.; c) $NaBH_4$, MeOH, rt, (combined 80%).*

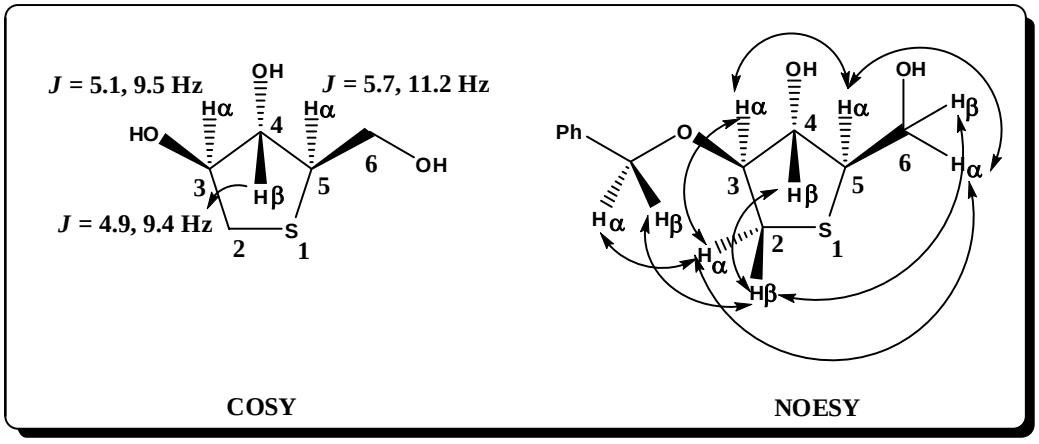
In ^{1}H NMR spectrum of diastereomer **47**, a broad singlet at δ 2.01 accounted for two protons corresponds to the two newly formed hydroxyl groups of the cyclic diol system. A triplet (J = 5.8 Hz) at δ 2.86 and a doublet of doublet (J = 6.8, 13.8 Hz) at δ 2.89 represented the protons of methylene group (-CH_2S) connected to sulfur atom while the protons of hydroxy methylene group (-CH_2OH) connected to newly formed center at donor methylene group appeared as two multiplate signals at δ 3.69-3.75 and 3.76-3.82 respectively. The proton at the stereocenter with benzyloxy group (-OBn) resonated as a doublet of doublet (J = 5.1, 9.5 Hz) at δ 3.67 whereas the protons on two newly formed stereocenters at donor methylene and acceptor aldehyde appeared as a quintet (J = 4.9, 9.4 Hz) at δ 2.96 and a doublet of doublet (J = 5.7, 11.2 Hz) at δ 3.85 respectively. The benzylic protons resonated in diastereotopic manner as two close triplets at δ 4.61 (J = 10.1 Hz) and δ 4.69 (J = 10 Hz) while aromatic protons sighted as multiplate at δ 7.32 to 7.38. In ^{13}C NMR and DEPT, the signal appeared at δ 39.33 (DEPT) in up field corresponds to the sulfur adjoined methylene carbon (-CH_2S) whereas the hydroxy methylene group (-CH_2OH) noticed at δ 62.94 (DEPT) in downfield. Among two newly formed stereocenters, the carbon of stereocenter formed at donor methylene appeared at δ 47.75 while the carbon of stereocenter formed at acceptor aldehyde sighted at δ 76.10. The benzylic carbon appeared at δ 72.03 whereas the carbon of stereocenter with benzyloxy group (-OBn) resonated at δ 78.20. Rests of the 13C NMR values were in good agreement with the assigned structure of

47. Further a broad absorption at 3458 cm^{-1} in IR spectrum indicating the presence of hydroxyl functionality and mass (ESI-TOF) m/z at 263.1 accounting for $[M+Na]^+$ along with its HRMS (TOF) m/z (calculated for $C_{12}H_{16}NaO_3S$ ($[M+Na]^+$) 263.0718, found 263.0713) also supported the assigned structure of **47**.

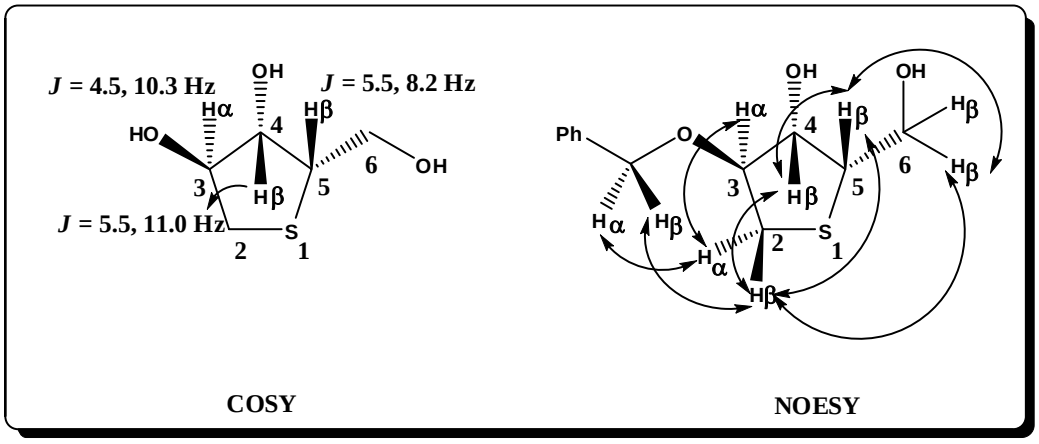
The ^1H NMR spectrum of **52** demonstrated more resolved and dissimilar pattern of signals than **47**. In ^1H NMR spectrum of diastereomer **52**, two close broad singlets at δ 1.93 and 2.03 stand for two newly formed hydroxyl groups of the cyclic diol system. The protons of methylene group connected to sulfur atom ($-CH_2S$) resonated as a multiplate up field at δ 3.05 to 3.13 whereas the protons of hydroxy methylene group ($-CH_2OH$) connected to newly formed center at donor methylene group sighted as a multiplate δ 3.83 to 3.91. A doublet of doublet (J = 4.5, 10.3 Hz) noticed at δ 3.68 corresponds to the proton at the stereocenter with benzyloxy group (-OBn) while the protons on two newly formed stereocenters at donor methylene and acceptor aldehyde appeared as a doublet of doublet (J = 5.5, 8.2 Hz) at δ 3.17 and a doublet of doublet (J = 5.5, 11.0 Hz) at δ 3.98 respectively. Two distinct doublet of doublets resonated at δ 4.60 (J = 5.5, 11.4 Hz) and δ 4.73 (J = 5.6, 11.6 Hz) correspond to the benzylic protons whereas aromatic protons appeared as multiplate at δ 7.32 to 7.38. In ^{13}C NMR and DEPT, the signal noticed at δ 39.14 (DEPT) up field corresponds to the sulfur connected methylene carbon ($-CH_2S$) while the hydroxy methylene carbon ($-CH_2OH$) appeared at δ 63.08 (DEPT) downfield. Among two newly formed stereocenters, the carbon of stereocenter formed at donor methylene resonated at δ 45.95 whereas the carbon of stereocenter formed at acceptor aldehyde sighted at δ 77.21. The benzylic carbon seen at δ 72.13 while the carbon of stereocenter with benzyloxy group (-OBn) resonated at δ 77.80. Rests of the 13C NMR values were in good agreement with the assigned structure of **52**. Presence of a broad absorption band at 3450 cm^{-1} in IR spectrum signified the existence of hydroxyl groups of cyclic diol system. In addition, mass (ESI-TOF) m/z at 263.2 accounting for $[M+Na]^+$ along with its HRMS (TOF) m/z (calculated for $C_{12}H_{16}NaO_3S$ ($[M+Na]^+$) 263.0718, found 263.0725) also supported the assigned structure of **52**.

Further, the exact structure and stereochemistry of diastereomer **47** and **52** was elucidated by their 2D-NMR studies. The exact structure and stereochemical outcome of both the diastereomer **20** and **38** could be determined and explained by their 2D-NMR studies. In ^1H-^1H COSY experiment of **47**, the proton on C_4 exhibited a strong

correlation with protons on both the neighboring stereocenters C_3 and C_5. The coupling constant observed for these protons suggested an *anti* relationship for C_4 -



Diastereomer 47



Diastereomer 52

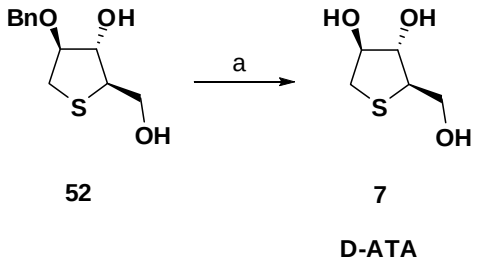
Figure 2. COSY and NOE correlation for diastereomers **47** and **52**.

proton (J = 5.7, 11.2 Hz) with both C_3 – proton (J = 5.1, 9.5 Hz) and C_5 – proton (J = 4.9, 9.4 Hz) indicating an *anti*-diol structure for **47**. In NOESY experiment of **47**, a strong NOE correlation was noticed between protons on C_3 and C_5 but no such correlation was seen for proton on C_4 with protons on C_3 and C_5 respectively. These observations indicated that the protons on C_3 and C_5 were on the same side but both of them are *anti* to the proton on C_4, which again supported the assigned *anti*-diol structure for **47** (Figure 2).

In COSY experiment of **52**, a strong correlation was seen for the proton on C_4 with the neighboring C_3 and C_5 protons. The observed coupling constant for C_4 -proton (J = 5.5, 11.0 Hz), C_3 – proton (J = 4.5, 10.3 Hz) and C_5 – proton (J = 5.5, 8.2 Hz) suggested an *anti* relationship between C_3 and C_4 – protons but *syn*-relationship between C_4 and C_5 – protons which signified a *syn*-diol structure for **52**. The NOESY experiment experienced a strong NOE correlation between C_4 and C_5 - protons whereas no such correlation was found between C_3 and C_4 – proton which once again indicated the *anti* relationship of C_3 and C_4 – protons and *syn*-relationship of C_4 and C_5 – protons and supported the assigned *syn*-diol structure for **52** (Figure 2).

2.5.5 Synthesis of 1,4-anhydro-4-thio-D-arabinitol (D-ATA) 7

The *anti*-isomer **47** further on treatment with BCl_3 in DCM at -78 ^oC underwent benzyl deprotection to furnish D-ATA **7** in 60% yield (Scheme 13).



52 **7**

D-ATA

Scheme 13. *Reagents and conditions*: *a) BCl_3, DCM, -78 ^oC, 1 h, 60%.*

In ^1H NMR of **7** taken in CD_3OD, two distinct doublet of doublet signals seen at δ 2.69 (J = 6.2, 6.3 Hz) and δ 2.99 (J = 5.7, 10.7 Hz) correspond to the protons on methylene group connected to sulfur (-CH_2S) while the protons of hydroxy methylene group (-CH_2OH) also noticed as two separate doublet of doublet signals at δ 3.61 (J = 6.8, 6.7 Hz) and δ 3.82 (J = 5.4, 10.7 Hz). Among the two newly formed stereocenters, the proton on the stereocenter adjoined to sulfur resonated as a quartet at δ 3.23 (J = 5.4 Hz) whereas the proton on other one noticed as a triplet at δ 3.86 (J = 5.6 Hz). The proton on the third stereocenter adjacent to –CH_2S appeared as quartet in downfield at δ 4.12 (J = 5.6 Hz). In ^{13}C NMR and DEPT, the signals sighted at δ 34.70 (DEPT) up field and δ 65.53 (DEPT) in downfield corresponded to the sulfur adjoined methylene and hydroxy adjoined methylene. The sulfur adjoined stereocenter resonated at δ 53.69 while carbon of its neighboring stereocenter sighted

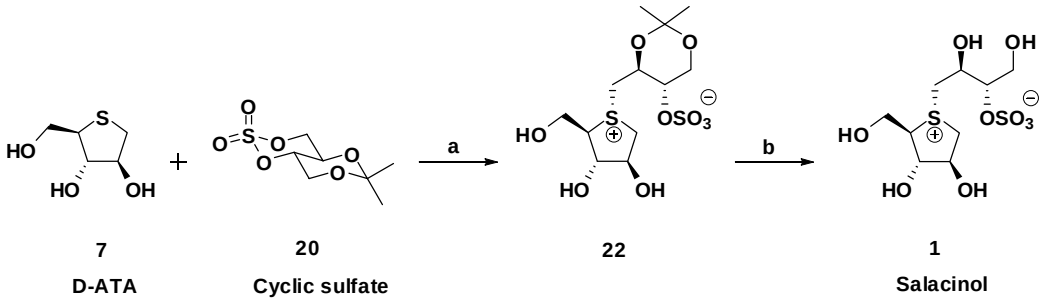
at δ 80.60. A signal at δ 79.26 indicated the carbon remaining stereocenter adjoined to $–CH_2S$. Further, all these ^1H and ^{13}C NMR values along with the optical rotation for **7** ($[\alpha]_D^{25}$ + 39.81, *c* 1.3, MeOH) were found in good accordance with that literature report.[6d]

2.5.6 Formal Synthesis of Salacinol, Salaprinol and Neosalaprinol

Being a core important part of the *Salacia* species thiosugars, the synthesized D-ATA **7** also establishes the formal synthesis of some of the *Salacia* species thiosugars. Salacinol, Salaprinol and Neosalaprinol are few notable *Salacia* species thiosugars which can be synthesized by using D-ATA **7** as a starting material as mentioned in the earlier literature reports.

2.5.6.1 Formal Synthesis of Salacinol 1

The synthesis of Salacinol **1** can be achieved by the reaction of D-ATA **7** and cyclic sulfate **53** by employing the synthetic protocol reported by Yuasa and coworkers (Scheme 14).[6d]

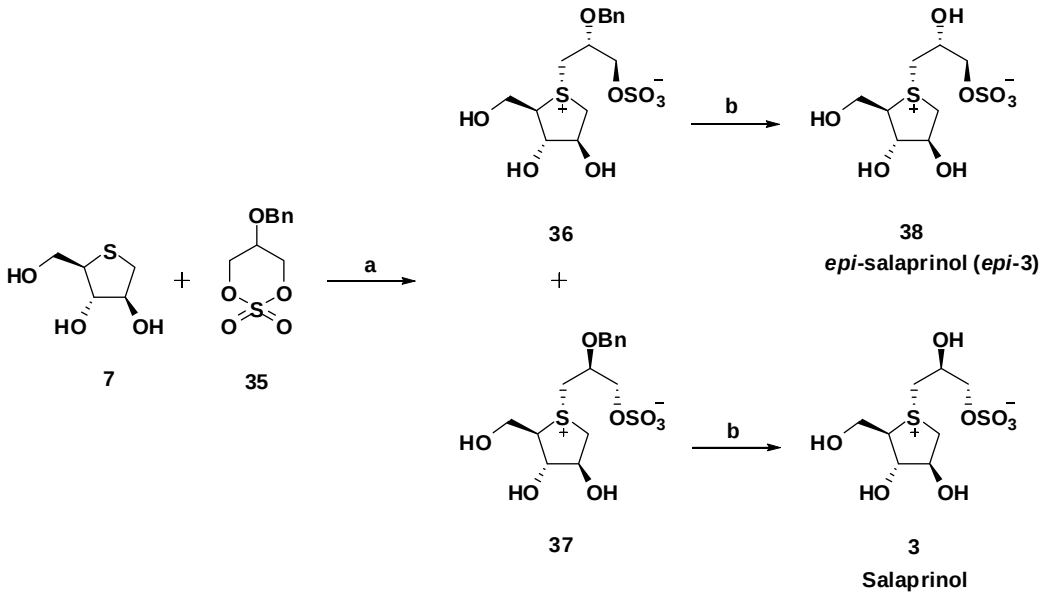


Scheme 14. *Reagents and conditions: a) DMF, 45 ºC, 13 h, 61%; b) 0.01% HCl, 40 ºC, 4 h, 75%.*

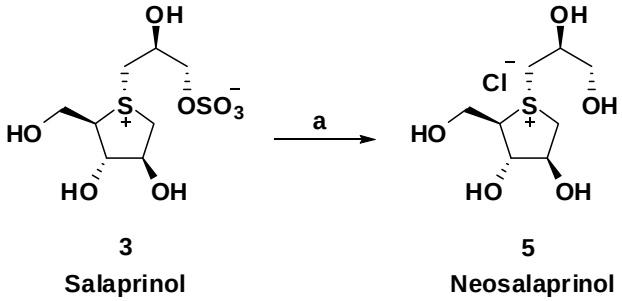
2.5.6.2 Formal Synthesis of Salaprinol 3 and Neosalaprinol 5

The synthesis of Salaprinol **3** can be accomplished by using the synthetic approach reported by Genzoh Tanabe.[7a] The Salaprinol 3 can be synthesized by reaction of D-ATA **7** and cyclic sulfate **35** in presence of K_2CO_3 in HFIP at 65–70 ^oC followed by catalytic hydrogenation under Pd/C, H_2 in 80% acetic acid at 50 ^{o}C condition (Scheme 15). The synthesis of Neosalaprinol **5** can be also established by using the synthetic route mentioned by Genzoh Tanabe in the literature.[7b] The Neosalaprinol **5** can be synthesized by the treatment of Salaprinol **3** with 5% methanolic hydrochloric acid at

50 ^{o}C followed by ion exchange with IRA 400J (Cl^{-}form) and CH_3OH at room temperature (Scheme 16).



Scheme 15. *Reagents and conditions: a) K_2CO_3, HFIP, 65-70 ^{o}C; b) H_2, Pd/C, 80% AcOH, 50 ^{o}C.*



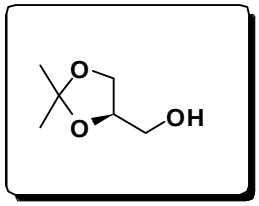
Scheme 16. *Reagents and conditions: a) (i) 5% methanolic HCl, 50 ^{o}C; ii) IRA 400J (Cl^{-}form), CH_3OH, rt.*

2.6 Conclusion

In conclusion, 1,4-anhydro-4-thio-D-arabinitol (D-ATA) was successfully synthesized by employing a novel synthetic route starting with D-mannitol and highly diastereoselective L-proline catalyzed 5-*enolexo* aldolization reaction as a key step. D-ATA is an important core part and major building block for the synthesis of Salacinol, Salaprinol and Neosalaprinol; hence the formal total synthesis of Salacinol, Salaprinol and Neosalaprinol was also accomplished. This synthetic sequence can provide a lead for the synthesis of Salacinol, Salaprinol and Neosalaprinol and their analogues, substituted α-to sulfur in thioarabinitol skeleton.

2.7 Experimental

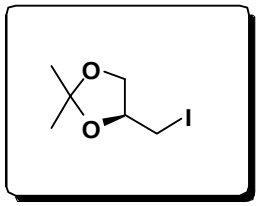
(*S*)-(2,2-Dimethyl-1,3-dioxolan-4-yl)methanol (51)



To the ice-cooled solution of (*R*)-glyceraldehyde **50** (13.0 g, 100 mmol) in methanol (200 mL) was slowly added $NaBH_4$ (4.56 g, 120 mmol, slight excess) in portions. The resulting solution was then stirred at room temperature for 2 h. The solvent methanol was evaporated under reduced pressure and residue was dissolved in water (50 mL) followed by the extraction with EtOAc (3 x 50 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated on rotary evaporator to give crude colorless liquid. The residual liquid was further vaccum distilled at 80-81 °C/12 mmHg to furnish alcohol **51** (12.61 g, 96%) as a colorless dense liquid.

Molecular Formula	: $C_6H_{12}O_3$.
Optical rotation	: $[\alpha]_D^{25}$ + 13.45 °, neat (Lit. $[\alpha]_D^{20}$ + 13.62 °, neat).[18]
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 1.31 (s, 3H), 1.38 (s, 3H), 2.85 (bs, 1H) 3.54 (quintet, J = 10.5, 5.0 Hz, 1H), 3.61-3.65 (m, 1H), 3.71 (t, J = 8.5 Hz, 1H), 3.98 (t, J = 8.3 Hz, 1H), 4.14-4.20 (m, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 25.09, 25.51, 62.83, 66.66, 76.11, 109.24.
IR (Neat) cm^{-1}	: 3421, 2949, 1378, 1262, 1216, 1159, 1051.
MS (ESI-TOF) m/z	: 155.12 ($[M+Na]^+$).

(*S*)-4-(Iodomethyl)-2,2-dimethyl-1,3-dioxolane (39)

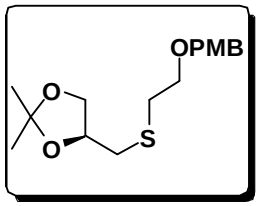


A solution of alcohol **51** (5.28 g, 15 mmol), triphenylphosphine (4.72 g, 18 mmol) and imidazole (3.06 g, 45 mmol) in toluene (100 mL) was refluxed under argon atmosphere till clear homogenous solution obtained. The reflux was stopped and iodine (4.95 g, 19.5 mmol) was carefully added and the reaction mixture was further refluxed for 30 min. After 30 min of reflux, the reaction mixture was cooled to room temperature and poured in a separatory funnel containing water (200 mL) and a 10% $Na_2S_2O_3$ aqueous solution (50 mL) and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under

diminished pressure to give dark reddish crude oil. The residual dark reddish crude oil was further purified by silica gel column chromatography using petroleum ether: ethyl acetate (9:1) as eluent to offer the iodo intermediate **39** (5.28 g, 90%) as colorless oil.

Molecular Formula	: $C_6H_{11}IO_2$.
Optical rotation	: $[\alpha]_D^{25}$ + 35.1 ^{o}, *c* 13.0, absolute ethanol (Lit. $[\alpha]_D^{23}$ + 35.5 ^{o}, *c* 12.7, absolute ethanol).[19]
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 1.33 (s, 3H), 1.44 (s, 3H), 3.13 (t, *J* = 8.3 Hz, 1H), 3.21-3.28 (m, 1H), 3.75-3.81 (m, 1H), 4.11 (t, *J* = 6.9 Hz, 1H), 4.23-4.28 (m, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 6.65, 25.44, 26.98, 69.38, 75.43, 110.23.
IR (Neat) cm^{-1}	: 3001, 2953, 2900, 1462, 1381, 1226, 1150, 1048, 839.
MS (ESI-TOF) m/z	: 265.1 ($[M+Na]^+$).

(*S*)-4-((2-(4-Methoxybenzyloxy)ethylthio)methyl)-2,2-dimethyl-1,3-dioxolane (41)

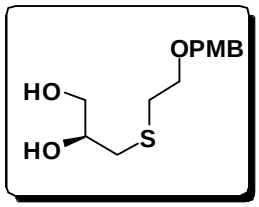


To a solution of thiol **40** (8.48 g, 40 mmol) in dry THF (80 mL) was added sodium hydride (60% dispersion in oil, 2.4 g, 60 mmol) at 0 °C and was then stirred at same temperature for 30 min. To this was added the solution of iodo intermediate **39** (10.65 g, 44 mmol) in dry THF (120 mL) at the same temperature and stirred for an additional 5 h at room temperature. The reaction mixture was then quenched with cold water at 0 °C and the two phases were separated. The aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give dark yellowish dense oil which was further purified by silica gel column chromatography using petroleum ether: ethyl acetate (9:1) as eluent to offer the desired thioether **41** (12.42 g, 96%) as dense pale yellowish oil.

Molecular Formula	: $C_{16}H_{24}O_4S$.
Optical rotation	: $[\alpha]_D^{25}$ + 19.92, *c* 1.0, $CHCl_3$.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 1.35 (s, 3H), 1.42 (s, 3H), 2.66 (dd, *J* = 13.4, 7.0 Hz, 1H), 2.76 (d, *J* = 5.5 Hz, 2H), 2.80 (dd, *J* = 7.0,

	5.5 Hz, 1H), 3.62 (t, *J* = 6.7 Hz, 2H), 3.70 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.79 (s, 3H), 4.08 (dd, *J* = 8.2, 6.1 Hz, 1H), 4.24 (quintet, *J* = 12.6, 6.4 Hz, 1H), 4.47 (s, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 25.35, 26.72, 32.08, 35.43, 55.01, 68.61, 69.33, 72.49, 75.40, 113.59, 129.09, 129.15, 129.92, 159.05.
IR (Neat) cm^{-1}	: 3065, 3034, 2905, 2882, 1602, 1575, 1448, 1384, 1217, 1149 (C-O-C), 1015 (C-S-C), 740 and 710 (aromatic).
MS (ESI-TOF) m/z	: 335.2 ($[M+Na]^+$)
HRMS (TOF) m/z	: calculated for $C_{16}H_{24}NaO_4S$ ($[M+Na]^+$) 335.1293, found 335.1298.

(*S*)-3-(2-(4-Methoxybenzyloxy)ethylthio)propane-1,2-diol (42)



A solution of **41** (6.52 g, 20 mmol) in MeOH (50 mL) was stirred with the catalytic amount of *p*-TSA at room temperature for 8 h followed by TLC. After completion of the reaction, MeOH was evaporated under reduced pressure to give a residual paste. The residual paste was then added water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give pale yellowish dense oil which upon silica gel column chromatography using petroleum ether: ethyl acetate (4:6) as eluent offorded the diol **42** (5.12 g, 90%) as dense pale yellowish oil.

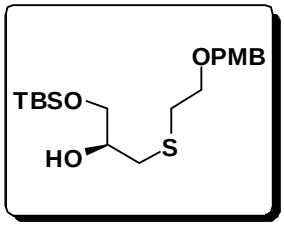
Molecular Formula	: $C_{13}H_{20}O_4S$.
Optical rotation	: $[\alpha]_D^{25}$ -16.23, *c* 1.0, $CHCl_3$.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 2.63 (dd, *J* = 13.5, 8.0 Hz, 1H), 2.74 (dddd, *J* = 6.3, 4.5, 1.8 Hz, 1H), 2.78 (t, *J* = 6.3 Hz, 2H), 2.93 (bs, 1H), 3.52 (dd, *J* = 11.2, 6.1 Hz, 1H), 3.64 (t, *J* = 6.1 Hz, 4H), 3.78 (bs, 1H), 3.81 (s, 3H), 4.49 (s, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), .
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 31.02, 35.85, 55.06, 65.05, 69.27, 70.73, 72.54, 113.64, 129.25, 129.62, 159.08.

IR (Neat) cm^{-1} : 3486 (broad), 2955, 2879, 1611, 1567, 1244, 1105 and (C-O-C), 995 (C-S-C), 741 and 712 (aromatic).

MS (ESI-TOF) m/z : 295.1 ($[M+Na]^+$).

HRMS (TOF) m/z : calculated for $C_{13}H_{20}NaO_4S$ ($[M+Na]^+$) 295.0980, found 295.0987.

(*S*)-1-(4-Methoxyphenyl)-10,10,11,11-tetramethyl-2,9-dioxa-5-thia-10-siladodecan-7-ol (43)



To a stirred solution of compound **42** (2.86 g, 10 mmol) and imidazole (0.816 g, 12 mmol) with a catalytic amount of DMAP in dry CH_2Cl_2 (20 mL), was added a solution of TBSCl (1.81 g, 1.1 mmol) in dry DCM (5 mL) at 0 ^oC for 10 min and mixture was stirred further for 1 h at the same temperature. After 1 h the reaction mixture allowed to stir at room temperature for next 4 h. The reaction was quenched with aqueous $NaHCO_3$ (20%) and the organic and aqueous layers were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent CH_2Cl_2 was evaporated under reduced pressure to give crude TBS-ether which was further purified by silica-gel column chromatography with petroleum ether: ethyl acetate (7:3) as eluent to offer the TBS-ether **43** (3.78 g, 95%) as colorless dense oil.

Molecular Formula : $C_{19}H_{34}O_4SSi$.

Optical rotation : $[\alpha]_D^{25}$ -8.12, *c* 1.0, $CHCl_3$.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 0.10 (s, 6H), 0.92 (s, 9H), 2.67 (bs, 1H), 2.70-2.90 (m, 4H), 3.62-3.68 (m, 4H), 3.76 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.83 (s, 3H), 4.50 (s, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H).

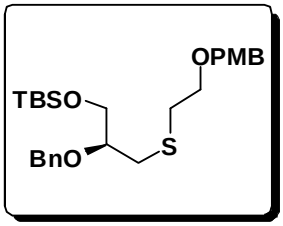
^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) -5.51, 18.13, 25.74, 32.17, 35.84, 55.07, 65.38, 69.33, 70.80, 72.57, 113.65, 129.20, 129.86, 159.10.

IR (Neat) cm^{-1} : 3450 (broad), 2930, 2873, 1610, 1569, 1380, 1245, 1090(C-O-C), 997 (C-S-C), 760 and 729 (aromatic).

MS (ESI-TOF) m/z : 409.20 ($[M+Na]^+$).

HRMS (TOF) m/z : calculated for $C_{19}H_{34}NaO_4SSi$ ($[M+Na]^+$) 409.1845, found 409.1840.

(*S*)-7-(Benzyloxy)-1-(4-methoxyphenyl)-10,10,11,11-tetramethyl-2,9-dioxa-5-thia-10-siladodecane (44)



To a solution of **43** (3.0 g, 7.5 mmol) in dry THF (20 mL) was added sodium hydride (60% dispersion in oil, 0.450 g, 11.25 mmol) at 0 °C and was then stirred at same temperature for 30 min. To this was added slowly BnBr (1.41 g, 1 mL, 8.25 mmol) at the same temperature and stirred for an additional 5 h at room temperature. The reaction mixture was then quenched with cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with water (2 x 10 mL), brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give colorless oil. The residual colorless oil was further purified by silica gel column chromatography using petroleum ether: ethyl acetate (8:2) as eluent to offer the ether **44** (3.51g, 96%) as colorless dense oil.

Molecular Formula : $C_{26}H_{40}O_4SSi$.

Optical rotation : $[\alpha]_D^{25}$ + 4.25, *c* 1.0, $CHCl_3$.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 0.09 (s, 6H), 0.93 (s, 9H), 2.72-2.87 (m, 4H), 3.61-3.68 (m, 4H), 3.74 (d, *J* = 4.9 Hz, 1H), 3.81 (s, 3H), 4.47 (s, 2H), 4.67 (s, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.31-7.39 (m, 5H).

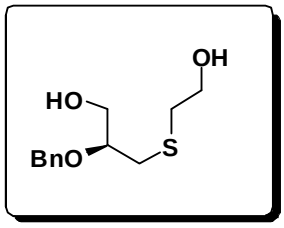
^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) -5.46, 18.19, 25.83, 32.42, 33.78, 55.14, 64.03, 69.50, 72.16, 72.56, 79.63, 113.71, 127.68, 128.22, 129.21, 130.15, 138.49, 156.13.

IR (Neat) cm^{-1} : 2932, 2870, 1625, 1577, 1373, 1258, 1101(C-O-C), 990 (C-S-C), 765 and 741 (aromatic).

MS (ESI-TOF) m/z : 499.3 ($[M+H]^+$).

HRMS (TOF) m/z : calculated for $C_{26}H_{40}NaO_4SSi$ ($[M+Na]^+$) 499.2314, found 499.2320.

(*S*)-2-(Benzyloxy)-3-(2-hydroxyethylthio)propan-1-ol (45)



A mixture of **44** (2.45 g, 5 mmol) and 10% Phosphotungstic acid (0.144 g, 0.05 mmol) in methanol (20 mL) was stirred at room temperature for 30 min. After completion of the reaction, as indicated by TLC, solvent methanol was removed under reduced pressure to give a crude yellow liquid. To the crude yellow liquid water (10 mL) was added and extracted with ethyl acetate (2 x 25 mL). The combined organic layers were then dried over anhydrous Na_2SO_4 and concentrated under diminished pressure to give a TBS-deprotected alcohol (1.83 g, 97%) as pale yellow liquid which without any further purification was used for oxidative cleavage of –OPMB group. To a stirred solution of TBS-deprotected alcohol (1.83 g, 4.87 mmol) in CH_2Cl_2 (51 mL) and water (3 mL) was added DDQ (3.32 g, 14.6 mmol) and stirred for 30 min at room temperature. After 30 min the precipitated DDQH was removed by filtration and the residue was washed with CH_2Cl_2. The combined organic layers were then washed with saturated $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and concentrated under diminished pressure to give dark brownish oil which was further purified by silica-gel column chromatography using petroleum ether: ethyl acetate (3:7) as eluent to offer the desired diol **45** (1.07 g, 83% after two steps) as a dense yellow oil.

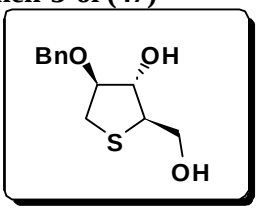
Molecular Formula	: $C_{12}H_{18}O_3S$.
Optical rotation	: $[\alpha]_D^{25}$ + 16.43, *c* 1.0, $CHCl_3$.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 2.35 (bs, 1H), 2.70 (bs, 1H), 2.72 (t, *J* = 6.0 Hz, 2H), 2.78 (dd, *J* = 6.0, 2.5 Hz, 2H), 3.64 (t, *J* = 4.5 Hz, 1H), 3.67-3.73 (m, 3H), 3.80 (dd, *J* = 11.5, 4.0 Hz, 1H), 4.64 (quartet, *J* = 24.6, 11.5 Hz, 2H), 7.30-7.37 (m, 5H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 32.35, 35.75, 60.81, 62.75, 71.88, 78.94, 127.78, 127.82, 128.37, 137.70.
IR (Neat) cm^{-1}	: 3480 (broad), 2961, 2876, 1616, 1558, 1247, 1131 and (C-O-C), 1005 (C-S-C), 727 and 716 (aromatic).
MS (ESI-TOF) m/z	: 265.1 ($[M+Na]^+$).
HRMS (TOF) m/z	: calculated for $C_{12}H_{18}NaO_3S$ ($[M+Na]^+$) 265.0874,

found 265.0869.

L-proline catalyzed 5-*enolexo* aldolization reaction

To the solution of diol **45** (0.484 g, 2 mmol) in EtOAc (30 mL) was added IBX (3.36 g, 12 mmol) and refluxed for 3.5 h at 80°C. After reaction completion (as checked by 2,4-DNP TLC test)[16], reaction mixture was cooled to room temperature and filtered and the filtrate was washed with 20% aqueous $NaHCO_3$ (2 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under diminished pressure to give pale yellowish syrupy crude dialdehyde **46** (0.456 g). The crude dialdehyde was immediately used as a starting material for an *enolexo* aldolization reaction without any further purification. To the solution of crude dialdehyde **46** (0.456 g) in dry DCM (20 mL) was added L-proline (0.066 g, 30 mol %) and stirred at room temperature for 45 min (reaction completion time as checked by TLC). After 45 min the reaction mixture was reduced *in situ* by adding 10 mL of MeOH and $NaBH_4$ (0.086 g, 2.2 mmol, slight excess) at room temperature for 1 h. The reaction mixture was concentrated on rotary evaporator, treated with cold water (15 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give syrupy mass which was further purified by flash silica-gel (230-400 mesh) column chromatography using petroleum ether: ethyl acetate (7:3) to give cyclized diol **47** (0.360 g) and **52** (0.022 g) with a combined 80% yield after three steps.

(2*R*,3*S*,4*S*)-4-(Benzyloxy)-2-(hydroxymethyl)tetrahydrothiophen-3-ol (47)



Physical appearance : Dense pale yellowish liquid.

Molecular Formula : $C_{12}H_{16}O_3S$.

Optical rotation : $[\alpha]_D^{25}$ -4.05 °, *c* 1, $CHCl_3$.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ (ppm) 2.01 (bs, 2H, D_2O exchangeable), 2.86 (t, *J* = 5.8 Hz, 1H), 2.89 (dd, *J* = 6.8, 13.8 Hz, 1H), 2.96 (quintet, *J* = 4.9, 9.4 Hz, 1H), 3.67 (dd, *J* = 5.1, 9.5 Hz, 1H), 3.69-3.75 (m, 1H), 3.76-3.82 (m, 1H), 3.85 (dd, *J* = 5.7, 11.2 Hz, 1H), 4.61 (t, *J* = 10.1 Hz, 1H), 4.69 (t, *J* = 10 Hz, 1H), 7.32-7.38 (m, 5H).

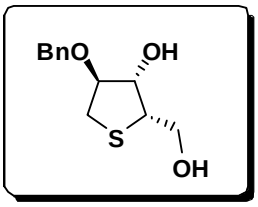
^{13}C NMR ($CDCl_3$, 100 MHz) : δ (ppm) 39.33, 47.75, 62.94, 72.03, 76.10, 78.20, 127.92, 128.01, 128.56, 137.79.

IR (Neat) : 3458 (broad), 2930, 2865, 1613, 1552, 1250, 1139 and (C-O-C), 1004 (C-S-C), 736 and 718 (aromatic).

Mass (ESI-TOF) m/z : 263.1 ($[M+Na]^+$).

HRMS (TOF) m/z : calculated for $C_{12}H_{16}NaO_3S$ ($[M+Na]^+$) 263.0718, found 263.0713.

(2*S*,3*S*,4*S*)-4-(Benzyloxy)-2-(hydroxymethyl)tetrahydrothiophen-3-ol (52)



Physical appearance : Dense yellow liquid

Molecular Formula : $C_{12}H_{16}O_3S$.

Optical rotation : $[\alpha]_D^{25}$ -7.92 °, *c* 1, $CHCl_3$.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ (ppm) 1.93 (bs, 1H, D_2O exchangeable), 2.03 (bs, 1H, D_2O exchangeable), 3.05-3.13 (m, 2H), 3.17 (dd, *J* = 5.5, 8.2 Hz, 1H), 3.68 (dd, *J* = 4.5, 10.3 Hz, 1H), 3.83-3.91 (m, 2H), 3.98 (dd, *J* =5.5, 11.0 Hz, 1H), 4.60 (dd, *J* = 5.5, 11.4 Hz, 1H), 4.73 (dd, *J* = 5.6,11.6 Hz, 1H), 7.32-7.38 (m, 5H).

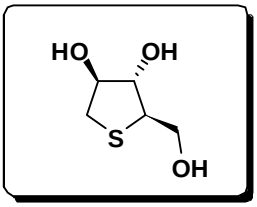
^{13}C NMR ($CDCl_3$, 100 MHz) : δ (ppm) 39.14, 45.95, 63.08, 72.13, 77.21, 77.80, 127.97, 128.07, 128.58, 137.76.

IR (Neat) : 3471 (broad), 2938, 2855, 1620, 1560, 1259, 1145 and (C-O-C), 996 (C-S-C), 740 and 721 (aromatic).

Mass (ESI-TOF) m/z : 263.2 ($[M+Na]^+$).

HRMS (TOF) m/z : calculated for $C_{12}H_{16}NaO_3S$ ($[M+Na]^+$) 263.0718, found 263.0725.

(2*S*,3*S*,4*S*)-2-(Hydroxymethyl)tetrahydrothiophene-3,4-diol or 1,4-Anhydro-4-thio-D-arabinitol (7)

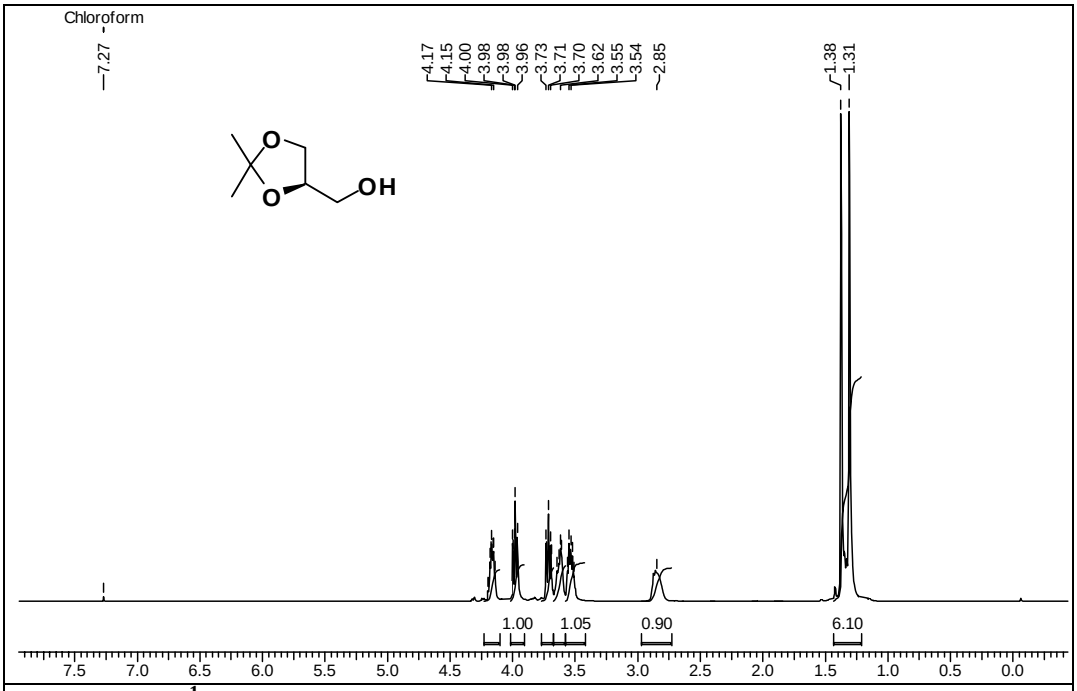


To a solution of **47** (0.06 g, 0.25 mmol) in 2 mL of dry CH_2Cl_2, borontrichloride (0.059 g, 0.5 mL, 0.5 mmol, 1 M solution in CH_2Cl_2) was added dropwise at -78 °C and allowed to stir at same temperature for 1 h. After 1 h the

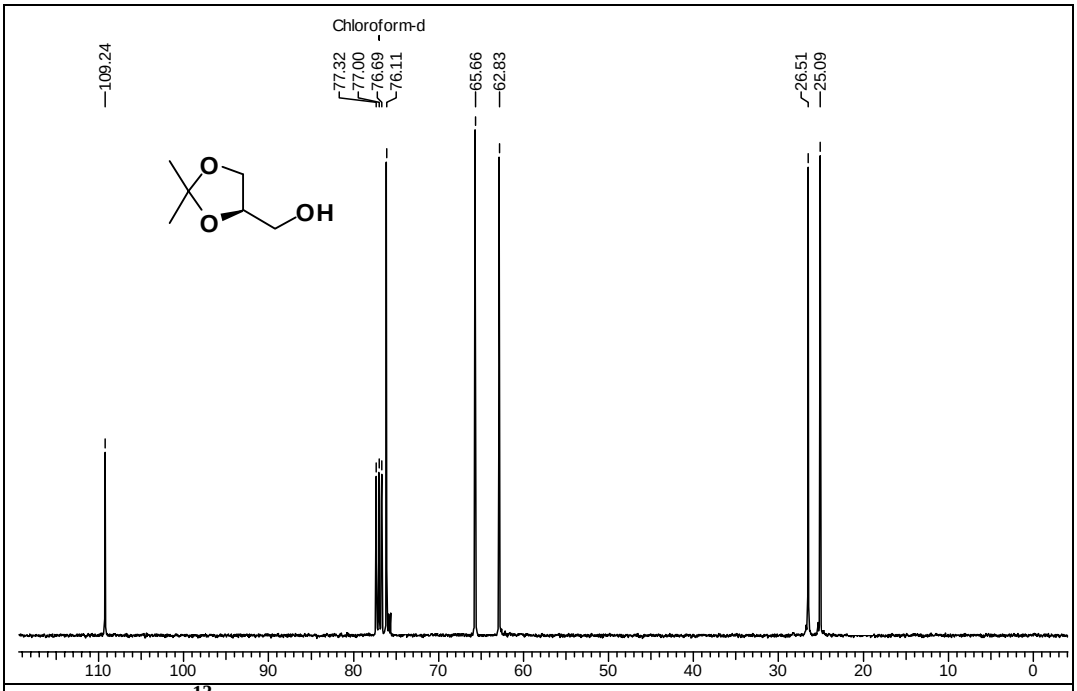
reaction mixture was quenched with aqueous saturated $NaHCO_3$ solution and extracted with ethyl acetate (2 x 2 mL). The organic layer was further washed with water (2 x 2 mL). The organic layer was discarded and the combined aqueous layers were concentrated under diminished pressure to give crude syrupy mass which was further dissolved in dry methanol (5 mL) and filtered over a pad of celite. The residue was washed with methanol (2 x 5 mL). The combined methanol layers were concentrated under reduced pressure to give the crude product which was further purified by silica-gel column chromatography using chloroform: methanol (9:1) as eluent to afford the pure 1,4-anhydro-4-thio-D-arabinitol **7** (0.022 g, 60%) as dense yellow liquid.

Molecular Formula	: $C_5H_{10}O_3S$.
Optical rotation	: $[\alpha]_D^{25}$ + 39.81, *c* 1.3, MeOH (Lit. +40.2, *c* 1.28, MeOH).[6d]
^{1}H NMR ($CDCl_3$, 400MHz)	: δ (ppm) 2.69 (dd, *J* = 6.2, 6.3 Hz, 1H); 2.99 (dd, *J* = 5.7, 10.7 Hz, 1H); 3.23 (q, *J* = 5.4 Hz, 1H); 3.61 (dd, *J* = 6.8, 6.7 Hz, 1H); 3.82 (dd, *J* = 5.4, 10.7 Hz, 1H), 3.86 (t, *J* = 5.6 Hz, 1H); 4.12 (q, *J* = 5.6 Hz, 1H).
^{13}C NMR ($CDCl_3$, 100MHz)	: δ (ppm) 34.70, 53.69, 65.53, 79.26, 80.60.
IR (Neat) cm^{-1}	: 3410 (broad), 2941, 1445, 1112, 1050.
MS (ESI-TOF) m/z	: 273.1 ($[M+Na]^+$).
HRMS (TOF) m/z	: calculated for $C_5H_{10}NaO_3S$ ($[M+Na]^+$) 273.0248, found 273.0243.

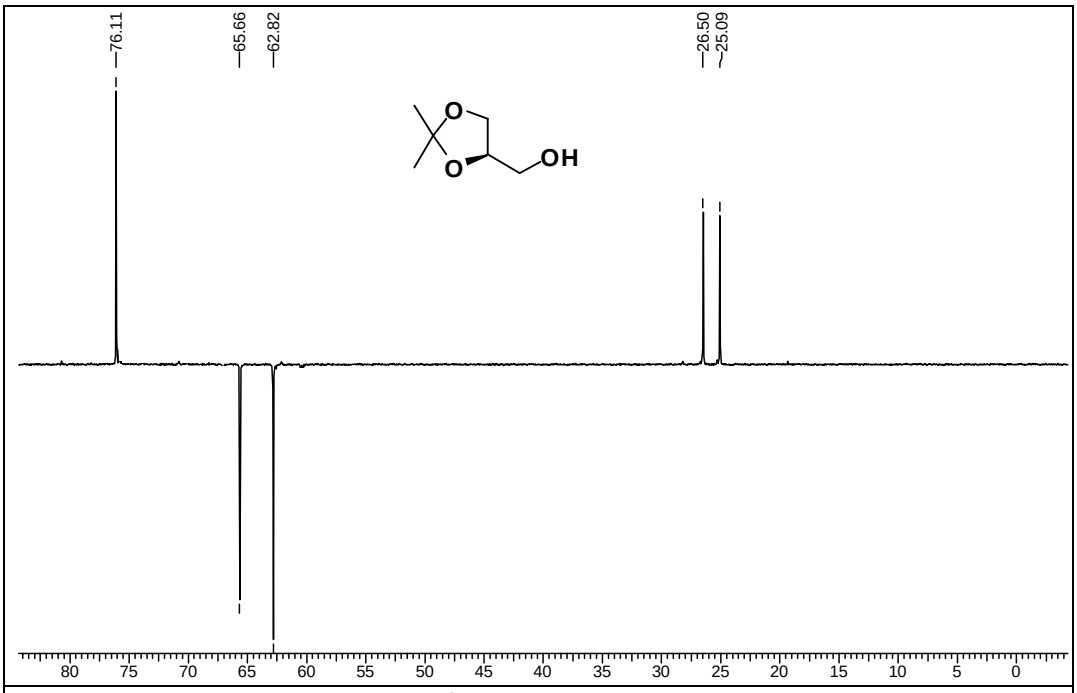
2.8 Analytical data



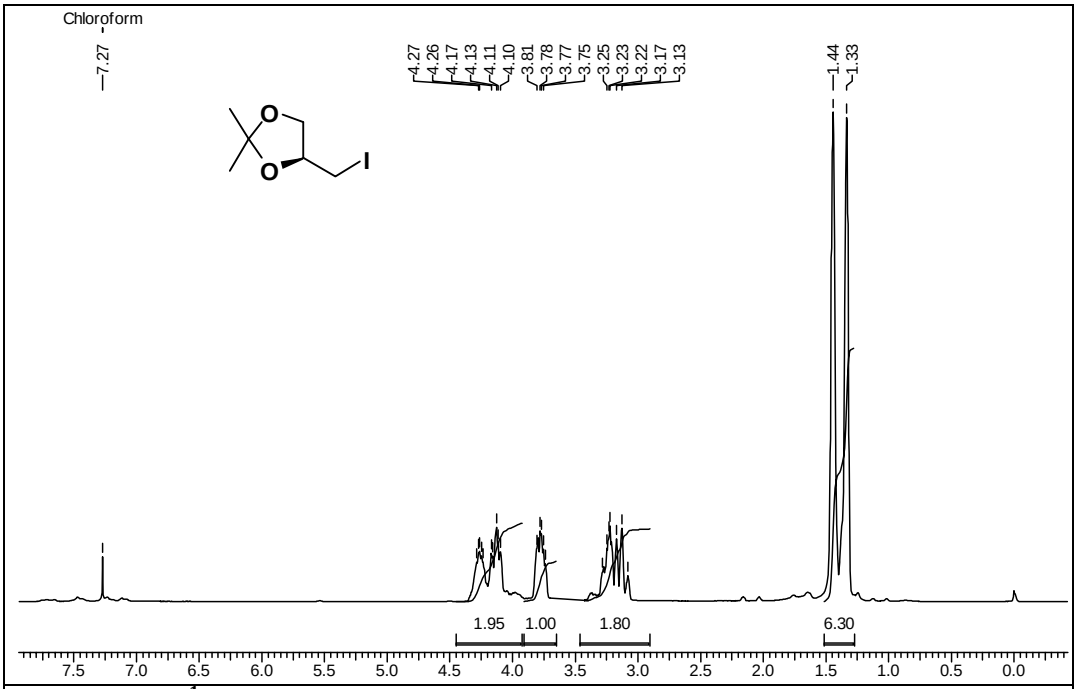
^{1}H NMR spectrum of compound 51 ($CDCl_3$, 200 MHz)



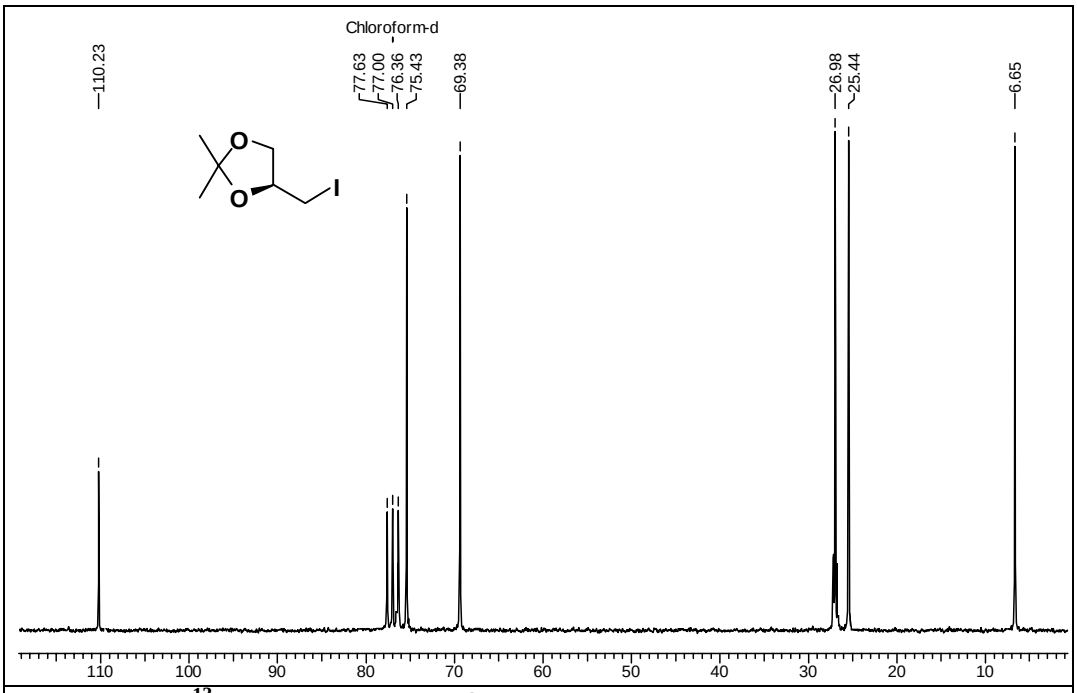
^{13}C NMR spectrum of compound 51 ($CDCl_3$, 50 MHz)



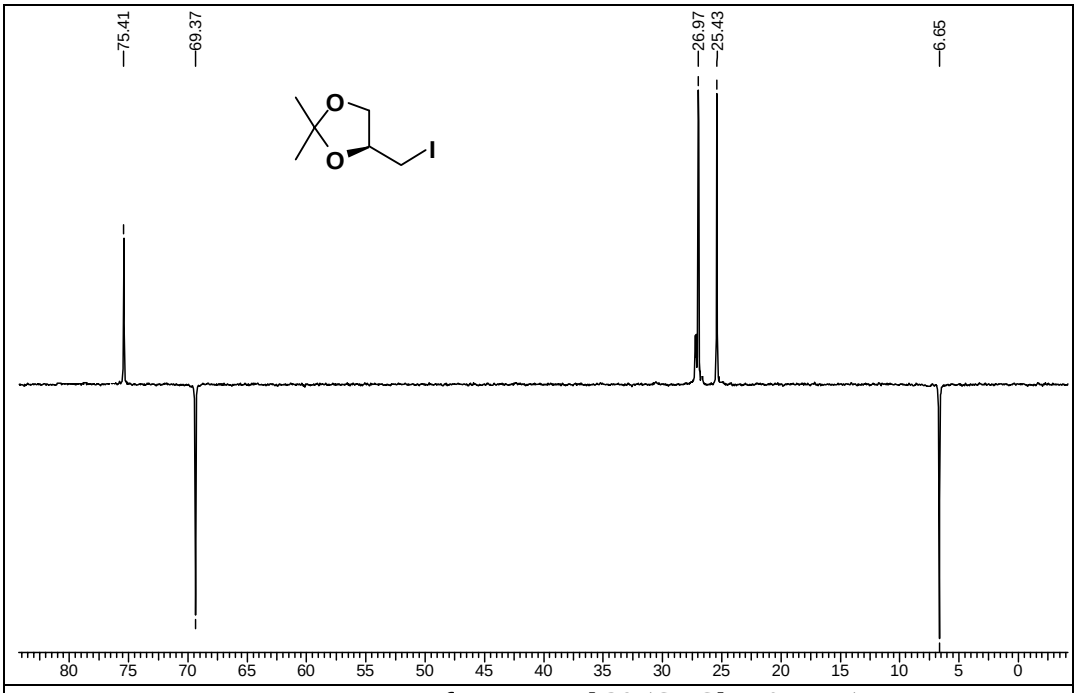
DEPT spectrum of compound 51 ($CDCl_3$, 50 MHz)



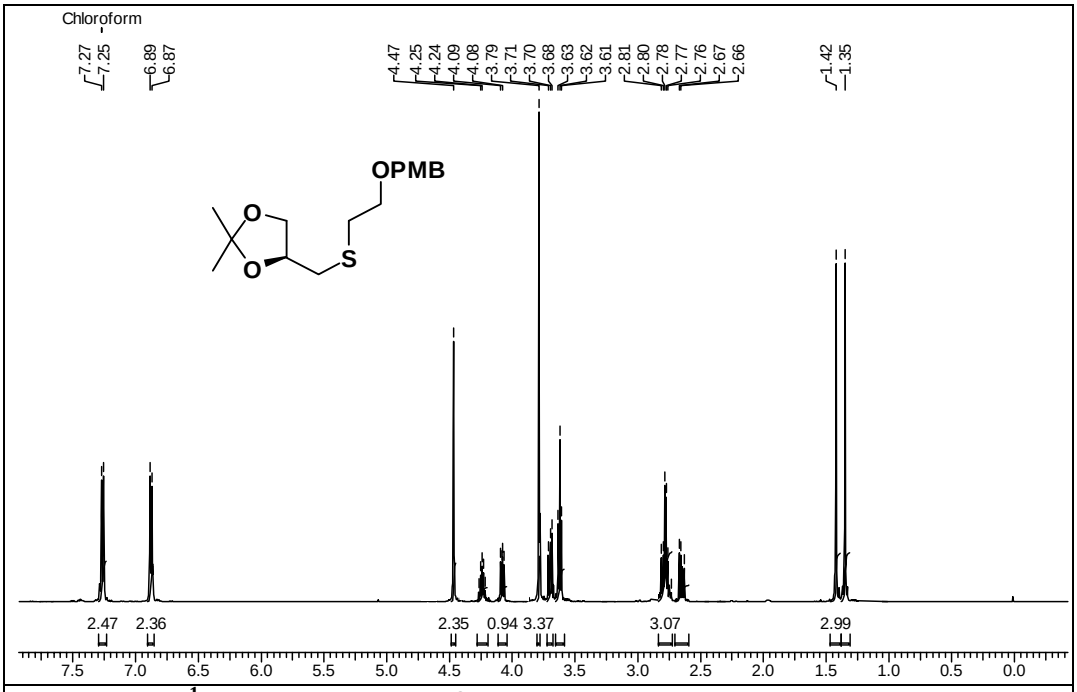
^{1}H NMR spectrum of compound 39 ($CDCl_3$, 200 MHz)



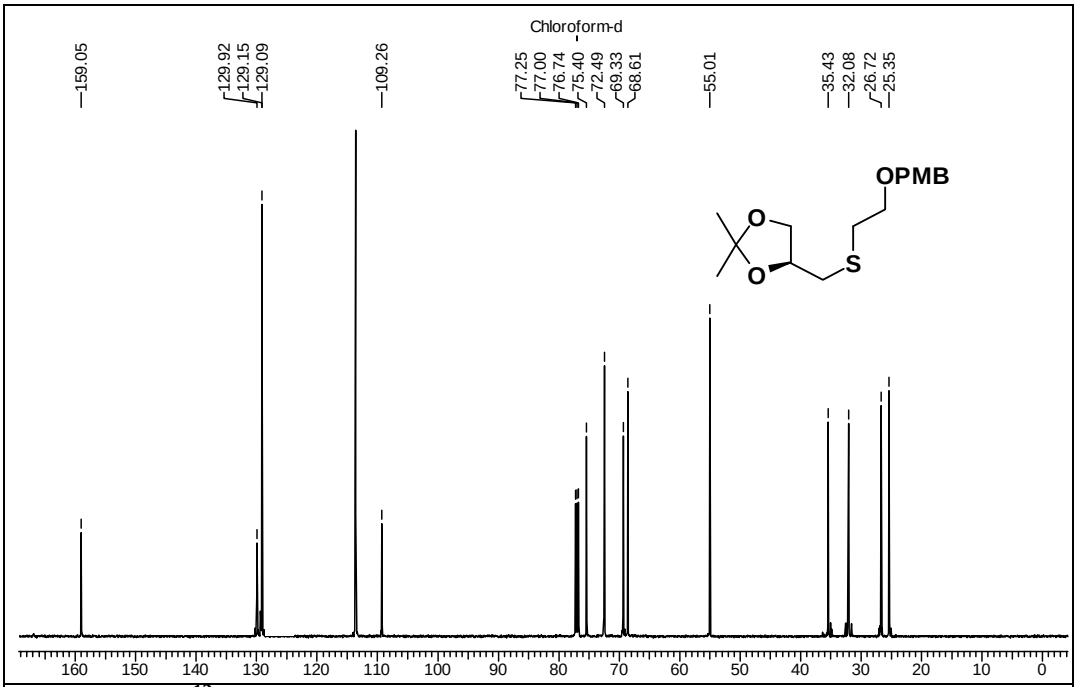
^{13}C NMR spectrum of compound 39 ($CDCl_3$, 50 MHz)



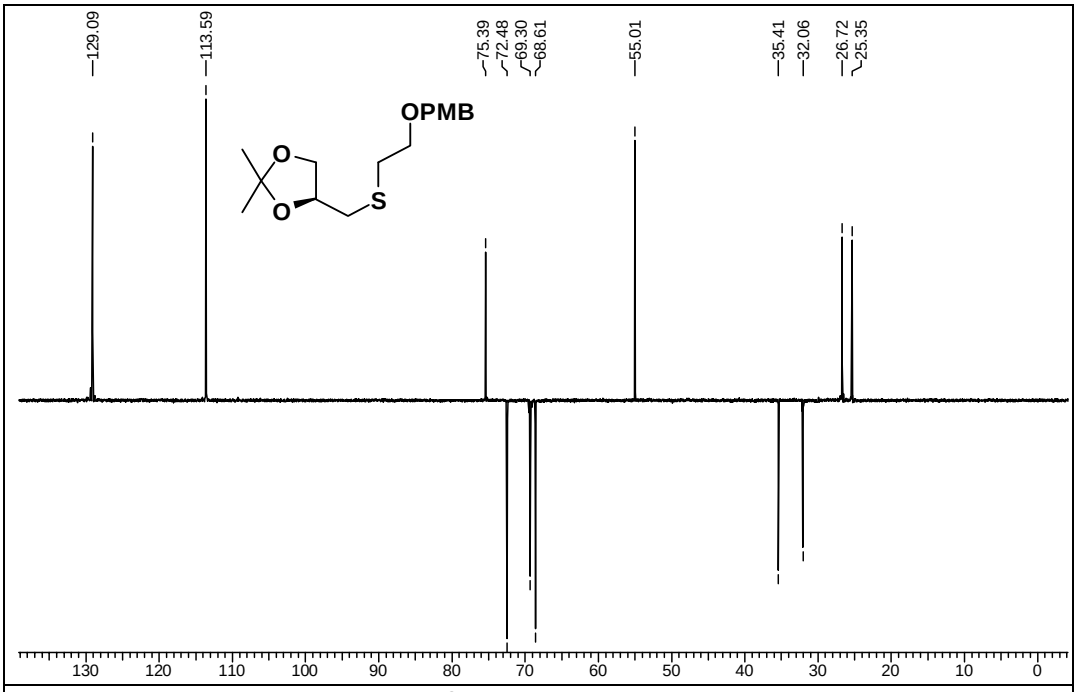
DEPT spectrum of compound 39 ($CDCl_3$, 50 MHz)



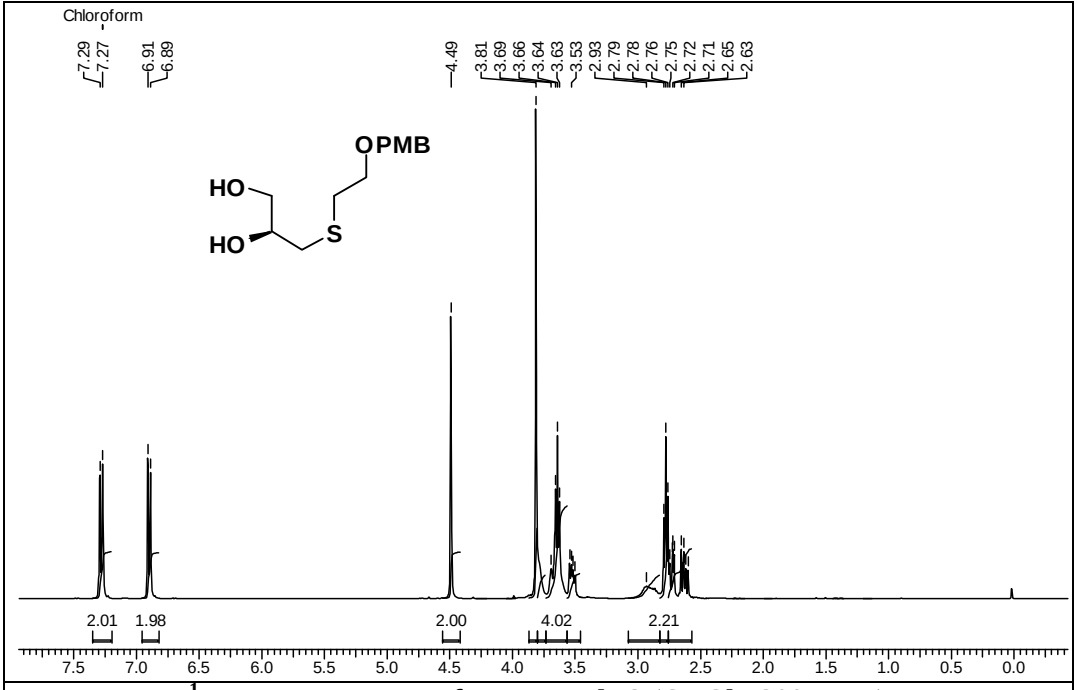
^{1}H NMR spectrum of compound 41 ($CDCl_3$, 200 MHz)



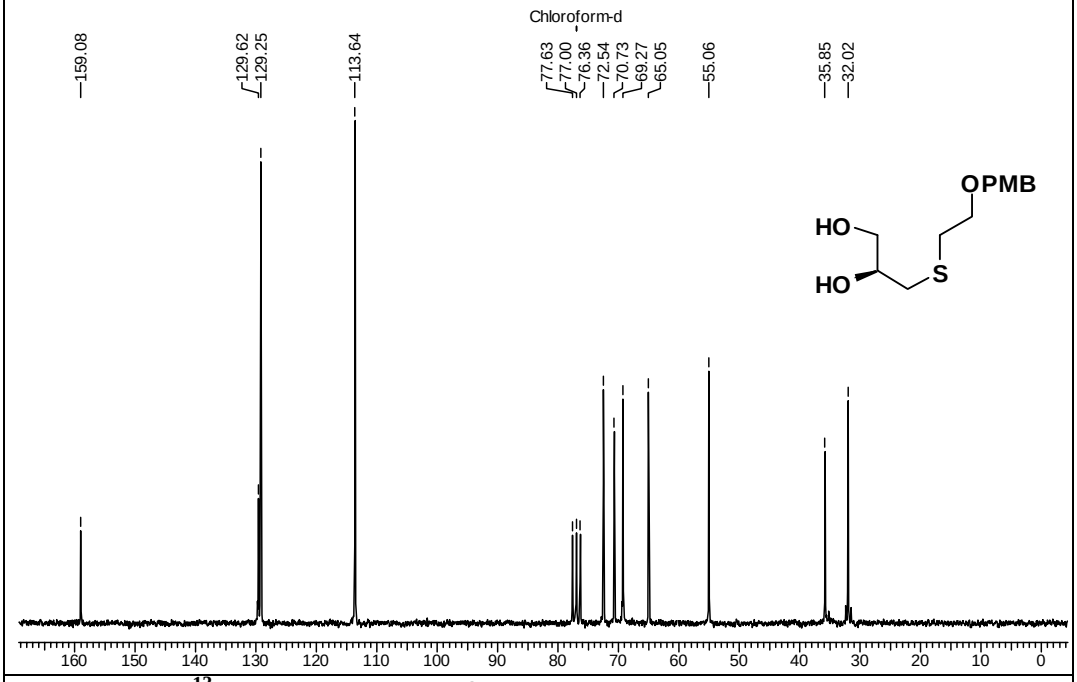
^{13}C NMR spectrum of compound 41 ($CDCl_3$, 50 MHz)



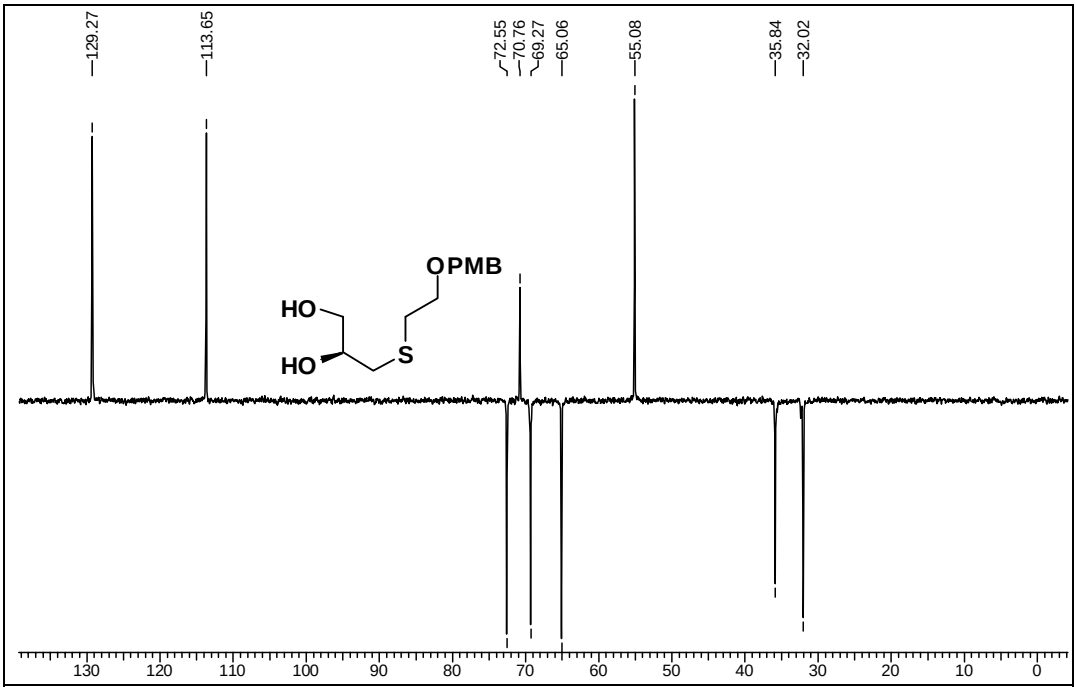
DEPT spectrum of compound 41 ($CDCl_3$, 50 MHz)



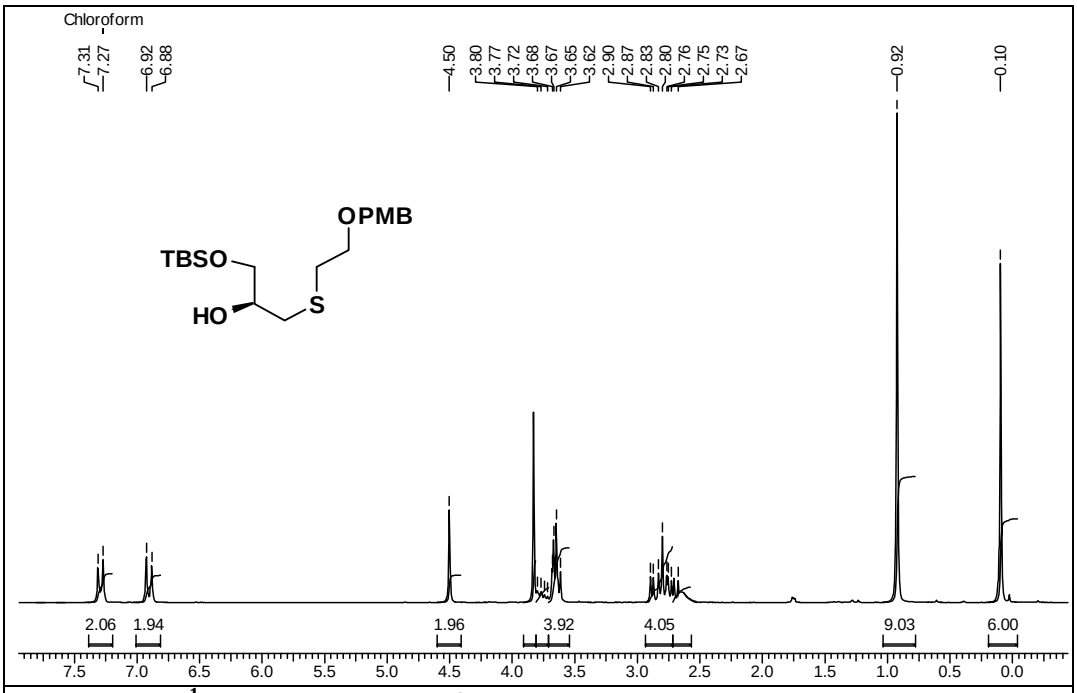
^{1}H NMR spectrum of compound 42 ($CDCl_3$, 200 MHz)



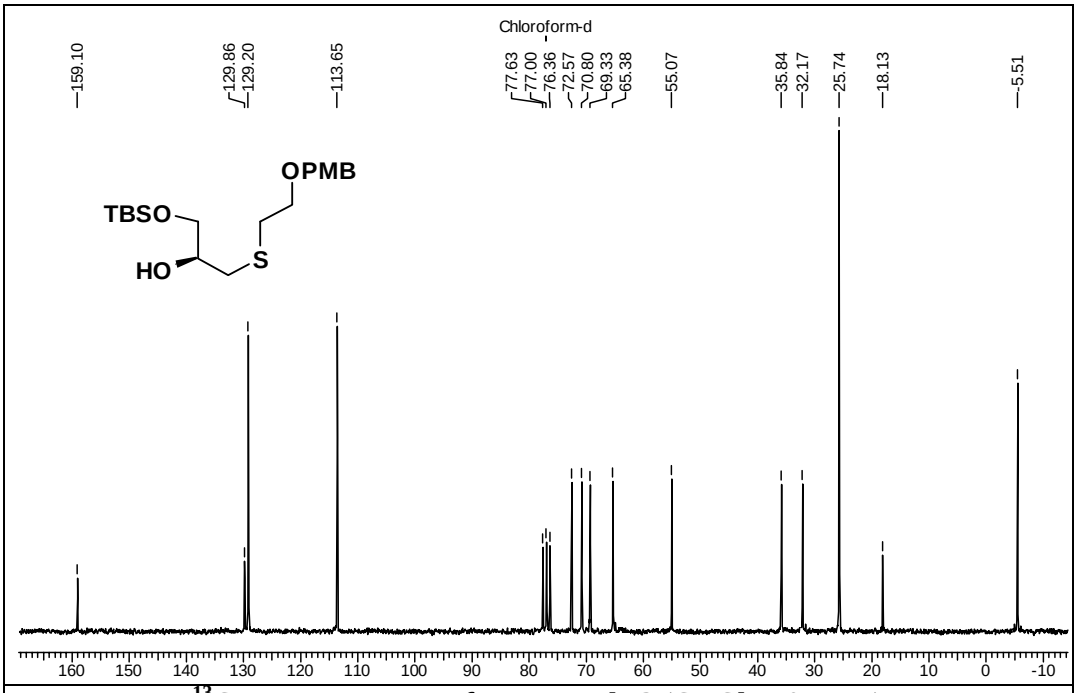
^{13}C NMR spectrum of compound 42 ($CDCl_3$, 50 MHz)



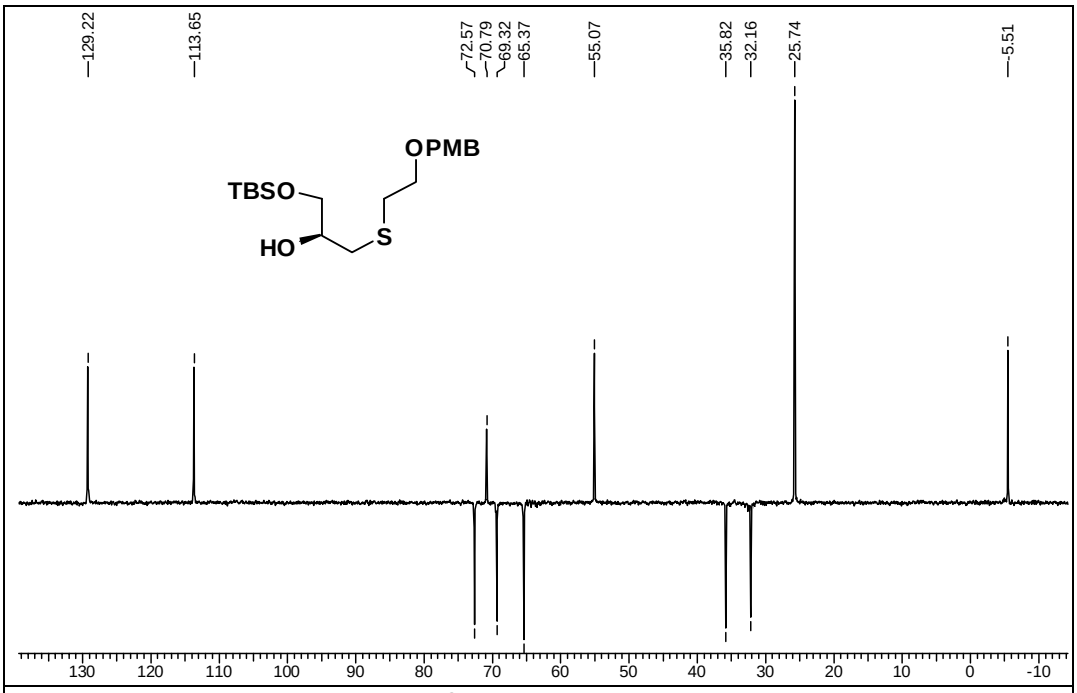
DEPT spectrum of compound 42 ($CDCl_3$, 50 MHz)



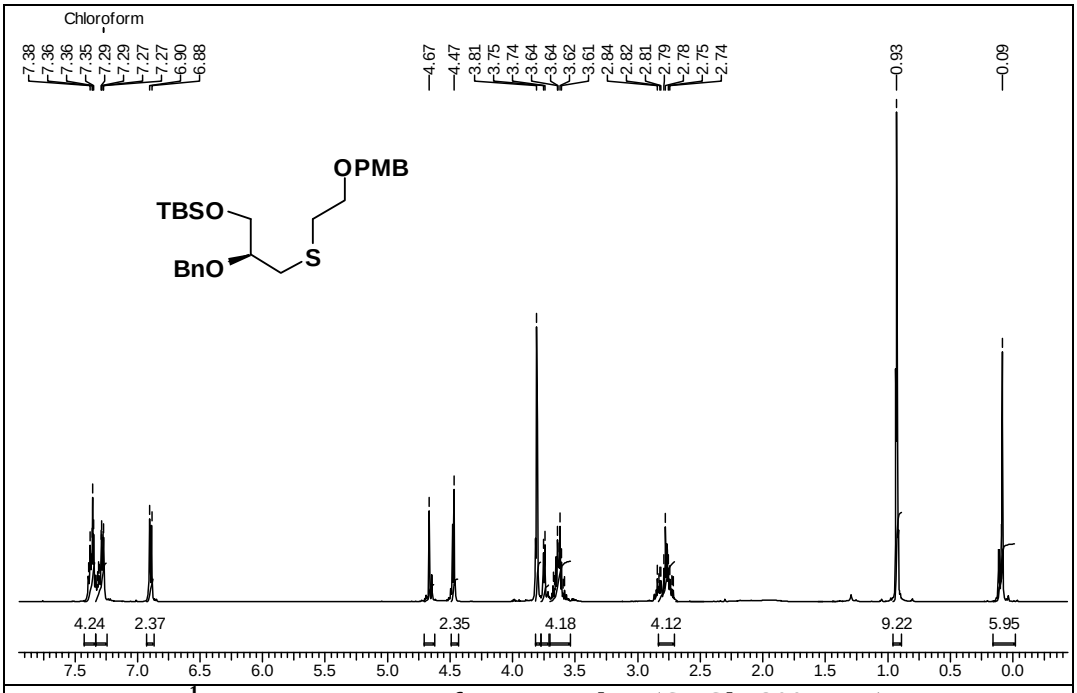
^{1}H NMR spectrum of compound 43 ($CDCl_3$, 200 MHz)



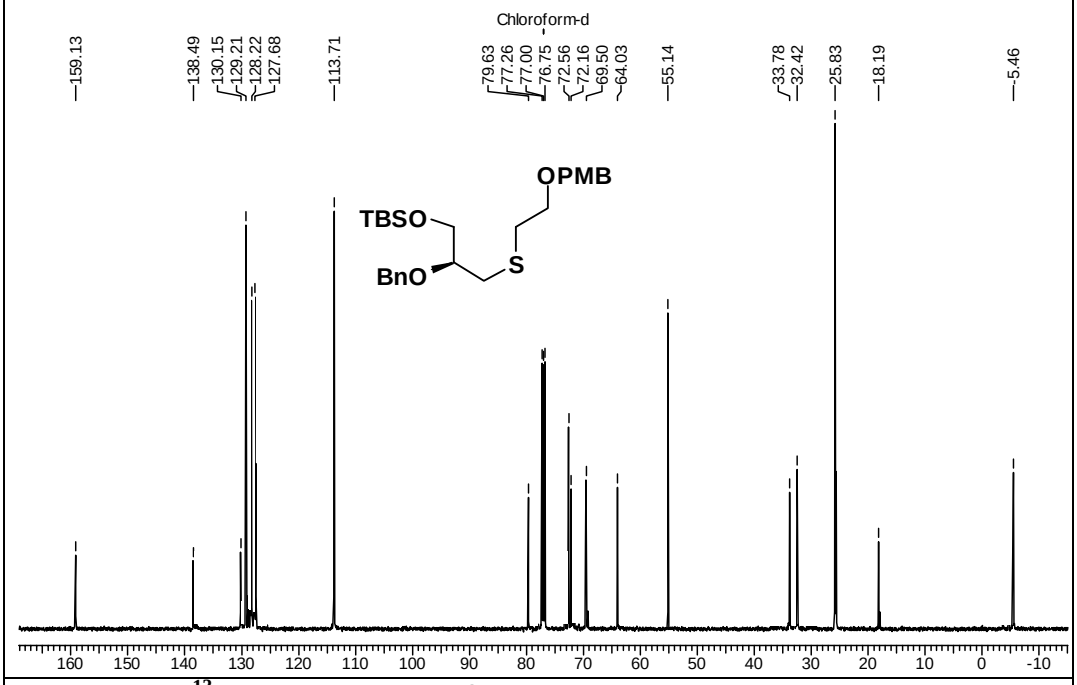
^{13}C NMR spectrum of compound 43 ($CDCl_3$, 50 MHz)



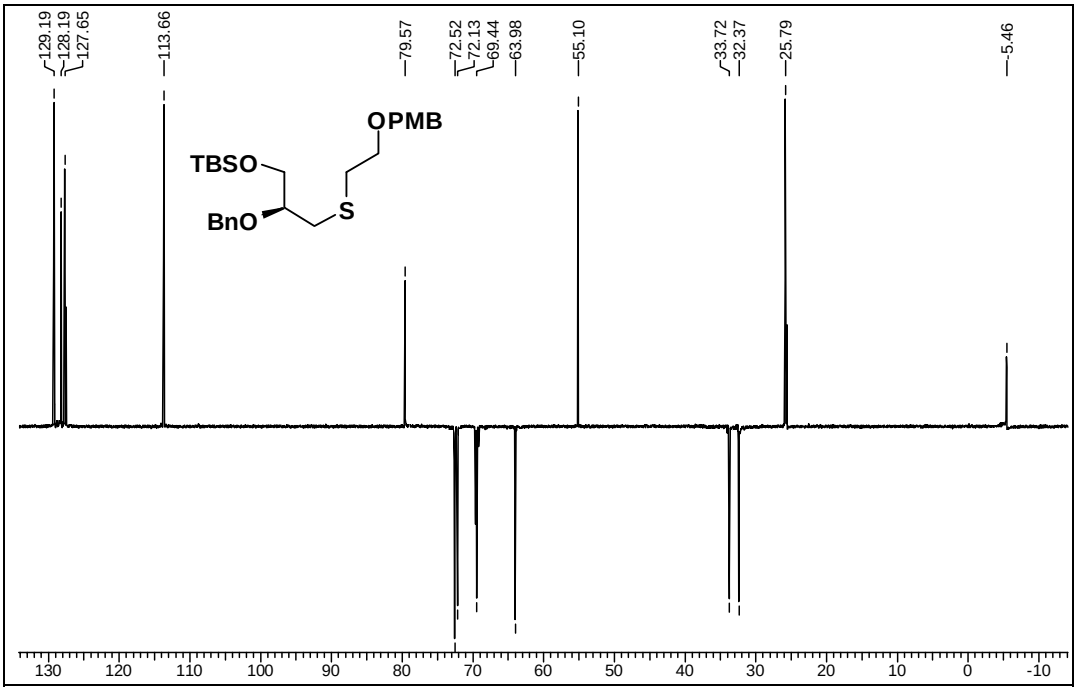
DEPT spectrum of compound 43 ($CDCl_3$, 50 MHz)



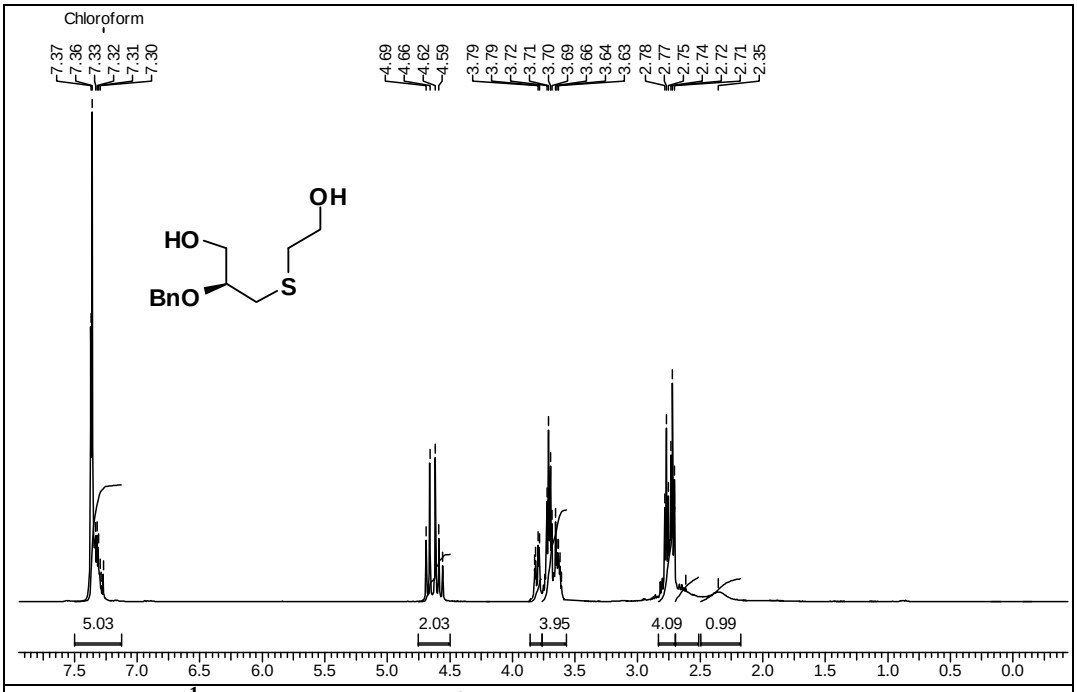
^{1}H NMR spectrum of compound 44 ($CDCl_3$, 200 MHz)



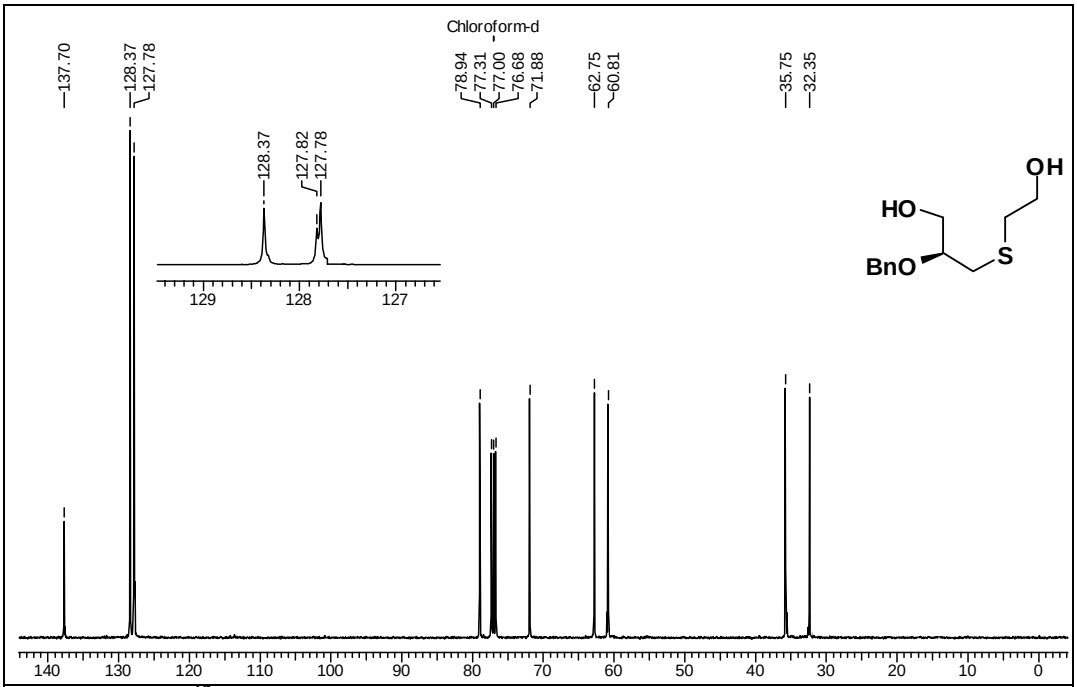
^{13}C NMR spectrum of compound 44 ($CDCl_3$, 50 MHz)



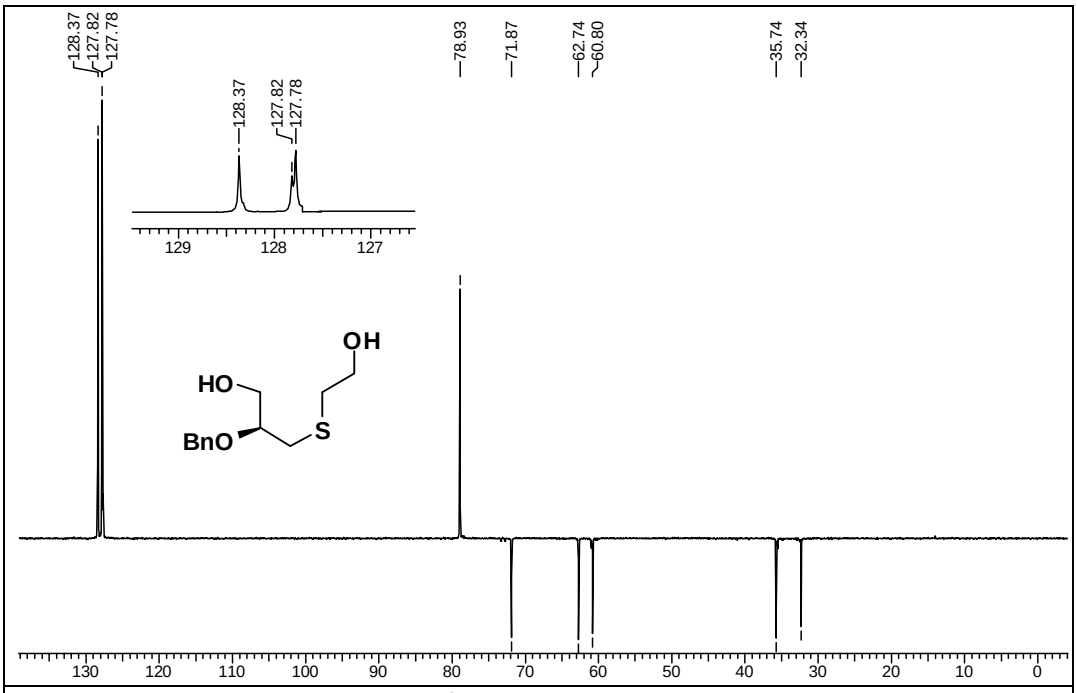
DEPT spectrum of compound 44 ($CDCl_3$, 50 MHz)



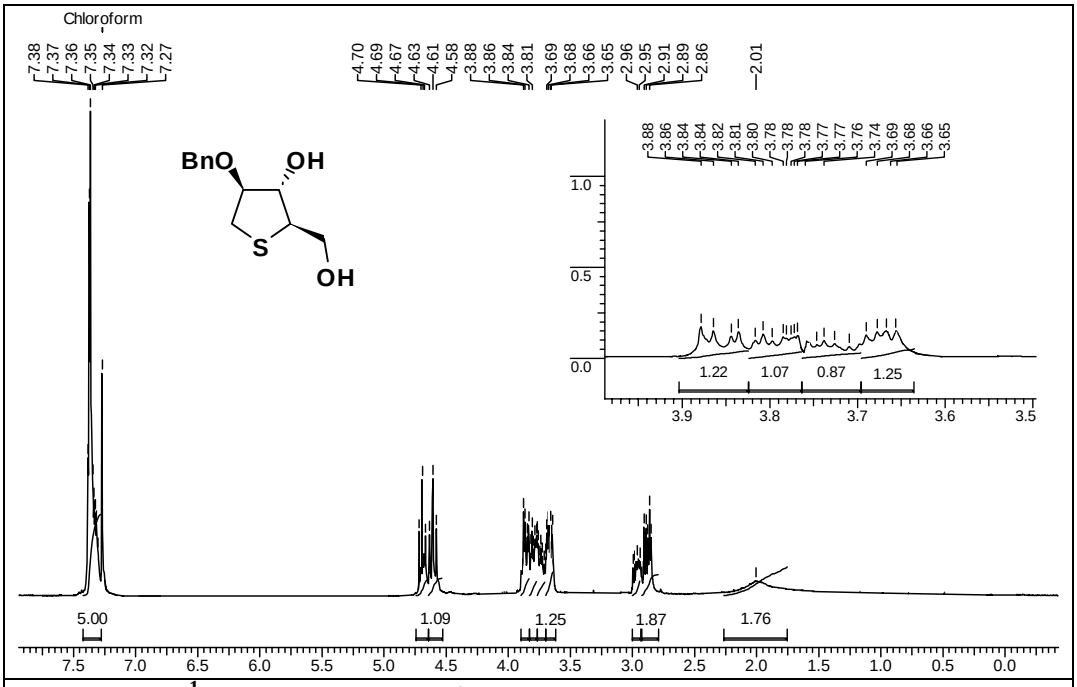
^{1}H NMR spectrum of compound 45 ($CDCl_3$, 200 MHz)



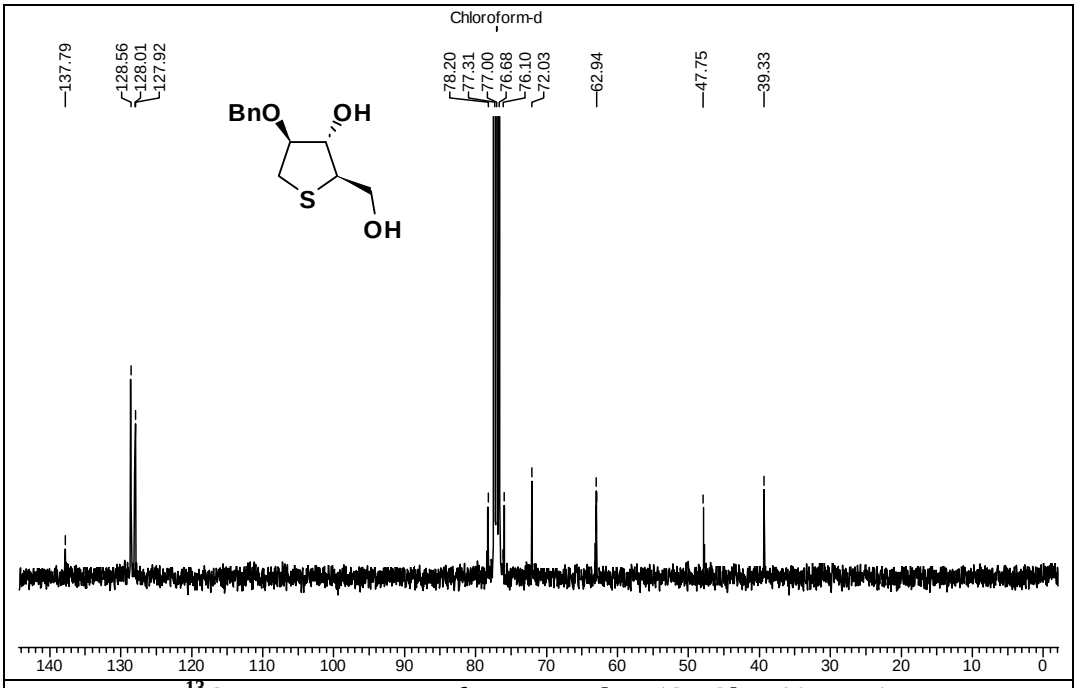
^{13}C NMR spectrum of compound 45 ($CDCl_3$, 50 MHz)



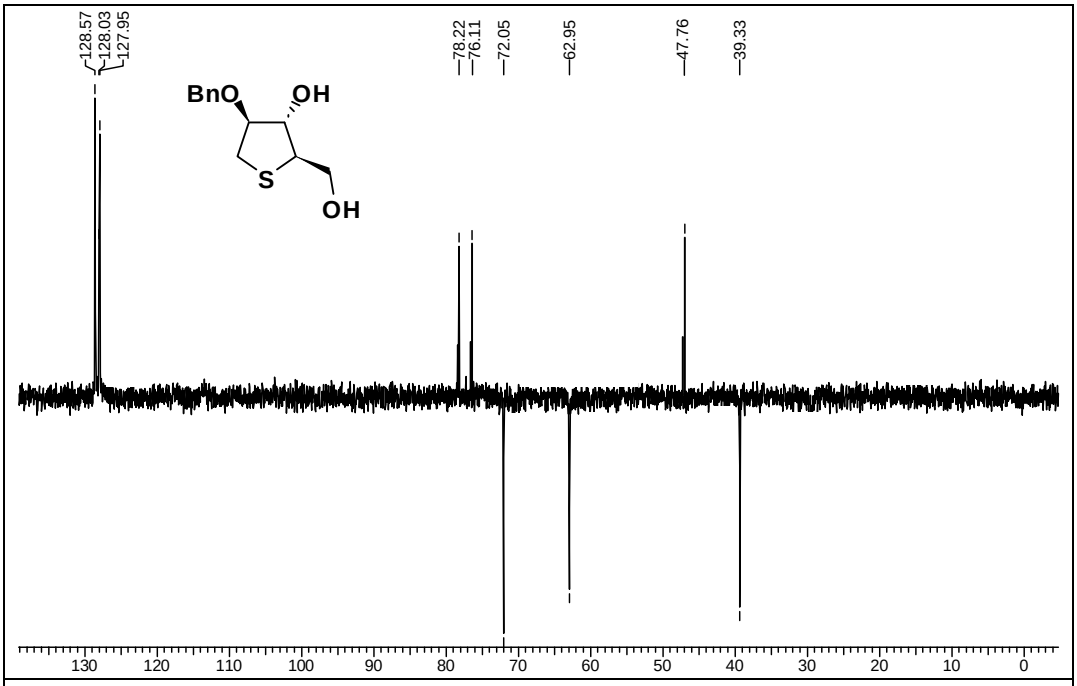
DEPT spectrum of compound 45 ($CDCl_3$, 50 MHz)



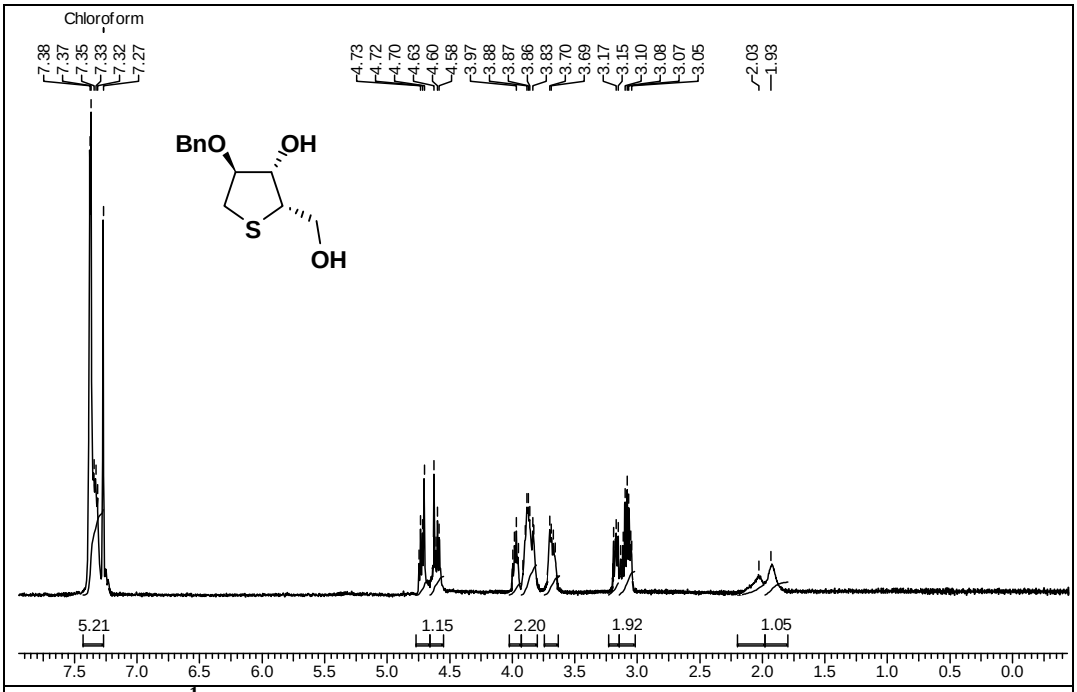
^{1}H NMR spectrum of compound 47 ($CDCl_3$, 400 MHz)



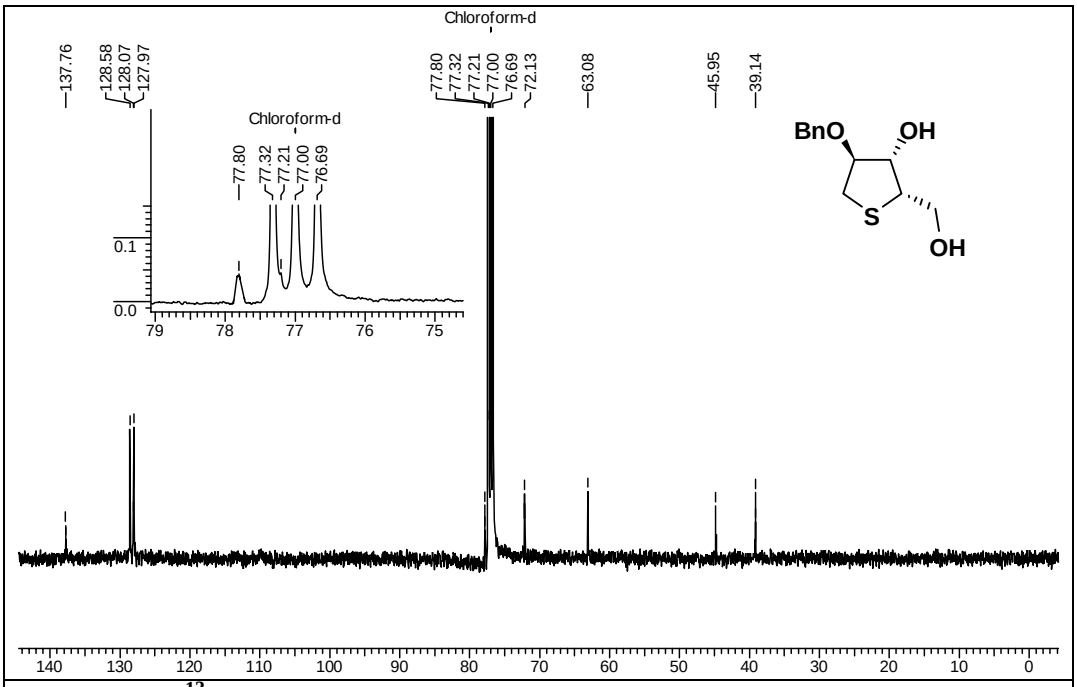
^{13}C NMR spectrum of compound 47 ($CDCl_3$, 100 MHz)



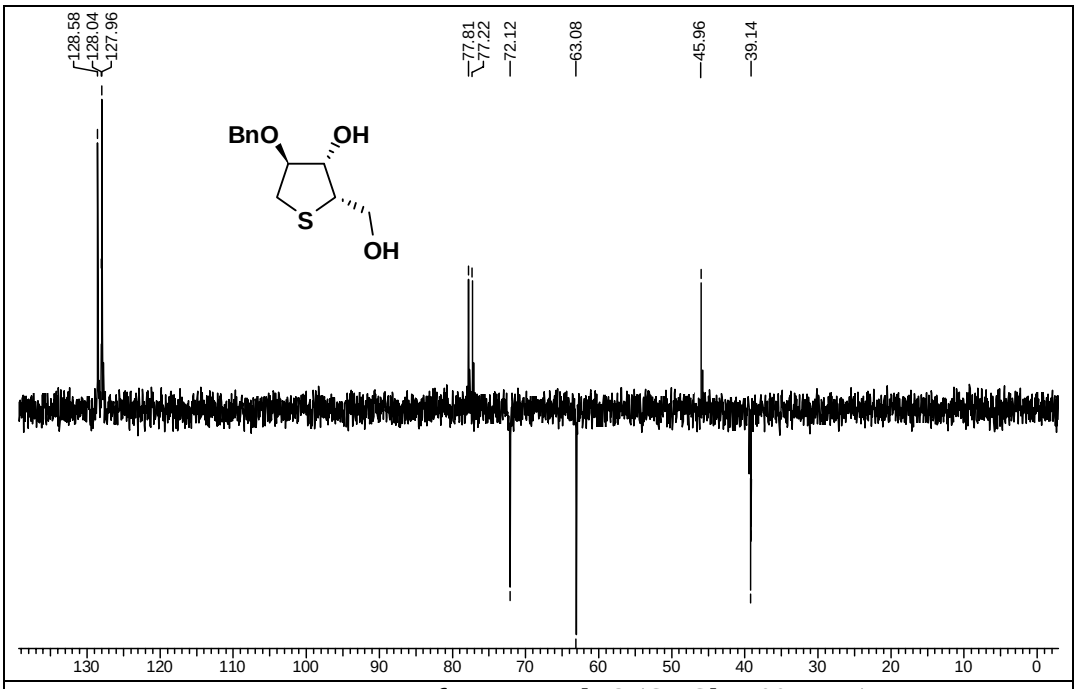
DEPT spectrum of compound 47 ($CDCl_3$, 100 MHz)



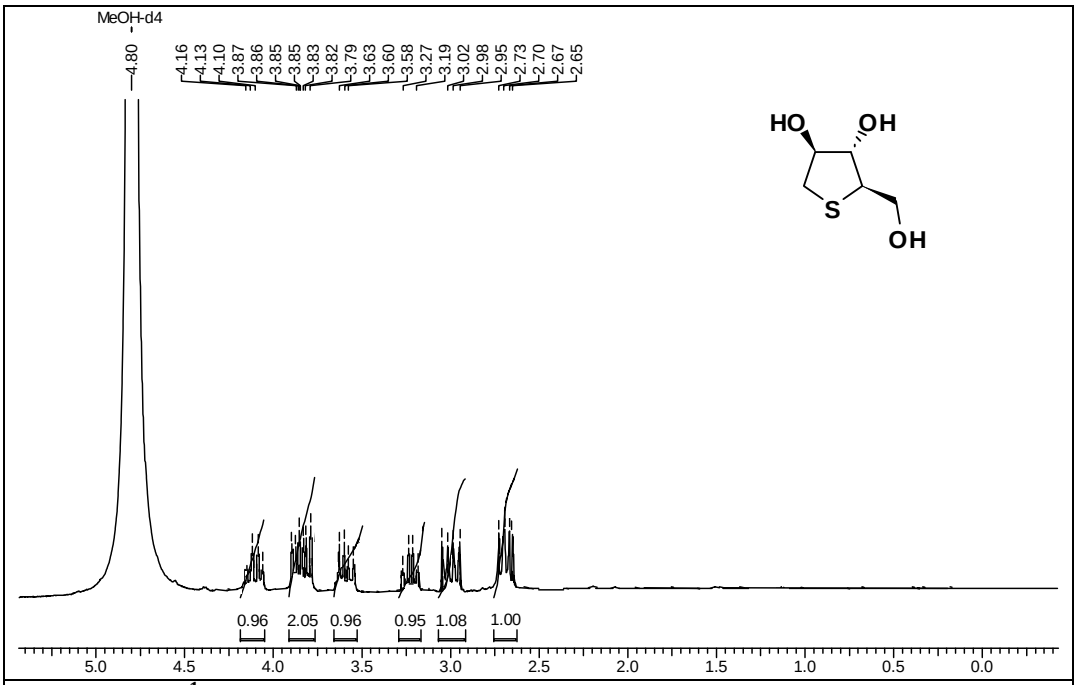
^{1}H NMR spectrum of compound 52 ($CDCl_3$, 400 MHz)



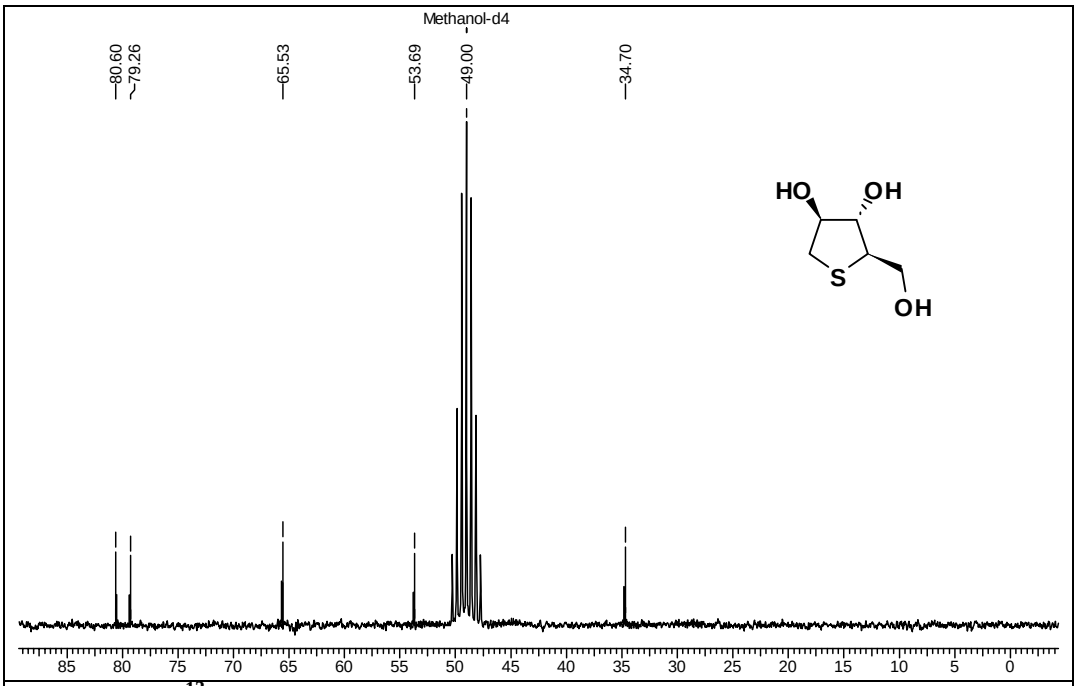
^{13}C NMR spectrum of compound 52 ($CDCl_3$, 100 MHz)



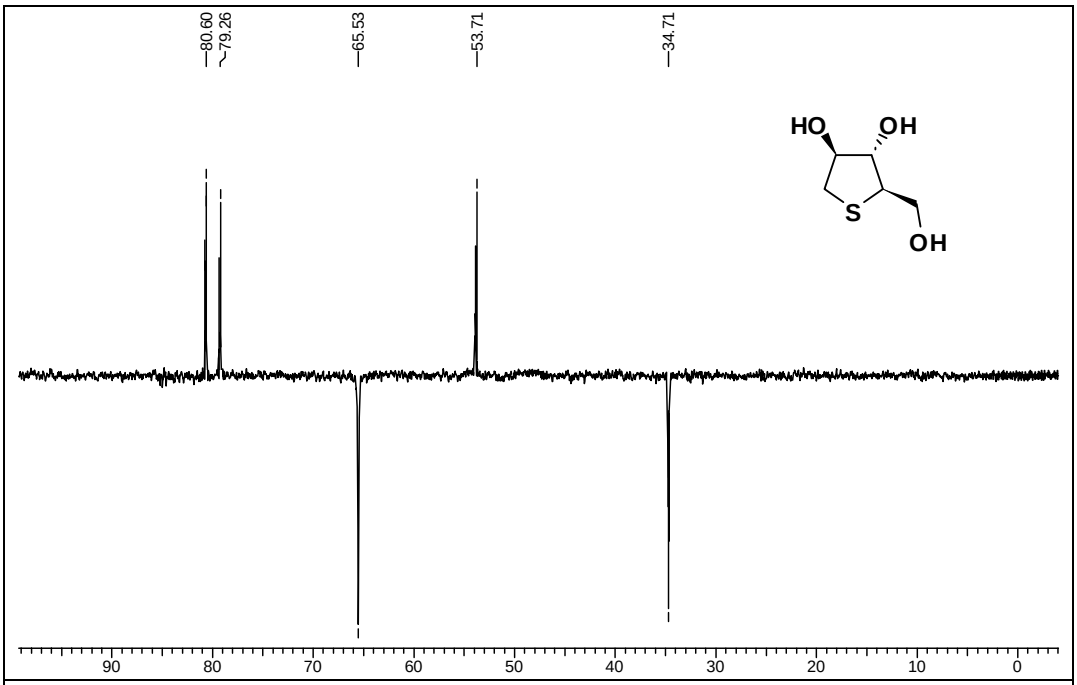
DEPT spectrum of compound 52 ($CDCl_3$, 100 MHz)



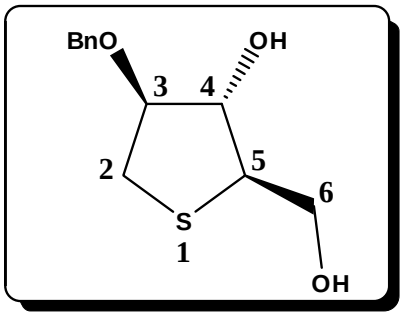
^{1}H NMR spectrum of compound 7 (CD_3OD, 400 MHz)



^{13}C NMR spectrum of compound 7 (CD_3OD, 400 MHz)



DEPT spectrum of compound 7 (CD_3OD, 400 MHz)



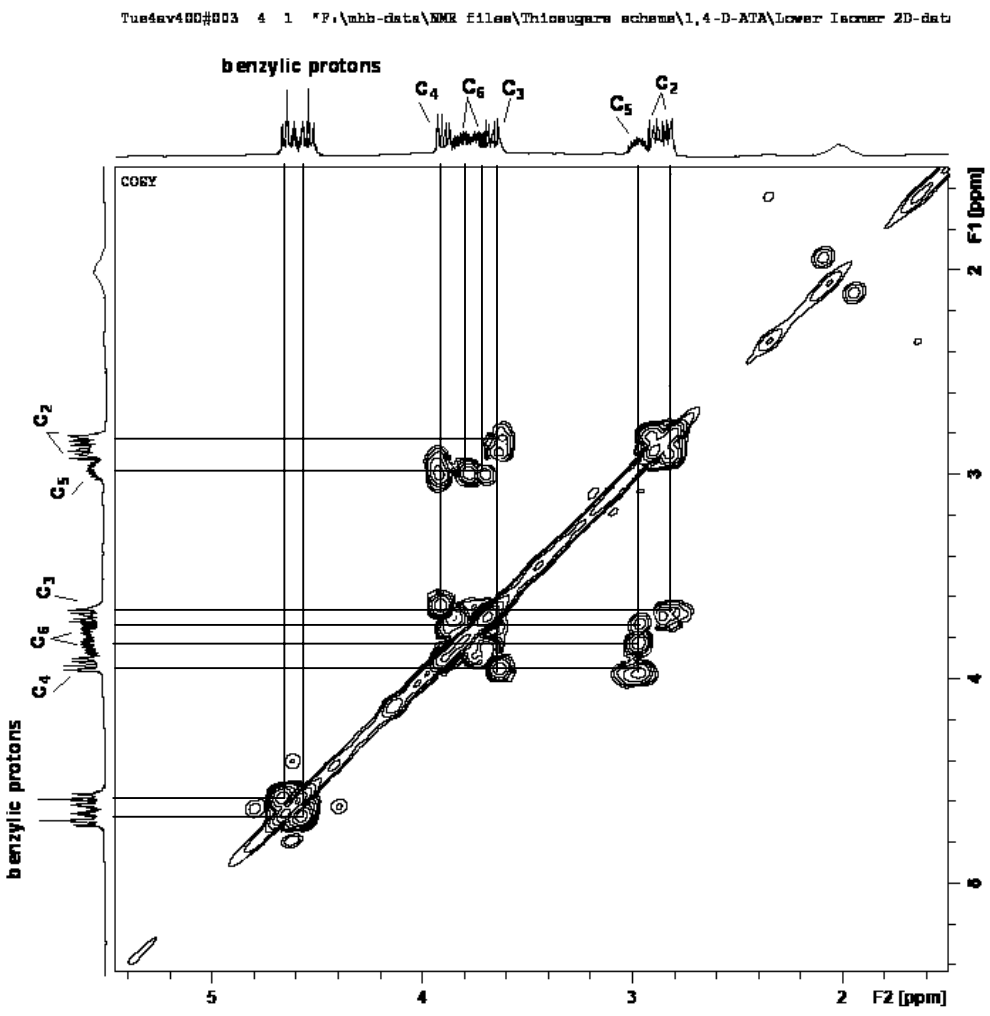
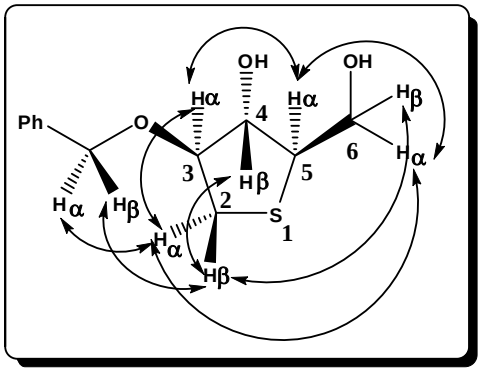


Figure 3. COSY spectrum of diastereomer 47.



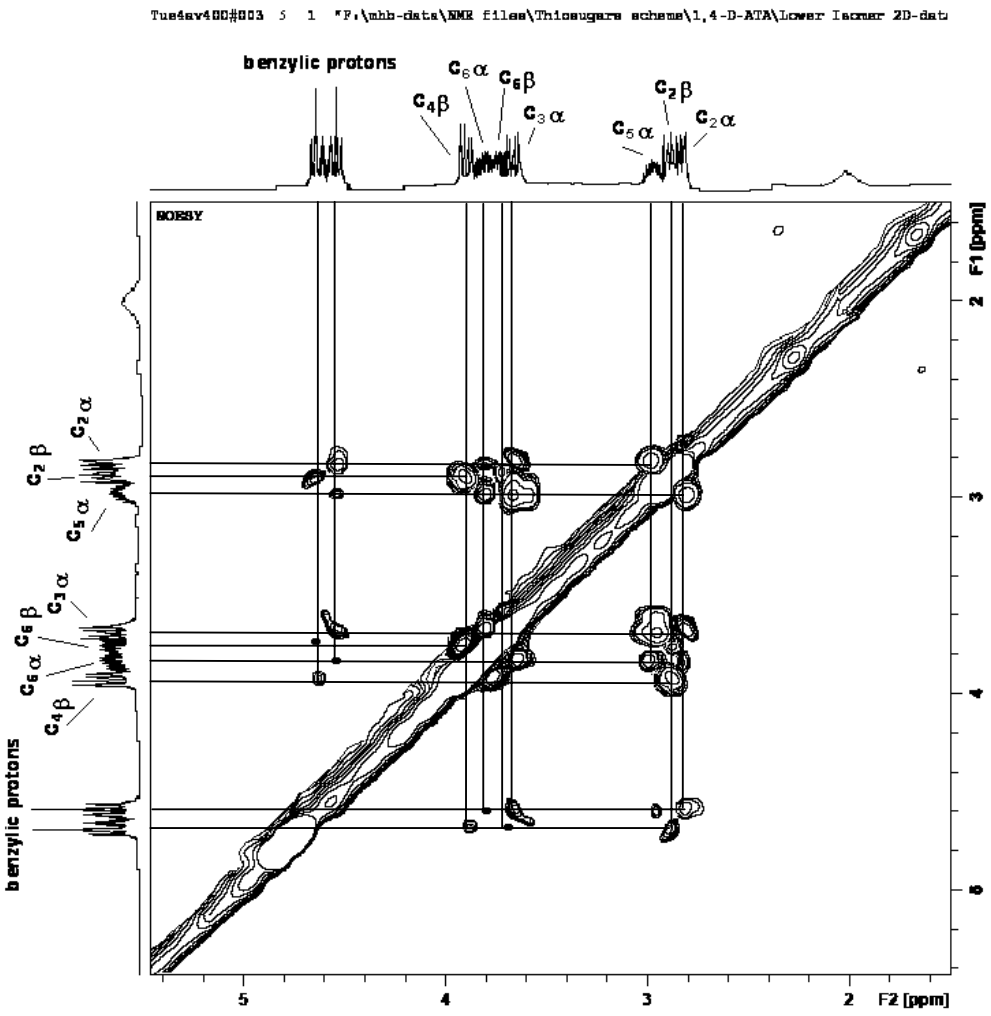
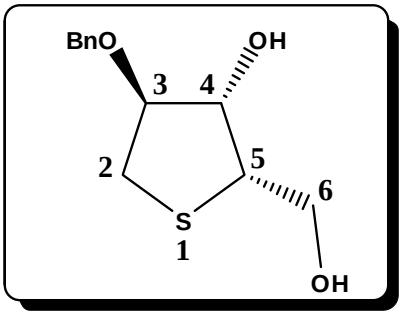


Figure 4. NOESY spectrum of diastereomer 47.



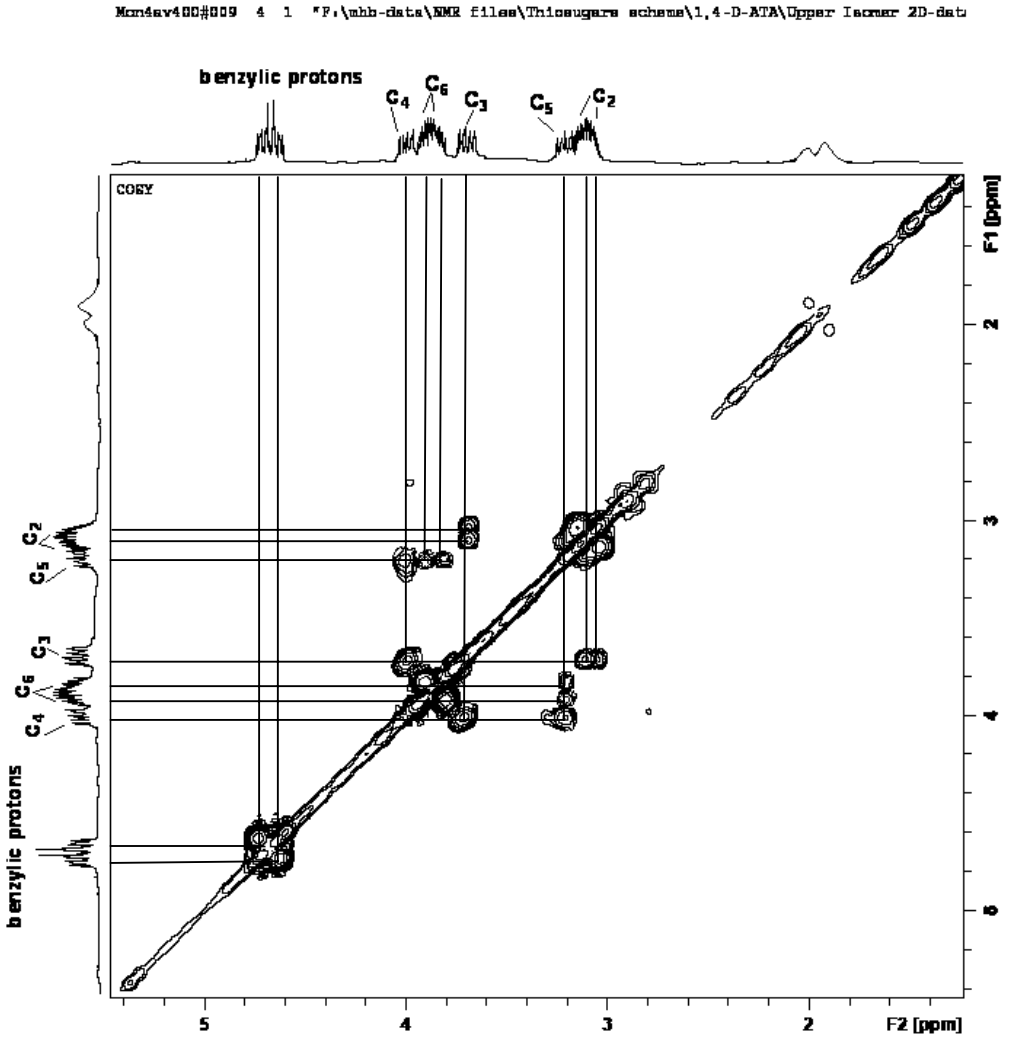
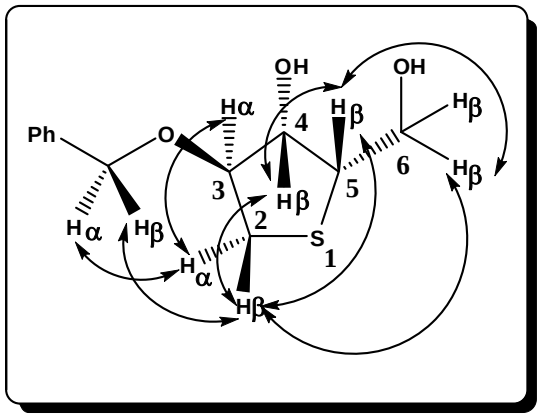


Figure 5. COSY spectrum of diastereomer 52.



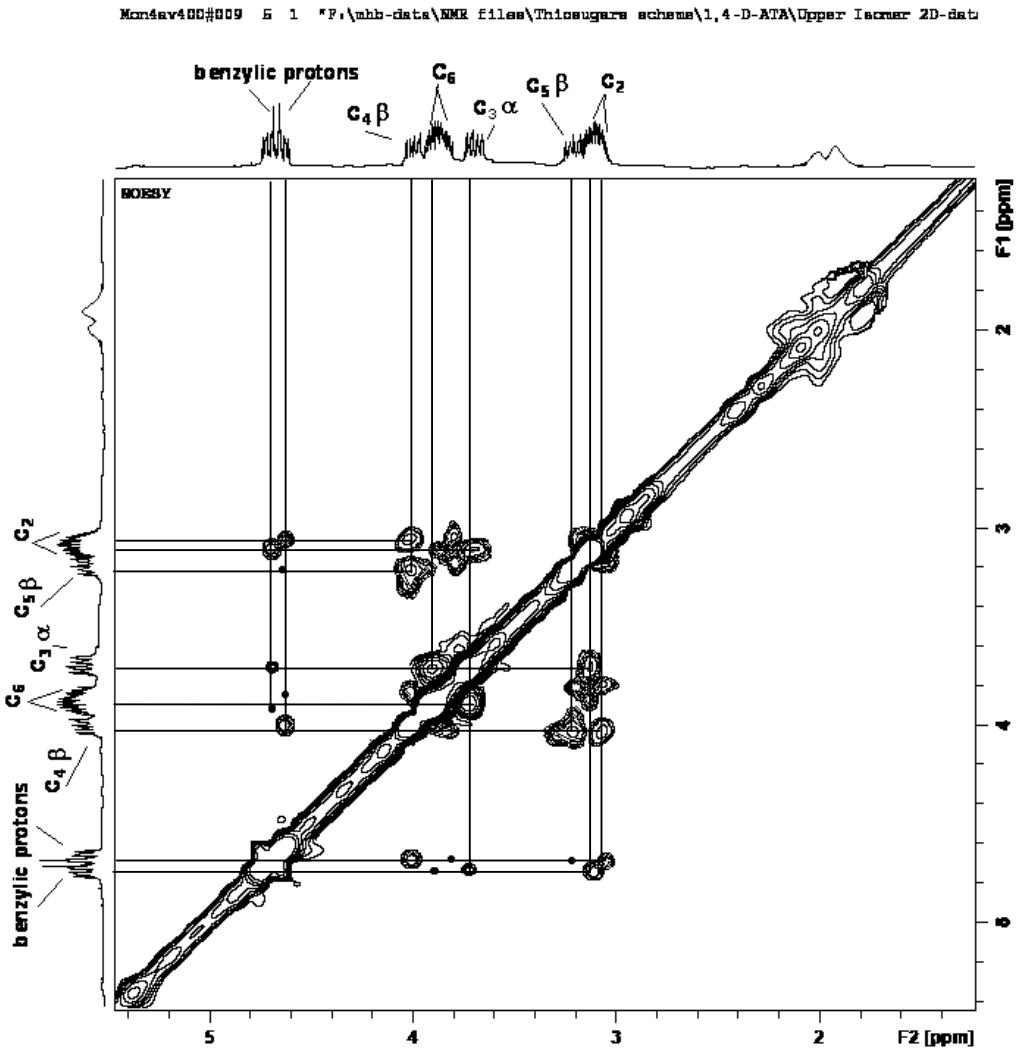


Figure 6. NOESY spectrum of diastereomer 52.

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16. In the oxidation reaction of diol **45** with IBX in EtOAc, the total consumption of diol **45** was confirmed by charring its TLC with *p*-anisaldehyde solution. The characteristic greenish spot of diol **45** [R_f = 0.25, Petroleum ether: EtOAc (3:7)] was totally disappeared which indicated the completion of reaction. But no spot was visualized for the dialdehyde **46** in the same TLC. Similar TLC dipped in 2,4-DNP solution in ethanol produced an orange colored characteristic spot of Schiff's base [R_f= 0.7, Petroleum ether: EtOAc (3:7)] on TLC which confirmed the formation of dialdehyde **46.**
17. Pidathala, C.; Hoang, L.; Vignola, N. and List, B. *Angew. Chem. Int. Ed*. **2003**, *42*, 2785.
18. Baer, E. and Fischer, H. *J. Biol. Chem.* **1939,** *128*, 463.
19. Baer, E. and Fischer, H. *J. Am. Chem. Soc.* **1948**, *70*, 609.

Chapter 3

Synthetic studies towards seven membered thiosugar and thio-mimic of Isofagomine

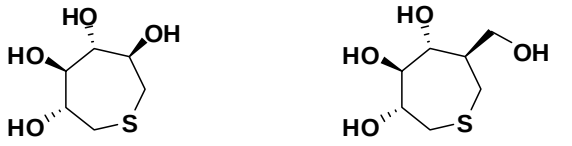
Section 1

Synthetic studies towards seven membered thiosugar

Synthetic studies towards seven membered thiosugar

3.1.1 Introduction

Like five and six membered thiosugars seven membered thiosugars are not available in the nature. Fuzier Myrielle and group first reported the synthesis of an unnatural seven membered thiosugar C_2-symmetric L-ido-thiepane **1** (Figure 1) by the thiocyclization (7-*endo*-tet process) of C_2-symmetric bis-epoxide issued from D-mannitol.[1] The C_2-symmetric L-ido-thiepane **1** was found to be a low inhibitor of α-D-glucosidase.[2] It was also utilized in developing the methodologies for the synthesis of other five and six membered thiosugars and related systems. Moreover, moderate glycosidase inhibitiors of this class can be exploited as conformationally constrained scaffolds for the rational drug design of potent HIV inhibitors.[1,2] In continuation with our programme on organocatalytic aldol reaction based synthetic strategies for thiosugars, we attempted the synthesis of a new seven membered thiosugar **2** (Figure 1). We also investigated a detailed literature search on intramolecular aldolization reaction of 1,8-dicarbonyls for finding out the possibilities of using it in the synthesis of proposed seven membered thiosugars **2** (Figure 1).



C_2-symmetric L-ido-thiepane

1

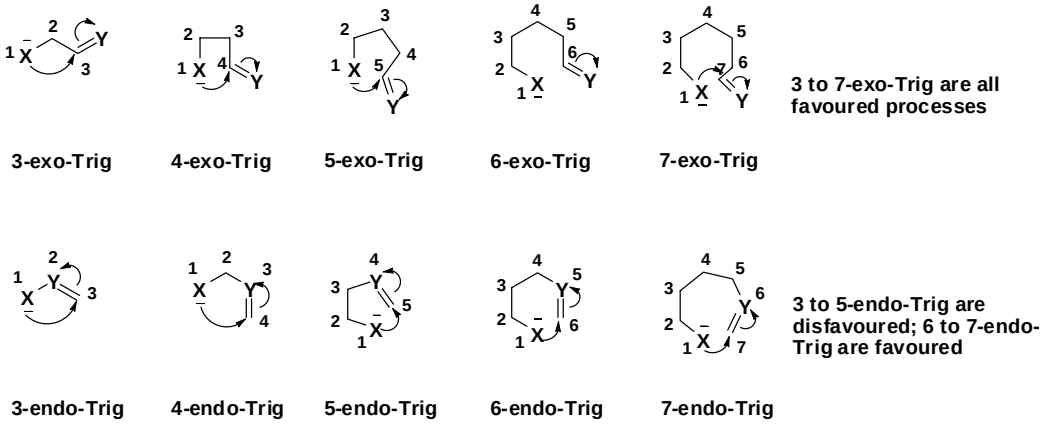
Proposed Seven membered thiosugar

2

Figure 1. C_2-symmetric L-ido-thiepane and proposed seven membered thiosugar.

3.1.2 Intramolecular Aldolization reaction of 1,8-dicarbonyl compounds

Baldwin's rules for ring closure give the qualitative set of generalization on the probability of a ring closure (RC).[3] Baldwin also discussed empirical rules which are formulated from the observations and stereoelectronic reasoning and describes kinetic feasibility of ring closure. According to Baldwin's rules, all 3 to7-*exo*-trig cyclisations

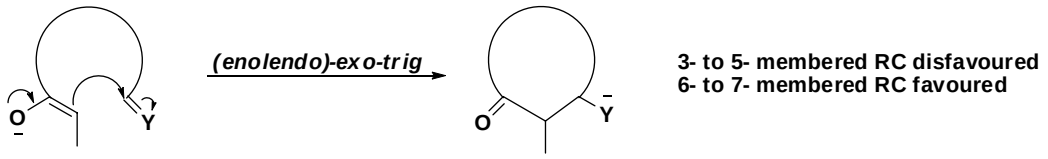


exo = when the breaking bond is *exocyclic* to the smallest ring formed, ***endo*** = when the breaking bond is *endocyclic* to the smallest ring formed, trig = trigonal geometry of the carbon undergoing RC.

Figure 2. Baldwin's rule of the ring closure for all possible *exo*- and *endo*-trig processes.

are favorable (Figure 2). An intramolecular endocyclic or exocyclic aldol (*enolendo* and *enolexo*) reaction is the best example of *exo*-trig cyclization (Figure 3). For an *enolendo* aldol reaction, 3 to 5 membered RCs are disfavoured while 6 and 7 membered RCs are favoured ; whereas all 3 to 7 membered RCs are favoured for an *enolexo* aldol reaction.

Endocyclic reactions



Exocyclic reactions

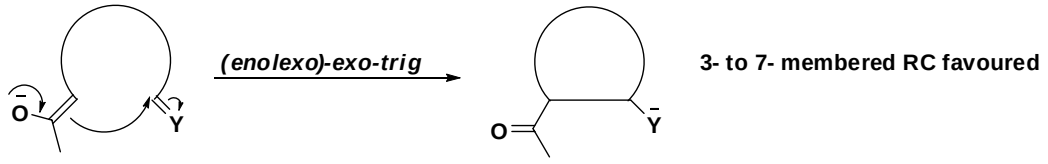
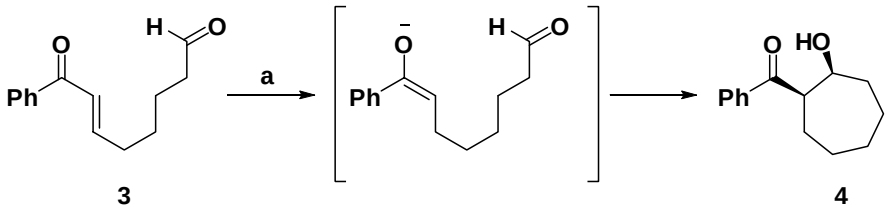


Figure 3. Endocyclic and exocyclic intramolecular aldol reactions.

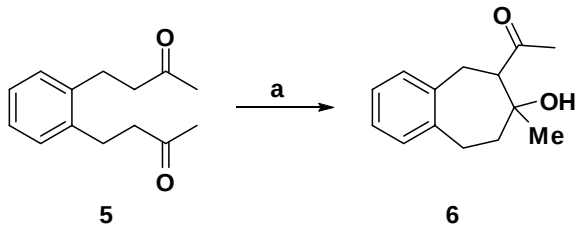
Hence, according to Baldwin's rule the 7-*enolexo* aldolization of 1,8-dicarbonyls should produce a seven membered ring but the literature survey showed that the aldolization reaction of 1,8-dicarbonyls to form seven membered rings are quite rare. Very few reports are available in the literature regarding the 7-*enolexo* aldolization reaction of 1,8-dicarbonyls.

Michael J. Krische and his group reported $Co(dpm)_2$ catalyzed 7-*enolexo* aldolization of a linear 1,8-dicarbonyl substrate **3** which produced a 7-membered ring aldol product **4**. The yield of 7-membered ring aldol product **4** was found low (35%) even after having a more reactive aldehyde electrophile in the substrate (Scheme 1).[4]



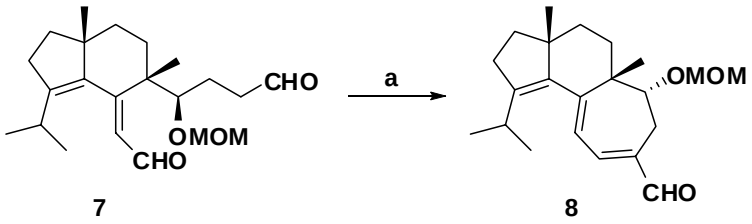
Scheme 1. *Reagents and conditions*: *a) 5% mol $Co(dpm)_2$, $PhSiH_3$, rt, 35% (dpm = dipivaloylmethane).*

Erin M. O'Brien and his group subjected 1,8-dicarbonyl substrate **5** to LiHDMS which underwent 7-*enolexo* aldolization to produce 7-membered ring aldol product **6** in poor yield (Scheme 2).[5]



Scheme 2. *Reagents and conditions*: *a) LiHDMS, -78 ^oC, 2 h, 11%.*

Motoo Tori and coworkers reported an intramolecular aldol condensation of a 1,8-dialdehyde **7** using 5% KOH/MeOH at room temperature conditions which gave 7-membered ring aldol condensation product **8** in 54% yield (Scheme 3).[6]

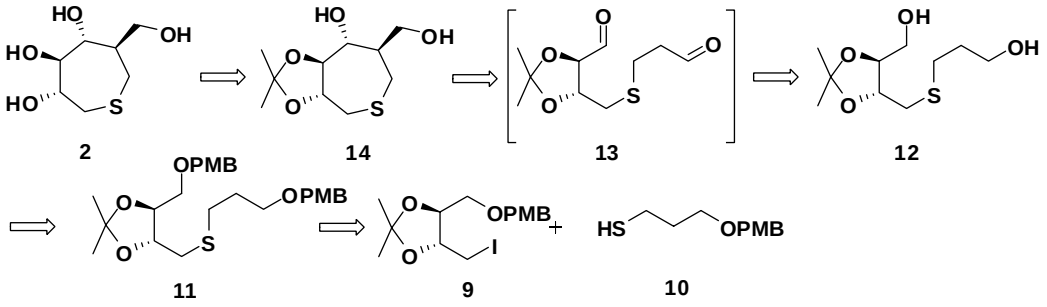


Scheme 3. *Reagents and conditions*: *a) 5% KOH-MeOH, 1 h, 54%.*

3.1.3 Present work

According to the literature survey seen the 7-*enolexo* aldolization reaction of 1,8-dicarbonyls are rarely explored. There is still much scope of using many other reagents/catalyst for 7-*enolexo* aldolization reaction of 1,8-dicarbonyls. The pioneering work of proline catalyzed intramolecular asymmetric 6-*enolexo* aldol reaction by Prof. List and coworker has fascinated synthetic organic chemists in the recent years.[7] Recently, the L-proline catalyzed 6- and 5-*enolexo* aldolization reactions were successfully used by our group for the synthesis of six and five membered thiosugars respectively. The speculative facts of ring closure studies by Baldwin along with the interesting result of proline catalyzed *enolexo* aldolization reaction inspired us to use 7-*enolexo* aldolization reaction in designing a novel approach towards synthesis of proposed 7-membered thiosugar **2**.

The retrosynthetic analysis for the diastereoselective synthesis of proposed 7-membered thiosugar **2** is showed in scheme 4.



Scheme 4. The retrosynthetic disconnections for proposed seven membered thiosugar.

It was observed that the proposed 7-membered thiosugar **2** could be easily achieved from an acid catalyzed deprotection of acetonide of cyclic diol **14**. The cyclic diol **14**

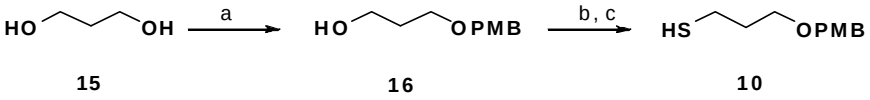
could come out as 7-*enolexo* aldolization product of dialdehyde **13** which in turn could be obtained by the oxidation of diol **12**. The diol **12** could be easily prepared by the deprotection of thioether **11** which could be synthesized by the coupling synthons, thiol **10** and iodo intermediate **9** (Scheme 4).

3.1.4 Result and disscussion

The synthesis and characterization of iodo intermediate **9** was previously attempted in chapter 1 (section 2), hence our actual synthesis starts with the preparation of thiol intermediate **10**.

3.1.4.1 Synthesis of thiol intermediate 10

The synthesis of thiol intermediate **10** started with cheap and easily available 1,3-propanediol **15** as a starting material. 1,3-propanediol **15** was mono-protected with PMBCl in presence of sodium hydride in THF: DMF (1:1) at 0 ^{o}C to give alcohol **16** in 75% yield. The alcohol **16** was then subjected for tosylation with TsCl in presence of TEA in dry DCM at 0 ^{o}C conditions to offer a tosyl derivative which without any further purification was refluxed with thiourea in absolute ethanol followed by *in situ* hydrolysis with aq. NaOH under similar reflux conditions afforded thiol **10** in 95% yield (Scheme 5).[8]



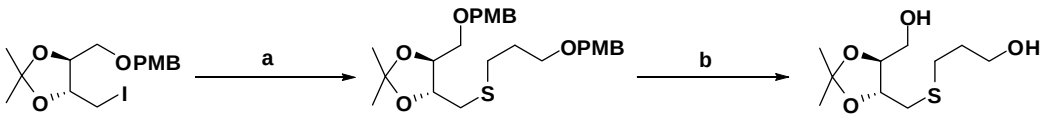
Scheme 5. *Reagents and conditions*: *a) NaH, PMBCl, THF:DMF(1:1), 0 ^{o}C, 75%; b) TEA, TsCl, DCM, 0 ^{o}C, 95%; c) (i) Thiourea, absolute ethanol, reflux, 3.5 h; (ii) NaOH, H_2O, reflux, 3.5 h, 95%.*

In the ^{1}H NMR spectrum of thiol **10** the characteristic -SH proton resonated up field as triplet (J = 8.1 Hz) at δ 1.34 while the methylene protons adjacent to –SH coupled with –SH and neighboring methylene group and appeared at δ 2.65 as quartet (J = 15.0, 7.1 Hz) signal. The protons of middle methylene group sighted in up field as quintet (J = 13.0, 6.1 Hz) at δ 1.90 whereas being a part of ether linkage (-CH_2-OPMB) its neighboring methylene group appeared down field at δ 3.55 as triplet (J = 6.0 Hz). In ^{13}C NMR and DEPT, the methylene carbon adjacent to –SH and middle

methylene group carbon appeared up field at δ 21.22 and 33.61 (DEPT) respectively whereas methylene carbon linked to ethereal linkage (-CH_2-OPMB) sighted downfield at δ 67.46 (DEPT). Rest of the ^{1}H and ^{13}C spectrum values and mass (ESI-TOF) m/z at 235.1 accounting for ([M+Na]$^+$) were in complete conformity with the assigned structure of thiol **10**.

3.1.4.2 Synthesis of diol 12

The thiol **10** and known iodo intermediate **9** were further coupled using sodium hydride as base in dry THF at 0 ^{o}C to offer thioether **11** in 96% yield (Scheme 6). In the ^{1}H NMR spectrum of thioether **10**, the acetonide protons appeared as two close singlets at δ 1.41, 1.42. The methylene group next to sulfur adjoined methylene resonated as quintet (*J* = 13.4, 6.6 Hz) at δ 1.86 while a doublet (*J* = 7.2 Hz) at δ 2.64 for one proton, doublet of doublet (*J* = 6.1, 2.4 Hz) at δ 2.71 for one proton and one more doublet signal (*J* = 5.1 Hz) at δ 2.73 for two protons represented the protons on two methylene groups adjoined to sulfur atom. Being a part of ethereal linkage (-CH_2-OPMB), the protons on another two methylene groups resonated in downfield as a triplet (*J* = 6.2 Hz) at δ 3.51 and a doublet (*J* = 4.4 Hz) at δ 3.60 respectively. In ^{13}C NMR and DEPT, the carbon of methylene group next to sulfur adjoined methylene appeared up field at δ 29.36. The carbons of two methylene adjoined to sulfur atom resonated distinctively in up field at δ 29.43 and 34.42 (DEPT) respectively, whereas the carbons of two methylene adjoined to ethereal linkage (-CH_2-OPMB) and two benzylic carbons were observed downfield at δ 68.03, 69.99 (DEPT) and δ 72.22, 72.80 (DEPT) respectively. Rest of the ^{1}H and ^{13}C spectrum values were in complete conformity with the assigned structure of thioether **11**.



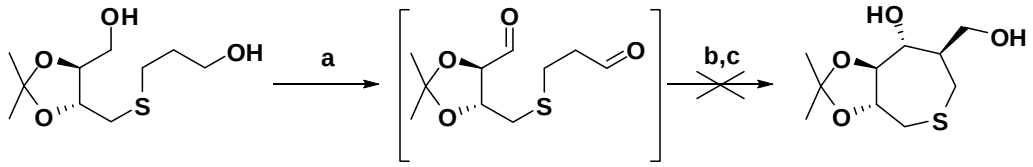
Scheme 6. *Reagents and conditions*: *a) NaH,* HS OPMB ***(10)****, THF, 0 ^{o}C, 96%; b) DDQ, DCM: H_2O (17:1), rt, 85%.*

Thioether **11** further on treatment with DDQ [9] in DCM: H_2O (17:1) at room temperature underwent oxidative cleavage of PMB groups to offer diol **12** in 85%

yield (Scheme 6). In ^{1}H NMR of diol **12**, the acetonide protons sighted at δ 1.39. The methylene group next to sulfur adjoined methylene resonated as a multiplate at δ 1.78 to 1.87 in up field. The protons on two methylene groups adjacent to sulfur atom appeared up field at δ 2.66 to 2.78 as multiplate whereas the protons of terminal hydroxy methylene groups resonated downfield at δ 3.67 to 3.83 as multiplate. The two multiplate signals sighted downfield at δ 3.84 to 3.90 and δ 4.00 to 4.07 correspond to the protons from two neighboring stereocenter to acetonide group while two terminal hydroxyl group resonated as two broad singlets at δ 2.82 and δ 2.85. In ^{13}C NMR, the carbon of methylene group next to sulfur adjoined methylene appeared up field at δ 28.92. The carbons of two methylene adjoined to sulfur atom resonated in up field at δ 31.69 and 34.28 (DEPT) respectively whereas hydroxy methylenic carbons sighted downfield at δ 60.56 and 62.09 (DEPT). Rest of the ^{1}H and ^{13}C spectral values and mass (ESI-TOF) m/z at 259.1 accounting for $[M+Na]^{+}$ along with its HRMS (TOF) m/z (calculated for $C_{10}H_{20}NaO_4S$ ($[M+Na]^{+}$) 259.0975, found 259.0982) were in complete accordance with the assigned structure of diol **12**.

3.1.4.3 L-proline catalyzed 7-*enolexo* aldolization

The diol **12,** the key starting material for the 7-*enolexo* aldolization was further oxidized with IBX in refluxing EtOAc to afford a dialdehyde **13** which without any further purification was directly used for the L-proline catalyzed 7-*enolexo* aldolization reaction.[10] The key step of direct 7-*enolexo* aldolization reaction of dialdehyde was carried out using L-proline (30 mol %) as an organocatalyst in solvent



12 **13** **14**

Scheme 7. *Reagents and conditions*: *a) (i) IBX, ethyl acetate, reflux, 96%; (ii) L-proline (30 mol%), DCM, rt, 45 min-20 h; (iii) $NaBH_4$, MeOH, rt, (starting material **12** recovered 85%).*

DCM at room temperature for 45 min and the reaction progress was monitored by TLC. No reaction progress was observed after 45 min so the reaction was kept for a

prolonged time period (45 min-20 h). The reaction was not progressed even after prolonged reaction time period and no aldolization was observed, therefore the reaction mixture was reduced *in situ* with $NaBH_4$ in MeOH and starting material diol **12** was recovered (Scheme 7).

The failure of 7-*enolexo* aldolization for the formation of proposed 7-membered thiosugar building block can be discussed with many facts. According to literature studies 5- and 6-*enolexo* aldolization reactions are found to be more feasible than 7-*enolexo* aldolization reaction.[3-6] 5- and 6-membered rings are relatively small and more stable than the bigger and strained 7-membered rings. Moreover, the stability and reactivity of generated enolate or enamine also affect the reaction success. This can be well explained with our 5- and 6-*enolexo* aldolizations in our earlier attempts in chapters 1 and 2 where lower reaction time period (45 min) was required for both 5- and 6-*enolexo* aldolization reactions. In L-proline catalyzed *enolexo* aldolization reactions an enamine act as an enolate equivalent. It is assumed that the basis of *enamine catalysis* is reversible and catalytic generation of enamine takes place from an amine and a carbonyl compound. An enamine formation is facilitated by the remarkable increase in C-H acidity of donor methylene upon initial conversion of carbonyl compound in to an iminium ion. The catalytically generated enamine should be able to undergo addition reaction with an electrophile (acceptor carbonyl carbon) similar to the well-studied chemistry of preformed enolates.[11] The presence of sulfur atom within the substrates (dialdehydes) of earlier 5- and 6-*enolexo* aldolizations might affect the stability of enamine produced. The donor methylene group is situated α-to sulfur atom in the substrates (dialdehydes) of 5- and 6-*enolexo* aldolization reaction. In general sulfur atom is very nucleophilic because of its large size, which makes it readily polarizable, and its lone pairs of electrons are readily accessible. Moreover it has dispersed electron density; long **C-S** bond (1.8 Å) and small **C-S-C** bond angle (95-100^o) which might help in stabilizing and activating the generated enamine throughout the course of the reaction which ultimately enhanced the rate of the *enolexo* aldolization reaction. In case of 7-*enolexo* aldolization reaction the donor methylene is situated β-to sulfur atom in the substrate (dialdehyde) which will offer comparatively a less stable and less active enamine which could be one of the reasons behind the failure of 7-*enolexo* aldolization reaction (Figure 4).

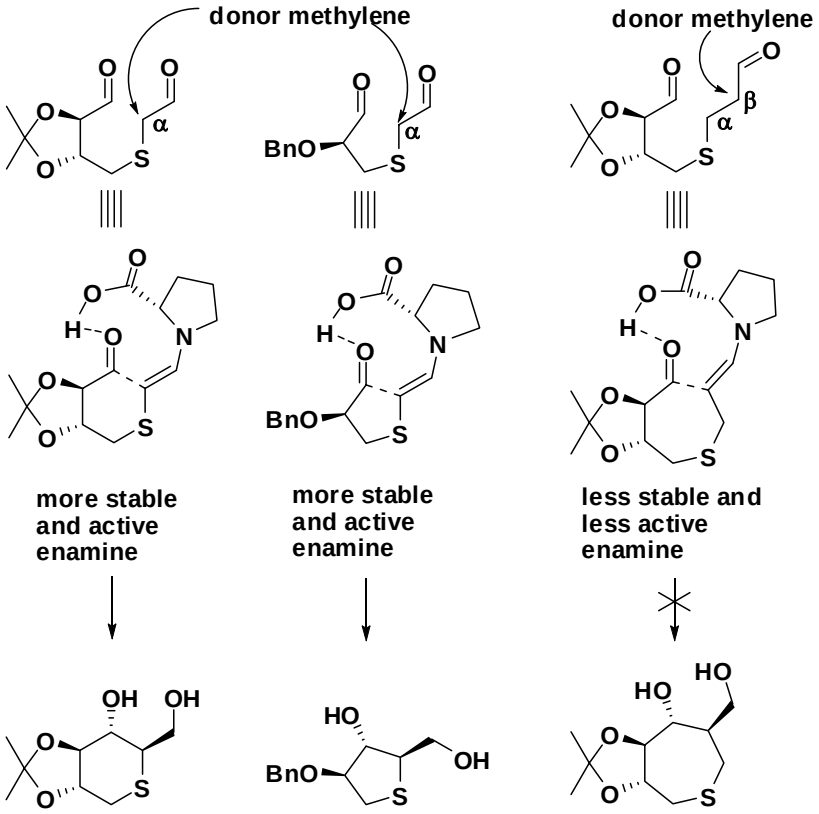


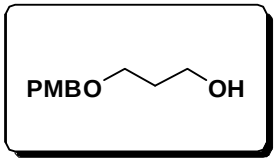
Figure 4. Effect of sulfur atom on *enolexo* aldolization.

3.1.5 Conclusion

In conclusion, we have proposed a novel protocol with L-proline catalyzed direct 7-*enolexo* aldolization reaction as a step for the synthesis of a new seven membered thiosugar. Unfortunately the key step of 7-*enolexo* aldolization reaction was found unsuccessful. The prolonged reaction time period for 7-*enolexo* aldolization reaction also failed to produce seven membered ring aldol product. The failure of 7-*enolexo* aldol reaction to form seven membered ring aldol was also discussed and compared with our earlier successful 5- and 6-*enolexo* aldolization reactions.

3.1.6 Experimental

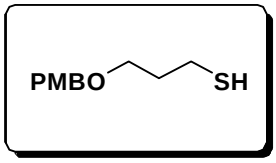
3-(4-Methoxybenzyloxy)propan-1-ol (16)



To a solution of 1,3-propanediol **15** (7.6 g, 100 mmol) in dry THF:DMF (1:1, 120 mL) was added sodium hydride (60%, 4.4 g, 110 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 °C. To this was added slowly *p*-methoxybenzyl chloride (17.226 g, 19.89 mL, 110 mmol) with further stirring for 6 h at the same temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with water (2 x 50 mL), brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual oil was purified by silica gel column chromatography using petroleum ether/EtOAc (7:3) as eluent to give the mono-PMB protected alcohol **16** (14.45 g, 75% yield) as a yellow oil.

Molecular Formula	: $C_{11}H_{16}O_3$.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 1.88 (quintet, *J* = 11.6, 5.8 Hz, 2H), 2.74 (bs, 1H), 3.66 (t, *J* = 5.9 Hz, 2H), 3.78 (t, *J* = 5.7 Hz, 2H), 3.83 (s, 3H), 4.48 (s, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 31.97, 55.01, 60.97, 68.33, 72.58, 113.60, 129.09, 130.02, 158.99.
MS (ESI-TOF) m/z	: 219.20 ($[M+Na]^+$).

3-(4-Methoxybenzyloxy)propane-1-thiol (10)

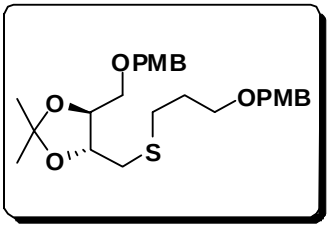


To a stirred solution of alcohol **16** (3.92 g, 20 mmol) and Et_3N (3.03 g, 4.17 mL, 30 mmol) in dry CH_2Cl_2 (40 mL) tosyl chloride (4.19 g, 22 mmol) was added in portions at 0 ^oC. The reaction mixture was then stirred further for 4 h at the same temperature. Then the reaction mixture was warmed to room temperature and solvent was evaporated under reduced pressure to give crude reaction mass. The crude mass was then taken in EtOAc (50 mL) and stirred with 3% aq. $NaHCO_3$. The organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated on rotary evaporator to give tosylate derivative as a dark yellowish liquid (6.8 g, 98%). The

resulting dark yellowish liquid without any further purification was used for thiol preparation. To the solution of tosylate (5.25 g, 15 mmol) in absolute ethanol (12 mL) was added thiourea (1.14 g 15 mmol) and the reaction mixture was refluxed for 3.5 h. Then a solution of sodium hydroxide (0.9 g, 22.5 mmol) in distilled water (9 mL) was added, and the reaction mixture was refluxed for further 3.5 h. The reaction mixture was allowed to cool to room temperature, concentrated and extracted with dichloromethane (3 × 20 mL). The organic layer was separated, dried over Na_2SO_4 and solvent was removed to give a crude brownish liquid. The residual brownish liquid was further purified by column chromatography on silica-gel eluting with petroleum ether: ethyl acetate (9:1) to give **10** (3.0 g, 95%) as a colorless oil.

Molecular Formula	: $C_{11}H_{16}O_2S$.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 1.34 (t, *J* = 8.1 Hz, 1H), 1.90 (quintet, *J* = 13.0, 6.1 Hz, 2H), 2.65 (quartet, *J* = 15.0, 7.1 Hz, 2H), 3.55 (t, *J* = 6.0 Hz, 2H), 3.81 (s, 3H), 4.44 (s, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.7 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 21.22, 33.61, 54.89, 67.46, 72.28, 113.47, 128.93, 130.18, 158.89.
IR (Neat) cm^{-1}	: 3025, 2900, 2850, 2565 (S–H), 1603, 1500, 1433, 1211, 1050, 845, 750.
MS (ESI-TOF) m/z	: 235.1 ($[M+Na]^+$).

(4*S*,5*R*)-4-((4-Methoxybenzyloxy)methyl)-5-((3-(4-methoxybenzyloxy)propylthio)methyl)-2,2-dimethyl-1,3-dioxolane (11)



To a solution of thiol **10** (2.12 g, 10 mmol) in dry THF (25 mL) was added sodium hydride (60%, 0.6 g, 10 mmol) at 0 °C and was then stirred at same temperature for 30 min. To this was added the solution of iodo intermediate **9** (3.92 g, 10 mmol) in dry THF (40 mL) at the same temperature and stirred for an additional 5 h at room temperature. The reaction mixture was then quenched with cold water at 0 °C and the two phases were separated. The aqueous phase was extracted with EtOAc (2 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give dark yellowish dense oil which was further purified by silica gel

column chromatography using petroleum ether: ethyl acetate (8.5:1.5) as eluent to give the desired thioether **11** (4.51 g, 96%) as dense pale yellowish oil.

Molecular Formula : $C_{26}H_{36}O_6S$.

Optical rotation : $[\alpha]_D^{25}$ -8.32, *c* 1.0, $CHCl_3$.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 1.41 (s, 3H), 1.42 (s, 3H), 1.86 (quintet, *J* = 13.4, 6.6 Hz, 2H), 2.64 (d, *J* = 7.2 Hz, 1H), 2.71 (dd, *J* = 6.1, 2.4 Hz, 1H), 2.73 (d, *J* = 5.1 Hz, 2H), 3.51 (t, *J* = 6.2 Hz, 2H), 3.60 (d, *J* = 4.4 Hz, 2H), 3.79 (s, 6H), 3.97-4.01 (m, 2H), 4.42 (s, 2H), 4.50 (s, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H).

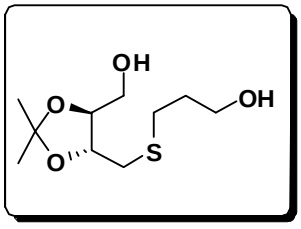
^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 26.75, 26.87, 29.36, 29.43, 34.42, 54.83, 68.03, 69.99, 72.22, 72.80, 77.84, 79.06, 108.97, 113.41, 128.86, 128.95, 129.68, 130.16, 158.89.

IR (Neat) cm^{-1} : 3095, 2925, 2845, 1619, 1568, 1415, 1357, 1223, 1092 and 995 (C-O-C and C-S-C), 750 and 712 (aromatic).

MS (ESI-TOF) m/z : 499.30 ($[M+Na]^+$).

HRMS (TOF) m/z : calculated for $C_{26}H_{36}NaO_6S$ ($[M+Na]^+$) 499.2130, found 499.2137.

3-(((4*R*,5*S*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methylthio)propan-1-ol (12)



To a stirred solution of thioether **11** (2.38 g, 5 mmol) in CH_2Cl_2 (51 mL) and water (3 mL) was added DDQ (3.41 g, 15 mmol) and stirred for 30 min at room temperature. After 30 min the precipitated DDQH was removed by mere filtration and the residue was washed with CH_2Cl_2. The combined organic layers were then washed with saturated $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and concentrated under diminished pressure to give dark brownish oil which was further purified by silica-gel column chromatography using petroleum ether: ethyl acetate (3:7) as eluent to offer the desired diol **12** (1.0 g, 85%) as a dense pale yellowish oil.

Molecular Formula : $C_{10}H_{20}O_4S$.

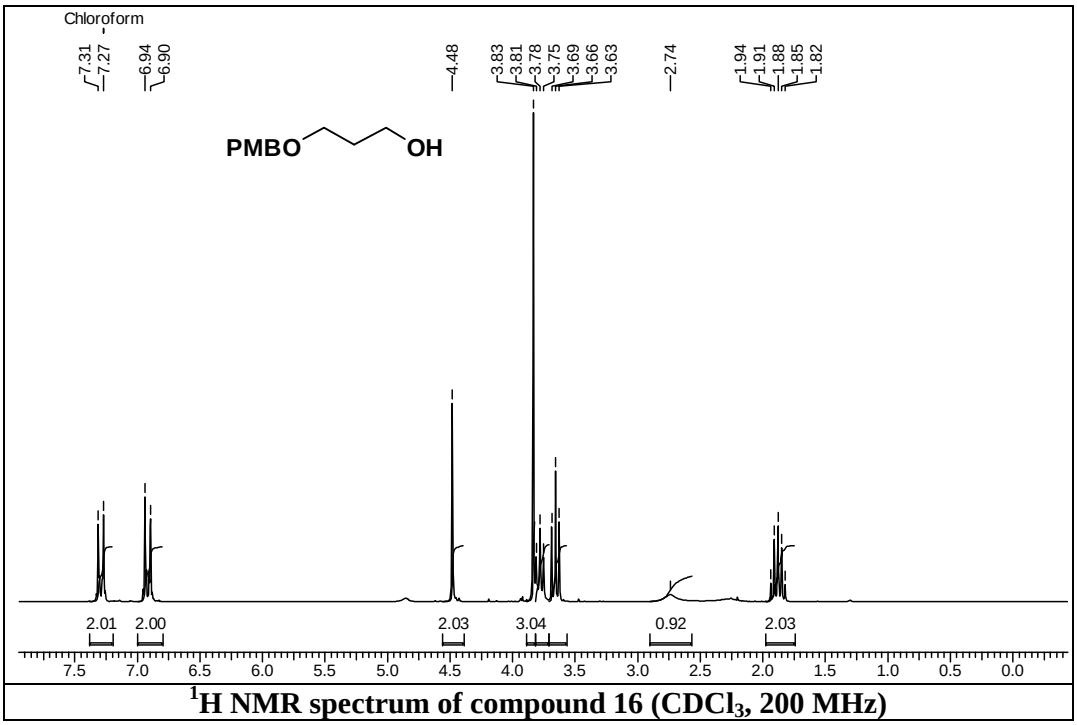
Optical rotation : $[\alpha]_D^{25}$ -4.17, *c* 1.0, $CHCl_3$.

^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 1.39 (s, 6H), 1.78-1.87 (m, 2H), 2.66-2.78 (m, 4H), 2.82 (bs, 1H, D_2O exchangeable), 2.85 (bs, 1H, D_2O exchangeable), 3.67-3.83 (m, 4H), 3.84-3.90 (m, 1H), 4.00-4.07 (m, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 26.79, 26.87, 28.92, 31.69, 34.28, 60.56, 62.09, 76.45, 80.88, 108.92.
IR (Neat)	: 3460 (broad), 2935, 2905, 1194, 1069, 976 (C-S-C).
MS (ESI-TOF) m/z	: 259.1 ($[M+Na]^+$)
HRMS (TOF) m/z	: calculated for $C_{10}H_{20}NaO_4S$ ($[M+Na]^+$) 259.0975, found 259.0982.

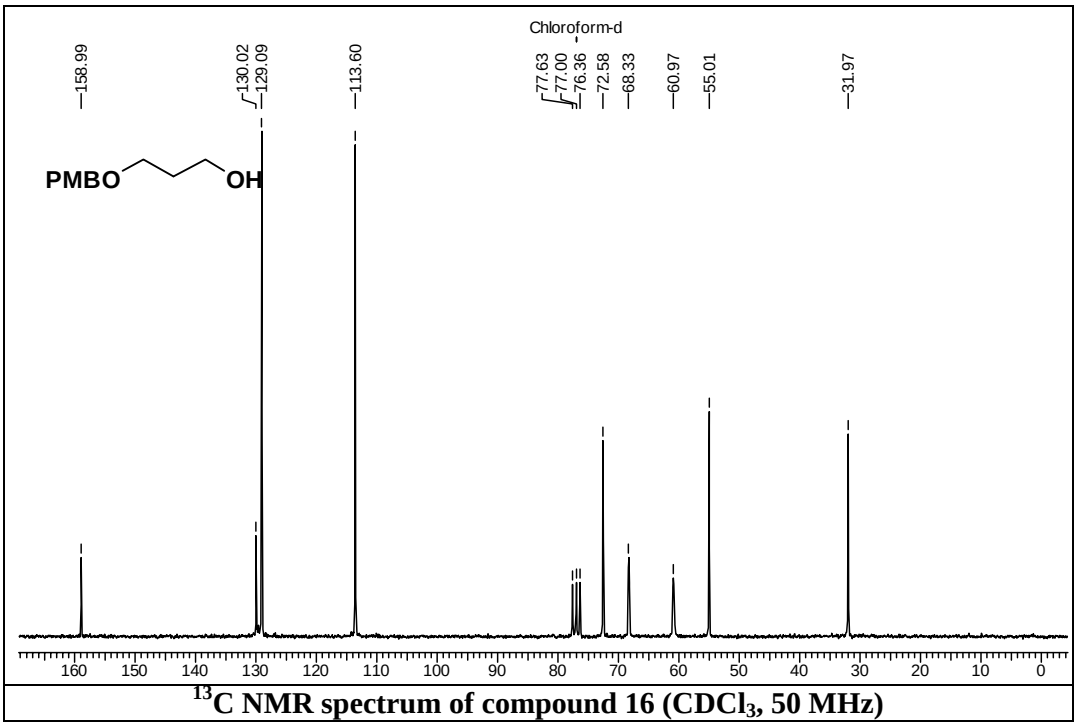
L-proline catalyzed 7-*enolexo* aldolization reaction

To the solution of diol **12** (0.236 g, 1 mmol) in EtOAc (15 mL) was added IBX (1.68 g, 6 mmol) and refluxed for 3.5 h at 80 ^oC. After reaction completion (as checked by 2,4-DNP TLC test)[10], reaction mixture was cooled to room temperature and filtered and the filtrate was washed with 20% aqueous $NaHCO_3$ (2 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under diminished pressure to give pale yellowish syrupy crude dialdehyde **13** (0.225 g). The crude dialdehyde was immediately used as a starting material for an *enolexo* aldolization reaction without any further purification. To the solution of crude dialdehyde **13** (0.225 g) in dry DCM (10 mL) was added L-proline (0.033 g, 30 mol %) and stirred at room temperature for 45 min (reaction completion time as checked by TLC). No reaction progress was observed after 45 min so the reaction was kept for a prolonged time period (45 min-20 h). The reaction did not proceed even after prolonged reaction time and no aldolization was observed, therefore the reaction mixture was reduced *in situ* by adding 5 mL of MeOH and $NaBH_4$ (0.043 g, 1.1 mmol, slight excess) at room temperature for 1 h. The reaction mixture was concentrated on rotary evaporator, added with cold water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to offer crude yellowish liquid which was further purified by silica-gel column chromatography using petroleum ether: ethyl acetate (3:7) to give back starting diol **12** (0.210 g, 85% recovered).

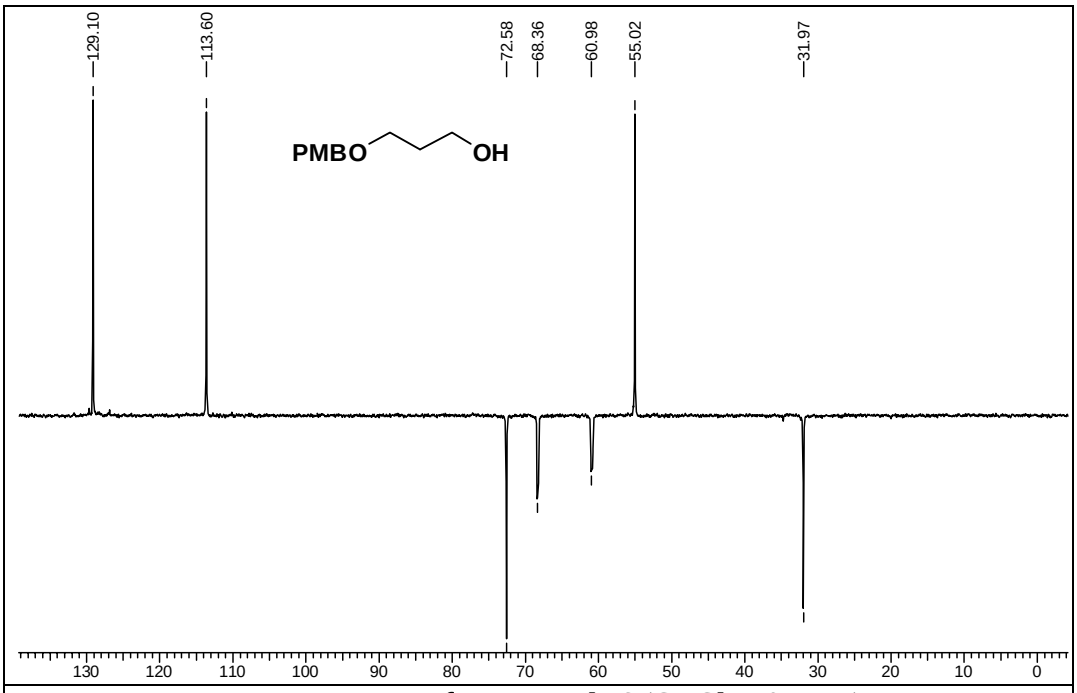
3.1.7 Analytical data



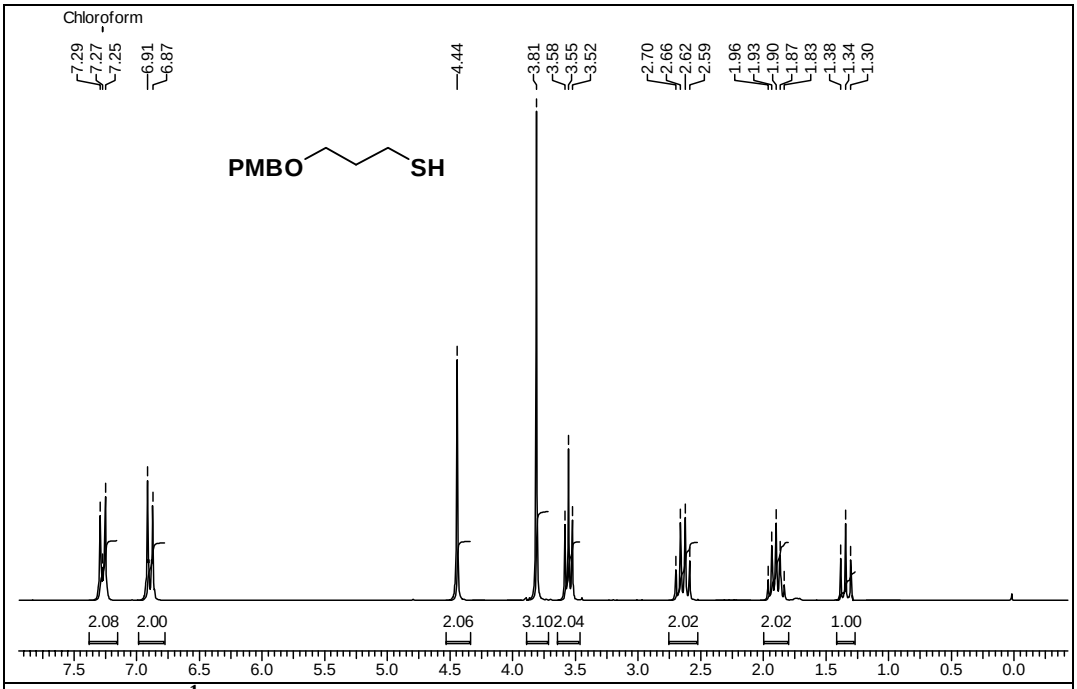
^{1}H NMR spectrum of compound 16 ($CDCl_3$, 200 MHz)



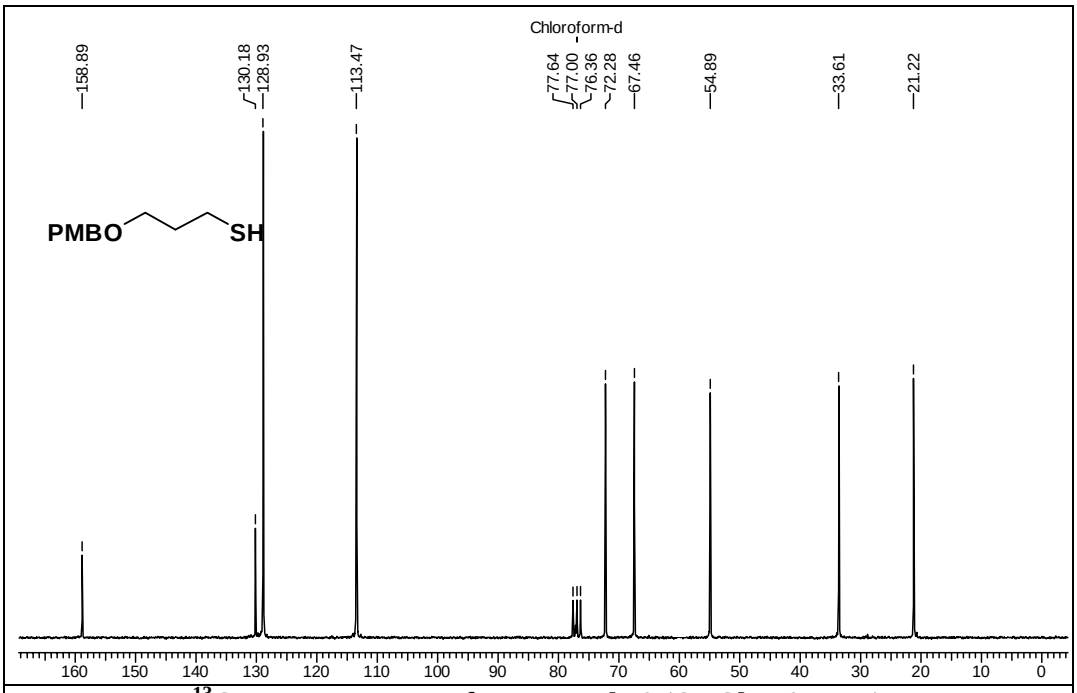
^{13}C NMR spectrum of compound 16 ($CDCl_3$, 50 MHz)



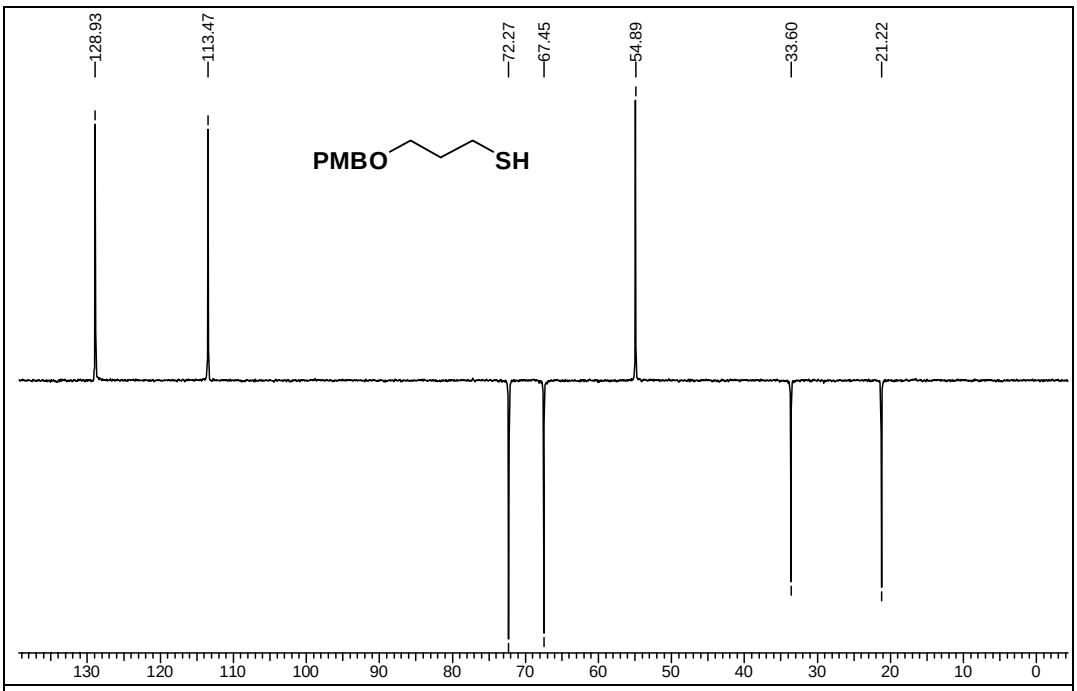
DEPT spectrum of compound 16 ($CDCl_3$, 50 MHz)



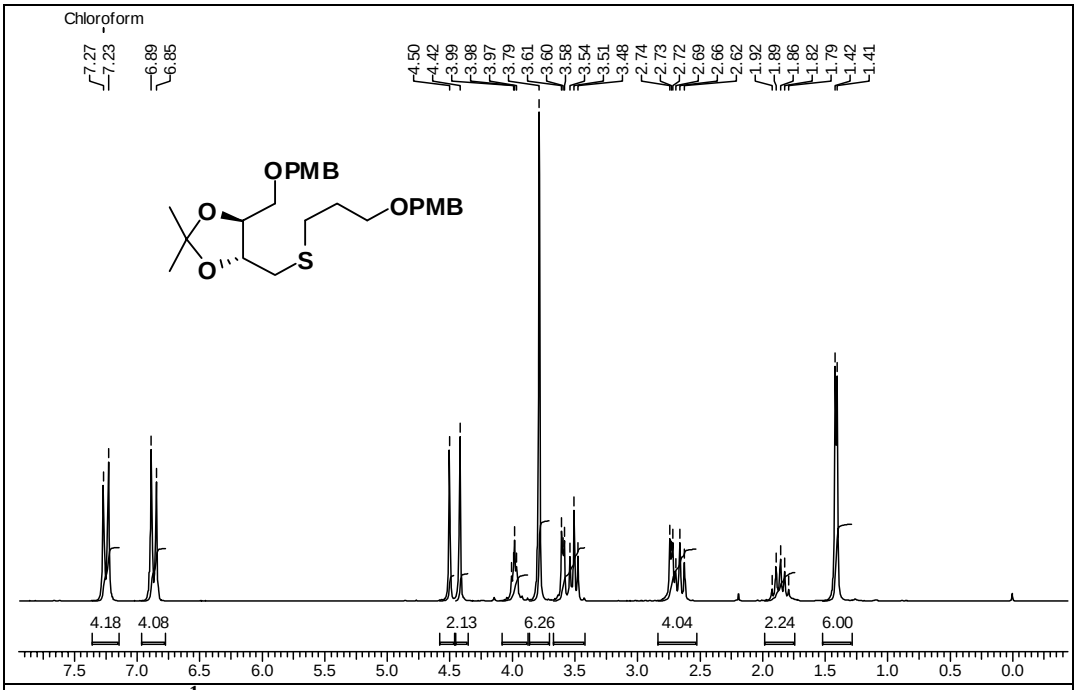
^{1}H NMR spectrum of compound 10 ($CDCl_3$, 200 MHz)



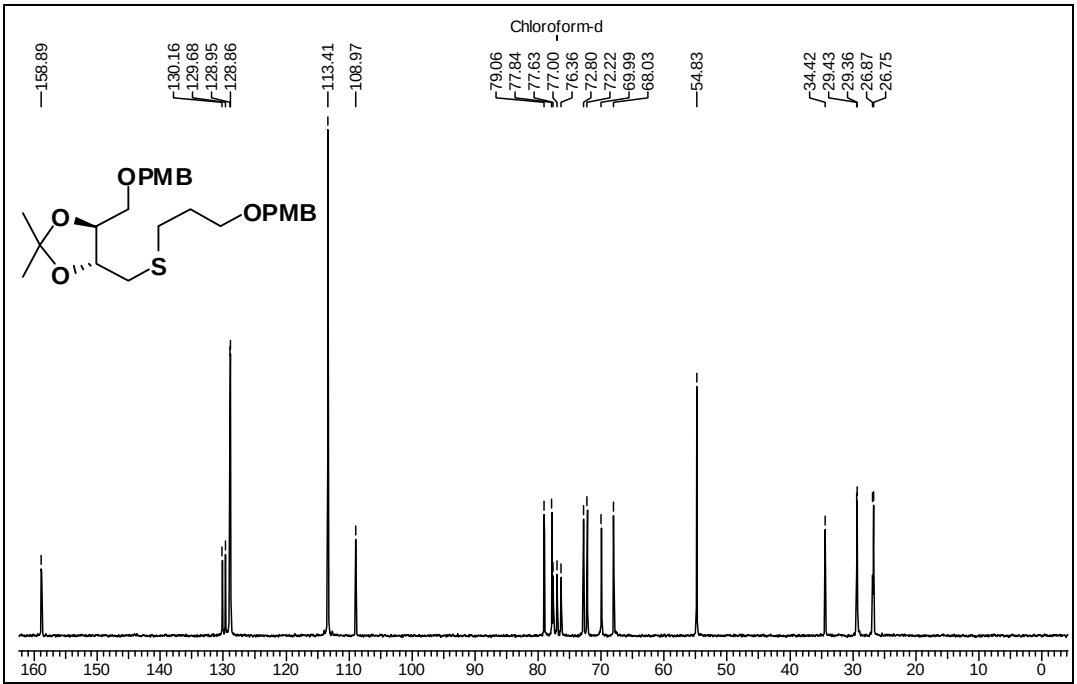
^{13}C NMR spectrum of compound 10 ($CDCl_3$, 50 MHz)



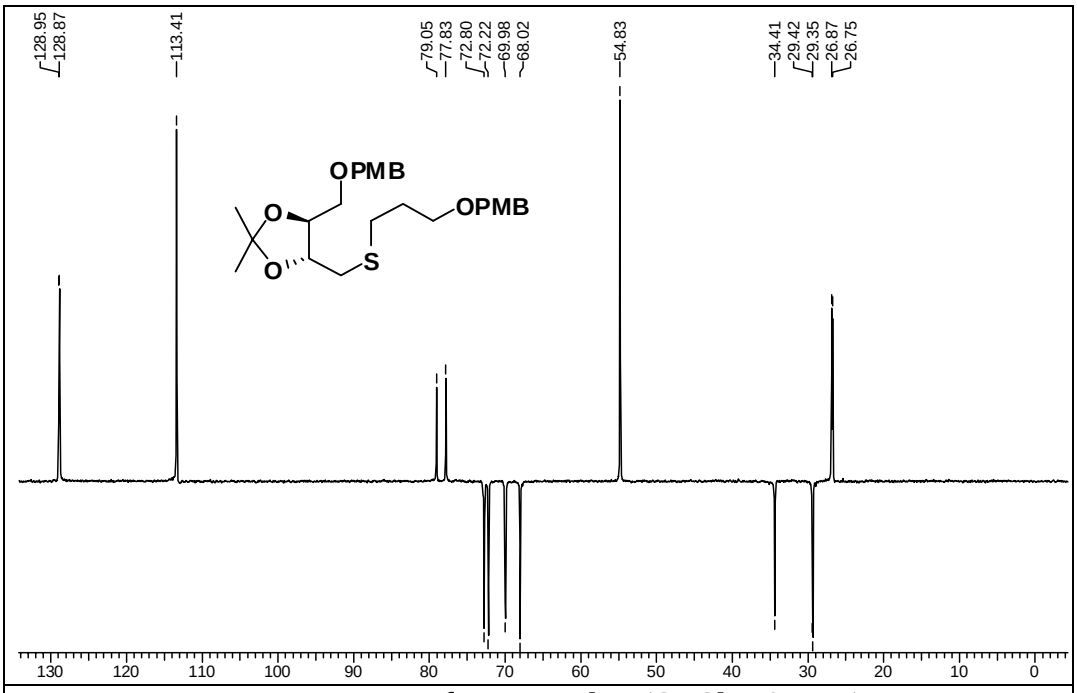
DEPT spectrum of compound 10 ($CDCl_3$, 50 MHz)



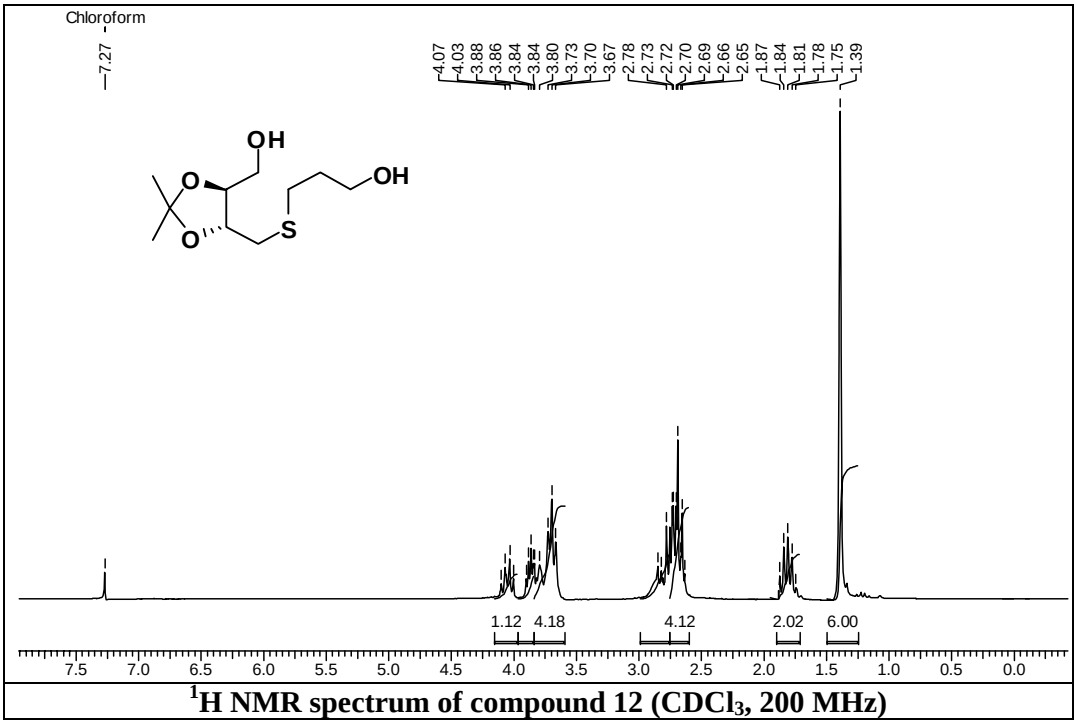
^{1}H NMR spectrum of compound 11 ($CDCl_3$, 200 MHz)



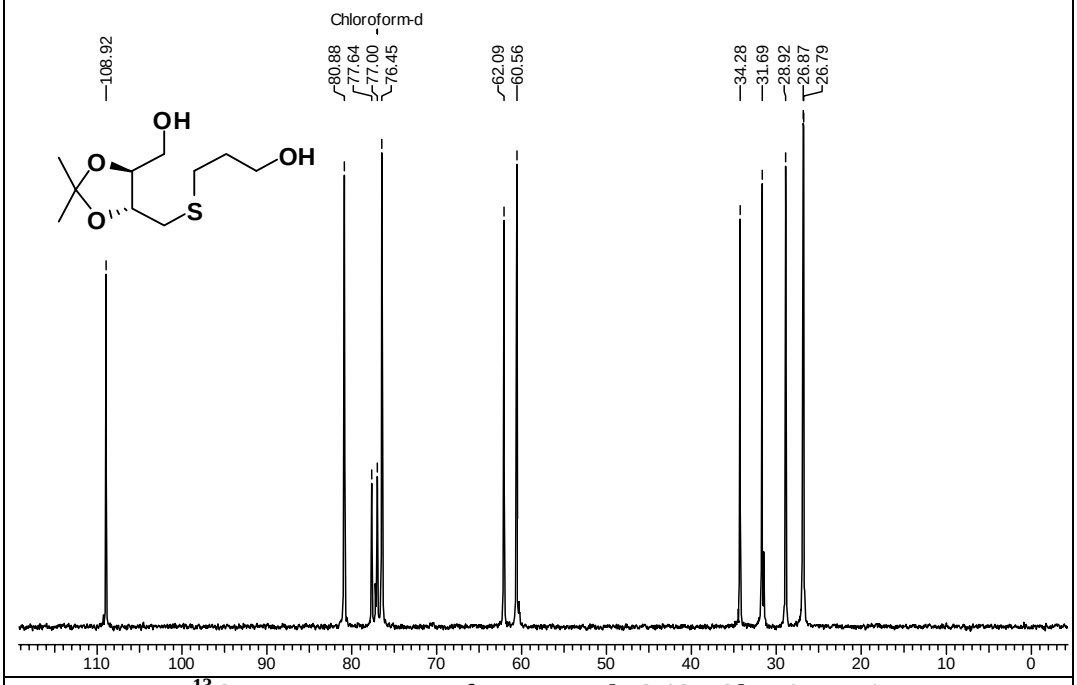
^{13}C NMR spectrum of compound 11 ($CDCl_3$, 50 MHz)



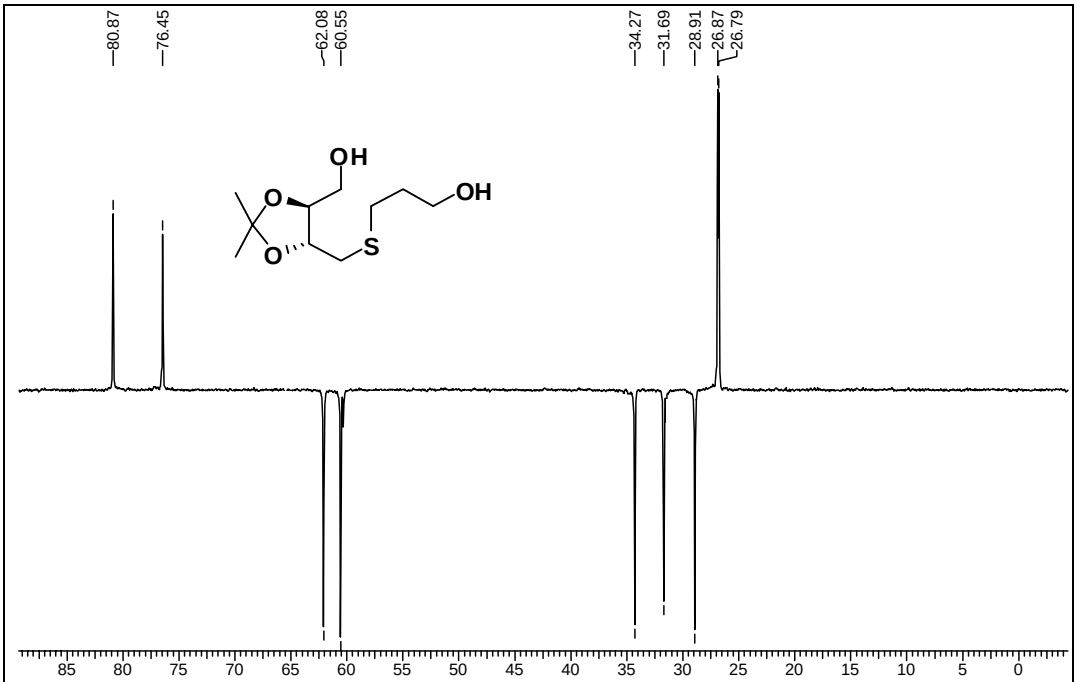
DEPT spectrum of compound 11 ($CDCl_3$, 50 MHz)



^{1}H NMR spectrum of compound 12 ($CDCl_3$, 200 MHz)



^{13}C NMR spectrum of compound 12 ($CDCl_3$, 50 MHz)



DEPT spectrum of compound 12 ($CDCl_3$, 50 MHz)

3.1.8 References

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5. O'Brien, E. M.; Li, J.; Carroll, P. J. and Kozlowski, M. C. *J Org Chem*. **2010**, *75*, 69.
6. Tori, M.; Toyoda, N. and Sono, M. *J. Org. Chem.* **1998,** *63,* 306.
7. Pidathala, C.; Hoang, L.; Vignola, N. and List, B. *Angew. Chem. Int. Ed*. **2003**, *42*, 2785.
8. (a) Snow, A. W. and Foos, E.E. *Synthesis* **2003**, *4*, 509; (b) Urquhart. G.; Gates, J. W. and Connor, R. *Org. Syn. Coll.* **1955**, *3*, 363.
9. (a) Horita, K.; Yosmota, T.; Tanaka, T.; Oikawa, Y. and Yonemitsu, A. *Tetrahedron* **1986**, *42*, 3021; (b) Oikawa, Y.; Yoshioka, T. and Yonemitsu, O. *Tetrahedron Lett*. **1982**, *23*, 885.
10. In the oxidation reaction of diol **12** with IBX in EtOAc, the total consumption of diol **12** was confirmed by charring its TLC with *p*-anisaldehyde solution. The characteristic greenish spot of diol **12** [R_f = 0.25, Petroleum ether: EtOAc (3:7)] was totally disappeared which indicated the completion of reaction. But no spot was visualized for the dialdehyde **13** in the same TLC. Similar TLC dipped in 2,4-DNP solution in ethanol produced an orange colored characteristic spot of Schiff's base [R_f= 0.7, Petroleum ether: EtOAc (3:7)] on TLC which confirmed the formation of dialdehyde **13.**

11. (a) Movassaghi, M. and Jacobsen, E. J. *Science* **2002**, *298*, 1904; (b) List, B. *Acc. Chem. Res.* **2004**, *37*, 584; (c) Notz. W.; Tanaka, F. and Barbas III, C. F. *Acc. Chem. Res.* **2004**, *37*, 580; (d) List, B. *Chem. Commun.* **2006**, 819.

Section 2

Synthetic studies towards thio-mimic of Isofagomine

Synthetic studies towards thio-mimic of Isofagomine

3.2.1 Introduction

Glycosidase inhibitors such as azasugars and related enzymes are subject of interest to many biologists and chemists in the recent years.[1-3] Few years ago a subtle modification in the core structure of classical azasugar 1-deoxynojirimycin (1-DNJ) **1** was experimented. The nitrogen in 1-deoxynojirimycin (1-DNJ) **1** was moved to the anomeric position which resulted in the formation of new class of 1-azasugar Isofagomine **2** which exhibited strong inhibitory action against β-glucosidase.[4] Further, similar modification were also practiced with other isomers of 1-DNJ and few more potent glycosidase inhibitors of Isofagomine family were synthesized and studied.[5-8] 1-deoxythionojirimycin (1-DTNJ) **3** and related thiosugars are also important class of glycosidase inhibitors which are yet not studied for repositioning of sulfur in place of anomeric carbon to form new class of thiosugars thio-mimic Isofagomine **4** and its analogues which are unnatural and not reported in the literature till date. The biological properties of Isofagomine **2** inspired us to design a novel route for the synthesis of thio-mimic of Isofagomine **4** (Figure 1).

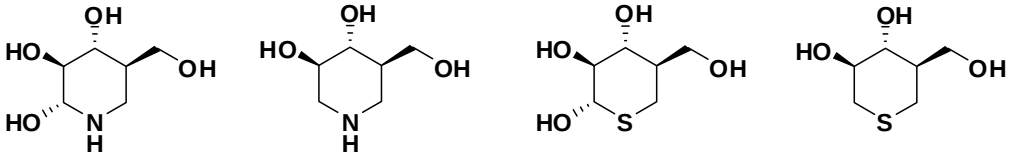
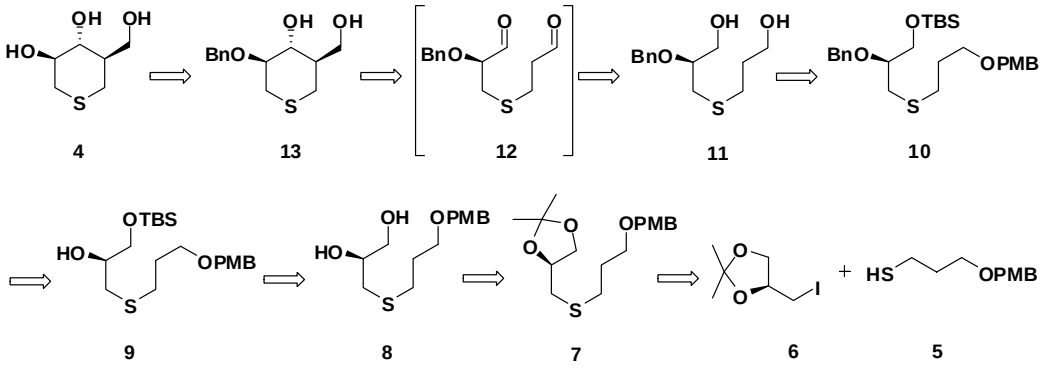


Figure 1. Structures of DNJ, Isofagomine and 1-DTNJ, thio-mimic of Isofagomine

3.2.2 Present work

While working on our programme on organocatalytic aldol reaction based synthetic strategies for thiosugars, we investigated a detailed literature search on 6-*enolexo* aldolization reaction for finding out the possibilities of using it in the synthesis of thio-mimic of Isofagomine **4.** We herewith propose a novel route for the synthesis of thio-mimic of Isofagomine **4** using 6-*enolexo* aldolization as a key step. The

retrosynthetic analysis for the diastereoselective synthesis of proposed thio-mimic of Isofagomine **4** is showed in scheme 2.



Scheme 2. The retrosynthetic disconnections for thio-mimic of Isofagomine.

It was seen that proposed thio-mimic of Isofagomine **4** could be easily achieved from benzyl deprotection of cyclic diol **13**. The cyclic diol **13** could come out as 6-*enolexo* aldolization product of dialdehyde **12** which in turn could be accessed by the oxidation of diol **11**. The diol **11** could be easily obtained by the sequential acid catalyzed TBS-deprotection followed by oxidative cleavage of PMB group from thioether **10**. The thioether **10** could be accessed by the benzyl protection of secondary hydroxyl group of alcohol **9** which could be synthesized by the TBS-protection of primary hydroxyl group of diol **8**. The diol **8** could be obtained by the acid catalyzed demasking of acetonide group of thioether **7** which could be synthesized by the coupling synthons, thiol **5** and iodo intermediate **6** (Scheme 2).

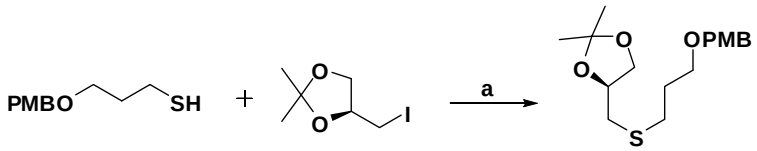
3.2.3 Result and discussion

The synthesis and characterization of thiol **5** and iodo intermediate **6** was previously attempted in the section 1 of this chapter and chapter 2 respectively, so our actual synthesis starts with the preparation of thioether **7**.

3.2.3.1 Synthesis of thioether 7

The thiol **5** and iodo intermediate **6** were coupled using sodium hydride as a base in dry THF at 0 ^{o}C to afford thioether **7** in 96% yield (Scheme 3). In ^{1}H NMR spectrum of thioether **7**, the terminal acetonide group protons appeared as two close singlets at δ 1.34 and 1.41. The methylene group next to sulfur adjoined methylene resonated as doublet of doublet (J = 7.2, 6.2 Hz) at δ 1.86 whereas a doublet of doublet (J = 13.3,

7.3 Hz) at δ 2.57 for one proton, triplet (J = 8.0 Hz) at δ 2.65 for one proton and a multiplate signal at δ 2.71-2.77 for two protons corresponds to the protons of two methylene groups connected to sulfur atom. The methylene group being a part of ethereal linkage (-CH_2-OPMB), resonated downfield as a triplet (J = 6.2 Hz) at δ 3.51 while two doublet of doublet signals at δ 3.69 (J = 6.3, 8.3 Hz) and at δ 4.07 (J = 6.0, 8.3 Hz) corresponds to the two protons of another methylene group situated in acetonide ring. The methoxy protons of –OPMB group and benzylic protons as usually appeared as two singlets at δ 3.77 and δ 4.41 while the proton on the only stereocenter in thioether **7** sighted at δ 4.19 to 4.25 as a multiplate. In ^{13}C NMR and DEPT, the methylene group next to sulfur adjoined methylene appeared up field at δ 29.27 (DEPT). The two methylene adjoined to sulfur atom resonated distinctively in up field at δ 29.66 and 35.04 (DEPT) respectively whereas the methylene groups linked to ethereal linkage (-CH_2-OPMB) and situated in acetonide ring appeared closely at δ 68.04 and 68.65 (DEPT) respectively. The *p*-methoxy benzylic carbon sighted at δ 72.36 (DEPT) whereas downfield signal at δ 75.25 corresponds to the carbon of single stereocenter present in thioether **7**. Rest of the ^{1}H and ^{13}C spectrum values were in complete agreement with the assigned structure of thioether **7**.



5 **6** **7**

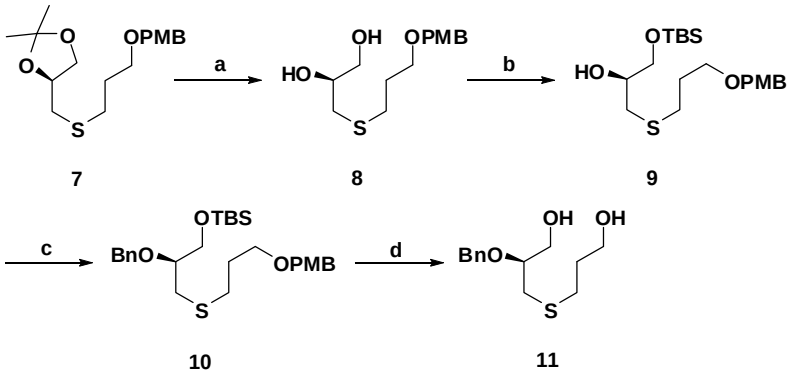
Scheme 3. *Reagents and conditions*: *a) NaH, THF, 0 °C, 96%.*

3.2.3.2 Synthesis of diol 11

The thioether **7** synthesized and characterized thus was then subjected for acetonide deprotection with *p*-TSA in MeOH at room temperature to afford diol **8** in 90% yield (Scheme 4). The primary hydroxyl group of diol **8** was then selectively protected with TBSCl (1.1 equivalent) and imidazole in dry CH_2Cl_2 at 0 °C to offer corresponding TBS-protected alcohol **9** with 95% yield (Scheme 4). The presence of two singlets at δ 0.10 and 0.93 accounted for 6 and 9 protons in ^{1}H NMR and two signals at δ -5.54, 18.09 and 25.71 in ^{13}C NMR confirmed the formation of TBS-protected alcohol **9**. TBS-protected alcohol **9** was further benzylated with sodium hydride and BnBr in dry THF at 0 °C to give thioether **10** in 96% yield. In ^{1}H NMR spectrum of thioether **10**,

two singlets at δ 0.01 and 0.85 correspond to TBS group while methylene group next to sulfur connected methylene appeared up field as quintet (J = 13.3, 6.4 Hz) at δ 1.81. Two methylene groups adjoined to sulfur atom appeared up field at δ 2.54 to 2.76 as multiplates whereas being a part of ethereal linkage, the protons on another two methylene groups (-CH_2-OPMB and –CH_2-OTBS) collectively resonated downfield at δ 3.43 to 3.57 as multiplate. The proton on the only stereocenter in thioether **10** viewed as doublet (J = 5.0 Hz) at δ 3.67 whereas the methoxy protons of –OPMB group as usually appeared as singlet at δ 3.74. Two singlets at δ 4.37 and δ 4.61 correspond to two benzylic groups (-OPMB and OBn) while two doublets at δ 6.82 (J = 8.7 Hz), δ 7.20 (J = 8.7 Hz) and a multiplate at δ 7.1 to δ 7.31 represent the rest of aromatic protons.

In ^{13}C NMR and DEPT, signals at δ -5.50, 18.10 and 25.76 signify the presence of TBS group while signal at δ 29.63 (DEPT) corresponds to the methylene group next to sulfur linked methylene. The carbons of two methylene adjoined to sulfur atom as usually resonated distinctively in up field at δ 29.67 and 33.22 (DEPT) respectively whereas the carbons of two methylene associated to ethereal linkages -CH_2-OTBS and -CH_2-OPMB appeared at δ 63.98 and 68.26 (DEPT) respectively. Two signals sighted downfield at δ 72.42 and 73.14 (DEPT) correspond to the two benzylic carbons from -OBn and -OPMB respectively while a signal at δ 79.42 signify the carbon of only stereocenter present in thioether **10**. Rest of the ^{13}C spectral values and mass (ESI-TOF) m/z at 513.3 accounting for ([M+Na]$^+$) along with its HRMS (TOF) m/z calculated for $C_{27}H_{42}$ NaO_4SSi ([M+Na]$^+$) 513.2471, found 513.2466 were in complete accordance with the assigned structure of thioether **10**.

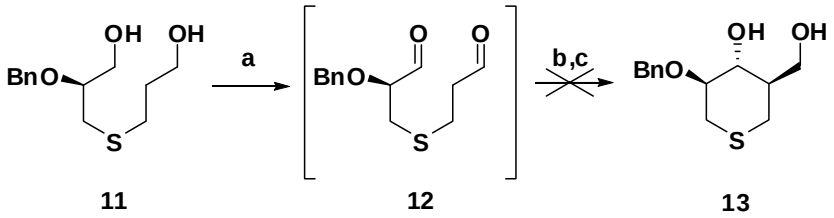


Scheme 4. *Reagents and conditions*: *a) p-TSA, MeOH, rt, 90%; b) Imidazole, TBSCl, DMAP, DCM, 0 °C, 95%; c) NaH, BnBr, THF, 0 °C, 96%; d) (i)Phosphotungstic acid, MeOH, rt, 97%; (ii) DDQ, DCM:H_2O (17:1), rt, 83%.*

The thioether **10** thus synthesized was then subjected for TBS-deprotection with catalytic Phosphotungstic acid[9] in MeOH at room temperature followed by oxidative cleavage of PMB group with DDQ[10] in DCM: H_2O (17:1) at room temperature to afford diol **11** in 83% yield. In ^{1}H NMR spectrum of diol **11**, methylene group next to sulfur associated methylene appeared up field as multiplate signal at δ 1.79 to 1.87 while a broad singlet signal accounted for two protons signify the two hydroxyl groups from diol **11**. Two methylene groups adjacent to sulfur atom appeared closely at δ 2.61 to 2.81 as a multiplate whereas two distinct multiplates at δ 3.49 to 3.59 and 3.63 to 3.75 represent two terminal hydroxy methylene groups. The proton on the single stereocenter in diol **11** viewed as multiplate signal at δ 3.83 to 3.94 while singlet at δ 4.57 and multiplate at δ 7.29 to 7.37 denote the benzylic and aromatic protons respectively. In ^{13}C NMR and DEPT, the methylene group next to sulfur linked methylene as usually viewed up field at δ 28.95 (DEPT). Two methylene linked to sulfur atom resonated distinctively at δ 31.87 and 35.58 (DEPT) respectively while the remaining two terminal hydroxy methylene groups resonated downfield at δ 60.86 and 62.81 (DEPT). The signal at δ 69.32 denotes the carbon of only stereocenter present in diol **11** whereas the benzylic carbon appeared at δ 73.29. Further a broad absorption at 3485 cm^{-1} in Infrared spectrum indicating the presence of hydroxyl functionality and mass (ESI-TOF) m/z at 279.2 accounting for ($[M+Na]^+$) along with its HRMS (TOF) m/z (calculated for $C_{13}H_{20}NaO_3S$ ($[M+Na]^+$) 279.1031, found 279.1036) also supported the assigned structure diol **11**.

3.2.3.3 L-proline catalyzed 6-*enolexo* aldolization

The diol **11,** the key starting material for the 6-*enolexo* aldolization was further oxidized with IBX in refluxing EtOAc to give a dialdehyde **12,** which without any further purification was directly used for the L-proline catalyzed 6-*enolexo* aldolization reaction.[11] The key step of direct 6-*enolexo* aldolization reaction of dialdehyde **12** was carried out using L-proline (30 mol %) as an organocatalyst in solvent DCM at room temperature and the reaction progress was monitored by TLC. No reaction progress was observed after 45 min therefore the reaction was kept for a prolonged time period (45 min-20 h). The reaction was not progressed even after prolonged reaction time period and no aldolization was observed, so the reaction mixture was reduced *in situ* with $NaBH_4$ in MeOH and starting material diol **11** was recovered (Scheme 5).



Scheme 5. *Reagents and conditions: a) IBX, ethyl acetate, reflux, 92%; b) L-proline (30 mol%), DCM, rt, 45 min-20 h; c) $NaBH_4$, MeOH, rt, (starting material* ***11*** *recovered 78%).*

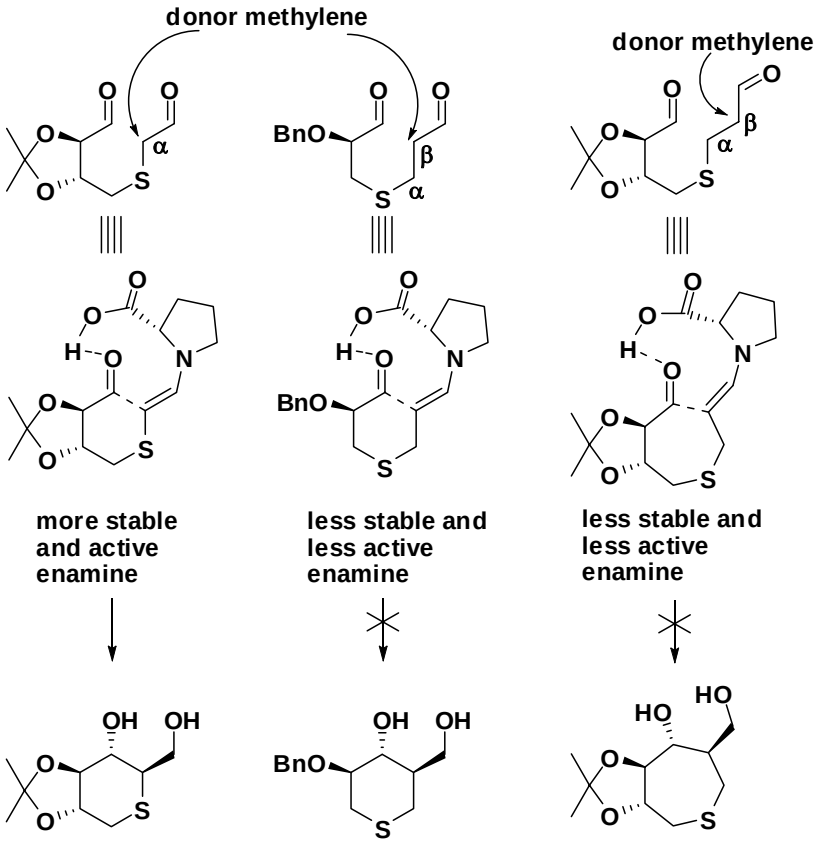


Figure 2. Effect of sulfur atom on *enolexo* aldolization.

It has been already discussed in section 1 of this chapter that the substrate dialdehyde with donor methylene situated α-to sulfur atom is supposed to produce more stable and active enamine than the substrate dialdehyde with donor methylene situated β-to sulfur atom. The substrate dialdehyde **12** of 6-*enolexo* aldolization reaction has donor

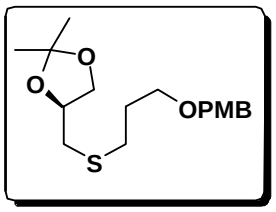
methylene situated *β*-to sulfur atom which is supposed to give less stable and less active enamine which could result in the poor reaction rate and failure of the 6-*enolexo* aldolization reaction. Similar result was observed in case of 7-*enolexo* aldolization reaction where the donor methylene is situated *β*-to sulfur atom in the substrate (dialdehyde) and failed to form seven membered ring aldol. Hence, direct *enolexo* aldolization reaction is unfavorable for the substrates (dialdehydes) with donor methylene situated *β*-to sulfur atom (Figure 2).

3.2.5 Conclusion

In conclusion, the proposed direct 6-*enolexo* aldolization protocol for the synthesis of thio-mimic of Isofagomine failed to produce six-membered ring aldol building block of thio-mimic of Isofagomine. Even after prolonged reaction time period, the 6-*enolexo* aldolization reaction failed to produce six-membered ring aldol building block of thio-mimic of Isofagomine. This result is parallel to the result of 7-*enolexo* aldol reaction which also failed to form seven membered ring aldol, which suggested that L-proline catalyzed direct *enolexo* aldolization reaction was unfavorable for the donor methylene β-to sulfur in the substrate (dialdehyde).

3.2.6 Experimental

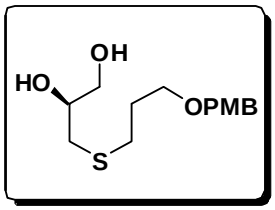
(*S*)-4-((3-(4-Methoxybenzyloxy)propylthio)methyl)-2,2-dimethyl-1,3-dioxolane (7)



To a solution of thiol **5** (8.48 g, 40 mmol) in dry THF (80 mL) was added sodium hydride (60% dispersion in oil, 2.4 g, 60 mmol) at 0 °C and was then stirred at same temperature for 30 min. To this was added the solution of iodo intermediate **6** (10.65 g, 44 mmol) in dry THF (120 mL) at the same temperature and stirred for an additional 5 h at room temperature. The reaction mixture was then quenched with cold water at 0 °C and the two phases were separated. The aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give dark yellowish dense oil which was further purified by silica gel column chromatography using petroleum ether: ethyl acetate (9:1) as eluent to offer the desired thioether **7** (12.42 g, 96%) as dense pale yellowish oil.

Molecular Formula	: $C_{17}H_{26}O_4S$.
Optical rotation	: $[\alpha]_D^{25}$ -21.03, *c* 1.0, $CHCl_3$.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 1.34 (s, 3H), 1.41 (s, 3H), 1.86 (dd, *J* = 7.2, 6.2 Hz, 2H), 2.57 (dd, *J* = 13.3, 7.3 Hz, 1H), 2.65 (t, *J* = 8.0 Hz, 1H), 2.71-2.77 (m, 2H), 3.51 (t, *J* = 6.2 Hz, 2H), 3.69 (dd, *J* = 6.3, 8.3 Hz, 1H), 3.77 (s, 3H), 4.07 (dd, *J* = 6.0, 8.3 Hz, 1H), 4.19-4.25 (m, 1H), 4.41 (s, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 25.34, 26.71, 29.28, 29.67, 35.05, 54.96, 68.05, 6867, 72.26, 75.36, 109.20, 113.51, 128.98, 130.22, 158.93.
IR (Neat) cm^{-1}	: 3150, 3045, 2915, 2890, 1609, 1580, 1451, 1380, 1213, 1145 (C-O-C), 1012 (C-S-C), 736 and 702. (aromatic).
MS (ESI-TOF) m/z	: 349.2 ($[M+Na]^+$).
HRMS (TOF) m/z	: calculated for $C_{17}H_{26}NaO_4S$ ($[M+Na]^+$) 349.1450, found 349.1455.

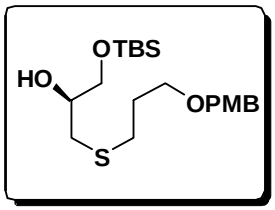
(*S*)-3-(3-(4-Methoxybenzyloxy)propylthio)propane-1,2-diol (8)



A solution of **7** (6.52 g, 20 mmol) in MeOH (50 mL) was stirred with the catalytic amount of *p*-TSA at room temperature for 8 h followed by TLC. After completion of the reaction, MeOH was evaporated under reduced pressure to give a residual paste. To the residual paste was then added water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give pale yellowish dense oil which upon silica gel column chromatography using petroleum ether: ethyl acetate (4:6) as eluent afforded the diol **8** (5.12 g, 90%) as dense pale yellowish oil.

Molecular Formula	: $C_{14}H_{22}O_4S$.
Optical rotation	: $[\alpha]_D^{25}$ -25.93, *c* 1.0, $CHCl_3$.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 1.88 (quintet, *J* = 13.0, 6.5Hz, 2H), 2.55-2.68 (m, 4H), 3.17 (bs, D_2O exchangeable, 1H), 3.53 (t, *J* = 6.0 Hz, 4H), 3.68-3.72 (m, 1H), 3.77 (bs, D_2O exchangeable, 1H), 3.80 (s, 3H), 4.44 (s, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 28.99, 29.50, 35.14, 54.97, 64.97, 68.08, 70.41, 72.33, 113.52, 129.06, 130.01, 158.89.
IR (Neat) cm^{-1}	: 3465 (broad), 2945, 2890, 1612, 1578, 1240, 1110 and (C-O-C), 1002 (C-S-C), 747 and 710 (aromatic).
MS (ESI-TOF) m/z	: 309.2 ($[M+Na]^+$).
HRMS (TOF) m/z	: calculated for $C_{14}H_{22}NaO_4S$ ($[M+Na]^+$) 309.1136, found 309.1143.

(*S*)-1-(4-Methoxyphenyl)-11,11,12,12-tetramethyl-2,10-dioxa-6-thia-11-silatridecan-8-ol (9)

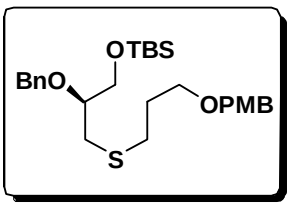


To a stirred solution of compound **8** (2.86 g, 10 mmol) and Imidazole (0.816 g, 12 mmol) with a catalytic amount of DMAP in dry CH_2Cl_2 (20 mL), was added a solution of TBSCl (1.81 g, 1.1 mmol) in dry DCM (5 mL) at 0 ^oC for 10 min and mixture was stirred further for 1 h at the same

temperature. After 1 h the reaction mixture allowed to stir at room temperature for next 4 h. The reaction was quenched with aqueous $NaHCO_3$ (20%) and the organic and aqueous layers were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent CH_2Cl_2 was evaporated under reduced pressure to give crude TBS-ether which was further purified by silica-gel column chromatography with petroleum ether: ethyl acetate (7:3) as eluent to offer the TBS-ether **9** (3.78 g, 95%) as colorless oil.

Molecular Formula	: $C_{20}H_{36}O_4SSi$.
Optical rotation	: $[\alpha]_D^{25}$ -2.15, *c* 1.0, $CHCl_3$.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 0.10 (s, 6H), 0.93 (s, 9H), 1.91 (quintet, *J* = 13.5, 6.5 Hz, 2H), 2.63 (bs, D_2O exchangeable, 1H), 2.65-2.73 (m, 4H), 3.56 (t, *J* = 6.1 Hz, 2H), 3.63-3.72 (m, 2H), 3.77 (dd, *J* = 11.3, 4.7 Hz, 1H), 3.83 (s, 3H), 4.46 (s, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) -5.54, 18.09, 25.71, 29.25, 29.70, 35.28, 55.01, 65.42, 68.15, 70.47, 72.43, 113.59, 129.04, 130.29, 159.00.
IR (Neat) cm^{-1}	: 3460 (broad), 2933, 2879, 1605, 1560, 1375, 1255, 1088(C-O-C), 992 (C-S-C), 756 and 723 (aromatic).
MS (ESI-TOF) m/z	: 423.2 ($[M+Na]^+$).
HRMS (TOF) m/z	: calculated for $C_{20}H_{36}NaO_4SSi$ ($[M+Na]^+$) 423.2001, found 423.2006.

(*S*)-8-(Benzyloxy)-1-(4-methoxyphenyl)-11,11,12,12-tetramethyl-2,10-dioxa-6-thia-11-silatridecane (10)

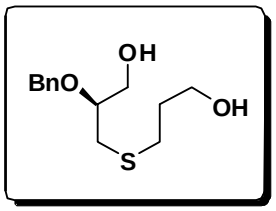


To a solution of **9** (3.0 g, 7.5 mmol) in dry THF (20 mL) was added sodium hydride (60% dispersion in oil, 0.450 g, 11.25 mmol) at 0 °C and was then stirred at same temperature for 30 min. To this was added slowly BnBr (1.41 g, 1 mL, 8.25 mmol) at the same temperature and stirred for an additional 5 h at room temperature. The reaction mixture was then quenched with ice cold water at 0

°C. The two phases were separated and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with water (2 x 10 mL), brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give colorless oil. The residual colorless oil was further purified by silica gel column chromatography using petroleum ether: ethyl acetate (8:2) as eluent to offer the ether **10** (3.51 g, 96%) as colorless oil.

Molecular Formula	: $C_{27}H_{42}O_4SSi$.
Optical rotation	: $[\alpha]_D^{25}$ -2.35, *c* 1.0, $CHCl_3$.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 0.01 (s, 6H), 0.85 (s, 9H), 1.81 (quintet, *J* = 13.3, 6.4 Hz, 2H), 2.54-2.76 (m, 4H), 3.43-3.57 (m, 4H), 3.67 (d, *J* = 5.0 Hz, 1H), 3.74 (s, 3H), 4.37 (s, 2H), 4.61 (s, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.21-7.31 (m, 5H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) -5.50, 18.10, 25.76, 29.63, 29.68, 33.24, 55.00, 63.99, 68.27, 72.42, 73.15, 79.44, 113.57, 127.59, 128.13, 129.04, 130.34, 138.42, 158.97.
IR (Neat) cm^{-1}	: 2925, 2867, 1619, 1580, 1371, 1253, 1109(C-O-C), 995 (C-S-C), 769 and 743 (aromatic).
MS (ESI-TOF) m/z	: 513.3 ($[M+Na]^+$).
HRMS (TOF) m/z	: calculated for $C_{27}H_{42}NaO_4SSi$ ($[M+Na]^+$) 513.2471, found 513.2466.

(*S*)-2-(Benzyloxy)-3-(3-hydroxypropylthio)propan-1-ol (11)



A mixture of **10** (2.45 g, 5 mmol) and 10% Phosphotungstic acid (0.144 g, 0.05 mmol) in methanol (20 mL) was stirred at room temperature for 30 min. After completion of the reaction, as indicated by TLC, solvent methanol was removed under reduced pressure to give a crude yellow liquid. Water (10 mL) was added to the crude yellow liquid and extracted with ethyl acetate (2 x 25 mL). The combined organic layers were then dried over anhydrous Na_2SO_4 and concentrated under diminished pressure to give TBS-deprotected alcohol (1.83 g, 97%) as pale yellow liquid which without any further purification was used for oxidative cleavage of –OPMB group. To a stirred solution of TBS-deprotected

alcohol (1.83 g, 4.87 mmol) in CH_2Cl_2 (51 mL) and water (3 mL) was added DDQ (3.32 g, 14.6 mmol) and stirred for 30 min at room temperature. After 30 min the precipitated DDQH was removed by filtration and the residue was washed with CH_2Cl_2. The combined organic layers were then washed with saturated $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and concentrated under diminished pressure to give dark brownish oil which was further purified by silica-gel column chromatography using petroleum ether: ethyl acetate (3:7) as eluent to offer the desired diol **11** (1.07 g, 83% after two steps) as a dense yellow oil.

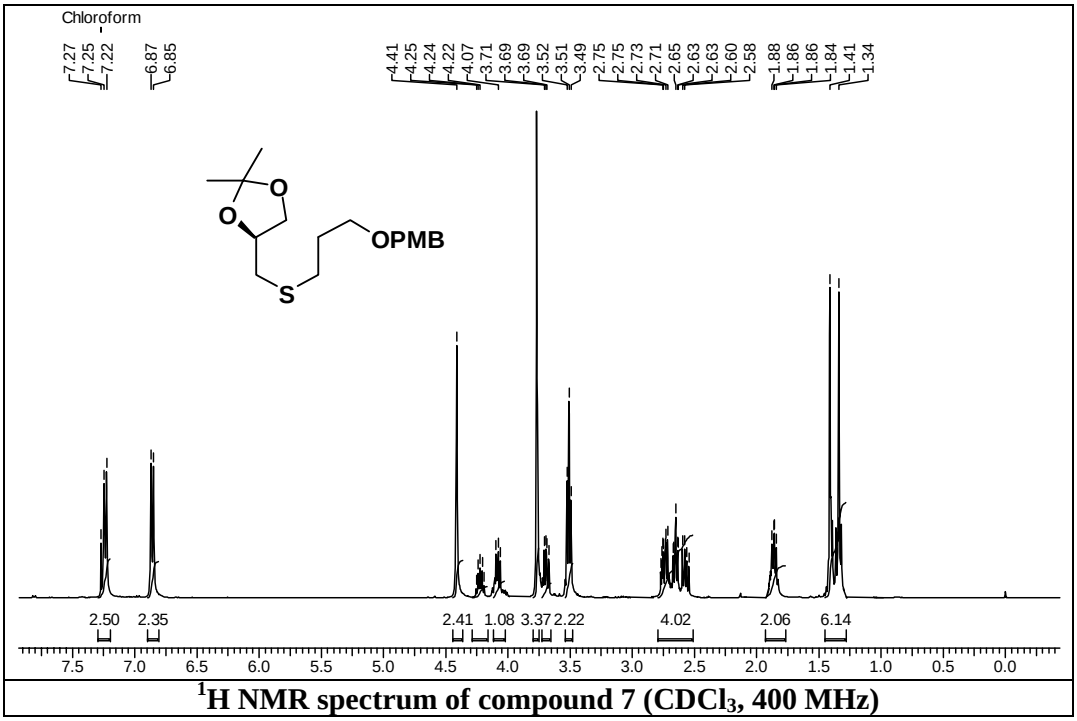
Molecular Formula	: $C_{13}H_{20}O_3S$.
Optical rotation	: $[\alpha]_D^{25}$ -6.47, *c* 1.0, $CHCl_3$.
^{1}H NMR ($CDCl_3$, 200MHz)	: δ(ppm) 1.79-1.87 (m, 2H), 2.05 (bs, D_2O exchangeable, 1H), 2.61-2.81 (m, 4H), 3.49-3.59 (m, 2H), 3.63-3.75 (m, 2H), 3.83-3.94 (m, 1H), 4.57 (s, 2H), 7.29-7.37 (m, 5H).
^{13}C NMR ($CDCl_3$, 50MHz)	: δ (ppm) 28.95, 31.87, 35.59, 60.86, 69.31, 72.79, 73.28, 127.65, 127.73, 128.29, 137.62.
IR (Neat) cm^{-1}	: 3485 (broad), 2954, 2885, 1615, 1568, 1252, 1137 and (C-O-C), 1009 (C-S-C), 732 and 711 (aromatic).
MS (ESI-TOF) m/z	: 279.2 ($[M+Na]^+$).
HRMS (TOF) m/z	: calculated for $C_{13}H_{20}NaO_3S$ ($[M+Na]^+$) 279.1031, found 279.1036.

L-proline catalyzed 6-*enolexo* aldolization reaction

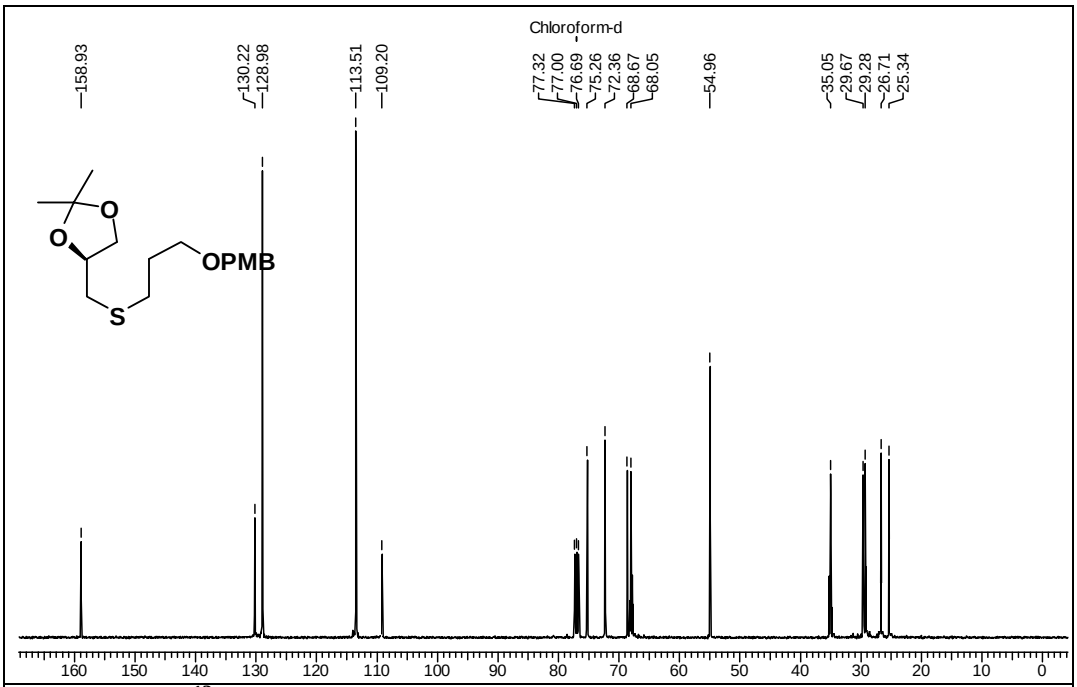
To the solution of diol **11** (0.256 g, 1 mmol) in EtOAc (15 mL) was added IBX (1.68 g, 6 mmol) and refluxed for 3.5 h at 80 ^oC. After reaction completion (as checked by 2,4-DNP TLC test)[11], reaction mixture was cooled to room temperature, filtered and the filtrate was washed with 20% aqueous $NaHCO_3$ (2 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under diminished pressure to give pale yellowish syrupy crude dialdehyde **12** (0.235 g). The crude dialdehyde was immediately used as a starting material for an *enolexo* aldolization reaction without any further purification. To the solution of crude dialdehyde **12** (0.235 g) in dry DCM (10 mL) was added L-proline (0.033 g, 30 mol %) and stirred at room temperature for 45 min (reaction completion time as checked by TLC). No reaction progress was

observed after 45 min so the reaction was kept for a prolonged time period (45 min-20 h). The reaction was did not proceed even after prolonged reaction time and no aldolization was observed, therefore the reaction mixture was reduced insitu by adding 5 mL of MeOH and $NaBH_4$ (0.043 g, 1.1 mmol, slight excess) at room temperature for 1h. The reaction mixture was concentrated on rotary evaporator, added with cold water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to offer crude yellowish liquid which was further purified by silica-gel column chromatography using petroleum ether: ethyl acetate (3:7) to give back starting material diol **11** (0.200 g, 78% recovered).

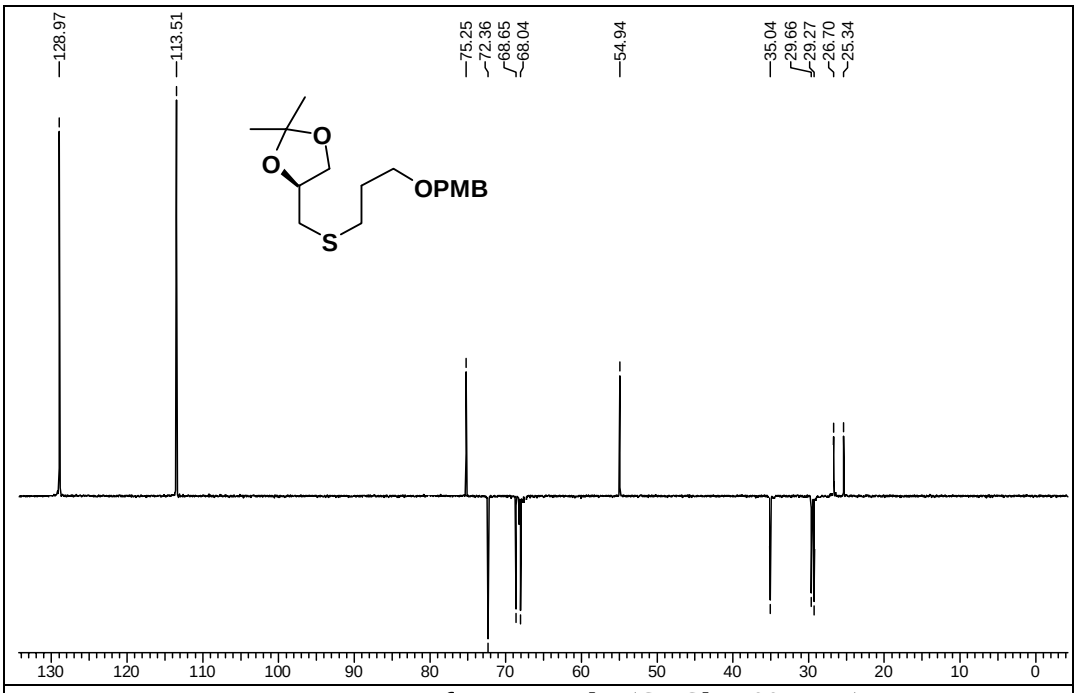
3.2.7 Analytical data



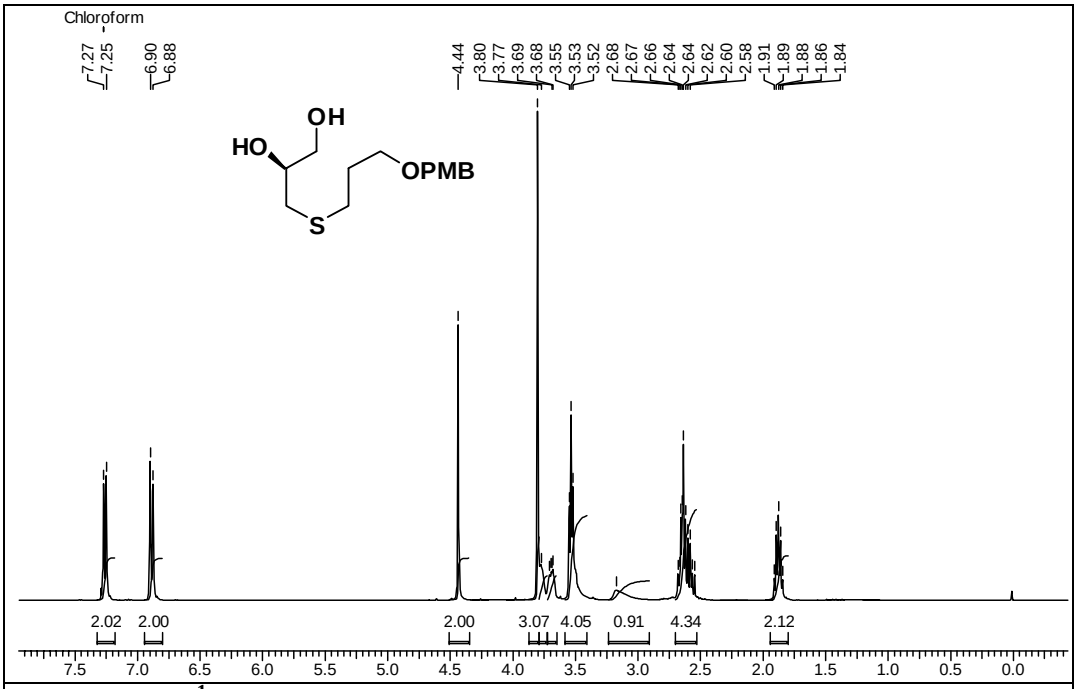
^{1}H NMR spectrum of compound 7 ($CDCl_3$, 400 MHz)



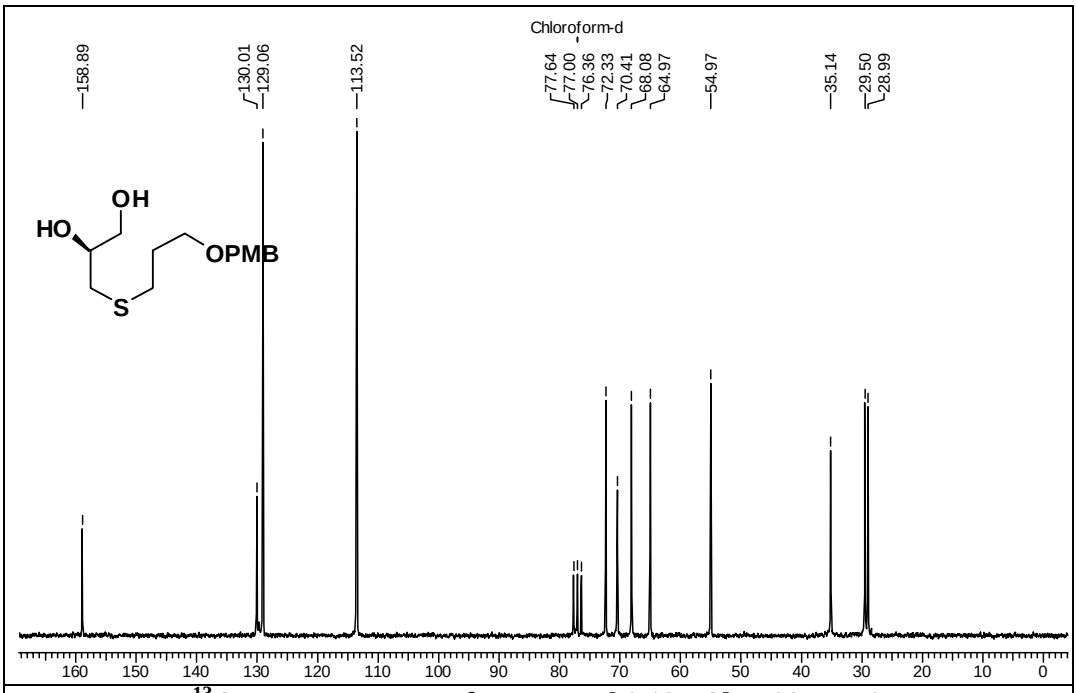
^{13}C NMR spectrum of compound 7 ($CDCl_3$, 100 MHz)



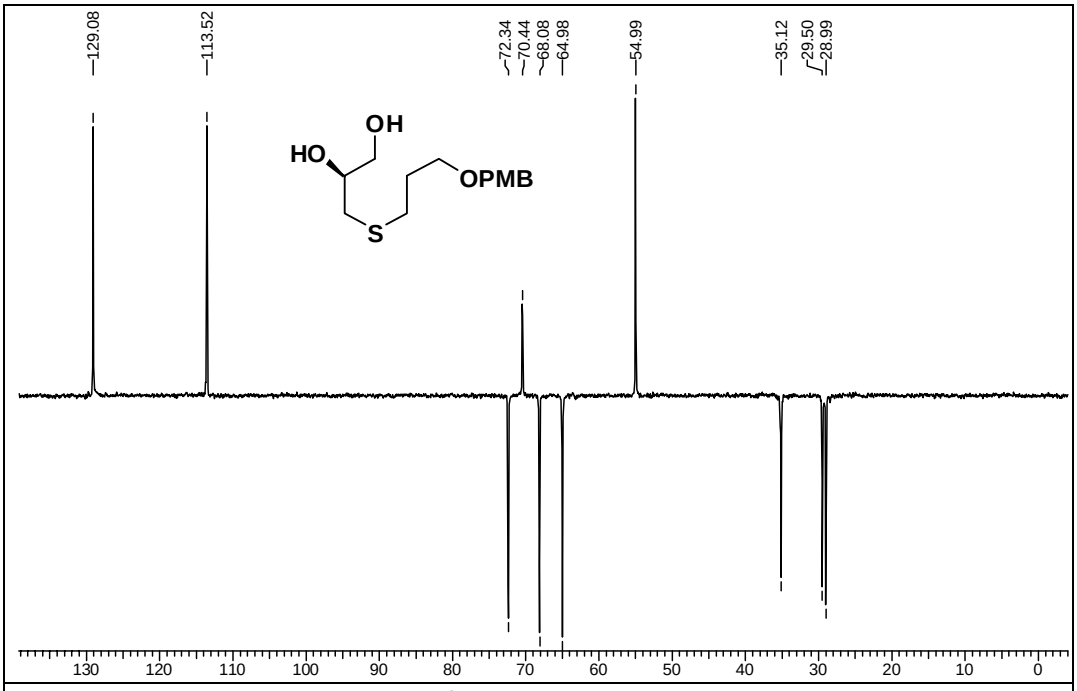
DEPT spectrum of compound 7 ($CDCl_3$, 100 MHz)



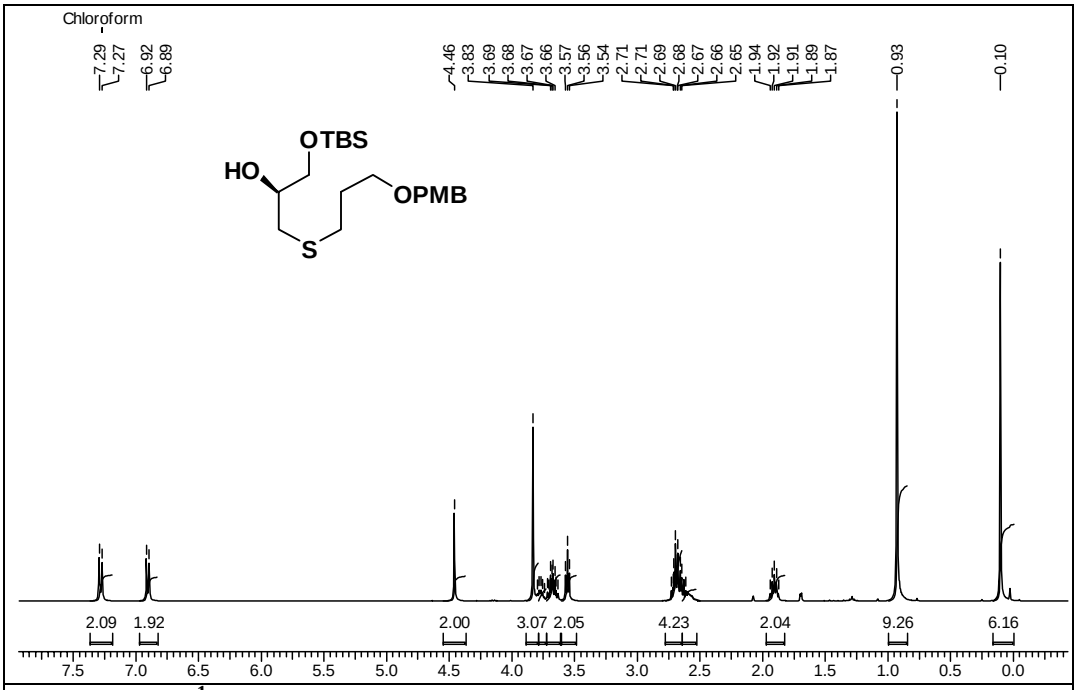
^{1}H NMR spectrum of compound 8 ($CDCl_3$, 400 MHz)



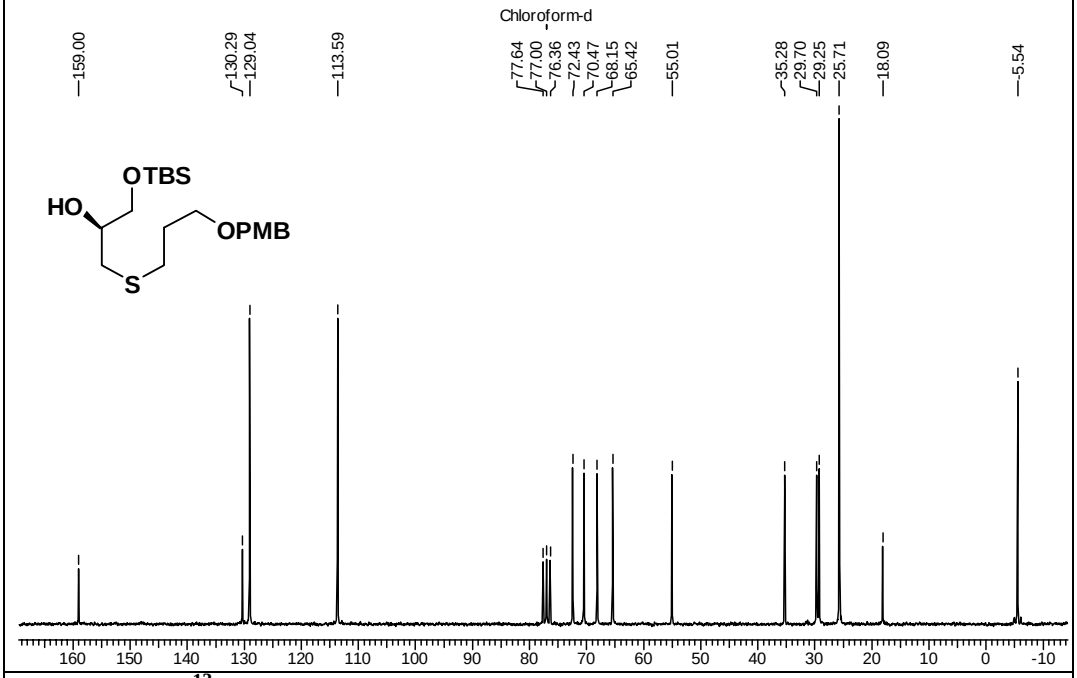
^{13}C NMR spectrum of compound 8 ($CDCl_3$, 100 MHz)



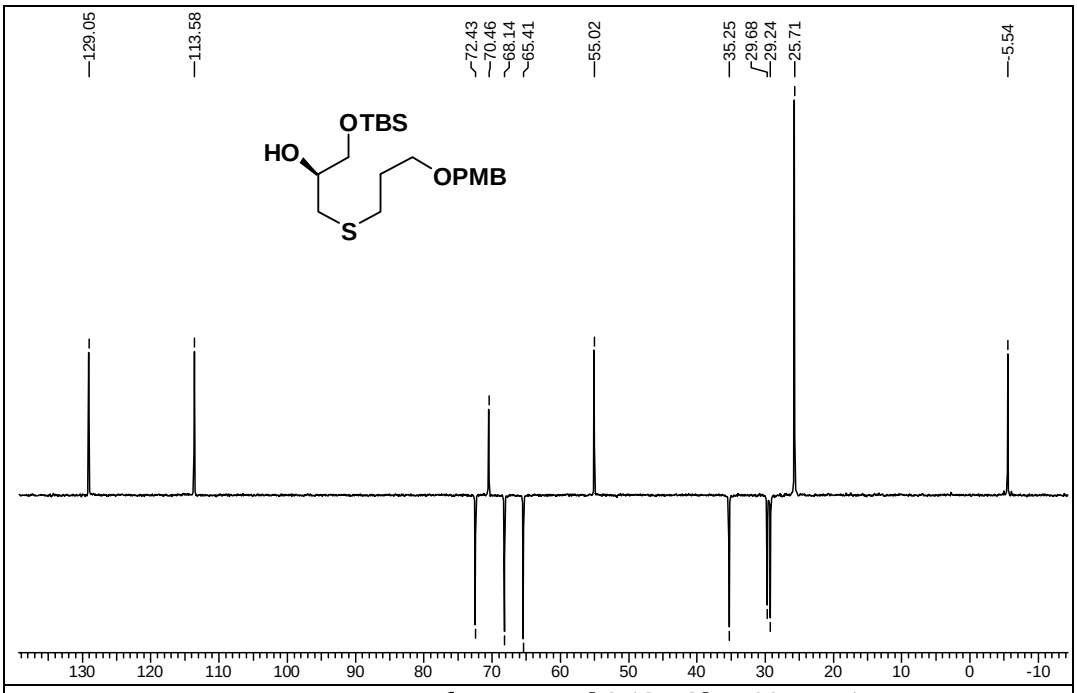
DEPT spectrum of compound 8 ($CDCl_3$, 100 MHz)



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



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



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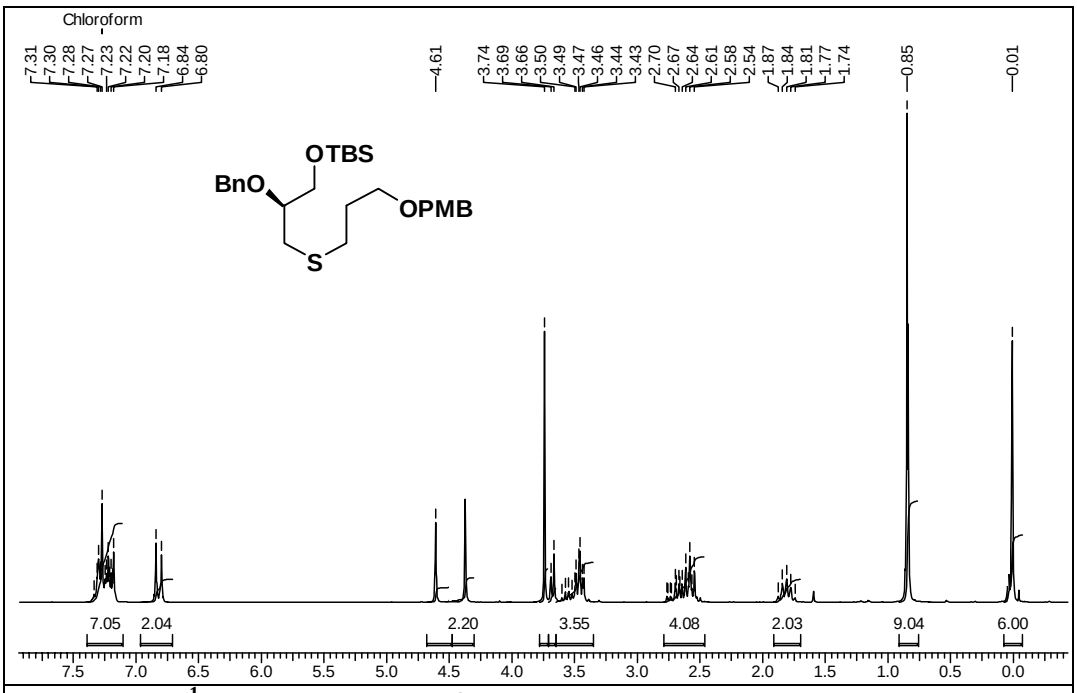
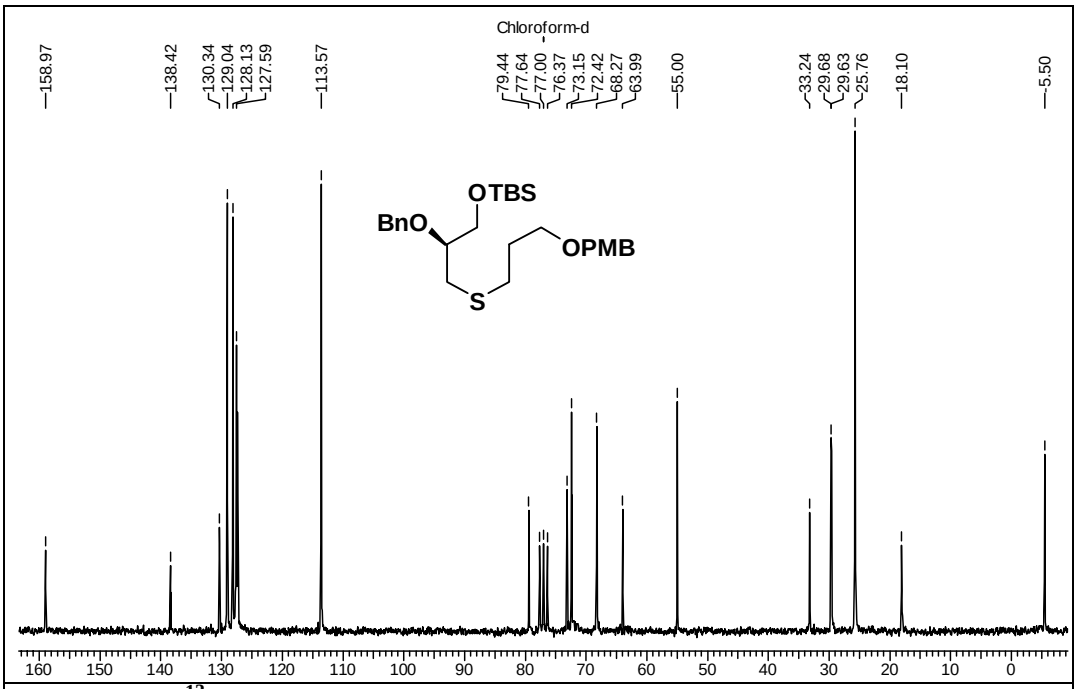
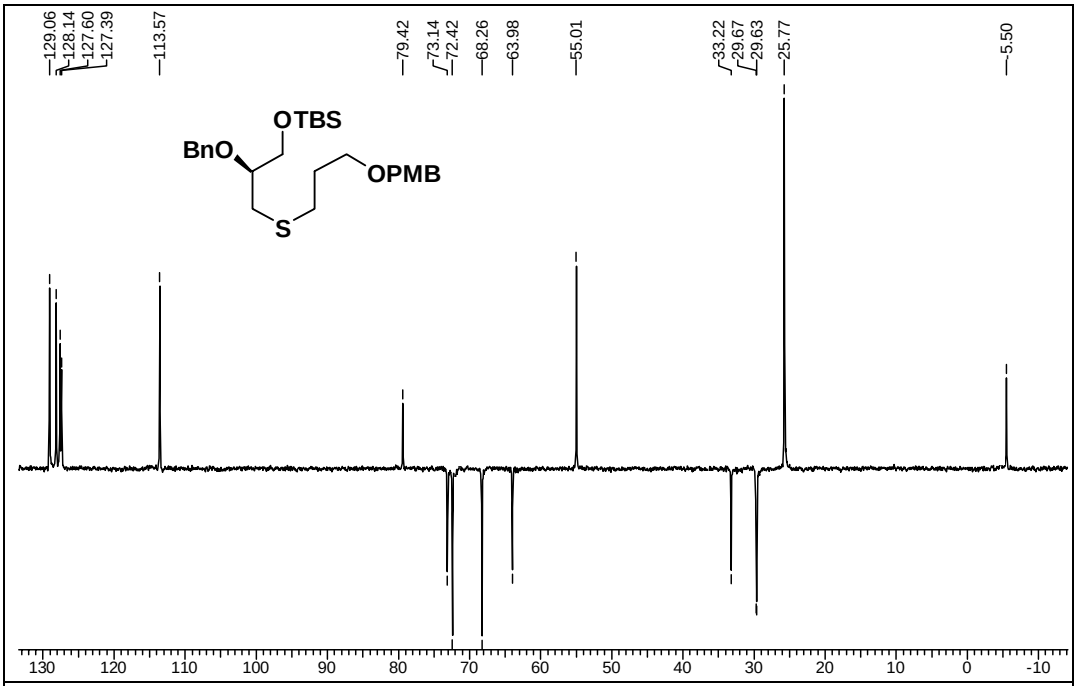


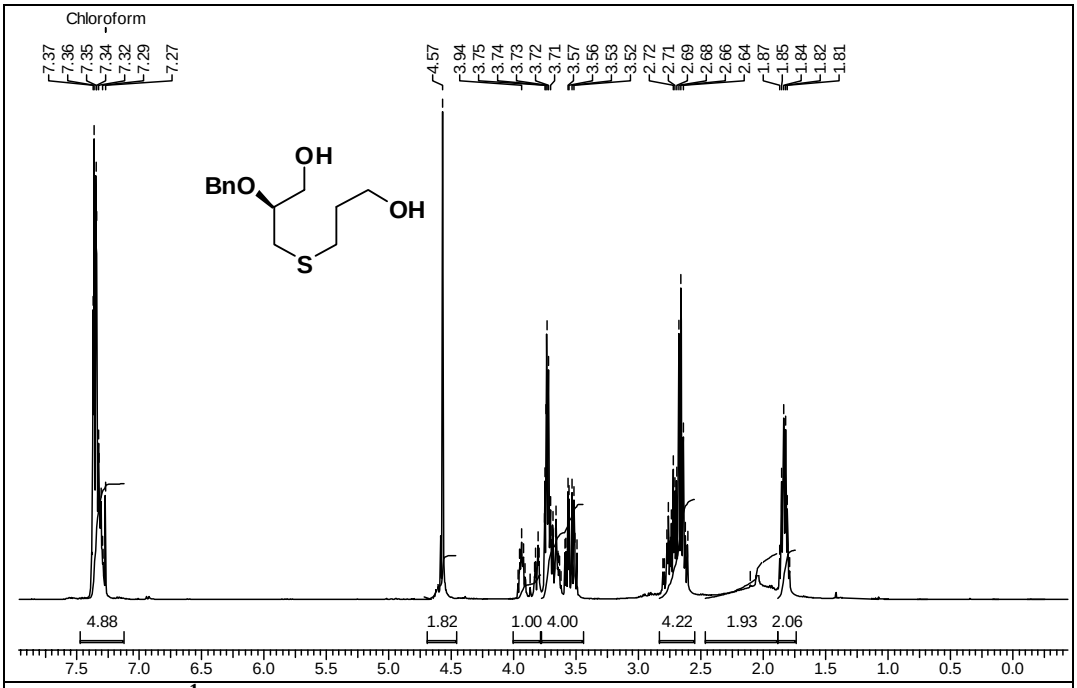
^{1}H NMR spectrum of compound 10 ($CDCl_3$, 400 MHz)



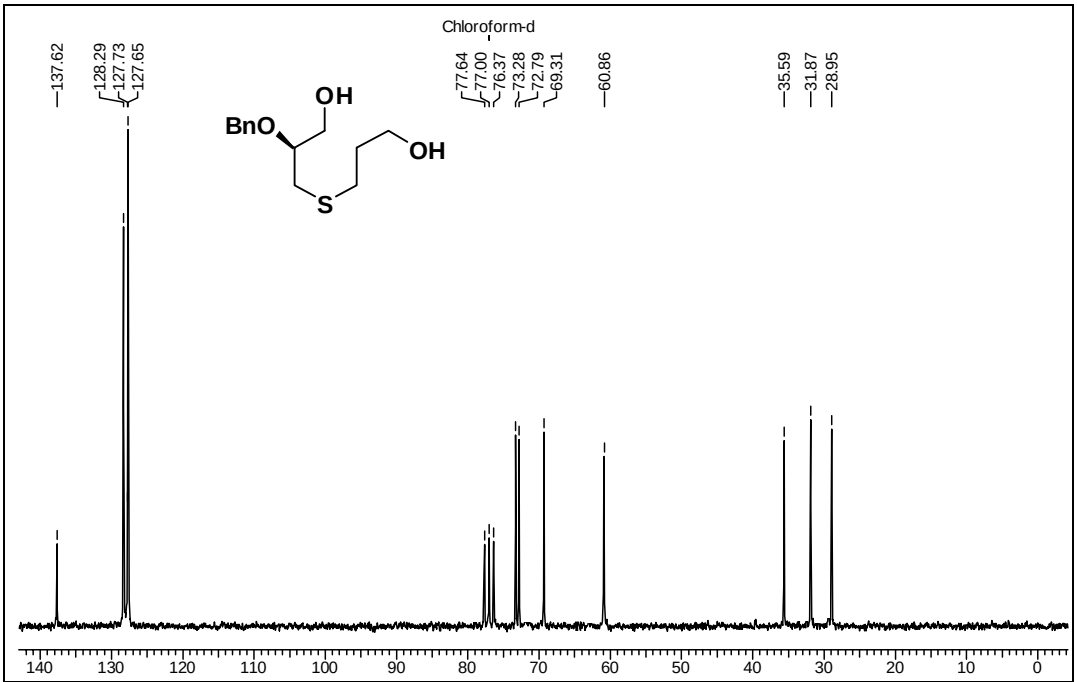
^{13}C NMR spectrum of compound 10 ($CDCl_3$, 100 MHz)



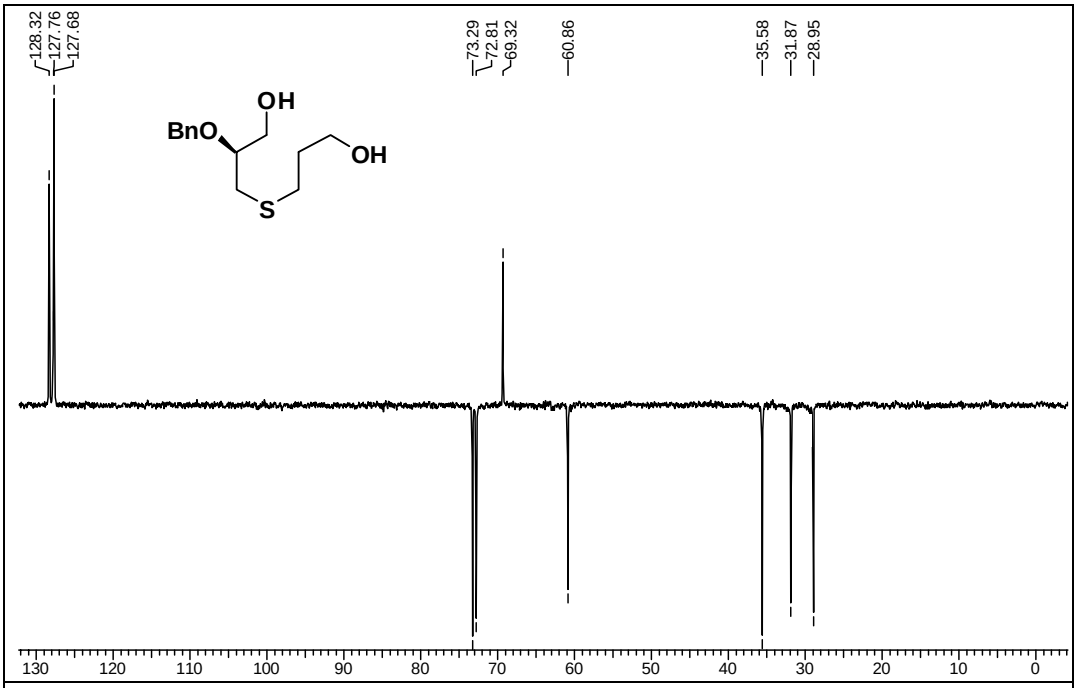
DEPT spectrum of compound 10 ($CDCl_3$, 100 MHz)



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



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



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

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11. In the oxidation reaction of diol **11** with IBX in EtOAc, the total consumption of diol **11** was confirmed by charring its TLC with *p*-anisaldehyde solution. The characteristic greenish spot of diol **11** [R_f = 0.25, Petroleum ether: EtOAc (3:7)] was totally disappeared which indicated the completion of reaction. But no spot was visualized for the dialdehyde **12** in the same TLC. Similar TLC dipped in 2,4-DNP solution in ethanol produced an orange colored characteristic spot of Schiff's base [R_f = 0.7, Petroleum ether: EtOAc (3:7)] on TLC which confirmed the formation of dialdehyde **12.**

Chapter 4

Introduction to ionic liquids, synthesis of crown ether and imidazolium based novel ionic liquids and development of ionic liquid mediated organic transformations

Section 1

Introduction to ionic liquids

Introduction to ionic liquids

4.1.1 Introduction

The progress towards more ecofriendly acceptable chemical processes and products is unanimously termed as "Green chemistry". The fields like education, research and commercial application across the entire supply chain for chemicals are encompassed by Green chemistry. Green chemistry can be achieved by applying ecofriendly technologies.[1] Every hour of every day, hundreds of tons of environmentally hazardous waste is released in the air, water, and land by industries all over the world. One of the biggest sources of such hazardous waste is a chemical industry. The present day challenge for chemists is to develop new products, processes and services with social, economic and environmental benefits. In this regard a new approach is required which sets out to reduce the materials and energy intensity of chemical processes and products, minimize or eliminate the dispersion of detrimental chemicals in the environment, maximize the use of renewable resources and extend the durability and recyclability of products. A high level of innovation and new technology will be required to make a clean technology in the chemical industry with an increasing emphasis on the reduction of waste at source. Solvents constitute a major factor in deciding the efficiency of an ecofriendly technology. The ideal solvent should have a very low volatility, it should be chemically and physically stable, recyclable and reusable, and eventually easy to handle. In addition, solvents that allow more selective and rapid transformations will have a significant impact.

4.1.2 Solvent alternatives for chemical synthesis

4.1.2.1 Solvent-free synthesis

The easiest way to prevent any form of solvent emission is to use no solvent at all. There have been many attempts to perform various reactions using no solvent at all.[2] Solvent-free synthesis offer several advantages such as reduced pollution, low costs, easy handling and simple processes. These advantages are quite essential especially for chemical industries. On the other hand few disadvantages are also there in performing solvent-free synthesis, for example strong exotherms can occur which can be difficult to deal with.

4.1.2.2 Water

The best solvent is no solvent and if a solvent (diluent) is needed then water is preferred. Water is nontoxic, nonflammable, abundantly available and inexpensive. Since last 30 years, water has been effectively used as a solvent in few biphasic industrial metal catalyzed reactions.[3-5] However, application of water in chemical synthesis is still limited due to (i) low miscibility of organic substrates in water, giving rise to low reaction rates; (ii) water is protic coordinating solvent and so it can react with halo organics and more vigorously with organometallic complexes by halide-carbon or metal-carbon bond hydrolysis; (iii) from an environmental perspective, trace amount of organic compounds in water are very difficult to remove.

4.1.2.3 Perflourinated solvents

The fluorous compounds were defined as compounds that are highly fluorinated and based upon sp^3-hybridized carbons. In recent times, perfluorinated solvents (perfluorinated hydrocarbons) have proven their usefulness for many organic and catalytic reactions.[6-7] On the other hand; specific ligands must be designed to solubilize catalyst in the perfluorinated phase. Moreover, the decomposition of fluorous solvents at high temperature leads to formation of toxic compounds. Fluorous compounds are often detected in the organic phase.

4.1.2.4 Supercritical fluids

A supercritical fluid (SCF) is defined as a material which can be either liquid or gas, used in a state above the critical temperature (T_c) and critical pressure (P_c); where gases and liquids can coexist. Recently, supercritical fluids have also been used to describe as new solvents for organic and catalytic reactions.[8,9] The physical properties and chemical stability of SCF make them eligible to be called as green solvents. For example, supercritical carbon dioxide ($scCO_2$) has been receiving increasing demand as an alternative reaction medium. Several features of $scCO_2$ make it an interesting solvent in the context of green chemistry and catalysis.[10] Unfortunately; critical conditions needed for SCF handling is still a limitation.

4.1.2.5 Poly (ethylene glycol) – PEG

Poly (ethylene glycol) is the linear polymer formed from the polymerization of ethylene oxide. PEG usually indicates the polyether of molecular weight less than 20,000 and is known to be inexpensive, thermally stable, recoverable, biologically compatible and nontoxic.[11] Furthermore, PEG and its monomethylethers have a low vapor pressure, are nonflammable, present simple workup procedures and can be recycled. For these reasons PEG is considered to be an environmentally benign alternative to chemical volatile solvents and a highly practical medium for organic reactions. Recently, PEG is used as green solvent in many organic reactions with low molecular weights (< 2000) because it is either liquid at room temperature or has a low melting point.[12] PEG is a biologically acceptable polymer due to which it is also used extensively in drug delivery and bioconjugates as tools for diagnostics but it can also be employed as an efficient medium for phase transfer catalysts.[13] Although less popular, PEG is commercially available and is much cheaper than ionic liquids but unlike the latter its properties can not be easily tuned. One of the major drawbacks in its use in organic reactions that also applies to ionic liquids is the inconvenience of using organic solvents to extract the products, even though scCO2 can also be used in both cases. Probably due to the higher popularity of other alternative solvents, especially ionic liquids, there are only a few examples in the literature that uses PEG as solvent in organic reactions

4.1.2.6 Ionic liquids

Since last two decades, Ionic liquids (ILs) have emerged as a novel class of solvents.[14,15] The history of ILs started from the first ionic compound which is a liquid at room temperature viz. ethyl ammonium nitrate ($[EtNH_3][NO_3]$) was synthesized by Walden, in 1914 from the reaction of ethylamine with concentrated nitric acid.[16] This IL had a melting point of 12-14 ^oC. These early studies on liquid salts did not lead to an explosion of interest in ionic liquids and it was not before the late 1940's that the next ionic liquids were discovered by Hurley and Wier. While looking for an inexpensive and facile method for aluminum electroplating they noted that by mixing powdered alkylpyridinium chlorides with $AlCl_3$, a reaction took place resulting in the formation of a liquid.[17] These ionic liquids incorporate organic cations, i.e. the type of cations used in the ionic liquids that now form the basis of modern synthetic

applications, and chloroaluminate anions. While such anions are still being used in synthesis and catalysis, they have become less popular than other more inert anions. This is mainly due to their sensitivity towards air and moisture and the fact that extraction of certain organic products may result in the destruction of these particular ionic liquids.

Osteryoung, Wilkes, Hussey and Zaworotko working on electrochemical aspects of the chloroaluminates were largely responsible for bringing ionic liquids to the attention of a wider scientific community.[18] They were studying chloroaluminates as solvents for transition metal complexes[19] and as reaction media for stoichiometric organic synthesis.[20] Chauvin and Osteryoung independently combined these two features, i.e. that ionic liquids could dissolve transition metal complexes and support organic chemistry. Chauvin showed that nickel complexes dissolved in acidic chloroaluminate ionic liquids represent an excellent system for the dimerisation of alkenes[21] while Osteryoung used Ziegler-Natta catalysts in acidic chloroaluminates to polymerise ethylene.[22] It was Zaworotko who made the next leap forward, this being the synthesis of water-stable ionic liquids that contain tetrafluoroborate, hexafluorophosphate, nitrate, sulfate and acetate anions.[23] However, one person who stands out as having made a considerable contribution to the field, looking at both the fundamental properties and applications of ionic liquids is K. Seddon at the University of Belfast. He is perhaps the person who has done most to popularize ionic liquids resulting in such intensive research activity around the world. Ionic liquids have since been utilized as in separation processes[24] as extractants for heavy metals with potential applications in the nuclear processing industry[25] as lubricants[26] as matrices in MALDI mass spectrometry[27] and even as propellants for small satellites.[28] The first industrial process using ionic liquid technology in chemical synthesis has also been reported[29] and numerous others are expected to follow. They also find additional use in enzyme catalysis or in multiphase bio-process operations.

Generally ILs refers to molten salts, which contain ions. Only those liquids, which are non-corrosive, and have low viscosity, are chosen to be called as Ionic Liquids. So classes belonging to molten inorganic salts like molten sodium chloride will not be considered under the heading ILs. Room temperature Ionic Liquids (RTILs) are emerging as novel replacements for volatile organic compounds (VOCs) conventionally used as industrial solvents. These solvents are often liquids at room

temperature and consist entirely of ionic species. They have many fascinating properties since both the thermodynamics and kinetics of reactions in ILs are different to those in conventional molecular solvents. These "Designer Solvents" suitably named-consists of an anionic and a cationic part, which can be varied for a particular end use or to possess a particular set of properties.

4.1.3 Classification of ionic liquids

ILs are classified into two categories.

i) Binary ionic liquids – salts where equilibrium is involved.

ii). Simple salts – made of single anion and cation.

The first category, the first generation ILs, contains a mixture of metal halide and dialkylimidazolium chloride. These contain several ionic species and their melting point and other properties depend on the mole fractions of the individual components. The second class, generally termed as second generation ILs, consists of simple cation and anion e.g. ethyl ammonium nitrate ($[EtNH_3][NO_3]$), dialkylimidazolium ILs such as [bmim]Br and [bbim]Br. The third generation ILs consist of chiral ILs (CILs) [30] made from either chiral cations or anions, Supported ionic liquid (SILs) [31] and task specific ILs (TSILs).[32] Usually ILs are composed of relatively large organic cations and inorganic or organic anions and have a melting range between 96-100 ^{o}C. Cations are mainly alkyl, quaternary ammonium or phosphonium moieties which may be a part of a heterocyclic ring.

4.1.4 Recent developments in cations and anions

4.1.4.1 Cations

Innovations in the field of ILs are being reported continuously in the form of novel cation and anion combinations. The cations are generally bulky, unsymmetrical ammonium or phosphonium salts, or heteroaromatics, with low symmetry, weak intermolecular interactions and lower charge densities. Those described in the literature are based on tetraalkylammonium **5**,[33] trialkylsulphonium **6**,[34] tetralkylphosphonium **7**,[34] 1,3-dialkylimidazolium **8**,[35] *N*-alkylpyridinium **9**,[36] *N*,*N*-dialkylpyrazolium **10**,[37] *N*-alkylthiazolium **11**,[38] *N*,*N*-dialkyloxazonium **12**,[39] *N*,*N*-dialkyltriazolium **13**,[40] *S*-alkylthiolanium **14**,[41] Organic polycations such as **15**[42] and **27**,[43] Warner's chiral cation **16**,[44] highly fluorinated phosphonium **17**,[45] cyclic

hexaalkylguanidinium **18**,[46] Wasserscheid's chiral cations **19**, **20** and **21**,[47] cholinium **22**,[48] isoquinolinium **23**,[49] dimeric imidazolium **24**,[50] *N*,*N*-dialkylpyrrolidinium **25**,[51] sulfonium **26** [52] and pyrrolidonium **28**[53] (Figure 1).

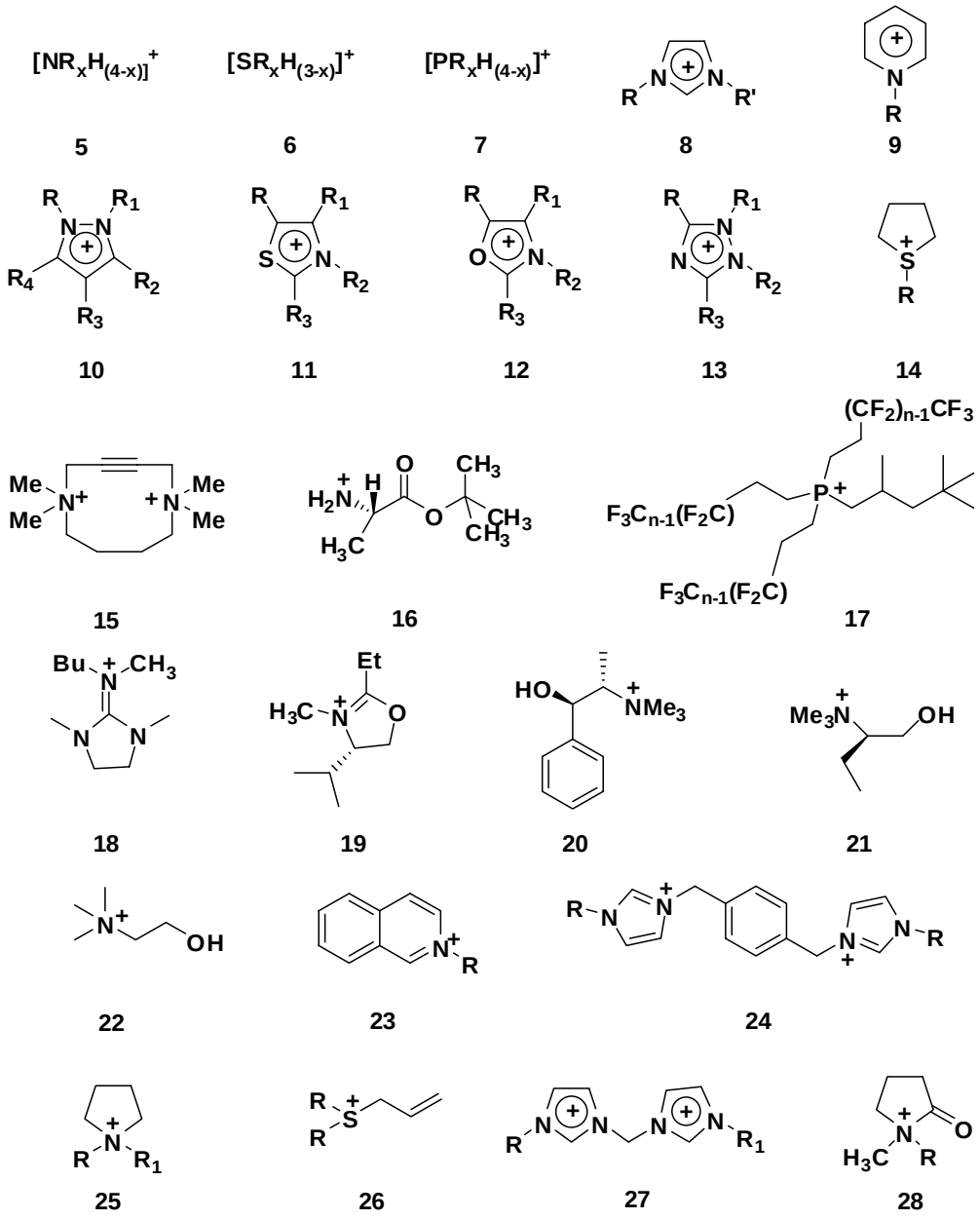

Figure 1. Different types of organic cations in ILs.

Besides organic cations based ionic liquids, lithium salts are increasingly being developed particularly for secondary batteries and storage of energy. They have often lower lattice energy and therefore, lower melting points than their neighboring

elements in the periodic table. As an example the mixture of LiCl and $EtCl_2$ gives a liquid, on a large range of composition, at temperatures lower than 0 ºC.[54]

4.1.4.2 Anions

The anion chemistry has a large influence on the properties of IL. The most commonly employed IL anions are polyatomic inorganic species. The introduction of different anions has become more popular as an increasing number of alternatives are being discovered. In future, the list of cations and anions will be extended to a nearly limitless number. Various combinations of cations and anions have provided finely designed ionic liquids for different applications. Number of anions has been reported in the literature as listed in Table 1.

Table 1. A list of some anions in ILs and their references.

Sr. No.	Anions	Ref.	Sr. No.	Anions	Ref.
1	$AuCl_4$	12	18	$AlCl_4$	64
2	$CF_3OCF_2CF_2BF_3$ [TFSA]	55	19	$ZnCl_3$	32
3	HBr_2	56	20	$CuCl_2$	32
4	H_2Br_3	57	21	$SnCl_3$	32
5	Br_3	58	22	$N(EtSO_2)$	32
6	SbF_6	59	23	$N(FSO_2)$	65
7	CH_3CO_2	14g	24	$C(CF_3SO_2)_3$	65
8	NO_3	14i	25	CH_3SO_3	32
9	NO_2	16	26	$N(CN)_2$	66
10	CF_3SO_3	17	27	halides	67
11	$(CF_3SO_2)_2N$ [NTf_2]	61	28	Al_2Cl_7	32
12	CF_3CO_2	18a, 61	29	Al_3Cl_{10}	32
13	$B(Et_3Hex)$	18b, 19, 62	30	Au_2Cl_7	32
14	OTs	63	31	Fe_2C_{17}	32
15	Carborane anion	20	32	Sb_2F_{11}	32
16	BF_4	21	33	(Glycerol) borate	68
17	PF_6	22	34	HSO_4	69

4.1.5 Features of ILs which make them as attractive potential solvents

ILs possesses a variety of special physical and chemical properties which make them attractive potential solvents in many organic reactions.

1. They show low or negligible vapor pressure and non-flammable.
2. They have high thermal stability.
3. They serve as a good medium to solubilize gases such as H_2, CO, O_2, CO_2 and many reactions are now being performed using ionic liquids and supercritical CO_2.
4. Their ionic character enhances the reaction rates to a great extent in many reactions including microwave assisted and ultrasound promoted organic synthesis.
5. Their ability to dissolve a wide range of inorganic, organic, organometallic compounds and even polymeric materials.
6. Highly polar yet non-coordinating solvents.
7. Most of the ionic liquids may be stored without decomposition for a long period of time.
8. They exhibit Brønsted, Lewis and Franklin acidity, as well as super acidity.
9. They are immiscible with a number of organic solvents and provide a non-aqueous, polar alternative for two-phase systems. Hydrophobic ionic liquids can also be used as immiscible polar phases with water.
10. Because of their non-volatile nature, products could be easily isolated by vacuum distillation, leaving behind the IL pure enough for recycling after the reaction.
11. They are relatively cheap, and easy to prepare.
12. ILs may be termed as "designer" and 'neoteric' solvents since their properties can be adjusted to suit for the particular process by changing anion/cation or both.

4.1.6 Applications of ionic liquids

Ionic liquid is a wide concept in modern synthetic organic chemistry. Recently, ILs has generated enormous interest in organic synthesis due to their unique solvent properties, in combination with their tunability. Applications of ILs are concentrated in two directions: (i) to replace organic solvents with ionic liquids; due to their unique

solvent properties and (ii) to replace liquid acid with ionic liquid due to their variable acidity. The former applications include Diels-Alder reaction, Heck reaction and Morita–Baylis–Hillman reaction, while the latter include coupling reactions and Friedel–Crafts reactions. ILs are widely used in organic synthesis especially in transition metal catalyzed reaction as reaction media, reagent or catalyst. In most of the cases, ILs enhance rate of reactions, yields, selectivity in comparison to conventional organic solvents. Some of the applications of ionic liquids as solvent and catalyst are recorded in Table 2.

Table 2. Reports on the applications of ILs as solvent and catalyst/promoter.

Reaction	Nature of the ILs	Catalyst	Ref.
Diels-Alder reaction	[EtPy][BF_4],	–	70
	[EtPy][CF_3COO]		
	[MePy][OTf]	$Er(OTf)_3$	71
	[BuPy][Cl]/$AlCl_3$	–	72
Diels-Alder cycloaddition	[PrPy]Br	–	73
Intramolecular Diels-Alder reaction	[BuPy][BF_4], [BuPy][NTf_2], [HePy][NTf_2]	–	74
Morita–Baylis–Hillman reaction	[EtPy][BF_4], [BuPy][NO_3]	DABCO or HMTA	75
Heck reaction	[HePy][BF_4],	$Pd(Oac)_2$, base	76
	[HePy][Cl]	$PdCl_2$	
	[BuPy][BF_4]	Pd	77
Three-component condensation	[BuPy][BF_4]	–	78
Knoevenagel condensation	[BuPy][NO_3]	NH_4Ac	79
	[BuPy][Cl]·$AlCl_3$	–	80
Synthesis of peptide	[EFPy][BF_4]	base	81
Bromination reaction	[BMPy][Br_3]	–	82
	[PrPy][Br_3	–	83
Arylation	[EtPy][Tf]	–	84
Acylation of β-D glucose	[BuPy][BF_4], [PrPy][BF_4]	CAL-B	85
Reduction of aldehydes and	[BuPy][BF_4]	$NaBH_4$	86

ketones			
Cycloaddition of CO_2 to butyl glycidyl ether	–	[BuPy][Cl]	87
Beckmann rearrangement	[BuPy][BF_4]	$POCl_3$ or PCl_5	88
Aromatic benzoylation	[BuPy][Cl]/$AlCl_3$	–	89
Fisher Indole synthesis	[BuPy][Cl]/$AlCl_3$	–	90
Friedel-crafts alkylation	[EtPy][BF_4],	$FeCl_3$	91
	[EtPy][CF_3COO]		
Friedel-Crafts acylation	[EtPy][BF_4],	–	92
	[EtPy][CF_3COO]		
Friedel-crafts reaction	[BuPy][Cl]-$AlCl_3$	[BuPy][Cl]-$AlCl_3$	93
Alkylation reactions	[BuPy][BF_4]	–	94
Vinyl acetate hydroformylation	[BuPy][$N(SO_2CF_3)_2$]	$Rh(CO)_2(acac)$	95
Etherification	[BMPy][Br]	[BMPy][Br]	96
Michael Reaction	[BMPy][BF_4] [BMPy][$N(CN)_2$]	PTC Organocatalyst	97 98
Copolymerization of styrene and CO	[HePy][NTf_2]	(bipy)$Pd(OAc)_2$	99a
Hydrosilylation of styrene	[EtPy][PF_6], [BuPy][PF_6], [HePy][PF_6], [OctPy][PF_6], [HeDePy][PF_6], [BnPy][PF_6]	$Rh(PPh_3)_3Cl$	99b,c
Demethylation	[PyH][Cl]	–	99d
Suzuki cross-coupling	[C_3CNPy][Tf_2N], [BuPy][Tf_2N]	Pd complex	99e
Stille coupling	[C_3CNPy][Tf_2N], [BuPy][$N(SO_2CF_3)_2$]	Pd complex	99e
Sonogashira reaction	[BuPy][BF_4], [BuPy][PF_6], [BuPy][NO_3] [BMPy]BF_4	$Pd(OAc)_2$, $PdCl_2$ Pd complex	99f 99g
Mizoroki–Heck reactions	[BMPy]BF_4	Pd complex	99g
Fischer esterification	[Py][CH_3SO_3],	–	99h

	[Py][*p*-TSA]		
Esterification	[PSPy][HSO_4] [Bupy][HSO_4] [PSPy][BF_4], [PSPy][HSO_4], [PSPy][H_2PO_4], [PSPy][*p*-TSA] [Etpy][CF_3CO_2]	[PSPy][HSO_4] [Bupy][HSO_4] [PSPy][BF_4], [PSPy][HSO_4], [PSPy][H_2PO_4], [PSPy][*p*-TSA] [Etpy][CF_3CO_2]	99i 99j 99k 99l
Synthesis of 1,5-Benzodiazepine	[Bupy][HSO_4]	[Bupy][HSO_4]	99m
Aromatic nitration	[BMPy][NTf_2]	–	99n,o
Kinetic resolution of amino acid esters	[Etpy][CF_3CO_2]	–	99p
Iodination of arenes	[BuPy][BF_4]	F-TEDA-BF_4	99q

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Section 2

Synthesis of crown ether and imidazolium based novel ionic liquids

Synthesis of crown ether and imidazolium based novel ionic liquids

4.2.1 Introduction

The hydrophobic character of some ionic liquids (ILs) allows them to extract hydrophobic compounds in biphasic separations. Metal cations tend to stay in the aqueous solution being hydrated. Therefore, in order to remove metal ions from the aqueous phase into hydrophobic ILs, extractants (or chelators, ligands) are normally needed to form complexes to increase the metal's hydrophobicity. The solvation of crown-ether complexes in ILs is more thermodynamically favored than conventional organic solvents.[1] This is a key advantage of using ILs for extractions of metal ions.

Varying the structure of an IL (especially the side chain of its cation) to change its hydrophobicity can improve the partition coefficients of metal ions. In this regard extractants (such as crown ethers) can be modified to achieve optimal selectivity for a specific application.[2]

Many conventional organic solvents are toxic and flammable volatile organic compounds (VOCs) which are detrimental to environment. To improve the safety and environmental friendliness of this conventional separation technique, ILs can be used as ideal substitutes because of their stability, nonvolatility and adjustable miscibility and polarity. ILs can be hydrophilic and hydrophobic depending on the structures of cations and anions. The anion seems more important in determining the water miscibility of ILs. Those ILs based on $-[PF_6]$ and $-[NTf_2]$ {=bis [(trifluoromethyl)sulfonyl]amide} are normally water immiscible, therefore, they are the solvents of choice for forming biphasic systems in most IL extraction applications. Introduction of an ether group on the N-position of the cation has resulted in some novel properties of ionic liquids (ILs) among which the report on using crown ether as a functional group is still rare.[3] Till date very few reports are available on crown ether-involving ILs. Crown ether's macrocyclic cavity, chelate ring, macrocycle rigidity, and number and type of donor atoms can be tuned to provide a high degree of metal ion selectivity, so they are arguably the most versatile type of ion-specific extractants. Incorporating these excellent properties into ILs may significantly improve the coordination of ILs with metal ions, and may therefore provide both ILs and crown ethers some promising features for the use in extraction, molecule

recognition, chemical sensing, and phase-transfer catalysis or transition metal catalysis.[4]

4.2.2 Present Work

In continuation of our collaborative research on the synthesis of crown ether and imidazolium based novel ILs possessing complexing cations or anions; towards novel task-specific extractants for metal ions and organic compounds, we have attempted the synthesis of novel 15-crown-5-ether and 18-crown-6-ether imidazolium based ILs with Br and NTf_2 as anions respectively (Figure 1).

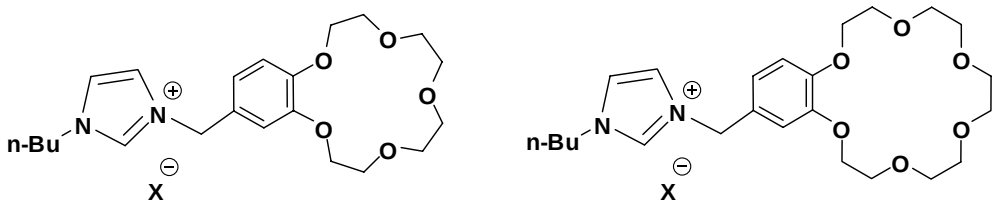
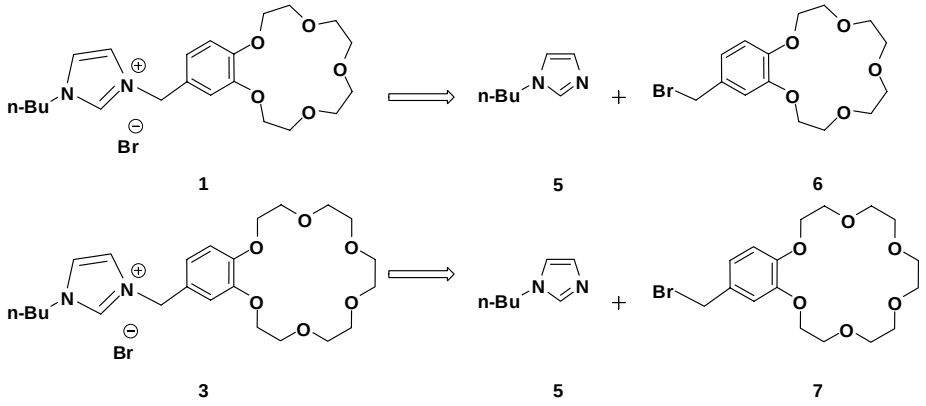


Figure 1. Proposed crown ether and imidazolium based novel ILs.

The synthesis of proposed 15-crown-5-ether and 18-crown-6-ether imidazolium based ILs could be achieved by the addition reaction of *N*-butyl imidazole **5** and bromo intermediate **6** or **7** (Scheme 1).



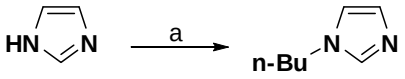
Scheme 1. Retro synthetic disconnections for ILs **1** and **3**.

4.2.3 Result and discussion

Therefore our actual synthesis starts with the preparation of *N*-butyl imidazole **5** and bromo intermediate **6** and **7**.

4.2.3.1 Synthesis of *N*-butylimidazole 5

N-butylimidazole **5** was prepared by the *N*-butylation of imidazole **8**.[5] Imidazole **8** on treatment with n-butyl bromide in the presence of KOH in acetonitrile at room temperature afforded *N*-butylimidazole **5** with yield 95% (Scheme 2).

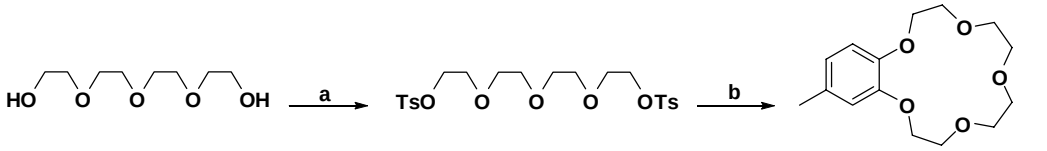


8 **5**

Scheme 2. *Reagents and conditions*: *a) N-Butyl bromide, KOH, acetonitrile, 4 h, rt, 95%.*

4.2.3.2 Synthesis of bromo intermediate 6

The synthesis of bromo intermediate **6** was started with tetraethylene glycol (TEG) **9**. TEG **9** was protected with TsCl in presence of TEA, DMAP in DCM at 0 ^{o}C to give its ditosyl derivative **10** in 90% yield. The ditosyl derivative was further treated with 4-methylcatechol in presence of CsF in refluxing acetonitrile to offer the 15-crown-5-ether **11** in 40% yield (Scheme 3).[6]

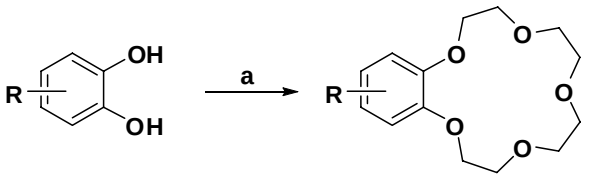


9 (TEG) **10** **11** (15-Crown-5-ether)

Scheme 3. *Reagents and conditions*: *a) TEA, TsCl, DMAP, DCM, 0 ^{o}C, 90%; b) CsF, acetonitrile, 4-methylcatechol, reflux, 40%.*

Formation of large amount of lumps of CsF within few min of its addition impended uniformity in the reaction stirring for longer period (reaction time is 22 h). Due to formation of sticky and polymeric mass formation, the reaction work-up also become tedious. To avoid these drawbacks we attempted this reaction using K_2CO_3 in refluxing acetone condition. Along with 4-methylcatechol, we have also screened

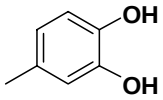
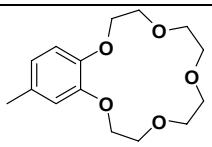
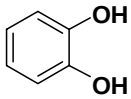
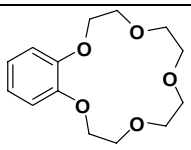
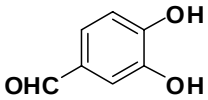
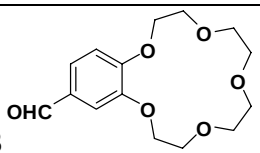
simple catechol and 3,4-dihydroxybenzaldehyde for the formation of respective 15-crown-5-ethers **12** and **13** under this condition (Scheme 4) and the results of the same are summarized in Table 1.



Substituted catechol **15-Crown-5-ether**

Scheme 4. *Reagents and conditions*: *a) K_2CO_3, acetone, substituted catechol, reflux, 18 h, R = H or 4-Me or 4-CHO.*

Table 1. Screening of substituted catechol for the formation 15-crown-5-ether using K_2CO_3 as a base.[a]

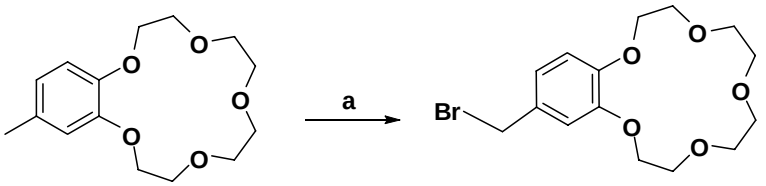
Entry	Substrate catechol [b]	Product 15-crown-5-ether [c]	%Yield [d]
1		 **11**	45
2		 **12**	43
3		 **13**	38

[a] Reaction condition: catechol (10 mmol), compound **10** (10 mmol), K_2CO_3 (60 mmol), dry acetone (100 mL), reflux, 18 h; [b] substrate catechol; [c] Product 15-crown-5-ether; [d] Isolated yield 15-crown-5-ether.

Although there was no remarkable increase in the yield, this reaction offered less reaction time period (18 h) as compared to the reaction time of previous reaction with CsF (22 h) and simple work-up procedure. 4-Methylcatechol **1a** and Simple catechol **2a** afforded comparable yields whereas 3,4-dihydroxybenzaldehyde **3a** offered

slightly less (38%) which might occur due to the -I effect of electron withdrawing –CHO group (Table 1).

The 15-crown-5-ether **11** was further brominated with *N*-bromosuccinimide (NBS) in refluxing CCl_4 under light irradiation afforded bromo intermediate **6** in 77% yield (Scheme 5).[7]



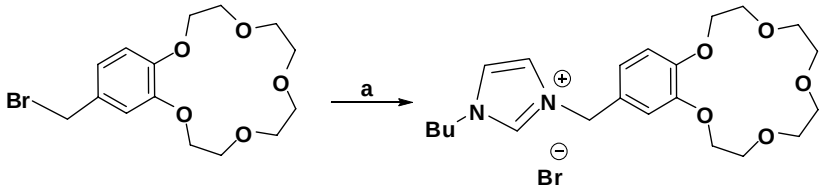
11
(15-Crown-5-ether)

6

Scheme 5. *Reagents and conditions*: *a) NBS, CCl_4, 500W light, reflux, 77%.*

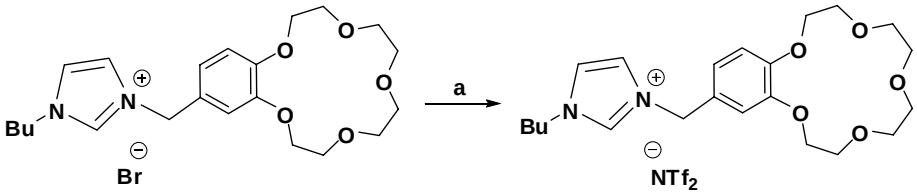
4.2.3.3 Synthesis of 15-crown-5- ether and imidazolium based ILs

The bromo intermediate **6** on refluxing with *N*-butylimidazole in acetonitrile afforded IL **1** in 68% yield (Scheme 6). The IL **1** further on treatment with $LiNTf_2$ in water at room temperature converted to its NTf_2 counterpart IL **2** in 75% yield (Scheme 7).



6 **1**

Scheme 6. *Reagents and conditions*: *a) N-Butylimidazole, CH_3CN, reflux, 68%.*

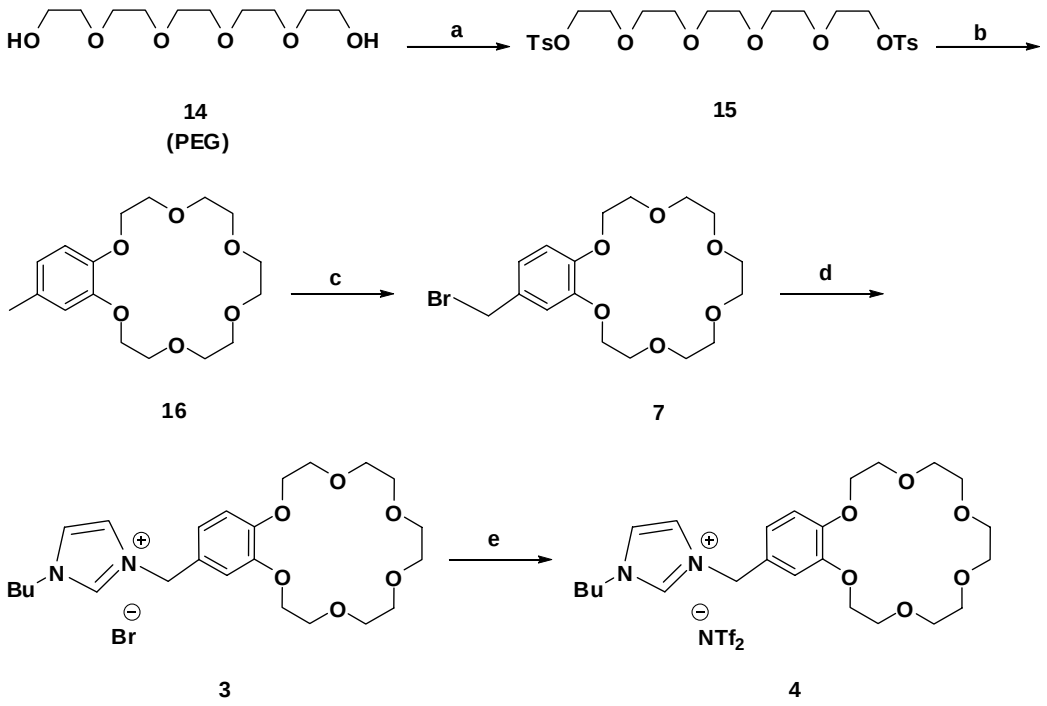


1 **2**

Scheme 7. *Reagents and conditions*: *a) $LiNTf_2$, water, rt, 75%.*

4.2.3.4 Synthesis of 18-crown-6-ether and imidazolium based ILs

The synthesis started with pentaethylene glycol (PEG) **14**, which was converted to its ditosyl-derivative **15** with TsCl in pyridine at -10 ^{o}C. The ditosyl-derivative **15** was then treated with 4-methylcatechol in presence of K_2CO_3 in refluxing acetone to offer 18-Crown-6-ether **16** in 45% yield. The 18-Crown-6-ether **16** was further brominated with *N*-bromosuccinimide (NBS) in refluxing CCl_4 under light irradiation to offer bromo intermediate **7** in 70% yield.[7] The bromo intermediate on refluxing with *N*-butylimidazole in acetonitrile afforded IL **3** in 65% yield. The IL **3** further on treatment with $LiNTf_2$ in water at room temperature converted to its NTf_2 counterpart IL **4** in 75% yield (Scheme 7).



Scheme 8. *Reagents and conditions*: *a) Pyridine, TsCl, -10 ^{o}C, 85%; b) K_2CO_3, acetone, 4-methylcatechol, reflux, 45%; c) NBS, CCl_4, 500W light, reflux, 70%; d) N-Butylimidazole, CH_3CN, reflux, 65%; e) $LiNTf_2$, water, rt, 75%.*

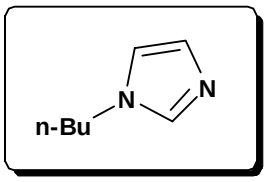
All the synthesized intermediates and crown ether and imidazolium based ILs was well characterized with their ^{1}H, ^{13}C NMR and mass analysis.

4.2.4 Conclusion

In conclusion, synthesis of crown ether and imidazolium based novel ILs has been successfully achieved. A general strategy for the synthesis of 15-crown-5-ether and 18-crown-6-ether and imidazolium based ILs with Br and NTf_2 anion is also established.

4.2.5 Experimental

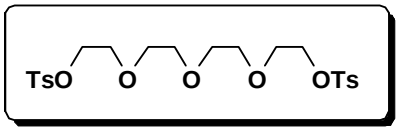
1-Butyl-1*H*-imidazole (5)



Imidazole **8** (6.8 g, 100 mmol) and KOH (6.16 g, 110 mmol) were dissolved in 20 mL CH_3CN at 0 ^{0}C and stirred for 1 h. To this *n*-butyl bromide (16.44 g, 120 mmol) was added drop wise over a period of 15-20 min (temperature maintained at 10-15 ^{0}C). After complete addition the reaction mixture was allowed to stir at room temperature for 3 h. The reaction completion was monitored by TLC. The reaction mixture was filtered to remove KBr and filtrate was concentrated under reduced pressure and residue remained was diluted with water and extracted with ethyl acetate (3 x 50 mL). The organic layer was dried over sodium sulfate and concentrated to give crude yellow liquid which was purified by chromatography on silica-gel eluting with petroleum ether: ethyl acetate (9:1) to afford *N*-butyl imidazole **5** (11.80 g, 95% yield) as a yellow liquid.

Molecular Formula	: $C_7H_{12}N_2$.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 0.87 (t, *J* = 7.2 Hz, 3H) , 1.16-1.35 (m, 2H), 1.62-1.76 (m, 2H), 3.86 (t, *J* = 7.1 Hz, 2H), 6.84 (s, 1H), 6.98 (s, 1H), 7.39 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 12.70, 18.86, 32.24, 45.92, 118.15, 128.09, 136.18.
MS (ESI-TOF) m/z	: 125.20 ($[M+H]^+$).

2,2'-(2,2'-Oxybis(ethane-2,1-diyl)bis(oxy))bis(ethane-2,1-diyl) bis(4-methylbenzenesulfonate) (10)

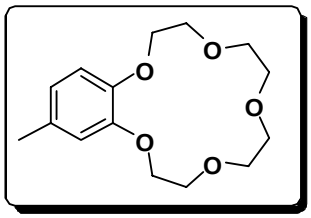


To a solution of tetraethyleneglycol **9** (9.7 g, 50 mmol), triethyl amine (15.15 g, 21 mL, 150 mmol) and DMAP (3.05 g, 25 mmol) in CH_2Cl_2 (50 mL) was added TsCl (20.02 g, 105 mmol) at 0 ^{o}C. After complete addition the reaction mixture was allowed to stir at room temperature for 1 h. After completion of reaction (as monitored by TLC) saturated solution of NH_4Cl (40 mL) was added and reaction mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to

give crude pale yellow dense oil. The crude oil such obtained was purified by chromatography on silica-gel eluting with petroleum ether: ethyl acetate (5:5) to offer **10 (**22.64 g, 90% yield) as a colorless dense oil.

Molecular Formula	: $C_{22}H_{30}O_9 S_2$.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 2.42 (s, 6H), 3.54 (s, 8H), 3.66 (t, *J* = 4.7 Hz, 4H), 4.13 (t, *J* = 4.7 Hz, 4H) , 7.33 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 21.32, 68.31, 69.10, 70.18, 70.34, 127.62, 129.61, 132.58, 144.65.
MS (ESI-TOF) m/z	: 503.61 ($[M+H]^+$).

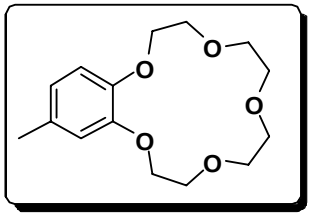
15-Methyl-2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,7,10,13]pentaoxacyclopentadecine (11)



A mixture of 4-methylcatechol (1.24 g, 10 mmol), ditosylate derivative **10** (5.03 g, 10 mmol), CsF (7.6 g, 50 mmol) in dry acetonitrile (120 ml) was refluxed at 90 ^{0}C for 22 h. Solvent acetonitrile was removed under reduced pressure. The residue was washed with ethyl acetate and filtered to remove CsF lumps. The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to give crude product. The crude product such obtained was purified by chromatography over neutral alumina eluting with petroleum ether: ethyl acetate (5:5) to furnish **11 (**1.13 g, 40 %) as a colorless syrup.

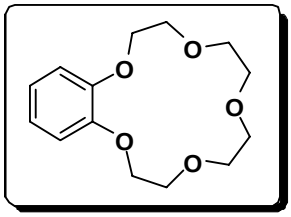
Molecular Formula	: $C_{15}H_{22}O_5$.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 2.28 (s, 3H), 3.76 (s, 8H), 3.88-3.93 (m, 4H), 4.09-4.14 (m, 4H) , 6.69 (d, *J* = 6.8 Hz, 1H), 6.70 (s, 1H), 6.78 (d, *J* = 8.7 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 20.65, 68.55, 68.89, 69.33, 69.38, 70.36, 114.03, 114.78, 121.17, 130.74, 146.37, 148.42.
MS (ESI-TOF) m/z	: 305.14 ($[M+Na]^+$).

15-Methyl-2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,7,10,13]pentaoxacyclopentadecine (11)



A mixture of 4-methyl catechol **3** (1.24 g, 10 mmol), ditosylate derivative **10** (5.03 g, 10 mmol), oven dried K_2CO_3 (8.28 g, 60 mmol) in dry acetone (100 mL) was refluxed at 90 ^oC for 18 h. The reaction mixture was filtered to remove K_2CO_3 and washed with acetone (2 x 15 mL). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to give crude product. The crude product such obtained was purified by chromatography over neutral alumina eluting with petroleum ether: ethyl acetate (5:5) to furnish **11 (**1.27 g, 45 %) as a colorless syrup.

2,3,5,6,8,9,11,12-Octahydrobenzo[*b*][1,4,7,10,13]pentaoxacyclopentadecine (12)



Procedure is similar to the preparation of **11** using K_2CO_3.

Yield : 1.15 g, 43%

Nature : White solid

Mp : 133 ^oC.

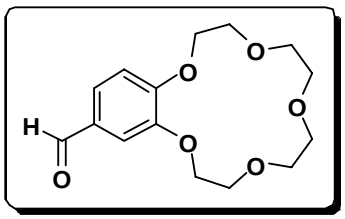
Molecular Formula : $C_{14}H_{20}O_5$.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 3.76 (s, 8H), 3.89-3.93 (m, 4H), 4.12-4.16 (m, 4H) , 6.89 (s, 4H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 68.60, 69.19, 70.09, 70.63, 113.82, 120.99, 148.79 .

MS (ESI-TOF) m/z : 291.25 ($[M+Na]^+$).

2,3,5,6,8,9,11,12-Octahydrobenzo[*b*][1,4,7,10,13]pentaoxacyclopentadecine-15-carbaldehyde (13)



Procedure is similar to the preparation of **11** using K_2CO_3.

Yield : 1.13 g, 38%

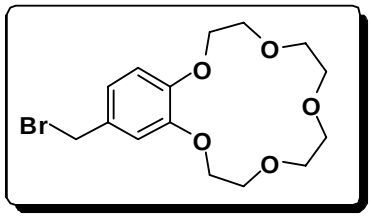
Nature : White solid

Mp : 197 ^oC.

Molecular Formula : $C_{15}H_{20}O_6$.

^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 3.72 (s, 8H), 3.86-3.92 (m, 4H), 4.13-4.19 (m, 4H) , 6.9 (d, *J* = 8.2 Hz, 1H), 7.35 (s, 1H), 7.41 (d, *J* = 1.5, 8.2 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 68.59, 69.10, 70.21, 71.14, 111.13, 111.83, 126.95, 130.16, 151.98, 161.14, 190.91.
MS (ESI-TOF) m/z	: 319.32 ($[M+Na]^+$).

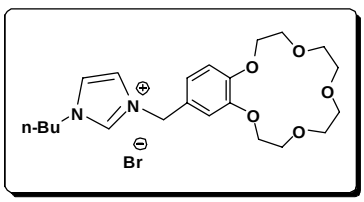
15-(Bromomethyl)-2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,7,10,13]pentaoxacyclopentadecine (6)



To the solution of crown ether **11** (0.83 g, 2.9 mmol) in CCl_4 (20 mL) *N*-bromo succinimide (0.516 g, 2.9 mmol) was added and stirred for 5 min under argon atmosphere at room temperature. The reaction mixture was then heated up to 60 ^oC and irradiated with 500W tungsten lamp for 1 h. After reaction completion (as checked by TLC) the reaction mixture was poured in an ice bath and filtered. Solvent CCl_4 was removed under reduced pressure to afford bromo compound **6** (0.82 g, 77%) as a white solid.

Molecular Formula	: $C_{15}H_{21}BrO_5$.
Mp	: 216 ^0C.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ (ppm) 3.76 (s, 8H), 3.89-3.94 (m, 4H), 4.11-4.18 (m, 4H), 4.48 (s, 2H), 6.8 (d, *J* = 8.1 Hz, 1H), 6.92 (s, 1H), 6.94 (d, *J* = 2.0, 8.2 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ (ppm) 32.74, 67.91, 68.25, 68.74, 69.72, 114.14, 115.10, 120.53, 130.10, 149.29, 150.24.
MS (ESI-TOF) m/z	: 361.23 ($[M+H]^+$).

1-butyl-3-((2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,7,10,13]pentaoxacyclopentadecin-15-yl)methyl)-1*H*-imidazol-3-ium bromide (1)



The solution of bromo intermediate **6** (0.361 g, 1 mmol) and *N*-butyl imidazole **5** (0.124 g, 1 mmol) in acetonitrile (10 mL) was refluxed for 10 h. After

reaction completion (as checked by TLC) solvent acetonitrile was evaporated under reduced pressure to give crude dense yellow liquid. The dense yellow liquid was purified by chromatography on silica-gel eluting with ethyl acetate: methanol (9:1) to furnish **1** (0.330 g, 68 %) as a pale yellow dense liquid.

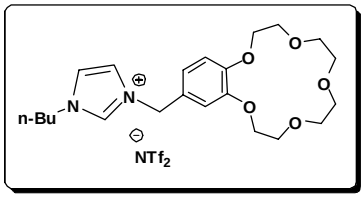
Molecular Formula : $C_{22}H_{33}BrN_2O_5$.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 0.74 (t, *J* = 7.2 Hz, 3H), 1.07-1.20 (m, 2H), 1.59-1.74 (m, 2H), 3.55 (s, 4H), 3.56 (s, 4H), 3.71 (s, 4H), 3.90-4.04 (m, 6H), 5.17 (s, 2H), 6.64 (d, *J* = 8.2 Hz, 1H), 6.83 (dd, *J* = 1.6, 8.2 Hz, 1H), 6.91 (s, 1H), 7.34 (dd, *J* = 1.5, 11.6 Hz, 2H), 9.70 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 13.08, 19.08, 31.69, 49.37, 52.36, 68.24, 68.48, 68.70, 69.59, 70.22, 113.37, 114.30, 121.76, 121.94, 126.32, 136.27, 148.81, 149.03.

MS (ESI-TOF) m/z : 405.33 ($[CrBIm]^+$).

1-Butyl-3-((2,3,5,6,8,9,11,12-octahydrobenzo[*b*][1,4,7,10,13]pentaoxacyclopentadecin-15-yl)methyl)-1*H*-imidazol-3-ium bis(trifluoromethylsulfonyl)amide (2)



To the solution of **1** (0.097 g, 0.2 mmol) in water (5 mL), $LiNTf_2$ (0.063 g, 0.22 mmol) was added slowly under stirring. The reaction mass was then stirred for 5 h at room temperature. After 5 h reaction mass was diluted with more water (5 mL) and extracted with chloroform (3 x 15 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford **2** (0.103 g, 75%) as a dense yellow liquid.

Molecular Formula : $C_{24}H_{33}F_2N_3O_9S_2$.

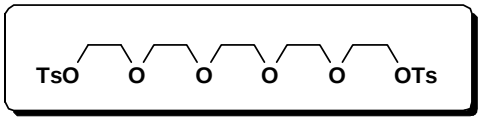
^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 0.96 (t, *J* = 7.2 Hz, 3H), 1.28-1.42 (m, 2H), 1.77-1.92 (m, 2H), 3.75 (s, 8H), 3.88-3.94 (m, 4H), 4.12-4.21 (m, 4H), 5.25 (s, 2H), 6.86 (d, *J* = 8.6 Hz, 1H), 6.93 (s, 1H), 6.96 (dd, *J* = 1.8, 9.0 Hz, 1H), 7.26-7.30 (m, 2H), 8.87 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 : δ (ppm) 13.06, 19.16, 31.75, 49.73, 53.10, 68.37,

MHz) 68.86, 69.71, 70.40, 113.65, 113.79, 122.07, 122.12, 122.30, 125.35, 134.85, 149.30, 149.59.

MS (ESI-TOF) m/z : 405.28 ($[CrBIm]^+$).

3,6,9,12-Tetraoxatetradecane-1,14-diyl bis(4-methylbenzenesulfonate) (15)



To the solution of PEG **14** (5 g, 21 mmol) in distilled pyridine (30 mL) at -10 ^oC, TsCl (8.4 g, 44 mmol) was added in portions. The mixture was then kept overnight at 4 ^oC. After reaction completion (as checked by TLC) the reaction mixture was diluted with water and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layer was washed with dilute HCl, water, saturated solution of $NaHCO_3$ solution and dried over anhydrous sodium sulfate. The solvent CH_2Cl_2 was evaporated under reduced pressure to give dense pale yellow liquid which was purified by chromatography on silica-gel eluting with petroleum ether: ethyl acetate (5:5) to furnish **15 (**1.13 g, 85 %) as a colorless dense liquid.

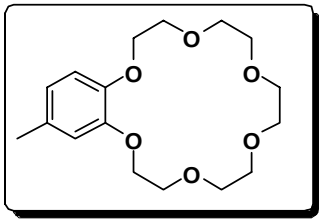
Molecular Formula : $C_{24}H_{34}O_{10}S_2$.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 2.45 (s, 6H), 3.58 (s, 8H), 3.60 (s, 4H), 3.68 (t, *J* = 4.8 Hz, 4H), 4.15 (t, *J* = 4.8 Hz, 4H), 7.34 (d, *J* = 8.3 Hz, 4H), 7.80 (d, *J* = 8.3 Hz, 4H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 21.27, 66.68, 68.28, 69.04, 70.10, 70.24, 127.58, 129.59, 132.57, 144.62.

MS (ESI-TOF) m/z : 547.16 ($[M+H]^+$).

18-Methyl-2,3,5,6,8,9,11,12,14,15-decahydrobenzo[*b*][1,4,7,10,13,16]hexaoxacyclooctadecine (16)



Procedure is similar to the preparation of **11** using K_2CO_3.

Yield : 1.47 g, 45%.

Nature : Colorless dense liquid.

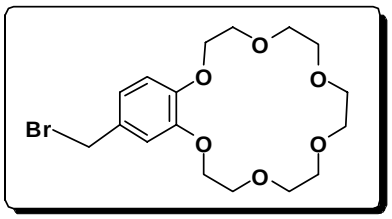
Molecular Formula : $C_{17}H_{26}O_6$.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 2.28 (s, 3H), 3.69 (s, 8H), 3.74-3.78 (m, 4H), 3.89-3.94 (m, 4H), 4.11-4.18 (m, 4H), 6.69 (d, *J* = 6.9 Hz, 1H), 6.70 (s, 1H), 6.78 (d, *J* = 8.7 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 20.01, 67.91, 68.25, 68.69, 68.74, 69.72, 113.39, 114.14, 120.53, 130.10, 145.73, 147.78.

MS (ESI-TOF) m/z : 349.39 ($[M+Na]^+$).

18-(Bromomethyl)-2,3,5,6,8,9,11,12,14,15-decahydrobenzo[*b*][1,4,7,10,13,16]hexaoxacyclooctadecine (7)



Procedure is similar to the preparation of **6**.

Yield : 0.71 g, 70%.

Nature : Yellow liquid.

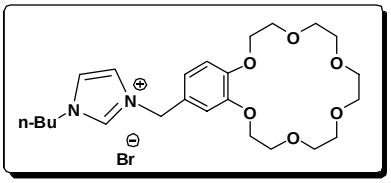
Molecular Formula : $C_{17}H_{25}BrO_6$.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 3.69 (s, 8H), 3.71-3.78 (m, 4H), 3.91-3.95 (m, 4H), 4.14-4.20 (m, 4H), 4.48 (s, 2H), 6.80 (d, *J* = 8.2 Hz, 1H), 6.91 (s, 1H), 6.93 (d, *J* = 8.5 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 33.08, 69.19, 69.53, 70.02, 71.00, 114.67, 115.42, 120.56, 130.19, 149.06, 150.16.

MS (ESI-TOF) m/z : 427.16 ($[M+Na]^+$).

1-Butyl-3-((2,3,5,6,8,9,11,12,14,15-decahydrobenzo[*b*][1,4,7,10,13,16]hexaoxacyclooctadecin-18-yl)methyl)-1*H*-imidazol-3-ium bromide (3)



Procedure is similar to the preparation of **1**.

Yield : 0.342 g, 65%.

Nature : Pale yellow dense liquid.

Molecular Formula : $C_{24}H_{37}BrN_2O_6$.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 6.79 (t, *J* = 7.2 Hz, 3H), 1.24-1.39 (m, 2H), 1.77-1.92 (m, 2H), 3.63-3.73 (m, 12H), 3.88 (d, *J* = 2.0 Hz, 4H), 4.08-4.12 (m, 2H), 4.20-4.27 (m, 4H), 5.47 (s, 2H), 6.77 (d, *J* = 8.2 Hz, 1H), 7.05 (dd, *J* = 1.8, 8.1 Hz,

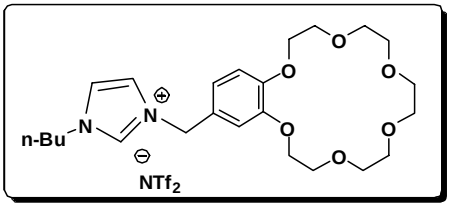
1H), 7.27 (s, 2H), 7.57 (s, 1H), 10.36 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 13.71, 32.32, 50.00, 53.00, 69.12, 69.34, 70.22, 70.86, 114.00, 114.94, 122.40, 122.57, 126.95, 136.90, 149.45, 149.66.

MS (ESI-TOF) m/z : 449.52 ($[CrBIm]^+$).

1-Butyl-3-((2,3,5,6,8,9,11,12,14,15-decahydrobenzo[*b*][1,4,7,10,13,16]hexaoxacyclooctadecin-18-yl)methyl)-1*H*-imidazol-3-ium bis(trifluoromethylsulfonyl)amide (4)

Procedure is similar to the preparation of **2**.



Yield : 0.136 g, 75%.

Nature : Yellow dense liquid.

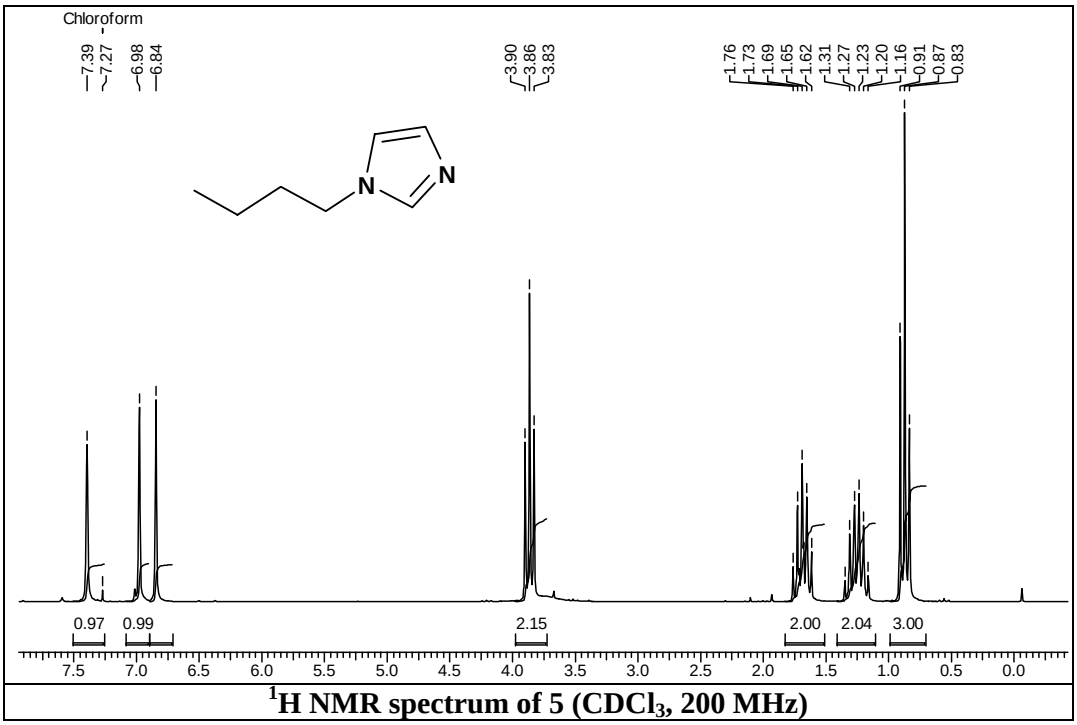
Molecular Formula : $C_{26}H_{37}F_6N_3O_{10}S_2$.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 0.94 (t, *J* = 7.2 Hz, 3H), 1.26-1.39 (m, 2H), 1.74-1.89 (m, 2H), 3.65-3.75 (m, 12H), 3.85-3.92 (m, 4H), 4.08-4.18 (m, 6H), 5.22 (s, 2H), 6.84 (d, *J* = 10.0 Hz, 1h), 6.85 (s, 1H), 6.92 (dd, *J* = 1.7, 8.1 Hz, 1H), 7.25 (s, 2H), 8.83 (s, 1H).

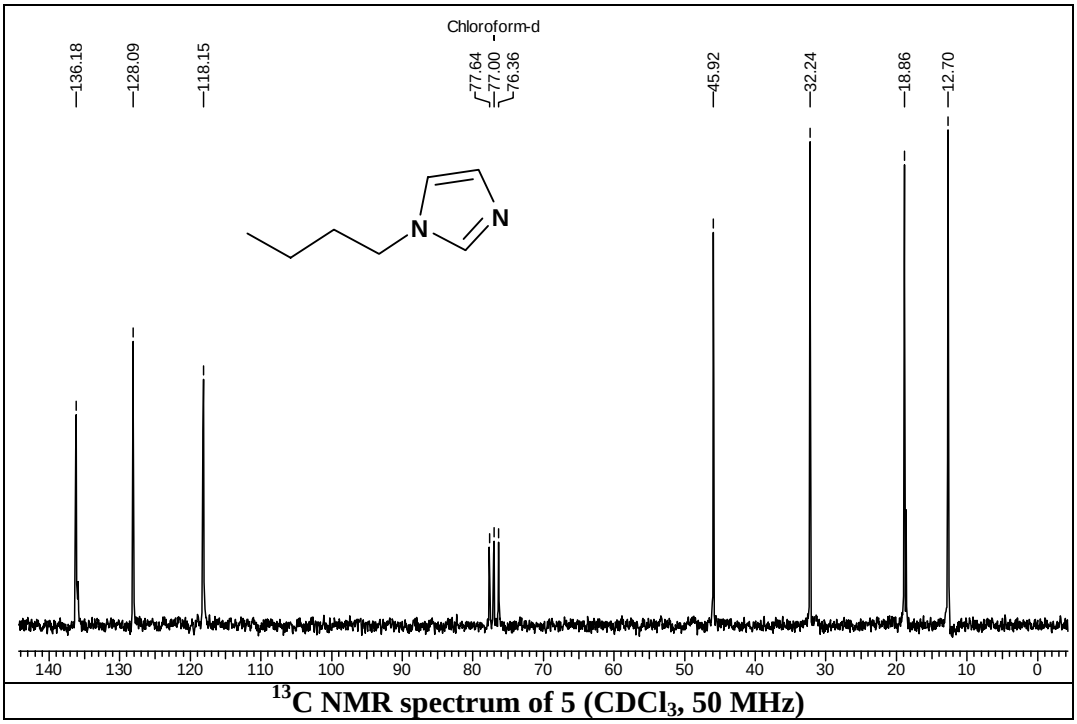
^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 13.69, 19.79, 32.38, 50.36, 53.73, 69.00, 69.50, 70.35, 71.01, 114.28, 114.43, 122.70, 122.75, 122.94, 125.98, 135.49, 149.93, 150.22.

MS (ESI-TOF) m/z : 449.48 ($[CrBIm]^+$).

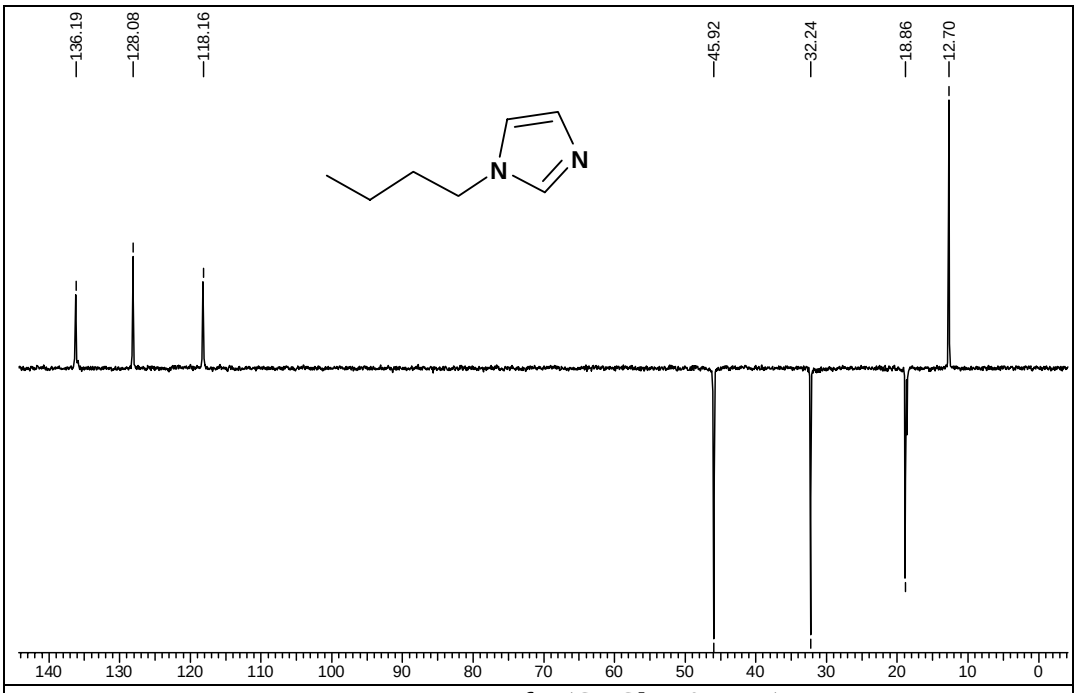
4.2.6 Analytical data



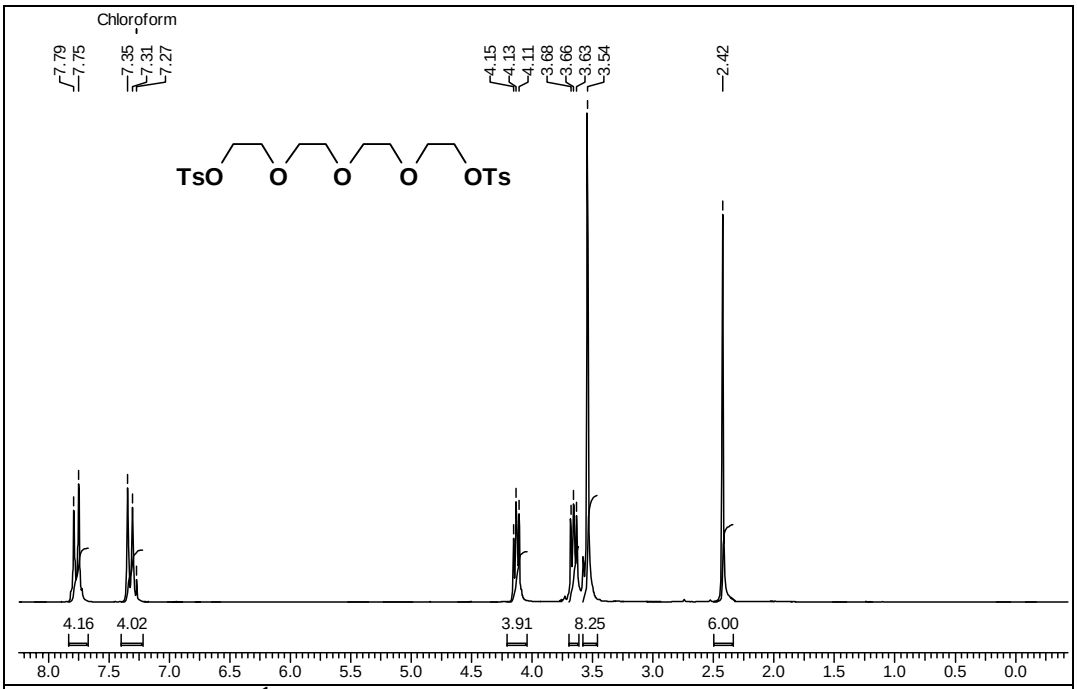
^{1}H NMR spectrum of 5 ($CDCl_3$, 200 MHz)



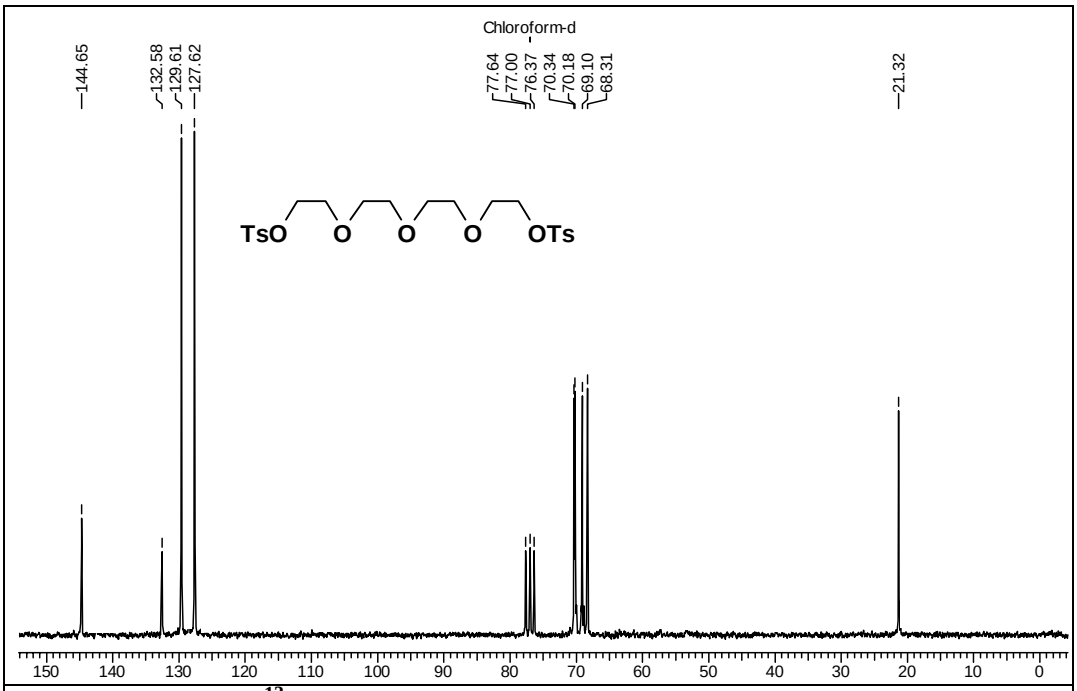
^{13}C NMR spectrum of 5 ($CDCl_3$, 50 MHz)



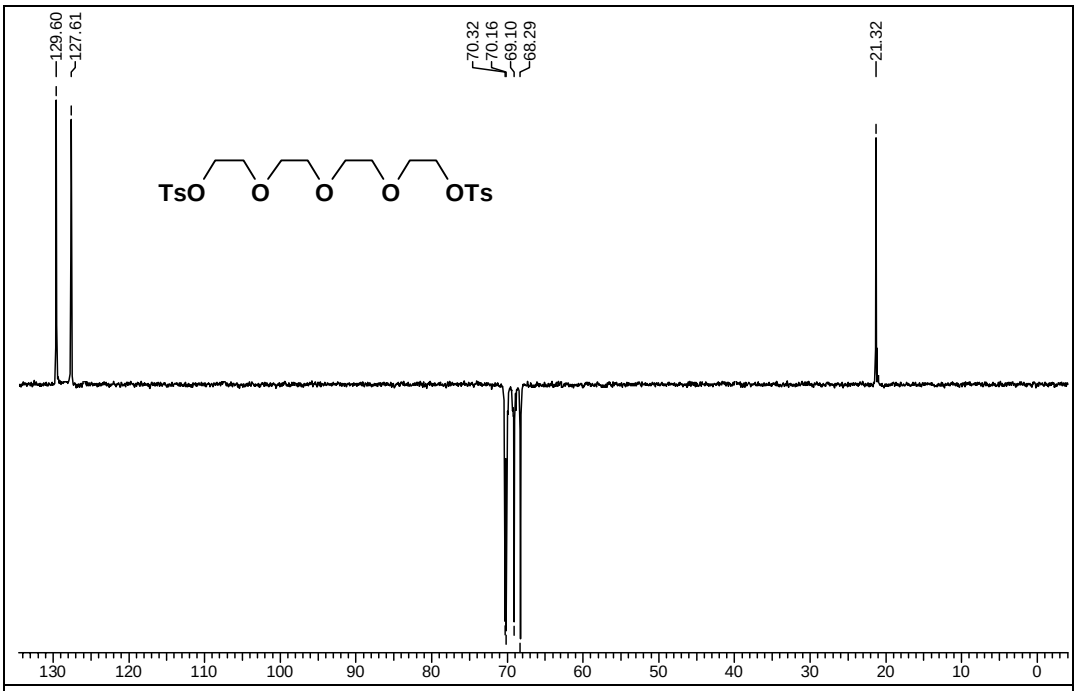
DEPT spectrum of 5 ($CDCl_3$, 50 MHz)



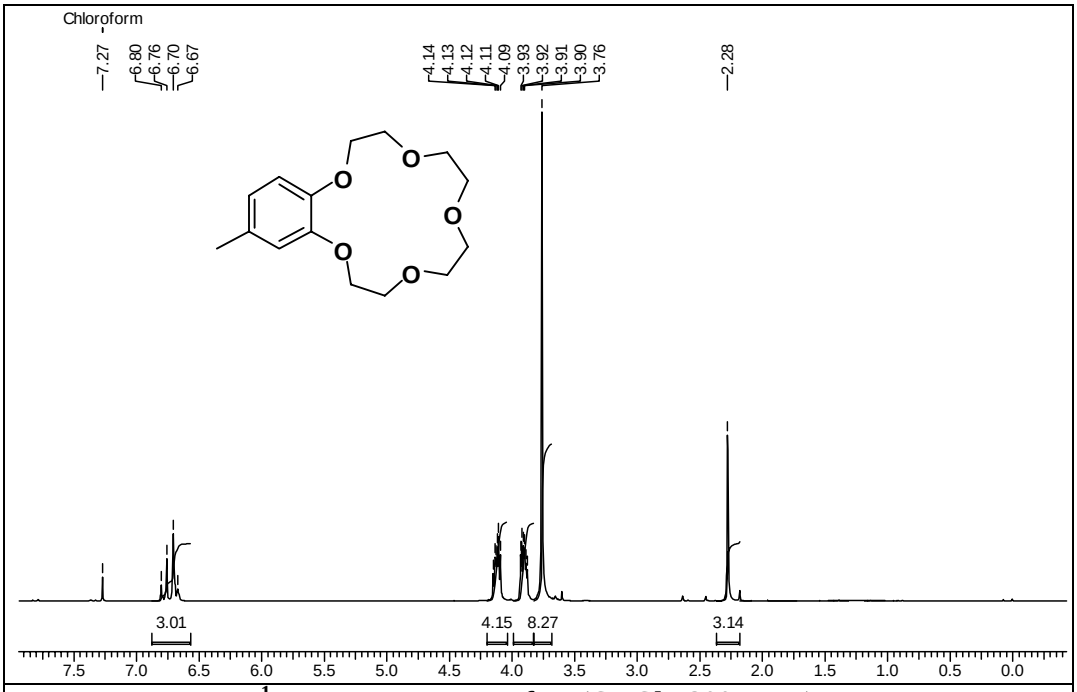
^{1}H NMR spectrum of 10 ($CDCl_3$, 200 MHz)



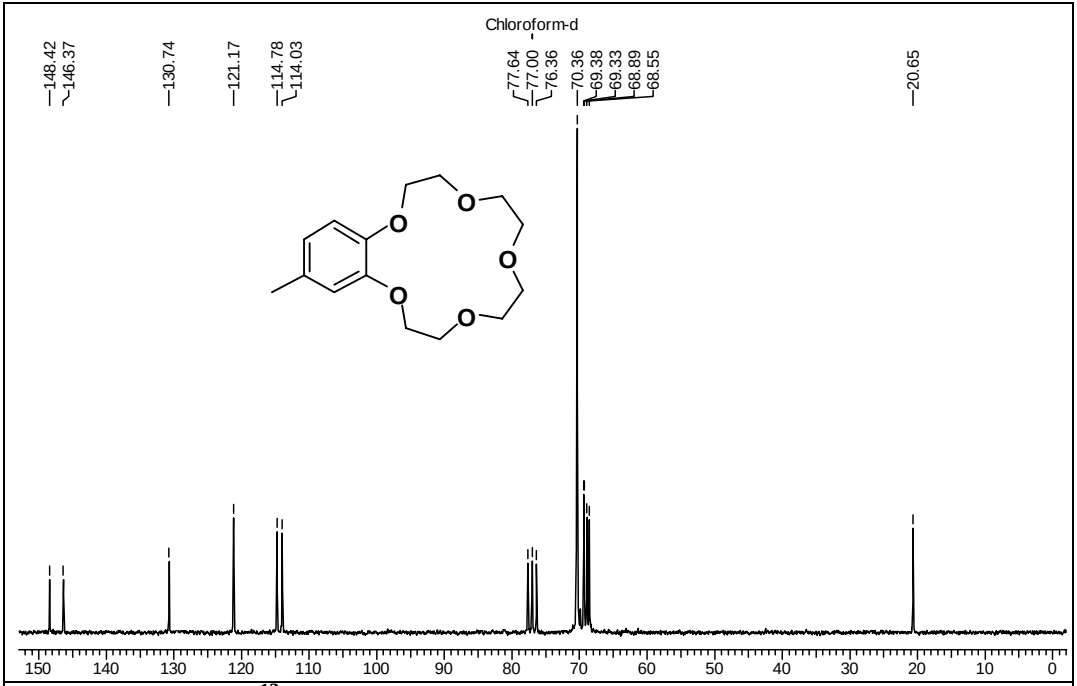
^{13}C NMR spectrum of 10 ($CDCl_3$, 50 MHz)



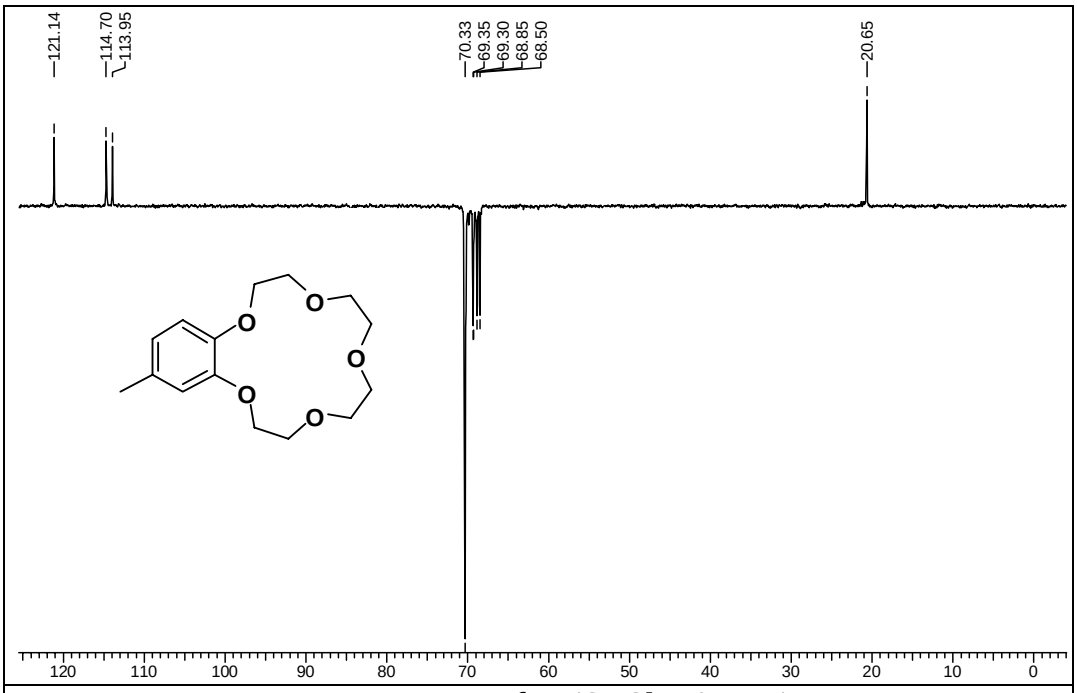
DEPT spectrum of 10 ($CDCl_3$, 50 MHz)



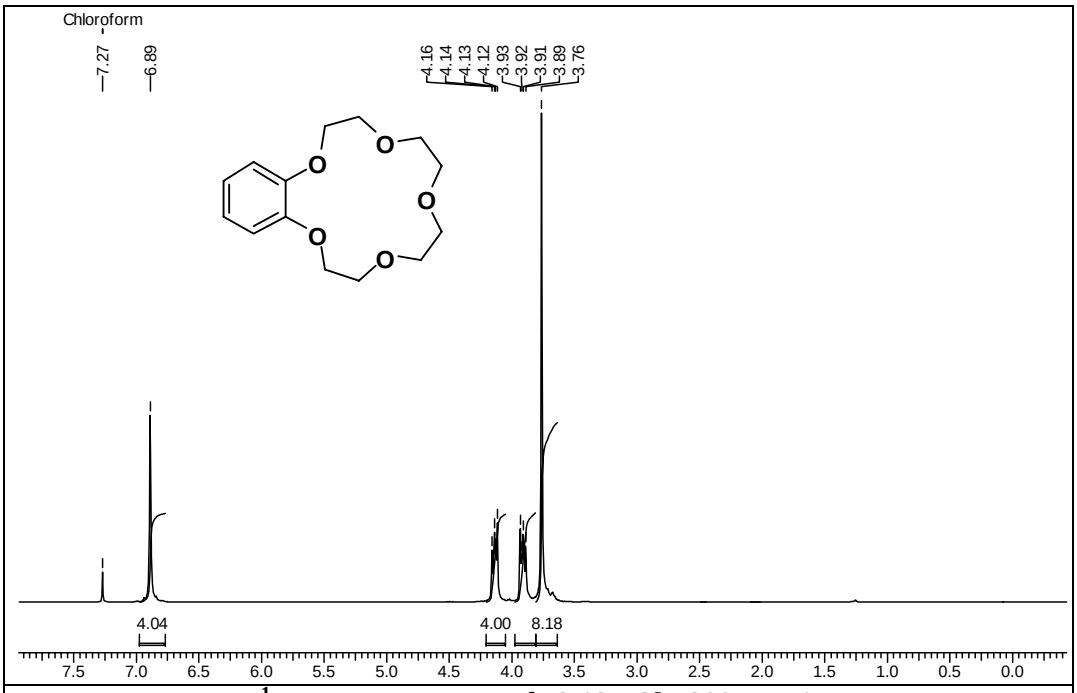
^{1}H NMR spectrum of 11 ($CDCl_3$, 200 MHz)



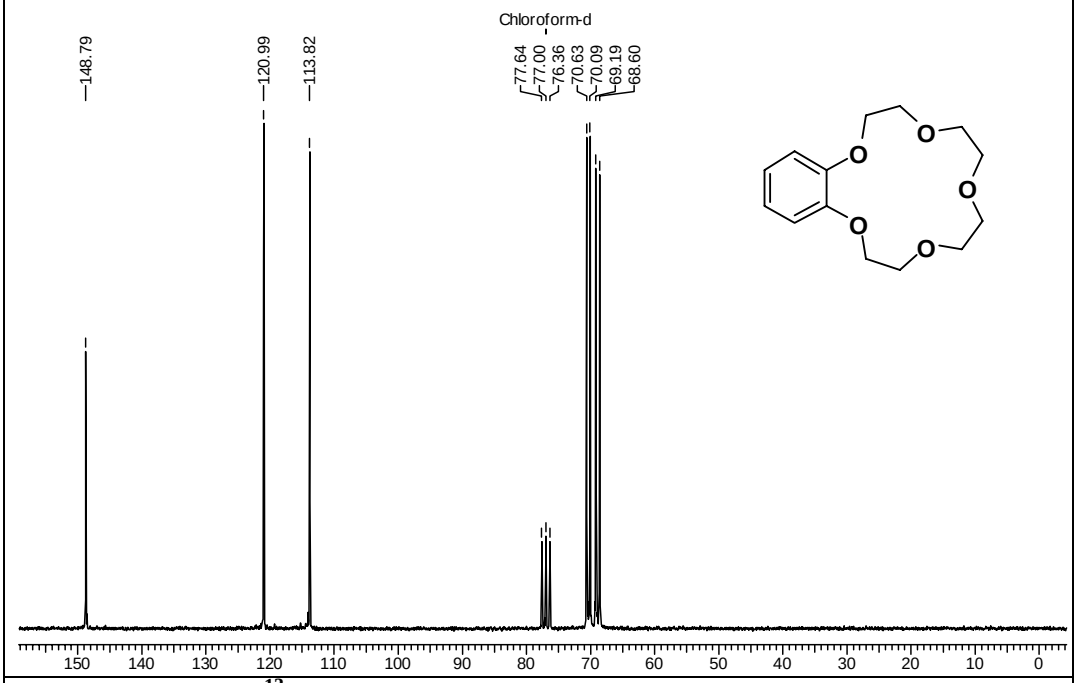
^{13}C NMR spectrum of 1b1($CDCl_3$, 50 MHz)



DEPT spectrum of 11 ($CDCl_3$, 50 MHz)

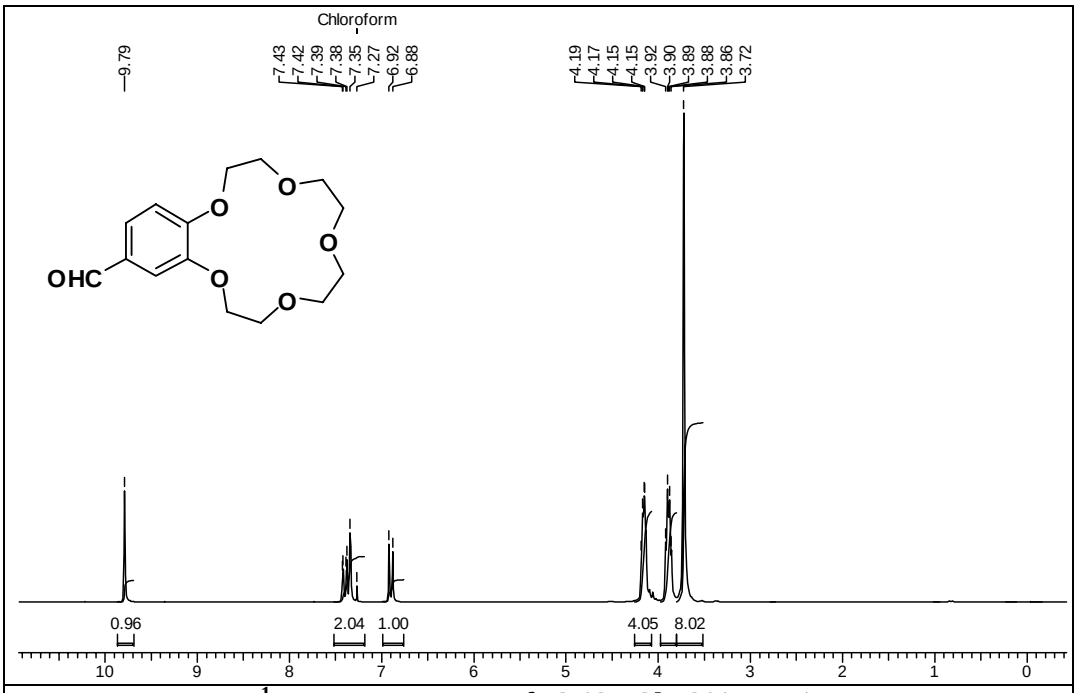


^{1}H NMR spectrum of 12 ($CDCl_3$, 200 MHz)

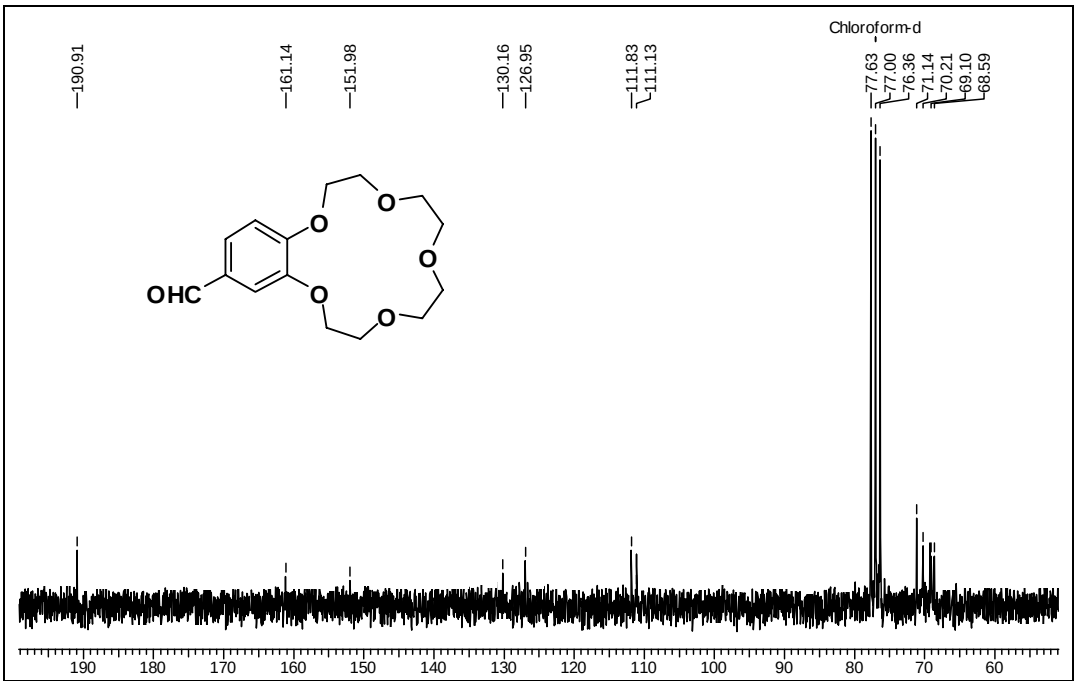


^{13}C NMR spectrum of 12 ($CDCl_3$, 50 MHz)

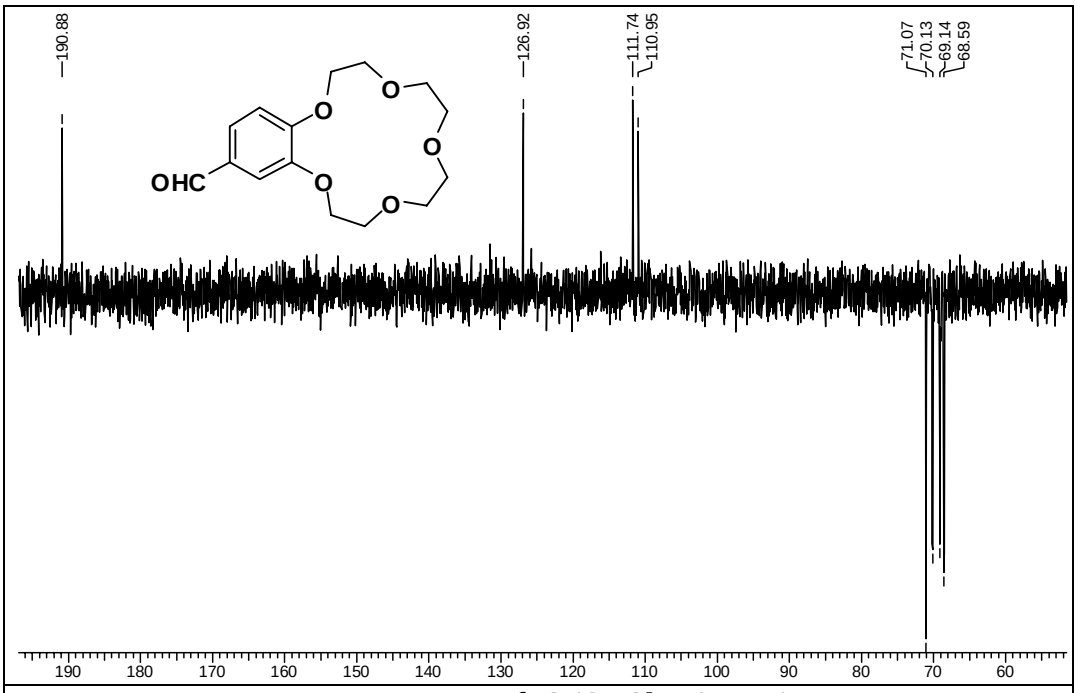
DEPT spectrum of 12 ($CDCl_3$, 50 MHz)



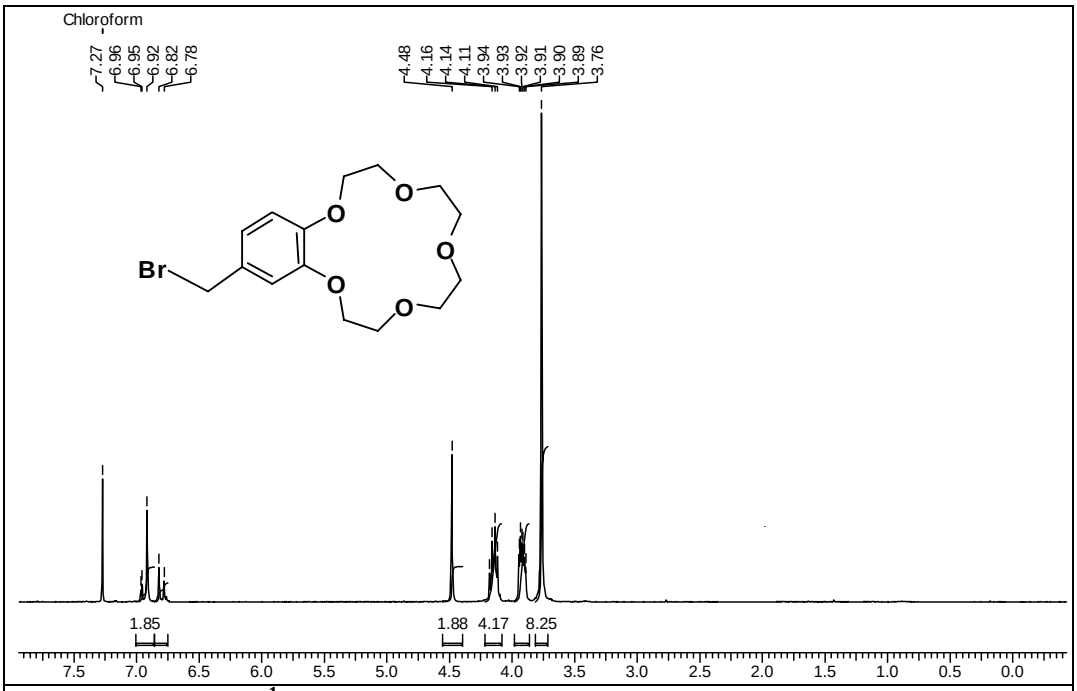
^{1}H NMR spectrum of 13 ($CDCl_3$, 200 MHz)



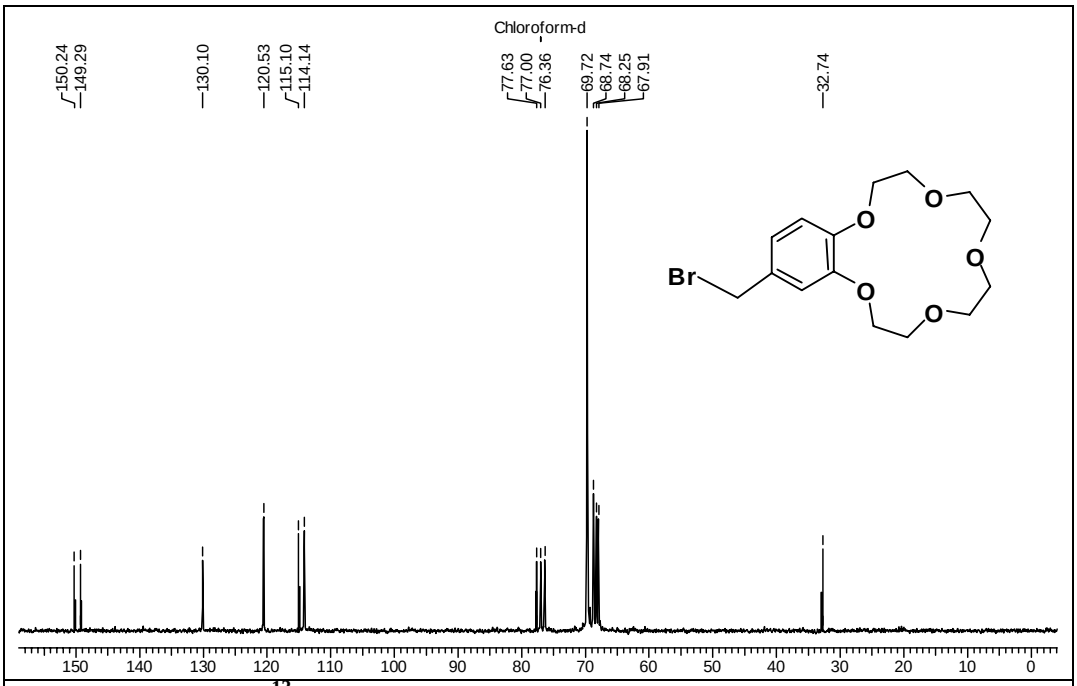
^{13}C NMR spectrum of 13 ($CDCl_3$, 50 MHz)



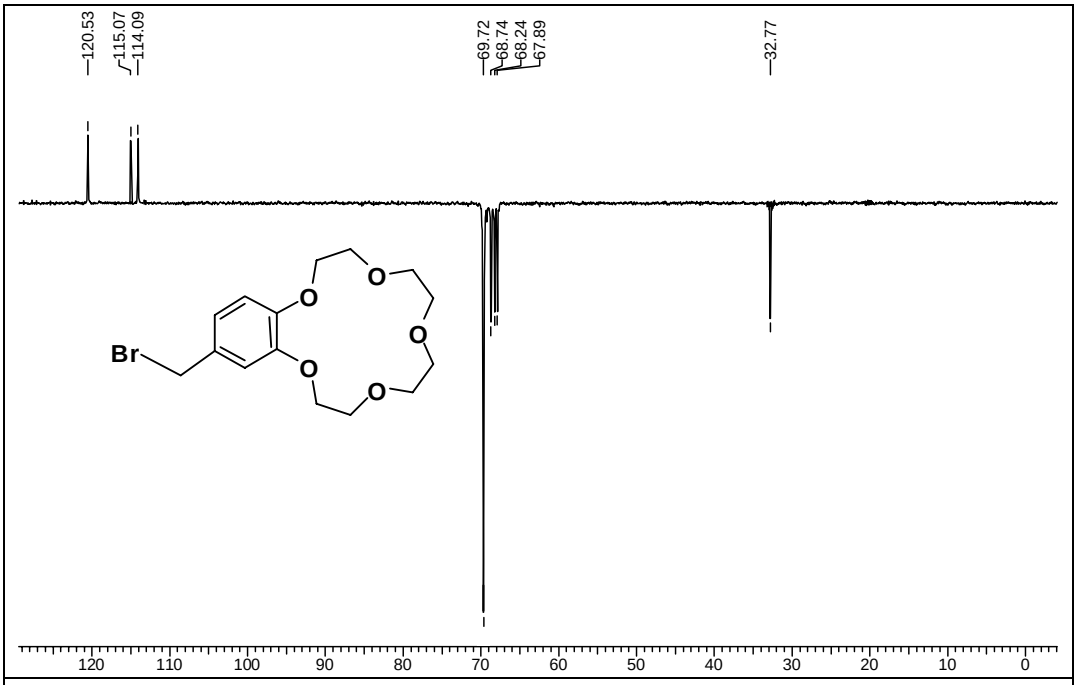
DEPT spectrum of 13 ($CDCl_3$, 50 MHz)



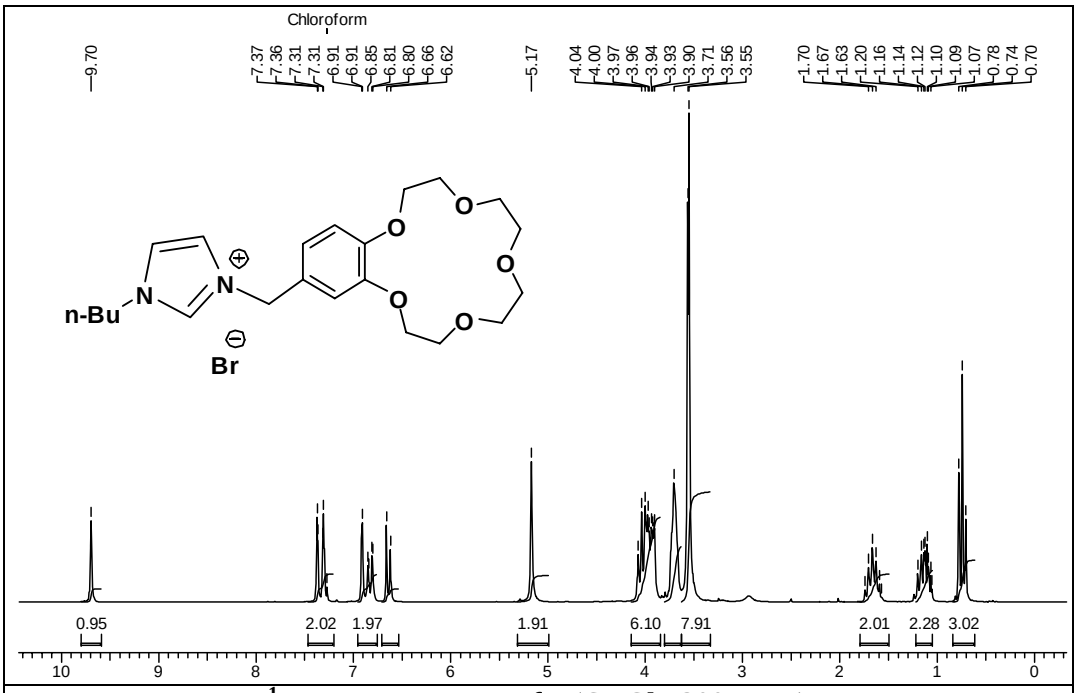
^{1}H NMR spectrum of 6 ($CDCl_3$, 200 MHz)



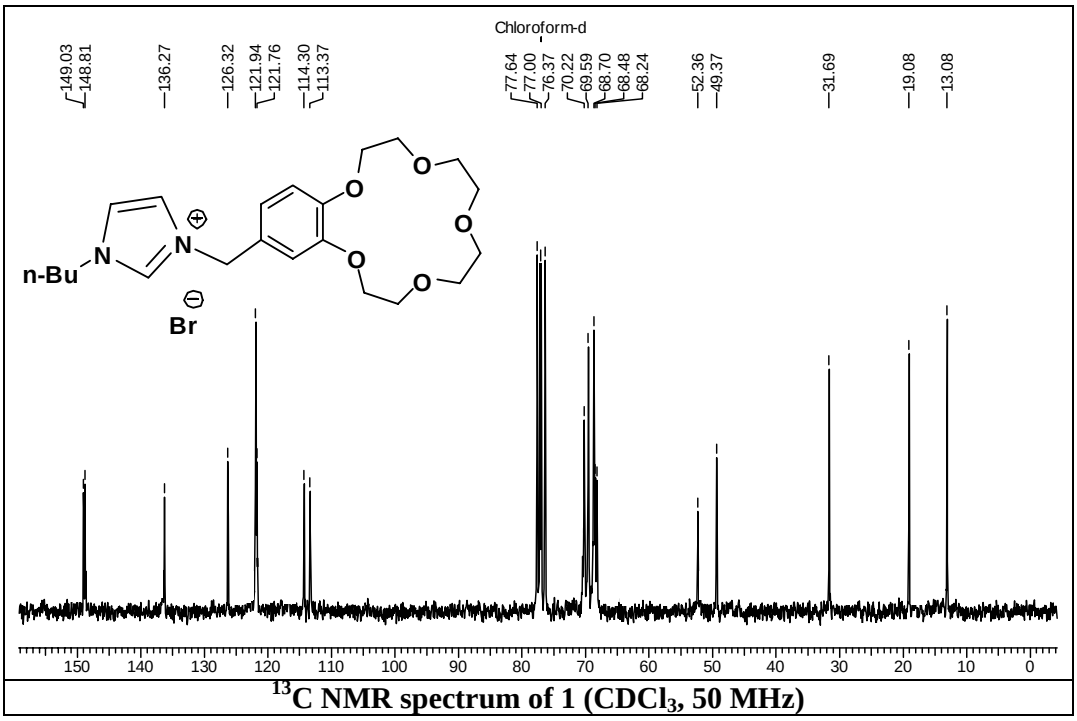
^{13}C NMR spectrum of 6 ($CDCl_3$, 50 MHz)



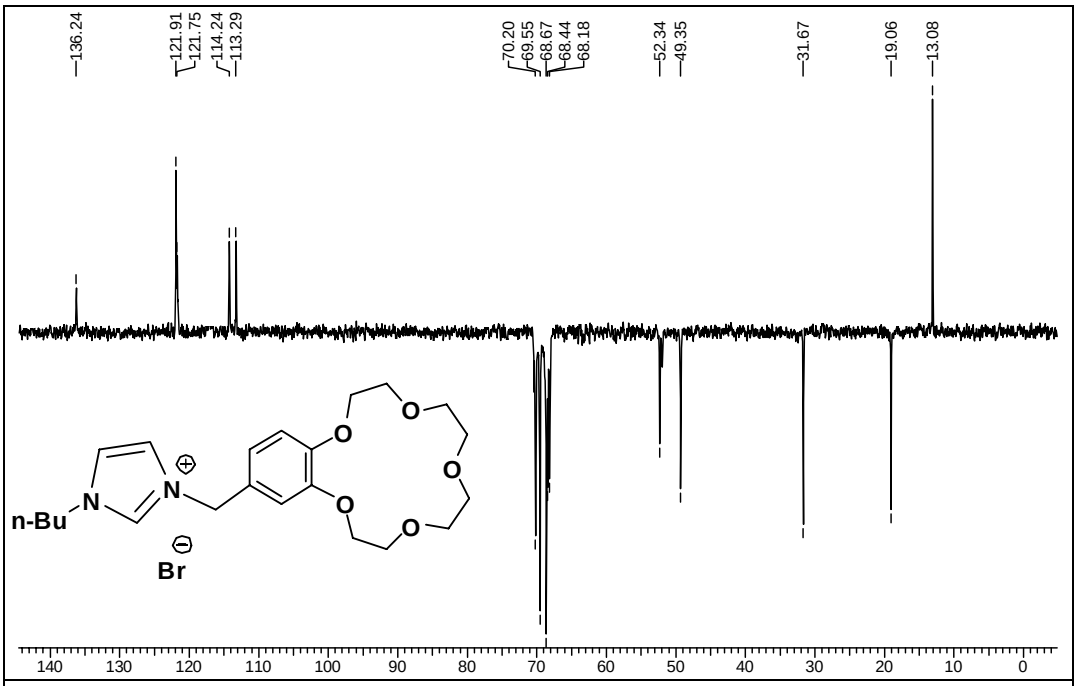
DEPT spectrum of 6 ($CDCl_3$, 50 MHz)



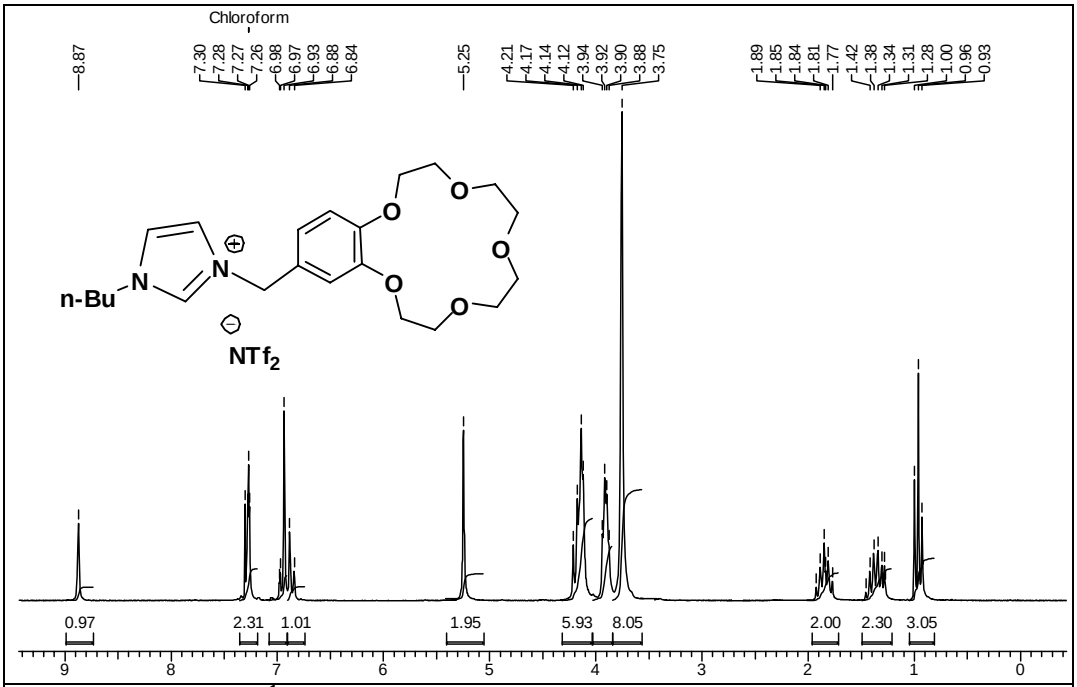
^{1}H NMR spectrum of 1 ($CDCl_3$, 200 MHz)



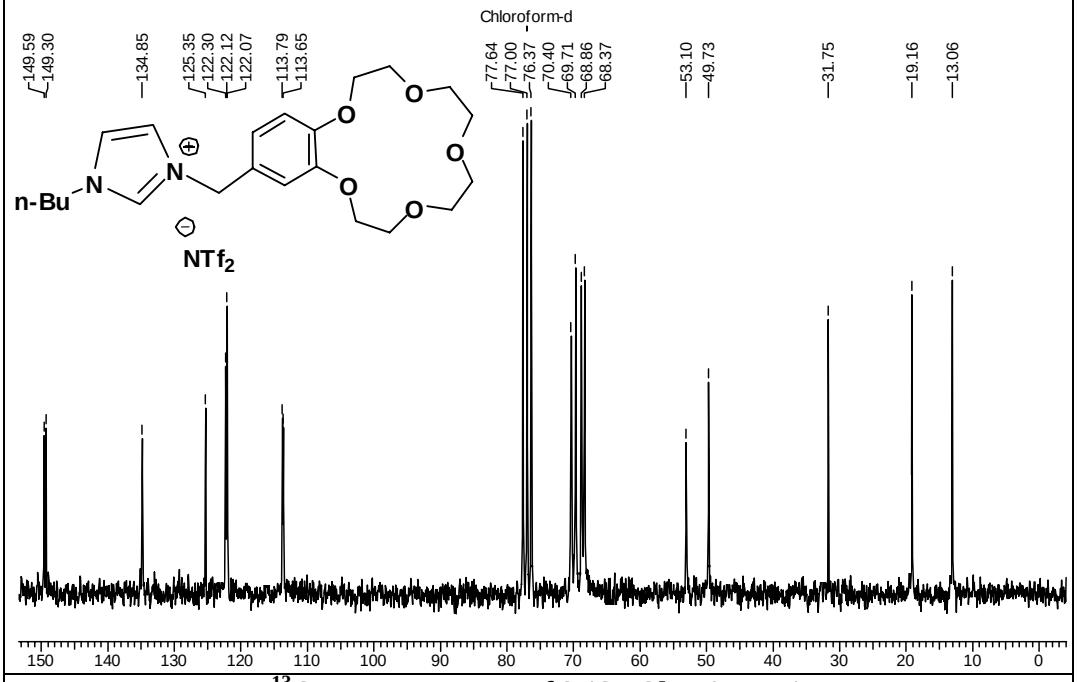
^{13}C NMR spectrum of 1 ($CDCl_3$, 50 MHz)



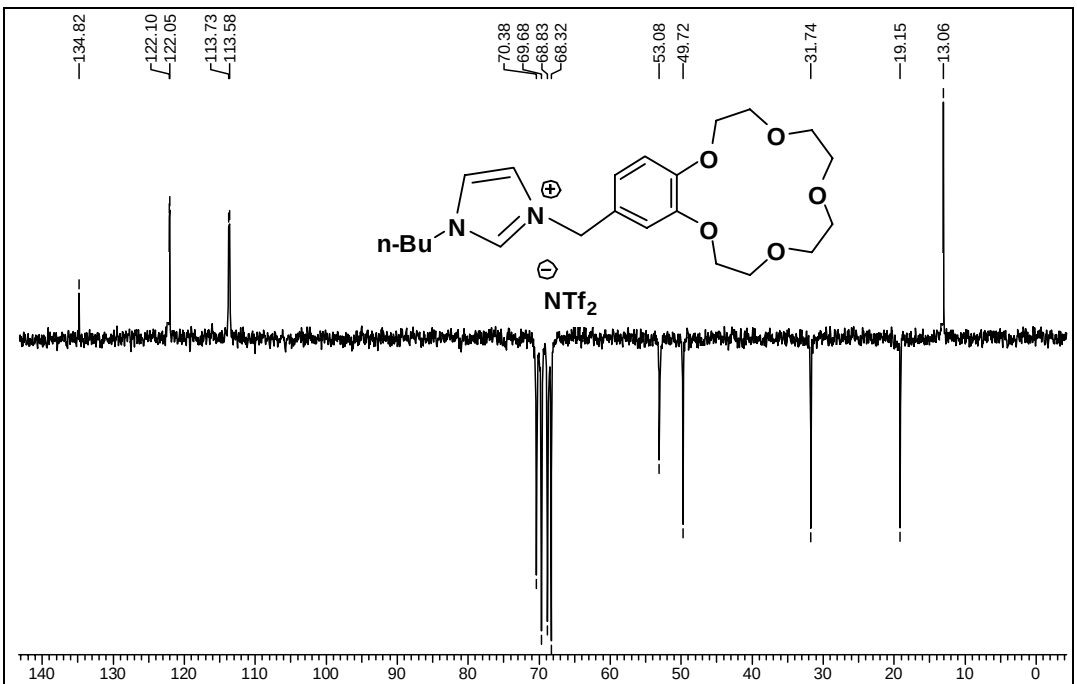
DEPT spectrum of 1 ($CDCl_3$, 50 MHz)



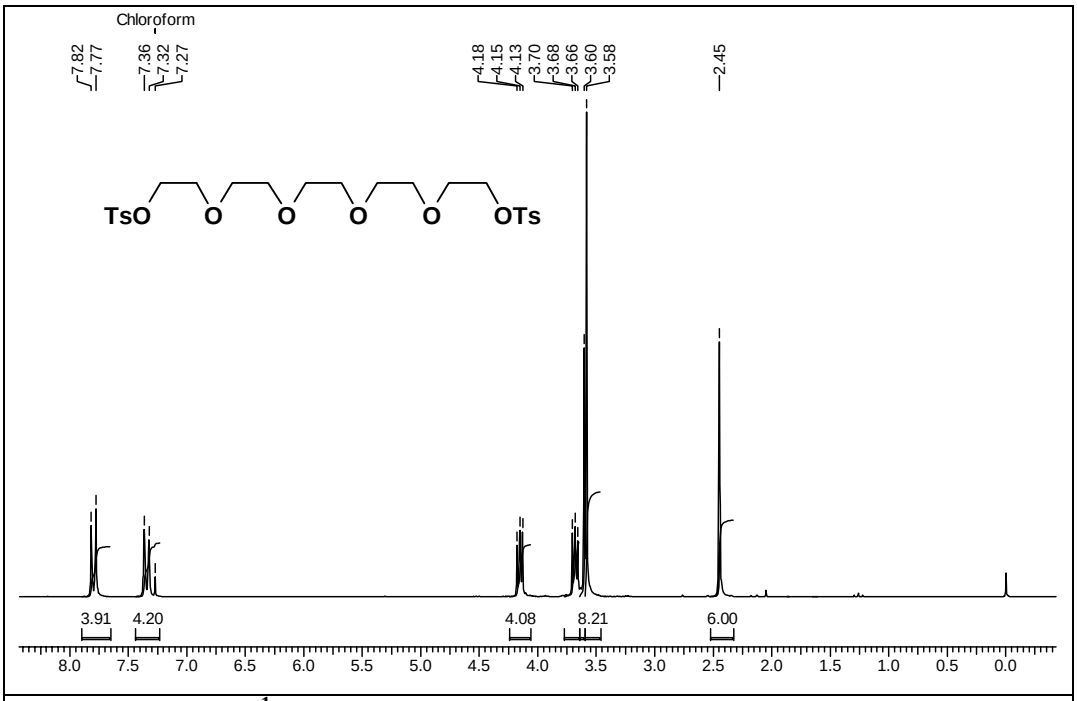
^{1}H NMR spectrum of 2 ($CDCl_3$, 200 MHz)



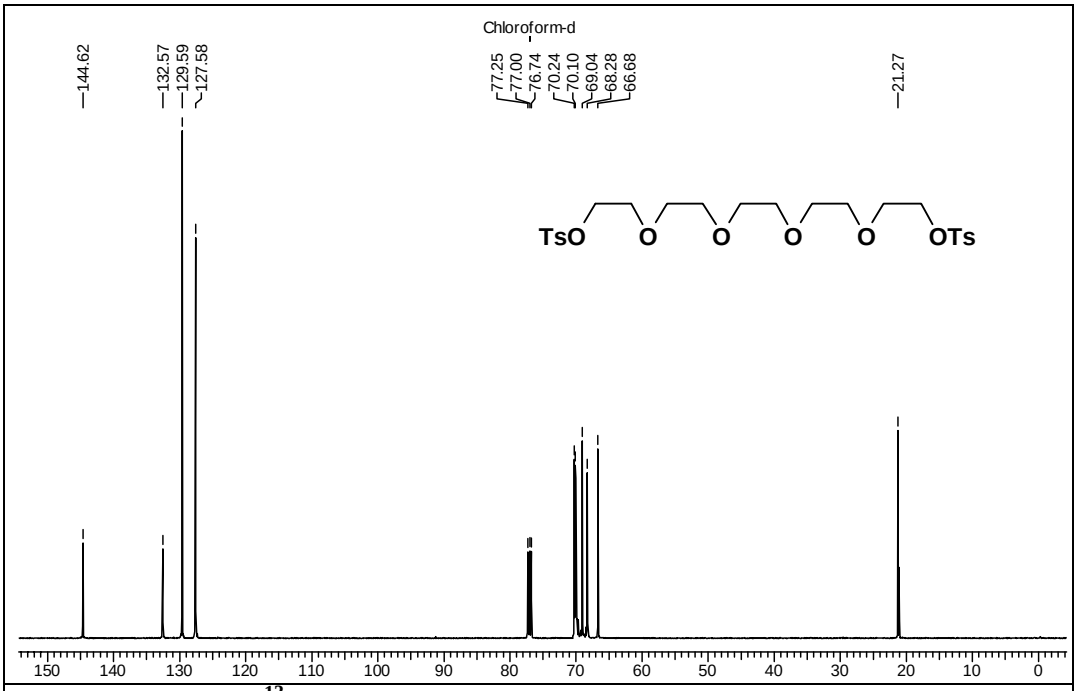
^{13}C NMR spectrum of 2 ($CDCl_3$, 50 MHz)



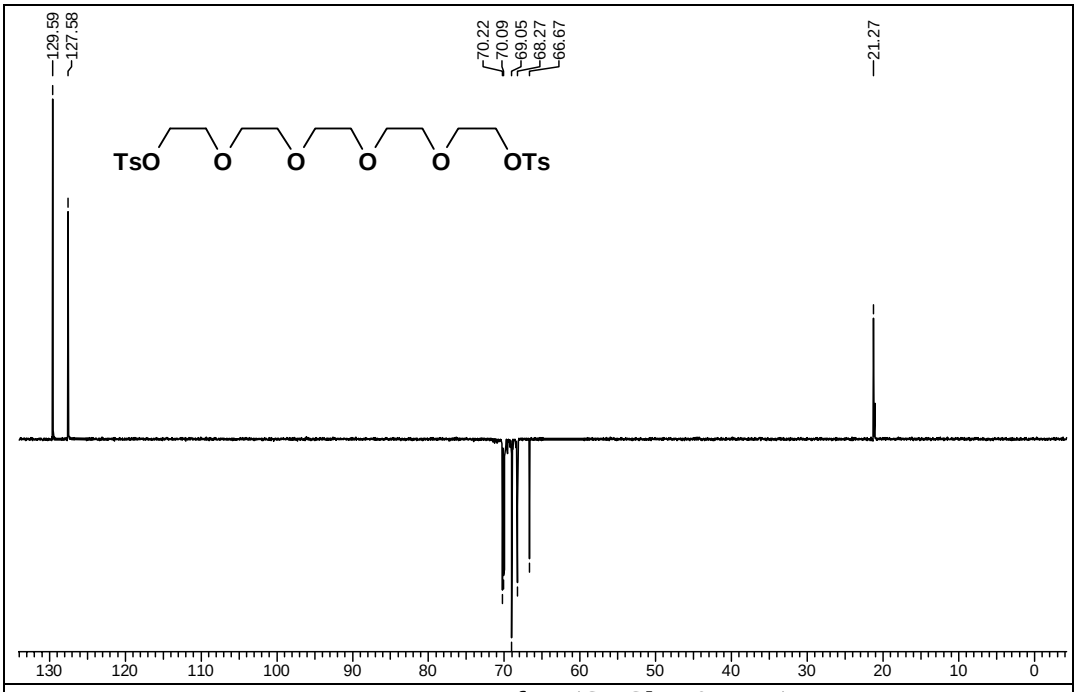
DEPT spectrum of 2 ($CDCl_3$, 50 MHz)



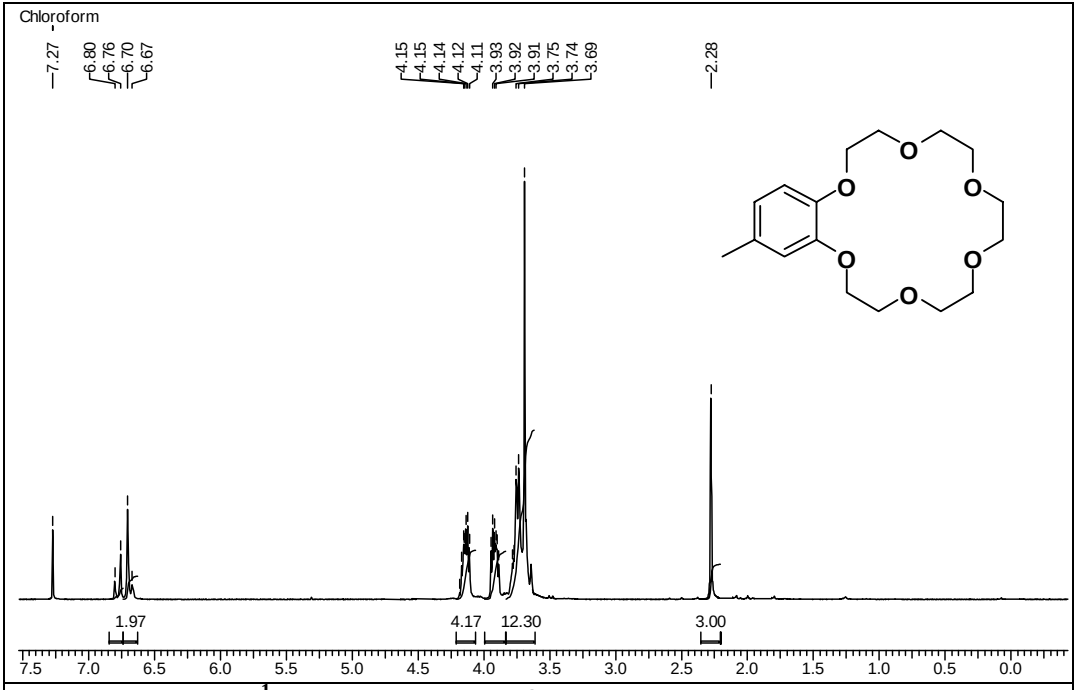
^{1}H NMR spectrum of 15 ($CDCl_3$, 200 MHz)



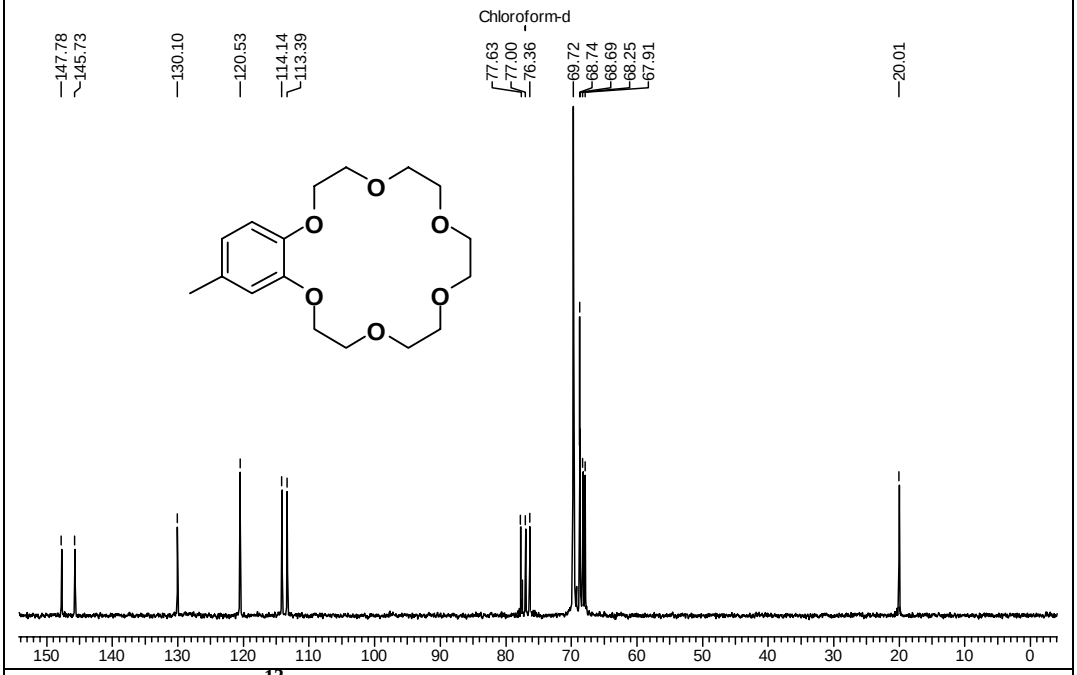
^{13}C NMR spectrum of 15 ($CDCl_3$, 50 MHz)



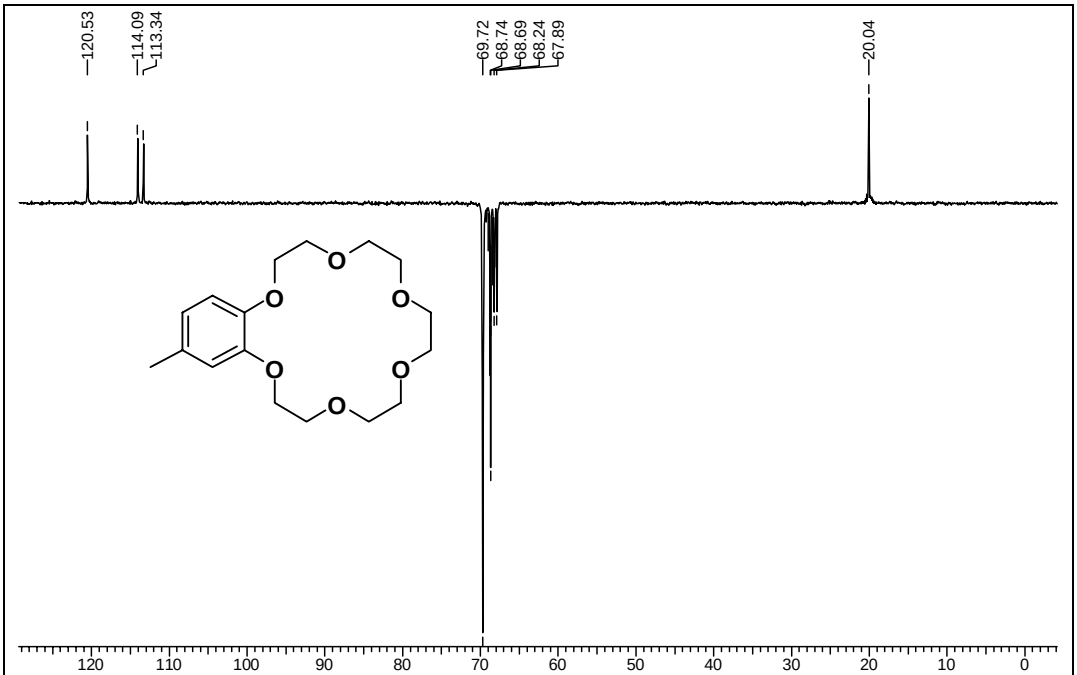
DEPT spectrum of 15 ($CDCl_3$, 50 MHz)



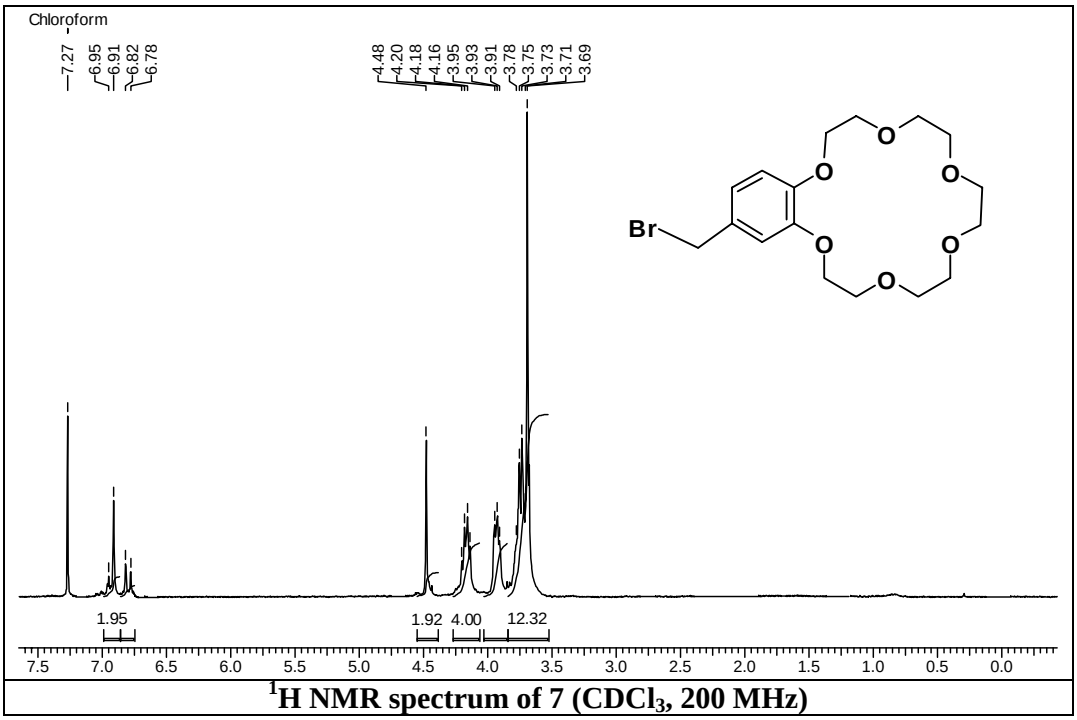
^{1}H NMR spectrum of 16 ($CDCl_3$, 200 MHz)



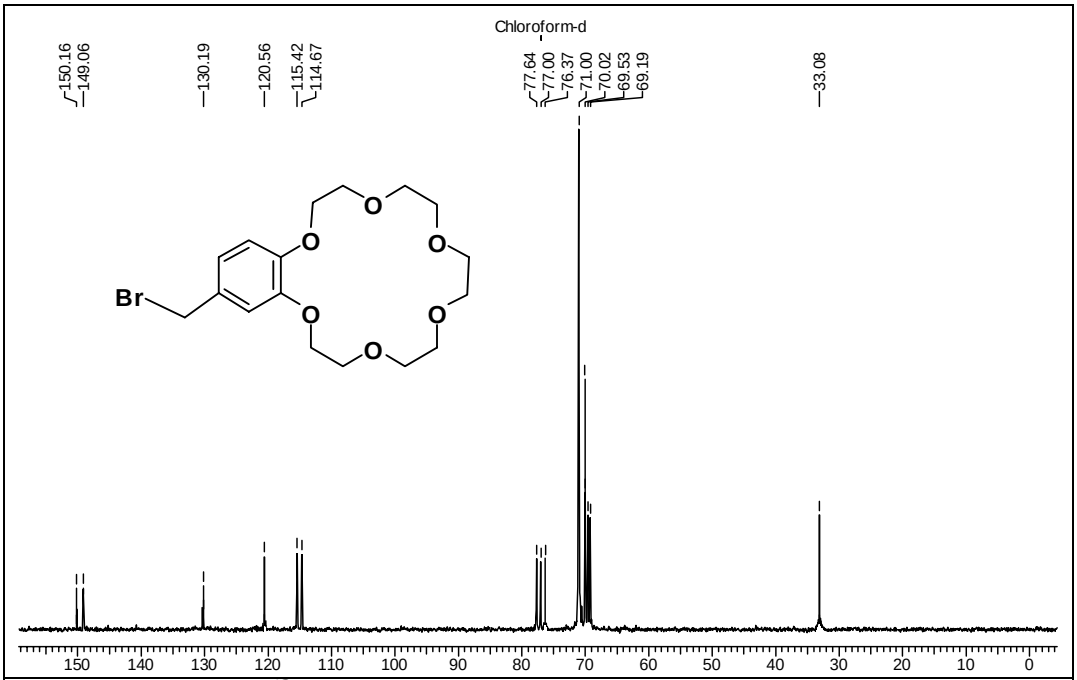
^{13}C NMR spectrum of 16 ($CDCl_3$, 50 MHz)



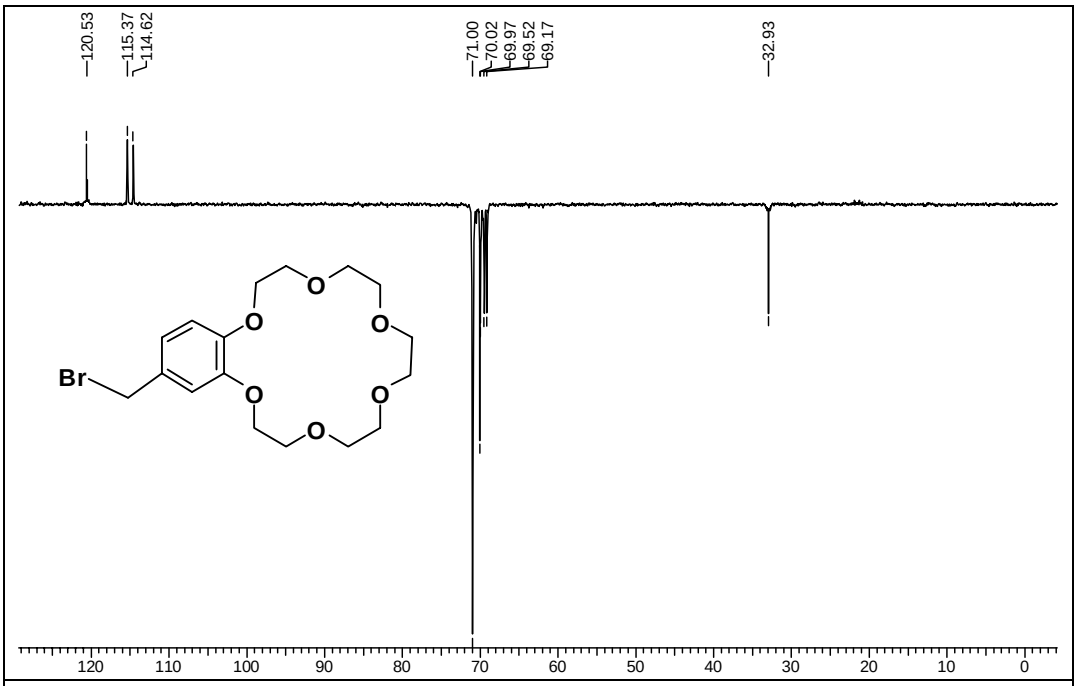
DEPT spectrum of 16 ($CDCl_3$, 50 MHz)



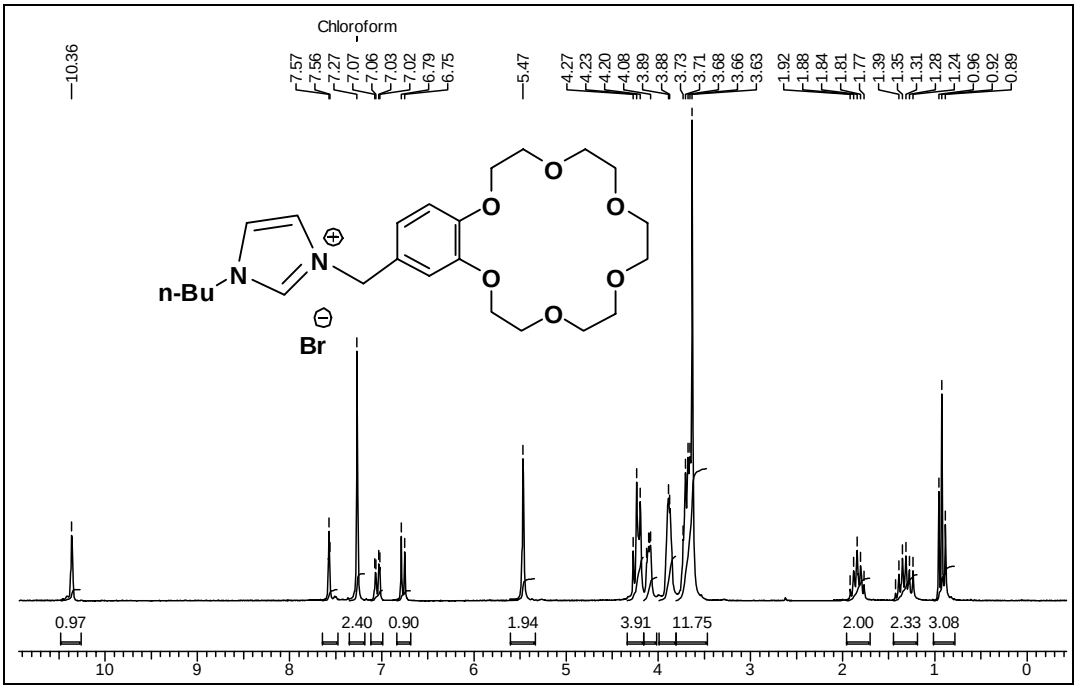
^{1}H NMR spectrum of 7 ($CDCl_3$, 200 MHz)



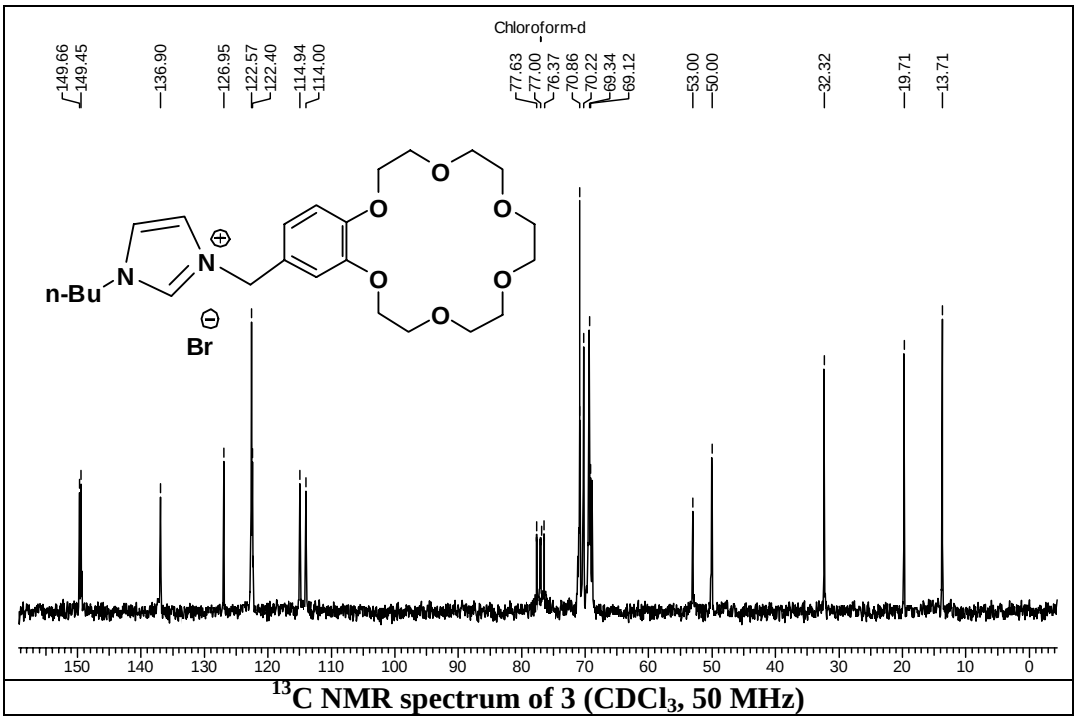
^{13}C NMR spectrum of 7 ($CDCl_3$, 50 MHz)



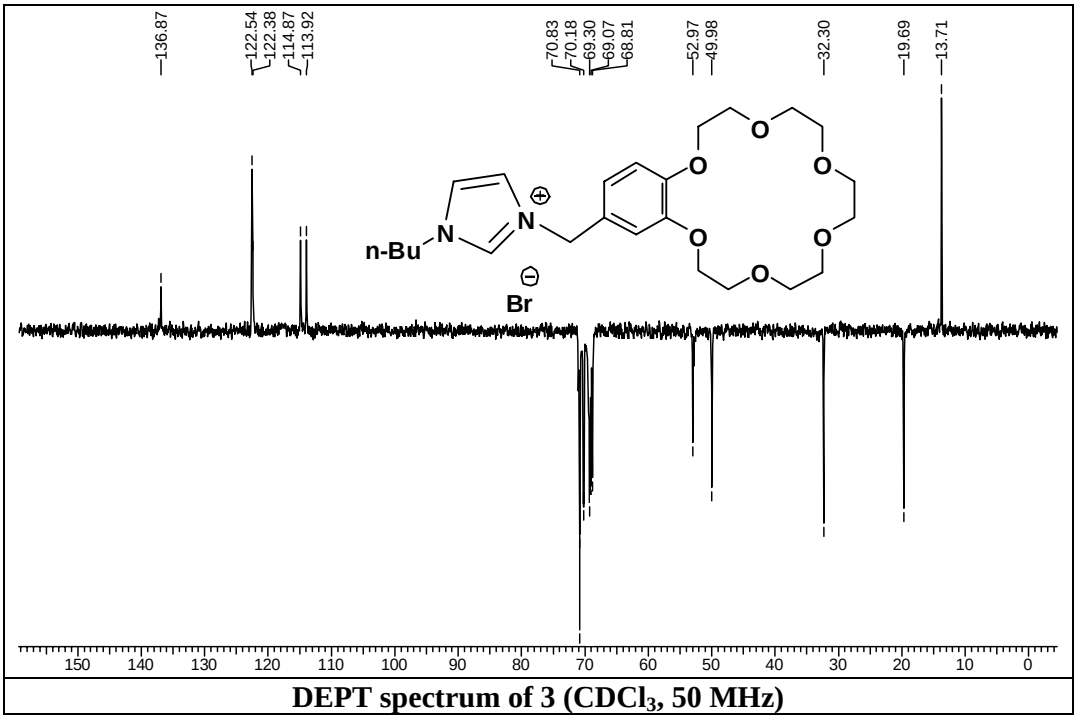
DEPT spectrum of 7 ($CDCl_3$, 50 MHz)



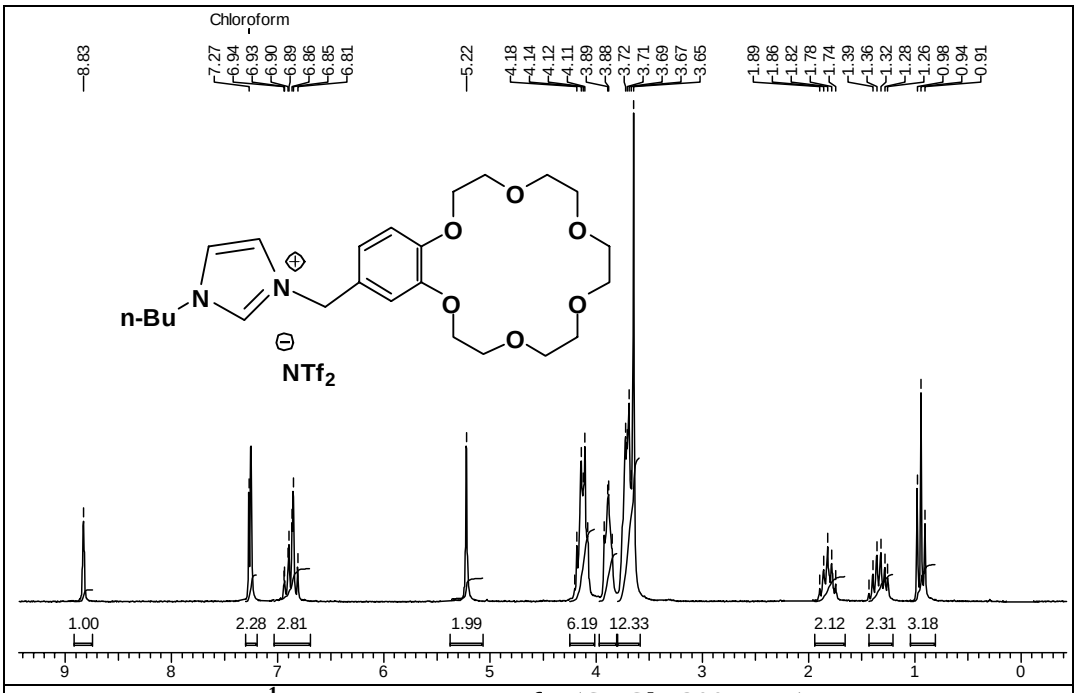
^{1}H NMR spectrum of 3 ($CDCl_3$, 200 MHz)



^{13}C NMR spectrum of 3 ($CDCl_3$, 50 MHz)



DEPT spectrum of 3 ($CDCl_3$, 50 MHz)



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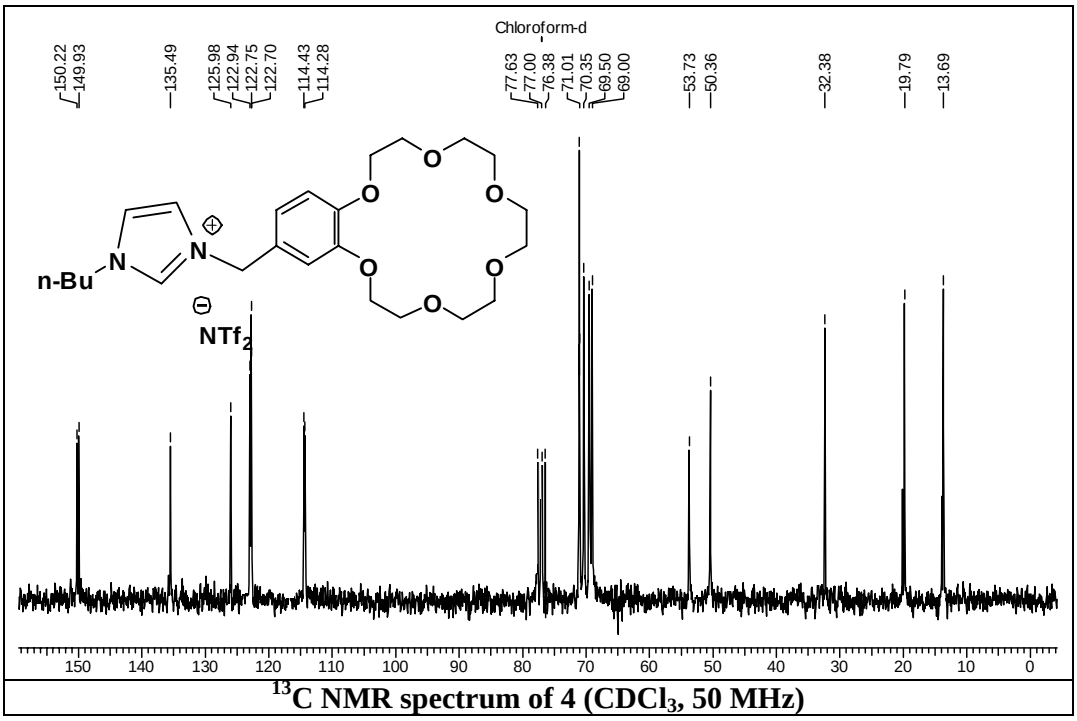
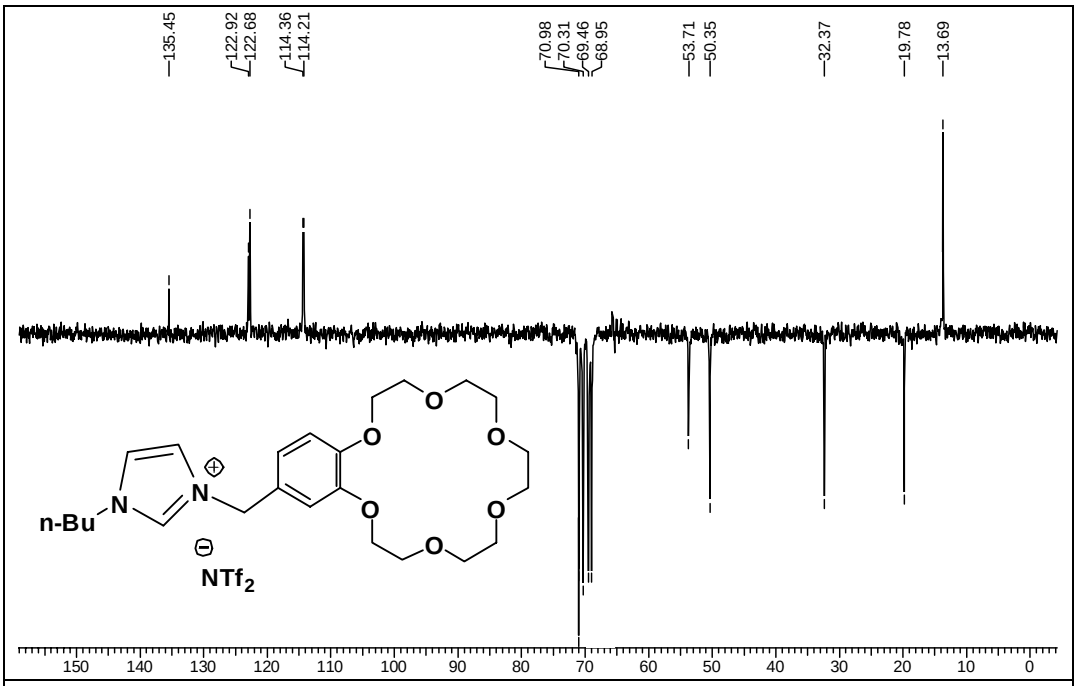


^{13}C NMR spectrum of 4 ($CDCl_3$, 50 MHz)



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

4.2.7 References

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Section 3

[Bbim]Br mediated *N*-Boc protection of alkyl/aryl amines

[Bbim]Br mediated *N*-Boc protection of alkyl/aryl amines

4.3.1 Introduction

Organic synthesis has not yet matured to the point where protective groups are not needed for the synthesis of natural and unnatural products; thus, the development of new methods for functional group protection and deprotection continues.[1,2] Since the introduction of *tert*-butyl carbamate (Boc) group in synthetic organic chemistry it has been extensively used as a protecting group for amine functionality in peptide, heterocyclic synthesis and various organic transformations.[3,4]

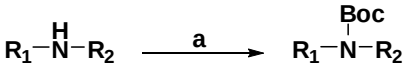
Among the several reagents used, di-*tert*-butyl dicarbonate ($(Boc)_2O$) is safe, cheap and easily available reagent which is most often used for the Boc-protection of amines. Several organic/inorganic base-catalyzed Boc-protection strategies are available in literature.[5-9] Protocols involving various Lewis acids such as $ZnClO_4.6H_2O$,[10a] $ZrCl_4$,[10b] $LiClO_4$,[10c] Sulfamic acid [10d] and tungstophosphoric acid-doped mesoporous silica [10e] have also been reported in recent years.

However, in most of these methods use of conventional bases and homogeneous Lewis acids escort to several drawbacks such as prolonged reaction times, poor yields, lower selectivity, several unwanted by-products and cumbersome workup procedures that are detrimental to the environment. Moreover, in nearly all cases the use of organic solvents (such as THF, tert-butanol, ethanol/methanol, acetonitrile and dichloromethane) is unavoidable, which are environmentally undesirable and some of them may even lead to potential explosion danger. Hence, there is still a need to develop highly efficient, selective and solvent free method which can offer operational simplicity together with mild reaction conditions.

4.3.2 Present Work

In recent years, the important class of imidazolium based room temperature ionic liquids (RTILs) have been the subject of considerable interest as munificent reaction media in organic synthesis because of their unique properties of non-volatility, non-flammability, recyclability and ability to dissolve a wide range of materials, among others.[11,12] During the past few years a variety of imidazolium based RTILs have been demonstrated as efficient and practical alternatives to organic solvents for many

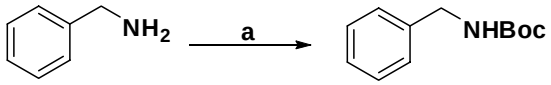
important organic transformations.[11-17] However, the ability of these RTILs to serve as promoter has not been explored yet to any great extent. As a part of our program to evade organic solvents and toxic reagents/catalysts in the several organic reactions we have scrutinized the use of 1, 3-*n*-dibutylimidiazolium based RTILs as an efficient promoter as well as reaction media for Boc-protection of amines (Scheme 1).



Scheme 1. *Reagents and Conditions: a) [bbim]X, $(Boc)_2O$, silent or sonication, rt. X = Br, Cl, BF_4, ClO_4; $R_1 = R_2$ = H or alkyl or aryl.*

4.3.3 Result and discussion

Initially separate experiments using [bbim]Br, [bbim]Cl, [bbim]ClO_4 and [bbim]BF_4 RTILs were carried out for the *N*-Boc protection of benzyl amine **4a** at room temperature under ultrasound and stirring without ultrasound (silent) condition (Scheme 2, Table 1). It was observed that with all the RTILs, it takes approximately half hour or an hour to complete *N*-Boc protection of benzyl amine **4a** at room temperature under silent condition with significant to quantitative yield of *N*-Boc product **4b**, among which, [bbim]Br accomplished with highest 95% yield (Scheme 2, Table 1). In case of *N*-Boc protection of benzyl amine **4a** under ultrasound condition, the reaction completion time for all RTILs was decreased and yields were significantly increased. Among these RTILs [bbim]Br was found to be superior with highest 98% yield for **4b** within shortest reaction time period of 5 min (Scheme 2, Table 1).



4a **4b**

Scheme 2. *Reagents and Conditions: a) [bbim]X, $(Boc)_2O$, silent or sonication, rt. X = Br, Cl, BF_4, ClO_4.*

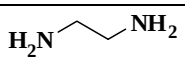
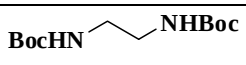
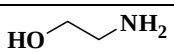
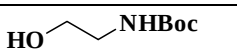
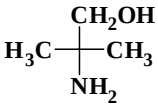
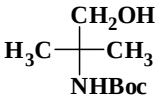
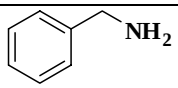
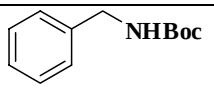
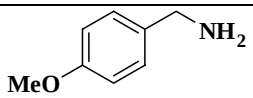
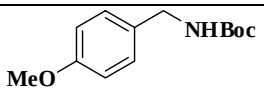
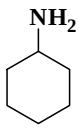
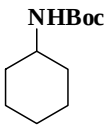
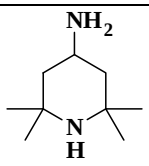
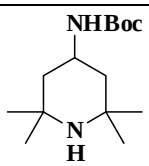
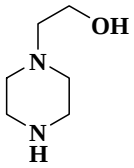
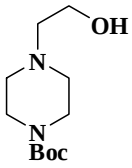
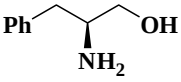
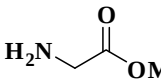
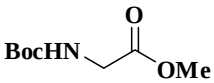
Table 1. Comparative study of *N*-Boc-protection of benzyl amine **(4a)** in various RTILs at room temperature.

Entry	Ionic liquid	Time (min)		%Yield [a]	
		Silent	(((((	Silent	(((((
1	[bbim]Br	30	5	95	98
2	[bbim]Cl	35	10	93	96
3	[bbim]ClO_4	50	20	87	90
4	[bbim]BF_4	70	25	85	88

[a] Isolated yield of *N*-Boc product **4b**.

Further, [bbim]Br was also tested for *N*-Boc protection of several structurally varied alkyl/aryl amines, amino acids and esters of amino acids and the results are summarized in Table 2. It was seen that long reaction time was required under silent (room temperature stirring) condition whereas sonication accelerates the reaction rate (up to five times faster than silent condition) of *N*-Boc protection of amines (Table 2). It was found that under sonication conditions *N*-Boc protection of all the primary amines resulted in excellent yields within few minutes (entries 1-7 and 9-14, Table 2). *N*-Boc protection of secondary amines (entries 8 and 15, Table 2) also resulted in almost quantitative yields (>90%) but took longer reaction time period as compared to *N*-Boc protection of primary amines. In addition, chemo-selective *N*-Boc protection of primary amine was also achieved in presence of secondary amines within shorter time period (entries 8, Table 2). Under the sonication condition, *N*-Boc protection of aryl amines also completes within few minutes with excellent yields of *N*-Boc aryl amines (entries 16-18, Table 2). All the *N*-Boc products of respective reactions carried out in this work were isolated in pure form and their structures were confirmed by ^{1}H and ^{13}C NMR spectral studies.

Table 2. *N*-Boc-protection of various alkyl/aryl amines in [bbim]Br at room temperature.

Entry	Substrate [a]	Product [b]	Time (min)		%Yield[c]	
			Silent	(((((	Silent	(((((
1			30	5	95	98
2			35	5	92	96
3			35	5	94	96
4			30	5	95	98
5			30	5	94	98
6			25	5	95	97
7			30	5	93	95
8			90	40	93	95
9			40	10	92	95
10			35	10	94	98

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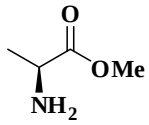
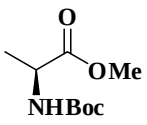
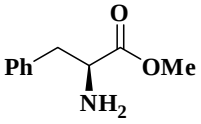
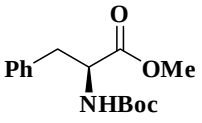
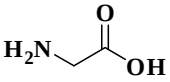
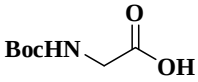
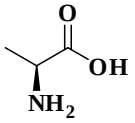
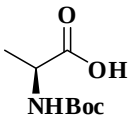
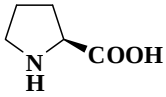
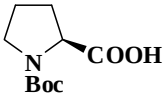
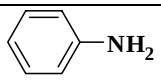
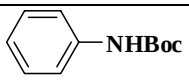
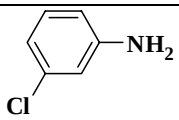
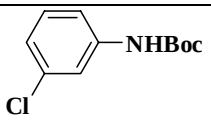
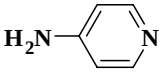
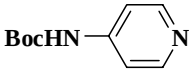
11			40	10	95	97
12			30	5	95	98
13			60	25	88	90
14			60	25	90	92
15			120	45	85	90
16			25	5	94	98
17			25	5	95	97
18			35	10	92	94

[a] Substrate; [b] *N*-Boc product; [c] Isolated yield for *N*-Boc product.

Hydrogen bonding in imidazolium ring depends on the basicity of the anion. It is known that H_c proton attached to the carbon atom between two electronegative nitrogen atoms is electron deficient compared to H_a and H_b (Figure 2). Thus, H_c proton is more prone for hydrogen bonding with counter anion than H_a and H_b. It is evident from NMR shifts of H_c proton of different 1,3-*n*-butylimidazolium based RTILs which decreased respectively in order of Br > Cl> ClO_4 > BF_4 anions of decreasing electro negativity.[18] Based on this, a plausible reaction pathway for the *N*-Boc protection of amines has also been proposed in which the possible hydrogen bond interaction of the most acidic hydrogen H_c of the imidazolium cation with the oxygen

of the Boc anhydride facilitates the generation of Boc cation required for the reaction leading to the formation of *N*-Boc protected amines (Scheme 3).

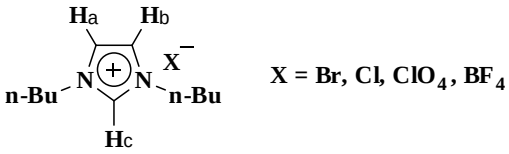
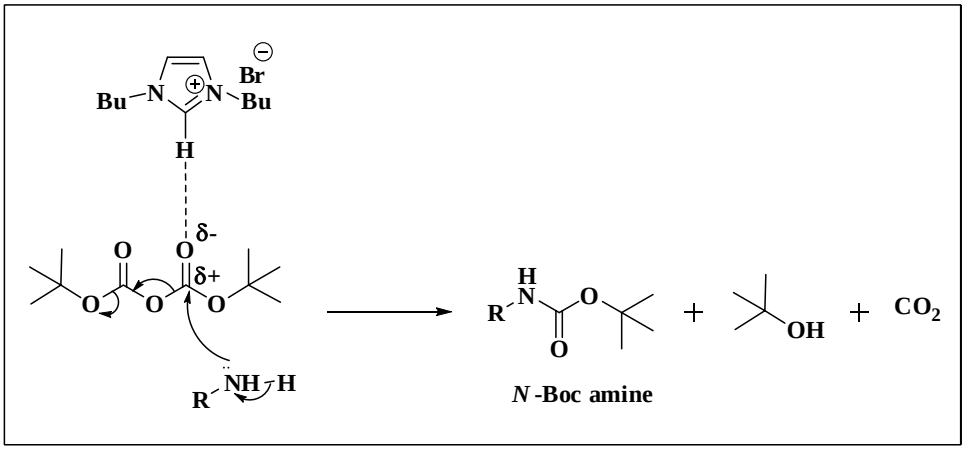


Figure 2: 1, 3-*n*-dibutylimidazolium based ionic liquids



Scheme 3. Proposed plausible mechanistic pathway for *N*-Boc protection in 1,3-*n*-diimidazolium based RTILs.

4.3.4 Conclusion

In conclusion, 1,3-di-*n*-butylimidazolium based RTILs were found to be promising reaction promoters as well as reaction media for the chemo-selective *N*-Boc protection of various alkyl/aryl amines, amino acids and amino acid esters under silent as well as ultrasound condition at room temperature. Among the all RTILs, [bbim]Br was found to be most efficient RTIL for the *N*-Boc protection of variety of amines under ultrasound condition. Based on the possible hydrogen bond interaction in imidazolium ring, a plausible mechanistic pathway for *N*-Boc protection of amines has been also proposed.

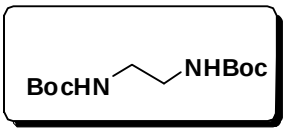
4.3.5 Experimental

All the 1,3-di-*n*-butylimidazolium based RTILs with variable anions used during this work were previously synthesized and studied in our group.[17]

General procedure for *N*-Boc-protection of alkyl/aryl amine using [bbim] Br

A mixture of alkyl/aryl amine (1 mmol) and di-*tert*-butyl dicarbonate (1.1 mmol) in 1, 3-di-n-butylimidazolium bromide ([bbim]Br, 2.0g) was sonicated in an argon atmosphere at ambient conditions in a thermostated (30 ± 1 ^{0}C) ultrasonic cleaning bath. The reactions were monitored by TLC. The same reactions were performed under similar conditions without ultrasound (silent reactions). After complete conversion, the reaction mixture was diluted with water (25 mL). The solid product separated was filtered, washed with water, and dried. The products which are liquids were extracted with ethyl acetate (2 x 10 mL) and dried over sodium sulfate, and solvent was evaporated under reduced pressure to furnish crude product. The crude products were further purified by column chromatography over silica-gel (100-200 mesh) to afford Boc-protected alkyl/aryl amine. The aqueous layer consisting of [bbim]Br was subjected to distillation (80 ^{0} C at 10 mm Hg) for 2 h to remove water, leaving behind [bbim]Br (recovery >98%), which could be reused for the next run.

***N, N'*-Bis (tert-butoxycarbonyl)-1, 2-ethanediamine (1b)**



Molecular Formula : $C_{12}H_{24}N_2O_4$.

Nature : White solid.

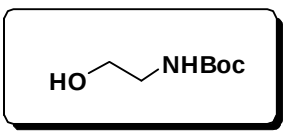
Mp : 146 ^{o}C.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 1.42 (s, 18H), 3.21 (t, *J* = 2.0 Hz, 4H), 5.00 (s, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 27.50, 39.67, 77.66, 155.42.

MS (ESI-TOF) m/z : 283.18 ($[M+Na]^+$).

***tert*-Butyl 2-hydroxyethylcarbamate (2b)**



Molecular Formula : $C_7H_{15}NO_3$.

Nature : Light yellow viscous liquid.

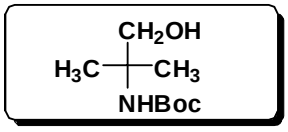
^{1}H NMR ($CDCl_3$, 200 : δ (ppm) 1.42 (s, 9H), 2.75 (bs, 1H), 3.21-3.29 (m, 2H),

MHz) 3.66 (t, *J* = 6.1 Hz, 2H), 5. 16 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 28.01, 42.58, 61.21, 78.97, 156.44.

MS (ESI-TOF) m/z : 184.21 ($[M+Na]^+$).

***tert*-Butyl 1-hydroxy-2-methylpropan-2-ylcarbamate (3b)**



Molecular Formula : $C_9H_{19}NO_3$.

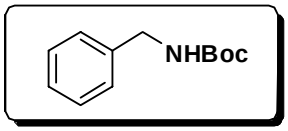
Nature : Dense yellow liquid.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 1.22 (s, 6H), 1.40 (s, 9H), 3.53 (s, 2H), 4.78 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 24.11, 28.14, 53.80, 70.27, 79.20, 155.88.

MS (ESI-TOF) m/z : 212.30 ($[M+Na]^+$).

***tert*-Butyl benzylcarbamate (4b)**



Molecular Formula : $C_{12}H_{17}NO_2$.

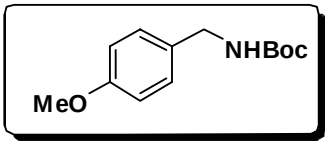
Nature : Dense yellow liquid.

H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 1.48 (s, 9H), 4.31-4.34 (d, *J* = 5.81 Hz, 2H), 4.96 (s, 1H), 7.27-7.39 (m, 5H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 27.95, 44.02, 78.67, 126.66, 126.89, 128.00, 138.77, 155.66.

MS (ESI-TOF) m/z : 230.10 ($[M+Na]^+$).

***tert*-Butyl 4-methoxybenzylcarbamate (5b)**



Molecular Formula : $C_{13}H_{19}NO_3$.

Nature : Brownish solid.

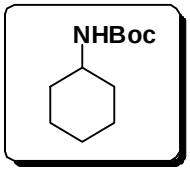
Mp : 122 ^oC.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 1.46 (s, 9H), 3.79 (s, 3H), 4.24 (d, *J* = 5.8 Hz, 2H), 4.87 (s, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 28.70, 43.67, 54.78, 78.77, 113.54, 128.39, 130.95, 138.77, 155.68, 158.44.

MS (ESI-TOF) m/z : 260.19 ($[M+Na]^+$).

***tert*-Butyl N-cyclohexylcarbamate (6b)**



Molecular Formula : $C_{11}H_{21}NO_2$.

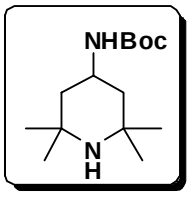
Nature : Pale yellow viscous liquid.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 0.97-1.23(m, 4H), 1.29-1.37 (m, 2H), 1.43(s, 9H), 1.64-1.74 (m, 2H), 1.81-1.95(m, 2H), 3.39 (s, 1H), 4.41 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 24.55, 25.13, 28.01, 49.03, 78.29, 154.48.

MS (ESI-TOF) m/z : 222.25 ($[M+Na]^+$).

***tert*-Butyl 2,2,6,6-tetramethyl-4-piperidinylcarbamate (7b)**



Molecular Formula : $C_{14}H_{28}N_2O_2$.

Nature : White solid.

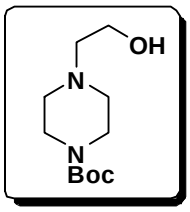
Mp : 219 ^{o}C.

^{1}H NMR ($CDCl_3$,200 MHz) : δ (ppm) 0.70-0.82 (dd, *J* = 12.4 Hz, 2H), 0.98 (s, 6H), 1.09 (s, 6H), 1.31 (s, 9H), 1.71-1.79 (dd, *J* = 12.4 Hz, 2H), 2.41 (bs, 1H), 3.73 (bs, 1H), 4.63 (bs, 1H).

^{13}C NMR (CD_3OD, 50 MHz) : δ (ppm) 27.98, 28.83, 34.27, 45.84, 52.43, 79.90, 157.73.

MS (ESI-TOF) m/z : 279.23 ($[M+Na]^+$).

***tert*-Butyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (8b)**



Molecular Formula : $C_{11}H_{22}N_2O_3$.

Nature : White solid.

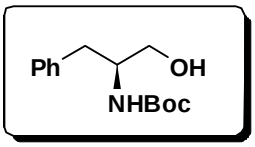
Mp : 127 ^{o}C.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 1.41 (s, 9H), 2.41-2.46 (t, *J* = 5.1 Hz, 4H), 2.51-2.56 (t, *J* = 5.4 Hz, 4H), 3.40-3.45 (t, *J* = 5.1 Hz, 4H), 3.59-3.64 (t, *J* = 5.4 Hz, 4H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 28.11, 52.59, 57.70, 59.52, 79.42, 154.41.

MS (ESI-TOF) m/z : 253.28 ($[M+Na]^+$).

(*S*)-*tert*-Butyl 1-hydroxy-3-phenylpropan-2-ylcarbamate (9b)



Molecular Formula : $C_{14}H_{21}NO_3$.

Nature : White solid.

Mp : 143 ^oC.

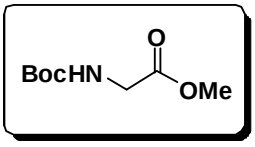
Optical rotation : $[\alpha]_D^{25}$ -26.82, *c* 1.0, $CHCl_3$.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 1.45 (s, 9H), 2.21 (bs, 1H), 2.86-2.89 (d, *J* = 7.1 Hz, 2H), 3.58 (dd, *J* = 11.0, 5.4 Hz, 1H), 3.3.71 (dd, *J* = 11.0, 3.7 Hz, 1H), 3.85 (bs, 1H), 4.81 (bs, 1H), 7.24-7.34 (m, 5H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 28.21, 37.30, 53.47, 63.49, 79.44, 126.24, 128.30, 129.21, 137.89, 156.06.

MS (ESI-TOF) m/z : 274.20 ($[M+Na]^+$).

Methyl 2-(*tert*-butoxycarbonylamino) acetate (10b)



Molecular Formula : $C_8H_{15}NO_4$.

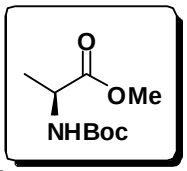
Nature : Dense yellow liquid.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 1.36 (s, 9H), 3.66 (s, 3H), 3.83 (d, *J* = 5.6 Hz, 2H), 5.26 (bs, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 27.74, 41.71, 51.49, 79.13, 155.53, 170.53.

MS (ESI-TOF) m/z : 212.10 ($[M+Na]^+$).

(*S*)-Methyl 2-(*tert*-butoxycarbonylamino) propanoate (11b)



Molecular Formula : $C_9H_{17}NO_4$.

Nature : Dense yellow liquid.

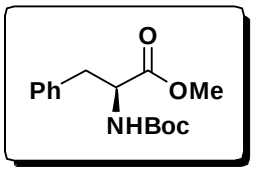
Optical rotation : $[\alpha]_D^{25}$ -44.60, *c* 1.0, MeOH (Lit. $[\alpha]_D^{25}$ -44.75, *c* 1.0, MeOH).[19]

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 1.26 (d, *J* = 7.2 Hz, 3H), 1.31 (s, 9H), 3.61 (s, 3H), 4.01-4.18 (m, 1H), 5.24 (bs, 1H) .

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 17.70, 27.78, 48.69, 51.62, 78.98, 154.77, 173.40.

MS (ESI-TOF) m/z : 226.11 ($[M+Na]^+$).

(*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-3-phenylpropanoate (12b)



Molecular Formula : $C_{15}H_{21}NO_4$.

Nature : Dense yellow liquid.

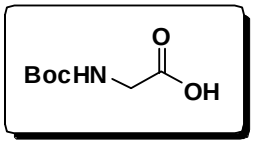
Optical rotation : $[\alpha]_D^{25}$ -3.95, *c* 1.0, MeOH. (Lit.$[\alpha]_D^{25}$ -4.2, *c* 1.0, MeOH).[19]

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 1.45 (s, 9H), 3.12 (t, *J* = 5.6 Hz, 2H), 3.74 (s, 3H), 4.62 (dd, *J* = 14.1, 6.0 Hz, 1H), 5.06 (d, *J* = 8.0 Hz, 1H), 7.11-7.33 (m, 5H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 27.85, 37.81, 51.65, 54.15, 79.24, 126.53, 128.08, 128.88, 135.85, 154.75, 171.96.

MS (ESI-TOF) m/z : 302.17 ($[M+Na]^+$).

2-(*tert*-Butoxycarbonylamino) acetic acid (13b)



Molecular Formula : $C_7H_{13}NO_4$.

Nature : White solid.

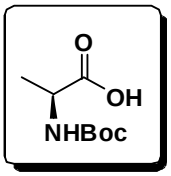
Mp : 152 ^{o}C.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 1.47 (s, 9H), 3.92 (dd, *J* = 13.5, 5.4 Hz, 2H), 5.23 (bs, 1H), 11.04 (bs, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 28.05, 41.95, 80.18, 156.11, 174.15.

MS (ESI-TOF) m/z : 198.1 ($[M+Na]^+$).

(*S*)-2-(*tert*-Butoxycarbonylamino) propanoic acid (14b)



Molecular Formula : $C_8H_{15}NO_4$.

Nature : White solid.

Mp : 82 ^{o}C.

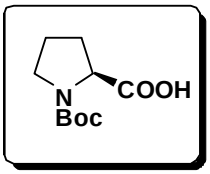
Optical rotation : $[\alpha]_D^{25}$ -25.02, *c* 2.0, acetic acid (Lit. $[\alpha]_D^{25}$ -25.5, *c* 2.0, acetic acid).[19]

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 1.36 (d, *J* = 7.0 Hz, 3H), 1.37 (s, 9H), 4.17 (dt, *J* = 13.0, 6.8 Hz, 1H), 3.36 (d, *J* = 6.8 Hz, 1H), 11.09 (bs, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 18.20, 28.08, 50.06, 81.54, 156.84,177.33.

MS (ESI-TOF) m/z : 212.12 ($[M+Na]^+$).

(*S*)-1-(*tert*-Butoxycarbonyl) pyrrolidine-2-carboxylic acid (15b)



Molecular Formula : $C_{10}H_{17}NO_4$.

Nature : White solid.

Mp : 134 °C.

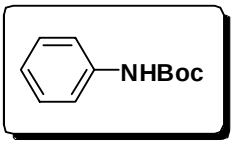
Optical rotation : $[\alpha]_D^{25}$ -60.37, *c* 1.0, acetic acid (Lit. $[\alpha]_D^{25}$ -60.5, *c* 1.0, acetic acid).[19]

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 1.43 (d, *J* = 10.5 Hz, 9H), 1.84-2.16 (m, 4H), 3.34-3.55 (m, 2H), 4.28 (dddd, *J* = 8.0, 4.2 Hz, 1H), 10.10 (bs, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 23.32, 27.92, 46.04, 58.70, 80.18, 153.88, 177.42.

MS (ESI-TOF) m/z : 238.2 ($[M+Na]^+$).

***tert-Butyl* phenylcarbamate (16b)**



Molecular Formula : $C_{11}H_{15}NO_2$.

Nature : White solid.

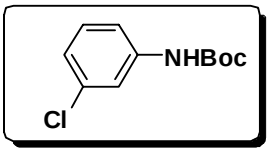
Mp : 136 °C.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 1.45 (s, 9H), 6.44 (bs, 1H), 6.96 (dd, *J* = 8.00 Hz, 1H), 7.17-7.32 (m, 4H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 27.55, 78.73, 117.74, 121.47, 127.76, 138.42, 152.40.

MS (ESI-TOF) m/z : 216.1 ($[M+Na]^+$).

tert-Butyl 3-chlorophenylcarbamate (17b)



Molecular Formula : $C_{11}H_{14}ClNO_2$.

Nature : White solid.

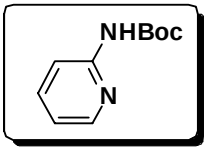
Mp : 105 ^{o}C.

^{1}H NMR ($CDCl_3$, 200MHz) : δ (ppm) 1.52 (s, 9H), 6.62 (bs, 1H), 6.97-7.02 (m, 1H), 7.16-7.19 (m, 2H), 7.53 (s, 1H).

^{13}C NMR ($CDCl_3$, 50MHz) : δ (ppm) 27.97, 80.49, 116.37, 118.33, 122.49, 129.53, 134.19, 139.59, 152.55.

MS (ESI-TOF) m/z : 250.1 ($[M+Na]^+$).

tert-Butyl pyridin-4-ylcarbamate (18b)



Molecular Formula : $C_{10}H_{14}N_2O_2$.

Nature : White solid.

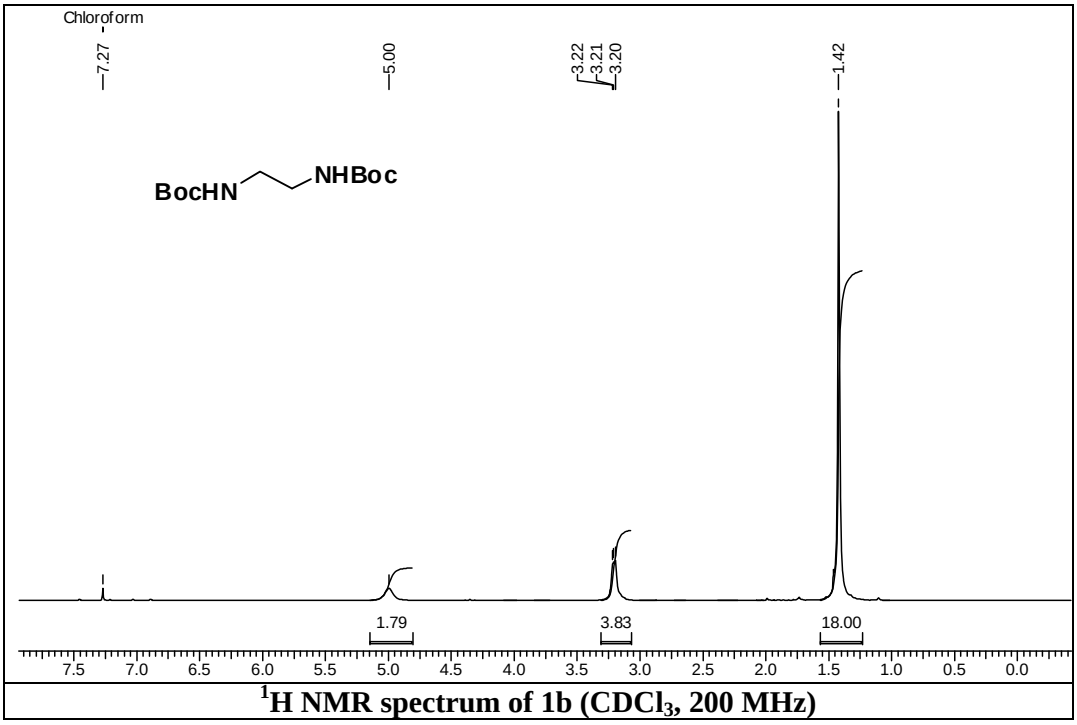
Mp : 123 ^{o}C.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 1.52 (s, 9H), 7.34 (dd, J = 1.6, 4.7 Hz, 2H), 8.43 (dd, J = 1.5, 4.80 Hz, 2H).

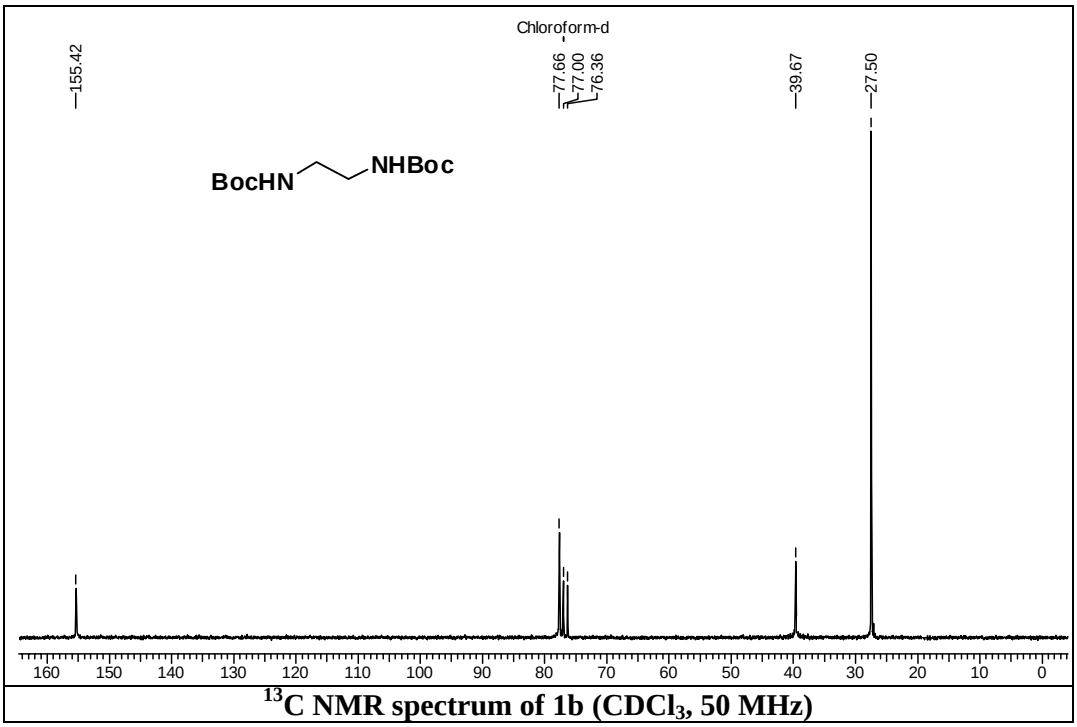
^{13}C NMR ($CDCl_3$, 50MHz) : δ (ppm) 27.91, 80.63, 112.38, 146.86, 149.45, 152.57.

MS (ESI-TOF) m/z : 217.2 ($[M+Na]^+$).

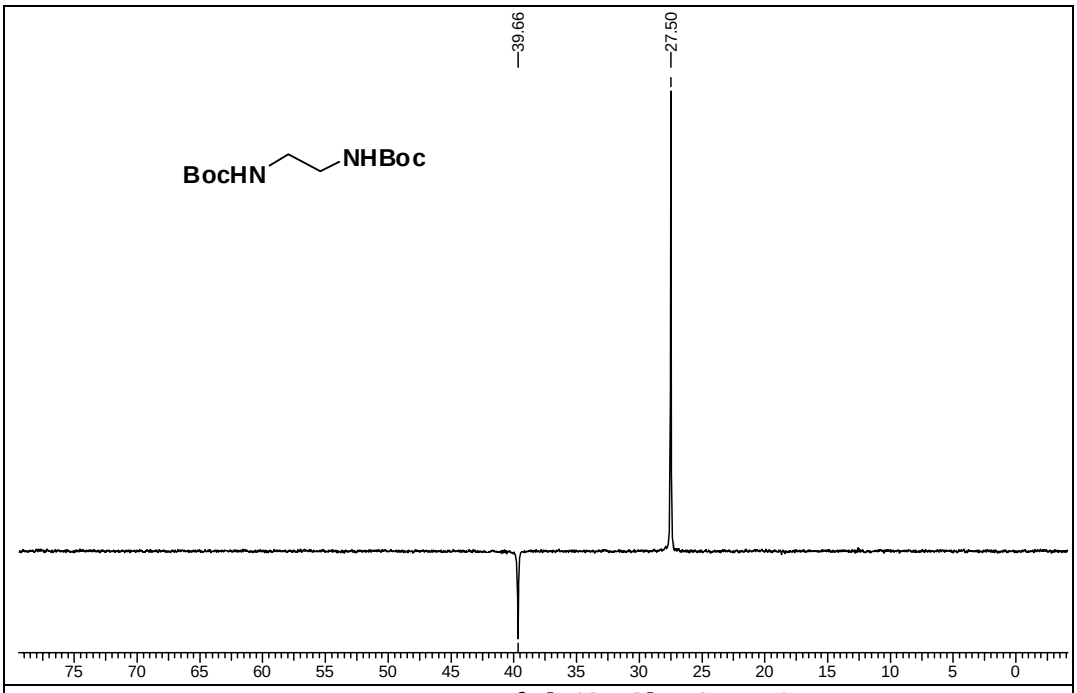
4.3.6 Analytical data



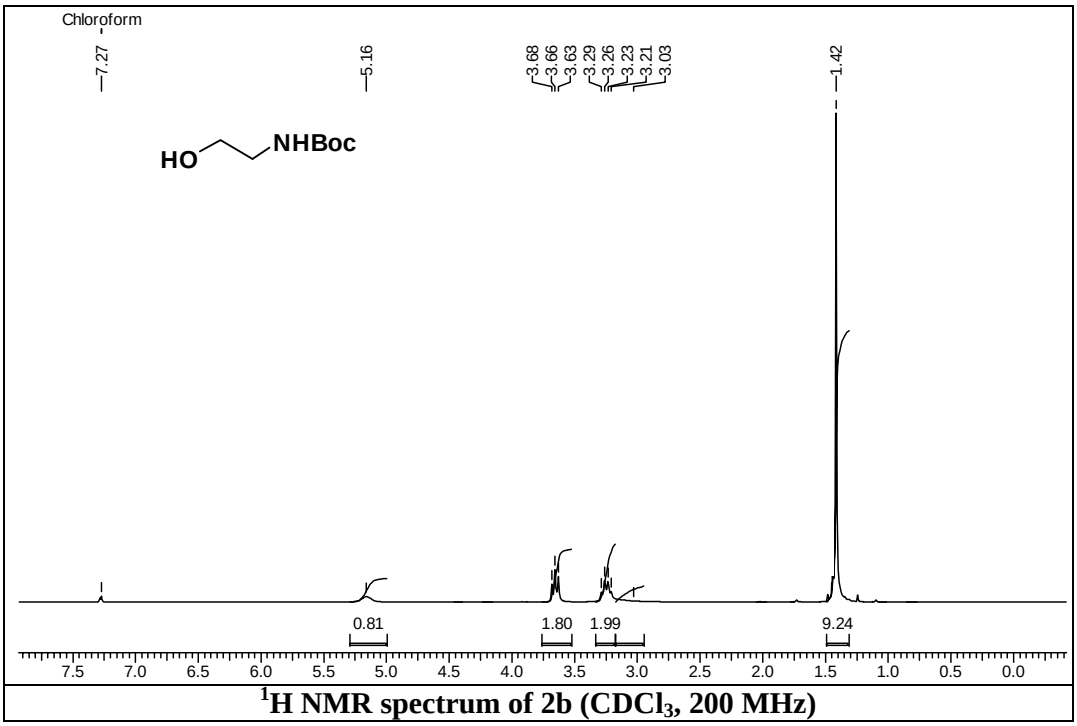
^{1}H NMR spectrum of 1b ($CDCl_3$, 200 MHz)



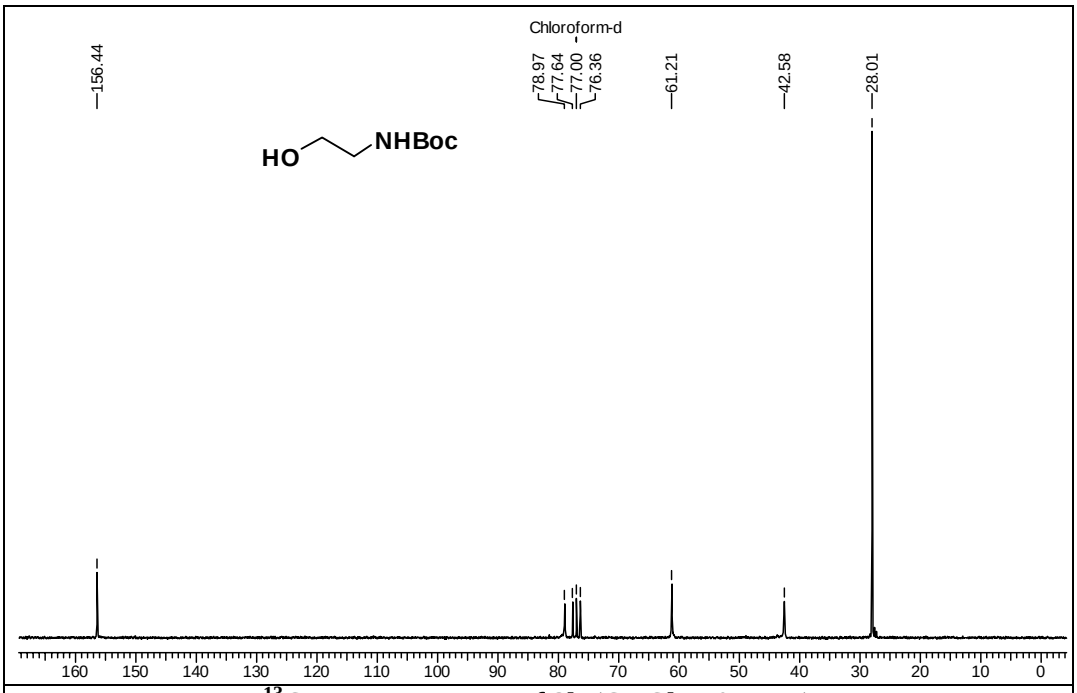
^{13}C NMR spectrum of 1b ($CDCl_3$, 50 MHz)



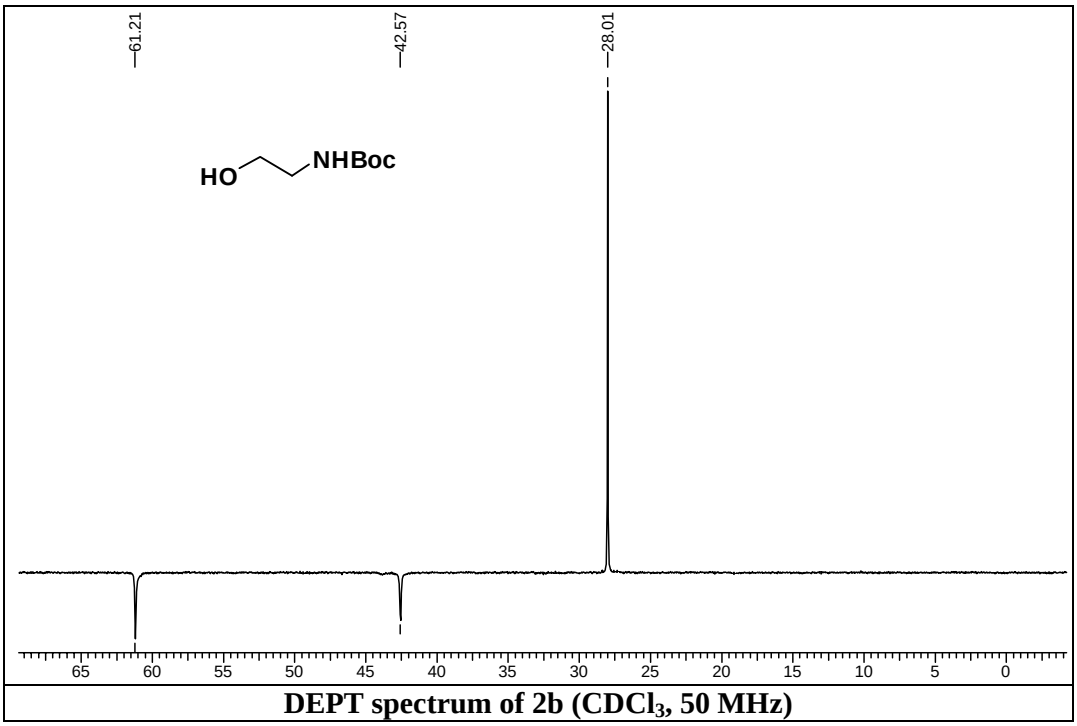
DEPT spectrum of 1b ($CDCl_3$, 50 MHz)



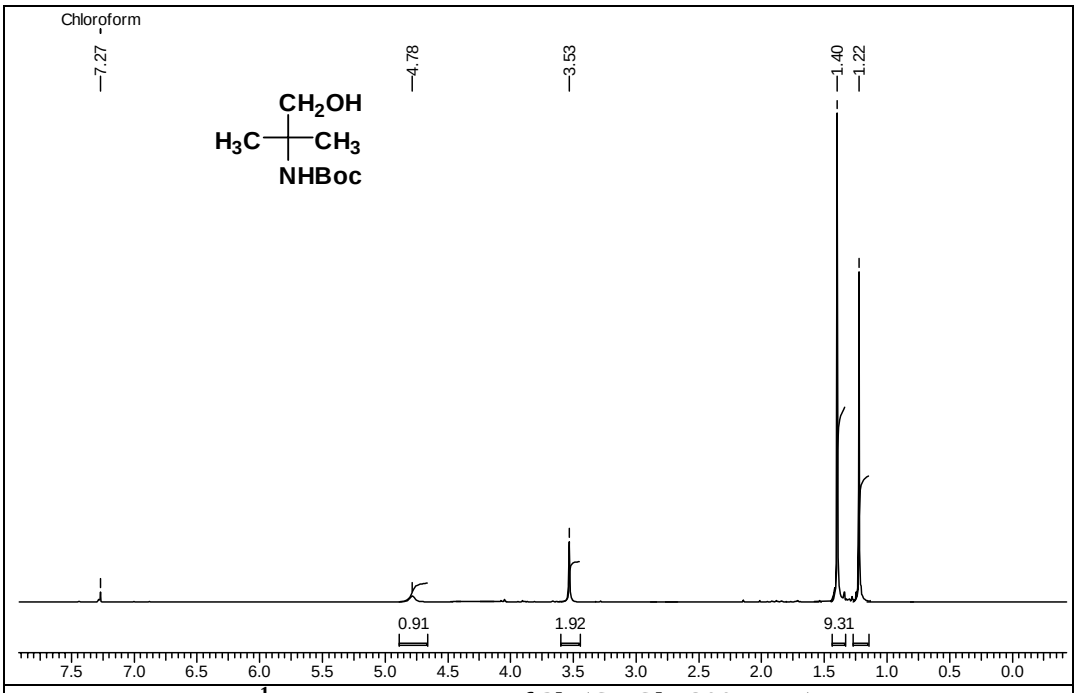
^{1}H NMR spectrum of 2b ($CDCl_3$, 200 MHz)



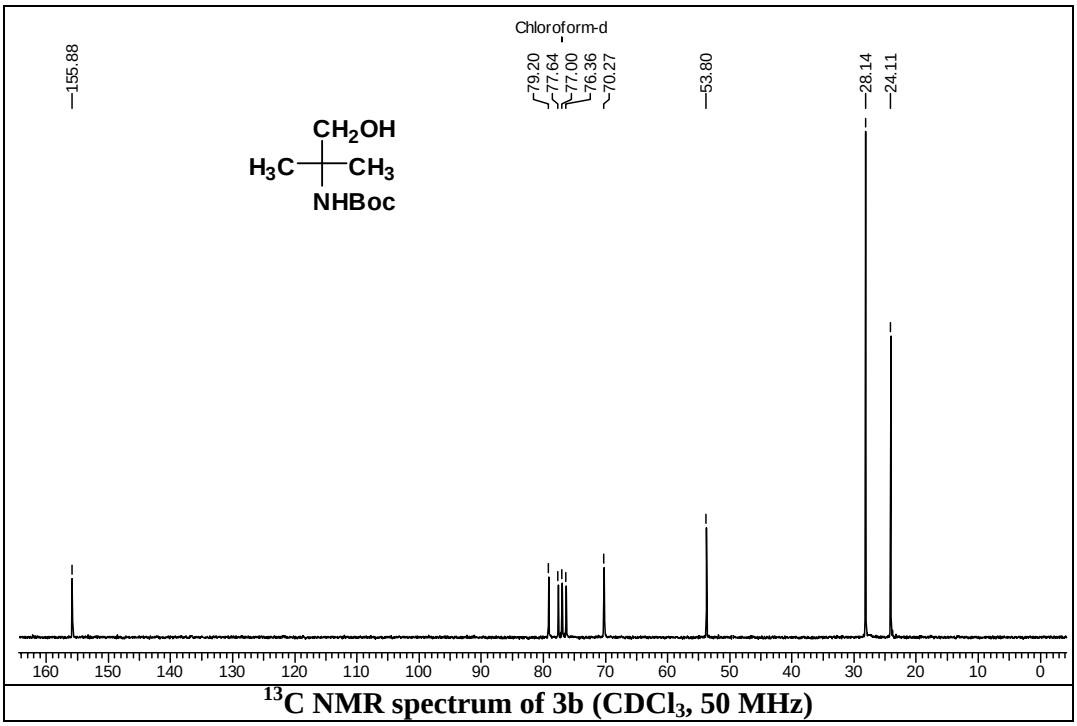
^{13}C NMR spectrum of 2b ($CDCl_3$, 50 MHz)



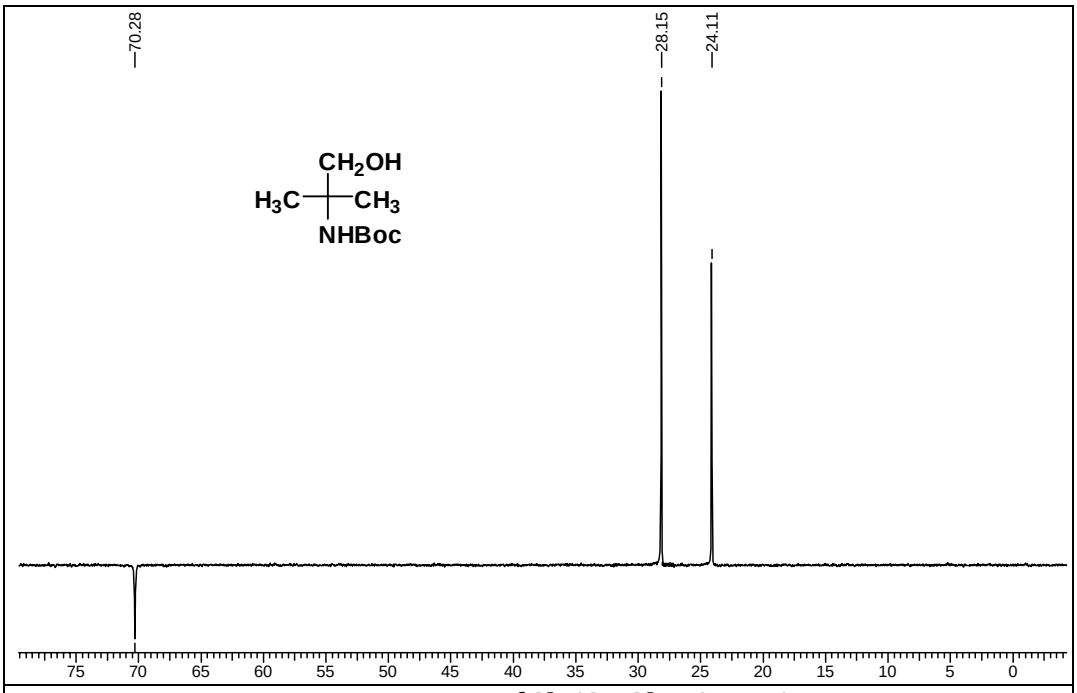
DEPT spectrum of 2b ($CDCl_3$, 50 MHz)



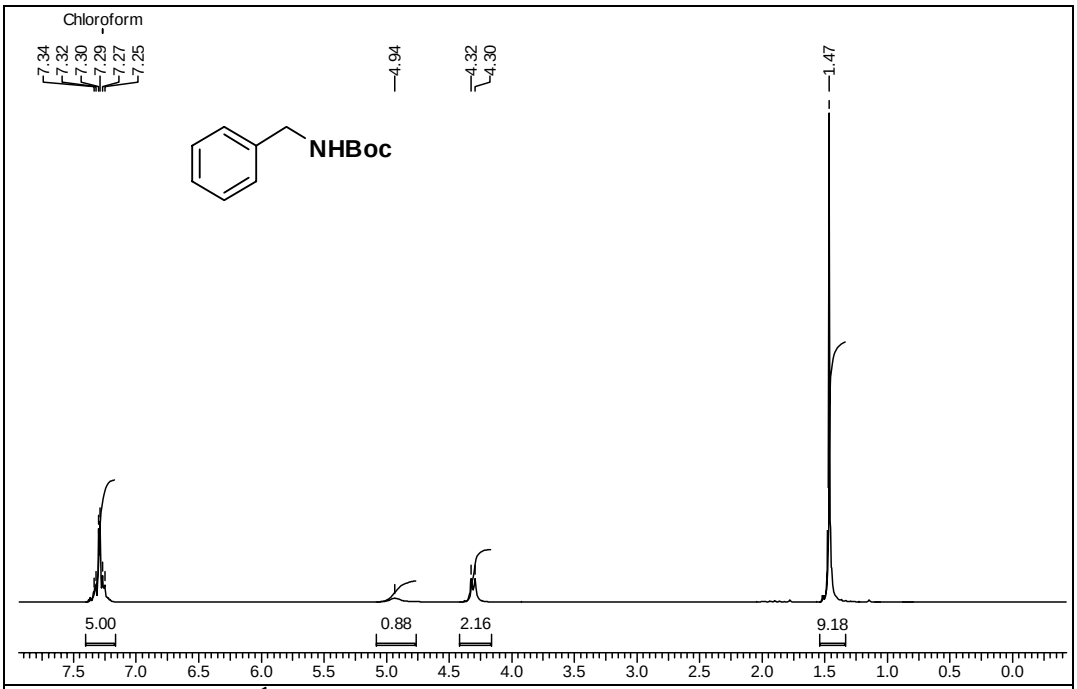
^{1}H NMR spectrum of 3b ($CDCl_3$, 200 MHz)



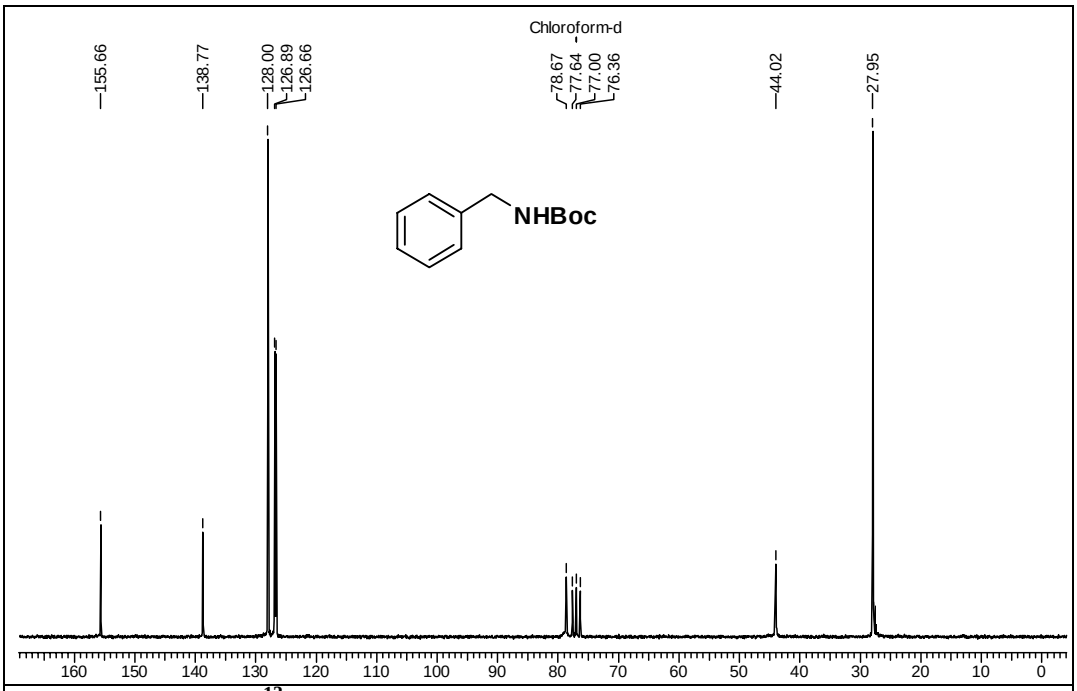
^{13}C NMR spectrum of 3b ($CDCl_3$, 50 MHz)



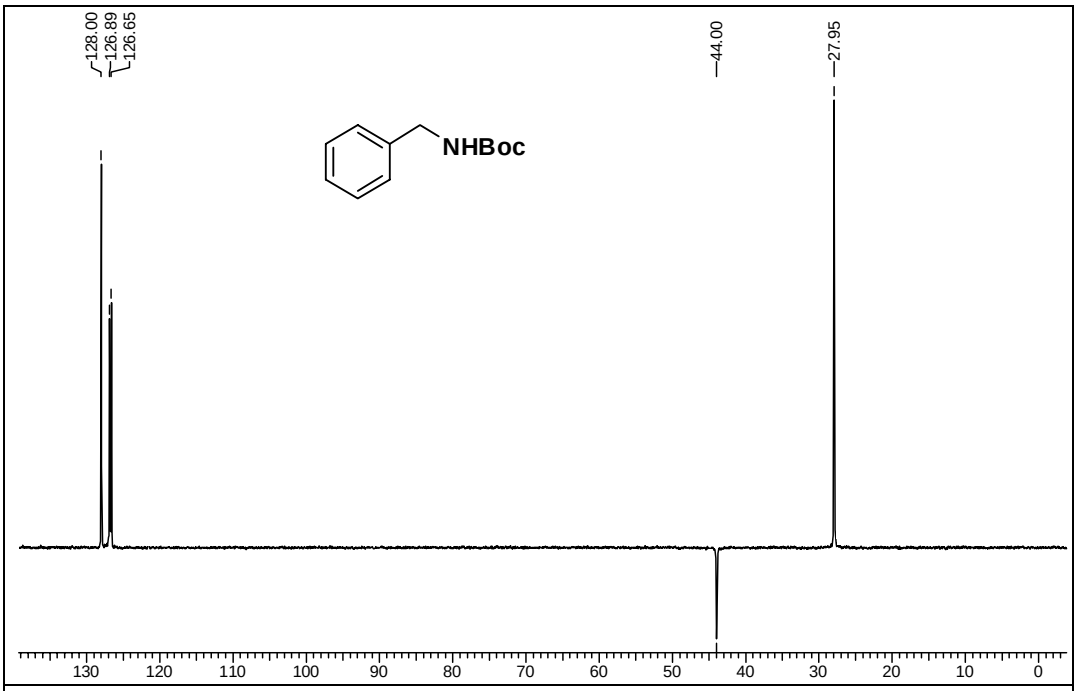
DEPT spectrum of 3b ($CDCl_3$, 50 MHz)



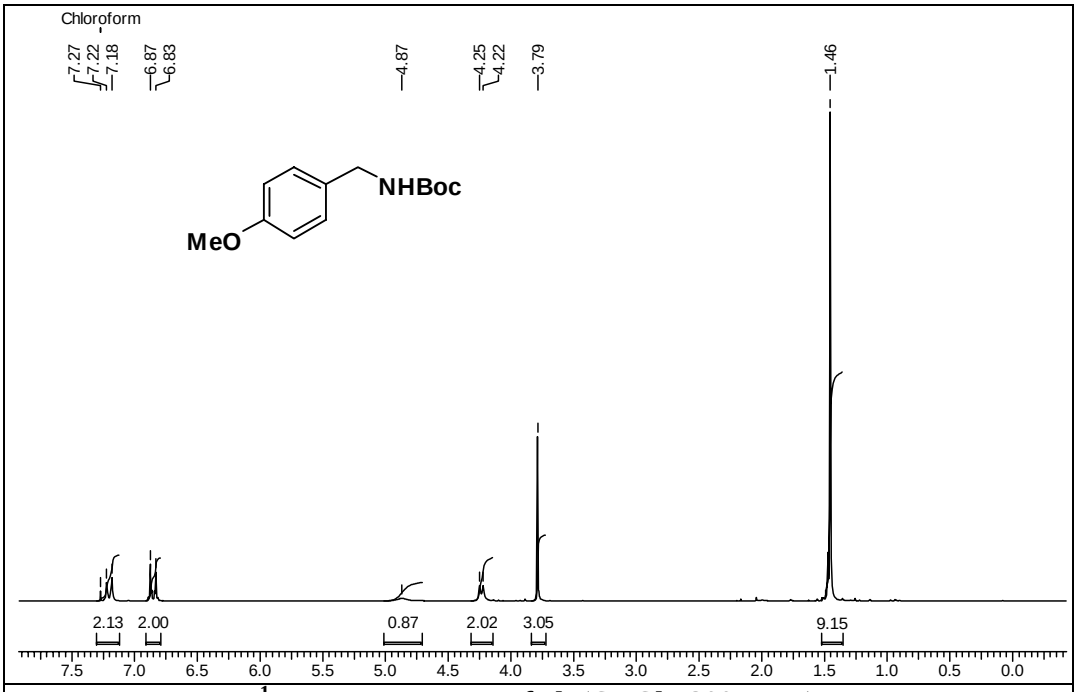
^{1}H NMR spectrum of 4b ($CDCl_3$, 200 MHz)



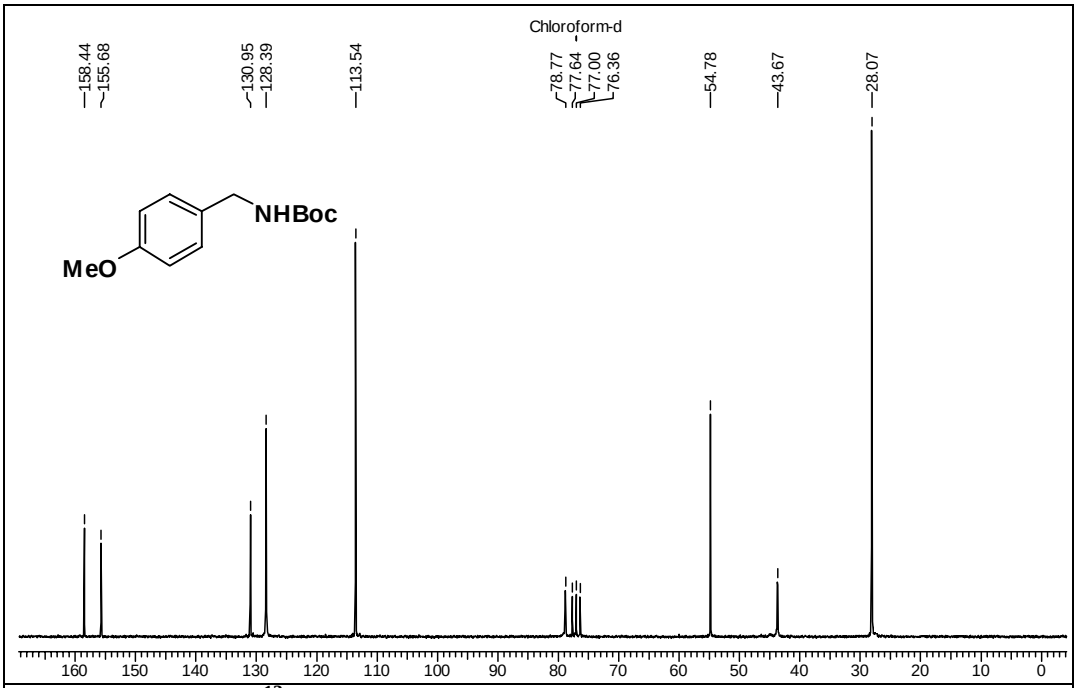
^{13}C NMR spectrum of 4b ($CDCl_3$, 50 MHz)



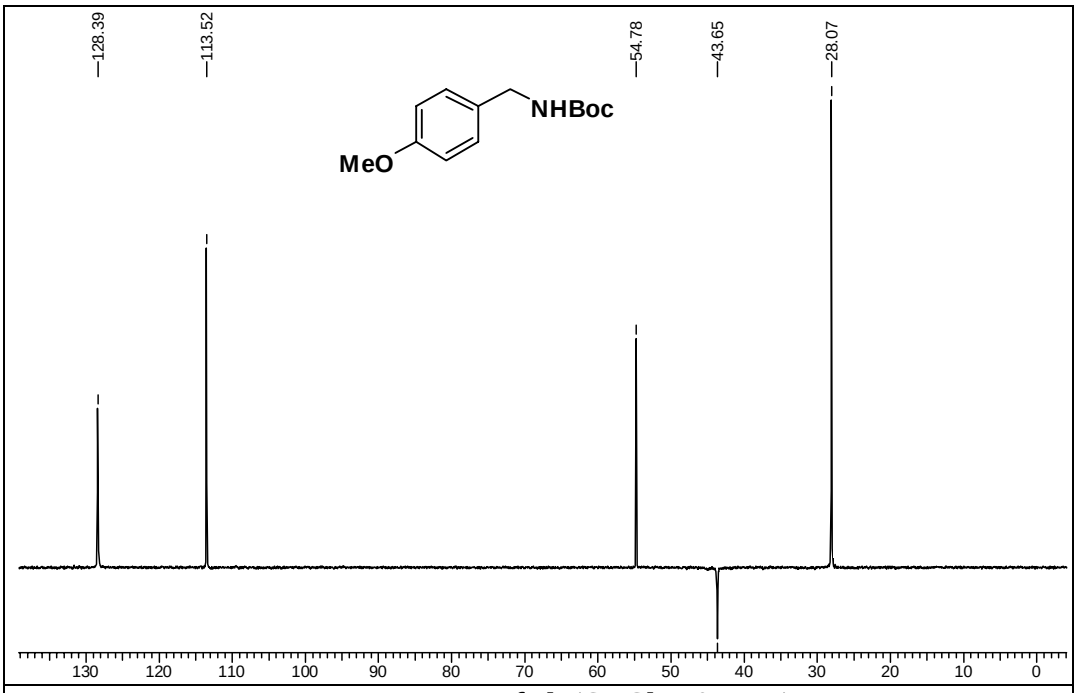
DEPT spectrum of 4b ($CDCl_3$, 50 MHz)



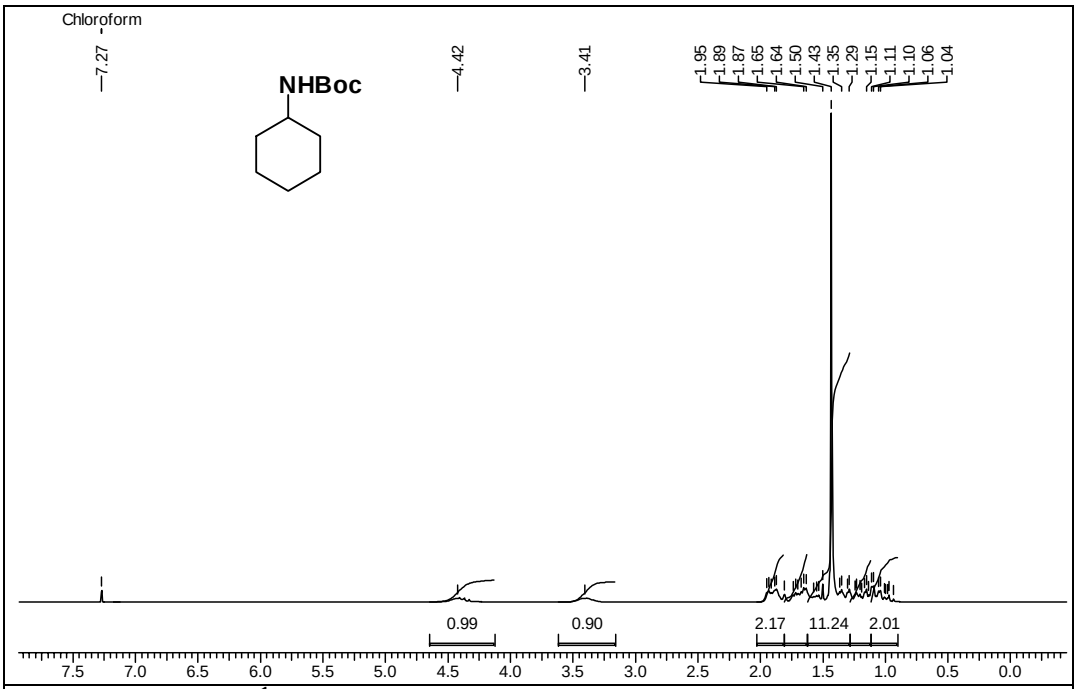
^{1}H NMR spectrum of 5b ($CDCl_3$, 200 MHz)



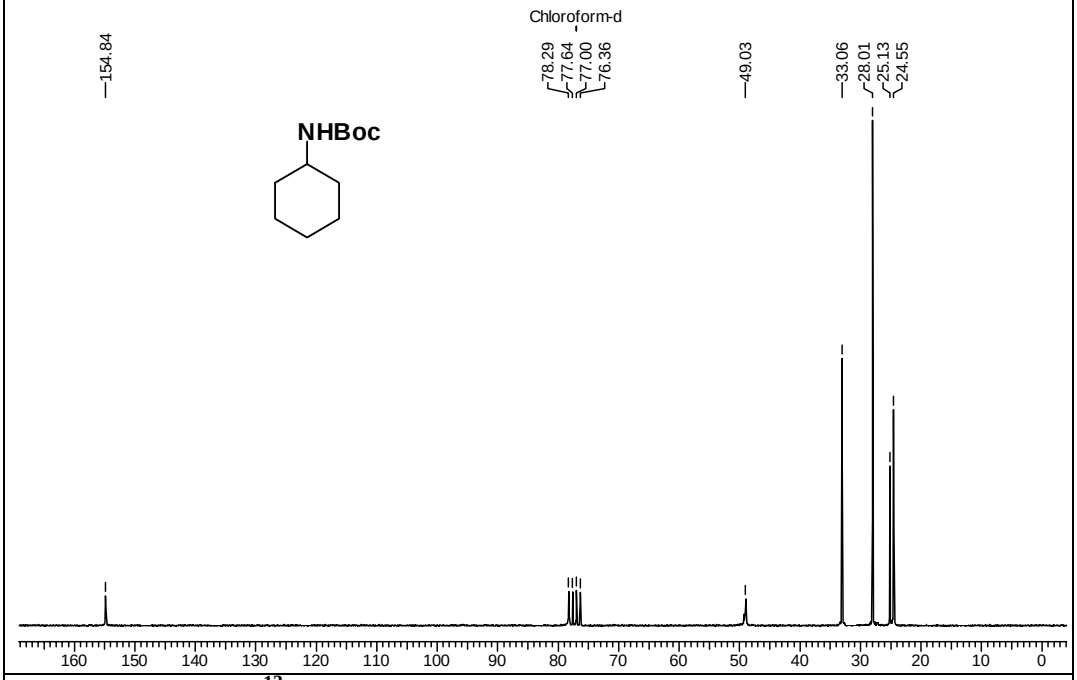
^{13}C NMR spectrum of 5b ($CDCl_3$, 50 MHz)



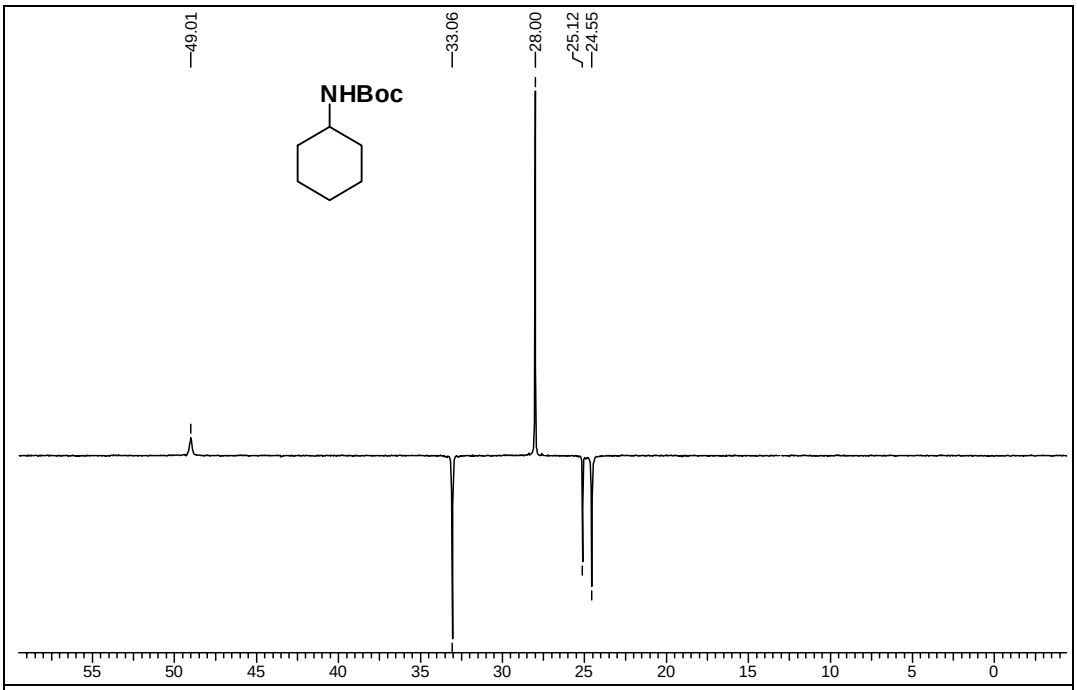
DEPT spectrum of 5b ($CDCl_3$, 50 MHz)



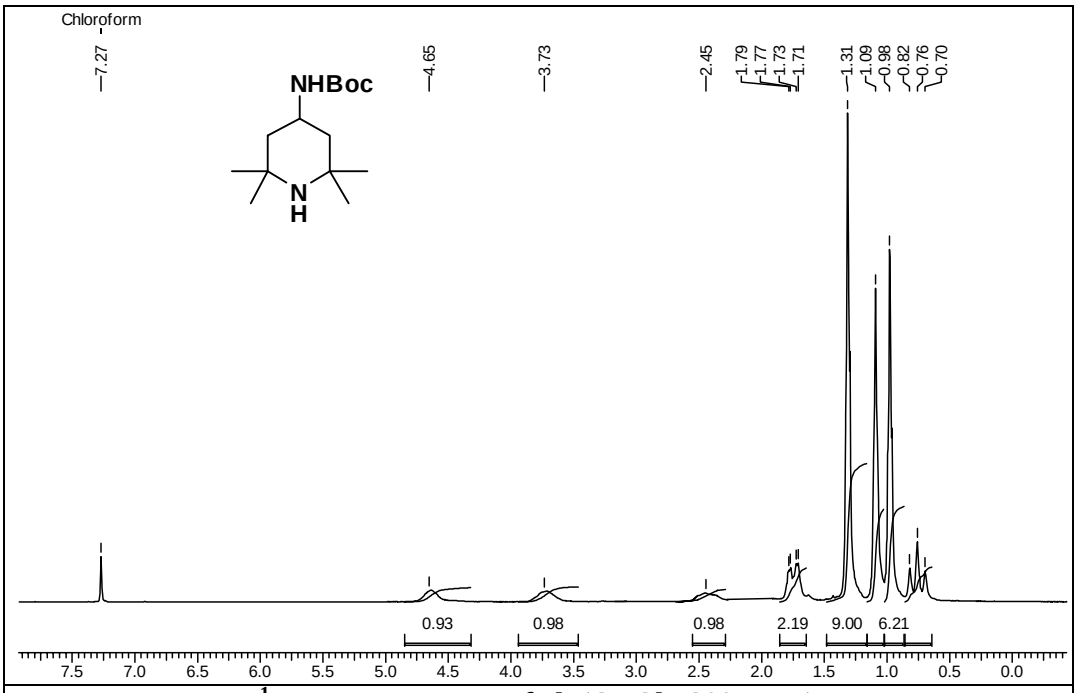
^{1}H NMR spectrum of 6b ($CDCl_3$, 200 MHz)



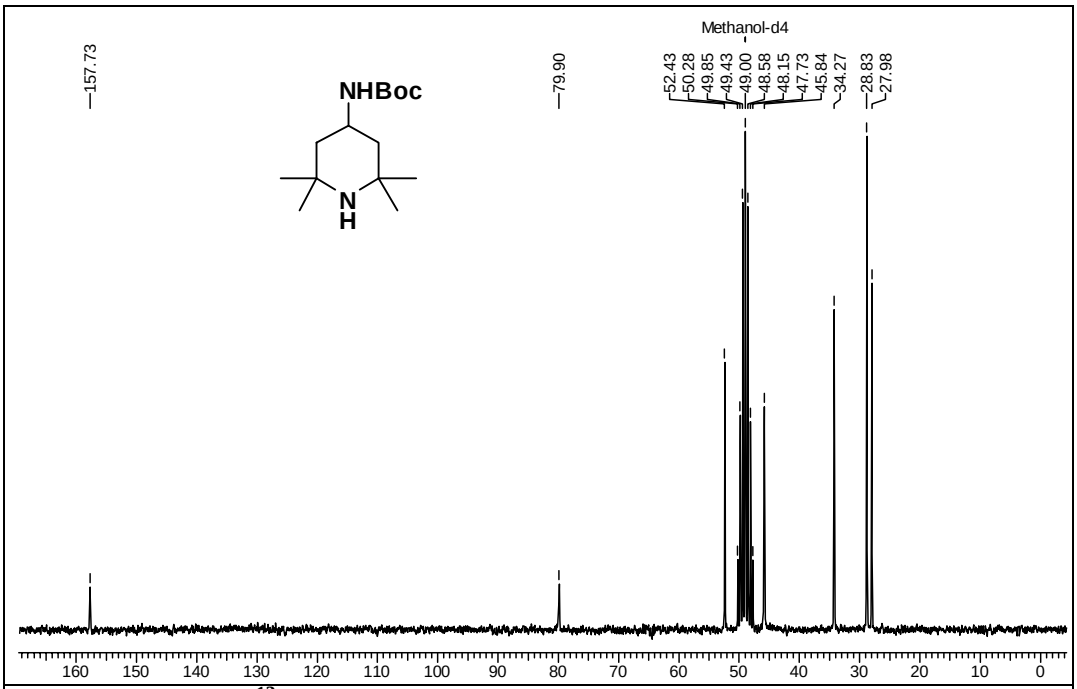
^{13}C NMR spectrum of 6b ($CDCl_3$, 50 MHz)



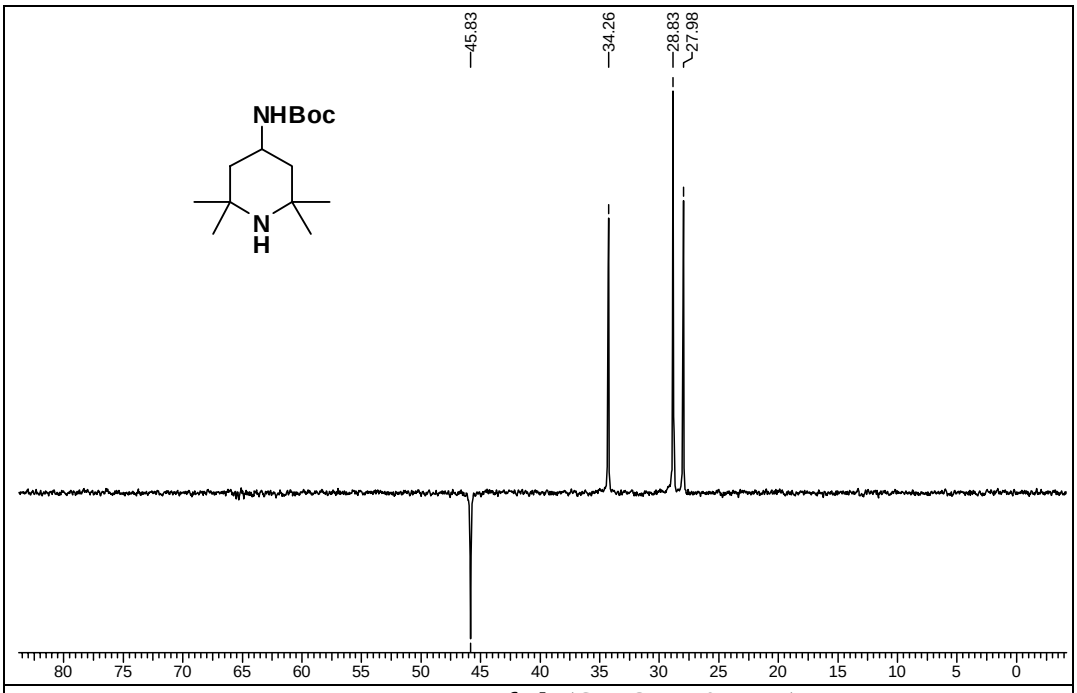
DEPT spectrum of 6b ($CDCl_3$, 50 MHz)



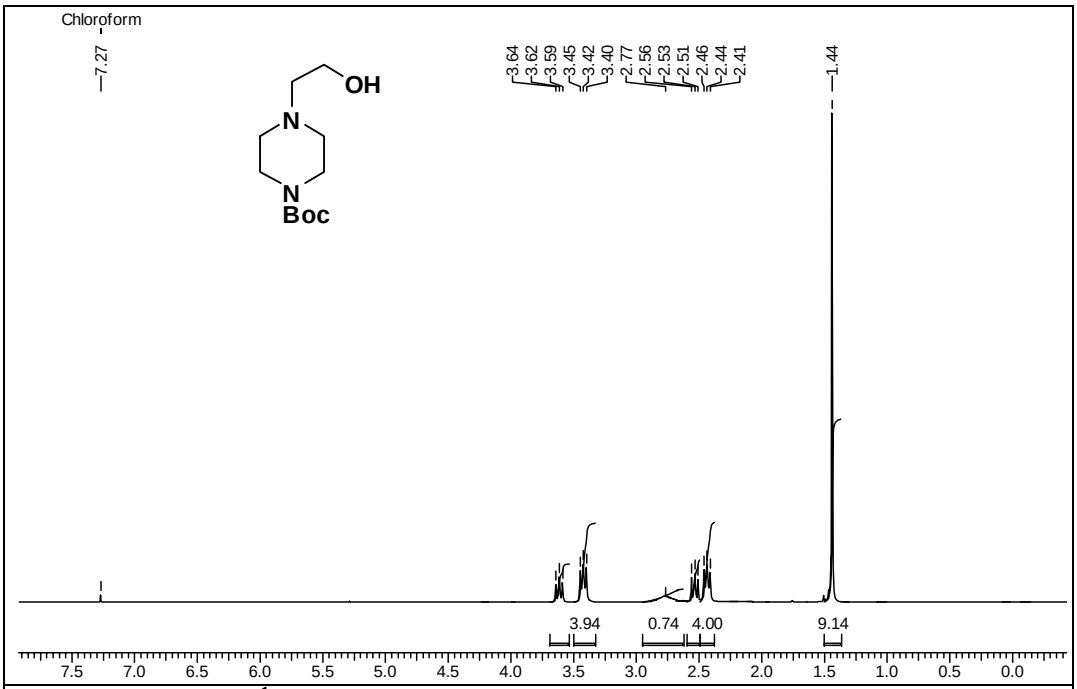
^{1}H NMR spectrum of 7b ($CDCl_3$, 200 MHz)



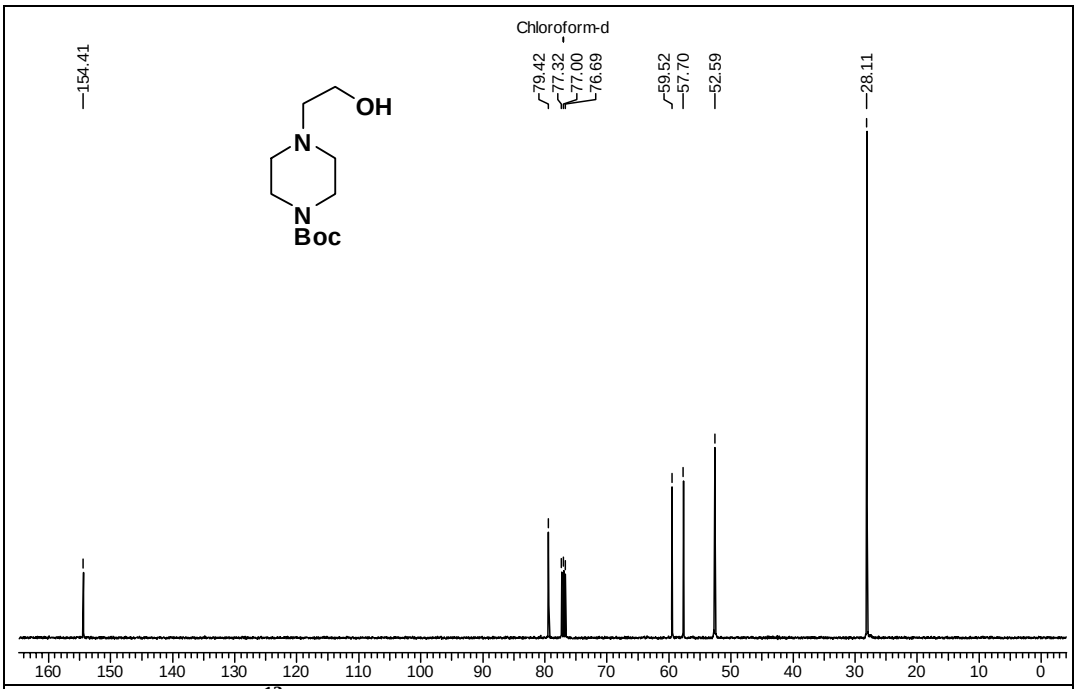
^{13}C NMR spectrum of 7b (CD_3OD, 50 MHz)



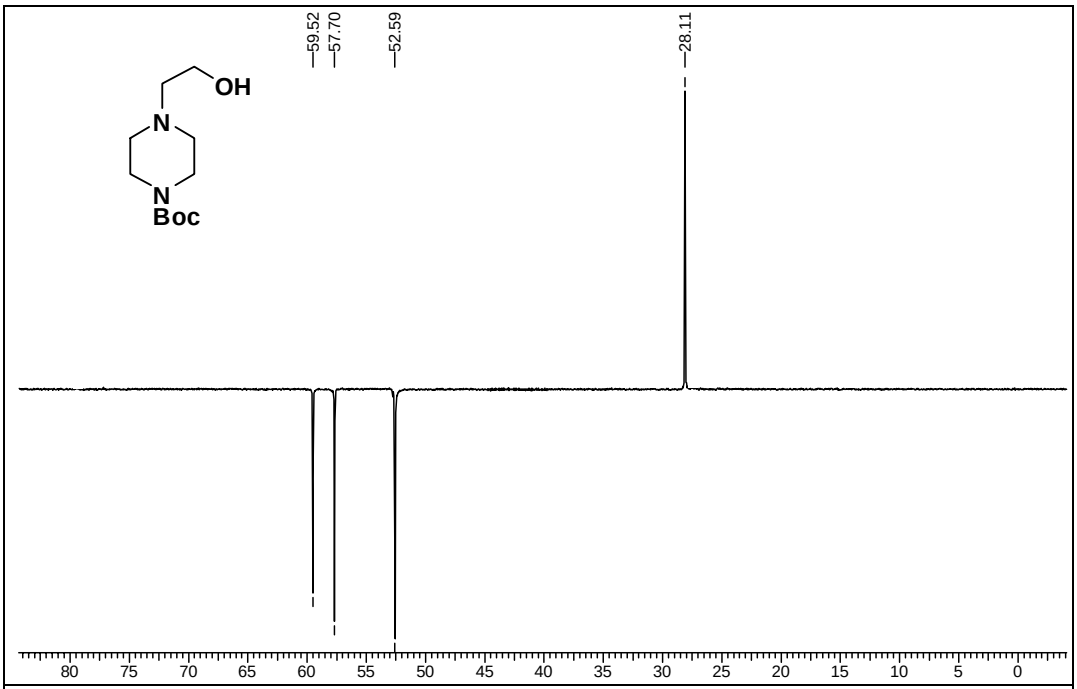
DEPT spectrum of 7b (CD_3OD, 50 MHz)



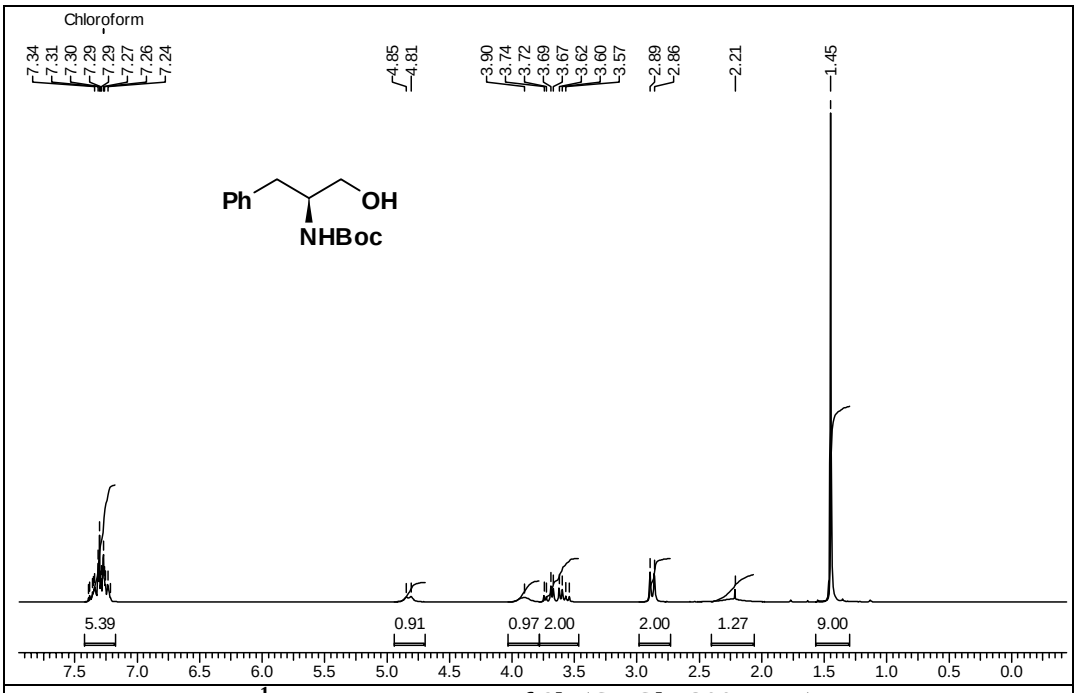
^{1}H NMR spectrum of 8b ($CDCl_3$, 200 MHz)



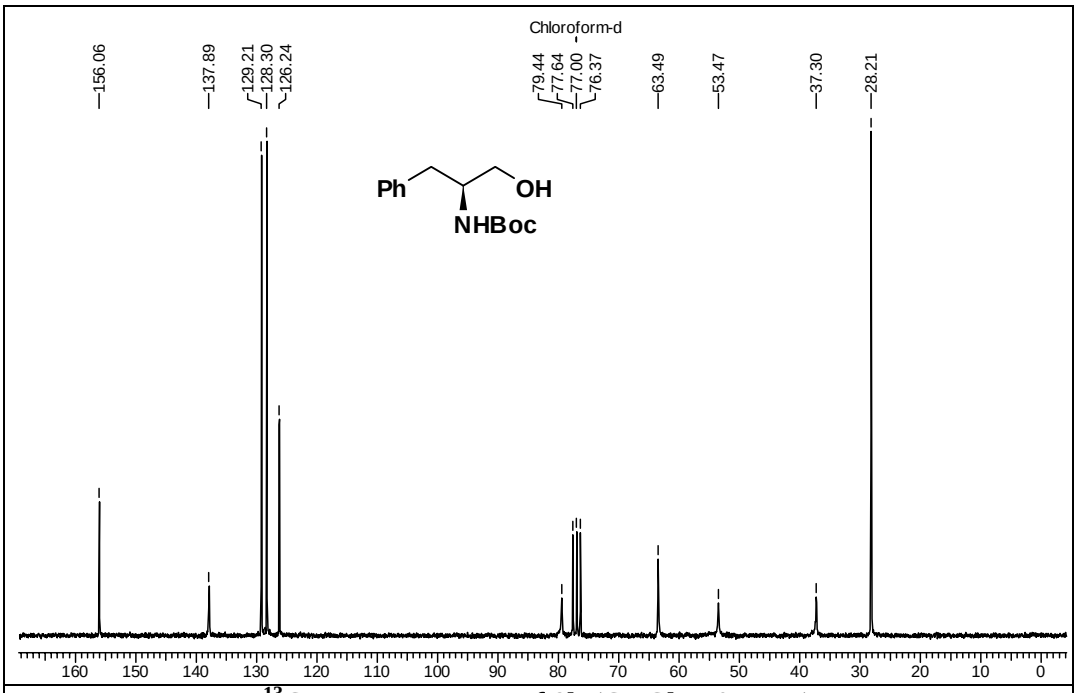
^{13}C NMR spectrum of 8b ($CDCl_3$, 50 MHz)



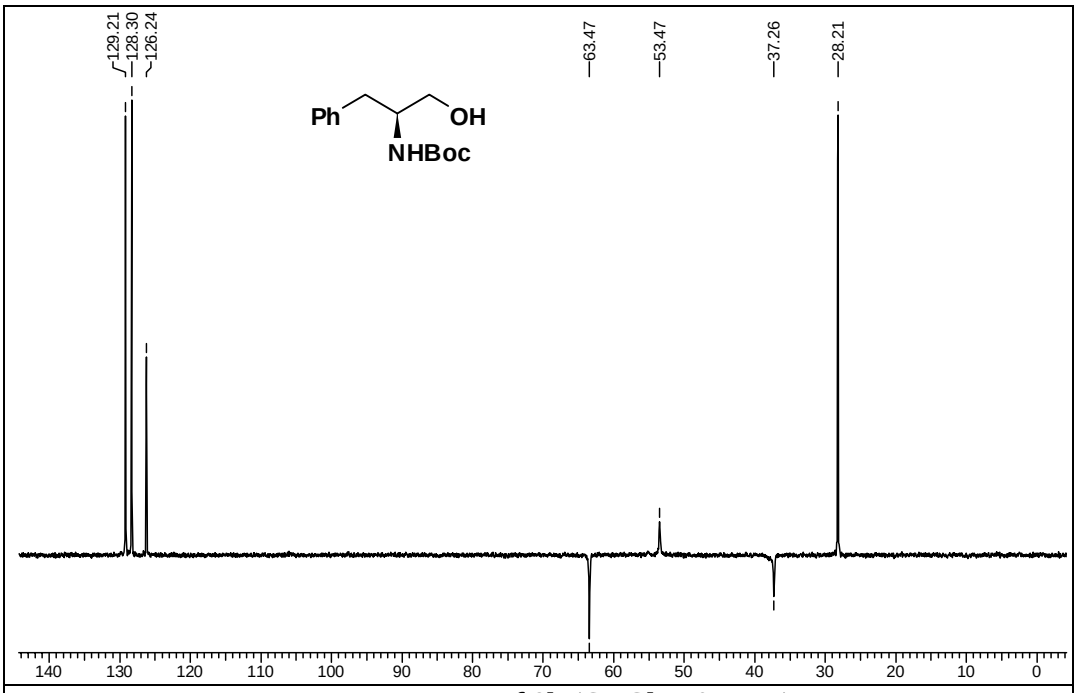
DEPT spectrum of 8b ($CDCl_3$, 50 MHz)



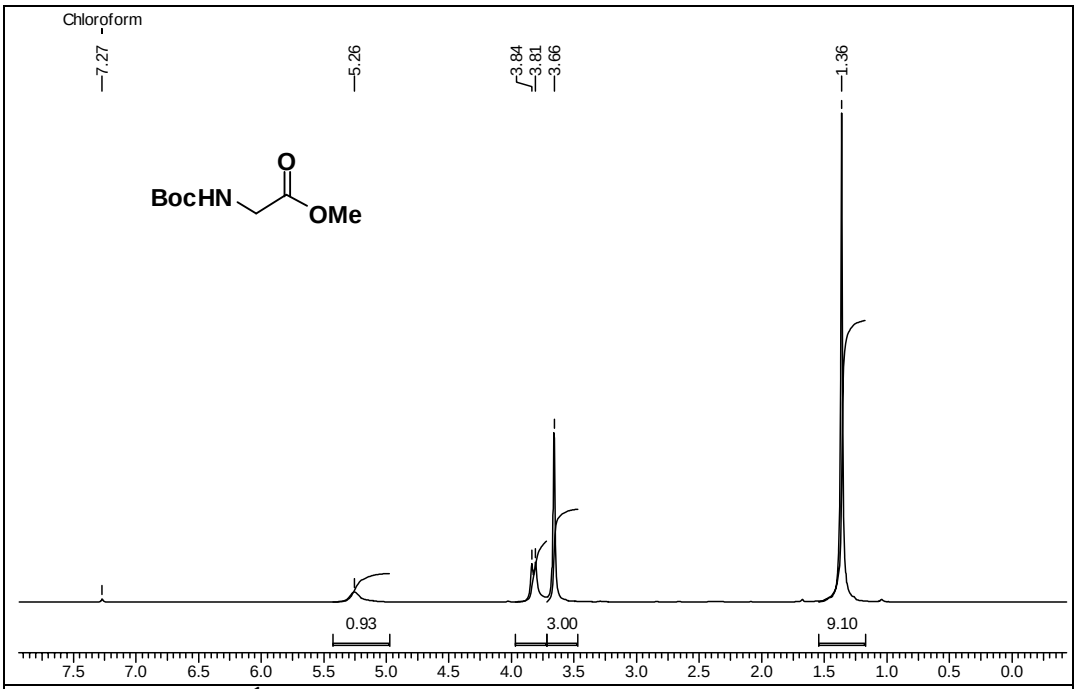
^{1}H NMR spectrum of 9b ($CDCl_3$, 200 MHz)



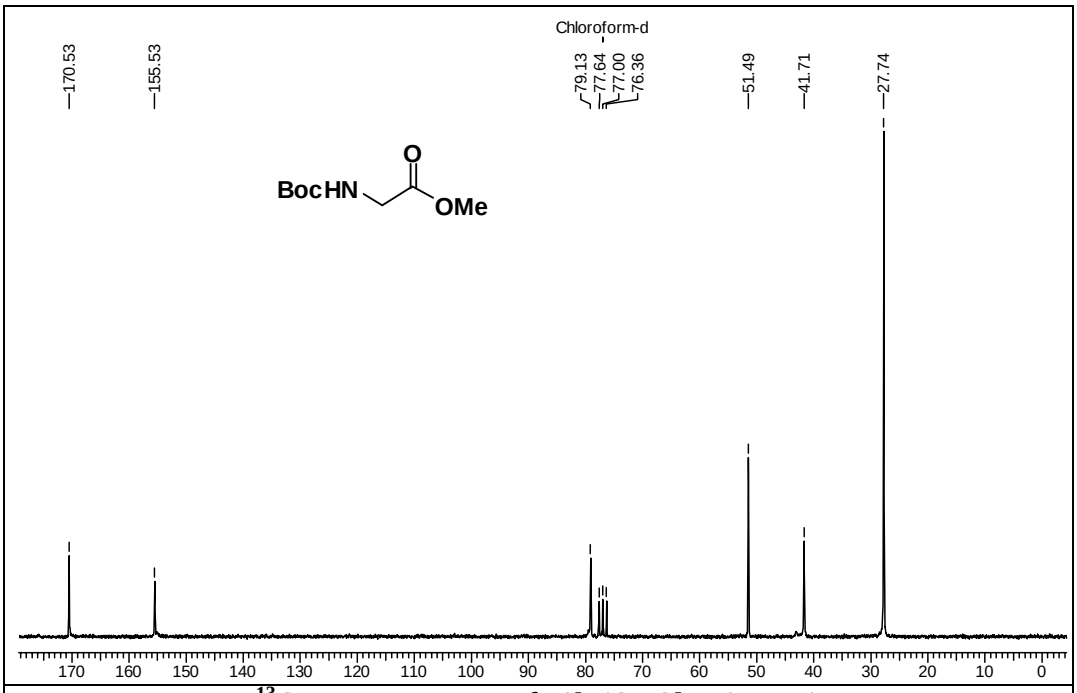
^{13}C NMR spectrum of 9b ($CDCl_3$, 50 MHz)



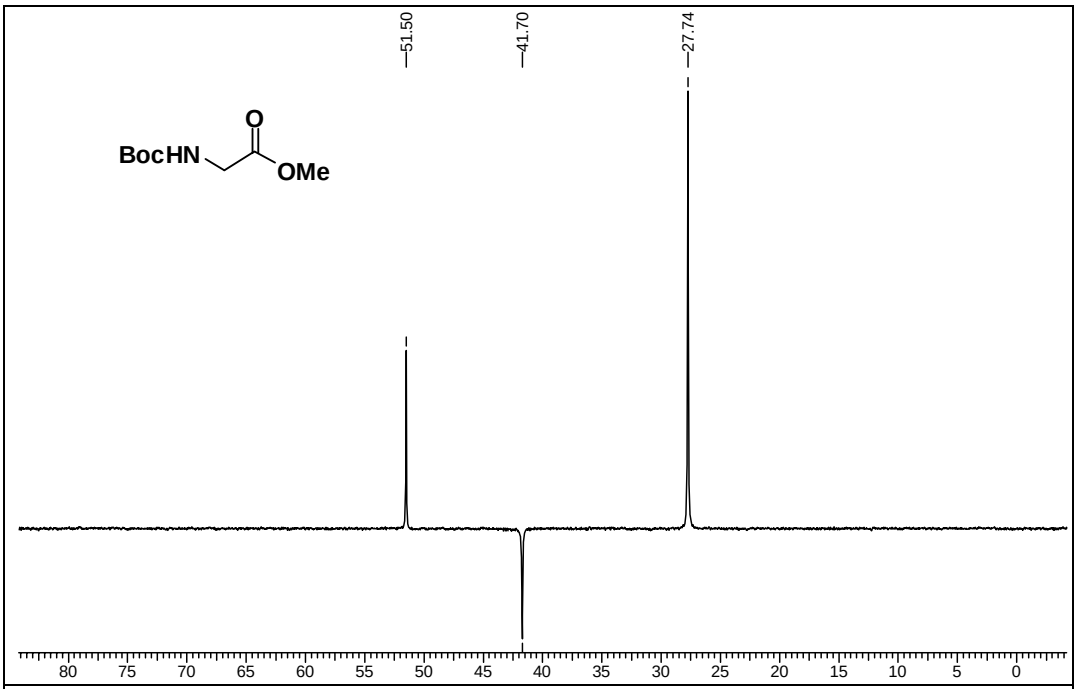
DEPT spectrum of 9b ($CDCl_3$, 50 MHz)



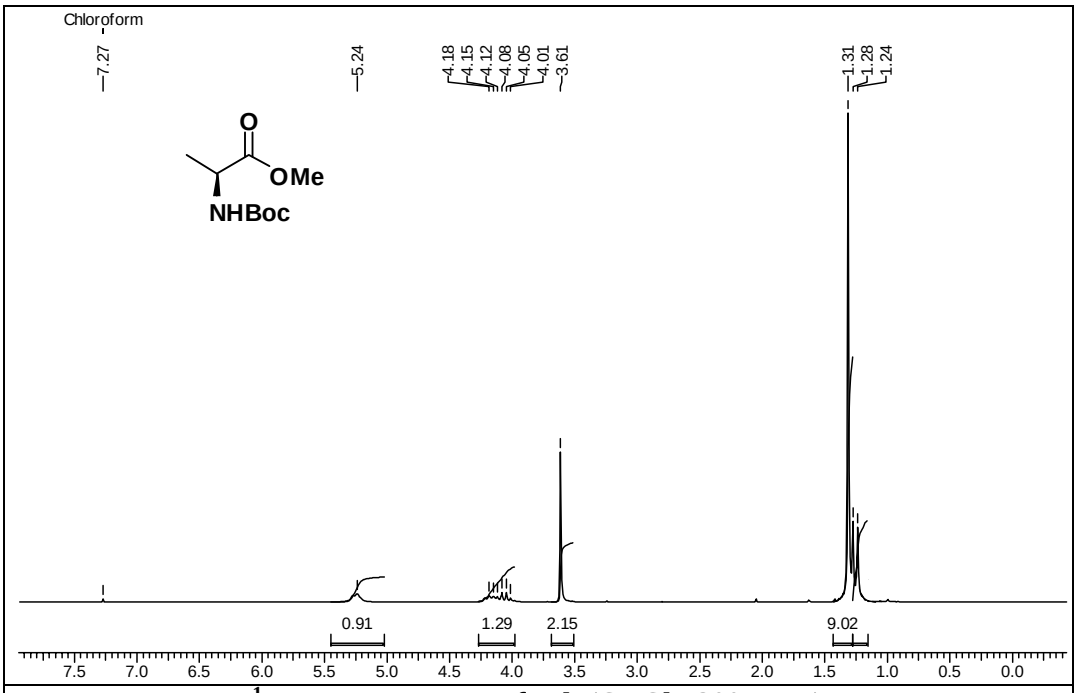
^{1}H NMR spectrum of 10b ($CDCl_3$, 200 MHz)



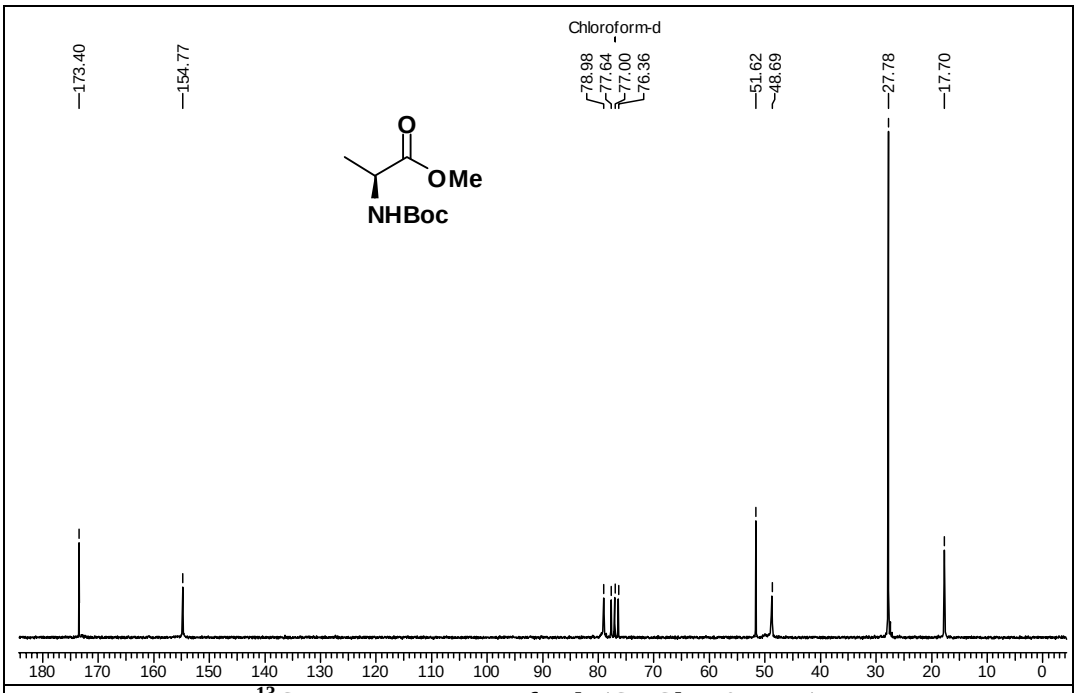
^{13}C NMR spectrum of 10b ($CDCl_3$, 50 MHz)



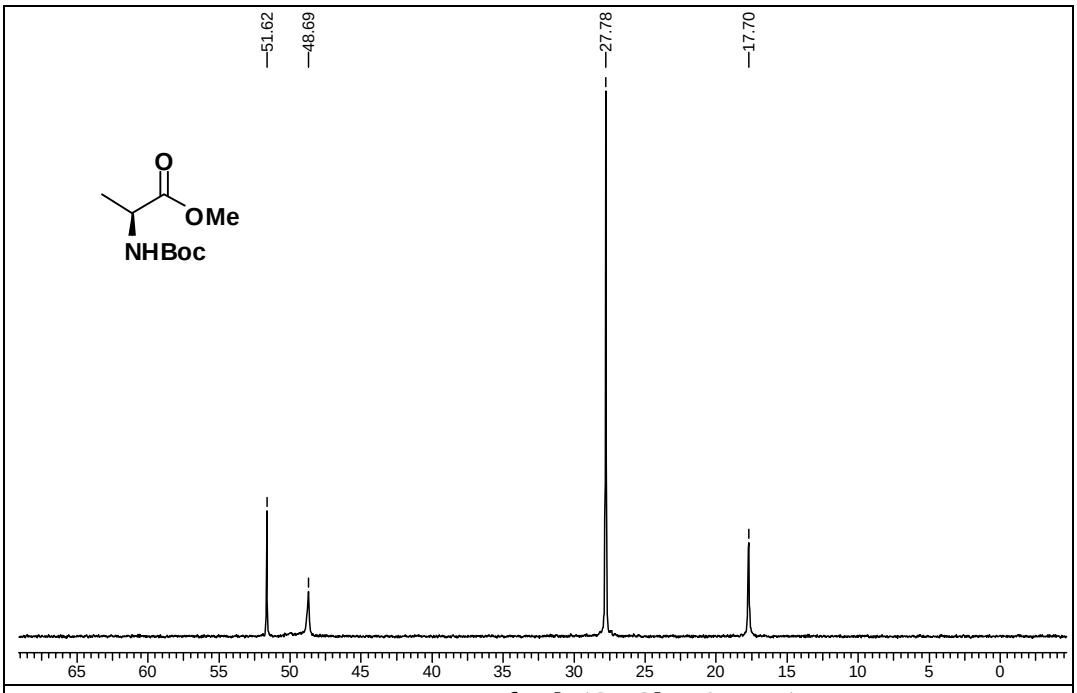
DEPT spectrum of 10b ($CDCl_3$, 50 MHz)



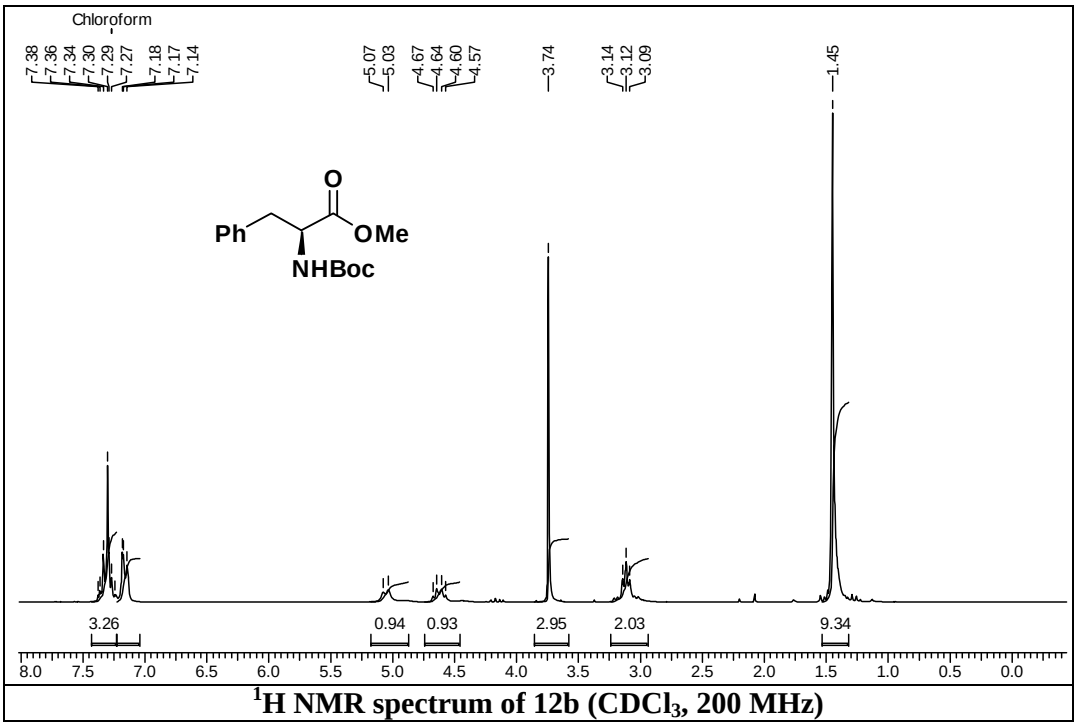
^{1}H NMR spectrum of 11b ($CDCl_3$, 200 MHz)



^{13}C NMR spectrum of 11b ($CDCl_3$, 50 MHz)



DEPT spectrum of 11b ($CDCl_3$, 50 MHz)



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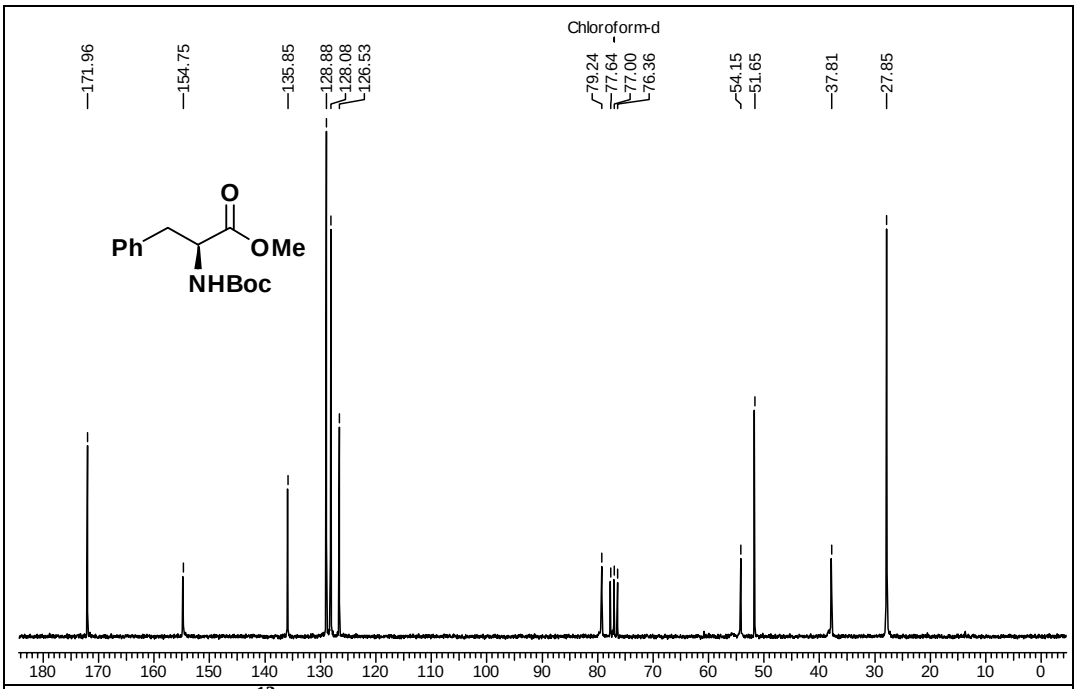

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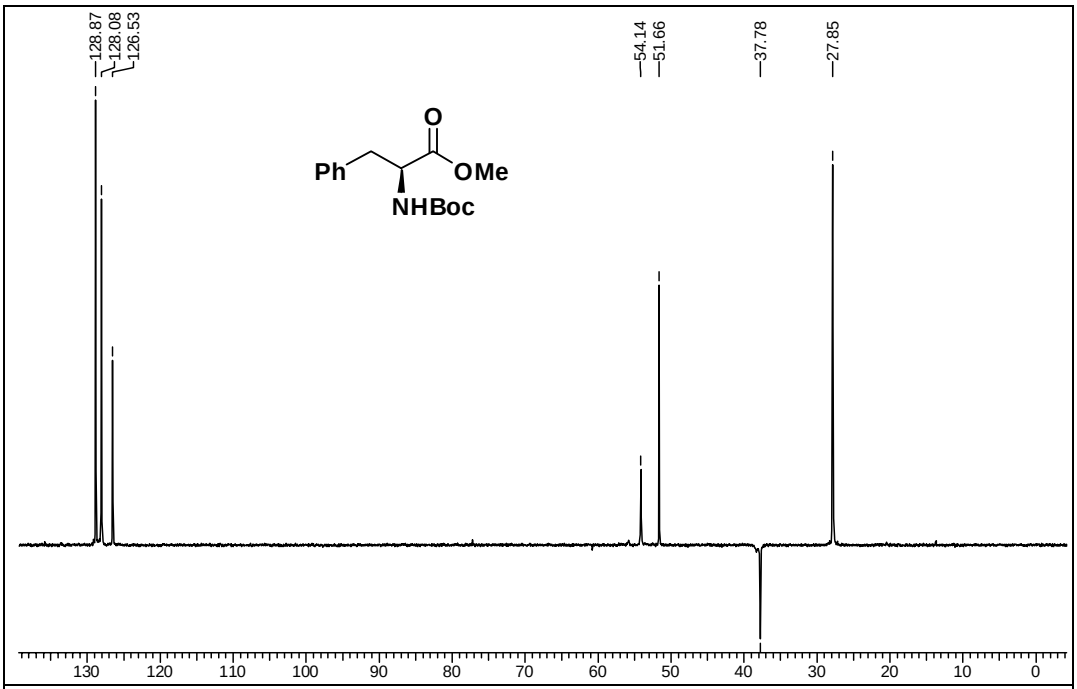
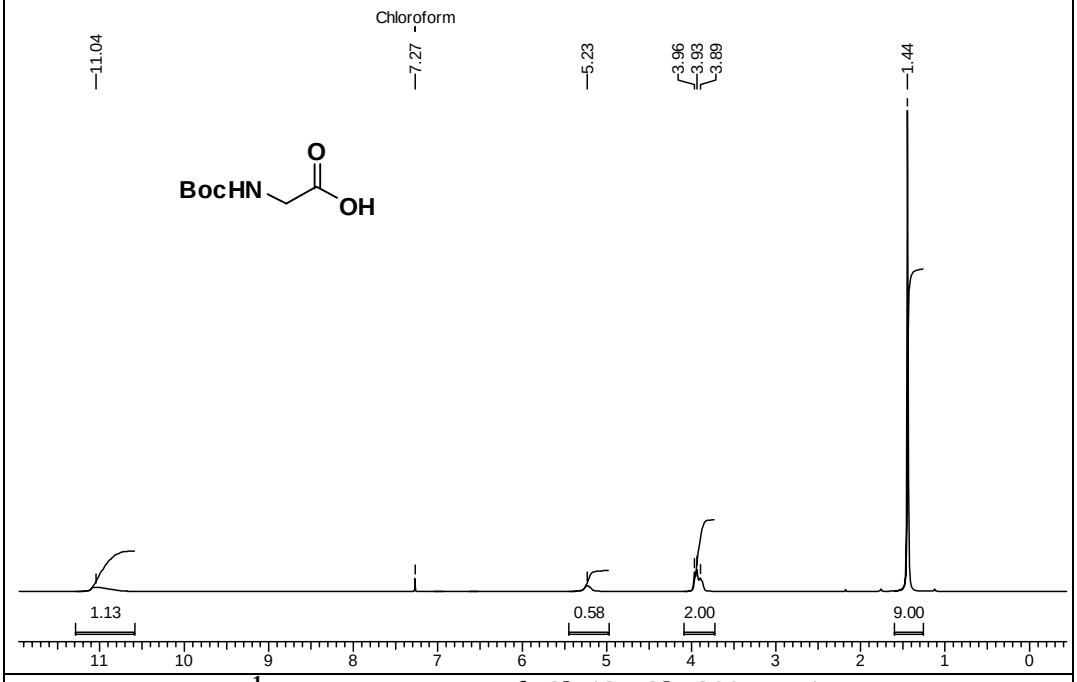


DEPT spectrum of 12b ($CDCl_3$, 50 MHz)



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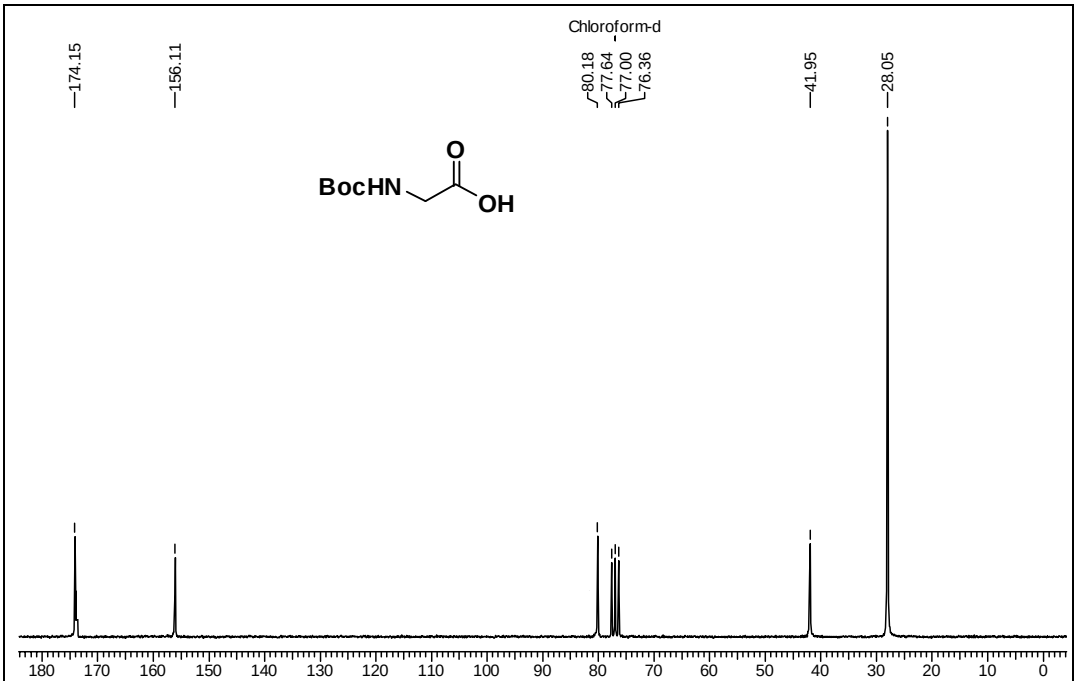

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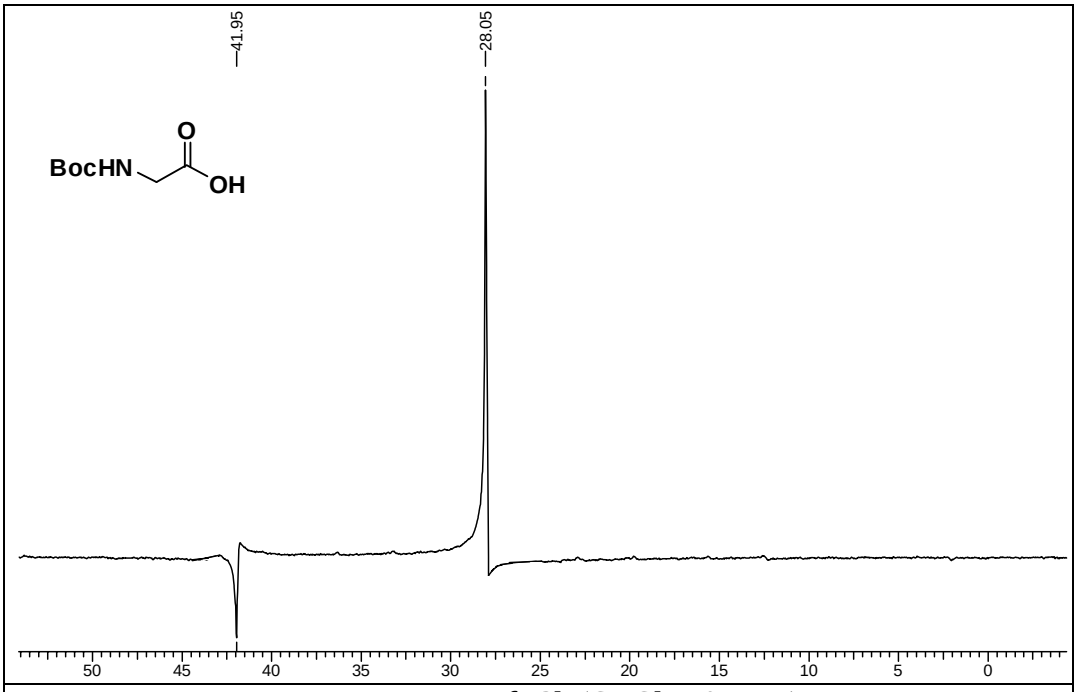
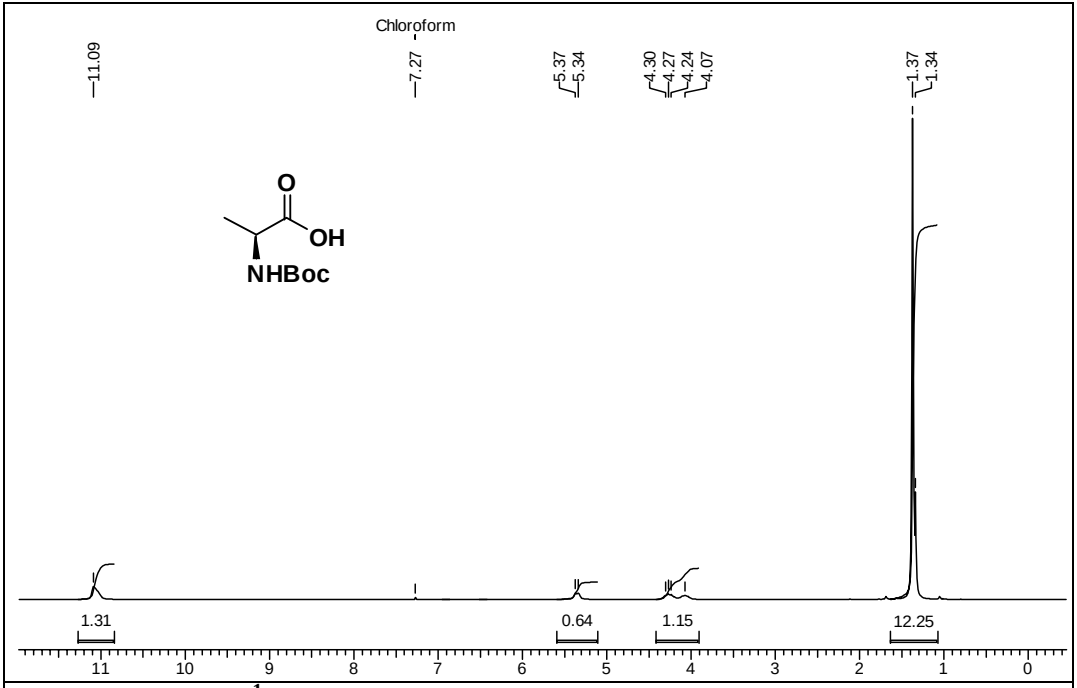
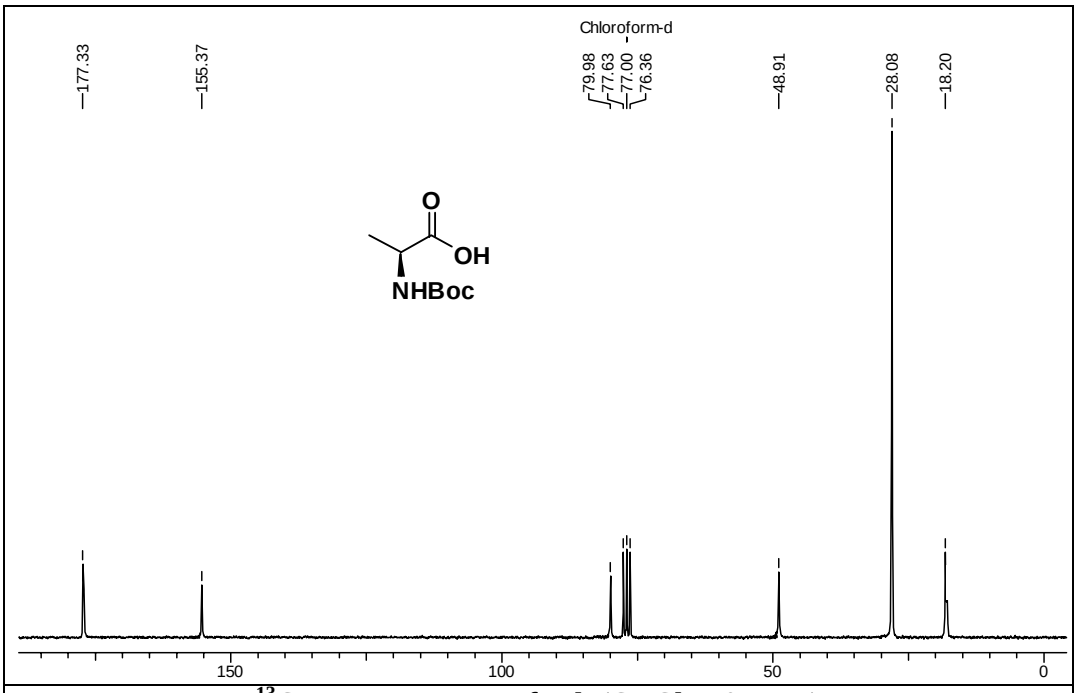


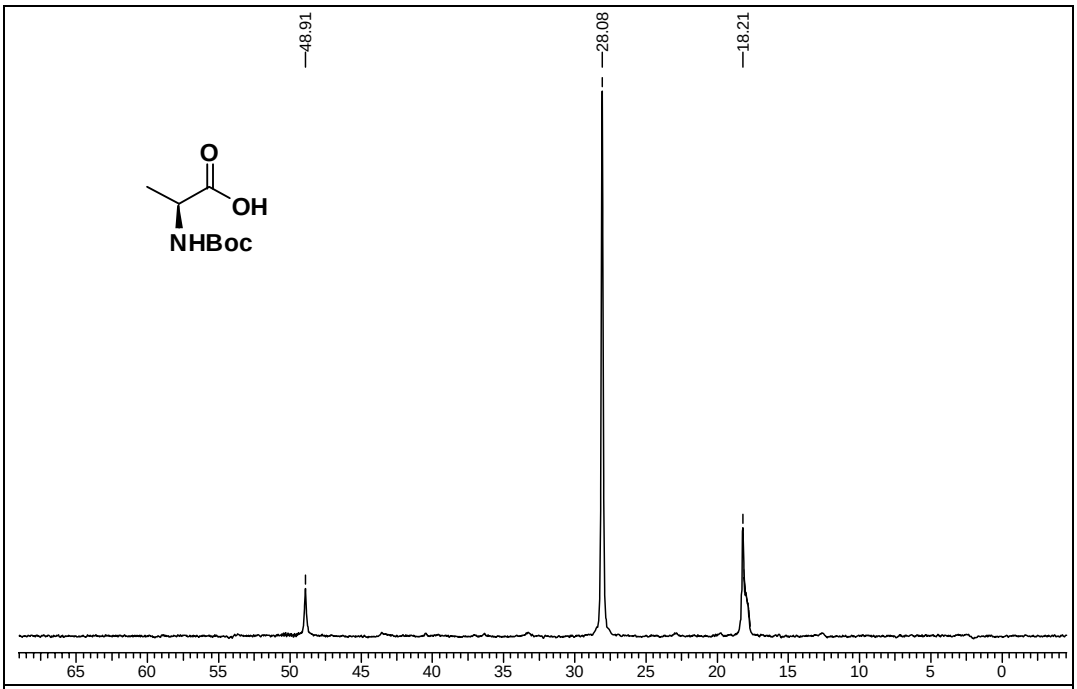
DEPT spectrum of 13b ($CDCl_3$, 50 MHz)



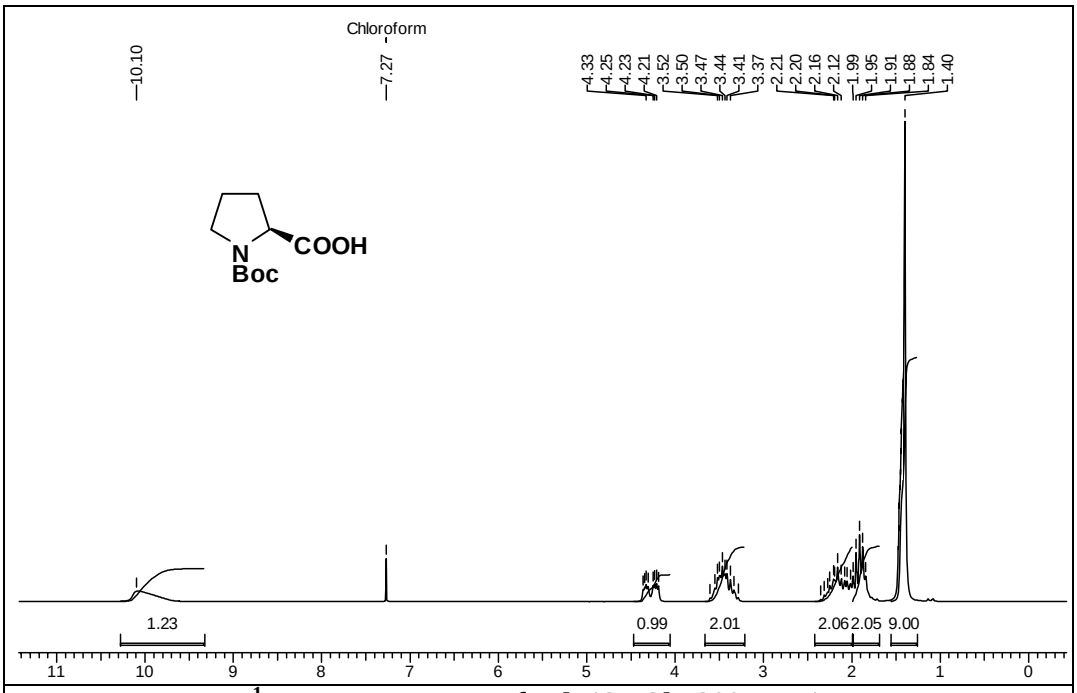
^{1}H NMR spectrum of 14b ($CDCl_3$, 200 MHz)



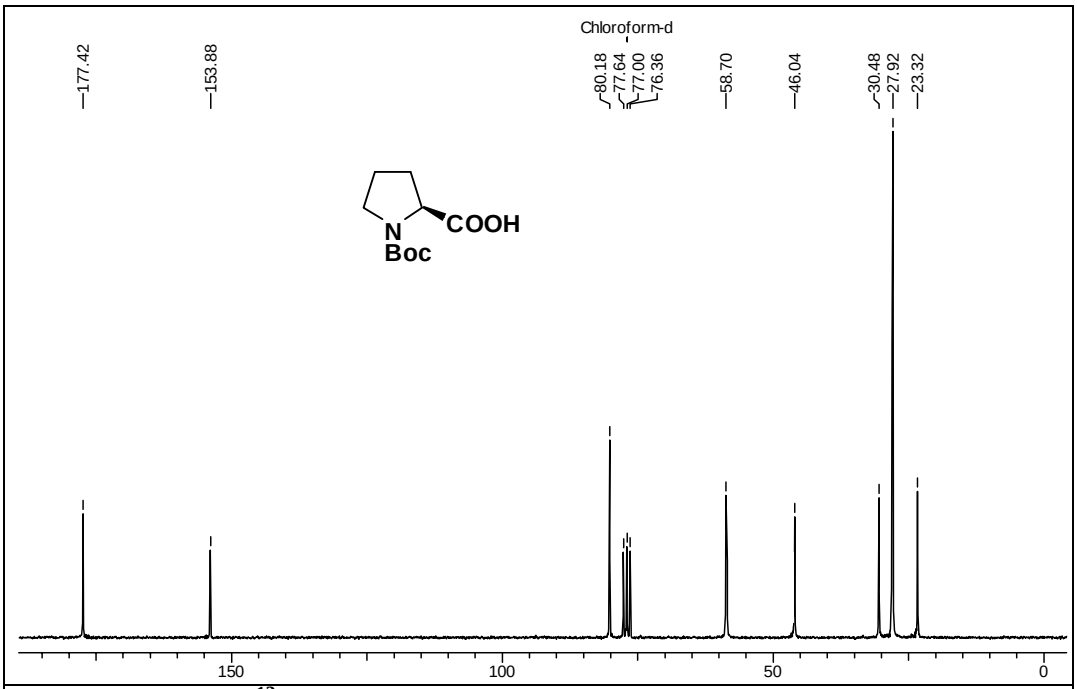
^{13}C NMR spectrum of 14b ($CDCl_3$, 50 MHz)



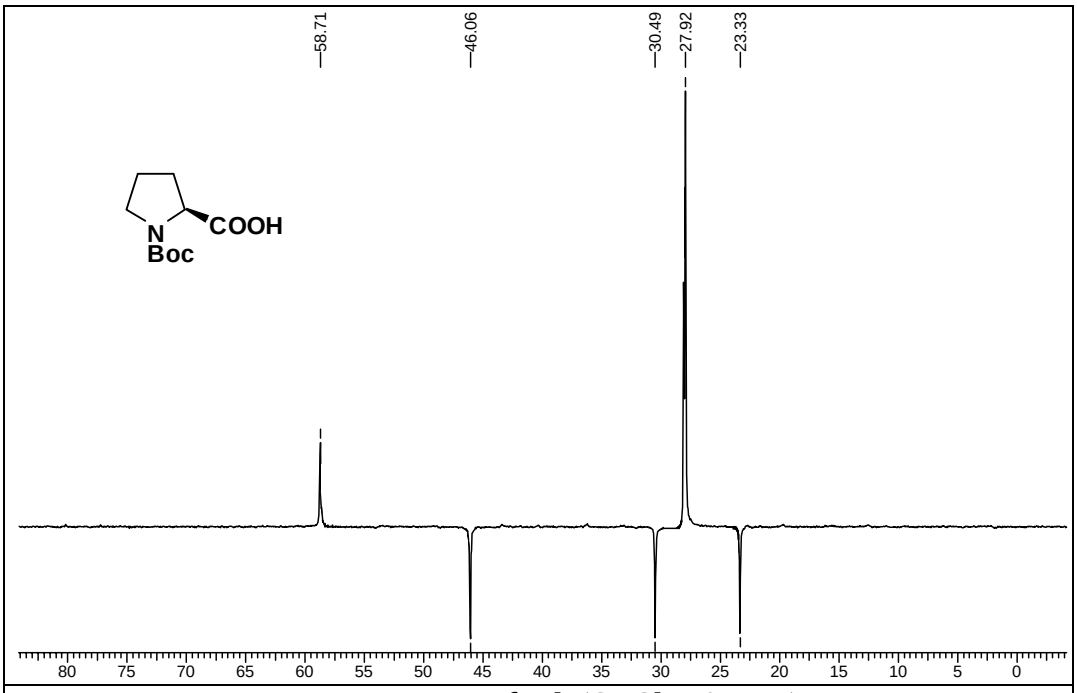
DEPT spectrum of 14b ($CDCl_3$, 50 MHz)



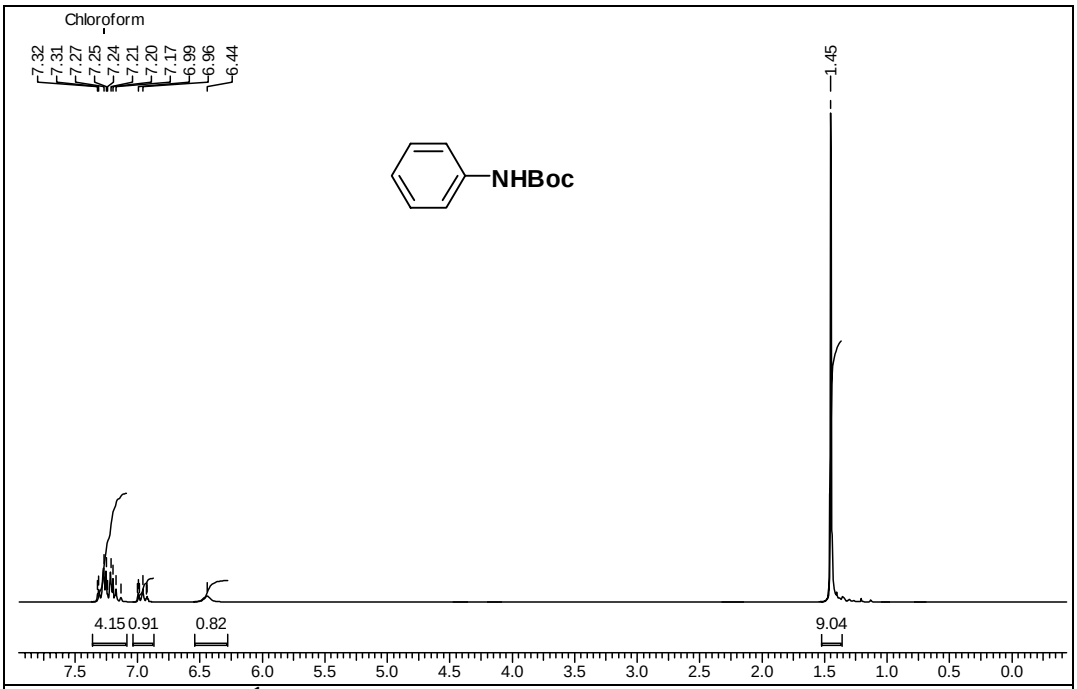
^{1}H NMR spectrum of 15b ($CDCl_3$, 200 MHz)



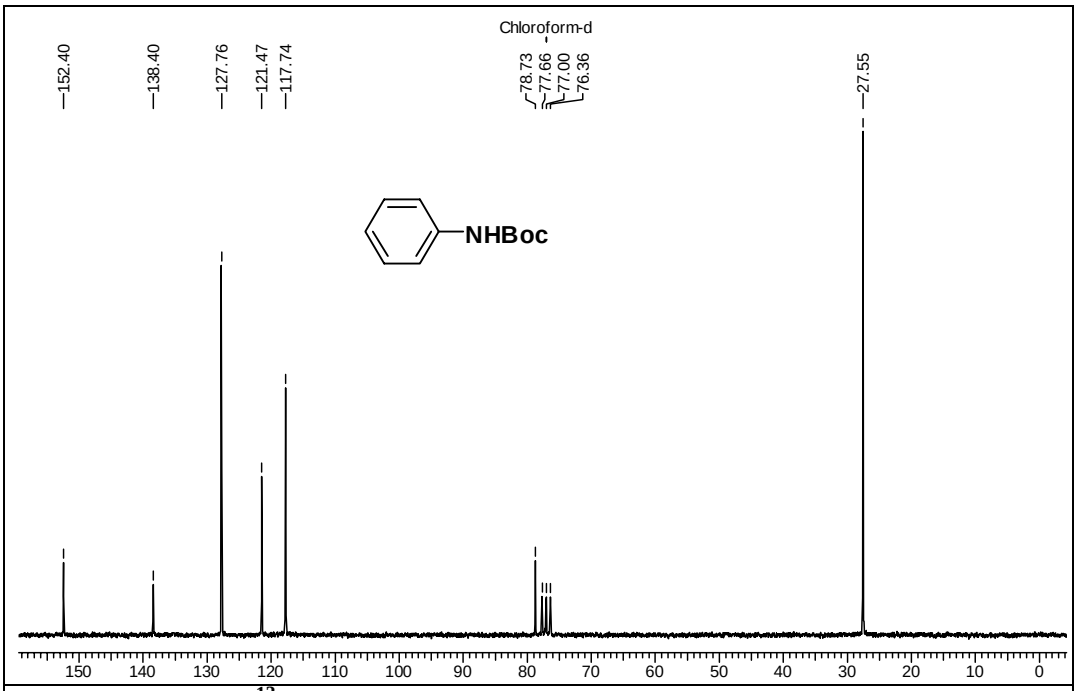
^{13}C NMR spectrum of 15b ($CDCl_3$, 50 MHz)



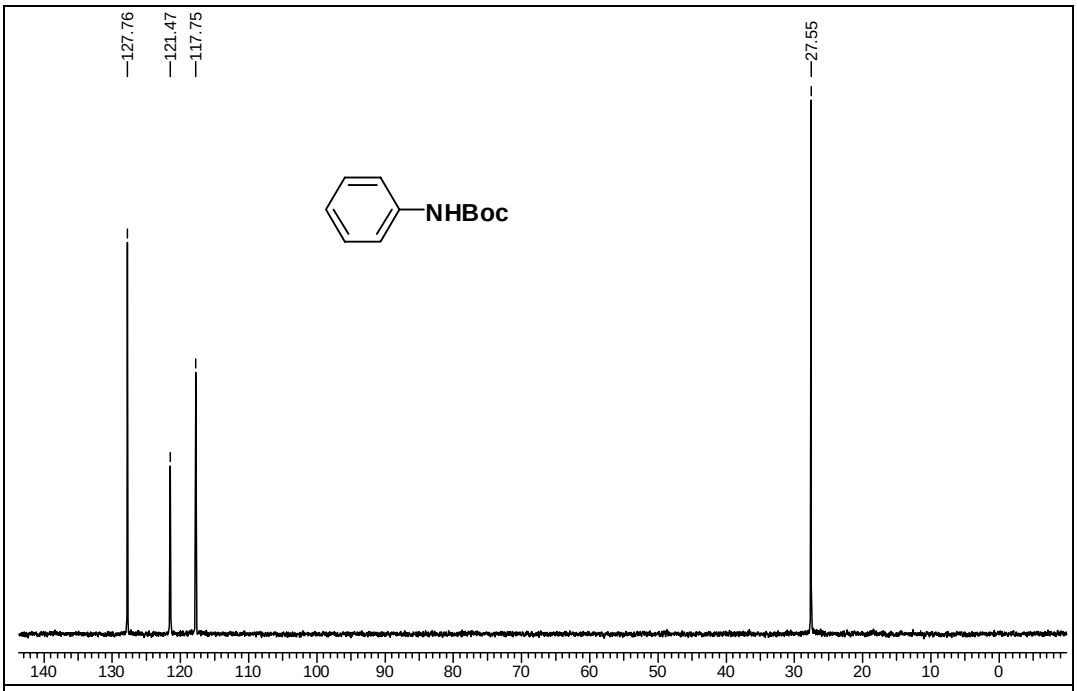
DEPT spectrum of 15b ($CDCl_3$, 50 MHz)



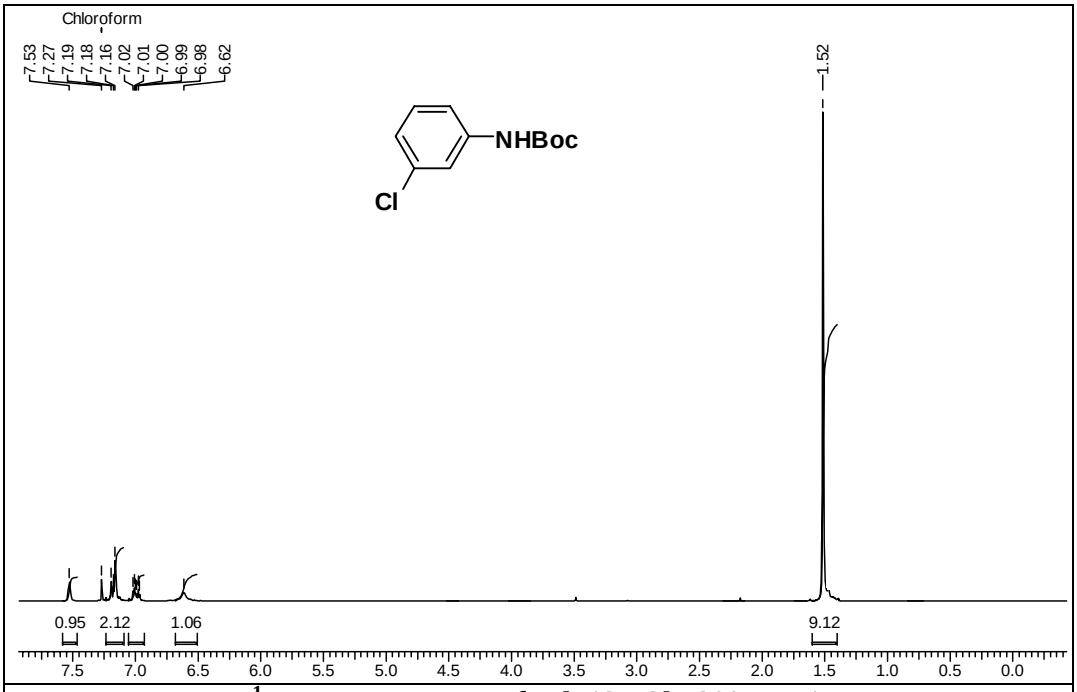
^{1}H NMR spectrum of 16b ($CDCl_3$, 200 MHz)



^{13}C NMR spectrum of 16b ($CDCl_3$, 50 MHz)



DEPT spectrum of 16b ($CDCl_3$, 50 MHz)



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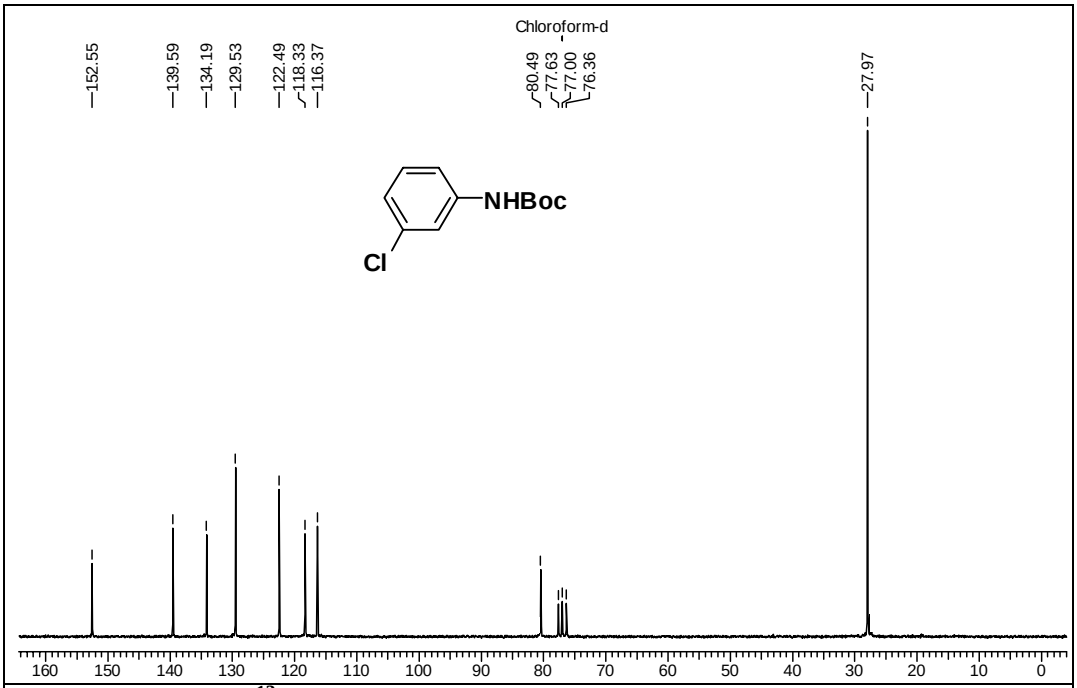
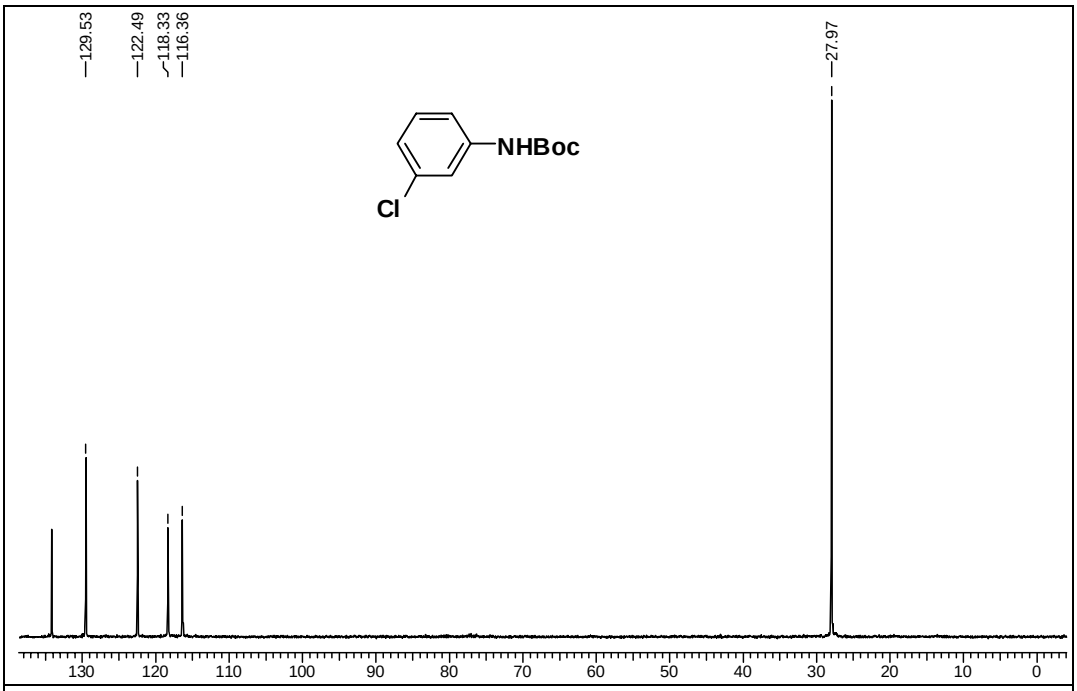
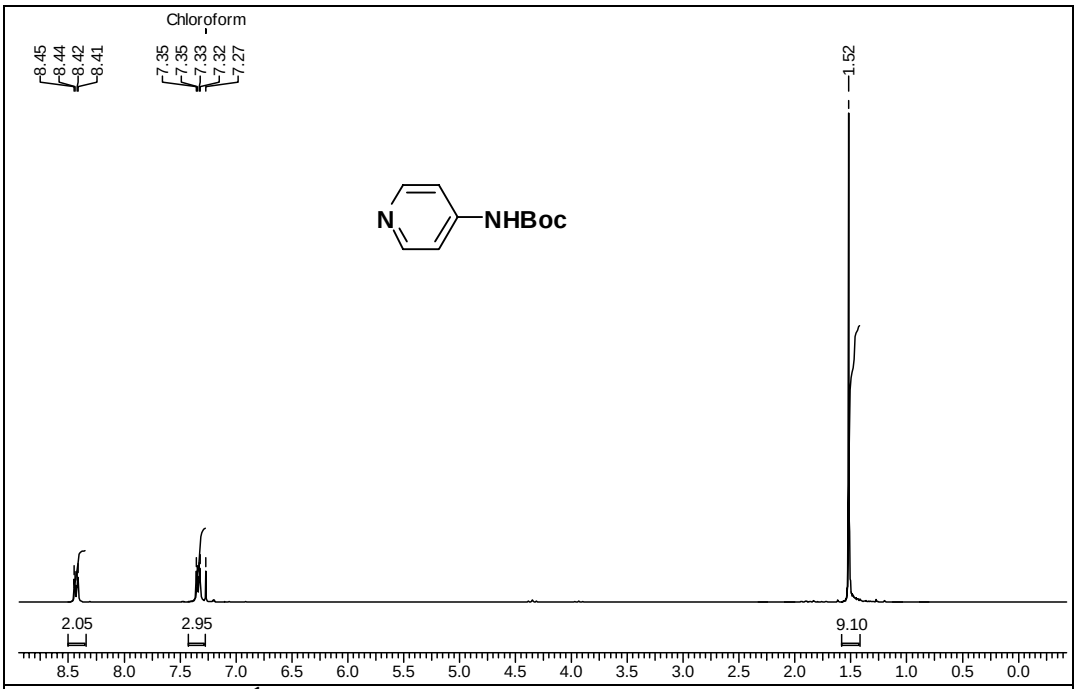


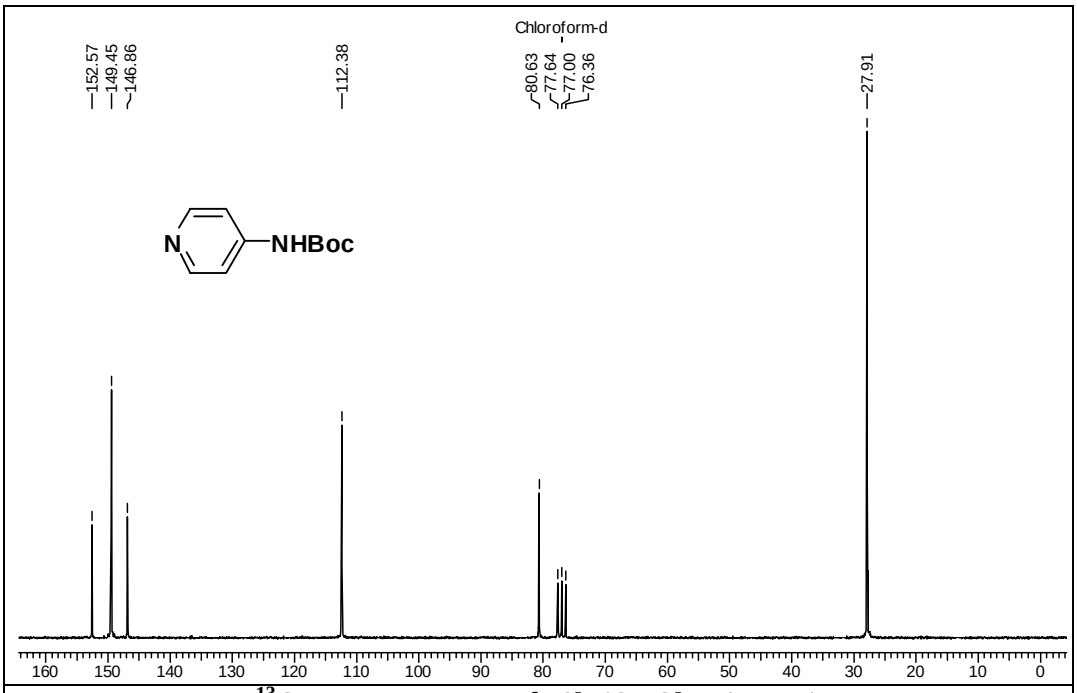
^{13}C NMR spectrum of 17b ($CDCl_3$, 50 MHz)



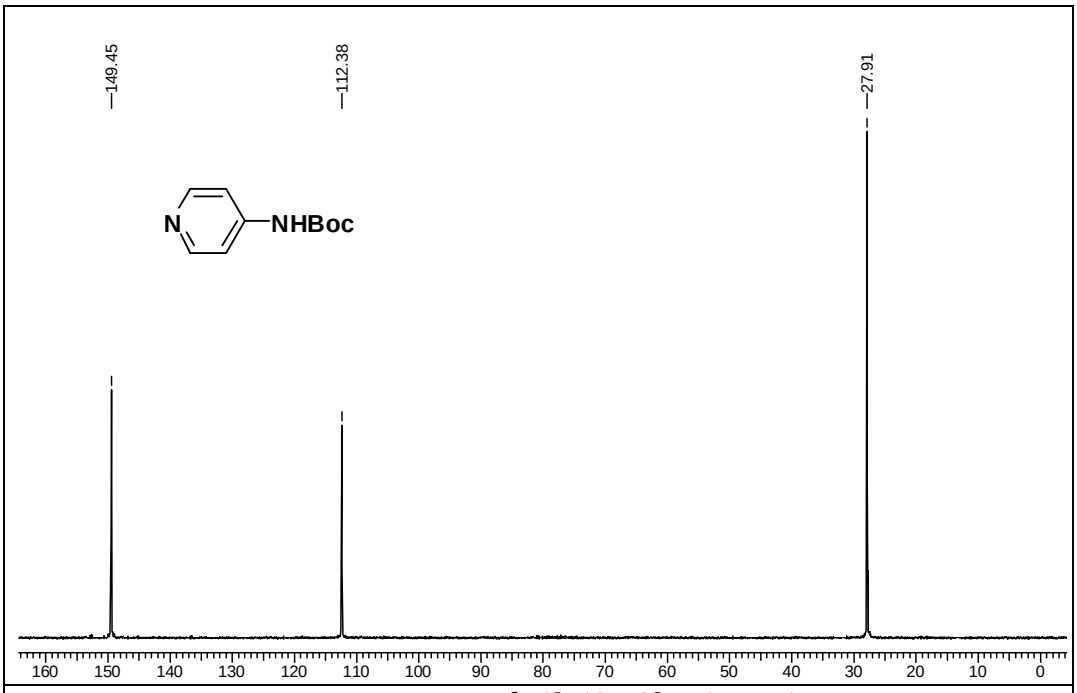
DEPT spectrum of 17b ($CDCl_3$, 50 MHz)



^{1}H NMR spectrum of 18b ($CDCl_3$, 200 MHz)



^{13}C NMR spectrum of 18b ($CDCl_3$, 50 MHz)



DEPT spectrum of 18b ($CDCl_3$, 50 MHz)

4.3.7 References

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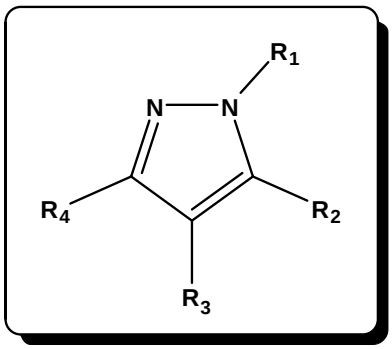
Section 4

[Bbim]Br mediated synthesis of 1,3,5-triphenyl-1*H*-pyrazoles

[Bbim]Br mediated synthesis of 1,3,5-triphenyl-1*H*-pyrazoles

4.4.1 Introduction

Aryl pyrazole, a five-membered heterocycle containing two adjacent nitrogen atoms, is a ubiquitous motif found in a number of small molecules with important biological activities (Figure 1). In the past decade, interest in aryl pyrazole chemistry has significantly increased mainly due to the discovery of the interesting properties exhibited by a large number of aryl pyrazole derivatives. Many of them are potentially used in agricultural activities and also exhibited a wide range of pharmacological properties, including anti-microbial, anti-inflammatory, hypoglycemic, anti-hypertensive, antifungal and analgesic properties.[1,2] The 1-arylpyrazole motif is present in drugs such as cyclooxygenase-2 (Cox-2) inhibitors and protein kinase inhibitors. Some 1,5-diarylpyrazole derivatives exhibit inhibitory activities of the HIV-1 reverse transcriptase, whereas 1,3,5-triaryl-4-alkylpyrazoles are efficient ligands for the estrogen receptor.[3] Moreover, some aryl pyrazoles are used in supramolecular and polymer chemistry, in the food industry and as cosmetic colorings and UV stabilizers, while some have liquid crystal properties.[4] Substituted aryl pyrazoles have also been applied as ligands for transition metal-catalyzed reactions.[5]



Aryl pyrazole

R_1 = R_2 = R_4 = aryl or substituted aryl
R_3 = H or aryl or substituted aryl

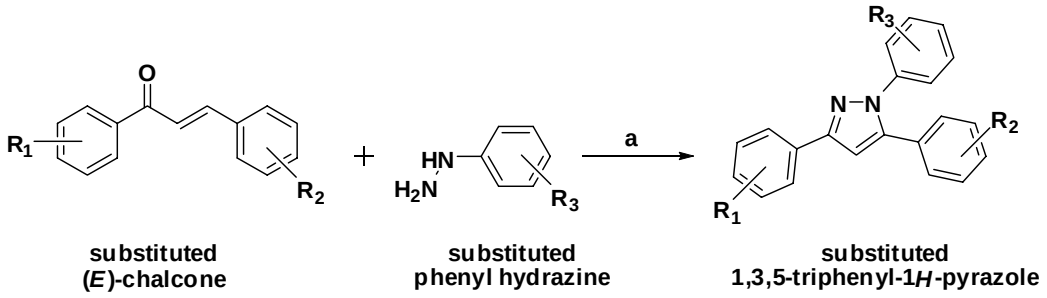
Figure 1. Structure of aryl pyrazole.

Conventional approaches for the preparation of substituted aryl pyrazoles involve either the construction of two C-N bonds by condensation of aryl hydrazines with 1,3-dicarbonyl compounds or their 1,3-dielectrophilic equivalents or the generation of one

C-N bond and one C-C bond by intermolecular [3 + 2]-cycloadditions of 1,3-dipoles to dipolarophiles.[6] Oxidative aromatization of chalcone 1,3,5-triphenylhydrazones or 1,3,5-triphenyl pyrazolines to 1,3,5-triphenyl-1*H*-pyrazole with several oxidizing agents/ systems such as MnO_2[7], *N*-bromo-sulphonamides[8], Iodine, H_2O_2/AcOH or SSA or oxalic acid/KI or NaI system [9], BNBTS [10], $PhI(OAc)_2$ [11] and Pd/C in acetic acid [12] are also reported in the literature. Each method has its own scope and efficiency limitations. However, in the past decade, general and efficient methodologies have been developed with the aim of increasing the regioselectivity in the preparation of substituted aryl pyrazoles. Among them, those involving the formation of C-N and C-C bonds by cross-coupling reactions of aryl electrophiles with substituted pyrazoles have emerged as a promising alternative to conventional methodologies.[2]

4.4.2 Present Work

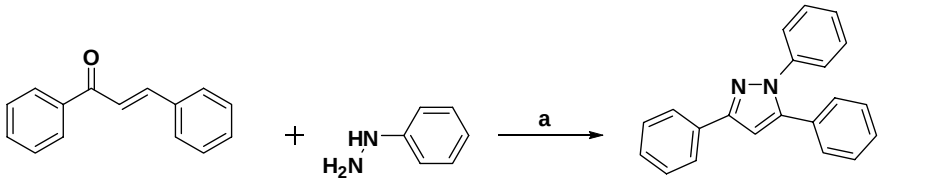
In spite of their potential utility, many of the reported method for the synthesis of aryl pyrazoles suffer from drawbacks such as lower yields, expensive transition metal oxidant, use of toxic organic solvent and complexity of work-up. In continuation of our work on ionic liquid mediated transformations, we have developed a simple, efficient and ecofriendly one pot synthesis of 1,3,5-triphenyl-1*H*-pyrazoles from (*E*)-chalcones and substituted phenyl hydrazines using [bbim]X as a promoter and reaction media (Scheme 1).



Scheme 1. *Reagents and Conditions: (a) [bbim]X, silent or sonication, rt. X = Br, Cl, BF_4, ClO_4.*

4.4.3 Result and discussion

Initially one pot synthesis of 1,3,5-triphenyl-1*H*-pyrazole **1c** from (*E*)-chalcone and phenyl hydrazine was carried out using various RTILs like [bbim]Br, [bbim]Cl, [bbim]ClO_4 and [bbim]BF_4 RTILs at room temperature under ultrasound or stirring without ultrasound (silent) condition (Scheme 2, Table 1). It was our perception that with all the RTILs, it took couple of hours or more than that to complete the reaction at room temperature under silent condition with good to significant yields of 1,3,5-triphenyl-1*H*-pyrazole **1c**, among which, [bbim]Br afforded the highest 90% yield (Scheme 2, Table 1). Under ultrasound condition, the reaction completion time for all RTILs was decreased and yields were considerably increased. Among these RTILs [bbim]Br was found to be superior and ended with highest 95% yield within shortest reaction time period of 30 min (Scheme 2, Table 1).



1a (*E*)-Chalcone | **1b** Phenyl hydrazine | **1c** 1,3,5-Triphenyl-1*H*-pyrazole

Scheme 2. *Reagents and Conditions: a)[bbim]X, $(Boc)_2O$, silent or sonication, rt; X = Br, Cl, BF_4, ClO_4.*

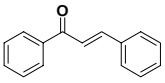
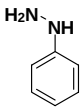
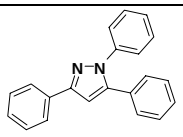
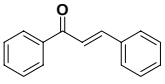
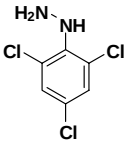
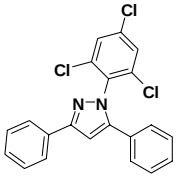
Table 1. Comparative study of synthesis of 1,3,5-triphenyl-1*H*-pyrazole **1c** in various RTILs at room temperature.

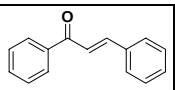
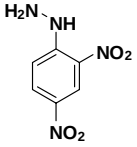
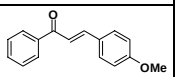
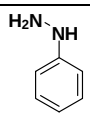
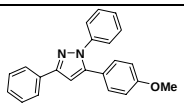
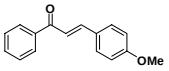
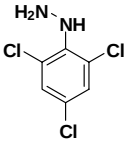
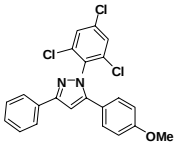
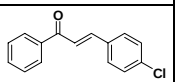
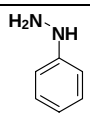
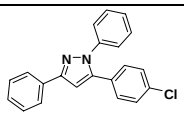
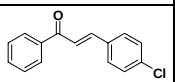
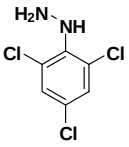
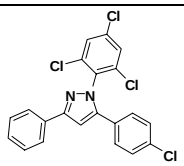
Entry	Ionic liquid	Time (min)[a]		%Yield[b]	
		Silent	)))))	Silent	)))))
1	[bbim]Br	2 h	30	90	95
2	[bbim]Cl	3 h	45	90	94
3	[bbim]ClO_4	6 h	1.5 h	85	92
4	[bbim]BF_4	6 h	1.5 h	85	90

[a] Reaction time in hours if not defined; [b] Isolated yield of 1,3,5-triphenyl-1*H*-pyrazole 1c.

Inspiring with these attractive results, the RTIL [bbim]Br was further used as promoter and reaction media for the synthesis of several other substituted 1,3,5-triphenyl-1*H*-pyrazoles and the results of the same are summarized in Table 2. It was noticed that a reaction time of one and half hour or a couple of hours was required under silent (room temperature stirring) condition where as sonication accelerated the reaction rate (up to four times faster than silent condition) and completed in 20-30 min (Table 2). Under silent condition the reaction gave good to significant yields (89-94%) while the sonication condition afforded significant to high yields (94-97%) of substituted 1,3,5-triphenyl-1*H*-pyrazoles (entries 1,2 and 4-7, Table 2). It was seen that the phenyl hydrazines with electron donating functional groups (-Cl and -OMe) facilitated the reaction whereas 2,4-dinitro phenyl hydrazine (2,4-DNP) **3b**, the phenyl hydrazine with electron withdrawing functional group (-NO_2) was found to be unsuccessful in producing respective 1,3,5-triphenyl-1*H*-pyrazole molecule. This may be due to the +I effect in phenyl hydrazines with electron donating functional groups (-Cl and -OMe) which offer an extra driving force to the amine groups of phenyl hydrazine to react with (*E*)-chalcone to give 1,3,5-triphenyl-1*H*-pyrazoles while the –I effect present in 2,4-DNP **3b** retard the reaction which resulted in ultimate failure of reaction to produce respective 1,3,5-triphenyl-1*H*-pyrazole. All the 1,3,5-triphenyl-1*H*-pyrazoles of respective reactions carried out in this work were isolated in pure form and their structures were confirmed by ^{1}H and ^{13}C NMR spectral studies.

Table 2. Synthesis of 1,3,5-triphenyl-1*H*-pyrazoles in [bbim]Br at room temperature.

Entry	Substrates		Product [c]	Time (min) [d]		%Yield [e]	
	Chalcone [a]	Phenyl hydrazine [b]		Silent	)))))	Silent	)))))
1				2 h	30	90	95
2				2 h	20	91	96

\3			No reaction	24 h	6 h	----	----
4				1.5 h	20	92	97
5				1.5 h	20	94	97
6				2 h	30	90	94
7				2 h	25	89	95

[a] Chalcone; [b] phenyl hydrazine; [c] product 1,3,5-triphenyl-1*H*-pyrazoles; [d] Reaction time in hours if not defined; [e] Isolated yield of 1,3,5-triphenyl-1*H*-pyrazoles.

4.4.4 Conclusion

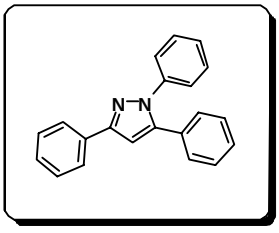
An efficient, simple and green method for one pot synthesis of 1,3,5-triphenyl-1*H*-pyrazoles from (*E*)-chalcones and substituted phenyl hydrazines using 1,3-di-*n*-butylimidazolium based RTILs as promoter and reaction media was successfully developed. Among the all RTILs, [bbim]Br was found to be most efficient RTIL for the synthesis of 1,3,5-triphenyl-1*H*-pyrazoles.

4.4.5 Experimental

General procedure for the synthesis of 1,3,5-triphenyl-1*H*-pyrazoles

A mixture of (*E*)-chalcone (1 mmol) and phenyl hydrazine (1 mmol) in 1, 3-di-*n*-butylimidazolium bromide ([bbim]Br, 2.0 g) was sonicated in ultrasonic cleaning bath at room temperature. The reactions were monitored by TLC. The same reactions were performed under similar conditions without ultrasound (silent reactions). After complete conversion, the reaction mixture was diluted with water (25 mL). The solid product separated was filtered, washed with water, and dried. The products which are liquids were extracted with ethyl acetate (2 x 20 mL) and dried over sodium sulfate, and solvent was evaporated under reduced pressure to furnish crude product. The crude products were further purified by column chromatography over silica-gel (100-200 mesh) to afford 1,3,5-triphenyl-1*H*-pyrazole. The aqueous layer consisting of [bbim]Br was subjected to distillation (80 ^{0} C at 10 mm Hg) for 2 h to remove water, leaving behind [bbim]Br (recovery >98%), which could be reused for the next run.

1,3,5-Triphenyl-1*H*-pyrazole (1c)



Molecular Formula : $C_{21}H_{16}N_2$.

Nature : Yellow solid.

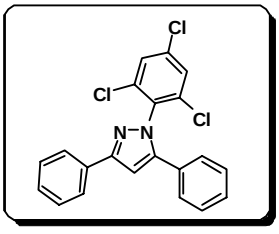
Mp :138 ^{o}C (Lit. 139-140 ^{o}C).[13]

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 6.85 (s, 1H), 7.32-7.39 (m, 13H), 7.95 (dd, *J* = 1.5, 8.1 Hz, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 105.10, 125.16, 125.69, 127.30, 127.89, 128.18, 128.37, 128.55, 128. 61, 128.79, 132.91, 144.24, 151.83.

MS (ESI-TOF) m/z : 319.21 ($[M+Na]^{+}$).

3,5-Diphenyl-1-(2,4,6-trichlorophenyl)-1*H*-pyrazole (2c)



Molecular Formula : $C_{21}H_{13}Cl_3N_2$.

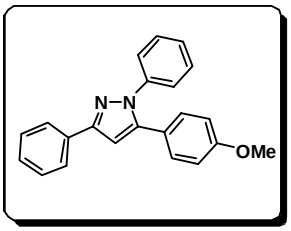
Nature : Yellow viscous liquid.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 6.90 (s, 1H), 7.33-7.38 (m, 5 H), 7.39-7.45 (m, 5 H), 7.93 (dd, *J* = 1.6, 8.3 Hz, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 103.74, 125.93, 127.62, 128.24, 128.46, 128.59, 128.76, 129.46, 132.63, 135.99, 146.87, 153.45.

MS (ESI-TOF) m/z : 421.05 ($[M+Na]^+$).

5-(4-Methoxyphenyl)-1,3-diphenyl-1*H*-pyrazole (4c)



Molecular Formula : $C_{22}H_{18}N_2O$.

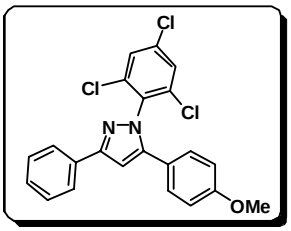
Nature : Pale yellow viscous liquid.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 3.83 (s, 3H), 6.79 (s, 1H), 6.87 (d, *J* = 8.9 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.31-7.49 (m, 8 H), 7.94 (dd, *J* = 1.5, 8.3 Hz, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 24.11, 28.14, 53.80, 70.27, 79.20, 155.88.

MS (ESI-TOF) m/z : 349.18 ($[M+Na]^+$).

5-(4-Methoxyphenyl)-3-phenyl-1-(2,4,6-trichlorophenyl)-1*H*-pyrazole (5c)



Molecular Formula : $C_{22}H_{15}Cl_3N_2O$.

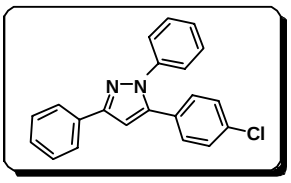
Nature : Pale yellow viscous liquid.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 3.81 (s, 3H), 6.83 (s, 1H), 6.86 (d, *J* = 9.4 Hz, 2H), 7.24 (d, *J* = 9.0 Hz, 2H), 7.31-7.48 (m, 5 H), 7.92 (dd, *J* = 1.6, 8.3 Hz, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ (ppm) 55.17, 103.24, 114.01, 121.87, 125.92, 128.18, 128.61, 128.99, 132.73, 135.11, 135.81, 136.06, 146.72, 153.38, 159.86.

MS (ESI-TOF) m/z : 451.10 ($[M+Na]^+$).

5-(4-Chlorophenyl)-1,3-diphenyl-1*H*-pyrazole (6c)



Molecular Formula : $C_{21}H_{15}ClN_2$

Nature : Yellow dense liquid

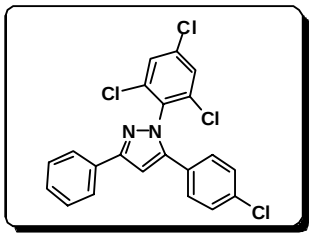
^{1}H NMR ($CDCl_3$, 200 MHz) : δ (ppm) 7.03 (s, 1H), 7.18-7.35 (m, 12H), 7.58 (d, *J* = 8.0 Hz, 2H).

^{13}C NMR ($CDCl_3$, : δ (ppm) 105.25, 125.23, 125.78, 127.60, 128.92,

50MHz) 129.20, 129.33, 131.56, 133.09, 135.57, 141.01, 143.91, 151.22.

MS (ESI-TOF) m/z : 353.15 ($[M+Na]^+$).

5-(4-Chlorophenyl)-3-phenyl-1-(2,4,6-trichlorophenyl)-1*H*-pyrazole (7c)



Molecular Formula : $C_{21}H_{12}Cl_4N_2$.

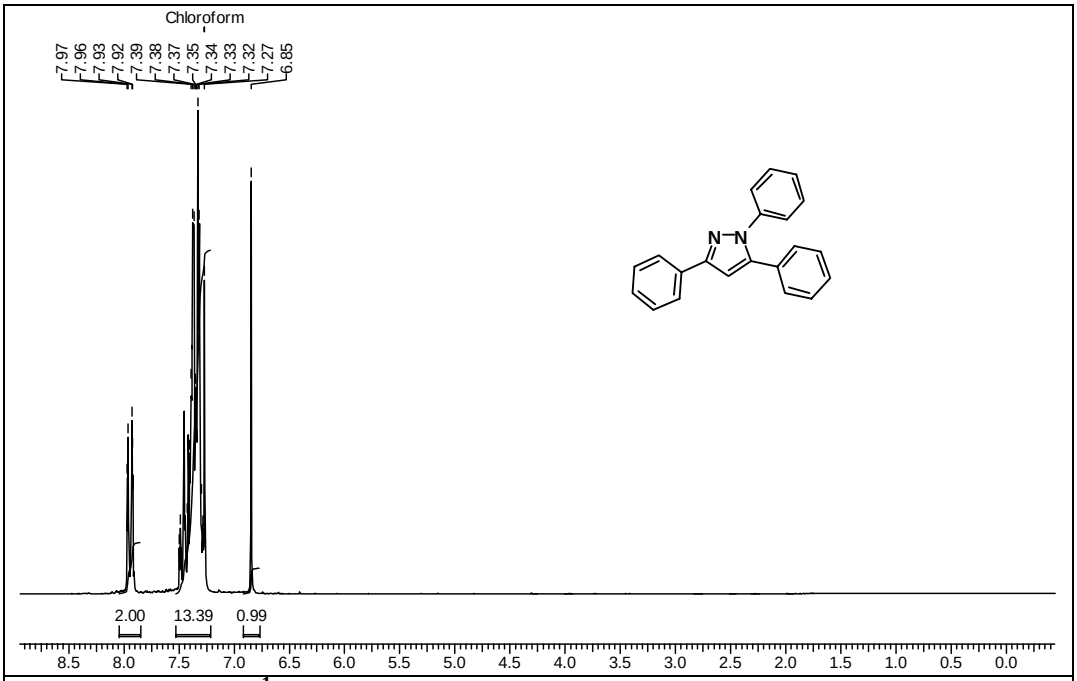
Nature : Pale yellow dense liquid.

^{1}H NMR ($CDCl_3$, 200MHz) : δ (ppm) 6.84 (s, 1H), 7.22-7.30 (m, 4H), 7.36-7.41 (m, 5H), 7.88 (dd, *J* = 1.4, 8.0 Hz, 2H).

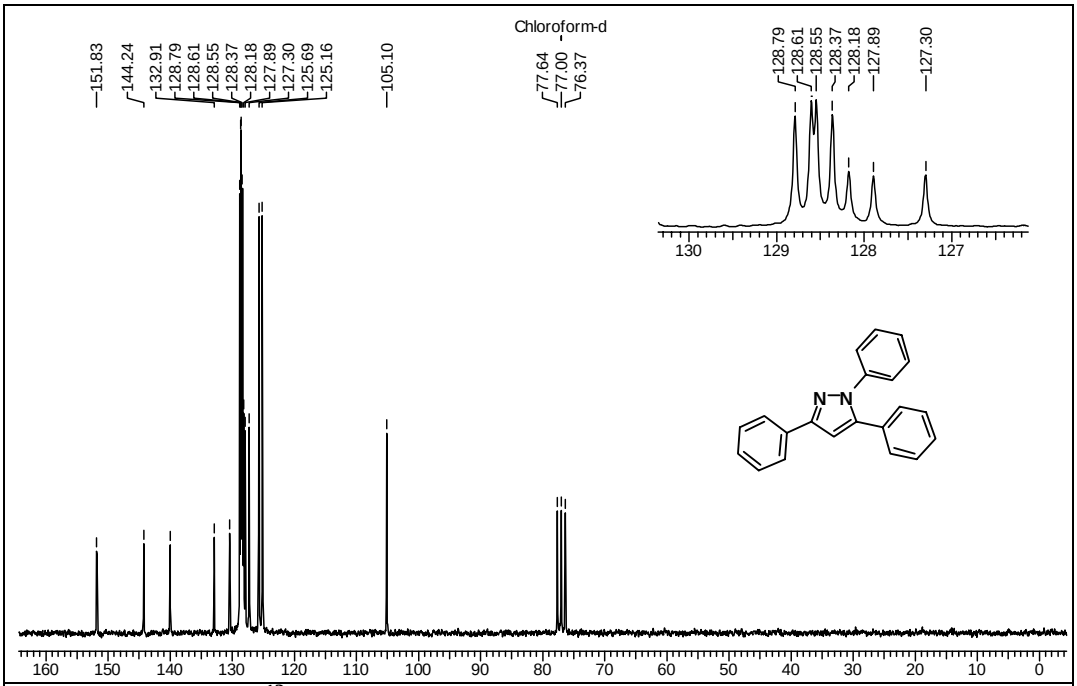
^{13}C NMR ($CDCl_3$, 50MHz) : δ (ppm) 103.92, 125.93, 127.95, 128.35, 128.66, 128.74, 128.92, 129.12, 129.30, 135.94, 136.13, 145.68, 153.56.

MS (ESI-TOF) m/z : 455.08 ($[M+Na]^+$).

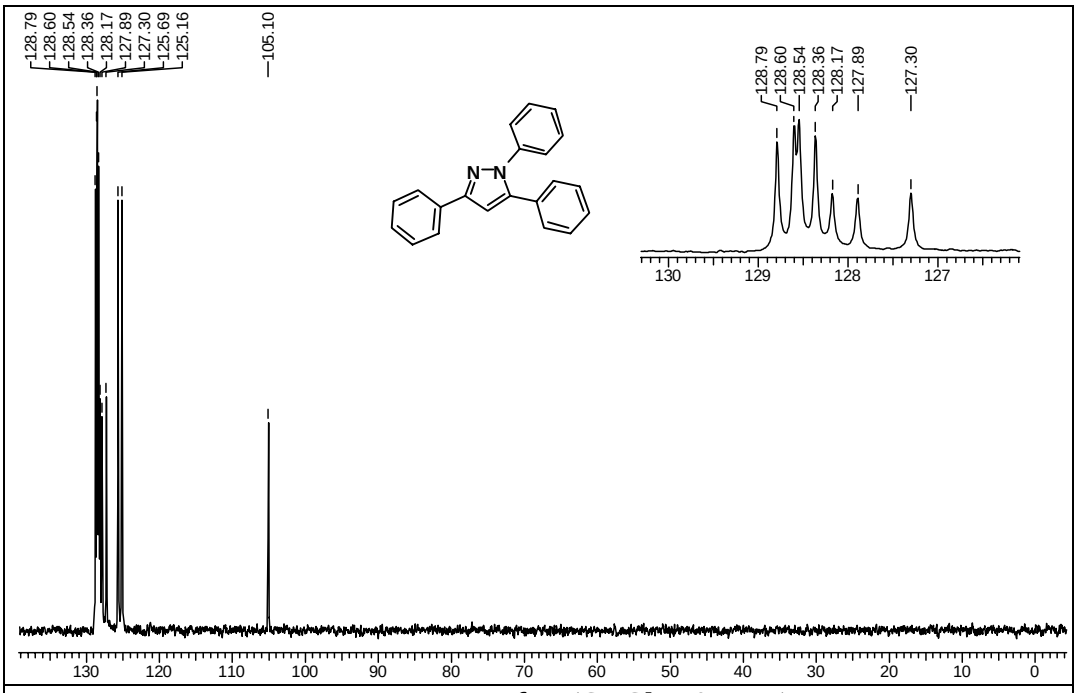
4.4.6 Analytical data



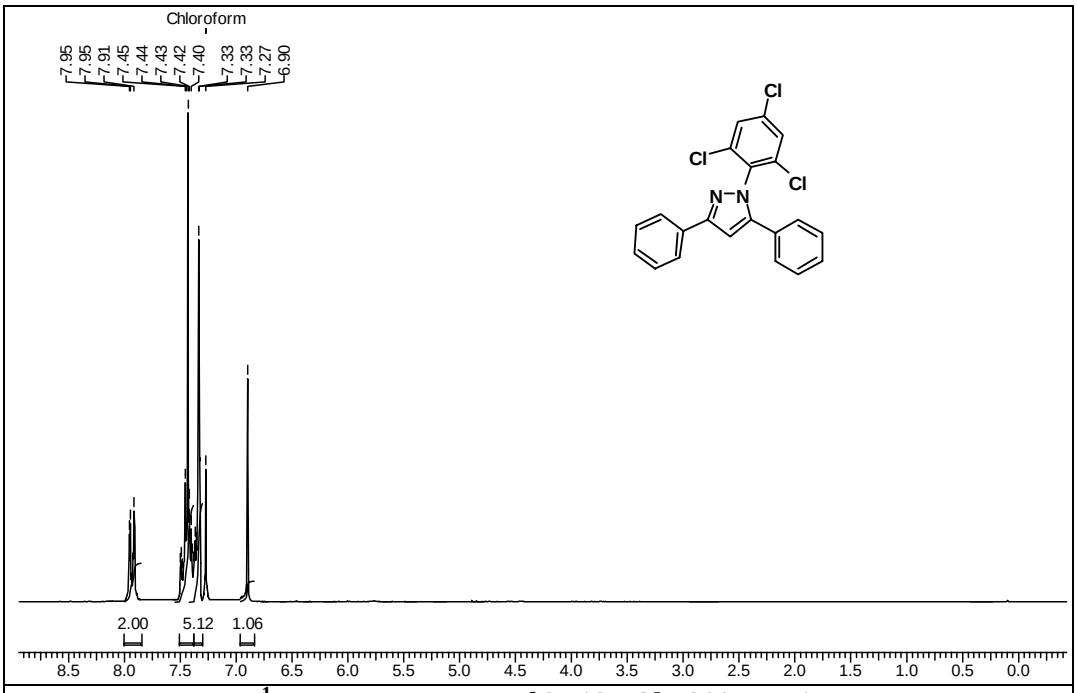
^{1}H NMR spectrum of 1c ($CDCl_3$, 200 MHz)



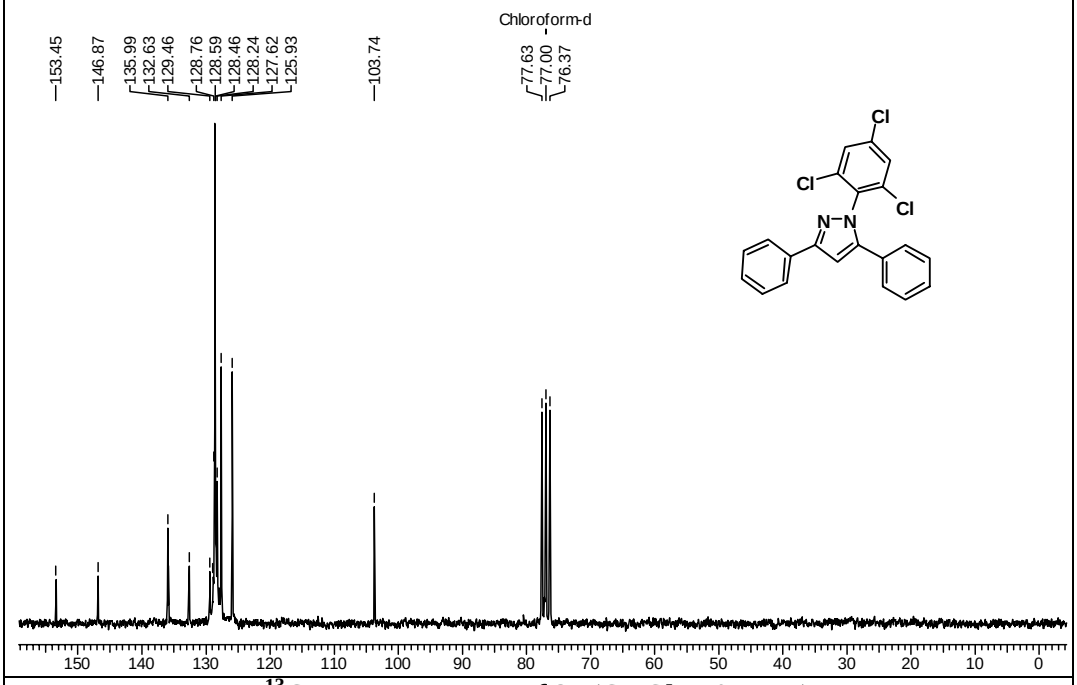
^{13}C NMR spectrum of 1c ($CDCl_3$, 50 MHz)



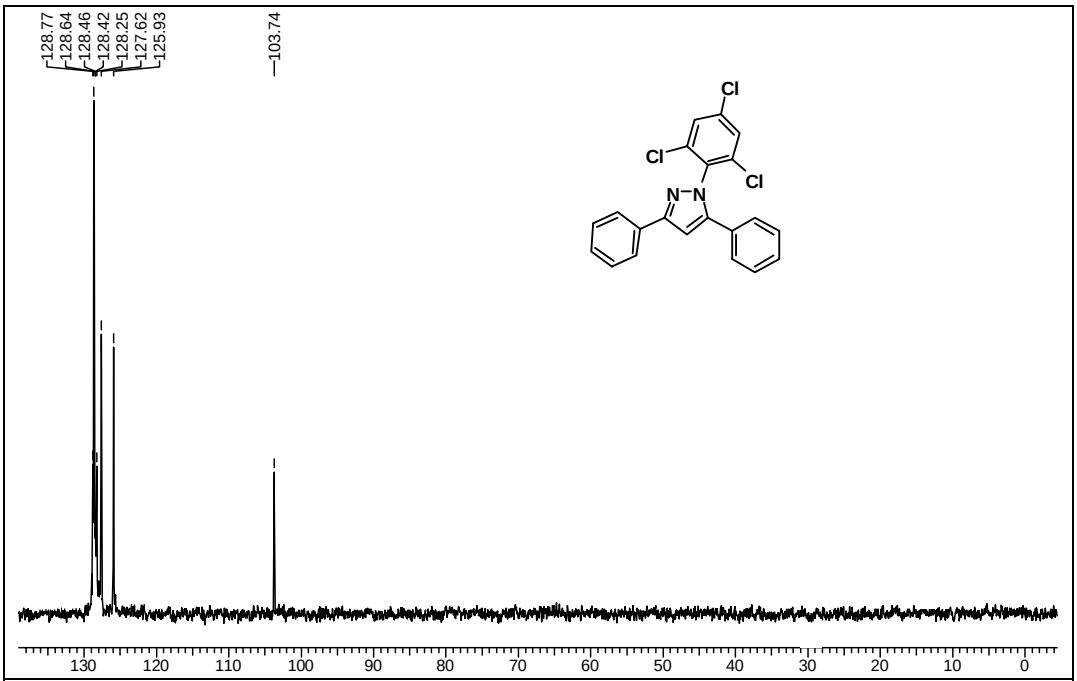
DEPT spectrum of 1c ($CDCl_3$, 50 MHz)



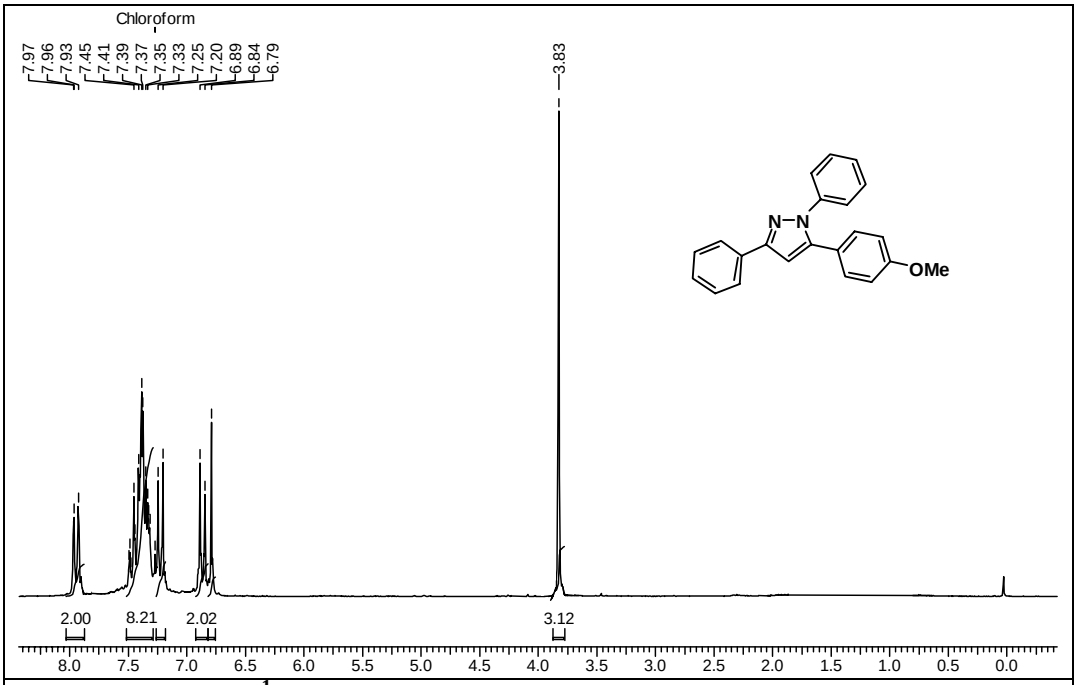
^{1}H NMR spectrum of 2c ($CDCl_3$, 200 MHz)



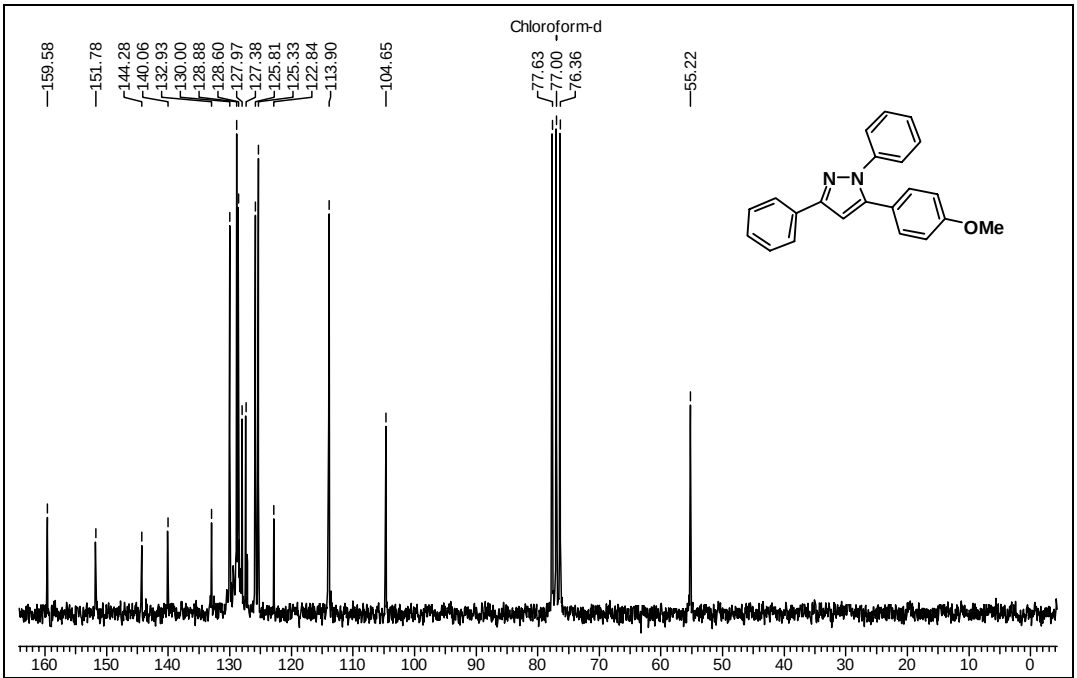
^{13}C NMR spectrum of 2c ($CDCl_3$, 50 MHz)



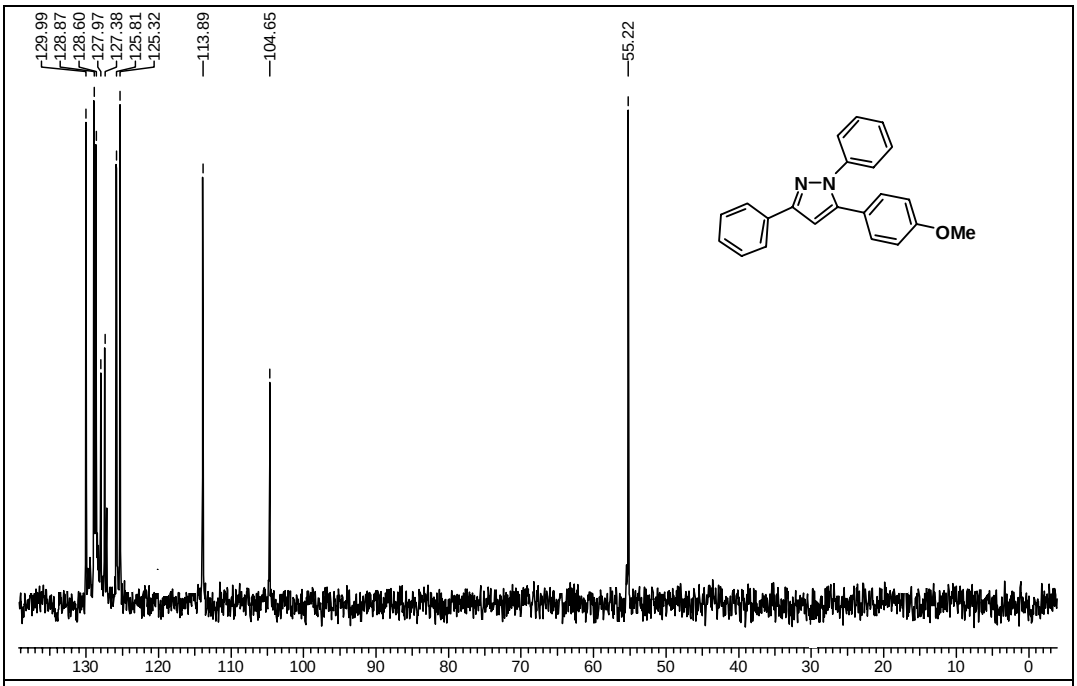
DEPT spectrum of 2c ($CDCl_3$, 50 MHz)



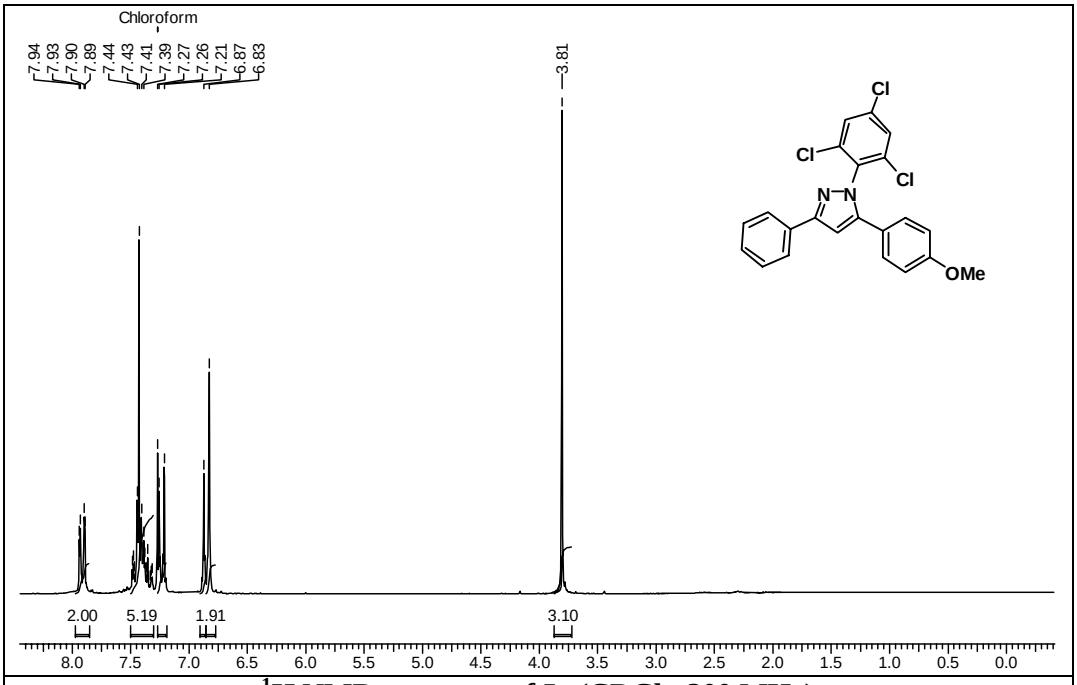
^{1}H NMR spectrum of 4c ($CDCl_3$, 200 MHz)



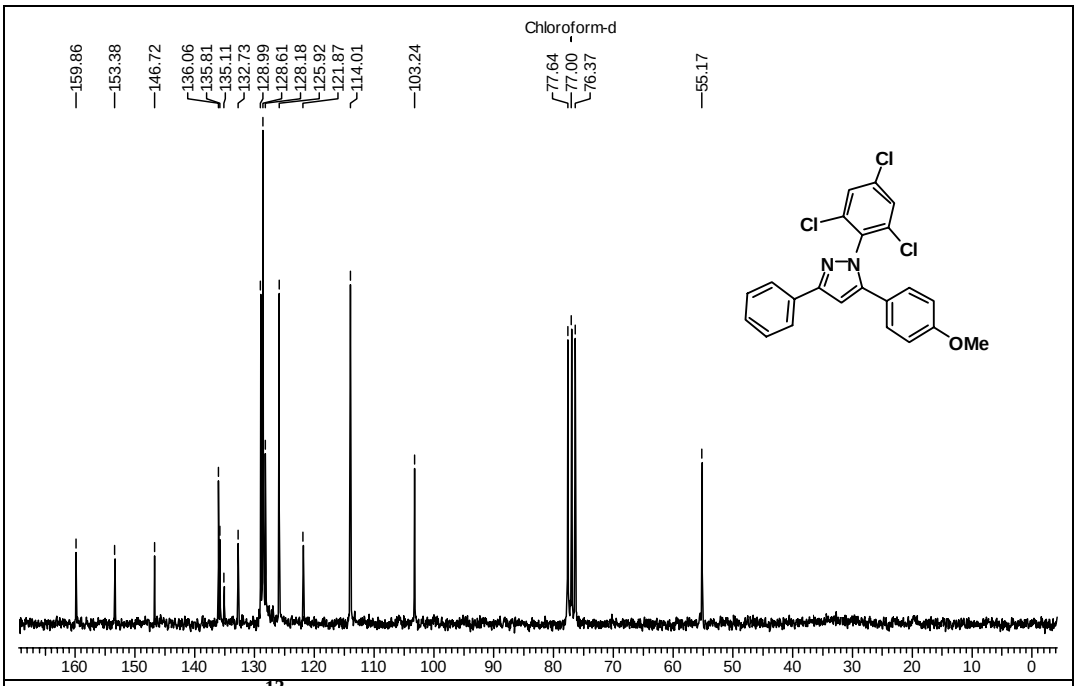
^{13}C NMR spectrum of 4c ($CDCl_3$, 50 MHz)



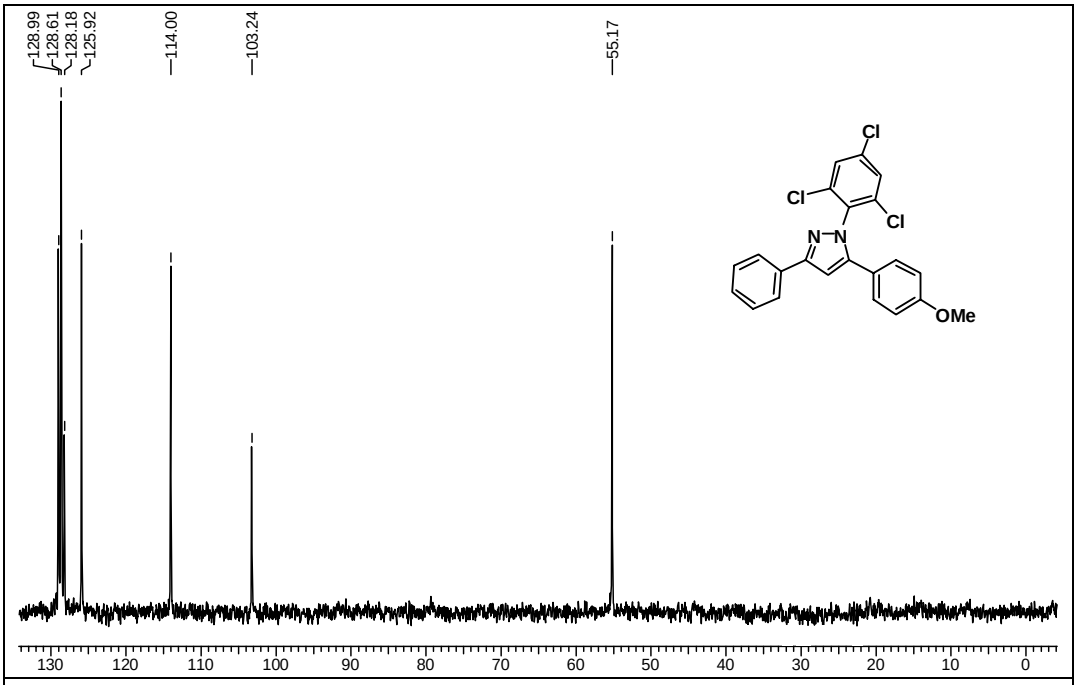
DEPT spectrum of 4c ($CDCl_3$, 50 MHz)



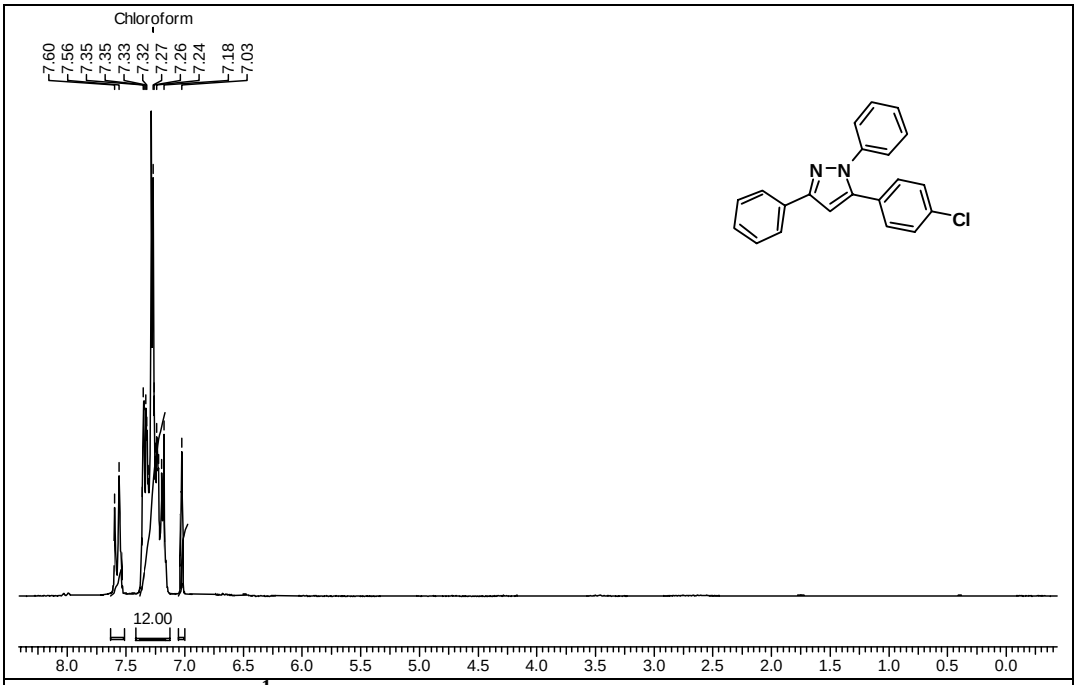
^{1}H NMR spectrum of 5c ($CDCl_3$, 200 MHz)



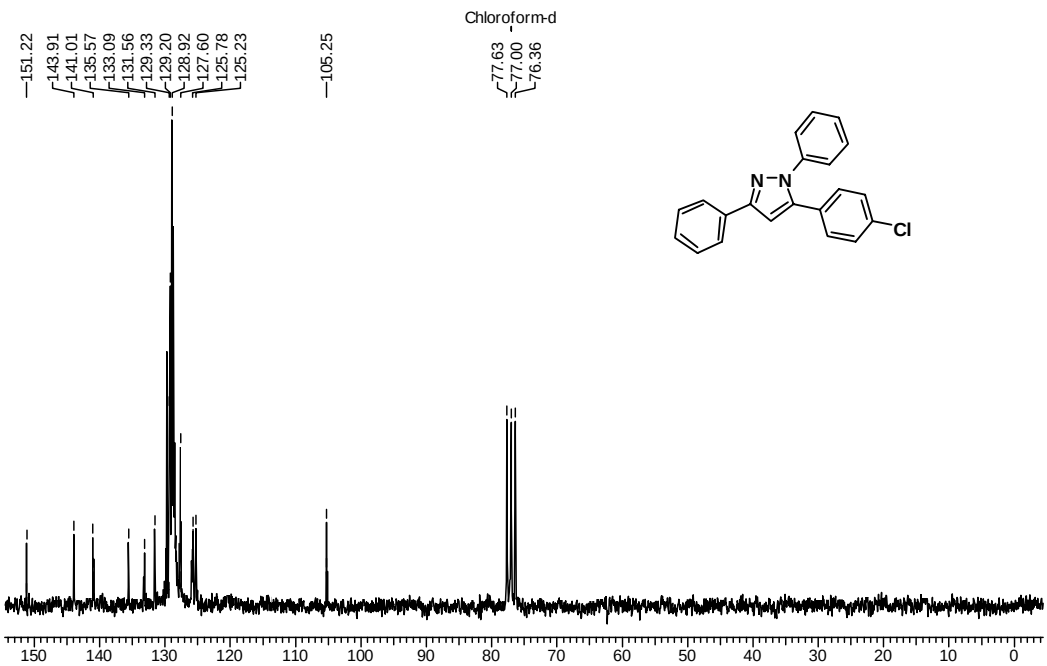
^{13}C NMR spectrum of 5c ($CDCl_3$, 50 MHz)



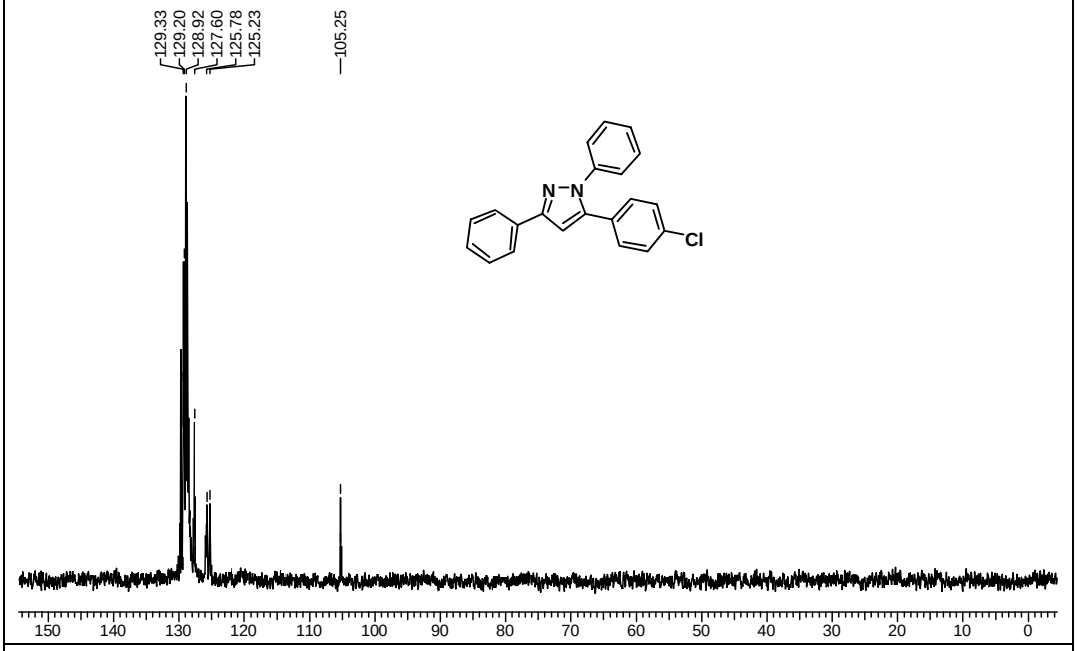
DEPT spectrum of 5c ($CDCl_3$, 50 MHz)



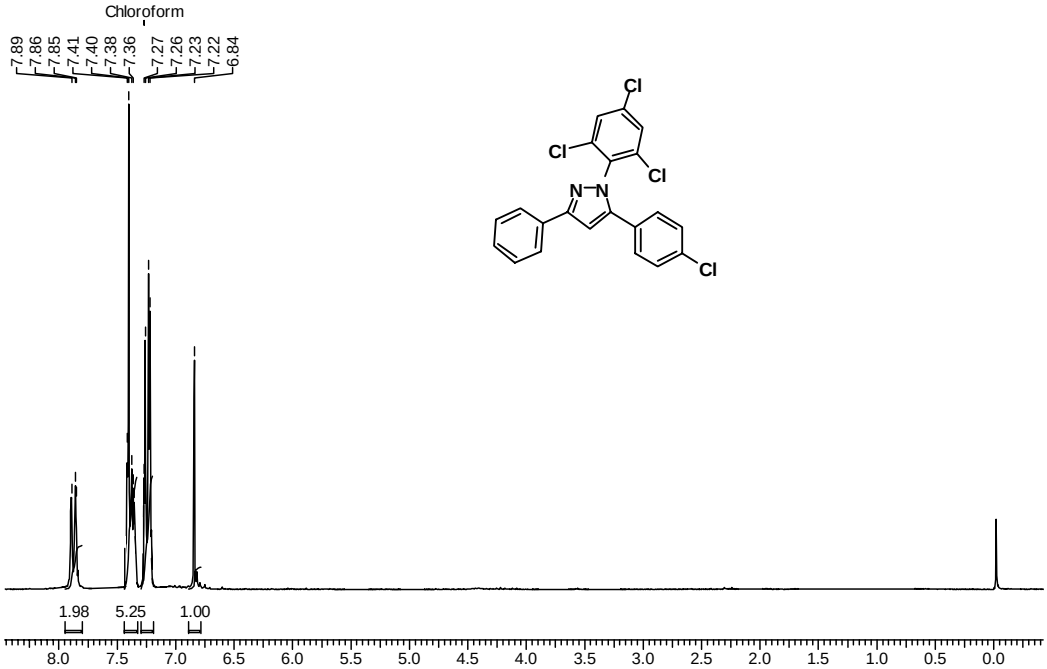
^{1}H NMR spectrum of 6c ($CDCl_3$, 200 MHz)



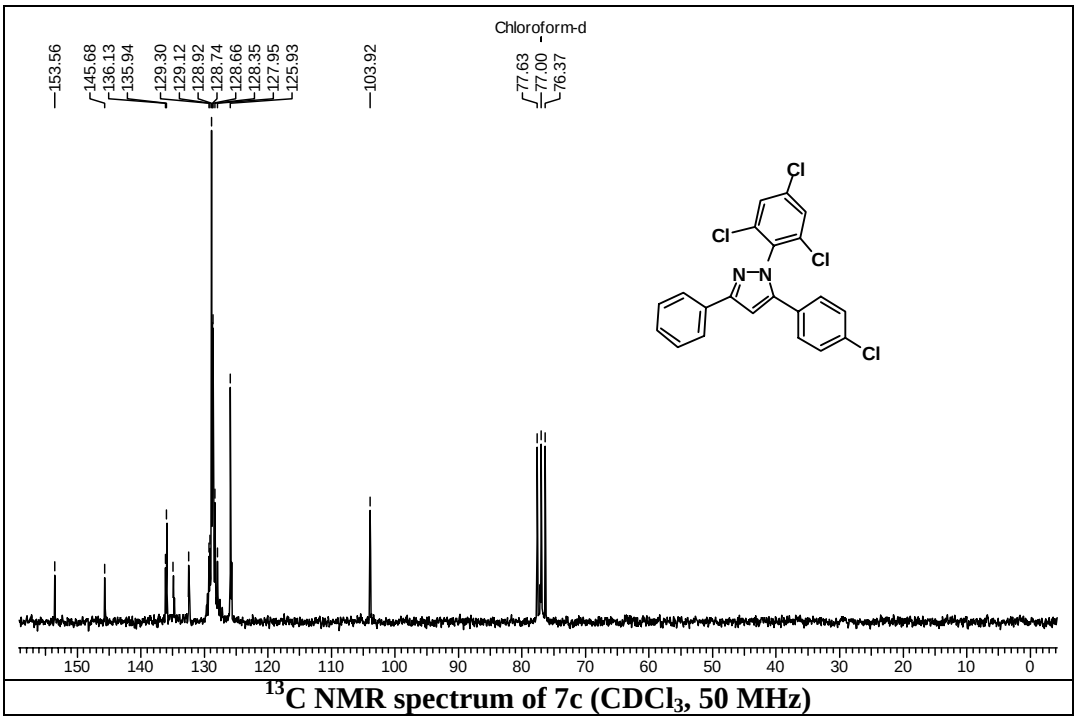
^{13}C NMR spectrum of 6c ($CDCl_3$, 50 MHz)



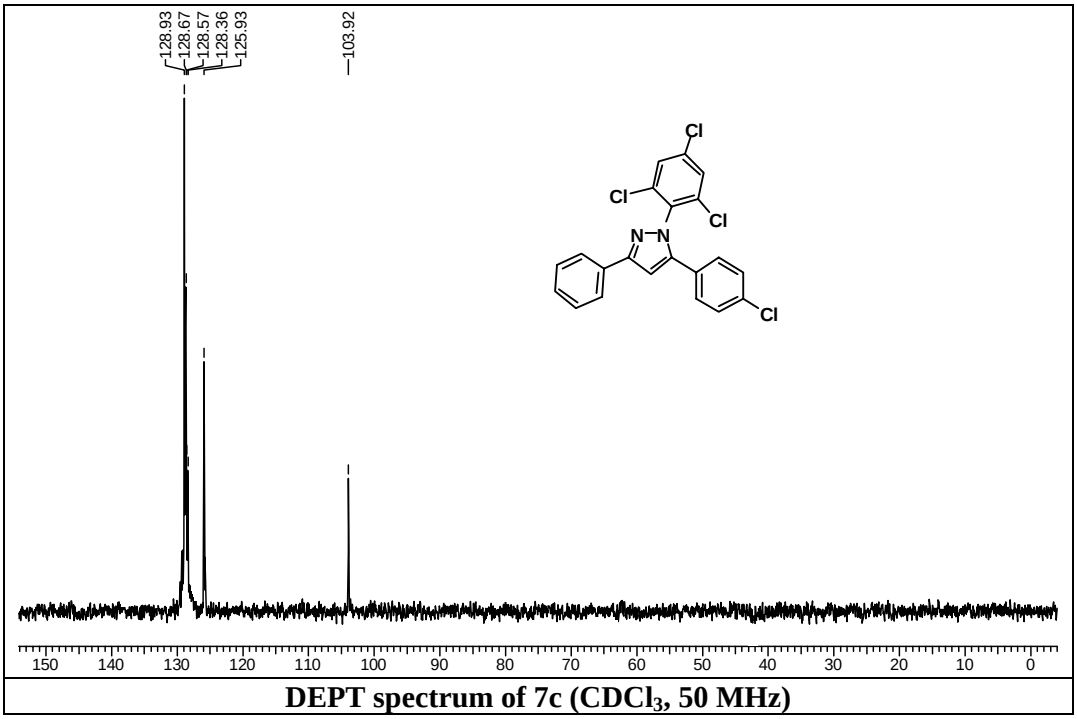
DEPT spectrum of 6c ($CDCl_3$, 50 MHz)



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



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



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

4.4.7 References

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List of publications, posters and patents

List of publications

1. Phosphotungstic acid as an efficient solid catalyst for intramolecular rearrangement of benzyl phenyl ether to 2-benzyl phenol.
   Mahesh H. Bhure, Chandrashekhar V. Rode, Rajeev C. Chikate, Neeraj Patwardhan and Shraddha Patil *Catal. Commun.* **2007**, *8*, 139-144.

2. Facile and Highly Selective Deprotection of tert-Butyldimethyl Silyl Ethers using Sulfated SnO2 as a Solid Catalyst.
   Mahesh H. Bhure, Indresh Kumar, Arun D. Natu, Chandrashekhar V. Rode *Synth. Commun.* **2008**, *3*, 346-353.

3. Phosphotungstic acid on silica with modified acid sites as a solid catalyst for selective cleavage of tert-butyldimethylsilyl ethers.
   Mahesh H. Bhure, Indresh Kumar, Arun D. Natu, Rajiv C. Chikate and Chandrashekhar V. Rode *Catal. Commun.* **2008**, *9*, 1863-1868.

4. L-proline catalyzed direct diastereoselective 6-*enolexo* aldolization: A novel approach for the synthesis of 1-Deoxythinojirimyicn.
   Mahesh H. Bhure and Thomas Daniel (manuscript ready for communication).

5. L-proline catalyzed diastereoselective synthesis of 1,4-anhydro-4-thio-D-arabinitol and formal synthesis of Salacinol, Salaprinol and Neosalaprinol.
   Mahesh H. Bhure and Thomas Daniel (manuscript ready for communication).

6. Synthesis and characterization of crown ether and imidazolium based novel ionic liquids.
   Mahesh H. Bhure and Thomas Daniel (manuscript ready for communication).

7. Highly efficient and solvent free *N*-Boc protection of alkyl/aryl amines using 1,3-*n*-dibutylimidazolium based ionic liquids.
   Mahesh H. Bhure and Thomas Daniel (manuscript ready for communication).

8. A novel one pot synthesis of 1,3,5-triphenyl-1*H*-pyrazoles using 1,3-*n*-dibutylimidazolium based ionic liquids.
   Mahesh H. Bhure and Thomas Daniel (manuscript under preparation).

List of posters presented in Conferences/Symposium

1. Poster entitled **"Proline Catalyzed Diastereoselective Synthesis of 1-Deoxythionojirimycin"** presented at National Chemical Laboratory, Pune (INDIA)-411008 on Science Day 27th February **2011**.
   Mahesh H. Bhure, Satyawan D. Nagane and Thomas Daniel

2. Poster entitled **"Organocatalytic distereoselective synthesis of thiosugars"** presented at 12th CRSI National Symposium in Chemistry jointly organized by IICT, Hyderabad and the National Institute of Pharmaceutical Education and Research (NIPER), held on the 5-7 February **2010**.
   M. H. Bhure, Vincent Paul, UMV Basavanag and Thomas Daniel.

3. Poster entitled **"Proline catalyzed stereoselective synthesis of thiosugars"** presented at 5th J-NOST held at IIT Kanpur on the 4-7 December **2009**.
   M. H. Bhure, Vincent Paul, UMV Basavanag and Thomas Daniel.

4. Poster entitled **"Solid acid catalyzed intramolecular rearrangement of benzyl phenyl ethers"** presented at National Chemical Laboratory, Pune (INDIA)-411008 on Science Day 27th February **2006**.
   M. H. Bhure, J. M. Nadgeri, Dr. C. V. Rode.

5. Poster entitled **"Design, synthesis and antitumor activity of substituted 2-benzylidene-1-tetralones"** presented in **"Ramanbhai 1st International Symposium."** at **Zydus Research Center, Ahmedabad** on 23-24 January, **2003**.
   M. H. Bhure, M. K. Gurjar, R. D. Wakharkar, H .B. Borate, P. D. Shinde, V. A. Mahajan.

List of patents

1. "A process for the preparation of 5-methylene-4-benzyl (substituted)-2(5H)-furanone."
   Gurjar, M. K., Wakharkar, R. D., Borate, H. B., Mahajan, V. A., **Bhure, M. H.**, Shinde, P. D.
   Application Number: 1559/DEL/2003, NCL number: 14/2002, CSIR number – NF- 257/2002.
2. "A novel 2,3-diaryl-5-tert-butyldimethylsilyloxy-cyclopent-2-en-ones and the process for the preparation thereof."
   Gurjar, M. K., Wakharkar, R. D., Borate, H. B., Shine, P. D., Mahajan, V. A., Jadhav, V. H., Wagh, A. M., Yadav, N. D., **Bhure, M. H.**, Deshpande, S. S.
   Application Number: 0723/DEL/2005A, NCL number: 76/2003, CSIR number: NF-17/2004.

Erratum