SYNTHETIC STUDIES TOWARDS MITRALACTONINE, PIPECOLIC ACID AND PIPERIDINE ALKALOIDS

A THESIS

SUBMITTED TO THE

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BY

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Synthetic studies towards Mitralactonine, Pipecolic acid and Piperidine alkaloids"** submitted by Mr. Nilesh B. Dumare 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.

January 2013

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DECLARATION

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

January 2013 Nilesh B. Dumare

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Dedicated to

……my beloved Parents

Acknowledgements

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have a Son like Mayuresh who is full of happiness, Joy and Curiosity, he brought everlasting cheerfulness in my life.
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NCL, Pune

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Chapter 3:

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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 F254 (Merck) and visualized by fluorescence quenching or Iodine or by charring after treatment with *p*-anisaldehyde.
6. In cases where chromatographic purification was done, silica gel (200-400 mesh) was used as the stationary phase or otherwise as stated.
7. IR spectra were recorded on **Perkin-Elmer Infrared Spectrophotometer Model 68B** or on **Perkin-Elmer 1615 FT Infrared Spectrophotometer.**
8. ^{1}H NMR and ^{13}C NMR were recorded on **Bruker AV-200** (50 MHz) or **Bruker AV-400** (100 MHz) or **Bruker DRX-500** (125 MHz). Figures in the parentheses refer to ^{13}C frequencies. Tetramethyl silane was used as the internal standard.
9. Mass spectra were recorded at an ionization energy of 70 eV on **Finnigan MAT-1020**, automated GC/MS instrument and on **API Q STARPULSAR** using electron spray ionization [(ESI), solvent medium: a mixture of water, acetonitrile and ammonium acetate] technique and mass values are expressed as *m/z*. HRMS were recorded on a micromass Q-T of micro with spray source (ESI^{+}) mode.
10. Starting materials were obtained from commercial sources or prepared using known procedures.
11. Microanalysis data were obtained using a **Carlo-Erba CHNS-O EA 1108** elemental analyzer within the limits of accuracy (± 0.4%).

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

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

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

ABSTRACT:-

The thesis entitled, **"Synthetic studies towards Mitralactonine, Pipecolic acid and Piperidine alkaloids"** is divided into three chapters.

Chapter one deals with the introduction, literature survey and formal synthesis of mitralactonine. The second chapter deals with the introduction and synthetic studies towards 3-hydroxypipecolic acid and polyhydroxy piperidine alkaloids. Third chapter deals with introduction and total synthesis of L-1-deoxyallonojirimycin (L-*allo*-1-DNJ) , D-*allo*-1-DNJ and L-*talo*-1-deoxynojirimycin (L-*talo*-1-DNJ).

Chapter 1. Formal synthesis of mitralactonine.

Section 1: Introduction to mitralactonine. Mitralactonine **1 (**Figure 1) is a highly conjugated pentacyclic corynanthe type indole alkaloid isolated in 1999 by Takayama *et al*[1] from the young leaves of *M. speciosa* found in Malaysia. Leaves of this class of plant are known to show narcotic effect when chewed or smoked. As its pharmacological assays are still in progress coupled with its having challenging pentacyclic structure, organic chemists are attracted to the synthesis of mitralactonine. So far in the literature three syntheses[1,2] are reported. Despite reported syntheses still there is a need to develop practical synthesis of mitralactonine.

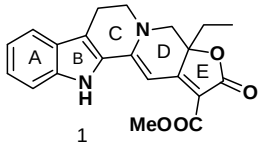

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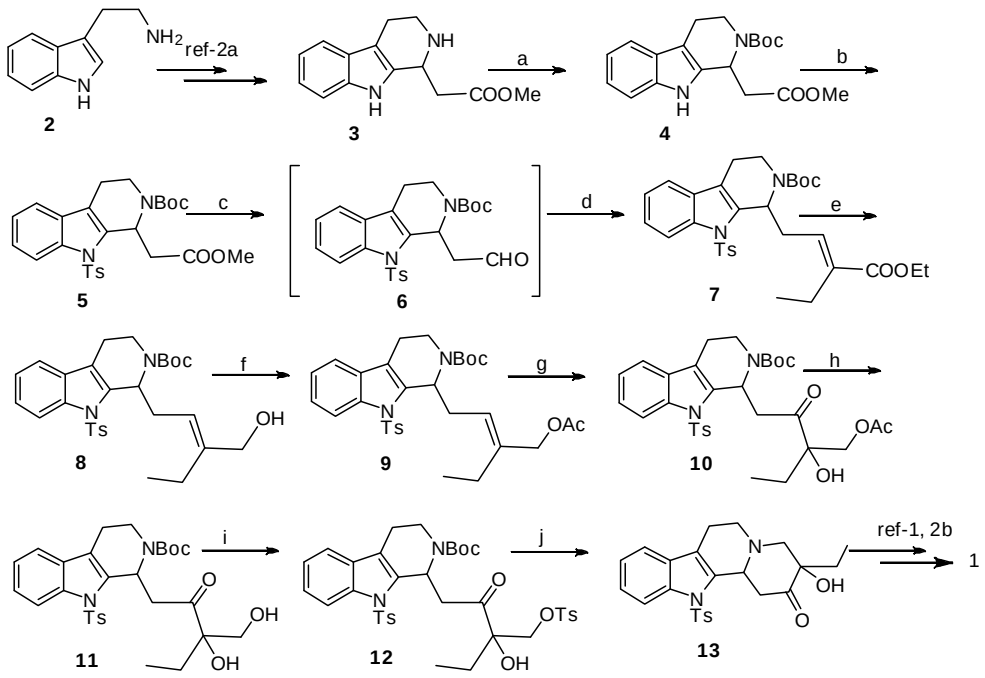
Figure 1. Structure of Mitralactonine

Section 2: Formal synthesis of Mitralactonine

This section describes the formal synthesis of mitralactonine. The formal synthesis of (±)-mitralactonine started from **2** as described in Scheme 1. The ester **3** was obtained from tryptamine **2** by carrying out some chemical transformations like imine formation, imine reduction, Pictet Spengler cyclisation[3] and *N*-debenzylation. The amine **3** was protected as its carbamate **4**. The aromatic nitrogen of carbamate **4** was protected as its *N*-tosyl derivative **5**, followed by selective reduction of ester and four carbon homologation provided ester **7**. The ester **7** was reduced to alcohol **8** and converted into its *O*-acetyl derivatives **9**. Olefin **9** was oxidized[4] to a non separable diastereomeric mixture of α-

hydroxy ketone **10**. The acetyl group of **10** on deprotection and its subsequent conversion into *O*-tosyl derivative **12** followed by cyclization provided separable diastereomeric mixture of tetracyclic ketone **13**. The tetracyclic ketone **13** is a known key intermediate for the synthesis of mitralactonine **1**, hence, the synthesis of **13** constitutes a formal synthesis of mitralactonine.[2a]



Scheme 1 *Reagents and conditions:- (a) Boc anhydride, TEA, DMAP(cat), THF, rt, 3 h, 75%; (b) p-TsCl, NaOH, TBAHSO$_4$, toluene, rt, 30 min, 80%; (c) DIBAL-H, DCM, -78 ^{o}C, 30 min; (d) CH$_3$CH$_2$C(=PPh$_3$)COOEt, DCM, rt, overnight, 75% (over two steps); (e) DIBAL-H, DCM, -40 ^{o}C, 2 h, 89%; (f) AcCl, TEA, DCM, 0 ^{o}C, 1 h, 88%; (g) RuCl$_3$, NaHCO$_3$, oxone, CH$_3$CN:H$_2$O:EA, 0 ^{o}C, 70%; (h) K$_2$CO$_3$, MeOH, rt, 90%; (i) p-TsCl, TEA, DMAP, DCM, 0 ^{o}C, 6 h, 80%; (j) TFA(10 eq.), DCM then NaOH (neutralization pH basic 13), 30%.*

Chapter 2: Synthetic studies towards 3-hydroxypipecolic acid and advanced intermediate for piperidine alkaloids

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

This section describes the biological activity and reported synthetic routes to 3-hydroxy pipecolic acid. (2*S*,3*S*)-3-Hydroxy pipecolic acid **14 (**Figure 2) belongs to the azasugar family compounds. It is a constituent of many biologically active compounds like

compound **15**, Swainsonine **16**,[5] Febrifugine **17,**[6] Prosopinene **18**, Nojirimycin **19** and Tetrazomine **20**[7] (Figure 2).

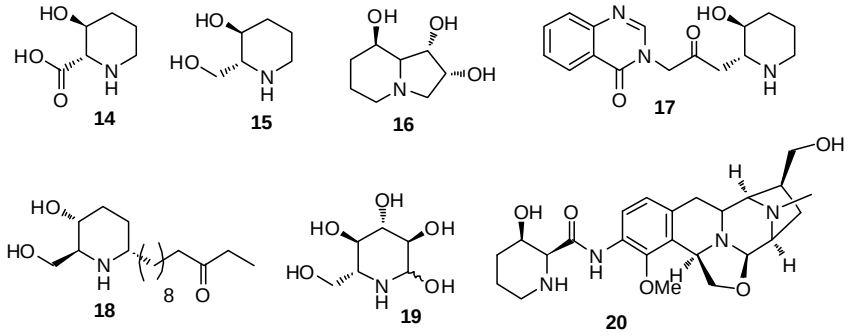
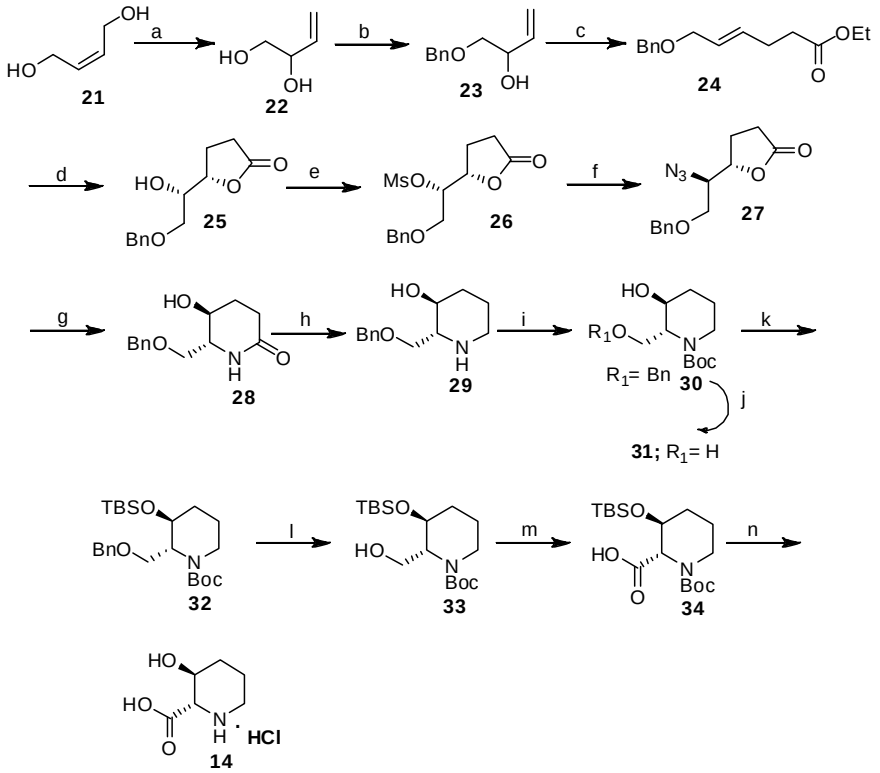


Figure 2. Pipecolic acid and analogues

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

The synthesis began from the commercially readily available *cis*-2-butene-1,4-ol **21** (Scheme 2). *Cis*-2-butene-1,4-ol **21** was converted into rearranged isomer 1,2-dihydroxy-3-butene **22**. Primary hydroxy group of **22** was converted to monobenzylether **23**. Olefin **23** was subjected to Claisen ortho rearrangement[8] conditions, to provide ester **24**.



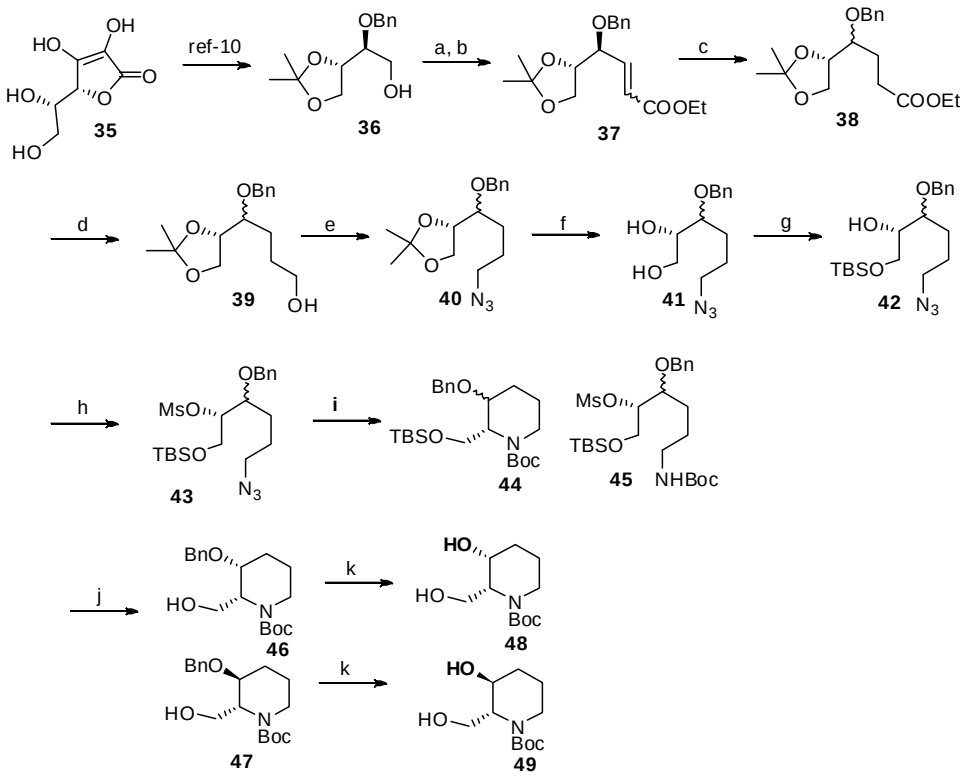
Scheme 2. Synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid

Reagents and conditions *: (a) $HgSO_4$, H_2SO_4(cat), H_2O, 65%; (b) KOH(1.1eq.), BnCl(1.1eq.), benzene reflux, 8 h, 60%; (c) $CH_3C(OEt)_3$, propanoic acid (cat.), 3 h, 85%; (d) $K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2PHAL$, OsO_4, $MeSO_2NH_2$, 0 ^oC, 24 h, 94%; (e) MsCl, Et_3N, DMAP(cat.), DCM, 5 h, 91%; (f) NaN_3, DMF, 90 ^oC, 18 h, 87%; (g) $Pd(OH)_2$, H_2, MeOH, 30 psi, rt, 3 h, 90%; (h) LAH, THF, 0 ^oC to rt, 3 h; (i) Boc anhydride, Et_3N, DMAP(cat.), THF, 0 ^oC- rt, 3 h, 90%; (j) Pd/C, H_2, MeOH, 70 psi, rt, 3 h, 93%; (k) TBSCl, imidazole, DMF, rt, 6 h, 90%; (l) Pd/C, H_2, 70 psi, rt, 3 h, 95%; (m) $RuCl_3$, $NaIO_4$, $CH_3CN:CCl_4:H_2O$ (1:1:3), rt, 30 min, 58%; (n) 6N HCl, reflux, 2 h.*

The olefin ester **24** was subjected to Sharpless asymmetric dihydroxylation[9] conditions to afford hydroxy lactone **25**. Hydroxy lactone **25** was converted into its mesyl derivatives **26**. Mesyl group of **26** was displaced by azide to furnish azidolactone **27**. Reductive lactamisation of **27** provided the desired six membered lactam **28**. Lactam **28** was reduced followed by its urethane protection to give hydroxy piperidine derivative **30**. To avoid further complications, hydroxy group in **30** was protected as its TBS ether **32** followed by *O*-debenzylation to provide primary hydroxy piperidine derivative **33**. Primary hydroxy of **33** was converted to its acid **34**. The global deprotection of urethane **34** furnished the target molecule **14**.

Chapter 2: Section 3: Synthetic studies towards (2*R*, 3*R*)-*tert*-butyl 3-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate and (2*R*, 3*S*)-*tert*-butyl 3-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate

Synthesis began from commercially available cheap starting material *viz*. L-ascorbic acid **35** (Scheme 3). L-ascorbic acid was converted into hydroxy compound **36** by known literature procedure.[10] Alcohol **36** was oxidized to corresponding aldehyde followed by Wittig reaction to provide unsaturated ester **37**. Chemoselective reduction of double bond **37** provided ester **38**. Intrestingly, there was epimerization observed during this transformation. Two non separable isomers **38** (6:4) were subjected for further reaction.



Scheme 3 *Reagents and conditions: (a) IBX, EA, reflux, 3 h; b) $PPh_3CHCOOEt$, DCM, 0 ^oC- rt, overnight, 80% (over two steps); (c) $Pd(OH)_2$, $HCOONH_4$, MeOH, reflux, 2 h, 92%; (d) LiBr, $NaBH_4$, MeOH:H_2O, 3 h, 88%: (e) i) MsCl, TEA, DCM, 0 ^oC, 30 min; ii) NaN_3, DMF, 90 ^oC, 6 h, 70% (over two steps); (f) AcOH:H_2O (8:2), rt, 85%; (g) TBSOTf, TEA, DCM, 0 ^oC, 30 min, 90%; (h) MsCl, TEA, DCM, 0 ^oC, 30 min, 92 %; (i) i) PPh_3, benzene:H_2O(9:1), reflux, ii) $(Boc)_2O$, TEA, DMAP (cat.), THF, rt, (j) TBAF, THF, 0 ^oC- rt, (k) Pd/C, H_2, MeOH, rt, 85%;*

Azide **40** was obtained from ester **38** involving reduction, mesylation and sodium azide treatment reaction sequence. Acetonide deprotection of **40** followed by selective TBS protection afforded compound **42**. Hydroxy compound **42** was converted into its mesyl derivatives **43** and its cyclisation was carried out by using Staudinger reaction conditions followed by Boc protection to afford piperidine carbamate **44** and non cyclized carbamate compound **45**. After TBS-ether of **44**, deprotection gave two isomers **46** and **47** which were readily separated by column chromatography. *O*-Debenzylation of **46** and **47** under hydrogenation conditions afforded diols **48** and **49** respectively.

Section 4: Introduction to polyhydroxy piperidine alkaloids

This section describes the biological activity and reported synthetic routes to polyhydroxy piperidine alkaloids. Polyhydroxy piperidine core have shown promising biological activity, specifically as glycosidase inhibitors, anticancer agents and as antiviral agents.[11] D-Fagomine **50** has inhibitory activity towards mammalian α-glucosidase and β-galactosidase[12] (Figure 3). There has been less attention paid towards the synthesis L-configuration of Fagomine **51** (Figure 3) and its isomers. Recently, there is a report on synthesis of L-configuration of Fagomine[13,14] and its isomers. In literature,[15] there are various protocols used for the syntheses of D-Fagomine **50** (Figure 3) and its isomer syntheses. Recently, 1-deoxynojirimycin (1-DNJ) **52** dervivatives such as miglitol **53** and *N*-butyl-1-deoxynojirimycin **54** have been used for the the treatment of type II diabetes and type I Gaucher's diseases. Recently, it has been found that L-*galacto*-1-deoxynojirimycin (L-*galacto*-1-DNJ**) 55**, L-*altro*-1-deoxynojirimycin (L-*altro*-1-DNJ) **56** and L-*allo*-1-deoxynojirimycin (L-*allo*-1-DNJ**) 57** and their derivatives are involved in various biological activities.

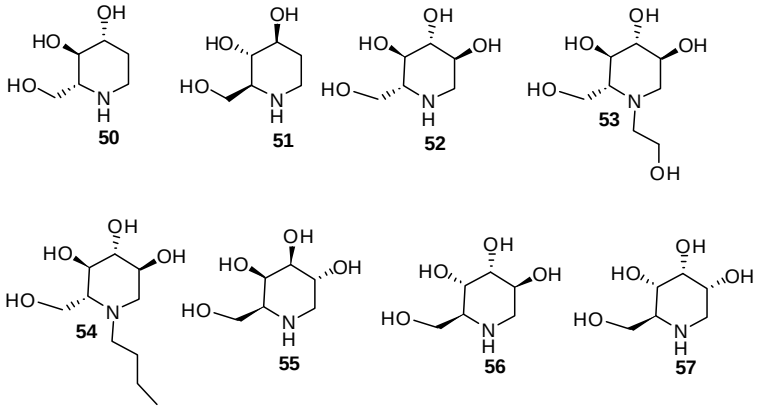


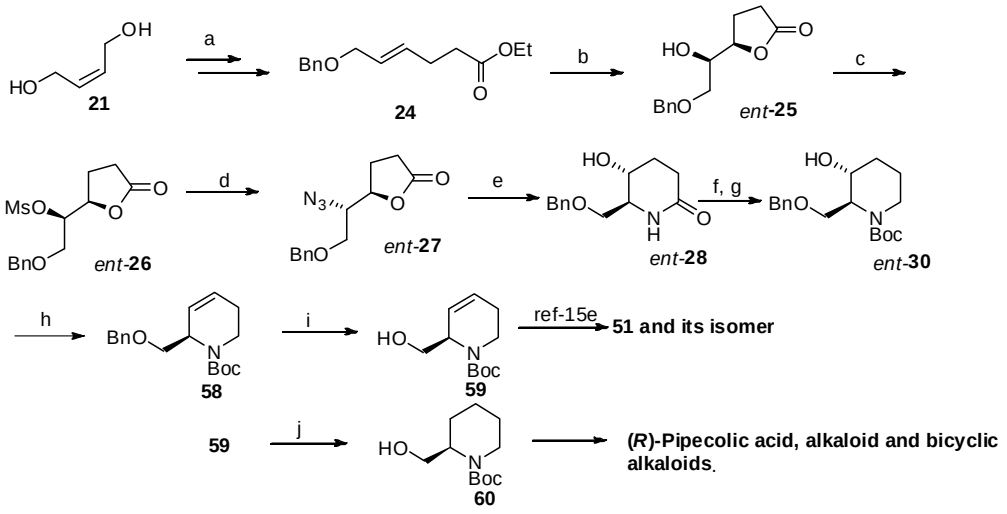
Figure 3

Section 5: Formal synthesis of L-fagomine and its isomers, L-*allo*-1-deoxynojirimycin (L-*allo*-1-DNJ), L-*altro*-1-deoxynojirimycin (L-*altro*-1-DNJ) and L-*galacto*-1-deoxynojirimycin (L-*galacto*-1-DNJ)

This section describes synthesis of advanced/ versatile intermediate and their application for the synthesis of many piperidine compounds bearing L-configuration. Based on the protocol developed by this group towards the asymmetric synthesis[16] of alkaloids, the utility of key synthon **58** for the synthesis of polyhydroxy piperidine alkaloids *viz*. Fagomine **51** and its isomers, L-*galacto*-1-deoxynojirimycin (L-*galacto*-1-DNJ) **55** L-

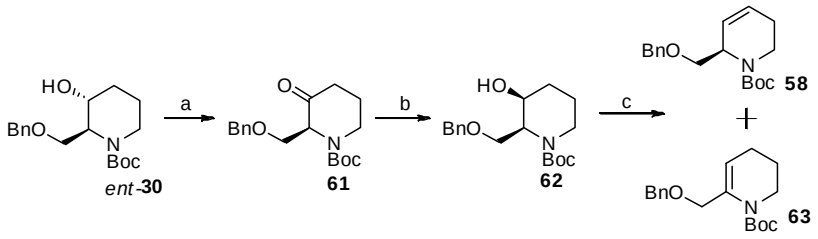
altro-1-deoxynojirimycin (L-*altro*-1-DNJ) **56**, and *allo*-1-deoxynojirimycin (L-*allo*-1-DNJ) **57** was undertaken.

Cis-butene-1,4-diol **21** was converted into enantiomerically pure hydroxy lactone *ent*-**25** (Scheme 4) by known literature procedure.[17] Hydroxy lactone *ent*-**25** was converted to its azido lactone *ent*-**27** *via* mesyl derivative *ent*-**26**. Reductive lactamisation of *ent*-**27** provided the desired six membered lactam *ent*-**28**. Lactam *ent*-**28** was reduced followed by its amine protection to afford urethane *ent*-**30**. Initial attempt was conversion of hydroxyl carbamate *ent*-**30** to its iodo derivative. Surprisingly, it gave olefin as a single isomer **58**. After *O*-Debenzylation of **58** provided alcohol **59** which is a known intermediate for the synthesis of L-fagomine **51** Hence, the synthesis of **51** constitutes a formal synthesis of L-fagomine **51** and its congeries.



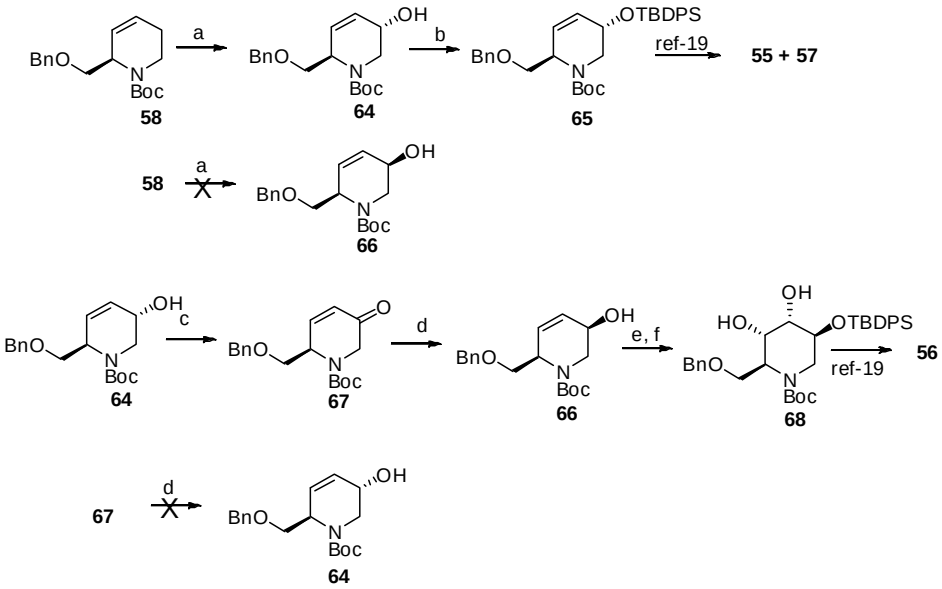
Scheme 4 *Reagents and conditions: (a) Ref.17; (b) $K_3Fe(CN)_6$, K_2CO_3, $(DHQD)_2PHAL$, OsO_4, $MeSO_2NH_2$, t-BuOH:H_2O (1:1) 0 ^oC, 24 h, 94%; (c) MsCl, Et_3N, DMAP (cat.), DCM, 5 h, 91%; (d) NaN_3, DMF, 80 ^oC, 18 h, 87%; (e) $Pd(OH)_2$, H_2, MeOH, 30 psi, rt, 3 h, 93%; (f) LAH, THF, 0 ^oC to rt, 3 h; (g) $(Boc)_2O$, TEA, DMAP (cat.), THF rt, overnight, 63% (over two steps); (h) PPh_3, imidazole, I_2, toluene, 120 ^oC, 10 min, 85%; (i) Na(metal), THF, ammonia, -78 ^oC, 30 min, 88%; (j) Pd/C, H_2, MeOH, 50 psi, 92%;*

Cis isomer **62** was obtained from hydroxyl derivative *ent*-**30** by oxidation- reduction sequence (Scheme 5). Subjecting alcohol **62** to the reaction with triphenyl phosphine, imidazole and iodine led to the formation of two regioisomeric olefins **58** and **63**.



Scheme 5 *Reagents and conditions: (a) IBX, EtOAc, reflux, 3 h, 90%; (b) $NaBH_4$, MeOH, 0 ^oC, 30 min, 88 %; (c) PPh_3, imidazole, I_2, toluene, reflux, 30 min, 60%;*

Olefin **58** was subjected to allylic oxidation[18] to furnish only one isomer **64** (Scheme 6). Hydroxy group of **64** was protected as its TBDPS ether to provide **65**. Since the TBDPS derivative **65** forms an important intermediate in the synthesis of L-*allo*-1-deoxynojirimycin (L-*allo*-1-DNJ) **57** and L-*galacto*-1-deoxynojirimycin (L-*galacto*-1-DNJ) **55**. Hence, the present work constitutes the formal synthesis of L-*allo*-1-DNJ **57,** L-*galacto*-1-DNJ **55**.



Scheme 6 *Reagents and conditions: (a) SeO_2, 1,4-dioxane, reflux, 3 h, 30%; (b) TBDPSCl, imidazole, DMAP (cat.), DCM, 15h; (c) IBX, EtOAc, reflux, 3 h, 90%; d) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 ^oC, 80%; e) TBDPSCl, imidazole, DMAP(cat.), DCM, 15 h; f) $RuCl_3$, $NaIO_4$, CH_3CN:EtOAc:H_2O, 0 ^oC, 54% (over two steps);*

The *cis* isomer **66** was obtained from hydroxy derivative **64** by employing oxidation and Luche's reduction sequence. The hydroxy group of **66** was protected as its TBS ether

followed by flash dihydroxylation to afford diol **68**. Since, diol **68** is a known intermediate in the synthesis of L-*altro*-1-deoxynojirimycin (L-*altro*-1-DNJ) **56.** This constitutes the formal synthesis L-*altro*-1-DNJ **56**.[19]

Chapter 3:

Section 1: Introduction of 1-deoxyallonojirimycin (*allo*-1-DNJ) and 1-deoxytalonojirimycin (*talo*-1-DNJ)

The present section describes the reported synthetic approaches for the synthesis of *allo*-1-DNJ (**57**, *ent*-**57**) and *talo*-1-DNJ (**69**, *ent*-**69**) (Figure 4). Azasugar or iminosugar have significant biological activity they act as glycosidase inhibitor and are extensively used for the treatment of AIDS, cancer, diabetes and viral infections.[20] Hashimoto *et al*. had first reported the synthesis of L-*talo*-1-DNJ **69**[21] (Figure 4) which was shown to be a potent inhibitor of α-glucosidase and α-L-fucosidase. Recently, it has been found that L-isomers of azasugars also exhibit remarkable activity against glycosidase inhibitor.[22]

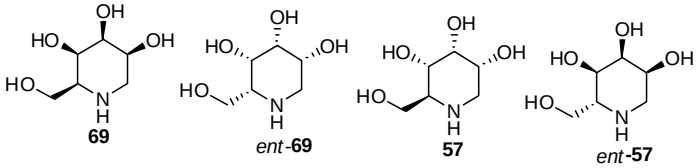
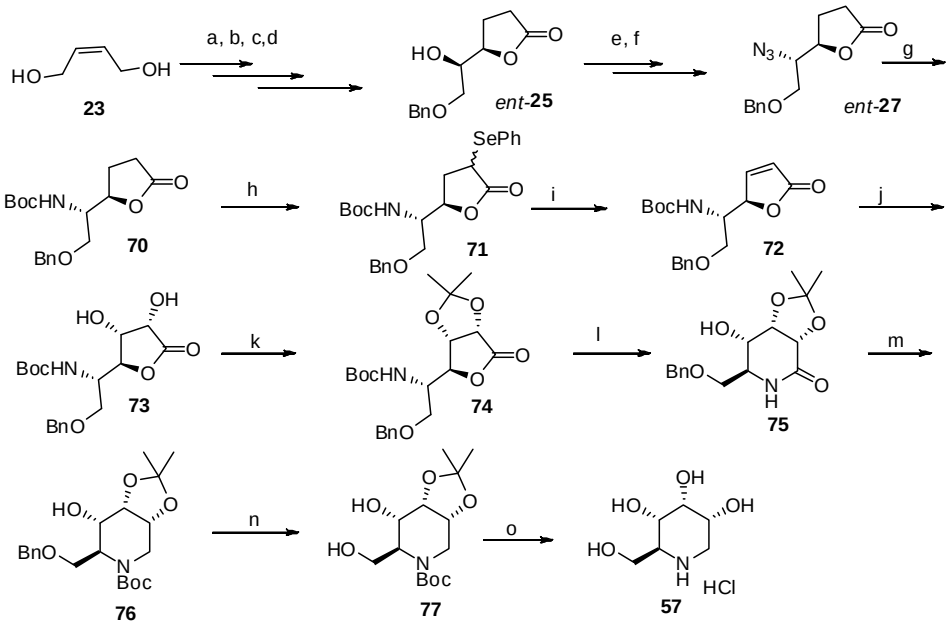


Figure 4

Chapter 2: Section 2: Asymmetric synthesis of L-*allo*-1-deoxynojirimycin (L-*allo*-1-DNJ)

The present section describes the synthetic approach for the synthesis of L-*allo*-1-DNJ **57**. Synthesis began from commercially available cheap starting material like *cis*-butene-1, 4-diol **21** (Scheme 7). Enantiomerically pure azidolactone *ent*-**27** was obtained from **21** which has been described in an earlier section.

Butenolide **72** was obtained from *ent*-**27** involving azide reduction, Boc-protection to furnish carbamate **70**, *α*-phenylselenation to furnish seleno compound **71** and elimination reaction sequence. Butenolide **72** was dihydroxylated followed by its acetonide protection to afford acetonide **74**. After Boc-deprotection of lactone **74** provided the desired six membered lactam ring **75**. The diol **77** was obtained from lactam **75** involving amide reduction, carbamate protection, *O*-debenzylation reaction sequence. Global deprotection of carbamate **77** furnished salt of L-*allo*-1-deoxynojirimycin **57**.



Scheme 7 *Reagents and conditions: (a) $HgSO_4$, H_2SO_4 (cat), H_2O, 100 ^oC, 3 h, 65%; (b) KOH, BnCl, benzene, reflux, 65%; (c) Triethyl orthoacetate, propanoic acid, 140 ^oC, 3 h, 85%; (d) $K_3Fe(CN)_6$, K_2CO_3, $(DHQD)_2PHAL$, OsO_4, $MeSO_2NH_2$, t-BuOH:H_2O (1:1) 0 ^oC, 24 h, 94%; (e) MsCl, Et_3N, DMAP (cat.), DCM, 5 h, 91%; (f) NaN_3, DMF, 80 ^oC, 18 h, 87%; (g) $Pd(OH)_2$, H_2, TEA, $(Boc)_2O$, ethyl acetate, 3 h, 88%; (h) LDA, dipheny diselenide, THF, -78 ^oC, 57%; (i) H_2O_2, CH_3COOH, THF, 30 min, 0^oC, 78%; (j) $RuCl_3$, $NaIO_4$, EtOAc:MeCN:H_2O, 0 ^oC, 71%; (k) DMP, CSA, DCM, rt, 91%; (l) TFA, DCM, 0 ^oC-rt, 3 h, 53%; (m) i) BH_3.DMS, THF, 0 ^oC-rt, 24 h, ii) TEA, $(Boc)_2O$, THF, rt, overnight, 58% (over two steps); (n) i) $Pd(OH)_2$, H_2, MeOH, rt o) MeOH, conc HCl, rt, 3 h, 80% (over two steps).*

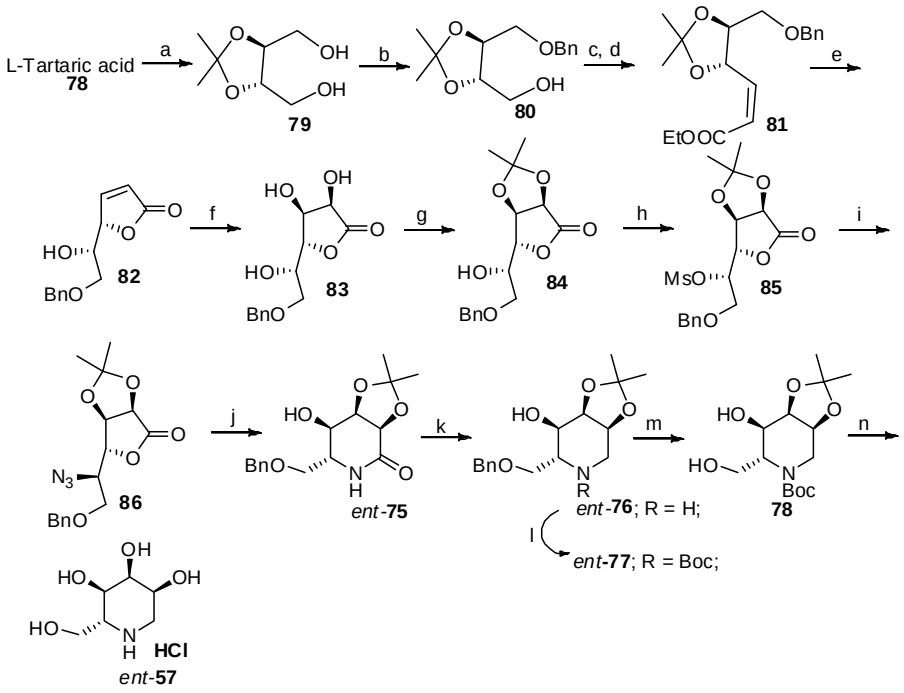
Chapter 2:

Section 3: Synthetic studies towards D-*allo*-1-deoxynojirimycin (D-*allo*-1-DNJ) and L-*talo*-1-deoxynojirimycin (L-*talo*-1-DNJ)

The present section describes the total synthesis of D-*allo*-1-DNJ (*ent*-**57**) and L-*talo*-1-DNJ **69** using L-tartaric acid as chiral template.

Symmetric diol **79** was derived from L-tartaric acid **78** by known literature procedure.[23] Diol of **79** was selectively monoprotected by benzyl group to provide monobenzyl ether **80** (Scheme 8). Butenolide **82** was obtained from benzyl ether **80** involving Swern oxidation, Wittig reaction and acid treatment reaction sequence. Butenolide **82** was dihydroxylated, followed by its acetonide protection to afford acetonide **84**.[24] Hydroxy group of lactone **84**

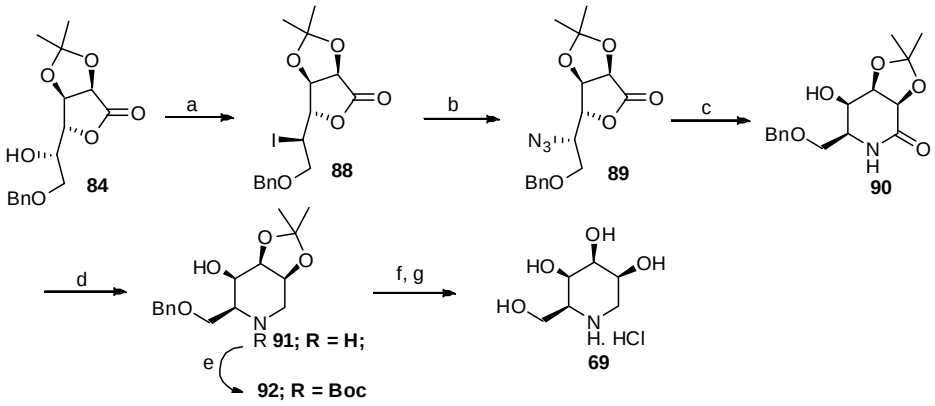
was converted into its mesylate **85** and displaced with azide to furnish azidolactone **86**. Azidolactone **86** was reduced under hydrogenation condition to furnish the desired six membered lactam *ent*-**75**. Lactam *ent*-**75** was reduced followed by its Boc-protection to afford urethane *ent*-**77**. The piperidine carbamate *ent*-**77** was subjected for hydrogenation and followed by acid treatment to afford salt of *ent*-**57**.



Scheme 8 *Reagents and conditions: a) Ref 23; b) BnBr, TBAB, NaH, THF 0 ^{o}C-rt, 3h, 75%; c) oxalyl chloride, DMSO, DCM, -78^{o}C, TEA, 30 min; d) $PPh_3CHCOOEt$, MeOH, -50^{o}C-rt, overnight, 70%; e) conc HCl (cat.), MeOH, 0^{o}C-rt, overnight, 70%; f) $RuCl_3$, $NaIO_4$, EtOAc:H_2O:MeCN 0 ^{o}C, 3 min, 53%; g) DMP, CSA, DCM, rt, overnight, 90%; h) MsCl, TEA, DMAP(cat.), DCM, 0^{o}C, 1 h, 91%; i) NaN_3, DMF, 90 ^{o}C, 18 h, 88%; j) $Pd(OH)_2$, H_2, MeOH, rt, 1 h, 90%; k) BH_3.DMS, THF 0 ^{o}C- rt, overnight; l) $(Boc)_2O$, TEA, DMAP (cat.), THF, rt, overnight, 58% (over two steps); m) $Pd(OH)_2$, H_2, MeOH, rt, 6 h; n) conc. HCl, MeOH, rt, 3 h, 90%;*

Taking advantage of hydroxy lactone **84** was converted to its iodo derivative **88** (Scheme 9). Iodo was replaced by azide functionality to afford azido lactone **89.** Azidolactone **89** was reduced under hydrogenation condition to provide desired six membered lactam **90**.

L-*talo*-1-DNJ **69** was obtained from lactam **90** involving reduction, Boc protection and global deprotection reaction sequence.



Scheme 9 *Reagents and conditions: a) PPh_3, imidazole, Iodine, toluene, 110 ^oC, 75%; b) NaN_3, DMF, 80 ^oC, 60%: c) $Pd(OH)_2$, H_2, MeOH, rt, 88%; d) BH_3.DMS, THF 0 ^oC- rt, overnight; e) $(Boc)_2O$, TEA, DMAP (cat.), THF, rt, overnight, 50% (over two steps); f) $Pd(OH)_2$, H_2, MeOH, rt, 6 h, g) conc. HCl, MeOH, rt, 3 h, 70% (over two steps).*

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Chapter 1 Formal synthesis of Mitralactonine

Section 1 Introduction to mitralactonine

1.1.1 Introduction

(-)-Mitralactonine **1** (Fiqure 1) was first isolated by Takayama *et al.*[1] from leaves of *Mitragyna speciosa* Korth. (Rubiaceae) found in Malaysia. The leaves also contain six known alkaloids having corynthe indole moiety as structural unit. The leaves of this plant have narcotic activity when smoked or chewed. Further, pharmacological assays are still in progress. The interesting biological activity and structural features of mitralactonine have attracted attention of many organic chemists towards its synthesis. The main synthetic challenge in mitralactonine synthesis is construction of

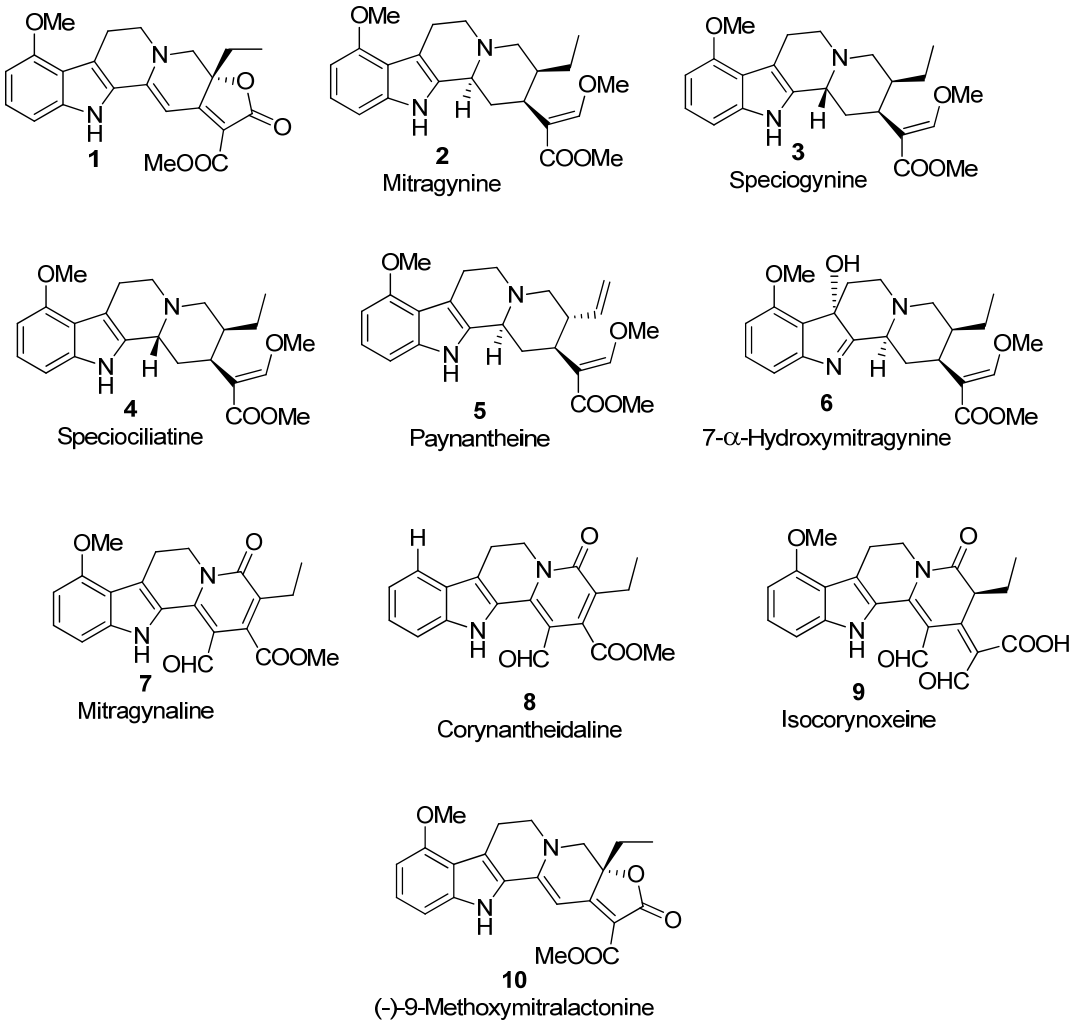


Figure 1

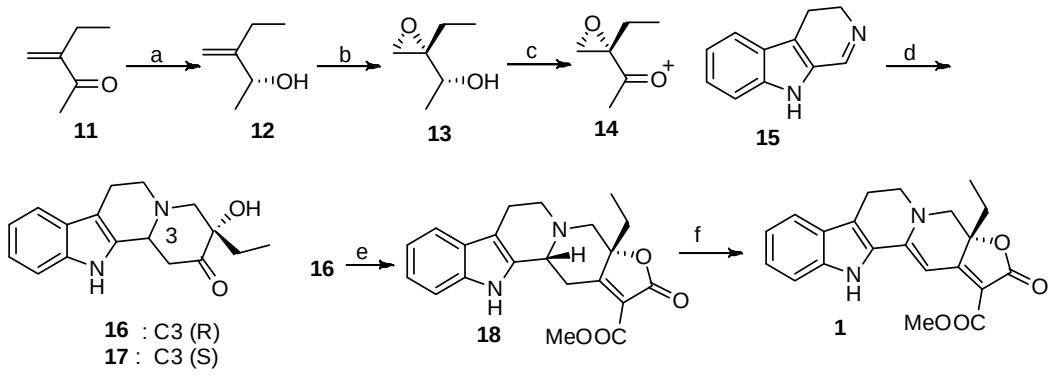
pentacyclic core and butenolide ring. Mitragynine **2**, speciogynine **3**, speciociliatine **4**, paynantheine **5**, 7-α-hydroxymitragynine **6**, mitragynaline **7**, corynantheidaline **8**, isocorynoxeine **9** and (-)-9-methoxymitralactonine **10** (Fiqure 1) are other alkaloids sharing this corynanthe framework.[2]

Structure elucidation, isolation and synthesis of mitralactonine was accomplished by Takayama *et al*[1] in both asymmetric as well as racemic fashion.

1.1.2 Litrature Survey : Reported syntheses

Takayama *et al.* [1] (*J. Org. Chem.* **1999**, *64*, 1772)

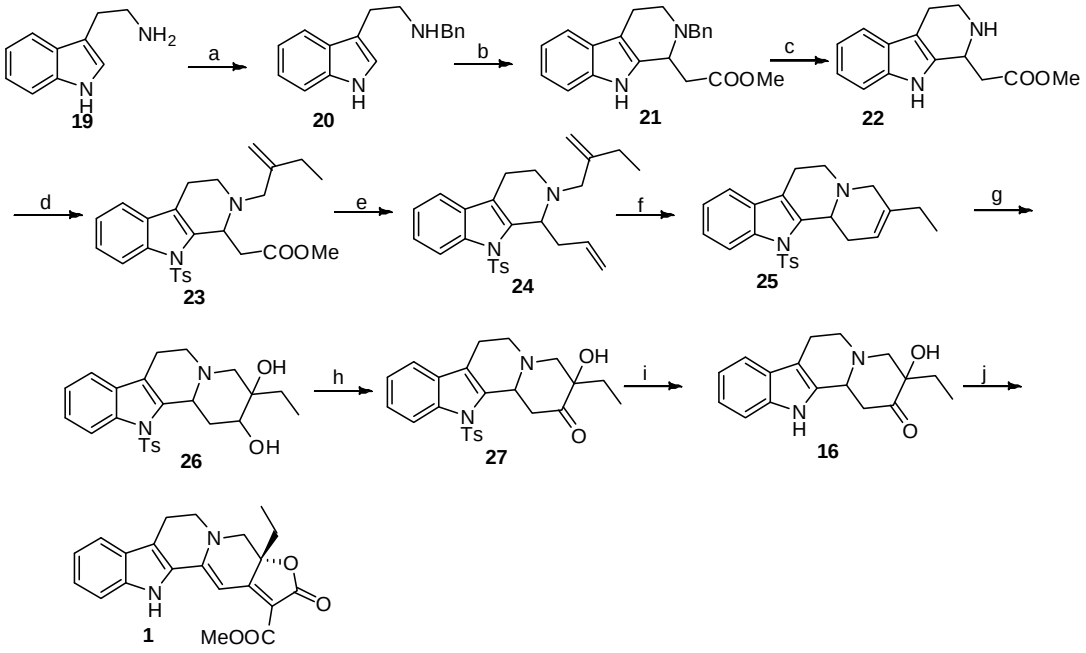
Takayama *et al.* accomplished asymmetric total synthesis of mitralactonine (Scheme 1) using Sharpless asymmetric epoxidation and enantioselective reduction as the key steps. Enantiomerically pure allylic alcohol **12** was obtained by asymmetric reduction of enone **11**. Allylic alcohol **12** was converted to epoxide derivative **13** by employing Sharpless asymmetric epoxidation. Hydroxy compound **13** was subjected under Swern reaction conditions to afford keto compound **14**. Condensation of carboline **15** with chiral epoxide **14** furnished diastereomeric mixture of **16** and **17**. Desired isomer **16** was subjected to Knoevenagel condensation with dimethyl malonate in refluxing toluene in the presence of $AcONH_4$ and AcOH to give directly the pentacyclic core **18** which was further exploited for the synthesis (-)-mitralactonine **1.**



Scheme 1 *Reagents and conditions: a) (S)-5,5-Diphenyl-2-methyl- 3,4-propano-1,3,2-oxazaborolidine (0.2 equiv), BH_3-THF complex, dry THF, -20 °C (65% after distillation); b) Diisopropyl D-tartrate, $Ti(i\text{-}PrO)_4$, t-BuOOH, CH_2Cl_2, -40 °C (56% after distillation); c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C (41% after distillation); d) MeOH, reflux (**16** 36%. **17** 9%); e) i) Dimethyl malonate, $AcONH_4$, AcOH, dry toluene, reflux (55%); f) i) t-BuOCl, Et_3N, CH_2Cl_2, 0 °C, iii) 5N Ethanolic HCl, 0 °C, then alkaline workup (83%).*

Chavan *et al*[3] (*Tetrahedron Lett.* **2006**, *47*, 9301)

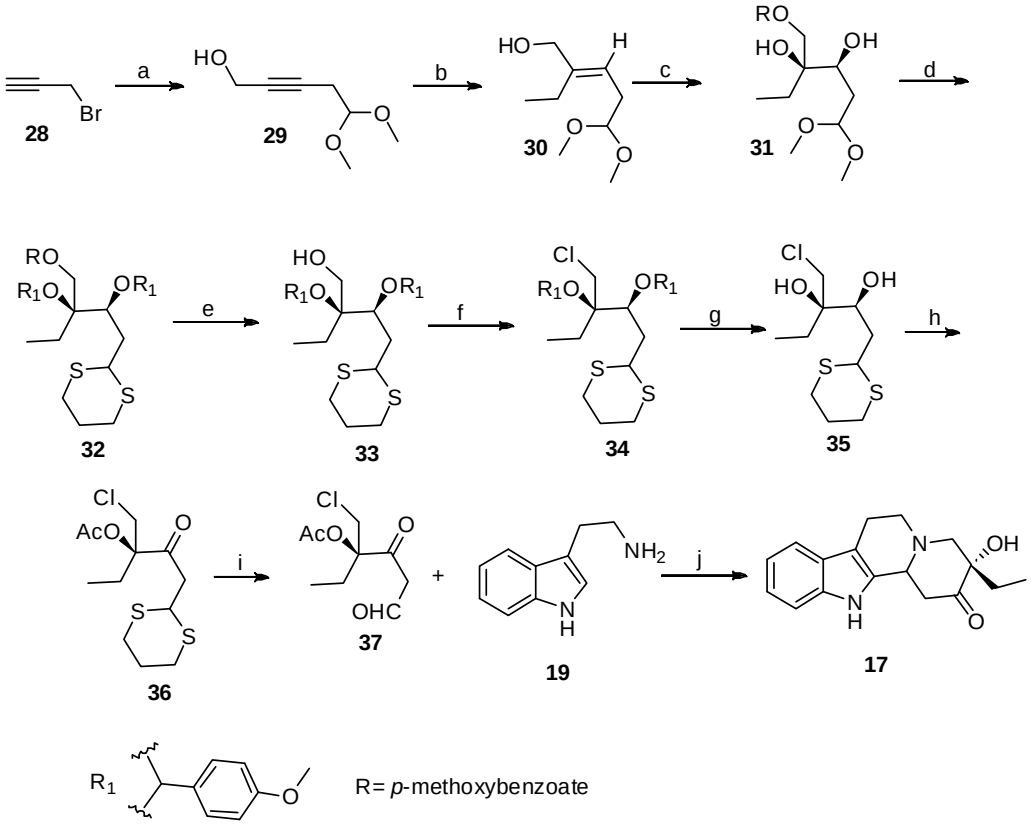
Chavan *et al*. reported formal synthesis of mitralactonine (Scheme 2) by employing ring closing metathesis as key step. Tricyclic amine **22** was derived from tryptamine by carrying some chemical transformations on tryptamine **19**. Free secondary nitrogen in **22** was allylated and the indole nitrogen was protected as its tosyl derivative to obtain **23**. Ester group in **23** was reduced to corresponding aldehyde which on one carbon Wittig homologation gave the diene **24**. Diene **24** was subjected to RCM reaction[4] followed by dihydroxylation to afford diol **26**. Keto compound **16** was obtained by oxidation and tosyl deprotection on **26**.



Scheme 2 *Reagents and conditions: (a) (i) Benzaldehyde, toluene, rt, 12 h, (ii) MeOH, $NaBH_4$, rt, 1/2 h; (b) Methyl propiolate, TFA, $CHCl_3$, rt, 1/2 h, 94%; c) Pd/C, H_2 (60 psi), rt, 10 h, quantitative; (d) i) $CH_3CH_2C(=CH_2)CH_2OMs$, K_2CO_3, DCM, rt, 24 h, 70%; ii) NaOH, $TBAHSO_4$, p-TsCl, benzene, rt, 20 min, 84%; e) (i) DIBAL-H, DCM, -78 ^oC, 2 h, (ii) $PPh_3=CH_2$, THF, rt, 12 h, 68% (two steps); f) Grubb's 2 nd gen. cat. (10 mol %), toluene, 80 ^oC, 3 h, 87%; g) $K_3Fe(CN)_6$, K_2CO_3, OsO_4 (cat.), t-BuOH:H_2O 1:1, rt, 24 h, 60%; h) DMSO, oxalyl chloride, DCM, Et_3N, -60 ^oC, 50%; i) TBAF, THF, reflux, 1.5 h, 60%; j) ref 1.*

Chavan et al. [5] (*Synlett*, **2007**, 79)

Chavan *et al.* achieved asymmetric formal total synthesis of mitralactonine (Scheme 3) using Sharpless asymmetric dihydroxylation and Pictet Spengler cyclisation as the key steps.



Scheme 3 *Reagents and conditions: (a) Ref. 6; (b) EtMgBr, Et_2O, reflux, 4 h, 75%; c) i) Anisyl chloride, Et_3N, CH_2Cl_2, r.t., 3 h, 85%; ii) $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, t-BuOH–H_2O, OsO_4, 0 °C, 24 h, 90%; d) Propane 1,3-dithiol, $BF_3{\cdot}Et_2O$, anhydr. CH_2Cl_2, r.t., 0.5 h, 70%; ii) Anisaldehyde dimethyl acetal, PTSA, anhydr. CH_2Cl_2, r.t., 0.5 h, 88%; e) K_2CO_3, MeOH, r.t., 12 h, 90%; f) PPh_3, CCl_4, imidazole, reflux, 3 h, 86%; g) PTSA, MeOH, r.t., 0.5 h, 87%; h) i) DMP, anhydr. CH_2Cl_2, 0–5 °C, 3 h, 40%; ii) Ac_2O, DMAP, r.t., 0.5 h, 87%; i) i) MeI, MeCN–H_2O, reflux, 24 h; j) Tryptamine, 2M HCl/(EtOH), r.t., 12 h, 40% (2 steps).*

Alcohol **29** was derived from propagyl bromide **28** by known literature protocol[6] which on Grignard addition furnished allylic alcohol **30**. Allylic alcohol **30** was protected and subjected subsequently to asymmetric dihydroxylation to furnish **31**. Diol **31** was treated with propane 1,3-dithiol in presence of $BF_3{\cdot}OEt_2$ to afford the

dithiane derivative which on diol protection gave **32**. Saponification of benzoate group in **32** followed by chlorination afforded chloro derivative **34**. Hydroxy group in **34** was oxidised using DMP followed by tertiary hydroxy protection, removal of benzylidene group and dithiane deprotection to furnish aldehyde **36**. Tetracyclic framework of mitralactonine **17** was constructed by condensation of tryptamine **19** and aldehyde **37**.

1.1.3 References

1. Takayama, H.; Kurihara, M.; Kitajima, M.; Said, M. I.; Aimi, N.; *J. Org. Chem.* **1999**, *64*, 1772.

2. Takayama, H. *Chem. Pharm. Bull.* **2004**, *52*, 916.

3. Chavan, S. P.; Sharma, P.; Sivappa, R.; Kalkote, U.R. *Tetrahedron Lett.* **2006**, *47*, 9301.

4 . (a) Grubbs, R. H. Handbook of Metathesis. In Applications in Organic Synthesis; WILEY-VCH, 2003; Vol. 2; (b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc*. **1992**, *114*, 7324.

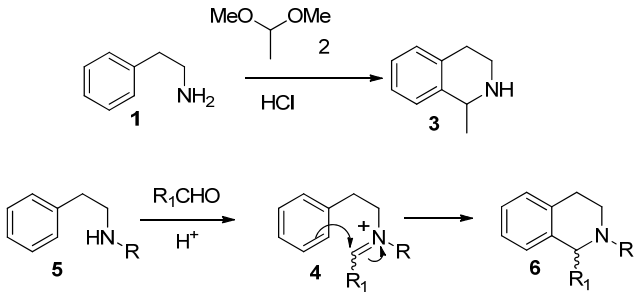
5. Chavan, S. P.; Sharma, P.; Sivappa, R.; Kalkote, U. R. *Synlett,* **2007**, 79.

6. Jung, M. E.; Gardiner, J. M. *Tetrahedron Lett.* **1994**, *35*, 6755.

Section 2: Formal synthesis of mitralactonine

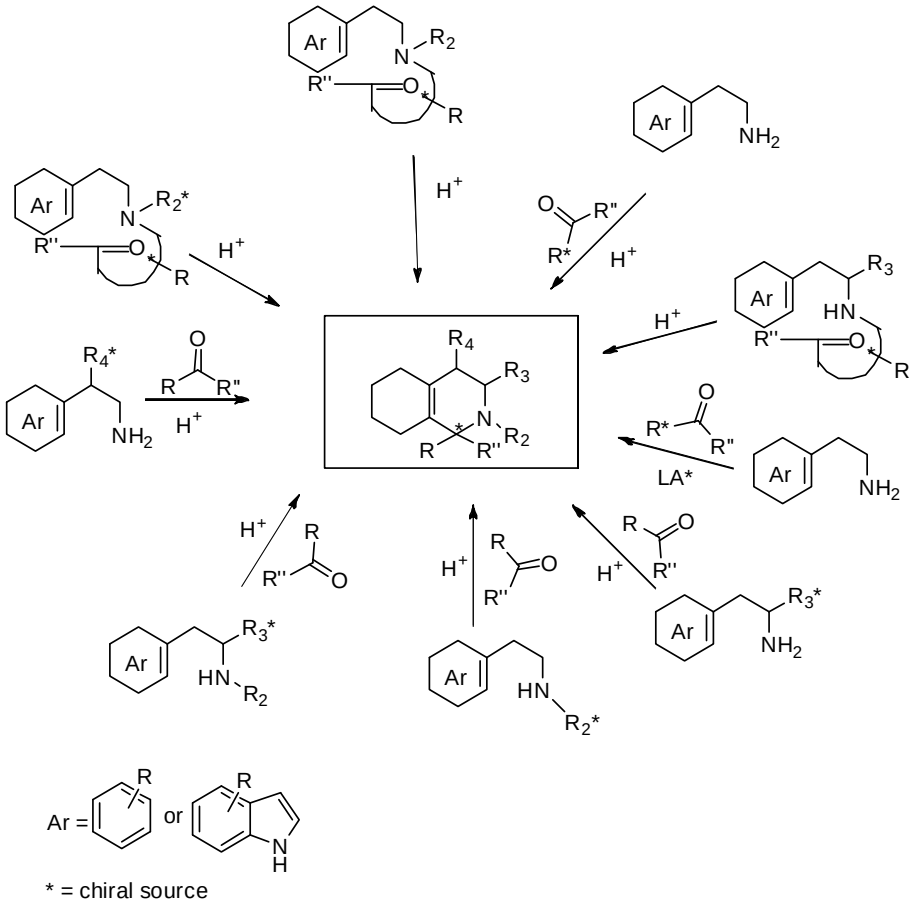
1.2.1 Introduction: A Brief Account on Pictet-Spengler Reaction[1]

The Pictet- Spengler condensation[2] is one of the most important strategies utilized by the modern chemists for the synthesis of substituted isoquinoline and indole alkaloids. It was discovered in **1911** by Amé Pictet and Theodor Spengler[3]. 1-Methyl-1,2,3,4-tetrahydroisoquinoline **3** was isolated from the condensation of *β*-phenethylamine **1** with acetal **2** in the presence of hydrochloric acid.[4] This reaction was later altered with other *β*-phenethylamines such as *N*-alkyl, *N*-acyl and *N*-sulfonyl derivatives, moving *via* iminium, *N*-alkyliminium, *N*-acyliminium or *N*-sulfonyliminium ion formation **4**, respectively and subsequent intramolecular electrophilic substitution, as summarized in Scheme 1.



Scheme 1

The literature survey revealed that multiple approaches to the asymmetric synthesis of 1-substituted tetrahydroisoquinoline (THIQ) and tetrahydro-*β*-carboline (THBC) derivatives by employing the Pictet-Spengler protocol are reported. These include the use of 1,4-chirality transfer,[5] 1,3-chirality transfer,[6] obliterable chiral auxiliaries attached to the nitrogen (N_b in case of THBC),[7] as well as chiral Lewis acids and other compounds as catalysts.[8] In advance, optically active aldehydes and ketones[9] as well as intramolecular versions where chiral aldehydes are tethered to the amino group of *β*-phenethylamine or tryptamine derivatives[10] have found wide applicability, part of these being the subject of this review. Other recorded syntheses include combinations of the above strategies,[11] as summed up in Scheme 2.



Scheme 2 A general protocol for the synthesis of substituted tetrahydroisoquinolines (THIQ) and tetrahydro-*β*-carbolines (THBC)

1.2.2 Present work

Mitralactonine like skeletons having interesting biological activity (narcotic activity) and structural features (pentacyclic framework) attracted many organic chemists towards their synthesis. In literature, there are three protocols reported for the construction of D-ring of mitralactonine which were based on a) carboline condensation with aldehyde b) RCM approach.

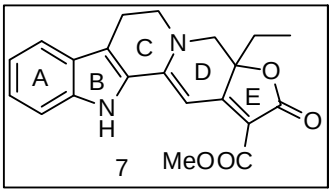
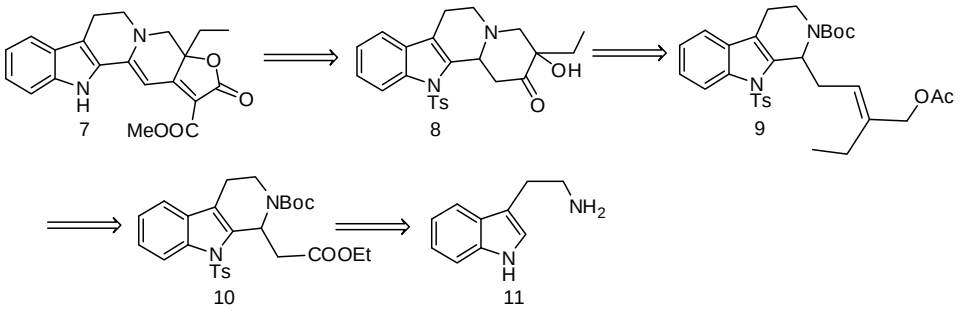


Figure 1

In the present work, C-N bond formation *via* intramolecular *N*-alkylation which is one of the most powerful tools in the synthesis of alkaloids[12] was utilized. This reaction was exploited in the present work for the synthesis of mitralactonine (Figure 1).

1.2.2.1 Retrosynthetic analysis

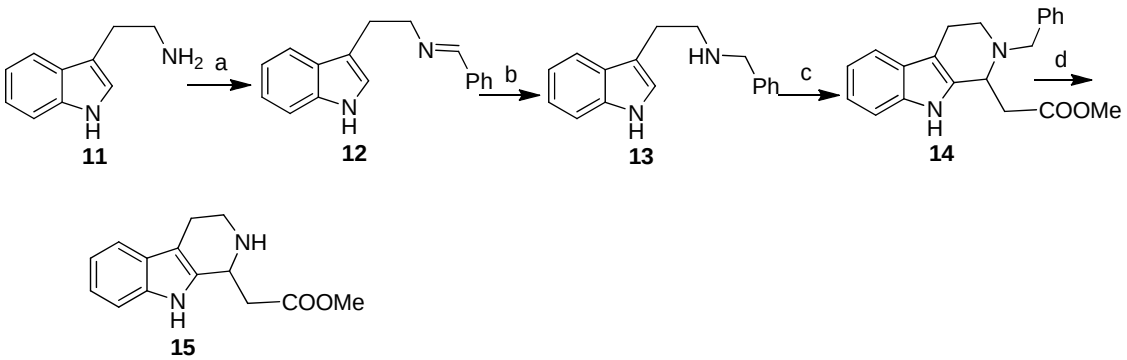
Retrosynthetic analysis (Scheme 3) revealed that pentacyclic core **7** could be obtained from tetracyclic α-hydroxy keto compound **8**. α-Hydroxy keto compound **8** in turn can be easily generated from allylic *O*-acetate derivative **9** which could be easily accessed from tricyclic ester **10**, for which tryptamine **11** would be ideal starting material.



Scheme 3 Retrosynthetic analysis of mitralactonine

1.2.2.2 Results and discussion

Accordingly, tricyclic amine **15** was prepared from tryptamine **11** by known literature protocol[13] involving formation of imine **12**, imine reduction to furnish **13**, Pictet-Spengler cyclisation to yield **14** and *N*-debenzylation to furnish amine **15** (Scheme 4).



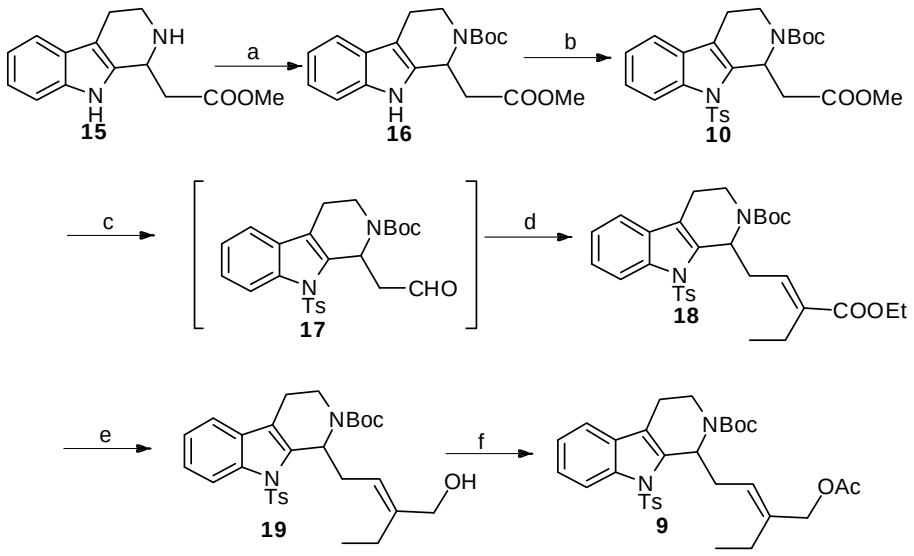
Scheme 4 *Reagents and conditions: a) PhCHO, toluene, rt, 24 h; b) $NaBH_4$, MeOH,*

0 ^{o}C, 2 h; c) methyl propiolate, TFA, $CHCl_3$, 0 ^{o}C, 1 h, 80%; d) Pd/C, MeOH, rt, 70 psi, 24 h, 95%.

Amine functionality in **15** was protected using $(Boc)_2O$, TEA followed by addition of DMAP (cat.) in THF to afford carbamate **16** (Scheme 5). Strong absorption band at 1690 cm^{-1} in its IR spectrum, indicated presence of carbamate moiety. Its ^{1}H NMR spectrum showed a singlet of δ 1.49 integrating for nine protons which was attributed to Boc group. The singlet that appeared at δ 3.75 integrating for three protons was assigned to ester methyl protons. ^{13}C NMR spectrum of **16** showed peaks at δ 28.5 and 154.1 and 151.5 (due to rotamers) confirming the presence of carbamate group. Finally mass spectrum of **16** showed the *m/z* peak at 367 $(M + Na)^{+}$ and elemental analysis was also found to be in good agreement with the calculated values.

To avoid further functional group complications, indole nitrogen in **16** was protected as its *N*-tosyl derivative **10** using NaOH (as base), *p*-TsCl, and $TBAHSO_4$ (as a phase transfer catalyst) in 80% yield. ^{1}H NMR spectrum of **10** showed disappearance of multiplet at δ 8.69-8.86 corresponding to the NH proton of indole moiety. The peaks appearing at δ 2.34 and δ 2.74 in its ^{1}H NMR spectrum, integrating for three protons each were assigned to the Ar-$\underline{CH_3}$ and CO-O$\underline{CH_3}$ protons. The peaks at δ 7.12 - 8.14 integrating for eight protons were assigned to aromatic ring protons. ^{13}C NMR spectrum showed a signal at δ 28.4 corresponding to aromatic methyl carbon (Ar-$\underline{CH_3}$) providing the strong support for the formation of **10**. The mass spectrum of **10** showed the *m/z* peak at 521.3 $(M +Na)^{+}$ thus confirming the structure of **10**. Further, its single crystal analysis confirmed the formation of **10** (described in spectra section). For the construction of D ring of mitralactonine, ester group in **10** was reduced to corresponding aldehyde **17** followed by four carbon homologation to deliver unsaturated ester **18**.

N-Tosyl derivative **10** was reduced using DIBAL-H in DCM at -78 ^{o}C for 30 minutes to provide aldehyde **17** which without purification was treated with four carbon phosphorane in DCM at room temperature to afford unsaturated ester **18**. Its ^{1}H NMR spectrum showed the peaks at δ 1.34 (t) integrating for three protons and peaks at δ 4.25 (q) integrating for two protons which were assigned for COO$\underline{CH_2CH_3}$ protons.



Scheme 5 *Reagents and conditions: a) Boc anhydride, TEA, DMAP(cat), THF, rt, 3 h, 90%; (b) p-TsCl, NaOH, TBAHSO$_4$, toluene, rt, 30 min, 80%; (c) DIBAL-H, DCM, -78 ^{o}C, 30 min; (d) CH$_3$CH$_2$C(=PPh$_3$)COOEt, DCM, rt, overnight, 75%; (e) DIBAL-H, DCM, -40 ^{o}C, 2 h, 89%; (f) AcCl, TEA, DCM, 0 ^{o}C, 1 h, 88%.*

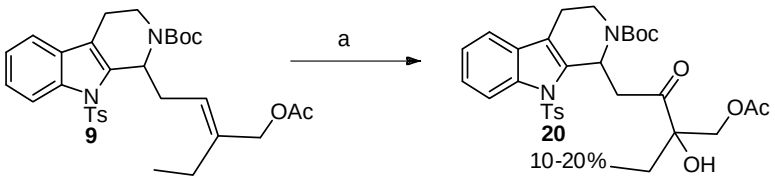
The characteristic *β*-olefin proton appeared at δ 6.93 as triplet supporting the formation of **18**. Signals that appeared at δ 13.8 (14.3), 20.2 (20.7), 60.21 and 167.3 in its ^{13}C spectrum, corresponded to the ester moiety (COOCH$_2$CH$_3$). Finally, appearance of a peak at *m/z* 589 $(M+Na)^+$ in the mass spectrum confirmed the structure of compound **18**.

Unsaturated ester **18** was reduced using DIBAL-H in DCM at -40 ^{o}C for 30 min to afford allylic alcohol **19** in 89% yield. The formation of **19** was confirmed by spectroscopic analysis. ^{1}H NMR spectrum showed the disappearance of peaks at δ 1.34 (t) and 4.25 (q) indicating consumption of ester functionality. A signal that appeared at δ 66.3 in its ^{13}C spectrum, corresponding to CH$_2$-OH carbon supported the formation of **19**. Further, appearance of a peak at *m/z* 544.2250 $(M+Na)^+$ in the HRMS spectrum confirmed the structure of allylic alcohol **19**.

To carry out other functional group transformations, the free hydroxy group of **19** was protected as its *O*-acetate derivative **9** using acetyl chloride, triethyl amine and DMAP (cat.) in DCM at 0 ^{o}C in 88% yield. Its IR spectrum showed the strong absorptions at 1735 cm^{-1} and 1685 cm^{-1} indicating presence of ester and carbamate functionality. ^{1}H

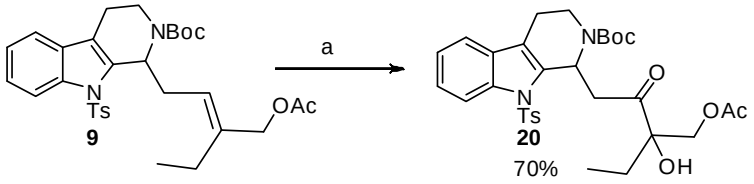
NMR spectrum revealed a singlet at δ 2.08 integrating for three protons corresponding to $\underline{CH_3}COO$- protons. Signal at δ 170.8 in its ^{13}C spectrum, corresponding to carbonyl carbon of ester functionality supported the formation of **9**. Finally, HRMS analysis showed the molecular ion peak at *m/z* 589.2345 $(M+Na)^+$ confirming the formation of **9**.

Attempted oxidation of double bond in **3** was carried out using $KMnO_4$ (as oxidizing agent) in acetone: water system (Scheme 6) but yield of this reaction was not satisfactory. Then, the attention was shifted towards the $RuCl_3$/ $NaIO_4$ mediated oxidation.[14] It was found that yield of this reaction was satisfactory furnishing the desired keto alcohol **20**.



Scheme 6 *Reagents and conditions: $KMnO_4$, acetone: H_2O, 0 ^oC, 10-20%;*

Accordingly, *O*-acetyl derivative **9** was treated with $RuCl_3$, oxone and $NaHCO_3$ in CH_3CN:H_2O: EtOAc at 0 ^oC to furnish non separable diastereomeric mixture of α-hydroxy ketone compound **20** (Scheme 7). Formation of keto compound **20** was confirmed by spectroscopic analysis. IR spectrum displayed the strong bands at 3444 cm^{-1}, 1719 cm^{-1} and 1685 cm^{-1} indicating the presence of hydroxy, ketone and carbamate functionalities. Disappearance of signal at δ 5.63 in its ^1H NMR spectrum integrating for one proton indicated the consumption of double bond.



Scheme 7 *Reagents and conditions: a) $RuCl_3$, $NaHCO_3$, oxone, CH_3CN:H_2O:EtOAc, 0 ^oC, 70%.*

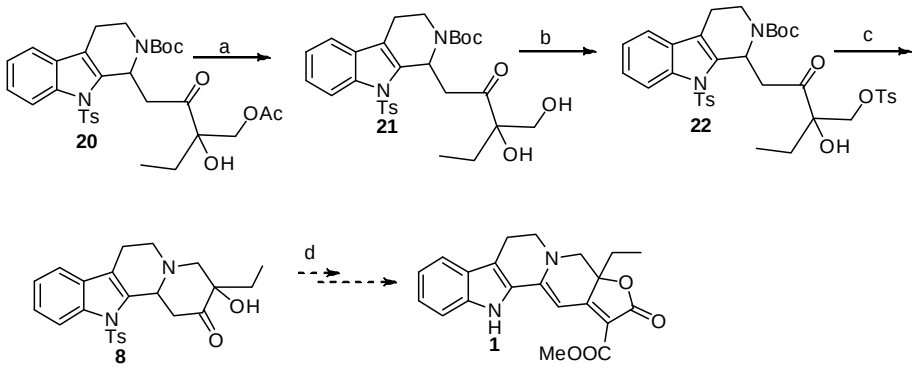
^{13}C NMR spectrum showed the signals at δ 207.3, 206.5 (due to rotamers and/or diastereomers) corresponding to the carbonyl ketone. Additionally, peaks

corresponding to carbonyl carbon of Boc and carbonyl carbon of acetate appeared at δ 154.4 and 170.88 respectively. The formation of rotamers of **20** and mixture of its isomer was evident from dobuling of peaks for many protons and ^{13}C signals, but unfortunatley the presence of diasteremeric mixture **20** could not be established by HPLC. Further, HRMS analysis showed the molecular ion peak at *m/z* 621.2244 $(M+Na)^+$ confirming the formation of **20**.

The non separable diastereomeric mixture of keto compound **20** was subjected for the next reaction wherein the keto compound **20** was hydrolyzed with K_2CO_3 in methanol to deliver again non-separable diastereomeric mixture of diol **21** in 90% yield (Scheme 8). Its IR spectrum displayed the strong absorption band at 3436 cm^{-1} indicating presence of hydroxy functionality. Its ^1H NMR spectrum showed the disappearance of singlet at δ 2.08 which indicated *O*-acetate deprotection. Disappearance of signal at δ 170.8 in its ^{13}C NMR spectrum corresponding to ester carbonyl carbon supported the formation of **21**. Finally, appearance of a peak at *m/z* 579.2152 $(M+Na)^+$ in the HRMS spectrum confirmed the structure of diol **21**. Diastereomeric ratio and purity of diol was estimated by HPLC analysis (*dr* 1:1).

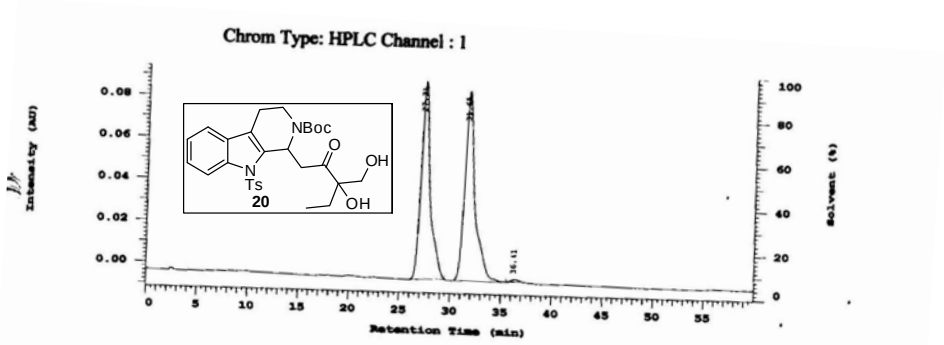
For the construction of D ring of mitralactonine, the primary hydroxy group in compound **20** was converted to good leaving group. Diol **21** was treated with *p*-TsCl, TEA and DMAP (cat.) in DCM at 0 ^oC to deliver the *O*-tosyl derivative **22**. Its diastereomeric purity was estimated by HPLC (1:1). Peaks displayed at δ 2.31 (s, 3H), 2.38 (s, 1.6 H) and 2.42 (s, 1.4 H) in its ^1H NMR spectrum were attributed to methyl protons of two tosyl group (Ar-$\underline{CH_3}$). ^{13}C NMR spectrum showed the signals at δ 21.6 corresponding to methyl carbon (Ar-$\underline{CH_3}$) of tosyl functionality. Finally, appearance of a peak at *m/z* 733.2246 $(M+ Na)^+$ in the HRMS spectrum confirmed the structure **22**.

Once *O*-tosyl derivative was in hand, the next concern was deprotection and *in situ* cyclisation. This was achieved using TFA in DCM followed by treatment with NaOH to furnish separable tetracyclic keto compound **8**. The tetracyclic ketone **8** is a known key intermediate for the synthesis of mitralactonine **1**, hence, the present work constitutes the formal synthesis of mitralactonine. Spectroscopic data of desired synthesized intermediate **8** was in good agreement with reported one.[13]



Scheme 8 *Reagents and conditions: a) K_2CO_3, MeOH, rt, 90%; b) p-TsCl, TEA, DMAP, DCM, 0 ^oC, 6 h, 80%; c) TFA (10 eq.), DCM then NaOH (neutralization pH basic 13), 30%; d) Ref.13.*

Leader	:- Dr.s.p.Chavan
COLUMN	:- GRACE DENALI-RP-18 (250 X 4.6mm)
MOBILE PHASE	:- MeOH:H2O(70:30)
WAVELENGTH	:- 254nm
FLOW RATE	:- 1 ml/min (2620psi)
SAMPLE CONC	:-2 mg/1ml (Ing voL-20ul)



No.	RT	Height	Area	Area %
1	27.31	47263	2962228	47.688
2	31.65	45351	3226223	51.938
3	36.41	558	23263	0.375
		93172	6211714	100.000

```
Leader          :- Dr.S P Chavan
COLUMN          :- Grace Denali RP-18(250 X 4.6mm)
MOBILE PHASE    :- MeOH:H2O:(75:25)
WAVELENGTH      :- 240nm
FLOW RATE       :- 1 ml/min (2280psi)
SAMPLE CONC     :-1mg/1ml       (Inj voL-20ul)
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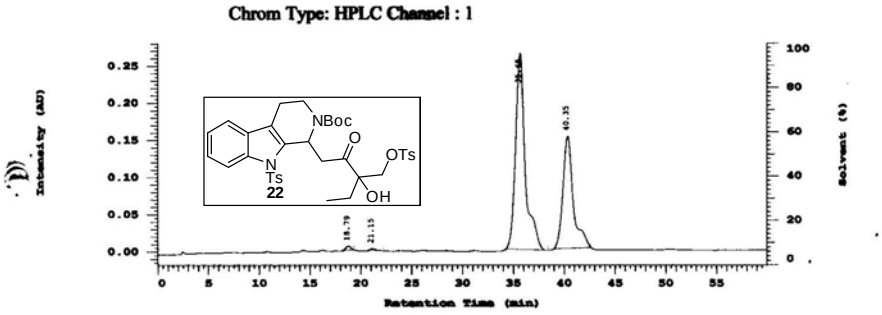


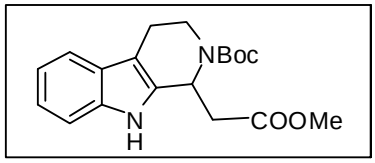
No.	RT	Height	Area	Area %
1	18.79	2551	79077	0.563
2	21.15	883	21364	0.152
3	35.65	131623	8667792	61.695
4	40.35	75281	5281248	37.590
		210338	14049481	100.000

1.2.3 Conclusion

A formal synthesis of mitralactonine by employing Pictet-Spengler cyclisation and intramolecular *N*-alkylation as the key steps has been accomplished.

1.2.4 Experimental Section

tert-Butyl 1-(2-methoxy-2-oxoethyl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (16)



To a stirred solution of amine **15** (2 gm, 8.19 mmol) in THF was added triethyl amine (2.27 mL, 16.38 mmol) at 0 ^{o}C, followed by dropwise addition of Boc anhydride (2.67 mL, 12.28 mmol) and DMAP. The reaction mixture was stirred to room temperature for 3 h and was diluted with water and extracted with ethyl acetate (2 X 60 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate-light petroleum (3:7) as an eluent to afford carbamate **16** (2.11 gm, 75%) as colorless liquid.

Chemical Formula: $C_{19}H_{24}N_2O_4$;

Yield: 75%;

IR ($CHCl_3$, cm^{-1}): 3421, 1690, 1171;

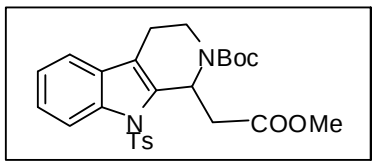
ESIMS (m/z): 367 $(M+Na)^+$;

^{1}H NMR (500 MHz, $CDCl_3$+ CCl_4): δ 1.49 (s, 9H), 2.62-3.16 (m, 5H), 3.75 (s, 3H), 4.29-4.54 (m, 1H), 5.57 (m, 1H), 7.01-7.16 (m, 2H), 7.24-7.31 (m, 1H), 7.24-7.45 (m, 1H), 8.69-8.86 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$+ CCl_4): δ 20.25, 20.60, 27.52, 37.20, 38.07, 38.44, 46.27, 47.04, 51.10, 79.35, 107.40, 107.98, 110.19, 117.15, 118.39, 120.98, 125.54, 131.83, 132.33, 134.96, 153.15, 153.53, 172.18;

Elemental Analysis: calculated C, 66.26; H, 7.02; N, 8.13; Found C, 66.16; H, 7.11; N, 8.18.

tert-Butyl 1-(2-ethoxy-2-oxoethyl)-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (10)



To a stirred solution of carbamate **16** (2 gm, 5.81 mmol) in toluene or benzene (25 mL) was added (2.32 gm, 58.1 mmol) of NaOH followed by $TBAHSO_4$ (0.19 gm, 0.581 mmol) and the reaction

mixture was stirred at room temperature for 15 min. After that *p*-TsCl (1.66 gm, 8.71 mmol) was added portion wise over 15 minutes and then reaction mixture was stirred for additional 30 min. at room temperature. The reaction mixture was diluted with cold water and extracted with ethyl acetate (3 X 50 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography using ethyl acetate-light petroleum (2:8) as an eluent to provide solid *N*-tosyl derivative **10** (2.31 gm, 80%).

Chemical Formula: $C_{26}H_{30}N_2O_6S$;

Yield: 80%;

M.P.: 143 ^oC;

IR ($CHCl_3$, cm^{-1}): 3421, 1692, 1171;

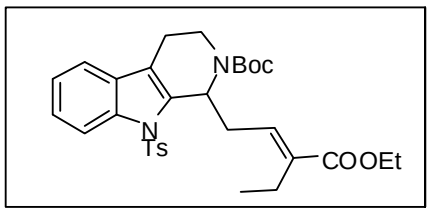
ESIMS (m/z): 521.3 $(M+Na)^+$;

^{1}H NMR (500 MHz, $CDCl_3$+ CCl_4): δ 1.49 (s, 4H), 1.58 (s, 5H), 2.32 (s, 3H), 2.59 (dd, *J* = 16 Hz, 4.2 Hz, 1H), 2.75 (m, 2H), 3.08-3.42 (m, 2H), 3.74 (s, 3H), 4.18-4.46 (m, 1H), 6.35-6.48 (m, 1H), 7.12 (bs, 2H), 7.20-7.23 (m, 1H), 7.27-7.32 (m, 2H), 7.65 (d, *J* = 6.7 Hz, 1H), 7.76 (d, *J* = 5.5 Hz, 1H), 8.14 (d, *J* = 8 Hz, 1H);

^{13}C (125 MHz, $CDCl_3$+ CCl_4): δ 20.70, 21.54, 28.37, 35.24, 36.62, 39.52, 49.11, 49.75, 51.71, 80.48, 115.42, 118.54, 119.68, 124.02, 125.05, 126.57, 126.44, 129.58, 130.02, 134.36, 136.66, 144.66, 154.26, 170.19;

Elemental Analysis: calculated C, 62.63; H, 6.06; N, 5.62; S, 6.43; Found: C, 62.68; H, 6.01; N, 5.67; S, 6.49.

(*E*)-*tert*-Butyl 1-(3-(ethoxycarbonyl)pent-2-enyl)-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (18)



The *N*-Tosyl derivative **10** (1 gm, 2.00 mmol) was taken in dry DCM (50 mL) under nitrogen atmosphere and temperature lowered to -78 ^oC. DIBAL-H (1.98 mL, 4.00 mmol, 2M) was added dropwise and stirred at same temperature till completion of reaction (TLC). The reaction mixture was quenched at -78 ^oC with addition of saturated solution of sodium-potassium tartrate and warmed to room temperature. The organic layer was separated and aqueous layer was extracted with DCM (3 X 40 mL). The combined organic layer was dried over anhydrous sodium

sulphate, filtered and concentrated under reduced pressure. The aldehyde **17** was used immediately for the next reaction. To a well stirred solution of aldehyde **17** (crude 1 gm, 2.13 mmol) in dry DCM (40 mL) under nitrogen atmosphere was added four carbon phosphorane (1.6 gm, 4.26 mmol) and left to stir at room temperature till completion of reaction (TLC). The crude residue was directly adsorbed on simple silica gel and was purified by flash silica gel column chromatography using ethyl acetate-light petroleum (2:8) as an eluent to provide unsaturated ester **18** (0.85 gm, 75%) as yellow syrup.

Chemical Formula: $C_{31}H_{38}N_2O_6S$;

Yield: 75%;

IR ($CHCl_3$, cm^{-1}): 1696, 1415, 1366, 1172;

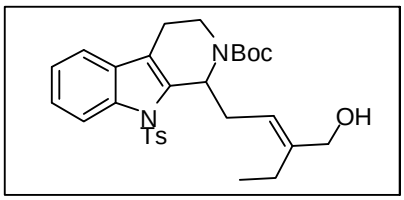
ESIMS (m/z): 589 $(M+Na)^+$;

^{1}H NMR (200 MHz, $CDCl_3$+ CCl_4): δ 1.05 (t, *J* = 7.5 Hz, 3H), 1.34 (t, *J* = 7 Hz, 3H), 1.51 (s, 3H), 1.57 (s, 6H), 2.25-2.29 (m, 1H), 2.33 (s, 3H), 2.38-2.46 (m, 1H), 2.57-2.84 (m, 3H), 3.03-3.31 (m, 2H), 4.25 (q, *J* = 7 Hz, 2H), 4.44-4.54 (m, 1H), 5.94-6.19 (m, 1H), 6.93 (t, *J* = 7 Hz, 1H), 7.06-7.16 (m, 2H), 7.23-7.39 (m, 3H), 7.59-7.76 (m, 2H), 8.19-8.23 (m, 1H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.86, 14.27, 20.24, 20.75, 21.38, 28.29, 33.86, 34.83, 51.88, 60.21, 80.40, 111.51, 118.48, 119.41, 124.12, 124.95, 126.27, 126.78, 129.51, 130.12, 134.39, 135.07, 135.71, 136.88, 137.26, 144.84, 154.13, 167.34;

Elemental Analysis: calculated C, 65.70; H, 6.76; N, 4.94; S, 5.66; Found C, 65.65; H, 6.71; N, 4.99; S, 5.61.

(*E*)-*tert*-Butyl 1-(3-(hydroxymethyl)pent-2-en-1-yl)-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (19)



To a stirred solution of unsaturated ester **18** (0.8 gm, 1.41 mmol) in dry DCM (25 mL) in an atmosphere of nitrogen was added DIBAL-H (2.12 mL, 4.2 mmol, 2M in toluene) dropwise at -40 ^oC over 30 min. and the reaction mixture was allowed to stir at -40 ^oC for 1h under the nitrogen atmosphere. After completion of reaction (monitored by TLC), the reaction mixture was quenched with saturated solution of sodium potassium tartrate salt and extracted with DCM (3 X 50 mL). The combined organic layer was dried

over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to provide crude alcohol which was purified by flash silica gel column chromatography using ethyl acetate : pet ether (4:6) as an eluent to afford **19** (0.65 gm, 89%) as colorless thick syrup.

Chemical Formula: $C_{29}H_{36}N_2O_5S$;

Yield: 89%;

IR ($CHCl_3$, cm^{-1}): 3443, 1682, 1417, 1170;

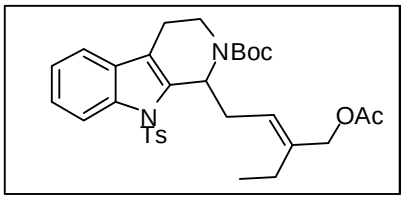
ESIMS (m/z): 547.5 $(M+Na)^+$;

HRMS calculated for $[C_{29}H_{36}N_2O_5S + Na]^+$ 547.2237; found: 544.2250;

^{1}H NMR (200 MHz, $CDCl_3$+ CCl_4): δ 1.02 (t, *J* = 7.5 Hz, 3H), 1.48 (s, 3.5H), 1.55 (s, 5.6H), 1.99-2.22 (m, 2H), 2.27 (s, 1.4H), 2.30 (s, 1.6H), 2.41-2.82 (m, 3H), 2.88-3.35 (m, 2H), 4.10 (bs, 2H), 4.17-4.49 (m, 1H), 5.58 (t, *J* = 7 Hz, 1H), 5.83-6.01 (m, 1H), 7.11 (d, *J* = 8 Hz, 2H), 7.22-7.39 (m, 3H), 7.58 (d, *J* = 8 Hz, 1H), 7.70 (d, *J* = 8 Hz, 1H), 8.16 (d, *J* = 8 Hz, 1H);

^{13}C NMR (50 MHz, $CDCl_3$+ CCl_4): δ 13.17, 20.80, 21.09, 21.36, 28.27, 28.43, 32.43, 32.85, 34.82, 36.39, 51.82, 66.35, 79.93, 80.08, 115.47, 118.26, 118.38, 118.88, 121.34, 121.72, 123.82, 124.0, 124.69, 126.28, 126.75, 129.42, 130.20, 134.19, 134.50, 135.85, 136.45, 136.78, 142.77, 144.39, 144.60, 154.41, 155.26.

(*E*)-*tert*-Butyl 1-(3-(acetoxymethyl)pent-2-en-1-yl)-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (9)



To a stirred solution of allylic alcohol **19** (0.5 gm, 0.95 mmol) in dry DCM (20 mL) was added triethyl amine (0.27 mL, 1.9 mmol) at 0 ^oC. The reaction was left to stir for 15 min. and acetyl chloride (0.074 mL, 1.05 mmol) was added dropwise to the reaction mixture at 0 ^oC. The reaction mixture was allowed to stir at 0 ^oC for 30 min. and was diluted with water and extracted with DCM (3 X 30 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give crude *O*-acetyl derivative which was purified by flash column chromatography using ethyl acetate: pet ether (2:8) as an eluent to afford *O*-acetyl derivative **9** (0.48 gm, 88%) as a colorless thick syrup.

Chemical Formula: $C_{31}H_{38}N_2O_6S$;

Yield: 88%;

IR ($CHCl_3$, cm^{-1}): 1735, 1685, 1417, 1366, 1171, 755;

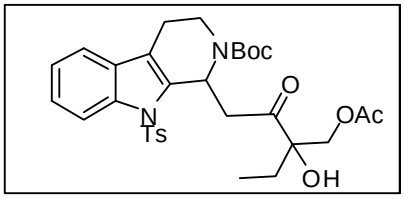
ESIMS (m/z): 589.5 $(M+Na)^+$;

HRMS calculated for $[C_{31}H_{38}N_2O_6S + Na]^+$ 589.2343; found: 589.2345;

^{1}H NMR (200 MHz, $CDCl_3$+ CCl_4): δ 1.03 (t, *J* = 7.5 Hz, 3H), 1.49 (s, 3H), 1.55 (s, 6H), 2.08 (bs, 3H), 2.14-2.22 (m, 2H), 2.26 (s, 1H), 2.30 (s, 2H), 2.45-2.82 (m, 3H), 2.92-3.22 (m, 2H), 4.10-4.48 (m, 1H), 4.55 (s, 2H), 5.63 (t, *J* = 7 Hz, 1H), 5.84-6.07 (m, 1H), 7.11 (d, *J* = 7.8 Hz, 2H), 7.19-7.34 (m, 3H), 7.57-7.73 (m, 2H), 8.17 (d, *J* = 9 Hz, 1H);

^{13}C NMR (50 MHz, $CDCl_3$+ CCl_4): δ 12.97, 20.78, 20.91, 21.40, 28.26, 28.42, 32.56, 32.90, 34.87, 36.39, 51.43, 52.34, 67.92, 79.82, 80.11, 115.52, 118.21, 118.42, 119.11, 123.85, 124.06, 124.64, 124.82, 125.05, 125.31, 126.30, 126.83, 129.47, 130.21, 134.13, 134.44, 135.65, 136.66, 137.46, 137.74, 144.49, 144.75, 154.39, 155.11, 170.84.

***tert*-Butyl 1-(3-(acetoxymethyl)-3-hydroxy-2-oxopentyl)-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (20)**



A round bottom flask was charged with $NaHCO_3$ (0.073 gm, 0.88 mmol). Aqueous solution of $RuCl_3$ (5 mg, 0.024 mmol, 1 mL) was added and the suspension was diluted with H_2O (0.9 mL), CH_3CN (6 mL), and ethyl acetate (6 mL). Oxone (1.09 g, 1.76 mmol) was added in one portion to the resulting brownish suspension resulting in the formation of a bright yellow suspension. At this point the reaction mixture was cooled to 0 ^oC. The olefin **9** (0.200 gm, 0.353 mmol) was added in one portion. After completion of reaction (monitored by TLC), the reaction mixture was diluted with ethyl acetate (20 mL). The resulting suspension was filtered and the filtrate was washed with of saturated Na_2SO_3 solution (10 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography using ethyl acetate: pet ether (4:6) to provide keto compound **20** (147 mg, 70%) as faint yellow syrup.

Chemical Formula: $C_{31}H_{38}N_2O_8S$;

Yield: 70%;

IR ($CHCl_3$, cm^{-1}): 3444, 1719, 1685, 1414, 1367, 1216;

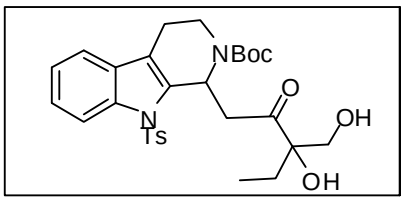
ESIMS (m/z): 621.3 $(M+Na)^+$;

HRMS calculated for $[C_{31}H_{38}N_2O_6S + Na]^+$ 621.2241; found: 621.2244;

^{1}H NMR (200 MHz, $CDCl_3$+ CCl_4): δ 0.76 (t, *J* = 7.5 Hz, 1.5 H), 0.85 (t, *J* = 7.5 Hz, 1.5 H), 1.41 (bs, 3H), 1.54 (bs, 6H), 1.60-1.78 (m, 2H), 1.98 (s, 1.5 H), 2.03 (s, 1.5 H), 2.24 (s, 3H), 2.40-2.72 (m, 2H), 2.81-3.41 (m, 4H), 3.99-4.41 (m, 3H), 6.44-6.60 (m, 1H), 7.07 (d, *J* = 7.5 Hz, 2H), 7.16-7.29 (m, 3H), 7.61-7.75 (m, 2H), 8.07 (d, *J* = 7.5 Hz, 1H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 6.61, 6.74, 20.52, 20.65, 21.43, 27.53, 27.77, 28.26, 35.28, 36.68, 41.51, 47.03, 47.93, 67.99, 68.38, 80.55, 80.77, 115.17, 115.40, 119.80, 123.97, 125.05, 126.25, 126.51, 126.91, 129.48, 129.60, 129.89, 134.23, 136.48, 144.88, 154.41, 170.88, 206.55, 207.27.

***tert*-Butyl 1-(3-hydroxy-3-(hydroxymethyl)-2-oxopentyl)-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (21)**



To a solution of acetate **20** (0.100 gm, 0.16 mmol) in methanol (5 mL) was added K_2CO_3 (0.46 gm, 0.32 mmol) at room temperature. The reaction mixture was left to stir for 30 min. After completion of reaction, the reaction mixture was concentrated under reduced pressure. The semisolid reaction mass was diluted with water (30 mL) and extracted with DCM (3 X 20 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford crude residue which was purified by flash column chromatography using ethyl acetate: pet ether (1:1) as an eluent to afford diol **21** (84 mg, 90%) as white semisolid mass.

Chemical Formula: $C_{29}H_{36}N_2O_7S$

Yield: 90%;

IR ($CHCl_3$, cm^{-1}): 3436, 1711, 1683;

ESIMS (m/z): 579.7 $(M+Na)^+$;

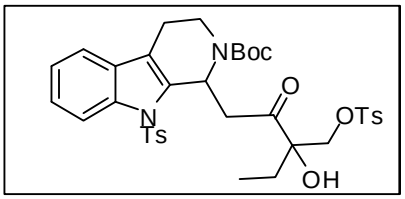
HRMS calculated for $[C_{29}H_{36}N_2O_7S + Na]^+$ 579.2135; found: 579.2152;

^{1}H NMR (200 MHz, $CDCl_3$+ CCl_4): δ 0.87 (m, 3H), 1.54 (s, 6H), 1.64 (s, 3H), 1.70-1.86 (m, 2H), 2.36 (s, 3H), 2.58-2.84 (m, 2H), 2.95-3.39 (m, 2H), 3.45-3.78 (m, 2H),

3.82-4.02 (m, 1H), 4.20-4.57 (m, 1H), 6.28-6.62 (m, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.27-7.39 (m, 3H), 7.33 (d, *J* = 7.8 Hz, 2H), 8.20 (d, *J* = 7 Hz, 1H);

^{13}C NMR (50 MHz, $CDCl_3$+ CCl_4): δ 7.12, 20.70, 21.18, 21.55, 27.22, 28.37, 29.68, 35.22, 36.48, 40.39, 41.59, 47.78, 48.05, 48.55, 66.25, 66.75, 67.28, 80.59, 80.96, 82.90, 83.57, 115.42, 118.49, 119.20, 119.87, 124.05, 126.75, 129.63, 129.96, 130.02, 134.18, 134.64, 134.82, 136.63, 144.74, 154.37, 155.16, 206.87, 209.44;

tert-Butyl 1-(3-hydroxy-2-oxo-3-((tosyloxy)methyl)pentyl)-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (22)



To a solution of diol **21** (0.05 gm, 0.089 mmol) in dry DCM (3 mL) was added triethyl amine (0.018 mL, 1.33 mmol) followed by addition of *p*-TsCl (18 mg, 0.097 mmol) at 0 ^{o}C under nitrogen atmosphere. Then, DMAP (cat.) was added to the reaction mixture. The reaction mixture was left to stir for 8 h at same temperature. After completion of reaction, the reaction mixture was diluted with water and extracted with DCM (3 X 20 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to provide residue. The residue was purified by flash silica gel column chromatography using ethyl acetate: pet ether (3:7) as eluent to furnish *O*-tosyl derivative **22** (51 mg, 80%) as yellow semisolid mass.

Chemical Formula: $C_{36}H_{42}N_2O_9S_2$

Yield : 80%;

IR ($CHCl_3$, cm^{-1}) : 3423, 1715, 1367;

ESIMS *(m/z)* : 711.5 $(M+H)^+$, 733.4 $(M+Na)^+$;

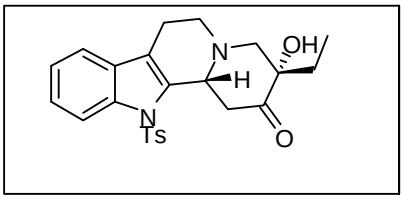
HRMS calculated for $[C_{36}H_{42}N_2O_9S_2+Na]^+$ 733.2224; found: 733.2246;

^{1}H NMR (200 MHz, $CDCl_3$+ CCl_4): δ 0.78-0.91 (m, 3H), 1.48 (s, 4H), 1.57 (s, 5H), 1.65-1.83 (m, 2H), 2.31 (s, 3H), 2.38 (s, 1.6H), 2.42 (s, 1.4H), 2.52-2.80 (m, 2H), 2.88-3.41 (m, 3H), 3.95-4.05 (m, 3H), 6.40-6.50 (m, 1H), 7.13 (d, *J* = 7.8 Hz, 2H), 7.22-7.36 (m, 5H), 7.60-7.86 (m, 4H), 8.06-8.22 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$+ CCl_4): δ 6.63, 6.74, 20.67, 21.53, 21.57, 21.61, 27.60, 28.34, 35.40, 36.84, 40.87, 41.56, 42.07, 47.98, 48.05, 48.14, 72.16, 72.34, 72.84,

80.22, 80.57, 80.77, 115.26, 118.52, 124.07, 125.07, 126.60, 127.05, 128.0, 128.08, 129.64, 129.84, 129.97, 130.04, 132.28, 132.42, 134.06, 134.30, 134.57, 134.87, 136.55, 136.58, 144.90, 154.31, 206.17, 206.34.

1st isomer:- 3-Ethyl-3-hydroxy-12-tosyl-1,3,4,6,7,12b-hexahydroindolo[2,3-*a*]quinolizin-2(12*H*)-one (8a)



To a well stirred solution of *O*-tosyl derivative **22** (70 mg, 0.098 mmol) in dry DCM (5 mL) was added TFA (0.016 mL) at 0 ^{o}C under nitrogen atmosphere. The reaction mixture was allowed to stir for 3 h at same temperature. After completion of reaction (monitored by TLC), the reaction mixture was neutralized and basified by using aq. NaOH solution. The reaction mixture was allowed to stir for 30 min. followed by extractive work up with DCM (3 X 30 mL). The combined organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to provide crude residue which was purified by flash silica gel column chromatography using ethyl acetate: pet ether (3:7) as an eluent to afford diastereomeric mixture of tetracyclic keto compound **8** (13 mg, 30% (*dr* 1:1) as brownish syrup.

Chemical Formula: $C_{24}H_{26}N_2O_4S$;

Yield : 15%;

IR ($CHCl_3$, cm^{-1}) : 3437, 1720, 1367;

ESIMS (m/z) : 439.3 $(M+Na)^+$;

^{1}H NMR (400 MHz, $CDCl_3$+ CCl_4): δ 0.82 (t, *J* =6.4 Hz, 3H), 1.75-1.85 (m, 1H), 2.11-2.20 (m, 1H), 2.28 (s, 3H), 2.54-2.63 (m, 2H), 2.69-2.92 (m, 3H), 3.09-3.18 (m, 1H), 3.25 (d, *J* = 11.5 Hz, 2H), 3.67 (dd, *J* = 13 Hz, 2.2 Hz, 1H), 4.01 (dd, *J* = 11 Hz, 2.02 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 2H), 7.22-7.32 (m, 3H), 7.41 (d, *J* = 8.5 Hz, 2H), 8.07 (d, *J* = 8.00 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$+ CCl_4): δ 7.1, 21.4, 23.1, 30.9, 45.0, 49.8, 60.8, 65.3, 79.0, 116.6, 118.6, 123.6, 124.5, 125.1, 126.6, 129.2, 130.8, 133.0, 135.4, 138.4, 144.7, 211.2.

Tetracyclic ketone 8b (2 nd isomer):-

Chemical Formula: $C_{24}H_{26}N_2O_4S$;

Yield: 15%;

IR ($CHCl_3$, cm^{-1}): 3437, 1724, 1368;

ESIMS *(m/z)*: 439.3 $(M+Na)^+$;

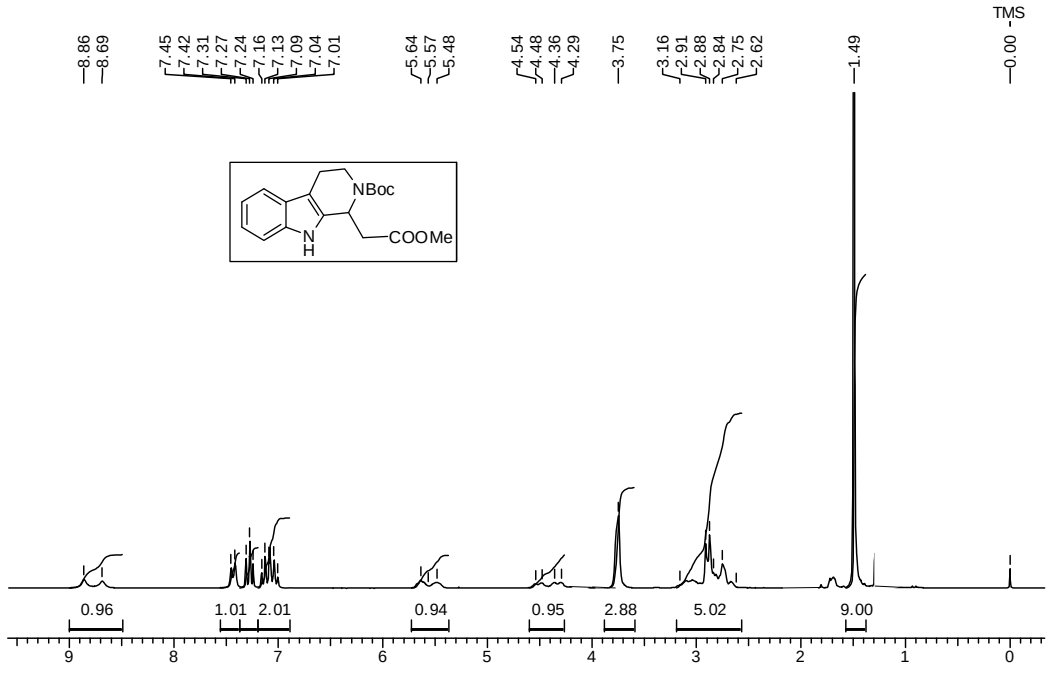
^{1}H NMR (400 MHz, $CDCl_3$+ CCl_4): δ 0.98 (t, *J* = 7.5 Hz, 3H), 1.68-1.78 (m, 1H), 1.83-1.92 (m, 1H), 2.29 (s, 3H), 2.54-2.64 (m, 1H), 2.76 (dt, *J* = 3.5 Hz, 11 Hz, 1H), 2.83-2.91 (m, 2H), 2.99 (d, *J* = 12 Hz, 1H), 3.11-3.15 (m, 1H), 3.19 (d, *J* = 12 Hz, 1H), 3.51 (dd, *J* = 15.3 Hz, 4.5 Hz, 1H), 4.21 (m, 1H), 7.08 (d, *J* = 8.5 Hz, 2H), 7.20-7.32 (m, 3H), 7.45 (d, *J* = 8.5 Hz, 2H), 8.06 (d, *J* = 7.7 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$+ CCl_4): δ 7.2, 21.5, 22.7, 26.9, 44.3, 49.9, 59.4, 64.9, 76.3, 116.5, 118.6, 122.8, 124.5, 125.1, 126.6, 129.3, 130.6, 133.3, 135.7, 138.3, 144.7, 207.9;

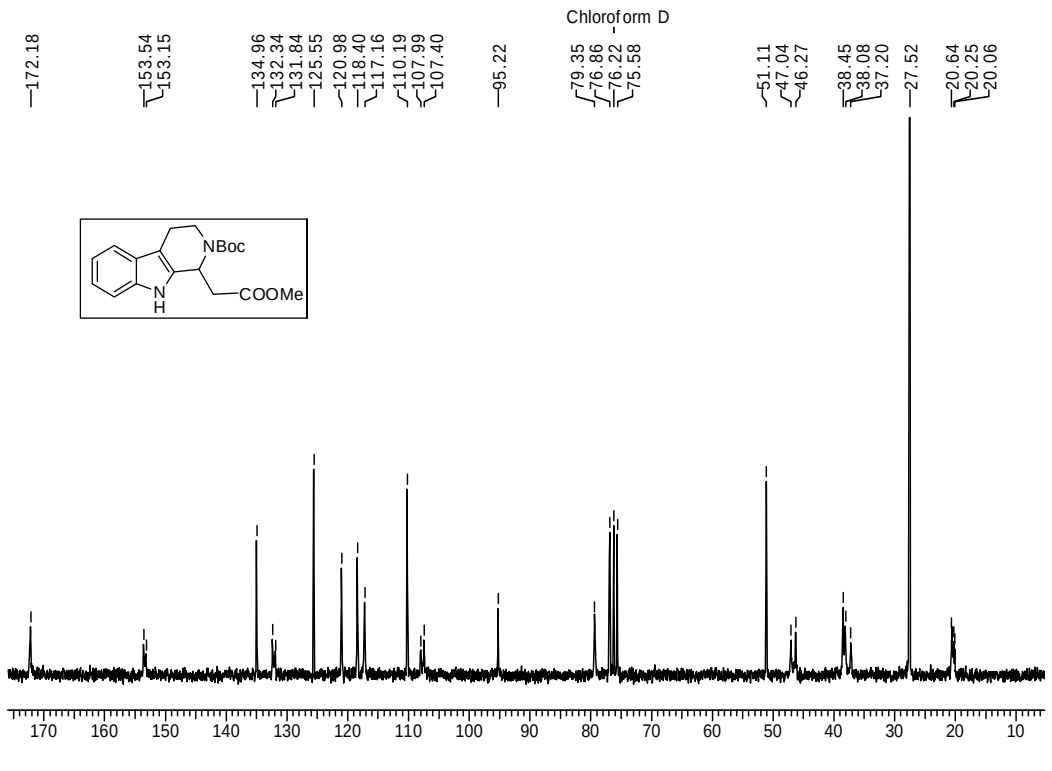
Elemental Analysis calculated for $C_{24}H_{26}N_2O_4S$; C, 65.73; H, 5.98; N, 6.39; S, 7.31; Found: C, 65.50; H, 5.88; N, 6.42; S, 7.23.

1.2.5 Spectra

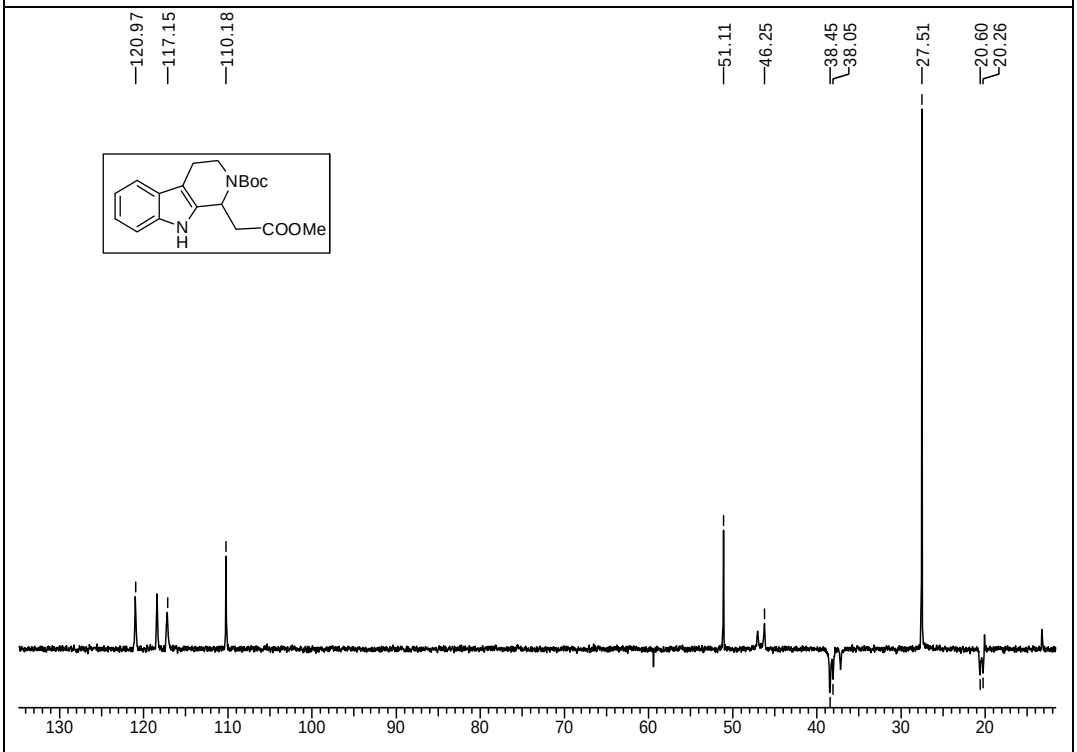
^{1}H NMR Spectrum of compound 16 ($CDCl_3$+CCl_4, 500 MHz)



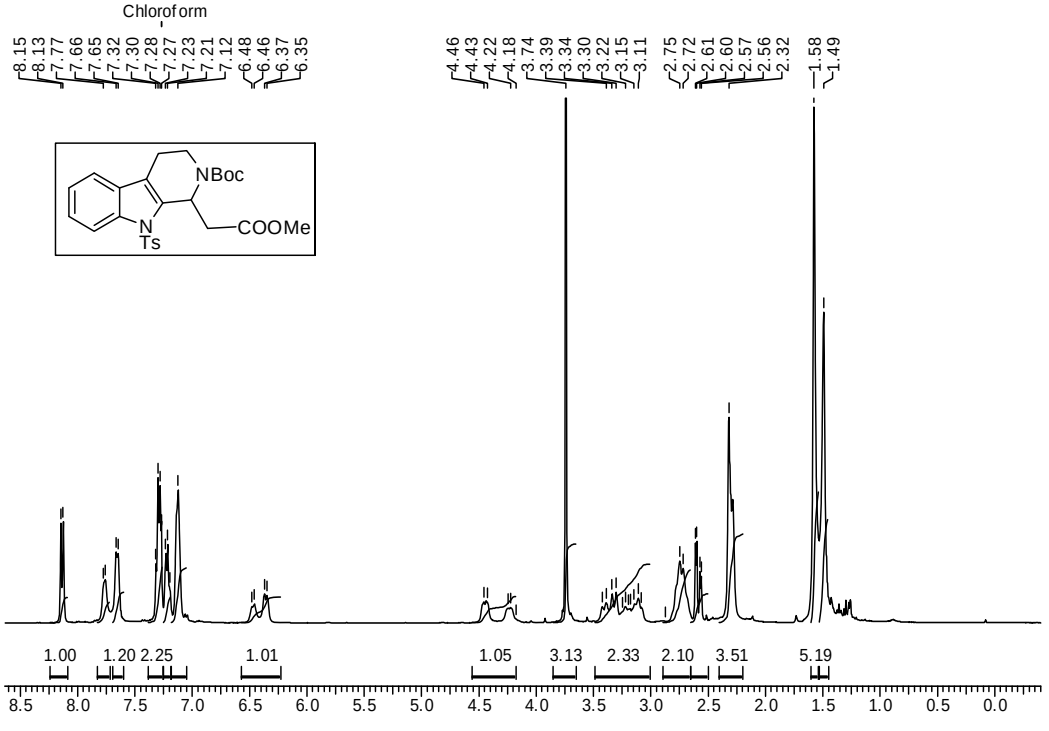
^{13}C NMR Spectrum of compound 16 ($CDCl_3$+CCl_4, 125 MHz)



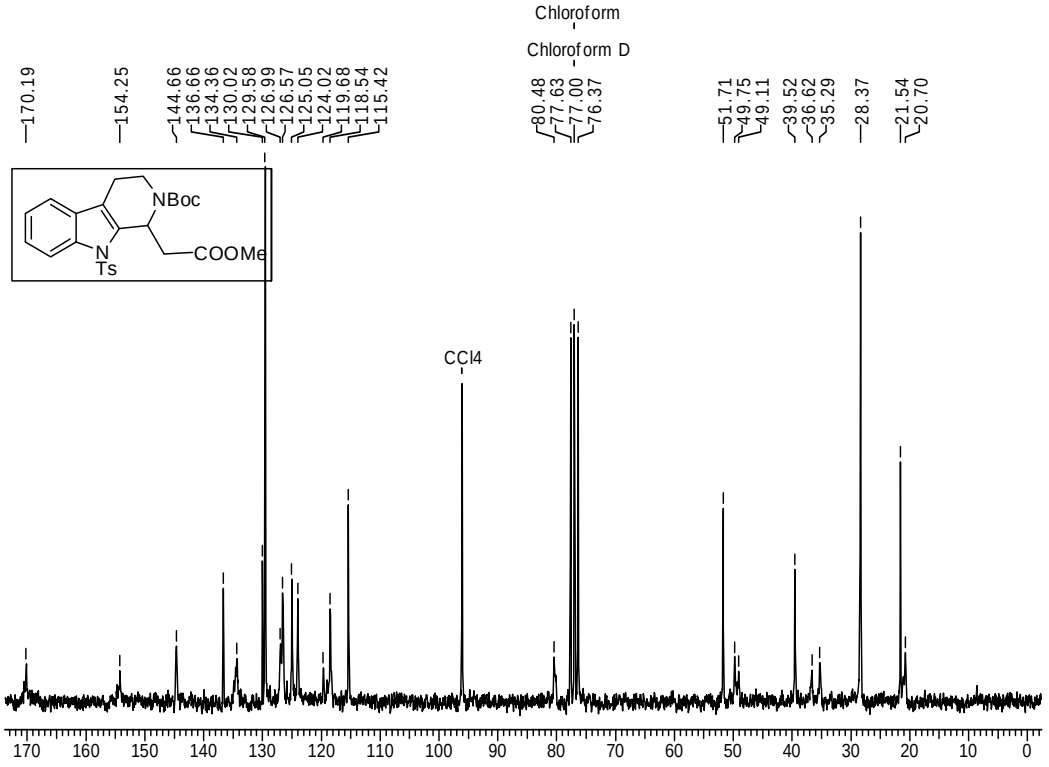
DEPT spectrum of compound 16 ($CDCl_3$+CCl_4, 125 MHz)



^{1}H NMR Spectrum of compound 10 ($CDCl_3$+CCl_4, 500 MHz)



^{13}C NMR Spectrum of compound 10 ($CDCl_3$+CCl_4, 125 MHz)



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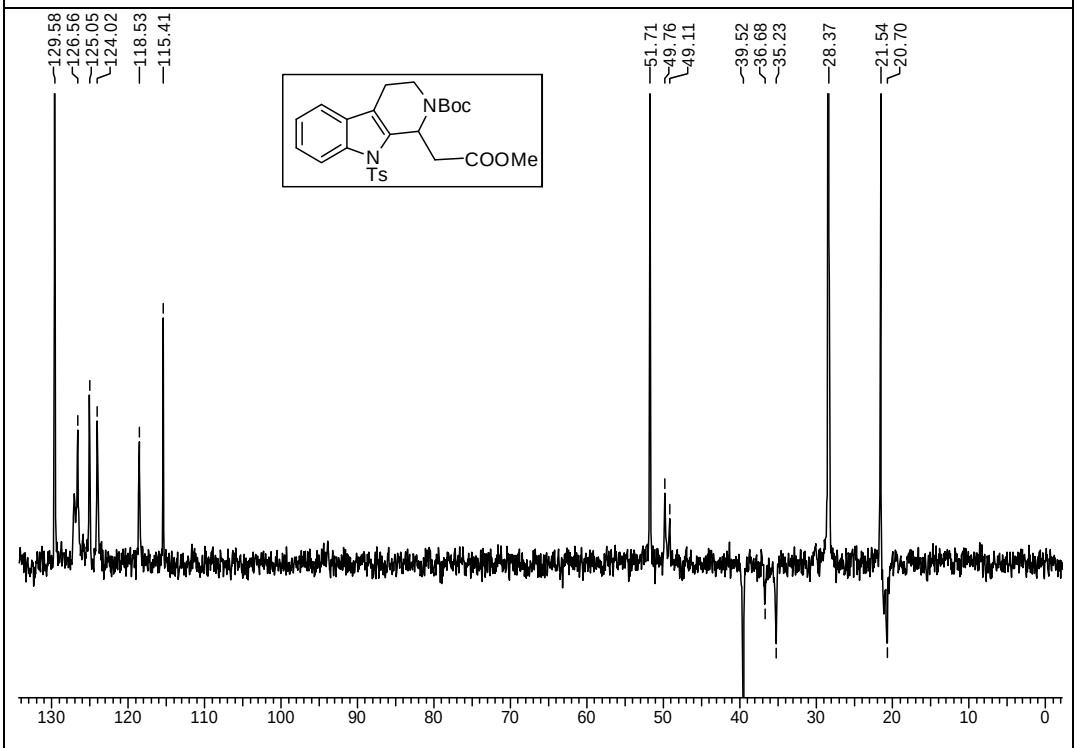

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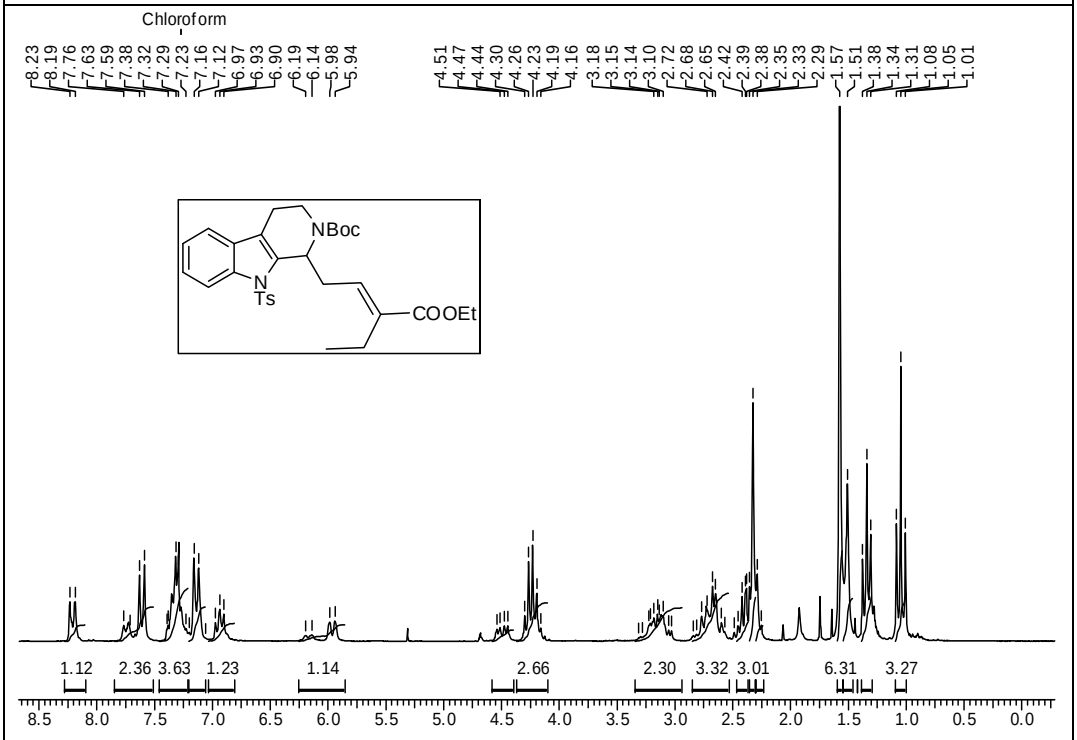
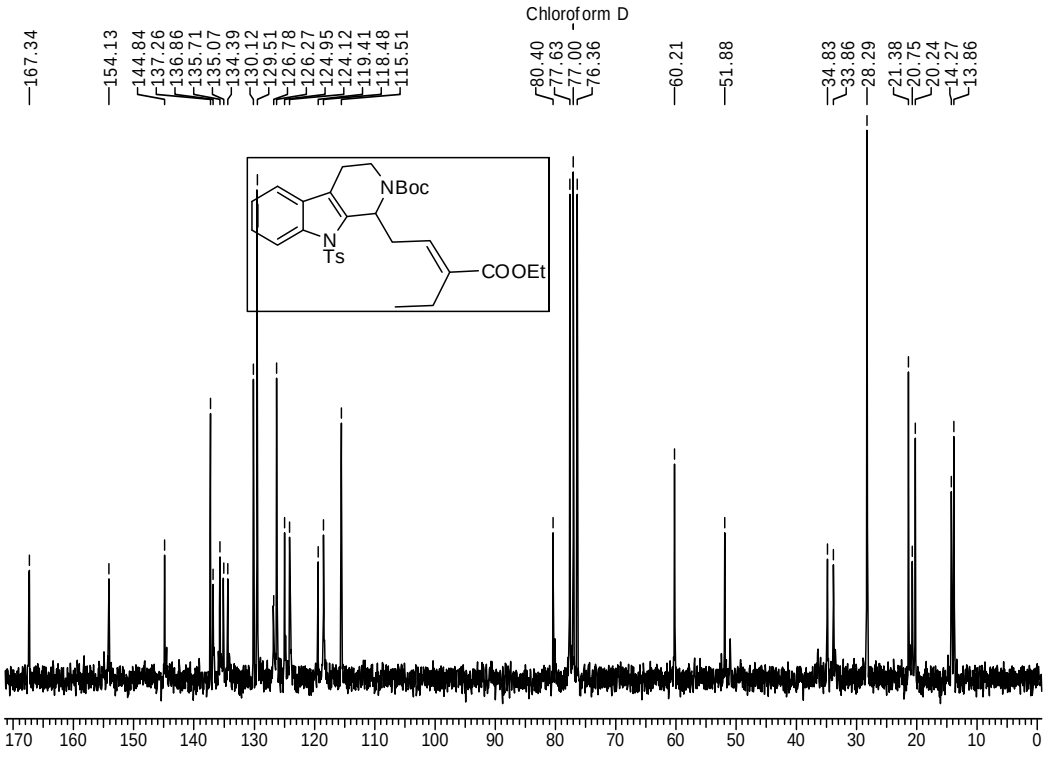
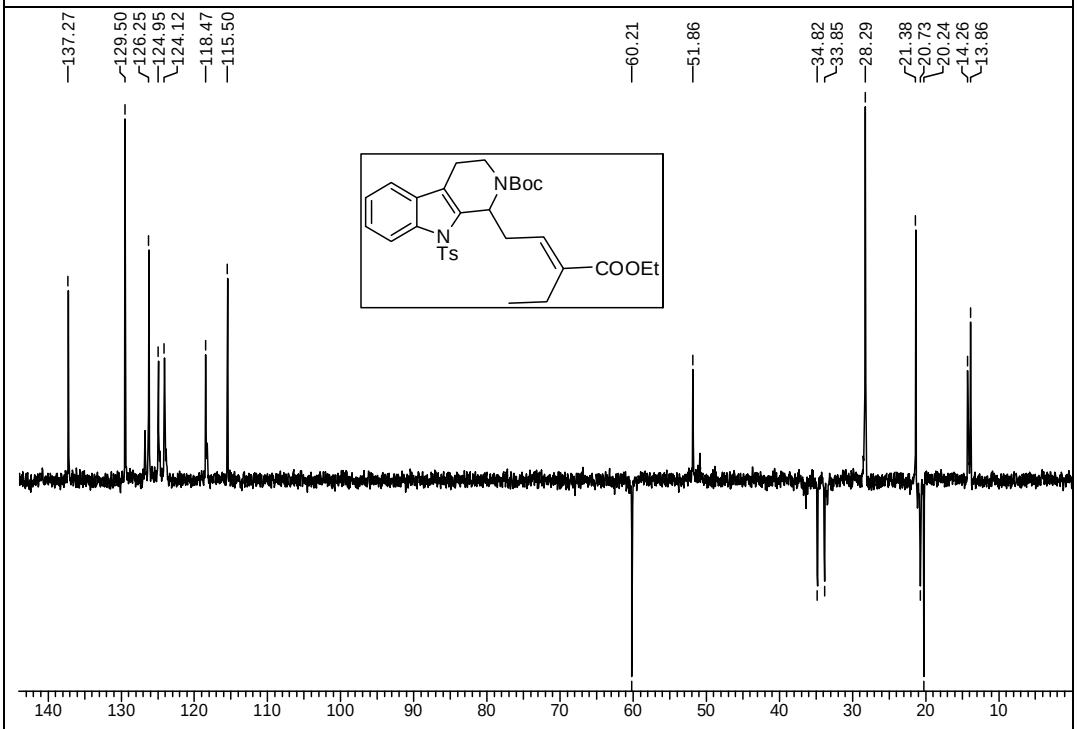


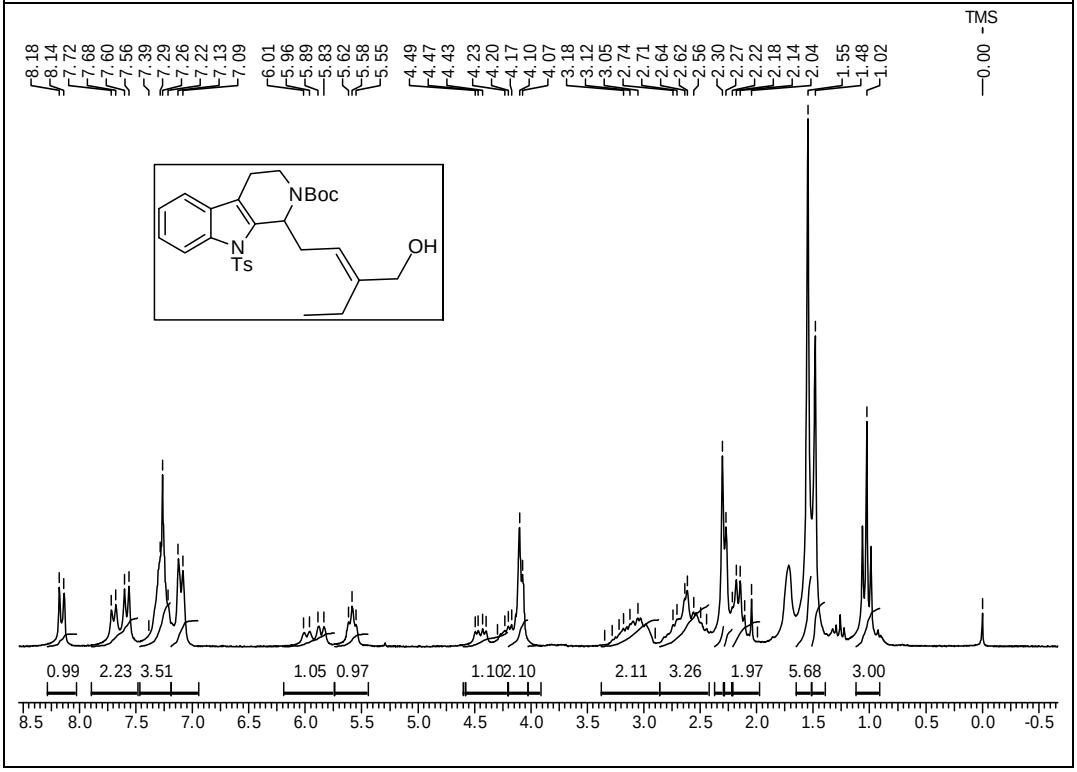
^{13}C NMR Spectrum of compound 18 ($CDCl_3$, 50 MHz)



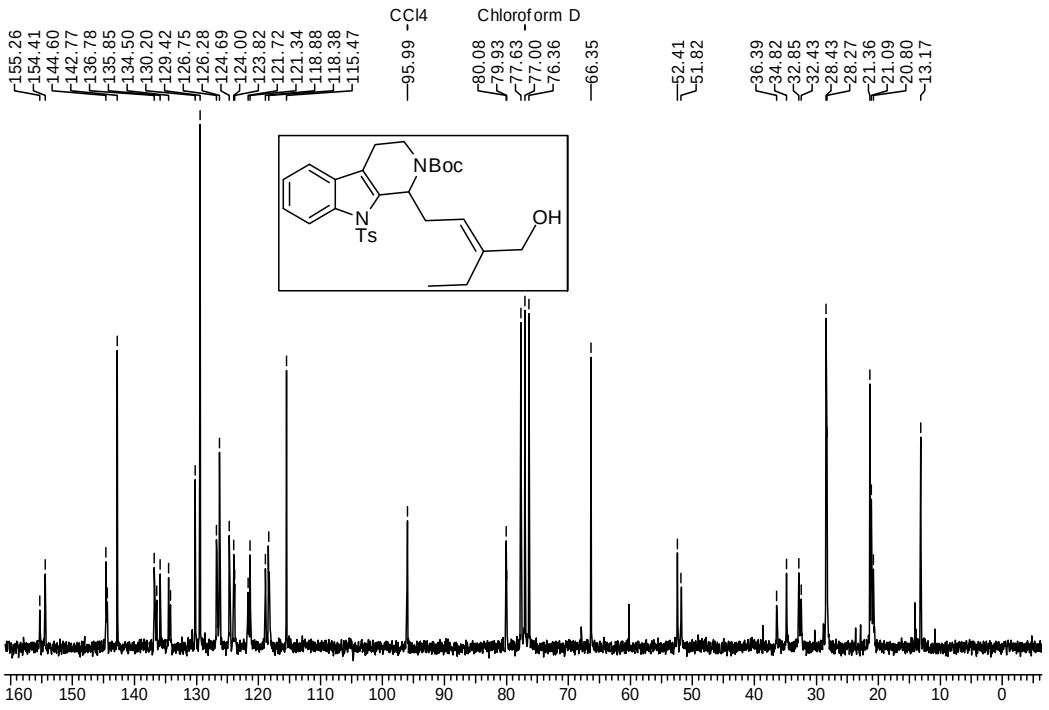
DEPT spectrum of compound 18 ($CDCl_3$, 50 MHz)



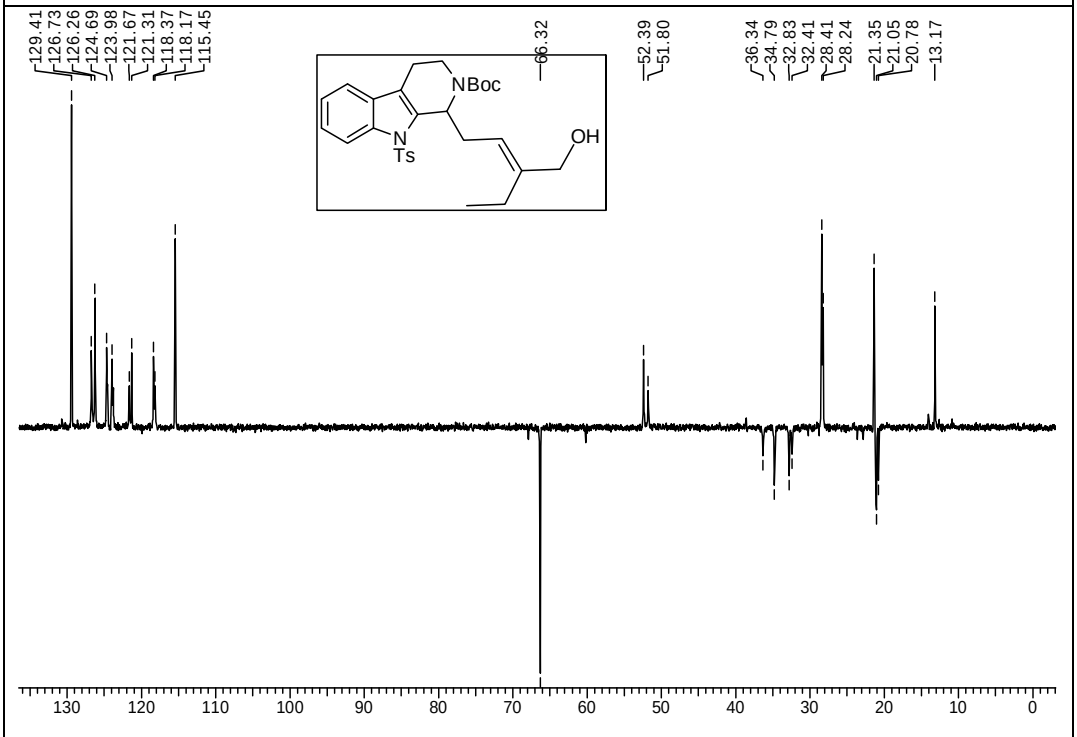
^{1}H NMR Spectrum of compound 19 ($CDCl_3$+CCl_4, 200 MHz)



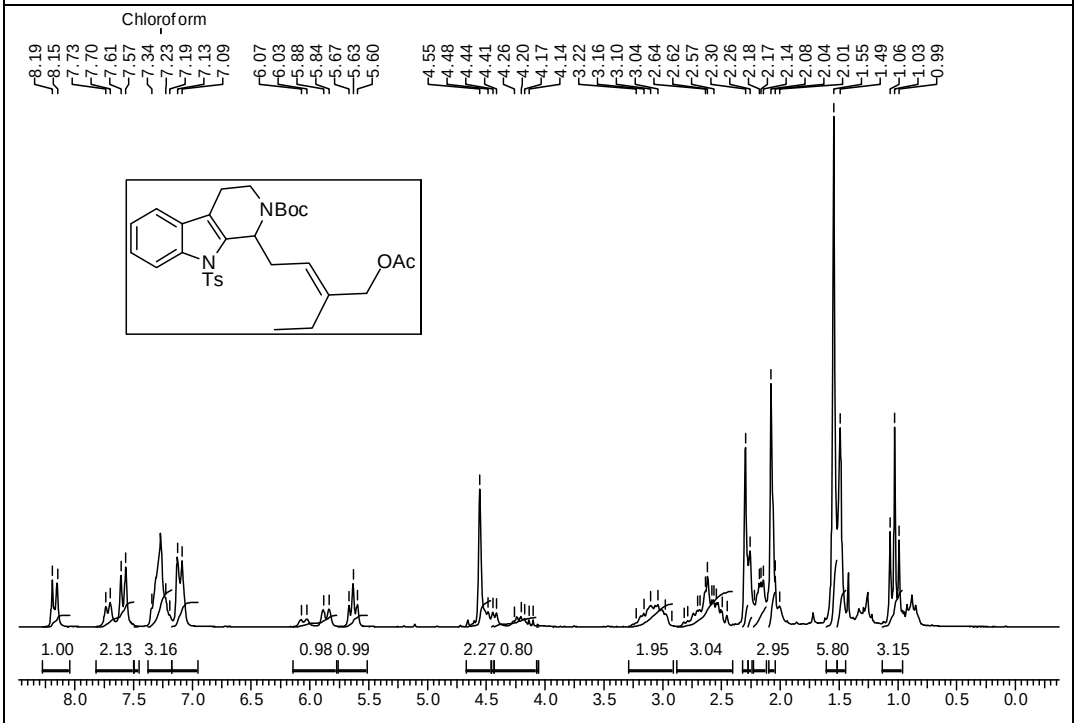
^{13}C NMR Spectrum of compound 19 ($CDCl_3$+CCl_4, 50 MHz)



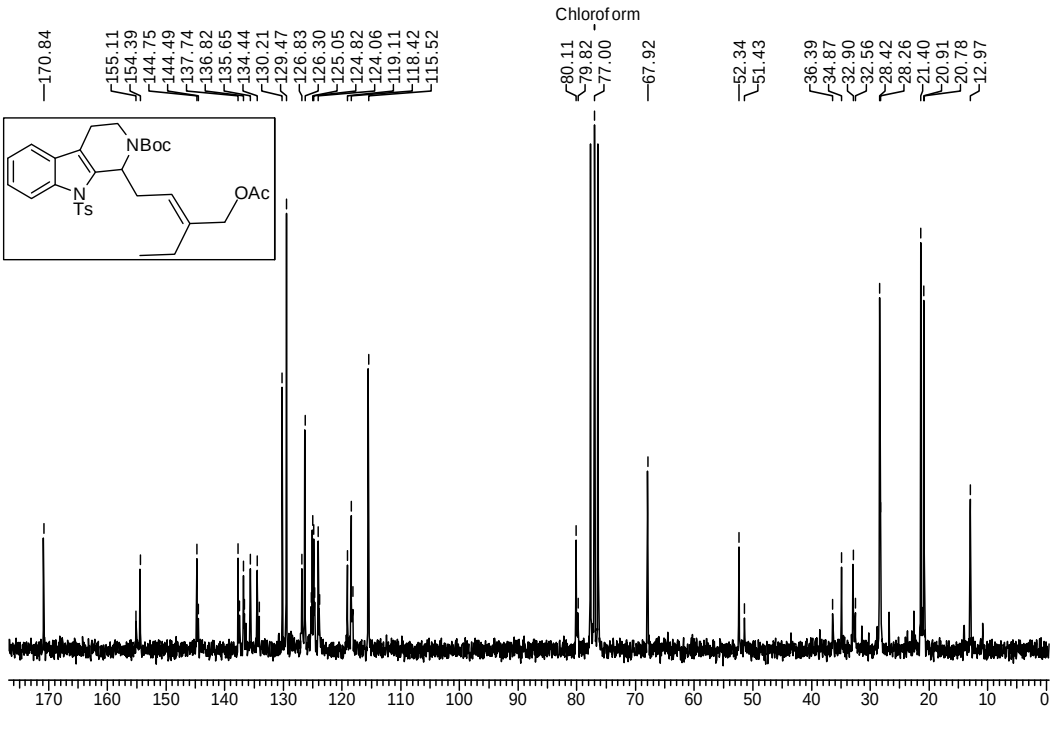
DEPT spectrum of compound 19 ($CDCl_3$+CCl_4, 50 MHz)



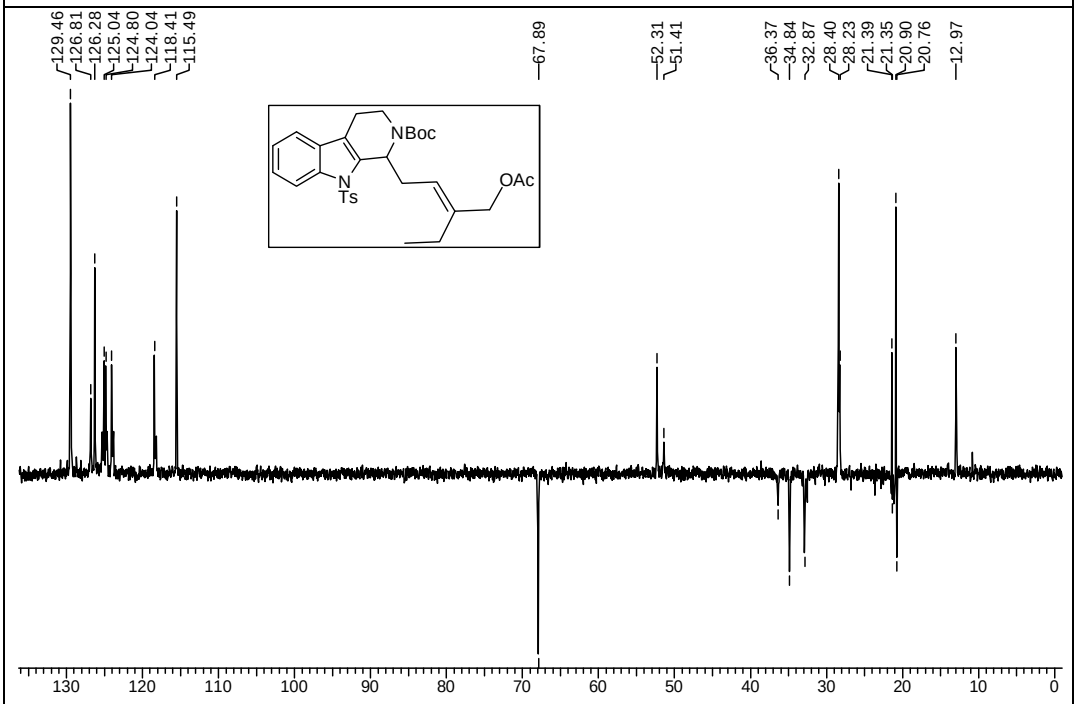
^{1}H NMR Spectrum of compound 9 ($CDCl_3$+CCl_4, 200 MHz)



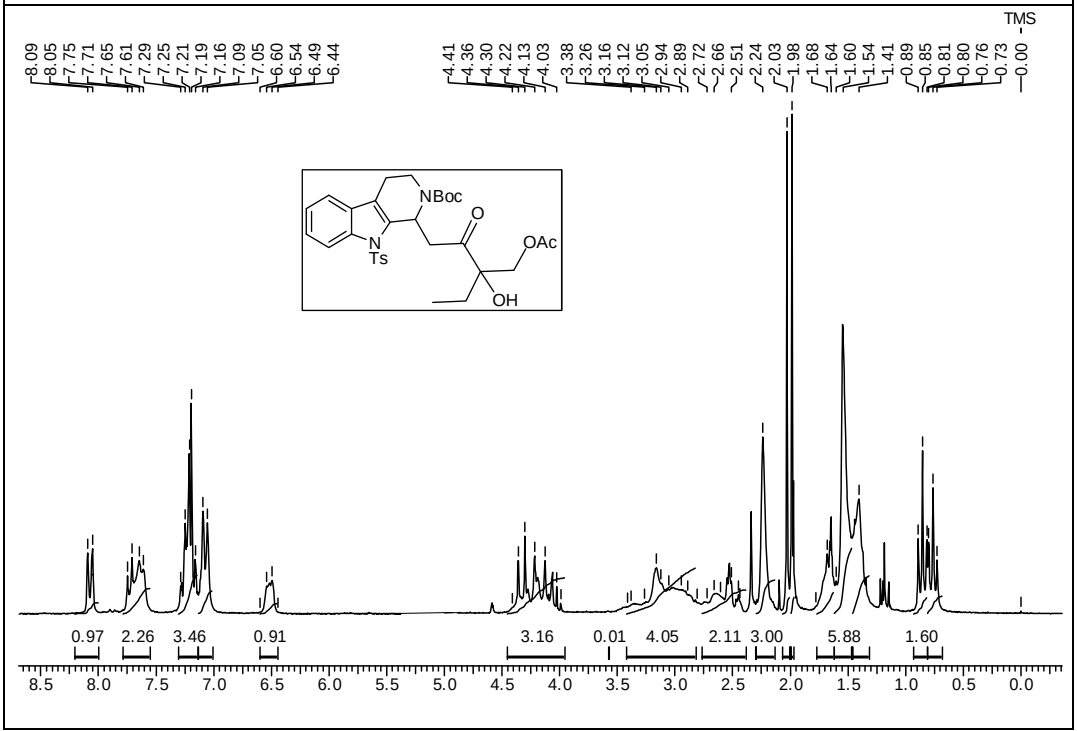
^{13}C NMR Spectrum of compound 9 ($CDCl_3$+CCl_4, 50 MHz)



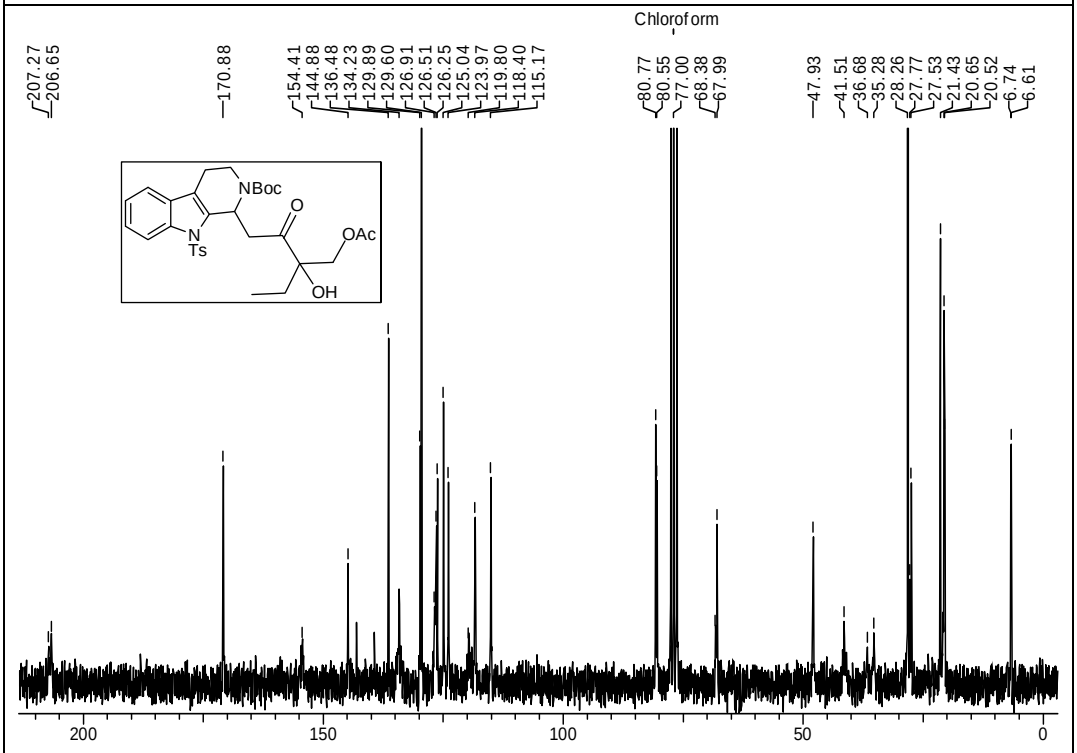
DEPT spectrum of compound 9 ($CDCl_3$+CCl_4, 50 MHz)



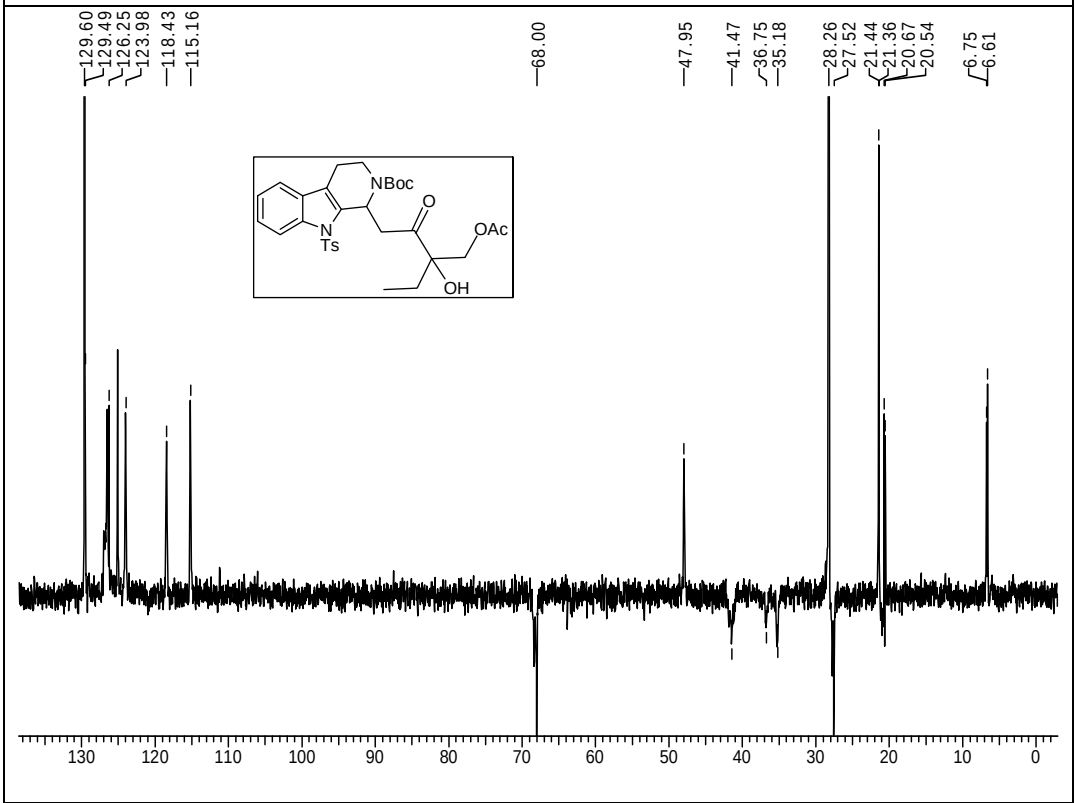
^{1}H NMR Spectrum of compound 20 ($CDCl_3$+CCl_4, 200 MHz)



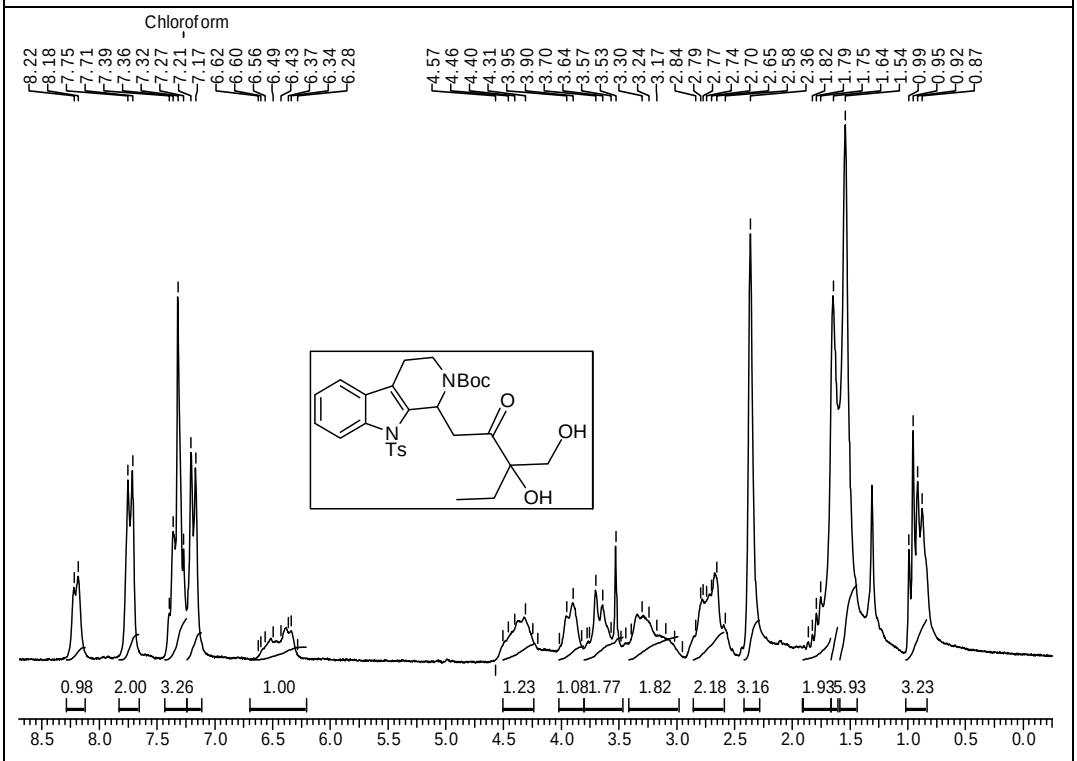
^{13}C NMR Spectrum of compound 20 ($CDCl_3$, 50 MHz)



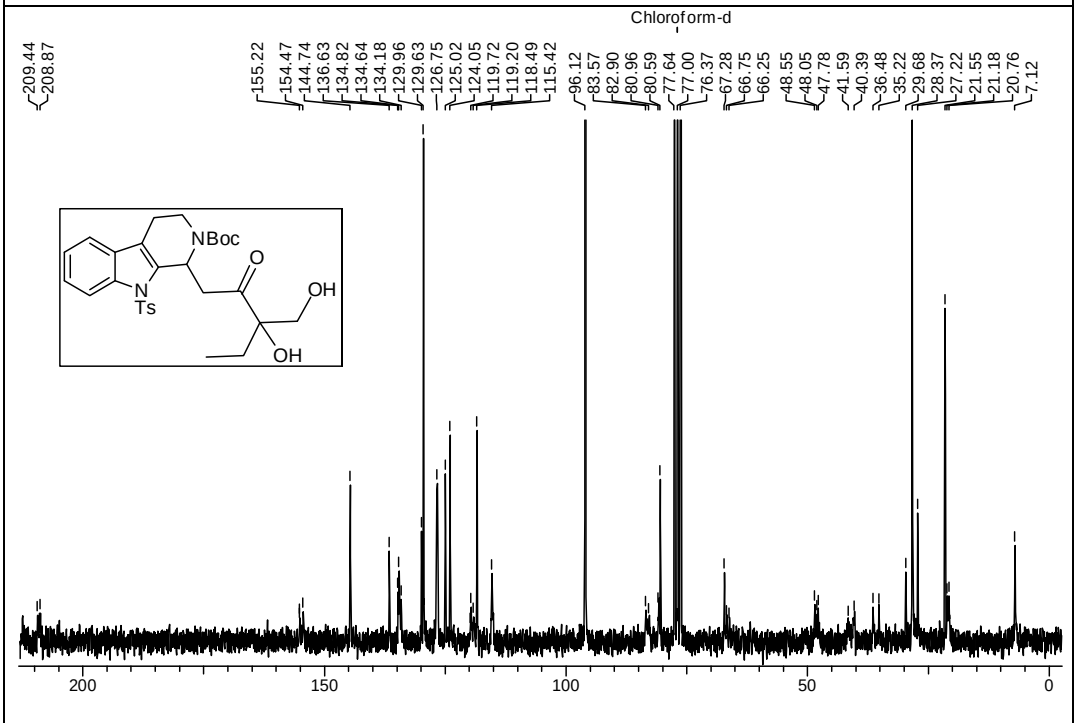
DEPT spectrum of compound 20 ($CDCl_3$, 50 MHz)



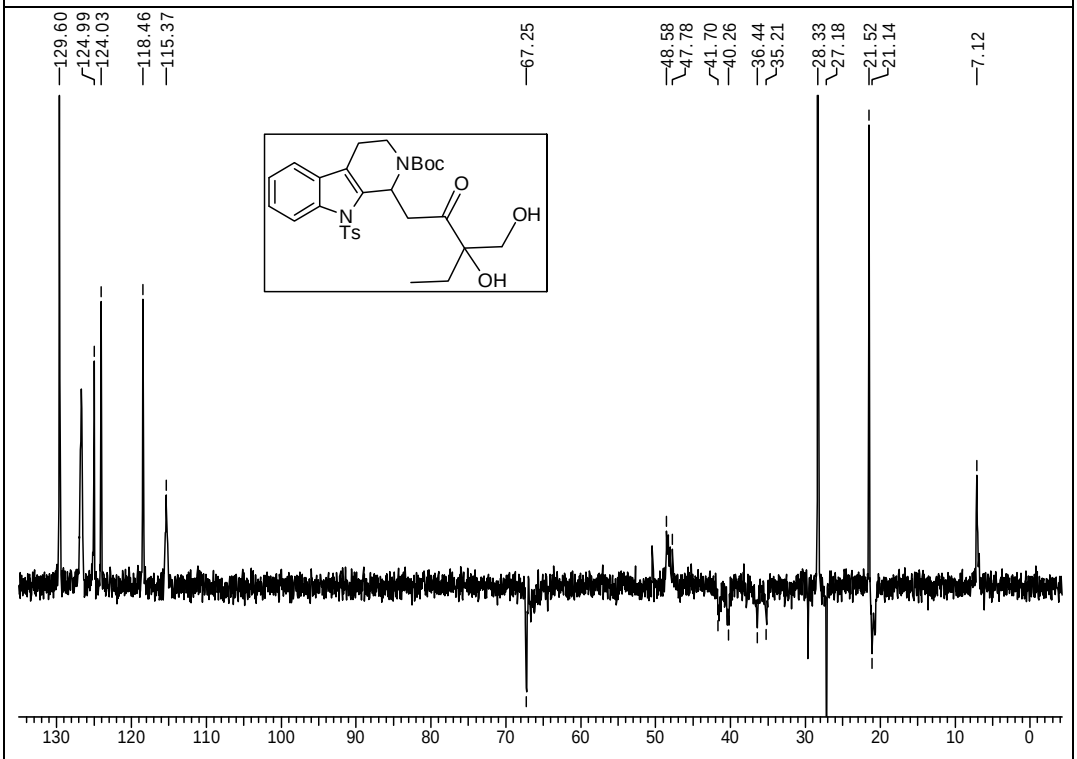
^{1}H NMR Spectrum of compound 21 ($CDCl_3$+CCl_4, 200 MHz)



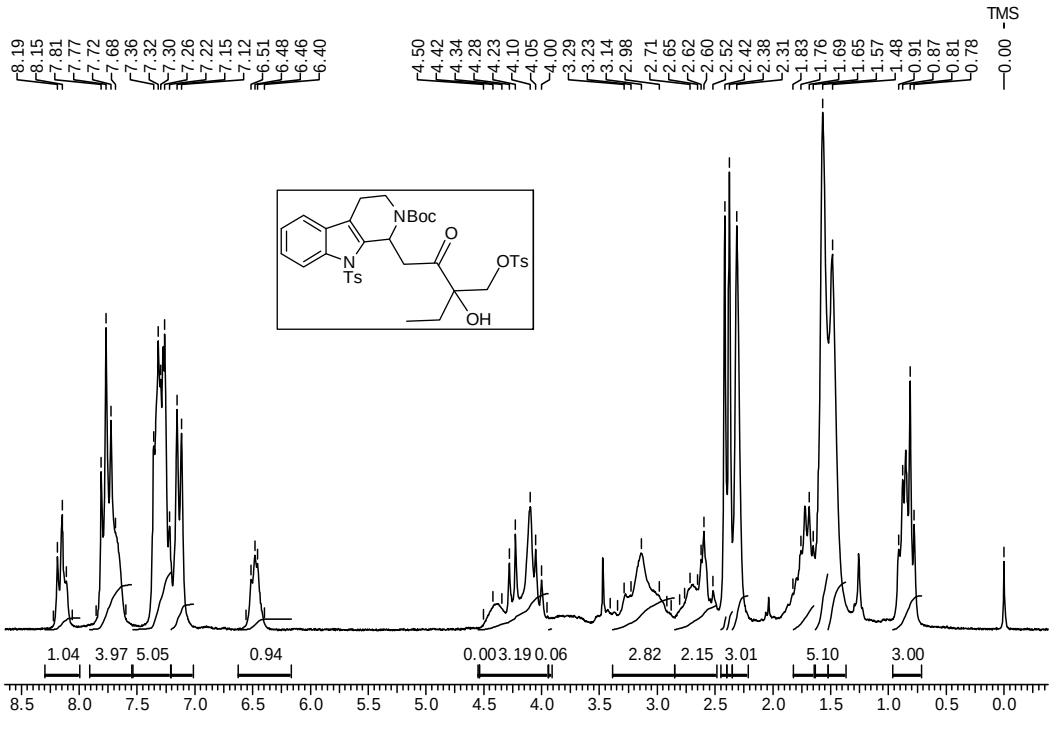
^{13}C NMR Spectrum of compound 21 ($CDCl_3$+CCl_4, 100 MHz)



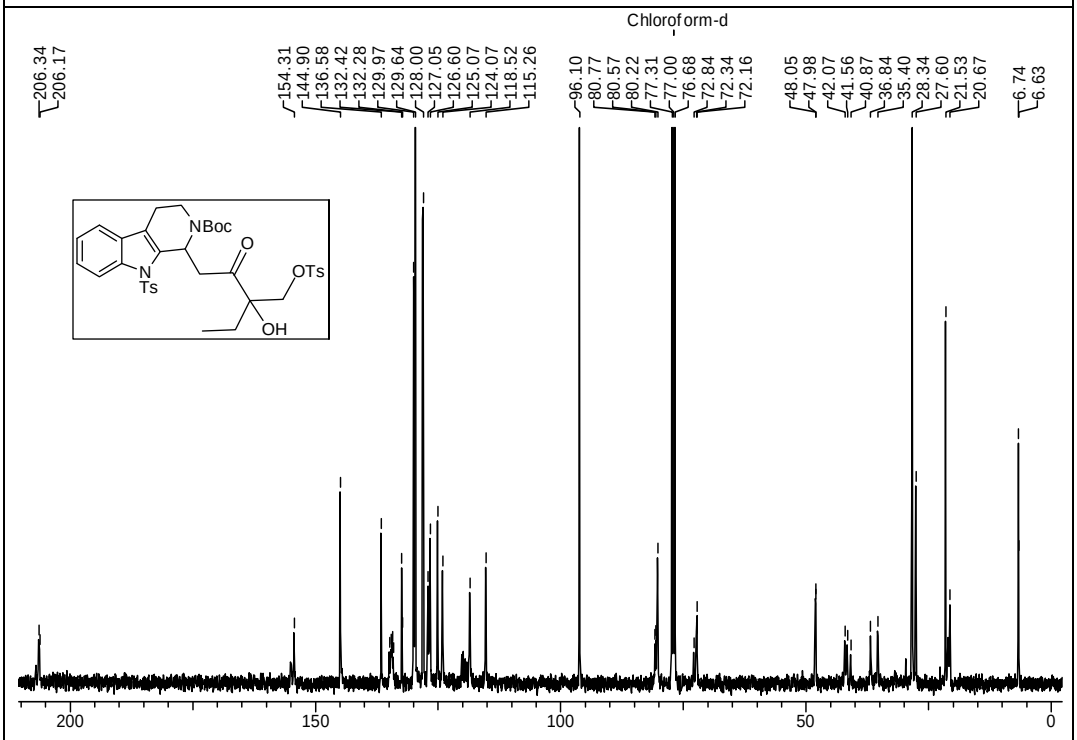
DEPT spectrum of compound 21 ($CDCl_3$+CCl_4, 100 MHz)



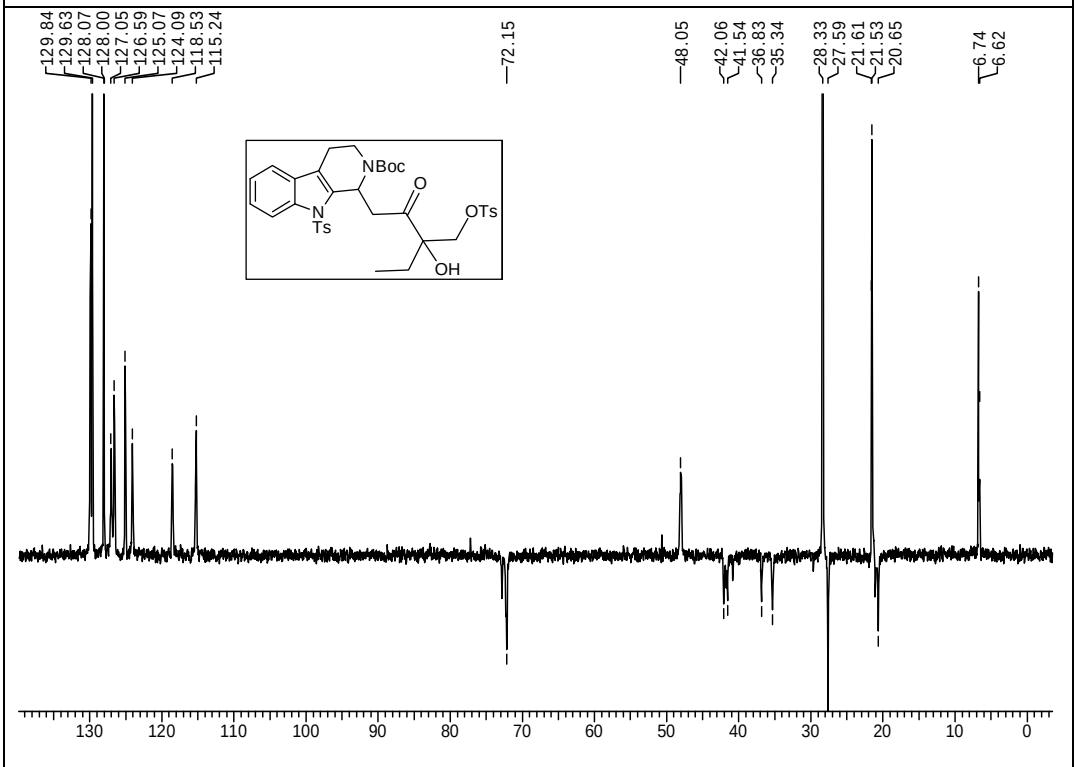
^{1}H NMR Spectrum of compound 22 ($CDCl_3$+CCl_4, 200 MHz)



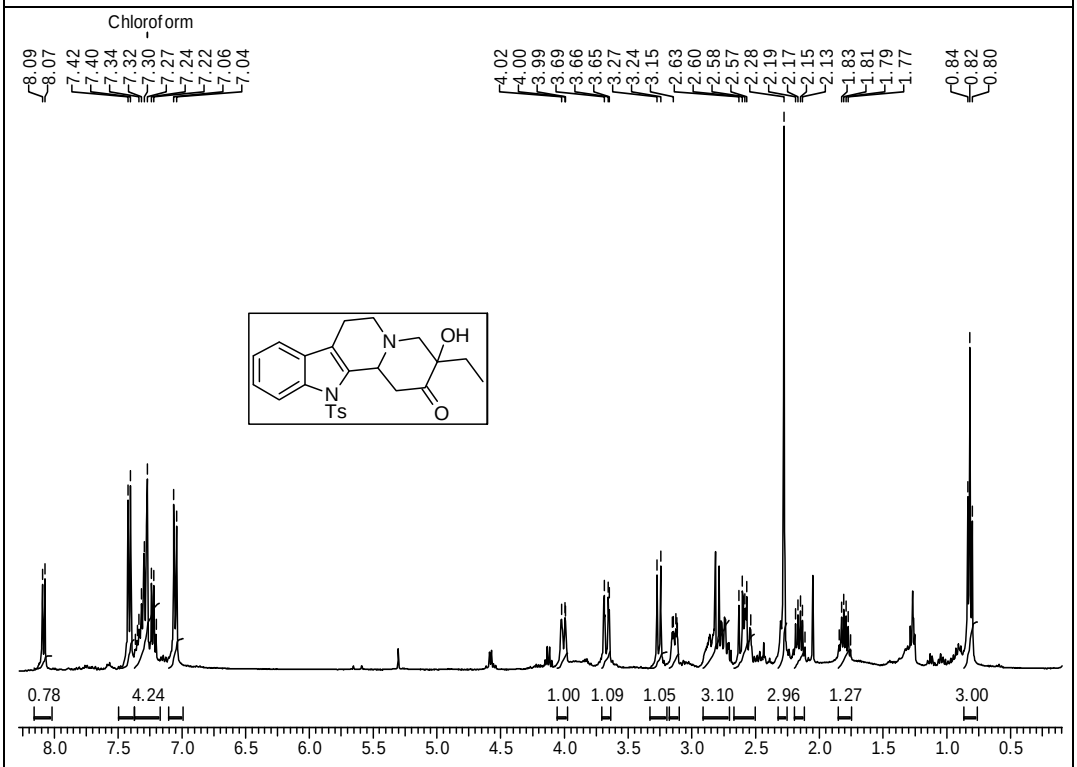
^{13}C NMR Spectrum of compound 22 ($CDCl_3$+CCl_4, 100 MHz)



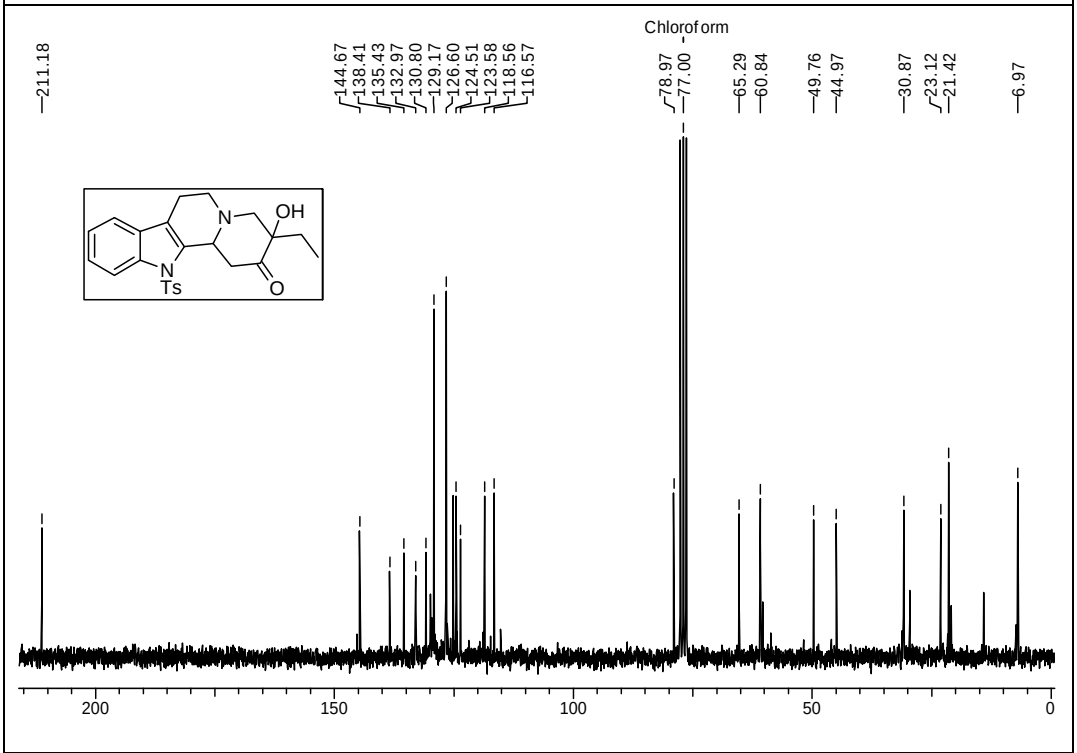
DEPT spectrum of compound 22 ($CDCl_3$+CCl_4, 100 MHz)



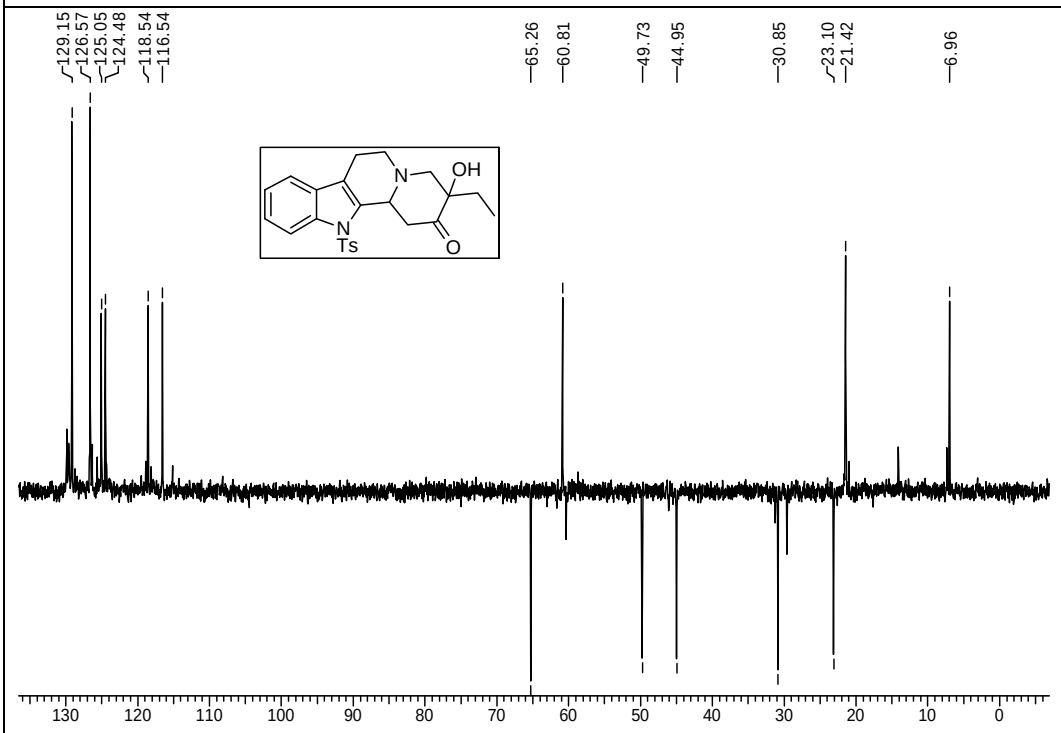
^{1}H NMR Spectrum of compound 8a ($CDCl_3$+CCl_4, 400 MHz)



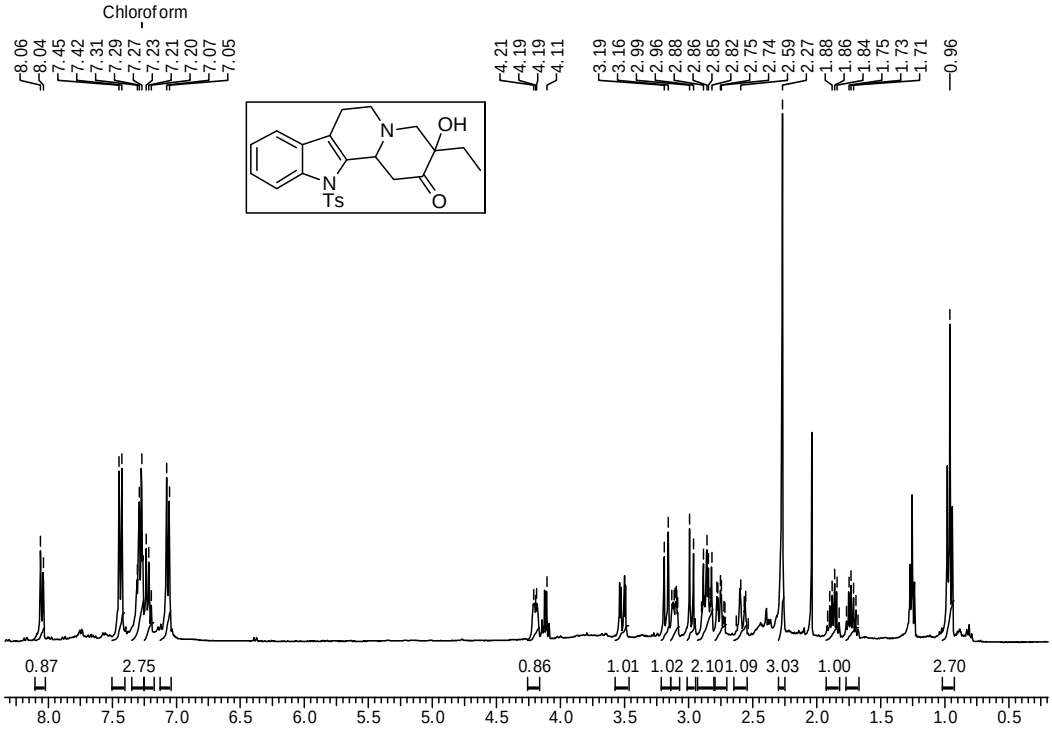
^{13}C NMR Spectrum of compound 8a ($CDCl_3$+CCl_4, 100 MHz)



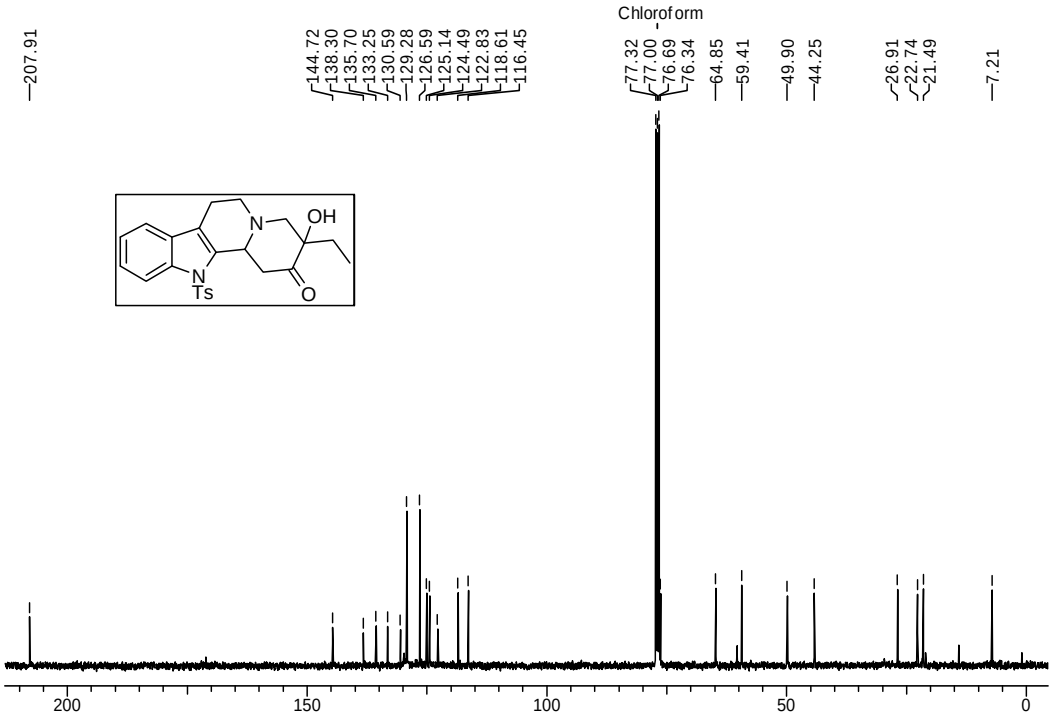
DEPT spectrum of compound 8a ($CDCl_3$+CCl_4, 100 MHz)



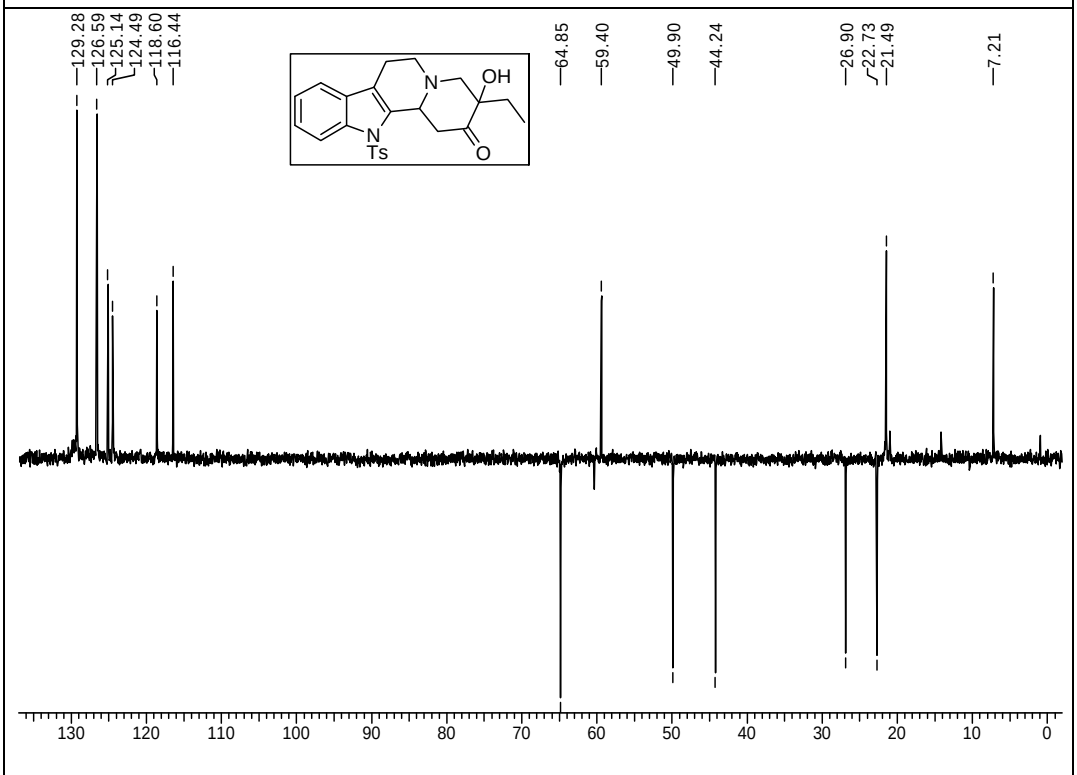
^{1}H NMR Spectrum of compound 8b ($CDCl_3$+CCl_4, 400 MHz)



^{13}C NMR Spectrum of compound 8b ($CDCl_3$+CCl_4, 100 MHz)

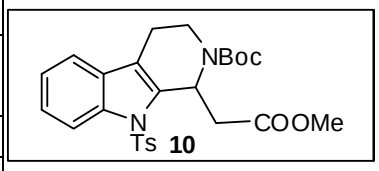


DEPT spectrum of compound 8b ($CDCl_3$+CCl_4, 100 MHz)



Single crystal analysis:

	M6q
Chemical formula	$C_{26}\ H_{30}\ N_2\ O_6\ S$
M_r	498.58
Temperature/K	298(2)
Morphology	prism, colorless
Crystal size	0.20 × 0.19 × 0.13
Crystal system	triclinic
Space group	*P*-1
a (Å)	9.528(6)
b (Å)	12.096(7)
c (Å)	12.267(8)
α (°)	87.536(10)
β (°)	76.788(9)
γ (°)	67.479(9)
V(Å^3)	1269.8(13)
Z	2
D_{calc} (g cm^{-3})	1.304
μ (mm^{-1})	0.171
F(000)	528
Ab. correction T_{min} / T_{max}	Multi-scan 0.967 / 0.978
θ_{max} (°)	25
h, k, l (min, max)	(–11,11), (–14,14), (–14,14)
Reflns collected	8865
Unique reflns	4373
Observed reflns	3972
No. of parameters	330
GoF	1.098
R_obs	0.0607
wR_2_obs	0.1674
R_all	0.0655
wR_2_all	0.1718
$\Delta\rho_{max}$,$\Delta\rho_{min}$(eÅ^{-3})	0.72, –0.40



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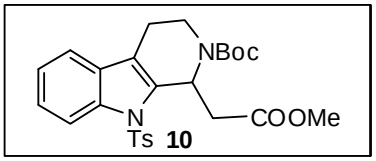

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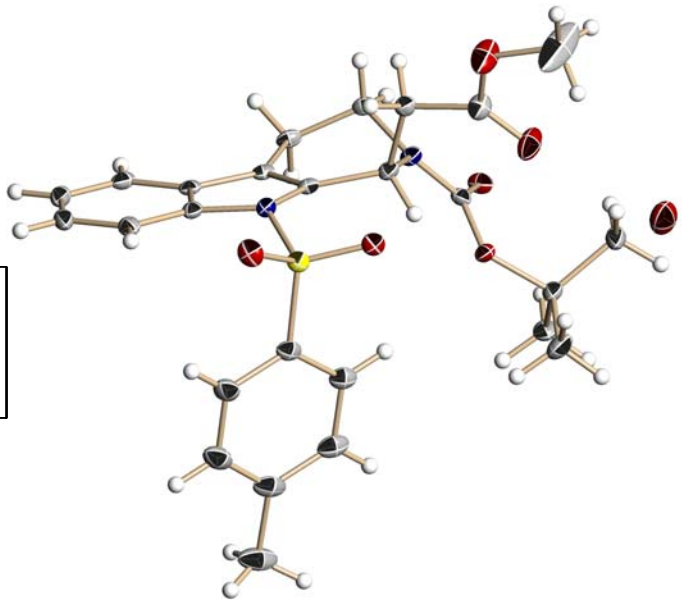

1.2.6 References

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Chapter 2: Synthetic studies towards 3-hydroxypipecolic acid and advanced intermediate for piperidine alkaloids

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

2.1.1. Introduction

Functionalized piperidine framework is important for many natural and synthetic compounds having medicinal significance[1] as represented by compound **1-12** (Figure 1). Pipecolic acid is a non proteogenic cyclic α-amino acid which is found abundantly in different species of plants and animals. It was first observed on paper chromatograms of extracts of *Phaseolus vulgaris* and later on its structure was elucidated.[2] Pipecolic acid was also found in potato tuber, green pepper, tulip, celery, several legumes, edible mushroom, asparagus,[3] barley,[4] Rhodesian teak,[5] and coconut milk.[6, 7] Pipecolic acid is a constituent of several secondary metabolites in plants and fungi. It is a constituent of a wide range of pharmacologically active compounds such as sandramycin[8] **11** which acts as the potent antitumour antibiotic agent and VX710[9] **12** which acts as anticancer agent.

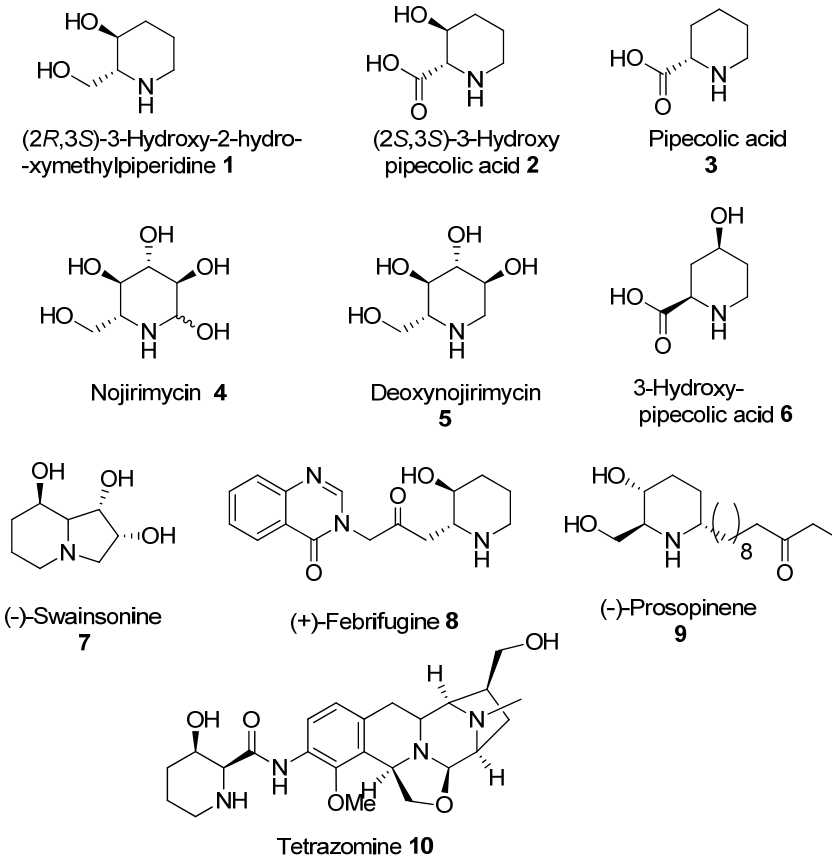
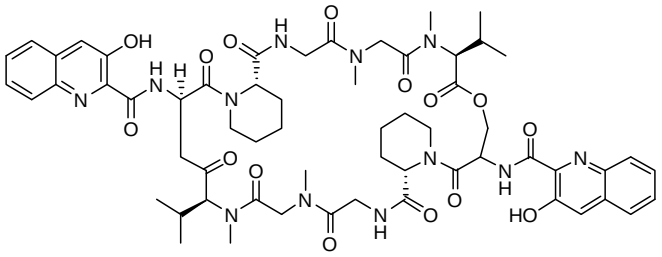
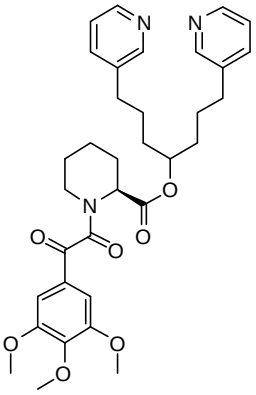


Figure 1



Sandramycin **11**



VX-710 **12**

(2*R*, 3*S*)-3-Hydroxy-2-hydroxymethyl piperidine **1**[10] (Figure 1) is an important core of many compounds having potential biological activities[11] like nojirimycin **4** which has significant biological activity against drug resistant strains of *shigella*, *lutea* and *sarcina*.[12] Some of the analogues of **1** also exhibit biological activities e.g. 1-deoxynojirimycin (DNJ) **5** acts as potent glycosidase inhibitor[13] while (–)-prosopinene **9** is known to possess an antibiotic and anaesthetic activity.[14]

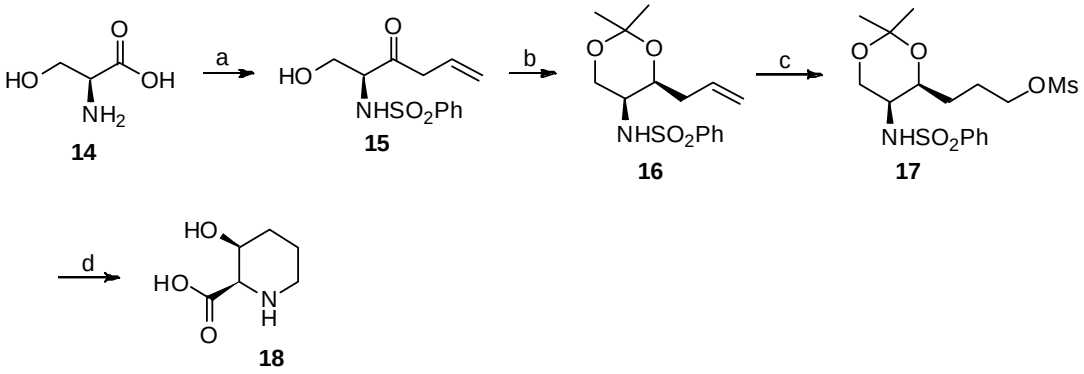
3-Hydroxypipecolic acid **2** is a non-proteinogenic cyclic *α*-amino *β*-hydroxy acid and is exploited in the synthesis of conformationally restricted peptides and ligand binding studies. (2*S*, 3*S*)-3-Hydroxypipecolic acid is also an important framework present in many natural as well as synthetic piperidine alkaloids. (–)-Swainsonine **7**, an analogue of **2**, acts as a potent α-mannosidase inhibitor[15] and (+)-febrifugine **8** one carbon homologue of **2** acts as a potent antimalarial agent.[16] The *cis*-isomer of **2** is a structural core of tetrazomine **10**[17] which acts as antitumor antibiotic agent.

2.1.2. Literature review

The interesting biological activity and structural features of this scaffold motivated attention of many organic chemists towards its synthesis.

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

Raporort *et al.* (Scheme 1) developed a method for alkylation of acids derived from L-serine and exploited it for the synthesis of *β*-hydroxy-*α*-amino acid **18**.[18]

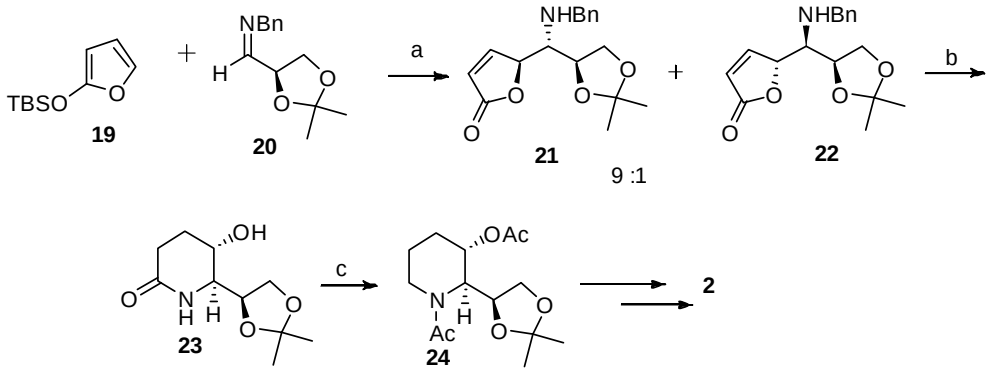


Scheme 1 *Reagents and conditions: (a)(i) $PhSO_2Cl$, K_2CO_3;(ii) n-BuLi, allyl magnesium bromide; b) i) L-Selectride, $LiBH_4$; ii) H^+, DMP; c) i) BH_3.DMS, NaOH, H_2O_2, ii) MsCl, TEA, DCM; d) i) K_2CO_3, MeOH ii) HCl, MeOH; iii) PtO_2, H_2O/EtOAc, 2e;*

The amine in L-serine **14** was converted into its sulphonamide derivative, and the resultant acid treated with allyl magnesium bromide to provide keto-sulphonamide **15**. The keto group in **15** was reduced followed by diol protection to give diastereomeric mixture of acetonide which was subjected to column chromatography to provide the desired diastereomer**15**. Acetonide derivative **16** was then subjected to hydroboration followed by mesylation to provide mesyl derivative **17**. Mesylate **17** was treated with base followed by acidification and oxidation to furnish *cis*-3-hydroxypipecolic acid **18**.

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

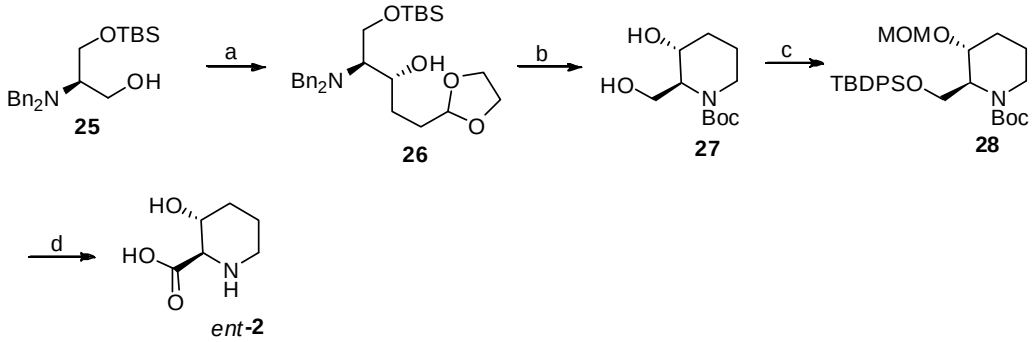
Casiraghi and co-workers (Scheme 2) reported a novel diastereoselective addition of silyloxy furan **19** to imines **20** (derived from L and D glyceraldehydes) in excellent diastereomeric excess and elaborated it for the synthesis of both the enantiomers of 3-hydroxypipecolic acid **2**.[19] Thus, the 2-silyloxyfuran **19** was coupled with imine **20** to afford a diastereomeric mixture of butenolides **21** and **22** in the ratio (*dr* 9:1). The butenolide **21** was subjected to hydrogenation followed by treatment with DBU to furnish the desired six membered lactam **23**. Lactam **23** was reduced using LAH in presence $AlCl_3$ followed by acetylation to give acetate derivative **24**. The acetate derivative **24** was converted to 3-hydroxypipecolic acid **2** by carrying out chemical transformations. The *ent*-**2** was also prepared starting from D-configuration of glyceraldehyde.



Scheme 2 *Reagents and conditions: a) TBSOTf, - 80 °C, DCM, 90%; b) i) H_2, Pd/C, NaOAc, 75%; ii) DBU, 80 °C, 82%; c) i) LAH, $AlCl_3$, THF, -80 °C-20 °C; ii) Ac_2O, pyridine, DMAP, DCM, 90%;*

Zhu's Approach[20] (*Tetrahedron Lett*. **2000**, *41*, 7033-7036)

Zhu *et al*. reported synthesis of 3-hydroxypipecolic acid (**2**) starting from amino alcohol **25** derived from serine (Scheme 3) by employing reductive cyclisation as key step.



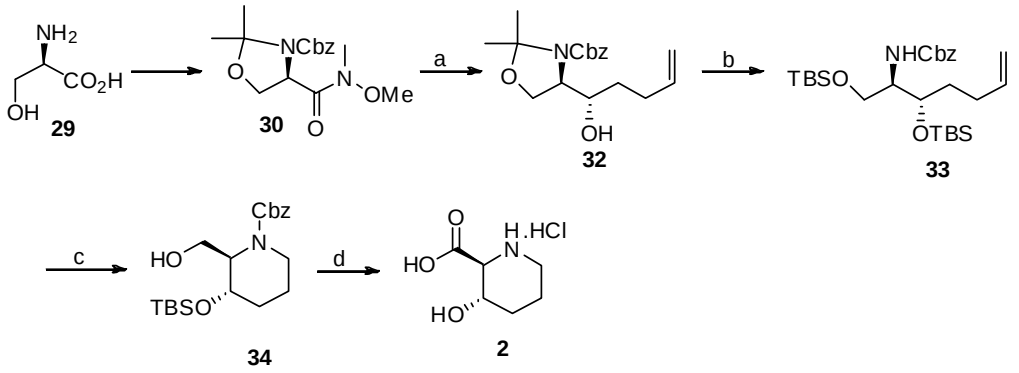
Scheme 3 *Reagents and conditions: a) (i) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, then Et_3N; (ii) 2-(2-Bromethyl)-1,3-dioxolane, Mg, THF, 86%; (b) (i) H_2, 10% Pd/C, 3 N HCl, THF:t-BuOH (1:1); (ii) Boc_2O, H_2O, dioxane, 1 N NaOH, 80%; (c) i) TBDPSCl, DMF, imidazole; ii) MOMCl, Hunig's base, CH_2Cl_2, reflux, 90%; d) i) HF (48%), pyridine, THF, 85%; ii) CrO_3/H_2SO_4, 2.67 M, acetone, 0 °C; iii) 6 N HCl, 80 °C, 2 h, 75%.*

Amino alcohol **25** was oxidized to corresponding aldehyde followed by treatment with Grignard reagent to afford anti- alcohol **26** as a major product which was elaborated for the synthesis of **2**. Amino compound **26** was subjected to hydrogenation and subsequently for Boc protection to provide carbamate diol **27**. The primary alcohol in diol **27** was protected with TBDPS group selectively and then the

secondary alcohol was protected with MOM, the TBDPS group was deprotected, and the resulting alcohol was subjected to oxidation and subsequently MOM group was deprotected to give (2*R*, 3*R*)- 3-hydroxypipecolic acid (*ent*-**2**).

Datta's Approach[21] (*J. Org. Chem.* **2005**, *70*, 10182-10185)

Datta *et al*. synthesized **2** starting from D-serine **29** (Scheme 4), utilizing diastereoselective reduction of ketone and reductive cyclization as the key steps.



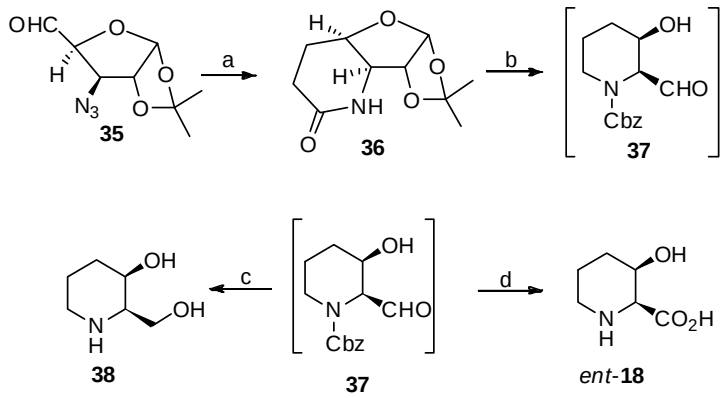
Scheme 4 *Reagents and conditions:a) i) Homoallyl magnesium bromide,73%; ii) $ZnBH_4$, $CeCl_3$. $7H_2O$, 90%; b) Dowex, MeOH, 93%; ii) TBSCl, imidazole, DCM, 95%; c) i) OsO_4, NMO, then $NaIO_4$, 83%; ii) Et_3SiH, $BF_3.OEt_2$; iii) CSA, MeOH, 72%; d) i) $RuCl_3$, $NaIO_4$, 72%; ii) aq. HCl, reflux, quantitative.*

The Weinreb amide **30** was derived from D-serine **29** by known literature protocol. Weinreb amide **30** was treated with Grignard reagent, followed by treatment with zinc borohydride in presence of cerium chloride to provide alcohol **32**. The acetonide deprotection of **32** and subsequent protection of diol with TBS group furnished di-TBS derivative **33**. TBS derivative **33** was dihydroxylated followed by cleavage of diol using $NaIO_4$ followed by reduction and deprotection to afford **34**. The substituted piperidine derivative **34** upon oxidation and deprotection resulted in the formation of hydrochloride salt of 3-hydroxypipecolic acid **2**.

Dhavale's Approach[22] (*J. Org. Chem.* **2008**, *73*, 3619–3622)

Dhavale *et al.* utilized reductive cyclisation as key step for the synthesis of **38** and *ent*-**18** from D-glucose as a chiral template (Scheme 5). D-Glucose was converted to aldehyde **35** by carrying out some chemical transformations. The azido aldehyde **35** was subjected to Wittig reaction followed by azide reduction to furnish the desired six

membered lactam **36**. Lactam **36** was reduced using LAH followed by Cbz protection, acetonide deprotection and cleavage to provide aldehyde **37**.

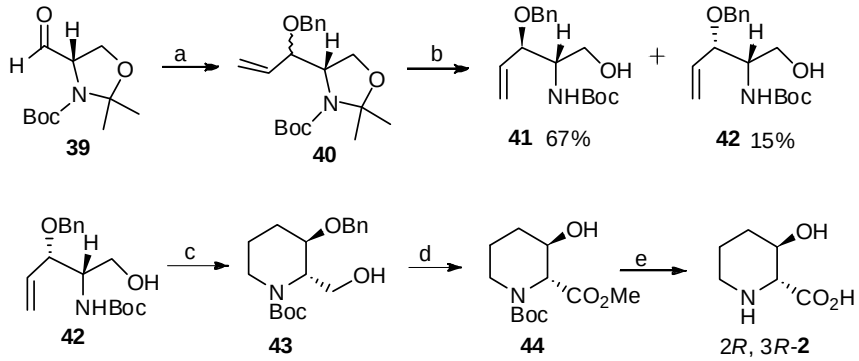


Scheme 5 *Reagents and conditions: a) i) Ph_3P=CHCOOEt, DCM, reflux, 0.5 h, 92%; ii) H_2, Pd/C, MeOH, rt, 12 h, 80 psi, 96%; b) i) LAH, THF, reflux, 7 h, 89%; ii) Cbz-Cl, $NaHCO_3$, rt, 3 h, 98%; iii) TFA:H_2O (3:2), 0 ^oC-rt, 7 h; iv) $NaIO_4$, acetone:H_2O, rt, 76%; c) i) $NaBH_4$, MeOH, 94%; ii) H_2, Pd/C, MeOH, 98%; d) $NaClO_2$, H_2O_2, MeCN: H_2O, -10 ^oC, 95%; ii) H_2, Pd/C, MeOH, 98%.*

Aldehyde **37** was converted to *cis*-3-hydroxypipecolic acid *ent*-**18** as well as *trans*-3-hydroxypipecolic acid **38** in two steps each.

Chiou's Approach[23] (*J. Org. Chem*. **2010**, *75*, 1748–1751)

Chiou *et al*. achieved the syntheses of *cis* and *trans*-3-hydroxypipecolic acid (*ent*-**2**) starting from Garner's aldehyde **39** utilizing diastereoselective Grignard reaction and Rh catalyzed cyclohydrocarbonylation as key steps (Scheme 6).



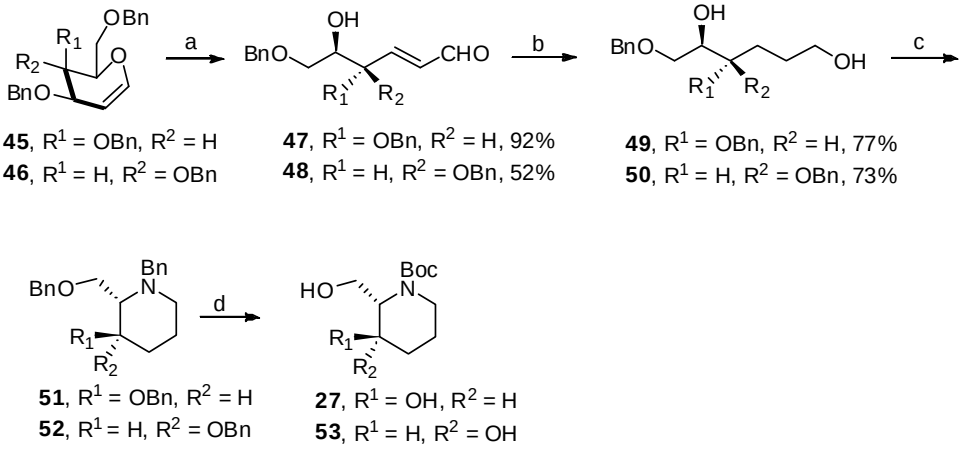
Scheme 6 *Reagents and conditions: (a) i) CH_2=CHMgBr (2.0 eq.), THF, -40 ^oC; (ii) BnBr (1.5 eq.), NaH (1.8 eq.), 18-crown-6 ether (0.5 eq.), THF, 0 ^oC to rt; (b) p-TSA*

(13 mol %), MeOH, rt; (c) i) Rh(acac)(CO)$_2$ (0.5 mol %), BIPHEPHOS (1.0 mol %), CO (2 atm), H_2 (2 atm), toluene, 60 ^oC, overnight (~16 h); (ii) Et_3SiH (3.0 eq.), BF_3OEt_2, CH_2Cl_2, -78 ^oC,16 h; (d) i) TEMPO (20 mol %), KBr (0.5 eq.), NaOCl (6.0 eq.), $NaHCO_3$, acetone, 4 ^oC, 3 h; (ii) CH_2N_2; (iii) Pd/C (5 mol %), H_2 (2 atm), MeOH, rt, 4 h; (e) (i) 6 N HCl, reflux, (ii) Propylene epoxide, EtOH, reflux.

Vinyl magnesium bromide was treated with aldehyde **39** to furnish diastereomeric mixture of alcohol, which was protected with benzyl bromide to give benzyl ether **40**. Carbamate **40** was subjected to acetonide deprotection to deliver mixture of alcohols **41** and **42**, which were separated. Alcohol **42** was subjected to cyclohydrocarbonylation followed by reduction to give piperidine derivative **43**, which was further elaborated to (2*R*, 3*R***)**-3-hydroxypipecolic acid**.** Similarly the alcohol **41** was elaborated for the synthesis of *cis* 3-hydroxypipecolic acid *ent*-**2**.

Vankar's Approach[24] (*J. Org. Chem*. **2010**, *75*, 4608–4611)

Vankar *et al*. (Scheme 7) accomplished formal synthesis of pipecolic acid along with deoxoprosophylline by taking advantage of Perlin hydrolysis, chemoselective saturation of olefins and reductive amination as the key steps.



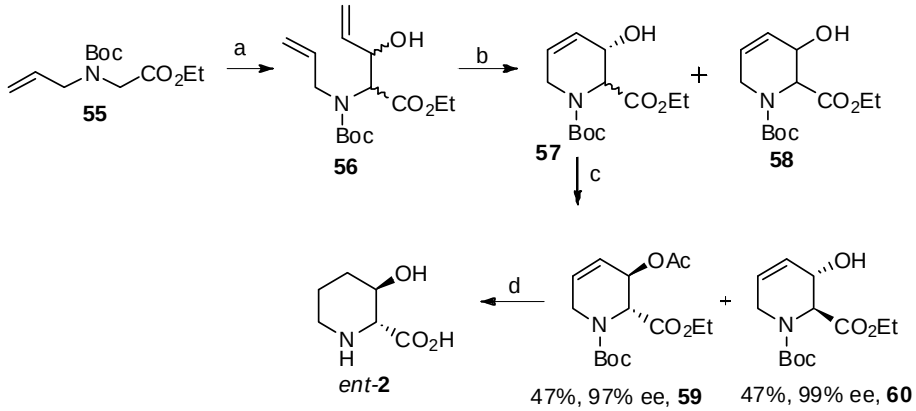
Scheme 7 *Reagents and conditions: a) Perlin Hydrolysis; b) i) $NaBH_4$, $CeCl_3$ .7H_2O, MeOH, rt, 1 h, ii) H_2, Pd/C, EtOAc, 30 min; c) i) MsCl, TEA, DCM, 20 min; ii) $BnNH_2$, 90 ^oC, 2 h; d) H_2, $Pd(OH)_2$/C, ii)$(Boc)_2O$, MeOH.*

D-Glycols **45** and **46** were subjected to Perlin hydrolysis to afford unsaturated aldehydes **47** and **48** respectively, which were subjected to using Luche's reduction conditions followed by hydrogenation to furnish diols **49** and **50**. Diols **49** and **50** on

mesylation and subsequent treatment with benzyl amine furnished piperidine derivatives **51** and **52**, which on hydrogenation and Boc protection gave carbamate diols **27** and **53** respectively.

Takahata's Approach[25] (*Bioorg. Med. Chem*. **2008**, *16*, 8273–8286)

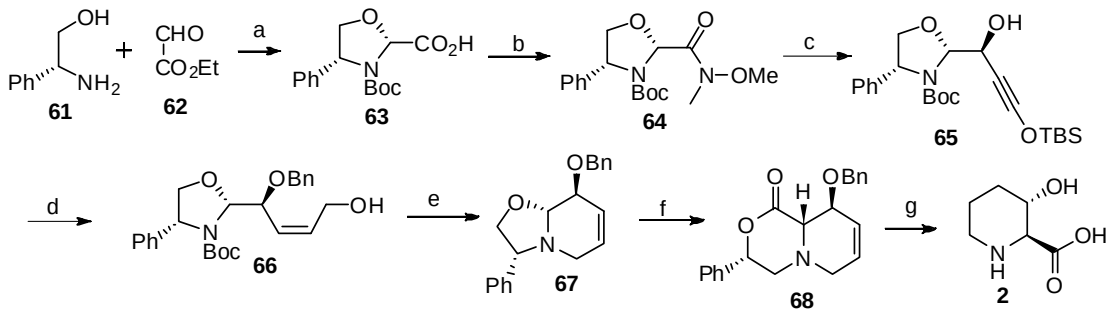
Takahata *et al*. reported total synthesis of **2** employing RCM and enzymatic resolution as the key steps (Scheme 8). Ester **55** was treated with LiHMDS and then with acrolein to deliver di-allyl compound **56**, which was subsequently subjected under RCM reaction conditions to afford a mixture of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



Scheme 8 *Reagents and conditions: a) LiHMDS, acrolein, THF; b) Grubb's 1st gen. cat., DCM; c) Lipase PS-C, vinyl acetate; d) H_2, Pd/C; ii) 5N HCl.*

Couty's Approach[26] (*Tetrahedron Lett.* **1996**, *37*, 4001)

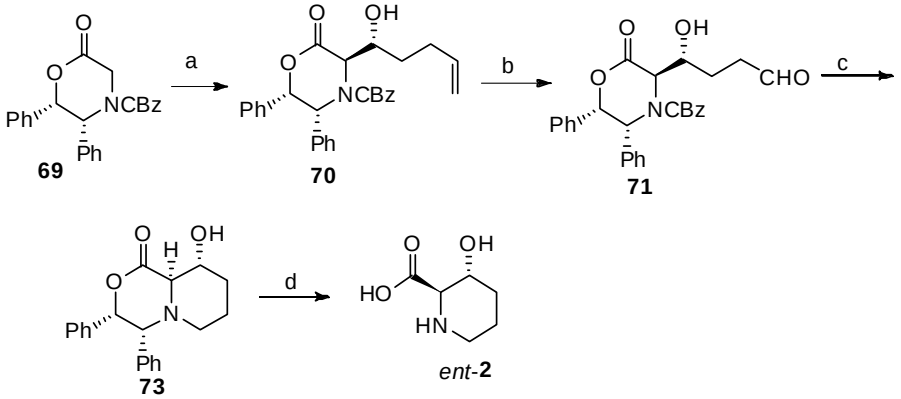
Couty *et al*. utilized diastereoselective reduction of ketone and stereoselective addition of cyanide as key steps for the synthesis of 3-hydroxypipecolic acid **2** (Scheme 9). The hemiaminal acid **63** was prepared from **61** in three steps. Acid **63** was converted to Wienreb amide **64** and subsequently treated with lithium acetalide to give ketone and the resulting ketone was reduced to afford alcohol **65**. Alcohol **65** was protected as its benzyl ether, the triple bond was reduced using LAH followed by TBS deprotection, mesylation and cyclization to give bicyclic compound **67**. Nucleophilic addition on **67** with cyanide anion followed by hydrolysis and hydrogenation resulted in to formation of 3-hydroxypipecolic acid **2**.



Scheme 9 *Reagents and conditions: (a) i) Toluene, reflux (-H_2O); ii) $(Boc)_2O$, reflux; iii) LiOH, THF/EtOH/H_2O, rt (86% overall yield); (b) i) N-Methyl morpholine, i-BuOCOC1, THF, then $Me(OMe)NH_2^+CI^-$, NEt_3, DMF, -20 °C (91%); (c) i) $LiCCCH_2OSiMe_2$ t-Bu, THF, -78 °C; ii) $NaBH_4$, $CeC1_3.7\ H_2O$, EtOH, -50 °C, 60%; (d) i) H_2, Lindlar catalyst, EtOH; ii) NaH, BnBr, DMF, 0°C; iii) n-Bu_4NF, THF, 80%; e) MsCI, Et_3N, CH_2CI_2, 0°C; ii) CF_3CO_2H, 1,2-dichloroethane, 0 °C; iii) Et_3N, 1,2-dichloroethane, 80% ; f) KCN, citric acid, THF/H_2O, 87%; g) i) 1N HCl in AcOEt, silica gel,50% (80% based on recovered* **68***); ii) H_2 , $Pd(OH)_2$, EtOH, 88%.*

Williams's Approach[27] (*Tetrahedron Lett*. **1998**, *39*, 3659-3662)

Williams *et al*. utilized diastereoselective aldol condensation between **69** and aldehyde (Pente-4-enal) to provide the olefinic alcohol **70** (Scheme 10).

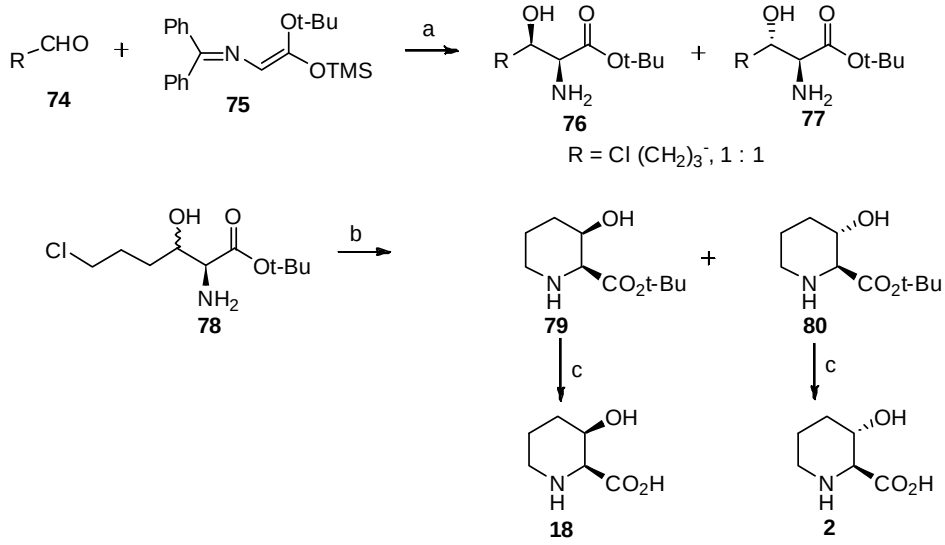


Scheme 10 *Reagents and conditions: a) i) Bu_2BOTf, TEA; ii) $CH_2=CH(CH)_2CHO$, DCM, -78 °C; b) O_3, DCM, -78 °C, Me_2S, 25 °C, 65 %; c) H_2, Pd/C, DCM, 66%; d) H_2, $PdCl_2$, 50 psi, EtOH, THF, 25 °C, 95%.*

Oxidative cleavage of the olefin **70** furnished aldehyde **71**, which on hydrogenation afforded bicyclic compound **73**. Finally piperidine derivative **73** on hydrogenation on Pd/C as catalyst furnished (2*R*, 3*R*)-3-hydroxypipecolic acid *ent*-**2**. Similarly, (2*S*, 3*S*)-3-hydroxypipecolic acid was derived using *ent*-**69** as the starting material.

Corey's Approach[28] (*Tetrahedron Lett*. **1999**, *40*, 3843-3846)

Corey *et al*. developed a novel protocol for the preparation of *β*-hydroxy-*α*-amino acids by aldol condensation catalyzed by cinchona derived chiral catalysts between various aldehydes and imine **75**. Thus, the aldol condensation between aldehyde **74** and silyl enol ether **75** gave a mixture of amino alcohols **76** and **77** in the ratio of 1:1. The method was elaborated for the synthesis of *cis* as well as *trans*-3-hydroxypipecolic acid (Scheme 11). The diastereomeric mixture of amino alcohol **78** was treated with weak base to afford a separable diastereomeric mixture of piperidine derivatives **79** and **80**. The piperidine derivatives **79** and **80** were treated with acid to provide (2*S*, 3*R*)-3-hydroxypipecolic acid (**18**) and (2*S*, 3*S*)-3-hydroxy pipecolic acid (**2**) respectively.

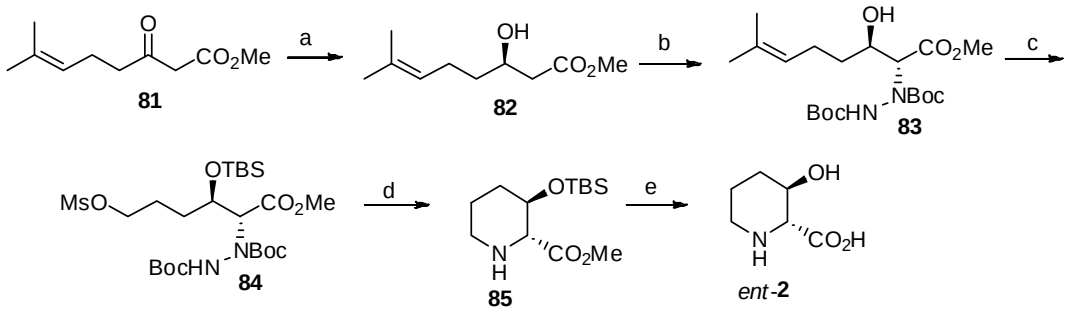


Scheme 11 *Reagents and conditions: a) i) Cinchonidine derived catalyst, DCM, -78 ^{o}C; ii) Citric acid; b) $NaHCO_3$, CH_3CN; c) TFA, DCM.*

Genêt's Approach[29] (*Tetrahedron Lett.* **1996**, *37*, 2031)

Genêt *et al*. accomplished the total synthesis of 3-hydroxypipecolic acid **2** starting from keto ester **81**, utilizing asymmetric reduction (Noyori reduction) of ketone and chiral amination as the key steps (Scheme 12). Keto ester **81** was reduced using Ru-

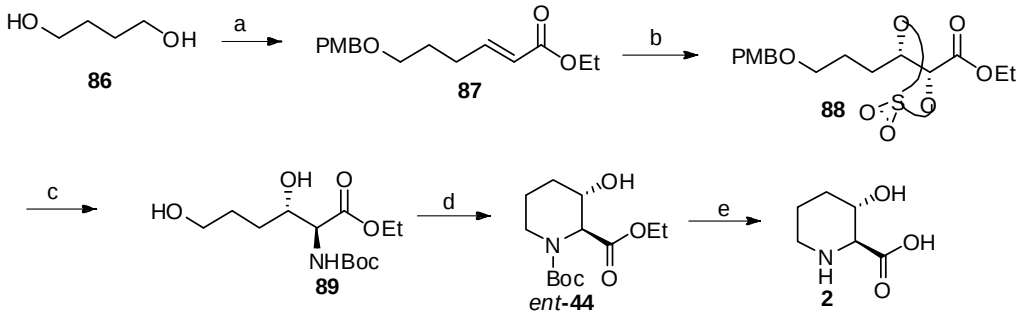
BINAP (Noyori reduction) as the catalyst to afford *β*-hydroxy ester **82**, which was subjected to α-amination to give carbamate **83**. The hydroxy functionality in **83** was protected as its TBS group and subsequently subjected to ozonolysis followed by mesylation of resulting alcohol to provide **84**. The mesylate **84** on acidification, treatment with Raney Ni and triethylamine afforded piperidine derivative **85** which was subjected to TBS deprotection and ester hydrolysis to furnish (2*R*, 3*R*)-3-hydroxypipecolic acid *ent*-**2**.



Scheme 12 *Reagents and conditions: (a) H_2, 1 atm.; $RuBr_2$[(R)-BINAP], 2%; MeOH, 50°C. (98%; ee--97%). (b) MeZnBr, 1 eq., 0 °C; LDA, -78 °C; DBAD, -78°C; NH_4CI, H_2O, (55%; de>98%). (c) i) TBDMSOTf, 2,6-1utidine, -78 °C; ii) O_3, CH_2C1_2, -78 °C; BH_3-Me_2S. iii) MsCI, py, 0 °C, 65%; d) i) TFA, CH_2Cl_2; ii) H_2, Raney Ni, ultrasound; iii) Et_3N, CH_2C1_2. 75%; e) i) HF, CH_3CN, 50 °C; ii) K_2CO_3, MeOH, H_2O; iii) Amberlite CG 50, 80%* .

Pradeep Kumar's 1st Approach[30] (*Tetrahedron Lett.* **2004**, *45*, 8461)

Pradeep Kumar *et al*. employed Sharpless asymmetric dihydroxylation as a key step for the synthesis of 3-hydroxypipecolic acid **2** starting from butane diol **86**.



Scheme 13 *Reagents and conditions: (a) i) DMF, NaH, p-$MeOC_6H_4CH_2Br$, 80%; ii) PCC, NaOAc, Celite, CH_2Cl_2, 0 ^oC; iii) Ph_3P=$CHCO_2Et$, benzene, reflux 4 h, 80%. b) i) K_2CO_3, $K_3Fe(CN)_6$, $CH_3SO_2NH_2$, $(DHQ)_2PHAL$ (1mol%), 0.1M OsO_4 (0.4 mol%), t-BuOH/H_2O (1:1), 85%. ii) $SOCl_2$, Et_3N, CH_2Cl_2, 0 ^oC, 20 min; iii) $RuCl_3.H_2O$,*

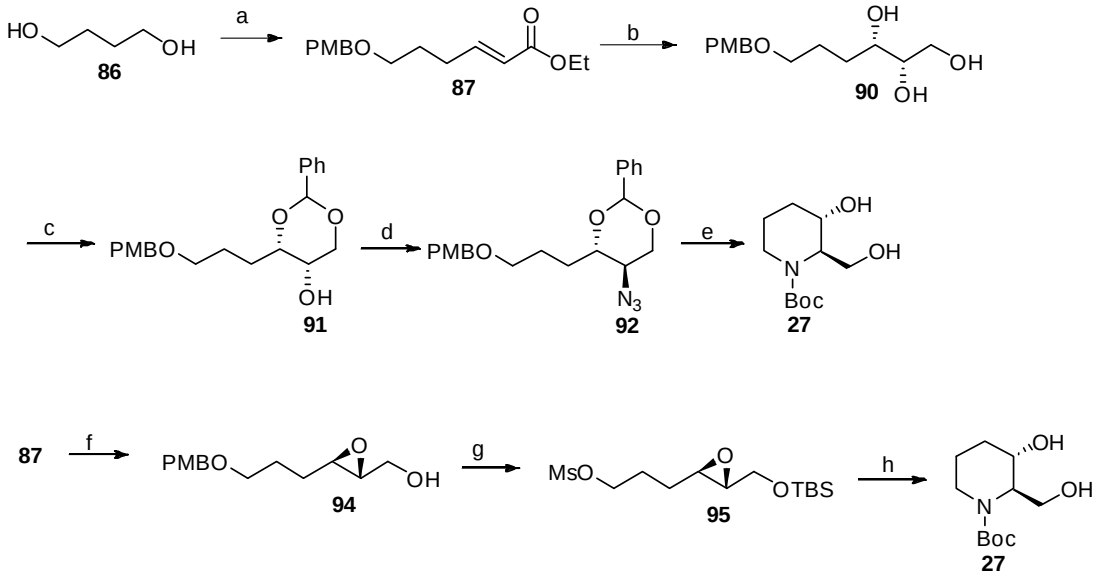
$NaIO_4$, $CCl_4/CH_3CN/H_2O$ (1:1:1.5), 0 ^oC, 2 h, 92%. c) i) NaN_3, DMF, 80 ^oC, 94%. ii) DDQ, CH_2Cl_2, H_2O; iii) H_2, Pd/C, Boc_2O, EtOAc, 70%. d) MsCl, Et_3N, CH_2Cl_2, -78 ^oC, 95%; e) i) $LiOH/H_2O$, THF, MeOH, H_2O, 6 h; ii) $TFA:CH_2Cl_2$ (1:1), 1.5 h; then Dowex 50, 90%.

Diol **86** was protected selectively, oxidized and subsequently subjected to Wittig reaction to provide unsaturated ester **87** (Scheme 13). Unsaturated ester **87** was subjected under Sharpless asymmetric di-hydroxylation conditions and resulting diol was protected as its sulfate **88**. Regioselective opening of sulfate **88** was carried out with sodium azide, which on reduction followed by Boc protection furnished carbamate-diol **89**. The diol **89** on selective mesylation gave piperidine **44**, which on acid hydrolysis followed by Boc deprotection furnished 3-hydroxypipecolic acid **2**.

Pradeep Kumar's 2nd Approach[31] (*J. Org. Chem.* **2005**, *70*, 360)

Pradeep Kumar *et al*. (Scheme 14) in their second approach accomplished formal synthesis of **2** starting from butane 1, 4-diol as the starting material as shown in **Scheme 13**. The mono-PMB protection of **86**, followed by oxidation and Wittig reaction gave unsaturated ester **87**. The ester functionality in **87** was reduced to alcohol followed by Sharpless dihydroxylation to afford triol **90**. The 1, 3-acetal protection was carried out to furnish alcohol **91** followed by mesylation and subsequent reaction with sodium azide to deliver azide **92**. The azido compound **92** was subjected to *p*-methoxybenzyl ether deprotection and the resulting hydroxy compound was mesylated and subsequently subjected to hydrogenation to give piperidine diol **27**.

The authors prepared **93** by an alternate route which involved reduction of ester **87** followed by Sharpless asymmetric epoxidation of the resulting allyl alcohol to provide epoxy alcohol **94**. The alcohol functionality in **94** was protected as its TBS derivative followed by PMB ether deprotection and mesylation to afford mesylate **95**. The mesyl group in **95** was displaced with azide followed by reduction of azide to furnish the diol **27**.

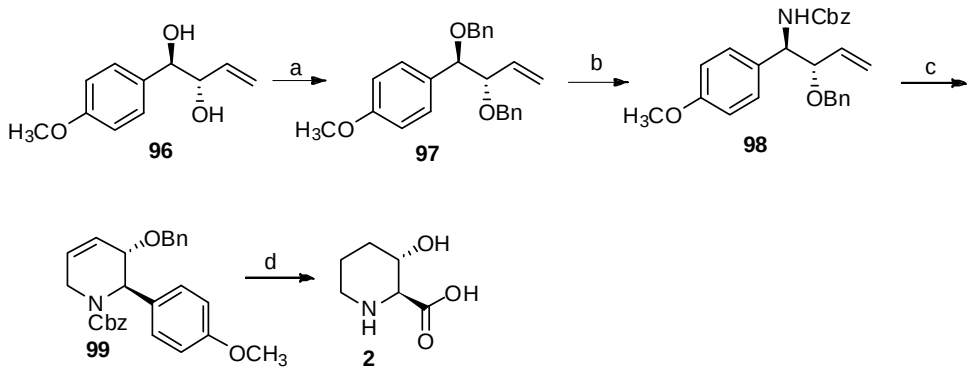


Scheme 14 *Reagents and conditions: (a) i) DMF, NaH, p-OMeC$_6$H$_4$CH$_2$Br,80%; ii) PCC, NaOAc, Celite, CH$_2$Cl$_2$, 6 h, rt, iii) Ph$_3$P=CHCO$_2$Et, benzene, reflux 4 h, 80%; b) DIBAL-H, CH$_2$Cl$_2$, rt, 1h, 80%. ii) K$_2$CO$_3$, K$_3$FeCN$_6$, CH$_3$SO$_2$NH$_2$, (DHQ)$_2$PHAL (1 mol %), 0.1 M OsO$_4$ (0.4 mol %), t-BuOH/H$_2$O (1:1), 0 °C, 18 h, 71%; c) i) C$_6$H$_5$CH(OMe)$_2$, CH$_2$Cl$_2$, TsOH, rt, 85%; d) (i) MsCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, rt, (ii) NaN$_3$, DMF, 80 °C, 24 h, 80%; e) (i) DDQ, CH$_2$Cl$_2$, H$_2$O, 3 h, rt, (ii) MsCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, rt, (iii) H$_2$, 10% Pd-C, MeOH, 30 h, then Boc$_2$O, 59%, f) i) DIBAL-H, CH$_2$Cl$_2$, rt, 1 h, 80%. ii) Ti(i-OPr)$_4$, (-)-DIPT, TBHP,CH$_2$Cl$_2$, -20 °C, 20 h, 67%; g) i) TBDMSCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, 10 h, rt, (ii) DDQ, CH$_2$Cl$_2$, H$_2$O, 3 h, rt, 90% (over two steps); iii) MsCl, Et$_3$N, CH$_2$Cl$_2$, rt, h) i) NaN$_3$, DMF, 70 °C, 82%, (over two steps); ii) Ph$_3$P, THF/H$_2$O (1:1), rt, 48 h; then Boc$_2$O, NaOH, TBAF, THF, rt, 1 h, 48%.*

Jung's Approach[32,33] (*Tetrahedron Lett.* **2006**, *47*, 7289; *Tetrahedron* **2007**, 63, 2622)

Jung *et al*. reported synthesis of **2** employing NGP (neighboring group participation) for installation of nitrogen heteroatom and ring closing metathesis as key steps (Scheme 15). Diol **96** was protected as dibenzyl ether **97** and further treated with chlorosulfonyl isocyanate (CSI) followed by treatment with base to provide carbamate **98**. Carbamate in **98** was allylated followed by RCM reaction to provide piperidine derivative **99**. Olefin in **99** was reduced using PtO_2 as the catalyst followed by

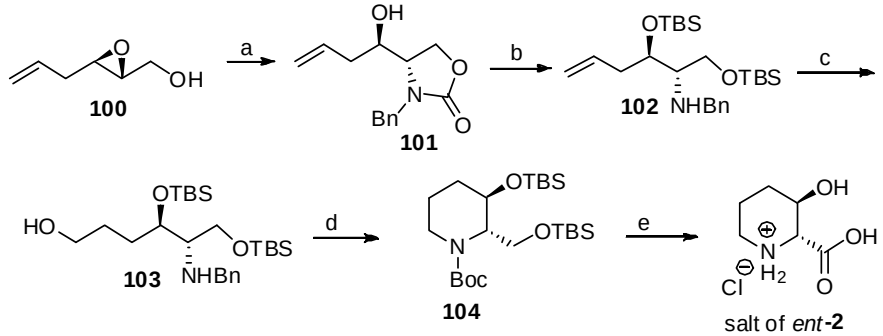
oxidative cleavage of aryl ring using Ru catalyst and acidification to furnish (2*S*,3*S*)-3-hydroxypipecolic acid (**2**).



Scheme 15 *Reagents and conditions: a) NaH, BnBr, THF/DMF, 99%; b) CSI, Na_2CO_3, toluene, -78 ^oC; ii) 25% Na_2SO_3, 90%; c) NaH, allyl bromide, THF/DMF, 100%; ii) Grubb's 1 st gen. catalyst, DCM, 91%; d) i) PtO_2, H_2, MeOH, 94%; ii) $RuCl_3$, $NaIO_4$, $H_2O/CH_3CN/EtOAc$; iii) 6N HCl, reflux, 72%, (over two steps).*

Riera's Approach[34] (*Eur. J. Org. Chem.* **2008**, 1789–1796)

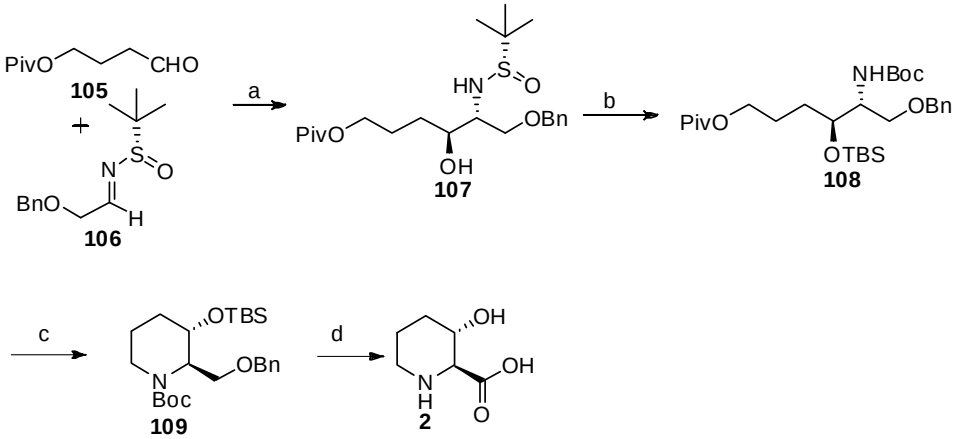
Riera *et al*. accomplished total synthesis of (2*R*,3*R*)- 3-hydroxypipecolic acid employing Sharpless asymmetric epoxidation, tethered epoxide opening and RCM reaction as key steps (Scheme 16). Epoxide **100** was intramolecularly opened at C-2 by nitrogen using benzyl isocyanate to afford cyclic carbamate **101**. Cyclic carbamate **101** was hydrolysed followed by TBS protection to deliver amine derivative **102**. The olefin **102** was subjected to hydroboration using 9-BBN followed by oxidation to afford alcohol **103**. Alcohol **103** was subjected to hydrogenation followed by Boc protection to provide carbamate. Subsequently the alcohol was converted to mesylate derivative followed by treatment with base to furnish piperidine derivative **104**. Selective primary OTBS ether deprotection was carried out using *p*-TSA followed by oxidation and acidification to afford hydrochloride salt of (2*R*, 3*R*)-3-hydroxypipecolic acid *ent*-**2**.



Scheme 16 *Reagents and conditions: a) i) BnNCO, THF; ii) NaN(TMS)$_2$, 86%; b) i) MeOH/H$_2$O, 6M NaOH; ii) TBSOTf, lutidine, DCM, 0 ^{o}C, 2 h, 96%; c) i) 9-BBN, THF/Hexane, -78 ^{o}C; ii) NaOH, H$_2$O$_2$, 81%; d) i) H$_2$, Pd(OH)$_2$/C, (Boc)$_2$O; ii) MsCl, py; iii) t-BuOK, THF, 72% (over two steps); e) p-TsOH, MeOH, 2 h, 74%; ii) NaIO$_4$, RuCl$_3$, CH$_3$CN/CCl$_4$/H$_2$O; iii) 6M, HCl, 63% over two steps.*

Wang's Approach[35] (*Eur. J. Org. Chem.* **2009**, 2845)

Wang *et al*. (Scheme 17) developed a Pinacol type reductive coupling protocol between aldehyde **105** and sulfinyl imine **106** and explored it for the synthesis of **2**. The removal of the sulfinyl auxiliary followed by selective *N*-protection with Boc_2O furnished carbamate **108**. The pivalyl group in **108** was deprotected and the resulting alcohol was converted in to its mesyl derivative followed by treatment with base to afford piperidine derivative **109**. Carbamate compound **109** was subjected to hydrogenation followed by oxidation of alcohol and acidification to provide target molecule 3-hydroxypipecolic acid (**2**).

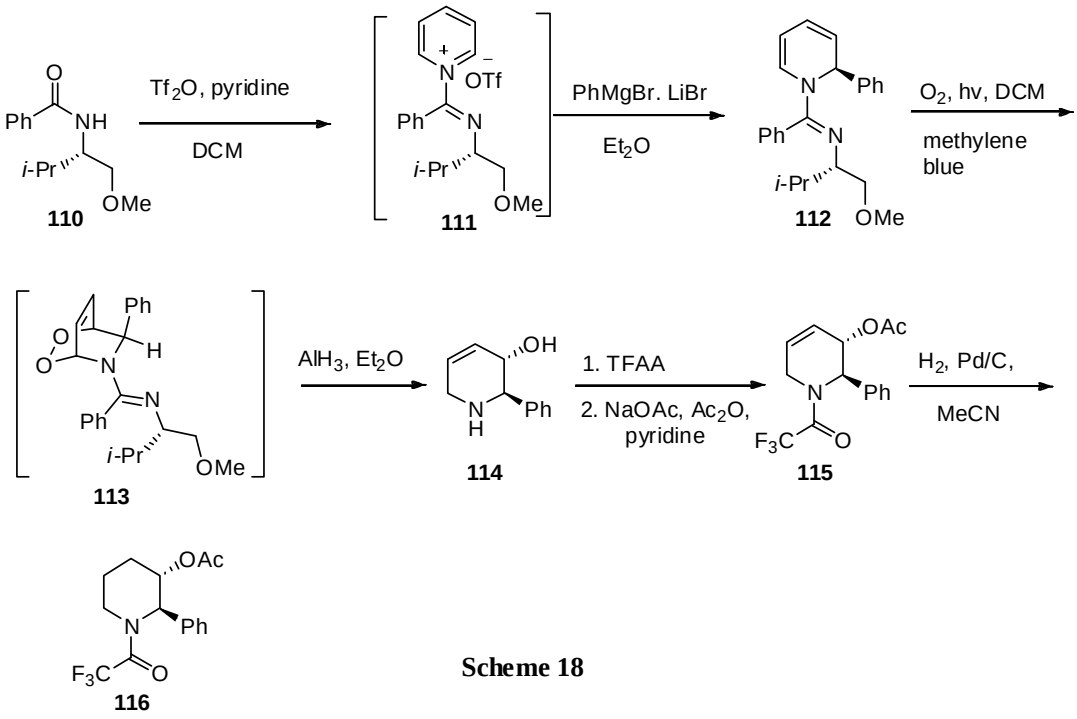


Scheme 17 *Reagents and conditions: a) SmI$_2$, THF, -78 ^{o}C, >98% ee; b) i) HCl, MeOH; ii) (Boc)$_2$O, DCM, 88% (over two steps), iii) TBSCl, imidazole, DMF, 93%; c) i) K$_2$CO$_3$, MeOH; ii) MsCl, DCM, TEA; iii) t-BuOK, THF, 79% (over two steps); d) H$_2$, Pd/C, MeOH, 98%; ii) RuCl$_3$ (cat.), NaIO$_4$; iii) 6M HCl, reflux, 74% (over two steps).*

Charette's Approach[36] (*J. Org. Chem*. **2010**, *75*, 2077)

Charette *et al*. synthesized 3-hydroxypipecolic acid (**2**) employing a diastereoselective addition of Grignard reagent (PhMgBr) on *N*-pyridinium salt **111** (Scheme 18). The imine derivative **112** was subjected under Diels Alder cycloaddition with oxygen followed by treatment with aluminum hydride to provide piperidine derivative **114**.

The protection of amine as well as alcohol functionality in **114** afforded **115** which on hydrogenation led to known intermediate **116**.



Scheme 18

2.1.3 References

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Chapter 2

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

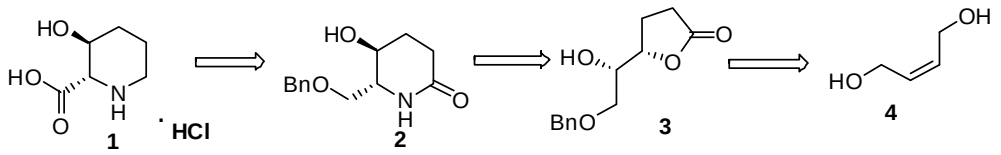
2.2.1 Present work

2.2.1.1 Objective

Although several syntheses of (2*S*,3*S*)-3-hydroxypipecolic acid are documented in the literature through varied synthetic routes, most involve a large number of steps and employ a chiral pool strategy. However, still there exists a need to develop a general strategy that provides a common versatile intermediate which can give access to 2,3-disubstituted piperidines with desired stereochemistry. With this in mind, it was envisaged that asymmetric synthesis of an enantiomerically pure 2,6-disubstituted piperidine framework starting from commercially available *cis*-2-butene-1,4-diol should be undertaken.

2.2.1.2 Retrosynthetic analysis

According to the retrosynthetic analysis shown in Scheme 1, the synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid **1** can be achieved from lactam **2**. Lactam **2** could be derived from hydroxy lactone **3** *via* reductive lactamisation. The hydroxy lactone **3** is the versatile intermediate in the synthesis which could be obtained from *cis*-2-butene-1,4-diol **4**.



Scheme 1

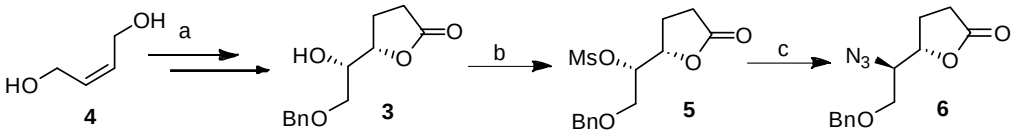
2.2.1.3 Results and discussion

The synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid **1** commenced from achiral *cis*-2-butene-1, 4-diol **4** as shown in Scheme **2.** The commercially available *cis*-2-butene-1,4-diol **4** was converted into enantiomerically pure hydroxy lactone **3** by known literature procedure[1] involving Claisen orthoester rearrangement[2] and Sharpless asymmetric dihydroxylation.[3]

Having the key synthon **3** in hand, the next concern was to convert it into azido lactone **6**. Thus treatment of hydroxy lactone **3** with mesyl chloride and Et_3N in anhydrous CH_2Cl_2 at 0 ^oC provided mesylate **5** in 91% yield. In the ^1H-NMR spectrum, the singlet at δ 3.06 integrating for three protons and a downfield shift of

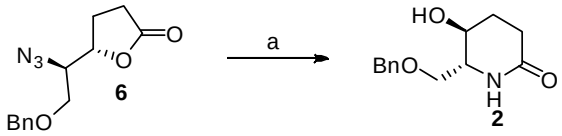
CH-OMs proton from 3.83 to 4.83 indicated the formation of mesylate **5**. All the spectral data were in good agreement with the assigned structure **5**.

Nucleophilic displacement of the mesylate **5** was carried out with NaN_3 in anhydrous DMF at 90 ^oC for 16 h to deliver the azido lactone **6** in 87 % yield. The IR spectrum showed strong absorption bands at 2106 and 1783 cm^{-1}. In the ^1H-NMR spectrum disappearance of singlet at δ 3.06 and an upfield shift of CH-N_3 proton from δ 4.83 to 3.79 was observed. It was further supported by ^{13}C-NMR spectrum, which showed disappearance of corresponding mesyl resonance at δ 38.6. All the spectral data including elemental analysis data were also in good agreement with the assigned structure **6**.



Scheme 2 *Reagents and conditions : (a) Ref. 1 (b) MsCl, Et_3N, DMAP(cat.), DCM, 5 h, 91%; (c) NaN_3, DMF, 90 ^oC, 16 h, 87%.*

Having the azidolactone **6** in hand, the next concern was to convert azidolactone **6** to lactam **2**. Thus Intramolecular lactone ring opening of **6** was achieved by using $Pd(OH)_2$ as catalyst under hydrogen atmosphere at 25 ^oC to deliver the desired six membered lactam **2** in 90% yield (Scheme 3). The IR spectrum of lactam **2** showed the disappearance of lactone absorption at 1783 cm^{-1} and appearance of strong absorptions at 3435 and 1654 $cm.^{-1}$ Its ^1H-NMR spectrum showed the characteristics singlet for amide proton at δ 6.54 integrating for one proton indicating the formation of lactam **2**. ^{13}C NMR spectrum showed signal at δ 172.1 corresponding to lactam carbonyl carbon (-NHCO-).



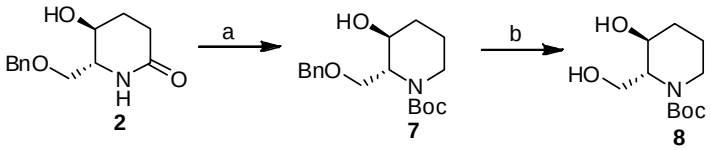
Scheme 3 *Reagents and conditions: (a) $Pd/(OH)_2$, H_2, MeOH, 30 psi, rt, 3 h, 90%.*

Additionally, DEPT NMR spectrum showed the disappearance of signals at δ 63.0 and δ 77.6 and appearnce of new signals at δ 57.89 and δ 71.47 indicating formation

of lactam **2**. Its mass spectrum showed molecular ion peak at *m/z* 236.3 $(M+H)^+$ which confirmed the formation of **2**.

Reduction of lactam **2** was carried out by using LAH in anhydrous THF at 0 ^oC to afford amine which without purification was treated with Boc anhydride, triethyl amine as base and DMAP (cat.) to furnish carbamate **7** in 63% yield (over two steps) (Scheme 4). Strong bands in its IR spectrum at 3435 and 1672 cm^{-1} indicated the presence of the free hydroxy and carbamate functionalities. Its ^{1}H-NMR spectrum showed a peak at δ 1.46 integrating for nine protons corresponding to Boc group. Its DEPT NMR spectrum showed presence of five CH and five CH_2 carbons which provided the strong support for the formation of structure **7**. Its mass spectrum showed molecular ion peak at *m/z* 322.3 $(M+H)^+$ which confirmed the formation of **7**.

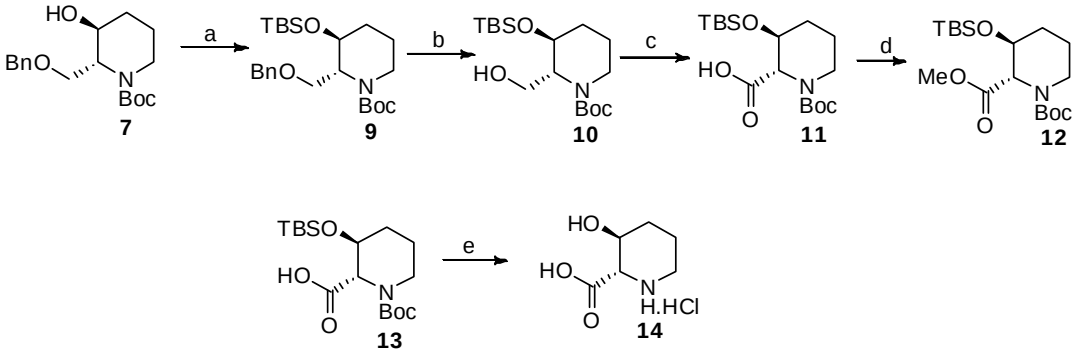
In order to check the chiral purity at C-2 and C-3 of the urethane **7**, it was subjected to hydrogenation using Pd/C as a catalyst in methanol at 25 ^oC to provide diol **8** in 93% yield. The chiral HPLC analysis[4] of the **8** revealed that the chiral purity of **8** is >99% (See HPLC in Spectral section). Relative stereochemistry of hydroxy and hydroxymethyl and structure was confirmed by single crystal X-ray analysis (shown in Spectral section).



Scheme 4 *Reagents and conditions: a) i) LAH, THF, 0 ^oC to rt, 3 h; ii) Boc anhydride, Et_3N, DMAP(cat.), THF, 0 ^oC to rt, 3 h, 63% (over two steps); b) Pd/C, H_2, MeOH, 70 psi, rt, 3 h, 93%.*

For the total synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid, free hydroxy of **7** was protected as its TBS ether. Thus protection was carried out using TBSCl, imidazole and DMAP (cat.) in DCM at room temperature for 24 h to afford TBS ether derivative **9** in 90% yield (Scheme 5). Its IR spectrum showed disappearance of peaks at 3435 cm^{-1}. In the ^{1}H-NMR spectrum appearance of the characteristics peaks at δ 0.06 and 0.09 each integrating for three protons and a peak at δ 0.9 intigrating for nine protons corresponding to protons of TBS group were observed. The ^{13}C NMR spectrum showed the signals at δ -5.0, -4.91, 18.0 and 18.9 corresponding to TBS carbons. Its mass spectrum showed molecular ion peak at *m/z* 346 $(M+H)^+$ and 368 $(M+Na)^+$ which confirmed the formation of **9**.

TBS-ether derivative **9** was subjected under hydrogen atmosphere using Pd/C as a catalyst in methanol to provide alcohol **10** (Scheme 5). In its IR spectrum strong absorption at 3435 cm^{-1} indicated the presence of hydroxy functionality. The ^{1}H-NMR spectrum displayed the disappearance of five protons at δ 7.33 supporting debenzylation and formation of the structure **10**. Its ^{13}C NMR spectrum exhibiting disappearance of three aromatic CH and presence of one quaternary carbon confirmed the structure **10**. All the spectral data including elemental analysis data were also in good agreement with the assigned structure **10.**



Scheme 5 *Reagents and conditions: a) TBSCl, imidazole, DMAP (cat.), DMF, rt, 90%; b) Pd/C, H_2, 70 psi, rt, 3 h, 95%; c) $RuCl_3$, $NaIO_4$, CH_3CN:CCl_4:H_2O (1:1:3), rt, 30 min, 58%; d) NMU, KOH, diethyl ether: H_2O, 3 h; e) 6N HCl, reflux, 2 h.*

Hydroxy compound **10** was treated with $RuCl_3$ as catalyst in presence of $NaIO_4$ as oxidant in MeCN: CCl_4: H_2O to give acid **11**. For characterization purpose the acid functionality of **11** was converted to its methyl ester **12** using NMU (*N*-nitroso-*N*-methyl urea) and KOH in diethyl ether. Its ^{1}H-NMR spectrum showed a characteristic peak at δ 3.73 integrating for three protons corresponding to methyl ester (–CO-O<u>CH$_3$</u>). The ^{13}C NMR spectrum showed signal at δ 170.5 corresponding to ester carbonyl carbon.

The carbamate and TBS deprotection of **13** was carried out using 6N HCl under reflux condition to provide **1**. Its ^{1}H-NMR spectrum revealed a multiplet at δ 4.13-4.17 and doublet at δ 3.83 which were attributed to –CH- protons. Other peaks included multiplets at δ 3.36-3.40, 3.07-3.12 and 1.64-1.80 and singlet at δ 2.22. Peak at δ 170.1 in its ^{13}C-NMR spectrum was attributed to the acid carbonyl carbon and the peaks at δ 65.5 and 61.0 were due to the tertiary carbons. The three carbons

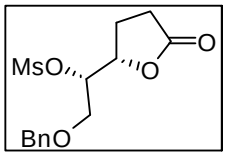
resonating at δ 42.5, 28.8 and 18.6 all corresponded to the CH_2 carbons. Its DEPT NMR spectrum displayed two carbons corresponding to -CH- carbons and three carbons due to the –CH_2- carbons. Spectroscopic data and optical rotation of **1** was in good agreement with the values reported in the literature.[5]

2.2.2 Conclusion

In conclusion, the total synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid has been accomplished starting from *cis*-butene-1,4-diol employing Sharpless asymmetric dihydroxylation and reductive lactamisation as the key steps.

2.2.3 Experimental Section

(*S*)-2-(Benzyloxy)-1-((*S*)-5-oxotetrahydrofuran-2-yl)ethyl methanesulfonate (5)



To a stirred a solution of hydroxy lactone **3** (1.5 g, 6.35 mmol) in dry DCM (20 ml) was added Et_3N (1.33 ml, 9.53 mmol) at 0 ^oC, followed by dropwise addition of mesyl chloride (0.57 ml, 6.99 mmol) and finally DMAP (cat.) was added. The reaction mixture was stirred at 0 ^oC for 6 h under nitrogen atmosphere, the reaction mixture was diluted with DCM (50 mL) and washed with saturated solution of sodium bicarbonate (20 ml) and water. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography in 40% ethyl acetate in pet ether to give *O*-mesyl compound **5** (1.8 g, 91 %);

Chemical Formula: $C_{14}H_{18}O_6S$;

Yield : 91% ;

$[\alpha]_D^{25}$: +9.02 (c 1, $CHCl_3$); lit.[1] for comp-**5 $[\alpha]_D^{24}$** +8.31 (c 1, $CHCl_3$);

IR ($CHCl_3$, cm^{-1}) : 1781, 1608, 1174;

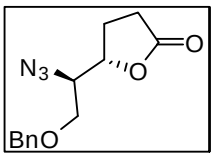
ESIMS (*m/z*) : 337.05 $(M+Na)^+$;

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 2.26 (m, 1H), 2.36 (m, 1H), 2.46 (ddd, *J* = 16.95, 10.08, 6.41 Hz, 1H), 2.67 (ddd, *J* = 16.95, 9.62, 6.41 Hz, 1H), 3.06 (s, 3H), 3.71 (dd, *J* = 10.57,3.67 Hz, 1H), 3.83 (dd, *J* = 10.54, 7.34 Hz, 1H), 4.65 (m, 2H), 4.68 (ddd, *J* = 8.25, 5.54, 3.27 Hz, 1H), 4.80 (m, 1H), 7.32 (m, 5H);

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 23.6, 27.3, 38.6, 68.5, 73.4, 77.5, 81.7, 127.7, 127.9, 128.4, 136.9, 176.0;

Elemental analysis for $C_{14}H_{18}O_6S$: C, 53.49; H, 5.77; S, 10.20. found: C, 53.40; H, 5.70; S, 10.19.

(*S*)-5-((*R*)-1-Azido-2-(benzyloxy)ethyl)dihydrofuran-2(3*H*)-one (6)



To a solution of *O*-mesyl compound **5** (1.8 g, 5.73 mmol) in anhydrous DMF (15 mL) was added sodium azide (0.74 g, 11.46 mmol) and the reaction mixture was stirred at 90 ^oC for 16 h under nitrogen atmosphere. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, diluted with water (60

mL) and extracted with ethyl acetate (3 X 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography using ethyl acetate/light petroleum ether (2:8) as an eluent to afford azido lactone **6** (1.32 g, 87 %) as colorless oil.

Chemical Formula: $C_{13}H_{15}N_3O_3$

Yield: 87 %;

$[\alpha]_D^{25}$: -16.61 (c 1, $CHCl_3$); lit.[1]for comp-**6 $[\alpha]_D^{24}$** -15.83 (c 1, $CHCl_3$);

IR ($CHCl_3$, cm^{-1}) : 2106, 1783, 1250, 1110;

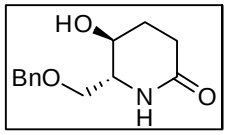
ESIMS (*m/z*) : 284.3 $(M+Na)^+$;

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 2.12 (m, 1H), 2.23 (m, 1H), 2.44-2.59 (m, 2H),3.62 (dd, *J* = 10.08, 6.41 Hz, 1H), 3.66 (dd, *J* = 10.08, 4.58 Hz, 1H), 3.79 (q, *J* = 5.82 Hz, 1H), 4.55 (m, 3H), 7.32 (m, 5H);

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 23.1, 27.6, 63.0, 68.9, 73.1, 77.6, 127.3, 127.6, 128.2, 137.1, 175.2;

Elemental analysis for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. found: C, 59.66; H, 5.84; N, 16.19.

(5*S*, 6*R*)-6-((Benzyloxy)methyl)-5-hydroxypiperidin-2-one (2)



A mixture of azido lactone **7** (1.6 g, 6.12 mmol) and 10 % Pd/C in methanol (10 mL) was stirred under hydrogen atmosphere at 30 *psi* at room temperature (25 ^oC) for 3 h. The reaction mixture was filtered through celite and the celite layer was washed thoroughly with methanol and concentrated under reduced pressure. The residue thus obtained was purified by flash silica gel chromatography using ethyl acetate: methanol (9:1) as an eluent to furnish lactam **2** (1.3 g, 90 %) as colorless syrup.

Chemical Formula: $C_{13}H_{17}NO_3$;

Yield : 90 %;

$[\alpha]_D^{25}$: +30.34 (c 1.45, MeOH); lit.[6] for *ent*-**2 $[\alpha]_D^{25}$** : -21.4 (*c* 0.9, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) : 3435, 1672;

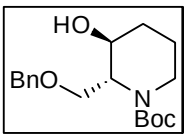
ESIMS (m/z) : 236.3 $(M+H)^+$;

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 1.70-2.05 (m, 2H), 2.17-2.56 (m, 2H), 3.38-3.54 (m, 2H), 3.64-3.84 (m, 2H), 4.52 (s, 2H), 6.54 (bs, 1H), 7.33 (s, 5H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.39, 28.0, 57.89, 65.33, 71.47, 73.15, 127.49, 127.68, 128.25, 172.11;

Elemental analysis for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. found: C, 66.30; H, 7.32, N, 5.90.

(2*R*, 3*S*)-*tert*-Butyl-2-((benzyloxy)methyl)-3-hydroxypiperidine-1-carboxylate (7)



To a stirred a solution of LAH (0.629 g, 16.5 mmol) in anhydrous THF (30 mL) at 0 ^oC was added lactam **2** (1.3 g, 5.53 mmol) in anhydrous THF (10 mL). The reaction mixture was stirred at 0 ^oC for 30 min. and allowed to attain room temperature and stirred for additional 4 h. After completion of reaction (monitored by TLC), the reaction mixture was cooled to 0 ^oC and quenched by dropwise addition of saturated sodium hydroxide solution (1 M, 30 mL) and the residue was filtered through celite and celite layer was washed thoroughly with methanol (3 X 30 mL). The organic layer was concentrated under reduced pressure to provide crude amine which without purification was subjected for next reaction. To a crude mixture of amino alcohol **13** (0.8 g, 3.61 mmol) in THF (30 mL) was added triethyl amine (0.75 mL, 5.42 mmol) followed by dropwise addition of $(Boc)_2O$ (0.75 mL, 4.34 mmol) at 0 ^oC. After stirring for 3 h at room temperature, the reaction mixture was extracted with ethyl acetate (3 x 50 mL), the organic layer was washed with water (50 mL) followed by brine and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography using petroleum ether/ethyl acetate (7:3) as an eluent to afford colorless oily carbamate **7** (1.1 g, 63% over two steps).

Chemical Formula: $C_{18}H_{27}NO_4$;

Yield : 63%;

$[\alpha]_D^{25}$: -28 (c 1.0, $CHCl_3$); lit.[7] for comp-**7** **$[\alpha]_D^{23}$** –33.8 (*c* = 0.40, $CHCl_3$);

IR ($CHCl_3$, cm^{-1}) : 3432, 1694;

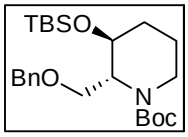
ESIMS (*m/z*) : 322.05 $(M+H)^+$;

HRMS calculated for $[C_{18}H_{27}NO_4 + H]^+$ 322.2013; found: 322.2008;

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 1.27-1.31 (m, 1H), 1.37 (s, 9H), 1.50-1.80 (m, 3H), 2.70 (m, *J* = 12.06 Hz, 1H), 3.47 (d, *J* = 7.07 Hz, 2H), 3.81-4.00 (m, 2H), 4.25-4.40 (m, 1H), 4.45 (s, 2H), 7.24 (s, 5H);

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 18.78, 26.42, 28.32, 39.63, 56.41, 64.75, 67.77, 72.75, 79.49, 127.40, 128.22, 137.94, 155.78;

(2*R*,3*S*)-*tert*-Butyl-2-((benzyloxy)methyl)-3-((*tert*-butyldimethylsilyl)oxy)piperidine-1-carboxylate (9)



To a solution of hydroxy carbamate **7** (1.8 g, 5.60 mmol) in anhydrous DMF (20 ml) or DCM (40 mL) was added imidazole (0.572 g, 8.40 mmol), TBS-Cl (1.27 g, 8.40 mmol) and DMAP (cat.) at 0 ^{o}C. The reaction mixture was allowed to stir at room temperature for 24 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (3 X 40 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by using flash silica gel column chromatography using ethyl acetate/light petroleum (1:9) as an eluent to afford TBS derivative **9** (2.2 g, 90 %) as colorless liquid.

Chemical Formula: $C_{24}H_{41}NO_4Si$;

Yield : 90%;

$[\alpha]_D^{25}$: -15 (c 0.45, $CHCl_3$); lit.[7] for comp-**9** **$[\alpha]_D^{23}$** –14.0 (*c* = 0.90, $CHCl_3$);

IR ($CHCl_3$, cm^{-1}) : 3435, 2930, 1691.

ESIMS (*m/z*) : 435 $(M+H)^+$, 458 $(M+Na)^+$;

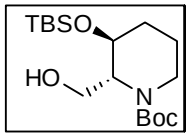
HRMS calculated for $[C_{24}H_{41}NO_4Si +H]^+$ 436.2878; found: 436.2886;

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 0.06 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.23-1.34 (m,1H), 1.45 (s, 9H), 1.52-1.61 (m, 2H), 1.80-1.91 (m, 1H), 2.70 (m, 1H), 3.44-3.60 (m, 2H), 3.95-4.13 (m, 2H), 4.26-4.41 (m, 1H), 4.54 (s, 2H), 7.33 (s, 5H);

^{13}C (50 MHz, $CDCl_3$): δ -4.91, 18.10, 18.99, 25.84, 27.53, 28.47, 39.67, 56.73, 65.21, 67.96, 72.78, 79.08, 127.39, 128.35, 138.21, 155.30;

Elemental analysis for $C_{24}H_{41}NO_4Si$: C, 66.16; H, 9.49; N, 3.21. found: C, 66.01; H, 9.22, N, 3.02.

(2*R*,3*S*)-*tert*-Butyl 3-((*tert*-butyldimethylsilyl)oxy)-2-(hydroxymethyl)piperidine-1-carboxylate (10)



A mixture of urethane **9** (2 g, 4.59 mmol) and 10% $Pd(OH)_2$/C in methanol was stirred under hydrogen atmosphere at 70 *psi* at room temperature (25 ^{o}C) for 6 h. The reaction mixture was filtered

through celite bed, bed was washed thoroughly with methanol (3 X 40 mL) and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography using ethyl acetate/pet ether (2:8) as an eluent to furnish colorless alcohol **10** (1.5 g, 95 %).

Chemical Formula : **$C_{17}H_{35}NO_4Si$;**

Yield : 95%;

$[\alpha]_D^{25}$: -17 (c 0.75, $CHCl_3$); lit.[7] for comp- **10 $[\alpha]_D^{23}$** –16.0 (*c* = 0.74, $CHCl_3$);

IR ($CHCl_3$, cm^{-1}) : 3435, 1669;

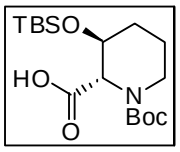
ESIMS (*m/z*) : 346 $(M+H)^+$, 368 $(M+Na)^+$;

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 0.05 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.27-1.38 (m, 1H), 1.46 (s, 9H), 1.56-1.65 (m, 2H), 1.81-1.99 (m, 1H), 2.84 (t, *J* = 12.3 Hz, 1H), 3.6-3.63 (m, 1H), 3.68-3 .71 (m, 1H), 3.85-4.01 (m, 2H), 4.12-4.17 (m, 1H);

^{13}C (125 MHz, $CDCl_3$ + CCl_4): δ -4.93, -4.84, 18.05, 19.26, 25.80, 28.12, 28.46, 39.70, 59.82, 60.48, 65.14, 79.48, 156.07;

Elemental analysis for $C_{17}H_{35}NO_4Si$: C, 59.09; H, 10.21; N, 4.05. Found: C, 59.20; H, 10.02, N, 4.10.

(2*S*,3*S*)-1-(*tert*-Butoxycarbonyl)-3-((tert-butyldimethylsilyl)oxy)piperidine-2-carboxylic acid (11)

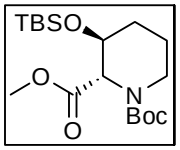


To a suspension of $NaIO_4$ (1.18 g, 5.50 mmol) in $CH_3CN/CCl_4/H_2O$ (16 mL; 3:3:10) was added $RuCl_3.H_2O$ (42 mg) in small portions, and the reaction mixture was stirred at room temperature for 30 min. and the resulting yellowish suspension was added to alcohol **10** (1 g, 2.89 mmol) dissolved in acetonitrile (3 mL), followed by the addition of second portion of $NaIO_4$ (0.619 g, 2.89 mmol). The resulting reaction mass was stirred at room temperature for 30 min and filtered through celite and the celite bed was washed with ethyl acetate (2 X 30 mL), the combined filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude residue was purified by flash chromatography ($MeOH/CHCl_3$) 5:95 to 20:80 to furnish acid (0.6 g, 58%) as brownish colored syrup. $[\alpha]^{25}_D$ = -76 (c 1.0, MeOH); *m/z* = 382.65 $(M+Na)^+$.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): 0.07 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 1.44 (s, 9H), 1.53 (m, 1H), 1.65-2.04 (m, 3H), 2.89 (bs, 1H), 4.04 (bs, 1H), 4.4 (bs, 1H), 4.64-4.84 (m, 1H).

For characterization purpose, the acid functionality was converted to ester derivative.

(2*S*,3*S*)-1-*tert*-Butyl 2-methyl 3-((*tert*-butyldimethylsilyl)oxy)piperidine-1,2-dicarboxylate (12)



To the solution of KOH (0.39 g, 6.95 mmol) in diethyl ether:H_2O (8:2, 50 mL) was added NMU (0.716 g, 6.95 mmol) portion wise at 0 ^oC. The reaction was allowed to stir for 10 min. and the yellow colored organic layer was separated by separating funnel and was added to the resulting acid solution (0.5 g, 1.39 mmol) in diethyl ether (20 mL) at 0 ^oC. The reaction mixture was stirred for 3 h at room temperature. After completion of reaction, the organic layer was washed with water (30 mL) and brine (30 mL). The separated organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography using ethyl acetate: pet ether (1:9) as an eluent to afford ester **12** (0.415 g, 80%) as faint yellow syrup.

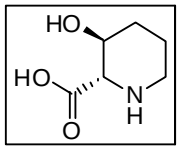
Chemical Formula: **$C_{18}H_{35}NO_5Si$;**

Yield : 80%;

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): 0.07 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 1.25-1.32 (m, 1H), 1.43 (s, 9H), 1.55-2.13 (m, 3H), 2.89 (bs, 1H), 3.73 (s, 3H), 3.99 (bs, 1H), 4.34 (bs, 1H), 4.74 (bs, 1H);

^{13}C (50 MHz, $CDCl_3$ + CCl_4): -5.11, -4.97, 18.0, 18.3, 25.7, 28.3, 28.7, 40.7, 41.4, 51.9, 60.2, 61.2, 65.9, 79.6, 155.4, 170.5.

(2S,3S)-3-hydroxypiperidine-2-carboxylic acid (1)



The solution of acid **11** (100 mg) in 6N HCl (6 ml) was refluxed for 2 h. The reaction mixture was cooled to room temperature and extracted once with CH_2Cl_2 (20 ml) to remove any organic impurities. The aq. mixture was loaded on an ion-exchange column (DOWEX 50W X8) and eluted with H_2O and then with aq. NH_3 solution. The eluent of aq. NH_3 was concentrated to dryness under reduced pressure to give **1** (46 mg, 91%) as a crystalline solid.

Molecular formula: $C_6H_{11}NO_3$;

Yield : 91%;

M.P. : 238-243 ºC (dec), lit.[8] 230-238 °C;

$[\alpha]_D^{25}$: +13.8 º (c 1.0, HCl 10% aq.); lit. +13º (*c* 0.49, HCl 10% aq.)[5c];

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

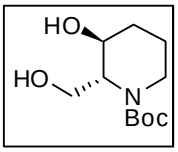
ESIMS (m/z) : 146 $(M+H)^+$;

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

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

Elemental analysis Calculated C, 49.65; H, 7.64; N, 9.65% ; Found C, 49.45; H, 7.80; N, 9.64%.

(2*R*,3*S*)-*tert*-Butyl 3-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate (8)



Carbamate **7** (0.200 g, 0.62 mmol) in methanol (10 mL) was subjected to hydrogen atmosphere in presence of 10 % $Pd/(OH)_2$ at room temperature (25 ^oC) at 70 *psi* for 3 h. The reaction mixture was filtered through celite. Celite was washed thoroughly with methanol and concentrated under reduced pressure. The residue thus obtained was purified by flash silica gel chromatography using ethyl acetate-light petroleum (1:1) as an eluent to furnish diol **8** (0.133 g, 93 %) as a colorless solid.

Chemical Formula : $C_{11}H_{21}NO_4$;

M.P : 133-135 ^oC;

$[\alpha]^{25}_D$: -27.58 (c 1.0, MeOH);

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

GCMS (m/z) **:** 231;

IR ($CHCl_3$, cm^{-1}): 3435, 1666;

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

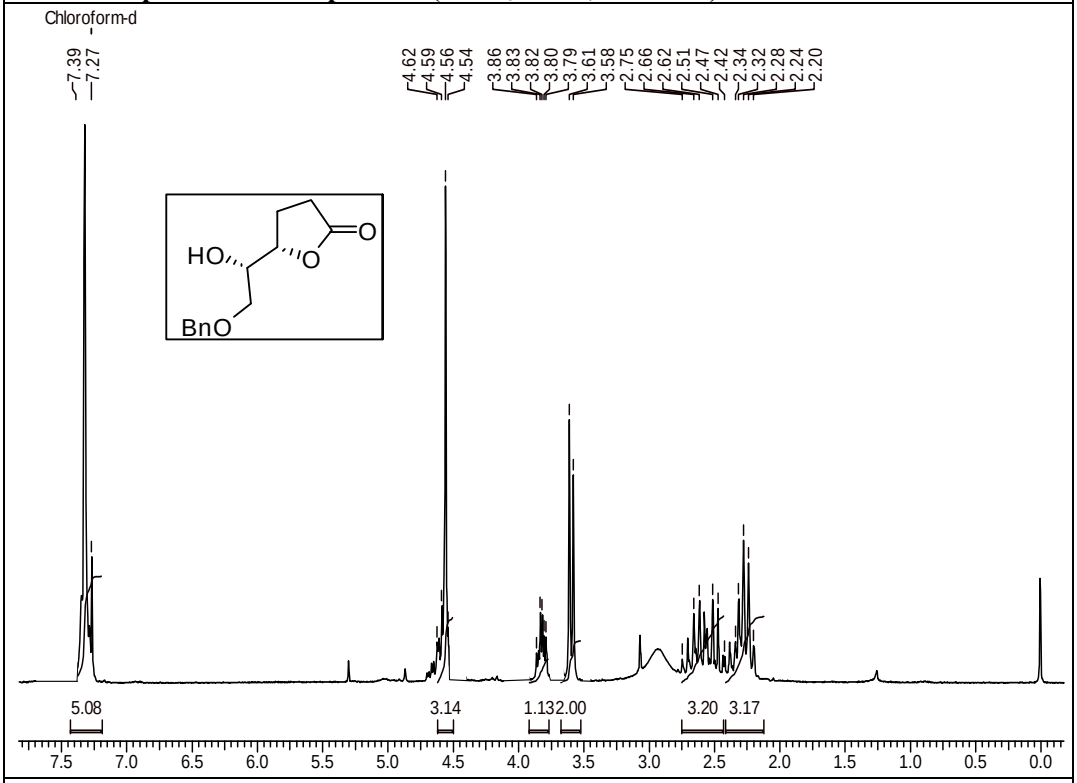
^{13}C NMR (125 MHz, C_2D_6SO+ $CDCl_3$+ CCl_4): δ 18.95, 26.57, 28.15, 39.79, 59.13, 59.91, 63.83, 79.12, 155.92;

Elemental analysis for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06; found: C, 57.10; H, 9.05, N, 6.03.;

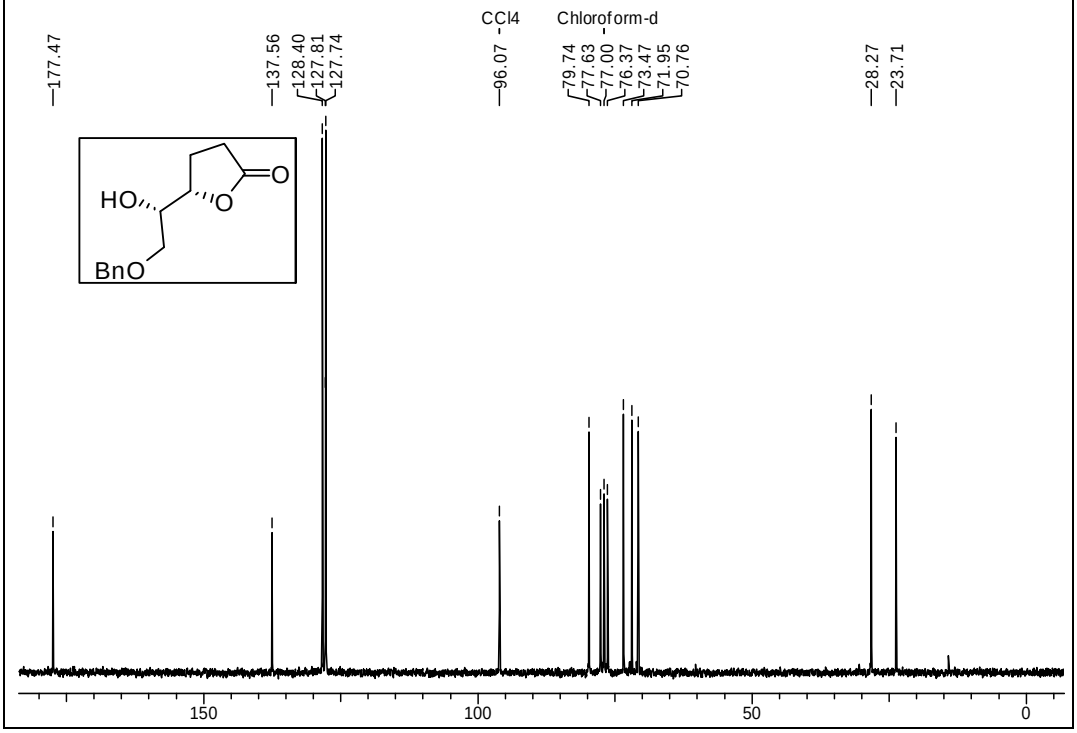
XRD Single crystal X-ray crystallography confirmed that the relative stereochemistry of hydroxy and hydroxymethyl groups and showed that both were *trans* to each other.

2.2.4 Spectra

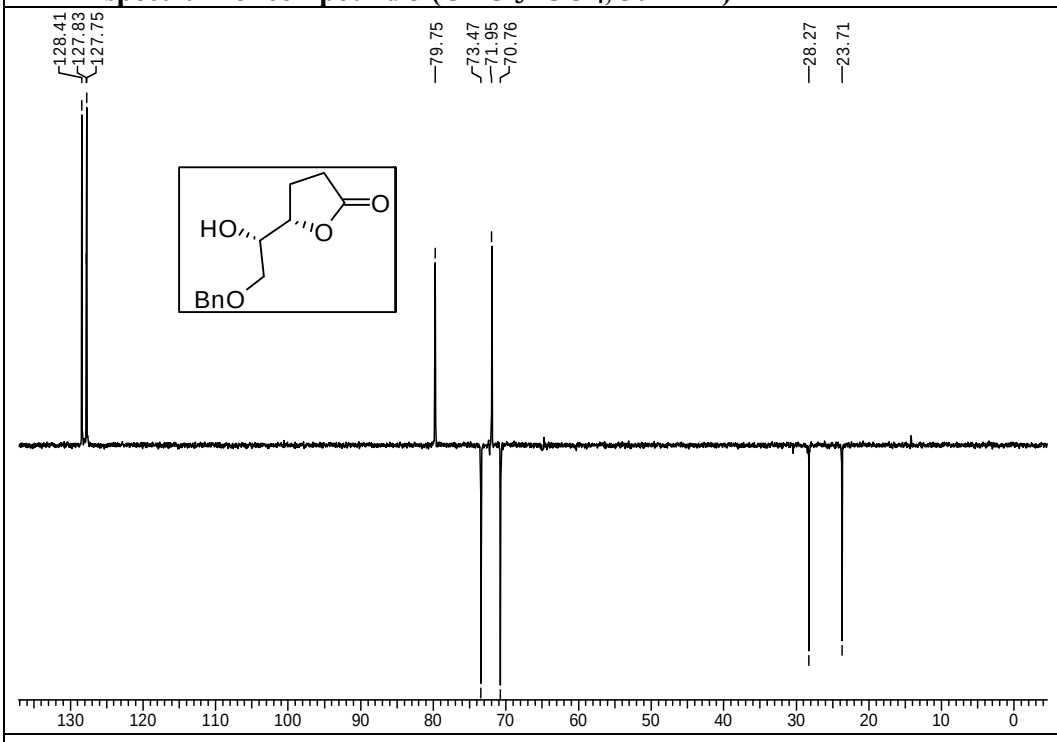
^{1}H NMR Spectrum of compound 3 ($CDCl_3$+CCl_4, 200 MHz)



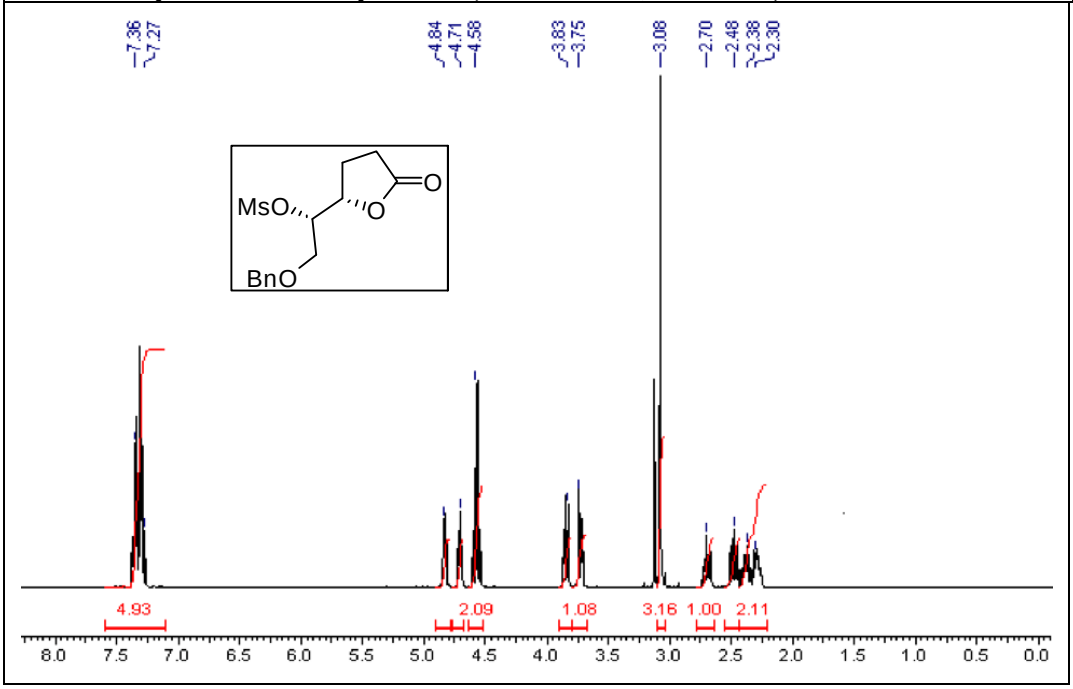
^{13}C NMR Spectrum of compound 3 ($CDCl_3$+CCl_4, 50 MHz)



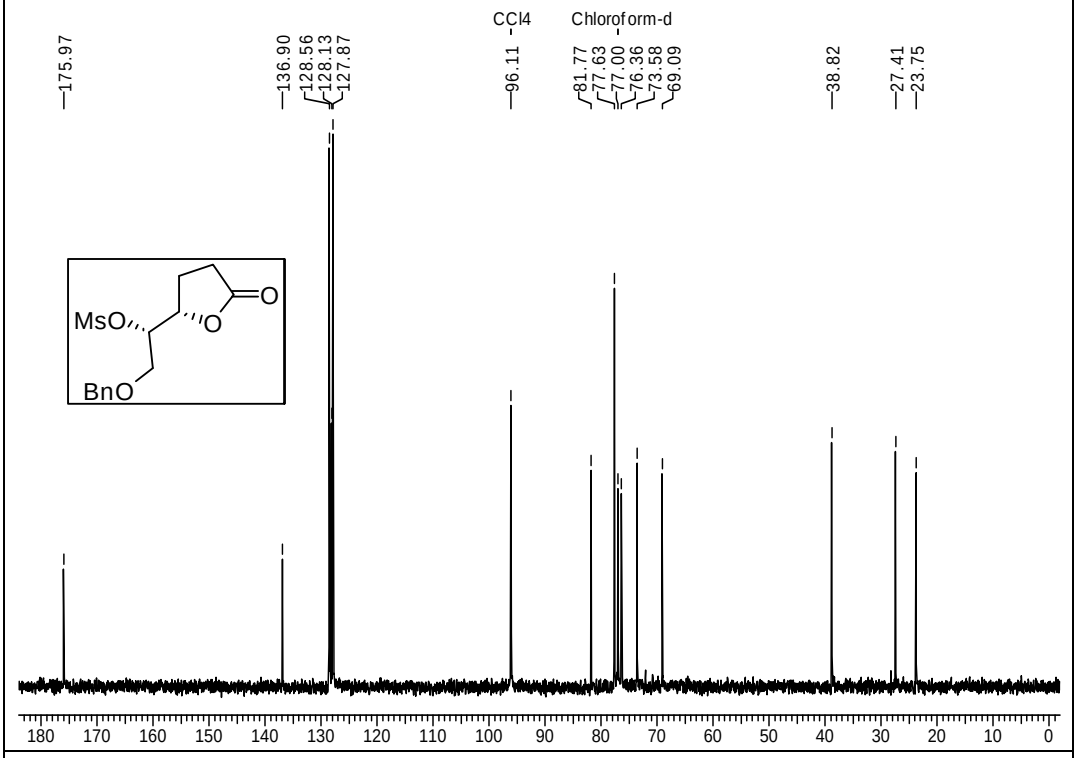
DEPT spectrum of compound 3 ($CDCl_3$+CCl_4, 50 MHz)



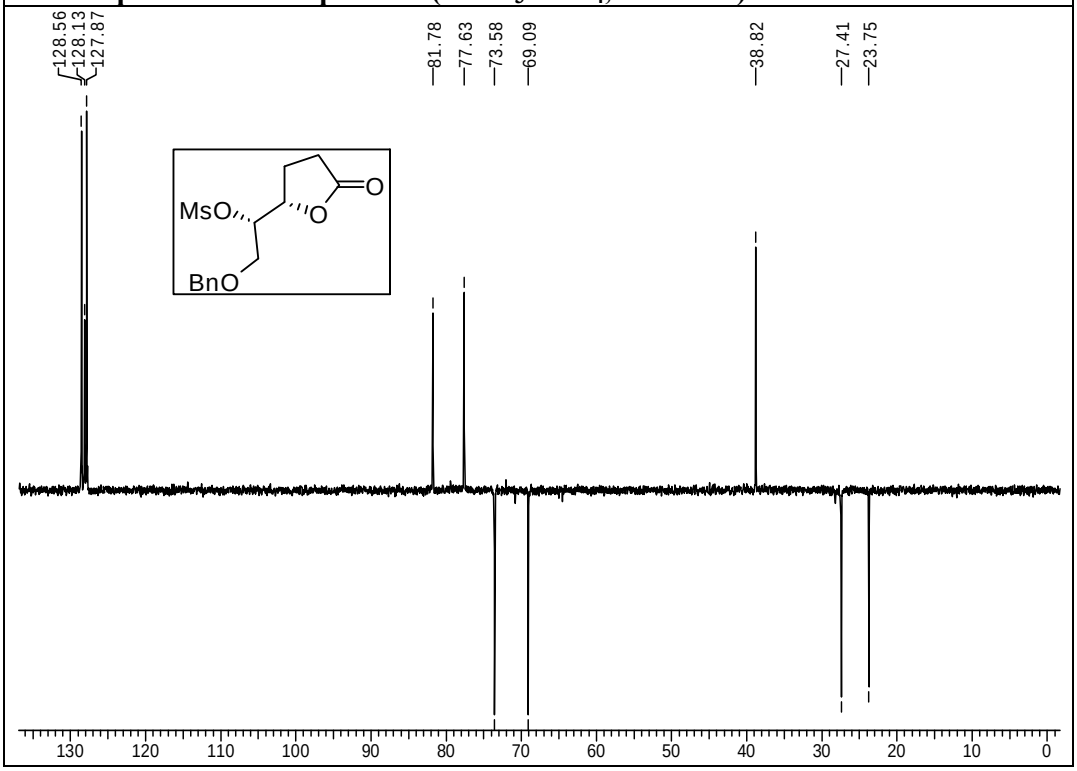
^{1}H NMR Spectrum of compound 5 ($CDCl_3$+CCl_4, 500 MHz)



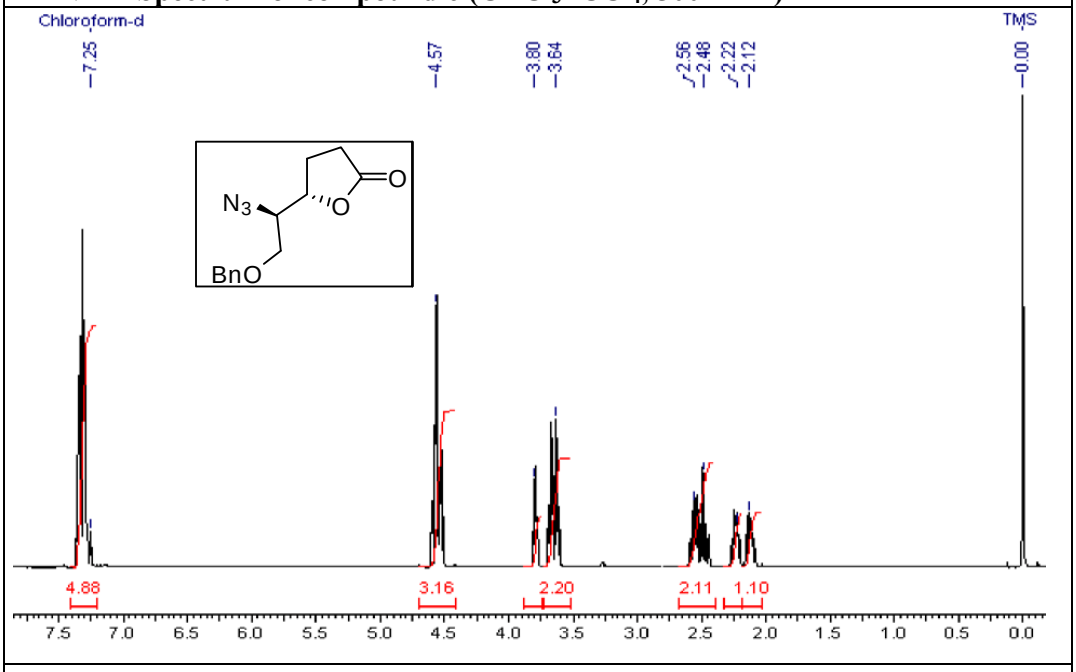
^{13}C NMR Spectrum of compound 5 ($CDCl_3$+CCl_4, 125 MHz)



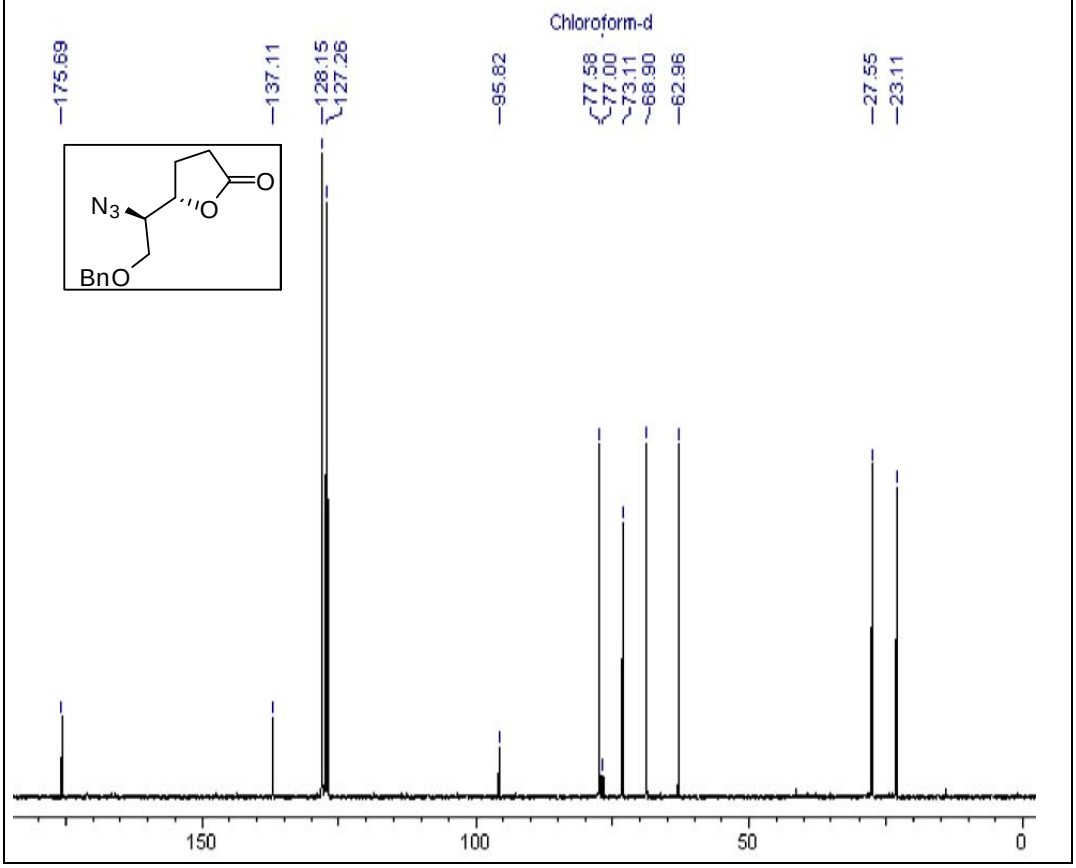
DEPT spectrum of compound 5 ($CDCl_3$+CCl_4, 125 MHz)



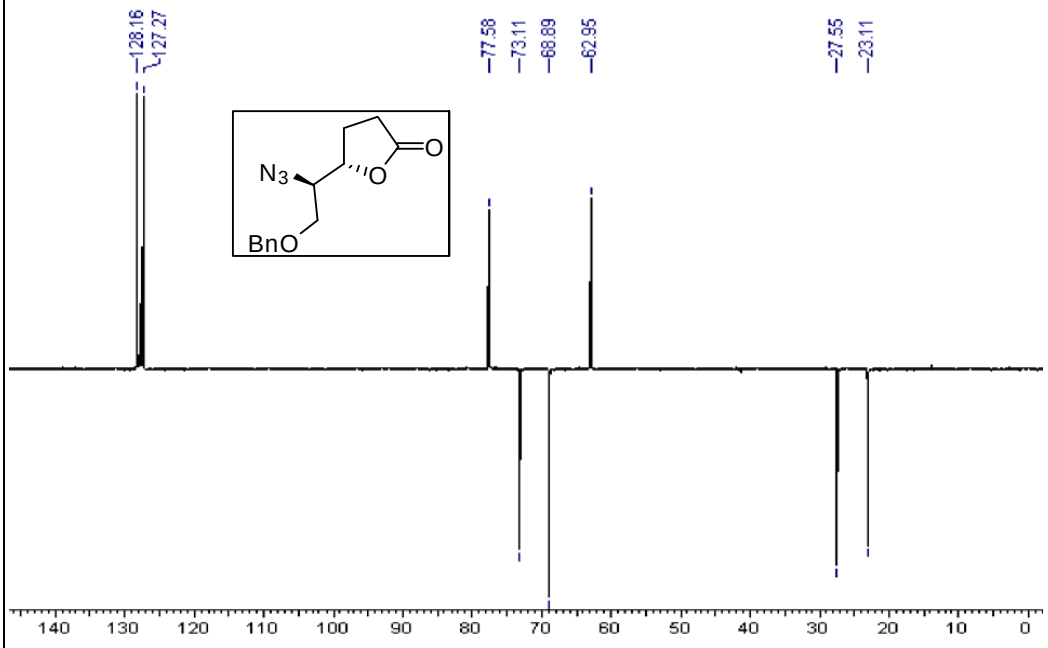
^{1}H NMR Spectrum of compound 6 ($CDCl_3$+CCl_4, 500 MHz)



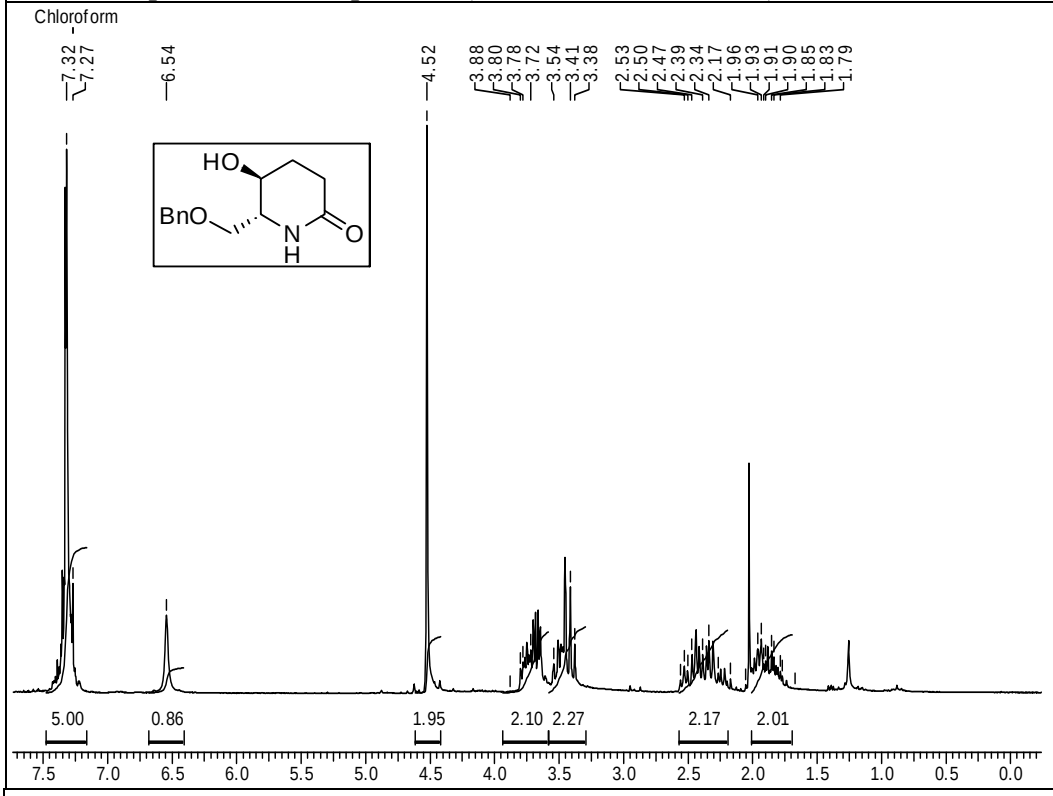
^{13}C NMR Spectrum of compound 6 ($CDCl_3$+CCl_4, 125 MHz)



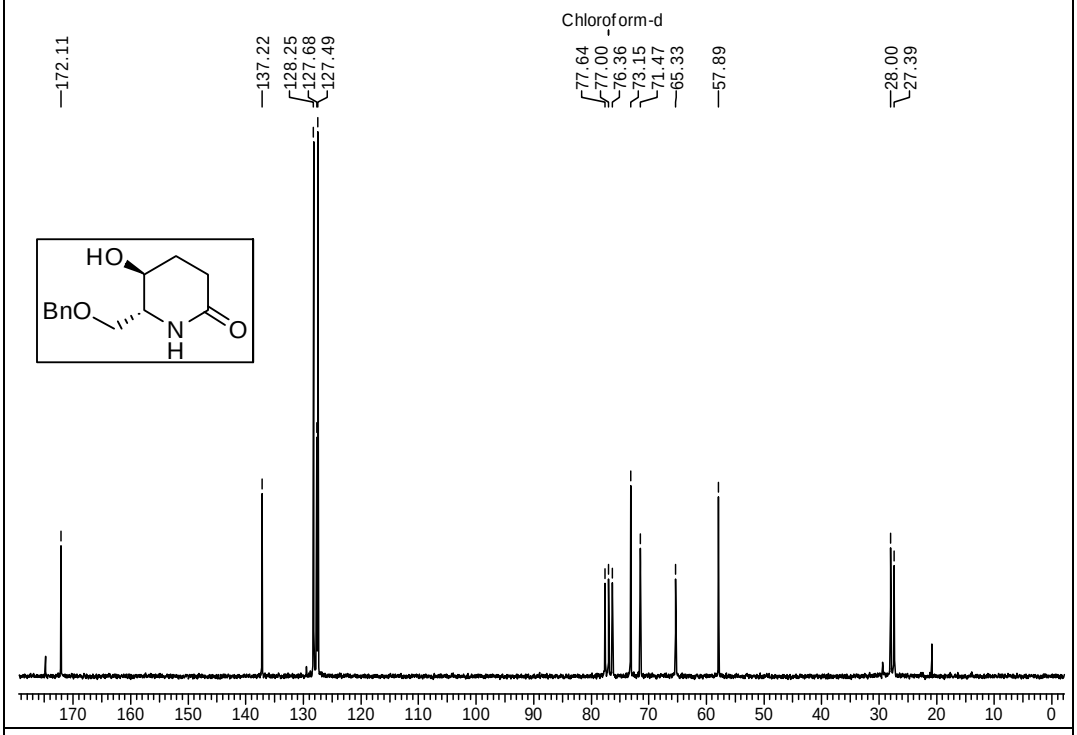
DEPT spectrum of compound 6 ($CDCl_3$+CCl_4, 125 MHz)



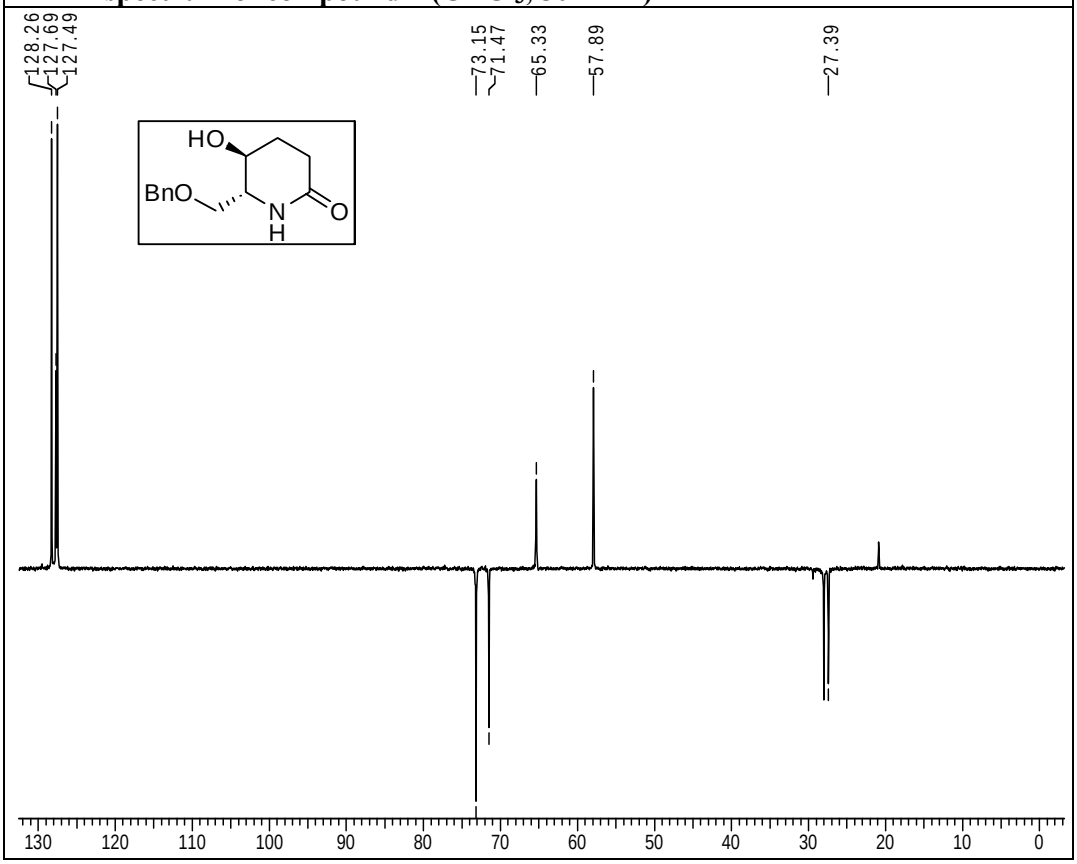
^{1}H NMR Spectrum of compound 2 ($CDCl_3$+CCl_4, 200 MHz)



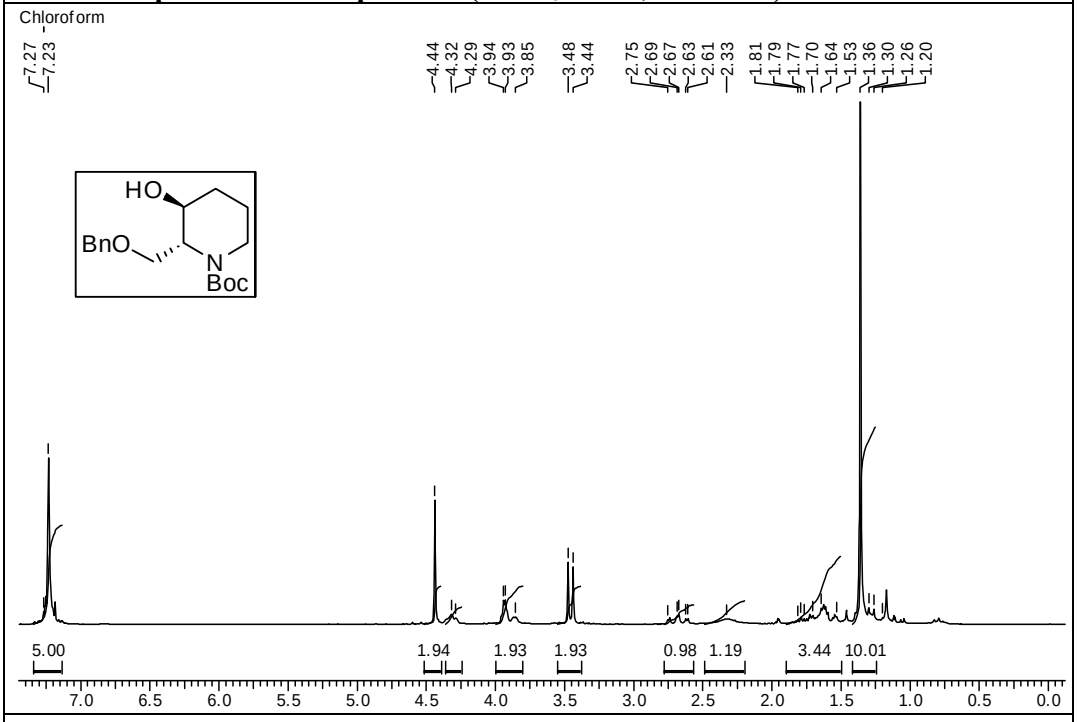
^{13}C NMR Spectrum of compound 2 ($CDCl_3$, 50 MHz)



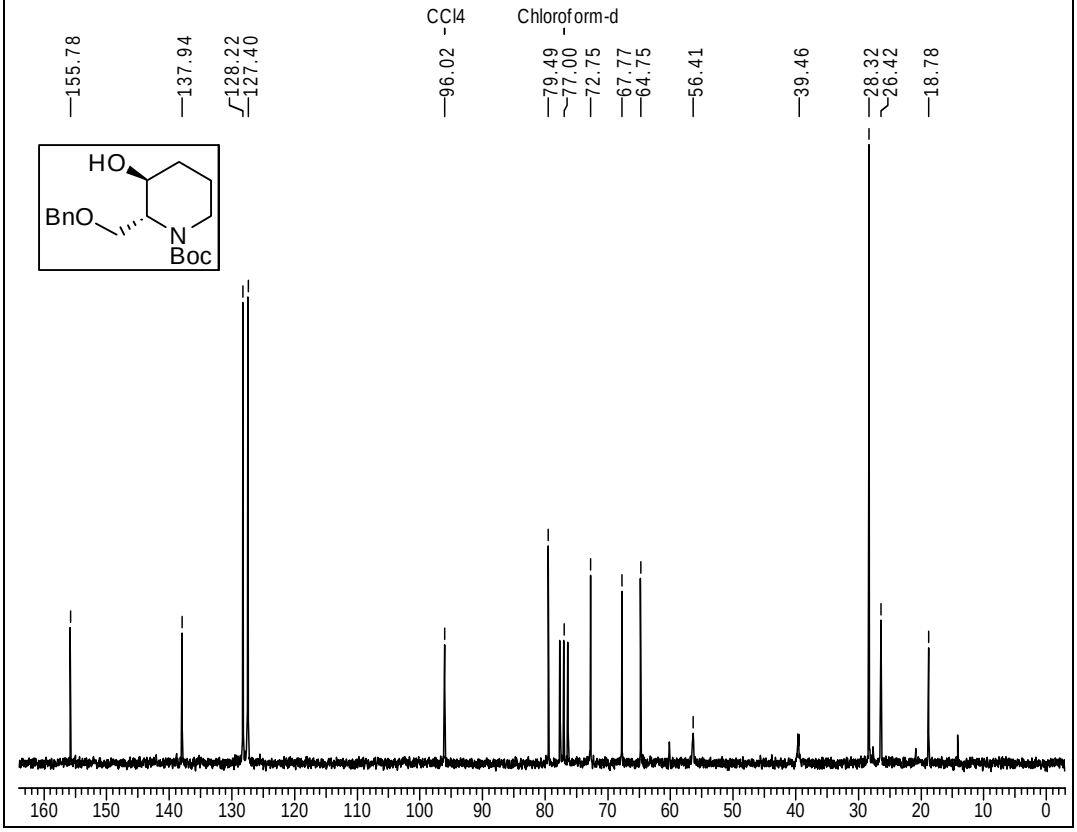
DEPT spectrum of compound 2 ($CDCl_3$, 50 MHz)



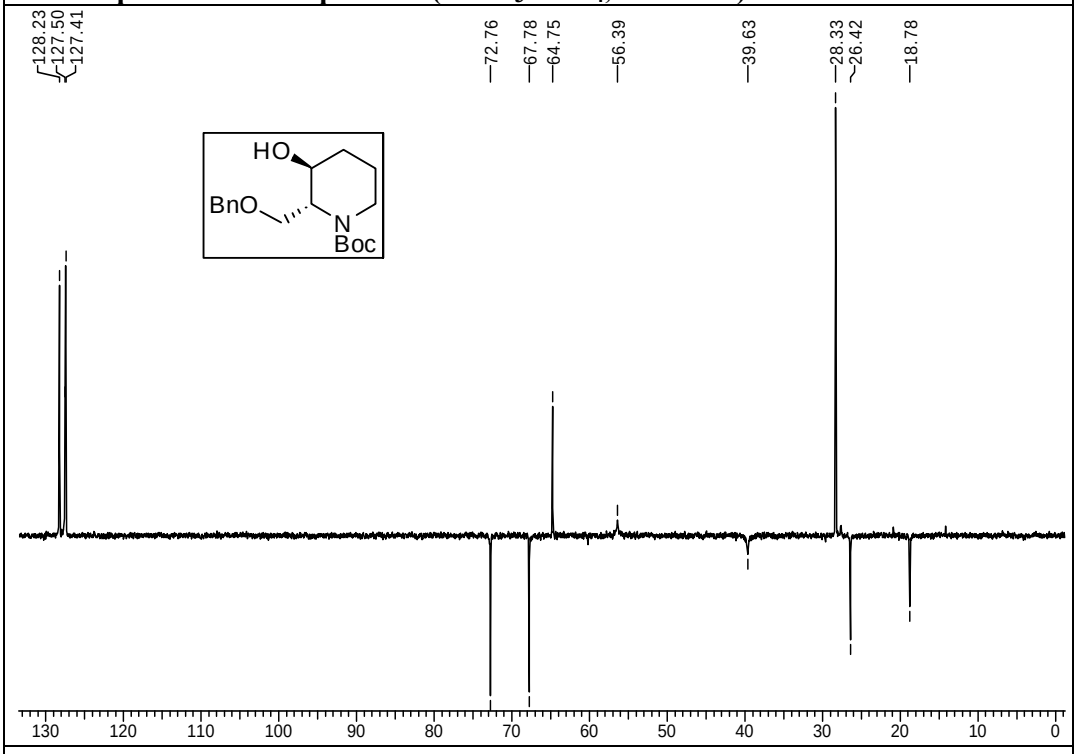
^{1}H NMR Spectrum of compound 7 ($CDCl_3$+CCl_4, 200 MHz)



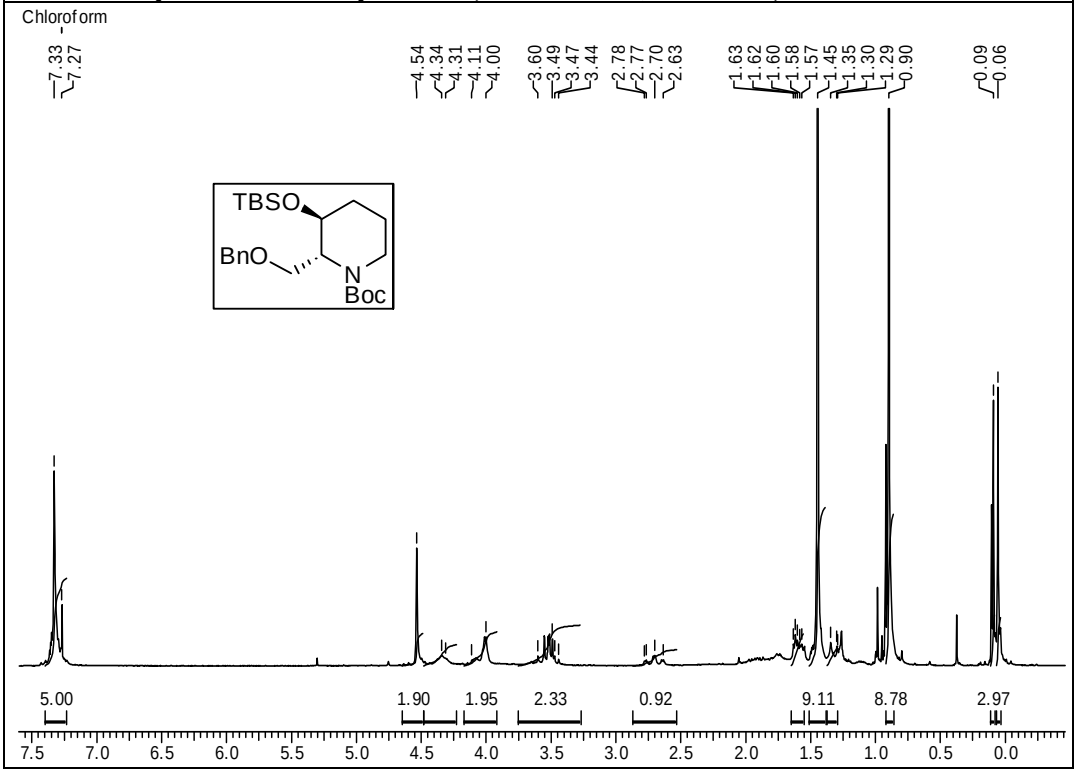
^{13}C NMR Spectrum of compound 7 ($CDCl_3$+CCl_4, 100 MHz)



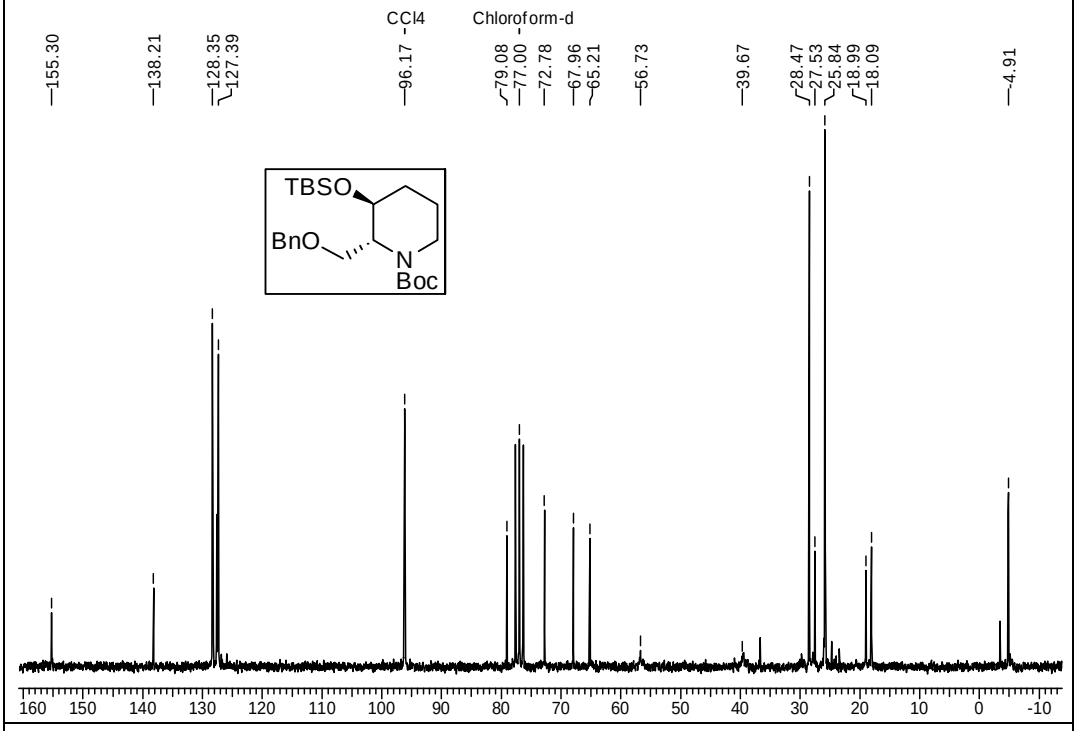
DEPT spectrum of compound 7 ($CDCl_3$+CCl_4, 100 MHz)



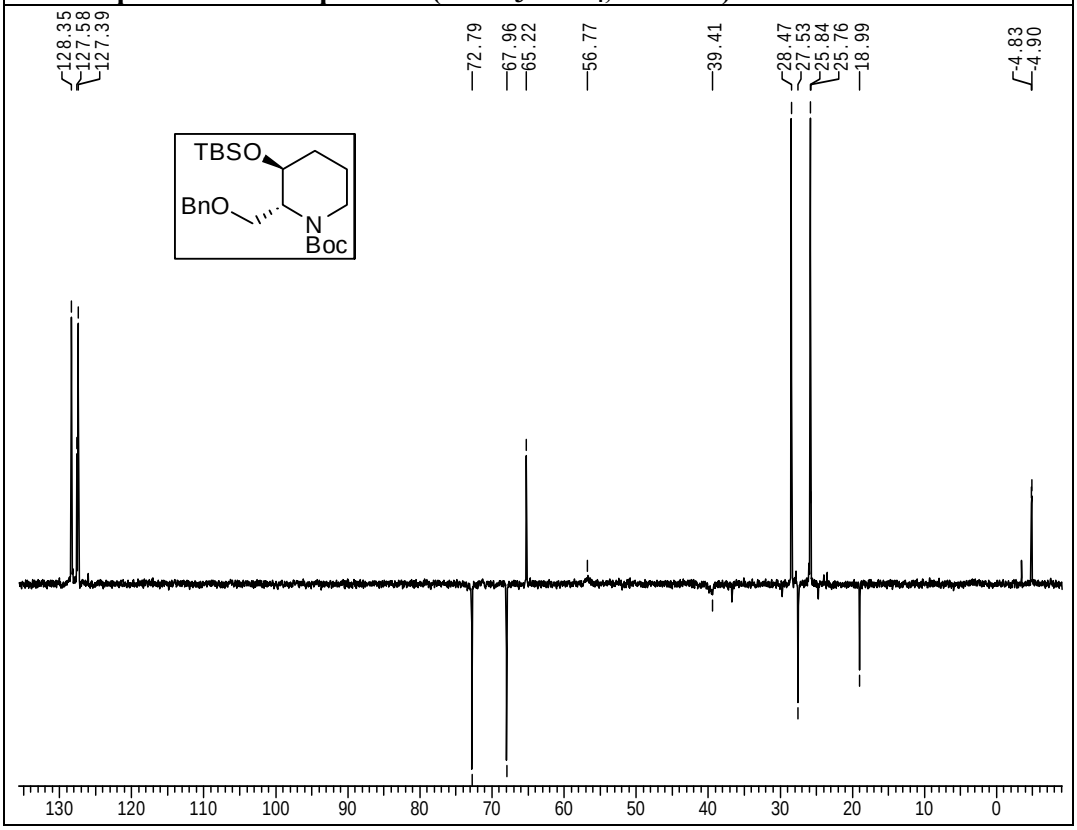
^{1}H NMR Spectrum of compound 9 ($CDCl_3$+CCl_4, 200 MHz)



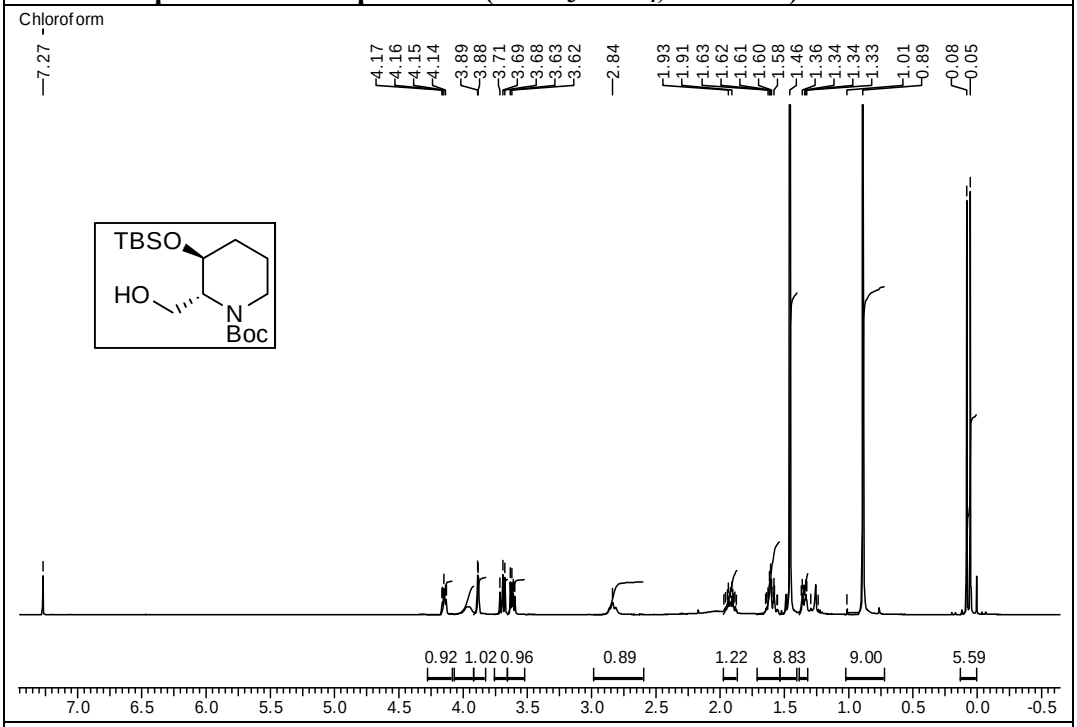
^{13}C NMR Spectrum of compound 9 ($CDCl_3$+CCl_4, 50 MHz)



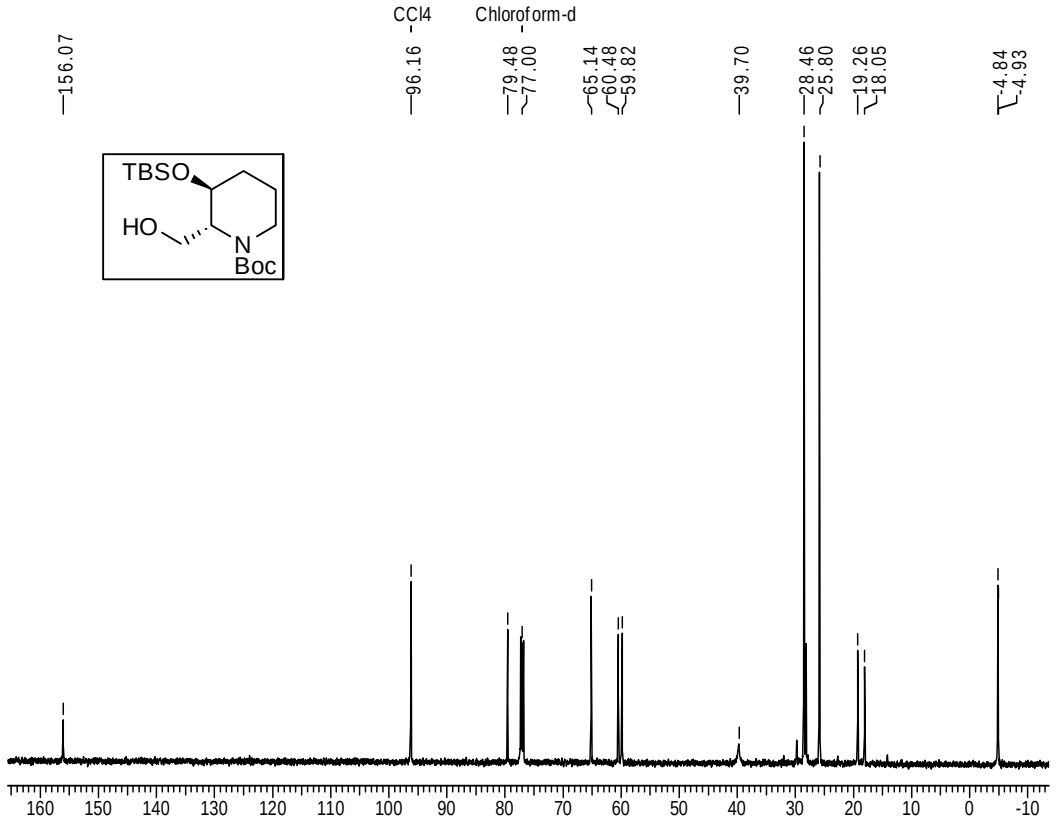
DEPT spectrum of compound 9 ($CDCl_3$+CCl_4, 50 MHz)



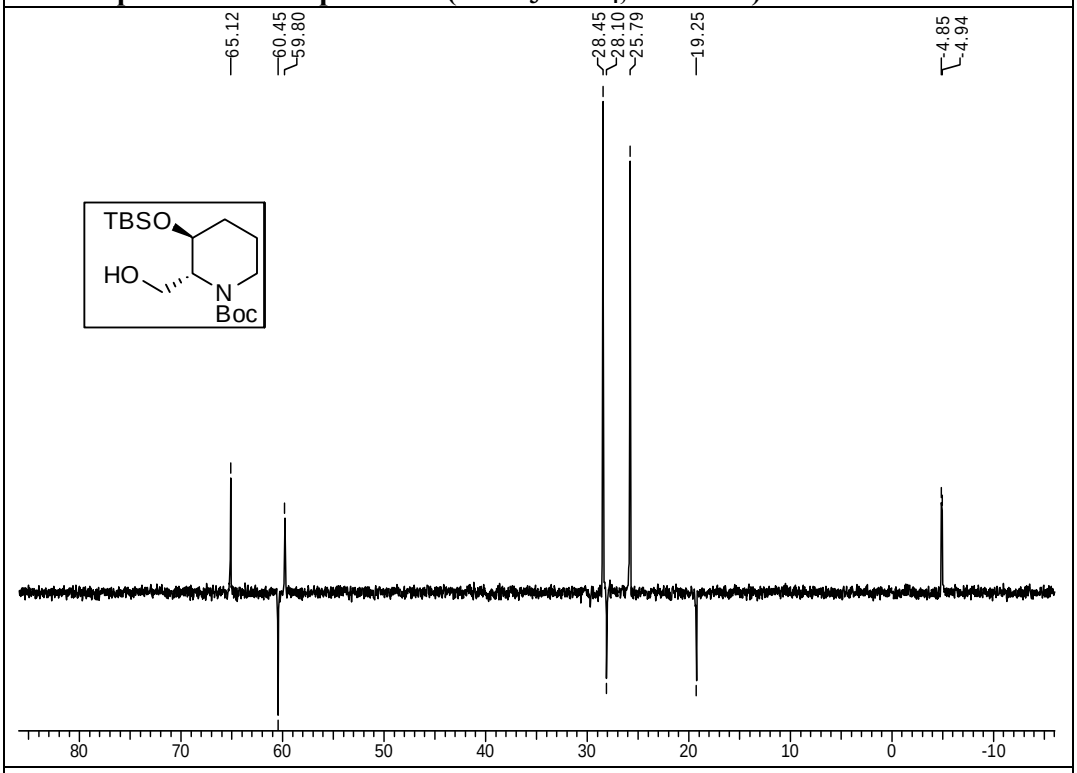
^{1}H NMR Spectrum of compound 10 ($CDCl_3$+CCl_4, 500 MHz)



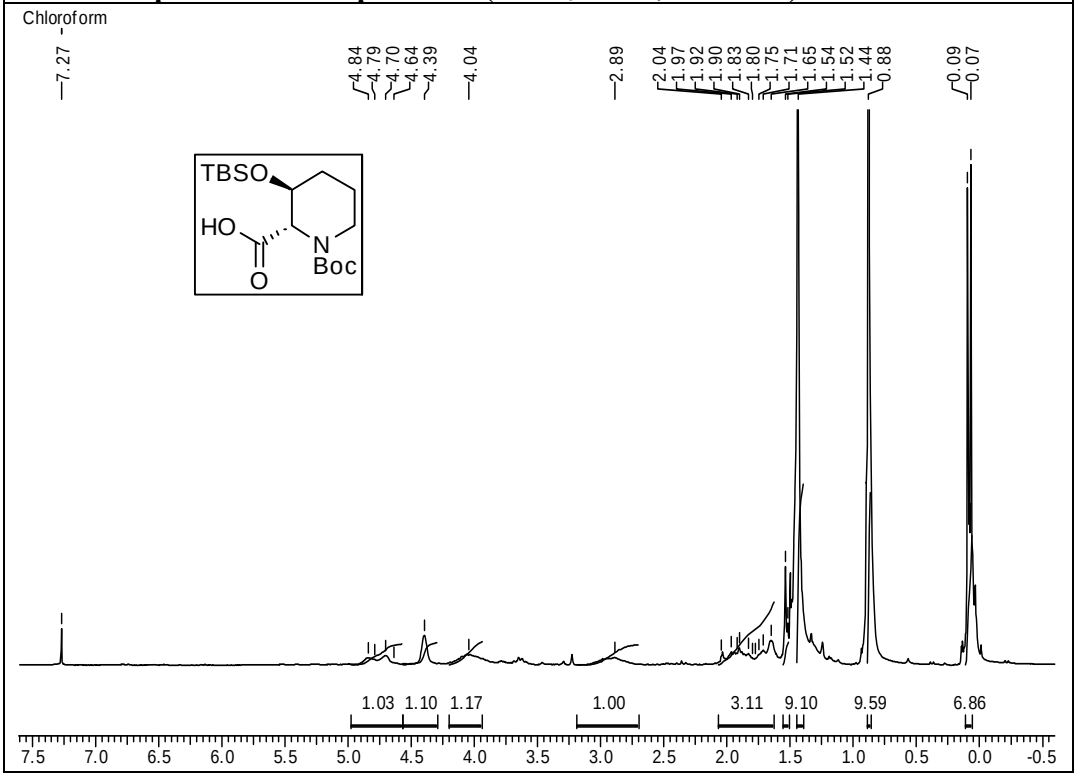
^{13}C NMR Spectrum of compound 10 ($CDCl_3$+CCl_4, 125 MHz)



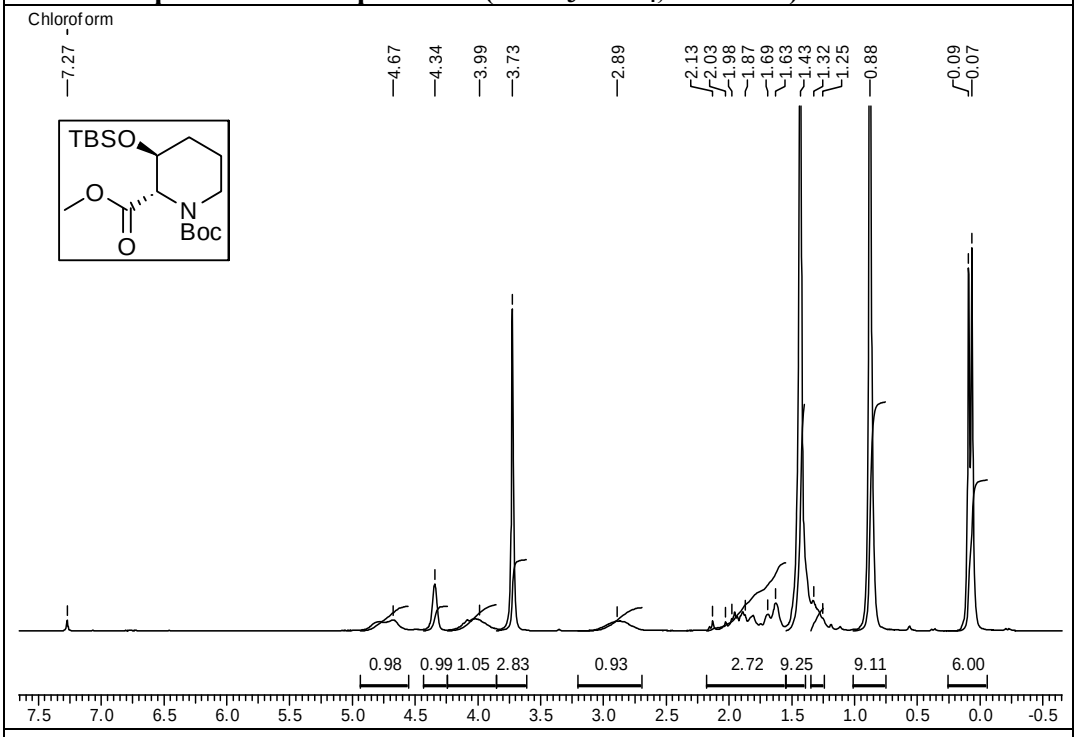
DEPT spectrum of compound 10 ($CDCl_3$+CCl_4, 125 MHz)



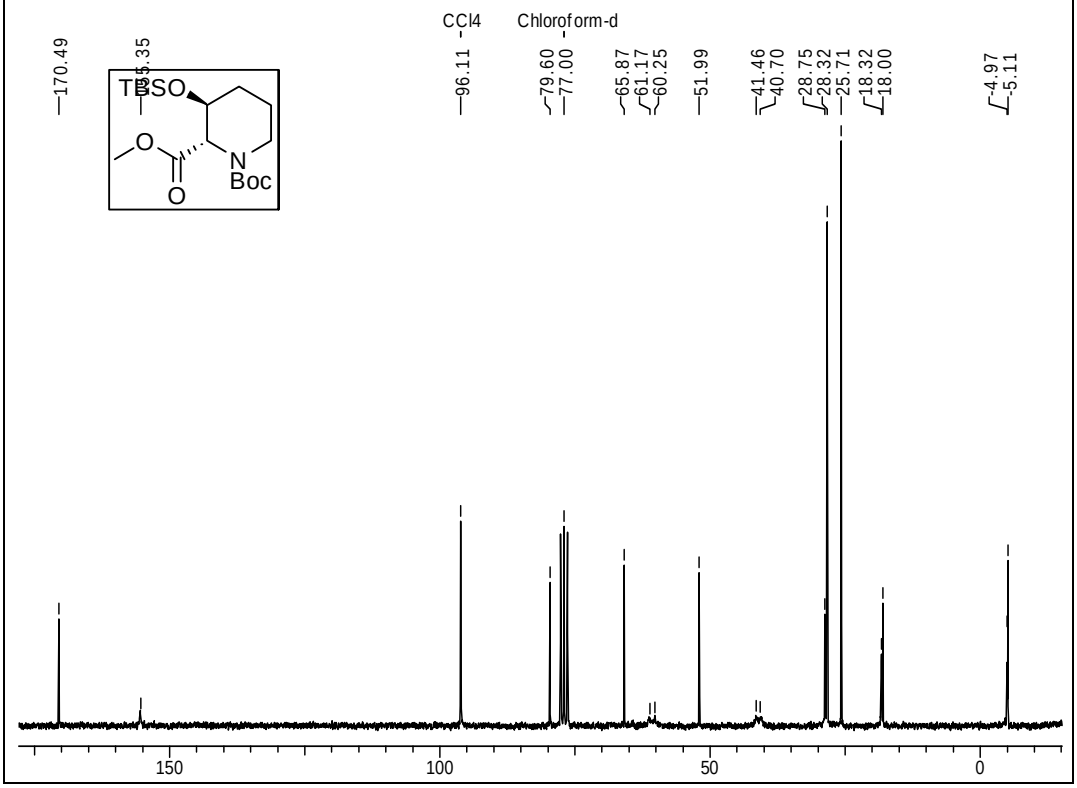
^{1}H NMR Spectrum of compound 11 ($CDCl_3$+CCl_4, 200 MHz)



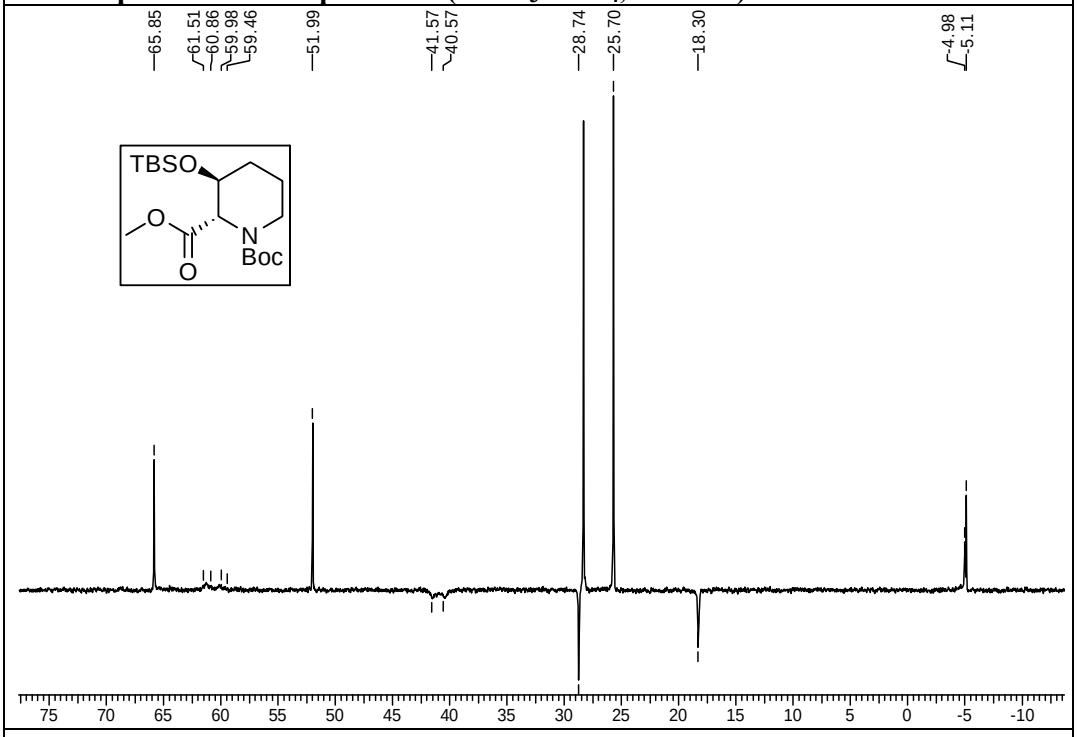
^{1}H NMR Spectrum of compound 12 ($CDCl_3$+CCl_4, 200 MHz)



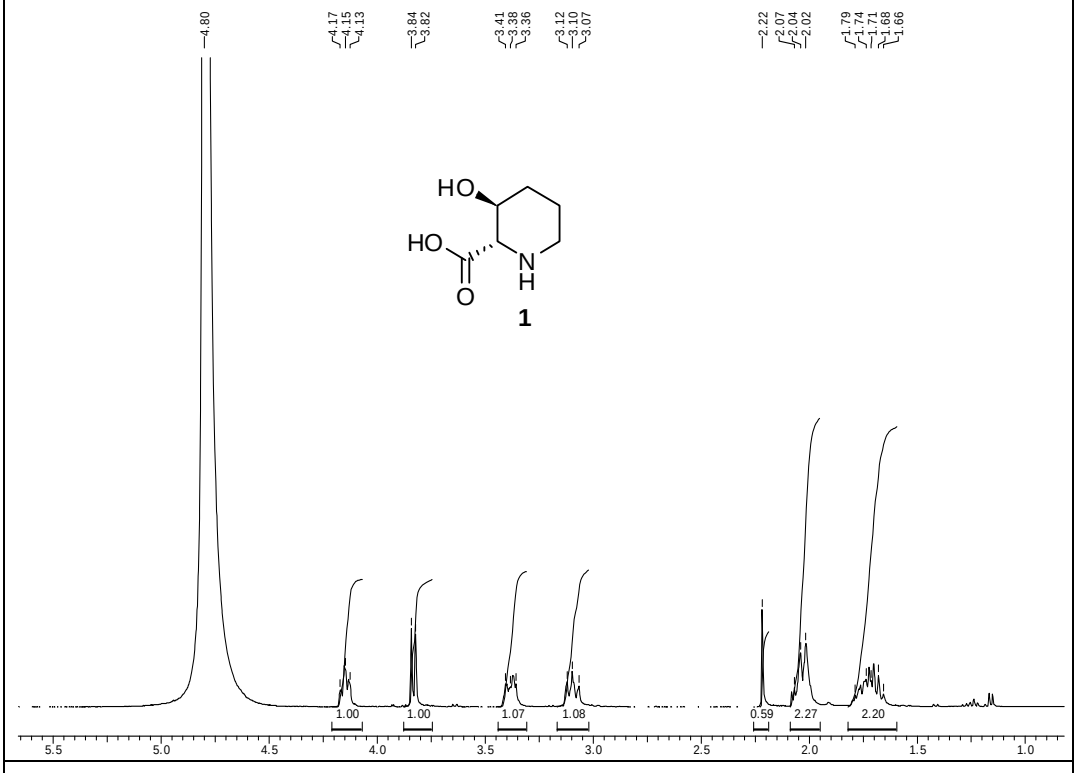
^{13}C NMR Spectrum of compound 12($CDCl_3$+CCl_4, 50 MHz)



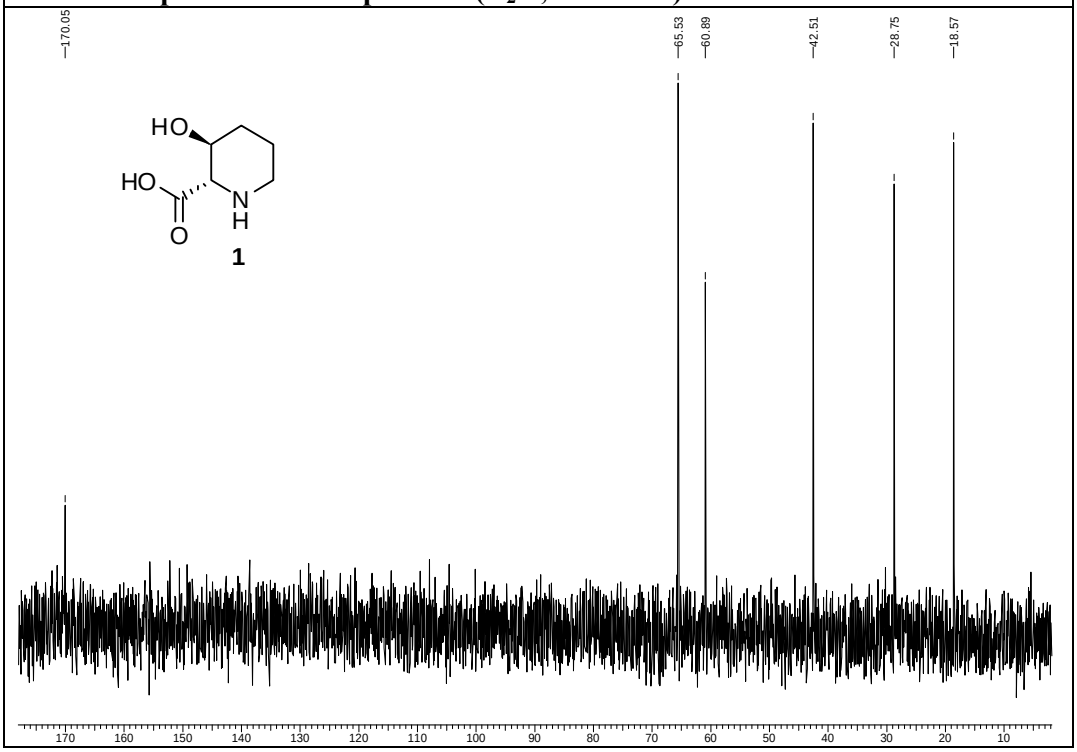
DEPT spectrum of compound 12 ($CDCl_3$+CCl_4, 50 MHz)



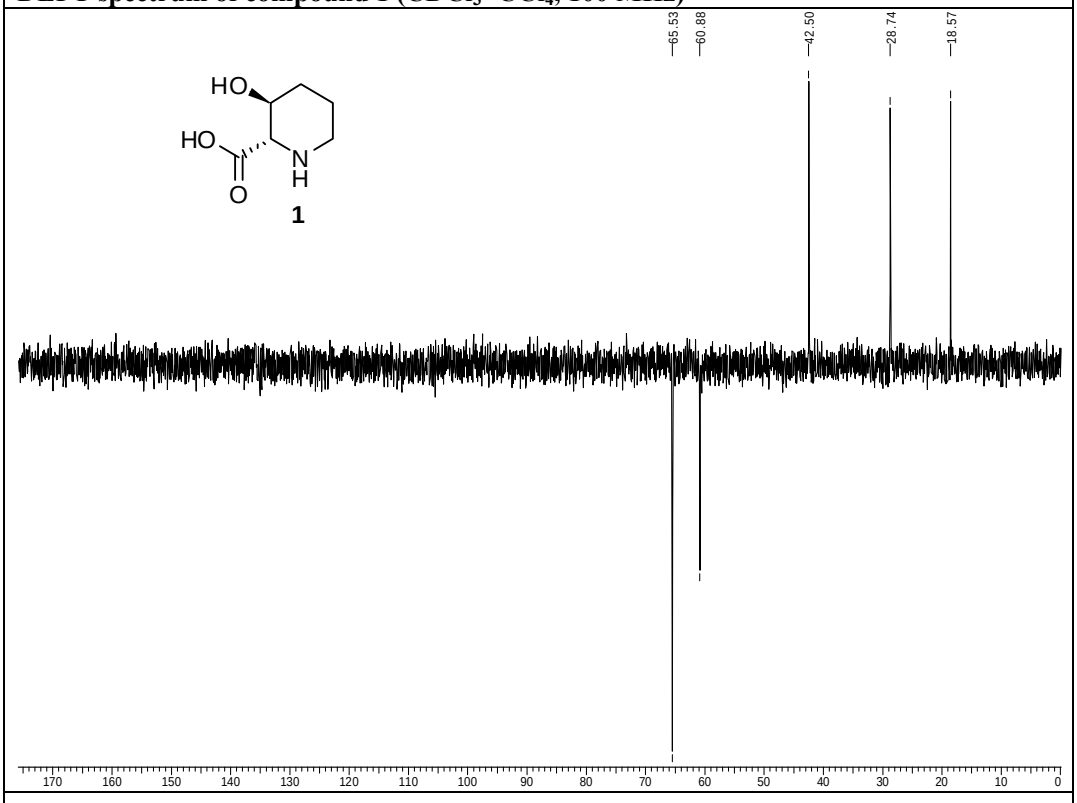
^{1}H-NMR spectrum of compound 11 (D_2O, 400 MHz)



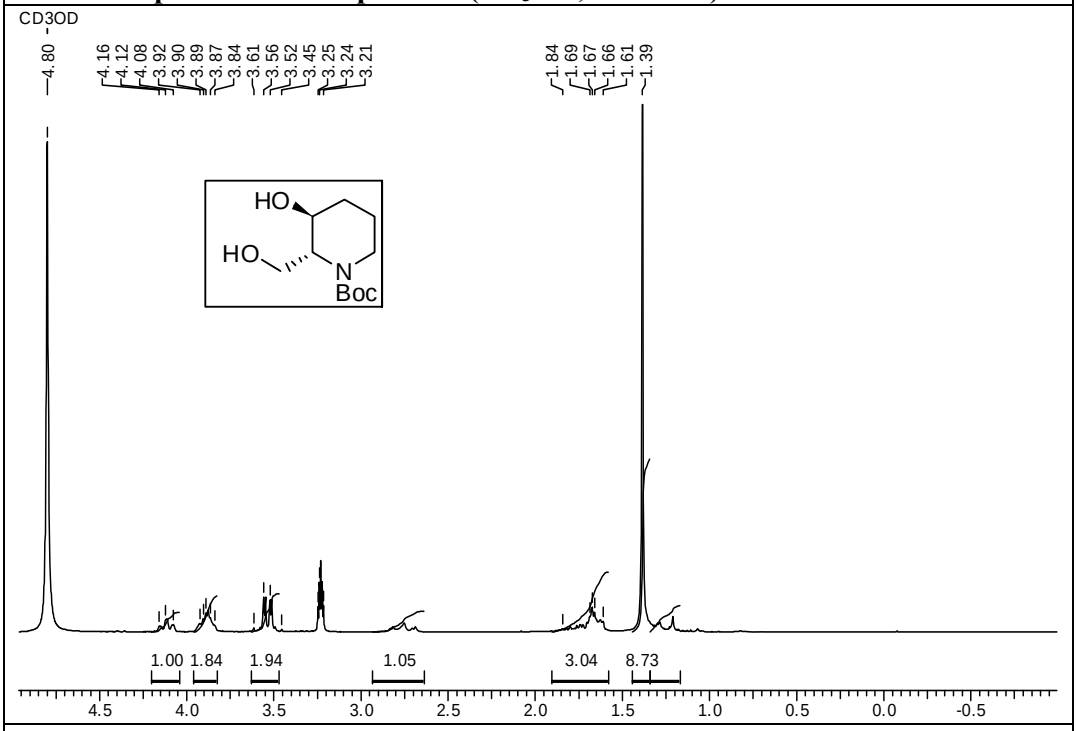
^{13}C-NMR spectrum of compound 1 (D_2O, 100 MHz)



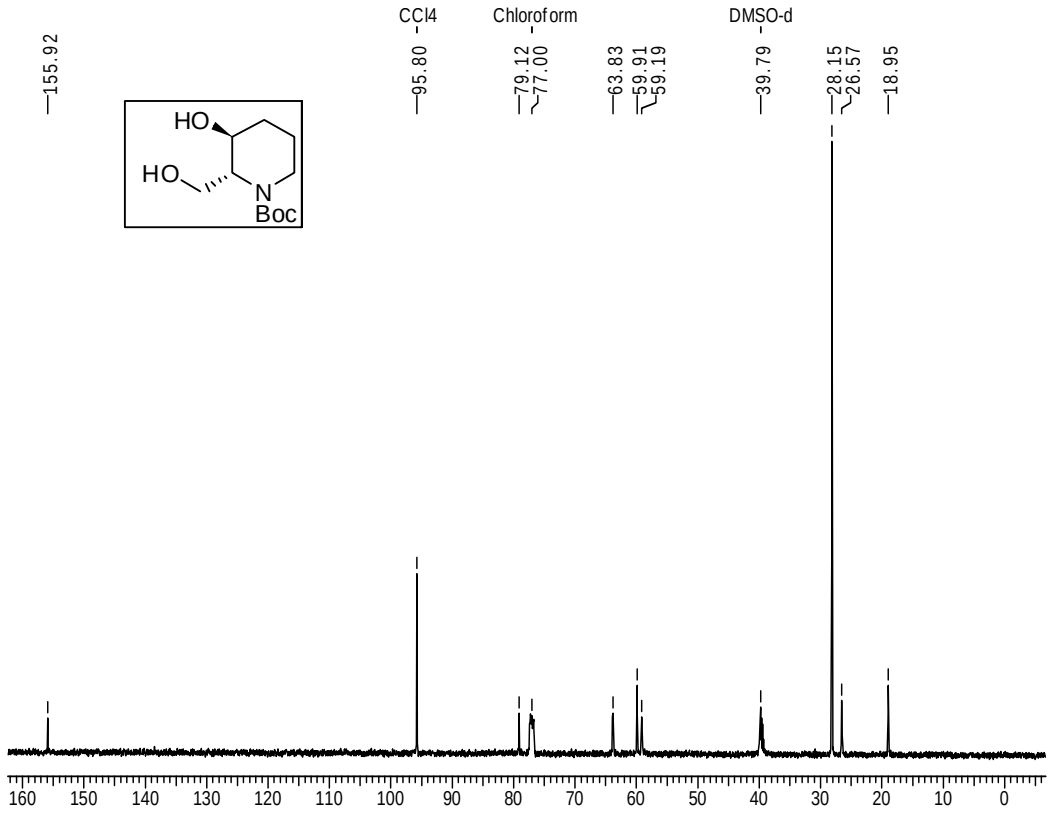
DEPT spectrum of compound 1 ($CDCl_3$+CCl_4, 100 MHz)



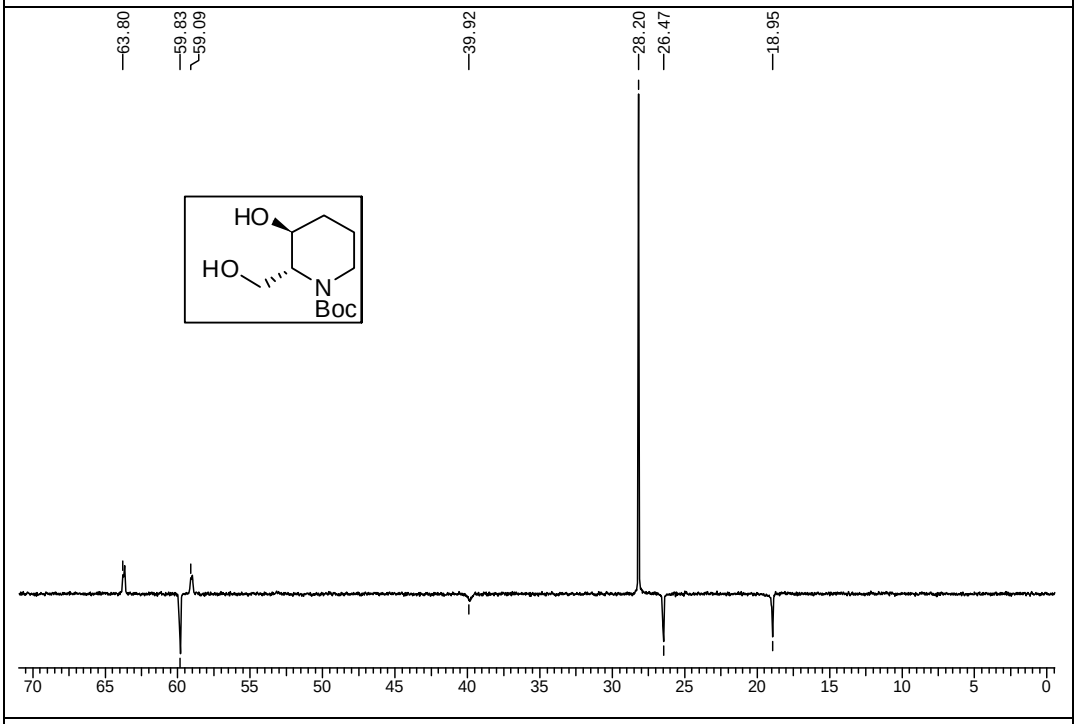
^{1}H NMR Spectrum of compound 8 (CD_3OD, 200 MHz)



^{13}C NMR Spectrum of compound 8 ($CDCl_3$+CCl_4+CD_6SO , 125 MHz)

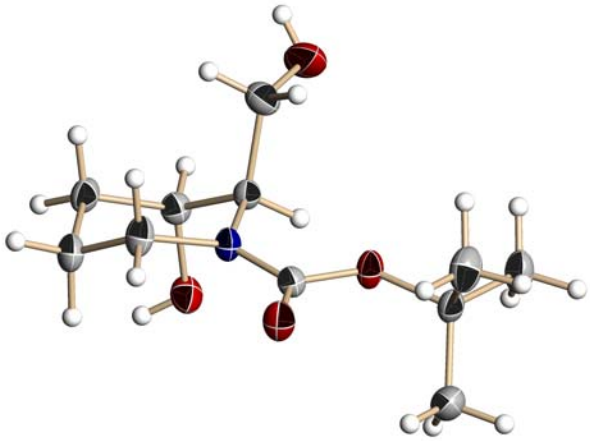


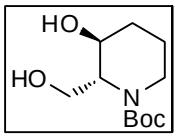
DEPT spectrum of compound 8 ($CDCl_3$+CCl_4+CD_6SO , 125 MHz)



Single crystal analysis and ORTEP Dig:-

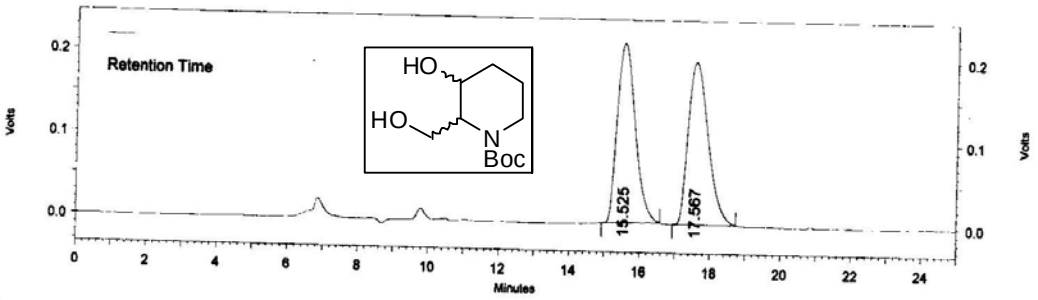
Chemical formula	C_{11} H_{21} N O_4
M_r	231.29
Temperature/K	298(2)
Morphology	Needle, colorless
Crystal size	0.32 × 0.30 × 0.22
Crystal system	monoclinic
Space group	$P2_1$
a (Å)	5.8954(10)
b (Å)	12.134(2)
c (Å)	9.1269(15)
α (°)	90
β (°)	107.103(2)
γ (°)	90
V(Å^3)	624.03(18)
Z	2
D_{calc} (g cm^{-3})	1.231
μ (mm^{-1})	0.093
F(000)	252
Ab. correction T_{min} / T_{max}	Multi-scan 0.971 / 0.980
θ_{max} (°)	26
h, k, l (min, max)	(–7,7), (–14,14), (–10,11)
Reflns collected	4122
Unique reflns	2338
Observed reflns	2265
No. of parameters	229
GoF	1.048
R_obs	0.0309
wR_2_obs	0.0729
R_all	0.0319
wR_2_all	0.0727
$\Delta\rho_{max}$,$\Delta\rho_{min}$(eÅ^{-3})	0.14, –0.15





Project Leader :- Dr. CHAVAN . S.P
Column :-CHIRACEL OJ-H(250x4.6mm)
M.P. :- IPA:PE (5:95)
Wavelength :- 210nm
Flow :- 0.5ml/min (211psi)
conc. :- 1.64mg/0.5ml(Mobile Phase)
njection vol :- 20ul

Nilesh



Detector A - 1
(210nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
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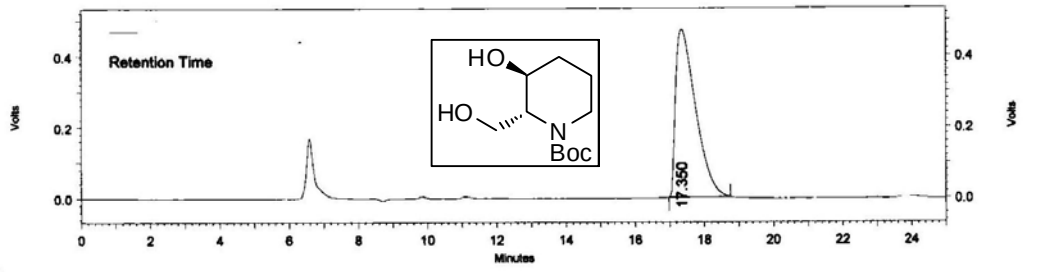
2	17.567	7740006	50.000	196381	47.50
Totals		15480078	100.000	413454	100.00



Detector A - 1
(210nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
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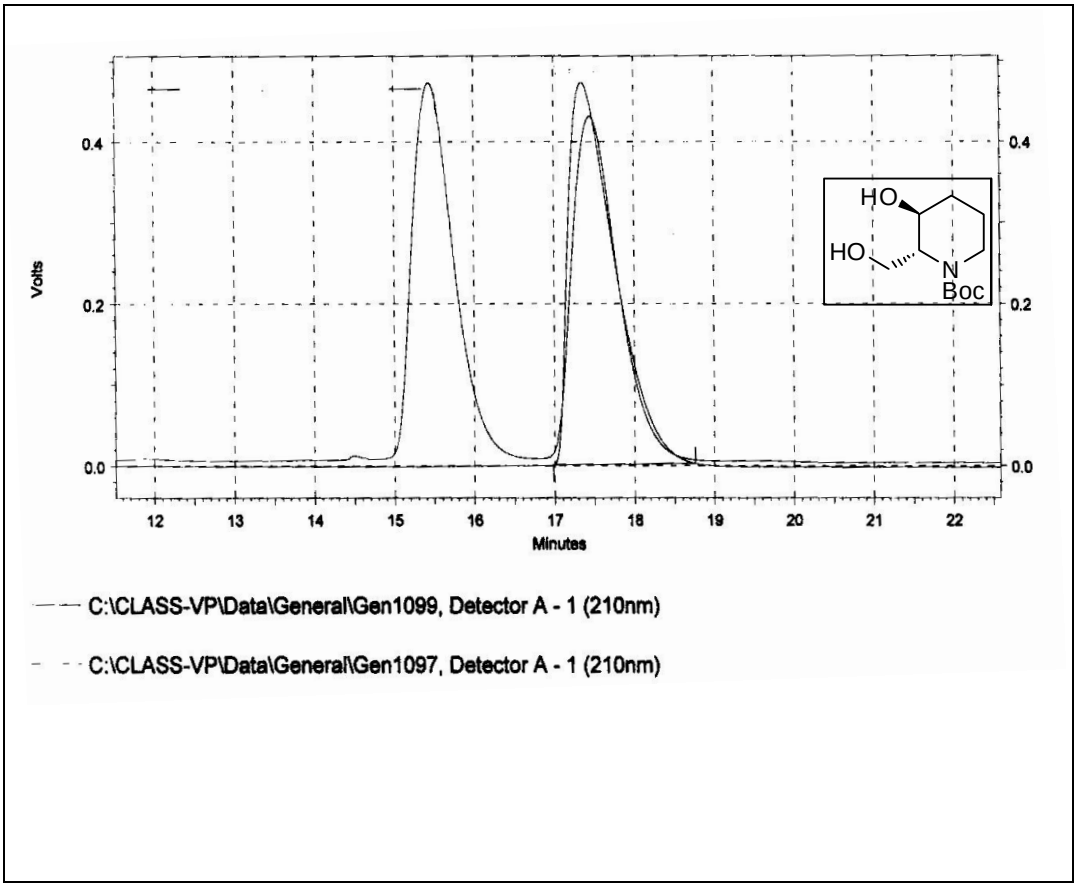
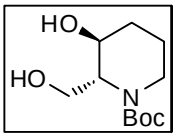
Totals		18970365	100.000	472091	100.00

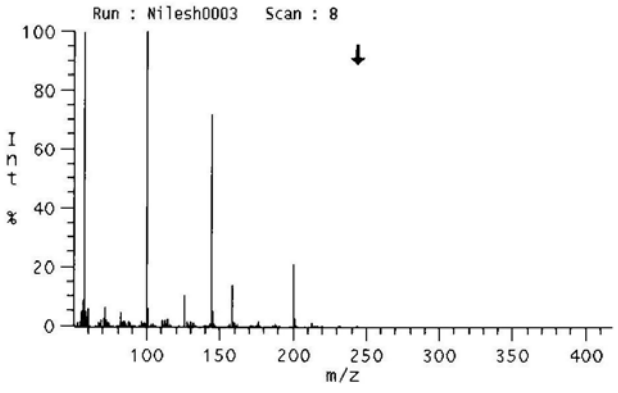

0.4
0.2
0.0
Volts
12
13
14
15
16
17
18
19
20
21
22
Minutes
HO
HO
N
Boc
C:\CLASS-VP\Data\General\Gen1099, Detector A - 1 (210nm)
C:\CLASS-VP\Data\General\Gen1097, Detector A - 1 (210nm)

Run : Nilesh0003 Scan : 8

Mass	Int %	Dev ppm	C	1 H	O	N
244.11496	0.04	No matches found				
232.15762	0.15	No matches found				
231.14848	0.07	6.1	11	21	4	1
220.07633	0.13	No matches found				
216.12231	0.17	No matches found				
214.13742	0.13	No matches found				
213.13472	0.94	No matches found				
202.11845	0.31	No matches found				
201.12759	2.46	No matches found				
200.12413	21.09	No matches found				
190.10334	0.06	No matches found				
189.03171	0.01	No matches found				
188.06373	0.72	No matches found				
186.08344	0.13	No matches found				
177.08265	0.08	No matches found				
176.09702	1.49	No matches found				
175.08038	0.07	No matches found				
174.07928	0.14	No matches found				
173.09825	0.04	No matches found				
172.11985	0.12	No matches found				
171.13901	0.03	No matches found				
162.07839	0.47	No matches found				
161.05709	0.03	No matches found				
160.08396	0.96	No matches found				

$C_{11}H_{21}O_4N$





Run : Nilesh0003 Scan : 8

Mass	Int %	Dev ppm	C	1 H	O	N
244.11496	0.04	No matches found				
232.15762	0.15	No matches found				
231.14848	0.07	6.1	11	21	4	1
220.07633	0.13	No matches found				
216.12231	0.17	No matches found				
214.13742	0.13	No matches found				
213.13472	0.94	No matches found				
202.11845	0.31	No matches found				
201.12759	2.46	No matches found				
200.12413	21.09	No matches found				
190.10334	0.06	No matches found				
189.03171	0.01	No matches found				
188.06373	0.72	No matches found				
186.08344	0.13	No matches found				
177.08265	0.08	No matches found				

2.2.5 References and Notes

1. Chavan, S. P.; Praveen, C.; Sharma, P.; Kalkote, U. R. *Tetrahedron Lett.* **2005**, *46*, 439.
2. Trust, R.; Ireland, R. E. *Org. Synth*. (Coll. Vol.) **1998**, *6*, 606.
3. a) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 448; (b) Torri, S.; Liu, P.; Bhuvaneswari, N.; Amatore, C.; Jutand, A. *J. Org. Chem*. **1996**, *61*, 3055; For a review on asymmetric dihydroxylation, see: (c) Kolb, H. C.; Van Niewenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
4. For racemic dihydroxy compound **(8)**
   HPLC chiralcel OJ-H column (250 x 4.6 mm) isopropanol/n-hexane = 5:95 flow rate 0.5 ml/min, λ=210 nm) retention time (min): Rt_1 = 15.525; Rt_2 = 17.340 (1:1)
   For enantiomerically pure dihydoxy compound **(8)**
   HPLC chiralcel OJ-H column (250 x 4.6 mm) isopropanol/n-hexane = 5:95 flow rate 0.5 ml/min, λ=210 nm) retention time (min): 17.340 (exclusive).
5. (a) Kim, I. S.; Oh, J. S.; Zee, O. P.; Jung, Y. H. *Tetrahedron* **2007**, *63*, 2622; (b) Chiou, W. H.; Lin, G. H.; Liang, C. W. *J. Org. Chem*. **2010**, *75*, 1748; (c) Lemire, A.; Charette, A. B. *J. Org. Chem.* **2010**, *75*, 2077.
6. Ruan, S. T.; Luo, J. M.; Du, Y.; Huang, P.-Q. *Org. Lett.* **2011***, 13*, 4938.
7. Wang, B.; Liu, R.-H. *Eur. J. Org. Chem.* **2009**, 2845.
8. Battistini, L.; Zanardi, F.; Rassu, G.; Spanu, P.; Pelosi, G.; Fava, G. G.; Ferrari, M. B.; Casiraghi, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2975.

Chapter 2

Section 3 Synthetic studies towards (2*R*, 3*R*)-*tert*-butyl 3-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate and (2*R*, 3*S*)-*tert*-butyl 3-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate

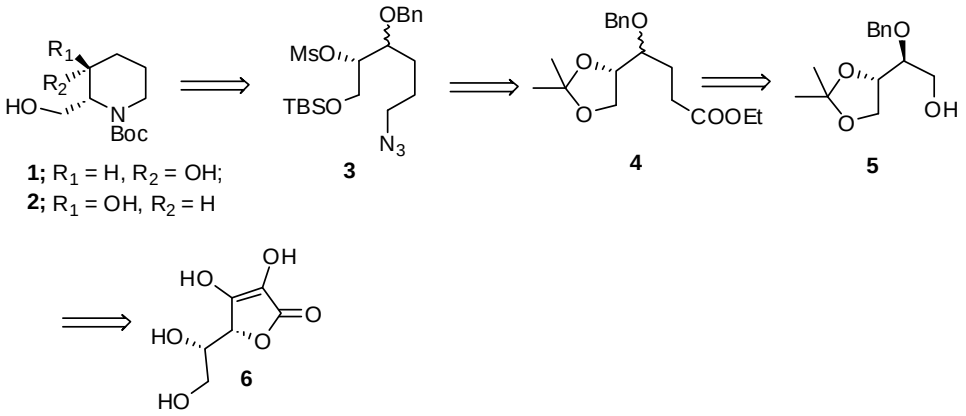
2.3.1. Present work

2.3.1.1 Objective

3-Hydroxypipecolic acid is an important scaffold of many natural and synthetic compounds having promising biological activity which has been described in earlier chapter (Chapter-2 Section-1). The total synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid was accomplished starting from nonchiral and commercially available starting material *viz*. *cis*- butene 1,4-diol (Chapter-2, section-2) by employing Sharpless asymmetric dihydroxylation and reductive cyclisation as the key steps.[1] The present section describes the synthesis of (2*R*,3*S*)-*tert*-butyl 3-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate and (2*R*,3*R*)-*tert*-butyl 3-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate using L-ascorbic acid as chiral template.

2.3.1.2 Retrosynthetic analysis

According to retrosynthetic plan (Scheme 1), it was envisioned that diols **1** and **2** can be easily generated from azide **3** *via* reductive intramolecular *N*-alkylataion. Azide **3** can be easily accessed from ester **4** by carrying out some functional group transformations. Ester **4** could be derived from alcohol **5** which can be generated from L-ascorbic acid **6**.

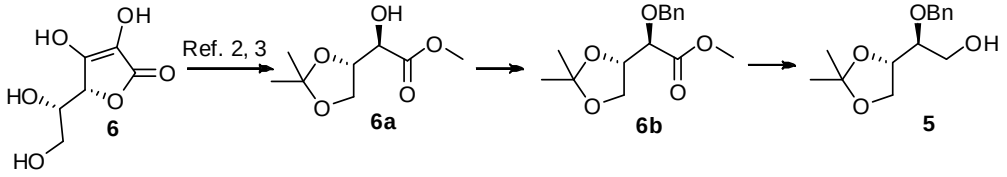


Scheme 1 Retrosynthetic analysis of diols **1** and **2**

2.3.1.3 Results and discussion

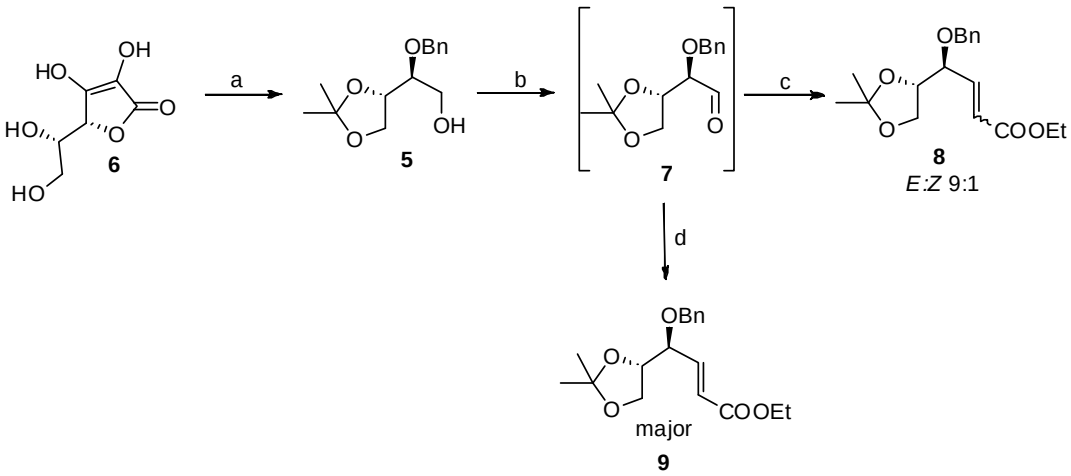
The synthesis started from commercially available starting material *viz*. L-ascorbic acid **6** (Scheme 2). The alcohol **5** was prepared from L-ascorbic acid by known

literature protocol[2,3] involving esterification to furnish **6a**, its benzyl protection to afford **6b** and ester reduction to afford **5** (Scheme 2).



Scheme 2

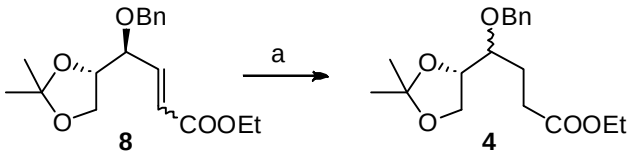
The alcohol **5** was subjected under Swern oxidation conditions to furnish aldehyde **7** which without purification was subjected to Wittig reaction using two carbon ylide (PPh_3CHCO_2Et) (derived from ethyl bromoacetate and triphenyl phosphine) in DCM at 0 ^oC to room temperature to give an inseparable mixture of *E* and *Z*-alkenes (10:90) **8**[3] (Scheme 3).



Scheme 3 *Reagents and conditions: (a) Ref 2, 3; (b) IBX, EA, reflux, 3 h; c) $PPh_3CHCOOEt$, DCM, 0 ^oC- rt, overnight, 80% (over two steps); d) $(EtO)_2P(O)CH_2COOEt$, NaH, benzene, 80% (over two steps).*

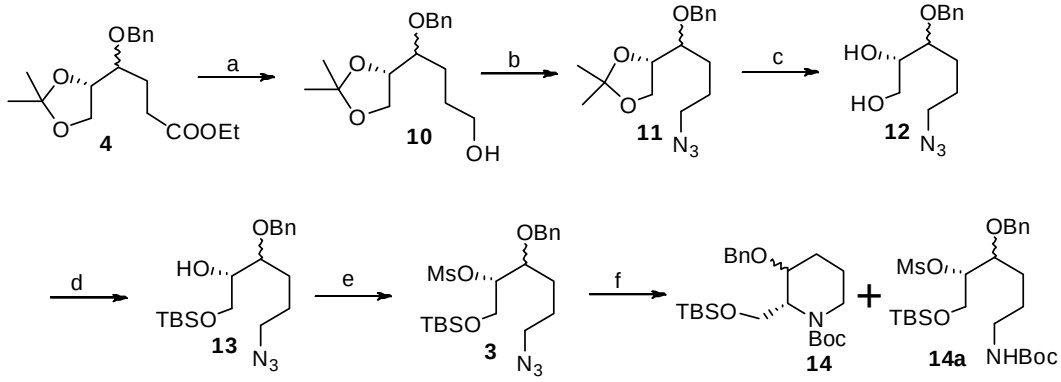
Gratifyingly, the same aldehyde **7** when was subjected to Wittig-Horner reaction in benzene as a solvent at 0 ^oC afforded unsaturated ester **9** (*E* isomer exclusively)., ^1H NMR spectrum of unsaturated ester **8** showed peaks at δ 6.86 and 6.12 each integrating for one protons indicating presence of olefinic moiety. Its ^{13}C NMR spectrum displayed the peak at δ 165.6 which was attributed to ester carbonyl carbon. Its DEPT NMR spectrum showed the three CH_2 carbons supporting the formation of

8. Further, molecular ion peak at 343.17 $(M+Na)^+$ in its mass spectrum supported the formation of **8**.



Scheme 4 *Reagents and conditions: a) $Pd(OH)_2/C$, $HCOONH_4$, MeOH, reflux, 2 h, 92%.*

Chemoselective reduction of double bond of **8** in presence of benzyl ether was carried out using $Pd(OH)_2/C$ as the catalyst and ammonium formate as hydrogen source in methanol under reflux conditions to furnish saturated ester **4** (Scheme 4). Unfortunately, epimerization took place during this transformation. It was confirmed by spectroscopic analysis. Its IR spectrum showed shifting of strong absorption band from 1721 to 1732 cm^{-1} indicating presence of saturated ester functionality. Its ^1H NMR spectrum showed peak multiplet at δ 1.22-1.27 for three protons corresponding to $COOCH_2\underline{CH_3}$ methyl protons. The absence of olefinic protons also indicated the formation of saturated ester further supported by the presence of peaks at 25.8, 29.4 and 30.0 (due to diastereomers). Its ^{13}C NMR spectrum showed doublet for each carbon indicating presence of other isomer and shifting of signals from δ 165.6 to δ 173.07 and δ 173.19 (due to presence of other isomer) and absence of peaks at δ 124.4 and δ 143.4 supported the formation of saturated ester **4**.



Scheme 5 *Reagents and conditions: a) LiBr, $NaBH_4$, MeOH:H_2O, 3 h, 88%: b) i) MsCl, TEA, DCM, 0 ^oC, 30 min; ii) NaN_3, DMF, 90 ^oC, 6 h, 70% (over two steps); c)*

AcOH:H_2O (8:2), rt, 85%; d) TBSOTf, TEA, DCM, 0 ^oC, 30 min, 90%; e) MsCl, TEA, DCM, 0 ^oC, 30 min, 92 %; f) i) PPh_3, Benzene:H_2O (9:1), reflux, ii) $(Boc)_2O$, TEA, DMAP (Cat.), THF, rt, 45-50% (over two steps).

Inseparable diastereomeric mixture of ester **4** was reduced using $NaBH_4$ in presence of LiBr in MeOH: H_2O system to provide alcohol **10** (Scheme 5). Its ^1H NMR spectrum displayed the disappearance of multiplet at δ 1.22-1.27 indicating the formation of **10**. In its ^{13}C NMR spectrum, absence of peaks at δ 14.2, 173.07 and 173.19 supported the reduction of ester functionality.

Additionally, its DEPT NMR spectrum showed the five –$\underline{CH_2}$- each as double peaks due to diastereomeric carbons supporting the formation of **10**. Molecular ion peak at *m/z* 303.13 $(M+Na)^+$ in its mass spectrum supported the formation of **10**. Further, it was confirmed by HRMS analysis.

Diastereomeric mixture of alcohol **10** was converted to its mesylate derivative followed by treatment with NaN_3 in DMF at 80 ^oC for 18 h to afford azido compound **11** in 70% yield (over two steps). Its IR spectrum showed the strong absorption band at 2097 cm^{-1} indicating presence of azide functionality. Its ^1H NMR spectrum showed the shifting of the signals from δ 3.44 to 3.23 supporting the formation of **11**. Its ^{13}C NMR spectrum displayed the signal at δ 51.43 which was attributed to $\underline{CH_2}$-N_3 carbon. Further, molecular ion peak at *m/z* 328.1643 $(M+Na)^+$ in its HRMS spectrum confirmed the formation of azido compound **11**.

Terminal acetonide deprotection in **11** was carried out by using AcOH:H_2O (8:2) at room temperature to provide diol **12** in 85% yield. Its IR spectrum showed strong absorption at 3391 cm^{-1} indicating presence of a hydroxy functionality. Its ^1H NMR spectrum displayed the disappearance of peaks at δ 1.38 and δ 1.45 corresponding to acetonide group. Its DEPT spectrum showed the disappearance of signals at δ 25.3 and 26.5 corresponding to acetonide methyl carbons. Further, its HRMS spectrum showed the molecular ion peak at *m/z* 288.1326 $(M+Na)^+$ which confirmed the assigned structure **11**.

Selective mono TBS protection of **11** was carried out using TBSOTf (1.2 eq.), TEA and DMAP (cat.) in DCM at 0 ^oC for 30 min to furnish the TBS ether **12** in 90% yield. Its ^1H NMR spectrum showed peaks at δ 0.02 and δ 0.86 each integrating for

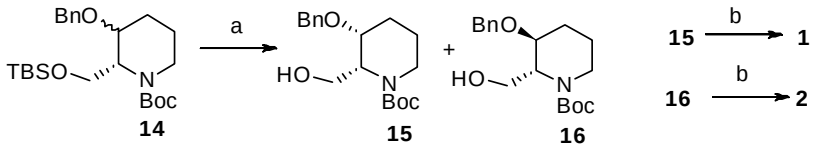
six and nine protons respectively corresponding to TBS group. In its ^{13}C NMR spectrum the appearance of new signals at δ -5.30 and 18.30 corresponding to methyl carbons of TBS group was observed. Further, its HRMS spectrum showed the molecular ion peak at *m/z* 380.2374 $(M+Na)^+$ which confirmed the formation of **12**.

Hydroxy group of **12** was converted to its *O*-mesylate derivative **3** first by converting the primary hydroxy group to its TBS derivatives followed by treatment with MsCl, TEA followed by addition of DMAP (cat.) in DCM as solvent at 0 ^oC for 30 min in 92% yield. Strong absorption band in its IR spectrum at 1359 cm^{-1} indicated presence of $-SO_2-$ group. ^1H NMR spectrum showed the peaks at δ 2.91 and δ 2.95 (due to presence of diastereomers) each integrating for one and two protons respectively corresponding to $\underline{CH_3}-SO_2-$ protons. The ^{13}C NMR spectrum showed the signals at δ 38.23 and 38.58 corresponding to methyl sulfonyl carbon which supported the formation of **3**. Further, its HRMS spectrum showed the molecular ion peak at *m/z* 480.1973 $(M+Na),^+$ which confirmed the formation of **3**.

Having the azido mesylate derivative **3** in hand, the next concern was to convert this azide derivative **3** to substituted piperidine derivative **14**. Thus intramolecular cyclisation was achieved by using PPh_3 in benzene: H_2O under reflux conditions to afford amine which without purification was treated with $(Boc)_2O$ to furnish a non-separable mixture of urethane derivative **14** in 45-50% yield (over two steps) along with non-cyclised compound **14a** in 10% yield. The IR spectrum of compound **14** showed strong absorption band at 1694 cm^{-1} indicating presence of carbamate functionality. The ^1H NMR spectrum of compound **14** showed a peak at δ 1.46 integrating for nine protons corresponding to Boc group and disappearance of peaks at δ 2.91 and δ 2.95 for methyl protons of mesyl group supporting the formation of **14**. The ^{13}C NMR spectrum of compound **14** showed the signal at δ 28.5 corresponding to Boc group. Further, its HRMS spectrum showed the molecular ion peak at *m/z* 436.2886 $(M+H)^+$ which confirmed the formation of **14**.

Desired urethane derivative **14** was treated with TBAF in an anhydrous THF at 0 ^oC to room temperature for 2 h to furnish a separable mixture of alcohols **15** and **16** (Scheme 6). Interestingly, the two diastereomers **15** and **16** were separated by flash silica gel column chromatography. Its IR spectrum showed strong absorption bands

at 3448, 1670 and 1680 cm^{-1} indicating presence of free hydroxy and urethane groups respectively. The ^1H NMR spectrum of **15** showed the disappearance of peaks at δ 0.06 and δ 0.88 corresponding to the protons of TBS group.



Scheme 6 *Reagents and conditions: a*) TBAF, THF, 0 ^oC- rt, 80%; b) $Pd(OH)_2$, H_2, MeOH, rt, 85%.

Spectroscopic analysis and optical rotation of *ent*-**15**[4] and **16**[1] was in good agreement with reported one. Urethanes **15** and **16** were subjected under hydrogen atmosphere using Pd/C as a catalyst to provide diol **1** and **2** respectively which were further exploited for the synthesis of 3-hydroxypipecolic acid by known literature protocol.[1,4]

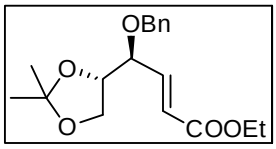
2.3.2 Conclusion

A formal synthesis of 3-hydroxypipecolic acid has been achieved by employing epimerization and intramolecular *N*-alkylation as the key steps.

2.3.3 Experimental Section

(*E*)-Ethyl 4-(benzyloxy)-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate (8)

To a solution of $(COCl)_2$ (0.83 mL, 9.52 mmol) in CH_2Cl_2 (10 mL) was added



DMSO (1.35 mL, 19.05 mmol) at -78 ^oC and the mixture was stirred for 10 min. A solution of alcohol **5** (1.20 g, 4.76 mmol) in CH_2Cl_2 was added to the resulting mixture and stirring was continued for another 30 min at -78 ^oC. Then TEA (6.75 mL, 38.09 mmol) was added at -78 ^oC and the resulting reaction mixture was warmed to 0 ^oC and stirred for 20 min, water (30 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (2 X 30 mL), dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent provided the crude aldehyde, which was directly used in the next step. To a solution of aldehyde **7** in CH_2Cl_2 (15 mL), $Ph_3PCHCOOEt$ (2.49 g, 7.14 mmol) was added at 0 ^oC and stirred for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure and directly adsorbed on silica gel. The residue was purified by flash silica gel column chromatography using ethyl acetate/pet. ether (1:9) to provide the unsaturated ester **8** in the ratio of *E/Z* 9:1 (1.22 g, 80% over two steps) as colorless liquid.

Chemical Formula: $C_{18}H_{24}O_5$

Yield : 80% (over two steps)

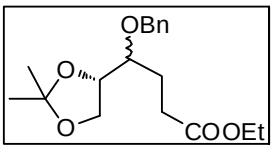
IR ($CHCl_3$, cm^{-1}) : 1721, 1659, 1455;

ESIMS (*m/z*) : 343.17 $(M+Na)^+$;

For major *trans*- isomer ^1H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 7.40–7.24 (m, 5H), 6.86 (dd, *J* = 16, 6 Hz, 1H), 6.12 (dd, *J* = 16, 1 Hz, 1H), 4.71 (d, *J* = 12 Hz, 1H), 4.50 (d, *J* = 12 Hz, 1H), 4.31 – 4.17 (m, 3H), 4.10 (td, *J* =6, 1 Hz, 1H), 3.99 (dd, *J* =9, 7 Hz, 1H), 3.80 (dd, *J* =9, 6 Hz, 1H), 1.41 (s, 3H), 1.36 (s, 3H), 1.33 (t, *J* = 7 Hz, 3H);

For major *trans*- isomer ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 14.3, 25.3, 26.3, 60.5, 65.3, 71.5, 76.7, 78.3, 109.8, 124.4, 127.8, 127.9, 128.5, 137.8, 143.4, 165.6.

Ethyl 4-(benzyloxy)-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)butanoate (4)



To a solution of unsaturated ester **8** (1 g, 3.12 mmol) in methanol (30 mL) was added ammonium formate (1.97 g, 31.21 mmol) followed by addition of $Pd(OH)_2/C$ (cat.) under

nitrogen atmosphere. The reaction mixture was refluxed for 3 h under nitrogen atmosphere. After completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature. The reaction mixture was filtered through the celite bed and the celite bed was thoroughly washed with additional methanol (3 X 30 mL). The solvent was removed under reduced pressure. The crude reaction mixture was purified by flash silica gel column chromatography using ethyl acetate: pet ether (1:9) as solvent to afford saturated ester **4** (0.92 g, 92%) as colorless syrup.

Chemical Formula: $C_{18}H_{26}O_5$;

Yield: 92%;

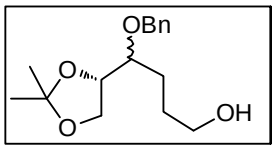
IR ($CHCl_3$, cm^{-1}): 1732, 1602, 1371, 1160;

ESIMS (*m/z*): 345.20 $(M+Na)^+$;

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 1.22-1.27 (m, 3H), 1.34 (s, 1H), 1.37 (s, 2H), 1.40 (s, 1H), 1.44 (s, 2H), 1.64-2.03 (m, 2H), 2.33-2.48 (m, 2H), 3.44-3.56 (m, 1H), 3.68-3.87 (m, 1H), 3.97-4.20 (m, 4H), 4.57-4.79 (m, 2H), 7.25-7.33 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 14.2, 25.2, 25.4, 25.8, 25.9, 26.5, 26.56, 29.43, 30.02, 60.13, 65.82, 66.43, 72.48, 72.85, 77.31, 77.96, 78.48, 78.51, 109.02, 109.33, 127.51, 127.60, 127.75, 127.93, 128.21, 128.27, 138.19, 138.47, 173.07, 173.19.

4-(Benzyloxy)-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)butan-1-ol (10)



To a solution of ester **4** (0.800 g, 2.48 mmol) in methanol: H_2O (20 mL, 9:1) was added LiBr (0.86 g, 9.93 mmol) at 0 ^oC. The reaction mixture was stirred for 10 min followed by portion wise addition of $NaBH_4$ (0.375 g, 9.93 mmol) over 10 min. The reaction mixture was stirred for additional 3 h at room temperature. After completion of reaction (monitored by TLC), the solvent was removed under reduced pressure. The excess sodium borohydride was quenched with saturated solution of ammonium chloride (30 mL). The reaction mixture was left to stir for 10 min and mixture was extracted with DCM (3 X 40 mL). The combined organic extract was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to provide crude mass. The residue was purified by flash silica gel column

chromatography using ethyl acetate: pet ether (4:6) as an eluent to afford alcohol **10** (0.612 g, 88%) as colorless thick syrup.

Chemical Formula: $C_{16}H_{24}O_4$;

Yield: 88%;

IR ($CHCl_3$, cm^{-1}): 3391;

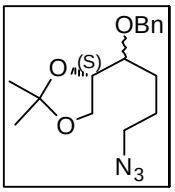
ESIMS (*m/z*): 303.13 $(M+Na)^+$;

HRMS calculated for $[C_{16}H_{24}O_4+Na]^+$ 303.1567; found: 303.1575;

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 1.34 (s, 1H), 1.37 (s, 2H), 1.40 (s, 1H), 1.44 (s, 2H), 1.48-1.74 (m, 4H), 1.91 (bs, 1H), 3.44-3.60 (m, 3H), 3.65-3.89 (m, 1H), 3.96-4.25 (m, 2H), 4.58-4.81 (m, 2H), 7.26-7.34 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 25.31, 25.43, 26.58, 27.13, 27.38, 28.02, 28.73, 62.53, 62.71, 65.71, 66.49, 72.65, 72.86, 77.48, 78.37, 78.88, 79.52, 109.03, 127.66, 127.86, 128.04, 128.32, 128.38, 138.22, 138.45.

(4*S*)-4-(4-Azido-1-(benzyloxy)butyl)-2,2-dimethyl-1,3-dioxolane (11)



To a solution of alcohol **10** (0.200 g, 0.71 mmol) in DCM was added triethylamine (0.149 mL, 1.07 mmol) followed by methanesulfonyl chloride (0.070 mL, 0.85 mmol) and DMAP (cat.) at 0 ^oC. The reaction mixture was allowed to stir for 30 min under nitrogen atmosphere. After completion of reaction, the reaction mixture was diluted with cold water and the product was extracted with DCM (2 X 50 mL). The combined organic extract were dried over anhydrous sulphate, filtered and concentrated under reduced pressure. The obtained crude product (2.1 g, 0.585 mmol) was diluted with anhydrous DMF (5 mL) and then sodium azide (76 mg, 1.17 mmol) was added under nitrogen atmosphere. After being stirred at 80 ^oC temperature for 16 h, the reaction mixture was diluted with water (60 mL) and extracted with pet. ether: ethyl acetate (8:2, 100 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography using ethyl acetate: pet. ether (1:9) as an eluent to afford azido compound **11** (0.152 g, 70% over two steps) as colorless liquid.

Chemical Formula: $C_{16}H_{23}N_3O_3$;

Yield: 70% (over two steps);

IR ($CHCl_3$, cm^{-1}): 2097, 1602, 1383, 1093;

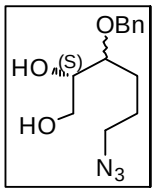
ESIMS (*m/z*): 328.16 $(M+Na)^+$;

HRMS calculated for $[C_{16}H_{23}N_3O_3+Na]^+$ 328.1632; found: 328.1643;

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 1.38 (s, 3H), 1.45 (s, 3H), 1.50-1.85 (m, 4H), 3.23 (t, J = 6 Hz, 2H), 3.45 (q, J = 6 Hz, 1H), 3.66-3.74 (m, 1H), 3.99 (m, 1H), 4.22 (q, J = 6 Hz, 1H), 4.55-4.82 (m, 2H), 7.34 (s, 5H);

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 24.23, 25.09, 25.36, 26.54, 26.62, 27.66, 27.97, 51.28, 51.43, 65.79, 66.53, 72.59, 72.83, 77.37, 78.15, 78.49, 78.85, 109.09, 109.40, 127.70, 128.01, 128.35, 138.20, 138.44.

(2*S*)-6-Azido-3-(benzyloxy)hexane-1,2-diol (12)



A solution of azido compound **11** (0.300 g, 0.98 mmol) in 80% aqueous acetic acid (5 mL) was stirred for 8 h. The reaction mixture was neutralized by the addition of saturated $NaHCO_3$ solution and extracted with EtOAc (2 X 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and the residue was purified by column chromatography with ethyl acetate/pet. ether (1:1), to give diol **12** (0.22 g, 85%) as colorless syrup.

Chemical Formula: $C_{13}H_{19}N_3O_3$;

Yield: 85%;

IR ($CHCl_3$, cm^{-1}): 3391, 2097, 1454, 1257;

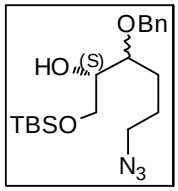
ESIMS (*m/z*): 288.2 $(M+Na)^+$

HRMS calculated for $[C_{13}H_{19}N_3O_3+Na]^+$ 288.1319; found: 288.1326;

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 1.59-1.76 (m, 4H), 2.71 (bs, 2H), 3.22-3.29 (m, 2H), 3.48-3.51 (m, 1H), 3.57-3.74 (m, 3H), 4.49-4.63 (m, 2H), 7.29-7.37 (m, 5H);

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 24.6, 27.2, 51.4, 63.4, 63.7, 72.42, 72.44, 72.76, 79, 79.63, 127.92, 127.98, 128.06, 128.52, 128.58, 137.73, 137.88.

(2*S*)-6-Azido-3-(benzyloxy)-1-((tert-butyldimethylsilyl)oxy)hexan-2-ol (13)



To a solution of diol **12** (0.250 g, 0.942 mmol) in anhydrous methylene chloride (30 mL) was added TEA (0.197 mL, 1.41 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 minutes followed by the addition of TBSOTf (0.27 mL, 1.04 mmol). After stirring at this

temperature for 30 min, the mixture was quenched with water (10 mL). The biphasic mixture was extracted with DCM (2 X 20 mL) and the organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography using 5% ethyl acetate/ pet. ether as an eluent to give *O*-TBS derivative **13** (0.320 g, 90%) as colorless syrup.

Chemical Formula: $C_{19}H_{33}N_3O_3Si$;

Yield: 90%;

IR ($CHCl_3$, cm^{-1}): 3443, 2098, 1604, 1463, 1256, 1087;

ESIMS (*m/z*): 402.17 $(M+Na)^+$;

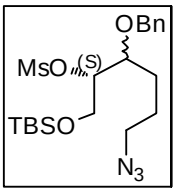
HRMS calculated for $[C_{19}H_{33}N_3O_3Si +H]^+$ 380.2364; found: 380.2374;

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 0.02 (s, 6H), 0.86 (s, 9H), 1.49-1.74 (m, 4H), 2.22 (bs, 1H), 3.21 (bs, 2H), 3.41-3.64 (m, 4H), 4.50-4.55 (m, 2H), 7.27 (s, 5H);

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ -5.30, 18.30, 24.35, 25.14, 25.73, 25.96, 27, 27.57, 51.48, 51.58, 63.73, 63.83, 72.14, 72.39, 72.73, 72.83, 78.14, 78.37, 127.77, 127.85, 127.90, 127.97, 128.43, 128.46, 138.22, 138.28.

(2*S*)-6-Azido-3-(benzyloxy)-1-((tert-butyldimethylsilyl)oxy)hexan-2-yl methanesulfonate (3)

To a stirred solution of hydroxy lactone **13** (0.1 g, 0.26 mmol) in dry DCM (10 mL)



was added Et_3N (0.073 mL, 0.52 mmol) at 0 ^oC followed by dropwise addition of mesyl chloride (0.026 mL, 0.32 mmol) and finally DMAP (cat.) was added. The reaction mixture was stirred at 0 ^oC for 6 h under nitrogen atmosphere. The reaction mixture was diluted with DCM (10 mL) and washed with saturated solution of sodium bicarbonate (20 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography using 5% ethyl acetate/ Pet. ether to give *O*-mesyl compound **3** (0.11 g, 92%) as colorless syrup.

Chemical Formula: $C_{20}H_{35}N_3O_5Ssi$;

Yield: 92%;

IR ($CHCl_3$, cm^{-1}) : 2930, 2858, 2097, 1463, 1359, 1176;

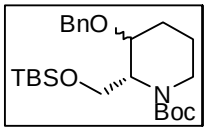
ESIMS (*m/z*): 480.2 $(M+Na)^+$;

HRMS calculated for $[C_{20}H_{35}N_3O_5SSi + Na]^+$ 480.1959; found: 480.1973;

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ -0.02 (s, 3H), 0.00 (s, 3H), 0.81 (s, 9H), 1.39 (m, 4H), 2.91 (s, 1H), 2.95 (s, 2H), 3.08-3.17 (m, 2H), 3.57 (s, 1H), 3.60-3.83 (m, 3H), 4.44-4.57 (m, 2H), 7.23 (s, 5H);

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ -5.40, 18.31, 25.02, 25.89, 26.85, 27.16, 38.23, 38.58, 51.19, 51.99, 72.52, 72.94, 77.18, 77.38, 83.63, 128.05, 128.17, 128.28, 128.51, 137.47, 137.60.

(2*R*)-*tert*-Butyl 3-(benzyloxy)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)piperidine-1-carboxylate (14)



To the solution of azido derivative **3** (0.250 g, 0.546 mmol) in benzene: H_2O (20 mL, 9:1) was added triphenyl phosphine (0.17 g, 0.65 mmol) and the reaction mixture was stirred at 80 ^oC for 8 h. After completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure to afford crude amine which without purification was subjected for the next reaction. To the crude reaction mass in THF (20 mL) was added triethyl amine (0.157 mL) and $(Boc)_2O$ (0.178 mL) followed by addition of DMAP in (cat.) at 0 ^oC and the reaction mixture was left to stir for 12 h at room temperature. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water and extracted with ethyl acetate (3 X 20 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography in 10% ethyl acetate in pet. ether to give cyclized compound **14** (0.118 g, 50%) as colorless thick syrup. Further elution afforded non-cyclized compound **14a**.

Chemical Formula: $C_{24}H_{41}NO_4Si$;

Molecular Weight: 435.67214;

Yield: 50%;

IR ($CHCl_3$, cm^{-1}) : 2930, 2857, 1694, 1417, 1364, 1252, 1107;

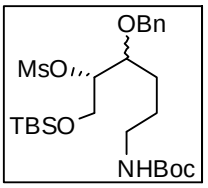
ESIMS (*m/z*) : 458.32$(M+Na)^+$;

HRMS calculated for $[C_{24}H_{41}NO_4Si + H]^+$ 436.2878; found: 436.2886;

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 0.06 (s, 6H), 0.88 (s, 4.5 H), 0.90 (s, 4.5 H), 1.46 (s, 9H), 1.53-1.57 (m, 1H), 1.73-1.99 (m, 3H), 2.81 (bs, 1H), 3.49-3.75 (m, 2H), 3.81-4.00 (m, 2H), 4.44-4.67 (m, 3H), 7.31-7.39 (m, 5H);

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ -5.35, -5.27, 18.22, 18.33, 19.48, 25.92, 26.04, 28.54, 58.23, 61.16, 69.98, 70.56, 71.12, 75.49, 79.22, 127.31, 127.46, 128.23, 128.37, 138.47, 138.85, 155.08, 155.39.

(6*S*)-7-(Benzyloxy)-2,2,3,3,14,14-hexamethyl-12-oxo-4,13-dioxa-11-aza-3-silapentadecan-6-yl methanesulfonate (14a)



Chemical Formula: $C_{25}H_{45}NO_7SSi$

Molecular Weight: 531.7778

Yield: 10%;

IR ($CHCl_3$, cm^{-1}): 2930, 2857, 1695, 1463, 1359;

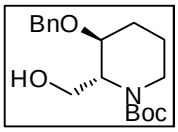
ESIMS (*m/z*) : 554.3 $(M+Na)^+$;

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.45 (s, 9H), 1.48-1.62 (m, 5H), 3.01 (s, 3H), 3.05-3.16 (m, 2H), 3.65-3.92 (m, 3H), 4.52-4.68 (m, 3H), 7.29-7.37 (m, 5H);

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ -5.34, 25.9, 26.9, 28.5, 38.3, 40.3, 62.2, 72.9, 83.8, 128.0, 128.2, 128.5, 137.8, 155.8.

(2*R*,3*S*)-*tert*-Butyl 3-(benzyloxy)-2-(hydroxymethyl)piperidine-1-carboxylate (16)

To a solution of carbamate **14** (0.100 g, 0.229 mmol) in anhydrous THF (5 mL) was added TBAB (0.46 mL, 0.46 mmol, 1M in THF) at 0 ^oC under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3 h. After completion of reaction (monitored by TLC), the reaction mixture was cooled to 0 ^oC and quenched with cold saturated solution of ammonium chloride (30 mL). The reaction mixture was extracted with ethyl acetate (3 X 10 mL). The organic layer was separated and combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography using 15% ethyl acetate in pet ether to give separable diastereomeric mixture of alcohols **15** and **16** (0.059 g, 80%, *dr* 6:4) as colorless thick syrup.



Chemical Formula: $C_{18}H_{27}NO_4$

Molecular Weight: 321.41128

Yield: 24 mg; 33%;

$[\alpha]_D^{25}$: -37.5 (c 0.5, $CHCl_3$); lit.[4] for *ent*-**16** **$[\alpha]_D^{20}$** +39.5 (c: 1.73, $CHCl_3$);

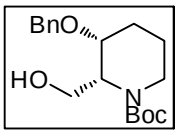
ESIMS (*m/z*): 344.19 $(M+Na)^+$;

HRMS calculated for $[C_{18}H_{27}NO_4 +H]^+$ 322.2013; found: 322.2008;

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4): δ 1.36-1.40 (m, 1H), 1.44 (s, 9H), 1.54-1.58 (m, 2H), 1.87 (m, 1H), 2.81-2.92 (m, 1H), 3.53 (bs, 1H), 3.56-3.64 (m, 1H), 3.70-3.76 (m, 1H), 3.95 (bs, 1H), 4.47 (d, J = 12 Hz, 2H), 4.61 (d, J = 12 Hz, 1H), 7.22-7.30 (m, 5H);

^{13}C (125 MHz, $CDCl_3$ + CCl_4): δ 19.7, 25.5, 28.5, 39.7, 55.8, 60.9, 70.2, 71.5, 79.9, 127.5, 128.3, 138.6.

(2*R*,3*R*)-*tert*-Butyl 3-(benzyloxy)-2-(hydroxymethyl)piperidine-1-carboxylate (15)



Chemical Formula: $C_{18}H_{27}NO_4$;

Yield: 35.4 mg; 47%;

$[\alpha]_D^{25}$: -17.5 (c 0.8, $CHCl_3$); lit.[4] for *ent*-**15** **$[\alpha]_D^{20}$** +16.7 (*c*: 1.31, $CHCl_3$),

IR ($CHCl_3$, cm^{-1}): 3448, 2934, 1686, 1670, 1420, 1157;

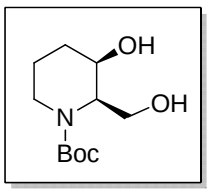
ESIMS (*m/z*): 344.19 (Na+);

HRMS calculated for $[C_{18}H_{27}NO_4 +H]^+$ 322.2013; found: 322.2008;

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 1.35-1.44 (m, 1H), 1.47 (s, 9H), 1.55-1.63 (m, 1H), 1.68-1.71 (m, 1H), 1.97 (bs, 1H), 2.22 (bs, 1H), 2.75 (bs, 1H), 3.61-3.67 (m, 1H), 3.73 (bs, 1H), 3.91 (bs, 1H), 4.02-4.06 (m, 1H), 4.61 (s, 3H), 7.27-7.37 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 23.9, 25.9, 28.5, 53.4, 59.1, 70.9, 76.5, 80.1, 127.6, 127.8, 128.5, 137.9.

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



To a solution of **15** (0.1 g, 0.23 mmol) in MeOH:AcOH (9:1, 5 mL) was added 10% Pd/C (0.03 g) and vigorously shaken under H_2 atmosphere for 4 hours at ambient temperature. The mixture was then filtered through a pad of celite and concentrated *in*

vacuo. Purification by column chromatography over silica gel (pet ether-ethyl acetate, 2:3) gave diol **1** (61 mg, 85%) as a white solid.

Chemical Formula: $C_{11}H_{21}NO_4$;

Molecular Weight: 231.2887;

M.P: 115-117 ^{o}C, lit.[4] 114-116 ^{o}C;

Yield: 85%;

$[\alpha]_D^{25}$: -24 (c 0.7, MeOH); lit.[4] for *ent*-**1** **$[\alpha]_D^{20}$** +23.1 (*c*: 1.03, MeOH);

IR ($CHCl_3$, cm^{-1}): 3448, 2934, 1686;

ESIMS (*m/z*): 232.3 $(M+H)^+$;

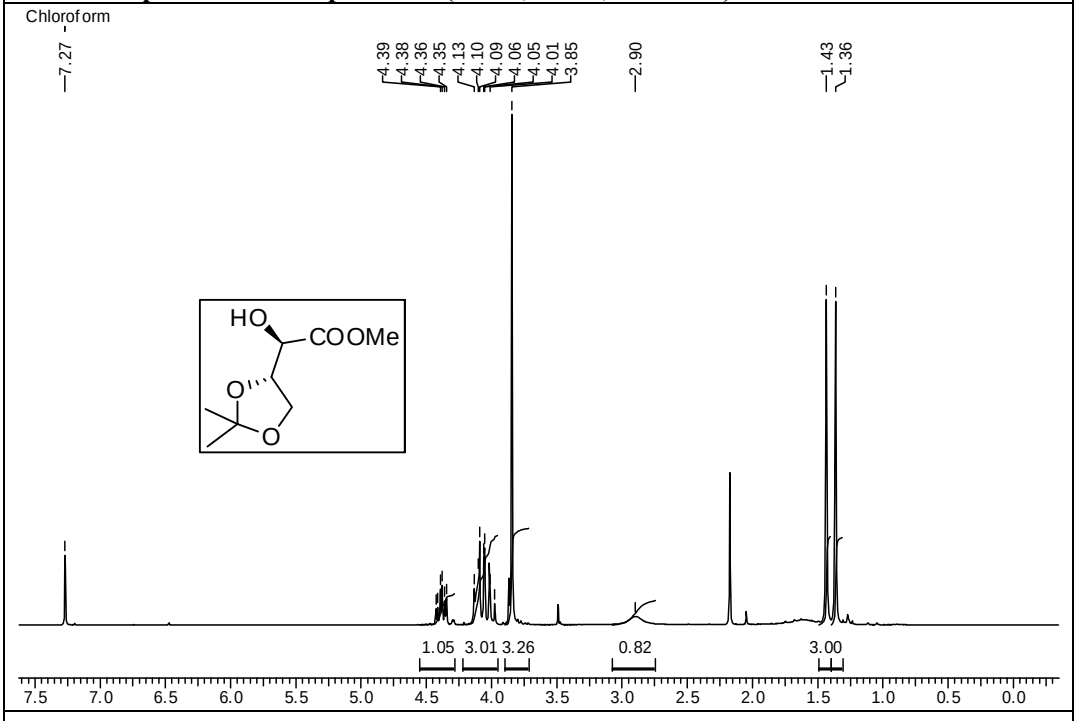
HRMS (CI+) calcd. For $C_{11}H_{21}NO_4$: 231.1470; found: 231.1484;

^{1}H NMR (400 MHz, $CDCl_3$): δ δ 1.48 (s, 9H), 1.59-1.82 (m, 4H), 2.89 (br s, 1H), 3.68-3.80 (m, 2H), 3.92-4.01 (m, 1H), 4.11 (dd, J = 6.0 & 11.0 Hz, 1H), 4.25-4.34 (m, 1H);

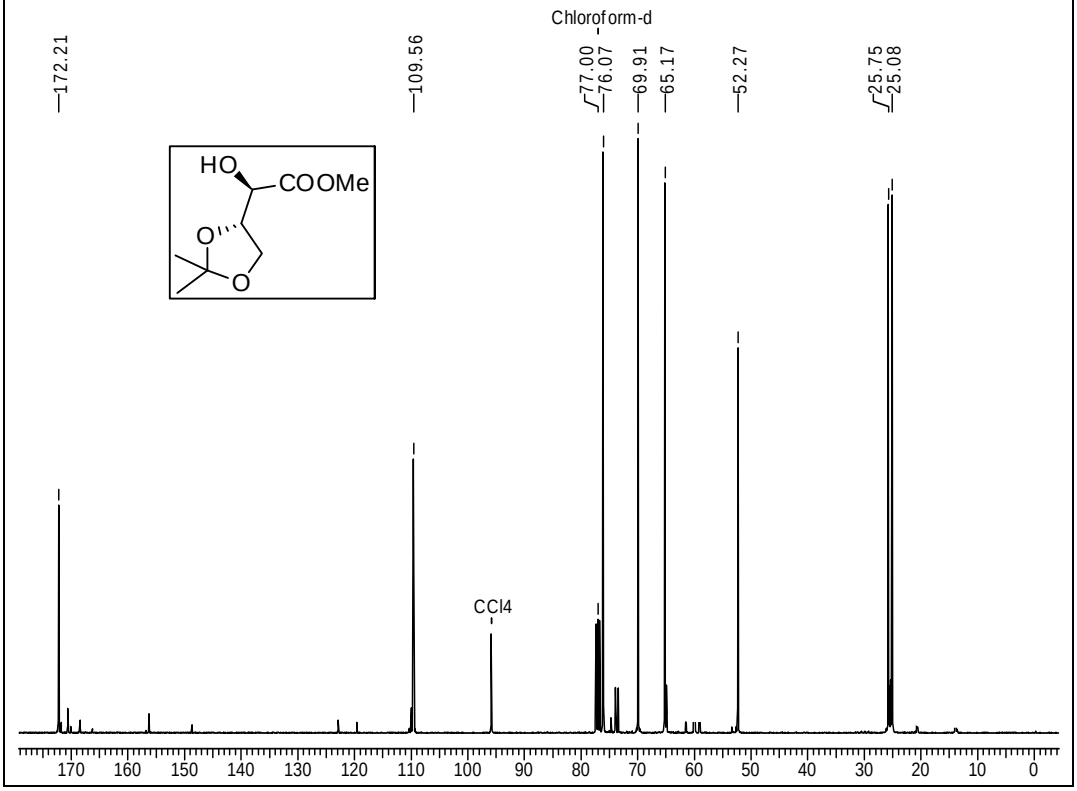
^{13}C NMR (100 MHz, $CDCl_3$): δ 23.7, 28.2, 28.3, 39.5, 55.9, 59.2, 69.3, 80.3, 155.6.

2.3.4. Spectra

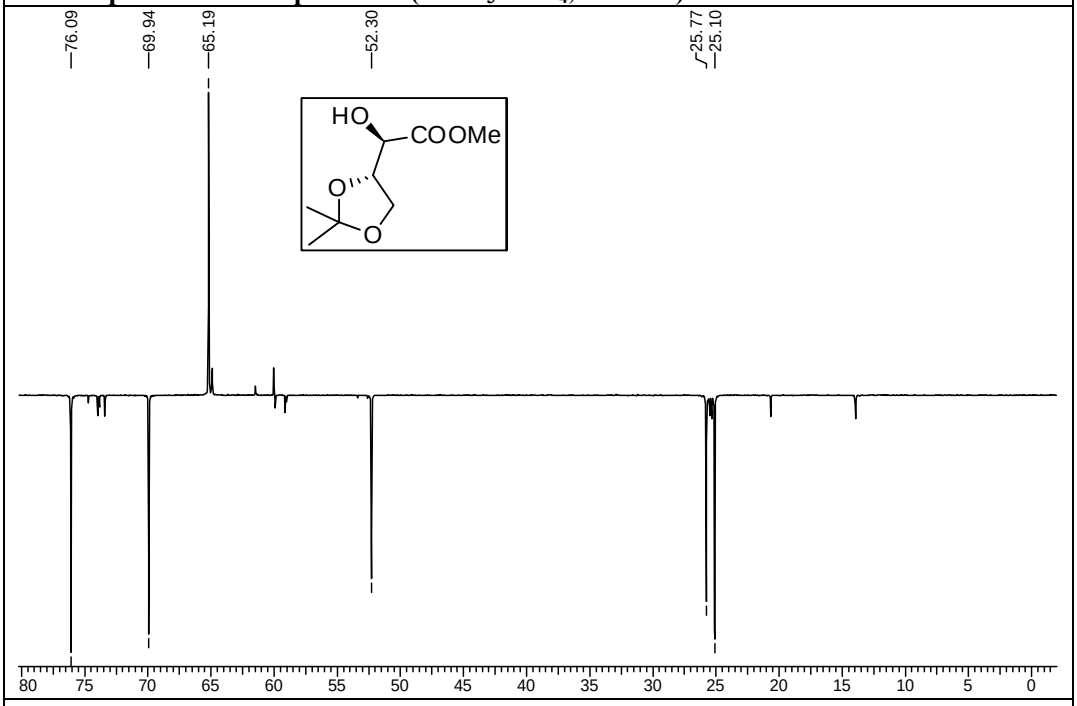
^{1}H NMR Spectrum of compound 6a ($CDCl_3$+CCl_4, 200 MHz)



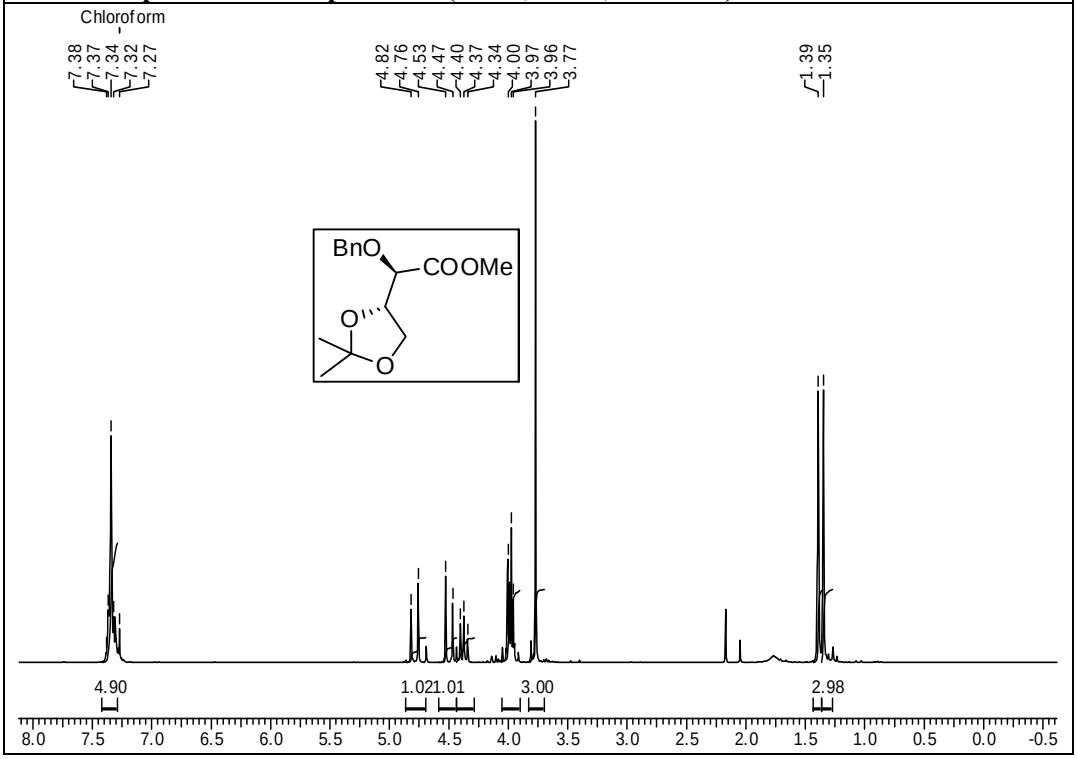
^{13}C NMR Spectrum of compound 6a ($CDCl_3$+CCl_4, 50 MHz)



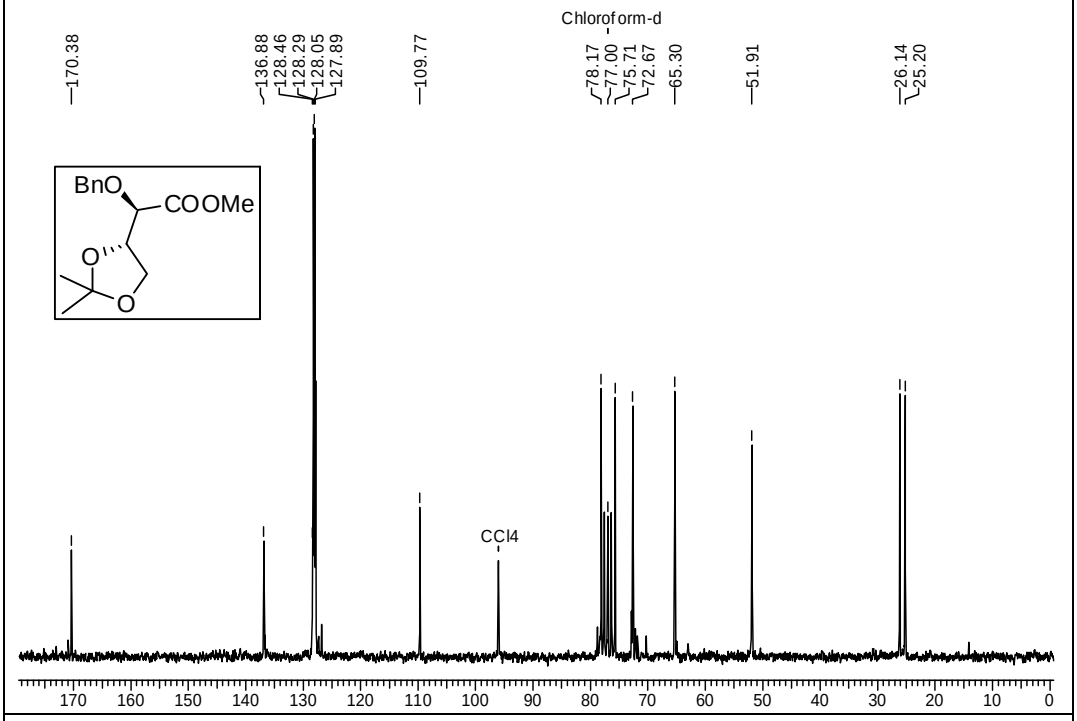
DEPT spectrum of compound 6a ($CDCl_3$+CCl_4, 50 MHz)



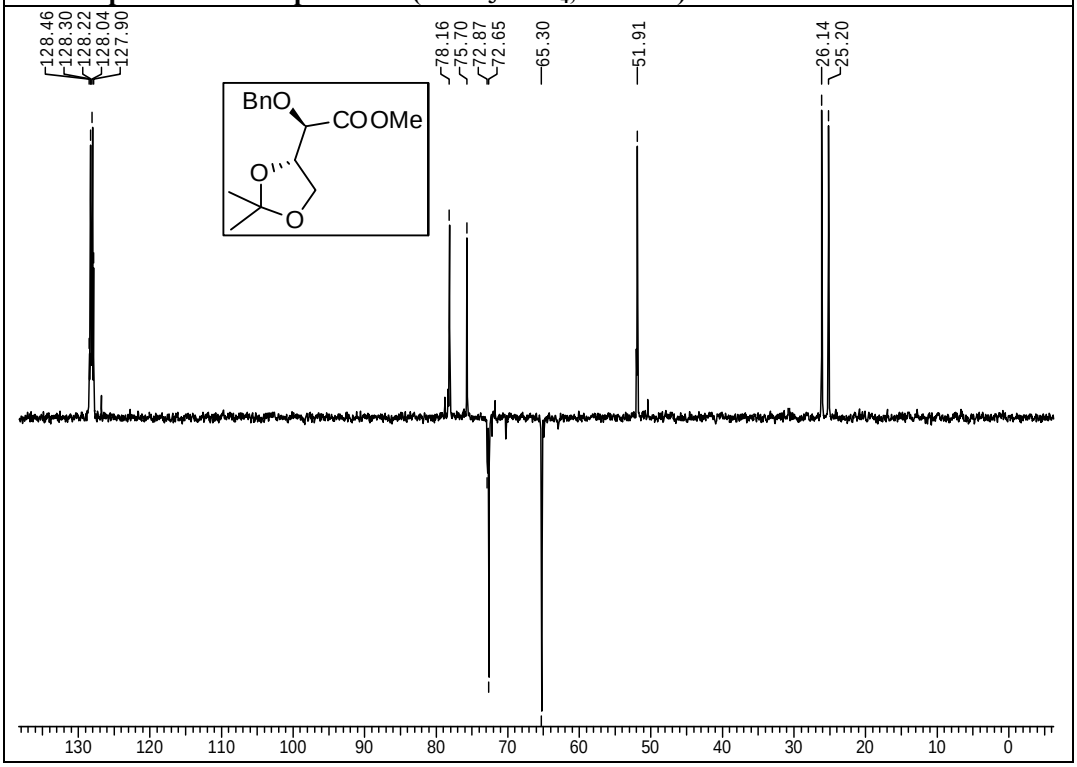
^{1}H NMR Spectrum of compound 6b ($CDCl_3$+CCl_4, 200 MHz)



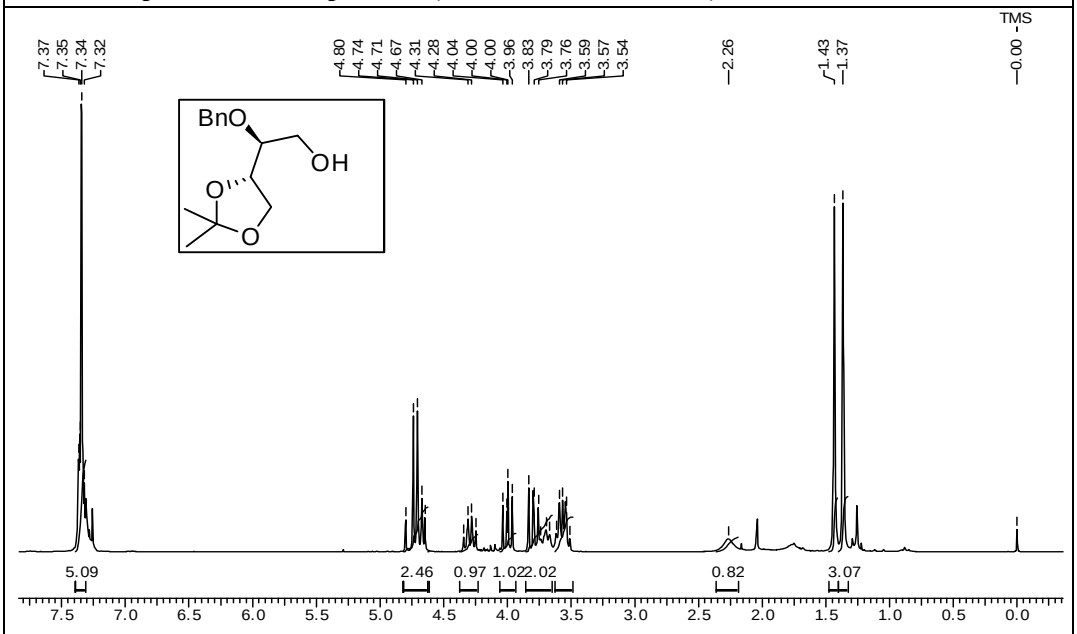
^{13}C NMR Spectrum of compound 6b ($CDCl_3$+CCl_4, 50 MHz)



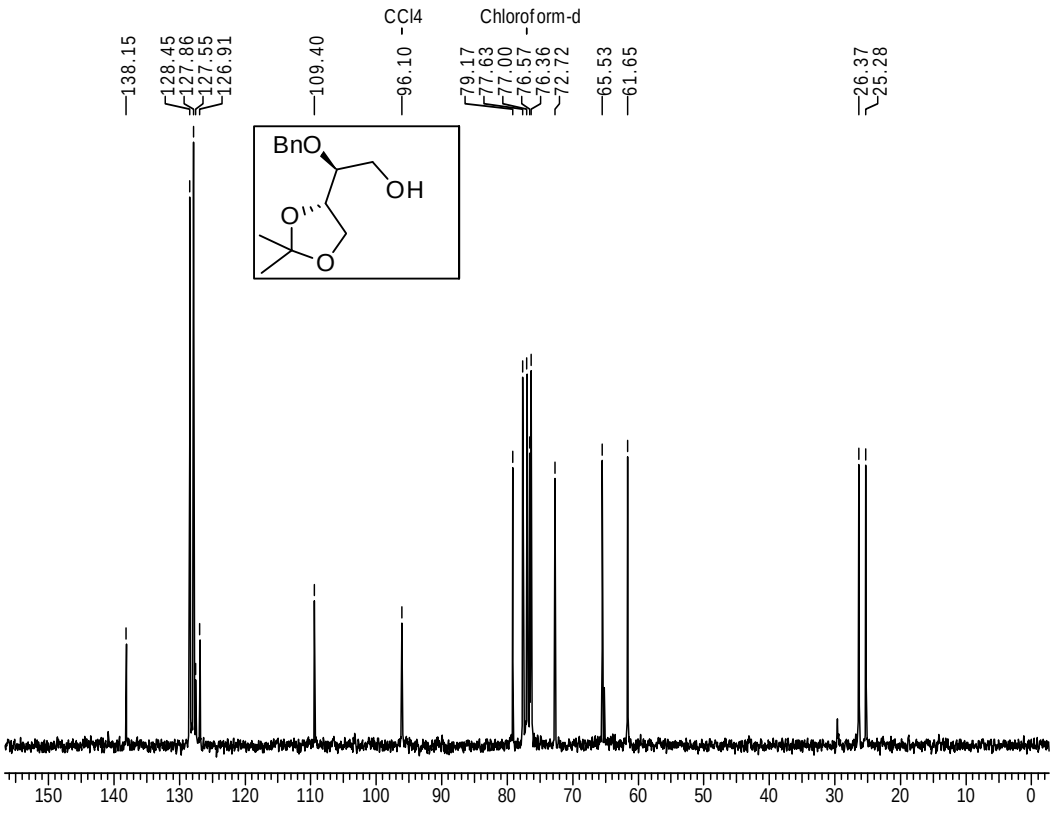
DEPT spectrum of compound 6b ($CDCl_3$+CCl_4, 50 MHz)



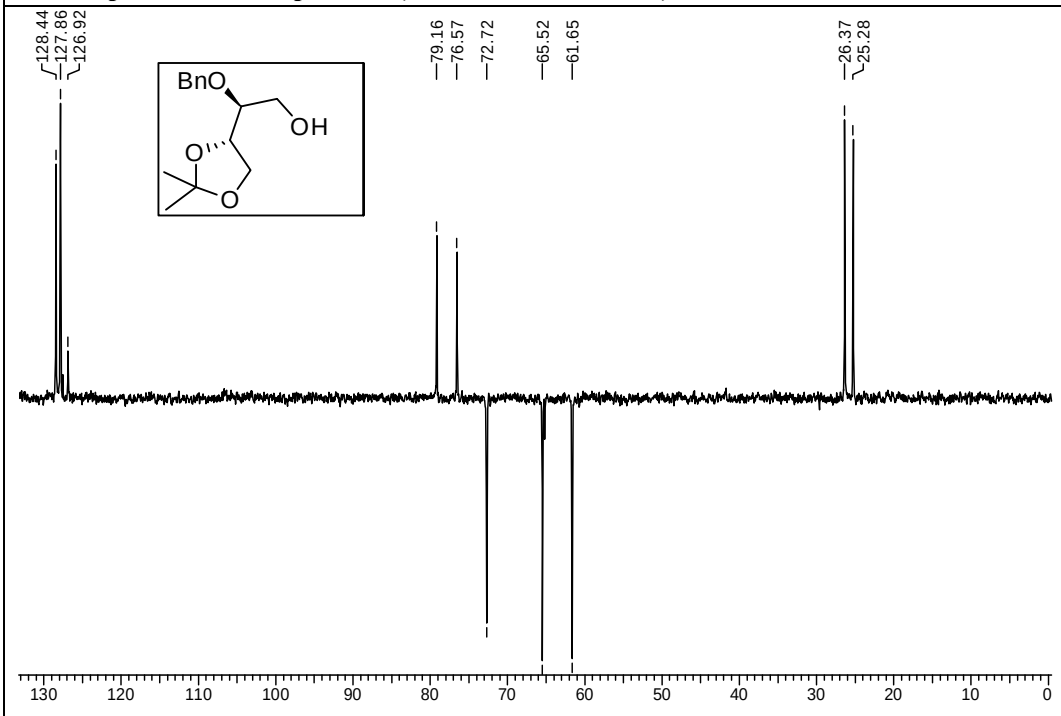
^{1}H NMR Spectrum of compound 5 ($CDCl_3$+CCl_4, 200 MHz)



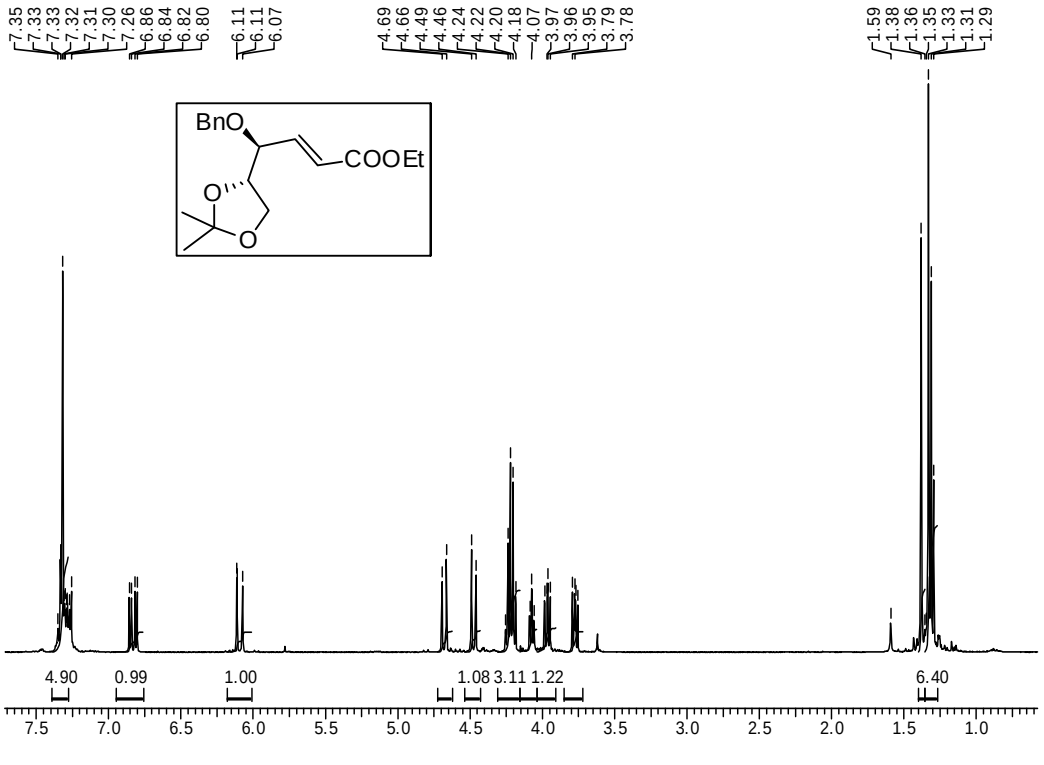
^{13}C NMR Spectrum of compound 5 ($CDCl_3$+CCl_4, 50 MHz)



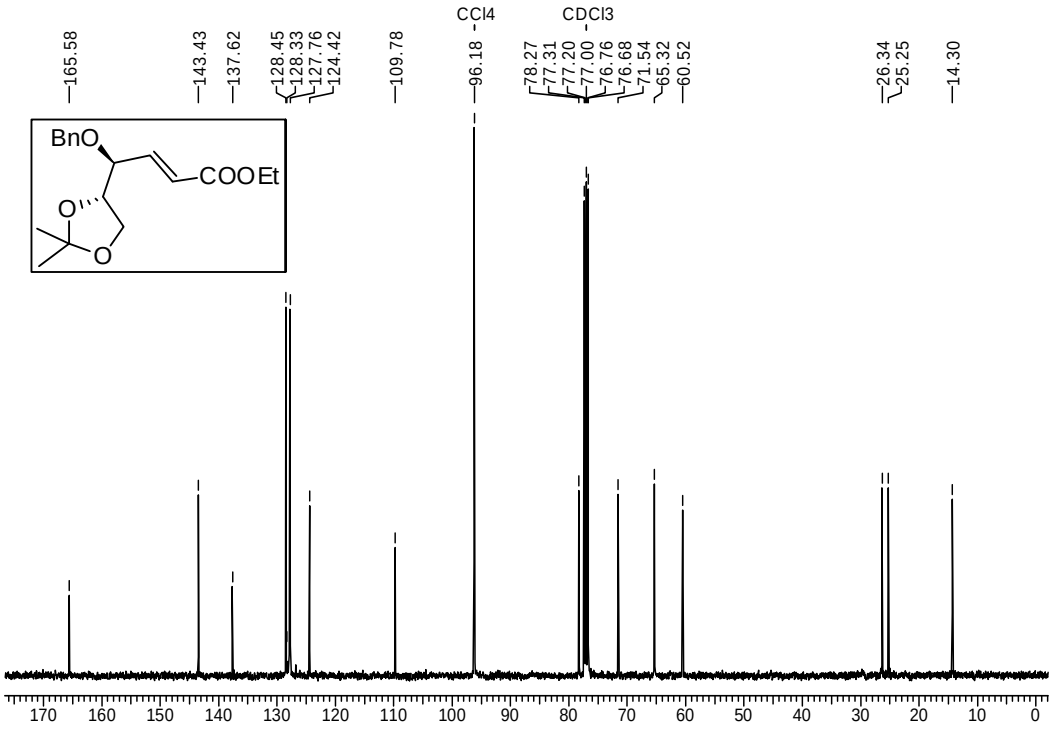
DEPT spectrum of compound 5 ($CDCl_3$+CCl_4, 50 MHz)



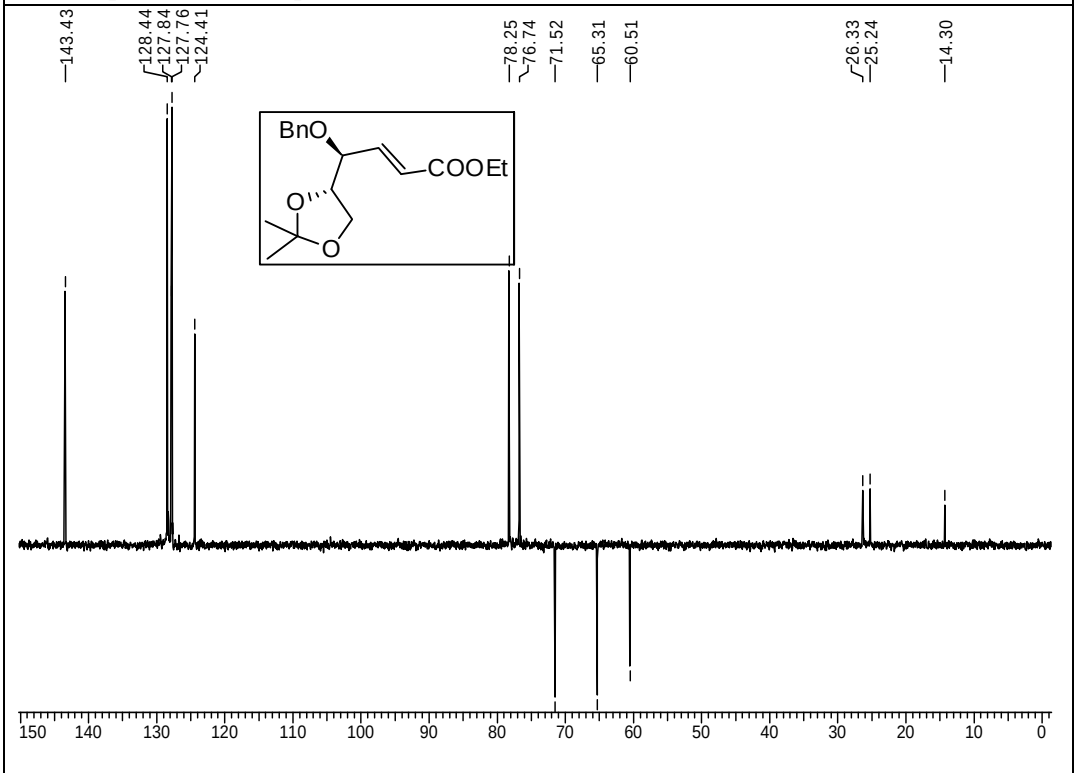
^{1}H NMR Spectrum of compound 8 ($CDCl_3$+CCl_4, 400 MHz)



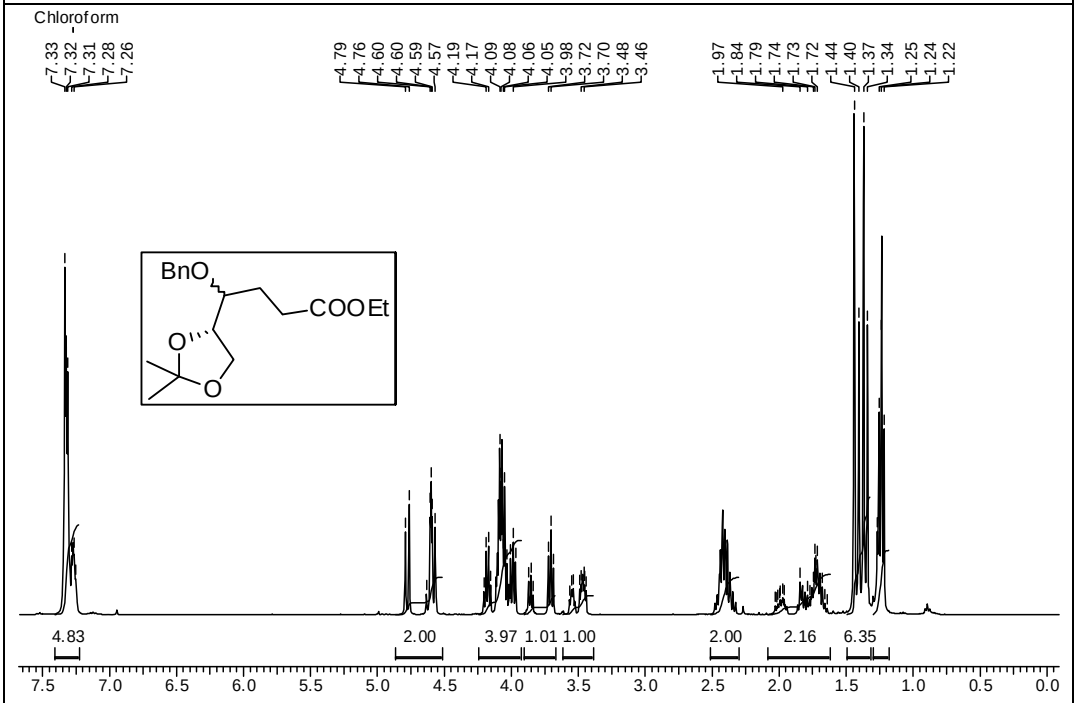
^{13}C NMR Spectrum of compound 8 ($CDCl_3$+CCl_4, 100 MHz)



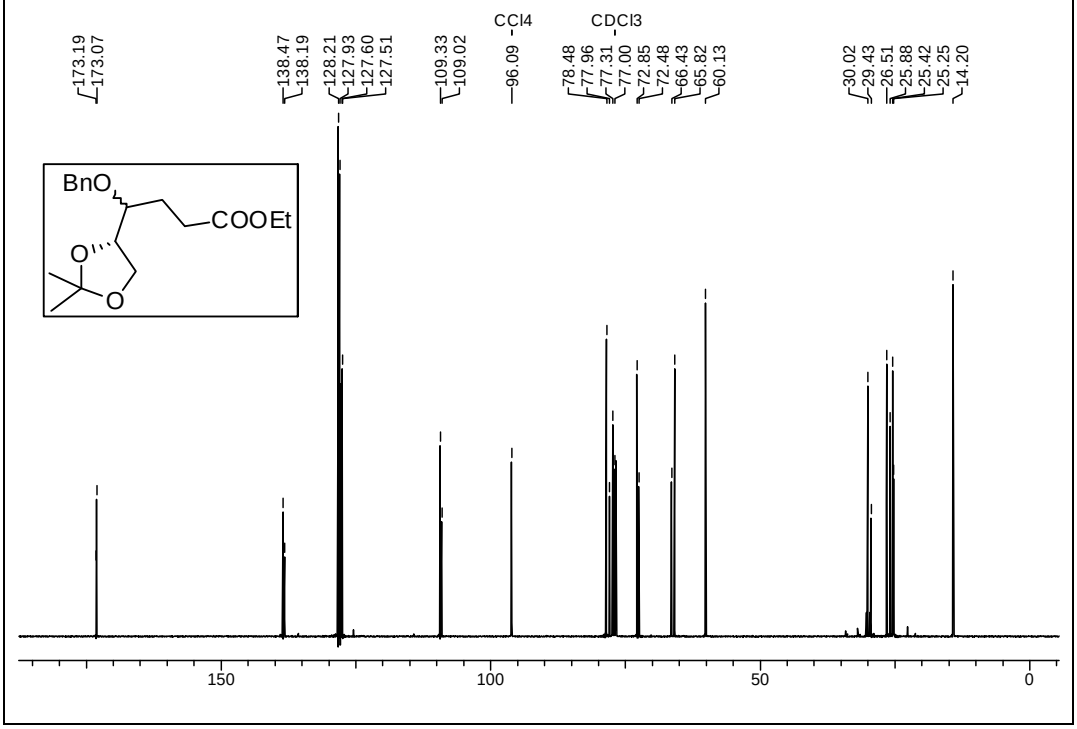
DEPT spectrum of compound 8 ($CDCl_3$+CCl_4, 100 MHz)



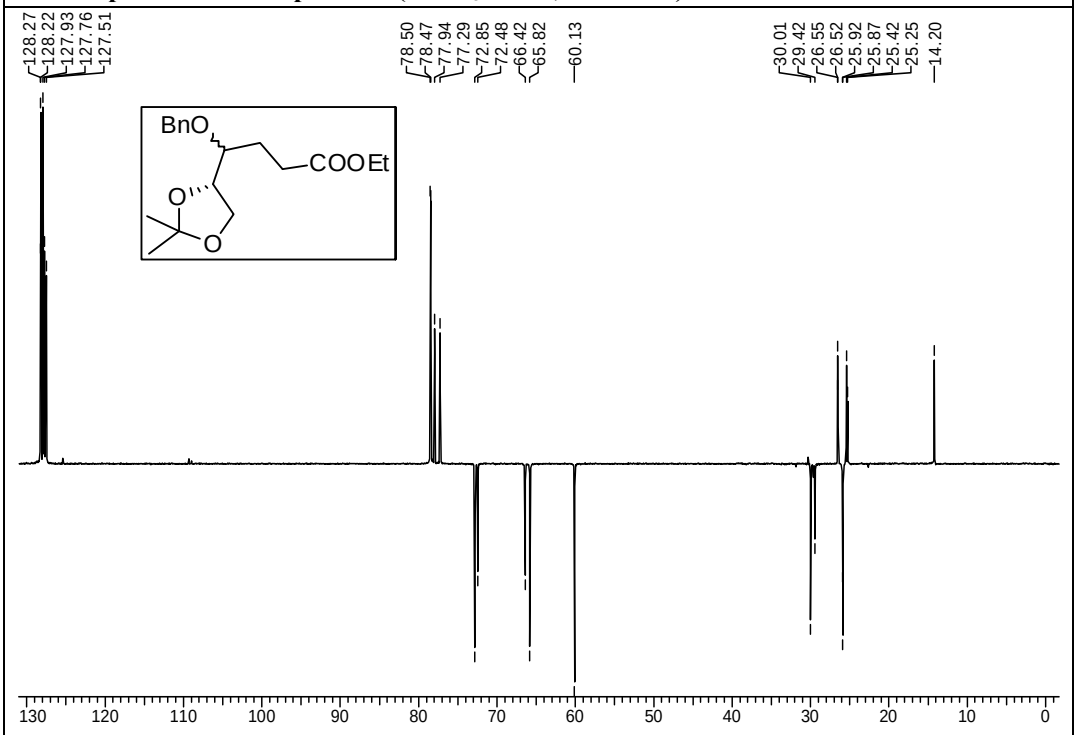
^{1}H NMR Spectrum of compound 4 ($CDCl_3$+CCl_4, 400 MHz)



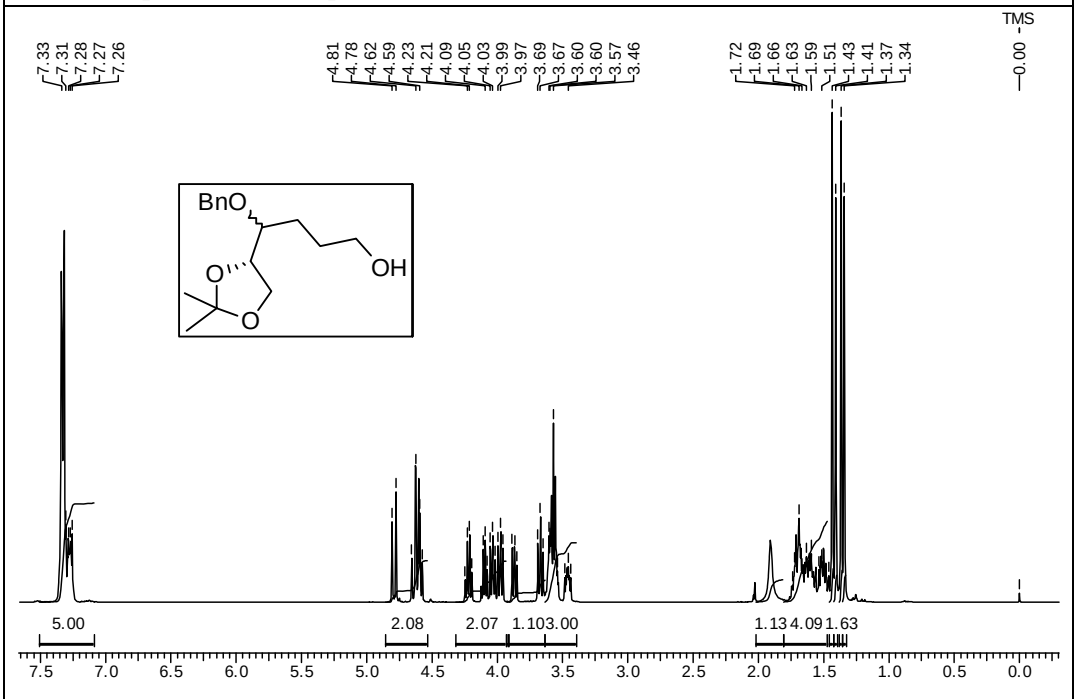
^{13}C NMR Spectrum of compound 4 ($CDCl_3$+CCl_4, 100 MHz)



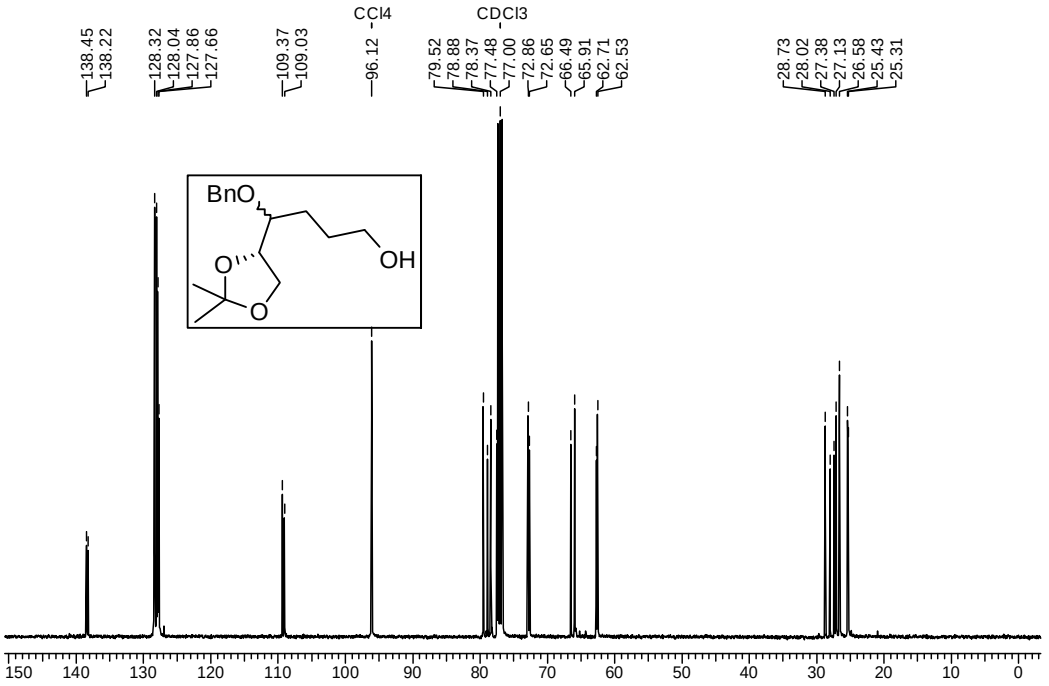
DEPT spectrum of compound 4 ($CDCl_3$+CCl_4, 100 MHz)



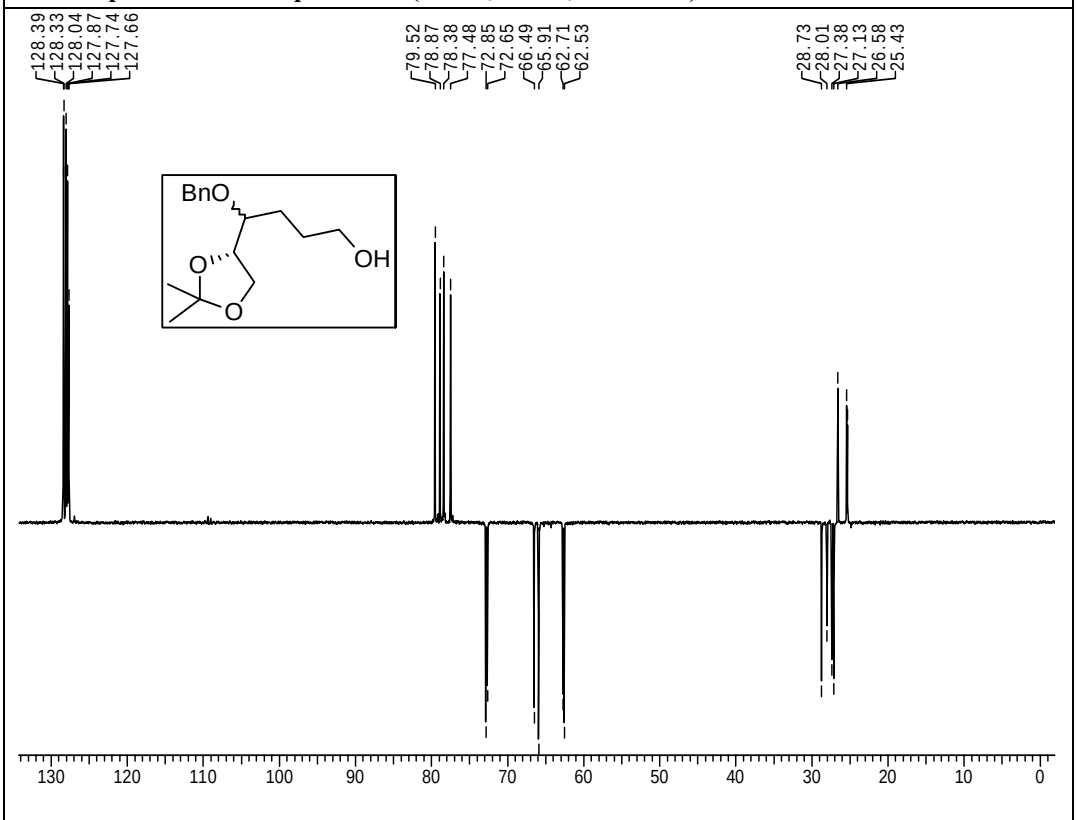
^{1}H NMR Spectrum of compound 10 ($CDCl_3$+CCl_4, 400 MHz)



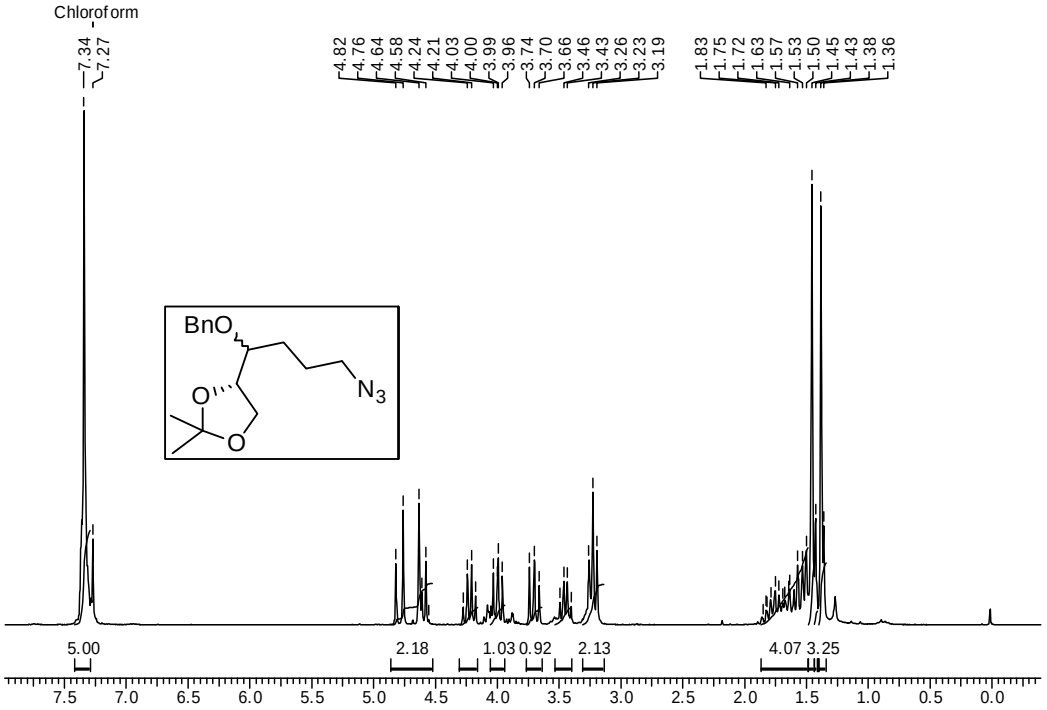
^{13}C NMR Spectrum of compound 10 ($CDCl_3$+CCl_4, 100 MHz)



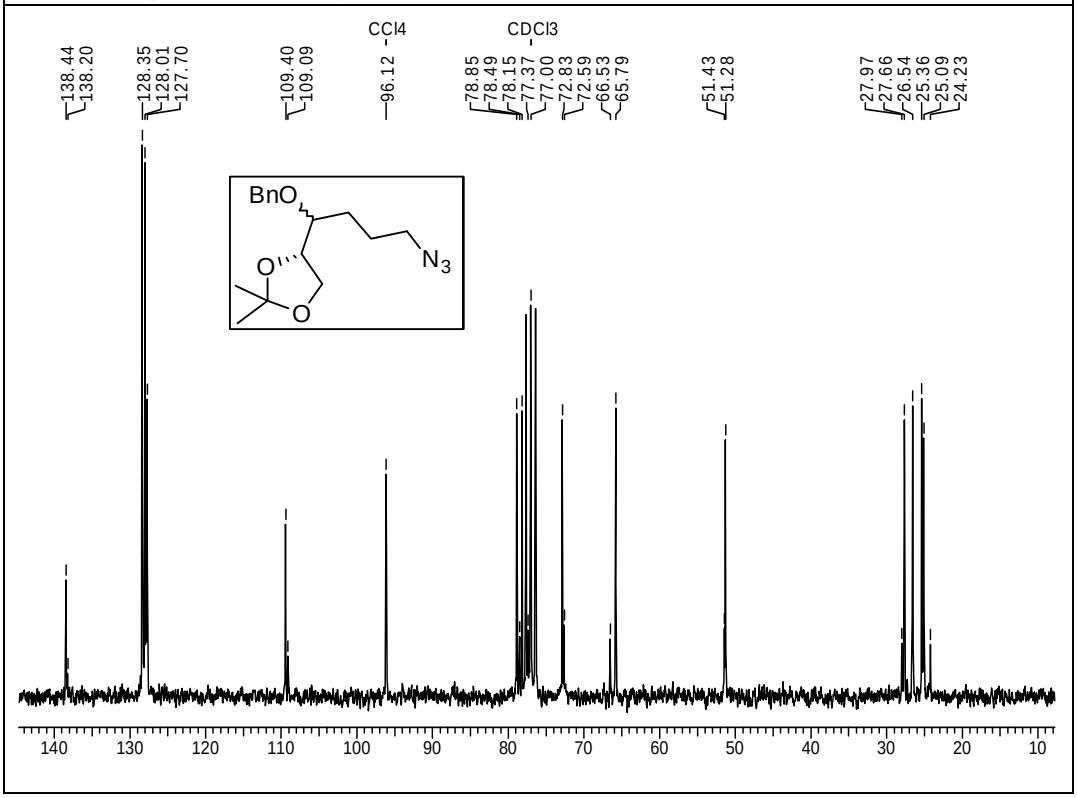
DEPT spectrum of compound 10 ($CDCl_3$+CCl_4, 100 MHz)



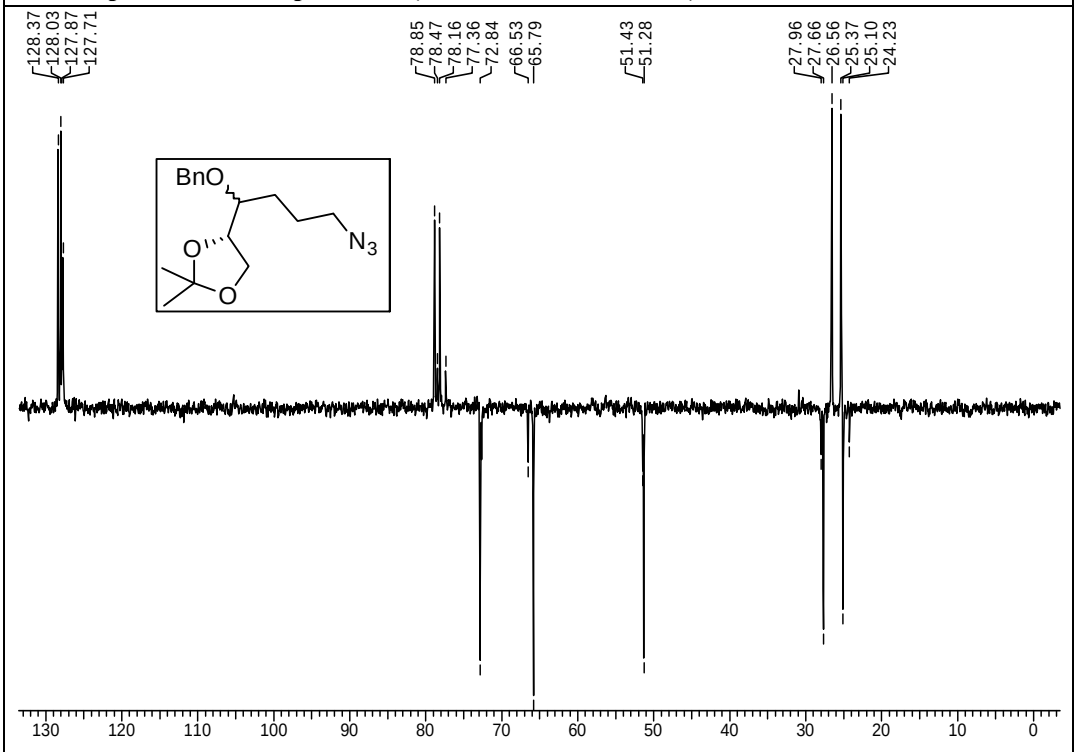
^{1}H NMR Spectrum of compound 11 ($CDCl_3$+CCl_4, 400 MHz)



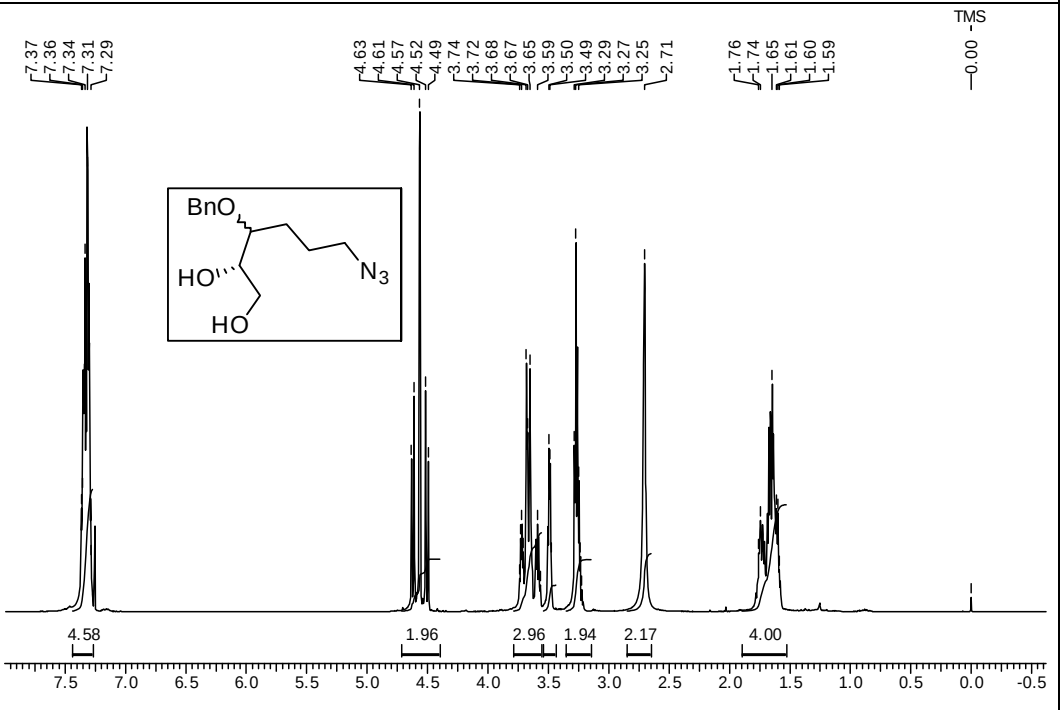
^{13}C NMR Spectrum of compound 11 ($CDCl_3$+CCl_4, 100 MHz)



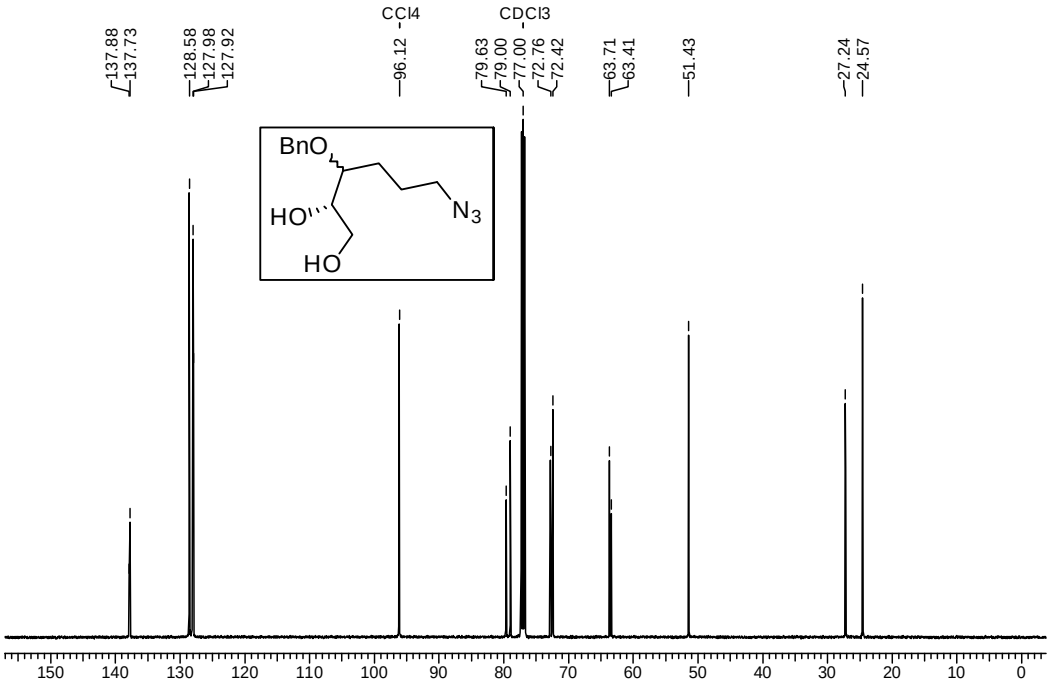
DEPT spectrum of compound 11 ($CDCl_3$+CCl_4, 100 MHz)



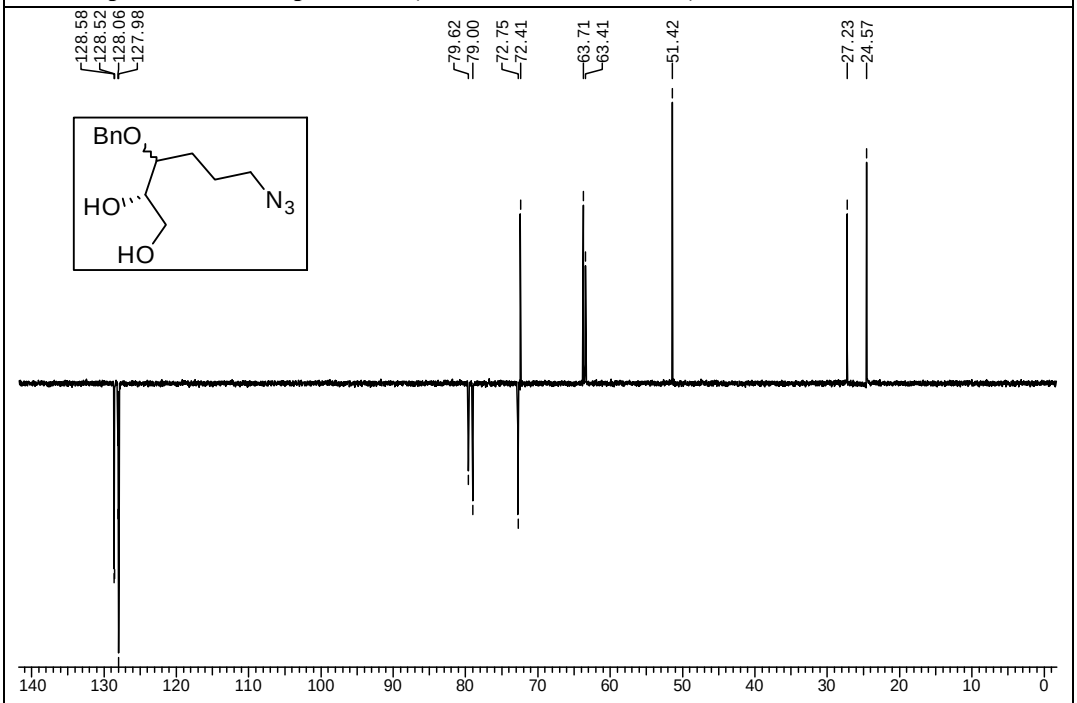
^{1}H NMR Spectrum of compound 12 ($CDCl_3$+CCl_4, 500 MHz)



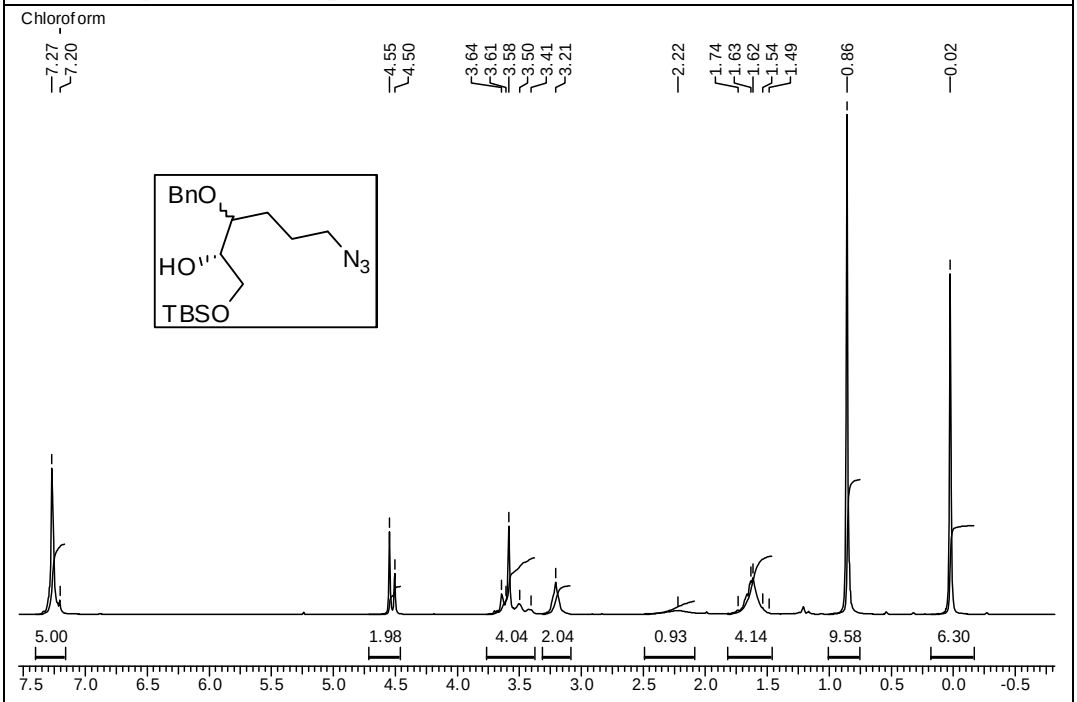
^{13}C NMR Spectrum of compound 12 ($CDCl_3$+CCl_4, 125 MHz)



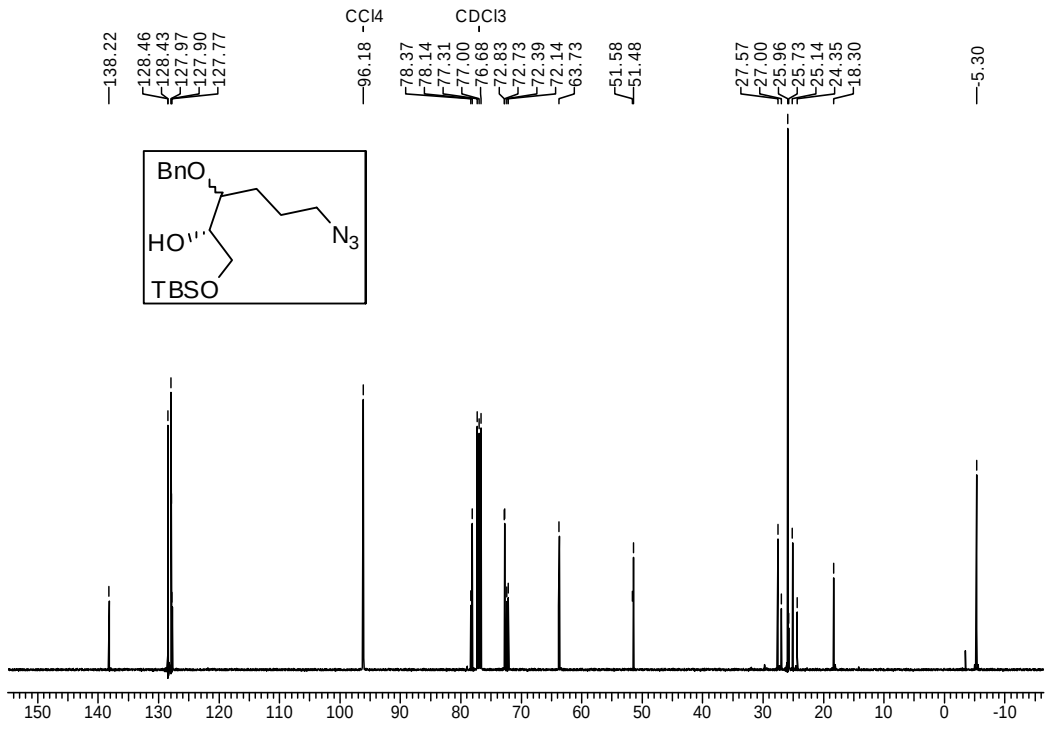
DEPT spectrum of compound 12 ($CDCl_3$+CCl_4, 125 MHz)



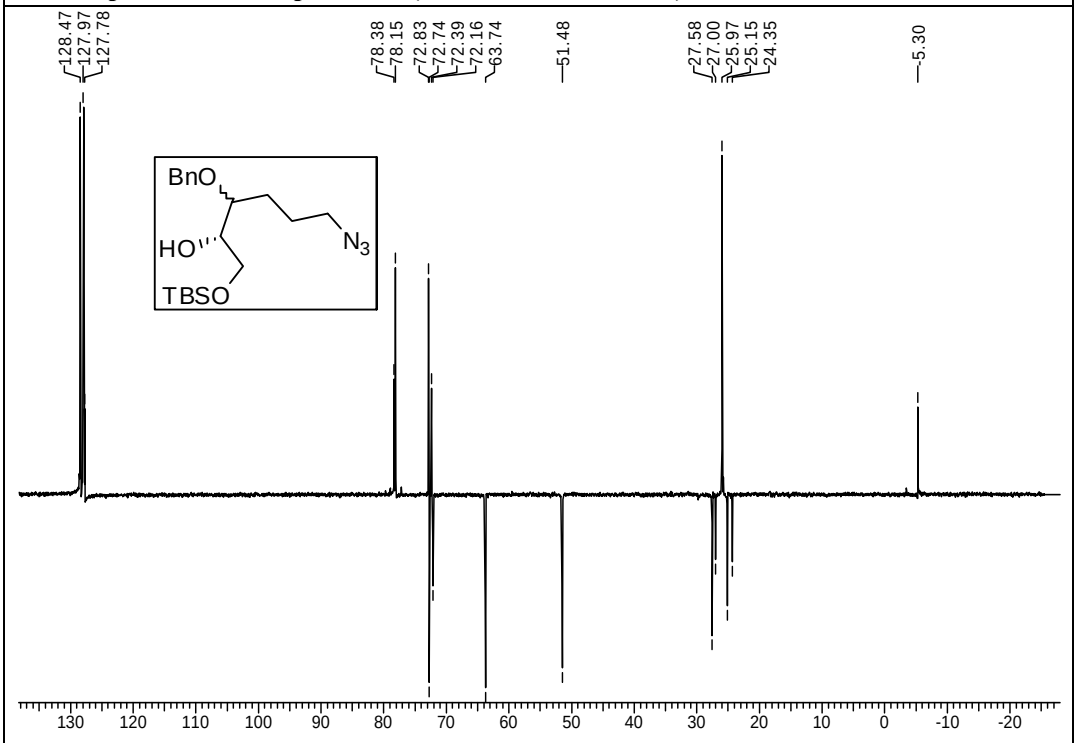
^{1}H NMR Spectrum of compound 13 ($CDCl_3$+CCl_4, 200 MHz)



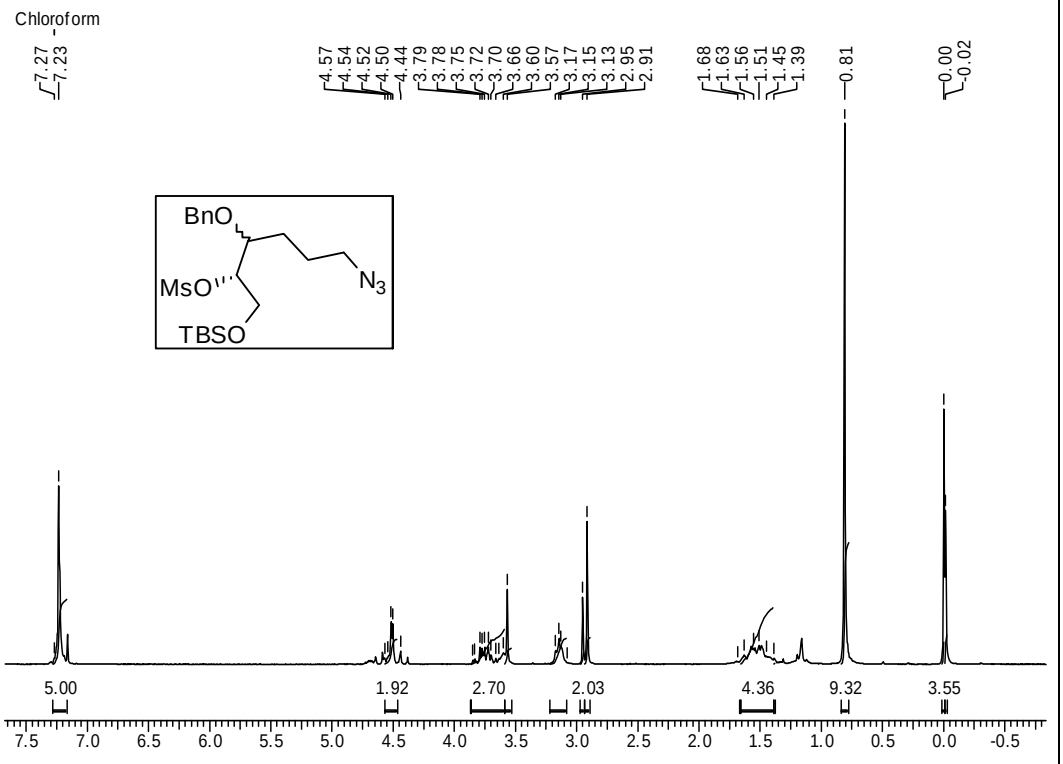
^{13}C NMR Spectrum of compound 13 ($CDCl_3$+CCl_4, 50 MHz)



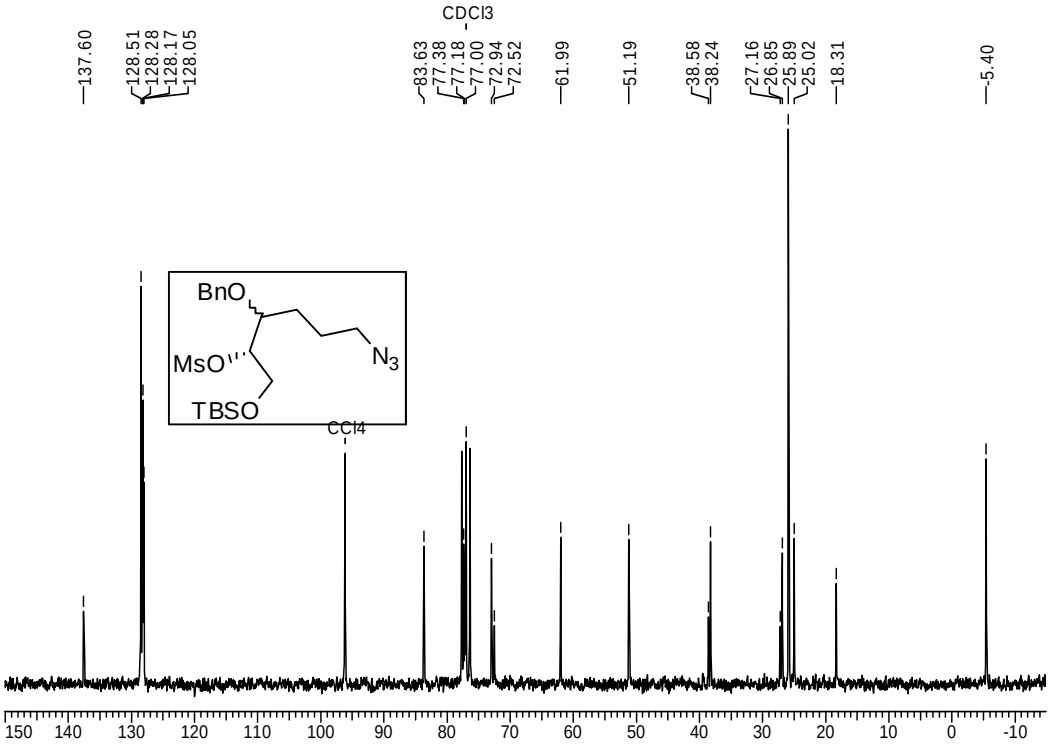
DEPT spectrum of compound 13 ($CDCl_3$+CCl_4, 50 MHz)



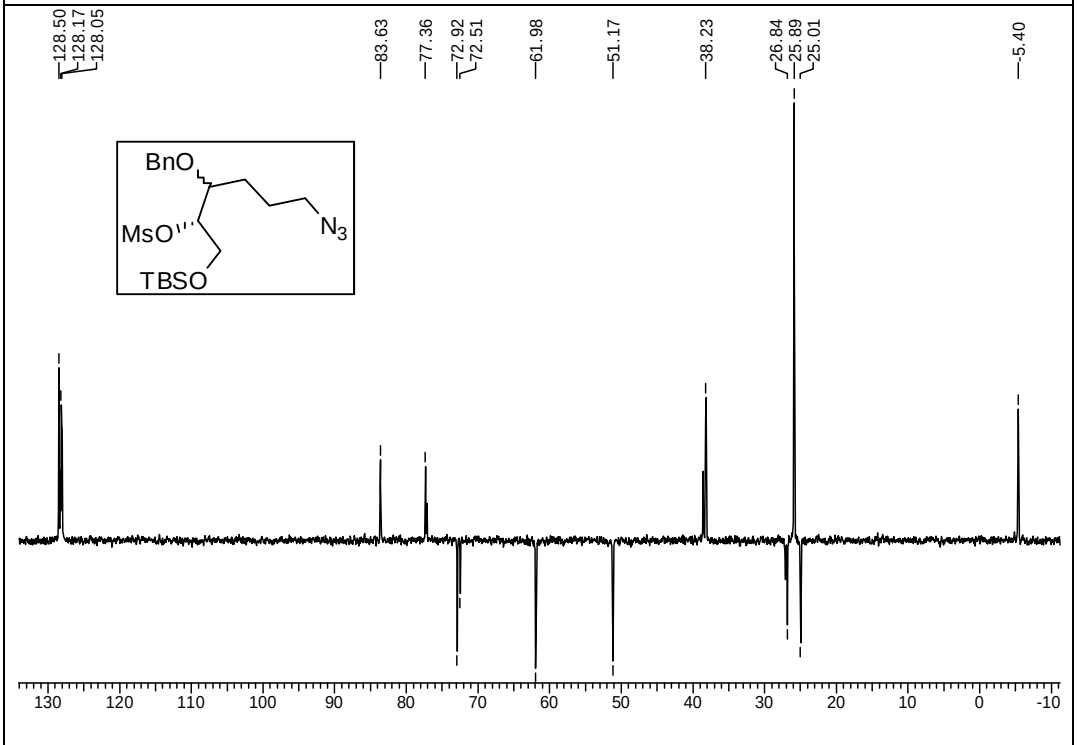
^{1}H NMR Spectrum of compound 3 ($CDCl_3$+CCl_4, 200 MHz)



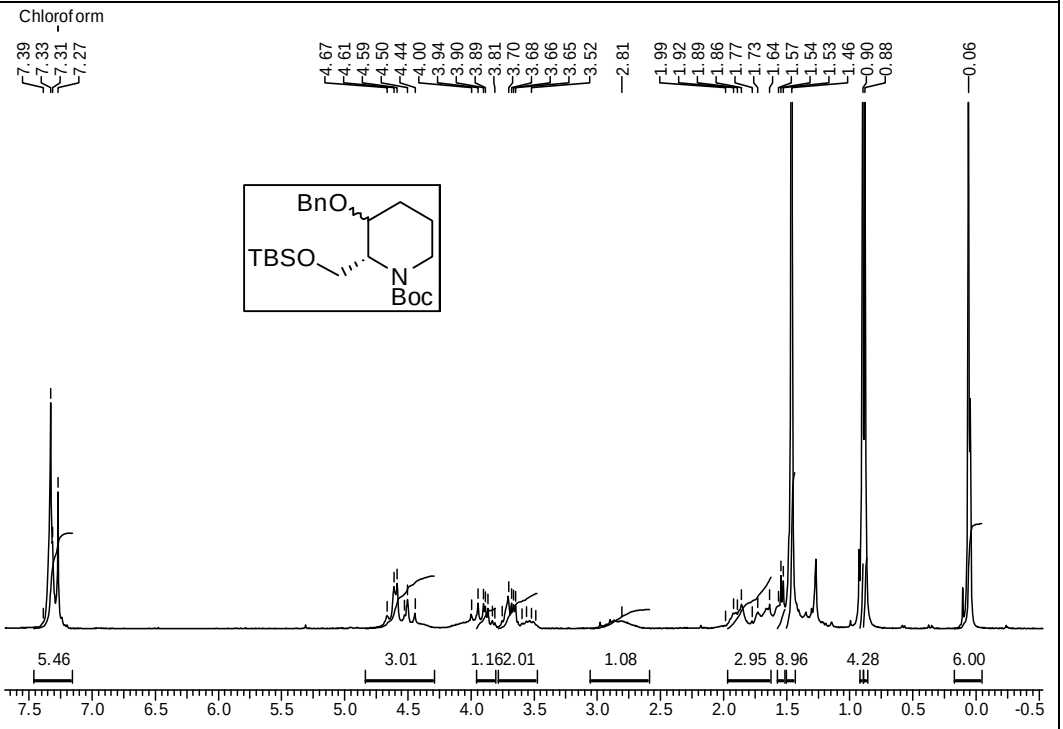
^{13}C NMR Spectrum of compound 3 ($CDCl_3$+CCl_4, 50 MHz)



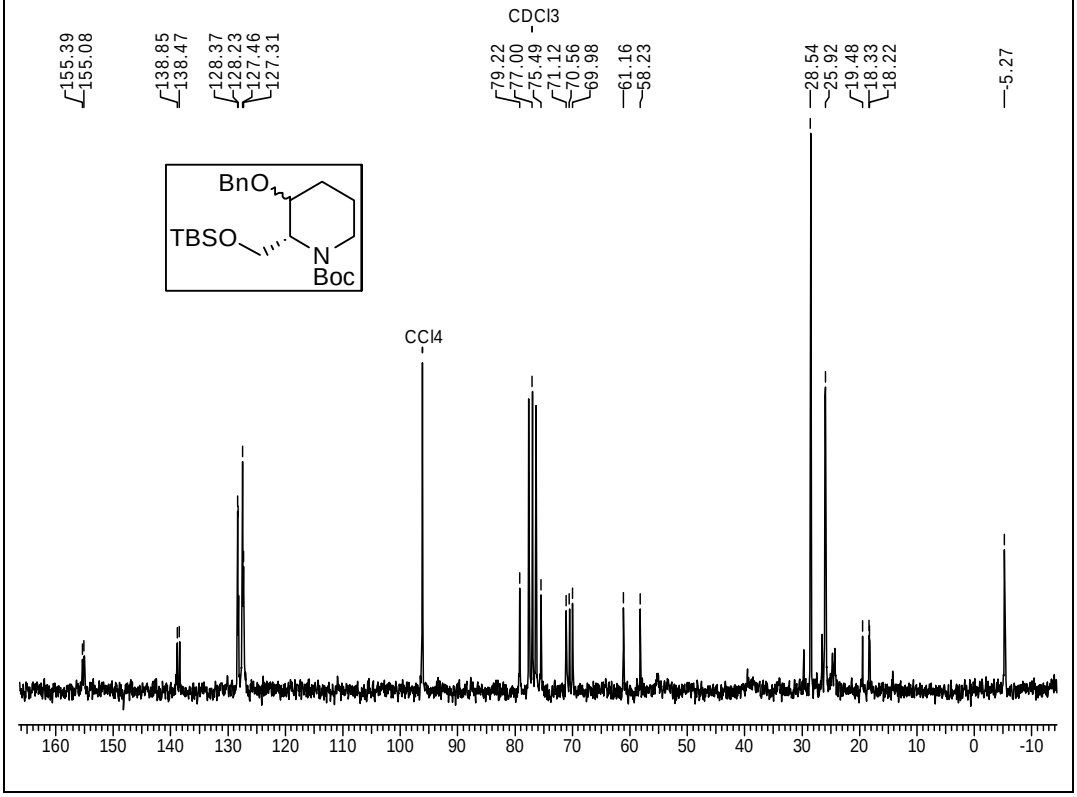
DEPT spectrum of compound 3 ($CDCl_3$+CCl_4, 50 MHz)



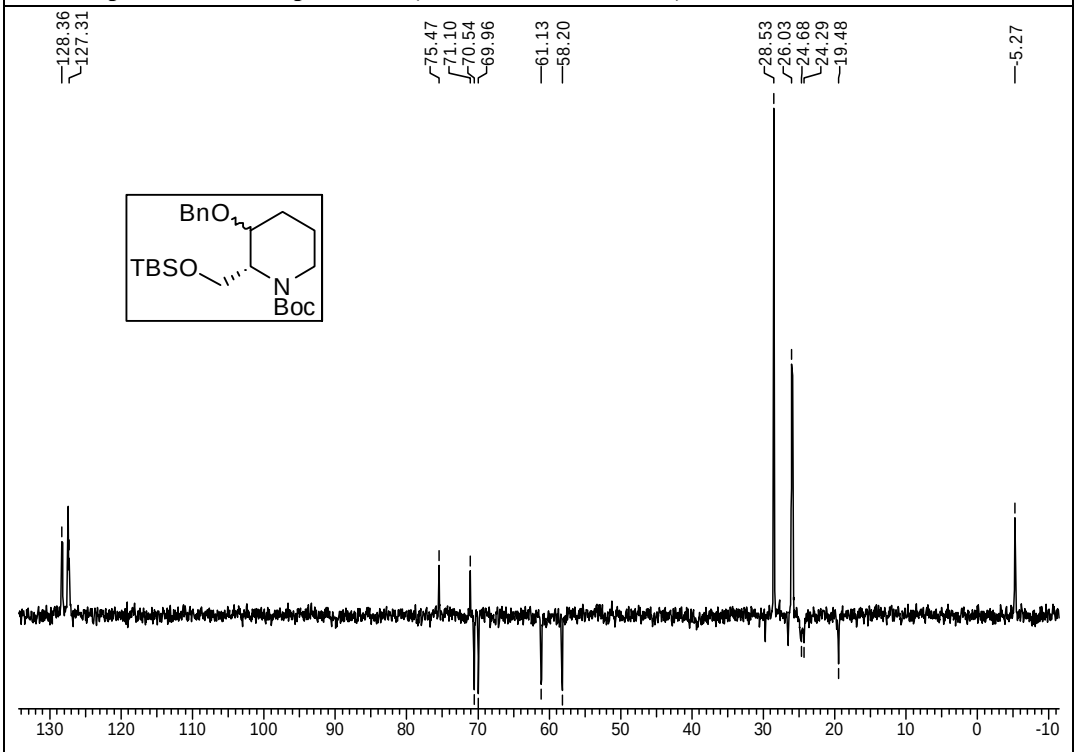
^{1}H NMR Spectrum of compound 14 ($CDCl_3$+CCl_4, 200 MHz)



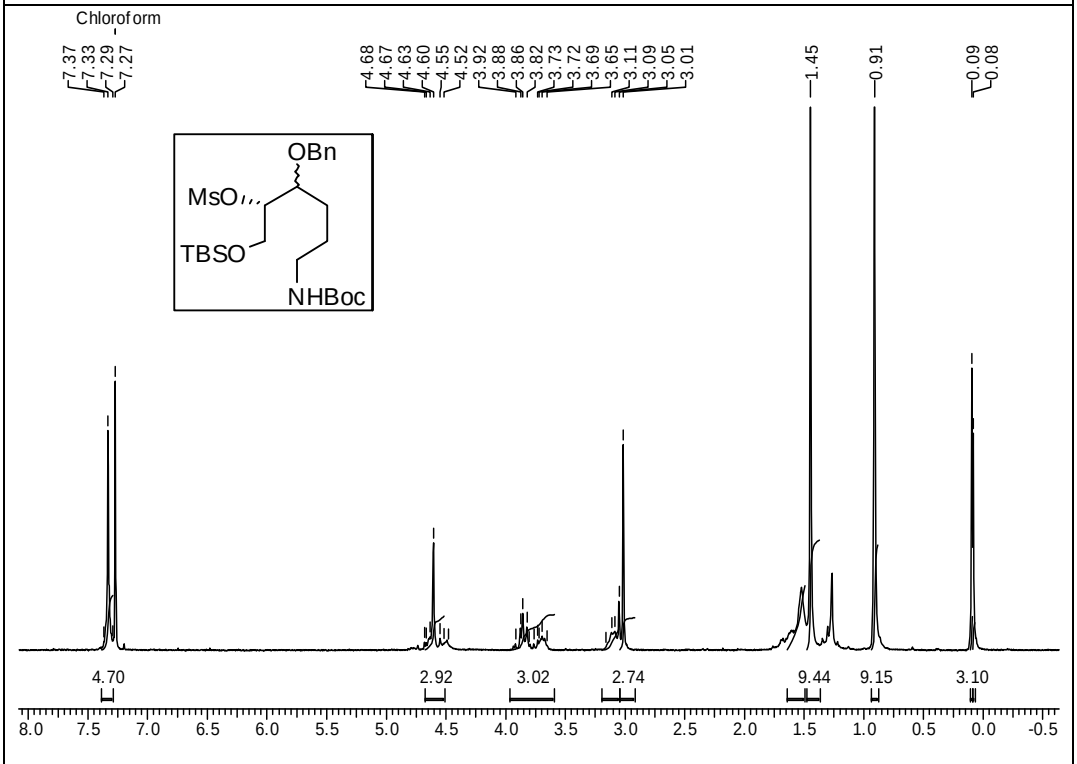
^{13}C NMR Spectrum of compound 14 ($CDCl_3$+CCl_4, 50 MHz)



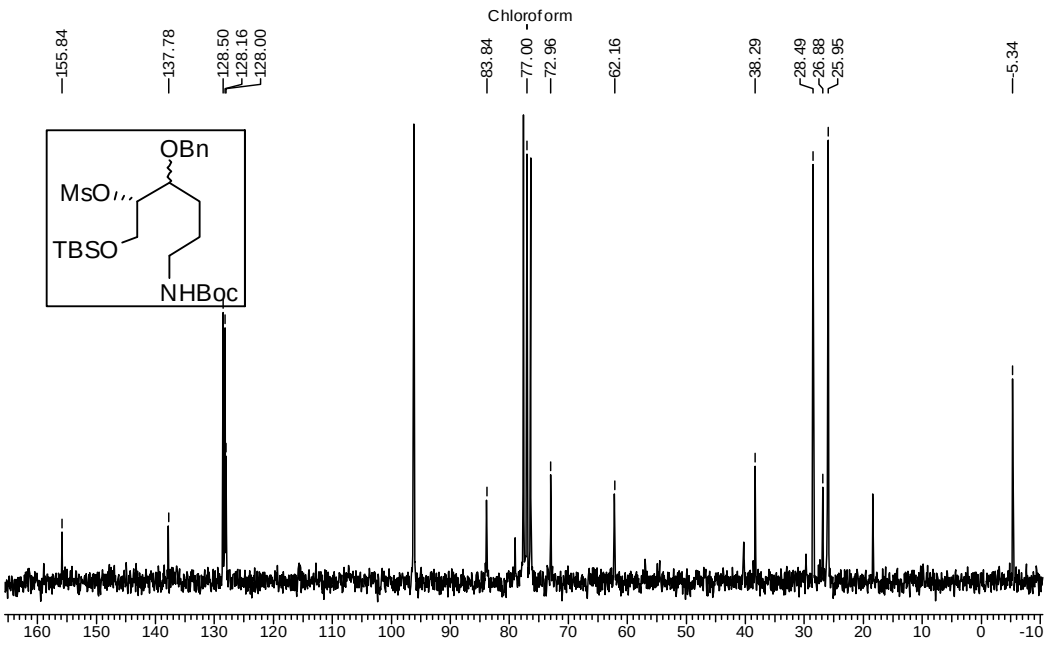
DEPT spectrum of compound 14 ($CDCl_3$+CCl_4, 50 MHz)



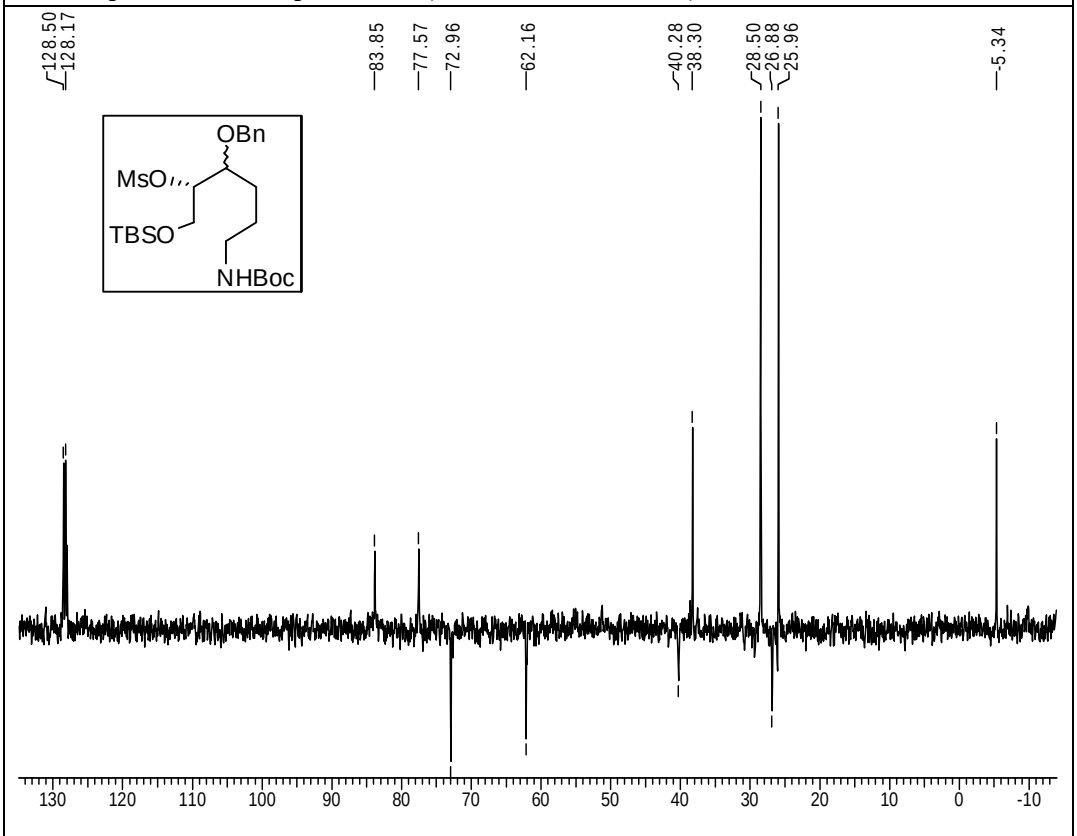
^{1}H NMR Spectrum of compound 14a ($CDCl_3$+CCl_4, 200 MHz)



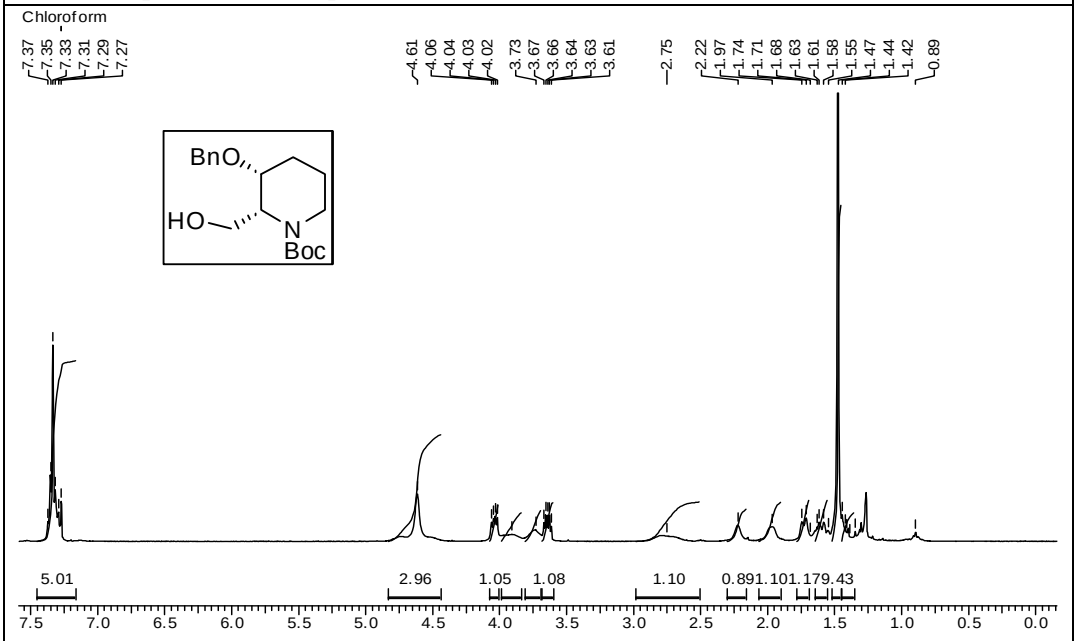
^{13}C NMR Spectrum of compound 14a ($CDCl_3$+CCl_4, 50 MHz)



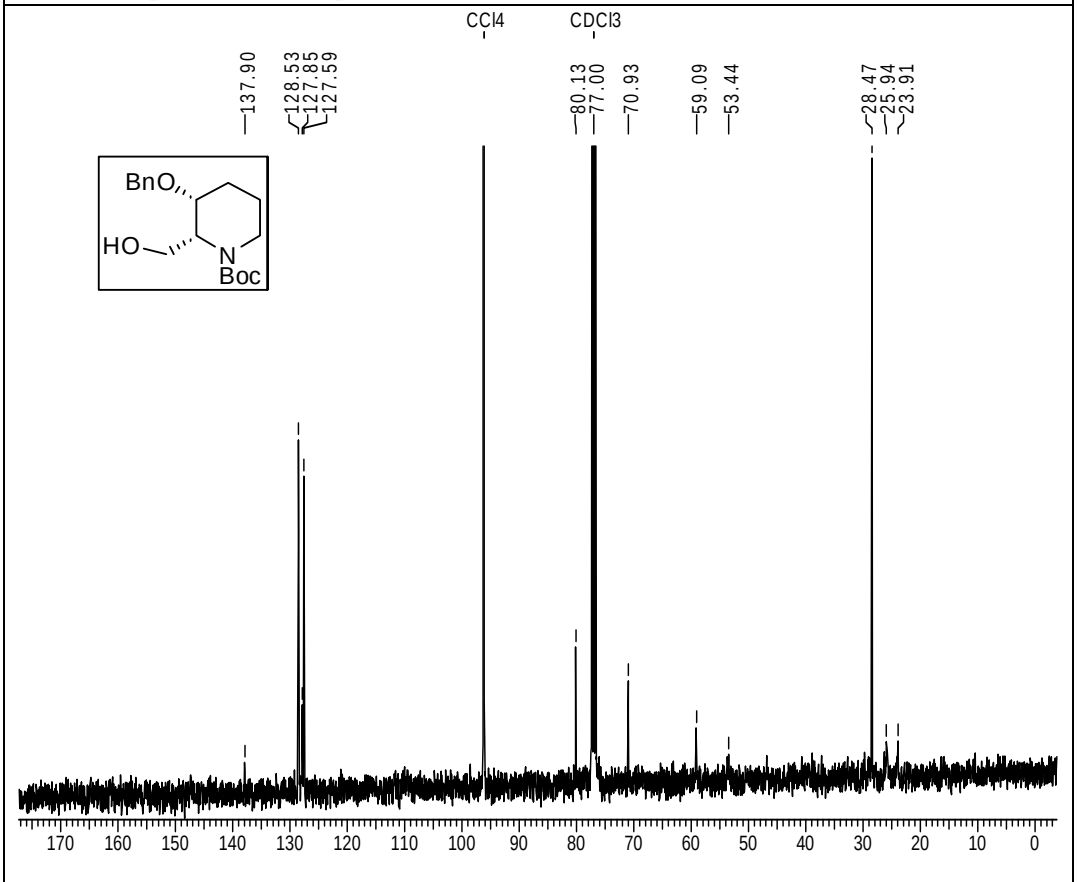
DEPT spectrum of compound 14a ($CDCl_3$+CCl_4, 50 MHz)



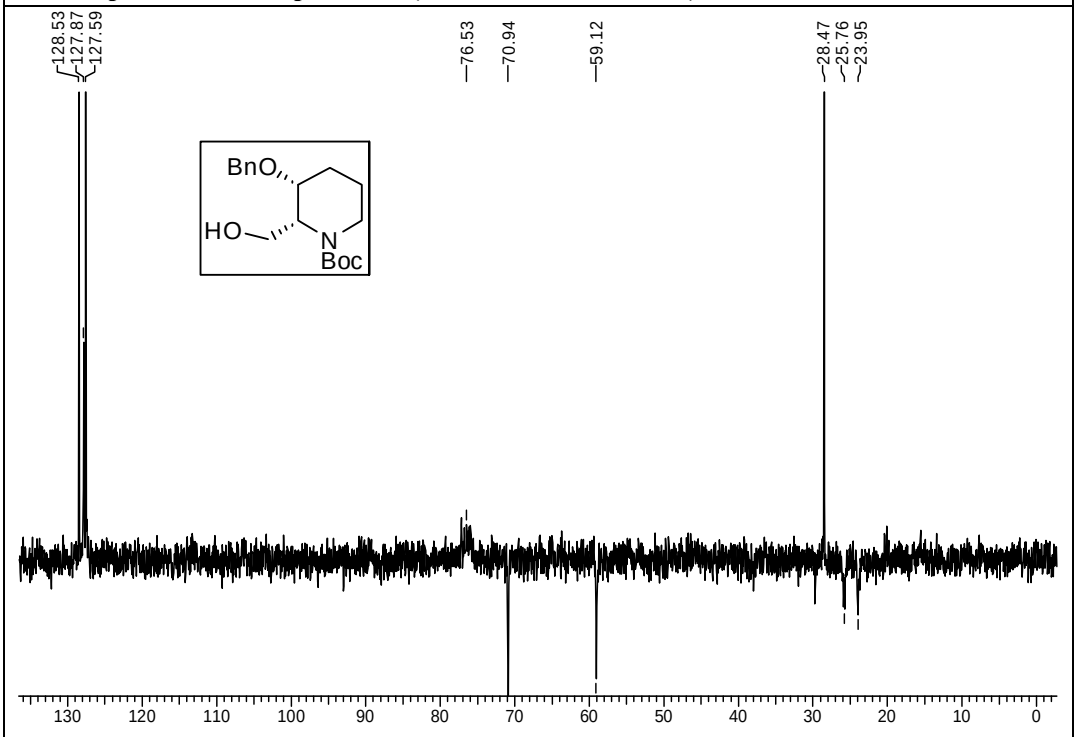
^{1}H NMR Spectrum of compound 15 ($CDCl_3$+CCl_4, 400 MHz)



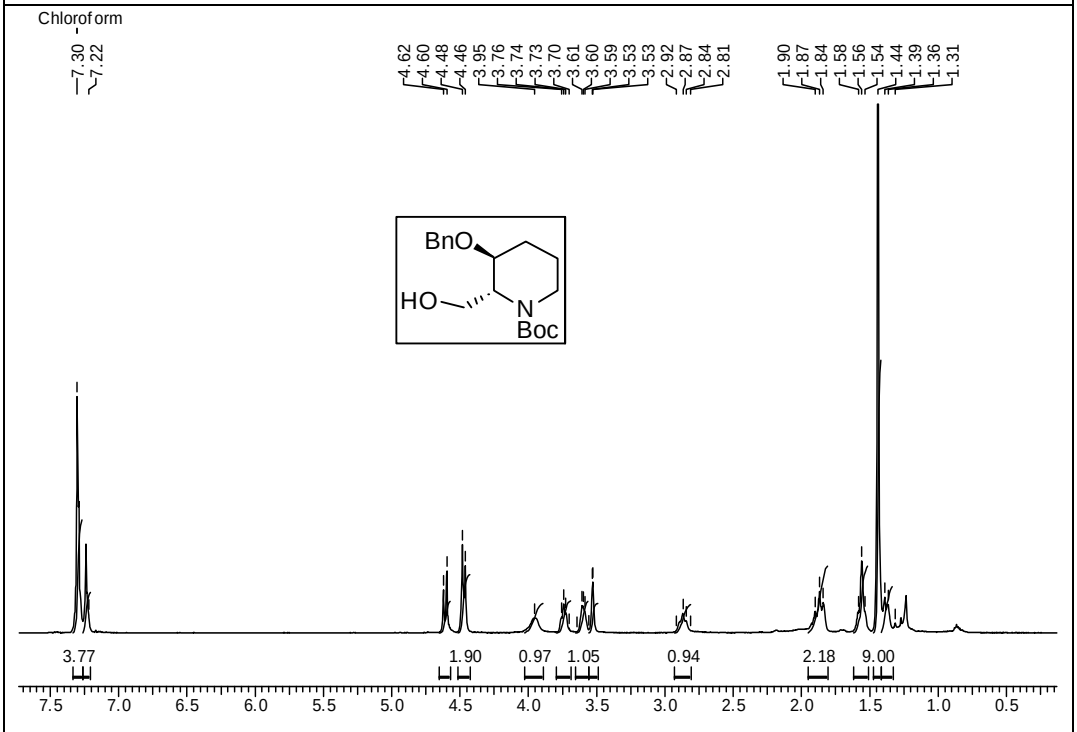
^{13}C NMR Spectrum of compound 15 ($CDCl_3$+CCl_4, 100 MHz)



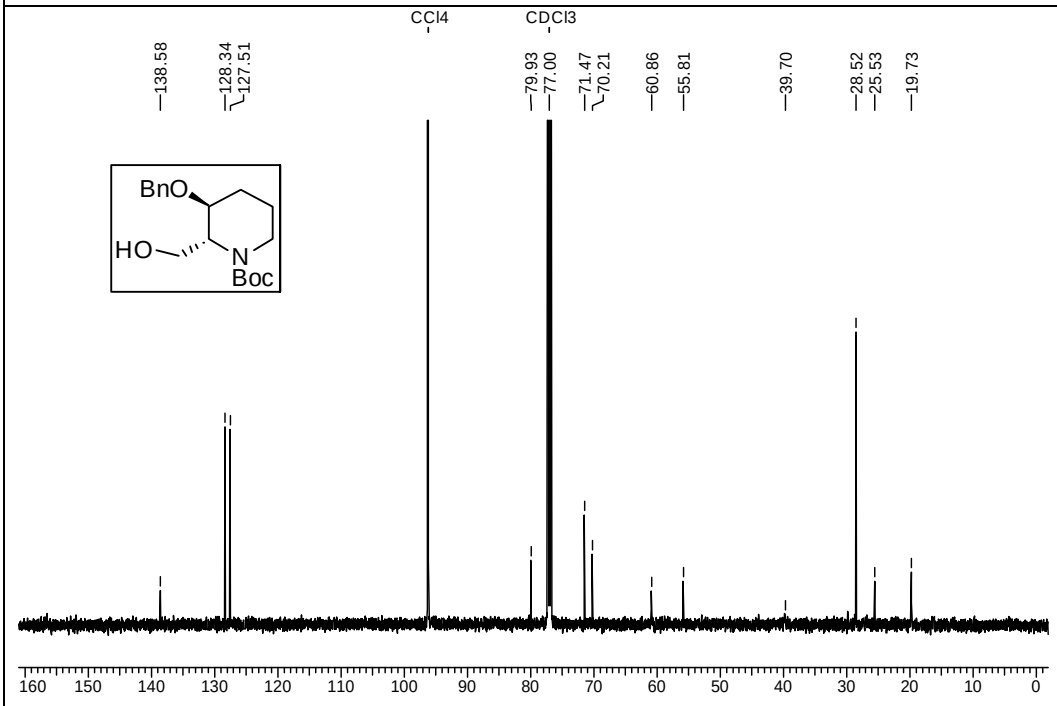
DEPT spectrum of compound 15 ($CDCl_3$+CCl_4, 100 MHz)



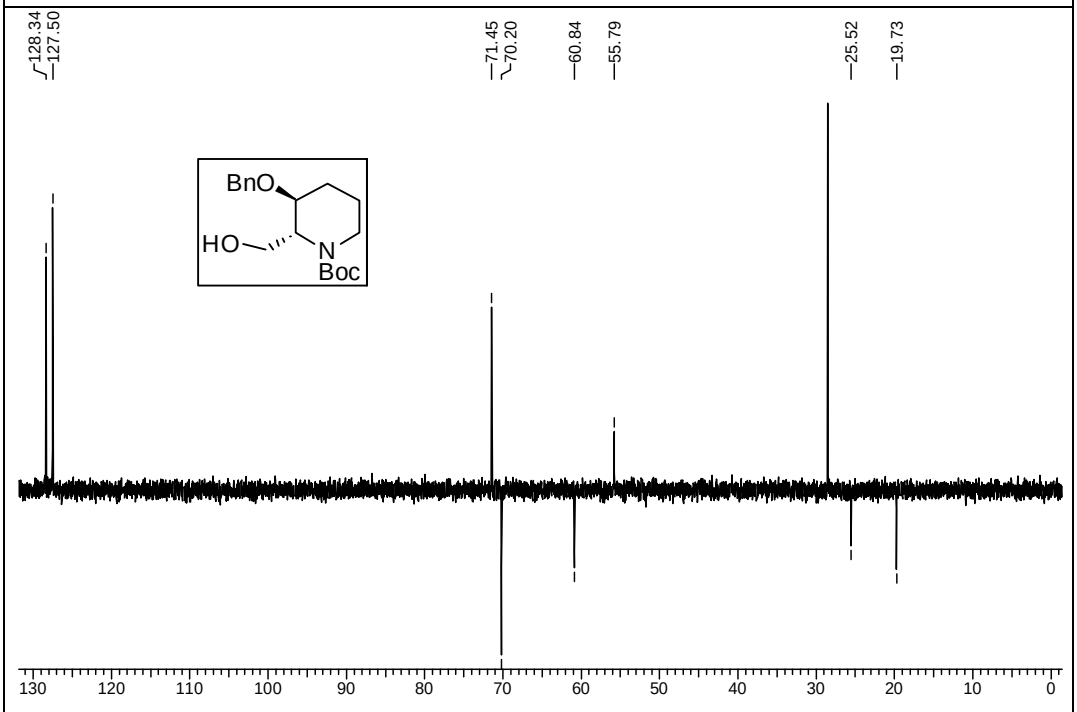
^{1}H NMR Spectrum of compound 16 ($CDCl_3$+CCl_4, 500 MHz)



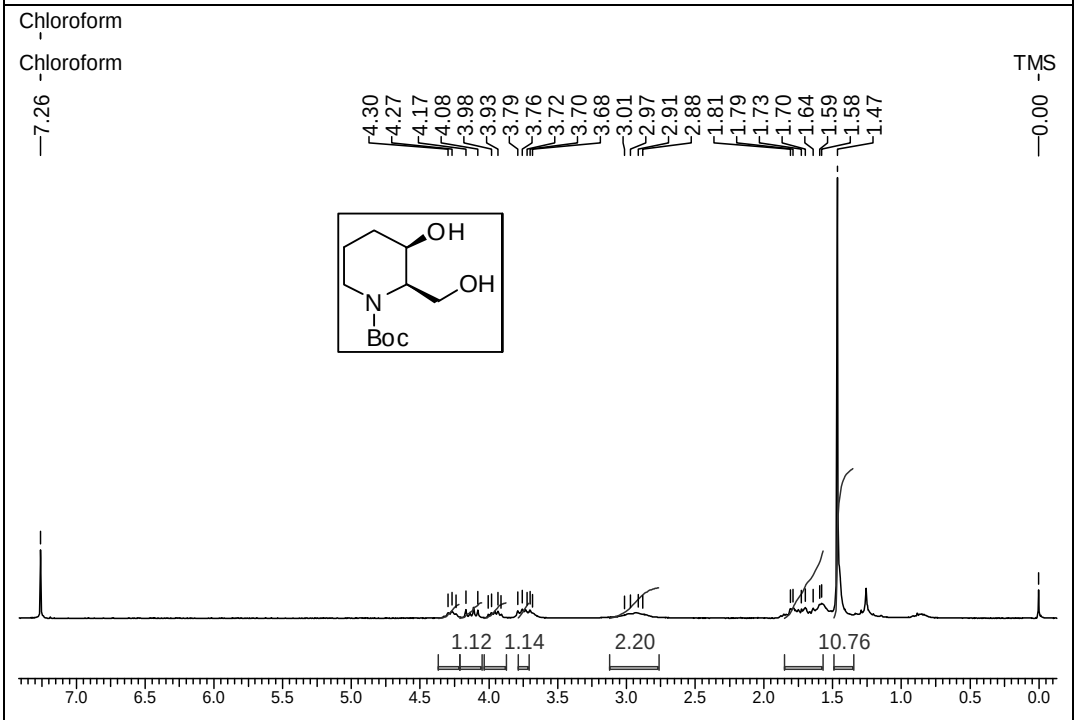
^{13}C NMR Spectrum of compound 16 ($CDCl_3$+CCl_4, 125 MHz)



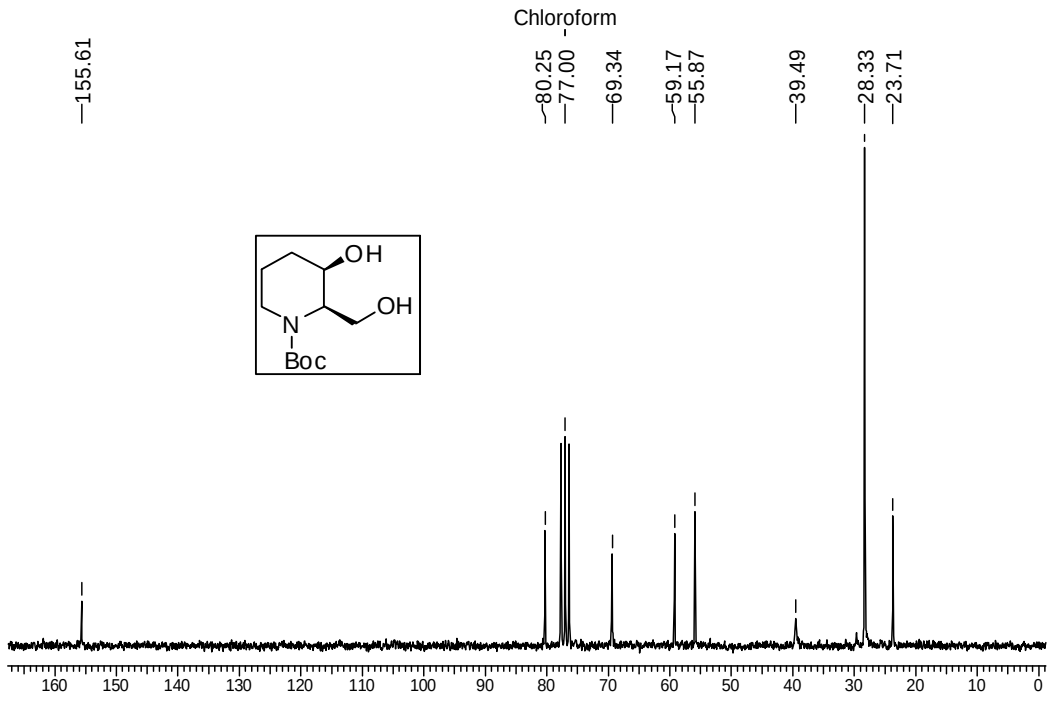
DEPT spectrum of compound 16 ($CDCl_3$+CCl_4, 125 MHz)



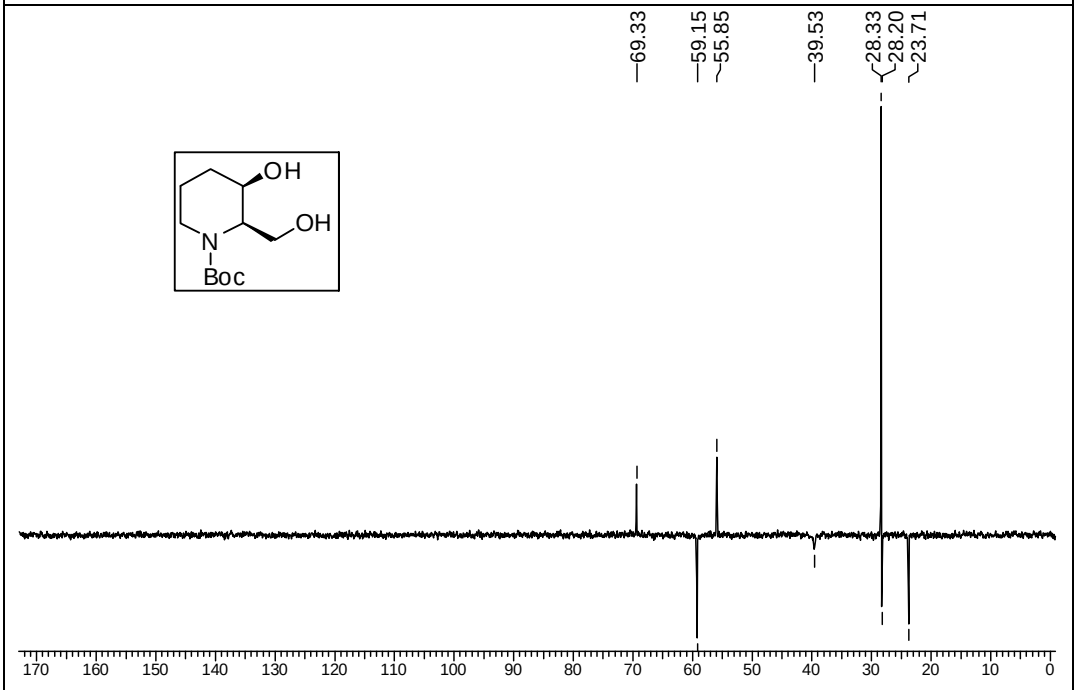
^{1}H-NMR spectrum of compound 1 ($CDCl_3$, 400 MHz)



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



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



^{1}H and ^{13}C NMR spectra of compound 2 have been given in Chapter 2 Section 2

2.3.5. References

1. Chavan, S. P.; Dumare, N. B.; Harale, K. R.; Kalkote, U. R. *Tetrahedron Lett.* **2011,** *52,* 404.
2. Ermolenko, L.; Sasaki, N. A. *J. Org. Chem.* **2005,** *71*, 693; (b) Abushanab, E.; Vemishetti, P.; Leiby, R. W.; Singh, H. K.; Mikkilineni, A. B.; Wu, D. C.-J.; Saibaba, R.; Panzica, R. P. *J. Org. Chem.* **1988**, *53*, 2598.
3. Rao, G. S.; Sudhakar, N.; Rao, B. V.; Basha, S. J. *Tetrahedron: Asymmetry,* **2010**, *21*, 1963.
4. Chiou, W.-H.; Lin, G.-H.; Liang, C.-W. *J. Org. Chem.* **2010**, 75, 1748.

Chapter 2

Section 4: Introduction to polyhydroxy piperidine alkaloids

2.4.1 Introduction to polyhydroxy piperidine alkaloids

Naturally and unnaturally occurring polyhydroxy compounds containing piperidine framework have shown significant biological activity, specifically as glycosidase inhibitors, anticancer agents and antiviral agents.[1] D-(+)-Fagomine **1** (Figure 1) was isolated from Japanese buckwheat *Fagopyrum esculentum*s Moench.[2] Recently, fagomine **1** and its isomers (**2** and **3**) were isolated fom *Xanthocercis zambesiaca*.[3] In addition, fagomine (**1**) and 3-4-di-*epi*-fagomine (**3**) were isolated from *Morus alba*.[4] D-Fagomine and its isomer **2** (3-*epi*-fagomine) have been shown to exhibit inhibitory activity towards mammalian α-glucosidase and β-galactosidase.[5] Literature survey revealed that fagomine **1** has shown a potent antihyperglycemic effect in streptozocin-induced diabetic mice and the potentiation for glucose-induced insulin secretion.[6] Very recently it was found that fagomine isomer **4** (not naturally occurring) is an inhibitor of lysosomal galactosidase activity in Fabry lymphoblasts.[7]

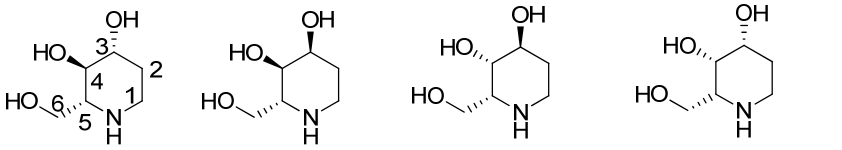


Figure 1.**Note**: The numbering followed throughout this section and next chapter is as shown above,[25] because there was contradictory nomenclature reported in different publications.

The inhibitory activities of L-fagomine isomers **5** and **6** (Figure 2) were tested against a few glycosidases.[8] Vanker *et al.* reported[9] that L-isomer of trihydroxypiperidine compounds (L-fagomine and its isomers) *e.g.* **5** exhibited moderate inhibition of β-glucosidase, α-galactosidase and β-galactosidase, whereas it showed no inhibition of α-glucosidase and α-mannosidase. On the other hand, compound **6** showed no inhibition of α-glucosidase, β-glucosidase and α-mannosidase, but reasonable inhibition of α-galactosidase and β-galactosidase at 0.8 mM concentration.

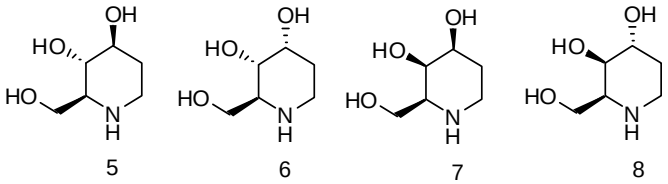


Figure 2.

The piperidine ring is an important scaffold of numerous secondary metabolites and biologically active compounds. The 2-substituted-piperidine[10] moiety is an important constituent of (*R*)-coniine **9**, indolizidine alkaloids[11] *e.g.* (*S*)-δ-coniceine **10**, and non-natural amino acids[12] *e.g.* (*S*)-pipecolic acid **11**, lentiginosine **12** (Figure 3) involved in various biological processes. Additionally, the piperidine core is a frequent structural moiety in many synthetic pharmaceuticals [*e.g.* anesthetic (*S*)-bupivacaine **13**].[13] Pipecolic acid is important framework in several clinically important natural products including the glycosidase inhibitor swainsonine **14**,[14] rapamycin **15**[15] and the immunosuppressant FK-506 **16**.[16]

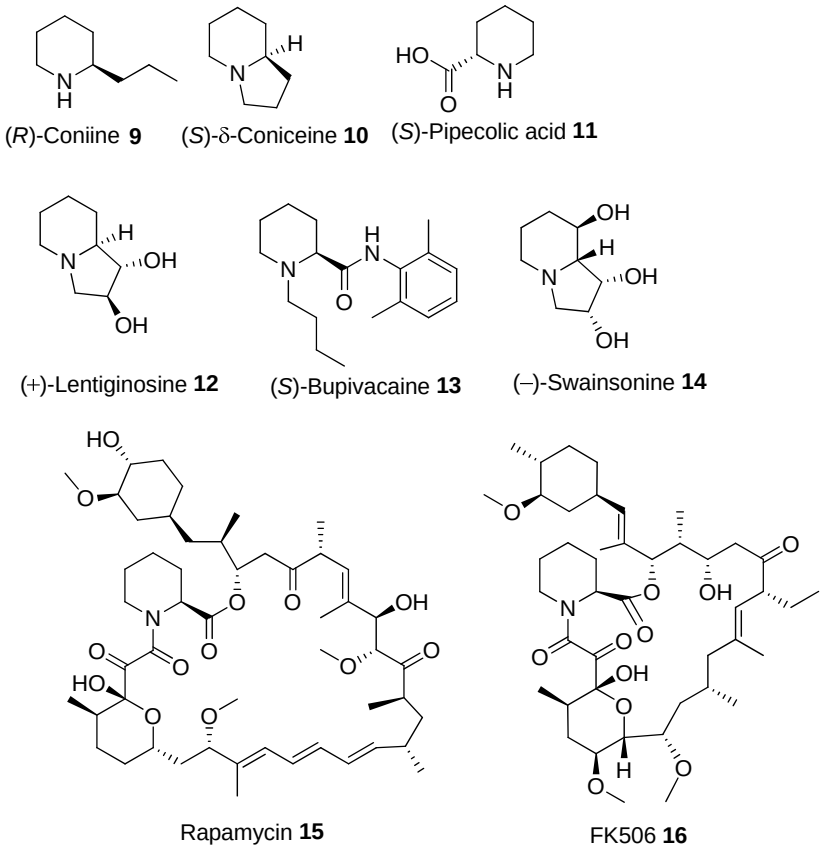


Figure 3.

The derivative of 1-deoxynojirimycin **17** (DNJ) (Figure 4) such as lipophilic iminosugar AMP-DNM (**18**, Figure 4), has been used in treatment of various rodent models of insulin resistance and potent inhibitor of glucosylceramide synthase (GCS), lowered circulating glucose levels, improved oral glucose tolerance (OGT), reduced HbA1c, and improved insulin sensitivity in muscle and liver.[17] Additionally, miglitol

19 and its analogue miglitate **20** both are having anti-diabetic activity. Miglitol **19** was observed to be absorbed appreciably from the gut into the bloodstream, where additional effects were noticed.

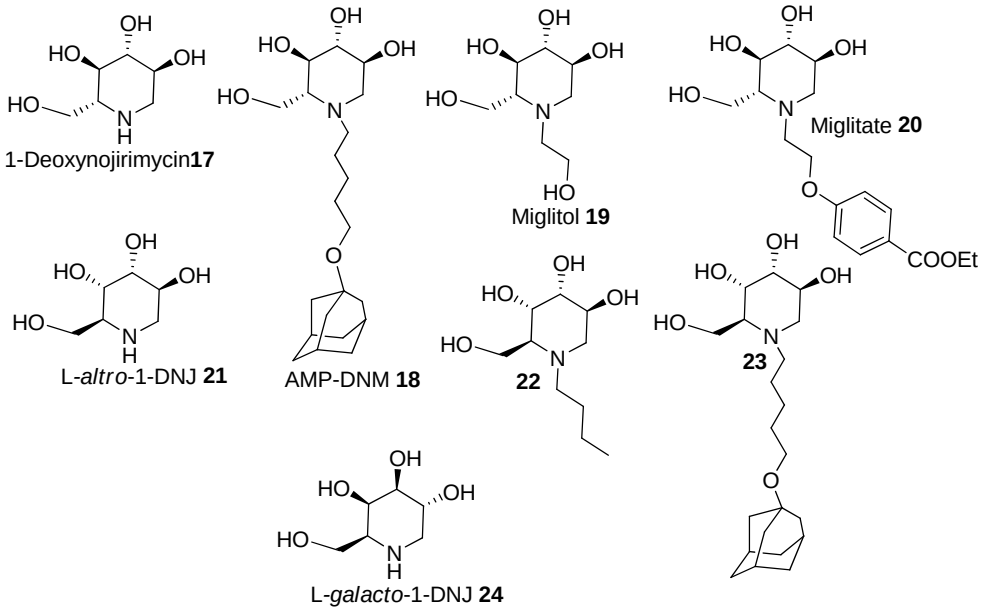


Figure 4.

Wennekes *et al.*[18] reported that derivatives of L-*altro*-1-deoxynojirimycin **21** (L-*altro*-1-DNJ) such as **22** and **23** have shown inhibitory capacity towards the relevant glycosidase and glucosylceramide synthase (GCS). Andersson and co-workers[19] reported promising inhibitions of porcine lactase by 1-deoxygalactonojirimycin (L-*galacto*-1-DNJ **24)**.

D-*galacto*-1-deoxynojirimycin *ent*-**24** (Figure 5) was isolated as its bisulfite adduct **25** from the culture broth of *Streptomyces lydicus* PA-57261−3 collected from a soil sample in Nagasaki Prefecture, Japan. Its derivative L-*galacto*-1-deoxynojirimycin **24** has been prepared from galactostatin bisulfate **25** (Figure 5).[20] Galactostatin **26** strongly inhibits *β*-galactosidase while *galacto*-1-deoxynojirimycin is also competitive inhibitor with high affinities for *Penicillium multicolor β*-galactosidase.

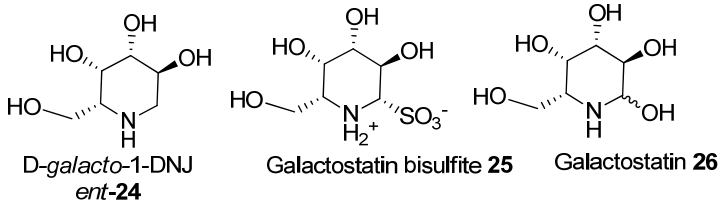


Figure 5.

Mannonojirimycin **27** (Figure 6) and 1-deoxymannonojirimycin **28** were isolated from *Streptomyces subrutilus* ATCC 27467 which was grown on medium containing glucose. Mannonojirimycin **27** was first produced and then underwent dehydration and reduction to give **28**.[21] D-*manno*-1-DNJ **28** was isolated from *Omphalea diandra* L.,[22] *Lonchocarpus sericeus* and *Lonchocarpus costaricensis.*[23] It possesses insecticidal and pesticidal properties, and its bark extracts are used to treat parasitic skin infections. Compound **28** is an inhibitor of bovine α-L-fucosidase[24a] and mannosidase I, a glycoprotein-processing enzyme. Recently, Clapés and co-workers[24b] reported synthesis of L-*manno*-1-DNJ derivatives (**29** and **30**) for biological screening.

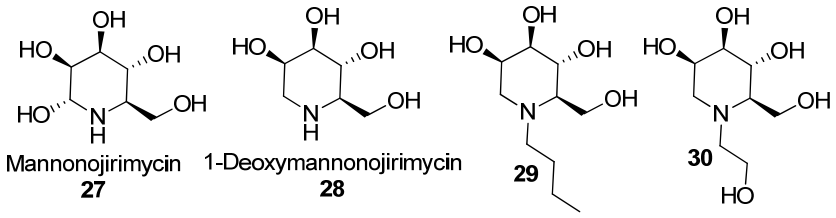


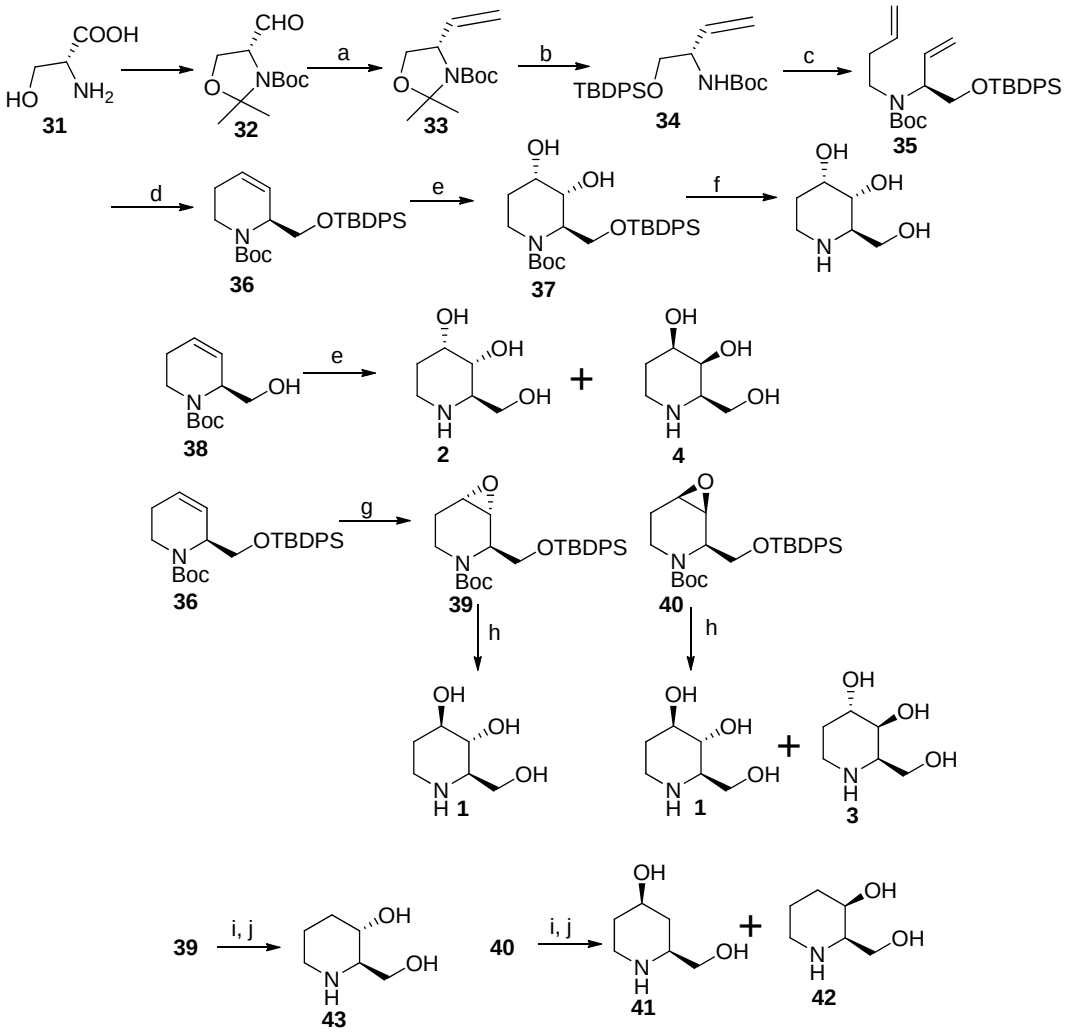
Figure 6.

Explanation of 1-deoxyallonojirimycin (*allo*-1-DNJ) see Chapter-3 Section-1

2.4.2 Literature Survey: Reported synthesis

Takahata *et al.*[25] (*J. Org. Chem.* **2003**, *68*, 3603)

Takahata *et al.* reported fagomine and its isomers by employing ring closing metathesis as the key step. Synthesis started from Garner aldehyde **32** (Scheme 1) (derived from D-serine) which on one-carbon homologation gave olefin **33**. Hydrolysis of **33** followed by *O*-silylation afforded **34**. A three-step sequence [(1) deprotection of the *N*-Boc group; (2) alkylation; and (3) *N*-protection] provided the butenylated product **35**. RCM of **35** with Grubbs' catalyst gave the desired intermediate olefin **36**. The stereoselective dihydroxylation of the double bond was achieved under modified Upjohn conditions, to give the diol **37** as a single diastereomer. Deprotection of **37** with 10% hydrochloric acid followed by treatment with ion-exchange resin afforded 3-*epi*-fagomine **2**. The oxidation of homoallylic alcohol **38** using a combination of OsO_4 with TMEDA followed by deprotection gave **2** and **4** in moderate selectivity. The dioxirane, generated *in situ* from oxone with 1,1,1-trifluoroacetone, was reacted with **36** to give a diastereomeric mixture of epoxy compounds **39** and **40** which were separated by column chromatography.

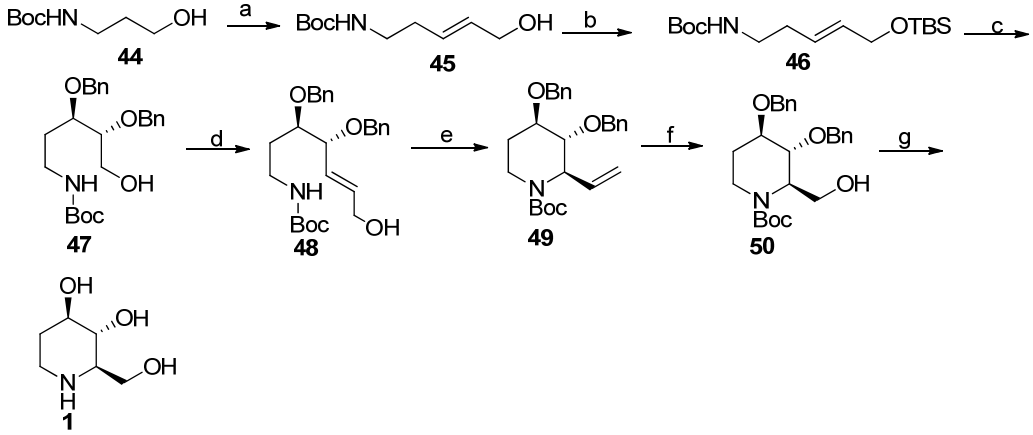


Scheme 1 *Reagents and conditions: (a) $Ph_3P^+CH_3I^-$, $NaN(TMS)_2$, THF. (b) (i) p-$TsOH.H_2O$, MeOH; (ii) TBDPSCl, DMAP, imidazole, CH_2Cl_2. (c) (i) CF_3COOH, CH_2Cl_2; (ii) 4-bromo-1-butene, K_2CO_3, CH_3CN; (iii) $(Boc)_2O$, Et_3N, THF; (d) Grubb's catalyst, CH_2Cl_2; (e) cat. $K_2OsO_4.2H_2O$, NMO, H_2O, acetone; f) 10% HCl, 1,4-dioxane. g) Oxone, CF_3COCH_3, $NaHCO_3$, aq $Na_2.EDTA$, CH_3CN; h) H_2SO_4, 1,4-dioxane, H_2O; i) Super hydride in THF; j) HCl, 1,4-dioxane, dowex.*

The acid hydrolysis of the epoxy ring of **39** followed by treatment with an ion-exchange resin gave single isomer of fagomine **1**. The acid hydrolysis of the epoxy ring of **40** followed by treatment with an ion-exchange resin gave two isomers **1** and **3**. Compound **39** and **40** were elaborated for the synthesis of dihydroxy piperidine compounds **41**, **42** and **43**.

Yokoyama *et al*.[26] (*Tetrahedron: Asymmetry* **2007**, *18,* 852)

Yokoyama *et al*. reported asymmetric synthesis of fagomine by employing Pd mediated cyclization and Sharpless asymmetric dihydroxylation as the key steps (Scheme 2).



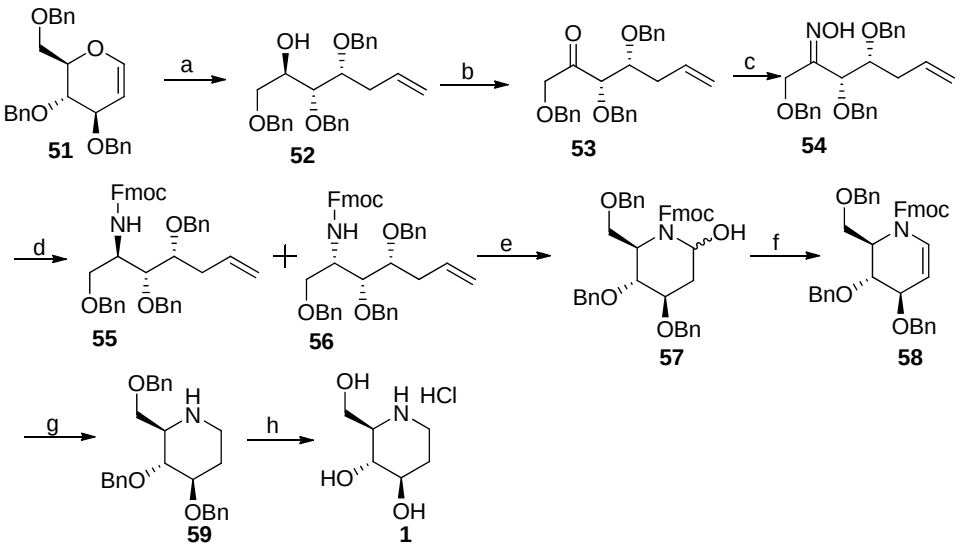
Scheme 2 *Reagents and conditions: (a) i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; ii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, -78 ^oC; iii) DIBAL, THF, -78 ^oC, 83% (over three steps); b) TBSCl, imidazole, DMF, 89%; c) i) AD-mix-β, $CH_3SO_2NH_2$, t-BuOH/H_2O; ii) BnBr, NaH, Bu_4NI, THF; iii) p-TsOH, MeOH, 29% (over three steps); d) i) IBX, THF/DMSO; ii) $(EtO)_2$ $P(O)CH_2CO_2Et$, NaH, THF; iii) DIBAL–H, THF, -78 ^oC, 40% (over three steps); e) i) $PdCl_2(MeCN)_2$, THF, rt, 90%; f) O_3, CH_2Cl_2/MeOH (1:4), -78 ^oC; $NaBH_4$, -78 ^oC, 80%; g) i) HCl, MeOH, 70 ^oC, 64%; ii) H_2, Pd/C, AcOH, 87%.*

O-TBS derivative **46** was obtained by oxidation, two-carbon homologation and ester reduction on **44**. The olefin **46** was dihydroxylated followed by dibenzyl protection and *O*-TBS deprotection to deliver alcohol **47**. Allylic alcohol **48** was obtained by oxidation, two-carbon homologation and ester reduction on **47**. Allyl alcohol **48** was treated with $PdCl_2(MeCN)_2$ in THF at room temperature to give cyclic compound **49**. Ozonolysis of **49** followed by reductive work-up with $NaBH_4$ provided the alcohol **50**. Deprotection of the Boc group of **50** under acidic conditions and removal of the benzyl groups by hydrogenation provided fagomine **1**.

Désiré *et al*.[27] (*Synlett* **2001**, 1329)

J. Désiré *et al.* reported total synthesis of (+)-fagomine from tri-*O*-benzyl-D-glucal by utilizing reductive cyclization as the key step.

Tri-*O*-benzyl-D-glucal **51** (Scheme 3) was converted into alkene **52** according to the known literature two-step protocol (Scheme 3).[28] Oxidation of the free hydroxyl group of **52** yielded ketone **53**, which was further converted into the corresponding oxime **54** upon treatment with hydroxylamine hydrochloride. Reduction of oxime **54** with lithium aluminum hydride provided the primary amine, which was immediately transformed into **55** in which the amino group was protected with the base labile Fmoc group. Ozonolysis of compound **55** followed by treatment with triphenylphosphine provided compound **57** in good yield. Finally, dehydration of **57** to imino glucal **59** was accomplished upon treatment with oxalyl chloride. Fmoc removal of imino glucal **58** in presence of morpholine yielded piperidine **59**. Hydrogenation of piperidine **59** in the presence of HCl effected removal of the benzyl ethers to furnish (+)-fagomine **1** as its hydrochloride salt.

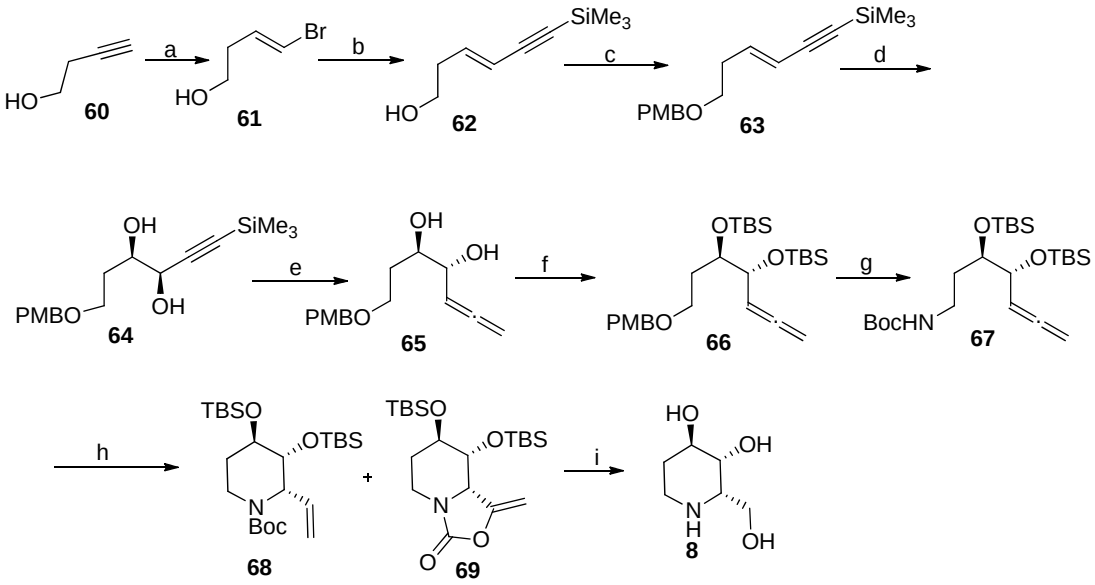


Scheme 3 *Reagents and conditions: a) Ref 28; b) TPAP, NMO, DCM, 4A^o sieves, 83%; c) NH_2OH, HCl, Py, EtOH, 60 ^oC, 98%: d) i) LAH, Et_2O; ii) FmocCl, K_2CO_3, THF/H_2O, 0 ^oC, 57%; e) O_3, DCM, -78 ^oC, PPh_3, 87%; f) $(COCl)_2$, DCM, DMF, 95%; g) H_2, Pd/C, morpholine, EtOH, 70%; h) H_2, Pd/C, EtOH, HCl, 85%.*

Bates *et al.*[29] (*Tetrahedron Lett.* **2011**, *52*, 2969)

Bates *et al.* reported total synthesis of 3,4-di-*epi*-fagomine **8** *via* gold catalyzed cyclisation as the key step.

The vinyl bromide **61** was prepared from 3-butyn-1-ol **60** by terminal bromination followed by selective *trans*-reduction of the alkyne (Scheme 4). Sonogashira coupling of vinyl bromide **61** with trimethylsilylacetylene followed by PMB protection delivered enyne **63**. Enyne **63** was subjected to Sharpless asymmetric dihydroxylation to give diol **64** in 97% of *ee*. Desilylation of **64** followed by Searles–Crabbé homologation afforded the allene moiety **65**. The nucleophilic nitrogen group was then installed by a sequence involving di-TBS protection to afford **66**, oxidative removal of the PMB group, mesylation, displacement of the mesylate by azide, reduction and carbamate formation on **65**. Allene **67** was subjected under Au-mediated cyclization to deliver the desired **68** and undesired compound **69**. Oxidative cleavage of the desired alkene **68** followed by deprotection under acidic condition gave compound **8**.

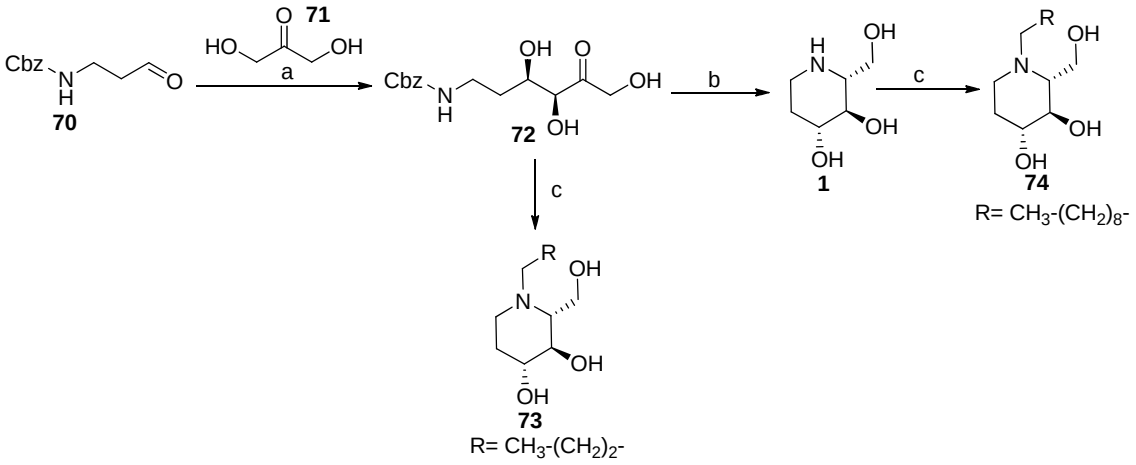


Scheme 4 *Reagents and conditions: a) NBS, $AgNO_3$; ii) $AlCl_3$, LAH, 66%; b) $CHCSiMe_3$, $(Ph_3P)_2PdCl_2$, TEA, THF, 70%; c) $MeOC_6H_4OH$, PPh_3, DIAD, 63%; d) AD-mix-β, $MeSO_2NH_2$, t-BuOH/H_2O, 86%; e) i) MeOH, K_2CO_3; ii) $(CH_2O)n$, Cy_2NH, CuBr, 75%; f) i) TBSOTf, 2,6-lutidine, 86%; g) i) $Ce(NH_4)_2(NO_3)_6$, py., aq. MeCN, 81%; ii) MsCl, TEA; iii) NaN_3, 66%; iv) PPh_3, H_2O; v) Boc_2O, i-PrNEt; h) Ph_3PAuCl, $CaCO_3$, $AgSbF_6$, 85%; i) i) O_3, $NaBH_4$; ii) HCl, MeOH, dioxane; iii) Amberlyst, 53% (over three steps).*

Castillo *et al.*[30] (*Org. Lett.* **2006,** *8,* 6067)

Castillo *et al.* reported total synthesis of D-fagomine and its *N*-allylated derivatives by employing D-fructose-6-phosphate aldolase (FSA) as the key step.

3-Aminopropanol **70** was prepared by known literature procedure.[31] The FSA-catalyzed aldol addition of DHA **71** with 3-aminopropanol **70**, furnished **72** (Scheme 5). D-Fagomine **1** was then obtained by selective catalytic reductive amination of **72** in 93:7 diastereomeric ratios estimated by NMR while *N*-alkylated derivatives **73** were easily obtained by catalytic reductive amination of compound **72** followed by addition of corresponding aldehyde. Most interestingly, an *N*-allylated derivative **73** was obtained by reductive amination of a mixture of **72** and the corresponding aldehyde in a one-pot reaction.



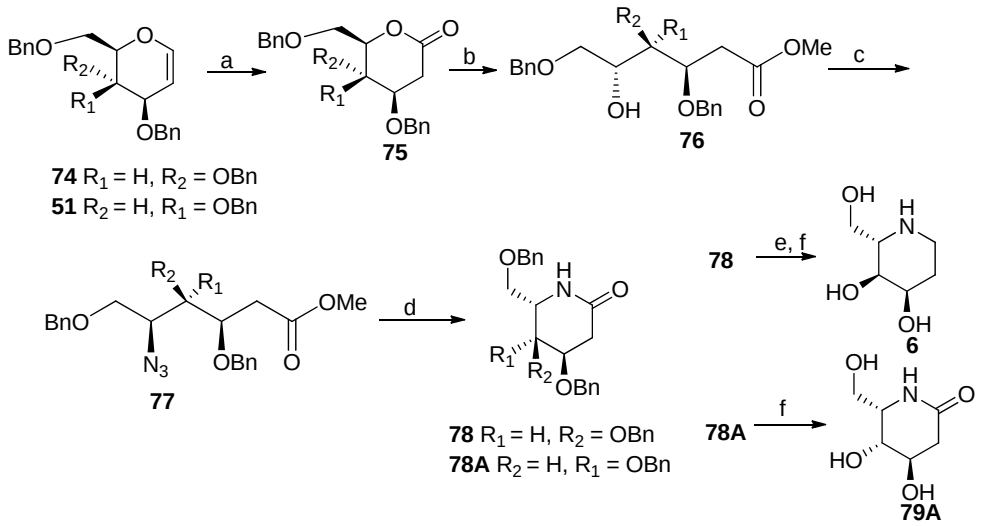
Scheme 5 *Reagents and conditions: a) FSA, DMF, buffer; b) H_2, Pd/C, EtOH/H_2O; c) RCHO, H_2, Pd/C, EtOH/H_2O;*

Squarcia *et al*.[32] (*Tetrahedron Lett.* **2002,** *43*, 4653)

Squarcia *et al*. reported total synthesis of L-3-*epi*-fagomine and δ-lactam from D-glucal as chiral template by employing reductive lactamisation as the key step (Scheme 6).

D-Glycals **74** and **51** (Scheme 6) were converted into the desired six memebered lactones **75**. Transesterification of **75** with MeOH/H_2SO_4 (cat.) led to the open chain hydroxy methyl esters **76** followed by mesylation and treatment with sodium azide to give azido derivative compound **77**. Finally, hydrogenation of **77** with palladium on

carbon as catalyst provided the lactams **78** and **79** in one step. Lactam **78** was reduced followed by *O*-debenzylation to yield compound **6**.

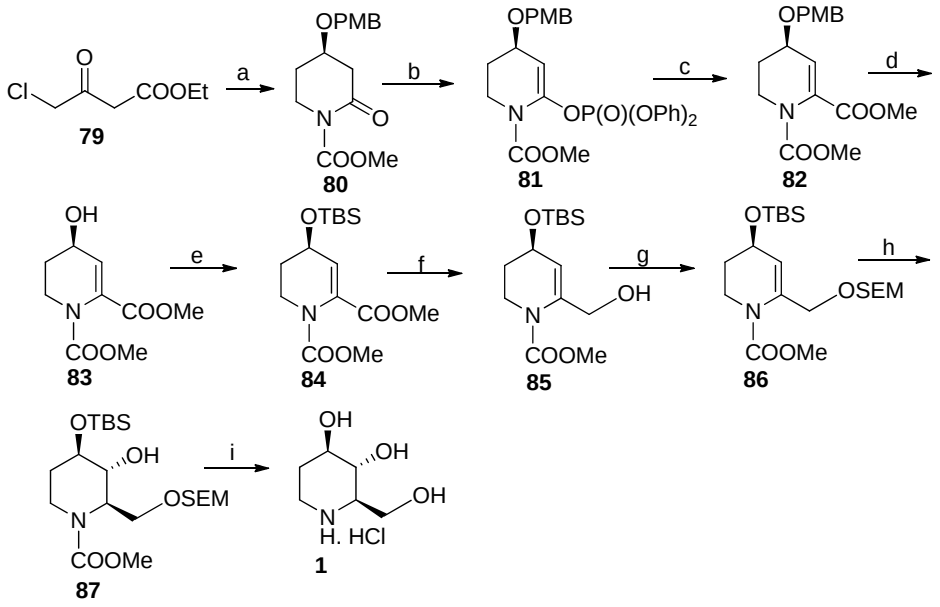


Scheme 6 *Reagents and conditions: (a) PCC, 1,2-dichloroethane, reflux, 6 h; (b) MeOH, H_2SO_4 cat., reflux, 6 h; (c) i) MsCl, pyridine, 0 °C- rt, 6 h; ii) NaN_3, DMF, reflux, 24 h; d) i) H_2, Pd/C, EtOH/MeOH (3:1), rt, 24 h e) $LiAlH_4$, THF, reflux, 4 h, 50%; f) H_2, Pd/C, EtOH, rt, 24 h, 50%.*

Bartali *et al* [33](*Synlett* **2009**, 913)

Bartali *et al.* accomplished total synthesis of fagomine by employing stereoselective hydroboration oxidation of enamine double bond as the key step.

Keto compound **79** was transformed into enantiomerically pure *N*-protected lactam **80** by reported methodology.[34] Phosphate **81** (Scheme 7) was prepared by treatment of **80** with KHMDS, followed by addition of diphenylchlorophosphate. Phosphate group of **81** was converted into methyl ester **82** using Pd catalyst in MeOH solvent. Removal PMB group of **82** and replacement by TBS as bulkier group afforded **84**. Ester **84** was reduced followed by SEM protection to give compound **86**. Olefin **86** was subjected under hydroboration-oxidation reactions to afford alcohol **87** as a single isomer. Global deprotection of **87** was achieved under acidic condition to deliver salt of D-fagomine **1**.

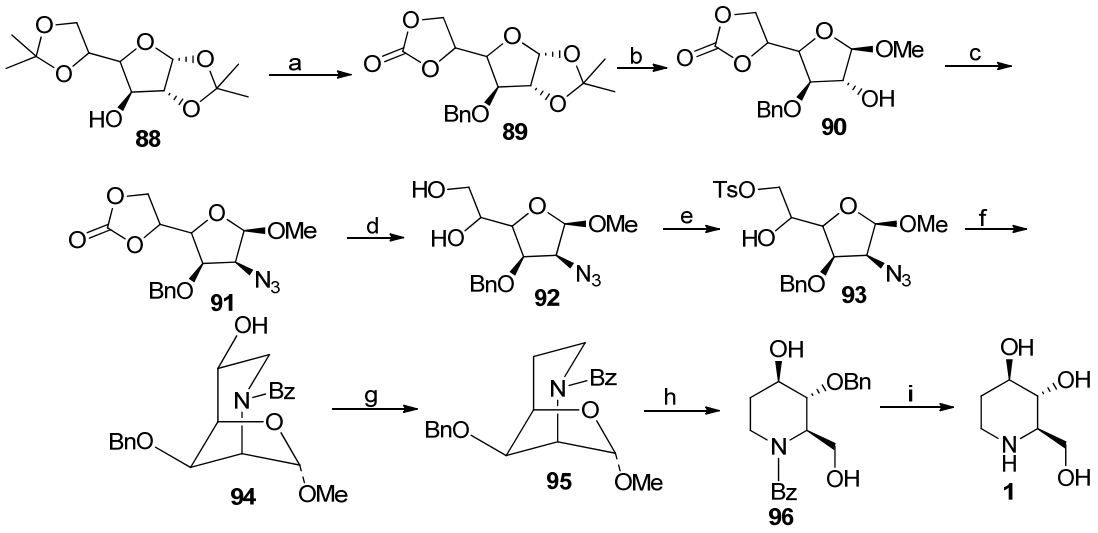


Scheme 7 *Reagents and conditions: a) Ref 34; b) i) KHMDS, THF, -78 ^{o}C; ii) $(PhO)_2POCl$, THF, -78 ^{o}C, 85%; c) $Pd(OAc)_2$, Ph_3P, CO, MeOH, TEA, DMF, 50 ^{o}C, 95%; d) DDQ, DCM/H_2O, 81%; e) TBSCl, imidazole, DMF, 40 ^{o}C, 91%; f) DIBAL-H, DCM, -78 ^{o}C, 73%; g) i) SEMCl, DIPEA, DCM, 76%; h) i) BH_3.THF, -78 ^{o}C- 0 ^{o}C; ii) Me_3NO, THF, 65 ^{o}C, 70%; i) 2N HCl, reflux, 100%.*

Fleet *et al.* [35] (*Tetrahedron Lett.* **1985**, *26*, 1469)

Fleet *et al.* accomplished the total synthesis of fagomine from diacetonide glucose by employing reductive cyclisation as the key step (Scheme 8).

Free hydroxy of **88** (Scheme 8) was transformed to its benzyl ether and deprotection of terminal acetonide followed by treatment with dimethyl carbonate furnished carbonate compound **89**. Treatment of carbonate **89** with acidic ion exchange resin gave a mixture of alcohols **90** (2.5:1) which were readily separated by column chromatography. Free hydroxy group of **90** was converted into azido compound **92**. Removal of carbonate group of **91** afforded diol **92**. Cyclized compound **94** was obtained from diol **92** by selective monotosylation to give **93**, azide reduction followed by base treatment and protection of the resultant amine as its carbamate. The removal of hydroxy group in **94** furnished **95**. Removal of the benzyl and benzyloxycarbonyl protecting groups in **95** by hydrogenolysis with palladium hydroxide catalyst gave D-fagomine **1**.



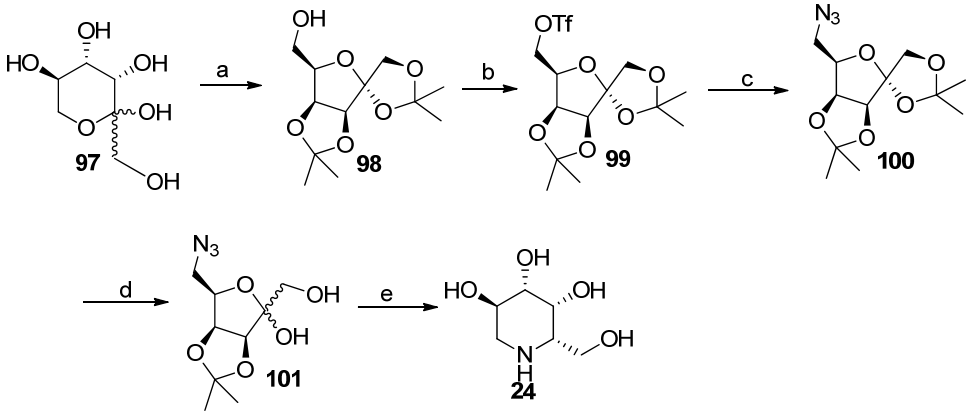
Scheme 8 *Reagents and conditions: a) i) $PhCH_2Br$; ii) 0.5% HCl in MeOH, room temp, 12 h; then $(MeO)_2CO$, NaOMe, reflux b) Dowex 50W-X8 resin (H^+ form), MeOH, reflux c) i) Triflic anhydride, pyridine, CH_2Cl_2, -20 ^oC, 20 min; then NaN_3, DMF, 50 °C, 2 d; d) MeOH with a trace of NaOMe, room temp. e) p-Toluene sulphonyl chloride, pyridine, room temp, 6 h f) i) Palladium black, H_2 EtOH, 30 min; then NaOAc, EtOH, 50 °C; ii) $PhCH_2OCOCl$, ether, H_2O containing $NaHCO_3$ g) i) Triflic anhydride, pyridine, -20 ^oC; then $LiBHEt_3$, THF; ii) $PhCH_2OCOCl$, ether, H_2O containing $NaHCO_3$ h) CF_3COOH: H_2O (1:1), room temp, 1 h; then $NaBH_4$ in EtOH - H_2O i) Palladium hydroxide, H_2, EtOH.*

Jenkinson *et al.*[36] (*Org. Lett.* **2011**, *13*, 4064)

Jenkinson *et al.* reported total synthesis of both enantiomers of *galcto*-1-DNJ from D and L-tagotase employing reductive cyclisation as the key step (Scheme 9).

Reaction of D-tagatose **97** (Scheme 9) with acetone, copper (II) sulfate and catalytic sulfuric acid gave the diacetonide compound **98**. Azide **100** was obtained from **98** by esterification followed by treatment with NaN_3.

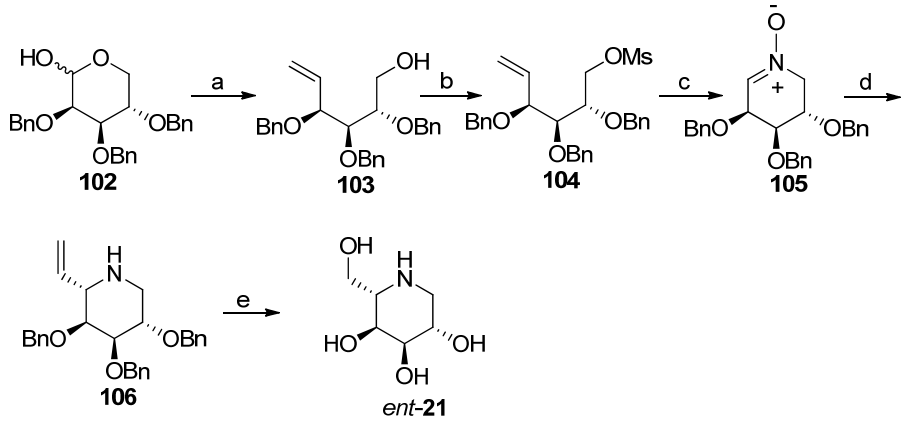
Removal of the acetonide protecting groups in **100** with Dowex resin in water proceeded slowly to give 6- azidotagatose **101** as a 3:1 mixture of anomers. Hydrogenation of the azide **101** gave the corresponding amine which underwent a highly stereoselective intramolecular reductive amination to afford L- *galcto*-1-DNJ **24**.



Scheme 9 *Reagents and conditions: a) Acetone, $CuSO_4$, H_2SO_4, rt, 18 h, 79%; b) Tf_2O, py., DCM, -30 °C to 10 °C, 3h; c) NaN_3, DMF, rt, 18 h, 93% (over two steps); d) Dowex, 1,4-dioxane, H_2O, rt, 3 d, 86%; e) H_2, Pd/C, EtOH/H_2O, rt, 18 h, 97%.*

Chan *et al.*[37] (*Eur. J. Org. Chem.* **2010**, 5555)

Chan *et al.* accomplished *altro*-1-DNJ employing diastereoselective nucleophilic addition of Grignard reagent on cyclic nitrone as the key step. The Wittig olefination of 2,3,4-tri-*O*-benzyl-D-arabinopyranoside **102** (Scheme 10) followed by mesylation gave mesyl derivative **104**. Ozonolysis of **104** followed by treatment with hydroxylamine furnished cyclic nitrone **105**, Cyclic nitrone **105** was treated with Grignard reagent in presence of different Lewis acids to furnish single isomer **106**. Ozonolysis of **106** followed by reductive work up with $NaBH_4$ afforded *ent*-**21**.



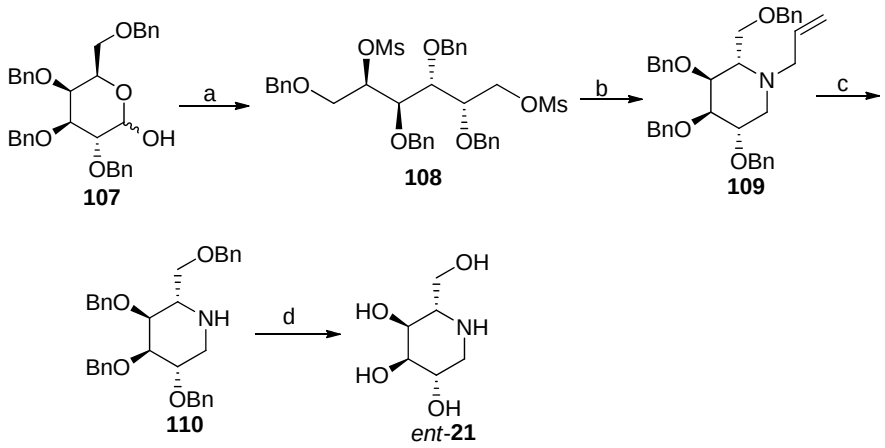
Scheme 10 *Reagents and conditions: (a) $MePPh_3Br$, nBuLi, THF, –78 °C to room temp.; (b) MsCl, Et_3N, DCM; (c) i) O_3, MeOH/DCM, –78 °C, then DMS; ii) $H_2NOH{\cdot}HCl$, $NaHCO_3$, MeOH, reflux; d) i) VinylMgBr, THF, 0 °C; ii) Excess Zn,*

AcOH, room temp.; e) i) $(Boc)_2O$, Et_3N, DCM; ii) O_3, MeOH/DCM, –78 °C, then DMS; iii) $NaBH_4$, MeOH, 10% HCl (aq.), MeOH, 70 °C; iv) H_2, $Pd(OH)_2$/C, 10% HCl (aq.)/MeOH, room temp.

Wennekes *et al.*[38] (*J. Med. Chem.* **2010,** *53*, 689)

Wennekes *et al.* accomplished synthesis of *galacto*-1-DNJ, *altro*-1-DNJ and their derivatives utilizing *N*-allylation as the key step.

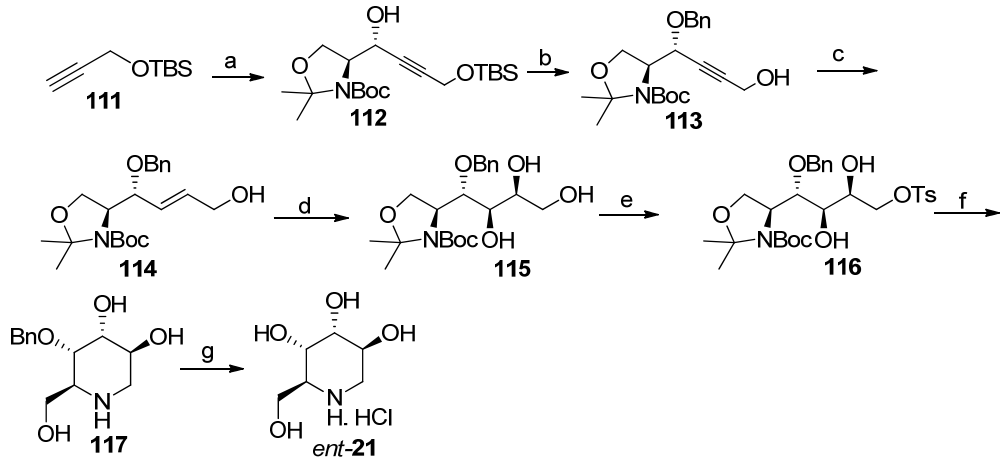
2,3,4,6-Tetra-O-benzyl-D-glucopyranose **107** (Scheme 11) was derived by known literature protocol.[39] Compound **107** was converted to di-mesyl derivative **108**, also by known literature protocol.[40] Di-mesyl compound **108** was treated with allyl amine to deliver the piperidine core **109** in excellent yield. Allyl deprotection in **109** followed by acid treatment afforded **110**. Benzyl deprotection of **110** furnished *ent*-**21**.



Scheme 11 *Reagents and conditions: a) Ref 39,40; b) Allylamine, reflux, 20 h, 82% over two steps; c) i) KOtBu, DMSO, 100 ^oC, 30 min; ii) 1 M aq. HCl, 15 min, 73%; d) BCl_3, CH_2Cl_2, 0 ^oC, 20 h.*

Karjalainen *et al.* [41] (*Org. Bio. Chem.* **2011**, *9*, 1231)

Karjalainen *et al.* reported total synthesis of *altro*-1-DNJ using Garner aldehyde as the chiral template. Addition of lithiated alkyne **111** on (-)-Garner aldehyde (Scheme 12) furnished **112** (diastereomeric ratio >15 : 1). To perform other functional group transformations, alcohol **112** was protected as its benzyl ether followed by TBS deprotection to obtain alcohol **113**.

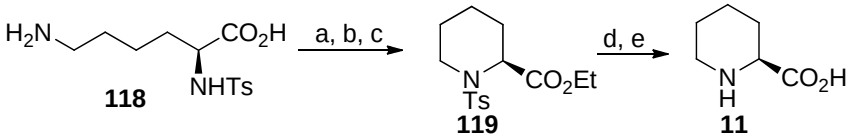


Scheme 12 *Reagents and conditions: a) BuLi, THF, , then Garner aldehyde -78 ^{o}C; b) BnBr, NaH, KI, DMF, 0 ^{o}C, ii) NH_3.HF. HF, MeOH, rt, 95%; c) Red Al, 0 ^{o}C, THF; d) OsO_4, NMO, citric acid, acetone : H_2O (8:2), 81%, dr 6:1; e) TsCl, N-methyl imidazole, DCM, 0 ^{o}C, 76%, f) HCl, MeOH, 50 ^{o}C, ii) $CaCO_3$, MeOH, 0 ^{o}C, 68%; g) Pd/C, MeOH, H_2, HCl.*

Triple bond of **113** was reduced by using Red-Al to provide *trans*-allylic alcohol **114**. Allylic alcohol **114** was dihydroxylated followed by selective monotosylation to deliver *O*-tosyl derivative **116**. Piperidine derivative **117** was obtained from **116** by treatment with HCl followed by treatment with $CaCO_3$. Hydrogenolysis of **117** furnished salt of L-*altro*-1-DNJ **21**.

Fujii's approach (*Bull. Chem. Soc. Jpn.* **1975**, *48*, 1341)

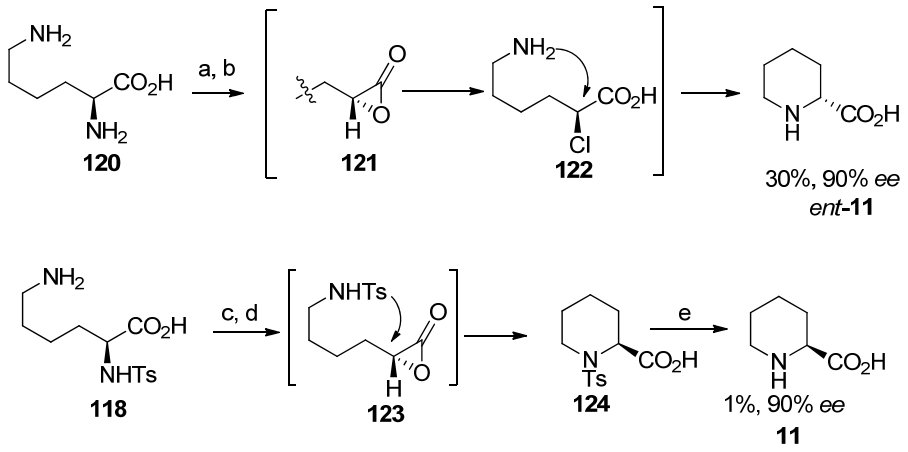
Fujii's approach[42] was based on protected lysine compound **118** (Scheme 13) which was treated with $NaNO_2$ followed by treatment with base to afford functionalized piperdine moiety **119**. Hydrolysis of ester in **119** followed by removal of tosyl group led to target molecule **11**.



Scheme 13 *Reagents and conditions:a) $NaNO_2$, aq. HBr, KBr; b) H^+, EtOH; c) NaH; d) NaOH; e) Na, Liq. NH_3.*

Yamada's approach (*Chem. Pharm. Bull.* **1976**, *24*, 621)

Yamada's approach[43] utilized sodium nitrite–hydrochloric acid as a deaminating agent for (*S*)-lysine **120**. The deamination was followed by barium hydroxide or sodium hydroxide treatment to afford (*R*)-pipecolic acid *ent*-**11** (Scheme 14). Net retention of configuration was explained by the formation of lactonic intermediate **121** followed by halogeno-acid **122**. On the other hand, (*S*)-lysine could be converted directly into natural (*S*)-pipecolic acid **11** starting from ε-tosyl-(*S*)-

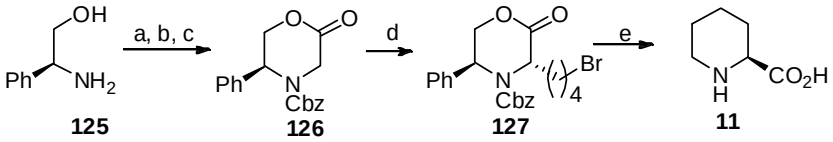


Scheme 14 *Reagents and conditions: a) $NaNO_2$, HCl; b) $Ba(OH)_2$; c) TFA, CF_3COONa; d) Na, Liq. NH_3.*

lysine **118** but in very low yield (~1%) in strong acidic conditions (Scheme 14). acid **118** starting from ε-tosyl-(*S*)-lysine **118** but in very low yield (~1%) in strong acidic conditions (Scheme 14).

Roos' approach (*Synth. Commun.* **2003**, *33*, (13), 2197)

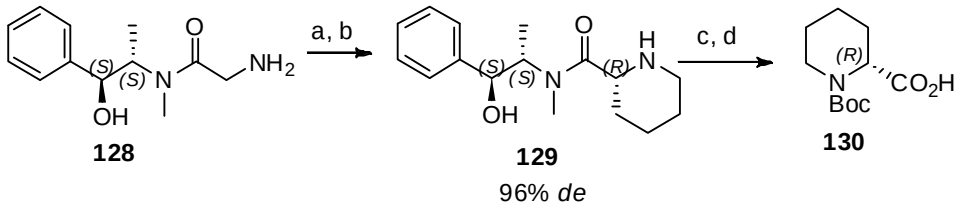
Roos and co-workers[44] used (*S*)-phenylglycinol as the starting material (Scheme 15). Lactone **126**, obtained in three steps from (*S*)-phenylglycinol **125**, was alkylated with a bromotriflate to afford diastereomerically pure compound **127**. Carbamate **127** was subjected under hydrogenation conditions to give enantiopure **11** (Scheme 15).



Scheme 15 *Reagents and conditions: a) $BrCH_2COOEt$; b) CbzCl; c) p-TSA, 73-80%; d) $BrCH_2(CH_2)_3OTf$, NaHMDS, 90%; e) H_2, Pd/C, 45%.*

Myers' approach (*J. Am. Chem. Soc.* **1995**, *117*, 8488)

Myers' approach[45] involves the direct alkylation of pseudoephedrine glycinamide **128**, without the need for protective groups (Scheme 16). Treatment of the enolate derived

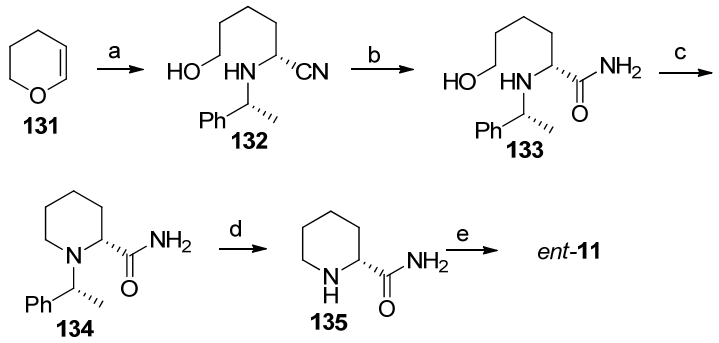


Scheme 16 *Reagents and conditions: a) n-BuLi, LiCl; b) $Cl\text{-}(CH_2)_4I$; c) NaOH; d) Boc_2O.*

from (*S*,*S*)-(+)-**128** with l-chloro-4-iodobutane under heating conditions afforded functionalized piperidine moiety **129** (96% *de*). Alkaline cleavage of the pseudoephedrine chiral auxiliary, free amine protection with $(Boc)_2O$ and recrystallization afforded *N*-Boc-(*R*)-pipecolic acid **130**.

Fadel's approach (*J. Org. Chem.* **2007**, *72*, 1780)

Enantiomerically pure (*R*)-pipecolic acid *ent*-**11** was synthesized in four steps starting from dihydropyran **131** and (*R*)-α-methylbenzylamine by Fadel's group.[46]

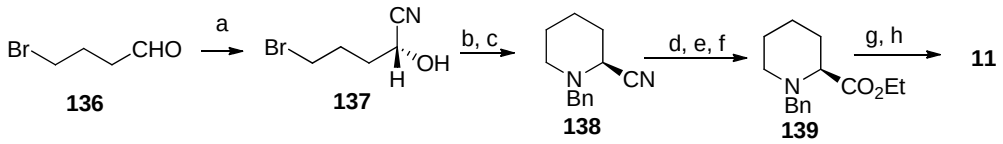


Scheme 17 *Reagents and conditions: a) Phenyl alanine, 2N HCl, NaCN, H_2O, 86%; b) H_2SO_4, DCM, 61%; c) PPh_3, I_2, imidazole, 97%; d) H_2, $Pd(OH)_2$, 85%; e) HCl, then 2-methyloxirane, 91%.*

The asymmetric Strecker reaction of 3,4-dihydro-2*H*-pyran **131** with phenyl alanine and NaCN in aq. HCl gave amino nitrile **132** with excellent diastereoselectivity (96% *de*) (Scheme 17). Hydrolysis of nitrile **132** to amide **133**, cyclisation, debenzylation and amide to acid conversion furnished (*R*)-pipecolic acid *ent*-**11** (Scheme 17).

Gotor's approach (*Tetrahedron: Asymmetry* **1998**, *9*, (9), 1597)

Gotor's approach involves the chemoenzymatic synthesis of (*S*)-2-cyanopiperidine **138** which was further elaborated to give an access to (*S*)-pipecolic acid.[47] Bromo aldehyde **136** was treated with (*R*)-oxynitrilase to provide cyano derivative **137** (Scheme 18). Cyano derivative **137** was reacted with triflic anhydride followed by treatment with benzyl amine to furnish cyclic compound **138**. Hydrolysis of cyno in **138** with subsequent esterification afforded ester **139**. Global deprotection of **139** afforded target molecule **11**.

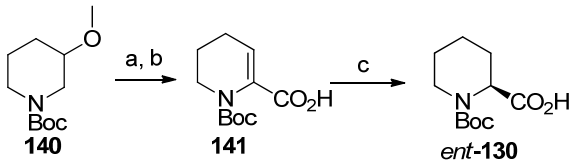


136 **137** **138** **139**

Scheme 18 *Reagents and conditions: a) (R)-Oxynitrilase; b) Tf_2O, pyridine; c) $BnNH_2$, TEA, 70%; d) EtOH, HCl gas, 0 ^oC; e) 0.5 N HCl, 0 ^oC; f) Na_2CO_3, 70%; g) 6N HCl; h) H_2, $Pd(OH)_2$/C, MeOH, 3N HCl, 96%.*

Beak's approach (*Org. Lett.* **2000**, *2*, 155)

Noyori reduction (asymmetric hydrogenation) has been employed by Beak *et al.* for the highly enantiomeric synthesis of pipecolic acid (Scheme 19).



140 **141** *ent*-**130**

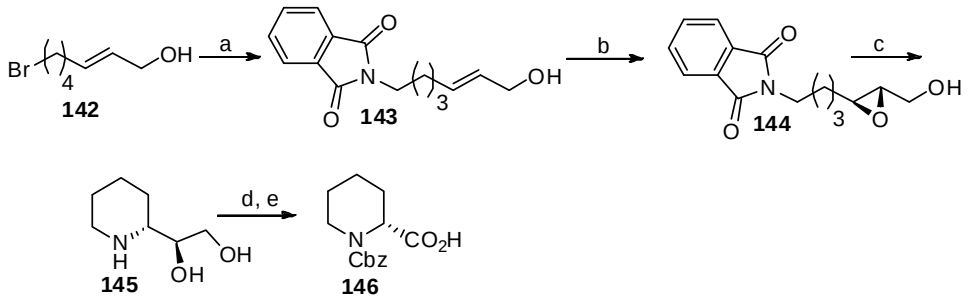
Scheme 19 *Reagents and conditions: a) s-BuLi; b) CO_2, 80%; c) (S)-BINAP-$RuCl_2$, H_2, MeOH, 87%.*

Treatment of *N*-Boc-3-methoxypiperidine **140** with s-BuLi, followed by the addition of carbon dioxide, afforded unsaturated acid **141**. Asymmetry is introduced into the

piperidine ring by the enantioselective hydrogenation of compound **141** with the Noyori catalyst to deliver (*S*)-*N*-Boc-pipecolic acid *ent*-**130** (Scheme 19).[48]

McKervey's approach (*Tetrahedron: Asymmetry* **1995**, *6*, 2905)

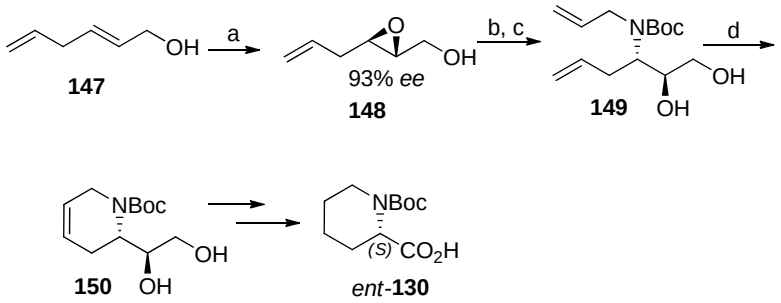
McKervey *et. al.*[49] reported total synthesis of (*R*)-pipecolic acid involving the Sharpless asymmetric epoxidation as the key step. *N*-Protected aminoheptenol **143** (Scheme 20) was subjected to Sharpless asymmetric epoxidation and subsequent treatment with hydrazine hydrate to provide piperidine derivative **145.** Amine protection in **145** followed by oxidative cleavage of the diol afforded (*R*)-*N*-Cbz-pipecolic acid **146** with >95% *ee*.



Scheme 20 *Reagents and conditions: a) PhthNK, DMF, 82%; b) Ti(OiPr)$_4$, (+)-DIPT, t-BuOOH, DCM, -40 ^{o}C, 78%; c) NH_2NH_2. H_2O, EtOH, quanti. d) Cbz-Cl, K_2CO_3; e) $RuCl_3$, $NaIO_4$, H_2O: CH_3CN: CCl_4, 44%.*

Riera's approach (*Tetrahedron Lett.* **2002**, *43*, 779)

Riera *et al.* reported asymmetric synthesis of (*S*)-pipecolic acid utilizing tethered cyclisation and ring-closing metathesis (RCM) as the key steps (Scheme 21).



Scheme 21 *Reagents and conditions: a) $Ti(OiPr)_4$, (-)-DET, t-BuOOH, DCM, -20 oC, 84%; b) Allyl amine, $LiClO_4$, CH_3CN; c) Boc_2O, MeOH, 60%; d) Grubbs 1 st generation catalyst, DCM, 72%.*

Enatiomerically pure epoxide compound **148** was coupled with allyl amine followed by treatment with $LiClO_4$ and $(Boc)_2O$ to deliver diene **149**. The key intermediate **150** was obtained by a RCM, catalyzed by the Grubbs' reagent, on **149**. Hydrogenation of **150** and subsequent oxidative cleavage of the intermediate diol led to (*S*)-*N*-Boc-pipecolic acid *ent*-**130**.[50]

2.4.3 References

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Chapter 2.

Section 5: Formal synthesis of L-fagomine and its isomers, L-*allo*-1-deoxynojirimycin (L-*allo*-1-DNJ), L-*altro*-1-deoxynojirimycin (L-*altro*-1-DNJ) and L-*galacto*-1-deoxynojirimycin (L-*galacto*-1-DNJ)

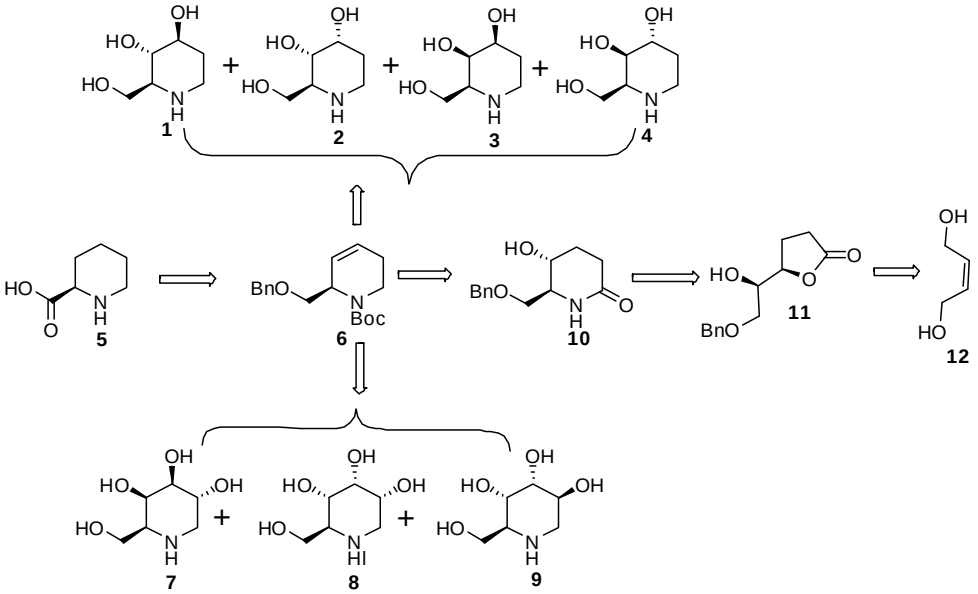
2.5.1 Present work

2.5.1.1 Objective

In literature, there are various protocols reported for the synthesis of fagomine, its isomers and polyhydroxy piperidine alkaloids. Most of the syntheses involved expensive reagents, chiral templates and lengthy routes. Very less attention has been paid towards the syntheses of non-natural (L-configuration) iminosugars which have shown promising biological activity. Still, there is need to develop a general strategy that will provide versatile intermediate which can be easily elaborated for the synthesis of different configurations of iminosugars. With this idea in mind, the synthesis of L-fagomine and its related isomer, L-deoxyallonojirimycin (L-*allo*-1-DNJ), L-deoxyaltronojirimycin (L-*altro*-1-DNJ) and L-deoxygalactonojirimycin (L-*galacto*-1-DNJ) was envisaged from common advanced intermediate.

2.5.1.2 Retrosynthetic analysis

According to retrosynthetic plan (Scheme 1), L-fagomine **1** and its isomers (3-*epi*-fagomine **2,** 4-*epi*-fagomine **3,** 3,4-di-*epi*-fagomine **4**) and azasugars (L-*galacto*-1-DNJ **7**, L-*allo*-1-DNJ **8**, L-*altro*-1-DNJ **9**) could be synthesized from advanced intermediate **6**. Unsaturated piperidine framework **6** can be obtained from lactam **10** which could be easily generated from enantiomerically pure hydroxy lactone **11** *via* reductive lactamisation. Lactone **11** could be obtained from *cis*-butene 1,4-diol **12**.

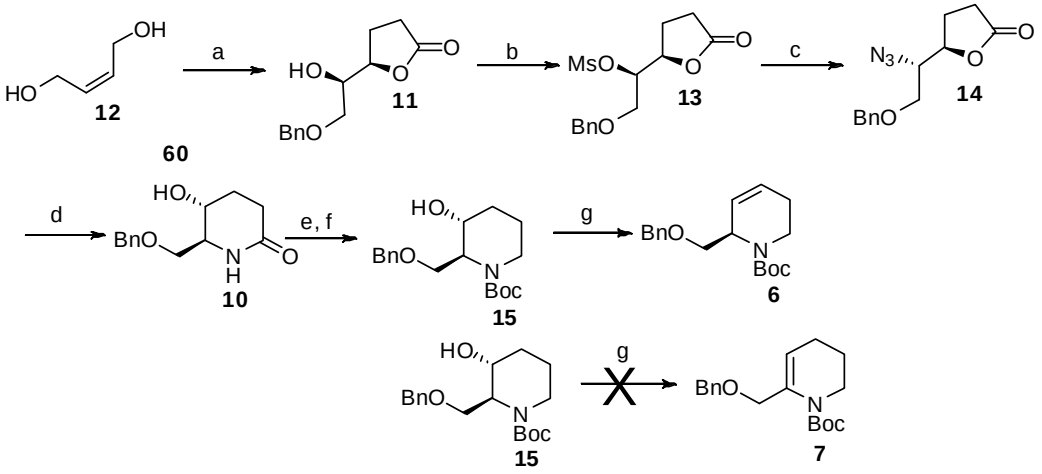


Scheme 1

2.5.1.3 Results and discussion

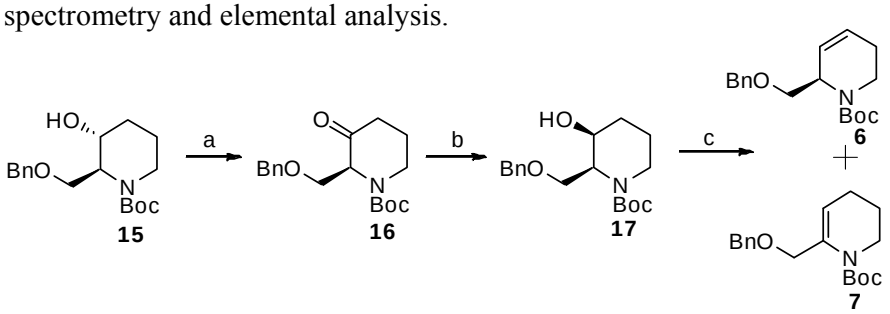
Enantiomerically pure *β*-hydroxyl lactone **11** was derived from *cis*-butene-1,4-diol **12** by known literature protocol[1] involving isomerisation,[2] Claisen orthoester rearrangement[3] and Sharpless asymmetric dihydroxylation.[4]

Lactone **11** was converted into urethane **15** by carrying out functional group transformations which have been described earlier in Chapter 2 section 2. Taking advantage of structural features of hydroxy compound **15**, advanced intermediate **6** was synthesized. Thus, hydroxy compound **15** was treated with PPh_3, imidazole and iodine in toluene under reflux for 30 min to give a novel regioselective eliminated compound **6**. The formation of other regioisomer **7** was not observed as proved by spectroscopic analysis. The IR spectrum showed disappearance of bands at 3435 cm^{-1} and appearance of strong absorption band at 1692 and 1418 cm^{-1} indicating the presence of urethane and double bond functionalities. Its ^1H NMR spectrum showed characteristic olefinic peaks at δ 5.70-5.79 (m, 1H) and 5.90-5.98 (m, 1H) which supported the formation of **6**. ^{13}C NMR specturm showed the disappearance of peak at δ 18.4 indicating the formation of compound **6**. Further, appearance of peak at *m/z* 326.1734 $(M+Na)^+$ in its HRMS spectrum confirmed the formation of **6**.



Scheme 2 *Reagents and conditions: (a) Ref.1; b) MsCl, Et_3N, DMAP (cat.), DCM, 5 h, 91%; c) NaN_3, DMF, 80 ^oC, 18 h, 87%; d) $Pd(OH)_2$, H_2, MeOH, 30 psi, rt, 3 h, 93%; e) LAH, THF, 0 ^oC to rt, 3 h; f) $(Boc)_2O$, TEA, DMAP (cat.), THF, rt, overnight, 63% (over two steps); g) PPh_3, imidazole, I_2, toluene, reflux, 30 min, 85%.*

To extend the application of this novel observation, the next concern was to explore its application on *cis* isomer **17**. α-Hydroxy **15** was oxidised using IBX in ethyl acetate under reflux condition to afford keto compound **16** in 95% yield (Scheme 3). Its IR spectrum displayed the strong absorption bands at 1717 and 1693 cm^{-1} suggesting the presence of keto and carbamate functionalities respectively. Peaks at δ 2.45-2.60 (m, 2H) in its ^{1}H NMR spectrum were attributed to methylene protons adjacent to carbonyl group. ^{13}C NMR spectum displayed the signal at δ 207.2 corresponding to carbonyl carbon. Additionally, DEPT spectrum showed the five CH_2 and four CH carbons supporting the formation of **16** which was further confirmed by mass spectrometry and elemental analysis.



Scheme 3 *Reagents and conditions: (a) IBX, EtOAc, reflux, 3 h, 90%; (b) $NaBH_4$, MeOH, 0 ^{o}C, 30 min, 88 %; (c) PPh_3, imidazole, I_2, toluene, 120 ^{o}C, 30 min, 60%.*

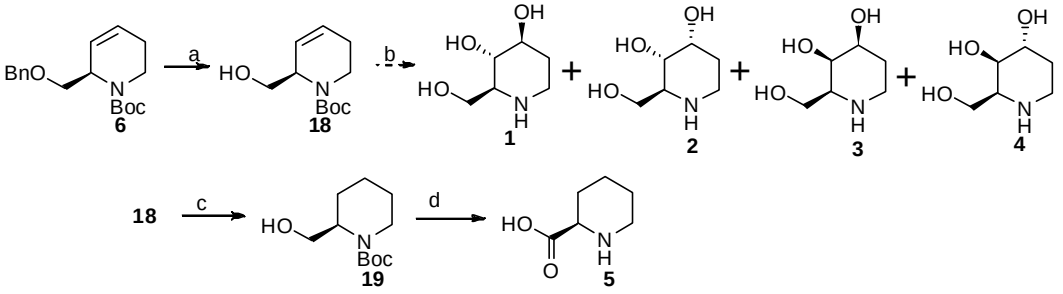
Keto compound **16** was reduced using $NaBH_4$ in methanol at 0 ^{o}C to provide *cis* isomer **17**.[5] Its IR spectrum showed the disappearance of band at 1717 cm^{-1} and appearance of strong band at 3435 cm^{-1} indicating presence of hydroxy functionality. Its ^{1}H NMR spectrum showed the peak at δ 1.48-1.94 supporting the formation of **17**. The ^{13}C NMR spectrum exihibited the peak at δ 69.5 corresponding to CH-OH carbon and disappearance of signal at δ 207.2 provided the strong support for formation of **17**. Further, appearance of a peak at *m/z* 322.2008 $(M+H)^{+}$ in the HRMS analysis confirmed the assigned structure of compound **17**.

Hydroxy compound **17** was treated with PPh_3, imidazole and iodine in toluene under reflux to afford separable regioisomeric olefins **6** and **7** (1.5:1) in 60% yield. ^{1}H NMR spectrum of **7** showed the peak at δ 5.27 as triplet integrating for one proton supporting the formation of **18**. Signals at δ 112.9 and 138.5 in its ^{13}C NMR spectrum

were attributed to olefinic carbons of compound **18**. Further, peak at *m/z* 326.2 $(M+Na)^+$ in its mass spectrum confirmed the formation of **18**.

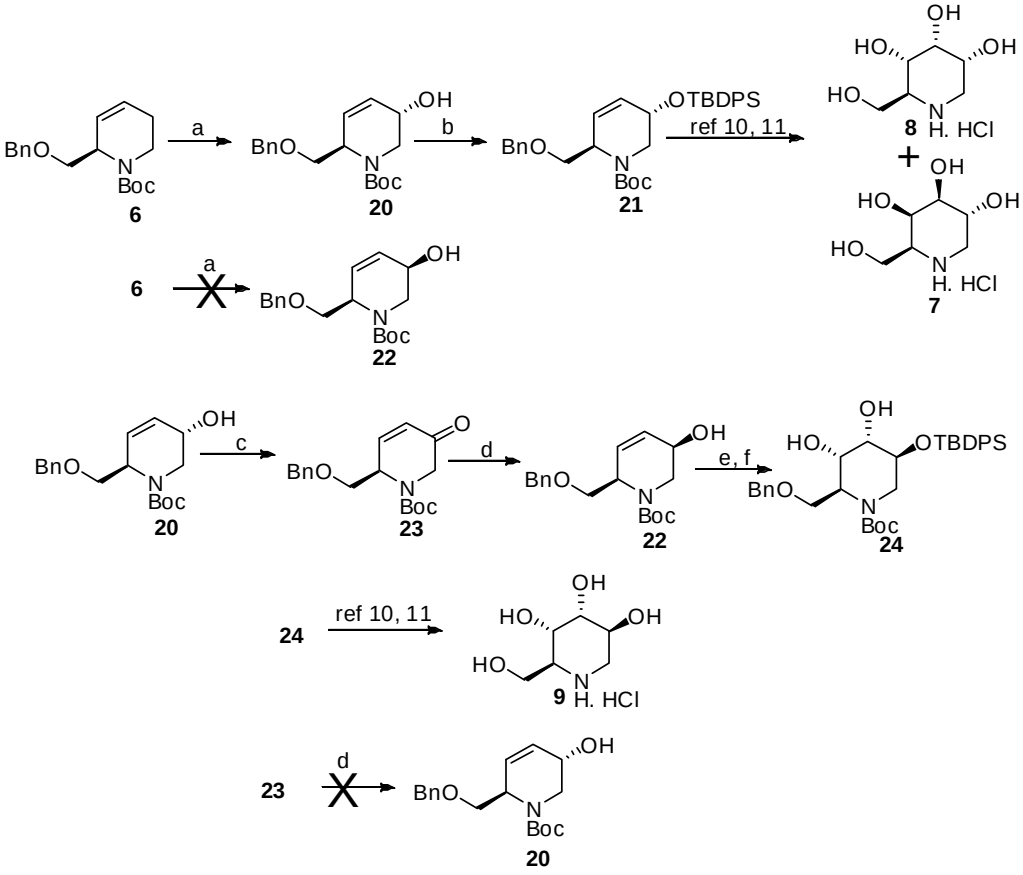
Compound **7** was subjected to Birch reduction conditions using Na (metal) in liquid ammonia at -78 ^oC for 10 min to give **18** (Scheme 4). Its IR spectrum showed strong absorption band at 3440 cm^{-1} indicating presence of hydroxy functionality. Its ^1H NMR spectrum showed disappearance of protons from aromatic region at δ 7.23 to 7.35 indicating the formation of **18**. Its ^{13}C NMR spectrum showed the appearance of peaks at δ 124.8 and 127.8 corresponding to double bond functionality and disappearance of signals from aromatic region supported the formation of **18**. Further, peak at *m/z* 236.1 $(M+Na)^+$ in its mass spectrum confirmed the formation of **18**. Earlier, compound **18**[6]/(*ent*-**18**)[7] was converted to L-fagomine/D-fagomine and its isomers hence the present work constitutes the formal synthesis of L-fagomine **1** and its isomers **2**, **3**, **4**.

Homoallylic alcohol **18** was subjected to hydrogenation using Pd/C as catalyst under hydrogen atmosphere in MeOH at 30 *psi* to provide hydroxymethyl piperidine core[8a] **19** in 92% yield. Strong absorption band at 3442 cm^{-1} in its IR spectrum, indicating presence of hydroxy functionality. Its ^1H NMR spectrum showed absence of peaks at δ 5.62, 5.95 indicating consumption of double bonds. Absence of signals at δ 124.8 and 127.8 in its ^{13}C NMR spectrum indicated the formation of **19**. Synthesied intermediate **19** (*ent*-**19**)[8b] was earlier converted to (*R*)-pipecolic acid **5** ((*S*)-pipecolic acid *ent*-**5**), hence the present work constitutes the formal synthesis of (*R*)-pipecolic acid **5** and bicyclic alkaloids.[8]



Scheme 4 *Reagents and conditions: a) Na (metal), THF, ammonia, -78 ^oC, 10 min, 88%; b) Ref 6, 7; c) Pd/C, H_2, MeOH, 50 psi, 92%;d) Ref.*8.

To extend the application of advanced intermediate **6**, olefinic compound **6** was subjected to allylic oxidation[9] by using SeO_2 in 1,4-dioxane under reflux for 3 h to afford allylic alcohol **20** in 35% yield (Scheme 5). Interestingly this oxidation took place regio and stereoselectively. The formation of other isomer **22**[10] was not observed.



Scheme 5 *Reagents and conditions: (a) SeO_2, 1-4 dioxane, reflux, 3 h, 30-35%; (b) TBDPSCl, imidazole, DMAP (cat.), DCM, 15 h; (c) IBX, EtOAc, reflux, 3 h, 90%; d) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 ^oC, 80%; e) TBDPSCl, imidazole, DMAP(cat.), DCM, 15 h; f) $RuCl_3$, $NaIO_4$, CH_3CN:EtOAc:H_2O, 0 ^oC, 54% (over two steps).*

Strong absorption band at 3421 cm^{-1} in its IR spectrum showed the presence of hydroxy functionality. Appearance of new signal at δ 62.8 in its ^{13}C NMR spectrum, corresponding to CH-OH carbon indicated the formation of **20**. Further, peak at *m/z* 342.1 $(M+Na)^+$ in its mass spectrum confirmed the formation of **20**.

Alcohol **20** was protected as its silyl ether by using imidazole, TBDPSCl in DCM at room temperature to furnish **21**. Disappearance of band at 3421 cm^{-1} in its IR spectrum indicated the absence of hydroxy functionality. Its ^{1}H NMR spectrum showed a characteristic peak at δ 1.05 integrating for nine protons of methyl TBDPS group. ^{13}C NMR spectrum showed the signals at δ 19.3 and aromatic region indicating the formation of **21**. The spectroscopic data and optical rotation of compound **21** was in good agreement with the values reported in the literature.[10,11] Earlier, the compound **21**[10] (*ent*-**21**) [11] was elaborated to the syntheses of L-*allo*-1-DNJ **7** (*ent*-**7**) and L-*galacto*-1-DNJ **8** (*ent*-**8**), hence the present work constitutes the formal synthesis of L-*allo*-1-DNJ **7** and L-*galacto*-1-DNJ **8**.

Taking advantage of structural features of allylic alcohol **20**, the next task was to synthesize the other isomer of DNJ. *Cis*-isomer **22** was synthesized by oxidation of **20**, followed by reduction with $NaBH_4$ in presence of $CeCl_3$. $7H_2O$ in 80% yield. During this transformation, The formation of other isomer **20**[10] was not observed Enone **23** was reduced stereoselectively. The ^{1}H NMR spectrum showed the absence of peak at δ 6.99 indicating the formation of **22**. Its ^{13}C NMR spectrum showed the peak at δ 63.7 corresponding to CH-OH carbon supporting the formation of **22**. A peak at *m/z* 342.1 $(M+Na)^{+}$ in its mass spectrum confirmed the formation of **22**. Further, its structure was confirmed by HRMS analysis.

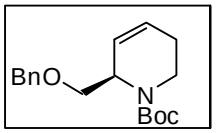
Hydroxy group in **22** was protected by using TBDPSCl, imidazole and DMAP (cat.) in DCM to TBDPS derivative which on flash dihydroxylation using $RuCl_3$ as catalyst and $NaIO_4$ as an oxidant furnished diol **24** as a single isomer. Its IR spectrum displayed the strong absorptions at 3434, 1693 and 1668 cm^{-1} indicating presence of hydroxy and carbamate functionalities. ^{1}H NMR spectrum showed the disappearance of dd at δ 5.82 and doublet at δ 5.95 indicating the consumption of olefin functionality. Signals appeared at δ 69.9 and δ 74.1 in its ^{13}C NMR spectrum, corresponding to two CH-OH carbons. The spectroscopic data of **24** was in good agreement with the data reported in the literature which was further exploited for the synthesis of L-*altro*-1-DNJ.[11]

2.5.2. Conclusion

Asymmetric syntheses of various compounds containing piperidine core were achieved by employing Sharpless asymmetric dihydroxylation, reductive lactamisation, novel regioselective elimination, regio and stereoselective allylic oxidation and stereoselective reduction as the key steps.

2.5.3 Experimental Section:

(*R*)-*tert*-Butyl 2-(benzyloxymethyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (6)



A mixture of alcohol **15** (0.5 g, 1.55 mmol), PPh_3 (1.34 g, 5.11 mmol), imidazole (0.33 g, 4.96 mmol) and I_2 (0.86 g, 3.41 mmol) in anhydrous toluene (10 mL) was refluxed under nitrogen atmosphere for 30 minutes. After completion of the reaction (TLC), the reaction mixture was diluted with ethyl acetate (60 mL) and washed with $Na_2S_2O_3$ solution, water, followed by brine. The organic solvent was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified on silica gel by eluting with light petroleum: EtOAc (9:1) to afford **6** as colorless syrup (0.40 g, 85% yield).

Chemical Formula: $C_{18}H_{25}NO_3$;

Yield : 85%;

$[\alpha]_D^{25}$: +106.31 (c 1.9, $CHCl_3$);

IR ($CHCl_3$, cm^{-1}) : 1692, 1418, 1172;

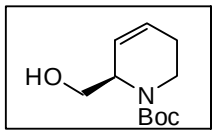
ESIMS (*m/z*): 326.28$(M+Na)^+$;

HRMS calculated for $[C_{18}H_{25}NO_3+Na]^+$ 326.1727; found: 326.1734;

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 1.88-2.04 (m, 1H), 2.13-2.30 (m, 1H), 2.94 (bs, 1H), 3.47-3.61 (m, 2H), 4.15 (bs, 1H), 4.49-4.66 (m, 3H), 5.70-5.79 (m, 1H), 5.90-5.98 (m, 1H), 7.23-7.35 (m, 5H);

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 24.9, 28.5, 71.3, 73.0, 79.5, 126.7, 127.4, 128.3, 138.3, 154.5.

(*R*)-*tert*-Butyl 2-(hydroxymethyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (18)



Benzyl ether **6** (0.100 g, 0.33 mmol, 1.0 eq.) was stirred in anhydrous THF (5 ml) at -78 °C under an atmosphere of nitrogen. Ammonia (3 mL) gas was condensed by passing into the flask, then sodium (0.023 g, 0.99 mmol, 3.0 eq.) was added and the deep blue mixture stirred for 10 min at -78 °C. After 10 min solid ammonium chloride (5 g) was added to reaction mixture. The ammonia was then allowed to evaporate by removing the

cooling bath, and the product was extracted with ethyl acetate (4 x 50 ml). The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield the crude product as yellow syrup. The residue was purified on silica gel by eluting with light petroleum: EtOAc (7:3) to afford homoallylic alcohol **18** as colorless oil (0.061 g, 88%).

Chemical Formula: $C_{11}H_{19}NO_3$;

Yield : 88%;

$[\alpha]_D^{25}$: +200 (c 0.6, $CHCl_3$); lit.[6] For comp-**18** **$[\alpha]_D^{24}$** +230.7 (c 1.75, $CHCl_3$);

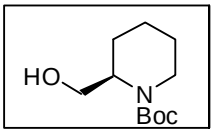
IR ($CHCl_3$, cm^{-1}) : 3440, 2975, 1693, 1674, 1423;

ESIMS *(m/z)*: 236.1 $(M+Na)^+$;

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 (s, 9H), 1.95-2.00 (m, 1H), 2.16-2.26 (m, 1H), 2.95 (br, 1H), 3.64 (m, 1H), 3.68-3.70 (m, 1H), 4.08 (bs, 1H), 4.53 (bs, 1H), 5.62 (dt, *J* = 10, 2.9 Hz, 1H), 5.95 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 24.9, 28.5, 38.1, 54.3, 64.9, 80.1, 124.8, 127.8, 156.2.

(*R*)-*tert*-Butyl 2-(hydroxymethyl)piperidine-1-carboxylate (19)



Olefin **18** (0.100 g, 0.46 mmol) and 10 % Pd/C in methanol (5 ml) was subjected under hydrogen atmosphere at 30 *psi* at room temperature (25 ^oC) for 3 h. The reaction mixture was filtered through celite and the celite layer was washed thoroughly with methanol (2 X 20 mL) and concentrated under reduced pressure. The residue thus obtained was purified by flash silica gel column chromatography using light petroleum: ethyl acetate (1:1) as an eluent to furnish alcohol **19** (0.092 g, 92% yield) as a colorless liquid.

Chemical Formula: $C_{11}H_{21}NO_3$;

Yield : 92%;

$[\alpha]_D^{25}$: +38.9 (c 1, $CHCl_3$); lit.[8] for *ent*-**20** -40.1 (c 1, $CHCl_3$);

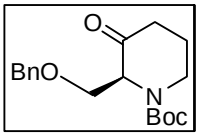
HRMS calculated for $[C_{11}H_{21}NO_3+H]^+$ 216.1594; found: 216.1600;

IR ($CHCl_3$, cm^{-1}): 3442, 2940, 2890, 1655, 1422, 1370, 1280, 1170, 1150, 1060;

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 9H), 1.55-1.68 (m, 4H), 2.11 (bs, 2H), 2.87 (m, 1H), 3.59 (dd, *J* = 10, 6 Hz, 1H), 3.75-3.85 (m, 1H), 3.93 (d, *J* = 12 Hz, 1H), 4.72-4.85 (m, 1H);

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 19.31, 24.8, 25.2, 28.3, 39.8, 52.1, 60.1, 79.5, 155.8.

(S)-*tert*-Butyl 2-((benzyloxy)methyl)-3-oxopiperidine-1-carboxylate (16)



To a solution of alcohol **15** (0.100 g, 0.311 mmol) in ethyl acetate (5 mL) was added IBX (0.17 g, 0.622 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was allowed to reflux for 3 h. After completion of reaction (monitored by TLC), the reaction mixture was allowed to cool at room temperature. The reaction mixture was filtered through a Whatmann filter paper. The combined organic layer was washed with saturated solution of $NaHCO_3$ (20 mL) followed by water (30 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to provide crude residue. The residue was purified by flash silica gel column chromatography using ethyl acetate and pet ether (3: 7) as an eluent to give keto carbamate **16** as colorless syrup (0.89 g, 90%).

Chemical Formula: $C_{18}H_{25}NO_4$;

Yield : 90%;

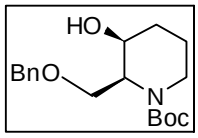
$[\alpha]_D^{25}$: +30.2 (c 1.27, $CHCl_3$);

IR ($CHCl_3$, cm^{-1}): 1717, 1693, 1404, 1117;

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.50 (s, 9H), 1.89-2.17 (m, 2H), 2.45-2.60 (m, 2H), 3.49 (bs, 1H), 3.69-4.32 (m, 3H), 4.52 (s, 2H), 4.63 (bs, 1H), 7.25-7.42 (m, 5H);

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 22.1, 28.5, 38.8, 72.3, 73.4, 80.2, 127.4, 127.7, 128.5, 207.2.

(2S,3S)-*tert*-Butyl 2-((benzyloxy)methyl)-3-hydroxypiperidine-1-carboxylate (17)



To a solution of keto carbamate **16** (0.1 g, 0.313 mmol) in methanol (5 mL) was added $NaBH_4$ (23.6 mg, 0.626 mmol) at 0 ^oC portionwise. The reaction mixture was allowed to stir for 30 min at room temperature. After completion of reaction, the reaction mixture was concentrated under reduced pressure. The aq. solution of NH_4Cl was added to the semisolid mass and allowed to stir for 30 min and the reaction mixture was extracted

with DCM (3 X 30 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford residue. The residue was purified by flash silica gel column chromatography using ethyl acetate and pet ether as an eluent to provide *cis* alcohol **17** (88.5 mg, 88%) as colorless syrup.

Chemical Formula : $C_{18}H_{27}NO_4$;

Yield : 88%;

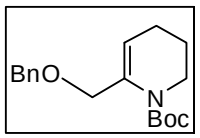
$[\alpha]_D^{25}$: +36.8 (c 0.5, $CHCl_3$); lit. [12] for *ent*-**17** **$[\alpha]_D^{23}$** –38.9 (*c* = 0.76, $CHCl_3$).

HRMS calculated for $[C_{18}H_{27}NO_4+H]^+$ 322.2013; found: 322.2008;

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 9H), 1.48-1.94 (m, 4H), 2.66 (br *t*, 1H), 3.61-3.69 (m, 1H), 3.76-3.97 (m, 3H), 4.53 (d, *J* = 1.5 Hz, 2H), 4.58-4.70 (m, 1H), 7.30 (s, 5H);

^{13}C (100 MHz, $CDCl_3$+CCl_4): δ 24.0, 28.5, 28.8, 39.2, 53.2, 66.6, 69.5, 73.3, 79.8, 127.7, 127.8, 128.5, 137.7, 154.9.

***tert*-Butyl 6-((benzyloxy)methyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (7)**



A mixture of alcohol **17** (0.05 g, 0.155 mmol), PPh_3 (0.134 g, 0.511 mmol), imidazole (0.033 g, 0.496 mmol) and I_2 (0.086 g, 0.341 mmol) in anhydrous toluene (10 mL) was refluxed under nitrogen atmosphere for 30 minutes. After completion of the reaction (TLC), the reaction mixture was diluted with ethyl acetate (60 mL) and washed with $Na_2S_2O_3$ solution followed by water. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified on silica gel by eluting with light petroleum: EtOAc (9:1) to afford olefin **7** (0.011 g) and olefin **6** (0.017 g) in 60% yield.

Chemical Formula: $C_{18}H_{25}NO_3$

Yield : 24%;

IR ($CHCl_3$, cm^{-1}): 1698, 1654, 1400, 1162;

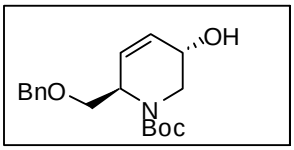
ESIMS (*m/z*): 326.28 $(M+Na)^+$;

HRMS calculated for $[C_{18}H_{25}NO_3+Na]^+$ 326.1727; found: 326.1734;

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48 (s, 9H), 1.78-1.81 (m, 2H), 2.09-2.18 (m, 2H), 3.50-3.57 (m, 2H), 4.33 (s, 2H), 4.48 (s, 2H), 5.27 (t, J = 3.5 Hz, 1H), 7.30-7.33 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 22.9, 23.5, 28.4, 44.4, 71.5, 71.9, 80.0, 112.9, 127.5, 127.8, 128.3, 136.8, 138.5, 153.3.

(2*R*,5*S*)-*tert*-Butyl 2-(benzyloxymethyl)-5-hydroxy-5,6-dihydropyridine-1(2*H*)-carboxylate (20)



To solution of alkene **6** (0.100 g, 0.33 mmol) in dry 1,4-dioxane (20 mL) was added SeO_2 (0.054 g, 0.49 mmol). The reaction mixture was stirred for 3 h under reflux condition. After completion of reaction (monitored by TLC), the reaction mixture was allowed to cool at room temperature. The reaction mixture was filtered through a celite bed and the residue was washed with 1,4-dioxane (5 X 10 mL). The filtrate was concentrated *in vacuo* and the obtained residue was dissolved in ethyl acetate (30 mL). The organic layer was washed with saturated $NaHCO_3$ solution followed by water. The organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude product. The crude residue was purified by flash silica gel column chromatography using 25% ethyl acetate in petroleum ether as an eluent to afford pure product **20** as colorless oil (0.031 g, 30%).

Chemical Formula: $C_{18}H_{25}NO_4$

Yield: 30%

$[\alpha]_D^{25}$: +284.94 (c 0.97, $CHCl_3$); For compound **20** lit.[10] **$[\alpha]_D^{20}$** +270 (*c* 1.0, $CHCl_3$);

IR ($CHCl_3$, cm^{-1}): 3421, 1690, 1171;

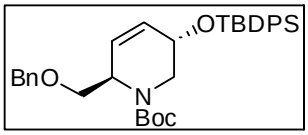
ESIMS (*m/z*) : 342.1 $(M+Na)^+$;

HRMS calculated for $[C_{18}H_{25}NO_4+Na]^+$ 342.1676; found: 342.1690;

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (s, 9H), 3.06-3.29 (m, 1H), 3.53 (bs, 2H), 3.98-4.31 (m, 2H), 4.49 (d, *J* = 12 Hz, 1H), 4.54 (d, *J* = 12 Hz, 1H), 4.60-4.70 (m, 1H), 5.92-5.96 (m, 1H), 6.06-7.10 (m, 1H), 7.26-7.34 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 28.46, 62.9, 70.3, 73.2, 80.1, 127.5, 127.7, 128.4, 138.1.

(2*R*,5*S*)-*tert*-Butyl 2-((benzyloxy)methyl)-5-((tert-butyldiphenylsilyl)oxy)-5,6-dihydropyridine-1(2*H*)-carboxylate (21)



To a solution of alcohol **20** (0.020 g, 0.062 mmol) in anhydrous DCM (5 mL) was added imidazole (0.0085 g, 0.124 mmol) followed by addition of TBDPSCl (0.024 mL, 0.093 mmol) and DMAP (cat.) at 0 ^{o}C under nitrogen atmosphere. The reaction was allowed to stir at room temperature for 15 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water (30 mL) and extracted with DCM (3 X 30 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography using ethyl acetate: pet ether (5: 95) as an eluent to afford TBS ether as colorless syrup **21** (0.020 g, 60%).

Chemical Formula : $C_{34}H_{43}NO_4Si$;

Yield : 60%;

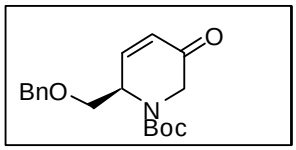
$[\alpha]_D^{25}$: +170 (c 0.7, $CHCl_3$), lit.[11] for *ent*-**21** **$[\alpha]_D^{21}$** -178 (c 1, $CHCl_3$);

IR ($CHCl_3$, cm^{-1}) : 1695, 1417, 1111;

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.49 (s, 9H), 2.76- 3.15 (m, 1H), 3.51 (s, 2H), 4.06 (s, 1H), 4.12- 4.41 (m, 1H), 4.47 (d, J = 12.2 Hz, 1H), 4.52 (d, J = 12.2 Hz, 1H), 4.55- 4.85 (m, 1H), 5.66 (bs, 1H), 5.81 (dd, J = 10.1, 3.8 Hz, 1H), 7.23-7.31 (m, 5H), 7.32- 7.44 (m, 6H), 7.66 (d, J = 6.6 Hz, 2H), 7.72 (d, J = 6.8 Hz, 2H);

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 19.3, 26.9, 28.5, 63.9, 70.6, 73.0, 79.5, 127.4, 127.5, 127.7, 128.3, 129.6, 129.7, 133.9, 135.8, 138.2, 154.9.

(*R*)-*tert*-Butyl 2-(benzyloxymethyl)-5-oxo-5,6-dihydropyridine-1(2*H*)-carboxylate (23)



To a solution of alcohol **20** (0.030 g, 0.094 mmol) in ethyl acetate (5 mL) was added IBX (0.052 g, 0.19 mmol). The reaction mixture was refluxed for 2h. After completion of reaction, the reaction mixture was allowed to cool to room temperature. The reaction mixture was filtered through a Whatman filter paper and the residue was washed with ethyl acetate (3 X 10 mL). The combined organic layer was washed with $NaHCO_3$, dried over anhydrous sodium sulphate,

filtered and concentrated under reduced pressure to obtain crude enone. The residue thus obtained was purified by flash silica gel column chromatography using light petroleum: ethyl acetate (8:2) as an eluent to furnish colorless alcohol **23** (0.026 g, 90% yield).

Chemical Formula: $C_{18}H_{23}NO_4$;

Yield: 90%;

$[\alpha]_D^{25}$: +119.4 (c 0.94, $CHCl_3$);

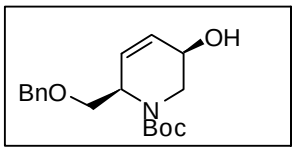
IR ($CHCl_3$, cm^{-1}): 3020, 1705, 1693, 1150;

ESIMS (*m/z*): 340.3 $(M+Na)^+$;

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 9H), 3.61-3.91 (m, 3H), 4.45-4.58 (m, 3H), 4.91 (bs, 1H), 6.20 (dd, *J* = 10, 1.5 Hz, 1H), 6.99 (dd, *J* = 10, 5 Hz, 1H), 7.22-7.33 (m, 5H);

^{13}C (100 MHz, $CDCl_3$+CCl_4): δ 28.4, 70.1, 73.3, 80.9, 127.2, 127.5, 127.8, 128.3, 128.4, 128.5, 193.1.

(2*R*,5*R*)-*tert*-Butyl 2-(benzyloxymethyl)-5-hydroxy-5,6-dihydropyridine-1(2*H*)-carboxylate (22)



To a stirred solution of enone **23** (0.025 g, 0.078 mmol) and cerium chloride heptahydrate (0.046 g, 0.18 mmol) in methanol (5 mL) was added sodium borohydride (0.006 g, 0.17 mmol) portion wise at 0 °C. The reaction mixture was stirred for one hour at that temperature, after which NH_4Cl was added to destroy excess $NaBH_4$ All volatiles were evaporated *in vacuo* and the residue was partitioned between water (20 mL) and CH_2Cl_2 (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2 X 20 mL), the combined organic phase washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude alcohol. The residue was purified by flash silica gel column chromatography using light petroleum: ethyl acetate (7:3) as an eluent to furnish colorless alcohol **23** (0.020 g, 80% yield).

Chemical Formula : $C_{18}H_{25}NO_4$;

Yield : 80%;

$[\alpha]_D^{25}$: +140.76 (c 0.43, $CHCl_3$); lit[10] for *ent*-**22** **$[\alpha]_D^{21}$** –146 (*c* = 1.0, $CHCl_3$);

IR ($CHCl_3$, cm^{-1}) : 3421, 1696, 1670, 1455, 1416, 1116.

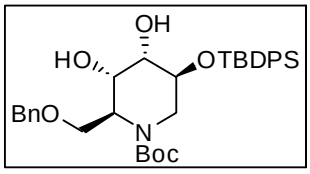
ESIMS (*m/z*) : 342 $(M+Na)^+$;

HRMS calculated for $[C_{18}H_{25}NO_4+Na]^+$ 342.1676; found: 342.1690;

^{1}H NMR (500 MHz, $CDCl_3$+CCl_4):δ 1.45 (s, 9H), 1.97 (s, 1H), 2.85 (bs, 1H), 3.47-3.72 (m, 2H), 4.22 (bs, 2H), 4.45 (bs, 1H), 4.53 (d, *J* = 12 Hz, 1H), 4.57 (d, *J* = 12 Hz, 1H), 5.82 (dd, *J* = 10, 3 Hz, 1H), 5.95 (d, *J* = 10 Hz, 1H), 7.26-7.35 (m, 5H);

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 28.5, 51.6, 63.7, 70.6, 73.3, 80.1, 127.6, 127.7, 128.4, 131.6, 138.0, 154.4.

(2*S*,3*S*,4*S*,5*S*)-*tert*-Butyl 2-((benzyloxy)methyl)-5-((tert-butyldiphenylsilyl)oxy)-3,4-dihydroxypiperidine-1-carboxylate (24)



To a solution of alcohol **22** (0.020 g, 0.062 mmol) in anhydrous DCM was added imidazole (0.0085 g, 0.124 mmol) followed by addition of TBDPSCl (0.024 mL, 0.093 mmol) at 0 ^oC under nitrogen atmosphere. The reaction was allowed to stir at room temperature for 6 h. After completion of reaction (monitored by TLC), reaction mixture was diluted with water. The reaction mixture was extracted with DCM (3 X 30 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was filtered by flash silica gel chromatography using ethyl acetate: pet ether as an eluent to afford impure TBS ether. To a solution of crude olefin (0.034 mg, 60.95 μmol) in CH_3CN: EtOAc (2 mL: 2 mL) at 0 ^oC was added a solution of $RuCl_3.H_2O$ (cat.) and $NaIO_4$ (19.5 mg, 91.43 μmol) in distilled water (2 mL). The mixture was stirred vigorously for 2 min. and quenched with saturated aqueous solution of $Na_2S_2O_3$ (30 mL). The aqueous phase was separated and extracted with EtOAc (3 X 20 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue thus obtained was purified by flash silica gel column chromatography using light petroleum: ethyl acetate (6:4) as an eluent to furnish colorless alcohol **24** (0.02 g, 54% over two steps).

Chemical Formula: $C_{34}H_{45}NO_6Si$;

Yield: 54%;

IR ($CHCl_3$, cm^{-1}): 3434, 2929, 2856, 1693, 1668, 1427, 1111;

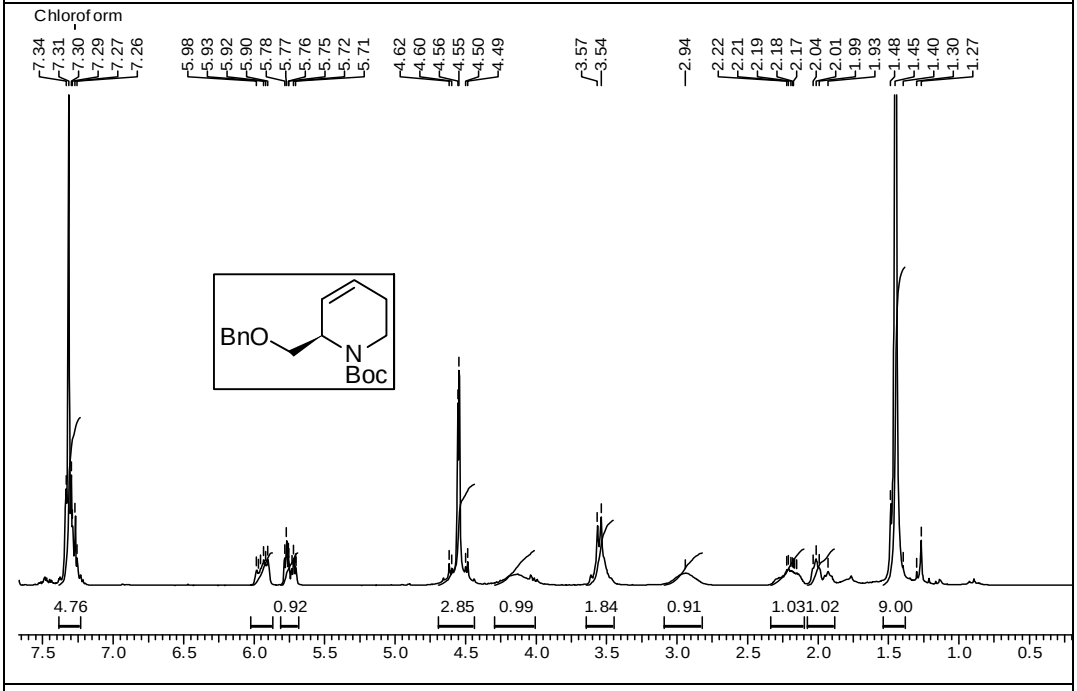
$[\alpha]_D^{25}$: +50 (c 052, $CHCl_3$), lit.[11] +52 (c 1, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): δ 1.08 (s, 9H), 1.34 (s, 9H), 2.10 (bs, 1H), 2.25 (s, 1H), 2.49 (s, 1H), 2.83 (bs, 1H), 3.55 (s, 2H), 3.76 (bs, 1H), 3.87- 3.95 (m, 1H), 4.01 (s, 1H), 4.36 (broad s, 1H), 4.48 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 7.25- 7.45 (m, 11H), 7.63 (d, J = 7.6 Hz, 2H), 7.72 (d, J = 7.6 Hz, 2H);

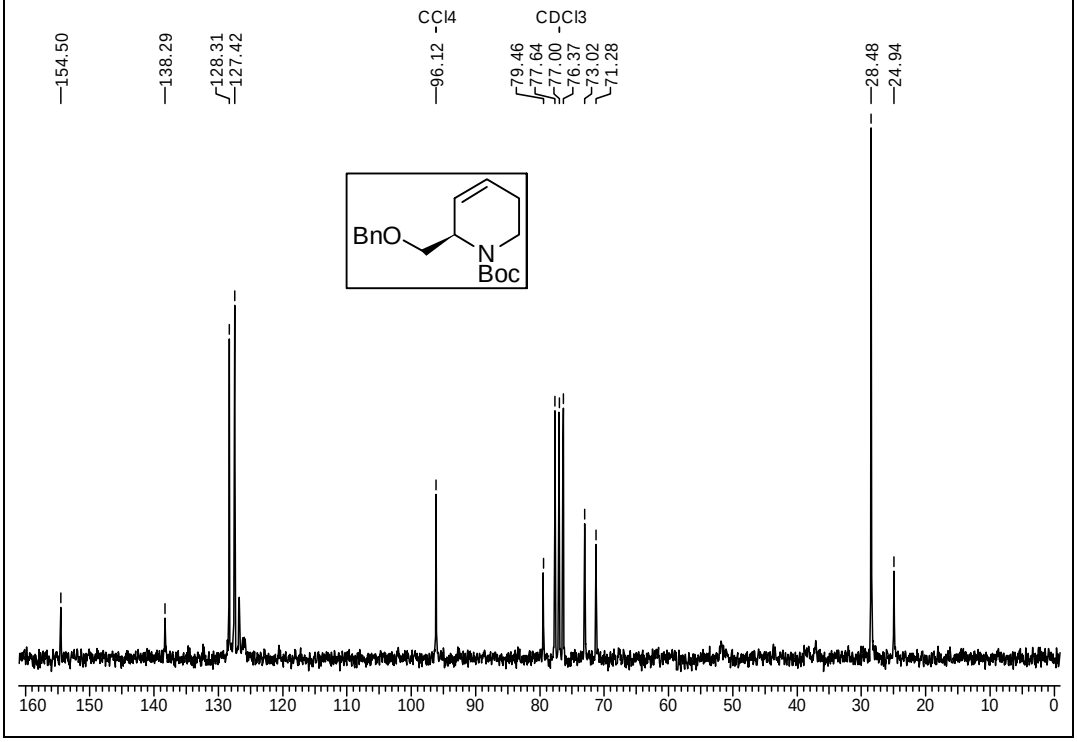
^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 19.4, 27.1, 28.4, 29.8, 68.9, 69.7, 69.9, 73.2, 74.1, 79.9, 127.5, 127.7, 127.9, 128.5, 130.1, 133.7, 135.8, 137.9, 155.1.

2.5.4. Spectra

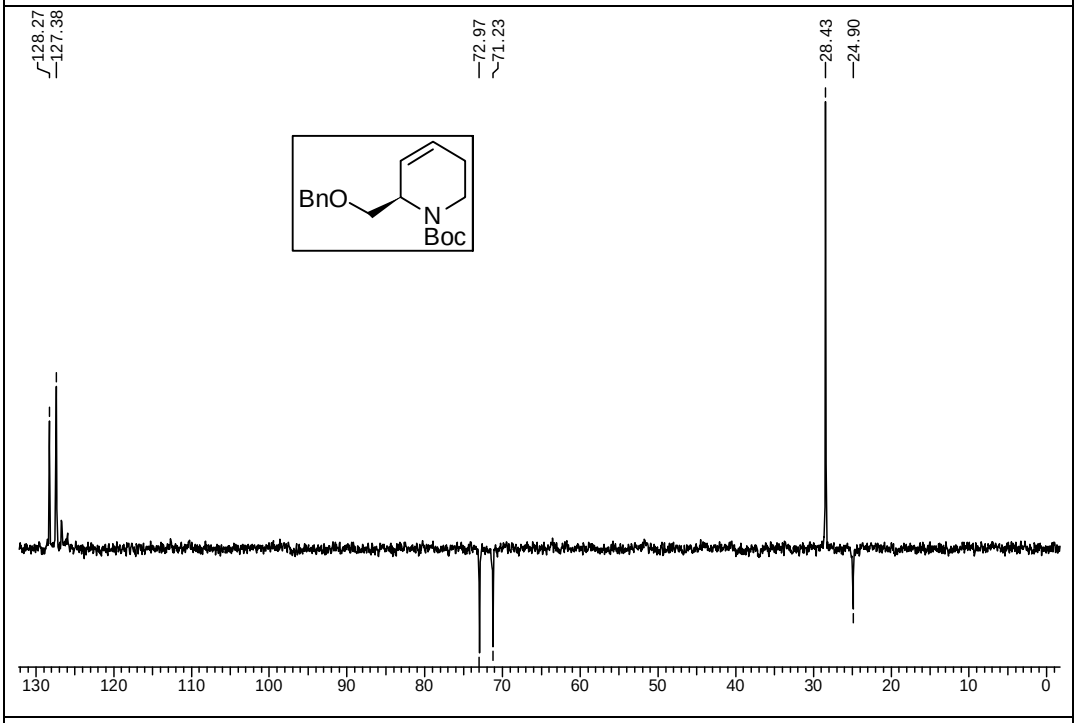
^{1}H NMR Spectrum of compound 6 ($CDCl_3$+CCl_4, 200 MHz)



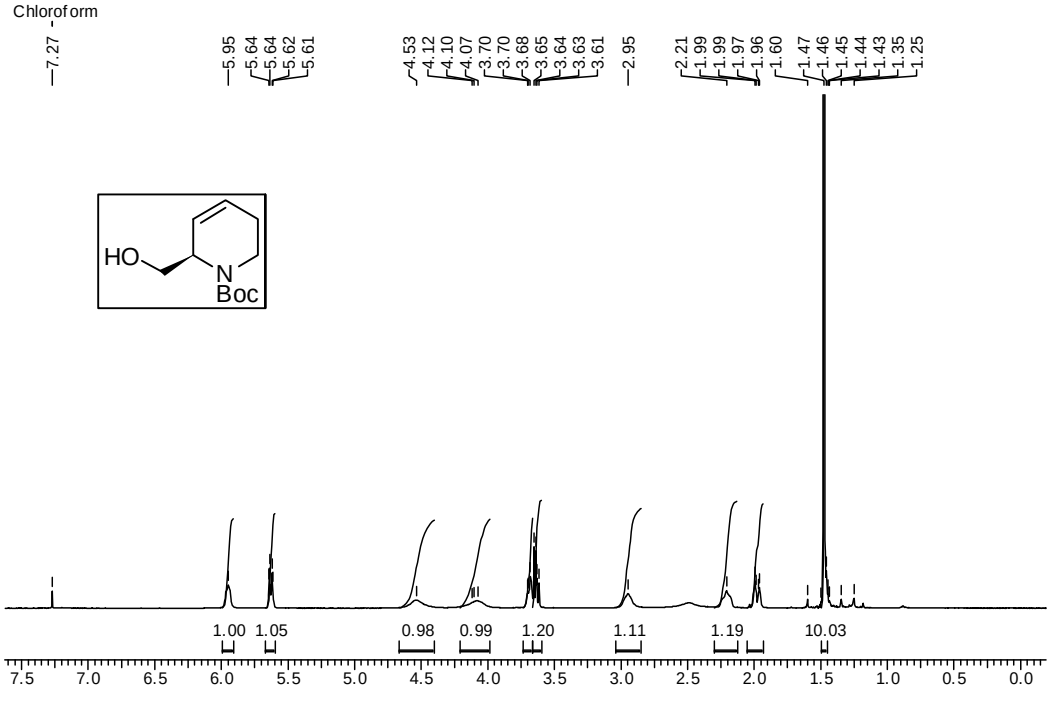
^{13}C NMR Spectrum of compound 6 ($CDCl_3$+CCl_4, 50 MHz)



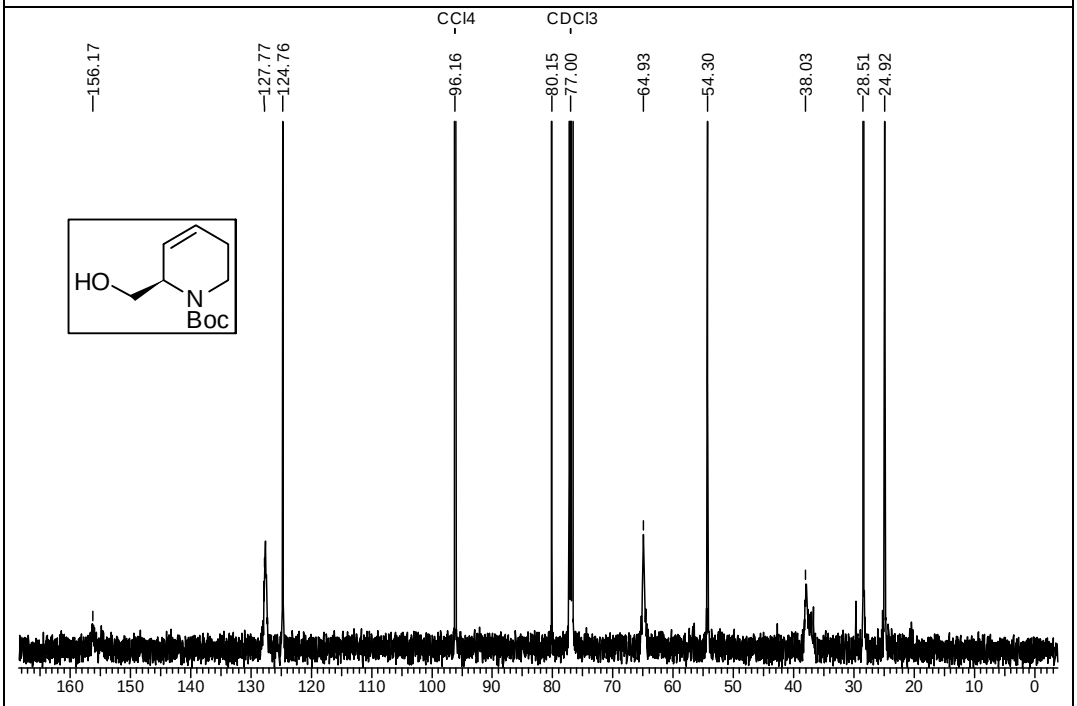
DEPT Spectrum of compound 6 ($CDCl_3$+CCl_4, 50 MHz)



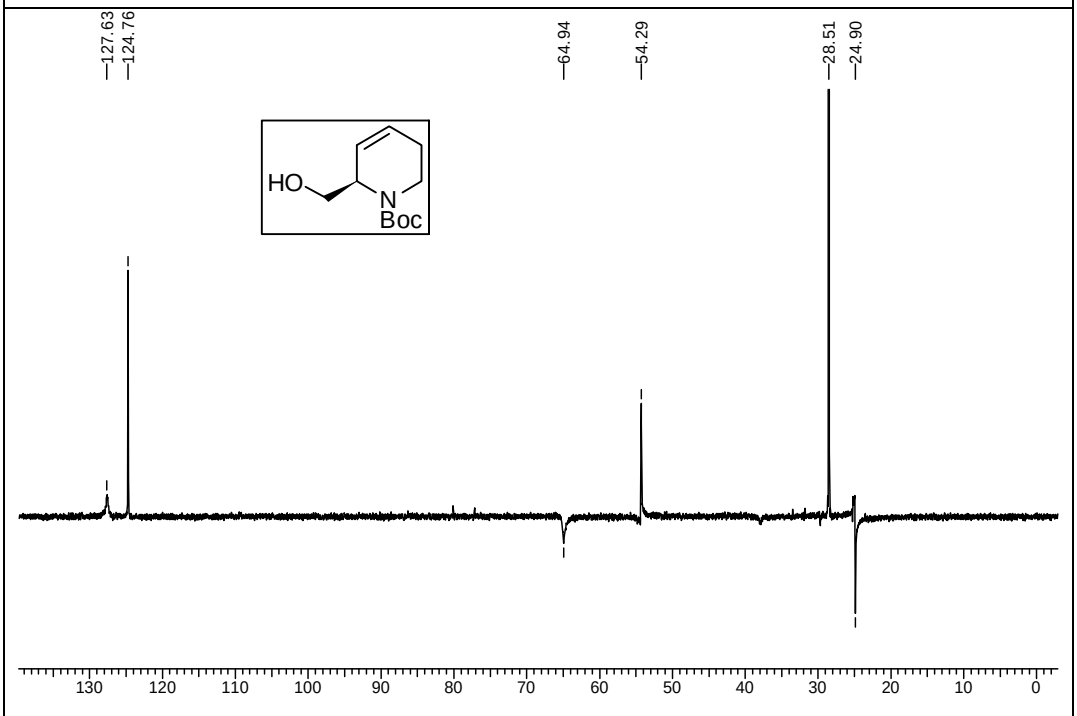
^{1}H NMR Spectrum of compound 18 ($CDCl_3$+CCl_4, 500 MHz)



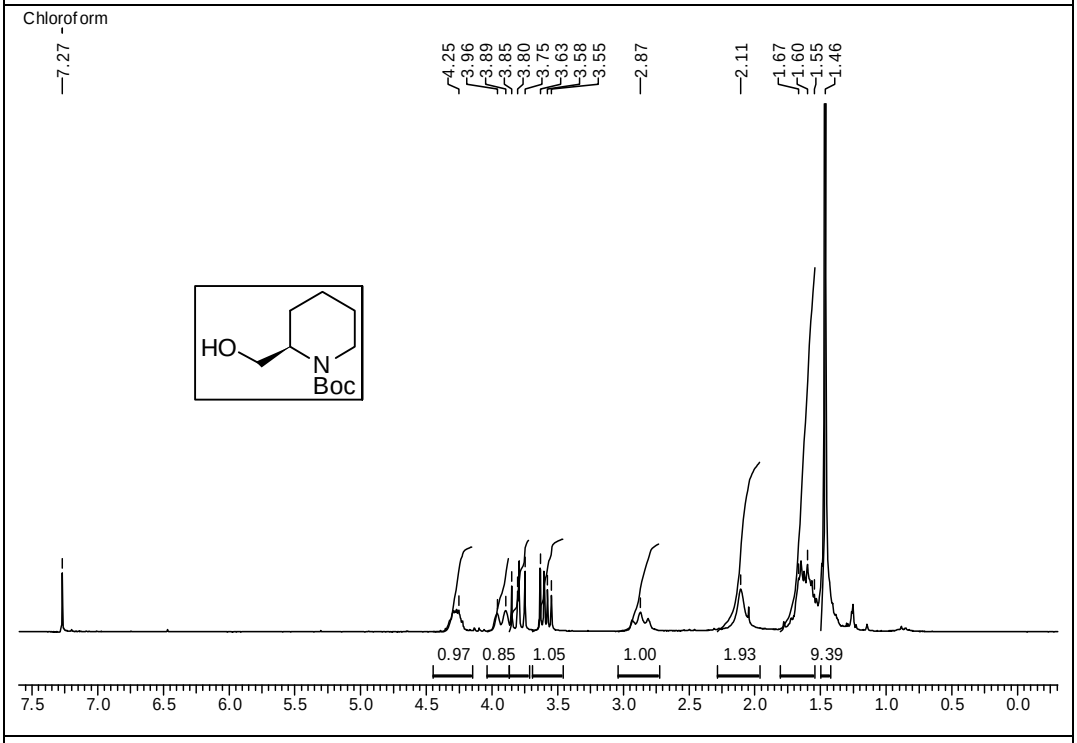
^{13}C NMR Spectrum of compound 18 ($CDCl_3$+CCl_4, 125 MHz)



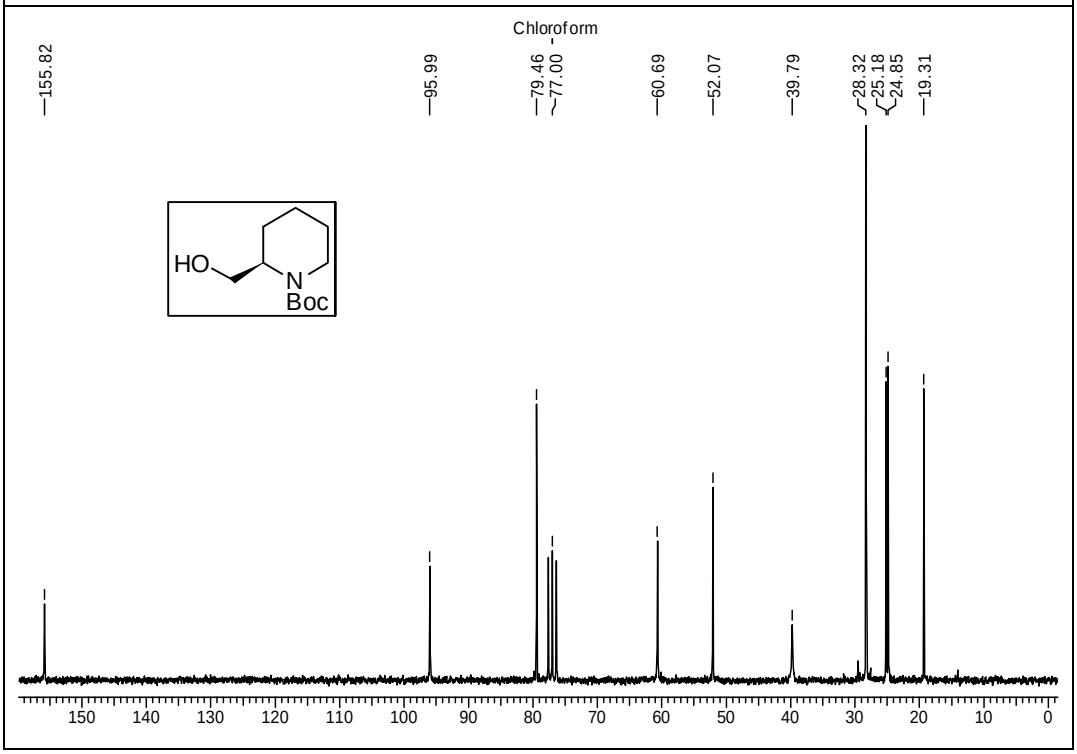
DEPT Spectrum of compound 18 ($CDCl_3$+CCl_4, 125 MHz)



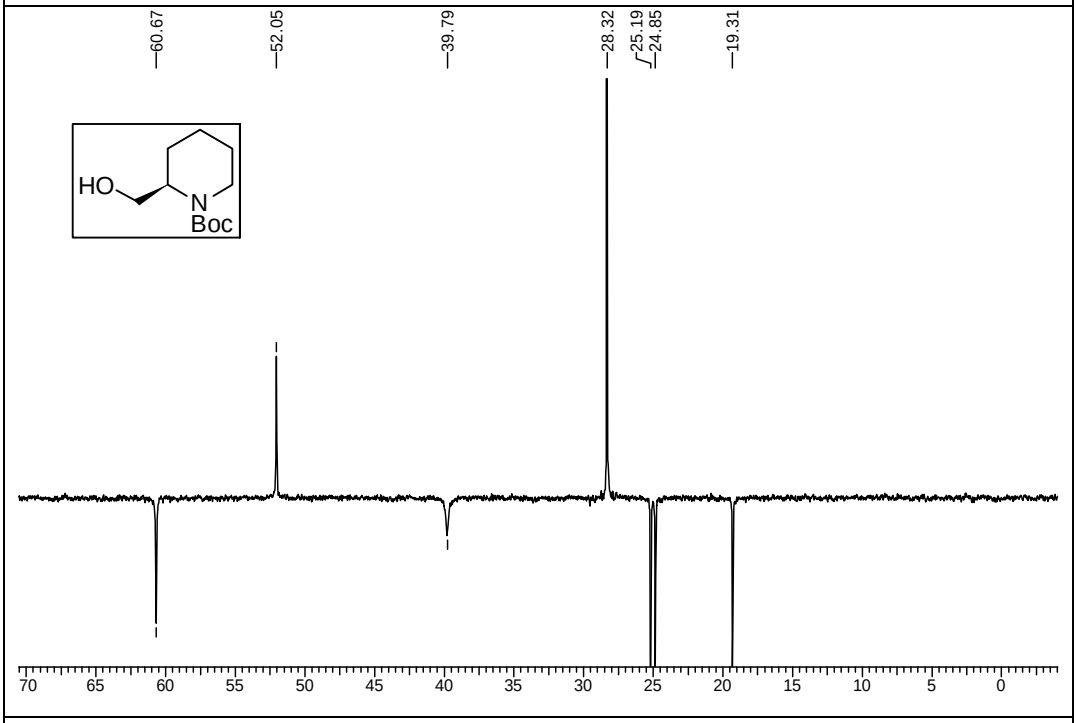
^{1}H NMR Spectrum of compound 19 ($CDCl_3$+CCl_4, 200 MHz)



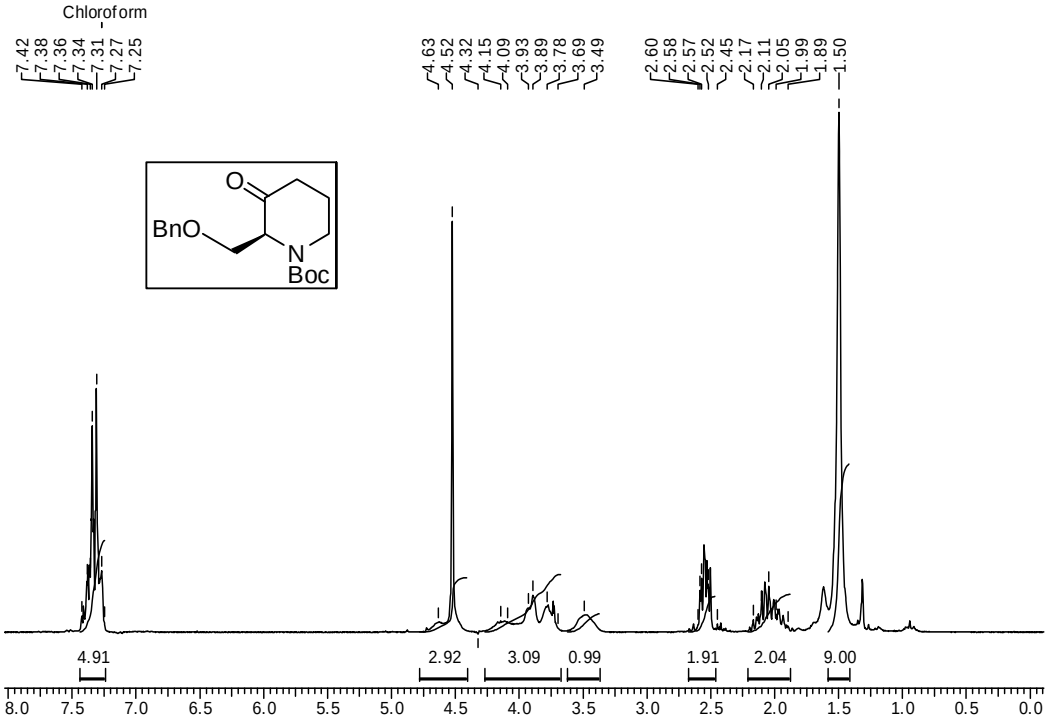
^{13}C NMR Spectrum of compound 19 ($CDCl_3$+CCl_4, 50 MHz)



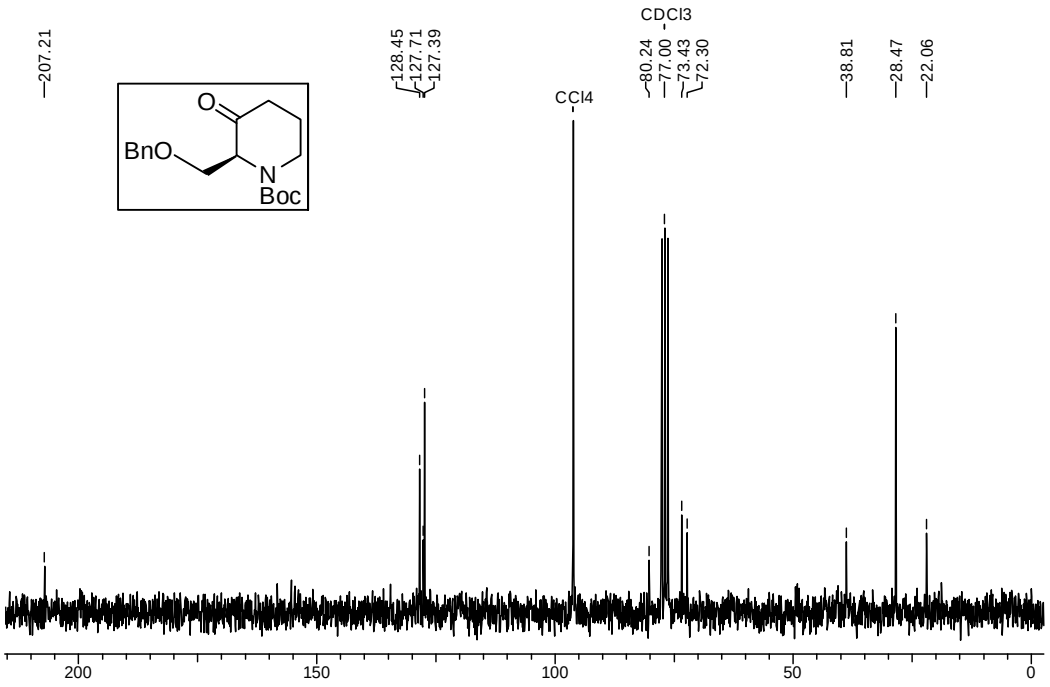
DEPT Spectrum of compound 19 ($CDCl_3$+CCl_4, 50 MHz)



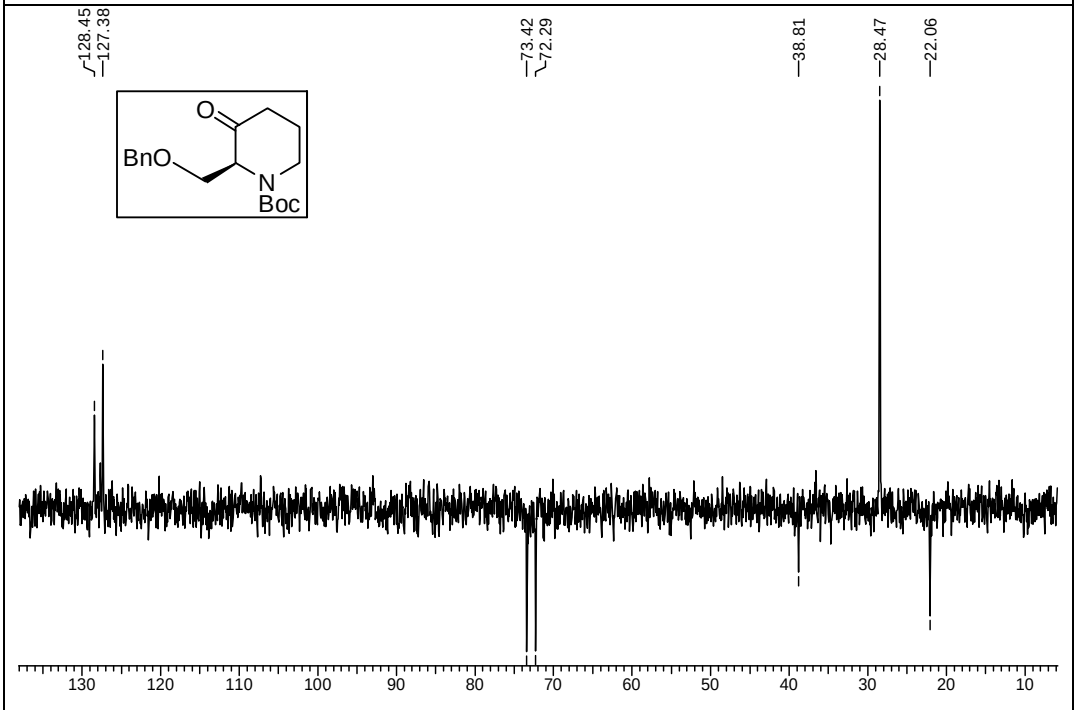
^{1}H NMR Spectrum of compound 16 ($CDCl_3$+CCl_4, 200 MHz)



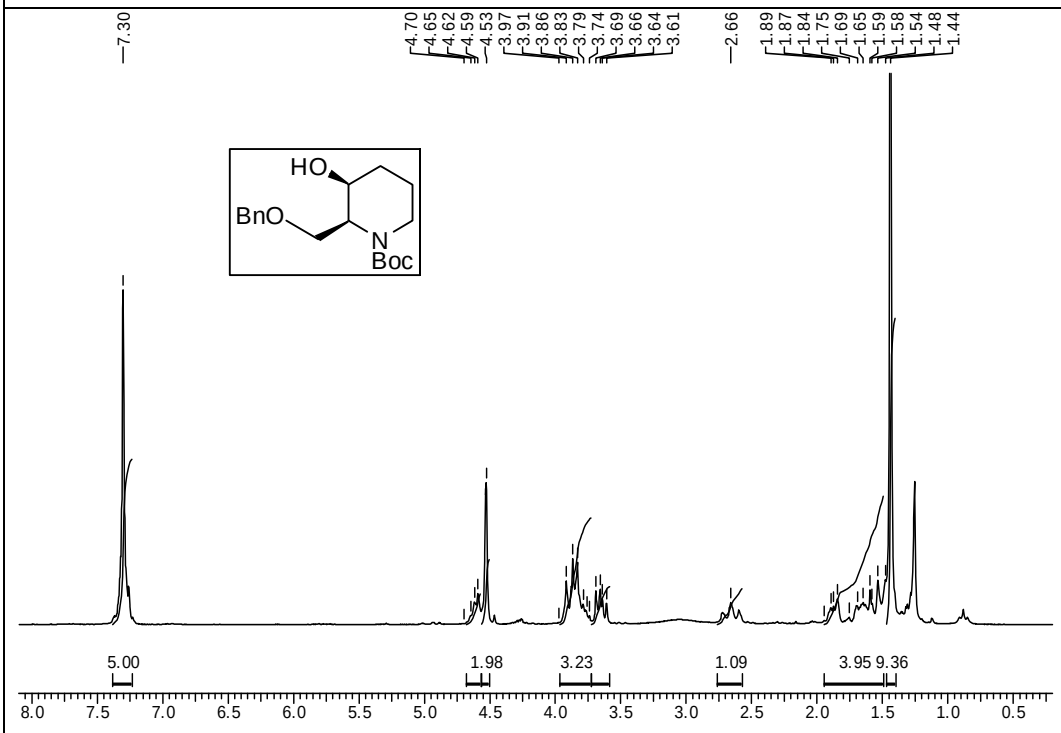
^{13}C NMR Spectrum of compound 16 ($CDCl_3$+CCl_4, 50 MHz)



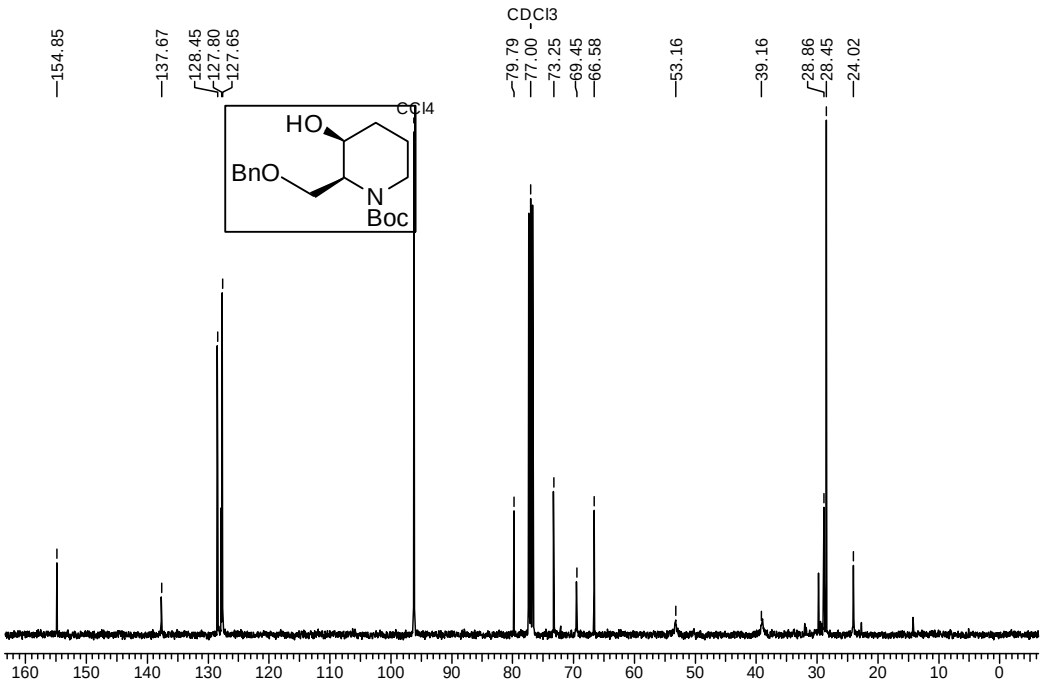
DEPT Spectrum of compound 16 ($CDCl_3$+CCl_4, 50 MHz)



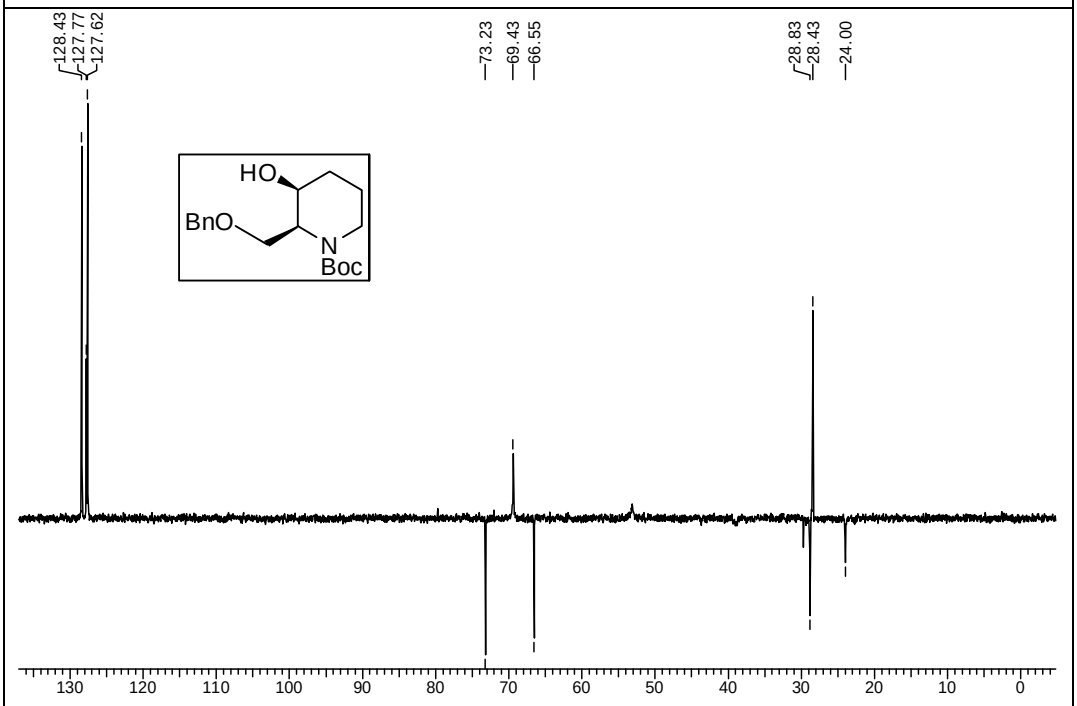
^{1}H NMR Spectrum of compound 17 ($CDCl_3$+CCl_4, 200 MHz)



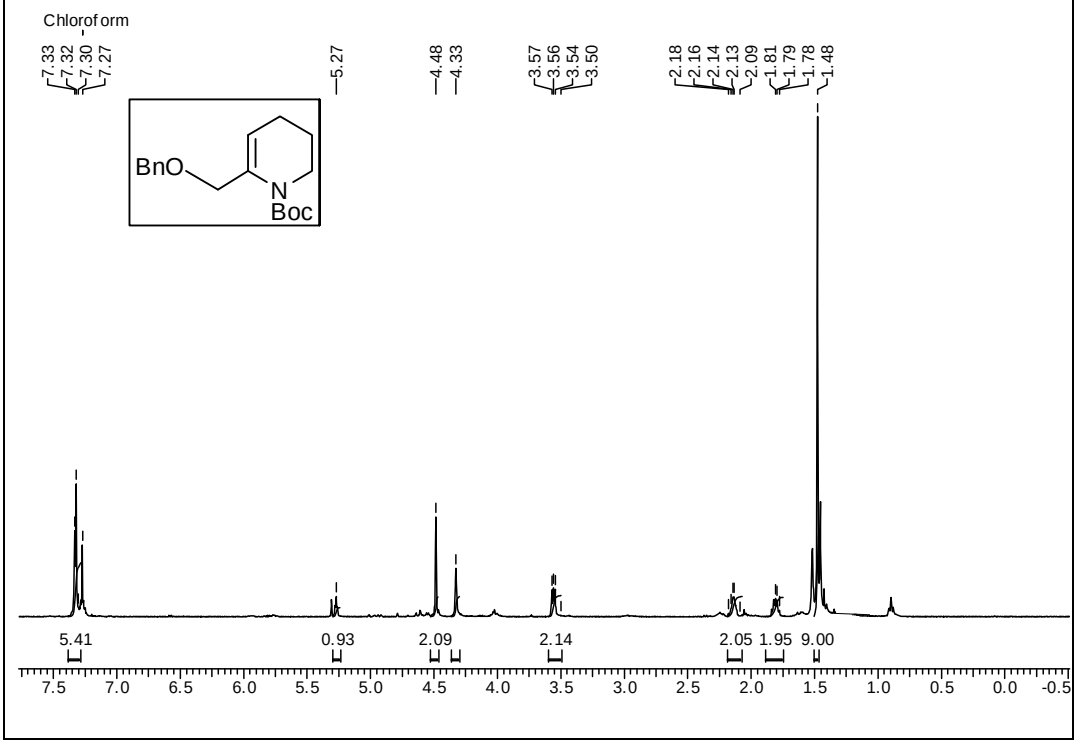
^{13}C NMR Spectrum of compound 17 ($CDCl_3$+CCl_4, 100 MHz)



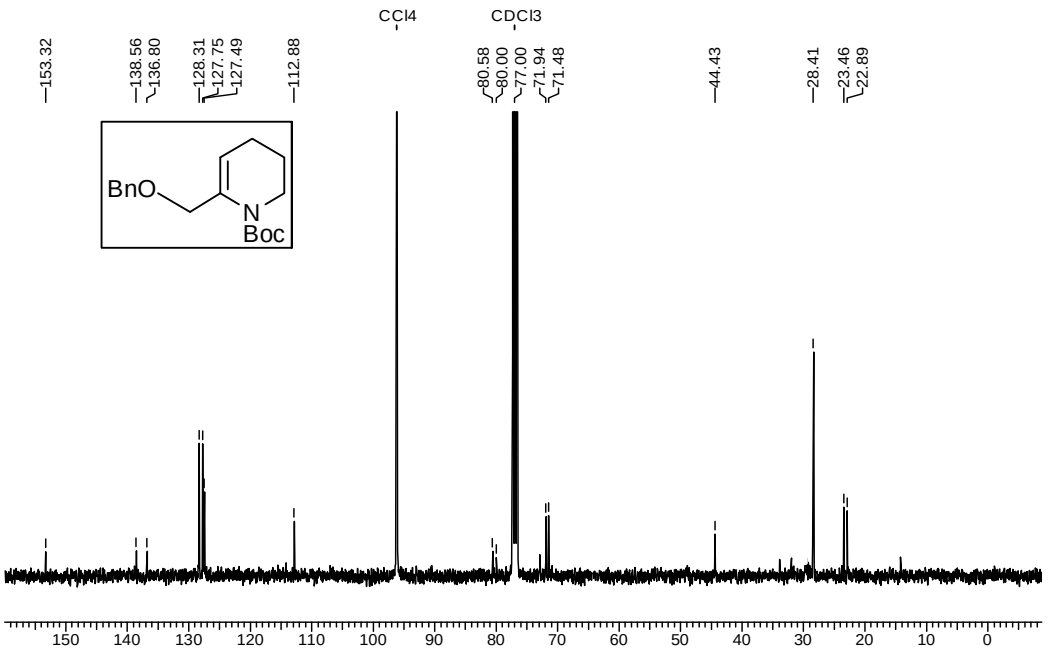
DEPT Spectrum of compound 17 ($CDCl_3$+CCl_4, 100 MHz)



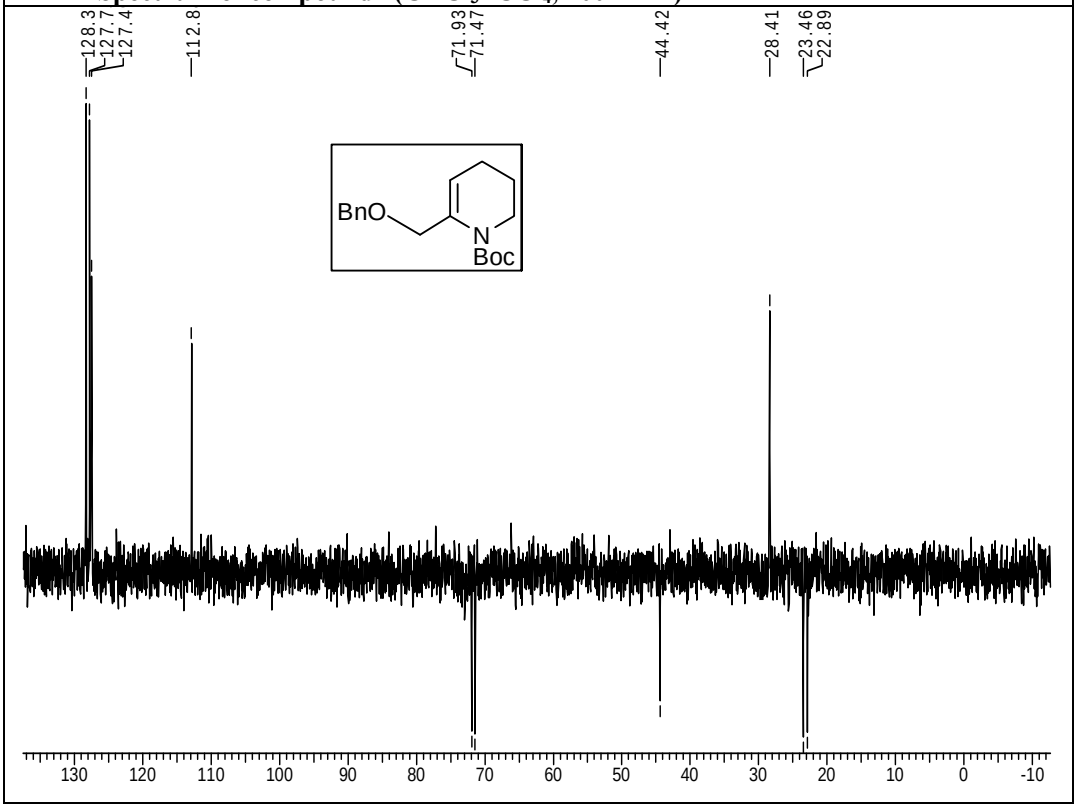
^{1}H NMR Spectrum of compound 7 ($CDCl_3$+CCl_4, 200 MHz)



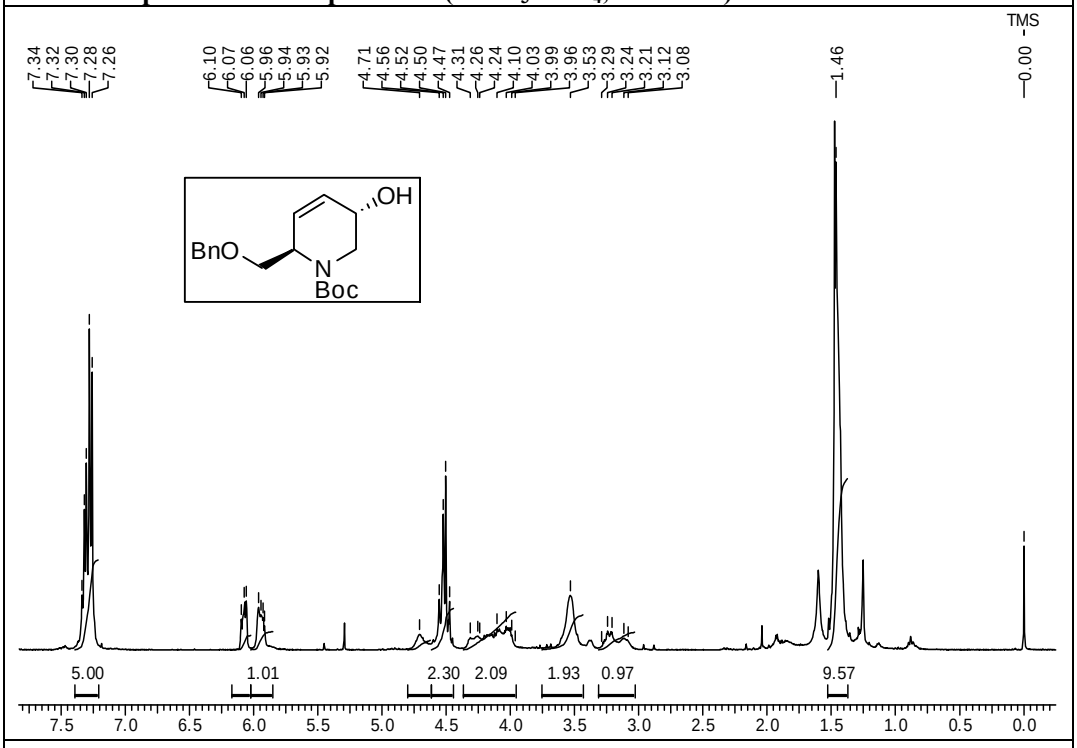
^{13}C NMR Spectrum of compound 7 ($CDCl_3$+CCl_4, 100 MHz)



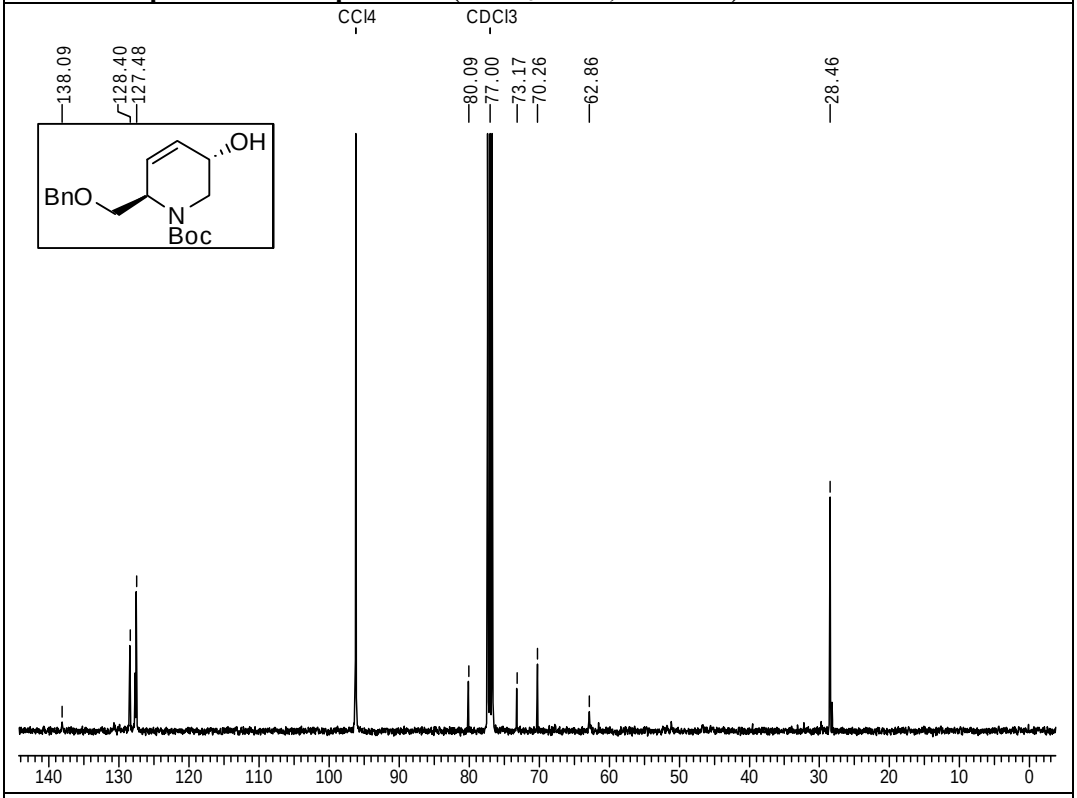
DEPT Spectrum of compound 7($CDCl_3$+CCl_4, 100 MHz)



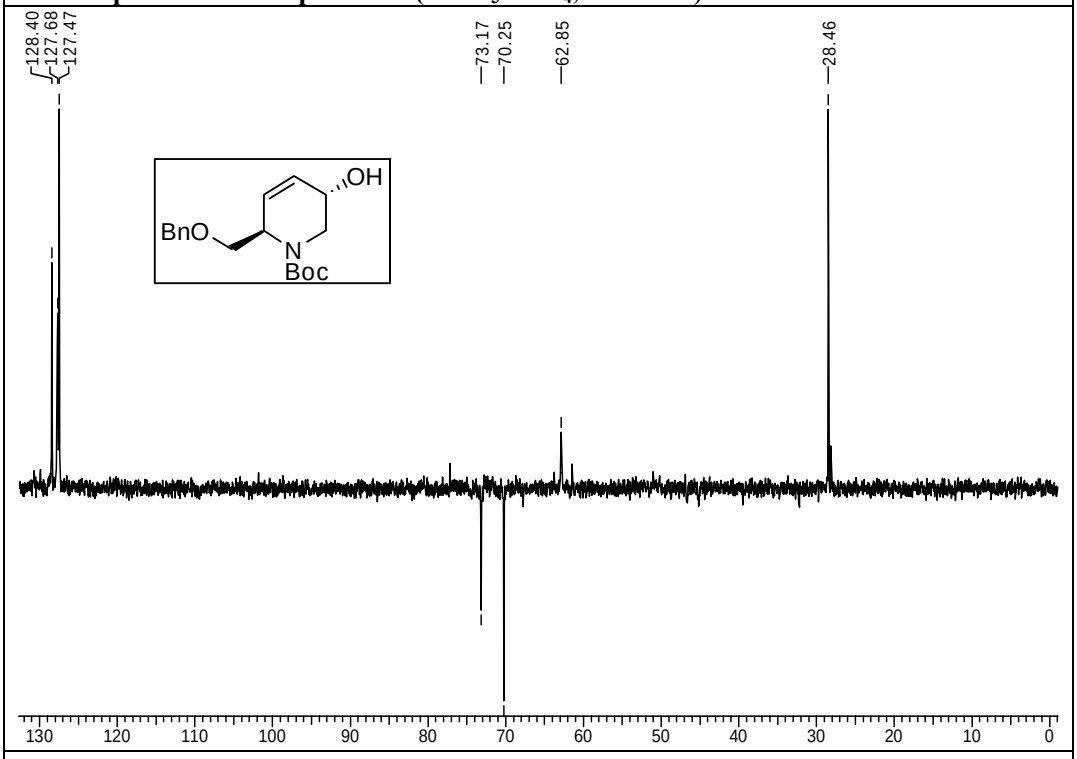
^{1}H NMR Spectrum of compound 20 ($CDCl_3$+CCl_4, 400 MHz)



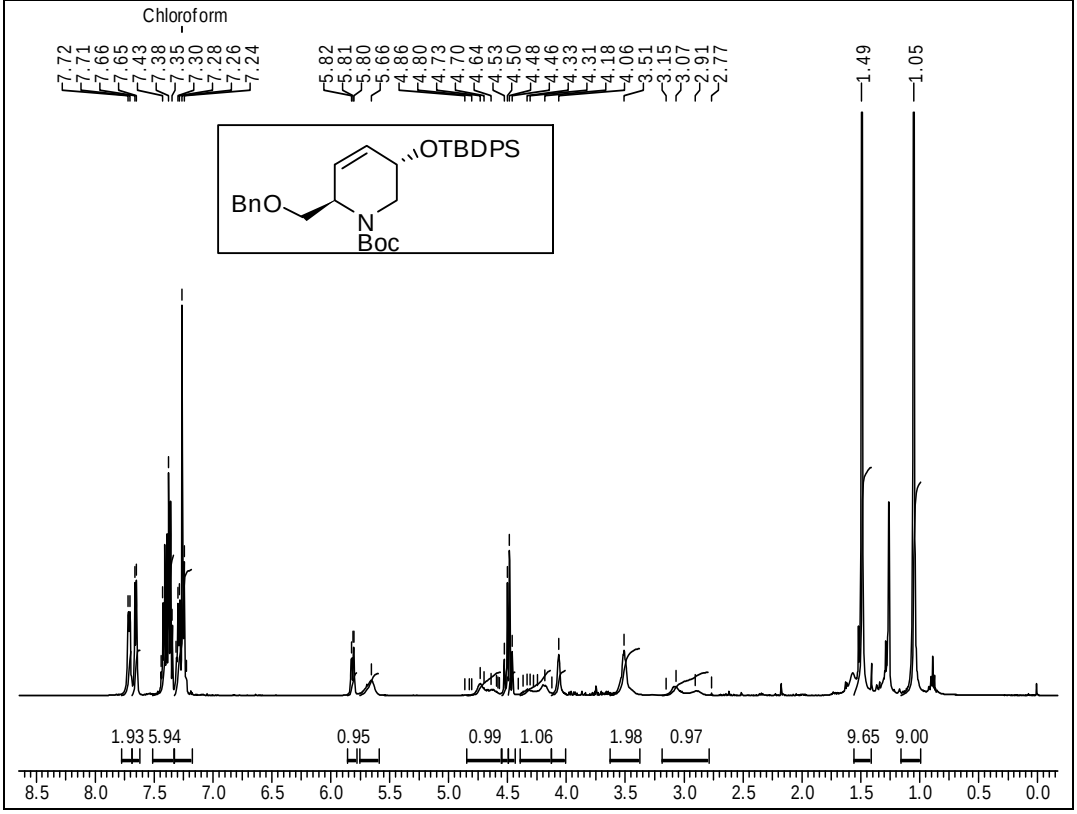
^{13}C NMR Spectrum of compound 20 ($CDCl_3$+CCl_4, 100 MHz)



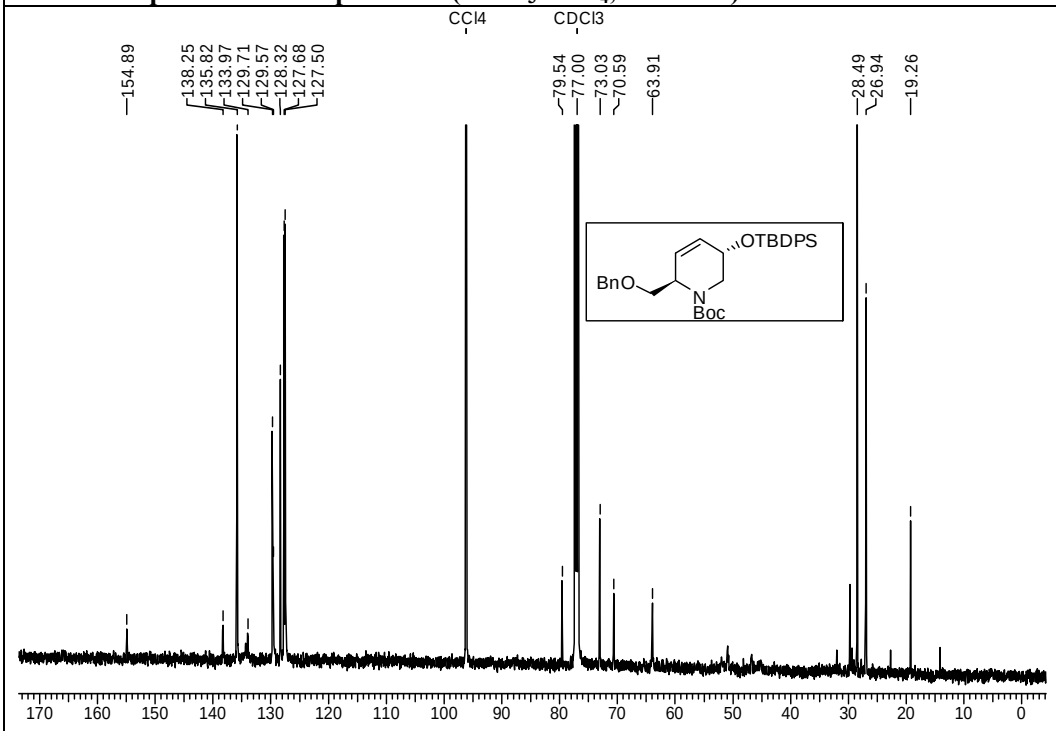
DEPT Spectrum of compound 20 ($CDCl_3$+CCl_4, 100 MHz)



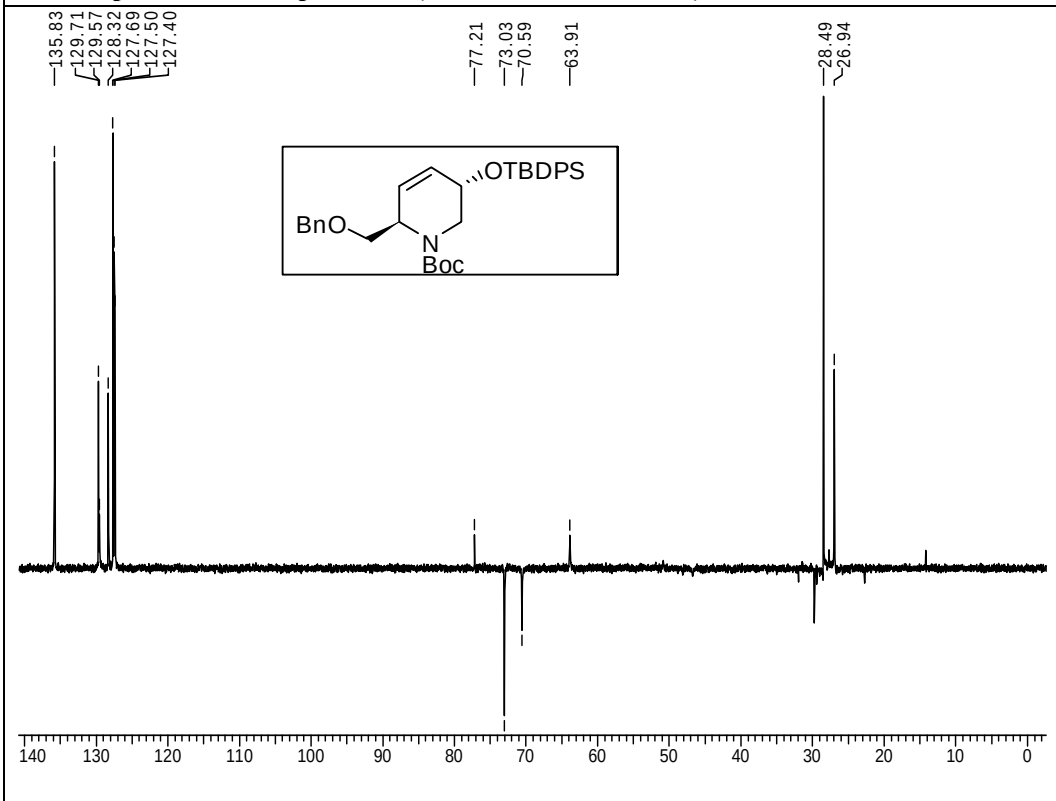
^{1}H NMR Spectrum of compound 21 ($CDCl_3$+CCl_4, 500 MHz)



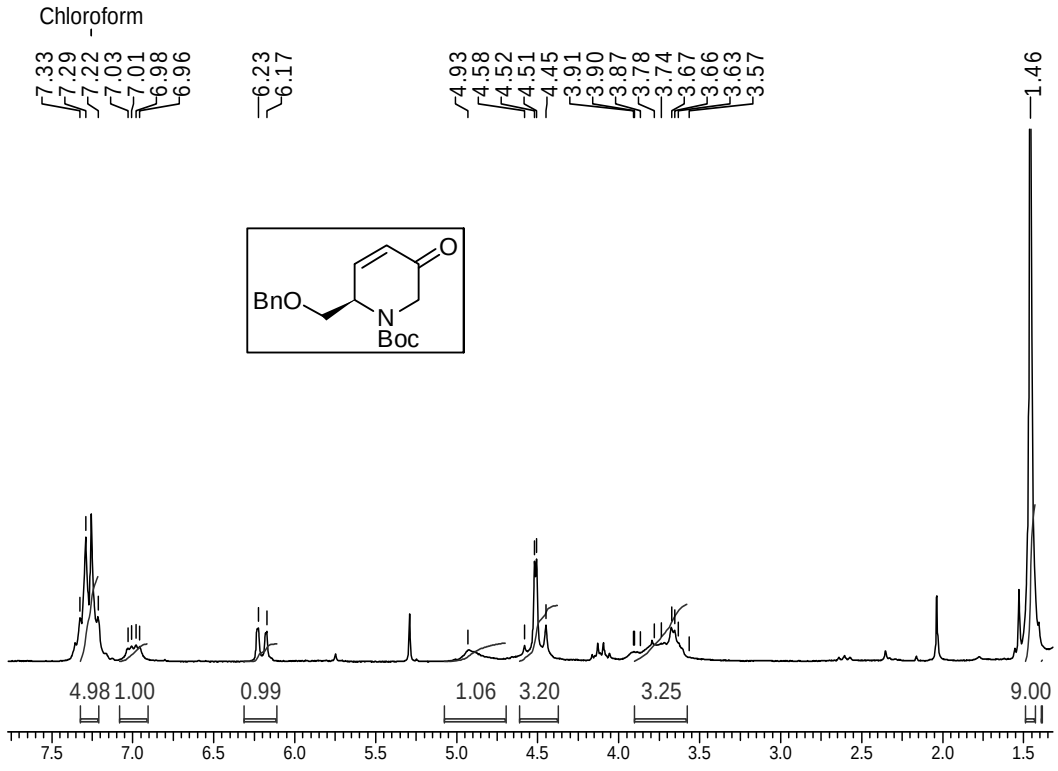
^{13}C NMR Spectrum of compound 21 ($CDCl_3$+CCl_4, 125 MHz)



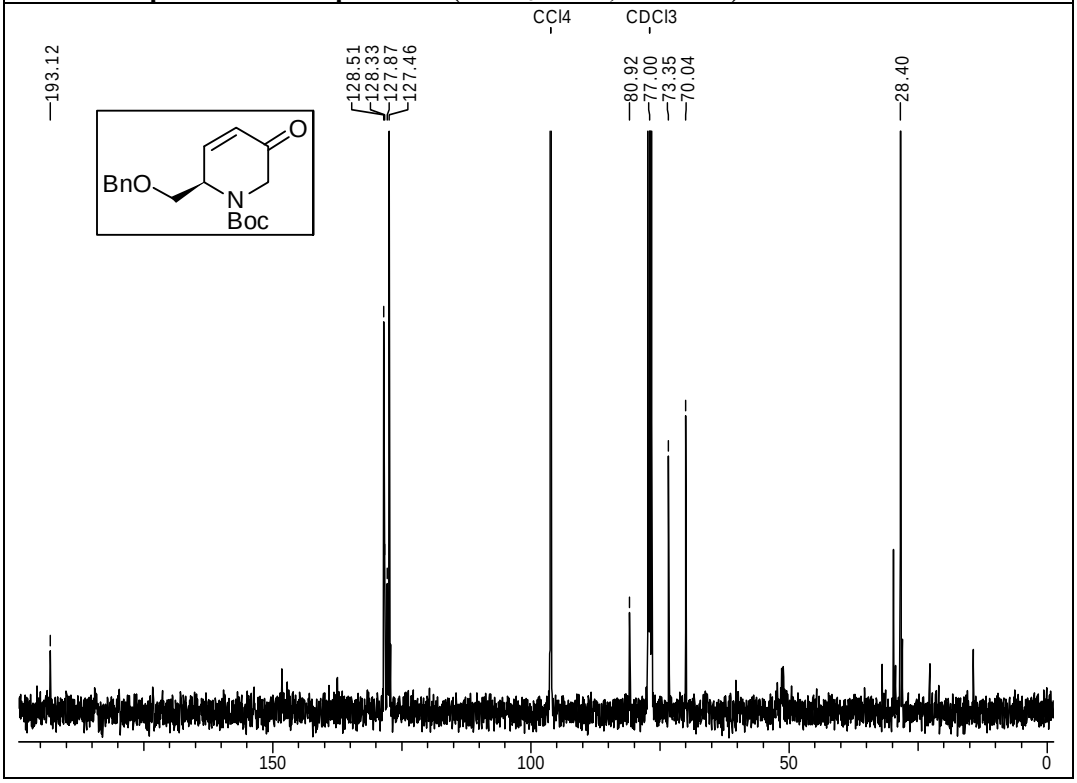
DEPT Spectrum of compound 21 ($CDCl_3$+CCl_4, 125 MHz)



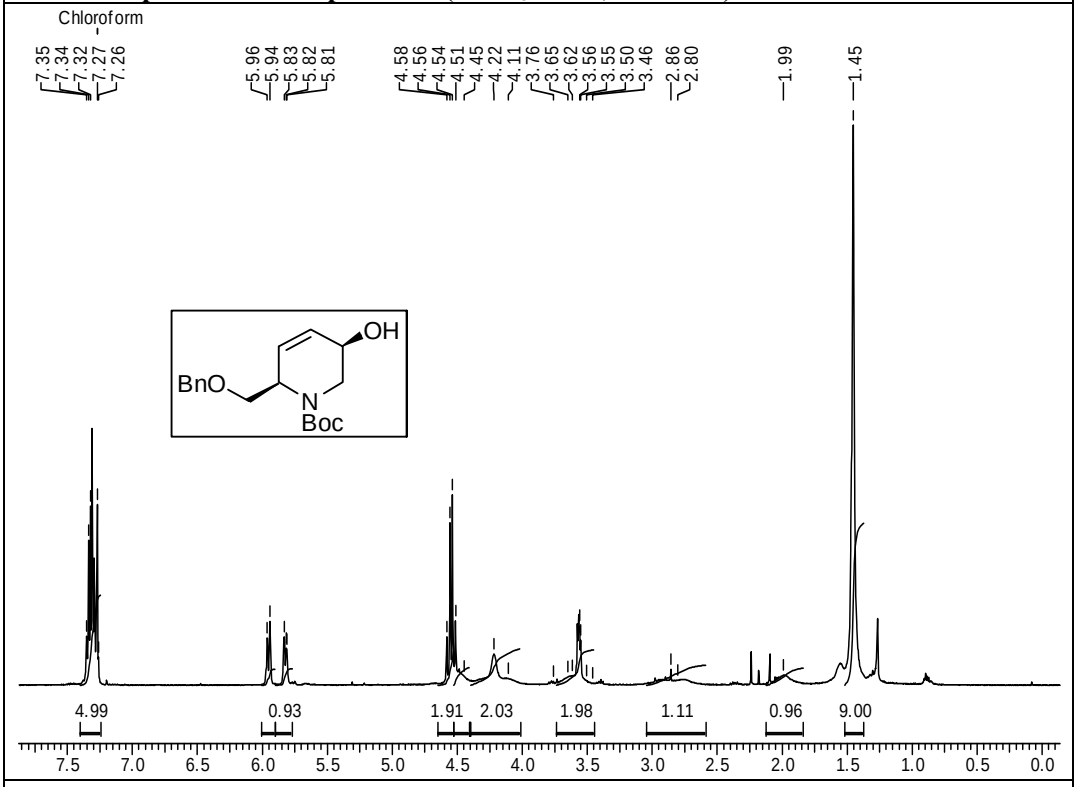
^{1}H NMR Spectrum of compound 23 ($CDCl_3$+CCl_4, 200 MHz)



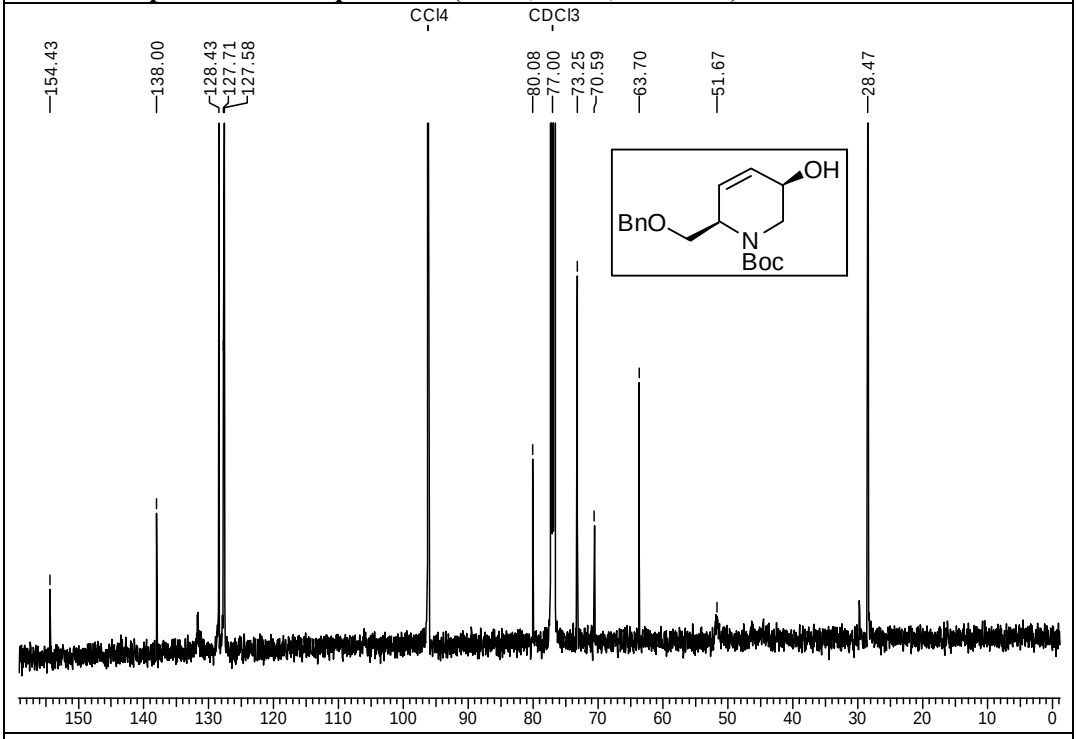
^{13}C NMR Spectrum of compound 23 ($CDCl_3$+CCl_4, 100 MHz)



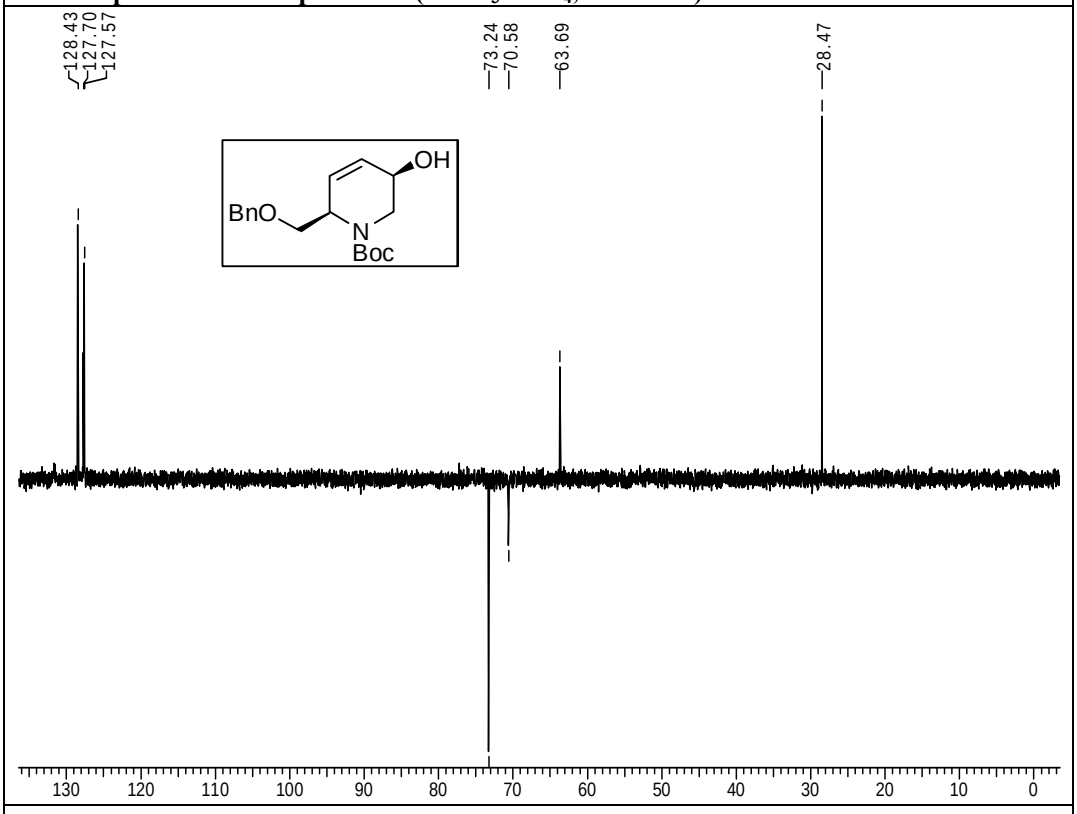
^{1}H NMR Spectrum of compound 22 ($CDCl_3$+CCl_4, 500 MHz)



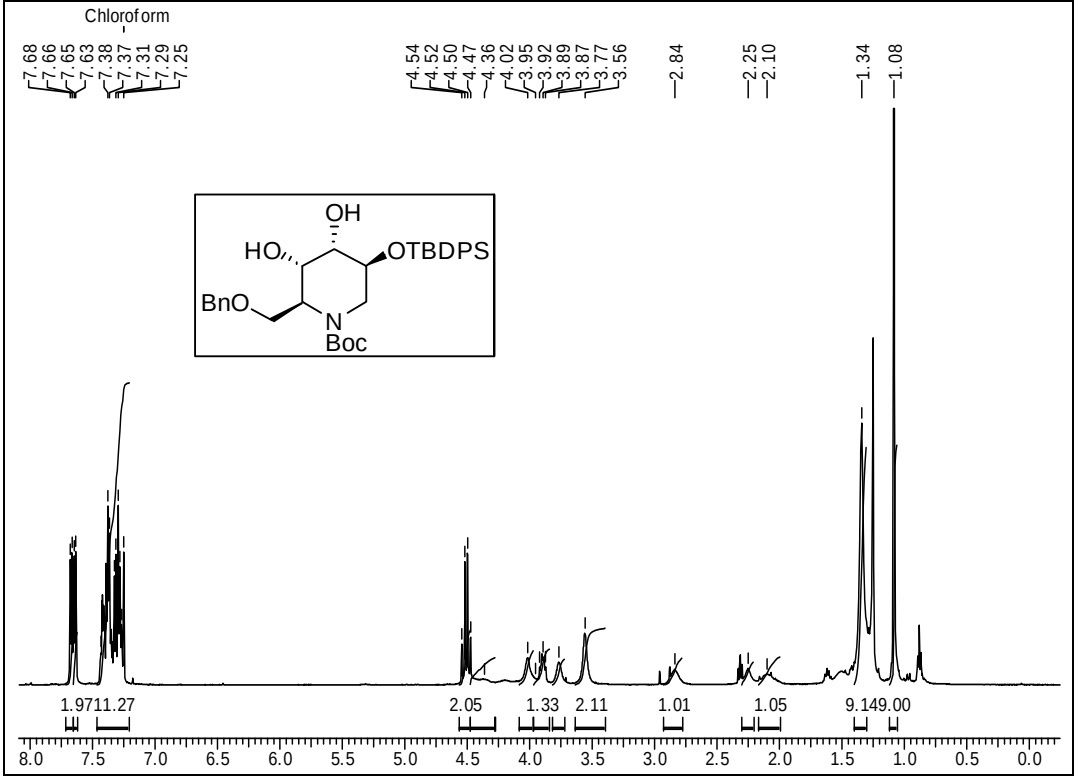
^{13}C NMR Spectrum of compound 22 ($CDCl_3$+CCl_4, 125 MHz)



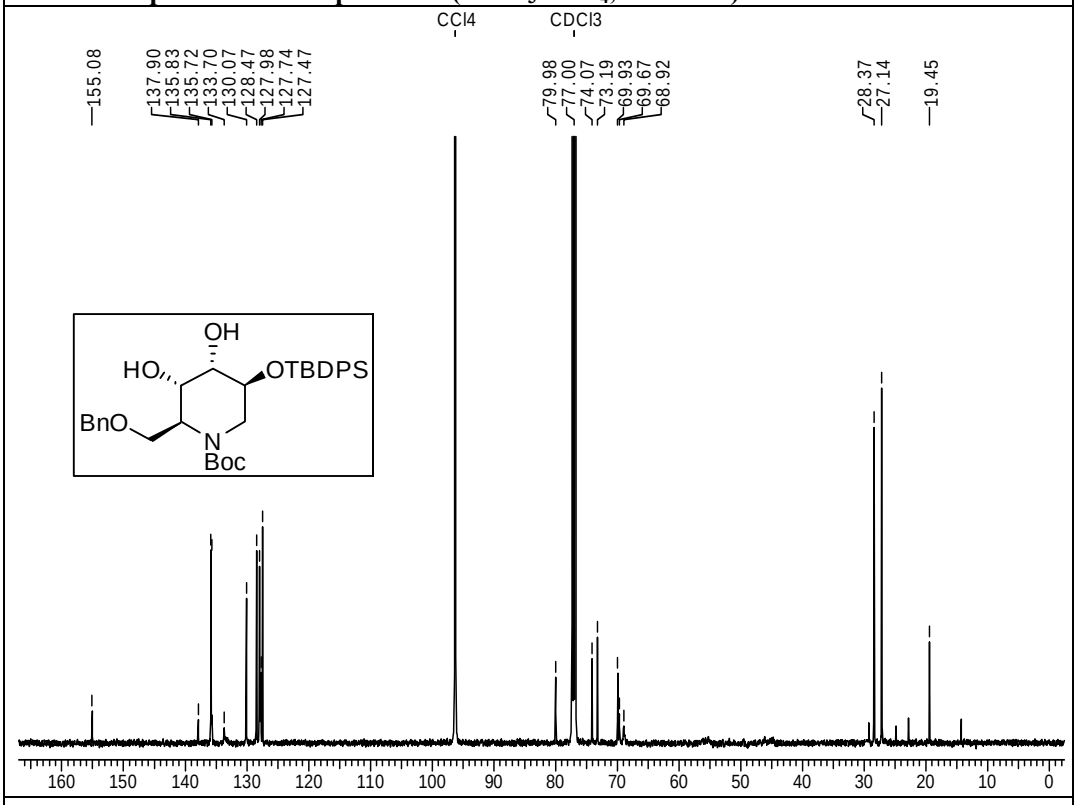
DEPT Spectrum of compound 22 ($CDCl_3$+CCl_4, 125 MHz)



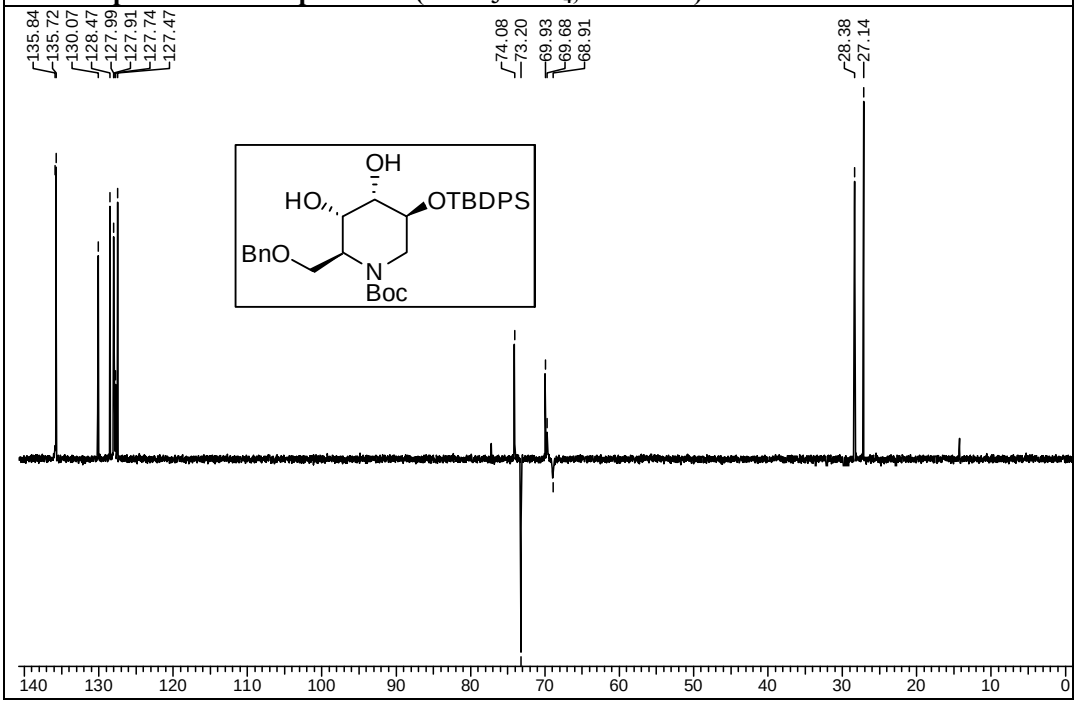
^{1}H NMR Spectrum of compound 24 ($CDCl_3$+CCl_4, 500 MHz)



^{13}C NMR Spectrum of compound 24 ($CDCl_3$+CCl_4, 125 MHz)

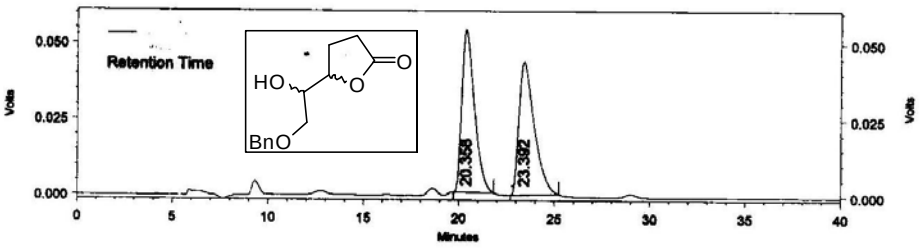


DEPT Spectrum of compound 24 ($CDCl_3$+CCl_4, 125 MHz)



Project Leader : Dr.S P Chavan
Column : Chiralcel OD-H (250x4.6mm)
Mobile Phase :IPAl:Petether: (20:80)
Wavelength : 254nm
Flow Rate : 0.5ml/min (26kgf)
Sample Con :1mg/1ml Inj vol-20ul

Kunte



Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
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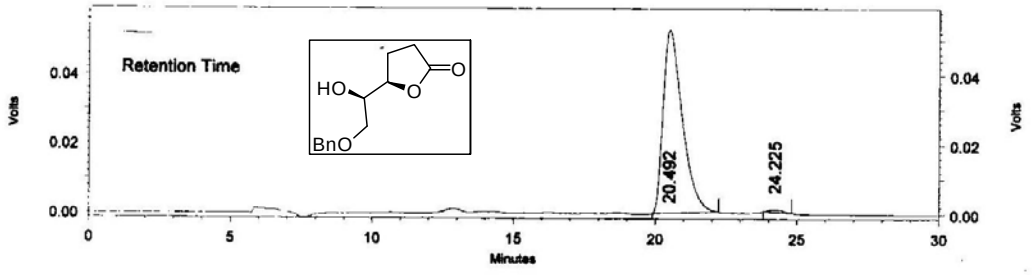
2	23.392	2453535	50.007
Totals		4906407	100.000



Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
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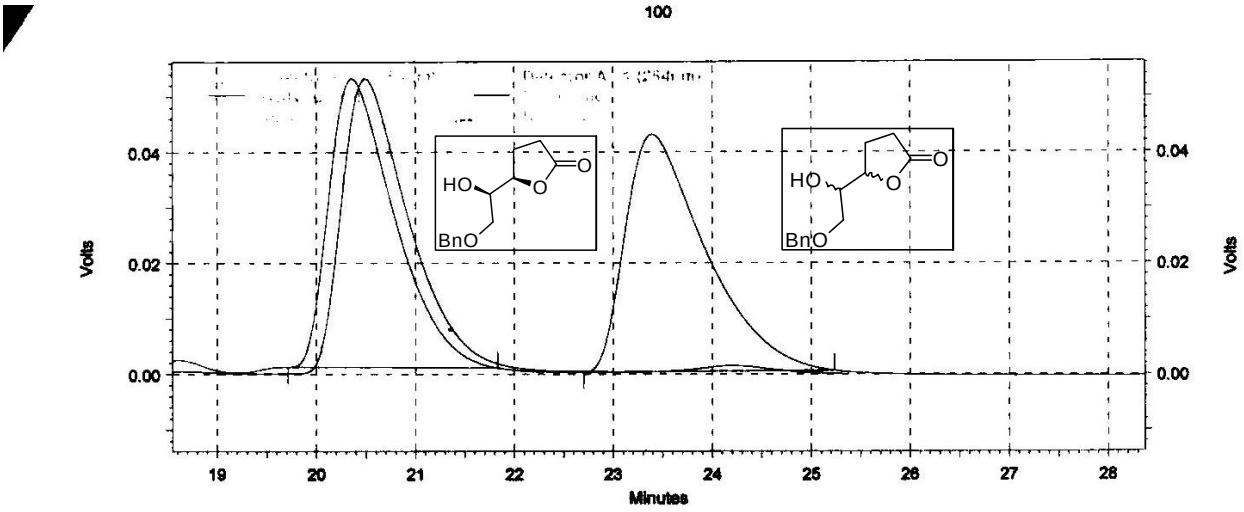
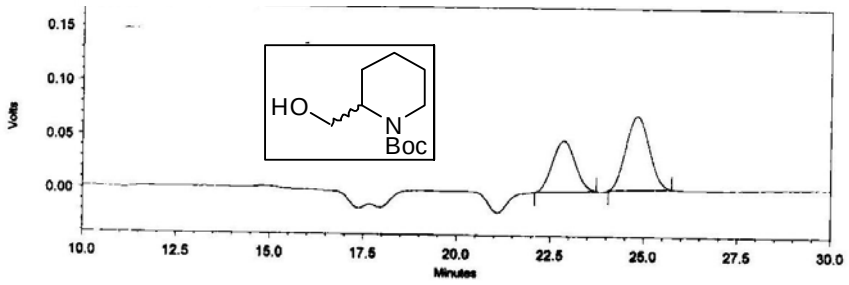
2	24.225	28051	1.115
Totals		2515444	100.000



C:\CLASS-VP\Data\Dr. CHAVAN S. P\NB 1013, Detector A - 1 (254nm)

C:\CLASS-VP\Data\Dr. CHAVAN S. P\NB 1012, Detector A - 1 (254nm)

Project Leader :- Dr. S P Chavan
Column :-Kromasil 5-AmyCoat (250 x 4.6mm)
M.Phase :-IPA:PE (4:96)
Wavelength :- 200 nm
Flow :- 0.5ml/min (288psi)
conc. :- 4mg/ 1 ml
Injection vol :- 5 ul



Detector A - 1 (200nm)

Pk #	Retention Time	Area	Area %
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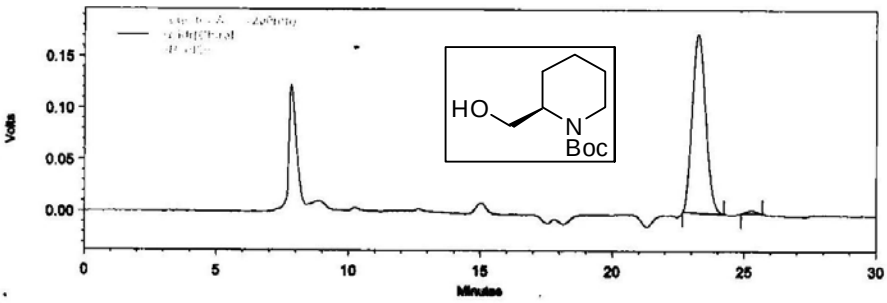
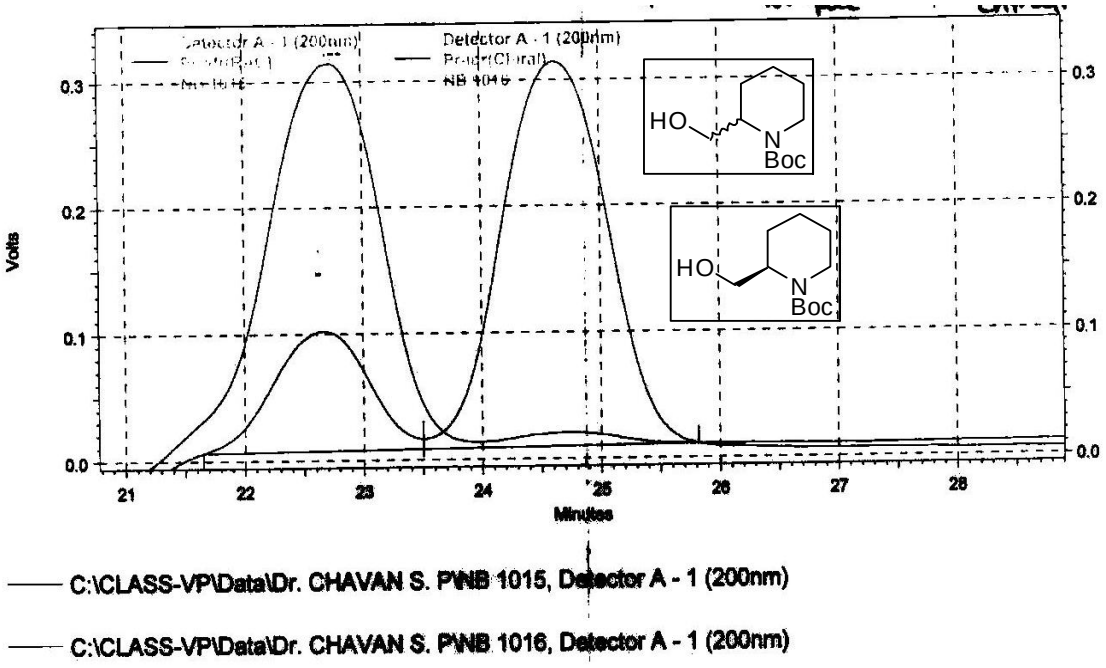
Totals		5000414	100.000



Detector A - 1 (200nm)

Pk #	Retention Time	Area	Area %
1	23.250	6194327	98.565
2	25.258	90176	1.435


Detector A - 1 (200nm)
Detector A - 1 (200nm)
HO
N
Boc
HO
N
Boc
Volts
0.3
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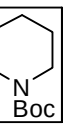
0.1
0.0
21
22
23
24
25
26
27
28
Minutes
C:\CLASS-VP\Data\Dr. CHAVAN S. PNB 1015, Detector A - 1 (200nm)
C:\CLASS-VP\Data\Dr. CHAVAN S. PNB 1016, Detector A - 1 (200nm)



2.5.5. References

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Chapter 3

Section 1 Introduction of 1-deoxyallonojirimycin (*allo*-1-DNJ) and 1-deoxytalonojirimycin (*talo*-1-DNJ)

3.1.1 Introduction

Azasugars or iminosugars (D or L-configuration) act as glycosidase inhibitors and are extensively used for the treatment of AIDS, cancer, diabetes and viral infections.[1] Nojirimycin (**1**, Fig. 1) was isolated from several strains of *Streptomyces*[2] in **1966** by Inuoye *et al.* In **1976**, Bayer chemists discovered that the stable, naturally occurring 1-deoxynojirimycin (DNJ) **2**, actually synthesized in **1966** by Paulsen *et al.*[3] is a potent α-glucosidase inhibitor. One of the isomers of 1-DNJ, D-*galacto*-1-deoxynojirimycin (D-*galacto*-1-DNJ) (**3**) (AT1001), is currently in phase B clinical trials for the treatment of Fabry's disease.[4] Recently, derivatives of 1-deoxynojirimycin (DNJ) **1** (Figure 1) such as miglitol **4** (Figure 1) and *N*-butyl-1-deoxynojirimycin **5** (Figure 1) have been used for the treatment of type II diabetes and type I Gaucher's diseases.

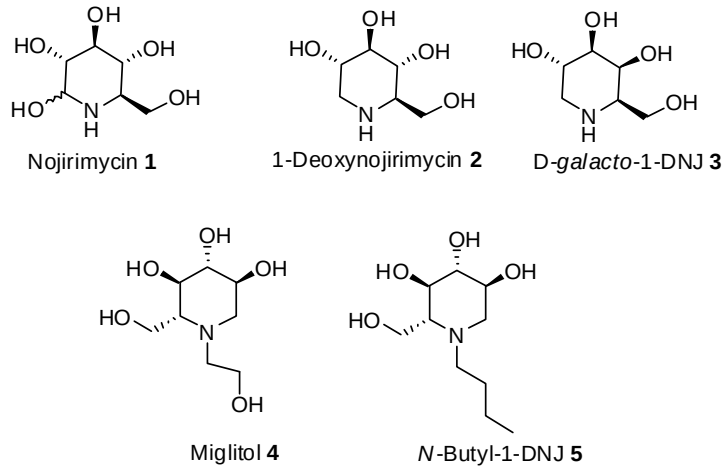
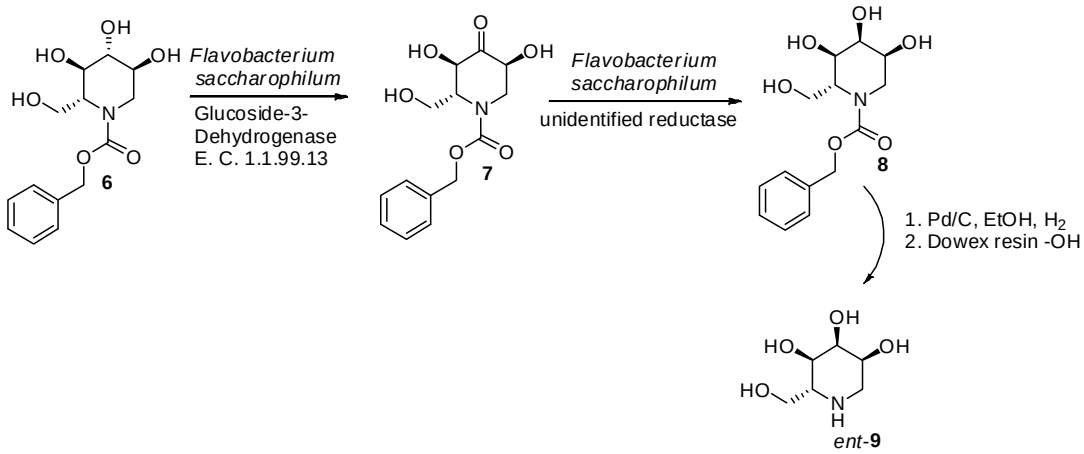


Figure 1

Asano *et al*[5] reported the isolation of D-1-deoxyallonojirimycin (D-*allo*-1-DNJ) **9** by the microbial conversion with *Flavobacterium saccharophilum* from *N*-(benzyloxycarbonyl)-1-deoxynojirimycin **6**. *F. saccharophilum* has glucoside 3-dehydrogenase [EC 1.1.99.131, which oxidizes the 3-OH group of D-glucose, D-galactose, 1,5-anhydro-D-glucitol, 1,5-anhydro-D-galactitol, glucosides and galactosides, and the carba-oligosaccharides such as validamycins to give the corresponding 3-keto derivative **7**[6] (Scheme 1). It was found that the incubation of a *F. saccharophilum* cell suspension containing **6** forms the *N*-benzyloxycarbonyl derivative of **9** by a redox reaction at C-3, as shown in Scheme 1.



Scheme 1

Recently, Kato *et al.* [7] reported the syntheses of D and L-isomers of azasugars and their screening against different enzymes inhibition. Kato *et al.* reported synthesis of L-1-deoxyallonojirimycin (L-*allo*-1-DNJ **9**, (*ent*-**9) 10**) (Figure 2) which has been shown to be more potent inhibitor of α-mannosidase as compared to D-*manno*-1-DNJ **11** (*ent*-**11 12**) (Figure 2). Hashimoto *et al*.[8] had first reported the synthesis of L-1-deoxytalonojirimycin (L-*talo*-1-DNJ **13** (*ent*-**13**) **14**) (Figure 2) which was shown to be a potent inhibitor of α-glycosidase and α-L-fucosidase. Recently, it has been found that L isomers of azasugars also possess remarkable activity as glycosidase inhibitor.[9] In azasugar synthesis, the main synthetic challenge is the construction of piperidine moiety and installation of hydroxy groups in stereoselective manner (four contiguous chiral centres). Different configuration of hydroxy groups on piperidine framework and derivatives of 1-DNJ possess different activity (earlier described in Chapter 2 Section 2). Due to the interesting biological activity and structural features, 1-deoxyallonojirimycin **9**, **10** (*allo*-1-DNJ) and 1-deoxytalonojirimycin (*talo*-1-DNJ) **13**, **14** attracted attention of many organic chemists towards their syntheses. Most of the synthetic approaches for D-*allo*-1-DNJ in literature were based on using chiral template and involved several steps.

In this chapter, the total syntheses of D-1-deoxyallonojirimycin **10**, L-1-deoxyallonojirimycin **9** and L-*talo*-1-DNJ **13** by chiral pool strategy using L-tartaric

acid and non chiral pool strategy (asymmetric synthesis) using *cis*-butene-1,4-diol as starting material are described.

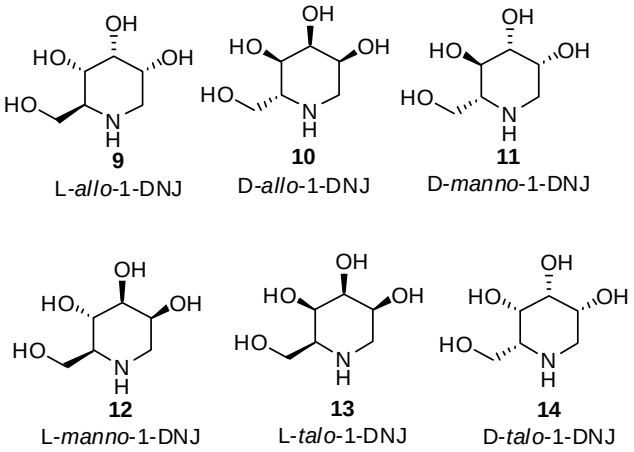
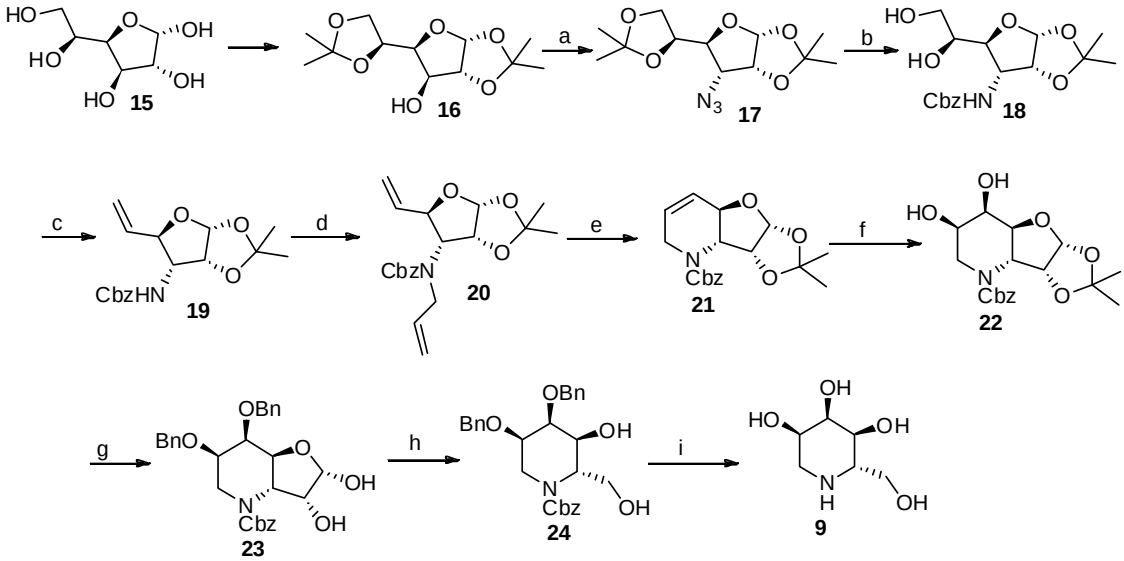


Figure 2

3.1.2 Literature Survey (Reported synthesis)

Ghosh *et al.* [10] (*Tetrahedron Lett.* **2006,** *47*, 6041)

Ghosh *et al.* accomplished the total synthesis of L-*allo*-1-DNJ by employing RCM strategy starting from glucose as the source of chirality.



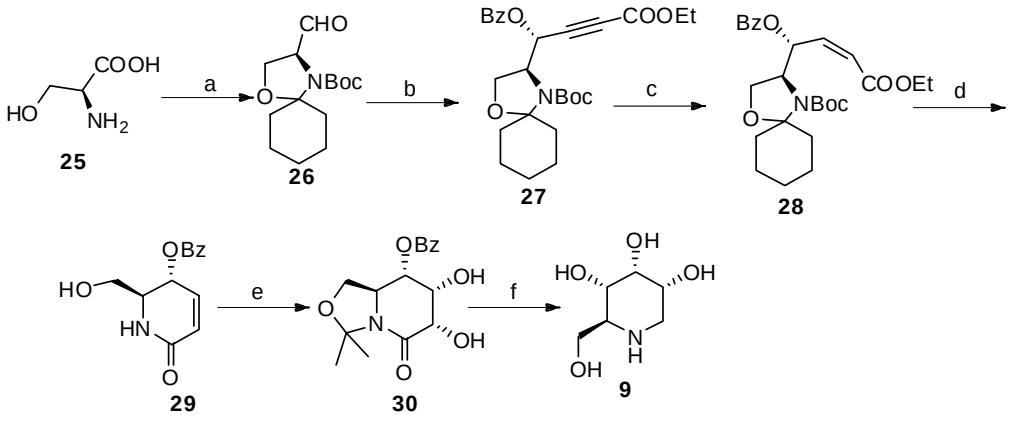
Scheme 2 *Reagents and conditions: a) (i) SO_2Cl_2, imidazole, CH_2Cl_2, rt, 5 h; (ii) NaN_3, DMF, 70 ^oC, 3 h, 50% (over two steps); (b) i) 50% aq AcOH, rt, 5 h; ii) H_2, Pd/C, MeOH, 1 h; iii) CbzCl, Et_3N, CH_2Cl_2, 30 min, 60% (over three steps); c) Ph_3P, imidazole, I_2, toluene, 50 ^oC, 90%; d) NaH, DMF, allyl bromide, 0 ^oC, 2 h, 88%; e) 10 mol % $(PCy_3)_2RuCl_2$=CHPh, CH_2Cl_2, 24 h, 90%; f) NMO, $NaIO_4$, OsO_4, acetone:water (2:1), 0 ^oC, 12 h, 72%; g) NaH, BnBr, TBAI (cat), THF, 0 ^oC to rt, 4 h,*

95%; h) i) 50% TFA in water, 0 °C, 8 h; ii) $NaIO_4$, 50% aq. EtOH, 45 min, followed by $NaBH_4$, 10 min, 80% (over two steps); i) Pd/C, H_2 under atmospheric pressure, 12 h, 90%.

Glucose derivative **16** was converted in to azide derivative **17**, which on terminal acetonide deprotection followed by azide reduction and cbz protection delivered the urethane **18** (Scheme 2). Diol in **18** was treated with PPh_3, imidazole and iodine to furnish olefin **19**. Piperidine framework **21** was obtained from compound **19** by *N*-allylation to afford **20** followed by RCM reaction. Dihydroxylation on **21** followed by benzyl protection delivered dibenzyl derivative **23**. Global deprotection of **24** furnished L-*allo*-1-DNJ **9**.

Altenbach *et al.* [11] (*Tetrahedron: Asymmetry* **1995**, *6*, 1077)

Altenbach *et al.* reported synthesis of L-*allo*-1-DNJ starting from L-serine **25**, employing stereoselective dihydroxylation as the key step.



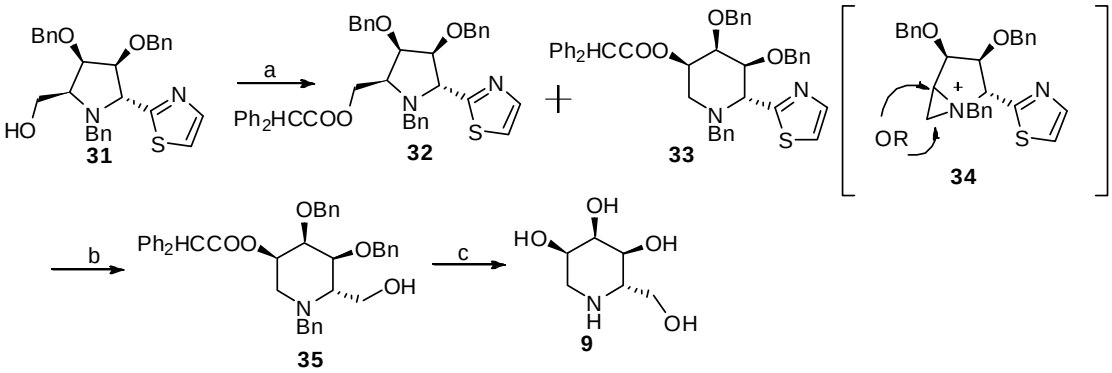
Scheme 3 *Reagents and conditions: a) Ref 12; b) $HCCCO_2Et$, BuLi, THF, HMPT, -90 °C to -35 °C; ii) BzC1, -50 °C to rt; c) Lindlar's cat., EtOAc, quinoline, rt; d) i) Et_2O/H_2O/TFA (1:1:3), rt, 1 h; ii) EtOAc, sat. $NaHCO_3$, rt, 15 h; e) PhH, DMP, PPTS, 78 °C; ii) OsO_4, NMO, acetone/H_2O (1:1), 55 h; f) i) MeOH/NEt_3 (9:1), rt, 18 h; ii) 2 N HCl, 50 °C, 5 h; iii) TDSCl, Py, rt, 40 h; iv) $BH_3.SMe_3$, THF, rt, 24 h, Dowex.*

Aldehyde **26** was derived from L-serine **25** by known literature protocol.[12] Alkynyl anion derived from ethyl acetylene carboxylate was reacted with Garner aldehyde **26** followed by benzoyl protection to furnish benzoate derivative **27** (Scheme 3). Alkyne **27** was reduced to *cis* alkene **28** by using Lindlar catalyst. The acid labile protecting group in **28** was removed using TFA followed by neutralization with $NaHCO_3$ to deliver unsaturated lactam **29**. Protection of lactam **29** followed by dihydroxylation gave diol **30** in high diastereoselctive ratio. Diol **30** on acidification, treatment with TDSCl and pyridine followed by borane reduction furnished L-*allo*-1-DNJ **9**.

Dondoni *et al.*[13] (*Synlett* **2004,** *2004*, 1711-1714.)

Dondoni *et al.* reported synthesis of L-*allo*-1-DNJ utilizing Mitsunobu conditions for the construction of substituted piperidine ring.

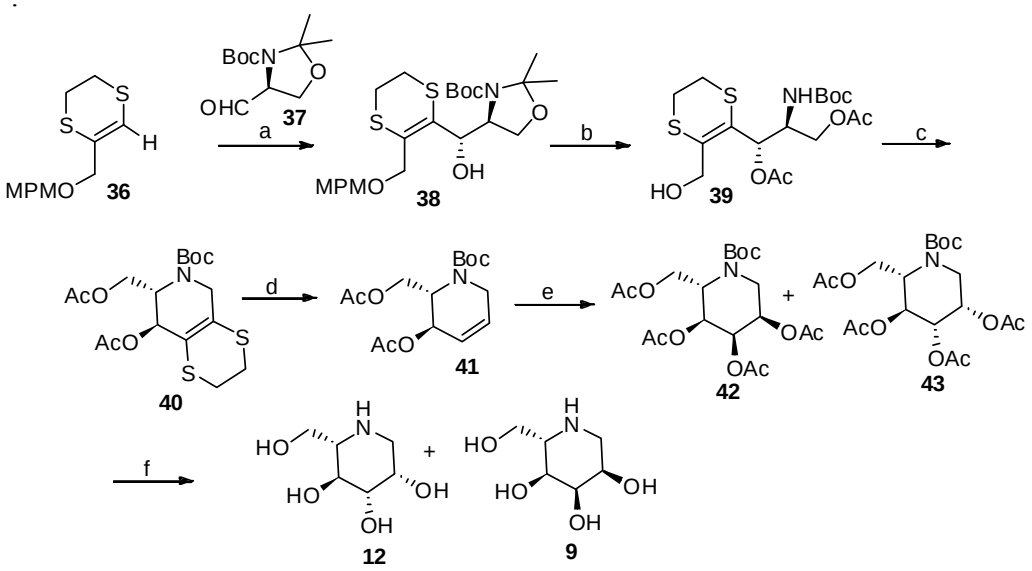
5-Hydroxymethyl pyrrolidine **31** was prepared *via* nitrone route from xylose. Pyrrolidine **31** on treatment with Ph_3P-DIAD and acid (as nucleophile) furnished a mixture of the pyrrolidine **32** and piperidine **33** in 2.5:1 ratio *via* aziridine intermediate **34** (Scheme 4). Desired thiazole **33** was converted to aldehyde followed by $NaBH_4$ reduction to furnish alcohol **35**. Removal of benzoyl group of **35** followed by hydrogenolysis afforded L-*allo*-1-DNJ **9**.



Scheme 4 *Reagents and conditions: a) $Ph_2CHCOOH$, PPh_3, DIAD, 80 ^oC, 2 h, 74%; b) i) MeOTf ; ii) $NaBH_4$ iii) $AgNO_3$, H_2O, 82%; iv) $NaBH_4$; c) i) NaOMe; ii) H_2, $Pd(OH)_2$, 72%;*

Guaragna *et al.* [14] (*Org. Lett.* **2007,** *9*, 3473-3476)

Guaragna *et al.* accomplished the total syntheses of L-*allo*-1-DNJ **9** and L-*manno*-1-DNJ **12** by intramolecular *N*-alkylation as the key step.

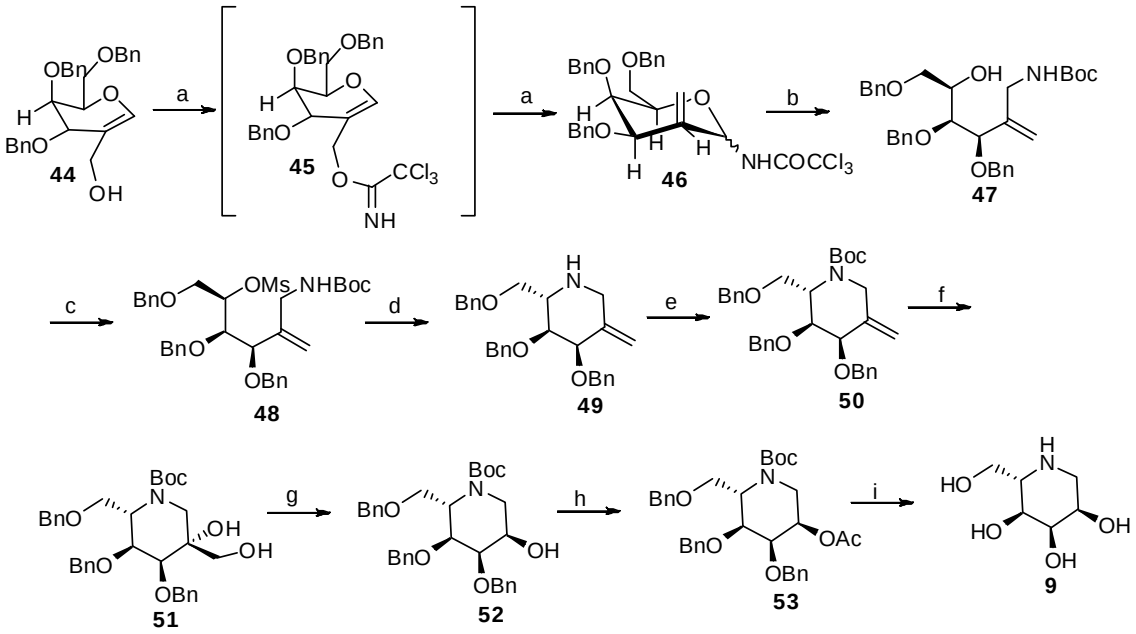


Scheme 5 *Reagents and conditions: a) BuLi, Et_2O, -78 ^oC, 72%; b) i) 80% AcOH, 50 ^oC; ii) Ac_2O, Py, rt, 86% (over two steps); iii) DDQ, DCM:H_2O, rt, 95%; c) Ag_2O, TsCl, THF, 40 ^oC, 85%; d) Raney-Ni, 0 ^oC, 76%; e) i) OsO_4, NMO, acetone: t-BuOH ; ii) Ac_2O, Py, 83% (over two steps); dr 6:4; f) 6N HCl, reflux, 90%.*

Coupling lithiated carbanion of **36** with Garner aldehyde **37** gave syn/anti diastereomeric mixture of alcohol **38** (Scheme 5). The *O*-acetyl derivative **39** was achieved from compound **38** involving acetonide deprotection, acylation and MPM deprotection. Intramolecular cyclization was then carried out under mild conditions by treatment of **39** with Ag_2O/TsCl in THF to deliver **40**. Finally, removal of the dithioethylene bridge on intermediate **40** was achieved by treatment with Raney-Ni leading to the olefin **41**. Exposure of **41** to the Upjohn conditions followed by acetylation of the crude residue yielded a fully separable mixture of the protected L-*manno*-1-DNJ **43** and L-*allo*-1-DNJ **42** in low diastereomeric ratio (6:4). Acidification of **43** and **42** furnished L-*manno*-1-DNJ **12** and L-*allo*-1-DNJ **9**.

Gupta *et al.*[15] (*Eur. J. Org. Chem.* **2009,** 1925-1933)

Gupta *et al.* reported the synthesis of L-*allo*-1-DNJ **9** by employing the aza-Claisen rearrangement for the installation of nitrogen atom and intramolecular *N*-alkylation for construction of piperidine moiety as the key steps.

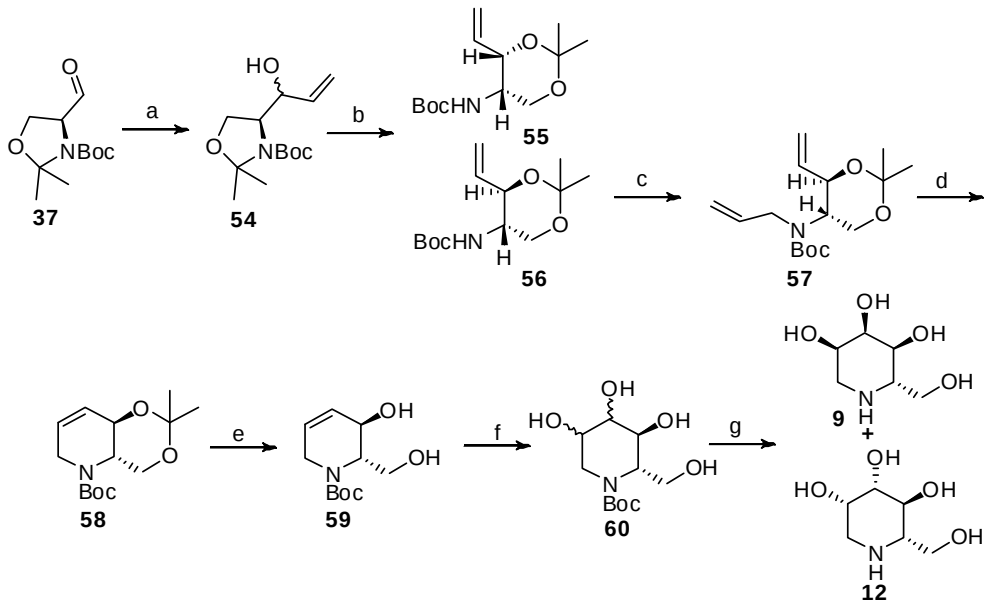


Scheme 6 *Reagents and conditions: a) NaH, Cl_3CCN, DCM, 83% α:β=9:1; b) $NaBH_4$, EtOH, 0°C- rt, ii) $(Boc)_2O$, $NaHCO_3$, EtOAc, 0 °C- rt, 75%; c) MsCl, TEA, DCM, 0 °C- rt, 86%; d) i) TFA, DCM, 0 °C- rt, 45 min; ii) K_2CO_3, MeCN, rt-70 °C, 8 h, 70%; e) $(Boc)_2O$, TEA, DCM, 0 °C- rt, 4 h, 80%; f) OsO_4, NMO:actone:t-BuOH, 24 h, 99%; g) i) $NaIO_4$, MeOH, 0 °C- rt, 45 min, 95%; ii) $NaBH_4$, MeOH, 0 °C – rt, 30 min; h) Ac_2O, TEA, DCM, 0 °C- rt, 4 h, 80%; i) H_2, Pd/C, MeOH; ii) 6 N HCl, reflux, 86%.*

Glycal **44** was subjected for aza-Claisen rearrangement condition to deliver *β-N*-glycosyltrichloroacetamidates **46** in high diastereomeric ratio (Scheme 6). Reaction of an anomeric mixture of glycosyl amides **46** with $NaBH_4$ led to the reduction of the amide followed by ring-opening to provide the corresponding free amine, which was immediately treated with $(Boc)_2O$ to give the Boc-protected amine **47**. Alcohol **47** was converted to corresponding mesylate derivative **48**. Removal of NHBoc group in **48** using TFA followed by base treatment gave the cyclized compound **49** with an inversion of the stereochemistry at C-2. Protection of the secondary amine **49** as carbamate derivative **50** and subsequent dihydroxylation afforded **51** as a single diastereomer. Oxidative cleavage of diol **51** followed by sodium borohydride reduction gave alcohol **52**. Acetylation of **52** gave *O*-acetyl derivative **53**. Finally, deprotection of the benzyl groups under hydrogenation condition, followed by treatment with acid provided salt of L-*allo*-1-DNJ **9**.

Kato *et al.*[16] (*J. Med. Chem.* **2005**, *48*, 2036)

Kato *et al.* reported synthesis of L-*allo*-1-DNJ and other isomers of 1-DNJ by utilizing RCM protocol.

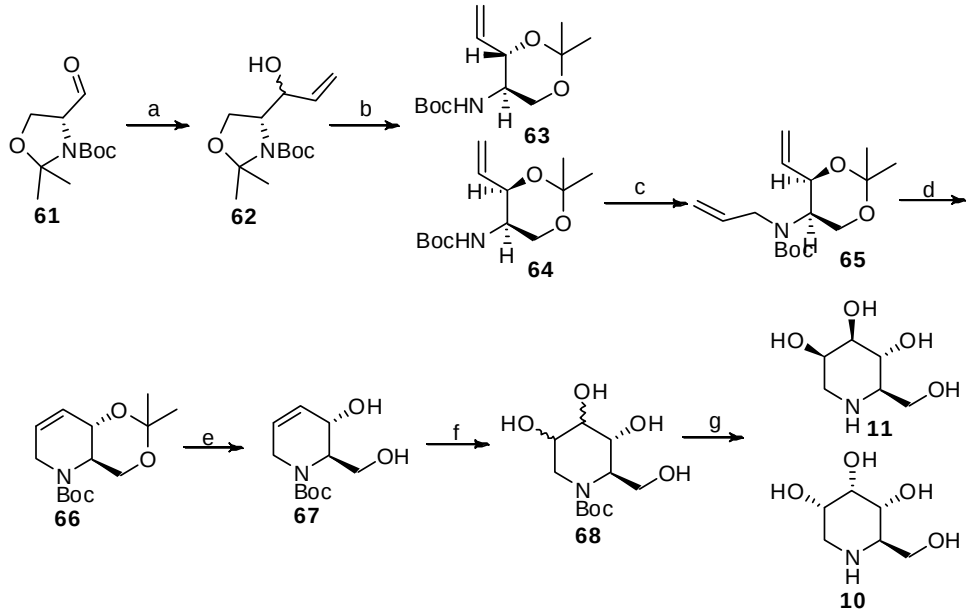


Scheme 7 *Reagents and conditions: a) Vinyl magnesium bromide, -78 °C, 2 h; b) 0.15 N HCI gas in $CHCl_3$, rt, overnight; c) Allyl iodide, NaH, THF, 0 °C, overnight, 95%; d) Cat. ($Cl_2(Cy_3P_2)Ru$=CHPh, CH_2Cl_2, rt, 2 h, 97%; e) p-TsOH, H_2O, MeOH, rt, 2 h; f) (i) Cat. $K_2OsO_4.2H_2O$, NMO, acetone, rt, overnight; ii) Ac_2O, pyridine, rt, overnight; g) 6 N HCl, MeOH, reflux, 8 h; iii) Dowex 50WX8 (H+ form).*

The synthesis began from commercially available material *viz.* Garner aldehyde **37** (derived from serine) (Scheme 7). Diastereomeric mixture of carbamate **55** and **56** was obtained from diastereomeric mixture of allylic alcohol **54** involving Grignard reaction and exchange protection sequence. Substituted piperidine derivative **58** was obtained by *N*-allylation and RCM reaction on **56**. 1,3-Acetonide deprotection of **58** followed by dihydroxylation delivered tetrol **60** in (1:1) ratio. Carbamate tetrol **60** was acylated followed by treatment with acid gave L-*allo*-1-DNJ **9** and L-*manno*-1-DNJ **12**.

Takahata *et al.* [17] (*Tetrahedron* **2004**, *60*, 8199**)**

Takahata *et al.* has synthesized 1,3-acetonide protected compounds **63** and **64** from Garner aldehyde **61** (Scheme 8). Major isomer of carbamate **64** was elaborated to the synthesis of D-*allo*-1-DNJ **10** and D-*manno*-1-DNJ **11**. Carbamate compound **64** was converted to its *N*-allylated derivative **65** followed by RCM reaction to deliver unsaturated piperidine framework **66**. 1,3-Acetonide deprotection of **66** followed by dihydroxylation afforded diastereomeric mixture of tetrol compound **68**. D-*allo*-1-DNJ **10** and L-*manno*-1-DNJ **11** were obtained from tetrol **68** involving acylation followed by acid treatment.



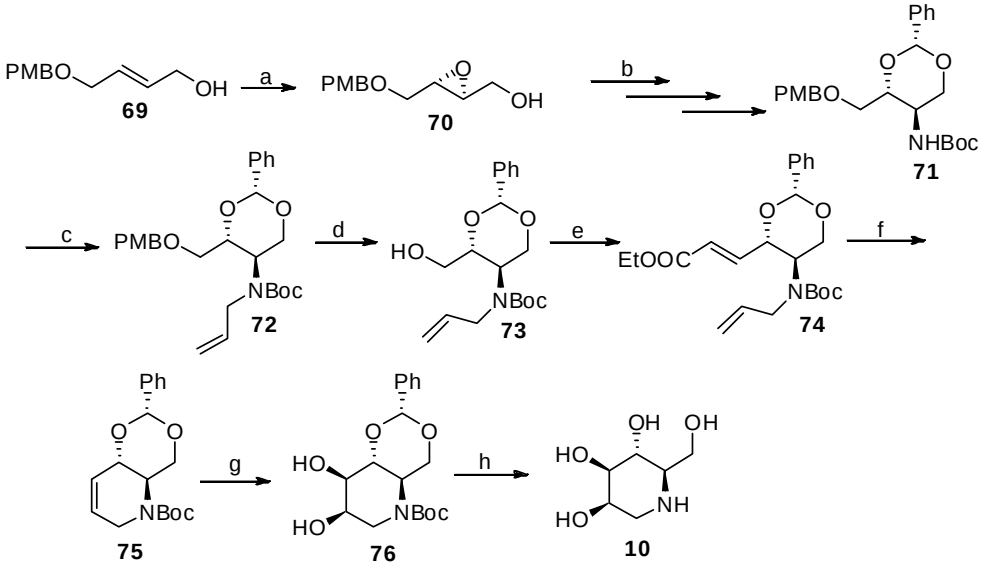
Scheme 8 *Reagents and conditions: (a) Vinyl magnesium bromide (b) 0.15 N HCI gas in $CHCl_3$, rt, overnight; (c) Allyl iodide, NaH, THF, 0 ^oC, overnight, 95%; d) Cat. ($Cl_2(Cy_3P_2)Ru$=CHPh, CH_2Cl_2, rt, 2 h, 97%; e) p-TsOH:H_2O, MeOH, rt, 2 h, 94%; f) Cat. K_2OsO_4:2H_2O, NMO, acetone, rt, overnight, 87%; g) i) Ac_2O, pyridine, rt, overnight; ii) 6 N HCI, MeOH, reflux, 8 h, DOWEX.*

Rao Approach[18] (*Tetrahedron* **2009,** *65*, 10701)

Rao and co-workers accomplished the synthesis of D-*allo*-1-DNJ by employing Sharpless asymmetric epoxidation, regioselective epoxide opening and RCM reaction as the key steps.

Allylic alcohol **69** was converted to carbamate derivative **71** *via* Sharpless asymmetric epoxidation, regioselective epoxide opening by NaN_3 as nucleophile and protection sequence (Scheme 9). Urethane **71** was treated with allyl bromide, sodium hydride as

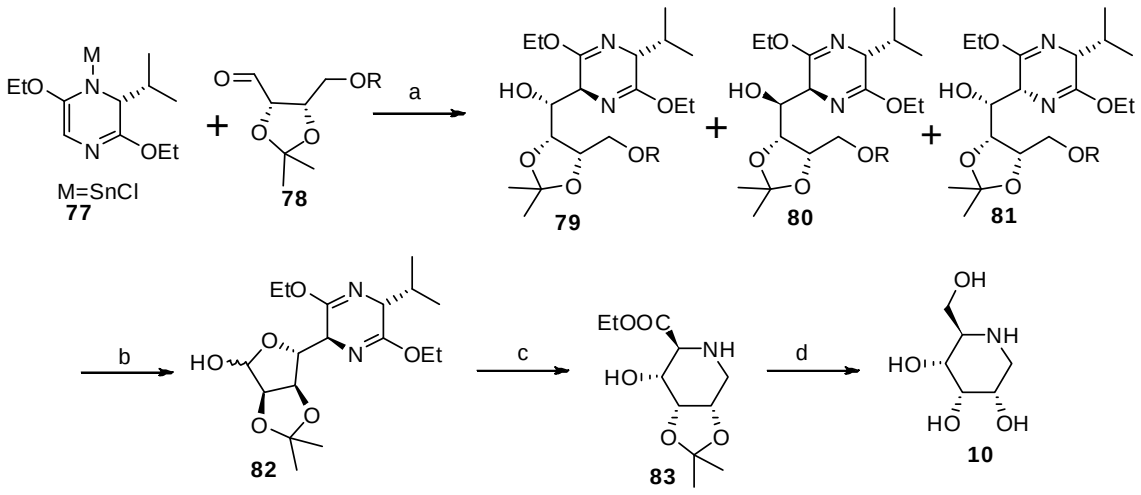
a base to furnish *N*-allylated derivative **72**. *O*-PMB deprotection followed by two carbon homologation on **72** afforded diene **74**. Diene **74** was subjected under RCM reaction to afford piperidine framework **75**. Unsaturated piperidine compound **75** was dihydroxylated followed by global deprotection to give D-*allo*-1-DNJ **10**.



Scheme 9 *Reagents and conditions: (a) L-(+)-DET, Ti(O^{i}Pr)$_4$, TBHP, 4 Å MS, DCM, –20 ^{o}C, 3 h, 80%; (b) i) (MeO)$_3$B, NaN$_3$, DMF, 50 ^{o}C, 3 h, 83%; ii) PhCH(OMe)$_2$, PPTS, benzene, reflux, 15 h, 92%; iii) H$_2$, Lindlar cat, MeOH, rt, 6 h; iv) (Boc)$_2$O, β-CD/H$_2$O, rt, 20 min, 90% over two steps; c) NaH, allyl bromide, 18-crown-6-ether, THF, 0 ^{o}C -rt, 3 h, 94%; d) DDQ, DCM/pH 7 buffer (5:1), rt, 2 h, 95%; e) (i) Oxalyl chloride, DMSO, TEA, DCM, -78 ^{o}C, 1 h; (ii) LiBr, triethylphosphonoacetate, DBU, THF, rt, 1 h, 94% for two steps; f) Grubbs' Ist generation catalyst, toluene, 90 ^{o}C, 2 h, 92%; g) OsO$_4$, NMO, acetone:water, 0 ^{o}C, overnight, 86%; h) 6 N HCl, MeOH, rt, overnight; DOWEX, 89%.*

Ruiz *et al.*[19] (*Tetrahedron: Asymmetry* **2002**, *13*, 795)

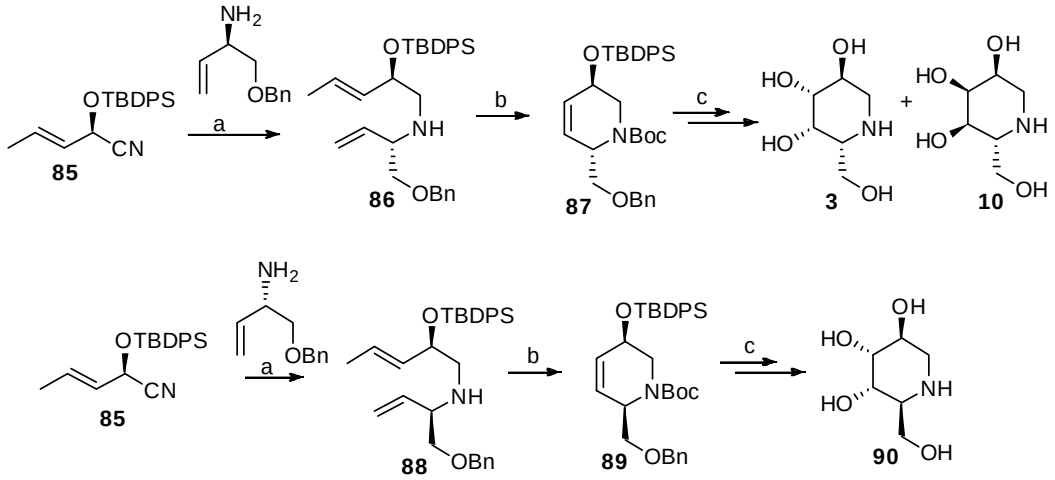
Ruiz *et al.* have synthesized aldol adducts by Lewis acid catalysed aldol reaction of aza-enolate **77** with aldehyde **78** (derived from tartaric acid) (Scheme 10). *O*-Debenzylation followed by chemoselective oxidation of **79** delivered lactol **82**. Treatment of **82** with acid followed by hydrogenolysis furnished ester **83**. Ester functionality of **83** was reduced followed by acetonide deprotection to furnish D-*allo*-1-DNJ **10**.



Scheme 10 *Reagents and conditions: (a) i) THF, −78°C, 2 h for* ***77****,* ***78****, 12 h; ii) NH_4Cl or phosphate buffer; b) i) H_2, Pd/C, THF, rt, 6 h., M=SnCl; R=Bn; ii) IBX, DMSO/THF (1:1), 8 °C, 24 h; c) H_2, Pd/C, rt, 3 h; d) i) $LiBEt_3H$, THF, rt, 5 h. (ii) Dowex-H^+.*

Nieuwendijk *et al.*[20] (*Org. Lett.* **2010**, *12*, 3957)

Nieuwendijk *et al.* utilized chemoezymatic and RCM protocol for the synthesis of D-*allo*-1-DNJ, D-*galacto*-1-DNJ and L-*altro*-1-DNJ.



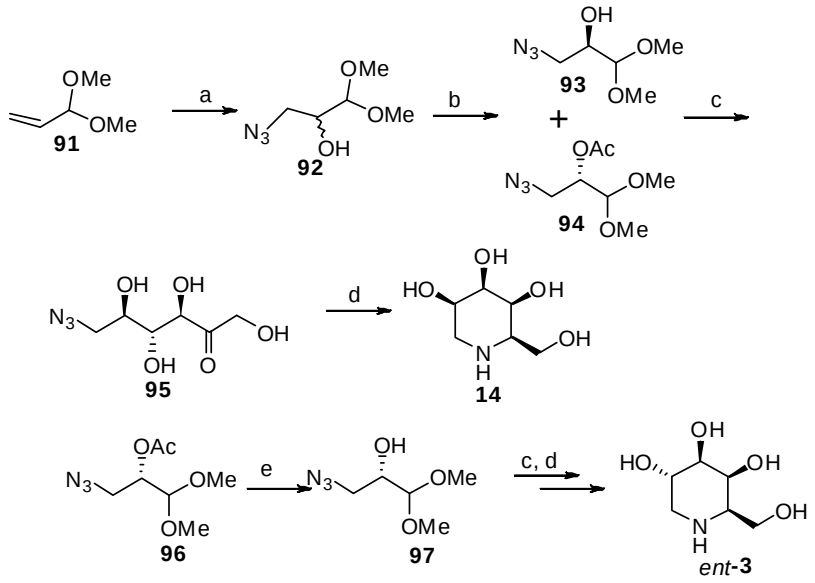
Scheme 11 *Reagents and conditions: (a) i) DIBAL-H, -78 ^oC-10 ^oC, ii) -90 ^oC, MeOH, iii) (S) or (R) Allyl amine, rt, 18 h; iv) $NaBH_4$, 0 ^oC-rt, 3 h, 80%; b) $(Boc)_2O$,*

Grubbs' Ist generation catalyst, 91%; c) (i) K_2OsO_4, NMO, THF:H_2O, rt, 24-48 h, ; c) (ii) TBAB, THF, rt, 18 h (iii) H_2, Pd/C, 6M HCl, MeOH, rt, 18 h.

Chiral cyanohydrin **85** was reduced to corresponding aldehyde followed by condensation with chiral amine to afford imine which was further reduced by $NaBH_4$ to afford diene **86** or **88** (Scheme 11). Amine **86** or **88** was protected as its carbamate followed by RCM reaction to deliver **87** or **89**. Salt of D-*allo*-1-DNJ **10**, D-*galacto*-1-DNJ **3** and L-*altro*-1-DNJ **90** were obtained from dienes **87** and **88** involving dihydroxylation, TBDPS deprotection and *O*-debenzylation sequence.

Lees *et al.* [21](*Bioorg. Chem.* **1992**, *20*, 173)

Lees *et al.* reported total synthesis of D-*talo*-1-deoxynojirimycin **14** and D-*galacto*-1-deoxynojirimycin **3** employing enzymatic resolution and reductive cyclisation as the key steps.



Scheme 12 *Reagents and conditions: a) H_2O_2, PhCN, MeOH; ii) NaN_3; b) Ac_2O, Lipase; c) i) H+; ii) DHPA; iii) Acid-base; d) i) H_2, $Pd(OH)_2$/C; ii) NaOMe.*

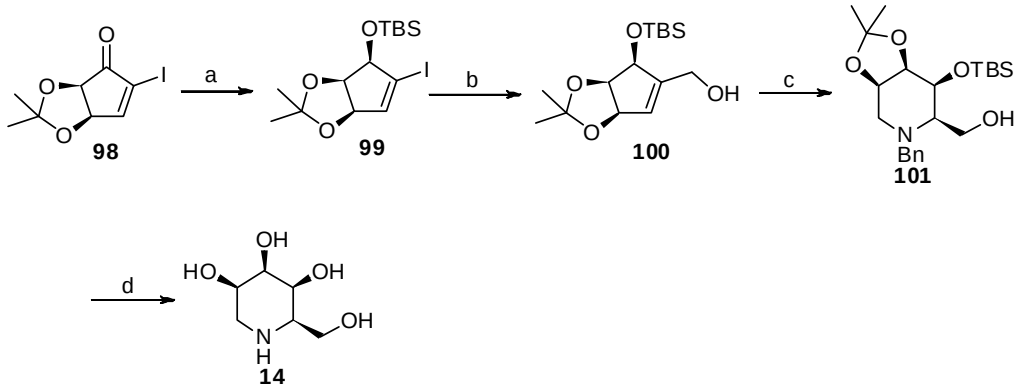
3-Azido-2-hydroxypropanal dimethyl acetal **92** was obtained from acetal **91** involving epoxidation and regioselective epoxide opening by sodium azide (Scheme 12). The alcohol **92** was acylated and the acetate resolved using lipase. Resolved acetal **93** was allowed to react with DHAP with catalysis by fuculose-l-phosphate aldolase to stereoselectively make the corresponding azido phosphate. The phosphate group was hydrolyzed with acid phosphatase to the corresponding azido compound **95**. The azide **95** was reduced under hydrogenation condition, to the amine, the amine formed a

Schiff's base with the ketone *in situ*, and the imine was reduced with H_2, from the face opposite to the axial hydroxy group, with high stereoselectively (> 10 : 1) to the corresponding piperidine derivative **14**. The same reaction sequence was employed on acetal **97** for the synthesis of *ent*-**3**.

Johnson *et al.*[22] (*Synlett* **1995**, 313)

Johnson *et al.* reported total synthesis of **14** by utilizing enzymatic desymmetrisation and reductive amination as the key steps.

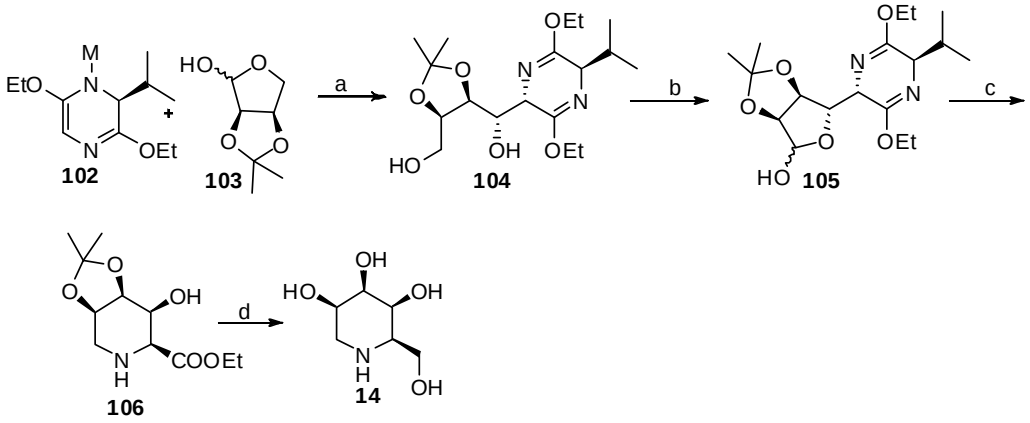
Cyclopentadiene was converted to optically active enone **98** *via* enzymatic asymmetrisation[23] and protecting group manipulation and α-iodination (Scheme 13). *O*-TBS derivative **99** was subjected under Stille mediated carbonylation conditions followed by Luche's reduction to provide allylic alcohol **100**. Ozonolysis of olefin **100** followed by reductive amination delivered partially protected *talo*-1-DNJ **101**. Acidic deprotection followed by hydrogenolysis of *N*-benzyl group in **101**, afforded D-*talo*-1-DNJ **14**.



Scheme 13 *Reagents and conditions: a) i) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -78 ^oC; ii) TBSCl, imidazole, DMF; b) CO, Bu_3SnH, $Pd(PPh_3)_4$, THF then $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -78 ^oC c) i) O_3, MeOH, -78 ^oC then DMS; ii) $BnNH_3Cl$, $NaBH_3CN$, MeOH; d) i) 1N HCl, MeOH; ii) H_2, Pd/C, MeOH, 30 psi.*

Ruiz *et al.* (*Synlett* **1999,** 204)

Ruiz *et al.*[24] reported total synthesis of D-1-deoxytalonojirimycin **14** by employing *syn*-aldol reaction between 2,3-isopropylidene-D-erythrose **103** and the stannous salt of the bislactam ether **102** as the key step (Scheme 14).



Scheme 14 *Reagents and conditions: a) i) THF, -78 to -10 °C, 5 h. ii) NH_4Cl (93%, de>95%). b) IBX, DMSO/ THF (1:1), 8 °C, 24 h, 64%; c) 0.25M HCl, H_2, Pd/C, EtOH, rt, 3 h, 67%; d) i) $LiBEt_3H$, THF, rt, 5 h; ii). Dowex-H,$^+$ 95%.*

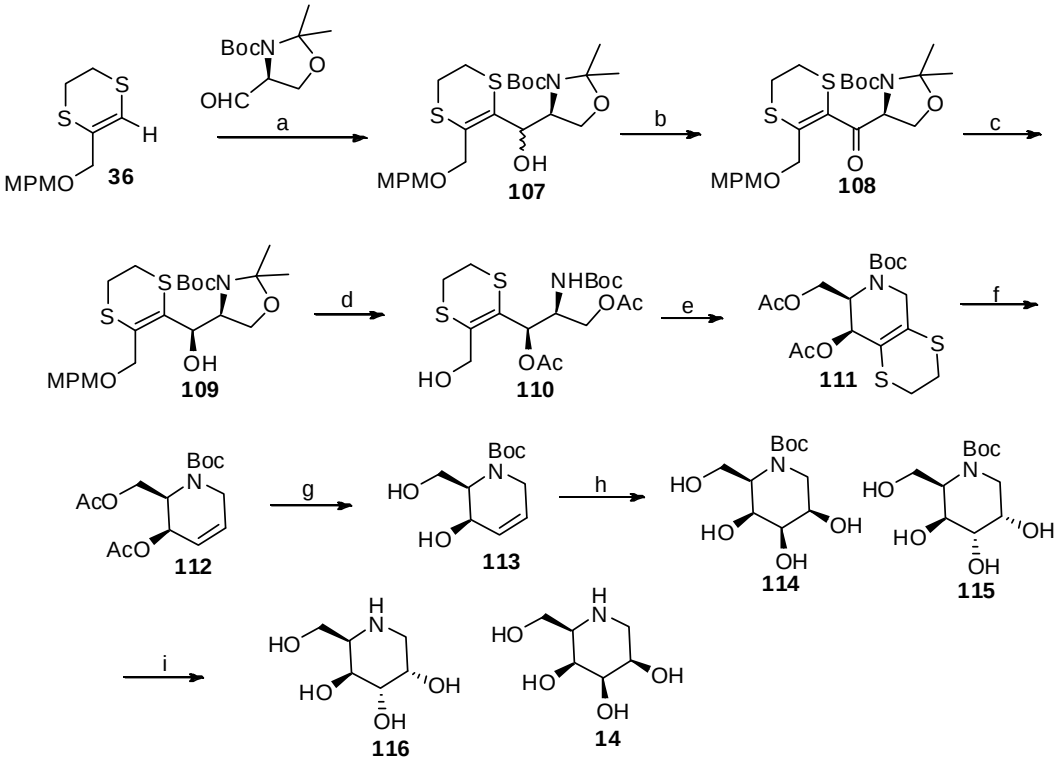
The excess of lithium azaenolate **102** was allowed to react with an equimolar amount of stannous chloride followed by addition of the lactol **103**, to give the desired adduct **104** in high yield with excellent stereoselectivity. Chemoselective oxidation of primary hydroxy in **104** gave lactol **105**. Lactal **105** was subjected under hydrogenation reaction to provide the substituted piperidine core **106**. D-*talo*-1-DNJ **14** was obtained from **106** involving reduction and acetonide deprotection sequence.

Guaragna *et al.*[25] (*Tetrahedron Lett.* **2009,** *50*, 2045)

Enol thioether **36** was coupled with the Garner's aldehyde to afford a mixture of diastereomers **107** (syn/ anti, *dr* = 1:9) (Scheme 15).

Anti isomer (undesired isomer) was converted to syn isomer **109** (which is the suitable precursor for L-*gulo*-1-DNJ and L-*talo*-1-DNJ syntheses), by employing oxidation/reduction reaction sequence. Free hydroxy group in compound **109** was converted into its *O*-acetate derivative followed by removal of MPM group to furnish *O*-diacetyl derivative **110**. Tosylation of primary hydroxyl group in **110** followed by *in situ* intramolecular attack on tosylate intermediate by the amino group gave piperidine **111**. Finally, removal of dithioethylene bridge of **111** using Raney-Ni led to olefin **112**. Deprotection of acetyl group in **112** furnished diol **113**. The olefin **113** was subjected under Donohoe's conditions to afford mixture of tetrols **114** and **115** (dr 6:4) which was readily separated by flash column chromatography.

Carbamate deprotection of **114** and **115** under acidic condition led to D-*talo*-1-DNJ **14** and L-*gulo*-1-DNJ **116** respectively.



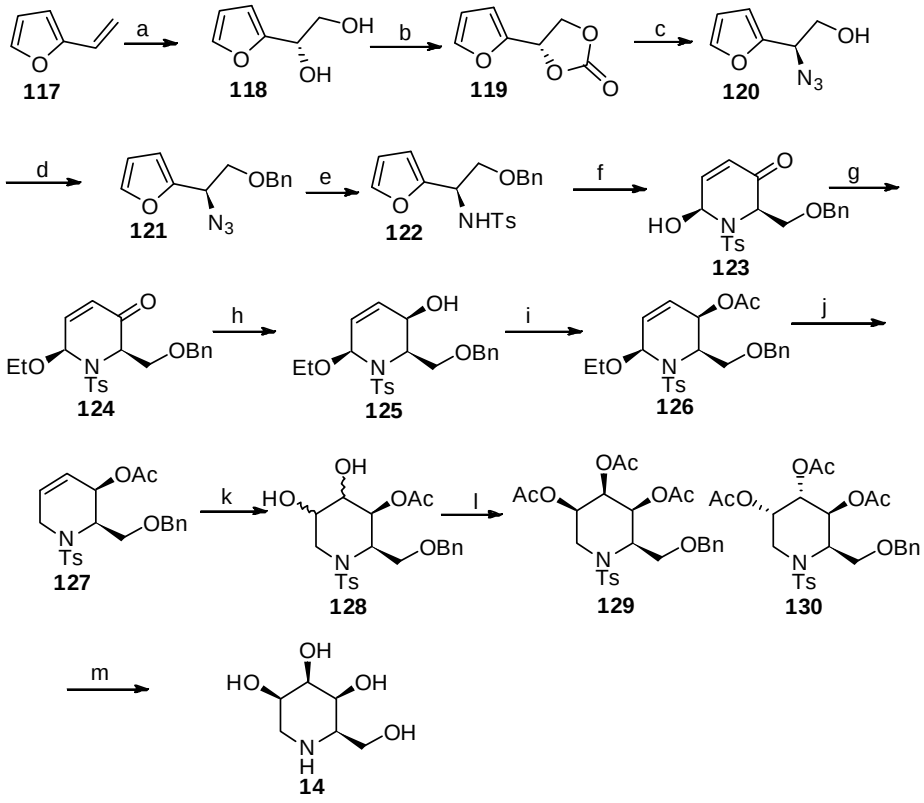
Scheme 15 *Reagents and conditions: a) BuLi, -78 ^{o}C, Et_2O, 72%; b) CrO_3, pyridine, Ac_2O, DCM, 80%; c) $NaBH_4$, MeOH, 91%; d) i) AcOH, 50 ^{o}C, 80%; ii) Ac_2O, py., rt, 90%; iii) DDQ, DCM/H_2O, rt, 95%; e) Ag_2O, TsCl, THF, 40 ^{o}C, 68%; f) Raney-Ni, EtOH, 0 ^{o}C, 68%; g) NaOMe, MeOH; h) OsO_4, TMEDA, DCM; i) 6N HCl.*

Liao *et al.* [26](*Tetrahedron: Asymmetry* **1999**, *10*, 3649)

Liao's *et al.* accomplished the total syntheses of D-*talo*-1-DNJ and D-*gulo*-1-DNJ by employing Sharpless asymmetric dihydroxylation and intramolecular cyclisation as the key steps.

Vinyl furan **117** was subjected under Sharpless asymmetric dihydroxylation to furnish furfuryl glycol **118** (Scheme 16). The dihydroxy group in **118** was protected with dimethyl carbonate to give carbonate compound **119**. Regioselective opening of carbonate in **119** with NaN_3 gave azido alcohol **120**. Free hydroxy in **120** was protected as its benzyl ether **121** followed by azide reduction and protection to deliver **122**. Enone **123** was obtained by oxidation of hydroxyfurfurylamine derivative **122** with *m*-CPBA. Hydroxy group of **123** was then protected with triethylorthoformate in

the presence of Lewis acid to give **124** which was reduced with $NaBH_4$ in the presence of $CeCl_3$ to give *β*-allylic alcohol **125**. Free hydroxy of **125** was converted to its *O*-acetate derivative **126**. Removal of ethoxy group in **126** gave olefin **127**. Olefin **127** was subjected under Sharpless asymmetric dihydroxylation conditions to give the mixture of diols **128**. After, acylation of **128** gave separable diastereomeric mixture of **129** and **130** in the ratio of 4:1. *O*-Debenzylation of **129** followed by deprotection of *N*-tosyl and acetate with sodium and liquid ammonia gave D-*talo*-1-DNJ **14**.



Scheme 16 *Reagents and conditions:* (*a) (DHQD)$_2$-PHAL, $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, 0 °C, 10 h, 92%; (b) $(MeO)_2CO$, KOH, 60 °C- 90 °C, 94%, 92% ee.; (c) NaN_3, DMF, H_2O, 120 °C, 10 h, 91%, 91% ee.; (d) NaH, BnBr, 80.7%; (e) (i) $LiAlH_4$, THF, reflux; (ii) TsCl, Py, 0 °C, 93% (over two steps), 94%, ee. (after recrystallization); f) m-CPBA, CH_2Cl_2, rt, 82.4%; g) $HC(OEt)_3$, $BF_3.Et_2O$, 4 Å molecular sieves, THF, 0 °C, 4 h, 90%; h) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -30 °C, 2 h, 97%; i) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 2 h, 86%; j) $NaBH_4$, HCOOH, 0 °C, 85.9%; k) (DHQD)$_2$PHAL, $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, tBuOH:H_2O (1:1), 0 °C, 94%; l) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 2 h, 86% in the ratio of 4:1; m) i) Pd/C, H_2, EtOAc, rt, 4 h; ii) Na/NH_3, -78 °C, 4 h.*

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Chapter 3

Section 2 Asymmetric synthesis of L-*allo*-1-deoxynojirimycin (L-*allo*-1-DNJ)

3.2.1. Present Work

3.2.1.1 Objective

Azasugars or iminosugars have significant biological activities. They act as glycosidase inhibitor and are extensively used for the treatment of AIDS, cancer, diabetes and viral infections.[1] Very less attention has been paid towards the synthesis of other isomers of deoxynojirimycin **1** (1-DNJ) (Figure 1) such as 1-deoxyallonojirimycin (*allo*-1-DNJ**) (**L-*allo*-1-DNJ **2**, D-*allo*-1-DNJ **3)**.[2] In literature, only three asymmetric synthesis of L-1-deoxyallonojirimycin **3** have been reported, based on Sharpless asymmetric epoxidation,[3] Sharpless asymmetric dihydroxylation[4] and chemoenzymatic approach.[5] Recently, L-1-deoxyallonojirimycin (L-*allo*-1-DNJ **2**) (Figure 1) has been shown to be more potent inhibitor of α-mannosidase as compared to D-*manno*-1-DNJ **4**[6] (Figure 1). Synthetic challenge in L-*allo*-1-DNJ **2** (*ent*-**3**) is the construction of piperidine moiety and installation of hydroxyl groups in stereoselective manner. Due to its interesting biological activity and structural feature, L-*allo*-1-DNJ **2** has attracted many organic chemists towards its synthesis. Recently, it has been found that L isomer of azasugar also exhibits remarkable activity against glycosidase inhibitor.[7]

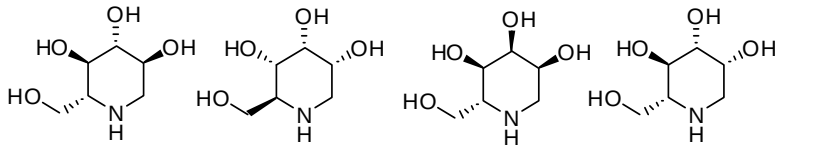
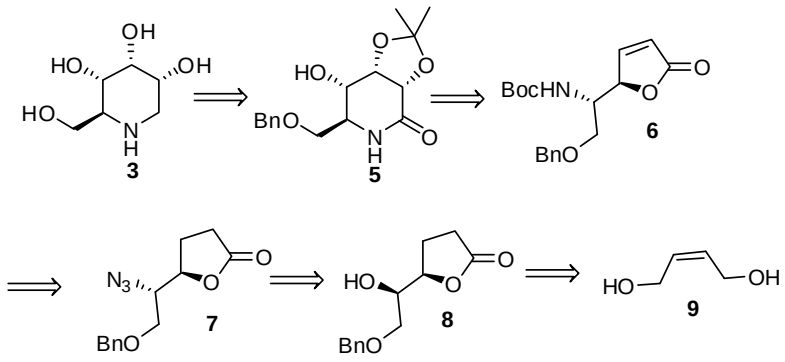


Figure 1

In view of interesting biologicl activity exhibited by the above derivatives the syntheses one of these derivatives **2** was undertaken.

3.2.1.2 Retrosynthetic analysis

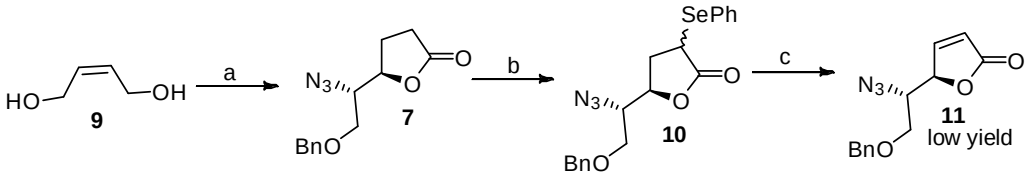
According to the retrosynthetic plan (Scheme 1), lactam **5** can be generated from butenolide **6** *via* dihydroxylation, protection and deprotection sequence. Azido lactone **7** could be easily accessed from *cis*-butene-1, 4-diol **1** by known literature procedure.[8,9]



Scheme 1 Retrosynthetic analysis of L-*allo*-1-DNJ

3.2.1.3 Results and discussion

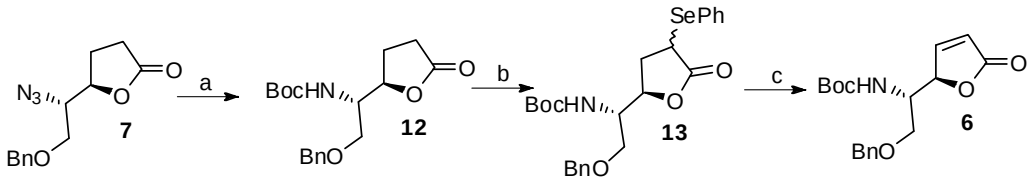
The synthesis initiated from *cis*-butene 1,4-diol **9** which was converted to its azidolactone **7** (as described in Chapter 2, Section 5) by known literature protocol developed in these laboratories.[9] Azido lactone **7** was treated with LDA (prepared from *n*-BuLi and diiospropyl amine) followed by addition of diphenyl diselenide to afford diastereomeric mixture of α-phenylseleno lactone **10** which on treatment with H_2O_2 in presence of acetic acid gave butenolide **11** in low yield (Scheme 2).



Scheme 2 *Reagents and conditions: (a) Ref 9; b) LDA, diphenyl diselenide, THF, -78 ^oC, c) H_2O_2, CH_3COOH, THF, 30 min, 0^oC, 10-20%.*

It was thought that, first azide reduction and its protection might improve yield of butenolide compound. A one-pot azide reduction of **7** and *in situ* amine protection was carried out using $Pd(OH)_2$ under hydrogen atmosphere in presence of $(Boc)_2O$, TEA to provide urethane **12** in 88% yield (Scheme 3). The formation of urethane **12** was confirmed by spectroscopic analysis. The IR spectrum of **12** displayed the strong absorption band at 1605 cm^{-1} indicating the presence of carbamate functionality while absence of absorption at 2106 cm^{-1} indicated azide reduction. ^1H NMR spectrum of compound **12** showed the presence of a new singlet which appeared at δ 1.45 integrating for nine protons which was attributed to Boc group while broad signal

appeared at δ 5.06 corresponding to proton of NH-CO-*t*Bu. ^{13}C NMR spectrum showed the signals that appeared at δ 28.0, 79.9 and 155.5 corresponding to Boc group.



Scheme 3 *Reagents and conditions:* a) *Pd(OH)$_2$, H$_2$, TEA, (Boc)$_2$O, ethyl acetate, 3 h, 88%; b) LDA, diphenyl diselenide, THF, -78 ^{o}C, 57%; c) H$_2$O$_2$, CH$_3$COOH, THF, 30 min, 0^{o}C, 78%;*

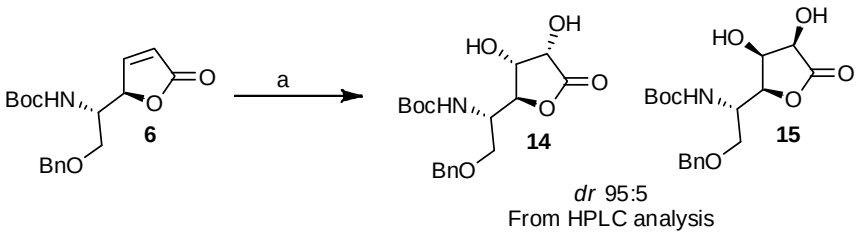
Additionally DEPT experiment also showed the presence of four CH_2 and five CH supporting the formation of **12**. Finally, appearance of a peak at *m/z* 336 $(M + H)^+$ in the mass spectrum confirmed the assigned structure of compound **12**.

Carbamate **12** was treated with LDA (4 eq.) in THF at -78 ^{o}C followed by addition of diphenyl diselenide to furnish diastereomeric mixture of *α*-phenylseleno lactone **13** in 57% yield (bsmr). The diastereomeric mixture of α-phenylseleno lactone **13** was subjected to elimination by using hydrogen peroxide in presence of acetic acid in THF to afford butenolide **6** in 78% yield. Its IR spectrum showed the strong absorption bands at 1757 and 1699 cm^{-1} indicating presence of butenolide and carbamate functionality. Peaks appeared at δ 6.10-6.14 and 7.49 in its ^{1}H NMR spectrum, indicating the presence of unsaturated double bond functionality. Its ^{13}C NMR spectrum showed the disappearance of peaks at δ 24.3 and 28.6 corresponding to CH_2 carbons of saturated lactone. Additionally, DEPT spectrum showed the only two CH_2 carbons at δ 68.63 and 73.31 indicating the formation of **6**. Finally, appearance of a peak at *m/z* 356.37 $(M+Na)^+$ in the mass spectrum and HRMS analysis confirmed the assigned structure of compound **6**.

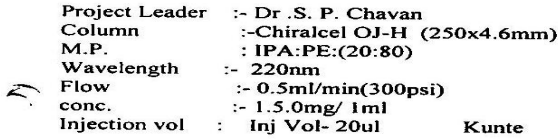
Butenolide **6** was treated with $RuCl_3$ (cat.) and $NaIO_4$ in EtOAc: H_2O: MeCN (1: 1: 1) for 2 min at 0 ^{o}C to afford non-separable diols[10] **14** (major) and **15** in 71% yield (Scheme 4). The IR spectrum of compound **14** showed the strong absorption bands at 3425, 1791 and 1701 cm^{-1} indicating presence of hydroxyl, saturated lactone and

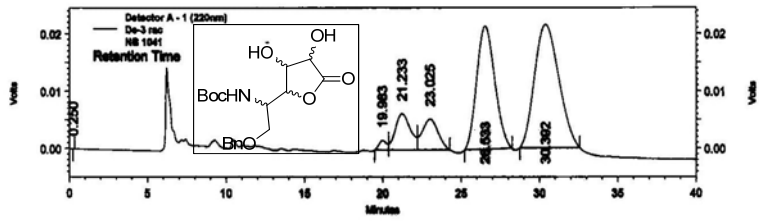
carbamate functionalities respectively. ^{1}H NMR spectrum showed the disappearance of peaks from δ 6.10-6.14 (m) and 7.49 (dd) corresponding to consumption of double bond functionality. Its ^{13}C NMR spectrum showed the signals at δ 68.4 and 68.5 corresponding to the two CH-OH carbons thus supporting the formation of **14**. Additionally, DEPT spectrum showed the seven CH and two CH_2 which confirmed the structure **14**. Finally, appearance of a peak at *m/z* 390.09 $(M+Na)^+$ in the mass spectrum and HRMS analysis confirmed the structure of compound **14**.

Literature survey for butenolide related compounds of **6** clearly demonstrates that stereogenic centre of butenolide directs the dihydroxylation reaction mediated by osmium tetraoxide[11] or $KMnO_4$[12] or $RuCl_3$/ $NaIO_4$.[13] The same reaction sequence strategy was employed for the synthesis of racemic diol **14** and its enantiomeric excess (97%) and diastereomeric ratio (95:5) were established by chiral HPLC.



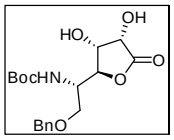
Scheme 4 *a) $RuCl_3$, $NaIO_4$, EtOAc:MeCN:H_2O, 0 °C, 71%;*

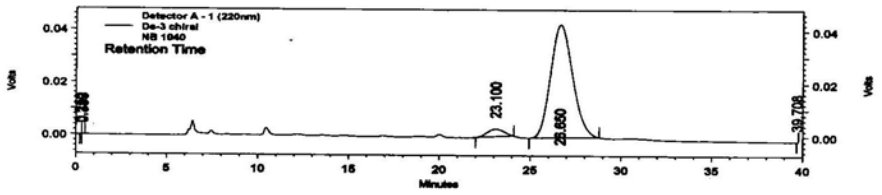




Detector A - 1 (220nm)

Retention Time	C Area	Area %
0.250	81	0.002
19.983	55970	1.144
21.233	423455	8.653
23.025	375807	7.679
26.533	1725077	35.251
30.392	2313317	47.271



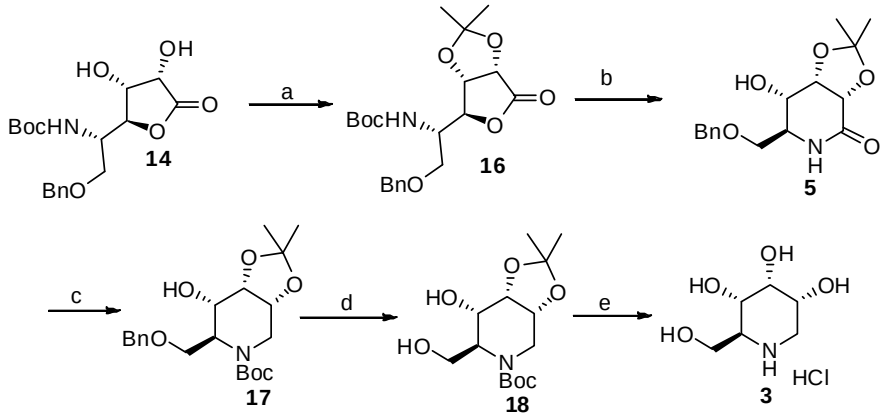


Detector A - 1 (220nm)

Retention Time	C Area	Area %
0.250	105	0.003
0.383	152	0.004
23.100	186961	4.918
26.650	3614229	95.073
39.708	74	0.002

To carry out other functional transformations, diol was protected as its acetonide using DMP and CSA (cat.) in DCM solvent to afford acetonide **16** in 91% yield (Scheme 5). Disappearance of absorption band at 3425 cm^{-1} in its IR spectrum indicated absence of free hydroxy functionality. ^{1}H NMR spectrum displayed the two singlets at δ 1.34 and 1.46 each integrating for three protons corresponding to acetonide group. ^{13}C NMR spectrum showed the peaks at δ 25.3, 26.6 and 111.3 corresponding to the acetonide carbons while its DEPT spectrum displayed additional two signals corresponding to methyl carbons of acetonide group. Finally, appearance of a peak at *m/z* 430.11 $(M+Na)^{+}$ in the mass spectrum and HRMS analysis confirmed the structure of compound **16**.

Finally, removal of the Boc protecting group and cyclisation was achieved in one-pot reaction using TFA in DCM followed by neutralization with TEA to furnish the desired six membered lactam **5**. The IR spectrum showed the strong absorption at 1676 cm^{-1} indicating presence of six membered lactam functionality while disappearance of absorption at 1794 and 1711 cm^{-1} corresponding to lactone and carbamate groups. ^{1}H NMR spectrum displayed the broad singlet at δ 6.21 corresponding to amide proton (-NH-CO-). A peak at δ 162.2 in its ^{13}C NMR spectrum was assigned to amide carbonyl carbon. Additionally, DEPT spectrum showed the seven CH and two CH_2 to provide the strong support the formation of lactam **5**. Finally, appearance of a peak at *m/z* 330.1322 $(M+Na)^{+}$ in the HRMS analysis confirmed the structure of compound **5**.



Scheme 5 *Reagents and conditions: a) DMP, CSA, DCM, rt, 91%; b) TFA, DCM, 0 ^{o}C-rt, 3 h, 53%; c) i) BH_3.DMS, THF, 0 ^{o}C-rt, 24 h, ii) TEA, $(Boc)_2O$, THF, rt, overnight, 58% (over two steps); d) i) $Pd(OH)_2$, H_2, MeOH, rt e) MeOH, conc HCl, rt, 3 h, 80%;*

Lactam **5** was reduced by using BH_3.DMS in THF to give corresponding amine, which without purification was protected using TEA, $(Boc)_2O$ and DMAP (cat.) in THF to afford urethane **17** in 58% yield (over two steps). Its IR spectrum showed the strong absorption bands at 3444 and 1698 cm^{-1} indicating presence of free hydroxy and urethane functionality. ^{1}H NMR spectrum showed the peak at δ 1.42 integrating for nine protons corresponding to the Boc group. Signals at δ 28.4, 79.7 and 154.9 cm^{-1} in its ^{13}C NMR spectrum were assigned to Boc group. Its DEPT spectrum displayed the three CH_2 and seven CH to provide the strong support for the formation of **17**. Finally, appearance of a peak at *m/z* 416.2060 $(M+Na)^{+}$ in the HRMS analysis confirmed the structure of compound **17**.

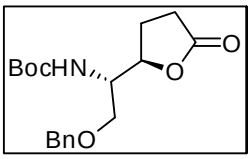
Urethane **17** was subjected to debenzylation under hydrogen atmosphere using $Pd(OH)_2$ as catalyst in methanol at room temperature for 6 h to deliver diol which on acid treatment led to the salt of deoxyallonojirimycine **3**. The ^{1}H NMR spectrum of compound **3** showed the absence of peaks at δ 1.34 (s, 3H), 1.42 (s, 9H) and 1.46 (s, 3H) which were assigned for carbamate and acetonide groups. ^{13}C NMR spectrum displayed the signals at δ 41.4, 54.6, 57.5, 64.4, 65.2 and 69.8 for six carbons while DEPT NMR spectrum showed the four CH and two CH_2 which confirmed the structure **3**. Spectroscopic analysis and rotation value of compound **3** was in good agreement with the values reported in literature. [14]

3.2.2 Conclusion

Asymmetric synthesis of L-1-deoxyallonojirimycin was achieved from *cis*-butene-1,4-diol by employing Sharpless asymmetric dihydroxylation, stereoselective dihydroxylation and ring enlargement as the key steps.

3.2.3 Experimental Section

tert-Butyl ((*S*)-2-(benzyloxy)-1-((*R*)-5-oxotetrahydrofuran-2-yl)ethyl)carbamate (12)



To a solution of azide **7** (2 gm, 7.6 mmol) in EtOAc (30 mL) were added Et_3N (1.6 mL, 11.4 mmol), $(Boc)_2O$ (1.8 mL, 8.36 mmol) and $Pd(OH)_2$ (10 mg) and stirred under hydrogen atmosphere for 3 h.. After completion of reaction (monitored by TLC), the reaction mixture was filtered through celite and celite was washed thoroughly with methanol (3 X 50 mL) and concentrated under reduced pressure and residue thus obtained was purified by silica gel column chromatography using light petroleum ether: EtOAc (7:3) as an eluent to afford pure urethane **12** (2.2 gm, 88% yield) as a colorless syrup.

Chemical Formula: $C_{18}H_{25}NO_5$;

Yield: 88%;

$[\alpha]_D^{25}$: - 1.97 (c 1, $CHCl_3$);

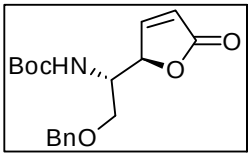
MS (EI) *m/z* : 336 $(M+H)^+$;

IR ($CHCl_3$, cm^{-1}): 3119, 1776, 1605, 1445, 758;

H^1 NMR (200 MHz, $CDCl_3$+ CCl_4): δ 1.45 (s, 9H), 2.19-2.31 (m, 2H), 2.48-2.61 (m, 2H), 3.59 (dd, J = 9 Hz, 3 Hz, 1H), 3.82 (bd, 2H), 4.53 (s, 2H), 4.57-4.64 (m, 1H), 5.06 (bs, 1H), 7.28-7.37 (m, 5H);

^{13}C NMR (50 MHz, ($CDCl_3$ + CCl_4): δ 24.6, 28.0, 28.3, 52.9, 68.9, 73.5, 78.5, 79.9, 127.7, 127.9, 128.4, 137.6, 155.5, 176.7.

tert-Butyl ((*S*)-2-(benzyloxy)-1-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)ethyl)carbamate (6)



Carbamate **12** (2.1 gm, 6.26 mmol) in dry THF (20 mL) was added to the solution of LDA (prepared from diisopropyl amine (3.5 mL, 25 mmol), butyllithium (15.7 mL, 25 mmol, 1.6 M in hexane) in dry THF (20 mL) at 0 ^oC under the nitrogen atmosphere at -78 ^oC. After 30 min, diphenyl diselenide (1.9 gm, 6.26 mmol) was added and the reaction mixture was stirred at -78 ^oC for 60 minutes. The reaction

mixture was quenched with saturated solution of NH_4Cl and extracted with ethyl acetate (3 X 30 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by flash column chromatography (SiO_2) using 20% ethyl acetate in pet ether as an eluent to obtain α-phenylseleno lactone **13** as white semisolid compound (1.2 gm, 40%) and recovered starting material **12** (0.6 gm).

To a solution of α-phenylseleno lactone **13** (75 mg, 0.15 mmol) in THF (5 mL) containing CH_3COOH (0.025 mL) cooled to 0 ^oC, was added 30% H_2O_2 (0.035 mL). The reaction mixture was stirred for 30 minutes at 0 ^oC, then poured into cold saturated solution of sodium carbonate solution and extracted with ethyl acetate (2 X 20 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over flash silica gel, eluting with 20% ethyl acetate in pet ether as an eluent to afford butenolide **6** (40 mg, 78%) as a white semisolid.

Chemical Formula : $C_{18}H_{23}NO_5$;

Yield : 78%;

$[\alpha]_D^{25}$: +51.4 (c 2.1, $CHCl_3$);

MS (EI): *m/z* : 356.37 $(M+Na)^+$;

IR ($CHCl_3$, cm^{-1}): 1757, 1699, 1683;

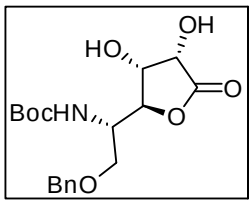
HRMS calculated for $[C_{18}H_{23}NO_5+Na]^+$ 356.1468; found: 356.1477;

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 3.57 (dd, *J* = 8.5, 3.0 Hz, 1H), 3.77-3.88 (m, 2H), 4.53 (s, 2H), 5.05-5.18 (m, 2H), 6.10-6.14 (m, 1H), 7.25-7.40 (m, 5H), 7.49 (d, *J* = 5.0 Hz, 1H);

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 28.1, 52.4, 68.6, 73.3, 79.8, 81.8, 121.2, 127.6, 127.7, 128.3, 137.2, 155.0, 172.1.

***tert*-Butyl ((*S*)-2-(benzyloxy)-1-((2*S*,3*R*,4*S*)-3,4-dihydroxy-5-oxotetrahydrofuran-2-yl)ethyl)carbamate (14)**

To a vigorously stirred solution of butenolide **6** (0.320 gm, 0.96 mmol) in acetonitrile: ethyl acetate (1:1, 12 mL) at 0 ºC, was added a solution of $RuCl_3.3H_2O$ (0.014 gm)



and $NaIO_4$ (0.3 gm, 1.44 mmol) in distilled water (6 mL). The reaction mixture was stirred for 2 min after which a saturated solution of $Na_2S_2O_3$ (30 mL) was added and extracted with ethyl acetate (3 X 20 mL). Organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 50% ethyl acetate in pet ether as an eluent to afford dihydroxylated lactone **14** (0.250 gm, 71%) in analytically pure form.

Chemical Formula: $C_{18}H_{25}NO_7$;

Yield: 71%;

$[\alpha]_D^{25}$: -8.42 (c 0.95, $CHCl_3$);

IR ($CHCl_3$, cm^{-1}): 3425, 1791, 1772, 1701, 1683, 1166.

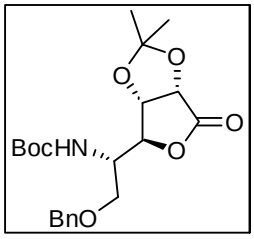
MS (EI): ***m/z*** 390.09 $(M+Na)^+$;

HRMS calculated for $[C_{18}H_{25}NO_7+Na]^+$ 390.1523; found: 390.1538;

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 1.43 (s, 9H), 3.42-3.55 (m, 2H), 3.66-3.79 (m, 2H), 4.34-4.40 (m, 1H), 4.52 (s, 2H), 4.65 (d, *J* = 4 Hz, 1H), 5.30 (d, *J* = 8 Hz, 1H), 7.24-7.37 (m, 5H);

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 28.3, 50.4, 68.4, 68.5, 69.1, 73.6, 80.5, 83.1, 127.7, 127.9, 128.5, 137.4, 155.8, 175.9.

***tert*-Butyl ((*R*)-2-(benzyloxy)-1-((3a*R*,4*R*,6a*R*)-2,2-dimethyl-6-oxotetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)ethyl)carbamate (16)**



To a solution of dihyroxy lactone **14** (0.2 gm, 0.54 mmol) in DCM was added *p*-TSA (cat) and 2,2-dimethoxypropane (0.28 mL, 2.7 mmol). After stirring under an atmosphere of nitrogen for 18 h at room temperature, the reaction mixture was concentrated under reduced pressure. Saturated solution of sodium carbonate was poured on residue and extracted with DCM (3 X 20 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 20% ethyl acetate in pet ether as an eluent to afford compound **16** (0.2 gm, 91%) as a colorless syrup.

Chemical Formula: $C_{21}H_{29}NO_7$;

Yield: 91%;

$[\alpha]_D^{25}$: +25.7 (c 0.7, $CHCl_3$);

MS (EI): *m/z* 430.11 $(M+Na)^+$;

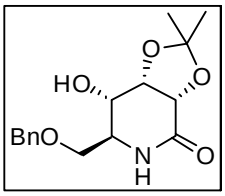
IR ($CHCl_3$, cm^{-1}): 3340, 1794, 1711, 1500, 1369, 1157, 1091;

HRMS calculated for $[C_{21}H_{29}NO_7+Na]^+$ 430.1836; found: 430.1849;

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 1.34 (s, 3H), 1.45 (s, 9 H), 1.46 (s, 3H), 3.50 (dd, *J* = 9.0, 4.8 Hz, 1H), 3.72 (dd, *J* = 9.0, 2.8 Hz, 1H), 3.78-3.88 (m, 1H), 4.51 (s, 2H), 4.60 (d, *J* = 7.3 Hz, 1H), 4.70 (d, *J* = 5.8 Hz, 1H), 4.80 (d, *J* = 5.8 Hz, 1H), 5.11 (d, *J* = 9.0 Hz, 1H), 7.22-7.42 (m, 5H);

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 25.3, 26.6, 28.3, 51.4, 68.1, 73.7, 74.7, 77.4, 80.4, 82.5, 113.5, 127.8, 128.1, 128.5, 137.0, 155.3, 173.5.

(3a*S*,6*S*,7*S*,7a*S*)-6-((Benzyloxy)methyl)-7-hydroxy-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*c*]pyridin-4(3a*H*)-one (5)



To a solution of lactone **16** (0.2 gm, 0.49 mmol) in anhydrous DCM (5 mL), was added TFA (0.2 mL, 2.45 mmol) at 0 ^oC under nitrogen atmosphere. The mixture was stirred for 30 minutes at room temperature. After completion of reaction (TLC), solvent and excess TFA was removed under reduced pressure. The reaction mixture was neutralized and basified by using triethyl amine and extracted with DCM (3 X 30 mL). Organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel chromatography using petroleum ether/ethyl acetate (2:8) as an eluent to afford white semisolid lactam **5** (79.5 mg, 53%).

Chemical Formula : $C_{16}H_{21}NO_5$;

Yield : 53%;

$[\alpha]_D^{25}$: -18.3 (c 1, $CHCl_3$);

MS (EI): *m/z* 330.22 $(M+Na)^+$;

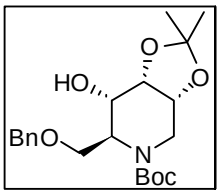
IR ($CHCl_3$, cm^{-1}): 3395, 1676, 1196;

HRMS calculated for $[C_{16}H_{21}NO_5+Na]^+$ 330.1312; found: 330.1322;

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 1.40 (s, 3H), 1.50 (s, 3H), 2.50 (bs, 1H), 3.48-3.56 (m, 1H), 3.70-3.82 (bs, 3H), 4.46 (d, *J* = 6.5 Hz, 1H), 4.58-4.59 (m, 3H), 6.21 (bs, 1H), 7.28-7.38 (m, 5H);

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 24.8, 26.5, 52.3, 67.7, 69.9, 73.7, 73.9, 74.9, 110.9, 127.8, 128.1, 128.6, 137.2, 168.2.

(3a*R*,6*S*,7*S*,7a*S*)-*tert*-Butyl 6-((benzyloxy)methyl)-7-hydroxy-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*c*]pyridine-5(6*H*)-carboxylate (17)



To a solution of lactam **6** (0.1 gm, 0.32 mmol) in an anhydrous THF (5 mL) was added BH_3.DMS (0.15 mL, 1.6 mmol) dropwise at 0 ^oC under the nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for 18 h. The reaction mixture was cooled to 0 ^oC and quenched by ethanol (5 mL). Solvent was removed under reduced pressure and the crude semisolid residue was treated with additional ethanol (5 mL) and refluxed for 4 h. Solvent was removed under reduced pressure to furnish crude amine. To the solution of crude amine in THF was added TEA (0.07 mL) followed by addition of $(Boc)_2O$ (0.089 mL) and DMAP (cat.) and was stirred at room temperature for 24 h. The reaction mixture was extracted with ethyl acetate (3 x 20 ml), washed with water, brine and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography using petroleum ether/ethyl acetate (7:3) as an eluent to afford colorless oily carbamate **17** (70 mg, 58% (over two steps)).

Chemical Formula: $C_{21}H_{31}NO_6$;

Yield: 58% (over two steps);

$[\alpha]_D^{25}$:+70.6 (c 0.53, $CHCl_3$);

IR ($CHCl_3$, cm^{-1}): 3445, 1698, 1682, 1455, 1416, 1161;

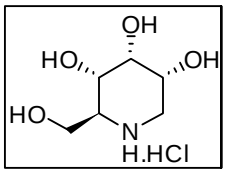
MS (EI): *m/z* : 416.51 $(M+Na)^+$;

HRMS calculated for $[C_{21}H_{31}NO_6+Na]^+$ 416.2044; found: 416.2060;

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 1.34 (s, 3H), 1.42 (s, 9H), 1.46 (s, 3H), 2.82 (m, 1H), 3.56-3.74 (m, 1H), 3.78-4.18 (m, 4H), 4.29 (m, 1H), 4.44-4.63 (m, 3H), 7.21-7.37 (m, 5H);

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 24.4, 26.2, 28.4, 41.9, 43.3, 53.3, 53.8, 67.3, 67.8, 69.7, 70.2, 73.4, 73.7, 74.2, 79.7, 109.4, 127.4, 127.7, 128.4, 138.2, 154.9.

(2*S*,3*S*,4*R*,5*R*)-2-(Hydroxymethyl)piperidine-3,4,5-triol hydrochloride (3)



To a solution of urethane **17** (30 mg, 0.076 mmol) in MeOH (5 mL) was added $Pd(OH)_2$ under the atmosphere of hydrogen. The reaction mixture was allowed to stir for 6 h. After completion of reaction (monitored by TLC), the reaction mixture was filtered through a celite bed and was thoroughly washed with methanol (3 X 20 mL). Concentration of the reaction mixture under reduced pressure provided the diol. To the solution of diol in methanol (3 mL) was added conc. HCl (0.1 mL) at 0 ^{o}C. The reaction mixture was stirred for 3 h at room temperature. After completion of reaction, the volatiles were concentrated under reduced pressure. The semisolid mass was dried under high vacuum for 3 h to provide the salt of deoxyallonojirimycine **3** (12 mg, 80% over two steps).

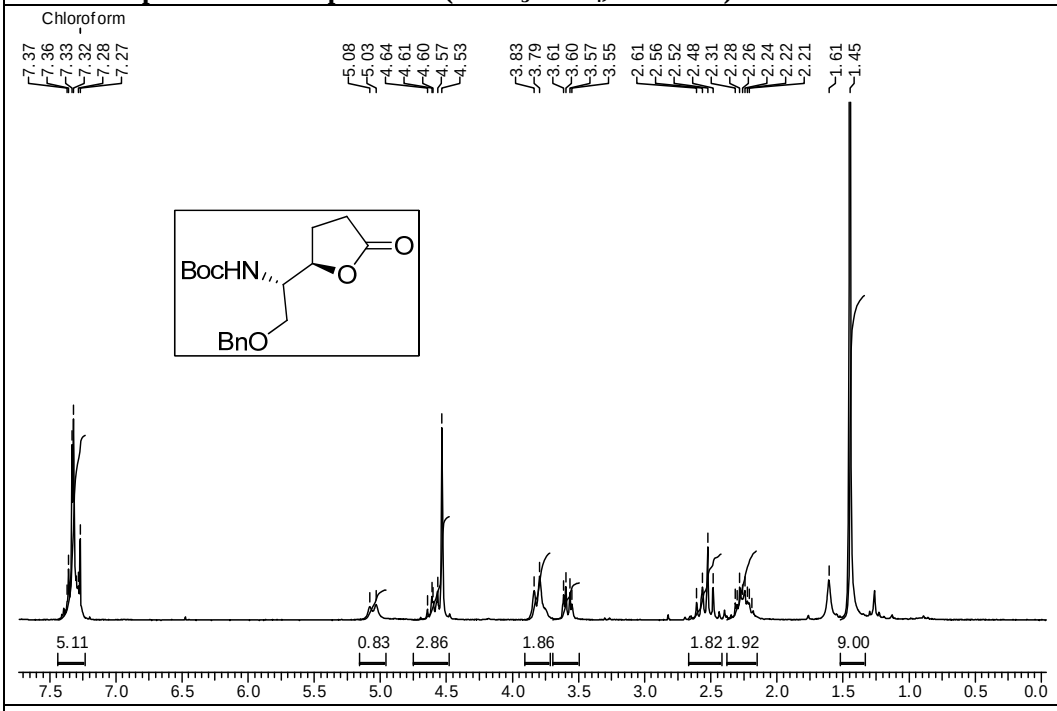
$[\alpha]_D^{25}$: -32.7 (c 1, MeOH); (lit.[15] for *ent*-**3** **$[\alpha]_D^{25}$**: +33.4 (c 1, MeOH);

^{1}H NMR (400 MHz, D_2O): δ 4.19 (s, 1H), 4.02 (ddd, *J* = 11.7, 5.0, 2.5 Hz, 1H), 3.96 (dd, *J* = 12.8, 3.1 Hz, 1H), 3.91-3.82 (m, 2H), 3.36 (ddd, *J* = 10.7, 5.1, 3.2 Hz, 1H), 3.29 (dd, *J* = 12.1, 5.0 Hz, 1H), 3.15 (t, *J* = 11.9 Hz, 1H);

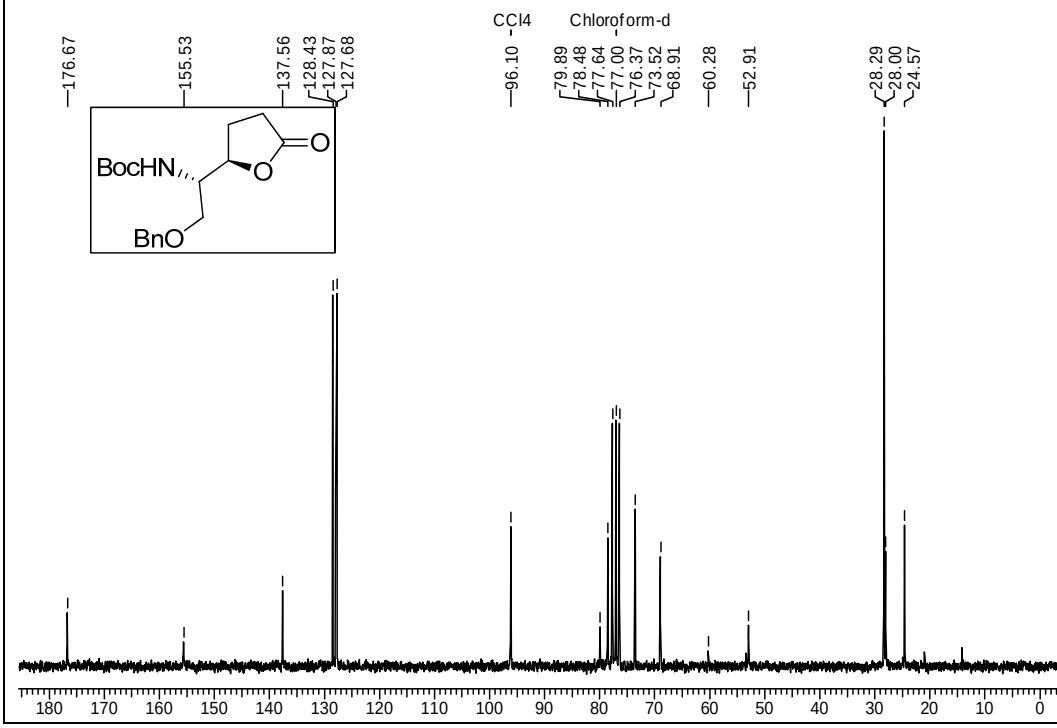
^{13}C NMR (125 MHz, D_2O): δ 41.4, 54.6, 57.5, 64.4, 65.2, 69.8.

3.2.4. Spectra

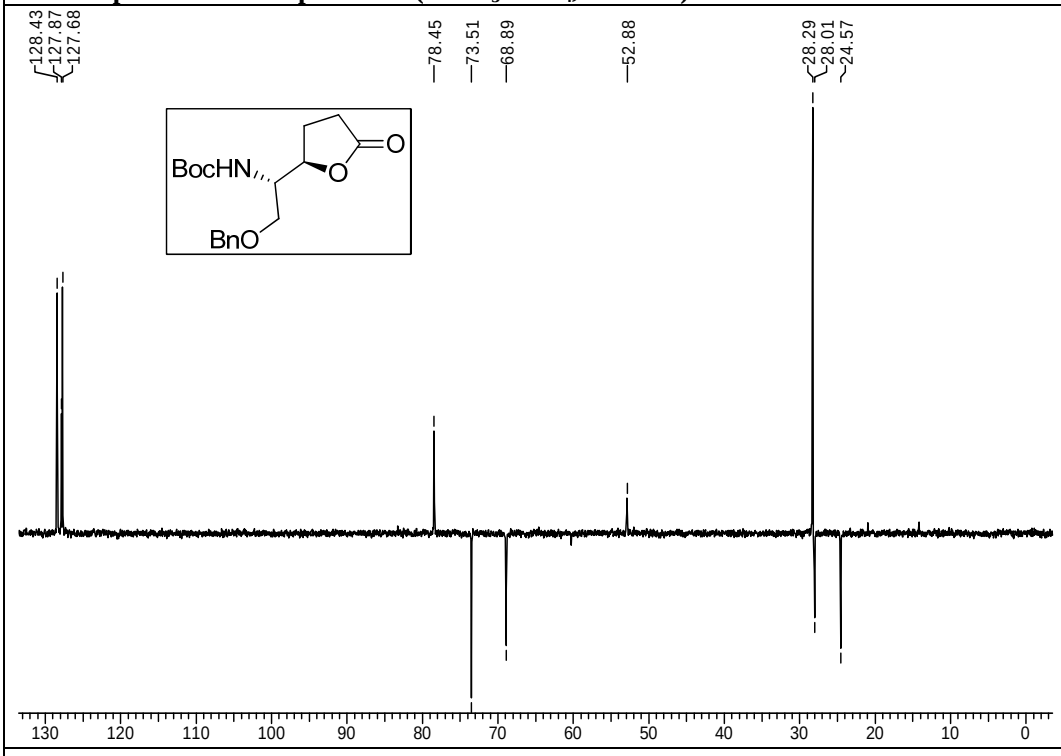
^{1}H NMR Spectrum of compound 12 ($CDCl_3$+CCl_4, 200 MHz)



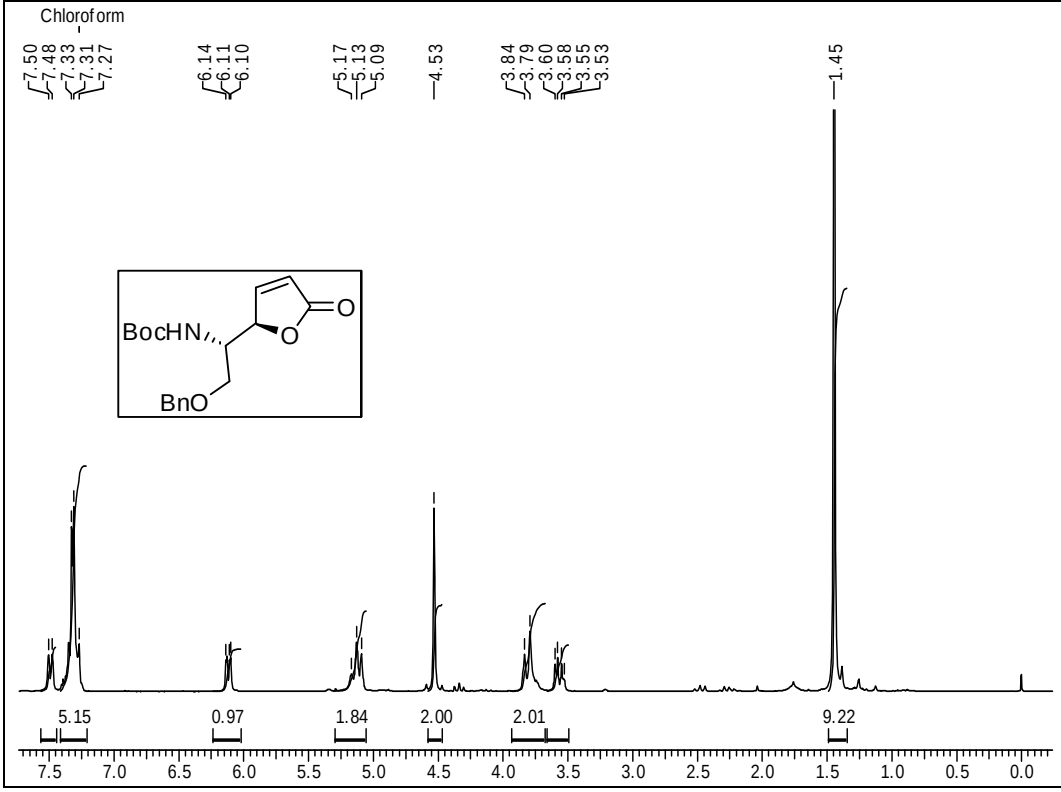
^{13}C NMR Spectrum of compound 12 ($CDCl_3$+CCl_4, 50 MHz)



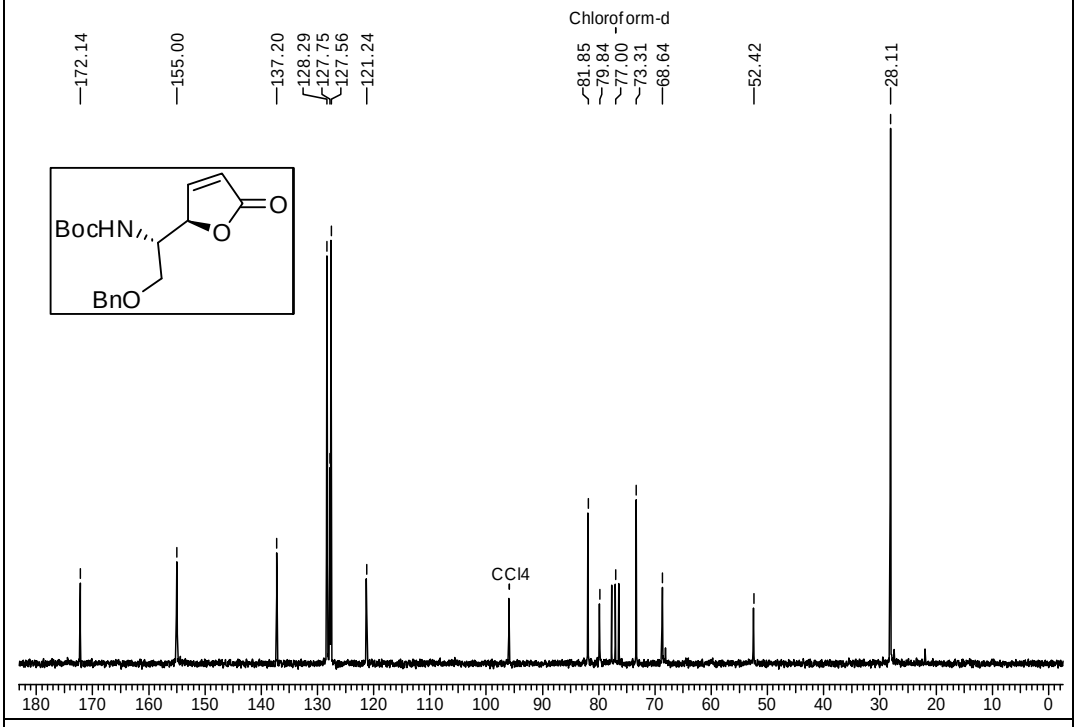
DEPT Spectrum of compound 12 ($CDCl_3$+CCl_4, 50 MHz)



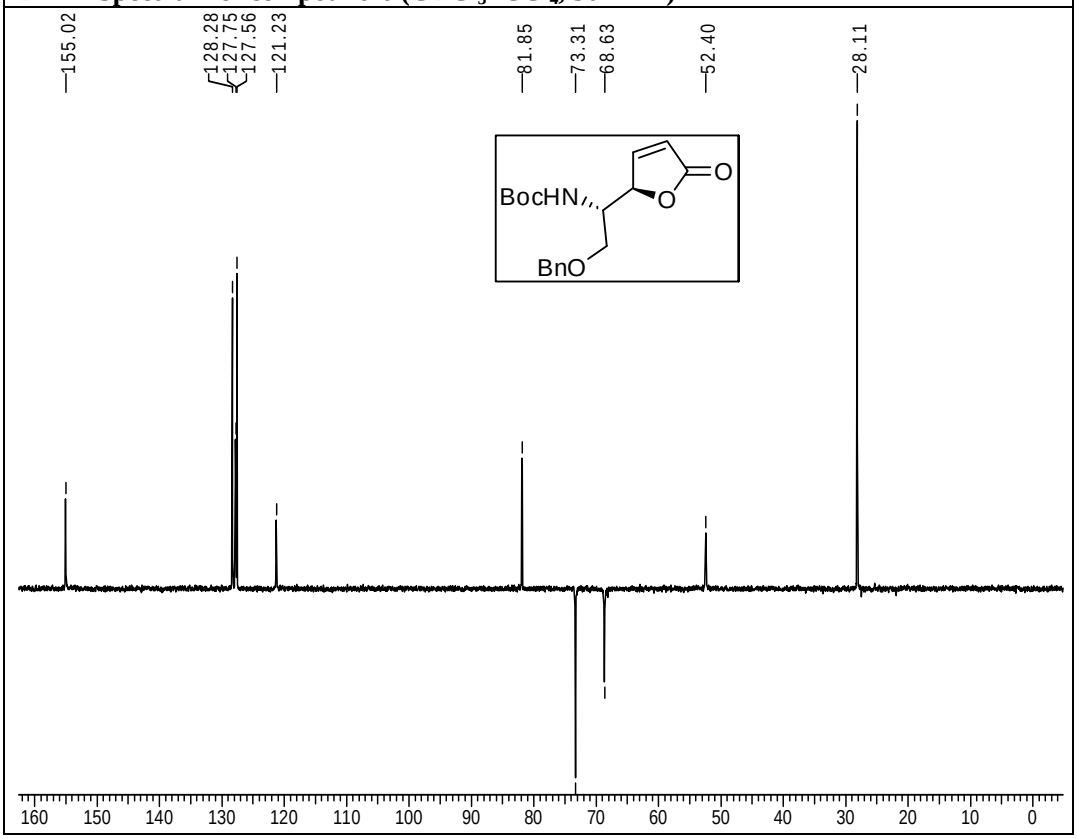
^{1}H NMR Spectrum of compound 6 ($CDCl_3$+CCl_4, 200 MHz)



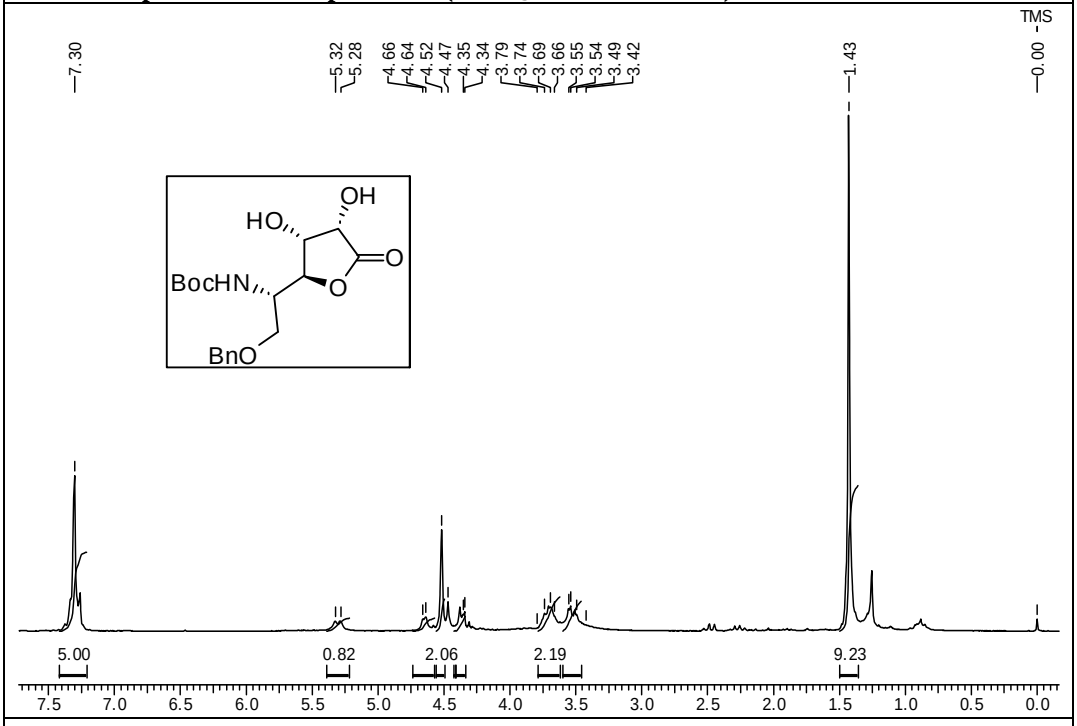
^{13}C NMR Spectrum of compound 6 ($CDCl_3$+CCl_4, 50 MHz)



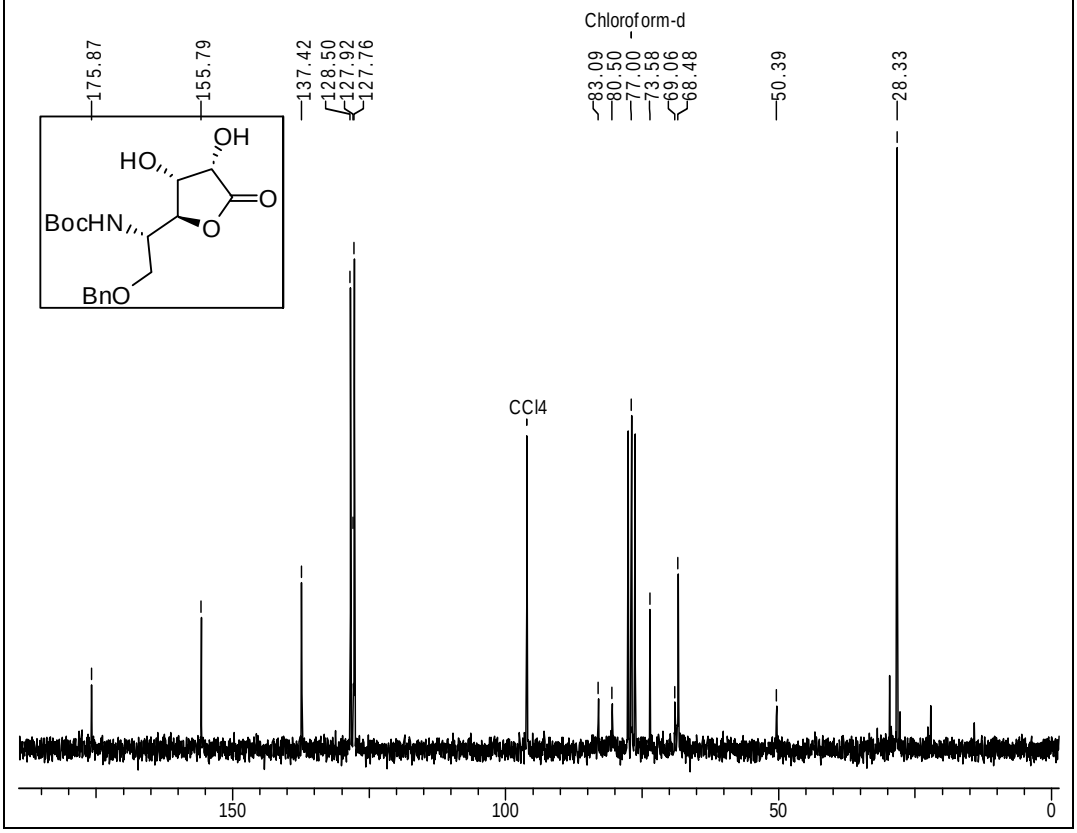
DEPT Spectrum of compound 6 ($CDCl_3$+CCl_4, 50 MHz)



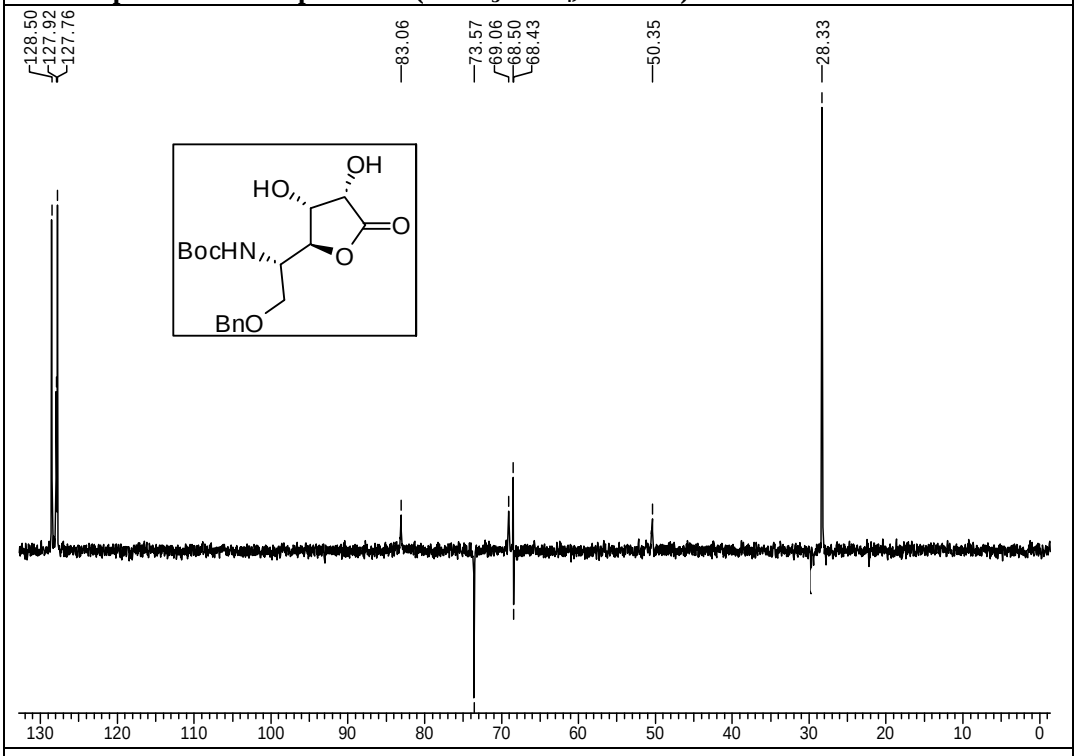
^{1}H NMR Spectrum of compound 14 ($CDCl_3$+CCl_4, 200 MHz)



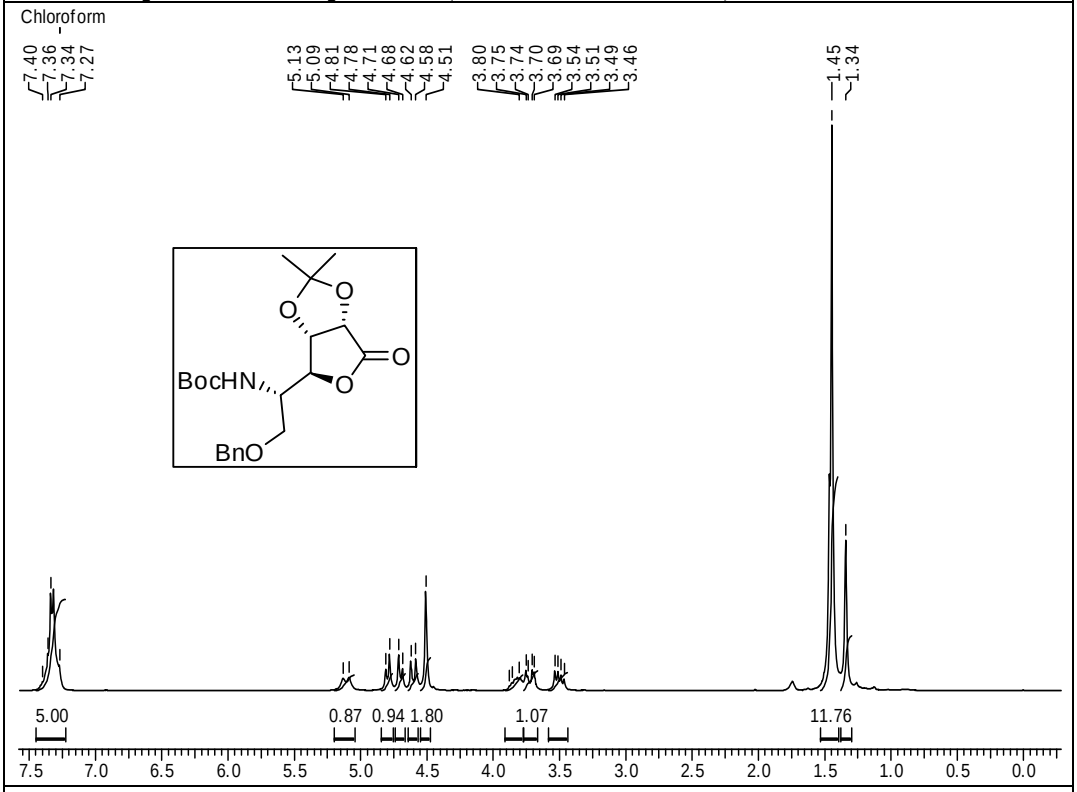
^{13}C NMR Spectrum of compound 14 ($CDCl_3$+CCl_4, 50 MHz)



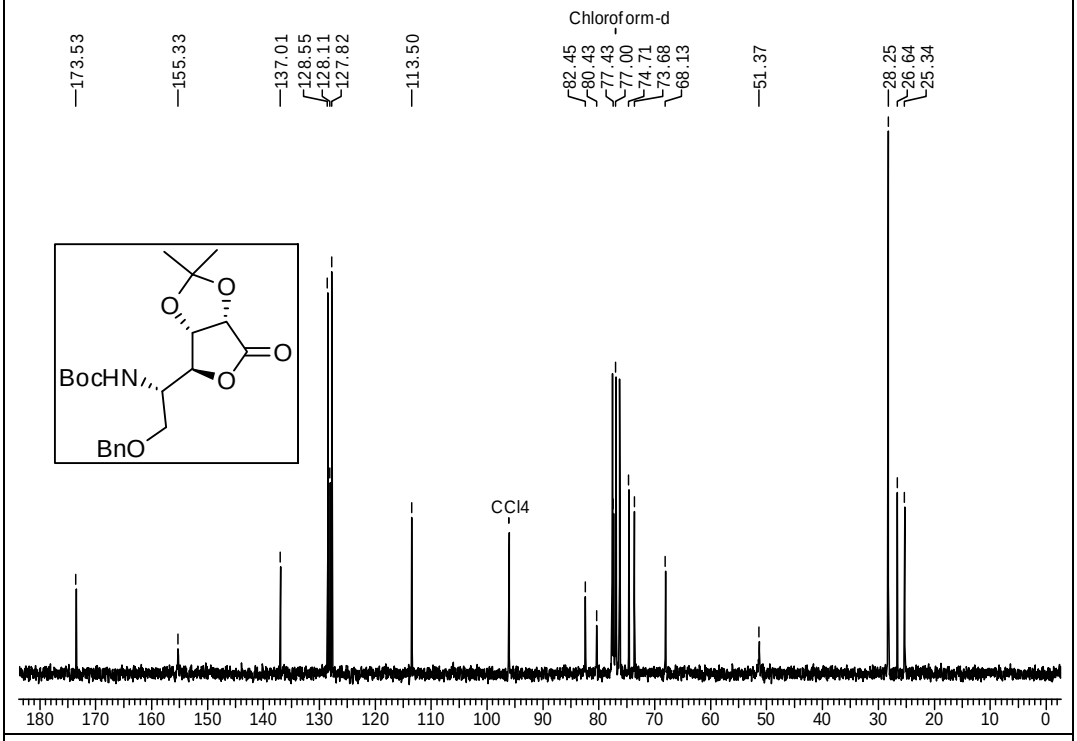
DEPT Spectrum of compound 14 ($CDCl_3$+CCl_4, 50 MHz)



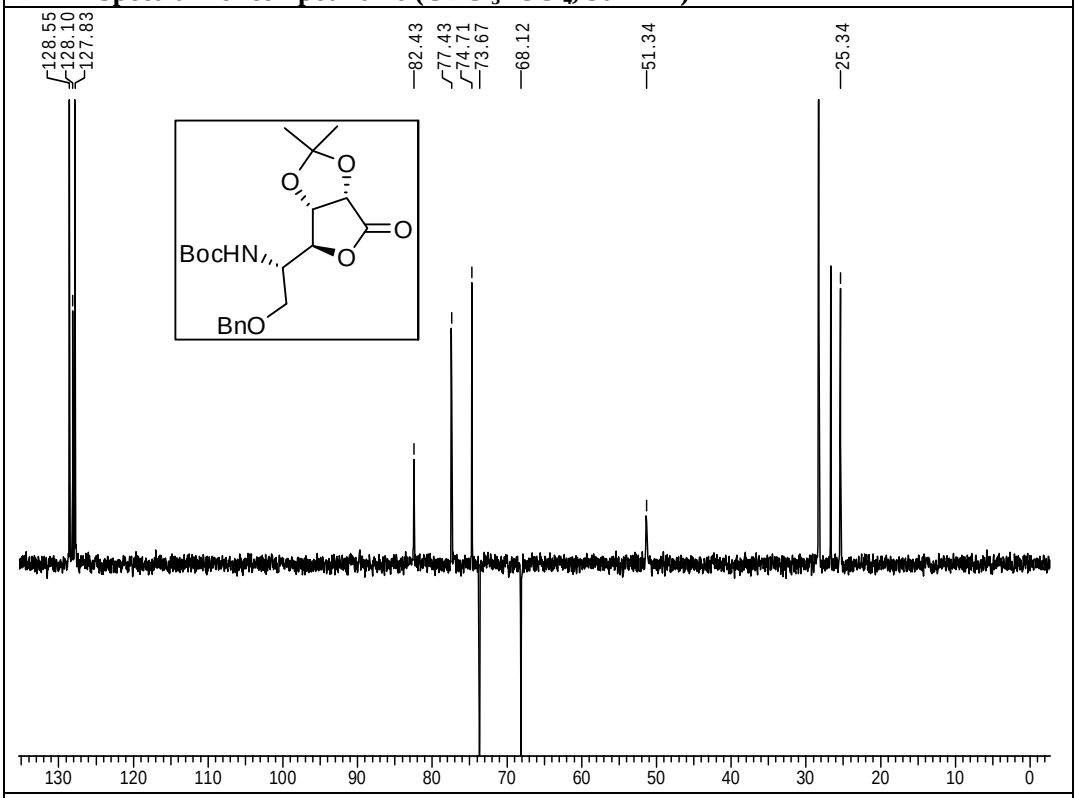
^{1}H NMR Spectrum of compound 16 ($CDCl_3$+CCl_4, 200 MHz)



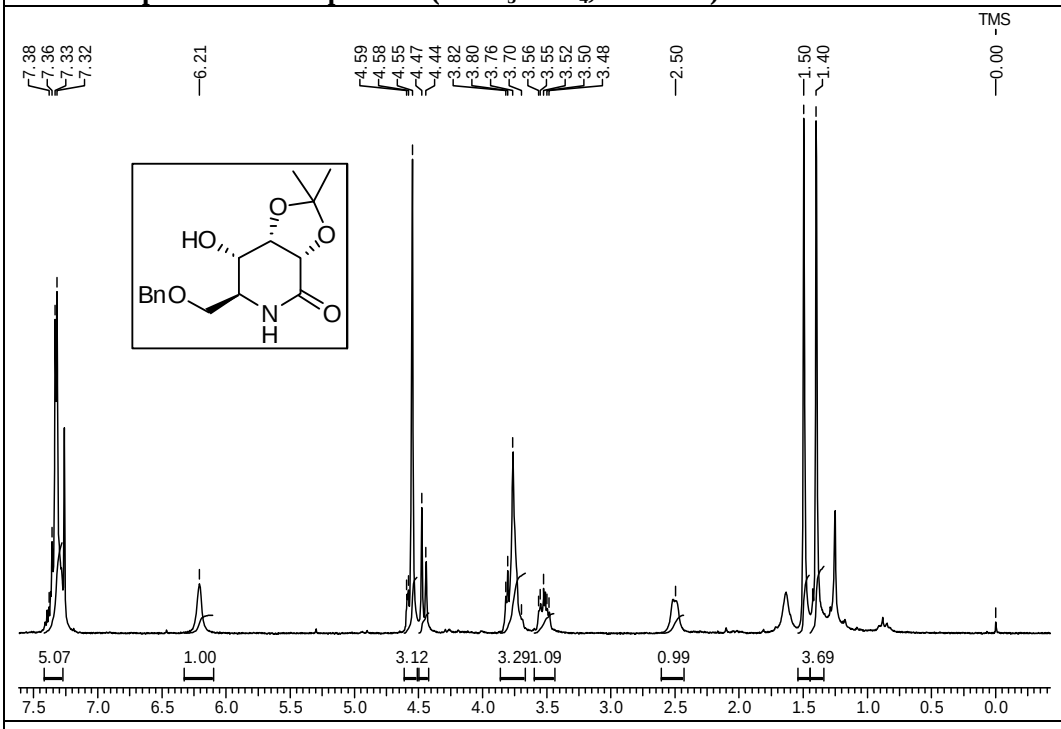
^{13}C NMR Spectrum of compound 16 ($CDCl_3$+CCl_4, 50 MHz)



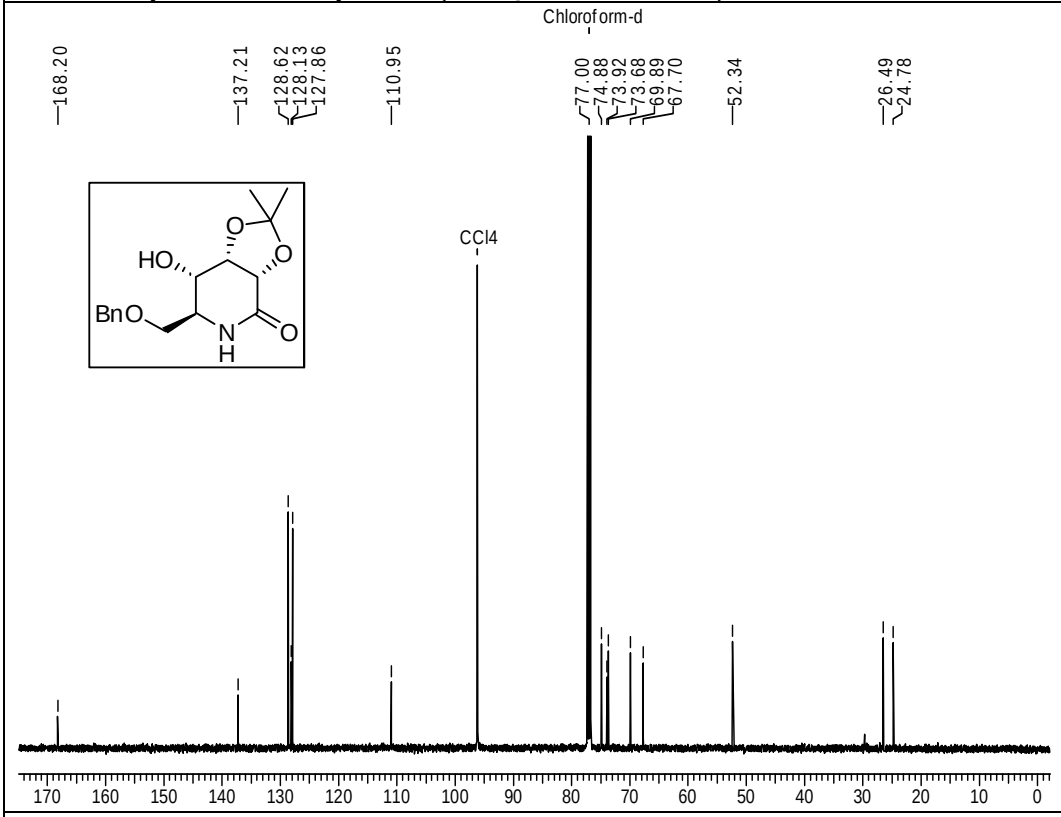
DEPT Spectrum of compound 16 ($CDCl_3$+CCl_4, 50 MHz)



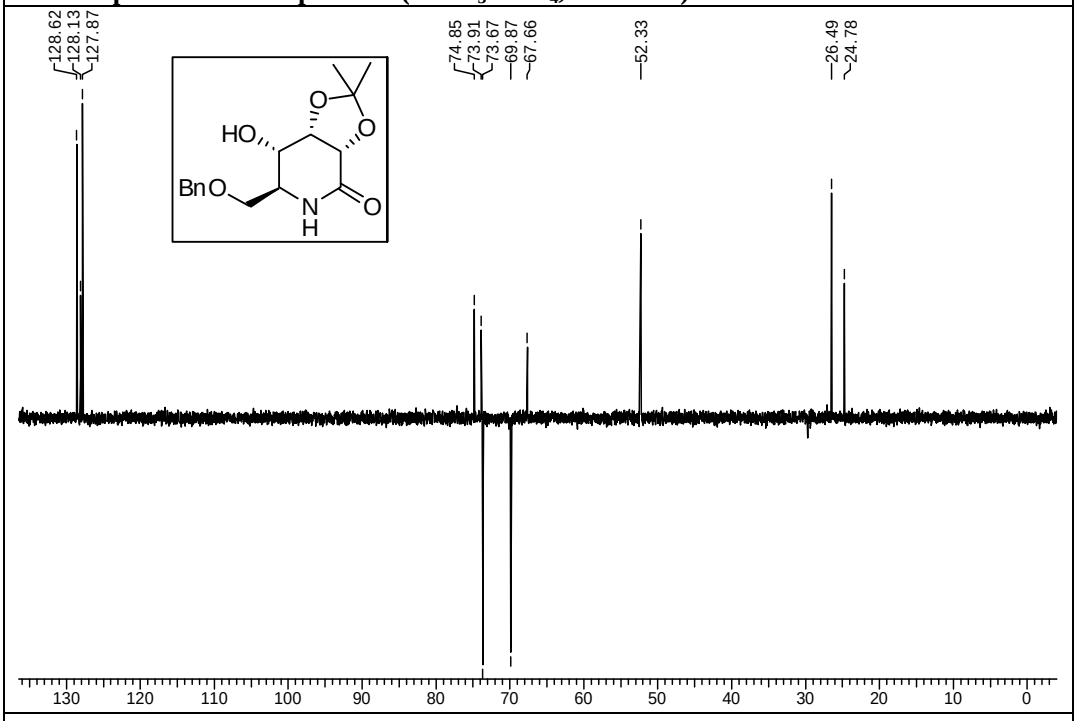
^{1}H NMR Spectrum of compound 5 ($CDCl_3$+CCl_4, 200 MHz)



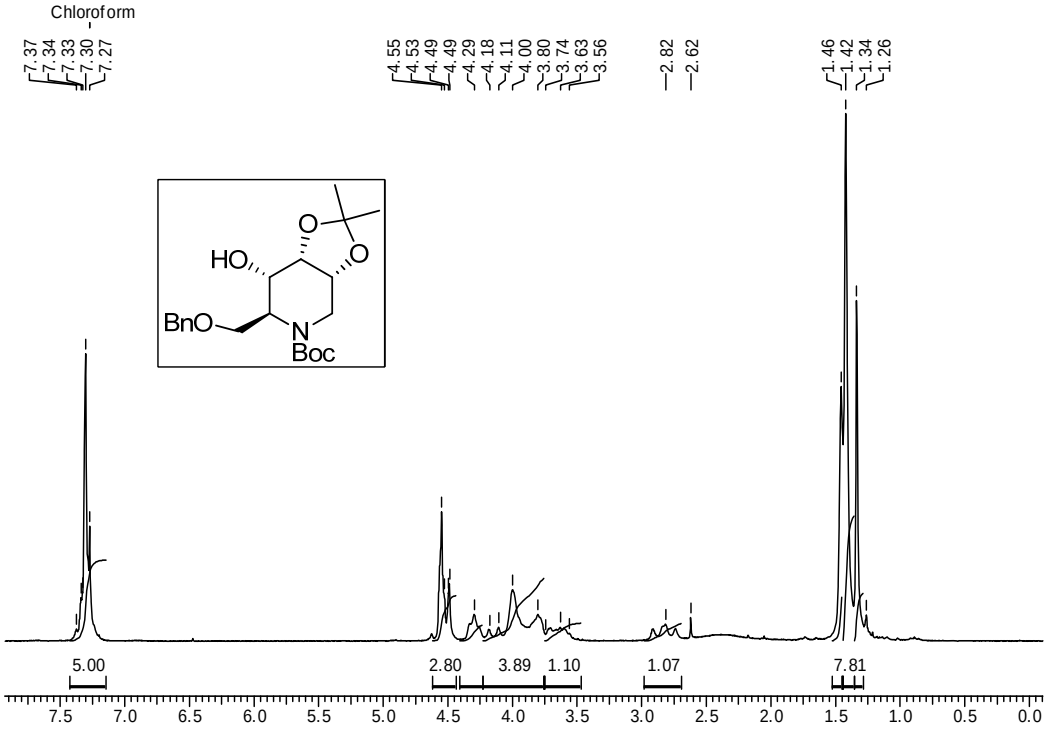
^{13}C NMR Spectrum of compound 5 ($CDCl_3$+CCl_4, 125 MHz)



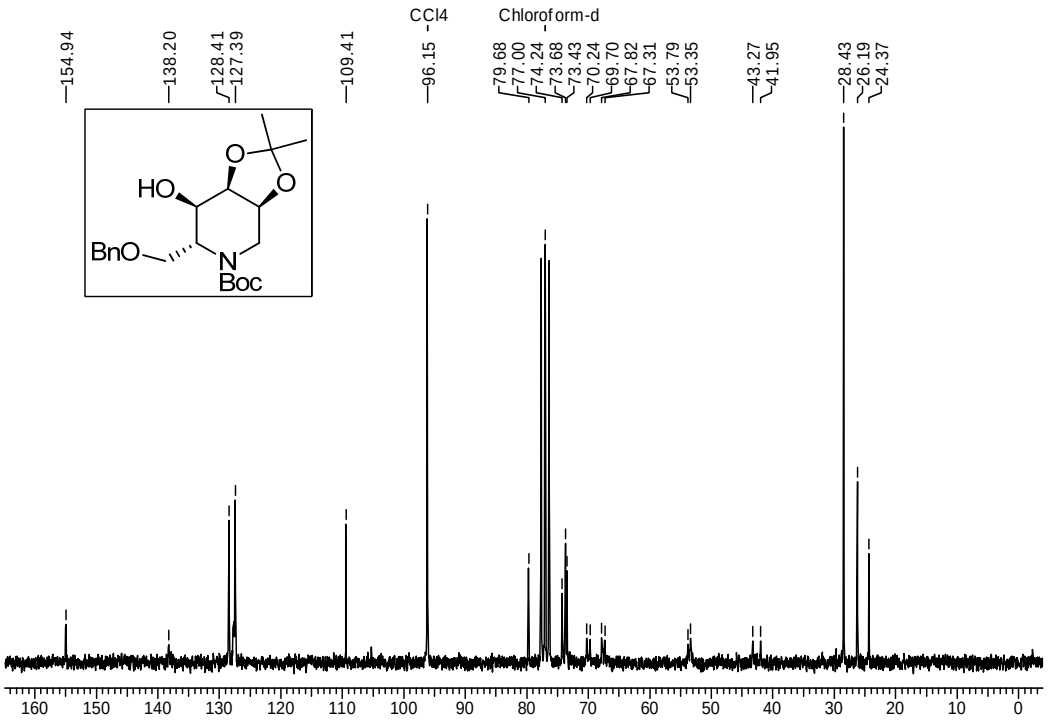
DEPT Spectrum of compound 5 ($CDCl_3$+CCl_4, 125 MHz)



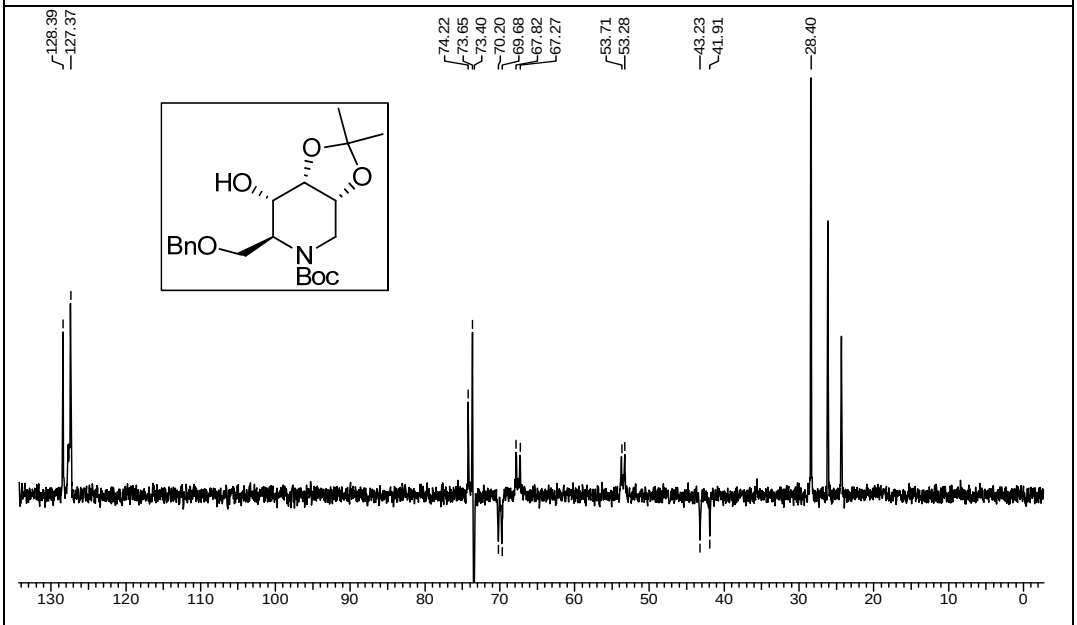
^{1}H NMR Spectrum of compound 17 ($CDCl_3$+CCl_4, 200 MHz)



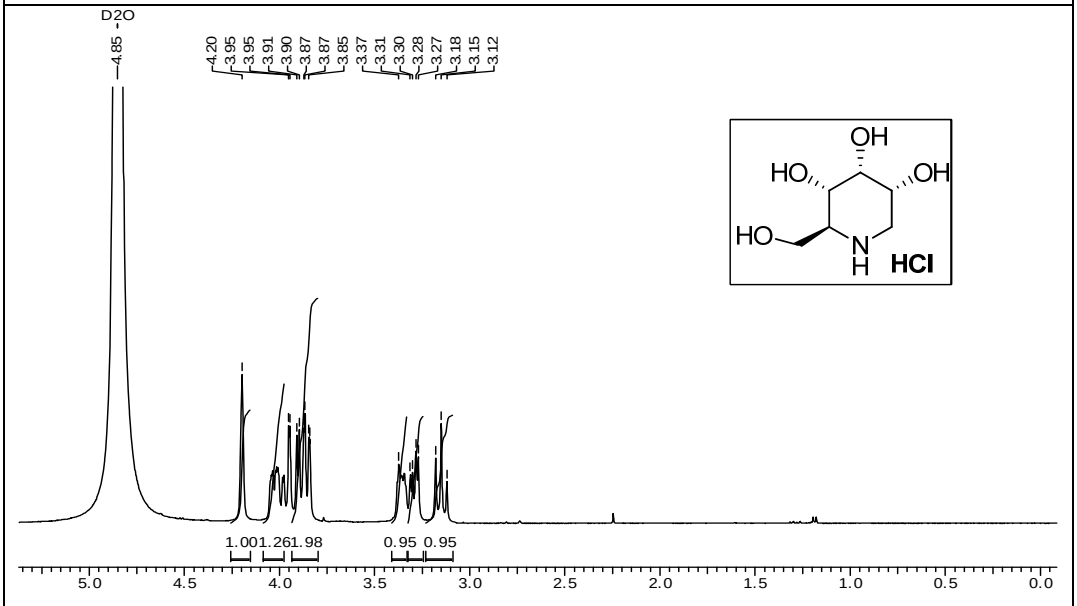
^{13}C NMR Spectrum of compound 17 ($CDCl_3$+CCl_4, 50 MHz)



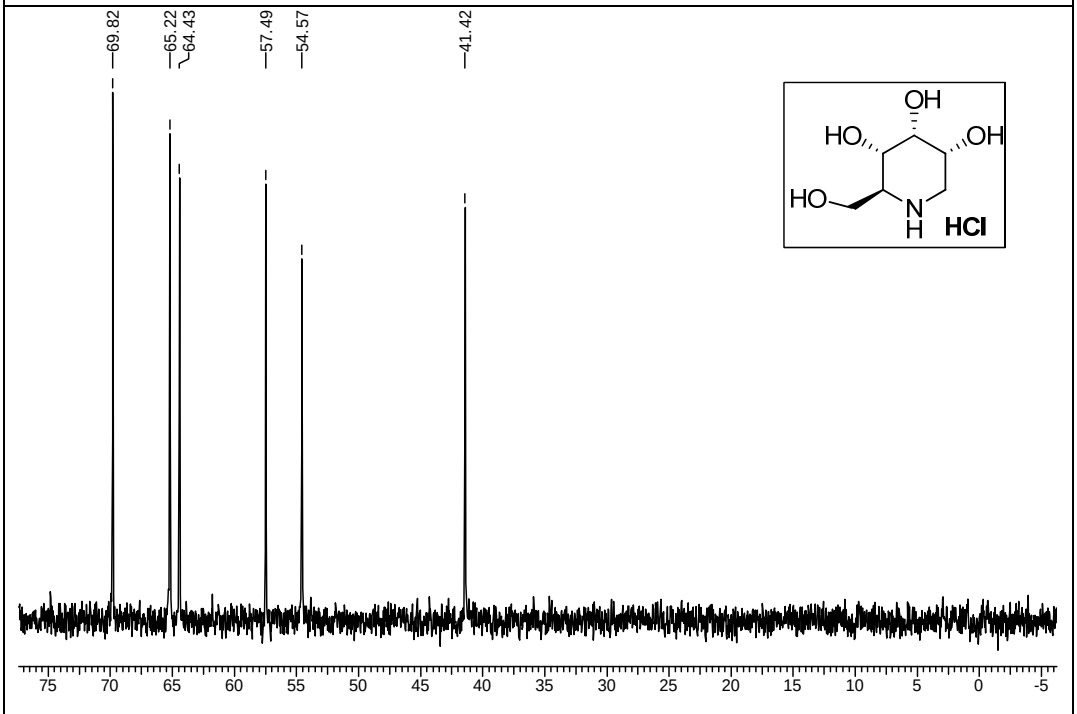
DEPT Spectrum of compound 17 ($CDCl_3$+CCl_4, 50 MHz)



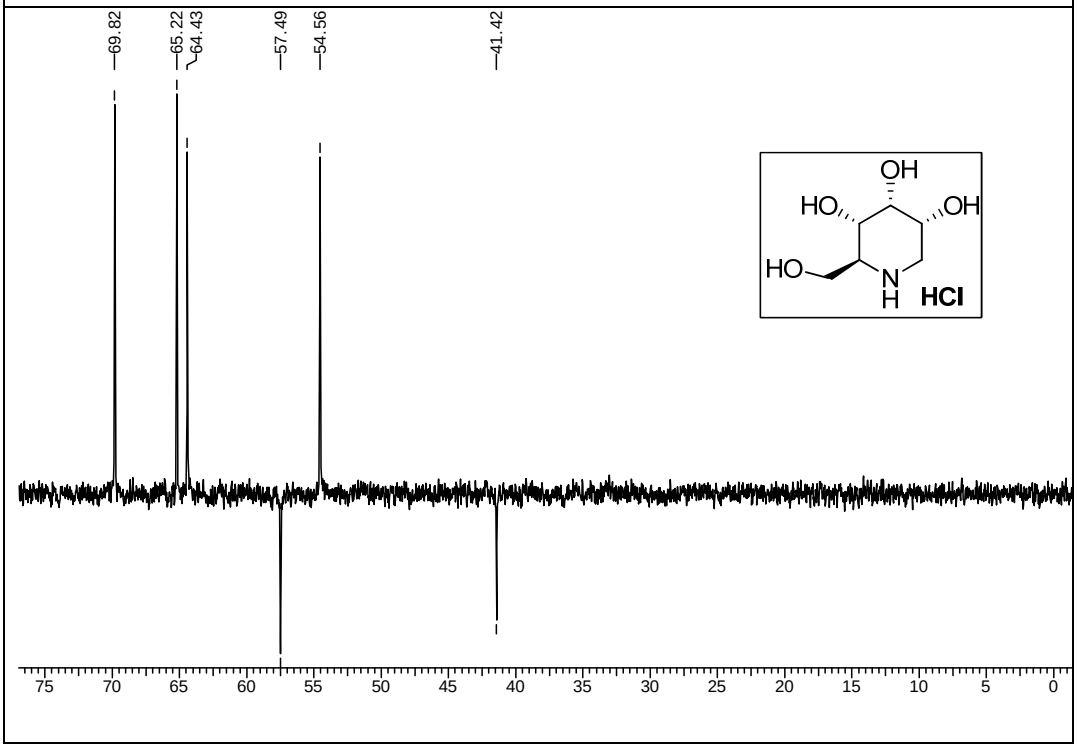
^{1}H NMR Spectrum of compound 3 (D_2O, 400 MHz)



^{13}C NMR Spectrum of compound 3 (D_2O, 125 MHz)



DEPT spectrum of compound 3 (D_2O, 125 MHz)



3.2.5 References:

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Chapter 3

Section 3 Synthetic studies towards D-*allo*-1-deoxynojirimycin (D-*allo*-1-DNJ) and L-*talo*-1-deoxynojirimycin (L-*talo*-1-DNJ)

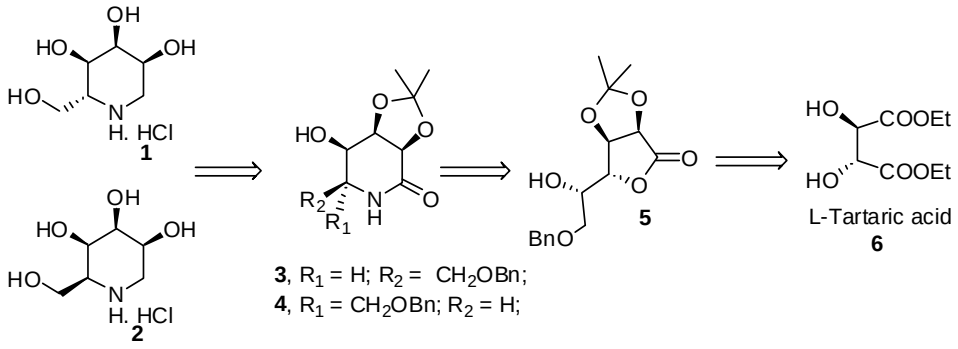
3.3.1 Present work

3.3.1.1 Objective

Although several syntheses of both D-1-deoxyallonojirimycin **1** (D-*allo*-1-DNJ) and L-1-deoxytalonojirimycin **2** (L-*talo*-1-DNJ) have been documented in literature through various synthetic routes, most of them involve a large number of steps. Herein, it was planned to synthesize of both L-*talo*-1-DNJ **2** and D-*allo*-1-DNJ **1** from common synthetic intermediate *i.e.* hydroxy lactone **5** by employing double inversion and reductive lacatmisation as key steps.

3.3.1.2 Retrosynthetic analysis

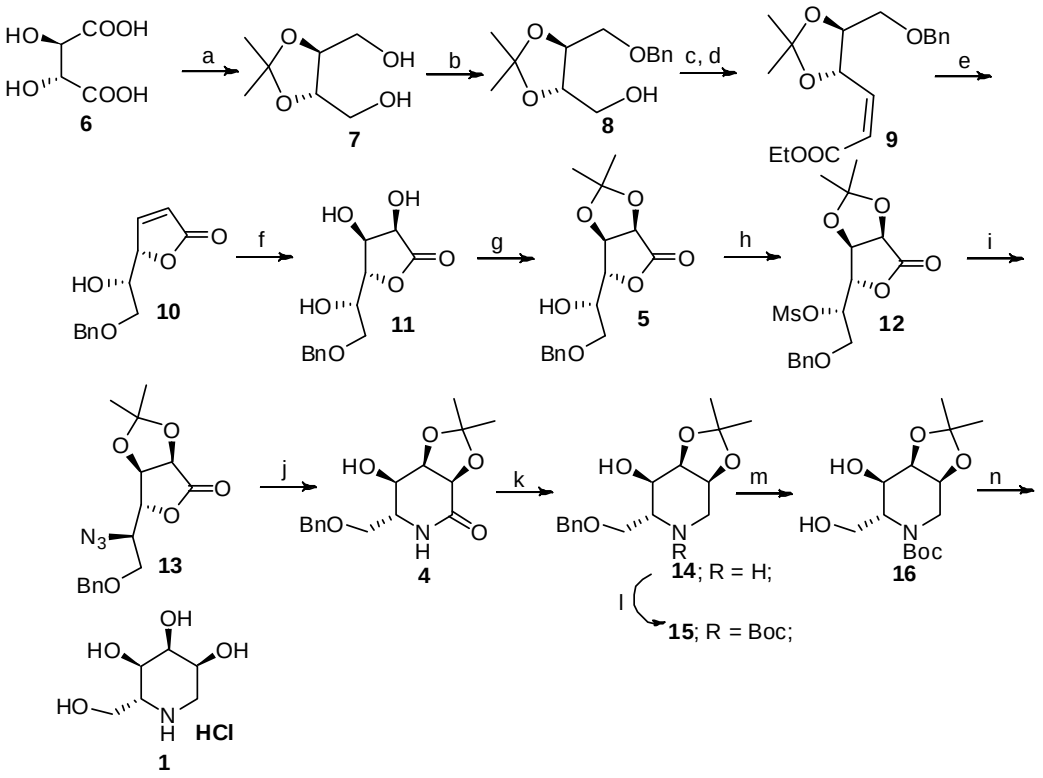
The retrosynthetic analysis for the L-*talo*-1-DNJ and D-*allo*-1-DNJ is depicted in Scheme 1. Salt of D-1-deoxyallonojirimycin **1** and L-1-deoxytalonojirimycin **2** can easily derived from lactams **3** and **4** respectively. Lactams **3** and **4** can be generated from hydroxy lactone **5** *via* reductive cyclisation. The versatile intermediate hydroxy lactone **5** can be easily derived from L-tartaric acid **6**.



Scheme 1 Retrosynthetic analysis of D-*allo*-1-DNJ and L-*talo*-1-DNJ

3.3.1.3 Results and discussion

The synthesis of **1** and **2** began from commercially available and cheap starting material *viz* L-tartaric acid **6**. L-Tartaric acid **6** was converted to symmetric diol **7** by known literature protocol.[1] The symmetric diol **7** was selectively protected by using NaH, BnBr and TBAB (phase transfer catalyst) to give mono benzylated ether **8** in 75% yield (Scheme 2). Its ^{1}H NMR spectrum showed a multiplet at δ 7.25-7.38 integrating for five protons and singlet at δ 4.58 integrating for two protons which were assigned for benzene protons and benzylic protons respectively.



Scheme 14 *Reagents and conditions: a) Ref. 1; b) BnBr, TBAB, NaH, THF 0 °C-rt, 3h, 75%; c) Oxalyl chloride, DMSO, DCM, -78°C, TEA, 30 min; d) $Ph_3PCHCOOEt$, MeOH, -50 °C-rt, overnight, 70%; e) Conc HCl (cat.), MeOH, 0 °C- rt, overnight, 70%; f) $RuCl_3$, $NaIO_4$, EtOAc:H_2O:MeCN, 0 °C, 3 min, 53%; g) DMP, CSA, DCM, rt, overnight, 90%; h) MsCl, TEA, DMAP (cat.), DCM, 0 °C, 1 h, 91%; i) NaN_3, DMF, 90 °C, 18 h, 88%; j) $Pd(OH)_2$, H_2, MeOH, rt, 1 h, 90%; k) BH_3.DMS, THF 0 °C- rt, overnight; l) $(Boc)_2O$, TEA, DMAP (cat.), THF, rt, overnight, 65% (over two steps); m) $Pd(OH)_2$, H_2, MeOH, rt, 6 h; n) Conc. HCl, MeOH, rt, 3 h, 90%.*

^{13}C NMR spectrum displayed the signals at δ 127.7, 127.8, 128.4 and 137.5 corresponding to aromatic ring carbons. Further elemental analysis confirmed the formation of **8**.

The primary alcohol of **8** was treated with DMSO, oxalyl chloride in DCM as solvent at -78 °C followed by addition of TEA to afford aldehyde which without purification was subjected to two carbon Wittig homologation in MeOH at -50 °C to room temperature to afford kinetically favored unsaturated ester **9** in 70% yield (*E/Z* = 1:9).

The IR spectrum of **9** showed the strong absorption band at 1719 cm^{-1} indicating presence of unsaturated ester. Its ^{1}H NMR and ^{13}C NMR spectrum revealed formation of *cis*-unsaturated ester as major product. A doublet of doublet at δ 6.12-6.23 as (*J* = 8, 12 Hz, 1H) integrating for δ 0.90 was attributed to *β*-hydrogen in *cis* alkene while the doublet of double at δ 6.96 corresponding to *β*-hydrogen in *trans* alkene integrating for 0.10 protons (*J* = 5, 15 Hz) clearly indicated *cis:trans* ratio to be 90:10.

Acetonide deprotection and cyclisation of compound **9** was achieved using conc. HCl (cat.) in MeOH to provide butenolide **10** in 70% yield. Its IR spectrum showed the strong absorptions at 3448, 1749 and 1637 cm^{-1} indicating the presence of hydroxy, butenolide and double bond functionalities respectively. Its ^{1}H NMR spectrum showed the peak at δ 7.48 corresponding to the *β*-hydrogen which appeared as dd while *α*-proton appeared at δ 6.15 as a dd in butenolide **10**. Its ^{13}C NMR spectrum showed the peaks at δ 172.9 and 153.8 corresponding to the butenolide carbonyl and *β*-carbon respectively. Further, mass spectrum showed the peak at *m/z* 256.95 $(M+Na)^{+}$ which confirmed the assigned structure of **10**.

For installation of hydroxy functionality, butenolide was treated with $RuCl_3$, $NaIO_4$ as oxidizing agent in EtOAc: H_2O: MeCN at 0 ^{o}C for 3 min to furnish diol[2] **11** in 53% yield. Its IR spectrum showed strong absorptions at 3393 and 1765 cm^{-1} indicating presence of free hydroxy and lactone functionalities respectively. The disappearance of peaks at δ 7.48 and 6.15 in its ^{1}H NMR spectrum and appearance of peaks at δ 4.58 (dd) corresponding to the *α*-protons of carbonyl group clearly indicated the formation of **11**. Peaks at δ 70.2 and 70.6 in its ^{13}C NMR spectrum were assigned to <u>CH</u>-OH carbons. Additionally, DEPT NMR spectrum showed the two CH_2 and four CH carbons to provide the strong support for the formation of **11**. Further, mass analysis and elemental analysis confirmed the assigned structure **11**.

To carry out other functional group transformations, diol **11** was protected as its acetonide by using DMP and CSA (cat.) in DCM solvent at room temperature to furnish acetonide[3] **5** in 81% yield. ^{1}H NMR spectrum showed the peaks at δ 1.38 and 1.46 each integrating for three protons corresponding to acetonide group. Signals at δ 25.6, 26.7 and 113.2 in its ^{13}C NMR spectrum were assigned to acetonide carbons. Further, mass spectrum showed the peak at *m/z* 331.05 $(M+Na)^{+}$ which confirmed for the formation of **5**.

For installation of amine functionality, hydroxy group of **5** was converted to its mesyl derivative **12** using MsCl, TEA and DMAP (cat.) in DCM solvent in 91% yield. Disappearance of absorption band at 3445 cm^{-1} in its IR spectrum and appearance of the absorption band at 1366 cm^{-1} indicated the presence of mesyl functionality. ^{1}H NMR spectrum showed the peak at δ 3.07 integrating for three protons corresponding to the mesyl group. Its ^{13}C NMR spectrum showed the characteristic peak at δ 39.1 which was assigned to methyl sulfonyl carbon. Additionally, DEPT spectrum showed the presence of three CH_3 carbons that appeared at δ 25.7, 26.8, and 39.1 in accordance with the structure of compound **12**.

Mesylate derivative **12** was treated with NaN_3 in DMF at 80 ^{o}C for 18 h to afford azido lactone **13** in 88% yield. Strong absorption bands at 2110 cm^{-1} and 1793 cm^{-1} in its IR spectrum indicated the presence of azide and lactone functionalities. Disappearance of singlet at δ 3.07 in its ^{1}H NMR spectrum and upfield shift of $\underline{CH}$-N_3 proton from δ 5.06 to 3.89-3.98 (m) indicated the formation of **13**. It was further supported by ^{13}C NMR spectrum, which showed disappearance of corresponding mesyl resonance at δ 39.1**.** Formation of **13** was further supported by its mass and HRMS analysis.

Having azido lactone **13** in hand the next concern was cyclisation which was achieved using $Pd(OH)_2$ as a catalyst under hydrogen atmosphere in methanol at room temperature to afford the desired six membered lactam **4**. Its IR spectrum displayed the strong absorptions at 3395 cm^{-1} and 1676 cm^{-1} indicating presence of hydroxy and lactam moieties respectively. Its ^{1}H NMR spectrum showed the broad singlet at δ 6.21 which was assigned to $\underline{NH}$-CO- proton. It was further supported by ^{13}C NMR spectrum, which showed the appearance of corresponding carbonyl lactam which resonated at δ 162.2. Additionally, DEPT spectrum showed the seven CH and five CH_2 carbons to provide the strong support for the formation of lactam **4**. Finally, appearance of a peak at *m/z* 330.1322 $(M+Na)^{+}$ in the HRMS analysis confirmed the assigned structure of compound **4**.

To carry out further functional group transformations and for ease of isolation, first lactam **4** was reduced to corresponding amine **14** followed by its protection to afford urethane **15**.

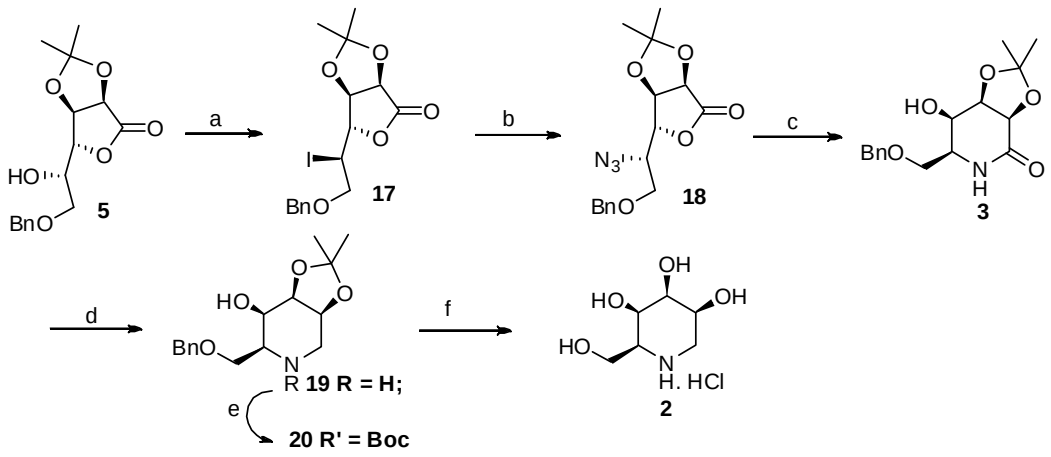
Lactam **4** was reduced by using BH_3.DMS in anhydrous THF at 0 ^{o}C to room temperature to give corresponding amine **14**, which without purification was protected using TEA, $(Boc)_2O$ and DMAP (cat.) in THF to afford urethane **15** in 58%

yield (over two steps). Its IR spectrum showed the strong absorption bands at 3444 and 1698 cm^{-1} indicating presence of free hydroxy and urethane functionalities. ^{1}H NMR spectrum showed the peaks at δ 1.42 integrating for nine protons corresponding to the Boc group. Signals at δ 28.4, 79.7 and 154.9 in its ^{13}C NMR spectrum were assigned to Boc group. Its DEPT spectrum displayed the three CH_2 and seven CH carbons to provide the strong support for the formation of **15**. Finally, appearance of a peak at *m/z* 416.2060 $(M+Na)^+$ in the HRMS analysis confirmed the structure of compound **15**.

Urethane **15** was subjected under hydrogen atmosphere using $Pd(OH)_2$ as catalyst in methanol at room temperature to deliver diol **16**. Its IR spectrum showed the strong absorption bands at 3437 and 1667 cm^{-1} indicating presence of free hydroxy and urethane functionalities respectively. Its ^{1}H NMR spectrum showed disappearance of protons at δ 7.30-7.37 (m) and δ 4.44-4.63 (m) indicating the formation of **16**. Absence of signals at δ 69.23, 70.3, 127.4, 127.7, 128.4, and 138.2 in its ^{13}C NMR spectrum, indicated the formation of **16**. Finally, appearance of a peak at *m/z* 326.1583 $(M+Na)^+$ in the HRMS analysis confirmed the formation of compound **16**.

Diol **16** on treatment with conc. HCl (cat.) in methanol at room temperature for 3 h furnished the salt of D-*allo*-1-DNJ **1**. Spectroscopic data of compound **1** was in good agreement with reported one. [4]

After successfully synthesizing D-*allo*-1-DNJ **1**, next concern was syntheses of the other isomers of 1-deoxynojirimycin. Taking advantages of structural features of hydroxy lactone **5**, it was exploited for the synthesis of L-*talo*-1-DNJ by employing double inversion strategy. Hydroxy lactone was treated with PPh_3, imidazole and iodine in toluene under reflux condition for 30 min to afford iodolactone **17** in 75% yield (Scheme 3). Strong absorption observed at 1790 cm^{-1} in its IR spectrum indicated presence of lactone functionality while disappearance of absorption at 3445 cm^{-1} indicated hydroxy consumption. ^{1}H NMR spectrum showed the multiplet at δ 4.35-4.39 integrating for one proton which was assigned to the CH-I. Its ^{13}C NMR spectrum showed the appearance of signal at δ 28.6 which was assigned to CH-I carbon. Additionally, DEPT spectrum showed the two CH_2 and seven CH carbons to confirm the formation of **17**. Finally, appearance of a peak at *m/z* 418 $(M)^+$ in the GCMS analysis confirmed the assigned structure of **17**.



Scheme 3 *Reagents and conditions: a) PPh_3, imidazole, iodine, toluene, reflux, 75%; b) NaN_3, DMF, 80 ^oC, 60%: c) $Pd(OH)_2$, H_2, MeOH, rt, 88%; d) BH_3.DMS, THF, 0 ^oC- rt, overnight; e) $(Boc)_2O$, TEA, DMAP (cat.), THF, rt, overnight, 50% (over two steps); f) i) $Pd(OH)_2$, H_2, MeOH, rt, 6 h; ii) Conc. HCl, MeOH, rt, 3 h, 70% (over two steps).*

Iodolactone **17** was treated with NaN_3 in DMF at 80 ^oC to deliver the azido lactone **18** in 60% yield. Its IR spectrum showed the strong absorption bands at 2114 and 1790 cm^{-1} indicating presence of azide and lactone functionalities respectively. The ^1H NMR spectrum displayed the peaks at δ 3.89-3.97 (m) integrating for one proton corresponding to CH-N_3. ^{13}C NMR spectrum showed the disappearance of signal at δ 28.6 and appearance of new signal at δ 61.5 which was assigned to CH-N_3 carbon. Further, appearance of a peak at *m/z* 356.1224 $(M+Na)^+$ in the HRMS analysis confirmed the structure of compound **18**.

Having azidolactone **18** in hand the next task was cyclisation which was achieved by using $Pd(OH)_2$ under hydrogen atmosphere in methanol at room temperature to deliver the desired six membered lactam **3**. Formation of lactam **3** was confirmed by spectral analysis. Its IR spectrum displayed the strong absorptions at 3444 and 1671 cm^{-1} indicating presence of hydroxy and lactam functionalities respectively. Disappearance of the absorption band at 2114 cm^{-1} in its IR spectrum indicated reduction of azide functionality. Peak at δ 6.08 as broad singlet in its ^1H NMR spectrum was assigned to amide (NH-CO-) proton. Its ^{13}C NMR spectrum displayed the signal at δ 168.9 corresponding to lactam carbonyl carbon. DEPT NMR spectrum revealed seven CH and two CH_2 carbons to provide the strong support for the

formation of **3**. Its HRMS spectrum showed the peak at *m/z* 330.1322 $(M+Na)^+$ which confirmed the formation of **3**.

Lactam **3** was reduced using BH_3.DMS in anhydrous THF followed by amine protection using $(Boc)_2O$, TEA and DMAP (cat.) in THF to deliver the urethane **20**. Its ^1H NMR spectrum showed the peaks at δ 1.41 (s, 4H), and 1.45 (s, 5H) (due to rotamers) corresponding to the Boc group and the disappearance of the peak at δ 6.08 indicating the formation of urethane **20**. Signals at δ 28.4, 80.3 and 154.7 in its ^{13}C NMR spectrum were attributed to Boc group. DEPT spectrum showed the seven CH and three CH_2 carbons to provide strong support for the formation of **20**. Further, appearance of a peak at *m/z* 416.2065 $(M+Na)^+$ in the HRMS analysis confirmed the structure of compound **20**.

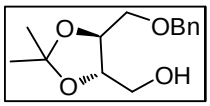
Benzyl group in **20** was removed under hydrogen atmosphere in presence of $Pd(OH)_2$ as a catalyst to deliver the crude diol which on HCl treatment furnished salt of L-*talo*-1-DNJ **2**. Its ^1H NMR spectrum showed the peaks at δ 3.51 (dt, J = 13.8, 2.2 Hz, 1H) and disappearance of signals at δ 1.41 and 1.45 to support for the formation of **2**. Signals at δ 50.4, 61.2, 62.3, 68.7, 69.2 and 69.7 in its ^{13}C NMR spectrum were assigned for six carbons. Additionally, DEPT spectrum showed the four CH and two CH_2 carbons which confirmed the formation of **2**. Spectroscopic data and optical rotation value of compound **2** were in good agreement with the values reported in literature. [5]

3.3.2 Conclusion

Total synthesis of D-*allo*-1-DNJ **1** and L-*talo*-1-DNJ **2** has been accomplished by employing flash dihydroxylation and reductive cyclisation as the key steps starting from L-tartaric acid as the cheap starting material.

3.3.3 Experimental Section

(4*S*,5*S*)-5-((Benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (8)



To a well stirred solution of symmetric diol **7** (3 g, 18.49 mmol) in anhydrous THF (50 mL), was added NaH (0.88 g, 22.19 mmol) portion wise at 0 ^{o}C over 30 min under nitrogen atmosphere. The reaction mixture was allowed to stir for 30 min at 0 ^{o}C and benzyl bromide (2.4 mL, 20.33 mmol) was added dropwise over 10 min followed by addition of TBAB (cat.). The reaction mixture was allowed to stir at 0 ^{o}C and allowed to warm to room temperature and stirred overnight. After completion of reaction, the saturated aq. solution of ammonium chloride was added to reaction mixture and extracted with ethyl acetate (2 X 60 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to provide crude monobenzylated compound. The residue was purified by flash silica gel column chromatography using light petroleum ether: EtOAc (7:3) as an eluent to afford **8** (3.4 g, 75%) as a colorless syrup.

Chemical Formula: $C_{14}H_{20}O_4$;

Yield: 75%;

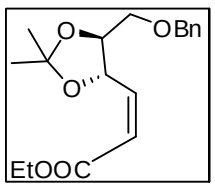
$[\alpha]_D^{25}$: +7.7 (c 2.58, $CHCl_3$);

Elemental analsis calculated for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. found: C, 66.25; H, 7.68;

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 1.41 (s, 6H), 2.17-2.28 (m, 1H), 3.50-3.58 (m, 1H), 3.62-3.82 (m, 3H), 3.88-3.97 (m, 1H), 4.02-4.09 (m, 1H), 4.58 (s, 2H), 7.25-7.38 (m, 5H);

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) : δ 26.9, 62.3, 70.3, 73.6, 76.5, 79.6, 109.2, 127.7, 127.8, 128.4, 137.5.

(*Z*)-Ethyl 3-((4*S*,5*S*)-5-((benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (9)



To a solution of $(COCl)_2$ (2.1 mL, 23.78 mmol) in CH_2Cl_2 (30 mL) was added DMSO (3.37 mL, 47.56 mmol) at -78 ^{o}C, and the mixture was stirred for 10 min. A solution of alcohol **8** (3 g, 11.89 mmol) in CH_2Cl_2 (20 mL) was added to the resulting

mixture and stirring was continued for another 15 min at -78 ^{o}C Then, TEA (6.6 mL, 47.56 mmol) was added at -78 ^{o}C and the reaction mixture was warmed to 0 ^{o}C and stirred for another 20 min. Water (20 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (2 X 60 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated to provide the crude aldehyde which was directly used in the next step. To a solution of aldehyde in methanol, $PPh_3CHCOOEt$ (6.2 g, 17.83 mmol) was added at -50 ^{o}C. Then reaction mixture was allowed to stir at -50 ^{o}C to room temperature for overnight. After completion of reaction, the reaction mass was adsorbed on silica gel and eluted with ethyl acetate: pet ether (1:9) to afford unsaturated ester **9** (2.66 g, 70%) as a mixture of E and Z isomers.

Chemical Formula: $C_{18}H_{24}O_5$;

Yield: 70%;

***E/Z* :** 1:9;

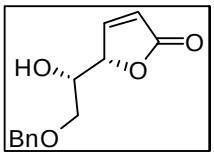
IR ($CHCl_3$, cm^{-1}): 1719, 1658, 1380, 1371, 1195, 1079;

ESIMS *(m/z)*: 346.37 $(M+Na)^+$;

For major *cis* somer ^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 1.25 (t, *J* = 7.0 Hz, 3H), 1.45 (s, 6H), 3.61-3.71 (m, 2H), 3.90-3.99 (m, 1H), 4.12 (q, *J* = 7 Hz, 2H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 5.37 (t, *J* = 8.2 Hz, 1H), 5.91 (d, *J* = 12.0 Hz, 1H), 6.12-6.23 (dd, *J* = 8.0, 12.0 Hz, 1H), 7.31 (s, 5H);

For major *cis* somer ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 14.2, 27.1, 60.3, 70.5, 73.4, 73.7, 80.4, 110.2, 122.7, 127.4, 127.6, 128.2, 138.1, 145.7, 165.2.

(*S*)-5-((*S*)-2-(Benzyloxy)-1-hydroxyethyl)furan-2(5*H*)-one (10)



To a solution of unsaturated ester **9** (2 g, 6.24 mmol) in methanol (20 mL) was added conc. HCl (0.1 mL) at 0 ^{o}C. The reaction mixture was stirred at room temperature for 6 h. The solvent was removed under reduced pressure and the residue was neutralized with sodium carbonate and extracted with DCM (3 X 60 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to provide crude residue. Residue was purified by flash silica gel chromatography using pet ether: ethyl acetate (6:4) as eluent to afford compound **10** as a white solid (1.46 g, 70%).

Chemical Formula: $C_{13}H_{14}O_4$;

Yield: 70%

$[\alpha]_D^{25}$: -72.7 (c 0.55, $CHCl_3$); lit.[3a] for comp-**10** **$[\alpha]_D^{21}$**: -73.2 (c 1, $CHCl_3$);

M.P.: 78 - 80 ^oC;

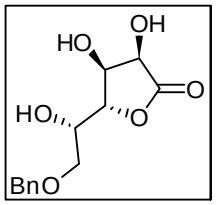
IR ($CHCl_3$, cm^{-1}): 3448, 1749, 1637, 1164, 1094;

ESIMS *(m/z)* : 256.95 $(M+Na)^+$;

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.41 (bs, 1H), 3.54-3.69 (m, 2H), 3.98-4.05 (m, 1H), 4.53 (d, *J* = 12 Hz, 1H), 4.60 (d, *J* = 12 Hz, 1H), 5.17 (dt, J = 4, 2 Hz, 1H), 6.15 (dd, *J* = 5.6, 2 Hz, 1H), 7.30-7.41 (m, 5H), 7.48 (dd, *J* = 5.6, 2 Hz, 1H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 70.0, 70.2, 73.6, 83.7, 122.2, 127.9, 128.0, 128.5, 137.3, 153.8, 172.9.

(3*R*,4*S*,5*R*)-5-((*S*)-2-(Benzyloxy)-1-hydroxyethyl)-3,4-dihydroxydihydrofuran-2(3*H*)-one (11)



To a vigorously stirred solution of butenolide **10** (0.700 g, 2.98 mmol) in CH_3CN:EtOAc (3 mL each) at 0 ºC, was added a solution of $RuCl_3.3H_2O$ (43 mg, 0.21 mmol) and $NaIO_4$ (0.95 g, 4.47 mmol) in distilled water (3 mL). The reaction mixture was stirred for 3 min after which saturated solution of $Na_2S_2O_3$ was added. Reaction mixture was extracted with ethyl acetate (3 X 50 mL) and dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give crude triol. The crude reaction mixture on purification by flash chromatography over silica gel afforded triol as thick yellow syrup **11** (0.42 g, 53%).

Chemical Formula : $C_{13}H_{16}O_6$

Yield: 53%

$[\alpha]_D^{25}$: +41 (c 1, MeOH);

IR ($CHCl_3$, cm^{-1}): 3393, 1765, 1142, 1094;

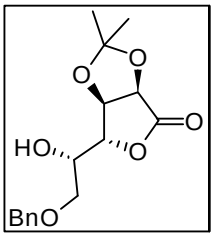
ESIMS *(m/z)*: 291 $(M+Na)^+$;

Elemental Analysis calculated for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01; O, 35.78; Found: C, 58.10; H, 6.20;

^{1}H NMR (200 MHz, CD_3OD): δ 3.47 (dd, *J* = 6.6, 2.6 Hz, 2H), 3.92 (dt, *J* = 6.6, 1.6 Hz, 1H), 4.27 (d, *J* = 5.6 Hz, 1H), 4.42 (d, *J* = 1.6 Hz, 1H), 4.50 (s, 2H), 4.58 (d, *J* = 5.6 Hz, 1H), 7.24-7.30 (m, 5H);

^{13}C NMR (125 MHz, CD_3OD): δ 70.3, 70.7, 71.7, 72.0, 74.6, 86.9, 128.9, 129.0, 129.5, 139.6, 178.9.

(3a*R*,6*R*,6a*R*)-6-((*S*)-2-(Benzyloxy)-1-hydroxyethyl)-2,2-dimethyldihydrofuro[3,4-*d*][1,3]dioxol-4(3a*H*)-one (5)



To a well stirred solution of triol **11** (0.300 g, 1.11 mmol) in DCM (10 mL) was added CSA (cat.) and 2,2-dimethoxy propane (1.1 mL, 11.1 mmol) and stirred under an atmosphere of nitrogen for 18 h at room temperature. Then reaction mixture was poured into cold saturated sodium carbonate solution and extracted with DCM (2 X 30 mL). Organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue which was purified by column chromatography over silica gel, eluting with 30% ethyl acetate in pet ether as an eluent to afford **5** (0.31 g, 90%) as white crystals.

Chemical Formula : $C_{16}H_{20}O_6$;

Yield: 90%;

M.P.: 82 ^oC; lit.[3b] for comp-**5**: 80-83 ^oC;

$[\alpha]_D^{25}$: -12.7 (c 1, $CHCl_3$); lit.[3b] For comp-**5** **$[\alpha]_D^{27}$**-10 (c 1, $CHCl_3$);

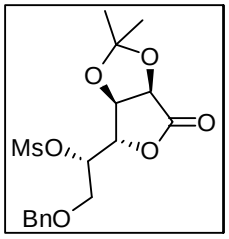
IR ($CHCl_3$, cm^{-1}): 3445, 1783, 1646, 1216, 1153, 1083, 729, 695;

ESIMS *(m/z)*: 331.05 $(M+Na)^+$;

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.46 (s, 3H), 2.51 (bs, 1H), 3.58 (t, *J* = 9.5 Hz, 1H), 3.61 (dd, *J* = 9.5, 4.5 Hz, 1H), 3.99-4.06 (m, 1H), 4.53 (s, 1H), 4.55-4.59 (m, 2H), 4.78 (d, *J* = 5.5 Hz, 1H), 4.83 (d, *J* = 5.5 Hz, 1H), 7.31-7.38 (m, 5H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 25.6, 26.7, 70.1, 70.3, 73.7, 75.1, 78.8, 81.2, 113.2, 127.9, 128.1, 128.6, 137.2, 174.5.

(*S*)-2-(Benzyloxy)-1-((3a*R*,4*S*,6a*R*)-2,2-dimethyl-6-oxotetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)ethyl methanesulfonate (12)



To a stirred solution of hydroxy lactone **5** (0.3 g, 0.97 mmol) in dry DCM (5 mL) was added Et_3N (0.27 mL, 1.94 mmol) at 0 ^oC, followed by dropwise addition of mesyl chloride (0.103 mL, 1.26 mmol) and finally DMAP (cat.) was added. The reaction mixture was stirred at 0 ^oC for 1 h under nitrogen atmosphere. After completion of reaction, the reaction mixture was diluted with dichloromethane (40 mL) and washed with saturated solution of sodium bicarbonate (20 mL) and water (20

mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography in 40% ethyl acetate in pet ether to afford O-mesyl compound **12** as colorless syrup (0.34 g, 91%).

Chemical Formula: $C_{17}H_{22}O_8S$;

Yield: 91%;

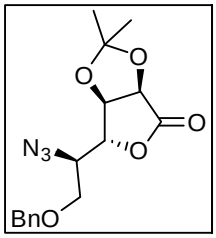
$[\alpha]_D^{25}$: -31.81 (c 4.4, $CHCl_3$);

IR ($CHCl_3$, cm^{-1}): 1797, 1366, 1176, 1092, 737, 699;

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) : δ 1.38 (s, 3H), 1.45 (s, 3H), 3.07 (s, 3H), 3.71 (dd, *J* = 10 Hz, 4 Hz, 1H), 3.79-3.88 (m, 1H), 4.56 (s, 2H), 4.71 (d, *J* = 1.2 Hz, 1H), 4.87 (dd, *J* = 9.5, 5.7 Hz, 2H), 5.06 (ddd, *J* = 8, 4, 2 Hz, 1H), 7.28-7.41 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 25.7, 26.8, 39.1, 68.7, 73.8, 74.5, 78.1, 79.4, 80.4, 113.6, 128.0, 128.4, 128.7, 136.6, 172.9.

(3a*R*,6*R*,6a*R*)-6-((*R*)-1-Azido-2-(benzyloxy)ethyl)-2,2-dimethyldihydrofuro[3,4-*d*][1,3]dioxol-4(3a*H*)-one (13)



To a solution of O-mesyl derivative **12** (200 mg, 0.51 mmol) in anhydrous DMF (5 mL) was added sodium azide (67 mg, 1.02 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 80 ^oC for 16 h. After completion of the reaction (monitored by TLC), it was cooled to room temperature, diluted with water and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography using ethyl acetate/light petroleum ether (1:9) as an eluent to afford **13** as colorless oil (150 mg, 88%).

Chemical Formula : $C_{16}H_{19}N_3O_5$

Yield: 88%

$[\alpha]_D^{25}$: -60 (c 1, $CHCl_3$), lit.[3b]for comp-**13** **$[\alpha]_D^{25}$** -61 (c 1, $CHCl_3$);

IR ($CHCl_3$, cm^{-1}): 2110, 1793, 1215;

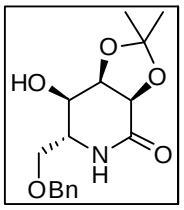
ESIMS *(m/z):* 356.08 $(M+Na)^+$;

HRMS calculated for $[C_{16}H_{19}N_3O_5+Na]^+$ 356.1217; found: 356.1224;

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ 1.36 (s, 3H), 1.46 (s, 3H), 3.68-3.74 (m, 2H), 3.89-3.98 (m, 1H), 4.56-4.63 (m, 3H), 4.65 (d, *J* = 6 Hz, 1H), 4.74 (d, *J* = 6 Hz, 1H), 7.32-7.39 (m, 5H);

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 25.5, 26.7, 62.2, 68.6, 73.8, 75.0, 76.5, 81.5, 113.6, 127.7, 128.2, 128.7, 136.8, 173.0.

(3a*R*,6*R*,7*R*,7a*R*)-6-((Benzyloxy)methyl)-7-hydroxy-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*c*]pyridin-4(3a*H*)-one (4)



A mixture of azido lactone **13** (100 mg, 0.300 mmol) and 10 % Pd/C in methanol (3 mL) was stirred under the hydrogen atmosphere at 10 *psi* at room temperature (25 ^oC) for 1 h. The reaction mixture was filtered through celite and the celite layer was washed thoroughly with methanol (3 X 20 mL) and concentrated under reduced pressure. The residue thus obtained was purified by flash silica gel chromatography using pet ether/ ethyl acetate (2:8) as an eluent to furnish white semisolid **4** (91 mg, 90%).

Chemical Formula: $C_{16}H_{21}NO_5$;

Yield: 90%;

$[\alpha]_D^{25}$: +18.3 (c 1.2, $CHCl_3$);

IR ($CHCl_3$, cm^{-1}): 3395, 1676, 1196;

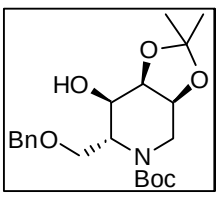
ESIMS *(m/z)* : 330.2 $(M+Na)^+$;

HRMS calculated for $[C_{16}H_{21}NO_5+Na]^+$ 330.1312; found: 330.1322;

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 1.40 (s, 3H), 1.50 (s, 3H), 2.50 (bs, 1H), 3.48-3.56 (m, 1H), 3.70-3.82 (bs, 3H), 4.46 (d, *J* = 6.5 Hz, 1H), 4.58-4.59 (m, 3H), 6.21 (bs, 1H), 7.28-7.38 (m, 5H);

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 24.8, 26.5, 52.3, 67.7, 69.9, 73.7, 73.9, 74.9, 110.9, 127.8, 128.1, 128.6, 137.2, 168.2.

(3a*S*,6*R*,7*R*,7a*R*)-*tert*-Butyl 6-((benzyloxy)methyl)-7-hydroxy-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*c*]pyridine-5(6*H*)-carboxylate (15)



To a solution of lactam **4** (0.1 g, 0.32 mmol) in anhydrous THF (5 mL) was added BH_3.DMS (0.15 mL, 1.6 mmol) dropwise at 0 ^oC under the nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for 18 h. The reaction

mixture was cooled to 0 ^{o}C and quenched by ethanol (5 mL). Solvent was removed under reduced pressure and the crude semisolid residue was treated with additional ethanol (5 mL) and refluxed for 4 h. Solvent was removed under reduced pressure to furnish crude amine **14**. To the solution of crude amine **14** in THF (5 mL) was added TEA (0.07 mL) followed by addition of $(Boc)_2O$ (0.089 mL) and DMAP (cat.) and was stirred at room temperature for 24 h. The reaction mixture was extracted with ethyl acetate (3 x 20 ml), washed with water, brine and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (7:3) as an eluent to afford colorless oily carbamate **15** (70 mg, 58% (over two steps).

Chemical Formula: $C_{21}H_{31}NO_6$;

Yield: 58 % (over two steps);

$[\alpha]_D^{25}$: -71.6 (c 0.53, $CHCl_3$);

IR ($CHCl_3$, cm^{-1}): 3445, 1698, 1682, 1455, 1416, 1161;

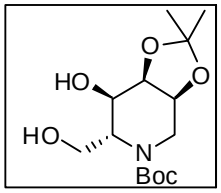
ESIMS *(m/z)*: 416.51 $(M+Na)^+$;

HRMS calculated for $[C_{21}H_{31}NO_6+Na]^+$ 416.2044; found: 416.2060;

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 1.34 (s, 3H), 1.42 (s, 9H), 1.46 (s, 3H), 2.82 (m, 1H), 3.56-3.74 (m, 1H), 3.78-4.18 (m, 4H), 4.29 (m, 1H), 4.44-4.63 (m, 3H), 7.21-7.37 (m, 5H);

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 24.4, 26.2, 28.4, 41.9, 43.3, 53.3, 53.8, 67.3, 67.8, 69.7, 70.2, 73.4, 73.7, 74.2, 79.7, 109.4, 127.4, 127.7, 128.4, 138.2, 154.9.

(3a*S*,6*R*,7*R*,7a*R*)-*tert*-Butyl 7-hydroxy-6-(hydroxymethyl)-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*c*]pyridine-5(6*H*)-carboxylate (16)



Urethane **15** (0.03 g, 0.076 mmol) in methanol was subjected to hydrogenation in presence of 10% $Pd/(OH)_2$ at room temperature (25 ^{o}C) at 70 psi for 3 h. The reaction mixture was filtered through celite, celite was washed thoroughly with methanol and concentrated under reduced pressure, and the residue was purified by flash silica gel chromatography using ethyl acetate-pet ether (9:1) as an eluent to furnish diol **16** (20.8 mg, 90%).

Chemical Formula: $C_{14}H_{25}NO_6$;

Yield: 90%;

$[\alpha]_D^{25}$: -47.14 (c 1.4, $CHCl_3$);

ESIMS *(m/z) :* 326.4 $(M+Na)^+$;

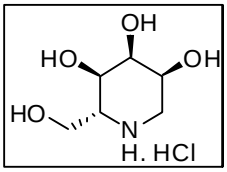
HRMS calculated for $[C_{14}H_{25}NO_6+Na]^+$ 326.1574; found: 326.1583;

IR ($CHCl_3$, cm^{-1}) : 3437, 1667, 1417, 1161;

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.42 (s, 3H), 1.47 (s, 9H), 2.83 (bs, 1H), 3.09 (bs, 1H), 3.73-3.95 (m, 4H), 3.95-4.01 (m, 1H), 4.30 (bs, 1H), 4.50 (bs, 1H);

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): δ 24.3, 26.2, 28.4, 42.1, 42.9, 55.3, 62.9, 63.6, 66.9, 67.3, 73.5, 73.6, 74.2, 74.4, 80.4, 109.6.

(2*R*,3*R*,4*S*,5*S*)-2-(Hydroxymethyl)piperidine-3,4,5-triol hydrochloride (1)



To a solution of diol **16** in methanol (3 mL) was added conc. HCl (0.1 mL) at 0 ^oC. The reaction mixture was stirred for 3 h at room temperature. After completion of reaction, the reaction mixture was concentrated under reduced pressure. The semisolid mass **1** was dried on high vacuum for 3 h to get **1** as slightly brownish semisolid mass (quantitative yield).

Chemical Formula : $C_6H_{14}ClNO_4$

Yield : quantitative;

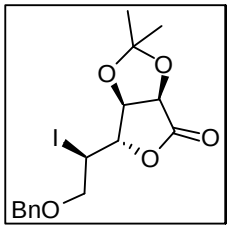
$[\alpha]_D^{25}$: +33.7 (c 1, MeOH); lit.[4] for comp-**1** **$[\alpha]_D^{23}$** +33.4 (*c* 1, MeOH);

ESIMS *(m/z)*: 164.08;

^{1}H NMR (400 MHz, D_2O): δ 4.20 (s, 1H), 4.02 (ddd, *J* = 11.7, 5.0, 2.5 Hz, 1H), 3.96 (dd, *J* = 12.8, 3.1 Hz, 1H), 3.91- 3.84 (m, 2H), 3.36 (ddd, *J* = 10.7, 5.1, 3.2 Hz, 1H), 3.29 (dd, *J* = 12.1, 5.0 Hz, 1H), 3.15 (t, *J* = 11.9 Hz, 1H);

^{13}C NMR (100 MHz, D_2O): δ 41.4, 54.6, 57.5, 64.4, 65.2, 69.8.

(3a*R*,6*S*,6a*S*)-6-((*R*)-2-(Benzyloxy)-1-iodoethyl)-2,2-dimethyldihydrofuro[3,4-*d*][1,3]dioxol-4(3a*H*)-one (17)



The mixture of hydroxy lactone **5** (500 mg, 1.62 mmol), PPh_3 (1.4 g, 5.34 mmol), imidazole (0.35 g, 5.18 mmol) and iodine (0.902 g, 3.56 mmol) was refluxed under nitrogen atmosphere in anhydrous toluene (20 mL) for 30 min. After completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature and diluted with saturated solution of $Na_2S_2O_3$. The reaction

mixture was extracted with ethyl acetate (2 X 50 mL). The organic layer was separated and dried over sodium sulphate, filtered and concentrated under reduced pressure to provide crude iodo lactone. The residue was purified by flash column chromatography using pet ether: ethyl acetate as eluent to afford **17** as a colorless liquid compound (0.508 g, 75%, HPLC purity 90%).

Chemical Formula: $C_{16}H_{19}IO_5$;

$[\alpha]_D^{25}$: -16.8 (c 1, $CHCl_3$);

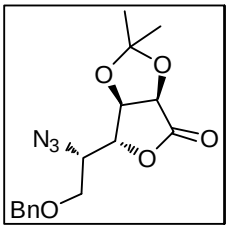
IR ($CHCl_3$, cm^{-1}) : 1790, 1628, 1153, 1076;

GCMS: 418;

^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): 1.39 (s, 3H), 1.48 (s, 3H), 3.77-3.88 (m, 2H), 4.35-4.39 (m, 1H), 4.55-4.62 (m, 2H), 4.72-4.77 (m, 2H), 4.87 (d, *J* = 6 Hz, 1H), 7.31-7.39 (m, 5H);

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): 25.3, 26.4, 28.6, 71.2, 73.3, 75.2, 79.5, 84.2, 113.8, 127.7, 128.1, 128.5, 136.8, 172.8.

(3a*R*,6*R*,6a*R*)-6-((*S*)-1-Azido-2-(benzyloxy)ethyl)-2,2-dimethyldihydrofuro[3,4-*d*][1,3]dioxol-4(3a*H*)-one (18)



To a solution of iodo-lactone **17** (100 mg, 0.239 mmol) in anhydrous DMF (3 mL) was added NaN_3 (31 mg, 0.47 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 80 ^oC for 12 h. After completion of the reaction (monitored by TLC), it was cooled to room temperature, diluted with water and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography using ethyl acetate/light petroleum ether (1:9) as an eluent to afford **18** as colorless oil (47.8 mg, 60%).

Chemical Formula : $C_{16}H_{19}N_3O_5$

Yield: 60%;

$[\alpha]_D^{25}$: +19 (c 1, $CHCl_3$);

IR ($CHCl_3$, cm^{-1}): 2114, 1790, 1087;

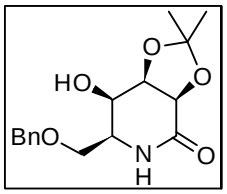
ESIMS *(m/z)*: 356 $(M+Na)^+$;

HRMS calculated for $[C_{16}H_{19}N_3O_5+Na]^+$ 356.1217; found: 356.1224;

^{1}H NMR (200 MHz, $CDCl_3$): 1.38 (s, 3H), 1.46 (s, 3H), 3.72-3.80 (m, 2H), 3.89-3.97 (m, 1H), 4.52-4.59 (m, 3H), 4.67 (d, *J* = 5.8 Hz, 1H), 4.82 (d, *J* = 5.8 Hz, 1H), 7.35 (s, 5H);

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): 25.5, 26.7, 61.5, 69.4, 73.8, 74.7, 78.5, 80.3, 113.5, 127.8, 128.1, 128.6, 136.9, 173.1.

(3a*R*,6*S*,7*R*,7a*R*)-6-((Benzyloxy)methyl)-7-hydroxy-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*c*]pyridin-4(3a*H*)-one (3)



Azido lactone **18** (50 mg, 0.15 mmol) in methanol (2 mL) was stirred with 10 % $Pd(OH)_2$/C under the hydrogen atmosphere at 10 *psi* at room temperature (25 ^oC) for 1 h. The reaction mixture was filtered through celite and the celite layer was washed thoroughly with methanol (3 X 20 mL) and concentrated under reduced pressure. The residue thus obtained was purified by flash silica gel chromatography using pet ether/ ethyl acetate (2:8) as an eluent to furnish **3** as a colorless thick liquid (40 mg, 88%).

Chemical Formula : $C_{16}H_{21}NO_5$;

Yield : 88%;

$[\alpha]_D^{25}$: -4 (c 1.5, $CHCl_3$);

IR ($CHCl_3$, cm^{-1}): 3444, 1671, 1089;

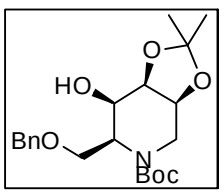
ESIMS *(m/z)*: 330.22 $(M+Na)^+$;

HRMS calculated for $[C_{16}H_{21}NO_5+Na]^+$ 330.1312; found: 330.1322;

^{1}H NMR (500 MHz, $CDCl_3$): 1.43 (s, 3H), 1.56 (s, 3H), 2.50 (bs, 1H), 3.60 (dd, *J* = 9, 4.2 Hz, 1H), 3.70 (dd, *J* = 9, 4.2 Hz, 1H), 3.75 (d, *J* = 9 Hz, 1H), 4.01 (d, *J* = 3 Hz, 1H), 4.43 (dd, *J* = 8, 3 Hz, 1H), 4.52-4.59 (m, 3H), 6.08 (bs, 1H), 7.31-7.37 (m, 5H);

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4) : 23.9, 25.9, 52.4, 63.6, 69.7, 72.1, 73.6, 74.8, 110.5, 127.8, 128.1, 128.6, 137.2, 168.9.

(3a*S*,6*S*,7*R*,7a*R*)-*tert*-Butyl 6-((Benzyloxy)methyl)-7-hydroxy-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*c*]pyridine-5(6*H*)-carboxylate (20)



To a solution of lactam **3** (0.15 g, 0.48 mmol) in anhydrous THF (7 mL) was added BH_3.DMS (0.23 mL, 2.4 mmol) dropwise at 0 ^oC under the nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for 18 h. The reaction mixture

was then cooled to 0 ^{o}C and quenched by ethanol (10 mL). Solvent was removed under reduced pressure and the crude semisolid residue was treated with additional ethanol (10 mL) and refluxed for 4 h. Solvent was removed under reduced pressure to furnish crude amine **19**. To the solution of crude amine **19** in THF was added TEA (0.14 mL) followed by addition of $(Boc)_2O$ (0.16 mL) and DMAP (cat.) and was stirred at room temperature for 24 h. The reaction mixture was extracted with ethyl acetate (3 x 20 ml), washed with water, brine and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (7:3) as an eluent to afford **20** as a colorless oily carbamate (95 mg, 50% over two steps).

Chemical Formula: $C_{21}H_{31}NO_6$;

Yield: 50% (over two steps);

$[\alpha]_D^{25}$: +44.4 (c 1.5, $CHCl_3$);

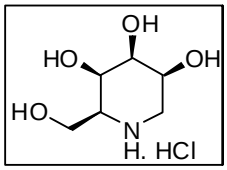
ESIMS *(m/z)*: 416.51 $(M+Na)^+$;

HRMS calculated for $[C_{21}H_{31}NO_6+Na]^+$ 416.2044; found: 416.2065;

^{1}H NMR (400 MHz, $CDCl_3$): 1.37 (s, 3H), 1.41 (s, 4H), 1.45 (s, 5H), 1.51 (s, 3H), 2.70 (bd, 1H), 3.14 (bs, 1H) 3.66-3.99 (m, 3H), 4.13 (bs, 2H), 4.30 (bs, 2H), 4.51-4.64 (m, 2H), 7.28-7.34 (m, 5H);

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4): 26.5, 27.7, 28.4, 40.9, 42.3, 52.3, 53.0, 65.6, 66.7, 66.8, 71.3, 71.5, 73.3, 74.8, 80.3, 109.6, 127.7, 128.4, 138.2, 154.7.

(2*S*,3*R*,4*S*,5*S*)-2-(Hydroxymethyl)piperidine-3,4,5-triol hydrochloride (2)



To a solution of urethane **20** (30 mg, 0.076 mmol) in MeOH (5 mL) was added $Pd(OH)_2/C$ under the atmosphere of hydrogen. The reaction mixture was allowed to stir for 6 h. After completion of reaction (monitored by TLC), the reaction mixture was filtered through a celite bed and the celite bed was thoroughly washed with methanol (3 X 30 mL). The reaction mixture was concentrated under reduced pressure to provide the diol. To a solution of diol in methanol (3 mL) was added conc. HCl (0.05 mL) at 0 ^{o}C. The reaction mixture was stirred for 3 h at room temperature. After completion of reaction, the reaction mixture was concentrated under reduced pressure. The semisolid

mass **2** was dried under high vacuum for 3 h to get **2** as slightly brownish semisolid (10.6 mg, 70% over two steps).

Chemical Formula: $C_6H_{14}ClNO_4$;

Yield: 70% (over two steps);

$[\alpha]_D^{25}$: +20.2 (c 1, MeOH); lit.[5] for comp-**2** **$[\alpha]_D^{25}$** +22.0 (c 0.5 MeOH);

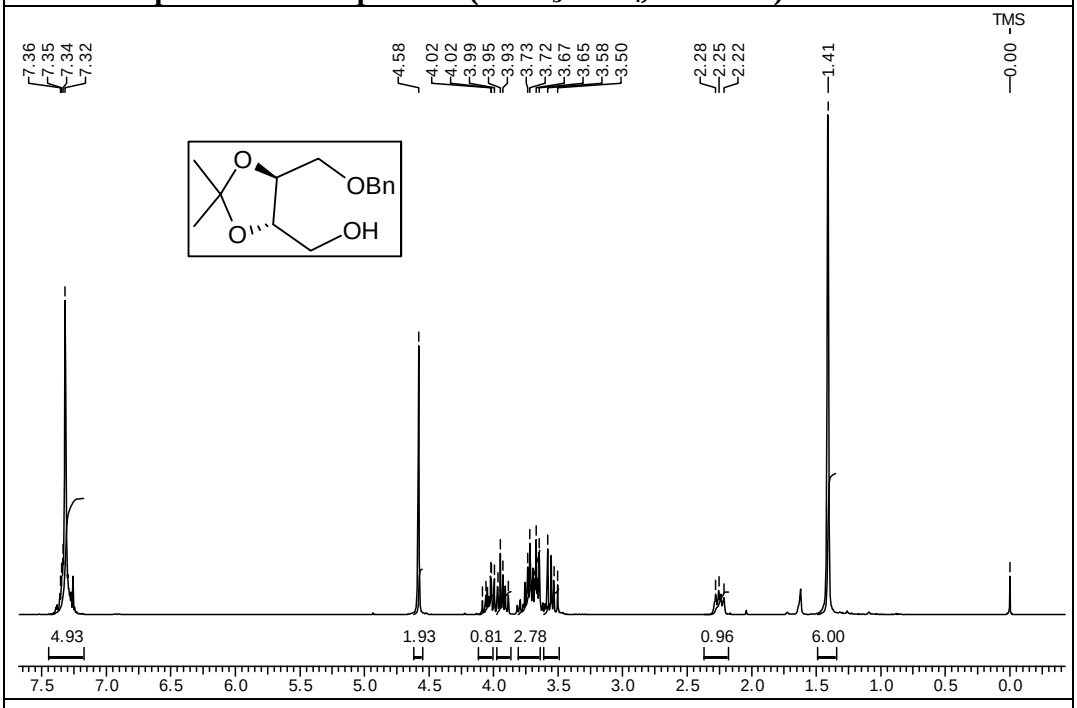
ESIMS *(m/z)*: 164.08;

^{1}H NMR 400 MHz, D_2O): δ 3.21-3.32 (m, 1H), 3.39 (t, *J* = 6.7 Hz, 1H), 3.51 (dt, J = 13.8, 2.2 Hz, 1H), 3.81-3.95 (m, 3H), 4.14 (bs, 1H), 4.23 (bs, 1H);

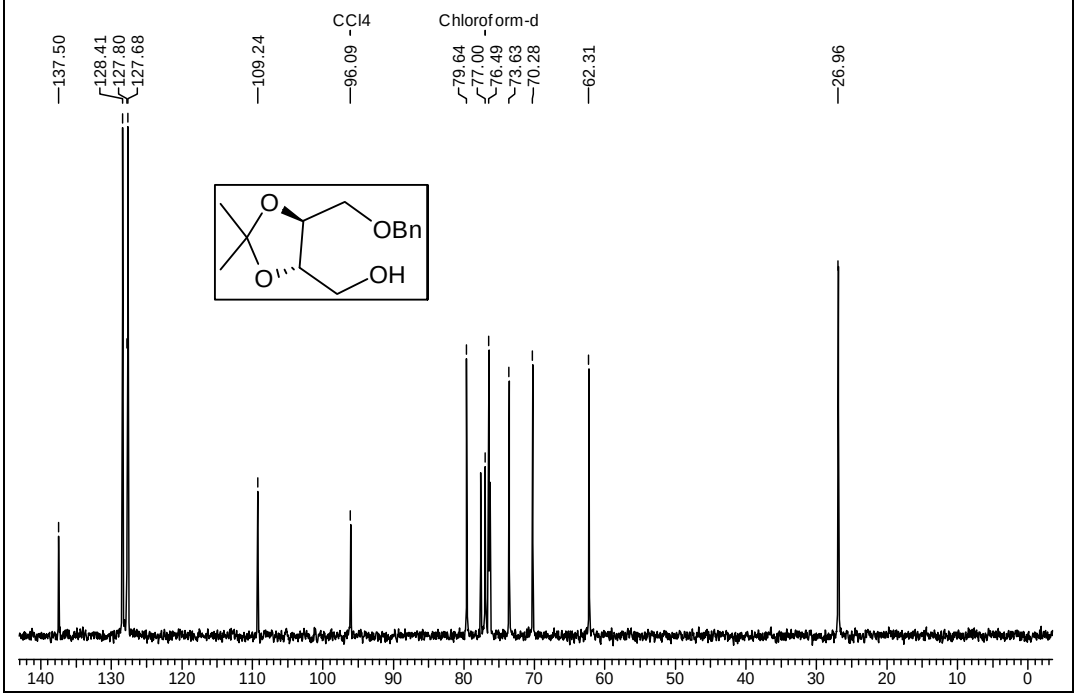
^{13}C NMR (100 MHz, D_2O): 50.4, 61.2, 62.3, 68.7, 69.2, 69.7.

3.3.4 Spectra

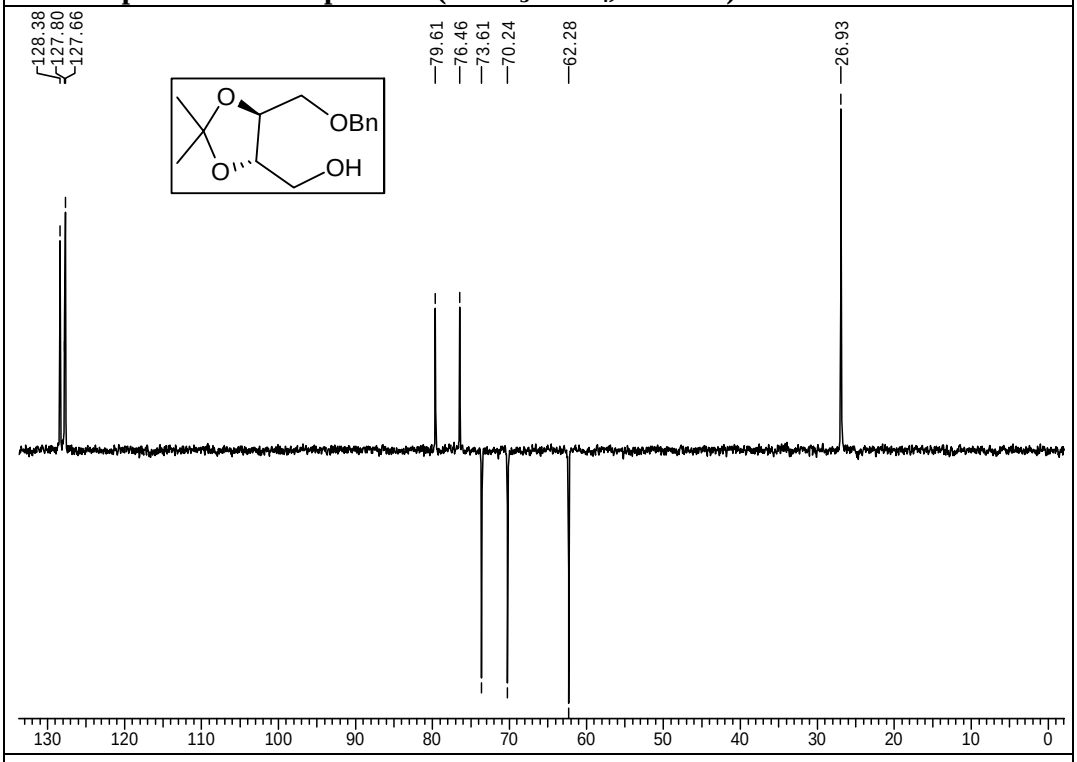
^{1}H NMR Spectrum of compound 8 ($CDCl_3$+CCl_4, 200 MHz)



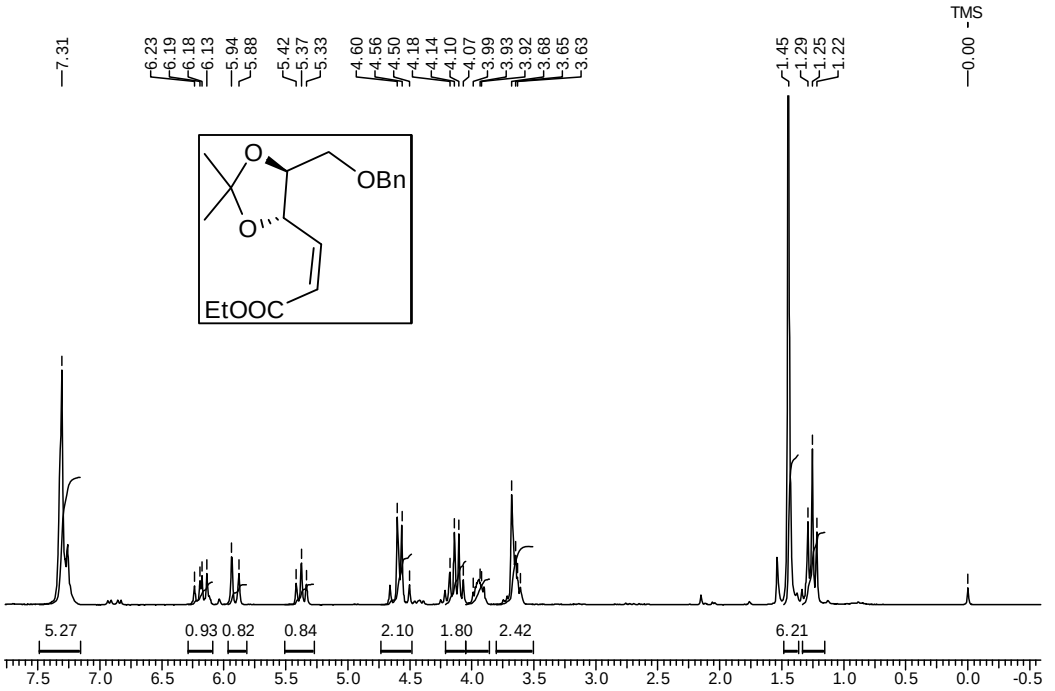
^{13}C NMR Spectrum of compound 8 ($CDCl_3$+CCl_4, 50 MHz)



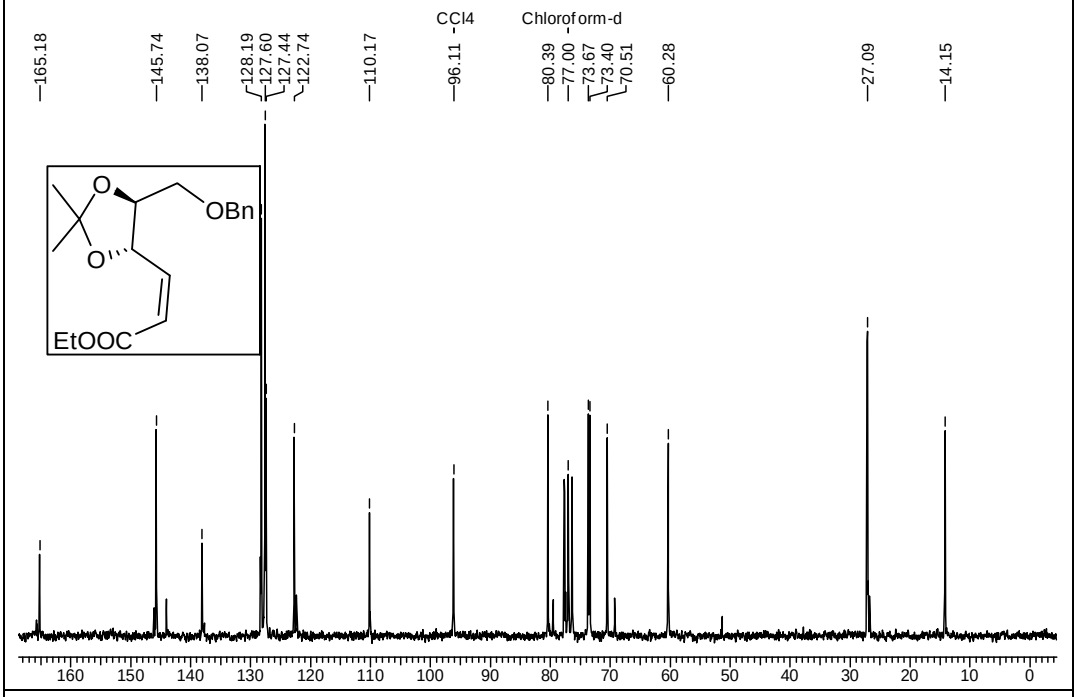
DEPT Spectrum of compound 8 ($CDCl_3$+CCl_4, 50 MHz)



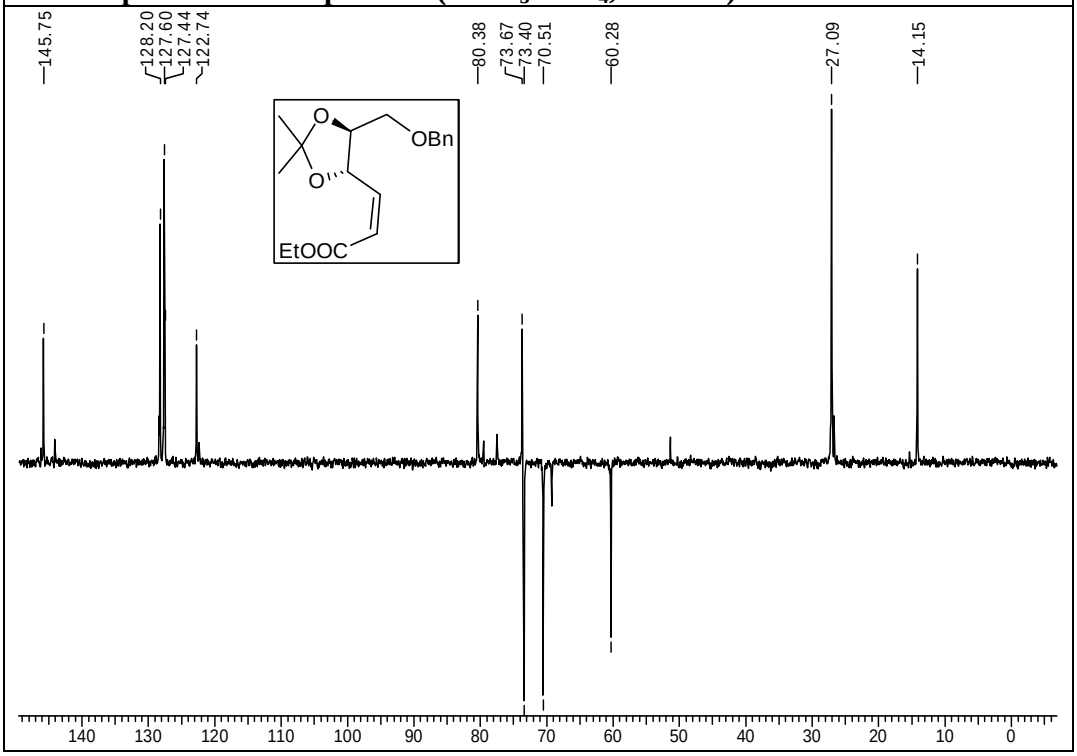
^{1}H NMR Spectrum of compound 9 ($CDCl_3$+CCl_4, 200 MHz)



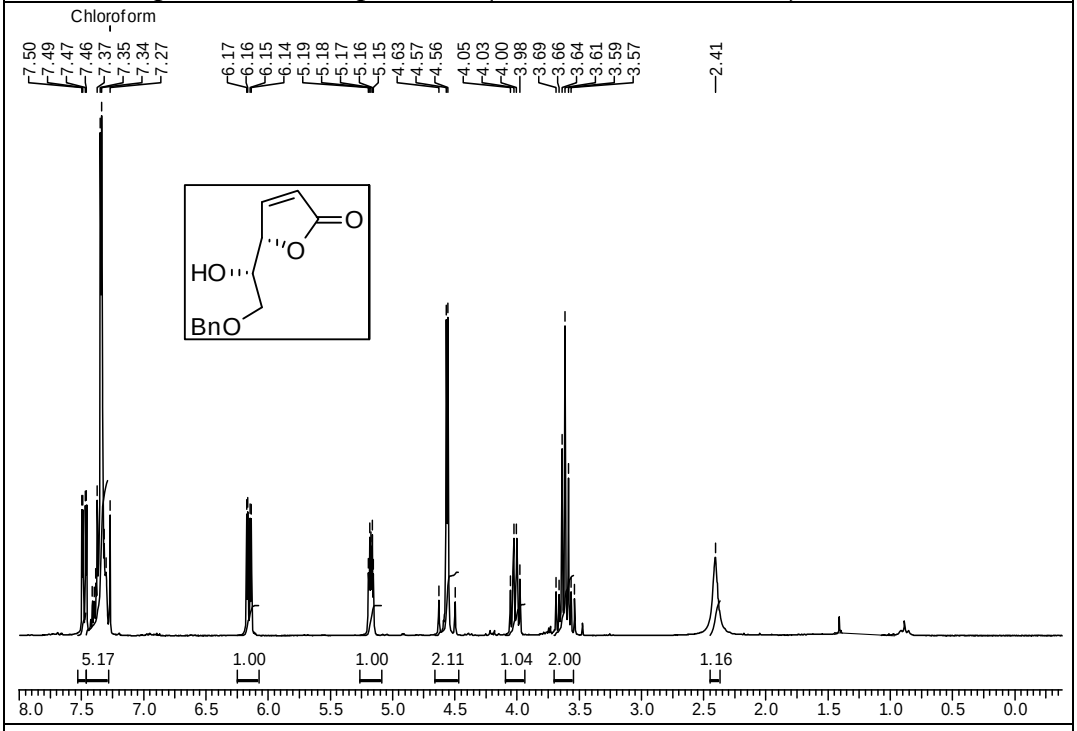
^{13}C NMR Spectrum of compound 9 ($CDCl_3$+CCl_4, 50 MHz)



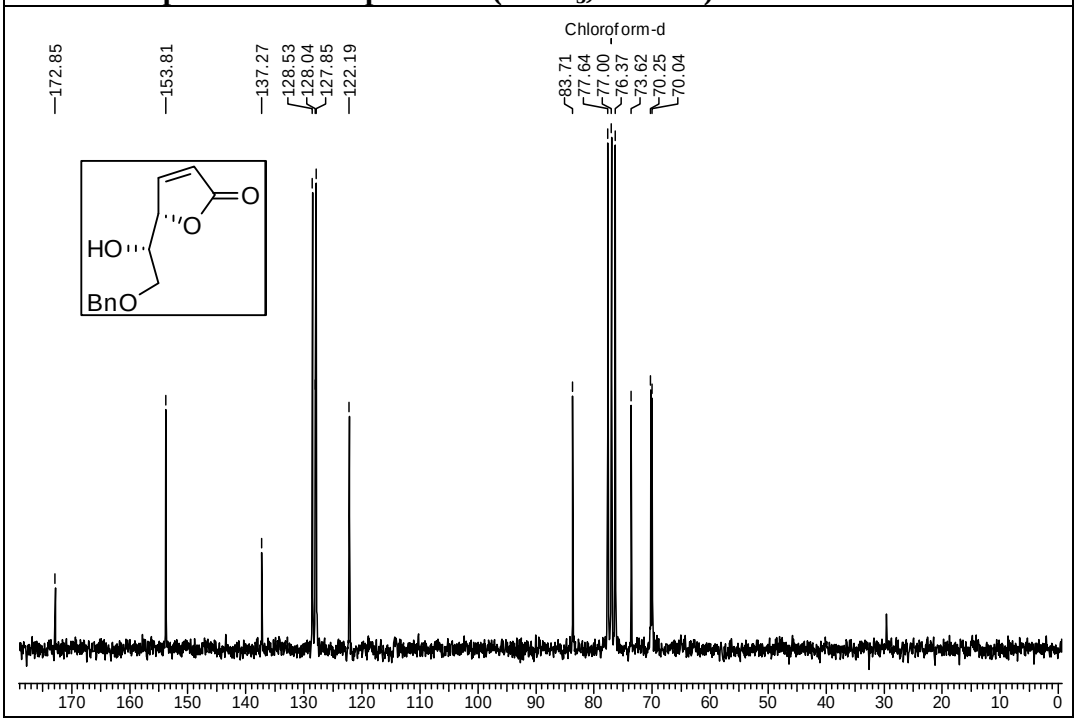
DEPT Spectrum of compound 9 ($CDCl_3$+CCl_4, 50 MHz)



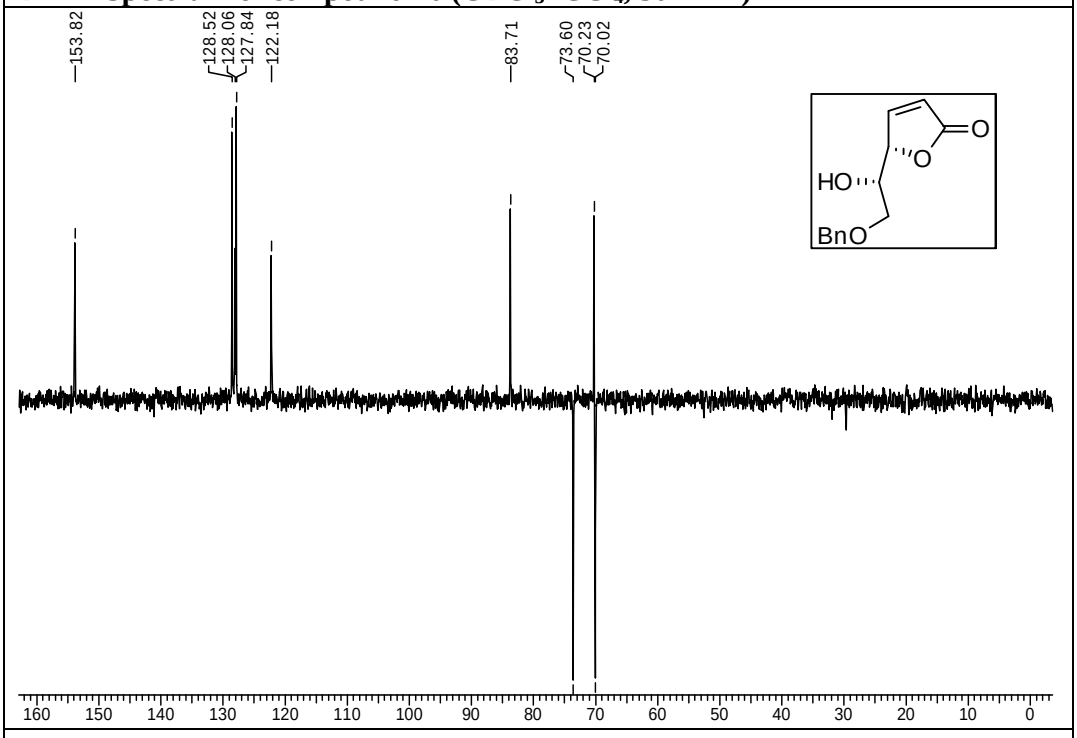
^{1}H NMR Spectrum of compound 10 ($CDCl_3$+CCl_4, 200 MHz)



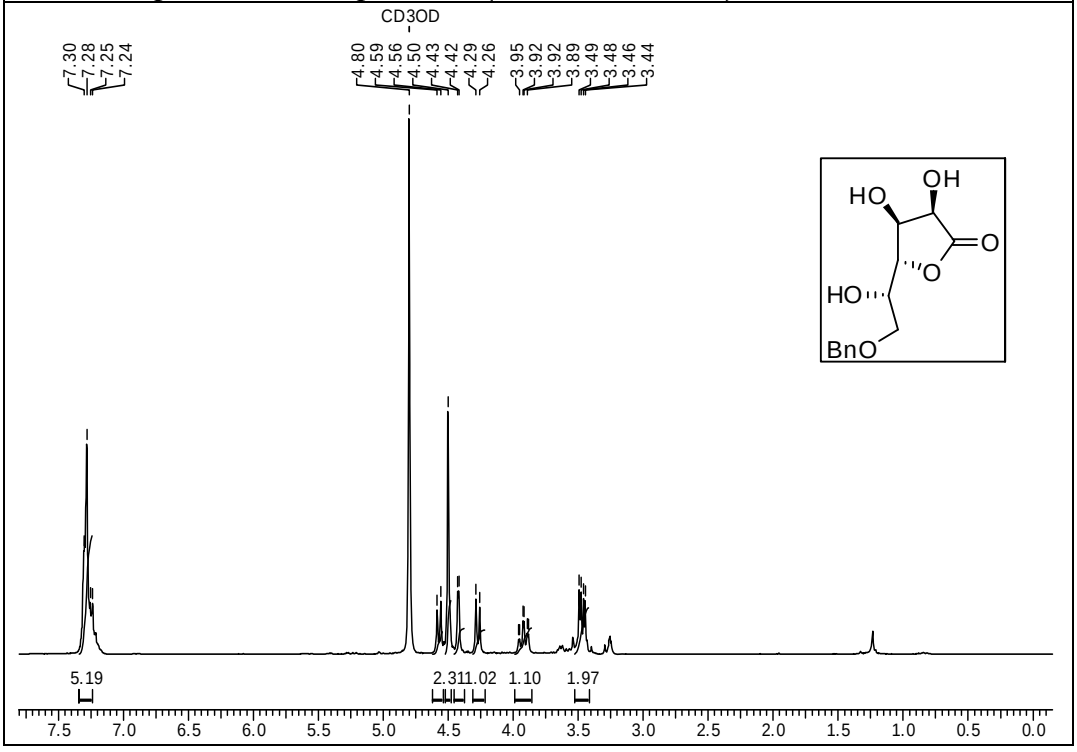
^{13}C NMR Spectrum of compound 10 ($CDCl_3$, 50 MHz)



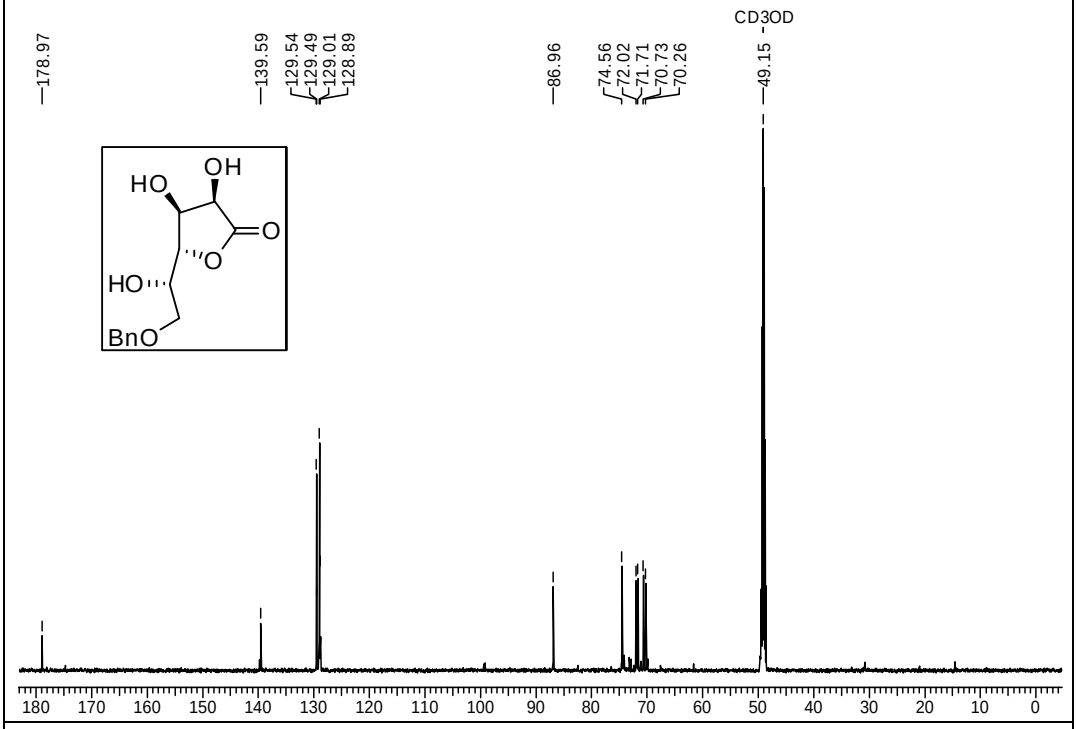
DEPT Spectrum of compound 10 ($CDCl_3$+CCl_4, 50 MHz)



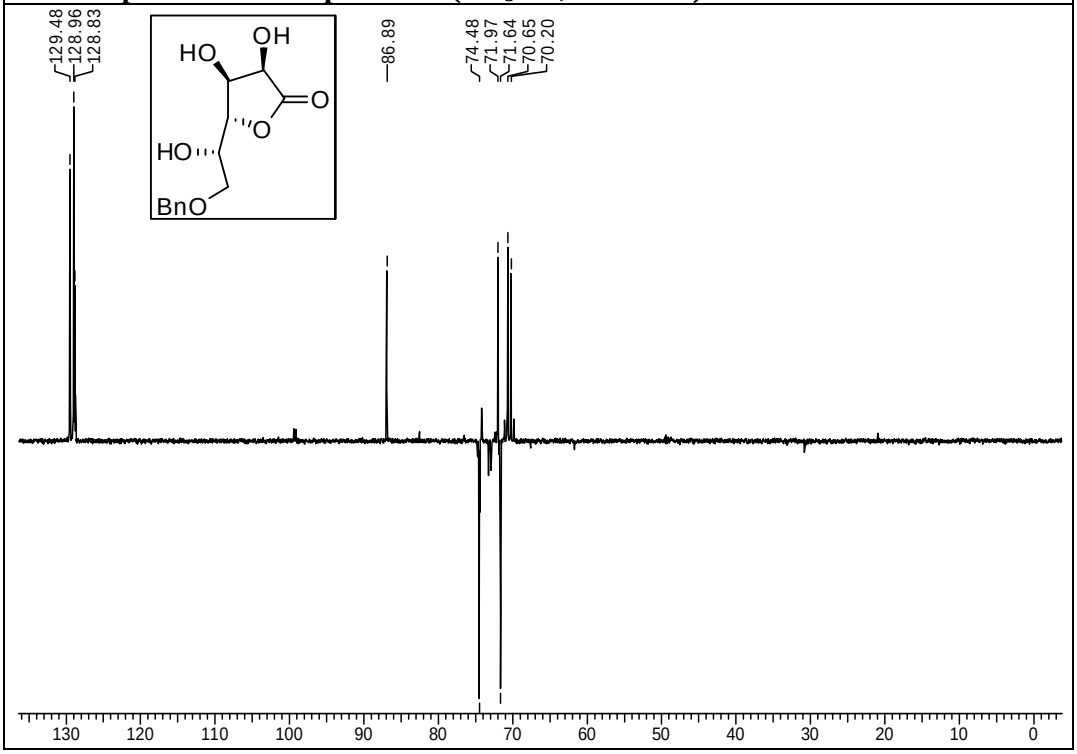
^{1}H NMR Spectrum of compound 11 (CD_3OD, 200 MHz)



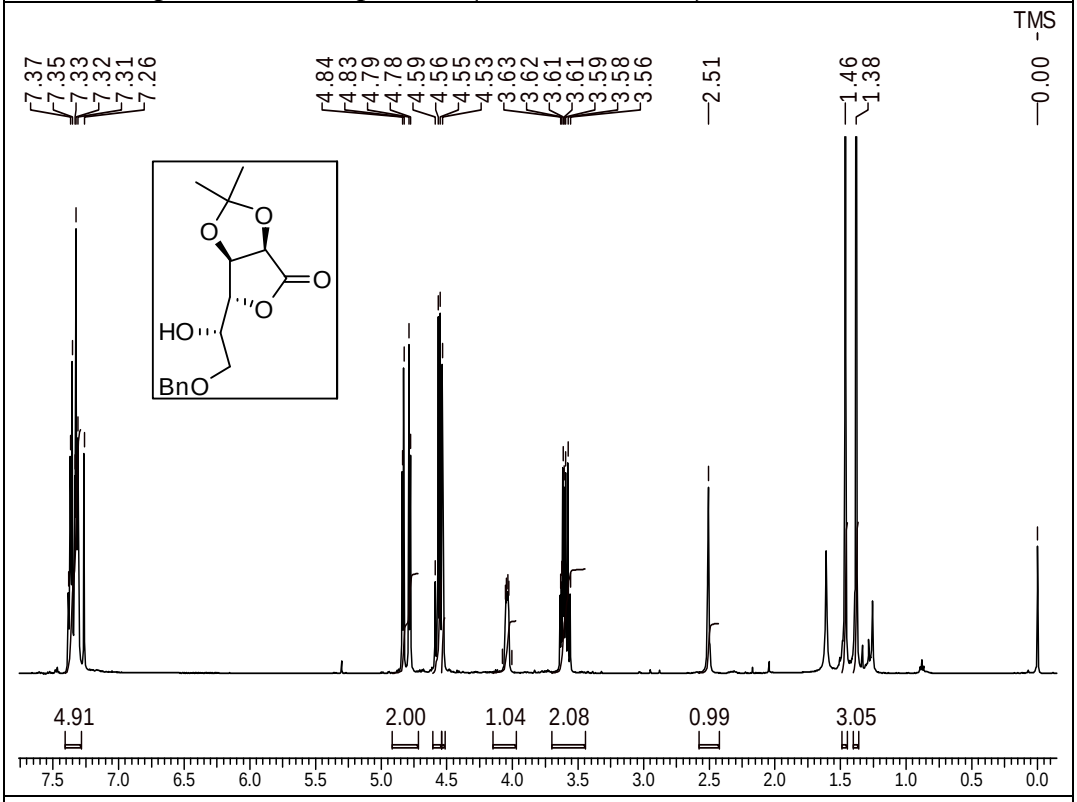
^{13}C NMR Spectrum of compound 11 (CD_3OD, 125 MHz)



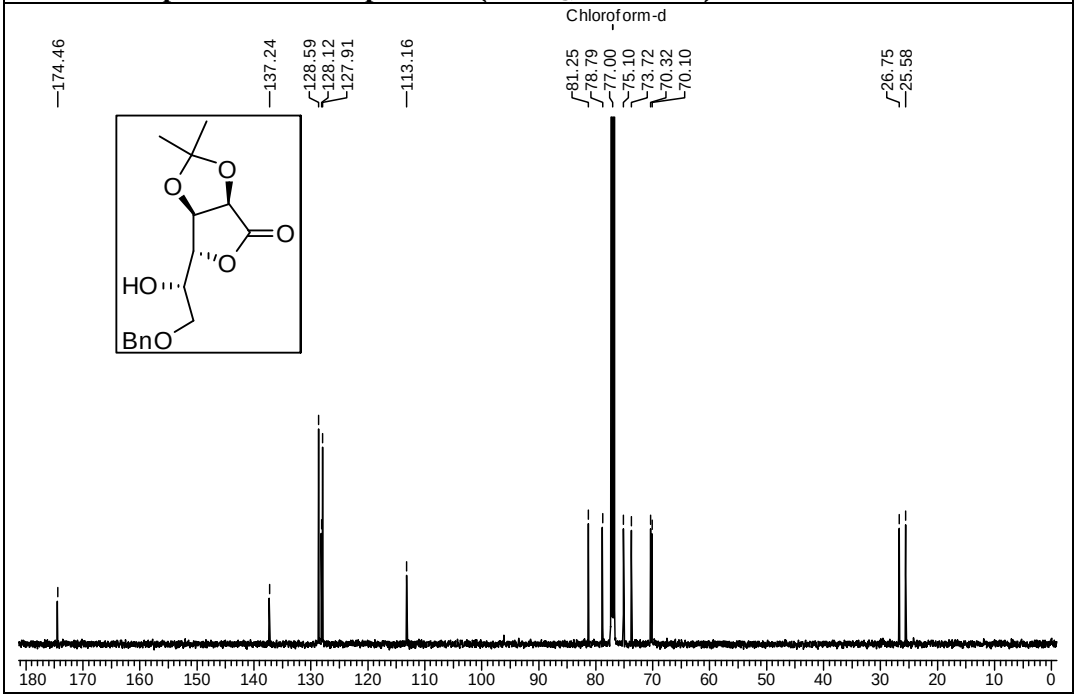
DEPT Spectrum of compound 11 (CD_3OD, 125 MHz)



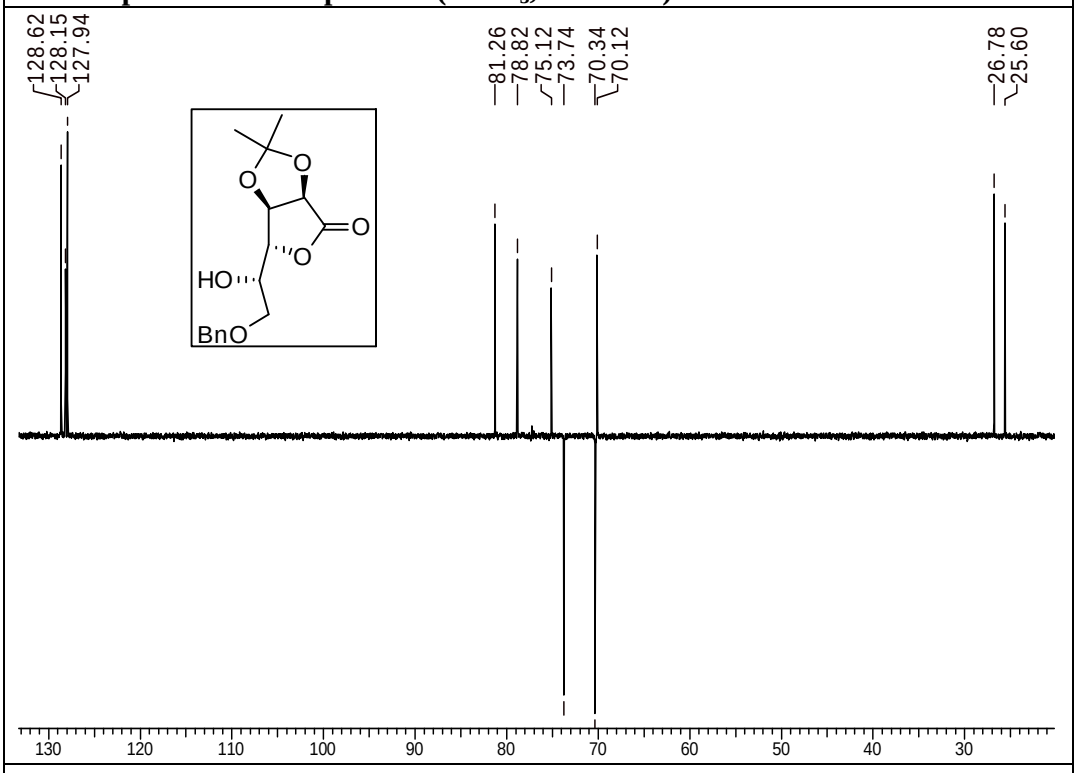
^{1}H NMR Spectrum of compound 5 ($CDCl_3$, 500 MHz)



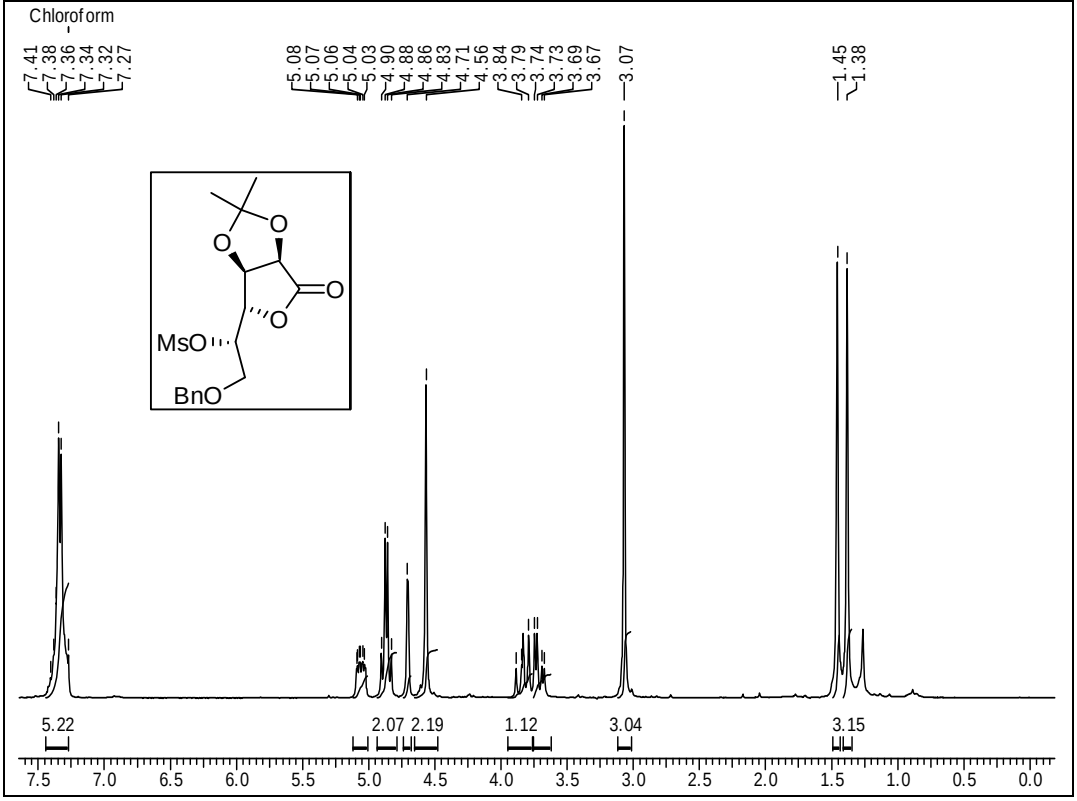
^{13}C NMR Spectrum of compound 5 ($CDCl_3$, 125 MHz)



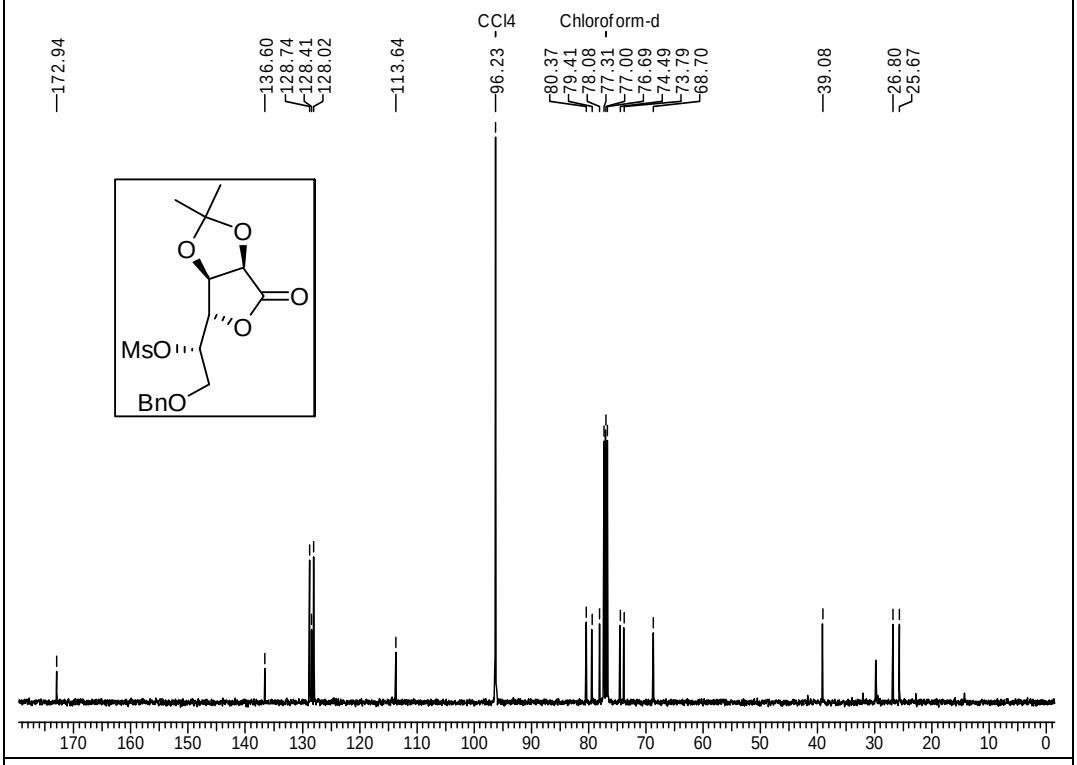
DEPT Spectrum of compound 5 ($CDCl_3$, 125 MHz)



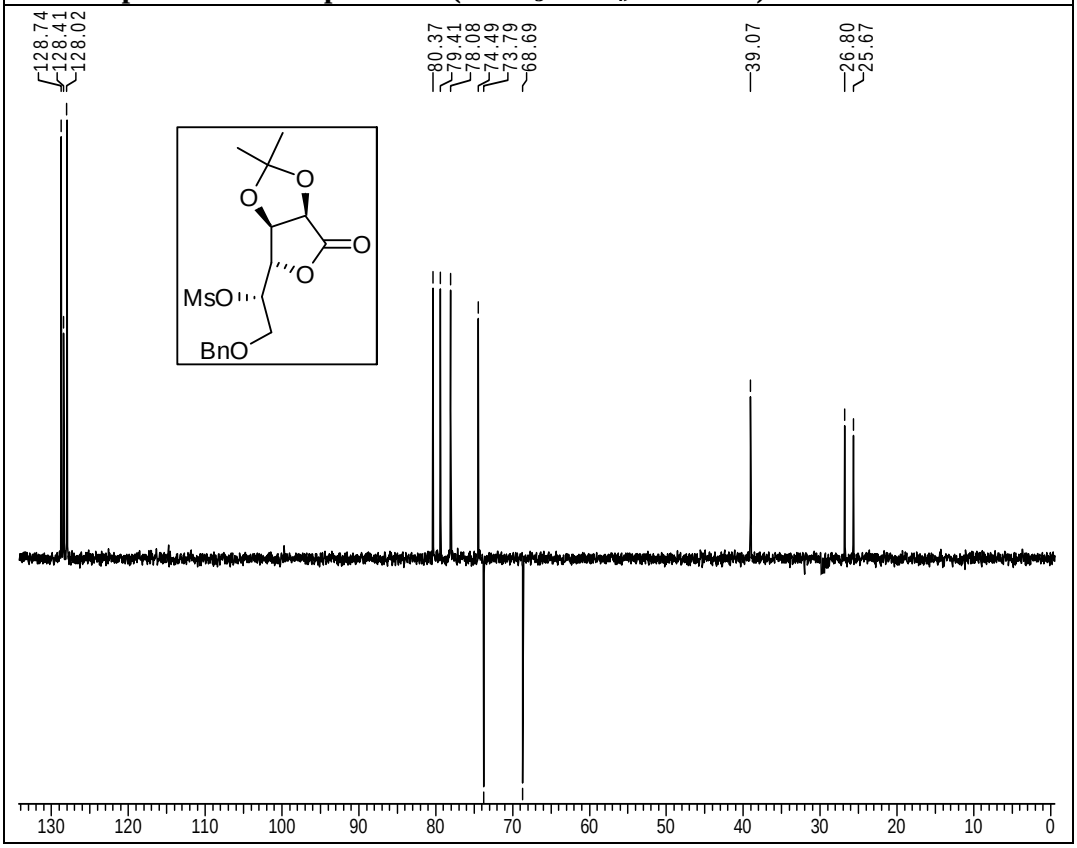
^{1}H NMR Spectrum of compound 12 ($CDCl_3$+CCl_4, 200 MHz)



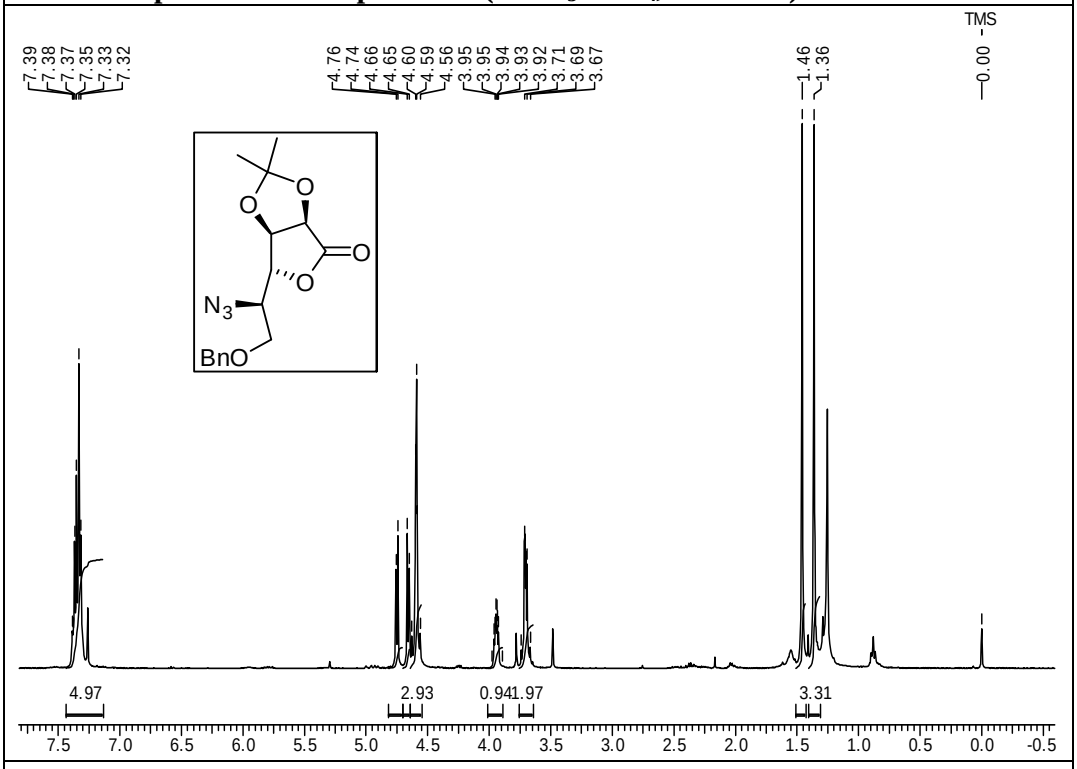
^{13}C NMR Spectrum of compound 12 ($CDCl_3$+CCl_4, 100 MHz)



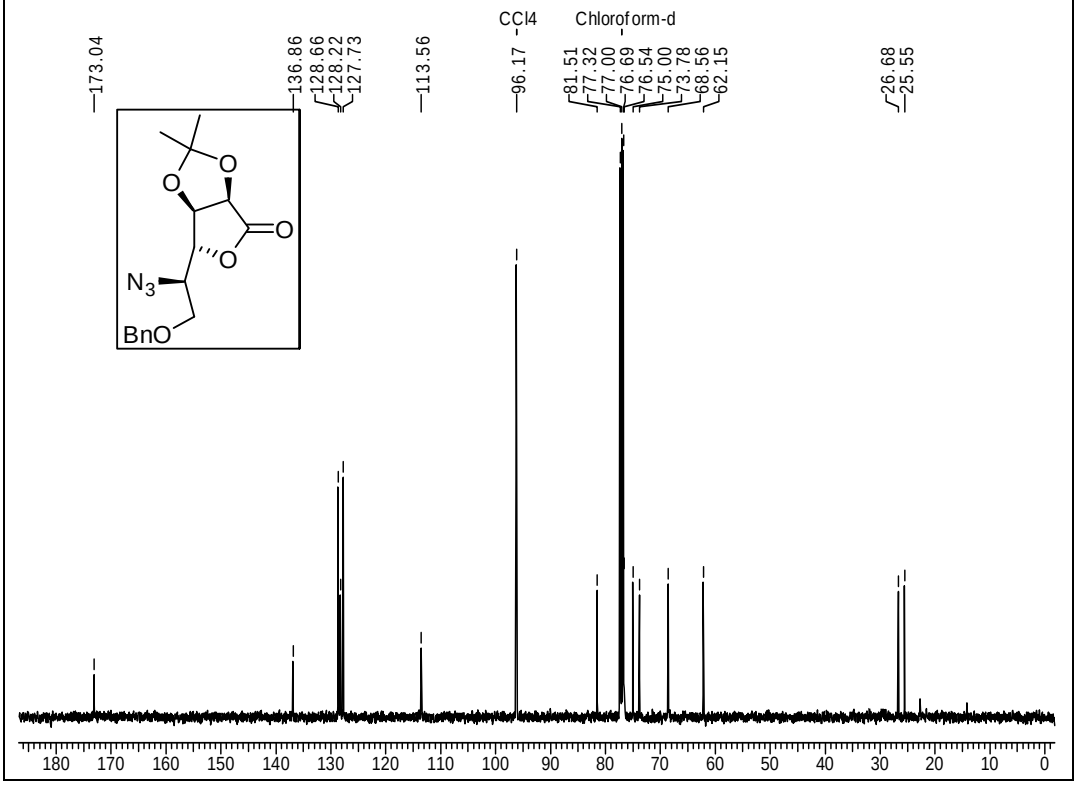
DEPT Spectrum of compound 12 ($CDCl_3$+CCl_4, 100 MHz)



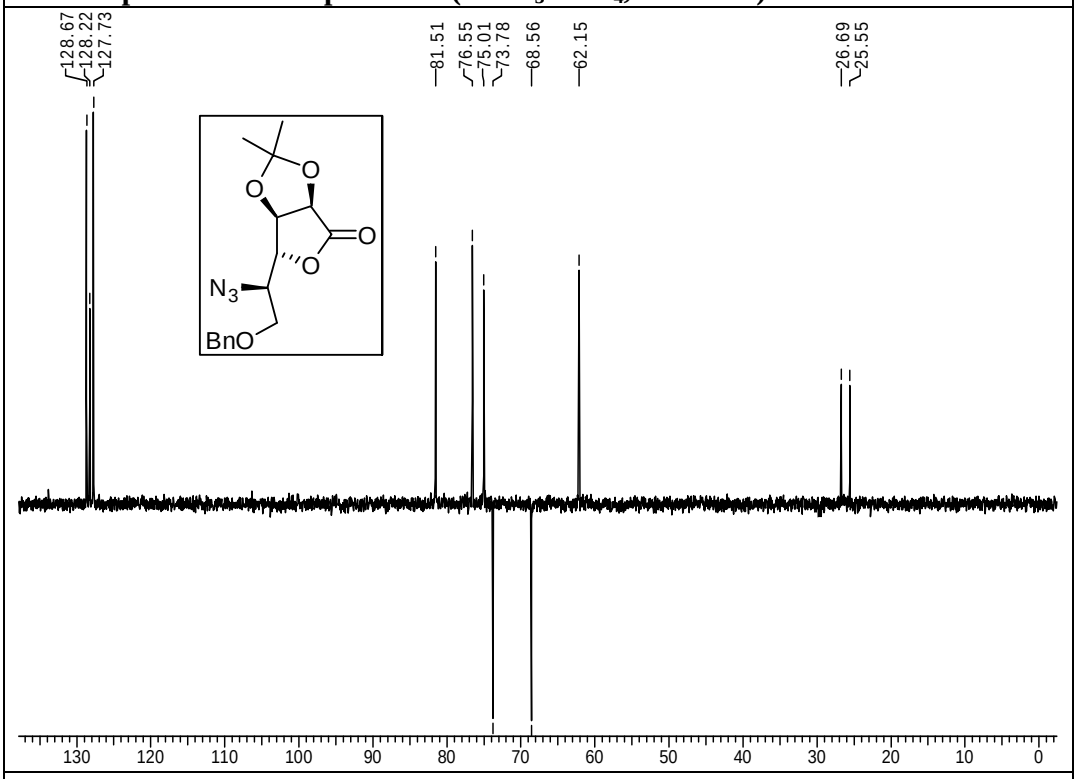
^{1}H NMR Spectrum of compound 13 ($CDCl_3$+CCl_4, 400 MHz)



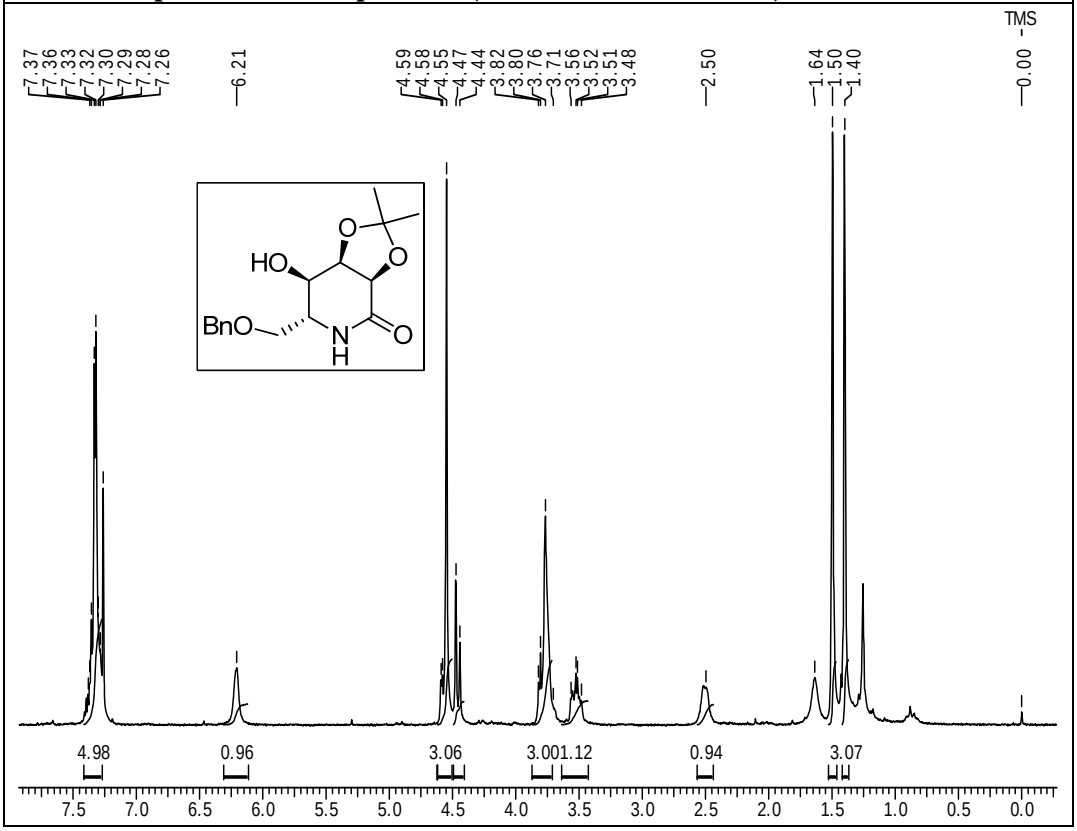
^{13}C NMR Spectrum of compound 13 ($CDCl_3$+CCl_4, 100 MHz)



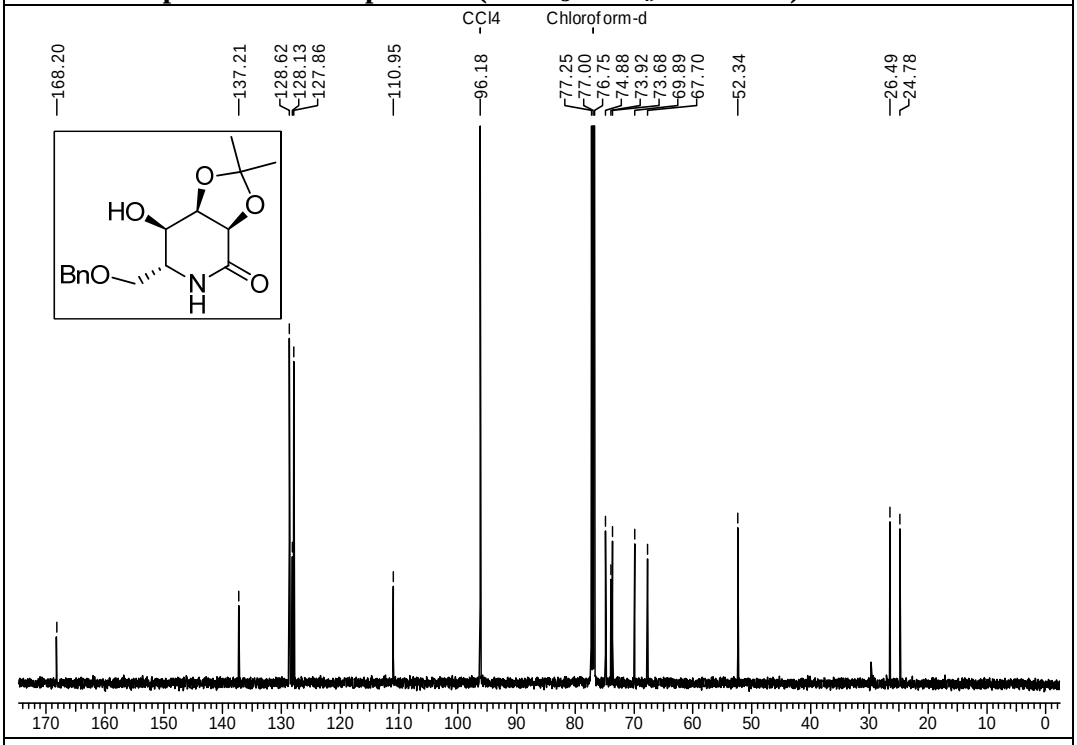
DEPT Spectrum of compound 13 ($CDCl_3$+CCl_4, 100 MHz)



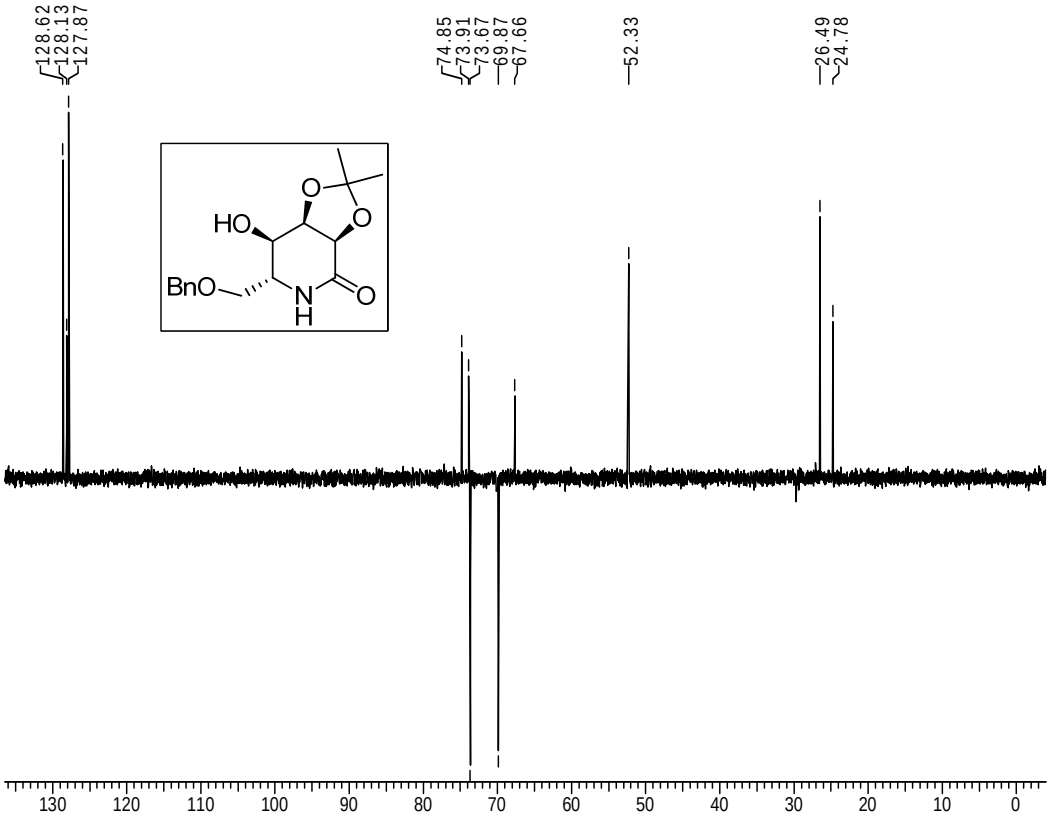
^{1}H NMR Spectrum of compound 4 ($CDCl_3$+CCl_4, 200 MHz)



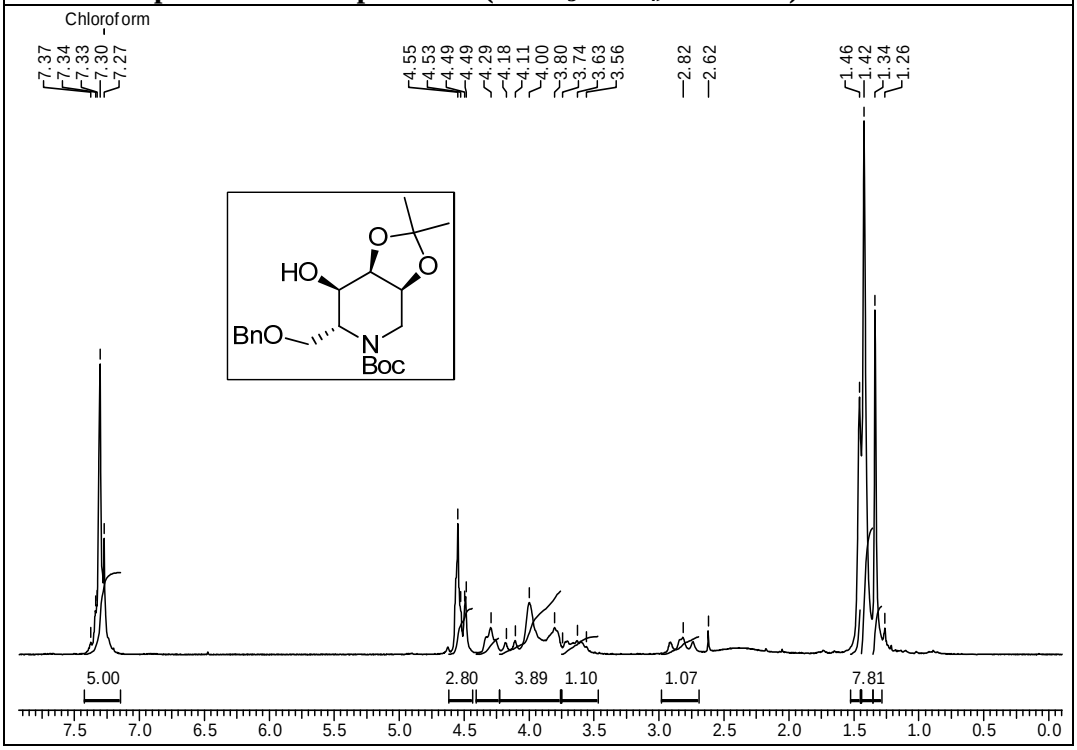
^{13}C NMR Spectrum of compound 4 ($CDCl_3$+CCl_4, 125 MHz)



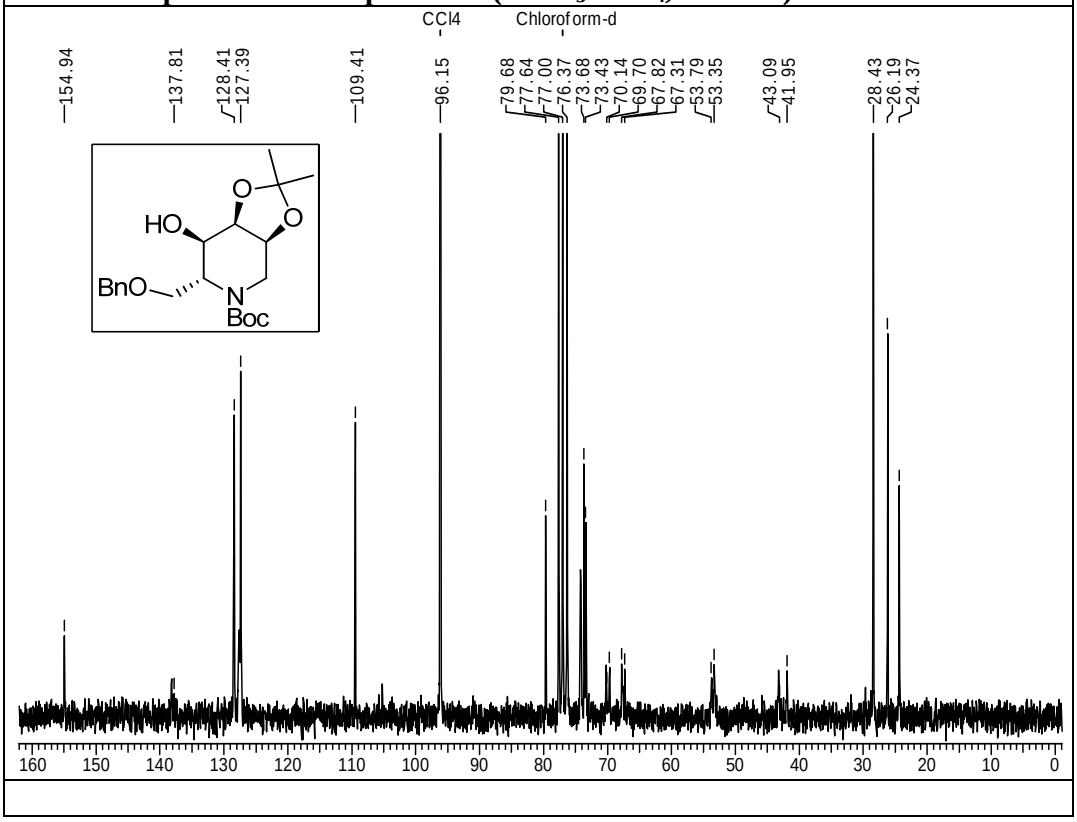
DEPT Spectrum of compound 4 ($CDCl_3$+CCl_4, 125 MHz)



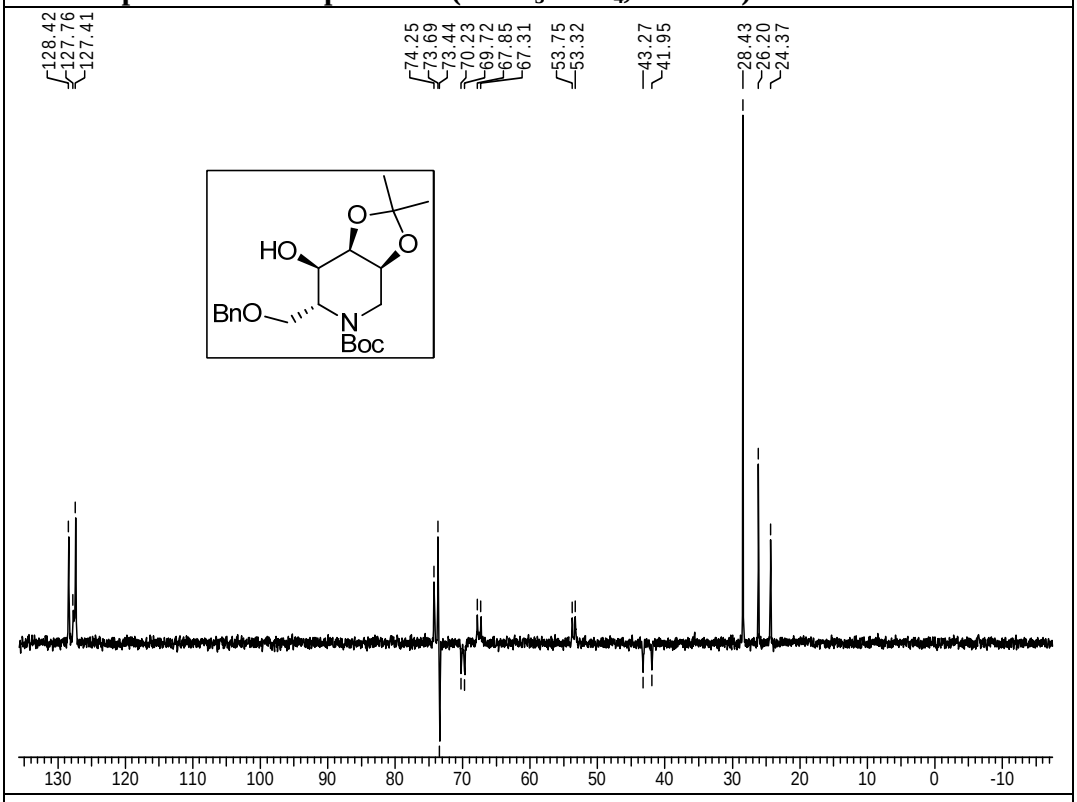
^{1}H NMR Spectrum of compound 15 ($CDCl_3$+CCl_4, 200 MHz)



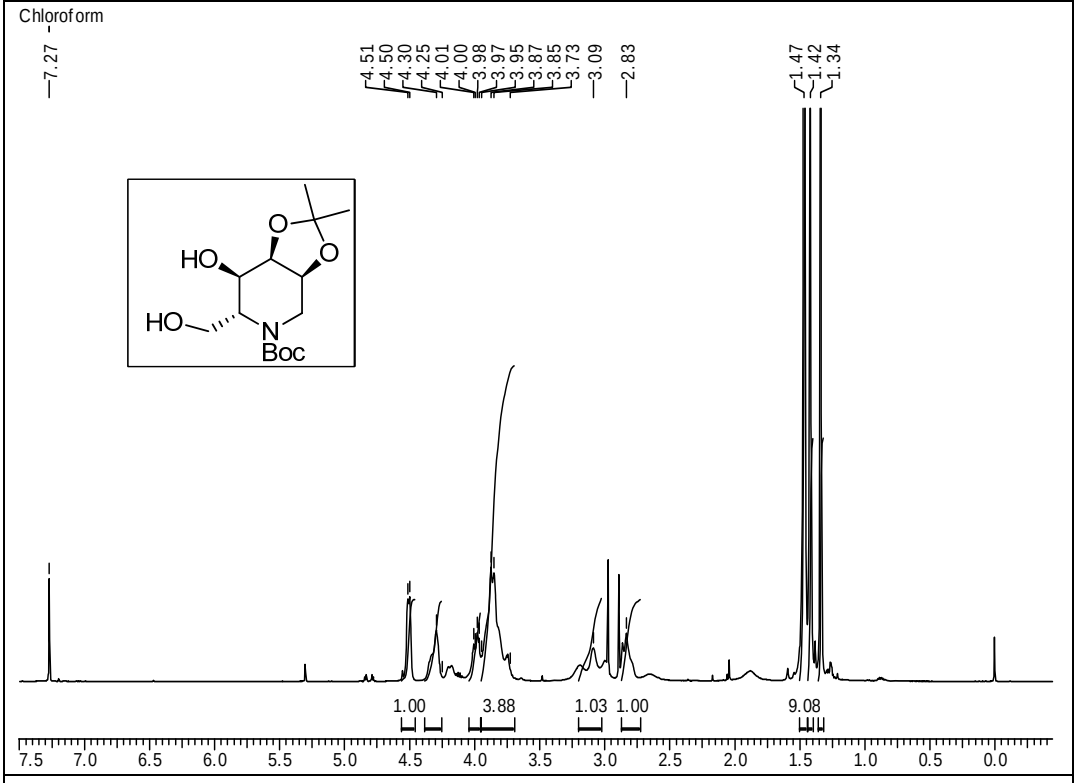
^{13}C NMR Spectrum of compound 15 ($CDCl_3$+CCl_4, 50 MHz)



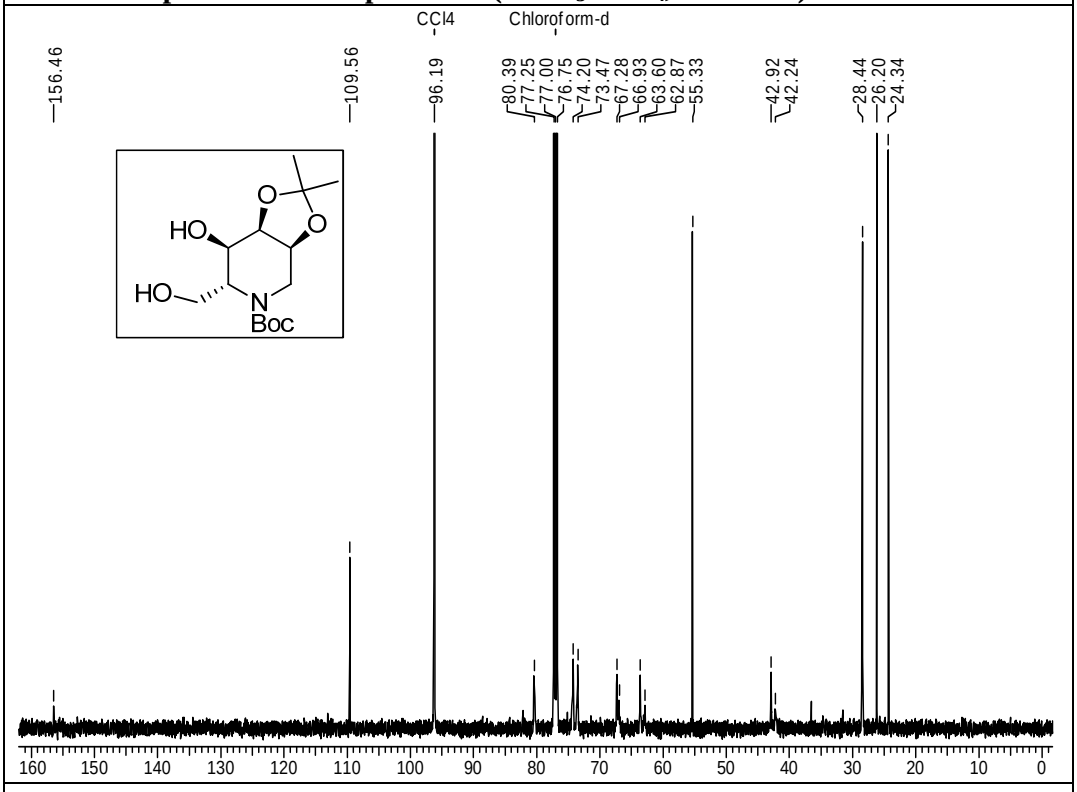
DEPT Spectrum of compound 15 ($CDCl_3$+CCl_4, 50 MHz)



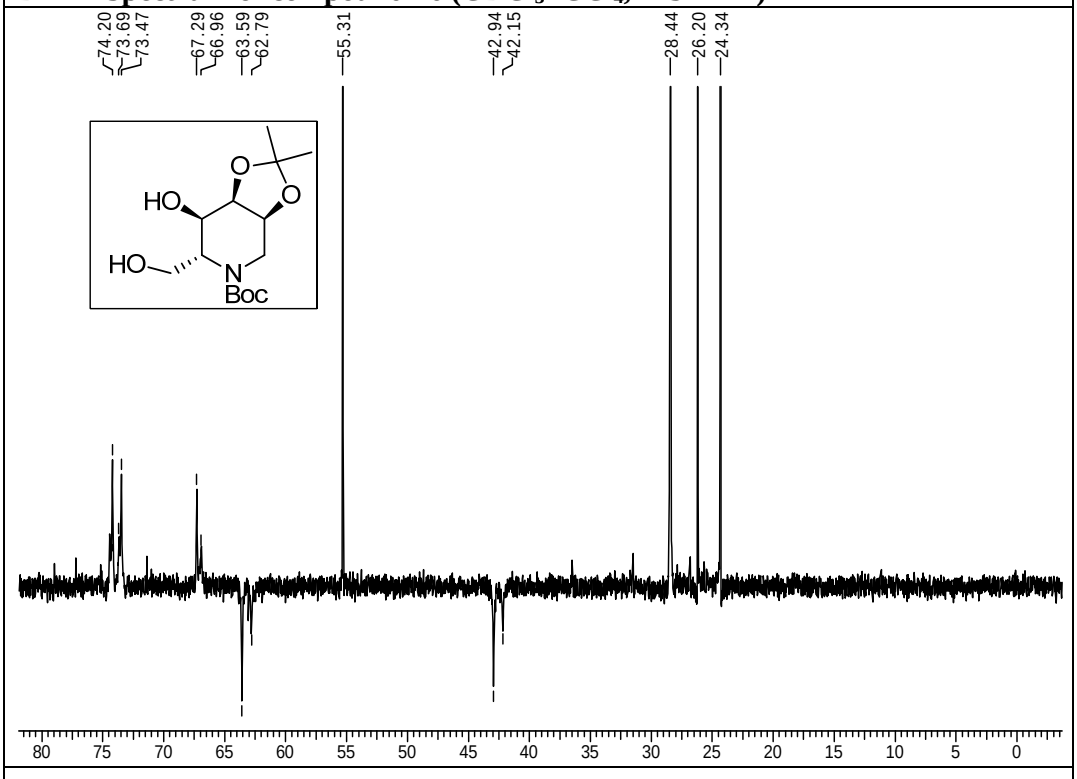
^{1}H NMR Spectrum of compound 16 ($CDCl_3$+CCl_4, 500 MHz)



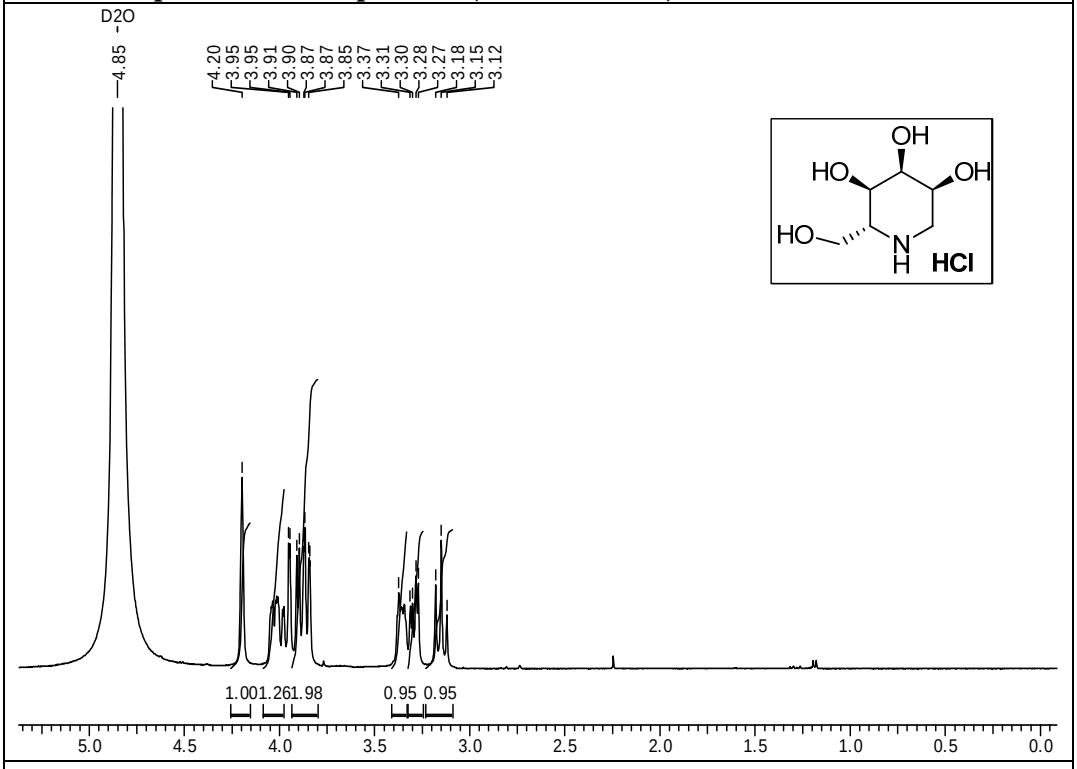
^{13}C NMR Spectrum of compound 16 ($CDCl_3$+CCl_4, 125 MHz)



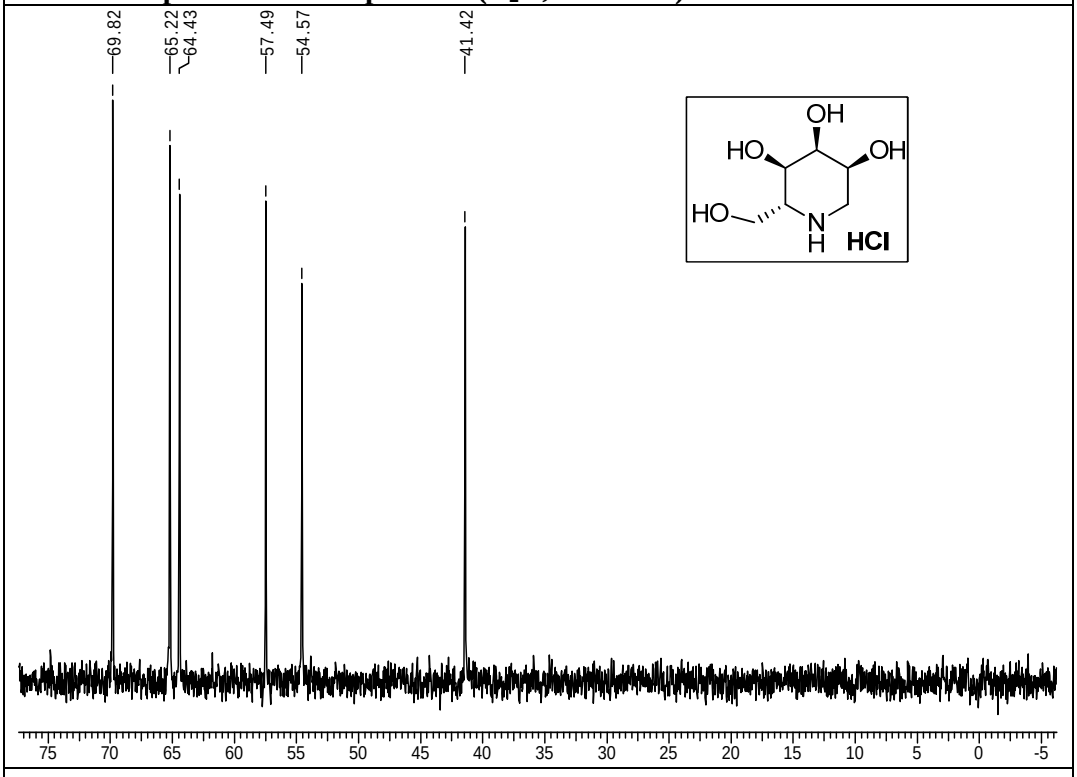
DEPT Spectrum of compound 16 ($CDCl_3$+CCl_4, 125 MHz)



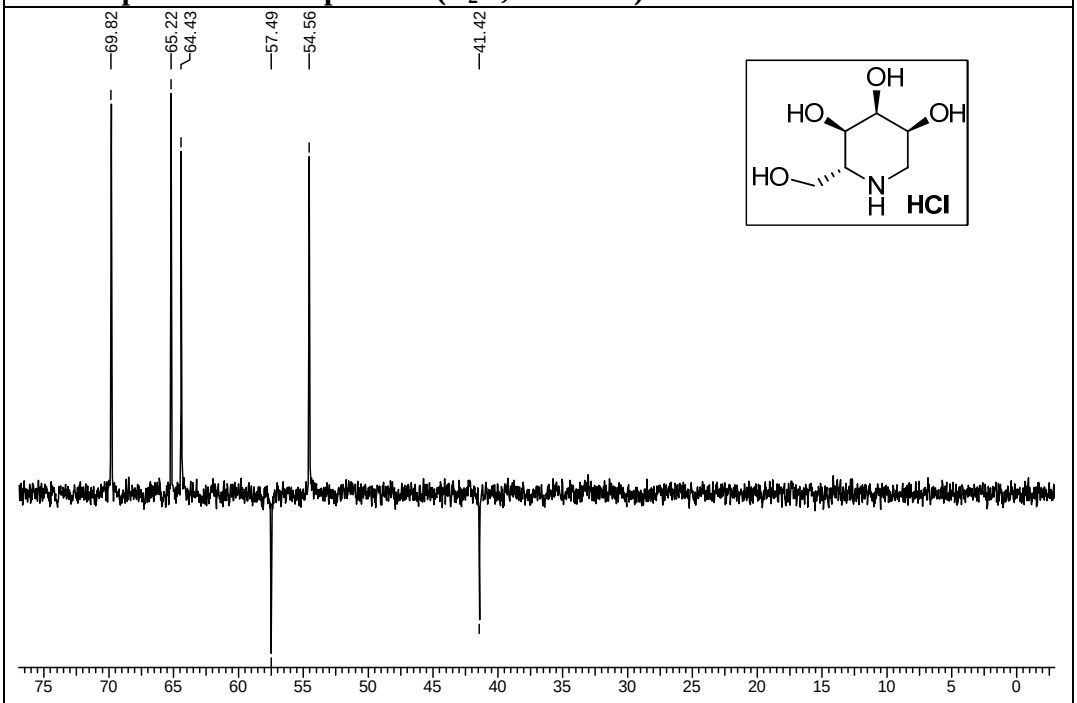
^{1}H NMR Spectrum of compound 1 (D_2O, 400 MHz)



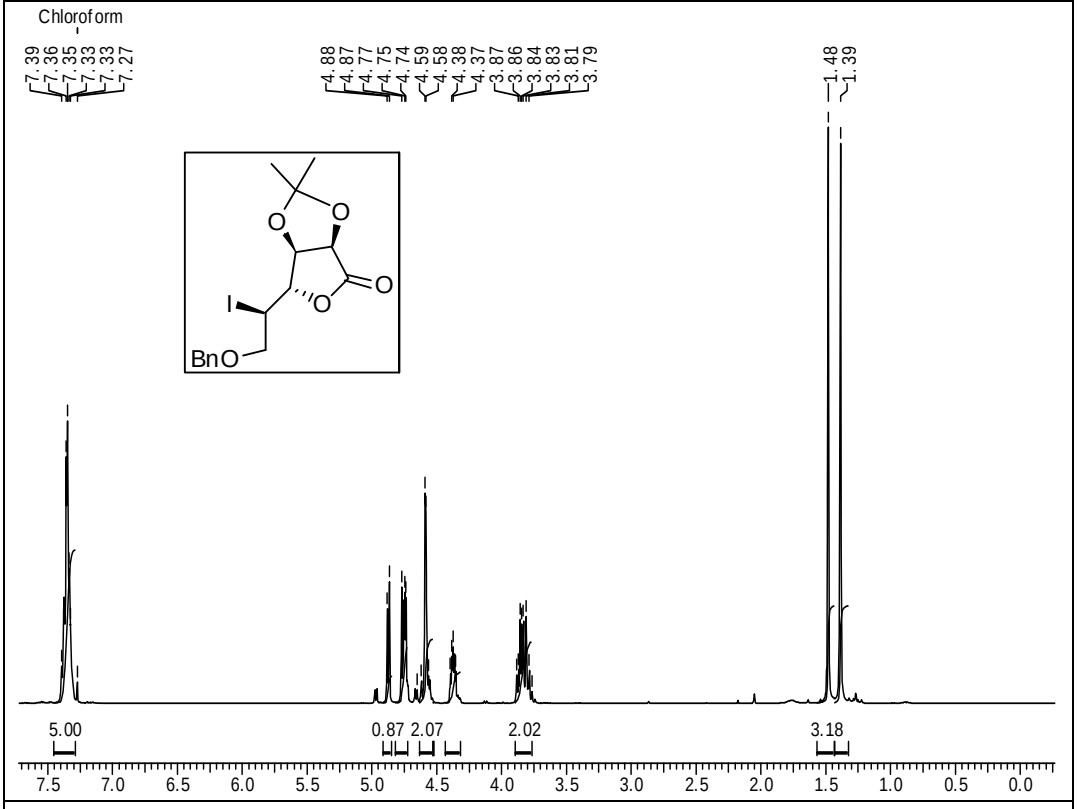
^{13}C NMR Spectrum of compound 1 (D_2O, 100 MHz)



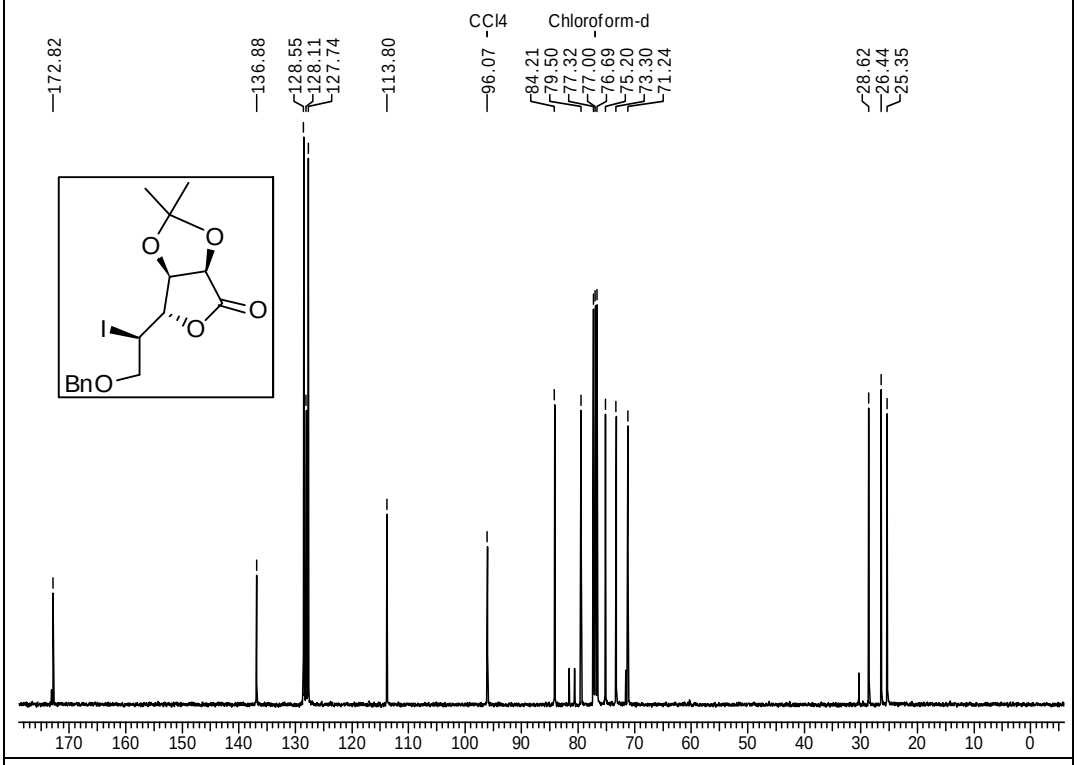
DEPT Spectrum of compound 1 (D_2O, 100 MHz)



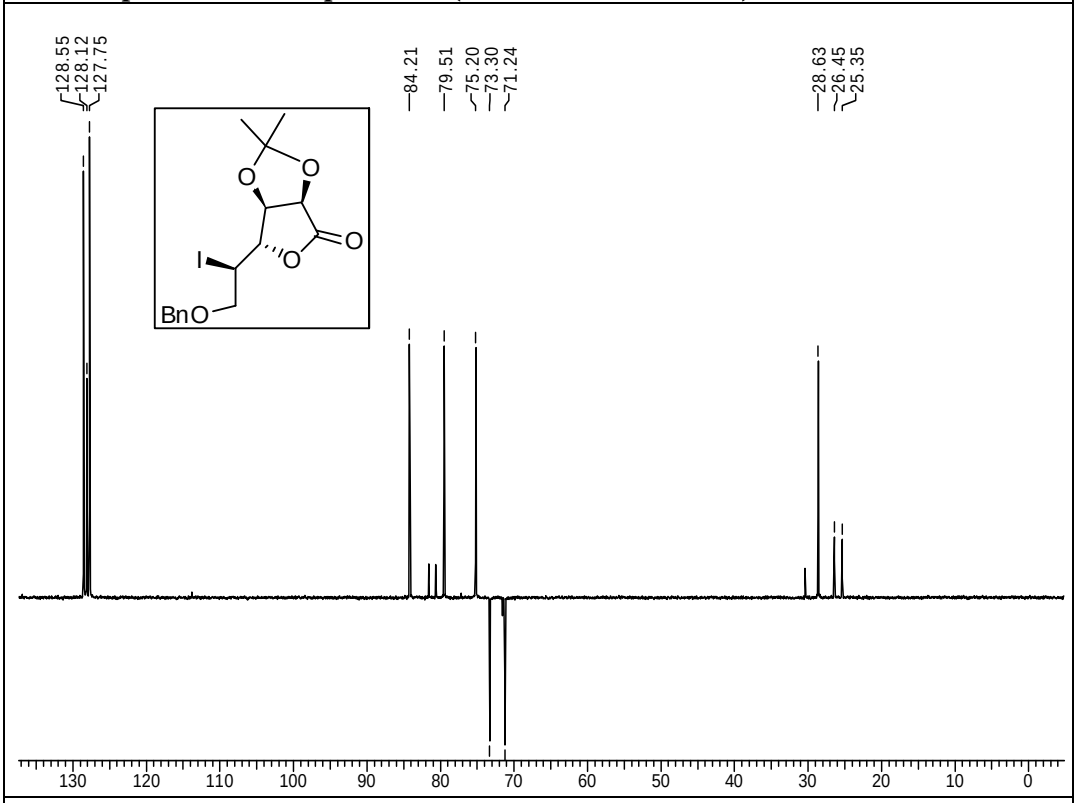
^{1}H NMR Spectrum of compound 17 ($CDCl_3$+CCl_4, 400 MHz)



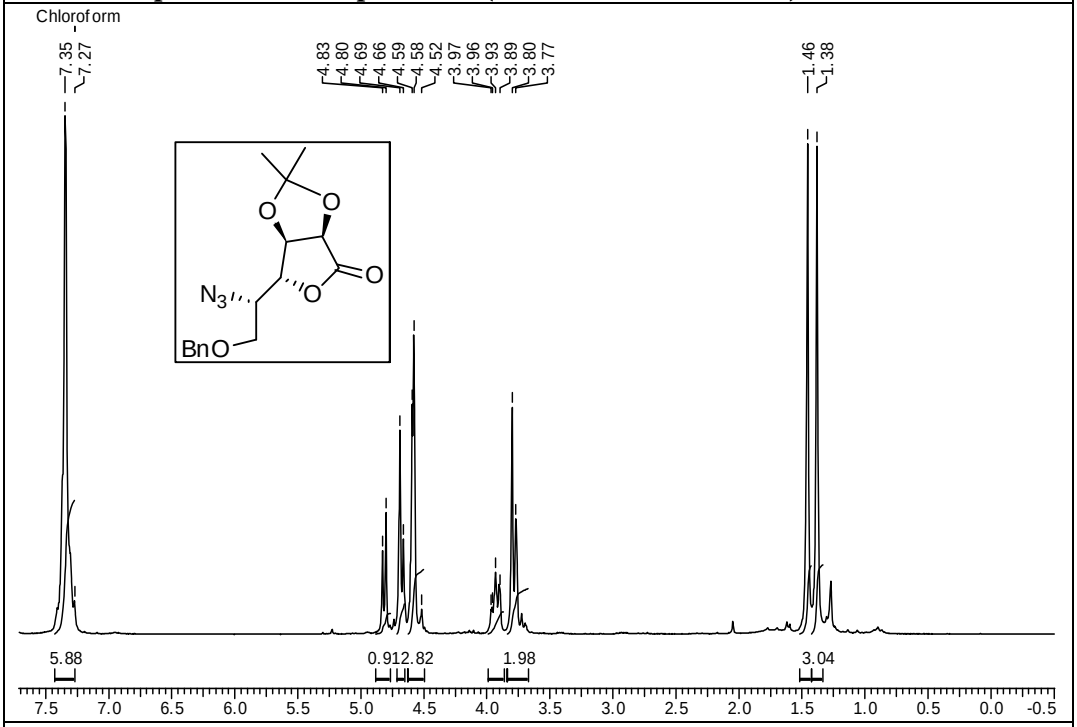
^{13}C NMR Spectrum of compound 17 ($CDCl_3$+CCl_4, 50 MHz)



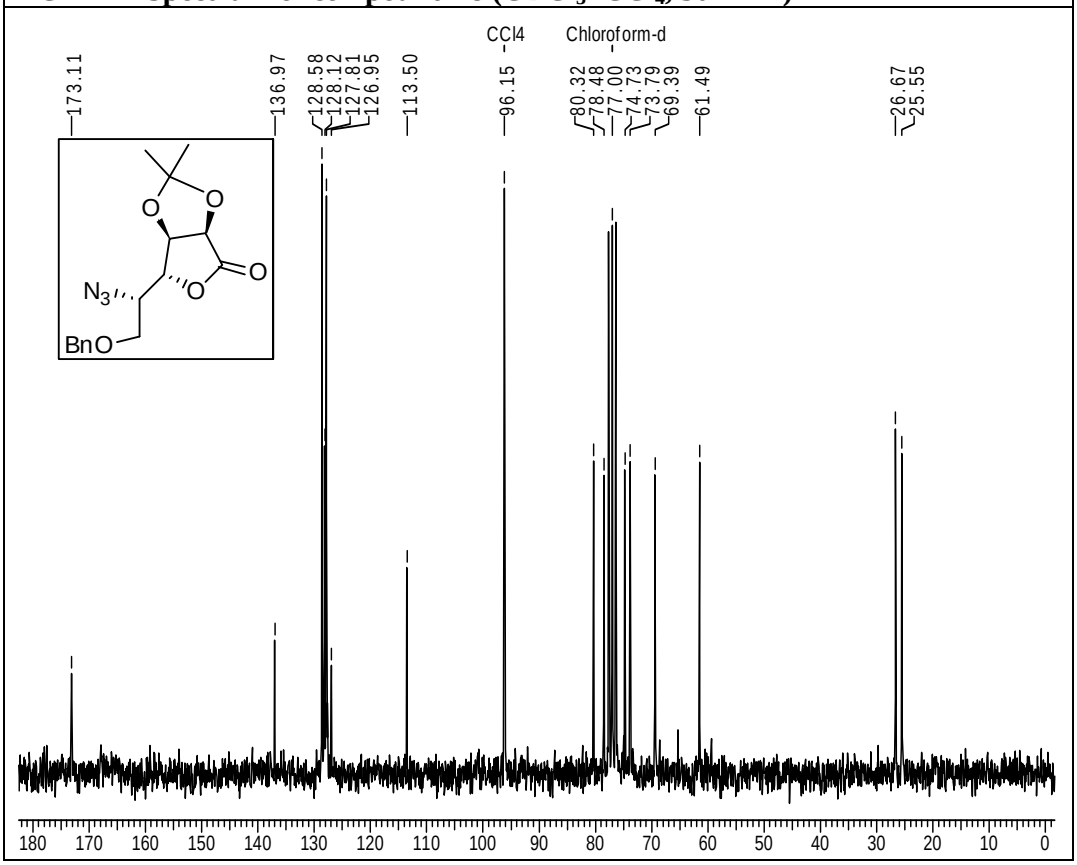
DEPT Spectrum of compound 17 ($CDCl_3$+CCl_4, 50 MHz)



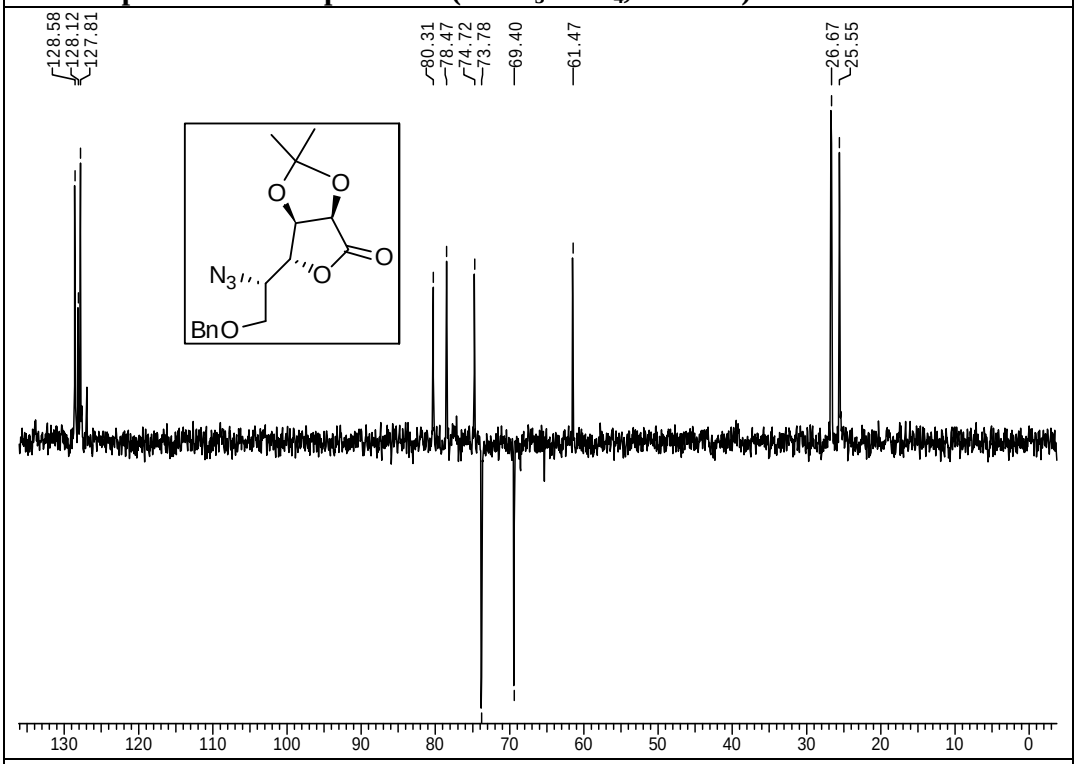
^{1}H NMR Spectrum of compound 18 ($CDCl_3$+CCl_4, 200 MHz)



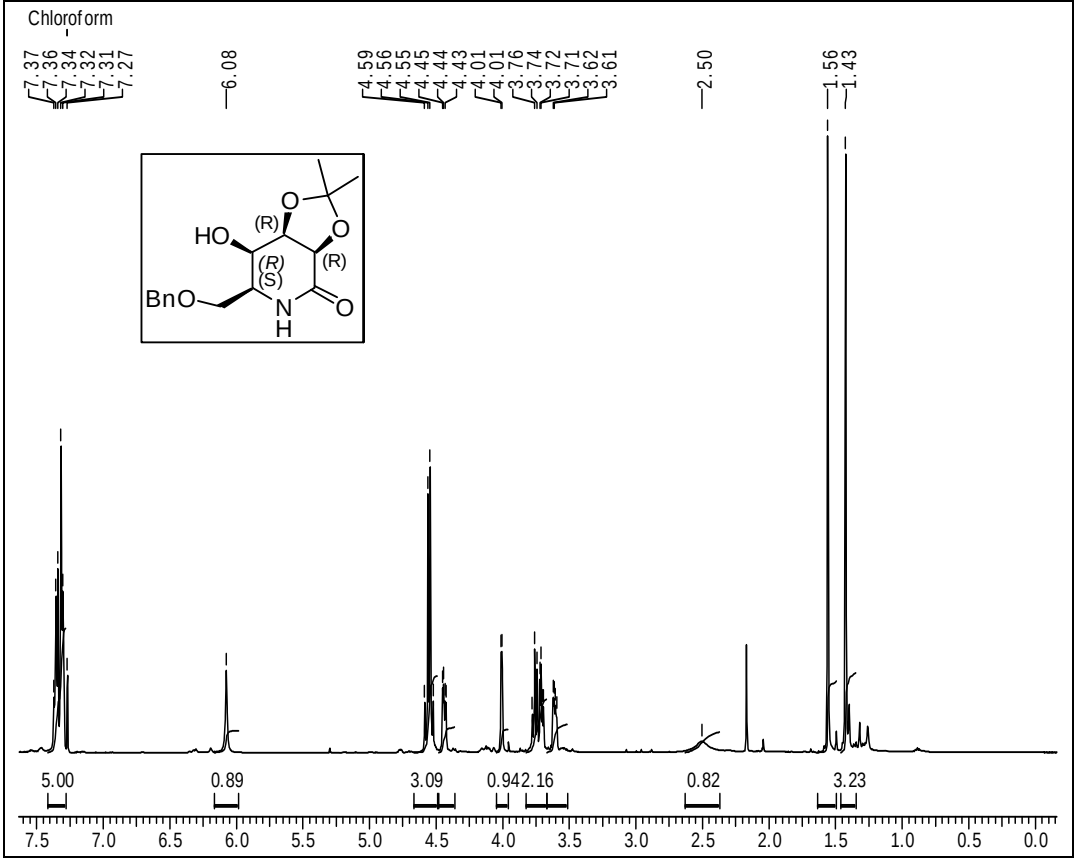
^{13}C NMR Spectrum of compound 18 ($CDCl_3$+CCl_4, 50 MHz)



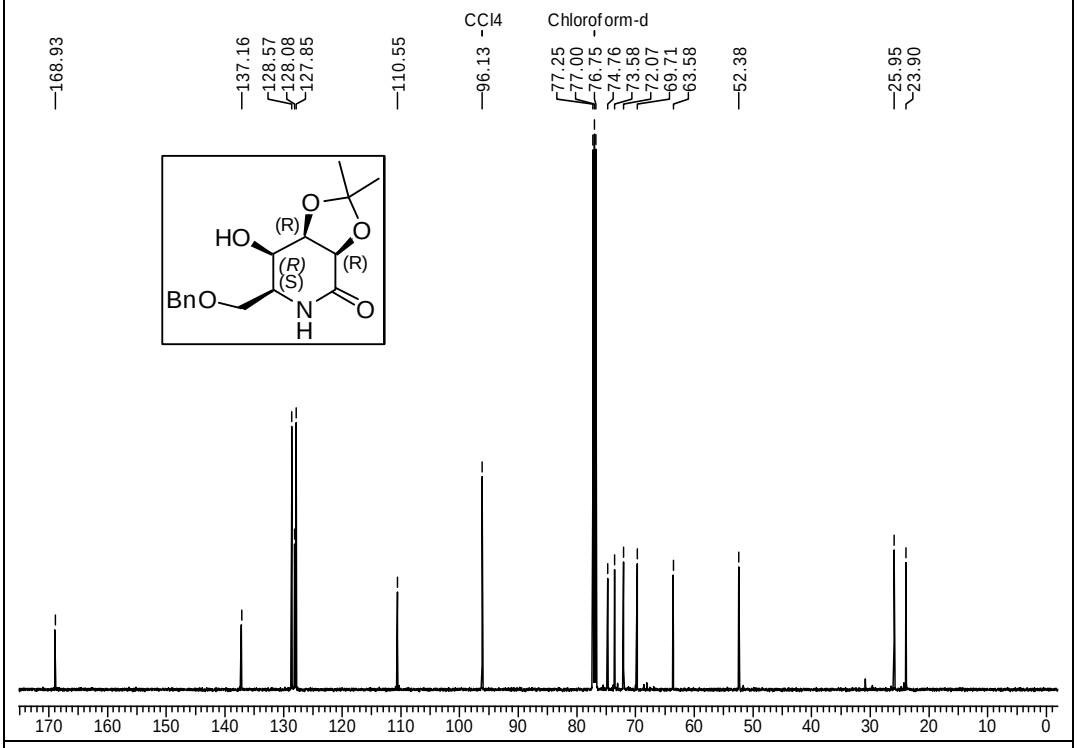
DEPT Spectrum of compound 18 ($CDCl_3$+CCl_4, 50 MHz)



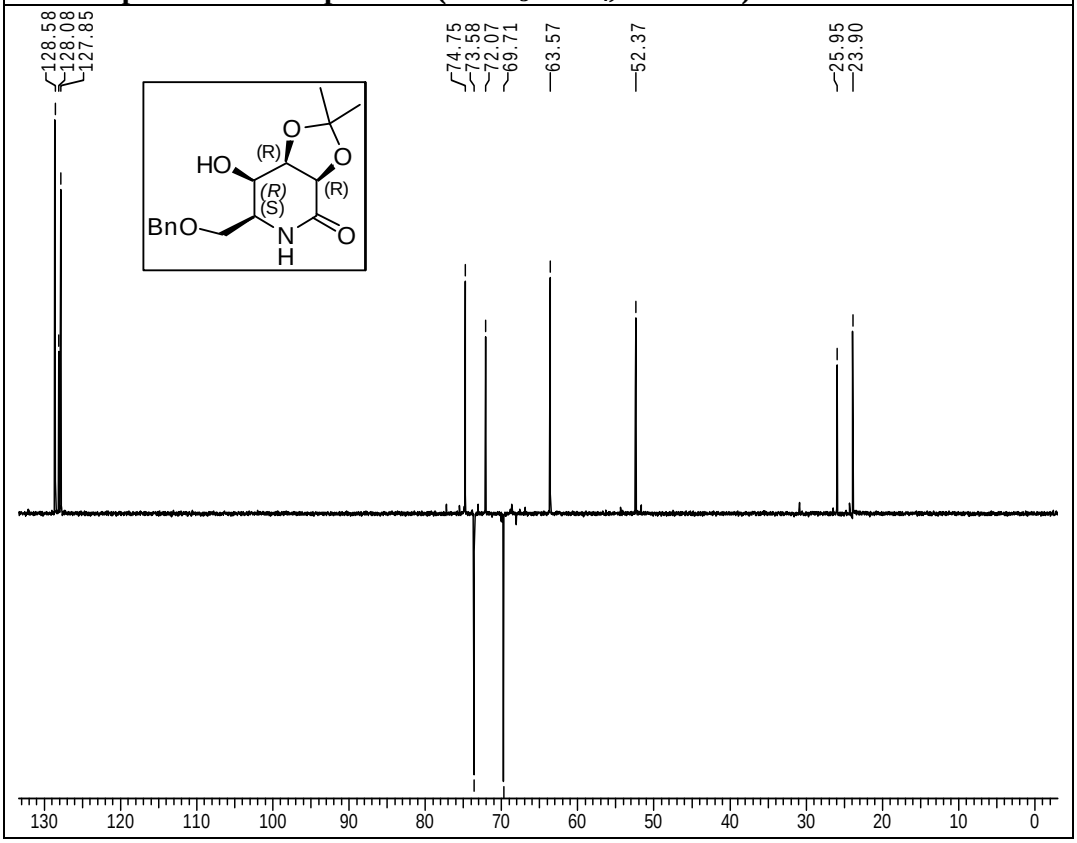
^{1}H NMR Spectrum of compound 3 ($CDCl_3$+CCl_4, 500 MHz)



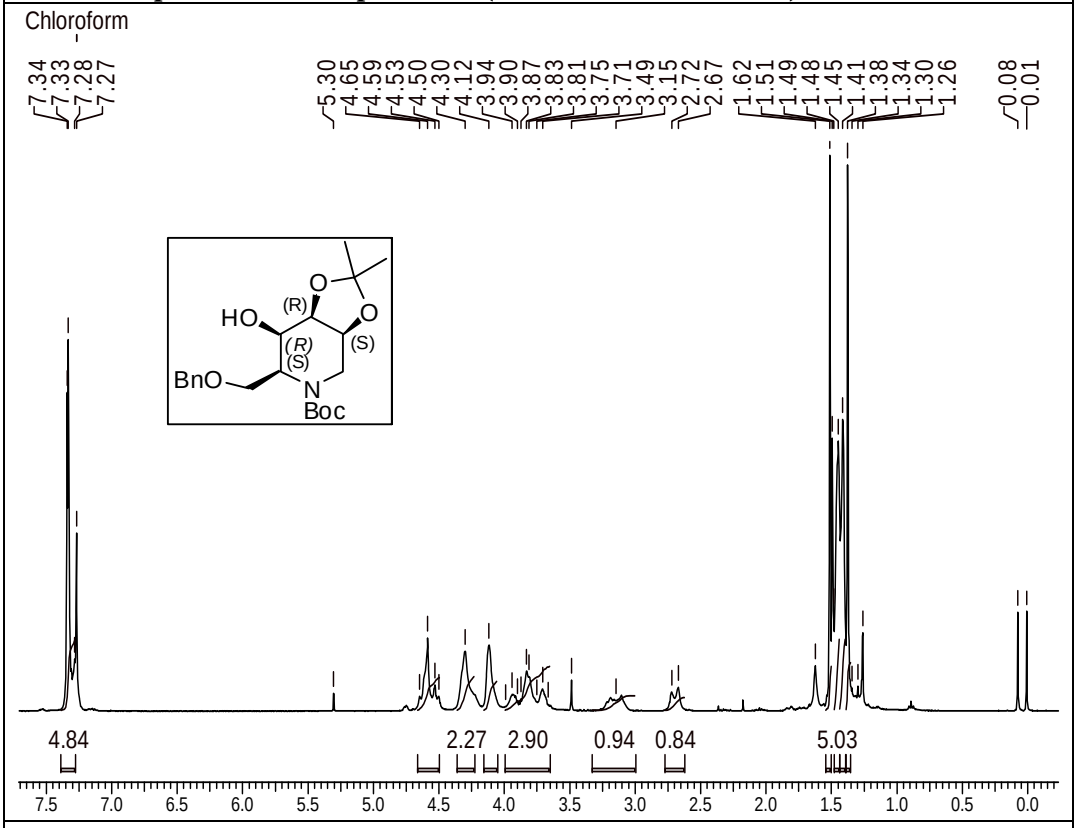
^{13}C NMR Spectrum of compound 3 ($CDCl_3$+CCl_4, 125 MHz)



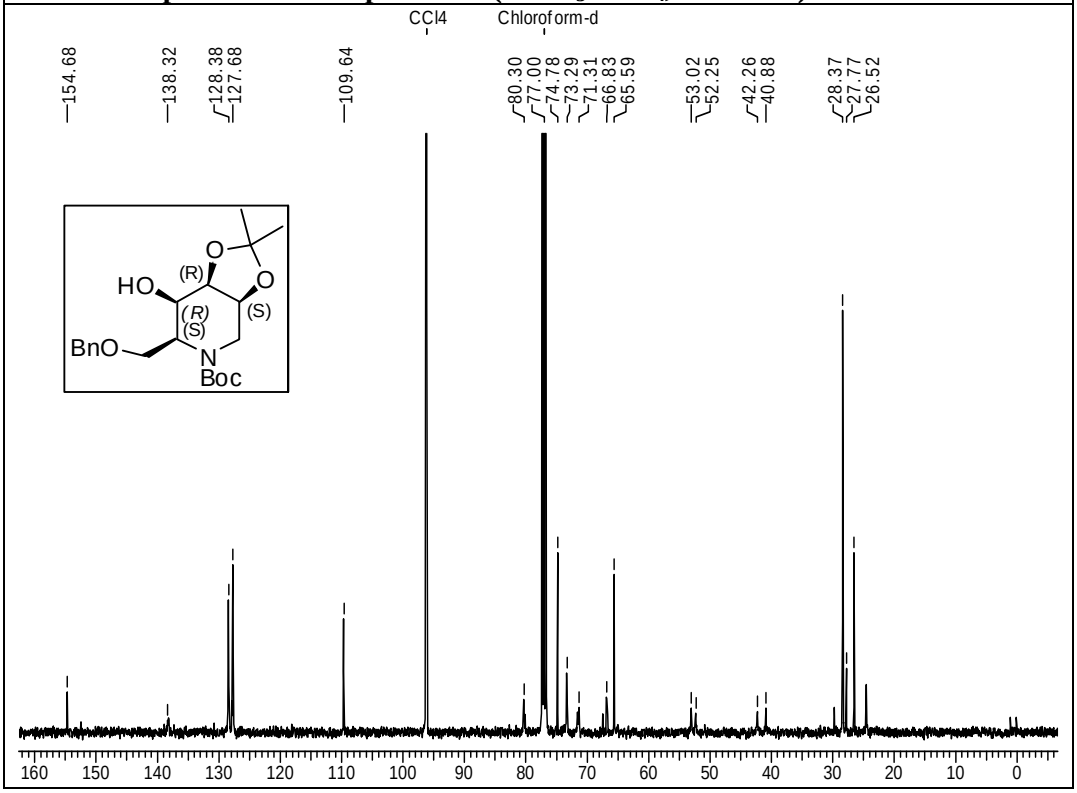
DEPT Spectrum of compound 3 ($CDCl_3$+CCl_4, 125 MHz)



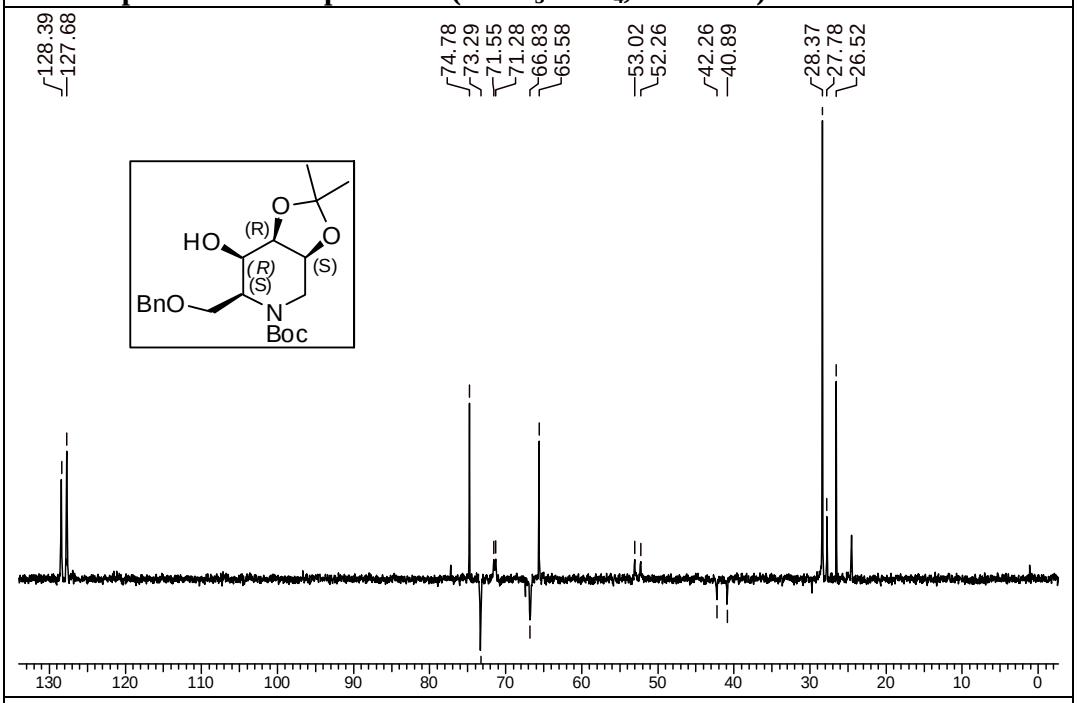
^{1}H NMR Spectrum of compound 20 ($CDCl_3$+CCl_4, 400 MHz)



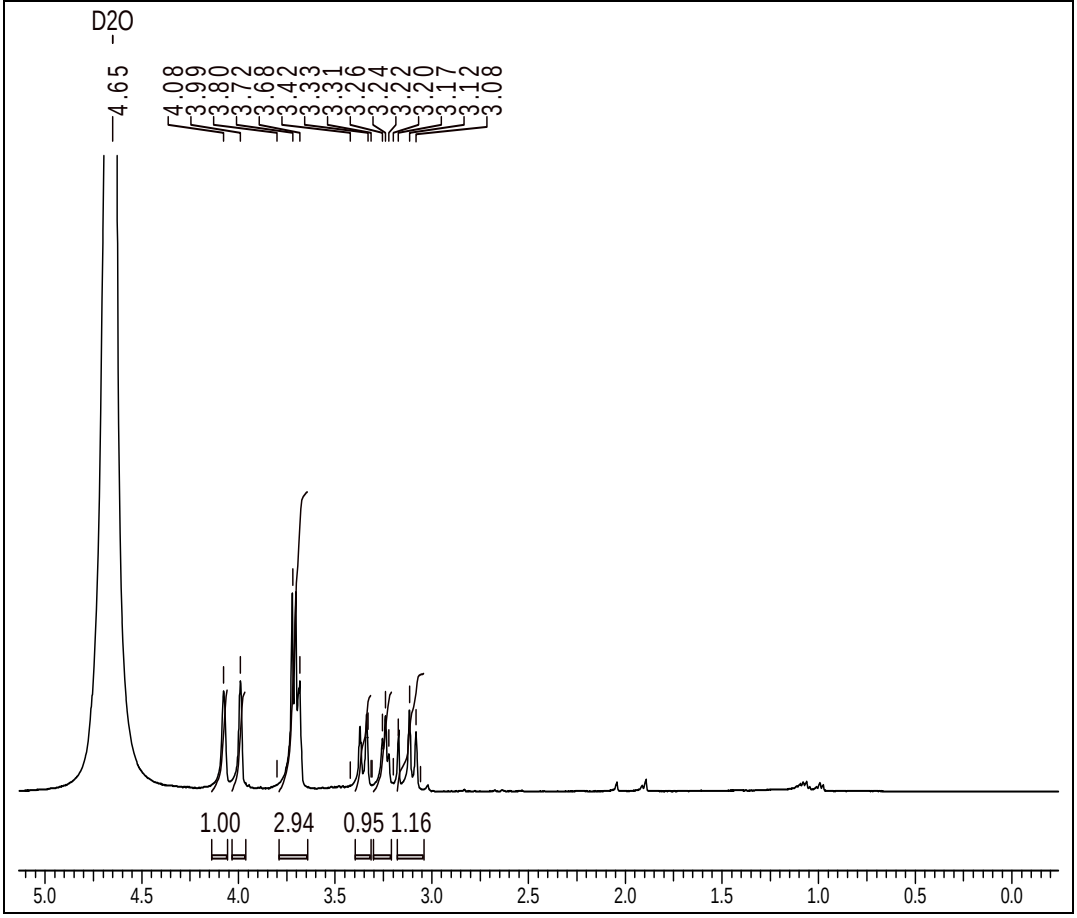
^{13}C NMR Spectrum of compound 20 ($CDCl_3$+CCl_4, 125 MHz)



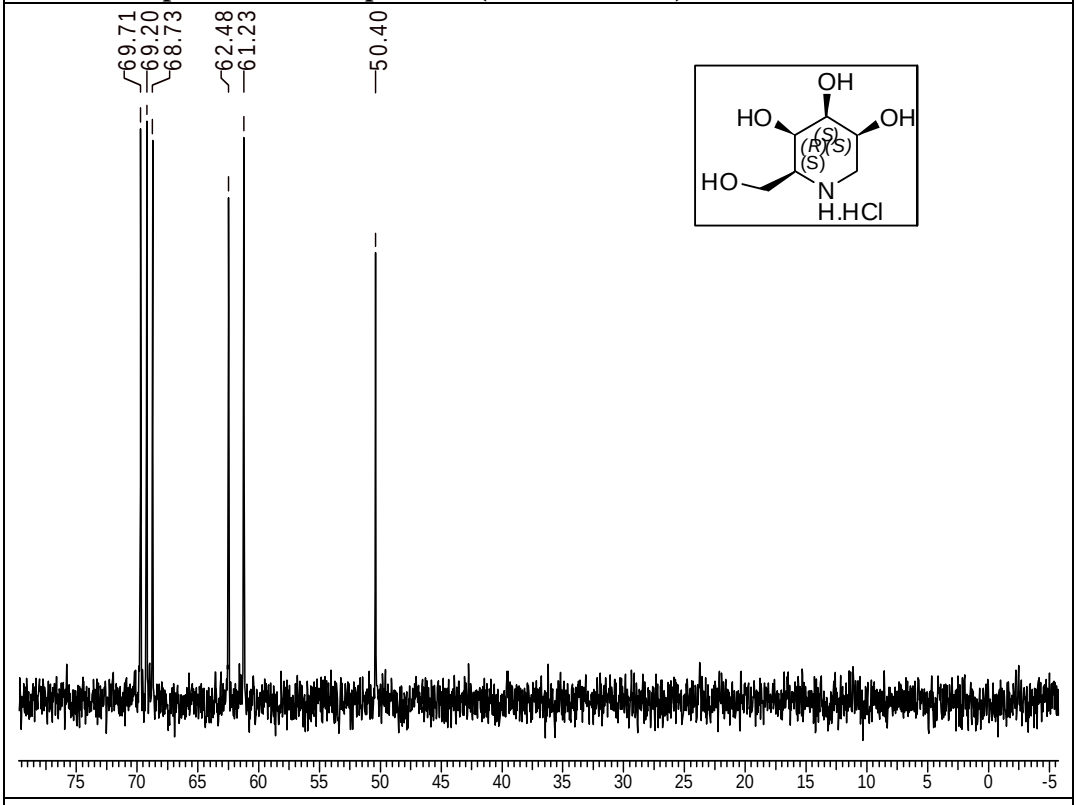
DEPT Spectrum of compound 20 ($CDCl_3$+CCl_4, 125 MHz)



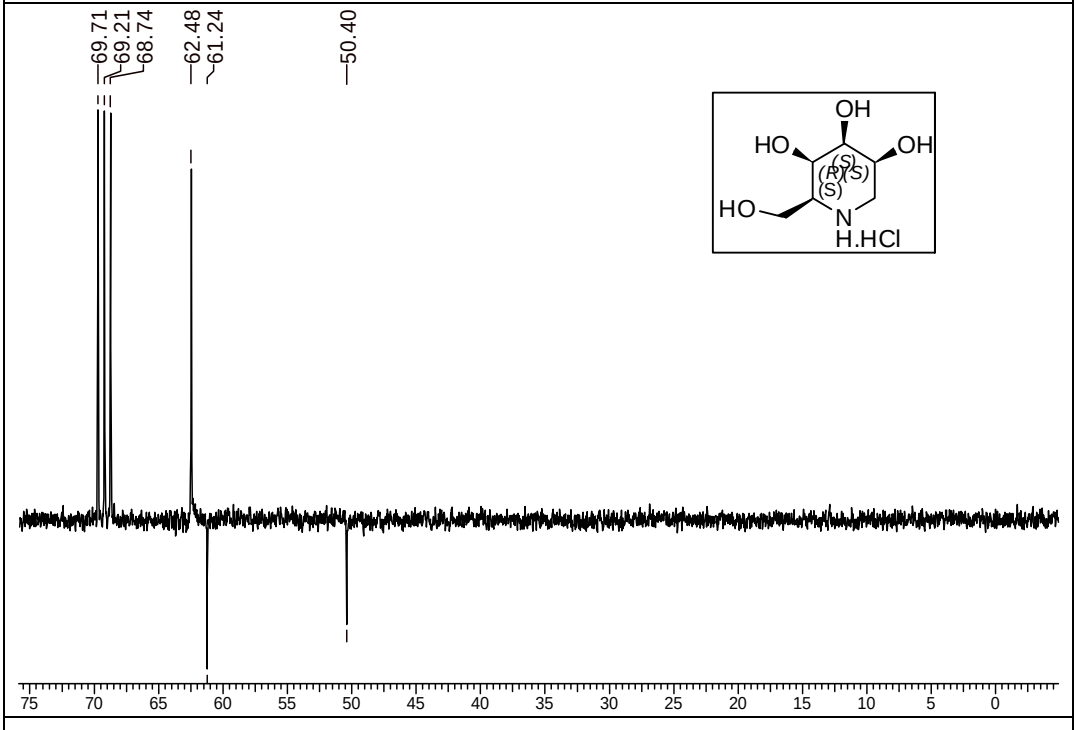
^{1}H NMR Spectrum of compound 2 (D_2O, 400 MHz)



^{13}C NMR Spectrum of compound 2 (D_2O, 100 MHz)



DEPT Spectrum of compound 2 (D_2O, 100 MHz)



3.3.5 References

1. Mash, E. A.; Nelson, K. A.; Deusen, S. V.; Hemperly, S. B.; *Org. Synth.* **1990***, 68,* 92

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5. Guaragna, A. D; Alonzo, D.; Paolella, C.; Palumbo, G. *Tetrahedron Lett.* **2009**, *50*, 2045.