SYNTHETIC STUDIES TOWARDS PIPECOLIC ACID, ITS 3-HYDROXY DERIVATIVES AND DEVELOPMENT OF SYNTHETIC METHODOLOGY

A THESIS
SUBMITTED TO THE
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IN
CHEMISTRY

BY
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UNDER THE GUIDANCE OF
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DECEMBER 2012

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Synthetic Studies towards Pipecolic acid, its 3-Hydroxy derivatives and development of synthetic methodology."** submitted by Mr. Lalit B. Khairnar was carried out by him under my supervision at National Chemical Laboratory, Pune. Material that has been obtained from other sources is duly acknowledged in this thesis.

Date: December 2012

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DECLARATION

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

Date: December, 2012 Lalit B. Khairnar

Division of Organic Chemistry

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Dedicated

To

My

Beloved Parents

Acknowledgements

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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/ninhydrine/PMA solutions.
6. In cases where chromatographic purification was done, silica gel (200-400 mesh) was used as the stationary phase or otherwise as stated.
7. IR spectra were recorded on **Perkin-Elmer Infrared Spectrophotometer Model 68B** or on **Perkin-Elmer 1615 FT Infrared Spectrophotometer.**
8. ^{1}H NMR and ^{13}C NMR were recorded on **Bruker AV-200** (50 MHz) or **Bruker AV-400** (100 MHz) or **Bruker DRX-500** (125 MHz). Figures in the parentheses refer to ^{13}C frequencies. Tetramethylsilane/residual $CHCl_3$ was used as the internal standard.
9. Mass spectra were recorded at an ionization energy of 70 eV on **Finnigan MAT-1020**, automated GC/MS instrument and on **API Q STARPULSAR** using electron spray ionization [(ESI), solvent medium: a mixture of water, acetonitrile and ammonium acetate] technique and mass values are expressed as *m/z*. HRMS were recorded on a micromass Q-T of micro with spray source (ESI^{+}) mode.
10. Starting materials were obtained from commercial sources or prepared using known procedures.
11. Microanalysis data were obtained using a **Carlo-Erba CHNS-O EA 1108** elemental analyzer within the limits of accuracy (± 0.4%).

Abbreviations

Ac	Acetyl
ACCN	1,10-Azobis(cyclohexanecarbonitrile)
acac	acetylacetonates
AIBN	2,2-Azobis(*iso*-butyronitrile)
Ar	Aryl
Aq.	Aqueous
9-BBN	9-Borabicyclo[3.3.1]nonane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BIPHEPHOS	6,6′-[(3,3′-Di-*tert*-butyl-5,5′-dimethoxy-1,1′-biphenyl-2,2′-diyl)bis(oxy)]bis(dibenzo[*d*,*f*][1,3,2]dioxaphosphepin)
BMS	Borane dimethyl sulfide
Bn	Benzyl
Boc	*tert*-Butoxy carbonyl
Bu	Butyl
s-Bu	*sec*-Butyl
t-Bu	*tert*-Butyl
CAN	Cerric ammonium nitrate
Cat.	Catalytic
Cbz	Carbobenzyloxy
CSA	Camphorsulfonic acid
m-CPBA	*meta*-Chloroperbenzoic acid
CSA	Camphor sulfonic acid
DBAD	Di-*tert*-butyl azodicarboxylate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DEPT	Distortionless Enhancement by Polarization Transfer
DET	Diethyl tartrate
$(DHQ)_2PHAL$	Hydroquinine 1,4-phthalazinediyl diether
$(DHQD)_2PHAL$	Hydroquinidine 1,4-phthalazinediyl diether

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

MOM	Methoxymethyl
MP	Melting point
Ms	Methanesulfonyl
MW	Molecular weight
NaHMDS	Sodium hexamethyl disilazide
NBS	*N*-bromosuccinimide
NCS	*N*-Chlorosuccinimide
NMO	*N*-Methyl morpholine oxide
NMR	Nuclear magnetic resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PCC	Pyridinium chlorocromate
PDC	Pyridinium dichromate
PMA	Phosphomolybdic acid
PMB	*para*-Methoxybenzyl
PTC	Phase transfer catalysis
PPTS	Pyridinium *para*-toluene sulfonate
PTSA	*para*-Toluene sulfonic acid
Py	Pyridine
rt	Room temperature
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TBSOTf	*tert*-Butyldimethylsilyl trifluoromethanesulfonate
TBTH	Tributyltinhydride
TEA	Triethylamine
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy, free radical, 2,2,6,6-Tetramethylpiperidine 1-oxyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride

THF	Tetrahydofuran
TLC	Thin layer chromatography
TMEDA	*N,N,N′,N′*-Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	Toluenesulfonyl

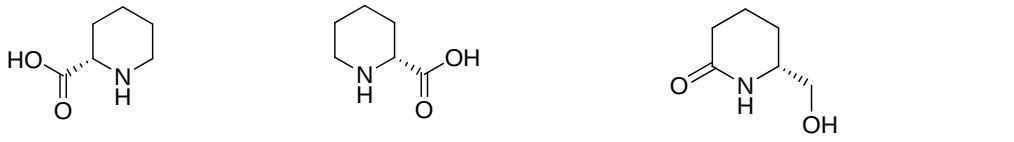
Abstract

The thesis entitled, **"Synthetic Studies towards Pipecolic acid, its 3-Hydroxy derivatives and development of synthetic methodology."** is divided into three chapters. Chapter one deals with the introduction and synthetic studies towards pipecolic acid. The second chapter deals with the introduction and synthesis of *trans*-(2*R*,3*R*)-3-hydroxypipecolic acid and (–)-swainsonine. The synthetic studies towards *cis*-3-hydroxypipecolic acid and the methodology for preparation of chiral allylic amines from chiral aziridine-2-alcohols are described in chapter three.

Chapter 1: Synthetic studies towards pipecolic acid.

Section 1: Introduction to pipecolic acid.

(*S*)-Pipecolic acid **1** (Figure 1) is a naturally occurring but non-proteinogenic amino acid.[1] Numerous natural or man-made derivatives of this amino acid have found widespread utility as a component of several biologically active secondary metabolites,[2] synthetic drug candidates,[3] as building blocks in organic synthesis,[4] as enzyme inhibitors,[5] and as an organocatalyst.[6] The synthesis of both forms of enantiopure pipecolic acid remains a centre of interest for chemists. Present section describes the biological activity and reported synthetic routes to pipecolic acid.

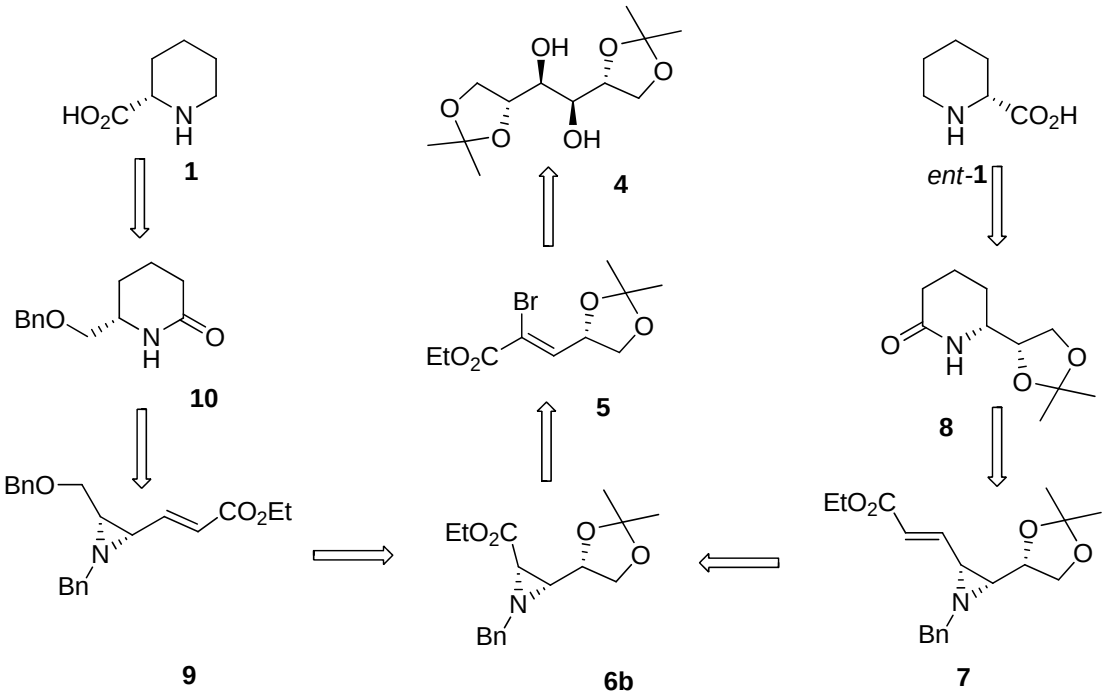


(*S*)-Pipecolic acid **1** (*R*)-Pipecolic acid *ent*-**1** (*R*)-6-(Hydroxymethyl)piperidin-2-one **2**

Figure 1

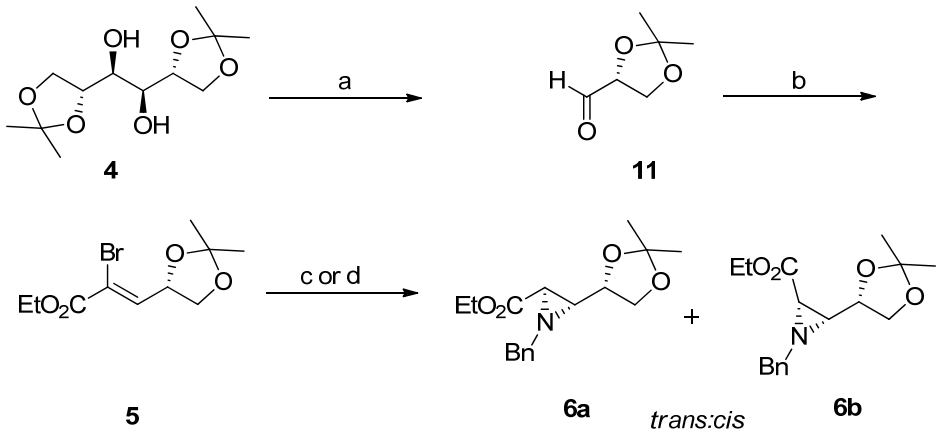
Section 2: Total synthesis of (*R*) and (*S*)-pipecolic acid

Enantiomerically pure aziridines have been considered to be prominent precursors in the synthesis of natural and unnatural amino compounds due to their inherent ability to undergo regio and chemo-selective nucleophilic ring opening reactions as well as cycloaddition pathways.[7] Although hydrogen is not characterized as a nucleophile, it serves the purpose of cleaving the aziridine ring. Catalytic hydrogenation of both activated and non-activated aziridines produces amines as useful building blocks for the synthesis of other biologically active products.[8]



Scheme 1: Retrosynthetic analysis for pipecolic acid **1**

Thus as shown in the retrosynthetic plan (Scheme 1), it was envisioned that aziridine-2-carboxylate **6b** can be exploited to build piperidine skeleton of pipecolic acid where as ester and acetonide functionality can serve as a handle to propagate on either side of aziridine to give convenient access to both antipodes.



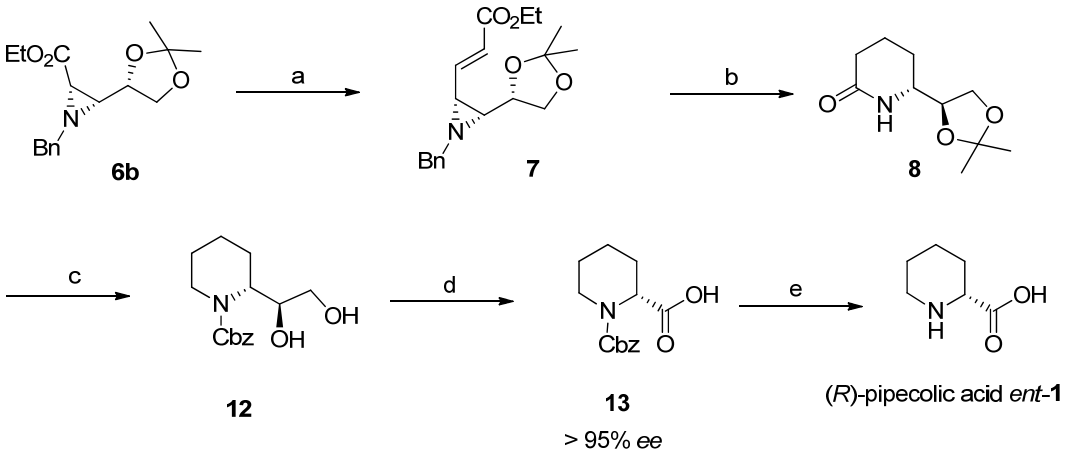
Scheme 2: ***Reagents and conditions:*** *a) $NaIO_4$, CH_2Cl_2, rt, 2h; b) $Ph_3PCBrCO_2Et$, CH_2Cl_2, rt, 84% over 2 steps; c) $BnNH_2$, Et_3N, EtOH, 0 °C to rt, 72h, 77%, trans:cis=1:0.9; d) $BnNH_2$, Et_3N, toluene, 0 °C to rt, 24h, 75%, trans:cis=9:1.*

Accordingly as shown in Scheme 2, D-mannitol diacetonide **4** was used to get mixture of *trans* and *cis*-aziridine-2-carboxylate[9,10] **6a** and **6b** which were separated by column chromatography and used for further synthetic elaborations.

Part 1: Exploitation of *cis* aziridine-2-carboxylate 6b towards synthesis of (*R*) and (*S*)-pipecolic acid

Total synthesis of (*R*)-pipecolic acid

The *cis*-aziridine-ester **6b** was converted to α,β-unsaturated ester **7** over two steps. Compound **7** was converted to (*R*)-pipecolic acid *ent*-**1** using palladium mediated one pot aziridine ring opening, hydrogenation and cyclisation as the key step with 95% *ee* (Scheme 3).

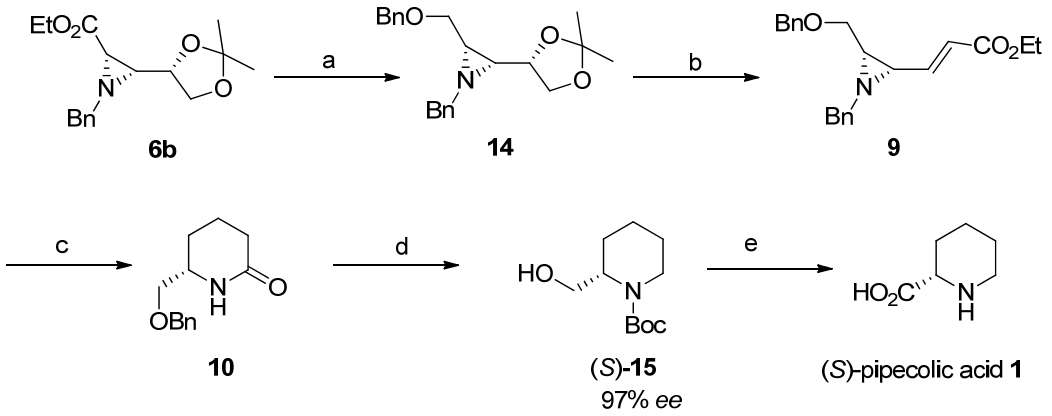


Scheme 3: ***Reagents and conditions:*** *a) 1) DIBAL-H (1M in toluene), CH_2Cl_2, -78˚C, 1h; 2) Ph_3PCHCO_2Et, cat. $PhCO_2H$, toluene, reflux, 5h, 82% over 2 steps; b) Pd/C (10%), HCO_2NH_4, MeOH, 60 ºC, 3h, 90%; c) 1) BH_3·DMS, THF, 0˚C to rt, 6h then 6N HCl, reflux, 3h; 2) Cbz-Cl, $NaHCO_3$, THF:H_2O (1:1), 75% over 2 steps; d) $RuCl_3$·$6H_2O$, $NaIO_4$, CH_3CN:CCl_4:H_2O (1:1:3), rt, 1h, 60%; e) H_2, Pd/C (10%), MeOH, 95%.*

Total synthesis of (*S*)-pipecolic acid

As mentioned in retrosynthetic analysis (Scheme 2), *cis*-aziridine-2-carboxylate **6b** which possesses hidden plane of symmetry if propagated as α,β-unsaturated ester on other side *viz.* towards the acetonide functionality followed by ring opening reaction would generate an enantiomer of newly formed amine functionality. Thus **6b** was converted to α,β-unsaturated ester **9**. Applying the similar protocol of aziridine ring cleavage under hydrogenation/hydrogenolysis condition using ammonium formate and 10% Pd/C, compound **9** underwent aziridine ring opening with concomitant olefin reduction,

debenzylation and cyclization in one pot to furnish δ-lactam **10** in 88% yield. Lactam **10** was converted to (*S*)-pipecolic acid over 4 steps with 97% *ee* (Scheme 4).

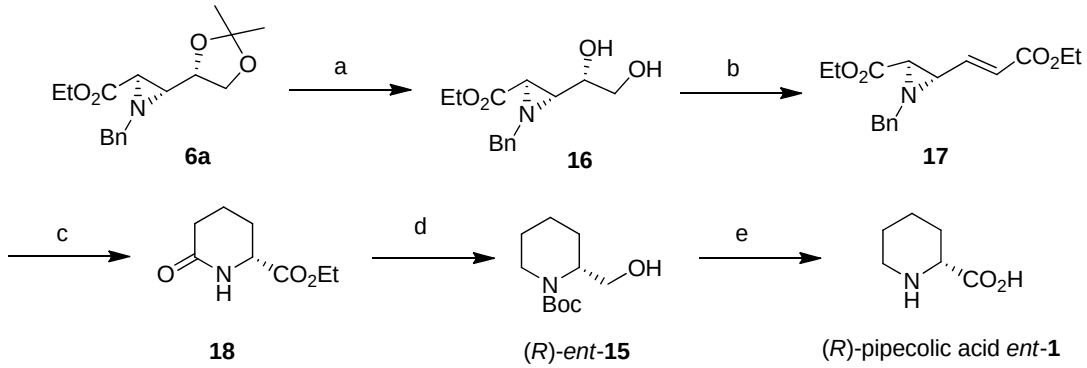


Scheme 4: ***Reagents and conditions:*** *a) 1) LAH, THF, 0° C, 1h, 90%; 2) BnBr, NaH, DMF, 95%; b) 1) PTSA, MeOH, 85%; 2) $NaIO_4$, acetone:water (2:1), rt, 0.25h; 3) Ph_3PCHCO_2Et, cat. $PhCO_2H$, toluene, reflux, 85% over 2 steps; c) Pd/C (10%), H_2, 3h, 88 %; d) 1) LAH, THF, 0 °C to rt, 6h; 2) Pd/C (10%), H_2, $(Boc)_2O$, MeOH, 75% over 2 steps; e) 1) TFA, CH_2Cl_2; 2) $KMnO_4$, 3N H_2SO_4, 69% over 2 steps.*

Part 2: Exploitation of *trans* aziridine-2-carboxylate 6a towards synthesis of pipecolic acid

Total synthesis of (*R*)-pipecolic acid and (*R*)-ethyl-6-oxopipecolate

This section describes the total synthesis of (*R*)-pipecolic acid *ent*-**1** as well as (*R*)-ethyl-6-oxopipecolate **18** which is a part of an important class of antitumor agents and is useful for the synthesis of pipecolic acid derivatives.[11]



Scheme 5: ***Reagents and conditions:*** *a) TMSOTf, CH_2Cl_2, 90%; b) 1) $NaIO_4$, acetone:water; 15 min; 2) $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0°C, 70% over 2 steps; c) (10%) Pd/C, HCO_2NH_4, MeOH, 60 °C, 85%; d) 1) LAH, THF; 2) $(Boc)_2O$, $NaHCO_3$,*

THF:H_2O, 70% over 2 steps; e) 1) TFA, CH_2Cl_2, 0 °C; 2) $KMnO_4$, 3N H_2SO_4, 69% over 2 steps.

Aziridine **6a** was subjected to acetonide deprotection, diol cleavage followed by Horner-Wadsworth-Emmons olefination to afford α,β-unsaturated aziridine-ester **17**. Applying the similar protocol of palladium mediated one-pot aziridine ring opening, hydrogenation and cyclisation as a key step (Scheme 5) gave efficient access to (*R*)-ethyl-6-oxopipecolate **18.** Pipecolate **18** was converted to (*R*)-*N*-Boc-2-piperidinemethanol *ent*-**15** over two steps. Finally compound (*R*)-*ent*-**15** was converted to (*R*)-pipecolic acid *ent*-**1** with known protocol.[12]

Chapter 2: Synthetic studies towards *trans*-(2*R*,3*R*)-3-hydroxypipecolic acid and (–)-swainsonine

Section 1: Introduction to *trans*-3-hydroxypipecolic acid

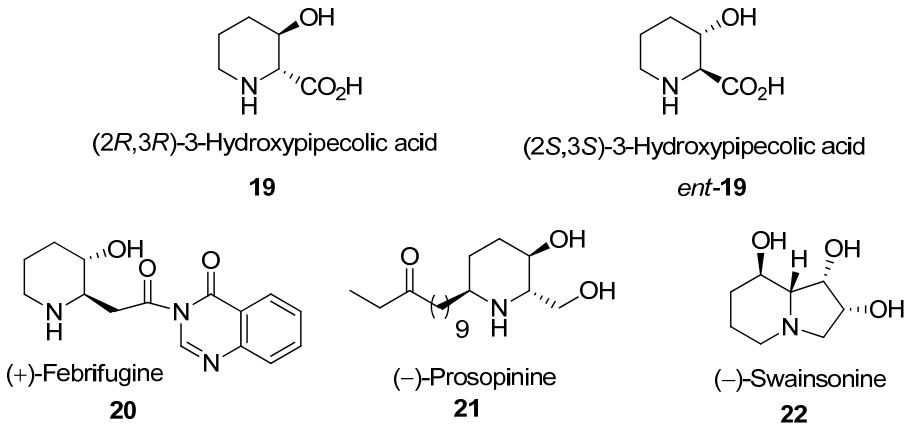
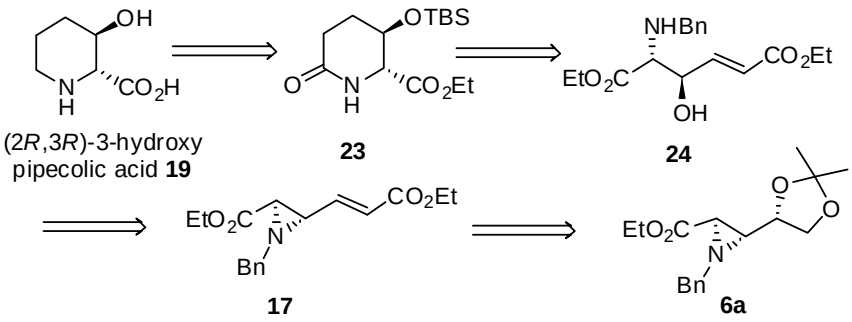


Figure 2

This section describes the biological activity and reported synthetic routes to *trans*-(2*R*,3*R*)-3-hydroxypipecolic acid **19**. The 3-hydroxypiperidine is one of the most privileged scaffolds found in a variety of natural products.[13] The t*rans*-3-hydroxy piperidine skeleton is constituent of many biologically active compounds like febrifugine **20**,[14] a potentially powerful antimalarial agent, its reduced derivative (–)-prosopinine **21** which exhibits analgesic, anaesthetic and antibiotic activities[15] and (–)-swaisonine **21**, which is found to be an effective inhibitor of both lysosomal α-mannosidase and mannosidase II. It also has antimetastastic, antitumor-proliferative and immunoregulating activity (Figure 2).[16]

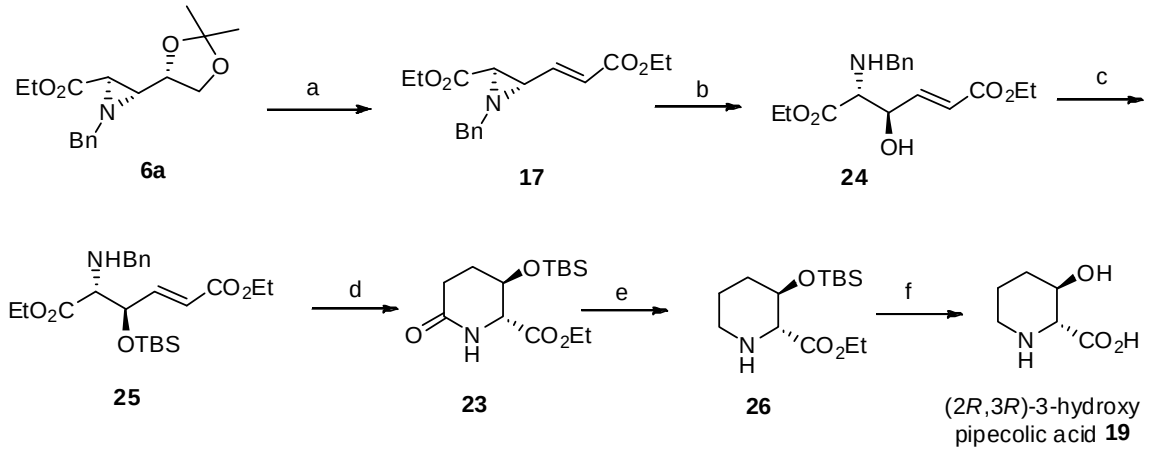
Section 2: Total synthesis of (2*R*,3*R*)-3-hydroxypipecolic acid

The present section describes the total synthesis of *trans*-(2*R*,3*R*)-3-hydroxypipecolic acid. Owing to their ring strain, aziridines are very prone to nucleophilic ring opening reactions with various nucleophiles with predictable chemo and regioselectivity to give either α or β-amino compounds. Taking account of this, as shown in Scheme 6, it was thought that *trans*-3-hydroxy skeleton of the acid **19** can be obtained from γ-hydroxy-δ-amino-α,β-conjugated ester **24** *via* amide **23.** Compound **24** can be easily obtained from α,β-unsaturated aziridine ester **17** by nucleophilic ring opening reaction using water as the nucleophile under acidic conditions.



Scheme 6. Retrosynthetic analysis for (2*R*,3*R*)-3-hydroxypipecolic acid

Thus as shown in Scheme 7, Compound **17** was treated with TFA (2 equiv.) in CH_3CN–H_2O (9:1) to undergo nucleophilic ring opening reaction using water as nucleophile to afford γ-hydroxy-δ-amino-α,β-conjugated ester **24** as the only isomer in 76% yield.[8g]



Scheme 7: ***Reagents and conditions:*** *(a) 1) TMSOTf, CH_2Cl_2, 0ºC, 90%; 2) $NaIO_4$, $(CH_3)_2CO$:H_2O (2:1); 3) NaH, $(EtO)_2POCH_2CO_2Et$, THF, 0ºC, 70% over 2 steps; (b)*

TFA, $CH_3CN:H_2O$ (9:1), 0 °C to rt, 76%; (c) TBSCl, Im, cat. DMAP, CH_2Cl_2, reflux,, 85%; (d) H_2, 10% $Pd(OH)_2/C$, NaOAc, EtOH, 85%; (e) BH_3·DMS, THF, 78%; (f) 6N HCl, 91%.

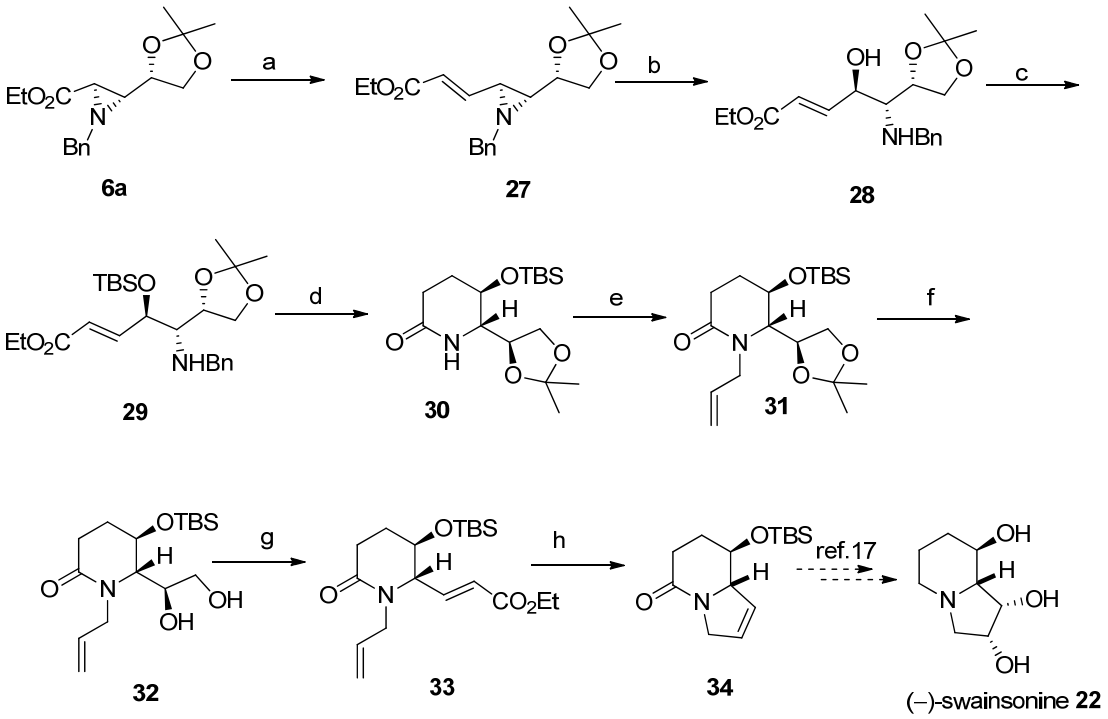
Protection of hydroxyl group as TBS ether **25** followed by hydrogenation furnished lactam **23** in 85% yield. Lactam **23** was easily converted to (2*R*,3*R)*-3-hydroxypipecolic acid **19** using two-step protocol of BH_3·DMS induced lactam reduction followed by acidic hydrolysis (Scheme 7).

Section 3: Introduction to (−)-swainsonine

Present section describes the introduction, biological activities and reported synthetic routes to the (−)-swainsonine **22** (Figure 2).

Section 4: Formal synthesis of (–)-swainsonine

This section describes the formal synthesis of (–)-swaisonine **22**. As shown in Scheme 8, its synthesis started from same *trans*-aziridine-2-carboxylate **6a** whose acetonide moiety was kept intact as a masked aldehyde while ester was propagated to give α,β-unsaturated ester compound **27**.



Scheme 8: ***Reagents and conditions:*** *(a) 1) DIBAL-H (1M in toluene), CH_2Cl_2,-78˚C, 1h; 2) $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0 ˚C, 2h, 75% over 2 steps; (b) TFA, $CH_3CN:H_2O$ (9:1), 0 °C to rt., 80%; (c) TBSCl, Im, cat. DMAP, CH_2Cl_2, reflux, 90%;*

(d) H_2, 10% $Pd(OH)_2/C$, MeOH, 92%; (e) NaH, allyl bromide, cat. TBAI, DMF, 85%; (f) Aq. 80% AcOH, 80 °C, 75%; (g) 1) $NaIO_4$, acetone:water; 2) Ph_3PCHCO_2Et, CH_2Cl_2, 75% over 2 steps; (h) Grubbs' 2nd gen. catalyst, CH_2Cl_2, reflux, 80%.

Following the reaction sequence which utilizes aziridine ring opening under acidic condition and ring closing metathesis reaction as key steps gave access to key intermediate lactam **34** which can be further elaborated to (–)-swainsonine according to the reported procedure.[17]

Chapter 3: Synthetic studies towards *cis*-3-hydroxypipecolic acid

Section 1: Introduction to *cis*-3-hydroxypipecolic acid

This section describes the biological activity and reported synthetic routes to both enantiomers of *cis*-3-hydroxypipecolic acid. Similar to *trans*-3-hydroxypipecolic acid, its c*is* isomer (**35**/*ent*-**35**) is also constituent of many biologically active compounds like antitumor, antibiotic drug tetrazomine[18] **36** and antimalarial agent iso-febrifugine[19] **37** (Figure 3).

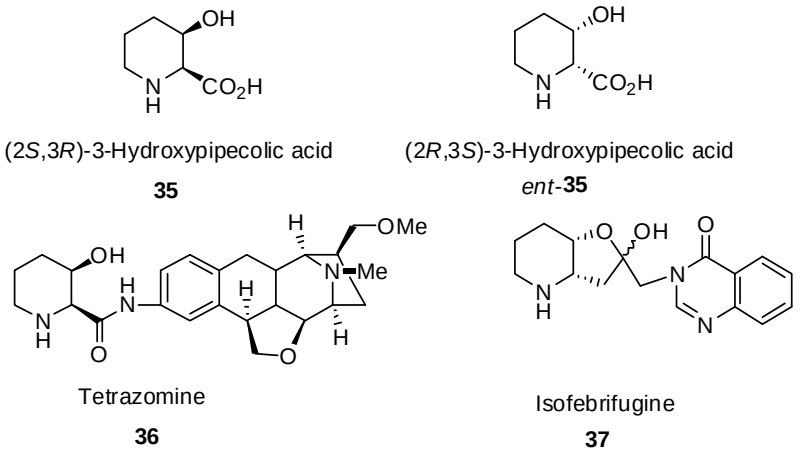
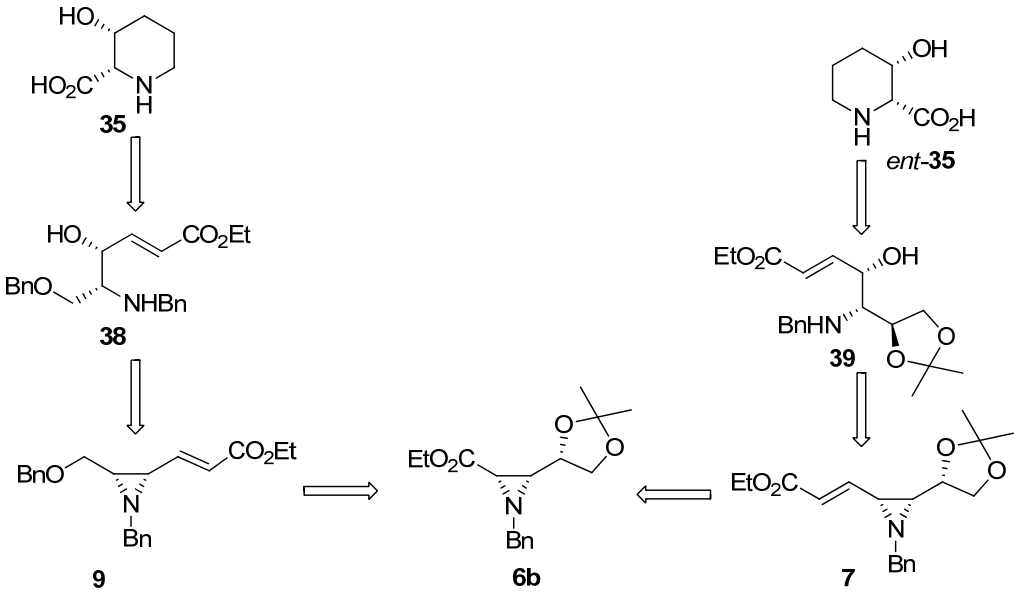


Figure 3

Section 2: Formal synthesis of both enantiomers of *cis*-3-hydroxypipecolic acid.

It was envisioned that *cis*-aziridine-2-caboxylate **4b** has hidden plane of symmetry where proper synthetic manipulation can give access to both enantiomers of *cis*-3-hydroxypipecolic acid (Scheme 9). The required *cis*-aziridine-2-caboxylate **6b** was prepared from D-mannitol diacetonide **4** as reported earlier (Scheme 2).[9] This *cis*-

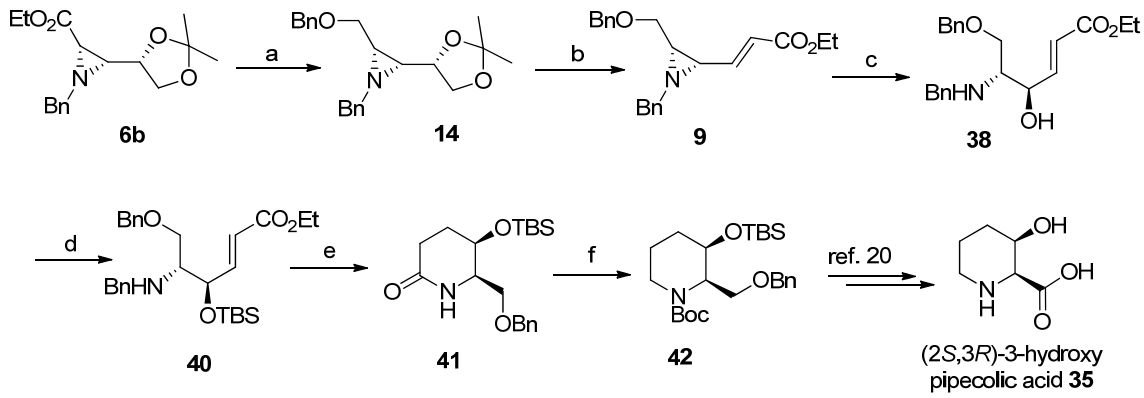
aziridine-caboxylate **6b** was used as the common synthetic precursor for synthesis of both enantiomers of *cis*-3-hydroxypipecolic acid



Scheme 9: Retrosynthetic analysis of *cis*-3-hydroxypipecolic acid

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

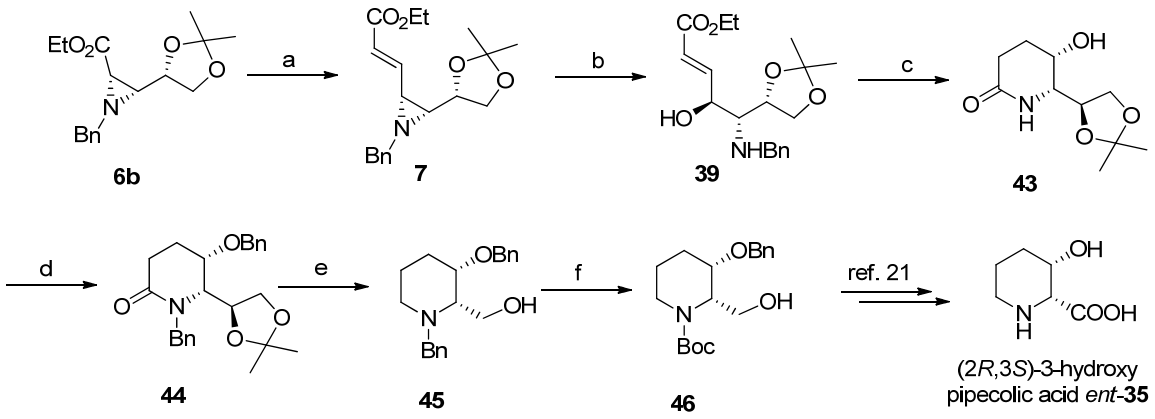
Our synthetic efforts towards the formal synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid using *cis* aziridine-2-caboxylate **6b** are described herein. As mentioned in the Scheme 10, compound **6b** was converted to compound **9** which underwent stereoselective aziridine ring opening under acidic conditions by water as nucleophile forming vicinal amino alcohol **38.** Compound **38** on TBS protection followed by hydrogenation gave δ-lactam **41**. Reduction of this lactam to amine followed by protection as Boc derivative gave intermediate **42** which is well reported in literature.[20]



Scheme 10: ***Reagents and conditions:*** *(a) 1) LAH, THF, 0 °C, 1h, 90%; 2) BnBr, NaH, DMF, 95%; (b) 1) PTSA, CH_3OH, 85%; 2) $NaIO_4$, $(CH_3)_2CO$:H_2O (2:1); 3) Ph_3PCHCO_2Et, cat. $PhCO_2H$, toluene, reflux, 85% (over 2 steps); (c) TFA, CH_3CN:H_2O (9:1), 85%; (d) TBSCl, Im, cat. DMAP, CH_2Cl_2, reflux, 90%; (e) H_2, 10% $Pd(OH)_2$/C, EtOH, 88%; (f) 1) BH_3·DMS, THF; 2) $(Boc)_2O$, CH_2Cl_2, Et_3N, 80% over 2 steps.*

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

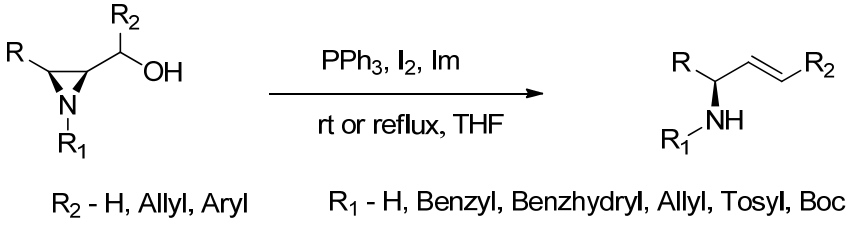
This section describes the formal synthesis of another enantiomer of *cis* 3-hydroxypipecolic acid *i.e.* (2*R*,3S)-3-hydroxypipecolic acid *ent*-**35**. Thus as shown in Scheme 11, the synthesis started with common synthetic precursor c*is*-aziridine-2-ester **6b** which on the two-carbon Wittig homologation with Ph_3PCHCO_2Et followed by nucleophilic aziridine ring opening reaction gave access to vicinal amino alcohol **39.** Compound **39** when subjected to transfer hydrogenation afforded 3-hydroxy substituted *δ*-lactam **43.** The lactam **43** was protected as its *N*-*O*-benzyl derivative **44** which on further manipulations furnished compound **46** which constitutes a formal synthesis of (2*R*,3*S*)-3-hydroxypipecolic acid *ent*-**35**.[21]



Scheme 11: ***Reagents and conditions:*** *(a) 1) DIBAL-H, CH_2Cl_2, -78 °C; 2) Ph_3PCHCO_2Et, cat. $PhCO_2H$, toluene, reflux, 82%, (over 2 steps); (b) TFA, $CH_3CN:H_2O$, (9:1), 75%; (c) 10% Pd/C, HCO_2NH_4, MeOH, 60 °C, 90%; (d) BnBr, NaH, cat. TBAI, DMF, 85%; (e) 1) 80% aq. AcOH; 2) $NaIO_4$, $(CH_3)_2CO:H_2O$, (2:1); 3) $BH_3 \cdot DMS$, THF, 65%, over 3 steps; (f) 1) H_2, 10 % $Pd(OH)_2/C$, EtOH; 2) $(Boc)_2O$, Et_3N, CH_2Cl_2, 80% over 2 steps.*

Section 3: Methodology for preparation of chiral allyl amines from chiral aziridine-2-alcohols

The present section describes an efficient, practical methodology for the preparation of chiral allyl amines from chiral aziridine-2-alcohols. Chiral allylic amines are versatile building blocks for the synthesis of α and β-amino acids, alkaloids and carbohydrate derivatives.[22] Chiral aziridine-2-alcohol represents an attractive tool for synthesis of chiral allyl amines because of its easy accessibility in chiral form and the disposition towards ring opening due to ring strain. Various chiral aziridines were converted to chiral allylic amines using PPh_3/I_2/imidazole protocol (Scheme 12). This methodology works well with activated, non-activated and NH-aziridines.



Scheme 12

Conclusion: Enantiomerically pure aziridine-2-carboxylates were successfully employed as chiral synthons for the synthesis of both the enantiomers of pipecolic acid, *cis*-3-hydroxypipecolic acid as well as for *trans*-(2*R*,3*R*)-3-hyroxypipecolic acid and (–)-swainsonine using nucleophilic aziridine ring opening as key reaction. An efficient, practical methodology for the preparation of chiral allyl amines from chiral aziridine-2-alcohols using PPh_3/I_2/imidazole was developed.

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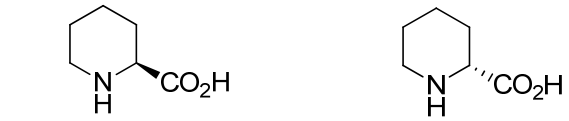
Chapter 1: Synthetic studies toward pipecolic acid

Section 1: Introduction to pipecolic acid

1.1 Introduction to pipecolic acid

1.1.1 Pipecolic acid: Introduction and biosynthesis

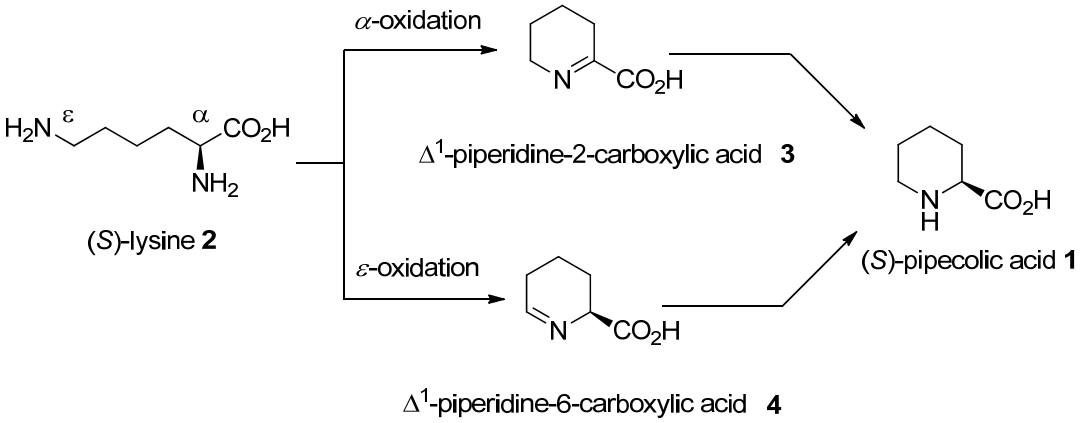
(*S*)-Pipecolic acid **1** (Figure 1), a cyclic non-proteogenic α-amino acid was first identified in 1952 as a constituent of leguminous plants.[1] It is now recognized as a universal lysine derived entity present in plants, animals and microorganisms.[2]



(*S*)-Pipecolic acid **1** *ent*-**1**

Figure 1

Over the years, many studies have sought to establish the biosynthetic routes to **1**. Different metabolic pathways (with different proposed mechanisms)[3] are involved in the formation of **1** (Scheme 1). Chemically speaking, these basic routes are distinguishable at the loss of the amino group of lysine **2**.



Scheme 1: Biosynthesis of pipecolic acid

The presence of piperidine carboxylic acids **3** and **4**, has been demonstrated by many feeding experiments.[1] The reverse pathways converting (*S*)-pipecolic acid **1** into **3**[4] or (*S*)-lysine **2**[5] are also known. (*R*)-Pipecolic acid *ent*-**1** was also reported from (*R*)-lysine **2** whereas (*S*)-**l** can be biosynthesized from both (*S*)- and (*R*)-lysine **2**.[6]

1.1.2 Pipecolic acid: Importance

In natural substances, **1** (Figure 1) is a key element in molecules as diverse as α-(+)-conhydrine **5** (a poisonous alkaloid found in poison hemlock),[7] 4-hydroxypipecolic acid **6** (constituent of the synthetic HIV protease inhibitor palinavir)[8] or lentiginosine **7** and swainsonine **8** (small indolizidine alkaloids known for their glycosidase-inhibiting properties) (Figure 2). Pipecolic acid, as well as other amino acids showing a 6-membered ring have been used in peptide chemistry as analogues of L-proline. Introduction of these compounds into peptides induces a *β*-turn, and this modification of the secondary structure can result in an advantageous change of the biological activity.[9] Thus pipecolic acid has been incorporated into a variety of bioactive peptides including vasopressin, oxytocin and angiotensin II.[10] It is a component of a wide range of pharmacologically active compounds such as the rapamycin[11] **9** and FK506/tacrolimus[12] **10** (a polyketide/non-ribosomal peptide hybrid clinically approved as immunosuppressant), the potent antitumour antibiotic sandramycin[13] **11**, the local anesthetic drugs like bupivacaine **12** and ropivacaine **13** (Figure 3),[14] the anti-human immunodeficiency virus (HIV) cyclodepsipeptide homophymia A **14**,[15] and the anticancer agent VX710[16] **15**.

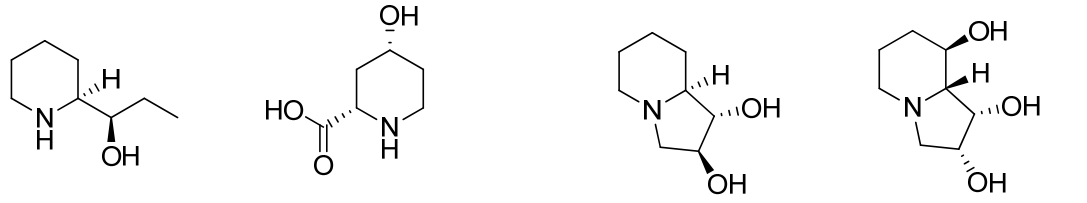


Figure 2: Pipecolic acid and its derivatives in natural products

It is also a precursor to numerous compounds such as antifungal agents,[17] local anaesthetics or potential enzyme inhibitors,[18] potent thrombin inhibitors,[19] the constrained lysine analogues,[20] the potential antirheumatoid arthritis drugs,[21] and the oxytocin antagonists L-366682 and L-366948.[22] It plays a central role in lysine metabolism, particularly in CNS tissue, and derivatives of pipecolic acid have been developed as inhibitors of the enzyme L-pipecolate oxidase which may offer potential as anticonvulsant drugs.[23] Simi-

larly (*R*)-pipecolic acid *ent*-**1** is a constituent of the histone deacetylase (HDAC) inhibitors which hold promise as anticancer drugs.[24] Pipecolic acid also started getting attention as an organo-catalyst.[25] The widespread use of pipecolic acid

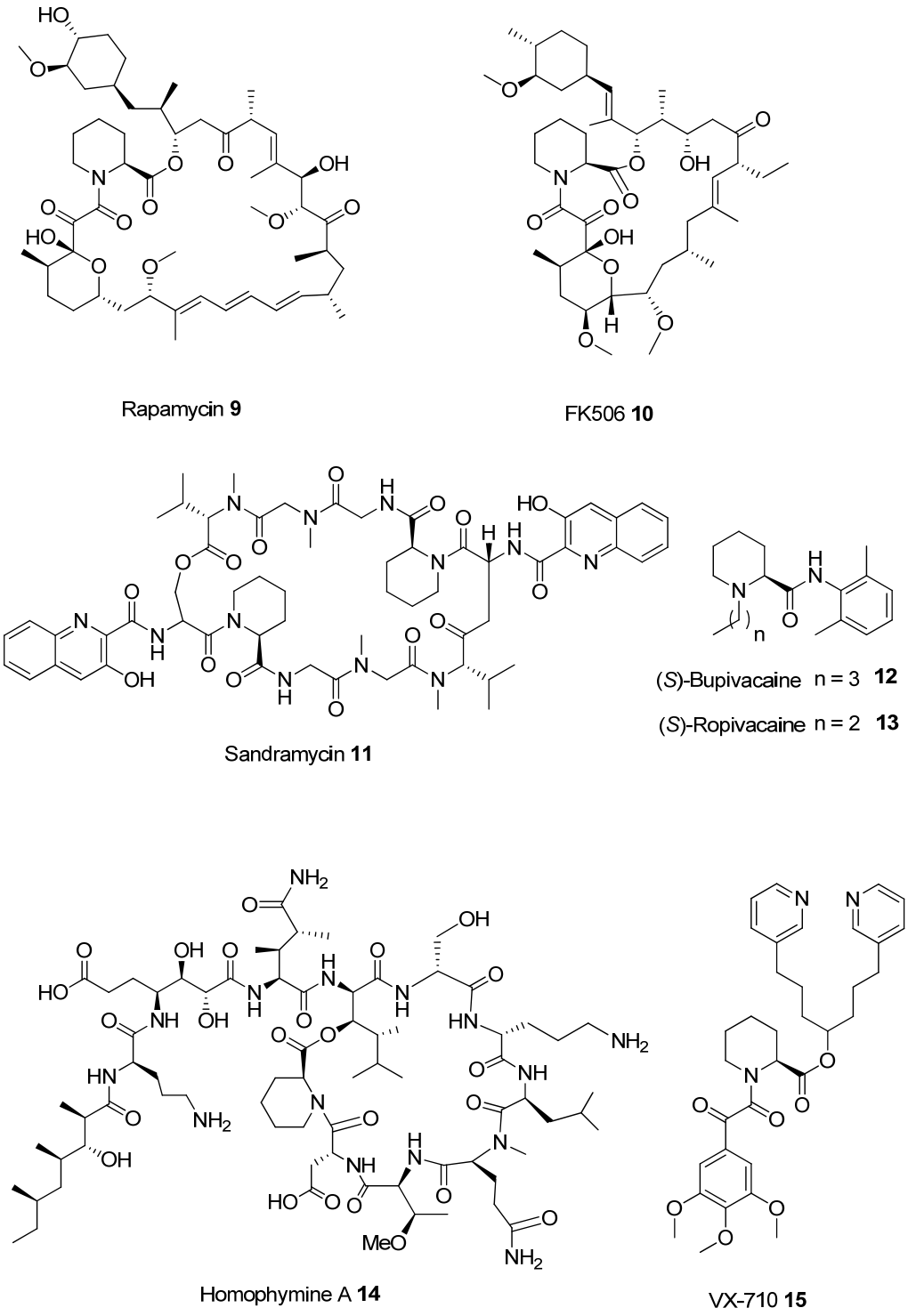


Figure 3: Pharmacologically active compounds having pipecolic acid as a key element.

and its derivatives in therapeutic chemistry and the fact that these compounds can be viewed as intermediates for the synthesis of alkaloids has boosted research towards preparations of these target molecules in optically pure form. Although pipecolic acid is available commercially, high cost associated with its enantiomerically pure form has prompted organic chemists to develop a convenient access to both enantiomers of pipecolic acid.

1.1.3 Literature review

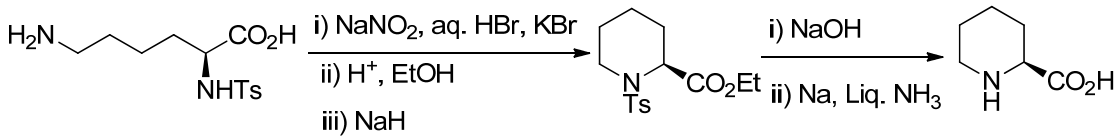
The chemical synthesis of pipecolic acid has been a subject of great interest. Powerful methods of asymmetric piperidine synthesis have been developed toward this aim and have been reviewed.[26]

(a) Synthesis from (*S*)-lysine

Lysine is an obvious synthetic precursor for pipecolic acid and many syntheses have been reported using **2** (or protected (*S*)-**2**) to access **1** in a somewhat biomimetic way.

Fujii's approach

Fujii's approach[27] was based on diazotation of a protected form of **3** with overall yield of 15%. The enantiomeric excess of the produced **1** is good, based on optical rotation (Scheme 2).

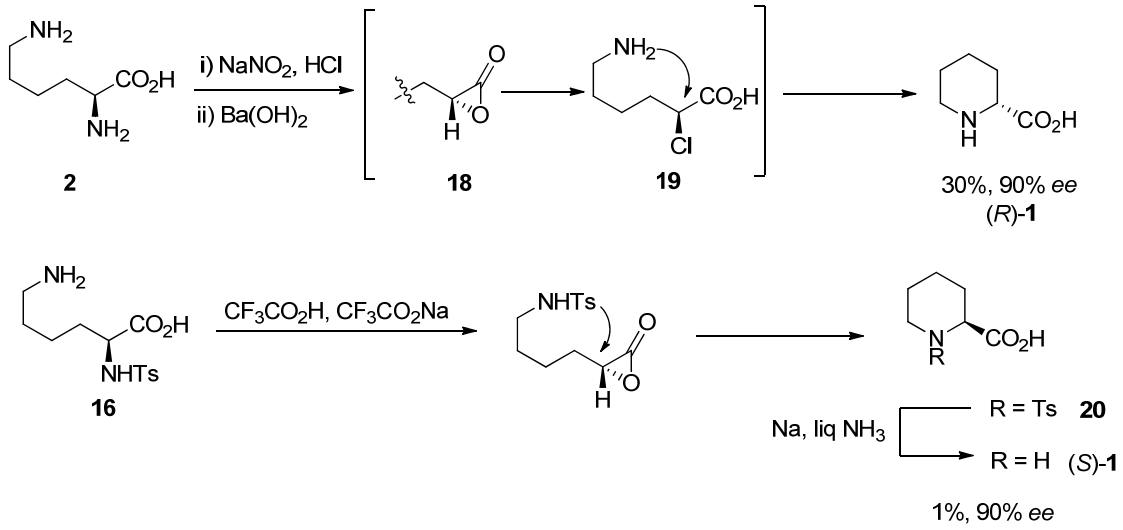


16 **17** (*S*)-**1**

Scheme 2

Yamada's approach

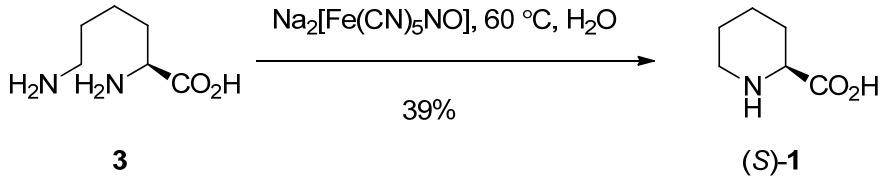
Yamada's approach[28] utilizes sodium nitrite–hydrochloric acid as a deaminating agent of (S)-lysine, followed by barium or sodium hydroxide treatment to afford (*R*)-pipecolic acid **1** with more than 90% optical purity and satisfactory overall yield. Net retention of configuration was explained by the formation of lactonic intermediate **18** followed by halogeno-acid **19**. On the other hand, (*S*)-lysine could be converted directly into natural (*S*)-pipecolic acid **1** starting from ε-tosyl-(*S*)-lysine **16** but in very low yield (~1%) under strong acidic conditions (Scheme 3).



Scheme 3

Kisfaludy's approach

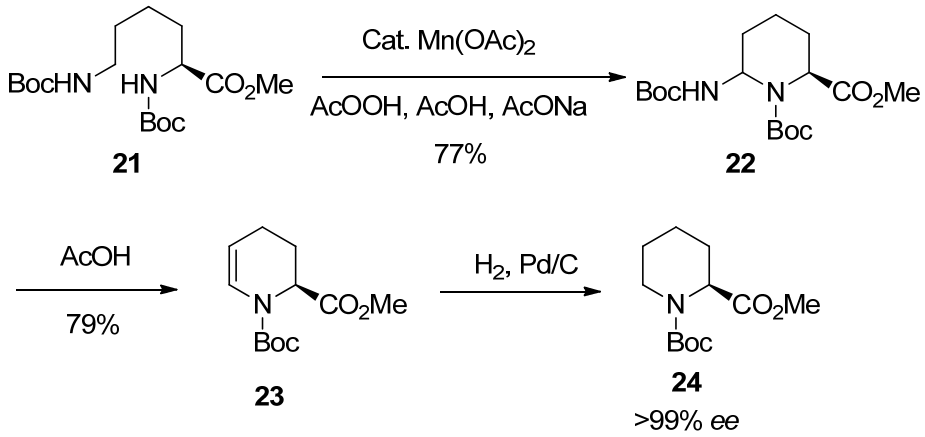
The one-step production of (*S*)-**1** using disodium nitrosyl-pentacyanoferrate (II) as the oxidant of the amine moiety of lysine is reported by Kisfaudy's group (Scheme 4).[29]



Scheme 4

Rossen's approach

The fully protected (*S*)-lysine **21** was converted into aminal **22** by selective oxidation

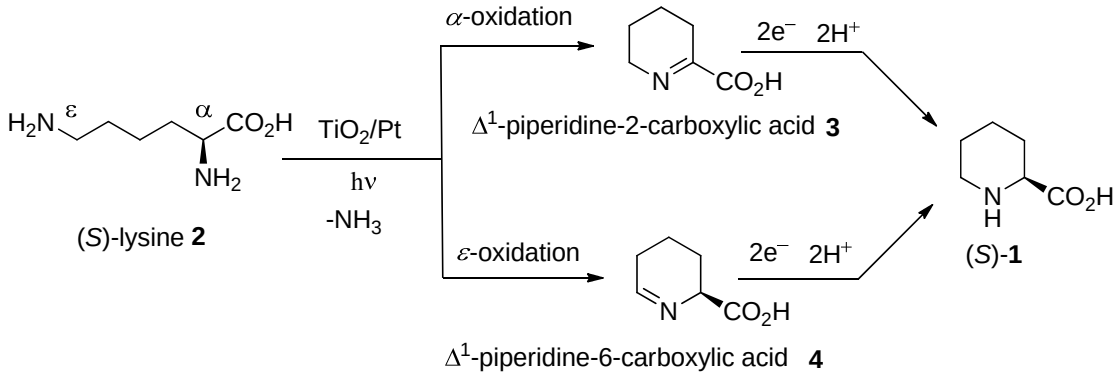


Scheme 5

of the side chain using a $Mn(OAc)_2$/peracetic acid system by the Rossen group (Scheme 5).[30] No epimerization occurred under the buffered oxidation conditions. Treatment under mild acidic conditions gave enamide **23**, which could be reduced to (*S*)-pipecolate **24** (Scheme 5).

Ohtani's approach

The photocatalytic redox synthesis of pipecolic acid was achieved in a one-step procedure directly from unprotected (*S*)-lysine by Ohtani's group.[31] The mechanism was proved to proceed *via* (i) oxidation of (S)-lysine leading to **3** and **4**, depending on the oxidized nitrogen and (ii) reduction of the imines with electron. Titanium oxides were



Scheme 6

shown to predominantly oxidize the ε-amino group, permitting enantiomeric excess up to 90% in truly biomimetic way.

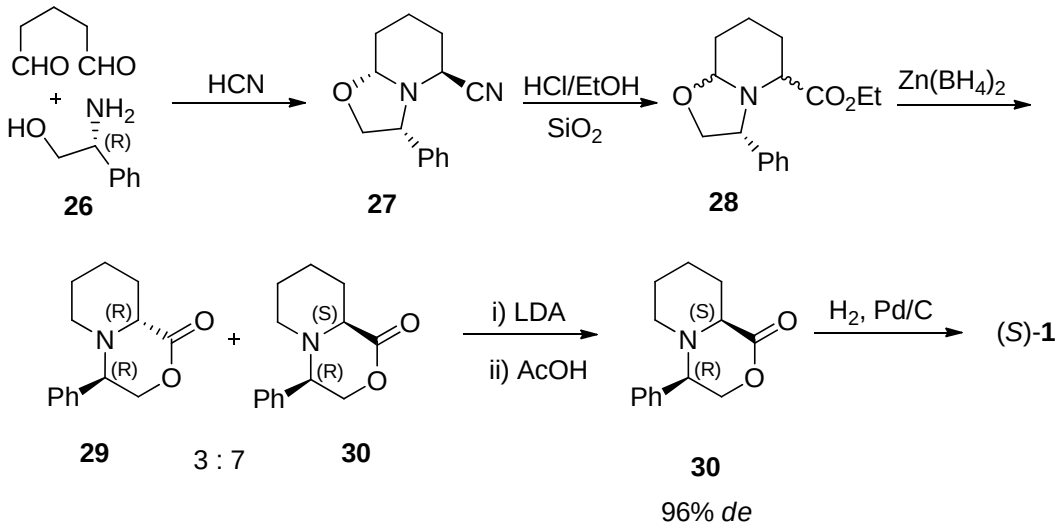
(b) Diastereoselective synthesis

Synthesis from phenyl glycinol

Many groups have used chiral phenyl glycinol as chiral inductor for a diastereoselective synthesis of pipecolic acid.

Royer's approach

Enantiomerically pure (*S*)-pipecolic acid **1** was synthesized in four steps and 47% overall yield starting from 2-cyano-6-phenyloxazolopiperidine **27** (Scheme 7) by Royer's group.[32] The oxazolidine function of **28** was easily reduced by $Zn(BH_4)_2$ followed by acidic workup, and lactones (9a*R*)-**29** and (9a*S*)-**30** were obtained in a 30:70

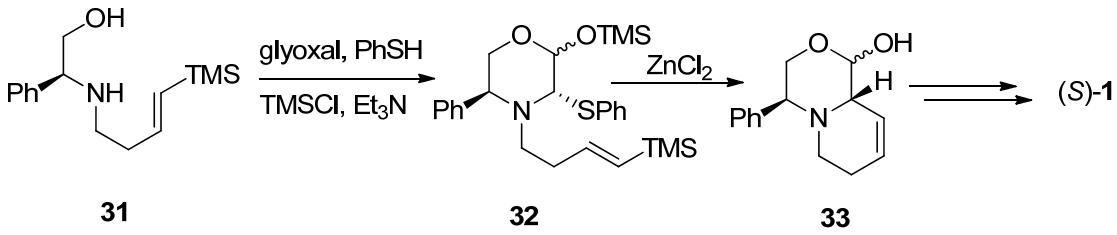


Scheme 7

ratio and 77% yield. Sequential deprotonation of lactones **29** and **30** with LDA (THF, -78 ˚C), followed by reprotonation (acetic acid, -78 ˚C), led to (9aS)-**30** in 96% *de* and 88% yield. Enantiomerically pure (*S*)-pipecolic acid **1** was obtained by simple hydrogenation of **30** using Pd/C in mild acidic medium (ethanol/acetic acid).

Agami's approach

Agami and co-workers[33] used (*S*)-phenyl glycinol as chiral inductor for a diastereoselective synthesis of (*S*)-pipecolic acid **1**. Substituted morpholine **32** was obtained from the condensation between phenylglycinol derived amino alcohol **31** and glyoxal in the presence of thiophenol. The key-step was a highly diastereoselective ene-iminium cyclisation between iminium ion (generated by action of Lewis acid) and the vinylsilane moieties. The intermediate **33** was converted in three steps into (*S*)-pipecolic acid **1**.

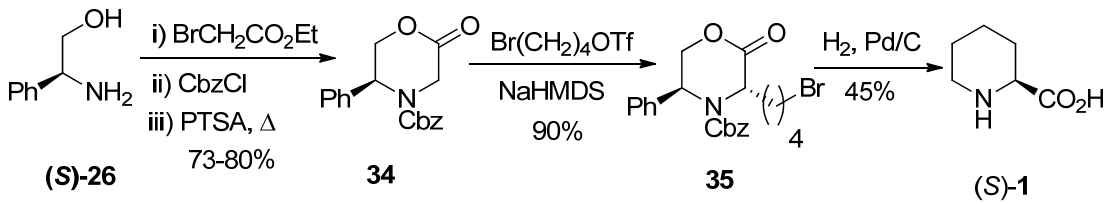


Scheme 8

Roos' approach

Roos and co-workers[34] also used (*S*)-phenylglycinol as starting material. Lactone **34**, prepared in three steps from (*S*)-phenylglycinol **26**, was alkylated with a bromotriflate to af-

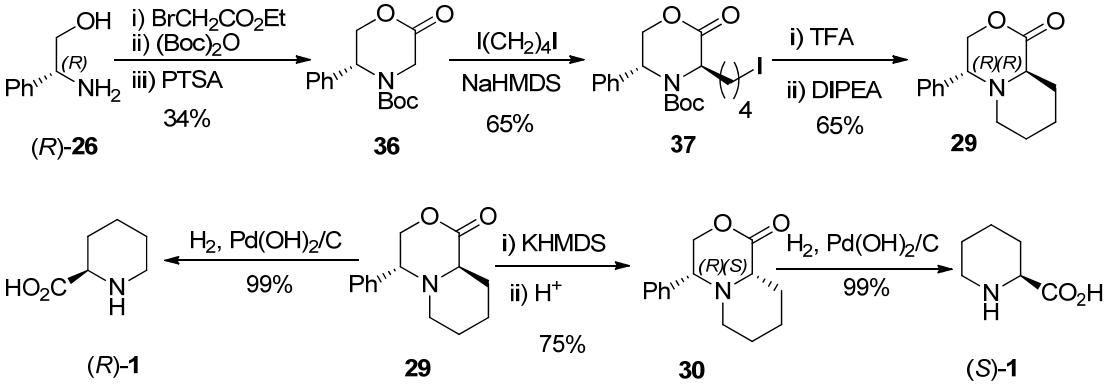
ford diastereomerically pure compound **35**. Treatment of **35** with hydrogen induced cleavage of the benzyloxycarbonyl group with concomitant cyclization and debenzylation of the cyclic lactone gave enantiopure pipecolic acid **1** (Scheme 9).



Scheme 9

Hou's approach

Access to diastereomerically pure **29** provides the route to both (*R*)- and (S)-pipecolic acid using a single chiral auxiliary by Hou's protocol.[35] Compound **36** was prepared from (*R*)-2-phenylglycinol in three steps. The enolate of **36** was formed and then monoalkylated with diiodobutane to give (3*R*,5*R*)-4-iodobutyl substituted compound **37**. Removal of the Boc group by TFA and cyclization under basic conditions provided the desired (4*R*,9a*R*)-oxazin-1-one **29**. The epimerization of **29** by deprotonation/protonation protocol provided only the (4*R*,9a*S*)-diastereomer **30**. Both (*R*)- and (*S*)-pipecolic acids were prepared after hydrogenation of morpholin-2-one **29** and **30** respectively (Scheme 10).

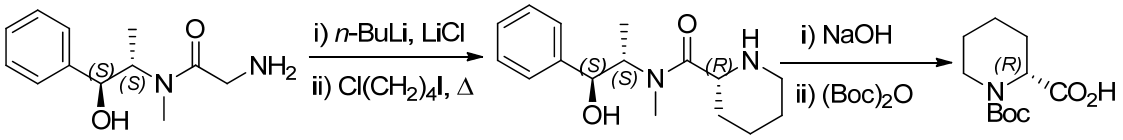


Scheme 10

Myer's approach

Myer's approach[36] involved the direct alkylation of pseudoephedrine glycinamide **38**, without the need for protective groups (Scheme 11). Treatment of the enolate derived

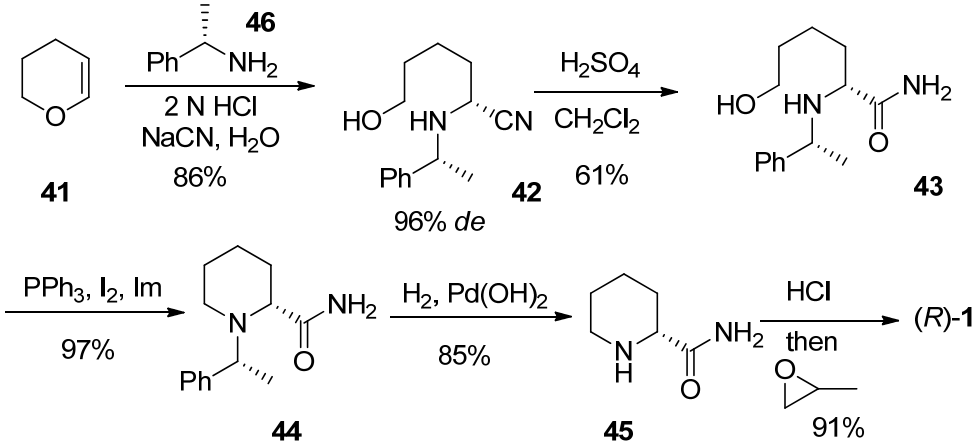
from **(*S*,*S*)-(+)-38** with l-chloro-4-iodobutane followed by heating of the crude reaction product to induce cyclization of the chloroalkylamine forms the (*R*)-pipecolinic acid amide **39** in 72% yield (96% *de*). Alkaline cleavage of the pseudoephedrine auxiliary, acylation of the crude product with $(Boc)_2O$, and recrystallization afforded *N*-Boc-(*R*)-pipecolic acid **40** in 77% yield.



Scheme 11

Fadel's approach

Enantiomerically pure (*R*)-pipecolic acid was synthesized in four steps and in 42% overall yield starting from dihydropyran **41** and (*R*)-*α*-methylbenzylamine **46** by Fadel's group.[37] The asymmetric Strecker reaction of 3,4-dihydro-2*H*-pyran **41** with chiral amine **46** and NaCN in aq. HCl gave amino nitrile **42** with excellent diastereoselectivity (96% *de*). Subsequent hydrolysis of nitrile to amide, cyclisation, debenzylation and amide to acid conversion afforded (*R*)-pipecolic acid *ent*-**1** in good overall yield (Scheme 12).

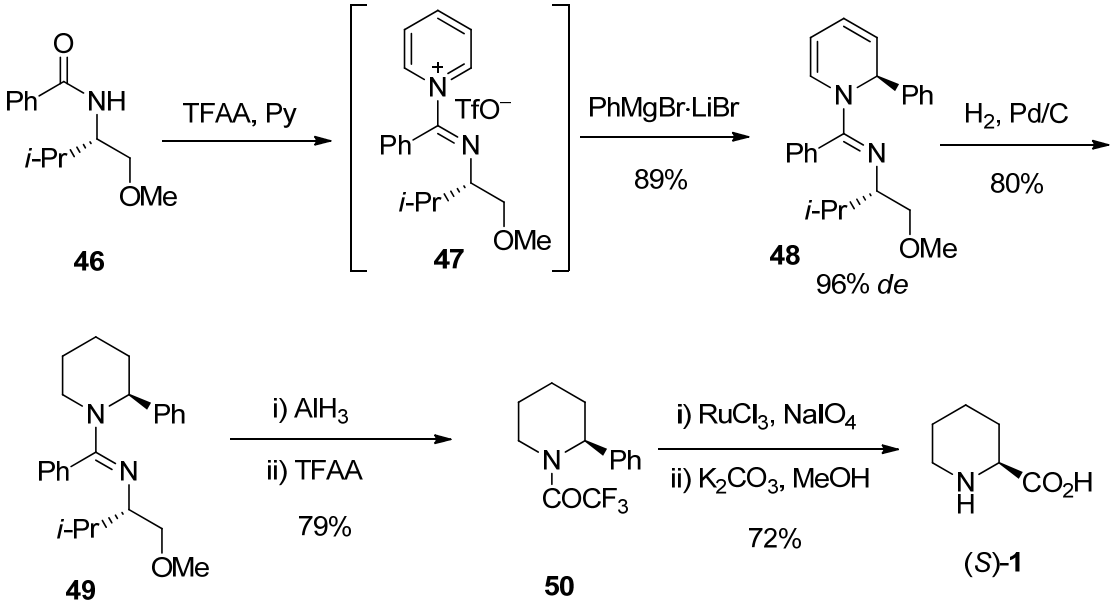


Scheme 12

Charette's approach

Valine-derived chiral auxiliary was utilized by Charette *et al*. to synthesize (*S*)-**1**. Thus, dihydropyridine **48** was prepared by region and diastereoselective addition of phenyl-

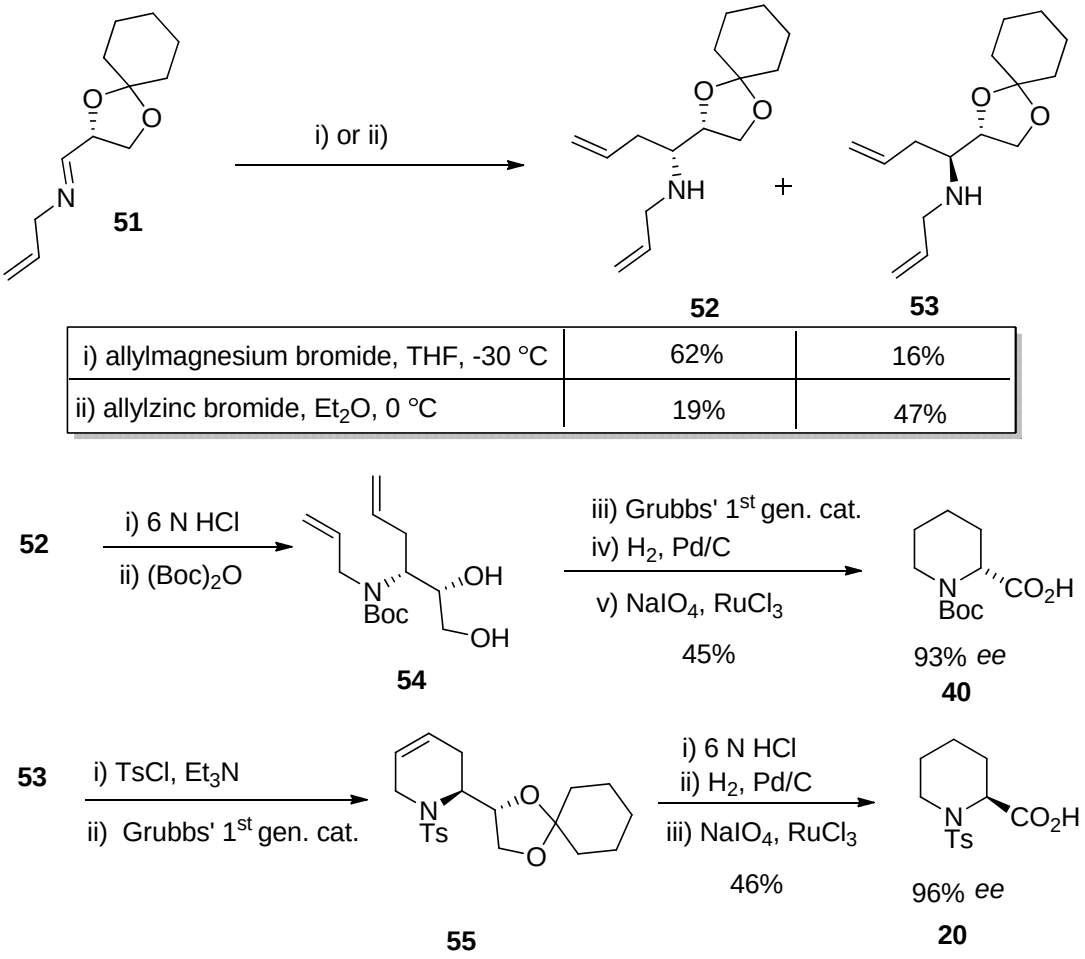
magnesium bromide to the valine-derived chiral pyridinium salt **47**. High-pressure hydrogenation ensured a complete hydrogenation to the *N*-iminopiperidine **49**. The valine derived chiral auxiliary was next removed by alane reduction, followed by protection of the piperidine nitrogen as a trifluoroacetamide to furnish compound **50**. Oxidation of the phenyl substituent to the carboxylic acid group followed by the deprotection of *N*-trifluoroacetyl group afforded (*S*)-pipecolic acid **1** in 40% yield (6 steps) from **46**.[38]



Scheme 13

Chattopadhyay's approach

Complementary routes to both enantiomers of *N*-protected pipecolic acid are developed by Chattopadhyay's group,[39] which involve stereo-divergent allylation of a chiral *N*-allylimine and ring-closing metathesis as key steps. Thus when imine **51** was reacted with allylmagnesium bromide under optimized conditions, it gave a mixture of the homoallylic amines **52** (62%) and **53** (16%) whereas reaction with allylzinc bromide led to the formation of the anti-isomer **53** as the major product (47%) together with **52** (19%). Compound **52** was converted to *N*-Boc-(*R*)-pipecolic acid **40** while compound **53** was converted into *N*-Ts-(*S*)-pipecolic acid **20** in total five steps with 45% and 46% overall yields from **52** and **53** respectively.

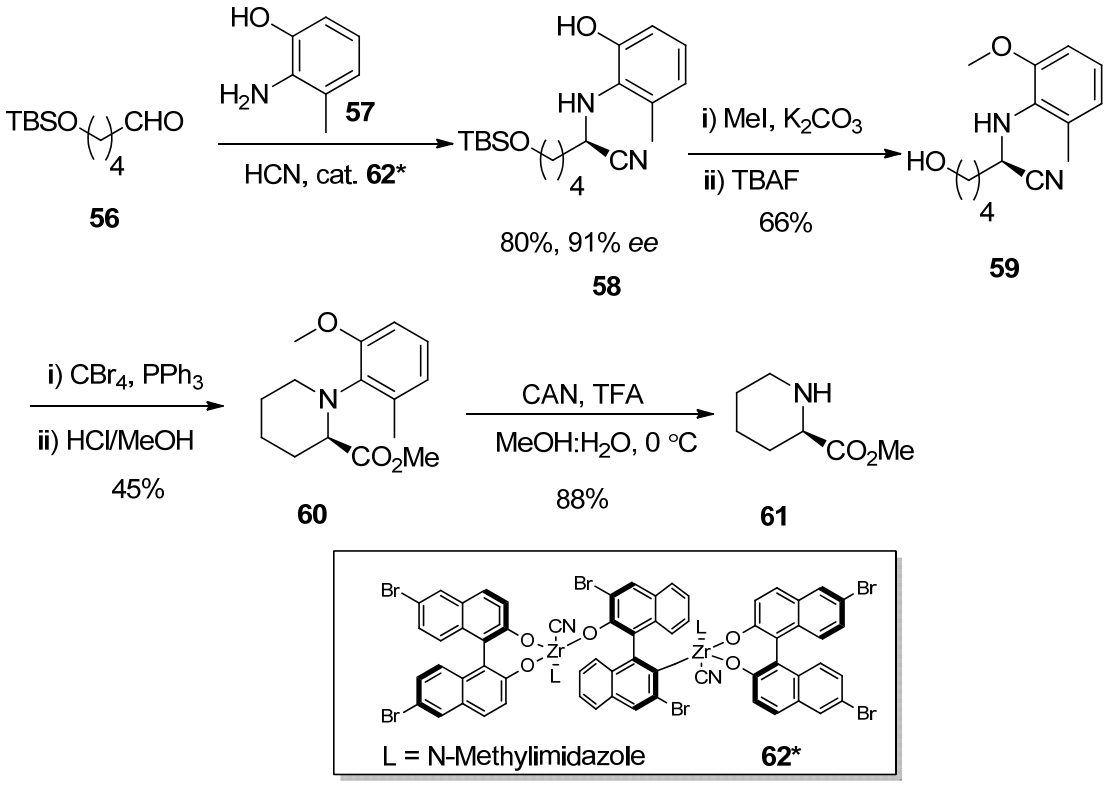


Scheme 14

(c) Enantioselective approaches

Kobayashi's approach

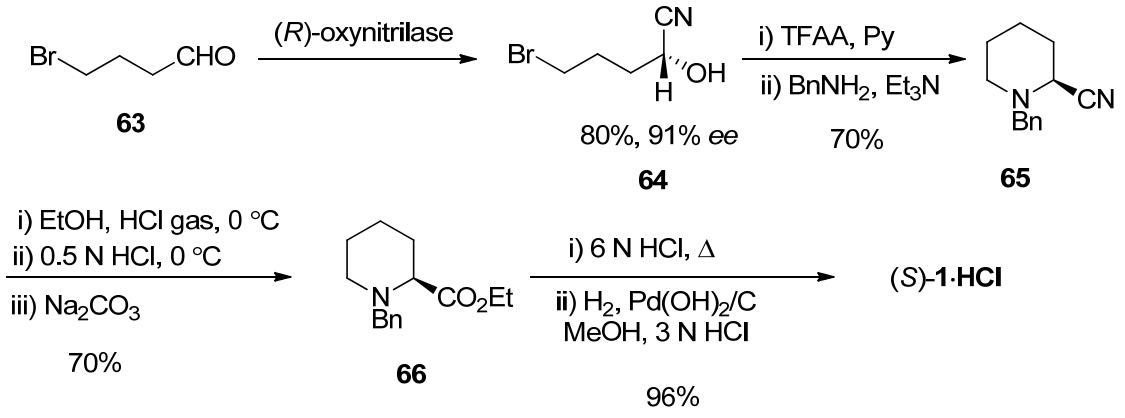
The three-component catalytic asymmetric Strecker reaction was developed starting from achiral aldehyde, amines, and HCN using a chiral zirconium catalyst by Kobayashi's group[40] to synthesize methyl pipecolate. The key Strecker reaction using 5-*tert*-butyldimethylsiloxypentanal **56** was successfully carried out in the presence of **62** (2.5 mol%) to afford *R*-amino nitrile **58** in 91% *ee*. Preparation of **59** from **58** was achieved by following standard transformations, in a good yield. Bromination of the hydroxyl group induced spontaneous cyclization, and acid treatment afforded *N*-protected (*R*)-pipecolic acid methyl ester **60**. Deprotection under standard conditions gave **61** in a good yield.



Scheme 15

Gotor's approach

Gotor's approach involves the chemoenzymatic synthesis of (*S*)-2-cyanopiperidine **65** which was further elaborated to give an access to (*S*)-pipecolic acid.[41] This synthesis is based on a (*R*)-oxynitrilase-catalysed reaction for the enantioselective preparation

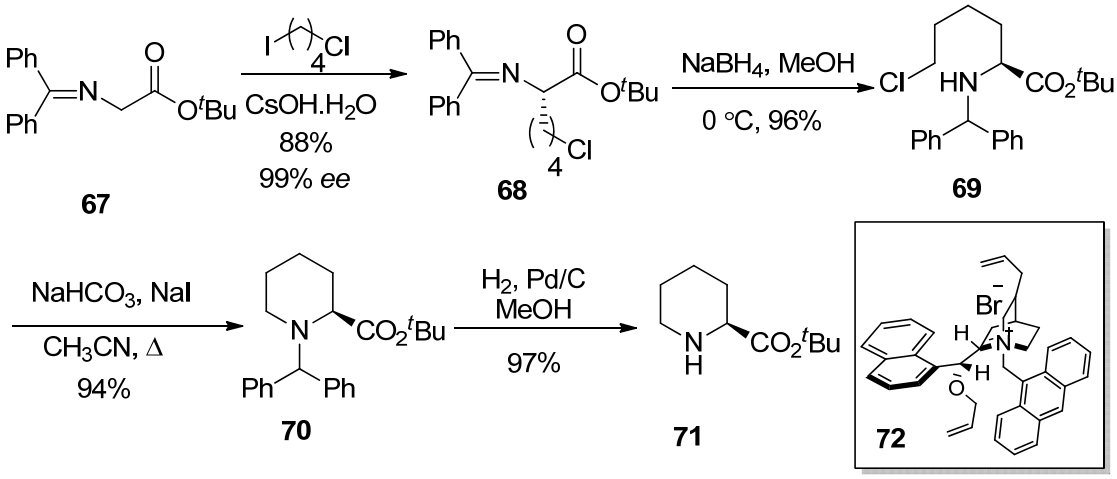


Scheme 16

of the bromo cyanohydrin derivative **64**. This compound was transformed into piperidine **65** in two steps (Scheme 16): first, the transformation of hydroxyl group in trifluoromethanesulfonyloxy group and its substitution by benzylamine, and second, the subsequent cyclization by a slower substitution of the bromine to yield compound **65**. A careful hydrolysis to prevent racemization followed by hydrogenolysis gave enantiopure (*S*)-pipecolic acid **1**.

Corey's approach

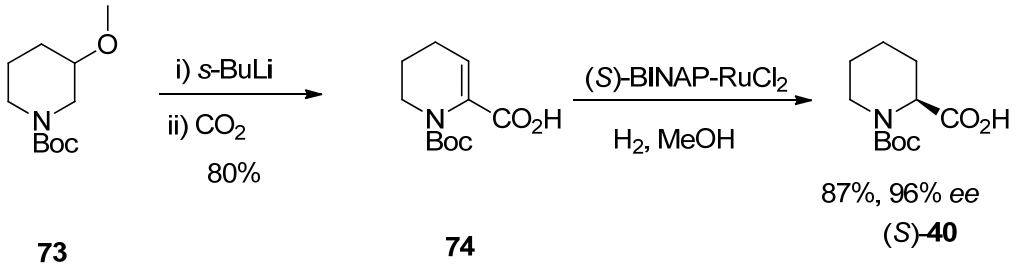
Corey *et al.* developed a highly enantioselective alkylation of glycine derivative using cinchonidine derived chiral catalyst to give access to a wide variety of *α*-amino acids. Catalytic phase transfer alkylation of glycine derived *tert*-butyl ester **67** with 1-chloro-4-iodobutane using quaternary cinchonidine salt **72** as chiral catalyst and solid $CsOH \cdot H_2O$ as base afforded the (*S*)-4-chlorobutylated ester **68** of 99% *ee*. The conversion of **68** to the *tert-butyl* ester of pipecolic acid **71** was accomplished in high yield by the sequence C=N reduction to **69**, cyclization to **70** and *N*-deprotection of **70**, according to Scheme 17.[42]



Scheme 17

Beak's approach

Asymmetric hydrogenation has been exploited by Beak *et al.* for the highly enantiomeric synthesis of pipecolic acid. The reaction of *N*-Boc-3-methoxypiperidine **73**

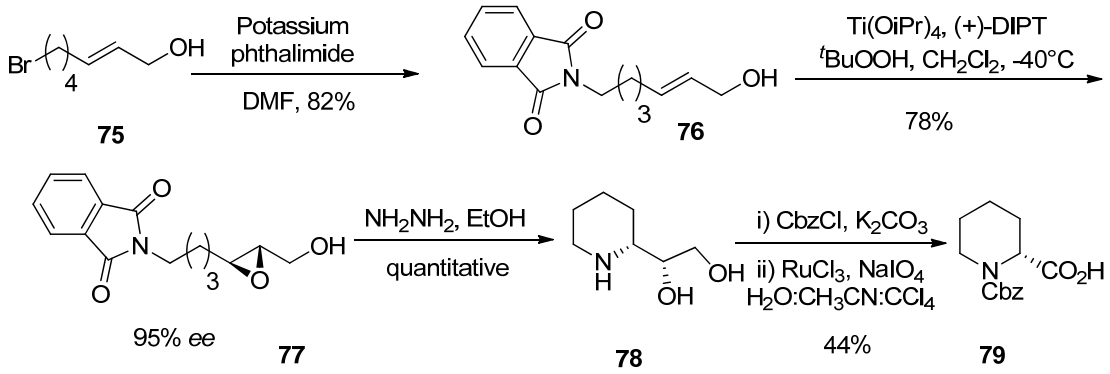


Scheme 18

with 2 equiv of *s*-BuLi/TMEDA (-78 °C, 5 h), followed by the addition of carbon dioxide, afforded 2-carboxy-*N*-Boc-1,4,5,6-tetrahydropyridine **74** in 80% yield. Asymmetry is introduced into the piperidine ring by the enantioselective hydrogenation of compound **74** with the Noyori catalyst (*S*)-BINAP-$RuCl_2$ to yield (*S*)-*N*-Boc-pipecolic acid **40** in 95% yield with an *er* of 98:2 as shown in Scheme 18.[43]

McKervey's approach

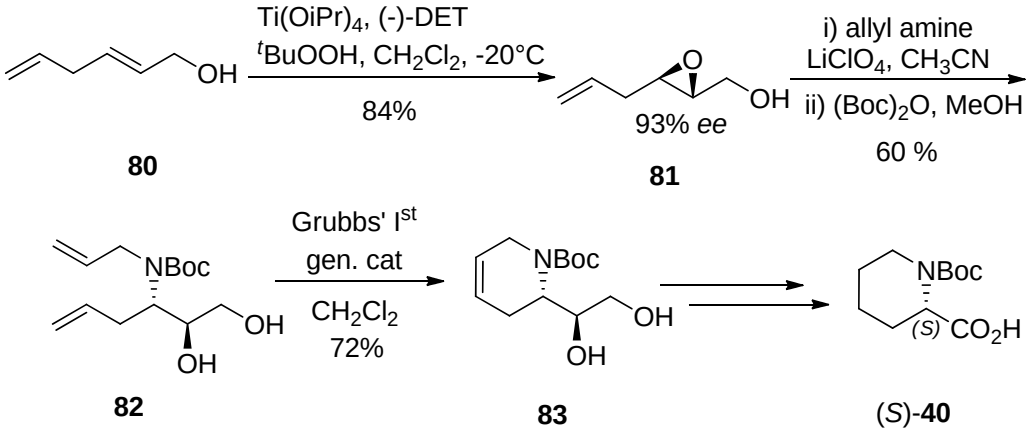
The simple enantioselective route to pipecolic acid is described by McKervey.[44] The key step involves the Sharpless asymmetric epoxidation of an *N*-protected aminoheptenol **76** which spontaneously cyclises to a piperidine derivative **78** on deprotection**.** To complete the synthesis, **78** was again *N*-protected with benzyl chloroformate followed by oxidative cleavage of the diol with $RuCl_3$/ $NaIO_4$ in CH_3CN:CCl_4:H_2O at 20 °C to afford (*R*)-*N*-Cbz-pipecolic acid **79** in 52% yield and >95% *ee*.



Scheme 19

Riera's approach

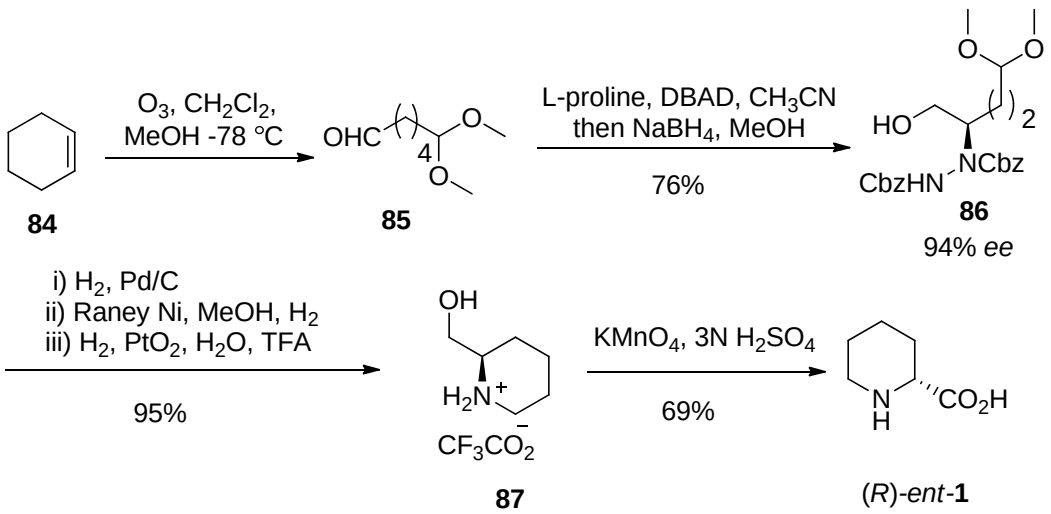
Ring-closing metathesis (RCM) has been exploited for the synthesis of pipecolic acid from the known enantiomerically enriched epoxyalcohol **81**, synthesized from the allylic alcohol **80** *via* a Sharpless epoxidation by Riera *et al*. (Scheme 20). Nucleophilic epoxide ring-opening using allylamine was followed by protection of the amino group by Boc_2O. The key intermediate **83** was obtained by a RCM, catalyzed by the Grubbs' reagent, of the doubly unsaturated amine **82** in 72% yield. Hydrogenation and oxidation led to (*S*)-*N*-Boc-pipecolic acid **40**.[45]



Scheme 20

Greck's approach

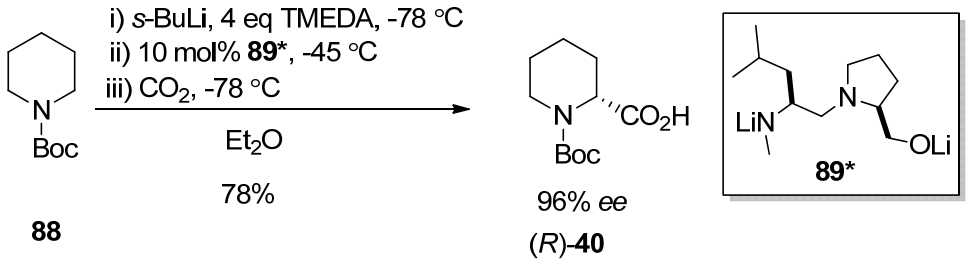
Greck and co-workers[46] used L-proline catalyzed asymmetric amination of aldehyde protocol for synthesis of (*R*)-pipecolic acid. Aldehyde **85** was obtained from cyclohexene **84** *via* ozonolysis. Aldehyde **85** on L-proline catalyzed amination followed by reduction with sodium borohydride afforded aminoalcohol **86**. Under hydrogenation conditions, aminoalcohol **86** underwent cyclization to afford cyclic aminoalcohol **87**. Alcohol **87** on oxidation with potassium permanganate afforded (*R*)-pipecolic acid *ent*-**1**.



Scheme 21

Gawley's approach

Gawley's approach involved the catalytic dynamic resolution (CDR) of 2-lithio-*N*-Boc-piperidine core followed by quenching it with electrophile. The catalytic dynamic resolution (CDR) of *N*-Boc-piperidine **88** using chiral ligand **89** has led to the highly enantioselective synthesis of *R*-pipecolic acid (Scheme 22).[47] Thus, a CDR was attempted by deprotonation of **88** at C-2 in Et_2O at -78 □C with *s*-BuLi/TMEDA followed by addition of 10 mol % **89**, warming to -45 □C for 3 h, cooling to -78 □C, and quenching with carbon dioxide to obtain (*R*)-**40** in 78% yield and 98:2 enantiomeric ratio.



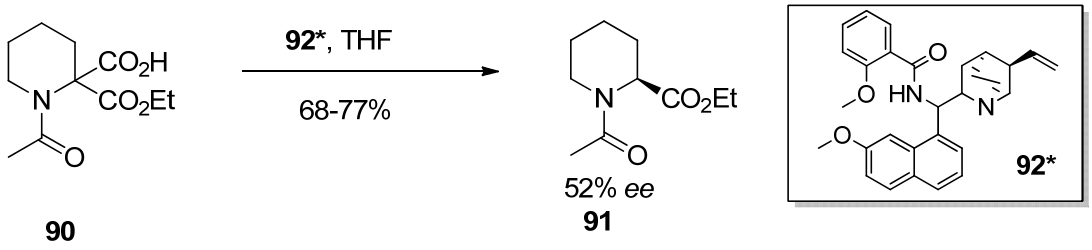
Scheme 22

(d) Deracemization approach

Lasne's approach

Enantioselective decarboxylation-reprotonation, in the presence of a chiral base, of the *N*-acyl malonate **90** has been examined as a route to optically enriched *N*-acetyl pipecolic acid ethyl ester by Lasne's group (Scheme 23).[48] The best result was obtained with the

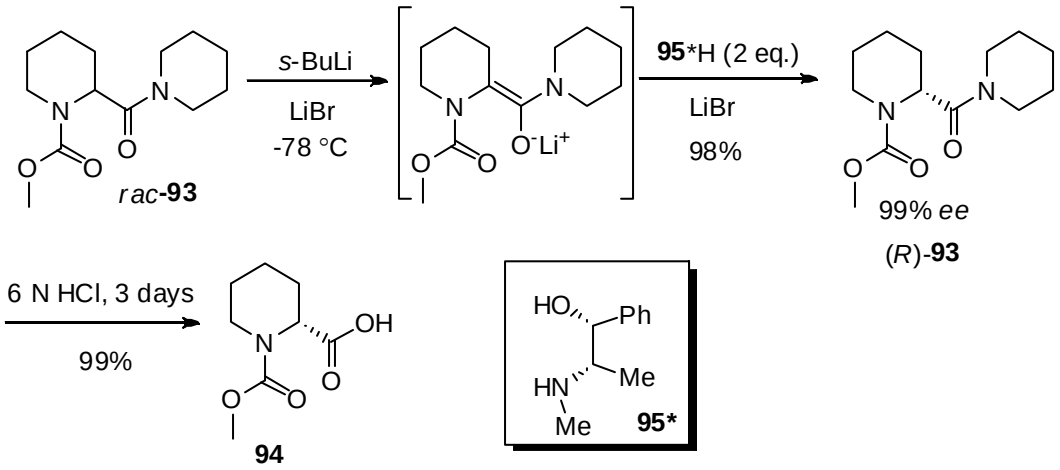
quinine alkaloid-derived base **92** *i.e.* 52% enantiomeric excess in favour of the (*S*)-pipecolate ester **91**.



Scheme 23

Martin's approach

An efficient method for deracemization of pipecolamides **95** has been developed by Martin's group. Enantioselective protonation of the lithium enolates of the amide **95** with use of commercially available ephedrine **98** led to pipecolamide **96** with enantiomeric excess higher than 99% (Scheme 24).[49]



Scheme 24

1.1.4 References

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Chapter 1: Synthetic studies toward pipecolic acid

Section 2: Total synthesis of (*S*) and (*R*)-pipecolic acid

1.2.1 Present Work

1.2.1.1 Objective

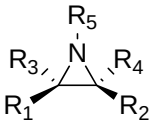
Literature survey revealed that pipecolic acid and its derivatives attracted the attention of many organic chemists towards its synthesis due to their wide range of biological activities, their pertinence in therapeutic chemistry and as intermediates for the synthesis of alkaloids.[1]

Although pipecolic acid is available commercially, high cost associated with its enantiomerically pure form has prompted organic chemists to develop a convenient access to both enantiomers of pipecolic acid. In this context, there is still a need of convenient and efficient route for the synthesis of these compounds from readily available and commercially cheap starting materials.

This group is engaged in the synthesis of biologically active compounds and earlier this group has developed a practical and efficient protocol for the synthesis of pipecolic acid derivatives using asymmetric as well as chiral pool approaches.[2] In continuation of search for practical routes for such molecules, synthesis of pipecolic acid from cheap and easily available starting material was undertaken.

1.2.1.2 Aziridines: an overview

1.2.1.2.1 Introduction



Aziridine

Figure 1

Aziridines (Fig. 1) are saturated three-membered heterocycles containing one nitrogen atom. They has been synthetic targets as well as useful building blocks in synthesis since Gabriel's 1888 discovery of the smallest nitrogen containing heterocycle.[3] Attracted by the increased ring strain and unique reactivity of the three-membered ring, synthetic chemists have extensively explored the various manipulations of aziridine-containing compounds.[4]

1.2.2.2 Physical properties of aziridines

Aziridines are less basic than acyclic amines (the aziridinium ion has p*K*a = 7.98) due to the increased **s** character of the nitrogen lone pair. Increased angle strain in aziridine is also responsible for increased barrier for nitrogen inversion. This barrier can be high enough for the isolation of separate invertomers, for instance the *cis* and *trans* invertomers of *N*-chloro-2-methylaziridine (Fig. 2).[5]

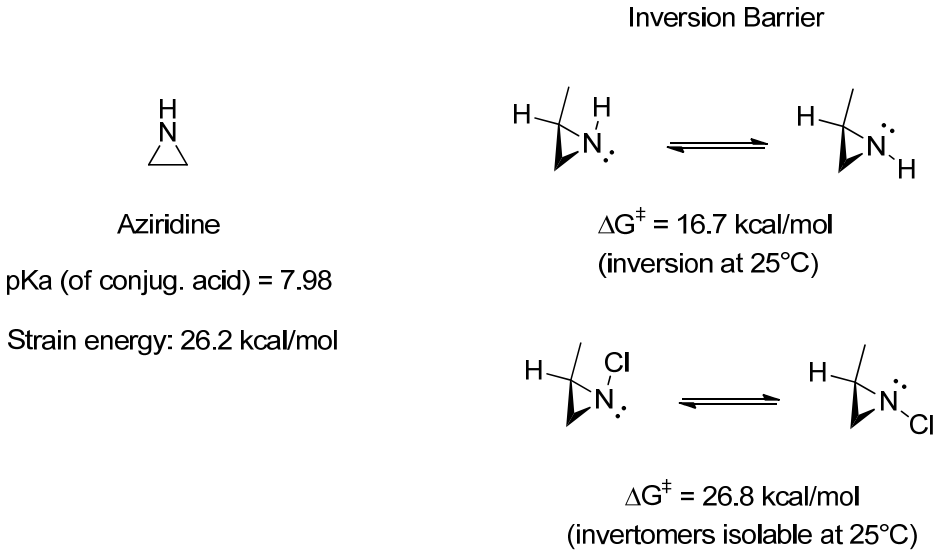


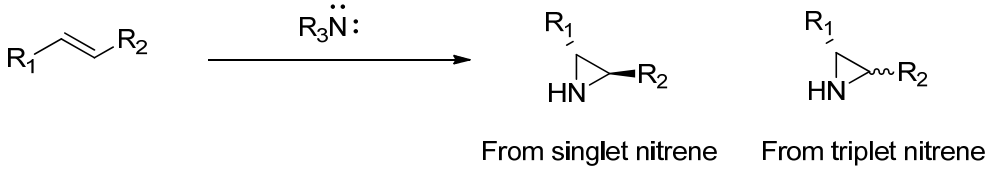
Figure 2

1.2.1.2.3 Synthesis of aziridines

By addition to alkenes

Nitrene methods

'Classical' methods for direct aziridination of alkenes have traditionally featured addition of *nitrenes* to the unsaturated partner (Scheme 1). Such *nitrenes* typically were generated by thermal or photochemical decomposition of the corresponding azides and these methods intrinsically lead to mixtures of (more reactive) singlet and (more stable) triplet *nitrenes*. Singlet *nitrenes* react stereospecifically with 1,2-disubstituted alkenes in a concerted process while triplet *nitrenes* react in a two-step process with alkenes, in which a *N–C* bond is formed in each step.[4g,6]

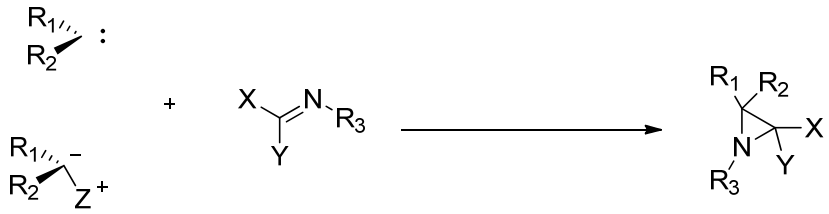


Scheme 1

By addition to imines

Carbene and ylide methods

A *carbene* or equivalent (such as an *ylide*) can react efficiently with an imine leading to the formation aziridine through the simultaneous formation of one *C–N* bond and one *C–C* bond (Scheme 2).[7]

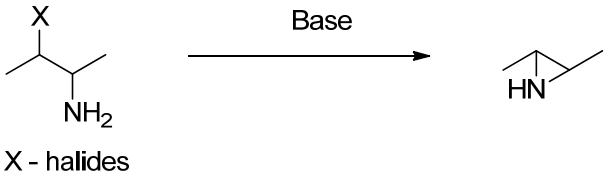


Scheme 2

From 1,2-aminoalcohols and 1,2-aminohalides

Gabriel aziridine synthesis

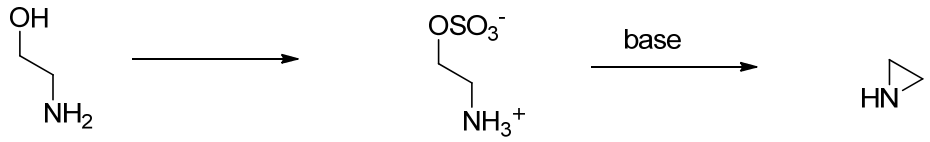
In 1888 Gabriel demonstrated that aziridines could be prepared in a two-step process, by chlorination of ethanolamines with thionyl chloride followed by alkali-mediated cyclization (Scheme 3).[3]



Scheme 3

Wenker aziridine synthesis

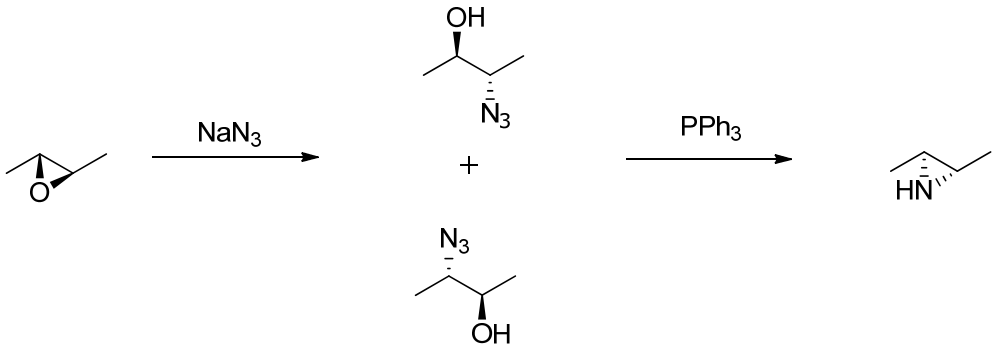
In 1935, Wenker showed that heating of ethanolamine in the presence of sulfuric acid to high temperature produced a compound, at that time termed '*β*-aminoethyl sulfuric acid'; which was distilled from aqueous base to give aziridine representing the first preparation of the parent compound in a pure condition (Scheme 4). After that wide range of conditions for activation of the hydroxy group has evolved, enabling the preparation of a wide range of achiral and enantiomerically-pure aziridines for use in synthesis. In particular, Mitsunobu-like oxyphosphonium activation has been used extensively to execute the transformation.[8]



Scheme 4

From 1,2-azidoalcohols

Given the ready availability of enantiomerically pure epoxides by a range of asymmetric processes, much use has been made of the multi-step preparation of aziridines from these precursors. In particular, the phosphine-mediated ring-closure of azido alcohols (a Staudinger reaction), themselves obtained from chiral epoxides by ring-opening reaction using a range of azide sources, followed by treatment with trialkyl- or triarylphosphine, led to the *N*-unsubstituted aziridine product (Scheme 5). The reaction is reliable for a wide range of chiral and achiral epoxides and both asymmetric centres are cleanly and predictably inverted during the process.[4d]

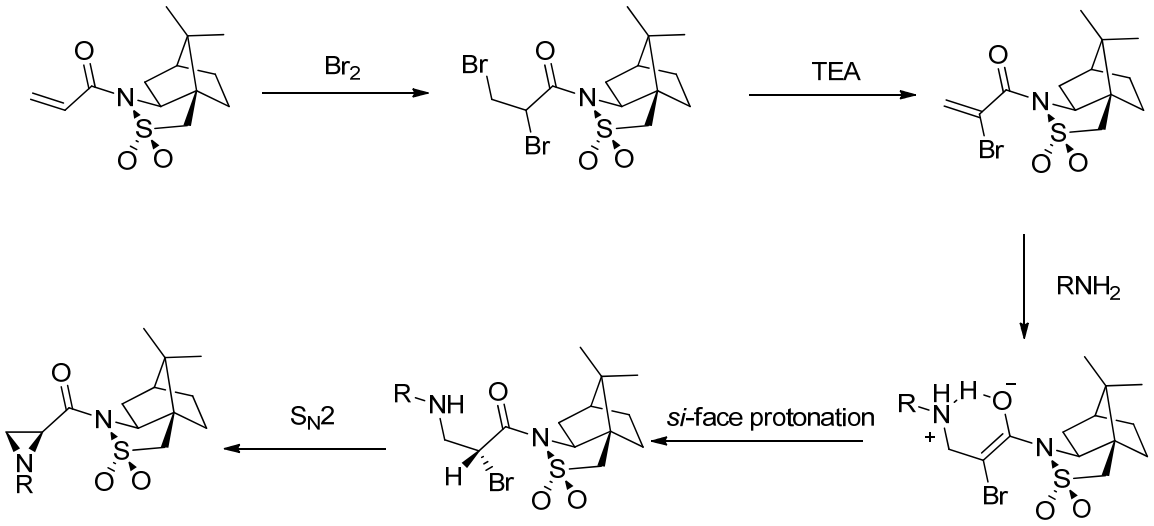


Scheme 5

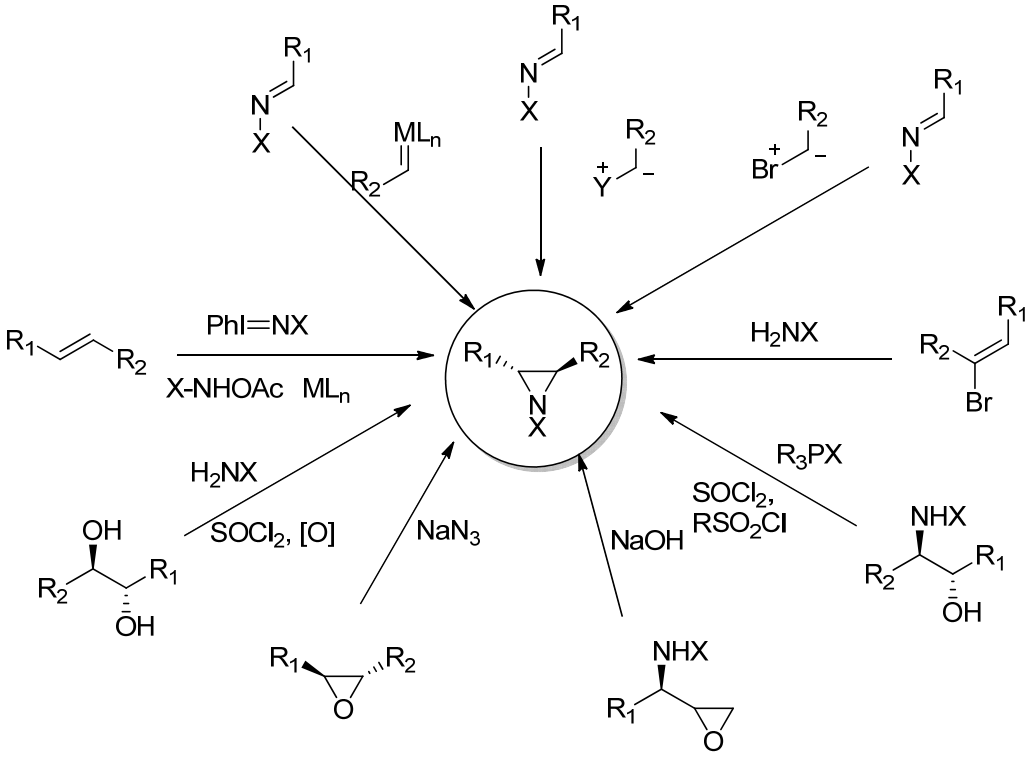
From α-bromoacrylates:

Gabriel–Cromwell reaction

The Gabriel-Cromwell reaction of *α*-bromoacrylates with amine led to a aziridine *via* conjugate addition, proton transfer and S_N2 ring closure (Scheme 6). A range of chiral derivatives of *α*-bromoacrylates undergo reaction with amines to yield chiral aziridines. Ammonia itself may be used as the nitrogen source, providing a useful entry to chiral *N*-unsubstituted aziridines.[9]



Scheme 6

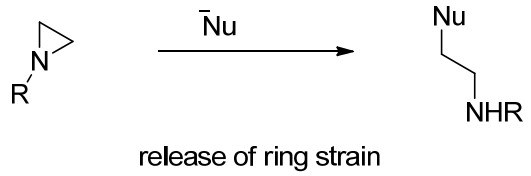


Scheme 7- Aziridine Synthesis - Overview[4]

1.2.1.2.4 Reactions of aziridines[4]

Ring-opening processes

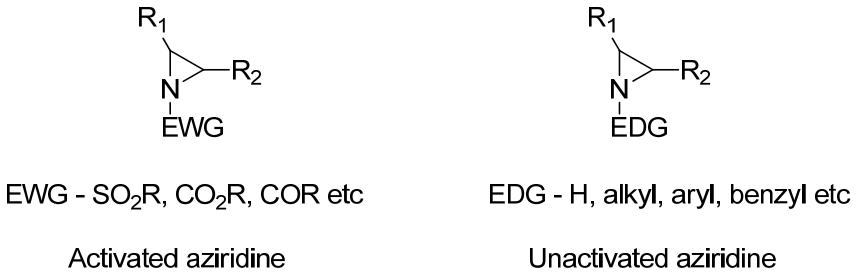
Aziridines readily undergo ring cleavage reactions under relatively mild conditions because of ring strain of three membered ring in combination of electronegativity of hetro atom (Scheme 8). As might be expected, due to the diminished electronegativity of nitrogen compared to oxygen, ring-opening reactions of these heterocycles are less facile than the corresponding reactions of epoxides, but there is still an extensive exploration of such chemistry. There are several features of these reactions which are worthy of consideration.[4q]



Scheme 8

The nature of the *N*-substituent

In general, two types of aziridine can be considered: activated and unactivated. The former contain substituents capable of stabilising the developing negative charge on nitrogen during nucleophilic ring opening (e.g. acyl, carbanoyl, sulfonyl *etc.*). The latter, also known as simple aziridines are generally unsubstituted or with alkyl substitution on nitrogen and usually require acid catalysis to facilitate ring opening (Scheme 9).[4m]

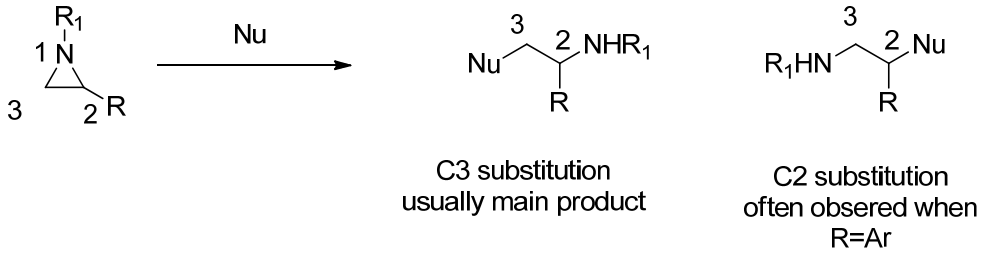


Scheme 9

Regioselectivity in ring-opening processes

Ring-cleavage reactions of aziridines proceed by nucleophilic attack at carbon, in an analogous manner to similar reactions of epoxides. Where an aziridine is unsymmetrically-substituted (as would typically be the situation), reaction with a nucleophile can lead to

two products of ring-opening. As would be expected, most nucleophiles preferentially direct their attack to the site of lesser substitution, though electronic considerations may perturb this preference (Scheme 10).[4c]

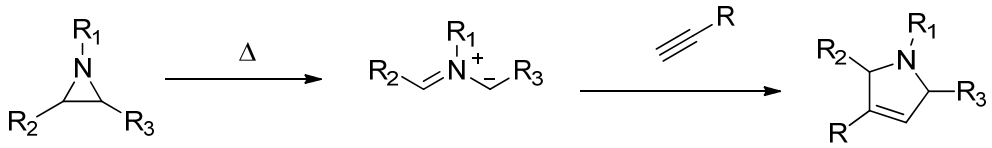


Scheme 10

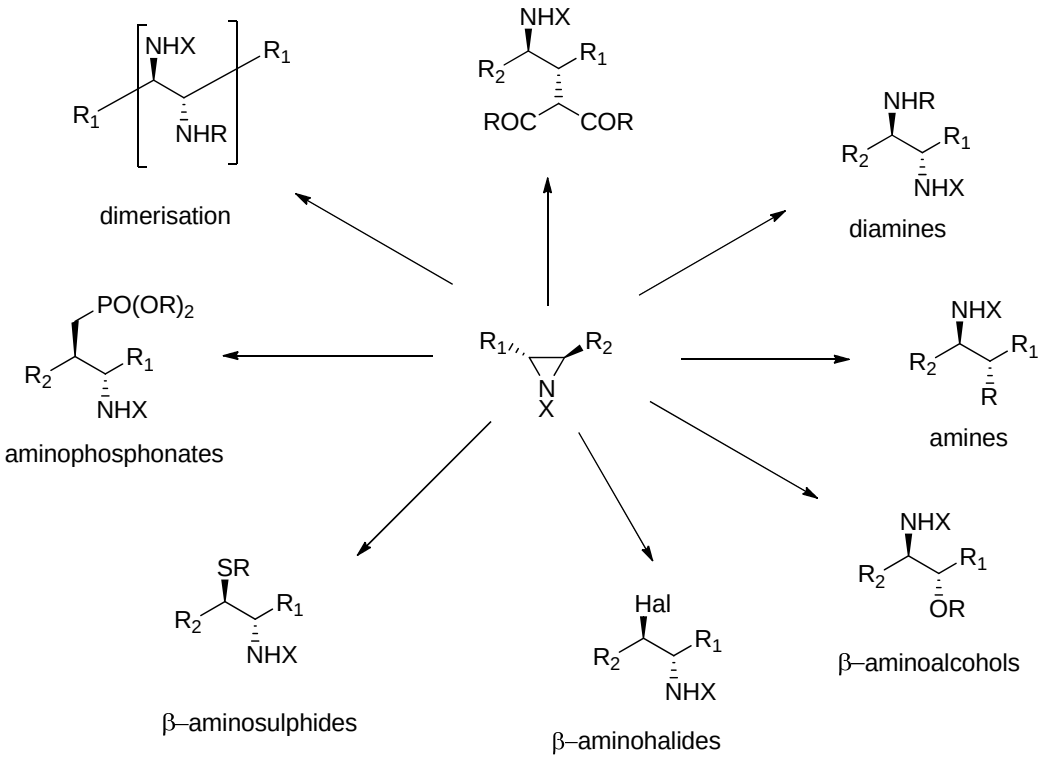
Regio and stereo-selective nucleophilic ring opening of aziridine made it possible to synthesize a number of functionalized compounds that exhibit 1,2- relationship between the incoming nucleophile and extensively reviewed using carbon, oxygen, sulfur, nitrogen, halogen, hydrogen, phosphorous, silanes, selenols, cobalt, *etc.* as nucleophiles.[4q]

Electrocyclic aziridine ring-opening

Aziridines may be considered as precursors to azomethine ylides: when heated, the three-membered ring ruptures stereospecifically to generate 1,3-dipoles efficiently and these-may be trapped *in situ* with dipolarophiles to give a range of substituted pyrrolidines (Scheme 11).[4q]



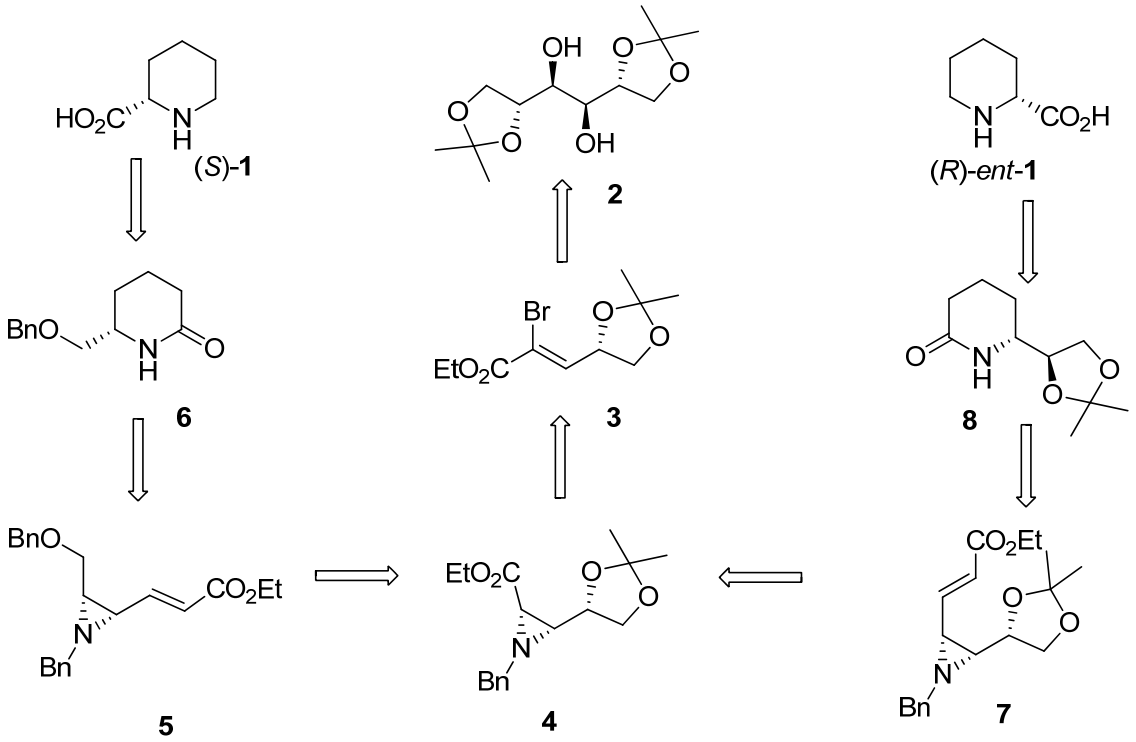
Scheme 11



Scheme 12 - Aziridine ring opening reactions- overview

1.2.1.3 Retrosynthetic analysis

The literature reports revealed that aziridines are less explored for the synthesis for pipecolic acid derivatives. There is no such report of synthesis of pipecolic acid itself from aziridines as chiral synthons. Enantiomerically pure aziridines have been considered to be prominent precursors in the synthesis of natural and unnatural amino compounds due to their inherent ability to undergo regio and chemoselective nucleophilic ring opening reactions as well as cycloaddition pathways.[4] Although hydrogen is not characterized as a nucleophile, it serves the purpose of cleaving the aziridine ring. Catalytic hydrogenation of both activated and non-activated aziridines produces amines as useful building blocks for the synthesis of biologically active products.[10] Thus as shown in the retrosynthetic plan (Scheme 13), it was envisioned that aziridine-2-carboxylate **4** can be exploited to build piperidine skeleton of pipecolic acid **6/8** by converting it into *α,β*-unsaturated ester **5/7** followed by reductive cleavage of aziridine ring whereas ester and acetonide functionality can serve as a handle to propagate on either side of aziridine **4** to give convenient access to both antipodes of pipecolic acid **1**.

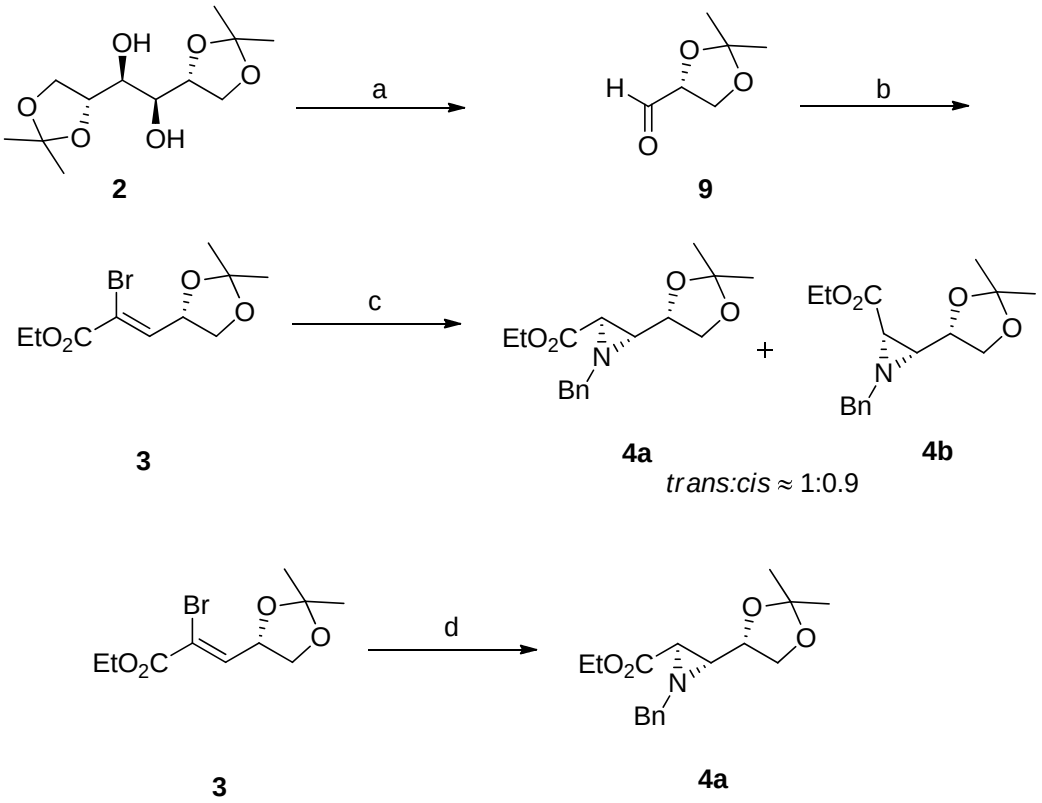


Scheme 13: Retrosynthetic analysis for pipecolic acid

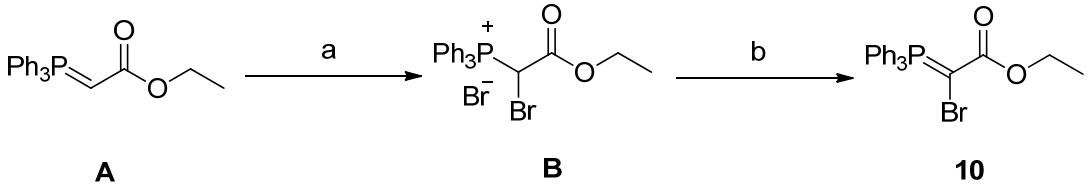
1.2.1.4 Results and discussion

The desired enantiomerically pure aziridine-2-carboxylate **4** can be accessed from D-mannitol diacetonide **2** following literature procedure.[11] Thus, the synthetic endeavor for pipecolic acid as given in Scheme 14 started with readily available and cheap starting material D-mannitol diacetonide **2**. Accordingly, D-mannitol diacetonide **2** on diol cleavage using $NaIO_4$ yielded acetonide protected (*R*)-glyceraldehyde **9**. For the Wittig olefination, the requisite bromophosphorane **10** was prepared by treatment of phosphorane **A** with bromine at −10 ºC to afford an adduct **B** which was concentrated and on treatment with 2N NaOH solution afforded bromophosphorane **10** as a crystalline yellow solid in 82% yield (Scheme 15). The Wittig olefination of (*R*)-glyceraldehyde **9** using bromophosphorane **3** in dichloromethane at 25 °C afforded a bromoester **3.** In the IR spectrum of **3**, broad bands at 1721 and 1661 cm^{-1} were assigned to the ester carbonyl and conjugated C=C, respectively. The bands at 847 and 771 cm^{-1} were due to C-Br stretching. ^1H NMR spectrum of **3,** in which downfield signals at δ 7.36 (1H) and 6.80 (0.08H) as a doublet were assigned to *β*-H which indicated formation of *E/Z*- isomers in the ratio of 93:7. The

β-H proton in major isomer (*E*)-**3** showed a considerable downfield shift and appeared at δ 7.36 [as compared to the (*Z*)-**3**, δ 6.80] due to the *diamagnetic anisotropic deshielding effect* induced by the ester carbonyl functionality, indicating the *cis* relative orientation of carboxylate group and the *β*-H. The presence of triplet integrating for three protons at δ 1.36 with $J = 7.2$ Hz indicated the presence of -CH_3 group of ethyl ester while two single-



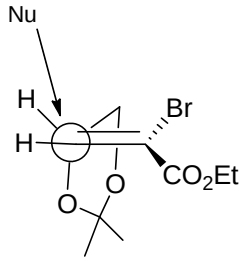
Scheme 14: ***Reagents and conditions:*** *a) $NaIO_4$, CH_2Cl_2, rt, 2h; b)* ***10****, CH_2Cl_2, rt, 84% over two steps; c) $BnNH_2$, Et_3N, EtOH, 0 ºC to rt, 72 h, 77%; d) $BnNH_2$, Et_3N, toluene, 0 ºC to rt, 24 h, 68%.*



Scheme 15: ***Reagents and conditions:*** *a) Br_2, CH_2Cl_2, -78 ºC to rt, overnight; b) 2N NaOH, 0 ºC to rt, 82% over two steps.*

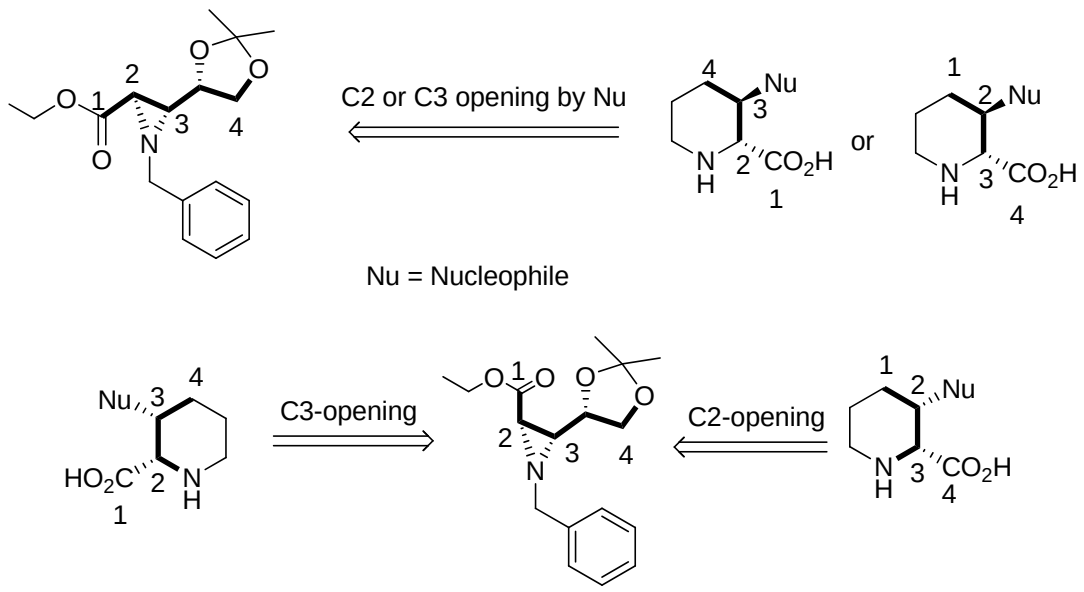
s integrating for three protons each at δ 1.34 and 1.33 were assigned to two -CH_3 groups of acetonide moiety respectively. The Gabriel-Cromwell reaction of 2-acrylic carboxylate

derivative **3** with benzyl amine led to a diastereomeric mixture of *trans* **4a** and *cis* **4b** aziridine-2-carboxylates *via* conjugate addition, proton transfer and S_N2 ring closure in 77% yield (1:0.9) which were separated using chromatography. According to a suggested mechanism from the literature,[12] benzylamine attacks the prochiral centre at C-3 of the 2-bromoacrylate **3** regardless of (*E*) or (*Z*) configuration, affording the *syn*-product with high selectivity. The observed high *syn* selectivity of the reaction between amines and *α*-bromoacrylates may be explained in the context of a modified Felkin-Anh model **I**. Thus, the nucleophile attacks the π system from the less hindered site anti-periplanar to the bulky oxygen substituent. The question of whether either the *cis* or the *trans* product is formed (configuration at C-2) depends on the solvent as well as the (*E*)/(*Z*) ratio. The decisive factor is whether, in an aprotic solvent, the protonation of the forming *α*-amino-*β*-bromo-carbanion occurs by intramolecular proton transfer from the ammonium ion onto the C-2 carbanion on the same side as the introduced nitrogen, or, in protic solvents, the protonation of the carbanion occurs non-selectively from both sides. An (*E*) product, for instance, would yield *cis* aziridines in the former case, and *cis*/*trans* mixtures in the latter.[12b] Thus when reaction was performed in aprotic solvent like toluene, *trans*-aziridine **4a** formed in range of 68% yield along with *cis*-aziridine **4b** in 5% yield. All spectral data for **4a** and **4b** were in accordance with reported one. In ^{1}H spectra of aziridine **4a**, C2-H showed doublet with characteristic J = 2.4 Hz value known for *trans* aziridines[11,13] while C2-H of aziridine **4b** showed doublet with J = 6.7 Hz indicating *cis* stereochemistry. Thus having enantiopure aziridines-2-caboxylates **4a** and **4b** in hand, it was decided to exploit them for the synthesis of pipecolic acid and derivatives as chiral synthons.



I

On careful observation of compounds **4a** and **4b** one can realize that the *trans* aziridine-2-carboxylate **4a** possesses hidden C_2 symmetry while *cis* **4b** possesses plane of symmetry elements. Thus *trans* aziridines on nucleophilc ring opening reaction at either C-2 or C-3 would end up having same configuration of newly formed amine functionality while *cis* aziridine-2-caboxylate would give both enantiomers (Scheme 16).



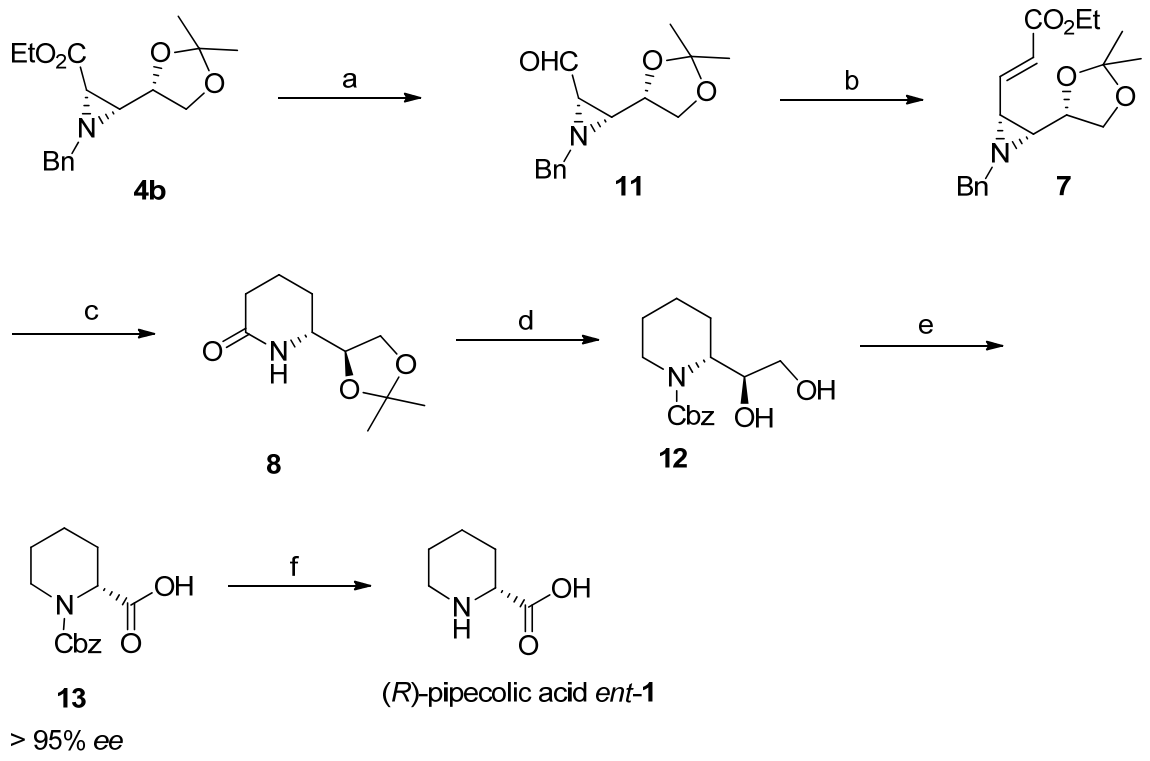
Scheme 16: Ring opening reactions of *trans/cis* aziridine-2-carboxylates **4a/b**

1.2.1.4.1 Exploitation of *cis* aziridine-2-carboxylate 4b towards synthesis of (*R*) and (*S*)-pipecolic acid

1.2.1.4.1.1 Total synthesis of (*R*)-pipecolic acid

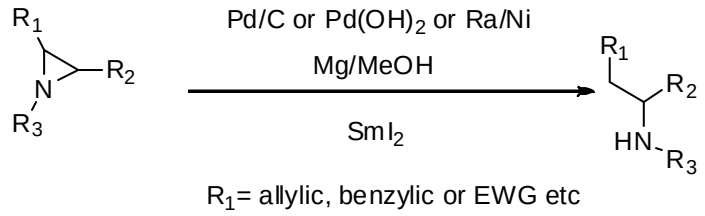
As shown in scheme **17** c*is* aziridine-2-carboxylate **4b** was reacted with 1 eq. of DIBAL-H (1M in toluene) in dichloromethane as solvent at –78 °C to afford aldehyde **11** as thick yellow liquid which was used as such for next reaction. Aldehyde was subjected for 2-C Wittig homologation with PPh_3CHCO_2Et using cat. benzoic acid under refluxing toluene (a method used for the formation of *E* as major isomer)[14] to afford *α,β*-unsaturated ester **7** in 82% yield over two steps. The IR spectrum of the compound **7** showed peaks at 1718 and 1624 cm^{-1} suggesting the presence of conjugated ester. In the ^1H NMR analysis of the product, peaks at δ 2.01 (dd, *J* = 6.9 & 8.08 Hz, 1H) and 2.22 (t, *J* = 6.9 Hz, 1H) indicated the presence of aziridine ring which is surprisingly stable to such harsh conditions given the few literature reports where aziridines are opened by Wittig reagents.[15] Peak at δ 6.73 (dd, *J* = 7.33 & 15.7 Hz) was assigned for *β*-H while peak at δ 6.08 (dd, *J* = 0.05 & 15.7 Hz) was assigned for the *α*-H of *α,β*-unsaturated ester functionality. The magnitude of *J* values indicated the exclusive formation of *E* isomer. ^{13}C

NMR spectrum showed peaks at δ 123.7, 144.3 and 165.4 corosponding to *α,β*-unsaturated ester.



Scheme 17: ***Reagents and conditions:*** *a) DIBAL-H (1M in toluene), CH_2Cl_2, -78˚C, 1h; b) Ph_3PCHCO_2Et, cat. $PhCO_2H$, toluene, reflux, 5h, 82% over two steps; c) Pd/C (10%), HCO_2NH_4, MeOH, 60 ˚C, 3h, 90%; d) i) BH_3·DMS, THF, 0˚C to rt, 6h then 6N HCl, reflux, 3h; ii) Cbz-Cl, $NaHCO_3$, THF:H_2O (1:1), 75% over two steps; e) $RuCl_3·6H_2O$, $NaIO_4$, CH_3CN:CCl_4:H_2O (1:1:3), rt, 1h, 60%; f) H_2, Pd/C (10%), MeOH, 95%.*

Aziridines irrespective of nature of *N*-substituent, having allylic, benzylic or electron withdrawing groups at the C-*α* position are known to undergo reductive ring opening at *Cα-N* bond with Pd/C, Pearlman's catalyst, Raney Ni under hydrogen atmosphere, and Mg/MeOH, SmI_2, *etc.* (Scheme 18).[10,16]



Scheme 18

Thus, this *α,β*-unsaturated aziridine carboxylate **7** (Scheme 17) when subjected to transfer hydrogenation conditions, underwent aziridine ring opening with concomitant olefin reduction, debenzylation and cyclization in one pot to furnish δ-lactam **8** in 90% yield. IR spectrum of **8** showed characteristic peak at 1664 cm^{-1} indicating the presence of a lactam functional group. In ^{1}H NMR spectrum, disappearance of peaks corresrponding to aromatic region (δ 7.27-7.35) as well as double bond region (δ 6.08 & 6.73) indicated the complete debenzylation of *N*-benzylamine and reduction of the corresponding unsaturated ester. Peak at δ 6.21 (br s, 1H) confirmed the presence of lactam proton. Cleavage of aziridine ring is supported by ^{13}C NMR spectrum where disapearance of peaks at δ 42.1 and 49.1 corresponding to aziridine ring were observed. Molecular ion peak at *m/z* $(M+H)^{+}$-200.11 and HRMS analysis (calculated $C_7H_{18}NO_3$-200.1281, observed-200.1277) further affirmed the structural assignement.

Having requisite piperidine skeleton in hand with C-2 acetonide functionality as masked aldehyde/acid, next task was to reduce lactam **8** to amine functionality (Scheme 17). Accordingly, lactam **8** was reduced to amine using BH_3·DMS/THF followed by *in situ* breaking of resulting borane complex as well as deprotection of acetonide functionality by subjecting it to acid hydrolysis using 6N HCl. Crude amine was immediately protected as benzyl carbamate derivative **12** by reacting it with Cbz-Cl, $NaHCO_3$ in THF/Water. IR specrum showed peak at 1670 cm^{-1} indicating a carbamate group. In ^{1}H NMR spectrum, disapearance of peaks at δ 1.33 (s, 3H) and 1.40 (s, 3H) indicated the acetonide deprotection. Appearance of new characteristic peaks at δ 5.13 (s, 2H) and 7.34-7.43 (m, 5H) suggested the *N*-Cbz protection. DEPT spectrum showed six peaks corresponding to $–CH_2$ group, two aliphatic –CH and three Ar-CH confirming amide reduction to $–CH_2$ group and protection of amine as *N*-Cbz derivative.

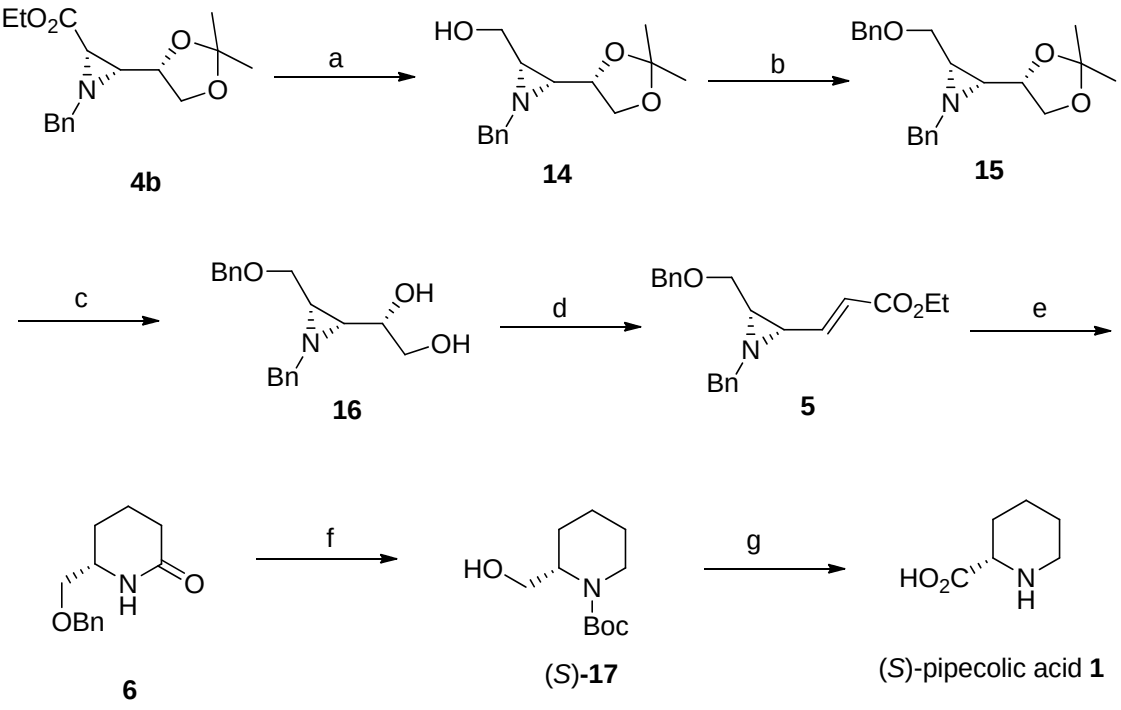
Oxidative cleavage of the diol **12** with $RuCl_3/NaIO_4$ in $CH_3CN:CCl_4:H_20$[17] at 20 °C afforded (*R*)-*N*-Cbz-pipecolic acid[18] **13** in 60% yield. Compound **13** is well documented in

literature and ^{1}H NMR and ^{13}C NMR spectral data of obtained compound is in complete agreement with the reported one. Finally, the molecular formula of **13** was confirmed by HRMS, which showed peak at m/z 286.1047 which is in good agreement with calculated value 286.1050 for $C_{14}H_{17}NO_4Na$. Chiral HPLC analysis showed the enantiomeric purity of (*R*)-*N*-Cbz-pipecolic acid more than 95%. Last task was the unmasking of the amino group to obtain (*R*)-pipecolic acid **1**. Pd/C catalyzed hydrogenation of acid **13** afforded (*R*)-pipecolic acid *ent*-**1** in 95% yield. Thus the present work constitutes a total synthesis of (*R*)-pipecolic acid *ent*-**1**.

1.2.1.4.1.2 Total synthesis of (*S*)-pipecolic acid

As mentioned earlier in retrosynthetic analysis (Scheme 13 and 16), *cis* aziridine-2-carboxylate **4b** posseses hidden plane of symmetry. So if aziridine propagated as *α,β*-unsaturated ester on other side *viz.* towards the acetonide functionality, ring opening reaction would generate an enantiomer of newly formed amine functionality (Scheme 17). Thus **4b** was reduced using LAH/THF to give alcohol **14** in 90% yield. IR spectrum showed strong band at 3369 cm^{-1} for hydroxy streching frequency. Disappearance of peak at 1728 cm^{-1} was clearly indicative of reduction of ester group. Similarly in ^{1}H spectrum peaks at δ 1.18 (t, 3H) and 4.17 (m, 3H) corresponding to ethyl ester were absent. Peaks at δ 1.76 (m, 2H) ppm were attributed to aziridine ring protons which appeared upfield as expected beacuse of absence of electron withdawing group (*i.e.* ethyl ester) due to reduction. Peaks at *δ* 1.35 (s, 3H) and 1.43 (s, 3H) ppm were assigned to acetonide functionality. ^{13}C NMR spectrum showed peaks at 25.3, 26.6, 43.1, 45.6, 59.8, 63.5, 67.2, 75.4, 109.1, 126.9, 127.8, 128.1, 138.1 with δ values as expected. Disapperance of peak at δ 168.9 clearly confirmed the reduction of ester cabonyl. Hydroxyl group of compund **14** was protected as benzyl ether using benzyl bromide, NaH in DMF as standard protection protocol to give compound **15** in 95% yield. ^{1}H NMR and ^{13}C NMR spectra showed peaks corresponding to benzyl ether which was further confirmed by HRMS analysis (calculated for $C_{15}H_{22}NO_3$-264.1594, observed-264.1603). Next task was to deprotect the acetonide functionality, cleavage of diol to aldehyde and 2-C Wittig homologation. Accordingly, compound **15** was subjected for acetonide deprotection using PTSA/MeOH to give diol **16** in 85% yield. Isolated yield (85%) is indicative of stability of such *cis* aziridines given their propensity towards ring opening reaction under

acidic conditions. IR spectrum showed strong absorption bond at 3359 for –OH group. ^{1}H NMR spectrum showed disappearance of peaks at δ 1.34 (s, 3H) and 1.43 (s, 3H) ppm pointing to the deprotection of acetonide group. In ^{13}C NMR spectrum also absence of peaks at δ 25.5 and 26.8 corresponding to acetonide group was observed. HRMS analysis affirmed the molecular formula (calculated for $C_{19}H_{24}O_3N$-314.1751, observed-314.1747).



Scheme 19: ***Reagents and conditions:*** *a) LAH, THF, 0° C, 1h, 90%; b) BnBr, NaH, DMF, 95%; c) PTSA, MeOH, 85%; d) i) $NaIO_4$, acetone:water (2:1), rt, 0.25h; ii) Ph_3PCHCO_2Et, cat. $PhCO_2H$, toluene, Δ, 85% over two steps; e) Pd/C (10%), H_2, 3h, 88 %; f) i) LAH, THF, 0 °C to rt, 6h; ii) Pd/C (10%), H_2, $(Boc)_2O$, MeOH, 75% over two steps; g) i) TFA, CH_2Cl_2; ii) $KMnO_4$, 3N H_2SO_4, 69% over two steps*.

In the next step, diol **16** was cleaved using sodium metaperiodate in acetone:water to give aldehyde which was used as such for next transformation. Thus the reaction of aldehyde with Ph_3PCHCO_2Et using cat. $PhCO_2H$ in refluxing toluene for 5 hours gave compound **5** in 85% yield over two steps. IR spectrum of **5** showed strong bands at 1715 and 1651 cm^{-1} for *α,β*-unsaturated ester. In ^{1}H NMR spectrum of **5**, peaks at δ 1.3 (t, *J* = 7 Hz, 3H) and 4.2 (q, *J* = 7 Hz, 2H) indicated the ethyl ester while peaks at δ 6.05 (d, *J* = 15.5 Hz, 1H)

and 6.77 (dd, J = 6.8 & 15.5 Hz, 1H) were assigned to α-H and β-H of unsaturated ester of **5** respectively. The magnitude of J value suggested the exclusive formation of E isomer. Peaks at δ 2.15-2.32 (m, 2H) were assigned to aziridine ring. ^{13}C NMR spectrum showed peaks at δ 14.2, 42.9, 46.2, 60.2, 63.8, 68.5 72.9, 123.6, 127.1, 127.5, 127.6, 127.8, 128.2, 128.3, 137.9, 138.2, 144.4, 165.7 representing the all requisite carbons. Lastly molecular formula was confirmed by HRMS analysis (calculated for $C_{22}H_{26}O_3N$-352.1907, observed-352.1902).

Applying the similar protocol of aziridine ring cleavage under hydrogenation/hydrogenolysis condition using ammonium formate and 10% Pd/C, compound **5** underwent aziridine ring opening with concomitant olefin reduction, debenzylation and cyclization in one pot to furnish δ-lactam **6** in 88% yield. Surprisingly the formation of *O*-debenzylated product was not observed even after keeping it for a longer time thus indicating its reluctance to *O*-debenzylation. IR spectrum showed strong absorption peak at 1660 cm^{-1} indicating the presence of amide. ^{1}H NMR spectrum showed peak at δ 6.44 (br s, 1H) indicating the presence of a lactam proton. Peak at δ 4.5 (d, 2H) indicated the presence of *O*-benzylic –CH_2 protons and 7.33 (m, 5H) were attributed to aromatic region of benzyl group. Remaining peaks at δ 1.25-1.44 (m, 1H), 1.62-1.93 (m, 3H), 2.16-2.47 (m, 2H), 3.27 (t, J = 8.9 Hz, 1H), 3.48 (dd, J = 3.7 & 8.9 Hz, 1H) and 3.62 (m, 1H) affirmed the desired skeleton. ^{13}C NMR spectral values were also in accordance with expected values. Mass spectrum showed peak at 220.67 for the $(M + H)^+$.

In next step lactam **6** was reduced to amine using LAH as reducing agent followed by one pot *O*-debenzylation/*N*-protection as Boc derivative to furnish (*S*)-*N*-piperidine-2-hydroxymethanol **17** in 75% yield. Chiral HPLC analysis of compound **17** showed enantiomeric excess of 97%. To complete the synthesis of (*S*)-pipecolic acid **1**, Boc group was deprotected by TFA to yield 2-hydroxymethyl piperidiniumtrifluoroacetates followed by final oxidation using $KMnO_4$ in aqueous 3 N H_2SO_4 to furnish (*S*)-pipecolic acid **1** in 69% yield, after elution on Dowex 50W-X4 ion exchange column.[19]

1.2.1.4.1.3 Conclusion

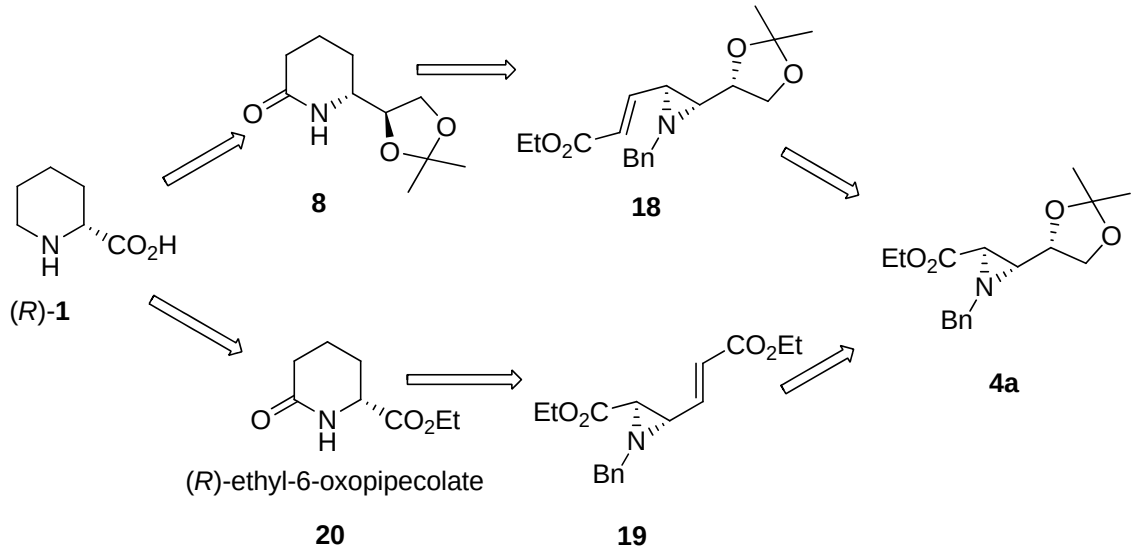
In conclusion, the convenient total syntheses of both enantiomers of pipecolic acid **1** starting from *cis* aziridine-2-carboxylate **4b** as a common synthetic precursor have been achieved. The synthesis of (*R*)-*ent*-**1** was achieved in 31% overall yield from *cis* aziri-

dine-2-carboxylate **4b** and 10% yield from D-mannitol diacetonide **2**. The synthesis of (*S*)**-1** was achieved in 28% overall yield from **4b** and 9.4% yield from **2**.

1.2.1.4.2 Exploitation of *trans* aziridine-2-carboxylate 4a towards synthesis of pipecolic acid

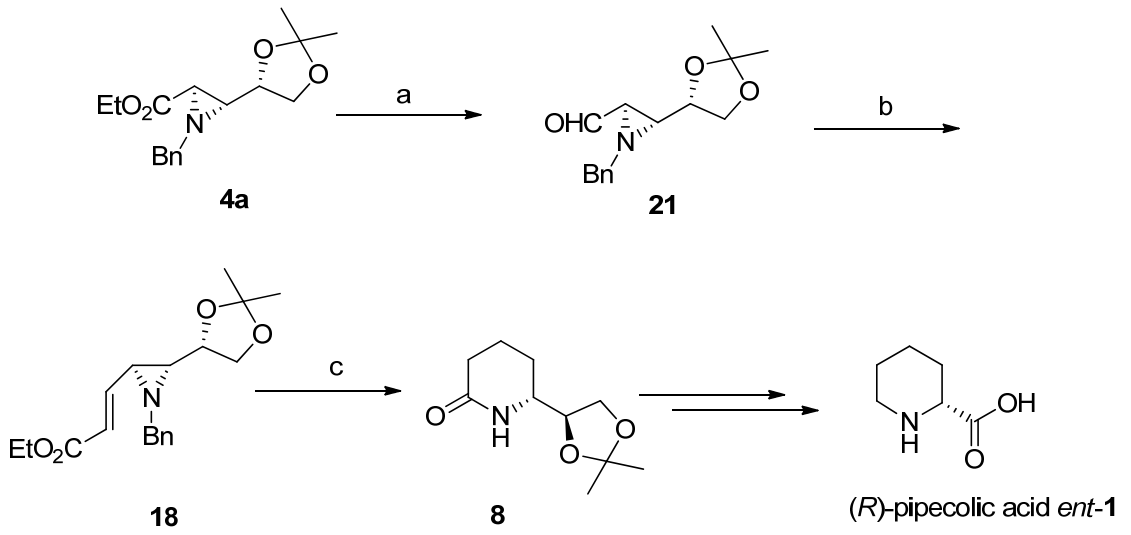
1.2.1.4.2.1 Total synthesis of (*R*)-pipecolic acid and (*R*)-ethyl-6-oxopipecolate

This section describes the total synthesis of (*R*)-pipecolic acid **1** as well as (*R)*-ethyl-6-oxopipecolate **20** which is useful intermediate for the synthesis of pipecolic acid derivatives.[21] As described earlier, *trans* aziridine **4a** having hidden C_2 symmetry would end up having same configuration at newly formed amine functionality on nucleophilic ring opening reaction (Scheme 16).



Scheme 20: Retrosynthetic analysis for (*R*)-pipecolic acid *ent*-**1** from *trans* aziridine **4a**

Thus as shown in retrosynthetic analysis (Scheme 20), *trans* aziridine **4a** on propagation from ester side would give intermediate **8** similar to that from *cis* aziridine (Scheme 17), which can be exploited to (*R*)-pipecolic acid **1** while propagation from acetonide group keeping ester functionality intact would give (*R*)-ethyl-6-oxo-pipecolate **20**, an important intermediate for pipecolic acid derivatives which can also be further converted to the same (*R*)-pipecolic acid **1**.

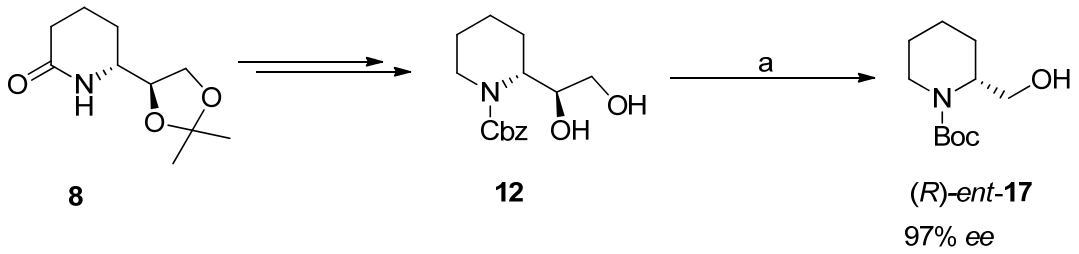


Scheme 21: ***Reagents and conditions:*** *a) DIBAL-H (1M in toluene), CH_2Cl_2, -78˚C, 1h; b) $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0 ˚C, 2h, 75% over two steps; c) Pd/C (10%), HCO_2NH_4, MeOH, 60 °C, 3h, 90%.*

Synthetic studies toward (*R*)-pipecolic acid *ent*-**1** using *trans*-aziridne-2-carboxylate **4b** are described herein (Scheme 21). Aziridne on reaction with DIBAL-H (1.2 eq.) yielded aldehyde **21**. The *trans* aziridine derived aldehyde **21** was found to be much less stable as compared to *cis* aziridine derived aldehyde **11**. 2-Carbon homologation reaction with Ph_3PCHCO_2Et resulted in low yields even at room temperature. However carrying out Horner-Wadsworth- Emmons reaction at 0 °C furnished *α,β*-unsaturated *trans* aziridine ester **18** in 75% yield over 2 steps. IR spectrum showed characteristic peaks at 1716 and 1644 cm^{-1} for *α,β*-unsaturated ester. In ^1H NMR spectrum, peaks at δ 1.33 (s, 3 H), 1.40 (s, 3H), 3.61 (dd, *J* = 5.5 & 7.9 Hz, 1H), 3.72-3.85 (m, 2H) and 3.91-4.09 (m, 2H) represented the acetonide functionality and –*N*-CH_2-benzyl protons. Peaks at δ 2.12 (dd, *J* = 2.4 & 4.9 Hz, 1H) and 2.72 (dd, *J* = 2.4 & 9.9 Hz, 1H) accounted for *trans* aziridine protons. Peaks at δ 1.30 (t, 3H), 4.20 (q, 2H), 6.13 (d, *J* = 15.2 Hz, 1H), 6.89 (dd, *J* = 9.9 & 15.2 Hz, 1H) were asigned to *α,β*-unsaturated ethyl ester. ^{13}C NMR spectrum showed all desired seventeen peaks with expected δ values as following- 14.2, 25.5, 26.7, 40.1, 49.6, 57.0, 60.3, 66.2, 76.1, 109.5, 125.1, 127.1, 127.9, 128.2, 138.6, 142.9, 165.3 ppm. Finally HRMS analysis confirmed the molecular formula (calculated for $C_{19}H_{26}O_4N$-332.1856, observed-332.1858). Following the similar protocol of aziridine ring cleavage,

lactam reduction and oxidative cleavage of diol on compound **18** similar to as shown in Scheme 17 furnished (*R*)-pipecolic acid *ent*-**1**.

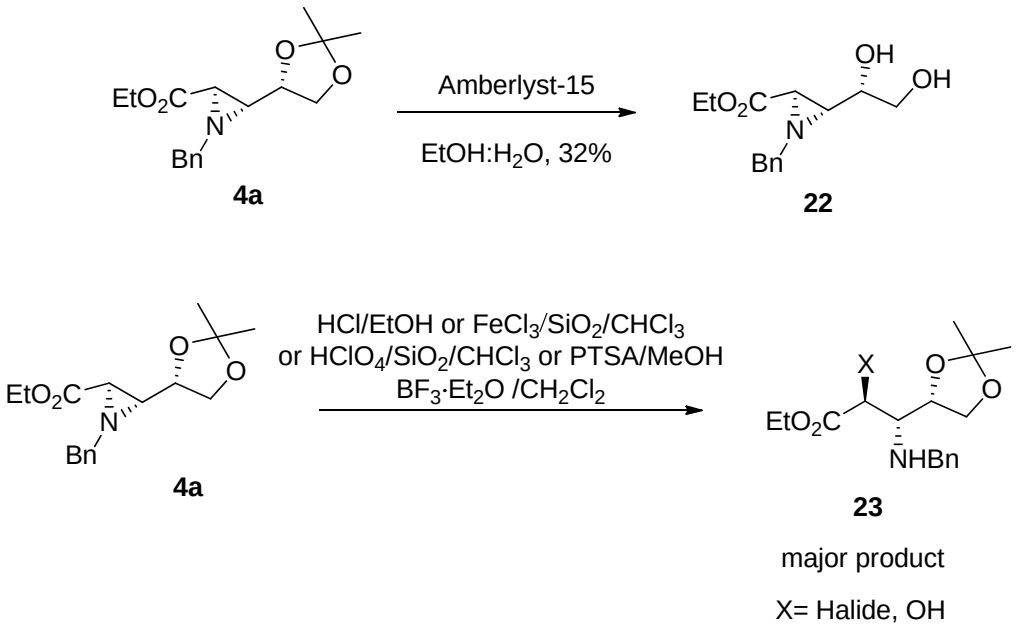
To know the enantiomeric excess of pipecolic acid, intermediate **12** derived from *trans* aziridine **4a** was converted to (*R*)-*N*-Boc-2-piperidinemethanol *ent*-**17**. Chiral HPLC analysis of (*R*)-*ent*-**17** showed enantiomeric excess of 97% (Scheme 22).



8 **12** (*R*)-*ent*-**17**
97% *ee*

Scheme 22: ***Reagents and conditions:*** *a) i) $NaIO_4$, acetone:water (2:1), 10 min; ii) $NaBH_4$, MeOH, 0 °C, 15 min; iii) Pd(C) 10%, H_2, $(Boc)_2O$, MeOH, 1h.*

To propagate on other side (*viz.* acetonide) of *trans* aziridine **4a**, major hurdle was selective deprotection of acetonide ring as it is very prone to aziridine ring opening reaction under acidic conditions because of activation by electron withdrawing group 2-ethylcarboxylate. In literature best reported yield was 32% using Amberlyst-15 (H^+) in ethanol:water as solvents (Scheme 23).[12a]



4a **22**

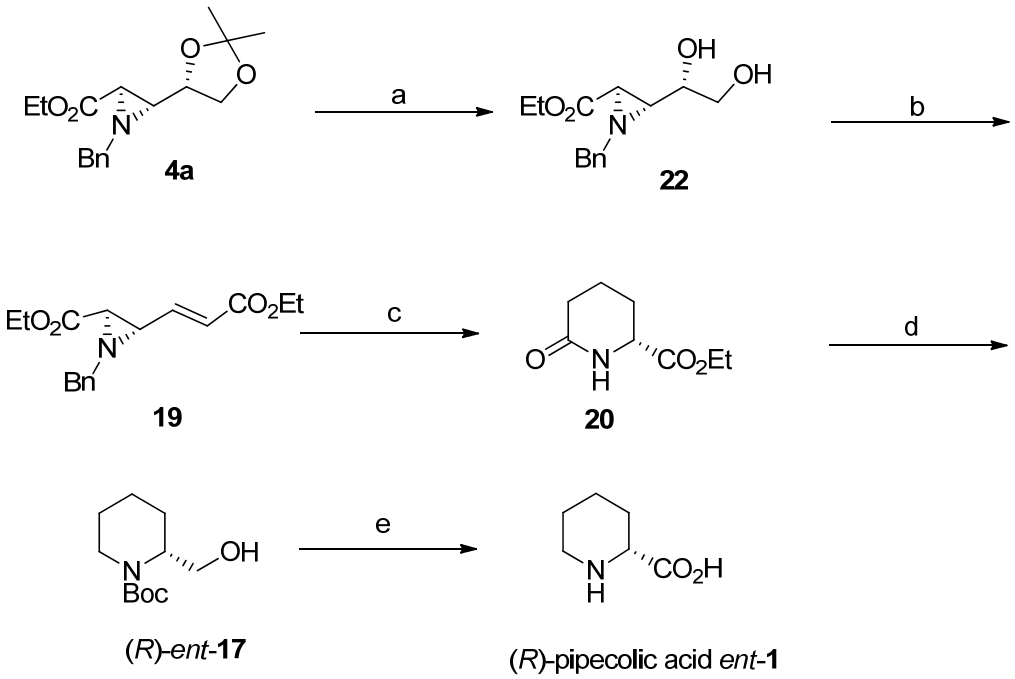
4a **23**

major product

X= Halide, OH

Scheme 23

Other Lewis acids were also tried such as HCl/EtOH, $BF_3 \cdot Et_2O/CH_2Cl_2$, $HClO_4$ adsorbed on silica, $FeCl_3 \cdot 7H_2O$ adsorbed on silica, PTSA/MeOH *etc*. However in all conditions ring opened compound was observed as major product (Scheme 23). Gratifyingly, using $TMSOTf/CH_2Cl_2$ at 0 °C,[21] led to selective deprotection of acetonide ring to furnish diol **22** with excellent yields (90%, Scheme 24).



Scheme 24: ***Reagents and conditions:*** *a) TMSOTf, CH_2Cl_2, 90%; b) i) $NaIO_4$, acetone:water; 15 min; ii) $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0 °C, 70% over two steps; c) (10%) Pd/C, HCO_2NH_4, MeOH, 60 °C, 85%; d) i) LAH, THF; ii) $(Boc)_2O$, $NaHCO_3$, $THF:H_2O$, 70% over two steps; e) i) TFA, CH_2Cl_2, 0 °C; ii) $KMnO_4$, 3N H_2SO_4, 69% over two steps.*

Diol **22** was then subjected to sodium metaperiodate mediated cleavage to yield crude aldehyde which was subjected to Horner-Wadsworth-Emmons olefination to afford *α,β*-unsaturated aziridine-ester **19** on opposite side in 70% yield over two steps. IR spectrum showed strong absorption peaks at 1720, 1651 cm^{-1} indicating ester carbonyl as well as C-C double bond functionality. ^1H NMR spectrum showed peaks at δ 1.22-1.32 (m, 6H) for $–CH_3$ group of ethyl ester. Peaks at δ 2.55-2.73 (m, 1H) and 2.59-3.17 (m, 1H) were assigned to aziridine protons. Peaks at δ 6.05-6.25 (m, 1H), 6.60.-6.89 (m, 1H) indicated

the presence of *α,β*-unsaturated ester. Remaining protons resonated at δ 3.84-4.20 (m, 8H). ^{1}H NMR pattern indicated that compound **19** exists as mixture of invertomers. ^{13}C NMR spectrum showed peaks at *δ* 14.0, 14.1, 42.9, 45.9, 54.4, 60.2, 61.1, 123.3, 127.6, 127.9, 128,2, 138.4, 145.3, 165.4 and 167.8 along with some additional peaks because of invertomerism. Finally molecular ion peak at *m/z* 326.21 $(M+Na)^+$ confirmed the formation of **19**.

Applying the similar protocol of palladium mediated one pot aziridine ring opening, hydrogenation and cyclisation as a key step on compound **19** thus gave efficient access to (*R*)-ethyl-6-oxopipecolate **20**. IR spectrum showed peaks at 1739 and 1666 cm^{-1} indicating ester and amide functinality. ^{1}H NMR spectrum showed peaks at δ 1.30 (t, *J* = 7.3 Hz, 3H) and 4.24 (q, *J* = 7.3 Hz, 2H) indicating the presence of ethyl ester. Peak at δ 6.65 (br s, 1H) indicated the presence of lactam proton. Molecular ion peak at *m/z* 194.08 $(M+Na)^+$ and HRMS analysis (calculated for $C_8H_{14}O_3N$-172.0968, observed-172.0966) confirmed the formation of pipecolate **20**.

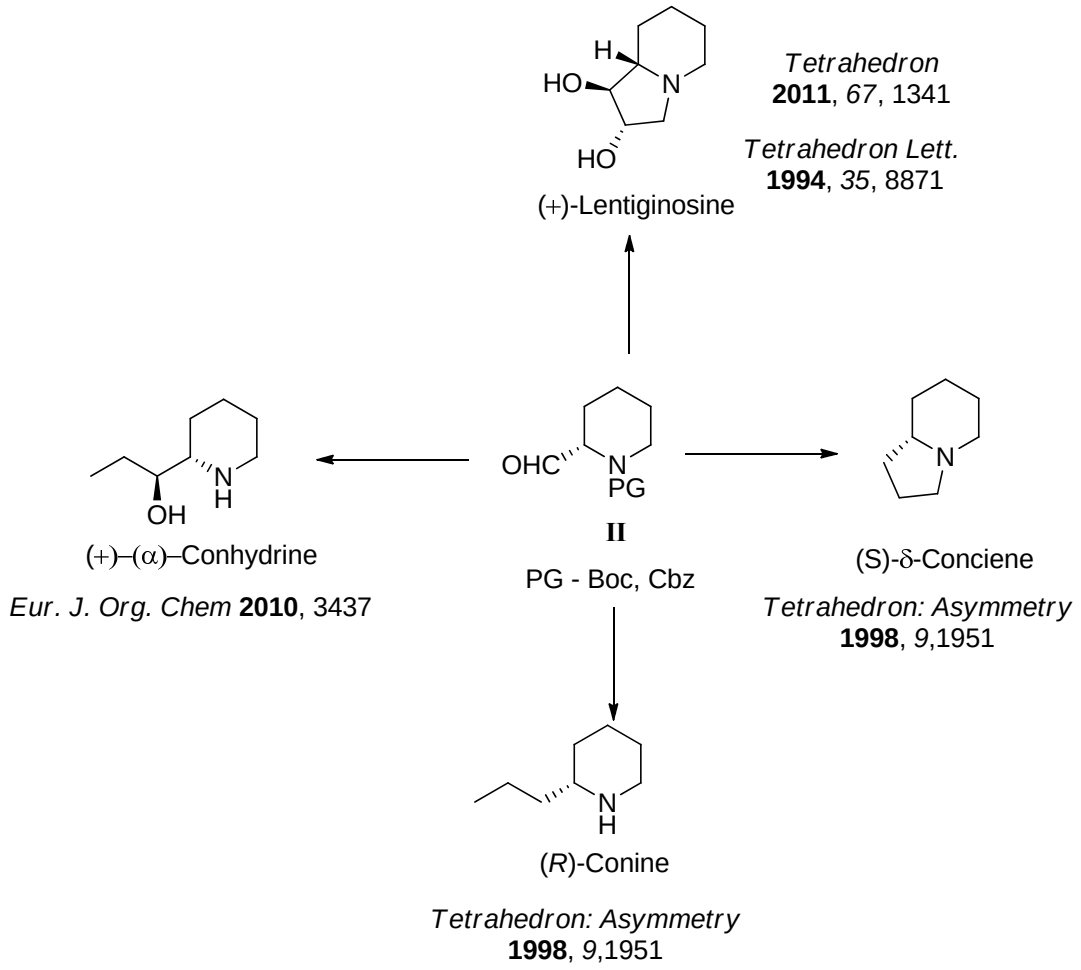
Pipecolate **20** was further converted to (*R*)-*N*-Boc-2-piperidinemethanol *ent*-**17** over two steps using LAH induced lactam/ester reduction followed by protection of resulting crude amino-alcohol as *N*-Boc derivative. Optical rotation of (*R*)-*ent*-**17** matched with (*R*)-*ent*-**17** derived from Scheme 22. Finally compound (*R*)-*ent*-**17** was converted to (*R*)-pipecolic acid *ent*-**1** by Boc deprotection using TFA followed by oxidation using $KMnO_4$ in aqueous 3 N H_2SO_4 (Scheme 24).[19]

1.2.1.4.2.2 Conclusion

In conclusion, the convenient total synthesis of (*R*)-pipecolic acid *ent*-**1** has been achieved starting from *trans* aziridine-2-carboxylate **4a** as a synthetic precursor. The synthesis of (*R*)-*ent*-**1** was achieved in 16% and 14.4% overall yields from ester side and acetonide side propagation respectively from D-mannitol diacetonide **2**. The synthesis of (*R*)-ethyl-6-oxo-pipecolate **20** was achieved in 30% overall yield from **2**.

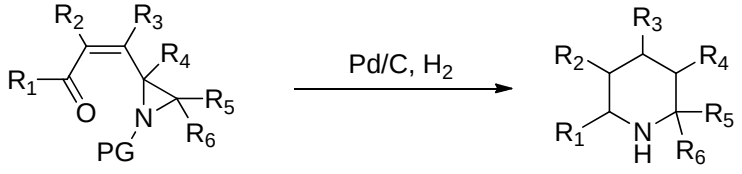
1.2.1.5 Conclusion

Thus synthetic utility of aziridine-2-carboxylates **4a/b** was successfully demonstrated by synthesizing both the enantiomers of pipecolic acid. Moreover, intermediates like pipecolate **20** and *N*-protected piperidine-2-aldehyde **II** (Scheme 25) are important precursors for various natural and non-natural biologically important products.



Scheme 25

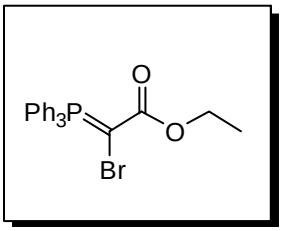
The present method not only involves simple and high-yielding reactions like one-pot aziridine ring cleavage, reduction, cyclisation to give an efficient access to piperidine skeleton but could also provide an easy practical access to the syntheses of a variety of structural analogues of substituted piperidines for evaluating their biological properties (Scheme 26).



Scheme 26

1.2.3. Experimental

Ethyl 2-bromo-2-(triphenylphosphoranylidene)acetate (10)



To the solution of Ph_3PCHCO_2Et **A** (20 g, 0.057 mol) in CH_2Cl_2 (400 mL) cooled to -78 ^oC was dropwise added equi-molar quantity of bromine (2.95 mL, 0.057 mol). The reaction was allowed to attain the room temperature and kept for overnight stirring. The CH_2Cl_2 was completely removed under vacuum, which gave a viscous compound. To this, refrigerated 2N NaOH solution was added. A fluorescent yellow coloured solid (bromophosphorane) crystallized out which was filtered and dried under suction to yield 23 g crude bromophosphorane which was recrystallized from acetone-hexane mixture, to yield yellow recrystallized product **10**.

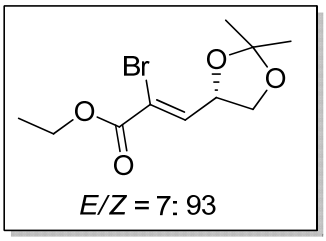
Yield: 82%.

MF: $C_{22}H_{20}BrO_2P$, **MW:** 427.27.

MP: 157-160 °C dec., lit[25] 157-158 °C.

IR ($CHCl_3$, cm^{-1}): vmax 1637, 1106, 847, 771.

(*S*)-Ethyl 2-bromo-3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (3)



Freshly prepared (*R*)-glyceraldehyde acetonide **9** (5.24 g, 0.020 mol) from Di-*O*-isopropylidene (D)-mannitol was taken in CH_2Cl_2 (75 mL). To this was added a solution of ethyl 2-bromo-2-(triphenylphosphoranylidene)acetate **10 (**18.8 g, 0.044 mol) in CH_2Cl_2 (150 mL) and stirred for 2 h at room temperature. Organic layer was separated and aqueous layer was extracted with CH_2Cl_2. Combined organic layer was dried over anhydrous Na_2SO_4, filtered and solvent was evaporated under reduced pressure. Residue was purified by column chromatography using pet ether: ethyl acetate (95:5) to give bromoester **3** (*E/Z* = 7:93).

***R_f*:** 0.5 (Pet ether-ethyl acetate, 1:9).

Yield: 10.5 g, 84% over two steps.

MF: $C_{10}H_{15}BrO_4$, **MW:** 279.12.

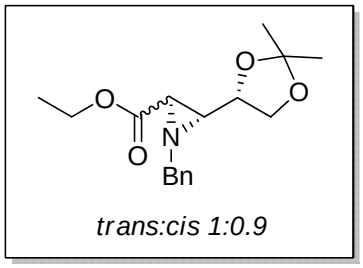
IR ($CHCl_3$, cm^{-1}): vmax 2980, 1720, 1620.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.36 (t, J = 8.0 Hz, 3H), 1.41 (s, 3H), 1.46 (s, 3H), 3.70 (dd, J = 6.6 & 8.3 Hz, 1H), 4.27 (q, J = 8.0 Hz, 3H), 4.95 (dd, J = 6.7 & 13.3 Hz, 1H), 7.36 (d, J = 6.6 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 14.1, 25.5, 26.4, 62.6, 68.0, 75.5, 110.2, 116.7, 144.0, 161.4.

MS (ESI): *m/z*: 279 $(M+H)^+$.

(*R*)-Ethyl 1-benzyl-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridine-2-carboxylate (4a/4b)



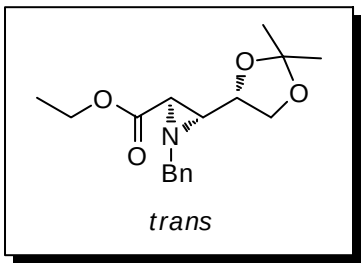
trans:cis 1:0.9

8.37 g (0.030 mol) of bromoacrylate **3** was dissolved in dry ethanol (100 mL) and the solution was stirred. To stirred solution was added 3.21 g (0.030 mol) of benzylamine and 3.03 g (0.030 mol) of triethylamine at −5 °C. The reaction mixture was stirred for 72 h at room temperature. Solvent was evaporated and residue was taken in CH_2Cl_2 (100 mL) and extracted with water (30 mL). CH_2Cl_2 was separated and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield yellow oil of *trans:cis* mixture of aziridine (**4a** and **4b**) (1:0.9) which was separated using flash chromatography (pet ether: ethyl acetate, 1:9).

Yield: 77 %.

MF: $C_{17}H_{23}NO_4$, **MW:** 305.37.

(2*R*,3*R*)-Ethyl 1-benzyl-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridine-2-carboxylate (4a)



trans

***R_f*:** 0.5 (Pet ether-ethyl acetate, 2:8)

Yield: 40 %.

IR ($CHCl_3$, cm^{-1}): νmax 2984, 1728, 1599, 1107.

$[\alpha]_D^{25}$ +52.41 (*c* 1, $CHCl_3$), {Lit.[11] **$[\alpha]_D^{25}$** +52.8 (*c* 1, $CHCl_3$)}.

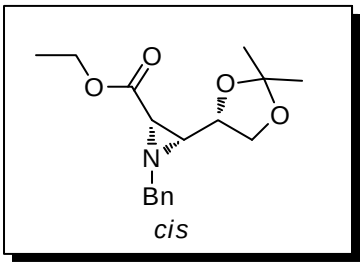
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.19 (t, J = 8 Hz, 3H), 1.34 (s, 3 H), 1.42 (s, 3 H), 2.48 (t, J = 2.4 Hz, 1H), 2.63 (d, J = 2.4 Hz, 1H), 3.63-3.68 (m, 1H), 3.86-3.97 (m, 3H), 4.07-4.17 (m, 3H), 7.27-7.32 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 14.0, 25.5, 26.6, 37.2, 47.4, 54.7, 61.2, 66.3, 75.9, 109.5, 126.9, 128.1, 138.7, 168.5.

MS (ESI): *m/z*: 306.71 $[M+H]^+$.

HRMS: Calculated for $C_{17}H_{24}NO_4$-306.1700, found-306.1694.

(2*S*,3*R*)-Ethyl 1-benzyl-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridine-2-carboxylate (4b)



***R*$_f$:** 0.4 (Pet ether-ethyl acetate, 2:8)

Yield: 37 %

IR ($CHCl_3$, cm^{-1}): vmax 2986, 1728, 1600, 1107.

$[\alpha]_D^{25}$ −9.7 (*c* 1, $CHCl_3$), {Lit.[1] **$[\alpha]_D^{25}$** −9.9 (*c* 1, $CHCl_3$)}

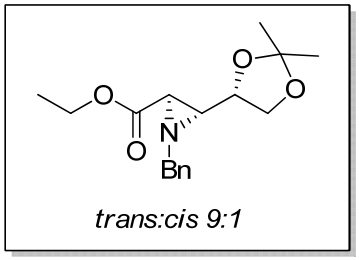
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.18 (t, 3H), 1.27 (s, 3 H), 1.37 (s, 3H), 2.08 (t, *J* = 6.7 Hz, 1H), 2.23 (d, *J* = 6.7 Hz, 1H), 3.42 (d, *J* = 13.0 Hz, 1H), 3.66 (dd, *J* = 6.0 & 8.0 Hz, 1H), 3.89-3.97 (m, 2H), 4.11-4.22 (m, 3H), 7.27-7.35 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 14.1, 25.3, 26.8, 40.4, 47.8, 61.0, 63.2, 66.9, 75.2, 109.6, 127.2, 127.9, 128.2, 137.2 , 168.9.

MS (ESI): *m/z*: 306.18 $[M+H]^+$.

HRMS: Calculated for $C_{17}H_{24}NO_4$-306.1700, found-306.1698.

(2*R*,3*R*)-Ethyl 1-benzyl-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridine-2-carboxylate (4a)



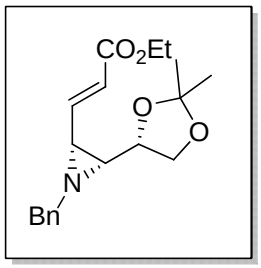
8.37 g (0.030 mol) of bromoacrylate **3** was dissolved in dry toluene (100 mL) and the solution was stirred. To stirred solution was added 3.21 g (0.030 mol) of benzylamine and 3.03 g (0.030 mol) of triethylamine at −5 °C. The reaction mixture was stirred for 24 h at room temperature. Solvent was filtered on simple filter paper, residue was again washed with toluene (20 mL) and concentrated under reduced pressure to yield yellow oil of *trans* aziridine **4a** as major isomer and *cis* aziridine **4b** as minor isomer in ratio of 9:1 which were separated using flash chromatography (pet ether-ethyl acetate, 1:9).

Yield: 75%

For **4a- Yield:** 68%.

For **4b- Yield:** 7%.

(*E*)-Ethyl-3-((2*R*,3*R*)-1-benzyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)aziridin-2-yl)acrylate (7)



To a stirred solution of *cis* aziridine 2-carboxylate **4b** (1 gm, 3.27 mmol) in dry CH_2Cl_2 (30 mL) was added DIBAL-H (3.94 mL, 3.59 mmol, 1 M solution in toluene) at -78 °C slowly over period of 15 min and stirred for another 15 min. TLC showed complete conversion of ester to aldehyde. Reaction was quenched by careful addition of pre-cooled MeOH (1 mL) and allowed to warm to 0 °C. Roche's salt (saturated solution of sodium potassium tartarate, 10 mL) was added and stirred for 0.5 h after which organic layer was separated and aqueous layer was washed with CH_2Cl_2 (3 × 20 mL). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and used as such for next reaction. To a stirred solution of aldehyde and (carboethoxymethylene) triphenylphosphorane (1.7 g, 4.9 mmol) dissolved in toluene (30 mL) was added benzoic acid (cat., 0.05 g) and refluxed for 6 h. Reaction mass was concentrated and purified on flash column chromatography (pet ether-ethyl acetate, 1:9) to give compound **7** (0.89 g) as thick colorless oil.

***R_f*:** 0.5 (Pet ether-ethyl acetate, 8:2).

Yield: 82%, over 2 steps.

MF: $C_{19}H_{25}NO_4$, **MW:** 331.40.

IR ($CHCl_3$, cm^{-1}): vmax 2983, 2925, 1716, 1651, 1261.

$[\alpha]_D^{25}$ +29.41 (*c* 1.7, $CHCl_3$).

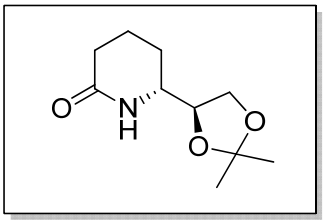
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.30 (t, J = 7.0 Hz, 3H), 1.35 (s, 3H), 1.43 (s, 3H), 2.01 (dd, J = 6.9 & 8.0 Hz, 1H), 2.22 (t, J = 6.9 Hz, 1H), 3.33 (d, J = 13.6 Hz, 1H), 3.57-3.69 (m, 1H), 3.84-4.02 (m, 2H), 4.18 (q, J = 7.0 Hz, 2H), 6.08 (dd, J = 0.05 & 15.7 Hz, 1H), 6.73 (dd, J = 7.3 & 15.7 Hz, 1H), 7.27-7.35 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 14.1, 25.4, 26.7, 42.1, 49.1, 60.1, 63.69, 66.9, 75.7, 109.4, 123.7, 127.0, 127.7, 128.1, 137.8, 144.3, 165.3.

MS (ESI): *m/z*: 354.10 $[M+Na]^+$.

HRMS: Calculated for $C_{19}H_{26}O_4N$-332.1856, found-332.1858.

(*R*)-6-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)piperidin-2-one (8)



To a stirred solution of aziridine ester **7** (0.66 g, 1.99 mmol) in methanol (10 mL) was added ammonium formate (1.24 g, 19.9 mmol) and 10% Pd/C (100 mg), and the mixture was refluxed for 3 h. The reaction mixture was filtered through Celite, concentrated and purified by column chromatography (pet ether-ethyl acetate, 2:8) to afford **8** as a thick yellowish liquid.

***R*$_f$:** 0.4 (Ethyl acetate)

Yield: 0.36 g, 90%.

MF: $C_7H_{17}NO_3$, **MW**: 199.25.

$[\alpha]_D^{25}$ −20 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): vmax 3402, 2985, 2936, 1664, 1457, 1371, 1072.

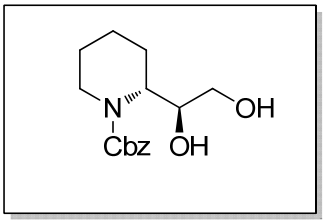
^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 1.20-1.28 (m, 1H), 1.33 (s, 3H), 1.40 (s, 3H), 1.63-1.83 (m, 2H), 1.85-2.01 (m, 1H), 2.17-2.49 (m, 2H), 3.31 (td, *J* = 5.4 & 8.7 Hz, 1H), 3.66 (dd, *J* = 5.4 & 8.2 Hz, 1H), 3.86-3.88 (m, 1H), 4.03 (dd, *J* = 6.0 & 8.2 Hz, 1H), 6.21 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 19.7, 24.8, 25.3, 26.8, 31.3, 56.2, 66.2, 79.1, 109.79, 171.2.

MS (ESI): *m/z*: 200.11 $(M+H)^+$, 222.10 $(M+Na)^+$.

HRMS: Calculated for $C_7H_{18}NO_3$-200.1281, found-200.1277.

(*R*)-Benzyl 2-((*S*)-1,2-dihydroxyethyl)piperidine-1-carboxylate (12)



The lactam **8** (0.5 g, 2.5 mmol) was dissolved in dry THF (15 mL) in an oven-dried flask under a nitrogen atmosphere, then borane–methyl sulfide (0.67 mL, 7.5 mmol) was added dropwise *via* syringe. Once the evolution of H_2 had ceased, the solution was heated under reflux for 5 h and the solvents were removed *in vacuo*. The resulting crude mass was carefully diluted with 6 M HCl (15 mL) and refluxed for 3 h. The resulting solution was evaporated under *vaccum*, was basified by adding aqueous $NaHCO_3$ (3 mL, ~ pH – 8-9), THF (3 mL) was added followed by Cbz-Cl (0.711 mL, 5 mmol) and stirred for 2 h. Resulting organic mass was extracted with ethyl acetate (3 × 15 mL), washed with brine, dried over anhydrous Na_2SO_4, filtered

and column purified over silica gel (pet ether:ethyl acetate, 1:9) to furnish diol **12** as thick liquid.

***R*$_f$:** 0.4 (Pet ether-ethyl acetate, 2:8)

Yield: 0.53 g, 75% over two steps.

MF: $C_{15}H_{21}NO_4$, **MW**: 279.33.

$[\alpha]_D^{25}$ +35.4 (*c* 1, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): νmax 3417, 2935, 2867, 1670, 1260.

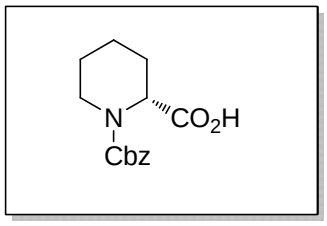
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.39-1.67 (m, 6H), 2.77 (br s, 2H), 3.48-3.57 (m, 1H), 3.68-3.82 (m, 2H), 3.88-4.13 (m, 2H), 4.27-4.31 (m, 1H), 5.13 (s, 2H), 7.34-7.43 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.5, 25.0, 26.4, 40.1, 52.4, 66.8, 67.1, 74.3, 109.3, 127.5, 127.6, 128.2, 136.8, 155.7.

MS (ESI): *m/z*: 280.22 $(M+H)^+$, 302.20 $(M+Na)^+$.

Elemental analysis: Calcd.**:** C-64.50, H-7.58, N-5.01; found: C-64.10, H-7.33, N-4.96.

(*R*)-1-((Benzyloxy)carbonyl)piperidine-2-carboxylic acid (13)



To a suspension of $NaIO_4$ (0.23 g, 1.1 mmol) in $CH_3CN/CCl_4/H_2O$ (4.8 mL, 1:1:10) was added $RuCl_3 \cdot H_2O$ (11.4 mg, 0.055 mmol) in small portions and the mixture was stirred at room temperature for 45 min. The resulting solution was added to the diol **8** (0.15 g, 0.55 mmol) dissolved in CH_3CN (3 mL) followed by the addition of a second portion of $NaIO_4$ (0.23 g, 1.1 mmol). The resulting mixture was stirred at room temperature for 1 h and filtered through Celite and the Celite layer was washed thoroughly with EtOAc. The combined filtrate was dried over Na_2SO_4, filtered and concentrated. The crude product thus obtained was purified by flash column chromatography (pet ether-ethyl acetate, 3:7) to yield the pure acid **13** as a white solid.

***R*$_f$:** 0.4 (Pet ether-ethyl acetate, 6:4)

Yield: 0.088 g, 60%.

MF: $C_{14}H_{17}NO_4$, **MW**: 263.28

MP: 111 °C, lit.[22] 111–113 °C.

IR ($CHCl_3$, cm^{-1}): νmax 3700–3000, 2972, 1733, 1652, 1470, 1280.

$[\alpha]_D^{25}$ +55.1 (*c* 1.15, AcOH), {lit.[23] **$[\alpha]_D^{25}$** +56.5, (c 0.55, AcOH)}

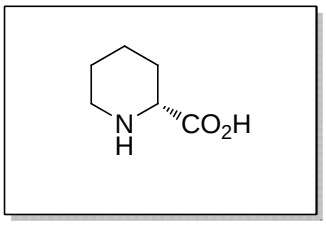
^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): δ 1.33-1.47 (m, 2H), 1.65-1.72 (m, 3H), 2.24-2.33 (m, 1H), 2.98-3.13 (m, 1H), 4.08 (dd, *J* = 8 Hz, 11 Hz, 1H), 4.89-5.02 (m, 1H), 5.16 (s, 2H), 7.27-7.32 (m, 5H), 10.63 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 20.6, 24.6, 26.6, 41.8, 54.3, 67.5, 127.8, 128.4, 136.4, 155.8, 156.6, 177.3.

MS (ESI): *m/z*: 264.26 $(M+H)^+$, 286.23 $(M+Na)^+$.

HRMS: Calculated for $C_{14}H_{17}NO_4Na$-286.1050, found-286.1047.

(*R*)-Piperidine-2-carboxylic acid (*ent*-1)



A solution of compound *N*-Cbz-(*R*)-pipecolic acid **7** (0.1 g, 0.49 mmol) in dry EtOH (5 mL) was mixed with Pd/C (10%) (20 mg) and AcOH (0.1 mL) in a hydrogenation flask (50 psi) and then the mixture was vigorously shaken at ambient temperature for 3 h. Then the mixture was filtered through a pad of Celite. After the evaporation of the solvent under vacuum, the precipitate was collected by filtration, washed with Et_2O and dried under high vacuum to afford pure (*R*)-pipecolic acid **4** (0.06 g).

***R_f*:** 0.4 (CH_2Cl_2-MeOH-NH_4OH, 9:1:1%)

Yield: 95%

MF: $C_6H_{11}NO_2$, **MW**: 129.07

MP: 271-273 °C; lit.[23] 271-274 °C.

$[\alpha]_D^{25}$ +24.9 (*c* 1.15, H_2O) {Lit.[23] **$[\alpha]_D^{25}$** +25.8 (*c* 1, H_2O)}.

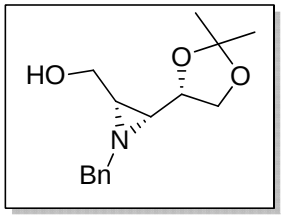
^{1}H NMR (400 MHz, D_2O): δ 1.46-1.64 (m, 3H), 1.73-1.80 (m, 2H), 2.14-2.18 (m, 1H), 2.87-2.94 (m, 1H), 3.31-3.54 (m, 1H), 3.78 (dd, *J* = 8.0 Hz & 10.0 Hz, 1H).

^{13}C NMR (100 MHz, D_2O): δ 21.5, 21.6, 26.0, 44.0, 57.2, 172.2.

MS (ESI): *m/z*: 152.28 $(M+Na)^+$.

((2*S*,3*R*)-1-Benzyl-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridin-2-yl)methanol (14)

To an ice-cooled suspension of LAH (0.124 g, 3.27 mmol) in dry THF (4 mL) was added ester **4b** (1 g, 3.27 mmol) in dry THF (10 mL) at 0 °C and the mixture was stirred for 10-15 min. The reaction mixture was quenched carefully with minimum amount of water,



followed by 15% NaOH (0.2 mL). Again 0.5 mL of water was added and stirred for 0.5 h at room temperature. Anhydrous Na_2SO_4 was added and again stirring continued for 0.5 h. Filtration through Celite, concentration under vacuum and purification by column chromatography (pet ether–ethyl acetate, 1:1) gave **14** as a white crystalline solid (0.77 g).

***R_f*:** 0.3 (Pet ether-ethyl acetate, 1:1)

Yield: 90 %.

MP: 82-84 °C (Lit.[1] 82-84 °C).

MF: $C_{15}H_{21}NO_3$, **MW**: 263.33.

$[\alpha]_D^{25}$ +32.1 (*c* 0.85, $CHCl_3$) {Lit.[11] **$[\alpha]_D^{25}$** +32.6 (*c* 1, $CHCl_3$)}.

IR ($CHCl_3$, cm^{-1}): vmax. 3369, 2984, 2930, 1604, 1454, 1372, 1061.

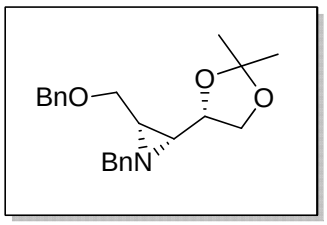
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.35 (s, 3H), 1.43 (s, 3H), 1.76 (m, 2H), 2.32 (br s, 1H), 3.25 (d, *J* = 13.2 Hz, 1H), 3.47-3.69 (m, 3H), 3.90 (d, *J* = 13.2 Hz, 1H), 3.94-4.04 (m, 2H), 7.35 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 25.3, 26.6, 43.1, 45.6, 59.8, 63.5, 67.2, 75.4, 109.1, 126.9, 127.8, 128.1, 138.1.

MS (ESI) *m/z*: 286.1 $(M+H)^+$.

HRMS: Calculated for $C_{15}H_{22}NO_3$-264.1594, found-264.1603.

(2*S*,3*R*)-1-Benzyl-2-((benzyloxy)methyl)-3-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridine (15)



To a slurry of NaH (0.053 g, 2.28 mmol) in dry DMF (5 mL) at 0 °C was added a solution of alcohol **14** (0.5 g, 1.9 mmol) in DMF (5 mL) followed by TBAI (cat.) and the mixture was stirred for five minutes. Benzyl bromide (0.27 mL, 2.28 mmol) was added dropwise and stirred well while warming to room temperature for 3 h. Reaction mixture was poured into water (30 mL) and the organic layer was extracted with ethyl acetate (3 ×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent was removed *in vacuo*. The crude compound was purified by flash column chromatography to afford **15** (0.64 g) as a colorless oil.

***R_f*:** 0.5 (Pet ether-ethyl acetate, 7:3)

Yield: 95 %.

MF: $C_{22}H_{27}NO_3$, **MW**: 353.45.

$[\alpha]_D^{25}$ −23 (c 1.2, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): vmax 2922, 1610, 1455, 1088.

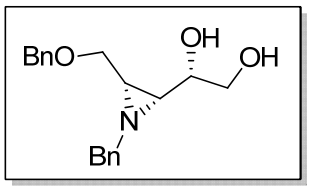
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.34 (s, 3H), 1.43 (s, 3H), 1.76 (t, J = 6.9 Hz, 1H), 1.89 (q, J = 6.9 Hz, 1H), 3.32-3.40 (m, 2H), 3.61-3.73 (m, 2H), 3.80-3.98 (m, 2H), 4.38, 4.46 (ABq, J = 11.9 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 25.5, 26.8, 41.1, 45.1, 63.9, 67.5, 69.2, 73.0, 76.0, 109.2, 127.0, 127.6, 128.0, 128.1, 128.3, 131.7, 138.5.

MS (ESI): *m/z*: 376.14 $(M+Na)^+$.

HRMS: Calculated for $C_{22}H_{28}O_3N$ -354.2064, found**:** 354.2074.

(*S*)-1-((2*R*,3*S*)-1-Benzyl-3-((benzyloxy)methyl)aziridin-2-yl)ethane-1,2-diol (16)



To a stirred solution of acetonide (0.8 g, 2.25 mmol) in methanol:water (10 mL, 9:1) was added PTSA·H_2O (0.2 g, 1 mmol) and stirring continued for 3 h. The reaction was monitored by TLC and on completion was quenched by solid $NaHCO_3$. Solvent was evaporated and reaction mixture was subsequently partitioned between H_2O (10 mL) and ethyl acetate (3 × 25 mL). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered and concentrated to obtain the residue which was purified by column chromatography (pet ether-ethyl acetate, 1:1) to give diol **16**.

***R_f*:** 0.45 (Pet ether-ethyl acetate, 1:1)

Yield: 0.603 g, 85 %

MF: $C_{19}H_{23}NO_3$, **MW**: 313.39.

$[\alpha]_D^{25}$ −20 (*c* 1, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): vmax 2935, 1604, 1496, 1453, 1095.

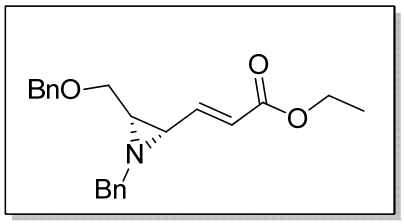
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.81 (t, J = 6.2, Hz, 1H), 2.09 (q, J = 6.2 Hz, 1H), 3.47-3.70 (m, 7H), 4.45, 4.49 (ABq, J = 11.8 Hz, 2H), 7.27-7.32 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 43.0, 44.5, 64.0, 65.3, 68.8, 68.8, 73.2, 127.5, 127.7, 128.3, 128.4, 128.5, 137.7, 138.2.

MS (ESI): *m/z*: 314.12 $(M+H)^+$.

HRMS: Calculated for $C_{19}H_{24}O_3N$-314.1751, found-314.1747.

(*E*)-Ethyl 3-((2S,3S)-1-benzyl-3-((benzyloxy)methyl)aziridin-2-yl)acrylate (5)



Diol **16** (0.5 g, 1.90 mmol) was dissolved in acetone–water (10 mL, 2:1) at 0 °C, treated with sodium meta-periodate (0.610 g, 2.85 mmol) and stirred at 15 °C for 15 min. The reaction was quenched using ethylene glycol (0.01 mL), extracted with CH_2Cl_2 (3 × 15 mL), washed with brine and dried over sodium sulfate. The combined organics were concentrated and dried to afford crude aldehyde which was used as such for next reaction.

To a solution of aziridine aldehyde from above reaction in dry toluene (25 mL) was added (carboethoxymethylene) triphenylphosphorane (1.3 g, 3.8 mmol) and catalytic benzoic acid (0.05 g) and the reaction mixture was refluxed for 4 h. The toluene was evaporated and the reaction mixture was adsorbed on silica gel. Purification by column chromatography (pet ether–ethyl acetate, 9:1) gave **5** as a thick liquid.

***R_f*:** 0.5 (Pet ether-ethyl acetate, 8:2)

Yield: 0.48 g, 85% over two steps.

MF: $C_{22}H_{25}NO_3$, **MW**: 351.44.

$[\alpha]_D^{25}$ −48.52 (*c* 1.03, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): νmax 2922, 1715, 1651, 1495, 1453, 1303, 1263.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.30 (t, *J* = 7.0 Hz, 3H), 2.15-2.32 (m, 1H), 3.41-3.69 (m, 4H), 4.20 (q, *J* = 7.0 Hz, 2H), 4.39, 4.53 (ABq, *J* = 12.0 Hz, 2H), 6.05 (d, *J* = 15.5 Hz, 1H), 6.77 (dd, *J* = 6.8 & 15.5 Hz, 1H), 7.24-7.36 (m, 10H).

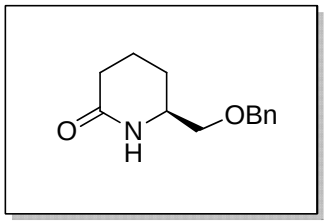
^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 14.2, 42.9, 46.2, 60.2, 63.8, 68.5, 72.9, 123.6, 127.1, 127.5, 127.6, 127.8, 128.2, 128.3, 137.9, 138.2, 144.4, 165.7.

MS (ESI): *m/z*: 374.09 $(M+Na)^+$.

HRMS: Calculated for $C_{22}H_{26}O_3N$-352.1907, found-352.1902.

(*S*)-6-((Benzyloxy)methyl)piperidin-2-one (6)

To a stirred solution of aziridine ester **5** (0.231 g, 0.66 mmol) in methanol (10 mL) was added ammonium formate (0.4 g, 6.6 mmol) and 10% Pd/C (200 mg), and the mixture



refluxed for 3 h. The reaction mixture was filtered through Celite, concentrated and purified by column chromatography (pet ether–ethyl acetate, 2:8) to afford **6** as a white solid.

***R*$_f$:** 0.35 (Ethyl acetate)

Yield: 0.127 g, 88%.

MF: $C_{13}H_{17}NO_2$, **MW**: 219.27.

MP: 59-62 ºC

[α]$_D^{25}$ +10.08 (*c* 1.19, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): vmax 2985, 2936, 1660, 1457.

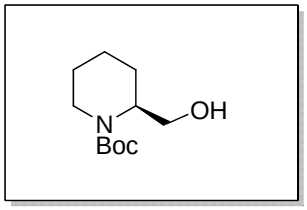
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.25-1.44 (m, 1H), 1.62-1.93 (m, 3H), 2.16-2.47 (m, 2H), 3.27 (t, *J* = 8.9 Hz, 1H), 3.48 (dd, *J* = 3.7 & 8.9 Hz, 1H), 3.57-3.67 (m,1H), 4.53, 4.56 (ABq, *J* = 12 Hz, 2H), 6.44 (br s, 1H), 7.24-7.37 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ 19.3, 24.5, 31.2, 52.2, 73.0, 73.4, 127.4, 127.6, 128.2, 137.3, 171.8.

MS (ESI): *m/z*: 220.67 $(M+H)^+$.

Elemental analysis: Calcd.**:** C-71.21, H-7.81, N-6.39; found: C-71.68, H-7.55, N-6.23.

(*S*)-*tert*-Butyl 2-(hydroxymethyl)piperidine-1-carboxylate (17)



To a stirred suspension of LAH (0.125g, 3.28 mmol) in dry THF (5 mL) was added amide **6** (0.24 g, 1.1 mmol) dissolved in dry THF (5 mL) slowly at 0 °C *via* syringe under inert atmosphere (N_2 gas). After refluxing for 6 h, the reaction mixture was cooled to 0 °C, quenched carefully with minimum amount of water followed by 15% NaOH (0.2 mL). Again 0.5 mL of water was added and stirred for 0.5 h at room temperature. Anhydrous Na_2SO_4 was added and stirring continued for another 0.5 h. Filtration through Celite and concentration under vacuum gave crude amine which was used as such for next reaction.

A solution of amine in dry MeOH (15 mL) was mixed with Pd/C (10%, 50 mg) and $(Boc)_2O$ (0.35 mL, 1.5 mmol) in a hydrogenation flask (50 psi) and then the mixture was vigorously shaken at ambient temperature for 6 h. The reaction mixture was filtered through Celite, concentrated and purified by column chromatography (pet ether–ethyl acetate, 8:2) to afford **17** as a white solid.

***R_f*:** 0.5 (Pet ether-ethyl acetate, 7:3).

Yield: 0.176 g, 75% over two steps.

MF: $C_{11}H_{21}NO_3$, **MW**: 215.289

MP: 81-84°C, lit[24] 81-84°C.

$[\alpha]_D^{25}$ −38.2 (*c* 1.2, $CHCl_3$), { Lit[24] **$[\alpha]_D^{25}$** −40.5 (*c* 1, $CHCl_3$)}.

IR ($CHCl_3$, cm^{-1}): vmax 3443, 2940, 2890, 1655, 1280.

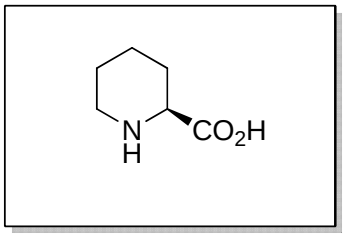
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.46 (s, 9H), 1.60-1.65 (m, 6H), 2.11 (br s, 1H), 2.87 (t, *J* = 13.0 Hz, 1H), 3.59 (dd, *J* = 5.9 & 11.0 Hz, 1H), 3.79 (dd, *J* = 9.0 & 11.0 Hz, 1H), 3.93 (br d, *J* = 13.5 Hz, 1H), 4.25-4.29 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 19.3, 24.8, 25.1, 28.3, 39.7, 52.0, 60.6, 79.4, 155.8.

MS (ESI): *m/z*: 238 $(M+Na)^+$.

HRMS: Calculated for $C_{11}H_{22}O_3N$-216.1954, found-216.1600.

(*S*)-Piperidine-2-carboxylic acid (1)



To a solution of alcohol (*S*)-**17** (0.1 g, 0.465 mmol) in CH_2Cl_2 (5 mL) at 0 °C, was slowly added TFA (0.1 mL, 1.3 mmol) and the reaction mixture was stirred at same temperature for 0.5 h, concentrated and resulting salt was used as such for next step.

To a solution of salt from above step in 3N H_2SO_4 (4.5 mL) at 10 °C, was slowly added $KMnO_4$ (0.12 g, 0.744 mmol) and the reaction mixture was stirred at room temperature for 3 h, filtered through a pad of Celite and concentrated. (*S*)-Pipecolic acid **1** was isolated after elution on Dowex 50W-X4 ion-exchange column (NH_4OH, 1 N).

Yield: 0.04 g, 69%.

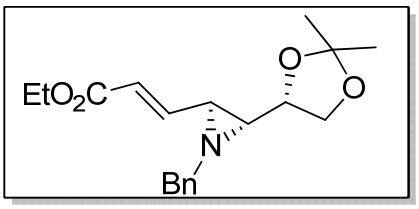
MF: $C_6H_{11}NO_2$, **MW**: 129.07

MP: 268-270 °C, lit.[23] 271-274 °C.

$[\alpha]_D^{25}$ −25.2 (*c* 0.4, water), {Lit.[23] **$[\alpha]_D^{25}$** −25.9 (*c* 1, water)}.

For ^{1}H NMR and ^{13}C NMR data please refer (*R*)-*ent*-**1.**

(*E*)-Ethyl 3-((2*S*,3*R*)-1-benzyl-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridin-2-yl)acrylate (18)



To a stirred solution of *trans* aziridine-2-carboxylate **4a** (1 g, 3.27 mmol) in dry CH_2Cl_2 (30 mL) was added DIBAL-H (3.6 mL, 3.6 mmol, 1 M solution in toluene) at −78 °C slowly over period of 15 min and stirred for another 15 min. TLC showed complete convertion of ester to aldehyde. Reaction was quenched by addition of MeOH (0.3 mL) and allowed to warm to 0 °C. Saturated aqueous NH_4Cl (10 mL) was added and stirred for 0.25 h after which organic layer was separated and aqueous layer was washed with CH_2Cl_2 (3 × 20 mL). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* and used as such for next reaction.

To a stirred solution NaH (0.09 g, 3.6 mmol, prewashed with dry *n*-hexane) dissolved in THF (10 mL) was added triethyl phosphonoacetate (0.71 mL, 3.6 mmol) slowly at 0 °C and stirred for 10 minutes. The aldehyde from above reaction dissolved in 5 ml of dry THF was added and stirring continued for another 2 h at same temperature until completion of reaction. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were then washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification on flash column chromatography (pet ether:ethyl acetate, 1:9) furnished compound **18** (0.75 g) as thick colorless oil.

***R_f*:** 0.5 (Pet ether-ethyl acetate, 8:2)

Yield: 75%, over two steps.

MF: $C_{19}H_{25}NO_4$, **MW:** 331.41.

IR ($CHCl_3$, cm^{-1}): vmax 2984, 2932, 1716, 1644, 1370, 1265.

$[\alpha]_D^{25}$ -34 (*c* 1, $CHCl_3$).

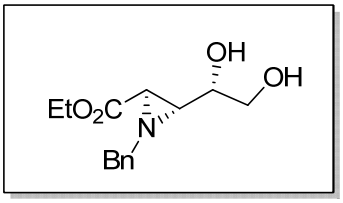
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.30 (t, *J* = 7.0 Hz, 3H), 1.33 (s, 3H), 1.40 (s, 3H), 2.12 (dd, *J* = 2.6 & 4.9 Hz, 1H), 2.72 (dd, *J* = 2.4 & 9.9 Hz, 1H), 3.61 (dd, *J* = 5.5 & 7.9 Hz, 1H), 3.72-3.85 (m, 2H), 3.91-4.09 (m, 2H), 4.20 (q, *J* = 7.0 Hz, 2H), 6.13 (d, *J* = 15.2 Hz, 1H), 6.89 (dd, *J* = 9.9 & 15.2 Hz, 1H), 7.26-7.35 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 14.2, 25.5, 26.7, 40.1, 49.6, 57.0, 60.3, 66.24, 76.1, 109.5, 125.1, 127.1, 127.9, 128.2, 138.6, 142.9, 165.3.

MS (ESI): *m/z*: 354.15 $[M+Na]^+$.

HRMS: Calculated for $C_{19}H_{26}O_4N$-332.1856, found-332.1858.

(2*R*,3*R*)-Ethyl -1-benzyl-3-((*S*)-1,2-dihydroxyethyl)aziridine-2-carboxylate (22)



To a stirred, ice-cold solution of the aziridine acetonide **4a** (0.163 g, 0.53 mmol) in anhydrous CH_2Cl_2 (2 mL) under an inert atmosphere, was added TMSOTf (0.24 mL, 1.3 mmol) through a syringe. The resulting solution was stirred at the same temperature for 1h, followed by quenching the reaction by addition of a saturated aqueous $NaHCO_3$ solution. After stirring the mixture for 5 min, the organic layer was separated and the aqueous layer was saturated with solid NaCl and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. Concentration of the solvent under reduced pressure and column chromatographic purification (pet ether-ethyl acetate, 7:3) of the residue provided the pure acetonide-cleaved product **22** as a thick liquid (0.127 g).

***R_f*:** 0.4 (Pet ether-ethyl acetate, 1.1)

Yield: 90%.

MF: $C_{14}H_{19}NO_4$, **MW**: 265.30.

$[\alpha]_D^{25}$ +20.22 (*c* 2.1, $CHCl_3$), {Lit[12a] **$[\alpha]_D^{25}$** +19.6 (*c* 0.56, $CHCl_3$)}.

IR ($CHCl_3$, cm^{-1}): vmax 3588, 3369, 2927, 1727, 1603, 1454, 1371, 1193.

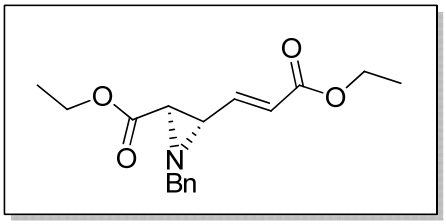
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.23 (t, *J* = 7.2 Hz, 3H), 2.52 (t, *J* = 2.9 Hz, 1H), 2.75 (d, *J* = 2.9 Hz, 1H), 3.26-3.32 (m, 1H), 3.44-3.50 (m, 1H), 3.61 (br s, 1H), 3.96 (s, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 7.27-7.31 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 14.1, 37.4, 46.4, 54.4, 61.3, 65.2, 69.1, 127.5, 128.5, 128.6, 138.4, 168.5.

MS (ESI): *m/z*: 266.13 $(M+H)^+$, 288.10 $(M+Na)^+$.

HRMS: Calculated for $C_{14}H_{20}O_4N$-266.1387, found-266.1385.

(2*R*,3*S*)-Ethyl 1-benzyl-3-((E)-3-ethoxy-3-oxoprop-1-en-1-yl)aziridine-2-carboxylate (19)



Diol **22** (0.21 g, 0.79 mmol) was dissolved in acetone–water (3 mL, 2:1) at 0 ℃, treated with sodium metaperiodate (0.203 g, 0.95 mmol) and stirred at 15 ℃ for 15 min. The reaction was quenched using ethylene glycol (0.01 mL), extracted with CH_2Cl_2 (3 × 15 mL), washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to afford crude aldehyde which was used as such for next reaction.

To a stirred solution of NaH (0.038 g, 1.58 mmol, prewashed with *n*-hexane) dissolved in THF (2 mL), was added triethyl phosphonoacetate (0.31 mL, 1.58 mmol) slowly at 0 °C and stirred for 10 minutes. The aldehyde from above reaction dissolved in dry THF (3 mL) was added and stirring continued for another 2 h at same temperature until completion of reaction. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were then washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification on flash column chromatography (pet ether-ethyl acetate, 1:9) furnished compound **19** (0.168 g) as thick colorless oil.

***R*$_f$:** 0.5 (Pet ether-ethyl acetate, 8:2)

Yield: 0.168 g, 70%

MF: $C_{17}H_{21}NO_4$, **MW**: 303.35.

$[\alpha]_D^{25}$ −36 (*c* 1, $CHCl_3$).

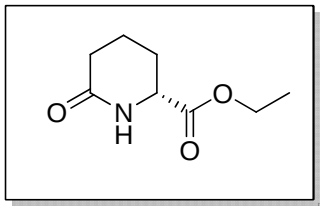
IR ($CHCl_3$, cm^{-1}): vmax 2926, 2850, 1720, 1651, 1456, 1368, 1265, 1180, 1030.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.22-1.32 (m, 6H), 2.55-2.73 (m, 1H), 2.59-3.17 (m, 1H), 3.84-4.20 (m, 8H), 6.05-6.25 (m,1H), 6.60-6.89 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 14.0, 14.1, 42.9, 45.9, 54.4, 60.2, 61.1, 123.3, 127.6, 127.9, 128,2, 138.4, 145.3, 165.4, 167.8.

MS (ESI): *m/z*: 303.28 $(M)^+$, 326.21 $(M+Na)^+$.

(*R*)-Ethyl 6-oxopiperidine-2-carboxylate (20)



To a stirred solution of compound **19** (0.15 g, 0.49 mmol) in ethanol (5 mL) was added ammonium formate (0.27 g, 4.9 mmol) and 10% Pd/C (0.05 g) and refluxed for 1 h under nitrogen atmosphere. Reaction mass was filtered through celite, dried and column purified (pet ether:ethyl acetate, 10:90) to yield 0.071 g of amide-ester **20** as colourless liquid.

***R*$_f$:** 0.3 (Ethyl acetate)

Yield: 85%

MF: $C_8H_{13}NO_3$, **MW**: 171.19

[α]$_D^{25}$ +13.4 (*c* 1.4, $CHCl_3$) {Lit.[20a] for *ent*-**20**, **[α]$_D^{25}$** −13.7 (*c* 0.3, $CHCl_3$)}.

IR ($CHCl_3$, cm^{-1}): vmax 2958, 1739, 1666, 1468, 1198.

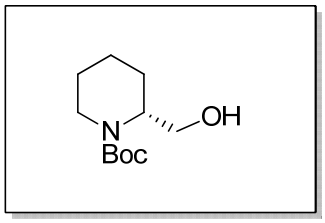
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.30 (t, *J* = 7.3 Hz, 3H), 1.78-1.98 (m, 3H), 2.20-2.22 (m, 1H), 2.36-2.47 (m, 2H), 4.1 (dd, *J* = 5.5 & 7.0 Hz, 1H), 4.24 (qd, *J* = 1.2 & 7.3 Hz, 2H), 6.65 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 14.1, 19.2, 25.2, 30.7, 54.7, 61.9, 170.7, 171.9.

MS (ESI): *m/z*: 194.08 $(M+Na)^+$.

HRMS: Calculated for $C_8H_{14}O_3N$-172.0968, found-172.0966.

(*R*)-*tert*-Butyl 2-(hydroxymethyl)piperidine-1-carboxylate (*ent*-17)



To a stirred suspension of LAH (0.22g, 5.85 mmol) in dry THF (5 mL) was added amide **6** (0.2 g, 1.17 mmol) dissolved in dry THF (5 mL) slowly at 0 °C *via* syringe under inert atmosphere (N_2 gas). After stirring for 24 h at room temperature, the reaction mixture was cooled to 0 °C, quenched carefully with minimum amount of water followed by 15% NaOH (0.25 mL). Again water (1 mL) was added and stirred for 0.5 h at room temperature. Anhydrous Na_2SO_4 was added and stirring continued for another 0.5 h. Filtration through Celite and concentration under vacuum gave crude amine which was used as such for next reaction.

To a solution of amine in THF:water (5 mL, 1:1) was added $NaHCO_3$ (0.2 g, 2.34 mmol) and $(Boc)_2O$ (0.536 mL, 2.34 mmol) and then the mixture was vigorously stirred at room temperature for 6 h. The reaction mixture was extracted with ethyl acetate (3 × 10 mL),

washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* and purified by column chromatography (pet ether–ethyl acetate, 8:2) to afford (*R*)-**17** as a white solid.

Yield: 0.176 g, 70% over two steps.

MF: $C_{11}H_{21}NO_3$, **MW**: 215.289

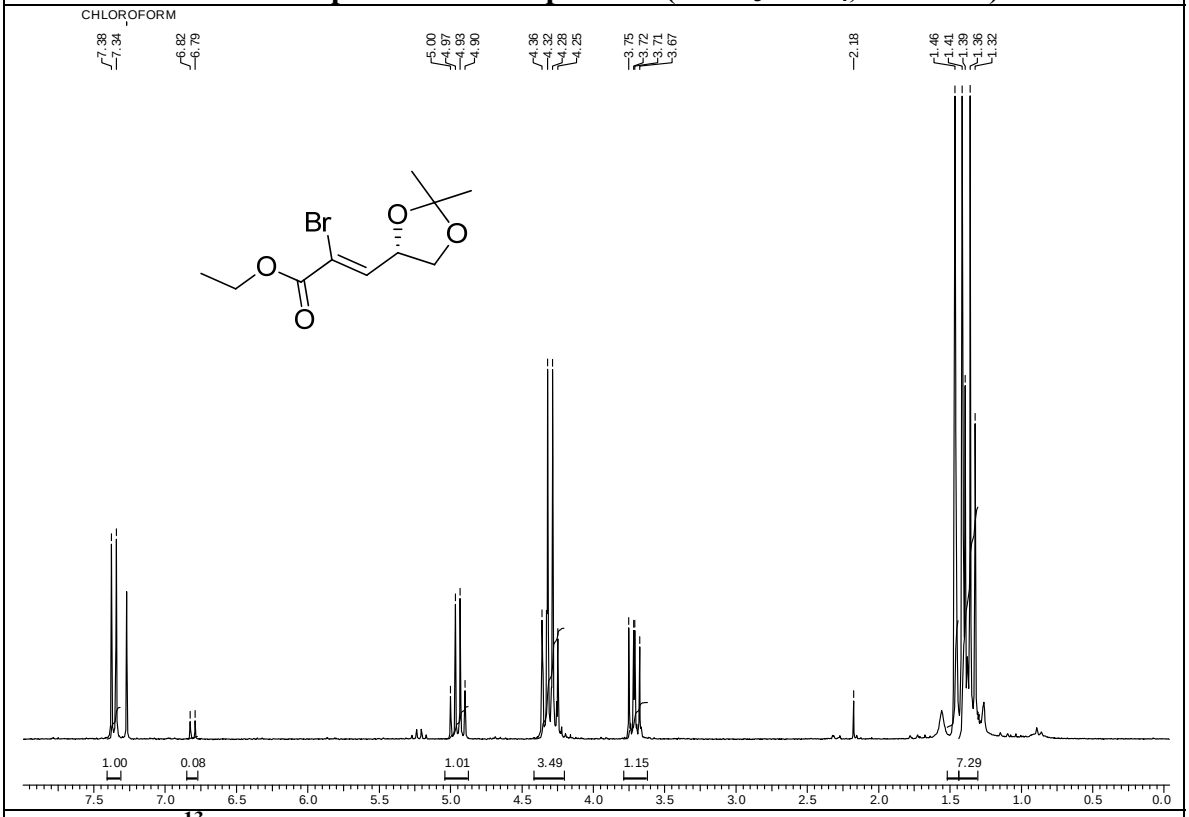
MP: 81-84 °C, lit[24] 81-84 °C.

$[\alpha]_D^{25}$ +38.5 (*c* 1, $CHCl_3$) {For *ent*-**17** Lit[24] $[\alpha]_D^{25}$ −40.5 (*c* 1, $CHCl_3$)}

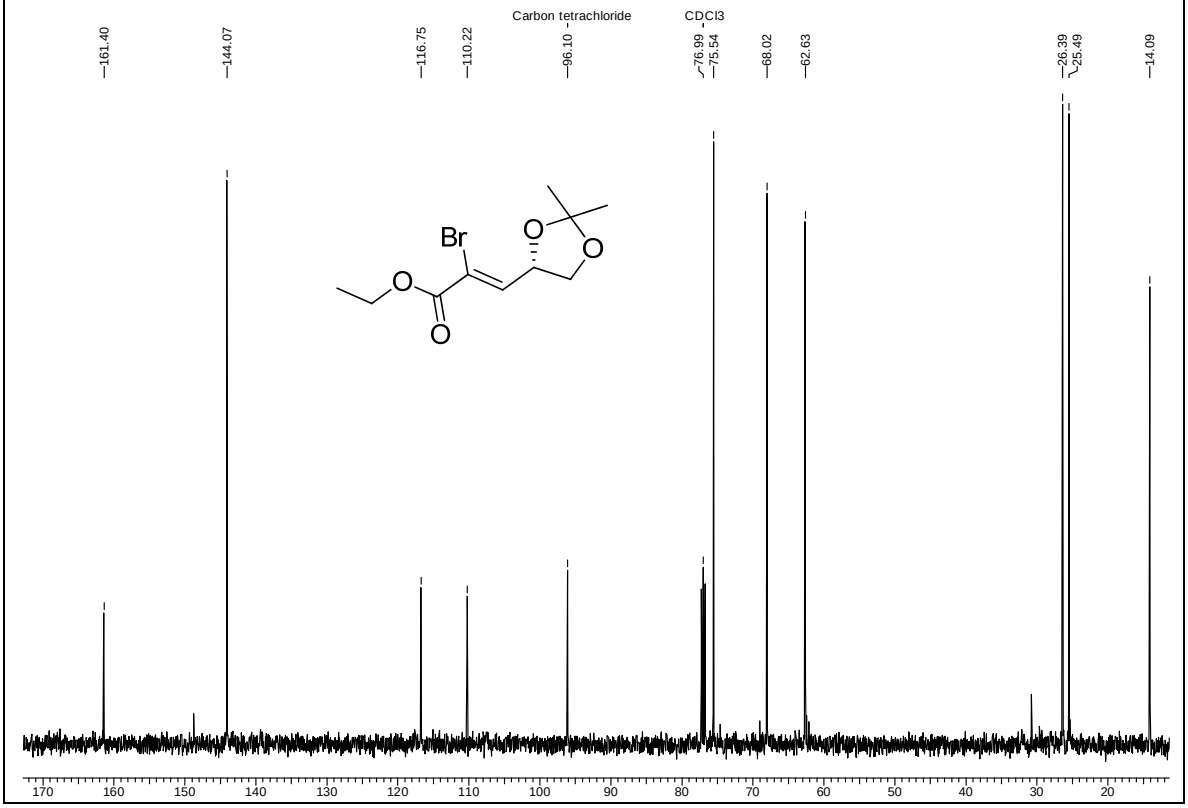
For other data please refer (*S*)-**17**.

1.2.4 Analytical Data

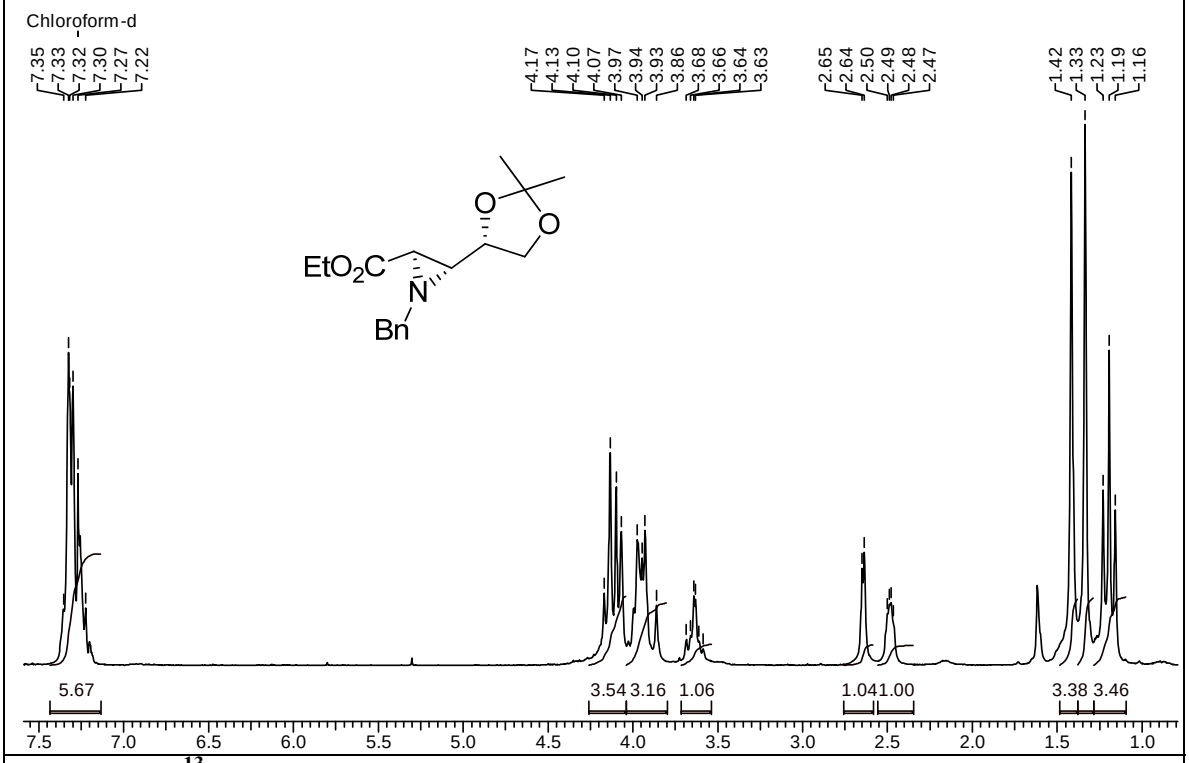
^{1}H-NMR spectrum of compound 3 ($CDCl_3$+CCl_4, 200 MHz)



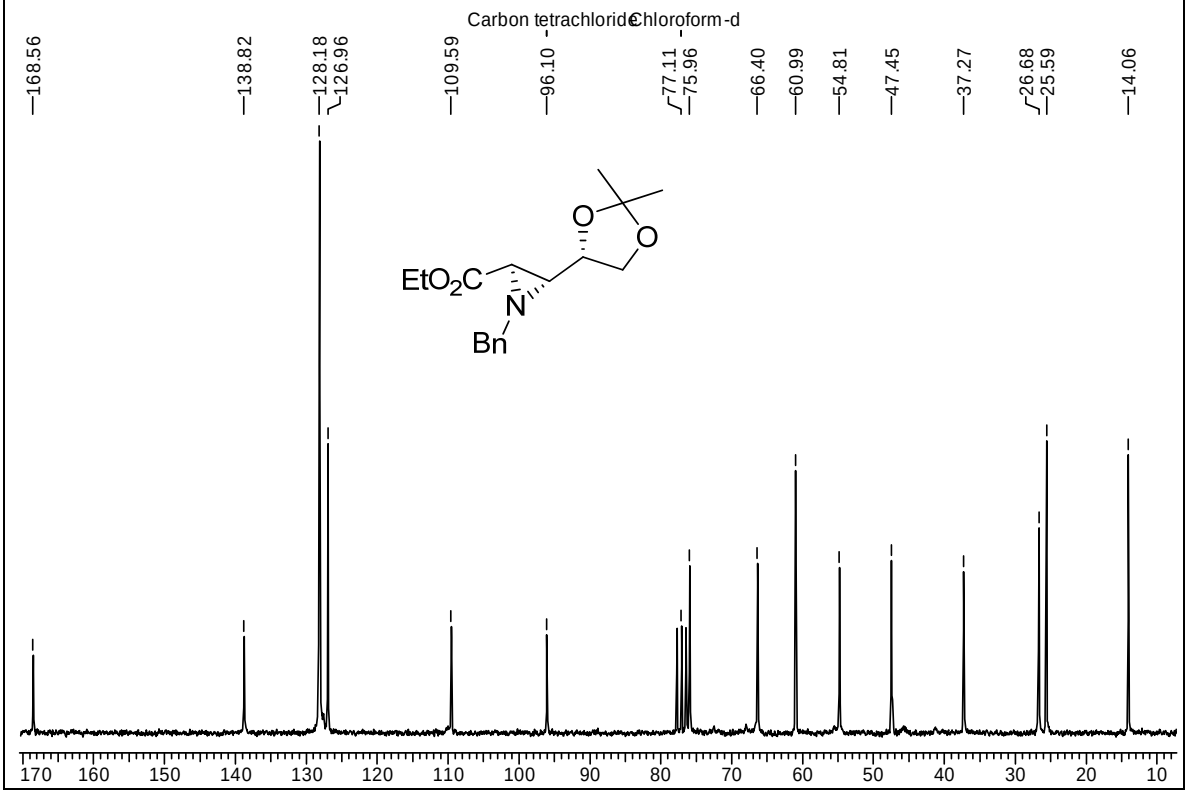
^{13}C-NMR spectrum of compound 3 ($CDCl_3$+CCl_4, 125 MHz)



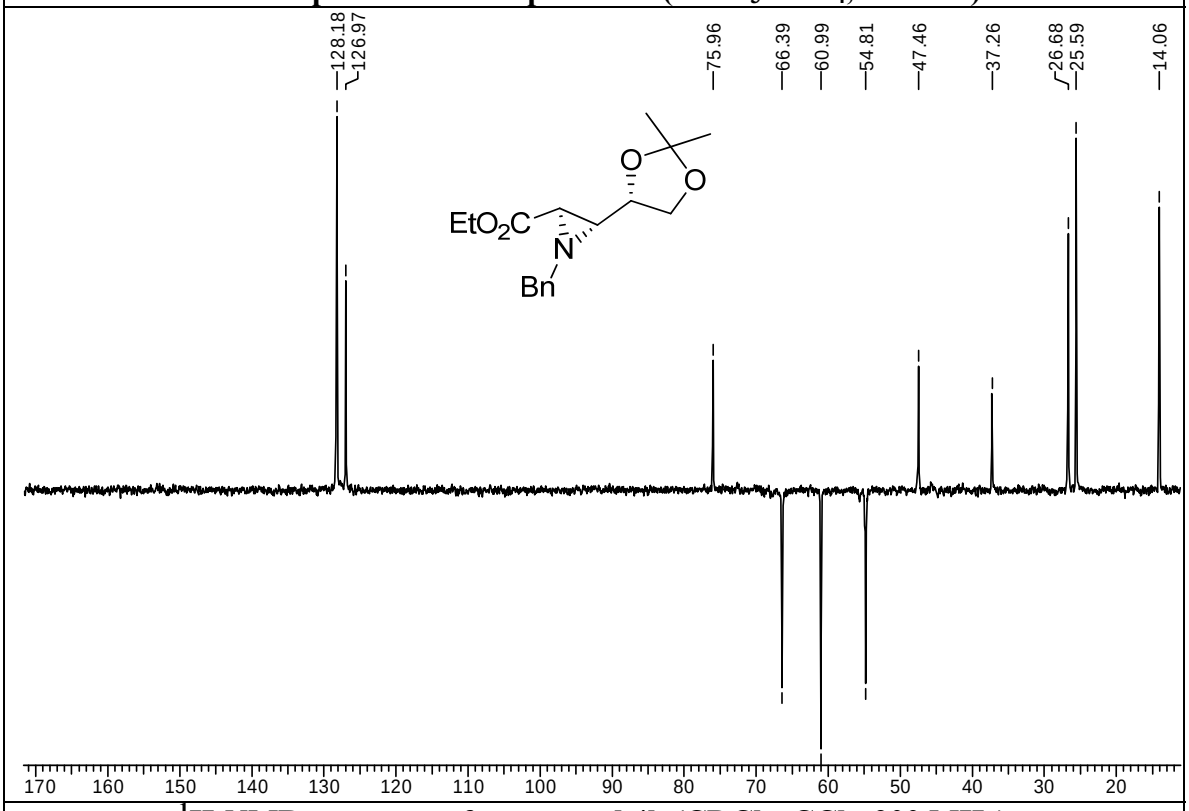
^{1}H-NMR spectrum of compound 4a ($CDCl_3$+CCl_4, 200 MHz)



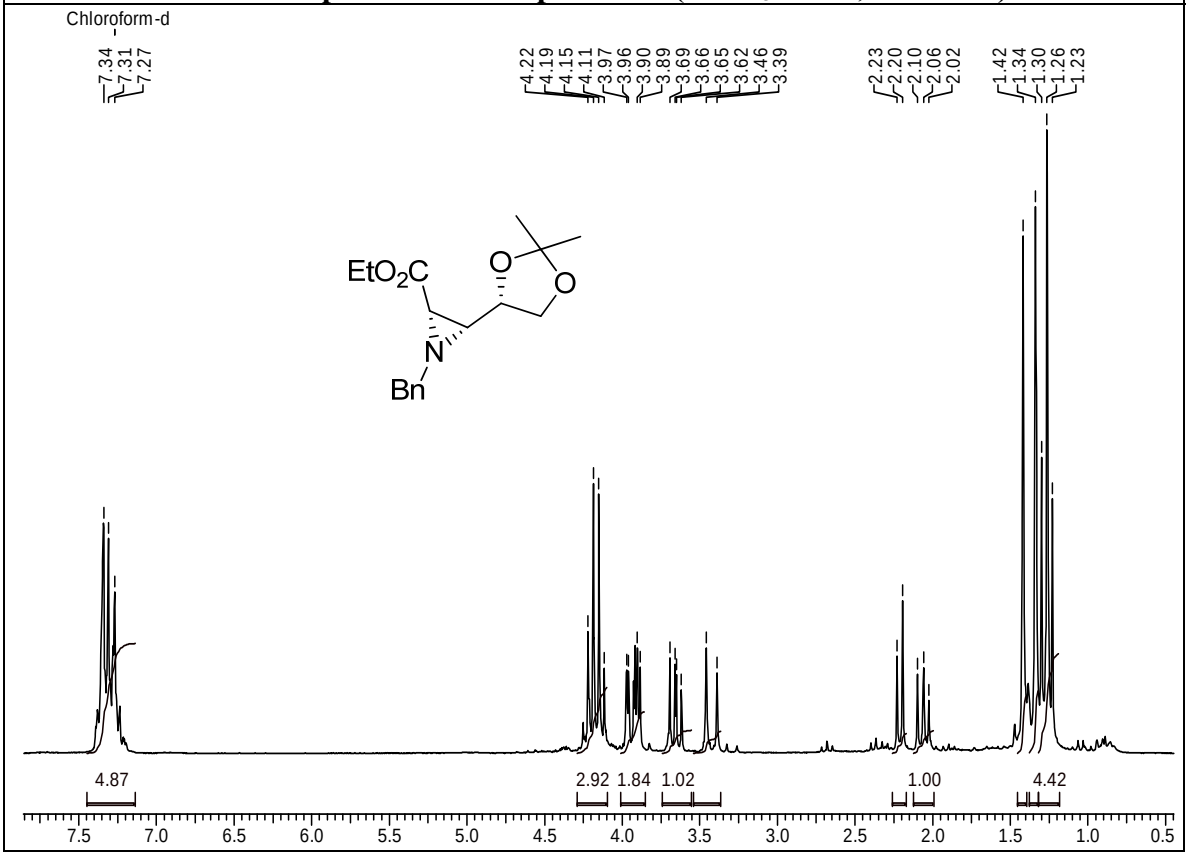
^{13}C-NMR spectrum of compound 4a ($CDCl_3$+CCl_4, 50 MHz)



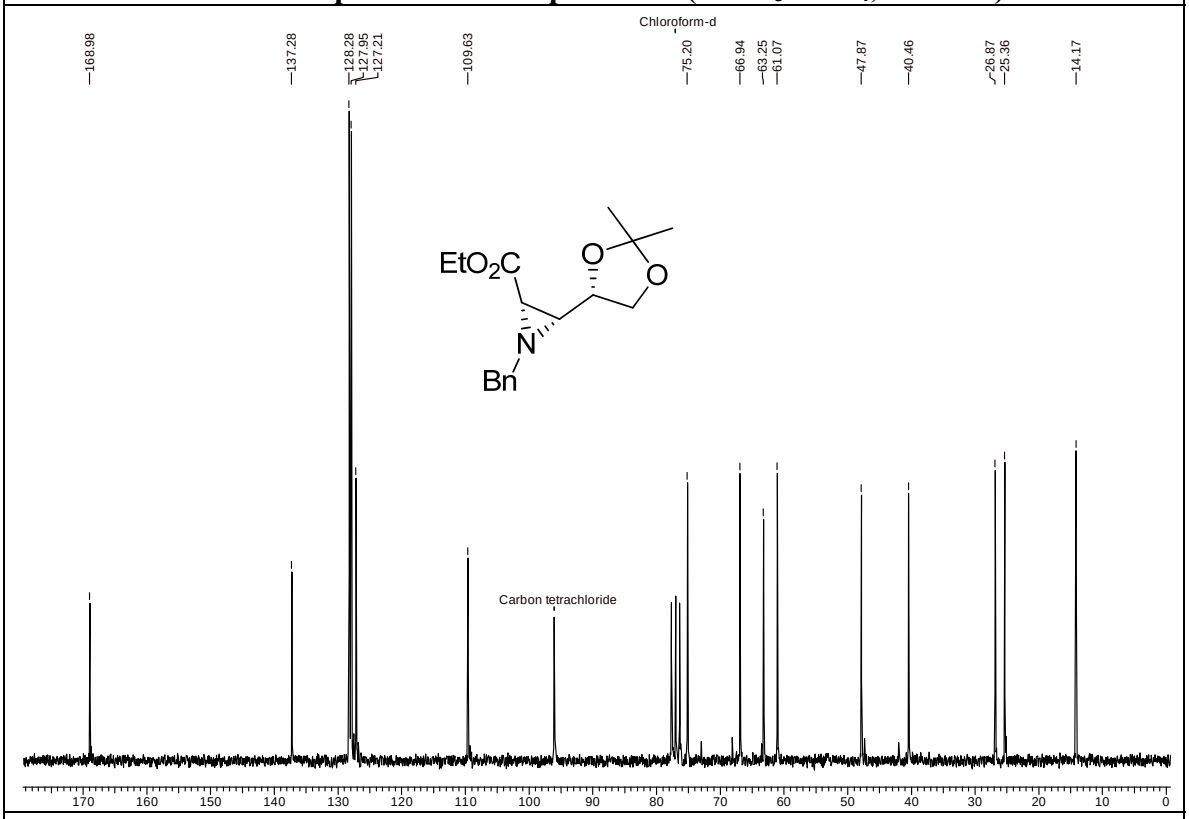
DEPT spectrum of compound 4a ($CDCl_3$+CCl_4, 50 MHz)



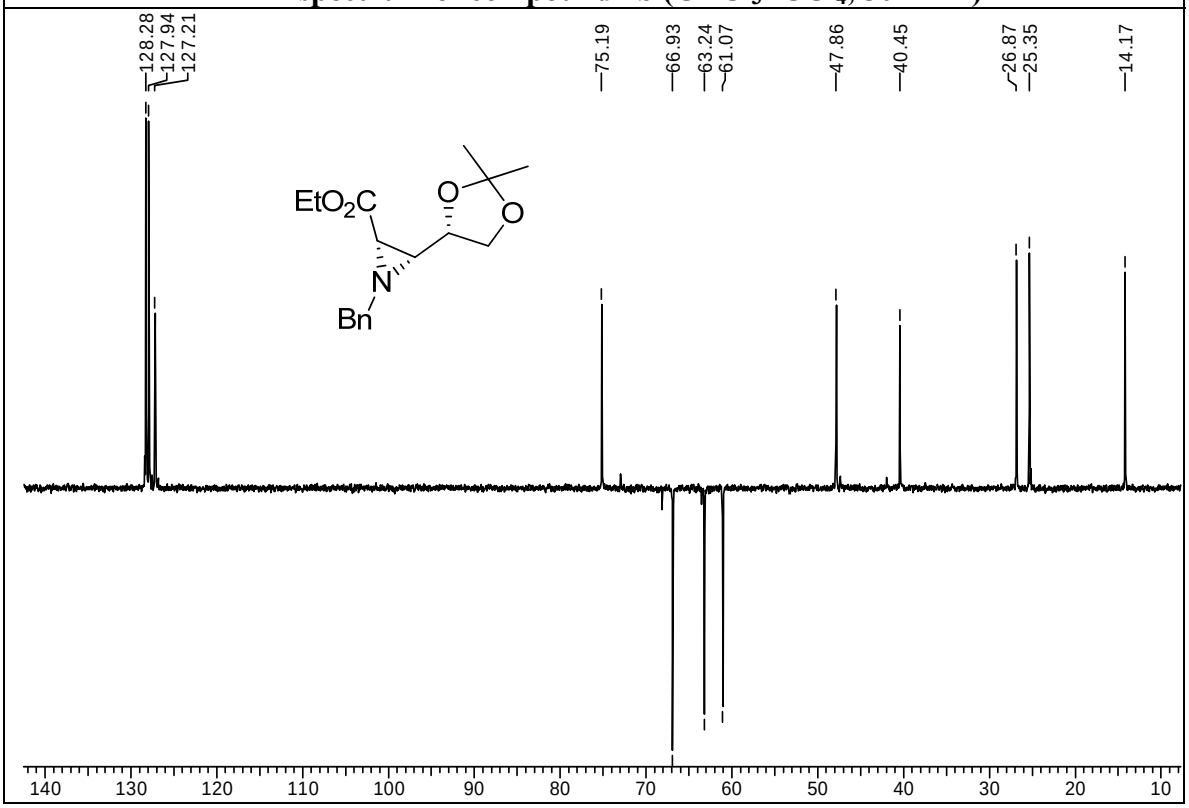
^{1}H-NMR spectrum of compound 4b ($CDCl_3$+CCl_4, 200 MHz)



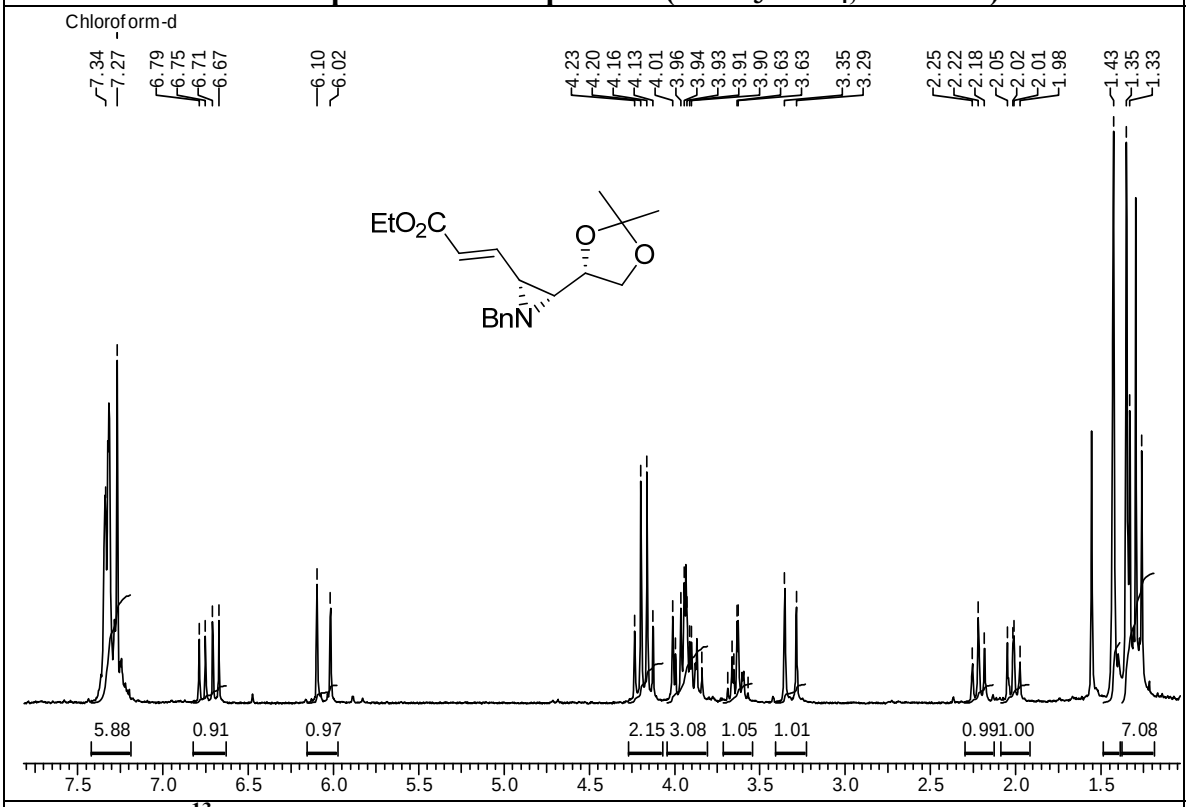
^{13}C-NMR spectrum of compound 4b ($CDCl_3$+CCl_4, 50 MHz)



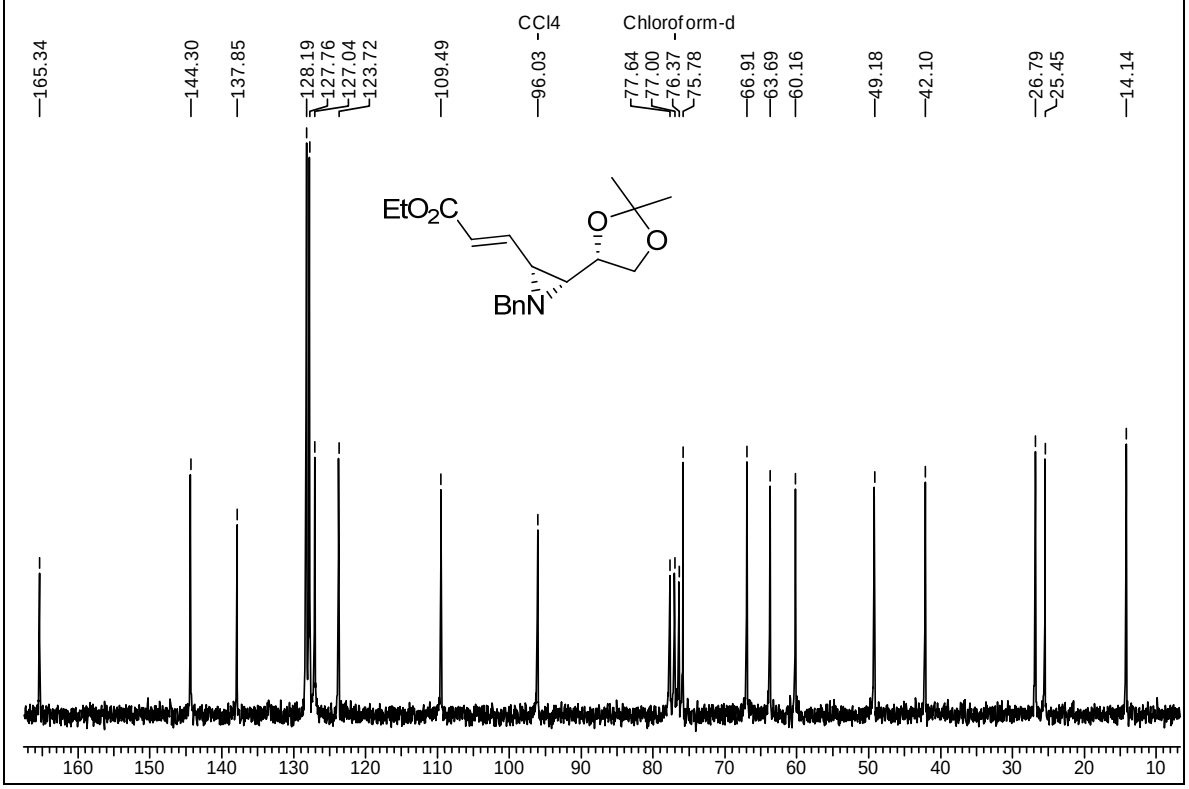
DEPT spectrum of compound 4b ($CDCl_3$+CCl_4, 50 MHz)



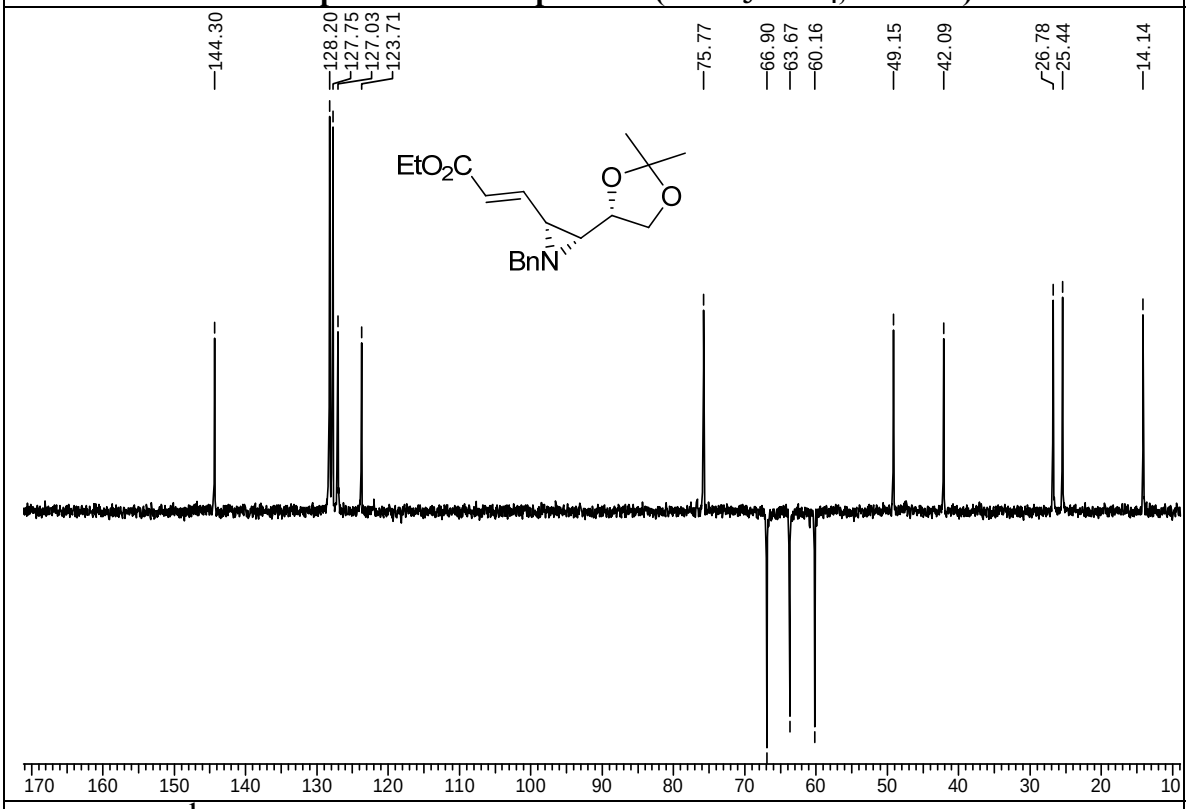
^{1}H-NMR spectrum of compound 7 ($CDCl_3$+CCl_4, 200 MHz)



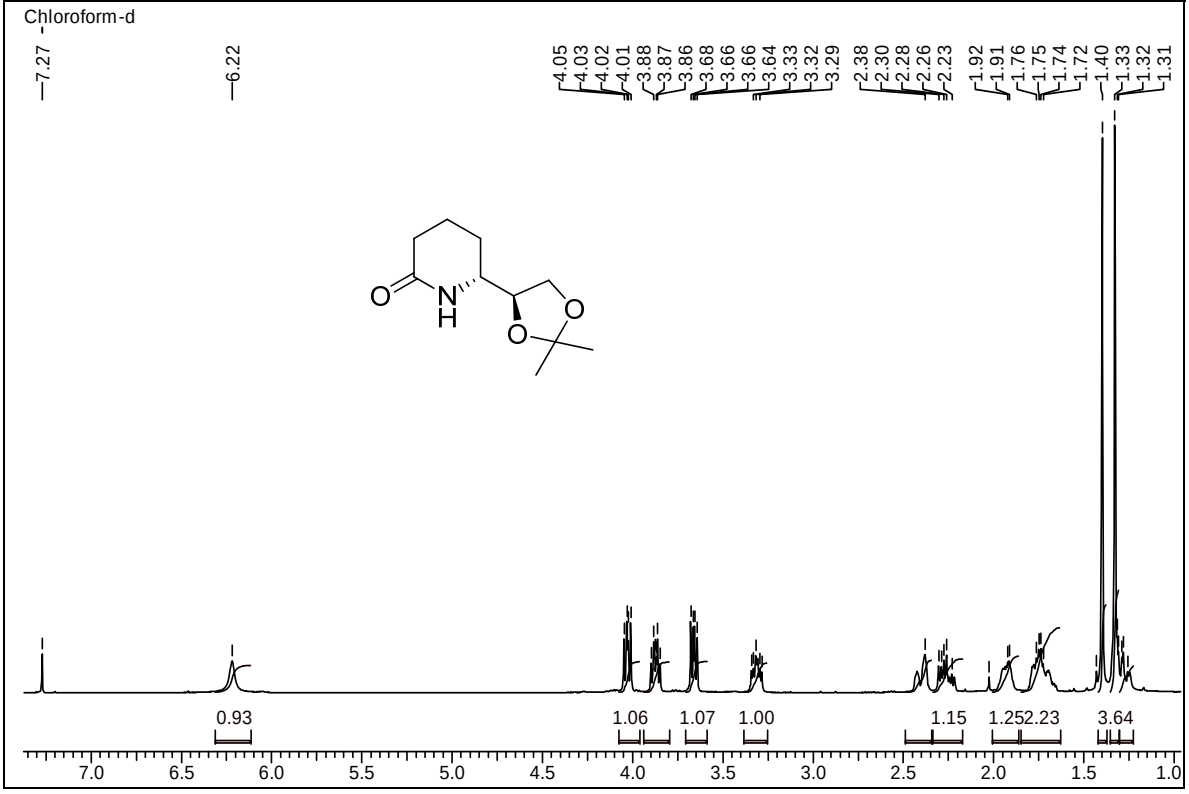
^{13}C-NMR spectrum of compound 7 ($CDCl_3$+CCl_4, 50 MHz)



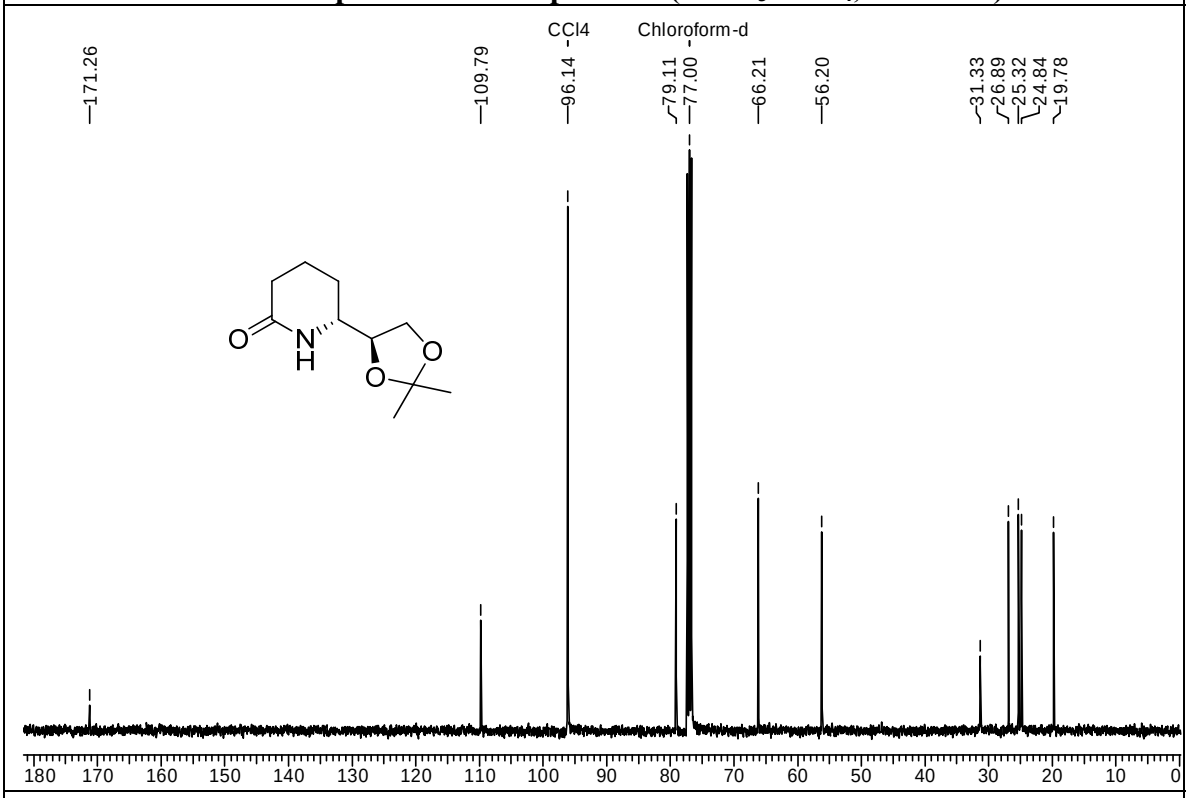
DEPT spectrum of compound 7 ($CDCl_3$+CCl_4, 50 MHz)



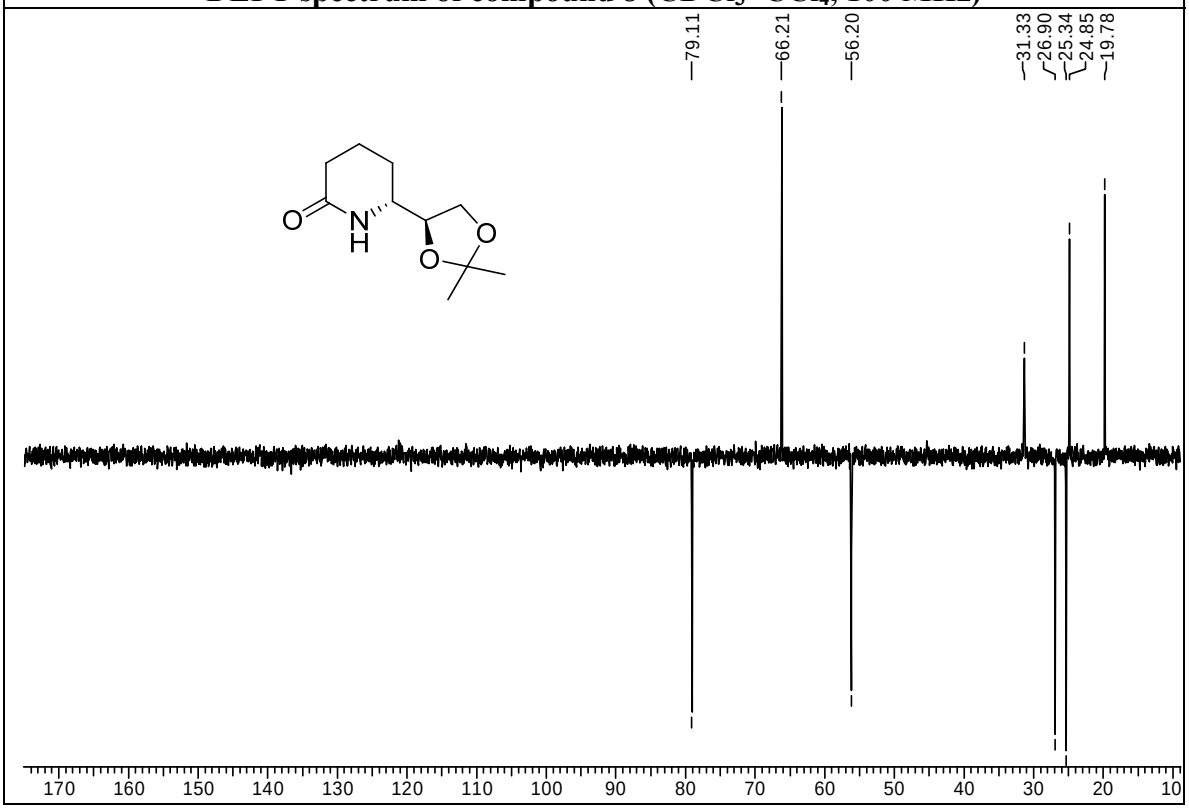
^{1}H-NMR spectrum of compound 8 ($CDCl_3$+CCl_4, 400 MHz)



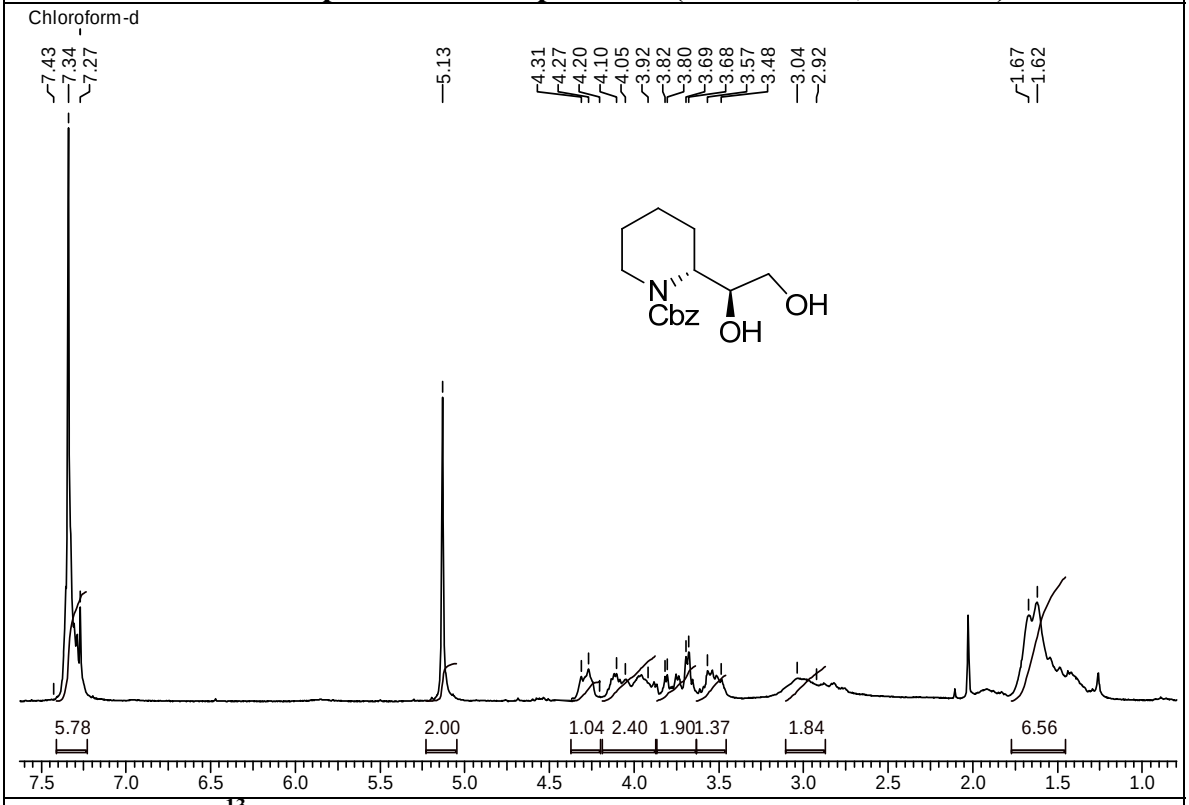
^{13}C-NMR spectrum of compound 8 ($CDCl_3$+CCl_4, 100 MHz)



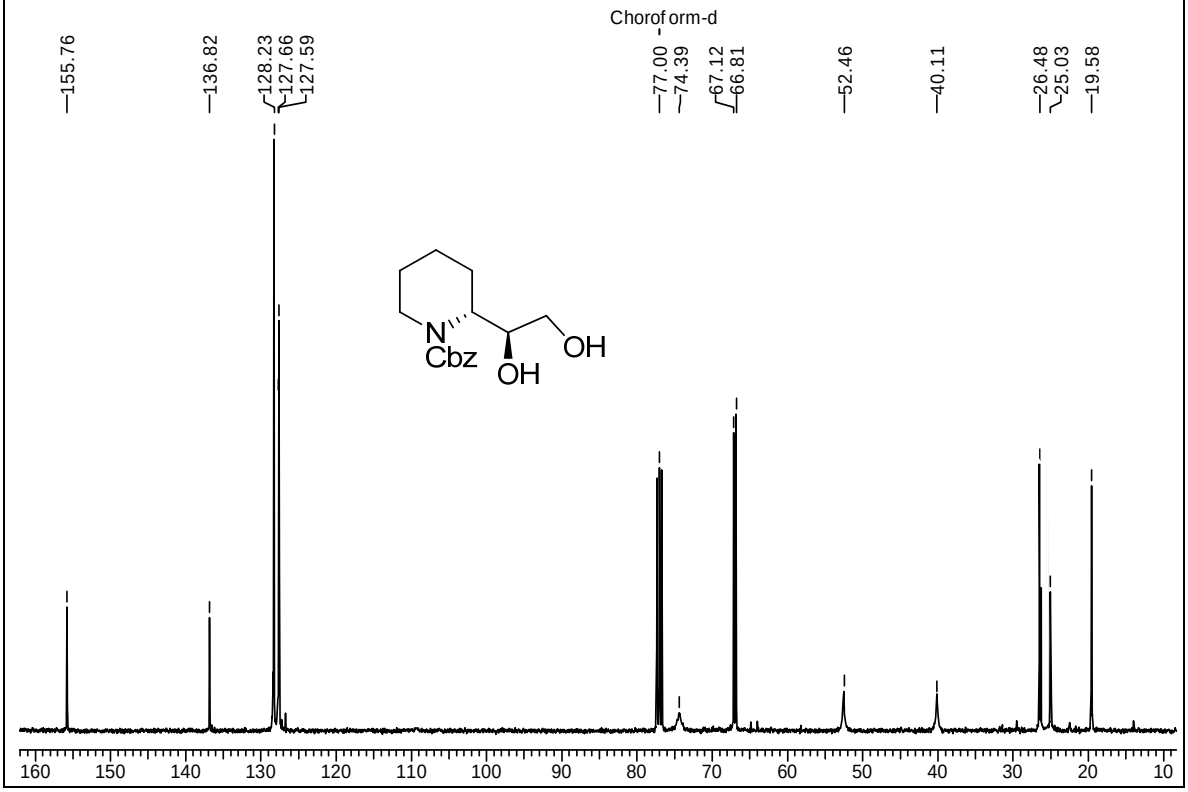
DEPT spectrum of compound 8 ($CDCl_3$+CCl_4, 100 MHz)



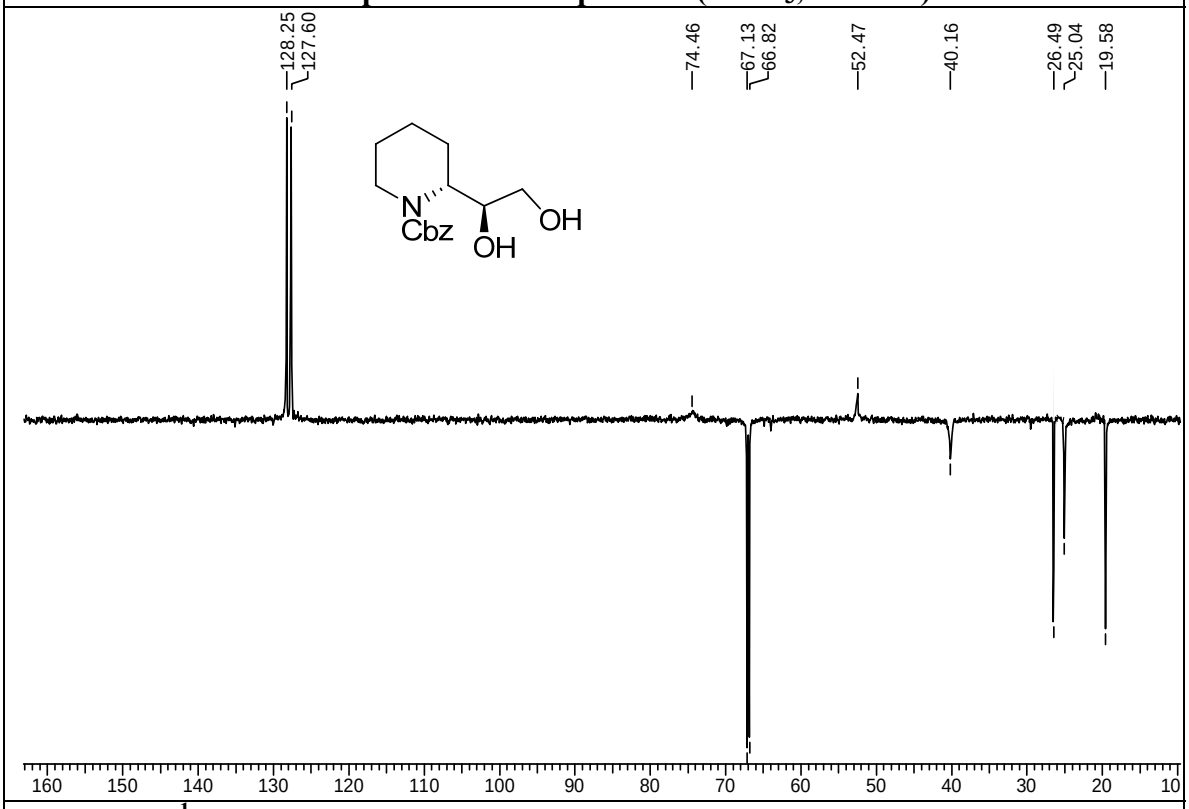
^{1}H-NMR spectrum of compound 12 ($CDCl_3$+CCl_4, 200 MHz)



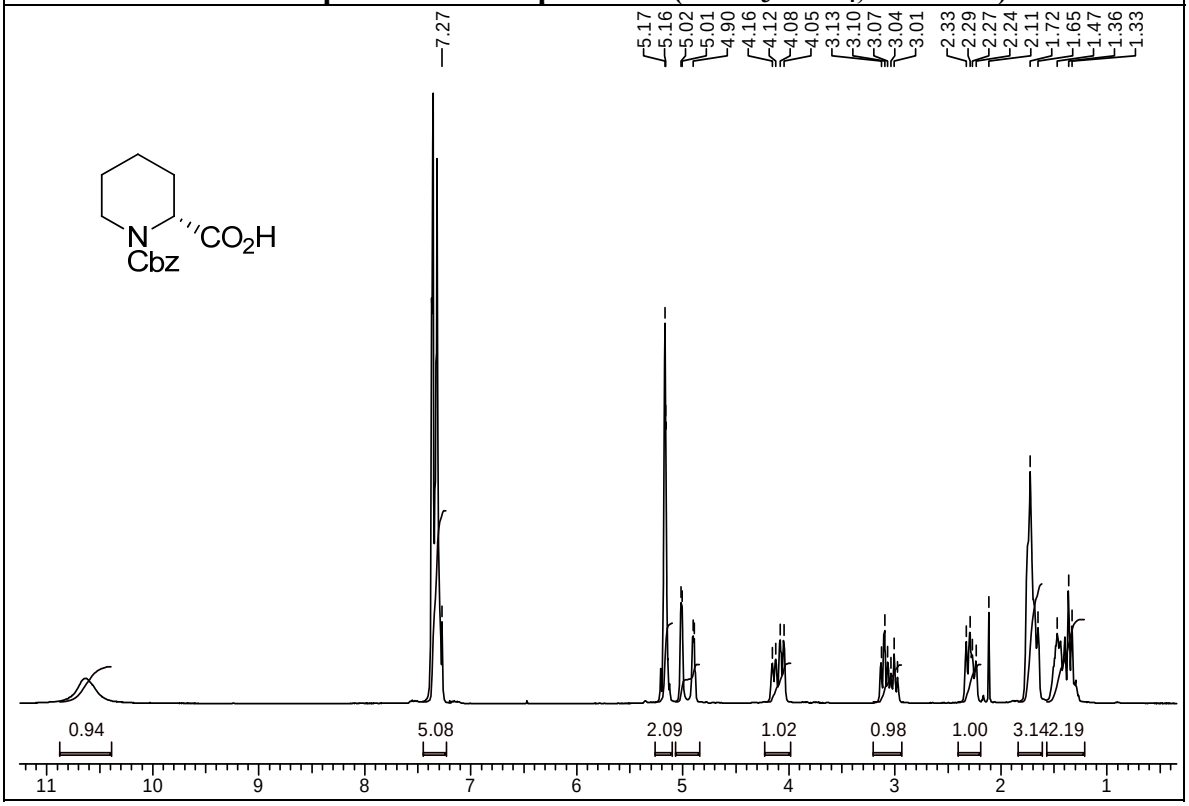
^{13}C-NMR spectrum of compound 12 ($CDCl_3$, 50 MHz)



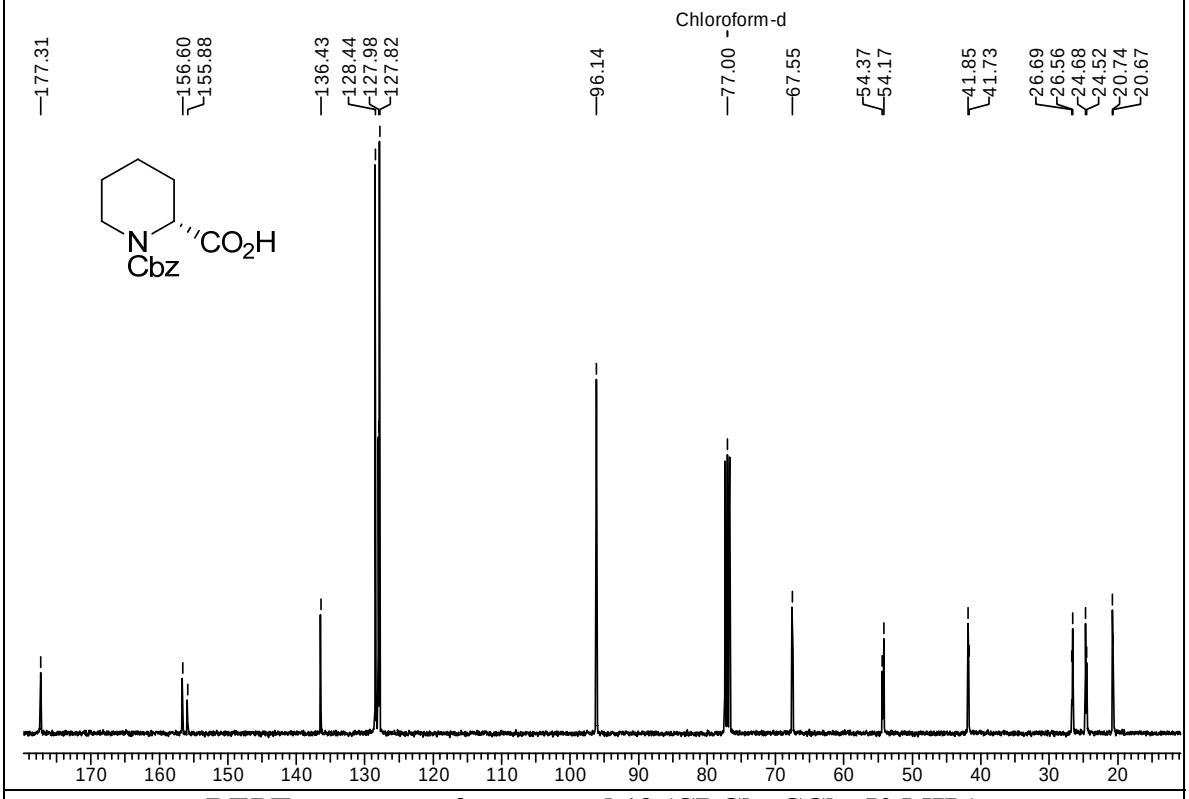
DEPT spectrum of compound 8 ($CDCl_3$, 50 MHz)



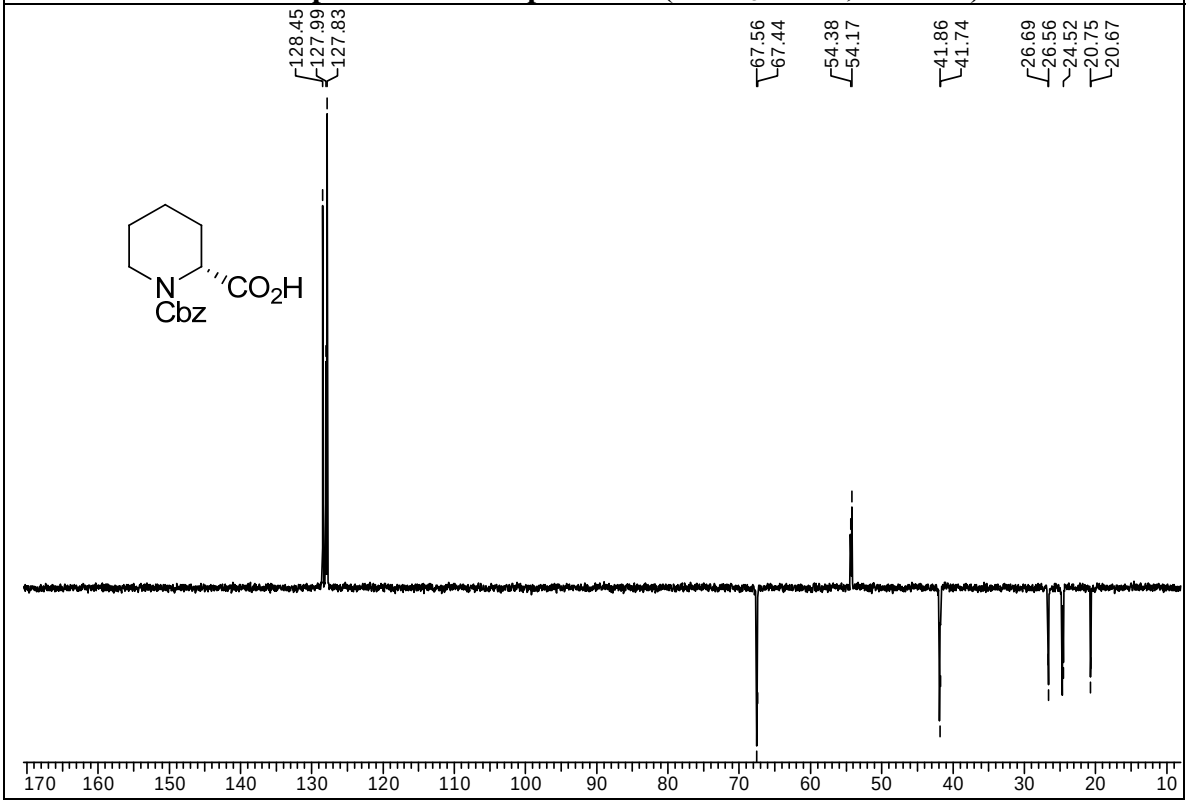
^{1}H-NMR spectrum of compound 13 ($CDCl_3$+CCl_4, 500 MHz)



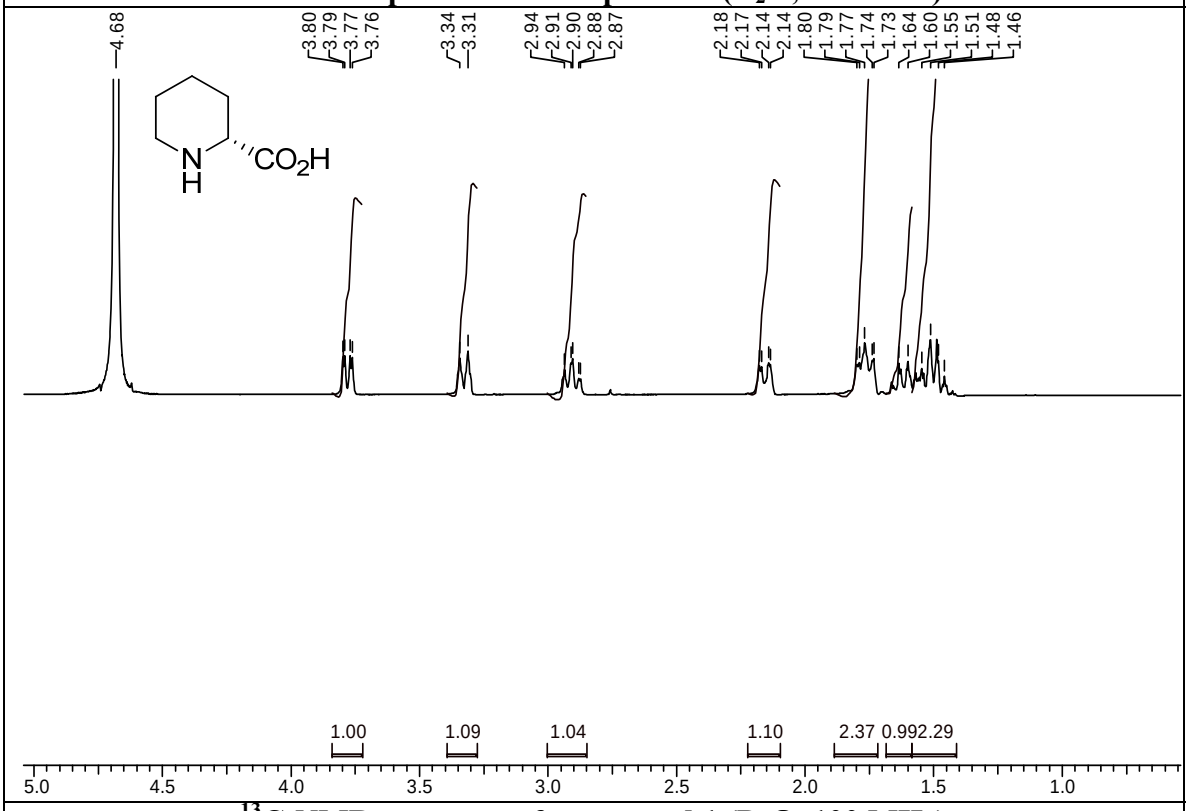
^{13}C-NMR spectrum of compound 13 ($CDCl_3$+CCl_4, 125 MHz)



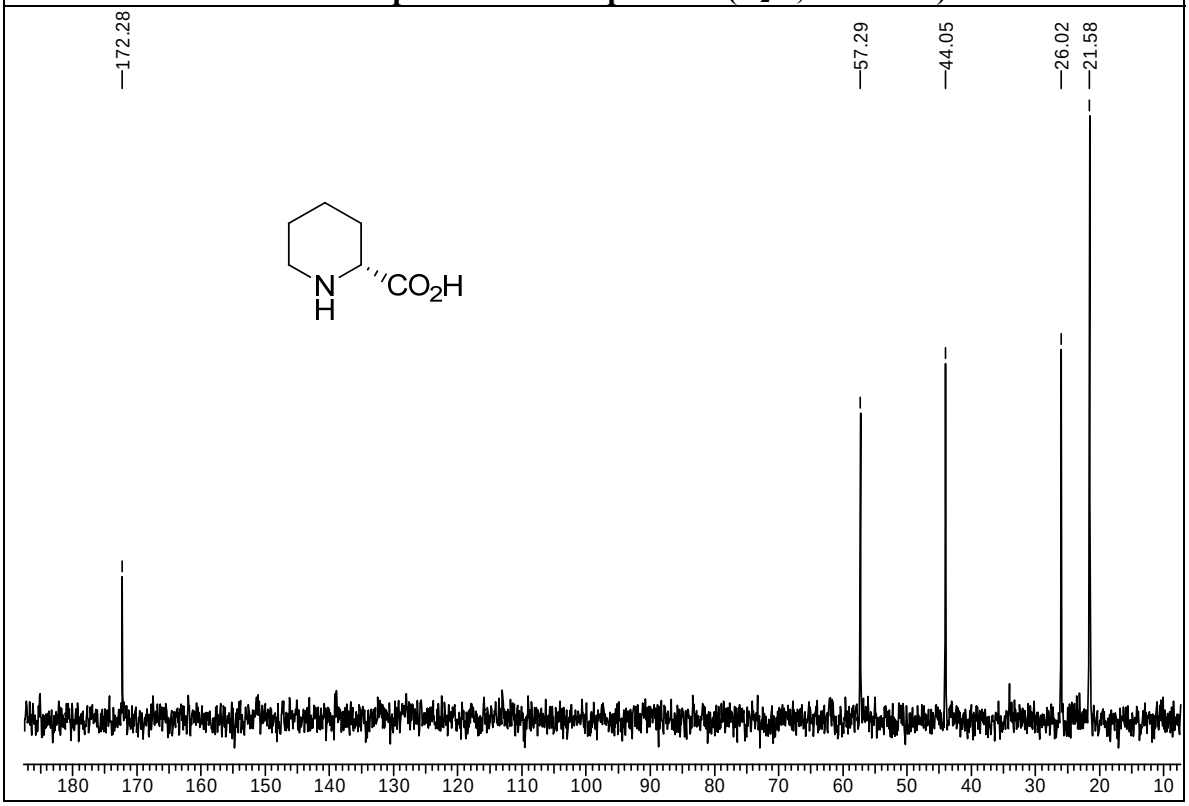
DEPT spectrum of compound 13 ($CDCl_3$+CCl_4, 50 MHz)



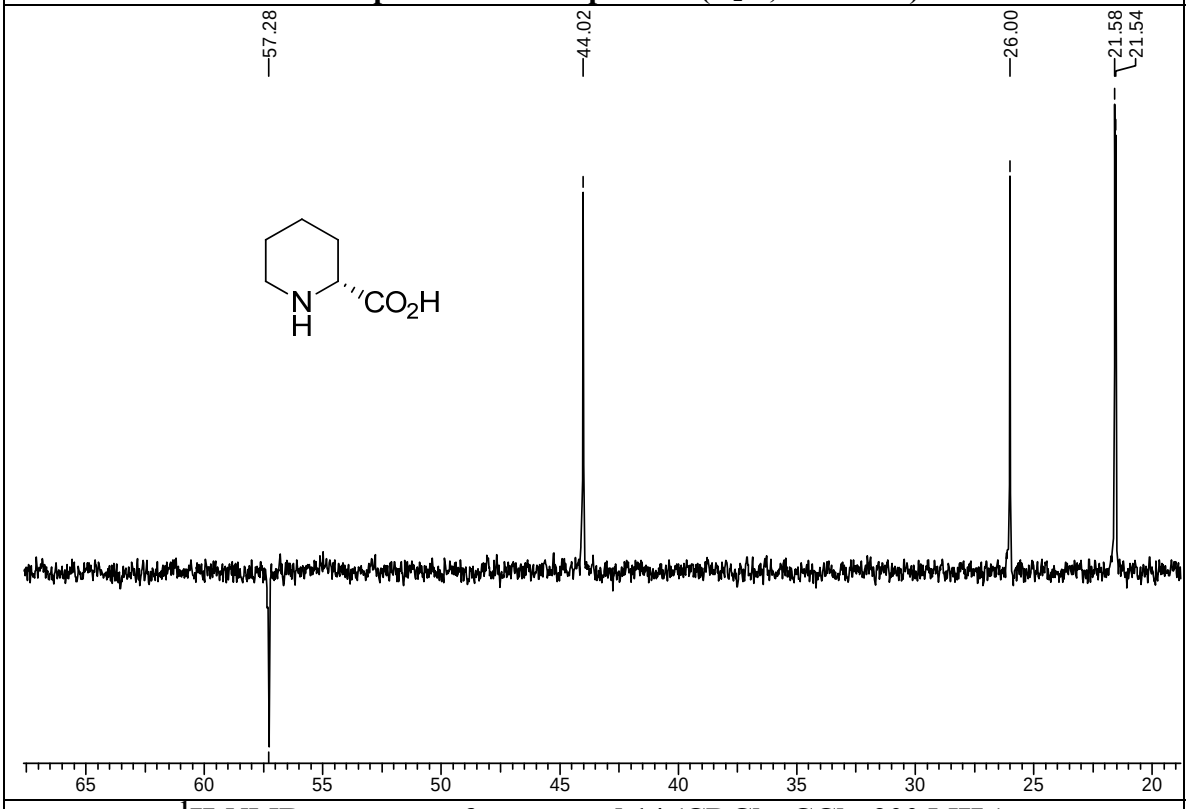
^{1}H-NMR spectrum of compound 1 (D_2O, 400 MHz)



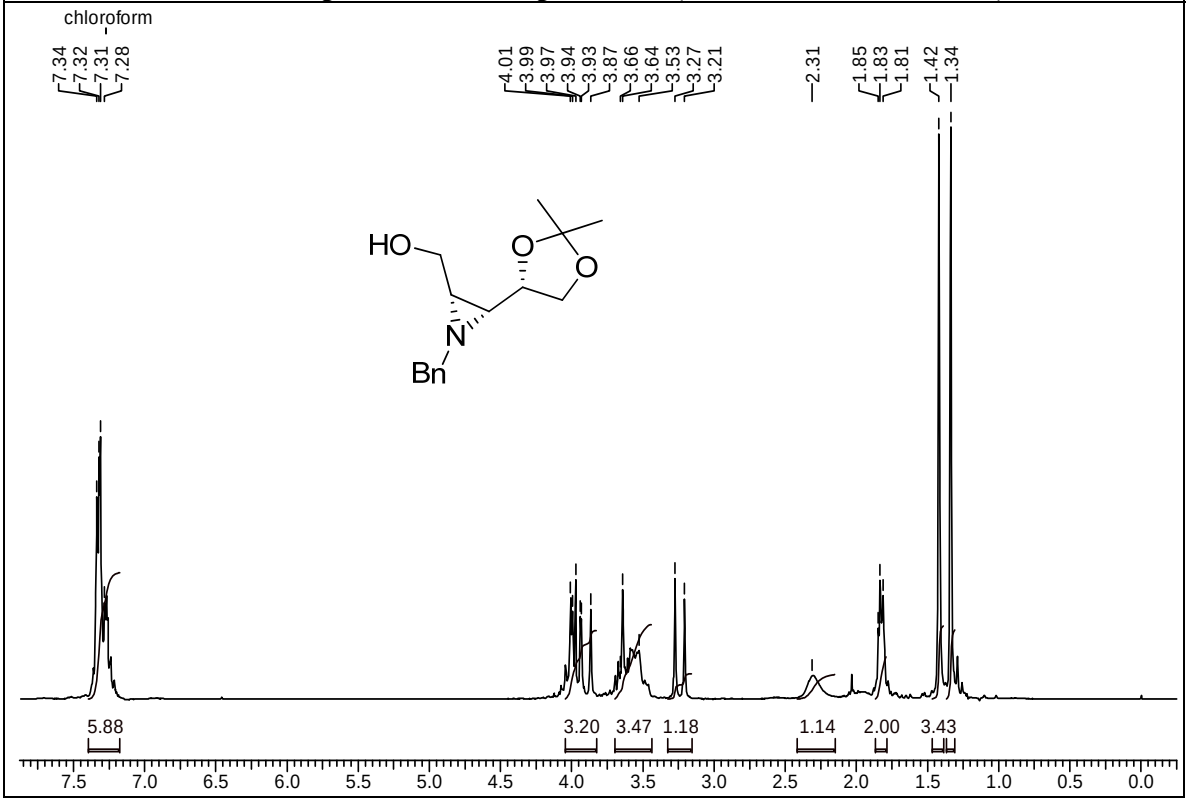
^{13}C-NMR spectrum of compound 1 (D_2O, 100 MHz)



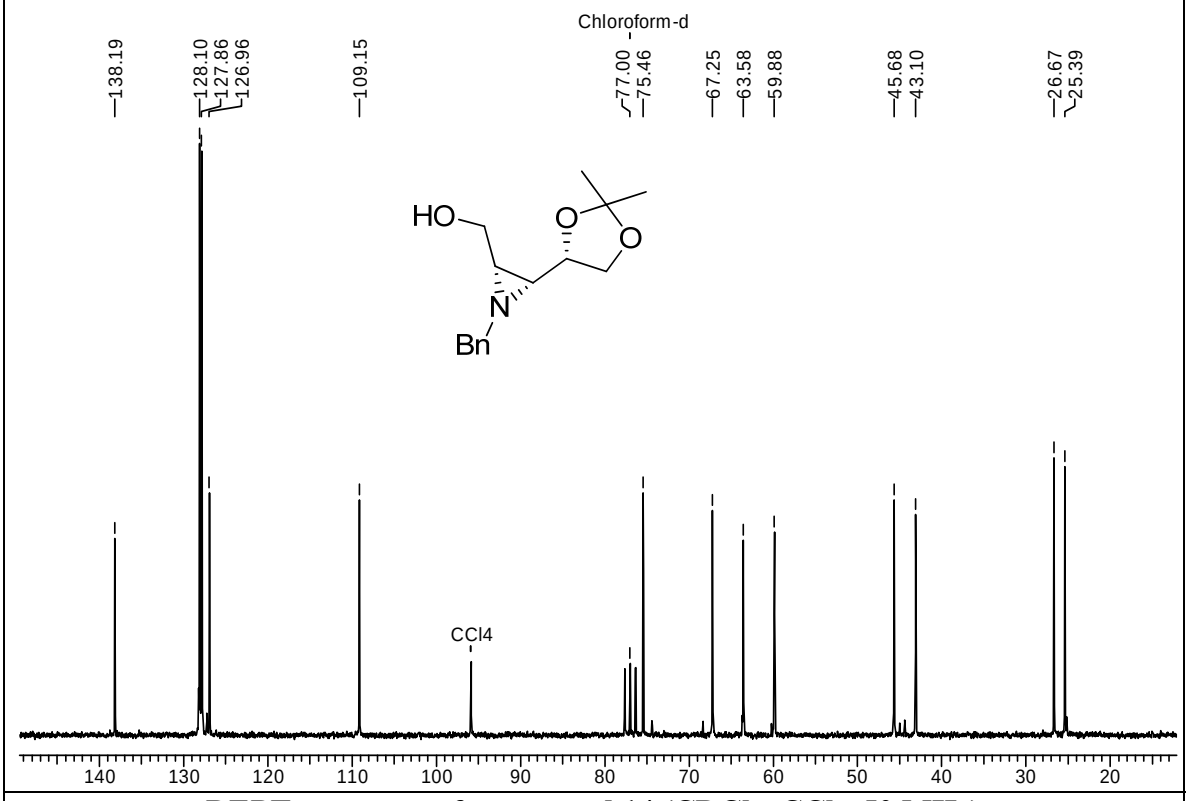
DEPT spectrum of compound 1(D_2O, 100 MHz)



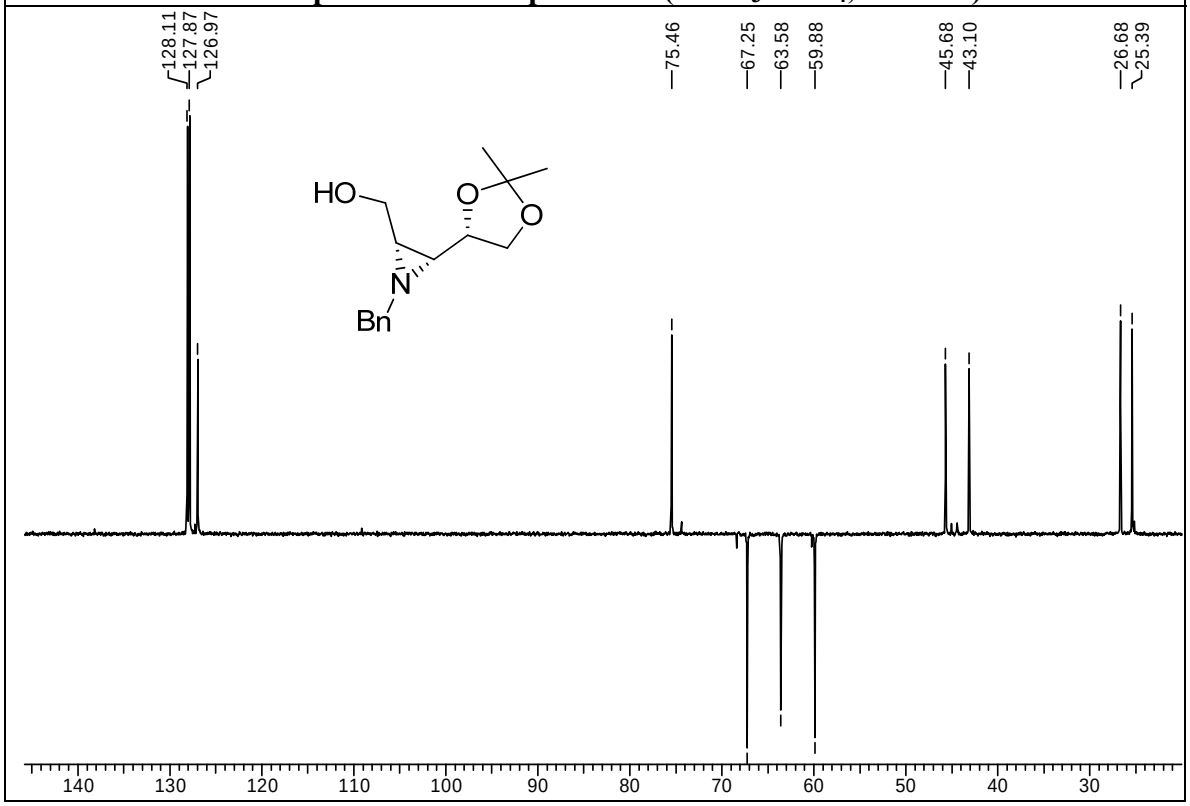
^{1}H-NMR spectrum of compound 14 ($CDCl_3$+CCl_4, 200 MHz)



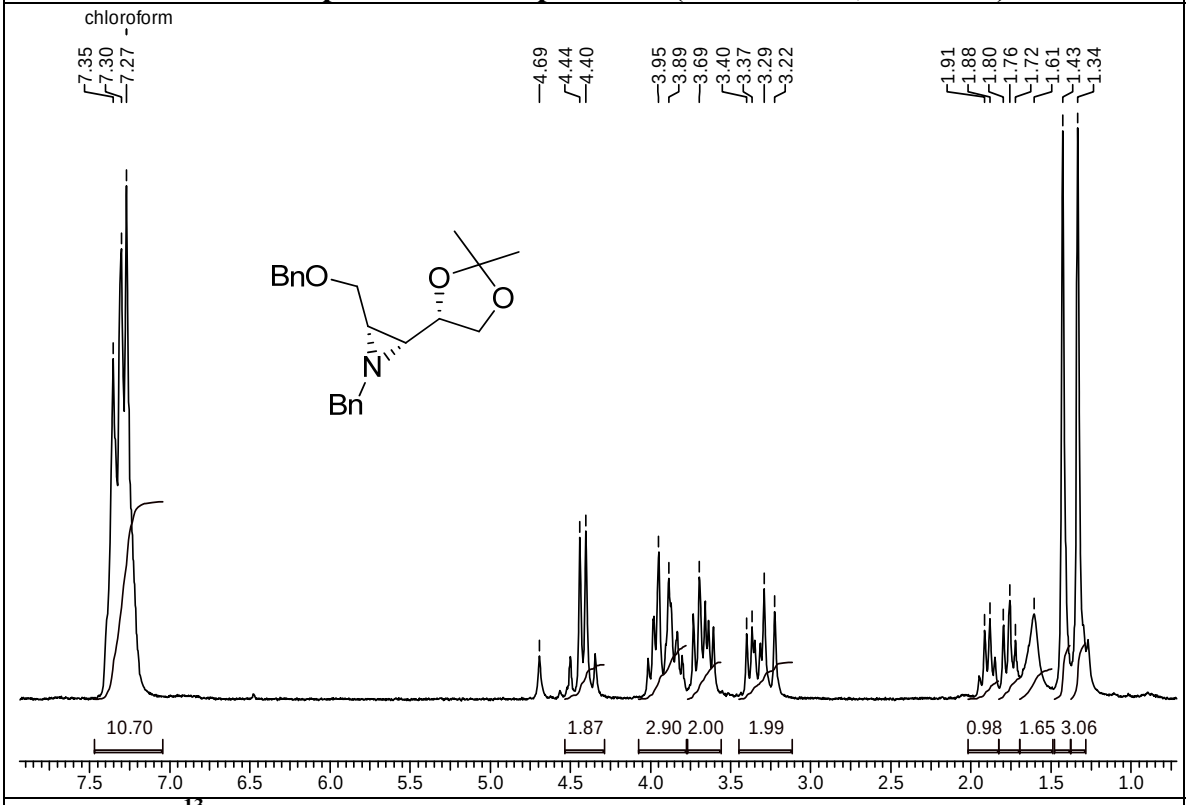
^{13}C-NMR spectrum of compound 14 ($CDCl_3$+CCl_4, 50 MHz)



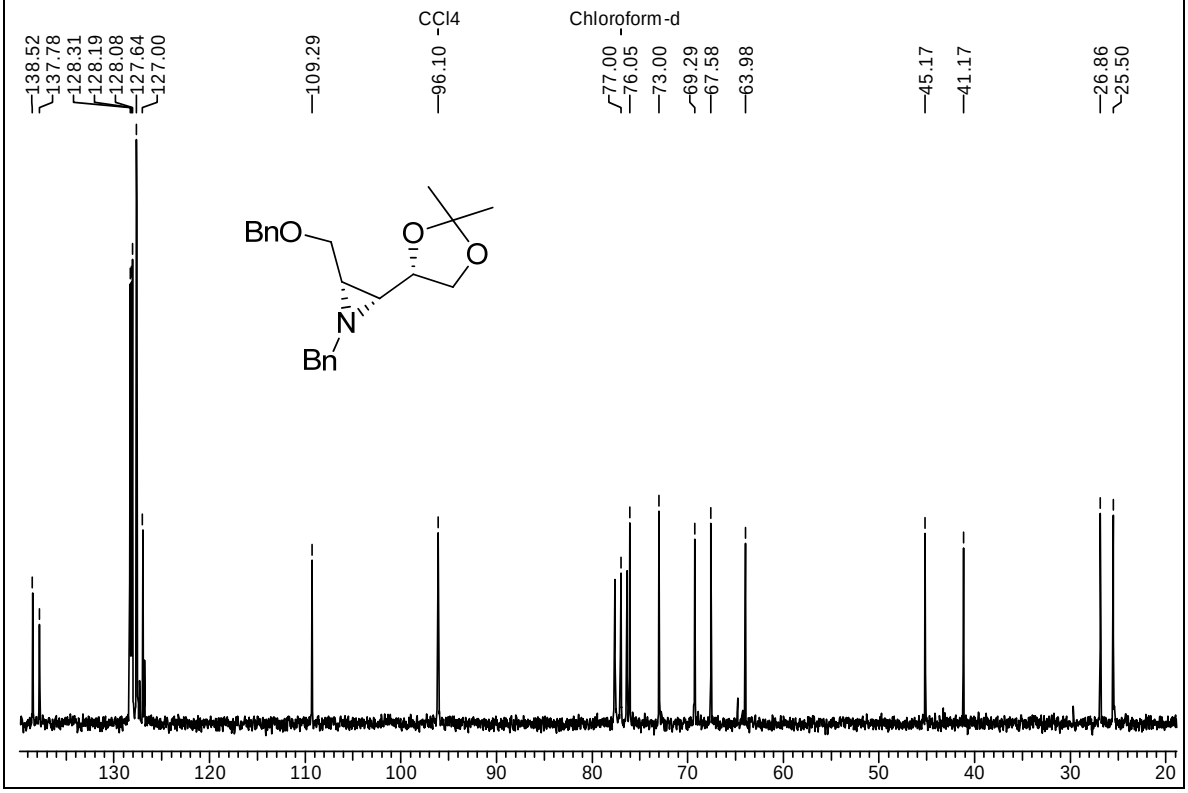
DEPT spectrum of compound 14 ($CDCl_3$+CCl_4, 50 MHz)



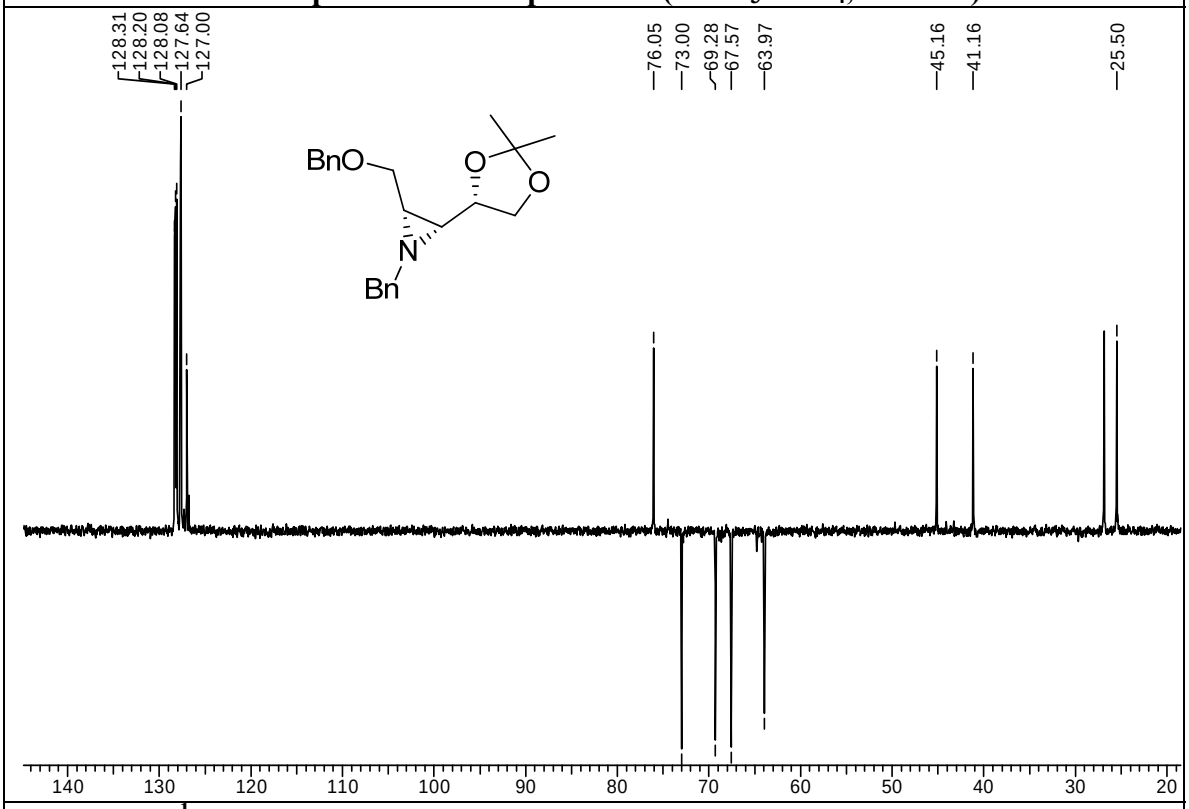
^{1}H-NMR spectrum of compound 15 ($CDCl_3$+CCl_4, 200 MHz)



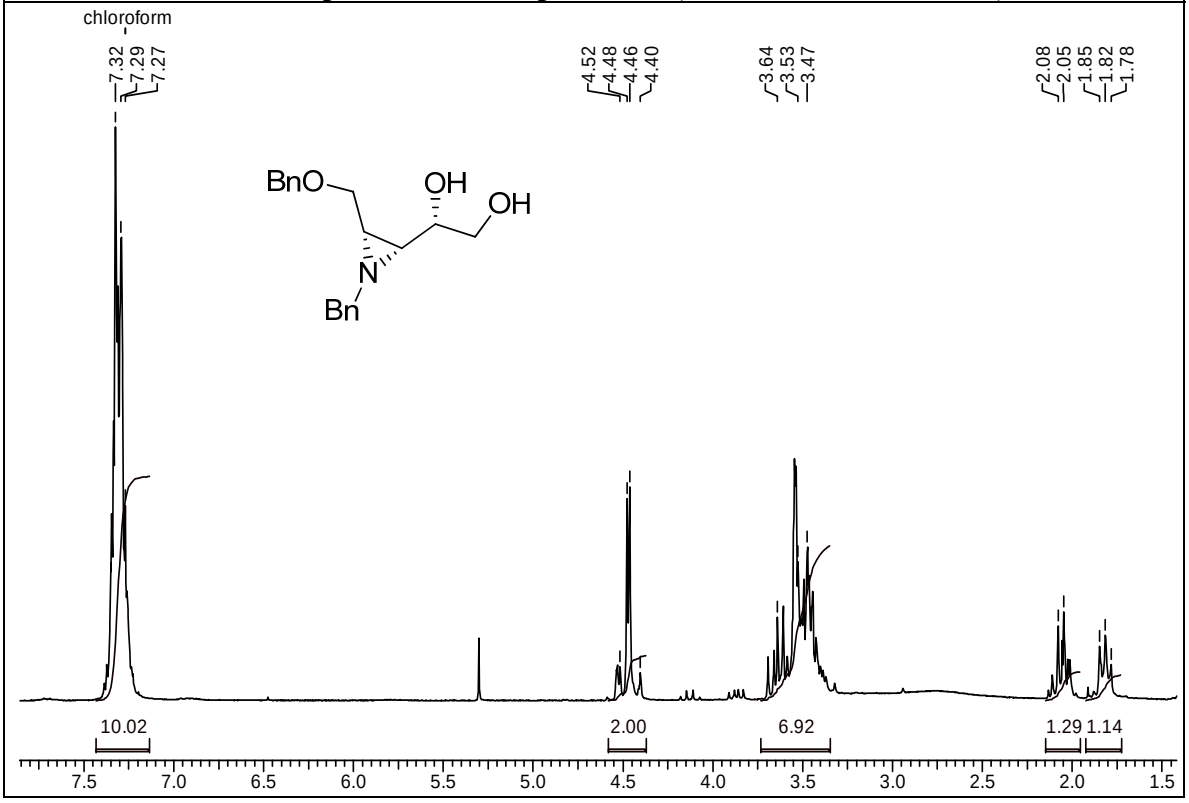
^{13}C-NMR spectrum of compound 15 ($CDCl_3$+CCl_4, 50 MHz)



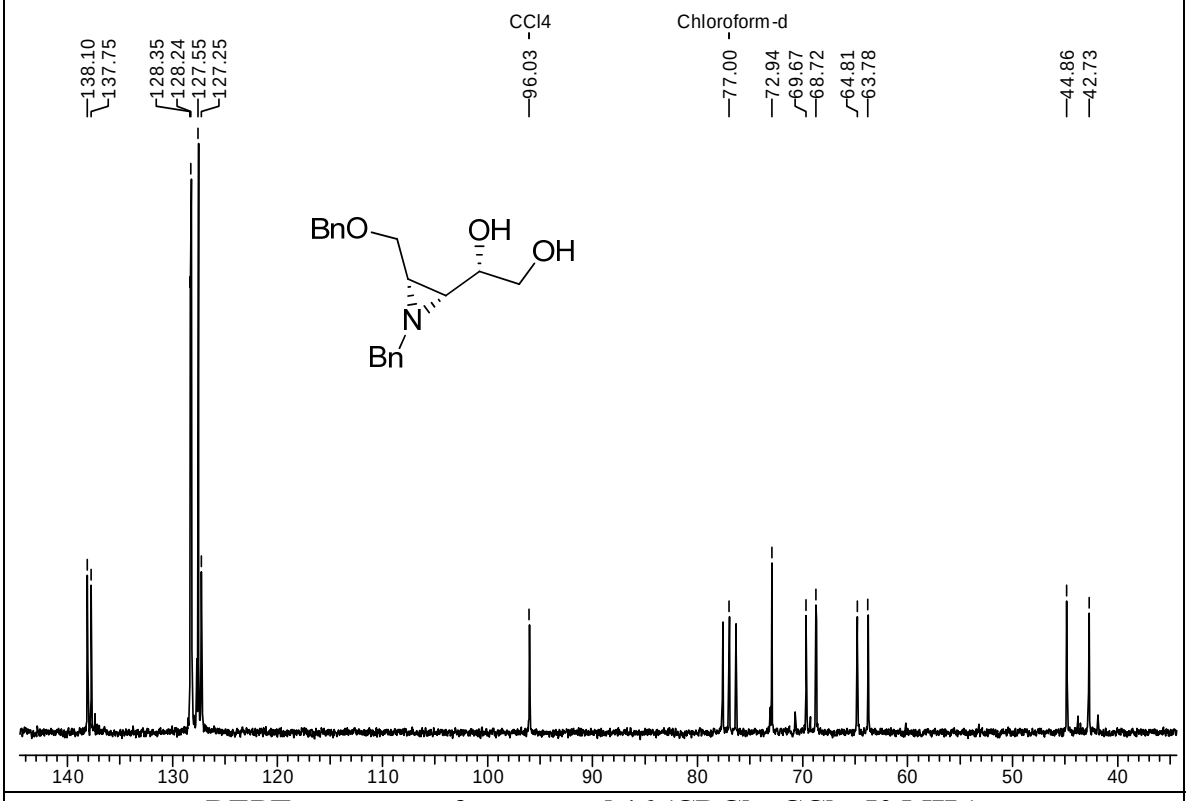
DEPT spectrum of compound 15 ($CDCl_3$+CCl_4, 50 MHz)



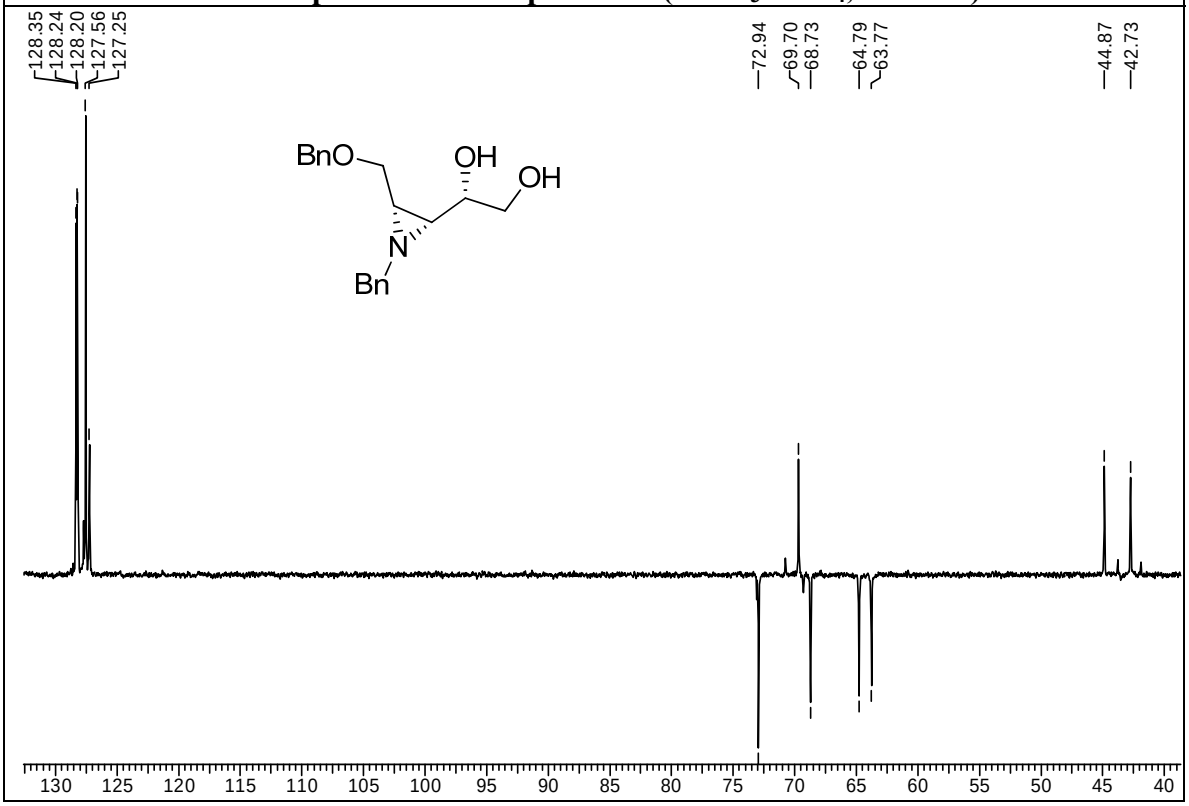
^{1}H-NMR spectrum of compound 16 ($CDCl_3$+CCl_4, 200 MHz)



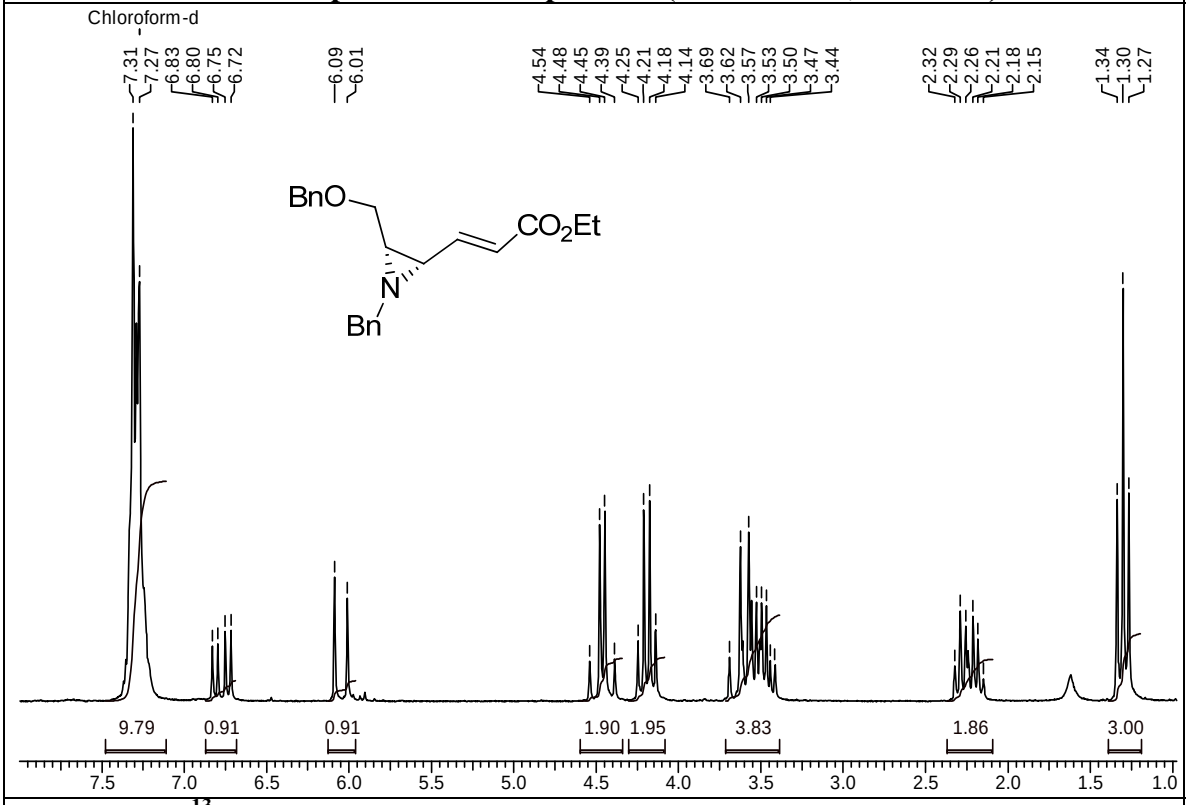
^{13}C-NMR spectrum of compound 16 ($CDCl_3$+CCl_4, 50 MHz)



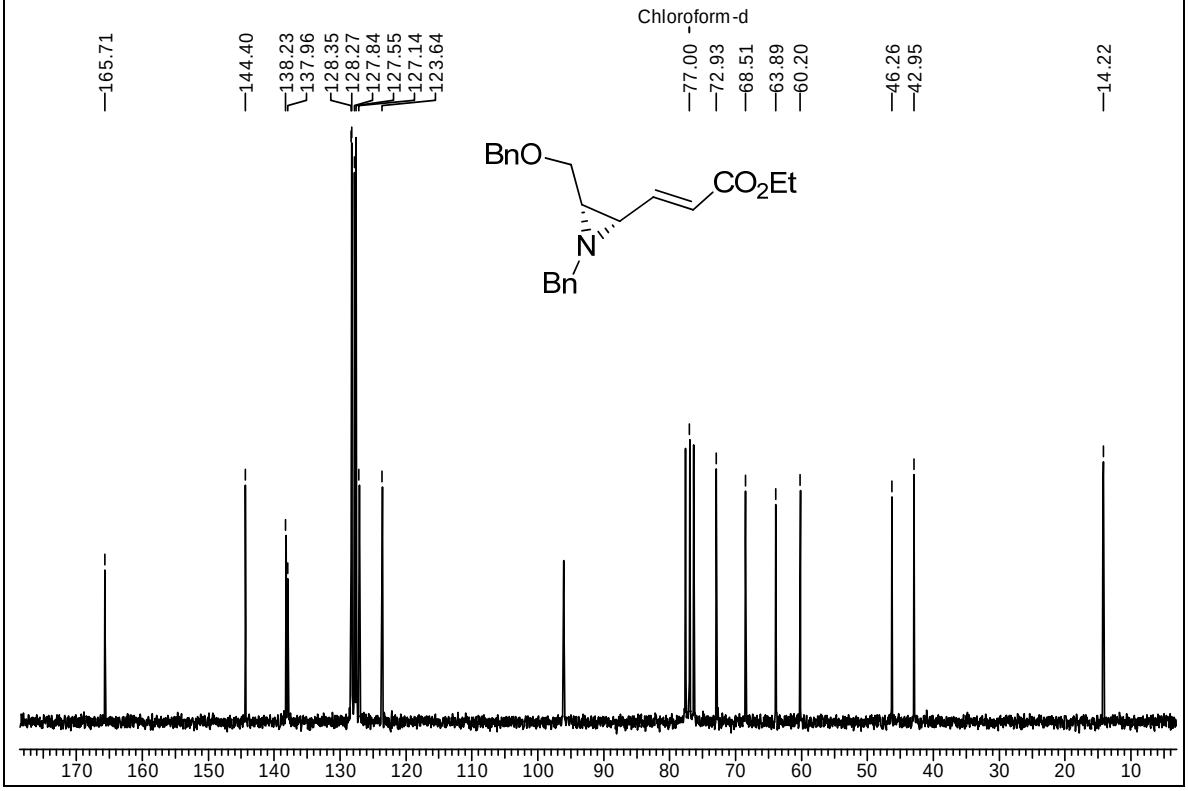
DEPT spectrum of compound 16 ($CDCl_3$+CCl_4, 50 MHz)



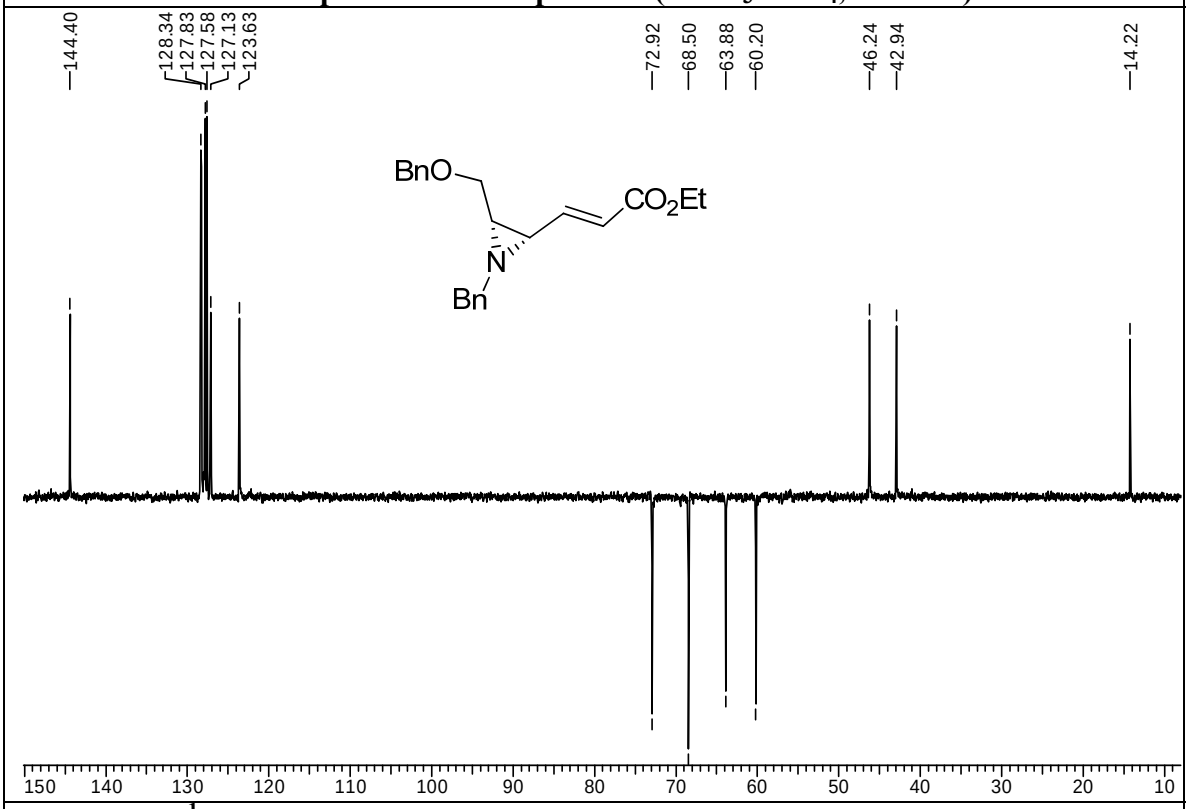
^{1}H-NMR spectrum of compound 5 ($CDCl_3$+CCl_4, 200 MHz)



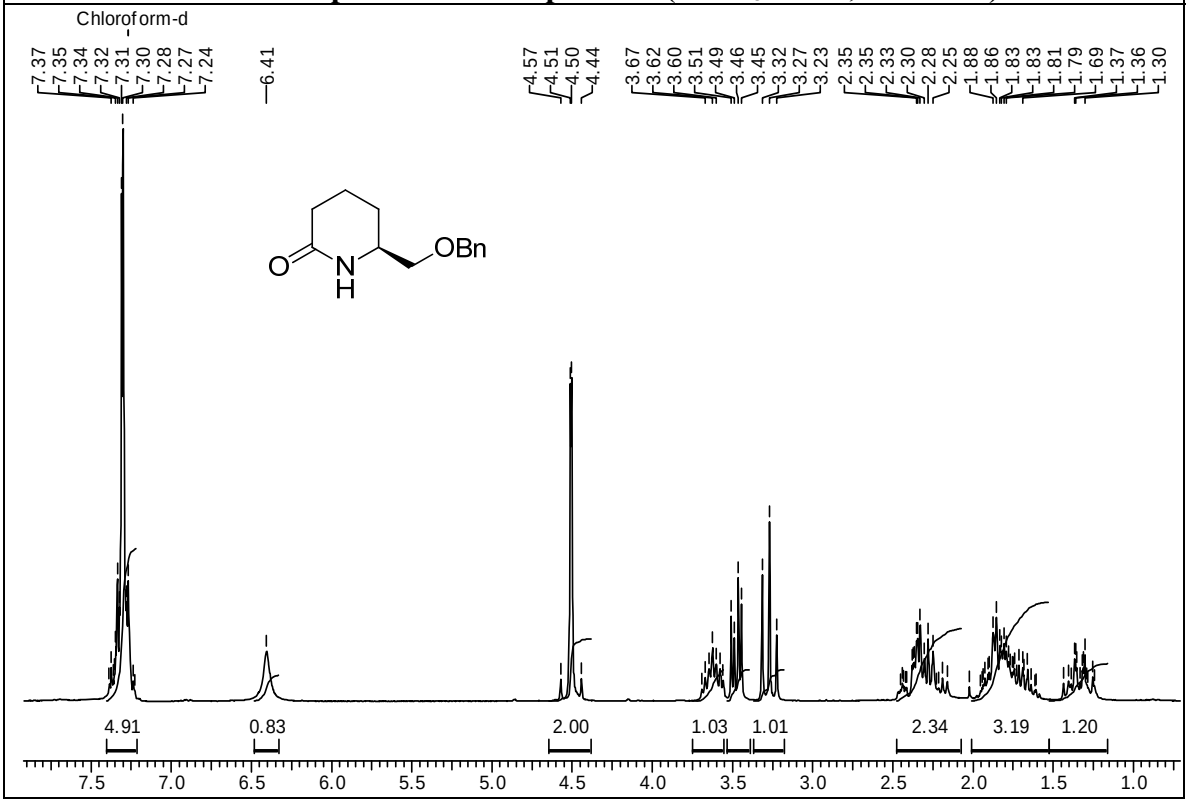
^{13}C-NMR spectrum of compound 5 ($CDCl_3$+CCl_4, 50 MHz)



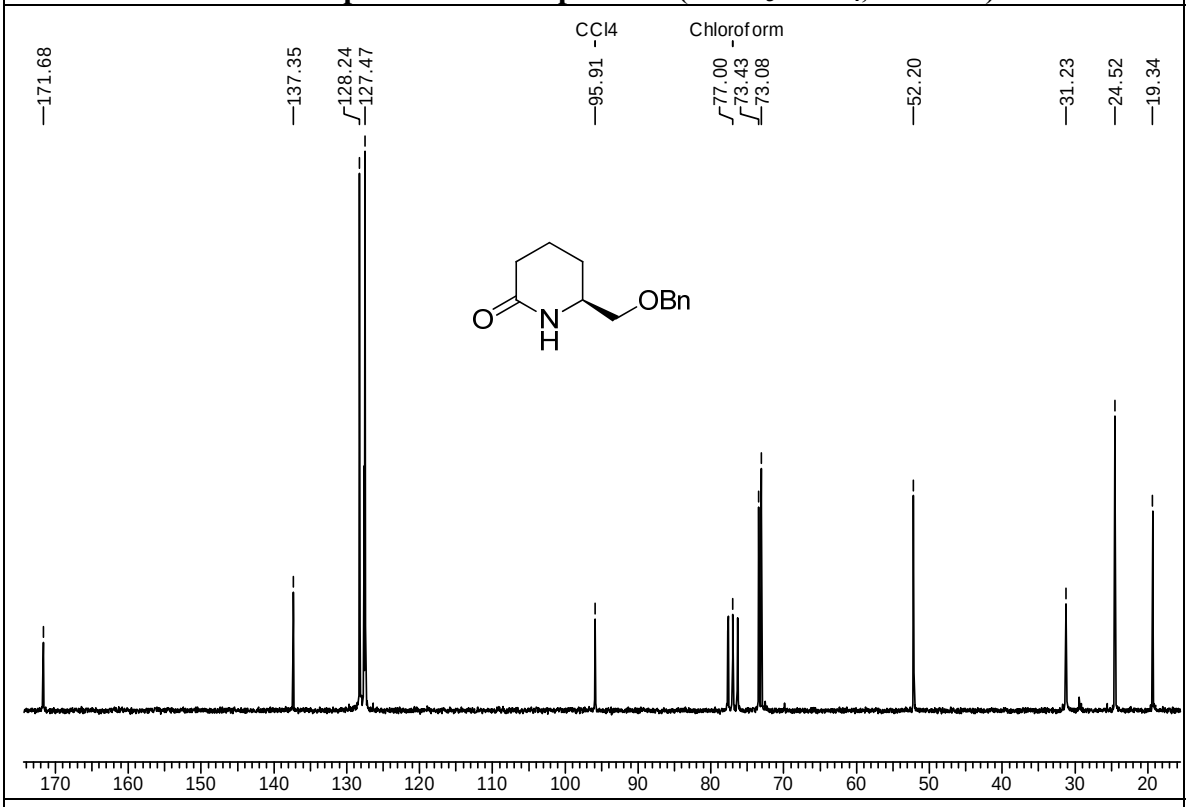
DEPT spectrum of compound 5 ($CDCl_3$+CCl_4, 50 MHz)



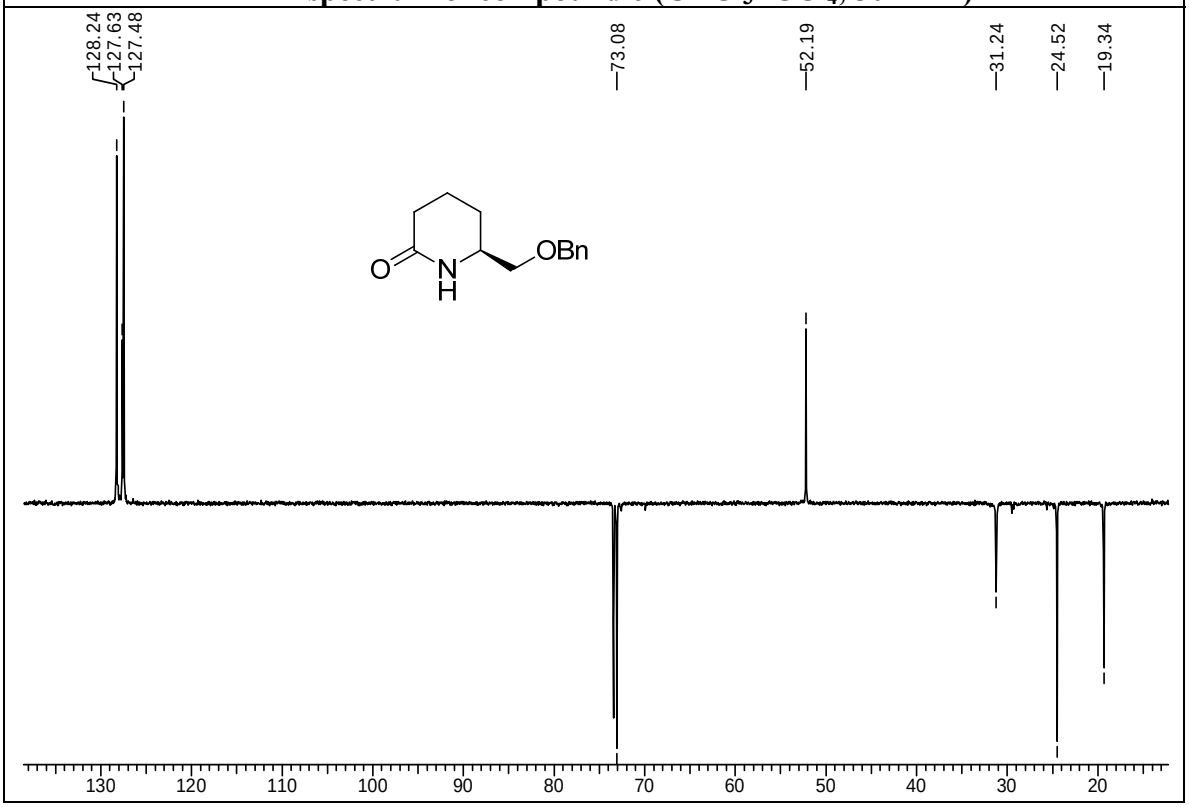
^{1}H-NMR spectrum of compound 6 ($CDCl_3$+CCl_4, 200 MHz)



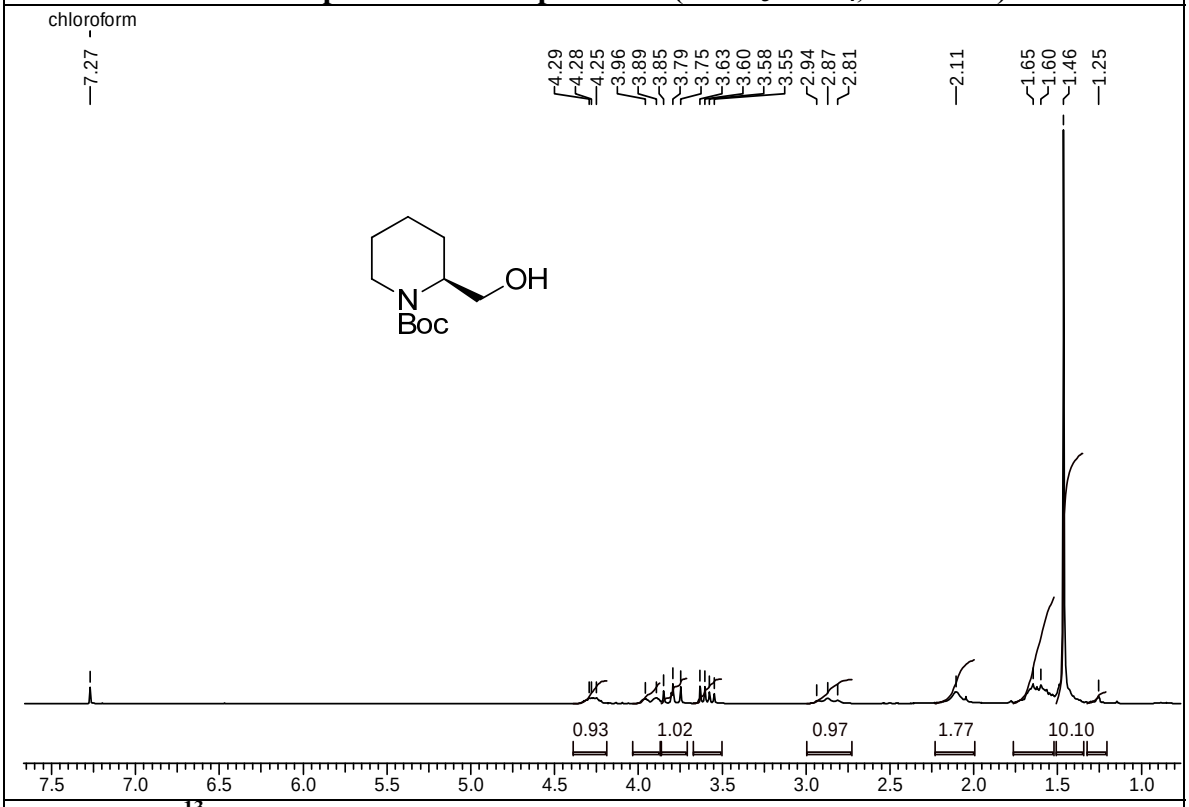
^{13}C-NMR spectrum of compound 6 ($CDCl_3$+CCl_4, 50 MHz)



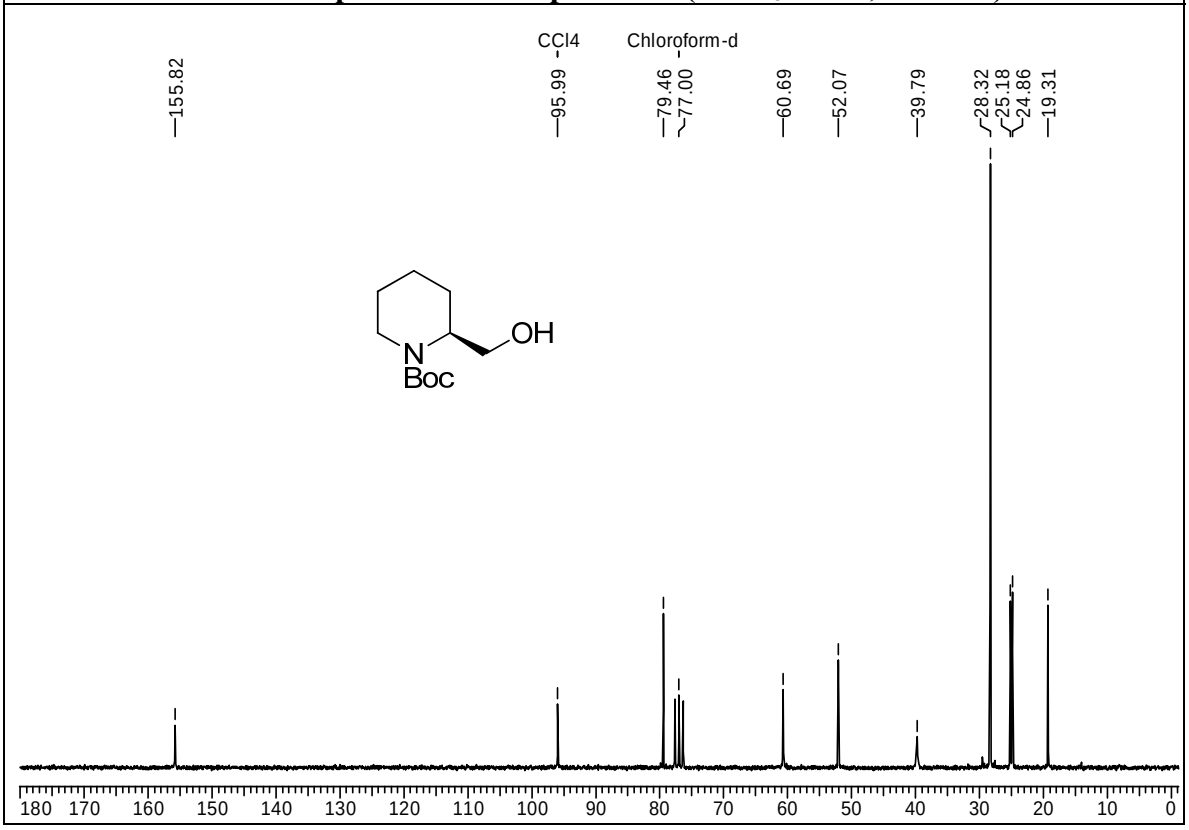
DEPT spectrum of compound 6 ($CDCl_3$+CCl_4, 50 MHz)



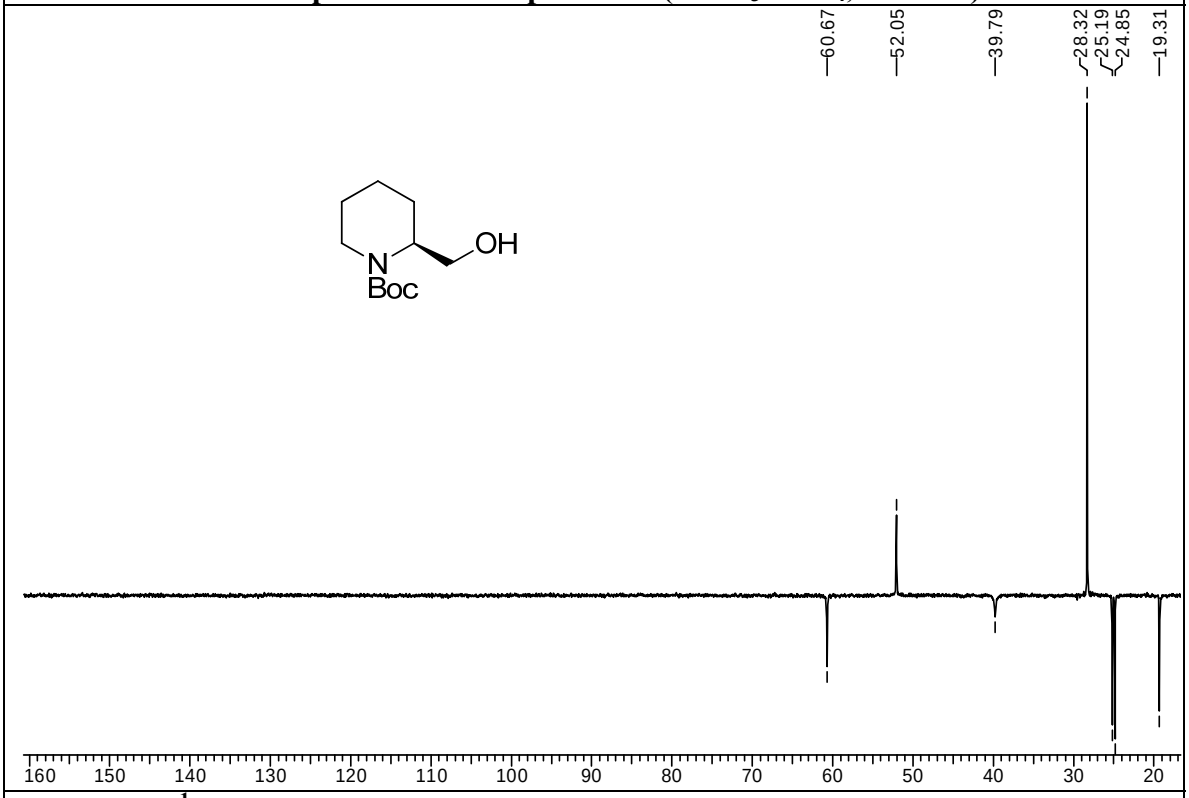
^{1}H-NMR spectrum of compound 17 ($CDCl_3$+CCl_4, 200 MHz)



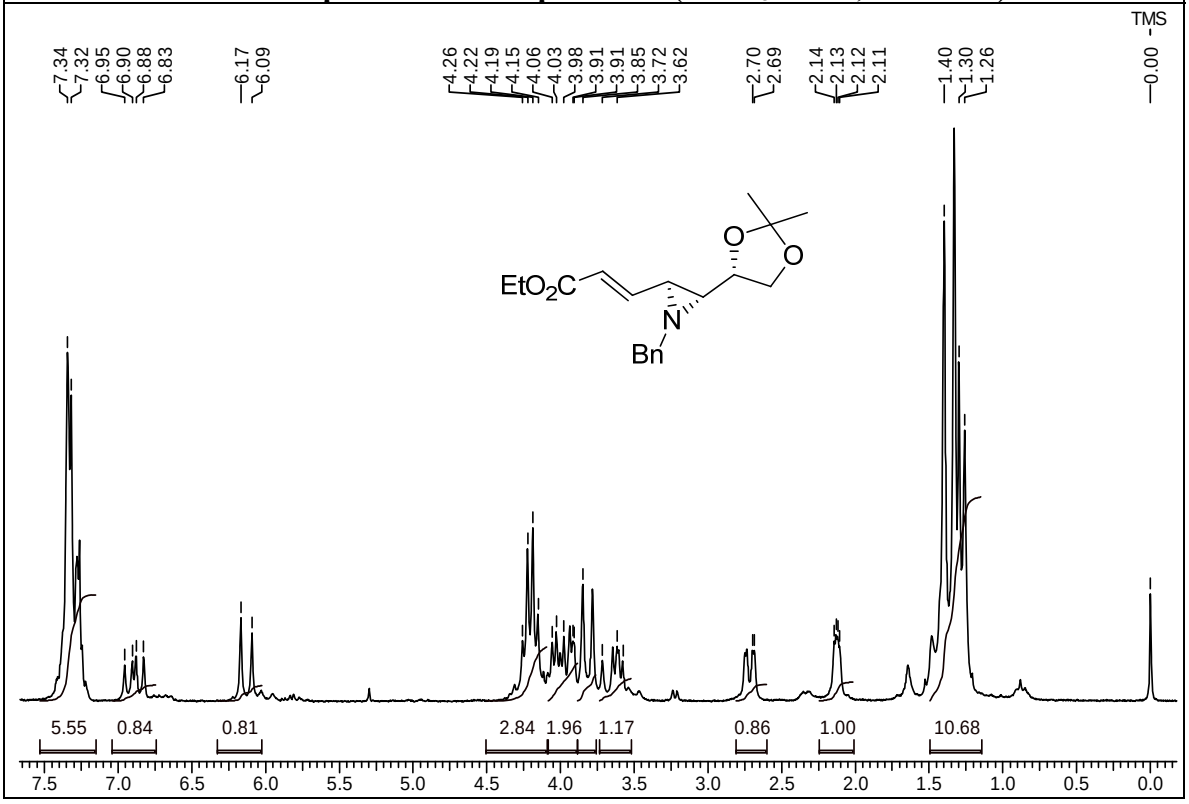
^{13}C-NMR spectrum of compound 17 ($CDCl_3$+CCl_4, 50 MHz)



DEPT spectrum of compound 17 ($CDCl_3$+CCl_4, 50 MHz)



^{1}H-NMR spectrum of compound 18 ($CDCl_3$+CCl_4, 200 MHz)



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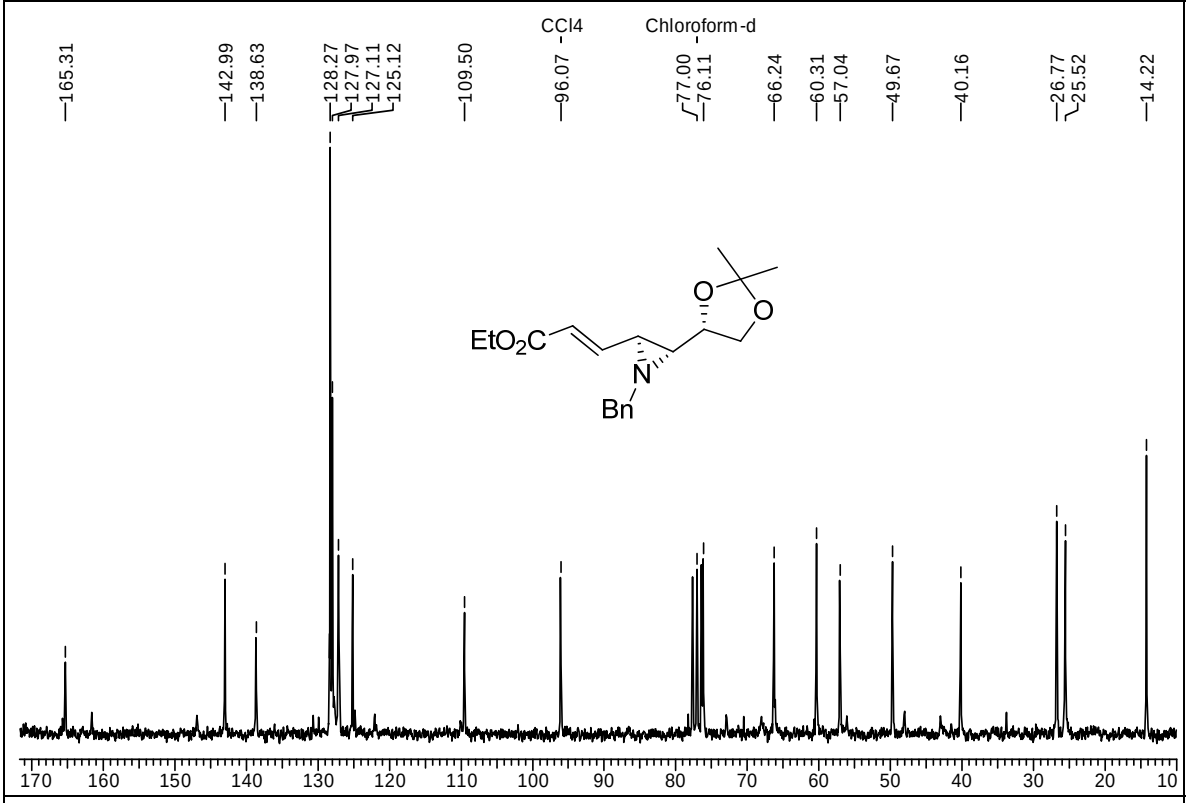
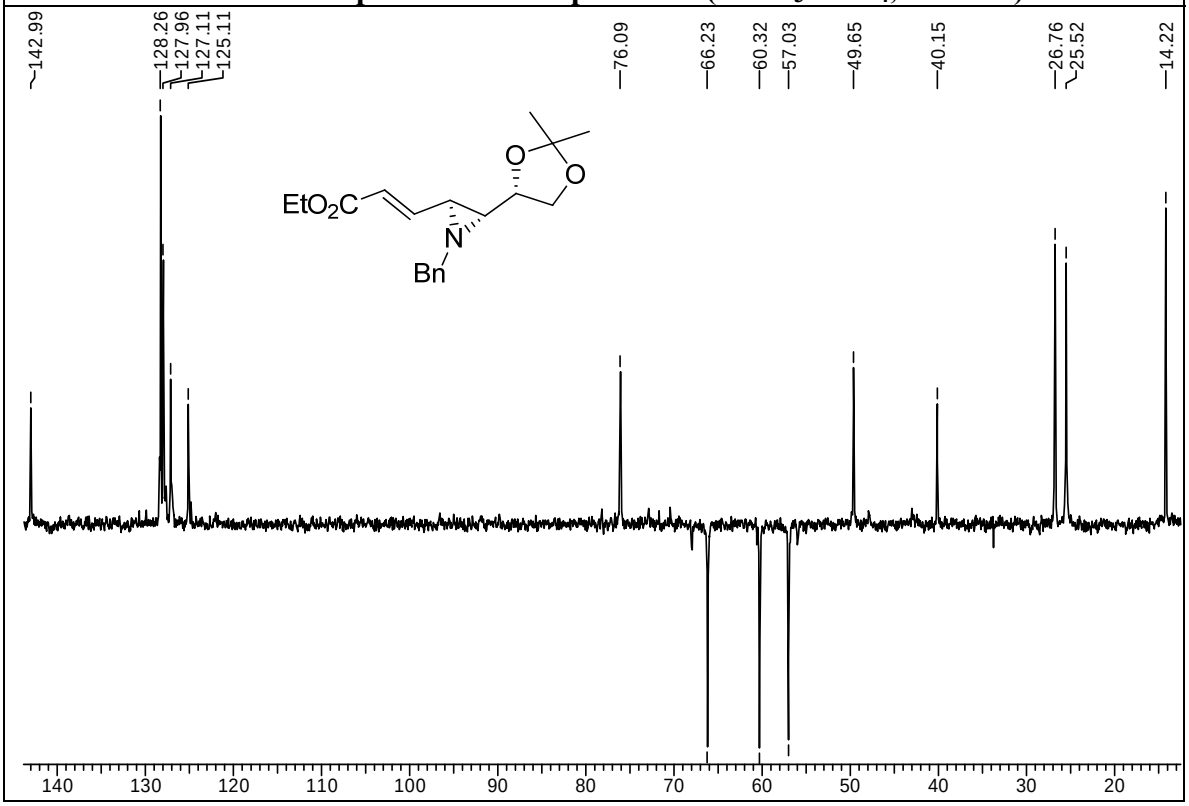


DEPT-NMR spectrum of compound 18 ($CDCl_3$+CCl_4, 50 MHz)



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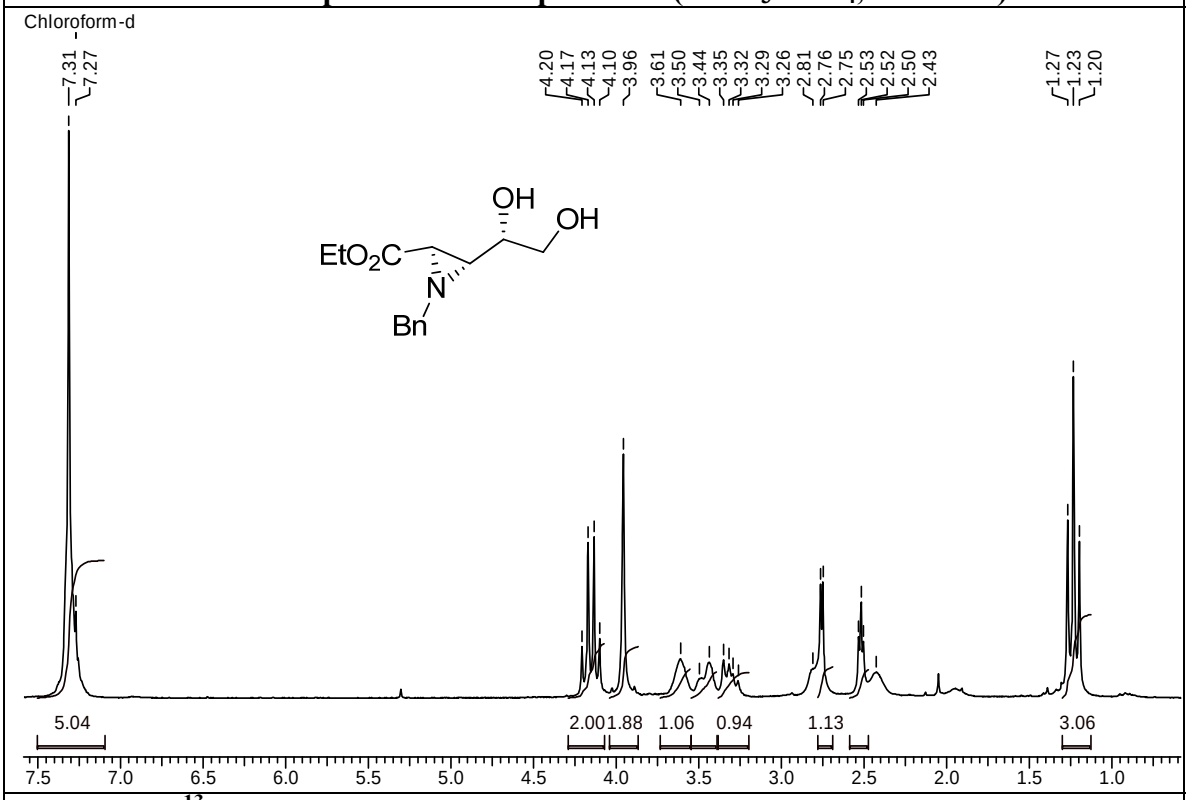
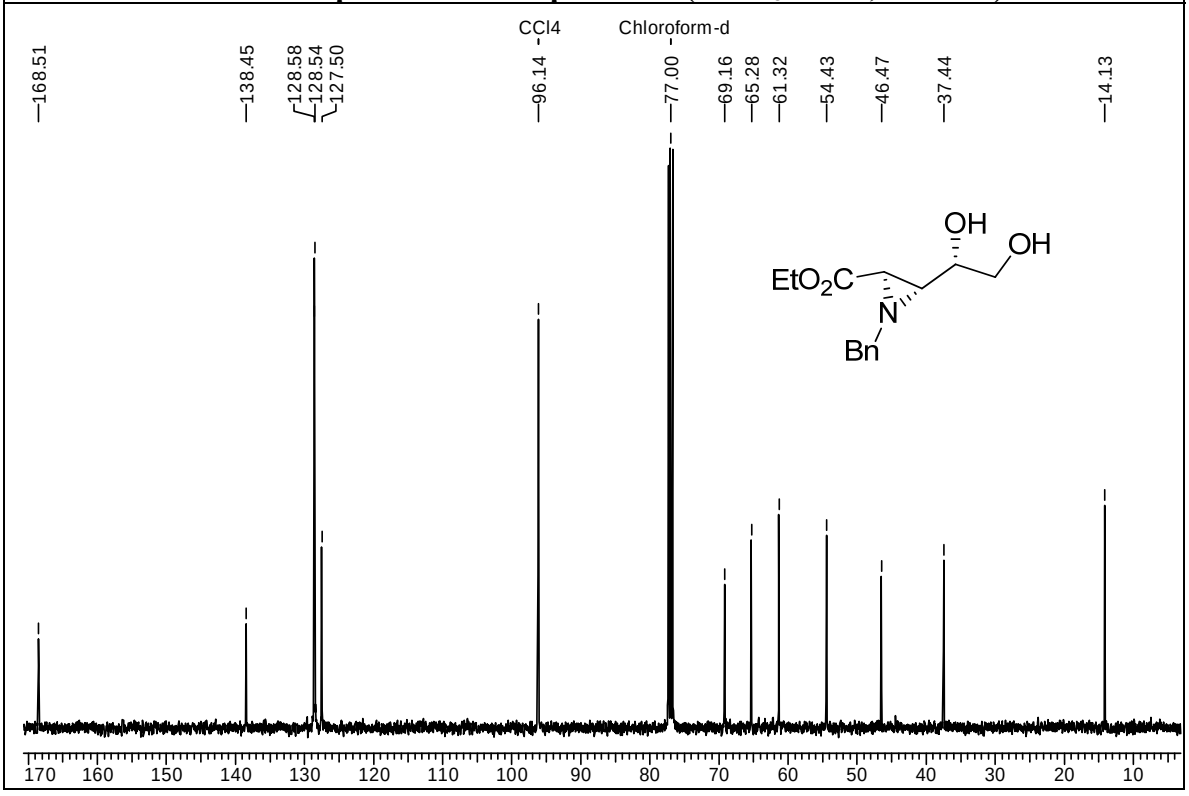
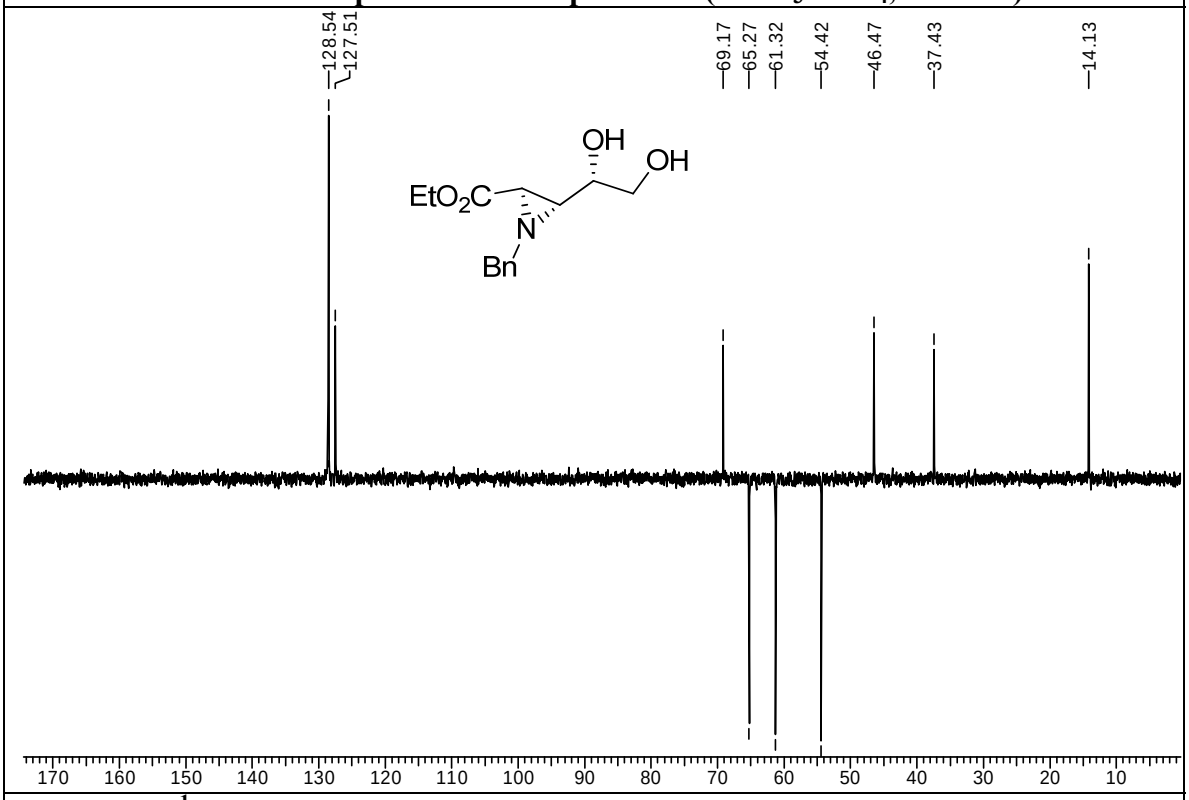


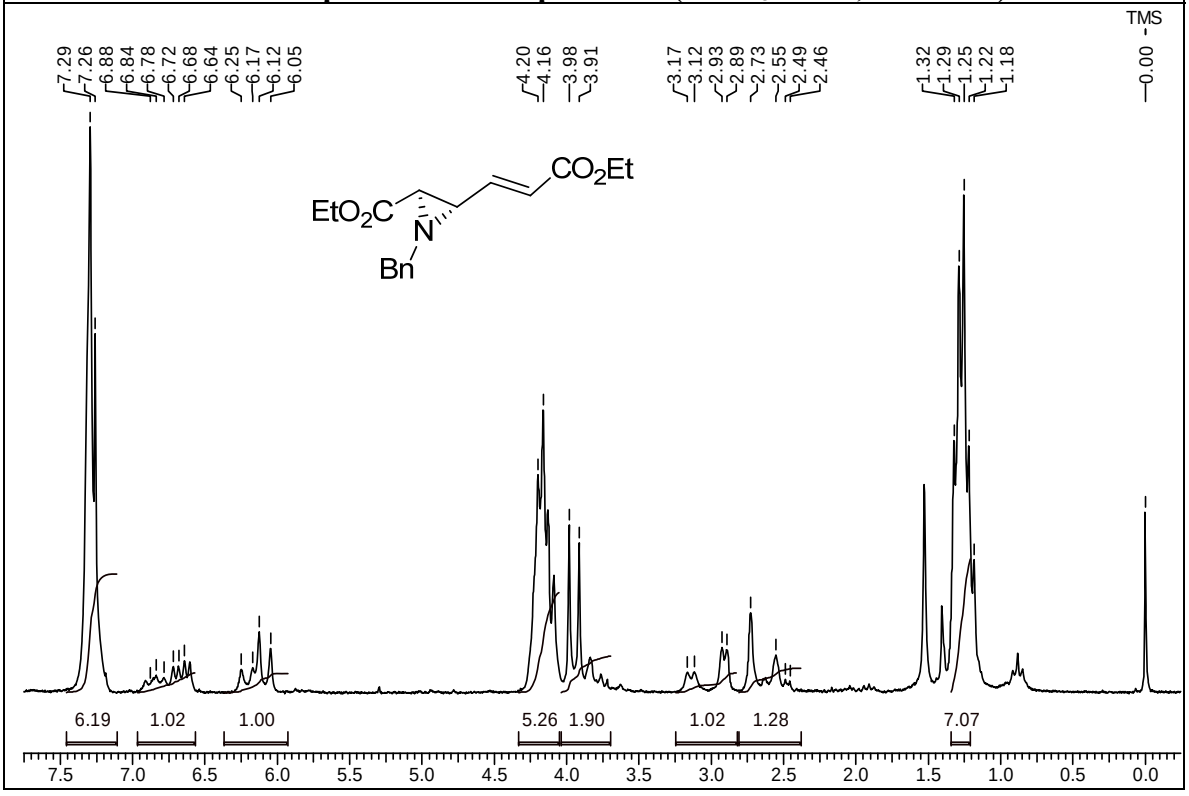
^{13}C-NMR spectrum of compound 22 ($CDCl_3$+CCl_4, 50 MHz)



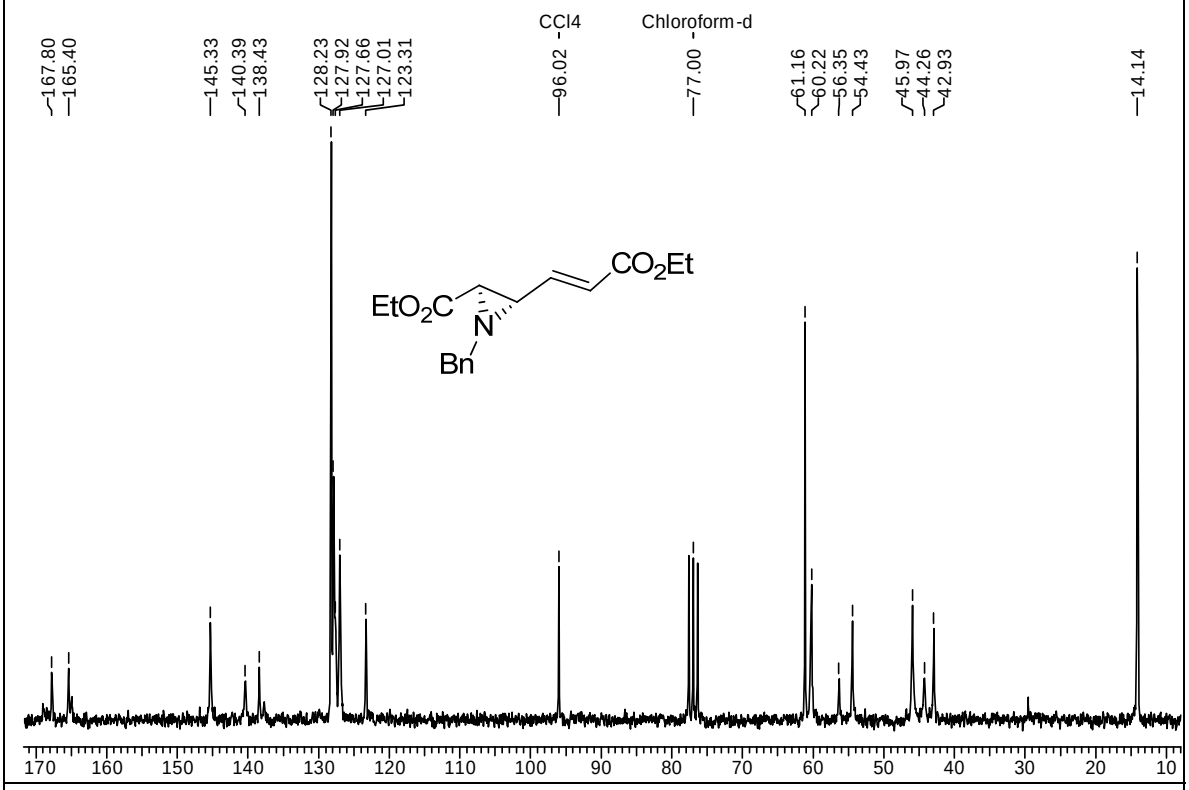
DEPT NMR spectrum of compound 22 ($CDCl_3$+CCl_4, 50 MHz)



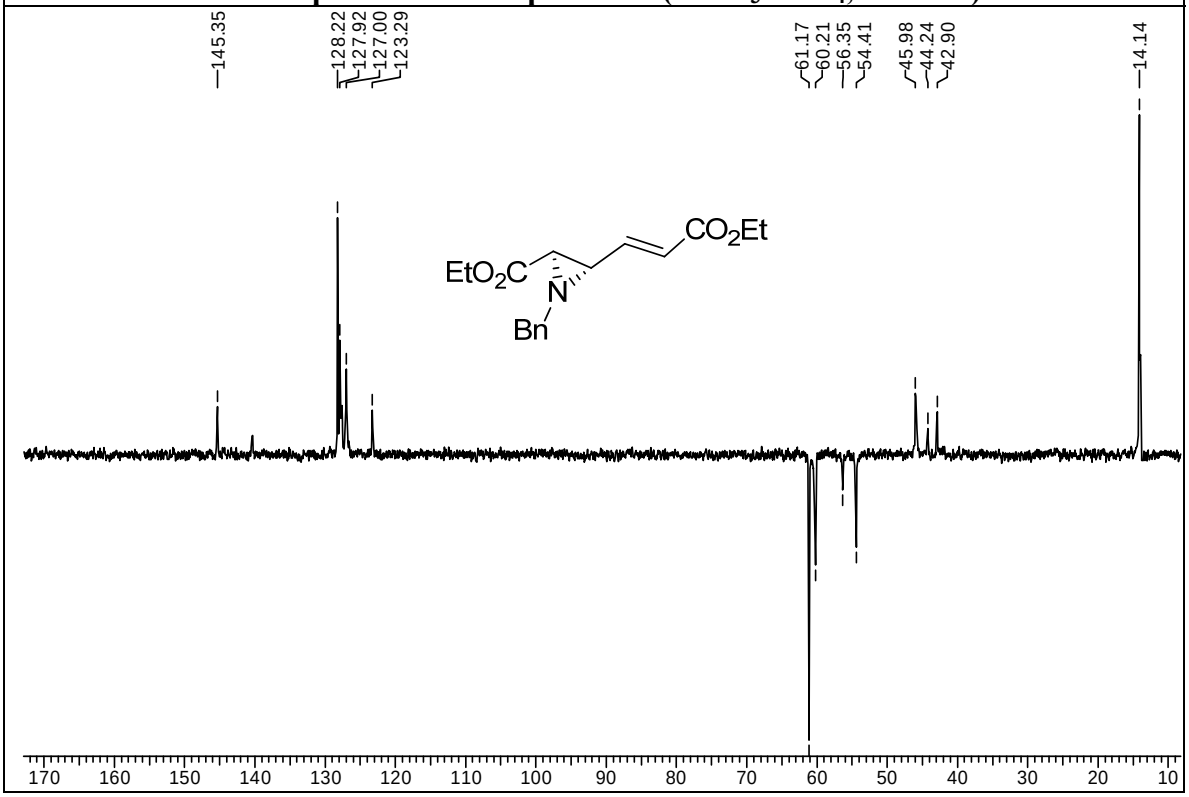
^{1}H-NMR spectrum of compound 19 ($CDCl_3$+CCl_4, 200 MHz)



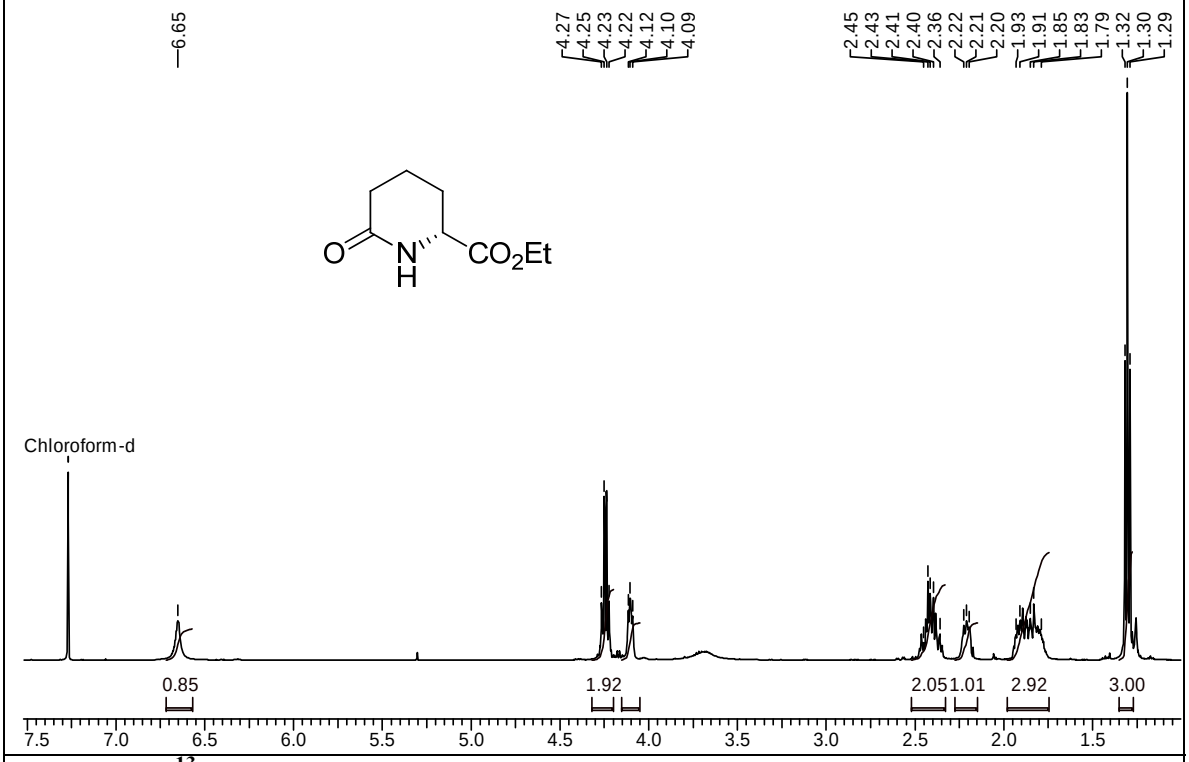
^{13}C-NMR spectrum of compound 19 ($CDCl_3$+CCl_4, 50 MHz)



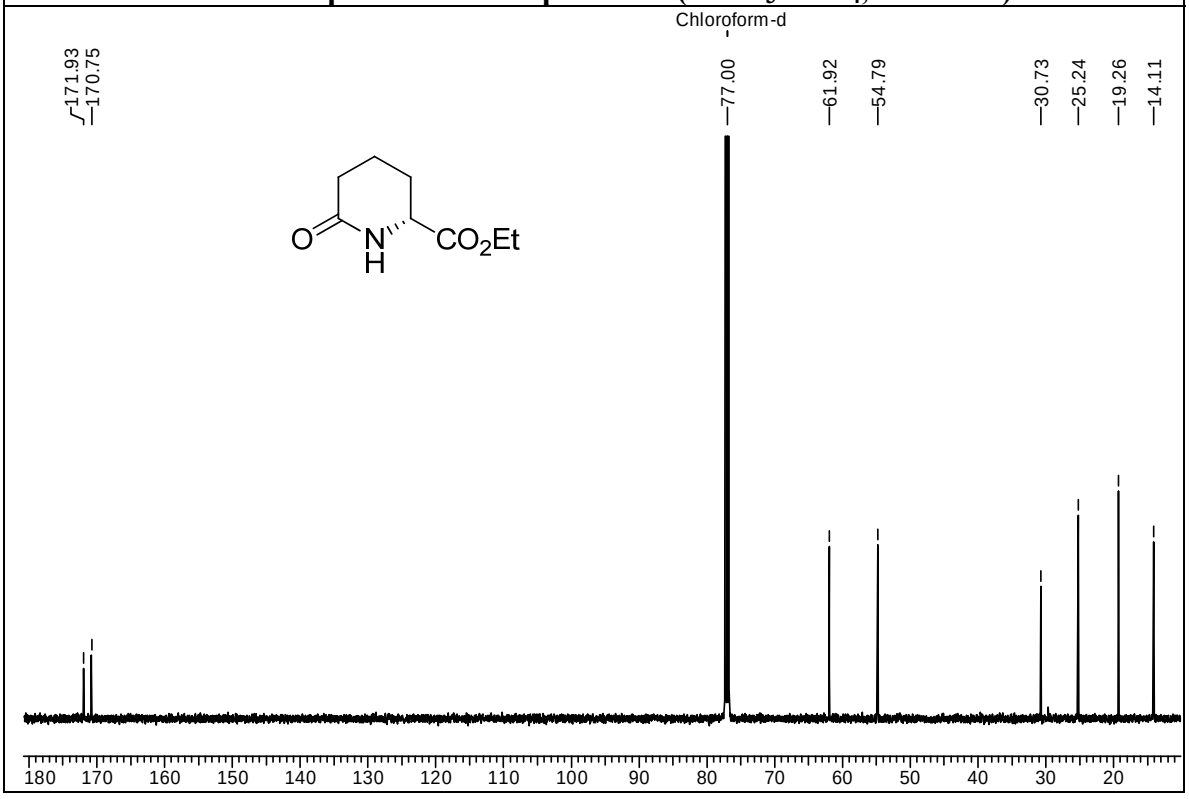
DEPT spectrum of compound 19 ($CDCl_3$+CCl_4, 50 MHz)



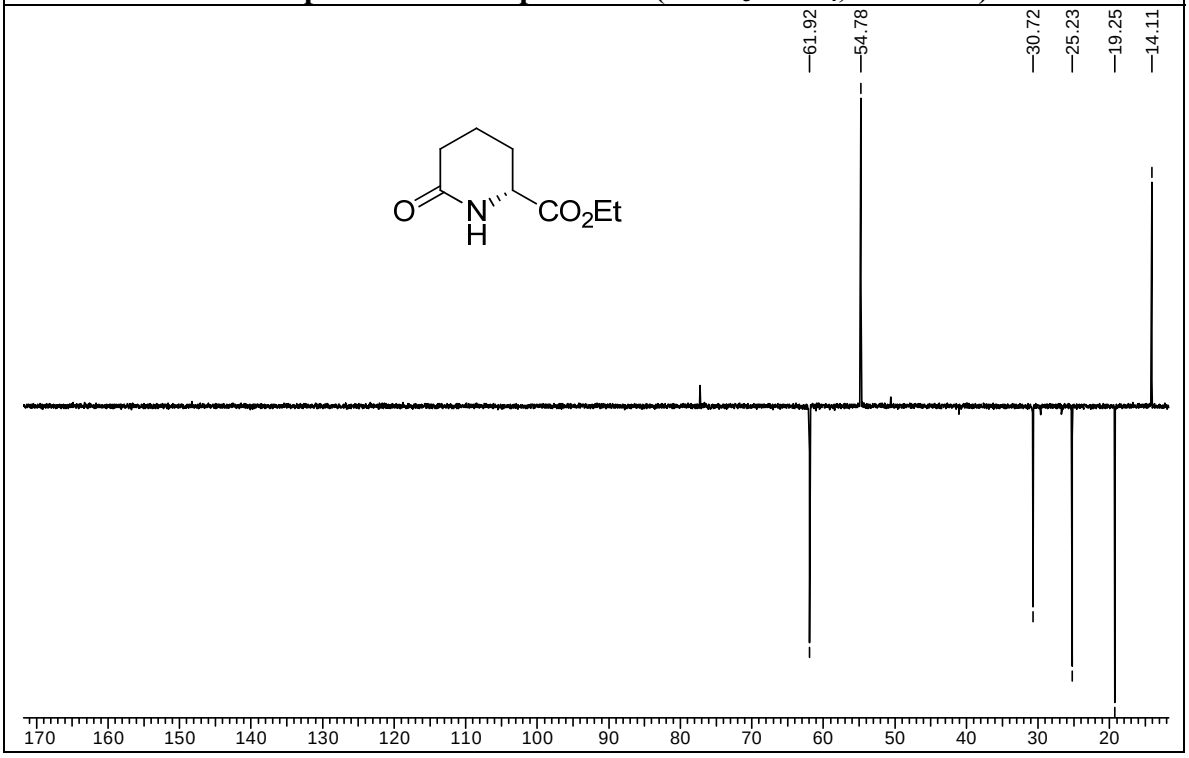
^{1}H-NMR spectrum of compound 20 ($CDCl_3$+CCl_4, 500 MHz)



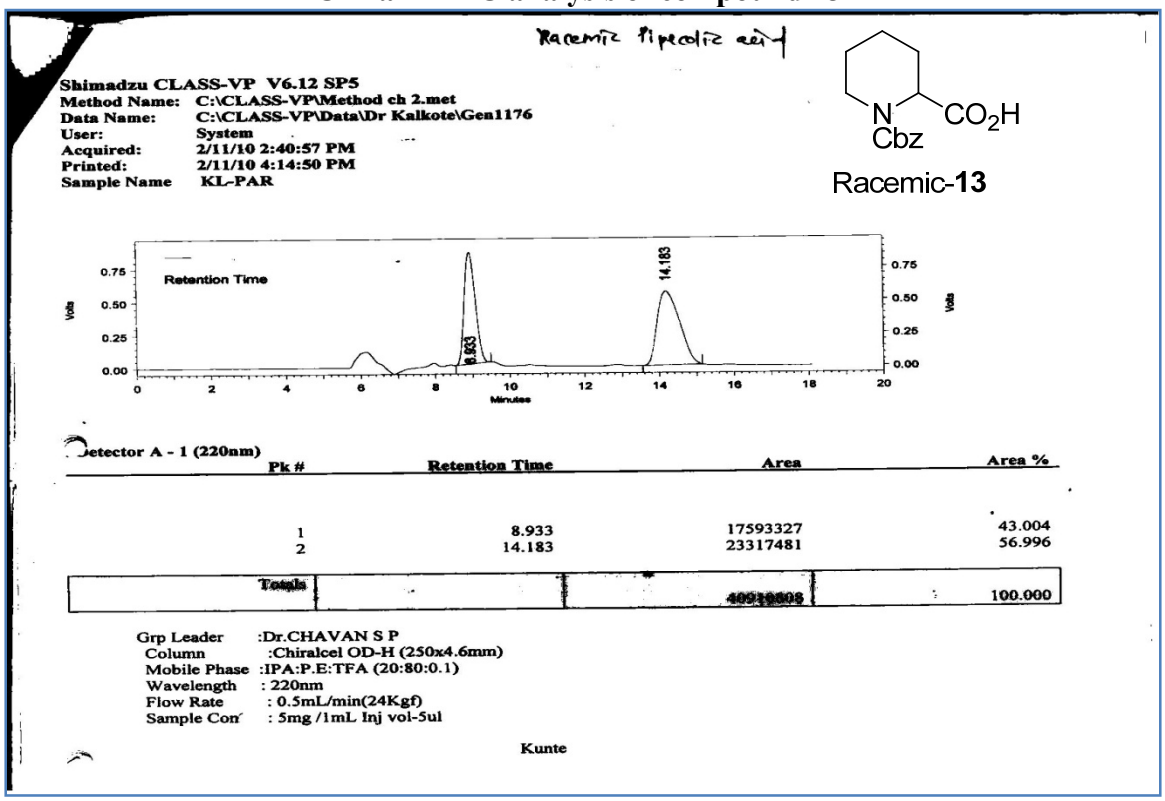
^{13}C-NMR spectrum of compound 20 ($CDCl_3$+CCl_4, 125 MHz)



DEPT spectrum of compound 20 ($CDCl_3$+CCl_4, 125 MHz)



Chiral HPLC analysis of compound 13



(R) Pipecolic acid

Shimadzu CLASS-VP V6.12 SP5
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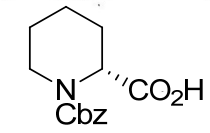
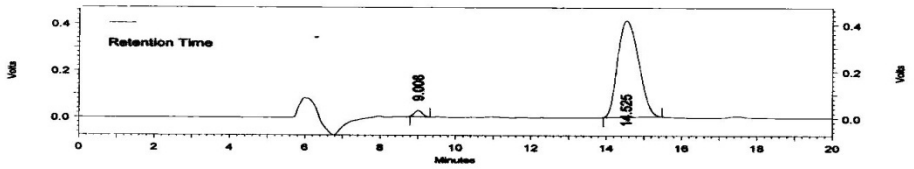
Data Name: C:\CLASS-VP\Data\Dr Kalkote\Gen1179
User: System
Acquired: 2/11/10 3:42:44 PM
Printed: 2/11/10 4:11:08 PM
Sample Name KL-PAC(R)



(*R*)-**13**



Detector A - 1 (220nm)

Pk #	Retention Time	Area	Area %
1	9.008	378896	2.301
2	14.525	16085480	97.699
Totals		[illegible]	100.000

Grp Leader :Dr.CHAVAN S P
Column :Chiralcel OD-H (250x4.6mm)
Mobile Phase :IPA:P.E:TFA (20:80:0.1)
Wavelength : 220nm
Flow Rate : 0.5mL/min(24Kgf)
Sample Con : 5mg /1mL Inj vol-5ul

Kunte

Chiral HPLC analysis of compound 17

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr. CHAVAN S. P\Lk1031
User: System
Acquired: 5/4/12 3:41:03 PM
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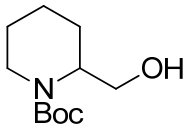
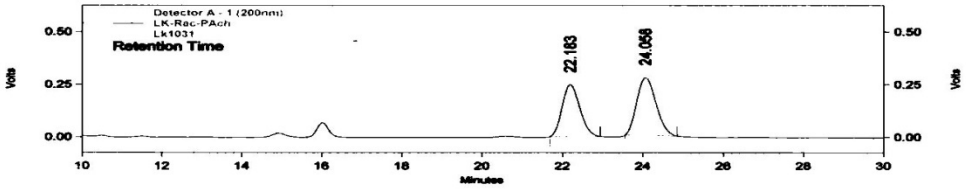
Sample Name LK-Rac-PAch



Racemic-**17**



Detector A - 1 (200nm)

Retention Time	C Area	Area %
22.183	7539900	45.080
24.058	9185600	54.920
Totals	16725500	100.000

Project Leader : Dr. S. P. Chavan
Column :Kromacil 5-Amycoat (250x4.6 mm)
Mobile Phase :IPA : n-Hexane (4:96)
Wavelength : 200nm
Flow Rate :0.5ml/min (312 psi)
conc. : X mg/1.5 ml.
Inj vol- :5 µl

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr. CHAVAN S. P\Lk1029
User: System
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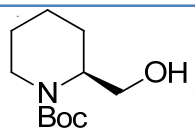
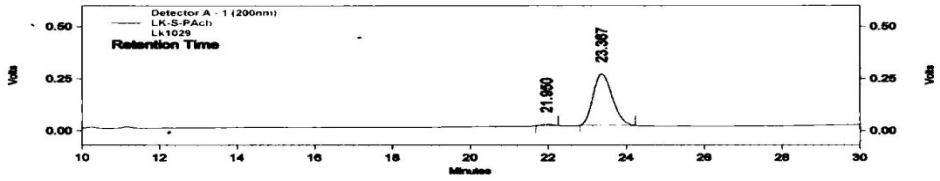
Printed: 5/4/12 3:22:46 PM
Sample Name LK-S-PAch



(*S*)-**17**



Detector A - 1 (200nm)

Retention Time	C Area	Area %
21.950	124948	1.453
23.367	8471818	98.547
Totals	**8596766**	**100.000**

Project Leader : Dr. S. P. Chavan
Column :Kromacil 5-Amycoat (250x4.6 mm)
Mobile Phase :IPA : n-Hexane (4:96)
Wavelength : 200nm
Flow Rate :0.5ml/min (312 psi)
conc. : X mg/1.5 mL
Inj vol- :5 ul

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr. CHAVAN S. P\Lk1030
User: System
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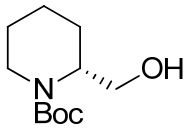
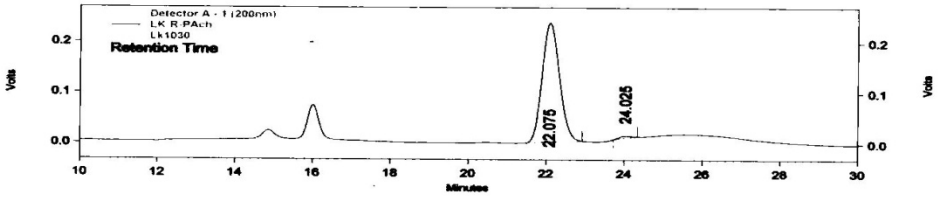
Sample Name LK-R-PAch



(*R*)-**17**



Detector A - 1 (200nm)

Retention Time	C Area	Area %
22.075	7297559	98.762
24.025	91497	1.238
Totals	**7389056**	**100.000**

Project Leader : Dr. S. P. Chavan
Column :Kromacil 5-Amycoat (250x4.6 mm)
Mobile Phase :IPA : n-Hexane (4:96)
Wavelength : 200nm
Flow Rate :0.5ml/min (312 psi)
conc. : X mg/1.5 mL
Inj vol- :5 ul

1.2.5 References

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Chapter 2: Synthetic studies toward *trans*-(2*R*,3*R*)-3-hydroxypipecolic acid and (−)-swainsonine

Section 1: Introduction of *trans*-(2*R*,3*R*)-3-hydroxypipecolic acid

2.1.1 Introduction

Functionalized piperidines especially polyhydroxylated ones represent one of the most ubiquitous skeleton found in varied natural and non- natural compounds and have demonstrated activity against a wide range of biochemical targets in diverse therapeutic.[1]

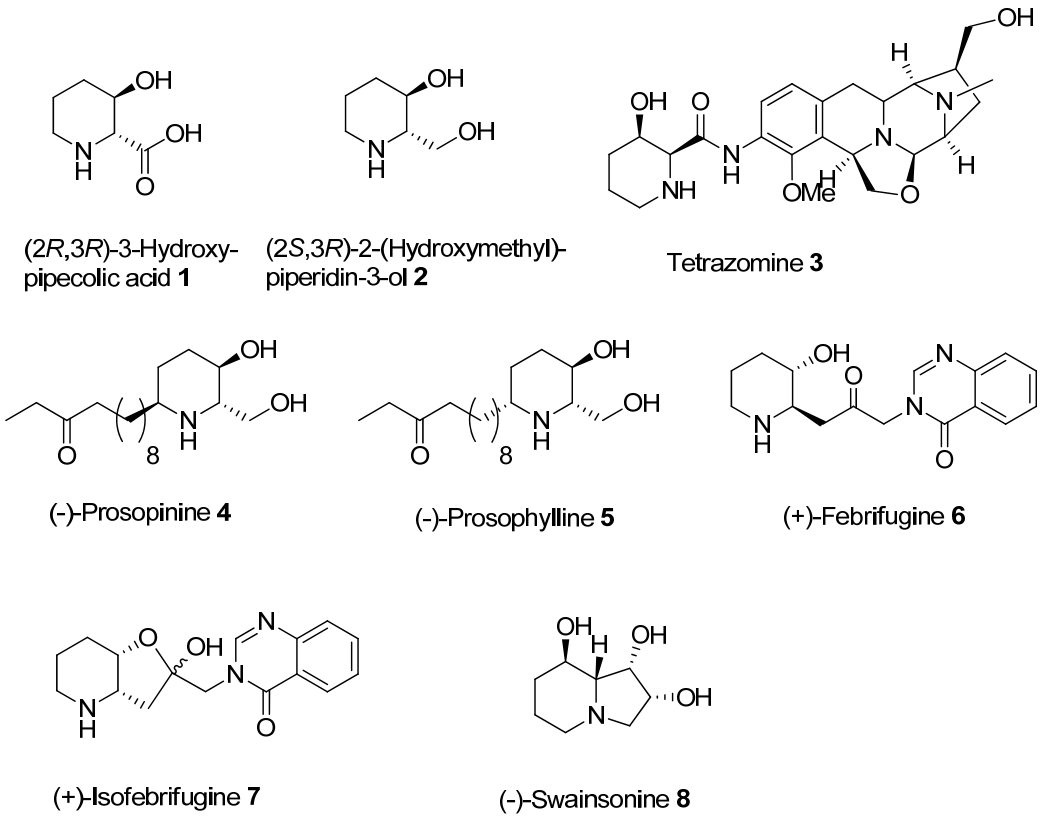


Figure 1

An important subclass of polyhydroxypiperidines is composed of natural products containing a 3-hydroxypiperidine scaffold. The 3-hydroxypiperidine is one of the most privileged scaffolds, which is present in a variety of natural products. The representative example is 3-hydroxypipecolic acid **1** which is a non-proteinogenic cyclic α-amino acid. It is used in the preparation of conformationally restricted peptides and ligand binding studies.[2] The *cis*-isomer of **1** is a structural unit of the antitumor antibiotic tetrazomine **3**.[3] The carboxyl group reduced analogues of **1**, namely 3-hydroxy-2-hydroxymethylpiperidine **2**, are known as fagomine congeners which are promising glycosyltransferases and glycosidase inhibitors.[4] It is also an important scaffold present in many natural as well as synthetic biologically active molecules having

potent biological activities like (–)-prosopinene **4** and **(–)-**prosophylline **5** which act as antibiotic and anaesthetic,[5] (+)-febrifugine **6** and (+)-isofebrifugine **7** which show antimalarial activities.[6] (−)-Swainsonine **8** which also contains this very significant 3-hydroxy piperidine skeleton was found to be an effective inhibitor of both lysosomal α-mannosidase, and mannosidase II along with antimestastic, antitumor-proliferative, anticancer, immunoregulating activity and attracted the attention of medicinal chemists due to its pharmacological properties and reached phase I clinical trials as an anticancer drug (Figure 1).[7]

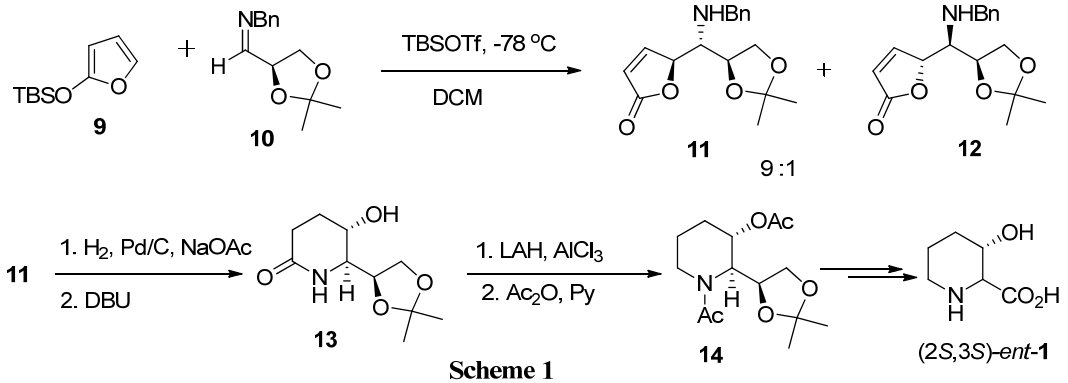
2.1.2 Literature review

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

(a) Syntheses using chiral pool approach:

Casiraghi's approach

Casiraghi *et al*. (Scheme 1) developed a novel diastereoselective addition of silyloxy furan TBSOF and imines derived from L and D glyceraldehydes with excellent diastereomeric excess and exploited it for the synthesis of both the enantiomers of 3-hydroxypipecolic acid **1**.[8]

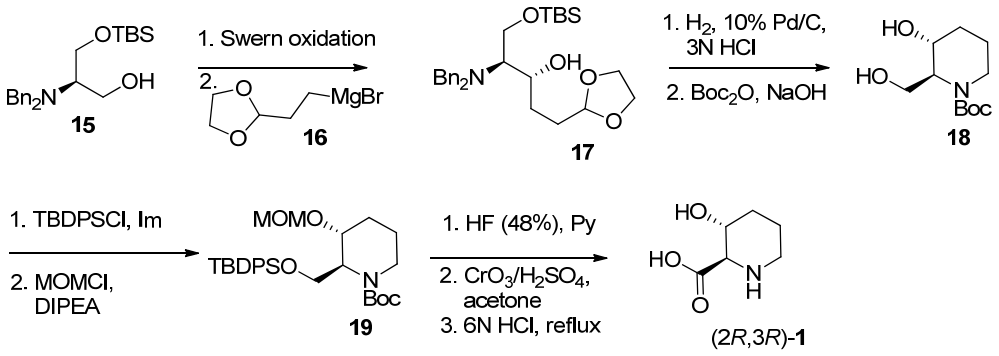


Scheme 1

Thus, the 2-silyloxyfuran **9** and imine **10** were coupled to provide butenolide amine **11** and **12** in the ratio 9:1. Butenolide amine **11** was subjected to hydrogenation followed by treatment with DBU to provide amide **13**. Amide **13** was reduced using LAH, $AlCl_3$ to provide aminol acetate **14** which on subsequent transformations was converted to 3-hydroxypipecolic acid **1**. The enantiomer of **1** was also prepared starting from D-glyceraldehyde.

Zhu's approach

Zhu *et al*. synthesized enantiomer of 3-hydroxypipecolic acid **1** starting from amino alcohol **15** derived from serine (Scheme 2). Amino alcohol **14** was oxidized to aldehyde and subjected to reaction with Grignard reagent **16** to obtain anti amino alcohol **17** as a major product which was exploited for the synthesis of (2*R*,3*R*)-**2**. Protected amino alcohol **17** was subjected to hydrogenation and subsequently for Boc protection to provide diol **18**. The primary alcohol in diol **18** was protected with TBDPS group selectively and then secondary alcohol with MOM, then the TBDPS group was deprotected, and the resulting alcohol was subjected to oxidation and subsequently MOM group was deprotected to provide (2*R*,3*R*)- 3-hydroxypipecolic acid **1**.[9]

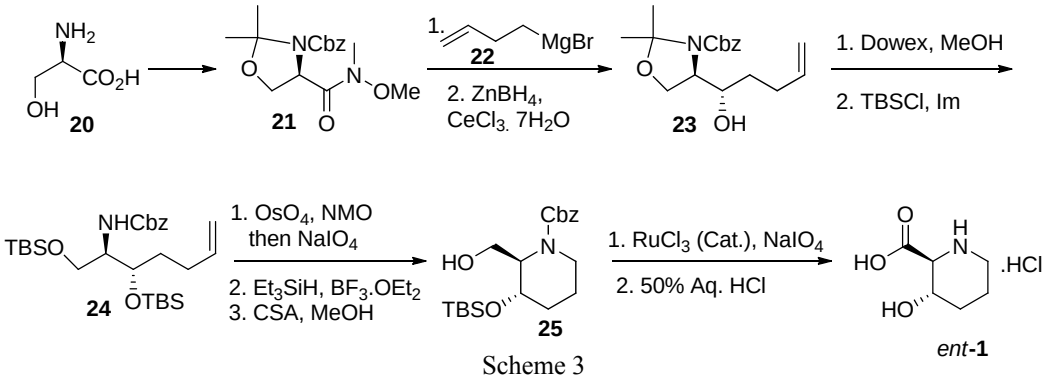


Scheme 2

Datta's approach

Datta *et al*. synthesized *ent*-**1** starting from D-serine **20** (Scheme 3), using diastereoselective reduction of ketone and reductive cyclization as the key steps. They prepared Weinreb amide **21** from **20** by known procedure.[10] Weinreb amide **21** on reaction with **22** forms ketone which was reduced using zinc borohydride along with cerium chloride to provide alcohol **23**. The acetonide deprotection of **23** and subsequent protection of diol with TBS provided aminol **24**. Aminol **24** was subjected to dihydroxyla-

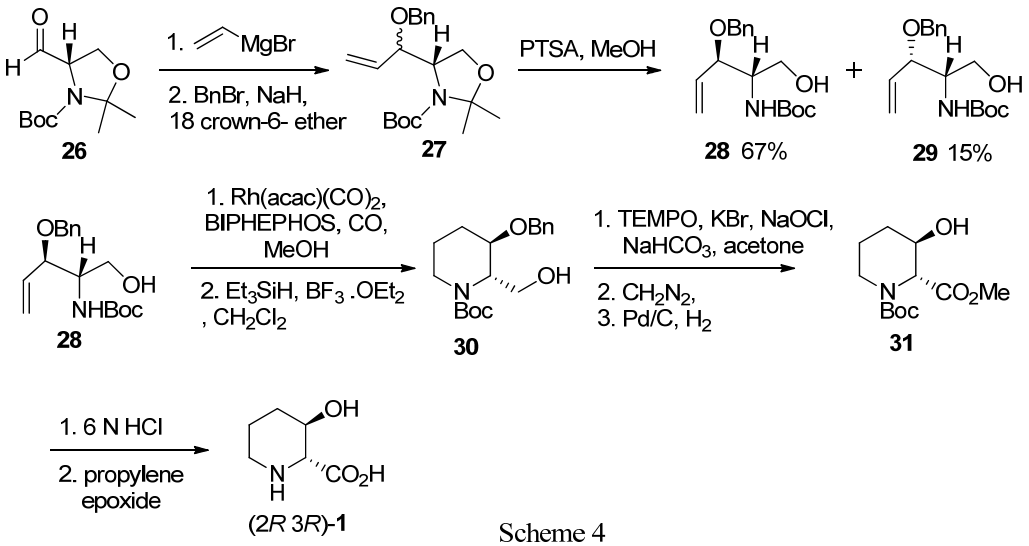
tion followed by cleavage of diol using $NaIO_4$ followed by reduction and deprotection to furnish **25**. Piperidine derivative **25** upon oxidation and deprotection resulted in to the formation of hydrochloride salt of 3-hydroxypipecolic acid *ent*-**1**.



Scheme 3

Chiou's approach

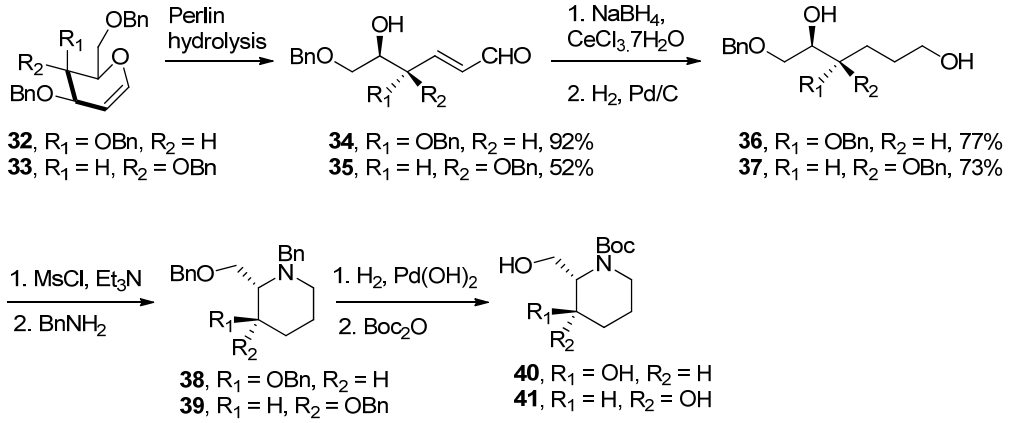
Chiou *et al*. synthesized *cis* and *trans* 3-hydroxypipecolic acid starting from Garner's aldehyde employing diastereoselective Grignard reaction and Rh catalyzed cyclohydrocarbonylation (Scheme 4). Nucleophilic addition of vinyl magnesium bromide on aldehyde **26** furnished diastereomeric mixture of alcohol, which was protected with benzyl bromide to give benzyl ether **27**. Compound **27** was subjected to acetonide deprotection to provide mixture of alcohols **28** and **29**, which were separated. Alcohol **28** was subjected to cyclohydrocarbonylation followed by reduction to provide piperidine alcohol **30**, which was further explored to (2*R*,3*R***)**-3-hydroxypipecolic acid**.** Similarly the alcohol **29** was explored for the synthesis of *cis* 3-hydroxypipecolic acid.[11]



Scheme 4

Vankar's approach

Vankar *et al*. (Scheme 5) completed formal synthesis of pipecolic acid along with



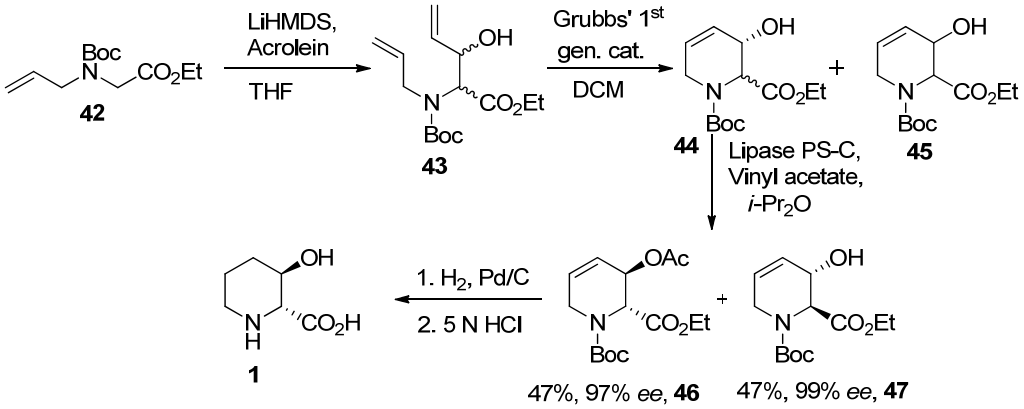
Scheme 5

deoxoprosophylline starting from D-glycal by taking advantage of Perlin hydrolysis, chemoselective saturation of olefins and reductive amination as the key steps.[12] D-Glycols **32** and **33** were subjected to Perlin hydrolysis to provide unsaturated aldehydes **34** and **35** respectively, which were subjected to reduction followed by hydrogenation to furnish diols **36** and **37**. Diols **36** and **37** on mesylation and subsequent treatment with benzyl amine provided piperidines **38** and **39**, which on hydrogenation and Boc protection gave diols **40** and **41** respectively.

(b) Synthesis using chiral induction:

Takahata's approach

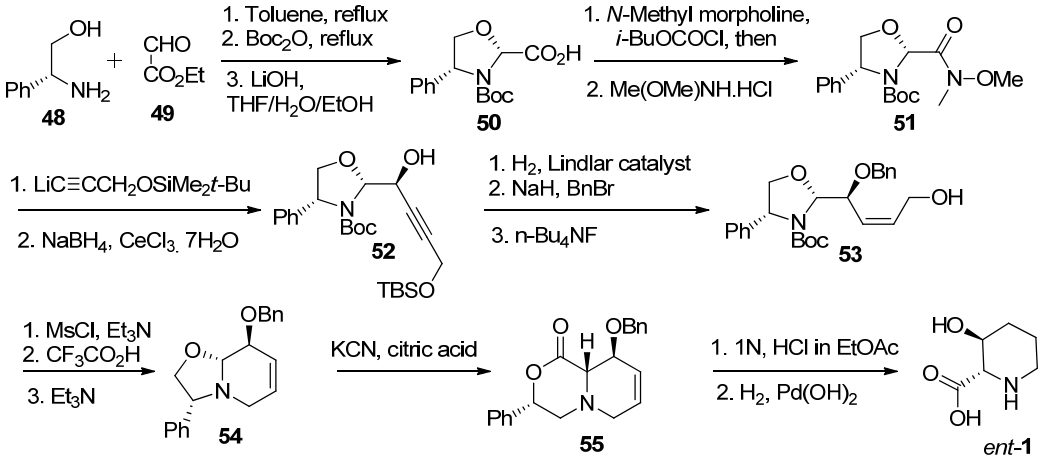
Takahata *et al*. reported synthesis of **1** using RCM and enzymatic resolution as the key steps (Scheme 6). Ester **42** was treated with LiHMDS and then with acrolein to provide di-allyl compound **43**, which was subsequently subjected to RCM reaction to furnish a mixture of piperidines **44** and **45**. The major piperidine derivative **44** on enzymatic resolution gave acetate **46** and alcohol **47** with excellent *ee*. The acetate ester **46** on hydrogenation followed by acidic hydrolysis provided 3-hydroxypipecolic acid **1**.[13]



Scheme 6

Couty's approach

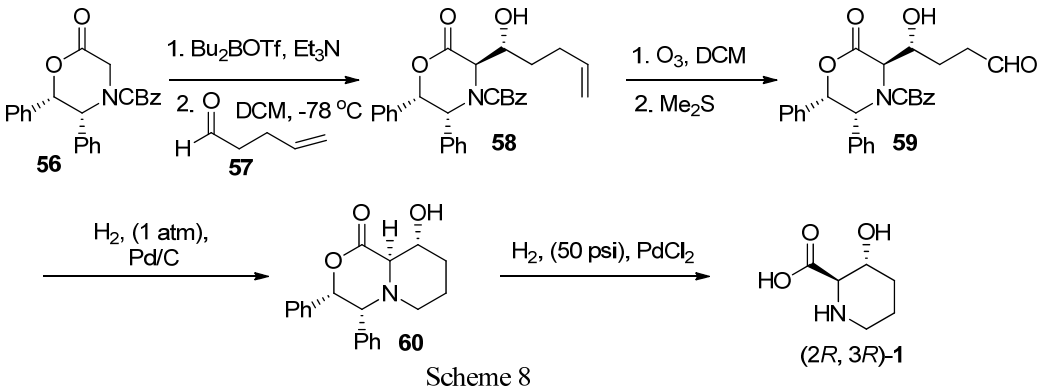
Couty *et al*. used diastereoselective reduction of ketone and stereoselective addition of cyanide as key steps in their route for the synthesis of **1** (Scheme 7).[14] Synthesis was carried out according to the sequence of steps shown in Scheme 9. The hemiaminal acid **50** was prepared from **48** in there steps. Acid **50** was converted to Wienreb amide **51** and subsequently treated with lithium acetalide to provide ketone and the resulting ketone was reduced to furnish alcohol **52**. Alcohol **52** was protected as benzyl ether, the triple bond was reduced using LAH followed by TBS deprotection, mesylation and cyclization to give bicyclic compound **54**. Nucleophilic addition on **54** with cyanide anion followed by hydrolysis and hydrogenation resulted in to formation of 3-hydroxypipecolic acid.



Scheme 7

Williams's approach

Williams *et al*. utilized commercially available lactone **56** for the synthesis of **1** using diastereoselective aldol condensation between **56** and aldehyde **57** to provide alcohol **58**. Ozonolysis of the olefin **58** furnished aldehyde **59**, which on mild catalytic hydrogenation afforded bicyclic compound **60**. Finally **60** on hydrogenation on carbon black furnished (2*R*,3*R*)-3-hydroxypipecolic acid. Similarly (2*S*,3*S*)-3-hydroxypipecolic acid was synthesized using enantiomer of **56** as the starting material (Scheme 8).[15]

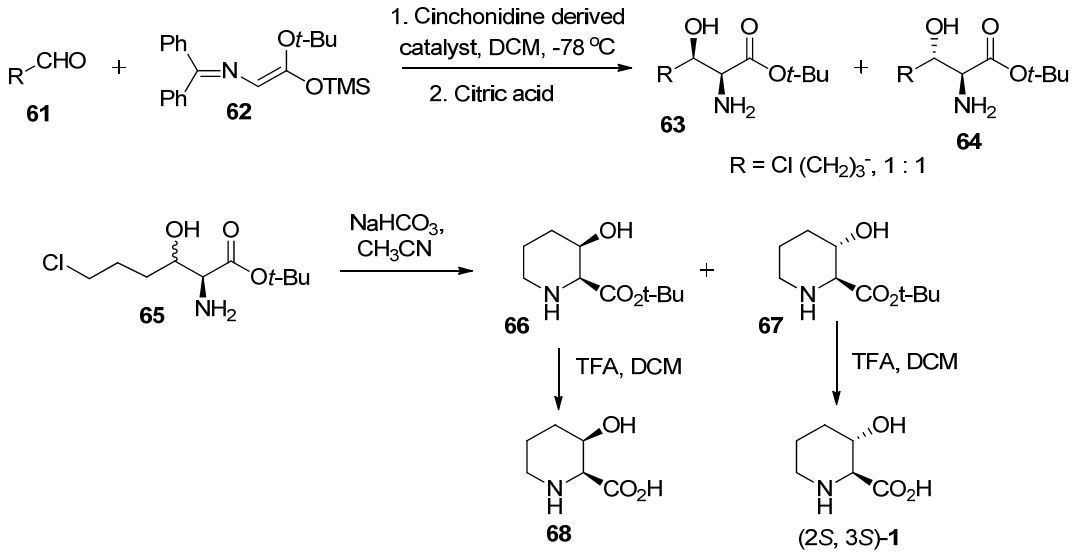


Scheme 8

Corey's approach

Corey *et al*. developed a novel method for the preparation β-hydroxy-α-amino acids by aldol condensation between various aldehydes and imine **62** catalyzed by cinchona derived chiral catalyst. Thus, the aldol condensation between aldehyde **61** and silyle-

nol ether **62** gave a mixture of amino alcohols **63** and **64** in the ratio 1:1. The method was exploited for the synthesis of *cis* as well as *trans* 3-hydroxypipecolic acid (Scheme 9).[16]

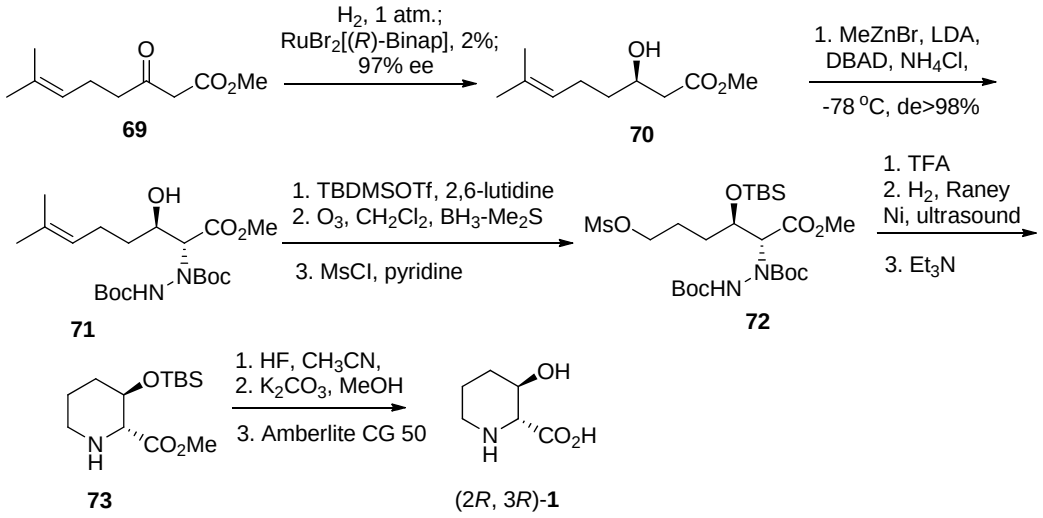


Scheme 9

The mixture of amino alcohols **63** and **64** was treated with sodium bicarbonate to provide a mixture of piperidine derivatives and separation on column chromatography gave pure diastereomeric piperidine alcohols **66** and **67**. The piperidine derivatives **66** and **67** were treated with TFA to provide (2*S*,3*R*)-3-hydroxypipecolic acid **68** and (2*S*,3*S*)-3-hydroxy pipecolic acid **1** respectively.

Genêt's approach

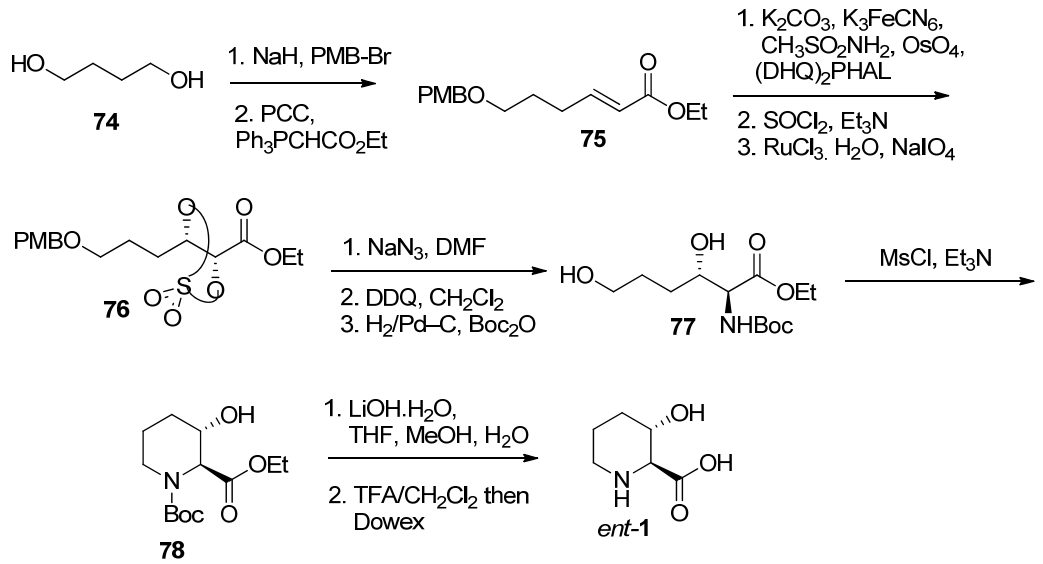
Genêt *et al*. reported synthesis of 3-hydroxypipecolic acid starting from keto ester **69**, employing chiral reduction of ketone and chiral amination as the key steps (Scheme 10). Keto ester **69** on reduction using Ru-BINAP catalyst furnished hydroxy ester **70**, which was subjected to α-amination to provide aminol **71**. The aminol **71** was protected with TBS and subsequently subjected to ozonolysis followed by mesylation of resulting alcohol to give **72**. The mesylate **72** on acidification, treatment with Raney Ni and triethylamine provided piperidine derivative **73** which was subjected to TBS deprotection and ester hydrolysis to give (2*R*, 3*R*)-3-hydroxypipecolic acid **1**.[17]



Scheme 10

Pradeep Kumar's approach

Pradeep Kumar *et al*. used Sharpless chiral dihydroxylation as a key step in the synthesis of 3-hydroxy pipecolic acid *ent*-**1** starting from butane diol **74** (Scheme 11).[18]



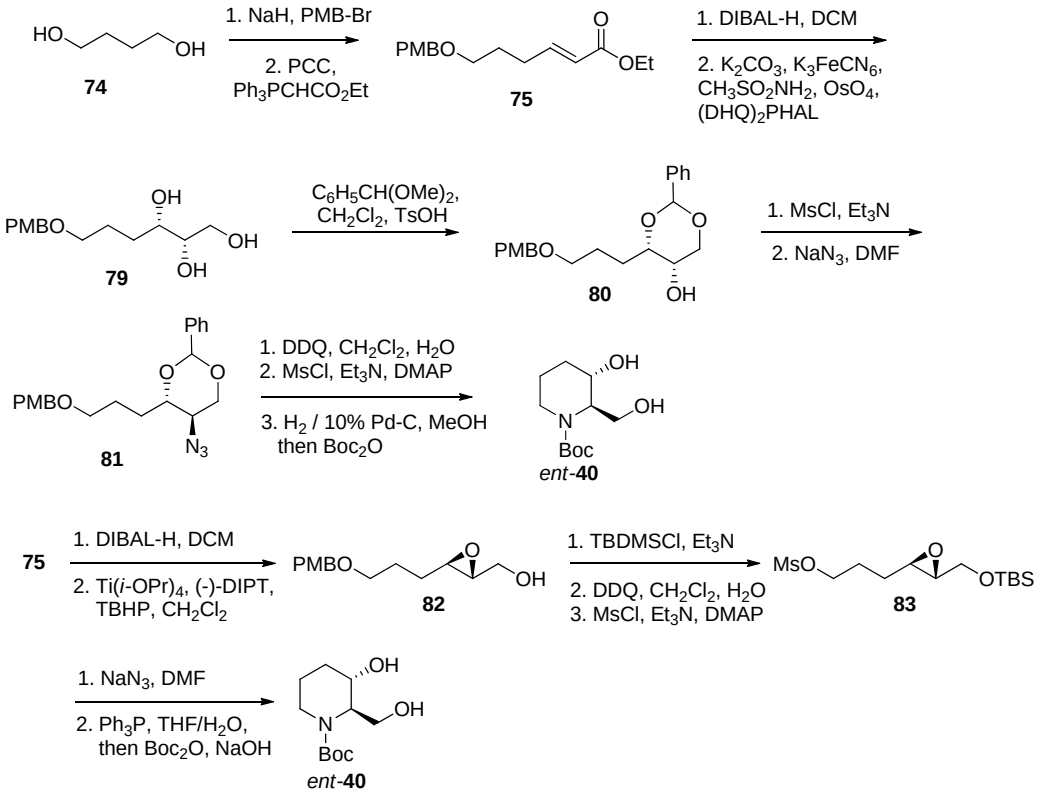
Scheme 11

Diol **74** was protected selectively, oxidized and subsequently subjected to Wittig reaction to give unsaturated ester **75**. Unsaturated ester **75** was subjected to Sharpless dihydroxylation and resulting diol was protected as a sulfate **76**. Sulfate **76** was opened with sodium azide, which on reduction followed by Boc protection provided amino-

diol **77**. The diol **77** on selective mesylation gave piperidine **78**, which on acid hydrolysis followed by Boc deprotection furnished 3-hydroxypipecolic acid *ent*-**1**.

Pradeep Kumar's 2nd approach

Pradeep Kumar *et al*. (Scheme 12) achieved formal synthesis of **1** starting from same starting material as in Scheme 11. The mono-PMB protection of **74**, followed by oxidation of resulting alcohol and Wittig reaction gave unsaturated ester **75**. The ester functionality in **75** was reduced using DIBAL-H, followed by asymmetric dihydroxylation employing Sharpless dihydroxylation to furnish triol **79**. The 1,3-acetal protection was carried out to provide **80** followed by mesylation and subsequent reaction with sodium azide to provide azide **81**.



Scheme 12

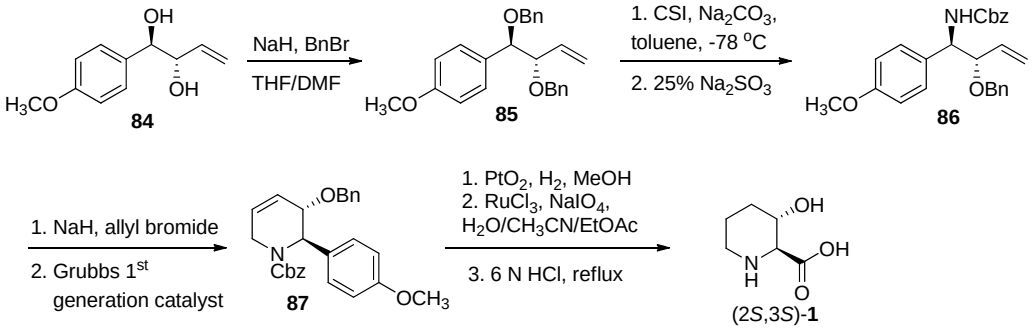
The compound **81** was subjected to *p*-methoxybenzyl ether deprotection and the resulting hydroxy compound was mesylated and subsequently subjected to hydrogenation to provide piperidine diol *ent*-**40**.

The authors prepared **82** by an alternate route which involved reduction of ester **75** with DIBAL-H followed by Sharpless epoxidation of the resulting allyl alcohol to

provide epoxy alcohol **82**. The alcohol moiety in **82** was protected as its TBS derivative followed by PMB ether deprotection and mesylation to give mesylate **83**. The mesyl group in **83** was replaced with azide followed by reduction of azide to furnish the diol *ent*-**40**.[19]

Jung's approach

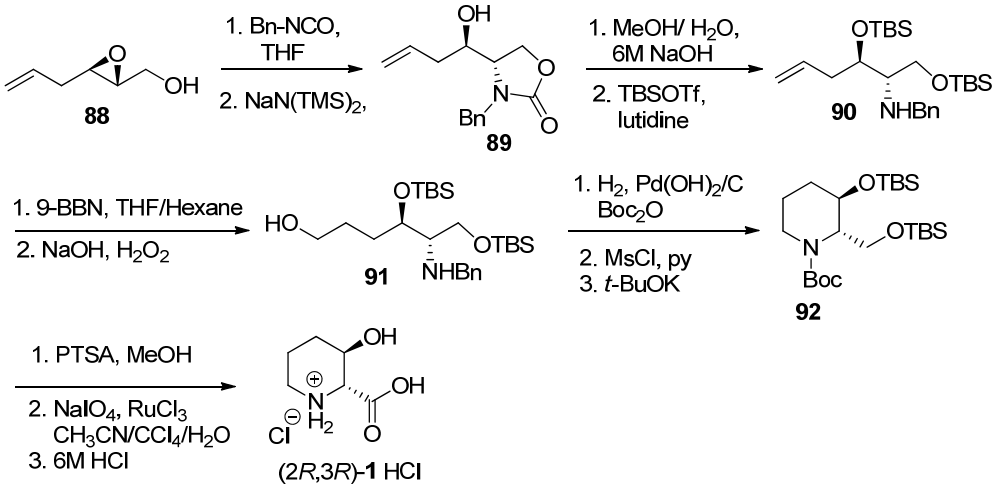
Jung *et al*. reported synthesis of *ent*-**1** starting from known diol **84** (Scheme 13). Diol **84** was protected as dibenzyl ether **85** and further reacted with chlorosulfonyl isocyanate (CSI) followed by treatment with base to provide amino alcohol **86**. Amine in **86** was allylated followed by RCM reaction to furnish piperidine derivative **87**. Olefin in **87** was reduced using PtO_2 as the catalyst followed by oxidation of aryl ring by Ru catalyst and acidification to furnish (2*S*,3*S*)-3-hydroxypipecolic acid *ent*-**1**.[20,21]



Scheme 13

Riera's approach

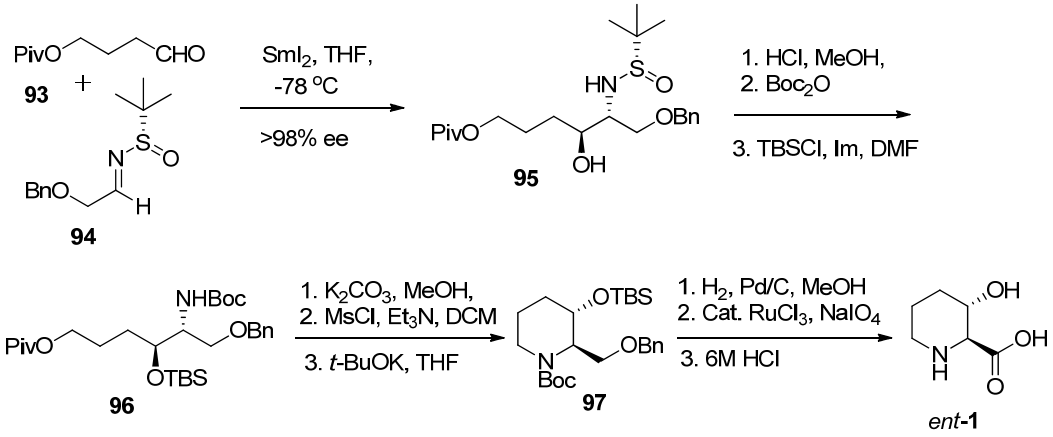
Riera *et al*. started synthesis of (2*R*,3*R*)- 3-hydroxypipecolic acid from epoxide **88** which in turn was prepared by Sharpless epoxidation (Scheme 14). Epoxide **88** was intramolecularly opened at C-2 by nitrogen using benzyl isocyanate to provide cyclic carbamate **89**. Cyclic carbamate **89** was deprotected under basic condition and the resulting diol was protected as its TBS derivative. The olefin **90** was subjected to hydroboration using 9-BBN followed by oxidation to furnish alcohol **91**. The *N*-benzyl in **91** was deprotected under hydrogenation conditions followed by protection with Boc. Subsequently alcohol was mesylated followed by treatment with base to furnish piperidine derivative **92**. Selective primary OTBS ether deprotection was carried out using PTSA followed by oxidation using Ru catalyst and acidification to give hydrochloride salt of (2*R*,3*R*)-3-hydroxypipecolic acid **1**.[22]



Scheme 14

Wang's approach

Wang *et al.* (Scheme 15) developed a Pinacol type reductive coupling between aldehyde **93** and sulfinyl imine **94** with excellent *ee* and exploited it for the synthesis of *ent*-**1**. The removal of the sulfinyl auxiliary followed by selective *N*-protection with Boc_2O afforded carbamate **95**. The pivalyl group in **95** was deprotected and the resulting alcohol was converted in to its mesyl derivative followed by treatment with base

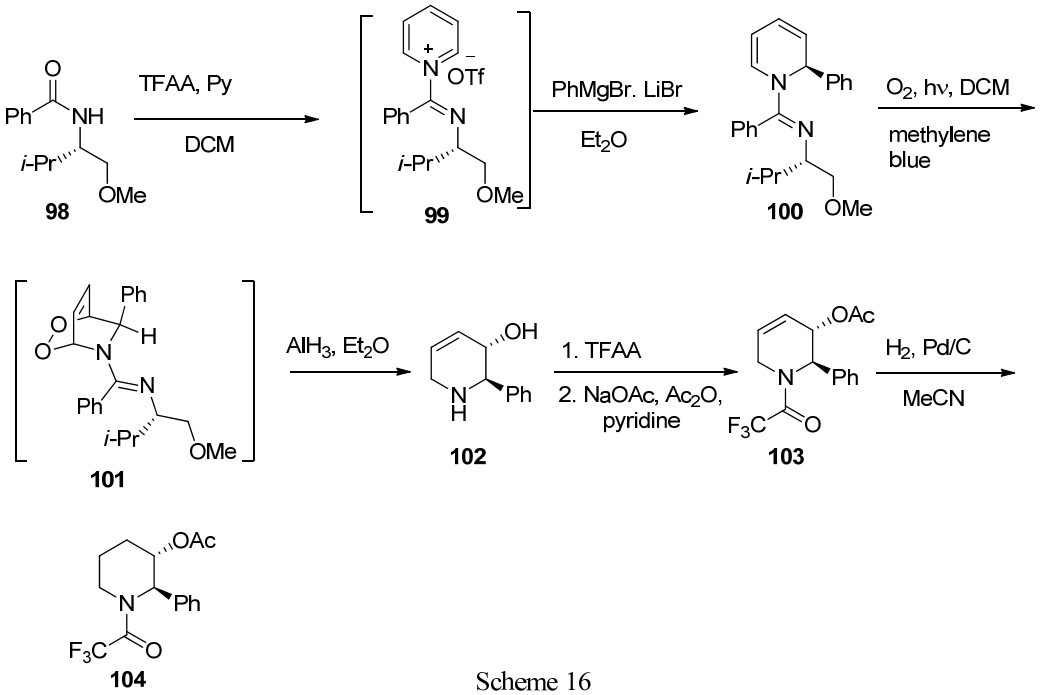


Scheme 15

to furnish piperidine derivative **97**. The benzyl group in **97** was deprotected under hydrogenation conditions followed by oxidation of alcohol and acidification to give final product 3-hydroxypipecolic acid *ent*-**1**.[23]

Charette's approach

Charette *et al*. reported the formal synthesis of 3-hydroxypipecolic acid *ent*-**1** using a diastereoselective addition of phenyl magnesium bromide on *N*-pyridinium salt **99** (Scheme 16). The dihydropyridine derivative **100** was subjected to (4+2) cycloaddition with oxygen followed by treatment with aluminum hydride to furnish piperidine derivative **102**. The protection of amine as well as alcohol gave **103** which on hydrogenation led to known intermediate **104**.[24]

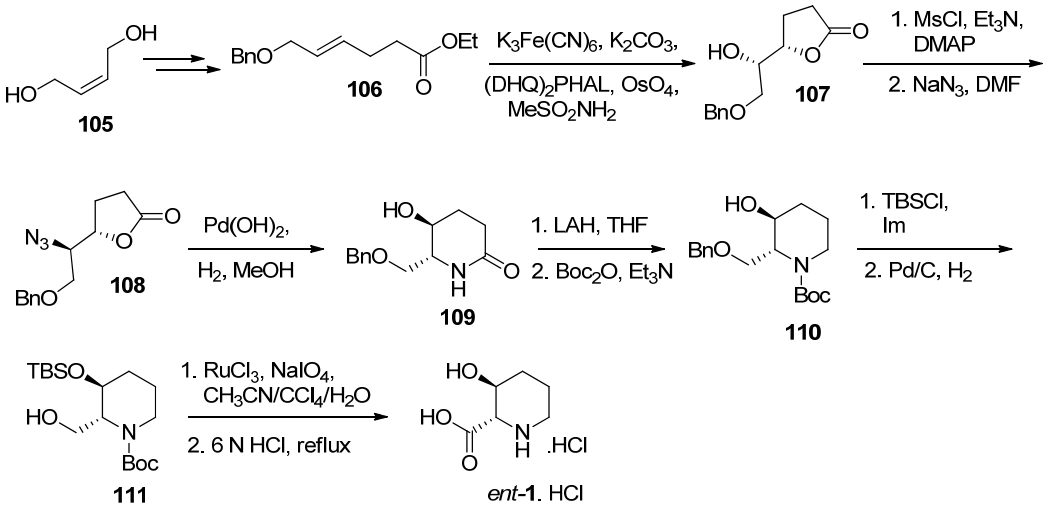


Scheme 16

Chavan's approach

This group has recently reported the enantioselective synthesis of 3-hydroxypipecolic acid *ent*-**1** by Sharpless dihydroxylation as a key step starting from commercially available starting material *cis*-2-butene-1, 4-diol **105** (Scheme 17). The *cis*-2-butene-1,4-diol **105** was converted in to γ,δ-unsaturated ester **106** by known method reported by this group. The ester **106** was subjected to Sharpless asymmetric dihydroxylation to provide lactone **107.** The hydroxy group in lactone **107** was mesylated followed by replacement with azide to give azido lactone **108** which on hydrogenation gave lactam **109**. Lactam **109** was reduced to give amine followed by protection with Boc_2O to furnish hydroxy piperidine **110**. Protection of hydroxy group in **110** as its TBS derivative followed by benzyl deprotection gave piperidine alcohol **111**. Alcohol in **111** was

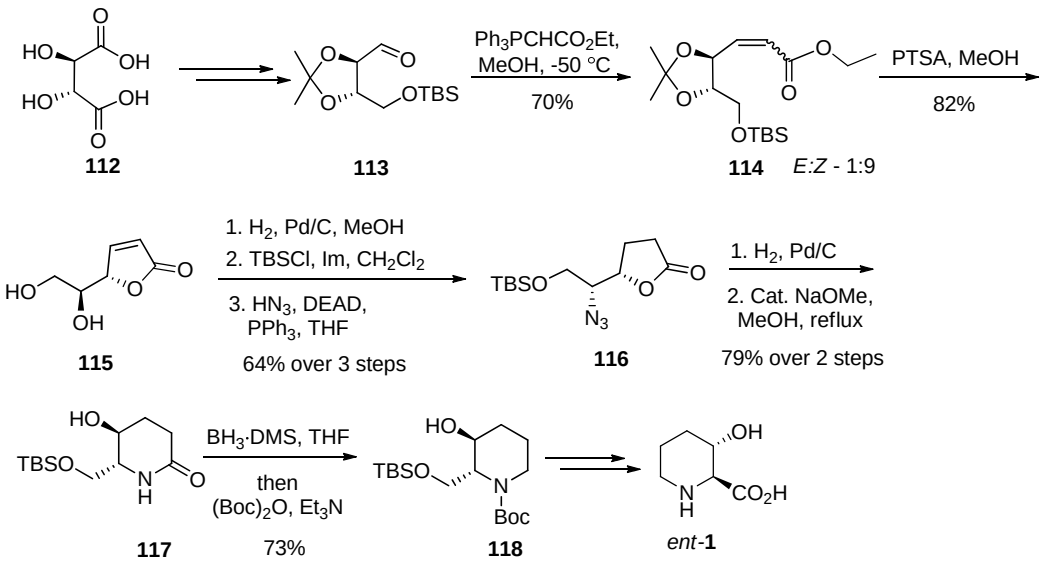
oxidized to acid using Ru catalyst followed by acidification to furnish hydrochloride salt of *ent*-**1**.[25]



Scheme 17

Chavan's 2nd approach

Yet another synthetic strategy for (2*S*,3*S*)-3-hydroxypipecolic acid *ent*-**1** as shown in Scheme 18 was reported by the same group using Mitsunobu reaction and kinetically controlled butenolide formation as the key steps. The C-2 and C-3 chiral centers in *ent*-**1** were fixed using the natural chirality in L-(+)-tartaric acid. The *Z*-alkene **114** was readily obtained from L-(+)-tartaric acid by simple functional group transformations *via* aldehyde **113**. Taking the advantage of kinetic control of formation of five membered lactone ring over six and seven membered lactone, butyrolactone **115** was constructed by deprotection of acetonide as well as TBS group in *Z*-alkene **114**. The azido alcohol **116** was obtained by protection of primary alcohol followed by conversion of secondary alcohol to azide using Mitsunobu reaction on **115**. The six membered piperidine core **117** was accessed from protected azido alcohol **116** by reduction followed by cyclisation which can be easily converted to *ent*-**1**.[26]



Scheme 18

2.1.3 References

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Chapter 2: Synthetic studies toward *trans*-(2*R*,3*R*)-3-hydroxypipecolic acid and (−)-swainsonine

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

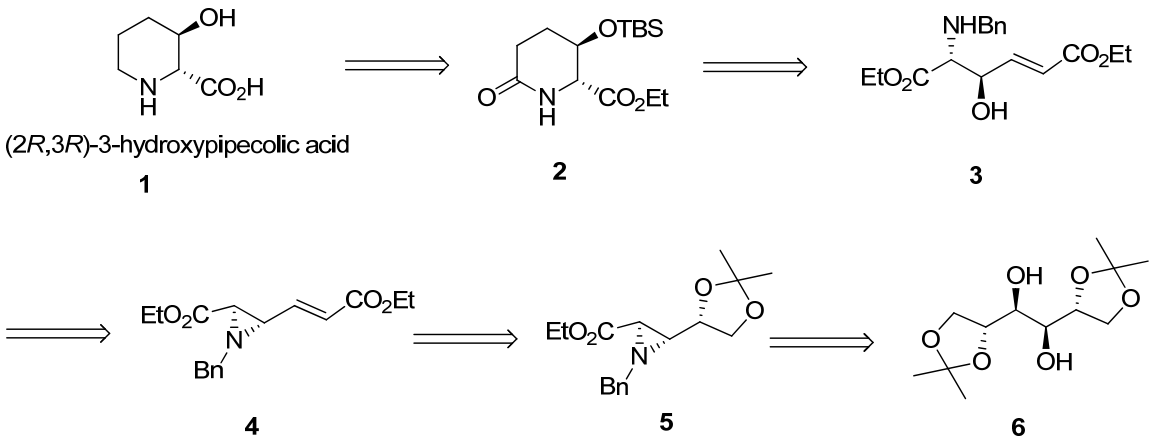
2.2.1 Present work

2.2.1.1 Objective

The literature survey revealed that (2*R*,3*R*)-3-hydroxypipecolic acid and its enantiomer have attracted the attention of many organic chemists due to their presence in number of natural as well as synthetic biologically active compounds. The literature reports also revealed that there are a few routes for the synthesis of 3-hydroxypipecolic acid **1** starting from chiral natural starting materials. The reported chiral pool approaches are associated with low yields and lengthy routes or involve usage of potentially hazardous chemicals such as azides. In this context, there is a need of convenient and efficient route for its enantiopure synthesis. This group over several years is engaged in the syntheses of biologically active compounds, including piperidine alkaloids. Recently this group accomplished the synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid (*ent*-**1**) employing Sharpless asymmetric dihydroxylation[1] as well as chiron approach utilizing L-(+)-tartaric acid.[2] In the present section an alternative approach based on chiral pool strategy is described. The current novel route for its synthesis involved the use of chiral aziridine-2-carboxylate derived from D-mannitol diacetonide which is cheap and commercialy available starting material.

2.2.1.2 Retrosynthetic analysis

Owing to their ring strain, aziridines are very prone to nucleophilic ring opening reactions with various nucleophiles with predictable chemo and regio selectivity to give either α or β-amino compounds. Taking account of this, as shown in Scheme 1, it was thought that *trans*-3-hydroxy skeleton of the acid **1** can be obtained from γ-hydroxy-δ-amino-α,β-conjugated ester **3** *via* amide **2**. Compound **3** can be easily obtained from α,β-unsaturated aziridine ester **4** by regioselective nucleophilic ring opening reaction using water as the nucleophile under acidic conditions which in turn can be easily accessed from aziridine-2-carboxylate **5**. Aziridine-2-carboxylate **5** can be synthesized from commercially available and cheap starting material like D-mannitol diacetonide **6**.

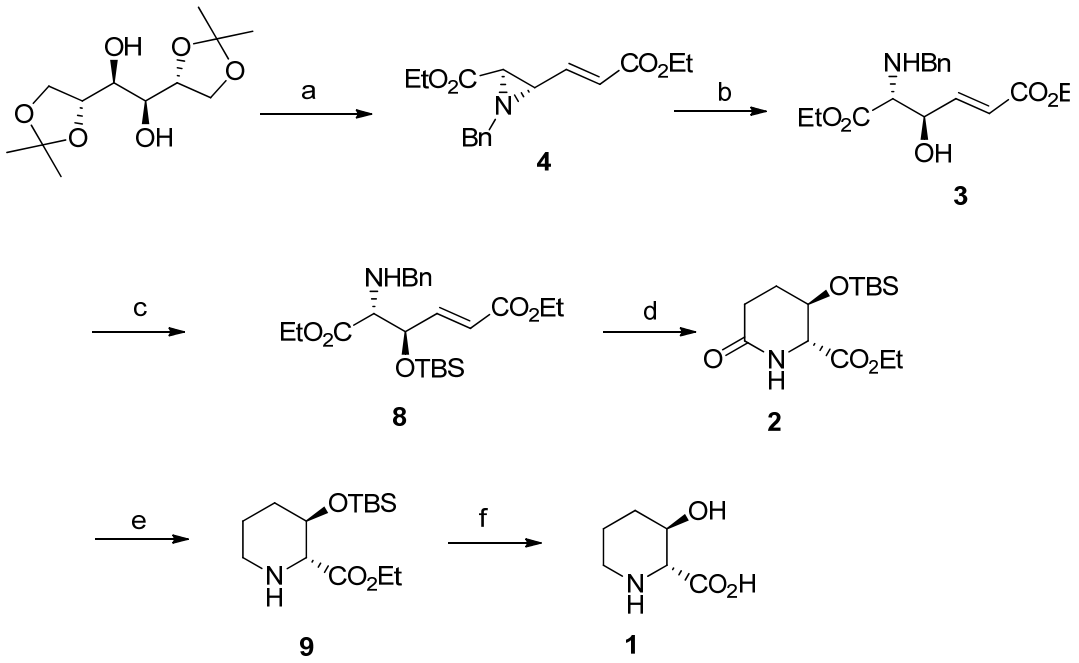


Scheme 1: Retrosynthetic analysis of (2*R*,3*R*)-3-hydroxypipecolic acid

2.2.1.3 Results and discussion

The present section describes the total synthesis of *trans* (2*R*,3*R*)-3-hydroxypipecolic acid **1** (Scheme 2). The *α*,*β*-unsaturated aziridine ester **4** was synthesized from D-mannitol diacetonide **6** over six steps and in 38% overall yield as described previously (chapter 1, section 2, Schemes 14 and 23). After achieving the site selective functionalization at the acetonide group of aziridine-2-carboxylate **5**, it was thought of regioselective ring opening of aziridine ring in compound **4**. Literature review revealed that ring opening reaction of aziridines flanked between ester and *α*,*β*-unsaturated ester generally occurs regioselectively from *α*,*β*-unsaturated ester side with a preference over simple ester.[3] Thus, in the next step, compound **4** was treated with TFA (2 equiv.) in $CH_3CN–H_2O$ (9:1)[4] to undergo regioselective nucleophilic ring opening reaction using water as nucleophile to afford *γ*-hydroxy-*δ*-amino-*α*,*β*-conjugated ester **3** as the only isomer in 76% yield (Scheme 2). ^{1}H NMR spectrum showed characteristic doublet at δ 3.53 (*J* = 5 Hz, 1H) indicating *α*-amino ester functionality (*α*-hydroxy ester proton would have given a doublet at much downfield δ value). Peak at δ 4.52-4.56 (m, 1H) was assingned to *γ*-hydroxy,*α*,*β*-unsaturated ester proton. Peaks at δ 3.68 (d, *J* = 13.0 Hz, 1H) and 3.94 (d, *J* = 13.0 Hz, 1H) indicated the presence of *N*-benzylic protons. Peaks at *δ* 1.29 (m, 6H) and 4.13-4.28 (m, 4H) were assigned to ethyl ester while peaks at 6.08 (dd,

J = 2.0 & 15.5 Hz, 1H) and 6.75 (dd, *J* = 2.0 & 15.5 Hz, 1H) confirmed the presence of *α,β*-unsaturated ester. Its ^{13}C and DEPT spectra showed peaks at δ 70.1 and 64.12 corresponding for two -CH groups clearly indicating opening of aziridine ring. Molecular ion peak at *m/z* 344.18 $(M+Na)^+$ further confirmed its molecular formula. In next step selective protection of hydroxyl group of amino-alcohol **3** was achieved using TBSCl, imidazole and cat. DMAP in refluxing dichloromethane to furnish TBS ether **8** in 85% yield.

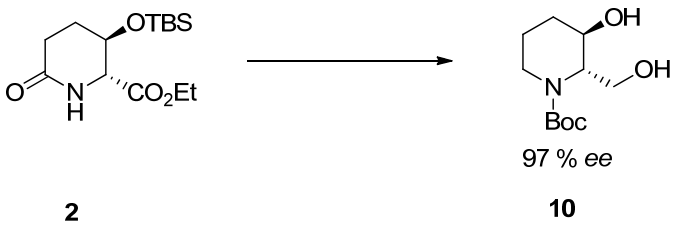


Total synthesis of (2*R*,3*R*)-3-hydroxypipecolic acid

Scheme 2. ***Reagents and conditions:*** *(a) 1) $NaIO_4$, aq. $NaHCO_3$, CH_2Cl_2; 2) $Ph_3PCBrCO_2Et$, CH_2Cl_2, 84% over two steps; 3) $BnNH_2$, Et_3N, toluene, 0ºC to rt, 68%; 4) TMSOTf, CH_2Cl_2, 0ºC, 90%; 5) $NaIO_4$, $(CH_3)_2CO:H_2O$ (2:1); 6) NaH, $(EtO)_2POCH_2CO_2Et$, THF, 0ºC, 70% over two steps; (b) TFA, $CH_3CN:H_2O$ (9:1), 0 °C to rt, 76%; (c) TBSCl, Im, cat. DMAP, CH_2Cl_2, reflux,, 85%; (d) H_2, 10% $Pd(OH)_2/C$, NaOAc, EtOH, 85%; (e) BH_3·DMS, THF, 78%; (f) HCl 6N, 91%.*

The crucial step *viz* reductive cyclization of **8** was carried out under hydrogenation conditions using hydrogen and palladium hydroxide over carbon in ethanol to provide amide **2** in 85% yield (Scheme 2). Absence of peaks at 1620 cm^{-1} in its IR spectrum strongly supported the reduction of double bond and appearance of peaks at 1643 and 1732 cm^{-1} clearly showed the presence of amide and ester functionalities respectively.

Disappearance of characteristic peaks of protons of double bond (δ 6.08 & 6.75) and aromatic region (δ 7.21-7.28) in its ^{1}H-NMR spectrum indicated the double bond reduction and *N*-benzyl deprotection. The broad singlet at δ 5.96 was assigned to the proton on amide nitrogen. The quartet at δ 4.23 and triplet at δ 1.30 integrating for two and three protons respectively were assigned to ethyl ester protons. Its ^{13}C-NMR spectrum showed peaks at δ 171 and 170 corresponding to ester and amide carbonyl carbons. Peak at δ 65 was assigned to methylene carbon in ethyl ester and peaks at δ 62 and 61 were assigned to two tertiary carbons. Its DEPT spectrum showed presence of three CH_2 carbons and six -CH and -CH_3 carbons which is in accordance with structure of amide **2**. Further, the formation of amide **2** was confirmed by its mass spectrum which showed a molecular ion peak at *m/z* 302 $(M+H)^+$. In order to check the chiral purity at C2 and C3, the amide **2** was subjected to reduction using lithium aluminum hydride in anhydrous THF. Gratifyingly the ester, amide reduction as well as TBS deprotection was observed in a single step. The LAH reduction of **2** followed by *N*-Boc protection provided *N*-Boc amine **11**. The chiral HPLC analysis of the **11** revealed that the chiral purity was ~97% *ee* (Scheme 3).



2 **10**

Scheme 3. ***Reagents and conditions:*** *(a) LAH, THF, 0 °C to reflux; (b) $(Boc)_2O$, $NaHCO_3$, THF:H_2O (2:1), 75% over two steps.*

In next step amido ester **2** was subjected to selective reduction of amide functionality using borane dimethyl sulfide complex in anhydrous THF to furnish the amino ester **10** in 78% yield. The presence of strong band at 1731 cm^{-1} and disappearance of band at 1643 cm^{-1} in its IR spectrum strongly supported the reduction of amide. In its ^{1}H-NMR spectrum, the -CH_2 protons of ethyl ester were split in to two multiplets, appearing at δ 4.31-4.39 and 4.10-4.18 and the triplet appearing at δ 1.36 was assigned to the methyl

protons of ester. Multiplet at δ 3.98 and doublet of triplet at δ 3.78 were attributed to the two -CH protons. The characteristic peaks of TBS group appeared at *δ* 0.86, 0.06 and 0.00. Peak at δ 170 in its ^{13}C-NMR spectrum corresponded to ester carbonyl and the two tertiary carbons appeared at δ 70.5 and 70.2. Further, the -CH_3 carbons appeared at δ 25.5, 13.9, –4.5, –5.3 and CH_2 carbons appeared at δ 61.8, 52.2, 32.2 and 23.1. Further, peaks at *m/z* 288 $(M+H)^+$ and 310 $(M+Na)^+$ in its mass spectrum confirmed the formation of **10**.

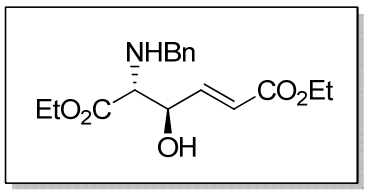
Finally the ester hydrolysis as well as TBS group deprotection of **9** was carried out in a single step using 6N HCl to provide 3-hydroxypipecolic acid **1** in 91% yield. Its ^{1}H-NMR spectrum showed multiplet at δ 4.13-4.17 and doublet at δ 3.83 corresponding to -CH protons. Other peaks included multiplets at δ 3.36-3.40, 3.07-3.12 and 1.64-1.80 and singlet at δ 2.22. Peak at δ 170.1 in its ^{13}C-NMR 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 appearing at δ 42.5, 28.8 and 18.6 all corresponded to the -CH_2 carbons. Its DEPT spectrum showed two carbons corresponding to CH carbons and three carbons due to the -CH_2 carbons. Molecular ion peak at *m/z* 146 $(M+H)^+$ in its mass spectrum confirmed the formation of **1**. The spectral data and optical rotation values were in good agreement with the reported one.[5]

2.2.2 Conclusion

In conclusion, a total synthesis of *trans* (2*R*,3*R*)-3-hydroxypipecolic acid **1** was achieved starting from cheap and abundant starting material D-mannitol diacetonide in 11 steps and in 14% overall yield. The main steps used are the regioselective aziridine ring opening reaction, reductive cyclization and selective amide reduction. The intermediate **3** could be further explored for the synthesis of other imino sugars.

2.2.3 Experimental

(4*R*,5*R*,*E*)-Diethyl 5-(benzylamino)-4-hydroxyhex-2-enedioate (3)



To a stirred solution of ester **4** (0.9 g, 2.97 mmol) in CH_3CN:water (9:1, 20 mL) was added TFA (0.45 mL, 5.94 mmol) dropwise at 0 ºC. The reaction mixture was slowly warmed to room temperature and stirred until complete disappearance of starting material (~ 5-6 h). Reaction was quenched by excess $NaHCO_3$, water (10 mL) was added and organic mass was extracted with ethyl acetate (3 × 15 mL). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure followed by column chromatographic purification using ethyl acetate:pet ether (15:85) to yield 1.18 g of amino-alcohol **3** as thick liquid.

***R*$_f$:** 0.5 (Pet ether-ethyl acetate, 3:7).

Yield: 76% over two steps.

MF: $C_{17}H_{23}NO_5$, **MW:** 321.36.

$[\alpha]_D^{25}$ +20 (*c* 0.5, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): vmax 3554, 3359, 2980, 1720, 1620.

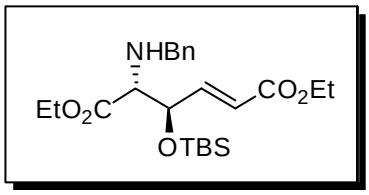
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 1.26-1.34 (m, 6H), 3.53 (d, *J* = 5Hz, 1H), 3.68 (d, *J* = 13 Hz, 1H), 3.94 (d, *J* = 13 Hz, 1H), 4.13-4.28 (m, 4H), 4.52-4.56 (m, 1H), 6.08 (dd, *J* = 2 & 15.5 Hz, 1H), 6.75 (dd, *J* = 4.0 & 15.5 Hz, 1H), 7.27-7.30 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 14.2, 52.6, 60.3, 61.3, 64.1, 70.1, 122.7, 127.5, 128.2, 128.4, 138.9, 145.2, 165.7, 171.6.

MS (ESI):*m/z*: 344.18 $(M+Na)^+$.

Elemental Analysis: Calculated:C-63.54, H-7.21, N-4.36%; found: C-63.22, H-7.31, N-4.60%.

(4*R*,5*R*,*E*)-Diethyl 5-(benzylamino)-4-((*tert*-butyldimethylsilyl)oxy)hex-2-enedioate (8)



To a stirred solution of hydroxyl amino ester **3** (0.7 g, 2.18 mmol), imidazole (0.3 g, 4.36 mmol) and DMAP (0.027 g, 0.22 mmol) in CH_2Cl_2 (20 mL) was added TBSCl (0.6 g,

4.36 mmol) dissolved in CH_2Cl_2 (5 mL) slowly at 0 ºC after which reaction was heated to reflux for 6 h until completion of reaction. Reaction mass was concentrated under reduced pressure followed by column chromatography using ethyl acetate-pet ether (5:95) to yield 0.8 g of TBS ether **8** as thick colorless liquid.

***R*$_f$:** 0.5 (Pet ether-ethyl acetate, 2:8).

Yield: 85% over two steps.

MF: $C_{23}H_{37}NO_5Si$, **MW:** 435.62.

[α]$_D^{25}$ −7.69 (*c* 1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): vmax 2980, 1720, 1620.

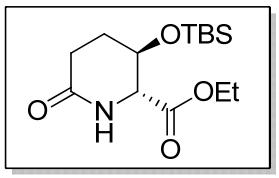
^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): 0.01 (s, 3H), 0.03 (s, 3H), 0.87 (s, 9H), 1.29-1.31 (m, 6H), 2.17 (br s, 1H), 3.28 (d, *J* = 5.5 Hz, 1H), 3.65 (d, *J* = 13 Hz, 1H), 3.84 (d, *J* = 13.0 Hz, 1H), 4.12-4.20 (m, 5H), 4.47-4.48 (m, 1H), 5.95 (dd, *J* = 1.5 & 15.5 Hz, 1H), 6.95 (dd, *J* = 5.2 & 15.5 Hz, 1H), 7.21-7.28 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): −4.9, −4.1, 14.3, 18.1, 25.7, 52.2, 60.3, 60.7, 65.7, 73.7, 121.7, 127.1, 128.2, 128.3, 139.4, 147.5, 166.0, 172.0.

MS (ESI): *m/z*: 436.68 $(M+H)^+$.

Elemental Analysis: Calculated C-63.41, H-8.56, N-3.22%; found C-63.45, H-8.36, N-3.35%.

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



The amino ester **8** (0.8 g, 2.2 mmol) was dissolved in ethanol (10 mL) and to that was added catalytic amount of palladium hydroxide over carbon (10%, 20 mg). The resulting reaction mixture was stirred under hydrogen atmosphere using balloon for 2 h. The reaction mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography using silica gel (pet ether-ethyl acetate, 7:3) to provide amide **2** (0.52 g) as a colorless thick oil.

***R*$_f$:** 0.4 (Pet ether-ethyl acetate, 8:2).

Yield: 85%.

MF: $C_{14}H_{27}NO_4Si$, **MW:** 301.

[α]$_D^{25}$ −26 (*c* 1.5, $CHCl_3$).

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

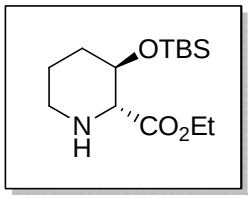
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.12 (s, 6H), 0.90 (s, 9H), 1.30 (t, J = 7.2 Hz, 3H), 1.68 (br s, 1H), 1.79-1.88 (m, 2H), 2.26-2.40 (m, 1H), 2.54-2.72 (m, 1H), 3.99-4.02 (m, 1H), 4.23 (q, J = 7.2 Hz, 2H), 4.35-4.39 (m, 1H), 5.96 (br s, 1H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ –5.1, –4.9, 14.1, 17.9, 25.6, 26.4, 26.5, 61.8, 62.3, 65.4, 170.1, 171.4.

MS (ESI): *m/z*: 302.2 $(M+H)^+$.

Elemental analysis: Calculated: C-55.78, H-9.03, N-4.65%; found: C-55.69, H-9.11, N-4.78%.

(2*R*,3*R*)-Ethyl 3-((*tert*-butyldimethylsilyl)oxy)piperidine-2-carboxylate (9)



To the amide **2** (0.2 g, 0.7 mmol) in anhydrous THF (5 mL) was added BH_3·DMS (0.2 mL, 2 mmol) dropwise at 0 ºC. The resulting reaction mixture was further stirred at 5 ºC for 20 h. Methanol (excess) was added to the reaction mixture, stirred for 4 h and concentrated under reduced pressure. Water (10 mL) was added and the reaction mixture was extracted using dichloromethane (3 × 10 mL). The collected organics were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified using flash chromatography over silica gel (70:30, EtOAc: pet ether) to furnish amine **9** (0.147 g, 78%) as a colorless dense liquid.

***R_f*:** 0.5 (Pet ether-ethyl acetate, 2:8).

Yield: 78%.

MF: $C_{14}H_{29}NO_3Si$; **MW:** 287.47.

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

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

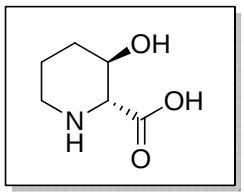
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 0.00 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 1.36 (t, J = 7.3 Hz, 3H), 1.41-1.51 (m, 2H), 1.58-1.68 (m, 2H), 1.84-1.87 (m, 1H), 2.01-2.05 (m, 1H), 2.53-2.64 (m, 1H), 3.11 (dd, J = 1.1 & 10.1 Hz, 1H), 3.32 (d, J = 13.5 Hz, 1H), 3.78 (dt, J = 5.4 & 10.5 Hz, 1H), 3.98 (m, 1H), 4.10-4.18 (m, 1H), 4.31-4.39 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$+CCl_4): δ –5.3, –4.2, 13.9, 17.8, 23.1, 25.5, 32.2, 52.2, 61.8, 70.2, 70.5, 170.8.

MS (ESI): *m/z*: 288.23 $(M+H)^+$, 310.14 $(M+Na)^+$.

Elemental analysis: Calculated: C-58.49, H-10.17, N-4.87%; found:C-58.52, H-10.26, N-4.95%.

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



A mixture of amine **9** (100 mg, 0.35 mmol) and 6 N HCl (10 mL) was kept at 120 ºC for 3 h. The solvent was removed under reduced pressure and the residue was dissolved in H_2O (50 mL). The mixture was loaded on an ion-exchange column (DOWEX 50W X8) and eluted with H_2O and then with aq. NH_3 solution. The eluate of aq. NH_3 was concentrated to dryness under reduced pressure to give **1** (46 mg, 91%) as a crystalline solid.

Yield: 91%.

MF: $C_6H_{11}NO_3$; **MW:** 145.15.

MP: 238–243 ºC (dec.), lit.[6] 230-238 °C.

$[\alpha]_D^{25}$ –13.8 (*c* 1.0, aq. HCl 10%), {lit.[5] $[\alpha]_D^{20}$ –14 (*c* 0.5, aq. HC1 10%)}

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

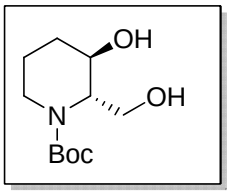
^{1}H NMR (400 MHz, D_2O): δ 1.64-1.80 (m, 2H), 2.02-2.08 (m, 2H), 2.22 (s, 1H), 3.07-3.12 (m, 1H), 3.40-3.36 (m, 1H), 3.83 (d, J = 7.8 Hz, 1H), 4.17-4.13 (m, 1H).

^{13}C-NMR (100 MHz, D_2O): δ 28.8, 42.5, 61.0, 65.5, 118.6, 170.0.

MS (ESI): *m/z***:** 146 $(M+H)^+$.

Elemental analysis: Calculated: C-49.65, H-7.64, N- 9.65%; found:C-49.73, H-7.45, N-9.74%.

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



To stirred suspension of LAH (0.152 g, 4 mmol) in anhydrous THF (3 mL) was added the lactam **2** (240 mg, 0.8 mmol) dissolved in anhydrous THF (3 mL) and the reaction mixture was stirred for 8 h at room temperature. Water (10 mL) was added to the reaction mixture and extracted with ethyl acetate (3 × 25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue thus obtained was

purified by flash chromatography (pet ether–ethyl acetate 10:90) to afford diol **2** (138 mg) as a white crystalline solid.

***R_f*:** 0.5 (Pet ether-ethyl acetate, 2:8).

Yield: 75%.

MF: $C_{11}H_{21}NO_4$, **MW:**231.28

MP: 126-128 ºC, lit.[7] 124-126 °C.

$[\alpha]_D^{25}$ +27 (c 1.0, MeOH), {lit.[7] **$[\alpha]_D^{25}$** +29.8 (*c* 0.99, MeOH)}**.**

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

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4+DMSO-d_6): 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).

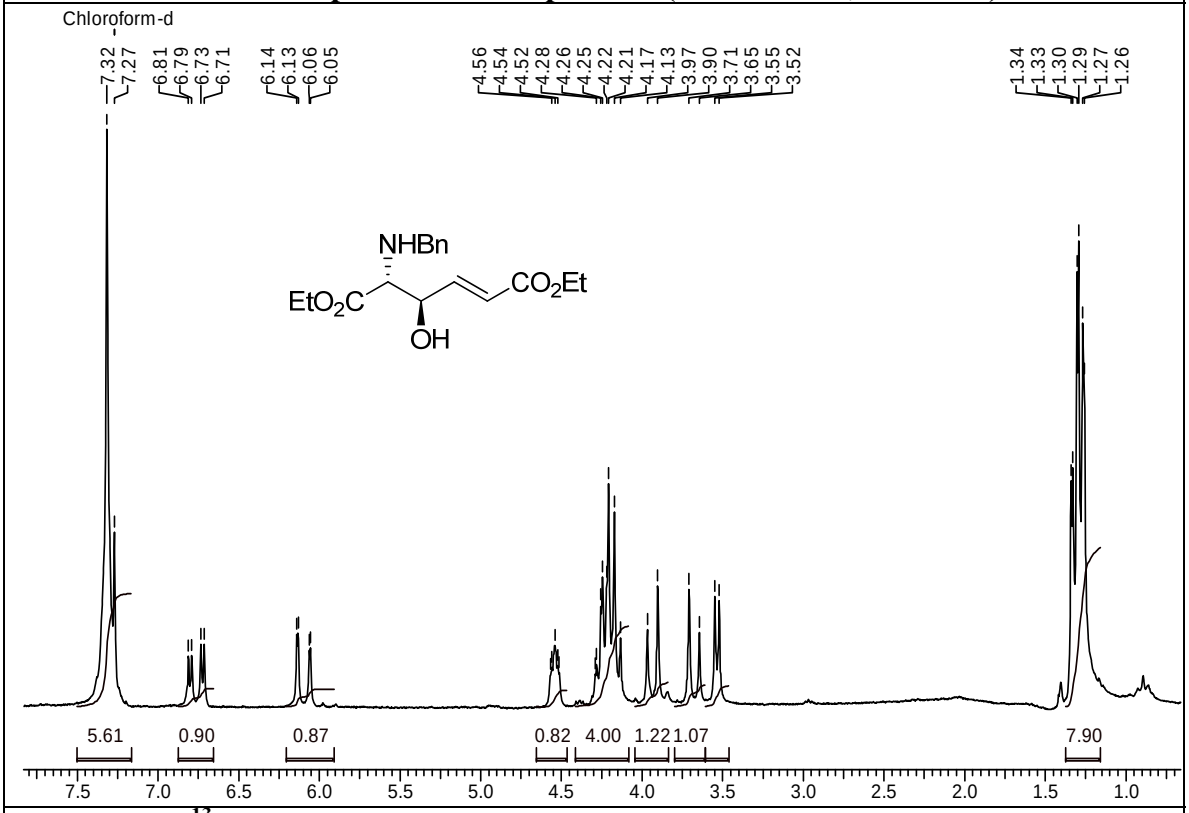
^{13}C (125 MHz, $CDCl_3$+CCl_4+DMSO-d_6): δ 18.8, 26.3, 28.0, 39.6, 59.1, 59.8, 63.8, 79.1, 155.9.

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

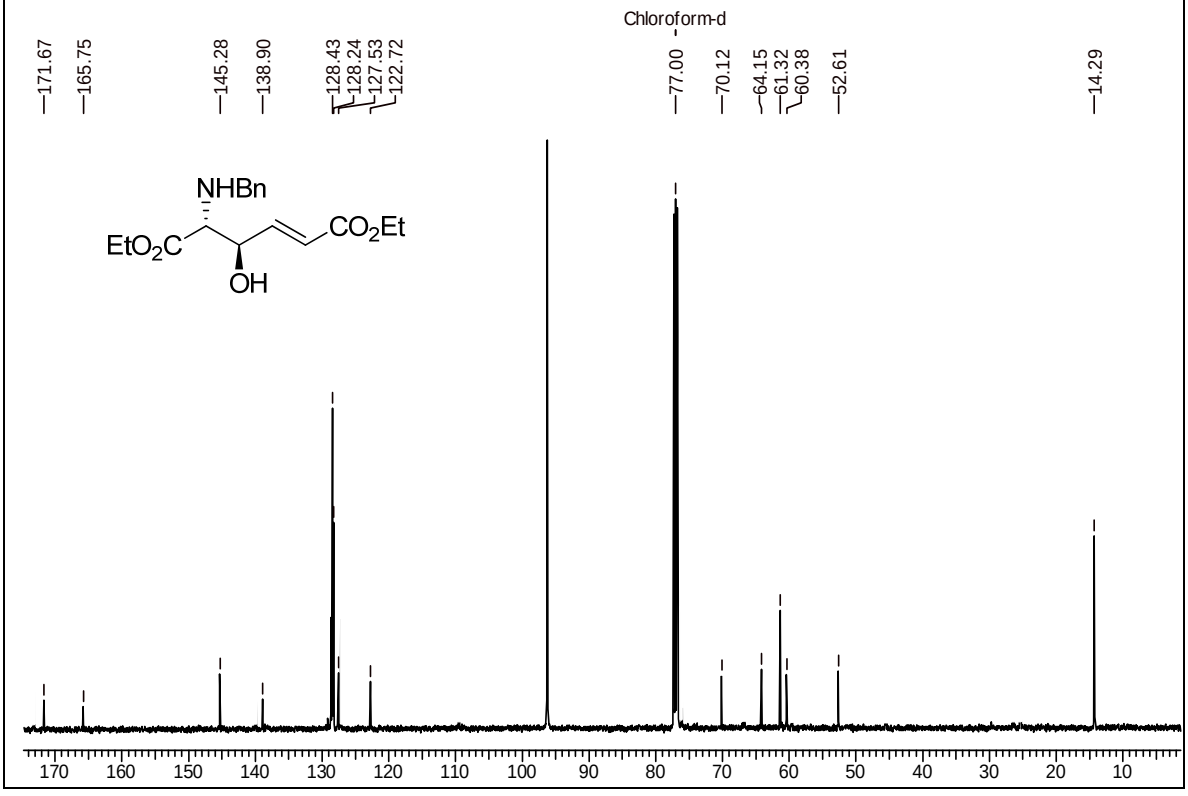
HRMS (CI+): Calcd for $C_{11}H_{21}NO_4$: 231.1484; found: 231.1470.

2.2.4 Analytical Data

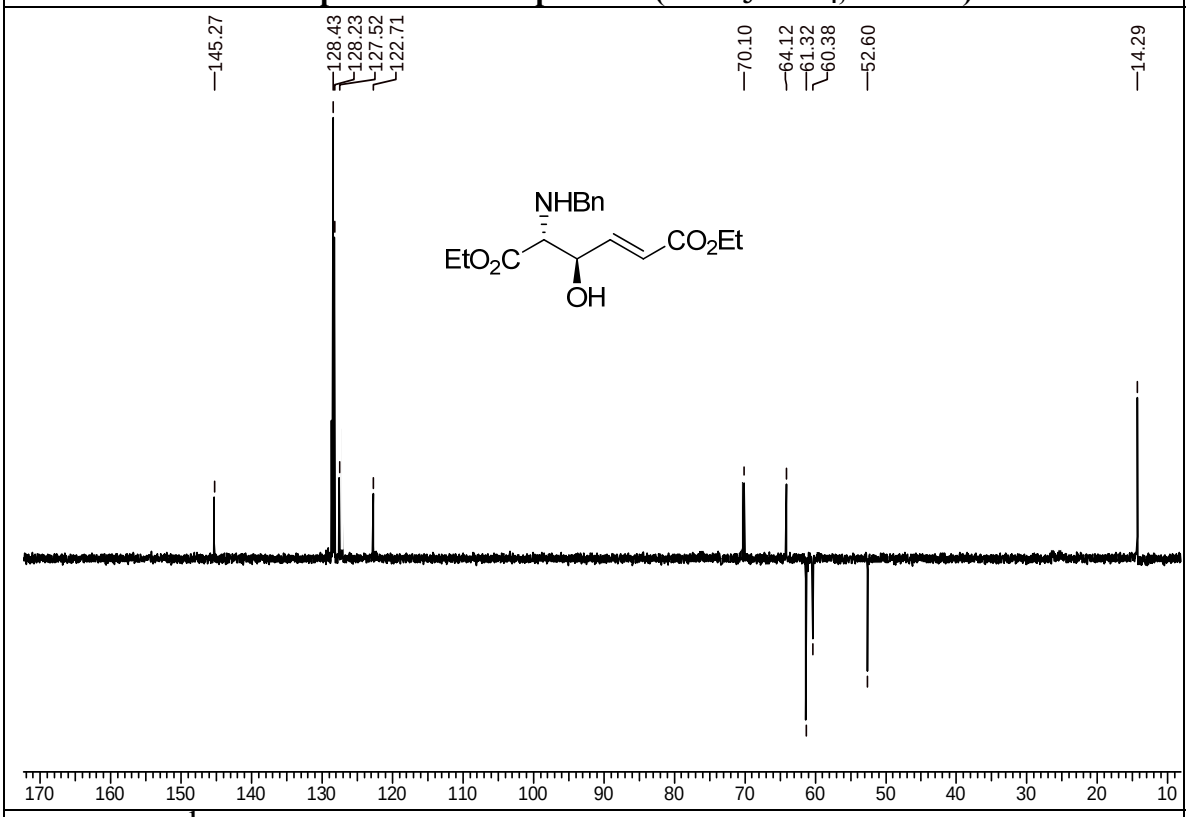
^{1}H-NMR spectrum of compound 3 ($CDCl_3$+CCl_4, 200 MHz)



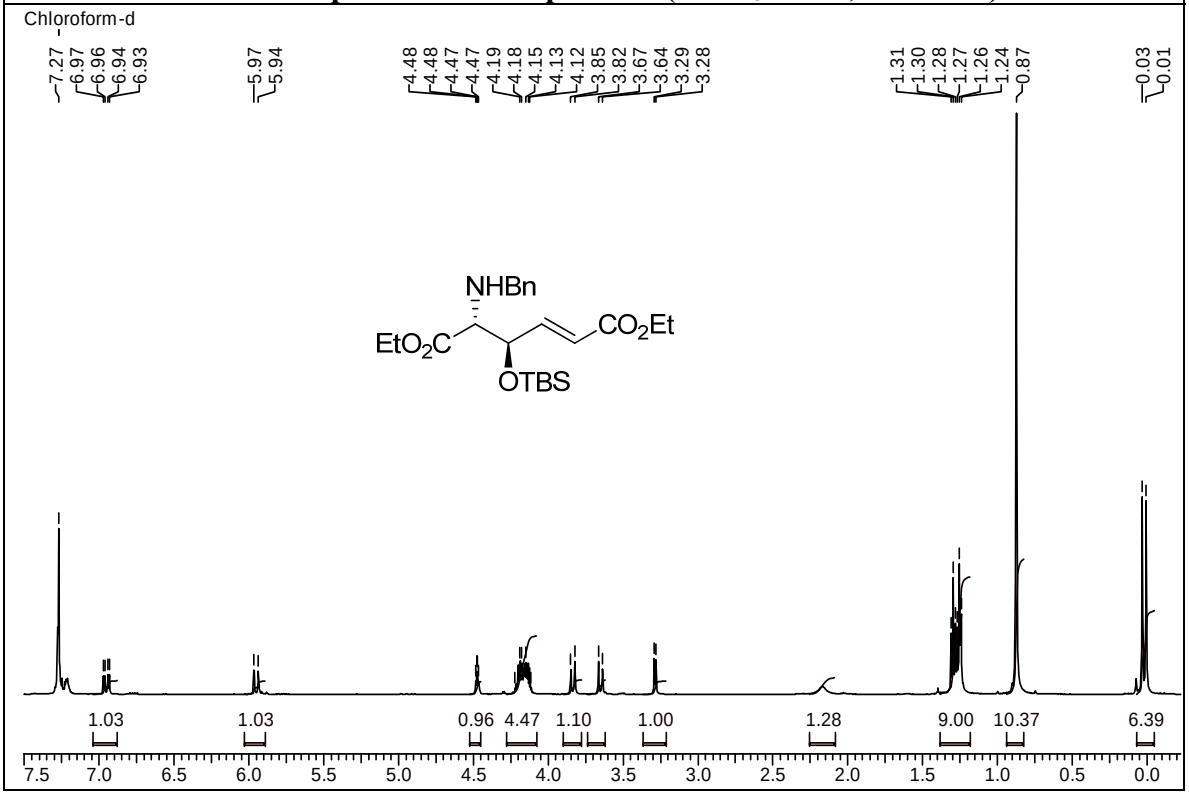
^{13}C-NMR spectrum of compound 3 ($CDCl_3$+CCl_4, 50 MHz)



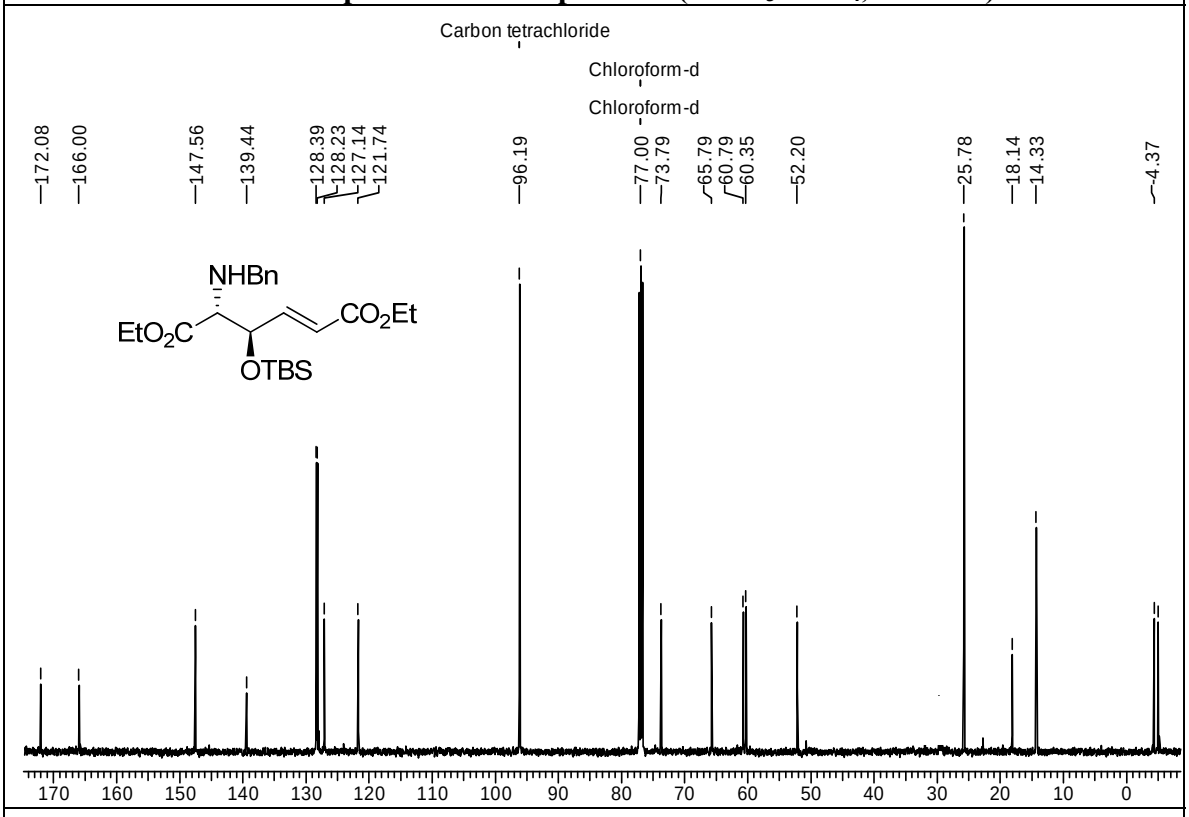
DEPT spectrum of compound 3 ($CDCl_3$+CCl_4, 50 MHz)



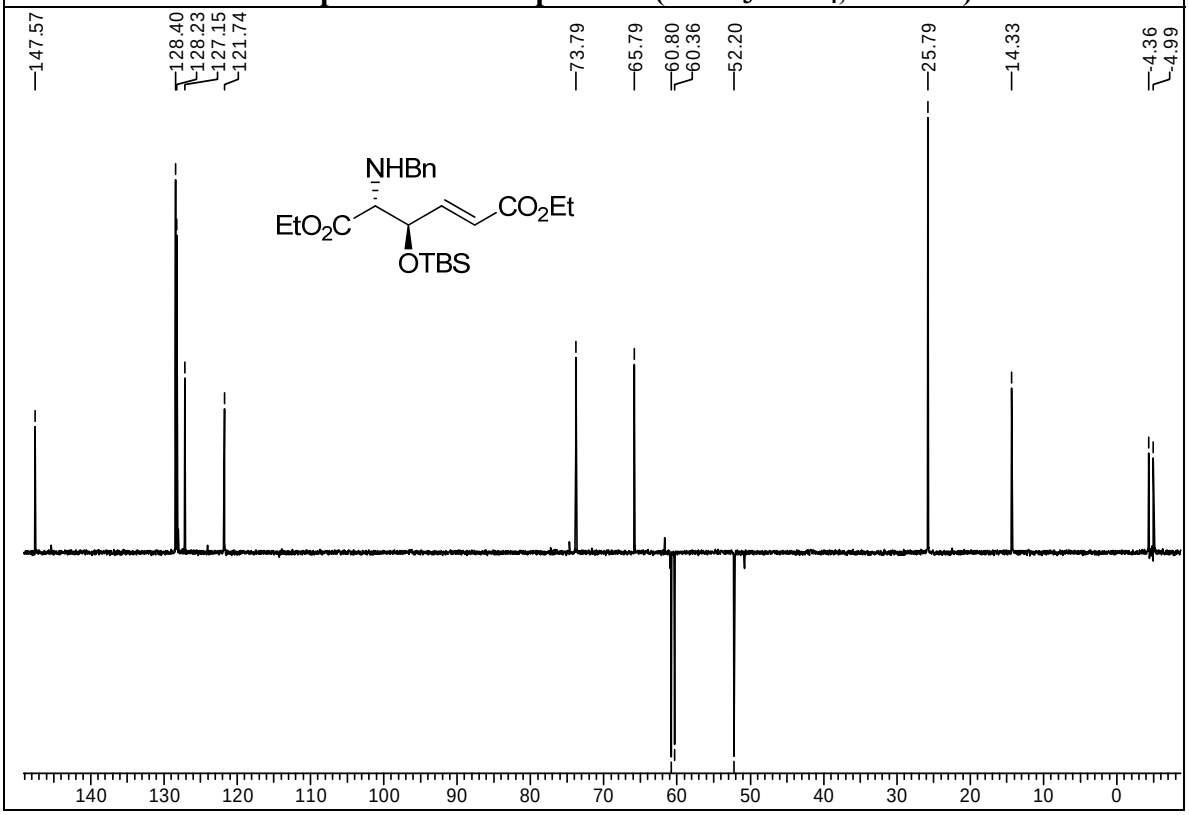
^{1}H-NMR spectrum of compound 8 ($CDCl_3$+CCl_4, 200 MHz)



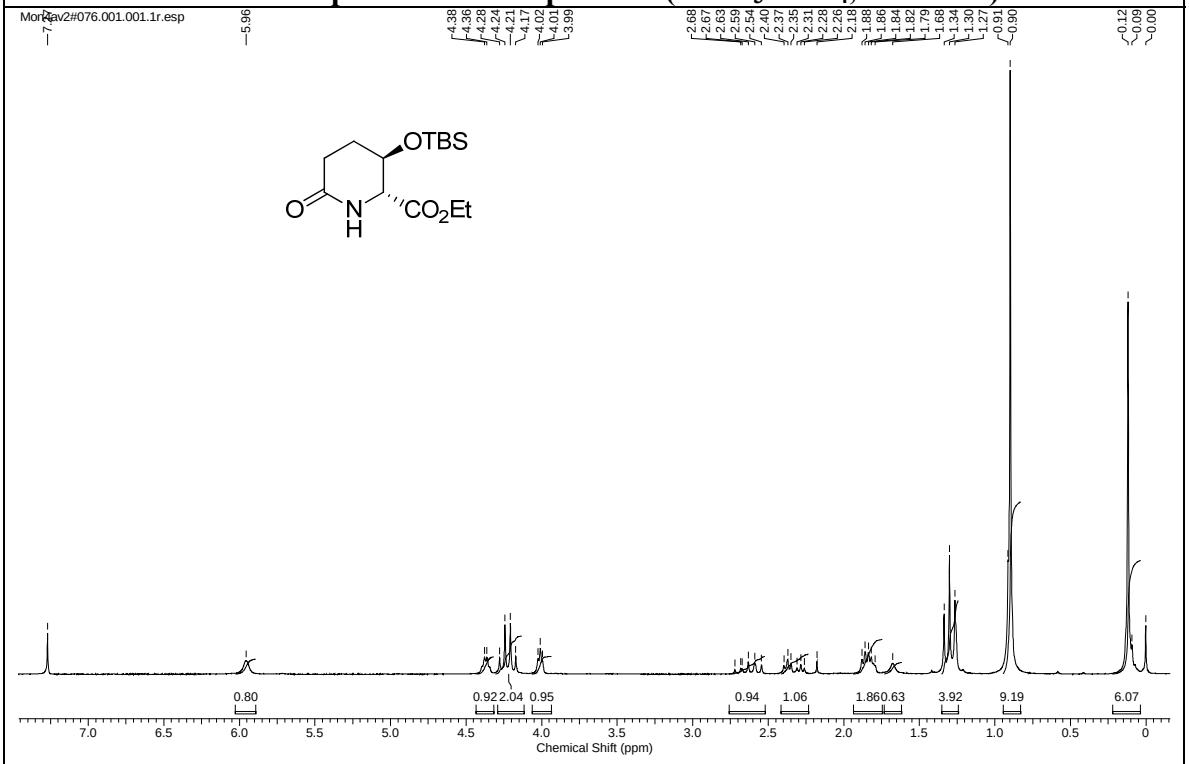
^{13}C-NMR spectrum of compound 8 ($CDCl_3$+CCl_4, 50 MHz)



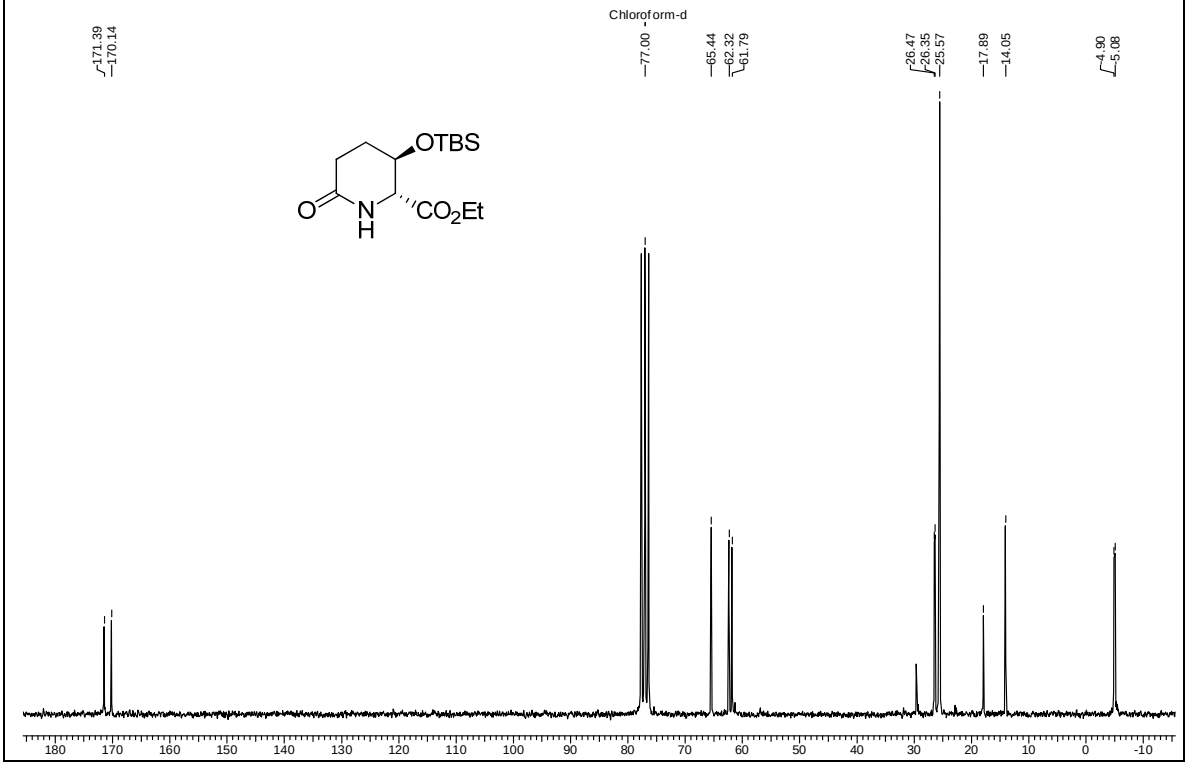
DEPT spectrum of compound 8 ($CDCl_3$+CCl_4, 50 MHz)



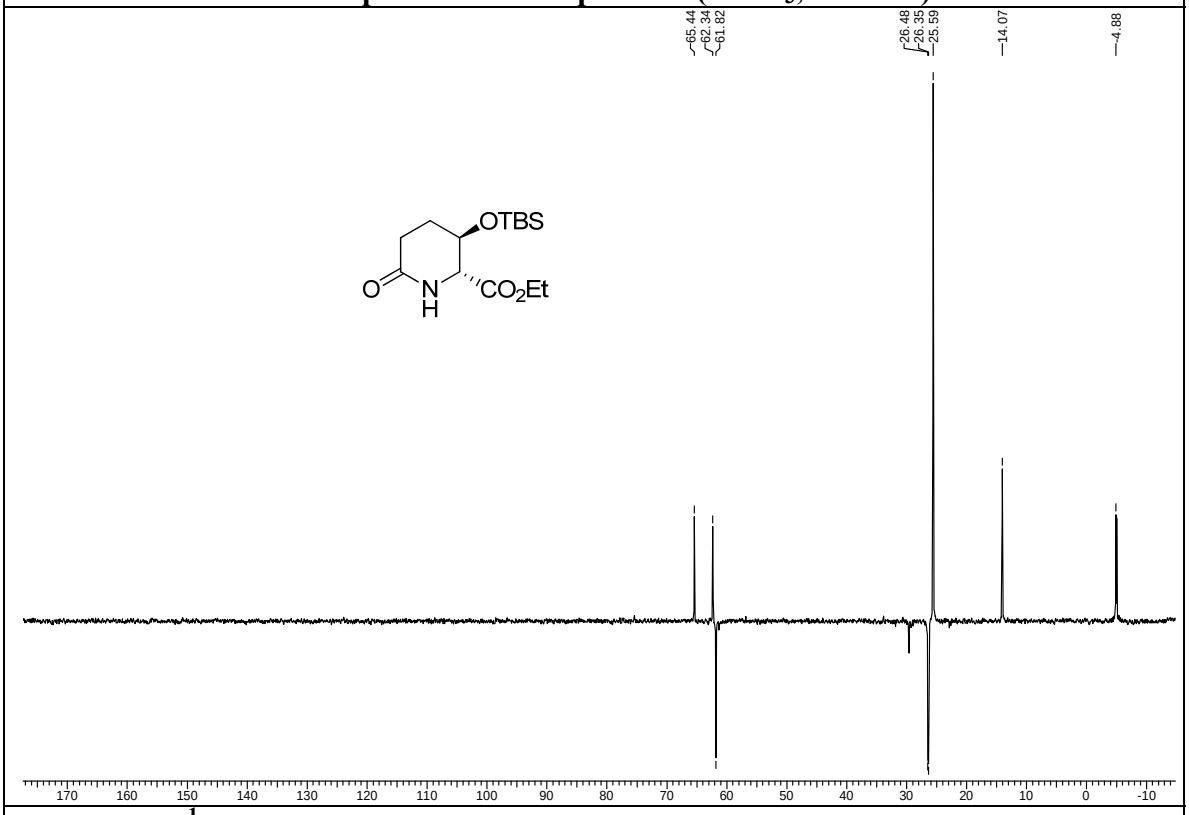
^{1}H-NMR spectrum of compound 2 ($CDCl_3$+CCl_4, 200 MHz)



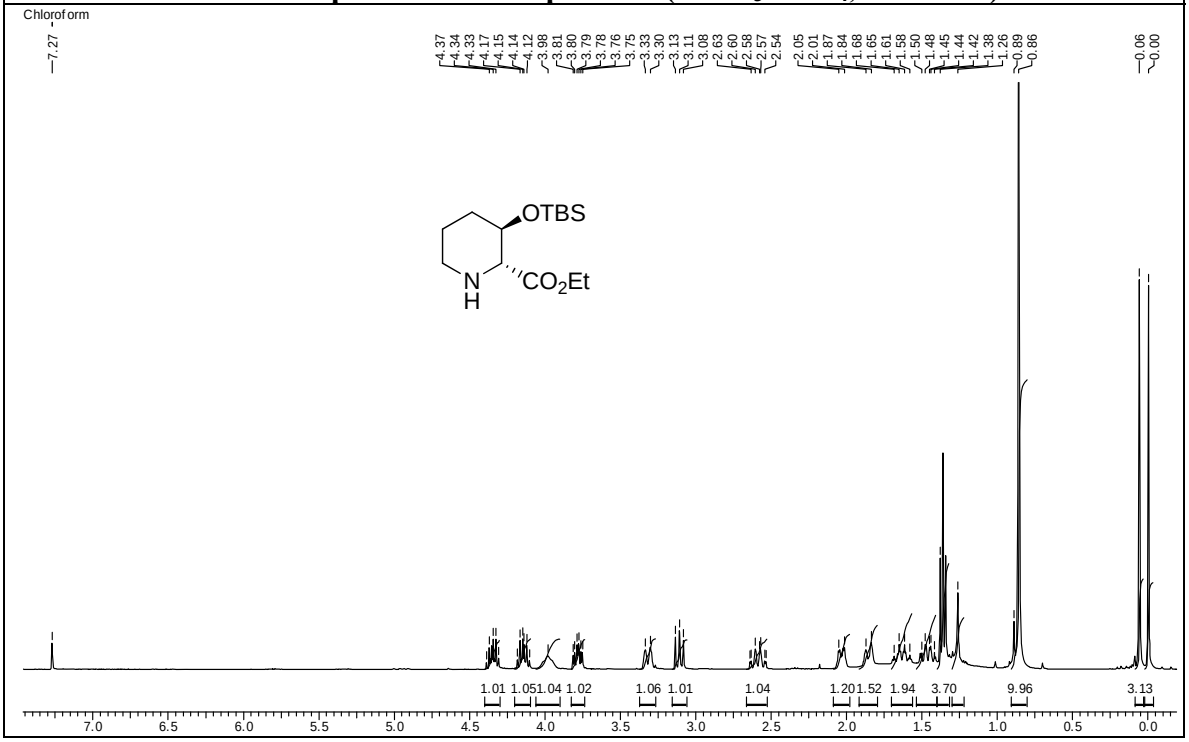
^{13}C-NMR spectrum of compound 2 ($CDCl_3$, 50 MHz)



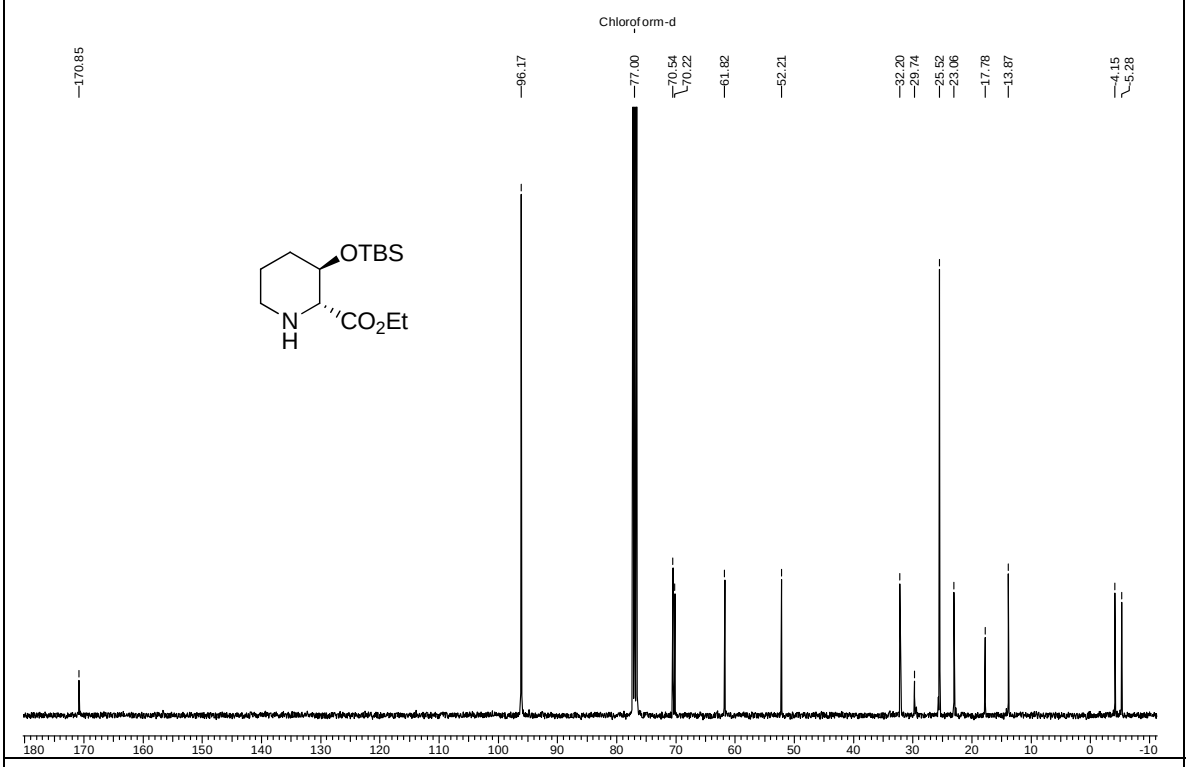
DEPT spectrum of compound 2 ($CDCl_3$, 50 MHz)



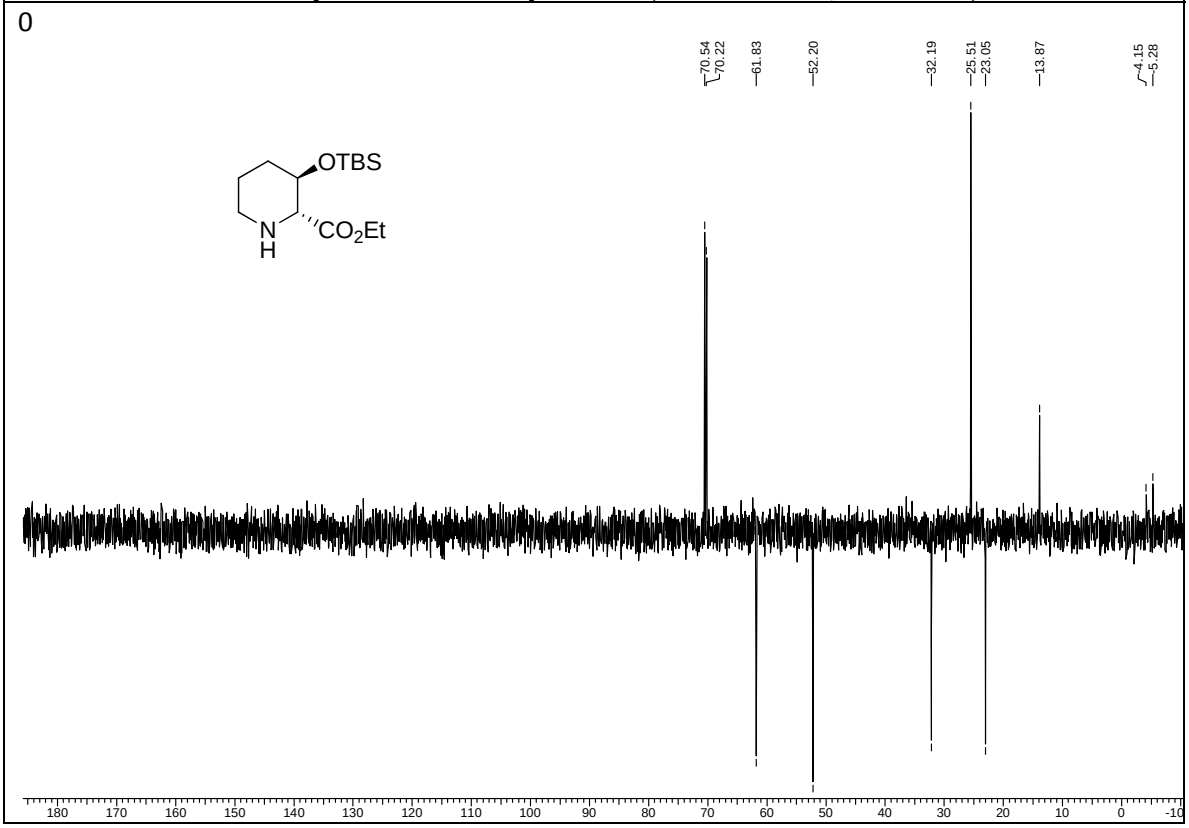
^{1}H-NMR spectrum of compound 9 ($CDCl_3$+CCl_4, 400 MHz)



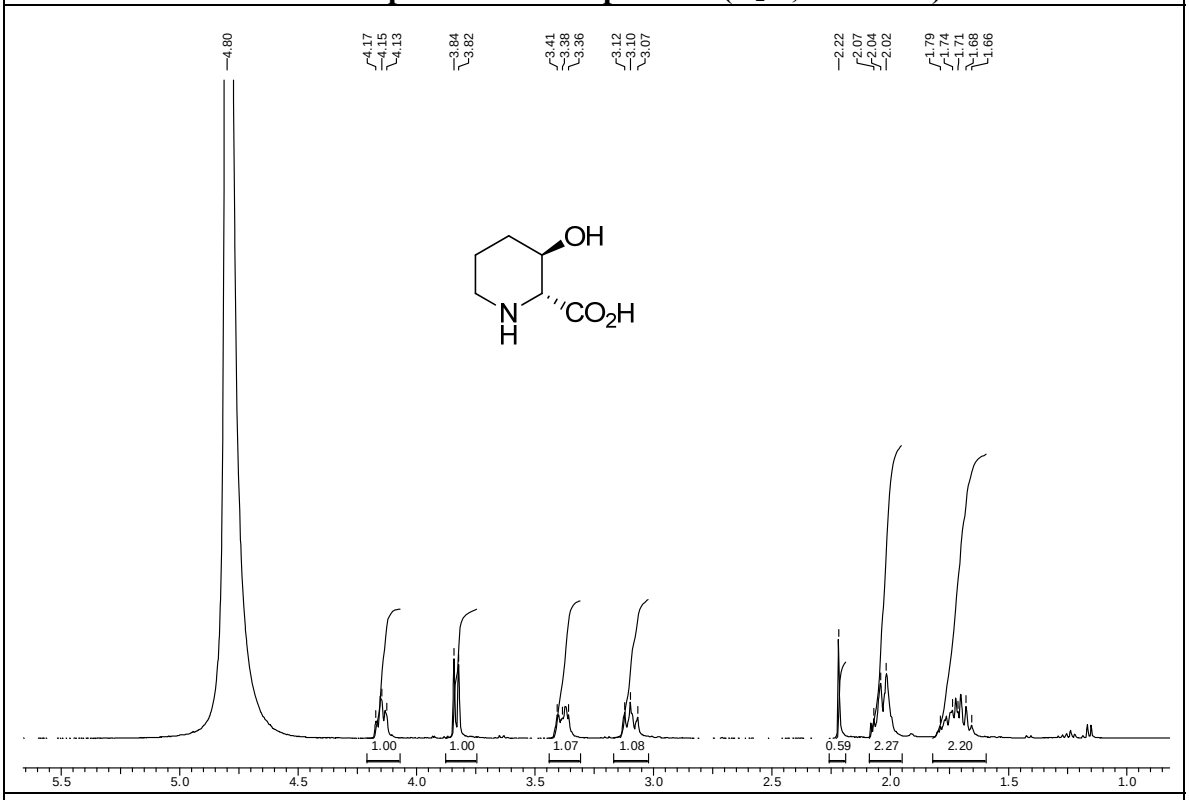
^{13}C-NMR spectrum of compound 9 ($CDCl_3$+CCl_4, 100 MHz)



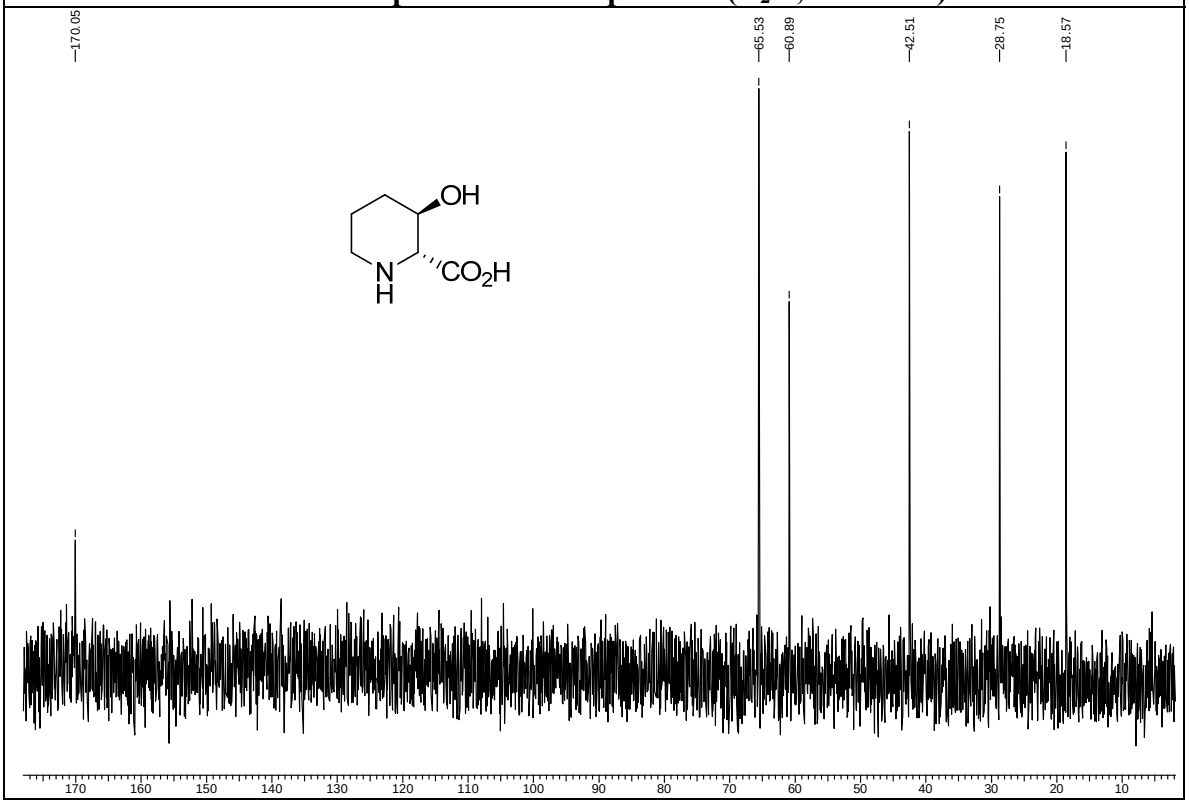
DEPT spectrum of compound 9 ($CDCl_3$+CCl_4, 100 MHz)



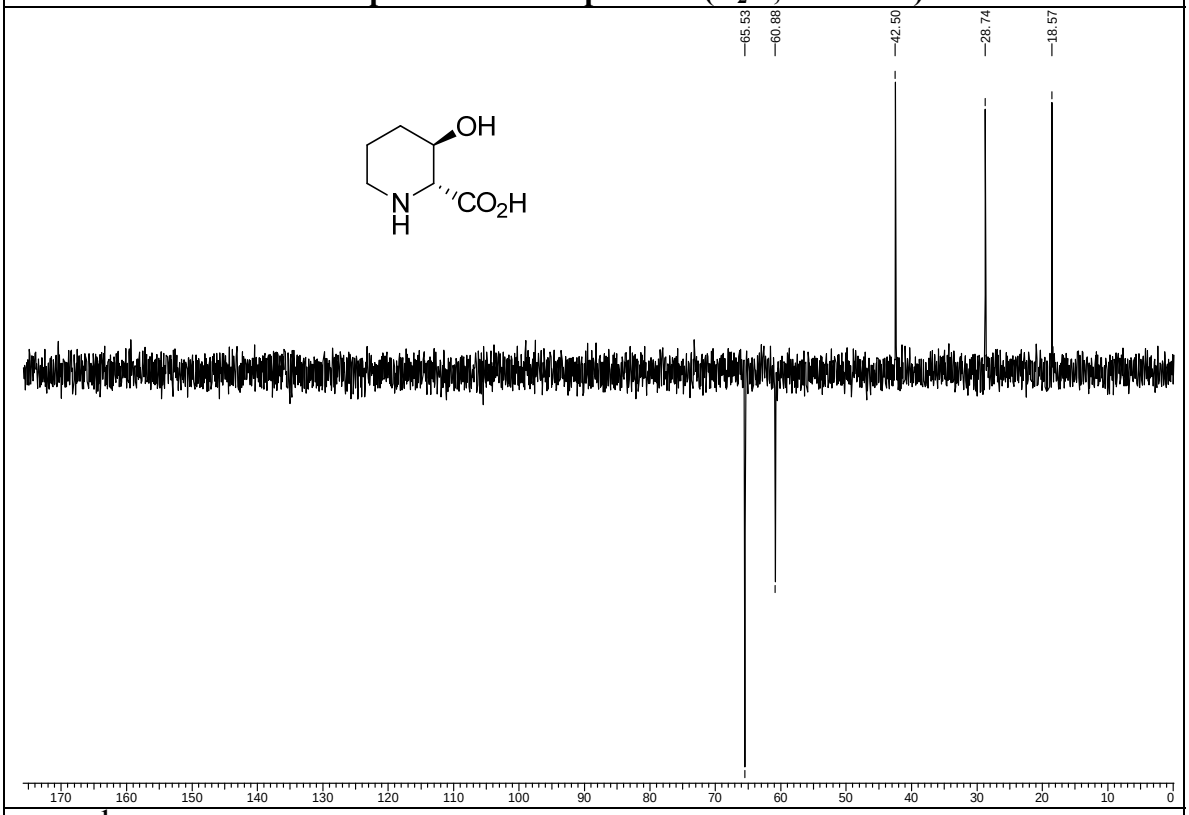
^{1}H-NMR spectrum of compound 1 (D_2O, 400 MHz)



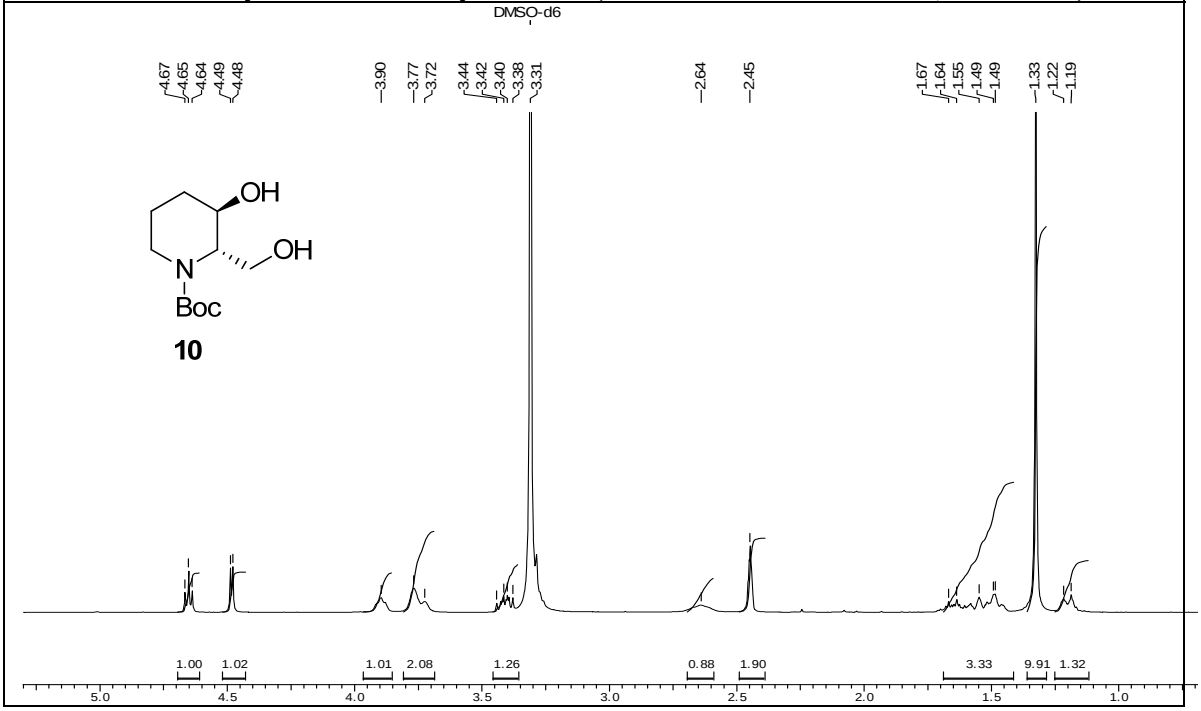
^{13}C-NMR spectrum of compound 1 (D_2O, 100 MHz)



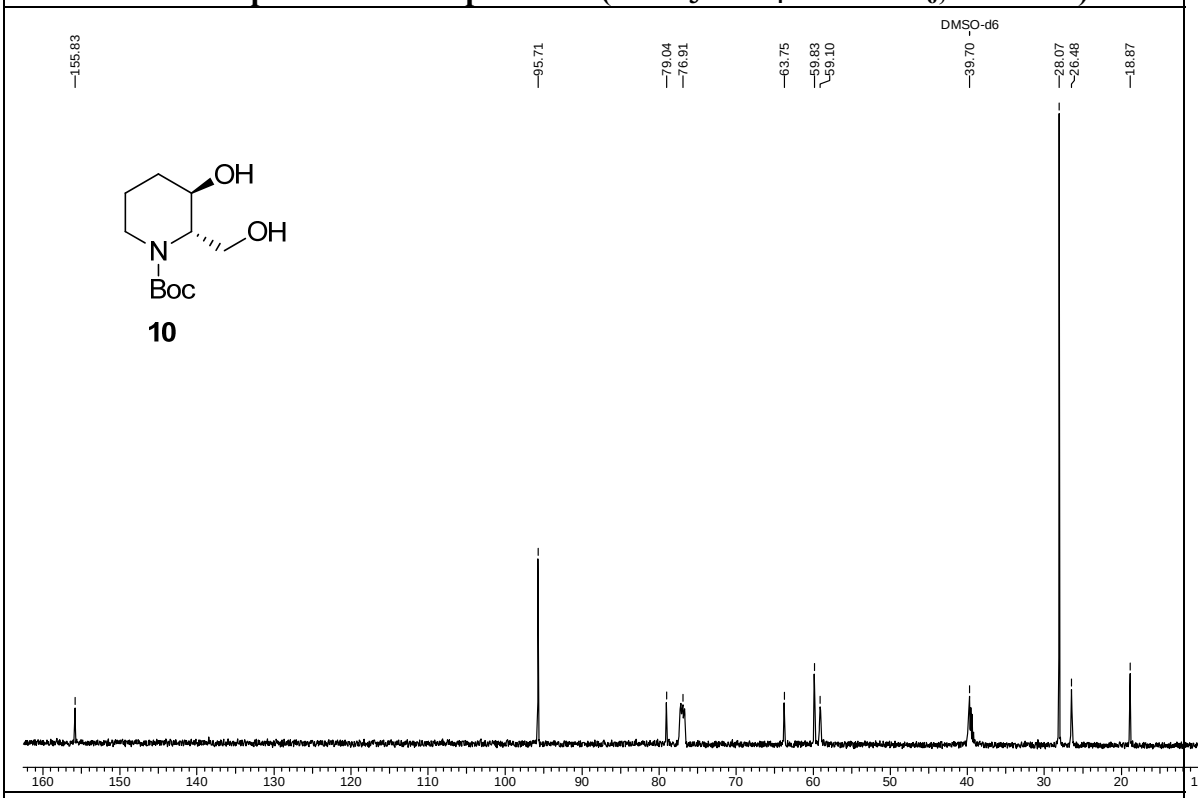
DEPT spectrum of compound 1 (D_2O, 100 MHz)



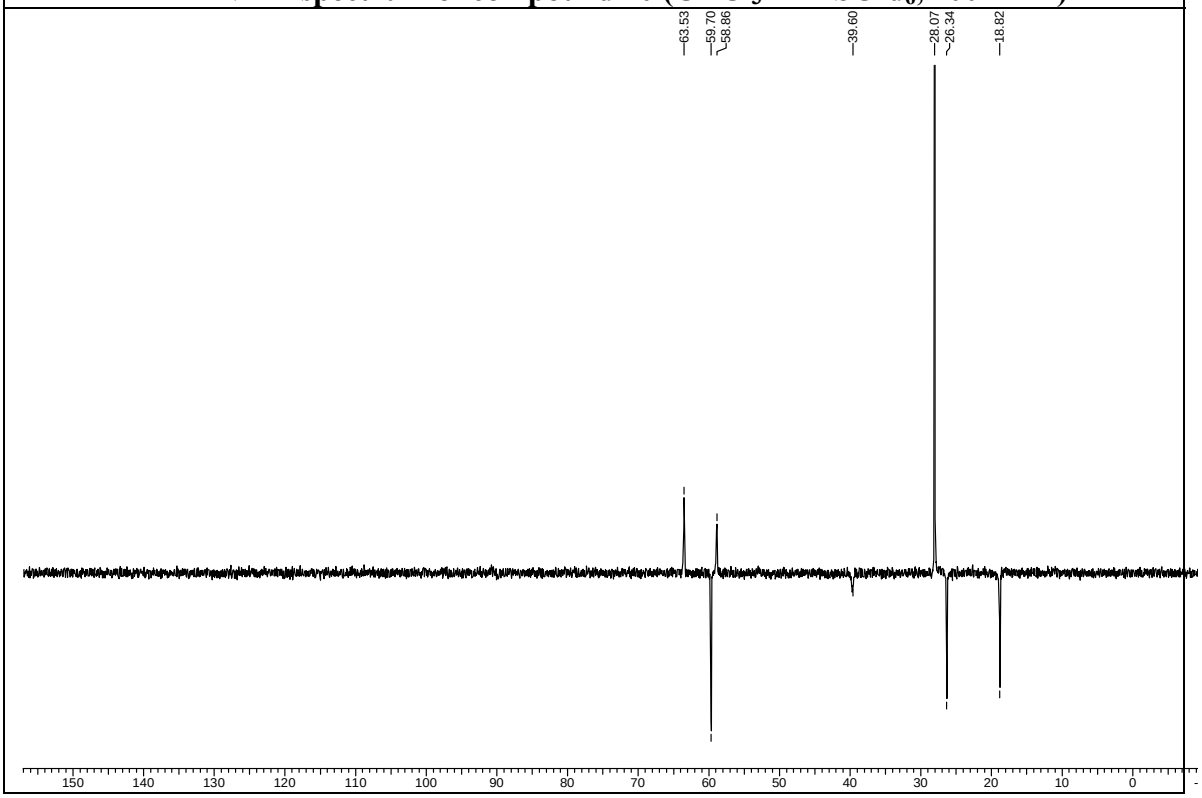
^{1}H-NMR spectrum of compound 10 ($CDCl_3$+CCl4+DMSO-d_6, 400 MHz)



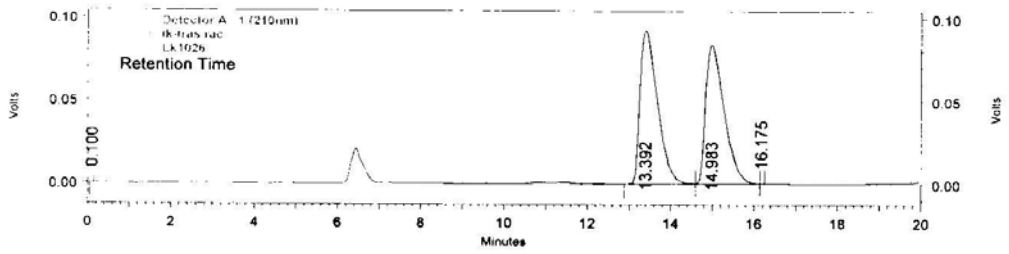
^{13}C-NMR spectrum of compound 10 ($CDCl_3$+CCl_4+DMSO-d_6, 100 MHz)



DEPT-NMR spectrum of compound 10 ($CDCl_3$+DMSO-d_6, 100 MHz)



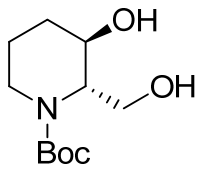
Chiral HPLC analysis of compound 10 (Racemic)



Detector A - 1 (210nm)

Retention Time	C Area	Area %
0.100	335	0.006
13.392	2694263	50.984
14.983	2589648	49.004
16.175	303	0.006
Totals	5284549	100.000

Project Leader : Dr. S P Chavan
Column :Chiracel OJ-H (250x4.6 mm)
Mobile Phase :Pet Ether:IPA (95:05)
Wavelength : 210 nm
Flow Rate :0.5ml/min (23Kgf)
conc. :1mg/1.0mL
Inj vol- :10 ul



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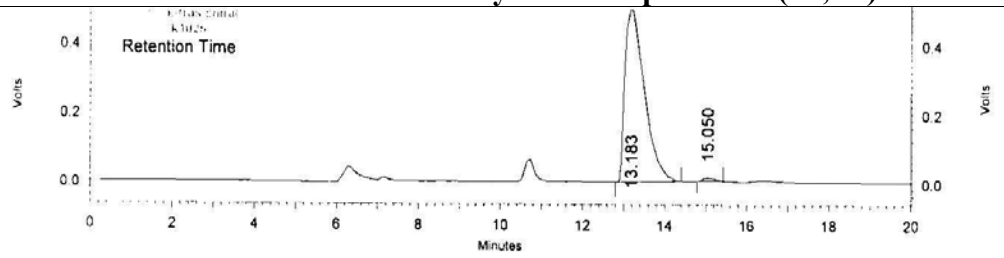
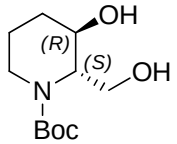
Chiral HPLC analysis of compound 10 (2*S*,3*R*)



Detector A - 1 (210nm)

Retention Time	C Area	Area %
13.183	16582875	98.896
15.050	185057	1.104
Totals	16767932	100.000

Project Leader : Dr. S P Chavan
Column :Chiracel OJ-H (250x4.6 mm)
Mobile Phase :Pet Ether:IPA (95:05)
Wavelength : 210 nm
Flow Rate :0.5ml/min (23Kgf)
conc. :1mg/1.0mL
Inj vol- :10 ul



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2.2.5 References

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2. Chavan, S. P.; Harale, K. R.; Dumare, N. B.; Kalkote, U. R. *Tetrahedron: Asymmetry* **2011**, *22*, 587.

3. Davis, F. A.; Reddy, G. V. *Tetrahedron Lett.* **1996,** *3*, 4349.

4. Ajish Kumar, K. S.; Chaudhari, V. D.; Dhavale, D. D. *Org. Biomol.Chem.* **2008,** *6*, 703.

5. Greck, C.; Ferreira, F.; Genêt, J. P. *Tetrahedron Lett.* **1996**, *37*, 2031.

6. Battistini, L.; Zanardi, F.; Rassu, G.; Spanu, P.; Pelosi, G.; Fava, G. G.; Ferrari, M. B.; Casiraghi, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2975.

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Chapter 2: Synthetic studies toward *trans*-(2*R*,3*R*)-3-hydroxypipecolic acid and (−)-swainsonine

Section 3: Introduction of (−)-swainsonine

2.3.1 Introduction to (−)-swainsonine

Iminosugars are small organic compounds that mimic carbohydrates or their hydrolysis transition states but contain a nitrogen atom instead of oxygen in the ring system templates. Ring size, poly-functionality, and multiple chirality are the factors that offer structural diversity among iminosugars that modulates the kind and the potency of the activity of each one of them.[1]

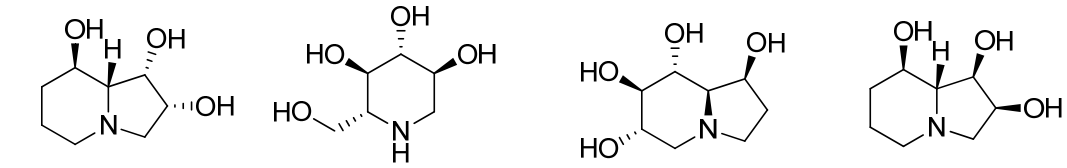


Figure 1. Structures of (−)-swainsonine **1**, deoxynojirimycin **2**, castanospermine **3**, and 1,2-di-*epi*-swainsonine **4**.

The first-generation iminosugars have been founded on three natural products: swainsonine **1**, deoxynojirimycin (DNJ, **2**), castanospermine **3** (Figure 1) and have been the starting point for the development of this class of compound as therapeutic agents. Iminosugars, although initially seen as anti-cancer or anti-HIV agents, they have subsequently demonstrated activity against a range of biochemical targets in diverse therapeutic areas.[2]

(–)-Swainsonine **1** (Figure 1) is a naturally occurring trihydroxylated indolizidine alkaloid first isolated from the fungus *Rhizoctonialeguminicola*.[3a] Since then, it has also been extracted from diverse fungi such as *Embellisia*[3b] and *Metharhiziumanisopliae F-36222b*[3c] and from other plantsof the *Swainsona*[3d] (flowering plants of western Australia), *Astragalus*, and *Oxytropis* species[3e] (herbs and smallshrubs of southwestern USA). These plants are collectively known as locoweeds because of their chronic intoxication effect with a variety of neurological disorders in livestock. Interest in this indolizidine stems principally from its role as a better inhibitor of Golgi α-mannosidase II (GMII)[4] *vs* lysosomal α-mannosidase (LM).[5] Furthermore, this molecule exhibits interesting activity against some mammalian tumor cell lines[6] and possesses immunomodulatory[7]and antiviral activities.[8] (–)-Swainsonine **1** also has potential uses as adjuvant for anticancer

drugs and other therapies in use.[9] It was the first glycoprotein processing inhibitor to be selected for clinical testing as an anticancer drug.[10]

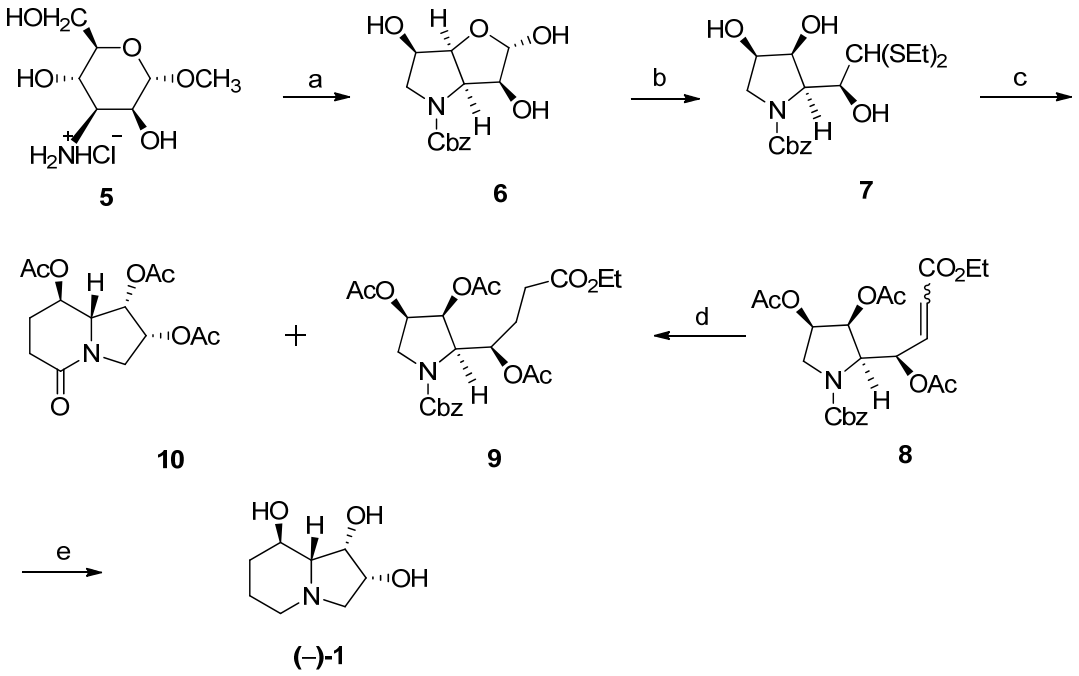
The high potential for using this alkaloid in a wide range of biological applications makes it an attractive target for synthesis. In particular, the preparation of unnatural epimers and other structural analogues of (−)-swainsonine **1** has created much interest since the biological activity of these compounds varies substantially with the number, position and stereochemistry of the hydroxy groups in the indolizidine skeleton. A number of syntheses of stereoisomers of **1** and other analogues have been developed nevertheless most of these target (–)-swainsonine **1** itself, thus reflecting the importance placed upon this molecule and remained as an attractive synthetic target for organic chemists.

2.3.2 Review of literature

Due to their 'sugar-like' structure it is not surprising that many syntheses of 1,2,8-trihydroxyindolizidines utilize carbohydrate starting materials. Hexoses and their derivatives are often used with four chiral centers required in the product. There is also a strategy based on the utilisation of pentoses. Many syntheses of 1,2,8-trihydroxyindolizidines also employ non-carbohydrate starting materials. Extensive work towards syntheses of swainsonine and its analogues has been done and reviewed.[11] A few interesting syntheses of swainsonine are described below.

Richardson's approach

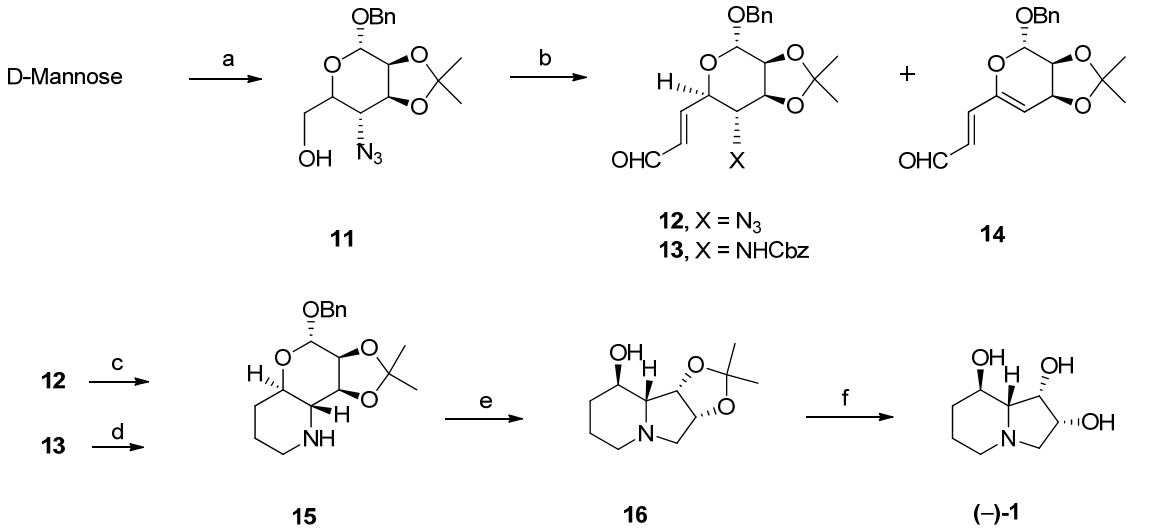
The first total synthesis of (−)-swainsonine **1** by Richardson's group established its absolute stereochemistry as (1*S*,2*R*,8*R*,8a*R*)-1,2,8-trihydroxyindolizidine (Scheme 1).[12] Compound **6** was obtained from the amino hydrochloride **5** over five steps in 31% overall yield. Reaction of **6** with ethanethiol afforded the dithioacetal **7**. Acetylation of **7** was followed by $HgCl_2/CdCO_3$ oxidation and subsequent treatment with Ph_3PCHCO_2Et to give **8** as a non-separable 1:1mixture of *E* and *Z* isomers. Hydrogenation of the *E/Z* mixture **8** gave a 1:1 mixture of the lactam **10** and the product **9** and, after chromatographic separation, the lactam **10** was converted in two steps to (−)-swainsonine **1**.



Scheme 1. ***Reagents and conditions:*** *(a) 1) $NaHCO_3$, 1:1 EtOH-H_2O, CbzCl, rt, 2 h; 2) TsCl, py, rt, 36 h, 82% over 2 steps; 3) H_2, 10% Pd/C, EtOH, then NaOAc, reflux, 8 h; 4) $NaHCO_3$, CbzCl, 2 h, 73% over 2 steps; 5) HCl, 95-100 °C, 16 h, 52%; (b) EtSH, conc. HCl, 74%; (c) 1) acetylation, 73%; 2) $HgCl_2$, $CdCO_3$, acetone, reflux, 96%; 3) Ph_3PCHCO_2Et, CH_3CN, reflux, 86%; (d) H_2, 10% Pd/C, 2 h,* **9** *(25%) and* **10** *(25%); (e) 1) BH_3·DMS, THF, under N_2, 71-94%;2) $NaOCH_3$, CH_3OH, 3 h, 100%.*

Fleets' approach

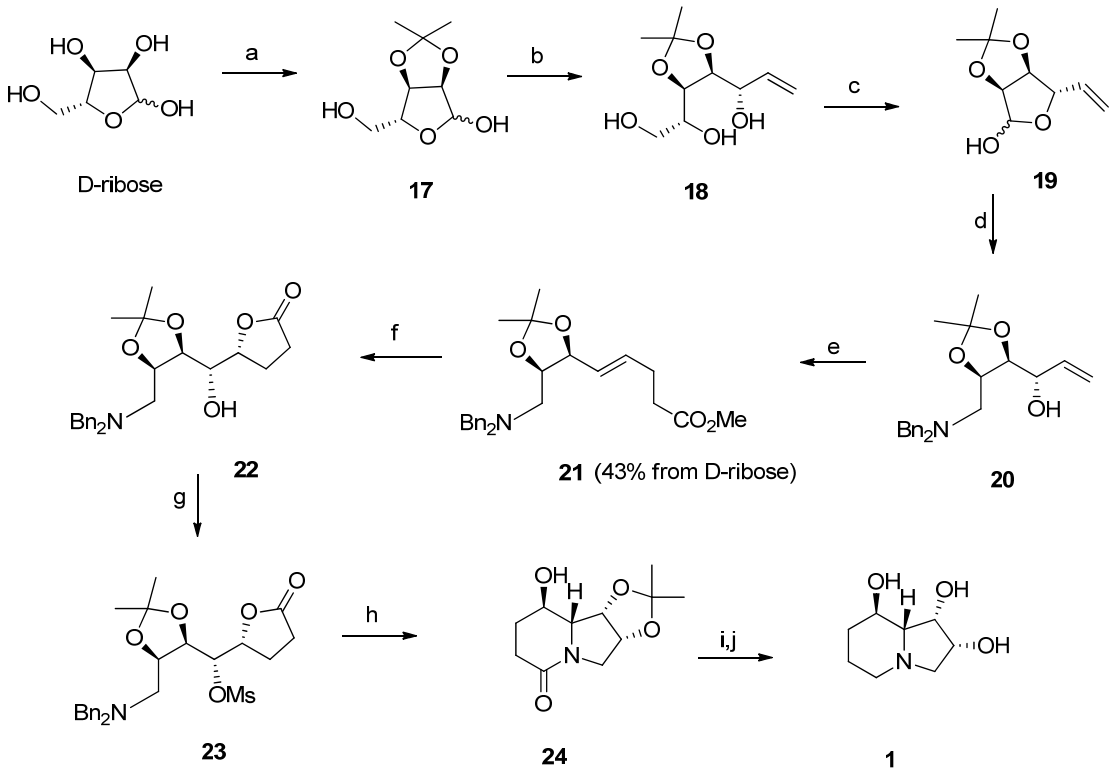
Another synthesis of (–)-swainsonine **1** was accomplished by Fleet's group utilizing D-mannose as the starting material (Scheme 2).[13] D-Mannose was transformed into the manno-azide **11** in eight steps, including double inversion at C-4, in 46% overall yield. Oxidation of the free hydroxyl group in **11** with PCC followed by treatment with $Ph_3PCHCHO$ gave **12** in 60-65% yield and the dienal **14** in 12% yield, which were separated by chromatography. Prolonged hydrogenationof **12** and **13** followed by removal of the isopropylidene protecting group in **16** afforded (−)-swainsonine **1**.



Scheme 2. ***Reagents and conditions:*** *(a) 1) BnOH-HCl, 83%, 2) TBDPSCl, imidazole, DMF, rt, 6 h, 89-97%; 3) DMP, CSA, acetone, 100%; 4) PCC, CH_2Cl_2, rt, 2 h; 5) $NaBH_4$, EtOH, 81% over 2 steps; 6) Tf_2O, py, CH_2Cl_2, −50−20°C; 7) NaN_3, DMF, rt, 68% over 2 steps; 8) Bu_4NF, THF, rt, 4 h; (b) 1) PCC, 3 Aº M.S., CH_2Cl_2, 45 min; 2) $Ph_3PCHCHO$, 45 min, 68%, over 2 steps; (c) H_2, 10% Pd/C, CH_3OH, 6 h; (d) H_2, Pd-black, CH_3OH, 48 h; (e) H_2, Pd-black, AcOH, rt, 3 days, 60-87% for c, d and e; (f) TFA, H_2O, rt, 50 h, 74%.*

Pearson's approach

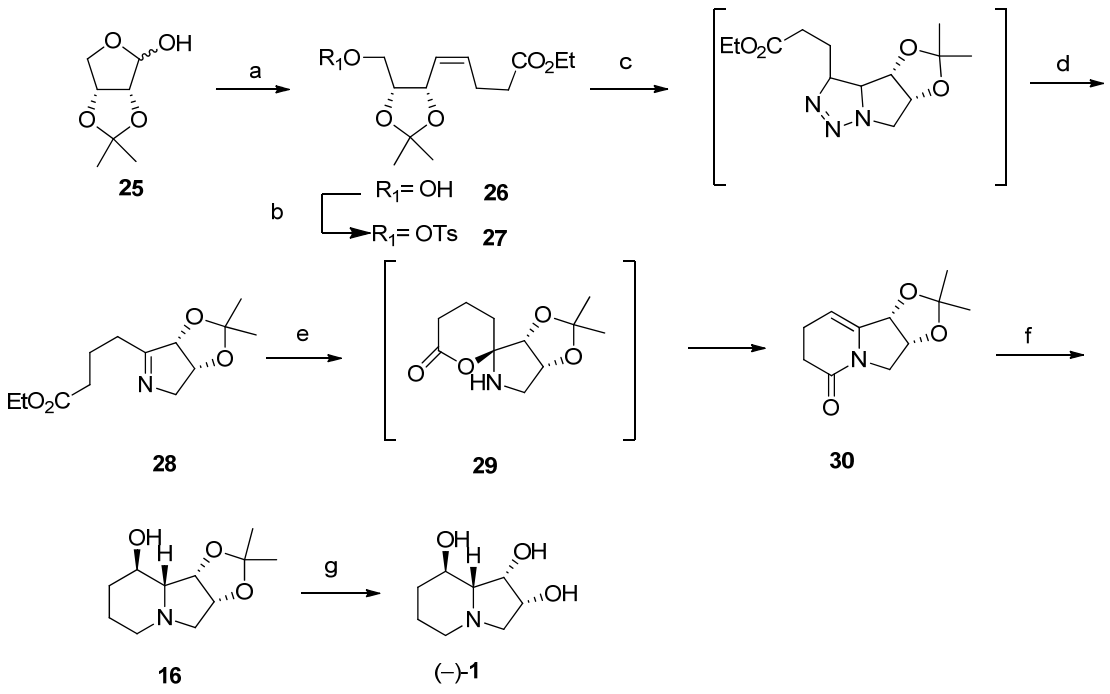
Pearson reported an efficient synthesis of (−)-swainsonine **1** which started with inexpensive D-ribose, which was converted to the known acetonide **17** in 99% yield (Scheme 3).[14] Treatment of **17** with vinylmagnesium bromide gave the crude triol **18** in 80% yield without the need for purification. Oxidative cleavage of the 1,2-diol moiety of **18** using sodium periodate on silica gel gave the lactol **19** in 96% yield without purification. Reductive amination of **19** with dibenzylamine gave the amino-alcohol **20,** which underwent a Johnson-Claisen ortho ester rearrangement to give the unsaturated ester **21.** Purification of this material by column chromatography provided **21** in 43% overall yield from D-ribose. Osmium catalysed *syn*-dihydroxylation of **21** using AD-mix-β gave the hydroxylactone **22** in 60% yield after purification by column chromatography. The hydroxyl group in **22** was converted to its mesylate **23** (60% yield), which upon transfer hydrogenolysis of the *N*-benzyl groups gave the bicyclic lactam **24** in 80% yield after crystallization. This compound was converted to (−)-swainsonine **1** in 96% overall yield. (−)-Swainsonine was prepared in 10 steps in 12% overall yield in a synthetic route that requires only 2 purifications by column chromatography and 1 crystallization.



Scheme 3. ***Reagents and conditions:*** *(a) Acetone, conc. HCl; (b) vinylmagnesium bromide, 5 equiv, THF; (c) $NaIO_4$ on SiO_2, CH_2C1_2; (d) Bn_2NH, AcOH, $NaBH_3CN$, MeOH; (e) $MeC(OMe)_3$, (cat.) $EtCO_2H$, toluene, reflux; (f) $K_3Fe(CN)_6$, $K_2OsO_4{\cdot}2H_2O$, K_2CO_3, $MeSO_2NH_2$, $(DHQD)_2PHAL$, H_2O, t-BuOH, 58%; (g) MsCl, Et_3N, CH_2C1_2, 60%; (h) $Pd(OH)_2$, HCO_2NH_4, AcOH, MeOH, reflux, 80%; (i) $BH_3{\cdot}DMS$, THF; (j) aq. HC1 96%.*

Cha's approach

A short enantioselective synthesis of (–)-swainsonine **1** has been reported in seven steps from 2,3-*O*-isopropylidene D-erythrose **25** in an overall yield of 35% (Scheme 4). [15] The olefinic ester **26**, prepared from **25** in two steps, underwent tosyl displacement with NaN_3 and subsequently 1,3-dipolar cycloaddition to afford the imino ester **28** in 81% overall yield. Mild hydrolysis of **28**, followed by cyclisation in refluxing toluene *via* the lactone **29**, gave the desired lactam **30**. This was then treated with borane and hydrogen peroxide to produce the swainsonine acetonide **16** as a single diastereomer and concomitant acid hydrolysis gave (–)-swainsonine **1**.

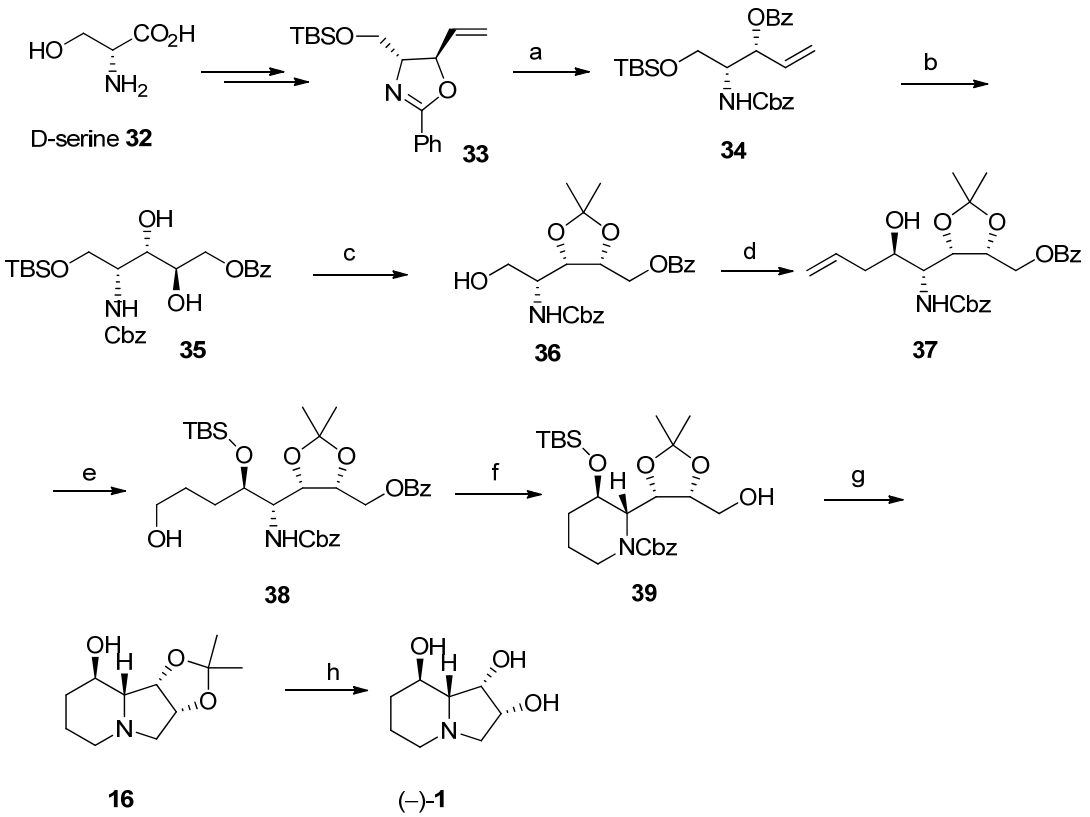


Scheme 4. ***Reagents and conditions:*** *(a) $BrPh_3P(CH_2)_3CO_2Et$, $KN(TMS)_2$, THF, -78 °C; (b) TsCl, Et_3N, CH_2Cl_2; (c) NaN_3, DMF; (d) NaOH, H_2O, CH_2Cl_2; (e) Toluene; (f) BH_3·DMS, THF, H_2O_2, H_2O, NaOH; (g) HCl, Dowex, OH^- resin.*

Ham's approach

Ham*et al*. reported a new asymmetric method for the synthesis of (−)-swainsonine **1** using a diastereoselective chiral oxazoline formation by Pd(0) catalyst, diastereoselective dihydroxylation and the stereocontrolled allylation with $TiCl_4$.[16]

The synthesis of (−)-swainsonine started with *trans*-oxazoline **33** which was treated with benzyl chloroformate in the presence of aqueous sodium bicarbonate, to afford the carbamate **34** in 96% yields. The dihydroxylation of **34** followed by acetonide protection of resulting diol **35** gave the compound **36**. Oxidation of alcohol **36** with Dess-Martin periodinane gave the corresponding aldehyde which was subsequently reacted with allyltrimethylsilane in the presence of $TiCl_4$ to give the adduct of amino alcohol **37** with high *anti*-selectivity (15:1) (Scheme 5). The protection of the alcohol **37** by TBSOTf and subsequent oxidation of the alkene with borane-methyl sulphide gave the corresponding alcohol **38** in 70% yield.

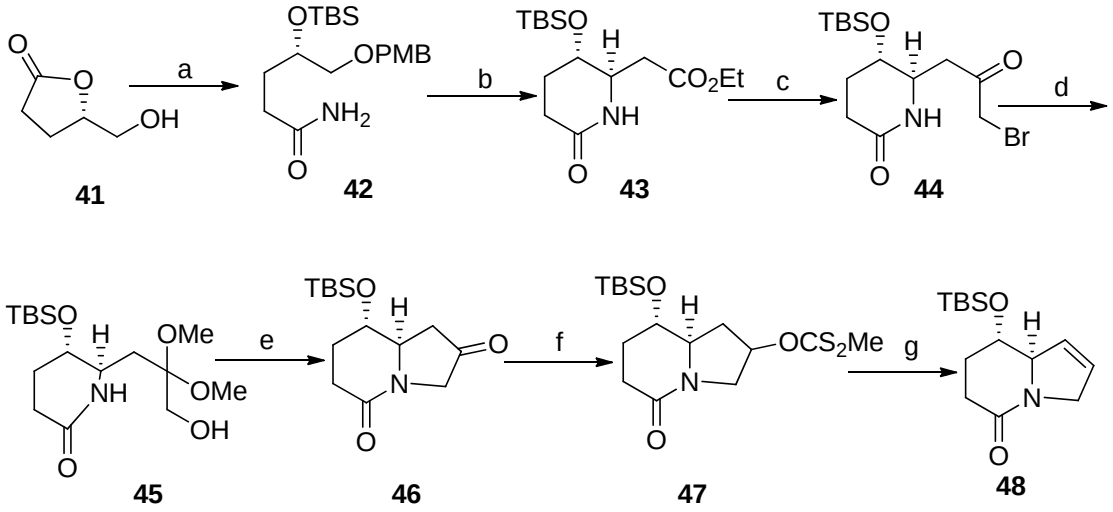


Scheme 5. ***Reagents and conditions:****(a) CbzCl, $NaHCO_3$, CH_2Cl_2, H_2O, 0 °C-rt, 3 h, 96%; (b) OsO_4, NMO, acetone:H_2O, then Na_2SO_3, 0 °C, 10 h, 99% (dr = 9 :1); (c) 1) DMP, PPTS, acetone, 40 °C, 8 h; 2) HF, py, THF, 0 °C-rt, 3 h, 78% (2 step); (d) 1) Dess-Martin periodinane; 2) Allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, -78°C, (e) 1) TBSOTf, 2,6-lutidine, CH_2Cl_2; 2) BH_3.DMS, THF, 0 °C - rt, 70% over 2 steps; (f) 1) MsCl, TEA, CH_2Cl_2; 2) NaH, THF, then 2N NaOH, 76% over 2 steps; (g) 1) MsCl, Et_3N, CH_2Cl_2; 2) $Pd(OH)_2/C$, H_2, MeOH, 84% over 2 steps; (h) 6N HCl, Dowex-50WX8-100, 82%.*

Mesylation of compound **38** and then exposure of the corresponding mesylate to NaH and then to 2N NaOH led to intramolecular cyclization and then benzoate hydrolysis provided **39** in 76% yield. Again mesylation of compound **39** followed by hydrogenolysis of mesylate afforded the protected (−)-swainsonine **16**. Finally, acidic hydrolysis of the acetonide group gave (−)-swainsonine **1** in 82% yield (Scheme 5).

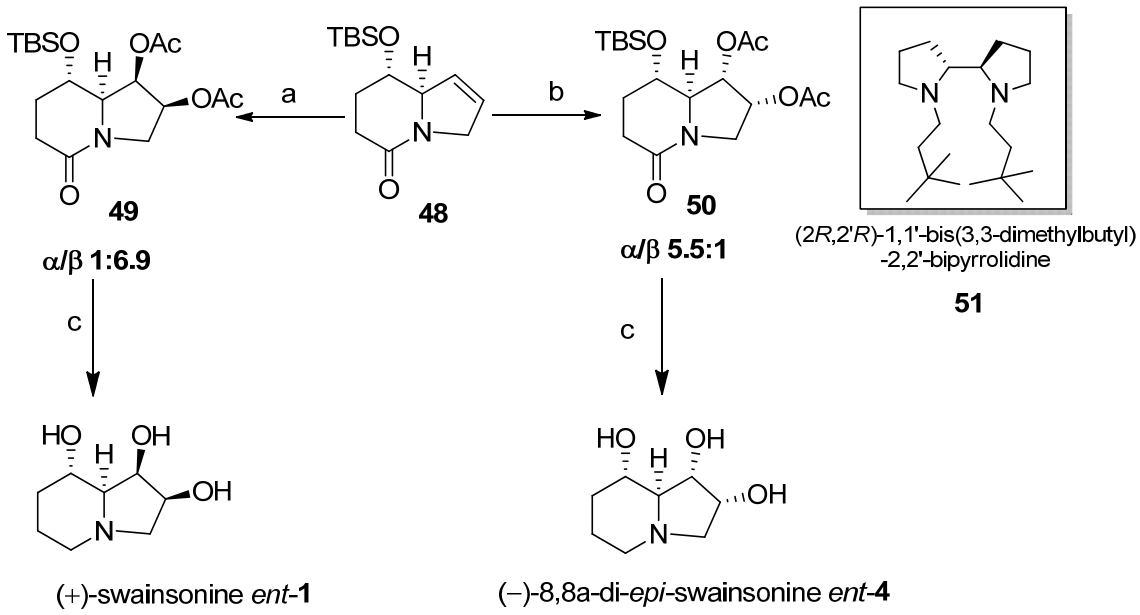
Hirama's approach

(+)-Swainsonine *ent*-**1** and (−)-8,8a-di-*epi*-swainsonine *ent*-**4** were synthesized stereoselectively using L-glutamic acid *via* highly diastereoselective intramolecular conjugate addition of amide. Another key step is stereoselective osmium catalysed dihydroxylation of indolizidine double bond.[17]



Scheme 6. ***Reagents and conditions:*** *(a) 1) NaH, PMBCl, THF, DMF, 76%; 2) NH_4OH, Et_2O,0°C, 79% ; 3) TBSCl, Im, DMF, 91%; (b) 1) KH, Boc-S, THF, -30-5°C, 81%; 2) DDQ, CH_2Cl_2, H_2O, 94%; 3) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, 81%; 4) $(CF_3CH_2O)_2P(O)CH_2CO_2CH_3$, 18-crown-6, KHMDS, toluene, –78°C, 85%, Z/E.4.3:1; separation; 5) TMSI, $CHCl_3$, 65%; 6) t-BuOK, THF, –55°C, 80%; (c) $LiCHBr_2$, THF, –90°C; then BuLi, –90°C, 59%; (d) (i) K_2CO_3, CH_3OH, 92%; (e) 1) MsCl, Et_3N, CH_2Cl_2, 94%; 2) KH, THF, 87%; 3) TsOH, acetone, 77%; (f) 1) $NaBH_4$, CH_3OH, 0°C, 98%; 2) NaH, THF, CS_2; then CH_3I, 98%; (g) 180°C, 68%.*

Butyrolactone **41** prepared from L-glutamic acid was converted to amide **42** over three steps. Amide **42** was protected as Boc derivative followed by PMB deprotection, oxidation, two carbon Wittig elongation and highly diastereoselective intramolecular conjugate addition of amide to give lactam **43.** Lactam **43** was converted to indolizidine framework **48** over eight steps (Scheme 6). Dihydroxylation of **48** under Upjohn conditions occurred predominantly from opposite face of OTBS group to give *β*-diacetate **49** while under reagent controlled conditions (catalyst **51**) gave *α*-diacetate **50** as major product which were converted to (+)-swainsonine *ent*-**1** and (−)-8,8a-di-*epi*-swainsonine *ent*-**4** respectively (Scheme 7).



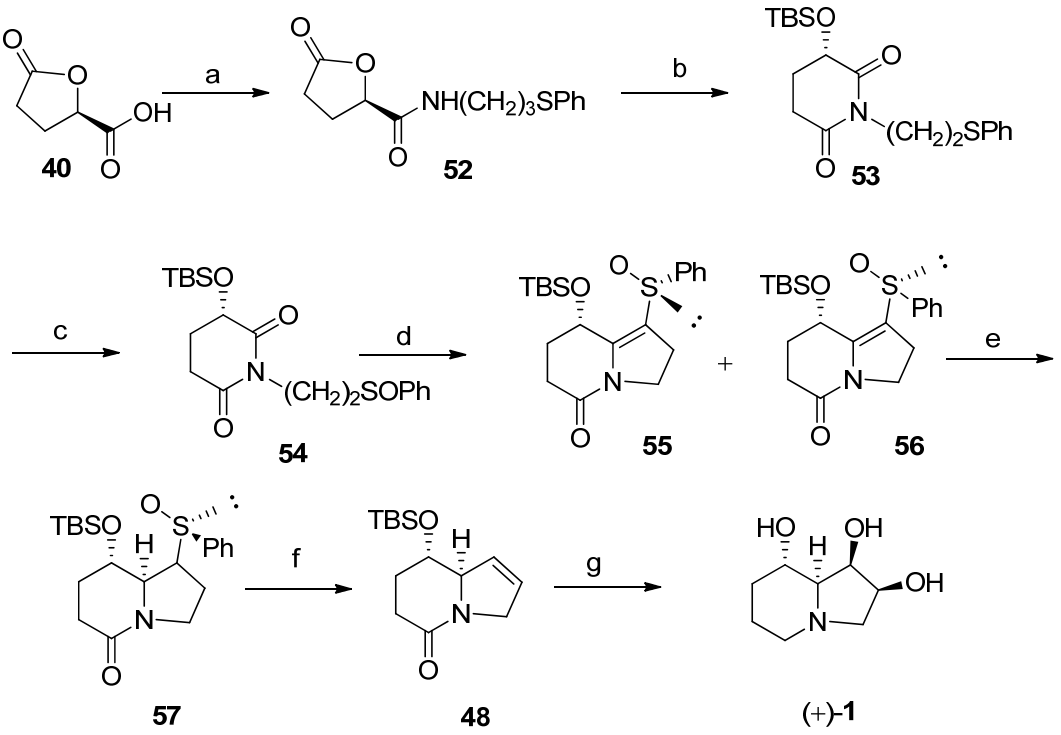
Scheme 7. ***Reagents and conditions:*** *(a) 1) OsO_4, NMO, acetone, H_2O, rt, 82%; 2) TFA, THF:H_2O; then Ac_2O, pyridine, CH_2Cl_2, 84%, α/β 1:6.9; (b)* **51**, *CH_2Cl_2, –78°C; then $Na_2S_2O_5$, aq THF, reflux; then Ac_2O, pyr, DMAP, 81%;c) BH_3·THF, reflux; K_2CO_3, CH_3OH; then 2M HCl, reflux, 85%.*

Pohmakotr's approach

A concise asymmetric synthesis of (+)-swainsonine *ent*-**1** in 11.8% overall yield in 10 steps is described by Pohmakotr'**s** group starting from **40**, which was readily prepared from commercially available L-glutamic acid. The method features installation of the indolizidine ring *via* an intramolecular cyclisation of *α*-sulfinyl carbanion as a key step to get intermediate **48**. Dihydroxylation of **48** under Upjohn conditions followed by amide reduction and TBS deprotection afforded (+)-swainsonine *ent*-**1** as a single diastereomer (Scheme 8).[18]

Cyclisation of compound **54** to **55** and **56** required treatment of **54** with 2.2 equiv of LHMDS in THF at -78 ºC followed by slowly warming up to room temperature for 16 hours *via* competitive proton abstraction that occurred preferentially at the *α*-imide proton rather than the α-proton adjacent to the phenylsulfinyl moiety of sulfinylimide **54**. Proton abstraction of the initially formed enolate by a second equivalent of LHMDS gave *α*-sulfinyl carbanion which readily underwent cyclisation to yield hydroxy indolizidine amide which on treatment with *p*-TsOH in refluxing CH_2Cl_2 furnished **55** and **56** in 15%

and 65% yields, respectively. Intermediate **56** was converted to (+)-**1** *via* known intermediate **48**.

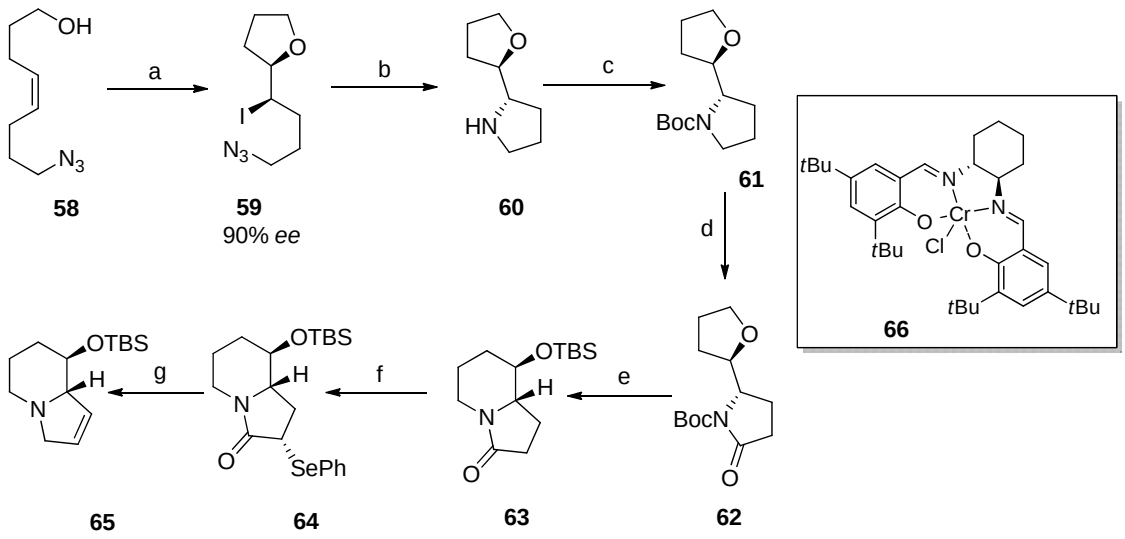


Scheme 8. ***Reagents and conditions:*** *(a) 1) $(COCl)_2$, CH_2Cl_2; 2) $NH_2(CH_2)_3SPh$, CH_2Cl_2, Et_3N, 16 h; (b) tBuOK, THF, 67%; (c) 1) TBSCl, Im, CH_2Cl_2, 87%; 2)$NaIO_4$, MeOH-H_2O, 90%; (d)* LHMDS, *THF, –78-0°C, LHMDS then pTsOH, 15% for* **55** *and 65% for* **56***; (e) $NaBH_3CN$, AcOH-TFA, 0°C then 50°C; (f) $CaCO_3$, tolune, reflux, 85%; (g) 1) NMO, acetone, H_2O, rt; 2) $LiAlH_4$, THF, reflux; 3) Dowex 50W-X8 (H^+), 84% over 3 steps.*

Kang's approach

Kang's approach involves highly enantioselective iodoetherification of *γ*-hydroxy-*cis*-alkenes **58** using iodine in the presence of salen–Co(II) complex **66** and *N*-chloro succinimide (NCS) and chemoselective oxidation as key steps to synthesize indizolide **65**, an important intermediate for (−)-swainsonine.[19] The synthesis commenced with the iodocyclization of the azidoalkenol **58** to afford the azido tetrahydrofuran **59** with 90% ee in 86% yield (Scheme 9). The azido group of **59** was reduced with stannous chloride and the resulting amino iodide was cyclized under basic conditions. The crude bicyclic tetrahy-

drofuranyl pyrrolidine **60** was protected to furnish carbamate **61** in 80% overall yield from **59**.

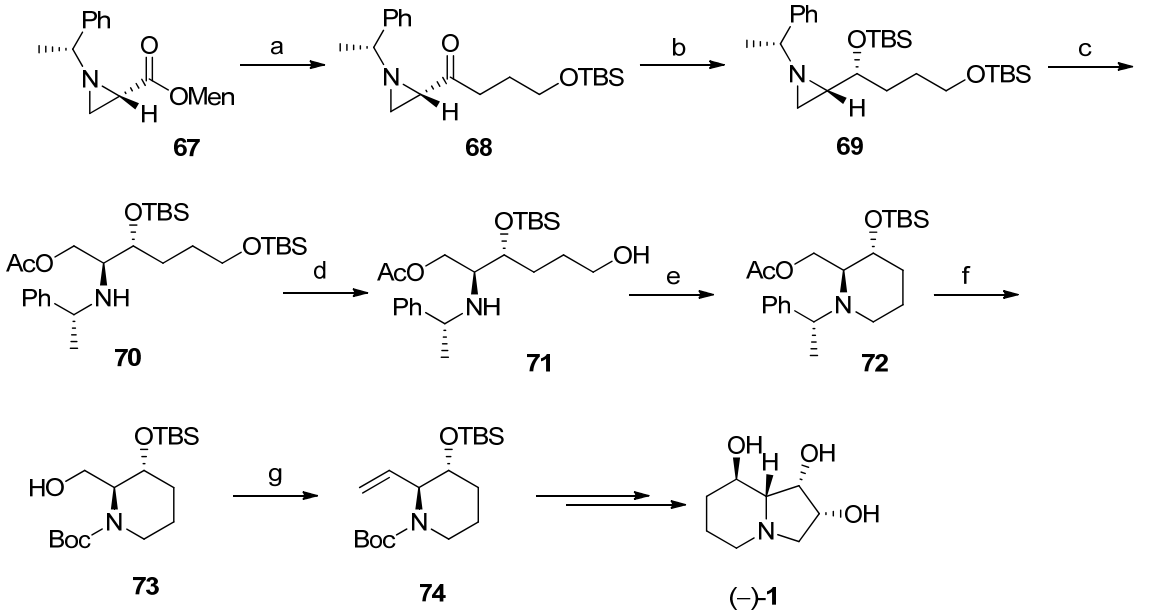


Scheme 9. ***Reagents and conditions:*** *(a)* ***66****, NCS, I_2, K_2CO_3, PhMe, −78°C, 86% (90% ee); (b) 1) $SnCl_2$, PhSH, Et_3N, MeCN, rt; 2) NaOAc, EtOH, reflux; (c) $(Boc)_2O$, $NaHCO_3$, H_2O, MeOH, rt, 80% (for steps b–d); (d) $RuCl_3{\cdot}3H_2O$, $NaIO_4$, CCl_4,H_2O, MeCN ,rt, 65%; (e) 1) TMSI, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C; 2) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C; 3) NaH, THF, 0°C, 88%; f) LDA (3 equiv), PhSeBr (1 equiv), THF, −78°C, then 2,6-di-tertbutyl-4-methylphenol, −78°C, 74%; (g) 1) $LiAlH_4$, $AlCl_3$, THF, −78°C, 97%; 2) $NaIO_4$, $NaHCO_3$, H_2O, MeOH, 0°C, 91%.*

When **61** was subjected to the oxidation conditions using $RuCl_3{\cdot}3H_2O/NaIO_4$, it gave 65% of the pyrrolidinone **62**. For the synthesis of swainsonine, compound **62** was treated with TMSI in the presence of BF_3–etherate to open the tetrahydrofuranyl ring. The resultant hydroxyl iodide was silylated, the carbamate group of which was concomitantly deprotected, and then cyclized to render the requisite indolizidinone **63** in 88% overall yield. Then compound **63** was phenylselenylated using LDA/PhSeBr to provide compound **64** (3:1 mixture of α and β) in 74% combined yield. After separation, α-**64** was reduced to indolizidine with alane generated *insitu* from $LiAlH_4$ and $AlCl_3$, and oxidatively eliminated to produce the known indoline **65** in 88% overall yield, which was readily converted to (−)-swainsonine **1** *via* stereoselective dihydroxylation.

Lee's approach

A formal synthesis of enantiomerically pure (−)-swainsonine **1** was successfully achieved using Intramolecular cyclization of the amino alcohol **71** which was derived from a readily available 1-(*R*)-α-methylbenzylaziridine-2-carboxylic acid (−)-menthol ester **67** (Scheme 10).[20] Compound **68** is readily available by application of general synthetic methods from the (2*S*)-aziridine carboxylic acid (−)-menthol ester **67**, *via* the Weinreb amide. The chelation-controlled reduction of the 2-acylaziridine **68** by$NaBH_4$ in the presence of $ZnCl_2$ was followed by protection of the secondary alcohol moiety to provide



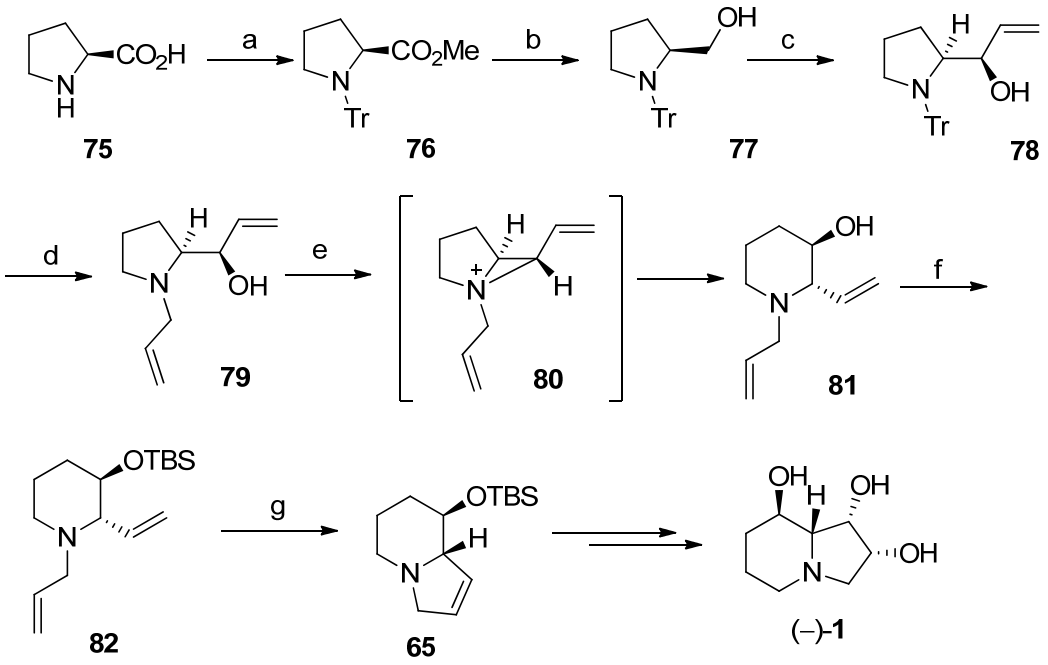
Scheme 10. ***Reagents and conditions:*** *(a) 1) N,O-dimethylhydroxylamine hydrochloride, i-PrMgCl, THF, 0 °C, 95%; 2) Mg, (3-bromopropoxy)-tert-butyl-dimethylsilane, THF, reflux, 67%; (b)1) $NaBH_4$, $ZnCl_2$, MeOH, −78°C, 94% (>99:1); 2) TBSCl, DMAP, CH_2Cl_2, 0°C to rt, 99%; (c) AcOH, CH_2Cl_2, rt, 88%; (d) AcOH/H_2O/THF = 3:1:1, rt, 90%; (e) MsCl, Et_3N, CH_2Cl_2, 0°C to rt, 61%; (f) 1) H_2, $Pd(OH)_2$, $(Boc)_2O$, MeOH, rt; 2) KOH, MeOH, rt; (g) 1) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C; 2) $MePPh_3Br$, LiHMDS, THF, 0°C, 46% (over 4 steps).*

69 in 99% yield. The regioselective ring-opening reaction of the resulting protected diol **69** with AcOH in CH_2Cl_2 at room temperature provided the ring-opening product **70** in 88% yield. Then, deprotection of the primary silyl ether in **70** was selectively achieved by reaction with AcOH/H_2O/THF (3:1:1) at room temperature, to give **71**. The primary alcohol of **71** was activated, after which the mesylate was transformed into the substituted-piperidine**72** in 61% yield *via* intramolecular cyclization under the hydrogenation reac-

tion conditions in the presence of 30% $Pd(OH)_2/C$ followed by reaction of the resulting disubstituted piperidine with $(Boc)_2O$ in methanol. Then the acetyl group was quantitatively hydrolyzed by KOH in methanol at room temperature to provide 2-hydroxymethyl-*N*-Boc-piperidine **73**. The Swern oxidation of the primary alcohol **73** provided the piperidine-2-carbaldehyde which, by Wittig olefination with methylenetriphenylphosphorane at 0 °C, provided the desired vinylpiperidine **74** in 46% overall yield from **73** which constitutes the formal synthesis of (−)-swainsonine **1**.

Cossy's approach

Formal synthesis of (−)-swainsonine **1** has been developed from L-proline by using a diastereoselective addition of vinyl Grignard reagent on *N*-trityl-prolinal, an enantioselective ring expansion of a substituted prolinol into a 3-hydroxypiperidine *via* an aziridinium ion, and a ring closing metathesis as the key steps by Cossy's group.[21] The synthesis of (−)-swainsonine **1** started with the preparation of prolinol **77**, obtained in four steps from L-proline. After esterification and *N*-alkylation by using trityl chloride, amino-ester **76** was obtained in 90% yield. A reduction by $LiAlH_4$ in THF gave prolinol **77** which on Swern oxidation, followed by the addition of vinylmagnesium chloride gave allylic alcohol **78** with a diastereomeric excess superior to 98:2 (88% yield). The trityl group in prolinol **78** was removed and replaced by an allyl group to produce the substituted prolinol **79** in 50% yield. Treatment of prolinol **79** under the ring enlargement conditions provided, after saponification, 3-hydroxy-piperidine **81** in 95% yield with a diastereomeric excess superior to 95%. The free hydroxy group at C3 was protected as a TBS ether group and piperidine **82** was isolated in 70% yield (Scheme 11). For ring closing metathesis, piperidine **82** was transformed to the ammonium salt by treatment with camphorsulfonic acid followed by the ring closing metathesis using first generation Grubbs' catalyst to give the unsaturated indolizidine **65** in 82% yield. This approach constitutes a formal synthesis of (−)-swainsonine **1** in 14 steps from L-proline with an overall yield of 14%.

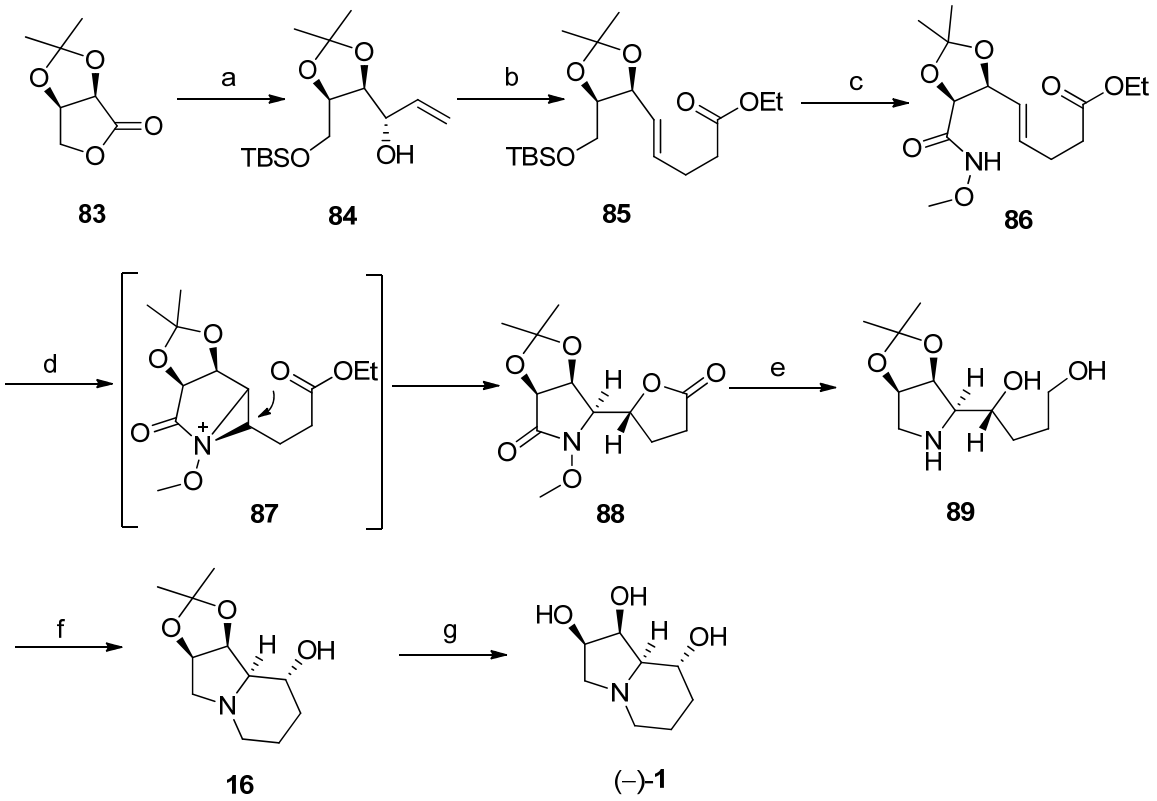


Scheme 11. ***Reagents and conditions:*** *(a) 1)$SOCl_2$, MeOH;2)Ph_3CCl, Et_3N, $CHCl_3$, 90%; (b) $LiAlH_4$, THF; (c) 1) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; 2) Vinylmagnesium bromide, Et_2O, -78 °C, 88%; (d) 1) HCl, Et_2O; 2) Allyl bromide, K_2CO_3, n-Bu_4NBr, toluene, 50%; (e) 1) TFAA, Et_3N, THF, reflux, 95%; 2) NaOH; f) TBSCl, DMAP, CH_2Cl_2, 0 °C to rt, 70%; (g) Grubbs' Ist gen. cat, CSA, CH_2Cl_2, reflux, 2) K_2CO_3 82%.*

Wardrop's approach

The total synthesis of (−)-swainsonine **1** from 2,3-*O*-isopropylidene-D-erythrose in 12 steps and an overall yield of 28% is reported by Wardrop's group. The pivotal transformation in this route to indolizidine alkaloid **1** is the formation of the pyrrolidine ring and C-8a/8 stereodiad through the diastereoselective, bis-cyclofunctionalization of an γ,δ-unsaturated *O*-alkyl hydroxamate **86**.[22] Synthetic route to (−)-swainsonine **1** began from 2,3-*O*-isopropylidene-D-erythronolactone **83**. Reduction of **83** with DIBAL-H yielded the corresponding D-erythrose derivative, which through stereoselective addition of vinylmagnesium bromide and selective *O*-silylation of the primary alcohol was converted to allylicalcohol **84** in excellent overall yield. Upon heating with trimethylorthoacetate in the presence of propionic acid, compound **84** underwent Johnson-Claisen rearrangement to provide *β*,*γ*-unsaturated ester **85** as the *E*-isomer. Compound **85** was then converted to

O-alkyl hydroxamate **86**. Cyclization of substrate **86** was accomplished by treatment with $PhI(OCOCF_3)_2$ and TFA to provide a bis-cyclization product **88**.

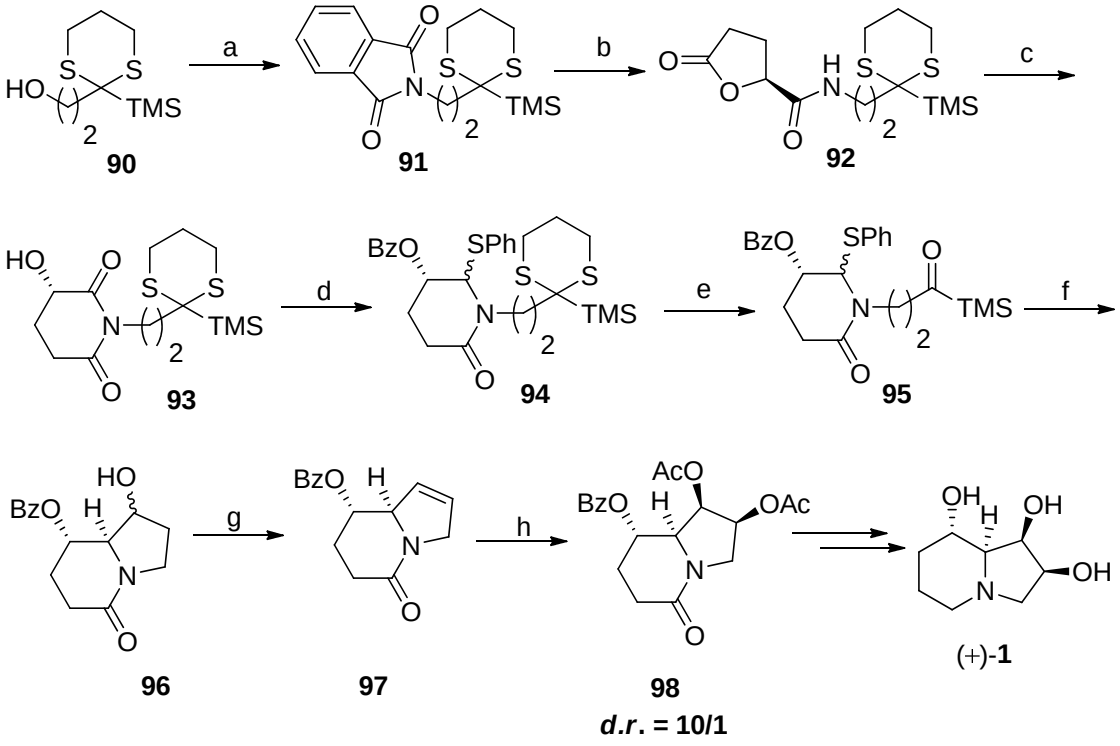


Scheme 12. ***Reagents and conditions:*** *(a) 1) DIBAL-H, CH_2Cl_2, −78°C; 2) Vinylmagnesium bromide, THF; 3) TBSCl, DMAP, CH_2Cl_2, 0 °C to rt, 71%; (b) $CH_3C(OCH_3)_3$, Et-CO_2H, 110 °C, 99%; (c) 1) TBAF, THF; 2) DMP, CH_2Cl_2; 3) $NaClO_2$, NaH_2PO_4; 4) iBuOCOCl, Et_3N, $MeONH_2$·HCl; d) $PhI(OCOCF_3)_2$, TFA, CH_2Cl_2, 0 °C, 60%; (e) $LiAlH_4$, 1,4-dioxane, reflux, 85%; (f) CBr_4, PPh_3, Et_3N, CH_2Cl_2, 88%; (g) aq. HCl, THF, rt, 96%.*

This transformation is believed to proceed *via* the intramolecular capture of an *N*-acyl-*N*-alkoxyaziridinium ion **87** generated by the diastereoselective addition of a singlet acylnitrenium ion to the pendant alkene. Reaction of **88** with $LiAlH_4$ leads to the reduction of allthree functional groups and formation of 1-amino-2,5-diol **89** in excellent yield. Formation of the indolizidine ring system was accomplished through use of an Appel reaction to generate **16**. Finally, removal of the acetonide group, using 6M HCl provided (−)-swainsonine **1**.

Tsai's approach

The synthesis of (+)-swainsonine (*ent*-**1**) was achieved using intramolecular free radical cyclization as key step by Tsai's group. As shown in Scheme 13, Mitsunobu coupling of alcohol **90** with phthalimide afforded imide **91** in 95% yield.[23] Imide **91** was deprotected by hydrazine to produce the crude amine and then reacted with (*S*)-5-oxotetrahydrofuran-2-carbonyl chloride to provide lactone **92** (65%). Rearrangement of lactone **92** to glutarimide **93** was achieved *via* potassium *tert*-butoxide treatment at low temperature in 91% yield. Sodium borohydride reduction of glutarimide **93** selectively reduced the more reactive carbonyl group, and then reaction of the crude carbinol with thiophenol under acidic condition followed by protection of the hydroxyl group as a benzoate gave compound **94**.



Scheme 13. ***Reagents and conditions:*** *(a) PPh_3, DIAD, phthalimide, 95%; (b) Hydrazine, Et_3N, 65%; (c) (S)-5-oxotetrahydrofuran-2-carbonyl chloride, t-BuOK, 91%; (d) 1) $NaBH_4$; 2) p-TsOH, PhSH; 3) BzCl, DMAP, 70%; (e)$PhI(OCOCF_3)_2$, 80%; (f) 1) Bu_3SnH, ACCN;2) TBAF, 86%; (g) Martin sulfurane, 73%; (h) 1) OsO_4, NMO; 2) Ac_2O, DMAP, 55%.*

Hydrolysisof the dithiane moiety of **94** using $PhI(OCOCF_3)_2$ gave acylsilane **95**. Radical cyclization reaction of **95** proceeded with TBTH and catalytic amount of 1,10-

azobis(cyclohexanecarbonitrile) (ACCN) in refluxing toluene to produce diastereomeric mixture of crude silyl ethers that was desilylated to afford corresponding mixture of alcohols **96**. Dehydrationof the alcohol mixture **96** by Martin sulfurane gave a 73% yield of olefin **97**. Dihydroxylation of **97** was accomplished by catalytic amount of osmium tetroxide in the presence of NMO and the resulting crude diol was acetylated to give ester **98**. Borane reduction of **98** followed by removal of the ester groups of **98** by sodium hydroxide treatment in methanol afforded (+)-swainsonine *ent*-**1**.

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Chapter 2: Synthetic studies toward *trans*-(2*R*,3*R*)-3-hydroxypipecolic acid and (−)-swainsonine

Section 4: Formal synthesis of (−)-swainsonine

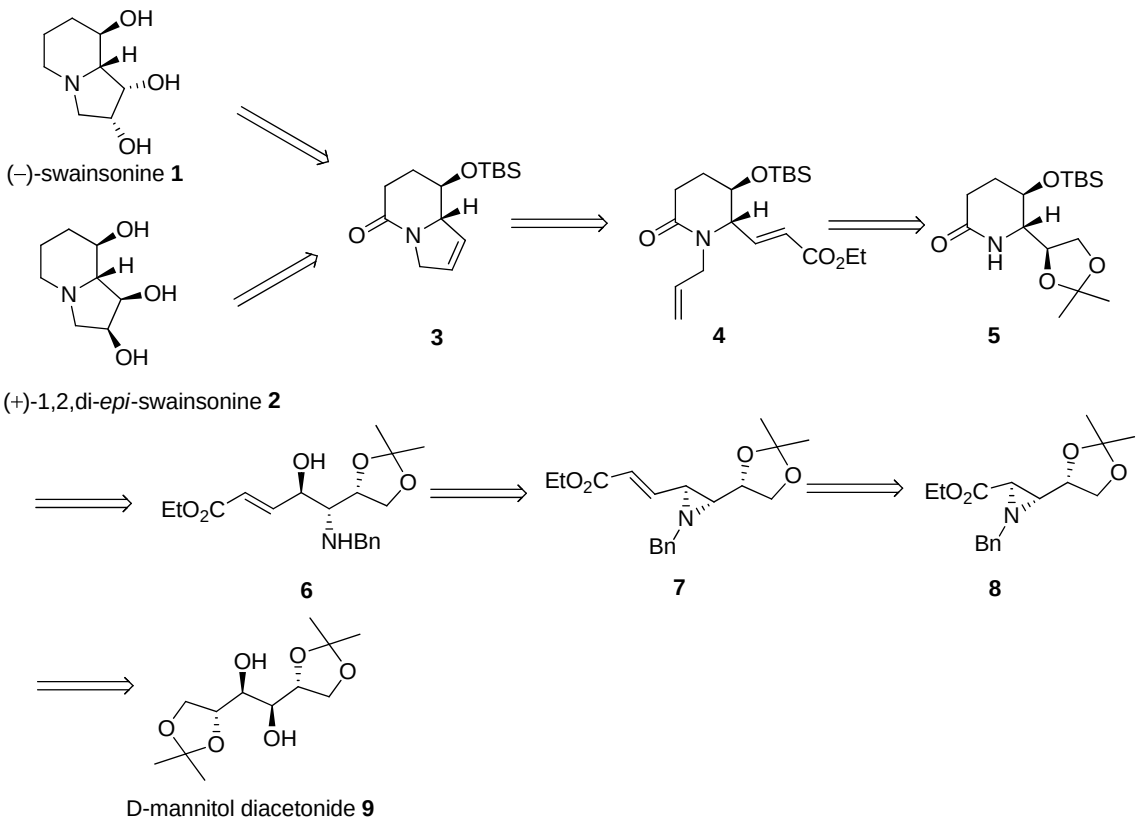
2.4.1 Present work

2.4.1.1 Objective

Since its isolation, (–)-swainsonine **1** has proven a highly popular target of both total and formal syntheses.[1] Furthermore, the search for more potent glycosidase inhibitors, which display improved GMII *vs* LM selectivity, has spurred the preparation of a large number of analogues. Swainsonine has recently been the subject of a process research study which further underscores the continued relevance of this natural product as a synthetic target.[2] As part of this group's effort toward an efficient syntheses of pharmaceutically important molecules,[3] this group was attracted towards the efficient synthesis of (−)-swainsonine **1** from commercially available and cheap starting material. A modern synthetic design demands better yielding sequences coupled with mild reaction conditions, high stereoselectivity as well as versatile template that could be used as platform to launch other analogues simultaneously from readily available starting materials. Keeping these features in mind, an efficient route to **1** and its analogue **2** has been chosen from D-mannitol diacetonide as a starting material for the synthetic endeavor because of its ready availability in enantiopure form.

2.4.1.2 Retrosynthetic analysis

From a retrosynthetic perspective, it was envisioned that the indolizidine skeleton of **1** and **2** could be generated from stereoselective/stereocontrolled dihydroxylation of the unsaturated bicyclic lactam **3**[4] which can be accessed by ring closing metathesis reaction[5] of compound **4** (Scheme 1). This di-alkene **4** can be easily prepared through *N*-allylation, selective deprotection of acetonide group, diol cleavage and Wittig reaction of lactam **5**. On the basis of our previous studies it was anticipated that this lactam **5** can be obtained from *γ*-hydroxy-*δ*-amino-*α*,*β*-conjugated ester **6** *via* *α*,*β*-unsaturated aziridine ester **7** by nucleophilic ring opening reaction using water as the nucleophile under acidic conditions which in turn can be accessed from aziridine-2-carboxylate **8**. Finally, aziridine-2-carboxylate **8** can be synthesized from commercially available and cheap starting material like D-mannitol diacetonide **9**.

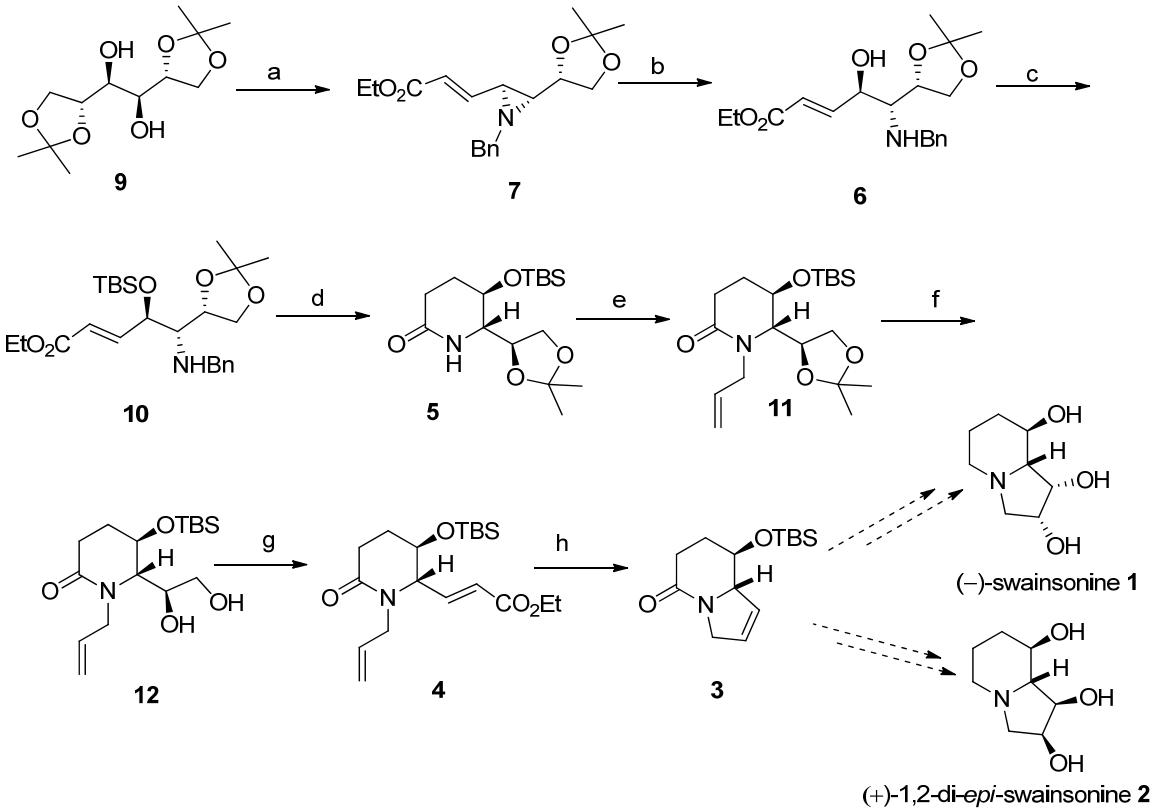


Scheme 1: Retrosynthetic analysis of (-)-swainsonine**1** and (+)-1,2-di-*epi*-swainsonine **2**.

2.4.1.3 Results and discussion

This section describes the formal synthesis of (–)-swaisonine **1**. As shown in Scheme 2, its synthesis started from D-mannitol diacetonide **9** as described previously *via* aziridine-2-carboxylate **8** whose acetonide moiety was kept intact as a masked aldehyde while ester group was propagated to give *trans*-aziridine-*α,β*-unsaturated ester **7** in five steps and 43% overall yield (Chapter 1, Section 2, Scheme 14 and 21). Following the aziridine ring opening reaction under acidic conditions, compound **7** gave aziridine ring opened product **6**. Its IR spectrum showed peak at 3453 cm^{-1} indicating hydroxy functinality. Its ^1H NMR spectrum showed disappearance of peak at δ 2.12 (dd, 1H), 2.72 (dd, 1H) and appearance of characteristic peaks at δ 2.74 (dd, 1H) and 4.55 (dd, 1H) indicating *γ*-hydroxy,*δ*-amino,*α,β*-unsaturated ester functionality. Other peaks appeared at expected positions. The DEPT-NMR spectrum also showed disappearnce of peaks at δ 40.1, 49.6 and

appearance of new peaks at δ 61.3 and 67.3 corrosponding to –CH group clearly suggesting the ring opening of aziridine **7**. Finally HRMS analysis affirmed the molecular formula (calculated for $C_{19}H_{28}O_5N$-350.1962, found-350.1967) of compound **6**.



Scheme 2. ***Reagents and conditions:*** *(a) 1) $NaIO_4$, aq. $NaHCO_3$, CH_2Cl_2; 2) $Ph_3PCBrCO_2Et$, CH_2Cl_2, 84% over two steps; 3) $BnNH_2$, Et_3N, toluene, 0ºC to rt, 68%; 4) DIBAL-H (1M in toluene), CH_2Cl_2, -78˚C, 1h; 5) $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0 ˚C, 2h, 75% over 2 steps; (b) TFA, CH_3CN:H_2O (9:1), 0 °C to rt., 80%; (c) TBSCl, Im, cat. DMAP, CH_2Cl_2, reflux, 90%; (d) H_2, 10% $Pd(OH)_2$/C, MeOH, 92%; (e) NaH, allyl bromide, cat. TBAI, DMF, 85%; (f) Aq. 80% AcOH, 80 °C, 75%; (g) 1) $NaIO_4$, acetone:water; 2) $Ph_3PCHCO2Et$, CH_2Cl_2, 75% over 2 steps; (h) Grubbs' 2nd gen. catalyst, CH_2Cl_2, reflux, 80%.*

Hydroxyl functionality of this amino-alcohol **6** was protected selectively using TBSCl, imidazole and cat. DMAP in refluxing dichloromethene to give TBS ether **10** in 90% yield. The ^{1}H NMR spectrum of compound **10** showed peaks at δ 0.04 (s,3H), 0.09 (s,3H) and 0.91 (s, 9H) corresponding to -OTBS group.

In next step, compound **10** was subjected to hydrogenation/hydrogenolysis condition using 10% $Pd(OH)_2/C$ in MeOH to afford lactam **5** in 92 % yield *via* one-pot concomitant double bond reduction, debenzylation and cyclisation. A characteristic strong band at 1670 cm^{-1} in its IR spectrum clearly indicated the formation of amide carbonyl. Its ^{1}H-NMR spectrum showed broad singlet at δ 6.02 corresponding to a characteristic peak of lactam proton. Its ^{13}C-NMR spectrum showed a peak at δ 170.6 indicating the presence of lactam carbonyl. Finally, HRMS analysis of lactam **5** provided further substantiation for its molecular formula (calculated for $C_{16}H_{32}O_4NSi$-330.2095, found-330.2095).

Allylation of lactam **5** was carried out in next step using allyl bromide and NaH in DMF as solvent to give *N*-allylated compound **11** in 85% yield. IR spectrum of compound **11** showed strong absorption peak at 1633 cm^{-1} indicating the presence of lactam carbonyl. In its ^{1}H NMR spectrum, disappearance of lactam proton at δ 6.02 and appearance of additional peaks at 4.02 (m, 2H), 4.90 (m, 1H), 5.16 (m, 2H) and 5.61-5.81 (m, 1H) corrosponding to *N*-allyl moiety were observed. In ^{13}C NMR spectrum, appearance of additional peaks at δ 48.4 (*N*-CH_2), 117.1 (-CH) and 133.41 (-CH_2) further ascertained the presence of *N*-allyl group. Its mass spectrum showed molecular ion peaks at *m/z* 356.41 $[M+H]^+$ confirming the formation of **11**. In next step, the lactam **11** was exposed to 80% aqueous acetic acid at 80 °C to furnish diol **12** by selective deprotection of terminal acetonide functionality in presence of secondary –OTBS group in 75% yield.[6] Disappearance of peaks at δ1.35 and 1.43 and presence of peaks at *δ* 0.06 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H) corrosponding to TBS group in its^{1}H NMR spectrum clearly indicated the selective deprotection of acetonide functionality over -OTBS group. In ^{13}C NMR spectrum, disappearance of peaks at δ 25.5, 26.6 and 109.6 corresponding to acetonide group supported the formation of diol **12**. Its mass spectrum showed molecular ion peak at *m/z* 352.41 $[M+Na]^+$ thus validating the formation of **12**.

Diol **12** was cleaved using $NaIO_4$ in acetone:water to furnish crude aldehyde which was subjected without purification to 2-carbon Wittig homologation in dichloromethane to yield *α,β*-unsaturated ester **4** in 75% yield over two steps. IR spectrum of compound **4** showed strong absorption band at 1723 cm^{-1} indicating ester carbonyl functionality. Its ^{1}H NMR spectrum showed peaks at δ 1.30 (t, 3H), 4.19 (q, 2H), 5.88 (dd, *J* = 1 and 16 Hz, 1H), 6.73 (dd, *J* = 6 and 16 Hz, 1H) pointing towards the formation of *α,β*-

unsaturated ethyl ester. The magnitude of *J* values indicated the exclusive formation of *E*-isomer. Appearance of peaks at δ 14.2 (-CH_3), 60.7 (-CH_2), 123.9, 144.5 (-CH) and 165.40 (-CO-) in its ^{13}C NMR and DEPT spectra ascertained the presence of *α,β*-unsaturated ethyl ester. Lastly MS(ESI) analysis revealed a peak at *m/z* 390.12 $[M+Na]^+$ and HRMS analysis peak at 368.2247 (calculated for $C_{19}H_{34}O_4NSi$-368.2252) validated the formation of diene **4**.

Finally performing the ring closing metathesis reaction on compound **4** using Grubbs' 2nd generation catalyst in refluxing anhydrous dichloromethane gave access to key intermediate *viz.* bicyclic lactam **3**. IR spectrum of lactam **3** showed strong absorption bands at 1640 and 1620 cm^{-1} indicating the presence of amide and double bond functionality. ^{1}H NMR spectrum showed disappearance of peaks corresponding to *α,β*-unsaturated ethyl ester and appearance of peak at δ 5.93 (m, 2H) indicating formation of alkene group. ^{13}C and DEPT spectra of compound **3** showed peaks at δ 126.8 and 128.5 for two alkene –CH groups along wtih peaks at δ −4.6, -4.1, 18.0 and 25.7 (for TBS group), 29.7 (-CH_2), 30.28 (-CH_2), 53.33 (-*N*-CH_2), 69.16 (-CH-N), 71.15 (-CH-O) and 168.29 (-CO-) confirming the formation of desired unsaturated indolizidine skeleton of compound **3**. MS(ESI) analysis revealed a peak at *m/z* 268.02 $[M+H]^+$ and HRMS analysis peak at 268.1741 (calculated for $C_{14}H_{26}NO_2Si$-268.1733) firmly substantiated the formation of unsaturated indolizidine **3**.

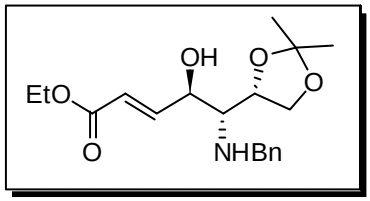
Enantiomer of **3** and its convertion to ***ent*-1**[4] and ***ent*-2**[4b] is well documented in the literature. The spectral data of **3** were in good agreement with the reported one except for the sign of optical rotation {$\mathbf{[\alpha]_D^{25}}$ +53 (*c* 1, $CHCl_3$); lit[4b] for *ent*-**3**-$\mathbf{[\alpha]_D^{25}}$ −53.73 (*c* 1.10, $CHCl_3$)}.

2.4.2 Conclusion

In conclusion, the present work constitutes an efficient formal synthesis of (–)-swainsonine **1** and (+)-1,2,di-*epi*-swainsonine **2** employing aziridines ring opening and ring closing metathesis reactions as the key steps from commercially available and cheap starting material D-mannitol diacetonide. Synthesis of (−)-swainsonine **1** was achieved in 11 purification steps with 9% overall yield.

2.4.3 Experimental

(4*R*,5*R*,*E*)-Ethyl 5-(benzylamino)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-hydroxypent-2-enoate(6)



To a stirred solution of ester **7** (1.4 g, 4.2 mmol) in CH_3CN: water (9:1, 25 mL) was added TFA (0.64 mL, 8.4 mmol) dropwise at 0 ºC. The reaction mixture was slowly warmed to room temperature and stirred until complete disappearance of starting material (~ 5-6 h). Reaction was quenched by addition of excess $NaHCO_3$, water (10 mL) was added and organic mass was extracted with ethyl acetate (3 × 20 mL). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure followed by column chromatographic purification using ethyl acetate-pet ether (15:85) to yield 1.11 g of amino-alcohol **6** as thick liquid.

***R*$_f$:** 0.5 (Pet ether-ethyl acetate, 1:1).

Yield: 80%.

MF: $C_{19}H_{27}NO_5$, **MW:** 349.40.

IR ($CHCl_3$, cm^{-1}): νmax 3453, 2985, 1717, 1656, 1455, 1370, 1263, 1175.

$[\alpha]_D^{25}$ −50 (*c* 1.8, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.29 (t, *J* = 7.0 Hz, 3H), 1.32 (s, 3H), 1.39 (s,3H), 2.74 (dd, *J* = 3.6 & 5.4 Hz, 1H), 3.77-4.03 (m, 4H), 4.1-4.26 (m, 3H), 4.55 (dd, *J* = 3.6 & 5.4Hz, 1H), 6.2 (dd, *J* = 2 & 15.6 Hz, 1H), 6.9 (dd, *J* = 3.7 & 15.6 Hz, 1H), 7.26-7.34 (m, 5H).

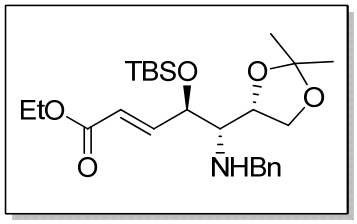
^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 25.1, 26.3, 51.0, 60.3, 61.3, 67.3, 69.0, 74.9, 109.0, 121.3, 127.1, 128.1, 128.4, 139.5, 147.0, 166.1.

MS (ESI):*m/z*: 372.14 $[M+Na]^+$.

HRMS: Calculated for $C_{19}H_{28}O_5N$-350.1962, found 350.1967.

(4*R*,5*S*,*E*)-Ethyl 5-(benzylamino)-4-((tert-butyldimethylsilyl)oxy)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-2-enoate (10)

To a stirred solution of hydroxyl amino ester **6** (1 g, 4.22 mmol), imidazole (0.4 g, 6 mmol) and DMAP (0.0.24 g, 0.2 mmol) in CH_2Cl_2 (20 mL) was added TBSCl (1.27 g, 8.44 mmol) dissolved in CH_2Cl_2 (5 mL) slowly at 0°C after which reaction was heated to



reflux for 6 h until completion of reaction. Reaction mass was concentrated under reduced pressure followed by column chromatography using ethyl acetate: pet ether (5:95) to yield 0.84 g of -OTBS protected amino-alcohol **10** as thick colourless liquid.

***R*$_f$:** 0.5 (Pet ether-ethyl acetate, 1:9).

Yield: 90 %.

MF: $C_{25}H_{41}NO_5Si$, **MW:** 463.68.

IR ($CHCl_3$, cm^{-1}): vmax 2984, 2931, 1721, 1657, 1472, 1369, 1260, 1160, 1059.

$[\alpha]_D^{25}$ +11.11 (*c* 2.7, $CHCl_3$).

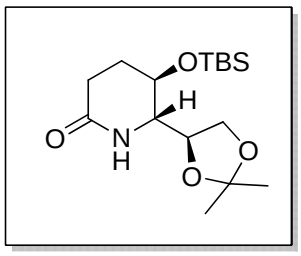
^{1}HNMR (200 MHz, $CDCl_3$+CCl_4): δ 0.04 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.31 (t, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 2.72 (br s, 1H), 3.70 (t, *J* = 7.7 Hz, 1H), 3.84-4.04 (m, 1H), 4.22 (q, 2H), 4.29-4.46 (m, 2H), 6.08 (dd, *J* = 1.4 & 15.6 Hz, 1H), 7.1 (dd, *J* = 5.2 & 15.6 Hz, 1H), 7.25-7.36 (m, 5H).

^{13}C NMR(50 MHz, $CDCl_3$): δ −4.9, −4.5, 14.1, 18.1, 25.2, 25.8, 26.8, 53.1, 60.3, 63.7, 66.9, 73.3, 75.5, 108.8, 121.4, 126.9, 128.2, 149.0, 166.2.

MS (ESI): *m/z*: 486.27 $[M+Na]^+$.

HRMS: Calculated for $C_{25}H_{42}O_5NSi$-464.2827, found-464.2847.

(5*R*,6*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)piperidin-2-one (5)



A suspension of **10** (0.9 g, 1.94 mmol) and 10% $Pd(OH)_2/C$ (60 mg) in MeOH (20 mL) was stirred under a H_2 atmosphere at room temperature for 2.5 h, filtered through Celite and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/Pet ether = 1:3) to afford **5**(0.59 g) as a colorless thick liquid.

***R*$_f$:** 0.4 (Pet ether-ethyl acetate, 1:1).

Yield: 92 %.

MF: $C_{16}H_{31}NO_4Si$,**MW:** 329.51

IR ($CHCl_3$, cm^{-1}): vmax 3408, 2927, 1670, 1457, 1380, 1216.

$[\alpha]_D^{25}$ –22.9 (*c* 1.15, $CHCl_3$).

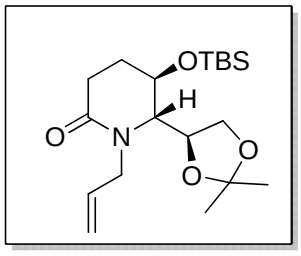
^{1}HNMR (400 MHz, $CDCl_3$+CCl_4): δ 0.1 (s, 3H), 0.11 (s, 3H), 0.91 (s, 9H), 1.34 (s, 3H), 1.41 (s, 3H), 1.78-1.87 (m, 1H), 1.94-2.01 (m, 1H), 2.29-2.38 (m, 1H), 2.47-2.85 (m, 1H), 3.20 (t, *J* = 7 Hz, 1H), 3.72-3.77 (m, 1H), 3.84 (dd, *J* = 5 & 8 Hz, 1H), 4.00-4.1 (m, 2H), 6.02 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ –4.5, –4.1, 17.9, 25.2, 25.8, 26.6, 28.5, 29.1, 61.7, 67.2, 68.1, 76.3, 109.3, 170.6.

MS (ESI): *m/z*: 352.18 $[M+Na]^+$.

HRMS: Calculated for $C_{16}H_{32}O_4NSi$-330.2095, found-330.2095.

(5*R*,6*S*)-1-Allyl-5-((*tert*-butyldimethylsilyl)oxy)-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)piperidin-2-one (11)



To the NaH (0.044 g, 1.8 mmol, prewashed with dry *n*-hexane) in DMF (2 mL) was added amide **5** (0.4 gm, 1.21 mmol) in DMF (2 mL) dropwise at 0 ºC and stirred for 1 h at room temperature. Allyl bromide (0.154 mL, 1.8 mmol) was added dropwise at 0 ºC. The resulting reaction mixture stirred for 3-4 h at room temperature. Reaction mixture was then quenched using water (20 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organics washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was column purified on flash chromatography (pet ether-ethyl acetate, 7:3) to afford the allylated product **11** as colorless liquid.

***R_f*:** 0.4 (Pet ether-ethyl acetate, 1:2).

Yield: 0.357 g, 85%.

MF: $C_{19}H_{37}NO_3Si$, **MW:** 355.59.

IR ($CHCl_3$, cm^{-1}): vmax 2986, 1630, 1420, 1107.

$[\alpha]_D^{25}$ –83.4 (*c* 1, $CHCl_3$).

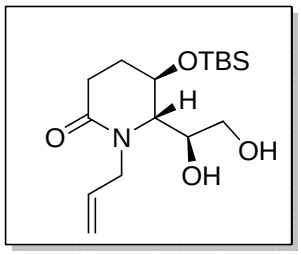
^{1}HNMR (200 MHz, $CDCl_3$+CCl_4): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 1.35 (s, 3H), 1.43 (s, 3H), 1.88-1.92 (m, 4H), 2.33-2.44 (m, 1H),), 2.53-2.67 (m, 1H), 3.33-3.37 (m, 1H), 3.54-3.75 (m, 3H), 4.03-4.05 (m, 2H), 4.9 (m, 1H), 5.11-5.24 (m, 2H), 5.61-5.81 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ –4.9, 17.8, 25.4, 25.5, 25.6, 26.3, 26.5, 48.4, 64.4, 65.4, 66.7, 78.5, 109.6, 117.1, 133.4, 168.8.

MS (ESI): *m/z*: 356.41 $[M+H]^+$.

Elemental analysis: Calcd.:C-61.75; H-9.55; N-3.79; found:C-61.57; H-9.51; N-3.56.

((5*R*,6*S*)-1-Allyl-5-((*tert*-butyldimethylsilyl)oxy)-6-((*S*)-1,2-dihydroxyethyl)piperidin-2-one (12)



Protected lactam **11** (0.2 g, 0.56 mmol) was treated with 80% aqueous acetic acid (2 mL), and the resulting mixture was allowed to react at 80 °C. The reaction was monitored by TLC and was judged to be complete after 3 h. The solution was then diluted with H_2O (8 mL) and extracted with EtOAc (3 × 10 mL). The extracts were treated with saturated $NaHCO_3$ solution, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to give a crude residue that was purified by flash chromatography (pet ether-ethyl acetate, 1:9). Pure terminal diol **12** (0.14 g) was obtained as a thick gummy liquid.

***R_f*:** 0.4 (Ethyl acetate).

Yield: 75 %.

MF: $C_{16}H_{31}NO_4Si$, **MW:** 329.50

IR ($CHCl_3$, cm^{-1}): νmax 3554, 3340, 2986, 1627, 1423, 1107.

$[\alpha]_D^{25}$ –34.9 (*c* 1, $CHCl_3$).

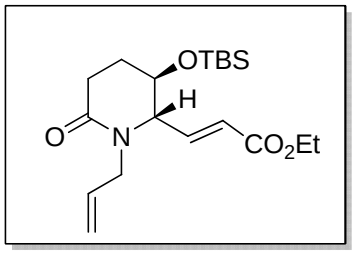
^{1}HNMR (200 MHz, $CDCl_3$+CCl_4): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.99-2.11 (m, 2H), 2.14-2.33 (m, 1H), 2.53-2.63 (m, 1H), 3.35-3.37 (m, 1H), 3.54-3.69 (m, 4H), 3.94 (s, 1H), 4.71-4.77 (m, 2H), 5.26-5.58 (m, 2H), 5.72-5.88 (m, 1H).

^{13}C NMR(100 MHz, $CDCl_3$+CCl_4): –4.8, –4.7, 18.0, 25.3, 25.8, 26.9, 50.3, 64.1, 64.7, 66.1, 73.6, 117.5, 132.8, 171.0.

MS (ESI): *m/z*: 352.23 $[M+Na]^+$.

(*E*)-Ethyl 3-((2*S*,3*R*)-1-allyl-3-((tert-butyldimethylsilyl)oxy)-6-oxopiperidin-2-yl)acrylate (4)

Diol **12** (0.2 g, 0.607 mmol) was dissolved in acetone–water (3 mL, 2:1) at 0 ºC, treated with sodium metaperiodate (0.2 g, 0.9 mmol) and stirred at 15 ºC for 15 min. The



reaction was quenched using ethylene glycol (0.01 mL), extracted with CH_2Cl_2 (3 ×10 mL), washed with brine, dried over anhydrous Na_2SO_4 and filtered. The combined organics were concentrated under reduced pressure to afford crude aldehyde which was used as such for next reaction.

To a solution of aldehyde from above reaction in CH_2Cl_2 (15 mL) was added (carboethoxymethylene) triphenylphosphorane (0.4 g, 1.2 mmol) and the reaction mixture was stirred for 6 h. Solvent was evaporated and the reaction mixture was adsorbed on silica. Purification by column chromatography (pet ether–ethyl acetate, 8:2) gave **4** as a thick liquid (0.167 g).

***R_f*:** 0.5 (Pet ether-ethyl acetate, 1:1).

Yield: 75% over two steps.

MF: $C_{19}H_{33}NO_4Si$, **MW:** 367.55.

IR ($CHCl_3$, cm^{-1}): vmax 2986, 1723, 1656, 1630, 1107.

$[\alpha]_D^{25}$ –45 (*c* 1, $CHCl_3$)

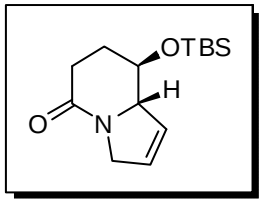
^{1}HNMR (200 MHz, $CDCl_3$+CCl_4): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.30 (t, *J* = *7* Hz, 3H), 1.73-1.75 (m, 1H), 1.86-1.93 (m, 1H),), 2.35 (m, 1H), 2.59-2.68 (m, 1H), 2.99 (dd, *J* = 7 & 16 Hz, 1H), 3.99 (m, 1H), 4.19 (q, *J* = *7* Hz, 2H), 5.84 (dt, *J* = 2 & 16 Hz, 1H), 5.11-5.18 (m, 1H), 5.62-5.72 (m, 1H), 5.88 (dd, *J* = 1 & 16 Hz, 1H), 6.73 (dd, *J* = 6 & 16 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ -4.8, 14.2, 24.8, 25.6, 26.7, 47.3, 60.7, 64.3, 67.0, 117.3, 123.9, 132.3, 144.5, 165.4, 169.1.

MS (ESI) *m/z*: 390.12 $[M+Na]^+$.

HRMS: Calculated for $C_{19}H_{34}O_4NSi$-368.2252, found-368.2247.

(8*R*,8a*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-6,7,8,8a-tetrahydroindolizin-5(3H)-one (3)



The olefinic compound **4** (0.075 g, 0.2 mmol) and Grubbs' 2nd generation catalyst (5 mg, 2 mol %) in anhydrous CH_2Cl_2 (50 mL) was refluxed for 5 h. The reaction mixture was filtered through Celite and concentrated *in vacuo* to provide crude **3**. The

crude product was purified using column chromatography (pet ether-ethyl acetate, 1:1) to provide the ring closed product **29** (0.044 g, 80%) as a colorless sticky liquid.

***R_f*:** 0.4 (Pet ether-ethyl acetate, 1:1).

Yield: 80 %.

MF:$C_{14}H_{25}NO_2Si$, **MW:** 267.43

IR ($CHCl_3$, cm^{-1}): νmax 1640, 1620.

$[\alpha]_D^{25}$ +53 (*c* 1, $CHCl_3$); lit[4b] {for *ent*-$[\alpha]_D^{25}$ –53.73 (*c* 1.10, $CHCl_3$)}.

^{1}HNMR (400 MHz, $CDCl_3$+CCl_4): δ 0.08 (s, 6H), 0.90 (s, 9H), 1.79-1.81 (m, 1H), 2.02-2.03 (m, 1H), 2.39-2.46 (m, 1H), 2.60-2.62 (m, 1H), 3.53-3.55 (m, 1H), 4.02-4.06 (m, 1H), 4.15-4.16 (m, 1H), 4.45-4.50 (m, 1H), 5.92-5.94 (m, 2H).

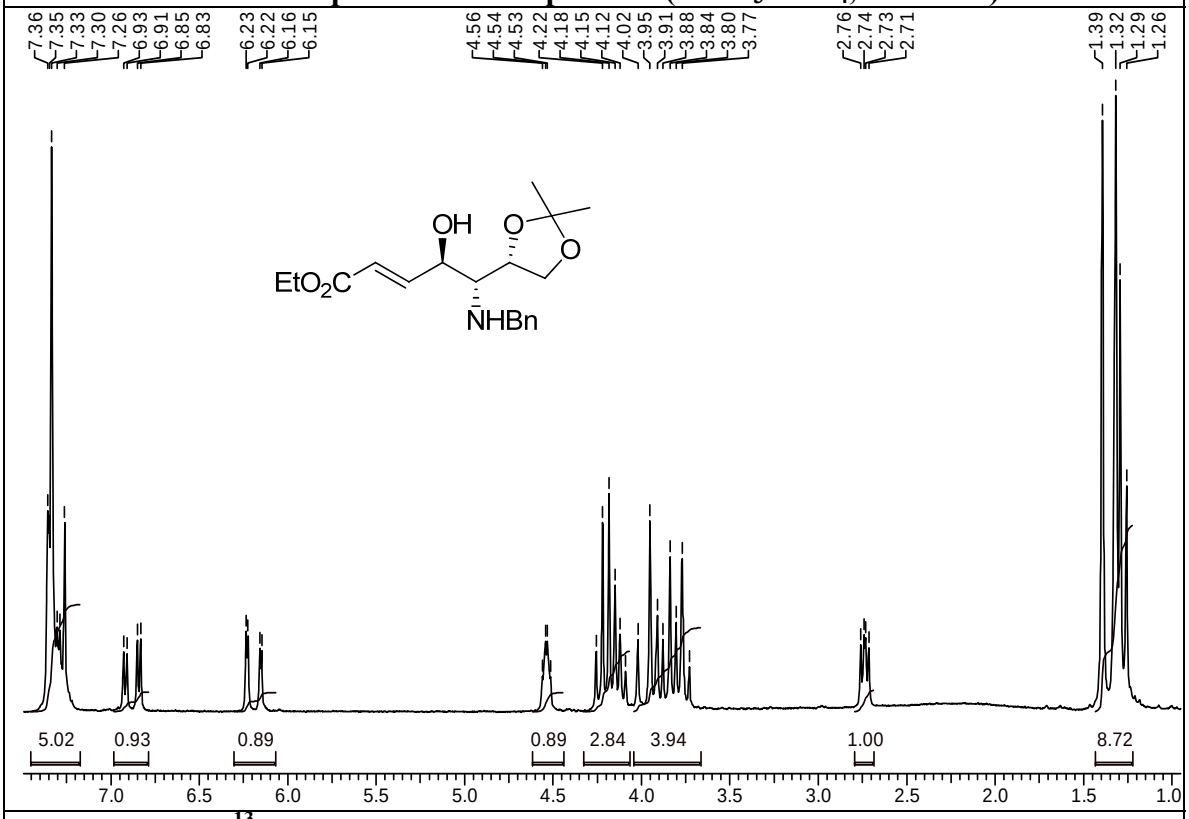
^{13}C NMR(100 MHz, $CDCl_3$+CCl_4): δ −4.6, −4.1, 18.0, 25.7, 29.7,30.2, 53.3, 69.1, 71.1, 126.8, 128.5, 168.2.

MS (ESI): *m/z*: 268.02 $[M+H]^+$.

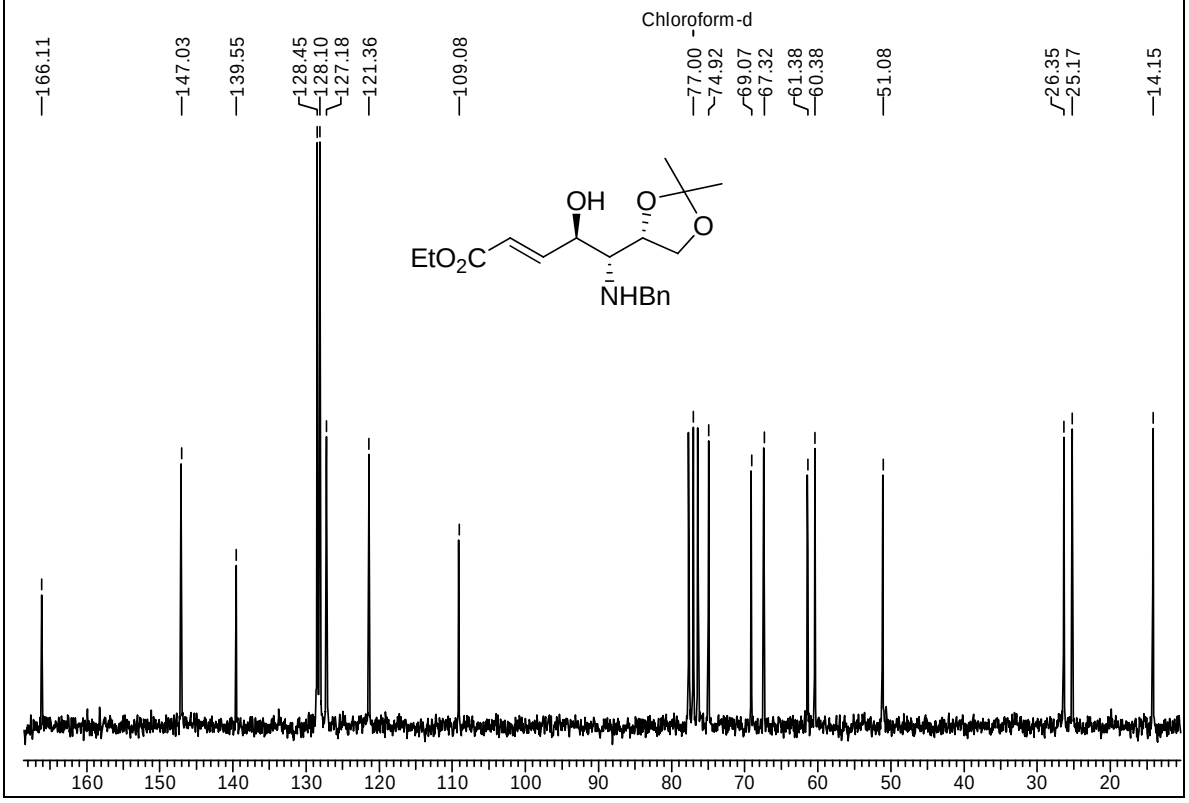
HRMS: Calculated for $C_{14}H_{26}NO_2Si$-268.1733; found-268.1741.

2.4.4 Analytical Data

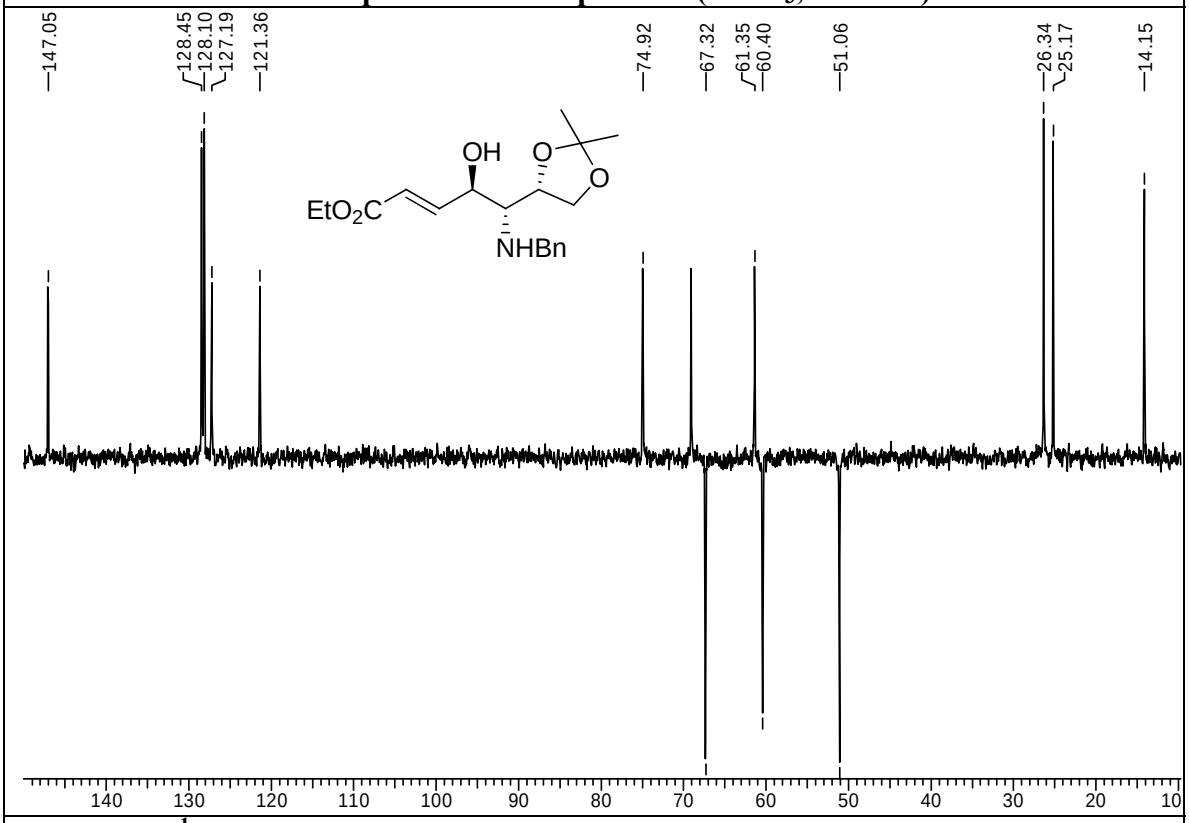
^{1}H-NMR spectrum of compound 6 ($CDCl_3$+CCl_4, 200 MHz)



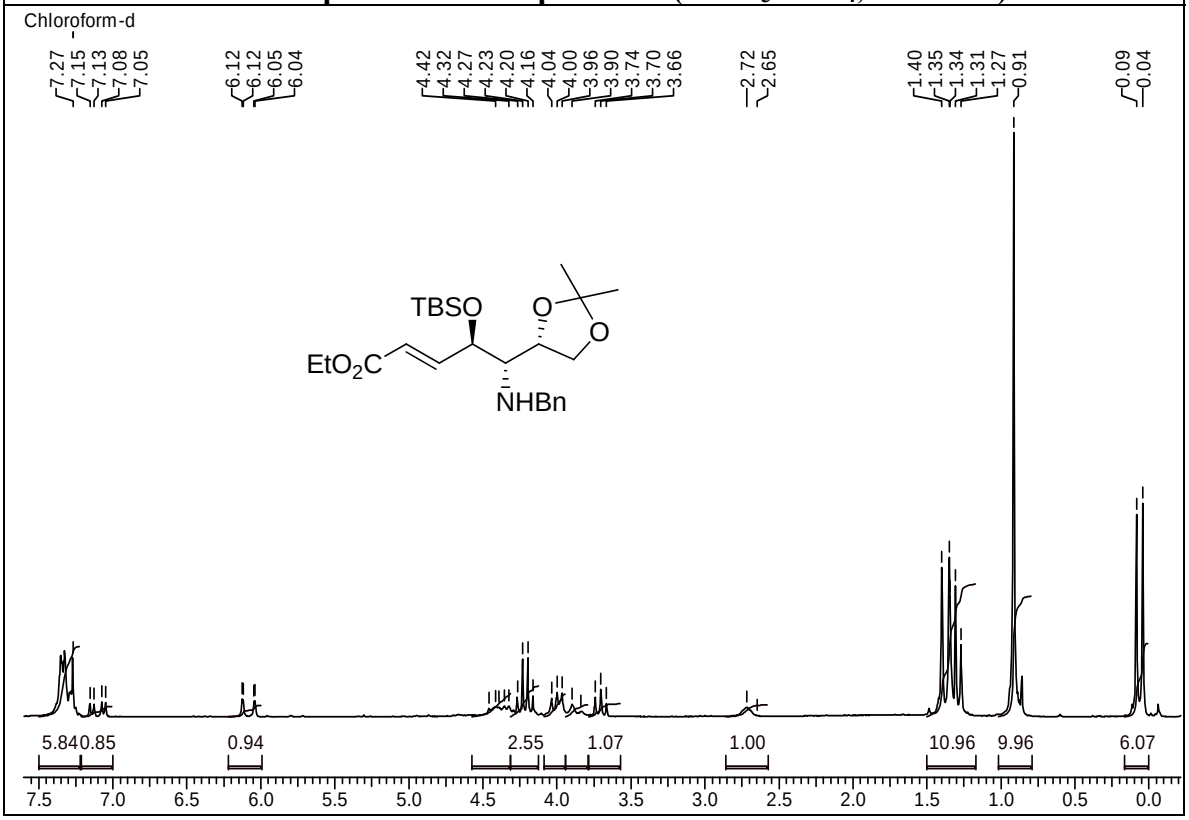
^{13}C-NMR spectrum of compound 6 ($CDCl_3$, 50 MHz)



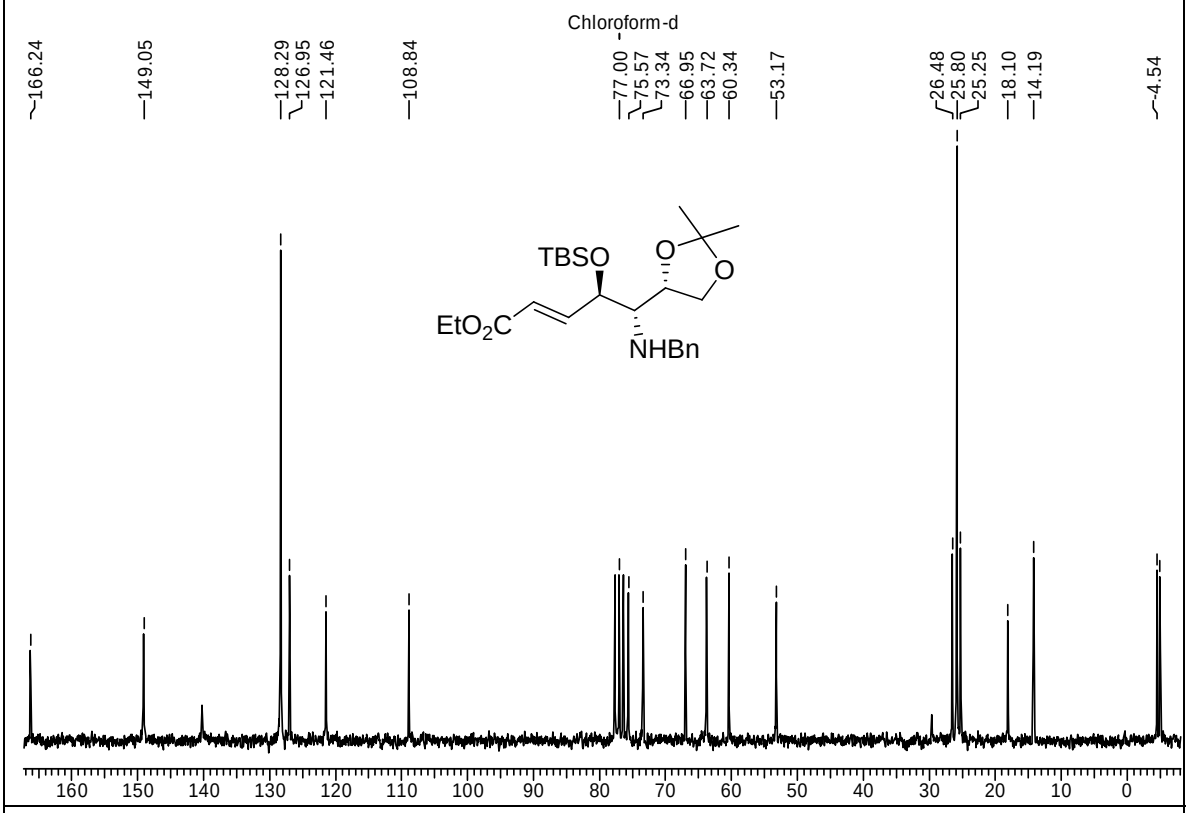
DEPT spectrum of compound 6 ($CDCl_3$, 50 MHz)



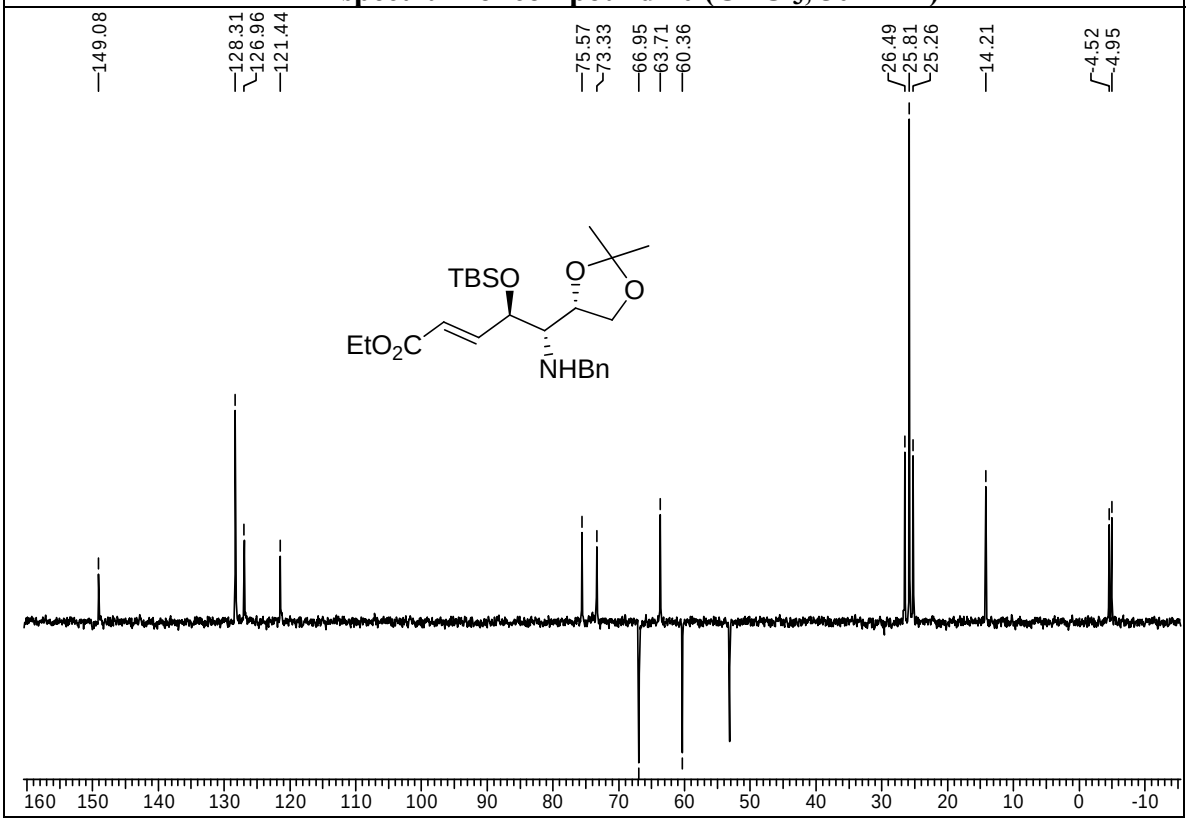
^{1}H-NMR spectrum of compound 10 ($CDCl_3$+CCl_4, 200 MHz)



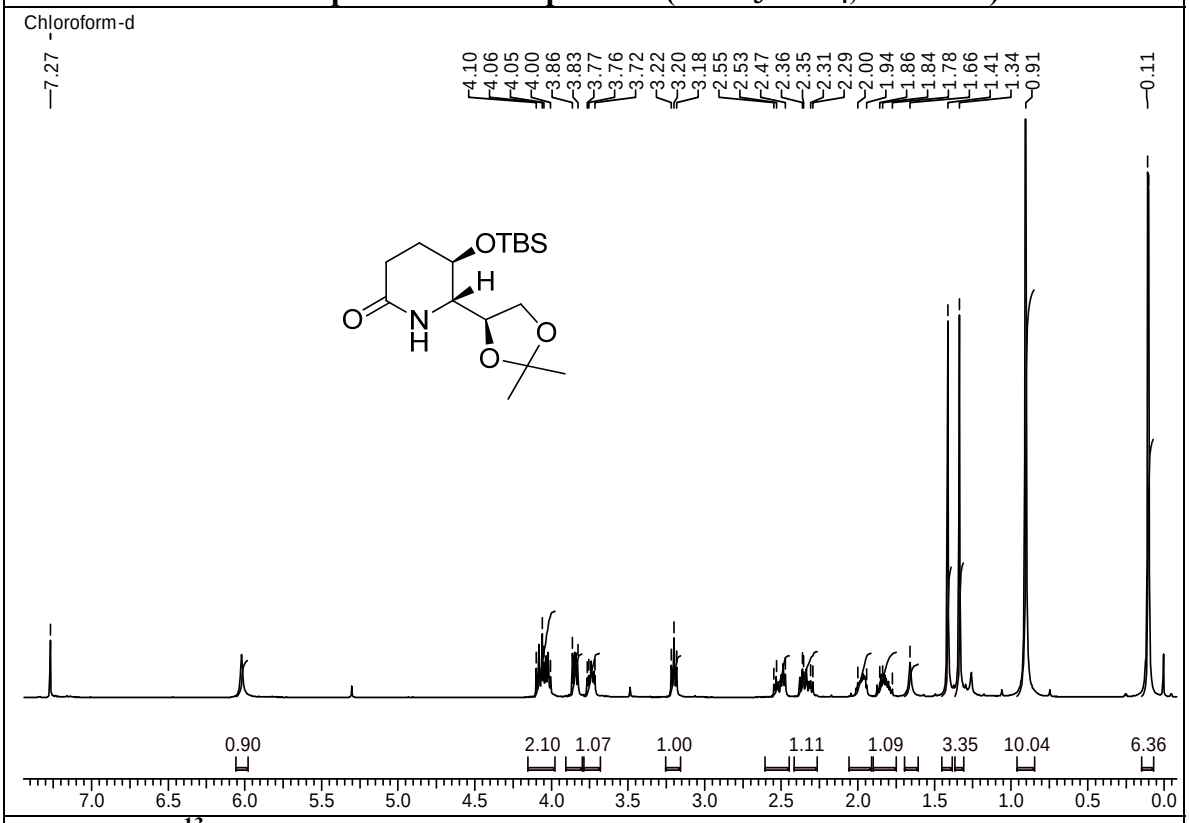
^{13}C-NMR spectrum of compound 10 ($CDCl_3$, 50 MHz)



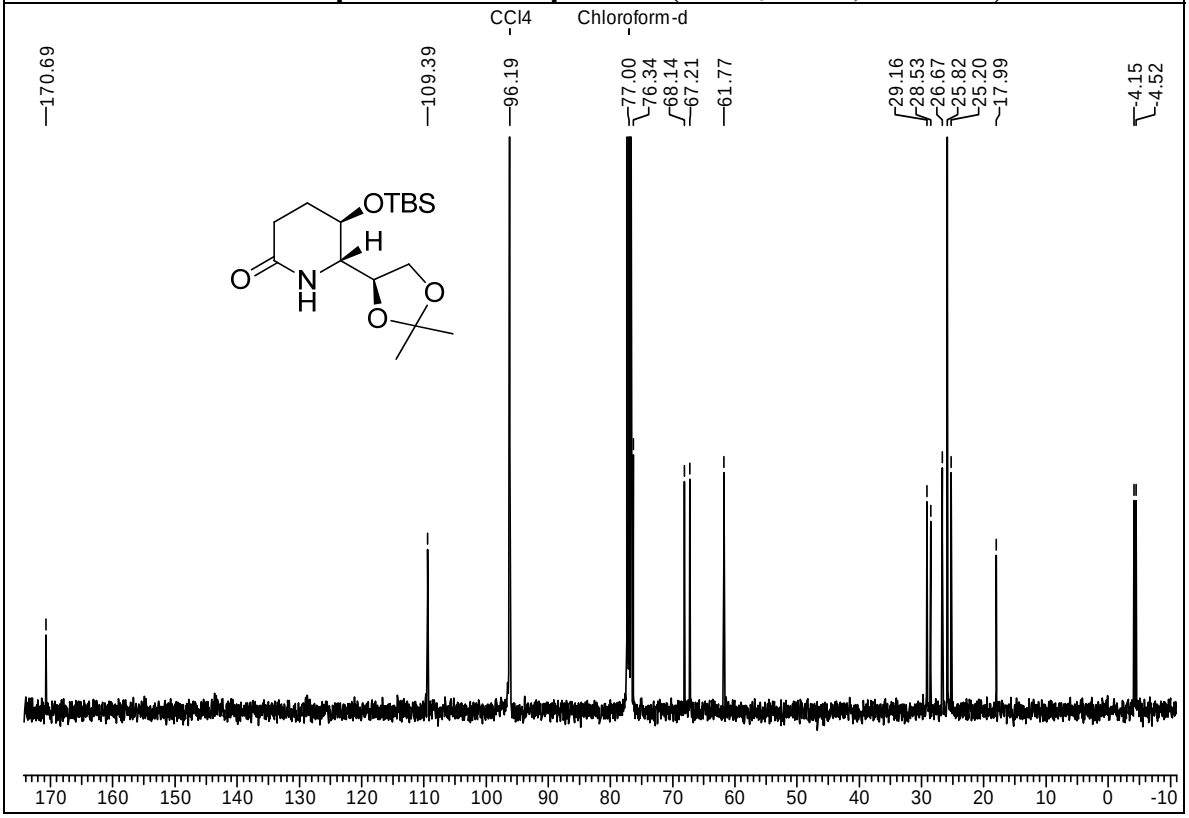
DEPT spectrum of compound 10 ($CDCl_3$, 50 MHz)



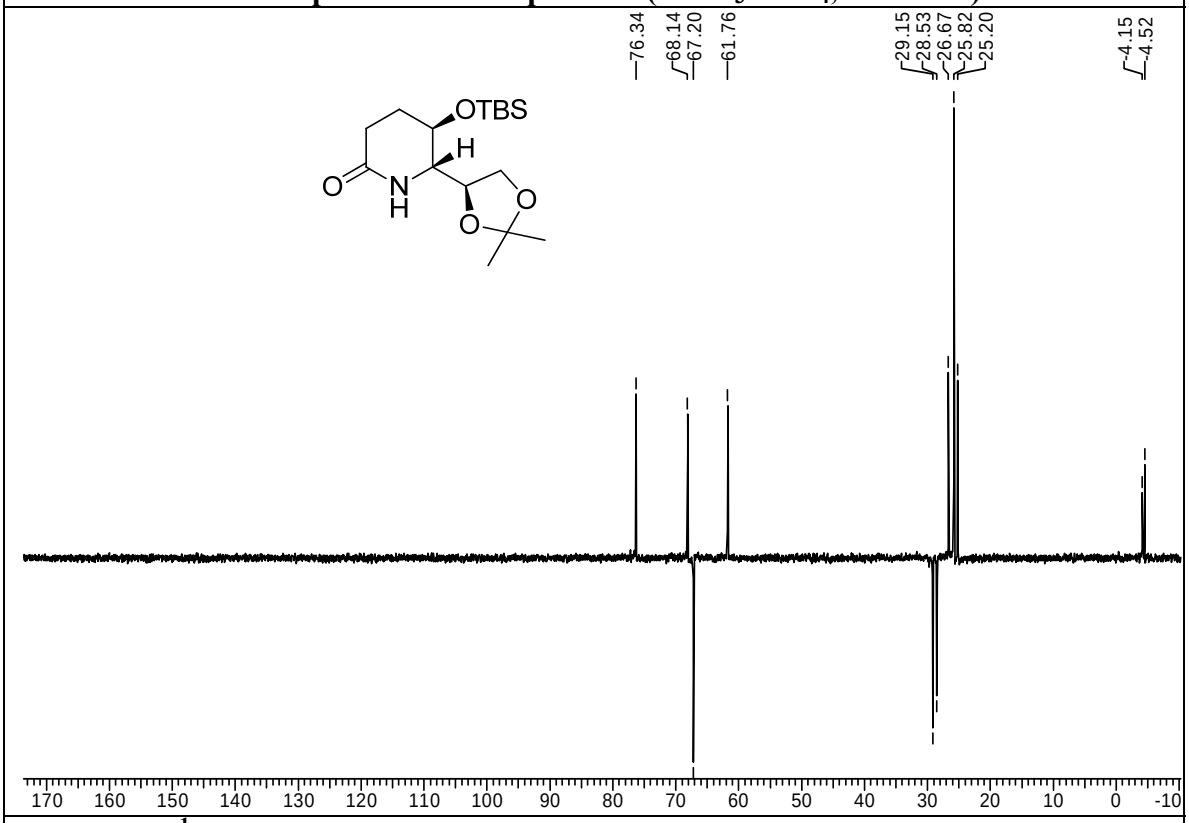
^{1}H-NMR spectrum of compound 5 ($CDCl_3$+CCl_4, 400 MHz)



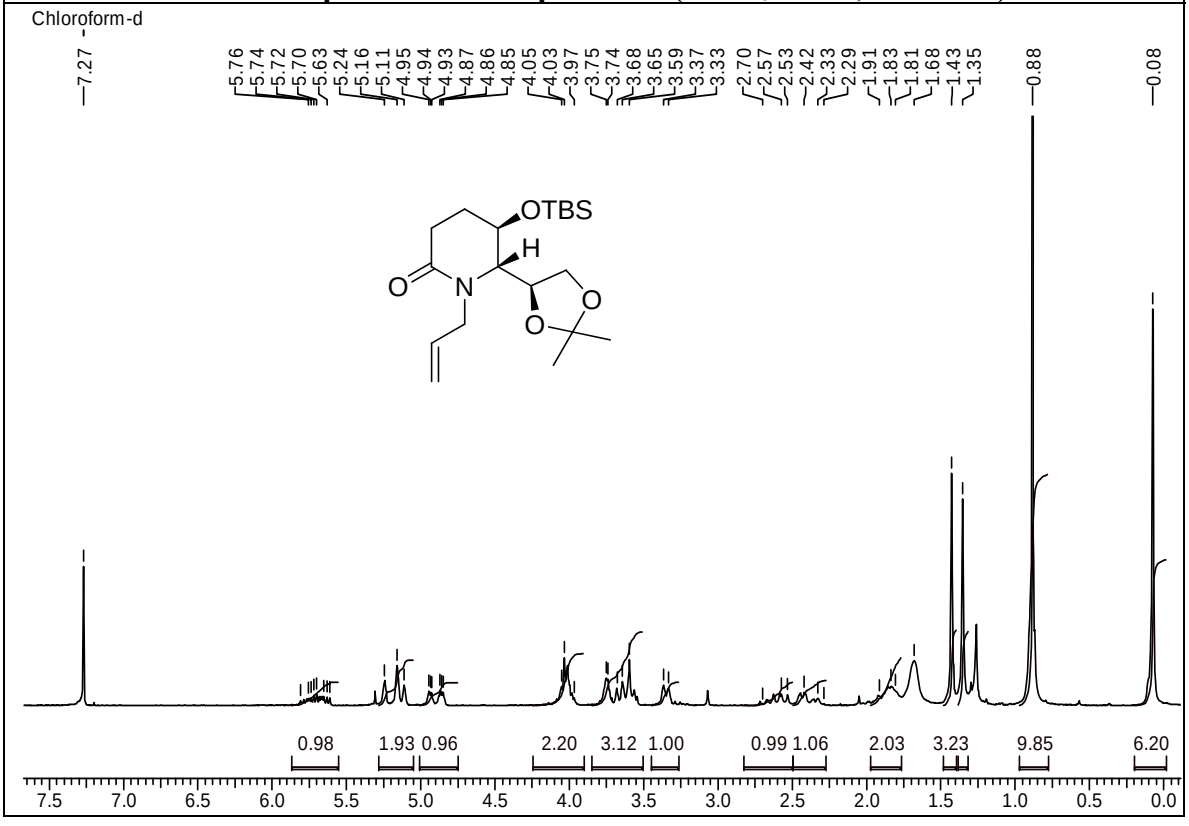
^{13}C-NMR spectrum of compound 5 ($CDCl_3$+CCl_4, 100 MHz)



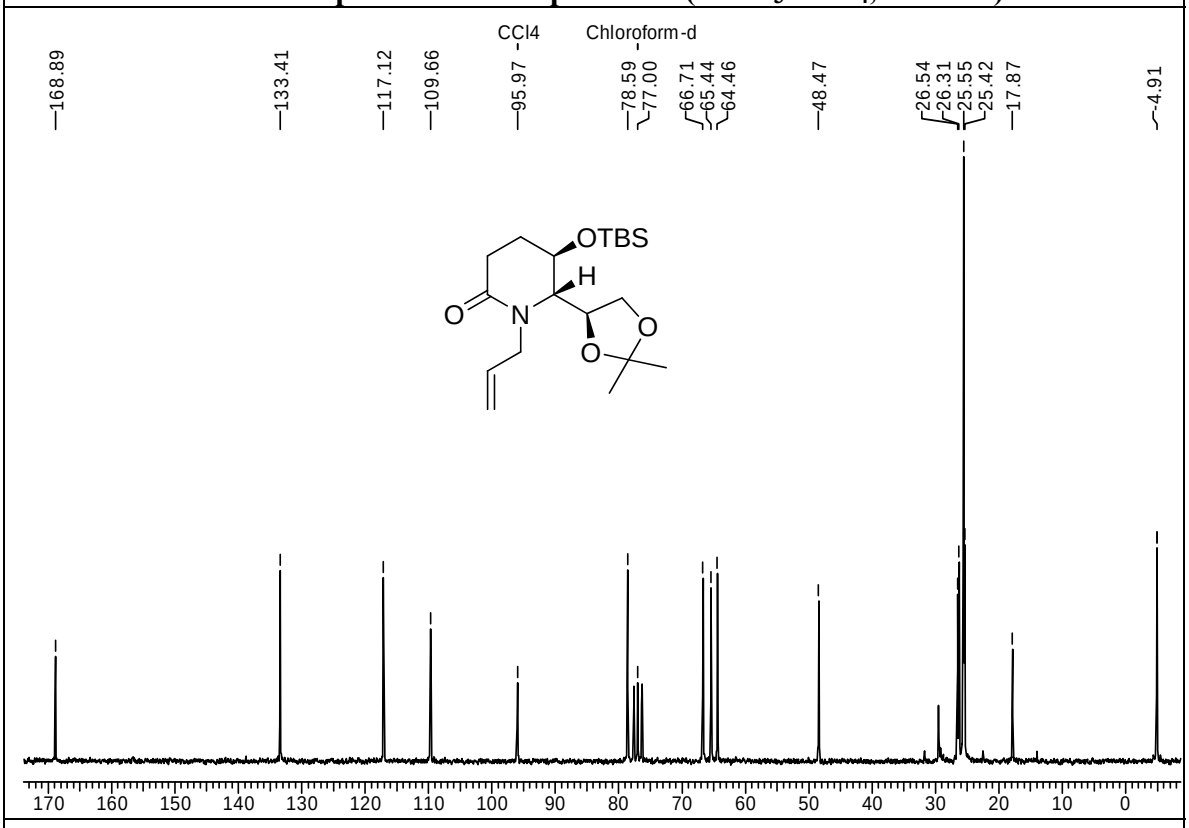
DEPT spectrum of compound 5 ($CDCl_3$+CCl_4, 100 MHz)



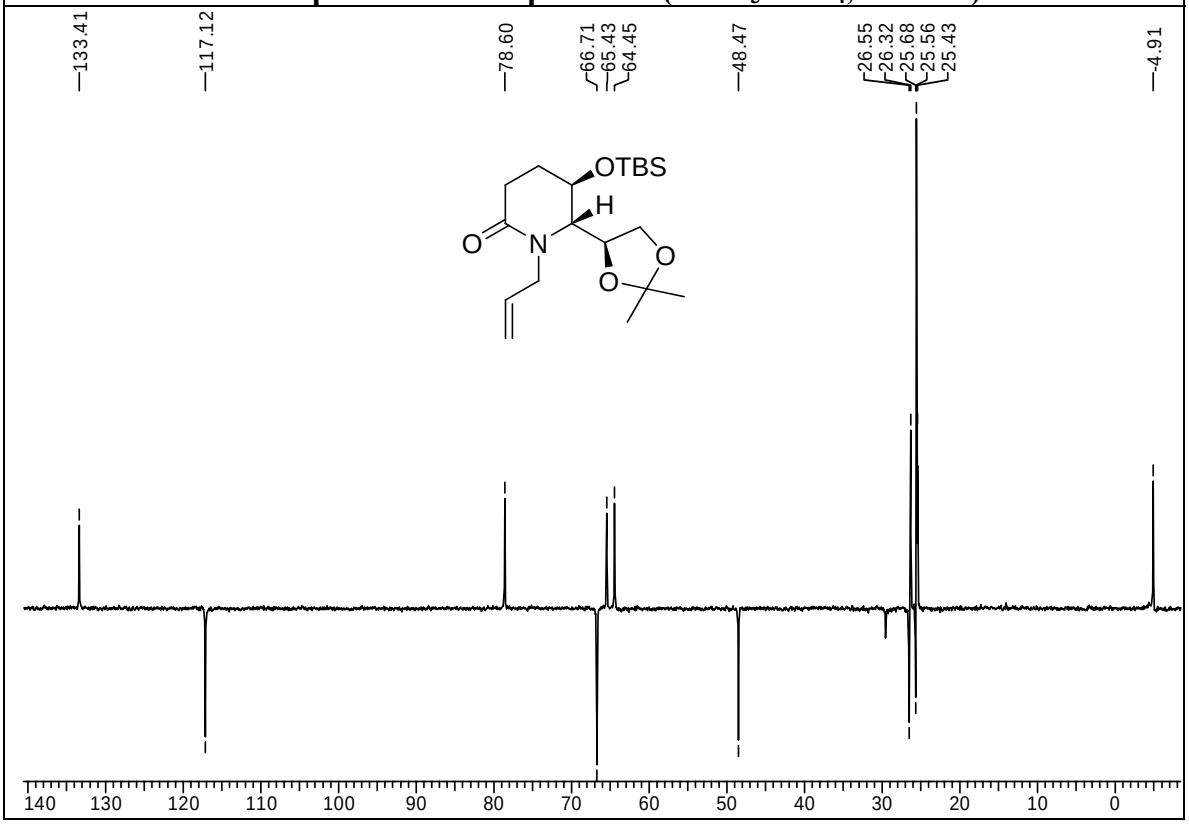
^{1}H-NMR spectrum of compound 11 ($CDCl_3$+CCl_4, 200 MHz)



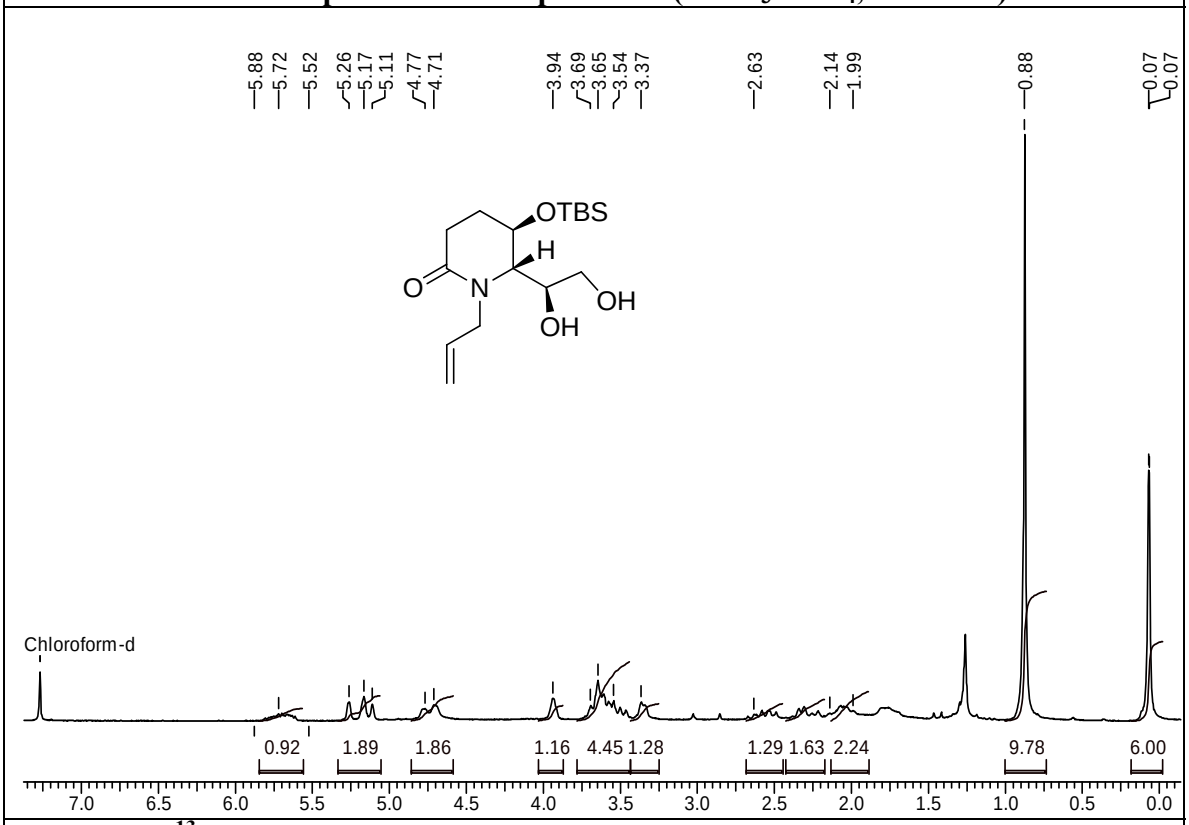
^{13}C-NMR spectrum of compound 11 ($CDCl_3$+CCl_4, 50 MHz)



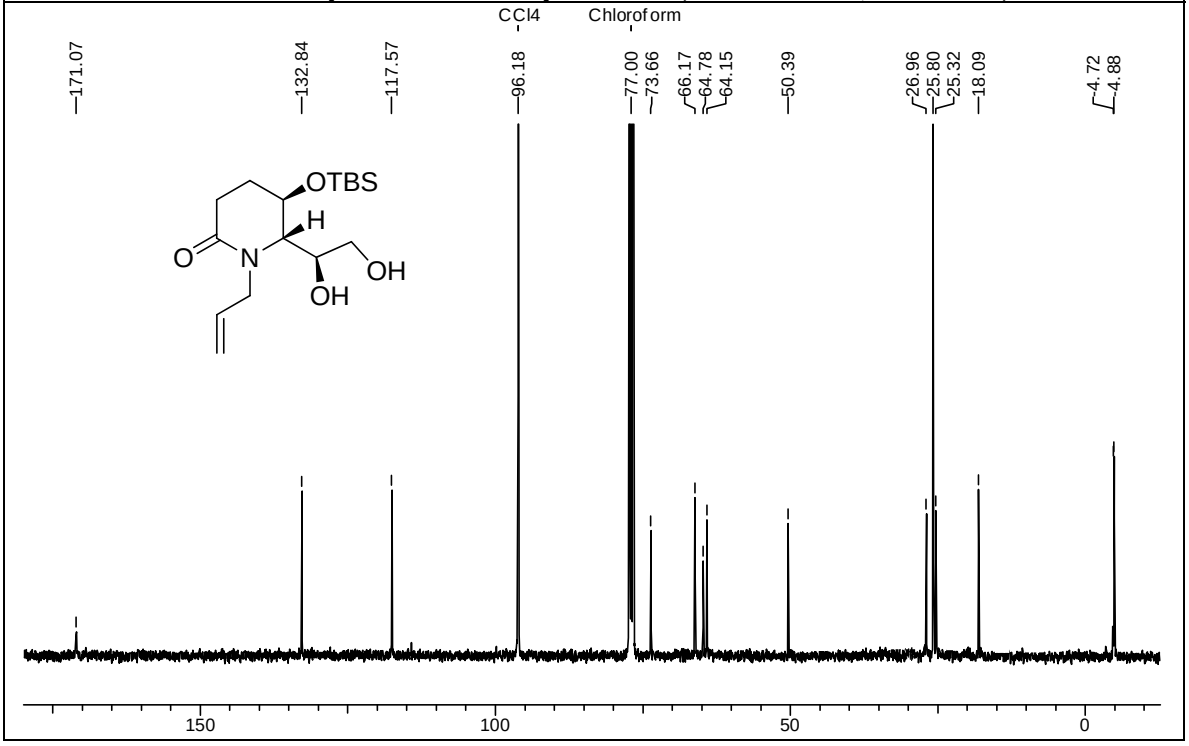
DEPT spectrum of compound 11 ($CDCl_3$+CCl_4, 50 MHz)



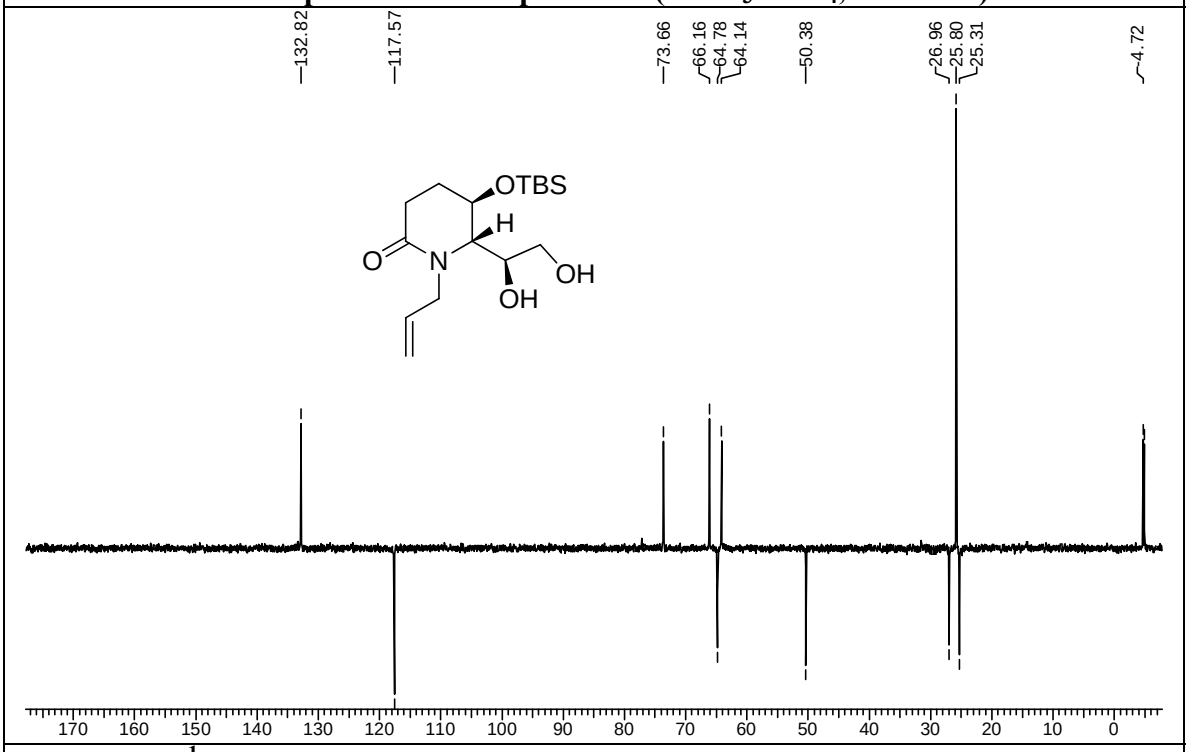
^{1}H-NMR spectrum of compound 12 ($CDCl_3$+CCl_4, 200 MHz)



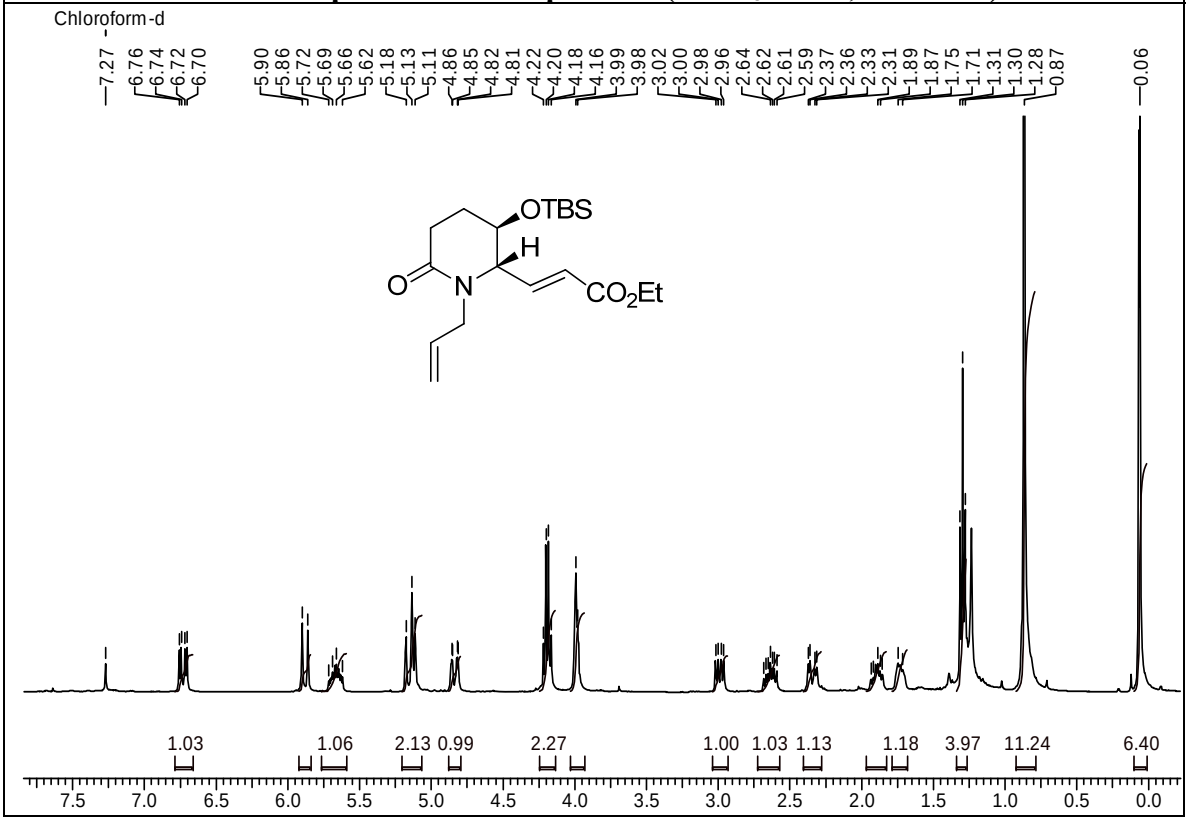
^{13}C-NMR spectrum of compound 12 ($CDCl_3$+CCl_4, 100 MHz)



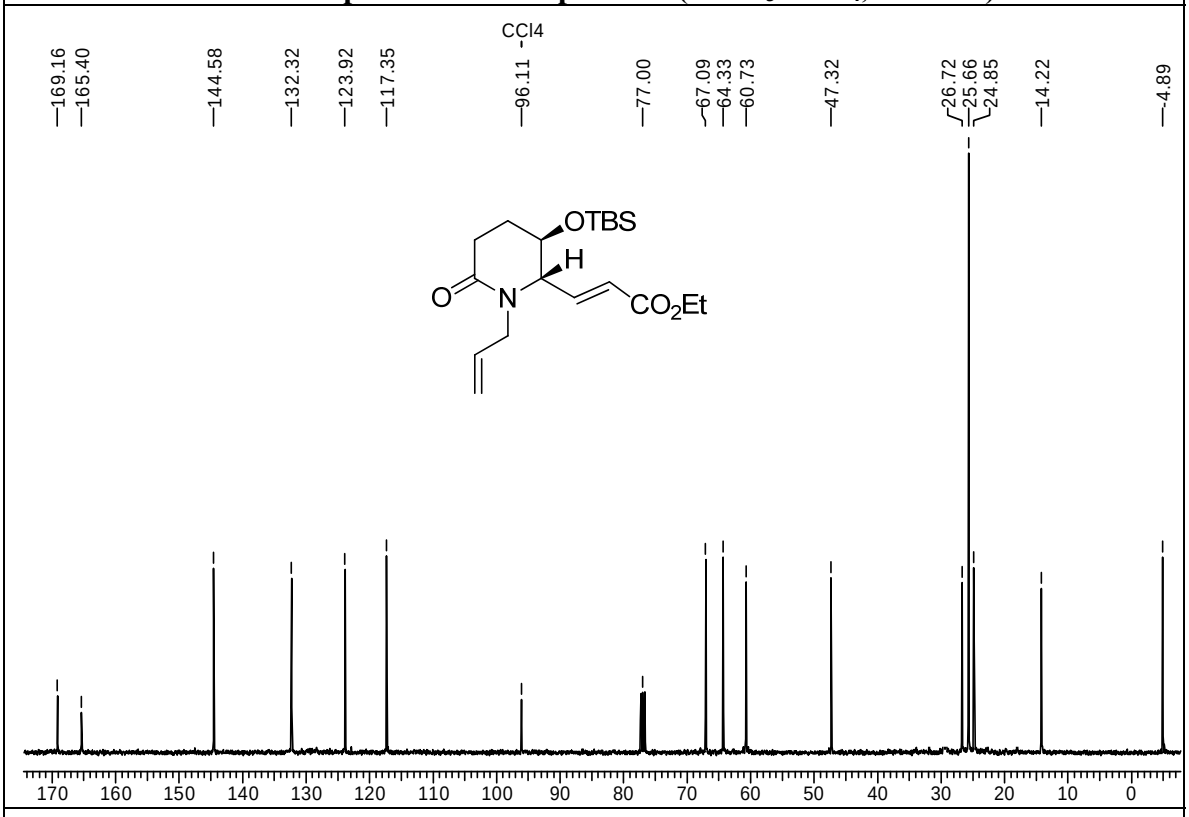
DEPT spectrum of compound 12 ($CDCl_3$+CCl_4, 100 MHz)



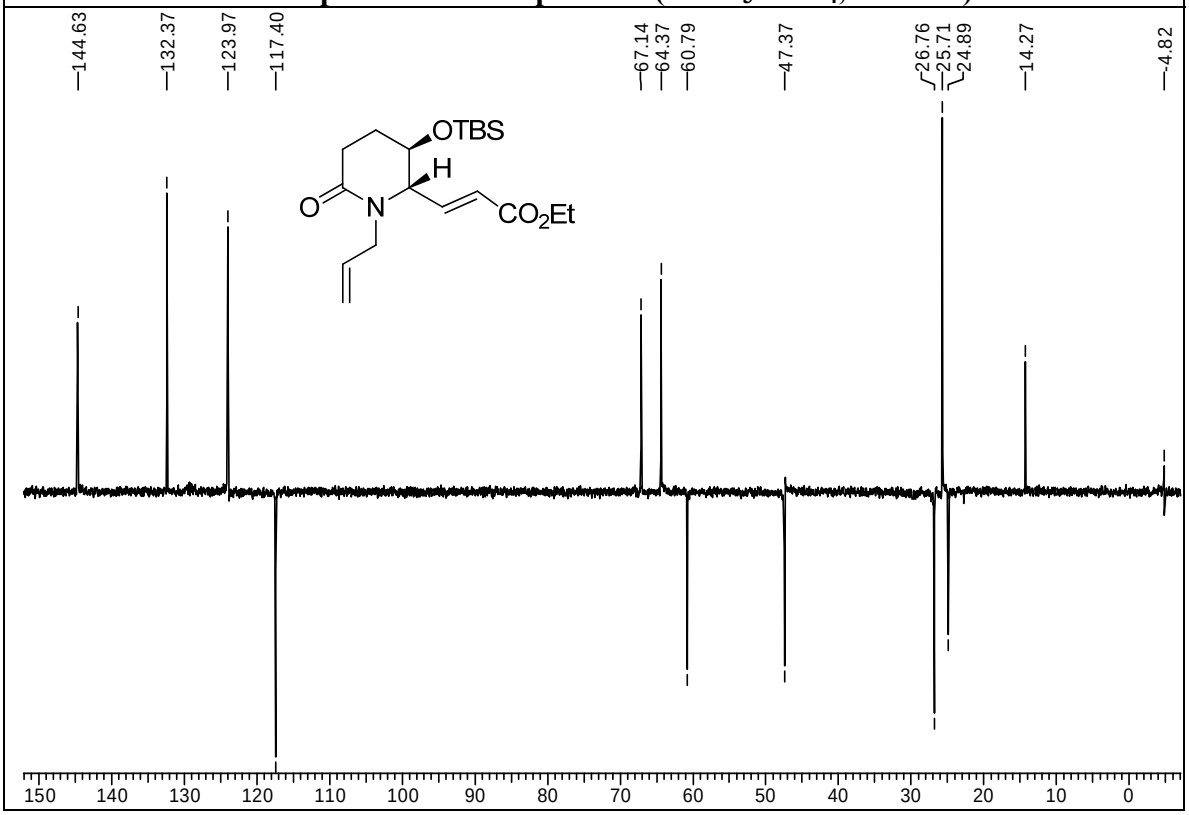
^{1}H-NMR spectrum of compound 4 ($CDCl_3$+CCl_4, 200 MHz)



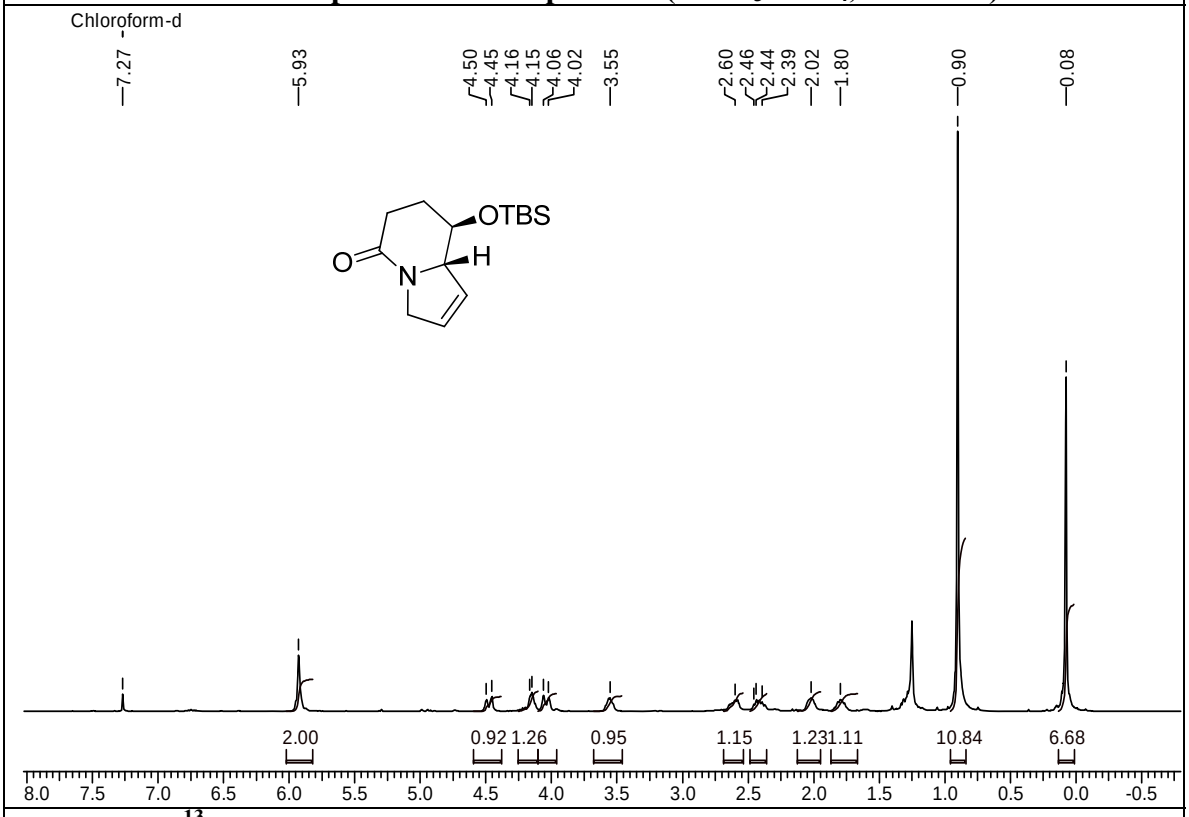
^{13}C-NMR spectrum of compound 4 ($CDCl_3$+CCl_4, 50 MHz)



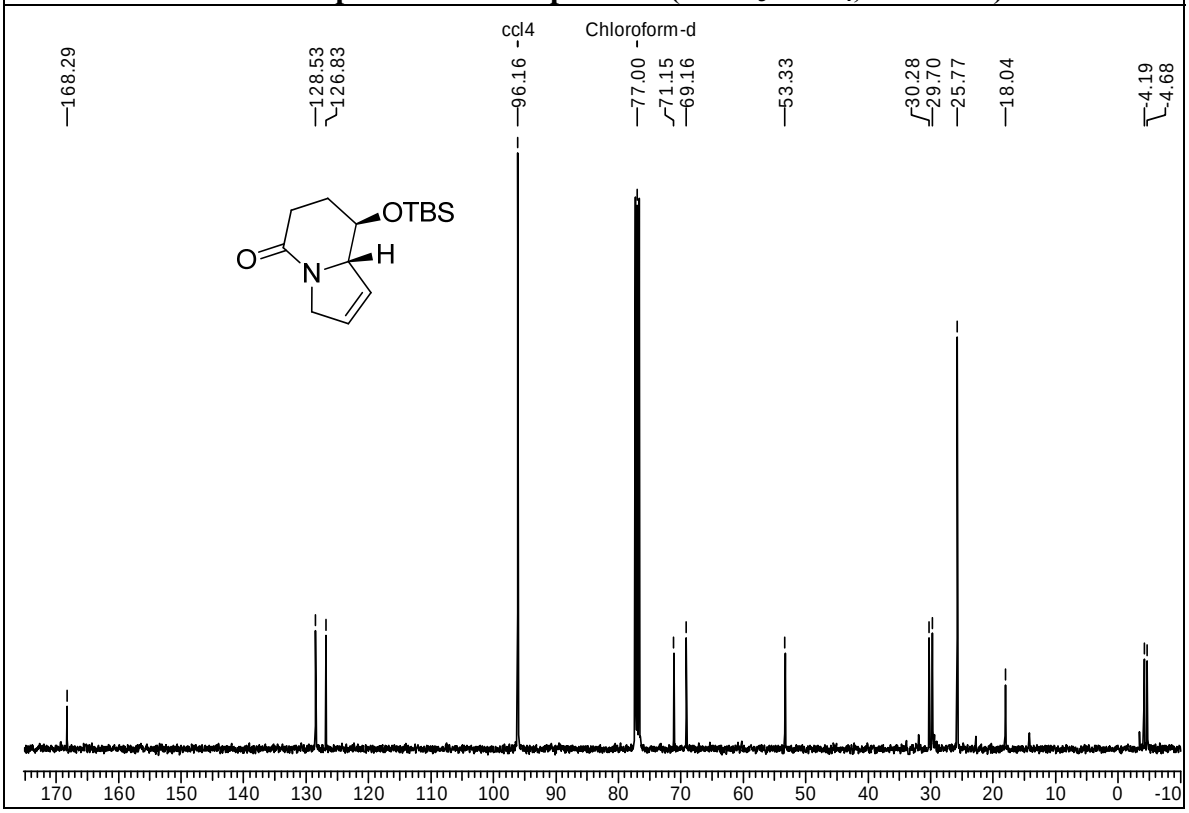
DEPT spectrum of compound 4 ($CDCl_3$+CCl_4, 50 MHz)



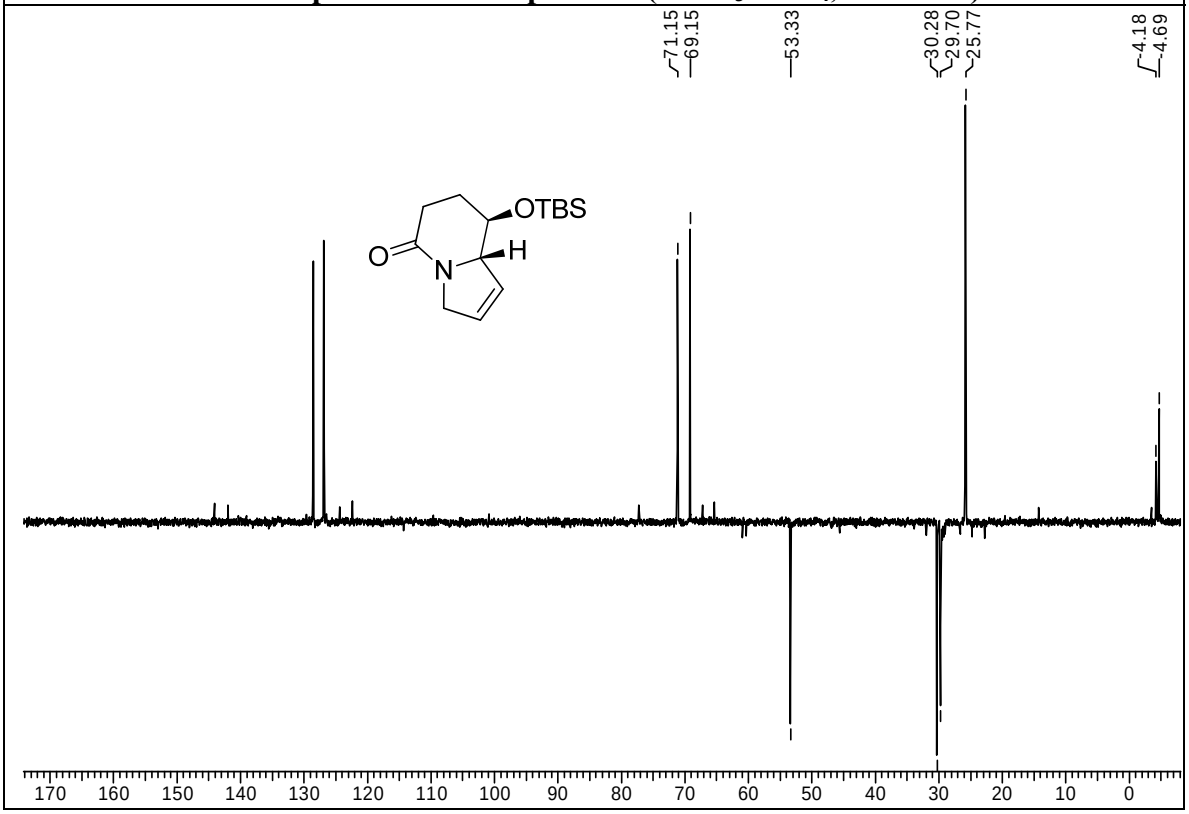
^{1}H-NMR spectrum of compound 3 ($CDCl_3$+CCl_4, 400 MHz)



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



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



2.4.5 References

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Chapter 3: Synthetic studies toward both enantiomers of *cis*-3-hydroxypipecolic acid and development of synthetic methodology for preparation of chiral allylic amines from chiral aziridine-2-alcohols

Section 1: Introduction to *cis*-3-hydroxypipecolic acid

3.1.1 Introduction

Pipecolic acid and its derivatives are found abundantly in different species of plants and animals and possess a wide range of biological activities.[1]

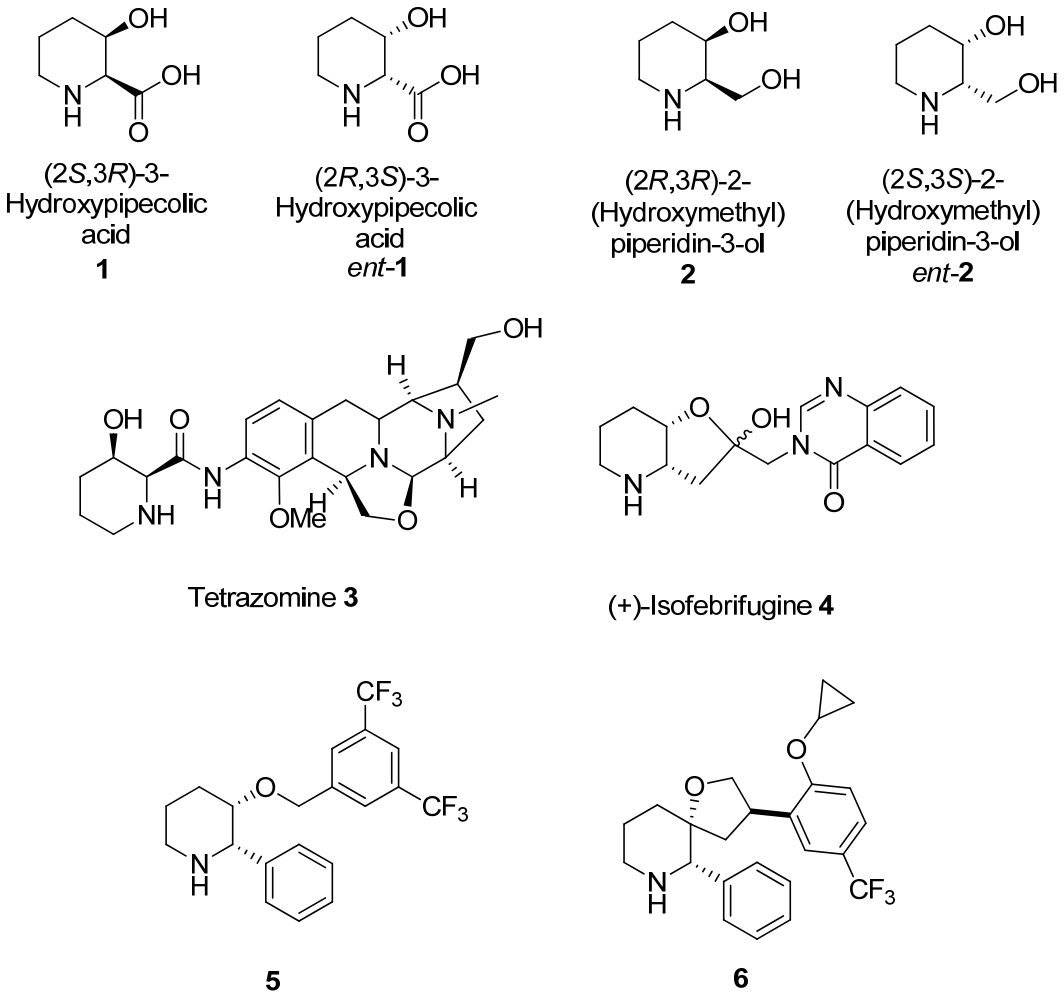


Figure 1

Cis derivatives of 3-substituted-pipecolic acid, *viz.***1** and *ent*-**1**[2] (Figure 1) are a constituent of many compounds having potent biological activities[3]and used in the preparation of conformationally restricted peptides and ligand binding studies. The *cis*-isomer **1** is a structural unit of the antitumor antibiotic tetrazomine **10**,[4] while reduced analogue of *ent*-**1** *viz ent*-**2** is component of isofebrifugine, an antimalarial agent.[5] 2-Phenylpiperidin-3-ols, which are precursors of non-peptidic NK-1 receptor antagonists such as **5**[6] and **6**,[7]

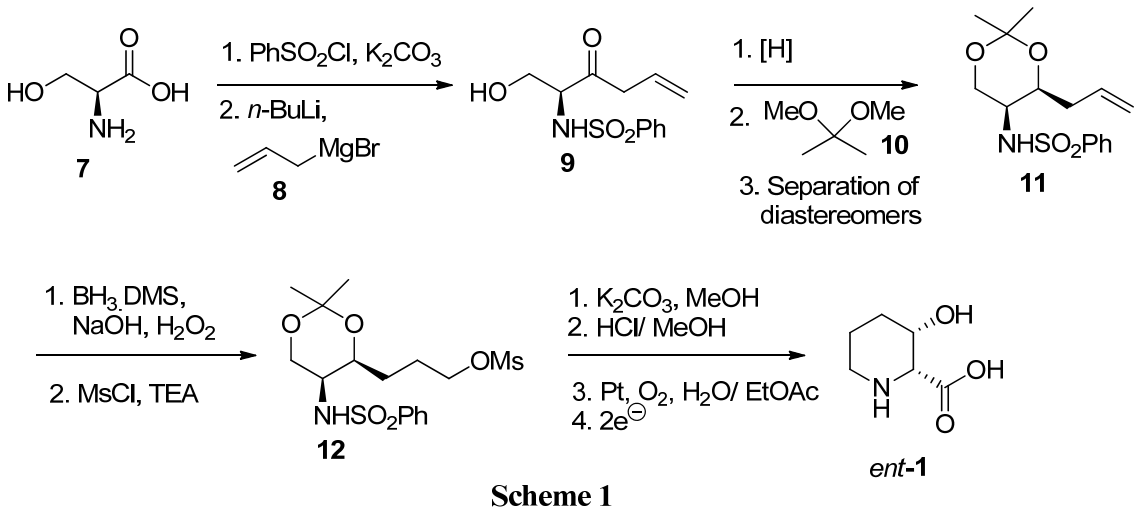
have a *cis*-relationship betweenthe phenyl and the ether group on the piperidinering, and are important for high-affinity binding to the human NK-1 receptor (Figure 1).[8]

3.1.2 Literature review

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

(a) Syntheses using chiral pool approach

Rapoport's approach

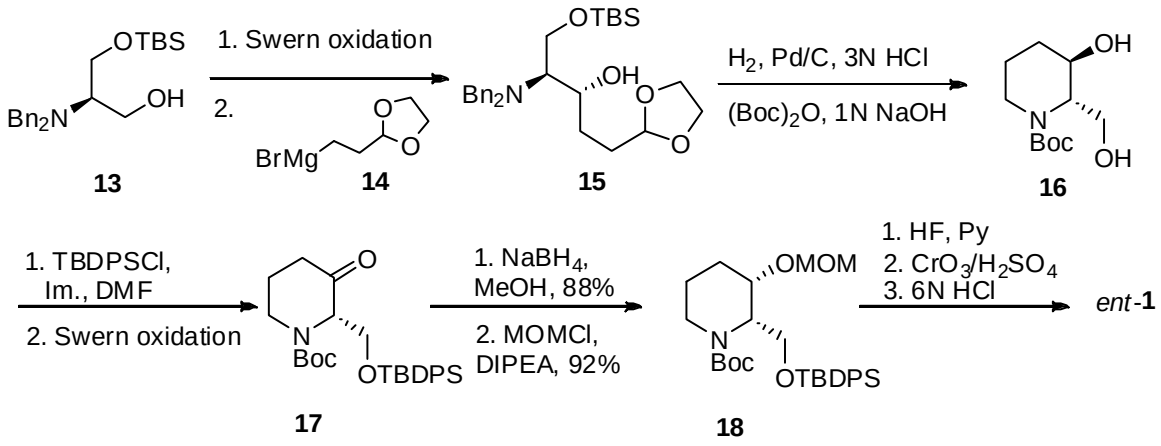


Scheme 1

Raporort *et al*. (Scheme 1) developed a method for alkylation of acids derived from L-serine and exploited for the synthesis of β-hydroxy-α-amino acids.[9] The amine in L-serine **7** was protected as a sulphonamide, and the resultant acid subjected to the reaction with allylmagnesium bromide in the presence of *n*-butyl lithium to provide keto- sulphonamide **9**. The sulphonamide **9** on reduction furnished 1,3-diol which on protection as its acetonide provided diastereomers which were separated to provide **11**. Compound **11** was then subjected to hydroboration followed by mesylation to provide mesyl sulfonamide **12.** Sulfonamide **12** was treated with base followed by acidification and oxidation to provide *cis*-(2*R*,3*S*)-3-hydroxypipecolic acid *ent*-**1** in good yield.

Zhu's approach

Zhu *et al*. synthesized (2*R*,3*S*)-3-hydroxypipecolic acid *ent*-**1** starting from amino alcohol **13**derived from serine (Scheme 2). Amino alcohol **13** was oxidized to aldehyde and subjected to reaction with Grignard reagent **14** to obtain anti amino alcohol **15** as a major



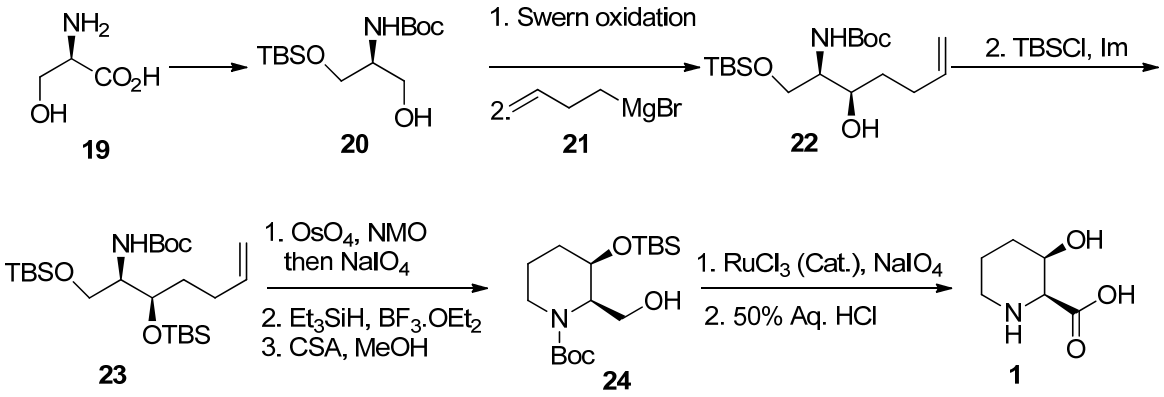
Scheme 2

product which was exploited for the synthesis of (2*R*,3*R*)-*ent*-**1**. Protected amino alcohol **15** was subjected to hydrogenation and subsequently for Boc protection to provide diol **16**. The primary alcohol in diol **16** was protected with TBDPS group selectively and secondary alcohol was oxidized to ketone. Highly stereoselective reduction of ketone **17** with $NaBH_4$ afforded a *cis* 2,3-disubstituted piperidine alcohol. Secondary alcohol was protected with MOM, then the TBDPS group was deprotected, and the resulting alcohol was subjected to oxidation and subsequently MOM group was deprotected to provide 3-hydroxypipecolic acid *ent*-**1**.[10]

Datta's approach

Datta *et al*. synthesized **1** starting from D-serine **19** (Scheme 3), using diastereoselective Grignard reaction on aldehyde and reductive cyclization as the key steps. They prepared alcohol **20** from **19** by known procedure.[11] Alcohol **20** on Swern oxidation followed by reaction with Grignard reagent **21** provided alcohol **22**. The subsequent protection of alcohol **22** with TBS provided compound **23**. Di-OTBS compound **23** was subjected to dihydroxylation followed by cleavage of diol using $NaIO_4$ followed by reduction and deprotection to furnish piperidine alcohol **24**. Piperidine derivative **24** upon oxidation and

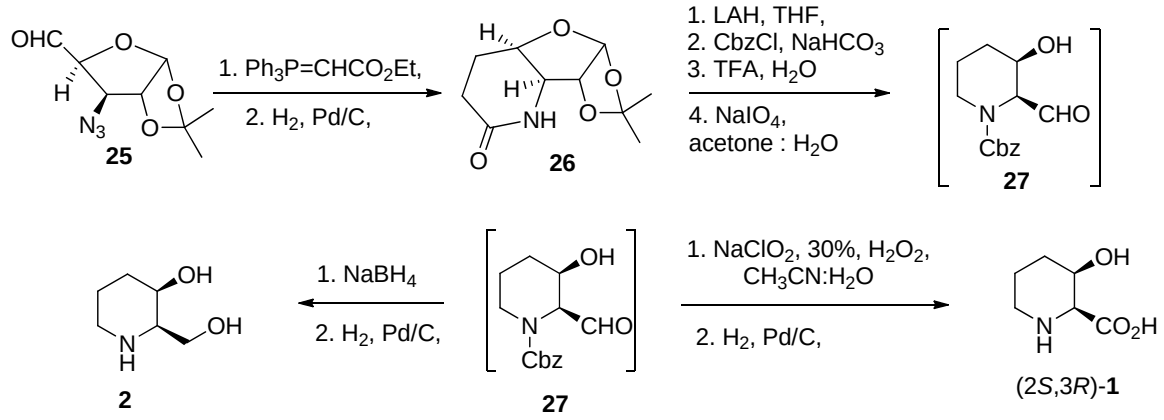
deprotection resulted in to the formation of hydrochloride salt of **(**2*S*,3*R*)-3-hydroxypipecolic acid **1**.



Scheme 3

Dhavale's approach

Dhavale *et al*. utilized D-glucose as the starting material for the synthesis of **1** and **2** (Scheme 4). The azido aldehyde **25** obtained from D-glucose by reported method was

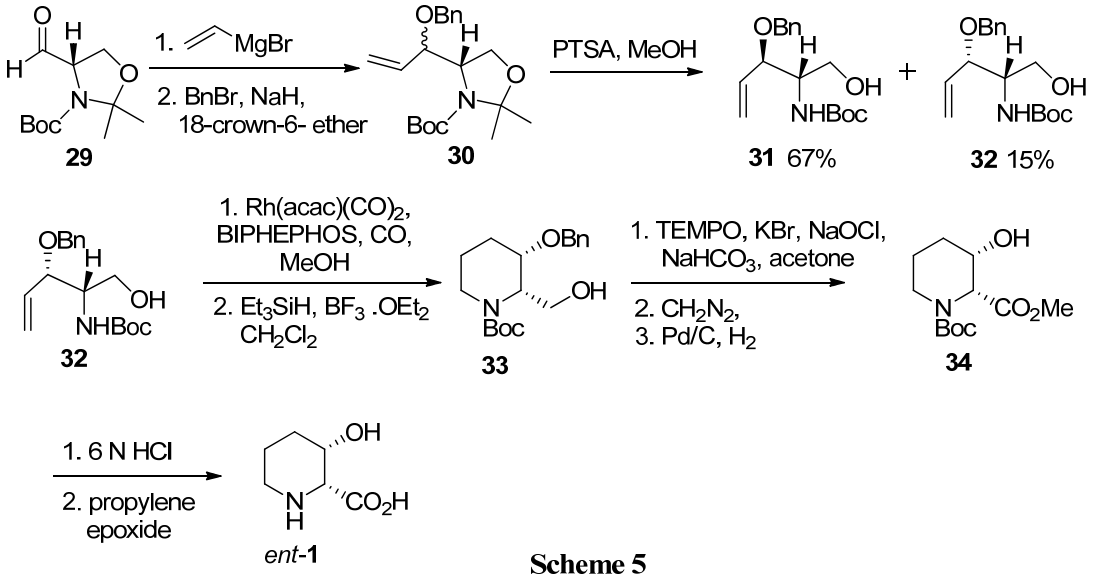


Scheme 4

subjected to Wittig reaction followed by azide reduction to furnish amide **26**. Amide **26** was reduced using LAH followed by Cbz protection, acetonide deprotection and cleavage to provide aldehyde **27**. Aldehyde **27** was converted to 3-hydroxypipecolic acid **1** as well as **2** in two steps each.[12]

Chiou's approach

Chiou *et al*. synthesized *cis* and *trans* 3-hydroxypipecolic acid starting from Garner's aldehyde employing diastereoselective Grignard reaction and Rh catalyzed cyclohydrocarbonylation (Scheme 5). Nucleophilic addition of vinyl magnesium bromide on aldehyde **29** furnished diastereomeric mixture of alcohol, which was protected with benzyl bromide to give benzyl ether **30**. Compound **30** was subjected to acetonide deprotection to provide mixture of alcohols **31** and **32**, which were separated. Alcohol **32** was subjected to cyclohydrocarbonylation followed by reduction to provide piperidine alcohol **33**, which was further explored to the synthesis of *cis* 3-hydroxypipecolic acid*ent*-**1**.[13]

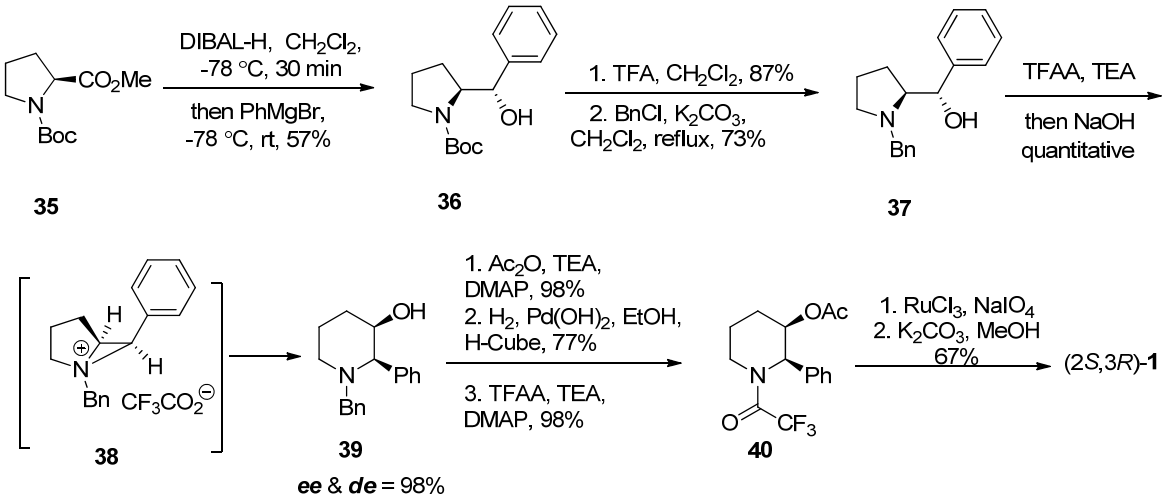


Scheme 5

Cossy's approach[14]

Cossy's approach uses two key steps: a one-pot diastereoselective DIBAL-H reduction /Grignard addition sequence applied to proline ester **35** and a ring expansion applied to the corresponding prolinol compound **37** which was transformed into 2-phenylpiperidin-3-ol **39** in two steps, which was transformed into 3-hydroxypipecolic acid **1** in five steps. Access to optically active prolinol **37** was achieved from the commercially available *N*-Boc-L-proline methylester **35**. This compound was transformed into the corresponding amino alcohol **36**, using DIBAL-H followed bythe addition of phenylmagnesium bromide with excellent diastereoselectivity (99:1). Compound **36** was converted into **37** by treatment with TFA followed by a *N*-benzylation. Prolinol **37** was transformed into 3-hydroxypiperidine **39** *via* aziridinium **38** employing ring expansion conditions to furnish

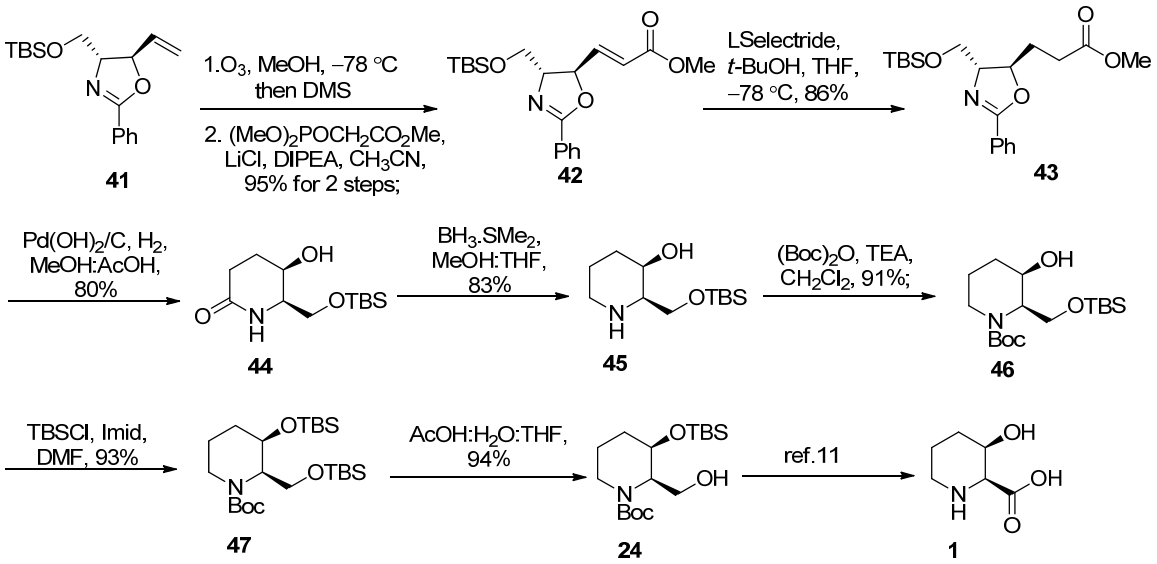
2-phenylpiperidin-3-ol **39**. The substituted piperidin-3-ol **39** was acetylated and, after careful hydrogenation, a trifluoroamidation was achieved leading to **40** in good yields. Treatment of this latter compound with $RuCl_3 \cdot 3H_2O/NaIO_4$ followed by saponification furnished the desired 3-hydroxypipecolic acid **1** (Scheme 6).



Scheme 6

Ham's approach

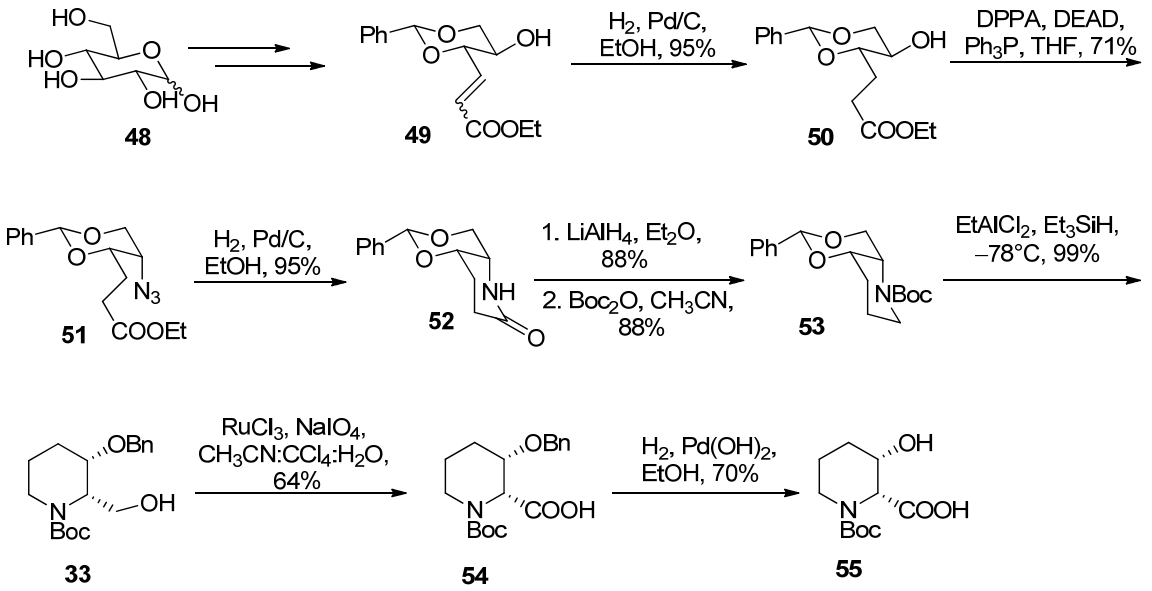
A concise, stereocontrolled synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid **1** is reported by Ham's group.[15] The synthesis of **1** commenced with ozonolysis of oxazoline **41** to give the corresponding aldehyde, which was reacted with trimethylphosphonoacetate to yield the *α*,*β*-unsaturated methyl ester **42** (Scheme 7). 1,4-Reduction of **42** with L-Selectride gave the saturated methyl ester **43**. Hydrogenolysis of **43** followed by reduction with $BH_3 \cdot DMS$ furnished **44**. The compound **44** was protected with $(Boc)_2O$, and subsequent silyl protection led to disilyl *N*-Boc compound **47**, which was reacted with acetic acid to afford the selectively deprotected free primary alcohol **24** in good yield. Subsequent oxidation of the primary hydroxylgroup including deprotection of the secondary silyl ether with $RuCl_3$ and $NaIO_4$ provided the corresponding carboxylic acid; acidic hydrolysis of the carbamate culminated in an efficient synthesis of the desired (2*S*,3*R*)-3-hydroxypipecolicacid **1**.



Scheme 7

Baskaran's approach

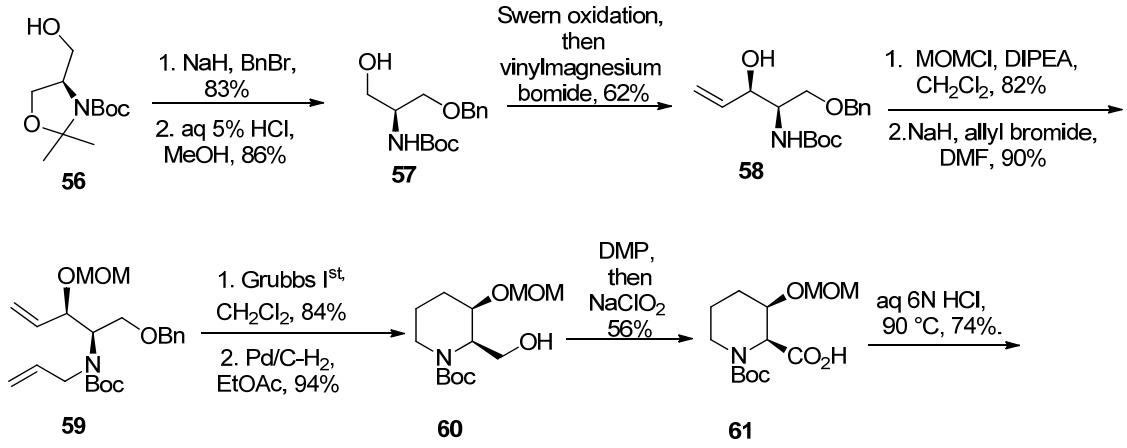
A stereoselective synthesis of *N*-Boc-protected *cis*-(2*R*,3*S*)-3-hydroxypipecolic acid **55**, starting from D-glucose **48** employing a highly regioselective reductive cleavage of benzylidene acetal **53** as the key step was achieved by Baskaran's group (Scheme 8).[16] Following the literature procedure,D-glucose **48** was readily converted to the corresponding azido ester **51** in a few steps. Azido ester **51** on catalytic hydrogenation over Pd/C and *in situ* cyclization furnished the lactam **52**. Reduction of amide **52** with $LiAlH_4$ followed by *N*-Boc protection of the resultant amine with $(Boc)_2O$ gave the corresponding *N*-Boc-protected benzylidene acetal **53**. The crucial regioselective reductive cleavage of benzylidene acetal **53** was achieved using $EtAlCl_2/Et_3SiH$ to give the requisite hydroxymethylpiperidine derivative **33** in excellent yield with high degree of regioselectivity. The oxidation of alcohol followed by catalytic hydrogenation with $Pd(OH)_2$ furnished the corresponding *N*-Boc-protected *cis*-(2*R*,3*S*)-3-hydroxypipecolic acid **55** in 70% yield.



Scheme 8

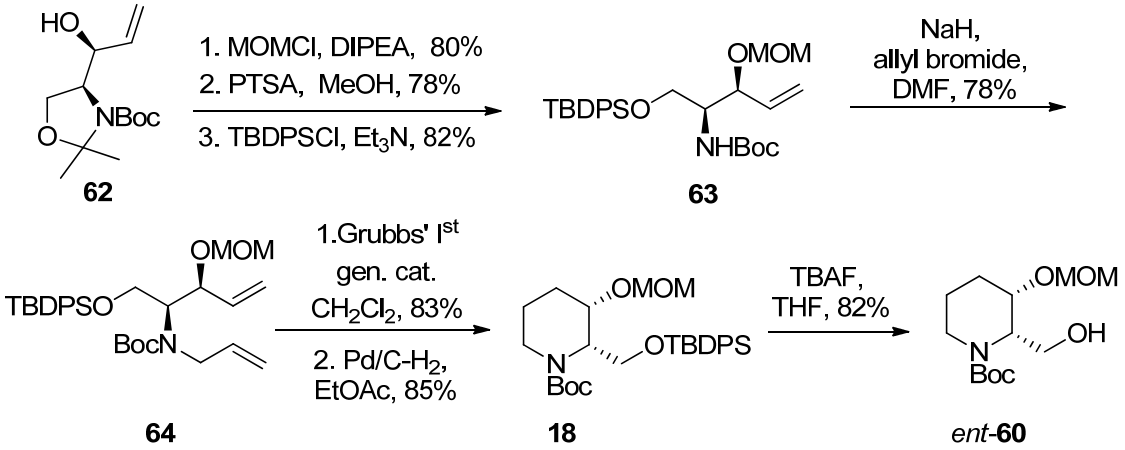
Chattopadhyay's approach

Stereoselective routes to *cis*-(2*S*,3*R*)-3-hydroxypipecolic acid **1** and two enantiomeric *cis*-2-hydroxymethyl-3-hydroxypiperidine derivatives from a common precursor have been developed, which featured stereocontrolled vinylation of a chiral aldehyde and ring-closing metathesis as key steps by Chattopadhyay's group.[17] Synthesis of the hydroxypipecolic acid derivative **1** started from the serinol derivative **56** (Scheme 9), which was protected as its benzyl ether, the oxazolidine ring deprotection followed by oxidation provided the aldehyde, which was added to a solution of vinylmagnesium bromide in one-pot manner, the desired *syn*-allyl alcohol **57** was indeed formed as the major isomer (87:13 by HPLC), was then converted to the corresponding MOM-ether, *N*-allylation with allyl bromide, and separation led access to the pure *syn*-isomer **59**. Ring closing metathesis of **59** with Grubbs' Ist generation catalyst followed by debenzylation and concomitant saturation of the double bond yielded the primary alcohol **60** which on oxidation gave acid **61**. Deprotection of *N*-Boc and *O*-MOM groups then gave the desired 3-hydroxypipecolic acid **1** in an overall yield of 11% over nine steps from **10**.



Scheme 9

L-serine, was converted into the piperidine derivative *ent*-**60** *via* allyl alcohol **62** following a seven-step sequence detailed below. Conversion of the allyl alcohol **62** to the corresponding MOM-ether, opening of the oxazolidine ring to the primary alcohol, and its subsequent conversion to the silyl ether **63** proceeded smoothly. Similarly, *N*-allylation of compound **63** into the *N*-tethered diene **64** followed by a subsequent RCM, saturationof the double bond leading to **18** followed by deprotection of the *O*-silyl group then led to the desiredpiperidine derivative *ent*-**60** (Scheme 10).

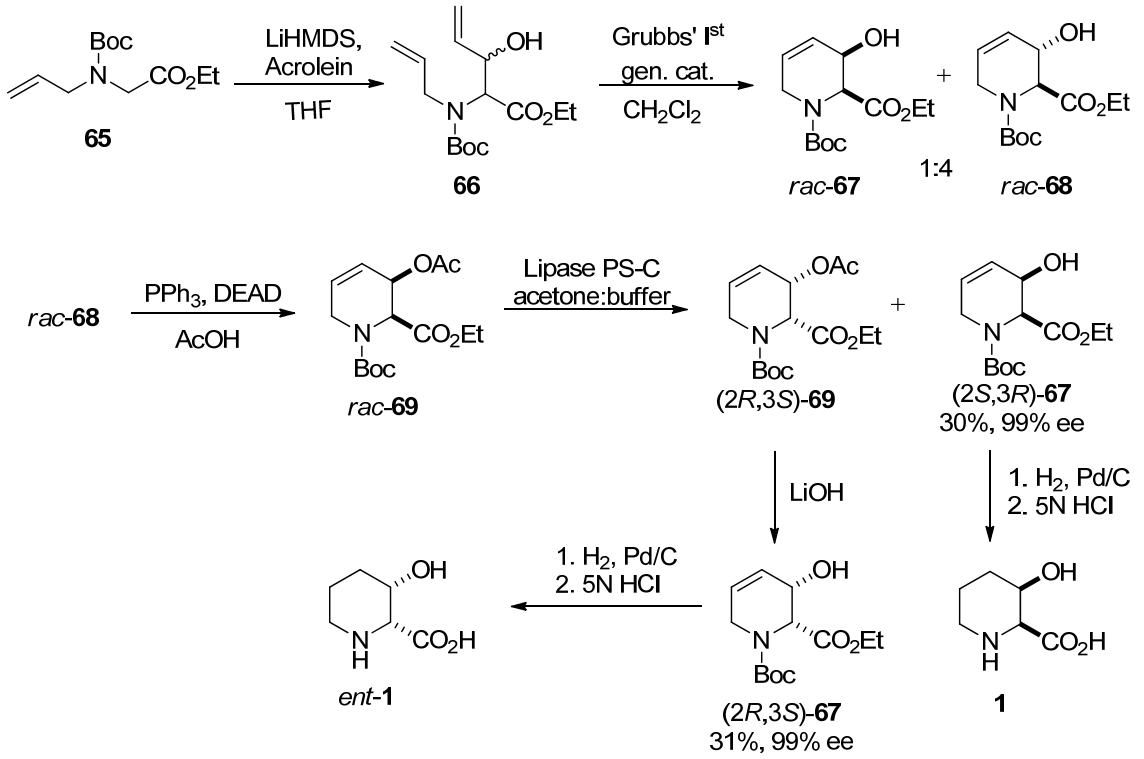


Scheme 10

(b) Synthesis using chiral induction

Takahata's approach

Takahata*et al*. reported synthesis of **1** using RCM and enzymatic resolution as the key steps (Scheme 11). Ester **65** was treated with LiHMDS and then with acrolein to provide di-allyl compound **66**, which was subsequently subjected to RCM reaction to furnish a mixture of piperidines **67** and **68**. The major piperidine derivative **68** on 3-hydroxy inversion and enzymatic resolution gave acetate **70** and alcohol **67** with excellent ee. The resolved acetate ester **67** and *ent*-**67** on hydrogenation followed by acidic hydrolysis provided 3-hydroxypipecolic acid **1** and *ent*-**1**.[18]

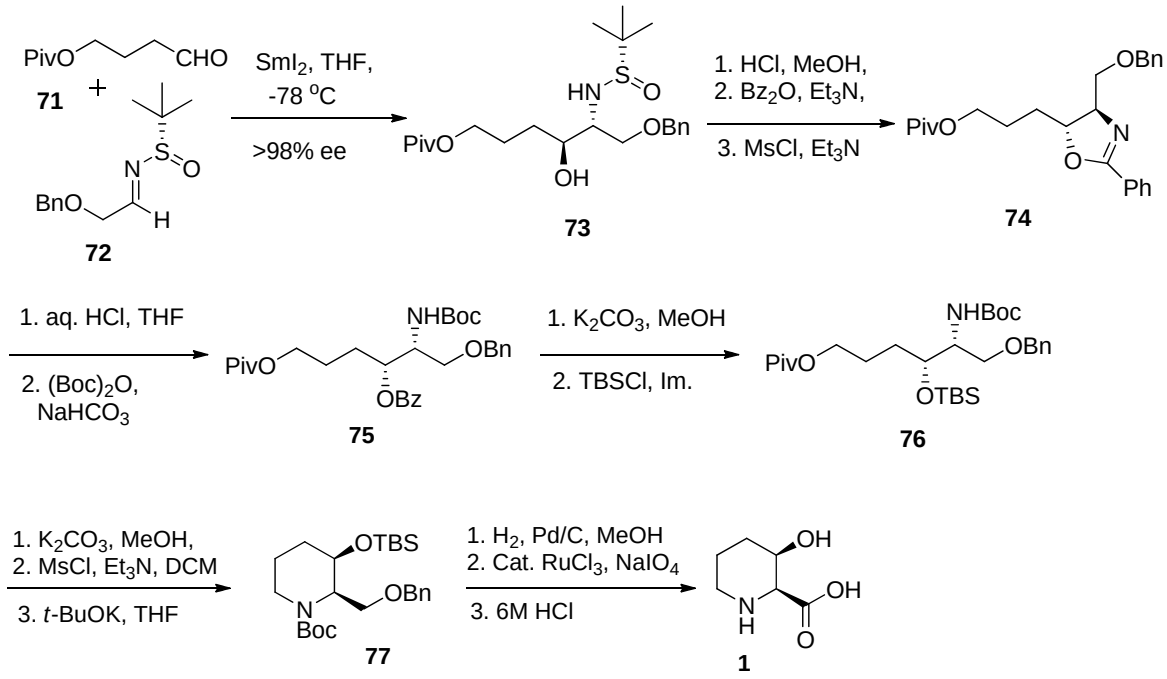


Scheme 11

Wang's approach

Wang *et al*. (Scheme 12) developed a Pinacol type reductive coupling between aldehyde **71** and sulfinyl imine **72** with excellent ee and exploited it for the synthesis of **1**. The removal of the sulfinyl auxiliary followed by selective *N*-protection with Bz_2O afforded benzoyl derivative which on reaction with MsCl, TEA underwent the stereospecific inversion at C-3 to forman oxazoline **74.** Oxazoline **74** on acidic ring cleavage and subse-

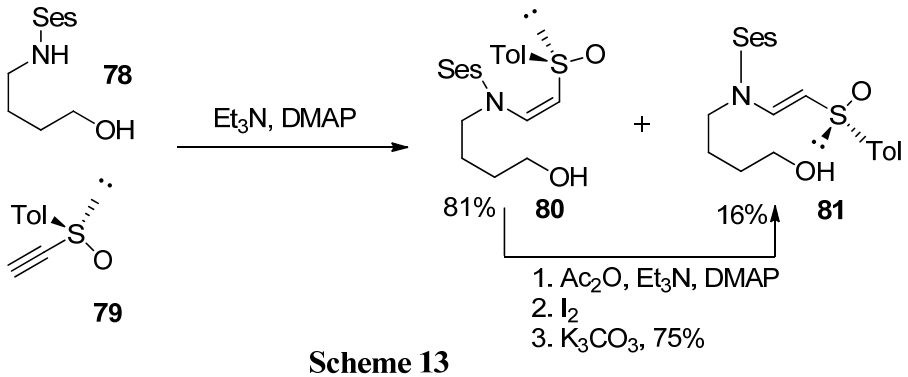
quent Boc protection of resultant amine furnished C-3 hydroxyl group inverted compound **75**. The pivaloyl group in **76** was deprotected and the resulting alcohol was converted in to its mesyl derivative followed by treatment with base to furnish piperidine derivative **77**. The benzyl group in **77** was deprotected under hydrogenation conditions followed by oxidation of alcohol and acidification to give final product 3-hydroxypipecolic acid **1.**[19]



Scheme 12

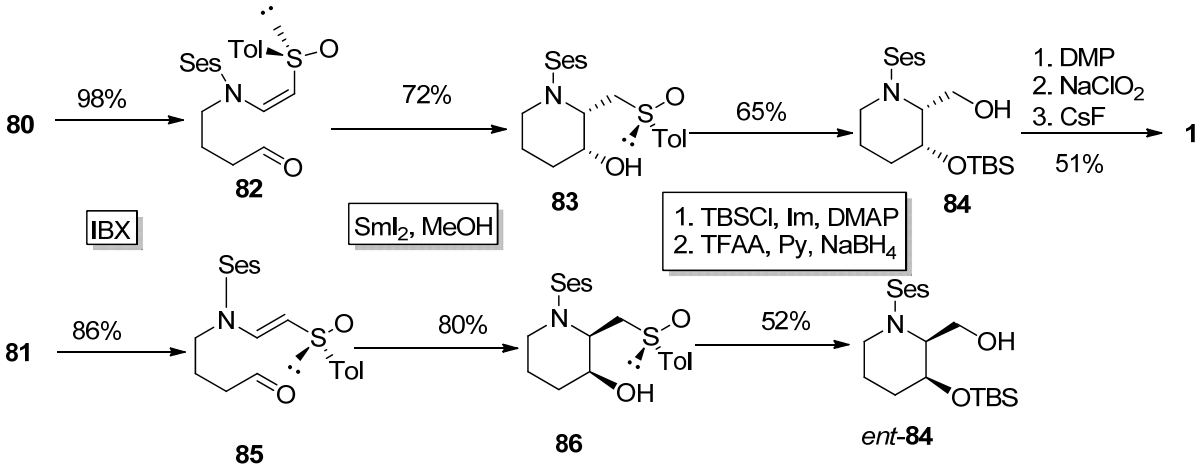
Lee's approach

Stereoselective synthesis of *cis*-3-hydroxypipecolic acid **1** was achieved *via* chirality transfer in the SmI_2-mediated cyclization reactions of aldehydo-*β*-aminovinyl sulfoxides.[20] Reaction of **78** with alkynyl sulfoxide **79** in the presence of TEA and DMAP produced a mixture of the (*Z*)-(*S*)- and (*E*)-(*S*)-*β*-aminovinylsulfoxides **80** (81%) and **81** (16%). The (*E*)-(*S*)-isomer **81** was also obtained from **80** *via* acetylation, treatment with iodine, and basic hydrolysis (Scheme 13).



Scheme 13

IBX oxidation of **80** and **81** yielded the corresponding aldehydes **82** and **85**, respectively. In the presence of SmI_2 and methanol in THF, the (*Z*)-(*S*)-aldehyde **82** was converted smoothly into the 3-hydroxypiperidine product **83**. The reaction of the (*E*)-(*S*)-isomer **85** proceeded more quickly producing another 3-hydroxypiperidine product **86** (Scheme 14). Pummerer rearrangement of the TBS derivatives of the products **83** and **86** and sodium borohydride reduction led to an enantiomeric pair of primary alcohols **84** and *ent*-**84**. Further conversion to (2*S*,3*R*)-3-hydroxypipecolic acid **1** involved Dess–Martin oxidation, Pinnick oxidation and cesium fluoride deprotection.



Scheme 14

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Chapter 3: Synthetic studies toward both enantiomers of *cis*- 3-hydroxypipecolic acid and development of synthetic methodology for preparation of chiral allylic amines from chiral aziridine-2-alcohols

Section 2: Formal synthesis of both enantiomers of *cis*-3-hydroxypipecolic acid

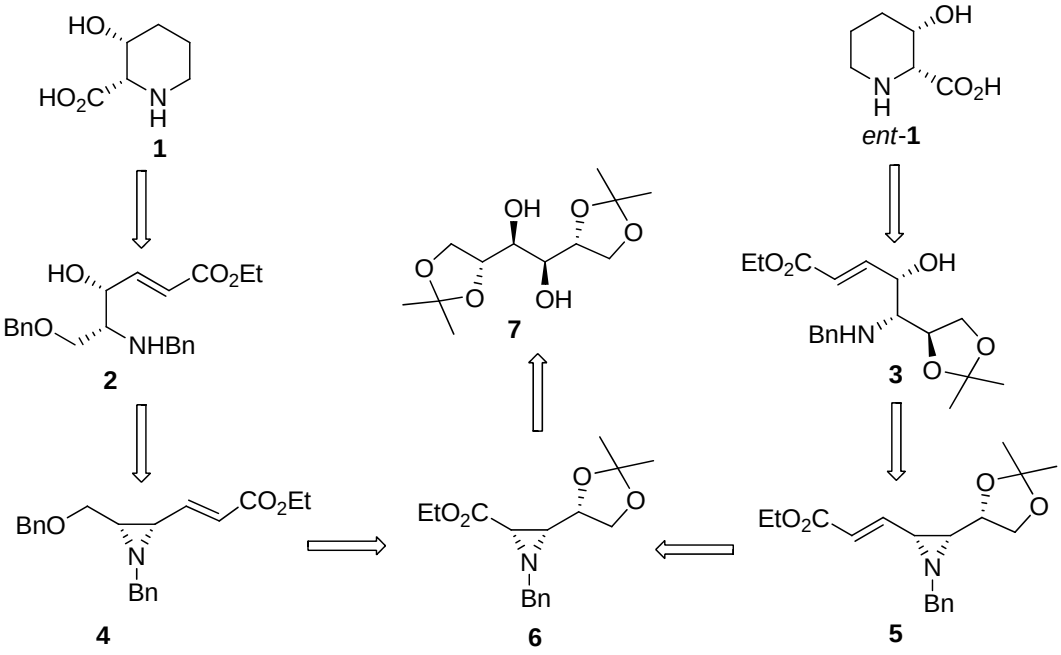
3.2.1 Present work

3.2.1.1 Objective

As a consequence of its biological significance, stereoisomeric 3-hydroxypipecolic acid has become an important target for many synthetic organic chemists and several synthetic strategies have been reported in the literature.[1] Unlike *trans* isomer, synthetic methods for *cis*-3-hydroxypipecolic acid are less prevalent, probably due to the easy outcome of the relative *trans* stereochemistry, on the adjacent carbon atoms, in the asymmetric pathways that involve either dihydroxylation or epoxidation followed by attack of the nitrogen nucleophile.[2] The potential application of 3-hydroxypipecolic acids coupled with our continued interest on the exploitation of enantiopure aziridines to highly functionalized chiral intermediates has inspired us to develop an efficient strategy for the synthesis of this class of molecules. In this section, we report stereoselective syntheses of both enantiomers of *cis*-3-hydroxypipecolic acid starting from *cis*-aziridine-2-carboxylate as common synthetic precursor derived from D-mannitol diacetonide.

3.2.1.2 Retrosynthetic analysis

On careful observation one can find that *cis*-aziridine-2-caboxylate **6** possesses hidden plane of symmetry where proper synthetic manipulation can give access to both enantiomers of *cis*-3-hydroxypipecolic acid.

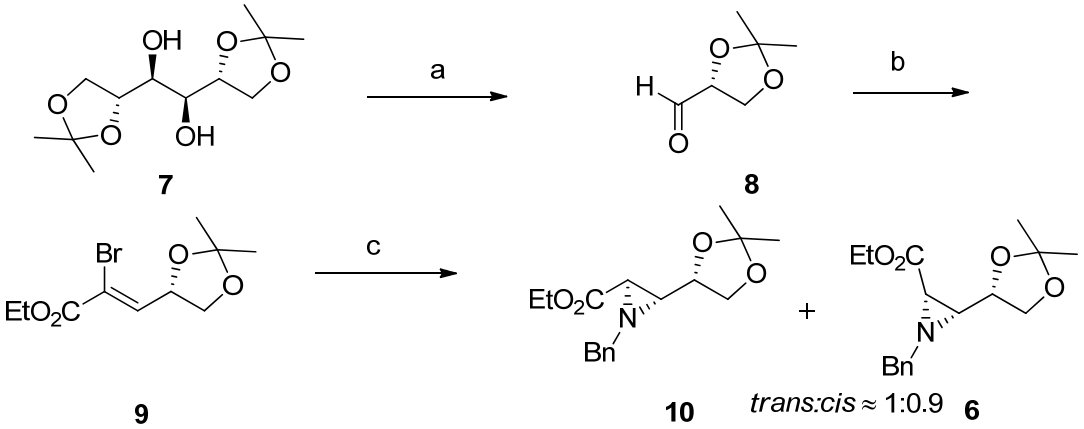


Scheme 1: Retrosynthetic analysis of *cis*-3-hydroxypipecolic acid

Accordingly as shown in retrosynthetic analysis (Scheme 1), it was envisioned that syntheses of both antipodes of *cis*-3-hydroxypipecolic acid *viz.* **1**/*ent*-**1** can be achieved by aziridine ring opening reaction of respective *α,β*-unsaturated aziridine esters **4**/**5**. The desired aziridines **4**/**5** can be easily accessed by regioselective functionalization on either side of *cis*-aziridine-2carboxylate **6** as the common synthetic precursor.

3.2.1.3 Results and discussion

The required *cis*-aziridine-2-caboxylate **6** was prepared from D-mannitol diacetonide **7** as reported earlier (Scheme 2).[3] Once the desired enantiopure *cis* aziridine-2-carboxylate **6** was in hand, it was decided to exploit its ester and acetonide functionalities as a handle to propagate on either side of aziridine-2-carboxylate **6** selectively.

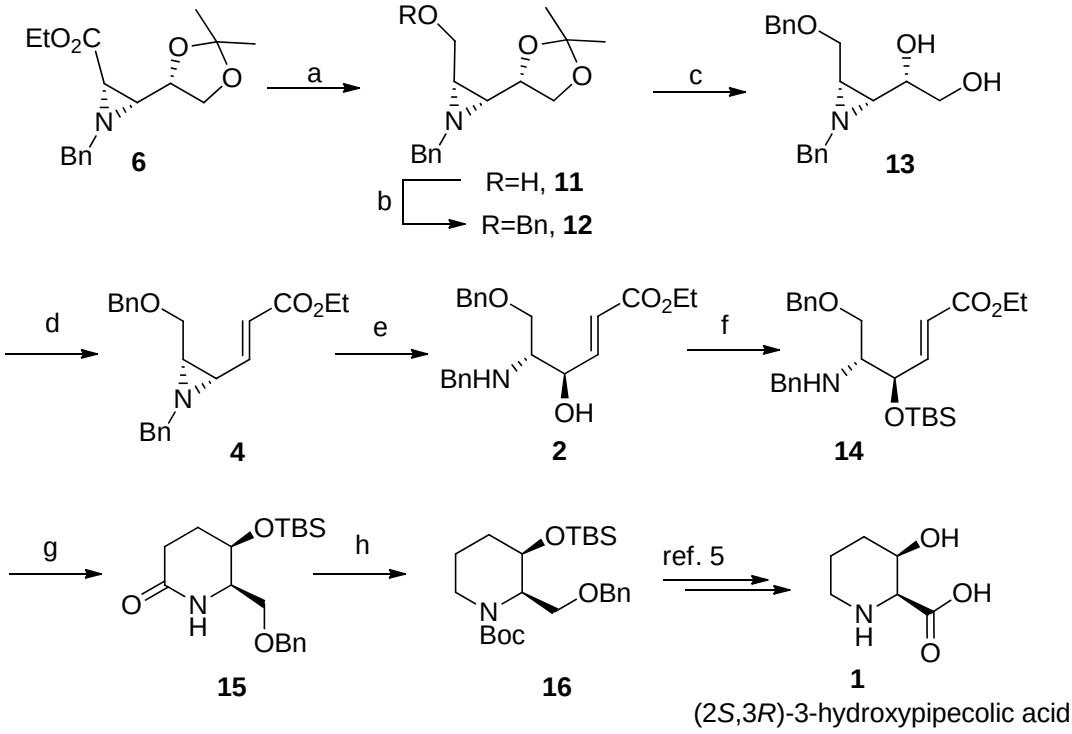


Scheme 2: ***Reagents and conditions:*** *a) $NaIO_4$, CH_2Cl_2, rt, 2h; b) $Ph_3PCBrCO_2Et$, CH_2Cl_2, rt, 84% over two steps; c) $BnNH_2$, Et_3N, EtOH, 0 ºC to rt, 72 h, 77%.*

3.2.1.3.1 Formal synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid

The synthetic effortstoward the formal synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid using *cis*-aziridine-2-caboxylate **6** are described herein. As mentioned in the Scheme 3, *α,β*-unsaturated aziridine ester **4** was synthesized from *cis*-aziridine-carboxylate **6** over five steps (for detailed description upto compound **4**, please refer to Chapter 1, Section 2, Schemes 14 and 19). This *α,β*-unsaturated aziridine ester **4** underwent regioselective and stereoselective aziridine ring opening reaction under acidic conditions[4] (TFA, 2 eq.) by water as nucleophile to form vicinal amino alcohol **2.** ^{1}H NMR spectrum of **2** showed disappearance of aziridine ring protons at δ 2.15-2.32 (m, 2H) and appearance of characteristic peak at δ 2.70-2.77 (m, 1H) indicated the opening of aziridine ring. The

magnitude of δ value suggested the δ-amino functionality. In ^{13}C NMR and DEPT spectra disappearance of characteristic peaks at δ 42.95 and 46.26 for aziridine ring -CH and appearance of new peaks at δ 60.8 and 69.7 for –CH group indicated the opening of aziridine ring. HRMS analysis (calculated for $C_{22}H_{28}O_4N$-370.2013, found-370.2017) further confirmed the molecular formula. Once the stereocenters at amine and hydroxyl functionality of amino-alcohol **2** were fixed with desired stereochemistry, the hydroxyl group of amino-alcohol **2** was selectively protected as TBS ether **14** using TBSCl, imidazole and cat. DMAP in refluxing dichloromethane in 90% yield.

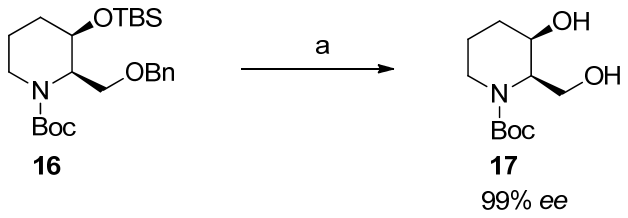


Scheme 3: ***Reagents and conditions:*** *(a) 1) LAH, THF, 0 °C, 1h, 90%;(b) BnBr, NaH, DMF, 95%;(c) PTSA, CH_3OH, 85%; (d) 1) $NaIO_4$, $(CH_3)_2CO:H_2O$ (2:1);2) Ph3PCHCO2Et, cat. $PhCO_2H$, toluene, reflux, 85% (over two steps);(e) TFA, $CH_3CN:H_2O$ (9:1), 85%; (f) TBSCl, Im, cat. DMAP, CH_2Cl_2, reflux, 90%; (g) H_2, 10% $Pd(OH)_2/C$, EtOH, 88%; (h) 1) BH_3·DMS, THF; 2) $(Boc)_2O$, CH_2Cl_2, Et_3N, 80%over two steps.*

In next crucial step, compound **14** on hydrogenation using 10% $Pd(OH)_2$ in ethanol (a condition can also be used for selective *N*-debenzylation over *O*-debenzylation)[5] underwent concomitant double bond reduction, selective *N*-debenzylation and cyclization

to furnish lactam **15** having requisite piperidine skeleton with desired stereocentres at C2 and C3 in 88% yield (Scheme 3). IR spectrum of **15** showed strong absorption band at 1657 cm^{-1} indicating the presence of lactam carbonyl. In ^1H NMR spectrum, appearance of peak at δ 6.51 (br s, 1H) and multiplet at δ 7.28-7.35 for five protons and disspearnce of double bond protons of unsaturated ester indicated the concomitant double bond reduction, selective *N*-debenzylation and cyclization to form the lactam ring.

In next step lactam **15** was reduced to amine using BH_3·DMS to furnish crude amine which without purification was protected as its *N*-Boc derivative using $(Boc)_2O$ to give intermediate **16** in 80% yield. Intermediate **16** is well reported in literature and can be converted into (2*S*,3*R*)-3-hydroxypipecolic acid **1** in three steps in 73% yield.[6]

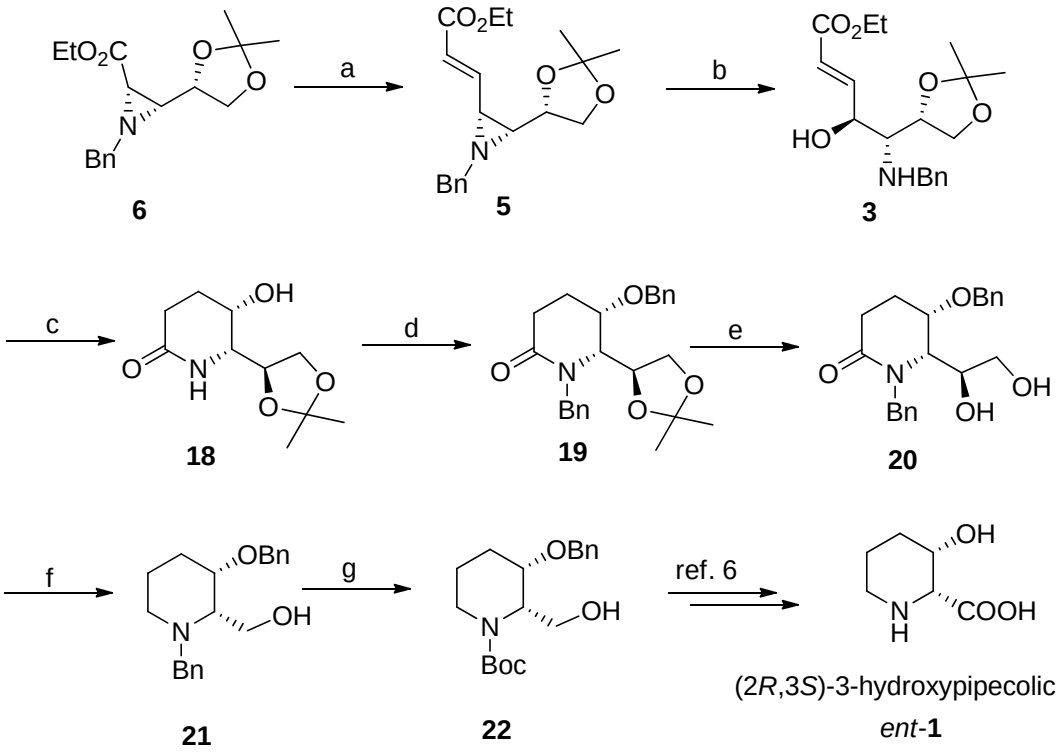


Scheme 4: ***Reagents and conditions:*** *(a) Pd/C (10%), CH_3OH:CH_3CO_2H, 9:1, 90%.*

In order to know the enantiomeric purity of the resultant acid, intermediate **16** was subjected to hydrogenation conditions using Pd/C (10%) in methanol:acetic acid (9:1) as solvent, delightfully underwent *O*-debenzylation as well as TBS deprotection simultaneously to furnish *N*-Boc diol derivative **17** in 90% yield. The chiral HPLC analysis of diol **17** concluded the enantiomeric purity of 99%. Hence present work constitutes a formal synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid **1**.

3.2.1.3.2 Formal synthesis of (2*R*,3*S*)-3-hydroxypipecolic acid

This section describes the formal synthesis of another enantiomer of *cis* 3-hydroxy *i.e.* (2*R*,3*S*)-3-hydroxypipecolic acid *ent*-**1**. Thus as shown in Scheme 5, the synthesis starts with common synthetic precursor c*is*-aziridine-2-ester **6** which on propagation from ester side using DIBAL-H reduction of ester to crude aldehyde followed by the two-carbon Wittighomologationwith Ph_3PCHCO_2Et and cat. benzoic acid in refluxing toluene gave (*E*)-*α*,*β*-unsaturated aziridine-ester **5** (for detailed description upto compound **5**, please refer to Chapter 1, Section 2, Schemes 14 and 17).



Scheme 5: ***Reagents and conditions:*** *(a) 1) DIBAL-H, CH_2Cl_2, -78 °C;2) Ph_3PCHCO_2Et, cat. $PhCO_2H$, toluene, reflux, 82%, (over two steps);(b) TFA, CH_3CN:H_2O, (9:1), 75%; (c) 10% Pd/C, HCO_2NH_4, MeOH, 60 °C, 90%; (d) BnBr, NaH, cat. TBAI, DMF, 85%; (e) 80%aq. AcOH; (f) 1) $NaIO_4$, $(CH_3)_2CO$:H_2O, (2:1); 2) BH_3·DMS, THF, 65%, over 3 steps; (g)1)H_2, (10 %) $Pd(OH)_2$/C, EtOH; 2) $(Boc)_2O$, Et_3N, CH_2Cl_2, 80% over 2 steps.*

In next important step, aziridine ester **3** on treatment with trifluoroacetic acid[4] in CH_3CN:H_2O underwent regioselective and stereoselective aziridine ring opening reaction to furnish *δ*-hydroxy,*γ*-amino,*α*,*β*-unsaturated ester **3** with desired stereocentres**.** Its ^{1}H NMR spectrum showed peak at δ 2.72 (dd, *J* = 3.2& 6.3 Hz, 1H) indicating *γ*-amino proton of **3**. ^{13}C and DEPT NMR spectra showed desired peaks indicating ring opened compound. Compound **3** was then subjected to transfer hydrogenation conditions under Pd/C (10%) and ammonium formate in refluxing methanol, which underwent concomitant double bond reduction, *N*-debenzylation and cyclisation to afford thermodynamically favored 3-hydroxy substituted *δ*-lactam **18** with excellent yield. IR spectrum of compound **18** showed strong absorption band at 1641 cm^{-1} indicating lactam carbonyl. ^{1}H and ^{13}C spectra showed desired peaks confirming the assigned structure. Finally, absolute stereochemistry was confirmed by single crystal XRD spectroscopy

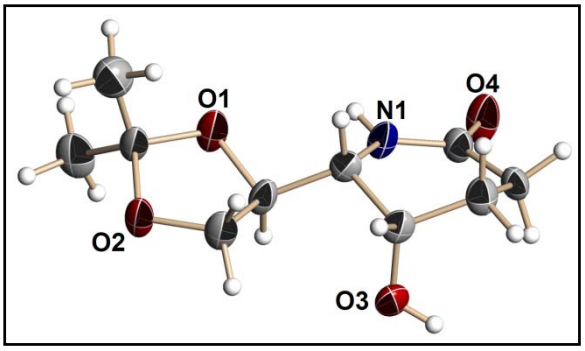
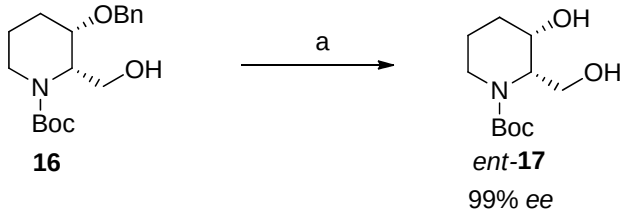


Figure 1: ORTEP diagram of compound **18**

which clearly showed the *cis* relationship between C3-hydroxy and C2-acetonide (with one fixed stereocentre) functionalities (Fig. 1).

Protection of lactam **18** as its *N* and *O*-benzyl derivative using BnBr, NaH and cat. TBAI in DMF furnished compound **19** in 85% yield. Deprotection of acetonide group of lactam **19** in 80% aq. acetic acid at 80 °C afforded diol **20** which without purification was subjected to acetonide cleavage to give crude aldehyde which was also subjected without purification to concomitant aldehyde and amide reduction using BH_3·DMS in THF to afford *N*-benzyl alcohol **21**. ^{1}H, ^{13}C and DEPT NMR spectral analysis showed the expected peaks. Finally HRMS analysis confirmed the molecular formula (calculated for $C_{18}H_{28}O_4N$-322.2013, found-322.2008). In next step, *N*-benzyl group of compound **21** was selectively deprotected over *O*-benzyl group[5] using 10% $Pd(OH)_2/C$ in ethanol followed by protection of resultant amine as *N*-Boc derivative to furnish compound **22** which is well reported in literature and can be exploited for the synthesis of (2*R*,3*S*)-3-hydroxypipecolic acid *ent*-**1** over four steps.[7] Enantiomeric purity was analyzed by converting the *N*-Boc derivative **22** to *N*-Boc diol *ent*-**17** under hydrogenation conditions. Chiral HPLC analysis of diol *ent*-**17** showed that it had 99% *ee*. Thus present work constitutes the formal synthesis of (2*R*,3*S*)-3-hydroxypipecolic acid *ent*-**1** (Scheme 6).



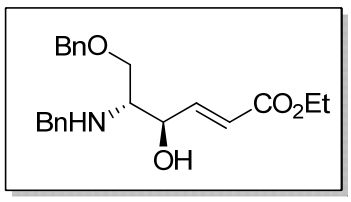
Scheme 6: ***Reagents and conditions:*** *(a) Pd/C (10%), CH_3OH, 90%.*

3.2.2 Conclusion

In conclusion, the efficient formal syntheses of both enantiomers of *cis*-3-hydroxypipecolic acid were accomplished from enantiopure *cis*-aziridine-2-carboxylate **6** as a common synthetic precursor. The key steps involved stereoselective and regioselective aziridine ring opening, reductive cyclization and selective *N*-debenzylation over *O*-debenzylation reactions. Synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid **1** was achieved in 24% overall yield over 8 purification steps while that of (2*R*,3*S*)-3-hydroxypipecolic acid *ent*-**1** was achieved in 12% overall yield and 9 purification steps starting from *cis*-aziridine-2-carboxylate **6**.

3.2.3 Experimental

(4*R*,5*R*,*E*)-Ethyl 5-(benzylamino)-6-(benzyloxy)-4-hydroxyhex-2-enoate (2)



To a stirred solution of aziridine ester **4** (0.85 g, 2.42 mmol) in acetonitrile–water (9:1, 20 mL) at 0 ℃ was added TFA (0.37 mL, 4.84mmol). The reaction mixture was allowed to warm to room temperature, stirred for 6-8 h, and neutralized with $NaHCO_3$. Reaction mixture was extracted with ethyl acetate (3 × 25 mL), washed with brine, dried over anhydrous Na_2SO_4 and filtered. Evaporation of solvent under reduced pressure and column chromatography (pet ether–ethyl acetate=4:1) afforded amino-alcohol **2** (0.79 g) as a thick liquid.

***R*$_f$:** 0.5 (Pet ether-ethyl acetate, 3:7).

Yield: 88%.

MF: $C_{22}H_{27}NO_4$, **MW**: 369.45.

[α]$_D^{25}$ −5.88 (*c* 1.02, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): vmax 3348, 2922, 1717, 1654, 1599, 1451, 1267.

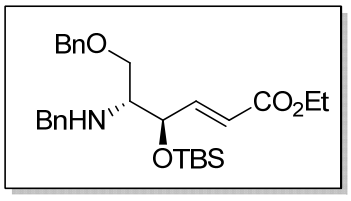
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.31 (t, *J* = 7.0 Hz, 3H), 2.35 (br s, 2H), 2.70-2.77 (m, 1H), 3.48 (dd, *J* = 5.0 & 10.0 Hz, 1H), 3.69 (dd, *J* = 5.0 & 10.0 Hz, 1H), 3.77, 3.85 (ABq, *J* = 14.0 Hz, 2H), 4.15-4.26 (m, 3H), 4.50 (s, 2H), 6.13 (dd, *J* = 2.0 & 16.0 Hz, 1H), 6.90 (dd, *J* = 6.0 & 16.0 Hz, 1H), 7.33 (m, 10H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 14.3, 51.8, 60.2, 60.8, 67.9, 69.7, 73.3, 121.8, 127.3, 127.7, 128.2, 128.5, 137.5, 139.2, 147.9, 166.2.

MS (ESI): *m/z*: 392.21 $(M + Na)^+$.

HRMS: Calculated for $C_{22}H_{28}O_4N$-370.2013, found-370.2017.

(4*R*,5*R*,*E*)-Ethyl 5-(benzylamino)-6-(benzyloxy)-4-((*tert*-butyldimethylsilyl)oxy)hex-2-enoate (14)



To a stirred solution of hydroxyl amino ester **4** (0.7 g, 1.9 mmol), imidazole (0.26 g, 3.8 mmol) and DMAP (0.024 g, 0.2 mmol) in CH_2Cl_2 (20 mL) was slowly added TBSCl (0.57 g, 3.8 mmol) dissolved in CH_2Cl_2 (5 mL) at 0°C after which reaction was heated to reflux for 6 h until completion of reaction. Reaction mass was concentrated under reduced pressure followed

by column chromatographic purification using ethyl acetate: pet ether (5:95) to yield 0.84 g of -*O*TBS protected amino-ester **14** as thick colourless liquid.

***R*$_f$:** 0.5 (Pet ether-ethyl acetate, 1:9).

Yield: 92%

MF: $C_{28}H_{41}NO_4Si$, **MW:** 483.71

[α]$^{25}_{D}$ +32 (*c* 0.8, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): vmax3350, 2923, 1720, 1665, 1277.

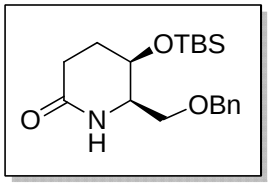
^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 1.31 (t, *J* = 7.2 Hz, 3H), 2.88 (q, *J* = 6 Hz, 1H), 3.35 (dd, *J* = 5.3 & 9.6 Hz, 1H), 3.55 (dd, *J* = 5.3 & 9.6 Hz, 1H), 3.84, 3.88 (ABq, 13.0 Hz, 2H), 4.16-4.23 (m,2H), 4.45-4.50 (m, 3H), 5.96 (dd, *J* = 1.7 & 15.6 Hz, 1H), 7.11 (dd, *J* = 4.4 & 15.6 Hz, 1H), 7.22-7.34 (m, 10H).

^{13}CNMR (100 MHz, $CDCl_3$+CCl_4): δ −4.5, −4.6, 14.3, 18.2, 25.9, 52.4, 60.2, 61.7, 69.1, 71.5, 73.1, 120.6,126.9,127.6,128.1,128.3,138.2,140.5,148.9,166.2.

MS (ESI): *m/z*: 506.22 $(M+Na)^+$.

HRMS: Calculated for $C_{28}H_{42}O_4NSi$-484.2878, found-484.2900.

(5*R*,6*R*)-6-((Benzyloxy)methyl)-5-((*tert*-butyldimethylsilyl)oxy)piperidin-2-one (15)



To a solution of **14** (0.6 g, 1.24 mmol) in EtOH (15 mL) was added 10% $Pd(OH)_2/C$ (0.05 g) and the reaction mixture was vigorously shaken under balloon of H_2 atmosphere for 4 h at ambient temperature. The mixture was then filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography over silica gel (pet ether-ethyl acetate, 2:3) gave lactam **15** (0.38g) as a thick liquid.

***R*$_f$:** 0.5 (Pet ether-ethyl acetate, 1:1).

Yield: 88%

MF: $C_{19}H_{31}NO_3Si$, **MW:** 349.54.

[α]$^{25}_{D}$ +24 (*c* 0.25, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): vmax 2989, 2940, 1657, 1457, 1275, 1194.

^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): δ 0.03 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 1.80-1.87 (m, 1H), 1.91-1.94 (m, 1H), 2.31 (br dd, *J* = 3.6 & 17.6 Hz, 1H), 2.53-2.60 (m, 1H),

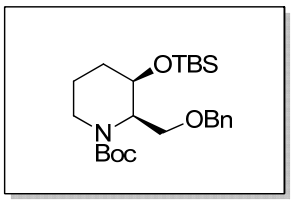
3.46 (t, *J* = 8.8 Hz, 1H), 3.53 (dd, *J* = 3.9 & 8.8 Hz, 1H), 3.60-3.63 (m, 1H), 4.06 (br s, 1H), 4.51 (s, 2H), 6.51(br s, 1H), 7.28-7.35 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ −5.1, −4.4, 18.1, 25.7, 26.4, 28.1, 57.05, 64.3, 71.0, 73.6, 127.8, 127.9, 128.5, 137.4, 171.0.

MS (ESI): *m/z*: 372.66 $(M+Na)^+$.

HRMS: Calculated for $C_{19}H_{32}NO_3Si$-350.2146, found-350.2138.

(2*R*,3*R*)-*tert*-Butyl 2-((benzyloxy)methyl)-3-((*tert*-butyldimethylsilyl)oxy) piperidine-1-carboxylate (16)



To an ice-cold solution of **15** (0.3 g, 0.86 mmol) in dry THF (5 mL) was added $BH_3{\cdot}SMe_2$ (0.29 mL, 4.29 mmol) dropwise under argon, and the reaction mixture was kept at room temperature for 8h. The excess of reducing agent was quenched by slow addition of EtOH (3 mL). After evaporation of the solvent, the residue was dissolved in EtOH (10 mL) and heated at reflux for 2 h. The cooled mixture was then evaporated and used as such for next transformation.

To a solution of crude amine from above reaction in CH_2Cl_2 (5mL) was added triethylamine (0.23 mL, 1.63 mmol) *via* syringe followed by $(Boc)_2O$ (0.38 mL,1.63 mmol) in one portion. The reaction mixture was stirred for 4 h after which the resulting yellow solution was poured into water (5 mL). The layer was separated, and the organic layer was washed with water (5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The crude compound was purified by flash column chromatography to afford compound **16** (0.31 g) as a colorless oil.

***R_f*:** 0.5 (Pet ether-ethyl acetate, 9:1).

Yield: 80% (Over two steps).

MF: $C_{24}H_{41}NO_4Si$, **MW:** 435.67

$[\alpha]_D^{25}$ +5.2 (*c* 1.2, $CHCl_3$), lit.[5] **$[\alpha]_D^{23}$** +5.3 (*c* 0.66, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): vmax 2930, 1691, 1630, 1450, 1289.

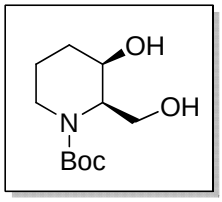
^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 1.46 (s, 9H), 1.40-1.54 (m, 2H), 1.63-1.66 (m, 2H), 2.72-2.76 (m, 1H), 3.70-3.97 (m, 4H), 4.40-4.62 (m, 3H), 7.27-7.30 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ −4.8, 18.1, 24.0, 25.8, 28.4, 29.7, 37.3, 56.1, 64.4, 69.4, 72.6, 79.3, 127.3, 128.2, 138.7, 155.0.

MS (ESI): *m/z*: 458.23 $(M+Na)^+$.

HRMS: Calculated for $C_{24}H_{42}O_4NSi$-436.2878, found-436.2886.

(2*R*,3*R*)-*tert*-Butyl 3-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate (17)



To a solution of **16** (0.1 g, 0.23 mmol) in MeOH:AcOH (9:1, 5 mL) was added 10% Pd/C (0.03 g) and the mixture was vigorously shaken under H_2 atmosphere for 4 h at ambient temperature. The mixture was then filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography over silica gel (pet ether-ethyl acetate, 2:3) gave diol **17** (0.05 g) as a white solid.

***R_f*:** 0.5 (Pet ether-ethyl acetate, 1:2).

Yield: 95%.

MF: $C_{11}H_{21}NO_4$, **MW:** 231.29.

MP: 114-116 °C, lit.[7]-114-116 °C

$[\alpha]_D^{25}$ –22.8 (*c* 1.1, MeOH), lit.[7] {for *ent*-**17** **$[\alpha]_D^{25}$** +23.1 (*c* 1.03, MeOH)}.

IR ($CHCl_3$, cm^{-1}): vmax 3372, 2932, 1666, 1178, 1072.

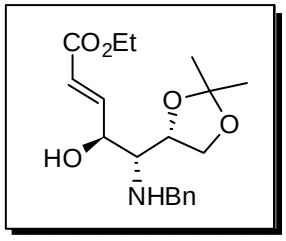
^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 1.48 (s, 9H), 1.59-1.82 (m, 4H), 2.89 (br s, 1H), 3.68-3.80 (m, 2H), 3.92-4.01 (m, 1H), 4.11 (dd, *J* = 6.0 & 11.0 Hz, 1H), 4.25-4.34 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4):δ 23.7, 28.2, 28.3, 39.5, 55.9, 59.2, 69.3, 80.3, 155.6.

MS (ESI): *m/z*: 254.23 $(M+Na)^+$.

HRMS: Calculatedfor $C_{11}H_{21}NNaO_4$-254.1368, found-254.1369.

(4*S*,5*R*,*E*)-Ethyl 5-(benzylamino)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-hydroxypent-2-enoate (3)



To a stirred solution of ester **5** (1 g, 2.86 mmol) in acetonitrile:water (9:1, 21 mL) was added TFA (0.44 mL, 5.73 mmol) dropwise at 0 ºC. The reaction mixture was slowly warmed to room temperature and stirred until complete

disappearance of starting material (~ 8 to 10 h). Reaction was quenched by solid $NaHCO_3$ and organic layer was extracted with ethyl acetate (3 × 15 mL). Combined orgnic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure followed by column chromatography using ethyl acetate:pet ether (15:85) to yield amino-alcohol **3** as a thick oil (0.84 g).

***R_f*:** 0.5 (Pet ether-ethyl acetate, 3:7).

Yield: 80%.

MF: $C_{19}H_{27}NO_5$,**MW:** 349.42

IR ($CHCl_3$, cm^{-1}):νmax 3448, 2986, 1717, 1655, 1454, 1371, 1262.

$[\alpha]_D^{25}$ −9.7 (*c* 3.1, $CHCl_3$)

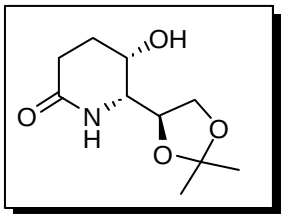
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.31 (t, *J* = 7.2 Hz, 3H), 1.35 (s, 3H), 1.39 (s, 3H), 2.73 (dd, *J* = 3.2 & 6.3 Hz, 1H), 3.74-3.86 (m, 3H), 4.03-4.13 (m, 3H), 4.24 (q, *J* = 7.2, 2H), 6.19 (dd, *J* = 2.0 & 15.6 Hz), 6.98 (dd, *J* = 3.9 & 15.6 Hz), 7.27-7.35 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 14.1, 25.1, 26.5, 53.3, 60.3, 62.8, 66.9, 69.6, 76.0, 109.3, 121.0, 127.2, 128.1, 128.4, 139.3, 149.2, 166.2.

MS (ESI): *m/z*: 350.41 $[M+H]^+$.

HRMS: Calculated for $C_{19}H_{28}O_5N$-350.1962, found-350.1967.

(5*S*,6*R*)-6-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-5-hydroxypiperidin-2-one (18)



To a stirred solution of amino-alcohol **3** (0.5 g, 1.43 mmol) in methanol (15 mL) was added ammonium formate (0.9 g, 14.3 mmol) and 10% Pd/C (80 mg), and the mixture refluxed for 3 h. The reaction mixture was filtered through Celite, concentrated and purified by column chromatography (methanol–ethyl acetate, 1:9) to afford lactam**18** (0.28 g) as a white solid.

***R_f*:** 0.35 (ethyl acetate-methanol, 9:1)

Yield: 90%, **MP:** 103-105 °C

MF: $C_{10}H_{17}NO_4$, **MW:** 215.25.

IR ($CHCl_3$, cm^{-1}): vmax 3315, 2996, 2985, 1641, 1474, 1378, 1213, 1081.

$[\alpha]_D^{25}$ −24.34 (*c* 2.3, $CHCl_3$).

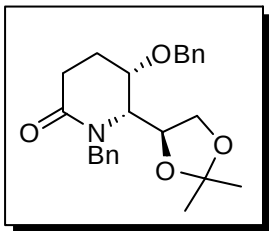
^{1}H NMR (400 MHz, $CDCl_3$+CCl_4+DMSO-d_6): δ 1.10 (s, 3H), 1.16 (s, 3H), 1.58 (br s, 1H), 1.78-1.79 (m, 1H), 1.99-2.01 (m, 1H), 2.29-2.34 (m, 1H), 3.04 (br d, J = 6.5 Hz, 1H), 3.52 (br s, 1H), 3.72 (s, 1H), 3.88 (br s, 1H), 4.04-4.08 (br m, 1H), 4.38 (br s, 1H), 4.58 (s, 1H), 5.88 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4+DMSO-d_6): δ 25.2, 26.0, 26.7, 27.3, 59.5, 62.1, 65.8, 75.6, 108.9, 171.0.

MS (ESI): *m/z*: 216.13 $[M+H]^+$, 238.11 $[M+Na]^+$.

Elemental Analysis: C-55.80; H-7.96; N-6.51; found: C-55.75, H-8.00, N-6.50.

(5*S*,6*R*)-1-Benzyl-5-(benzyloxy)-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)piperidin-2-one (19)



A suspension of sodium hydride (0.09 g, prewashed using dry *n*-hexane, 3.72 mmol) in dry DMF (1 mL) was cooled in an ice bath and stirred for 15 min under a nitrogen atmosphere. A solution of lactam **18** (0.2 g, 0.93 mmol) in dry DMF (2 mL) was added slowly, followed by addition of TBAI (0.03 g, 0.1 mmol) and dropwise addition of benzyl bromide (0.33 mL, 2.8 mmol). The reaction mixture was warmed to room temperature and stirred for additional 3 h. Water (5 mL) was added slowly, and the volatiles were removed under reduced pressure. Further water (10 mL) was added, and the aqueous phase was extracted with ethyl acetate (3 × 15 mL), and the organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure and purified by chromatography on silica gel to give protected lactam **19** (0.31 g) as a colourless liquid.

***R_f*:** 0.5 (Pet ether-ethyl acetate, 1:1).

Yield: 85%.

MF: $C_{24}H_{29}NO_4$, **MW:** 395.49.

IR ($CHCl_3$, cm^{-1}): νmax 2985, 2934, 1645, 1453, 1371, 1252, 1155.

$[\alpha]_D^{25}$ +25.33 (*c* 1.5, $CHCl_3$).

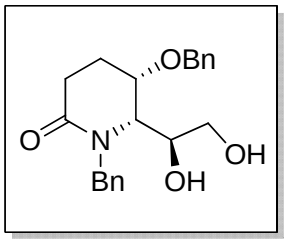
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.35 (s, 3H), 1.43 (s, 3H), 1.92-2.01 (m, 2H), 2.45-2.77 (m, 2H), 3.39-3.42 (m, 1H), 3.50-3.73 (m, 2H), 3.98-4.16 (m, 2H), 4.28-4.43 (m, 3H), 5.63 (d, J = 15.0 Hz, 1H), 7.06-7.23 (m, 10H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 23.0, 25.5, 26.3, 28.8,49.1, 58.1, 68.0, 71.0, 74.0, 75.4, 108.8, 127.4, 127.8, 128.0, 128.4, 128.5, 137.3, 169.83.

MS (ESI): *m/z*: 396.41 $[M+H]^+$.

HRMS: Calculated for $C_{24}H_{30}NO_4$-396.2169, found-396.2162.

(5*S*,6*S*)-1-Benzyl-5-(benzyloxy)-6-((*S*)-1,2-dihydroxyethyl)piperidin-2-one (20)



Protected lactam **19** (0.3 g, 0.76 mmol) was treated with 80% aqueous acetic acid (3 mL), and the resulting mixture was allowed to react at 80 °C. The reaction was monitored by TLC and was judged to be complete after 3 h. The solvent was then evaporated to dryness under reduced pressure to yield thick gummy mass which was used as such for next reaction. Small amount of mass from above reaction was purified using column chromatography (pet ether-ethyl acetate, 1:9) for spectroscopic analysis to yield pure terminal diol **20** as a thick gummy liquid.

***R_f*:** 0.5 (Pet ether-ethyl acetate, 1:9).

MF: $C_{21}H_{25}NO_4$, **MW:** 355.43.

IR ($CHCl_3$, cm^{-1}): vmax 3419, 2923, 1621, 1495, 1455, 1269.

$[\alpha]_D^{25}$ −75 (*c* 0.8, $CHCl_3$).

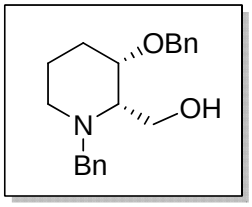
^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 1.85-1.90 (m, 1H), 1.97-2.09 (m, 1H), 2.35-2.42 (m, 1H), 2.56-2.66 (m, 1H), 3.38 (t, *J* = 3.0 Hz, 1H), 3.47-3.49 (m, 1H), 3.50-3.53 (m, 1H), 3.59-3.63 (m, 1H), 3.73-3.90 (m, 2H), 4.03-4.06 (m, 1H), 4.22, 4.27 (ABq, *J* = 12.0 Hz, 2H), 5.45 (d, *J* = 15.0 Hz, 1H), 6.99-7.23 (m, 10H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 23.0, 29.2, 50.5, 56.7, 65.8, 70.1, 74.3, 76.9, 127.6, 127.8, 128.2, 128.4, 136.9, 137.4, 171.7.

MS (ESI) *m/z*: 378.21 $[M+Na]^+$.

HRMS: Calculated for $C_{21}H_{25}O_4NNa$-378.1676, found-378.1683.

(5*S*,6*S*)-1-Benzyl-5-(benzyloxy)-6-(hydroxymethyl)piperidin-2-one (21)



Crude diol **20** from above reaction was dissolved in acetone–water (3 mL, 2:1) at 0 °C, treated with sodium metaperiodate (0.3 g, 1.4 mmol) and stirred at 15 °C for 15 min. The reaction was quenched using ethylene glycol (0.01 mL), extracted with CH_2Cl_2 (3 × 10

mL), washed with brine, dried over anhydrous Na_2SO_4 and filtered. The combined organics were concentrated under reduced pressure to afford crude aldehyde which was used as such for next reaction.

To a solution of crude aldehyde from above reaction in dry THF (5mL) at 0 ºC was added BH_3·DMS (0.5 mL, 4.65 mmol) dropwise under argon atmosphere and stirred for 12 h while warming the solution slowly to room temperature. The excess of reducing agent was quenched by slow addition of EtOH (5 mL). After evaporation of solvent, the residue was dissolved in EtOH (10 mL) and heated at reflux for 2 h. The cooled mixture was then column purified using ethyl acetate-pet ether (7:3) to yield compound **21** (153 mg) as thick liquid.

***R_f*:** 0.5 (Pet ether-ethyl acetate, 3:7).

Yield: 65% over three steps.

MF: $C_{20}H_{25}NO_2$, **MW:** 311.42.

IR ($CHCl_3$, cm^{-1}): vmax 3448, 2986, 1655, 1454, 1371, 1262.

$[\alpha]_D^{25}$ −12.7 (*c* 0.3, $CHCl_3$)

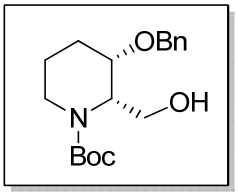
^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 1.62-1.66 (m 1H), 1.77-1.85 (m, 3H), 2.62 (br s, 1H), 2.83 (br s, 1H), 3.30 (br s, 1H), 3.84-3.87 (m, 1H), 3.95 (d, *J* = 6.4 Hz, 2H), 4.01 (br s, 2H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 7.30-7.39 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4):δ22.6, 25.9, 31.9, 46.4, 57.9, 61.7, 70.9, 127.6, 127.9, 128.5, 129.2, 137.8.

MS (ESI): *m/z*: 334.16 $[M+Na]^+$.

HRMS: Calculated for $C_{20}H_{26}O_2N$-312.1958, found-312.1964.

(2*S*,3*S*)-*tert*-Butyl 3-(benzyloxy)-2-(hydroxymethyl)piperidine-1-carboxylate (22)



To a solution of *N*-benzyl alcohol **21** (0.1 g, 0.32 mmol) in EtOH (3 mL) was added 10% $Pd(OH)_2$/C (0.03 g) and was vigorously shaken under balloon H_2 atmosphere until disappearance of starting material (2 h) as judged by TLC. The mixture was then filtered through a pad of Celite, concentrated *in vacuo* and used as such for next reaction.

To a solution of crude amine in CH_2Cl_2 (5 mL) was added triethylamine (0.09 mL, 0.64 mmol) followed by di(*tert*-butyl)dicarbonate (0.17 mL, 0.64 mmol). The reaction mixture was stirred for 6 h after which the resulting solution was poured into water (10 mL).

Organic layer was extracted using CH_2Cl_2 (2 × 15 mL), washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by flash column chromatography to furnish compound **22** (83 mg) as colourless oil.

***R_f*:** 0.5 (Pet ether-ethyl acetate, 4:6).

MW: $C_{18}H_{27}NO_4$, **MF:** 321.41.

IR ($CHCl_3$, cm^{-1}): νmax 3448, 2986, 1655, 1454, 1371, 1262.

$[\alpha]_D^{25}$ +16.3 (*c* 0.3, $CHCl_3$), lit[6]- {**$[\alpha]_D^{25}$** +16.7 (*c* 1.31, $CHCl_3$)}

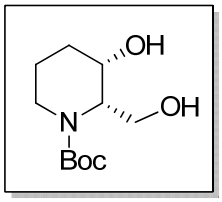
^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 1.42-1.44 (m, 1H), 1.47 (s, 9H), 1.55-1.68 (m, 1H), 1.63-1.74 (m, 1H), 1.97-2.22 (m, 1H), 2.75 (br s, 2H), 3.61-3.64 (m, 1H), 3.74 (br s, 1H), 3.87 (br s, 1H), 4.02 (dd, *J* = 6.0 & 12.0Hz, 1H), 4.61-4.72 (m, 3H), 7.25-7.35 (m, 5H)

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 23.9, 25.8, 28.4, 39.2, 53.5, 59.1, 70.9, 76.5, 80.1, 127.5, 127.8, 128.5, 137.9.

MS (ESI): *m/z*: 344.16 $[M+Na]^+$.

HRMS: Calculated for $C_{18}H_{28}O_4N$-322.2013, found-322.2008.

(2*S*,3*S*)-*tert*-Butyl 3-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate (*ent*-17)



To a solution of **16** (0.05 g, 0.23 mmol) in MeOH (3 mL) was added 10% Pd/C (0.02 g) and was vigorously shaken under H_2 atmosphere for 4 h at ambient temperature. The mixture was then filtered through a pad of silica and concentrated *in vacuo*. Purification by column chromatography over silica gel (pet ether-ethyl acetate, 2:3) gave diol *ent*-**17** (0.035 g) as a white solid.

***R_f*:** 0.5 (Pet ether-ethyl acetate, 1:2).

Yield: 90%.

MF: $C_{11}H_{21}NO_4$, **MW**: 231.29.

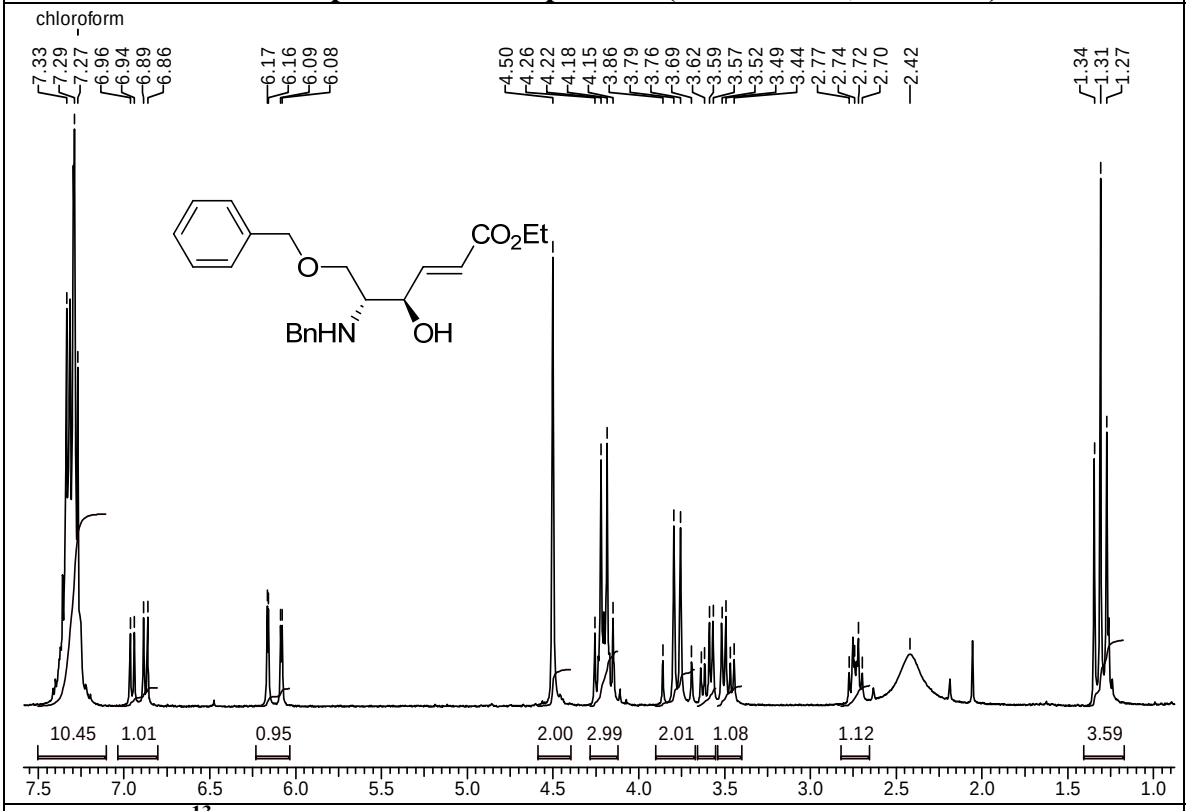
MP: 113-114 °C, lit.[7] - 114-116 °C.

$[\alpha]_D^{25}$ +22.5 (*c* 0.8, MeOH), lit.[7]-{**$[\alpha]_D^{25}$** +23.1 (*c*1.03, MeOH)}.

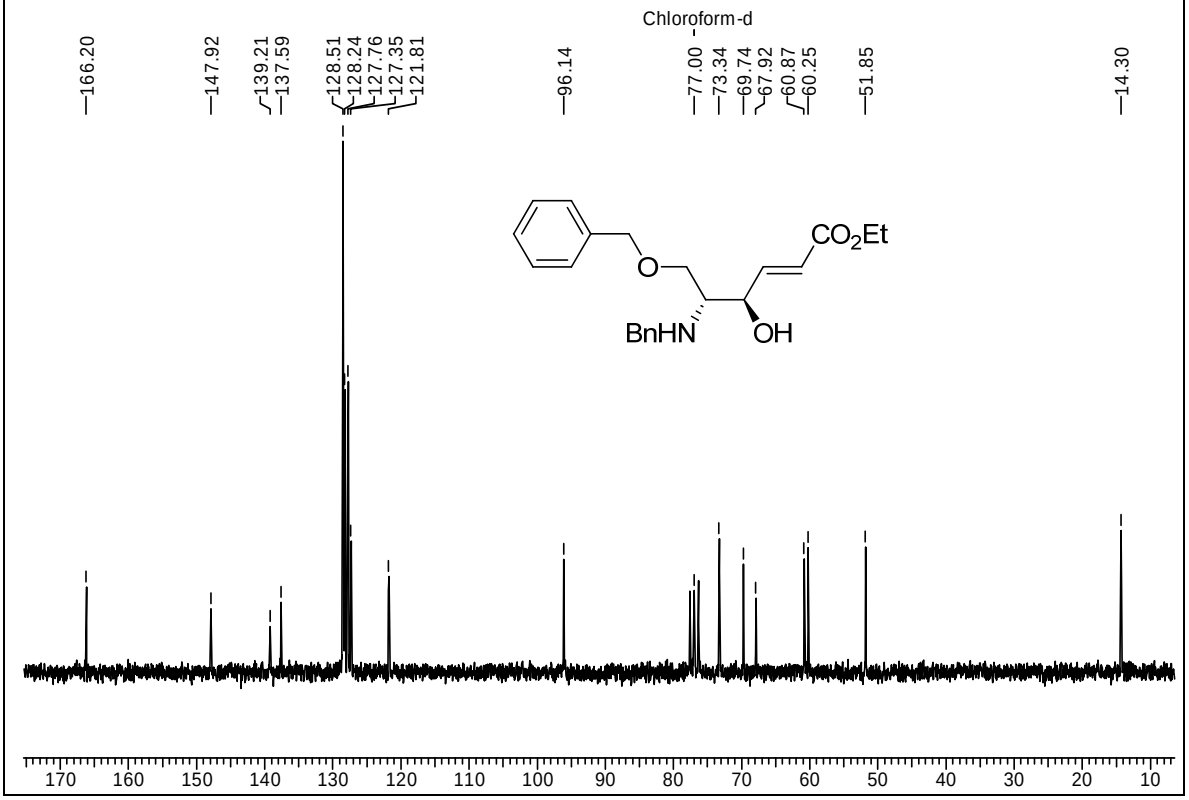
For other data please refer to (2*R*,3*R*)-**17**.

3.2.4 Analytical data

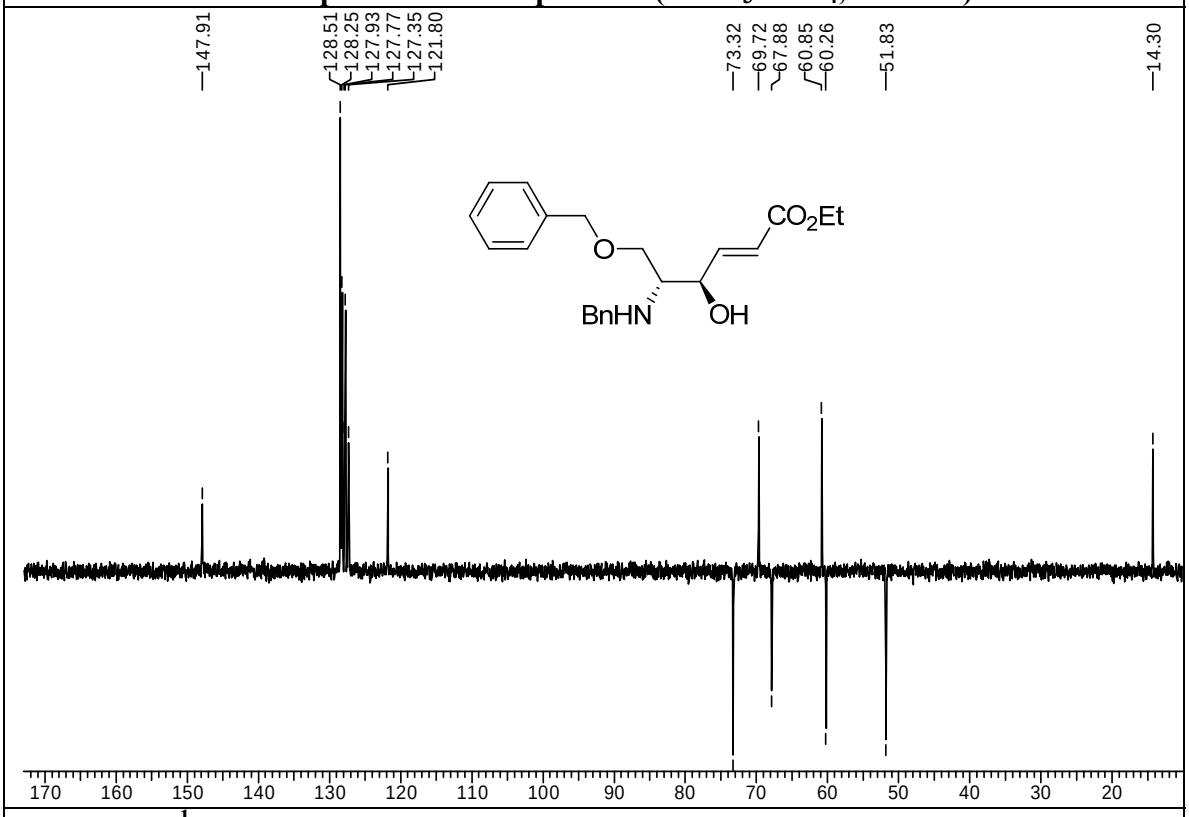
^{1}H-NMR spectrum of compound 2 ($CDCl_3$+CCl_4, 200 MHz)



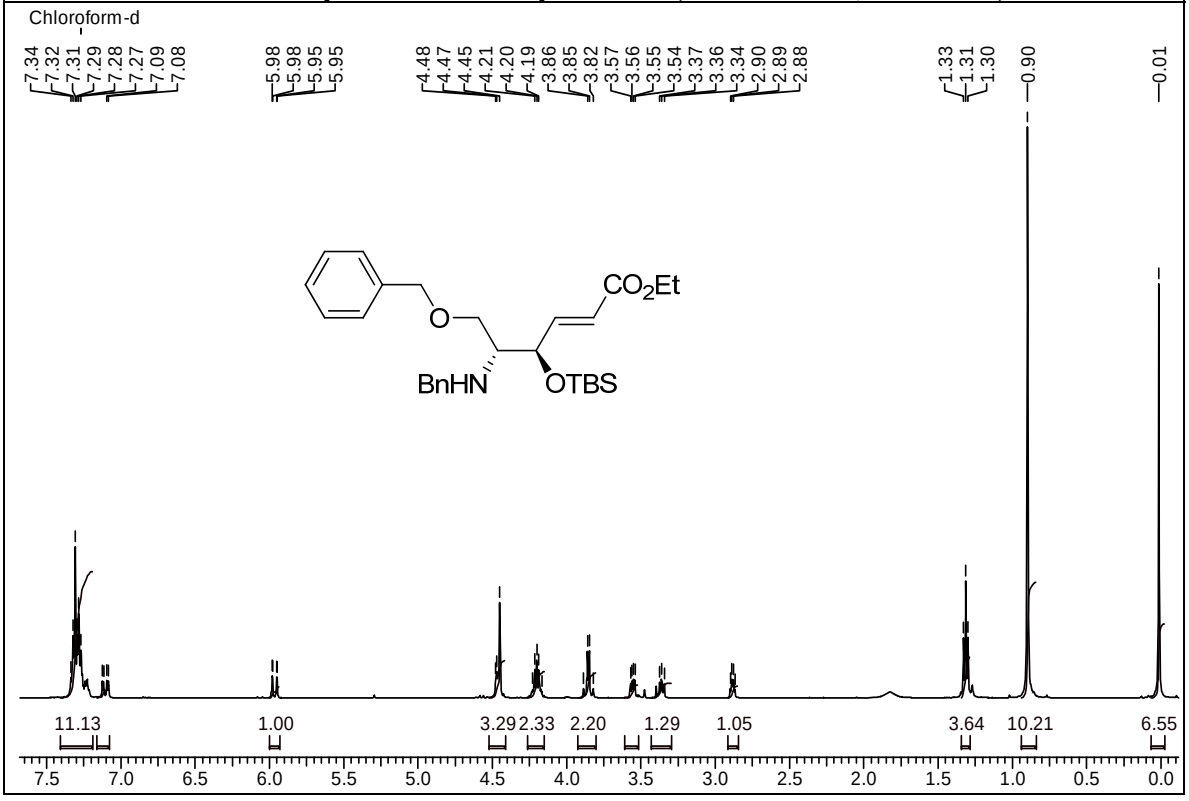
^{13}C-NMR spectrum of compound 2 ($CDCl_3$+CCl_4, 50 MHz)



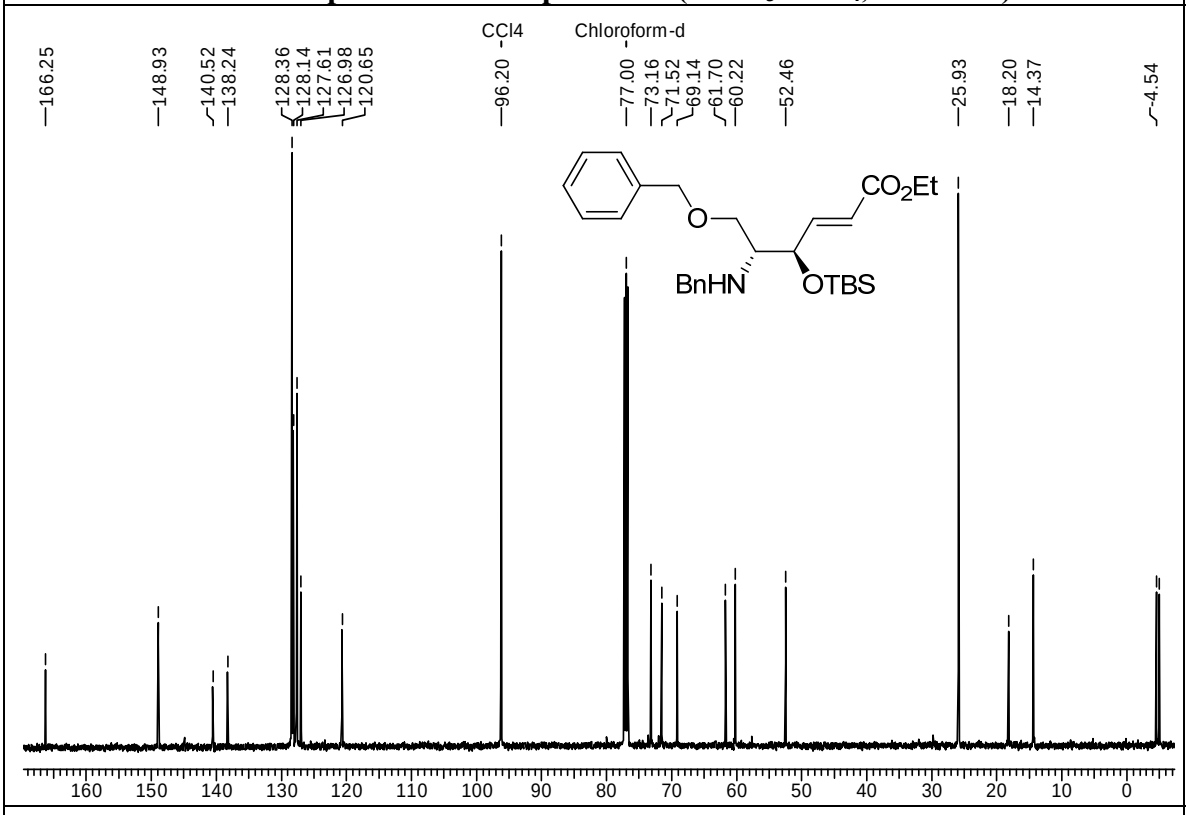
DEPT spectrum of compound 2 ($CDCl_3$+CCl_4, 50 MHz)



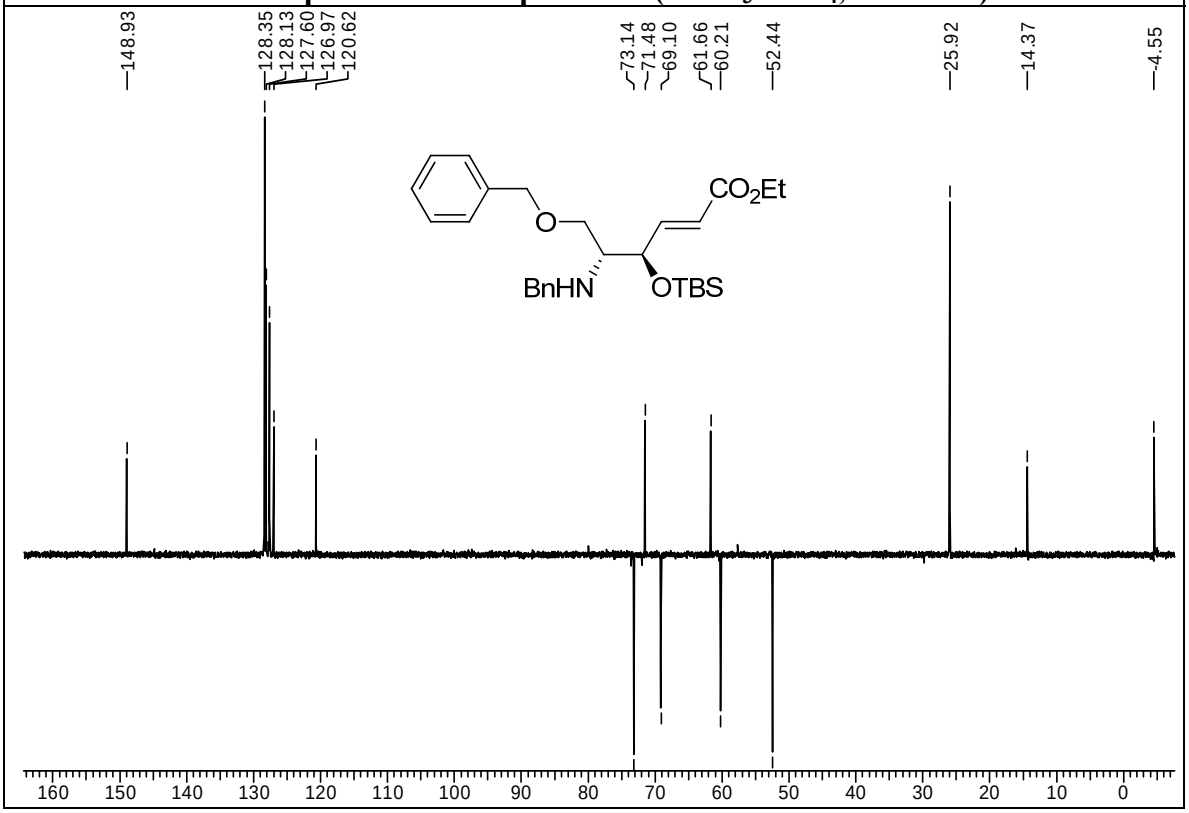
^{1}H-NMR spectrum of compound 14 ($CDCl_3$+CCl_4, 400 MHz)



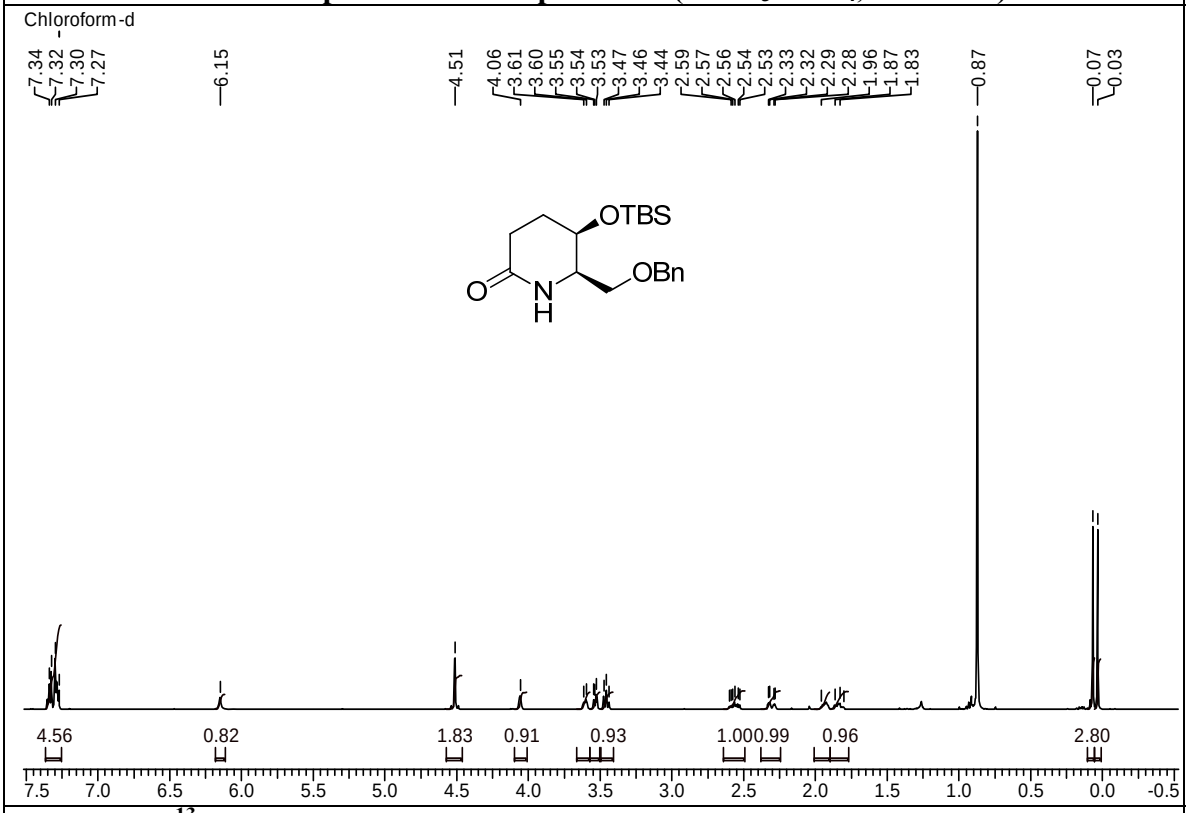
^{13}C-NMR spectrum of compound 14 ($CDCl_3$+CCl_4, 100 MHz)



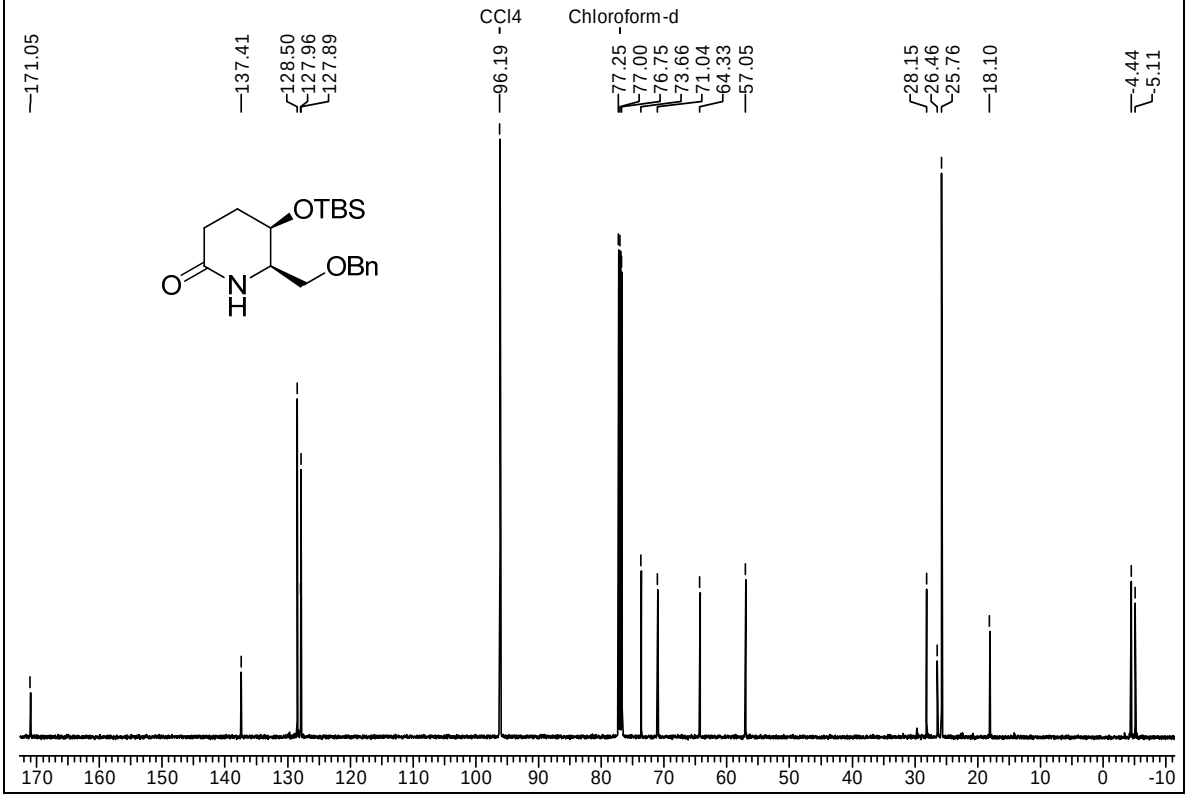
DEPT spectrum of compound 14 ($CDCl_3$+CCl_4, 100 MHz)



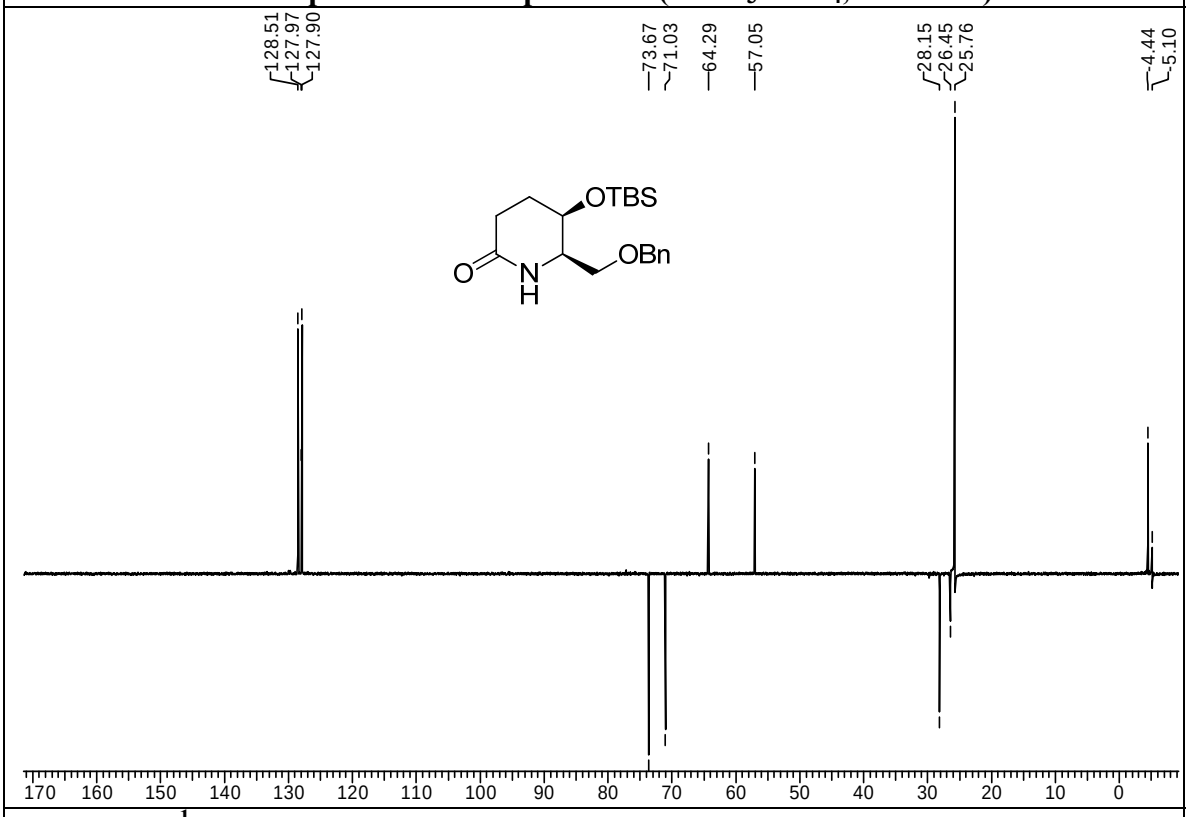
^{1}H-NMR spectrum of compound 15 ($CDCl_3$+CCl_4, 500 MHz)



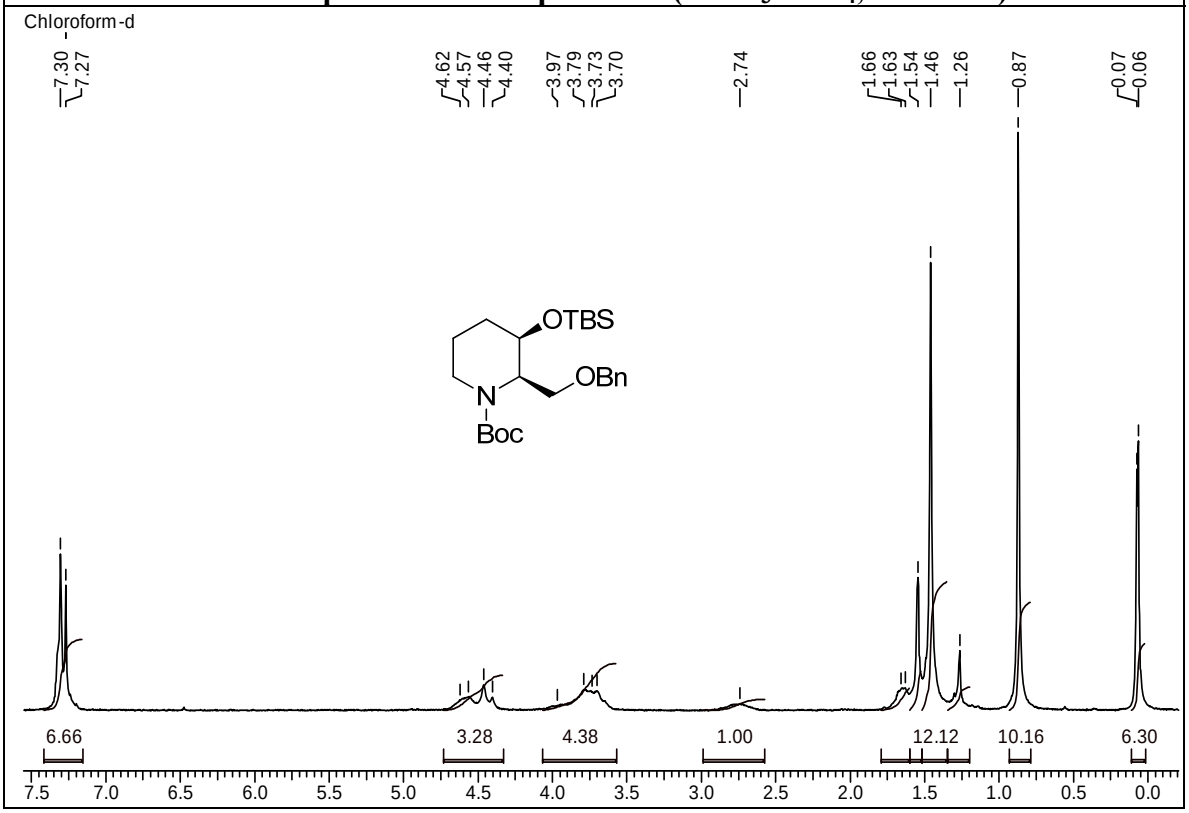
^{13}C-NMR spectrum of compound 15 ($CDCl_3$+CCl_4, 125 MHz)



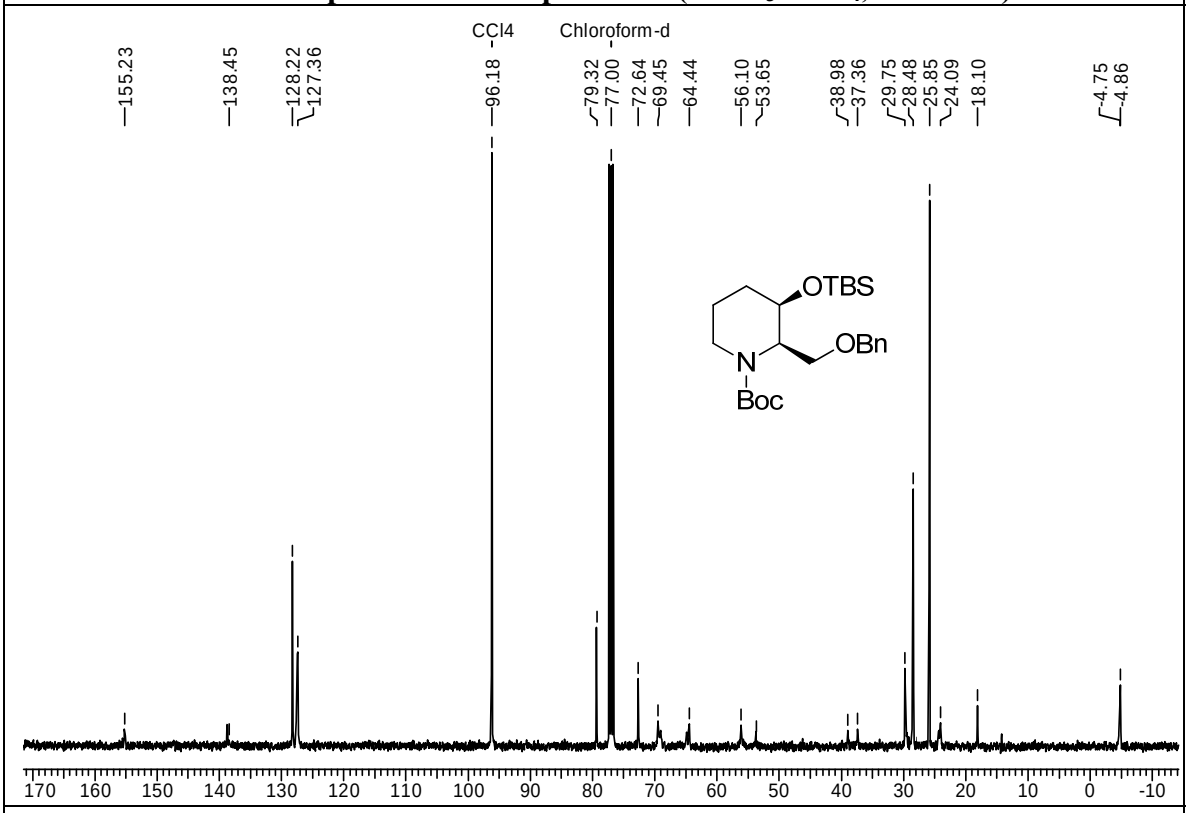
DEPT spectrum of compound 15 ($CDCl_3$+CCl_4, 125 MHz)



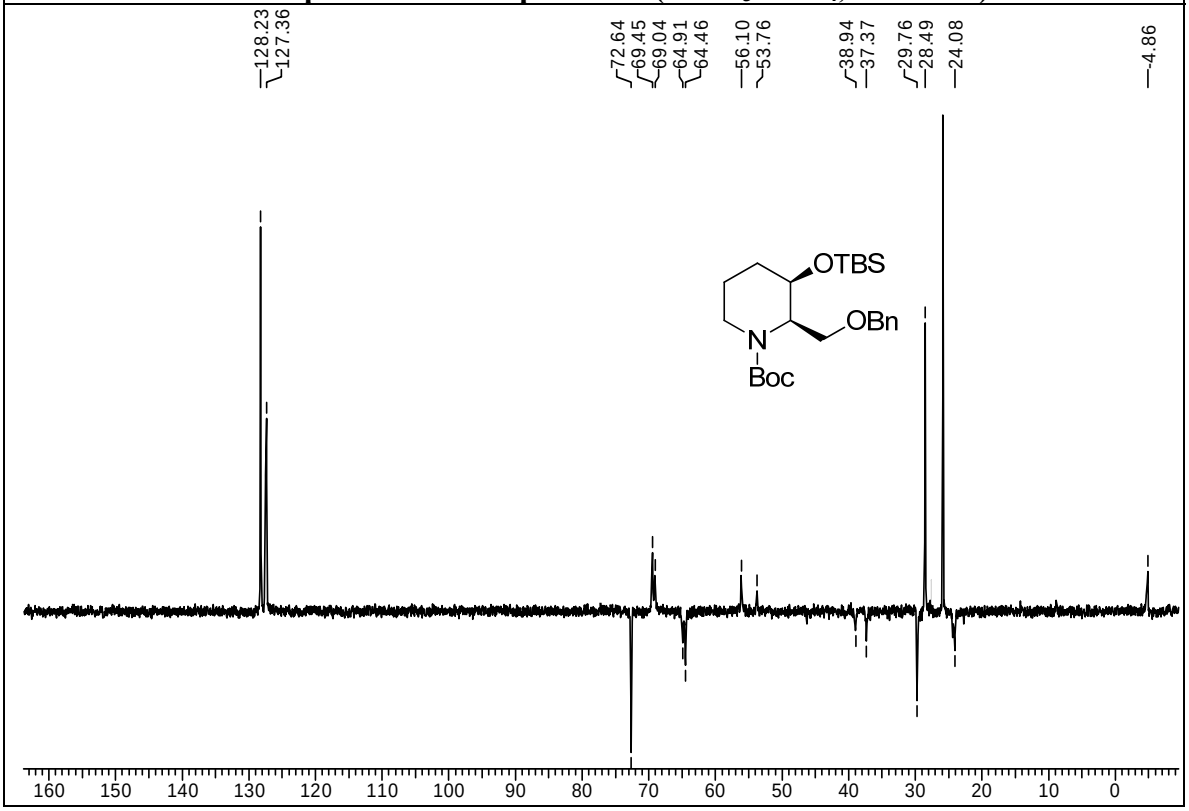
^{1}H-NMR spectrum of compound 16 ($CDCl_3$+CCl_4, 400 MHz)



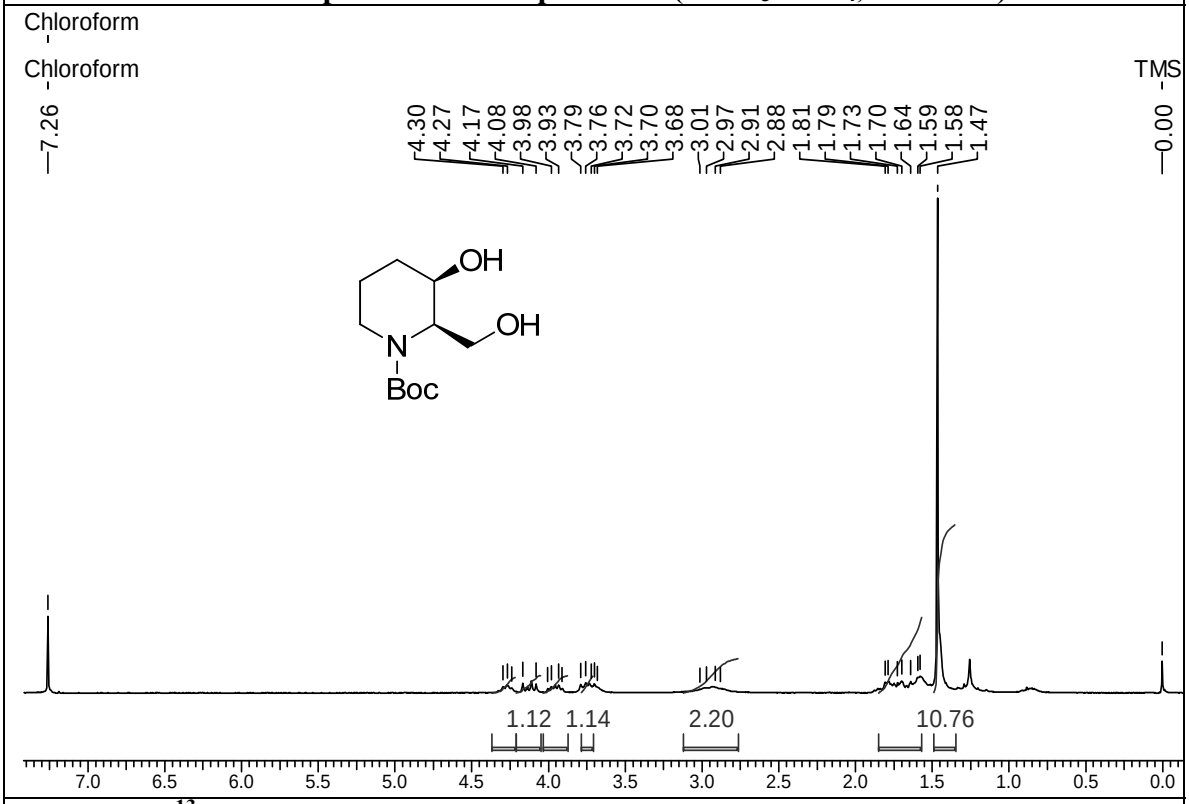
^{13}C-NMR spectrum of compound 16 ($CDCl_3$+CCl_4, 100 MHz)



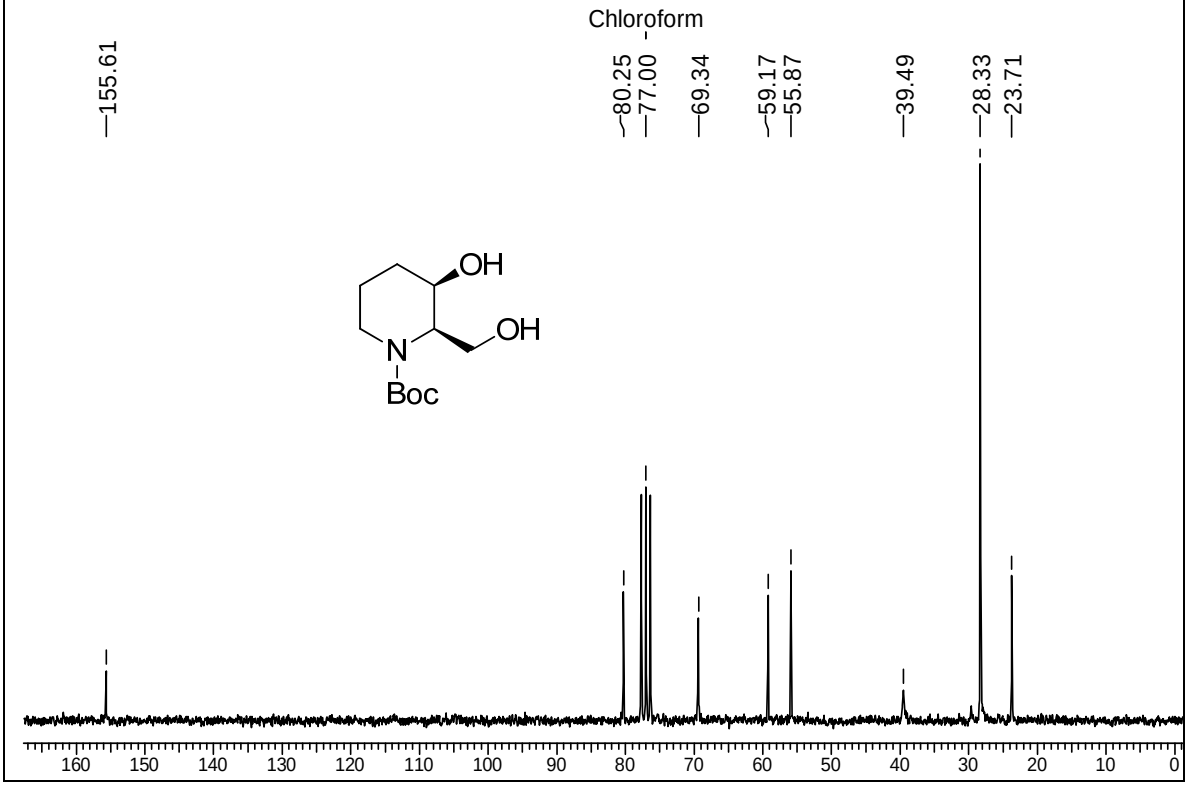
DEPT spectrum of compound 16 ($CDCl_3$+CCl_4, 100 MHz)



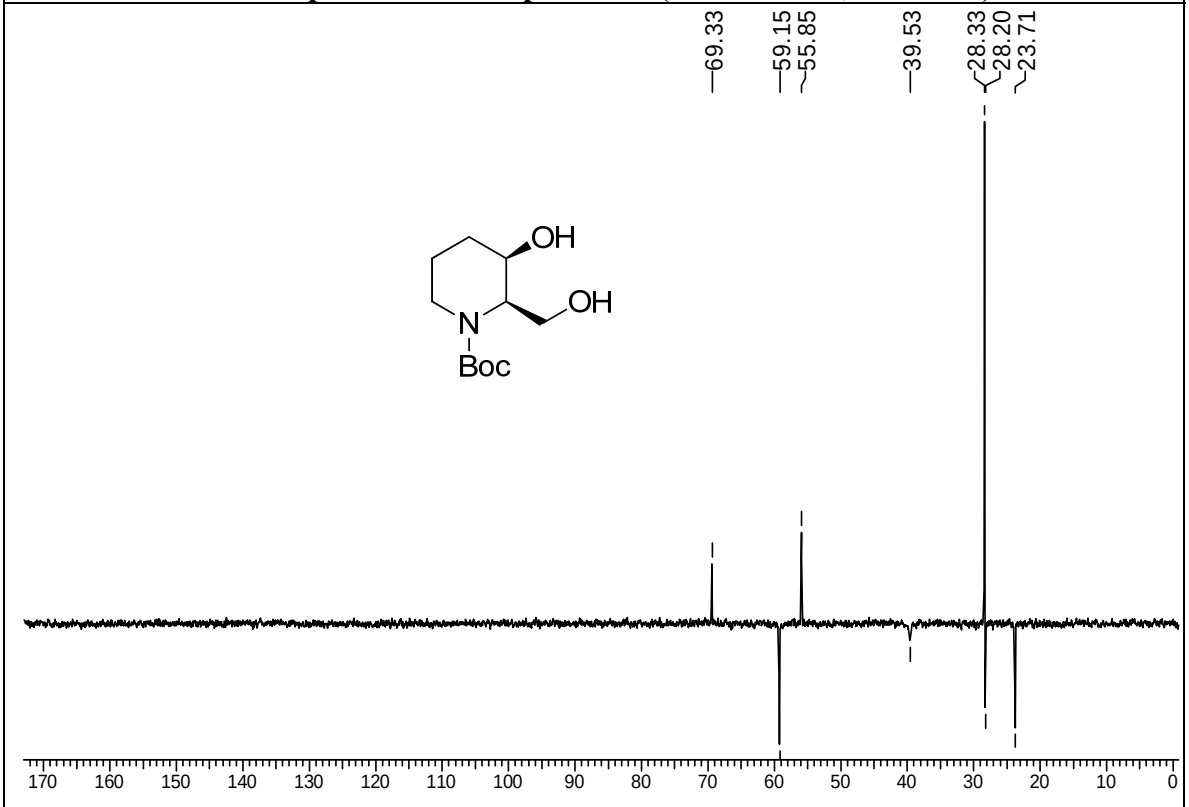
^{1}H-NMR spectrum of compound 17 ($CDCl_3$+CCl_4, 400 MHz)



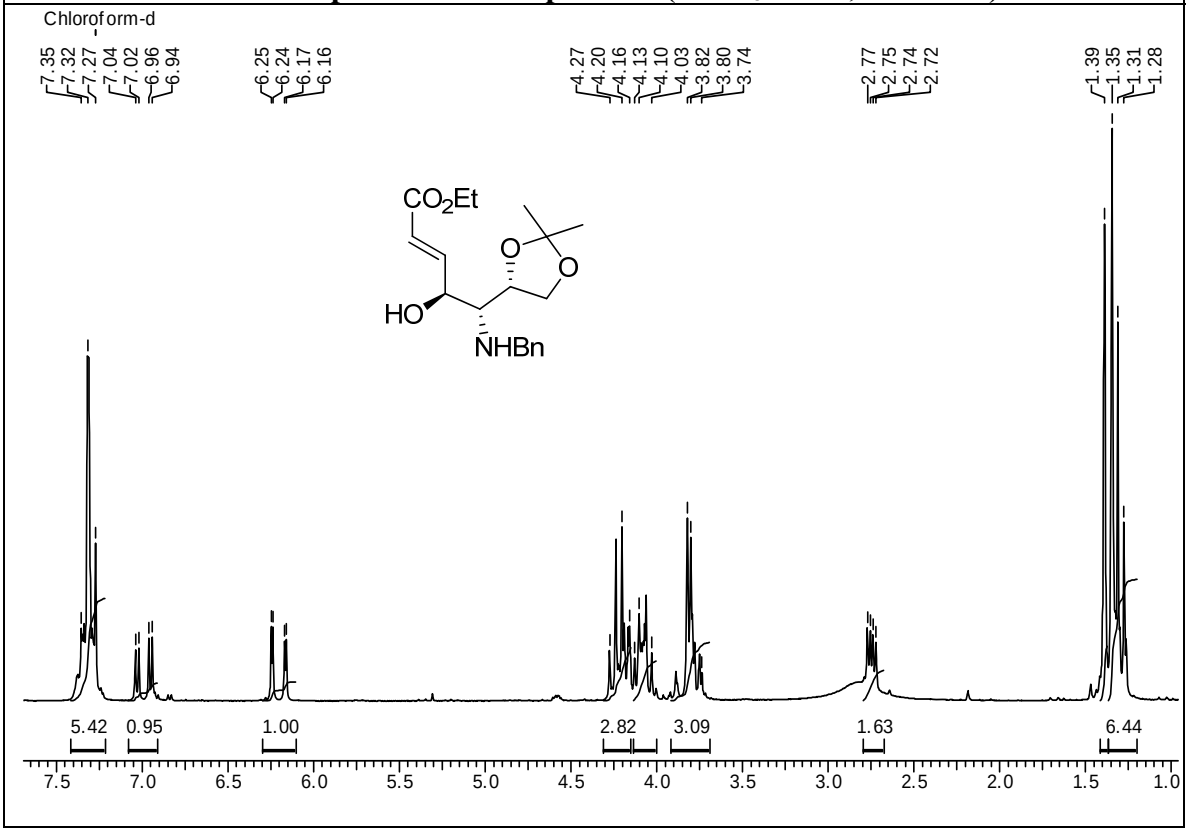
^{13}C-NMR spectrum of compound 17 ($CDCl_3$+CCl_4, 100 MHz)



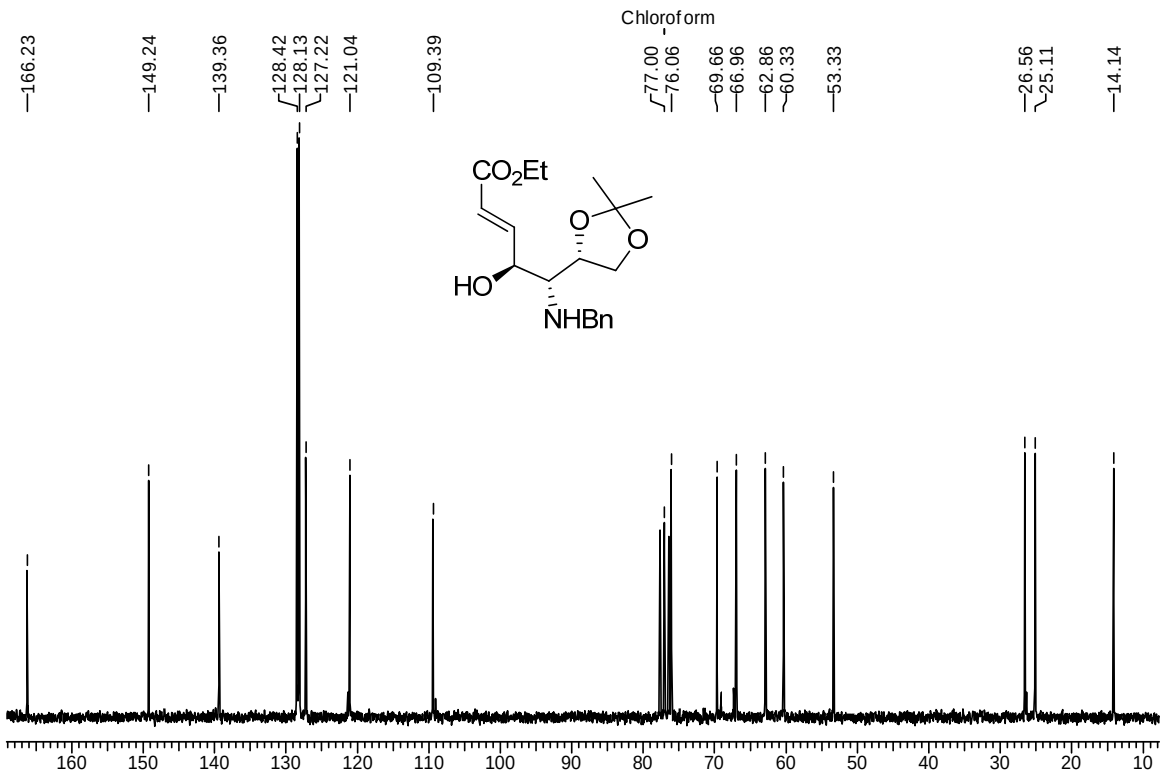
DEPT spectrum of compound 17 ($CDCl_3$+CCl_4, 100 MHz)



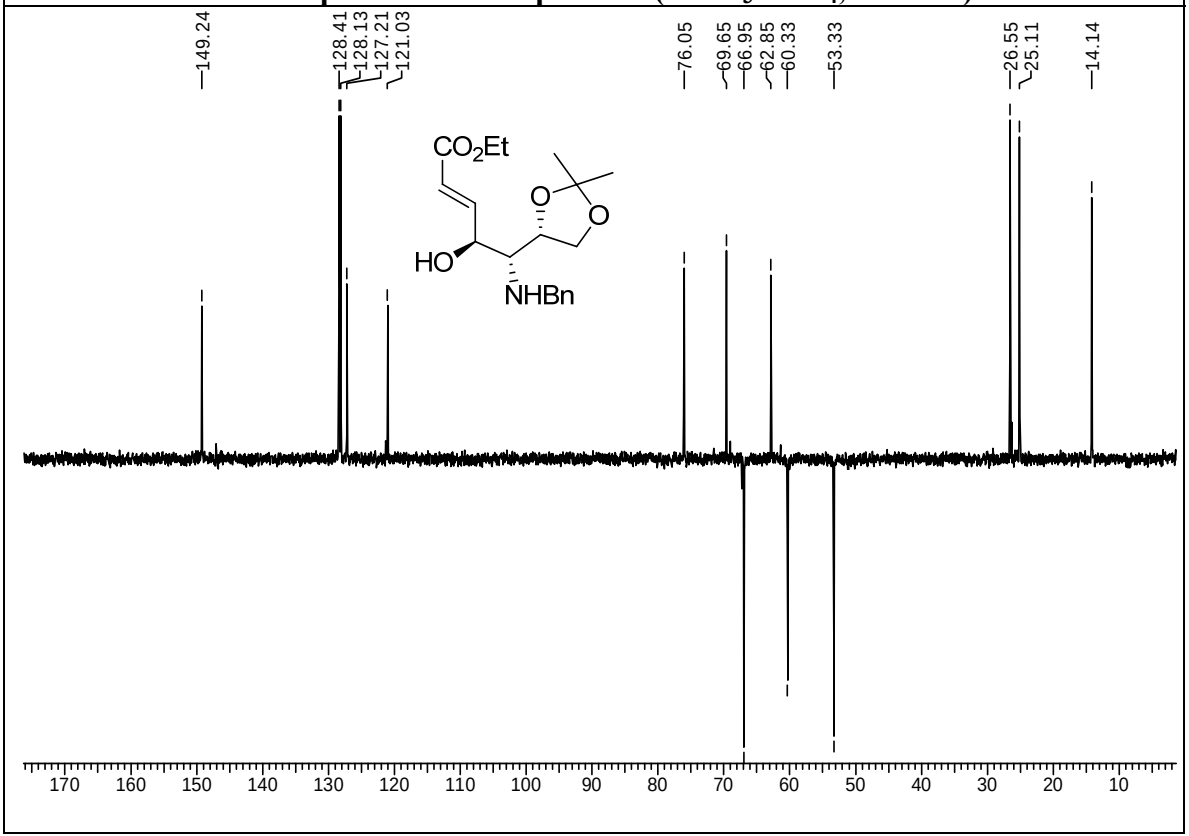
^{1}H-NMR spectrum of compound 3 ($CDCl_3$+CCl_4, 200 MHz)



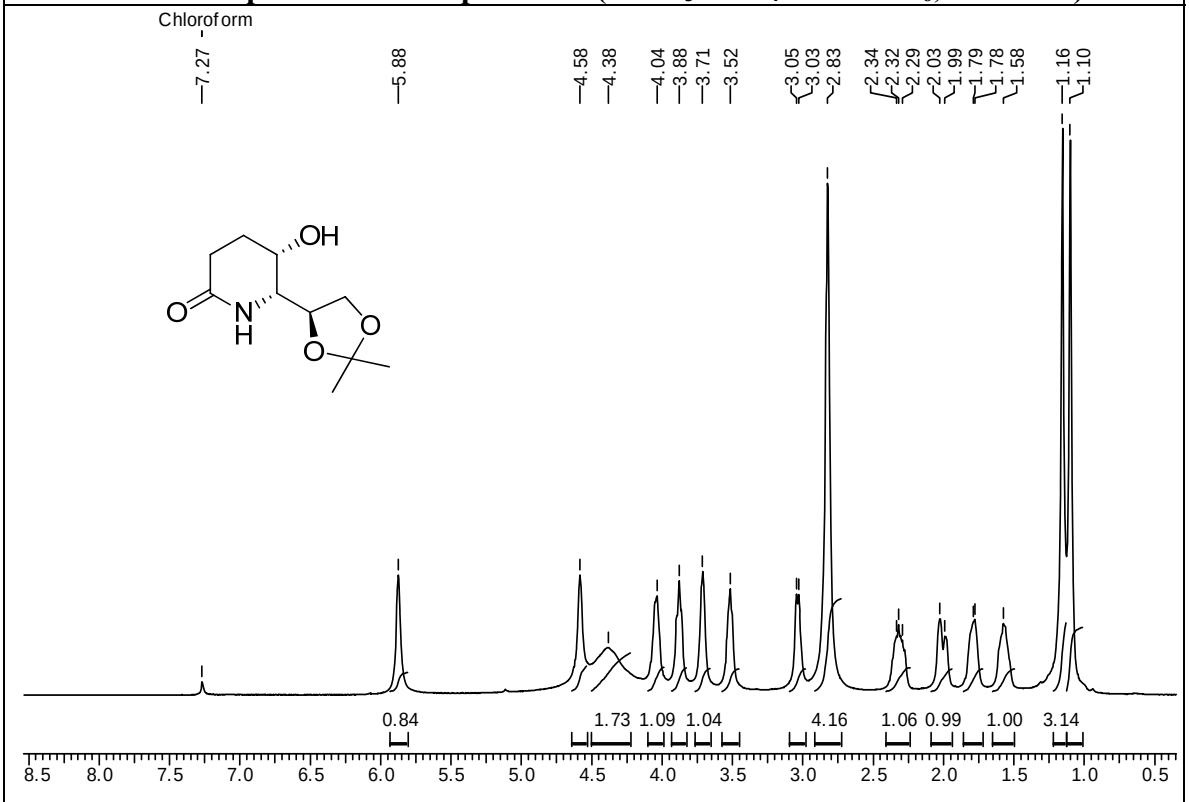
^{13}C-NMR spectrum of compound 3 ($CDCl_3$+CCl_4, 50 MHz)



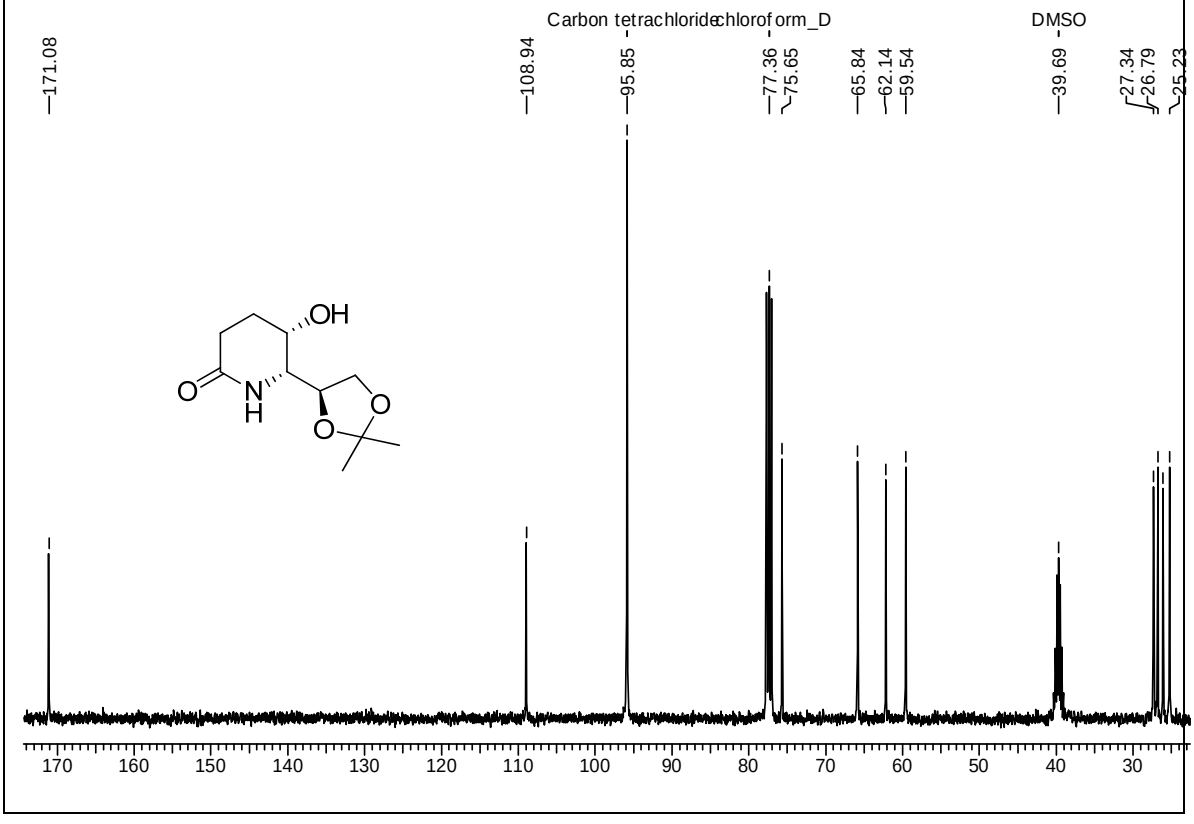
DEPT spectrum of compound 3 ($CDCl_3$+CCl_4, 50 MHz)



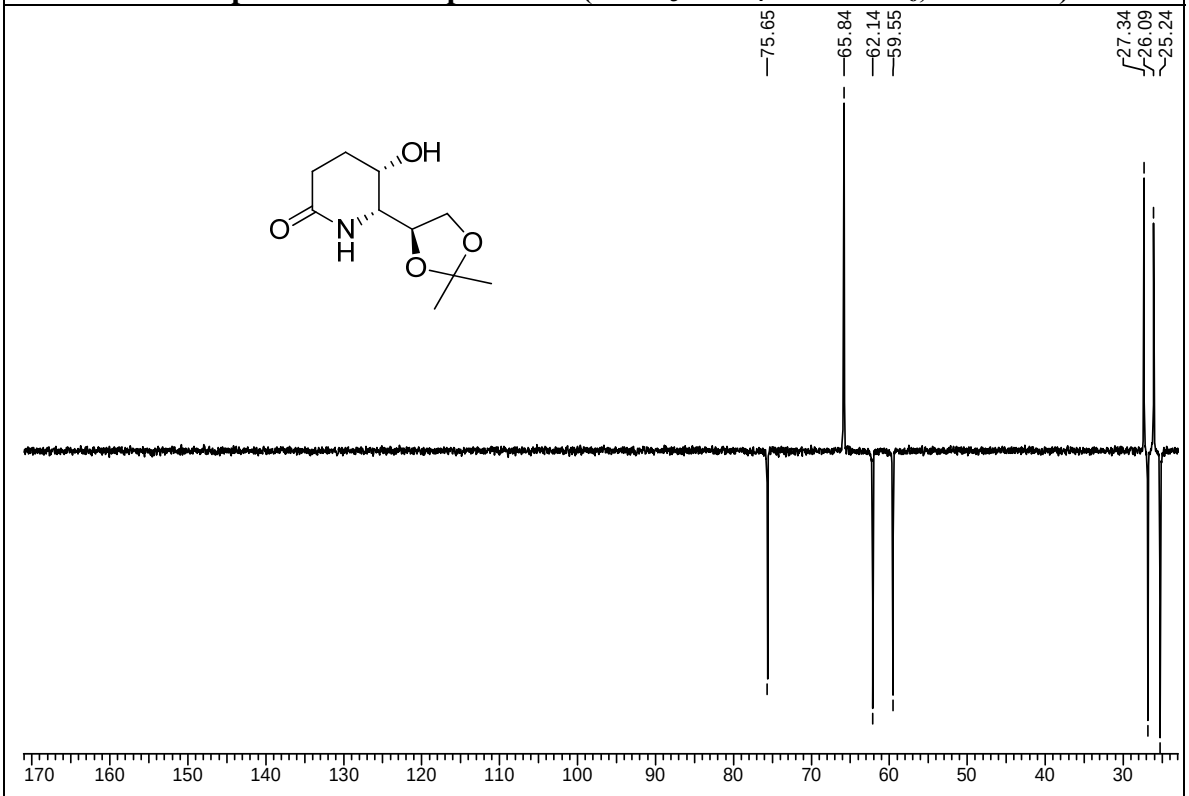
^{1}H-NMR spectrum of compound 18 ($CDCl_3$+CCl_4+DMSO-d_6, 400 MHz)



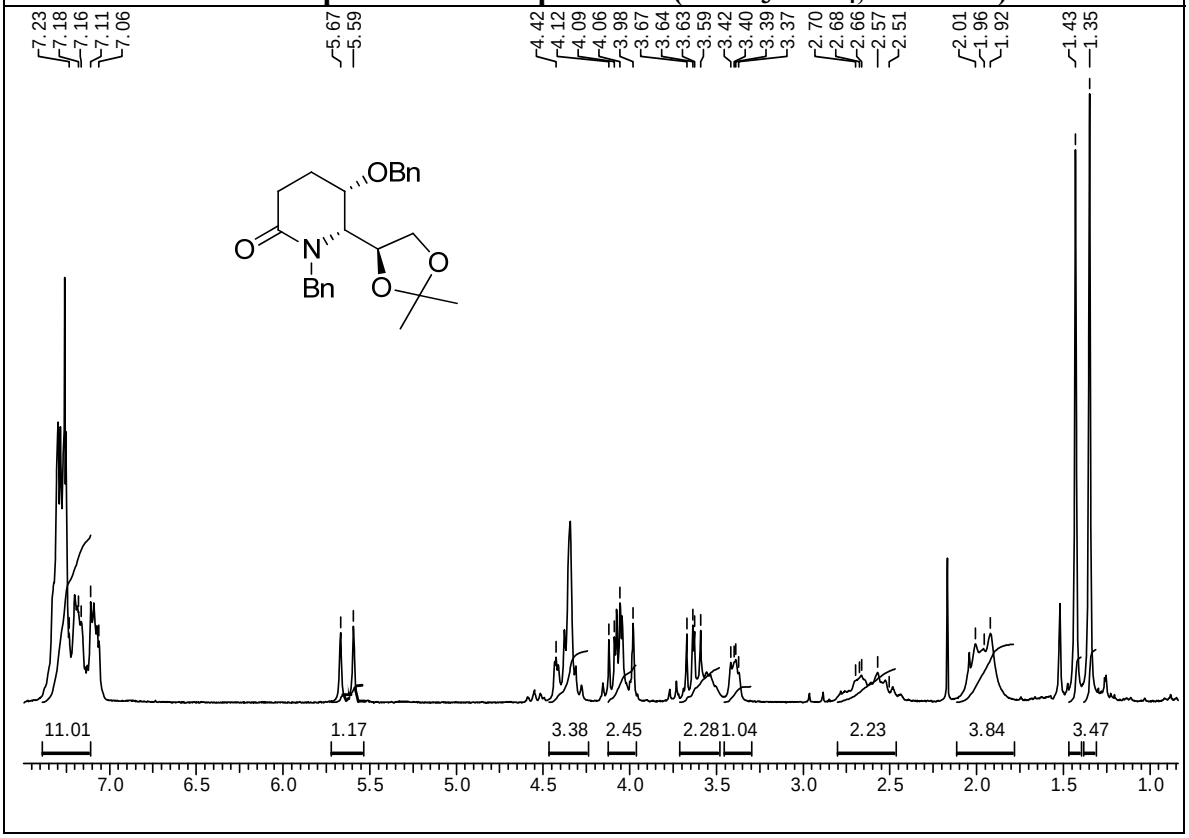
^{13}C-NMR spectrum of compound 18 ($CDCl_3$+CCl_4+DMSO-d_6, 100 MHz)



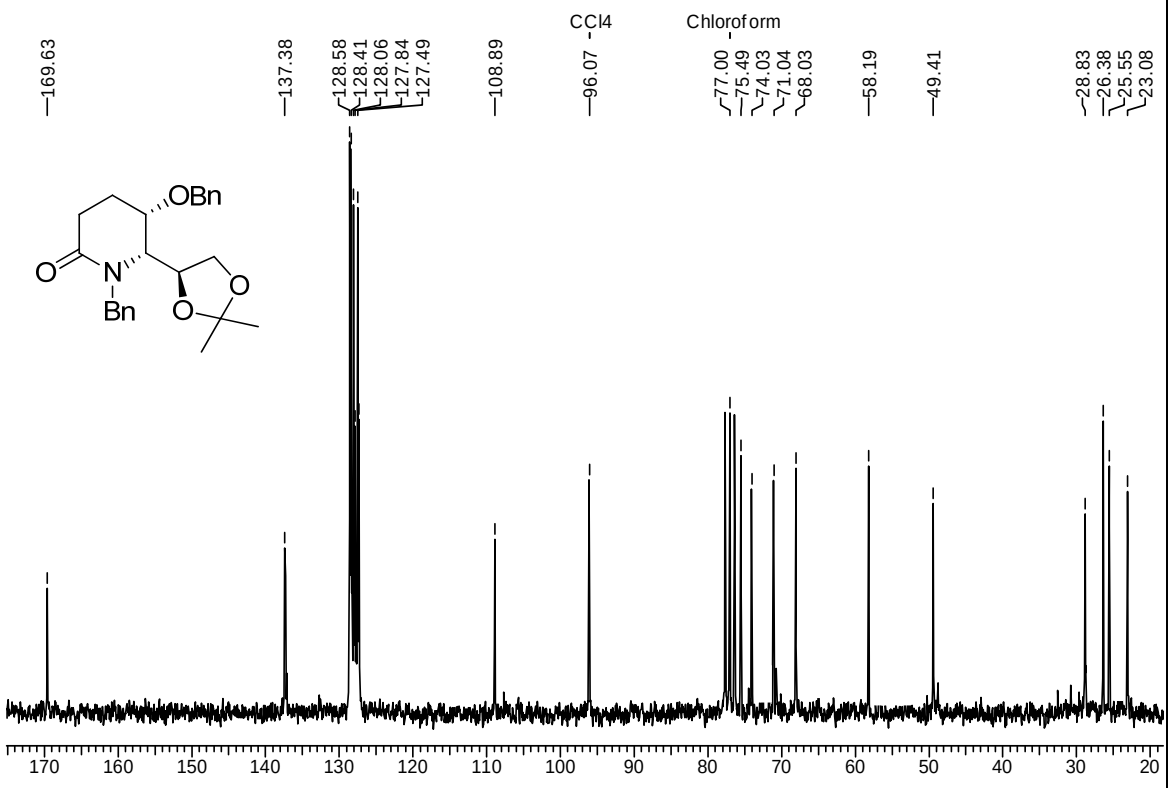
DEPT spectrum of compound 18 ($CDCl_3$+CCl_4+DMSO-d_6, 100 MHz)



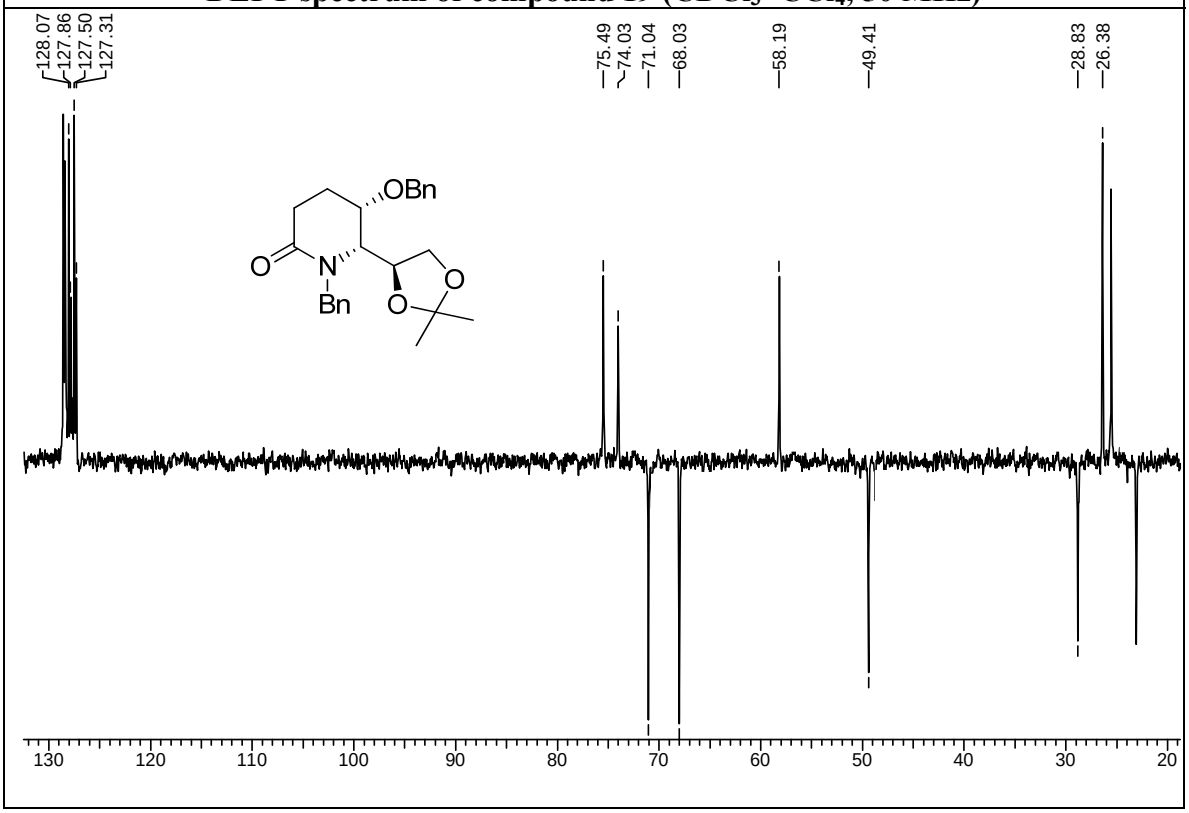
^{1}H-NMR spectrum of compound 19 ($CDCl_3$+CCl_4, 200 MHz)



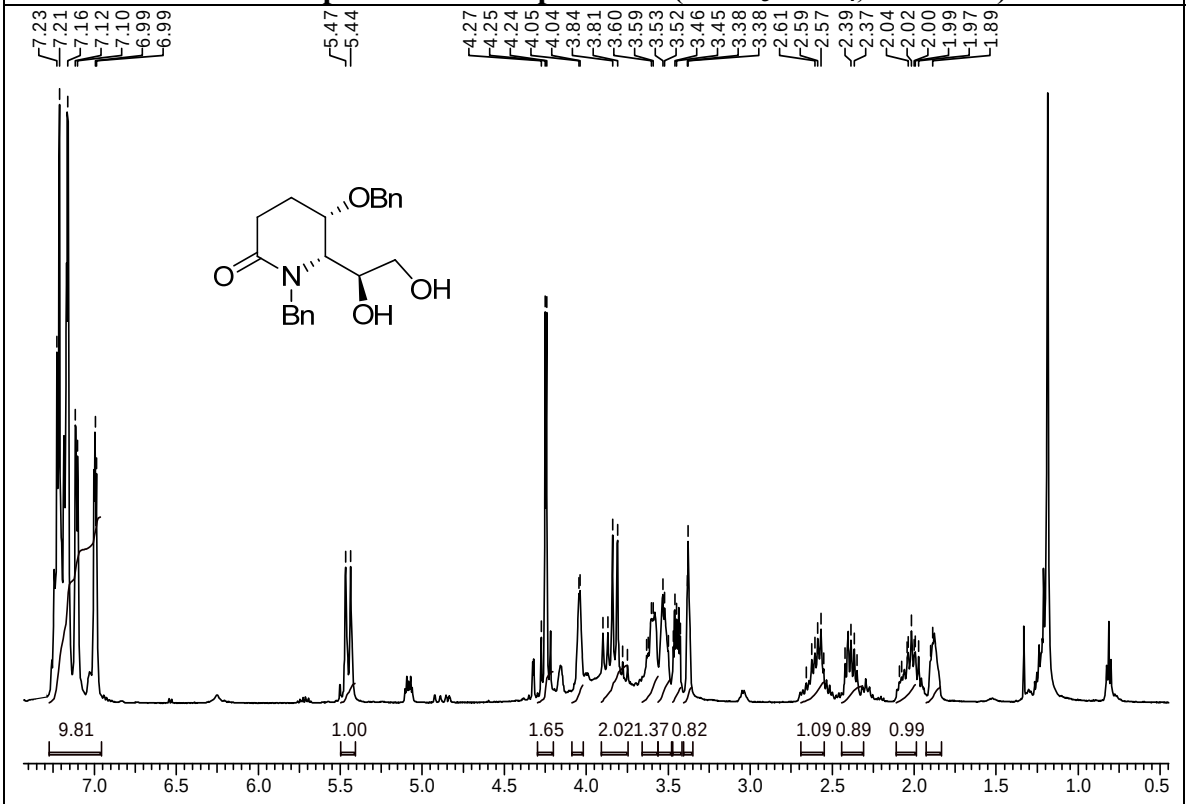
^{13}C-NMR spectrum of compound 19 ($CDCl_3$+CCl_4, 50 MHz)



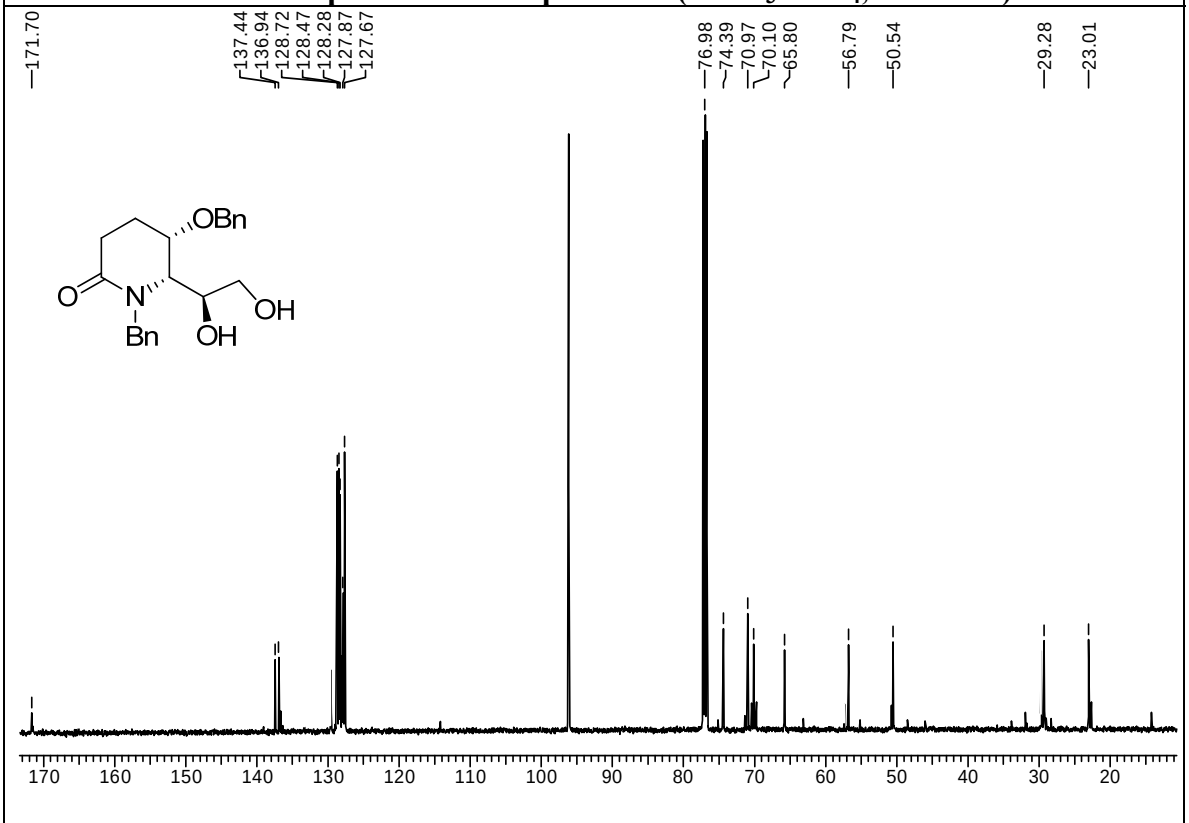
DEPT spectrum of compound 19 ($CDCl_3$+CCl_4, 50 MHz)



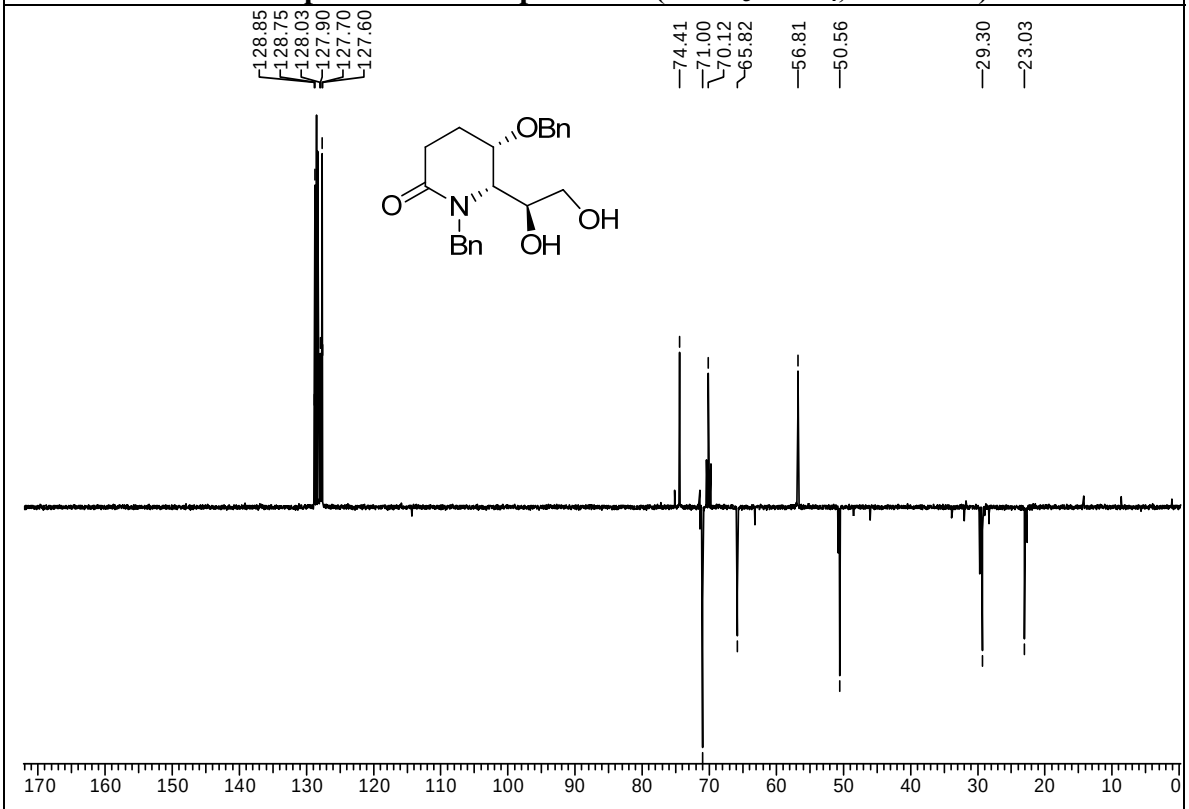
^{1}H-NMR spectrum of compound 20 ($CDCl_3$+CCl_4, 400 MHz)



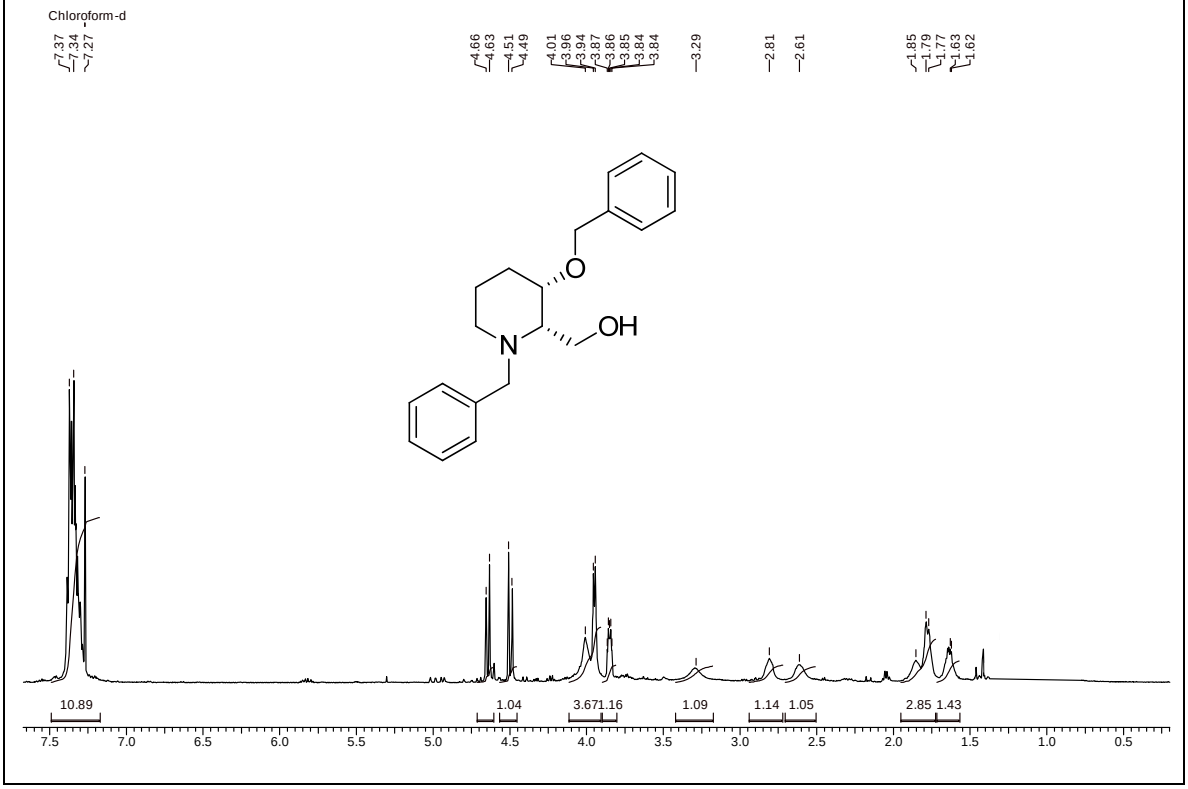
^{13}C-NMR spectrum of compound 20 ($CDCl_3$+CCl_4, 100 MHz)



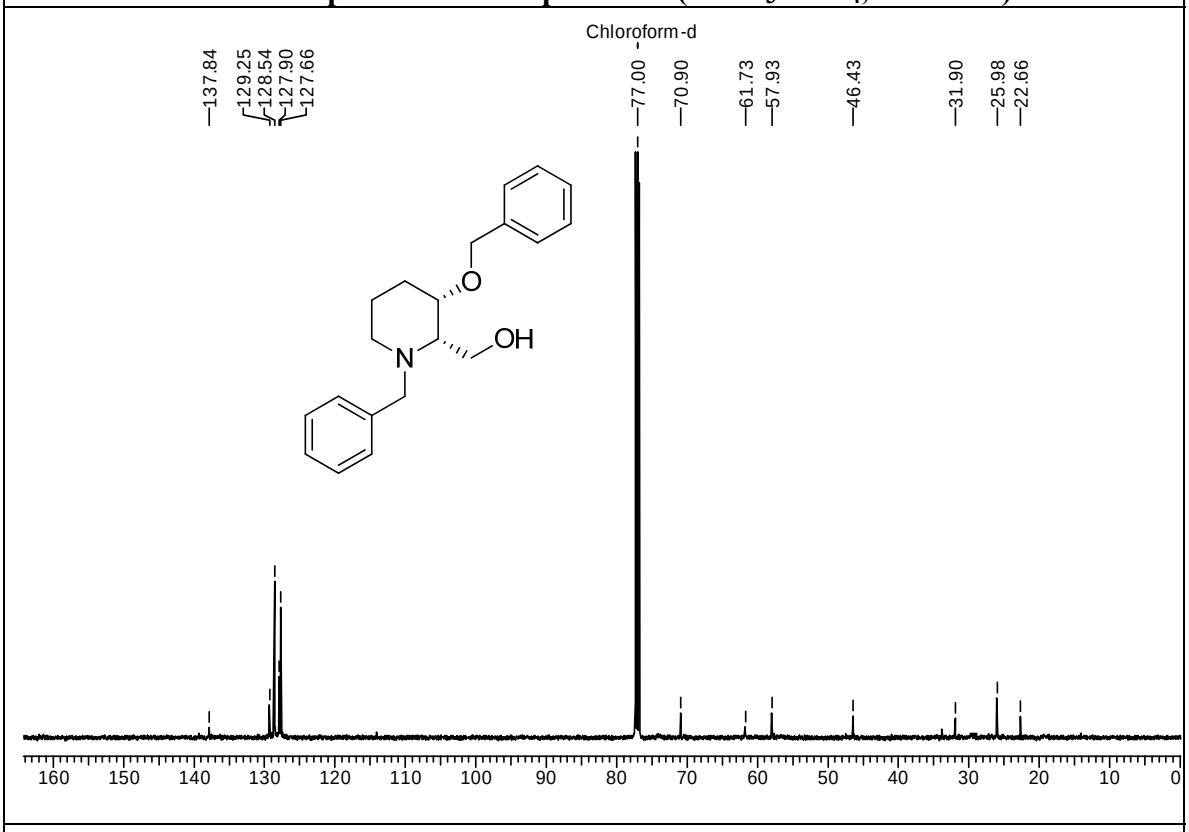
DEPT spectrum of compound 20 ($CDCl_3$+CCl_4, 100 MHz)



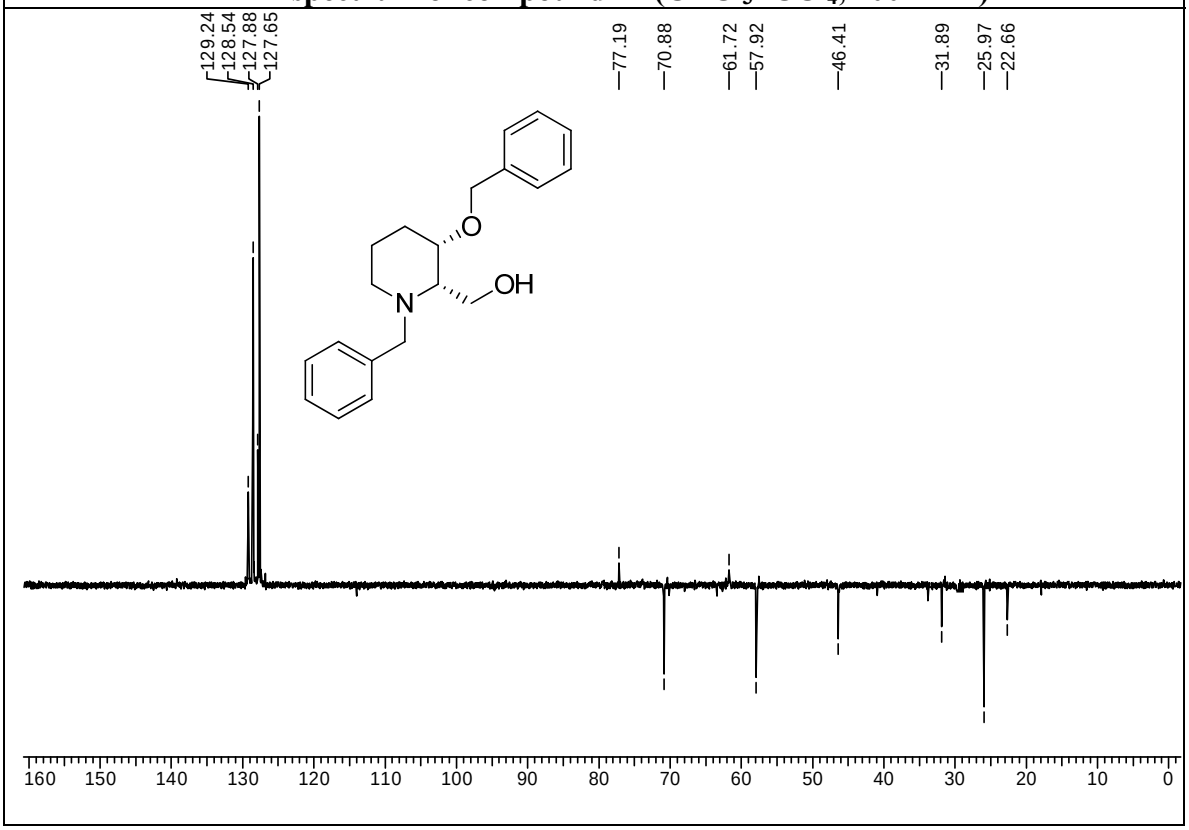
^{1}H-NMR spectrum of compound 21 ($CDCl_3$+CCl_4, 400 MHz)



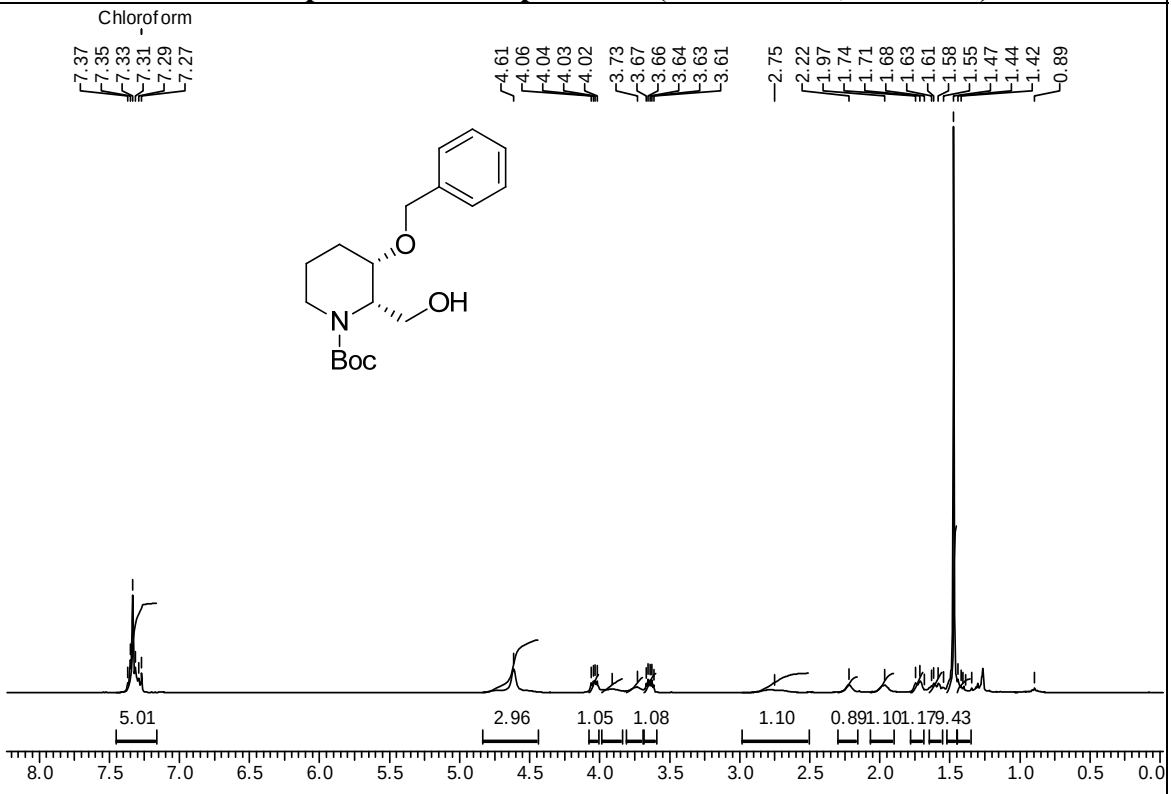
^{13}C-NMR spectrum of compound 21 ($CDCl_3$+CCl_4, 100 MHz)



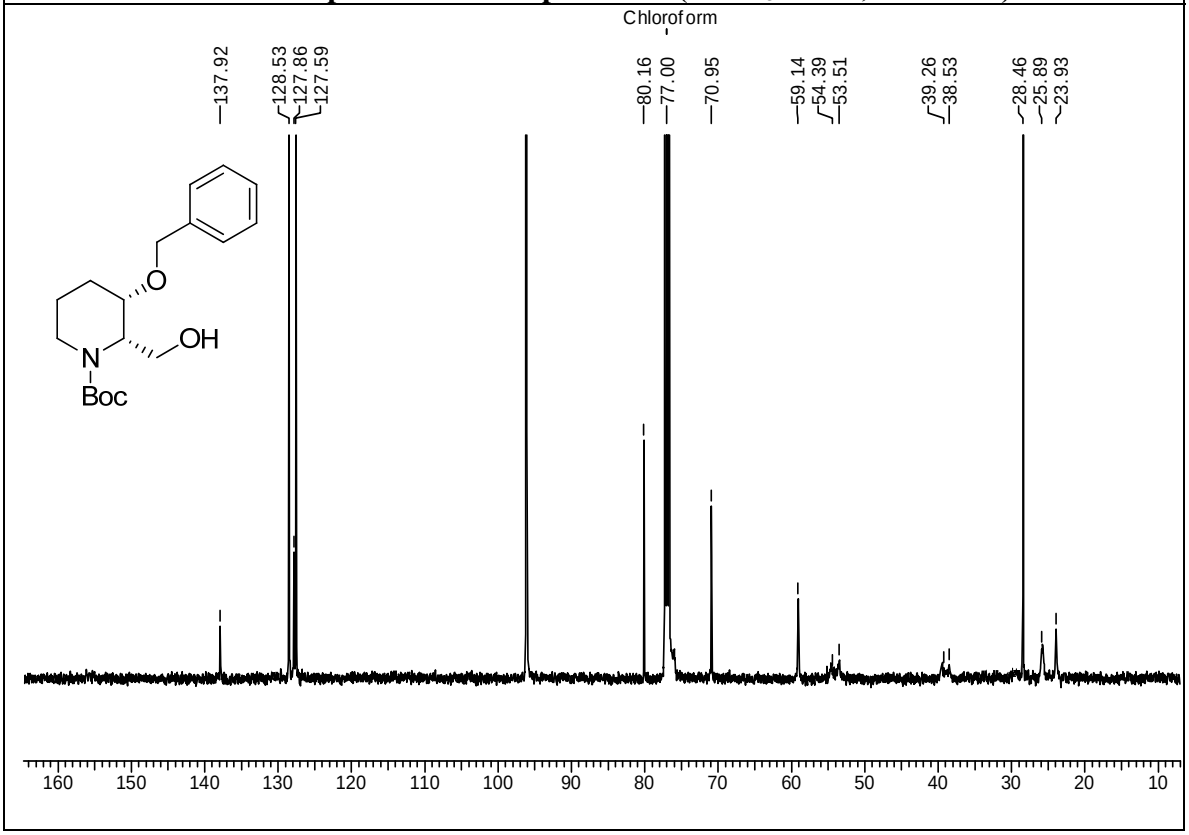
DEPT spectrum of compound 21 ($CDCl_3$+CCl_4, 100 MHz)



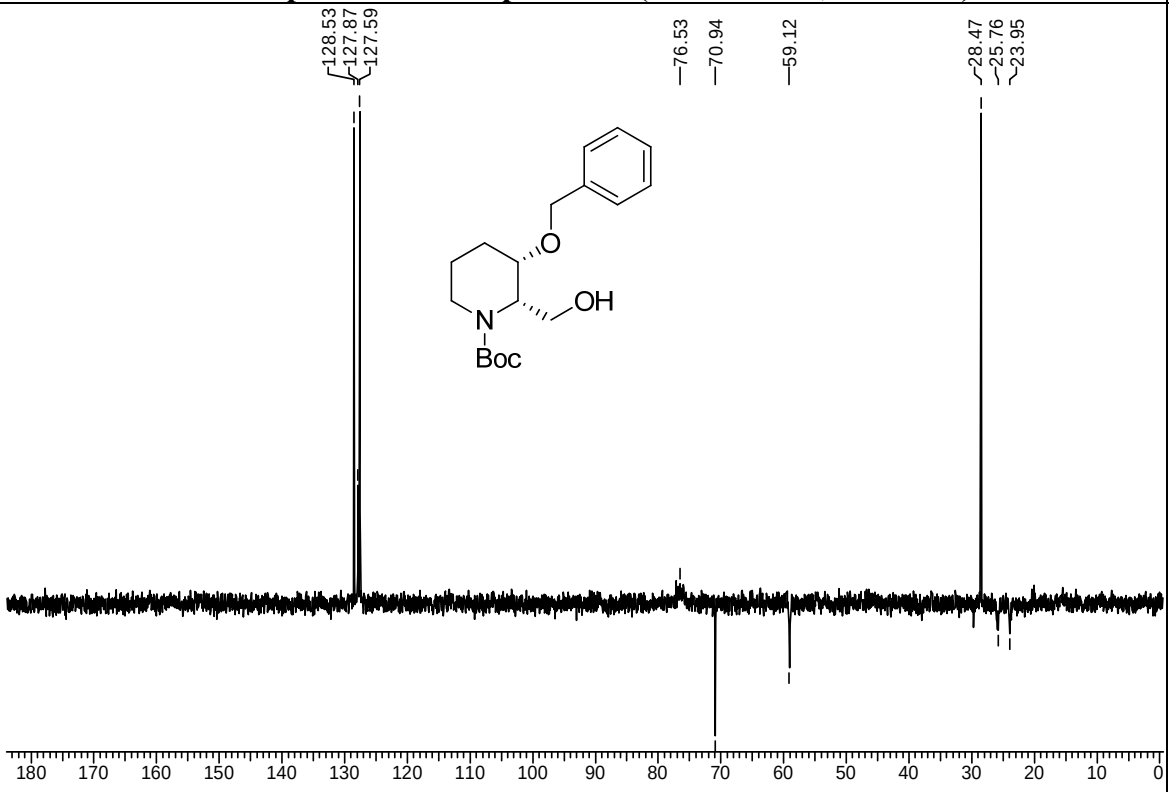
^{1}H-NMR spectrum of compound 22 ($CDCl_3$+CCl_4, 400 MHz)



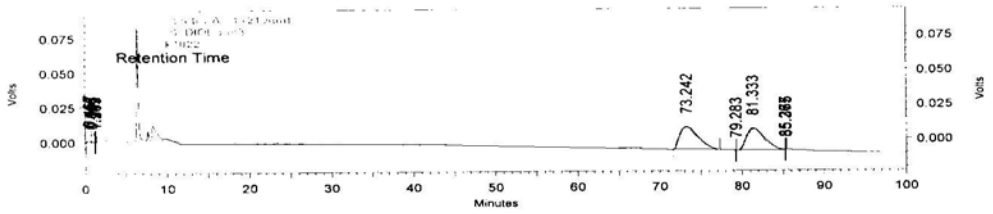
^{13}C-NMR spectrum of compound 22 ($CDCl_3$+CCl_4, 100 MHz)



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



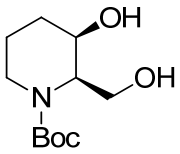
Chiral HPLC analysis of rac-17



Detector A - 1 (210nm)

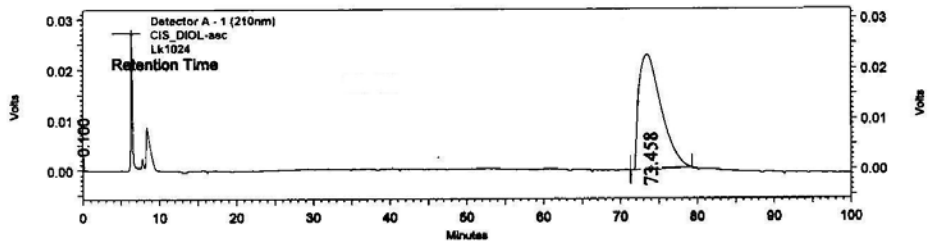
Retention Time	C Area	Area %
0.467	33255	0.658
0.808	4195	0.083
1.142	338	0.007
1.233	71	0.001
1.317	40	0.001
73.242	2591471	51.314
79.283	238	0.005
81.333	2420045	47.919
85.267	427	0.008
85.375	157	0.003
Totals	5050237	100.000

Project Leader : Dr. S P Chavan
Column :Chiracel OJ-H (250x4.6 mm)
Mobile Phase :Pet Ether:IPA ~~(80:20)~~ (99:1)
Wavelength : 210 nm
Flow Rate :0.5ml/min (23Kgf)
conc. :1mg/1.0mL
Inj vol- :10 ul



rac-**17**

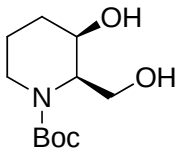
Chiral HPLC analysis of (2*R*,3*R*)-17



Detector A - 1 (210nm)

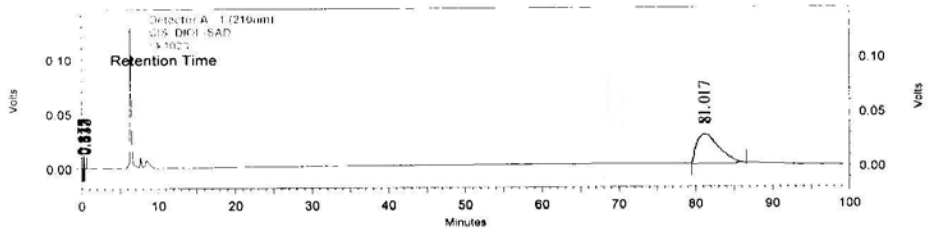
Retention Time	C Area	Area %
0.100	77	0.005
73.458	4585971	99.995

Project Leader : Dr. S P Chavan
Column :Chiracel OJ-H (250x4.6 mm)
Mobile Phase :Pet Ether:IPA ~~(80:20)~~ (99:1)
Wavelength : 210 nm
Flow Rate :0.5ml/min (23Kgf)
conc. :1mg/1.0mL
Inj vol- :10 ul



(2*R*,3*R*)-**17**

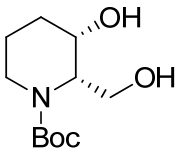
Chiral HPLC analysis of (2S,3S)-*ent*-17



Detector A - 1 (210nm)

Retention Time	C Area	Area %
0.175	82	0.002
0.317	175	0.003
0.533	516	0.010
81.017	5132265	99.985
Totals	5133038	100.000

Project Leader : Dr. S P Chavan
Column :Chiracel OJ-H (250x4.6 mm)
Mobile Phase :Pet Ether:IPA ~~(80:20)~~ (99:1)
Wavelength : 210 nm
Flow Rate :0.5ml/min (23Kgf)
conc. :1mg/1.0mL
Inj vol- :10 ul



(2*S*,3*S*)-*ent*-**17**

X-ray analysis of compound 18

The following crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number **CCDC 908092**

Name	KL71
Chemical formula	C10 H17 N O4
M_r	215.25
Temperature/K	297(2)
Morphology	plate, colorless
Crystal size	0.34 × 0.23 × 0.06
Crystal system	monoclinic
Space group	$P2_1$
a (Å)	10.650(5)
b (Å)	10.547(4)
c (Å)	14.831(6)
α (°)	90
β (°)	102.693(7)
γ (°)	90
V(Å^3)	1625.2(12)
Z	6
D_{calc} (g cm^{-3})	1.320
μ (mm^{-1})	0.102
F(000)	696
Ab. correction T_{min}/T_{max}	Multi-scan 0.966/ 0.994
θ_{max} (°)	25
h, k, l (min, max)	(–12,12), (–12,12), (–17,17)
Reflns collected	10935
Unique reflns	5648
Observed reflns	4773
No. of parameters	433
GoF	1.009
R_obs	0.0685
wR_2_obs	0.1592
R_all	0.0809
wR_2_all	0.1660
$\Delta\rho_{max}$,$\Delta\rho_{min}$(eÅ^{-3})	0.24, –0.29

3.2.4 References

1. For reviews, see: (a) Agami, C.; Couty, F.; Puchot-Kadouri, C. *Synlett* **1998**, 449; (b) Couty, F. *Amino Acids* **1999**, *16*, 297; (c) Rutjes, F. P. J. T.; Wolf, L. B.; Schoemaker, H. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4197; (d) Park, K.-H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629; (e) Kadouri-Puchot, C.; Comesse, S. *Amino Acids* **2005**, *29*, 101; (e) Cant, A. A.; Sutherland, A. *Synthesis* **2012**, *44*, 1935.

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5. Marzia, M.; Misitib, D.; *Tetrahedron Lett.* **1989**, *30*, 6075; (b) Yoshida, K.; Nakajima, S.; Wakamatsu, T.; Bau, Y.; Shibasaki, M. *Heterocycles* **1988**, 27, 1167; (c) Zilcha, A.; Rachiman, E.S.; Rivlin, J. *J. Org. Chem*. **1961**, *26*, 376.

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Chapter 3: Synthetic studies toward both enantiomers of *cis*- 3-hydroxypipecolic acid and development of synthetic methodology for preparation of chiral allylic amines from chiral aziridine-2-alcohols

Section 3: Development of synthetic methodology for preparation of chiral allylic amines from chiral aziridine-2-alcohols

3.3.1 Introduction

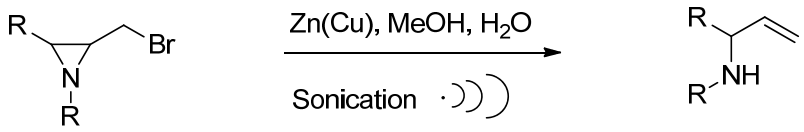
Allyl amines are important building blocks in organic chemistry, and therefore methods for their preparation are of great importance. Chiral allylic amines are versatile building blocks for the synthesis of amino acids, alkaloids and carbohydrate derivatives.[1] The allylic amines are transformed to more complex derivatives. In addition, they are also structural components of peptide isosteres, and act as *β*-turn promoters.[2] Thus, the synthesis of chiral allylic amines is an important industrial and synthetic goal and as a result several procedures have been developed for the synthesis of chiral allylic amines.

3.3.2 Literature review

Because of the increasing availability of chiral aziridines, and their propensity towards ring opening reactions, the eliminative ring-opening of aziridines represents an attractive strategy to access allylamines. Several methods towards this aim have been developed.

Kimpe's approach

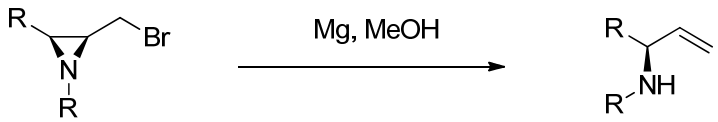
1-Alkyl and l-arylmethyl-2-(bromomethyl)aziridines are readily cleaved by the sonochemical zinc-copper couple in aqueous methanol at room temperature to afford allylamines by Kimpe's approach (Scheme 1).[3]



Scheme 1

Kimpe's second approach

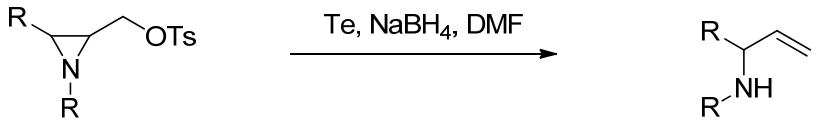
Kimpe's second approach involves magnesium metal in methanol as reagent to cleave 2-(bromomethyl)aziridines to afford allylamine derivatives in good yields (Scheme 3).[4]



Scheme 2

Dittmer's approach

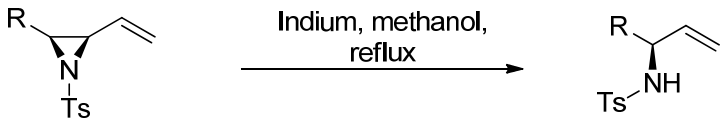
Sulfonate esters of aziridinemethanols are converted to allylic amines by treatment with telluride ion obtained by reduction of elemental tellurium by Dittmer's group (Scheme 3).[5] In the course of the reaction, tellurium (0) is reformed and may be reused, thus removing the need to dispose of a key reagent. The telluride reaction yields optically active allylic amines from optically active aziridinemethanols. Activation by an electron-withdrawing substituent on nitrogen is not necessary.



Scheme 3

Yadav's approach

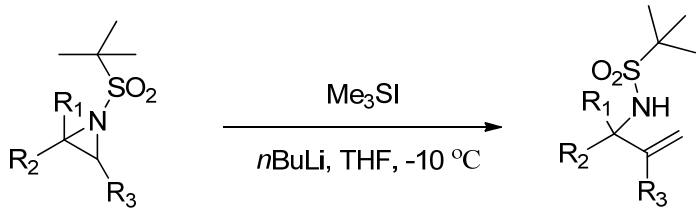
Chiral allylic amines are synthesized in high yields by treatment of 2-iodomethyl *N*-tosyl aziridines with metallic indium in methanol at reflux by Yadav's group (Scheme 4).[6]



Scheme 4

Hodgson's approach

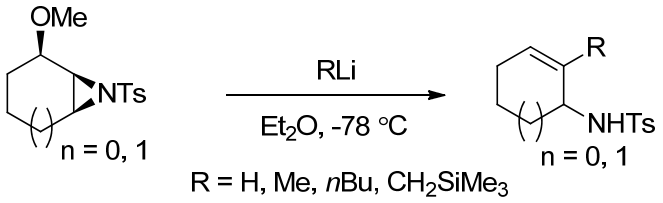
Regio and stereodefined allylic *N*-sulfonylamines are synthesized in high yields and under experimentally straightforward conditions by reaction of *N*-sulfonylaziridines with excess dimethylsulfonium methylide by Hodgson's group (Scheme 5).[7]



Scheme 5

O'Brien's approach

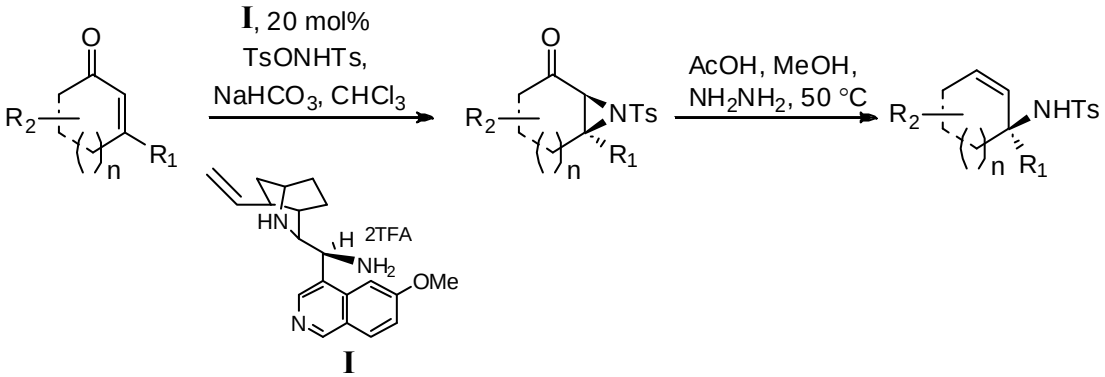
A new route to cyclic substituted allylic amines *via* the reductive alkylation of *cis* α-methoxy aziridines has been established by O'Brien's group (Scheme 6).[8]



Scheme 6

Jørgensen's approach

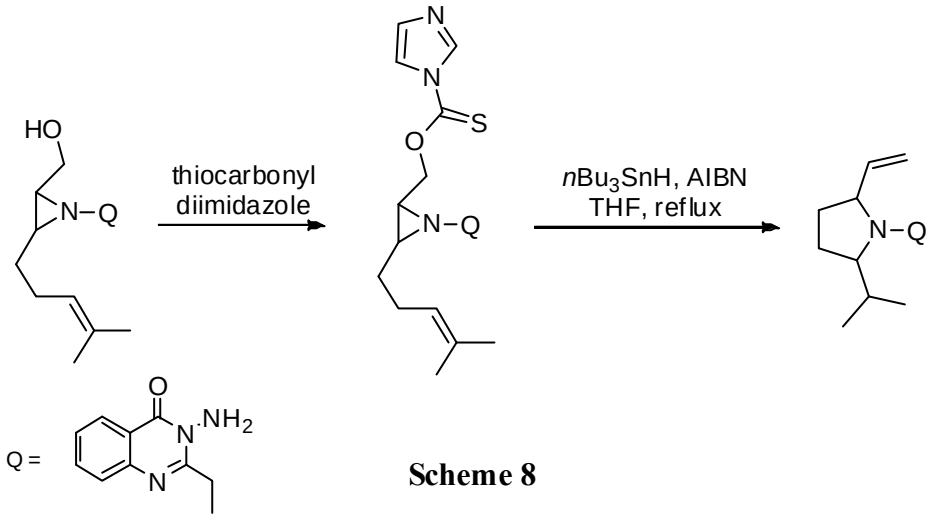
Jørgensen's approach involves a simple organocatalytic one-pot protocol for the construction of optically active allylic amines using readily available reactants and catalyst (Scheme 7).[9] The described reaction is enabled by an enantioselective enone aziridination-Wharton-reaction sequence affording highly privileged and synthetically important chiral allylic amines in an easy and benign way. The advantages of the described sequence include easy generation of stereogenic allylic centers, also including quaternary stereocenters, with excellent enantio- and diastereomeric-control. Furthermore, using monosubstituted enones as substrates, having moderate enantiomeric excess, the one-pot reaction sequence proceeds with an enantioenrichment of the products and high diastereoselectivity was achieved.



Scheme 7

Murphy's approach

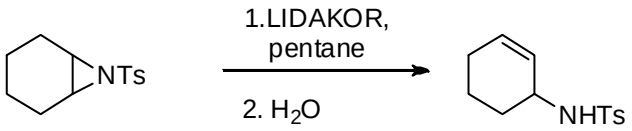
Radical induced cleavage of α-aziridinylalkyl radicals has been achieved by Murphy's group (Scheme 8). The resulting aminyl radicals react with tributyltin hydride to form amines or cyclise onto appropriately sited alkenes to give pyrrolidines.[10]



Scheme 8

Mordini's approach

The base-promoted isomerization of aziridines to allyl amines is reported by Mordini's group (Scheme 9).[11] The use of superbasic reagents has shown to be able to promote a regio- and stereoselective conversion of monocyclic and bicyclic sulfonyl aziridines. Moreover, the use of alkoxy substituted aziridines opens new routes to non-natural α- and β-amino acids. The *N*-tosyl aziridines on treatment with the superbasic mixtures butyllithium/potassium *tert*-butoxide (LICKOR) or lithium diisopropylamide/potassium *tert*-butoxide (LIDAKOR) afforded allylic amines.



Scheme 9

3.3.3 Present work

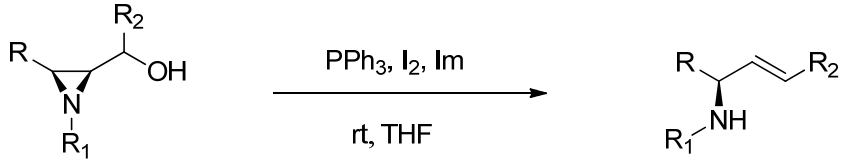
3.3.3.1 Objective

Literature survey revealed that eliminative cleavage of aziridine ring represents one of the most sought after protocol for preparation of allylic amines. Moreover in most protocols, starting with chiral aziridines one could end up with chiral allylic amines. However in most of cases it was observed that methodologies have limitations with the range of protecting group especially the need for activating group like tosyl of which deprotection is itself a cumbersome task. Also in most of cases, aziridine-2-methanols were converted to suitably poised eliminating groups like halides, -*OTS*, thiocarbonyls, -*O*alkyls *etc* before elimination. Similarly few methods utilize strong reagents thus severelly limiting the applicability of protocol. Thus in this pretext, a new mild protocol that can work with a range of substrates with or without activating the aziridine ring is highly desirable.

3.3.3.2: Results and discussion

The present section describes an efficient, practical methodology for the preparation of chiral allyl amines from chiral aziridine-2-alcohols. Chiral aziridine-2-alcohols represents an attractive tool for synthesis of chiral allyl amines because of their easy accessibility in chiral form and the disposition towards ring opening due to ring strain.

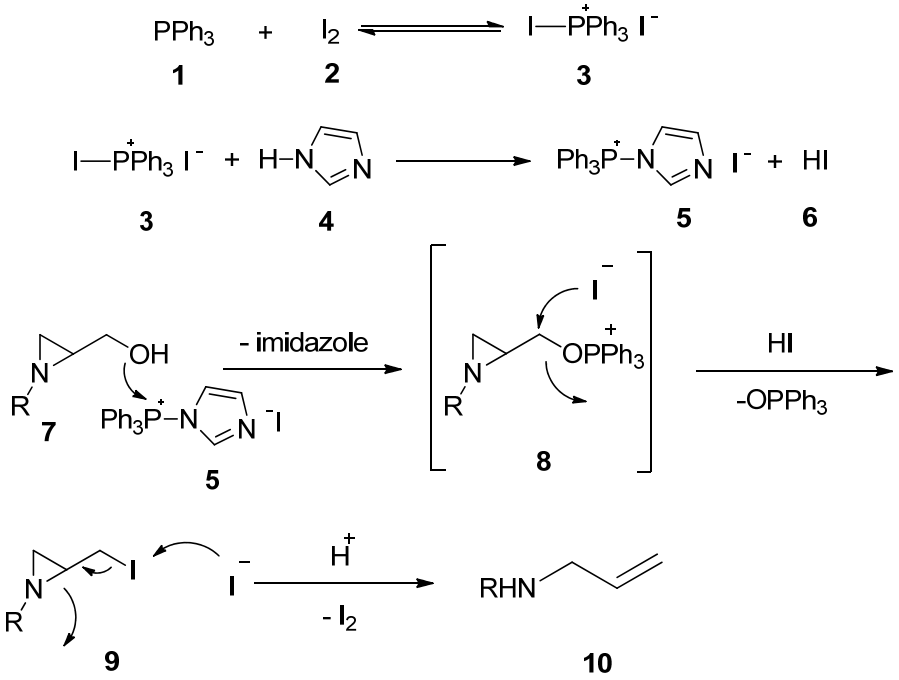
As described in Scheme 10, aziridine-2-alcohols on treatment with PPh_3/I_2/imidazole in THF as solvent undergo eliminative cleavage to form allyl amines.



R_2 - H, Allyl, Phenyl R_1 - H, Benzyl, Allyl, Tosyl, Boc

Scheme 10

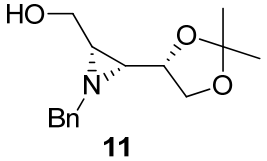
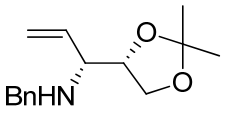
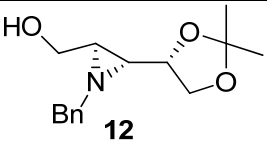
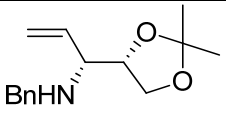
The proposed mechanism leading to the formation of **10** is depicted in scheme 11. It seems likely that at first the aziridine-2-alcohol **7** is converted *in situ* into the corresponding aziridine iodide **9** under standard iodination conditions using Ph_3P, iodide and imidazole.[12] Aziridine iodide **9** then undergoes reductive elimination by reaction with iodide ion similar to the halide-aziridine opening by Mg/Zn(Cu)/In or as in case of 2-CH_2OTs aziridines ring opening by tellurium to furnish allylic amine **10** (Scheme 11).

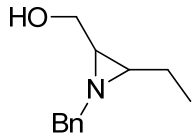
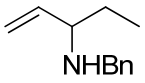
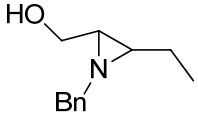
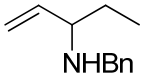
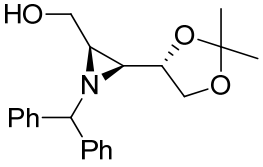
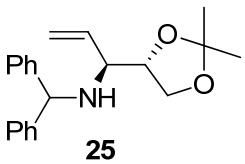
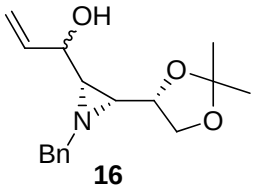
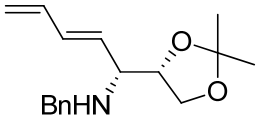
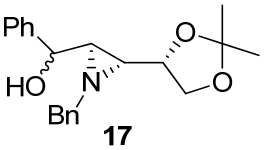
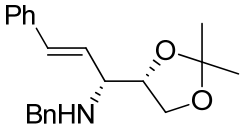
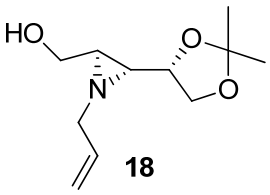
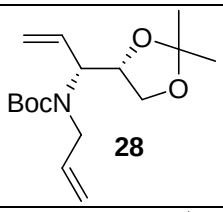
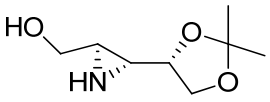
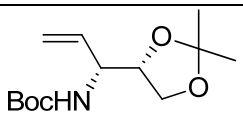
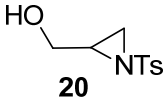
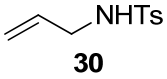
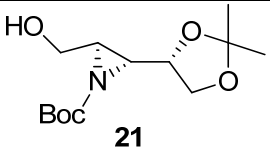
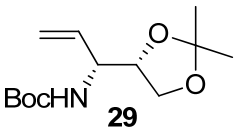


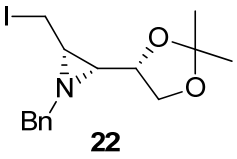
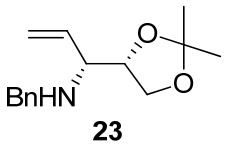
Scheme 11

We have examined this process on a range of substrates (Table 1). As can be seen from Table 1, the reductive ring opening worked well for various chiral aziridines which were converted to chiral allylic amines using PPh_3/I_2/imidazole (3 eq. each) in THF as solvent (Table 1) in good to excellent yields. Release of ring strain of such strained three membered ring system seems to be major factor for such reductive elimination reaction.

Table 1. Allylic amines from aziridine-2-alcohols using PPh_3/I_2/imidazole

Sr. No.	Reactant	Condition[a]	Product	Yield[b] (time)
1	 **11**	A	 **23**	85 (12 h)
2	 **12**	A	 **23**	90 (12 h)

3	 **13**	A	 **24**	90 (12 h)
4	 **14**	A	 **24**	90 (12 h)
5	 **15**	A	 **25**	75 (12 h)
6	 **16**	A	 **26**	80 (12 h)
7	 **17**	A	 **27**	75 (12 h)
8	 **18**	B	 **28**	75[c] (12h)
9	 **19**	B	 **29**	75[c] (12 h)
10	 **20**	A	 **30**	85 (6 h)
11	 **21**	A	 **29**	90 (6 h)

12	 **22**	C	 **23**	75 (12 h)

[a] (A) PPh_3, I_2, imidazole, THF, rt. (B) 1) PPh_3, I_2, imidazole, THF, rt; then $(Boc)_2O$, THF:H_2O. (C) NaI, acetone, reflux. [b] Isolated yield. [c] Yield over two steps.

This methodology works efficiently with unactivated aziridines (entries 1-9) which are generally reluctant towards ring opening reactions unless activated. In order to support proposed mechanism, the iodo-aziridine **22** (entry 12) was treated with NaI (3 eq.) in acetone which also as per expectation underwent reductive elimination to form allylamine **23** thus supporting the proposed mechanism (Scheme 11).

3.3.4 Conclusion

In conclusion, an efficient and mild one-step protocol was developed for preparation of chiral allylic amines directly starting from chiral aziridine-2-alcohols using PPh_3/I_2/imidazole in good to excellent yields. Methodology works well with unactivated as well as activated and NH aziridines.

3.3.5 Experimental

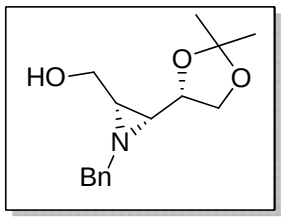
General procedure for preparation of chiral allylamines from chiral aziridine-2-alcohols

Condition A: To a well stirred solution of PPh_3 (3 mmol), iodine (3 mmol) and imidazole (3 mmol) in THF (10 mL) at 0 °C was added aziridine-2-alcohol [(1 mmol), (entries 1-7 and 9-10)] dissolved in THF (5 mL). Reaction was allowed to warm slowly to room temperature and stirred overnight. Reaction mass was poured into CH_2Cl_2 (30 mL) and treated with aq. $Na_2S_2O_3$ solution. Organic layer was separated and aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated and column purified to yield pure allylamines.

Condition B: To a well stirred solution of PPh_3 (3 mmol), iodine (3 mmol) and imidazole (3 mmol) in THF (10 mL) at 0 °C was added aziridine-2-alcohol [(1 mmol), (entries 8 and 11)] dissolved in THF (5 mL). Reaction was allowed to warm slowly to room temperature and stirred overnight. To the reaction mass was added H_2O (5 mL), $(Boc)_2O$ (3 mmol) and stirred for 6 h. Reaction mass was then poured into CH_2Cl_2 (30 mL) and treated with aq. $Na_2S_2O_3$ solution. Organic layer was separated and aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL), the combined organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated and column purified to yield pure Boc protected allylamines.

Condition C: To a well stirred solution of 2-iodo-aziridine **22** (entry 12, 1 mmol) in dry acetone (10 mL) was added NaI (3 mmol) and reaction mass was refluxed overnight. Reaction mass was then poured into CH_2Cl_2 (30 mL) and treated with aq. $Na_2S_2O_3$ solution. Organic layer was separated and aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated and column purified to yield pure allylamine **23**.

((2*S*,3*R*)-1-Benzyl-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridin-2-yl)methanol (11)



MP: 82-84 °C (Lit.[13] 82-84 °C).

MF: $C_{15}H_{21}NO_3$, **MW**: 263.33.

$[\alpha]_D^{25}$ +32.1 (*c* 0.85, $CHCl_3$) {Lit.[13] $[\alpha]_D^{25}$ +32.6 (*c* 1,$CHCl_3$)}.

IR ($CHCl_3$, cm^{-1}):νmax. 3369, 2984, 2930, 1604, 1454, 1372, 1061.

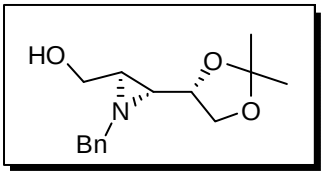
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.35 (s, 3H), 1.43 (s, 3H), 1.76 (m, 2H), 2.32 (br s, 1H), 3.25 (d, J = 13.2 Hz, 1H), 3.47-3.69 (m, 3H), 3.90 (d, J = 13.2 Hz, 1H), 3.94-4.04 (m, 2H), 7.35 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 25.3, 26.6, 43.1, 45.6, 59.8, 63.5, 67.2, 75.4, 109.1, 126.9, 127.8, 128.1, 138.1.

MS (ESI):*m/z*: 286.13 $(M+Na)^+$.

HRMS: Calculated for $C_{15}H_{22}NO_3$-264.1594, found-264.1603.

((2*R*,3*R*)-1-Benzyl-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridin-2-yl)methanol (12)



MF: $C_{15}H_{21}NO_3$, **MW**: 263.33.

$[\alpha]_D^{25}$ +22.1 (*c* 0.70, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}):vmax. 3369, 2982, 2930, 1610.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.48 (s, 3H), 1.38 (s, 3H), 1.77-1.81 (m, 1H). 1.93 (t, J = 6 Hz, 1H), 2.20-2.26 (m, 1H), 3.36-3.43 (m, 2H), 3.62-3.82 (m, 3H), 4.13-4.26 (m, 2H), 7.26-7.35 (m, 3H).

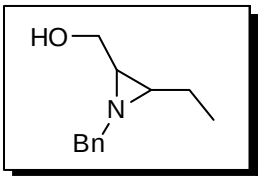
^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 25.7, 26.9, 41.7, 44.0, 56.0, 61.5, 68.1, 73.2, 109.9, 127.1, 127.8, 128.3, 139.2.

Doubling of peaks in ^{1}H and ^{13}C NMR was attributed to invertomerism.[13]

MS (ESI): *m/z*: 263.23 $(M+H)^+$.

HRMS: Calculated for $C_{15}H_{22}NO_3$-264.1594, found-264.1603.

***Cis*-(1-Benzyl-3-ethylaziridin-2-yl)methanol (13)**



MF: $C_{12}H_{17}NO$, **MW**: 191.27

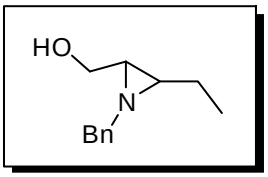
IR ($CHCl_3$, cm^{-1}): vmax 3350, 1610, 1444, 1210.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 0.88 (t, J = 7.3 Hz, 3H, 1.36-1.49 (m, 2H), 1.53-1.68 (m, 1H), 1.82-1.91 (m, 1H), 2.34 (br s, 1H), 3.58 (d, J = 13.0 Hz, 1H), 3.41-3.54 (m, 2H), 3.72 (dd, J = 4.8 & 11.4 Hz, 1H), 7.23-7.35 (m, 5H).

MS (ESI): *m/z*: 192.14 $(M+H)^+$.

HRMS: Calculated for $C_{12}H_{18}NO$ -192.1383, found-192.1389.

***Trans*-(1-Benzyl-3-ethylaziridin-2-yl)methanol (14)**



MF: $C_{12}H_{17}NO$, **MW**: 191.27.

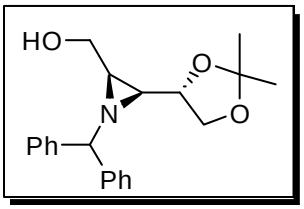
IR ($CHCl_3$, cm^{-1}): νmax 3350, 1612, 1449, 1339, 1229.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.06 (t, J = 7.3 Hz, 3H), 1.41-1.48 (m, 1H), 1.55-1.75 (m, 2H), 1.99-2.09 (m, 1H), 3.38 (dd, J = 5.3 & 11.5 Hz, 1H), 3.55 (d, J = 13.7 Hz, 1H), 3.66-3.88 (m, 3H), 7.25-7.41 (m, 5H).

MS (ESI): *m/z*: 192.16 $(M+H)^+$.

HRMS: Calculated for $C_{15}H_{22}NO_3$-192.1383, found-192.1390

((2*R*,3*S*)-1-Benzhydryl-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridin-2-yl)methanol (15)



MF: $C_{21}H_{25}NO_3$, **MW**: 339.43.

$[\alpha]_D^{25}$ +20.0 (*c* 0.8, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): νmax3350, 1610, 1444, 1210.

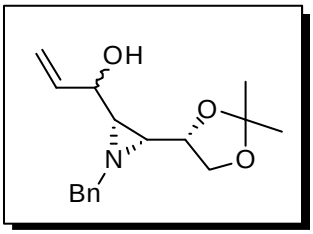
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.28 (s, 3H), 1.37 (s, 3H), 1.79 (dd, J = 6.0 & 8.0 Hz, 1H), 2.05-2.12 (m, 1H), 3.12 (dd, J = 6.0 & 8.0 Hz, 1H), 3.63-3.67 (m, 2H), 3.77-3.92 (m, 3H), 7.25-7.34 (m, 10H).

^{13}C NMR(50 MHz, $CDCl_3$ + CCl_4): δ 25.4, 26.8, 44.9, 61.4, 68.5, 75.3, 77.2, 109.2, 126.9, 127.3, 127.4, 128.5, 142.7, 142.9.

MS (ESI): *m/z*: 340.13 $(M+H)^+$.

HRMS: Calculated for $C_{21}H_{25}NO_3Na$-362.1727, found-362.1736.

1-((2*S*,3*R*)-1-Benzyl-3-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridin-2-yl)prop-2-en-1-ol (16)



MF: $C_{17}H_{23}NO_3$, **MW:** 289.37

IR ($CHCl_3$, cm^{-1}): νmax 3360, 2934, 1620, 1464, 1214.

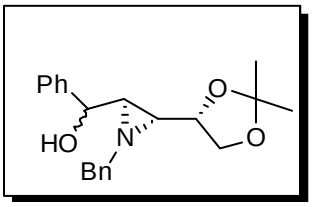
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ1.35 (s, 3H), 1.44 (s, 3H), 1.71-1.87 (m, 2H), 3.18-3.32 (m, 1H), 3.65-3.73 (m, 2H), 3.96-4.03 (m, 3H), 4.04-4.19 (m, 1H), 5.06-5.24 (m, 2H), 5.63-5.74 (m, 1H), 7.27-7.34 (m, 5H).

Doubling of peaks in ^{1}H NMR was attributed to diastereomeric mixture.

MS (ESI):*m/z*: 290.41 $(M+H)^+$.

HRMS: Calculated for $C_{17}H_{24}NO_3$-290.1751, found-290.1761.

((2*R*,3*R*)-1-Benzyl-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridin-2-yl)(phenyl)methanol (17)



MF: $C_{21}H_{25}NO_3$, **MW**: 339.43

IR ($CHCl_3$, cm^{-1}): νmax 3454, 2927, 1624, 1455, 1209.

^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): δ 1.49(s, 3H), 1.51(s, 3H), 2.35 (dd, *J* = 2.7 & 9.2 Hz, 1H), 2.41(dd, *J* = 2.7 & 9.2 Hz,1H), 3.36 (s, 1H), 3.40 (dd, *J* = 6.4 & 7.3Hz, 1H), 3.53 (d, *J* = 13.4Hz, 1H), 3.59-3.68 (m,1H), 3.81 (dd, *J* = 6.4 & 8.2 Hz, 1H), 3.99 (dd, *J* = 6.4 & 7.9Hz, 1H), 4.03 (brs, 1H), 4.06-4.18 (m,2H), 4.22 (d,*J* = 12.8 Hz, 1H), 4.29 (d, *J* = 13.4 Hz, 1H), 4.34(d, *J* = 4.8 Hz, 1H),4.75(d, *J* = 2.7 Hz,1H),7.17-7.38 (m,20H)

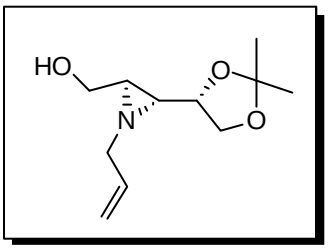
^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 25.7, 26.9, 39.8 (42.8), 47.8 (49.2), 55.4 (56.2), 67.8, 69.3, 73.1, 110.0, 125.5 (125.6), 127.1, 127.9, 128.4, 128.5, 128.6, 139.0, 139.1, 141.5, 142.0.

Doubling of peaks in ^{1}H and ^{13}C NMR was attributed to invertomerism and diastereomeric mixture.

MS (ESI): *m/z*: 362.11 $(M+Na)^+$.

HRMS: Calculated for $C_{21}H_{26}NO_3$-340.1907, found-340.1923.

((2*R*,3*R*)-1-Allyl-3-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridin-2-yl)methanol (18)



MF: $C_{11}H_{19}NO_3$, **MW**: 213.27

$[\alpha]_D^{25}$ +30.2 (*c*0.3, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): νmax 3444, 1611, 1422, 1013.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.35 (s, 3H), 1.45 (s, 3H), 1.63-1.68 (m, 1H), 2.11-2.18 (m, 1H), 2.91-3.07 (m, 1H), 3.10-3.44 (m, 1H), 3.46-3.66 (m, 1H), 3.66-3.71 (m, 3H), 3.95-4.09 (m, 3H), 5.12-5.28 (m, 2H), 5.94-6.03 (m, 1H).

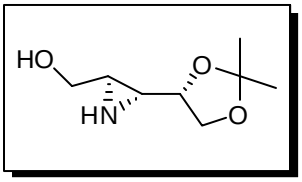
^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 25.8, 26.9, 41.4, 43.4, 54.7, 61.5, 68.1, 73.0, 109.9, 116.6, 138.4.

Doubling of peaks in ^{1}H and ^{13}C NMR was attributed to invertomerism.

MS (ESI):*m/z*: 214.17 $(M+H)^+$.

HRMS: Calculated for $C_{11}H_{20}NO_3$-214.1438, found-214.1445.

((2*R*,3*R*)-3-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)aziridin-2-yl)methanol (19)



MF: $C_8H_{15}NO_3$, **MW**: 173.21

[α]$_D^{25}$ −15.8 (*c* 0.5, $CHCl_3$)

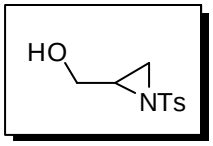
IR ($CHCl_3$, cm^{-1}): νmax 3455, 3349, 1387, 1210, 1087.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.33 (s, 3H), 1.40 (s, 3H), 2.05 (t, *J* = 3.5 Hz, 1H), 2.18-2.21 (m, 1H), 3.43 (dd, *J* = 6.0 & 12.0 Hz, 1H), 3.76-3.84 (m, 2H), 4.09-4.14 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 25.2, 26.4, 34.7, 35.1, 61.5, 67.5, 74.5, 109,3.

MS (ESI): *m/z*: 174.23 $(M+H)^+$.

(1-Tosylaziridin-2-yl)methanol (20)



MF: $C_{10}H_{13}NO_3S$, **MW**: 227.28

IR ($CHCl_3$, cm^{-1}): νmax3340, 2928, 2850, 1580, 1150, 1080, 833.

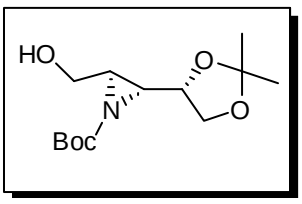
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.03 (br s, 1H), 2.39 (d, *J* = 4.6 Hz, 1H), 2.46 (s, 3H), 2.60 (d, *J* = 7.0 Hz, 1H), 2.97-3.07 (m, 1H), 3.53 (br dd, *J* = 4.4 & 12.1 Hz, 1H), 3.85 (br dd, *J* = 1.8 & 12.1 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 21.6, 30.8, 40.3, 60.7, 128.0, 129.7, 134.7, 144.6.

MS (ESI): *m/z*: 228.14 $(M+H)^+$.

HRMS: Calculated for $C_{10}H_{13}NO_3SNa$-250.0508, found-250.0514.

(2*R*,3*R*)-*tert*-Butyl 2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(hydroxymethyl)aziridine-1-carboxylate (21)



MF: $C_{13}H_{23}NO_5$, **MW**: 273.33

[α]$_D^{25}$ +16.3 (*c* 0.2, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): νmax 3360, 1640, 1610, 1449, 1230, 1077.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (3H), 1.42 (s, 3H), 1.49 (s, 9H), 2.04 (br s, 1H), 2.26 (br s, 1H), 3.74-3.79 (m, 2H), 3.83-3.93 (m, 1H), 4.00-4.15 (m, 3H).

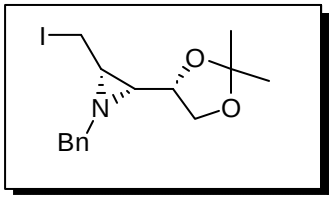
^{13}C NMR (100 MHz, $CDCl_3$): δ 25.2, 26.4, 27.7, 36.4, 42.9, 60.3, 67.6, 68.4, 73.8, 82.4, 109.5, 153.3.

Doubling of peaks in ^{1}H and ^{13}C NMR was attributed to invertomerism/rotamers.

MS (ESI): *m/z*: 296.28 $(M+Na)^+$.

HRMS: Calculated for $C_{13}H_{23}NO_5Na$-296.1468, found-296.1474.

(2*R*,3*S*)-1-Benzyl-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(iodomethyl)aziridines (22)



MF: $C_{15}H_{20}INO_2$, **MW**: 373.23

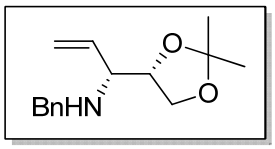
$[\alpha]_D^{25}$ −32.3 (*c* 0.45, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): νmax 2929, 1633, 1454, 1289, 1089.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.36 (s, 3H), 1.42 (3, 3H), 1.84 (dd, *J* = 6.0 & 8.0 Hz, 1H), 2.01-2.11 (m, 1H), 2.99 (dd, *J* = 8.5 & 10.1 Hz, 1H), 3.28-3.43 (m, 2H), 3.71-3.95 (m, 3H), 4.14 (dd, *J* = 6.2 & 8.0 Hz, 1H), 7.25-7.38 (m, 5H).

MS (ESI): *m/z*: 374.14 $(M+H)^+$.

(*R*)-*N*-Benzyl-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-amine (23)



Yield: 85% from alcohol **11**, 90**%** from alcohol **12** and 75% from compound **22**

MF: $C_{15}H_{21}NO_2$, **MW**: 247.33

$[\alpha]_D^{25}$ −30.2 (*c* 0.9, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): νmax 3385, 2928, 1644, 1460, 1290.

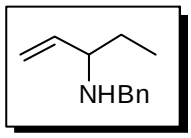
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.32 (3H), 1.33 (s, 3H) 1.90 (s, 2H), 3.05 (t, *J* = 8 Hz, 1H), 3.47-3.79 (m, 2H), 3.80-4.11 (m, 3H), 5.10-5.38 (m, 2H), 5.60 (ddd, *J* = 8.0, 10.0 & 18.0 Hz, 1H), 7.08-7.48 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 25.4, 26.8, 50.7, 64.3, 66.5, 109.37, 119.0, 126.7, 128.0, 137.0, 140.1.

MS (ESI): *m/z*: 248.28 $(M+H)^+$.

HRMS: Calculated for $C_{15}H_{22}NO_2$-248.1645, found-248.1652.

***N*-Benzylpent-1-en-3-amine (24)**



Yield: 90% each from alcohol **13** and alcohol **14.**

MF: $C_{12}H_{17}N$, **MW**: 175.27

IR ($CHCl_3$, cm^{-1}): νmax 3367, 2922, 1622, 1454, 1277.

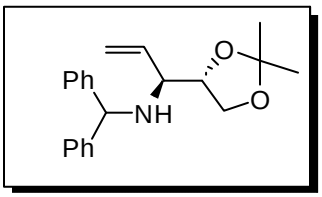
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 0.9 (t, 3H), 1.45-1.58 (m, 2H),

1.73 (br s, 1H), 2.96 (td, *J* = 5.0 & 8.0 Hz, 1H), 3.65 (d, J = 13.0 Hz, 1H), 3.85 (d, *J* = 13.0 Hz, 2H), 5.08-5.20 (m, 2H), 5.62 (ddd, *J* = 8.0, 10.0 & 17.0 Hz).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 10.2, 28.2, 51.0, 62.6, 116.2, 126.7, 128.0, 128.1, 140.2, 140.6.

MS (ESI): *m/z*: 176.13 $(M+H)^+$.

(*S*)-*N*-Benzhydryl-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-amine (25)



Yield: 80% from alcohol **15**

MF: $C_{21}H_{25}NO_2$, **MW**: 323.43

$[\alpha]_D^{25}$ −24.2 (*c* 1.3, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): νmax 3436, 2931, 1643, 1598, 1453, 1370, 1213, 1054.

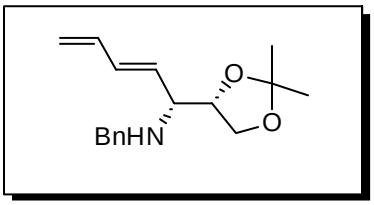
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.33 (s, 3H),1.36 (s, 3H),2.96 (dd, *J* = 4.8 & 8.4 Hz, 1H), 3.79 (m, 1H), 4.04 (t, *J* = 6.7Hz, 1H), 4.09-4.21 (m, 1H), 4.89 (s, 1H), 5.05 (dd, *J* = 1.0 & 17.2 Hz, 1H), 5.22-5.38 (m, 2H), 5.67 (ddd, *J* = 8.7, 10.2 & 17.2 Hz, 1H), 7.05-7.50 (m, 10H)

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 25.41, 26.89, 44.84, 44.93, 61.43, 68.58, 75.33, 77.28, 109.27, 126.93, 127.3, 127.4, 128.5, 142.7, 142.9.

MS (ESI): *m/z*: 324.33 $(M+H)^+$.

HRMS: Calculated for $C_{21}H_{26}NO_2$-324.1958, found-324.1971.

(*R*,*E*)-*N*-Benzyl-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)penta-2,4-dien-1-amine (26)



Yield: 75% from alcohol **16**

MF: $C_{17}H_{23}NO_2$, **MW**: 273.37

$[\alpha]_D^{25}$ −42.7 (*c* 0.6, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): νmax 3342, 2926, 1604, 1495, 1454, 1370, 1213, 1064.

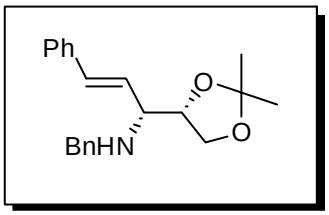
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.34 (s,3H), 2.04 (brs , 1H),3.10 (t, *J* = 8.0Hz, 1H), 3.62 (d, *J* = 13.0 Hz, 1H),3.72-3.76 (m, 1H), 3.86-4.09 (m, 3H), 5.10-5.18 (m, 2H), 5.40 (dd, *J* = 8.8 & 14.5 Hz,1H), 6.17-6.39 (m, 2H),7.25-7.32 (m,5H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.4, 26.8, 50.7, 63.2, 66.8, 78.0, 109.5, 117.7, 126.9, 128.1, 128.3, 131.9, 135.1, 136.1, 139.9.

MS (ESI):*m/z*: 274.13 $(M+H)^+$.

HRMS: Calculated for $C_{17}H_{24}NO_2$-274.1802, found-274.1802.

(*R*,*E*)-*N*-Benzyl-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-phenylprop-2-en-1-amine (27)



Yield: 75% from alcohol **17**

MF: $C_{21}H_{25}NO_2$, **MW**: 323.43

$[\alpha]_D^{25}$ −51.3 (*c* 0.5, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): νmax 3450, 2928, 1610, 1446, 1390, 1210.

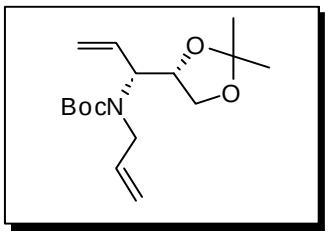
^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 1.38 (s, 3H), 1.40 (s, 3H), 2.49 (br s, 1H), 3.27 (t, *J* = 8.5 Hz, 1H), 3.71 (d, *J* = 13.6 Hz, 1H), 3.84 (dd, *J* = 5.8 & 8.5 Hz, 1H), 3.95-3.99 (m, 2H), 4.12-4.17 (m, 1H), 6.03 (dd, *J* = 8.8 & 16.0 Hz, 1H), 6.60 (d, *J* = 16.0 Hz, 1H), 7.25-7.43 (m, 10H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 25.5, 26.9, 50.9, 63.7, 66.7, 78.2, 109.6, 126.5, 126.9, 127.8, 128.0, 128.2, 128.4, 128.6, 134.2, 136.4, 140.0.

MS (ESI): *m/z*: 324.23 $(M+H)^+$.

HRMS: Calculated for $C_{21}H_{26}NO_2$-324.1958, found-324.1972.

***tert*-Butylallyl((*R*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)carbamate (28)**



Yield: 75% from alcohol **18** over two steps.

MF: $C_{16}H_{27}NO_4$**MW**: 297.39

$[\alpha]_D^{25}$ +16.5 (*c* 0.6, $CHCl_3$)

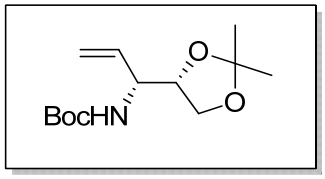
IR ($CHCl_3$, cm^{-1}): νmax 29333, 1660, 1622, 1611, 1445, 1214, 1090.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.34 (s, 3H), 1.42 (s, 3H), 1.46 (s, 9H), 3.65 (br t, *J* = 6.6 Hz, 1H), 3.75-3.87 (m, 2H), 3.95-4.03 (m, 1H), 4.28-4.38 (m, 2H), 5.05-5.25 (m, 4H), 5.73-6.65 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 25.4, 26.7, 28.4, 48.9, 61.2, 67.1, 75.7, 79.8, 109.2, 115.7, 118.6, 134.0, 135.8, 155.3.

MS (ESI): *m/z*: 298.28 $(M+H)^+$.

***tert*-Butyl ((*R*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)carbamate (29)**



Yield: 75 % from alcohol **19** over two steps and 90% from alcohol **21**.

MF: $C_{13}H_{23}NO_4$, **MW**: 257.33

$[\alpha]_D^{25}$ +16.2 (*c* 0.56, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): νmax 3455, 2930, 1660, 1622, 1455, 1210.

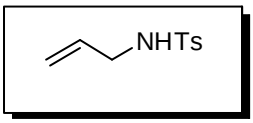
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 3H), 1.46 (s, 3H), 3.75 (ddd, *J* = 2.0, 7.0 & 8.0 Hz, 1H), 4.04 (ddd, *J* = 2.0, 6.0 & 7.0 Hz, 1H), 4.21-4.22 (m, 2H), 4.81 (br s, 1H), 5.20-5.30 (m, 2H), 5.80-5.88 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 26.2, 28.3, 66.2, 77.3, 79.7, 109.4, 116.1, 136.0, 155.0.

MS (ESI): *m/z*: 258.14 $(M+H)^+$.

HRMS: Calculated for $C_{13}H_{23}NO_4Na$-280.1519, found-280.1530.

***N*-Allyl-4-methylbenzenesulfonamide (30)**



Yield: 85% from alcohol **20**

MF: $C_{10}H_{13}NO_2S$, **MW**: 211.28

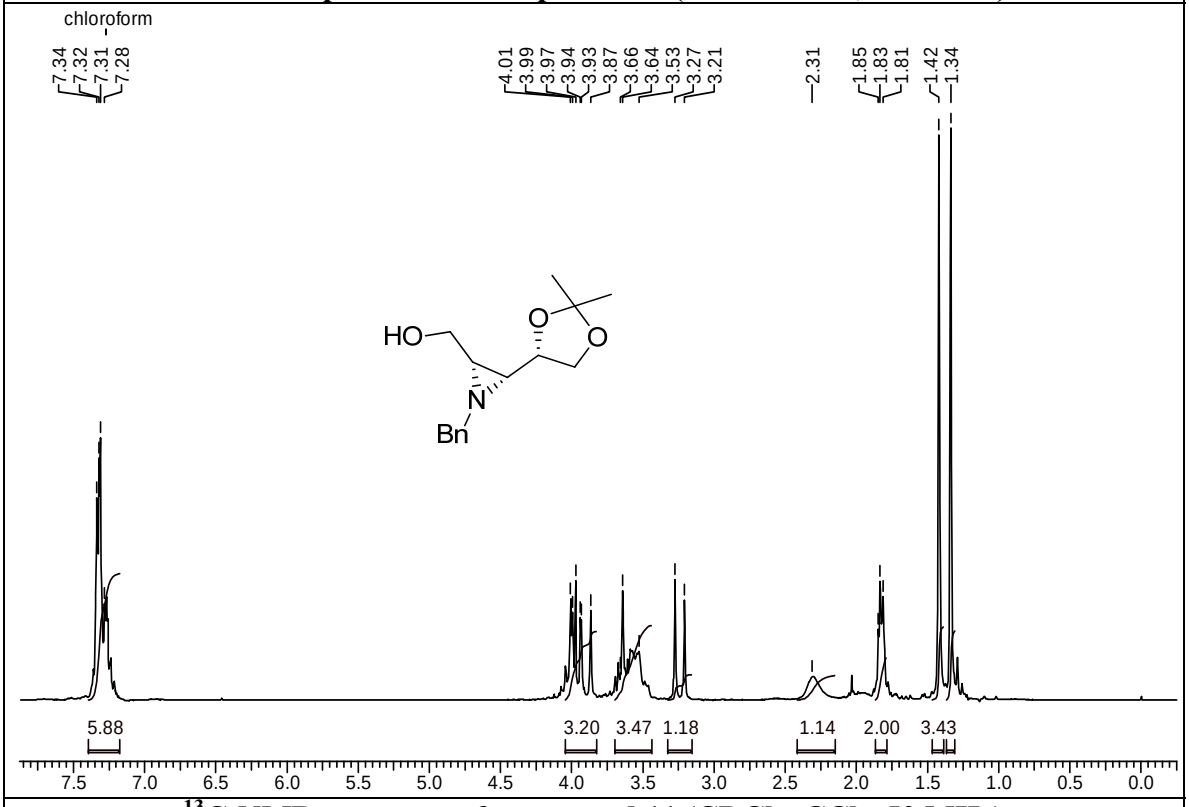
IR ($CHCl_3$, cm^{-1}): νmax 3340, 2928, 2850, 1580, 1150, 1080, 833.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.45 (s, 3H), 3.58 (d, *J* = 4.0 Hz, 2H), 4.68-5.13 (m, 2H), 5.66-5.80 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H).

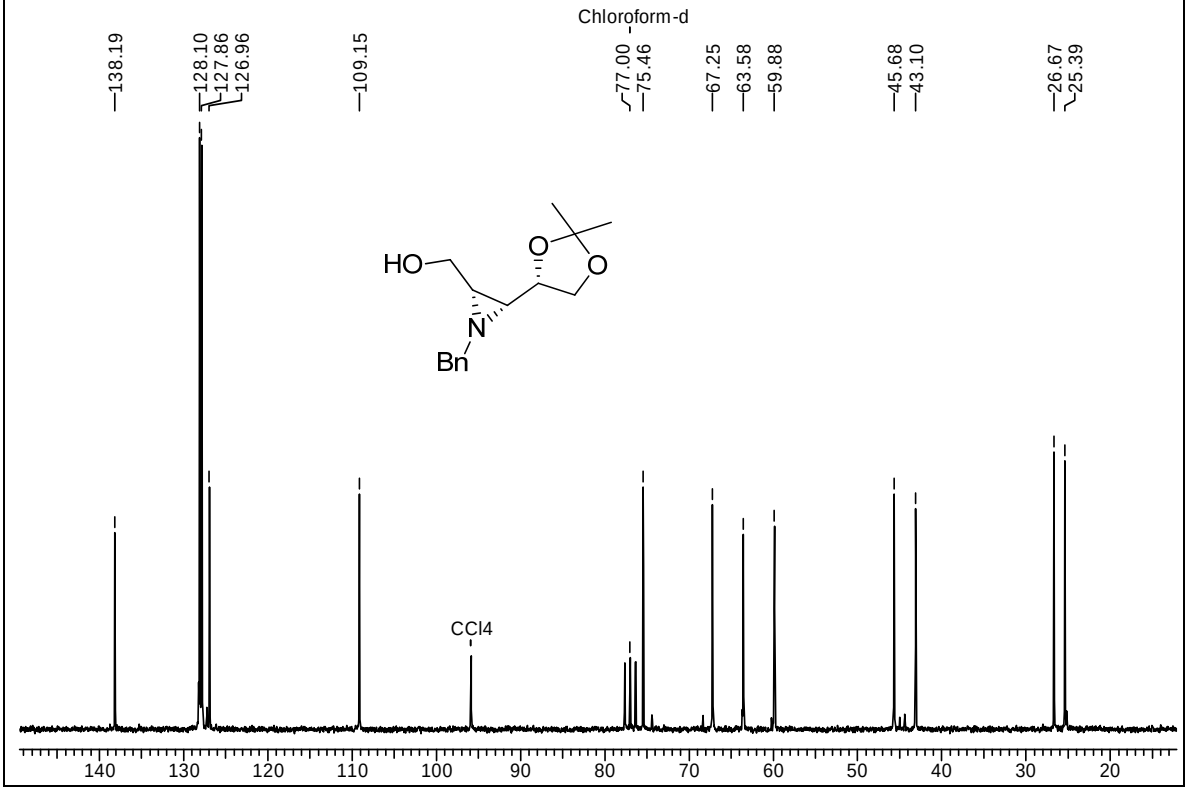
MS (ESI):*m/z*: 212.13 $(M+H)^+$.

3.3.6 Analytical data

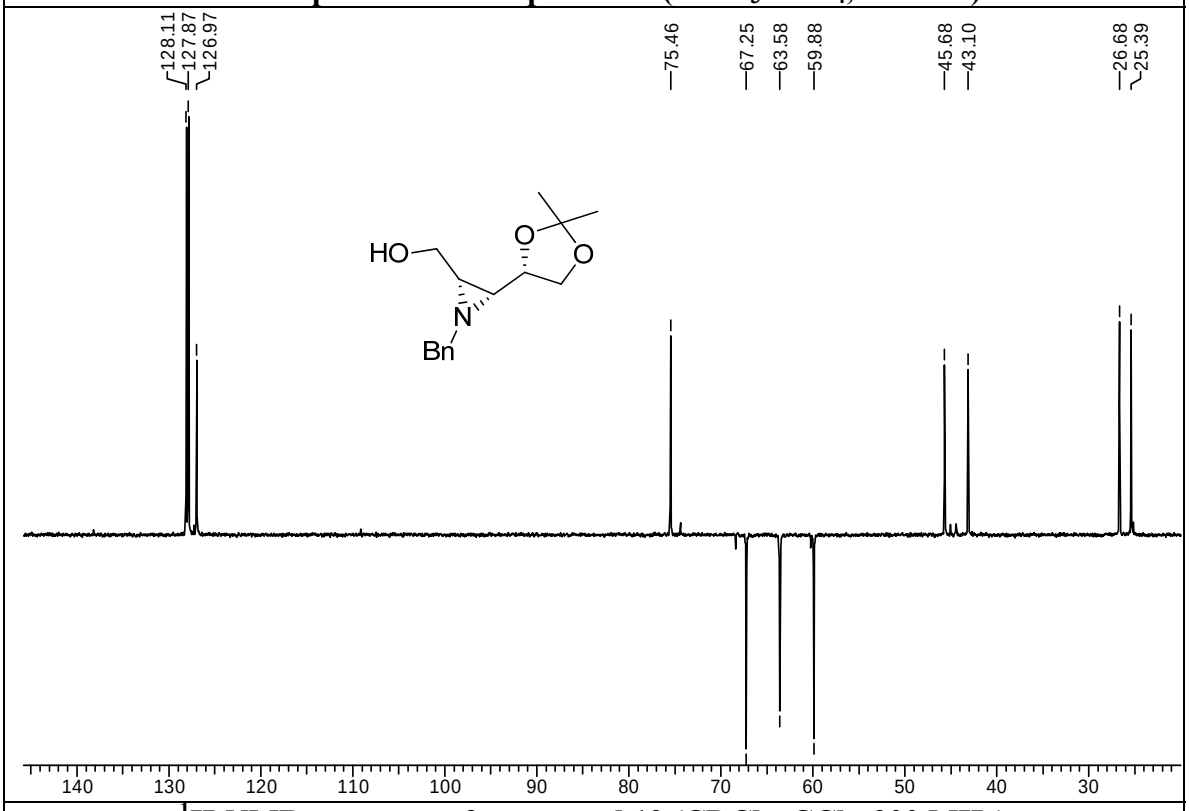
^{1}H-NMR spectrum of compound 11 ($CDCl_3$+CCl_4, 200 MHz)



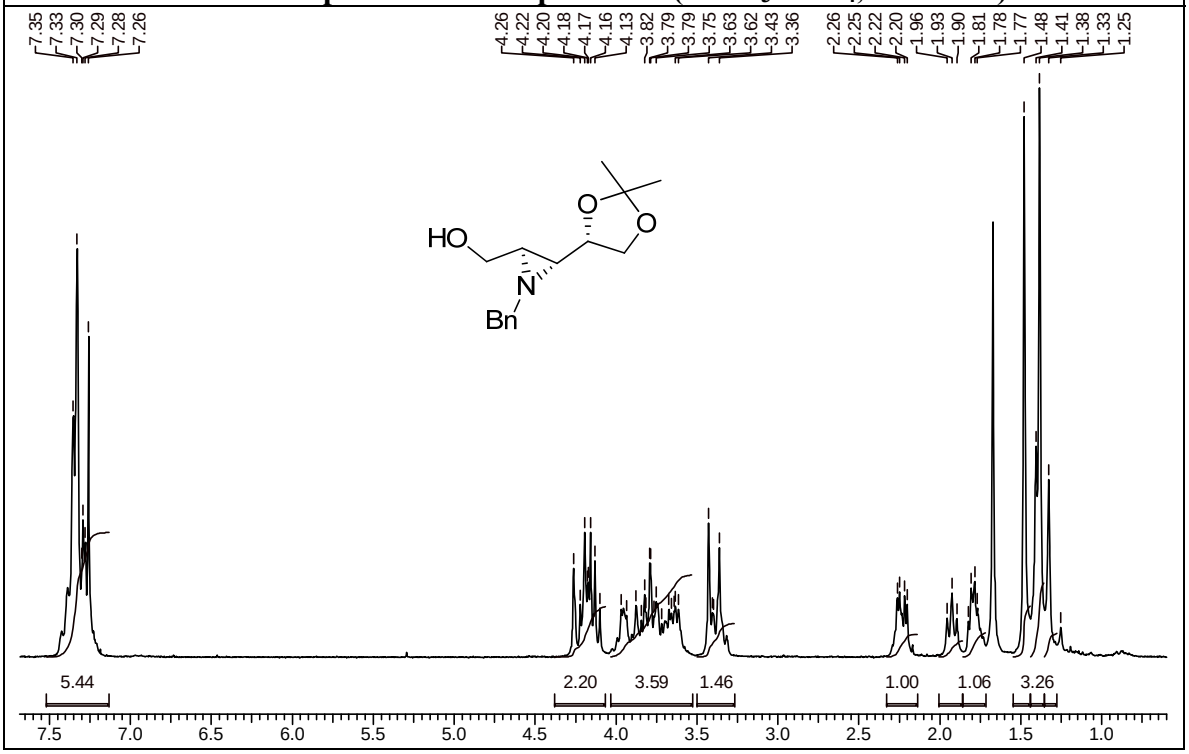
^{13}C-NMR spectrum of compound 11 ($CDCl_3$+CCl_4, 50 MHz)



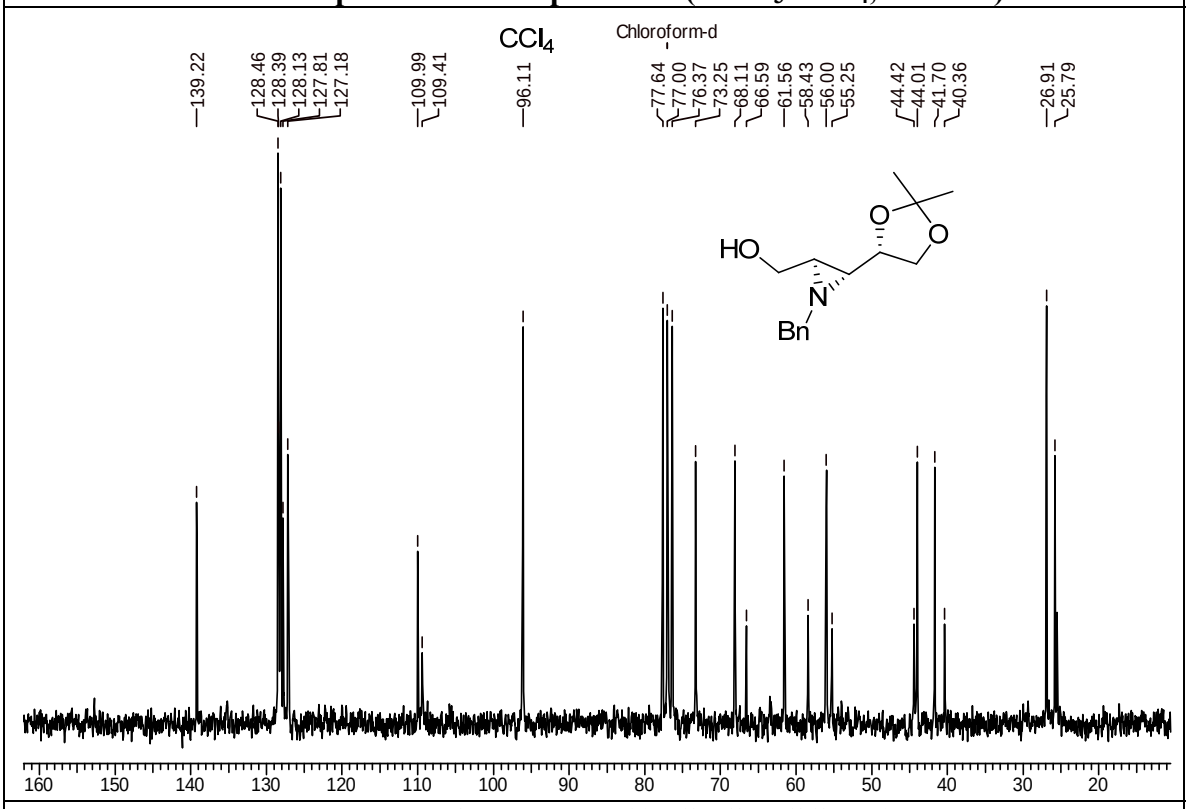
DEPT spectrum of compound 11 ($CDCl_3$+CCl_4, 50 MHz)



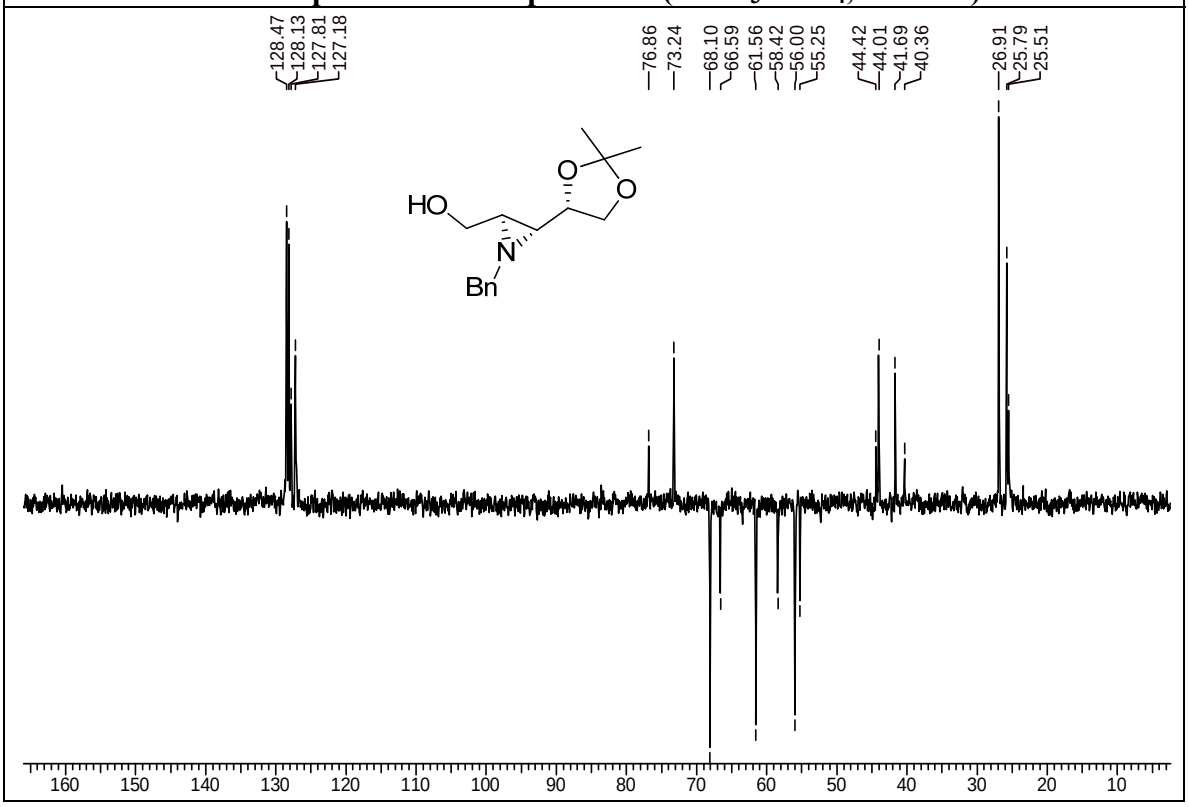
^{1}H-NMR spectrum of compound 12 ($CDCl_3$+CCl_4, 200 MHz)



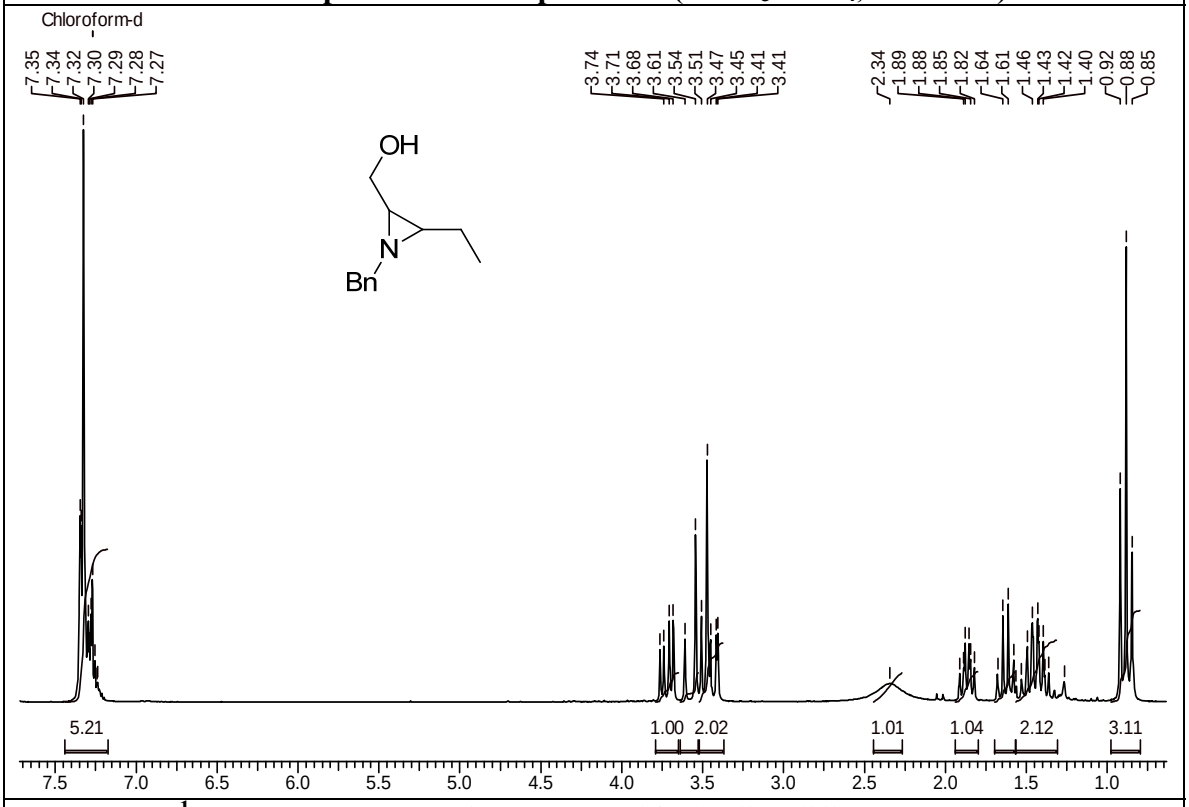
^{13}C-NMR spectrum of compound 12 ($CDCl_3$+CCl_4, 50 MHz)



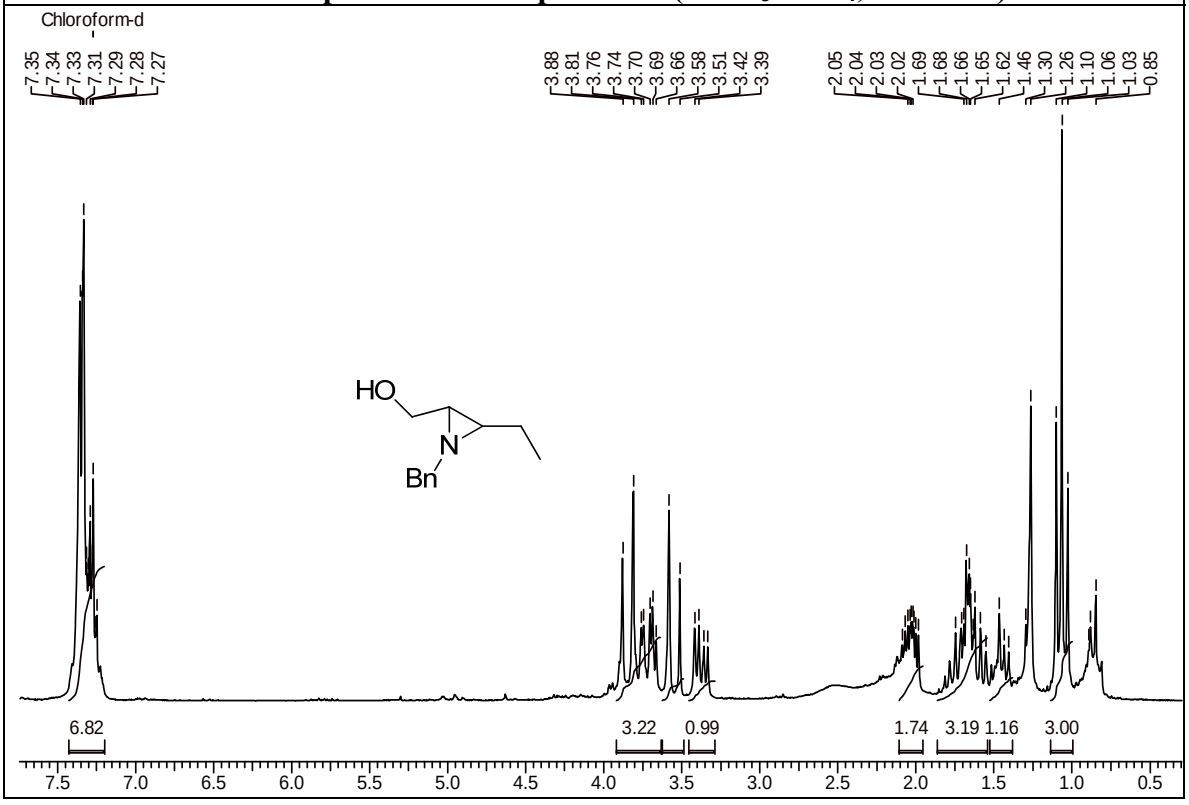
DEPT spectrum of compound 12 ($CDCl_3$+CCl_4, 50 MHz)



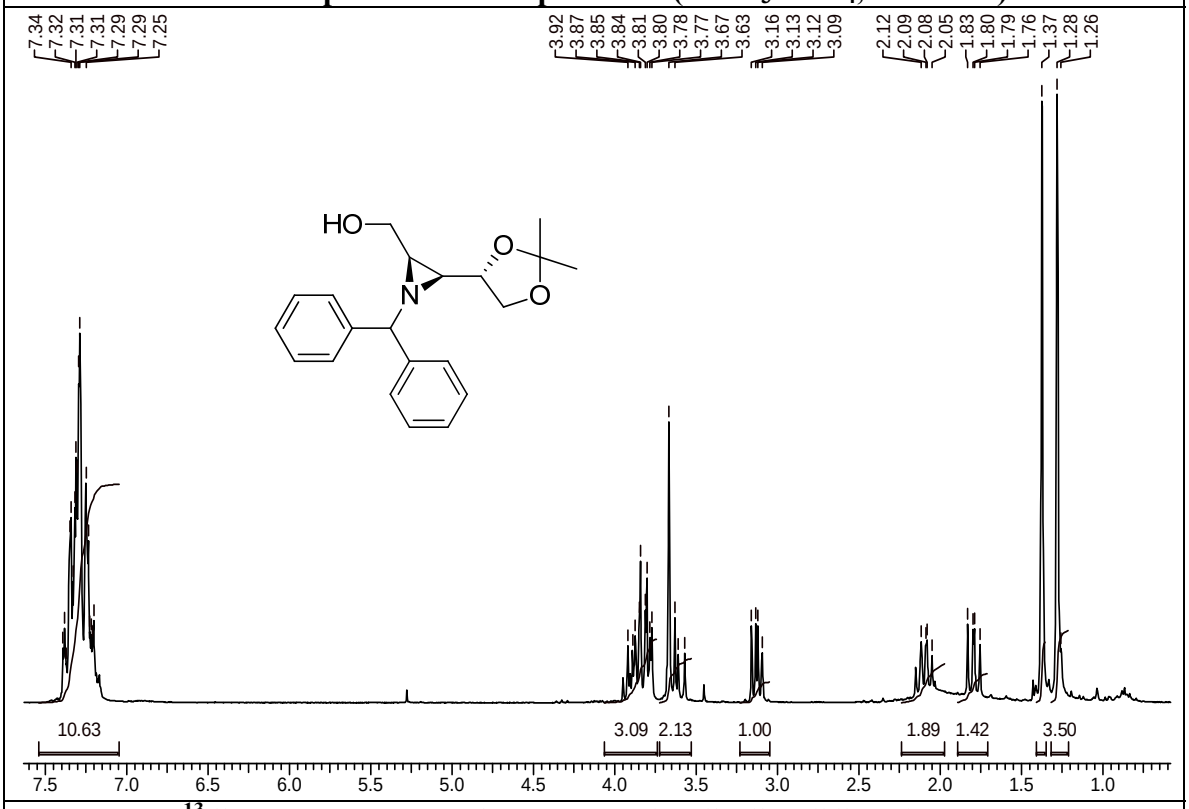
^{1}H-NMR spectrum of compound 13 ($CDCl_3$+CCl_4, 200 MHz)



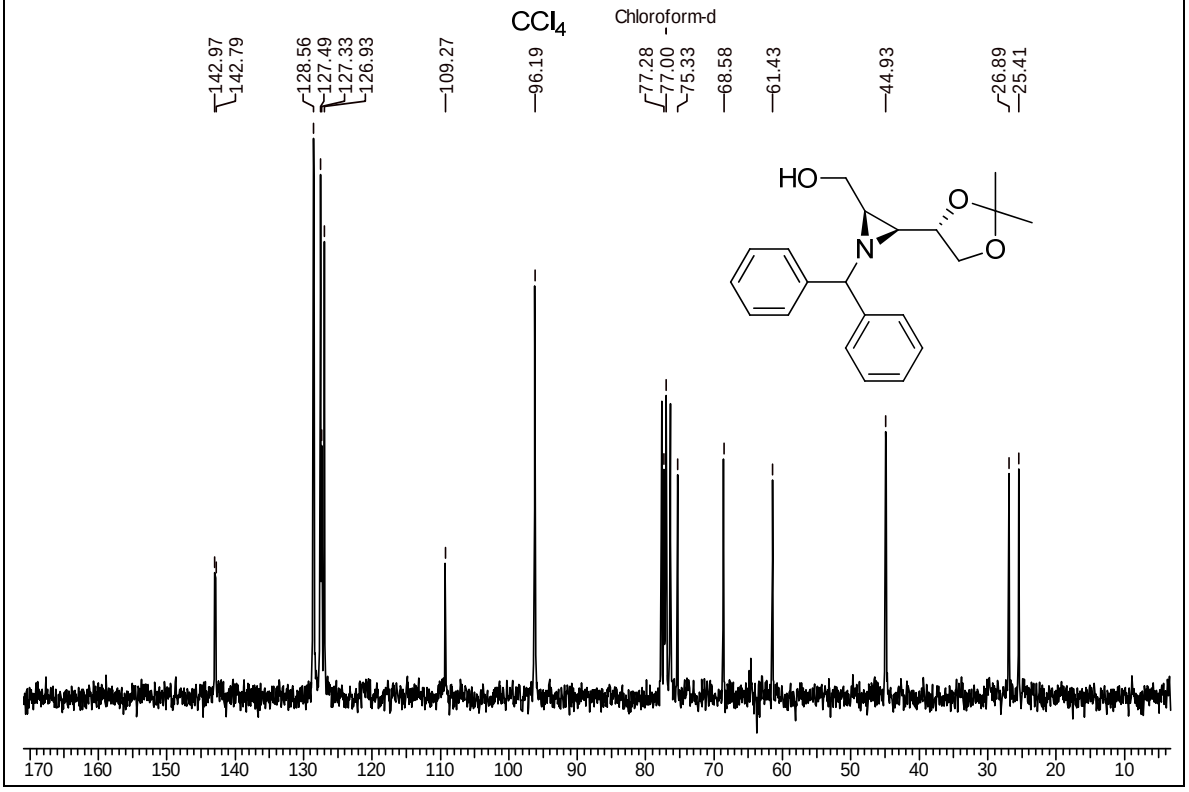
^{1}H-NMR spectrum of compound 14 ($CDCl_3$+CCl_4, 200 MHz)



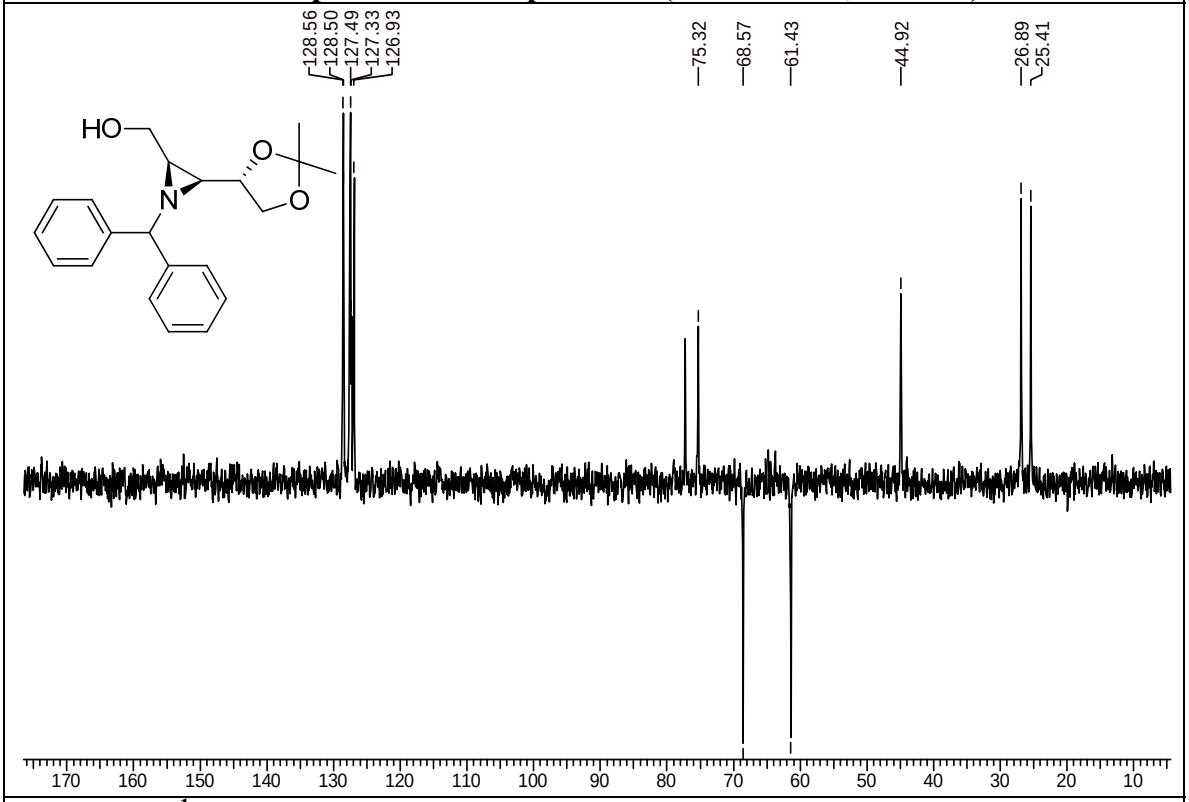
^{1}H-NMR spectrum of compound 15 ($CDCl_3$+CCl_4, 200 MHz)



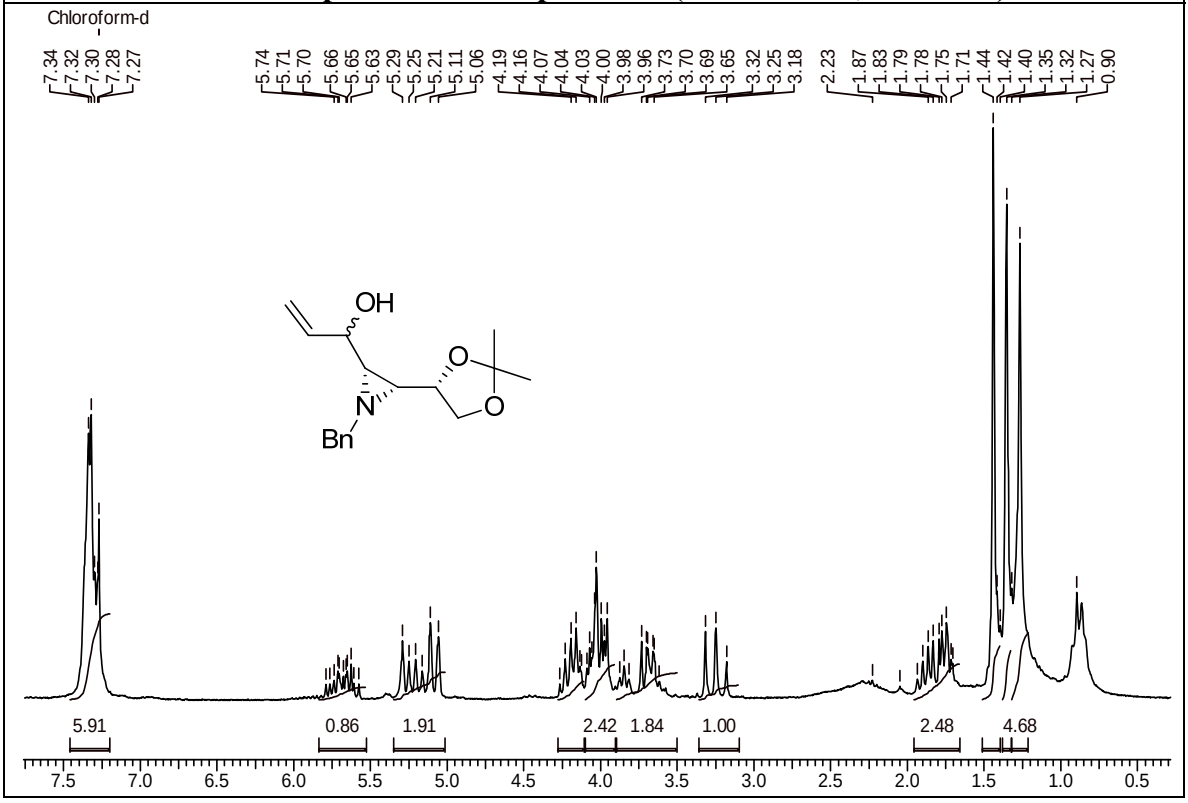
^{13}C-NMR spectrum of compound 15 ($CDCl_3$+CCl_4, 50 MHz)



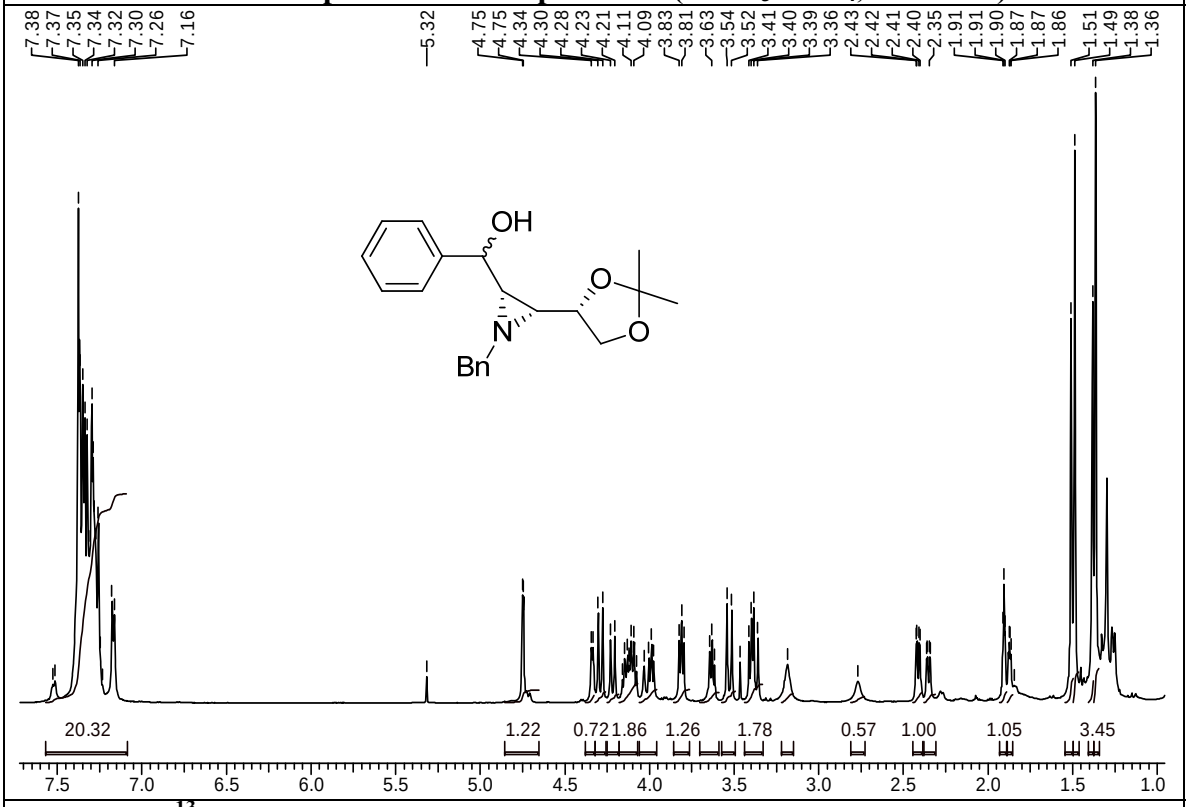
DEPT spectrum of compound 15 ($CDCl_3$+CCl_4, 50 MHz)



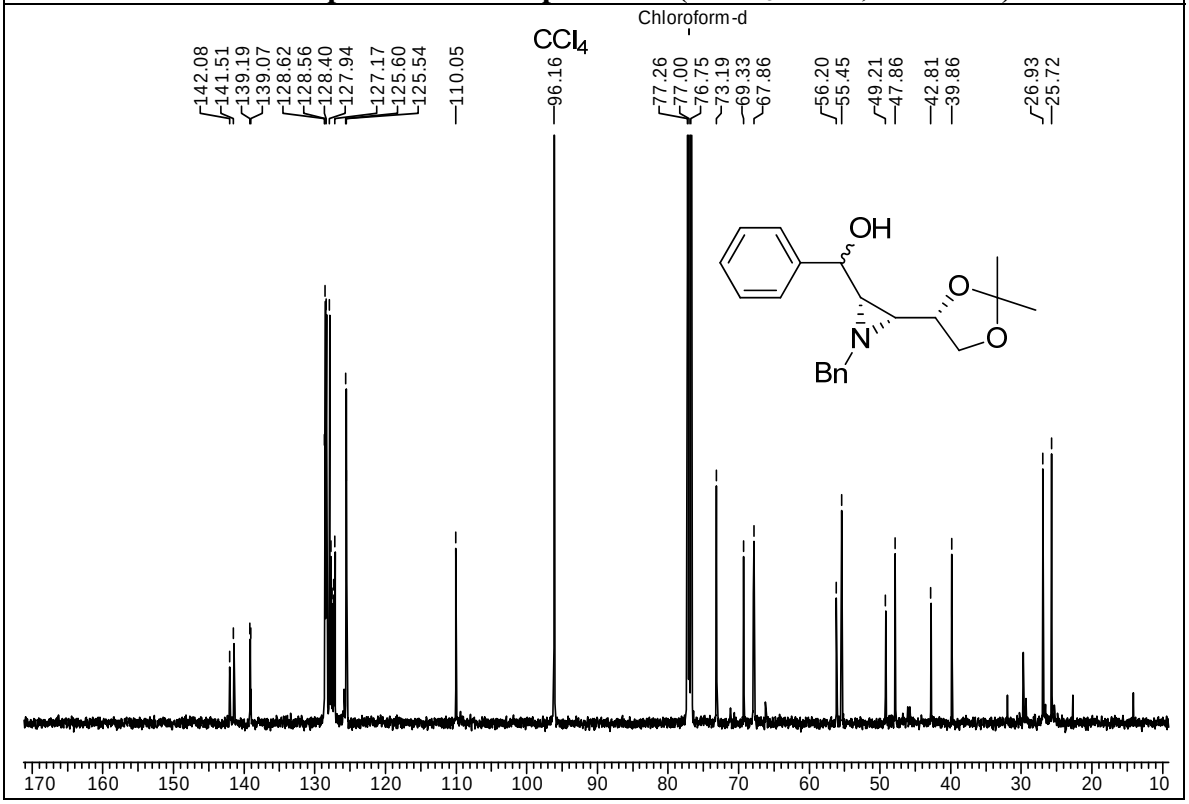
^{1}H-NMR spectrum of compound 16 ($CDCl_3$+CCl_4, 200 MHz)



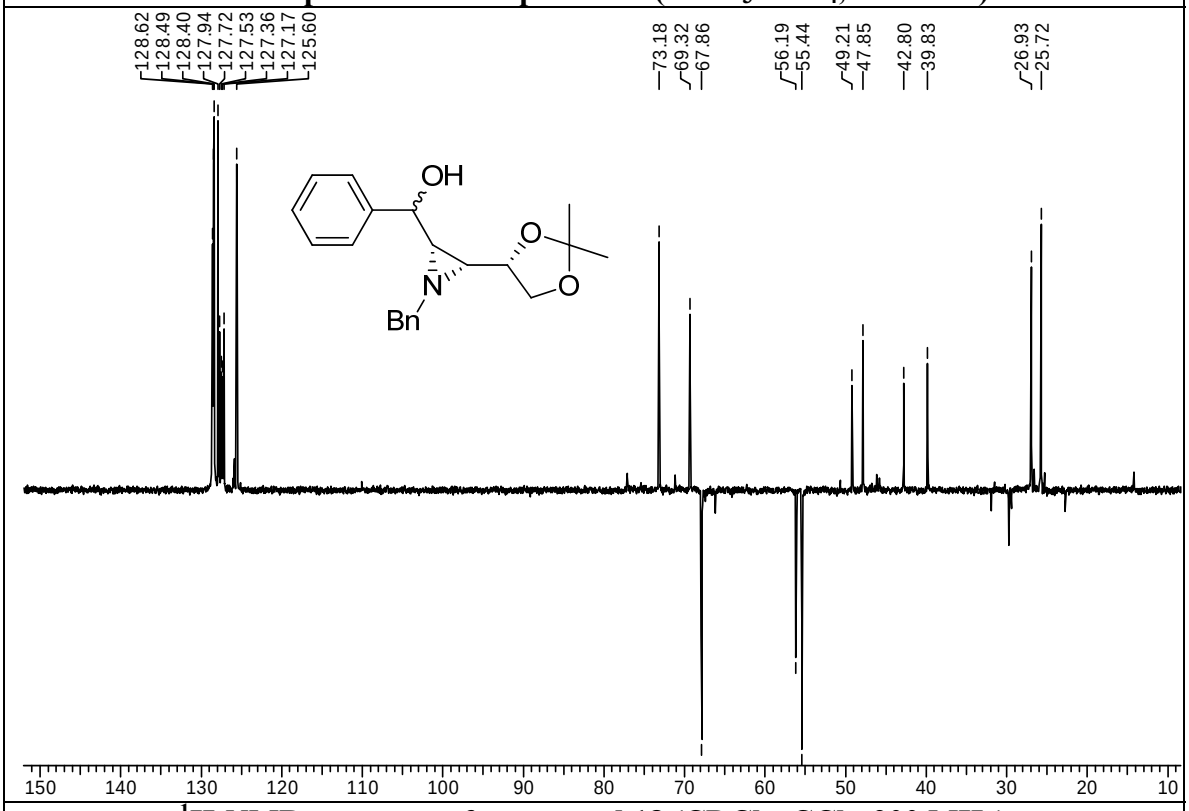
^{1}H-NMR spectrum of compound 17 ($CDCl_3$+CCl_4, 500 MHz)



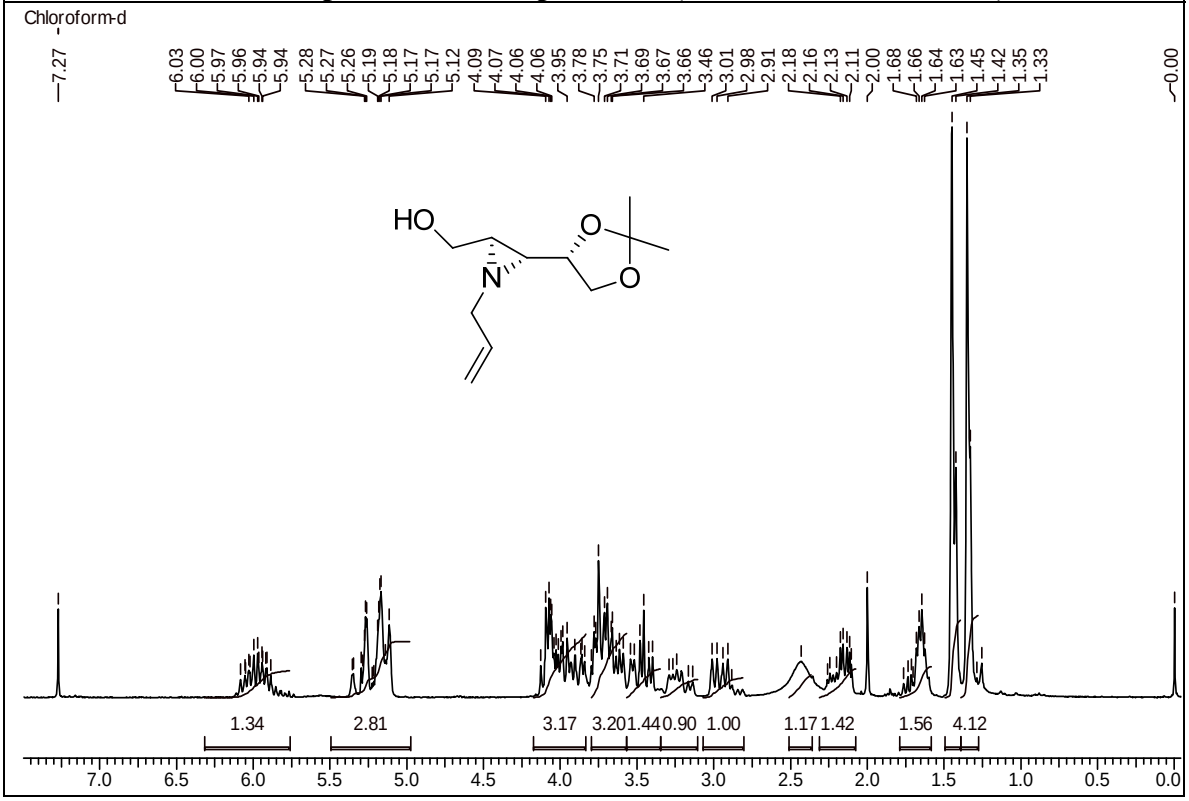
^{13}C-NMR spectrum of compound 17 ($CDCl_3$+CCl_4, 125 MHz)



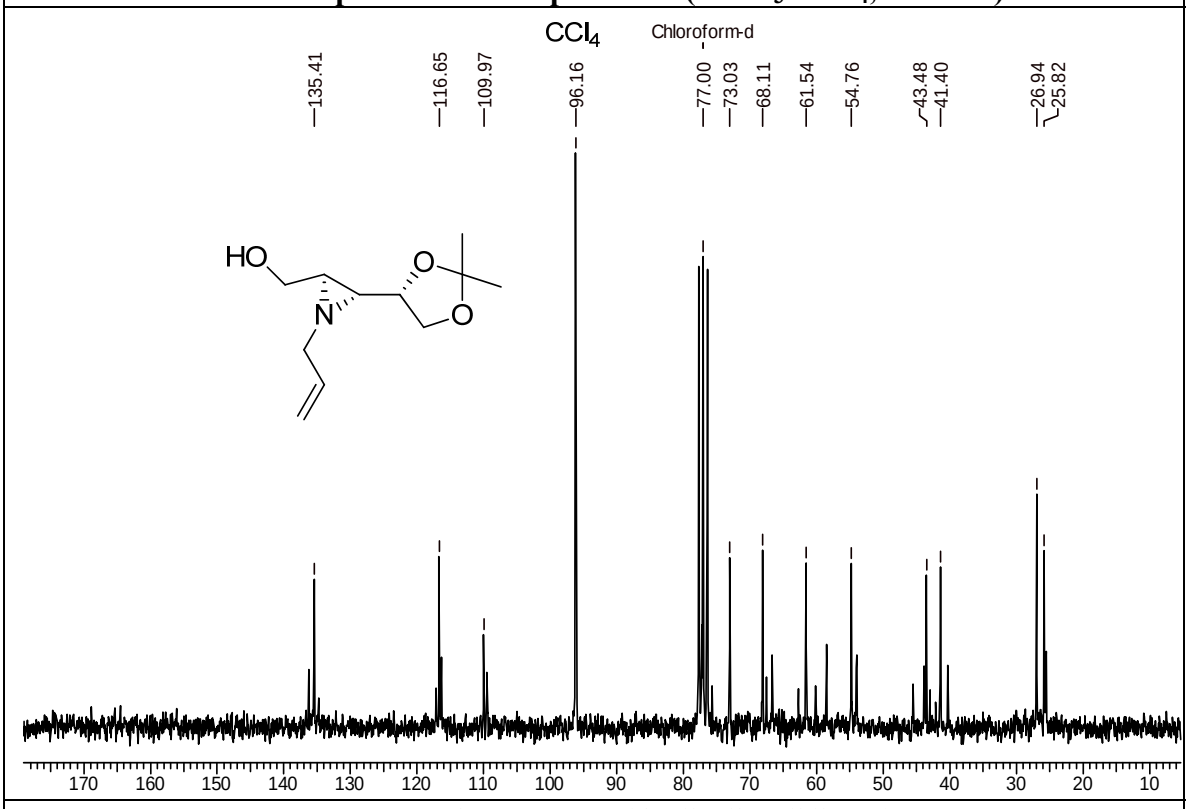
DEPT spectrum of compound 17 ($CDCl_3$+CCl_4, 125 MHz)



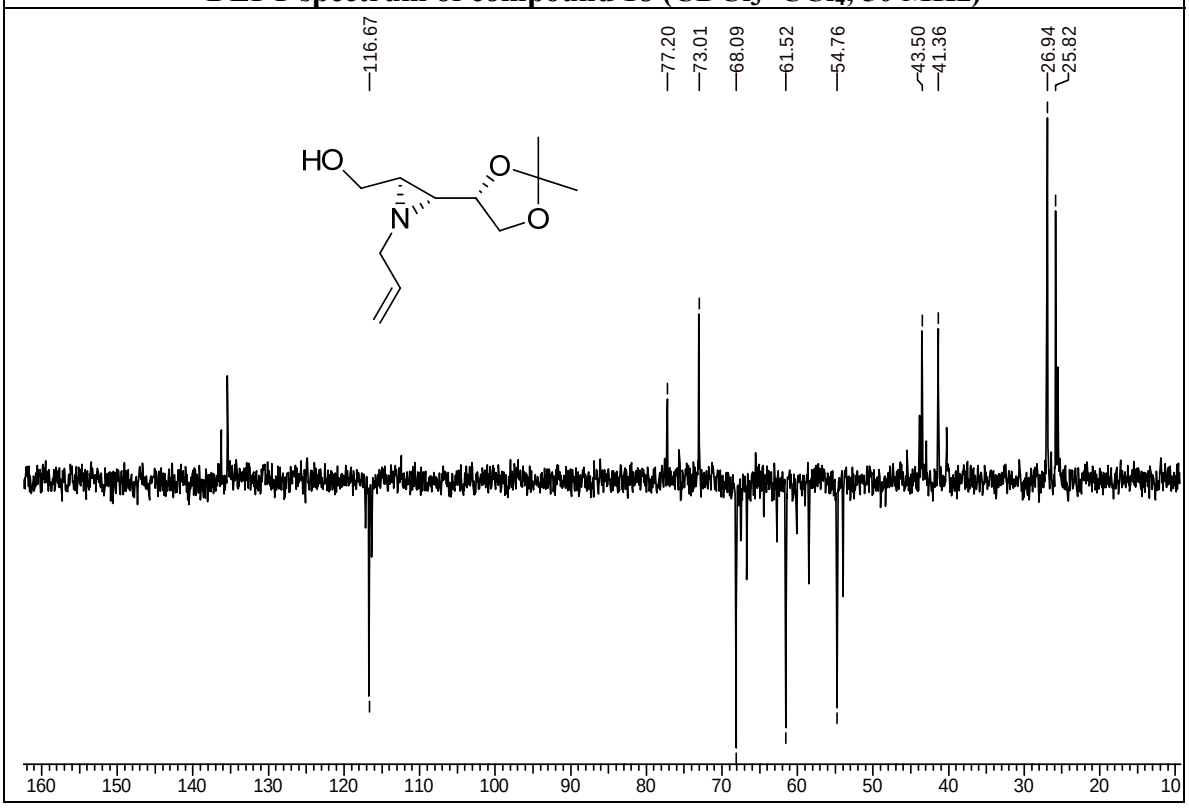
^{1}H-NMR spectrum of compound 18 ($CDCl_3$+CCl_4, 200 MHz)



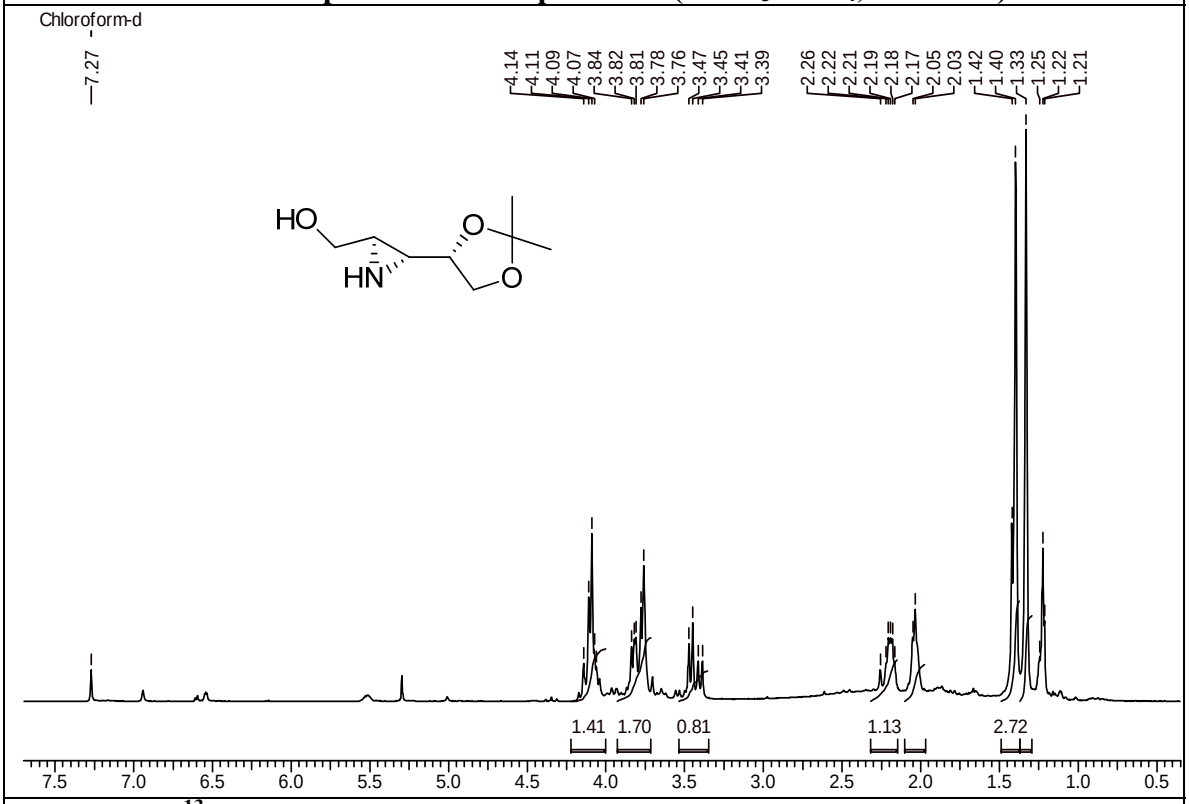
^{13}C-NMR spectrum of compound 18 ($CDCl_3$+CCl_4, 50 MHz)



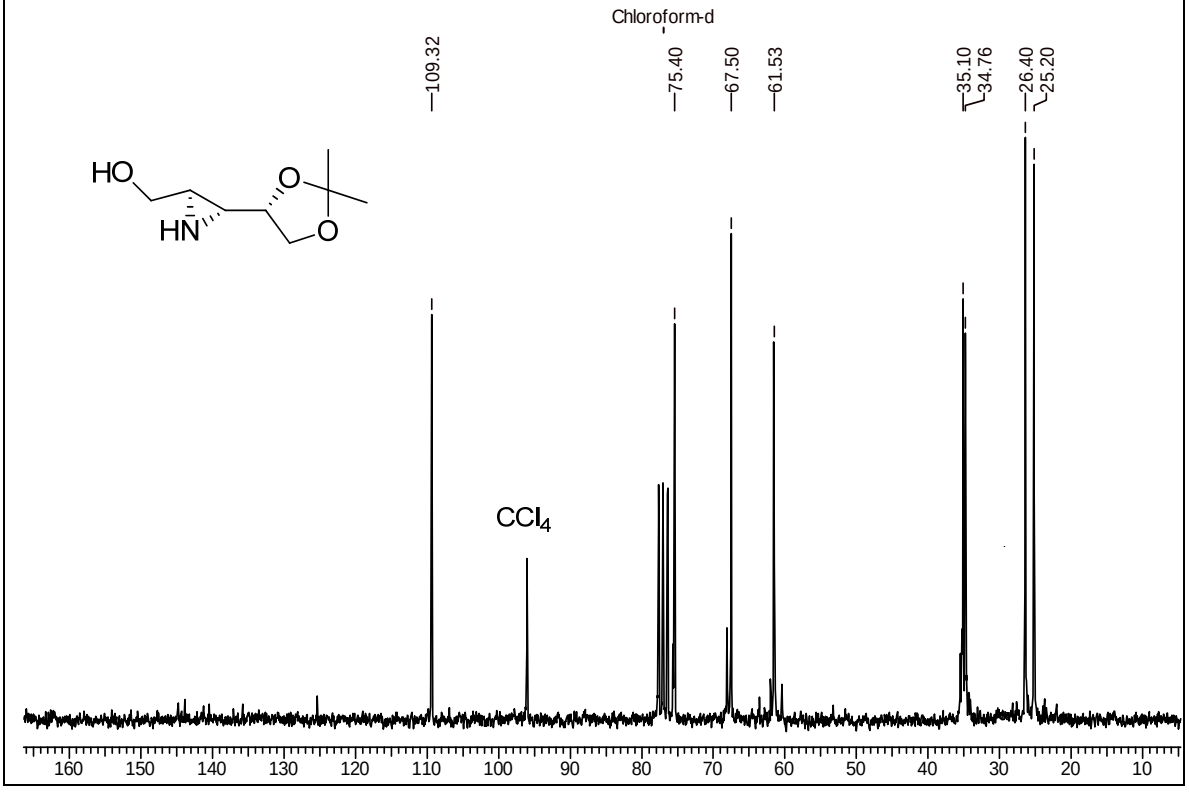
DEPT spectrum of compound 18 ($CDCl_3$+CCl_4, 50 MHz)



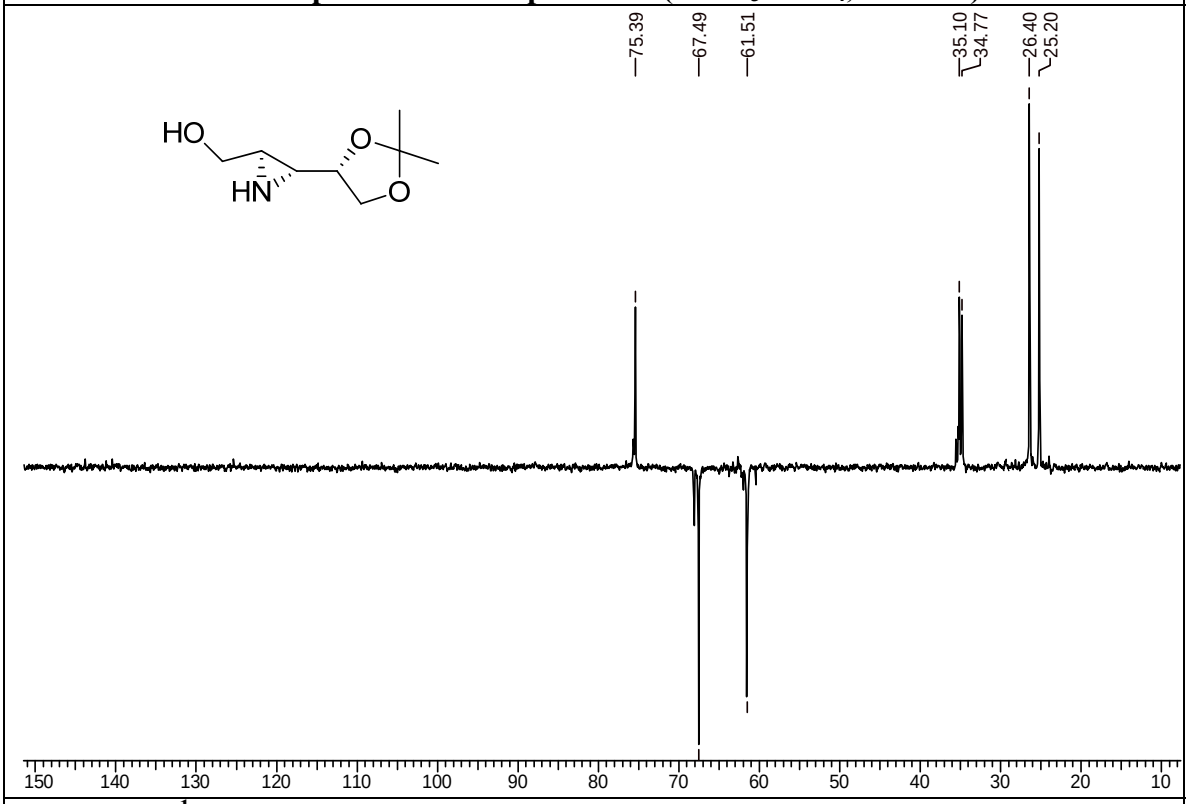
^{1}H-NMR spectrum of compound 19 ($CDCl_3$+CCl_4, 200 MHz)



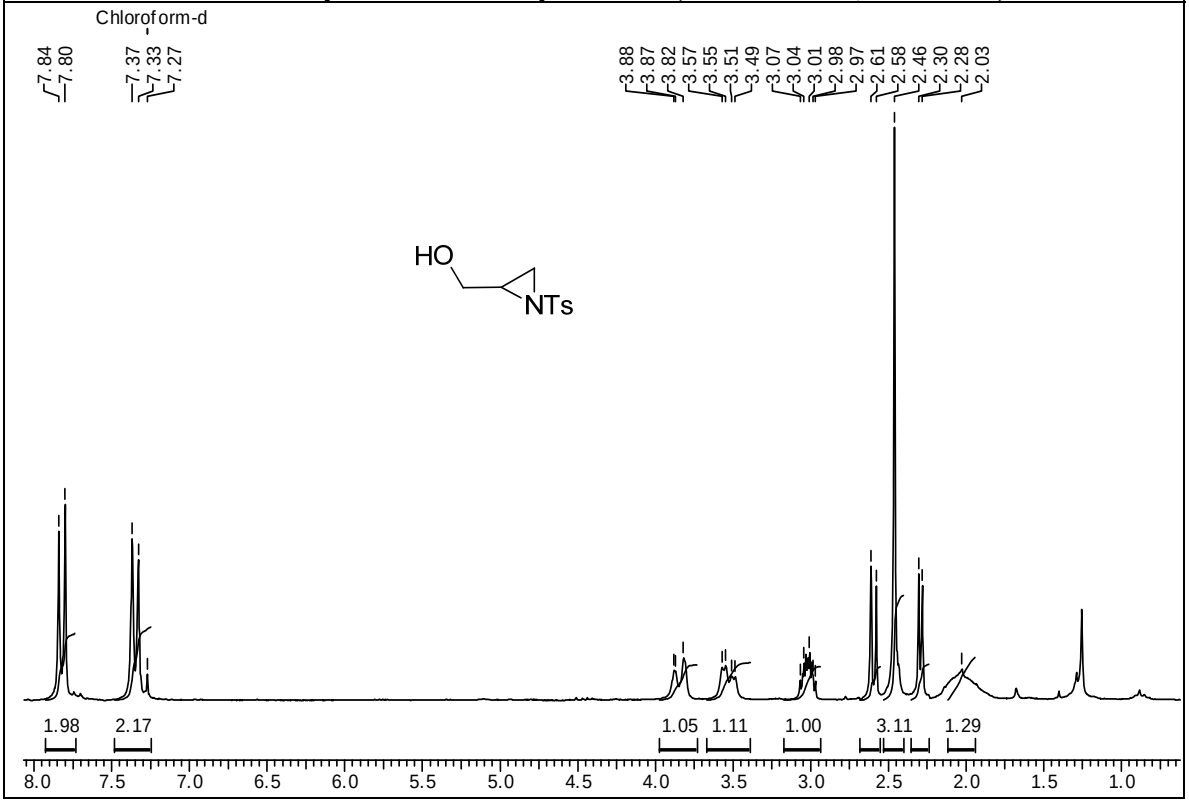
^{13}C-NMR spectrum of compound 19 ($CDCl_3$+CCl_4, 50 MHz)



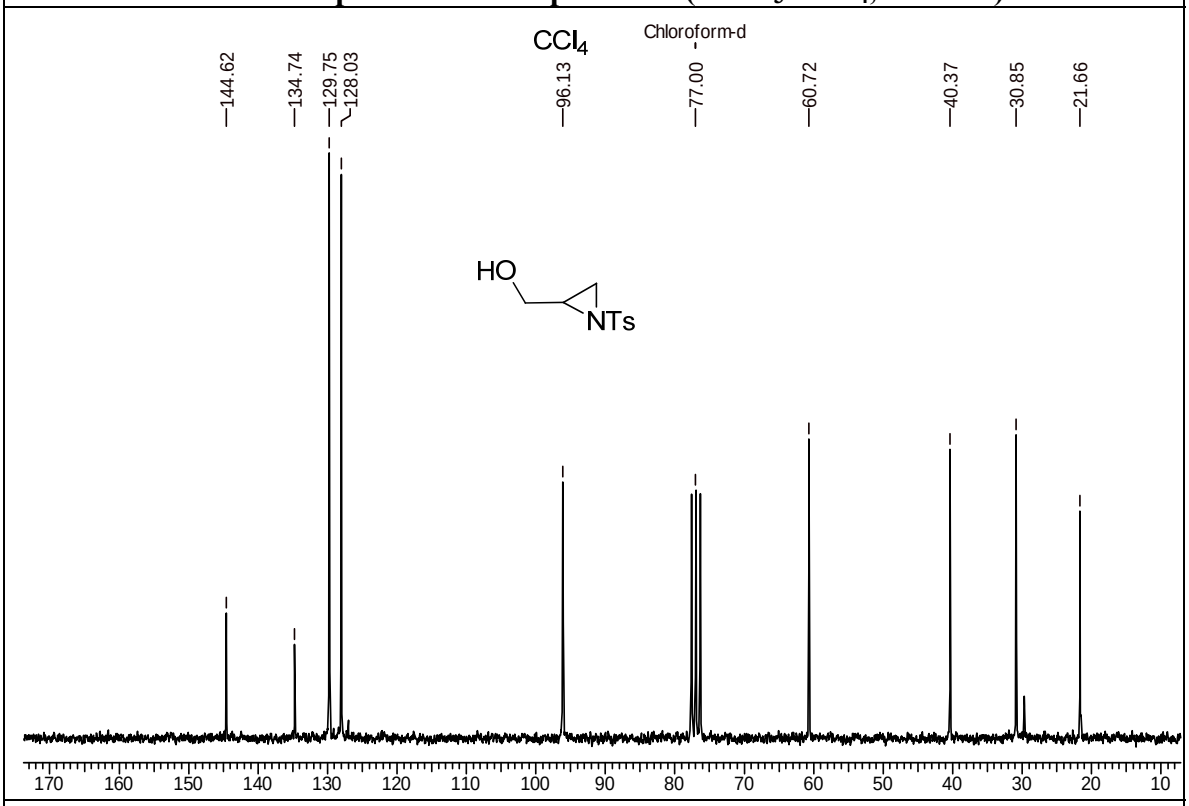
DEPT spectrum of compound 19 ($CDCl_3$+CCl_4, 50 MHz)



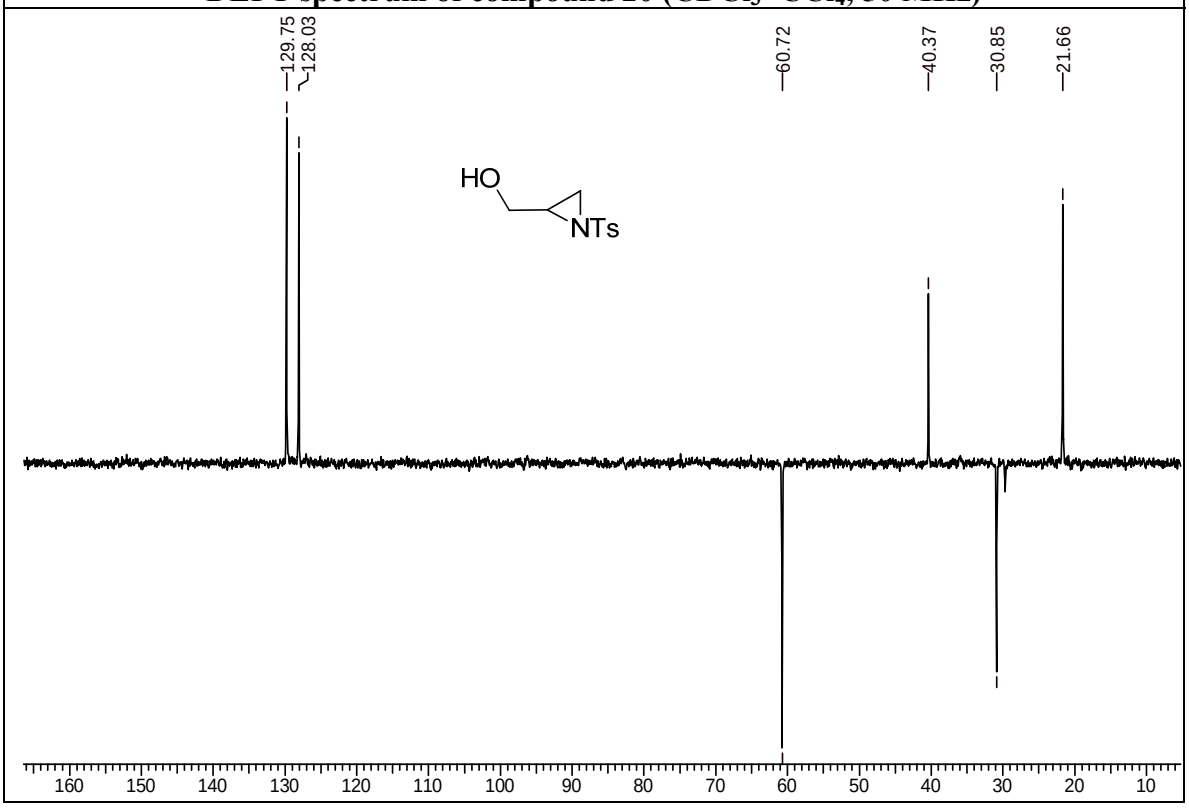
^{1}H-NMR spectrum of compound 20 ($CDCl_3$+CCl_4, 200 MHz)



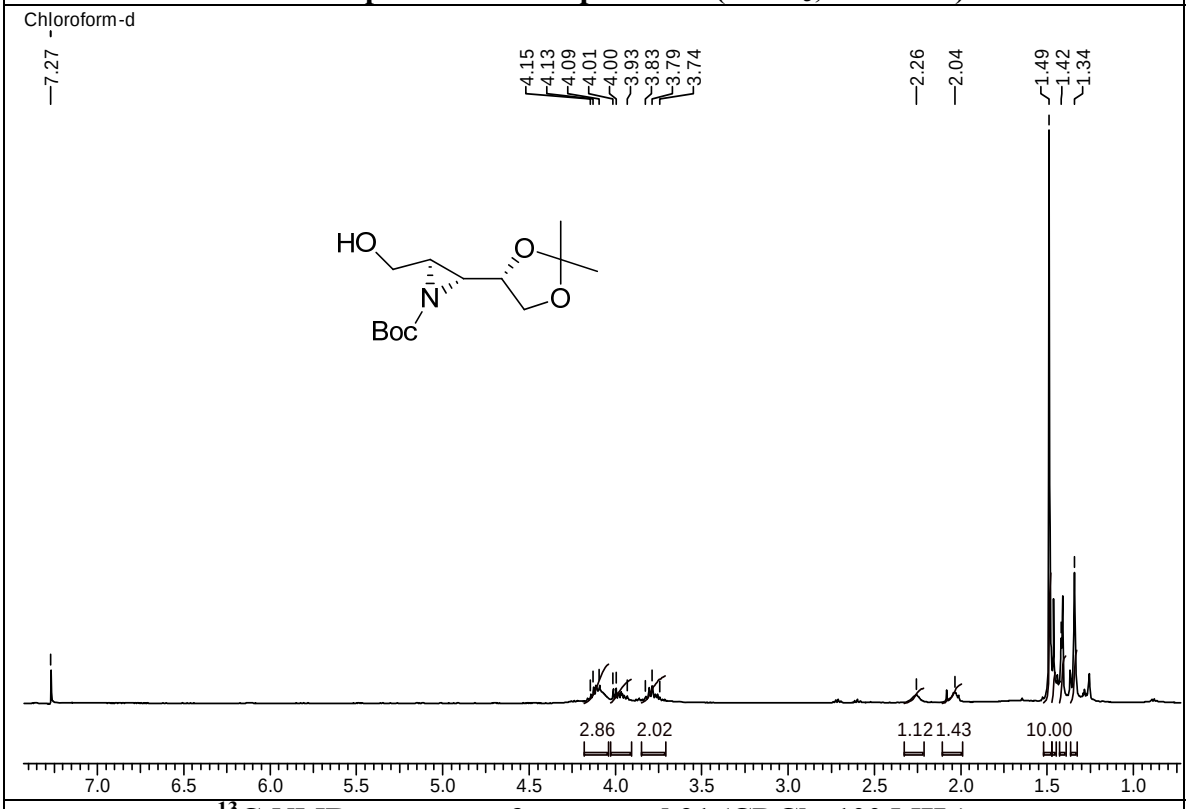
^{13}C-NMR spectrum of compound 20 ($CDCl_3$+CCl_4, 50 MHz)



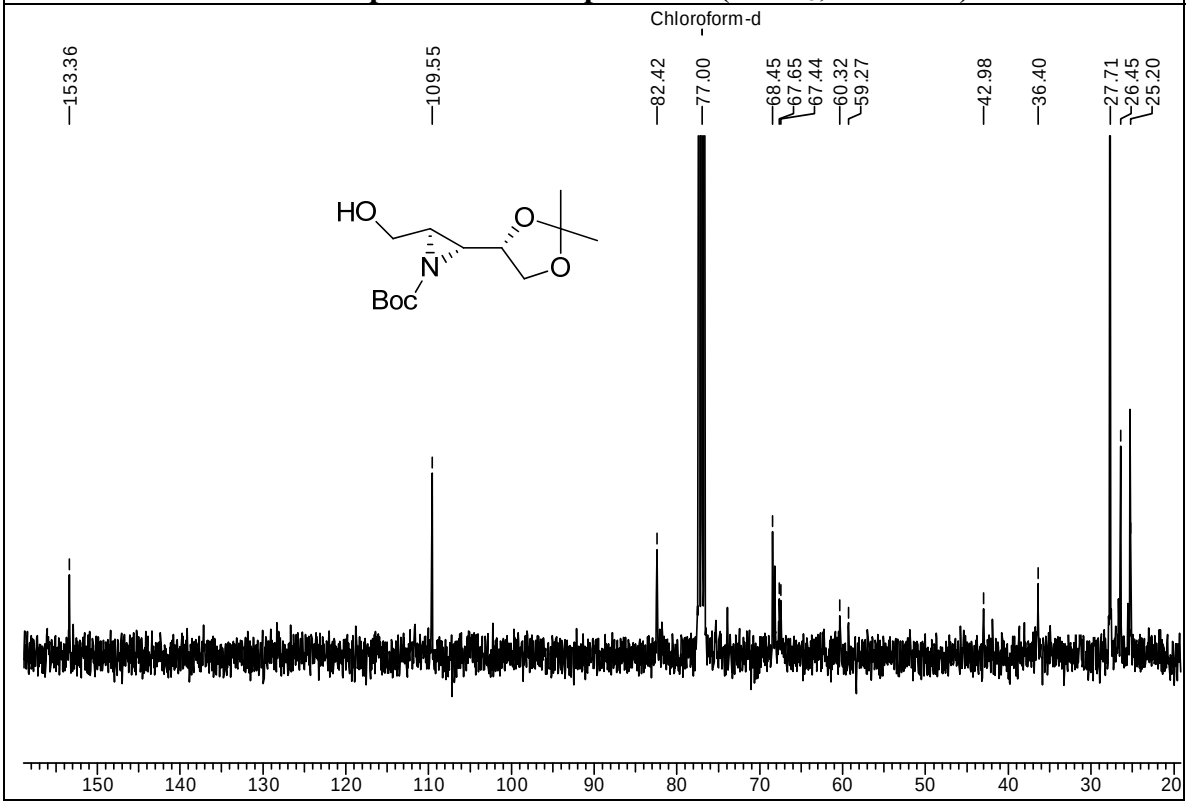
DEPT spectrum of compound 20 ($CDCl_3$+CCl_4, 50 MHz)



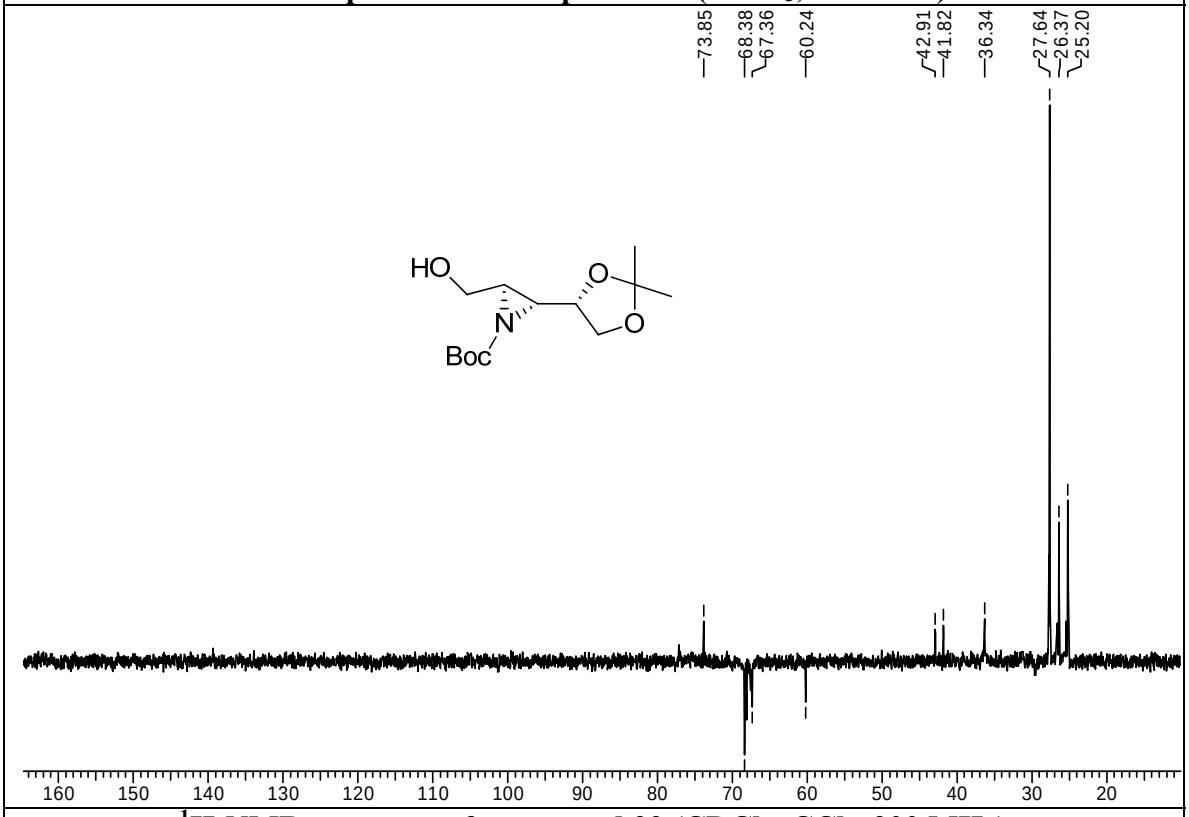
^{1}H-NMR spectrum of compound 21 ($CDCl_3$, 400 MHz)



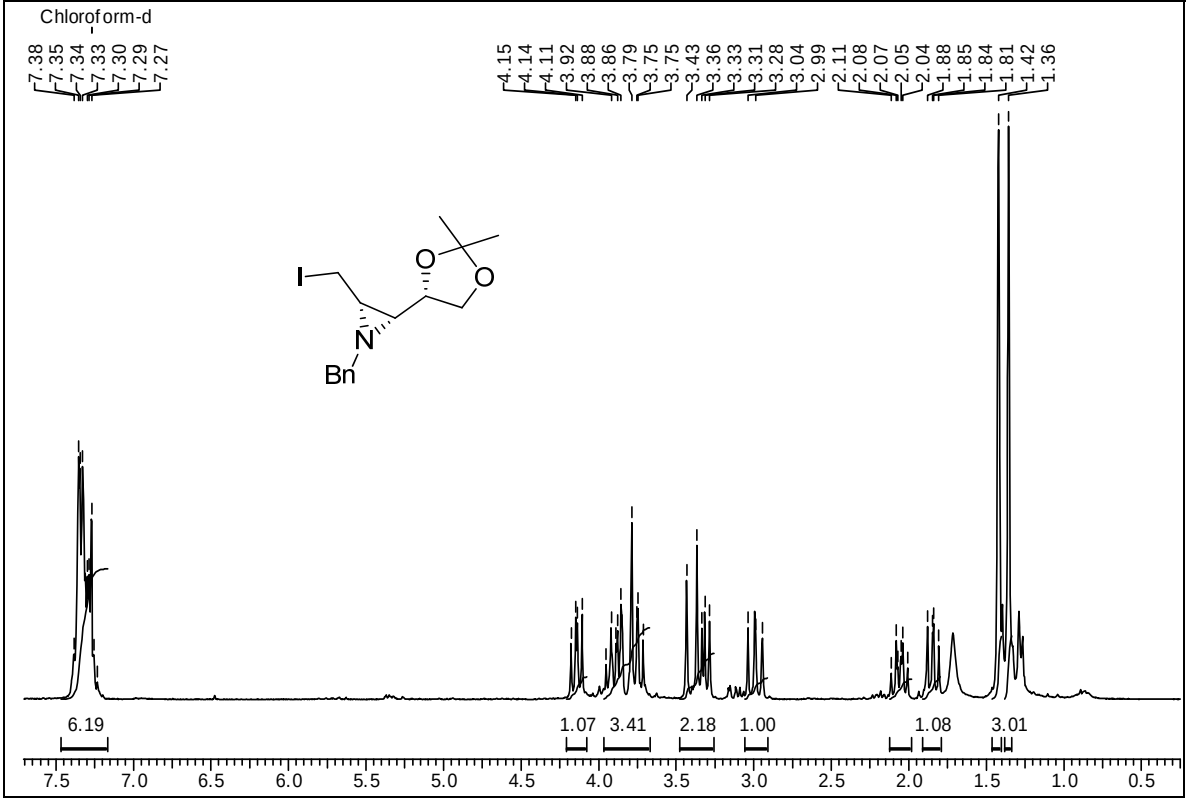
^{13}C-NMR spectrum of compound 21 ($CDCl_3$, 100 MHz)



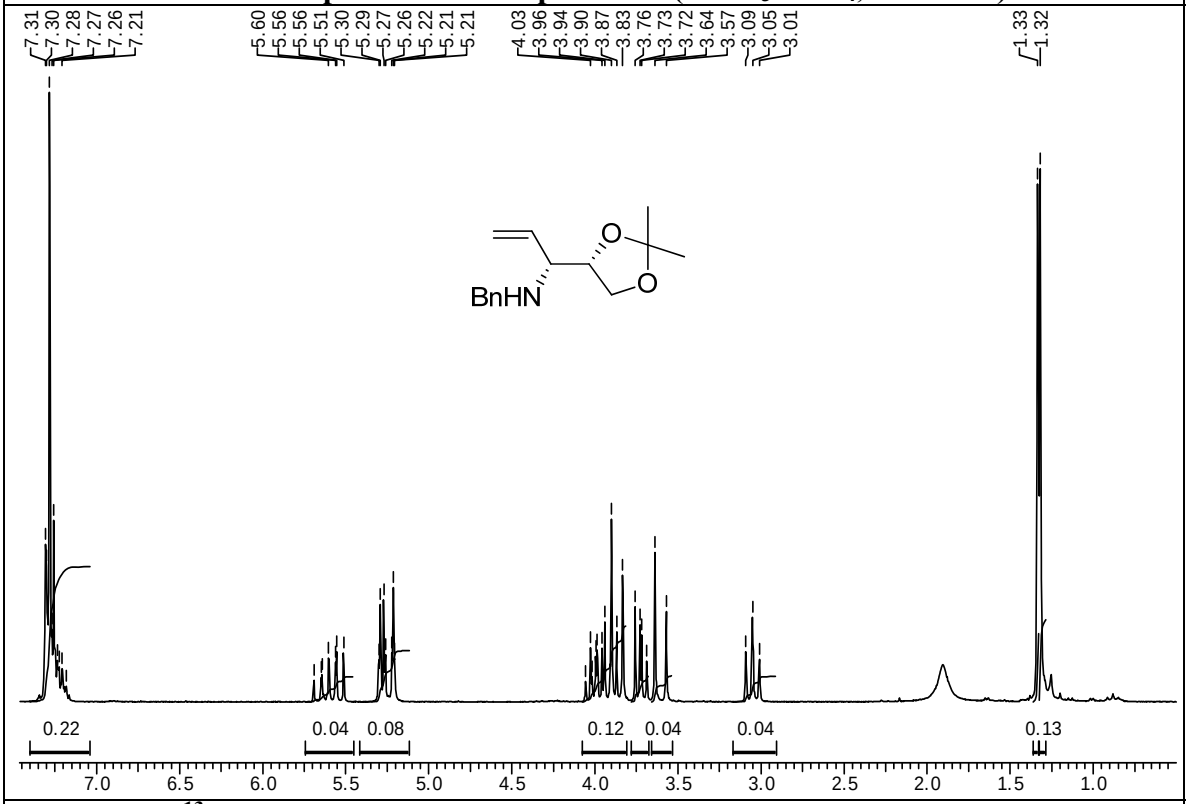
DEPT spectrum of compound 21 ($CDCl_3$, 100 MHz)



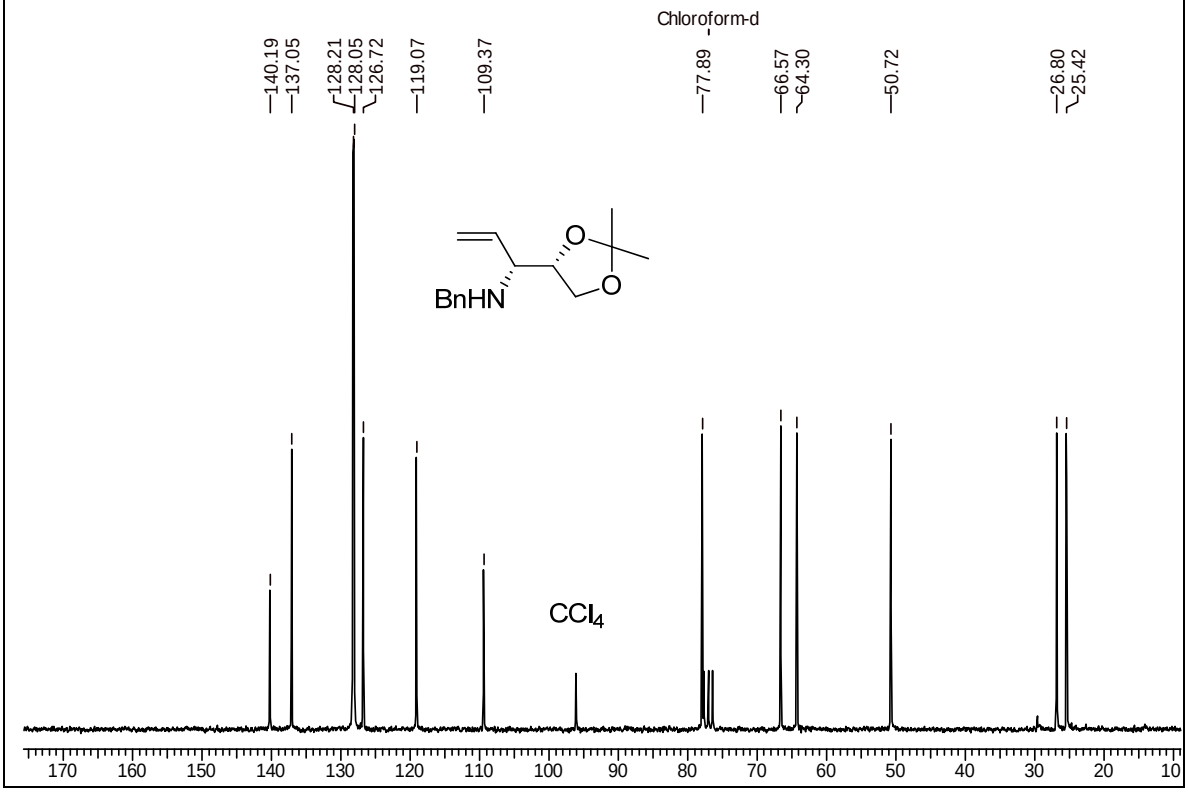
^{1}H-NMR spectrum of compound 22 ($CDCl_3$+CCl_4, 200 MHz)



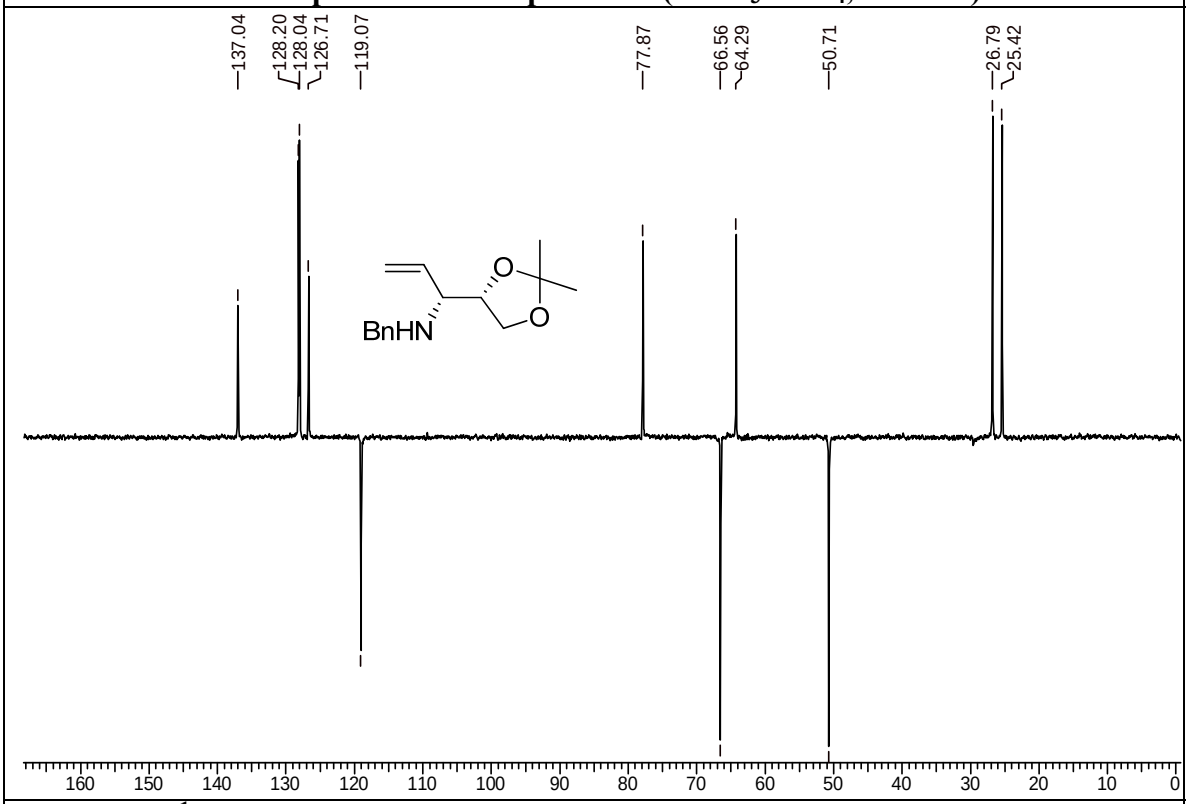
^{1}H-NMR spectrum of compound 23 ($CDCl_3$+CCl_4, 200 MHz)



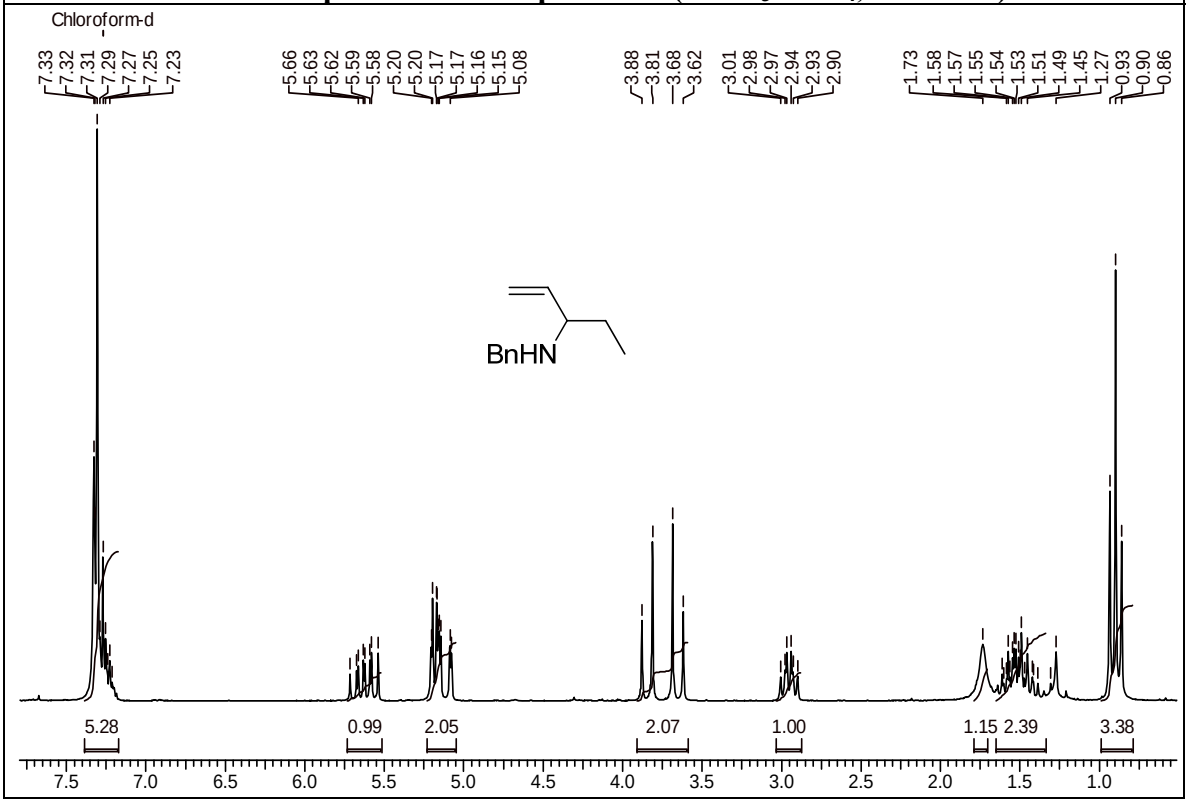
^{13}C-NMR spectrum of compound 23 ($CDCl_3$+CCl_4, 50 MHz)



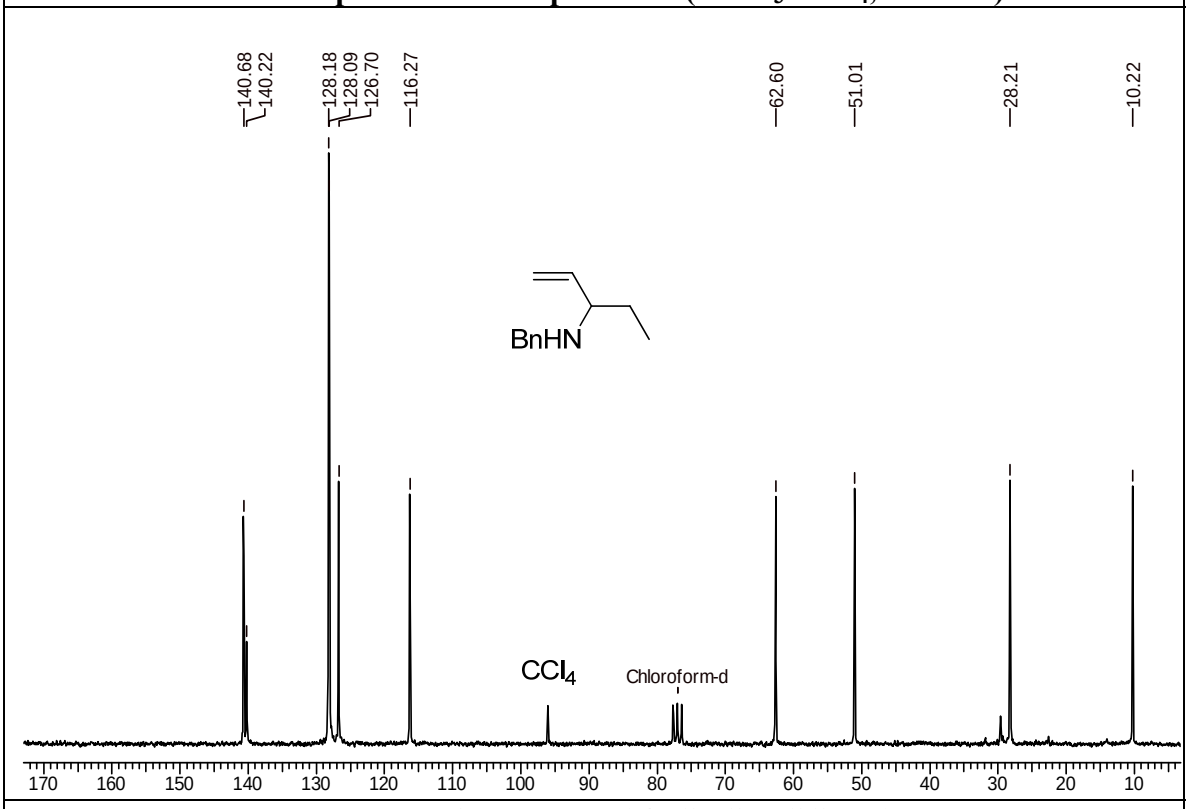
DEPT spectrum of compound 23 ($CDCl_3$+CCl_4, 50 MHz)



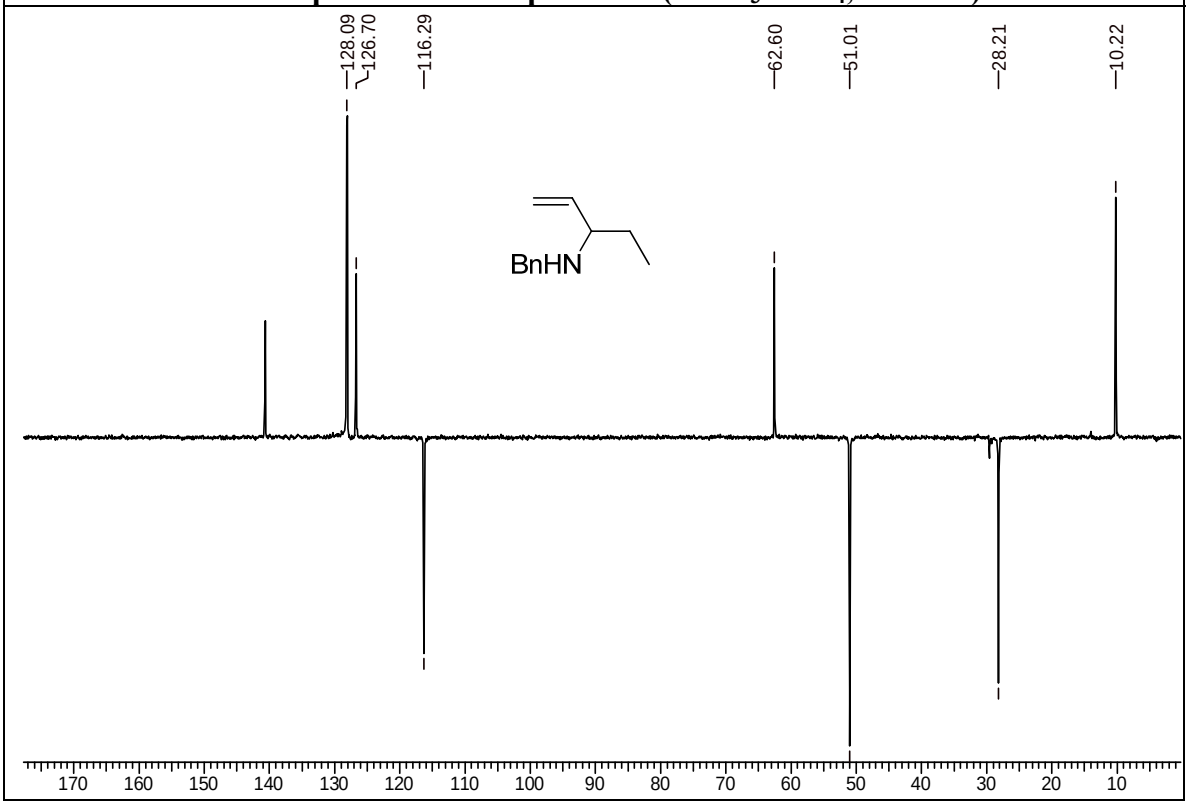
^{1}H-NMR spectrum of compound 24 ($CDCl_3$+CCl_4, 200 MHz)



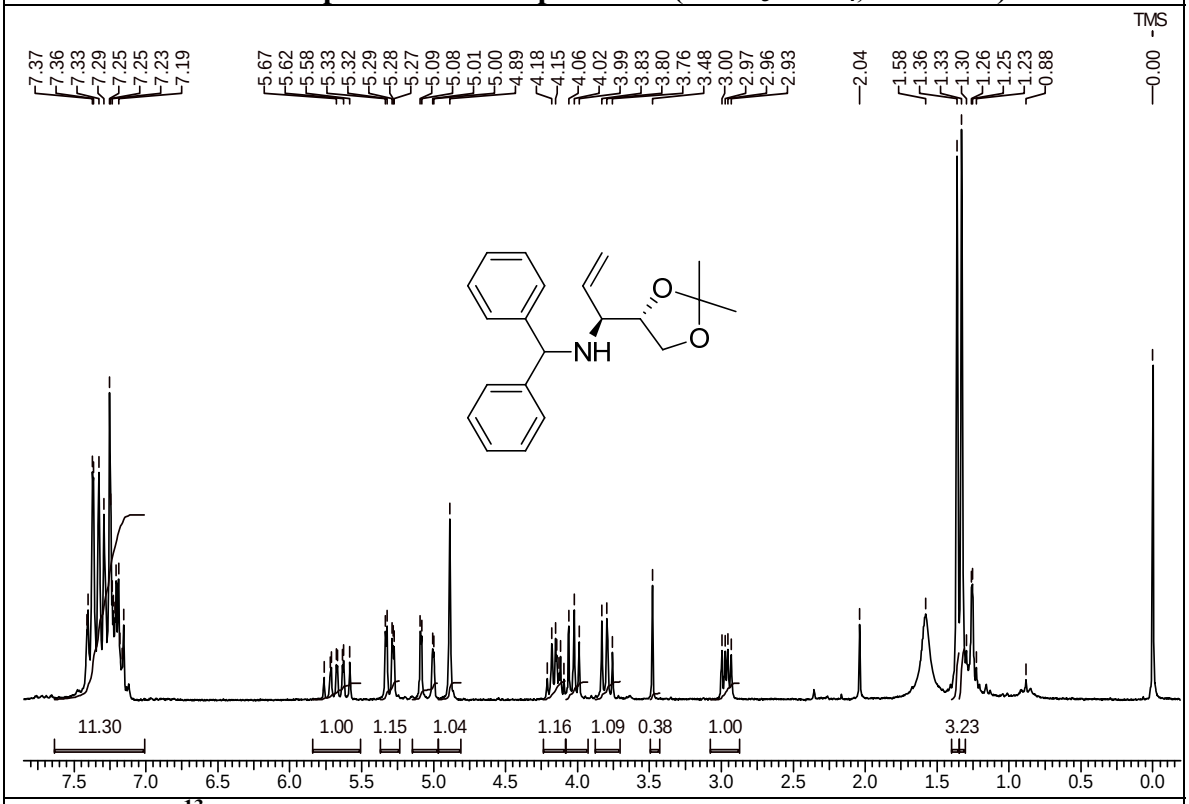
^{13}C-NMR spectrum of compound 24 ($CDCl_3$+CCl_4, 50 MHz)



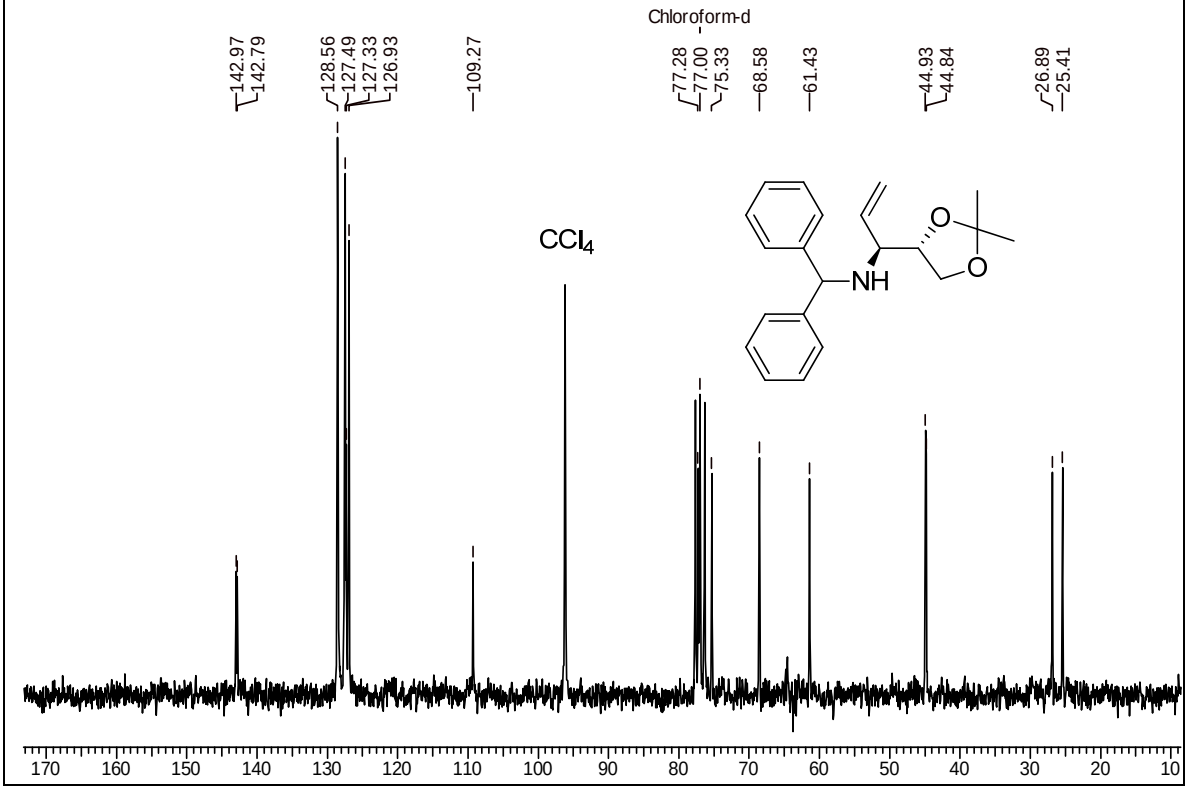
DEPT spectrum of compound 24 ($CDCl_3$+CCl_4, 50 MHz)



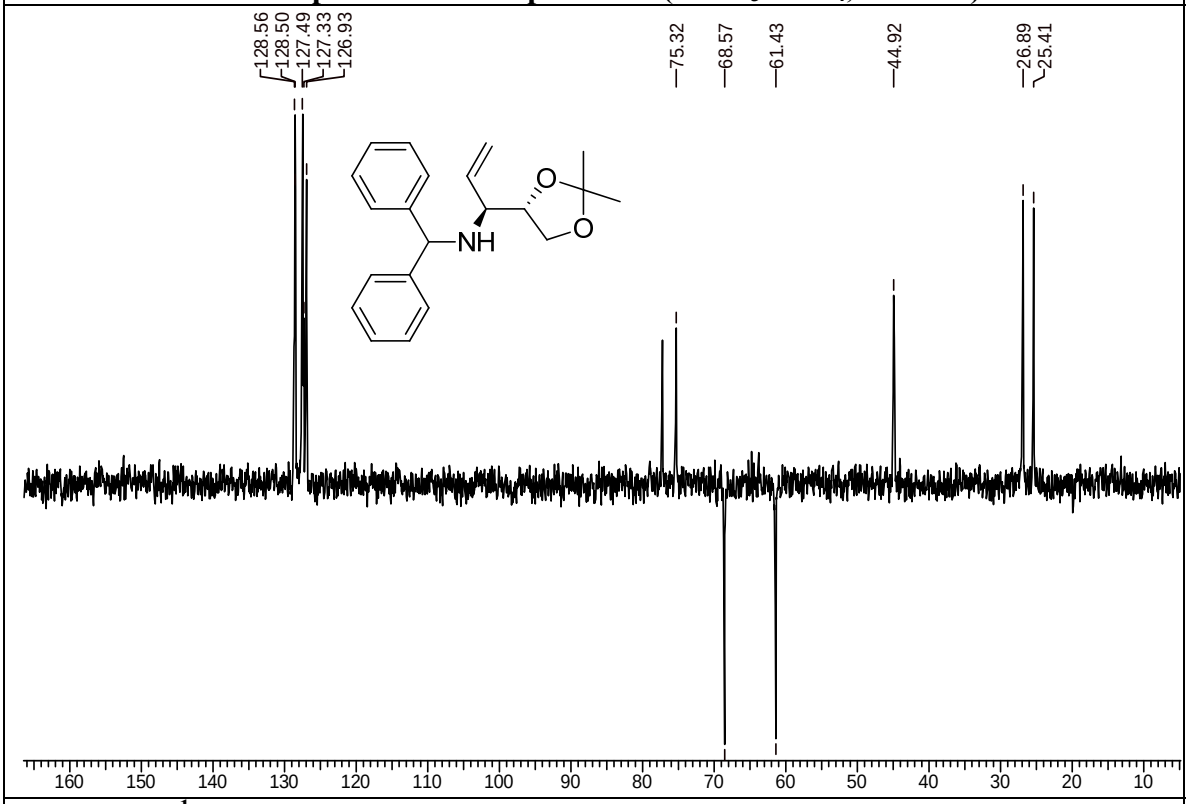
^{1}H-NMR spectrum of compound 25 ($CDCl_3$+CCl_4, 200 MHz)



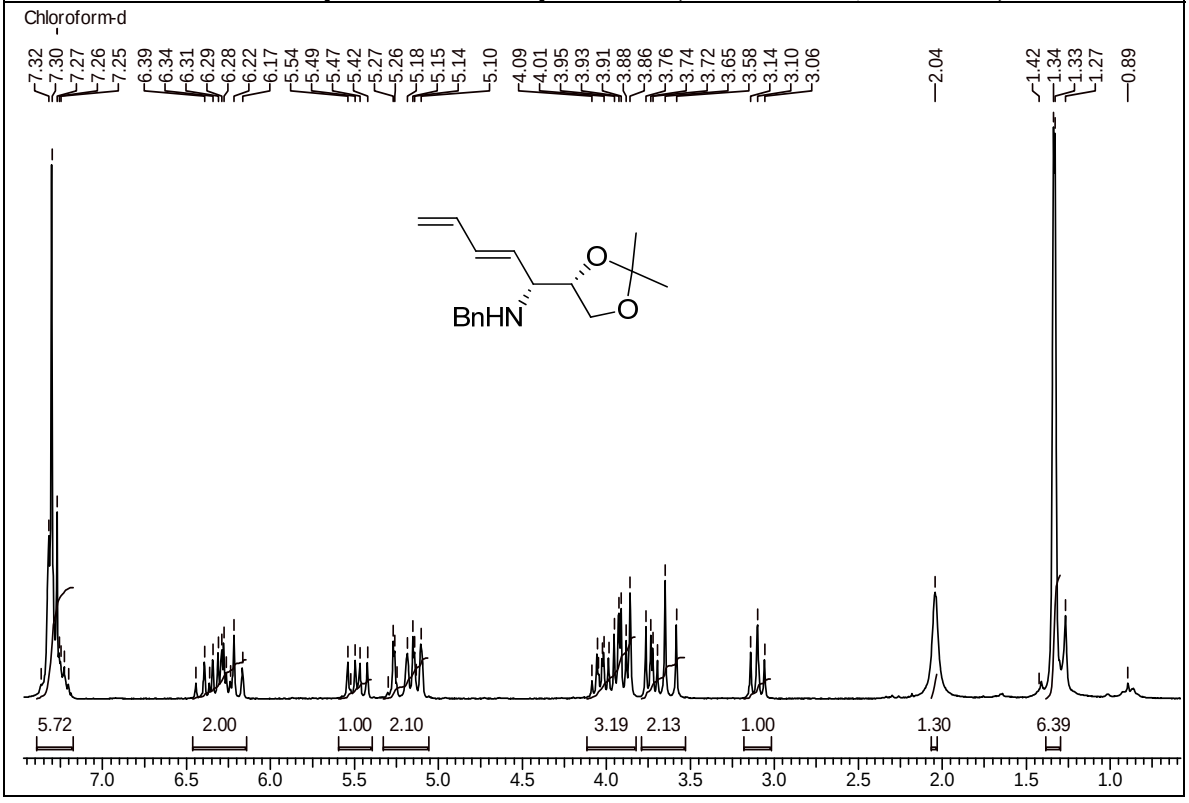
^{13}C-NMR spectrum of compound 25 ($CDCl_3$+CCl_4, 50 MHz)



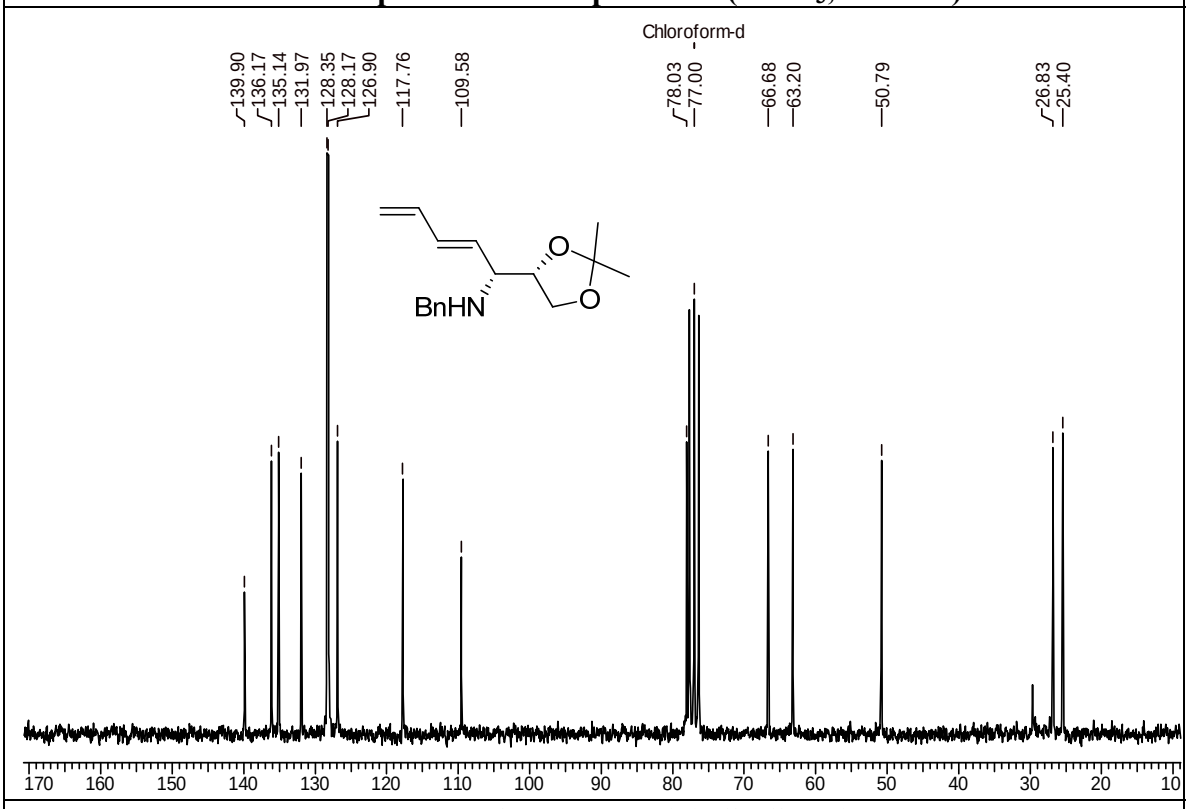
DEPT spectrum of compound 25 ($CDCl_3$+CCl_4, 50 MHz)



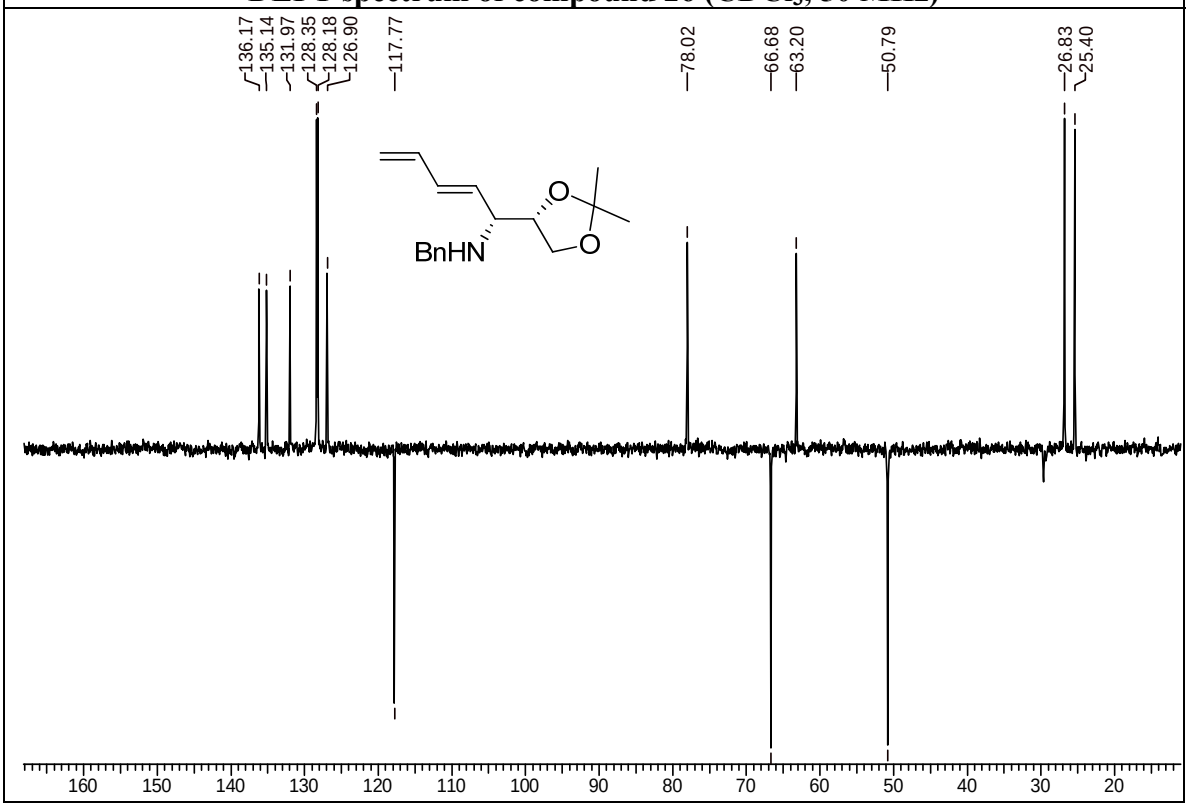
^{1}H-NMR spectrum of compound 26 ($CDCl_3$+CCl_4, 200 MHz)



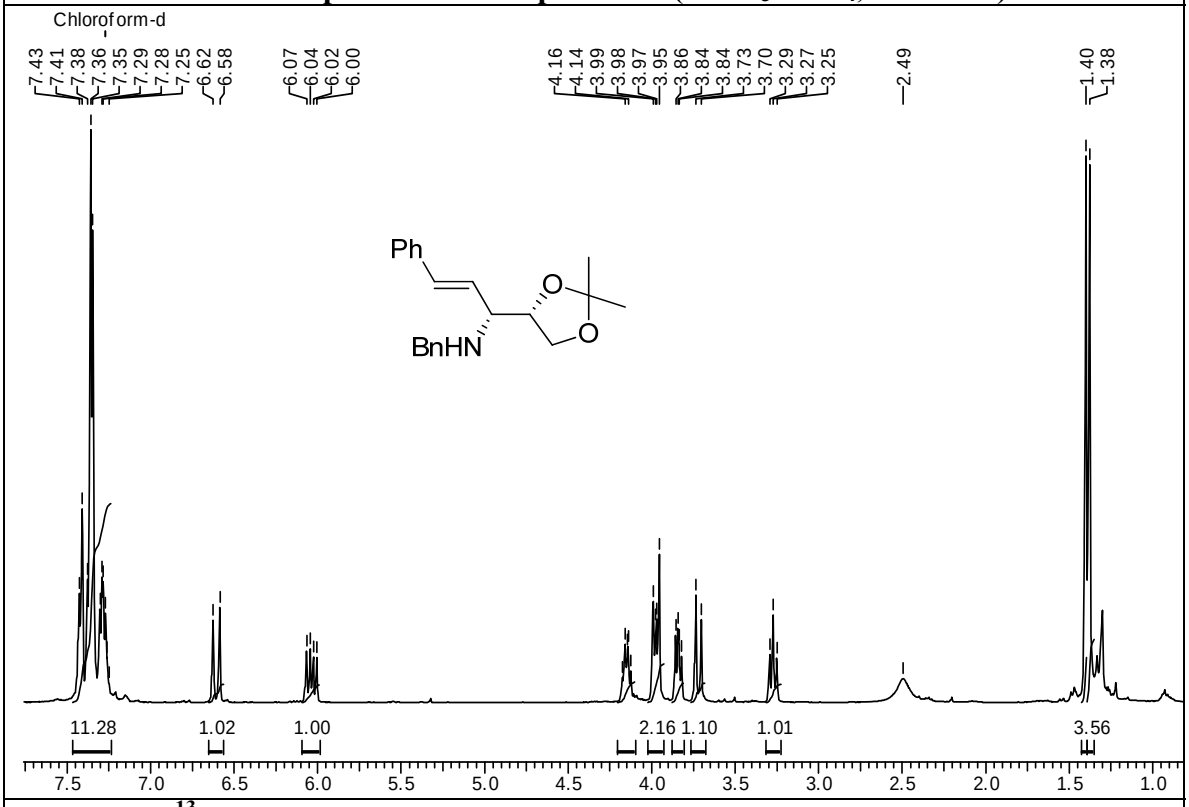
^{13}C-NMR spectrum of compound 26 ($CDCl_3$, 50 MHz)



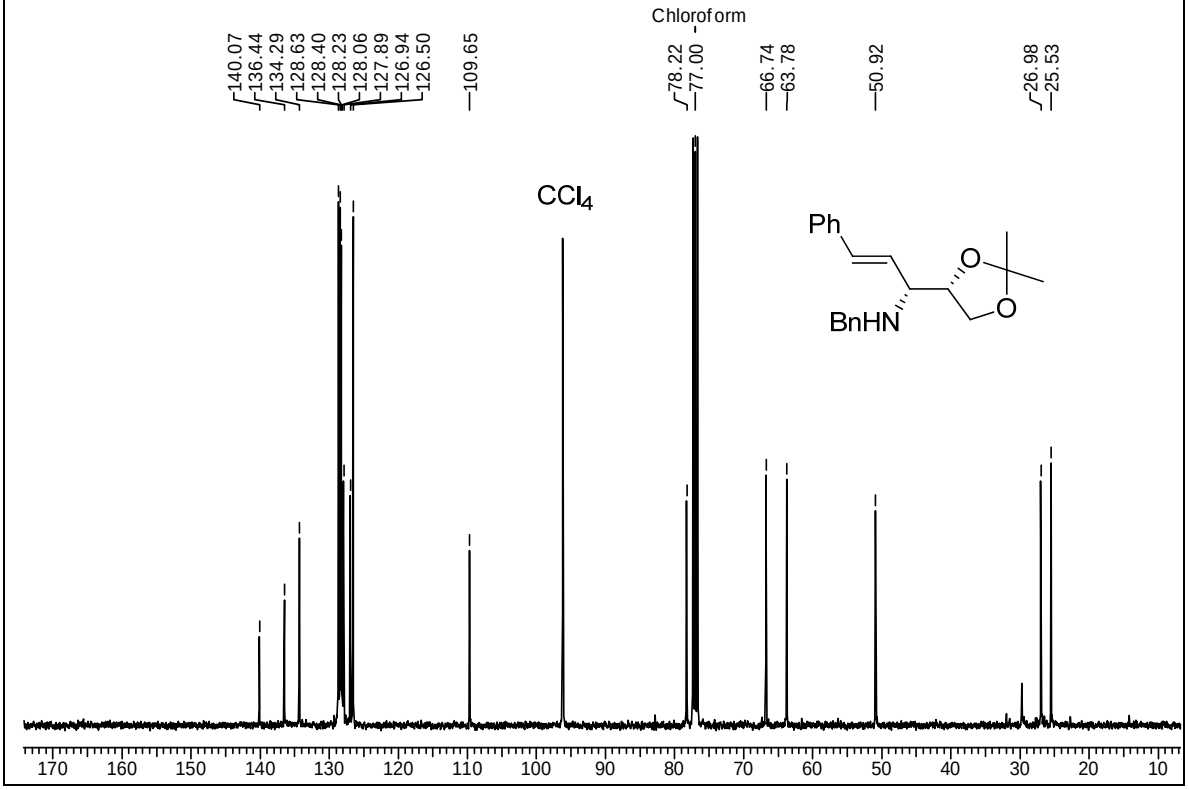
DEPT spectrum of compound 26 ($CDCl_3$, 50 MHz)



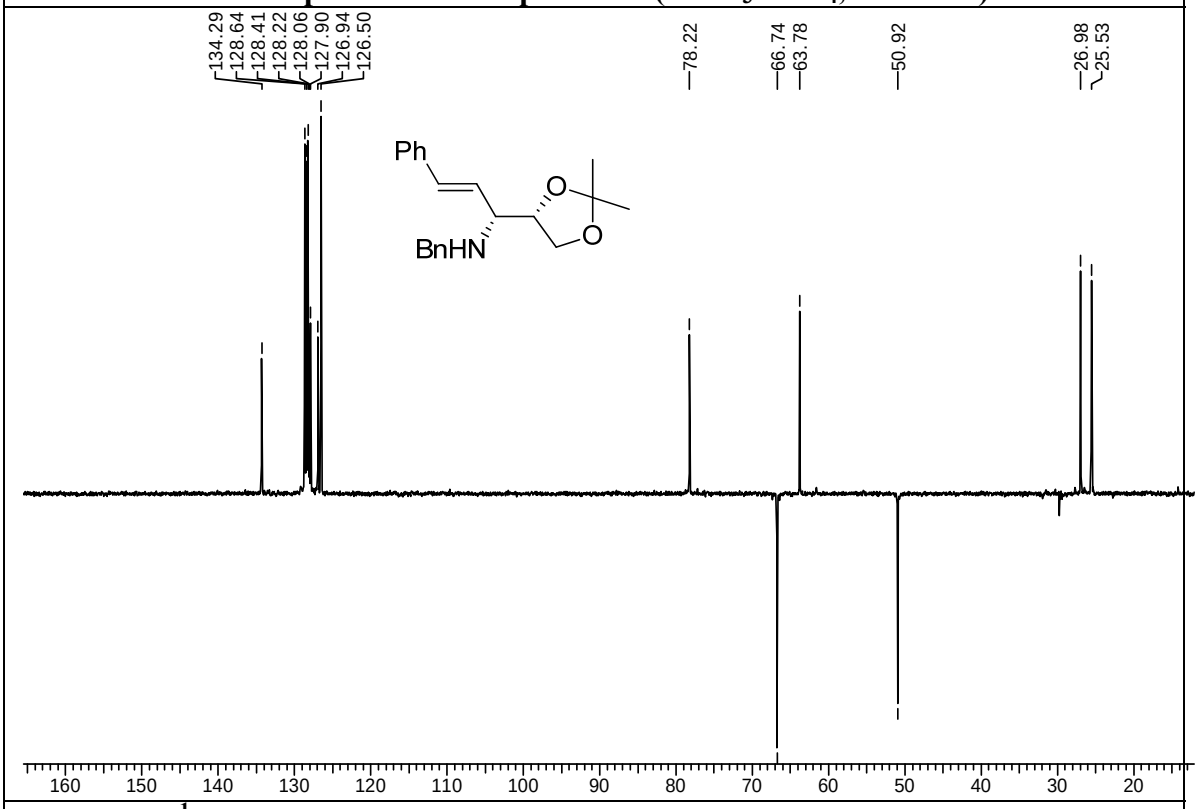
^{1}H-NMR spectrum of compound 27 ($CDCl_3$+CCl_4, 400 MHz)



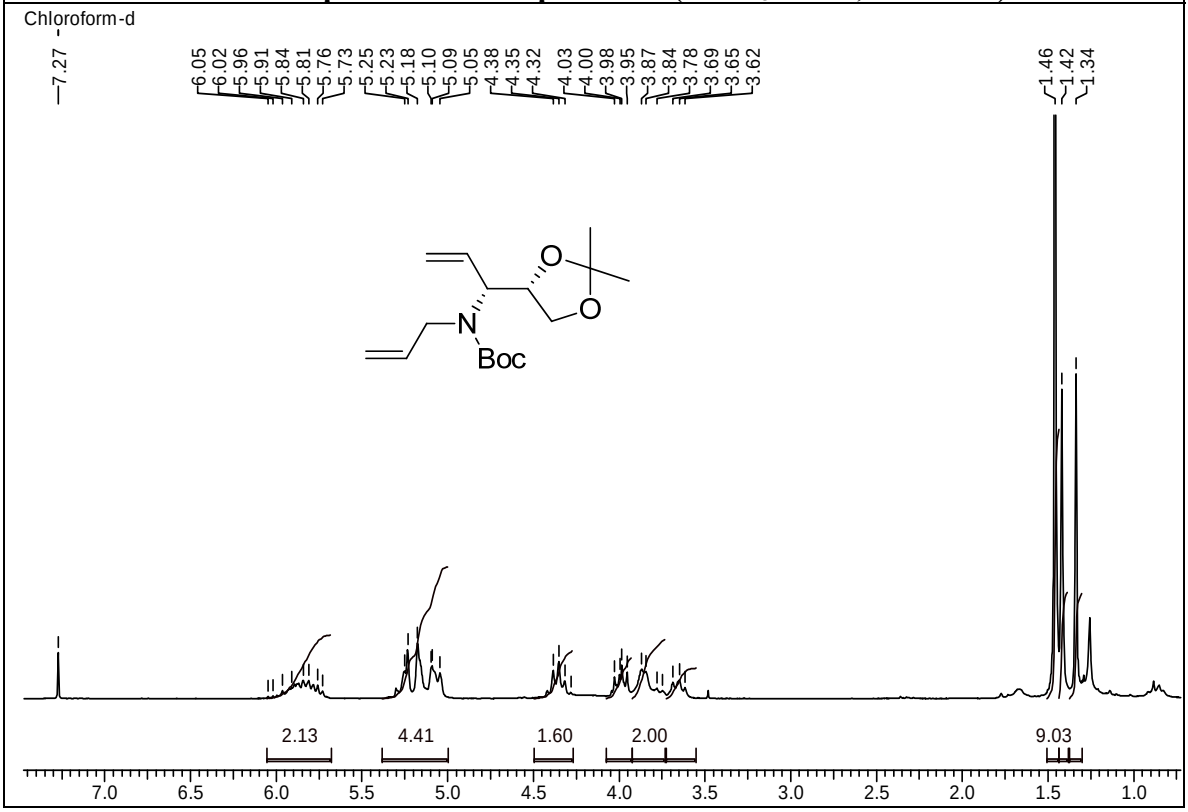
^{13}C-NMR spectrum of compound 27 ($CDCl_3$+CCl_4, 100 MHz)



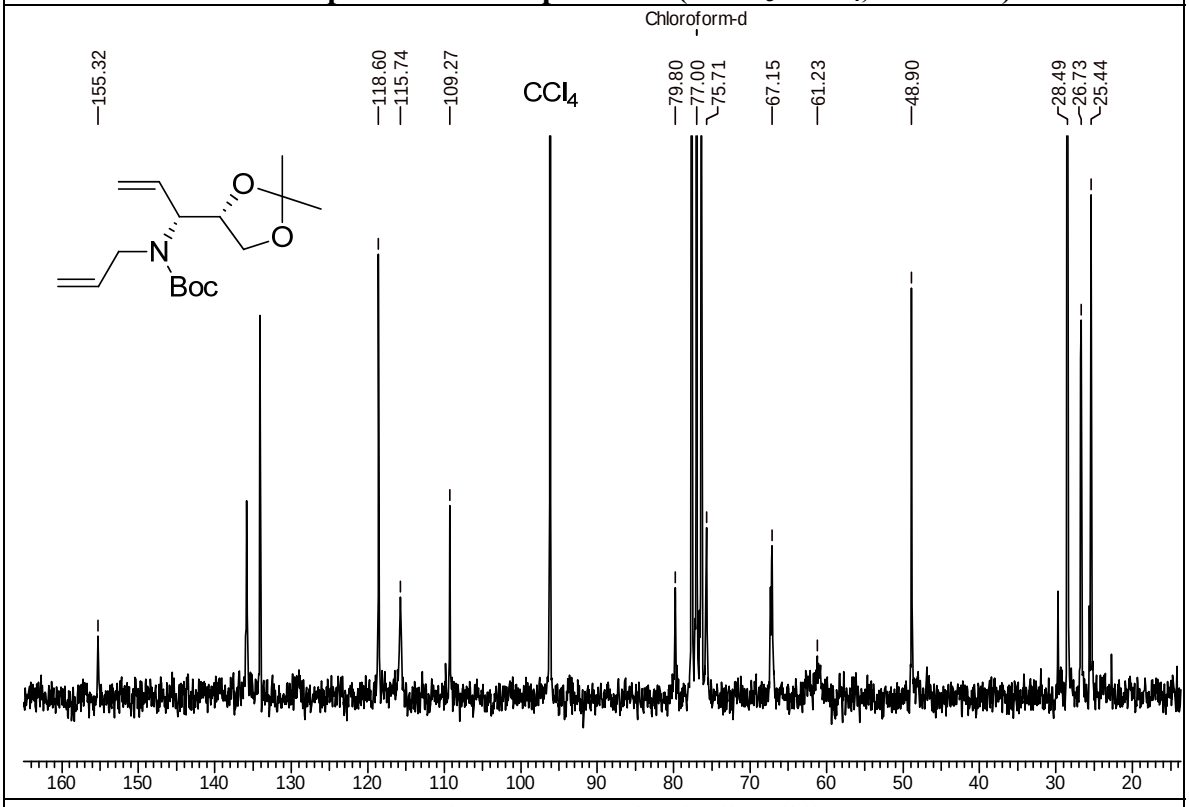
DEPT spectrum of compound 27 ($CDCl_3$+CCl_4, 100 MHz)



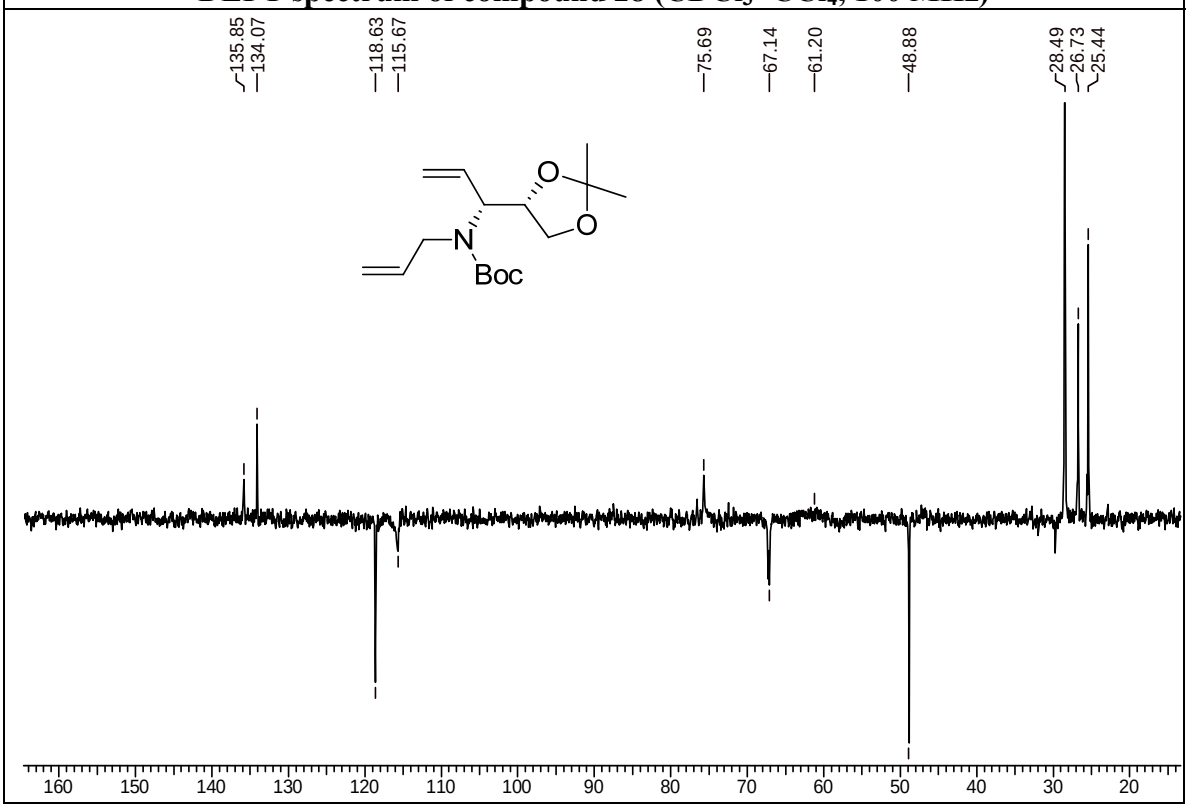
^{1}H-NMR spectrum of compound 28 ($CDCl_3$+CCl_4, 200 MHz)



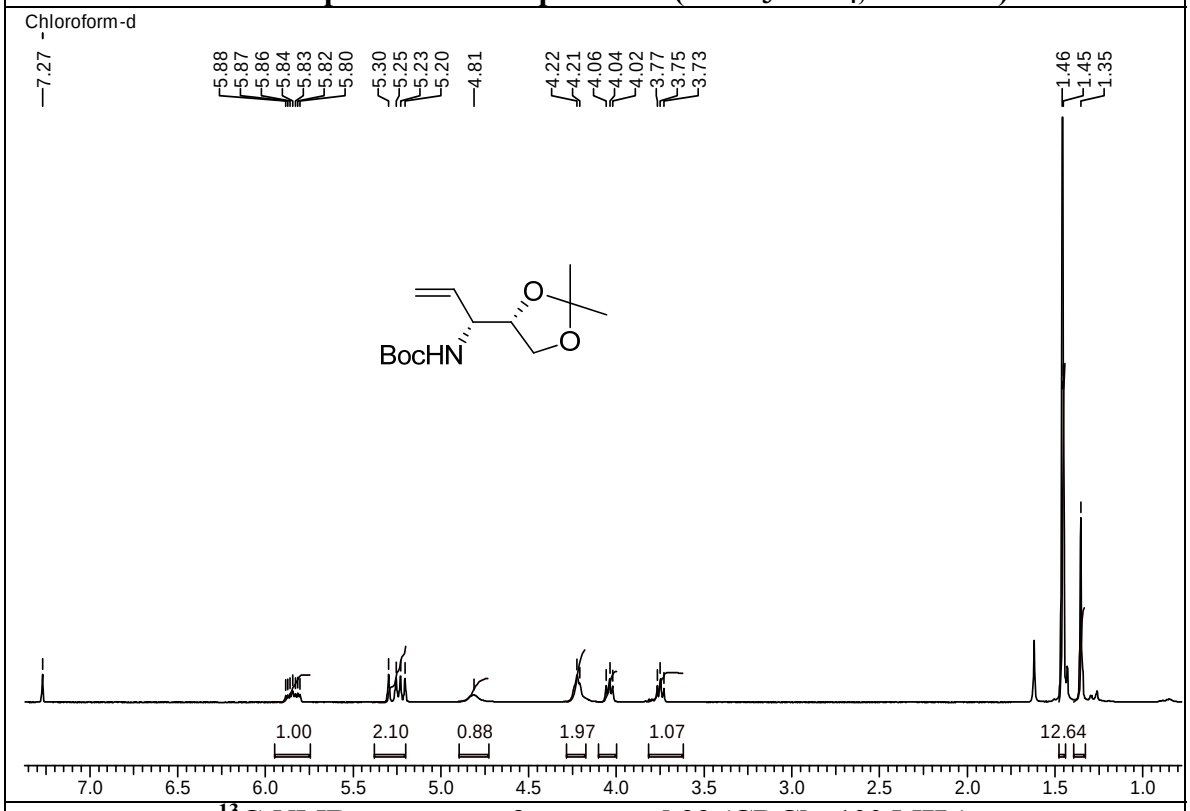
^{13}C-NMR spectrum of compound 28 ($CDCl_3$+CCl_4, 100 MHz)



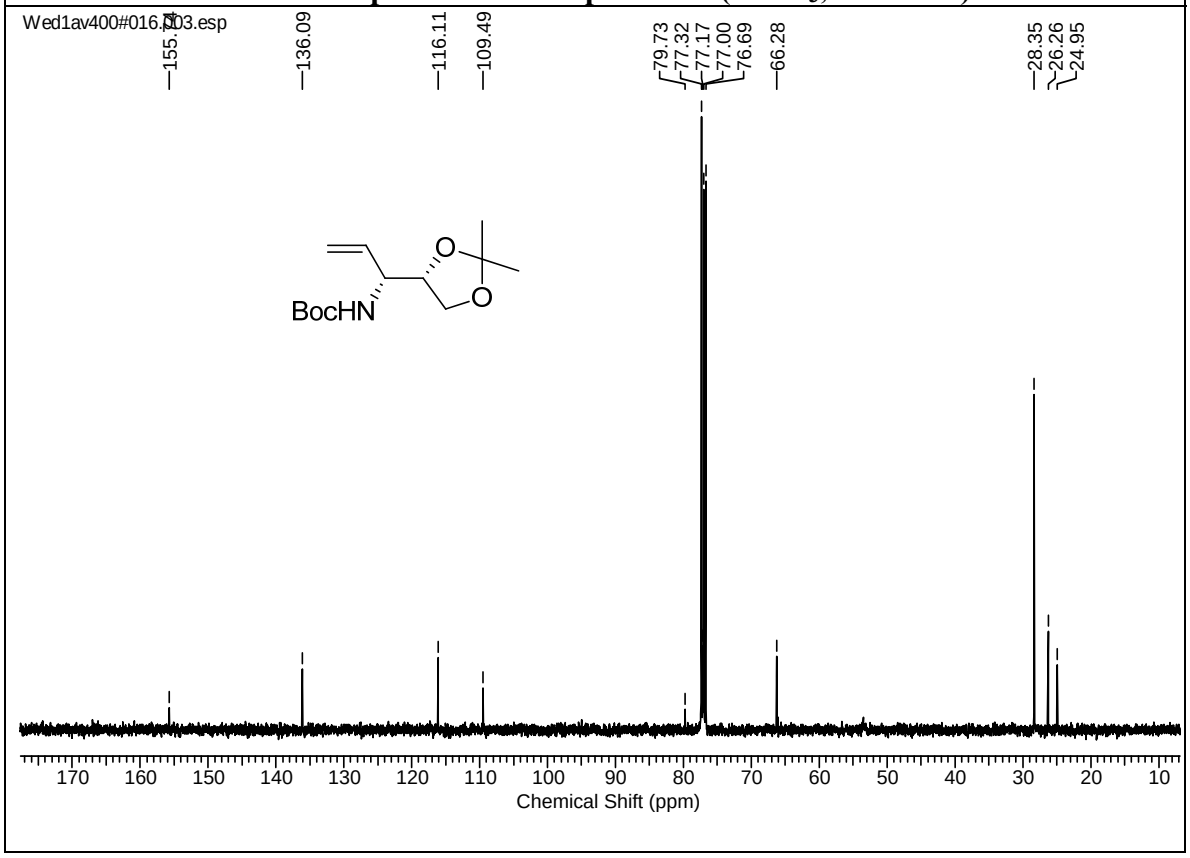
DEPT spectrum of compound 28 ($CDCl_3$+CCl_4, 100 MHz)



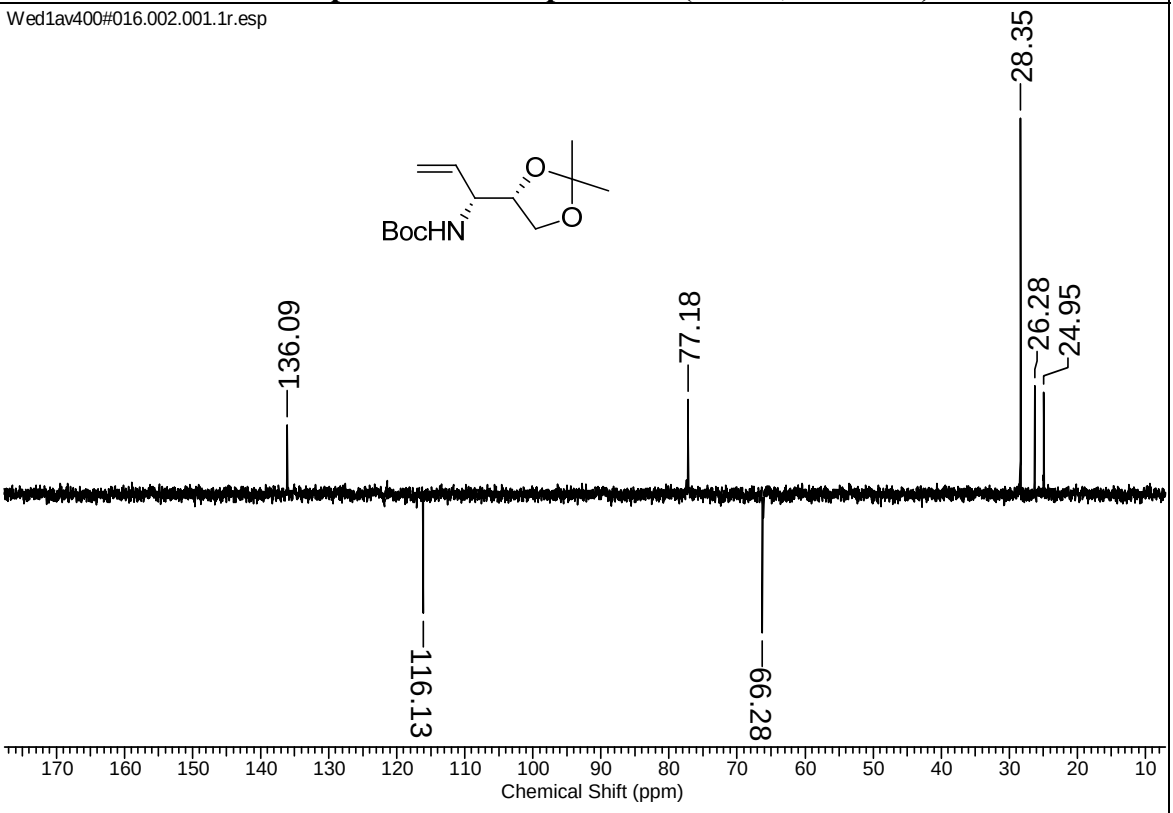
^{1}H-NMR spectrum of compound 29 ($CDCl_3$+CCl_4, 400 MHz)



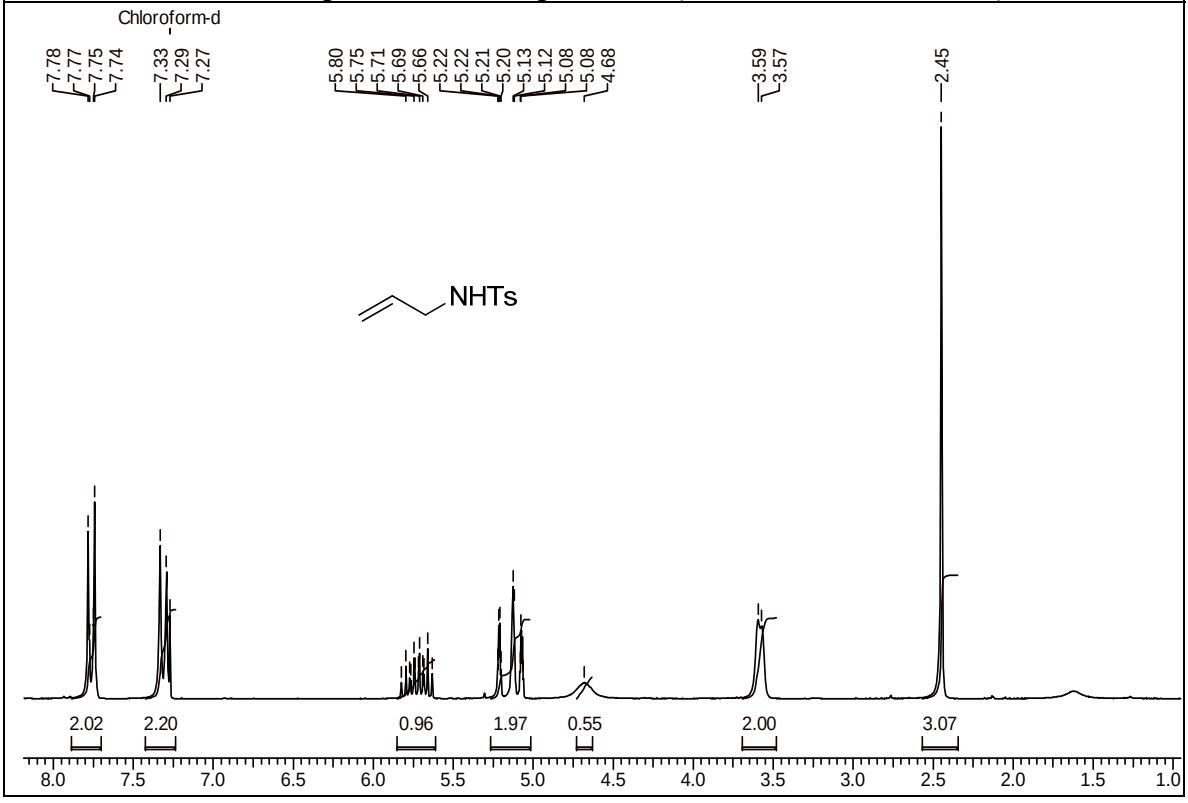
^{13}C-NMR spectrum of compound 29 ($CDCl_3$, 100 MHz)



DEPT spectrum of compound 29 ($CDCl_3$, 100 MHz)



^{1}H-NMR spectrum of compound 30 ($CDCl_3$+CCl_4, 200 MHz)



3.3.7 References

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