SYNTHETIC STUDIES OF ALKALOIDS CONTAINING PYRROLIDINE AND PIPERIDINE STRUCTURAL MOTIFS

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In

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By

Mr. Chinmaya Bhat

Research Guide

Prof. S. G. Tilve

GOA UNIVERSITY

TALIEGAO PLATEAU

2013

CERTIFICATE

This is to certify that the work incorporated in this thesis entitled, "**SYNTHETIC STUDIES OF ALKALOIDS CONTAINING PYRROLIDINE AND PIPERIDINE STRUCTURAL MOTIFS**" submitted by **Mr. Chinmaya Bhat**, has been carried out by the candidate under my supervision and the same has not been submitted elsewhere for the award of a degree.

Goa University
January 2013

Prof. Santosh G. Tilve
Research Guide and Head
Department of Chemistry
Goa University

DECLARATION

I hereby declare that the matter embodied in this thesis entitled, **SYNTHETIC STUDIES OF ALKALOIDS CONTAINING PYRROLIDINE AND PIPERIDINE STRUCTURAL MOTIFS**" is the result of investigation carried out by me, in the Department of Chemistry, Goa University, Goa-India, under the supervision of **Prof. S. G. Tilve** and it has not previously formed basis for any other titles.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

Goa University — Mr. Chinmaya Bhat

June 2013

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The divine power is the strongest unseen power, I believe. Even a piece of particle will be unmoved without his/her/its permission. I am really surrendered to that giant almighty which is forwarding me with a great decision. I close my remarks of acknowledgment by thanking the power of God and praying for surge of blessings during the hours of trial.

Mr. Chinmaya Bhat

Dedicated

to

My Beloved Parents

Contents

GENERAL REMARKS

1) The compound numbers, figure numbers, scheme numbers and reference numbers given in each chapter refer to that particular chapter only.

2) All melting points and boiling points were recorded using Thiele's tube and are uncorrected.

3) Commercial reagents were used without further purification.

4) All solvents were distilled prior to use and then dried using standard procedure.

5) Petroleum ether refers to the hydrocarbon fraction collected in the boiling range 60 - 80 °C.

6) All reagents were prepared using literature methods.

7) Chromatographic purification was conducted by column chromatography using silica gel (60 – 120 mesh size) or by flash chromatography using silica gel (200-400 mesh size). Chemical shifts within square brackets give the values of the amide torsion isomer while those in the round bracket represent the minor isomers formed during the reactions.

8) Thin layer chromatography (TLC) were carried out on glass plates using silica gel G and were developed in iodine.

9) The IR spectra were recorded on Shimadzu FT-IR spectrophotometer.

10) ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Brucker AVANCE 400 instrument and the multiplicities of carbon signals were obtained from DEPT experiment.

11) The high resolution mass spectra (HRMS) were recorded on MicroMass ES-QTOF mass spectrometer.

DEFINITION OF ABBREVIATIONS

1) General Abbreviations

g	Gram/s
mg	Milligram/s
mmol	Millimole
mL	Milliliter
m.p.	Melting point
b.p.	Boiling point
Eq.	Equation/s
lit.	Literature
d	Day/s
h	Hour/s
min	Minute/s
sec	Second/s
Z	Zussamen (together)
E	Eentegegen (opposite)
R	Rectus
S	Sinister
fig.	Figure
conc.	Concentrated
dil.	Dilute
sat.	Saturated
aq.	Aqueous
anhyd.	Anhydrous
hv	Irradiation
$^{\circ}$C	Degree Celcius
%	Percentage
RT / r.t.	Room temperature
Expt.	Experiment
Temp.	Temperature
MW / μW	Microwave
o	Ortho
m	Meta
p	Para

MS	Molecular sieves
psi	Pounds per square inch
cat.	Catalytic
atm.	Atmospheric
et al	Et alia (and others)
TLC / tlc	Thin layer chromatography
ORTEP	Oak ridge thermal ellipsoid plot
RCM	Ring closure metathesis
SAD	Sharpless asymmetric dihydroxylation
AD	Asymmetric dihydroxylation
Calcd.	Calculated

2) Compound Abbreviations

Ac	Acetyl
Ac_2O	Acetic anhydride
TBAF	Tetrabutyl ammonium fluoride
Ph	Phenyl
Boc	*tert*-Butyl carbonyl
Bn	Benzyl
Bz	Benzoyl
t-Bu	*tert*-Butyl
TFA	Trifluoro acetic acid
TFAA	Trifluoro acetic anhydride
Et_3N	Triethyl amine
AcOH	Acetic acid
MeOH	Methanol
EtOH	Ethanol
m-CPBA	*m*-Chloroperbenzoic acid
p-TsOH/ *p*-TSA	*p*-Toluene sulfonic acid
DMSO	Dimethyl sulfoxide
DMF	N,N-Dimethylformamide
THF	Tetrahydrofuran
Et	Ethyl
Me	Methyl
LDA	Lithium diisopropylamide

LAH	Lithium aluminium hydride
NBS	*N*-Bromosuccinimide
EtOAc	Ethyl acetate
n-BuLi	*n*-Butyl lithium
t-BuLi	*t*-Butyl lithium
ECz	*N*-Ethylcarbazole
Pd/C	Palladium on activated charcoal
Ph	Phenyl
PMB	*p*-Methoxybenzyl
PPh_3	Triphenylphosphine
TBAF	Tetrabutylammonium fluoride
Ms	Methane sulfonyl
TMS	Trimethylsilyl
TMSCN	Cyanotrimethyl silane
Ts	*p*-Toluene sulfonyl
Py	Pyridine
NMO	*N*-Methyl morpholine oxide
DCM	Dichloromethane
DCE	1,2-Dichloroethane
PCC	Pyridinium chlorochromate
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
Pet ether	Petroleum ether
TsCl	Tosyl chloride
DMAP	4-Dimethyl amino pyridine
HMPA	Hexamethylphosphoramide
TBSOTf	*t*-Butyldimethylsilyl triflormethane sulphonate
DCC	Dicyclohexyl cabodiimide
CAN	Cerric ammonium nitrate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMP	Dess-Martin periodinane
DIBALH	Diisobutyl aluminium hydride
MOM	Methoxymethyl ether
Boc_2O	*tert*-Butyl dicarbonate
i-PrOH	Iso-propanol
TBHP	*tert*-Butyl hydroperoxide

3) Spectroscopic Abbreviations

IR	Infrared
υ_{max}	Frequency maximum
cm^{-1}	Frequency in wavenumber
UV	Ultra violet
NMR	Nuclear magnetic resonance
$CDCl_3$	Deuterated chloroform
DMSO-d_6	Deuterated dimethyl sulfoxide
DEPT	Distortionless Enhancement by Polarization Transfer
ppm	Parts per million
δ	Delta (Chemical shift in ppm)
MHz	Megahertz
Hz	Hertz
J	Coupling constant
br s	Broad singlet
s	Singlet
d	Doublet
t	Triplet
q	Quartet
m	Multiplet
dd	Doublet of doublet
td	Triplet of a doublet
HRMS	High Resolution Mass Spectrum
M^+	Molecular ion
m/z	Mass to charge ratio

LIST OF PUBLICATIONS

(i) Tandem approaches for the synthesis of functionalized pyrrolidones: efficient routes towards allokainic acid and kainic acid.
Chinmay Bhat and Santosh G. Tilve *Tetrahedron Lett* **2013***, 54,* 245.

(ii) Asymmetric synthesis of (-)-hygrine, (-)-norhygrine, (-)-pseudohygroline and (-)-hygroline via Nef reaction.
Chinmay Bhat and Santosh G. Tilve *Tetrahedron Lett* **2011**, *52*, 6566.

(iii) Henry-Nef reaction: a practical and versatile chiral pool route to 2-substituted pyrrolidine and piperidine alkaloids.
Chinmay Bhat and Santosh G. Tilve *Tetrahedron* **2013**, *69*, 6129.

(iv) A concise diastereoselctive approach to (+)-dexoxadrol, (-)-epi-dexoxadrol, (-)-conhydrine and (+)-lentiginosine.
Chinmay Bhat and Santosh G. Tilve *Tetrahedron* **2013** (Accepted).

(v) Recent advances in the synthesis of naturally occurring pyrrolidines, pyrrolizidines and indolizidine alkaloids using proline as a synthetic precursor.
Chinmay Bhat and Santosh G. Tilve *RSC advances* **2013** (A*ccepted*).

(vi) Synthesis of (*R*)-norbgugaine and its potential as quorum sensing inhibitor against *Pseudomona aeruginosa.*
Mahesh S. Majik, Deepak Naik, **Chinmay Bhat**, Santosh G. Tilve, Supriya Tilvi, Lisette D'Souza *Bioorg. Med. Chem. Lett*. **2013**, *23*, 23.

(vii) Chemoselective reduction of aromatic nitro compounds using magnetically recoverable Co-Co_2B nanocatalyst.
Amit Vernekar, Sagar Patil, **Chinmay Bhat**, Santosh G. Tilve *RSC advances* **2012**, *2*, 6057.

CONFERENCES ATTENDED

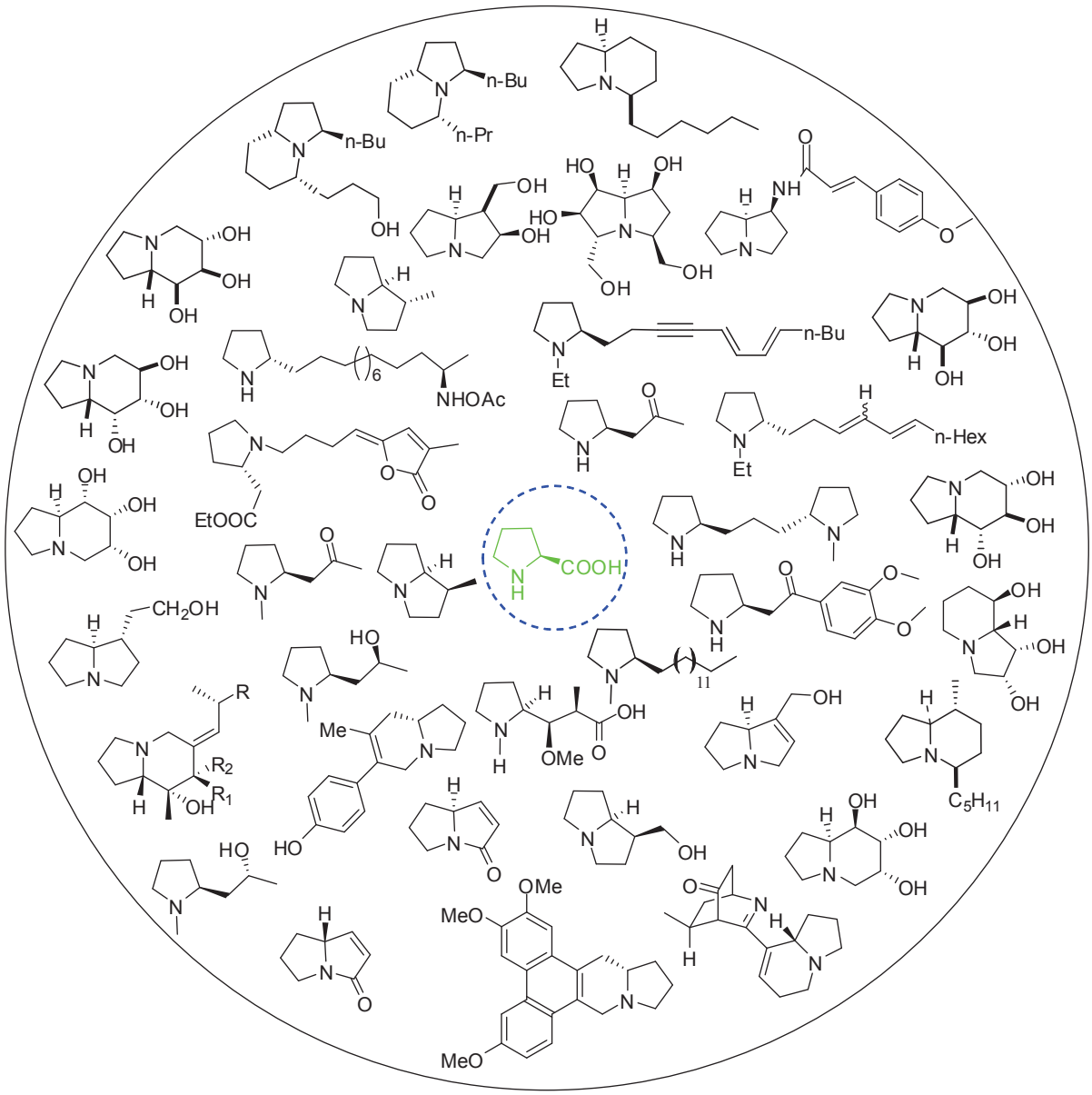
(1) Paper entitled "*Asymmetric synthesis of (-)-hygrine, (-)-norhygrine, (-)-pseudohygroline and (-)-hygroline via Nef reaction".*
Poster Presented at Royal Society of Chemistry-West India Section **2010**, Goa University.

(2) Paper entitled "*Asymmetric synthesis of pyrrolidine and piperidine alkaloids*"
Oral Presentation at IIT Guwahati, 8th National Organic Symposium Trust, J-NOST **2012**.

(3) Participated in the 3-day conference on Chemical (Industrial) Disaster Management (CIDM): Chemical, Pharmaceutical and hydrocarbon Industry: held at Cidade De Goa, Goa, April 16-18, 2013.

The thesis entitled "***Synthetic Studies of Alkaloids Containing Pyrrolidine and Piperidine Structural Motifs***" is organized into 5 chapters.

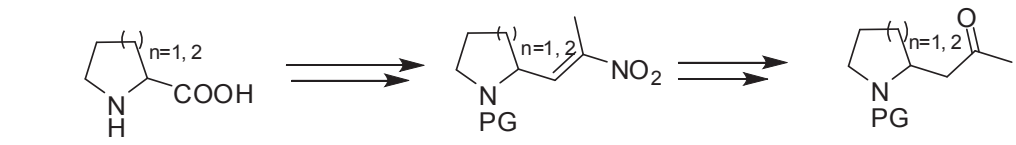
Chapter 1*:* Presents an overview of comprehensive compilation of synthesis of naturally occurring pyrrolidines, pyrrolizidines and indolizidine alkaloids using proline as a synthetic precursor. The detail coverage of literature work since 1990 to 2013 has been done and presented with brief summary.



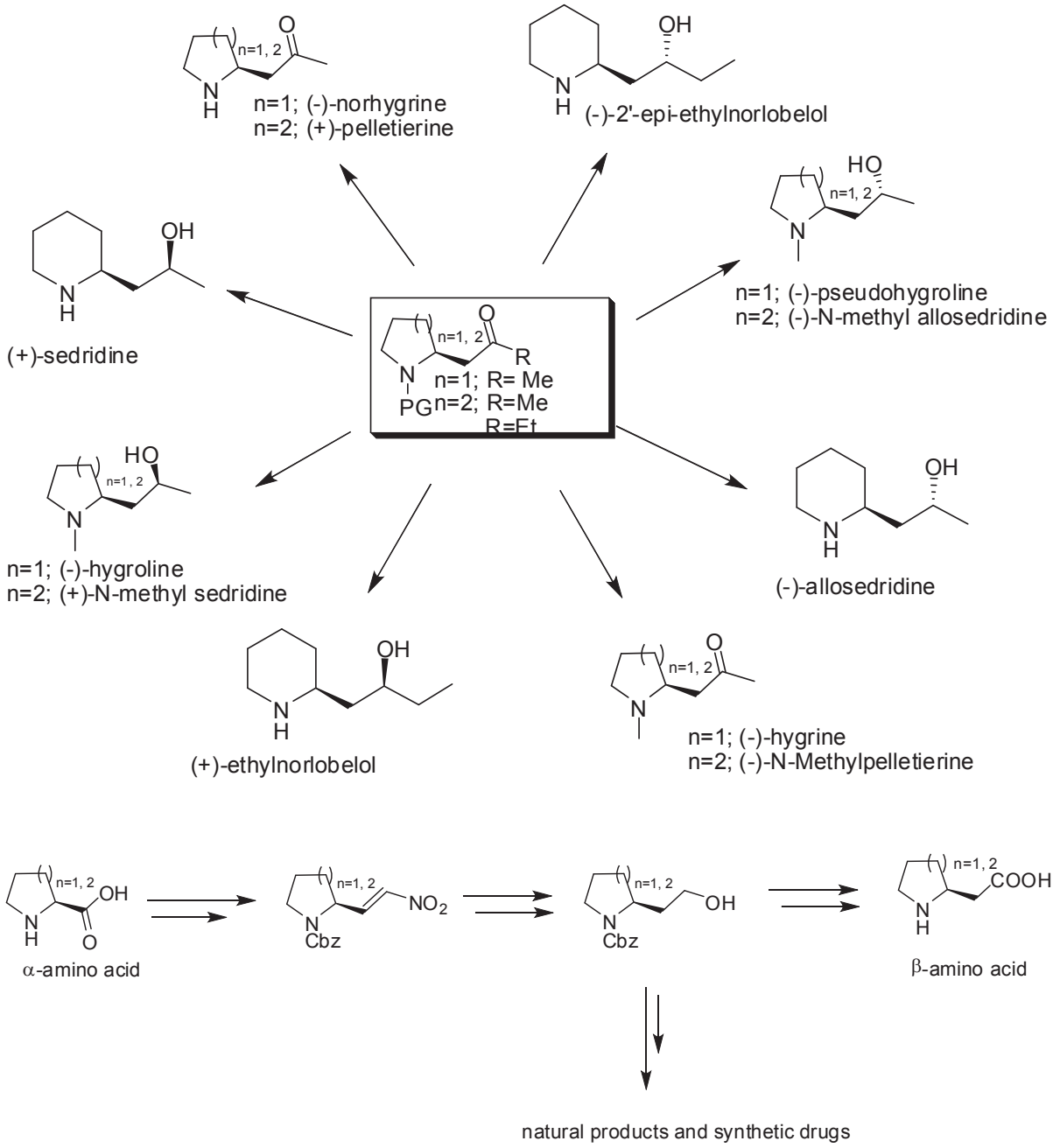
Proline with two functional groups; NH & COOH and a pyrrolidine ring with one stereogenic

nitrogen centre undoubtedly emerged as an efficient chiral tool in asymmetric synthesis. It is a highly versatile and unique amino acid, displayed its vast applications as oganocatalyst as well as a chiral source in "chiral pool" synthesis. There are enough reports compiled on proline displaying its potent organocatalytic activities, but lack of specific report available for its potential in chiral pool synthesis as a unique chiral synthon, prompted us to collect the research work done since 1990 to 2013 for the synthesis of pyrrolidines, pyrrolizidines and indolizidine alkaloids. The chapter discuses the synthesis of myriad of molecules ranging from simple to complex of the above mentioned families and provides useful information of various synthetic protocols from different research groups with a brief summary.

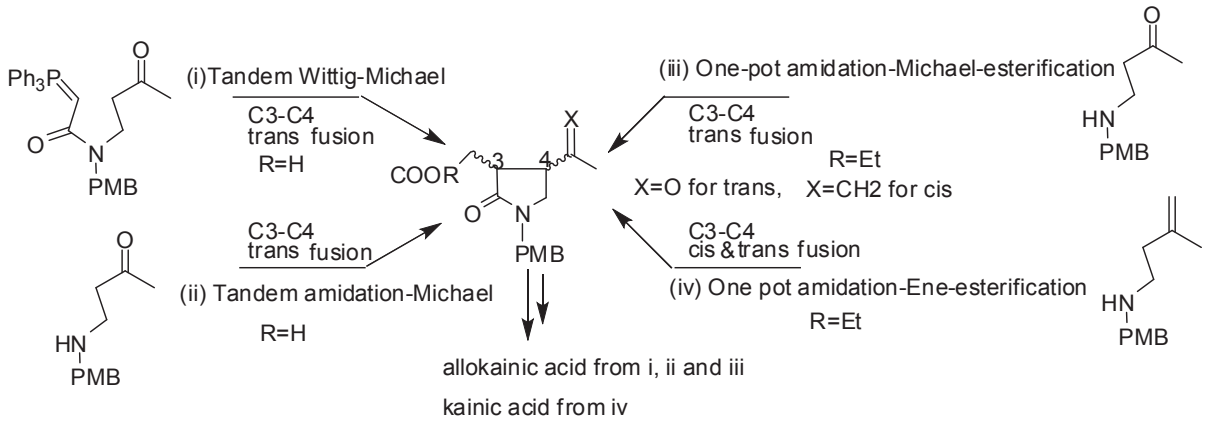
Chapter 2*:* Deals with the development and application of Henry-Nef protocol for the synthetic studies of 2-substituted pyrrolidine and piperidine alkaloids. The "chiral pool" synthesis, being an effectual synthetic paradigm has numerous advantages over other asymmetric synthetic methods, drawn our attention to design the synthesis of some useful pyrrolidine and piperidine natural products using easily available chiral sources like L-proline and L-pipecolinic acid with some bench-top chemicals. The chapter is further divided into 3 sections; the first and second sections deals with synthetic studies of pyrrolidine and piperidine alkaloids respectively by synthesizing some useful intermediates and delineates the diastereoselective reduction of carbonyl groups with different reducing agents. The 3rd section provides a study on construction of some useful intermediates for the synthesis of plethora of naturally bioactive molecules and synthetic drugs. The 1-carbon homologation of amino acid (proline and pipecolinic acid) opens a new route for the construction of β-amino acid from α-amino acid.



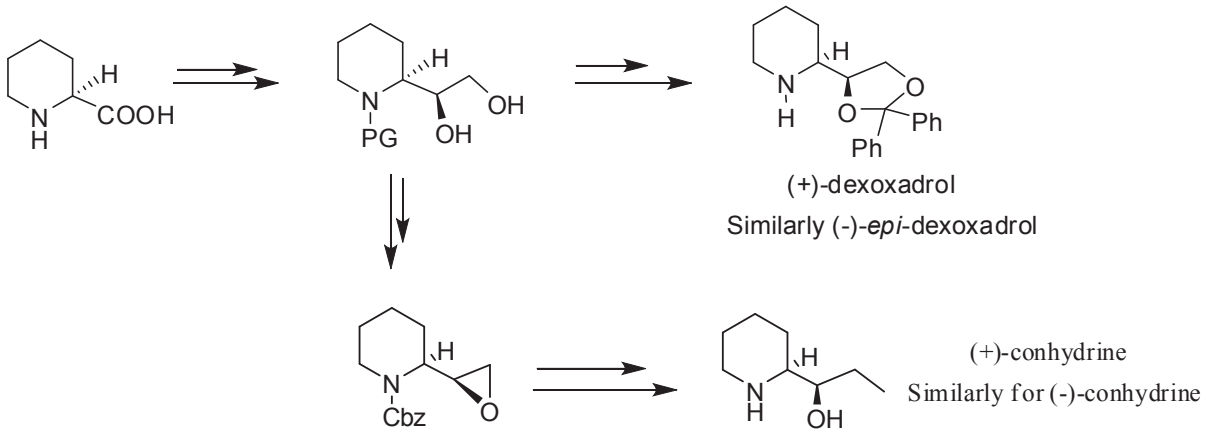
L-proline / L-pipecolinic acid PG= Cbz, Boc, COOEt Key intermediates



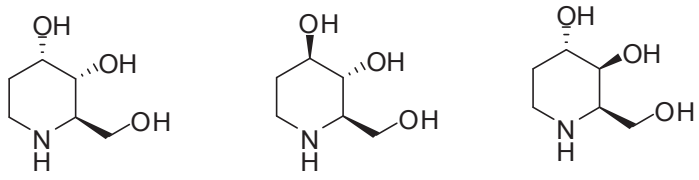
Chapter 3*:* Delineates synthetic studies of allokainic acid and kainic acid, important members of kainoid family, through two tandem methods and two one pot processes. Domino processes for the synthesis of allokainic acid precursor involve tandem Wittig-Michael and tandem amidation-Michael whereas 'one-pot amidation-Michael-esterification' and 'one-pot amidation-ene-esterification' for the construction of key building blocks of allokainic acid and kainic acid respectively via one-pot strategies.



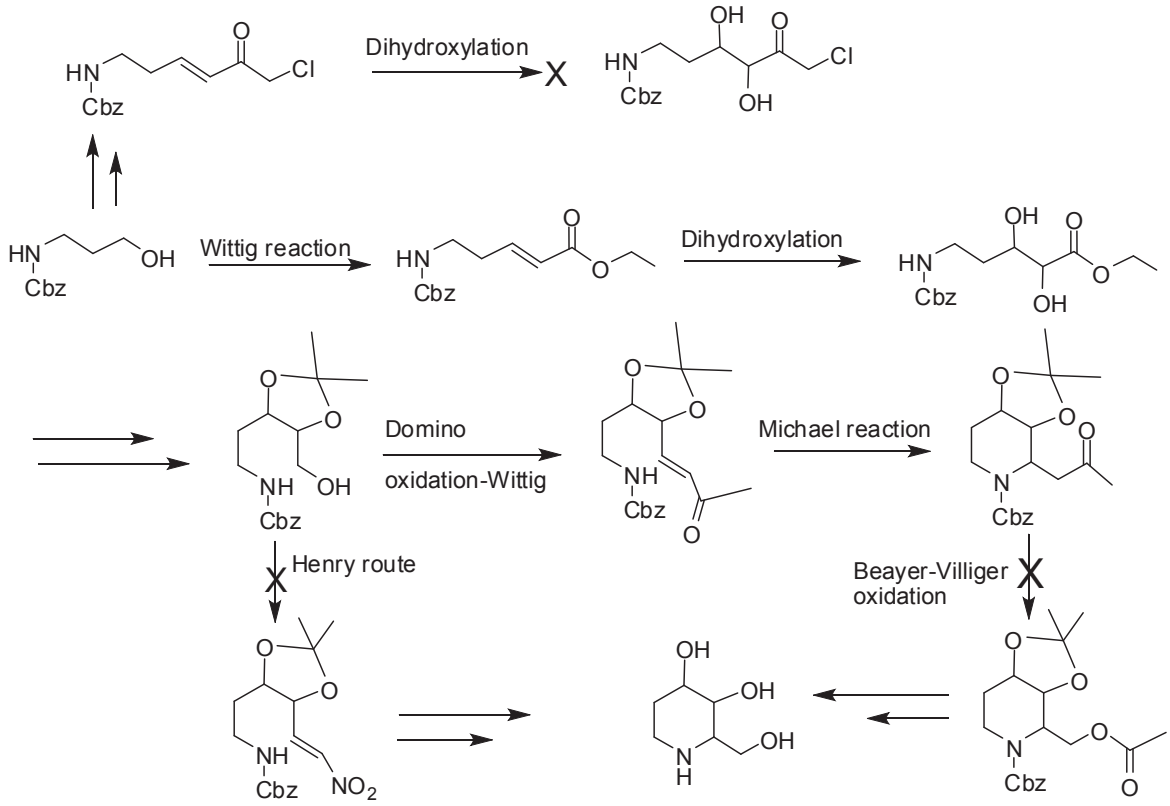
Chapter 4*:* Describes the synthesis of NMDA receptor antagonist (+)-dexoxadrol and its epi isomer through Sharpless asymmetric dihydroxylation. The chapter also discloses a very short formal synthesis of (+)-conhydrine and (-)-conhydrine.



Chapter 5*:* Discuses the synthetic endeavors towards sugar mimics; D-fagomine and its other isomers mainly through Wittig Olefination and Sharpless asymmetric dihydroxylation. The synthetic route planned via Henry and Nef reaction is also presented.

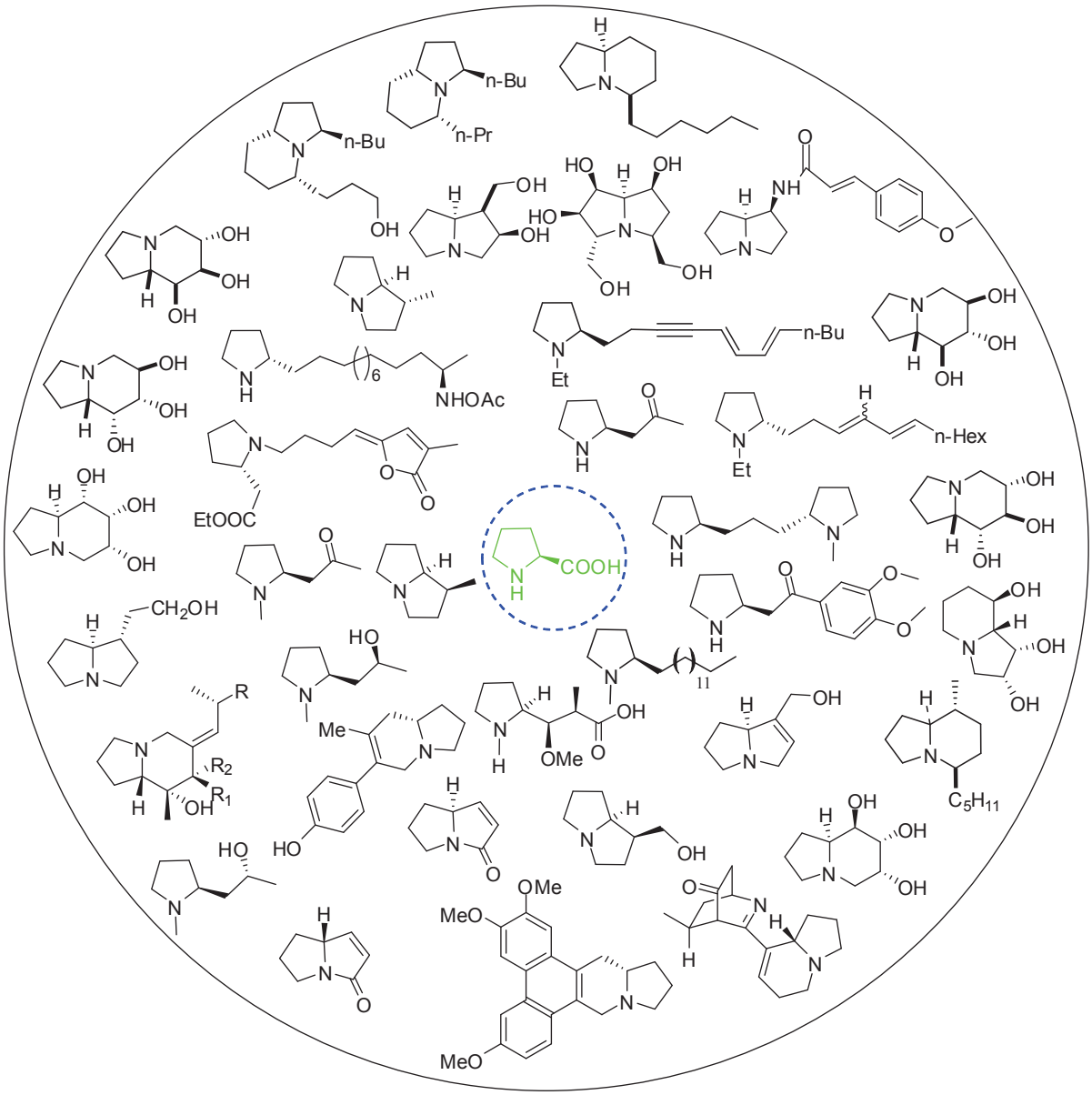


D-Fagomine and its isomers


Dihydroxylation
Wittig reaction
Dihydroxylation
Domino
oxidation-Wittig
Michael reaction
Henry route
Beayer-Villiger
oxidation

CHAPTER 1

Recent Advances in the Synthesis of Naturally Occurring Pyrrolidines, Pyrrolizidines and Indolizidine Alkaloids Using Proline as a Unique Chiral Synthon



Recent Advances in the Synthesis of Naturally Occurring Pyrrolidines, Pyrrolizidines and Indolizidine Alkaloids Using Proline as a Unique Chiral Synthon

1. Introduction

Over the last few decades, asymmetric synthesis of natural products is gaining major importance from industrial and academic relevance.[1] Asymmetric synthesis mainly involve; carrying out the reaction with the integrity of the chiral centre *viz* "chiral pool" strategy, introducing new chiral centres by chiral induction methods, use of chiral auxiliaries and organocatalysis. It is always difficult to carry out a selective transformation of the molecules to generate new chiral centres. Although the organocatalysis is soaring nowadays, selectivity towards the substrates, efficacy of the systems and cost of organocatalysts make cumbersome from economic point of view. On the other hand, the "chiral pool" approach, being an effectual paradigm, plays a very prominent role from synthetic relevance[2] as the starting materials are easily carved from readily available materials like amino acids, carbohydrates, terpenes and organic acids. A vast number of natural products are derived from different amino acids[3] due to the availability of the functional groups suitable for various transformations to effect the required modifications and constitute new appendages. As a consequence, several amino acids have prompted the synthetic chemists to contemplate the designing of various synthetic routes for embodying the different natural products and their structural entities.

Proline is a bifunctional, non essential amino acid prevalent in the various natural and synthetic bioactive molecules. It is the only cyclic amino acid, synthesized in our body. Despite being structurally an imino acid, popularly called as an amino acid. L-Proline, being abundant in nature, cheaply available commercially, finds application in various pharmacological and biotechnological applications due to its osmoprotectant behaviour. Proline is a widely distributed osmolyte found to accumulate in several environmentally stressed plants as well as microorganisms.[4] It is also used as a nitrogen source during fermentation of grape musts for the production of wine. It is the only amino acid which attains *cis* configuration in peptides unlike other amino acids which normally exist in *trans*

form. Due to this unique behaviour, it assisted the detail study of protein folding and *cis-trans* isomerisation. L-Proline is one of the two amino acids which disobeys the popular "Ramachandran plot", the other being glycine.

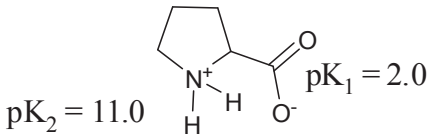


Figure 1. Proline; a cyclic amino acid

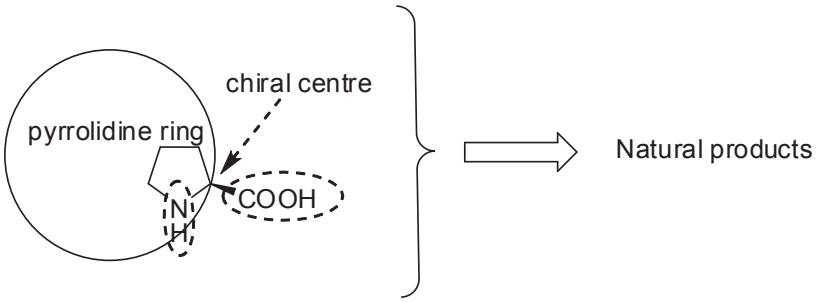
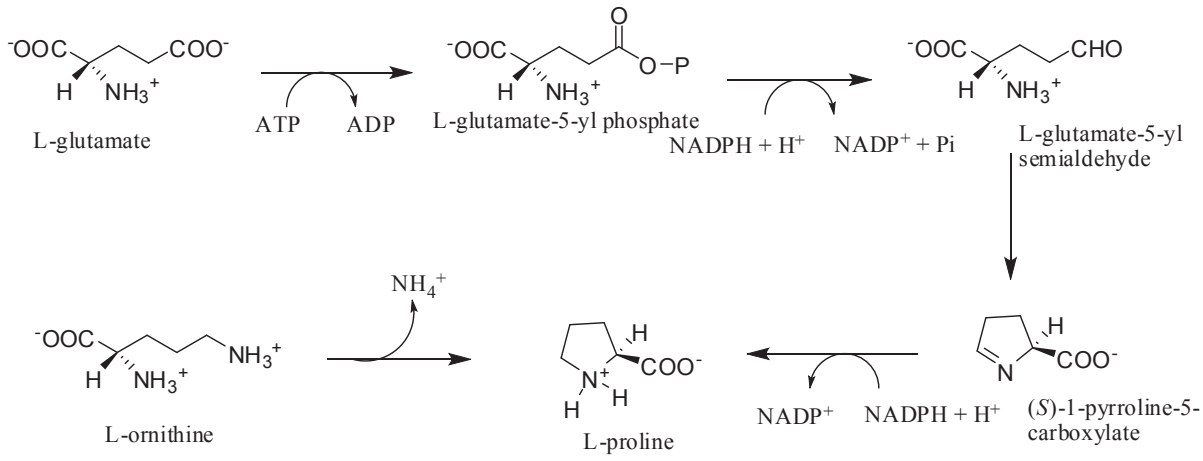


Figure 2. Proline as a chiral source for natural products

The unique structure of proline, having both carboxylic and imino groups (figure 1) prevails as a versatile organocatalyst through enamine and iminium ion mechanism. Consequently, over the last few decades various proline derived organocatalysts with multitudinous embellishment have been articulated by appropriate transformation of its functional groups and efficiently applied for enantioselective and diastereoselective reactions.[5] The proline also enunciated its effect as a profound versatile ligand by complexing with the various metals for synthetic transformation of the organic molecules.[6] The availability of the five member ring with a stereogenic nitrogen centre and the two functional groups (figure 2) in combinations inflict the transformation of the molecule into myriad of naturally occurring pyrrolidines, pyrrolizidines, piperidines, quinolizidines, indolizidines and macrocycles ranging from simple to complex molecules. The proline being a natural product; conversion of it to other natural products reflects the competency in adaptation of one natural product into another. The biosynthesis of L-proline is derived from L-glutamate and L-ornithine (scheme 1).[4] The synthetic proline was reported by Willstätter in 1900 using sodium salt of diethyl malonate and 1, 3-dibromopropane.

The present chapter delineates the use of (*R*) and (*S*) proline for the synthesis of aforementioned types of alkaloids. The comprehensive coverage of the syntheses of these alkaloids is done (since 1990 to 2013) using proline as a starting material or major synthetic precursor.



Scheme 1. Biosynthesis of proline.

2. Synthesis of Pyrrolidine alkaloids

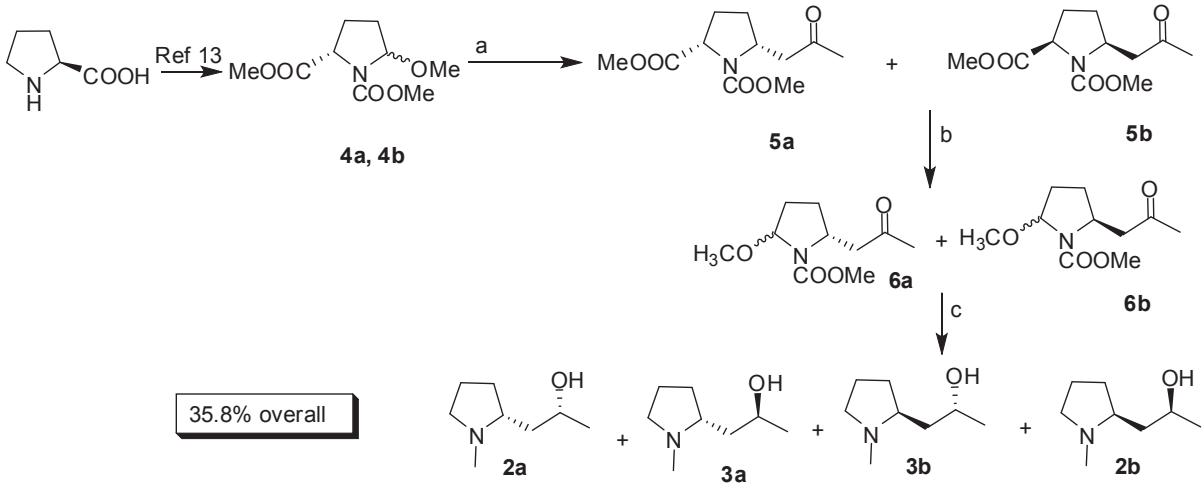
2.1 Introduction

Pyrrolidine alkaloids bearing five member *N*-heterocycles, enormously ubiquitous in the various natural[7] and unnatural components.[8] There are about 80 pyrrolidine alkaloids known with the hygrine being the simplest. They are mainly extracted from the plants of families *Colanaceae*, *Convolvunaceae* and *Erythroxylaceae.* These classes of alkaloids constitute a part of organocatalysts[9] and building blocks in organic synthesis.[10] They are endowed with host of biological activities and pharmacological behaviours. The difficulties in the isolation and purification of these alkaloids and the global scarcity imposed the synthetic chemists to contemplate for designing novel synthetic schemes. Proline, being one of the simple pyrrolidine alkaloids, has been found to be a viable precursor for the synthesis of these alkaloids through systematic transformation of the functional groups. The simplest pyrrolidine alkaloid, hygrine, acts as a biogenetic precursor for tropane alkaloids.

2.2 Tropane and sedum alkaloids

These classes of alkaloids are mainly 2-substituted pyrrolidine and piperidine members with the different functional groups on the side chain and have been of immense interest for the synthetic chemists due to their intriguing pharmacological activities and hallucinogenic characteristics.[11] These alkaloids were mainly isolated from the plants *Schizanthus hookeri*, *Carallia brachiata* and *Erythroxylon coca*. Some of the representative members of five member alkaloids include (+)-hygrine **1**, (+)-hygroline **2** and (+)-pseudohygroline **3** etc.

Shono *et al* have synthesized (+)-hygroline **2** and (+)-pseudohygroline **3** starting from proline using anodic oxidation as a key step (scheme 2).[12] The L-proline was efficiently converted to **4** as a mixture of diastereomers **4a** and **4b** according to previously reported methods.[13] The mixture was separated on column chromatography. The further reaction of either **4a** or **4b** with isopropenyl acetate in the presence of $TiCl_4$ resulted in an enantiomeric mixture of **5a** and **5b** which was as such hydrolysed using alkaline solution and electrochemically oxidised in MeOH to give a mixture of **6a** and **6b**. Further reduction of carbamate with LAH gave a mixture of isomers of hygroline **2a** and **2b** and pseudohygroline **3a** and **3b** which were separated with the optical purity of 42.60% and 45.62% respectively using preparative GLC.

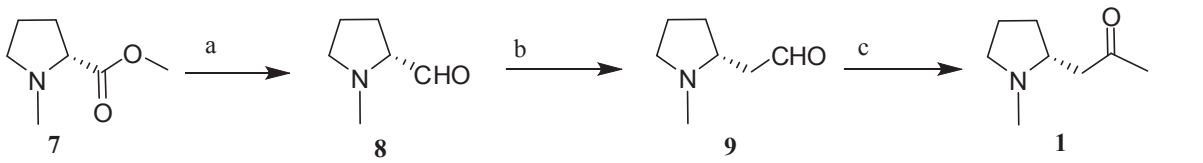


hygroline $[a]_D^{21}$ = +21.32 (c 3, EtOH) pseudohygroline $[a]_D^{21}$ = +45.62 (c 3, EtOH)

Scheme 2

Reagents and conditions : (a) Prenyl acetate, $TiCl_4$, 85%; (b) (i) KOH (ii) -2e, CH_3OH, NaOMe (anodic oxidation), 52%; (c) LAH, THF, refux, 81%.

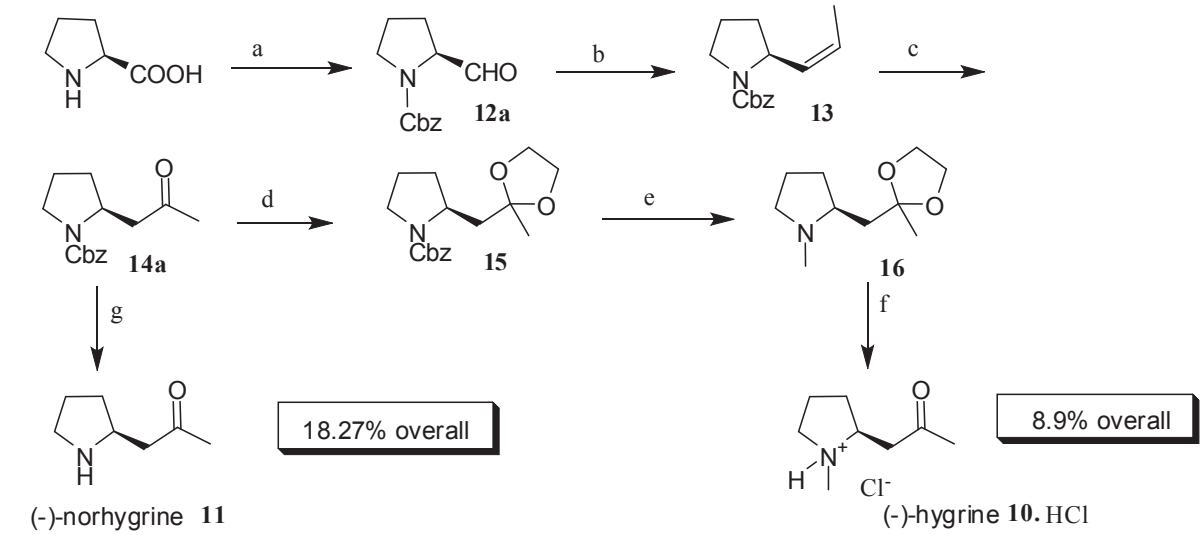
Arévalo-García and Colmenares synthesized the tropane pyrrolidine alkaloid (+)-hygrine **1**, mainly found in *coca* leaves, in six steps (scheme 3) using (*R*)-proline derived ester **7** as a chiral precursor.[14] *N*-Methylated proline ester **7** was reduced to aldehyde **8** using DIBAL which was further homologated to **9** by reaction with PPh_3=$CHOCH_3$ followed by acid hydrolysis. The Grignard reaction on **9** with MeMgBr and subsequent oxidation with DMP gave (+)-hygrine **1**.



$[\alpha]_D$ = +34.0 (*c* 0.5, H_2O)

Scheme 3

Reagents and conditions : (a) DIBAL, DCM, -30 ºC; (b) $PPh_3CH_2OCH_3Br$, KO^{t}Bu, THF, 10% HCl-THF; (c) (i) MeMgBr, THF; (ii) DMP, DCM.



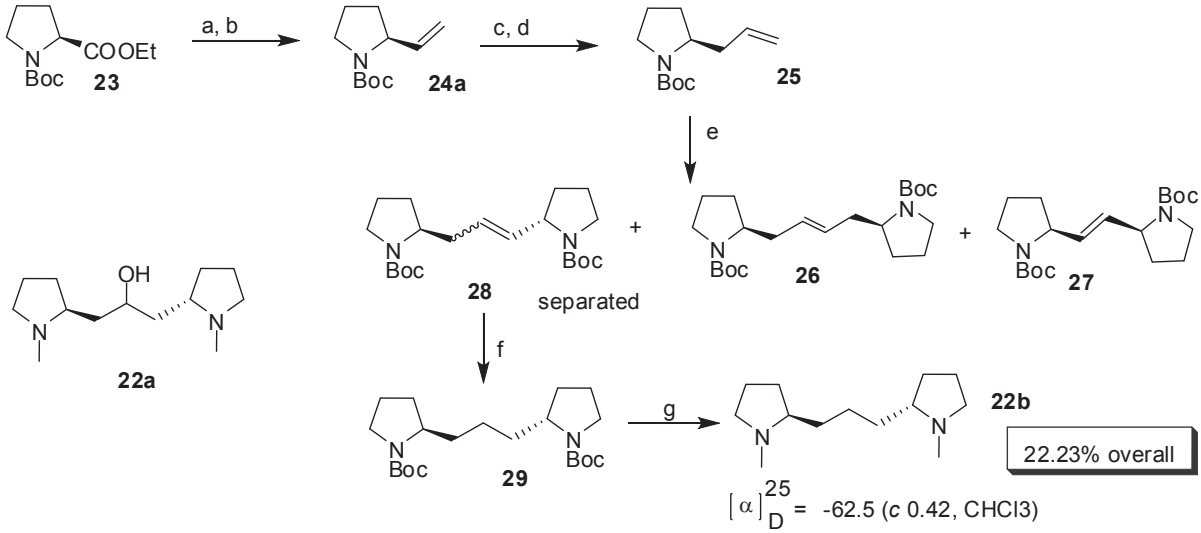
$[\alpha]_D^{33}$ = -29.6 (*c* 0.14, $CHCl_3$)

$[\alpha]_D^{30}$ = -32.1 (*c* 0.25, H_2O)

Scheme 4

Reagents and conditions : (a) (i) LAH, THF, reflux, 90%; (ii) CbzCl, K_2CO_3, CH_3CN, 85%; (iii) PCC, DCM, 70%; (b) ethyltriphenylphosphonium bromide, *n*-BuLi, Et_2O, 56%; (c) $PdCl_2$, CuCl, O_2, DMF–H_2O, 76%; (d) $HOCH_2CH_2OH$, *p*-TsOH, 82%; (e) LAH, THF, 66%; (f) 6 N HCl, THF, 73%: (g) H_2, Pd/C, EtOH, 81%.

(-)-Hygrine **10** and (-)-norhygrine **11** were synthesized using regioselective Wacker oxidation as a key step (scheme 4).[15] The synthesis started with commercially available L-proline, converted to *N*-Cbz-prolinal **12a**. The aldehyde **12a** on Wittig reaction with ethylidinephosphorane afforded *cis* olefin **13**. The Wacker oxidation of the non terminal double bond of **13**, performed using $PdCl_2$/CuCl in O_2 took place regioselectively at the carbon atom more away from the ring due to bulky Cbz group, delivering the keto product **14a**. The keto group of **14a** was converted to its acetal form to give **15** before reducing the *N*-Cbz group to *N*-methyl using LAH in refluxing THF giving **16**. The amine **16** thus formed was treated with HCl to afford the natural product (-)-hygrine **10** as hydrochloride salt**.** Incidentally the first synthesis of (-)-norhygrine **11** which is usually found along with hygrine in nature, was carried out by selective deprotection of Cbz group of **14a** by hydrogenation over Pd/C.



Scheme 6

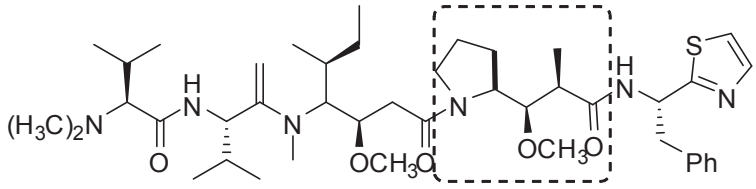
Reagents and conditions : (a) LAH, THF, 0 ºC to rt, 1 h, 95%; (b) (i) DMSO, $(COCl)_2$, Et_3N, DCM, -78 ºC, 1 h; (ii) $PPh_3{=}CH_2$, THF, -10 ºC, 3 h (69% two steps); (c) BH_3.DMS, THF, 0 ºC, 2 h, 87%; (d) (i) DMSO,

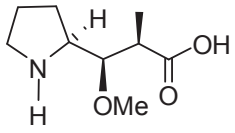
$(COCl)_2$, Et_3N, DCM, -78 ºC, 1 h; (ii) $PPh_3{=}CH_2$, THF, -10 ºC, 3 h (70% two steps); (e) 10 mol% Grubbś II catalyst, DCM, 40 ºC, 12 h, 69%; (f) H_2, Pd/C, MeOH, 2 h, 90%; (g) LAH, THF, reflux, 5 h, 77%.

Another important pyrrolidine alkaloid (-)-dihydrocuscohygrine **22a** was isolated from *Erythroxylon coca* in 1981 by Turner.[16] Recently Yerri *et al* synthesized (-)-deoxocuscohygrine **22b** using proline as a starting material employing cross metathesis as a key step (scheme 6).[17] The commercially available *N*-Boc-proline ester **23** on reduction followed by Swern oxidation and Wittig olefination afforded **24a**. The alkene **24a** on hydroboration followed by subsequent oxidation and Wittig reaction produced the homologated alkene **25**, a key intermediate for metathesis. The cross metathesis of **25** and **24a** using Grubbś second generation catalyst resulted in the mixture of homodimers **26** and **27** along with an inseparable *cis* and *trans* mixture of required **28** in less yield. It was envisioned that the compound **24a** showed sluggish behaviour towards metathesis due to the presence of bulky Boc group nearer to the olefin group and also the formation of the homodimer **26** was favoured due to less reversibility of it. The formation of dimers was then minimised by reacting excess **25** (1.6 equiv.) with **24a**, furnishing the required product **28** in 69% yield along with dimer **26** (55% with respect to **27**). The product **28** was then separated and subjected to hydrogenation over Pd/C to give **29**, followed by LAH reduction to furnish (-)-deoxocuscohygrine **22b**.

2.3 Dolastatin: Synthesis of dolaproine unit

Dolastatin 10



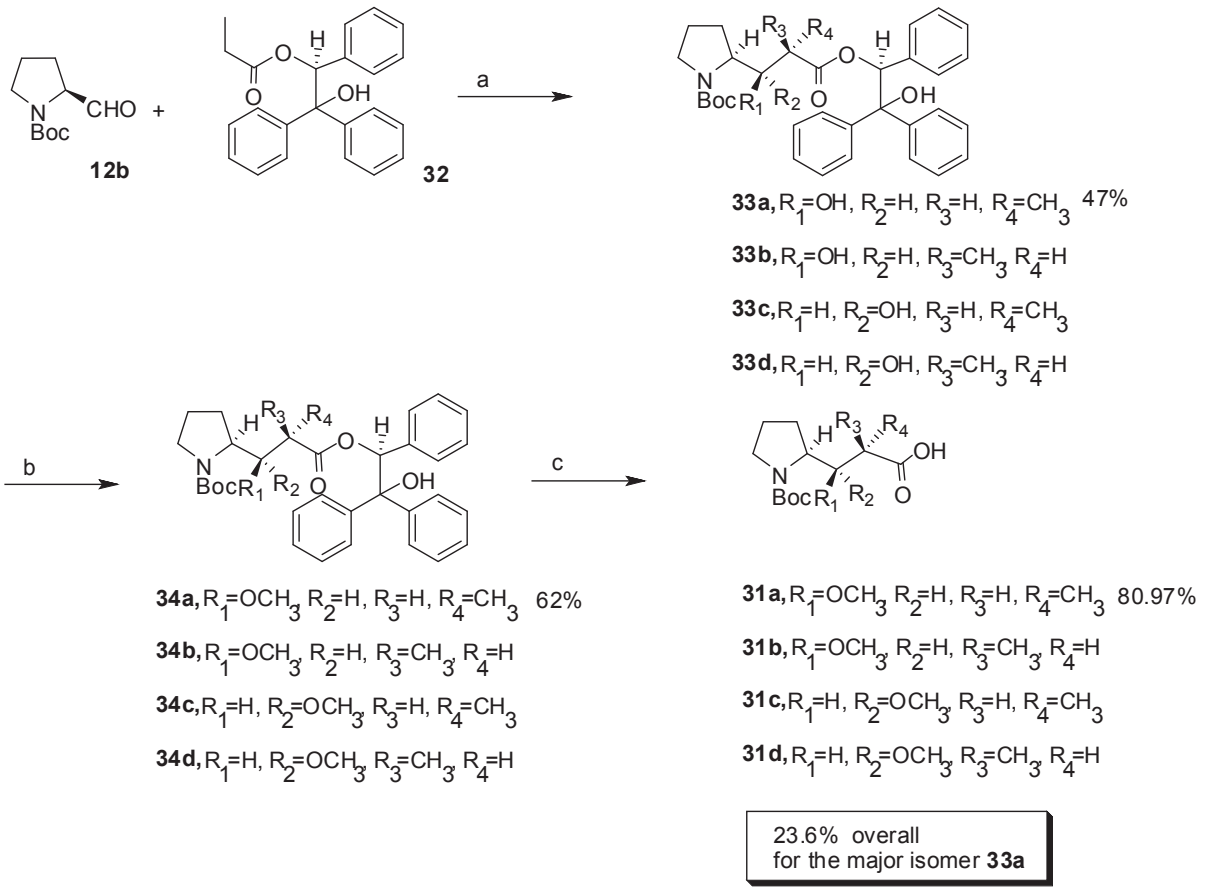


Dolaproine **30**

Dolastatin 10 is a marine natural product consisting of 8 chiral centres, isolated in 1984 by Petit *et al* from the sea hare *Dolabella auricularia*.[18] After the elucidation of the structure in 1987, the first synthesis was reported by the same group in 1989.[19] The alkaloid has shown a remarkable antineoplastic activity and is under clinical trial for anticancer

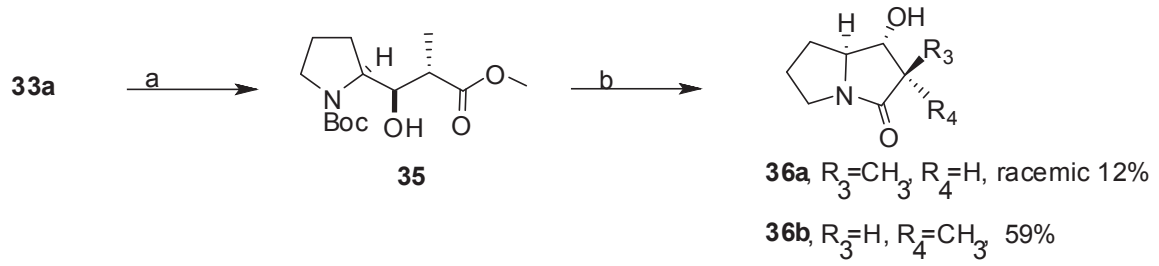
characteristics.[20] Dolastatin 10 is comprised of the 3-chiral centred β-methoxy-γ-aminoacid, dolaproine (Dap) **30**. Most of the available reports approached the synthesis of Dolastatin 10 through the synthesis of Dap **30** unit which can conveniently be accessed from proline.

In continuation of isolation research on Dolastatin 10, Petit *et al* have synthesized the 4 isomers of Boc-Dap **31** unit through aldol condensation (scheme 7).[21] The compound Boc-prolinal **12b** on aldol reaction with an enolate of chiral ester **32** using a strong base LDA in combination with $MgBr_2$ resulted in a mixture of diastereomers **33** separable by column chromatography. The compound **33** on treatment with $(CH_3)_3OBF_4$ afforded the methoxy compound **34** which on hydrogenolysis produced Boc-Dap isomers **31**. The configuration of the major isomer **31a** was confirmed by converting **33a** to the lactam **36** (scheme 8) through ester **35** and systematic NMR studies. However the required isomer for the synthesis of Dolaproine **30** was **33b**, found to be formed in low yield.



Scheme 7

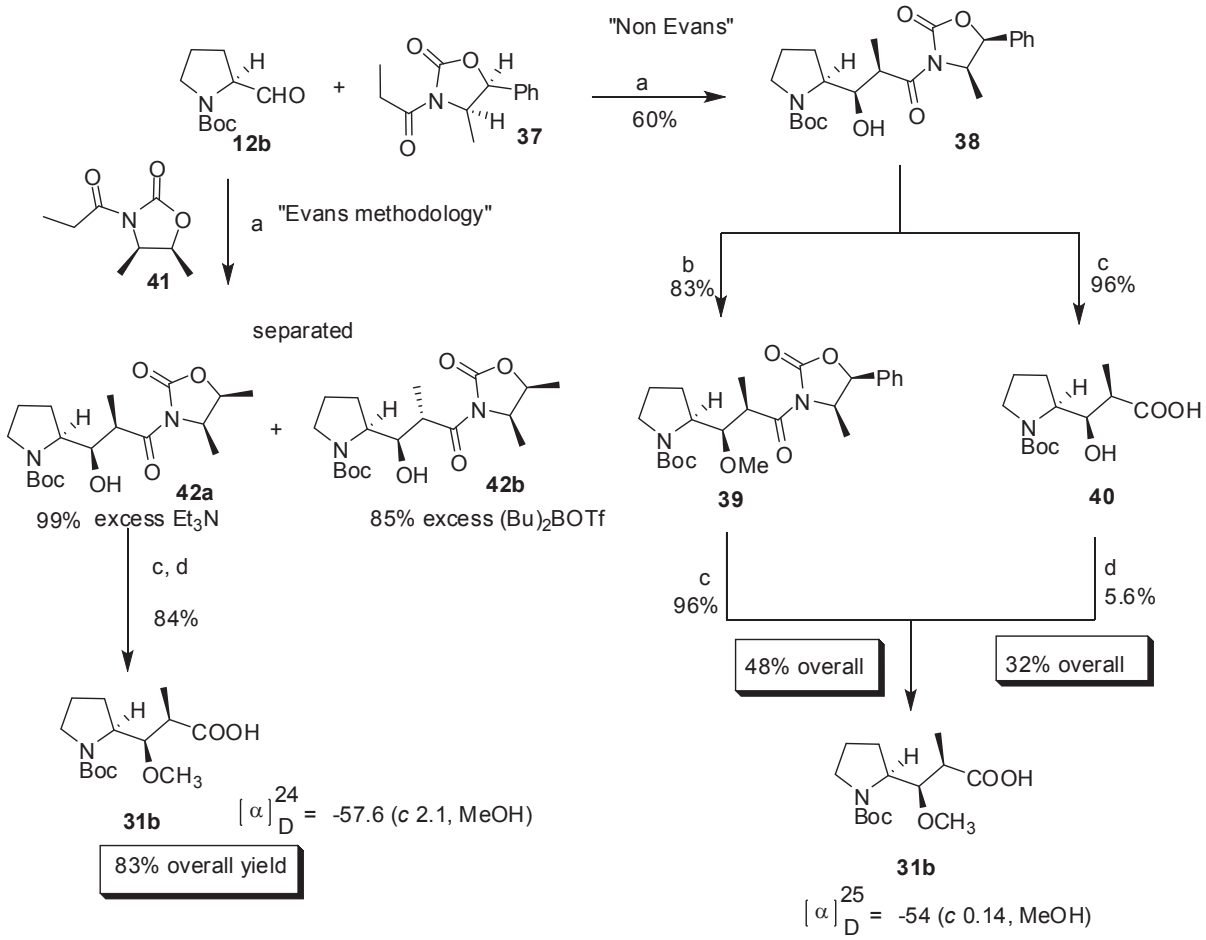
Reagents and conditions: (a) *i*Pr_2NLi, $MgBr_2.Et_2O$; (b) $(CH_3)_3OBF_4$, proton sponge; (c) H_2, 10% Pd/C.



Scheme 8

Reagents and conditions: (a) (i) H_2/5% Pd/C (ii) CH_2N_2; (67% for two steps) (b) (i) TFA (ii) K_2CO_3 (71% for two steps).

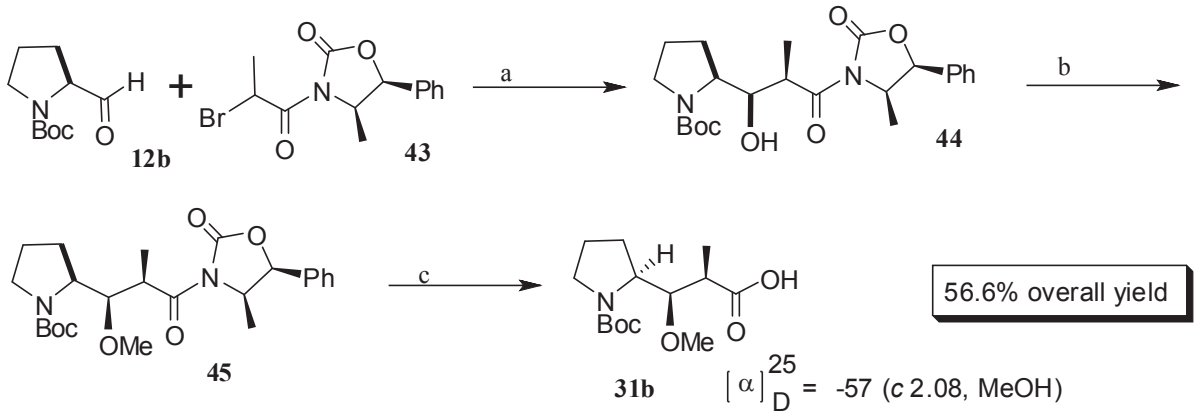
Petit *et al* further improved the chiral synthesis of Dap **30**, enantioselectively and diastereoselectively through dibutly boron triflate [$(Bu)_2BOTf$] mediated aldol condensation (Non-Evans type *syn* aldol) (scheme 9).[22] The Boc-prolinal **12b** was treated with chiral oxazolidinone **37** in the presence of $(Bu)_2BOTf$ and Et_3N to furnish the compound **38** as a single diastereomer. The synthesis of the Boc-Dap **31b** was then achieved through two converging routes, either by methylation followed by hydrolysis of the chiral auxiliary (**38-39-31b**) or by hydrolysis of the chiral auxiliary followed by methylation (**38-40-31b**). In a similar way Hamada and co-workers approached the synthesis of Dolastatin 10 by synthesizing the intermediate N-Boc-Dap **31b** using Evans methodology.[23] The reaction of Boc prolinal **12b** with chiral auxiliary **41** gave a separable mixture of isomers **42a** and **42b**. The compound **42a** was then converted to **31b** by hydrolysis of the chiral auxiliary followed by methylation. The configuration of the isomers was confirmed by converting them to known compounds and comparing with the reported. An interesting phenomenon was observed that only the *cis* isomer **42a** was formed with complete diastereoselection using slight excess Et_3N while major *anti* product **42b** was formed when $(Bu)_2BOTf$ was used in excess. The required *cis* product **42a** was then converted to the dolaproine unit **31b** by hydrolysing the chiral auxiliary using LiOH and H_2O_2 and followed by methylation of -OH using MeI.



Scheme 9

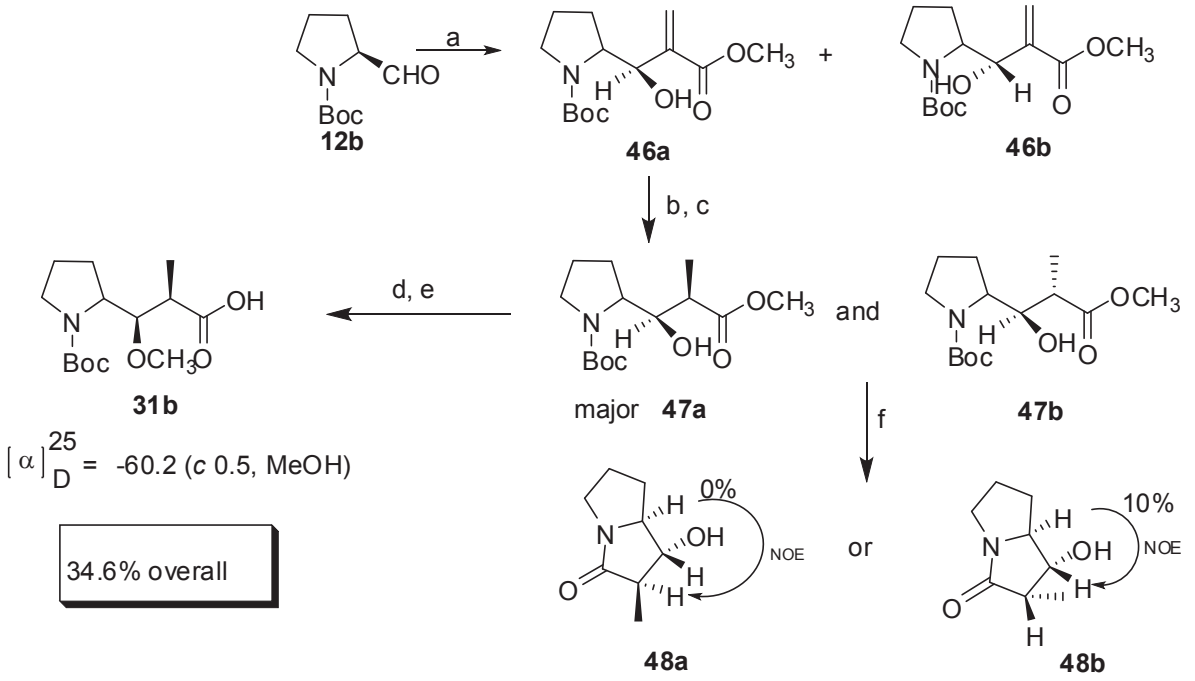
Reagents and conditions: (a) $(Bu)_2OTf$, Et_3N, -75 ºC to rt; (b) $(CH)_3O^+ BF_4^-$, proton sponge, 0 ºC to rt, 46 h; (c) LiOH-H_2O_2, Na_2SO_3, 3 ºC to rt, 16 h; (d) NaH, MeI, 0 ºC, 48 h.

Few years later, Petit and Grealish once again succeeded in getting the required isomeric intermediate for Dap **30** in major amount by carrying out stereoselective Reformatsky reaction assisted by a cobalt-phosphine complex (scheme 10).[24] The reaction of the Boc protected prolinal **12b** with bromo amide **43** diastereoselectively led to **44**. The free –OH in **44** was methylated using trimethyloxonium tetrafluoroborate $BF_4O(CH_3)_3$ to give **45**. The chiral auxiliary unit was then hydrolysed using LiOH and H_2O_2 to furnish Boc-Dap **31b**.



Scheme 10

Reagents and conditions: (a) $Co[P(PPh_3)_4]$, THF, 0 ºC, 70%; (b) $BF_4O(CH_3)_3$, proton sponge, 4 Aº MS, DCM, 86%; (c) LiOH, H_2O_2, 94%.

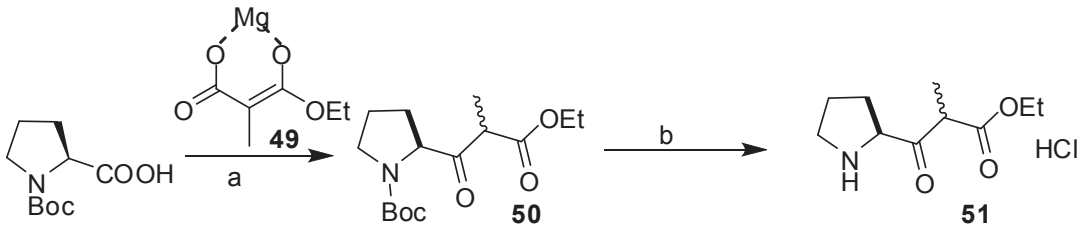


Scheme 11

Reagents and conditions : (a) methyl acrylate, ultrasound sonication, 2-5 days, 70-75%; (b) H_2, 5% Pd/C; EtOAC, rt, 1 atmospheric pressure, 91% of a 83:17 diastereoisomeric mixture; (c) flash chromatographic separation (EtOAc–hexane 1:9; major isomer: 79% yield); (d) LiOH/THF, rt, 16 h, 87%; (e) Me_3OBF_4, DCM, proton sponge, rt, 18 h, 70%; (f) (i) CF_3CO_2H/DCM, 68%; (ii) K_2CO_3/MeOH, overnight (**47a** to **48a**: 82% yield; **47b** to **48b**: 71% yield).

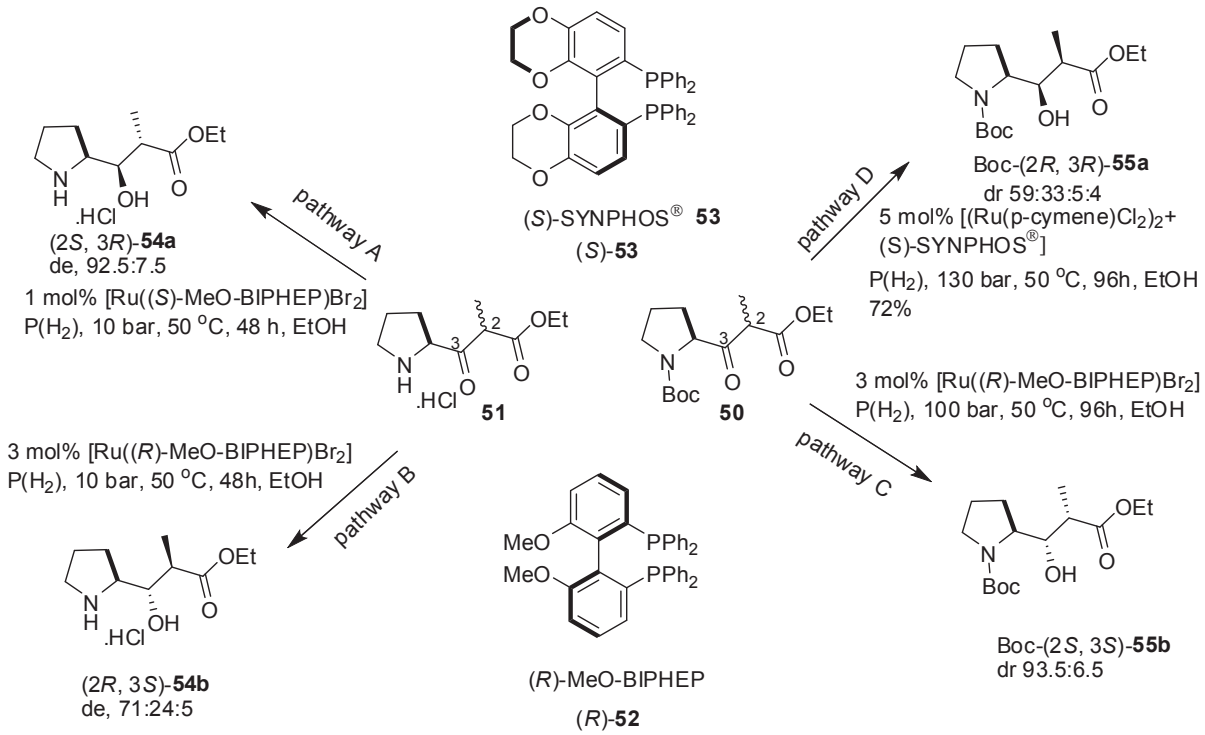
Almeida and Coelho have synthesized Boc-Dap **31b** by coupling *N*-Boc-prolinal **12b** and methyl acrylate through Baylis-Hillman reaction (scheme 11)[25] in four steps with an overall yield of 27%. The Baylis-Hillman reaction was performed using ultrasound sonication, which without racemisation led to a mixture of diastereomers **46**, separable on column chromatography. The major isomer formed was predicted to be **46a** based on Felkin–Ahn open-chain model which on hydrogenation afforded a mixture of isomers **47a** and **47b** in the ratio of 87:17. To determine the configuration of the chiral centres, the separated diastereomers of **47** were subjected to cylclisation to give lactam **48a** and **48b**, whose NOE study confirmed the formation of the required isomer in major amount. The further confirmation of the structure was done by converting **47a** to well known compound Boc-Dap **31b** by successful methylation of hydroxyl group and hydrolysis of the ester group, which completed the formal synthesis of Dolastatin 10.

Genet and co-workers approached the synthesis of dolastatin 10 via dynamic kinetic resolution (DKR) of **50** & **51** by performing an efficient catalytic asymmetric hydrogenation using Ru complexed with chiral ligands (scheme 12, 13).[26] The great discovery of manipulation of catalyst, temperature, solvent conditions and nature of protecting groups on N atom were studied for DKR of different amino substrates during the synthetic manoeuvring of γ-amino acids. For the synthesis of Boc-dap isomers, the Boc-protected and deprotected proline units showed remarkable change in diastereoselectivity. The anti selectivity at the 2nd and 3rd positions was observed with unprotected proline unit **51** with Ru complexed ligands (*S*)-**52** and (*R*)-**52** to give **54a** and **54b**. The best selectivity was observed in pathway A. Surprising failure in achieving the high *cis* selectivity turned the attention to perform the reaction with Boc protected unit **50**. The moderate *cis* selectivity was then achieved using (*S*)-**53** and (*R*)-**52** giving **55a** and **55b** respectively as major isomers by performing the hydrogenation under very high pressure and elongated reaction period. The product **55a** synthesized this way was efficiently transformed to Boc-dap **31** (scheme 14) after separating it from minor isomers which on further synthetic conversions was eventually converted to dolastatin 10.

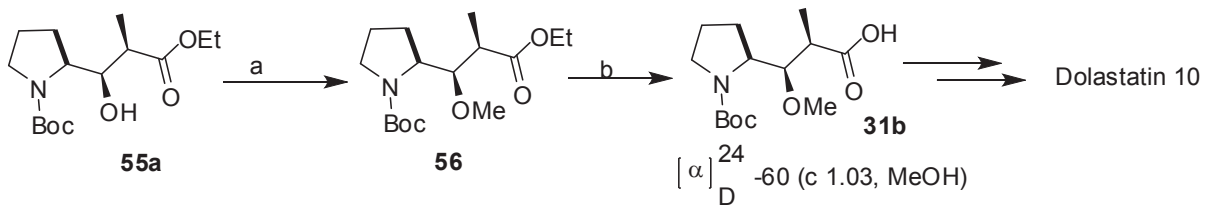


Scheme 12

Reagents and conditions: (a) (i) ImCOIm, THF, 0 °C – rt, 3 h; (ii) **49**, THF, Et_2O, -10 °C – rt, 4 days, (82% for two steps); (b) HCl gas, EtOH, 0 °C, 2 h.

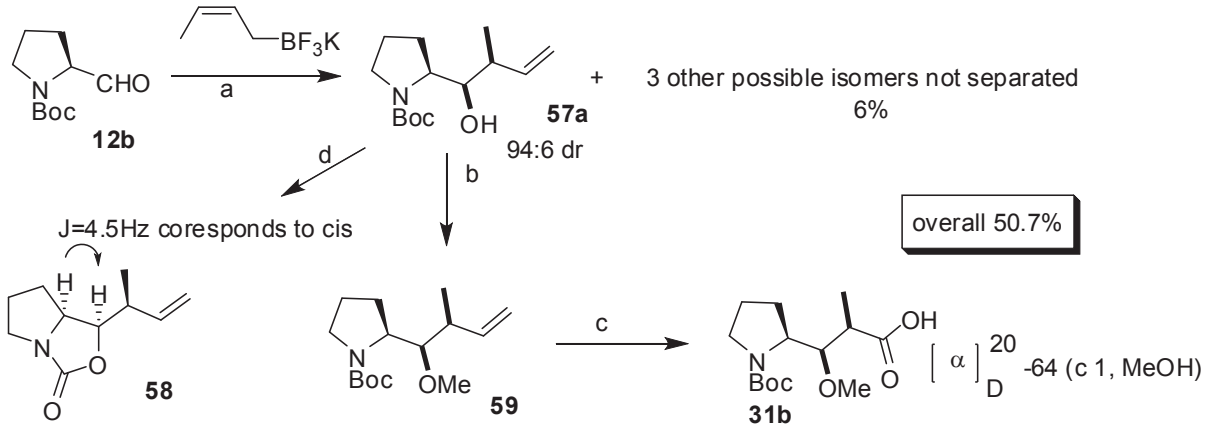


Scheme 13



Scheme 14

Reagents and conditions: (a) LHMDS, HMPA, THF, -78 °C, 25 min, then MeOTf, -20 °C, 15 min, 45%; (b) LiOH, EtOH/H_2O, overnight, 59%.



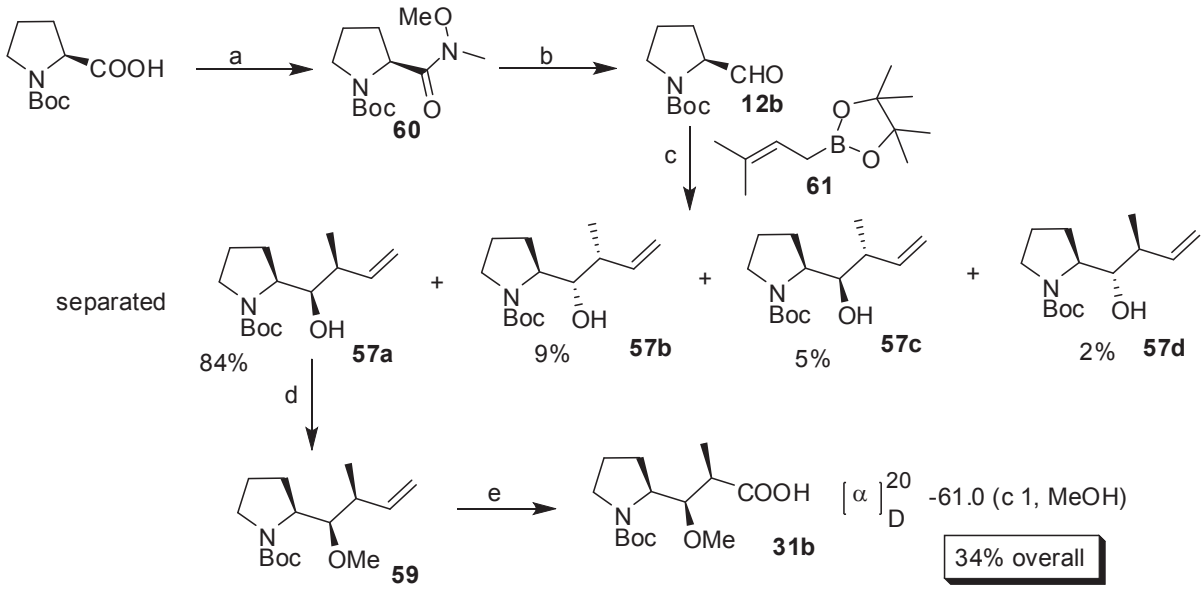
Scheme 15

Reagents and conditions: (a) *n*-Bu_4NI (10 mol%), DCM/H_2O, 89%; (b) NaH, MeI, DMF, 76%; (c) RuO_2, $CH_3CN/H_2O/CHCl_3$, 75%; (d) NaH, THF, 90%.

Cella *et al* studied the diastereoselective addition of crotyltrifluoroborate salts on α-amino aldehydes and could successfully synthesize Boc-dap **31b** in the presence of PTC (Bu_4NI) (scheme 15).[27] The configuration of **57a** was confirmed by converting it to **58** and measuring the proton coupling constant of vicinal protons. The compound **57a** was methylated and further converted to acid **31b** using RuO_2 which constituted the formal synthesis of Dolastatin 10.

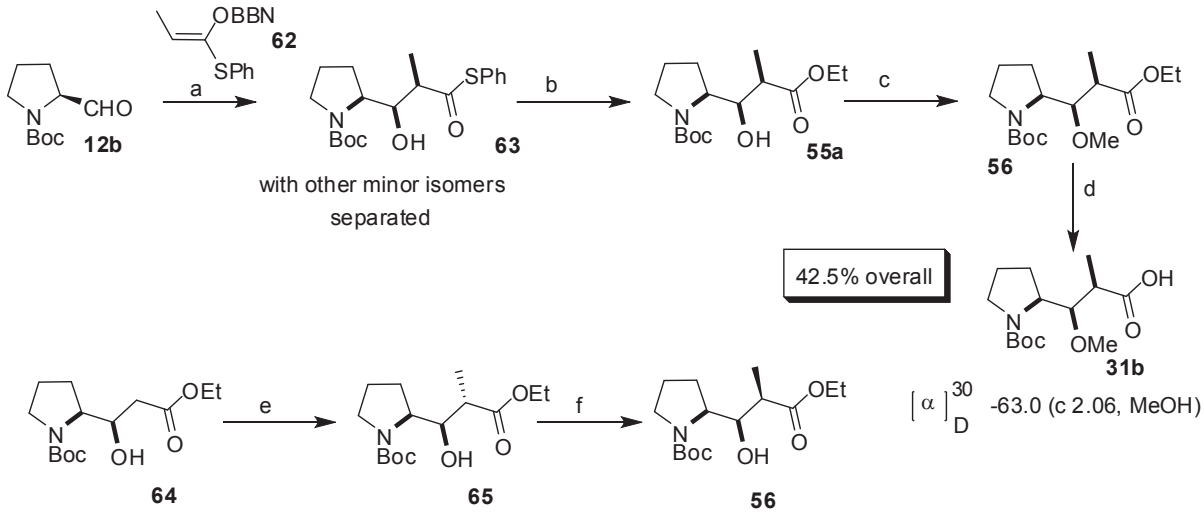
The work done by Poncet and co-workers involves the addition of crotyl boronate **61** to Boc-prolinal **12b** giving all the possible four isomers **57** with the requisite **57a** as a major isomer.[28] The configuration of each isomer was determined by different experimentation. The compound **57a** on methylation and subsequent oxidation using RuO_4 afforded Boc-dap **31b** unit (scheme 16).

A notable aldol condensation carried out by Koga and co-workers of boron enolate of thiophenyl propionate **62** with Boc prolinal **12b** afforded **63** as a major isomer along with other minor isomers (scheme 17).[29] The compound **63** was then dethionated and esterified to give **55a** which on subsequent methylation and ester hydrolysis gave Boc-dap **31b**. The configuration of **56** was confirmed by preparing it from the known ester **64**.



Scheme 16

Reagents and conditions: (a) MeNHOMe.HCl, BOP, DIEA, DCM, 82%; (b) LAH, THF, 89%; (c) **61**, THF, 64%; (d) NaH, MeI, DMF, 90%; (e) RuO_4, CCl_4, CH_3CN, H_2O, 81%.



Scheme 17

Reagents and conditions: (a) **62**, Et_2O, -20 °C, 64%; (b) K_2CO_3, EtOH, 88%; (c) LHMDS, MeOTf, HMPA-THF, 83%; (d) LiOH, aq. EtOH, 91%; (e) LDA, MeI, HMPA-THF, -78 °C to -20 °C, 2.5 h, 77%; (f) (i) LDA, THF, -20 °C, 1 h; (ii) MeOH, -78 °C (two steps 30%).

3. Synthesis of pyrrolizidine alkaloids

3.1 Introduction

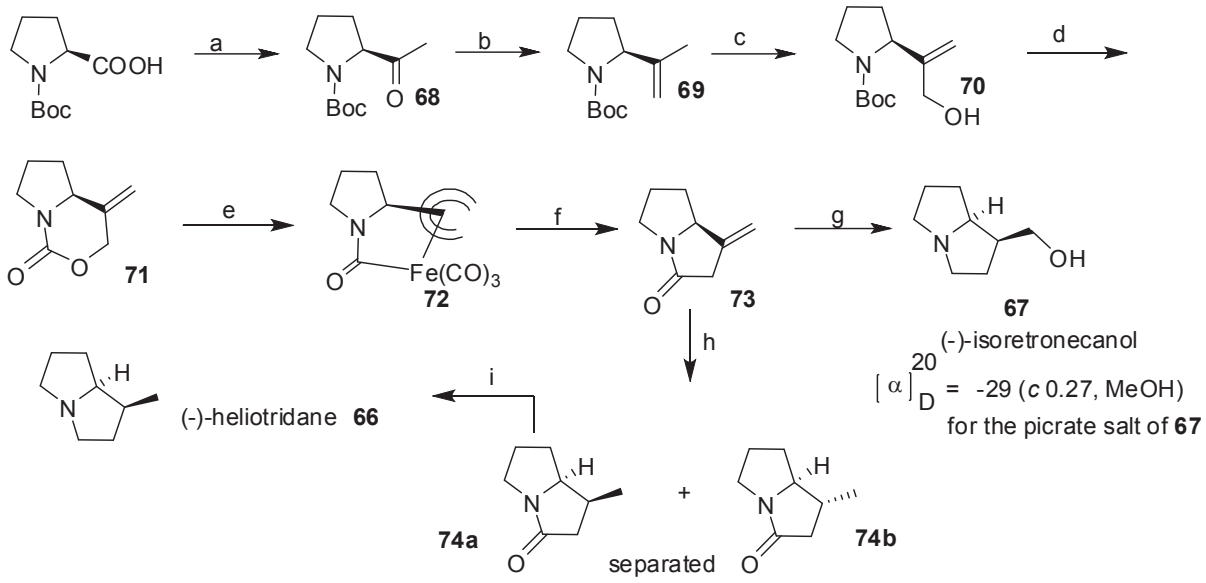
Pyrrolizidine alkaloids (PAs) bearing an azabicyclic [3, 3, 0] octane structural motif, are a large family of natural products endowed with vast array of pharmacological and biological properties.[30] These alkaloids are generally isolated from flowering and leguminous plants while few have been found in frogs, moths, ants and butterflies.[31] The vast range of alkaloids ranging from simple to highly substituted have been found in the nature. Manifolds of polyhydroxy PAs are used as potential sugar mimics and have been extensively studied for their potent glycosidase inhibitory activities, making them good candidates as new drugs for the treatment of several diseases like cancer, viral infections and diabetes.[32] Proline can attribute to the synthesis of PAs with a suitable transformation on 2nd position and subsequent 5 member cyclisation with the amino group.

3.2 Simple substituted pyrrolizidines

The synthesis of methyl substituted pyrrolizidine alkaloids (-)-heliotridane **66** and (-)-isoretronecanol **67** was successfully accomplished by Knight and Ley using commercially available (*S*)-*N*-Boc proline (scheme 18).[33] The Boc-proline was converted to the keto compound **68** through the formation of Weinreb amide followed by Grignard reaction with MeMgI. The keto compound **68** on Wittig reaction with CH_2=PPh_3 afforded the alkenated product **69**. The hydroxyl product **70** was prepared by SeO_2 oxidation of **69** which on subsequent Boc deprotection of NH and reaction with CH_3COCl produced the cyclic compound **71.** The key intermediate **73** was synthesized by converting **71** to л-allyltricarbonyliron lactam complex **72** by reacting with diiron nonacarbonyl in benzene under ultrasonication followed by the exhaustive carbonylation under high pressure. The (-)-isoretronecanol **67** was synthesized from **73** by reduction of amide and hydroxylation of alkene using borane. The intermediate **73** was hydrogenated to produce the separable diastereomers **74a** and **74b** from which **73a** upon LAH reduction afforded the natural product (-)-heliotridane **66**.

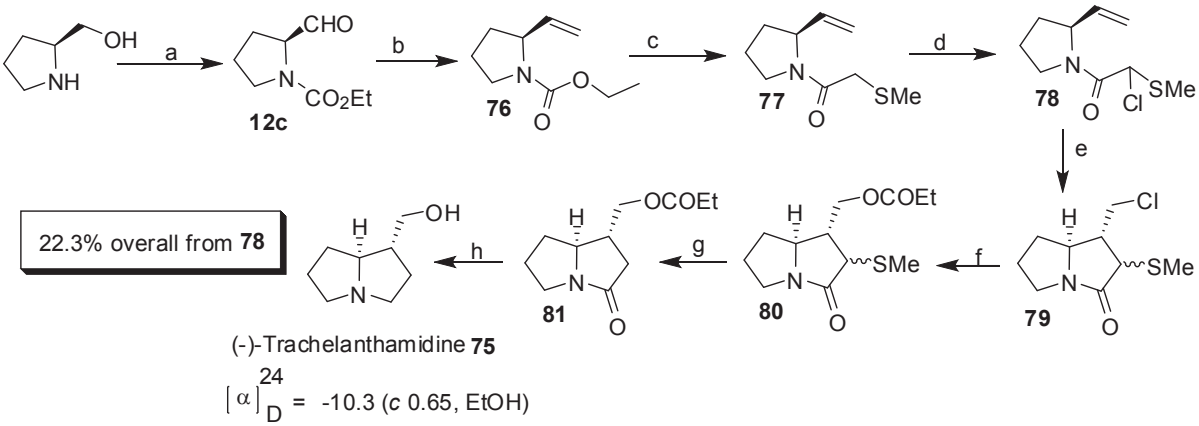
Synthesis of (-)-trachelanthamidine **75** was achieved by Ishibashi *et al* via ruthenium catalyzed chlorine atom transfer cyclization using proline as a chiral source (scheme 19).[34] The aldehyde **12c** prepared from prolinol was subjected to Wittig olefination to afford

alkene **76**. The NH group was deprotected and further protected with methyl thio acetyl chloride to give **77**. The regioselective chlorination of **77** was accomplished using NCS to provide **78** which on cyclisation performed using $RuCl_2(PPh_3)_3$ by heating at 140 ºC in benzene solution in a sealed tube afforded the bicyclic lactams **79** after removing the minor isomers by column purification. The compound **79** was subjected to nuecleophilic substitution of Cl by CsOCOEt to give **80** which underwent desulfurization on treatment with Raney Nickel to render **81**. The LAH reduction of lactam **81** afforded the natural product (-)-trachelanthamidine **75**.



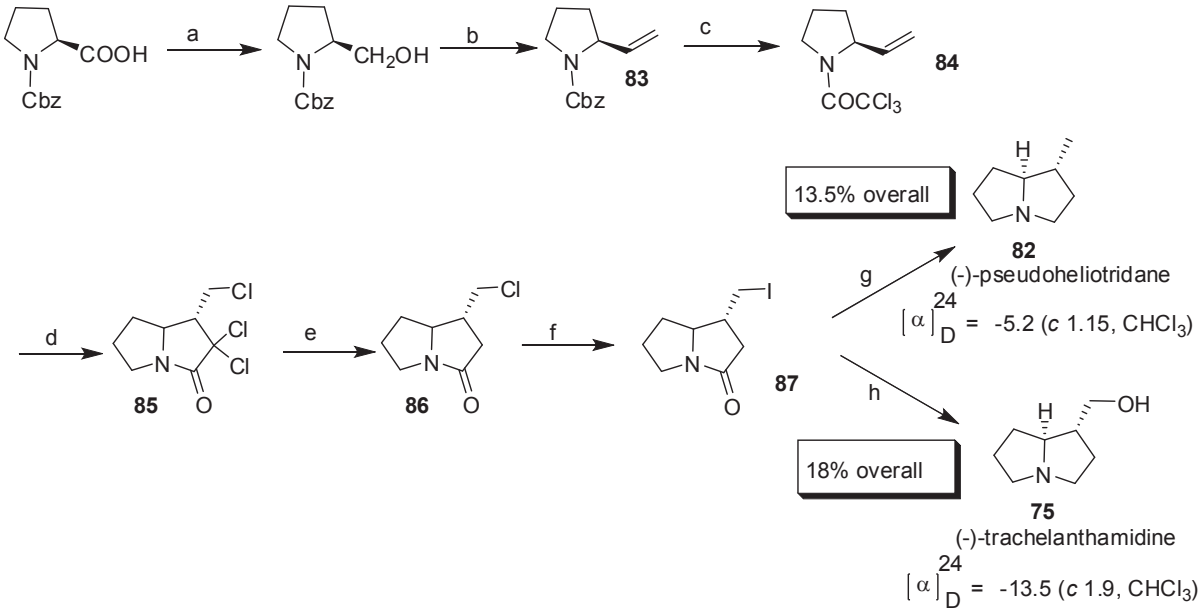
Scheme 18

Reagents and conditions: (a) (i) CDI, THF, rt, 1 h; (MeO)MeNH.HCl, 24 h, 98%; (ii) MeMgCl (3.0 equiv.), THF, 0 ºC- rt, 16 h, 91%; (b) $Ph_3P{=}CH_2$ (2.0 equiv.), Et_2O, 0 ºC, 2 h, 98%; (c) (i) SeO_2, *t*-BuOOH, DCM, 35 ºC, 4 h, 58%; (d) (i) HCl, $CHCl_3$, rt, 15 min, 100%; (ii) MeOCOCl, Et_3N, DCM, rt, 4 h; NaH, PhMe, rt, 2 h, 60%; (e) $Fe_2(CO)_9$, benzene, sonication, 4 h, 98%; (f) CO (305 atm), benzene, 105 ºC, 48 h, 80%; (g) BH_3.THF, reflux, 1.5 h; NaOH, H_2O_2, 1 h; HCl, MeOH, reflux, 2 h ; (h) H_2, 10% Pd/C, EtOAc, rt, 16 h, 73%; (i) LAH.



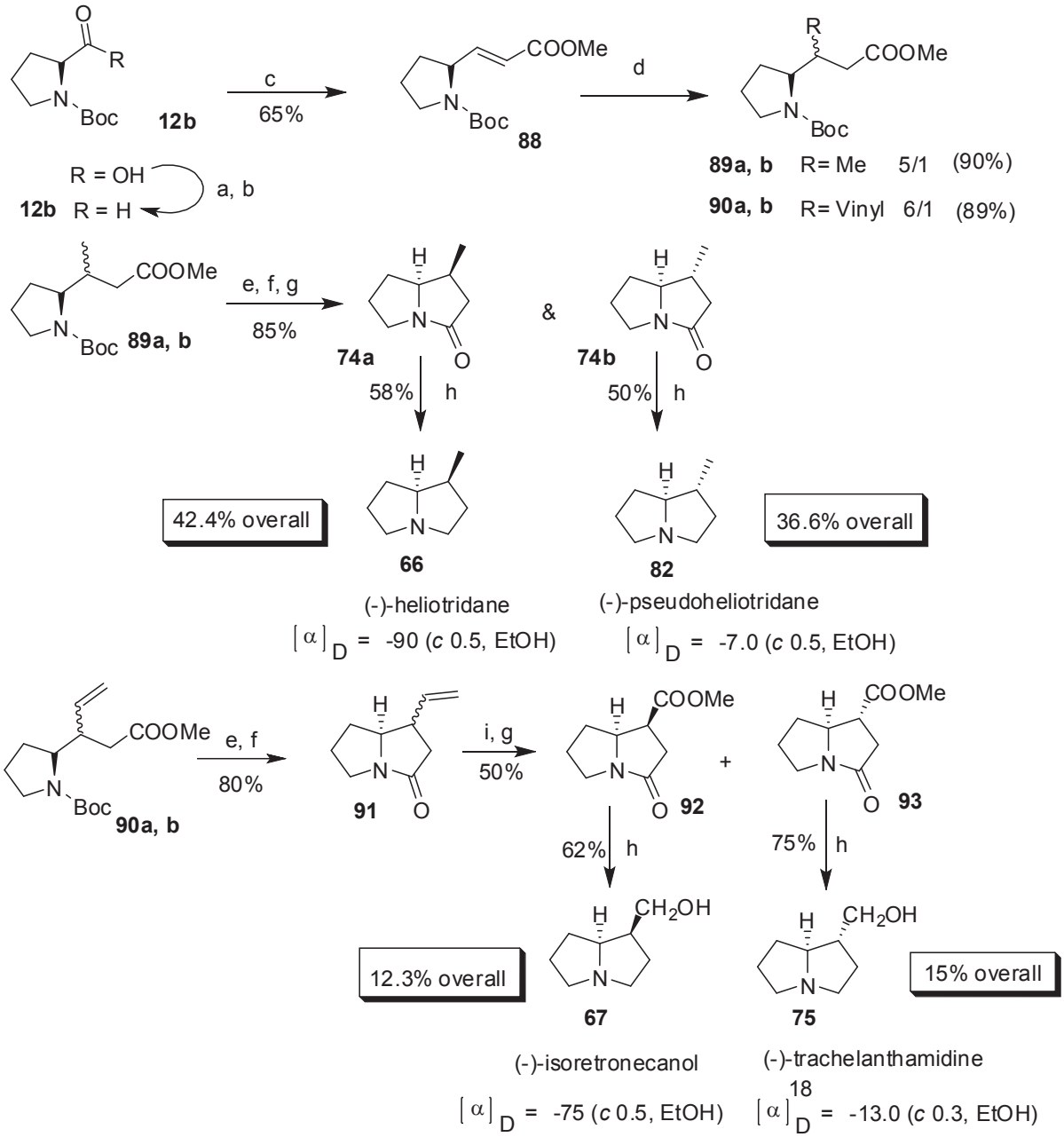
Scheme 19

Reagents and conditions : (a) a-d ref [35]; (e) $RuCl_2(PPh_3)_3$, 140 ºC (sealed tube), 59%; (f) CsOCOEt, DMF, 80 ºC, 1 h, 50%; (g) Raney Nickel, EtOH, reflux, 2.5 h, 86%; (h) LAH, THF, reflux, 5 h, 88%.



Scheme 20

Reagents and conditions : (a) (i) Et_3N, ClCOOEt; (ii) $NaBH_4$ (78% for two steps); (b) (i) Swern, 98%; (ii) $PPh_3{=}CH_2$, 51%; (c) (i) HBr, AcOH; (ii) Cl_3CCOCl, DMAP (82% for two steps); (d) CuCl, CH_3CN, 150 ºC, 93%; (e) H_2, Pd/C, 96%; (f) NaI, 81%; (g) (i) H_2, Pd/C, Et_3N, 86%; (ii) LAH, THF, reflux (Ref 36) 68%; (h) (i) AgOAc; (ii) LAH (Ref 37) (77% for two steps).



Scheme 21

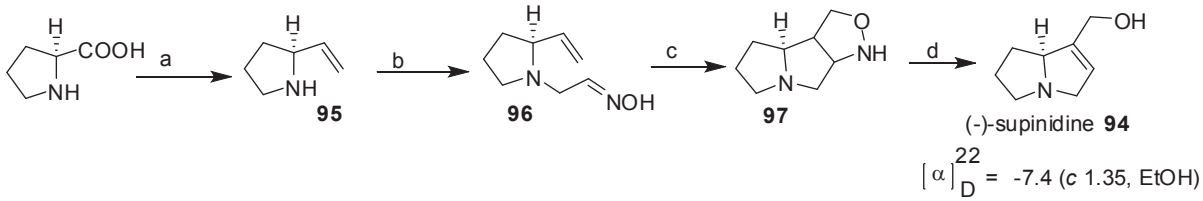
Reagents and conditions : (a) TEA, pivaloyl chloride, Me(NH)(OMe), 89%; (b) LAH, 0 ºC, 96%; (c) PPh_3=CH_2COOMe, THF, rt; (d) R_2CuLi, TMSCl, -30 ºC; (e) HCl, AcOH; (f) pyridine, DMAP, reflux; (g) Flash chromatography; (h) LAH, reflux; (i) Ref [37].

Seijas *et al* described the synthesis of (-)-pseudoheliotridane **82** and (-)-trachelanthamidine **75**, using radical cyclization (scheme 20).[38] The strategy utilized Cbz protected prolinol, prepared by reacting Cbz-proline with ClCOOEt with concomitant reduction using $NaBH_4$.

It was oxidised and further converted to alkene **83** using Wittig olefination with $PPh_3=CH_2$. The Cbz group was hydrogenolysed and protected with Cl_3CCOCl to afford **84**. The earlier Cbz protection was necessary since Cl_3CCOCl group was labile under $NaBH_4$ condition. The radical cyclization of chorocompound **84** took place by refluxing with CuCN in CH_3CN in a sealed tube. The reaction was highly diastereoselective affording only **85** due to stearic hindrance of the pyrrolidine nucleus. The trichloro compound **85** was further converted to monochloro compound **86** under catalytic hydrogenation condition. The nucleophilic substitution of Cl of **86** by I furnished **87** which could conveniently be transformed to the aforementioned natural products.

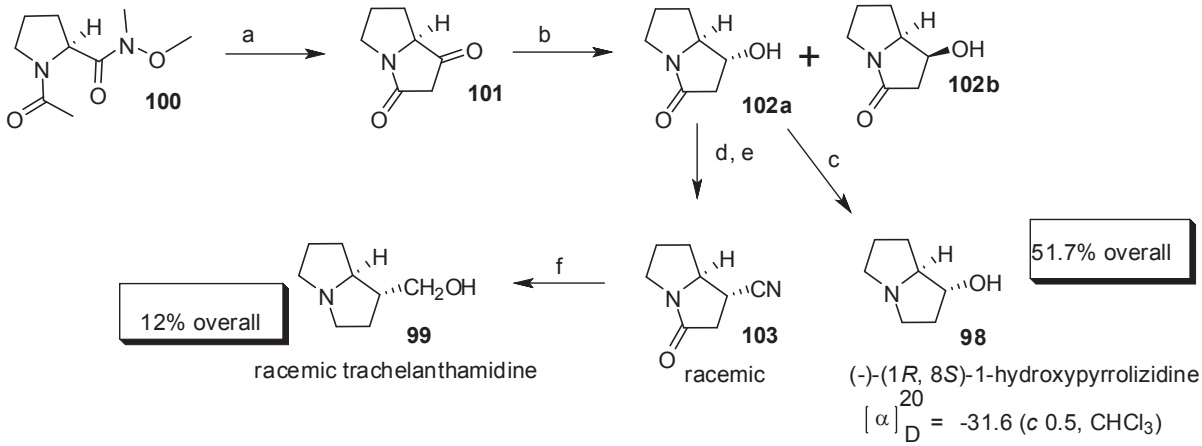
Taddei and co-workers disclosed the synthesis of (-)-heliotridane **159**, (-)-pseudoheliotridane **175**, (-)-isoretronecanol **160** and (-)-trachelanthamidine **168** through diastereoselective Michael addition of alkyl cuprate to γ-aminocunjugated alkene (scheme 21).[39] The synthetic strategy utilized the conversion of (*S*)-Boc-proline to aldehyde **12b** through the formation of Wienreb amide followed by LAH reduction. The olefinic compound **88** prepared by Wittig olefination was subjected to Michael addition with methyl cuprate and vinyl cuprate to afford the diastereomeric mixture **89** and **90** respectively. The mixture **89** was subjected to cyclization to give lactams **74a** and **74b** which were separable by flash chromatography. The synthesis of (-)-heliotridane **66** and (-)-pseudoheliotridane **82** was then furnished by LAH reduction of the lactams **74a** and **74b** respectively. Similarly the vinylated compound **90** was transformed to diastereomeric mixture **91** which was further converted to cyclic esters **92** and **93**. The compounds **92** and **93** were then reduced to the natural products (-)-isoretronecanol **67** and (-)-trachelanthamidine **75** respectively, using LAH.

Hassner *et al* achieved the synthesis (-)-supinidine **94** by applying intramolecular oxime-olefin cycloaddition (scheme 22).[40] The unstable vinyl compound **95** prepared from proline was converted to oxime **96** which on heating at 180 °C afforded the cyclic product **97** along with some by-products. The compound **97** on reductive cleavage with LAH followed by diazotisation afforded the natural product (-)-supinidine **94**.



Scheme 22

Reagents and conditions : (a) & (b) Ref [41]; (c) 180 ºC, 15 h, 56%; (d) (i) LAH, 87%; (ii) 2N HCl, $NaNO_2$, 0 ºC, 53%;

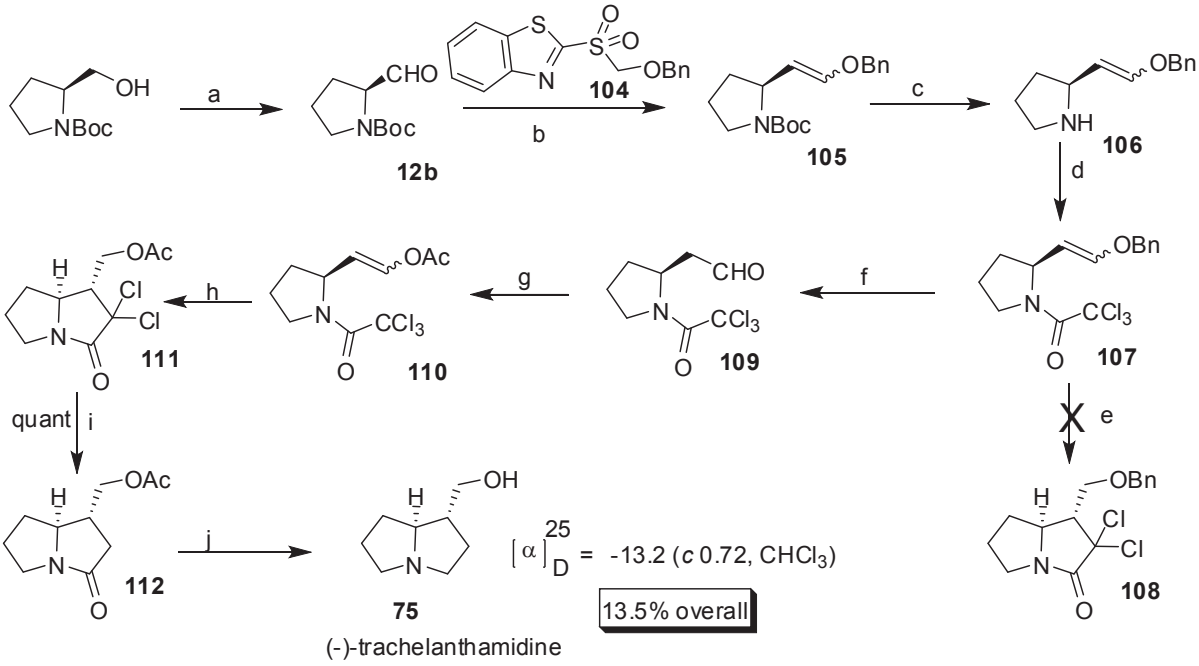


Scheme 23

Reagents and conditions : (a) LDA, THF, -78 ºC; (b) $NaBH_4$, EtOH, rt, 24 h; (39-69% for two steps); (c) LAH, THF, reflux, 75%; (d) MsCl, Et_3N, DCM, 0 ºC-rt, 5 h, 85%; (e) NaCN, DMSO, 90 ºC, 3 h, 50%; (f) (i) HCl (gaseous), MeOH, 0 ºC, 24 h, 55%; (ii) LAH, THF, reflux, 18 h, 64%.

Murray and Proctor continued their well developed strategy, *N*-acyl anion cyclisation for the synthesis of some of the naturally occurring pyrrolizidines like (-)-(1*R*, 8*S*)-1-hydroxypyrrolizidine **98** and (±)-trachelanthamidine **99** (scheme 23).[42] The successful *N*-acyl anion cyclisation was ventured with optimal use of either LDA or LHMDS at -78 ºC on *N*-methoxy-*N*-methyl amide **100** prepared from L-proline to afford **101** with a very slight racemisation. The reduction of **101** with $NaBH_4$ afforded the mixture of diastereomers **102a** and **102b**. The synthesis of (-)-(1*R*, 8*S*)-1-hydroxypyrrolizidine **98** was achieved by direct LAH reduction of **102a**. The major isomer **102a** was then mesylated and further treated with NaCN to afford cyano compound **103**, but surprisingly with a

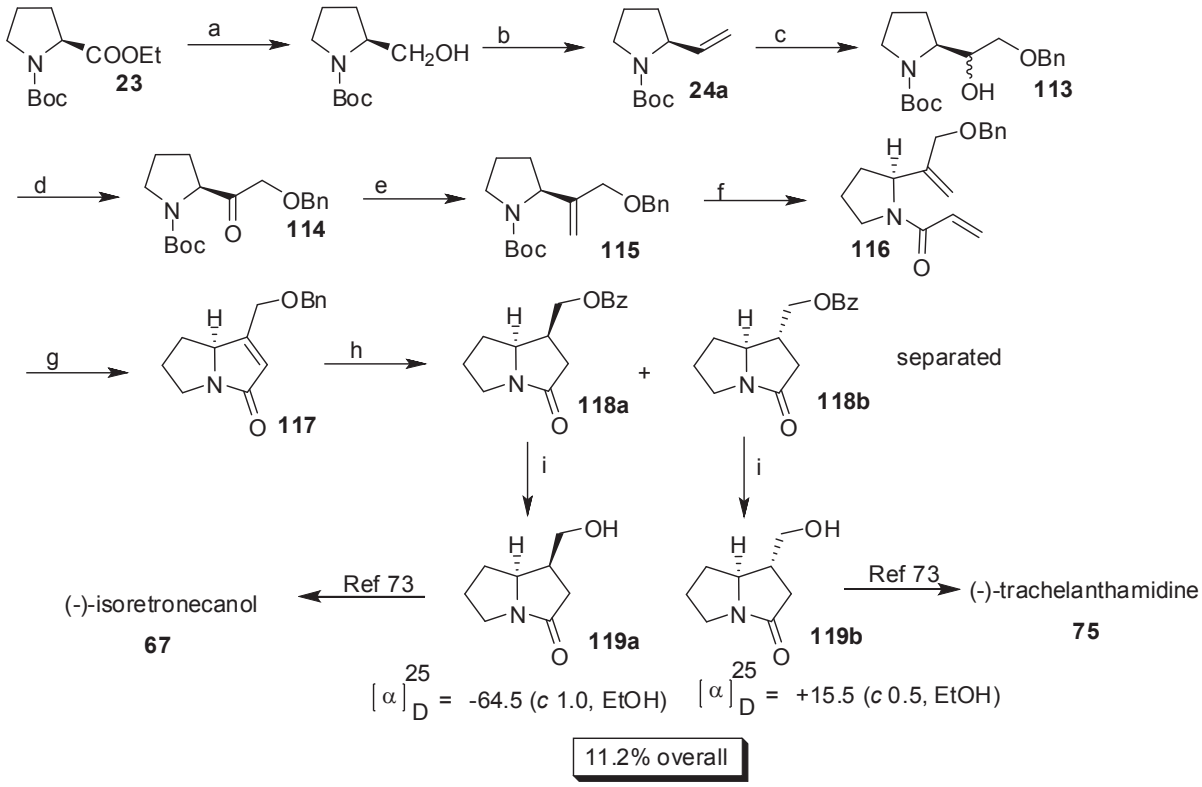
complete loss of enantiomeric purity. The compound (±)-trachelanthamidine **99** was then prepared on methanolysis of **103** followed by LAH reduction.



Scheme 24

Reagents and conditions : (a) Swern oxidation; (b) **104**, LiHMDS, THF, 0 ºC, 65%; (c) TMSOTf, 2, 6-lutidine, DCM, 0 ºC, 92%; (d) CCl_3COCl, Et_3N, DCM, 0 ºC, 95%; (e) 1, 4-dimethylpiperazine, reflux; (f) 1% HCl, THF, rt, 96%; (g) Ac_2O, KOAc, Et_3N, 120 ºC, 59%; (h) 1, 4-dimethylpiperazine, reflux, 52%; (i) H_2, Pd/C, NaOAc, EtOH, rt, quant; (j) LAH, THF, reflux, 86%.

With continuing interest in radical cyclization and its applications to pyrrolizidines, Ishibashi *et al* recently reported the synthesis of (-)-trachelanthamidine **75** through their well developed single electron transfer strategy (scheme 24).[43] The requisite alkene **105** was prepared by Julia olefination of Boc-prolinal **12b** with α-benzyloxy sulfone **104** which on deprotection of the Boc group afforded **106**. The compound **106** on trichloroacetylation gave **107** which was subjected to cyclisation by refluxing with 1, 4-dimethylpiperazine. The surprising failure of the method in giving the product **108** turned the attention to prepare **110** through the formation of aldehyde **109**. The compound **110** underwent expected cyclisation affording the product **111** which on dechlorination gave the product **112**. The targeted compound (-)-trachelanthamidine **75** was achieved by direct LAH reduction of **112**.

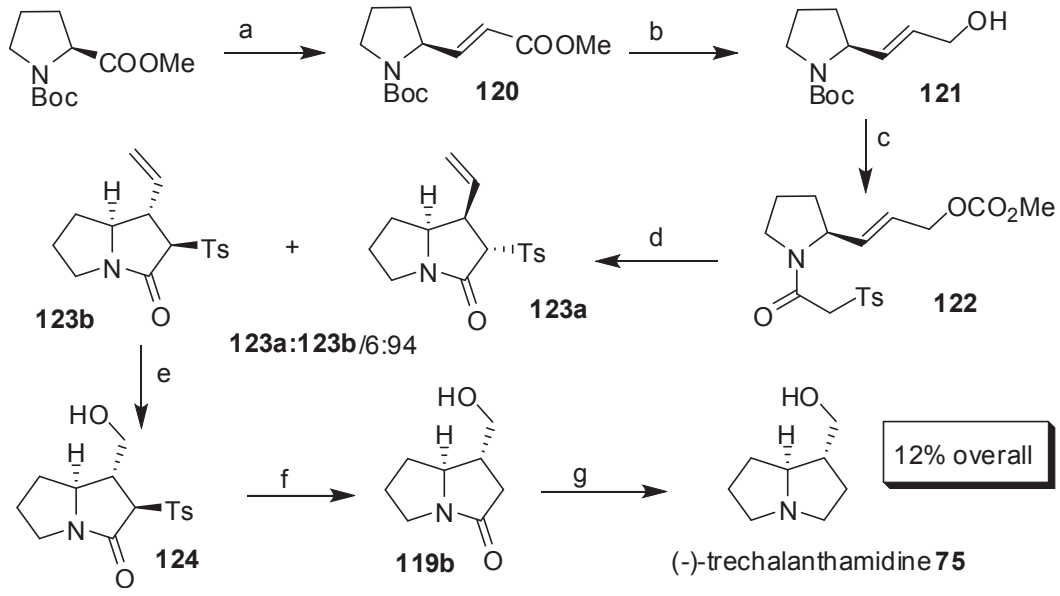


Scheme 25

Reagents and conditions : (a) $LiAlH_4$, THF, 0 ºC to rt, 1 h, 95%; (b) (i) DMSO, $(COCl)_2$, Et_3N, DCM, -78 ºC, 1 h; (ii) $Ph_3P{=}CH_2$, THF, -10 ºC, 3 h (69% for two steps); (c) (i) OsO_4, NMO, monohydrate, acetone/H_2O (3:1), 0 ºC to rt, 6 h, 89%; (ii) Bu_2SnO, toluene, reflux, 8 h, (iii) BnBr, TBAI, reflux, 16 h, (88% for two steps); (d) TEMPO, NaBr, NaOCl, $NaHCO_3$, toluene/EtOAc/H_2O (3:3:1) 0 ºC, 1 h, 91%; (e) $Ph_3P{=}CH_2$, THF, -10ºC, 4 h, 61%; (f) (i) TFA/DCM (1:1), Et_3N, 0 ºC, 1 h; 99%; (ii) acryloyl chloride, Et_3N, cat DMAP, DCM, 0 ºC, 3 h, 65%; (g) 10 mol % Grubbś 2nd generation catalyst, benzene, 90 ºC, 36 h, 76%; based on the recovery of starting material (h) (i) H_2, Pd/C, MeOH, rt, 2 h, 95%, (ii) benzoyl chloride, Et_3N, cat DMAP, DCM, 0 ºC, 2 h, 95%; (i) K_2CO_3, MeOH, rt, 2 h, 90%.

Reddy *et al* succeeded in the formal synthesis of (-)-isoretronecanol **67** and (-)-trachelanthamidine **75** starting from proline using ring closing metathesis (scheme 25).[44] The alkene **24a** was prepared according to the well developed procedure from ethyl ester of Boc-proline **23** which on dihydroxylation followed by the protection of terminal –OH afforded **113**. The compound **113** was oxidised to ketone **114** and subjected to Wittig olefination to give **115**. The deprotection of the Boc group followed by reaction with acryloyl group afforded the ready intermediate **116** for RCM. The RCM of **116** using Grubbś second generation catalyst gave compound **117** which on hydrogenation followed

by benzoylation afforded a separable mixture of **118a** and **118b**. The deprotection of benzoyl group of **118a** and **118b** gave **119a** and **119b** respectively which constituted the formal synthesis[45] of (-)-isoretronecanol **67** and (-)-trachelanthamidine **75**.

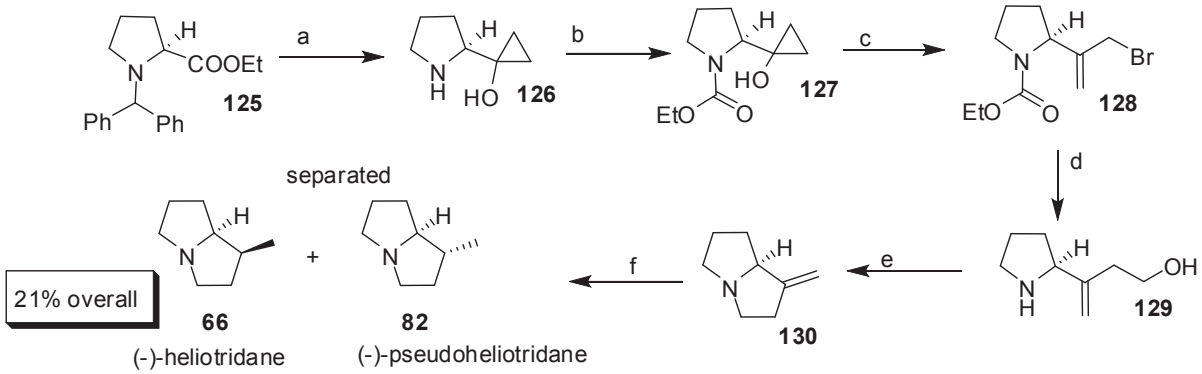


Scheme 26

Reagents and conditions : (a) (i) DIBAL-H (1.2 equiv.), PhMe, –78 °C, 3.5 h; (ii) $Ph_3P{=}CHCO_2Et$ (2.0 equiv.), DCM, rt, 12 h, (72% 2 steps); (b) DIBAL-H (3.0 equiv.), $BF_3{\cdot}OEt_2$ (1.0 equiv.), DCM, –78 °C to 0 °C, 3 h, 72%; (c) (i) TFA (50 equiv.), DCM, rt, 30 min; (ii) $TsCH_2CO_2H$ (1 equiv.), PyBOP (1 equiv.), Hünigs base (5.5 equiv.), DCM, rt, 12 h; (iii) methyl chloroformate (2.0 equiv.), pyridine (2.0 equiv.), DMAP (cat.), DCM, 12 h, (53% for 3 steps); (d) $Pd(dba)_3$ (5 mol%), $P(O\textit{i}\text{-}Pr)_3$ (0.5 equiv.), MeCN, 12 h, rt, 72%; (e) O_3 (g), DCM, –78 °C, 1 h; (ii) DMS (4.0 equiv.), r.t., 12 h; (iii) $NaBH_4$ (4.0 equiv.), EtOH–H_2O, rt, 1 h, 82%; (f) 6% Na(Hg) (6.0 equiv.), MeOH, –15 °C, 1 h, 75%; (g) $LiAlH_4$ (2.1 equiv.), THF, reflux, 12 h, 99%.

Craig and co workers successfully synthesized (-)-trachelanthamidine **75** using Pd catalysed intramolecular cyclisation (scheme 26).[46] The methyl ester of Boc proline was converted to allyl alcohol **121** by DIBAL reduction with subsequent Wittig reaction. After several experimentations the ester **122** was subjected to Pd catalysed cyclisation successfully delivering the products **123** with **123b** as the major isomer after purification. The olefin **123b** was transformed to **124** by reductive ozonolysis which on subsequent detosylation uneventfully produced the lactam **119b** whose relative configurations were

assigned by X-ray crystallography. The LAH reduction of **119b** gave the natural product **75**.



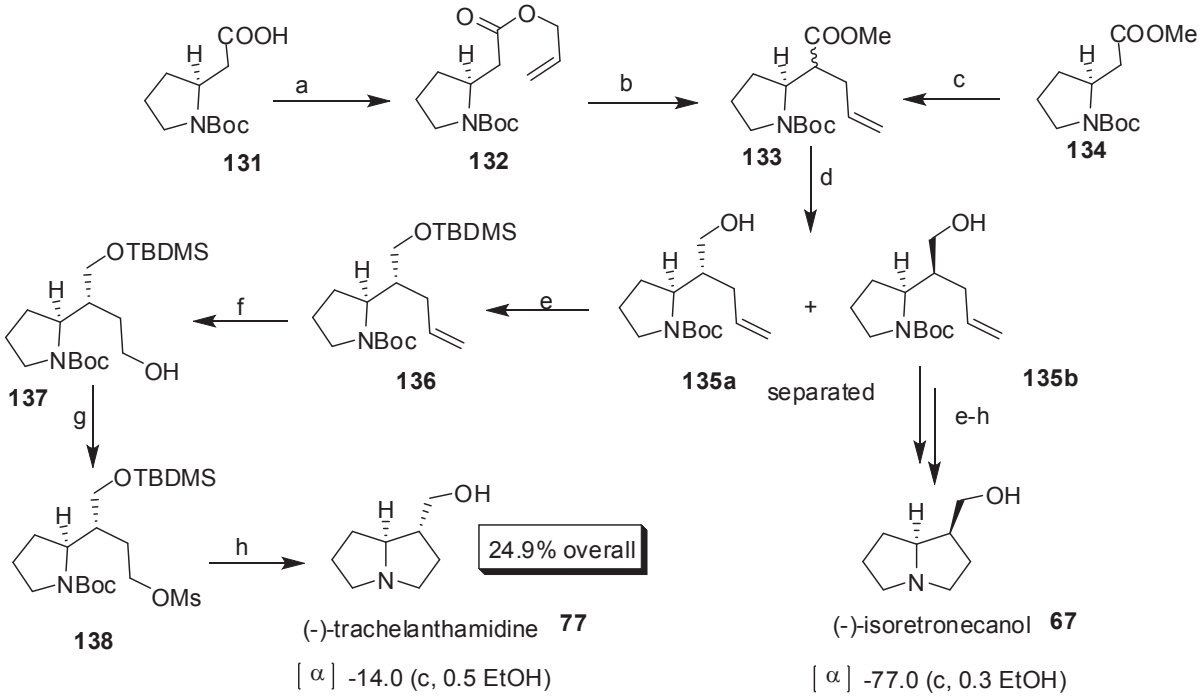
Scheme 27

Reagents and conditions : (a) 3.0 equiv. EtMgBr, 0.2 equiv. $Ti(OPr)_4$; (ii) H_2, $Pd(OH)_2$ /C (78% for two steps); (b) EtOCOCl, Et_3N, 77%; (c) (i) $MeSO_2Cl$, Et_3N; (ii) 3.0 equiv. $MgBr_2.Et_2O$; (88% for two steps); (d) (i) Zn, $(CH_2O)n$; (ii) KOH, H_2O (52% for two steps); (e) PPh_3, CCl_4, Et_3N, DMF, 80%; (f) $NaBH_4$-$NiCl_2$, MeOH, 95%;

Kulinkovich and Lysenko accomplished the synthesis of (-)-heliotridane **66** and (-)-pseudoheliotridane **82** using cyclopropanation of ester group using titanium mediated Grignard reaction (scheme 27).[47] The synthesis commenced with the cyclopropanation of proline ester **125** with $Ti(OPr)_4$ in the presence of 3.0 equiv. of Grignard reagent, followed by hydrogenolysis to afford **126**. After protecting the free NH with chloroformate, the compound **127** was subjected to mesylation in the presence of $MgBr_2$ to give **128**. The compound **128** on Reformatsky condenastaion with formaldehyde produced **129** which underwent cyclisation to afford **130** under Mitsunobu condition. The hydrogenation of **130** in the presence of $NiCl_2$ / $NaBH_4$ gave a mixture of **66** and **75** (11: 1) separable by column purification.

Knight and co-workers synthesized (-)-trachelanthamidine **75** and (-)-isoretronecanol **67** (scheme 28).[48] Claisen rearrangement of ester **132** prepared from Boc-homoproline **131** gave and inseparable diastereomeric mixture of **133**. The ester **133** was also visualized from Boc-homoproline methyl ester **134**. The DIBAL reduction of **133** gave a separable mixture of **135**. The less polar *erythro* isomer **135a** was successfully transformed to **77**

through classical synthetic sequences. In a similar way the more polar *threo* **135b** was converted to **67**.



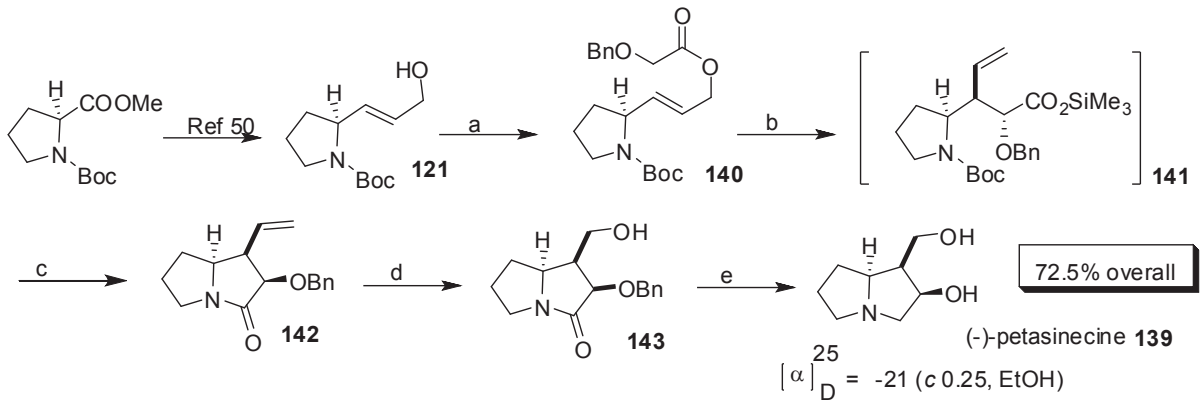
Scheme 28

Reagents and conditions: (a) DCC, DMAP, DCM, -20 °C, 16 h, 89%; (b) (i) LiHMDS, THF, -78 °C, 20 min, TMSI, 20 min, then +60 °C, 4 h; (ii) MeOH, H_2O, 20 °C, 0.5 h, then CH_2N_2, Et_2O, (78% two steps); (c) LHMDS, THF, 5.0 equiv., HMPA, -78 °C, 25 h, allyl bromide, -78 °C, 0.5 h, warmed to +20 °C, 1 h, 84%; (d) DIBAL, $BF_3.OEt_2$ (ref 2d); (e) TBDMSCl, 87%; (f) OsO_4, $NaIO_4$, $NaBH_4$, 77%; (g) MsCl, Et_3N, DCM, 0 °C, 1 h, 98%; (h) 20% TFA, DCM, 0.5 h, basified with NaOH, 65% .

3.3 Hydroxylated pyrrolizidines

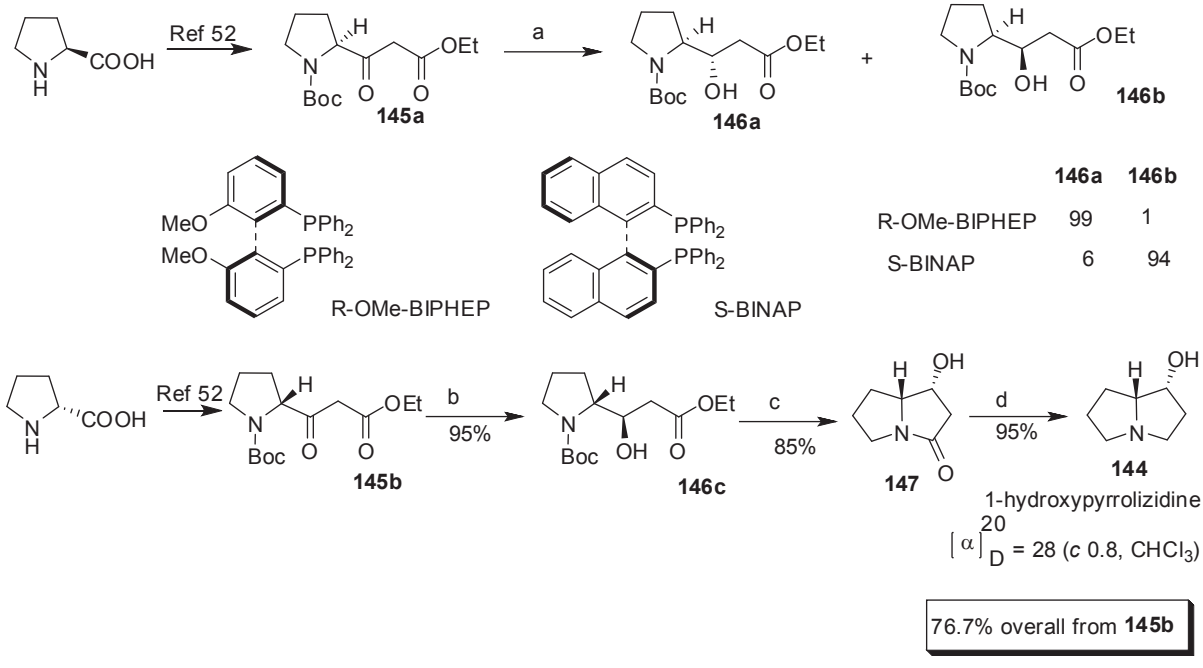
Shanyoor and Mulzer revealed a synthesis of (-)-petasinecine **139** through Ireland-Claisen type rearrangement (scheme 29).[49] Initially Boc-proline methyl ester was converted to allylic alcohol **121** by following a literature report.[50] The allyl ester **140** prepared by treatment of **121** with benzoxyacetoyl chloride was subjected to Claisen rearrangement using TMSCl and LiHMDS at -110 ºC to afford the compound **142** as the only diastereomer through the intermediacy of **141**. The reductive ozonolysis of **142** with

subsequent borane reduction followed by hydrogenolysis furnished the natural alkaloid **139**.



Scheme 29

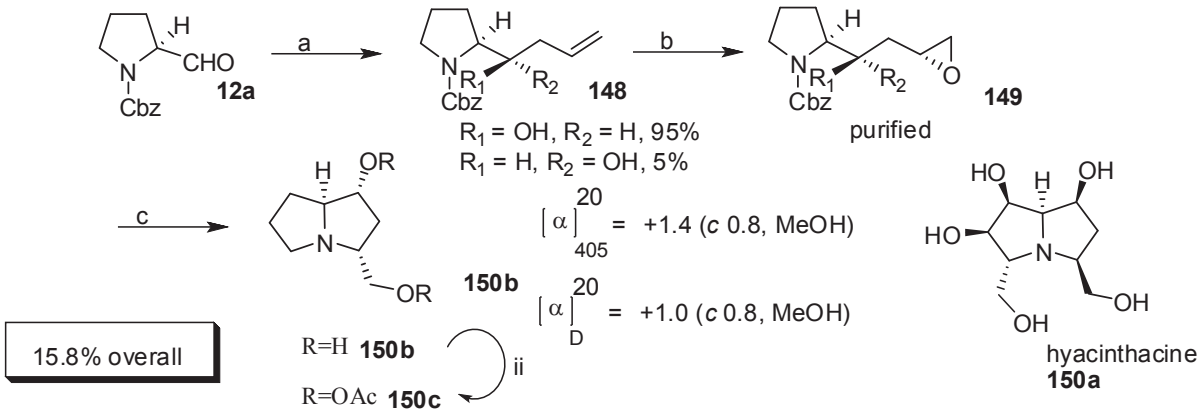
Reagents and conditions: (a) $BnOCH_2COCl$, Pyridine, rt, 5 h, 98%.; (b) LiHMDS / TMSCl / THF, -110 ºC, 2 h, then 5 h at 0 °C; (c) CF_3COOH, BuOH, -20 ºC, 1 h, rt, 16 h, 60 ºC, 48 h, 82%; (d) (i) O_3, MeOH, -78 ºC, 16 h, 92%; (ii) $NaBH_4$, MeOH, -78 ºC, 16 h, 92%; (d) (i) BH_3.THF, 60 ºC, 48 h; (ii) 10% Pd-C, H_2, MeOH, rt, 48 h, 98%;



Scheme 30

Reagents and conditions: (a) H_2, 1% Ru catalyst, ligands, 10bar, 50 ºC, MeOH, 24 h; (b) *in situ* $RuBr_2$(*S*) Binap,10 bar H_2, 50 °C, MeOH, 24 h, 95%; (c) TFA then K_2CO_3 EtOH/H_2O, 85%; (d) $LiAlH_4$, THF, reflux, 95%.

The naturally occurring alkaloid 1-hydroxyprrolizidine **144** was synthesized by Guerreiro *et al* using diastereofacial hydrogenation of carbonyls using chiral ligands (scheme 30).[51] The compounds **145a** and **145b** were synthesized from L-proline and R-proline respectively using the literature methods.[52] The reduction of the carbonyl with chiral ligands complexed with Ru (II) under hydrogenation displayed the concept of matched and mismatched pair. The selectivity was determined by two factors, the chirality of the proline moiety and the chirality of the ligand complexed with Ruthenium. Thus the ideal case for matched pair was when (*S*)-**145a** gave diastereoselectively **146a** with (*R*)-BINAPRu (II) and (*R*)-MeO-BIPHEPRu (II) while (*R*)-**145b** gave diastereoselectively **146c** with (*S*)-BINAPRu(II). The mismatching was observed for the opposite stereoisomers. The optically pure **147** was then subjected to Boc deprotection and subsequent intramolecular cyclization leading to the synthesis of optically pure 1-hydroxypyrrolizidine **144**.

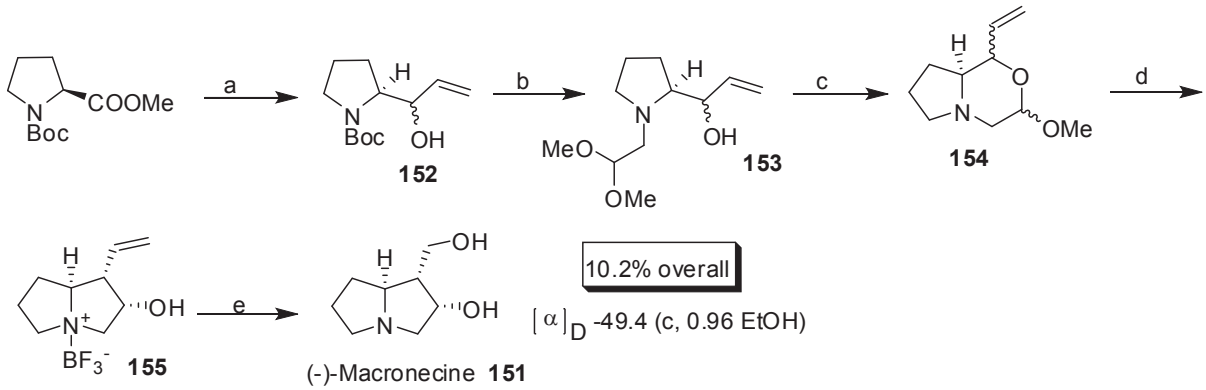


Scheme 31

Reagents and conditions: (a) CH_2=$CHCH_2InBr$, THF, -78 ºC, 78%; (b) MCPBA, DCM, rt, 75%; (c) (i) 10% Pd/C, H_2; (ii) Ac_2O, Pyridine, rt (27% two steps).

Synthesis of deoxy congener **150b** of the pyrrolizidine alkaloid hyacinthacine **150a** was achieved by Izquierdo *et al* via indium mediated diastereoselective addition of allyl indium bromide to Cbz-prolinal **12a** (scheme 31).[53] The compound **148** obtained was subjected to epoxidation using MCPBA to afford **149** whose structure was elucidated by different

spectroscopic techniques. Further, catalytic hydrogenolysis of Cbz gave the cyclised product **150b** which was isolated by acetylating with acetic anhydride as **150c** for the characterisation purpose.



Scheme 32

Reagents and conditions: (a) DIBAL (1.1 equiv., -78 °C/THF), then vinylmagnesium bromide, 83%; (b) (i) TFA, 91%; (ii) α-bromoacetaldehyde dimethyl acetal, *N, N*-diisopropylethylamine, CH_3CN reflux, 68%; (c) TsOH, benzene reflux, 58%; (d) 'Cp_2Zr"/THF, then $BF_3.OEt_2$, 57%; (e) (i) O_3, -78 °C, then $NaBH_4$, (ii) 10% NaOH, 60%.

Ito *et al* synthesized (-)-macronecine **151** during the synthetic invention of zirconium mediated diastereoselective ring contraction of vinyl morpholine derivatives prepared from amino acids.[54] The proline based morpholine derivative **154** prepared from Boc-proline was subjected to react with "Cp_2Zr" in the presence of $BF_3.OEt_2$ to afford pyrrolizidine-BF_3 complex **155** as a single diastereomer which on subsequent reductive ozonolysis and neutralisation gave **151** (scheme 32).

4.0 Synthesis of indolizidine alkaloids

4.1 Introduction

Indolizidine alkaloids are comprised of [4. 3. 0] azabicyclic nonane core, present in the numerous bioactive natural and unnatural scaffolds.[55] They are mainly isolated from skin secretions of amphibians.[56] It attracted synthetic chemists due to their potent biological and medicinal applications. The coniceine is the simplest indolizidine with unsubstituted 5-member and six member rings fused to each other. The indolizidine moieties even with

alkyl substituted at various positions exhibit unique character especially in blocking the neuromuscular transmission.[57] The polyhydroxy substituted indolizidines like swainsonine, castanospermine alkaloids have attracted the special interest for their anti HIV and anti cancer properties and also known for the best mimics of sugars to act as potential glycosidase inhibitors.[58] The formulation of indolizidine alkaloids can be achieved either by starting with a six member heterocycle and then annulating a five member on it or vice versa. The proline being a 5 member heterocycle can efficiently be used for the construction of indolizidines by appropriate manipulation of the side chain and wrapping up it to form a six member ring over it.

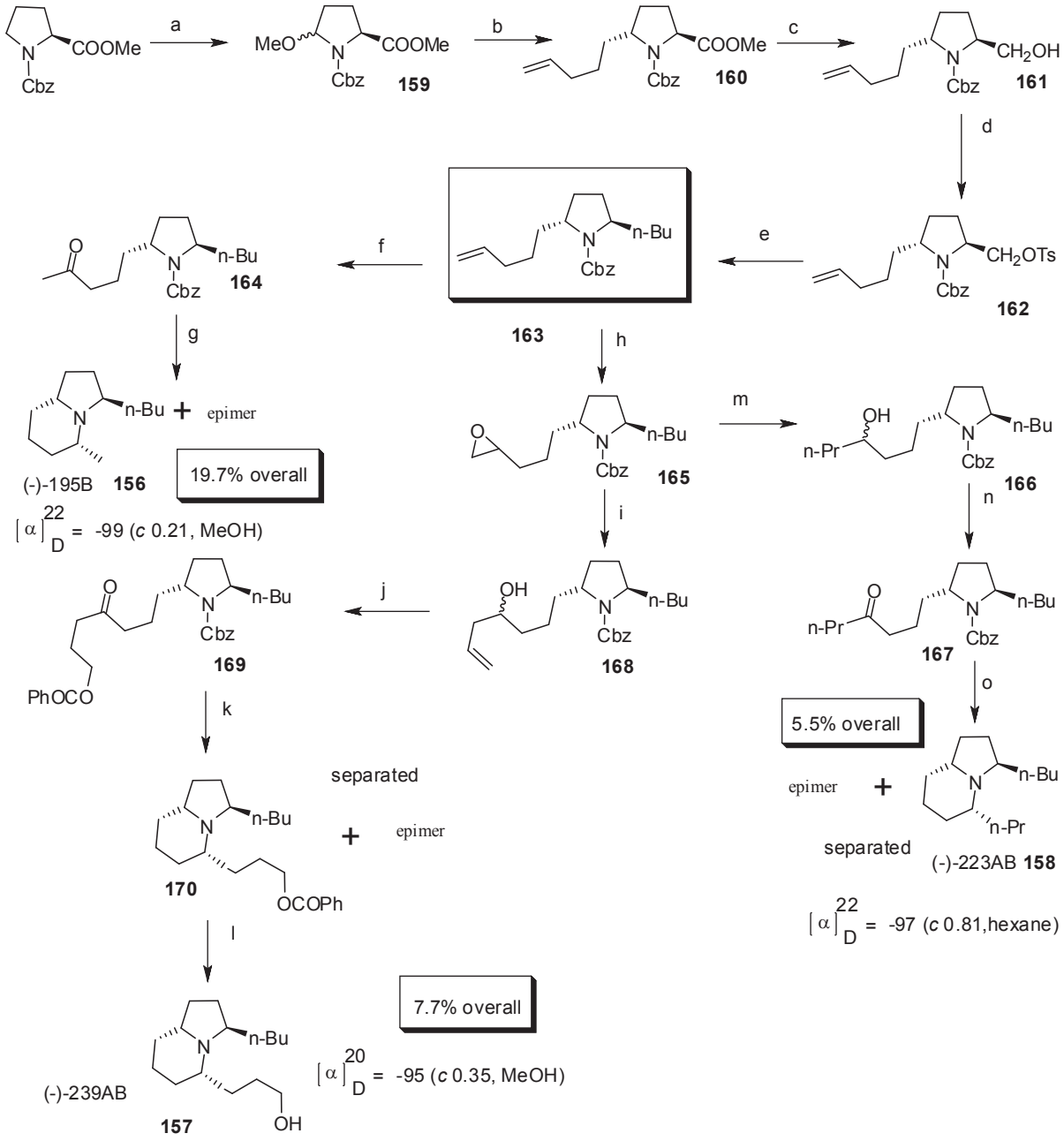
4.2 Simple substituted indolizidines

Lhommet and co-workers explored the synthesis of three different substituted indolizidine alkaloids namely, (-)-195B **156**, (-)-239AB **157**, (-)-223AB **158**, using proline as an original chiral source by synthesizing a versatile common intermediate **163** (scheme 33).[59] The pivotal steps involve the diastereoselective metal mediated coupling at the C-5 of the pyrrolidine and the reductive amination of the imine formed *in situ.* Initially the Cbz-proline ester was methoxylated at C-5 using anodic oxidation, a method developed by T. Shono,[60] to afford **159**. The compound **159** on BF_3 mediated coupling with pent-4-enylcopper succeeded with high diastereoselectivity to afford **160** (*trans: cis* / 96:4) which was subjected to chemoselective reduction to alcohol **161** to separate as a single isomer. The compound **161** was tosylated to **162** and further, the homologation was achieved by the nucleophilic displacement of OTs by reacting with excess of *n*-Pr_2CuLi to give the key building block **163**.

The synthesis of aforementioned indolizidines was achieved by a systematic transformation of the olefinic part of **163**.

The synthesis of **156** was furnished by Wacker oxidation of **163** followed by hydrogenolysis of Cbz group.

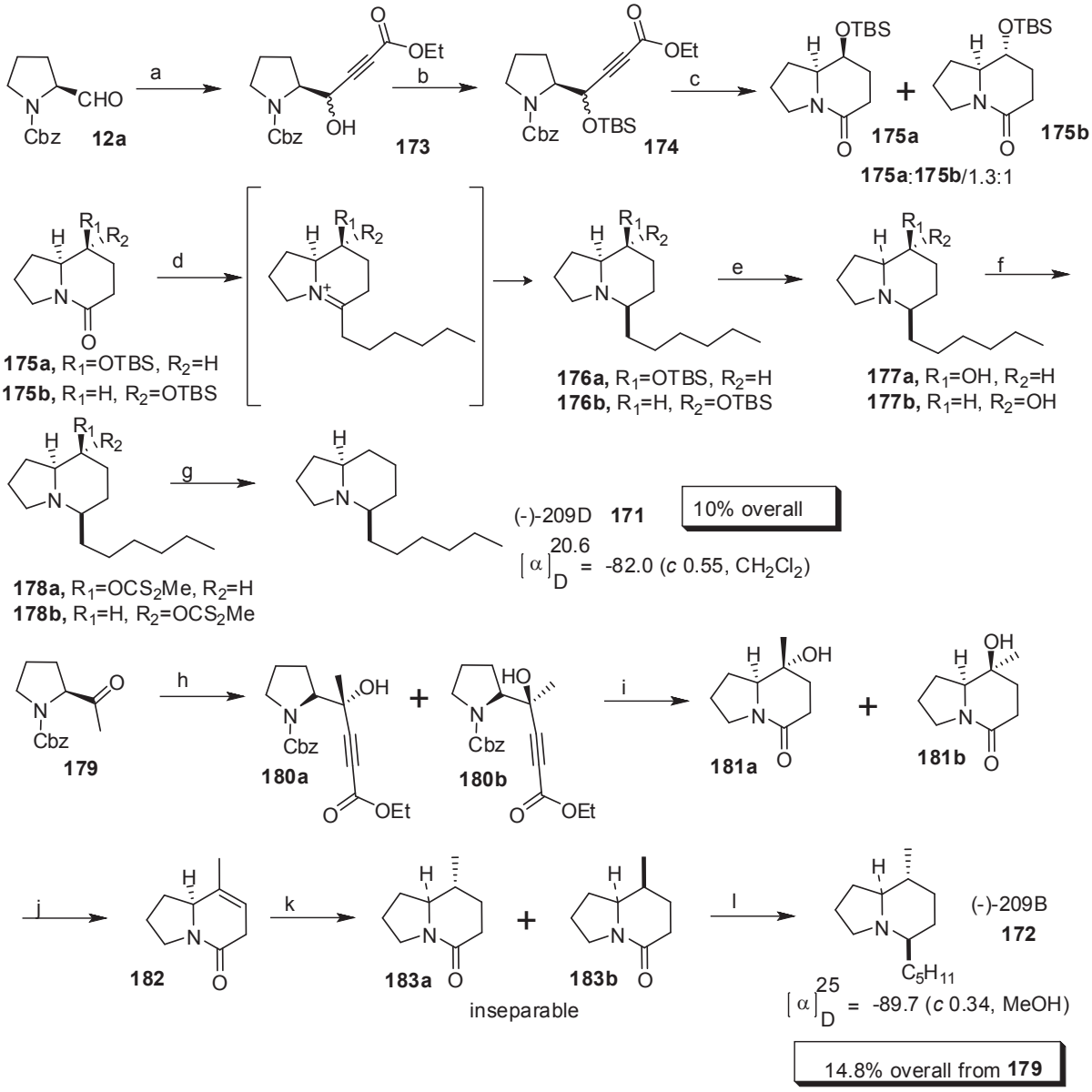
For the synthesis of **158** the olefinic part of **163** was epoxidised to **165** and further treated with excess Grignard reagent EtMgBr to give a diastereomeric mixture **166** which on



Scheme 33

Reagents and conditions *:* (a) electrolysis, -5 ºC, 75%; (b) CH_2=$CH(CH_2)_3Cu$, $BF_3.OEt_2$, -78 ºC to rt, 79.5%; (c) $NaBH_4$/ $CaCl_2$, THF/EtOH, -5 ºC, 73.6% for *trans* isomer separated; (d) TsCl, Et_3N, 96%; (e) nPr_2CuLi, Et_2O, -20 ºC, 75%; (f) O_2, $PdCl_2$, $Pd(PhCN)_2$, CuCl, H_2O-DMF (7:1), 60 ºC, 77%; (g) H_2 (1 atm), cat. Pd/C, MeOH, 81% after separation from epimer; (h) MCPBA, DCM, $NaHPO_4/NaH_2PO_4$ (pH=8), 69%; (i) CH_2=CHMgBr, (excess), CuI (0.05 eq), THF, -40 ºC to -20 ºC, 88%; (j) (i) BH_3.DMS then H_2O_2/NaOH, 82%; (ii) PhCOCl, pyridine, -40 ºC to rt, 18 h, 72%; (iii) PDC, DCM, 96%; (k) H_2, 10% Pd/C, MeOH, 82%

after separation from its epimer; (l) MeONa, MeOH, 86%; (m) EtMgBr (excess), CuI (0.1 eq), THF, -20 ºC, 73%; (n) PDC, DCM, 86%; (o) H_2, 10% Pd/C, MeOH, 40%.



Scheme 34

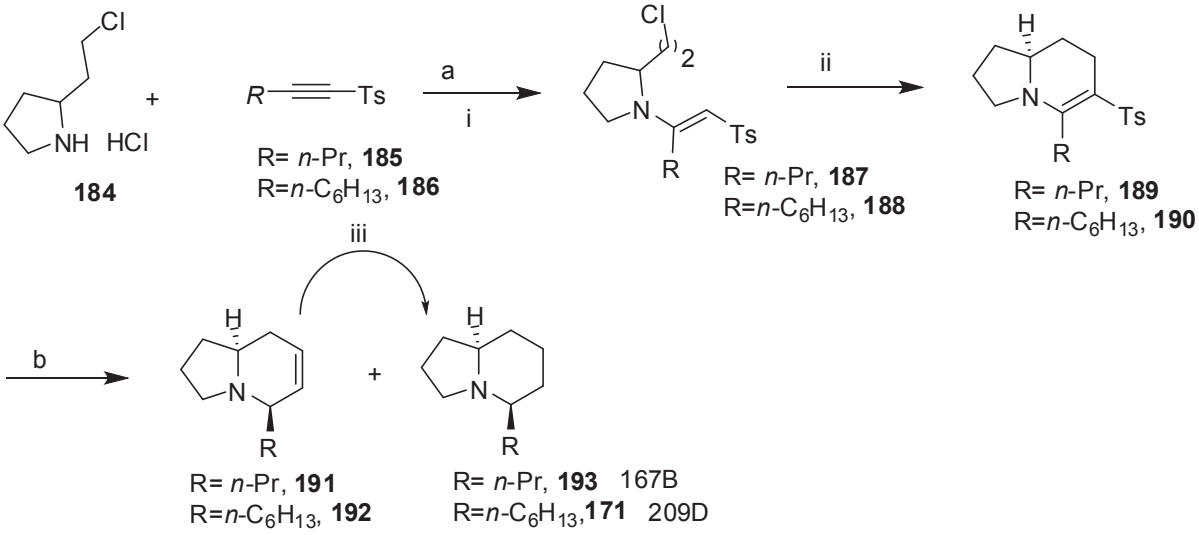
Reagents and conditions *:* (a) Ethyl propiolate, LiHMDS, THF, -78 ºC, 89%; (b) TBSCl, imidazole, DCM, rt, 24 h, 70.5%; (c) H_2, Pd/C, MeOH, 83%; (d) (i) $C_6H_{13}MgBr$; (ii) AcOH, $NaBH_4$, 63% for **176a**, 62% of **176b**; (e) 4 M HCl/MeOH, 50 °C, 92% for **177a**, 93% of **177b**; (f) NaH, CS_2, MeI, rt, 53% for **178a**, 55% for **178b**; (g) Bu_3SnH, AIBN, toluene, reflux, 60%; (h) ethyl propiolate, *n*-BuLi, THF, -78 ºC, 87%; (i) H_2, 10% Pd/C, MeOH, 77% of **181a**, 77% of **181b**; (j) $SOCl_2$, Et_3N, DCM, -78 ºC, 75%; (k) 506.625 kPa H_2, 10% Pd/C, MeOH, 70%; (l) (i) $C_5H_{11}MgBr$; (ii) AcOH, $NaBH_4$, 42% of **172** in two steps.

direct oxidation gave the compound **167**. The hydrogenolysis of **167** as earlier afforded the compound **158** along with its separable epimer.

For the synthesis of **157**, the epoxide **165** was treated with excess of vinyl magnesium bromide to afford a diastereomeric mixture **168**. The mixture **168** was as such oxidised followed by the hydroboration oxidation of the terminal double bond and protection as benzoyl group gave **169**. The compound **169** on hydrogenolysis and subsequent benzoyl deprotection of the resultant **170** provided the indolizdine **157**.

Gang and co-workers synthesized indolizidines (-)-209D **171** and 209B **172** (scheme 34).[61] The nucleophilic addition of ethylpropiolate anion to carbonyl of **12a** afforded a mixture of diastereomers **173** which on hydroxyl protection with TBSCl afforded **174**. The subsequent hydrogenation of **174** over Pd/C in MeOH contributed the deprotection of carbamate, reduction of triple bond and the cyclisation to lactam to take place in one pot affording a mixture of **175a** and **175b** in a ratio of 1.3:1, separated by column chromatography. The compound **175a** (**175b)** was then treated with $C_6H_{13}MgBr$ followed by iminium ion reduction afforded single isomer **176a** (**176b**), the stereochemical control was attributed to the less hindered α-H atom of pyrrolidine ring which favoured the formation of β-isomer. The TBS group of **176a** (**176b**) was deprotected in acid condition to afford **177a (177b)**. The successful synthesis of **171** was reached by converting the hydroxyl group of **177a** (**177b**) to thiocarbamate ester **178a** (**178b**) and then by deoxygenation with Bu_3SnH under Barton-McCombie deoxygenation conditions.

For the synthesis of indolizidine 209B **172**, the keto compound **179** was subjected to nucleophilic addition of lithiopropiolate-ion to afford a mixture of **180a** and **180b** (2.5:1) separable by column chromatography. The mixture **180** was subjected to hydrogenation furnishing **181a** and **181b** which was as such dehydrated to give the olefin **182**. The hydrogenation of **182** under high pressure afforded an inseparable mixture of **183a** and **183b** which upon addition of $C_5H_{11}MgBr$ followed by iminium ion reduction gave the pure indolizidine **172** after column purification.

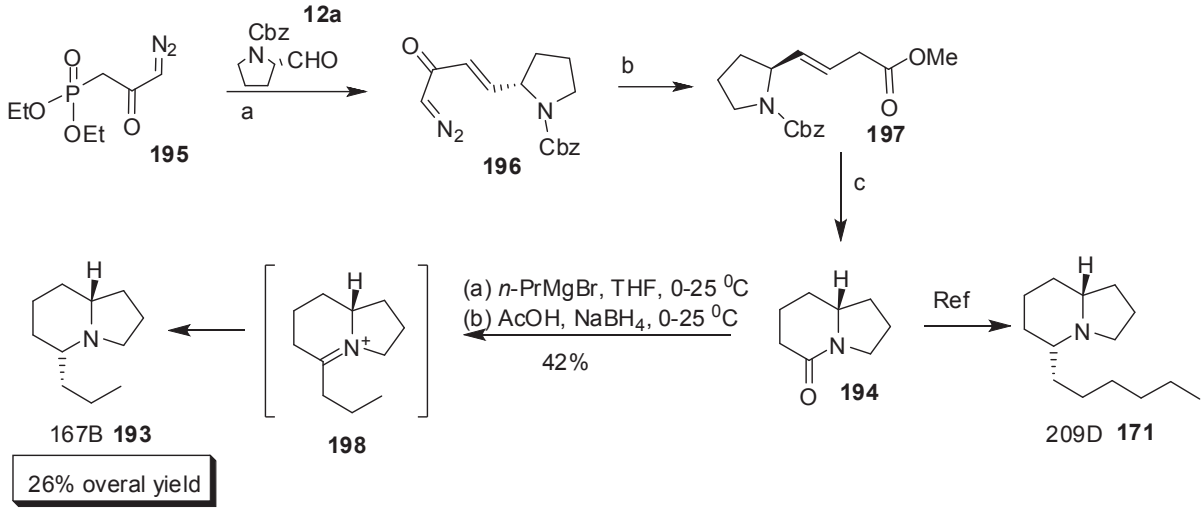


Scheme 35

Reagents and conditions: (a) For **189**: (i) DCM, rt, 5 h; (ii) LDA (excess), THF, -78 ºC 5-45 min; (94% with slight excess **184;** 84% with equimolar amount of **184** and **185**; For **190**: (i) DCM, rt, 40h; (ii) LDA (excess), THF, -78 ºC, 5-45 min, 86%; (b) (i) $NaCNBH_4$, TFA, DCM; (ii) Na-NH_3; (iii) H_2, Pd/C; (60% for **193** and 74% for **171** for three steps).

Back and Nakajima developed a method to construct (-)-indolizidine 167B **193** and (-)-indolizidine 209D **171** through conjugate addition of γ-chloroamines **184** to acetylenic sulfones **185** and **186** respectively.[62] The deprotonation of chloro compounds **187** (**188**) using LDA gave cyclised product **189** (**190**). The reduction of the double bond of **189** (**190**) using $NaCNBH_4$ and subsequent desulfonation produced required products with a tiny amount of **191** (**192**). The crude mixture as such was subjected to hydrogenation over Pd/C to afford (-)-indolizidine 167B **193** (209D **171**) (scheme 35).

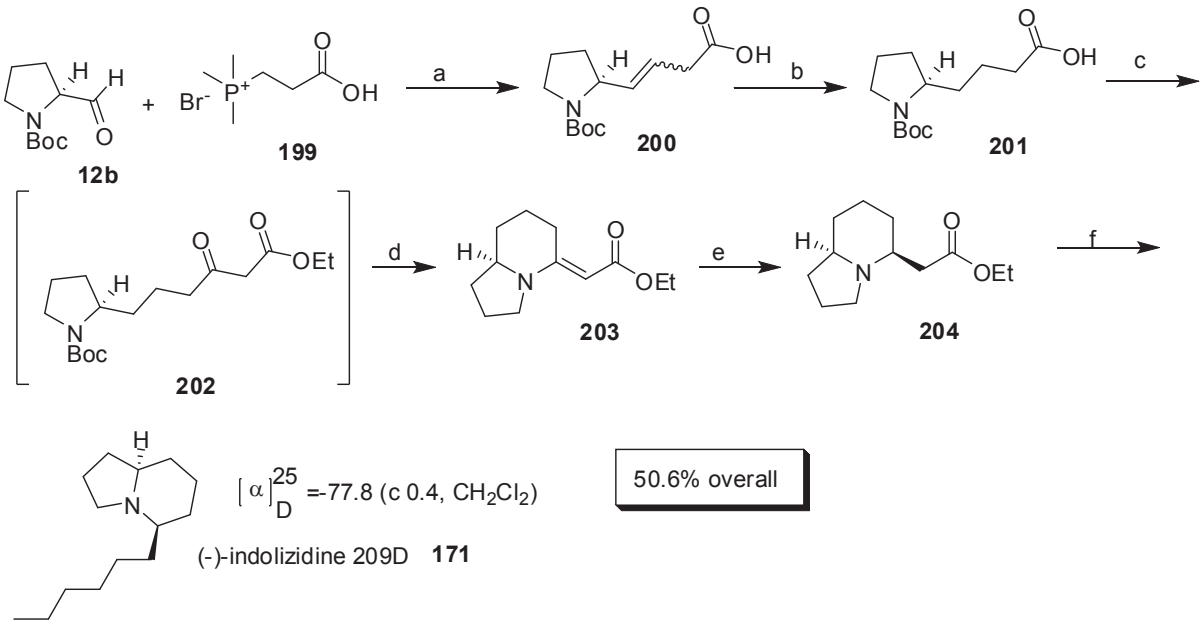
Pinho and Burtoloso also approached the total synthesis of (-)-indolizidine 167B **193** and formal syntheses of (-)-indolizidine 209D **171** by employing an unusual Wolf rearrangement.[63]The synthesis of bicyclic lactam **194** constituted the formal synthesis of (-)-indolizidine 209D **171**. The synthesis of **193** was achieved by diastereoselective addition of *n*-PrMgBr to **194** followed by iminium ion reduction (scheme 36).



Scheme 36

Reagents and conditions *:* (a) NaH, THF, -78 ºC, 70%; (b) MeOH, hν, 25 ºC, 4 h, 97%; (c) Pd/C, MeOH, Et_3N, 48 h, 25 ºC, 92%.

Stereoselective synthesis of (-)-indolizidine 209D **171** was furnished by Ponpandian and Muthusubramanian using sequential deprotection-cyclisation protocol (scheme 37).[64] After overcoming the several consequences of epimerisation and inconvenient routes, authors emerged with an appropriate sequence to bring about the deprotection and cyclisation of **202** efficiently. The compound **201** was prepared by hydrogenation of **200** which in turn accessed from Boc-prolinal **12b** using Wittig reaction with the phosphorane of the corresponding salt **199**. The β-ketoester **202** was prepared by condensing CDI with acid **201** followed by treatment with ethyl potassium malonate in the presence of anhy. $MgCl_2$. The $BF_3.OEt_2$ mediated deprotection of the Boc group of **202** with subsequent cyclisation by treatment with $NaHCO_3$ gave the *trans* olefin **203**. The hydrogenation of **203** afforded the pure isomer **204**. The LAH reduction of **204** followed by tosylation and subsequent CuI mediated coupling with *n*-BuLi furnished indolizidine alkaloid 209D **171**.



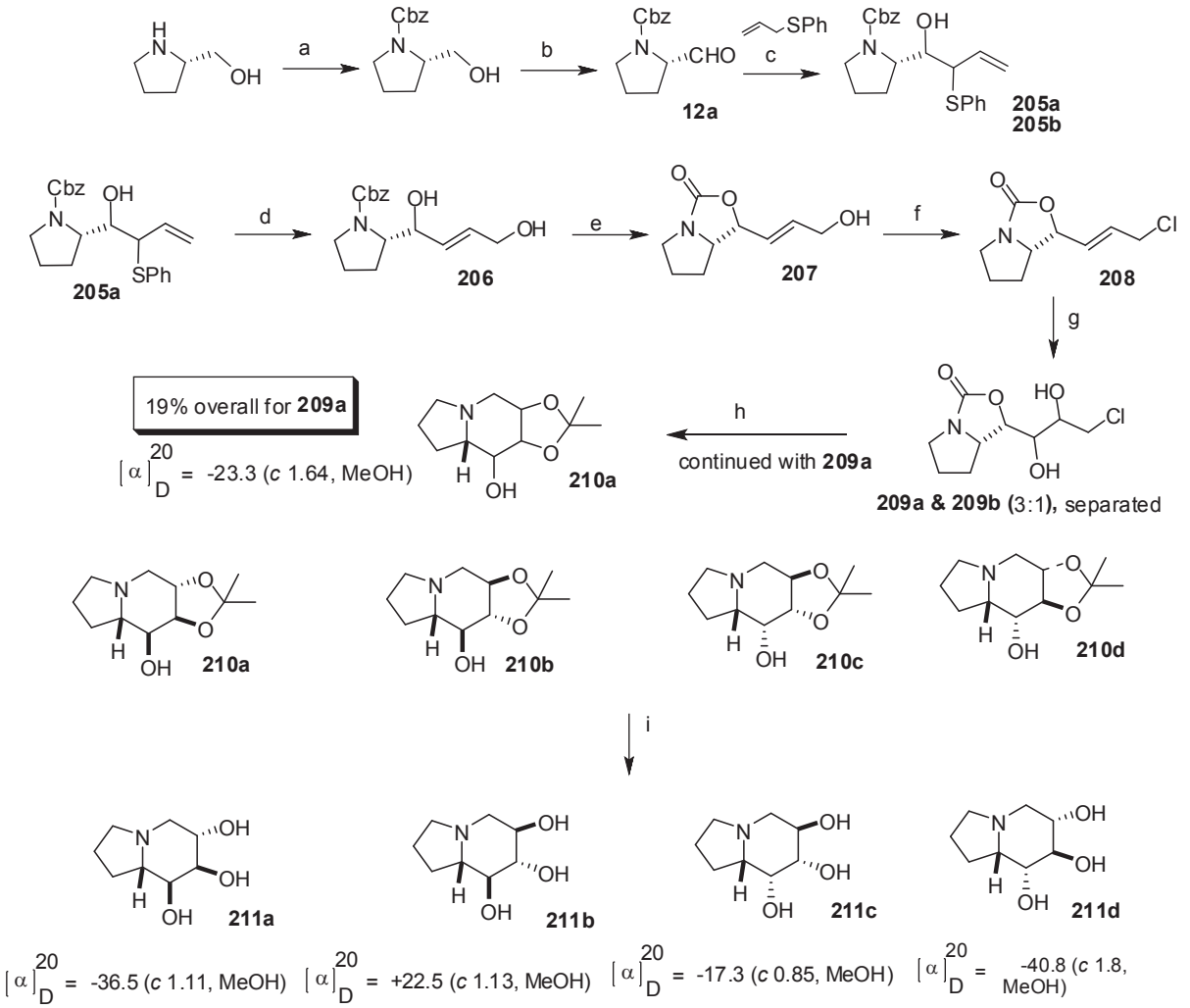
Scheme 37

Reagents and conditions: (a) LiHMDS, THF, 0 °C; (b) 10% Pd/C, MeOH, 69% for (a) and (b); (c) Ethyl potassium malonate, CDI, anhy. $MgCl_2$, 60 °C; (d) $BF_3.OEt_2$, MDC, aq. $NaHCO_3$ work-up, 92% for (c) and (d); (e) H_2/PtO_2, EtOH, 95%; (f) (i) LAH, THF, rt, 30 min, 96%; (ii) TsCl, Et_3N, DCM, rt, 3 h, 92%; (iii) CuI/*n*-BuLi, ether, -30 ºC, 1 h, 95%.

4.3 Hydroxyindolizidines

St-Denis and Chan accomplished the synthesis of all four diastereomers of 1-deoxycastenospermine **211** through diastereoselective addition of anion of allyl phenyl sulphide and Sharpless dihydroxylation (scheme 38).[65] The synthetic strategy utilized **12a** obtained from L-proline. The titanium mediated addition of anion of allyl phenyl sulphide to **12a** occurred diastereoselectively affording only two isomers **205a** and **205b** out of four possible isomers. The isomers were separated by column purification and the synthesis was furthered with the major isomer **205a**. The oxidation of thio group of **205a** followed by allylic rearrangement using $P(OMe)_3$ afforded the allyl alcohol **206** which on treatment with NaOH furnished the cyclic carbamate **207**. The compound **207** was chlorinated to give **208** prior to dihydroxylation affording the diastereomers **209a** and **209b** (3:1), separated by column chromatography to further the synthesis with the major isomer **209a**.

The protection of the diol **209a** as acetonide group followed by opening up of the carbamate using NaOH afforded the cyclised product **210a**. The stereochemistry of the

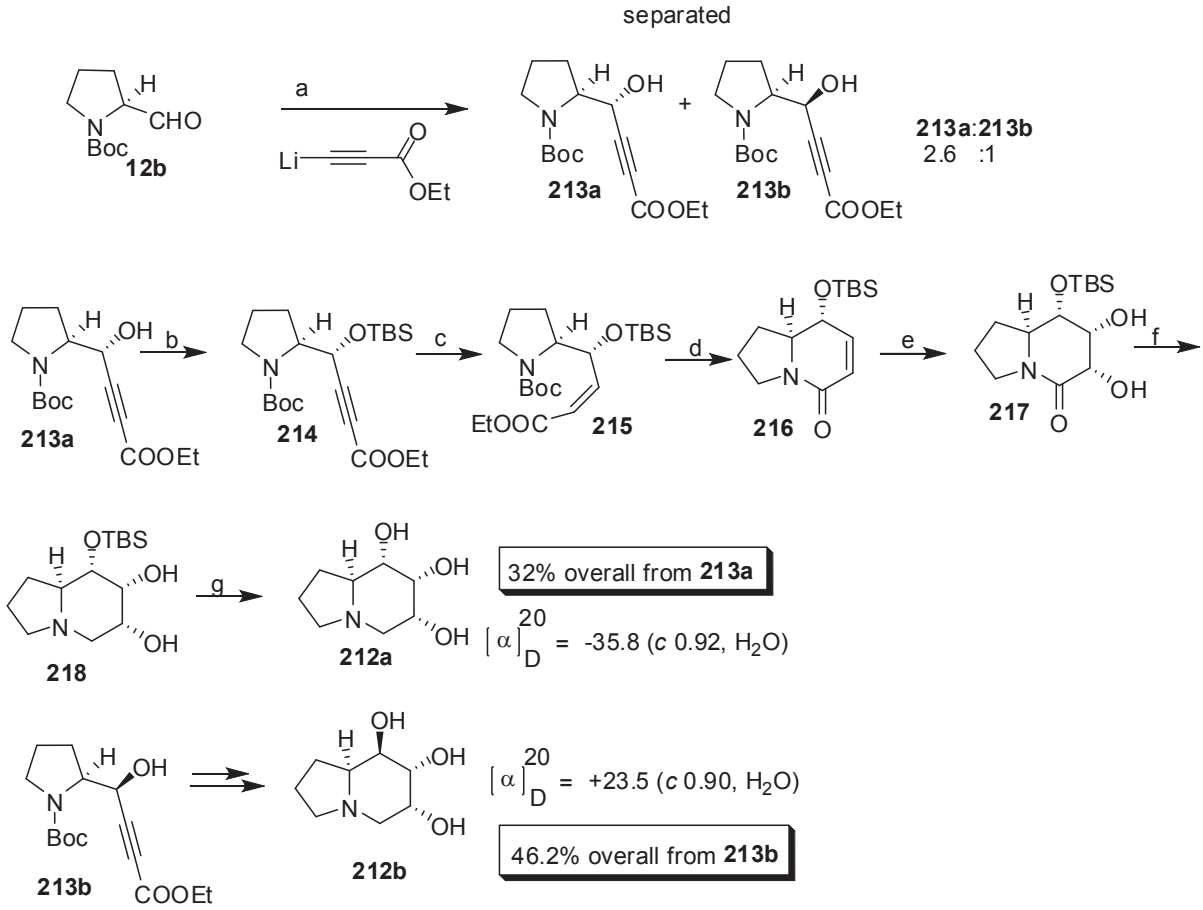


Scheme 38

***Reagents and conditions*:** (a) CbzCl, K_2CO_3, CH_3CN, -20 ºC, 87%; (b) Swern oxidation, 87%; (c) allyl phenyl sulphide, *n*-BuLi, Ti(*i*-OPr)$_4$, THF, -78 ºC, 82%; (d) (i) MCPBA, DCM, -78 ºC; (ii) $P(OMe)_3$, MeOH, 77%; (e) NaOH, IPA/H_2O, 70 ºC, 70%; (f) PPh_3, CCl_4, reflux, 94%; (g) OsO_4, NMO, *t*BuOH, H_2O, acetone, 88%; (h) (i) 2, 2-dimethoxypropane, CSA, acetone, 87%; (ii) NaOH, MeOH, H_2O, 80 ºC, 79%; (i) TFA, H_2O, rt, quant.

compound was established at this stage through various spectroscopic techniques to confirm the structure of **210a.** In a similar way all the isomers **210b**, **c**, **d** were synthesized by utilizing the other isomers formed during the synthetic sequence. The synthesis of all

four diastereomers of 1-deoxycastenospermine **211** (**a**-**d**) was then smoothly achieved by the deprotection of the acetonide group of **210** (**a**-**d**) using TFA.

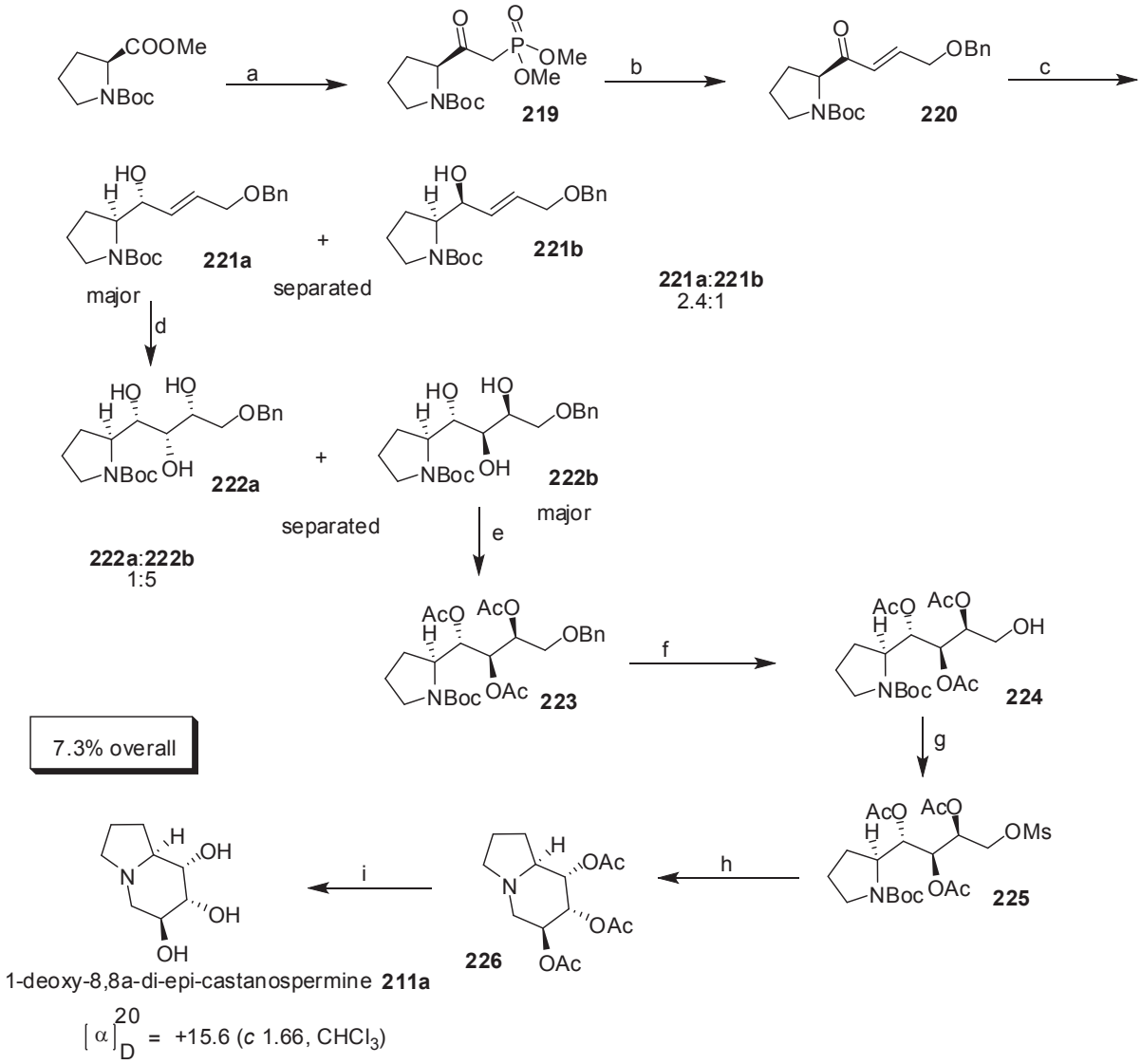


Scheme 39

Reagents and conditions *:* (a) Li propiolate, *n*-BuLi, THF, HMPA (2.0 equiv.), -78 ºC, 3 h, (**213a**:**213b**/2.6:1), 78%; (b) TBSCl, imidazole, DCM, rt, 12 h, 98%; (c) H_2, Lindlar's catalyst, 1 atm, quinoline, MeOH, rt, 3days, 96%; (d) (i) TFA, DCM, 0 ºC to rt, 1.5 h; (ii) Et_3N, DCM, rt, 2 days, 45%; (e) OsO_4, NMO, acetone/water (10:1), 25 ºC, 8 h, 88%; (f) (i) $BH_3.Me_2S$, THF, rt, 4 h, reflux, 1 h; (ii) EtOH, reflux (95% for two steps); (g) TBAF, THF, 25 ºC, 1 h, 90%.

Zhang *et al* achieved the synthesis of two isomers of 1-Deoxy-8a-*epi*-castanospermine **212a** and **212b** by diastereoselective addition of ethyl lithiopropiolate and Sharpless dihydroxylation as key steps (scheme 39).[66] The diastereoselective addition of ethyl lithiopropiolate to carbonyl derived from Boc-prolinal **12b** in the presence of HMPA afforded the two separable diastereomers **213a** and **213b** (2.6:1). The secondary hydroxyl

group of **213a** was then protected using TBSCl to afford **214**. The selective triple bond reduction to double bond was achieved using Lindlar's catalyst to give olefin **215** which on Boc deprotection using TFA followed by treatment with Et_3N furnished the cyclised product **216**. The compound **216** was subjected to Sharpless dihydroxylation to give diol **217** which on subsequent reduction with borane gave **218**. The deprotection of TBS group of **218** using TBAF produced the natural product **212a** whose structural elucidation was done using different spectroscopic techniques. Similar synthetic steps were repeated for the synthesis of the other isomer **212b** from **213b**.

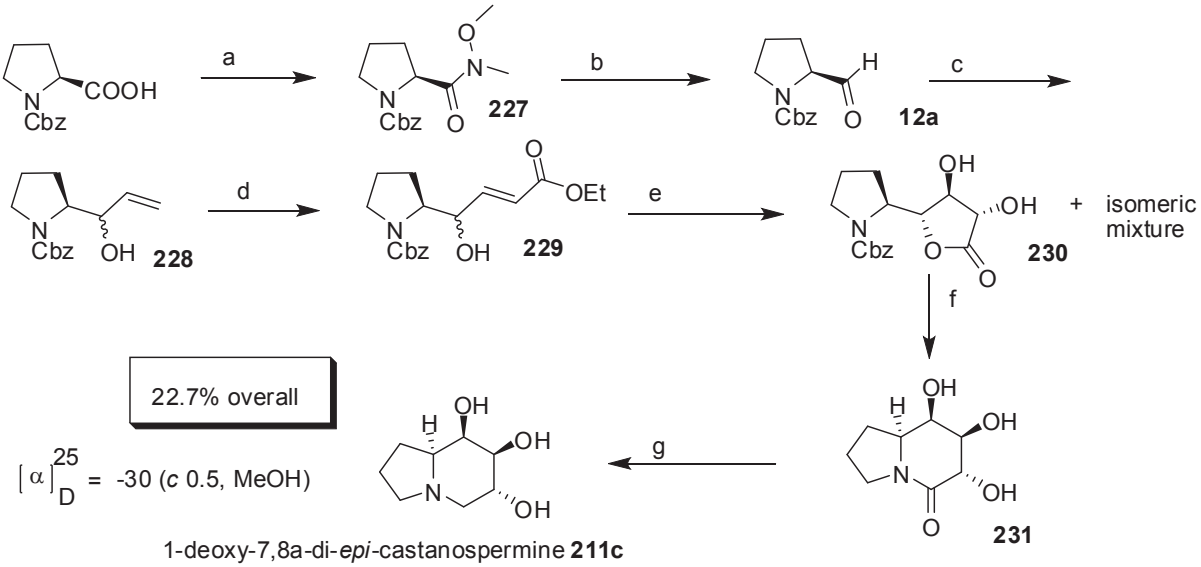


$[\alpha]_D^{20}$ = +15.6 (*c* 1.66, $CHCl_3$)

Scheme 40

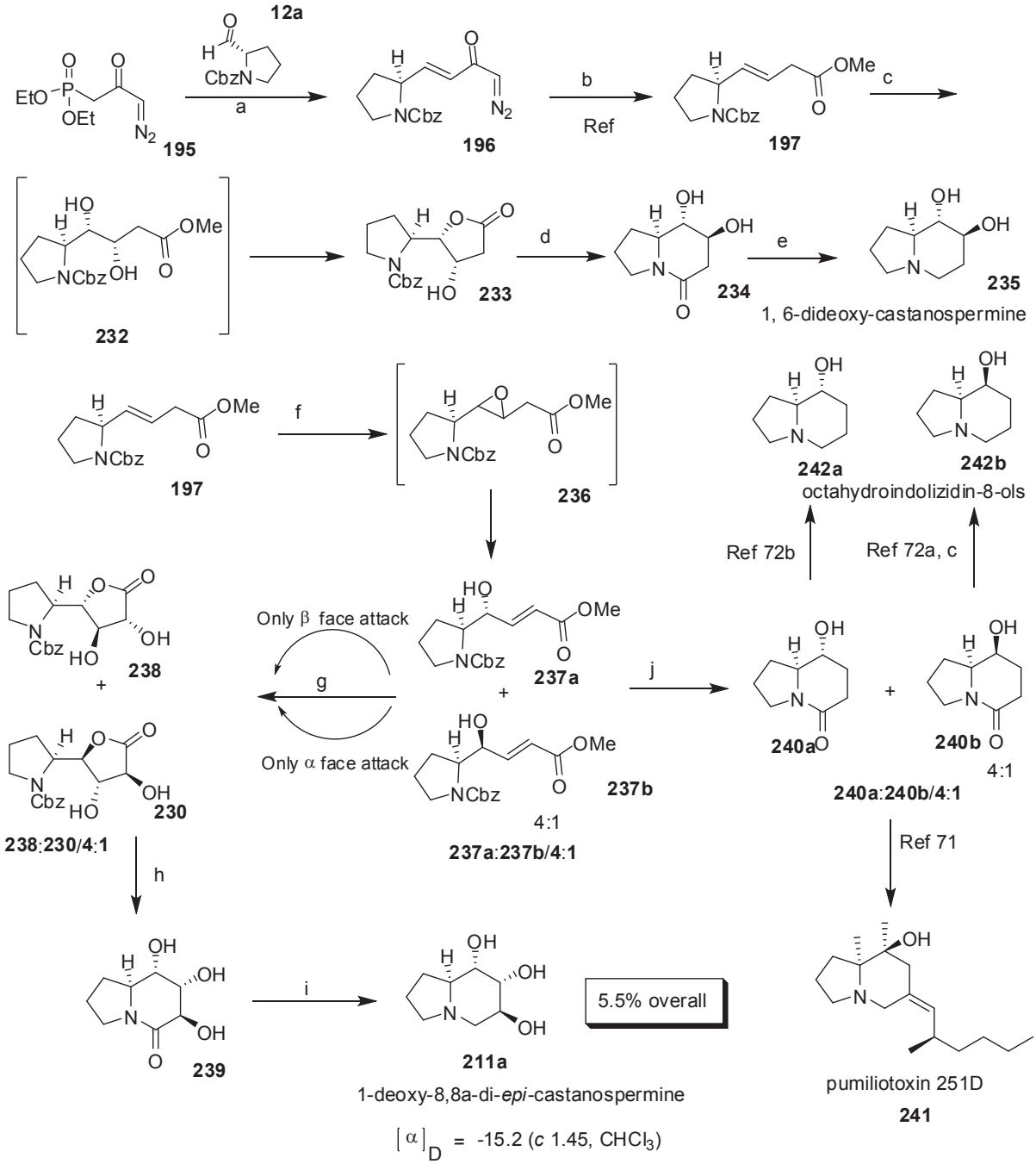
Reagents and conditions *:* (a) *n*-BuLi, DMMP, THF, -78 ºC, 85.2%; (b) $BnOCH_2CHO$, K_2CO_3, CH_3CN, 68%; (c) $NaBH_4$-$CeCl_3$, MeOH, rt, 63.6% for **221a**, 9.1% for **221b**; (d) OsO_4, NMO, actone-water, 57% for **222b**, 17% for **222a**; (e) Ac_2O, Pyridine, DMAP, DCM, 96%; (f) H_2, Pd/C, MeOH, 94%; (g) MsCl, Et_3N, DCM, quant; (h) (i) TFA, DCM; (ii) TEA, CH_3CN, 50%; (i) NaOMe, MeOH, 77%.

Koskinen and Kallatsa formulated the synthesis of 1-deoxy-8,8a-di-epi-castanospermine **211a** using proline as an efficient starting material (scheme 40).[67] The phosphonate **219** was prepared from Boc-proline ester according to the procedure reported by Heathcock and von Geldern.[68] The Horner–Wadsworth–Emmons olefination was then achieved on **219** to afford **220** using mild base K_2CO_3. The stereoselective reduction of carbonyl of **220** rendered the separable mixture of **221a** and **221b**. The dihydroxyalation of isomer **221a** gave a mixture of **222a** and **222b**, separated by column chromatography. The major compound **222b** was furthered by acetylating the free hydroxyl groups to give **223** and subsequently hydrogenated to give **224**. The terminal free OH group of **224** was mesylated to give **225**. The compound **225** on Boc deprotection using TFA underwent cyclisation to give **226** which on subsequent treatment with NaOH furnished **211a**.



Scheme 41

Reagents and conditions *:* (a) MeNH(OMe).HCl, DCC, HOBt, Et_3N, 0 ºC to rt, 6 h, 92%; (b) LAH, THF, 0 ºC, 30 min, 90%; (c) CH_2=CHMgBr, 0 ºC, 3 h, 70%; (d) Methyl acrylate, Grubbś II (3 mol%), toluene, rt, 2 h, 92%, (E:Z/20:1); (e) OsO_4, NMO, acetone-H_2O, rt, 3 h, 61% for the major isomer **230**; (f) Pd/C, H_2, MeOH, rt, 85%; (g) $BH_3.Me_2S$, THF, reflux, then EtOH, reflux, 82%.



Scheme 42

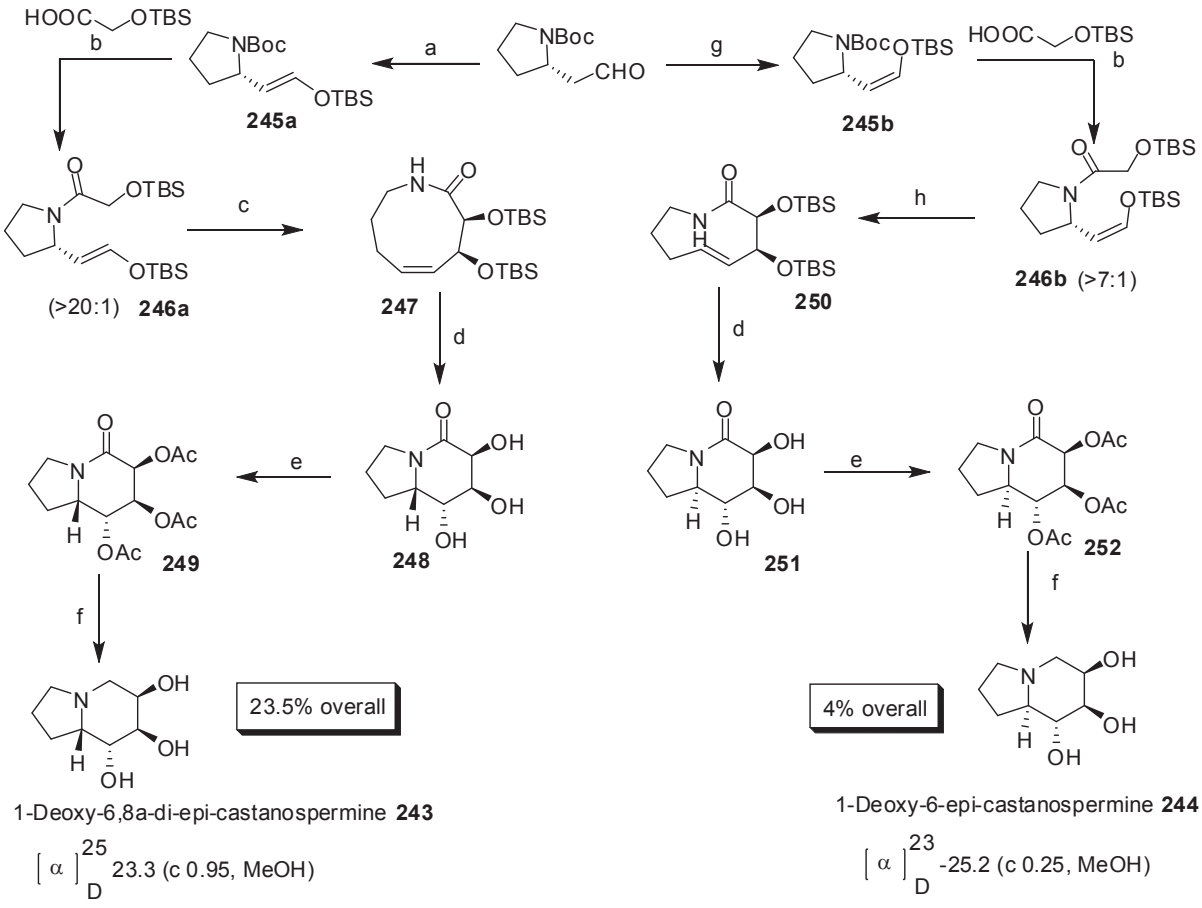
Reagents and conditions *:* (a) **12a**, NaH, THF, -78 ºC, 70%; (b) MeOH, hν, 25 ºC, 4 h, 97%; (c) OsO_4, NMO, acetone: water, 25 ºC, 48 h, 66%; (d) H_2, Pd, 94%; (e) $BH_3.Me_2S$, THF, 0 to 25 ºC, 12 h, 71%; (f) (i) MCPBA, DCM, 25 ºC, 10 h; (ii) DBU, 0 to 25 ºC, 4 h, 67% ; (g) OsO_4, NMO, actone:water, 6 h, 71%; (h) H_2, Pd/C, MeOH, 25 ºC, 24 h, 73%; (i) $BH_3.Me_2S$, THF, 0 to 25 ºC, 12 h, 70%; (j) H_2, Pd/C, MeOH, 25 ºC, 24 h, 76%.

Bhat and co-workers made an entry into the synthesis of castenospermine alkaloid by synthesizing 1-deoxy-7,8a-di-epi-castanospermine **211c** through RCM and Upjohn dihydroxylation (scheme 41).[69] The Cbz-prolinal **12a** was prepared by condensing the Cbz-proline with methoxy methyl amine chloride followed by LAH reduction of the Weinreb amide **227**. The Grignard addition of vinyl magnesium bromide on **12a** produced an inseparable mixture of diastereomers **228** which as such subjected to cross olefin metathesis with methyl acrylate in the presence of 2nd generation Grubbś catalyst to afford **229**. The dihydroxylation of **229** gave a mixture of isomers which on purification by column chromatography afforded the major pure isomer **230**, the structure of which was confirmed by single X-ray analysis. The diol **230** without prior protection of –OH, hydrogenated to give amide **231** which on subsequent reduction using borane produced the targeted compound **211c**.

Bernardim *et al* synthesized several castanospermine analogues by synthesizing a robust intermediate **197** (scheme 42)[70] by well known efficient Wolf rearrangement of **196** prepared from phosphonate **195** and Cbz-prolinal **12a** under photocatalytic condition. The dihydroxylation of **197** afforded **232** which on subsequent hydrogenation gave **233**. The synthesis of 1, 6-dideoxy-castenospermine **235** was furnished by direct reduction of the lactam **234** using $BH_3.Me_2S$. Similarly, the compound **197** on epoxidation followed by treatment with DBU produced a diastereomeric mixture of **237a** and **237b** (4:1). The mixture of alkene **237** when dihydroxylated gave a mixture of **238** and **230** (4:1) with facial selectivity. The hydrogenation of **238** provided **239** after purification using column chromatography. The reduction of the lactam **239** afforded castanospermine analogue 1-deoxy-8,8a-di-epi-castenospermine **211a**. Interestingly the synthesis of **240a** and **240b** by hydrogenation of **237a** and **237b** constituted the formal syntheses of pumiliotoxin 251D **241** [71] and of octahydroindolizidin-8-ols **242a** and **242b**.[72]

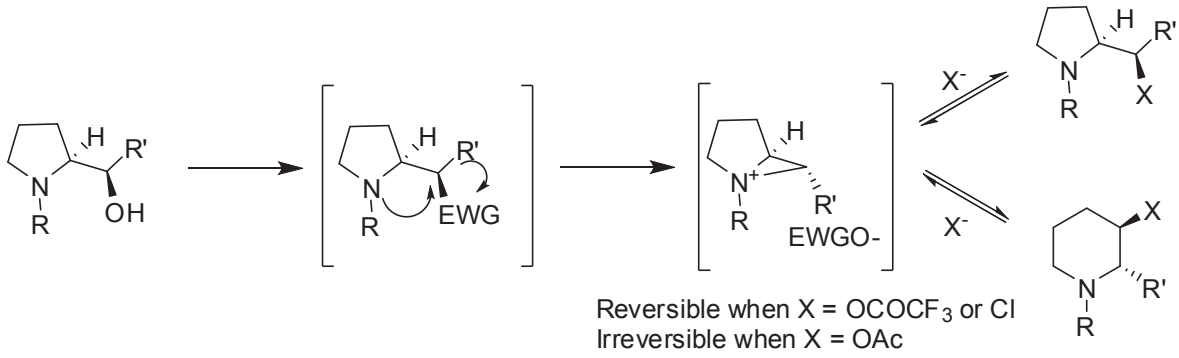
Suh and co-workers efficiently applied their ACR-induced stereoselective ring-expansions of lactams for the synthesis of 1-deoxy-6, 8a-di-epi-castenospermine **243** and 1-deoxy-6-epi-castenospermine **244** (scheme 43).[73] The 1-carbon homologated Boc prolinal was converted diastereoselectively to **245a** and **245b** by differential selection of base DBU and NaH respectively. The selective deprotection of **245a** using TMSOTf and 2, 6-lutidine followed by coupling with protected glycolic acid resulted **246a**. The compound **246a** on

ACR execution afforded the 7 member lactam **247** which on treatment with oxone resulted in the formation of **248** via *trans* annulations and concomitant TBS deprotection. The formation of **247** was elegantly explained by the authors by invoking different transition states. The triol **248** was acetylated and reduced with LAH to afford **243**. In a similar way the *cis* isomer **245b** was transformed to **244** with ACR induced technique.

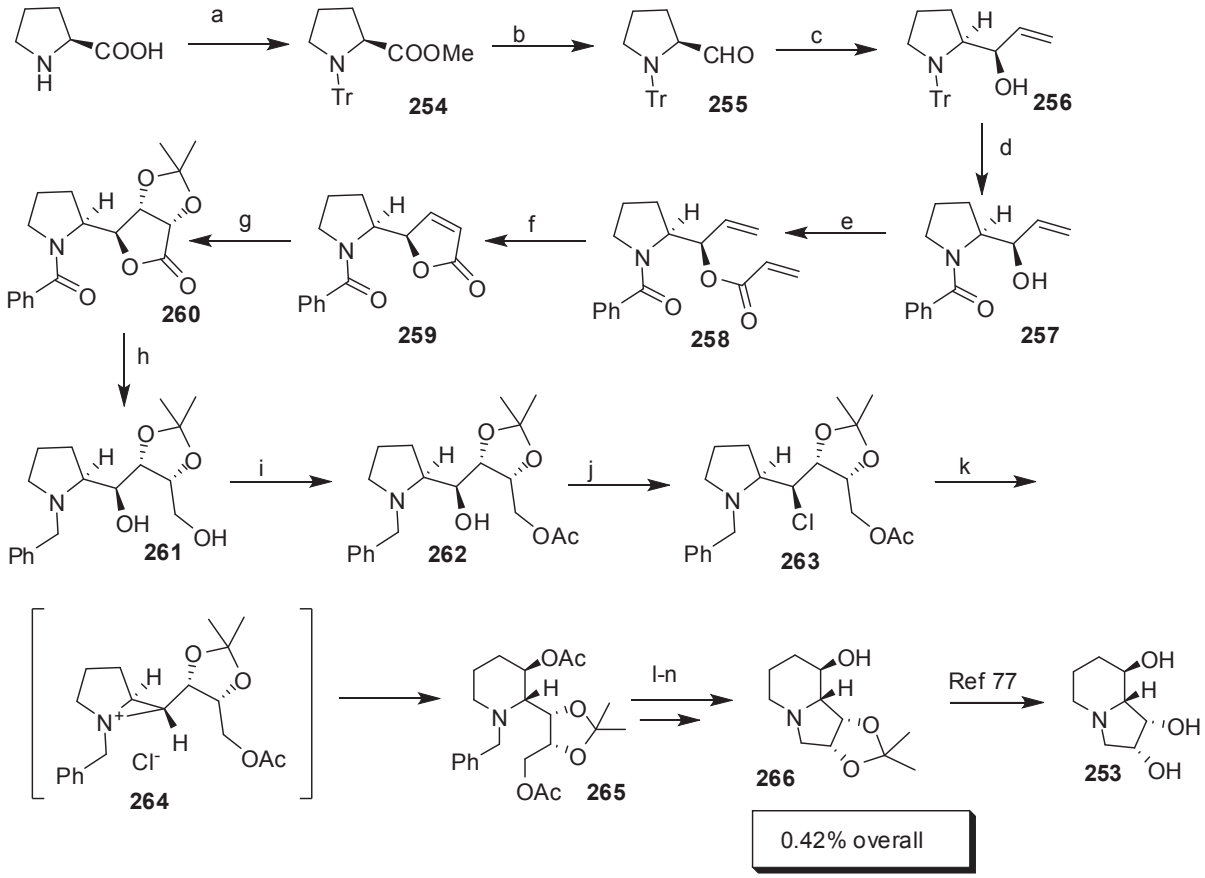


Scheme 43

Reagents and conditions: (a) TBSCl, DBU, DCM, reflux, 88%; (b) (i) TMSOTf, 2, 6-lutidine, DCM, 0 °C; (ii) EDCI, HOBt, NMM, DCM (60% two steps); (c) LHMDS, toluene, reflux, 66%; (d) Oxone, MeOH/H_2O, 63%; (e) Ac_2O, pyridine, 71%; (f) LAH, THF, reflux, 86%; (g) TBSCl, NaH, THF, 0 ^oC, 83%; (h) LDA, MW, benzene, 21%; (d)-(f) 38%.



Scheme 44



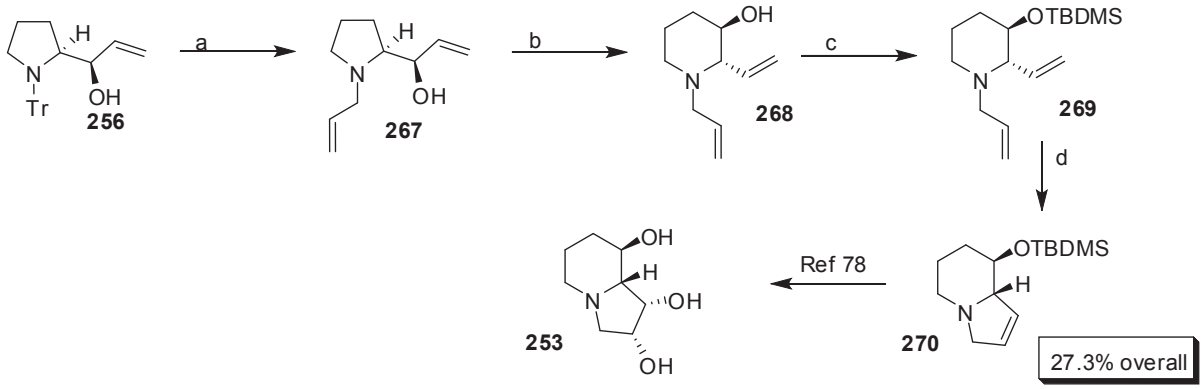
Scheme 45

Reagents and conditions *:* (a) (i) $SOCl_2$, MeOH, 36 h; (ii) Ph_3CCl, Et_3N, $CHCl_3$, (90% for two steps); (b) (i) LAH, THF; (ii) Swern oxidation; (95% for two steps); (c) vinyl magnesium chloride, Et_2O, -78 ºC, 93%; (d) (i) HCl, 5 M, Et_2O; (ii) NaOH, PhCOCl (68% for two steps); (e) acryloyl chloride, DMAP, Et_3N, DCM, 65%; (f) Grubbś II catalyst, toluene, 80 ºC (crude product filtered on Celite pad); (g) $RuCl_3$, $NaIO_4$ (1.5

equiv.), cat H_2SO_4, EtOAC/CH_3CN/H_2O; (ii) $Me_2C(OMe)_2$, APTS, DCM, (41% for f, g); (h) LAH, THF, reflux, 94%; (i) AcCl, 2, 4, 6-Collidine, DCM, 88%; (j) MsCl (4.5 equiv.), Et_3N (8.0 equiv.), microwave, 100 ºC, THF, 24%; (k) AgOAc, THF, 120 ºC, microwave, 46%; (l) NaOMe, MeOH, THF, 83%; (m) H_2, Pd/C, EtOH, 93%; (n) DEAD, PPh_3, Pyridine, 43%.

Cossy and co-workers have accomplished two formal synthesis of (-)-swainsonine **253** by enantioselective ring expansion of prolinol derivatives.[74] The ring expansion traverses through the formation of aziridinium ion (scheme 44) which was first proposed by Fuson and Zirkle in 1948[75] and successfully utilised by O'Brien's group.[76] The commercially available proline was converted to trityl ester **254** which on LAH reduction followed by Swern oxidation afforded the aldehyde **255**. The diastereoselective addition of vinyl magnesium chloride to the aldehyde **374** afforded the hydroxyl derivative **256** diastereoselectively (98:2). In order to obviate the further synthetic consequences, the trityl group was converted to benzoyl to give the compound **257**. The compound **257** on treatment with acryloyl chloride produced the compound **258** which on RCM using 2nd generation Grubbś catalyst afforded the product **259**. The *syn* dihydroxylation of the olefin **259** followed by diol protection provided the compound **260** which on LAH reduction gave **261**. When the attempted ring expansion of this **261** was unsuccessful, the compound **262** was prepared by protecting primary –OH with acetyl group and the secondary –OH of **262** was transformed to –Cl under microwave condition to afford **263**. The treatment of **263** with AgOAc effected the ring expansion smoothly to give **265** through the formation of aziridinium ion **264**. The further conventional synthetic steps performed over **265** gave **266** to complete the formal synthesis of (-)-swainsonine **253** (scheme 45).[77]

The second strategy utilized the hydroxyl allyl intermediate **256** which was converted to N-allylic compound **267**, suitable for ring expansion. The ring expansion of **267** was performed in the presence of $(CF_3COO)_2O$ followed by treatment with NaOH to afford **268** whose OH was further protected with TBDMS giving **269**. The RCM on HCl salt of **269** using Grubbś 1st generation catalyst gave the compound **270** which completed the formal synthesis of (-)-swainsonine **253** (scheme 46).[78]



Scheme 46

Reagents and conditions *:* (a) (i) HCl, Et_2O; (ii) AllylBr, K_2CO_3, *n*-Bu_4NBr, toluene, 50%; (b) (i) $(CF_3COO)_2O$, Et_3N, THF; (ii) NaOH, 95%; (c) TBDMSCl, Et_3N, DMAP, DCM, 70%; (d) (i) CSA; (ii) Grubbś I, DCM, reflux; (iii) K_2CO_3; 82%.

Summary

The present chapter explicitly describes the versatility of the proline particularly emphasizing as a unique chiral synthon for the synthesis of naturally occurring pyrrolidines, pyrrolizidines and indolizidine alkaloids. The synthesis of wide spectrum of natural products has been derived ranging from simple to complex molecules placed the proline on a cutting edge in chiral pool synthesis. The construction of various heteroatom-impregnated cyclic compounds deemed to be useful for the synthetic chemists for further tuning of the strategies. It is noteworthy to mention that manifolds of proline-derived heterocyclic scaffolds, similar to those natural products described in this chapter, have been synthesized and undoubtedly emerged the proline as a robust "chiral tool" in the pharmaceuticals and biotechnological fields. The collection also provides a room for the synthetic chemists to alleviate or obviate the indigenous racemisation of the intermediates and final natural products cuased by several reagents and reaction conditions during the synthetic manipulations. More specifically, the present report established the proline as a competent and leading amino acid for the synthesis of asymmetric natural products besides its 'universal application' as an organocatalyst.

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CHAPTER 2

Synthetic Studies of Pyrrolidine and Piperidine Alkaloids

Synthetic Studies of Pyrrolidine and Piperidine Alkaloids

Section 1: Synthesis of pyrrolidine alkaloids

Introduction

Pyrrolidine alkaloids containing a stereogenic nitrogen centre with five member *N*-heterocycles are widely dispersed among the various natural[1] and unnatural[2] components and found to show potent biological activities. They are mainly extracted from numerous plant extracts, generally of the families *Colanaceae*, *Convolvunaceae* and *Erythroxylaceae*. They are endowed with host of pharmacological behaviours and have been active targets of synthetic interests from industrial and academic prospective. The manifolds of alkaloids of this class constitute an intriguing part of organocatalysts[3] and building blocks in organic synthesis.[4] It has been a formidable challenge for the synthetic chemists to keep in designing the novel and economically favourable synthetic schemes due to the scarcity of several biologically relevant natural products and difficulties in extraction and purification processes of these alkaloids.

There have been various methods elaborated in the literature for the synthesis of these classes, mainly involving radical cyclisation, photo induced cyclisation, organometalic reactions etc.[5] The asymmetric versions of these structural units have been accessed mainly using organocatalysis, chiral auxiliary methods and chiral pool synthesis. It has been a difficult task to carry out selective transformations of the molecules for the introduction of new chiral centres in the system. The cost of organocatalysis and the systematic manipulation for achieving the enantioselectivity is of major concern from economical point of view. Turning to an end, "chiral pool" methods wherein the starting materials are derived from available chiral sources like amino acids, carbohydrates and several acids have drawn major attention in devising the novel synthetic schemes for the construction of pyrrolidine structural motifs.[6] The molecules of dynamic interest also involve 1, 3-amino ketones and 1, 3-amino alcohol units (fig. 1); principal units present in the various natural bioactive molecules and also as potent key building blocks in organic synthesis.[7] They enunciated their impacts as versatile chiral auxiliaries and ligands in organic synthesis.[8] Some of the molecules of major interest are hygrine **1**, norhygrine **2**, hygroline **3** and pseudohygroline **4** which specifically come underneath the class of

tropane and *sedum* alkaloids. The *tropane* alkaloids are generally isolated from the plants of families *Schizanthus hookeri*, *Carallia brachiata* and *Erythroxylon coca*. They are gaining major importance nowadays due to their intriguing pharmaceutical and hallucinogenic characteristics.[9] Hygrine **1** being the simplest alkaloid constitutes a biogenetic pathway for *tropane* alkaloids (scheme 1). *Sedum* alkaloids are generally isolated from the 60 species of plants *Sedum*[10] and are gaining paramount of interest due to their memory-enhancing properties and application as anti-Alzheimer agents.[11]

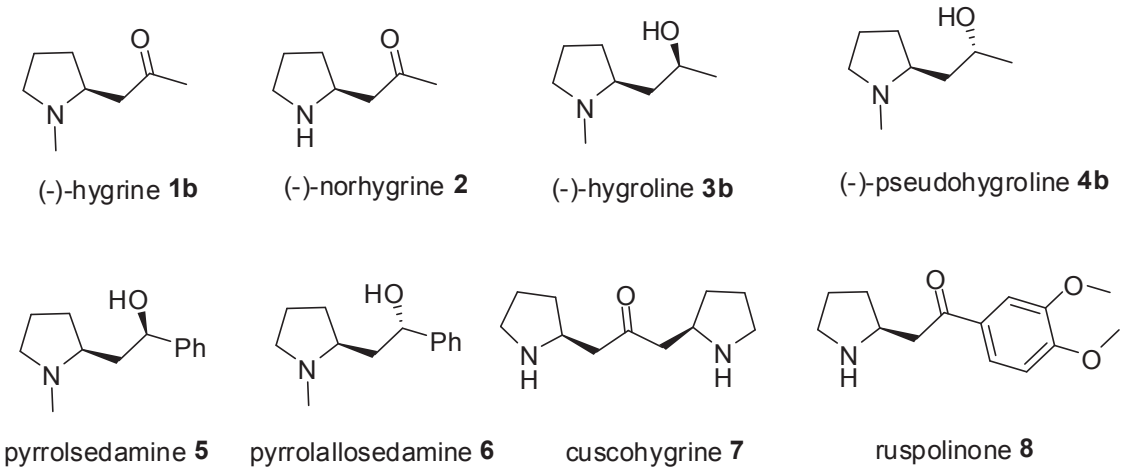
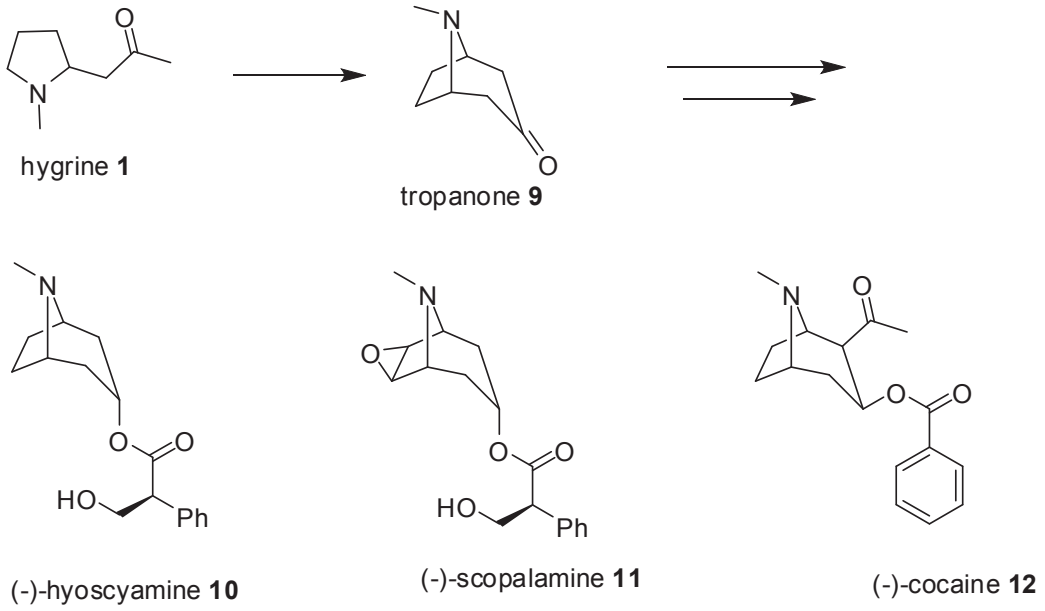


Figure 1. Pyrrolidine alkaloids containing 1, 3-aminoketone and 1, 3-amino alcohol units



Scheme 1. Hygrine as a biogenetic precursor for *tropane* alkaloids

Literature Review

Isolation

Hygrine **1** and norhygrine **2** were isolated together from plant extracts[12] and numerous racemic and asymmetric syntheses have been reported.

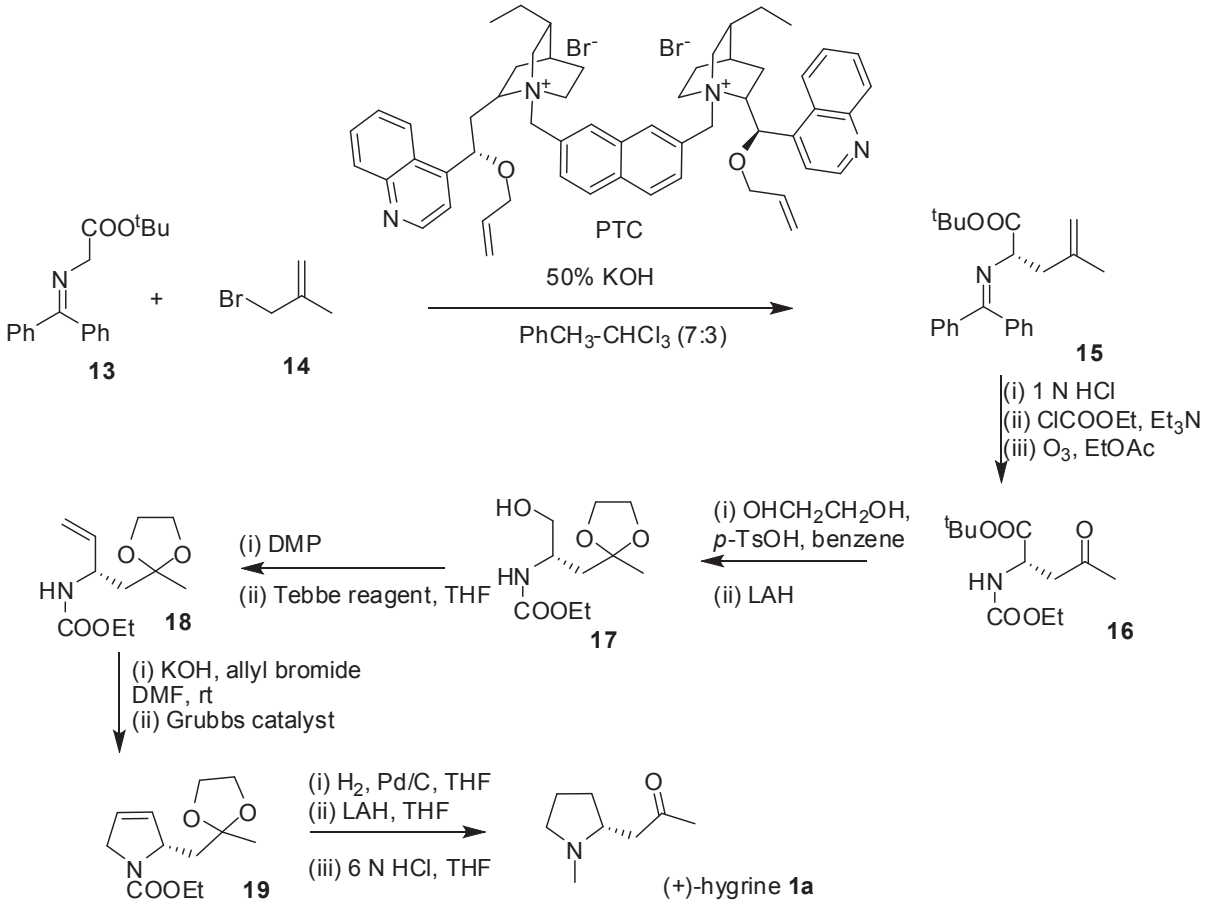
Pseudohygroline **4** and hygroline **3** are mainly isolated from *Carallia brachiata* and *Erythroxylon coca*.[13]

There are nine synthetic reports for hygrine **1** including 6 racemic syntheses and 3 asymmetric syntheses.[14] The chiral synthesis has been achieved in 3 different ways including the first synthesis of (-)-norhygrine **2** from our lab. There are altogether 7 reports on synthesis of hygroline **3** and pseudohygroline **4**.[15] The recent updates on asymmetric synthesis of hygrine **1**, norhygrine **2**, hygroline **3** and pseudohygroline **4** are briefly described here.

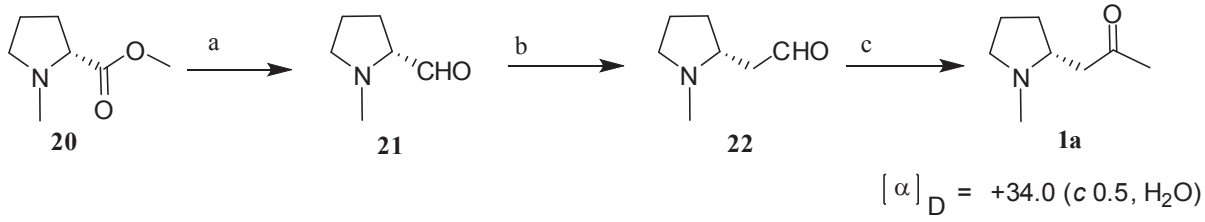
Synthesis

Lee *et al* achieved the first asymmetric synthesis of (+)-hygrine **1a** using cinchona alkaloid derived PTC for the asymmetric alkylation of N-(diphenylmethylene) glycine *ter*-butyl ester **13** with methallyl bromide **14** in 50% KOH by synthesizing the requisite benzophenone imine **15**.[14h] The compound **15** on ozonolysis followed by acetal formation and LAH reduction of the terminal ester afforded alcohol **17**. The DMP oxidation of terminal –OH followed by subsequent treatment with Tebbe reagent provided olefin **18**. The N-alkylation of compound **18** with allyl bromide and subsequent RCM furnished the pyrrolidine product **19** which was conveniently transformed to (+)-hygrine **1a**.

Arévalo-García and Colmenares synthesized the tropane pyrrolidine alkaloid (+)-hygrine **1a**, in six steps using (*R*)-proline derived ester **20** as a chiral precursor.[14i] *N*-Methylated proline ester **20** was reduced to aldehyde **21** using DIBAL which was further homologated to **22** by reaction with PPh_3=$CHOCH_3$ followed by acid hydrolysis. The Grignard reaction on **20** with MeMgBr and subsequent oxidation with DMP gave (+)-hygrine **1a**.



Scheme 2

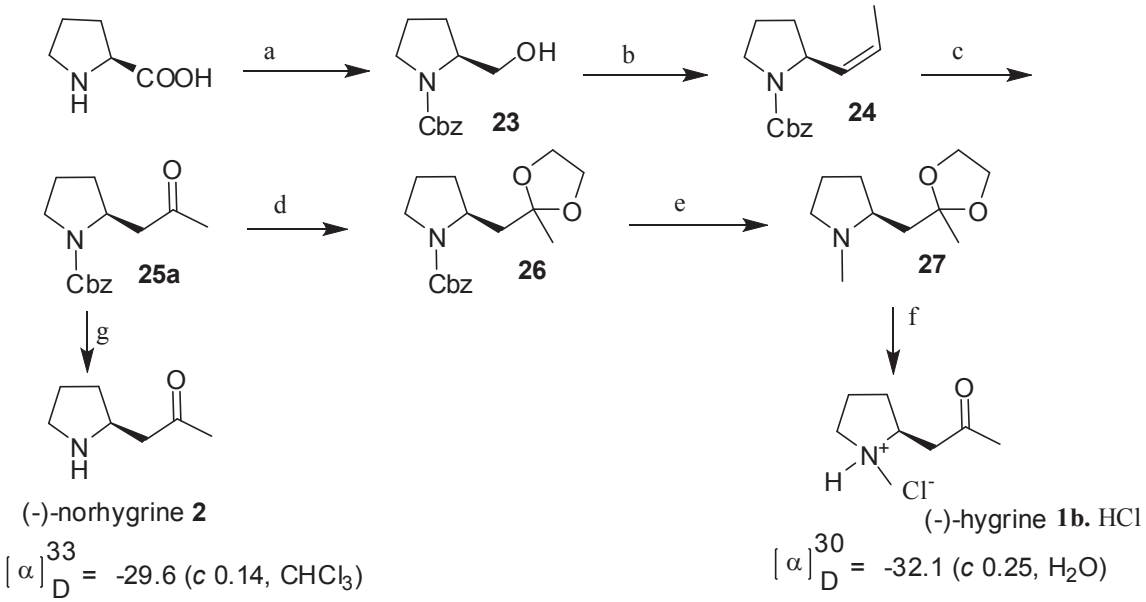


Scheme 3

Reagents and conditions : (a) DIBAL, DCM, -30 ºC; (b) $PPh_3CH_2OCH_3Br$, KO-*t*Bu, THF, 10% HCl-THF; (c) (i) MeMgBr, THF; (ii) DMP, DCM.

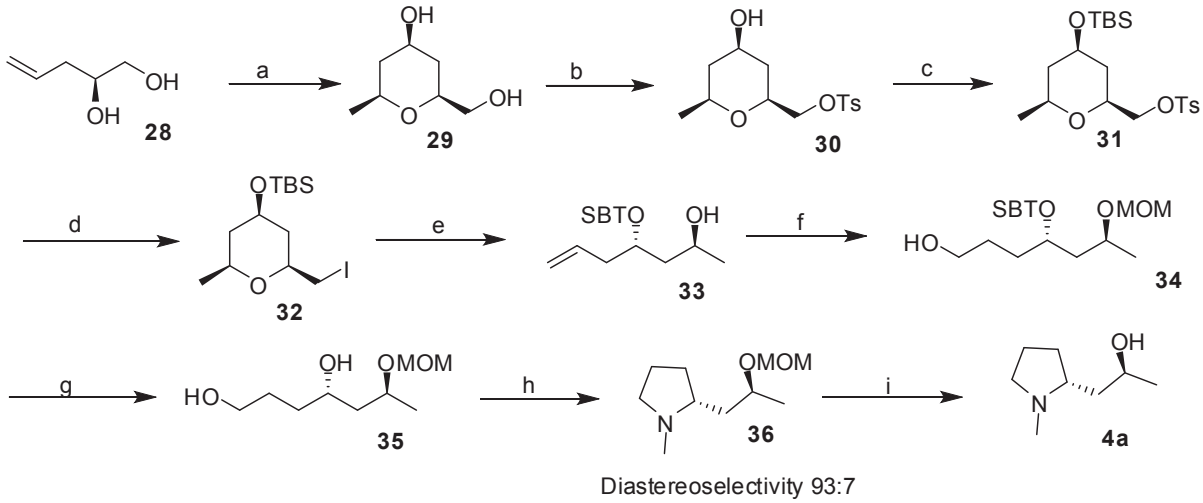
Our research group has recently reported the synthesis of (-)-hygrine **1b** and (-)-norhygrine **2** using regioselective Wacker oxidation of olefinic double bond.[14j]The strategy successfully utilized L-proline as a chiral source. The Cbz-prolinal **23** synthesized from

proline was converted to olefin **24** using Wittig olefination. The Wacker oxidation of the non terminal double bond of **24** performed using $PdCl_2$/CuCl in O_2 took place regioselectively at the carbon atom more away from the ring due to bulky Cbz group, delivering the keto product **25a** which on subsequent hydrogenolysis completed the first total synthesis of (-)-norhygrine **2**. The conversion of keto compound **25a** to acetal **26** followed by LAH reduction and deprotection of the acetal group to regenerate keto functionality produced (-)-hygrine **1b** as its hydrochloride salt.



Scheme 4

Reagents and conditions : (a) (i) LAH, THF, reflux, 90%; (ii) CbzCl, K_2CO_3, CH_3CN, 85%; (b) (i) PCC, DCM, 70%; (ii) ethyltriphenylphosphonium bromide, *n*-BuLi, Et_2O, 56%; (c) $PdCl_2$, CuCl, O_2, DMF–H_2O, 76%; (d) $HOCH_2CH_2OH$, *p*-TsOH, 82%; (e) LAH, THF, 66%; (f) 6 N HCl, THF, 73%: (g) H_2, Pd/C, EtOH, 81%.

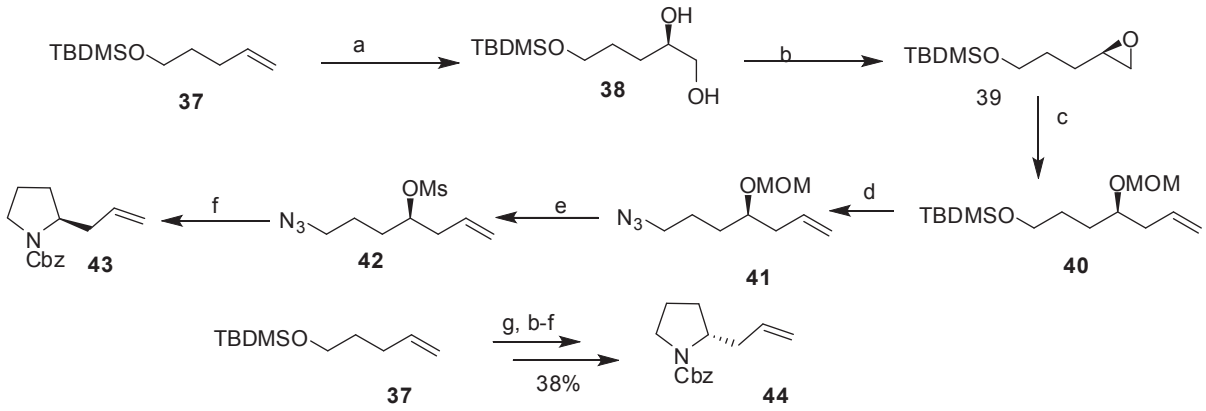


Scheme 5

Reagents and conditions: (a) (i) CH_3CHO, TFA, DCM; (ii) K_2CO_3, MeOH, rt, 4 h (52% for the two steps); (b) TEA, TsCl, DCM, 0 °C to rt, 3 h, 96%; (c) TBSCl, DMAP, imidazole, DCM; (d) NaI, acetone, reflux, 24 h, 94%; (e) Zn, EtOH, reflux, 1 h, 96%; (f) MOMCl, DIPEA, 0 °C to rt, 4 h, 98%; (g) (i) BH_3.DMS, THF, 8h, 0 °C; (ii) H_2O_2, NaOH, H_2O, 3 h (80% for two steps); (h) TBAF, THF, 0 °C-rt, 4 h, 85%; (i) (i) TEA, DMAP, MsCl, 0 °C, 1 h; (ii) $MeNH_2$, DMF-H_2O, 60 °C, 7 h, 76%; (j) TMSCl, MeOH, rt, 2 h, $NaHCO_3$, 96%.

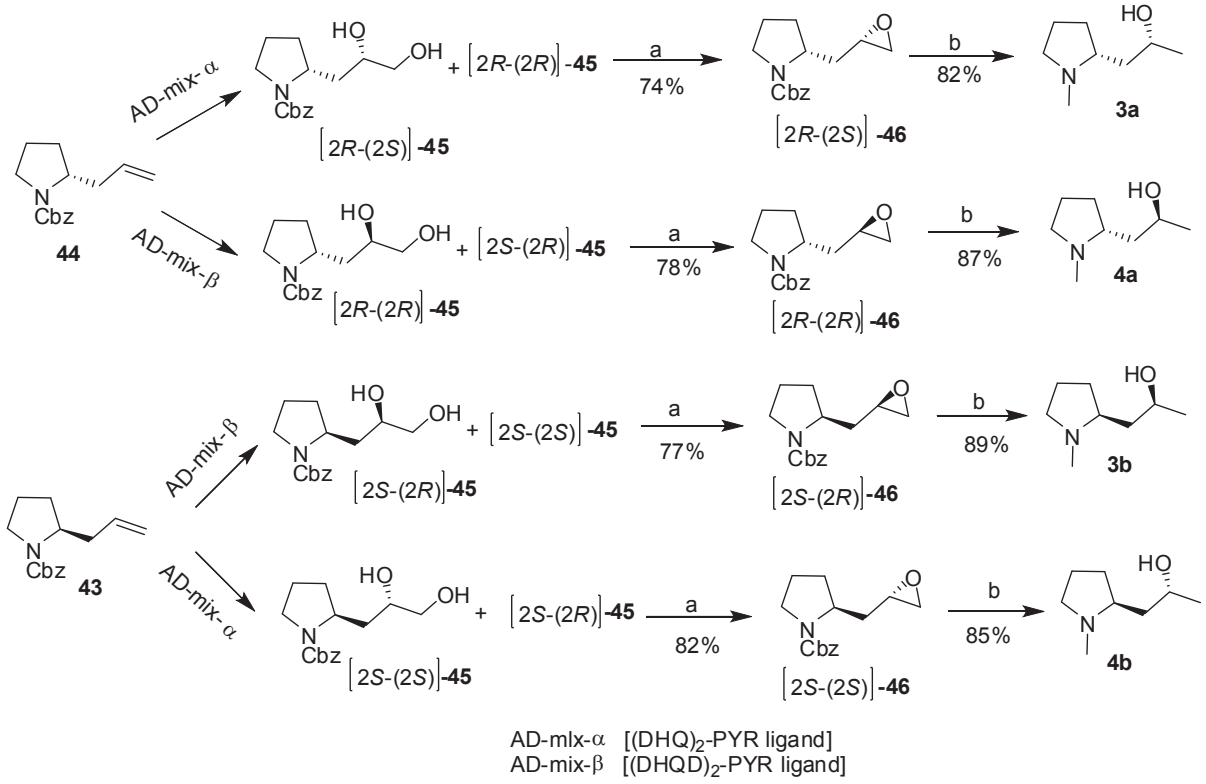
Yadav and co-workers accomplished the synthesis of (+)-pseudohygroline **4a** in continuation of their synthetic research on Prins cyclisation.[15f] Thus the diol **28** was successfully converted to **29** on Prins cyclisation using CH_3CHO in TFA followed by treatment with methanolic K_2CO_3. The compound **29** on further synthetic conversions was transformed to (+)-pseudohygroline **4a** with an overall yield of 22%.

Momose and co-workers synthesized all four isomers of hygroline **3** and pseudohygroline **4** using iterative asymmetric dihydroxylation (scheme 6 & 7).[15a] The key pyrrolidines **43** and **44** were synthesized starting from alkene **37** via Sharpless asymmetric dihydroxylation (SAD) using AD-mix-β [$(DHQD)_2$-PYR ligand] and AD-mix-α [$(DHQ)_2$-PYR ligand] respectively, after following the synthetic sequences b-f. The pyrrolidines **43** and **44** were in turn subjected to SAD using the same ligands as earlier giving diols **45** with different configurations. The epoxidation of each diol **45** followed by subsequent treatment with LAH afforded all the expected isomers of **3** & **4**.



Scheme 6

Reagents and conditions: (a) AD-mix-β [$(DHQD)_2$-PYR ligand], 95%;(b) (i) $(CH_2O)_3CCH_3$/PPTS; (ii) CH_3COBr; (iii) Amberlite IRA410 (85% three steps) (c) (i) vinylmagnesium bromide/$(CH_3)_2S$-CuBr; (ii) MOMCl/$i$$Pr_2NEt$ (91% two steps); (d) (i) TBAF; (ii) MsCl/pyridine; (iii) NaN_3 (80% three steps); (e) (i) NCl; (ii) MsCl/pyridine, 96%; (f) (i) Ph_3P/H_2O; (ii) $CbzCl/K_2CO_3$ (61% two steps); (g) AD-mix-α [$(DHQ)_2$-PYR ligand].



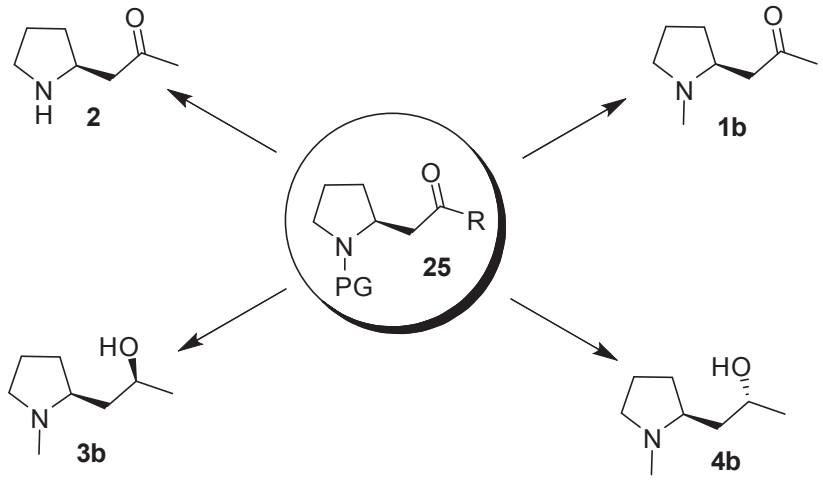
Scheme 7

Reagents and conditions: (a) (i) $(CH_3O)_3CCH_3$; (ii) CH_3COBr; (iii) K_2CO_3/CH_3OH; (b) $LiAlH_4$

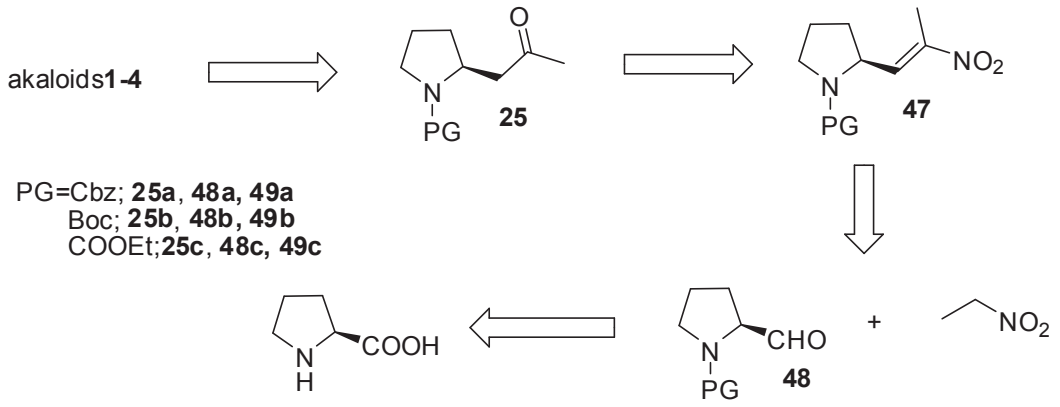
Results and Discussion

Our molecules of interests were 2-substituted pyrrolidine alkaloids with a stereogenic nitrogen centre, ubiquitously present in nature and of considerable synthetic interests due their potent pharmaceutical and medicinal applications. The available methods in the literature mainly include chiral auxiliary mediated synthesis, organocatalysis and very few chiral pool methods. In continuation of our research interest in chiral pool synthesis using easily available chiral sources, we undertook the synthesis of some of the 2-substituted pyrrolidine alkaloids containing 1, 3-aminoketone and 1, 3-amino alcohol units, namely (-)-hygrine **1b**, (-)-norhgyrine **2**, (-)-hygroline **3b** and (-)-pseudohygroline **4b**.

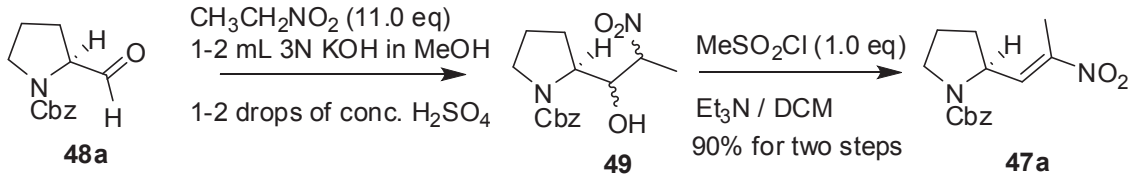
Our main objective of this work was to develop a new practical and versatile synergistic protocol by combinatorial Henry and Nef reaction for the synthesis of some of the useful 2-substituted pyrrolidine and piperidine alkaloids. This protocol even though well known in the literature,[16] surprisingly not well efficiently explored for the synthetic purposes. Proline, a leading amino acid was chosen to be a facile chiral source for our synthetic studies. We envisioned the intermediates **25** can serve as ideal precursors for the synthesis of our targeted alkaloids (scheme 8). These units could be derived by performing Nef reaction on the corresponding nitro alkenes **47**. Based on this we formulated a retro synthetic sequence as outlined in the in scheme 9.



Scheme 8. Synthesis of alkaloids through a common precursor



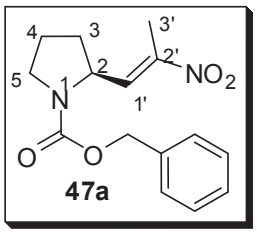
Scheme 9. Retrosynthesis



Scheme 10. Successful Henry reaction using catalytic KOH

At the outset of our study, we undertook several investigative methods to arrive with the nitrofunctional intermediate **47a**. The integrity of the chirality was of major concern since the aldehyde **48a** having a chiral centre existing between carbonyl and nitrogen with a lone pair of electrons was readily racemisable under any drastic condition. Henry reaction of **48a** was thus carried out initially with nitroethane using weak bases like piperidine, K_2CO_3, pyridine and Et_3N, but resulted either in the low yield with the starting material remaining unreacted or total decomposition. The change of solvent and reaction conditions did not affect much to improve the fate of the reaction. Recent elegant work carried out by Fioravanti *et al* for the diastereoselective synthesis of *E* and *Z* nitroalkenes,[17] prompted us to employ the same method on our substrates. The initial reaction carried out on Cbz-prolinal **48a** with nitroethane gave us the nitroalkenes *E* & *Z* using piperidine base in DCM over molecular sieves and only one *E* isomer in toluene at reflux. But unfortunately, in our hand, failed to produce good yield when applied for the large scale synthesis of it. Then we thought of carrying out the Henry reaction with excess of nitroethane in the presence of catalytic amount of KOH (0.1-0.2 mol %) in methanol. The reaction smoothly took place giving us different possible isomers (four diastereomers) of the nitro alcohol **49**

within 1hour. The broad peak of IR stretching at 3500 cm^{-1} indicated the formation of hydroxyl products **49**. Since the requisite nitro olefin was desired irrespective of *E* and *Z* isomeric forms, the alcoholic mixture **49** was as such subjected to mesylation and subsequent elimination of the mesylate formed in the reaction mixture to furnish **47a** as a single isomer (scheme 10). The structure of **47a** was confirmed by spectroscopic elucidation.



47a

$[\alpha]_D^{28}$ +13.0 (c 0.1, $CHCl_3$); IR (neat): ν_{max} = 3108, 2979, 2934, 2882,1698, 1526 and 1356 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.64-1.71 (m, 2H, H-3), 1.80-1.87 (m, 2H, H-4), 1.8 (s, 3H, H-3'), 3.45 (m, 2H, H-5), 4.3-4.5 (m, 1H, H-2), 4.9-5.2 (m, 2H, CH_2Ph), 7.24-7.26 (d, 1H, H-1'), 7.31-7.36 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.7 (C-3'), 24.4 (C-3), 31.5 (C-4), 46.9 (C-5), 55.0 (C-2), 67.6 (*C*H_2-Ph), 127. 8 (PhCH), 128.5 (PhCH), 128.5 (PhCH), 135.1 (C-1'), 136.4 (Ph*C*), 148.2 (C-2'), 154.8 (N*CO*); HRMS: *m/z* calcd for $C_{15}H_{18}N_2O_4Na$ $[M + Na]^+$: 313.1164; found: 313.1169.

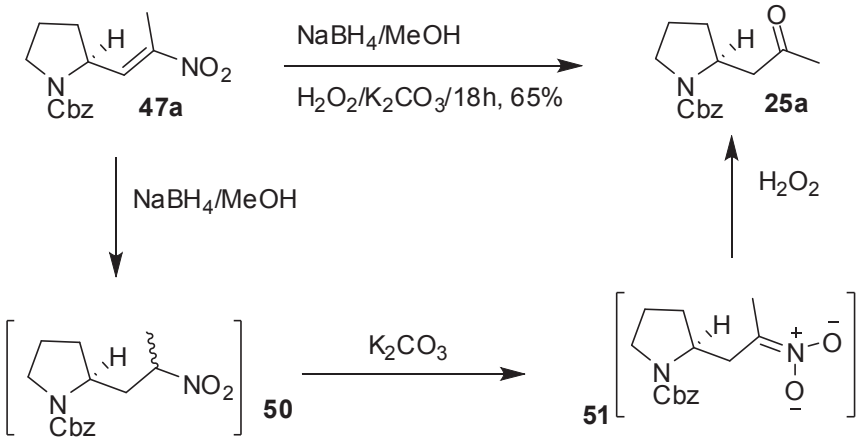
On obtaining the requisite nitro olefin **47a**, our next job was to introduce the carbonyl functionality to arrive at the key intermediate **25a** through Nef reaction.

The application of general conventional Nef method using strong acid-base treatment for the generation of carbonyl group from nitro was strictly ruled out in order to avoid the consequences of racemisation and deprotection of the carbamate protecting group. The alternate methods were probed for the suitable Nef conditions. Initially we thought of converting nitroalkene **47a** to nitroalkane by reduction using $NaBH_4$ and then transforming to carbonyl. But it was observed reduction gave poor yield with stoichiometric ratio of $NaBH_4$ and slight excess resulted in polymerisation.[18] We then directly applied some of the mild Nef methods on the nitro olefin **25a** as depicted in the table 1. Initially we subjected the nitro alkene **47a** for the treatment with activated Al powder in the presence of $NiCl_2$[19] which resulted in immediate total decomposition of the substrate showing very high exothermic change. The reaction of nitro olefin **47a** with $SnCl_2$[20] also resulted in decomposition. The application of McMurray Nef reaction using $TiCl_3$[21] which even though produced the product **25a**, the poor yield disfavoured us for adapting it. The

substrate **47a** was then subjected to react with $NaBH_4$ in methanol, after two hours H_2O_2 and K_2CO_3 were added and left overnight.[22] It gave a clean keto product **25a** after column chromatographic purification in 65% yield (scheme 11).

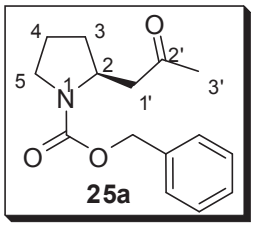
Reaction conditions	Observations
Al-$NiCl_2.H_2O/NaBH_4$	Decomposition of the reactants
$SnCl_2.2H_2O$ / THF	Decomposition of the reactants
McMurray method	10% yield
$NaBH_4/H_2O_2/K_2CO_3$	Product **25a** in 65% yield

Table 1



Scheme 11. Successful Nef reaction with plausible mechanism

The structure of **25a** was confirmed by spectroscopic techniques.



$[\alpha]_D^{28}$ -38.0 (*c* 0.5, $CHCl_3$).; IR (neat) ν_{max} =1693, 1711 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.66-2.15 (m, 7H, H-3, H-4, H-3'), 2.42-2.45 (m, 1H, H-1'A), 2.82-3.15 (m, 1H, H-1'B), 3.41-3.42 (m, 2H, H-5), 4.20-4.23 (m, 1H, H-2), 5.08-5.17 (m, 2H, C*H*$_2$Ph), 7.29-7.36 (m, 5H, Ar-H).; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.6 (C-3), 30.3 (C-3'), 30.9 (C-4),

46.6 (C-1'), 47.6 (C-5), 54.0 (C-2), 66.6 (*C*H_2Ph), 127.3 (PhCH), 127.6 (PhCH), 128.2 (PhCH), 137.0 (PhC), 153.6 (N*C*O), 206.8 (C-2').; HRMS: *m/z* calcd for $C_{15}H_{19}NO_3Na$ [M + Na]$^+$: 284.1263; found: 284.1266.

Once a platform was set-up for the optimised Nef reaction conditions, we prepared different nitro olefinic compounds **47** (**a**, **b**, **c**) with different carbamate protecting groups and successfully converted them to carbonyl intermediates **25** (**a**, **b**, **c**) with yield ranging from 56 to 65% using the same method (scheme 4) (table 2). However, Henry reaction of phenylnitromethane with any of the aldehyde **48** could not be accomplished (table 2).

Each of the isomers were charachtersided by IR and NMR and further confirmed by HRMS. The retention of chirality was visualized by comparing the optical rotation values of **25a** with that reported in the literature.

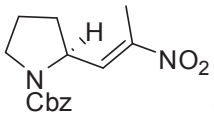
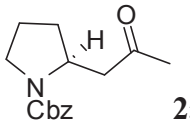
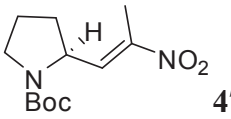
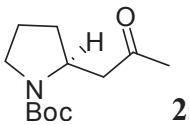
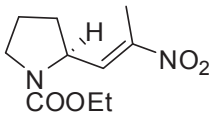
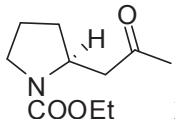
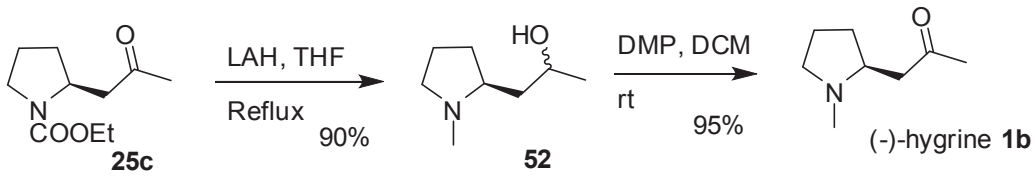
Nitro compounds	Nef produtcs	Yield
 **47a**	 **25a**	65%
 **47b**	 **25b**	56%
 **47c**	 **25c**	56%

Table 2. Synthesis of conjugated nitro olefins and Nef products

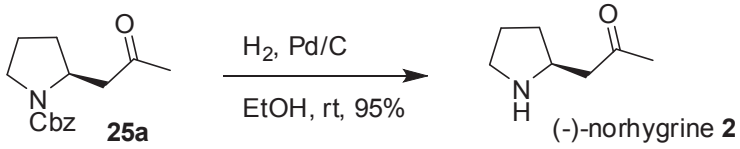
The compounds hygrine **1** and norhygrine **2** differ w. r. t the presence of methyl group on nitrogen atom. For the synthesis of (-)-hygrine **1b**, the ethyl carbamate protected compound **25c** was subjected to LAH reduction to furnish the diastereomeric mixture of amino alcohol **52** whose formation was indicated by the appearance of broad IR stretching at 3500 cm^{-1} and disappearance of NCO & CO stretching at 1690-1710 cm^{-1}. The crude alcohol was as such oxidised using Dess-Martin periodinane (DMP) in DCM to give **1b**

(scheme 12). The compound **1b** was purified by column chromatography and converted to hydrochloride salt whose structure was analysed using spectroscopic techniques for confirming the formation of it. The specific optical rotation observed was in good agreement with the literature. $[\alpha]_D^{30}$ -33.2 (c 0.2, H_2O); {Lit.[14h] $[\alpha]_D^{30}$ +34.5 (c 0.5, H_2O) for *R* isomer.

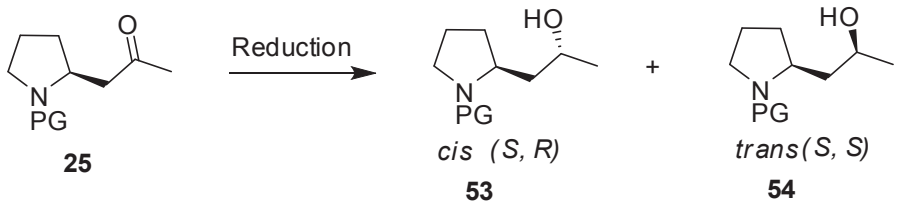


Scheme 12. Synthesis of (-)-hygrine

The synthesis of (-)-norhygrine **2** was easily achieved by chemoselective hydrogenolysis of Cbz group of **25a** over Pd/C (scheme 13). The formation of **2** was confirmed by spectroscopic techniques $[\alpha]_D^{30}$ -30.2 (c 0.2, $CHCl_3$); {Lit.[14j] $[\alpha]_D^{33}$ -29.6 (c 0.14, $CHCl_3$)}.



Scheme 13. Synthesis of (-)-norhygrine

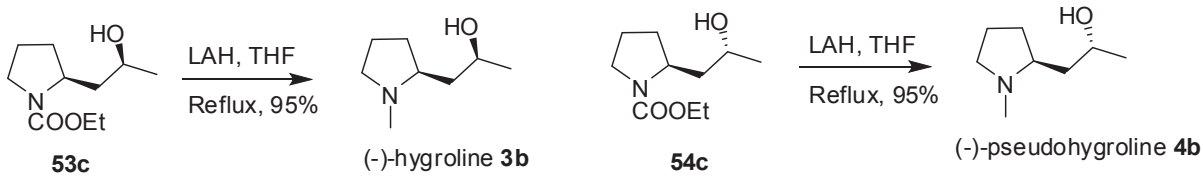


25, 53, 54; **a**, PG=Cbz; **b**, PG=Boc; **c**, PG=COOEt

Carbonyl compound	Reducing agents	Diastereomeric ratio with different protecting groups		
		PG=Boc	PG=Cbz	PG=COOEt
	$NaBH_4$	79:21	50:50	58:42
25	$Li(t\text{-}OBu)_3AlH$	**99:1**	92:8	81:19
	$Zn(BH_4)_2$	**15:85**	45:55	54:46

Scheme 14. Diastereoselective reduction of carbonyls

For the synthesis of sedum alkaoids (-)-pseudohygroline **4b** and (-)-hygroline **3b,** which differ in their hydroxyl configuration, we probed the selective reduction of **25a-c** with different reducing agents (scheme 14). Results of these studies show that there is a very little diastereoselectivity for the protecting groups ethoxycarbonyl and benzyloxycarbonyl when $NaBH_4$ was used as a reducing agent, while when the *tert*-butoxycarbonyl is the protecting group there was 80% *cis* diastereoselectivity. The *cis* diastereoselectivity was found to increase for all the protecting groups when bulky lithium *tri-tert*-butoxyaluminium hydride was used, the maximum (98%) being for the *tert*-butoxy protecting group. Interestingly, *trans* selectivity of 85% was observed for the *tert*-butoxy protected **25** when $Zn(BH_4)_2$ was used as the reducing agent. The *tert*-butoxycarbonyl group shows a better discrimination for diastereoselective reduction with bulky reducing agent $Li(t\text{-}OBu)_3AlH$ giving maximum *syn* diastereoselectivity. A noteworthy *trans* diastereoselectivity was obtained when $Zn(BH_4)_2$ was used as a reducing agent for **25b** which is normally difficult to get.[23] The synthesis of (-)-hygroline **3b** and (-)-pseudohygroline **4b** were achieved by LAH reduction of **53c** and **54c** respectively. The products obtained did show the required ^1H NMR signals with matching integration certified the purity of the synthesized compounds. The optical rotation values for (-)-pseudohygroline $[\alpha]^{28}_D$ -90 (c 0.2, EtOH; {Lit.[15e] $[\alpha]_D$ +70.7 (*c* 2.0, EtOH); Lit.[15a] $[\alpha]_D^{25}$ +97.0 (*c* 3.4, EtOH) for *RR* isomer; for (-)-hygroline, $[\alpha]^{23}_D$ -50 (c 0.2, EtOH); {Lit.[15b] $[\alpha]_D^{20}$ -50.2 (c 0.466, EtOH), Lit.[15a] $[\alpha]^{22}_D$ -49 (c 0.4, EtOH)}.



Scheme 15. Synthesis of (-)-hygroline and (-)-pseudohygroline

Section 2: Synthesis of piperidine alkaloids

Introduction

Piperidine alkaloids derive their name from plant black pepper and responsible for the spicy taste of it. These alkaloids are mainly isolated from different plant extracts and also from insects and amphibians.[24] Manifolds of piperidine alkaloids are under pharmaceutical research and over 12000 alkaloids are under clinical trial since last ten years due to their notable biological activities.[25] The piperidine alkaloids with substitution at the 2nd position attracted special synthetic interests due to their wide spectrum of pharmaceutical applications. The molecules of specific interest in 2-substituted piperidine alkaloids are those consisting 1, 3-aminoketones and 1, 3-amino alcohols; principal units present in various natural products (fig. 2).[7] Another attraction was the potential of 1, 3-amino alcohol units to act as chiral ligands and chiral auxiliaries.[8] A vast variety of methods are available in the literature for the synthesis of these amino alcohols, however only few asymmetric methods are reported,[26] mainly involving proline catalysed α-aminoxylation,[26a] rhodium catalysed asymmetric transformations[26b] and asymmetric Mannich reaction.[26c] These alkaloids are isolated from 60 species of the genus *sedum* and are usually referred as *sedum* alkaloids which has already been introduced under section 1.

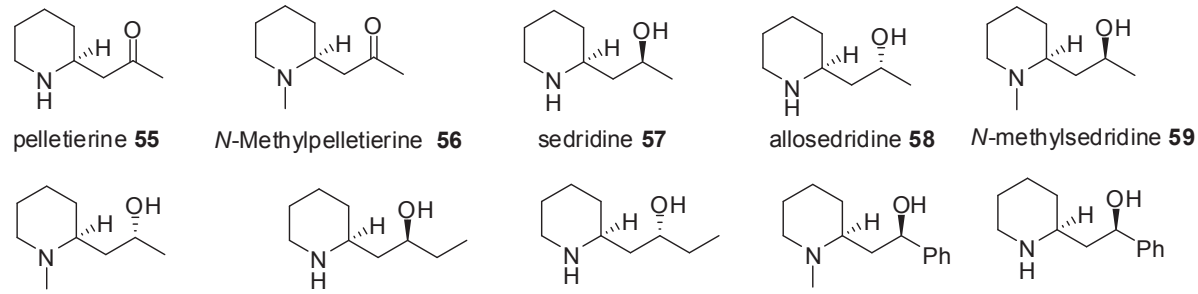


Figure 2. 2-Substituted piperidine alkaloids with 1, 3-aminoketone and 1, 3-amino alcohol units

Literature Review

Isolation

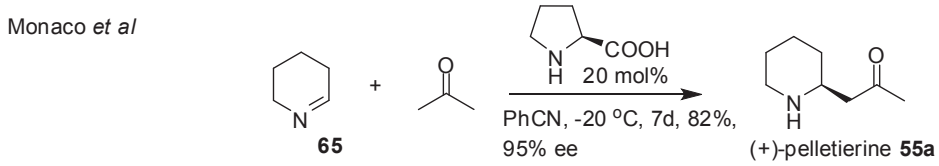
(-)-*N*-Methylpelletierine **56** was isolated[27c] along with (-) & (±)-pelletierine **55** from the same source.[27] (+)-Sedridine **57** was isolated from *Sedum acre*,[28] (-)-allosedridine **58** was isolated from *Sedum nedum*[29] while *N*-methylsedridine **59** and *N*-methylallosedridine **60** were first isolated from *Sedum polytrichoides*[30] and *Sedum sarmentosum.*[31] Ethylnorlobelol **61** & **62** were isolated from *Loberia inflate.*[32]

Synthesis

Various synthetic approaches are available for the synthesis of pelletierine **55**, sedridine **57**, ethyl norlobelol **62** both for racemic and asymmetric forms.[33, 34, 15h] Some of the recent asymmetric syntheses are elaborated below.

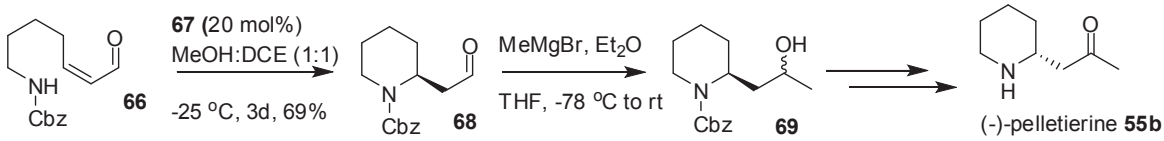
Organocatalytic approach

Monaco *et al*



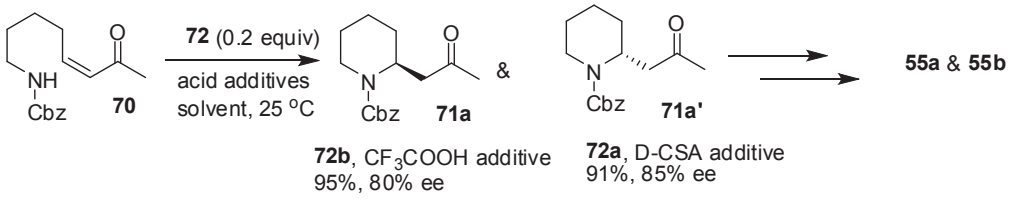
Scheme 16

Carter and co-workers

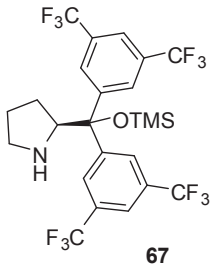


Scheme 17

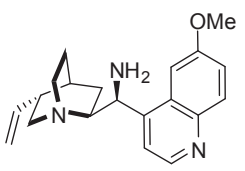
Fan and co-workers



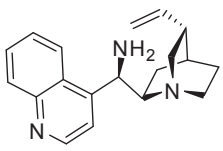
Scheme 18



67



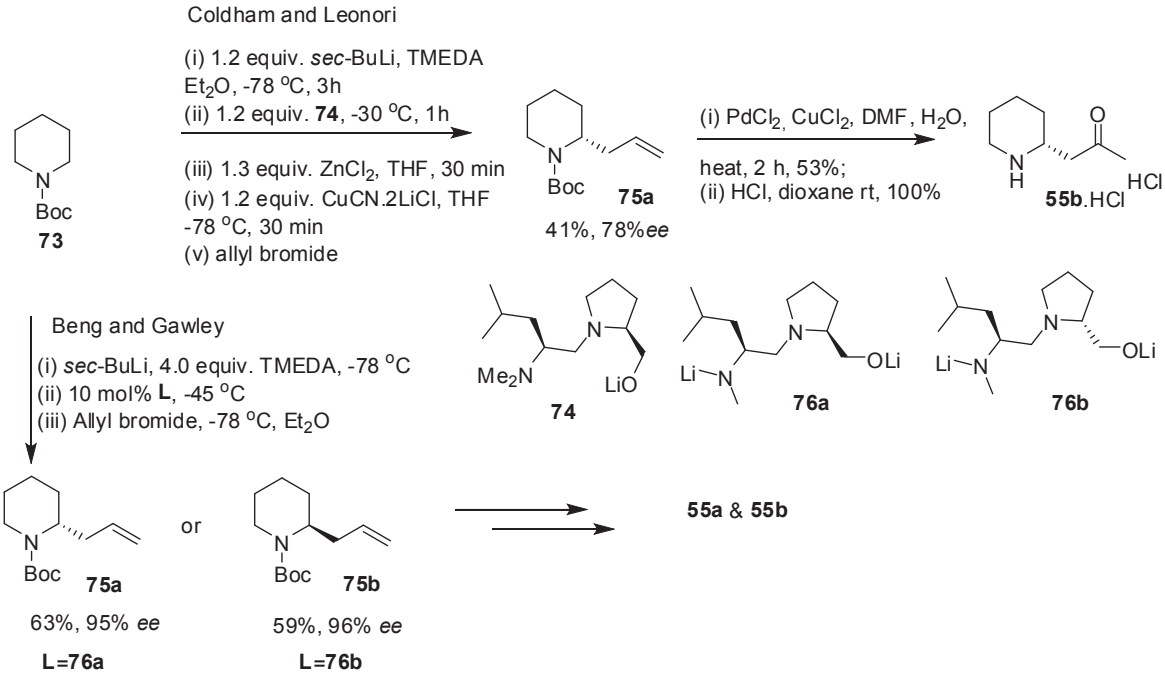
72a



72b

Monaco *et al* successfully accomplished the synthesis of (+)-pelletierine **55a** via biomimetic organocatalysis using L-proline.[33m]The addition of acetone across imine **65** took place enentioselectively to furnish **55a** with 95% *ee* in 7 days. Different organocatalysts were screened and the configuration was rationalised by invoking different transition states (scheme 16). Carter and co-workers persuaded the synthesis of (-)-pelletierine **55b** via intramolecular aza-Michael reaction of reactive carbamate with α, β-unsaturated aldehyde like **66** using organocatalyst of the type **67** (scheme 17).[33s] Fan and co-workers achieved the synthesis of both (+)-pelletierine **55a** and (-)-pelletierine **55b** by establishing an organocatalytic route for the intramolecular aza-Michael reaction of less reactive α, β-unsaturated ketone, like **70**.[33n] Various organocatalysts of the type **72** were screened with different acidic additives to ensure high enentioselectivity (scheme 18).

Organometallic approaches

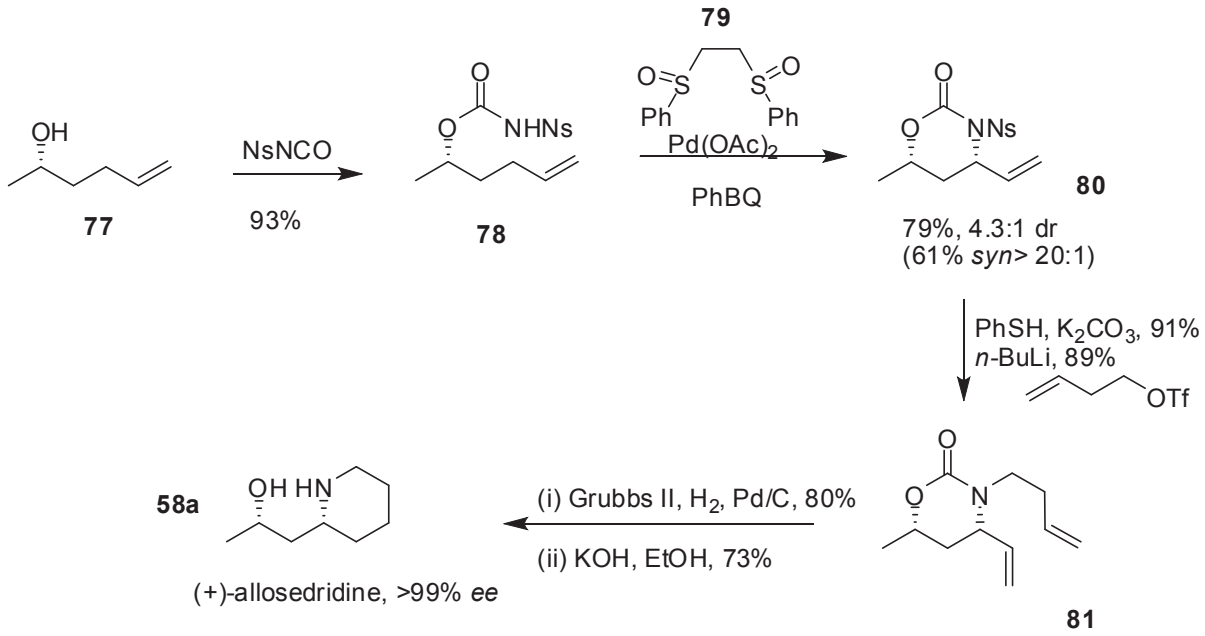


Scheme 19

Coldham and Leonori approached the synthesis of various 2-substituted pyrrolidine and piperidine alkaloids using asymmetric lithiation at the second position using the ligand **74** followed by in vitro transmetalation and nucleophilic substitution.[34d] Thus the compound

75a obtained in this manner was subjected to Wacker oxidation and deprotection to give (-)-pelletierine **55b** (scheme 19).

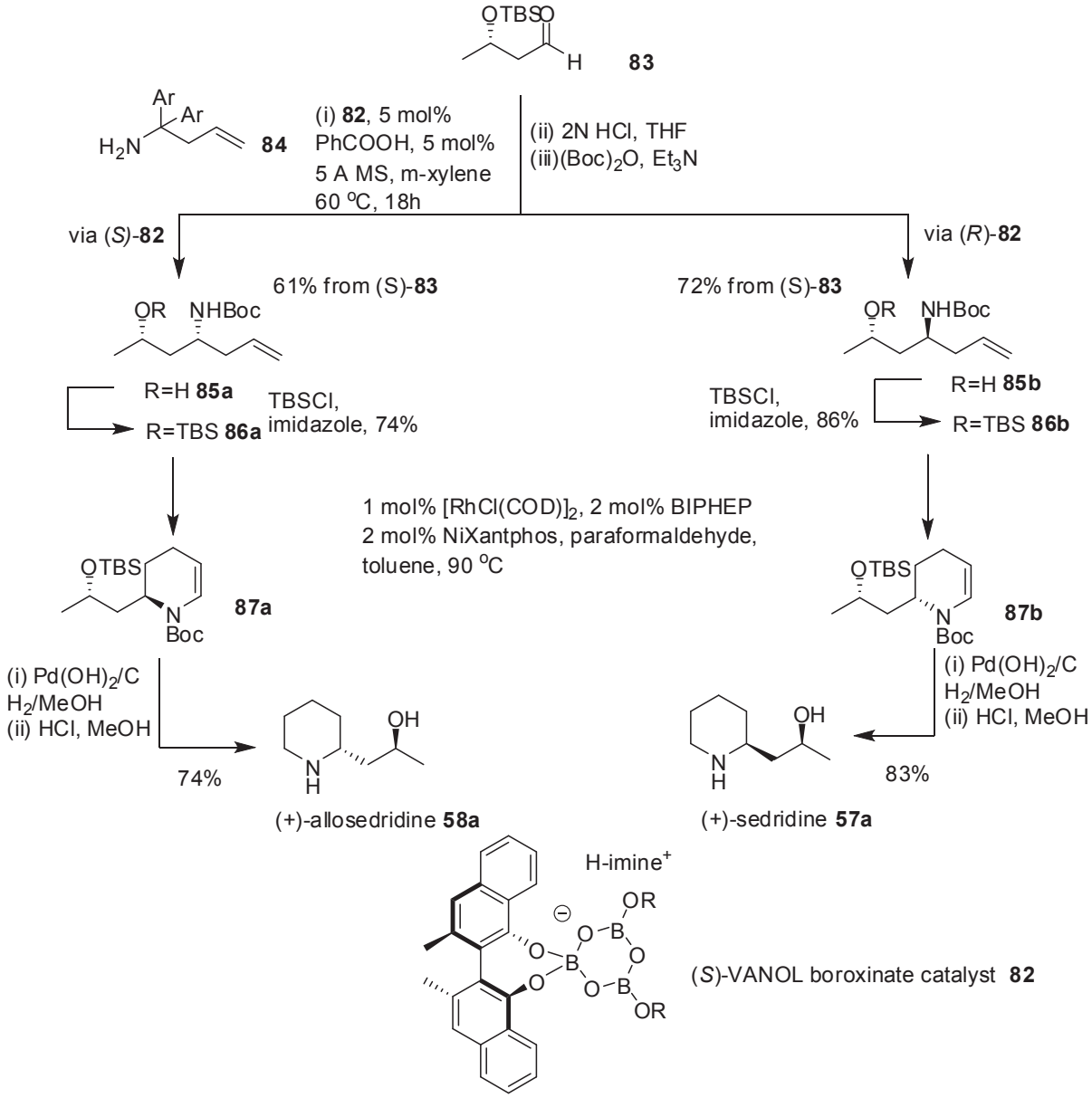
In a similar way, Beng and Gawley could accomplish the enentioselective synthesis of **75a** and **75b** using **76a** and **76b** respectively (scheme 19) which was further transformed to both the isomers **55a** and **55b**.[33q]



Scheme 20

Rice and White developed a new method for the construction of *syn* 1, 3-amino alcohols using Pd/sulfoxide catalysed C-H amination and successfully synthesized (+)-allosedridine **58a.**[34c] The key steps involved were the C–H amination of **78** giving diastereoselectively **80** which on further *N* substitution and RCM with subsequent hydrolysis of carbamate furnished the natural product (+)-allosedridine **58a** (scheme 20).

Ren and Wulff achieved the synthesis of sedum alkaloids via catalyst controlled aza-Cope rearrangement and Rh catalysed hydroformylation.[34a] Thus compound **83** on condensation with amine **84** followed by aza-Cope rearrangement using (*S*)-**82** and (*R*)-**82** afforded diastereoselectively **85a** and **85b** respectively. Hydroformylation of **86a** and **86b** and further synthetic conversions afforded the natural products **58a** and **57** respectively (scheme 21).

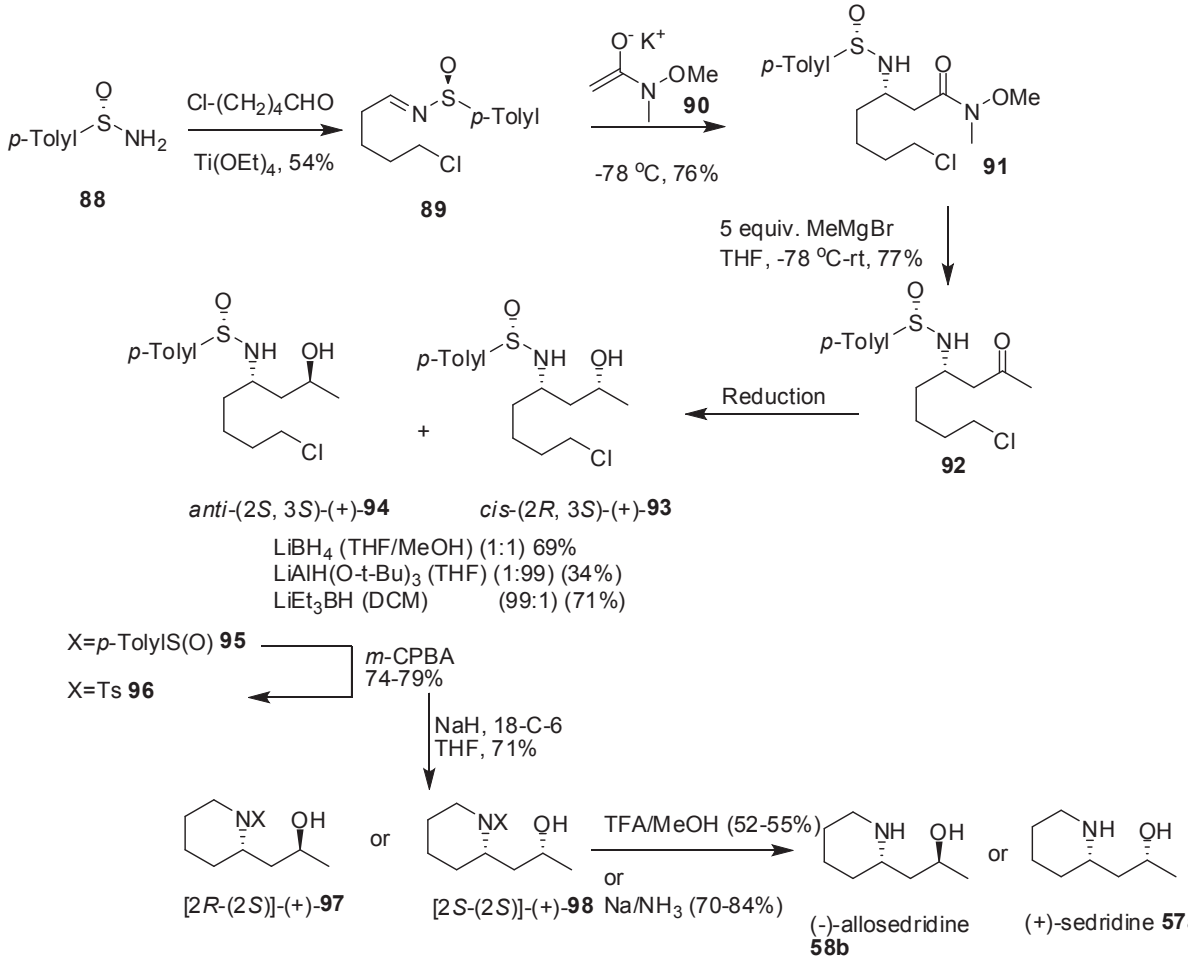


Scheme 21

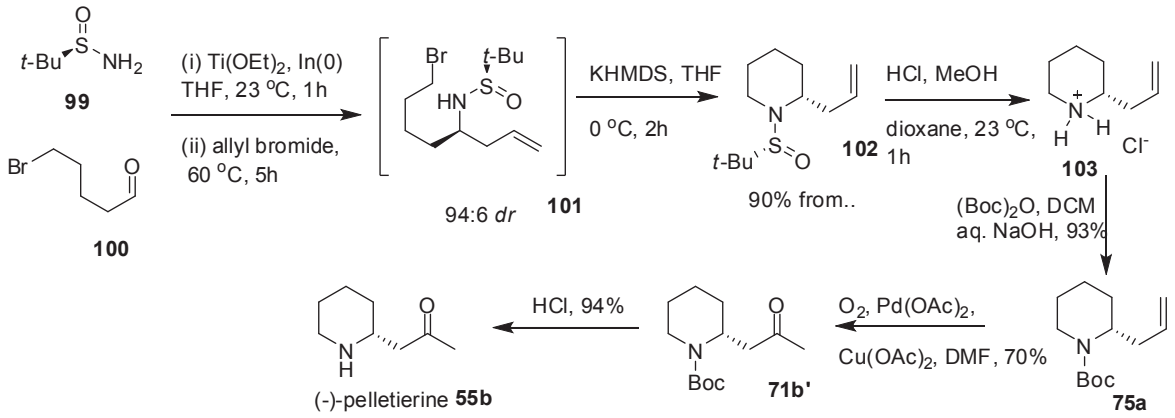
Chiral auxiliary methods

Davis and co-workers accomplished the synthesis of (-)-allosedridine **58b** and (+)-sedridine **57a** by chiral group impregnated *N*-sulfinyl β-amino Weinreb amides (scheme 22).[34l] The chiral sulfinyl compound **88** was condensed with 5-chloro-1-pentanal giving **89** which were subjected to nucleophilic addition by Weinreb amide **90** giving diastereoselectively **91**. The compound **92** prepared by Grignard reaction on **91** using

MeMgBr was subjected for the diastereoselective reduction of carbonyl using different reducing agents. A remarkable distinct diastereoselection was observed by using $LiAl(O^tBu)_3H$ and $LiEt_3BH$, giving **94** and **93**. The further synthetic conversions of **94** and **93** culminated in the synthesis of natural products (-)-allosedridine **58b** and (+)-sedridine **57a** respectively.

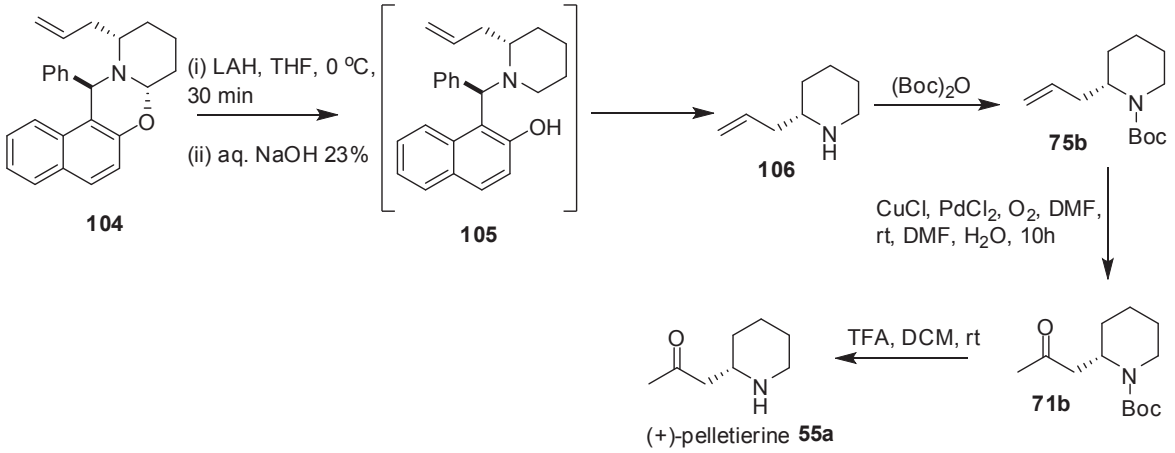


Scheme 22



Scheme 23

Foubelo and co-workers recently developed a one-pot protocol for the synthesis of chiral 2-substituted allyl piperidine (scheme 23).[33p] The synthesis of **101** was achieved using indium mediated addition of allyl bromide to a mixture of chiral sulphonamide **99** and 1-bromopantenal **100**, which exclusively produced **101** both chemo- and diastereoselectively. Without further purification, the compound **101** was subjected to cyclisation using KHMDS giving **102** which on subsequent deprotection furnished **103**. The further classical synthetic transformations performed on **103** produced the *sedum* alkaloid (-)-pelletierine **55b**.



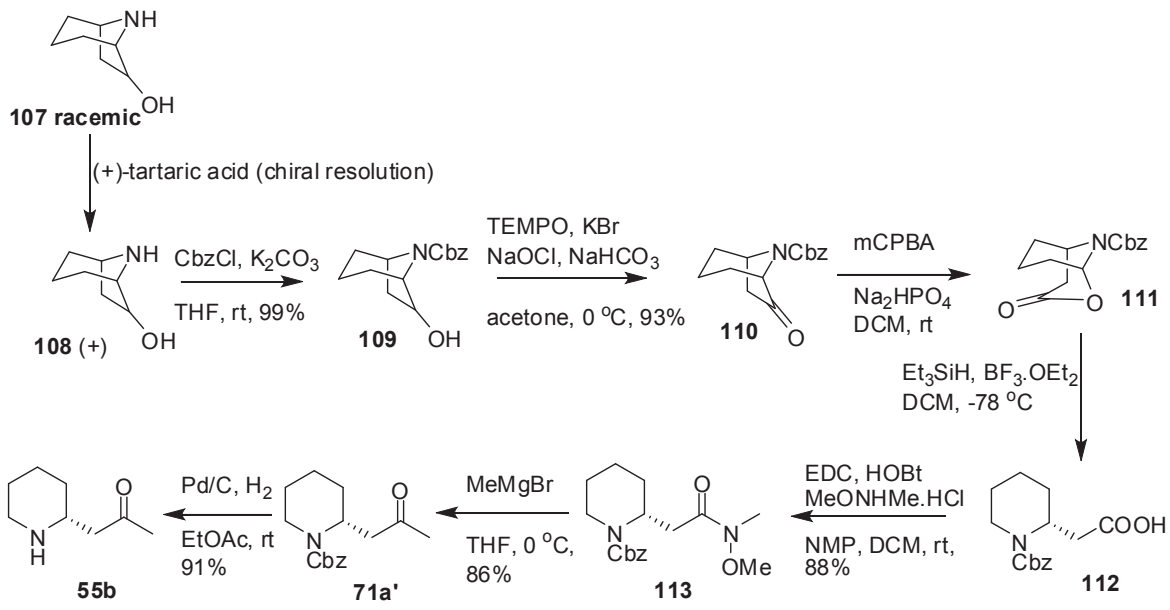
Scheme 24

Cheng *et al* performed the synthesis of 2-substituted piperidine alkaloids using Betti base as a chiral auxiliary (scheme 24).[33j] The key step was the novel deprotection of chiral auxiliary of Betti base **104** using LAH and base NaOH with the retention of allyl unit

which could lead to desired enentioselective synthesis of allyl piperidine unit **106** which was characterised as **75b.** The compound **75b** was then transformed to (+)-pelletierine **55a**.

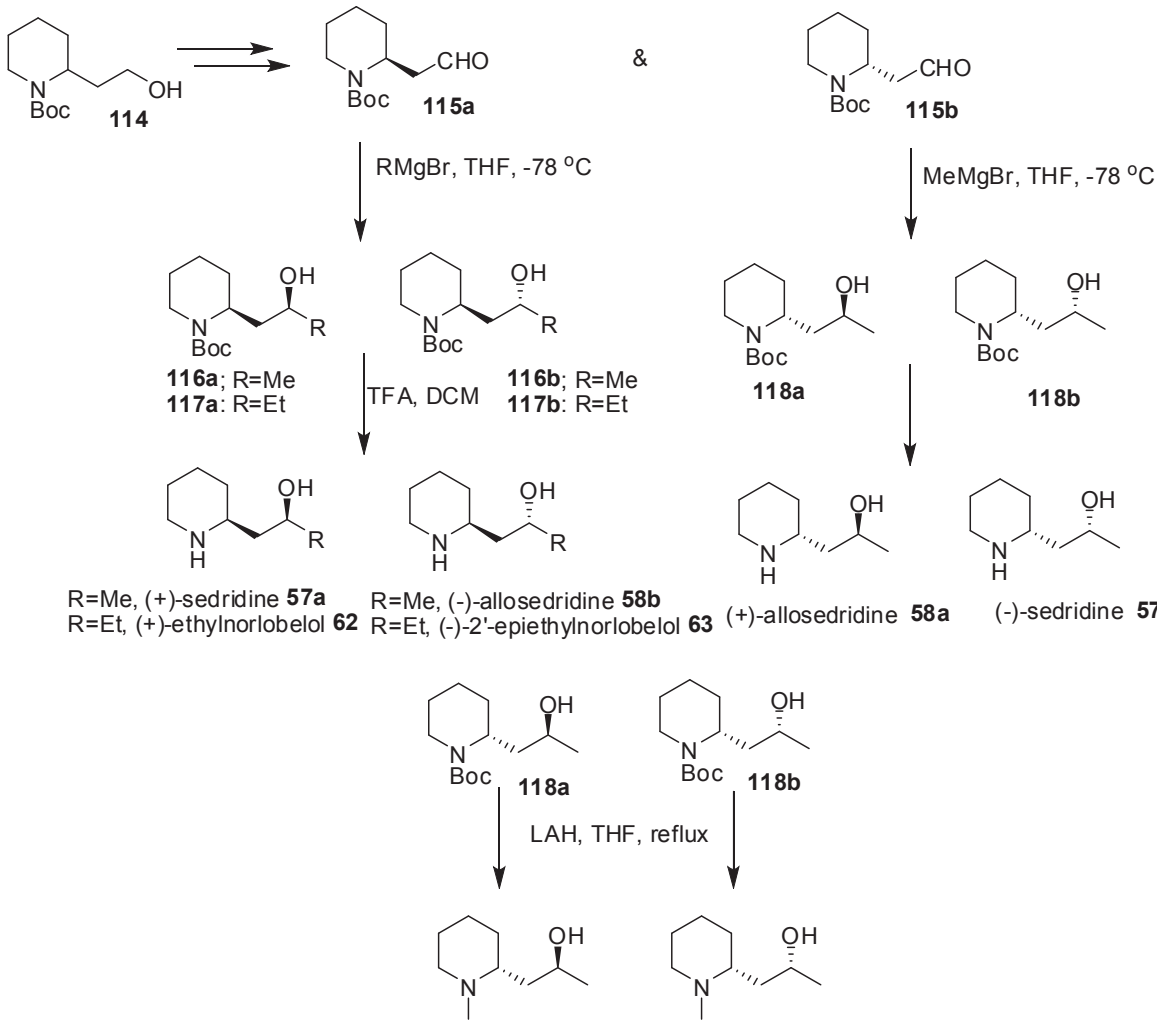
Chiral pool methods

Chiou and co-workers could successfully synthesize (-)-pelletierine **55b** by employing chiral resolution of racemic 6-tropanol **107** using (+)-tartaric acid (scheme 25).[33r] The optically pure **108** thus synthesized was subjected to Cbz protection of secondary amine followed by oxidation to **110**. The mCPBA reaction on **110** gave **111** which were subsequently transformed to homopipecolinic acid derivative **112**. The further conversion to Wienreb amide **113**, Grignard reaction with MeMgBr and Cbz hydrogenolysis afforded (-)-pelletierine **55b**.



Scheme 25

Passarella and co-workers synthesized different sedum alkaloids using enentiopure aldehyde **115** synthesized by racemic **114** through enzymatic chiral resolution.[34k]The direct diastereoselective Grignard reaction, deprotection and reduction of the Boc protecting group afforded the various *sedum* alkaloids as shown in the scheme 26.



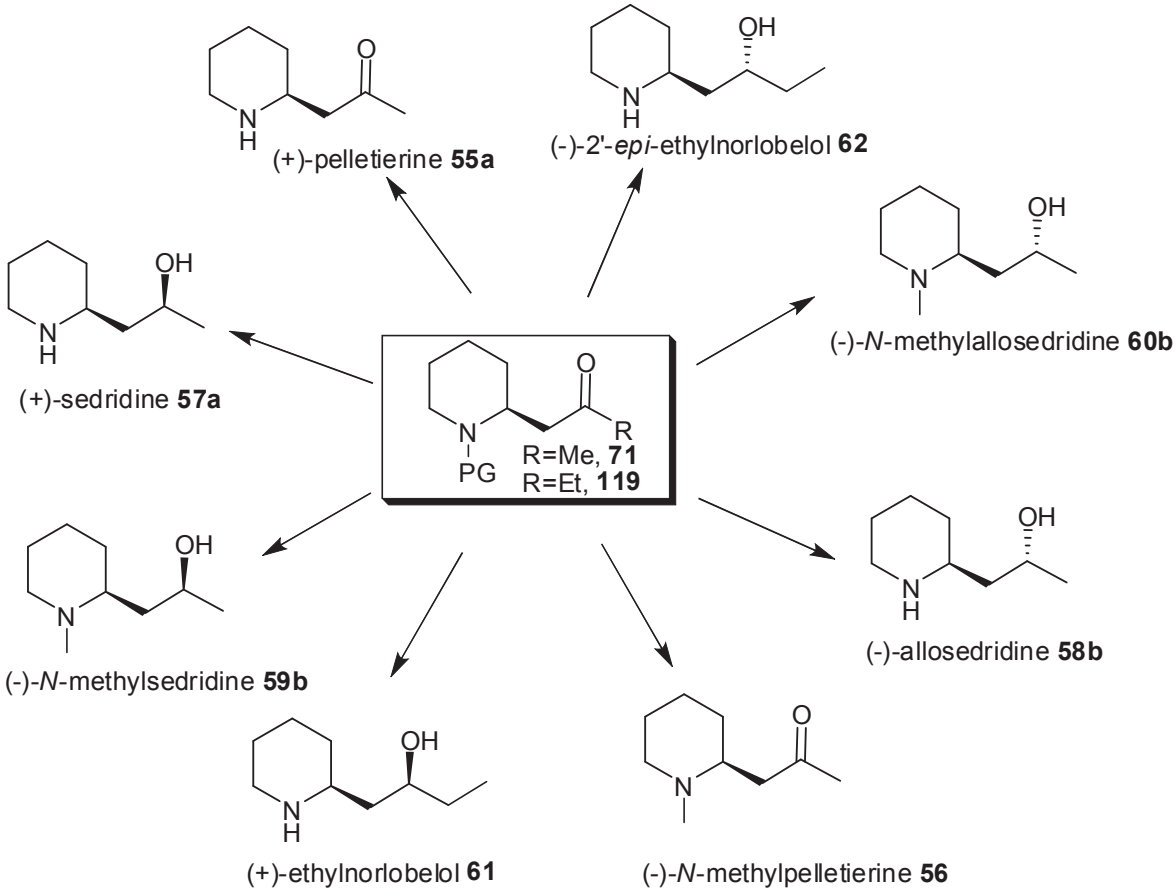
Scheme 26

Results and Discussion

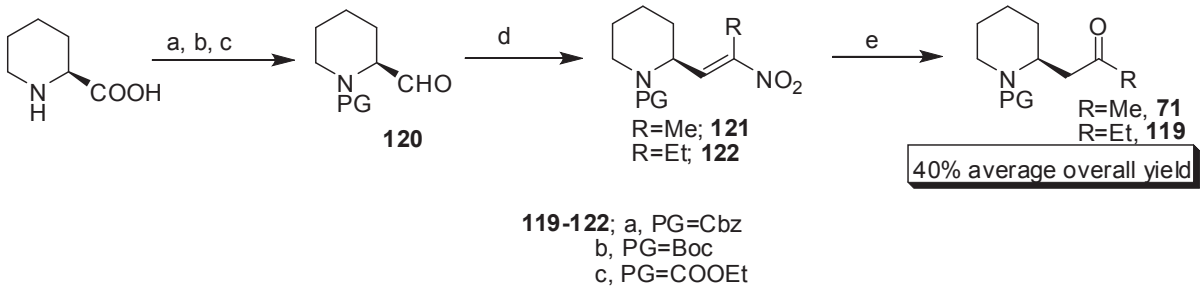
Our objective was in the continuation of synthetic studies using the Henry-Nef protocol, described for pyrrolidine alkaloids, for the synthesis of some of the piperidine alkaloids specifically *sedum* alkaloids.

The skeleton **71** & **119** envisioned to be the most viable precursor for the synthesis of some of the *sedum* alkaloids (scheme 27) which were to be obtained using Henry-Nef protocol as discussed in the previous section.

The synthesis started with commercially available (-)-pipecolinic acid, which on LAH reduction followed by protecting with different carbamates and further oxidation afforded **120**. The Henry reaction performed on **120** with nitro ethane and nitro propane produced nitro olefins **121** and **122** respectively after the treatment with $MeSO_2Cl$ and Et_3N.



Scheme 27. Synthetic approach from a common intermediate



Scheme 28. General synthetic route from L-pipecolinic acid

Reagents and conditions: (a) LAH, THF, reflux, 8 h, 90%; (b) For PG = –Cbz: Cbz–Cl, K_2CO_3, CH_3CN, 0 °C, 6 h, 85-90%; For PG = –Boc: $(Boc)_2O$, Et_3N, DCM, 0 °C, 80-90%; For PG = –COOEt: ClCOOEt, K_2CO_3, CH_3CN, 0 °C, 80-90%; (c) $(COCl)_2$, DMSO, Et_3N, DCM, –78 °C, 95%; (d) (i) $CH_3CH_2NO_2$ (*n*-$PrNO_2$), 0.1-0.2 mol% of 3N KOH, two drops of conc. H_2SO_4; (ii) $MeSO_2Cl$, Et_3N, DCM, (80%-90%, two steps); (e) $NaBH_4$, MeOH, K_2CO_3, H_2O_2, rt, 18 h (56-75%).

The Nef reaction performed on these nitro olefins gave us the corresponding carbonyl compounds **71** and **119** (scheme 28). The formation of Nef products were confirmed by spectroscopic techniques.

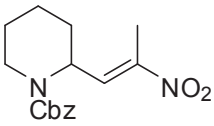
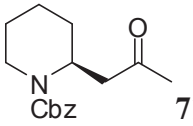
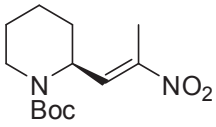
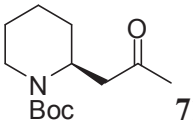
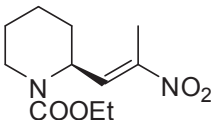
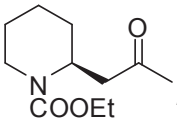
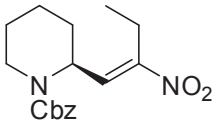
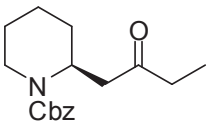
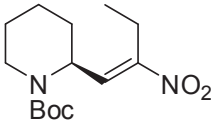
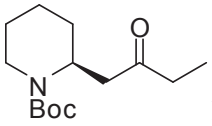
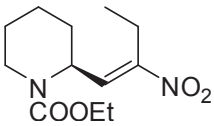
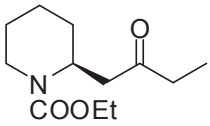
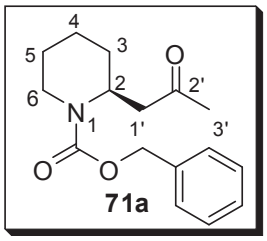
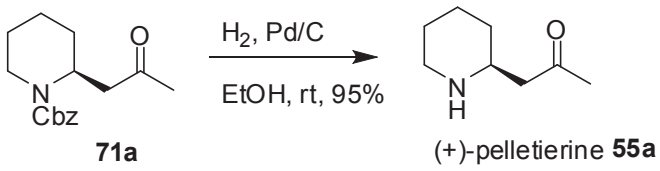
Nitro compounds	Nef produtcs	Yield
 **121a**	 **71a**	65%
 **121b**	 **71b**	60%
 **121c**	 **71c**	60%
 **122a**	 **119a**	75%
 **122b**	 **119b**	70%
 **122c**	 **119c**	65%

Table 2. Preparation of requisite Nef products for the synthesis of natural products



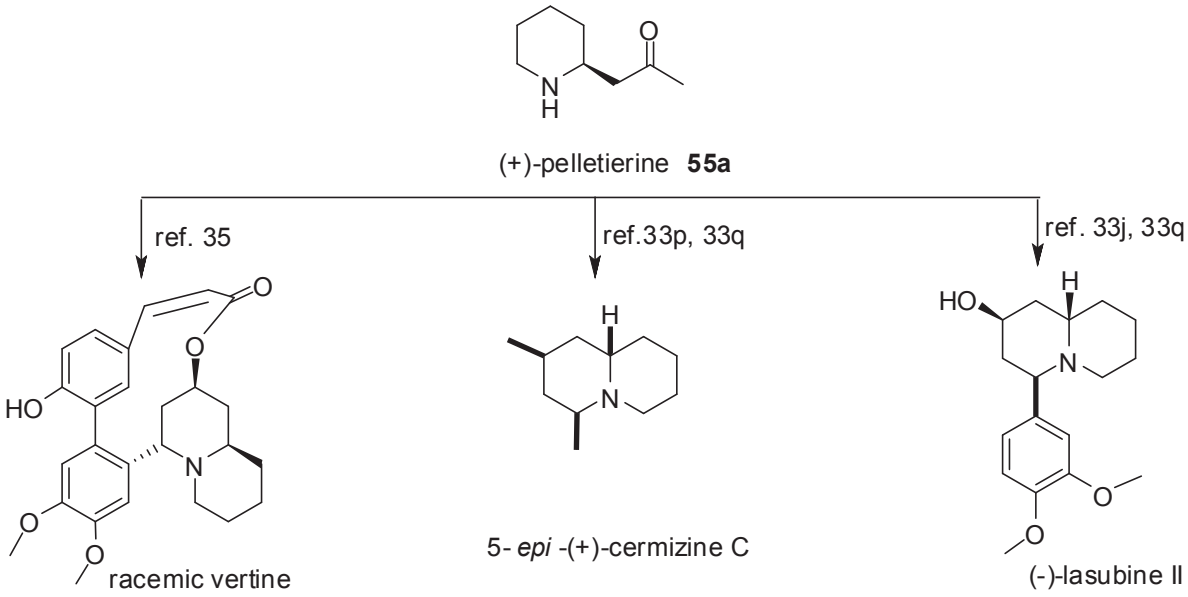
$[\alpha]_D^{28}$ -10.0 (*c* 0.5, $CHCl_3$) {Lit[33f] $[\alpha]_D^{26}$ +10.2 (*c* 2.5, $CHCl_3$) for (*R*)-isomer}; IR (neat) 2990, 1693, 1711 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.41-1.66 (m, 6H, H-4, H-5, H-3), 2.01-2.29 (m, 4H, H-3'), 2.69-2.86 (m, 2H, H-1'), 4.01-4.07 (buried m, 1H, H-6A), 4.70-4.72 (buried m, 1H, H-6B), 4.80-4.82 (buried m, 1H, H-2), 5.09-5.19 (m, 2H, C*H*$_2$Ph), 7.28-7.37 (m, 5H, Ph*H*); ^{13}C NMR ($CDCl_3$, 100MHz) : δ 18.8 (C-4), 25.2 (C-5), 28.3 (C-3), 30.1 (C-3'), 39.8 (C-1'), 44.3 (C-6), 47.5 (C-2), 65.3 (O*C*H$_2$Ph), 126.9 (Ph*C*H), 127.6 (Ph*C*H), 127.9 (Ph*C*H), 128.5 (Ph*C*H), 128.5 (Ph*C*H), 136.7 (PhC), 155.3 (N*C*O), 206.9 (C-2').

For the synthesis of (+)-pelletierine **55**, the carbobenzyloxy group of **71a** was chemo selectively deprotected using hydrogenation over Pd/C without affecting the carbonyl group (Scheme 29). The physical and spectral properties of thus synthesized **3** as its HCl salt matched very well with the literature values.

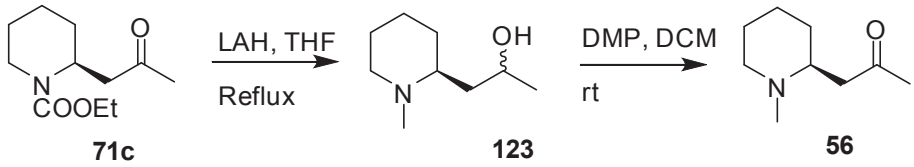


Scheme 29. Synthesis of (+)-pelletierine

Synthesis of compound **55** also constituted the formal synthesis of natural products like (±)-vertine, 5-*epi*-(+)-cermizine C and (-)-lasubine (scheme 30).[35, 33j, p, q]



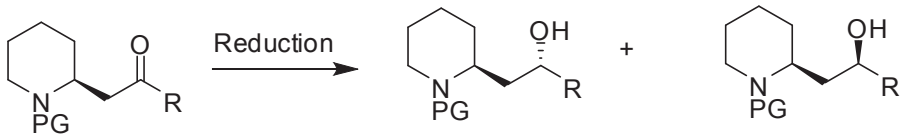
Scheme 30. Formal synthesis from (+)-pelletierine



Scheme 31. Synthesis of (-)-*N*-methylpelletierine

The LAH reduction of the compound **71c** gave the mixture of diastereomers **123** which as such were oxidised with Dess-Martin periodinane (DMP) to give (-)-*N*-methylpelletierine **56**, the spectral data was well consistent with the reported data (scheme 31). Incidentally this is a first asymmetric synthesis of (-)-*N*-methylpelletierine **56**.

The other alkaloids of our interest sedridine and norlobelol are 1, 3-amino alcohols and differ w. r. t configuration of hydroxyl group. The investigation of diastereoselective reduction was necessary for us to achieve good diastereoselection. Thus we subjected carbonyl functionality to reduction using different reducing agents as shown in the scheme 32. From this it was clear that in all the cases *cis (SR)* isomer was preferentially obtained over *trans* (*SS*). The *trans* selectivity over *cis* using $ZnBH_4$ as in the case of five member ring was not observed.



71; R=Me
119; R=Et

124; R=Me
125; R=Et

126; R=Me
127; R=Et

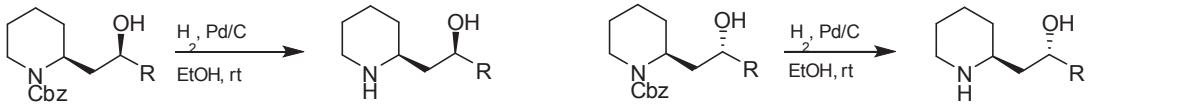
124-127; **a**, PG=Cbz; **c**, PG=COOEt

PG=Boc, R=Me; **116a** & **116b**
PG=Boc, R=Et; **117a** & **117b**

Carbonyl compound	Reducing agents	Diastereomeric ratio with different protecting groups		
		PG=Boc	PG=Cbz	PG=COOEt
R=Me	$NaBH_4$	72:28	56: 44	62: 38
	$LiAl(O^tBu)_3H$	**99.7: 0.3**	94: 6	75: 25
	$Zn(BH_4)_2$	63: 37	58: 42	60: 40
R=Et	$NaBH_4$	71: 29	55: 45	62: 38
	$LiAl(O^tBu)_3H$	**99.7: 0.3**	95: 5	75: 25
	$Zn(BH_4)_2$	64: 36	58: 42	60: 40

Scheme 32. Diastereoselective reduction of carbonyls

A straightforward deprotection of benzyloxycarbonyl group of compounds **126a, 124a, 127a** and **125a** resulted in accomplishing the synthesis of (+)-sedridine **57a**, (-)-allosedridine **58b**, (+)-ethylnorlobelol **61** and (-)-*epi*-ethylnorlobelol **62** (scheme 33).



R=Me, **126a**
R=Et, **127a**

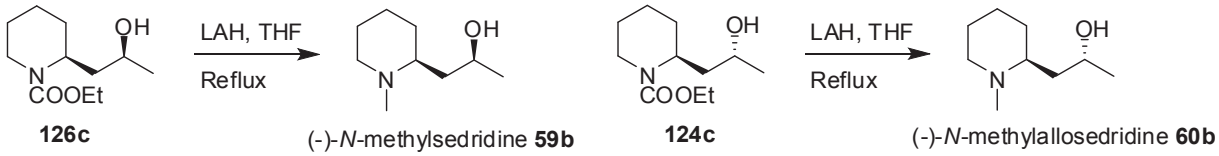
R=Me, (+)-sedridine **57a**
R=Et, (+)-ethylnorlobelol **61**

R=Me, **124a**
R=Et, **125a**

R=Me, (-)-allosedridine **58b**
R=Et, (-)-2'-*epi*-ethylnorlobelol **62**

Scheme 33. Synthesis of sedridine and ethylnorlobelol

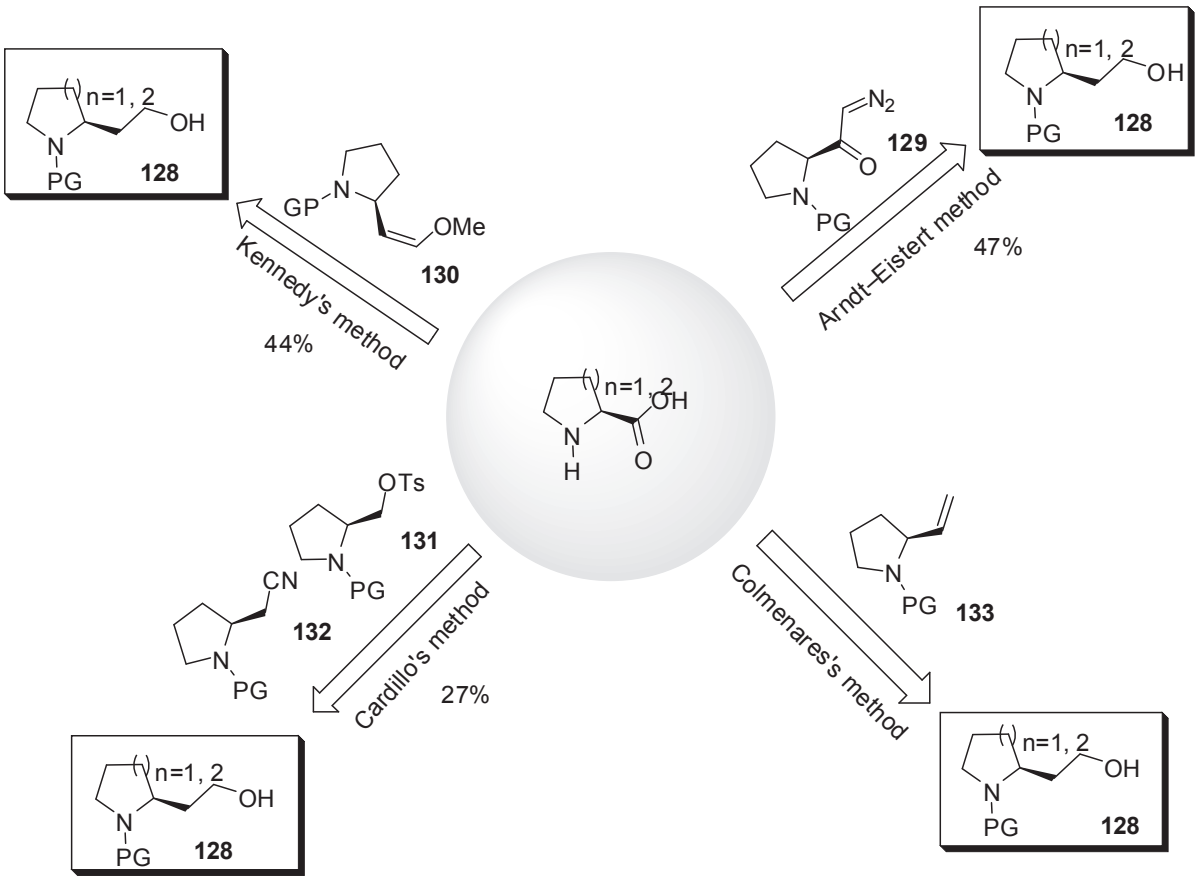
The synthesis of (-)-*N*-methylsedridine **59b** and (-)-*N*-methylallosedridine **60b** was achieved by LAH reduction of compounds **126c** and **124c** by reducing the ethoxycarbamate to methyl group (scheme 34).



Scheme 34. Synthesis of *N*-methylsedridine and *N*-methylallosedridine

Section 3: *Synthesis of homologated prolinol and pipecolinol*

Literature Review

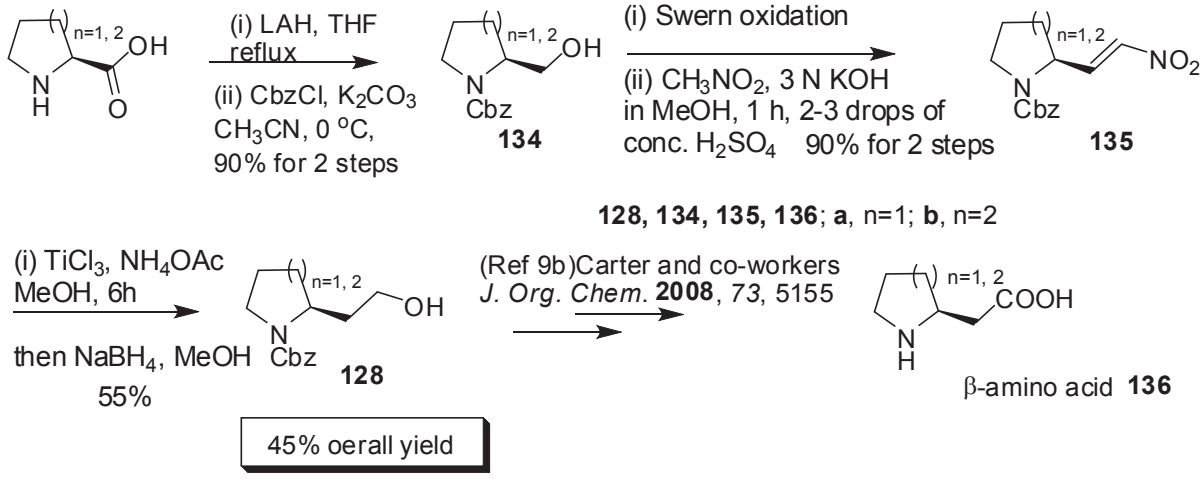


Scheme 35. Methods for 1-carbon homologation of proline and pipecolinic acid

Homologated proline and pipecolinic acids are also important as they constitute important intermediates for the straightforward synthesis of natural products. The very few methods reported in the literature for such homologation are depicted in scheme 35. The old and frequently used method for homologation of acids is Arndst-Eistert reaction.[36] Cardillo *et al* successfully homologated proline through tosylation, cyanation and subsequent reduction during the synthetic evolution of endomorphin-1 analogues[37] whereas Kennedy and Fürstner could achieve this through hydroboration reaction for the synthesis of tylophora alkaloids.[38] The homologation was also done through the Wittig olefination strategy for the synthesis of (+) hygrine.[14i]

Results and Discussion

We thought of evaluating our Henry-Nef protocol by preparing nitro olefin **135** and subsequent transformations. However our earlier Nef method using $NaBH_4$, H_2O_2 and K_2CO_3 failed in effecting the conversion of nitro olefin **135** to corresponding aldehyde. After several experimentations, McMurray[21] Nef method using $TiCl_3$ and NH_4OAc proved to be effective for the transformation of the terminal nitro olefin to aldehyde which was further reduced in situ using $NaBH_4$ to furnish the alcohol **128** in an average 45% overall yield starting from proline and pipecolinic acid (scheme 34).

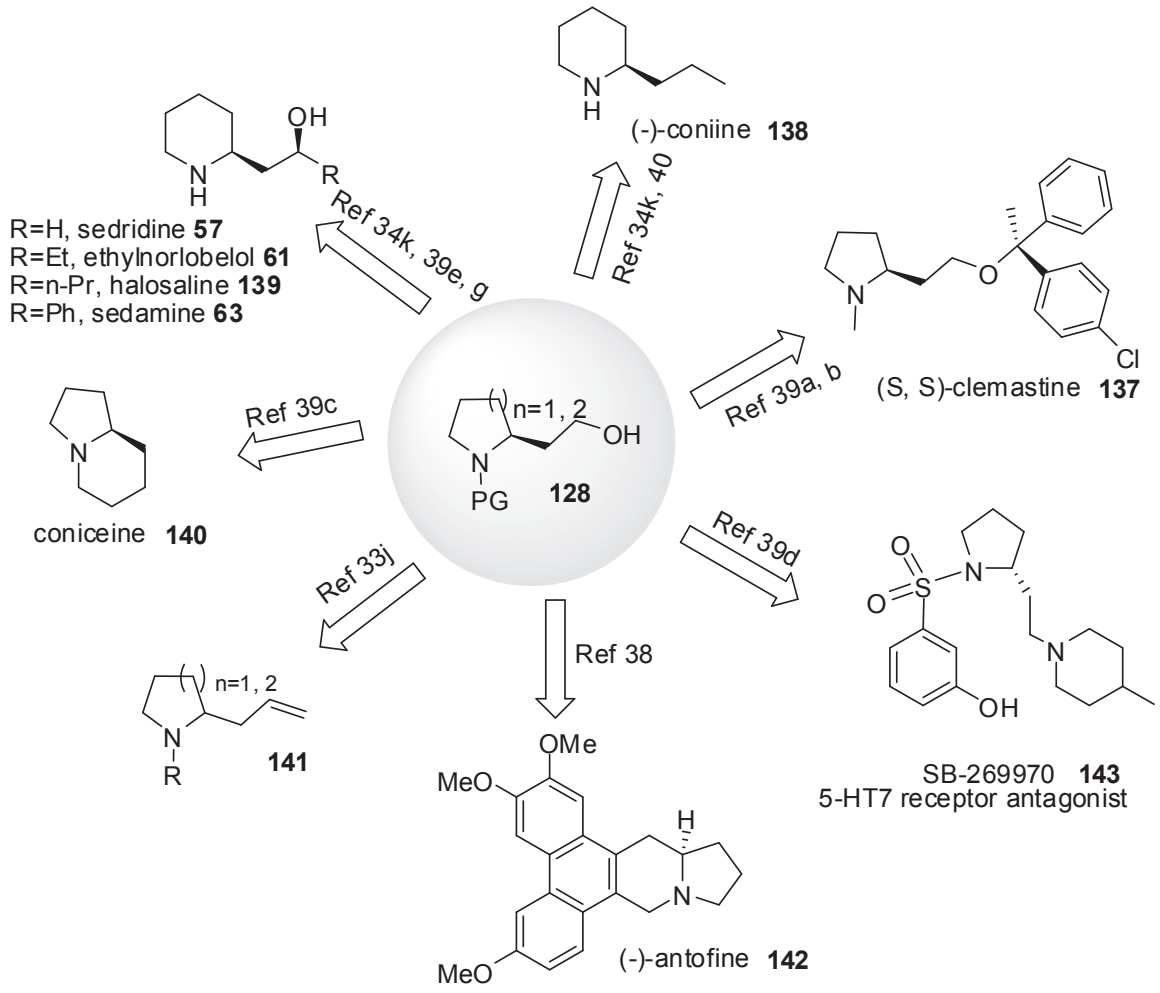


Scheme 34. Reductive Nef method for homologation of proline and pipecolinic acid

Applications of protected homologated prolinol and pipecolinol

The homologated prolinol and pipecolinol have found application in the synthesis of numerous natural and unnatural products as depicted in the scheme 14.[39, 38, 34k] The synthesis of histamine H1 antagonist, clamastine **137**, was achieved by Clayden and co-workers by synthesizing homologated prolinol via Arndst-Eistert method followed by chlorination and subsequent nucleophilic substitution by biphenyl alcoholic compound.[39a, b] A simplest 2-sustituted piperidine alkaloid coniine **138** and some of the *sedum* alkaloids have been synthesized by Paserella and co-workers using enzymatic reagent based differentiation of protected pipecolinols.[34k,39g,e,40] Davies and Mackervey have synthesized coniceine **140** involving the synthesis of homologated prolinol as a major step.[39c] The

compound **128** has been transformed to alkene **141** whose synthetic utility is well explored and smoothly described recently by Cheng *et al* by synthesizing it using Betti base as a chiral auxiliary.[33j] Recent work by Foubelo and co-workers has demonstrated the applicability of alkene **141** by synthesizing various natural products.[33p] The synthesis of tylophora alkaloid (-)-antofine **142** was accomplished by Fürstner and Kennedy using homologated prolinol.[38] Some of the active drugs like SB-269970 **143** have also been obtained through one carbon homologation of prolinol.[39d] Very recently Gómez *et al* fabulously described the chemoenzymatic synthesis of polyhdroxy indolizidines and quinolizidines starting from racemic **128b**.[39f]



Scheme 35. Synthetic application of homologated prolinol and pipecolinol

The conversion of proline/pipecolinic acid to 1-carbon homologated proline/pipecolinic acid through our Henry-Nef protocol opens a new route for the synthesis of β-amino acid

136 from α-amino acids.[41] The synthesis of β-amino acids remains challenge for synthetic chemists as they are of paramount importance to pharmaceutical applications.[42]

Conclusion

Thus we have successfully developed a practical and versatile protocol of combinatorial Henry and Nef reaction for the synthesis of 2-substituted pyrrolidine and piperidine alkaloids containing 1, 3-amino alcohol and 1, 3-aminoketone units. For Henry reaction catalytic amount of KOH was found to be most appropriate base while for Nef reaction $NaBH_4/H_2O_2$ found to be useful for 1, 3-amino secondary alcohols and $TiCl_3$ for 1, 3-amino primary alcohols. The versatility of this protocol was demonstrated by synthesizing twelve naturally occurring alkaloids which includes the first asymmetric synthesis of (-)-*N*-methylpelletierine. The synthesis of homoprolinol and homopipecolinol constitutes the formal synthesis of plethora of alkaloids and also opens an alternate route for the synthesis of β-amino acids from α-amino acids.

Experimental Section:

General procedures

(I) General procedure of Henry reaction

To a stirred solution of nitroethane (11.0 mmol) in methanol (5 mL) was added 3 N KOH (1-2 mL). After 10 min, was added prolinal/pipecolinal **48/120 (a-c)** (1.0 mmol) in methanol (5 mL). The reaction mixture was stirred at room temperature for 1 h. It was then acidified with conc. H_2SO_4, diluted with water (20 mL) and extracted with EtOAc (3 X 25 mL). The combined organic layer was washed with brine (2 X 25 mL) and dried over anhy. Na_2SO_4. To the crude residue obtained after concentrating the solvent, was added DCM (20 mL) followed by drop wise addition of CH_3SO_2Cl (2.0 mmol) at 0 °C. The reaction mixture was stirred for 20 min, Et_3N (3.0 mmol) was added and stirring continued further for 20 min. After the reaction mixture had attained the room temperature, 2 N HCl (15 mL) was added. The DCM layer was separated and the aqueous layer was extracted with DCM (2 X 25 mL). The combined organic extract was washed with brine (2 X 25 mL), dried over anhy. Na_2SO_4 and concentrated under reduced pressure. The crude product obtained was further purified by column chromatography (SiO_2, hexane/ EtOAc, 9:1).

Note: For the synthesis of nitro olefins **122** (**a-c**) and **135** (**a**, **b**), the intermediate nitro aldol products obtained were purified by column chromatography (SiO_2, hexane/ EtOAc, 7:3) giving mixture of diastereomers. The diastereomeric mixture was then treated with of $MeSO_2Cl$ (1.0 mmol) and Et_3N (2.0 mmol) and same procedure was carried out further as earlier.

(II) General procedure of Nef reaction.

To a pre cooled solution of nitro-alkene **47, 121, 122 (a-c)** (1.0 mmol) in MeOH (10 mL) was added $NaBH_4$ (2.0 mmol) in portion. After two hours stirring at rt, the reaction mixture was cooled to 0 °C. To this cold mixture, 30% H_2O_2 (2.6 mL) and K_2CO_3 (7.9 mmol) were added and the reaction mixture was further stirred for 18 h at rt. The reaction mixture was then acidified with 2 N HCl (5 mL), extracted with DCM (3 X 20 mL). The combined organic layer was washed with brine (2 X 20 mL), dried over anhy. Na_2SO_4 and

concentrated under reduced pressure. The crude product obtained was purified by column chromatography (SiO_2, hexane/ EtOAc, 8.5:1.5).

(III) General procedures for diastereoselective reduction of keto to hydroxyl group using different reducing agents.

(a) Reduction with $LiAl(O^tBu)_3H$:- To a cooled solution of $LiAl(O^tBu)_3H$ (3.0 mmol) in THF (5 mL), the ketone **25, 71, 119 (a-c)** (1.0 mmol) in THF (5 mL) was added drop wise under nitrogen atmosphere. The reaction mixture was stirred further for 8 h at 0 °C and then quenched with ice-cold water (5 mL), acidified with 1 N HCl (2 mL). It was then extracted in ethyl acetate (3 X 15 mL). The combined organic layer was dried over anhy. Na_2SO_4 and concentrated under reduced pressure. The residue was column chromatographed (SiO_2, eluent hexane: EtOAc 1:1) to give a diastereomeric mixture (**53:54/124:126/125:127**) [Yield 90-95%]. The diastereomeric mixture was subjected to HPLC using Kromasil column (*n*-hexane / IPA 9:1) to find the ratio of (**53:54/124:126/125:127)** [*cis* (*SR*): *trans* (*SS*)] as shown in the table of scheme 14 & 32.

The separation of diastereomeric mixtures was done using Flash Chromatography for the characterization purpose (*n*-hexane: EtOAc 9:1).

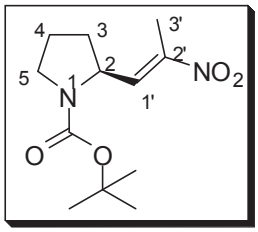
(b) Reduction with $NaBH_4$:- To a cooled solution of $NaBH_4$ (3.0 mmol) in CH_3OH (5 mL), the ketone **25, 71, 119 (a-c)** (1.0 mmol) in CH_3OH (5 mL) was added drop wise under nitrogen atmosphere. The reaction mixture was stirred further for 8 h at 0 °C and then quenched with ice-cold water (5 mL) and acidified with 1N HCl (2 mL). It was then extracted in ethyl acetate (3 X 15 mL). The combined organic layer was dried over anhy. Na_2SO_4 and concentrated under reduced pressure. The residue was column chromatographed (hexane / EtOAc 1:1) to give a diastereomeric mixture (**53:54/124:126/125:127)** [Yield 90-95%]. The diastereomeric mixture was subjected to HPLC using Kromasil column (*n*-hexane/ IPA 9:1) to find the ratio of **53:54/124:126/125:127** [*cis* (*SR*): *trans* (*SS*)] as shown in the table of scheme 14 & 32.

The separation of diastereomeric mixture was done using Flash Chromatography for the characterization purpose (*n*-hexane: EtOAc 9:1).

(c) Reduction with $Zn(BH_4)_2$:- A solution of the ketone **25**, **71**, **119 (a-c)** (1.0 mmol) in THF (5 mL) was stirred at 0 °C, $Zn(BH_4)_2$ solution (0.3 mL) [prepared in the laboratory using $ZnCl_2$ (2.0 g) and $NaBH_4$ (1.3 g) in 28 mL THF according to the procedure reported by S. Narasimhan and R. Balakumar in *Aldicrhimica Acta*, vol *33*, No. 1, 1998. Approximately 4.4 M in hydride strength and used as such] was added under nitrogen atmosphere. The reaction mixture was stirred further for 8 h. It was then quenched with ice-cold water and acidified with 1N HCl (5 mL). It was then extracted with ethyl acetate (3 X 15 mL). The combined organic layer was dried over anhy. Na_2SO_4 and concentrated under reduced pressure. The residue was column chromatographed (hexane: EtOAc 1:1) to give a diastereomeric mixture (**53:54/124:126/125:127**) [Yield 90-95%]. The diastereomeric mixture was subjected to HPLC using Kromasil column (*n*-hexane/ IPA 9:1) to find the ratio of (**53:54/124:126/125:127**) [*cis* (*SR*): *trans* (*SS*)] as shown in the table of scheme 14 & 32.

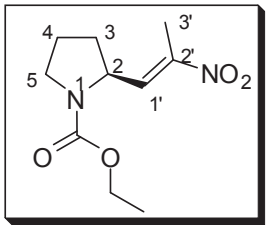
The separation of diastereomeric mixture was done using Flash Chromatography for the characterization purpose (*n*-hexane: EtOAc, 9:1).

2.01 *tert*-Butyl (2*S*)-2-[(1'*E*)-2'-nitroprop-1'-en-1'-yl] pyrrolidine-1-carboxylate (47b)



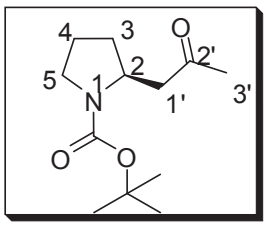
Following the general procedure **I**, Henry-olefination of compound **48b** (0.19 g, 1.0 mmol), with nitroethane (0.83 mL, 11.0 mmol) gave the product **47b** as a pale yellow thick liquid (0.23 g, 90% for two steps); $[\alpha]_D^{28}$ -12.0 (c 0.1, $CHCl_3$); IR (neat) ν_{max} = 3100, 2970, 2936, 2880, 1690, 1536 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.44 (s, 9H, ^{t}Bu*H*), 1.64-1.71 (m, 2H, H-3), 1.8-2.2 (m, 2H, H-4), 2.2 (s, 3H, H-3'), 3.41-3.54 (m, 2H, H-5), 4.40-4.51 (m, 1H, H-2), 6.96 (d, J=7.6 Hz, 1H, H-1'); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.7 (C-3'), 24.3 (C-3), 28.8 (OC(CH_3)$_3$), 32.5 (C-4), 48.0 (C-5), 54.8 (C-2), 89.1 (O*C*Me$_3$), 137.1 (C-1'), 147.5 (C-2'), 154.3 (N*C*O); HRMS: *m/z* calcd for $C_{12}H_{20}N_2O_4Na$ $[M + Na]^+$: 279.1321; found: 279.1320.

2.02 Ethyl (2*S*)-2-[(1'*E*)-2'-nitroprop-1'-en-1'-yl] pyrrolidine-1-carboxylate (47c).



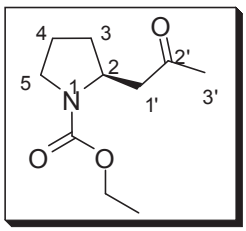
Following the general procedure **I**, Henry-olefination of compound **48c** (0.17 g, 1.0 mmol) with nitroethane (0.83 mL, 11.0 mmol) gave **47c** as a pale yellow dense liquid (0.2 g, 90%); $[\alpha]_D^{28}$ +12.0 (c 0.1, $CHCl_3$); IR (neat) ν_{max} = 3008, 2979, 2934, 1690, 1385 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.19-2.29 (m, 9H, H-4, H-3, H-3', OCH_2CH_3), 3.26-3.56 (m, 2H, H-5), 4.10-4.12 (m, 2H, OCH_2CH_3), 4.47-4.54 (m, 1H, H-2), 6.91 (d, J=8 Hz, 1H, H-1'); ^{13}C NMR ($CDCl_3$, 100MHz) : δ 12.7 (CH_2CH_3), 14.7 (C-3'), 24.4 (C-3), 32.4 (C-4), 46.7 (C-5), 54.9 (C-2), 61.3 (OCH_2), 135.4 (C-1'), 155.0 (NCO); HRMS: *m/z* calcd for $C_{10}H_{16}N_2O_4Na$ $[M + Na]^+$: 251.1008; found: 251.1006.

2.03 *tert*-Butyl (2*S*)-2-(2'-oxopropyl) pyrrolidine-1-carboxylate (25b)



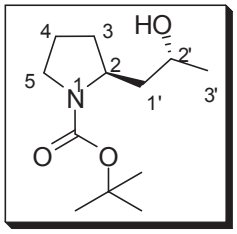
Following the general procedure **II**, the compound **47b** (0.25 g, 1.0 mmol) on Nef reaction gave **25b** as a thick liquid (0.13 g, 56%); $[\alpha]_D^{28}$ -43.3 (c 0.1, $CHCl_3$); IR (neat) ν_{max} = 2974, 1713, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz): δ 1.50 (s, 9H, ^tBuH), 1.62-2.15 (m, 4H, H-4, H-3), 2.40-2.42 (m, 1H, H-1'A), 2.90-3.11 (m, 1H, H-1'B), 3.14-3.36 (m, 2H, H-5), 4.10-4.16 (m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.4 (C-3), 28.5 ($OC(CH_3)_3$), 30.6 (C-3'), 30.7 (C-4), 46.4 (C-5), 48.6 (C-1'), 53.4 (C-2), 79.5 (O-CMe_3), 154.3 (NCO), 206.9 (C-2'); HRMS: *m/z* calcd for $C_{12}H_{21}NO_3Na$ $[M + Na]^+$: 250.1419; found: 250.1418.

2.04 Ethyl (2*S*)-2-(2'-oxopropyl)pyrrolidine-1-carboxylate (25c).



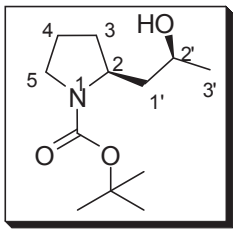
Following the general procedure **II,** the compound **47c** (0.23 g, 1.0 mmol) on Nef reaction gave **25c** as a viscous liquid (0.11 g, 56%); $[\alpha]_D^{28}$ -39.3 (c 0.1, $CHCl_3$); IR (neat) ν_{max} = 2974, 1713, 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz): δ 1.2 (t, 3H, OCH_2CH_3), 1.65-1.83 (m, 1H, H-3A), 1.85-1.87 (m, 2H, H-4), 2.01-2.05 (m, 1H, H-3B), 2.12 (s, 3H, H-3'), 2.42-2.45 (m, 1H, H-1'A), 2.89-3.23 (m, 1H, H-1'B), 3.36-3.40 (m, 2H, H-5), 4.11-4.21 (m, 3H, H-2, -OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100MHz): δ 14.7 (-CH_2CH_3), 23.6 (C-3), 30.2 (C-4), 31.7 (C-3'), 46.4 (C-5), 48.5 (C-1'), 53.4 (C-2), 60.8 (OCH_2CH_3), 154.9 (NCO), 206.0 (C-2'); HRMS: *m/z* calcd for $C_{10}H_{17}NO_3Na$ $[M + Na]^+$: 222.1106; found: 222.1102.

2.05 *tert*-Butyl (2*S*)-2-[(2'*R*)-2'-hydroxypropyl] pyrrolidine-1-carboxylate (53b)



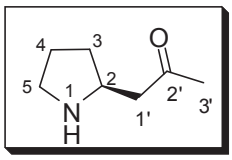
Following the general procedures **IIIa-c,** reduction of **25b** (0.23 g, 1.0 mmol) gave **53b** as a thick liquid (0.12 g, 98%) (Yield after separation of the diastereomers as mentioned in the general procedure **IIIa-c**); $[\alpha]_D^{28}$ -11.2 (c 0.2, $CHCl_3$) {Lit[15h] $[\alpha]_D^{28}$ +10.9 (c 0.7, $CHCl_3$) for *RS* isomer}; IR (neat) ν_{max} = 3426, 2971, 1694, 1673 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.18 (d, 3H, H-3'), 1.46–2.02 (m, 15H, ^{t}Bu*H*, H-3, H-4, H-1'), 3.31–3.34 (m, 2H, H-5), 3.80-3.87 (buried m, 1H, H-2'), 3.90-3.98 (buried m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100MHz): 23.8 (C-3), 23.9 (C-3'), 28.5 (OC(CH_3)$_3$), 32.5 (C-4), 45.8 (C-1'), 46.4 (C-5), 55.7 (C-2), 66.5 (C-2'), 79.7 (O*C*Me$_3$), 155.6 (N*C*O); HRMS: *m/z* calcd for $C_{12}H_{23}NO_3Na$ $[M + Na]^+$: 252.1576; found: 252.1581.

2.06 *tert*-Butyl (2*S*)-2-[(2'*S*)-2'-hydroxypropyl] pyrrolidine-1-carboxylate (54b)



Following the general procedures **IIIa-c,** reduction of **25b** (0.23 g, 1.0 mmol) gave **54b** as thick liquid. (0.12 g, 98%) (Yield after separation of the diastereomers as mentioned in the general procedure **IIIa-c**); $[\alpha]_D^{28}$ -80.2 (c 0.1, $CHCl_3$) {Lit[15h] $[\alpha]_D^{23}$ +78.5 (c 0.7, $CHCl_3$) for *RR* isomer}; IR (neat) ν_{max} = 3426 , 2971, 1694, 1673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.17-2.01 (d, 3H, H-3'), 1.32–2.01 (m, 6H, H-1', H-3, H-4), 1.46 (s, 9H, ^{t}Bu*H*), 3.26–3.37 (m, 2H, H-5), 3.65–3.70 (m, 1H, H-2), 3.71–4.18 (m, 1H, H-2'), 4.97 (br s, O*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): 22.5 (C-3), 23.6 (C-3'), 28.4 (OC(CH_3)$_3$), 31.1 (C-4), 45.6 (C-1'), 46.5 (C-5), 53.7 (C-2), 63.6 (C-2'), 79.2 (O*C*Me$_3$), 156.6 (N*C*O); HRMS: *m/z* calcd for $C_{12}H_{23}NO_3Na$ $[M + Na]^+$: 252.1576; found: 252.1573.

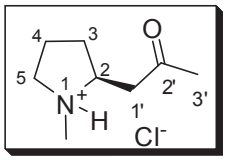
2.07 1'-[(2*S*)-Pyrrolidin-2-yl] acetone (2)



Acetonyl carbamate **25a** (0.18 g, 6.8 mmol) in EtOH (15 mL) was stirred with 10% Pd/C (20 mg) under H_2 atmosphere (2 kg/ cm^2) for 8 h in Parr hydrogenator at rt. The mixture was then filtered, washed with EtOH and then concentrated to give (-)-norhygrine **2** as a pale yellow thick liquid (0.07 g, 81%); $[\alpha]_D^{30}$-30.2 (*c* 0.2, $CHCl_3$) {Lit[14] $[\alpha]_D^{33}$ -29.6 (*c* 0.14, $CHCl_3$); IR (neat) ν_{max} = 3310, 1712 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.62-2.25 (m, 4H, H-4, H-3), 2.22

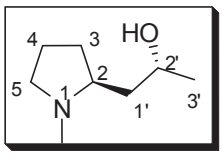
(s, 3H, H-3'), 2.96 (dd, *J* = 6.0, 18.6 Hz, 2H, H-1'), 3.33-3.42 (m, 2H, H-5), 3.89-3.94 (m, 1H, H-2), 9.43 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.6 (C-3), 30.3 (C-4), 30.1 (C-3'), 44.9 (C-1'), 45.2 (C-5), 55.1 (C-2), 205.8 (C-2').

2.08 1'-[(2*S*)-1-Methylpyrrolidin-2-yl] acetone.HCl (1.HCl)



To a cooled suspension of LAH (0.114 g, 3.0 mmol) in THF (15 mL) was added compound **25c** (0.20 g, 1.0 mmol) in THF (5 mL) drop wise under nitrogen atmosphere and refluxed further for 6h. It was quenched with drop wise addition of ice-cold water (1 mL) and further treated with 2 N NaOH (1 mL) solutions. The reaction mass was filtered and directly dried over anhy. Na_2SO_4 to give **52** (0.18 g, 90%). The crude mass was as such dissolved in DCM (20 mL) and cooled to 0 °C under nitrogen atmosphere, added $NaHCO_3$ (0.1 g, 1.2 mmol) and DMP (0.5 g, 1.2 mmol), brought to rt in 30 min. The reaction mass was filtered and concentrated under reduced pressure. The crude mass was then treated with 5 N HCl (2 mL) in 10 mL DCM for 2 h, concentrated and further purified by column chromatography (SiO_2, $CHCl_3$ / MeOH, 8.5:1.5) to afford the compound **1.**HCl as pale yellow thick liquid (0.17g, 95%); $[\alpha]_D^{30}$ -33.2 (c 0.2, H_2O) {Lit[14h] $[\alpha]_D^{30}$ +34.5 (c 0.5, H_2O) for *R*-isomer]; IR (neat) ν_{max} = 3390, 2900, 1721 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.87-2.41 (m, 4H, H-3, H-4), 2.27 (s, 3H, H-3'), 2.81 (d, *J* = 6.0 Hz, NC*H*$_3$), 2.80-2.82 (m, 1H, H-5A), 3.11 (dd, *J* = 6.6, 18.6 Hz, 1H, H-1'A), 3.45 (dd, *J* = 18.6, 6.6 Hz, 1H, H-1'B), 3.59-3.75 (m, 1H, H-5B), 3.76-3.83 (m, 1H, H-2), 11.67 (s, 1H, N*H*).; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.0 (C-3), 30.3 (C-3'), 30.5 (C-4), 40.3 (N*C*H$_3$), 44.2 (C-1'), 56.2 (C-5), 64.2 (C-2), 204.9 (C-2'); GCMS: *m/z* calcd for $C_8H_{15}NO$ $[M]^+$: 141; found: 141.

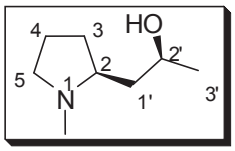
2.09 (2'*R*)-1'-[(2*S*)-1-Methylpyrrolidin-2-yl] propan-2'-ol (4b)



To a suspension of LAH (0.076 g, 2.0 mmol) in THF (10 mL) cooled at 0 °C was added the compound **53c** (0.1g, 0.5 mmol) in THF (5 mL) drop wise under nitrogen atmosphere. The reaction mixture was then refluxed for 8h. It was quenched with drop wise addition of ice-cold water (1 mL) and further treated with of 2N NaOH (1 mL) solution. The organic compound was extracted with EtOAc (3 X 10 mL). The combined organic layer was then dried over anhy. Na_2SO_4.

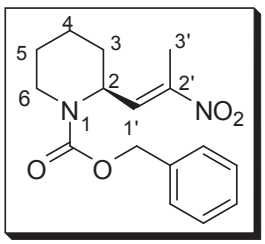
The organic layer was filtered and concentrated in vacuo to get the product **4b** as a very thick liquid (0.07g, 95%). $[\alpha]_D^{28}$ -90 (c 0.2, EtOH) {Lit[15f] $[\alpha]_D^{29}$ +70.7 (c 2.0, EtOH); Lit[15a] $[\alpha]_D^{29}$ +97.0 (c 3.4, EtOH) for *RR* isomer}; IR (neat) ν_{max} = 3362, 2964, 1418 cm^{-1}; ^{1}HMR ($CDCl_3$, 400 MHz): δ 1.15 (d, J=6.4 Hz, 2H, H-3'), 1.32–1.49 (m, 3H, H-1'A, H-3A), 1.72–1.78 (m, 2H, H-4), 1.97–2.03 (1H, m, H-3B), 2.31–2.36 (m, 4H, NCH_3, H-5A), 2.67–2.69 (m, 1H, H-2), 3.02-3.06 (m, 1H, H-5B), 3.88–3.92 (m, 1H, H-2'); ^{13}C NMR ($CDCl_3$, 100 MHz): 22.6 (C-4), 24.2 (C-3'), 30.4 (C-3), 42.7 (N*C*H_3), 42.8 (C-1'), 55.4 (C-5), 65.5 (C-2), 67.3 (C-2'); HRMS: *m/z* calcd for $C_8H_{17}NONa$ $[M + Na]^+$: 144.1388; found: 144.1397.

2.10 (2'*S*)-1'-[(2*S*)-1-Methylpyrrolidin-2-yl] propan-2'-ol (3b)



Following the similar procedure described for the compound **4b**, the compound **54c** (0.1 g, 0.5 mmol) on LAH (0.076 g, 2.0 mmol) reduction gave the product **3b** as a very thick colourless liquid (0.065 g, 95%); $[\alpha]_D^{23}$ -50 (c 0.2, EtOH) {Lit[15a] $[\alpha]_D^{22}$ -49.0 (c 0.4, EtOH) for *RR* isomer}; IR (neat) ν_{max} = 3362, 2964 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400MHz): δ 1.04-1.08 (m, 3H, H-3'), 1.32–1.49 (m, 3H, H-1'A, H-3A), 1.72–1.78 (m, 2H, H-4), 2.01-2.09 (m, 1H, H-3B), 2.20 (s, 3H, NCH_3), 2.30-2.32 (m, 1H, H-5A), 2.8-2.90 (m, 1H, H-5B), 3.70–3.60 (m, 1H, H-2'), 3.80 (s br, 1H, -O*H*); ^{13}C NMR($CDCl_3$, 100MHz): δ 23.3 (C-4), 23.7 (C-3'), 28.3 (C-3), 37.1 (C-1'), 40.6 (N*C*H_3), 57.1 (C-5), 62.7 (C-2), 64.8 (C-2'); HRMS: *m/z* calcd for $C_8H_{17}NONa$ $[M + Na]^+$: 144.1388; found: 144.1384.

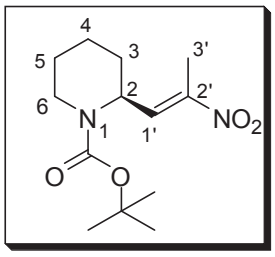
2.11 Benzyl (2*S*)-2-[(1'*E*)-2'-nitroprop-1'-en-1'-yl] piperidine-1-carboxylate (121a)



Following the general procedure **I**, Henry-olefination of compound **120a** (0.25 g, 1.0 mmol) with nitroethane (0.83 mL, 11.0 mmol) gave a pale yellow thick liquid **121a** (0.26 g, 85% for two steps); $[\alpha]_D^{28}$ -33.0 (c 0.1, $CHCl_3$); IR (neat) ν_{max} = 3108, 2979, 2934, 2882,1698, 1526 and 1356 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.50-1.53 (m, 2H, H-4), 1.56-1.84 (m, 4H, H-3 & H-5), 2.17 (s, 3H, H-3'), 2.97-3.03 (t, J=12 Hz, 1H, H-6), 4.11-4.15 (m, 1H, H-2), 5.08-5.18 (m, 3H, PhCH_2 & H-1'), 7.28-7.36 (m, 5H, Ph*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.7 (C-3'), 19.5 (C-4), 24.9 (C-5), 29.4

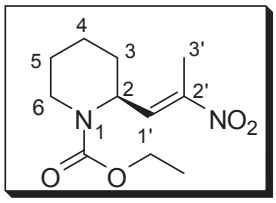
(C-3), 40.4 (C-6), 48.8 (C-2), 67.5 (Ph*C*H_2), 128.0 (Ph*CH*), 128.2 (Ph*C*H), 128.5 (Ph*C*H), 128.6 (Ph*C*H), 131.7 (Ph*C*H), 133.5 (C-1'), 136.3 (Ph*C*), 148.8 (C-2'), 155.4 (N*C*O); HRMS: *m/z* calcd for $C_{16}H_{20}N_2O_4Na$ $[M + Na]^+$: 327.1322; found: 327.1321.

2.12 *tert-B*utyl (2*S*)-2-[(1'*E*)-2'-nitroprop-1'-en-1'-yl] piperidine-1-carboxylate (121b)



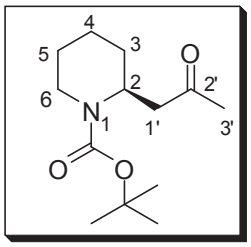
Following the general procedure **I**, Henry-olefination of compound **120b** (0.213 g, 1.0 mmol), with nitroethane (0.83 mL, 11.0 mmol) gave the product **121b** as a pale yellow crystalline solid; (0.23 g, 85% for two steps); MP= 80 °C; $[\alpha]_D^{28}$ -48.4 (c 0.1, $CHCl_3$); MP= 80 °C; IR (neat) ν_{max} = 3108, 2979, 2934, 2882, 1694, 1526 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.42 (s, 9H, ^{t}Bu*H*), 1.47-1.78 (m, 6H, H-4, H-5, H-3), 2.22 (s, 3H), 2.88 (t, J=12.4 Hz, 1H, H-6), 3.99-4.02 (m, 1H, H-6), 4.90-5.10 (buried m, 1H, H-2), 7.27-2.29 (d, J=8.8 Hz, 1H, H-1'); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.7 (C-3'), 19.6 (C-4), 24.9 (C-5), 28.3 (OC(*C*H_3)$_3$), 29.5 (C-3), 40.1 (C-6), 48.5 (C-2), 80.1 (O*C*Me_3), 132.5 (C-1'), 148.4 (C-2'), 154.6 (N*C*O); HRMS: *m/z* calcd for $C_{13}H_{22}N_2O_4Na$ $[M + Na]^+$: 293.1477; found: 293.1479.

2.13 Ethyl (2*S*)-2-[(1'*E*)-2'-nitroprop-1'-en-1'-yl] piperidine-1-carboxylate (121c)



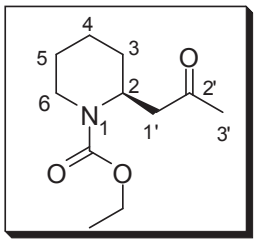
Following the general procedure **I**, Henry-olefination of compound **120c** (0.18 g, 1.0 mmol) with nitroethane (0.83 mL, 11.0 mmol) gave 1**21c** as a pale yellow dense liquid (0.20 g, 85%); $[\alpha]_D^{28}$ -32.3 (c 0.1, $CHCl_3$); IR (neat) ν_{max} = 3108, 2979, 2934, 2882, 1692, 1380 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.26-1.30 (buried m, 3H, CH_2CH_3), 1.47-1.90 (m, 6H, H-4, H-5, H-3), 2.26 (s, 3H, H-3'), 2.92-2.98 (m, 1H, H-6A), 4.06-4.13 (m, 3H, H-6B, CH_2CH_3), 5.01-5.07 (buried m, 1H, H-2), 7.28-7.32 (d, J=9.2 Hz, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100MHz) : δ 12.7 (CH_2CH_3), 14.5 (C-3'), 19.4 (C-4), 24.9 (C-5), 29.4 (C-3), 40.2 (C-6), 48.6 (C-2), 61.6 (OCH_2CH_3), 131.8 (C-1'), 148.7 (C-2'), 155.5 (N*C*O); HRMS: *m/z* calcd for $C_{11}H_{18}N_2O_4Na$ $[M + Na]^+$: 265.1164; found: 265.1162.

2.14 *tert*-Butyl (2*S*)-2-(2'-oxopropyl) piperidine-1-carboxylate (71b)



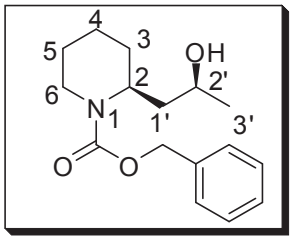
Following the general procedure **II,** the compound **121b** (0.25 g, 1.0 mmol) on Nef reaction gave **71b** as a thick yellow liquid (0.15 g, 60%); $[\alpha]_D^{28}$ -14.0 (c 0.1, $CHCl_3$) {Lit[33j] $[\alpha]_D^{33}$ -12.7 (*c* 0.22, $CHCl_3$)}; IR (neat) ν_{max} = 2974, 1720, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz): δ 1.43 (s, 9H, ^{t}Bu*H*), 1.22-1.60 (m, 6H, H-4, H-5, H-3), 2.16 (s, 3H, H-3'), 2.61-2.63 (m, 2H, C-1'), 2.72-2.78 (m, 1H, H-6A), 3.94 (br s, 1H, H-6B), 4.60-4.70 (buried m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.8 (C-4), 25.2 (C-5), 28.3 (O-C(*C*H_3)$_3$), 28.4 (C-3), 30.0 (C-3'), 39.3 (C-1'), 44.2 (C-6), 47.2 (C-2), 79.6 (O*C*Me_3), 154.7 (N*C*O), 207.1 (C-2').

2.15 Ethyl (2*S*)-2-(2'-oxopropyl) piperidine-1-carboxylate (71c)



Following the general procedure **II,** the compound **121c** (0.242 g, 1.0 mmol) on Nef reaction gave **71c** as a pale yellow viscous liquid (0.13 g, 60%); $[\alpha]_D^{28}$ -10.6 (c 0.1, $CHCl_3$); IR (neat) ν_{max} = 2970, 1710, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz): δ 1.21 (t, J=4 Hz, 3H, CH_2CH_3), 1.35-1.60 (m, 6H, H-4, H-5, H-3), 2.15 (s, 3H, H-3'), 2.60-2.65 (m, 2H, H-1'), 2.76-2.82 (m, 1H, H-6A), 3.90-4.00 (buried m, 1H, H-6B), 4.07-4.08 (m, 2H, OCH_2CH_3), 4.70-4.80 (buried m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100MHz): δ 13.6 (OCH_2CH_3), 17.8 (C-4), 24.2 (C-5), 27.3 (C-3), 29.0 (C-3'), 38.5 (C-2'), 43.2 (C-6), 46.3 (C-2), 60.2 (OCH_2CH_3), 154.5 (N*C*O), 205.9 (C-2'); HRMS: *m/z* calcd for $C_{11}H_{19}NO_3Na$ $[M + Na]^+$: 236.1263; found: 236.1261.

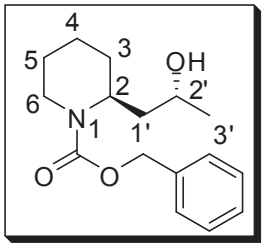
2.16 Benzyl (2*S*)-2-[(2'*S*)-2'-hydroxypropyl] piperidine-1-carboxylate (126a)



Following the general procedures **IIIa-c,** reduction of **71a** (0.29 g, 1.0 mmol) gave **126a** as a thick liquid (0.27g, 95%) (Yield after separation of the diastereomers as mentioned in the general procedure **IIIa-c**); $[\alpha]_D^{28}$ -25.82 (c 0.1, $CHCl_3$) {Lit[34m] $[\alpha]_D^{25}$ -28.52 (c 2.920, $CHCl_3$)}; IR (neat) ν_{max} = 3420, 2970, 1690, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.19-1.76 (m, 10H, H-4, H-5, H-3, H-3', O*H*), 2.00 (t, J=13.2 Hz, 1H, H-1'A), 2.77 (t, J=12.8 Hz, 1H, H-1'B), 3.20-3.33 (buried m, 1H, H-2'), 3.50-3.55 (buried m, 1H, H-6A), 4.05-4.08 (m, 1H, H-6B), 4.40-4.60 (buried m, 1H, H-2),

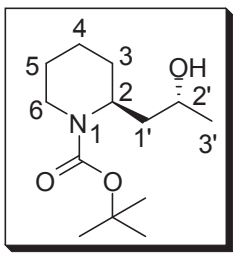
5.16-5.19 (m, 2H, PhC*H*$_2$), 7.30-7.37 (m, 5H, PhCH); ^{13}C NMR ($CDCl_3$, 100MHz): δ 19.1 (C-4), 22.5 (C-3'), 25.4 (C-5), 29.3 (C-3), 39.3 (C-1'), 39.3 (C-6), 47.4 (C-2), 65.2 (C-2'), 67.5 (Ph*C*H$_2$),, 126.9 (PhCH), 127.9 (PhCH), 128.1 (PhCH), 128.3 (PhCH), 128.5 (PhCH), 136.5 (PhC), 156.8 (N*C*O).

2.17 Benzyl (2*S*)-2-[(2'*R*)-2'-hydroxypropyl] piperidine-1-carboxylate (124a)



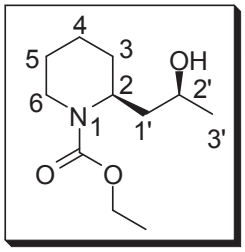
Following the general procedures **IIIa-c,** reduction of **71a** (0.29 g, 1.0 mmol) gave **124a** as a thick liquid (0.27 g, 95%) (Yield after separation of the diastereomers as mentioned in the general procedure **IIIa-c**); $[\alpha]_D^{28}$ -50.6 (c 0.1, $CHCl_3$) {Lit^{34m} $[\alpha]_D^{25}$ -52.37 (c 1.275, $CHCl_3$) }; IR (neat) ν_{max} = 3430, 2990, 1680, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20-1.84 (m, 11H, H-4, H-3', H-5, H-3, H-1'A, O*H*), 2.21-2.40 (buried m, 1H, H-1'B), 2.88-2.94 (m, 1H, H-6A), 3.70-3.90 (buried m, 1H, H-6B), 4.05-4.07 (m, 1H, H-2), 4.40-4.43 (m, 1H, H-2), 5.14 (s, 2H, C*H*$_2$Ph), 7.34-7.37 (m, 5H, Ph*H*); ^{13}C NMR ($CDCl_3$, 100MHz): δ 18.9 (C-4), 23.6 (C-3'), 25.4 (C-5), 25.5 (C-3), 28.9 (C-1'), 39.3 (C-6), 48.7 (C-2), 65.8 (C-2'), 67.1 (Ph*C*H$_2$), 127.8 (Ph*C*H), 127.9 (Ph*C*H), 128.4 (Ph*C*H), 136.7 (Ph*C*H), 136.7 (Ph*C*), 155.7 (N*C*O).

2.18 *tert*-Butyl (2*S*)-2-[(2'*R*)-2'-hydroxypropyl] piperidine-1-carboxylate (116a)



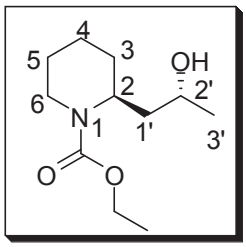
Following the general procedures **IIIa-c,** reduction of **71b** (0.25 g, 1.0 mmol) gave **124b** as a thick liquid (0.24 g, 94%) (Yield after separation of the diastereomers as mentioned in the general procedure **IIIa-c**); $[\alpha]_D^{28}$ -63.4 (c 0.05, $CHCl_3$) {Lit^{34k} $[\alpha]_D^{33}$ +56.0 (*c* 1.15, $CHCl_3$) for *RS* isomer, 85% ee}; IR (neat) ν_{max} = 3426, 2971, 1694, 1673 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20-1.82 (m, 11H, H-4, H-5, H-3, H-3', H-1'A, O*H*), 1.45 (s, 9H, ^{t}Bu*H*), 2.67-2.85 (m, 2H, H-1'B, H-6A), 3.80-3.83 (buried m, 1H, H-6B), 3.90-3.94 (buried m, 1H, H-2), 4.30-4.33 (buried m, 1H, H-2'); ^{13}C NMR ($CDCl_3$, 100MHz): δ 19.0 (C-4), 23.5 (C-3'), 25.5 (C-3 & C-5), 29.0 (O-C(*C*H$_3$)$_3$), 29.6 (C-1'), 39.9 (C-6), 40.5 (C-2), 66.5 (C-2'), 79.7 (O*C*Me$_3$), 156.5 (N*C*O).

2.19 Ethyl (2*S*)-2-[(2'*S*)-2'-hydroxypropyl] piperidine-1-carboxylate (126c)



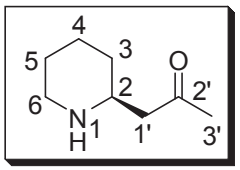
Following the general procedures **IIIa-c,** reduction of **71c** (0.23 g, 1.0 mmol) gave **126c** as a thick liquid (0.23 g, 95%) (Yield after separation of the diastereomers as mentioned in the general procedure **IIIa-c**); $[\alpha]_D^{28}$ -16.0 (c 0.04, $CHCl_3$); IR (neat) ν_{max} = 3450, 2900, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.22-1.90 (m, 12H, H-4, H-5, H-3, OCH_2CH_3, H-3'), 1.90-1.97 (m, 1H, H-1'A), 2.62-2.69 (m, 1H, H-1'B), 3.10-3.20 (buried m, 1H, H-6), 3.40-3.60 (buried m, 1H, H-6B), 3.92-3.95 (m, 1H, H-2), 4.05-4.10 (q, J=6.8 Hz, 2H, OCH_2CH_3), 4.40-4.42 (buried m, 1H, H-2'); ^{13}C NMR ($CDCl_3$, 100MHz): δ 13.6 (C-3'), 18.1 (C-4), 21.4 (OCH_2CH_3), 24.4 (C-5), 28.3 (C-3), 38.1 (C-1'), 38.3 (C-6), 46.1 (C-2), 60.7 (OCH_2CH_3), 62.3 (C-2') 156.1 (NCO).

2.20 Ethyl (2*S*)-2-[(2'*R*)-2'-hydroxypropyl] piperidine-1-carboxylate (124c)



Following the general procedures **IIIa-c,** reduction of **71c** (0.23 g, 1.0 mmol) gave **124c** as a thick liquid (0.23 g, 95%) (Yield after separation of the diastereomers as mentioned in the general procedure **IIIa-c**); $[\alpha]_D^{28}$ -56.8 (c 0.2, $CHCl_3$); IR (neat) ν_{max} = 3510, 2994, 1680, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.22-1.67 (m, 12H, H-3', H-4, H-5, H-3, OCH_2CH_3), 1.84-1.87 (m, 1H, -OH), 2.15-2.35 (m, 2H, H-1'), 2.84-2.91 (m, 1H, H-6A), 3.81-3.86 (m, 1H, H-6B), 4.00-4.03 (m, 1H, H-2), 4.13 (m, 2H, OCH_2CH_3), 4.38-4.39 (m, 1H, H-2'); ^{13}C NMR ($CDCl_3$, 100MHz): δ 13.6 (C-3'), 17.9 (C-6), 25.4 (OCH_2CH_3), 25.4 (C-5), 29.0 (C-3) 39.2 (C-1'), 39.5 (C-6), 49.5 (C-2), 61.3 (OCH_2CH_3), 65.1 (C-2'), 155.0 (NCO).

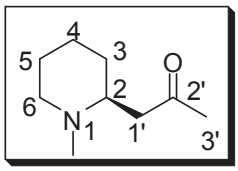
2.21 1'-[(2*S*)-Piperidin-2-yl] acetone (55a)



The compound **71a** (0.28 g, 1.0 mmol) was dissolved in EtOH and hydrogenated over Pd/C (1 atmosphere) at rt for 6 h. The reaction mixture was then filtered and concentrated under reduced pressure to give **55a** as a colourless thick liquid. It was then treated with 5 N HCl (2 mL) in chloroform (10 mL) for 2 h at rt and dried under reduced pressure. The crude mass was subjected to column chromatography (SiO_2, chloroform/ Methanol, 9:1) to give **55a**.HCl as pale yellow thick liquid (0.13 g, 70%); IR (neat) ν_{max} = 3310, 1710 cm^{-1};

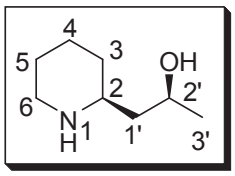
$[\alpha]_D^{28}$ -16.2 (c 0.05, EtOH) {Lit[33k] $[\alpha]_D^{23}$= -9.2 (1.2, EtOH)}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.41-1.90 (m, 6H, H-5, H-5, H-3), 2.15 (s, 3H, H-3'), 2.70-2.90 (m, 2H, H-1'), 3.21-3.27 (m, 1H, H-6A), 3.35-3.45 (m, 2H, H-6B, H-5); ^{13}C NMR ($CDCl_3$, 100MHz): δ 24.3 (C-4), 25.4 (C-5), 30.6 (C-3'), 31.9 (C-3), 46.4 (C-1'), 49.9 (C-6), 52.37 (C-2), 208.4 (CO).

2.22 1'-[(2*S*)-1-Methylpiperidin-2-yl] acetone (56)



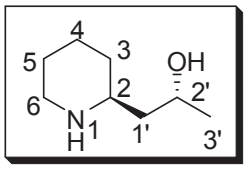
Following the similar procedure as described for the compound **1b**, the compound **119c** (0.22 g, 1.0 mmol) gave the compound **56.**HCl as pale yellow thick liquid (SiO_2, $CHCl_3$/MeOH, 9:1) (0.09g, 60%); $[\alpha]_D^{28}$ -25.0 (c 0.2, H_2O); IR (neat) ν_{max} = 3390, 2920, 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20-1.70 (m, 6H), 1.94 (s, 3H, H-3'), 2.32 (s, 3H, NC*H*$_3$), 2.32-2.51 (m, 2H, H-1'), 2.80-2.95 (buried m, 1H, H-6A), 3.03-3.08 (m, 2H, H-6B & H-2); ^{13}C NMR ($CDCl_3$, 100MHz): δ 23.1 (C-4), 24.2 (C-5), 29.6 (C-3), 29.8 (C-3'), 42.0 (C-2), 44.5 (C-1'), 55.0 (C-6), 59.0 (N*C*H$_3$), 205.5 (CO).

2.23 (2'*S*)-1-[(2*S*)-Piperidin-2-yl] propan-2'-ol (57a)



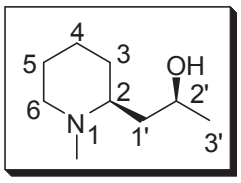
The compound **126a** (0.25 g, 0.9 mmol) was dissolved in EtOH and direclty hydrogenated (1atmosphere) over Pd/ C (0.025 g) for 6 h at rt. The reaction mixture was then filtered and dried under reduced pressure to give the product **7** as colourless crystaline compound turning viscous on exposure to atmosphere (0.12, 95%); $[\alpha]_D^{28}$ +27.5 (c 0.07, EtOH) {Lit[34m] $[\alpha]_D^{25}$= +28.4 (1.13, EtOH)}; IR (neat) ν_{max} = 3375, 2960 ,1418 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.11 (d, J=7.2 Hz, 3H, H-3'), 1.28-1.78 (m, 8H, H-4, H-5, H-3, H-1'), 1.50-1.60 (m, 3H), 2.50-2.57 (m, 1H, H-6A), 2.85-2.89 (m, 1H, H-6B), 3.03-3.05 (m, 1H, H-2), 3.50 (br s, 2H, OH & NH), 4.02-4.10 (m, 1H, H-2'); ^{13}C NMR ($CDCl_3$, 100MHz): δ 23.6 (C-3'), 24.4 (C-4), 25.4 (C-5), 30.9 (C-3), 43.3 (C-1'), 46.6 (C-6), 54.8 (C-2), 64.8 (C-2').

2.24 (2'*R*)-1-[(2*S*)-Piperidin-2-yl] propan-2'-ol (58b)



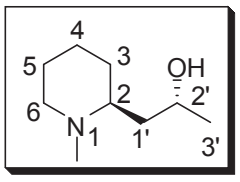
Following the same procedure as for (*SS*) isomer the compound **124a** on hydrogenation gave **58b** as a pale yellow crystalline solid becoming viscous on exposure to atmosphere (0.12, 95%); $[\alpha]_D^{28}$ -15.6 (c 0.05, EtOH) {Lit[34m] $[\alpha]_D^{23}$= -16.2 (1.5, MeOH)}; IR (neat) ν_{max} = 3350, 2924 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.06 (d, J=6 Hz, 3H, H-3'), 1.18-1.78 (m, 8H, H-4, H-5, H-3, H-1'), 2.49-2.69 (m, 1H, H-6A), 2.96-3.01 (m, 1H, H-6B), 3.30 (br s, 2H, NH & OH), 3.91-3.95 (m, 1H, H-2'); ^{13}C NMR ($CDCl_3$, 100MHz): δ 23.9 (C-3'), 24.4 (C-4), 27.0 (C-5), 34.1 (C-3), 44.1 (C-1'), 45.9 (C-6), 58.3 (C-2), 69.1 (C-2').

2.25 (2'*S*)-1-[(2*S*)-1-Methylpiperidin-2-yl] propan-2'-ol (59b)



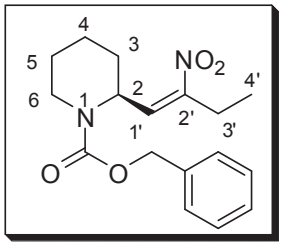
Following the similar procedure as for compound **4b**, the compound **126c** (0.1g, 0.5 mmol) gave **59b** as a pale yellow thick liquid (0.06g, 90%); $[\alpha]_D^{28}$ -35.0 (c 0.06, EtOH) {Lit[34k] $[\alpha]_D$ = +34.5 (0.85, EtOH) for (*RR*) isomer}; IR (neat) ν_{max} = 3380, 2967, 1420 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.10 (d, J=6 Hz, 3H, H-3'), 1.20-1.82 (m, 8H, H-4, H-5, H-3, H-1'), 2.35 (s, 3H, NCH_3), 2.39-2.42 (m, 1H, H-6A), 2.57-2.60 (m, 1H, H-6B), 2.90-2.95 (m, 1H, H-2), 3.60 (br s, 1H, OH), 3.75-3.91 (m, 1H, H-2'); ^{13}C NMR ($CDCl_3$, 100MHz): δ 20.9, 22.6, 24.1, 26.2, 30.0, 39.1, 39.3, 50.2, 60.8, 62.5, 68.0.[ref 34k]

2.26 (2'*R*)-1-[(2*S*)-1-Methylpiperidin-2-yl] propan-2'-ol (60b)



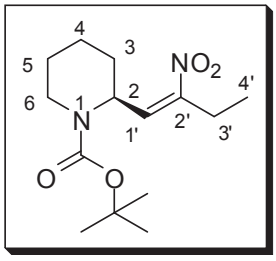
Similar procedure followed as for the compound **4b**, the compound **124c** (0.1g, 0.5 mmol) furnished the product **60b** (0.06g, 90%) as thick colourless liquid; $[\alpha]_D^{28}$ -70.0 (c 0.05, EtOH) {Lit[34k] $[\alpha]_D$ = +67.5 (0.65, EtOH) for (*SR*) isomer}; IR (neat) ν_{max} = 3362, 2964 ,1418 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.10 (d, J=6.4 Hz, 3H, H-3'), 1.14-1.82 (m, 8H, H-4, H-5, H-3, H-1'), 2.35 (s, 3H, NCH_3), 2.38-2.44 (m, 1H, H-6A), 2.55-2.58 (m, 1H, H-6B), 2.90-2.95 (m, 1H, H-2), 3.85-3.93 (m, 1H, H-2'); ^{13}C NMR ($CDCl_3$, 100MHz): δ 20.8 (C-4), 22.6 (C-5), 24.1 (C-3'), 26.1 (C-3), 39.2 (C-1'), 39.2 (C-2), 51.8 (C-6), 60.8 (C-2'), 68.1 (NCH_3).

2.27 Benzyl (2*S*)-2-[(1'*Z*)-2'-nitrobut-1'-en-1'-yl] piperidine-1-carboxylate (122a)



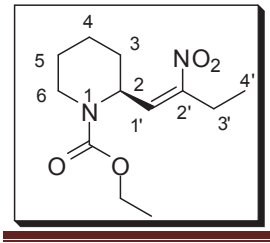
Following the general procedure **I**, Henry-olefination of compound **120a** (0.25 g, 1.0 mmol), with nitroethane (0.83 mL, 11.0 mmol) gave the product **122a** as a pale yellow thick liquid. (0.24g, 80% for two steps); $[\alpha]_D^{26}$ -39.1 (c 0.14, $CHCl_3$); IR (neat) ν_{max} = 3100, 2989, 2934, 2800,1690, 1520 and 1348 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.90-1.81 (m, 9H, H-4, H-5, H-3, H-4'), 2.48-2.62 (m, 2H, H-3'), 2.89-2.96 (m, 1H, H-6A), 4.03-4.06 (m, 1H, H-6B), 5.00-5.08 (m, 3H, H-2, C*H*$_2$Ph), 7.18-7.31 (m, 6H, H-1', Ph*H*); ^{13}C NMR ($CDCl_3$, 100MHz): δ 12.6 (C-4'), 19.4 (C-4), 20.2 (C-5), 24.9 (C-3), 29.9 (C-3'), 40.3 (C-6), 48.5 (C-2), 67.6 (*C*H$_2$Ph), 127.9 (PhCH), 128.1 (PhCH), 128.2 (PhCH), 128.6 (PhCH), 128.7 (PhCH), 130.9 (C-1'), 136.3 (PhC), 155.7 (C-2'), 155.8 (N*C*O); HRMS: *m/z* calcd for $C_{17}H_{22}N_2O_4Na$ $[M + Na]^+$: 341.1477; found: 341.1478.

2.28 *tert*-Butyl (2*S*)-2-[(1'*Z*)-2'-nitrobut-1'-en-1'-yl] piperidine-1-carboxylate (122b)



Following the general procedure **I**, Henry-olefination of compound **120b** (0.22 g, 1.0 mmol), with nitroethane (0.83 mL, 11.0 mmol) gave the product **122b** as a pale yellow thick liquid. (0.24 g, 85% for two steps); $[\alpha]_D^{26}$ -46.8 (c 0.05, $CHCl_3$); IR (neat) ν_{max} = 2964, 2900, 1690, 1520 and 1340 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.06 (t, J=7.2 Hz, 3H, H-4'), 1.38 (s, 9H, ^{t}Bu*H*), 1.41-1.80 (m, 6H, H-4, H-5, H-3), 2.58-2.68 (m, 2H, C-3'), 2.80-2.87 (m, 1H, H-6A), 3.94-3.97 (m, 1H, H-6B), 4.90-4.98 (buried m, 1H, H-2), 7.20 (d, J=3.2 Hz, 1H, H-1'); ^{13}C NMR ($CDCl_3$, 100MHz): δ 12.7 (C-4'), 19.6 (C-4), 20.2 (C-5), 25.1 (C-3), 28.4 (OC(*C*H$_3$)$_3$), 30.0 (C-3'), 40.1 (C-6), 48.1 (C-2), 80.3 (O*C*(CH$_3$)$_3$), 131.7 (C-1'), 154.4 (C-2'), 154.5 (N*C*O); HRMS: *m/z* calcd for $C_{14}H_{24}N_2O_4Na$ $[M + Na]^+$: 307.1634; found: 307.1637.

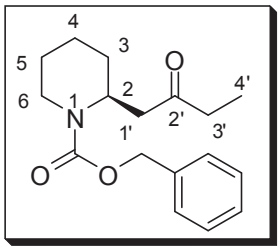
2.29 Ethyl (2*S*)-2-[(1'*Z*)-2'-nitrobut-1'-en-1'-yl] piperidine-1-carboxylate (122c)



Following the general procedure **I**, Henry-olefination of compound **120c** (0.18 g, 1.0 mmol), with nitroethane (0.83 mL, 11.0 mmol) gave the product **122c** as a colourless thick liquid. (0.20g, 80% for two steps); $[\alpha]_D^{26}$ -50.9 (c 0.04, $CHCl_3$); IR (neat) ν_{max} = 2960,

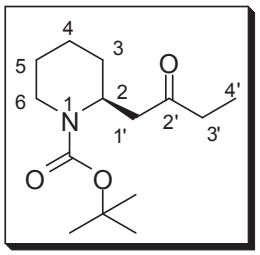
1690, 1550 and 1360 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.07 (t, J=6 Hz, 3H, H-4'), 1.89 (t, J=7.2 Hz, 3H, CH_2CH_3), 1.37-1.82 (m, 6H, H-4, H-5, H-3), 2.57-2.72 (m, 2H, H-3'), 2.86-2.93 (m, 1H, H-6A), 4.00-4.09 (m, 2H, H-6B, OCH_2CH_3), 4.95-5.01 (buried m, 1H, H-2), 7.19 (d, J=2.4 Hz, 1H, H-1'); ^{13}C NMR ($CDCl_3$, 100MHz): δ 12.7 (C-4'), 14.6 (OCH_2CH_3), 19.5 (C-4), 20.2 (C-5), 24.9 (C-3), 29.9 (C-3'), 40.1 (C-6), 48.3 (C-2), 61.2 (OCH_2CH_3), 131.1 (C-1'), 154.2 (C-2'), 155.5 (NCO); HRMS: *m/z* calcd for $C_{12}H_{20}N_2O_4Na$ $[M + Na]^+$: 279.1321; found: 279.1321.

2.30 Benzyl (2*S*)-2-(2'-oxobutyl) piperidine-1-carboxylate (119a)



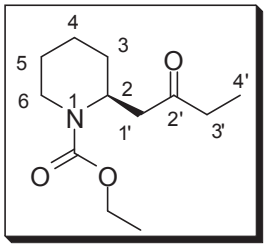
Following the general procedure **II**, Nef reaction on **122a** (0.32 g, 1.0 mmol) gave **119a** as a thick liquid (0.22 g, 75%); $[\alpha]_D^{26}$ -10.1 (c 0.32, $CHCl_3$); IR (neat) ν_{max} = 2974, 1710, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.92 (t, J=7.2 Hz, 3H, H-4'), 1.35-1.61 (m, 6H, H-4, H-5, H-3), 2.34-2.42 (m, 2H, H-3'), 2.53-2.65 (m, 2H, H-1'), 2.76-2.82 (m, 1H, H-6A), 3.96-3.99 (m, 1H, H-6B), 4.71-4.72 (m, 1H, H-2), 5.04 (s, 2H, $PhCH_2$), 7.21-7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 100MHz): 7.6 (C-4'), 18.8 (C-4), 25.2 (C-5), 28.3 (C-3), 39.8 (C-3'), 42.9 (C-1'), 47.6 (C-2), 67.1 ($PhCH_2$), 126.9 (PhCH), 127.8 (PhCH), 127.9 (PhCH), 128.4 (PhCH), 128.5 (PhCH), 136.8 (PhC), 155.3 (NCO), 209.5 (C-2').

2.31 *tert*-Butyl (2*S*)-2-(2'-oxobutyl) piperidine-1-carboxylate (119b)



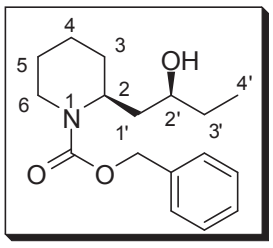
Following the general procedure **II**, Nef reaction on **122b** (0.28 g, 1.0 mmol) gave **119b** as a thick liquid (0.18 g, 70%); $[\alpha]_D^{26}$ -10.5 (c 0.18, $CHCl_3$); IR (neat) ν_{max} = 2994, 1711, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.96 (t, J=7.2 Hz, 3H, H-4'), 1.37 (s, 9H, ^tBuH), 1.30-1.55 (m, 6H, H-4, H-5, H-3), 2.33-2.57 (m, 4H, H-1', H-3'), 2.69-2.75 (m, 1H, H-6A), 3.89-3.99 (buried m, 1H, H-6B), 4.60-4.64 (buried m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100MHz): 7.6 (C-4'), 18.9 (C-4), 25.3 (C-5), 28.38 ($OC(CH_3)_3$), 28.5 (C-3), 36.1 (C-3'), 39.3 (C-1'), 42.9 (C-6), 47.4 (C-2), 79.6 ($OC(CH_3)_3$), 154.7 (NCO), 209.7 (CO); HRMS: *m/z* calcd for $C_{14}H_{25}NO_3Na$ $[M + Na]^+$: 278.1732; found: 278.1735.

2.32 Ethyl (2*S*)-2-(2'-oxobutyl) piperidine-1-carboxylate (119c)



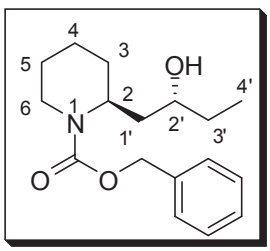
Following the general procedure **II**, Nef reaction on **122c** (0.32 g, 1.0 mmol) gave **119c** as a thick liquid (0.15 g, 60%); $[\alpha]_D^{26}$ -10.1 (c 0.05, $CHCl_3$); IR (neat) ν_{max} = 2990, 1718, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.96 (t, J=7.2 Hz, 3H, H-4'), 1.17 (t, J=6.8 Hz, 3H, OCH_2CH_3), 1.31-1.62 (m, 6H, H-4, H-5, H-3), 2.34-2.49 (m, 2H, H-3'), 2.53-2.65 (m, 2H, H-1'), 2.73-2.79 (m, 1H, H-6A), 3.93-3.95 (m, 1H, H-6B), 4.03 (q, J=7.2 Hz, 2H, OCH_2CH_3), 4.67-4.68 (m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100MHz): δ 7.7 (C-4'), 14.6 (OCH_2CH_3), 18.8 (C-4), 25.2 (C-5), 28.3 (C-3), 36.1 (C-3'), 39.5 (C-1'), 42.9 (C-6), 47.4 (C-2), 61.3 (OCH_2CH_3), 115.5 (NCO), 209.6 (C-2'); HRMS: *m/z* calcd for $C_{12}H_{21}NO_3Na$ $[M + Na]^+$: 250.1419; found: 250.1418.

2.33 Benzyl (2*S*)-2-[(2'*S*)-2'-hydroxybutyl] piperidine-1-carboxylate (127a)



Following the general procedure **III** (**a-c**), compound **119a** (0.29 g, 1.0 mmol) gave **127a** (0.27g, 95%) as a colourless thick liquid; $[\alpha]_D^{26}$ -27.9 (c 0.08, $CHCl_3$); IR (neat) ν_{max} = 3430, 2990, 1680, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.70-0.90 (3H, m, H-4'), 1.10-1.97 (m, 10H, H-4, H-5, H-3, H-1', H-3'), 2.59-2.71 (m, 2H, H-6A, OH), 3.10-3.20 (buried m, 1H, H-6B), 3.96-3.99 (m, 1H, H-2'), 4.42-4.47 (m, 1H, H-2'), 5.02-5.13 (m, 2H, $PhCH_2$), 7.25-7.30 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$, 100MHz): δ 10.5 (C-4'), 19.2 (C-4), 25.5 (C-5), 29.2 (C-3), 29.4 (C-3'), 37.1 (C-1'), 39.3 (C-6), 47.3 (C-2), 67.5 (OCH_2Ph), 68.6 (C-2'), 127.9 (PhCH), 128.1 (PhCH), 128.4 (PhCH), 128.5 (PhCH), 136.6 (PhC), 156.8 (NCO).

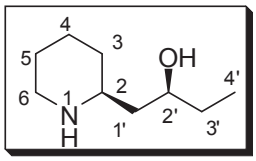
2.34 Benzyl (2*S*)-2-[(2'*R*)-2'-hydroxybutyl] piperidine-1-carboxylate (125a)



Following the general procedure **III** (**a-c**), compound **119a** (0.29 g, 1.0 mmol) gave **125a** (0.27 g, 95%) as a colourless thick liquid; $[\alpha]_D^{26}$ -46.8 (c 0.13, $CHCl_3$); IR (neat) ν_{max} = 3400, 2995, 1680, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.70-0.84 (buried m, 3H, H-4'), 1.32-1.70 (m, 10H, H-4, H-5, H-3, H-3', H-1'), 2.79-

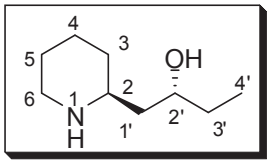
2.85 (m, 1H, H-6A), 3.40-3.45 (buried m, 1H, H-6B), 3.95-3.97 (m, 1H, H-2), 4.36-4.37 (m, 1H, H-2'), 5.01-5.08 (m, 2H, C*H*$_2$Ph), 7.20-7.28 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$, 100MHz): δ 10.0 (C-4'), 18.9 (C-4), 25.5 (C-5), 29.2 (C-3), 30.3 (C-3'), 37.6 (C-1'), 39.6 (C-6), 48.9 (C-2), 67.1 (*C*H$_2$Ph), 71.4 (C-2'), 127.9 (PhCH), 128.0 (PhCH), 128.1 (PhCH), 128.2 (PhCH), 128.3 (PhCH), 136.8 (PhC), 155.9 (NCO).

2.35 (2'*S*)-1'-[(2*S*)-Piperidin-2-yl] butan-2'-ol (61)



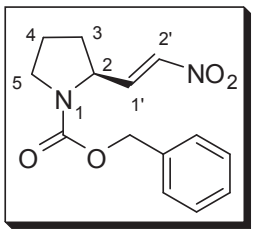
Following the similar procedure as for the compound **2**, the compound **127a** (0.29 g, 1.0 mmol) gave **61** as a colourless thick liquid (0.15 g, 95%); $[\alpha]_D^{26}$ +18.6 (c 0.05, EtOH) {Lit^{34k} $[\alpha]_D$ = +17.5 (0.80, EtOH)}; IR (neat) ν_{max} = 3370, 2970 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.90 (t, J=7.2 Hz, 3H, H-4'), 1.17-1.93 (m, 10H, H-4, H-5, H-3, H-3', H-1'), 2.80-2.83 (m, 1H, H-6A), 3.23-3.24 (m, 1H, H-6B), 3.40-3.43 (m, 1H, H-2), 3.56-3.67 (m, 1H, H-2' & NH), 3.87 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 100MHz): δ 10.1 (C-4'), 22.1 (C-4), 22.6 (C-5), 28.8 (C-3), 30.2 (C-3'), 39.3 (C-1'), 45.1 (C-6), 54.7 (C-2), 67.9 (C-2').

2.36 (2'*R*)-1'-[(2*S*)-Piperidin-2-yl] butan-2'-ol (62)



Smilar procedure was followed as for the compound **2**, compound **125a** (0.29 g, 1.0 mmol) gave **62** (0.15 g, 95%); $[\alpha]_D^{26}$ -7.6 (c 0.06, EtOH) {Lit^{34k} $[\alpha]_D$ = -6.6 (0.80, EtOH)}; IR (neat) ν_{max} = 3370, 2980, 1410 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.85 (t, J=7.2 Hz, 3H, H-4'), 1.31-1.79 (10H, H-4, H-5, H-3, H-3', H-1'), 2.62-2.68 (m, 1H, H-6A), 2.82-2.87 (m, 1H, H-6B), 3.12-3.15 (m, 1H, H-2), 3.68-3.74 (m, 1H, H-2'), 4.60 (br s, 2H, OH & NH); ^{13}C NMR ($CDCl_3$, 100MHz): δ 9.9 (C-4'), 23.6 (C-4), 25.0 (C-5), 31.0 (C-3), 32.4 (C-3'), 40.9 (C-1'), 45.4 (C-6), 58.2 (C-2), 73.7 (C-2').

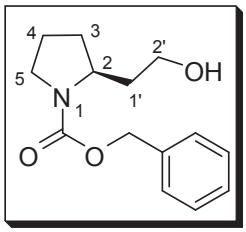
2.37 Benzyl (2*S*)-2-[(*E*)-2'-nitrovinyl] pyrrolidine-1-carboxylate (135a)



Following the general procedure **I**, Henry-olefination of compound **48a** (0.23 g, 1.0 mmol) with nitromethane (0.66 mL, 11.0 mmol) gave a pale yellow thick liquid **135a** (0.24 g, 90% for two steps); $[\alpha]_D^{26}$ -76.1 (c 0.13, $CHCl_3$); IR (neat) ν_{max} = 2989, 2934,

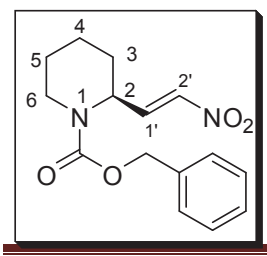
2800,1690, 1520 and 1350 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.76-2.11 (m, 4H, H-4, H-3), 3.39-3.45 (m, 2H, H-5), 4.46-4.54 (m, 1H, H-2), 4.49-5.09 (m, 2H, OC*H*$_2$Ph), 6.76-6.95 (m, 1H, H-2'), 7.00-7.04 (m, 1H, H-1'), 7.21-7.28 (m, 5H, Ph*H*); ^{13}C NMR ($CDCl_3$, 100MHz): δ 23.4 (C-4), 31.2 (C-3), 46.7 (C-5), 55.2 (C-2), 67.3 (Ph*C*H$_2$), 127.9 (PhCH), 128.2 (PhCH), 128.3 (PhCH), 128.6 (PhCH), 136.0 (PhC), 140.0 (C-1'), 141.4 (C-2'), 154.6 (N*C*O); HRMS: *m/z* calcd for $C_{14}H_{16}N_2O_4Na$ $[M + Na]^+$: 299.1008; found: 299.1004.

2.38 Benzyl (2*S*)-2-(2'-hydroxyethyl) pyrrolidine-1-carboxylate (128a)



To a solution of ammonium acetate (4.0 g, 52 mmol) in MeOH: H_2O (4:3, 16 mL) was added 15% aq. $TiCl_3$ (3.6 mL, 3.5 mmol) followed by a solution of **135a** (0.28 g, 1.0 mmol) in MeOH (5 mL) at 0 °C. After stirring for 3 h at rt, the mixture was extracted with ether (20 mL X 3). The ether layer was washed with saturated aq. $NaHCO_3$ (15 mL X 4) and saturated aq. NaCl (20 mL X 2), dried over anhy. Na_2SO_4 and concentrated under reduced pressure. The crude product was immediately treated with $NaBH_4$ (0.37 g, 1.0 mmol) in 10 mL MeOH. After 1 h stirred at rt, the reaction mixture was concentrated and diluted with ethyl acetate (30 mL), washed with dil HCl (10 mL X 3). The crude mixture was column chromatographed (SiO_2, *n*-hexane: EtOAc, 7:3) to give **128a** as colourless thick liquid (0.14g, 55%); $[\alpha]_D^{26}$ -7.0 (c 0.04, $CHCl_3$) {Lit[39a] $[\alpha]_D$ = -7.6 (c 1.1, $CHCl_3$)}; IR (neat) ν_{max} = 3400, 2900, 1690; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.52-2.05 (m, 6H, H-4, H-3, H-1'), 3.41-3.45 (m, 2H, H-2'), 3.55-3.61 (m, 2H, H-5), 4.18-4.26 (m, 1H, H-2), 5.15-5.16 (m, 2H, PhC*H*$_2$), 7.33-7.38 (m, 5H, PhCH); ^{13}C NMR ($CDCl_3$, 100MHz): δ 23.6 (C-4), 31.1 (C-3), 38.2 (C-1'), 46.3 (C-5), 54.3 (C-2), 59.0 (C-2'), 67.1 (Ph*C*H$_2$), 126.8 (PhCH), 127.0 (PhCH), 127.5 (PhCH), 135.6 (PhC), 155.7 (NCO).

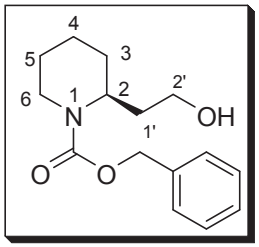
2.39 Benzyl (2*S*)-2-[(*E*)-2'-nitrovinyl] piperidine-1-carboxylate (135b)



Following the general procedure **I**, Henry-olefination of compound **120a** (0.25g, 1.0 mmol), with nitromethane (0.66 mL, 11.0 mmol) gave the product **135b** as a pale yellow thick liquid. (0.26 g, 90% for two steps); $[\alpha]_D^{26}$ -64.0 (c 0.05, $CHCl_3$); IR (neat) ν_{max} = 2900,

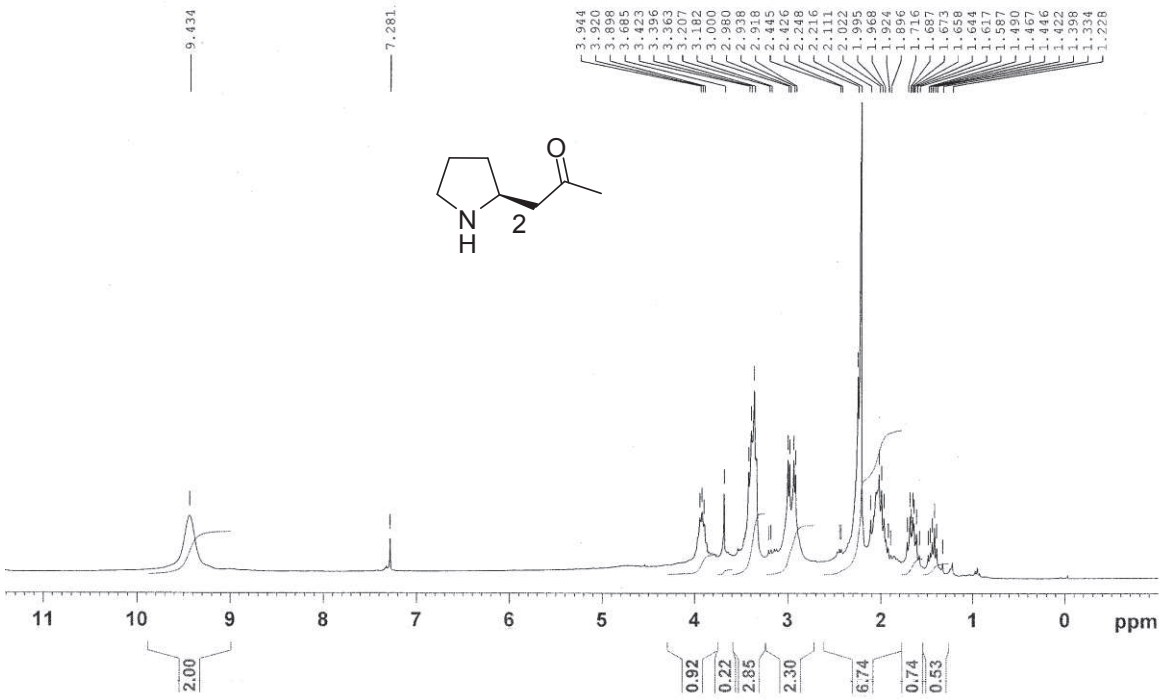
2800,1690, 1520 and 1340cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.34-1.67 (m, 4H, H-4, H-5), 1.76-1.77 (m, 2H, H-3), 2.78-2.84 (m, 1H, H-6A), 4.00-4.06 (m, 1H, H-6B), 5.04-5.11 (m, 3H, H-2, PhCH_2), 6.86 (d, J=13.2 Hz, 1H, H-2'), 7.14-7.19 (dd, J=8.8 Hz & J=4.8 Hz, 1H, H-1'), 7.26-7.32 (m, 5H, Ph*H*); ^{13}C NMR ($CDCl_3$, 100MHz): δ 19.7 (C-4), 24.9 (C-5), 28.8 (C-3), 40.6 (C-6), 49.6 (C-2), 67.7 (Ph*C*H_2), 128.0 (PhCH), 128.3 (PhCH), 128.6 (PhCH), 136.2 (PhC), 140.6 (C-1'), 140.9 (C-2'), 155.3 (NCO); HRMS: *m/z* calcd for $C_{14}H_{16}N_2O_4Na$ $[M + Na]^+$: 313.1164; found: 313.1163.

2.40 Benzyl (2*S*)-2-(2'-hydroxyethyl) piperidine-1-carboxylate (128b)



Following the similar procedure as for the compound **128a**, the compound **135b** gave **128b** as a pale yellow thick liquid (0.15g, 55%); $[\alpha]_D^{26}$ -20.2 (c 0.06, $CHCl_3$) {Lit[39d] $[\alpha]_D^{25}$ = -18.5 (c 1.0, $CHCl_3$)}; IR (neat) ν_{max} = 3400, 2900, 1690; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.35-1.92 (m, 8H, H-4, H-5, H-3, H-1'), 2.65-2.71 (m, 2H, H-2'), 3.20-3.30 (m, 1H, H-6A), 3.51-3.54 (m, 1H, H-6B), 3.97-4.00 (m, 1H, H-2), 4.40-4.41 (m, 1H, O*H*), 5.03-5.06 (m, 2H, PhCH_2), 7.23-7.28 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$, 100MHz): δ 19.1 (C-4), 25.2 (C-5), 29.2 (C-3), 32.3 (C-1'), 39.3 (C-6), 46.9 (C-2), 58.5 (C-2'), 67.4 (Ph*C*H_2), 127.8 (PhCH), 127.9 (PhCH), 128.0 (PhCH), 128.1 (PhCH), 128.5 (PhCH), 136.5 (PhC), 156.7 (NCO).

Spectra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3.898
3.685
3.423
3.396
3.363
3.207
3.182
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2.980
2.938
2.918
2.445
2.426
2.248
2.216
2.111
2.022
1.995
1.968
1.924
1.896
1.716
1.687
1.673
1.658
1.644
1.617
1.587
1.490
1.467
1.446
1.422
1.398
1.334
1.228
O
N
H
2
11
10
9
8
7
6
5
4
3
2
1
0
ppm
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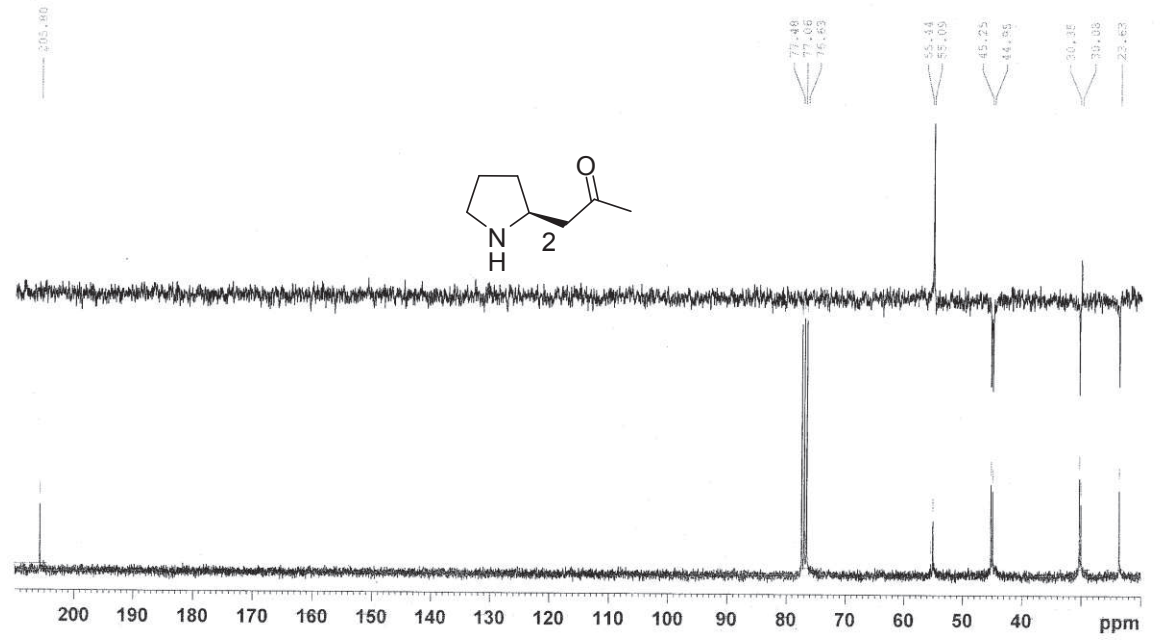
0.92
0.22
2.85
2.30
6.74
0.74
0.53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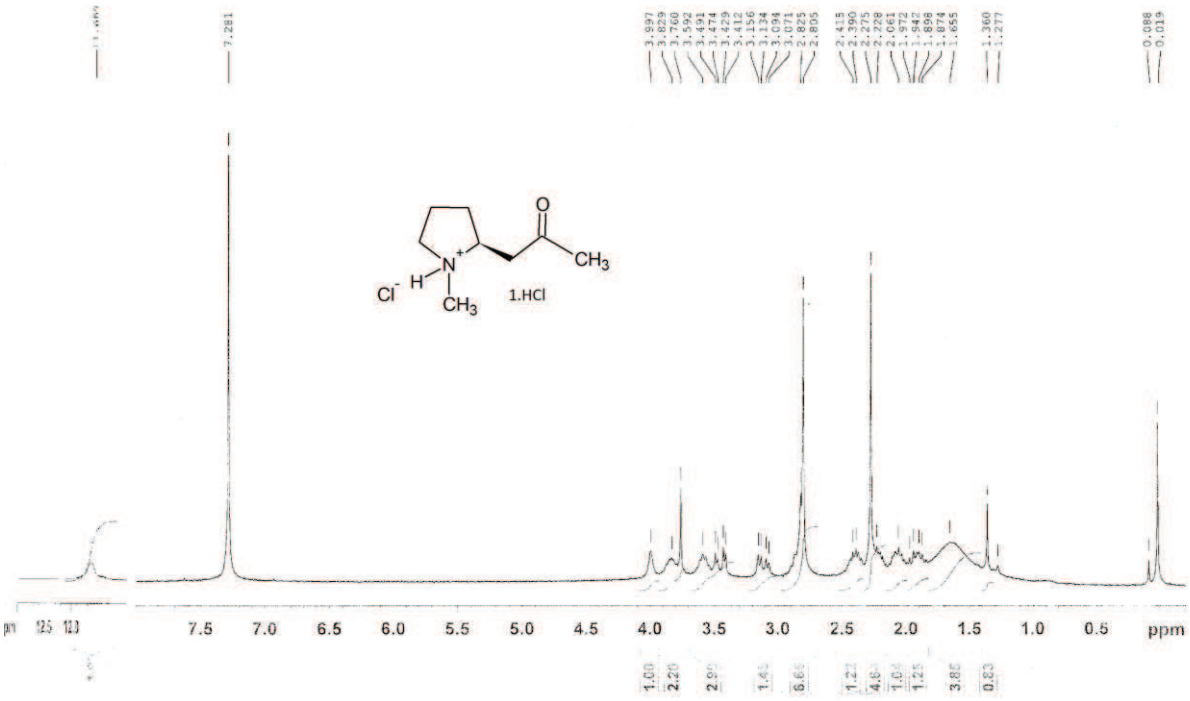
77.48
77.06
76.63
55.44
55.09
45.25
44.85
30.38
30.08
23.62
O
N
H
2
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm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3.997
3.829
3.760
3.752
3.491
3.474
3.429
3.412
3.156
3.134
3.094
3.071
2.825
2.805
2.415
2.390
2.275
2.228
2.061
1.972
1.947
1.898
1.874
1.655
1.360
1.277
0.088
0.019
O
CH3
Cl-
H
N+
CH3
1.HCl
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
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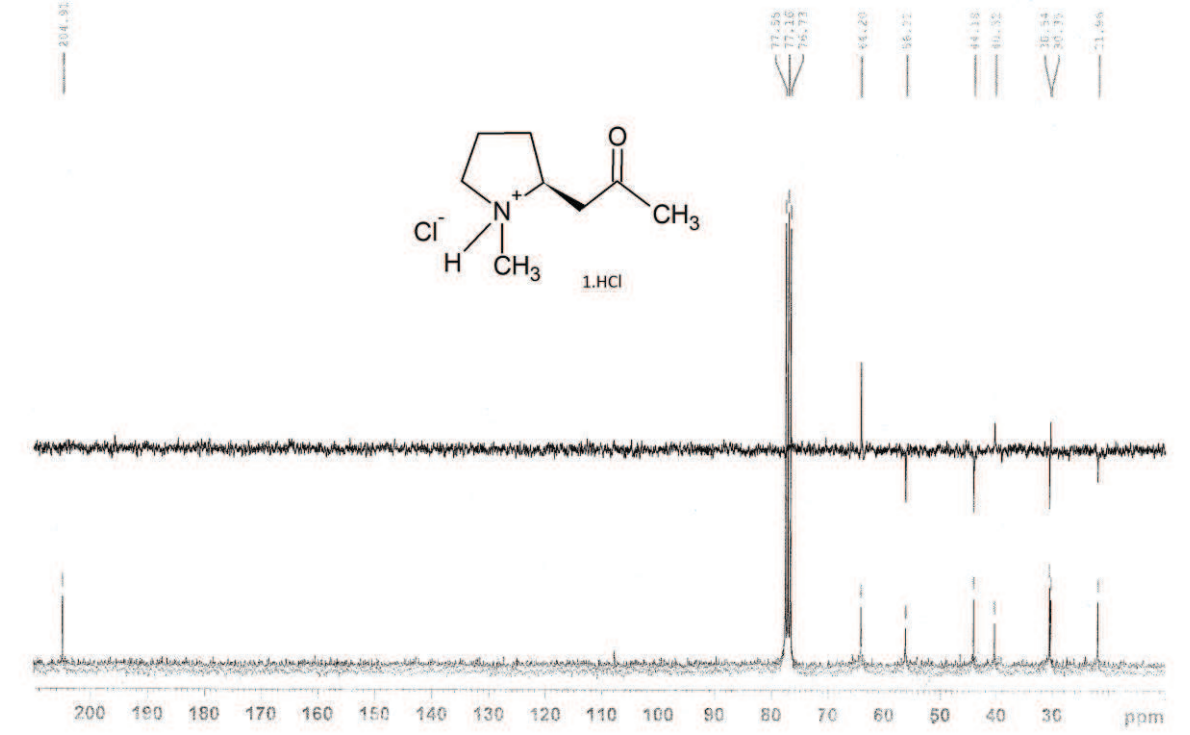
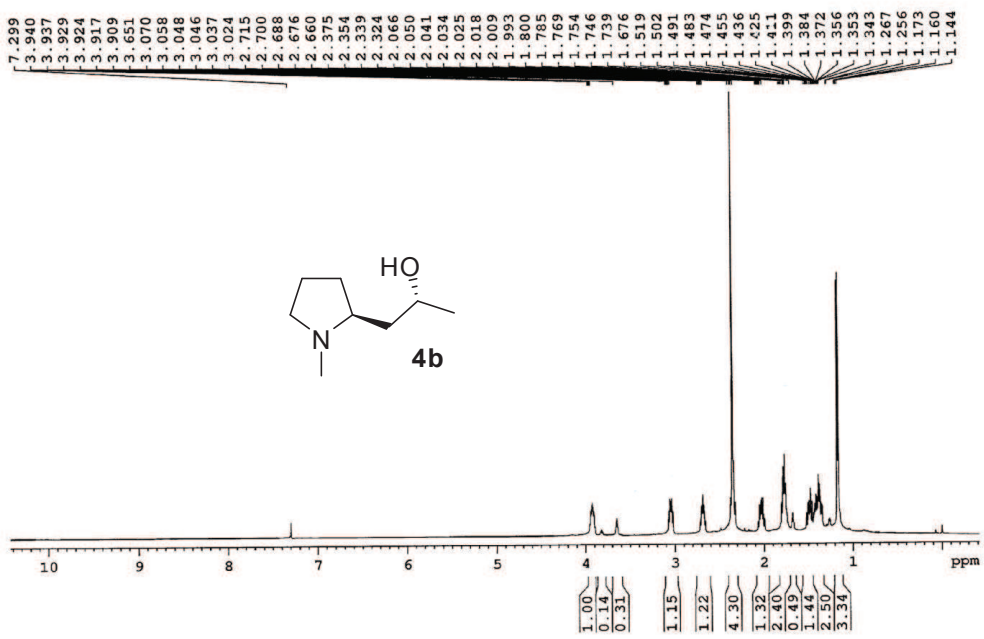
2.0
1.5
1.0
0.5
ppm


204.93
77.59
77.16
76.73
65.20
56.32
44.18
40.32
30.54
30.35
21.96
O
CH3
Cl-
H
N+
CH3
1.HCl
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm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3.940
3.937
3.929
3.924
3.917
3.909
3.651
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3.058
3.048
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3.024
2.715
2.700
2.688
2.676
2.660
2.375
2.354
2.339
2.324
2.066
2.050
2.041
2.034
2.025
2.018
2.009
1.993
1.800
1.785
1.769
1.754
1.746
1.739
1.676
1.519
1.502
1.491
1.483
1.474
1.455
1.436
1.425
1.411
1.399
1.384
1.372
1.356
1.353
1.343
1.267
1.256
1.173
1.160
1.144
HO
N
4b
10
9
8
7
6
5
4
3
2
1
ppm
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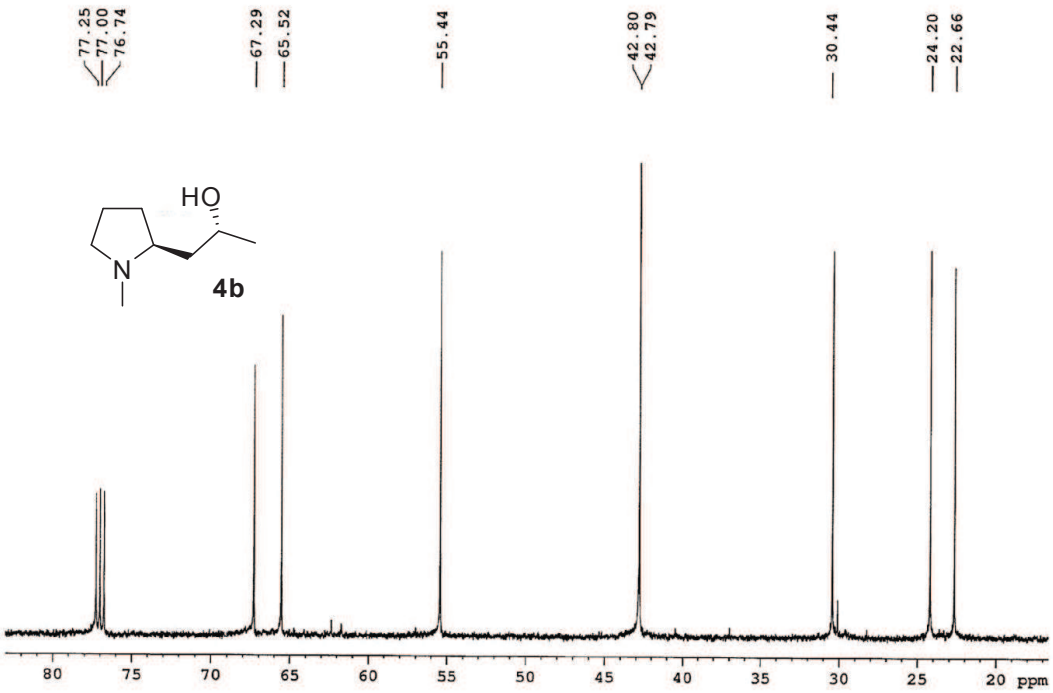
0.31
1.15
1.22
4.30
1.32
2.40
0.49
1.44
2.50
3.34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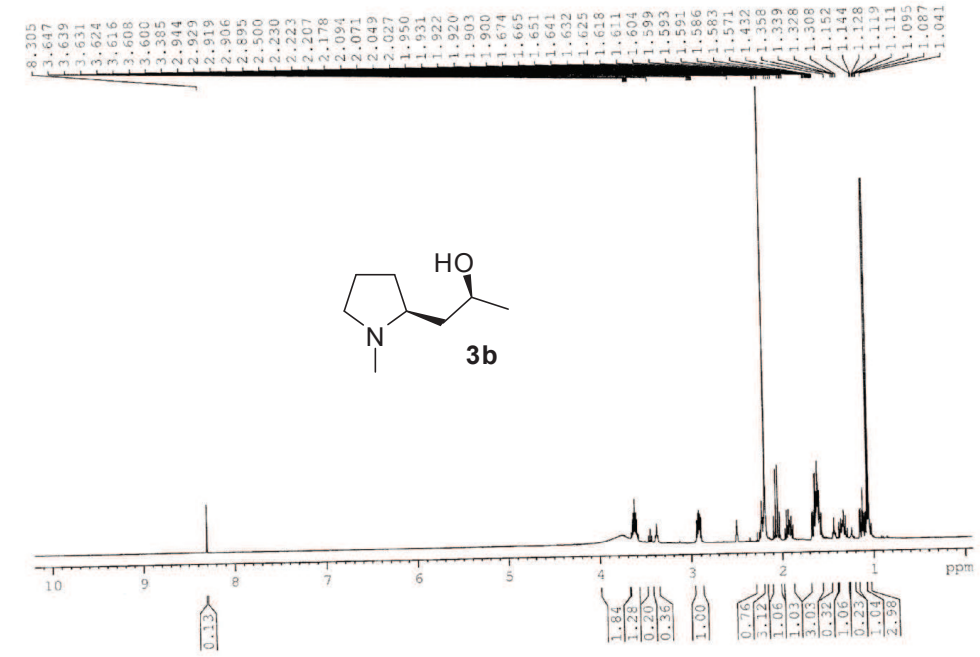
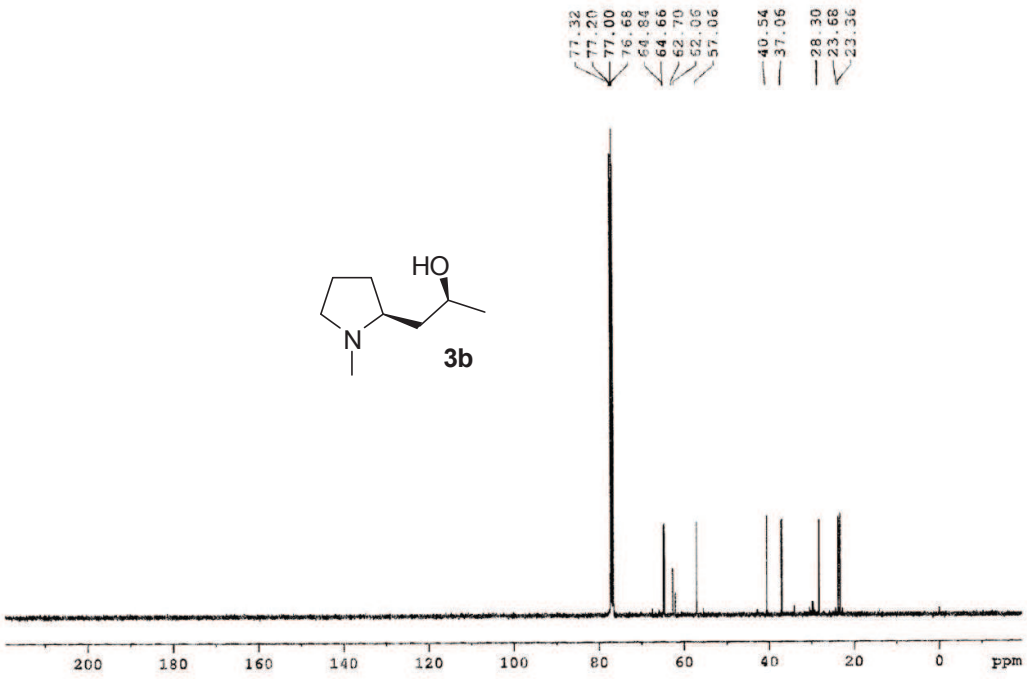
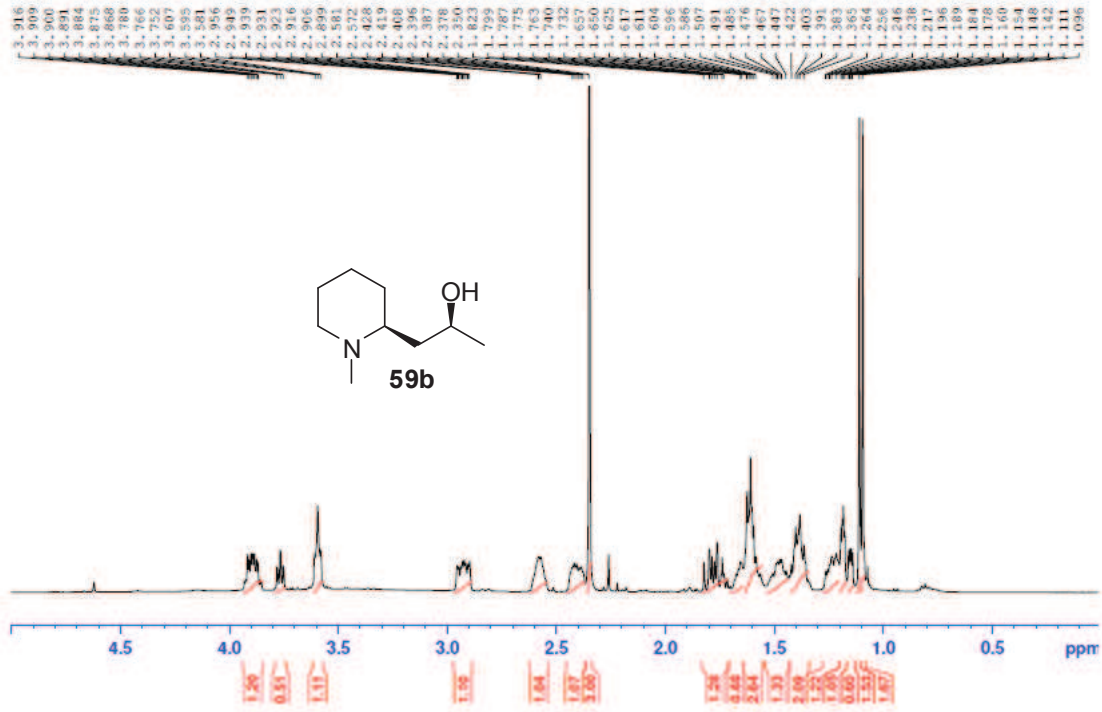
77.00
76.74
67.29
65.52
55.44
42.80
42.79
30.44
24.20
22.66
HO
N
4b
80
75
70
65
60
55
50
45
40
35
30
25
20 ppm


HO
N
3b
ppm


HO
N
3b
ppm


OH
N
59b
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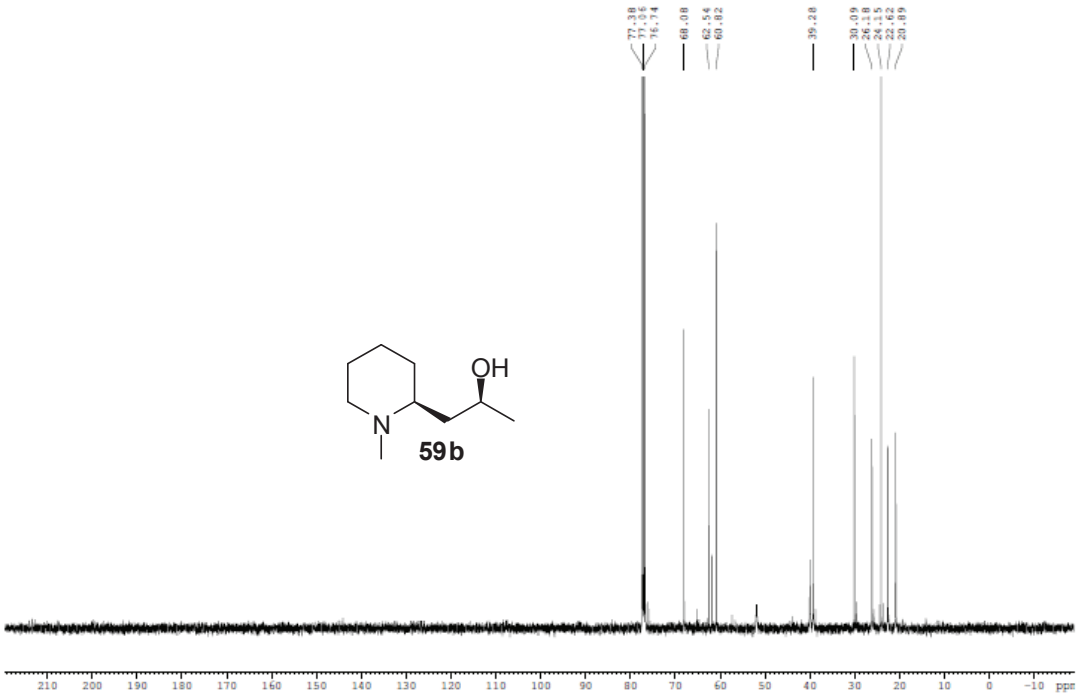
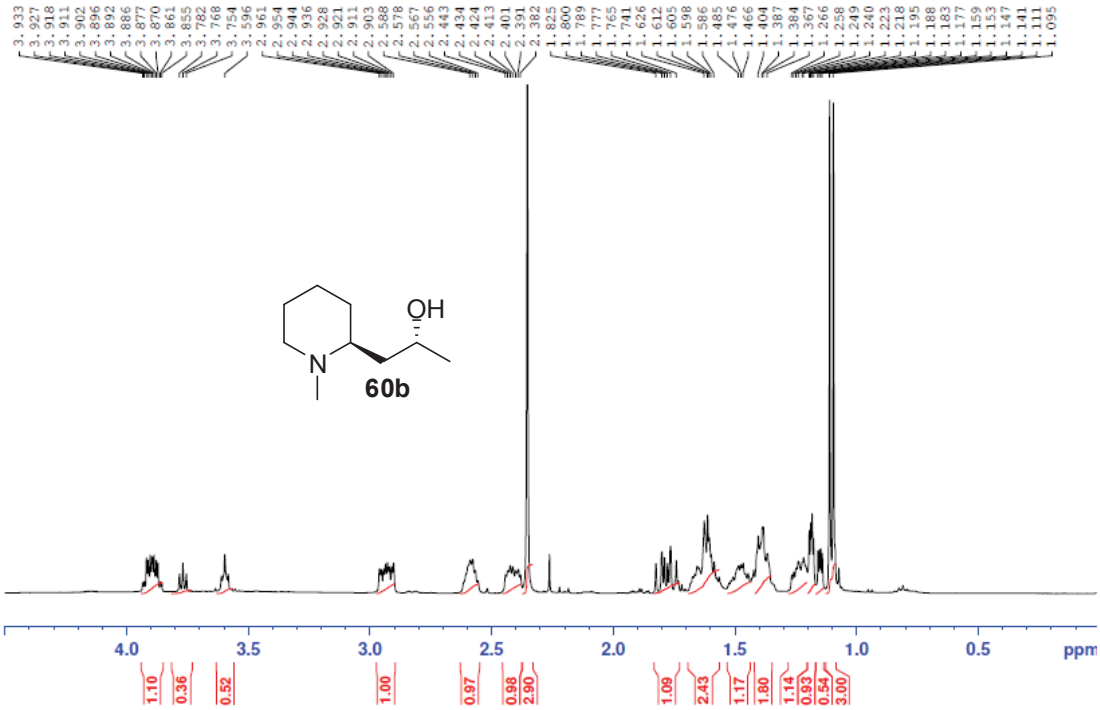
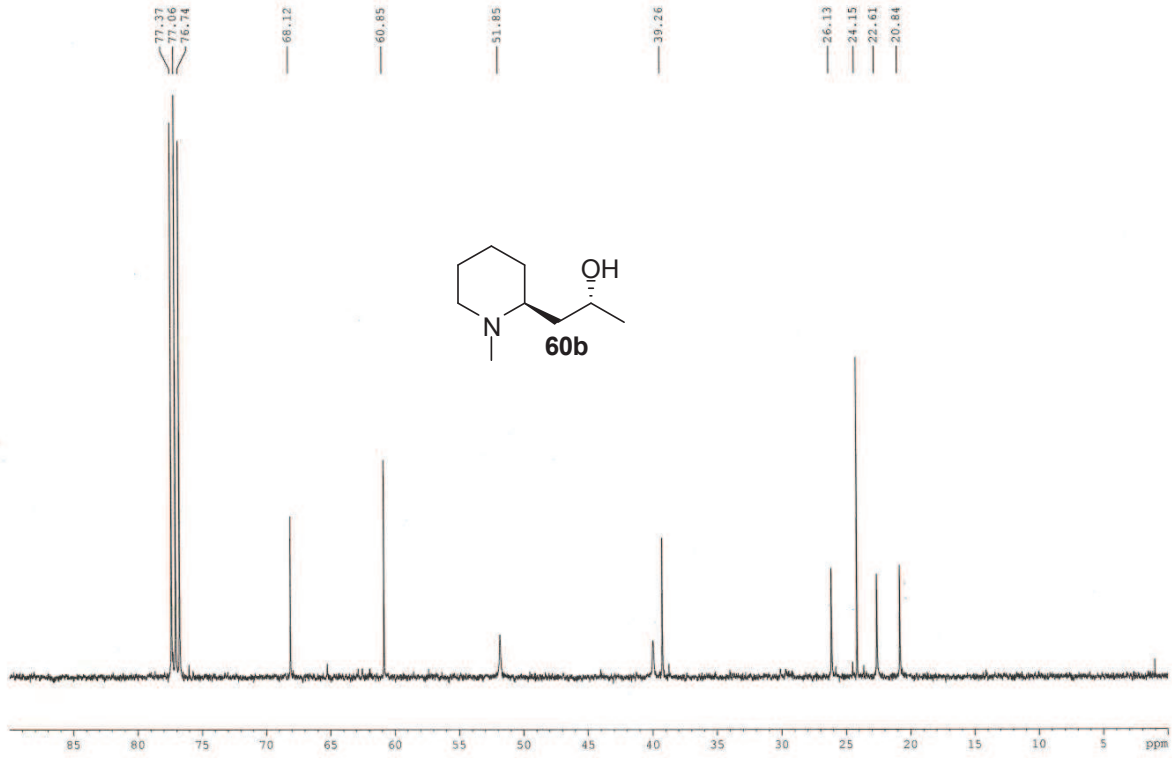
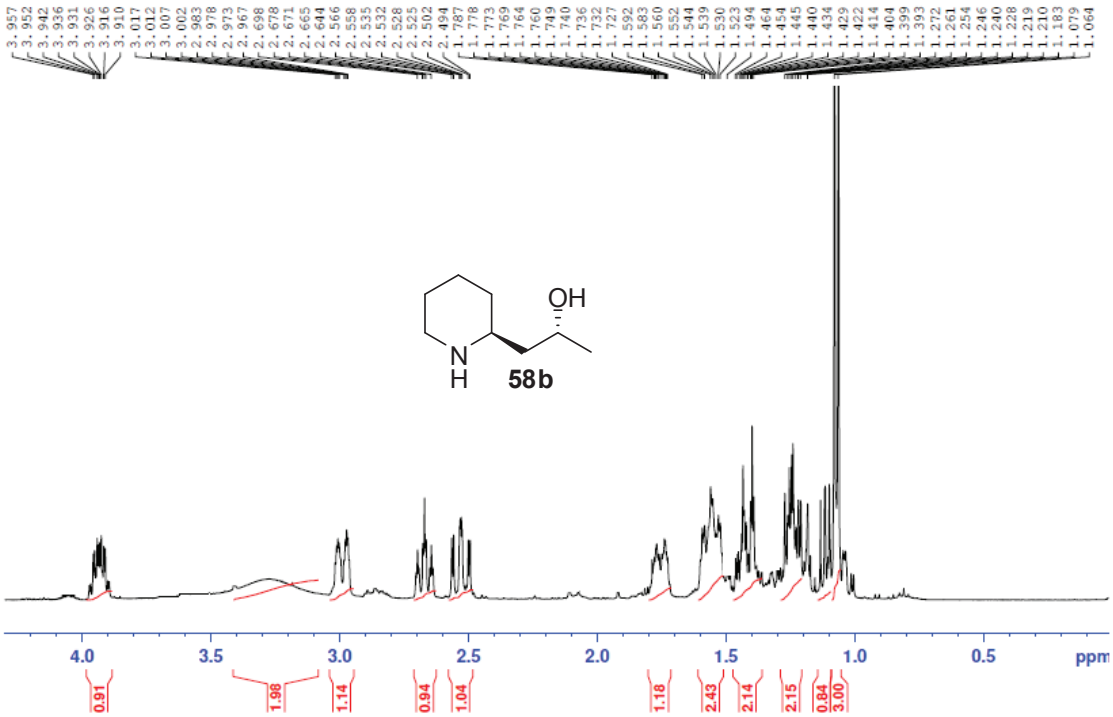
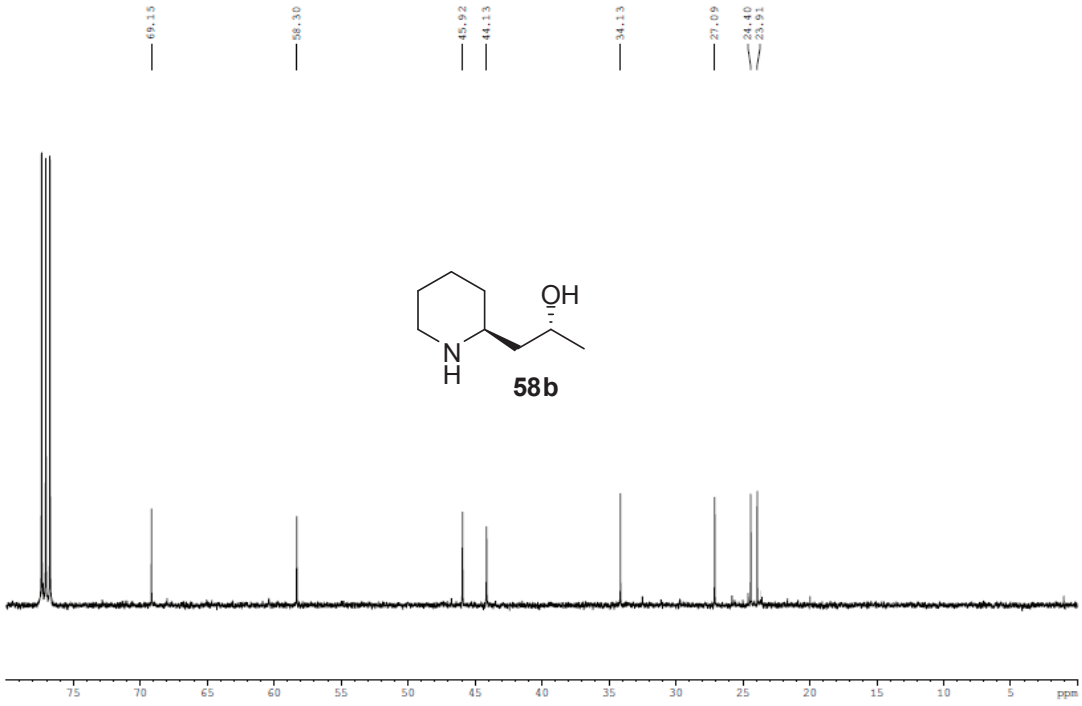
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

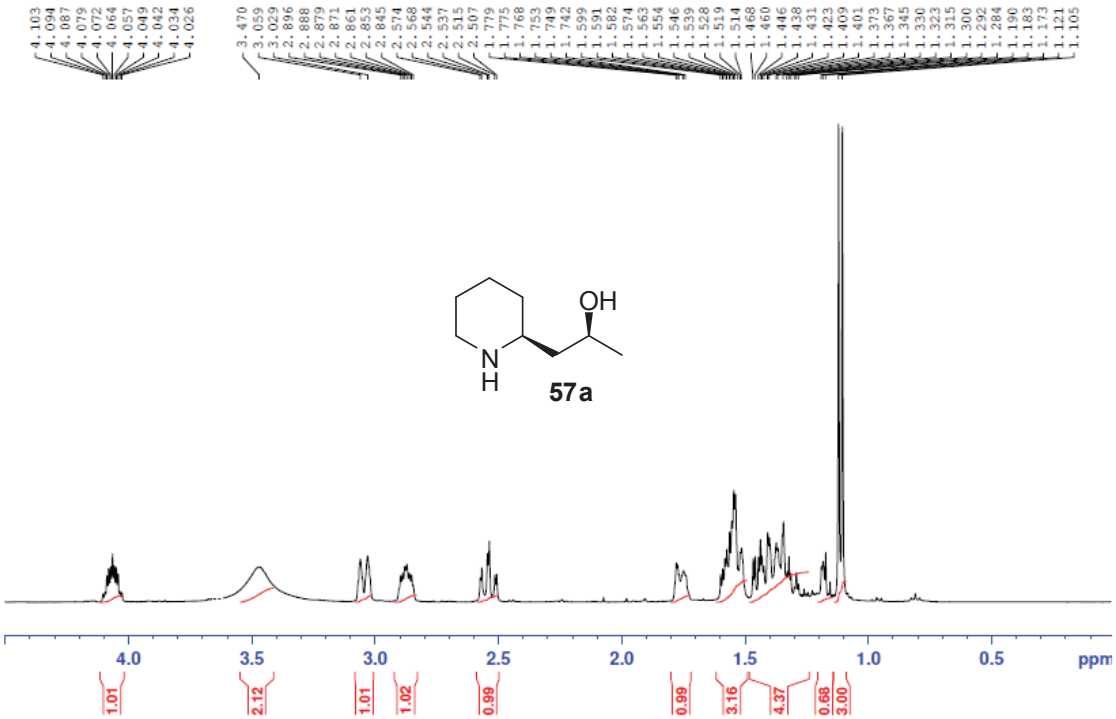

77.38
77.06
76.74
68.08
62.54
60.82
39.28
30.09
26.18
24.15
22.62
20.89
OH
N
59b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
ppm

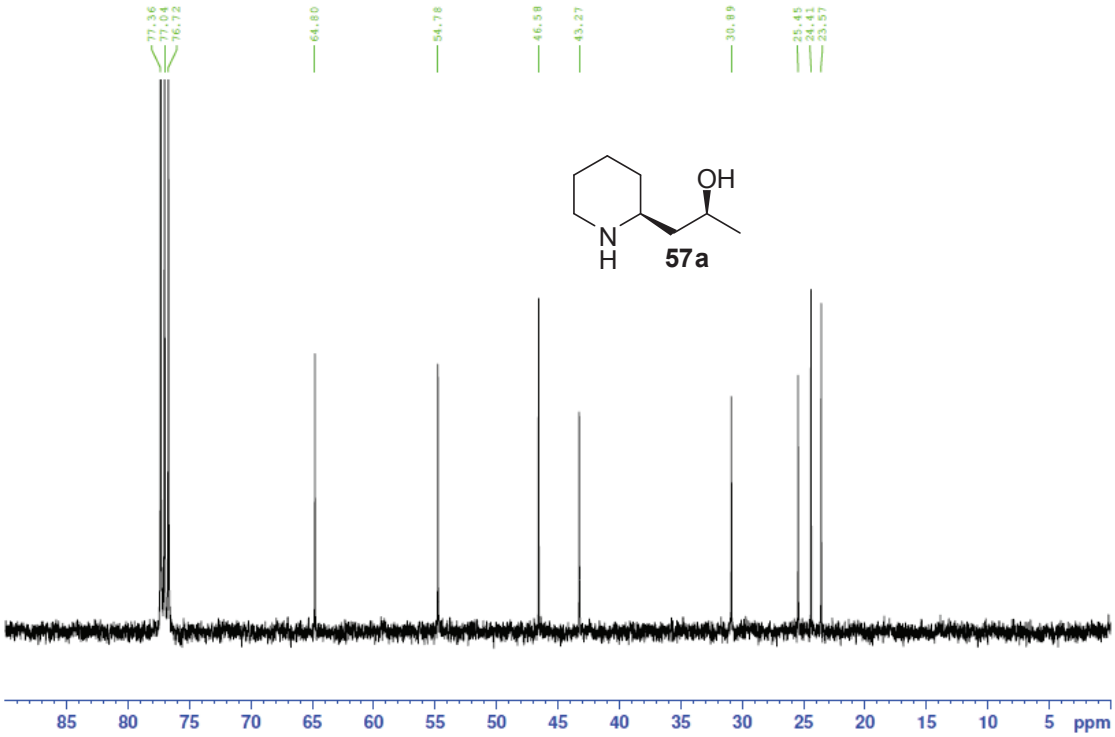

OH
N
60b
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

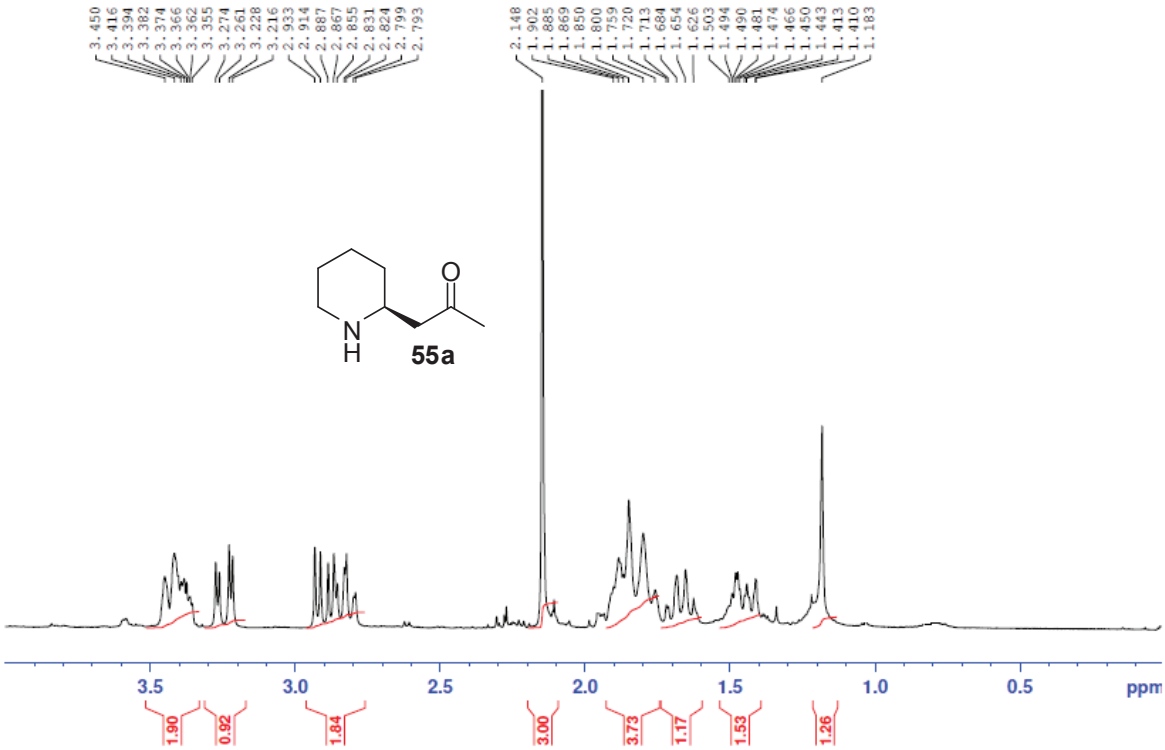

OH
N
60b
ppm


OH
N
H
58b
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


OH
N
H
58b
ppm


OH
N
H
57a
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


OH
N
H
57a
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
ppm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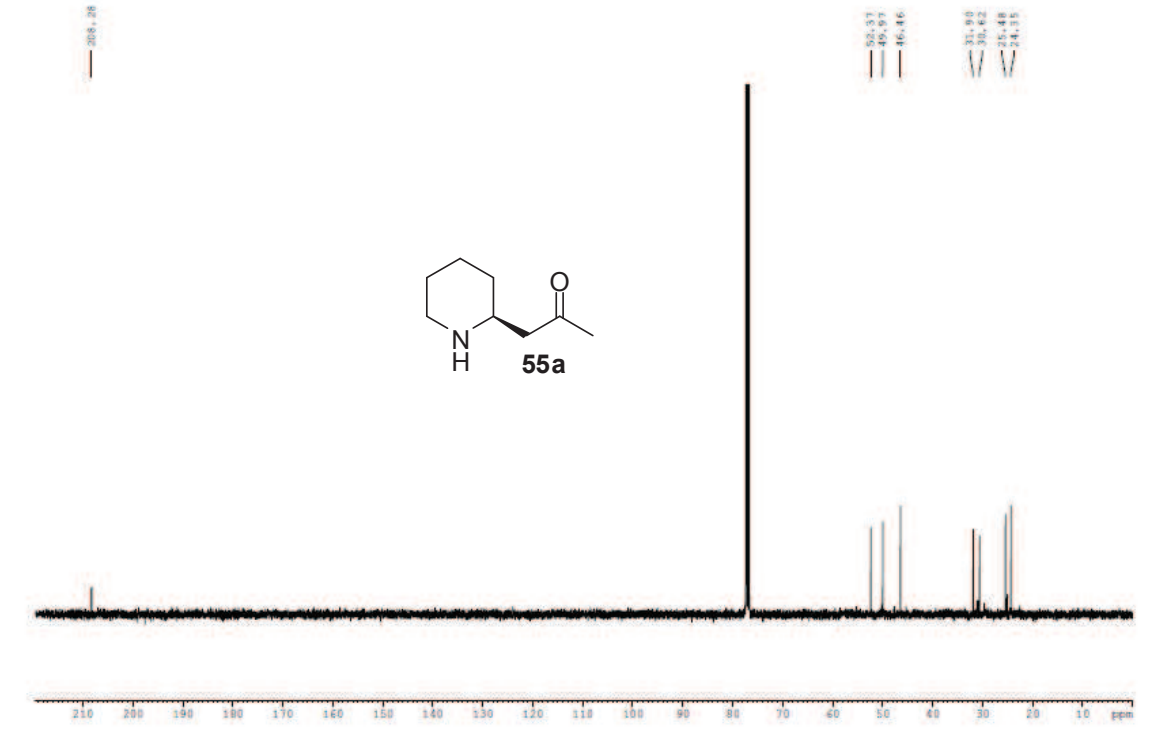
3.416
3.394
3.382
3.374
3.366
3.362
3.355
3.274
3.261
3.228
3.216
2.933
2.914
2.887
2.867
2.855
2.831
2.824
2.799
2.793
2.148
1.902
1.885
1.869
1.850
1.800
1.759
1.720
1.713
1.684
1.654
1.626
1.503
1.494
1.490
1.481
1.474
1.466
1.450
1.443
1.413
1.410
1.183
O
N
H
55a
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.90
0.92
1.84
3.00
3.73
1.17
1.53
1.26


208.28
52.37
49.97
46.46
31.90
30.62
25.48
24.35
O
N
H
55a
210
200
190
180
170
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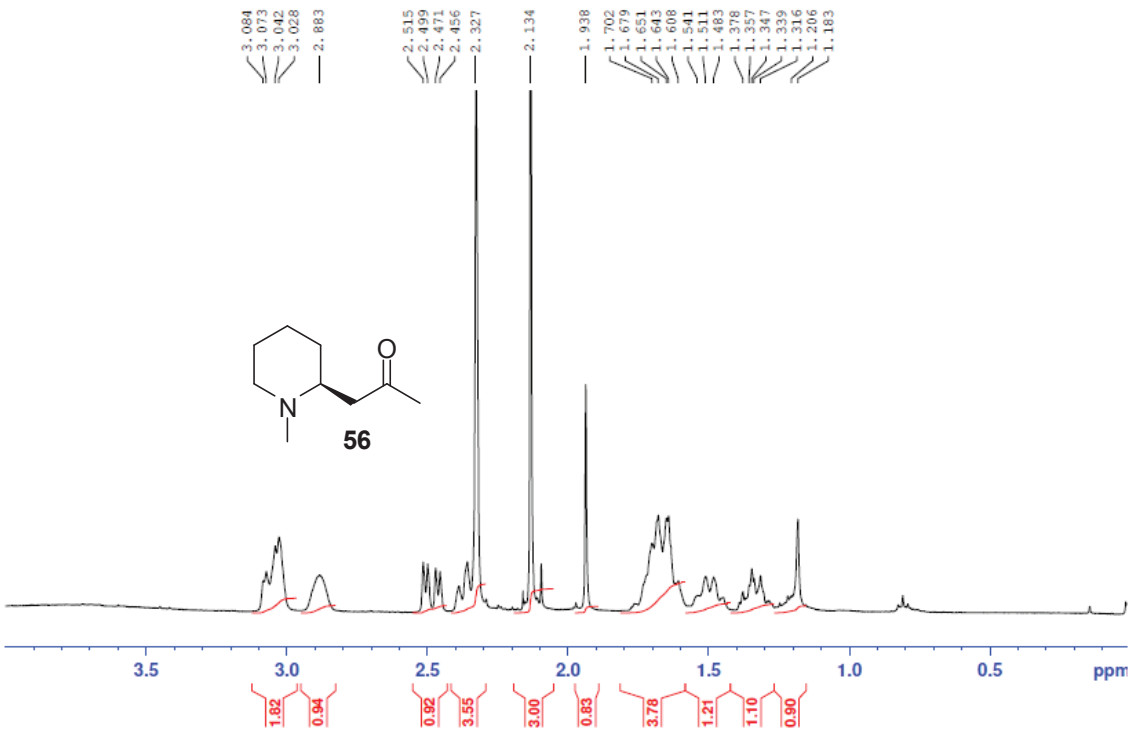
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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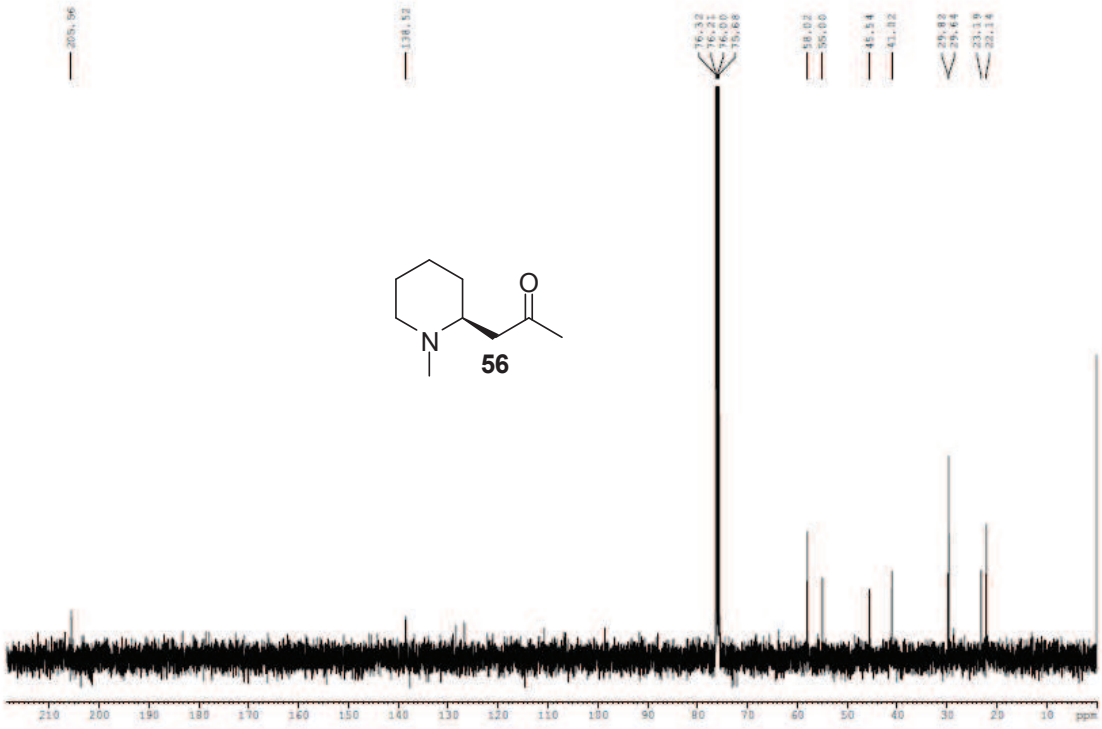
3.073
3.042
3.028
2.883
2.515
2.499
2.471
2.456
2.327
2.134
1.938
1.702
1.679
1.651
1.643
1.608
1.541
1.511
1.483
1.378
1.357
1.347
1.339
1.316
1.206
1.183
O
N
56
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.82
0.94
0.92
3.55
3.00
0.83
3.78
1.21
1.10
0.90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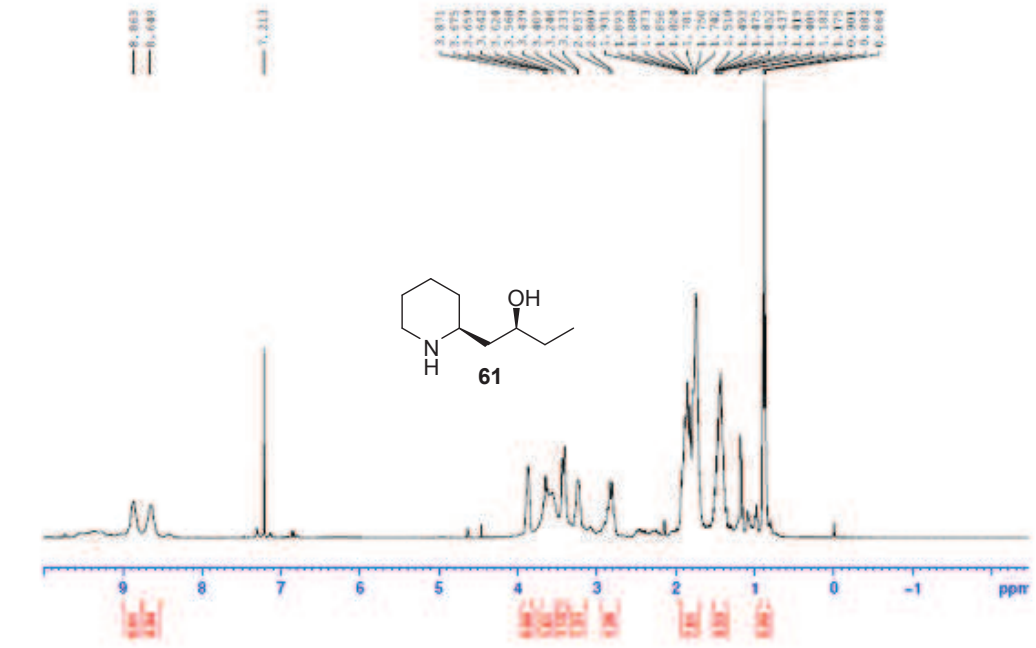
76.00
75.68
58.02
55.60
45.54
41.82
29.82
29.64
23.19
22.14
O
N
56
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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N
H
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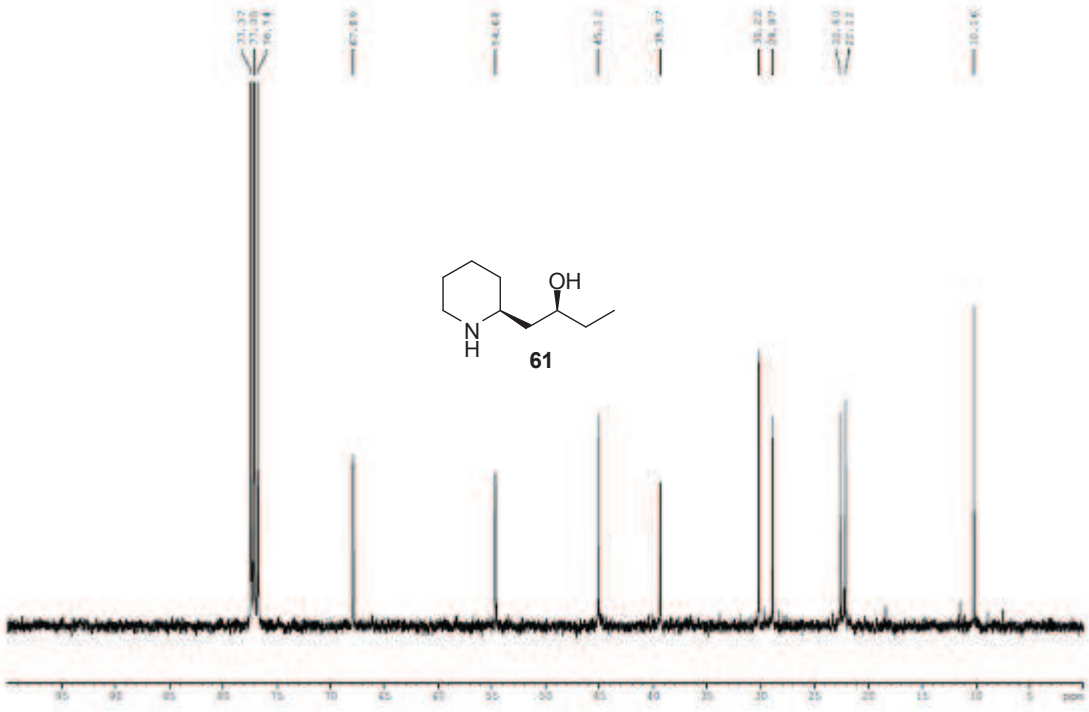
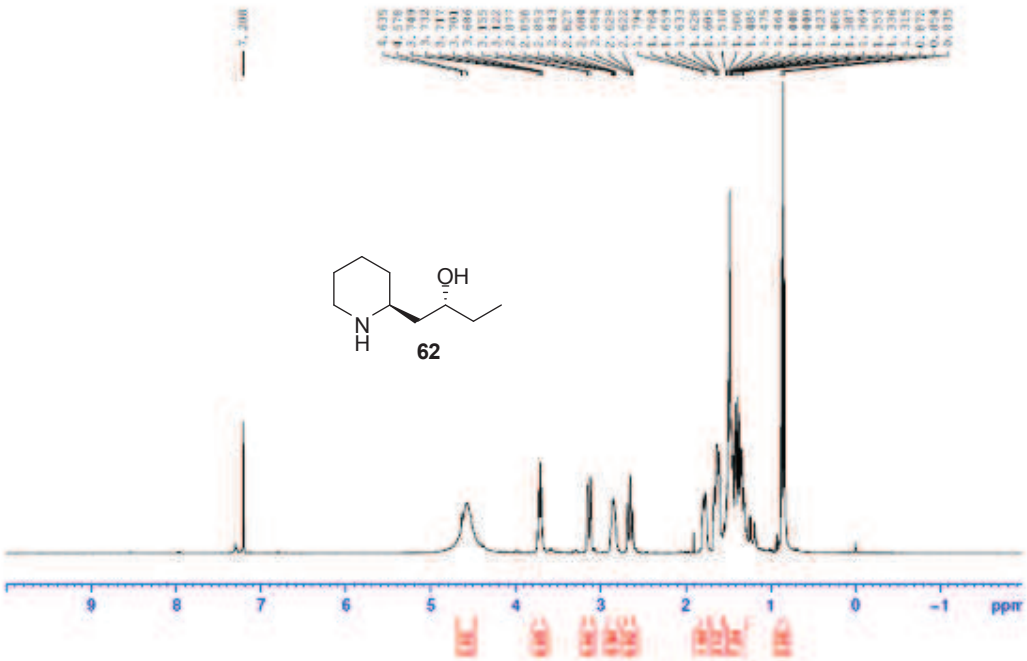
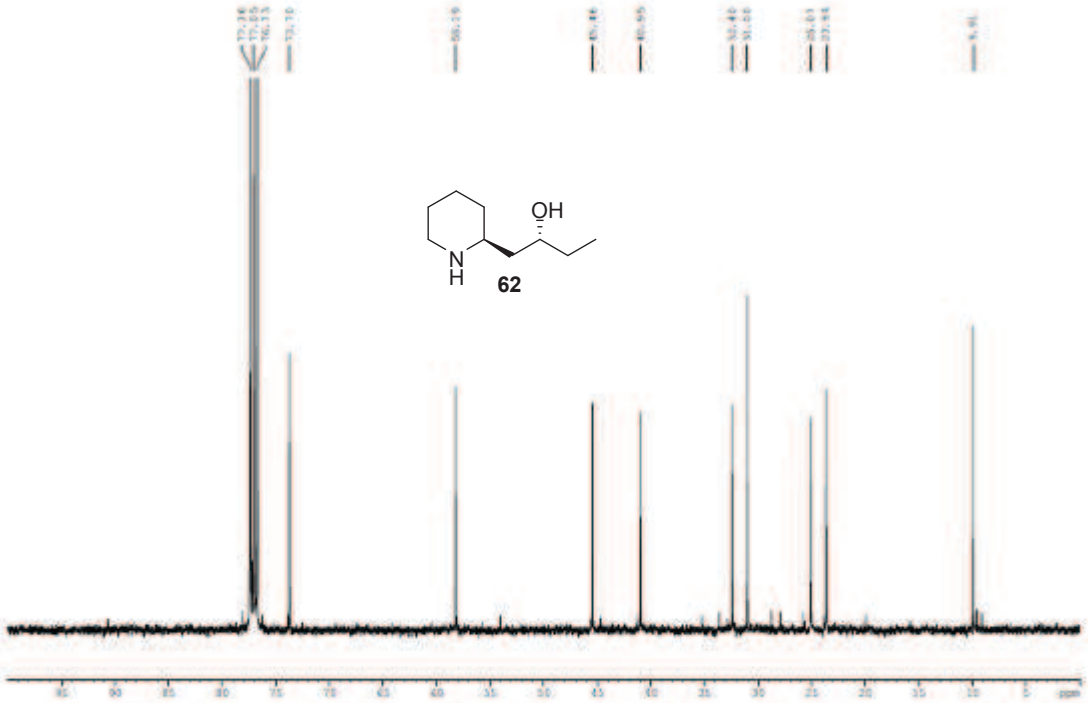
9
8
7
6
5
4
3
2
1
0
-1
ppm


OH
N
H
61


OH
N
H
62
9
8
7
6
5
4
3
2
1
0
−1
ppm


OH
N
H
62

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CHAPTER 3

Synthetic Studies towards Allokainic acid and Kainic acid

Synthetic Studies towards Allokainic acid and Kainic acid

Introduction

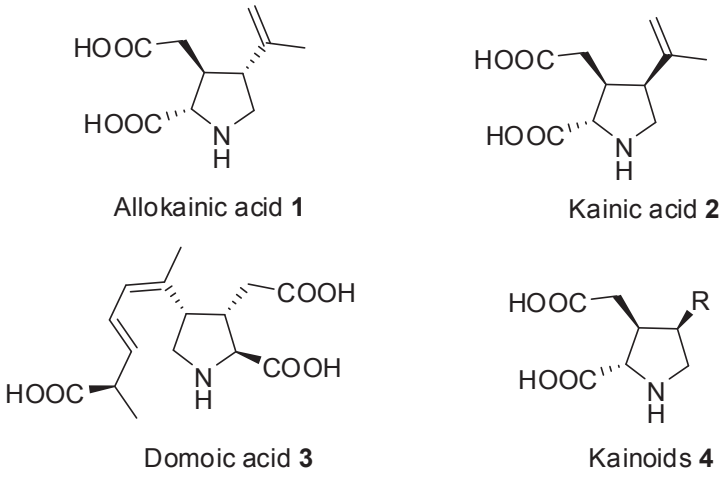


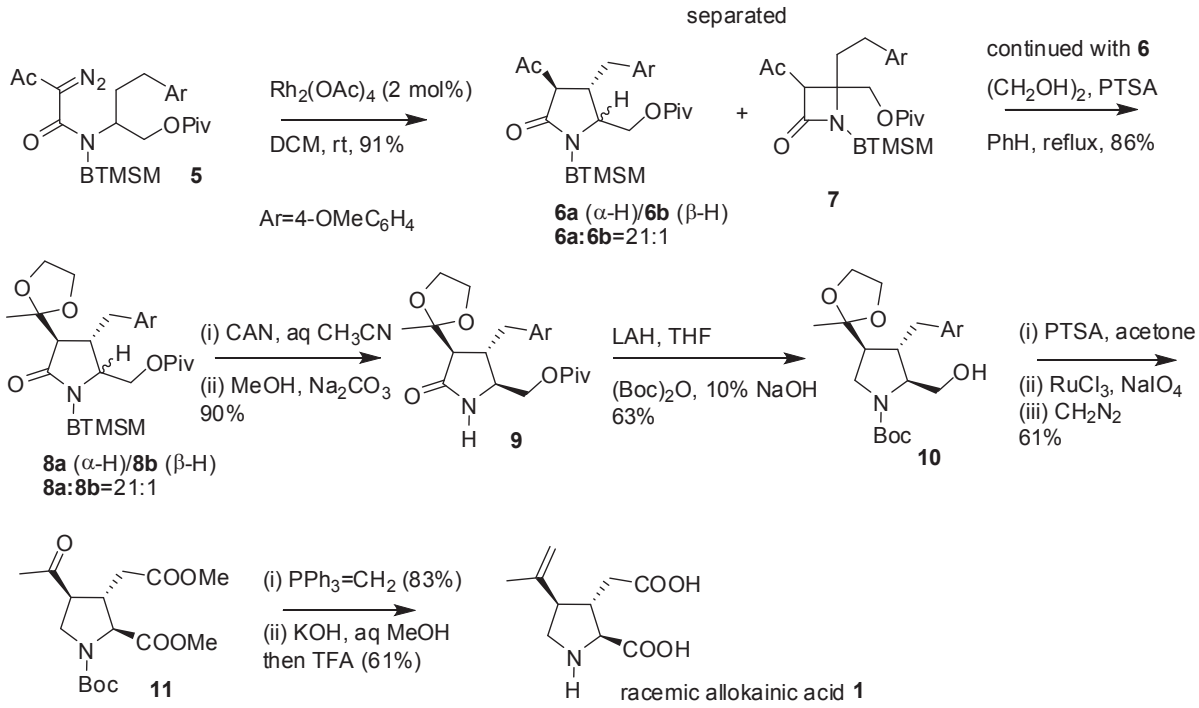
Figure 1. Members of kainoid family

Kainoids **4** are nonproteinogenic amino acids (fig. 1), consisting of *trans*-2, 3-dicarboxylic groups on pyrrolidine core, attracted major attention in neurological science. The important members of this family are kainic acid **2**, allokainic acid **1** and domoic acid **3**. It was observed that highly functionalized trisubstituted pyrrolidine ring with three contiguous stereogenic centres with *cis* substitution at 3, 4 positions are responsible for their potent biological activities.[1] Allokainic acid **1** was isolated by Takemoto from Japanese marine algae *Digenea simplex AG* in 1953 along with its C-4 epimer kainic acid **2.**[2] Both these molecules display potent inhibition of neurotransmitting activities of the central nervous system (CNS).[1] Owing to their pronounced biological activities; they find vast applications in the treatment of Alzheimer's disease, Huntington's chorea and epilepsy.[3]

Literature Reviews

The potent biological activities and global scarcity[4] of these molecules prompted the synthetic chemists to develop efficient routes for these. As a consequence several synthetic routes have been developed for the synthesis of kainic acid[5] and allokainic acid.[6] Some of the important and very recent syntheses are described below.

Synthesis of allokainic acid

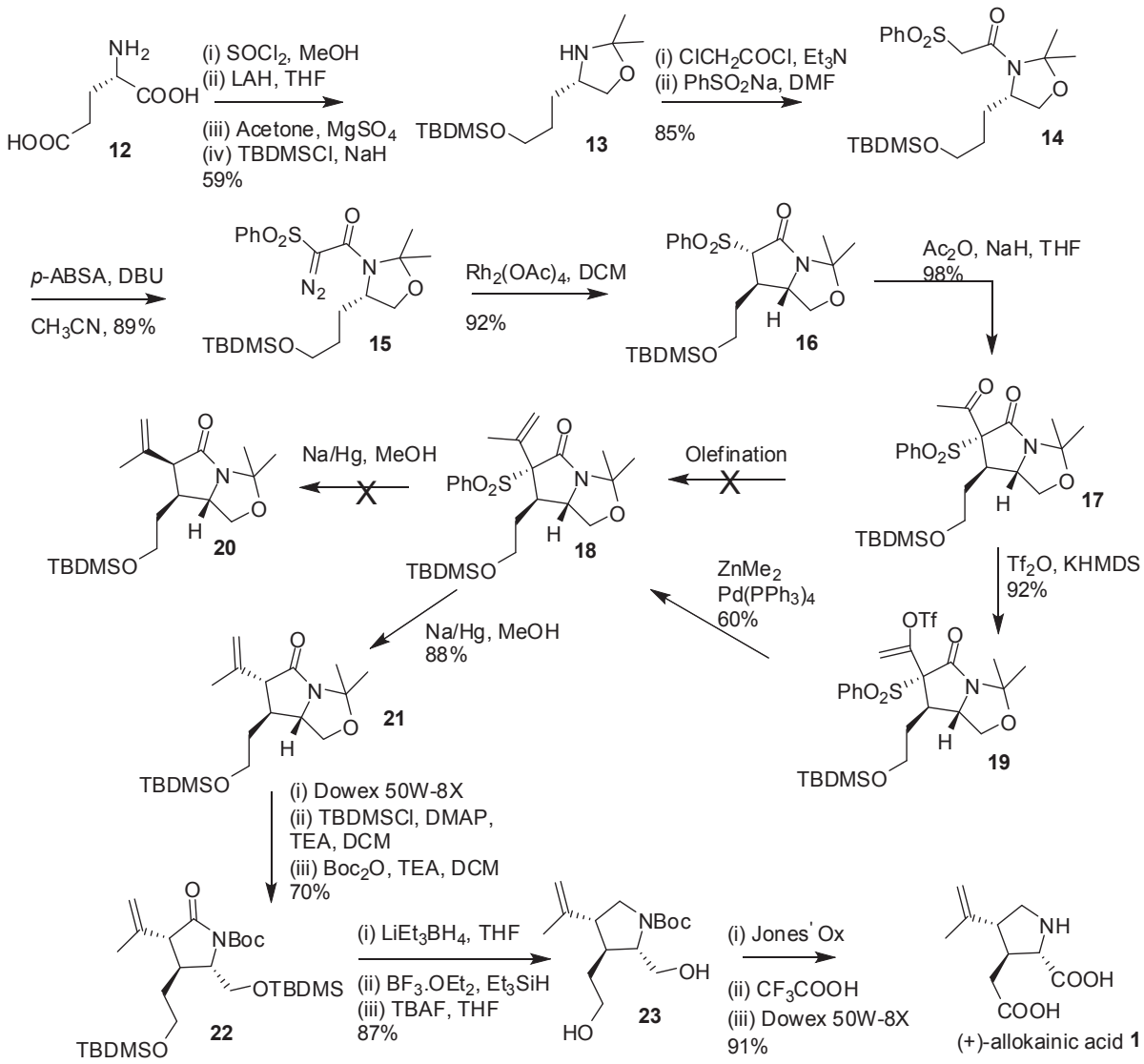


Scheme 1

Zhang and Wee achieved the total synthesis of (±)-allokainic acid via Rh(II)-catalyzed carbenoid C-H insertion of α-diazomides of the type **5** (scheme 1).[6y] The compound **5** on treatment with $Rh_2(OAc)_4$ afforded a mixture **6** and **7** amenable to separation on column chromatography. The inseparable diastereomeric mixture **6** was acetonide protected to give diastereomeic mixture of **8**. The compound **8a** was subjected to *N*-deprotection to provide **9** which on LAH reduction gave **10**. The deprotection of acetonide followed by vinylation and Boc deprotection afforded the natural product **1**.

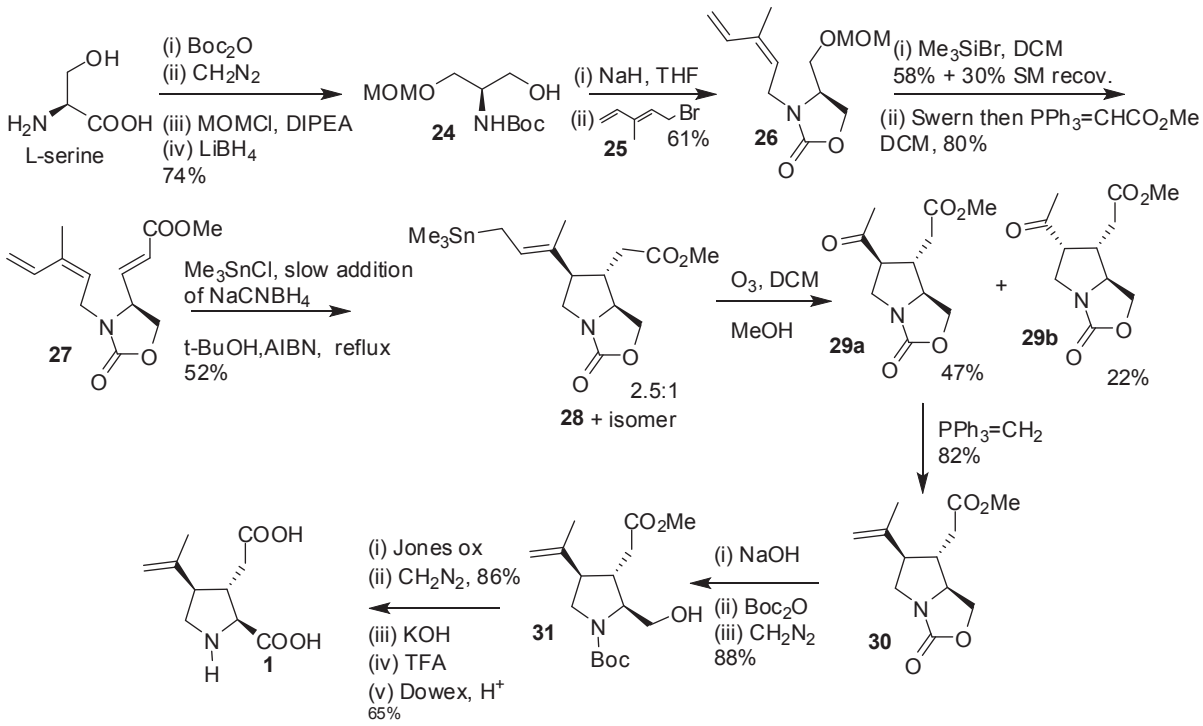
Jung and co-workers synthesized (+)-allokainic acid **1** in an application of the methodology of Rh(II)-catalyzed intramolecular CH insertion of α-diazo-α-(phenylsulfonyl)-acetamides to afford γ-lactams with notable stereo and regioselectivity (scheme 2).[6x] The precursor for C-H insertion **15** was synthesized starting from amino acid **12**. The treatment of compound **15** with $Rh_2(OAc)_4$ in DCM afforded the desired lactam **16** with appreciable regio and diastereoselctivity. The compound **16** was acetylated to give **17** and when direct olefination was unsuccessful, it was converted to triflate **19** and then subjected to Negishi type Pd (0) catalyzed alkylation to afford **18**. The *trans* isomer **21** was formed upon desulfonation of **18** by treatment with Na/Hg which was further transformed

to **22**. The amide reduction, successive deprotection of the protecting groups and oxidation of alcoholic groups produced the natural product **1**.

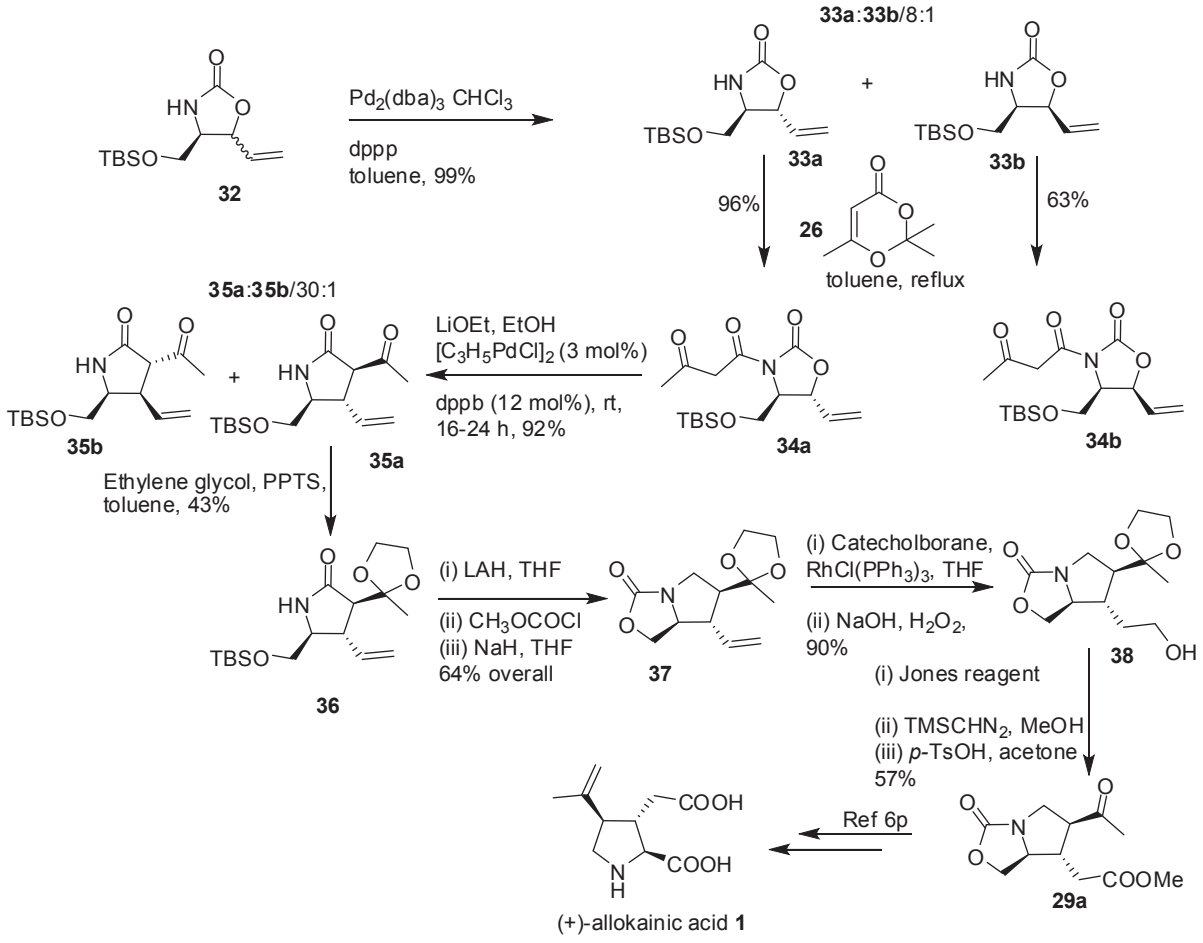


Scheme 2

Hanessian and Ninkovic persuaded the synthesis of allokainic acid **1** using trimethylstannyl radical carbocyclization (scheme 3).[6p] The triene **27** synthesized by sequential conversion of L-serine was subjected to trimethyltin radical addition-carbocyclization conditions, the *trans* isomer **28** was formed predominantly along with minor isomers separated on column chromatography. The stereochemistry of **28** was confirmed by NMR studies. The ozonolysis of **28** followed by subsequent Wittig olefination afforded **30** which was eventually transformed to (+)-allokainic acid **1**.

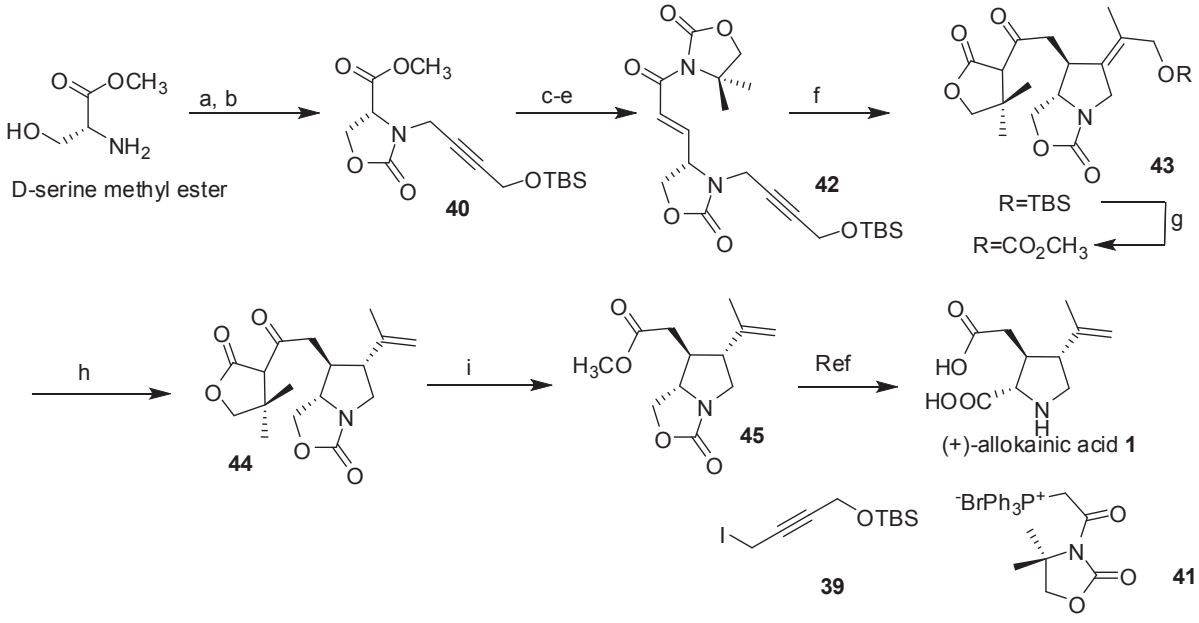

(i) Boc2O
(ii) CH2N2
(iii) MOMCl, DIPEA
(iv) LiBH4
74%
L-serine
24
(i) NaH, THF
(ii)
25
Br
61%
26
(i) Me3SiBr, DCM
58% + 30% SM recov.
(ii) Swern then PPh3=CHCO2Me
DCM, 80%
27
Me3SnCl, slow addition
of NaCNBH4
t-BuOH,AIBN, reflux
52%
28 + isomer
2.5:1
O3, DCM
MeOH
29a
47%
29b
22%
PPh3=CH2
82%
30
(i) NaOH
(ii) Boc2O
(iii) CH2N2
88%
31
(i) Jones ox
(ii) CH2N2, 86%
(iii) KOH
(iv) TFA
(v) Dowex, H+
65%
1

Scheme 3


32
Pd2(dba)3 CHCl3
dppp
toluene, 99%
33a:33b/8:1
33a
33b
96%
63%
26
toluene, reflux
35a:35b/30:1
35b
35a
LiOEt, EtOH
[C3H5PdCl]2 (3 mol%)
dppb (12 mol%), rt,
16-24 h, 92%
34a
34b
Ethylene glycol, PPTS,
toluene, 43%
36
(i) LAH, THF
(ii) CH3OCOCl
(iii) NaH, THF
64% overall
37
(i) Catecholborane,
RhCl(PPh3)3, THF
(ii) NaOH, H2O2,
90%
38
(i) Jones reagent
(ii) TMSCHN2, MeOH
(iii) p-TsOH, acetone
57%
29a
Ref 6p
(+)-allokainic acid 1

Scheme 4

Cook and Sun illustrated the Pd-catalyzed carbocyclization of oxazolidinones to oxazolines with high degree of diastereoselectivity and successfully applied for the formal synthesis of (+)-allokainic acid **1** (scheme 4).[6v] After several synthetic manipulations, the compound **32** prepared from L-serine was efficiently transformed to requisite **34a** with high level of diastereoselectivity via Pd-catalyzed isomerisation and amidation. The conversion of oxazolidinone **34a** to oxazolines **35** was best effected using $[C_3H_5PdCl]_2$ with ligand dppb in the presence of base LiOEt to afford exclusively **35a** which was sequentially transformed to **29a** to constitute the formal synthesis of (+)-allokainic acid **1**.



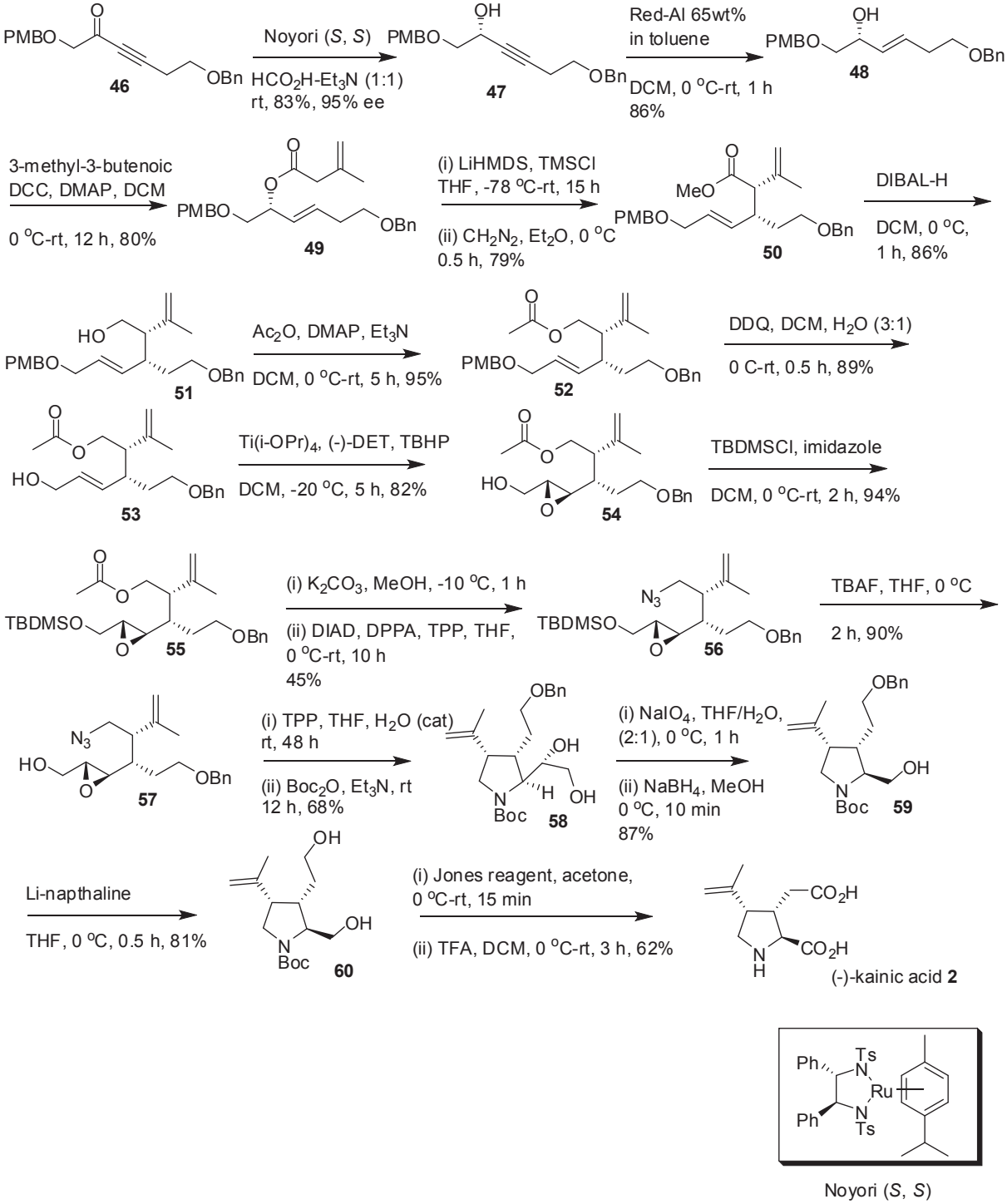
Scheme 5

(a) Triphosgene, THF, 65 °C, 4 h; (b) KHMDS (1.1 equiv), THF, 0 °C, 30 min; then **39** (3 equiv) in THF; 40 °C, 24 h, 49% (2 steps); (c) $NaBH_4$, EtOH, 0 ± 25 °C, 3 h, 91%; (d) $(COCl)_2$ (1.5 equiv), DMSO (3 equiv), Et_3N (4 equiv), DCM, -78 °C; (e) 3 (1.5 equiv), DMAP (3 equiv), DCM , -20 to 25 °C, 1.5 h, 81% (two steps); (f) Me_3Al (3 equiv), 10 mol% $[Ni(cod)_2]$, THF, 0 °C, 40 min., 73% (97:3 diastereoisomeric ratio); (g) HF.pyridine, THF, 0 ± 25 °C, 24 h, 86%; then methylchloroformate (3 equiv), pyridine, DCM, 0 ± 25 °C, 3 h, 83%; (h) 10 mol% $[Pd_2(dba)_3]$, 40 mol% PBu_3 , Et_3N (1.5 equiv), HCO_2H (1.5 equiv), THF, 65 °C, 74%, (95:5 diastereomeric ratio); (i) MeOMgBr (3 equiv), 25 °C, 3 h, 54%.

Chevliakov and Montgomery achieved the formal synthesis of allokainic acid **1** using D-serine as a chiral source (scheme 5).[6t] The compound **42** synthesized from D-serine was subjected to pivotal cyclisation using $Ni(cod)_2$ and Me_3Al to afford exclusively *trans*

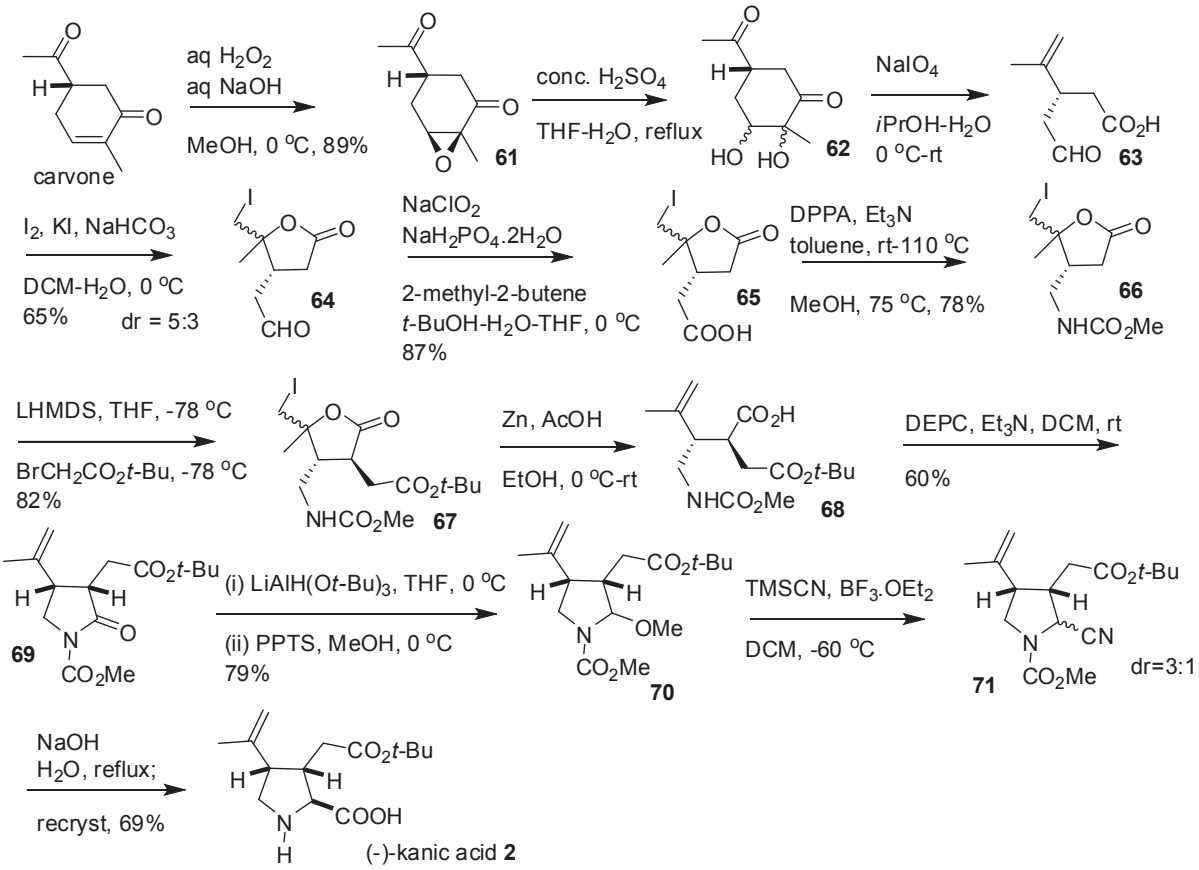
isomer **43**. The silyl group was converted to carbonate and then treated with $Pd_2(dba)_3$/ PBu_3 in the presence of HCO_2H/Et_3N to give diastereoselectively **44** with 74% yield. The acyloxazolidinone **44** upon treatment with excess MeOMgBr produced **45** to complete the formal synthesis of (+)-allokainic acid **1**.

Synthesis of kainic acid



Scheme 6

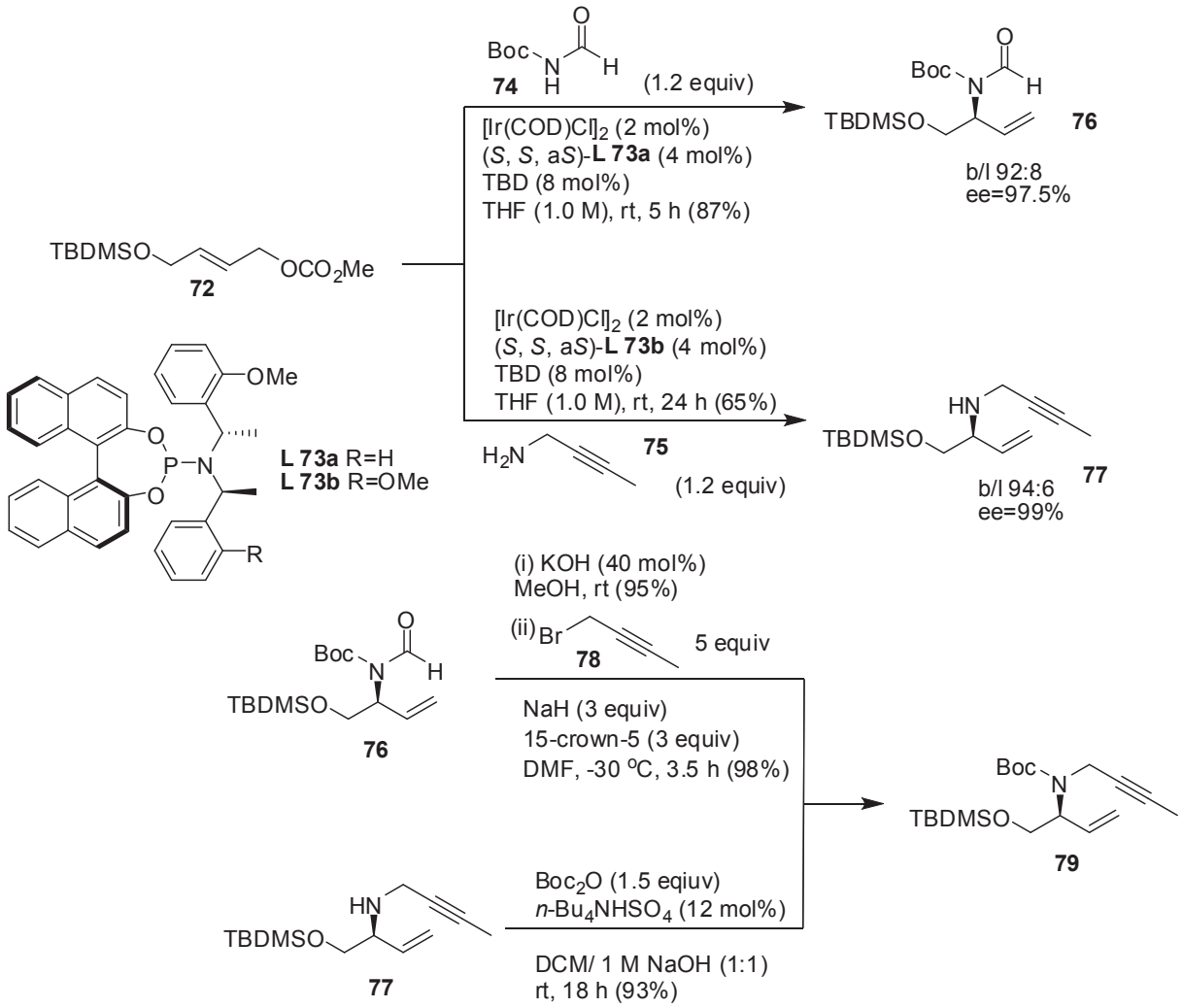
A recent elegant work done by Reddy and Chandrasekhar explained the synthesis of (-)-kainic acid via chirality transfer through Ireland–Claisen rearrangement (scheme 6).[5b] The alkyne **46** transformed to chiral allyl ether **49** was subjected to Claisen condensation resulting diastereoselectively **50**. The epoxide **54** synthesized from **49** was further transformed uneventfully to azide **57** which on reduction using PPh_3 opened up epoxide to give a secondary amine isolated after Boc protection as **58**. The diol **58** was oxidatively cleaved and successfully transformed to (-)-kainic acid **2** through classical synthetic sequences.

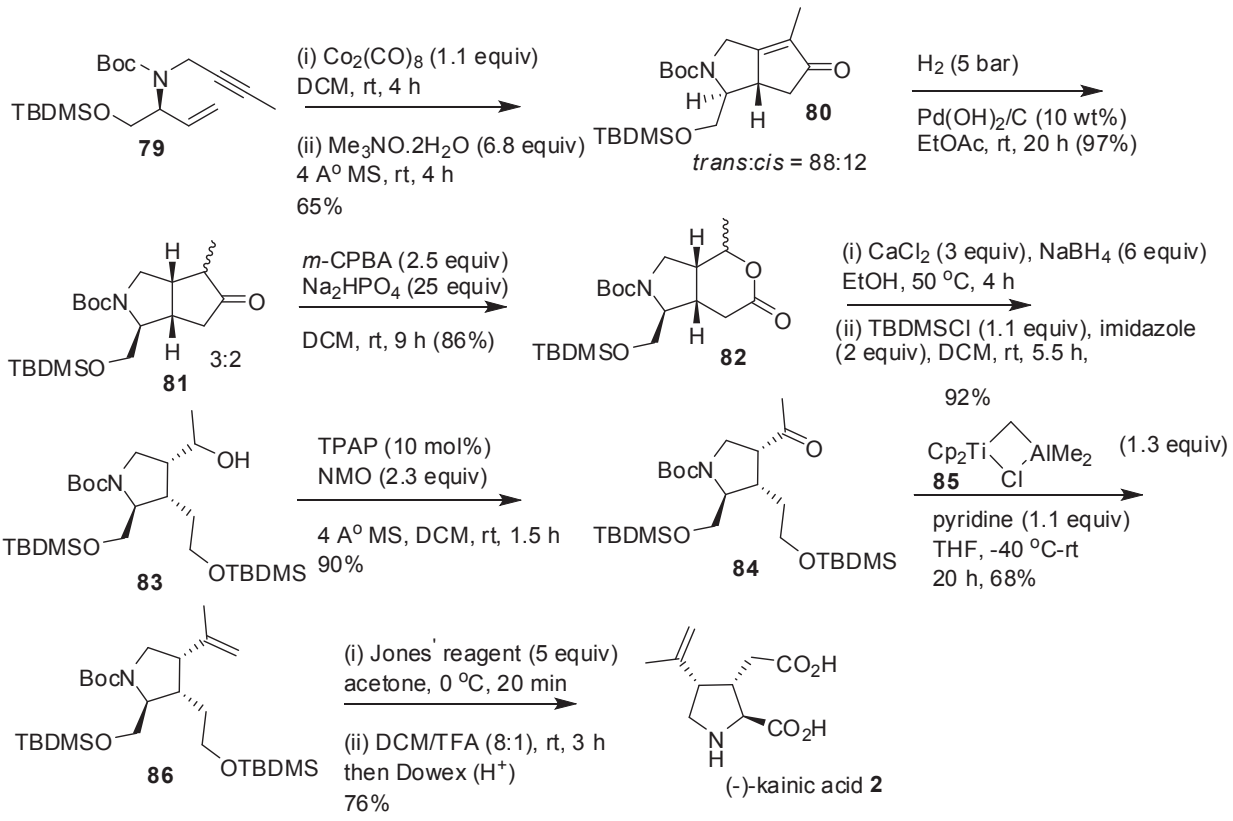


Scheme 7

Fukuyama and co-workers developed a practical method for the large scale synthesis of (-)-kainic acid **2** using the chiral source (-)-carvone (scheme 7).[5c] The key step involves the iodolactonization of **63** to give iodo compound **64** which was further oxidised and converted to carbamate **66** via Curtius rearrangement. The deprotonation and alkylation of **66** gave **67** which on subsequent ring opening by treatment with Zn /AcOH afforded **68**.

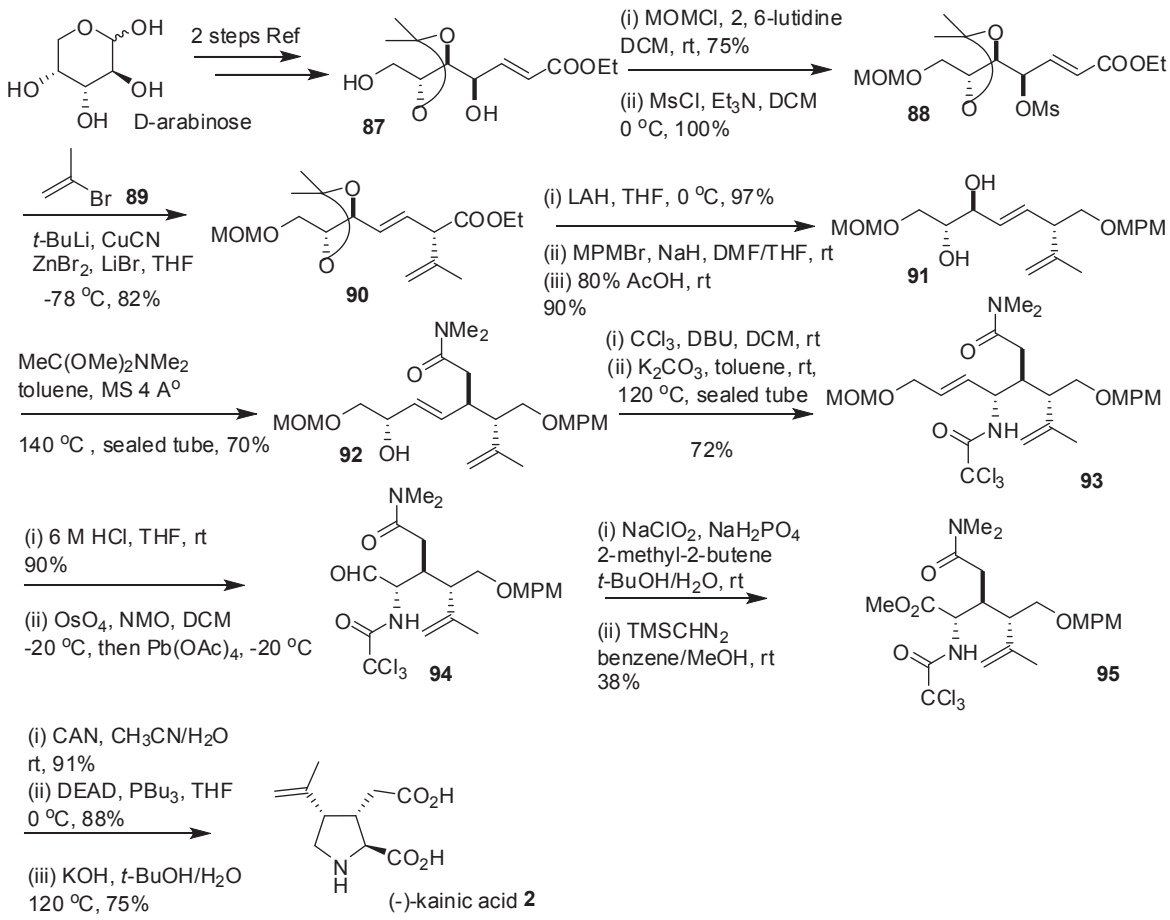
The compound **68** upon treatment with DEPC and Et_3N underwent expected cyclisation in the desired *cis* fashion to furnish the lactam **69**. The selective reduction of lactam **69**, cyanation and subsequent base hydrolysis produced the natural product (-)-kainic acid **2**.





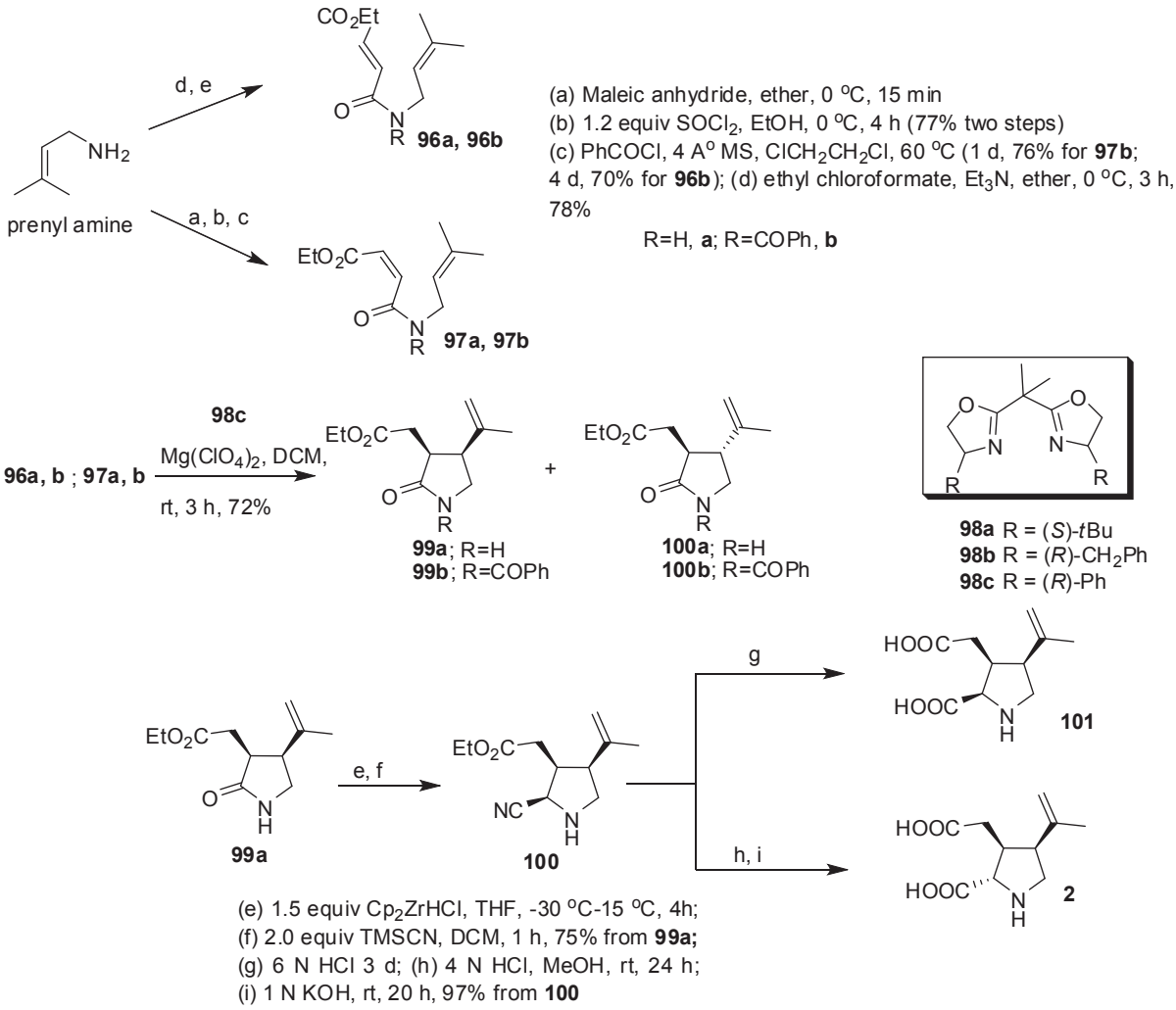
Scheme 8

Farwick and Helmchen explored Ir-mediated enentioselective allylic amination and diastereoselective Pauson-Khand reaction for the total synthesis of (-)-kainic acid **2** (scheme 8).[5d] The allylic amination of **72** by **74** and **75** was accomplished using $[Ir(COD)Cl]_2$ in the presence of ligand **73** to give **76** and **77** respectively. The requisite **79** was then synthesized by two converging routes either by decarbonylation and alkylation of **76** or Boc protection of amine **77**. The 1, 6-enyne **79** was then subjected to Pauson-Khand reaction to afford **80**. The major *trans* isomer of **80** was separated on column chromatography and hydrogenated to give diastereomeric mixture **81**. The Beayer-Villeger oxidation of **81** followed by opening of the lactone using $Ca(BH_4)_2$ and subsequent protection of primary OH produced **83**. The alcohol **83** on Ley-Griffith oxidation and subsequent olefination using Tebbe's reagent **85** provided **86** which was eventually transformed to (-)-kainic acid **2** through oxidation and deprotection of the protecting groups.



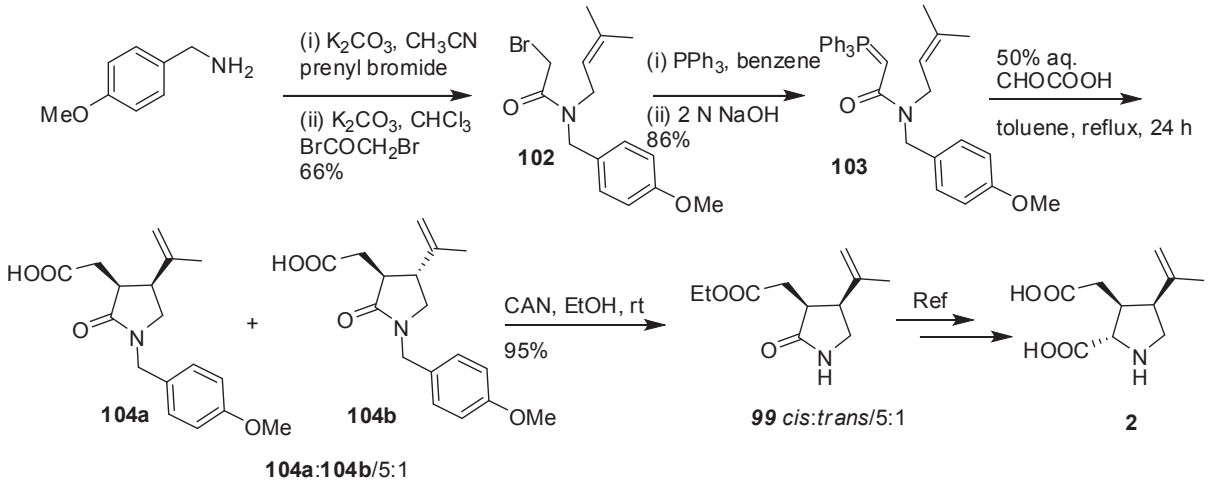
Scheme 9

Kitamoto *et al* achieved the total synthesis of (-)-kainic acid **2** via chirality transfer through sequential Claisen/Overmann rearrangement (scheme 9).[5e] D-arabinose was initially converted to **87** according to the reported methods. The secondary –OH of **87** was mesylated and subjected to modified SN_2 displacement by bromo compound **89** to furnish **90** which upon LAH reduction and protection of terminal OH afforded **91**. The compound **91** on Claisen rearrangement and sub sequential Overmann rearrangement gave exclusively **92** with complete dastereoselectivity. The deprotection of MOM group and selective oxidative cleavage of double bond using $OsO_4/Pb(OAc)_4$ afforded the aldehyde **94** which on Kraus-Pinnick oxidation and esterification provided the methyl ester **95**. The CAN mediated amide deprotection, Mitsunobu cyclisation and base hydrolysis produced the natural product (-)-kainic acid **2**.



Scheme 10

Xia and Ganem disclosed a notable research by synthesizing a very useful intermediate **99a** for the synthesis of (-)-kainic acid **2** (scheme 10).[5f] The alkenes **96** & **97** synthesized from prenyl amine through classical synthetic steps were best transformed to **99** along with minute amount of **100** via asymmetric Ene reaction using $MgClO_4$ and the ligand **98c**. The enentiomerically pure **99a** was further treated with Schwartz's reagent (Cp_2ZrHCl) and TMSCN to afford the cyano compound **100** which on acid base hydrolysis gave (-)-kainic acid **2**.



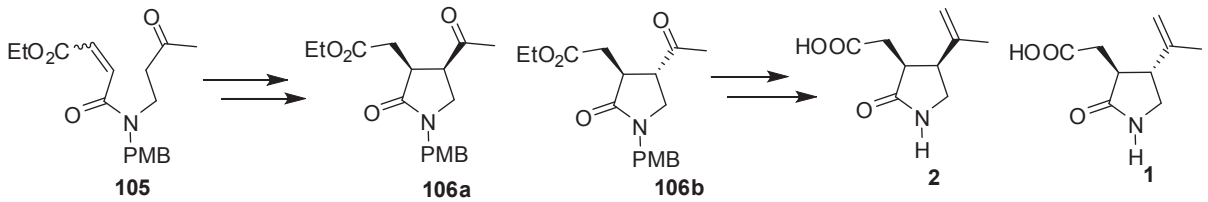
Scheme 11

Majik *et al* accomplished the formal synthesis of (±)-kainic acid **2** by synthesizing popular Ganem intermediate **99a** in racemic form through domino Wittig-Ene reaction (scheme 11).[5g] The key requisite phosphorane **103** was synthesized with systematic synthetic conversions of *p*-methoxy benzylamine (PMB). The tandem Wittig-Ene reaction was best effected by refluxing **103** with 50% aq. CHOCOOH in toluene to furnish **104** in *cis* and *trans* forms in the ratio of 5:1. The mixture **104** was subjected for one pot PMB deprotection and esterification using CAN/EtOH to furnish the Ganem intermediate **99** (5:1).

Results and Discussion

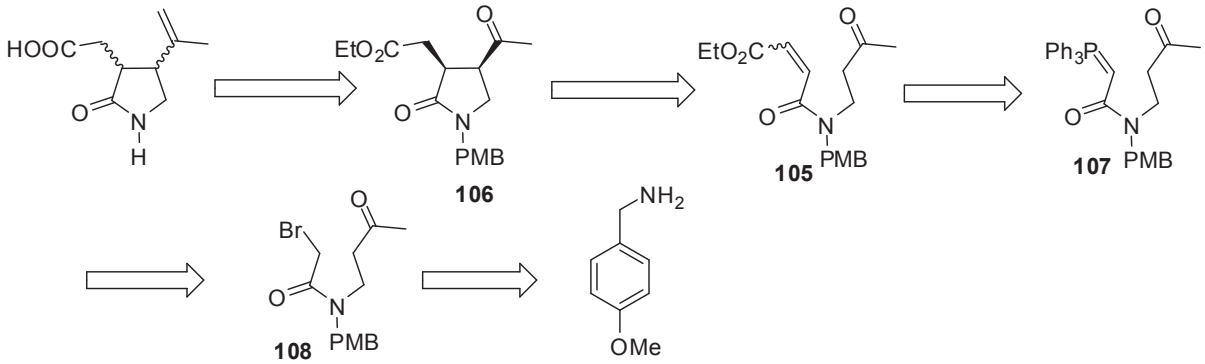
Our main objective of this work was to develop some efficient and simple methods for the synthesis of allokainic acid **1** and kainic acid **2** using commercially available chemicals.

At the onset of our study, we envisaged the alkene **105** can be an ideal precursor for the synthesis of precursors of kainic acid **2** and allokainic acid **1** via organocatalytic or organometallic routes (scheme 12).



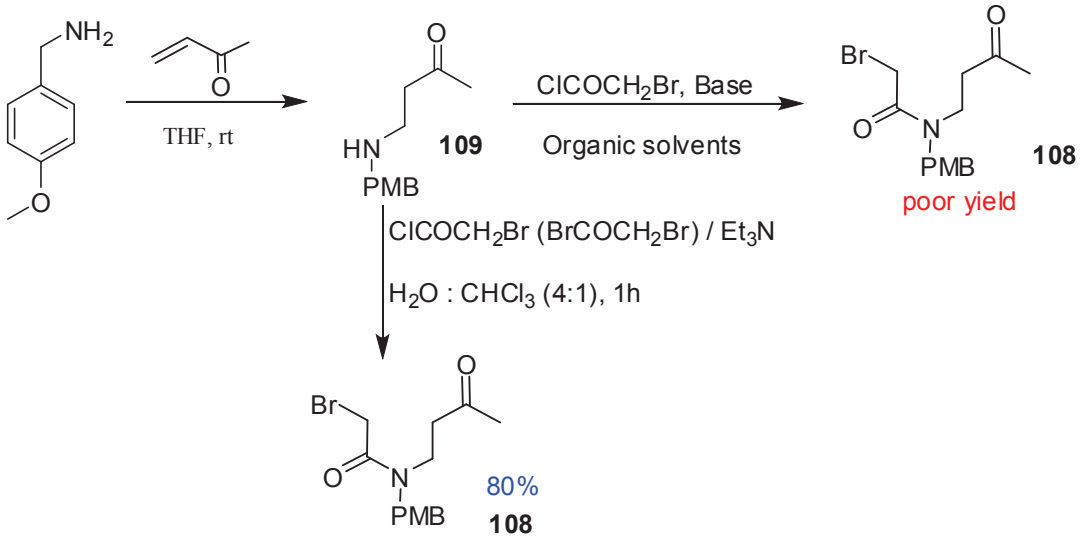
Scheme 12

The construction of the double bond in the compound **105** can be best visualized by Wittig olefination with phosphorane **107** which can conveniently be obtained from the corresponding bromo amide **108**. The amide **108** can be best generated from p-methoxybenzylamine (PMB). The selection of PMB as a starting amine source was justified according to earlier work reported in our laboratory to circumvent the consequences of final deprotection (scheme 13).



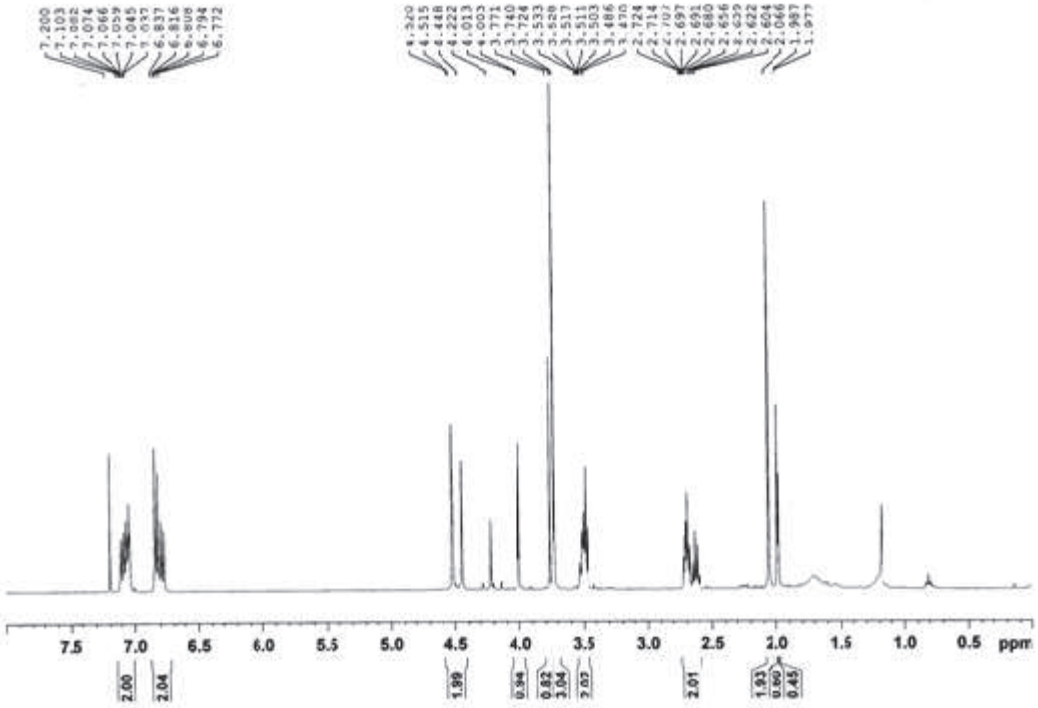
Scheme 13. Retrosynthesis

Thus our synthesis started with the treatment of PMB with exactly one equivalent of methyl vinyl ketone (MVK) in THF to give Michael addition product, secondary amine **109** (scheme 14). Gratifyingly, the normal problem of double Michael reaction was not observed. Initially, the preparation of requisite bromo compound **108** was attempted from amine **109** and $ClCOCH_2Br$ in the presence of mild base under anhydrous condition. But the various conditions tried for the synthesis of **108** in different organic solvents resulted either in the decomposition of the substrates or gave very poor yield. The same reaction was then tried in H_2O afforded the product **108** in a moderate yield. From this it was clear that some unwanted substance formed during the course of the reaction was now defused by water. With this standpoint of view, the same reaction was tried in a biphasic medium of H_2O and chloroform in the ration of 4:1. To our delight, the yield was exemplified considerably giving almost a clean product **108** with minor impurities remaining at the bottom of the TLC plate. The normal chromatographic separation produced 80% requisite bromo amide **108**. The structure was established by spectroscopic techniques. The 3 different singlets observed for methyl peaks at δ 1.93 in ^1H NMR were attributed to the existence of three different torsional isomers as shown in the scheme 15.

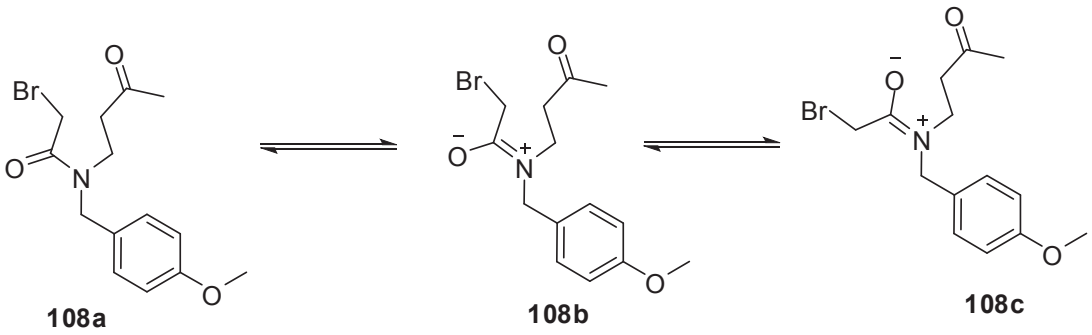


Reaction conditions	Results
$CHCl_3$, Et_3N, rt/reflux	Traces
Acetone, K_2CO_3, rt / reflux	Traces
Acetonitrile, K_2CO_3, rt / reflux	Traces
Benzene, K_2CO_3, rt/reflux	Traces
H_2O	60%
H_2O: $CHCl_3$ (4:1), 0 °C-rt, 1h	**80%**

Scheme 14. Synthesis of requisite bromo amide

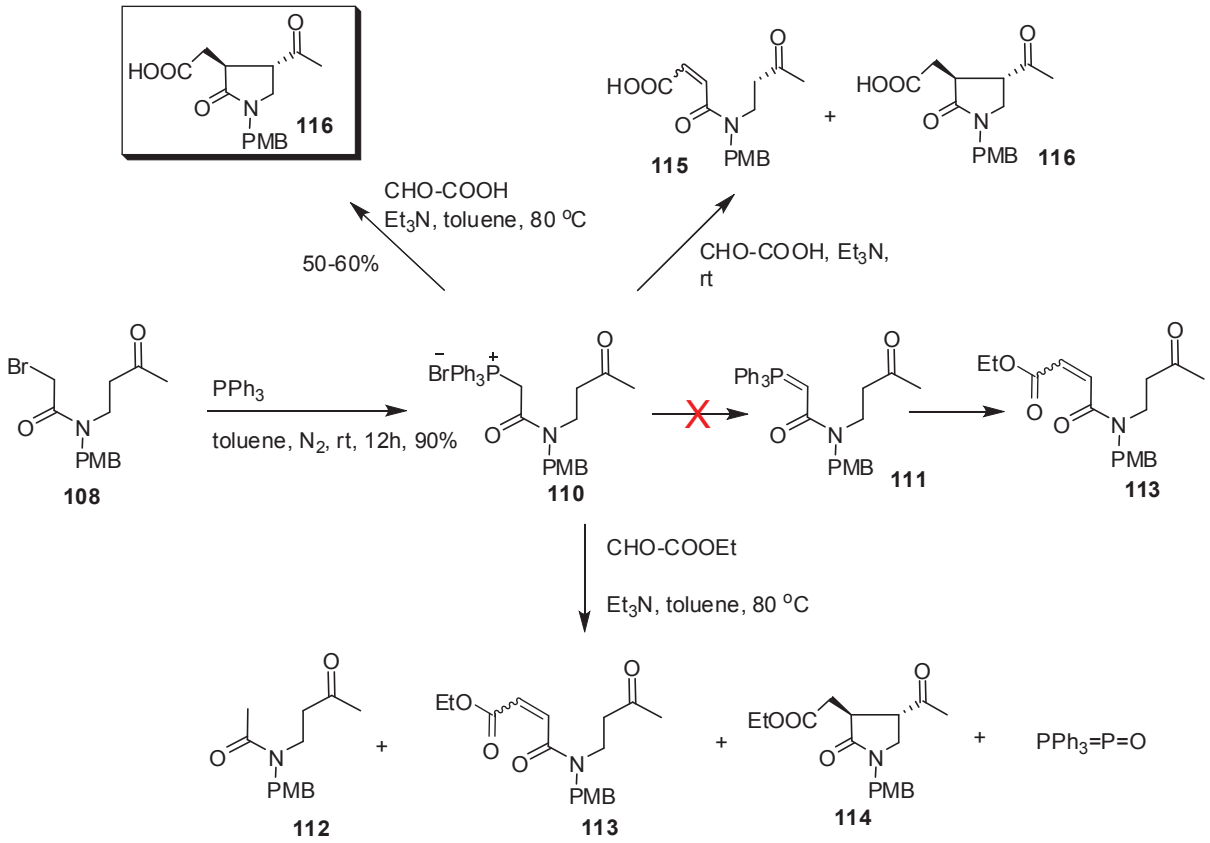


IR (neat): ν_{max} = 3108, 2979, 1715, 1644 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.06 [1.97, 1.98] (s, 3H, H-1'), 2.60-2.72 (m, 2H, H-4), 3.47-3.53 (m, 2H, H-5), 3.74 [3.72] (s, 3H, OMe), 3.77 [4.00, 4.01] (s, 2H, H-3), 4.52 [4.44] (s, 2H, PhCH_2), 6.82 [6.78] (d, J= 8.4Hz [8.8Hz] 2H, PhH), 7.06 [7.09, 7.05] (d, J= 8.4Hz [8.4Hz, 8.8Hz], 2H, PhH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.5 [25.4] (C-4), 29.3 [29.2, 29.1] (C-1'), 40.6 [40.4, 40.3, 40.0] (C-5), 41.4 [41.3, 40.9, 40.7] (C-3), 51.6 [51.2, 47.2, 47.1] (PhCH_2), 54.3 [54.2] (OCH_3), 113.1 (PhCH), 113.4 (PhCH), 126.9 [126.8, 126.7] (PhCH), 128.2 [128.1, 127.9] (PhCH), 158.0 (PhC), 158.3 (PhC), 166.3 [166.0] (PhC), 158.3 [158.1] (NCO), 206.3 [205.0] (C-2) (extra signals are observed due to the presence of torsional isomers).



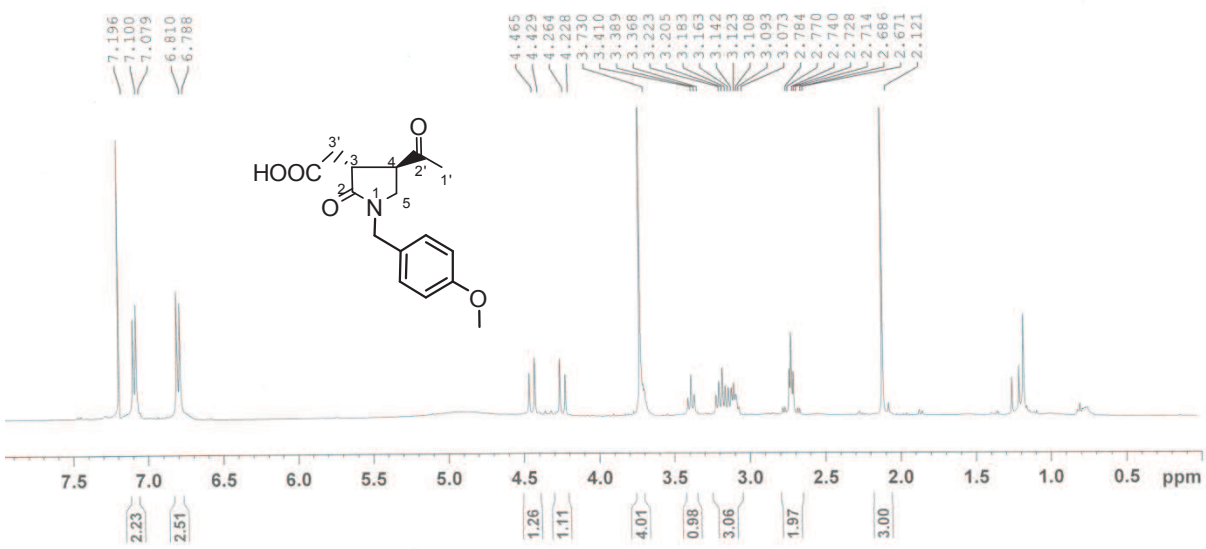
Scheme 15. Existence of **108** in different torsional forms

The synthesis of requisite Wittig salt **110** from **108** even though looked straightforward, the maintenance of dry condition and the solvent toluene was necessary. The reaction carried out in $CHCl_3$, CH_3CN and dry THF resulted in slow decomposition without any notable formation of the required salt. The formation of **110** was noticed by very low mobile dark spot on TLC plate and further confirmed by ^1H NMR. Our next job was to synthesize the key requisite keto ester **113** through the formation of phosphorane **111** which could further be transformed to kainic acid precursors through enentioselective and diastereoselective cyclisation. But to our surprise, all the attempts made for the synthesis of phosphorane **111** failed. The different reaction conditions by varying the bases and solvents resulted in decomposition of the salt **110**. We then thought of preparing the phosphorane *in situ* and immediately condensing with ethyl glyoxalate, being optimistic in isolating **113**. But the reaction produced mixture of products **112-113** making practically impossible for separation of the desired compound. To obviate this quandary, we slightly changed the strategy, instead of CHO-COOEt, we treated the salt **110** with CHO-COOH anticipating the possibility of separation by chemical method. Accordingly we reacted the



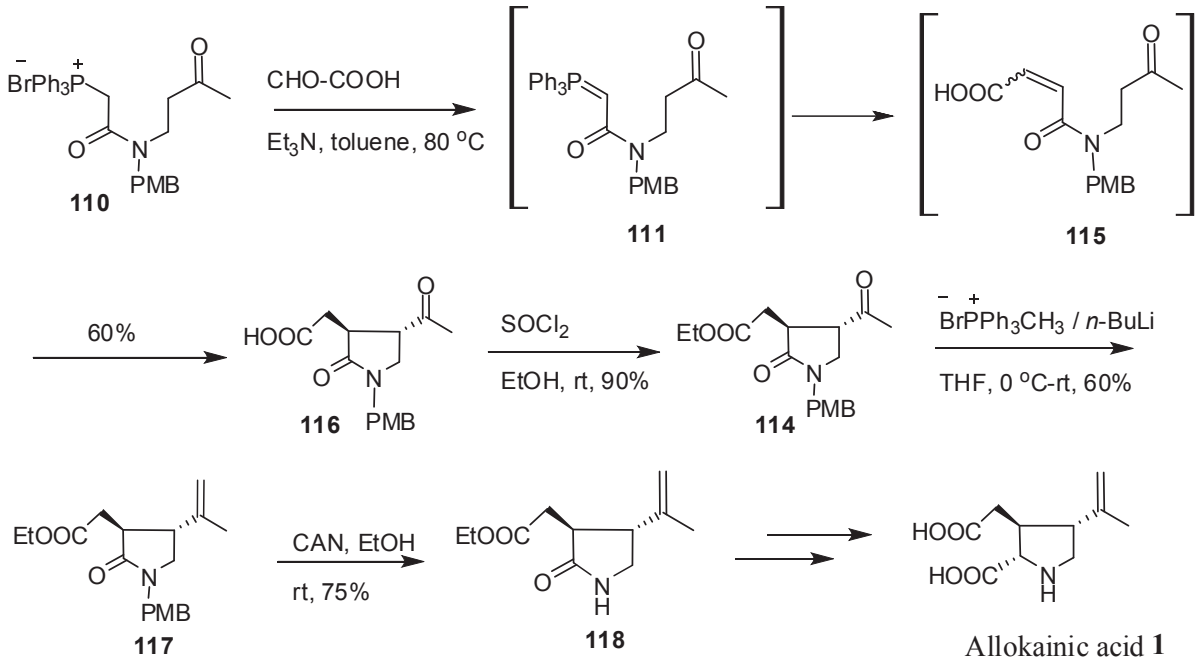
Scheme 16. Synthetic manipulation to key precursor **116**

salt **110** with glyoxalic acid at rt in the presence of Et_3N. The product obtained was purified by chemical method and showed the presence of single spot on TLC plate. The H^1 NMR spectrum displayed various signals indicating the mixture of products **115** and **116,** drawing a conclusion that the control of cyclisation of **115** to **116** is very difficult even under placid condition used. To this end, it was necessary for us to alter the reaction condition to check the feasibility of cyclisation and evade the problem of separation. Consequently, the mixture of **110** and CHO-COOH/Et_3N was initially refluxed overnight and the product obtained was separated as earlier. We were delighted to see the formation of single cyclised product **115** according to ^1H NMR signals (scheme 16). The reaction condition was then manipulated to heating it in toluene at 80 °C for 6 h without producing any notable change. The formation of **116** was envisioned through the intermediary of **111** and **115**, traversing in tandem fashion, can be well said as **tandem-Wittig-Michael** reaction as shown in the scheme 17. The compound **116** was structurally confirmed by NMR studies. The broad IR band at 3500 cm^{-1} conferred the presence of COOH group and the observance of singlet methyl peak at δ 2.11 inferred the presence of acetonyl part.



IR (neat): ν_{max} = 3600-3000 br, 2945, 1710, 1698, 1526 cm^{-1} ; ^1H NMR ($CDCl_3$, 400 MHz): 1.97 (s, 1H, H-1'), 2.10 (s, 2H, H-1'), 2.68-2.78 (m, 1H, H-3), 3.05-3.21 (m, 2H, H-5), 3.34-3.40 (m, 1H, H-4), 3.72 (s, 3H, OMe), 4.21-4.45 (m, 2H, H-3'), 6.78 (d J= 8.4 Hz, 2H, PhH), 7.08 (d J= 8.4 Hz, 2H, PhH); HRMS: *m/z* calcd for $C_{16}H_{19}NO_5Na$ $[M + Na]^+$: 328.1161; found: 328.1161.

Since the assignment of stereochemistry at C_3-C_4 was a difficult task for us at this stage, the synthetic sequence was carried forward. The acid **116** was ethyl esterified using $EtOH/SOCl_2$ to give **114** and further alkenated through Wittig olefination to produce **117**. The CAN mediated deprotection of PMB afforded **118**.



Momose and co-workers *Heterocycles* **1991**, *32*, 7

Scheme 17. Tandem-Wittig Michael approach

A platform was now set up for the determination of stereochemistry at C-3 and C-4. We compared the ^1H NMR of **118** with that reported in the literature.[5f, g] The differentiation of the *cis* and *trans* isomer of the kainoids is well explained by Baldwin *et al*.[7] based on δ values of the methylene protons attached to carboxyl part of the side chain and they demonstrated that (i) one of the protons of CH_2 (either Ha or Hb) shows significantly lower chemical shift in the case of *cis* isomer compared to the corresponding proton in the *trans* isomer due to shielding effect (Ha or Hb of *cis* < Ha or Hb of *trans*) and (ii) The difference in the chemical shift values for these two protons in the *cis* isomer is larger than that for trans i.e. δ (Ha-Hb) of *cis* > δ (Ha-Hb) of *trans*. The δ values of compound **118** for the protons attached to carboxyl part are 2.66Hz and 2.4Hz and the difference is smaller than that reported for *cis* **119** compound confirmed the formation of *trans* isomer (fig. 2). And also the higher δ value observed for CH_3 attached to olefinic part in compound **118** due to

less shielding than in the case of *cis* isomer further confirmed the formation of *trans* isomer **118** exclusively which is a key building block for allokainic acid **1**.

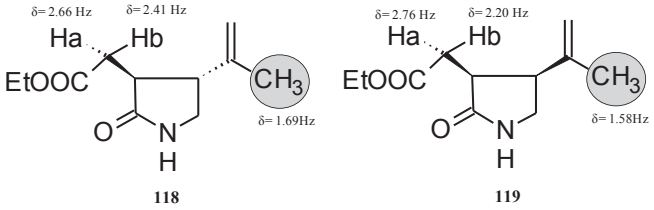
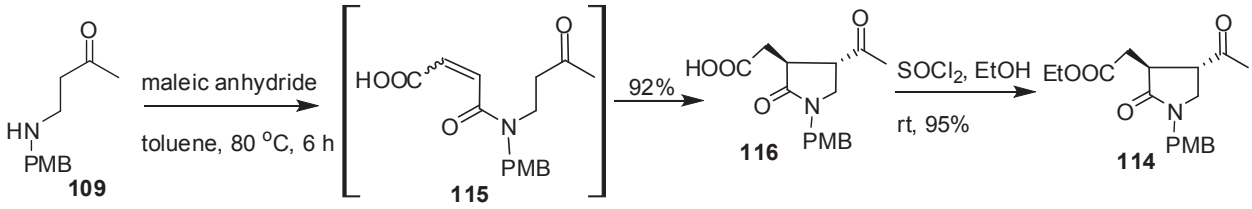


Figure 2

Tandem amidation-Michael approach

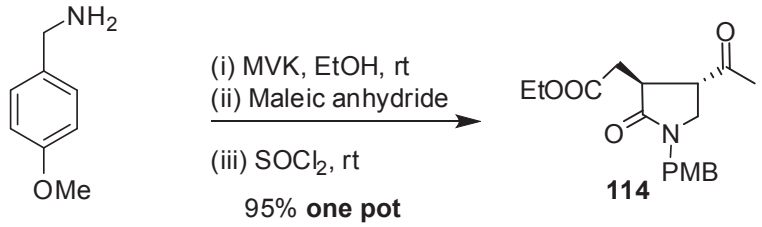
After achieving the success in getting the precursor of allokainic acid through tandem Wittig-Michael reaction, we thought of a still shorter route *via* tandem amidation-Michael reaction (Scheme 18). This time secondary amine **109** was directly reacted with maleic anhydride in toluene at 80 °C. The acid **116** formed was separated by chemical separation and further treated with $SOCl_2$ in ethanol to furnish the product **114**.



Scheme 18. Tandem amidation-Michael approach

One pot Michael-amidation-Michael-esterification for 114

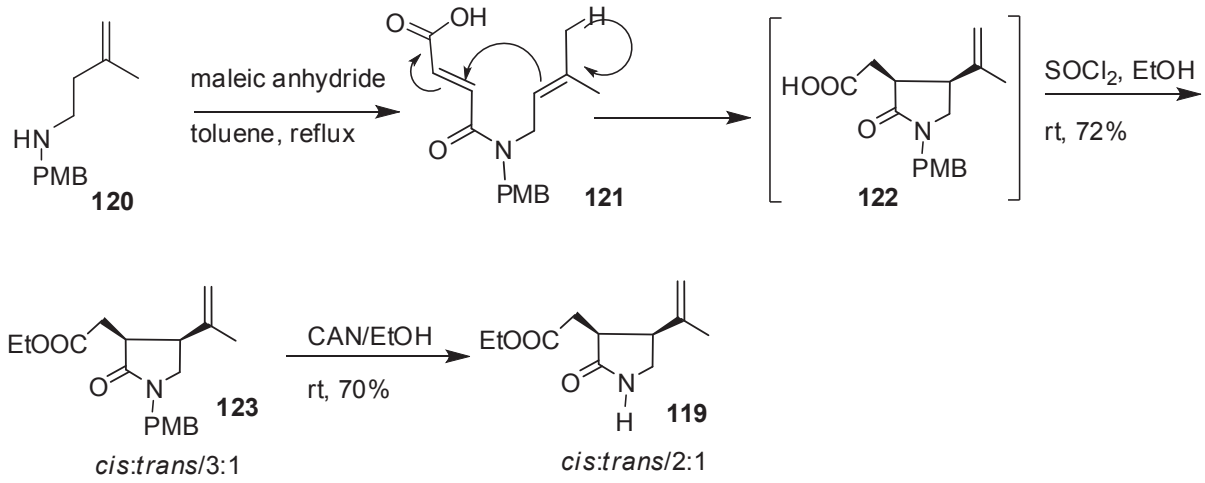
We then thought of carrying out the entire sequences in one pot (Scheme 19) which nowadays is another emerging tool in synthetic organic chemistry.[8] This time PMB was reacted with MVK in absolute ethanol. Maleic anhydride was added to the reaction mixture once the primary amine was totally consumed, further stirred till the disappearance of the secondary amine. $SOCl_2$ was added in the same pot and stirred further at room temperature to afford the key intermediate **114** in 95% yields.



Scheme 19. One-pot approach for allokainic acid precursor

One pot amidation-Ene-esterification for Ganem intermediate

Further we visualised that similar one pot strategy can be adapted for the synthesis of all important Ganem intermediate **119** employed in the synthesis of kainic acid. Thus mixture of prenylated PMB **120** and maleic anhydride was refluxed in toluene and then treated with EtOH and $SOCl_2$ in the same pot. The three reactions namely, amidation, Ene and esterification took place in one pot to give a mixture of diastereomers **123** and **117** in a 3:1 ratio. The PMB group was then deprotected using CAN to give **119** (scheme 20).



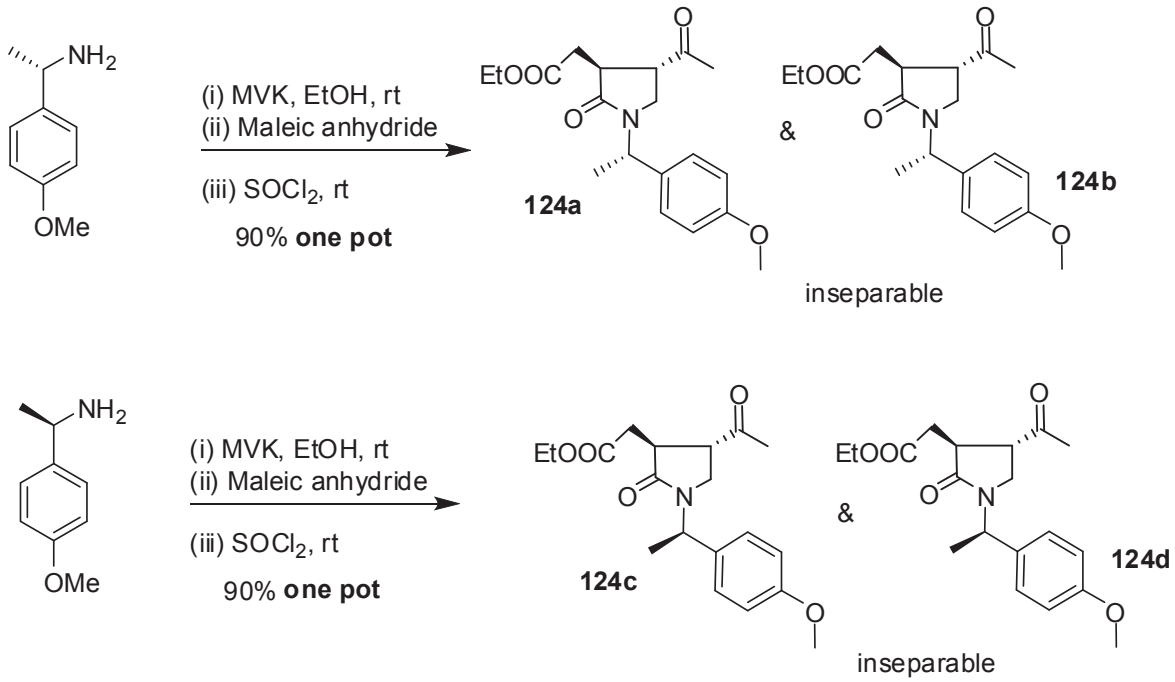
Scheme 20. One-pot approach for kainic acid precursor

Chiral Auxiliary approach

Even though the synthesis of precursors of allokainic and kainic acid was possible for us, our desire to construct the core units in chiral form was not fulfilled due to inability of isolation of the key alkene unit **113**. In this context, we explored a chiral auxiliary method thinking that the two different diastereomers formed after cyclisation would be distinguishable and separable in chiral form.

Thus we started our modified synthesis using (*S*)-Me-PMB, subjected to one-pot reaction condition with MVK/ maleic anhydride/ $SOCl_2$ (scheme 21). It was already observed that cyclisation was favoured in *trans* fashion producing the isomers **124a** and **124b**. We were expecting the separation of these two isomers which could eventually end up in the synthesis of chiral structural units. But, to our surprise, single spot was observed on TLC plate and no distinct peaks were observed in ^1H NMR spectrum for differentiating one

from other. When we repeated the synthesis with (*R*)-Me-PMB, similar observation was noticed producing the NMR signals indistinguishable from the earlier one. The appearance of two singlets at δ 3.17 ppm accounting for 3H corresponding to methyl group of acetonyl part indicated the formation of mixture in each case.



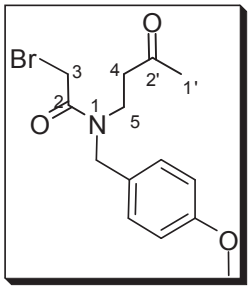
Scheme 21. Auxiliary approach

Conclusion

In summary we successfully constructed the core units for allokainic and kainic acid in racemic forms. It is noteworthy to mention that the key units derived are densely functionalised pyrrolidin-2-ones, popularly known as γ-lactams are prevalent structural motifs present in various natural products. The tandem and one-pot methods developed for the construction of pyrrolidin-2-one units are novel, metal free and ligand free which can conveniently be utilized for designing more such entities. The one pot method developed for the synthesis of allokainic acid precursor using EtOH/maleic anhydride/$SOCl_2$ found to be of special interest from synthetic point of view. The present work opens several options for further tuning the strategies in the construction of chiral core units.

Experimental Section:

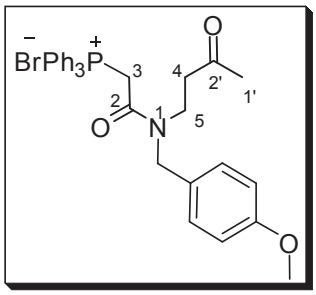
3.01 Preparation of key bromo compound (108)



To a mixture of **109** (1.0 g, 4.8 mmol) and Et_3N (4.85 mL, 14.5 mmol) in a biphasic medium of water and $CHCl_3$ (4:1, 10 mL), $ClCOCH_2Br$ (24 mmol, 2.0 mL) was added drop wise over a period of 10 min at 0 °C. It was further stirred for 30 min and brought to rt. Once the secondary amine **109** was consumed (TLC), the reaction mixture was diluted with $CHCl_3$ (15 mL) and the organic layer was separated. The $CHCl_3$ layer was washed with dil. HCl (15 mL X 2), dried over anhy. Na_2SO_4 and concentrated in vacuo. The residue was then purified by column chromatography (hexane: EtOAc, 8:2) to give thick pale yellow liquid **108** (1.26 g, 80%).

IR (neat): ν_{max} = 3108, 2979, 1715, 1644 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.06 [1.97, 1.98] (s, 3H, H-1'), 2.60-2.72 (m, 2H, H-4), 3.47-3.53 (m, 2H, H-5), 3.74 [3.72] (s, 3H, OMe), 3.77 [4.00, 4.01] (s, 2H, H-3), 4.52 [4.44] (s, 2H, PhC*H*$_2$), 6.82 [6.78] (d, J= 8.4Hz [8.8Hz] 2H, PhH), 7.06 [7.09, 7.05] (d, J= 8.4Hz [8.4Hz, 8.8Hz], 2H, PhH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.5 [25.4] (C-4), 29.3 [29.2, 29.1] (C-1'), 40.6 [40.4, 40.3, 40.0] (C-5), 41.4 [41.3, 40.9, 40.7] (C-3), 51.6 [51.2, 47.2, 47.1] (Ph*C*H_2), 54.3 [54.2] (O*C*H_3), 113.1 (PhCH), 113.4 (PhCH), 126.9 [126.8, 126.7] (PhCH), 128.2 [128.1, 127.9] (PhCH), 158.0 (PhC), 158.3 (PhC), 166.3 [166.0] (PhC), 158.3 [158.1] (NCO), 206.3 [205.0] (C-2) (extra signals are observed due to the presence of torsional isomers).

3.02 Preparation of phosphonium salt 110

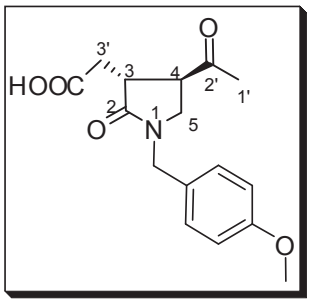


The compound **108** (1.0 g, 3 mmol) was mixed with PPh_3 (0.8 g, 3.2 mmol) and stirred overnight in toluene (20 mL) at rt. The toluene layer was decanted and the salt was washed with hexane to remove excess PPh_3 to give **110** as a thick pale yellow semi solid (0.16 g, 90%).

^1H NMR ($CDCl_3$, 400 MHz): δ 1.83 [2.05] (s, 3H, H-1'), 2.69-2.73 [3.49-3.53] (m, 2H, H-4), 2.82 [3.93] (s, 2H, H-4), 3.73 [3.73] (s, 3H, OMe), 4.37 [4.99] (s, 2H, PhC*H*$_2$), 5.61 [6.14] (d, J= 12.8Hz, 2H, H-3), 6.56-6.80 (m, 3H, PhH), 7.09-7.95 (m, 16H, PhH); ^{13}C NMR ($CDCl_3$, 100 MHz): 30.2 (C-1'), 34.8 [34.2, 34.0] (C-4), 41.4 [41.1] (C-5), 44.9

[42.8] (Ph*C*H_2), 52.5 [48.8] (C-3), 55.3 (O*C*H_3), 113.9 (PhCH), 114.4 (PhCH), 127.8 (PhCH), 128.6 (PhCH), 129.8 (PhCH), 129.9 (PhCH), 129.9 (PhCH), 130.0 (PhCH), 133.8 (PhCH), 133.9 (PhCH), 134.0 (PhCH), 134.1 (PhCH), 134.2 (PhCH), 134.3 (PhCH), 159.0 [158.8] (PhC), 165.1 [164.8] (PhC), 207.9 [207.1] (PhC) (extra signals are seen due to the presence of torsional isomers); HRMS: *m/z* calcd for $C_{32}H_{32}NO_3PH$ [M + H]: 510.2198; found: 510.2197.

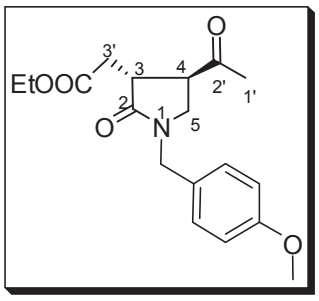
3.03 Procedure for Domino Wittig-Michael reaction for the synthesis of [(3*S*, 4*S*)-4-acetyl-1-(4-methoxybenzyl)-2-oxopyrrolidin-3-yl] acetic acid 116



The Wittig salt **110** (1.0 g, 1.7 mmol) was heated with excess glyoxalic acid (50%) (2.5 mL, 17 mmol) and Et_3N (3.5 mL, 25.5 mmol) in toluene (20 mL) at 80 °C for 6 h. It was then washed with dil. HCl (15 mL X 2). The acid product formed was extracted with aq. $NaHCO_3$ (20 mL X 2) and neutralised using dil. HCl. The regenerated acid was extracted with EtOAc (25 mL X 3) and dried over anhy. Na_2SO_4. The organic layer was concentrated under reduced pressure to afford crude acid **116** as a pale yellow thick liquid (0.3 g, 60%).

IR (neat): ν_{max} = 3600-3000 br, 2945, 1710, 1698, 1526 cm^{-1} ; ^1H NMR ($CDCl_3$, 400 MHz): 1.97 (s, 1H, H-1'), 2.10 (s, 2H, H-1'), 2.68-2.78 (m, 1H, H-3), 3.05-3.21 (m, 2H, H-5), 3.34-3.40 (m, 1H, H-4), 3.72 (s, 3H, OMe), 4.21-4.45 (m, 2H, H-3'), 6.78 (d J= 8.4 Hz, 2H, PhH), 7.08 (d J= 8.4 Hz, 2H, PhH); HRMS: *m/z* calcd for $C_{16}H_{19}NO_5Na$ [M + Na]$^+$: 328.1161; found: 328.1161.

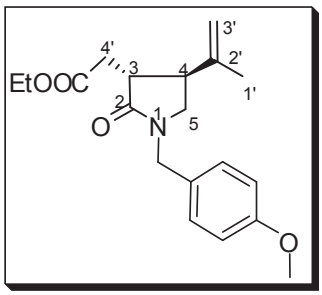
3.04 Ethyl [(3*S*, 4*S*)-4-acetyl-1-(4-methoxybenzyl)-2-oxopyrrolidin-3-yl] acetate 114



To a solution of acid **116** (0.5 g, 1.6 mmol) in EtOH (10 mL) was added $SOCl_2$ (0.16 mL, 2.4 mmol) drop wise at 0 °C for 5 min. It was further stirred at rt for 2 h. The reaction mixture was then quenched by saturated aq. $NaHCO_3$ (10 mL) and extracted with DCM (20 mL X 3). The organic layer was dried over anhy. Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography (Hexane: EtOAc, 8: 2) to give **114** as a thick oily liquid (0.48 g, 90%).

IR (neat): ν_{max} = 2995, 1745, 1700, 1690, 1500 cm^{-1} ; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.25 (t J= 7.2Hz, 3H, OCH_2CH_3), 2.19 (s, 3H, H-1'), 2.64-2.70 (m, 1H, H-3'A), 2.82-2.87 (m, 1H, H-3'B), 3.09-3.14 (m, 1H, H-3), 3.21-3.27 (m, 2H, H-5), 3.39-3.45 (m, 1H, H-4), 3.80 (s, 3H, OMe), 4.12 (q J= 8Hz, 2H, OCH_2CH_3), 4.32-4.50 (m, 2H, $PhCH_2$), 6.85-6.87 (m, 2H, PhH), 7.16 (d J= 8.4Hz, 2H, $PhCH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (OCH_2CH_3), 19.1 (C-1'), 34.2 (C-3'), 40.8 (C-3), 46.2 (C-5), 46.3 (OCH_2CH_3), 49.4 (C-4), 55.3 (OCH_3), 63.8 ($PhCH_2$), 114.1(PhCH), 127.8 (PhC), 129.4 (PhCH), 159.2 (PhCOMe), 171.6 (NCO), 172.9 (COO), 206.1 (CO).; HRMS: *m/z* calcd for $C_{18}H_{23}NO_5Na$ $[M + Na]^+$: 356.1474; found : 356.1475.

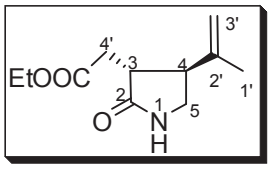
3.05 Ethyl [(3*S*, 4*R*)-4-isopropenyl-1-(4-methoxybenzyl)-2-oxopyrrolidin-3-yl] acetate 117



To a pre-cooled mixture of **114** (0.5 g, 1.5 mmol) and $Br^-PPh_3^+CH_3$ (1.07 g, 3.0 mmol) in dry THF (10 mL) under inert atmosphere was added *n*-BuLi (1.6 M in hexane) (1.9 mL, 3.0 mmol) at 0 °C through a syringe. The reaction mixture was further stirred for 2 h at rt. It was then quenched with 10 mL of saturated NH_4Cl and extracted with DCM (25 mL X 3), dried over anhy. Na_2SO_4. The crude product was concentrated and subjected to column chromatography (Hexane: EtOAc, 9: 1) to give **117** as pale yellow thick liquid (0.29 g, 60%).

IR (neat): ν_{max} = 2910, 1745, 1696 cm^{-1} ; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.18 (t J= 7.2 Hz, 3H, OCH_2CH_3), 1.61 (s, 3H, H-1'), 2.41-2.47 (m, 1H, H-4'A), 2.67-2.79 (m, 1H, H-4'B), 2.82-2.84 (m, 1H, H-3), 2.93-2.98 (m, 1H, H-5A), 3.15-3.19 (m, 1H, H-5B), 3.73 (s, 3H, OMe), 4.03-4.05 (m, 2H, OCH_2CH_3), 4.28-4.72 (m, 2H, $PhCH_2$), 4.7 (s, 2H, H-3'), 6.78-6.80 (m, 2H, PhH), 7.09-7.11 (m, 2H, PhH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (OCH_2CH_3), 19.0 (C-1'), 34.4 (C-4'), 42.2 (C-3), 46.1 (C-5), 46.2 (C-4), 48.8 (OCH_2), 55.3 (OCH_3), 60.6 ($PhCH_2$), 113.2 (C-3'), 114.1 (PhCH), 128.3 (C-2'), 129.5 (PhCH), 142.6 (PhC), 159.1 (PhC), 171.8 (NCO), 174.1 (COO).

3.06 Ethyl [(3*S*, 4*R*)-4-isopropenyl-2-oxopyrrolidin-3-yl] acetate 118



The compound **117** (0.5 g, 1.5 mmol) was stirred overnight with CAN (2.5 g, 3.0 mmol) in 10 mL EtOH. The reaction mixture was quenched with aq. $NaHCO_3$ (15 mL) and extracted with DCM (20 mL X 3). The organic layer was dried over anhy. Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (Hexane: EtOAc, 1: 1) to give **118** as a thick liquid (0.48 g, 75%).

IR (neat): ν_{max} = 3325, 1730, 1690 cm^{-1} ; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.18 (t J= 7.2 Hz, 3H, OCH_2CH_3), 1.69 (s, 3H, H-1'), 2.38-2.44 (m, 1H, H-4'A), 2.64-2.69 (m, 1H, H-4'B), 2.73-2.79 (m, 1H, H-5A), 2.85-2.92 (m, 1H, H-5B), 3.11-3.16 (m, 1H, H-3), 3.34-3.38 (m, 1H, H-4), 4.03-4,09 (m, 2H, OCH_2CH_3), 4.78-4.80 (m, 2H, H-3'), 5.98 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.1 (OCH_2CH_3), 18.0 (C-1'), 32.7 (C-4'), 39.9 (C-3), 43.5 (C-5), 47.9 (C-4), 59.6 (OCH_2CH_3), 112.5 (C-3'), 141.4 (C-4'), 170.7 (C-2), 176.8 (COO).; HRMS: *m/z* calcd for $C_{11}H_{17}NO_3Na$ $[M + Na]^+$: 234.1106; found: 234.1105.

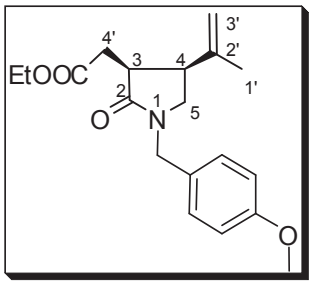
3.07 Synthesis of 116 through tandem amidation-Michael reaction

The mixture of PMB (1.0 g, 8.1 mmol) and MVK (0.8 mL, 9.7 mmol) was stirred for 1 h at rt in toluene (20 mL). Maleic anhydride (1.19 g, 12.15 mmol) was then added directly to the reaction mixture and heated at 80 °C for 6 h. The product was purified by chemical separation as described earlier (Procedure 3) to give **116** (2.28 g, 92%).

3.08 Procedure for one pot synthesis of 114

To a solution of PMB (1.0 g, 8.1 mmol) in EtOH (10 mL) was added MVK (0.8 mL, 9.7 mmol) drop wise over a period of 10 min. It was stirred at rt for 1h. Maleic anhydride (1.19 g, 12.15 mmol) was then added and stirred further for 1h. The reaction mixture was cooled to 0 °C and added $SOCl_2$ (2.0 mL, 29 mmol) drop wise, brought to rt and stirred further for 1h. It was then quenched with saturated cold aq. $NaHCO_3$ (10 mL) and extracted with DCM (25 mL X 3). The organic layer was washed with dil. HCl (20 mL X 2), dried over anhy. Na_2SO_4 and concentrated under reduced pressure to give the crude **114** which was purified by column chromatography (Hexane: EtOAc, 8: 2) (2.5 g, 95%).

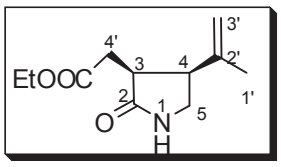
3.09 Procedure for one pot synthesis of 123



The compound **120** (1.0 g, 5.2 mmol) (prepared from PMB and prenyl bromide) was refluxed with maleic anhydride (0.611 g, 6.24 mmol) in toluene (10 mL) for 24 h. The reaction mixture was then cooled to 0 °C and 10 mL of ethanol was added. $SOCl_2$ (0.53 mL, 7.8 mmol) was added drop wise for 15 min. The reaction mixture was then stirred at rt for 1h and quenched with saturated aq. $NaHCO_3$ (15 mL). The product was extracted in EtOAc and washed with dil. HCl (15 mL X 2). The organic layer was dried over anhy. Na_2SO_4 and concentrated under vacuum, purified by column chromatography (Hexane: EtOAc, 8: 2) to afford **123** (1.2 g, 72%).

IR (neat): ν_{max} = 3100, 1735, 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.17 (t J= 7.2Hz, 3H, CH_2CH_3), 1.36 (s, 2H, H-1'), 1.60 (s, 1H, H-1'), 2.17-2.22 (m, 1H, H-4'A), 2.40-2.83 (m, 1H, H-4'B), 2.93-2.98 (m, 1H, H-3), 3.05-3.35 (m, 2H, H-5), 3.31-3.40 (m, 1H, H-4) 3.71 (s, 3H, OMe), 4.00-4.05 (m, 2H, OCH_2CH_3), 4.59-4.72 (m, 2H, $PhCH_2$), 6.76-6.79 (m, 2H, PhH), 7.09-7.12 (m, 2H, PhH) (a mixture of *cis* and *trans* isomers found in the ratio of 3:1).

3.10 Synthesis of Ganem's intermediate 119 (2:1)



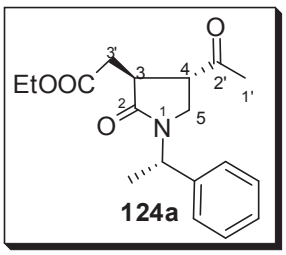
Compound **123** (0.2 g, 0.6 mmol) was stirred with CAN (1.0 g, 1.8 mmol) in 5 mL EtOH overnight. It was then quenched with 10 mL of saturated aq. $NaHCO_3$ solution and diluted with DCM (25 mL). The organic layer was separated, dried over anhy. Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (Hexane: EtOAc, 1: 1) to afford **119** and further recrystallized from ethyl acetate: hexane (1:3); mp 102 °C; to isolate as a pale yellow solid (0.09 g, 70%); (Lit mp = 104-107 °C).

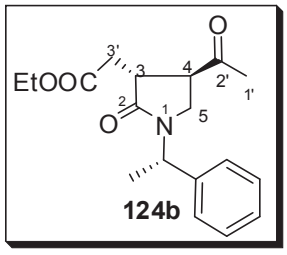
IR (neat): ν_{max} = 3300, 1730, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.18 (t J= 7.2Hz, 3H, OCH_2CH_3), 1.58 (s, 2H, H-1'), 1.69 (s, 1H, H-1'), 2.17-2.24 (m, 1H, H-4'A), 2.38-2.47 (m, 1H, H-5A), 2.63-2.79 (m, 1H, H-4'B), 2.86-3.01 (m, 1H, H-5B), 3.11-3.23 (m, 2H), 3.34-3.52 (m, 2H), 4.05-4.08 (m, 2H, OCH_2CH_3), 4.70-4.79 (m, 2H, H-3'), 6.5 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (OCH_2CH_3), 19.0 (C-1'), 30.6 (C-4'), 40.5 (C-3), 44.6 (C-4), 44.8 (C-5), 60.6 (OCH_2CH_3), 113.5 (C-3'), 142.9 (C-2'), 172.4 (C-2), 178.2 (COO).

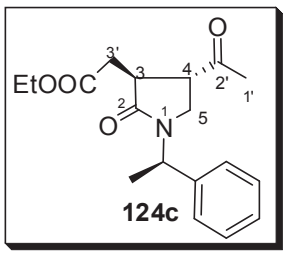
3.11 Synthesis of 124

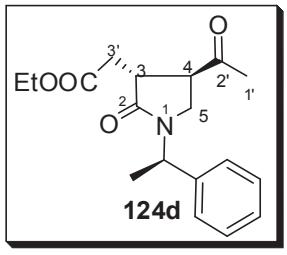
The similar procedure for the one-pot synthesis of **114** was repeated to produce **124** as pale yellow thick liquid with similar yield.

IR (neat): ν_{max} = 2910, 1745, 1696 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.24 (t J=7.2 Hz, 3H, OCH_2CH_3), 1.54 (t J=8 Hz, 3H, $PhCHCH_3$), 2.17 (2s, 3H, H-1'), 2.60-2.66 (m, 1H, H-3'A), 2.67-2.71 (m, 1H, H-3'B), 2.91-2.96 (m, 1H, H-5A), 3.08-3.20 (m, 1H, H-5B), 3.22-3.32 (m, 1H, H-3), 3.50-3.55 (m, 1H, H-4), 4.12-4.14 (m, 2H, OCH_2CH_3), 5.48-5.50 (m, 1H, PhCH), 7.28-7.32 (m, 2H, PhH), 7.34-7.36 (m, 2H, PhH).

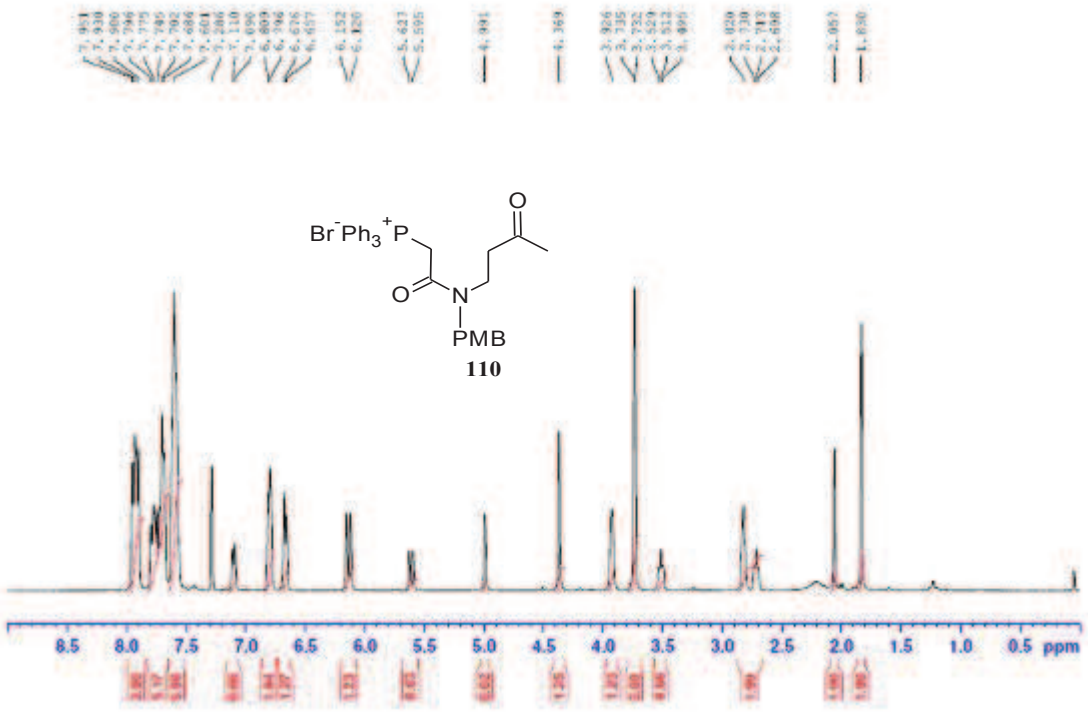








Spectra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O
N
PMB
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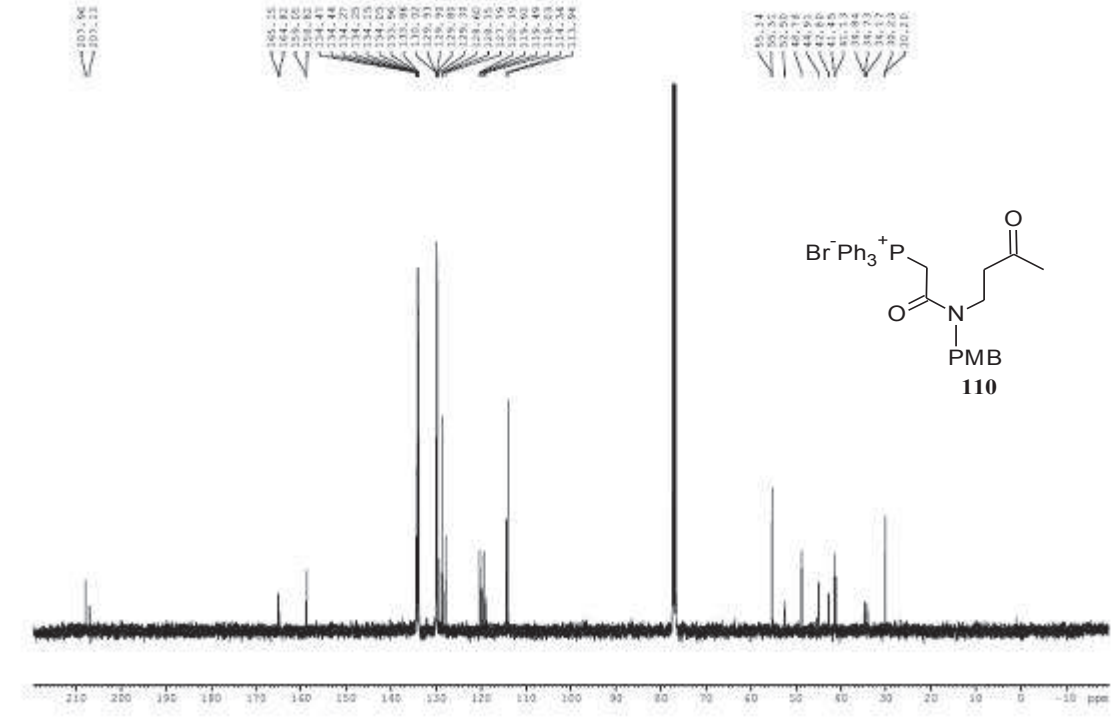
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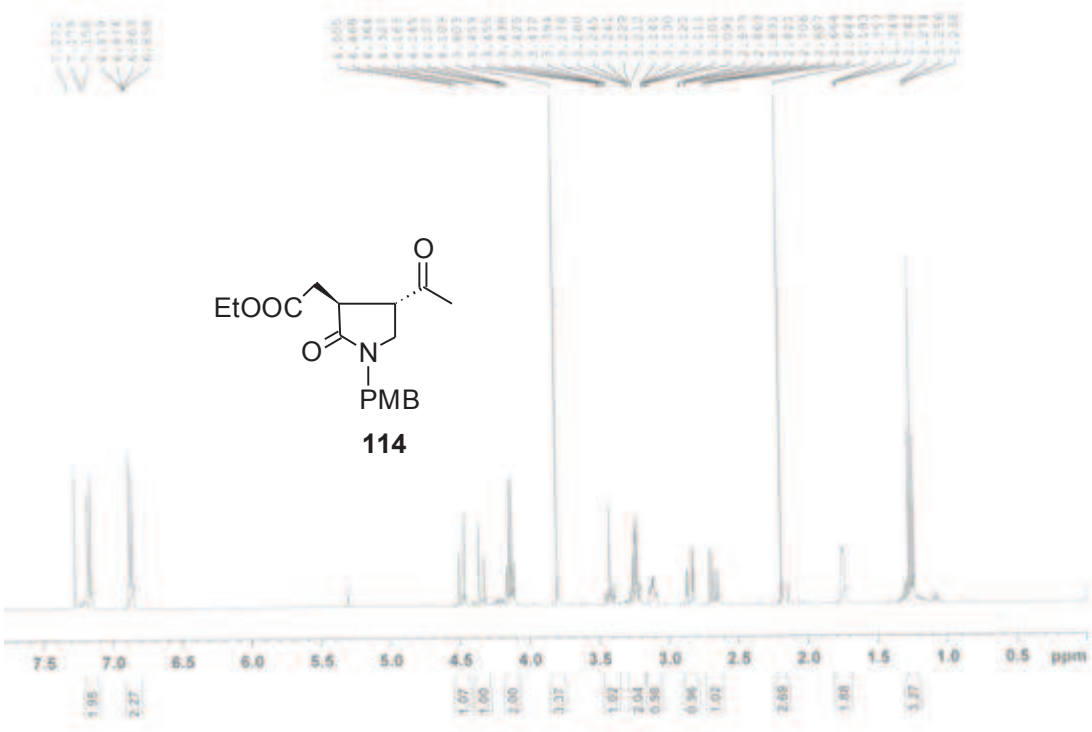
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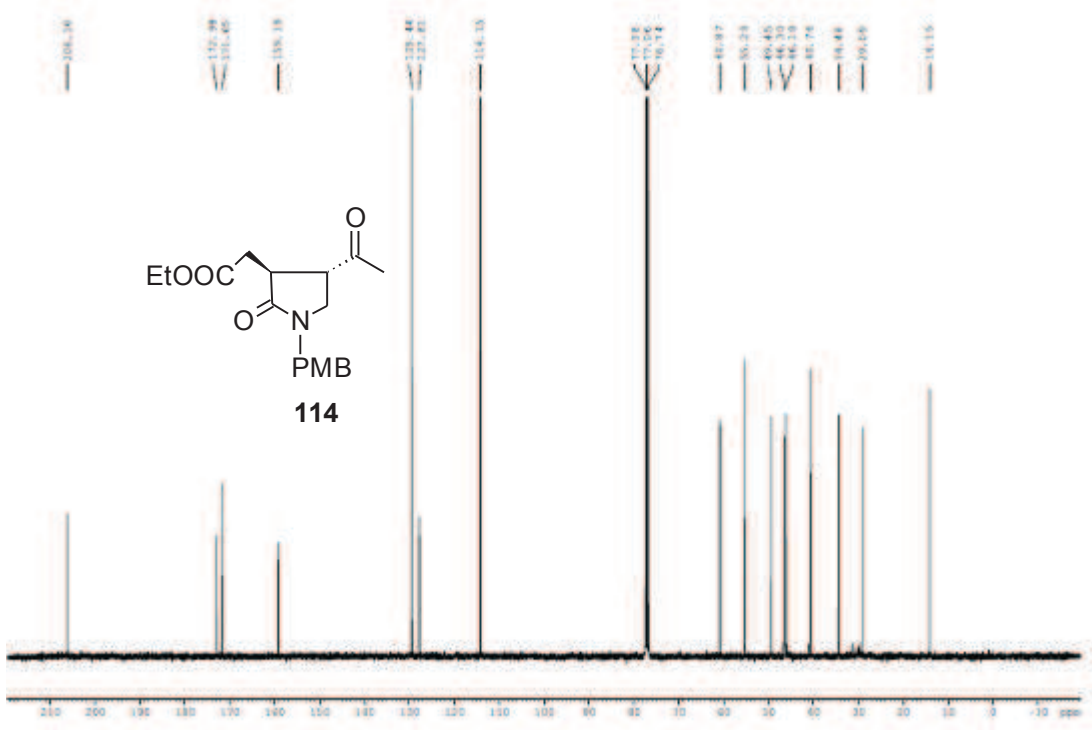
0.5
ppm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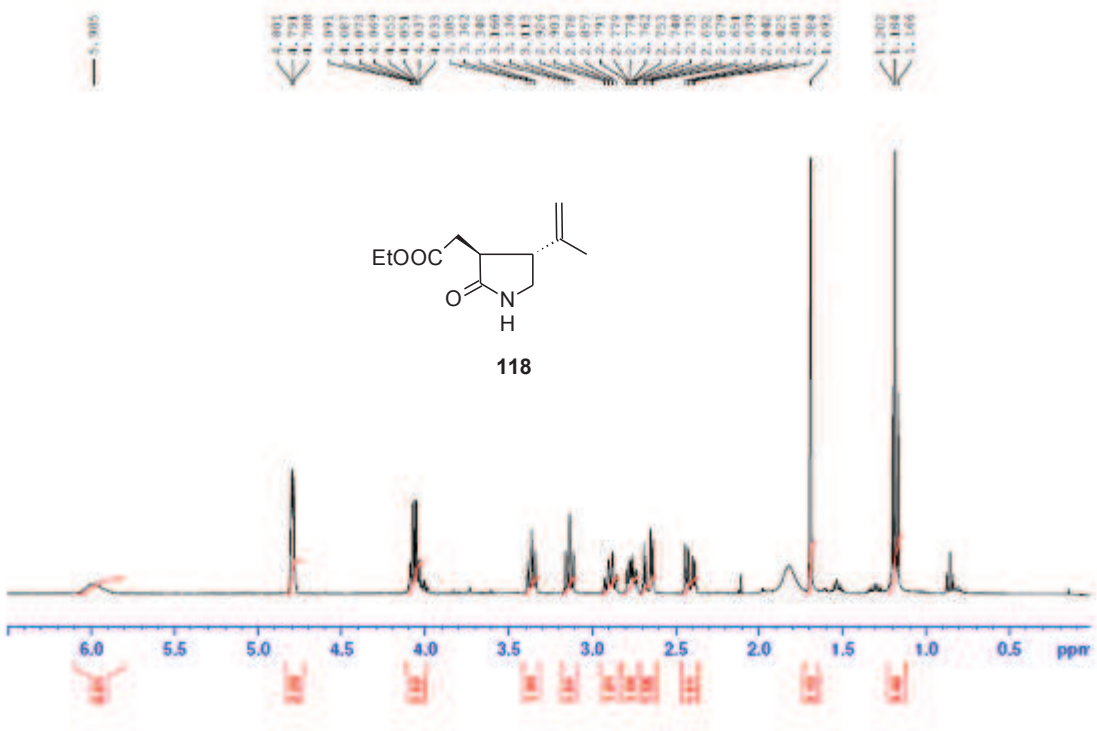
114



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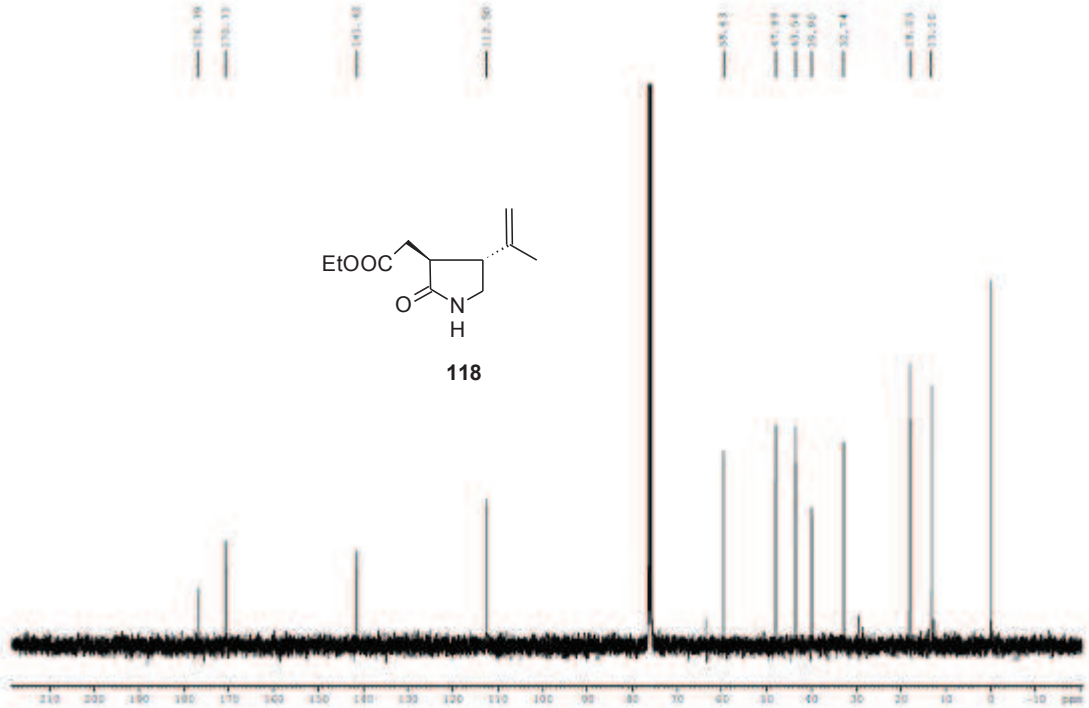

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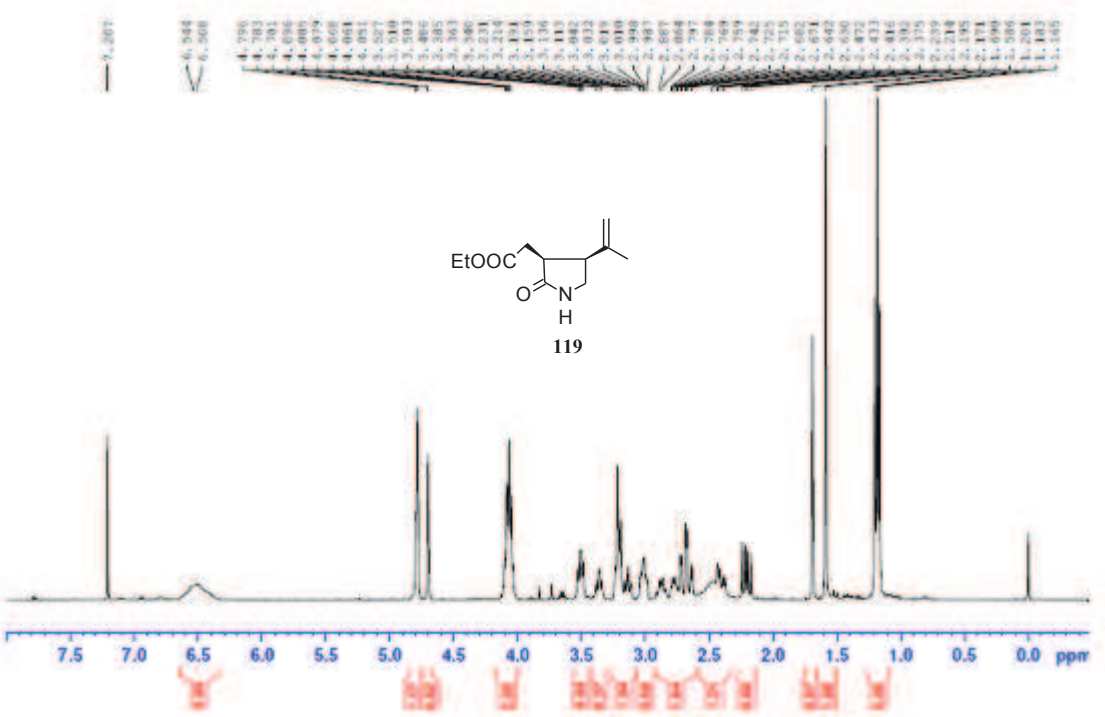
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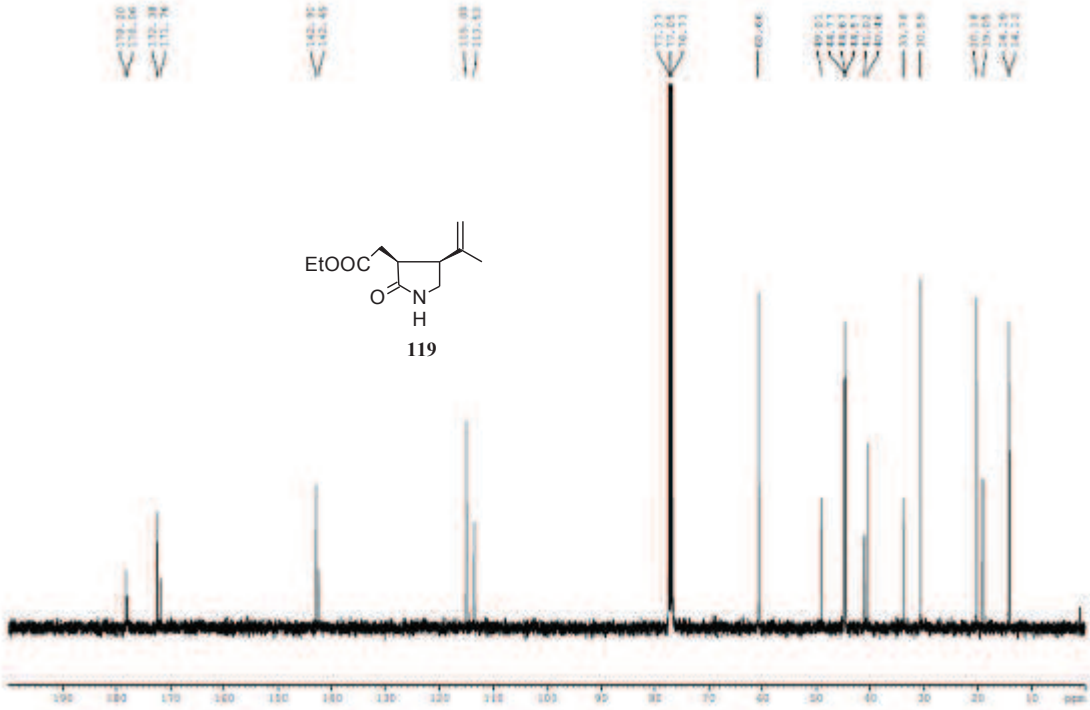
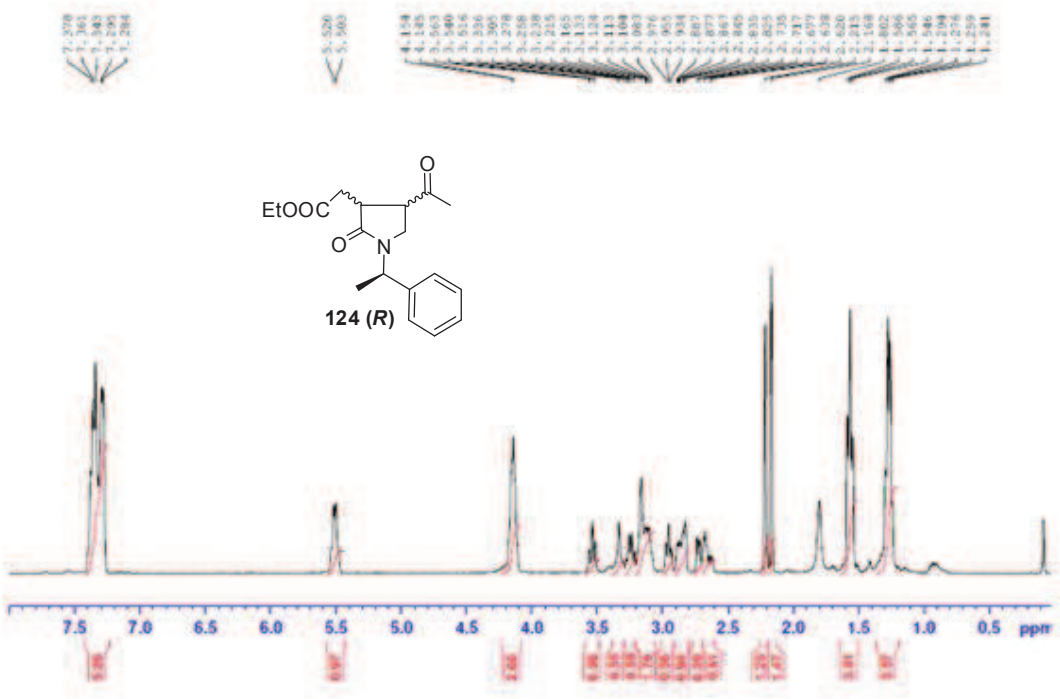
119


EtOOC
O
N
H

119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O
N
124 (R)
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6.0
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4.0
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1.5
1.0
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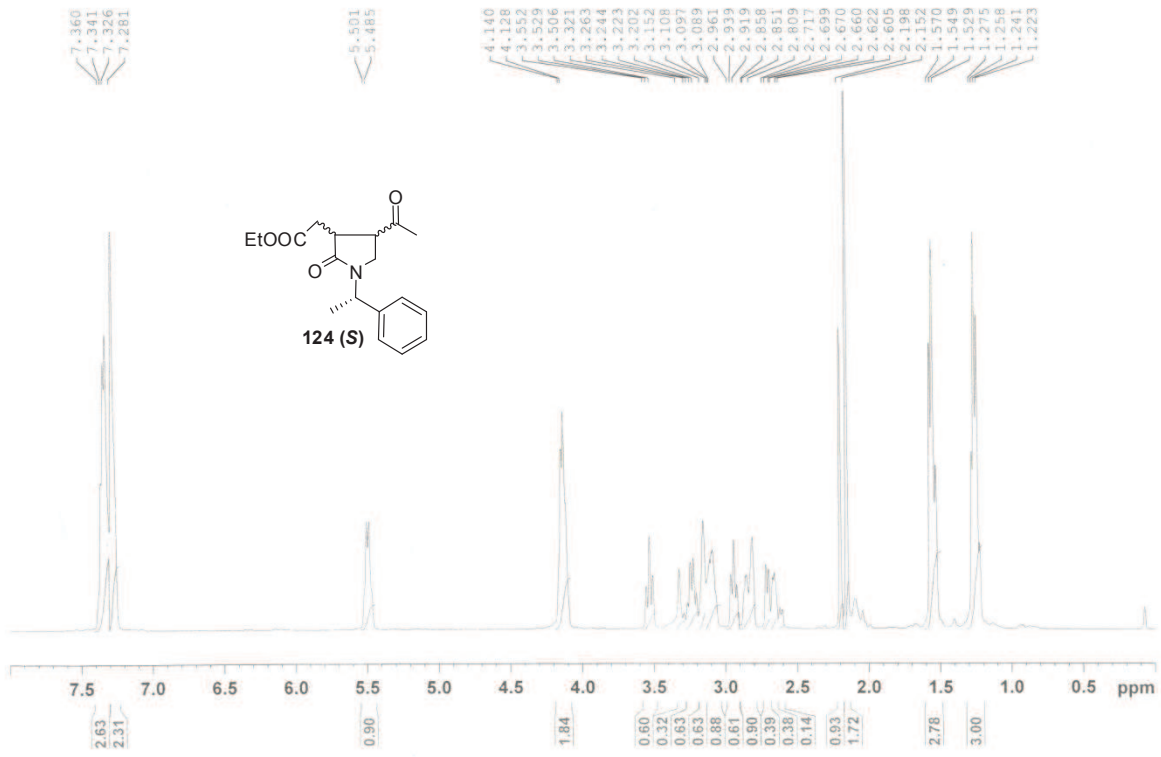
ppm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5.5
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3.0
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1.0
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ppm

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CHAPTER 4

Synthetic Studies towards Dexoxadrol, Conhydrine and Lentiginosine

Synthetic Studies towards Dexoxadrol, Conhydrine and Lentiginosine

Section 1: Synthetic studies towards dexoxadrol and epi-dexoxadrol

Introduction

The NMDA (N-methyl-D-aspartate) receptor is the best ionotropic glutamate receptor and a ligand gated ion channel activated by the neurotransmitter (*S*)-glutamate which controls the influx of cations into neurons, specifically Ca^{2+} ions.[1] The activation of NMDA receptor is necessary as it helps in several neurological processes like learning and memory.[2,3] But over activation of the NMDA receptor leads to an opening of the cation channel and hence an influx of Ca^{2+} ions into the neuron.[4] This increase in the concentration leads to the damage of neuron which is normally observed in brain injury. The NMDA receptor's over activation is also responsible for certain chronic diseases like Alzheimer's disease, Parkinson's disease, epilepsy etc. Therefore, this branch of medicine became challenging for the synthetic chemists to develop new drugs which can effectively bind with the NMDA receptor binding site and regulate the cation influx.[5]

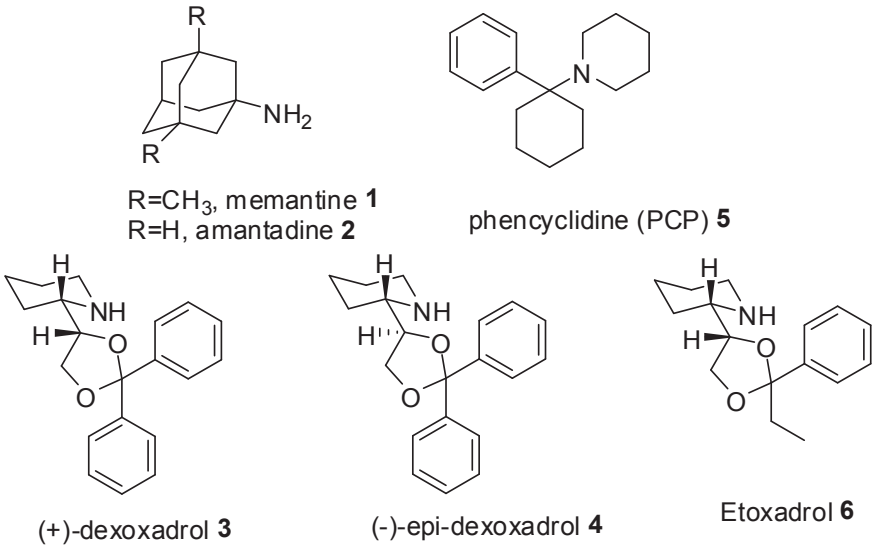


Figure 1

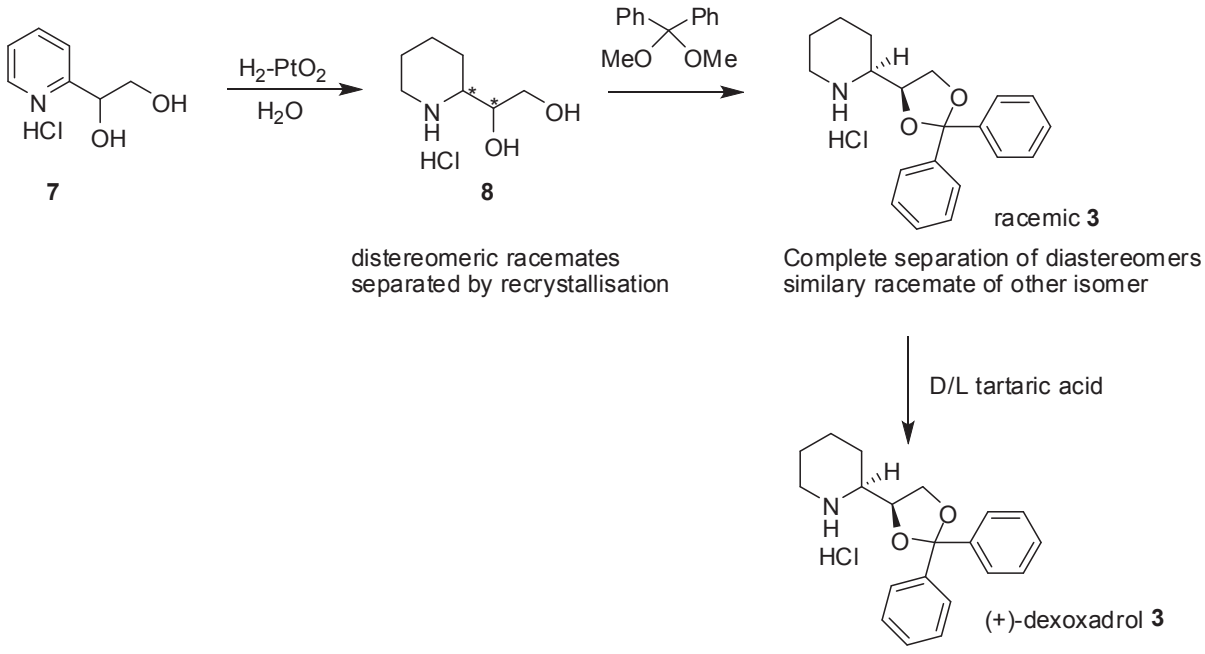
The opening of the NMDA receptor channel is controlled by different ligands interacting with various binding cites existing at the receptor proteins. The receptor proteins comprise the binding cites for (*S*)-glutamate, polyamines, H^+, Mg^{2+}, Zn^{+2} and PCP (phencyclidine). In this context, the compounds memantine **1** and amantadine **2** were found to be the best NMDA receptor antagonist and used efficiently even till today.[6] In the mid 1960s, the

piperidine derivatives substituted by acetalic group at the second position were first synthesized by Hardie *et al*.[7]These compounds, namely dexoxadrol **3** and etoxadrol **6** were found to be more active than memantine **2** and act by binding with the PCP **5** site (fig 1). The detailed study on the biological behavior of these molecules revealed that, the presence of secondary amine, piperidine ring, five member oxygenated ring and the (*SS*) stereochemistry[8] altogether play a crucial role for its enhanced activity. The interesting structure and its potent biological activity prompted the synthetic chemists to design the methods for several analogues of **3**. Turning to an end, recent research has elaborated the synthesis of various substituted side chain homologues and rigorously tested for several biological activities to boost the efficacy in this area.[9]

Literature Review

There are very few syntheses of dexoxadrol and its derivatives those have been reported so far.[10]

The first synthesis of dexoxadrol was reported by Hardie *et al* in a development to synthesize a local anesthetic drug (scheme 1).[10a]

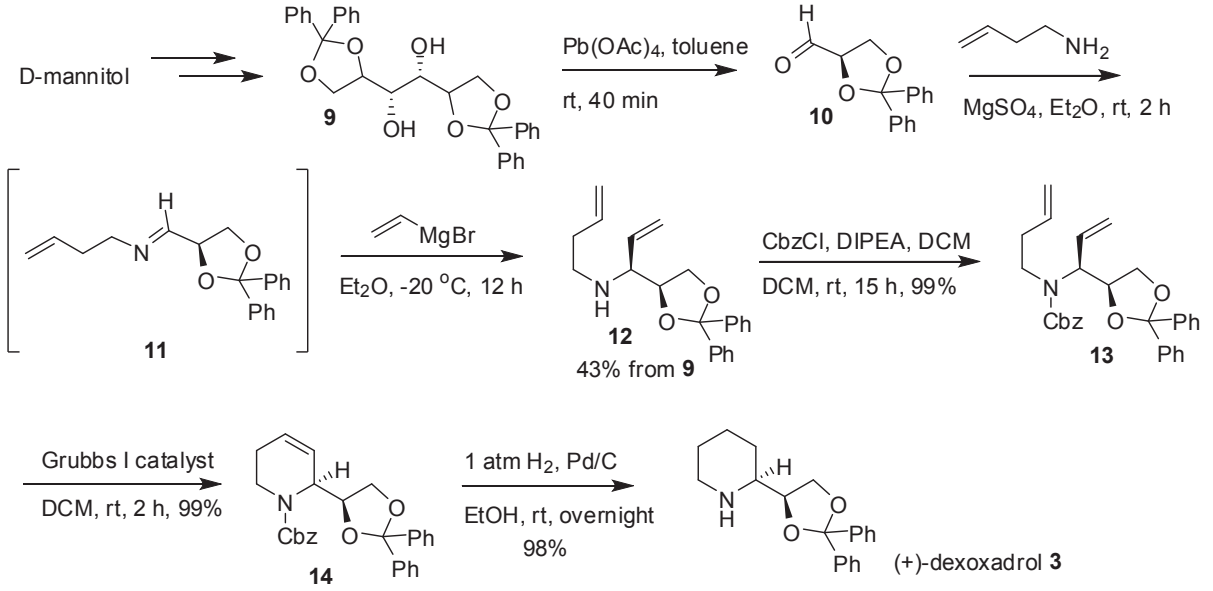


Scheme 1

The requisite diol **8** was synthesized by high pressure hydrogenation of (2-pyridyl)-1, 2-ethanediol hydrochloride **7**. The diol **8** consisting of two chiral centers were obtained as a

mixture of two diastereomeric racemates. The maximum diastereomeric separation was achieved through fractional crystallization using 2-propanaol. The treatment of diol **8** with dimethoxybenzophenone afforded the racemic **3** in a diastereomeric mixture form. The racemic mixture was eventually converted to pure enentiomer by repeated crystallization using optically active tartaric acid. Several other analogues have also been synthesized to explore the different activity studies.

The first asymmetric synthesis of (+)-dexoxadrol **3** was achieved recently by Etayo *et al* using D-mannitol as a starting chiral source (scheme 2).[10c] The requisite diol **9** was synthesized according to the reported methods. The diol **9** on oxidative cleavage using $Pb(OAc)_4$ followed by immediate condensation with 3-buten-1-amine afforded the diastereomeric imine mixture with major *trans* isomer **11**. The addition of vinyl magnesium bromide across the imine **11** gave diastereoselectively **12** in 43% overall yield from diol **9**. The free NH was protected to give diene **13**, an immediate precursor for RCM. The treatment of compound **13** with Grubbś I catalyst afforded the compound **14** exclusively. The targeted **3** was then enentiomerically synthesized by hydrogenolysis of Cbz group over Pd/C.

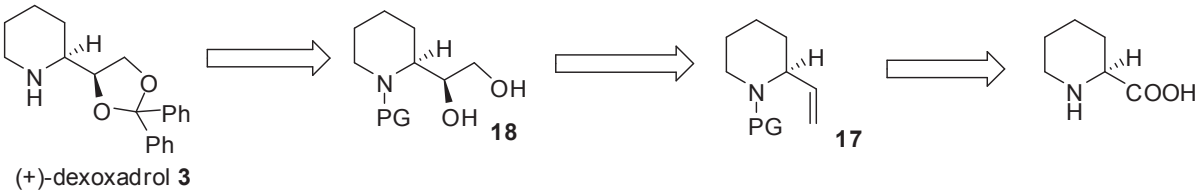


Scheme 2

Results and Discussion

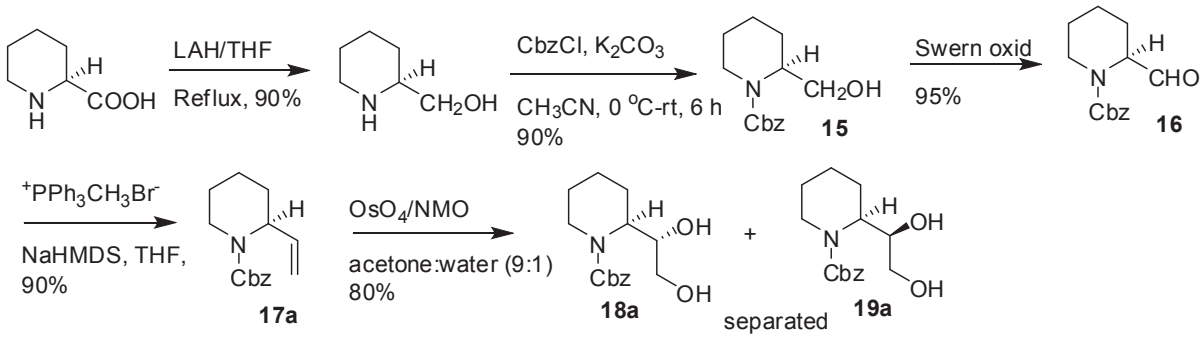
The major objective of this work was to synthesize (+)-dexoxadrol **3** and (-)-epidexoxadrol **4** through systematic study of Sharpless asymmetric dihydroxylation (SAD) of a terminal olefin attached to the piperidine system.

The synthetic approach made by Hardie *et al* involves the separation of racemic mixture through crystallisation method to end up with the enentiomerically pure dexoxadrol **3**. We envisioned the diol **8** could also be synthesized enentiomerically starting from chiral source rather than pyridine system. The pipecolic acid was found to be the most appropriate starting material for deriving this. Accordingly we rationalised a retro synthesis as outlined in scheme 3.



Scheme 3

The synthesis commenced with the LAH reduction of commercially available (-)-pipecolic acid to pipecolinol in good yield (scheme 4). The pale yellow thick liquid obtained turned to a solid. The disappearance of carbonyl peak in IR spectrum & change in physical properties of the substance indicated the formation of the product. Without further characterization, the amino alcohol was treated with Cbz-Cl at 0 °C for 6 h. The product formed was purified by column chromatography and characterized by spectroscopic techniques. The presence of IR stretching at 3500 cm^{-1} and aromatic proton signals in ^{1}H NMR confirmed the formation of Cbz-pipecolinol **15**. The compound **15** was subjected to Swern oxidation and the aldehyde **16** formed was olefinated through Wittig reaction with $PPh_3{=}CH_2$. The pivotal dihydroxylation of **17a** was initially performed using OsO_4/NMO without any chiral ligand. After stirring for 3 h, the two low mobile close spots were seen on TLC which were then separated by column chromatography to give expected mixture of **18a** and **19a** (60:40). We were unable to predict the configuration of stereo centres at this stage. The ratio was determined by HPLC method. The separated products were characterised by spectroscopic techniques to confirm the formation of diastereomers whose configurations were tentatively assigned as **18a** and **19a**.



Scheme 4

In order to achieve the diastereoselectivity, it was necessary for us to employ the Sharpless ligands. If we look back the literature, the Sharpless earlier rule for explaining the differential diastereoselectivity for the substituted olefin does not hold good for the system involving monosubstituted terminal double bonds.[11] For achieving the mismatching double diastereoselection (MDD), a different pneumonic was proposed by Sharpless for explaining the reversal of facial selectivity for AD of terminal olefins.[12, 11] Accordingly, the MDD could be achieved by selection of appropriate ligands for the monosubstituted terminal olefins.

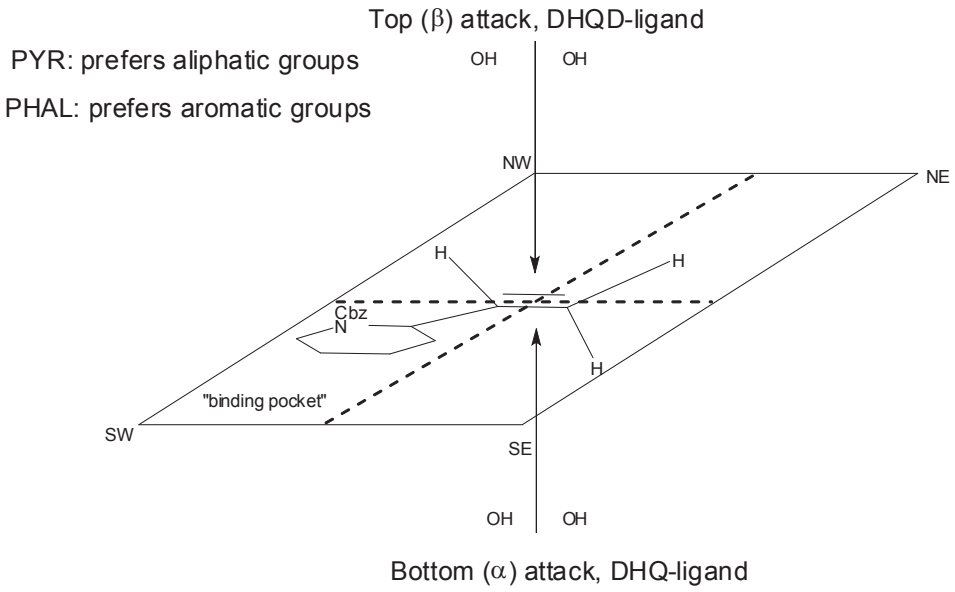


Figure 2

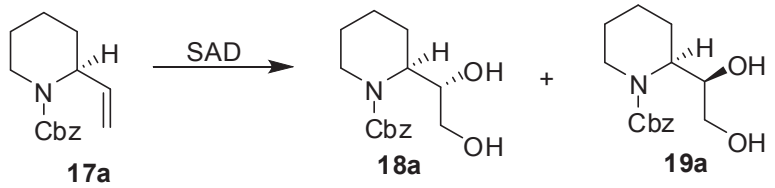
Sharpless experimentally established the different mnemonic "Binding Pocket" particularly for mono substituted terminal olefin. According to this,

(i) The molecule with terminal double bond should be placed as shown in the figure 2. With the double bond at the centre and the substituent at the 4th quadrant which is called "Binding Pocket".

(ii) If the molecule is aromatic the MDD can be best achieved with the ligands of the spacer PHAL i.e. $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$. On the other hand, if the molecule is aliphatic the MDD is shown by PYR spacer i.e. using the ligands $(DHQ)_2PYR$ and $(DHQD)_2PYR$.

(iii) The DHQD based ligand preferentially considered for β-attack whereas DHQ for α-attack.

Very few systems have been demonstrated for manifesting this kind of unusual behaviour. Smith and co-workers observed this kind of same sense of diastereoselectivity while synthesizing calyculin.[13]During the synthesis of zaragozic acids similar unexpected diastereomeric outcomes were observed by Carreira's group.[14] It was also explained by Gardiner *et al* by conducting the similar experiments for pyrrolidine system.[15] Recently, once again this abnormal behaviour was noticed by Urones and co-workers while synthesizing new proline analogues for organocatalysis.[16]



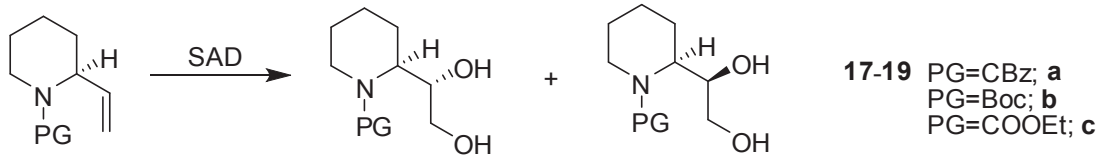
Ligands	18a (%)	19a (%)
No ligand	60	40
$(DHQ)_2PHAL$	79	21
$(DHQD)_2PHAL$	77	23
$(DHQ)_2AQN$	75	25
$(DHQD)_2AQN$	80	20
$(DHQ)_2Pyr$	85	15
$(DHQD)_2Pyr$	**31**	**69**

The products were obtained in 80-85% yield after column purification.

Scheme 5

With these, we intended to study the Sharpless rules for our novel monosubstituted terminal olefin attached to piperidine system. The dihydroxylation was initially carried out in PHAL spacer using $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ (scheme 5). Only one diastereomer, showing the top spot on TLC plate was preferred by both the ligands. We then switched to AQN spacer and the similar results were noticed with the further improvement in the formation of the top spot. The same reaction was carried out shifting to ligands of PYR spacer. A remarkable diastereoselective differentiation was observed with enhancement of the lower spot product with $(DHQD)_2PYR$. The HPLC chromatogram showed the formation of **19a** and **18a** with diastereoselective ratio of 7:3.

In an extensional study to this behaviour, we also studied the effect of protecting groups on MDS in piperidine system using PYR spacer. In this context, we prepared the Boc and COOEt protected alkenes **17b** and **17c** and subjected for dihydroxylation using PYR based ligands (scheme 6). Though there was no much difference in the diastereoselection by changing to **17b** from **17a**, the considerable change was observed with **17c**. The COOEt being very less hindered, offered a complete MDD to give exclusively **18c** and **19c** with $(DHQ)_2PYR$ and $(DHQD)_2PYR$ respectively.



17 **18** **19**

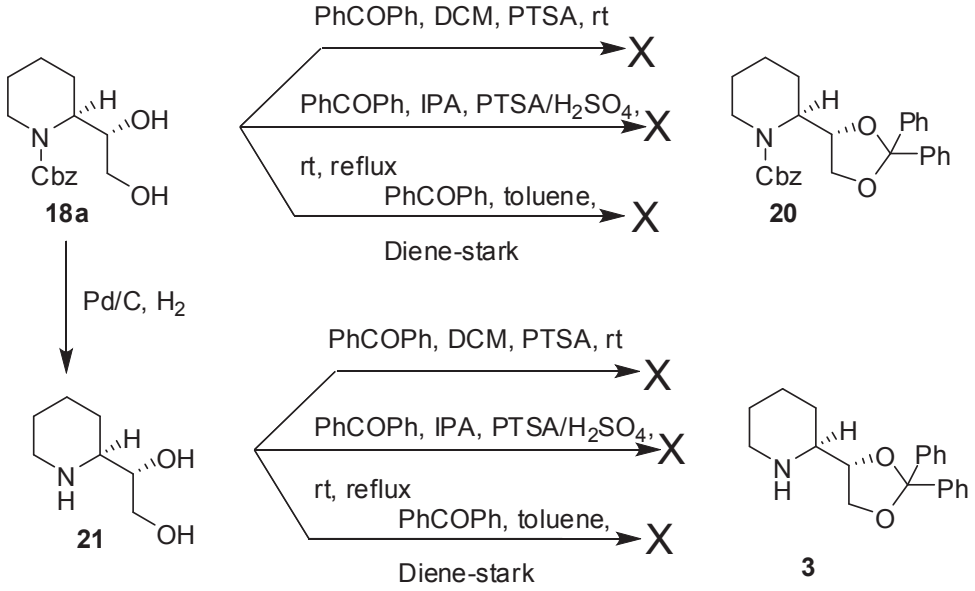
Ligands	**$(DHQ)_2PYR$** (% ratio)	**$(DHQD)_2PYR$** (% ratio)
PG=Cbz	85:15	31:69
PG=Boc	82:18	41:59
PG=COOEt	90:10	15:85

For PG=Cbz, 86%; PG=Boc, 80%; PG=COOEt, 85% after column purification

Scheme 6

The present results evidently supported the Gardiner's view that the extent of differential diastereoselectivity also depends on hindrance of the substituent influenced on the double bond.

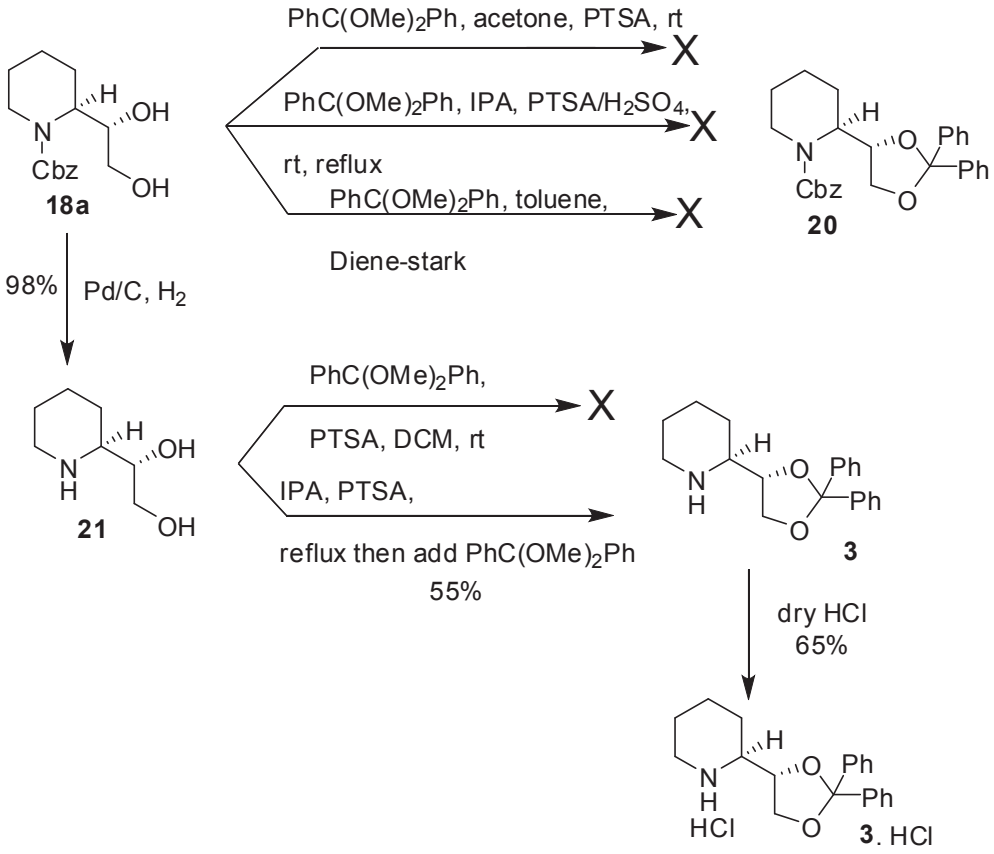
The planned synthetic approach was then proceeded to accomplish the total synthesis of dexoxadrol and its *epi* isomer (scheme 7). Initially we thought of direct acetalation of diol **17a** and then deprotecting the Cbz to furnish the requisite product. Accordingly, the diol **17a** was treated with benzophenone in the presence of *p*-TSA which did not result any noticeable change. The various attempts tried for the synthesis of **20** failed with the recovery of starting material. Thinking that the hindrance by Cbz group was interrupting the feasibility of the reaction, the compound **21** was prepared by hydrogenolysis of Cbz and subjected for diol protection. But the similar failure of the reaction under any condition forced us to investigate an alternate method.



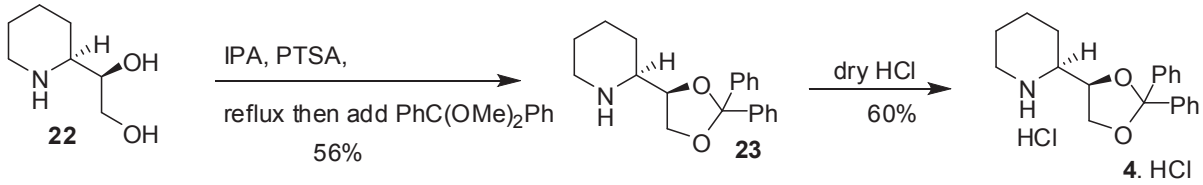
Scheme 7

The diol **18a** was then treated with the commercially available dimethoxy benzophenone. The reactant was recovered without any noticeable change after certain hours (scheme 8). The compound **18a** was subjected to hydrogenolysis and the same protection was tried again. Even though the reaction took place, the poor yield was disappointing us. The procedure was then slightly modified this time. Initially the mixture of diol **21** and PTSA was refluxed in IPA for 15 min. To the refluxing solution was then added solid dimethoxybenzophenone from the top and continued reflux. A moderate yield (55%) of **3** was then obtained after column chromatographic purification. The compound **3** was then treated with dry HCl gas liberated by the reaction of NaCl and conc. H_2SO_4. The dexoxadrol thus obtained was characterised by ^1H NMR, ^{13}C NMR and compared well

with the literature values. The optical activity of this indicated the formation of the required product.

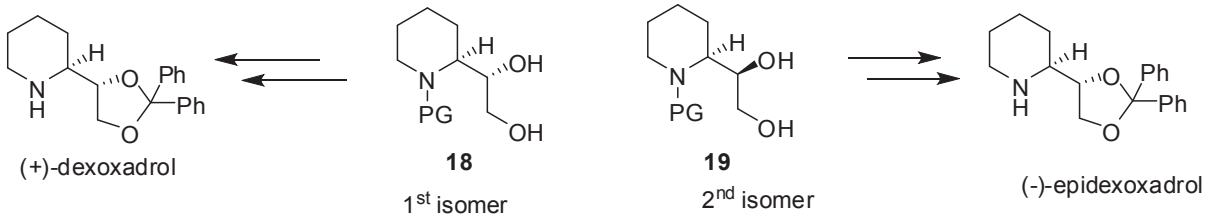


Scheme 8



Scheme 9

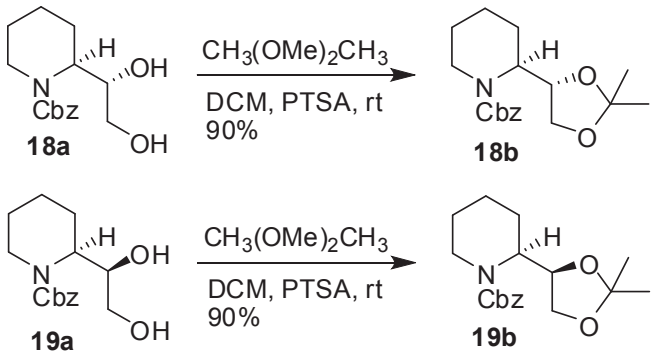
In a similar way the (-)-*epi*dexoxadrol **4** was synthesized from **22**. Incidentally, this is the first asymmetric synthesis of (-)-*epi*dexoxadrol **4** (scheme 9).



Scheme 10

Based on the value and sign of optical rotation the configuration of diol **18a** and **19a** were now assigned (scheme 10).

For further confirmation of configuration, acetals **18b** and **19b** were prepared form the diol **18a** and **19a** respectively (scheme 11). The model study performed using the software Chem 3D, clearly showed the difference in interaction mode of one of the methyl groups with H-9. The first isomer **18b** in the model did not show any interaction whereas the second isomer **19b** showed a mutual interaction with H-9 (fig 3 & 4). Accordingly, when the methyl groups were irradiated with a frequency in NOE, the proton H-9 was strongly affected in the second isomer **19b** while the H-9 of isomer **18b** remain unaffected (fig 5).



Scheme 11

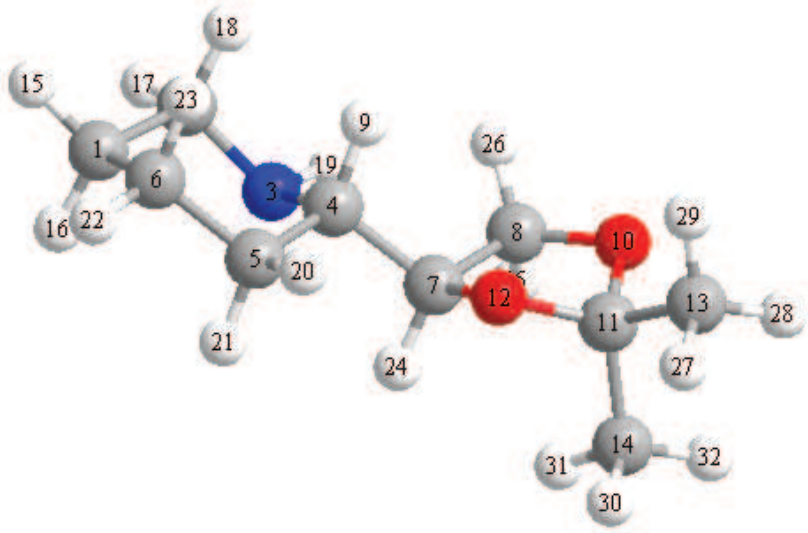


Figure 3. Predicted model for **18b**

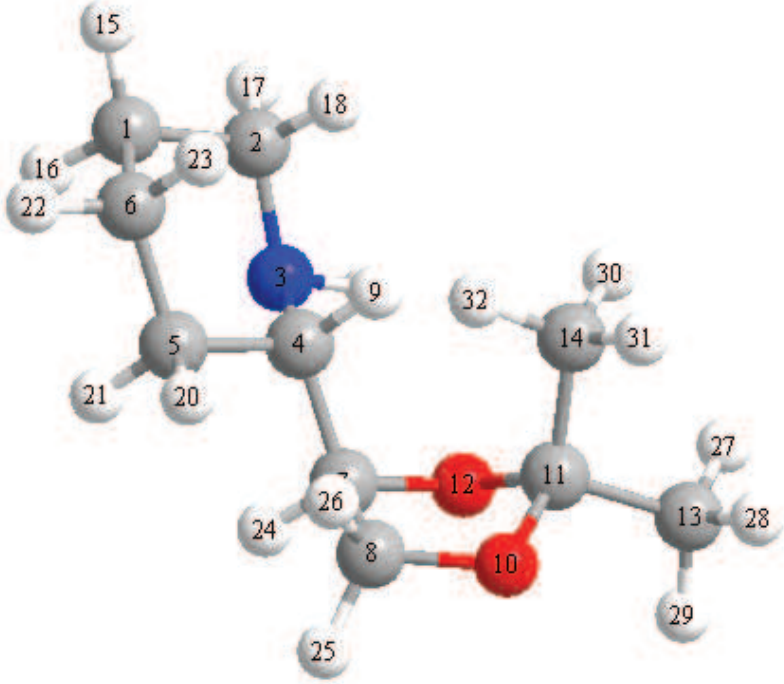


Figure 4. Predicted model for**19b**

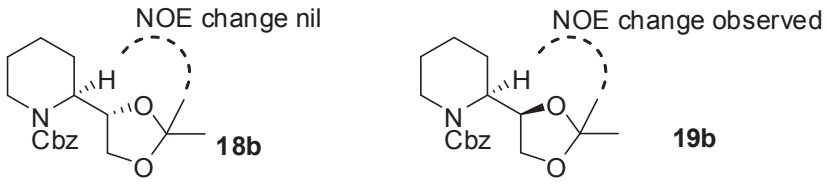


Figure 5. NOE interaction

Section 2. Formal synthesis of (-)-conhydrine, (+)-epiconhydrine and lentiginosine

Introduction

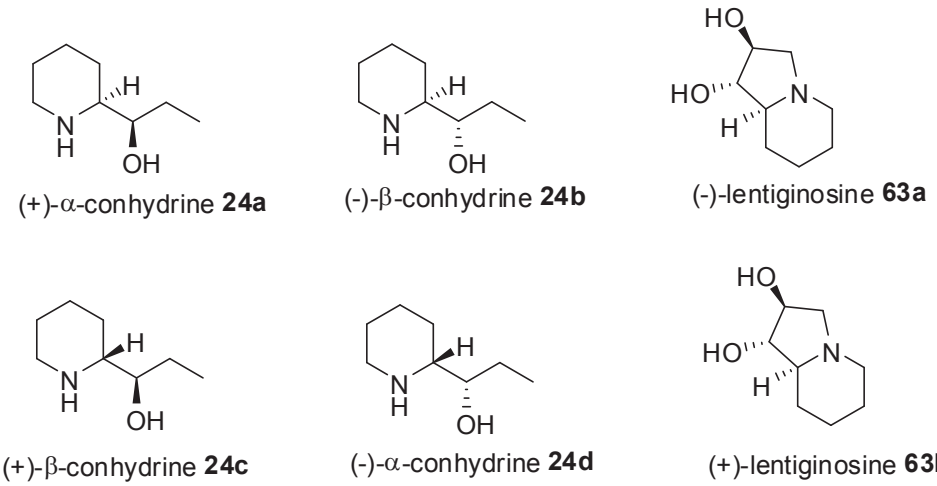
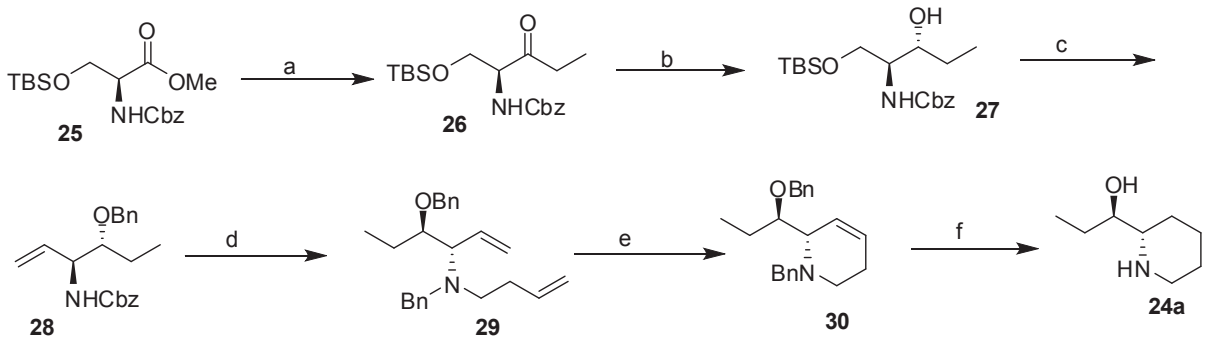


Figure 6

Alkaloid nucleus with 1-hydroxyalkyl side chain at the α-position constitutes a major framework widely dispersed among the natural products (fig 6).[17] Conhydrine **24** is one such alkaloid of hemlock family isolated basically from the leaves and seeds of the plant *Conium Maculatum L*.[18] The structure was first elucidated in 1933.[19] During the ancient time of Greece, the extracts of these plants were used for the execution of criminals. The (+)-conhydrine has attracted considerable synthetic interests due to its potent antitumor, antiviral and glycosidase inhibitory activities.[20] As a consequence, several synthetic routes have been manifested in the literature[21] for the synthesis of different isomers **24** (**a-d**) and actively studied for numerous biological activities.

(+)-Lentiginosine **63b**, a naturally occurring isomer was isolated from *Astragalus lentiginosus* in 1990.[22] Being a hydroxylated alkaloid, serves as sugar mimics by acting as potent selective inhibition of α-glucosidase and amyloglucosidase.[23] The nonnatural (-)-lentiginosine **63a** is frequently used in the treatment of tumour cells.[24] Due to its unique structure and interesting biological activities, various synthetic routes have been established involving mainly chiral pool, organocatalytic and chiral auxiliary methods.[25, 21e]

Literature Review

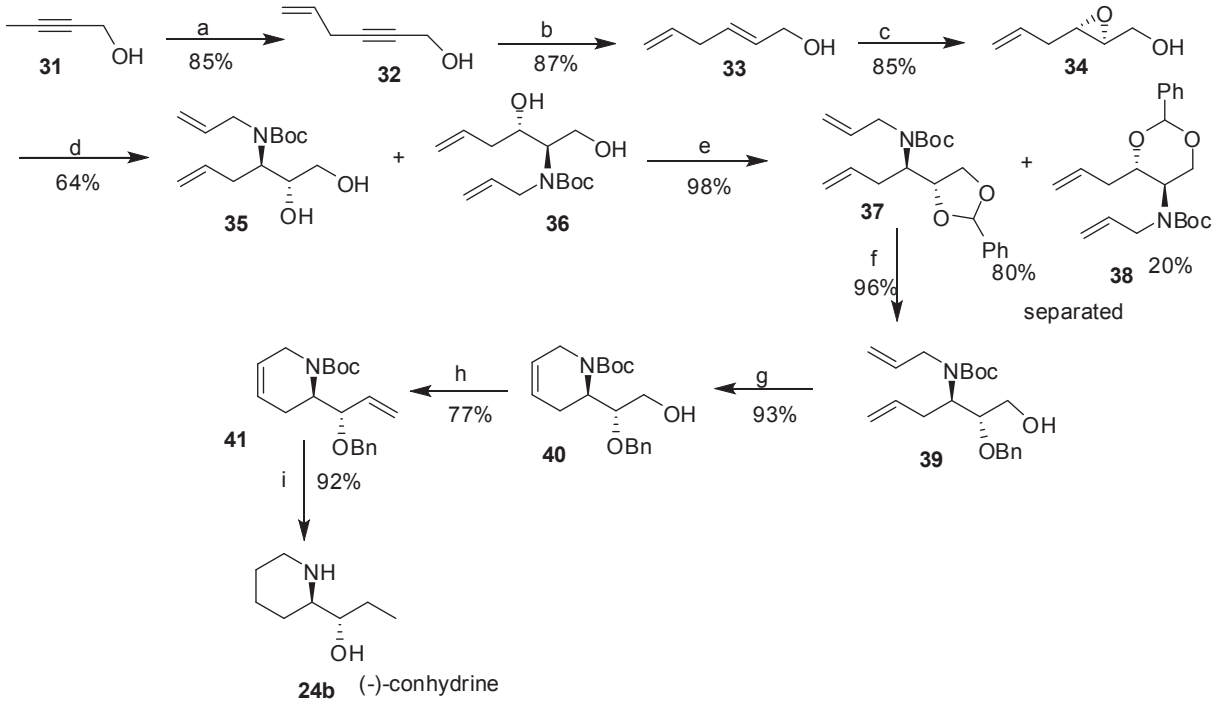


Scheme 12

Reagents and conditions: (a) (i) NH(OMe)Me, $AlMe_3$, DCM, 0 °C, 92%; (ii) EtMgBr, THF, 0 °C, 98%; (b) (i) $LiAlH(OtBu)_3$, EtOH, -78 °C, 93%; (ii) BnBr, KOH, THF/DMF (4:1), rt, 82%; (c) (i) TBAF, THF, rt, 90%; (ii) Dess–Martin periodinane, DCM, rt; (iii) Ph_3PCH_3Br, *n*-BuLi, THF, 0 °C, 73% over two steps; (d) (i) 40% aqueous KOH, MeOH, reflux; (ii) Homoallyl bromide, K_2CO_3, DMF, 45 °C, 76% over two steps; (iii) BnBr, NaH, DMF, rt, 91%; (e) Grubbś second generation catalyst, DCM, rt, 87%; (f) Pd/C, H_2, MeOH, rt, 92%.

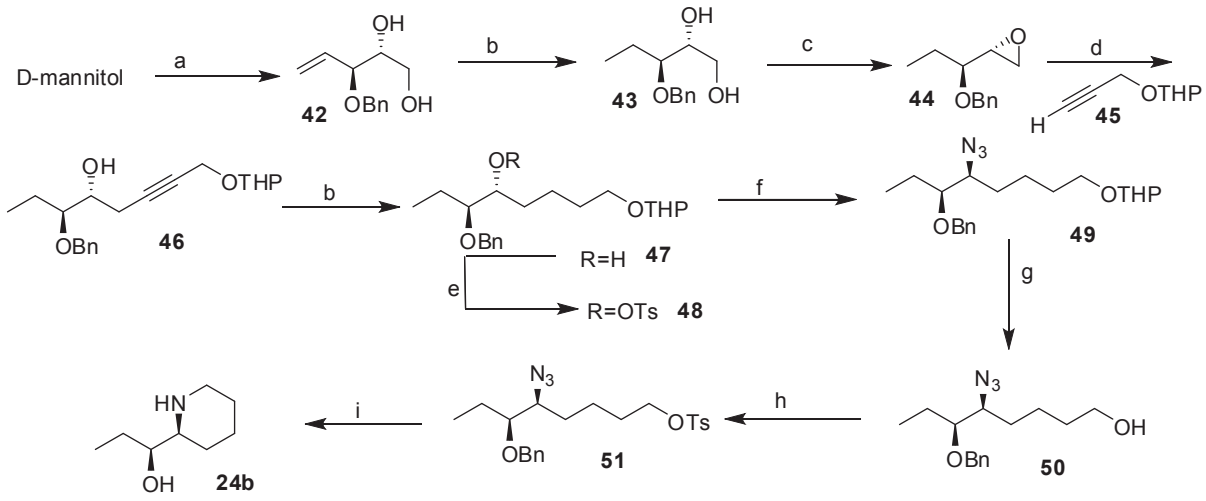
Ham and co-workers achieved the total synthesis of (+)-conhydrine **24a** via highly diastereoselective reduction of carbonyl of α-aminoketone (scheme 12).[21a]The ester **25** obtained from L-serine was effectively transformed to **26** via formation of Wienreb amide. The chelation-controlled hydride reduction of **26** using $LiAlH(OtBu)_3$ at -78 °C afforded exclusively **27**. The OTBS was deprotected and converted to olefin **28**. The deprotection of Cbz was imparted using KOH and further free NH was benzylated to give **29**. The RCM using Grubbs II catalyst afforded **30** which on subsequent hydrogenolysis furnished the natural product **24a**.

Reddipalli *et al* constituted a novel approach for the synthesis of (-)-conhydrine **24b** starting from propargyl alcohol using chiral epoxidation and RCM as key steps (scheme 13).[21d]The commercially available propargyl alcohol **31** was converted to **32** which on LAH reduction afforded the olefin **33**. The asymmetric epoxidation of **33** gave **34** which on treatment with allyl amine opened up the epoxide giving an inseparable mixture of **35** & **36**. The mixture was as such converted to benzaldehyde acetal mixture **37** & **38** amenable to separation on column chromatography. The diene **39** was subjected to RCM to afford **40** which on further synthetic conversions transformed to (-)-conhydrine **24b**.



Scheme 13

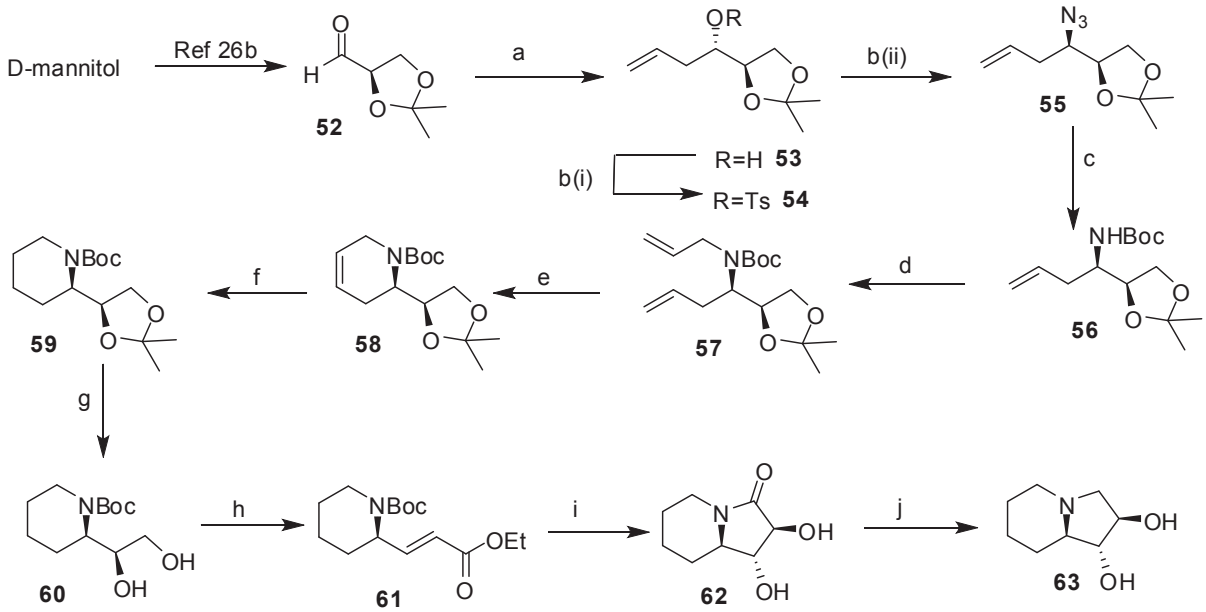
***Reagents and conditions*:** (a) allyl bromide, NaI, K_2CO_3, CuI, acetone, 3 h; (b) LAH, THF, 4 h; (c) (+)-DET, TBHP, Ti $(OiPr)_4$, dry DCM, -20 °C, 12 h; (d) (i) $LiClO_4$, allyl amine, CH_3CN, 10 h, (ii) $(Boc)_2O$, $NaHCO_3$, MeOH, 16 h; (e) benzaldehyde dimethyl acetal, PTSA, DCM, 10 h; (f) DIBAL-H, DCM, 0 °C–rt, 1 h; (g) 5 mol % Grubbs's first generation catalyst, DCM, 40 °C, 5 h; (h) (i) DMSO, $(COCl)_2$, DCM, -78 °C, 45 min; (ii) $CH_3{}^+PPh_3I^-$, KO*t*Bu, THF, 0 °C, 6 h; (i) 10% Pd/C, methanolic HCl, 20 h.



Scheme 14

***Reaction conditions*:** (a) Ref. 11a; (b) Lindlar's catalyst-H_2, ethanol, rt, 4 h, 95%; (c) *p*-toluenesulfonyl chloride, dibutyltin oxide, triethylamine, dry DCM, 0 °C to rt, 4 h, then K_2CO_3, MeOH, rt, 3 h, 92%; (d) *n*-

BuLi, $BF_3.Et_2O$, dry THF, -78 °C, 3 h, 78%; (e) *p*-toluenesulfonyl chloride, pyridine, 0 °C to rt, 16 h; (f) NaN_3, DMF, 60 °C, 14 h, 72% (for two steps); (g) PTSA, MeOH, rt, 5 h, 96%; (h) *p*-toluenesulfonyl chloride, TEA, dry DCM, rt, 92%; (i) 10% Pd-C/H_2, EtOAc, one drop 30% NaOH, rt, 6 h, 85%.

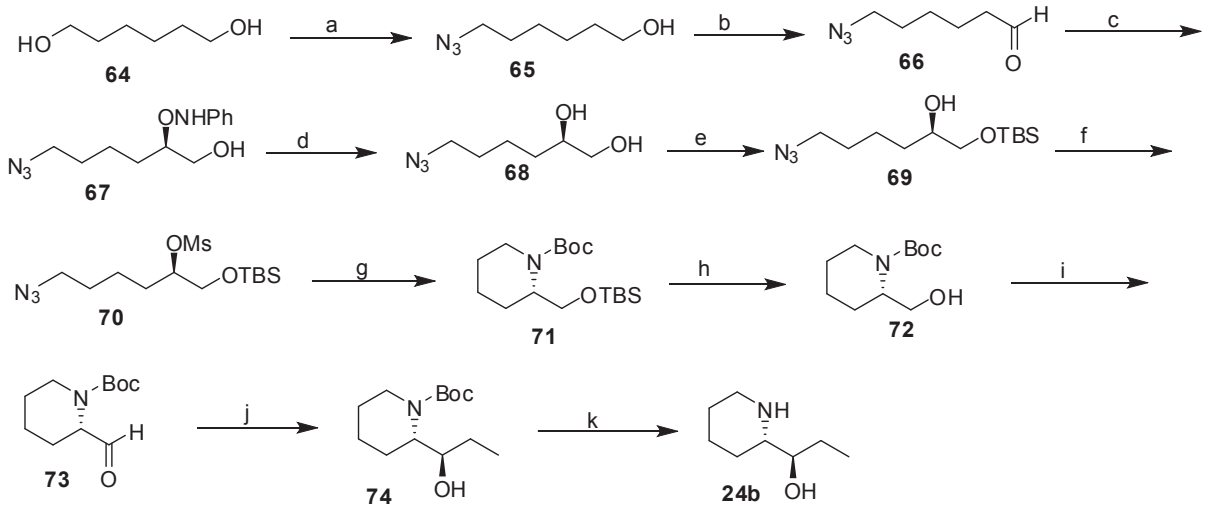


Scheme 15

Reaction conditions: (a) Zn, allyl bromide, THF, saturated aq NH_4Cl, 0 °C to rt, 8 h, 65%; (b) (i) *p*-toluenesulfonyl chloride, pyridine, 0 °C to rt, 91% (ii) NaN_3, DMF, 60 °C, 14 h, 85%; (c) (i) $LiAlH_4$, THF, 0 °C to rt, 1 h (ii) 15% NaOH, $(Boc)_2O$, 0 °C to rt, 4 h, 88%; (d) NaH, allyl bromide, THF, saturated aq NH_4Cl, 0 °C to rt, 18 h, 85%; (e) first generation Grubb's catalyst, dry DCM, reflux, 8 h, 91%; (f) 10% Pd-C/H_2, EtOAc, rt, 6 h, 96%; (g) PTSA, MeOH, rt, 5 h, 85%; (h) (i) $NaIO_4$, saturated aq $NaHCO_3$, DCM, rt; (ii) $Ph_3P{=}CHCO_2Et$, dry benzene, 50 °C; (i) (i) AD-mix-β, $CH_3SO_2NH_2$, H_2O:*t*-BuOH (1:1), 0 °C, 24 h; (ii) TFA, rt, 10 h; (iii) EtOH, reflux, 6 h, 62% (for three steps); (j) $LiAlH_4$, THF, reflux, 12 h, 84%.

Kamal and Vangala described a chiral pool strategy for the synthesis of (-)-conhydrine **24b** and (-)-lentiginosine **63a** from D-mannitol.[21e]The synthesis began with the known conversion of D-mannitol to compound **42**[26a] which on hydrogenation over Lindlar's catalyst afforded **43**. The preparation of oxirane **44** was effected using Mertinelli standard conditions which on subsequent opening with **45** gave the alkyne **46**. The compound **46** was saturated to **47** and the –OH group was tosylated to afford **48** which on nucleophilic substitution of azide furnished **49**. The further classical synthetic steps involving azide reduction and cyclisation culminated in the natural product (-)-conhydrine **24b** (scheme 14).

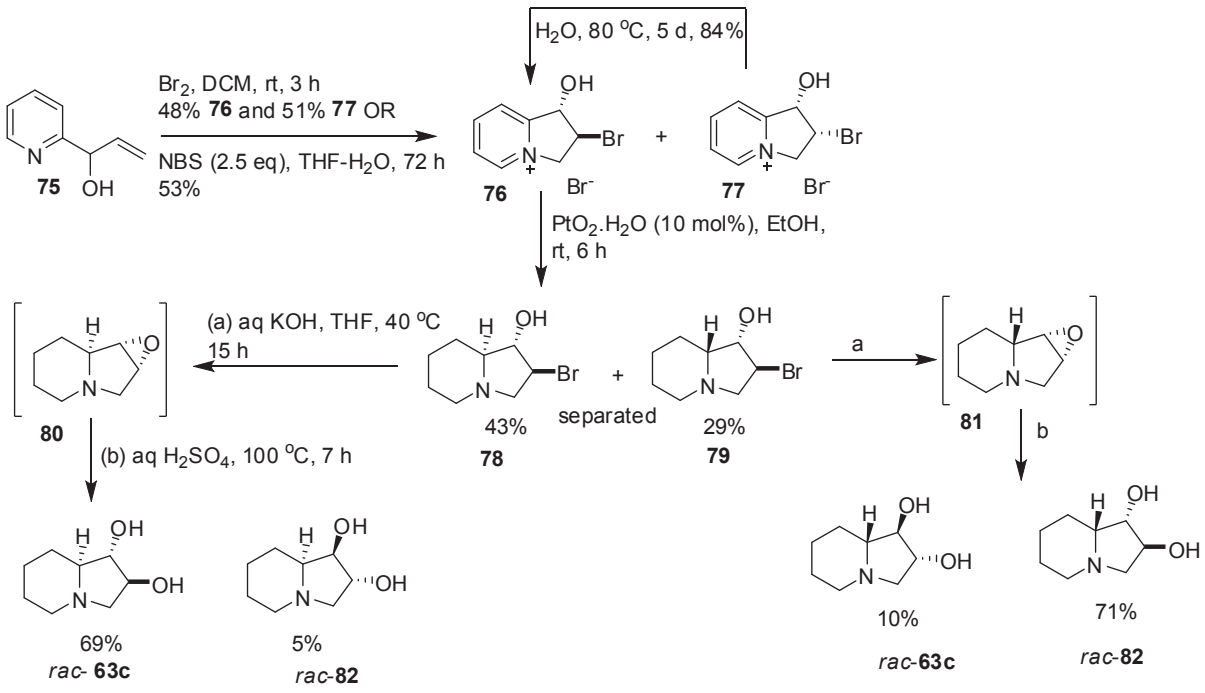
For the synthesis of (-)-lentiginosine **63a**, the aldehyde **52** prepared from D-mannitol[26b] was subjected to Barbier allylation reaction to give exclusively **53** (scheme 15).[21e]The tosylated compound **54** was converted to azide **55** and transformed to the key alkene **57**. The RCM on **57** using Grubbś I catalyst produced **58** which on subsequent hydrogenation afforded **59**. The acetal group was hydrolysed to diol **60** and converted to olefin **61** via oxidative cleavage and *in situ* Wittig reaction. The compound **61** was dihydroxylated to **62** and eventually transformed to (-)-lentiginosine **63**.



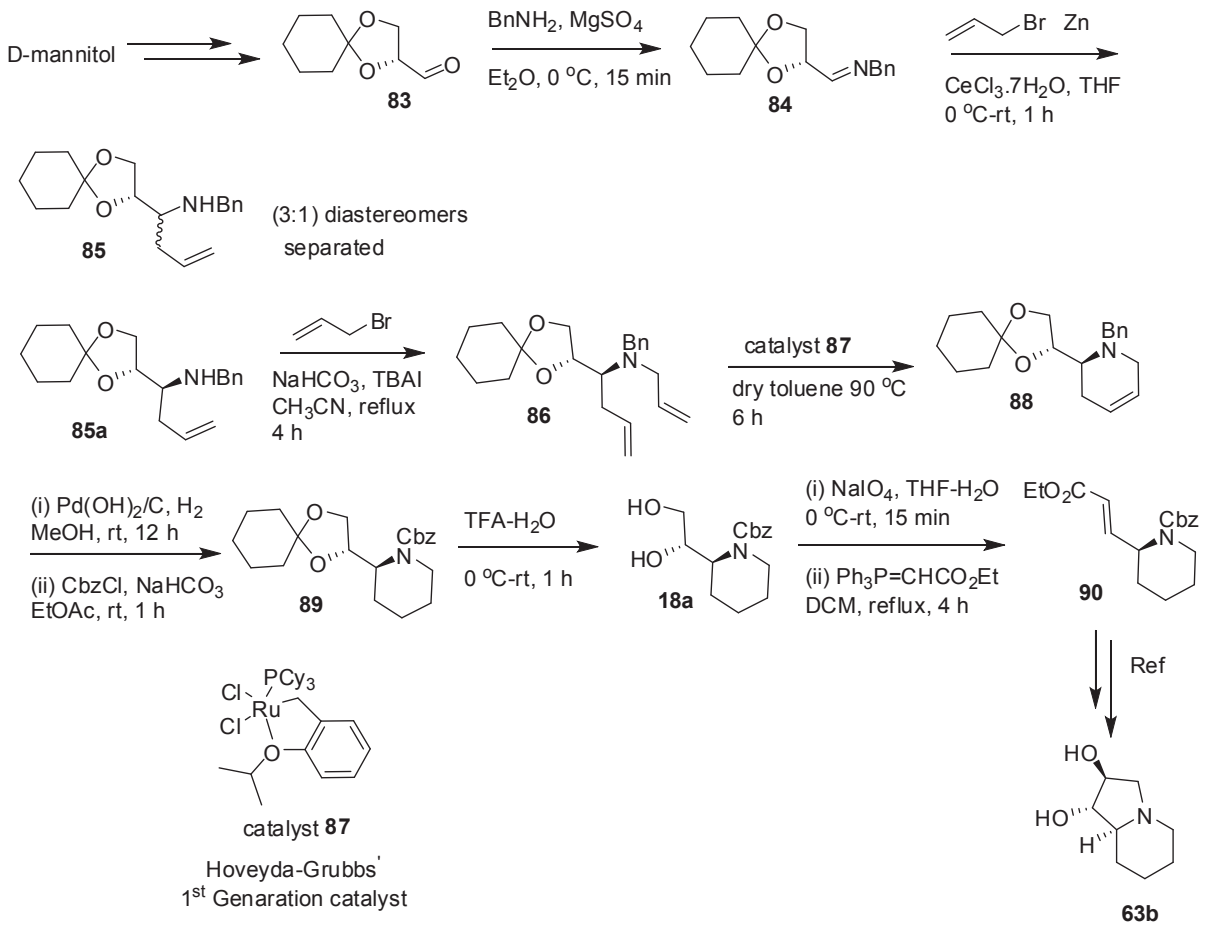
Scheme 16

***Reaction conditions*:** (a) TsCl, Et_3N, DCM, 0 °C; then NaN_3, dry DMF, 80 °C, 16 h, 80%; (b) $(COCl)_2$, DMSO, Et_3N, DCM, –78 °C, 1 h, 96%; (c) L-proline (25 mol%), PhNO, CH_3CN, –20 °C, 24 h; then MeOH, $NaBH_4$, 0 °C, 1 h; (d) $CuSO_4$ (30 mol%), MeOH, 12 h, 61%; (e) TBSCl, imidazole, DCM, 0 °C, 1 h, 95; (f) MsCl, Et_3N, DCM, 0 °C, 1 h; (g) 10% Pd/C, H_2 (20 psi), MeOH, Et_3N, 25 °C, 7 h; then $(Boc)_2O$, I_2 (10 mol%), 3 h, 76%; (h) TBAF, THF, 0 °C, 8 h, 92%; (i) $(COCl)_2$, DMSO, Et_3N, DCM, –78 °C, 1 h, 90%; (j) excess EtMgBr, Et_2O, –78 °C, 3 h, 87%; (k) TFA/DCM (1:1), 25 °C, 12 h, 86%.

Shaikh and Sudalai achieved the total synthesis of (-)-conhydrine **24b** using organocatalytic aminoxylation strategy (scheme 16).[21g] The aldehyde **66** prepared from synthetic conversion of **64** was subjected to aminoxylation using L-proline and PhNO in CH_3CN and reduced *in situ* to alcohol **67**. The compound **67** was transformed to **70** which on subsequent azide reduction underwent expected cyclisation to afford the key requisite **71**. The oxidation of alcoholic group to aldehyde, Gringnard addition and Boc deprotection afforded the natural product **24b**.


H2O, 80 °C, 5 d, 84%
Br2, DCM, rt, 3 h
48% 76 and 51% 77 OR
NBS (2.5 eq), THF-H2O, 72 h
53%
75
76
77
PtO2.H2O (10 mol%), EtOH, rt, 6 h
(a) aq KOH, THF, 40 °C 15 h
(b) aq H2SO4, 100 °C, 7 h
80
43%
78
separated
29%
79
a
b
81
69%
rac- 63c
5%
rac-82
10%
rac-63c
71%
rac-82

Scheme 17


D-mannitol
BnNH2, MgSO4
Et2O, 0 °C, 15 min
83
84
CeCl3.7H2O, THF
0 °C-rt, 1 h
85
(3:1) diastereomers separated
85a
NaHCO3, TBAI
CH3CN, reflux
4 h
86
catalyst 87
dry toluene 90 °C
6 h
88
(i) Pd(OH)2/C, H2
MeOH, rt, 12 h
(ii) CbzCl, NaHCO3
EtOAc, rt, 1 h
89
TFA-H2O
0 °C-rt, 1 h
18a
(i) NaIO4, THF-H2O
0 °C-rt, 15 min
(ii) Ph3P=CHCO2Et
DCM, reflux, 4 h
90
Ref
63b
catalyst 87
Hoveyda-Grubbs'
1st Genaration catalyst

Scheme 18

Recently Giomi *et al* furnished the total synthesis of racemic lentiginosine **63** and its isomer starting from a 2-substituted pyridine derivative (scheme 17).[25c]The bromination of **75** was achieved successfully using brominating source like Br_2 or NBS. The formation of **76** and **77** as an isomeric mixture was improved to produce only **76** after heating the mixture of **76** and **77** in water at 80 °C for 5 days. The pure compound **76** obtained as a black solid was effectively transformed to **78** and **79** by hydrogenation over $PtO_2.H_2O$ and separated. The treatment of **78** and **79** with aq KOH followed by acidification provided the racemic mixture (±)-lentiginosine **63c** and its isomer **82** respectively.

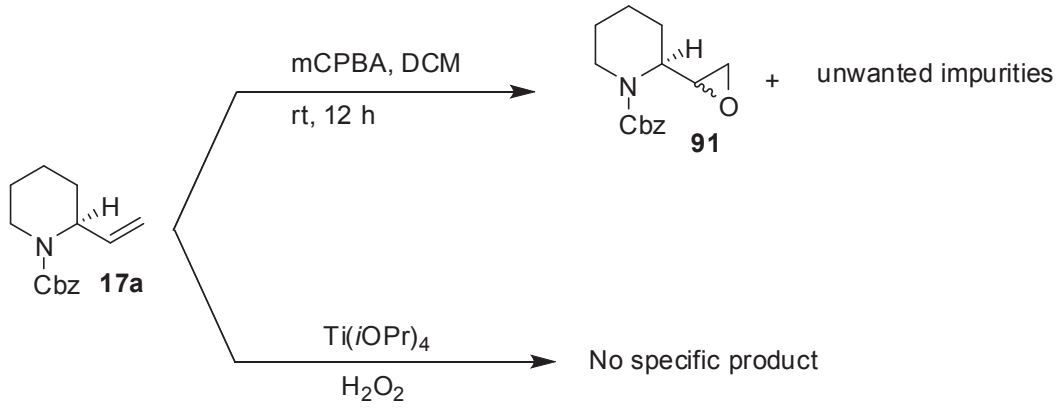
An elegant work disclosed by Vankar and co-workers involves a new tactic developed for RCM for the synthesis of (+)-lentiginosine **63b** (scheme 18).[25d]Initially the D-mannitol was converted to Schiff's base **83** and subjected to Barbier reaction using allyl bromide to afford a diastereomeric mixture **85** amenable to separation on column chromatography. The isomer **85a** was then alkylated to give **86**. Even though the initial small scale RCM on **86** using catalyst **87** was successful, the scaling up the reaction was not favourable in the usual reaction conditions. A different tactic developed involving the portion-wise addition of catalyst **87** in intervals throughout the reaction resulted the product in 94% yield. The compound **88** was then furthered to produce diol **18a** which was converted to alkene **90** through classical synthetic sequences. The synthesis of compound **90** constituted the formal synthesis of (+)-lentiginosine **63a**.

Results and Discussion

The present work involves an efficient utility of the intermediates produced during the synthesis of dexoxadrol (section 1) to encompass the formal synthesis of aforementioned alkaloids.

We envisaged that the epoxide **91b** could constitute the formal synthesis of (+)-α-conhydrine **24a** according to the work done by Moyano and co-workers.[21p] In this context, initially we tried to synthesize this by direct epoxidation of olefin **17a** using mCPBA. The reaction produced a mixture of diastereomers with several other spots shown on TLC plate making practically tedious for separation. The methods using H_2O_2/ Ti(O*i*Pr)$_4$ resulted in complex mixture without producing any product of interest after column chromatographic separation (scheme 19). We thought the reason may be due to the lability of the epoxide

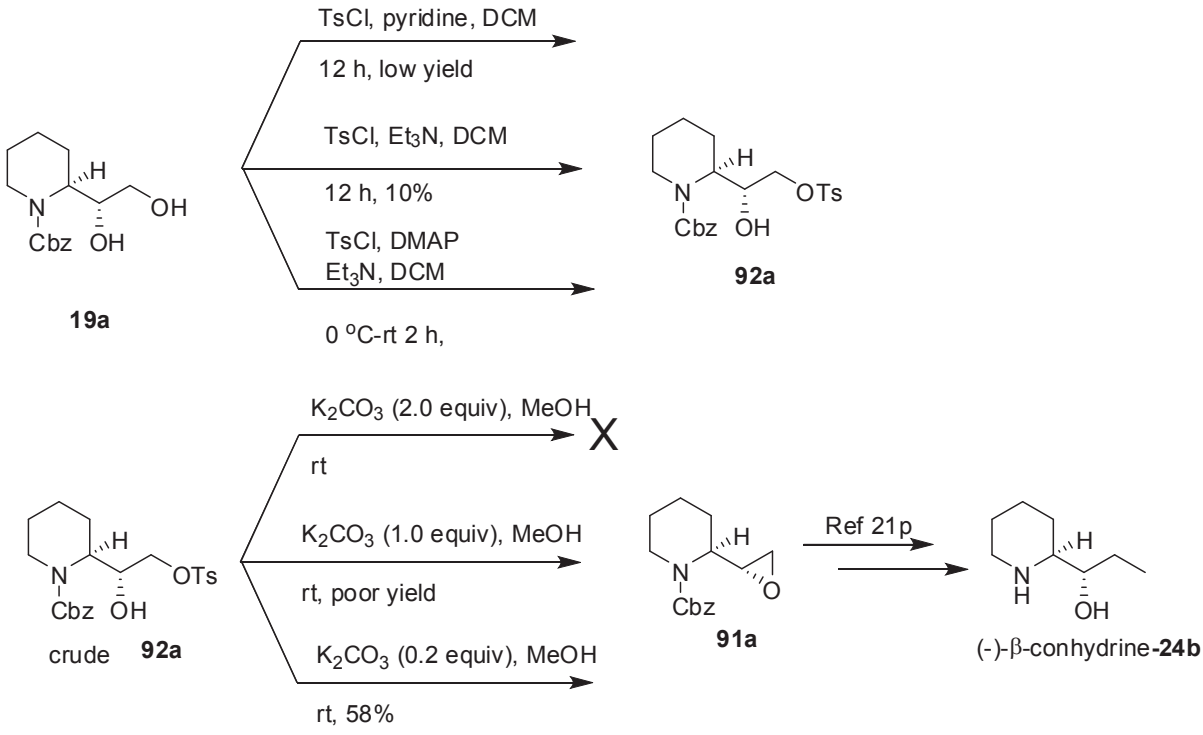
under the reaction conditions used. We probed an alternate method for the preparation of the requisite epoxide.



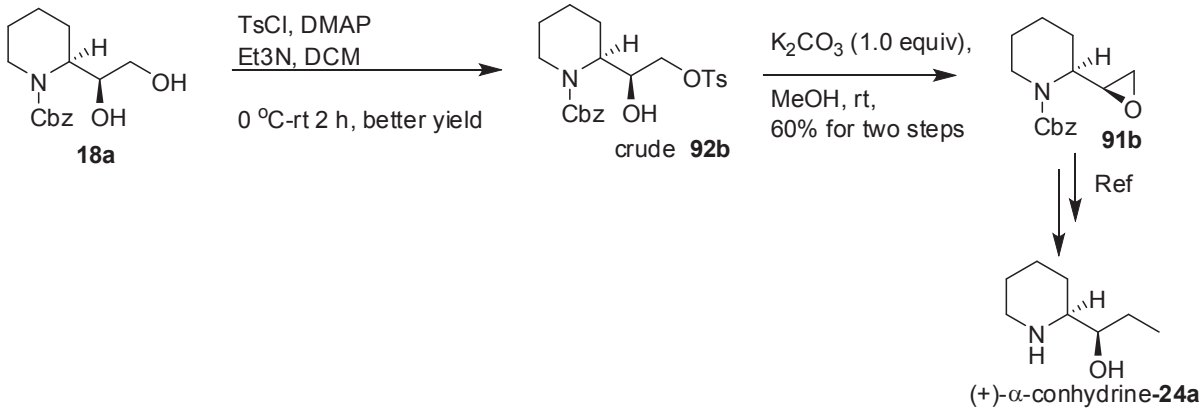
Scheme 19

This time the diol **19a** was subjected for monotosylation. Even though the synthesis of monotosylated compound **92a** looked to be simple and efficient, the initial sets of reactions in usual methods tried using different stochiometric ratio of pyridine and Et_3N resulted either the ditosylated product or poor yield with the starting material remaining unreacted. The different alternate methods tried for this did not produce any product. Most of the times we ended in substantial amount of ditosylated compound with a very less formation of the anticipated **92a**. Recently Zhu *et al* described the selective monotosylation for the synthesis of several antimalarial drugs.[27] Inspired by this, we adopted the exact procedure in our case. Initially the compound **19a**, being solid in nature was chosen for the standardisation of the reaction conditions. Accordingly, **19a** was treated with exactly 1.0 mmol of TsCl with 1.4 equiv. of Et_3N and cat. DMAP. The reaction mixture was further stirred for 2 h at rt. We were delighted to see the formation of essentially single spot corresponding to monotosylated compound. After the work up, the crude **93a** was treated with catalytic amount of K_2CO_3 (20 mol%) in MeOH. The pale low mobile spot obtained was separated and characterised by spectroscopic techniques to confirm the formation of the product **91a** (scheme 20).

The similar procedure was then repeated for the synthesis of another isomer **91b** from **18a**. But the use of catalytic amount of K_2CO_3 in the second step failed to effect the total consumption of the starting material. The same reaction was then tried with exact 1.0 equiv. of K_2CO_3 to produce the required product in 60% yield (scheme 21).



Scheme 20

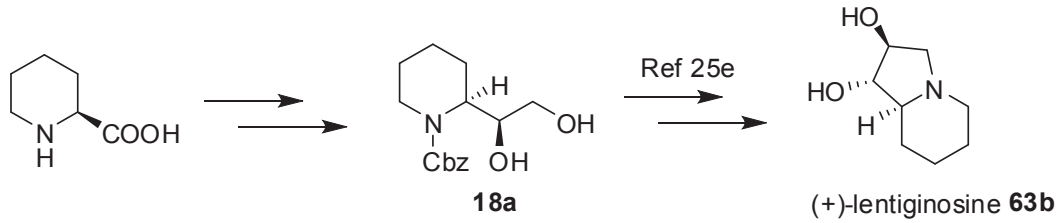


Scheme 21

The synthesis of oxiranes **91a** and **91b** constitute the formal synthesis of (-)-β-conhydrine **24b** and (+)-α-conhydrine **24a** respectively.

It was very interesting to note that recent synthetic work by Vankar and co-workers have accomplished the total synthesis of (+)-lentiginosine **63b** by synthesizing the protected diol **18a** by synthetic manoeuvring performed on chiral source D-mannitol.[25d] Our strategy which involves the synthesis of this diol **18a** from another chiral source (-)-pipecolic acid,

provides a straightforward route to this with lesser and efficient synthetic efforts. Thus we successfully approached the formal synthesis of (+)-lentiginosine **63b** (scheme 22).



18a (+)-lentiginosine **63b**

Scheme 22

Conclusion

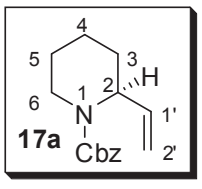
In summary the present chapter provides an asymmetric synthesis of NMDA receptor antagonist (+)-dexoxadrol and its *epi* isomer through SAD. Incidentally, this is the first asymmetric synthesis of (-)-*epi*dexoxadrol. Unusual diastereofacial selectivity during SAD of the terminal olefin of piperidine system was disclosed. This abnormal behaviour was tested for the present piperidine system with different protecting groups so as to study the effect of them on diastereoselectivity. The high selectivity obtained for the ethyl carbamate protected piperidine alkene system supported the Gardiner's view that the diastereofacial selectivity also depends on the bulkiness of the substituent present on the double bond.

Experimental Section:

4.01 Synthesis of benzyl (2*S*)-2-vinylpiperidine-1-carboxylate 17a

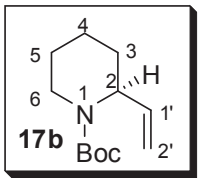
To a solution of $(COCl)_2$ (0.17 mL, 2 mmol) in DCM (10 mL) cooled to -78 °C was added DMSO (0.16 mL, 2.1 mmol) drop wise. It was then stirred at the same temperature for 15 min. The solution of **15** (0.25 g, 1 mmol) in DCM (5 mL) was added for the period of 10 min. The reaction mixture was warmed to -50 °C, added Et_3N (0.53 mL, 4 mmol) drop wise for 5 min and brought to rt in 1 h. The reaction mixture was diluted with DCM (5 mL), added 1 N HCl (10 mL) and the organic compound was extracted into DCM. The organic layer was further washed with 1 N HCl (10 mL X 2), the extracted organic layers were combined, dried over anhy. Na_2SO_4 and concentrated under reduced pressure to afford an essentially pure pale yellow liquid of **16** (0.24 g, 97%).

The commercially available salt $^{+}PPh_3CH_3Br^{-}$ (1.07 g, 3.0 mmol) was stirred at 0 °C with dry THF (10 mL) in a 3-necked 50 mL RBF under N_2 atm. sealed with a septum at one end. NaHMDS (0.15 mL, 1.5 mmol) was purged with the help of a syringe into the reaction mixture and appearance of the yellow colour was noticed. The stirring was continued for further 10 min and aldehyde **16** (0.24 g, 1 mmol) was added as earlier. The disappearance of the yellow colour was observed. The reaction mixture was then brought to rt and stirred for 2 h. It was concentrated in vacuo and quenched with aq. NH_4Cl (5 mL). The solution was diluted with DCM (25 mL) and the organic layer was separated. It was then washed with NH_4Cl solution (10 mL X 3) and dried over anhy. Na_2SO_4, concentrated under vacuum and purified by column chromatography (SiO_2, hexane: EtOAc, 9.5:1) to afford **17a** (0.22 g, 90%).

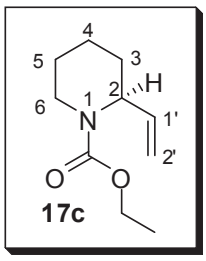


$[\alpha]_D^{28}$ -17.5 (c 0.2, $CHCl_3$); IR (neat): ν_{max} = 1690, 1675, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.45-1.80 (m, 6 H, H-4, H-5, H-3), 2.91-2.98 (m, 1H, H-6A), 4.06-4.09 (m, 1H, H-6B), 4.91-4.92 (m, 1H, H-2), 4.92-5.24 (m, 2H, H-2'), 5.17 (s, 2H, CH_2Ph), 5.76-5.84 (m, 1H, H-1'), 7.32-7.38 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.4 (C-4), 25.2 (C-5), 28.9 (C-3), 40.1 (C-6), 52.7 (C-2), 67.0 (*C*H_2Ph), 115.9 (C-2'), 127.7 (PhCH), 127.9 (PhCH), 128.5 (PhCH), 136.5 (C-1'), 136.9 (PhCH), 155.8 (N*C*O).

4.02 Similar procedure was repeated for the synthesis of **17b** and **17c** from the corresponding aldehydes.



Obtained as a pale yellow thicky iquid (70%); IR (neat): ν_{max} = 1700, 1670, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.18-1.69 (m, 6H, H-4, H-5, H-3), 1.38 (s, 9H, *t*Bu*H*), 2.72-2.79 (m, 1H, H-6A), 3.85-3.89 (m, 1H, H-6B), 4.70-4.71 (m, 1H, H-2), 5.04 (dd J= 58.8 & 10.4 Hz, 2H, H-2'), 5.64-5.72 (m, 1H, H-1'); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.4 (C-4), 24.5 (C-5), 27.4 (OC(CH_3)$_3$), 27.9 (C-3), 38.7 (C-6), 51.4 (C-2), 76.2 (CH_2Ph), 114.4 (C-2'), 135.8 (C-1'), 154.4 (N*C*O).



Obtained as a pale yellow thicky iquid (68%); IR (neat): ν_{max} = 1695, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.18 (t J=7.2 Hz, 3H, OCH_2CH_3), 1.32-1.1.71 (m, 6H, H-4, H-5, H-3), 2.77-2.84 (m, 1H, H-6A), 3.91-3.95 (m, 1H, H-6B), 4.04-4.09 (m, 2H, OCH_2CH_3), 4.70-4.80 (m, 1H, H-2), 4.97-5.14 (m, 2H, H-2'), 5.65-5.74 (m, 1H, H-1'); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.7 (OCH_2CH_3), 19.4 (C-4), 25.5 (C-5), 28.8 (C-3), 39.8 (C-6), 52.5 (C-2), 61.2 (OCH_2CH_3), 115.8 (C-2'), 136.6 (C-1'), 155.1 (N*C*O).

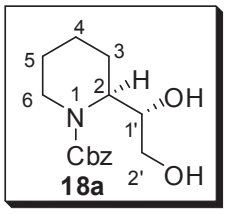
4.03 Procedure for SAD of 17 for the synthesis of 18 and 19

Preparation of AD-mix α: Prepared by premixing K_2CO_3 (0.41 g, 3 mmol), $K_3Fe(CN)_6$ (0.98 g, 3 mmol), $CH_3SO_2NH_2$ (0.28 g, 3 mmol), $K_2OsO_4.2H_2O$ (4 mol%), Ligand [$(DHQ)_2PYR$/ $(DHQ)_2AQN$/ $(DHQ)_2PYR$] (10 mol%).

Preparation of AD-mix β: Prepared by premixing K_2CO_3 (0.41 g, 3 mmol), $K_3Fe(CN)_6$ (0.98 g, 3 mmol), $CH_3SO_2NH_2$ (0.28 g, 3 mmol), $K_2OsO_4.2H_2O$ (4 mol%), Ligand [$(DHQD)_2PYR$/ $(DHQD)_2AQN$/ $(DHQD)_2PYR$] (10 mol%).

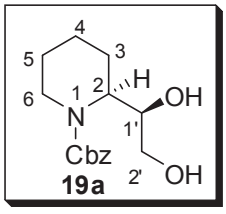
A solution of AD-mix α/ AD-mix β in 10 mL *t*-BuOH: H_2O (1:1) was stirred for 30 min at rt. The reaction mixture was cooled to 0 °C, added requisite alkene **17** (1 mmol) in 1 mL *t*BuOH and the stirring was continued for 30 min at the same temperature. It was then brought to rt and further stirred till the completion of reaction indicated by TLC. The reaction mixture was then quenched by saturated Na_2SO_3 (5 mL) and extracted with EtOAc (15 mL X 2). The combined organic layer was dried over anhy. Na_2SO_4, concentrated and subjected to column chromatography to remove the impurities without separating the isomers **18** & **19** (Silica gel, 100% EA). The diastereomeric mixture was then subjected to HPLC to find the diastereomeric ratio of **18** & **19** (Chromacil, eluent

IPA/*n*-hexane, 2:8). The separation of diastereomers **18** & **19** was then achieved by very slow elution through column chromatography (SiO_2, hexane: EtOAc, 7:3).



18a

$[\alpha]_D^{28}$ -22.5 (c 0.07, $CHCl_3$); IR (neat): ν_{max} = 3500, 1699, 1650, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.43-1.66 (m, 6H, H-5, H-4, H-3), 2.19 (br s, 1H, -OH), 2.70-2.76 (m, 1H, H-6A), 3.10 (br s, OH), 3.48-3.51 (m, 1H, H-6B), 3.59-3.62 (m, 1H, H-2), 3.72-3.83 (m, 1H, H-1'), 4.06-4.12 (m, 2H, H-2'), 5.11-5.20 (m, 2H, C*H*$_2$Ph), 7.33-7.40 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.9 (C-4), 24.2 (C-5), 25.1 (C- 3), 40.9 (C-6), 50.1 (C-2), 62.5 (C-2'), 67.7 (*C*H$_2$Ph), 67.8 (C-1'), 127.1 (PhCH), 128.1 (PhCH), 129.0 (PhCH), 136.1 (PhC), 155.1 (N*C*O).



19a

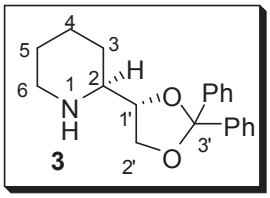
$[\alpha]_D^{28}$ -17.4 (c 0.05, $CHCl_3$); IR (neat): ν_{max} = 3400, 1699, 1650, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.46-1.68 (m, 6H, H-5, H-4, H-3), 2.90-3.11 (br s, 2H, -OH), 3.50-3.61 (m, 1H, H-6A), 3.73-3.76 (m, 1H, H-6B), 3.99-4.01 (m, 1H, H-2), 4.01-4.20 (m, 2H, H-2'), 4.30-4.32 (m, 1H, H-1'), 5.16 (s, 2H, C*H*$_2$Ph), 7.33-7.37 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.6 (C-4), 25.0 (C-5), 25.9 (C-3), 40.7 (C-6), 51.2 (C-2), 64.3 (C-2'), 67.4 (*C*H$_2$Ph), 71.1 (C-1'), 127.8 (PhCH), 128.0 (PhCH), 128.5 (PhCH), 136.6 (PhC), 155.5 (N*C*O).

4.04 Synthesis of (+)-dexoxadrol 3 and (-)-*epi*dexoxadrol 4

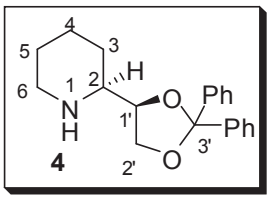
To a solution of **18a** (0.28 g, 1 mmol) in EtOH (10 mL) was added 10% Pd/C (0.028 g, 10% w/W) and hydrogenated using Parr hydrogenator at rt. The solution was filtered and concentrated under reduced pressure to afford essentially pure **21** (0.13 g, 95%).

To a refluxing solution of **21** (0.14 g, 1 mmol) in IPA with PTSA (cat), was added dimethoxybenzophenone (1.61 g, 7 mmol) and refluxed further for 1 h. The reaction mixture was cooled, concentrated and as such subjected to column purification to give pure **3** (SiO_2, hexane: EtOAc, 7:3) (0.18 g, 60%). To the compound **3** (0.31 g, 1 mmol) in EtOAc (5 mL), passed dry HCl gas liberated from the reaction of conc. H_2SO_4 over NaCl. The reaction mixture was concentrated to dryness to give pure **3**. HCl (0.27 g, 80%).

Similar procedure was followed for the synthesis of (-)-*epi*dexoxadrol **4.**



$[\alpha]_D^{26}$ +34.5 (c 0.05, MeOH) (of HCl salt); IR (neat): ν_{max} = 3330 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.10-1.13 (m, 1H), 1.27–1.49 (m, 3H), 1.60–1.63 (m, 1H), 1.72–1.75 (m, 2H), 1.82–1.85 (m, 1 H), 2.59-2.65 (m, 1 H), 2.85-2.88 (m, 1 H), 3.09-3.12 (br d, *J* = 11.6 Hz, 1 H), 3.94-3.97 (m, 1 H), 4.09-4.10 (m, 1 H), 4.14-4.15 (m, 1H), 7.28–7.37 (m, 6 H), 7.48–7.50 (m, 2 H), 7.54–7.55 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 26.1, 28.1, 46.5, 57.9, 65.9, 79.3, 109.5, 126.1, 126.2, 128.0, 128.2, 141.9, 142.1.

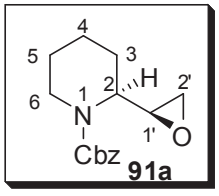


$[\alpha]_D^{26}$ -72.5 (c 0.04, $CHCl_3$) (of HCl salt); IR (neat): ν_{max} = 3330 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.14-1.17 (m, 1H), 1.25-1.35 (m, 1H), 1.36-1.51 (m, 2H), 1.60-1.63 (m, 1H), 1.78-1.81 (m, 1H), 2.39 (br s, 2H), 2.59-2.65 (m, 2H), 3.11-3.14 (m, 1H), 3.85 (br s, 1H), 4.04 (s, 2H), 7.28-7.33 (m, 6H), 7.49-7.54 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.9, 25.6, 27.9, 46.2, 59.9, 67.3, 80.1, 109.8, 126.1, 126.3, 128.0, 128.1, 128.2, 142.0, 142.3.

4.06 Synthesis of 91a

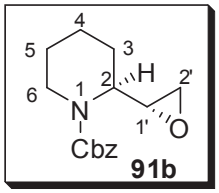
To a mixture of **18a** (0.26 g, 1 mmol), Et_3N (0.2 mL, 1.4 mmol) and DMAP (0.007 g, 0.06 mmol) in DCM (10 mL) was added TsCl (1 mmol) at 0 °C. The reaction mixture was brought to rt in 30 min and further stirred for 2 h at rt. It was then diluted with DCM (20 mL), washed with saturated $NaHCO_3$ (10 mL X 3) and 1 N HCl (10 mL X 3). The combined organic layer was dried over anhy. Na_2SO_4 and concentrated under reduced pressure to give essentially pure monotosylate **92a**. The crude compound **92a** was stirred in MeOH (10 mL) at rt, added K_2CO_3 (0.03 g, 0.2 mmol). The reaction mixture was further stirred for 30 min and then concentrated to dryness. It was diluted with DCM (25 mL), washed with H_2O and saturated aq. $NaHCO_3$ (15 mL X 3). The organic layer was dried over anhy. Na_2SO_4 and purified by column chromatography (SiO_2, hexane: EtOAc, 9:1) to afford **91a** (0.15 g, 58%).

Similar procedure was repeated for the synthesis of **91b** (60%).



$[\alpha]_D^{28}$ -30.3 (c 0.04, $CHCl_3$); IR (neat): ν_{max} = 1700, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.58-1.75 (m, 6H, H-4, H-5, H-3), 2.65-2.67 (m, 1H, H-6A), 2.95-3.01 (m, 1H, H-6B), 3.08-3.11 (m, 1H, H-2),

3.80-4.03 (m, 1H, H-2'A), 4.23-4.30 (m, 1H, H-2'B), 4.62-4.63 (m, 1H, H-1'), 5.01-5.08 (m, 2H, $PhCH_2$), 7.19-7.30 (m, 5H, PhH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7 (C-4), 24.2 (C-5), 30.4 (C-3), 41.3 (C-6), 54.2 (C-2), 69.0 (C-2'), 71.9 (*C*H_2Ph), 76.5 (C-1'), 127.9 (PhCH), 128.0 (PhCH), 128.6 (PhCH), 128.7 (PhCH), 129.0 (PhCH), 136.8 (PhC), 144.5, 155.8 (NCO) (some extra signals are observed due to the presence of rotamers).

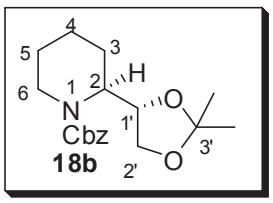


91b

$[\alpha]_D^{28}$ -25.0 (c 0.05, $CHCl_3$); IR (neat): ν_{max} = 1700, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.17-1.84 (m, 6H, H-4, H-5, H-3), 2.43 (br s, 1H), 2.65-2.66 (m, 1H), 2.94-2.98 (m, 1H), 3.05-3.08 (m, 1H), 3.99-4.02 (m, 1H), 4.20-4.23 (m, 1H), 4.62 (s, 1H), 5.04 (s, 1H), 7.23-7.28 (5H, PhH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2 (C-4), 25.1 (C-5), 27.5 (C-3), 41.5 (C-6), 44.5 (C-2'), 53.4 (C-1'), 65.3 (C-2'), 67.1 (*C*H_2Ph, C-1'), 126.9 (PhCH), 127.6 (PhCH), 127.8 (PhCH), 127.9 (PhCH), 128.5 (PhCH), 136.8 (PhC), 155.8 (NCO) (some extra signals are observed due to the presence of rotamers).

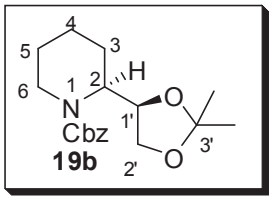
4.07 Synthesis of diol protected compounds 18b and 19b.

To a cooled mixture of diol **18a** (**19a**) (0.28 g, 1 mmol) and PTSA (10 mol%, 0.02 g) in DCM (15 mL), was added 2, 2-dimethoxypropane (0.15 mL, 1.2 mmol). The reaction mixture was brought to rt and stirred further for 12 h. It was then washed with sat. $NaHCO_3$ (10 mL X 3), dried over anhy. Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography (SiO_2, hexane: EtOAc, 9.5:0.5) to give **18b** (**19b**) as a colourless thick liquid (0.29, 90%).



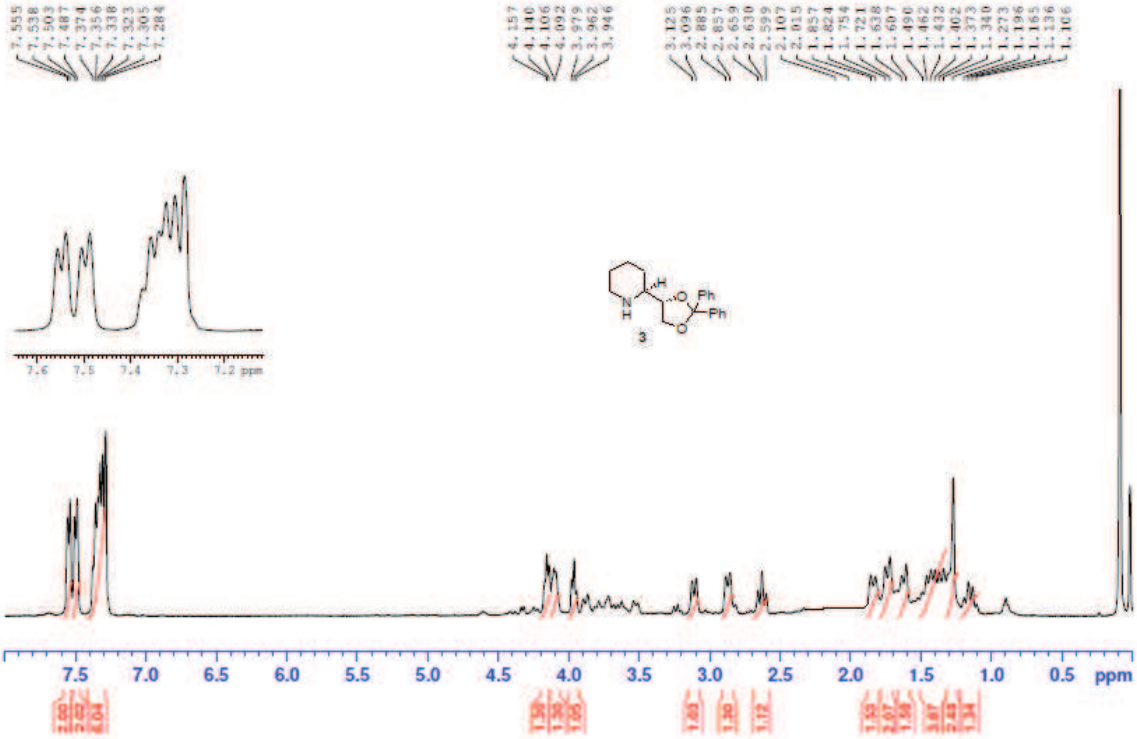
18b

$[\alpha]_D^{28}$ -20.3 (c 0.18, $CHCl_3$); IR (neat): ν_{max} = 1700, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.35 (s, 6H, 2 X C*H*$_3$), 1.37-1.68 (m, 6H, H-4, H-5, H-3), 3.01-3.09 (m, 1H, H-6A), 3.61-3.70 (m, 1H, H-6B), 4.03-4.06 (m, 1H, H-2), 4.15-4.18 (m, 1H, H-2'A), 4.20-4.29 (m, 1H, H-2'B), 4.40-4.46 (m, 1H, H-1'), 5.15 (s, 2H, CH_2Ph), 7.31-7.37 (m, 5H, PhH); ^{13}C NMR (100 MHz, $CDCl_3$): 18.9 (C-4), 24.7 (C-5, C-3), 25.7 (CH_3), 26.8 (CH_3), 39.9 (C-6), 53.2 (C-2), 67.8 (*C*H_2Ph), 77.3 (C-1'), 109.6 (C-3'), 127.8 (PhCH), 128.0 (PhCH), 128.5 (PhCH), 136.7 (PhC), 155.4 (N*C*O) (some extra signals are observed due to the presence of rotamers).



$[\alpha]_D^{28}$ -23.6 (c 0.07, $CHCl_3$); IR (neat): ν_{max} = 1698, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.37 (s, 6H, $2XCH_3$), 1.41-2.02 (m, 6H, H-4, H-5, H-3), 2.80-2.90 (m, 1H, H-6A), 3.70-3.90 (m, 1H, H-6B), 3.90-4.01 (m, 1H, H-2), 4.10-4.35 (m, 2H, H-2'), 4.38-4.43 (m, 1H, H-1'), 5.14 (s, 1H, C*H*$_2$Ph), 7.31-7.37 (m, 5H, PhCH); ^{13}C NMR (100 MHz, $CDCl_3$): 18.9 (C-4), 25.6 (C-5), 25.7 (CH3), 26.4 (CH3), 26.8 (C-3), 41.1 (C-6), 52.5 (C-2), 67.0 (C-2'), 67.3 (CH_2Ph), 74.5 (C-1'), 109.5 (C-3'), 127.7 (PhCH), 127.8 (PhCH), 128.0 (PhCH), 128.4 (PhCH), 128.5 (PhCH), 136.9 (PhC), 155.9 (NCO) (extra signals are observed due to the presence of rotamers).

Spectra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7.356
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7.284
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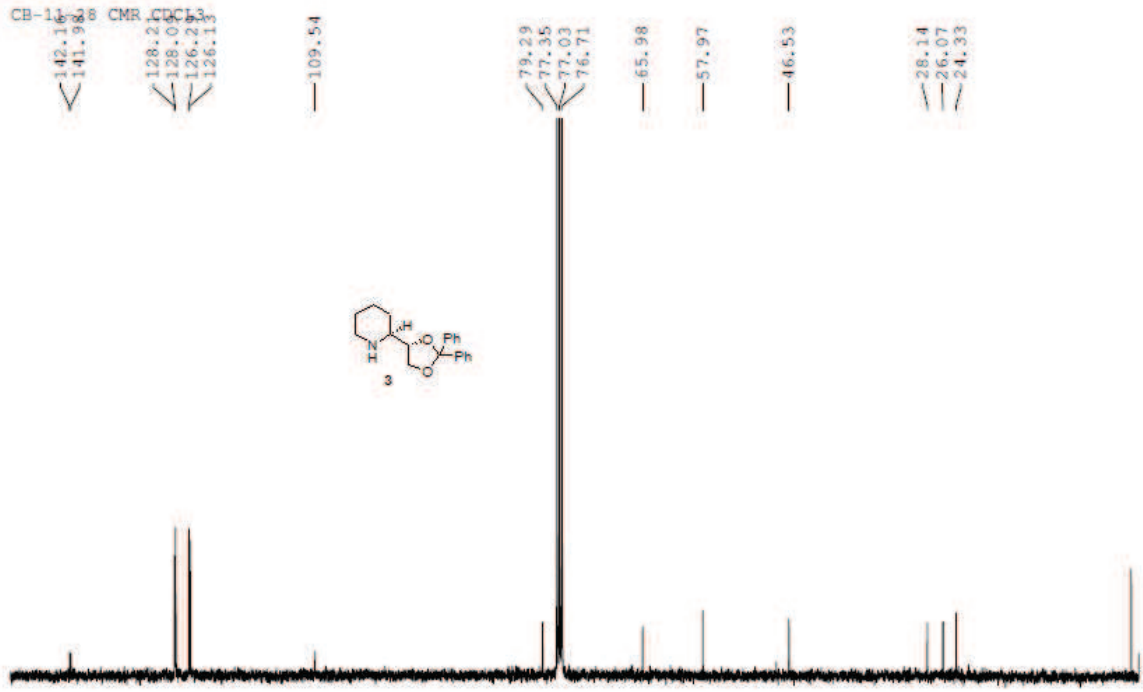
4.092
3.979
3.962
3.946
3.125
3.096
2.885
2.857
2.659
2.630
2.599
2.107
2.015
1.857
1.824
1.754
1.721
1.638
1.607
1.490
1.462
1.432
1.402
1.373
1.340
1.273
1.196
1.165
1.136
1.106
7.6
7.5
7.4
7.3
7.2 ppm
Ph
Ph
3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


CB-11-28 CMR CDCl3
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141.98
128.21
128.05
126.29
126.13
109.54
79.29
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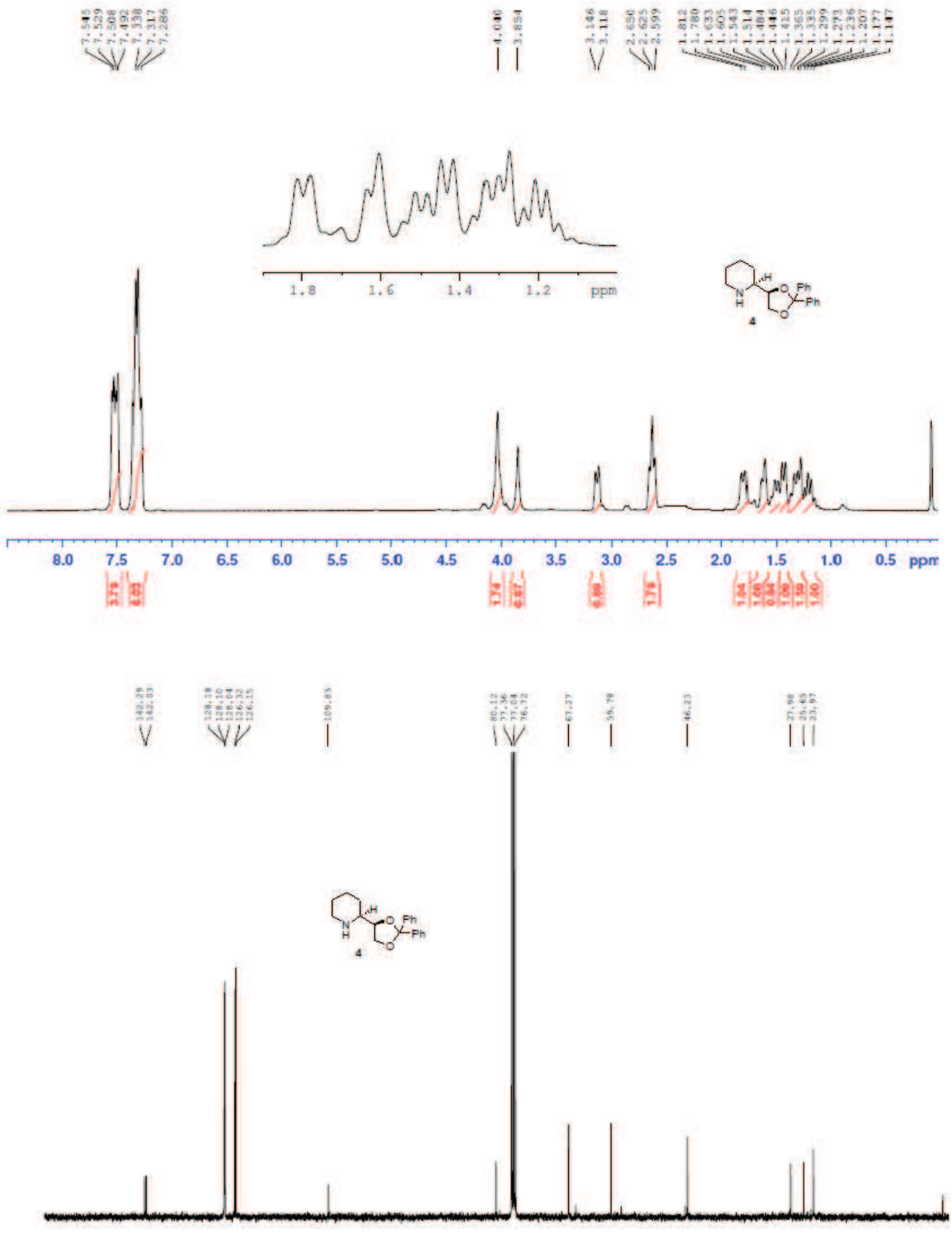
77.03
76.71
65.98
57.97
46.53
28.14
26.07
24.33
Ph
Ph
3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3.146
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2.625
2.599
1.812
1.780
1.633
1.605
1.543
1.514
1.484
1.446
1.415
1.365
1.335
1.299
1.273
1.236
1.207
1.177
1.147
1.8
1.6
1.4
1.2
ppm
Ph
Ph
4
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
142.29
142.03
128.18
128.10
128.04
126.32
126.15
109.85
80.12
77.36
77.04
76.72
67.37
59.79
46.23
27.98
25.65
23.97
Ph
Ph
4

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CHAPTER 5

New Approaches towards Fagomine and its Isomers

New Approaches towards Fagomine and its Isomers

Introduction

Polyhydroxy piperidines, also called as aza sugars, have been the active targets for the synthetic discoveries since they mimic best with the sugar molecules in terms of their various biological activities by binding with the active sites of glycosidase inhibitors.[1] These classes of compounds were found to display remarkable medicinal applications as they are used in the treatment of broad range of diseases including cancer, diabetes, AIDS and viral infections.[2] As a consequence, various polyhydroxy piperidine derivatives have been synthesized and exploited[3] for their several biological studies. 1, 2-Dideoxy azasugars are notable representatives of natural components of this class of compound and constitute an important family of glycosidase inhibitors (fig. 1). D-fagomine **1**, (2*R*, 3*R*, 4*R*)-2-hydroxymethylpiperidine-3, 4-diol, and its congeners are attractive members of this family from the synthetic stand point of view. D-Fagomine **1** was first isolated in 1974 from the Japanese buckwheat seeds of *Fagopyrum esculentum* Moench.[4] It was also found in the seeds of *Castanospermum australe.*[5] D-Fagomine **1** is mainly known for its potent antihyperglycemic effect in streptozocin-induced diabetic mice and activates the release of immunoreactive insulin.[6] The slight variation in the structure of fagomine led to the difference in biological behaviour, as for example, unnatural 4-*epi*-fagomine **2** is a reactive inhibitor of β-galactosidases and isomaltase than D-fagomine **1** but inactive towards α-galactosidase.

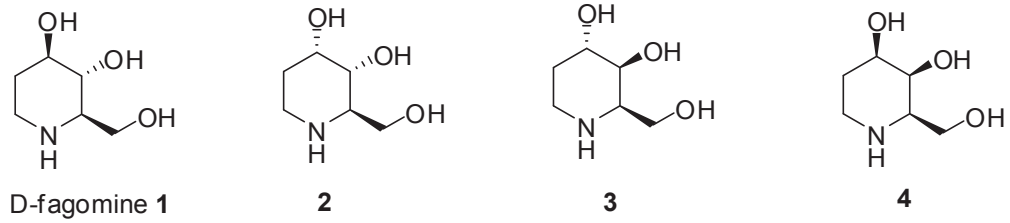
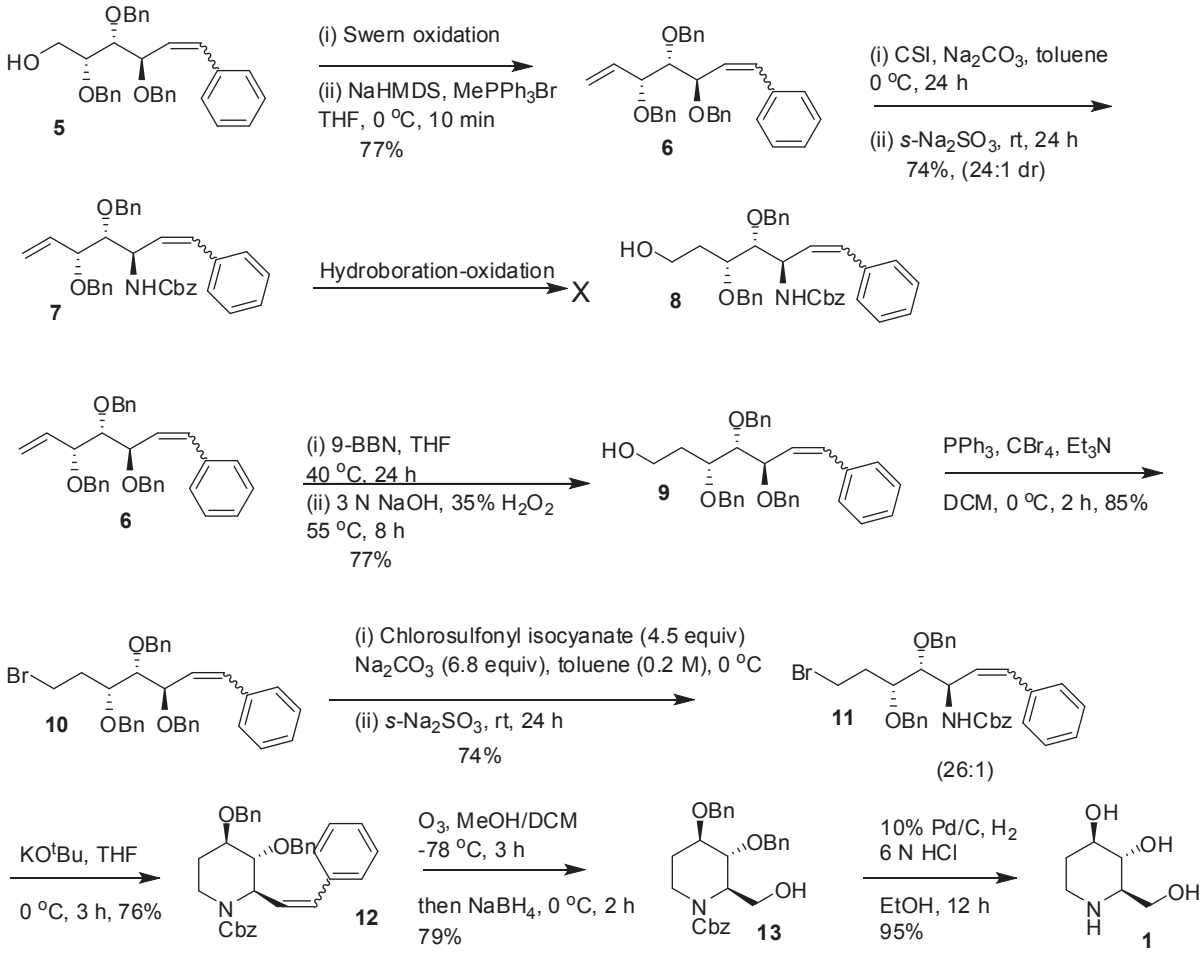


Figure 1. D-fagomine and its isomers

Literature Review

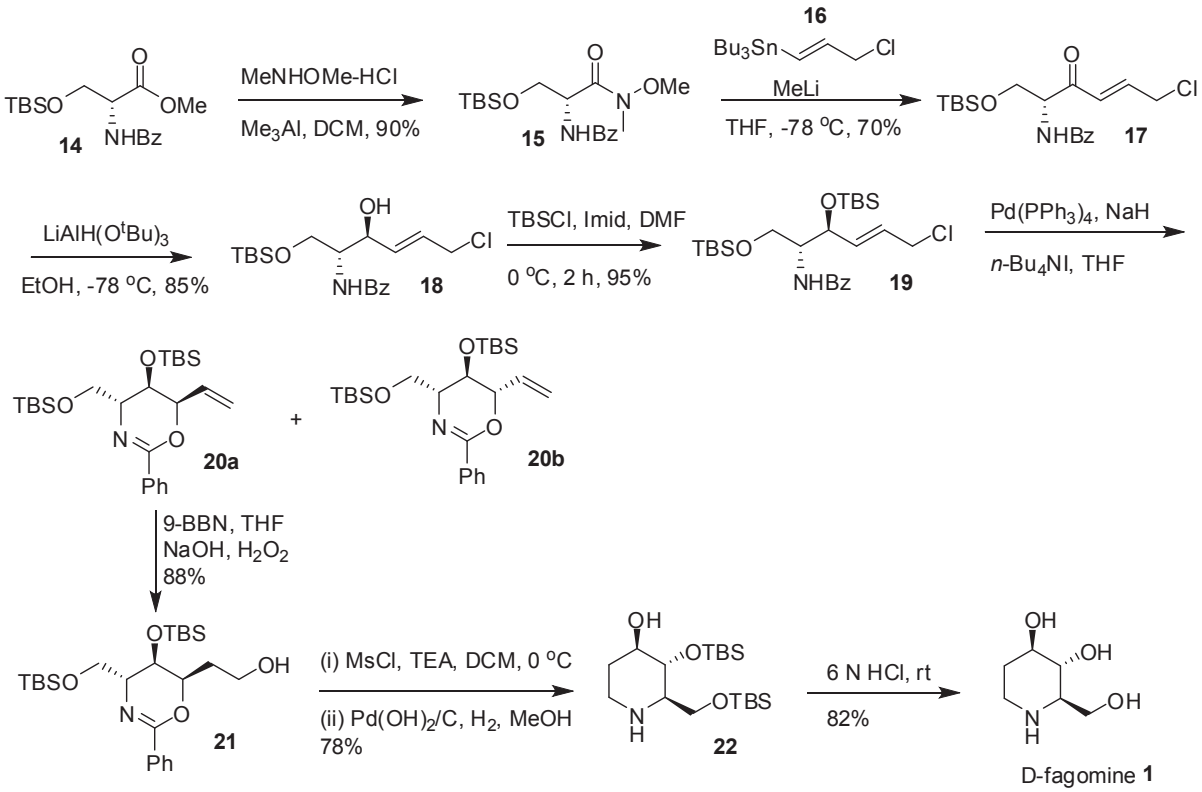
D-fagomine **1** and its isomers have attracted considerable synthetic interest due to their potent biological activities. Numerous reports are available for the synthesis of these compounds[7] and very few recent syntheses are described below.



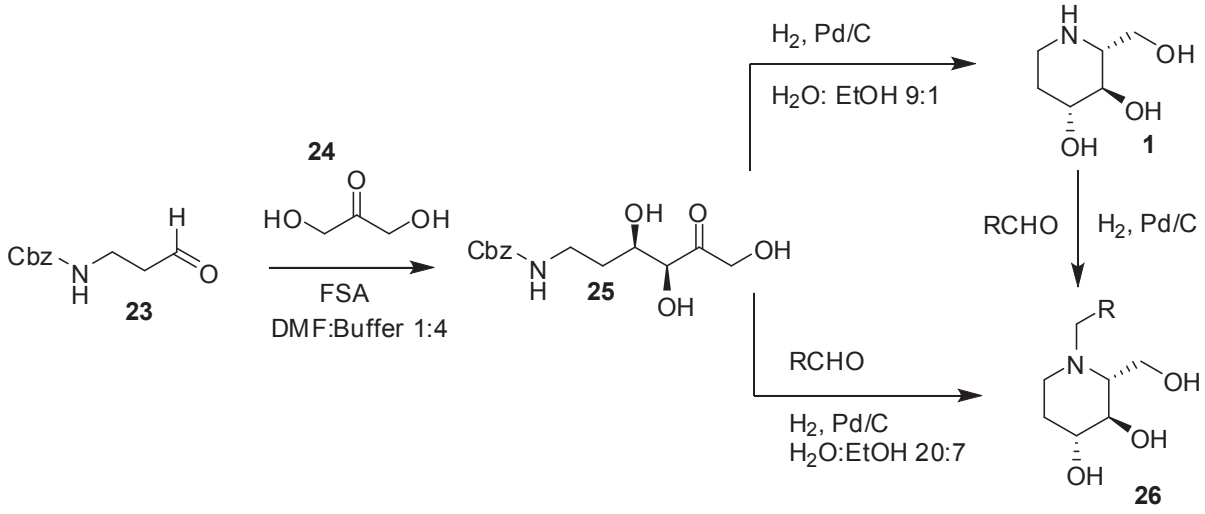
Scheme 1

Jung and co-workers achieved the total synthesis of D-fagomine **1** using diastereoselective amination of chiral ether (scheme 1).[7a]The compound **5** prepared from D-xylose was converted to **7** through chiral amination. The various conditions tried for the hydroboration-oxidation of olefin **7** failed to produce **8**. As an alternate, the compound **6** was when subjected to the same reaction condition underwent expected hydroboration-oxidation affording **9**. The Apple reaction on **9** smoothly furnished **10**. Several conditions were tried for chiral amination of **9** and it was best effected with CSI/Na_2CO_3/*solid*-Na_2SO_3 in toluene to afford exclusively **11** (26:1). The compound **11** on intramolecular cyclization, reductive ozonolysis and deprotection of Cbz group furnished the synthesis of D-fagomine **1**.

Kim *et al*. successfully synthesized D-fagomine **1** through palladium catalyzed stereoselective formation of oxazine (scheme 2).[7e]The requisite precursor **18** was synthesized from L-serine according to the reported procedure. Before subjecting compound **18** to cyclisation, the secondary OH was protected with TBS group. It was observed that the bulky TBS group best affected the diastereoselectivity during $Pd(PPh_3)_4$ catalysed intramolecular cyclisation to furnish **20** (**20a**:**20b**/30:1). The configuration of each was independently established by spectroscopic techniques. The pendant vinyl group of oxazine **20a** was further elaborated to give alcohol **21** on hydroboration-oxidation using 9-BBN. The terminal OH of **21** was mesylated and subjected to hydrogenation to afford exclusively **22** which on subsequent deprotection of TBS groups furnished the natural product **1**.



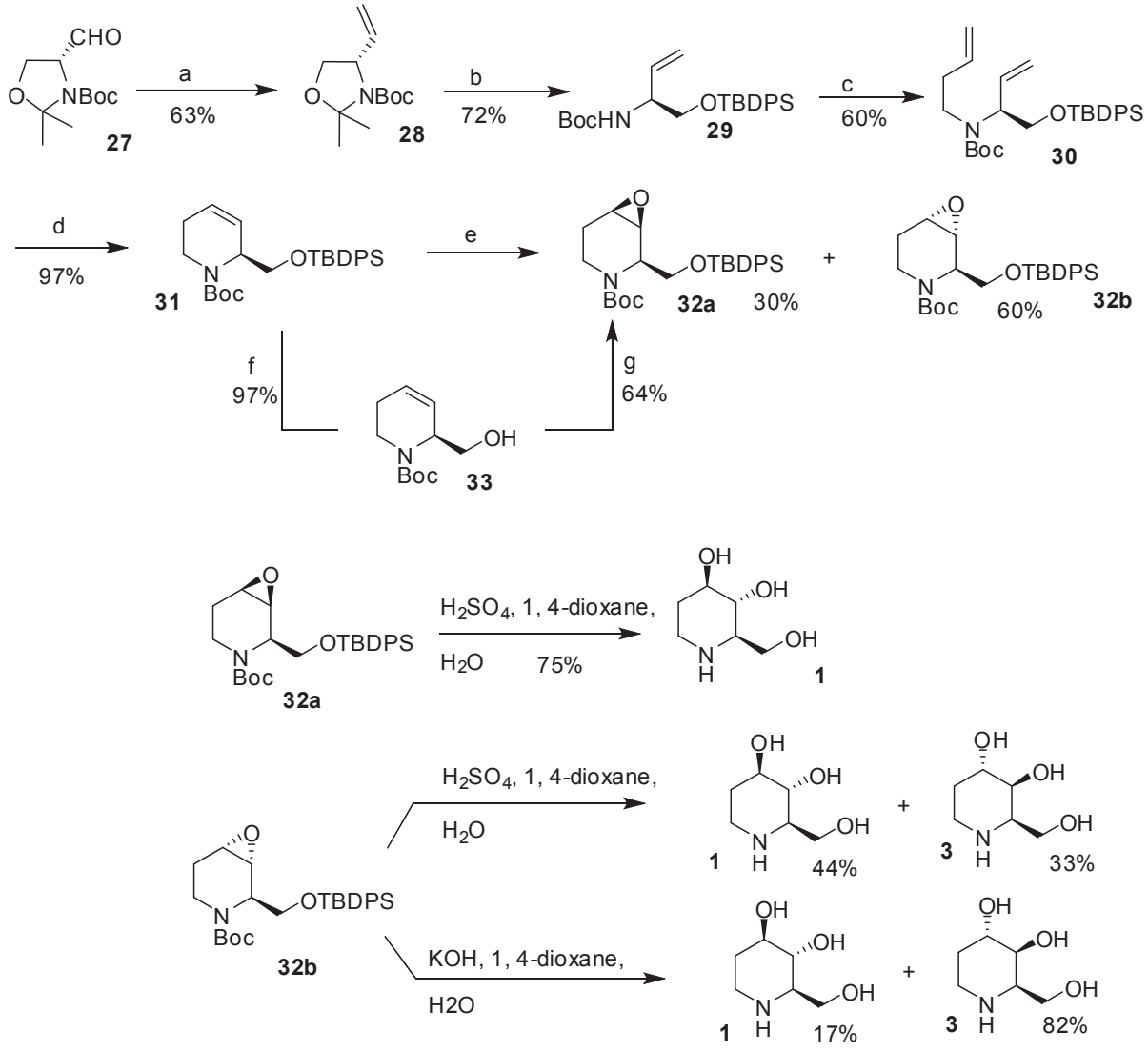
Scheme 2



R	Isolated yield
$CH_3(CH_2)_2$-; **a**	47%
$CH_3(CH_2)_4$-; **b**	40%
$CH_3(CH2)_6$-; **c**	54%
$CH_3(CH_2)_7$-; **d**	40%
$CH_3(CH_2)_{10}$-; **e**	57%
$PhCH_2$-; **f**	23%

Scheme 3

A two-step chemoenzymatic synthesis of D-fagomine **1** was demonstrated by Joglar and co-workers (scheme 3).[71] The synthesis involves the FSA (D-Fructose-6-phosphate aldolase) catalysed aldol addition of dihydroxy acetone (DHA) **24** to **23** to give enentiomerically & diastereomerically **25**. This pivotal aldol reaction was successfully conducted at 4 °C and in a buffer medium containing 20% v/V DMF and pH of 7. The synthesis of D-fagomine **1** was then furnished in 89% yield with 93:7 diastereomeric ratios by reductive amination of **25** under catalytic hydrogenation condition. Different *N*-alkylated compounds **26** (**a**-**f**) were also prepared and studied for antimicrobial activities.

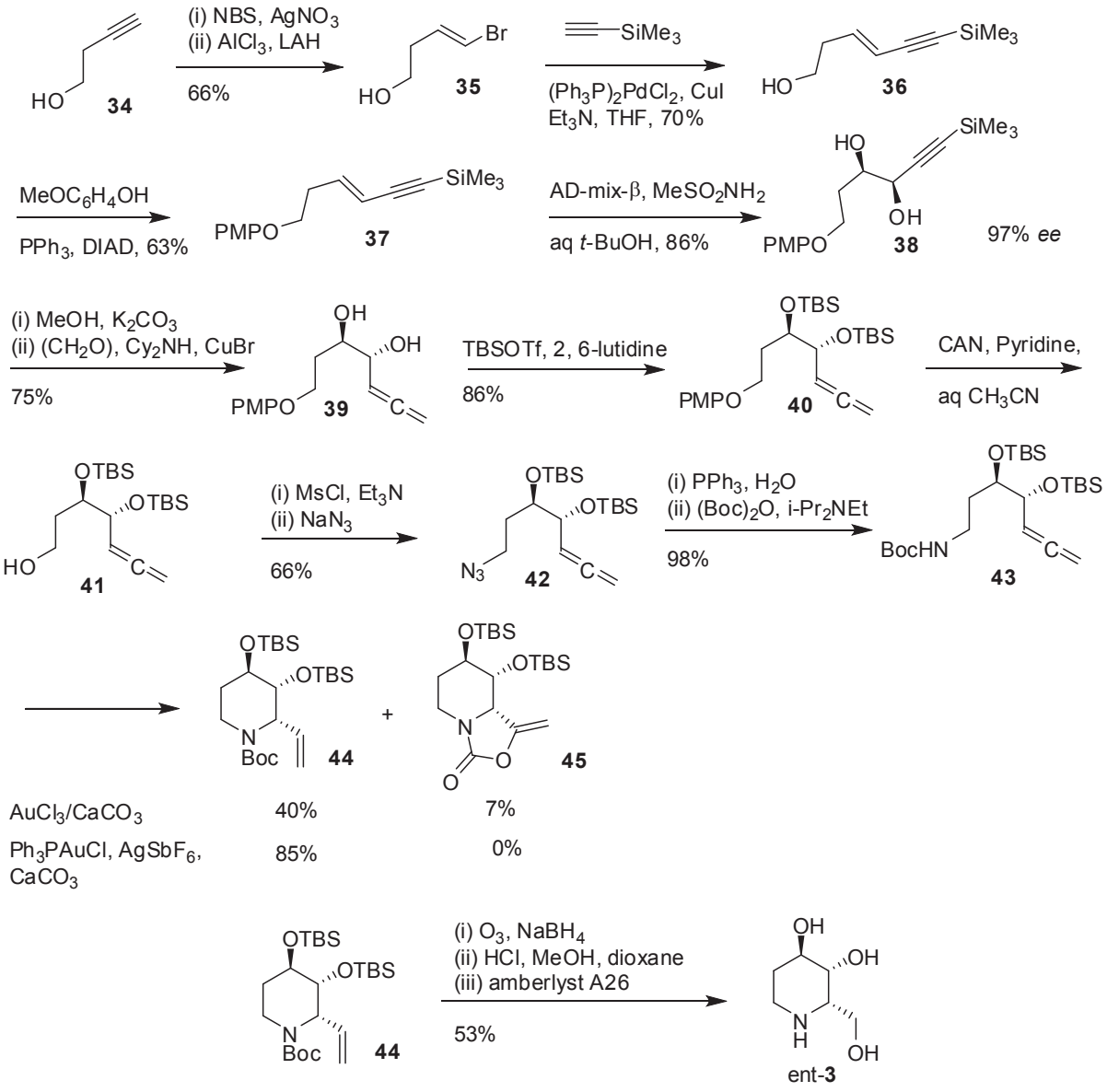


Scheme 4

Reagents and conditions: (a) $Ph_3P^+CH_3I^-$, $NaN(TMS)_2$, THF; (b) (i) *p*-TsOH.H_2O, MeOH; (ii) TBDPSCl, DMAP, imidazole, DCM; (c) (i) CF_3COOH, DCM; (ii) 4-bromo-1-butene, K_2CO_3, CH_3CN; (iii) $(Boc)_2O$, Et_3N, THF; (d) Grubbs' catalyst, DCM; (e) Oxone, CF_3COCH_3, $NaHCO_3$, aq Na_2.EDTA, CH_3CN; (f) TBAF, THF; (g) (i) (i) *m*-CPBA, $NaHCO_3$, DCM; (ii) TBDPSCl, DMAP, imidazole, DCM.

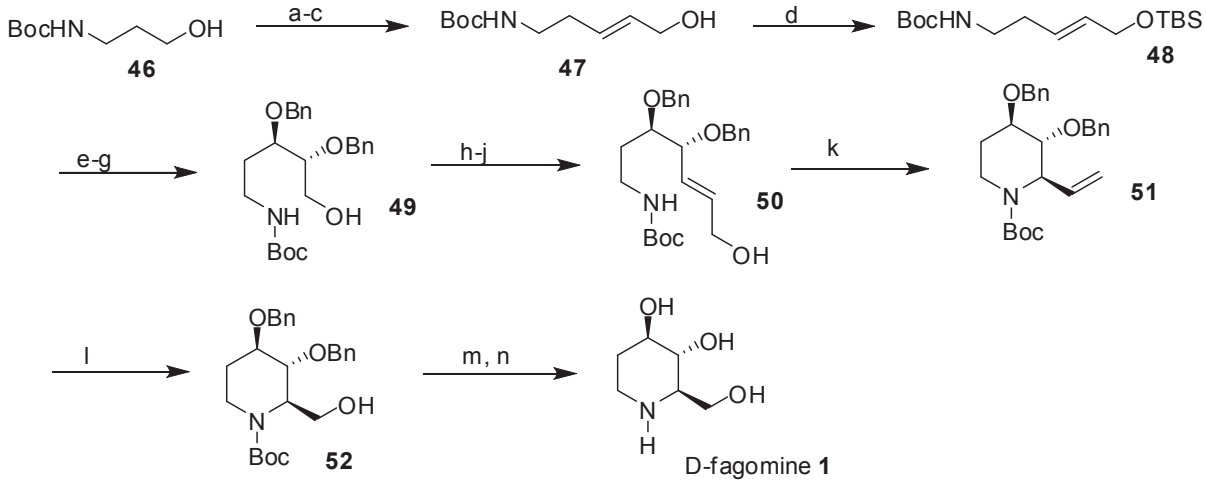
Takahata *et al* synthesized all four isomers of fagomine (**1-4**) using D-serine derived Garner aldehyde **27** (scheme 4).[7n]The olefin **28** prepared from **27** was hydrolysed to **29** which on 3 step sequence converted to the requisite olefin **30**, ready intermediate for metathesis. The RCM on **30** using Grubbs catalyst afforded the cyclic carbamate **31** in 97% yields. The oxone mediated epoxidation of **31** afforded a separable mixture of **32a**

and **32b**. The stereochemistry of each was established by different experimentation. Since it was realized, the requisite **32a** was formed in low yield (30%), an alternate method involving deprotection of TBDPS first, epoxidation and then protection by TBDPS of the terminal -OH was successfully probed and produced **32a** exclusively. The direct acid treatment of **32a** resulted in the complete hydrolysis of oxirane and concomitant deprotection of protecting groups giving the natural product **1**. Turning towards the completion of the synthesis, the acid hydrolysis of **32b** afforded **1** & **3** without considerable diastereoselectivity whereas base hydrolysis gave preferentially **3**.



Scheme 5

Bates and Shuyi Ng achieved the total synthesis of 2-*epi*-fagomine using gold catalysed allene cyclisation (scheme 5).[7d]The vinyl bromo compound **35** was prepared by bromination of 3-butyn-1-ol followed by selective reduction of alkyne. The compound **35** on Sonogashira coupling with trimethylsilylacetylene produced **36** in a moderate yield. The terminal –OH was protected using 4-OMe-phenol under Mitsunobu condition and subjected to SAD using AD-mix β to afford **38**. The compound **38** was subjected to disilylation and subsequent Searles-Crab-bé homologation to give allene **39**. The hydroxyl groups were protected with TBS and the terminal -OPMP was sequentially transformed to -NHBoc producing the requisite allene **43.** The intramolecular cyclisation was best affected using $Ph_3PAuCl/AgSbF_6/CaCO_3$ to produce exclusively **44** without unwanted side product **45**. The **44** on further classical synthetic conversions converted to the natural product 2-*epi*-fagomine, ent-**3**.



Scheme 6

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

Hirai and co-workers approached the synthesis of D-fagomine through asymmetric dihydroxylation and Pd (II) catalyzed intramolecular cyclization (scheme 6).[7k] Initially the Boc protected amino alcohol **46** was converted to **47** through Swern oxidation, Horner-Wittig Olefination and DIBAL reduction. The primary OH was TBS protected and subjected to SAD using AD-mix β to afford **49**. The requisite key intermediate was prepared through 3 steps sequences as done earlier. The pivotal cyclisation of **50** to **51** was successfully carried out using $PdCl_2(MeCN)_2$. The alkene **51** thus synthesized was subjected to reductive ozonolysis and further transformed to the natural product D-fagomine **1**.

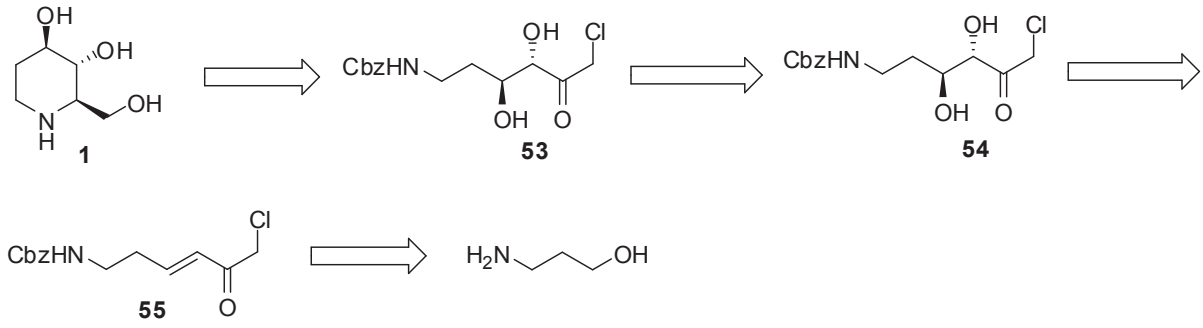
Results and Discussion

Our main objective was centred in the synthesis of some of the polyhydroxy piperidine natural products by making use of some of the bench-top chemicals.

We made three different approaches for achieving the target.

(I) Wittig reaction and SAD method

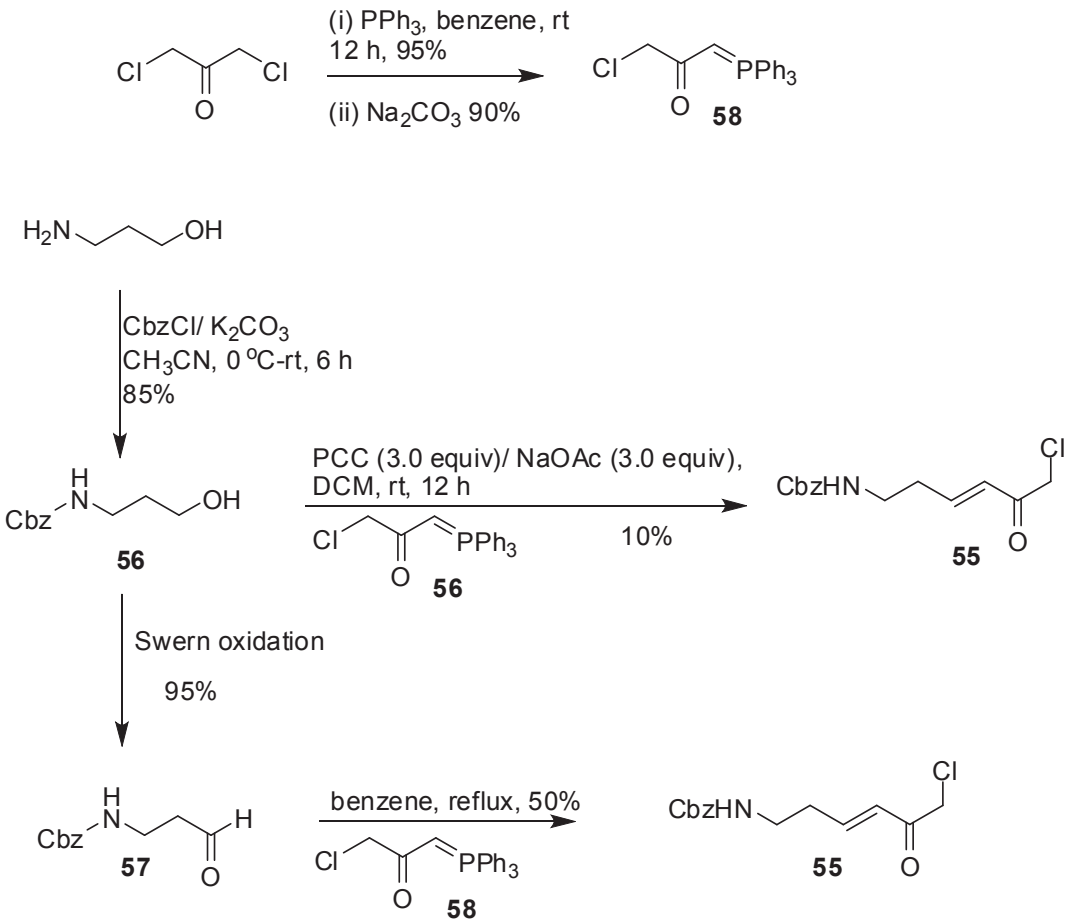
Initially we thought of undertaking some simple and straightforward synthetic routes. Our first approach was planned involving SAD of an unsaturated alkene as a key step. Accordingly the retro synthetic sequence was designed as shown in scheme 7.



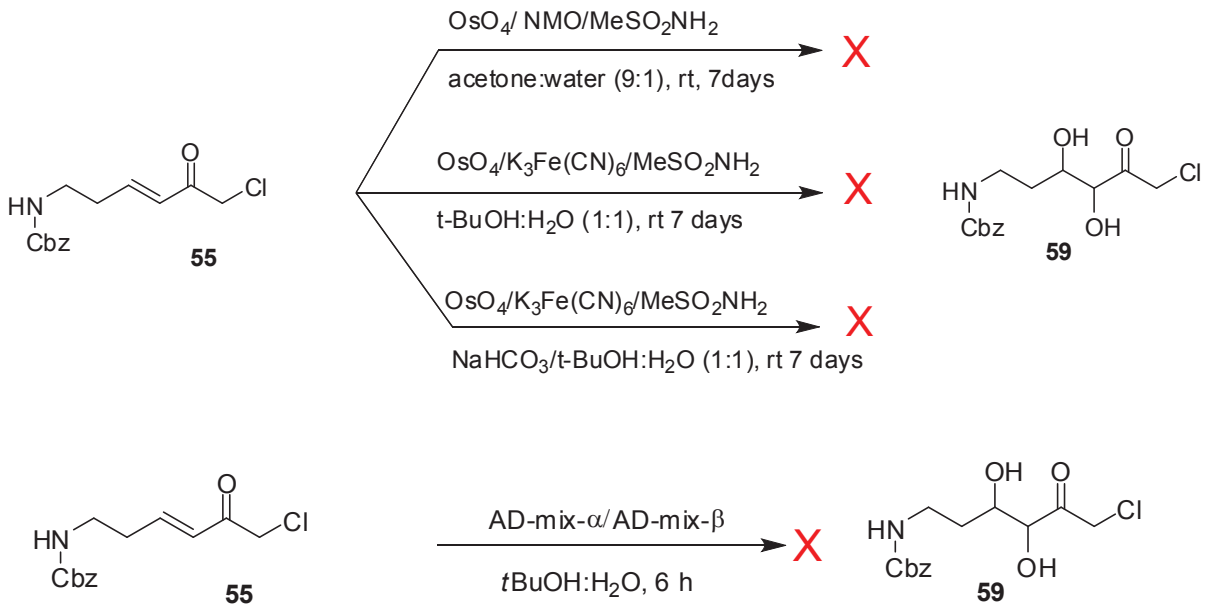
Scheme 7

Accordingly, the commercially available 3-amino-propan-1-ol was selectively protected with Cbz group to give **56** in 85% yields (scheme 8). The requisite phosphorane **58** was prepared from corresponding dichloroacetone. The domino oxidation-Wittig on alcohol **56**

using PCC/NaOAc and phosphorane **58** was disappointing giving the key olefin **55** in 10% yield leaving the starting unreacted even with 3.0 equiv of PCC and NaOAc. The separation of the product from column chromatography was also cumbersome due to the overlapping of the product spot with starting substance and phosphine oxide. So the alcohol **56** was initially converted to aldehyde **57** using Swern oxidation and then subjected to Wittig reaction by refluxing with the phophorane **58** in benzene. The product formed was showing an overlapping spot just below the phosphine oxide on TLC. It was purified by column chromatography and fully characterised by spectroscopic techniques. The disappearance of 3500 cm^{-1} broad band in IR and the appearance of proton signals in NMR at δ 6.26 (d, J=16Hz) & 6.80-6.87 (m, 1H) corresponding to olefinic group, clearly indicated the formation of the desired product **55**.



Scheme 8

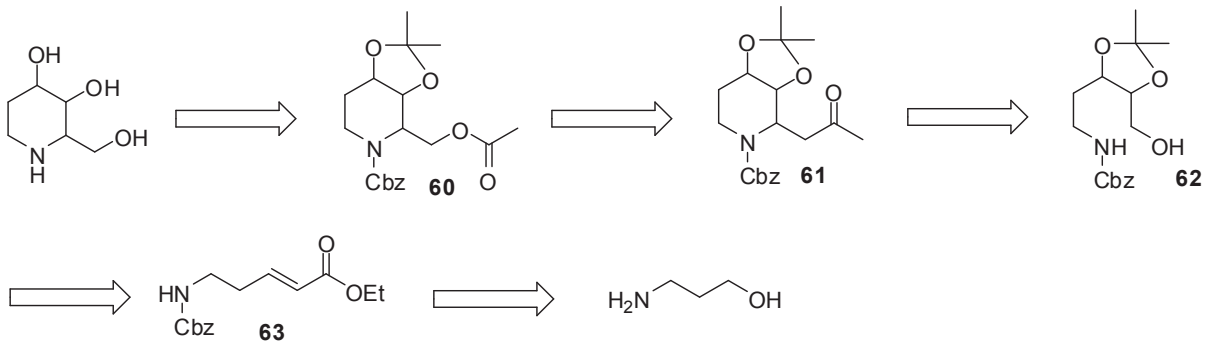


Scheme 9

With this, our next job was to insert dihydroxyl goups across the double bond to derive the compound **59**. Thus initially we subjected the compound **55** for direct Upjohn dihydroxylation using OsO_4 and NMO in acetone: water (scheme 9). The reaction mixture was stirred overnight to ensure the reaction. But, it was observed that there was no change in the reactant even after stirring it for 7 days. According to the literature reports, the dihydroxylation of keto compounds, though slow, found to occur in many cases with a moderated yield, but with our olefin **55**, it was completely unsuccessful. We then changed the reaction conditions by changing the oxidant to $K_3[Fe(CN)_6]$ and with 1.0 equiv of $MeSO_2NH_2$, the same reaction was repeated. But it was observed that there was a not even a trace of the compound **59** obtained even after stirring the reaction mixture for many days. On contemplation of this result, we speculated, the use of Sharpless ligands could dwell the issue by activating OsO_4 compatible to react with less reactive conjugated double bond. The same reaction was then repeated with AD-mix α/ AD-mix-β and initially it was observed some rapid colour change, which delighted us to anticipate the formation of desired product. The various TLC combinations indicated formation of no specific spot corresponding to our compound of interest. Even then, the reaction mixture was worked-up and subjected to column chromatographic purification, but yielded no trace of product.

(II) Intramolecular Aza-Michael and Baeyer-Villiger oxidation

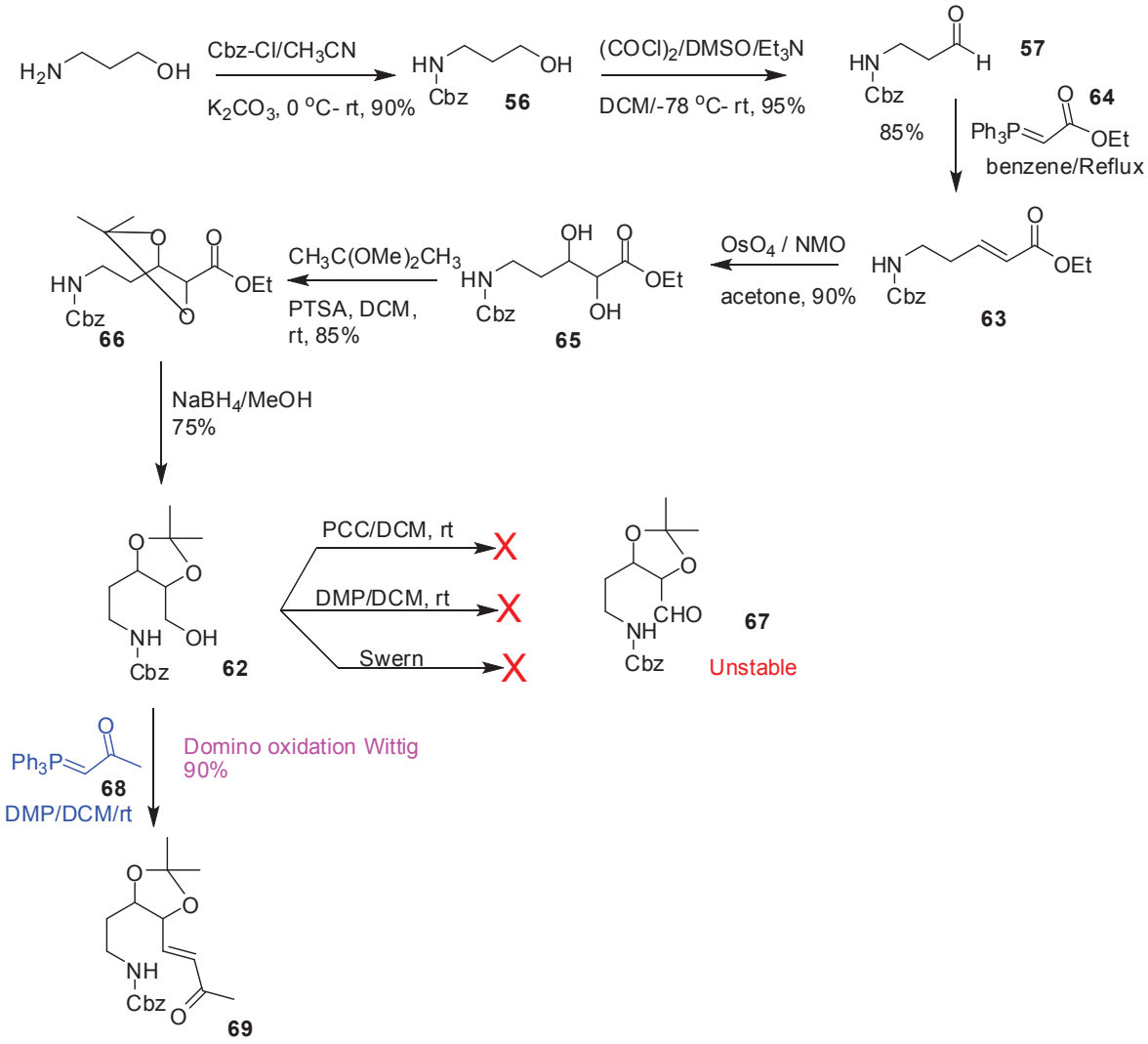
Failure of our earlier strategy provoked us to investigate an alternate method for the synthesis of fagomine analogues. We now formulated an alternate strategy involving aza-Michael and Baeyer-Villiger oxidation as key steps. The proposed retro synthesis is depicted in the scheme 10.



Scheme 10

We envisaged that the compound **60** could serve as a better intermediate to synthesise fagomine isomers. The target **60** can be derived from the corresponding keto compound **61** via Baeyer-Villiger oxidation. The keto framework **61** could conveniently be constructed from **62** which in turn could be synthesized starting from 3-amino-propan-1-ol.

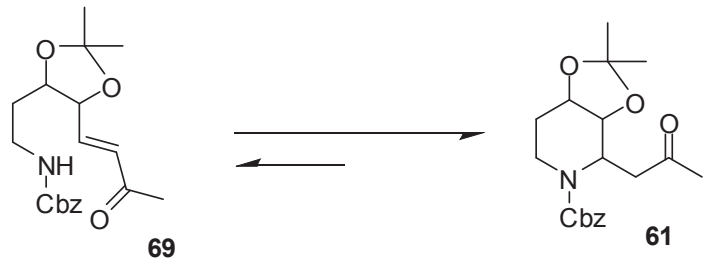
Thus our synthesis started with preparation of aldehyde **57** as done earlier, which now condensed with the phosphorane **64** to provide the olefin **63** in 85% yield. It was then subjected to dihydroxylation using OsO_4/NMO in acetone: water to afford the diol **65** exclusively. To proceed further, the dihydroxyl group was transformed to acetonide **66** which on subsequent reduction of ester group using $NaBH_4$ produced the alcohol **62**. With **62** in hand, we tried several methods for the synthesis and isolation of aldehyde **67**. But it was observed, all the time the reaction mixture was decomposed indicating the aldehyde **67** was very labile even under placid oxidation conditions. We then thought of condensing the aldehyde immediately with the phosphorane **68** in the same pot. Thus, alcohol **62** was treated with DMP and keto phosphorane **68** prepared from monochloroacetone. To our delight, the desired product **69** was formed in 90% yield. The disappearance of broad IR band at 3500 cm^{-1} and appearance of doublet at δ 6.33 ppm (J=16 Hz, 1H) and 6.65 ppm (dd, J=6 Hz & 16Hz, 1H) in ^1H NMR spectrum confirmed the formation of the product **69** (scheme 11).



Scheme 11

Our next task was to cyclise **69** to **61** via intramolecular aza-Michael reaction. Initially the compound **69**, impregnated with the labile acetonide moity, the cyclisation was tried in mild bases like Et_3N, pyridine, K_2CO_3 and proline. But in all the cases the starting got recovered without any noticeable change. We then treated **69** with 1.0 equiv of KOH in MeOH. The reaction mixture slowly got decomposed and a dark red colour was noticed. The same reaction was then tried with catalytic amount of KOH in MeOH indicating a very slow colour change from colourless to pale yellow and TLC showed a very close spot overlapping with the reactant spot. The reaction mixture was neutralised, extracted with organic solvent and characterised by spectroscopic techniques. From ^{1}HNMR it was

concluded that the reaction mixture was containing the product **61** along with the starting material **69**. The percentage ratio of **61** to **69** was 86:14, confirmed by comparing the integration of the corresponding protons in ^{1}HNMR. The repetition of the same reaction with prolonged time to ensure the complete formation of the product **61** was unsuccessful and it was observed, the anticipated product was formed along with some reactant (86:14) even after two days, indicating the reversibility of the reaction (scheme 12).



69 **61**

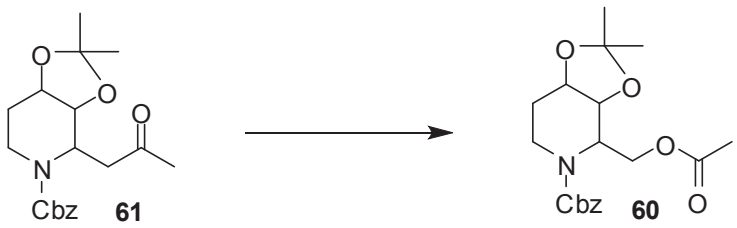
Reaction conditions	**Results**
Et_3N, DCM, 24 h, rt / reflux	Reactant remained
Pyridine, DCM, 24 h, rt / reflux	Reactant remained
K_2CO_3, acetone, MeOH, rt / refulx	Reactant remained
Proline, THF, rt	No reaction
KOH (1.0 eq), MeOH, rt	Decomposition
KOH (cat), MeOH, rt	**87% product with 13% starting**

Scheme 12

With compound **61** as a major isomer, we furthered the synthesis to reach the synthesis of natural products. Our next job was to prepare **60** by using Baeyer-Villiger oxidation. Thus

the reaction was initially tried in a conventional method using mCPBA in DCM at rt. Even after a prolonged stirring, no reaction was observed. The same reaction tried under refluxing condition also did not favour us to get any desired product. According to the literature reports, the Baeyer-Villiger oxidation of aliphatic ketones normally use harsh conditions involving string acid like TFA unlike oxidation involving mild conditions for aromatic ketones/aldehydes.

In this context, we treated **61** with TFA/H_2O_2 and stirred for 2 days. The TLC analysis did not show formation of the expected product. The reaction mixture was worked-up and characterised by spectroscopic techniques. The proton NMR showed a complicated pattern making us difficult for analysis. This may be due to the formation of acetonide deprotected products along with the other unwanted products. The crude mixture was then analysed by GCMS, which indicated the formation of the product in trace amounts (10%) along with several other products (scheme 13).

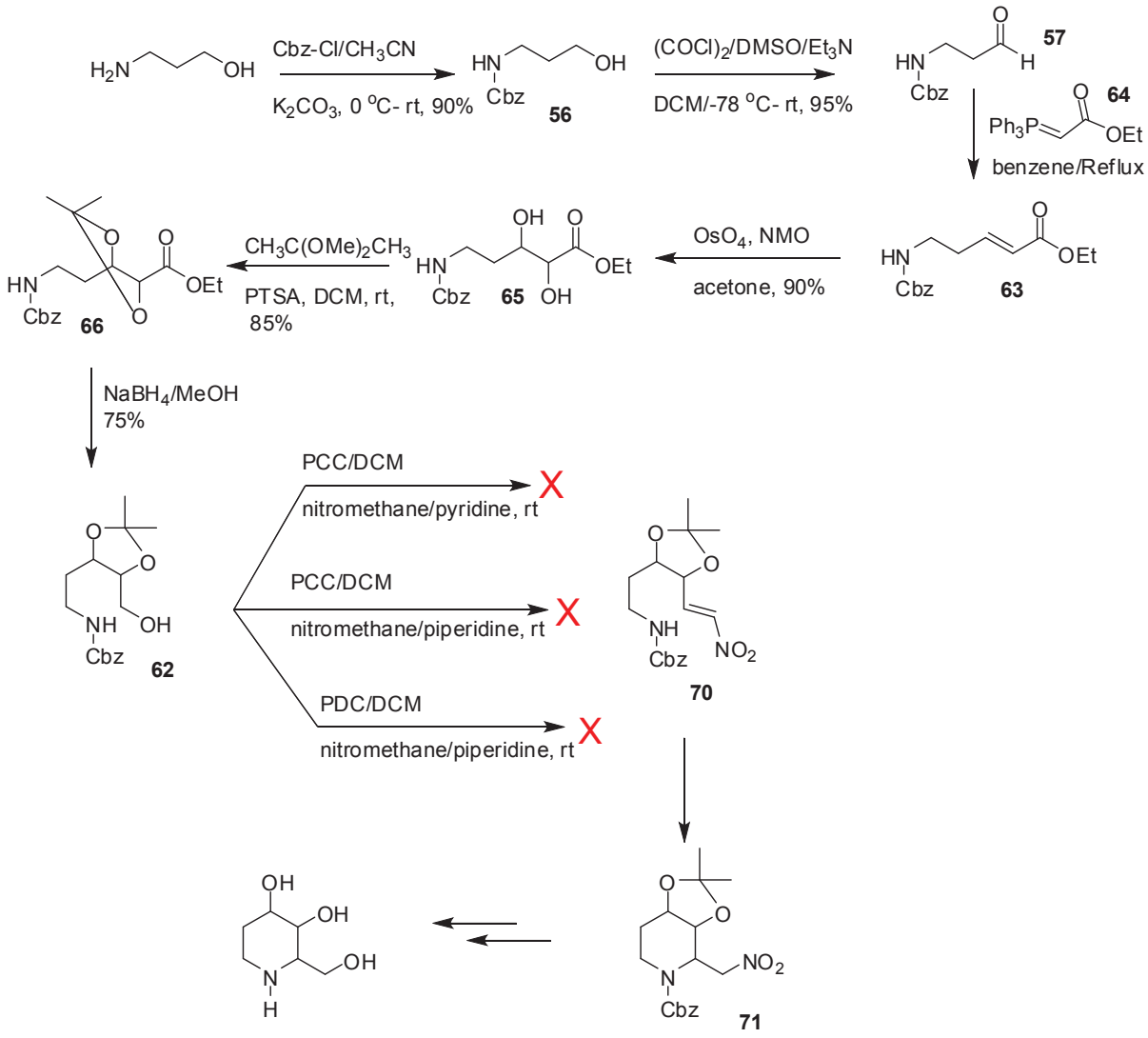


Reaction conditions	Observations
mCPBA (3. 0 equiv), DCM, rt/reflux	No reaction
mCPBA (3. 0 equiv), DCM, reflux	No reaction
TFA (1.0 equiv), H_2O_2 (3.0 equiv), rt	10% product with starting observed in GCMS

Scheme 13

(III) Henry-Nef reaction method

The failure of our earlier two strategies forced us to develop some alternate method to achieve the synthesis of fagomine alkaloids. We now recalled our well developed Henry-Nef protocol for the synthesis of this.



Scheme 14

Similar to our earlier developed strategy, the alcohol **62** was efficiently synthesized starting from **56** (scheme 14). Since it was already observed, the aldehyde **67** was highly unstable, we thought of performing a novel one-pot oxidation-Henry reaction using some commercially available reagents to synthesize the requisite nitro olefin **70**, which could easily be transformed to the key nitro compound **71**. Further the synthesis of fagomine can be realized by performing Nef reaction on **71** which could further be transformed to

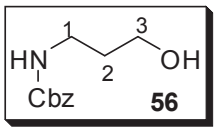
fagomine alkaloids. But all the attempted reactions for one-pot oxidation-Henry reaction failed in producing the product **70**. Thus failure of our strategy at Henry stage stopped our synthesis.

Conclusion

In summary, the three different strategies were attempted for the synthesis of fagomine alkaloids. Even though, the methods failed to reach the destination, the synthetic endeavours deemed to be useful for the synthetic chemists for further manipulations and optimise the reaction conditions to make them effective in the synthetic transformations.

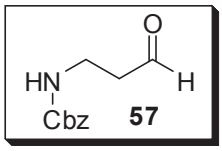
Experimental Section:

5.01 Benzyl-(3-hydroxypropyl) carbamate 56



To a cooled solution of 3-aminopropan-1-ol (0.075 mL, 1 mmol) and K_2CO_3 (0.28 g, 2.0 mmol), was added CbzCl (50% in toluene) (0.37 mL g, 1.1 mmol) drop wise over a period of 15 min. The reaction mixture was further stirred at 0 °C for 6 h. It was concentrated under vacuum and added H_2O (10 mL) to dissolve completely the solid residue of K_2CO_3. The aqueous phase was treated with DCM (20 mL X 3) and the organic layer was separated. The DCM layer was further washed with dil. HCl (20 mL X 3), dried over anhy. Na_2SO_4 and concentrated in vacuo. The crude mixture was subjected to column chromatographic separation (SiO_2, hexane: EtOAc, 6: 4) to afford **56** as an amorphous solid (0.18 g, 88%); IR (neat): ν_{max} = 3445, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.61-1.69 (m, 2H, H-2), 2.59 (br s, 1H, OH), 3.30 (t, J=6 Hz, 2H, H-1), 3.62 (t, J= 6 Hz. 2H, H-1), 5.06 (s, 3H, CH_2Ph & NH), 7.27-7.32 (m, 5 H, PhCH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 32.4 (C-2), 37.8 (C-1), 59.7 (C-3), 66.8 (CH_2Ph), 128.0 (PhCH), 128.5 (PhCH), 128.1 (PhCH), 136.5 (PHC), 157.3 (NCO).

5.02 Benzyl (3-oxopropyl) carbamate 57

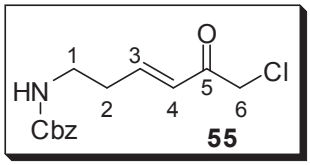


The compound **56** (0.2 g, 1 mmol) on Swern oxidation gave pale yellow thick liquid of **57** (0.2 g, 98%) (The procedure is similar to that described under chapter 4).

5.03 Synthesis of phosphorane 58

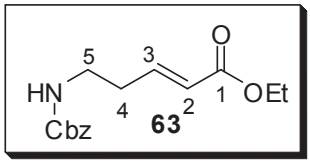
The mixture of 1, 3-dichloroacetone (0.13 g, 1 mmol) and PPh_3 (0.29 g, 1.1 mmol) was refluxed in THF (15 mL) for 6 h. The solid obtained was filtered and the residue obtained was just dissolved in MeOH (5 mL). To this vigoursly stirring solution was added sat. Na_2CO_3 solution (1 mL) and further stirred for 10 min. The solid obtained was filtered and dried under vacuum to afford **58** (0.30 g, 86%) as a white amorphous shiny solid.

5.04 Benzyl-[(3*E*)-6-chloro-5-oxohex-3-en-1-yl]carbamate 55



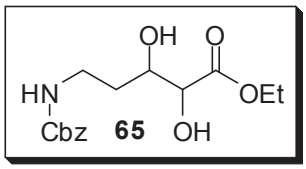
The mixture of aldehyde **57** (0.2 g, 1.0 mmol) and phosphorane **58** (0.53 g, 1.5 mmol) was refluxed in benzene for 24 h. It was then concentrated under vaccum and subjected to column purification (SiO_2, hexane: EtOAc, 6.5: 2.5) to give **55** (0.14 g, 50%) as a pale yellow thick liquid; IR (neat): ν_{max} = 1700, 1690, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.34-2.42 (m, 2H, H-2), 3.27-3.30 (m, 2H, H-1), 4.10 (s, 2H, H-6), 5.01 (s, 2H, C*H*$_2$Ph), 6.26 (d, J=16Hz, H-4), 6.80-6.87 (m, 1H, H-3), 7.20-7.27 (m, 5H, PhCH); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 33.2 (C-2), 39.3 (C-1), 47.1 (C-6), 66.8 (Ph*C*H$_2$), 127.8 (PhCH), 127.9 (PhCH), 128.1 (PhCH), 128.2 (PhCH), 128.5 (PhCH), 128.6 (C-4), 136.3 (PhC), 146.3 (C-3), 156.3 (NCO), 190.8 (CO).

5.05 Ethyl-(2*E*)-5-{[(benzyloxy) carbonyl] amino} pent-2-enoate 63



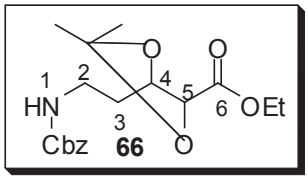
The mixture of aldehyde **57** (0.2 g, 1.0 mmol) and phosphorane **64** (0.42 g, 1.2 mmol) was refluxed in benzene for 12 h. The reaction mixture was then concentrated under vacuum and subjected to column purification (SiO_2, hexane: EtOAc, 8: 2) to give alkene **63** (0.24 g, 85%) as a pale yellow thick liquid.

5.06 Preparation of diol 65



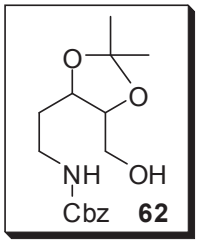
To a cooled solution of OsO_4 (0.05 g, 2 mol %) and NMO (0.12 g, 1 mmol) in acetone: water, (5 mL, 9:1) was added alkene **63** (0.28 g, 1 mmol) in acetone (1 mL). The reaction mixture was brought to rt and stirred for 6 h. It was then quenched with sat Na_2SO_3 (2 mL) and the organic compound was extracted with EtOAc (5 mL X 3). The organic layer was then continuously washed with sat Na_2SO_3 (5 mL X 3); the organic layer was dried over anhy. Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by column chromatography (SiO_2, hexane: EtOAc, 5: 5) to give diol **65** (0.28 g, 90%) as a colourless thick liquid.

5.07 Preparation of acetonide protected diol 66



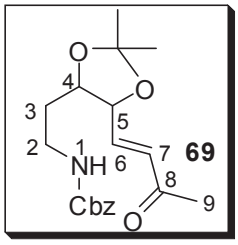
To a cooled solution of diol **65** (0.31 g, 1 mmol) and PTSA (cat) in DCM (10 mL), was added a solution of 2, 2-dimethoxyacetone (0.15 mL, 1.2 mmol) drop wise over a period of 5 min. The reaction mixture was then brought to rt and stirred for 6 h. It was then washed with sat. $NaHCO_3$ (5 mL X 3), dried over anhy. Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography (SiO_2, hexane: EtOAc, 8: 2) to afford the protected diol **66** (0.3 g, 85%) as a colourless thick liquid.

5.08 Preparation of alcohol 62



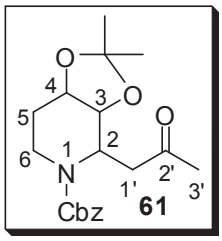
To a cooled solution of **66** (0.35 g, 1 mmol) in MeOH (10 mL) was added $NaBH_4$ (0.11 g, 3 mmol) in two portions and stirred for 30 min. The reaction mixture was then brought to rt and stirred for further 12 h. It was then concentrated and added DCM (15 mL). The organic layer was washed with dil HCl (5 mL X 3), dried over anhy. Na_2SO_4 and concentrated under vacuum to give essentially pure alcohol **62** (0.23 g, 75%).

5.09 Preparation of olefin 69



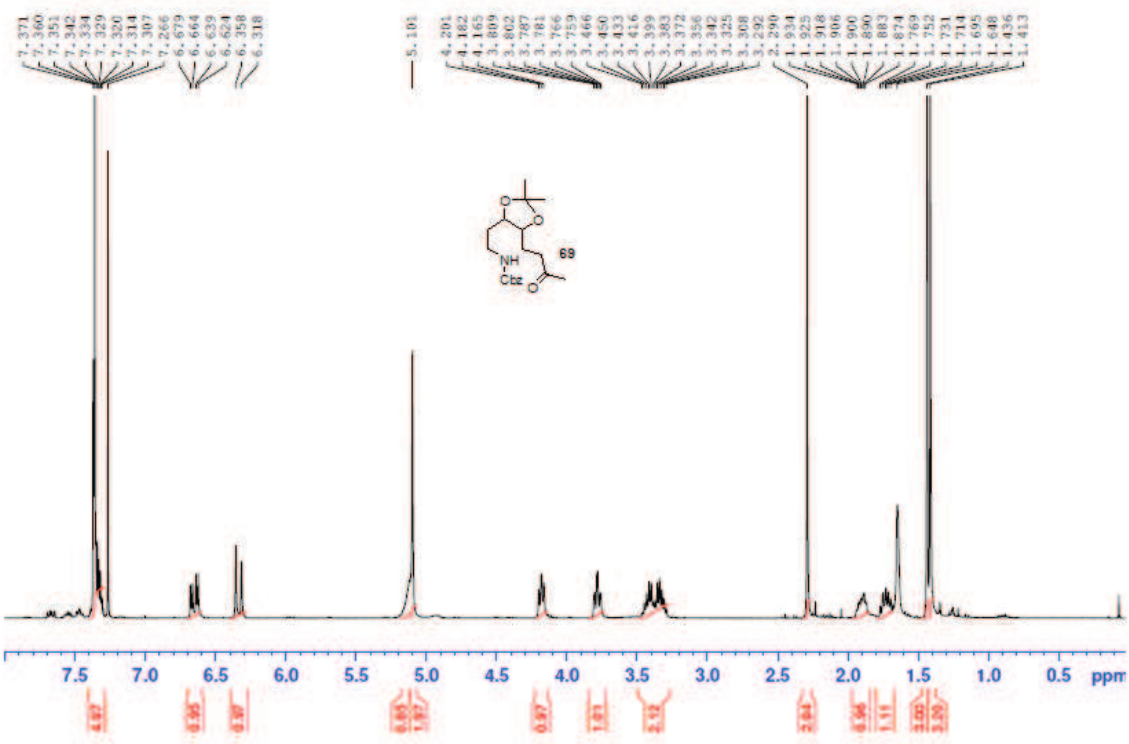
To a cooled mixture of **62** (0.3 g, 1 mmol), phosphorane **68** (0.48 g, 1.5 mmol) and $NaHCO_3$ (0.25 g, 3 mmol) in DCM (10 mL) under N_2 atmosphere was added DMP (0.5 g, 1.2 mmol). The reaction mixture was slowly brought to rt in 15 min and further stirred for 8 h. It was then diluted with Et_2O (25 mL), filtered, the filtrate was washed with sat $NaHCO_3$ (15 ml X 3). The organic layer was dried over anhy. Na_2SO_4 and concentrated under vacuum. The crude product was subjected to column purification (SiO_2, hexane: EtOAc, 8:2) to afford **69** (0.3 g, 90%) as a pale yellow thick liquid; IR (neat): ν_{max} = 1700, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.41 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.69-1.75 (m, 1H, H-3A), 1.88-1.92 (m, 1H, H-3B), 2.29 (s, 3H, H-9), 3.29-3.46 (m, 2H, H-2), 3.75-3.80 (m, 1H, H-4), 4.16-4.20 (m, 1H, H-5), 5.10 (s, 2H, $PhCH_2$), 6.33 (d, J=16 Hz, 1H, H-7), 6.65 (dd, J=6 Hz & 16Hz, 1H, H-6), 7.30-7.37 (m, 5H, PhCH).

5.10 Preparation of the key precursor 61



The compound **69** (0.3 g, 1 mmol) was stirred with catalytic amount of KOH (0.005 g, 10 mol %) in MeOH (10 mL) for 12 h. The reaction mixture was concentrated and treated with DCM (20 mL). The organic layer was washed with water (10 mL X 3), concentrated, dried over anhy. Na_2SO_4 to give essentially pure **61** (0.28, 90%); IR (neat): ν_{max} = 1710, 1700, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.34 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.67-1.75 (m, 2H, H-5), 2.20 (s, 3H, H-3'), 2.67-2.70 (m, 1H, H-1'A), 3.33-3.44 (m, 4H, H-1'B, H-6, H-2), 3.73-3.79 (m, 1H H-4), 3.85-3.89 (m, 1H, H-3).

Spectra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7.334
7.329
7.320
7.314
7.307
7.266
6.679
6.664
6.639
6.624
6.358
6.318
5.101
4.201
4.182
4.165
3.809
3.802
3.787
3.781
3.766
3.759
3.466
3.450
3.433
3.416
3.399
3.383
3.372
3.356
3.342
3.325
3.308
3.292
2.290
1.934
1.925
1.918
1.906
1.900
1.890
1.883
1.874
1.769
1.752
1.731
1.714
1.695
1.648
1.436
1.413
O
O
O
NH
Cbz
O
69
7.5
7.0
6.5
6.0
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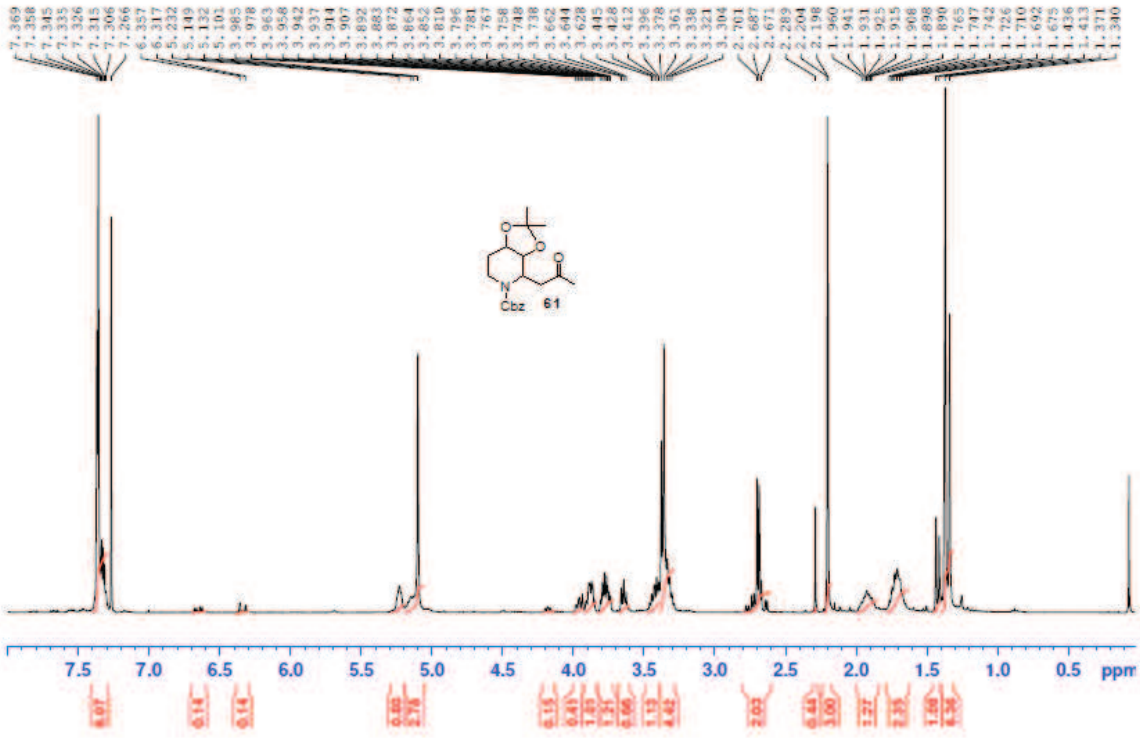
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm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7.315
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7.266
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5.149
5.132
5.101
3.985
3.978
3.963
3.958
3.942
3.937
3.914
3.907
3.892
3.883
3.872
3.864
3.852
3.810
3.796
3.781
3.767
3.758
3.748
3.738
3.662
3.644
3.628
3.445
3.428
3.412
3.396
3.378
3.361
3.338
3.321
3.304
2.701
2.687
2.671
2.289
2.204
2.198
1.960
1.941
1.931
1.925
1.915
1.908
1.898
1.890
1.765
1.747
1.742
1.726
1.710
1.692
1.675
1.436
1.413
1.371
1.340
O
O
O
N
Cbz
O
61
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6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

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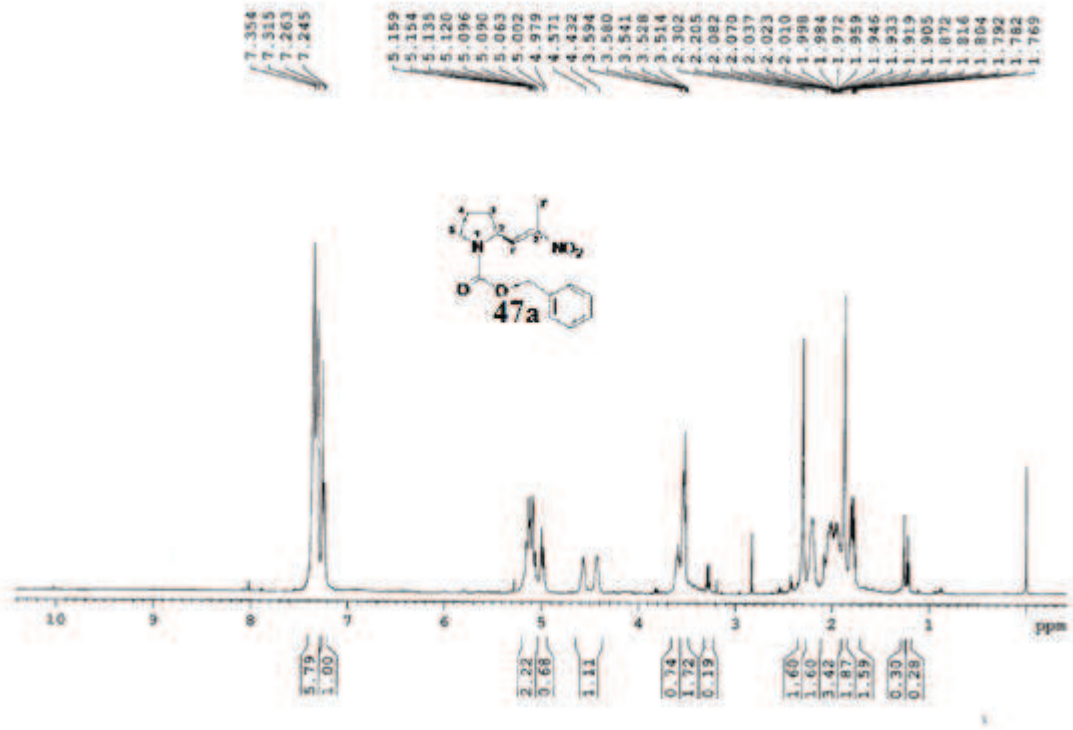
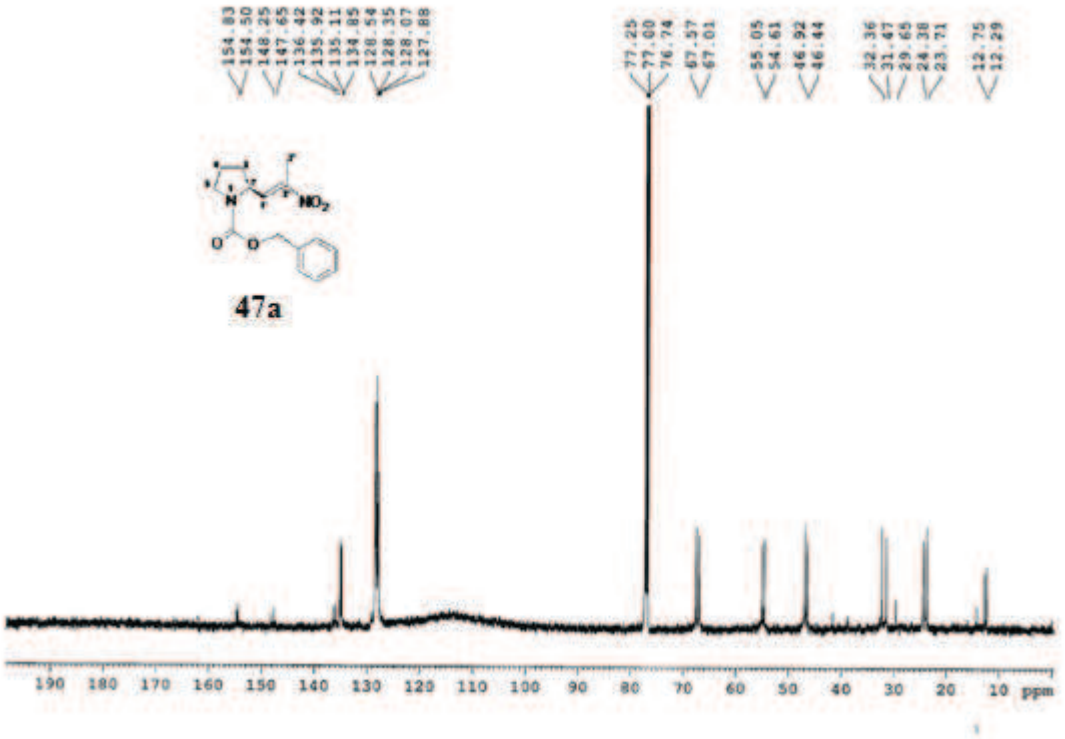
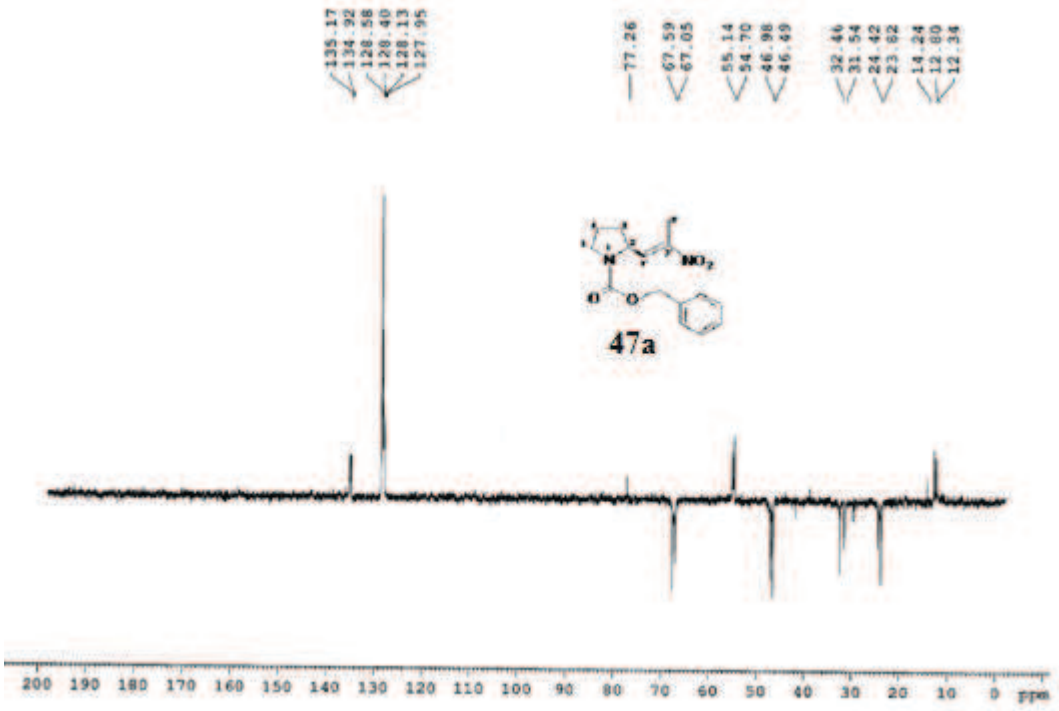
Chapter 2



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127.95
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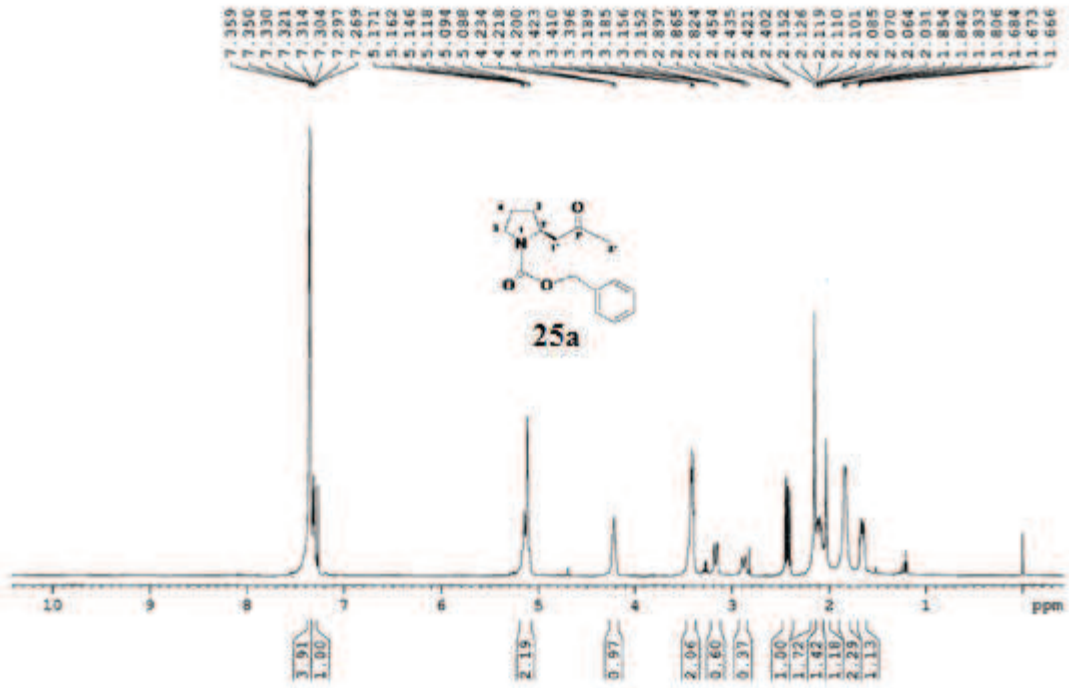
67.59
67.05
55.14
54.70
46.98
46.69
32.46
31.54
24.42
23.62
14.24
12.60
12.34
47a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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3.410
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3.389
3.185
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3.152
2.897
2.865
2.824
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2.435
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2.402
2.132
2.126
2.119
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2.101
2.085
2.070
2.064
2.031
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1.806
1.684
1.673
1.666
25a
10 9 8 7 6 5 4 3 2 1 ppm
3.91
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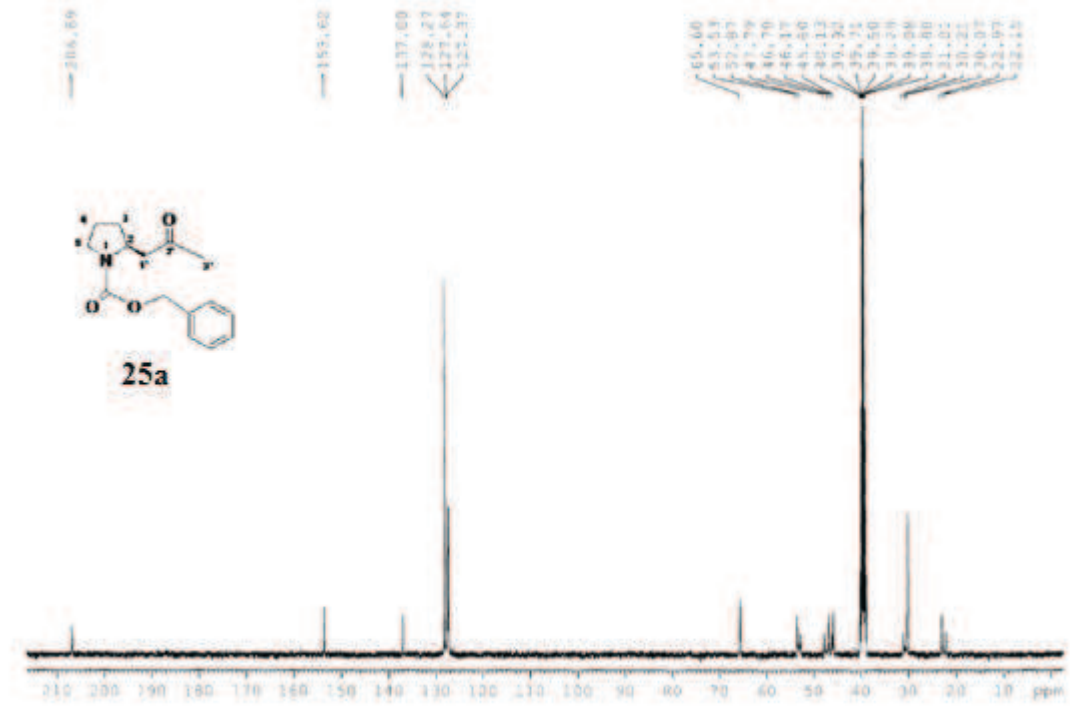
2.06
0.80
0.37
1.00
1.72
1.42
1.18
2.29
1.13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125.37
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46.79
46.17
45.60
40.13
36.32
35.71
30.50
30.20
30.08
30.00
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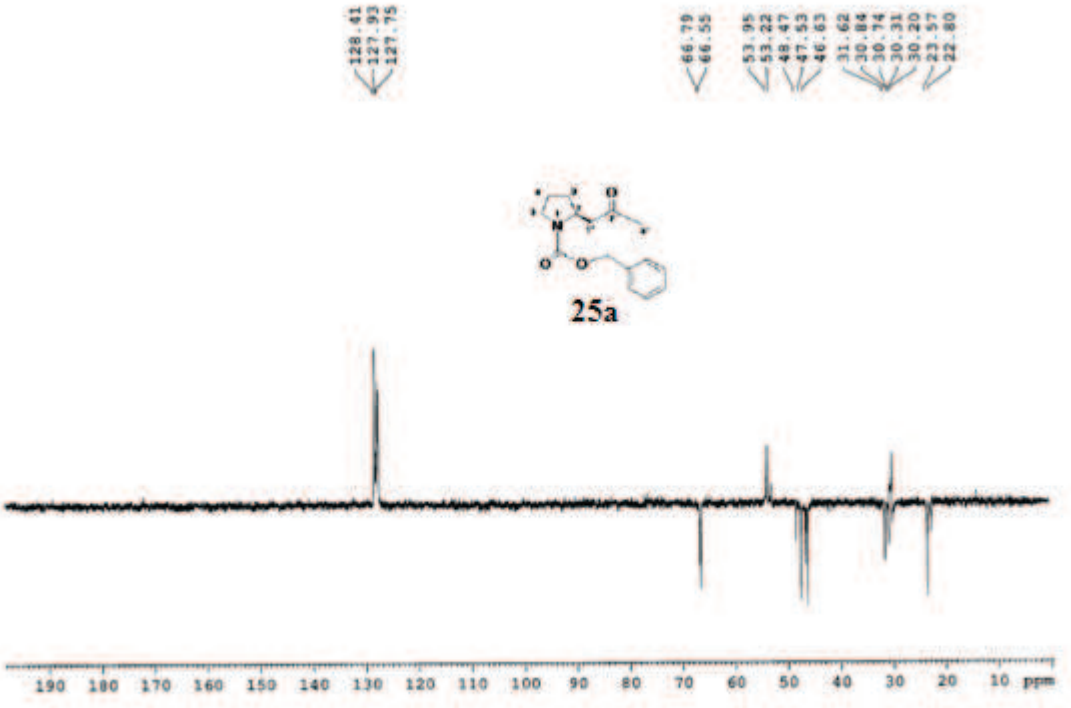
20.21
20.03
22.97
22.10
25a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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30.31
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23.57
22.80
25a
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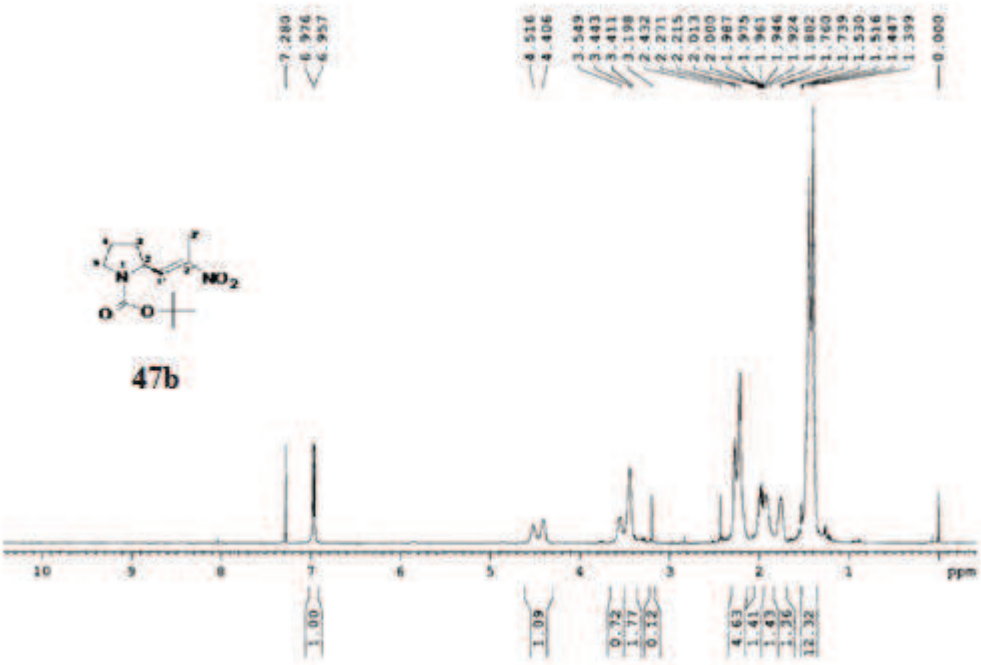
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2.000
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1.975
1.961
1.946
1.924
1.802
1.760
1.739
1.530
1.516
1.447
1.399
0.000
NO2
47b
10
9
8
7
6
5
4
3
2
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ppm
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1.43
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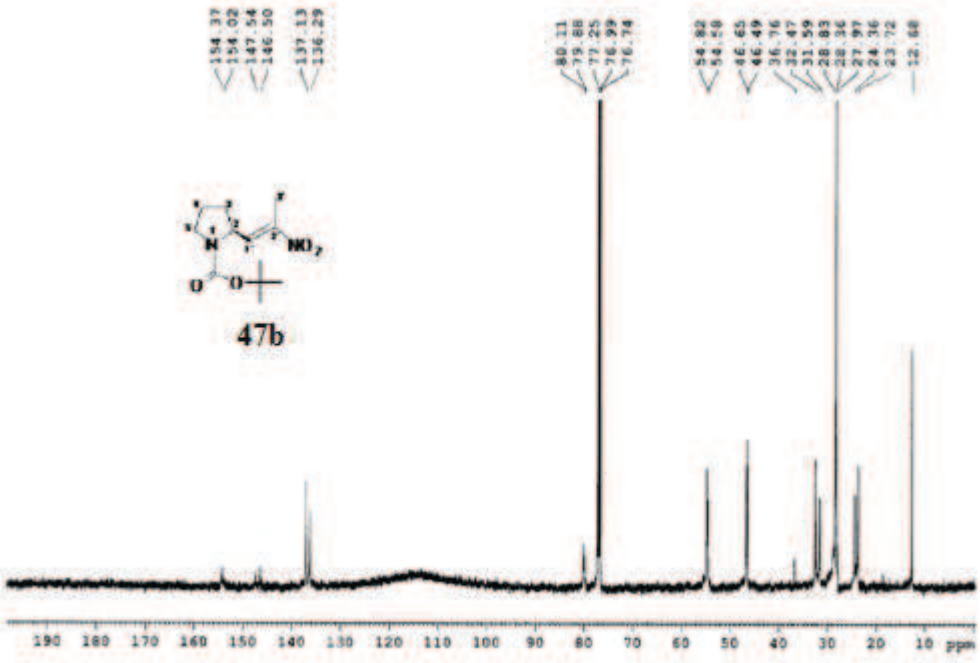
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136.29
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79.88
77.25
76.99
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54.82
54.50
46.65
46.49
36.76
32.47
31.59
28.83
28.36
27.97
24.36
23.72
12.68
NO2
47b
190
180
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160
150
140
130
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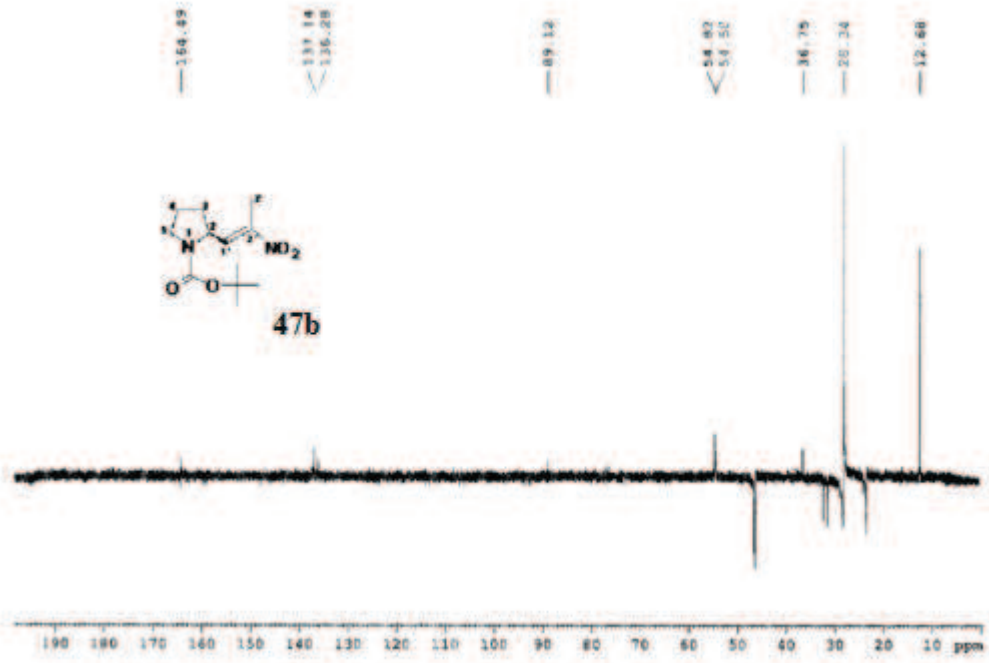
80
70
60
50
40
30
20
10
ppm


47b
NO2
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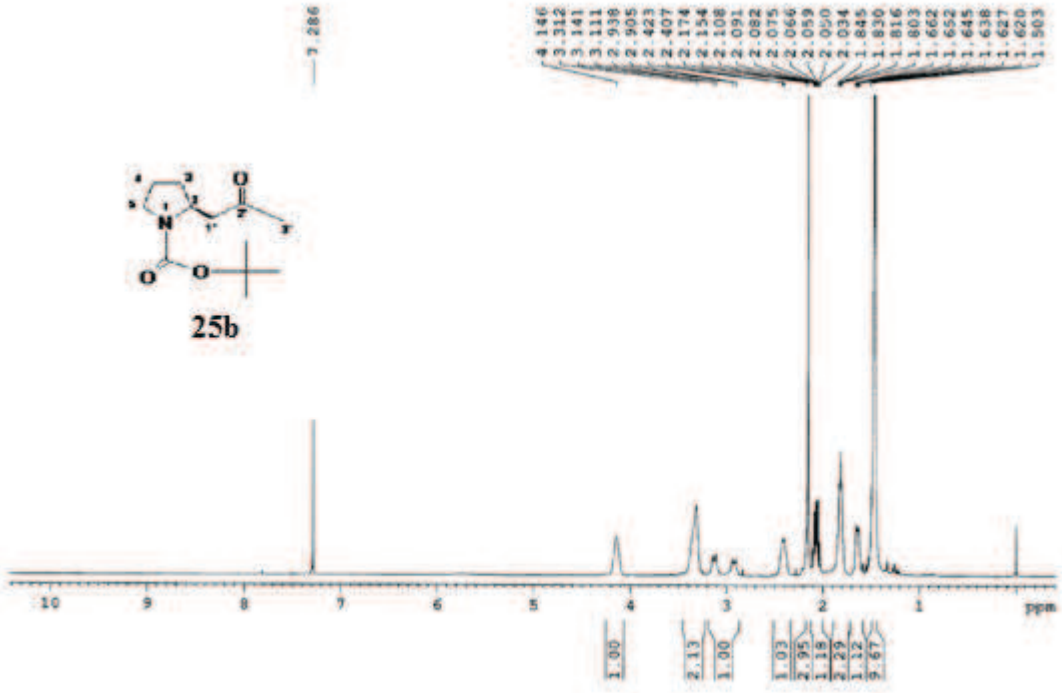
25b
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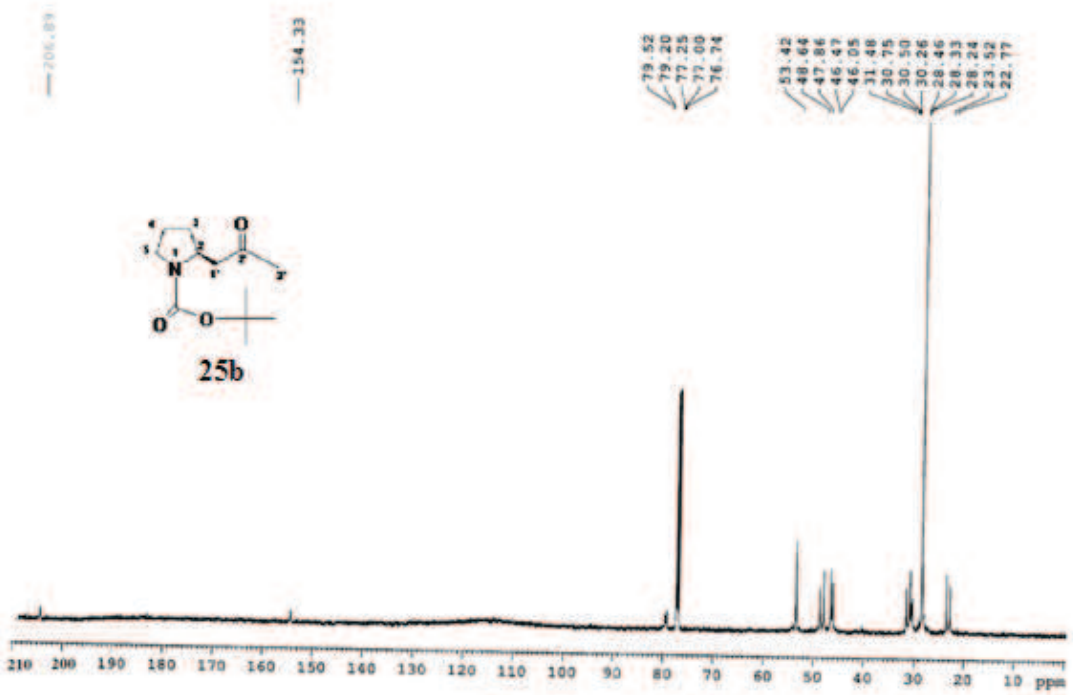
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77.00
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30.75
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25b
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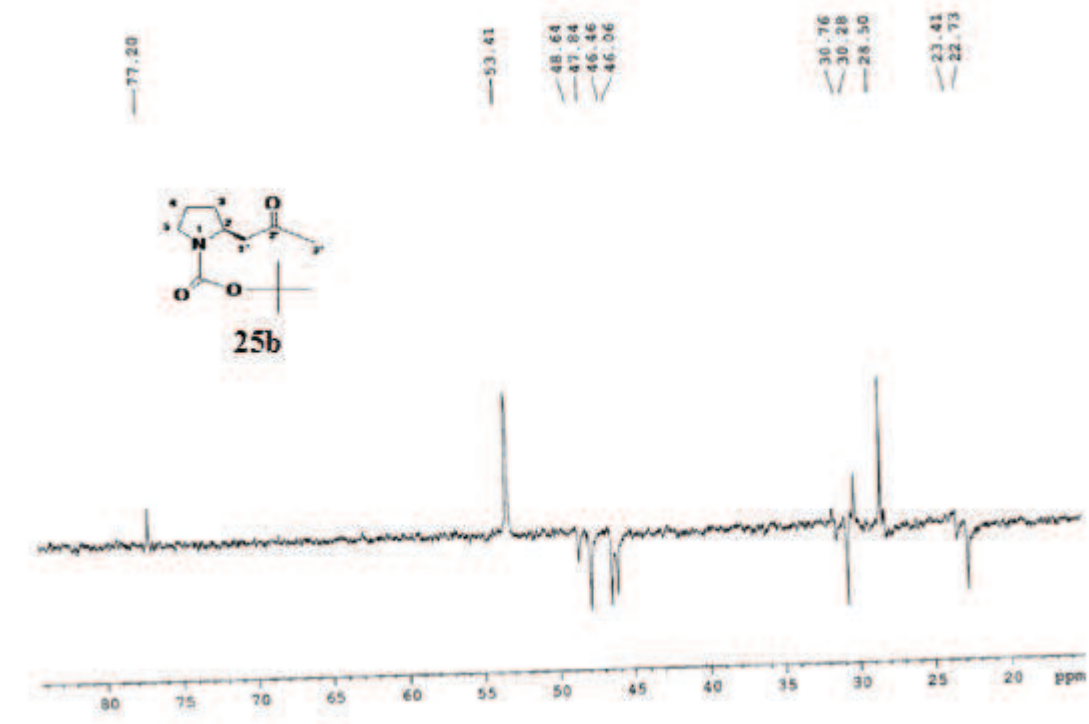
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22.73
25b
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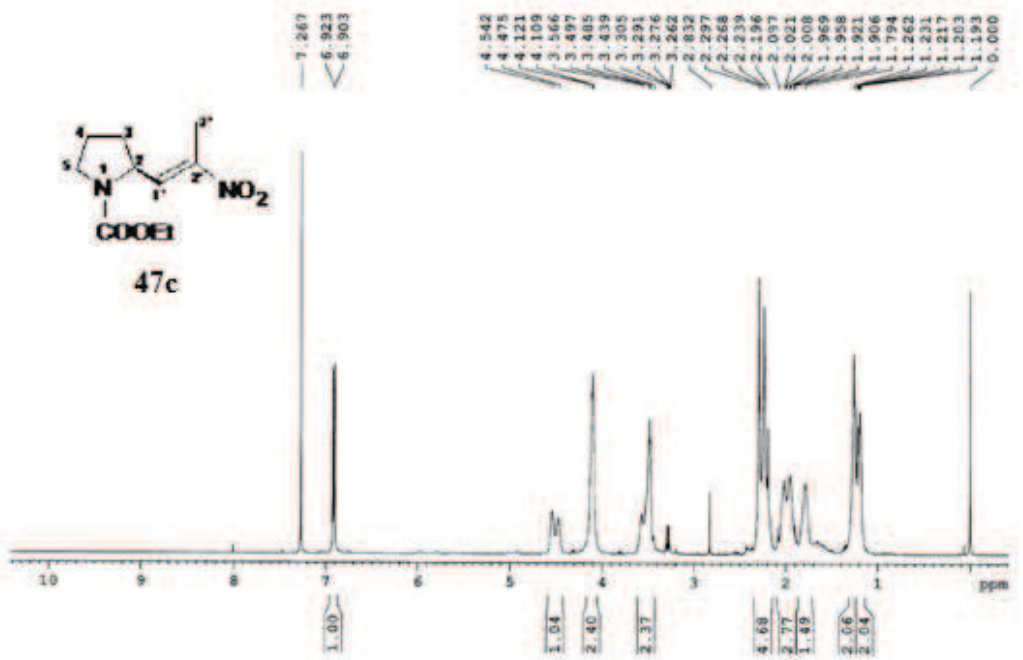
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3.262
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2.297
2.268
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2.037
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1.958
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1.262
1.231
1.217
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0.000
NO2
COOEt
47c
10
9
8
7
6
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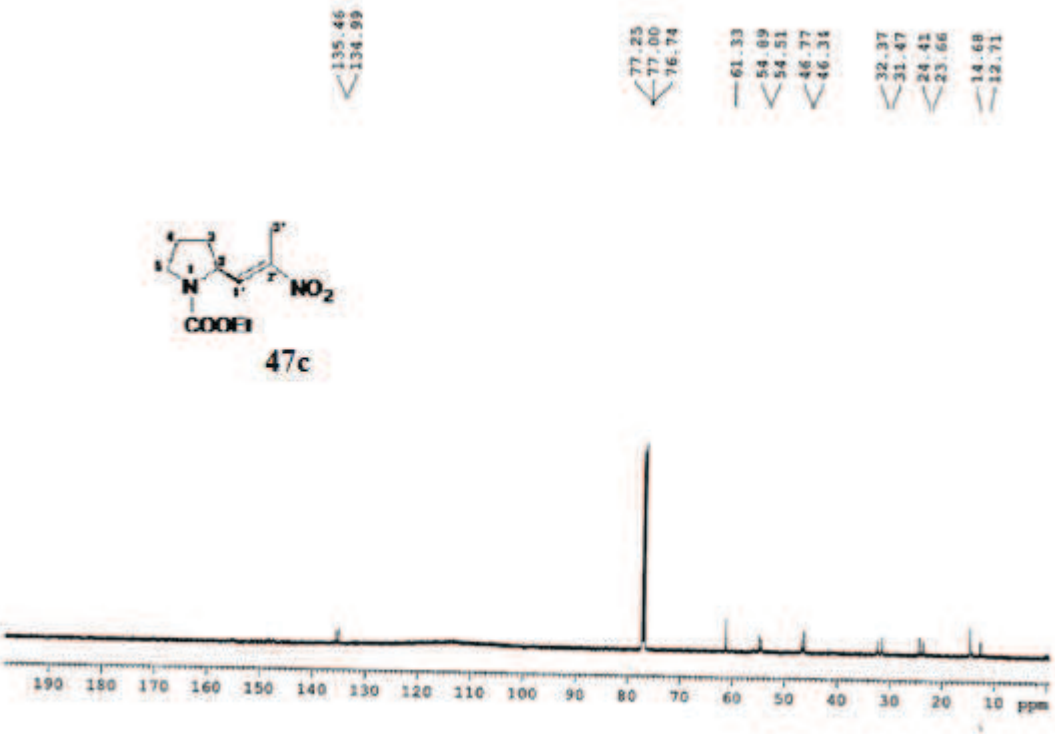
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COOEt
47c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


135.45
134.99
77.21
61.34
54.91
54.52
46.80
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32.40
31.46
24.44
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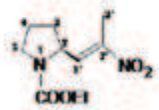
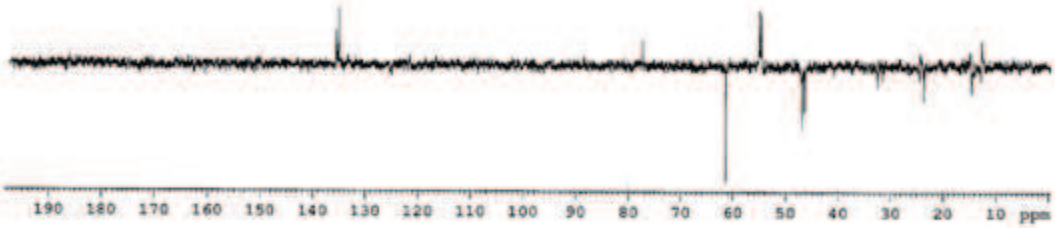
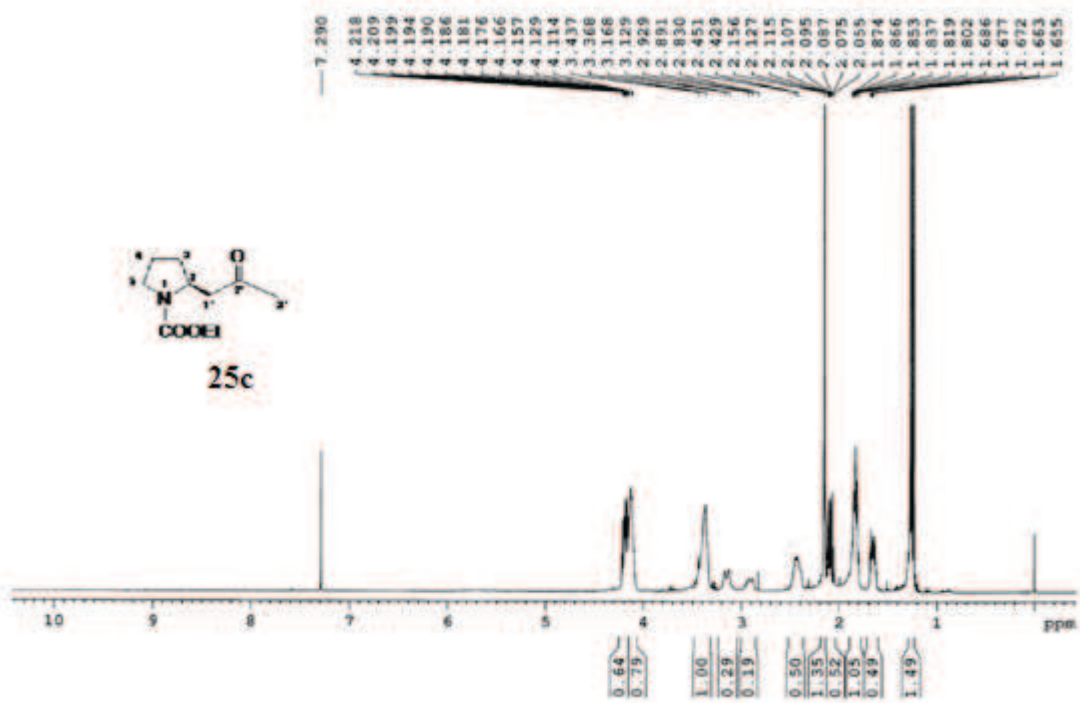
14.63
12.66

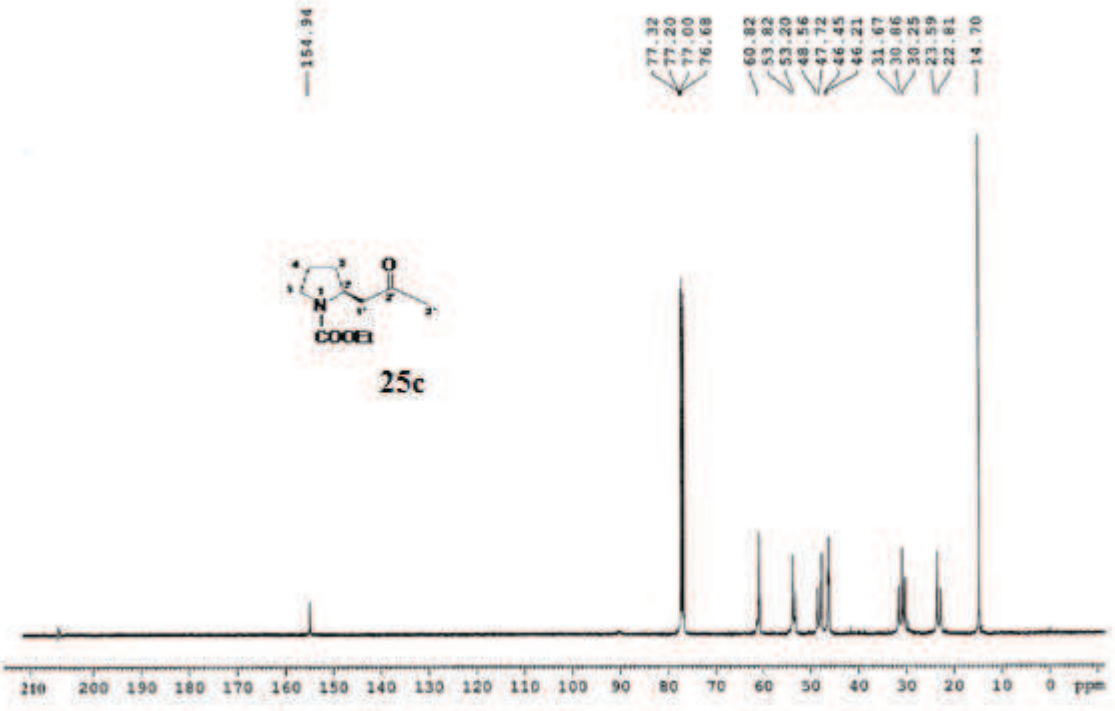

NO2
COOEt

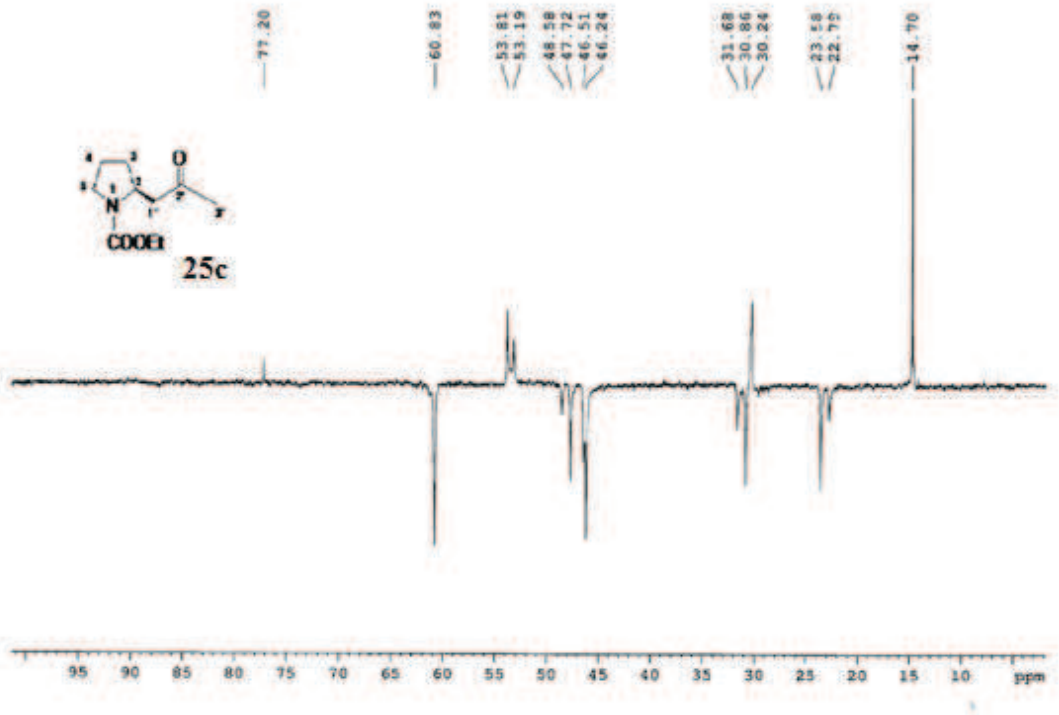
47c

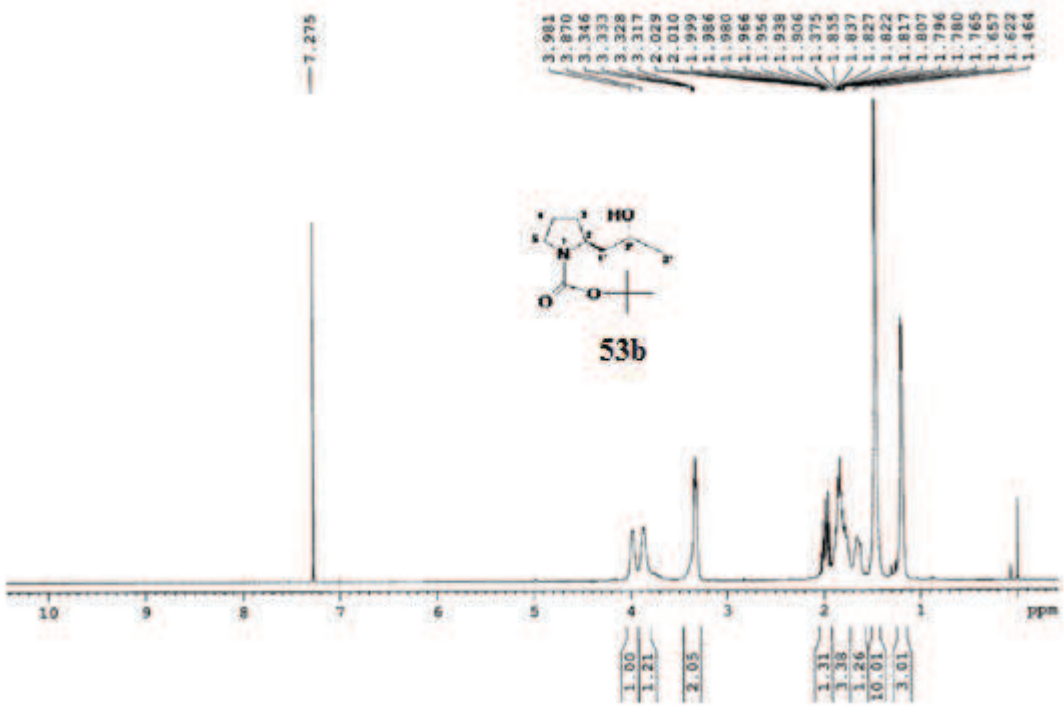

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

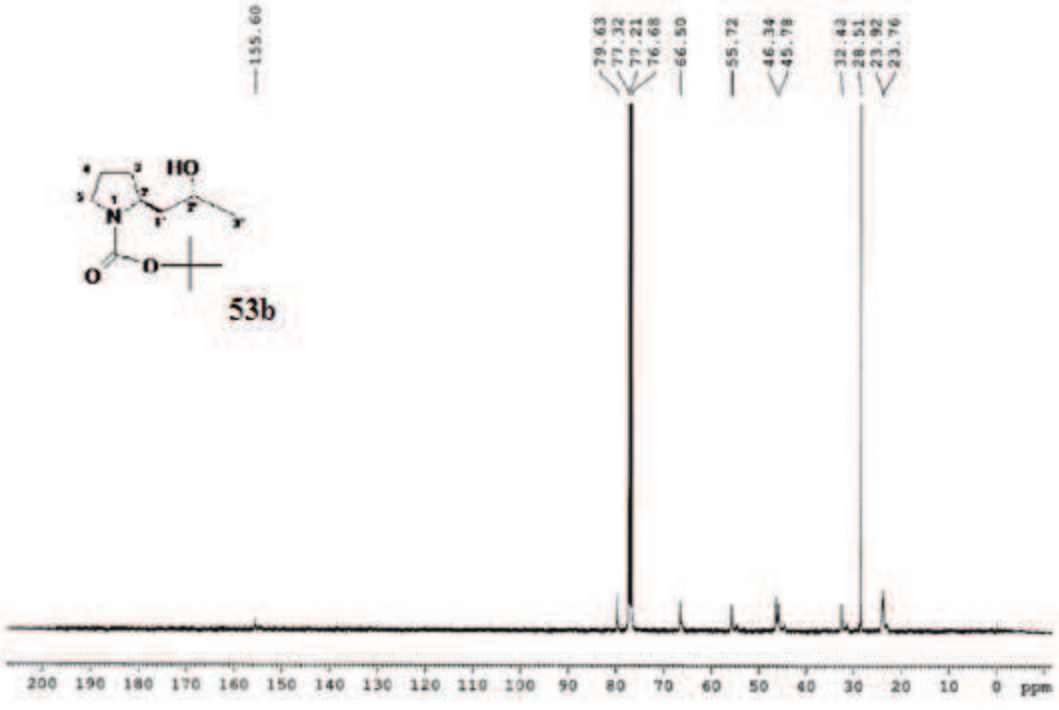

7.290
4.218
4.209
4.199
4.194
4.190
4.186
4.181
4.176
4.166
4.157
4.129
4.114
3.437
3.368
3.168
3.129
2.929
2.891
2.830
2.451
2.429
2.156
2.127
2.115
2.107
2.095
2.087
2.075
2.055
1.874
1.866
1.853
1.837
1.819
1.802
1.686
1.677
1.672
1.663
1.655
O
COOEt
10 9 8 7 6 5 4 3 2 1 ppm
0.64
0.79
1.00
0.29
0.19
0.50
1.35
0.52
1.05
0.49
1.49

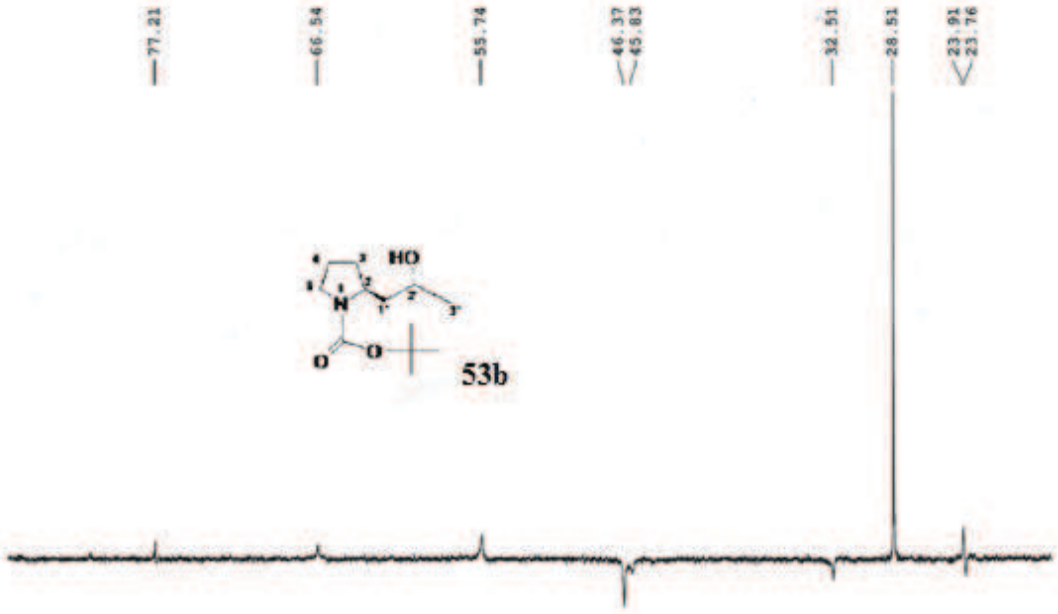
25c

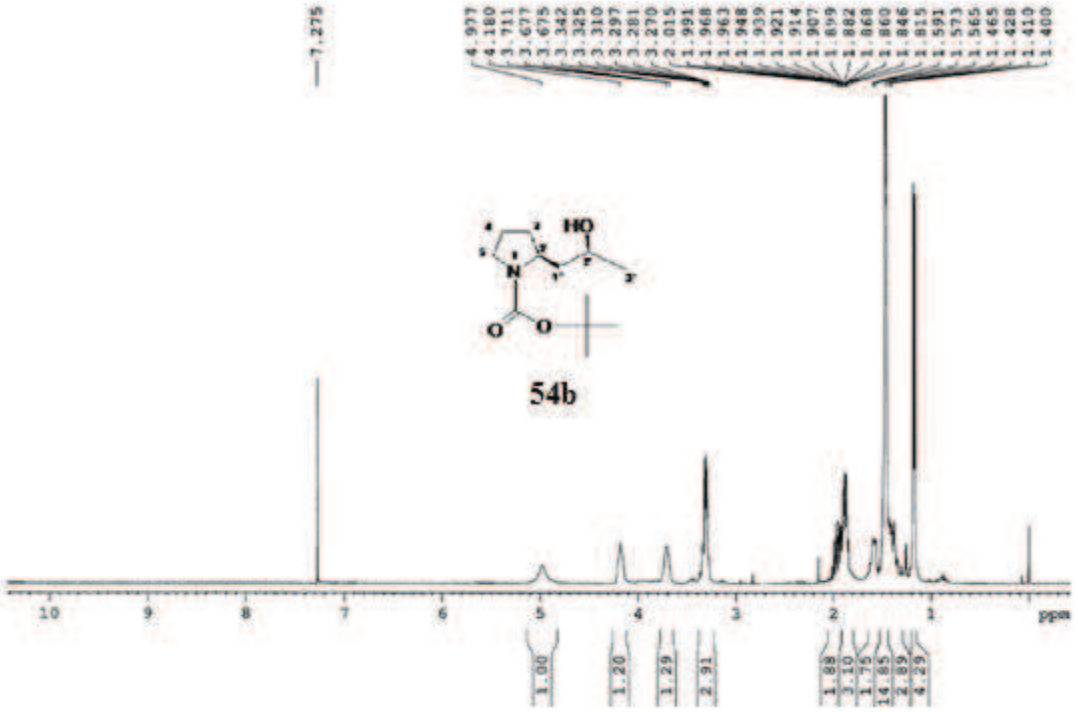

154.94
77.32
77.20
77.00
76.68
60.82
53.82
53.20
48.56
47.72
46.45
46.21
31.67
30.86
30.25
23.59
22.81
14.70
COOEt
25c
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

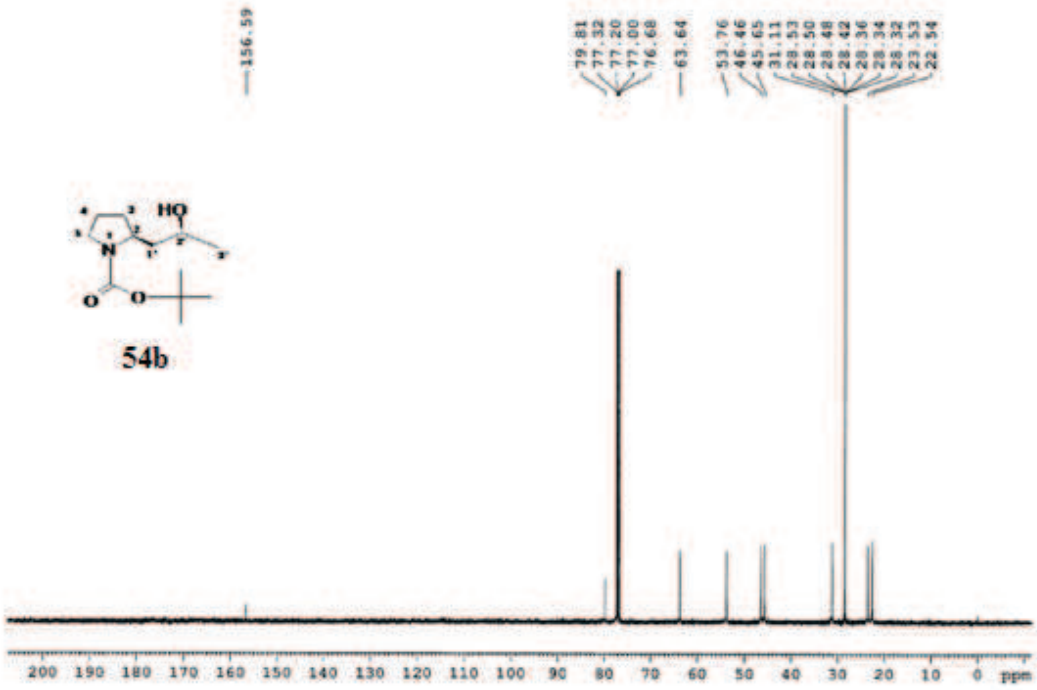

77.20
60.83
53.81
53.19
48.58
47.72
46.51
46.24
31.68
30.86
30.24
23.58
22.79
14.70
COOEt
25c
95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 ppm


7.275
3.981
3.870
3.346
3.333
3.328
3.317
2.029
2.010
1.999
1.986
1.980
1.966
1.956
1.938
1.906
1.375
1.855
1.837
1.827
1.822
1.817
1.807
1.796
1.780
1.765
1.657
1.622
1.464
HO
53b
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.21
2.05
1.31
3.38
1.26
10.01
3.01

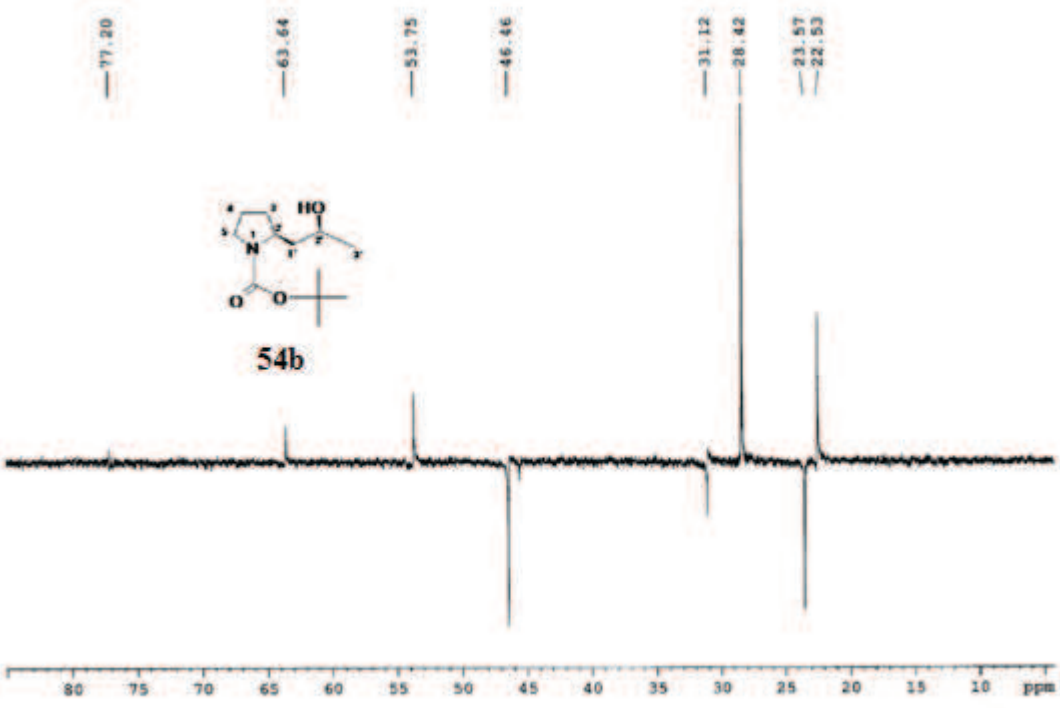

155.60
79.63
77.32
77.21
76.68
66.50
55.72
46.34
45.78
32.43
28.51
23.92
23.76
HO
53b
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


77.21
66.54
55.74
46.37
45.83
32.51
28.51
23.91
23.76
HO
N
O
O
53b

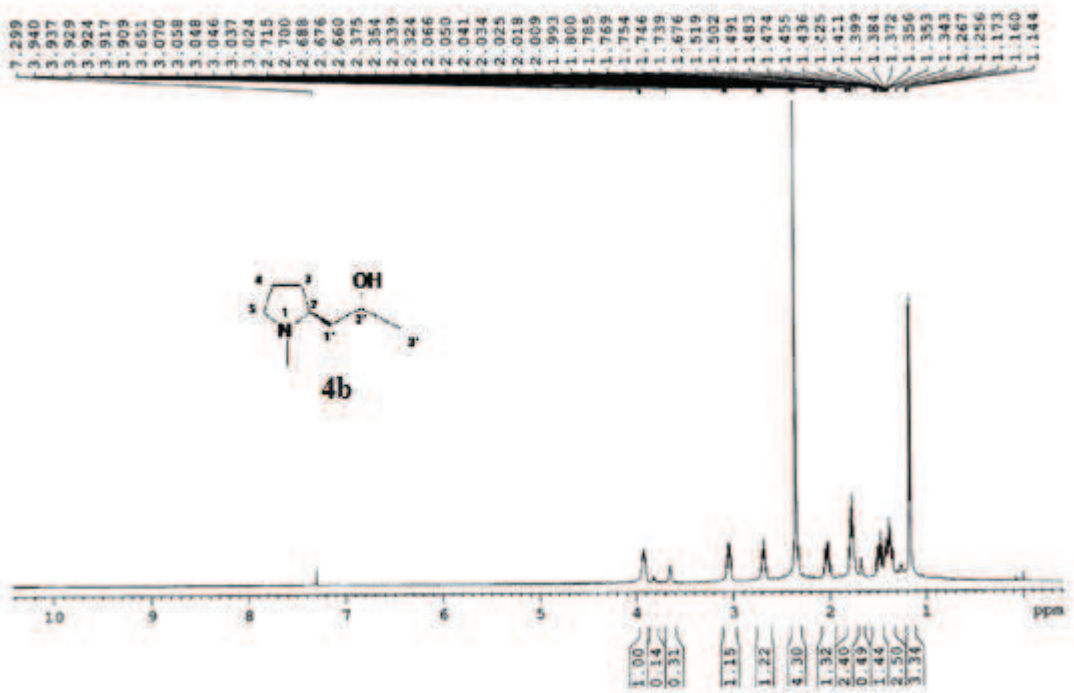

7.275
4.977
4.160
3.711
3.677
3.675
3.342
3.325
3.310
3.297
3.281
3.270
2.015
1.991
1.968
1.963
1.948
1.939
1.921
1.914
1.907
1.899
1.882
1.868
1.860
1.846
1.815
1.591
1.573
1.565
1.465
1.428
1.410
1.400
HO
N
O
O
54b
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.20
1.29
2.91
1.88
3.10
1.75
14.85
2.89
4.29

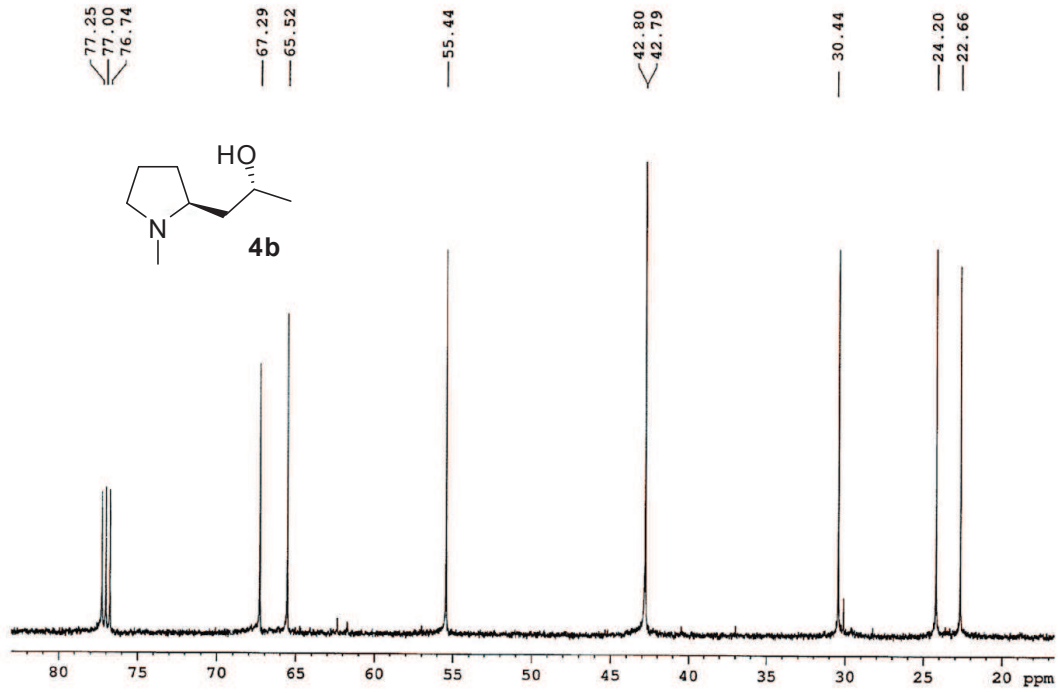

156.59
79.81
77.32
77.20
77.00
76.68
63.64
53.76
46.46
45.65
31.11
28.53
28.50
28.48
28.42
28.36
28.34
28.32
23.53
22.54
HO
N
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

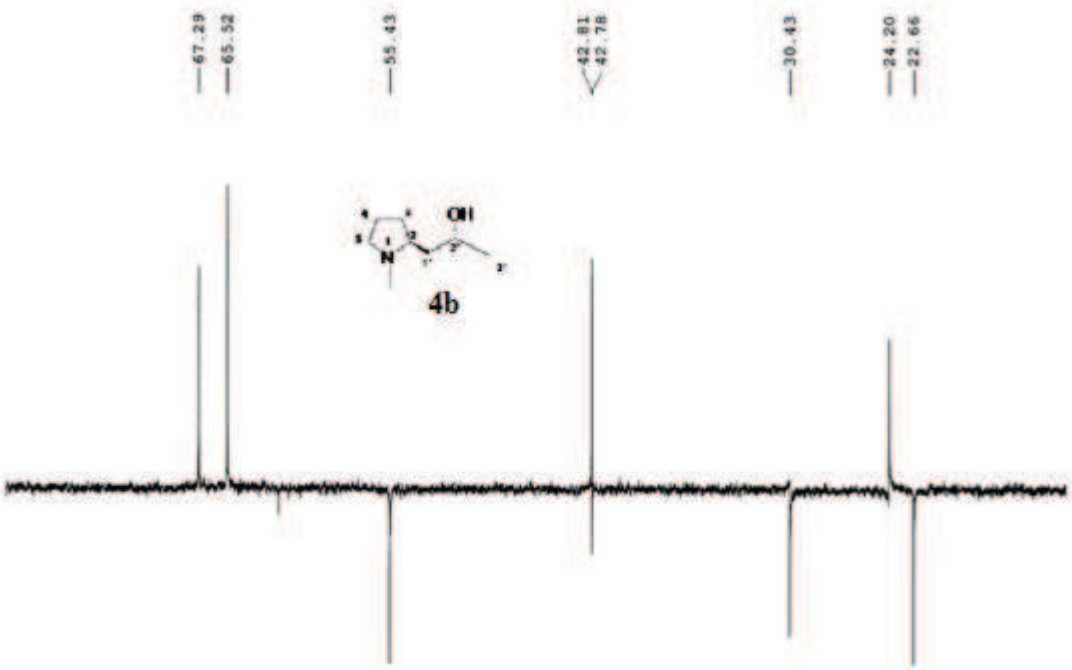
54b

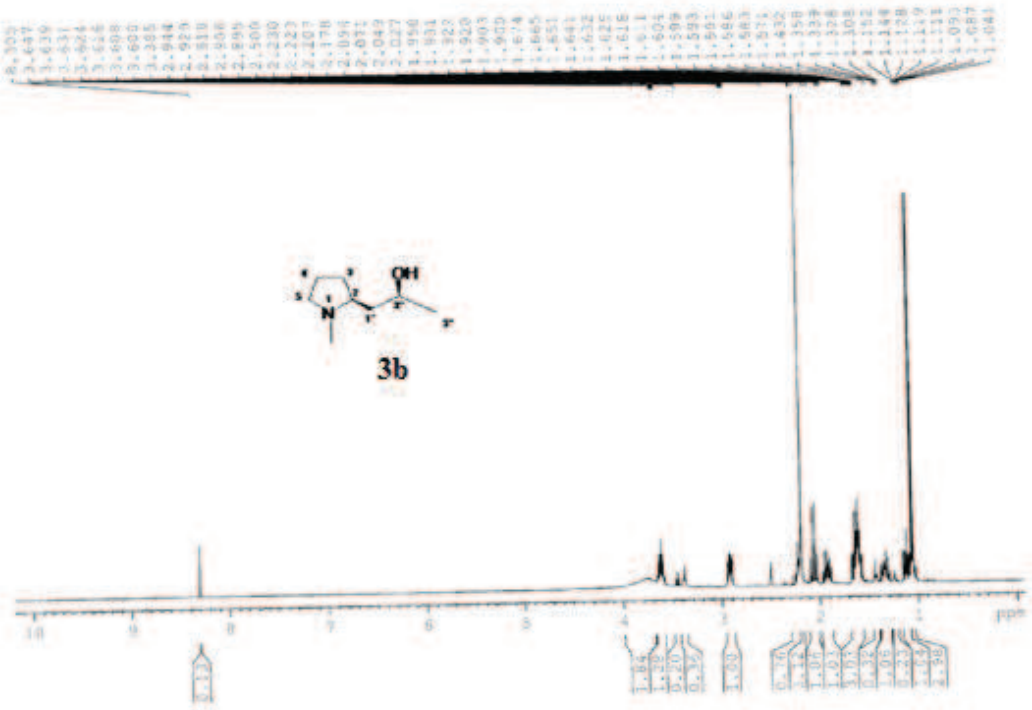

77.20
63.64
53.75
46.46
31.12
28.42
23.57
22.53
HO
N
O
O
80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 ppm

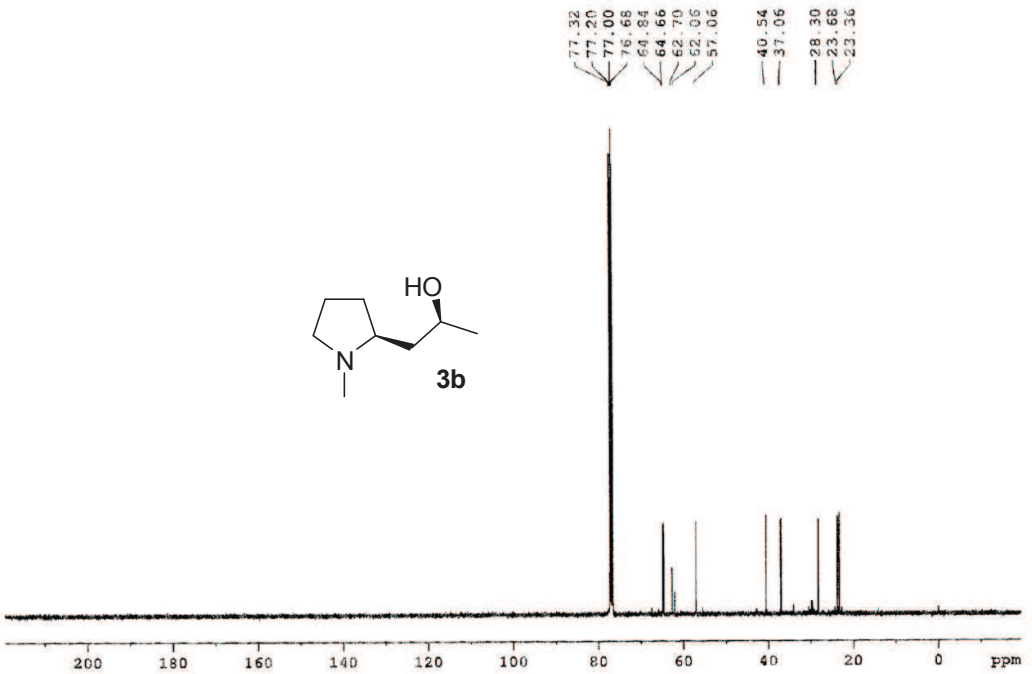
54b

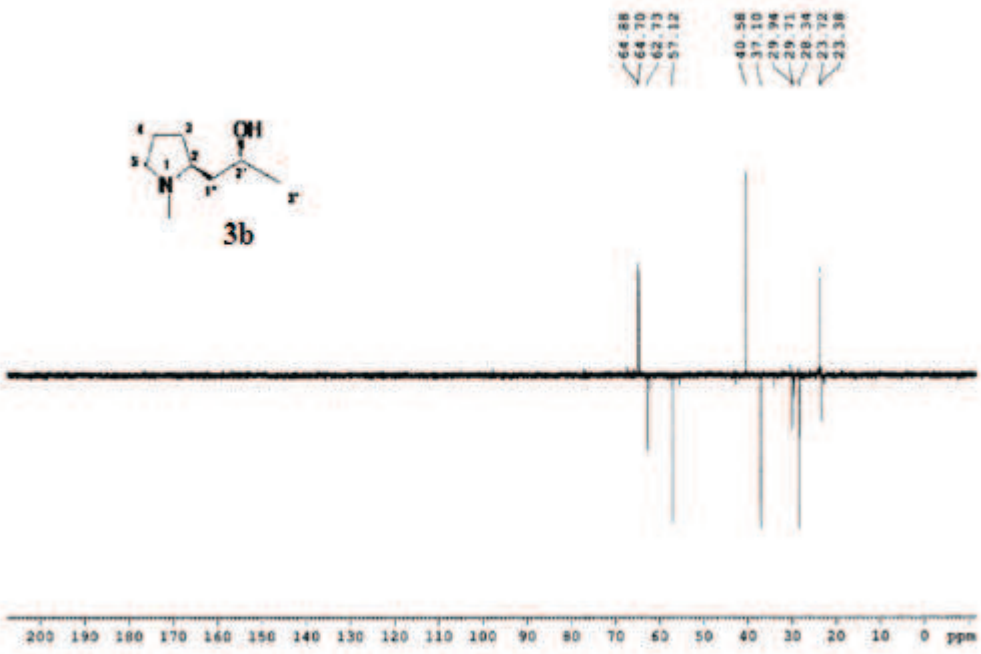

OH
4b
ppm

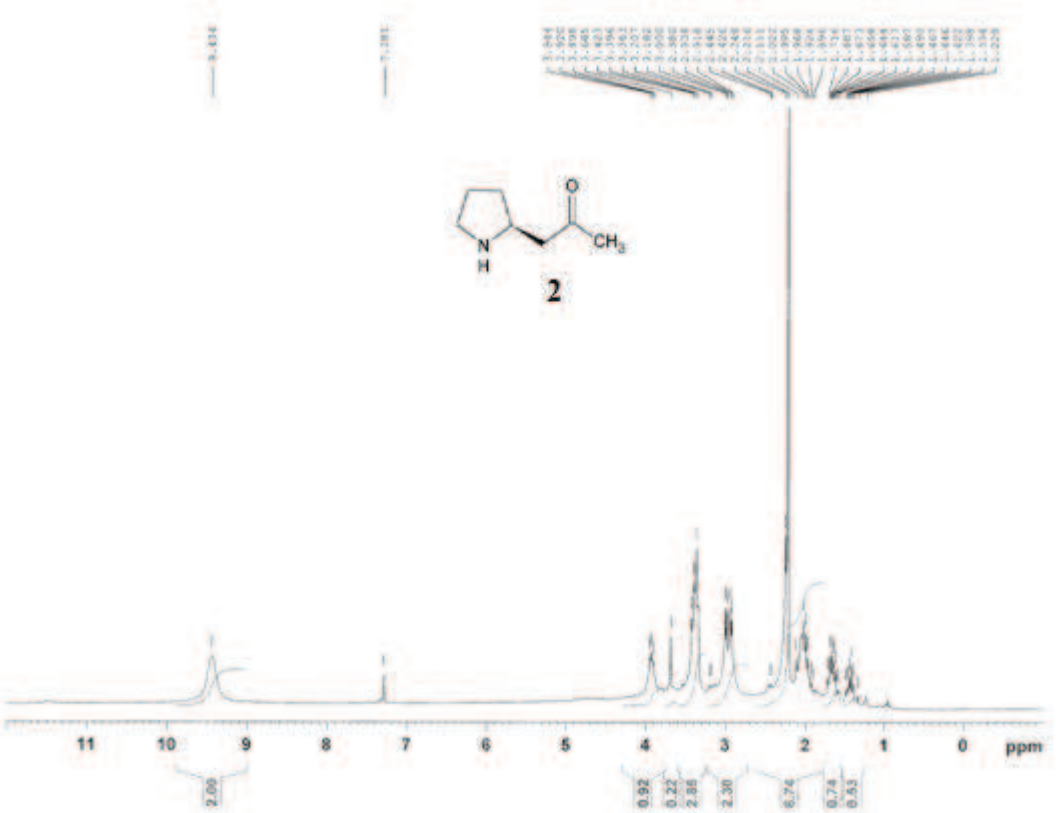

77.25
77.00
76.74
67.29
65.52
55.44
42.80
42.79
30.44
24.20
22.66
HO
4b
ppm

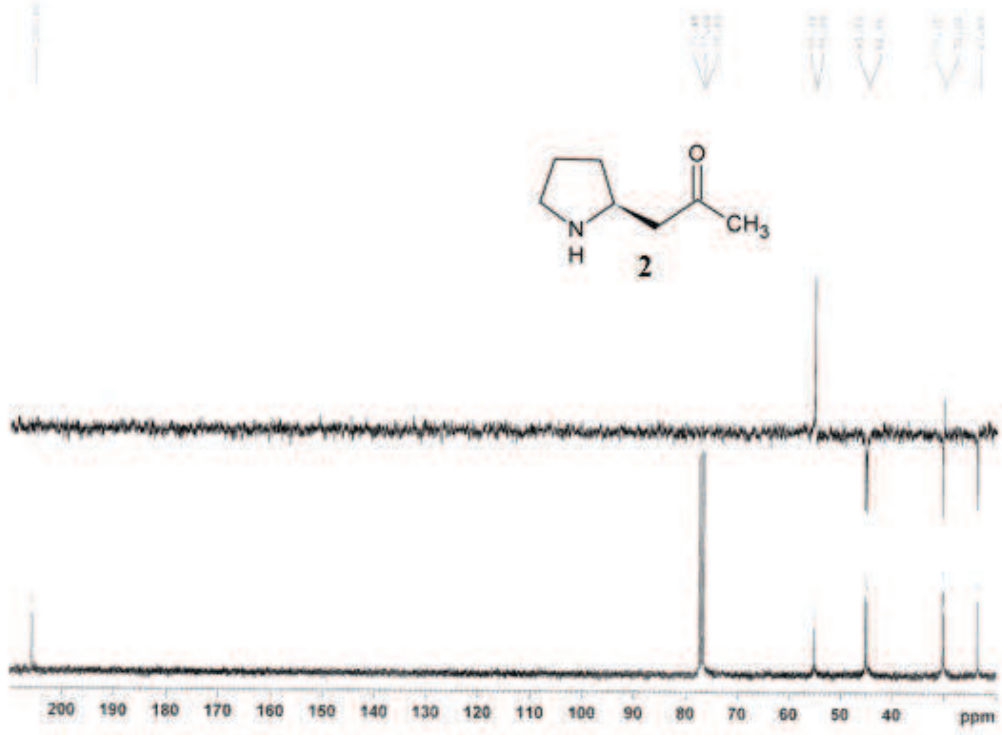

67.29
65.52
55.43
42.81
42.78
30.43
24.20
22.66
OH
4b

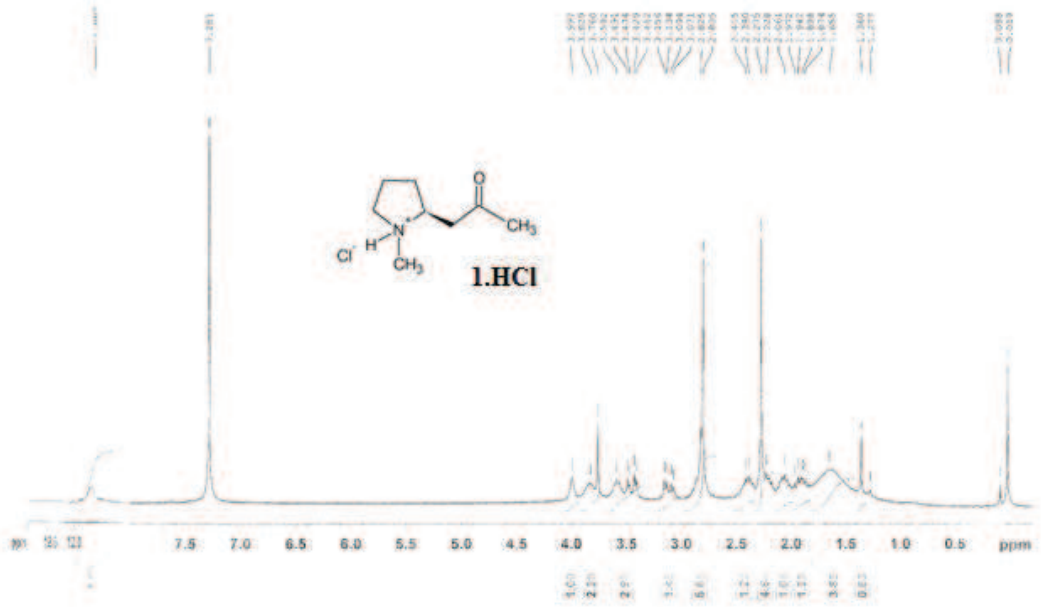

OH
3b

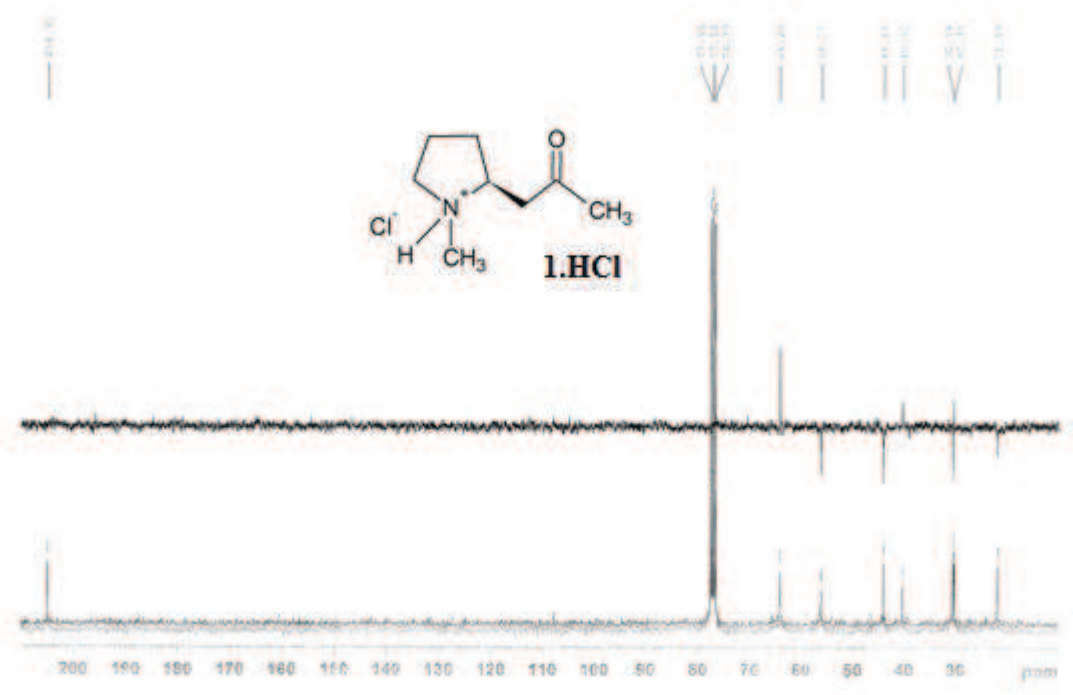

77.32
77.20
77.00
76.68
64.84
64.66
62.70
52.06
57.06
40.54
37.06
28.30
23.68
23.36
HO
N
3b
200
180
160
140
120
100
80
60
40
20
0
ppm


64.88
64.70
62.73
57.12
40.58
37.10
29.94
29.71
28.34
23.72
23.38
OH
N
3b
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

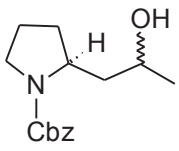

O
N
H
CH3
2
11 10 9 8 7 6 5 4 3 2 1 0 ppm
2.00
0.92
0.22
2.85
2.30
6.74
0.74
0.53


O
N
H
CH3
2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 ppm





HPLC Data of the diastereomeric seperation with different reducing agents.



Wavelength= 242nm, eluent n-hexane / IPA (9:1), Flow rate 1mL / min

Reduced by $Li(O\text{-}terBu)_3AlH$

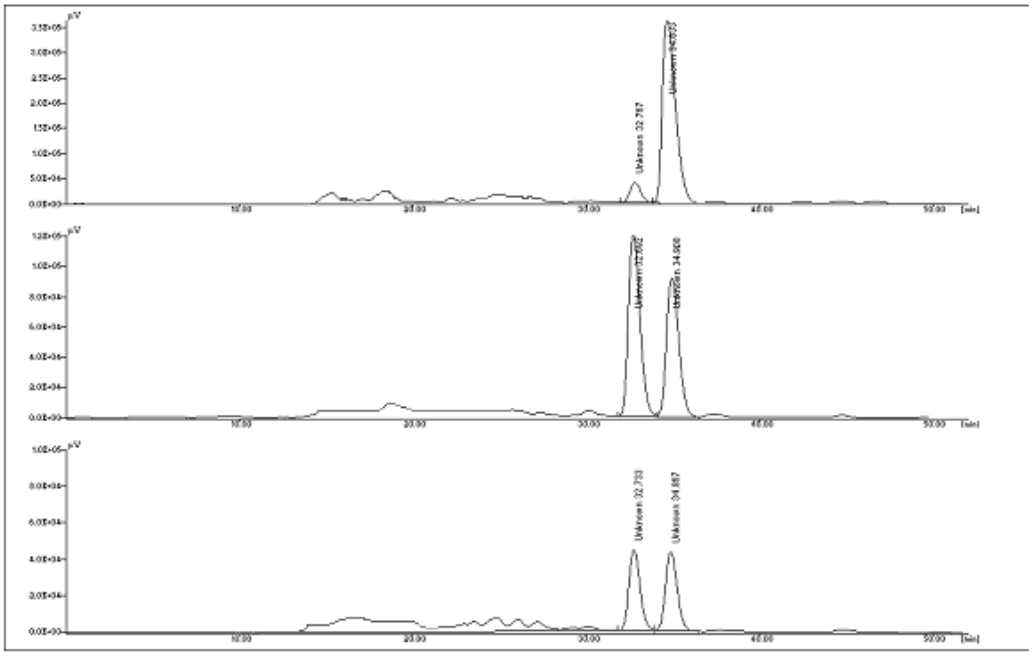
#	Name	RT	Area[μV.Sec]	%Area
1	*trans*	32.767	1638135.537	8.43
2	*cis*	34.633	17786858.963	91.57

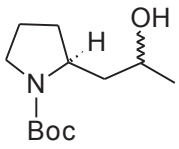
NaBH4 reduction

#	Name	RT	Area[μV.Sec]	%Area
1	*trans*	32.692	5203150.830	55.31
2	*cis*	34.908	4204360.170	44.69

$Zn(BH_4)_2$ reduction

#	Name	RT	Area[μV.Sec]	%Area
1	*trans*	32.733	1904060.106	49.84
2	*cis*	34.867	1916412.617	50.16





Wavelength = 224nm, eluent n-hexane / IPA (9:1), Flow rate 1mL / min

Reduced by Li(*ter*-BuO)$_3$AlH

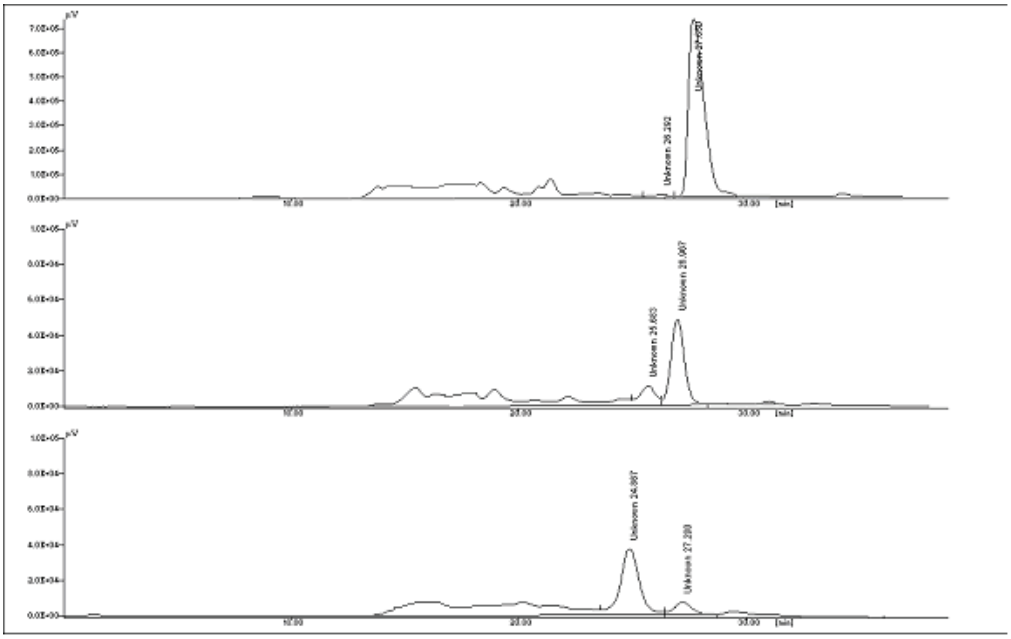
#	Name	RT	Area[μV.Sec]	%Area
1	*trans*	26.29	458588.842	1.38
2	*cis*	27.650	32885897.708	98.62

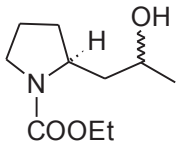
Reduced by $NaBH_4$

#	Name	RT	Area[μV.Sec]	%Area
1	*trans*	25.683	505283.215	21.10
2	*cis*	26.967	1889796.883	78.90

Reduced by $Zn(BH_4)_2$

#	Name	RT	Area[μV.Sec]	%Area
1	*trans*	24.867	2073043.020	85.32
2	*cis*	27.200	356719.801	14.68





Wavelength= 215nm , eluent n-hexane / IPA (9:1), Flow rate 1mL / min

Reduced by $Li(O\text{-}tBu)_3AlH$

#	Name	RT	Area[μV.Sec]	%Area
1	*trans*	42.850	2519210.685	19.12
2	*cis*	44.383	10653223.322	80.88

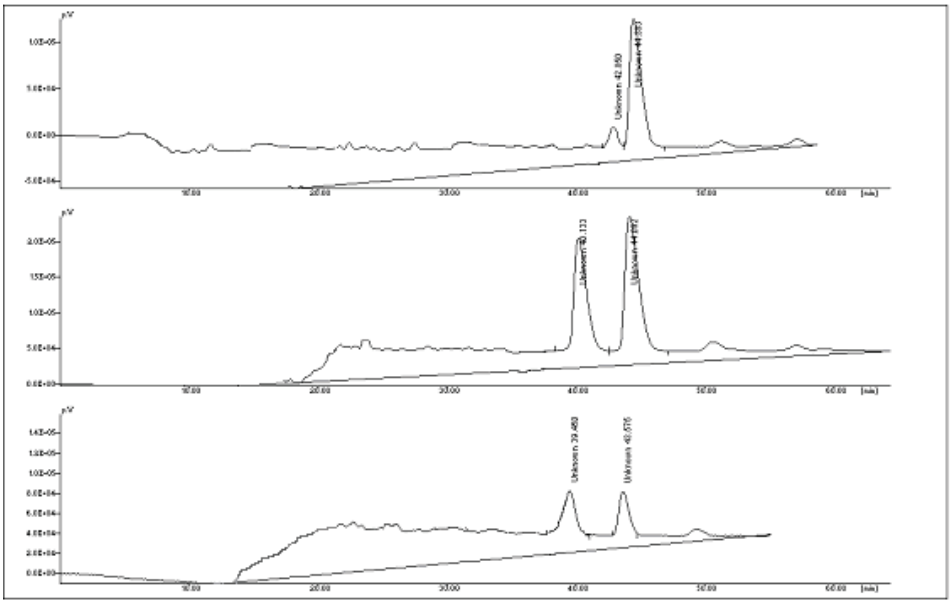
Reduced by $NaBH_4$

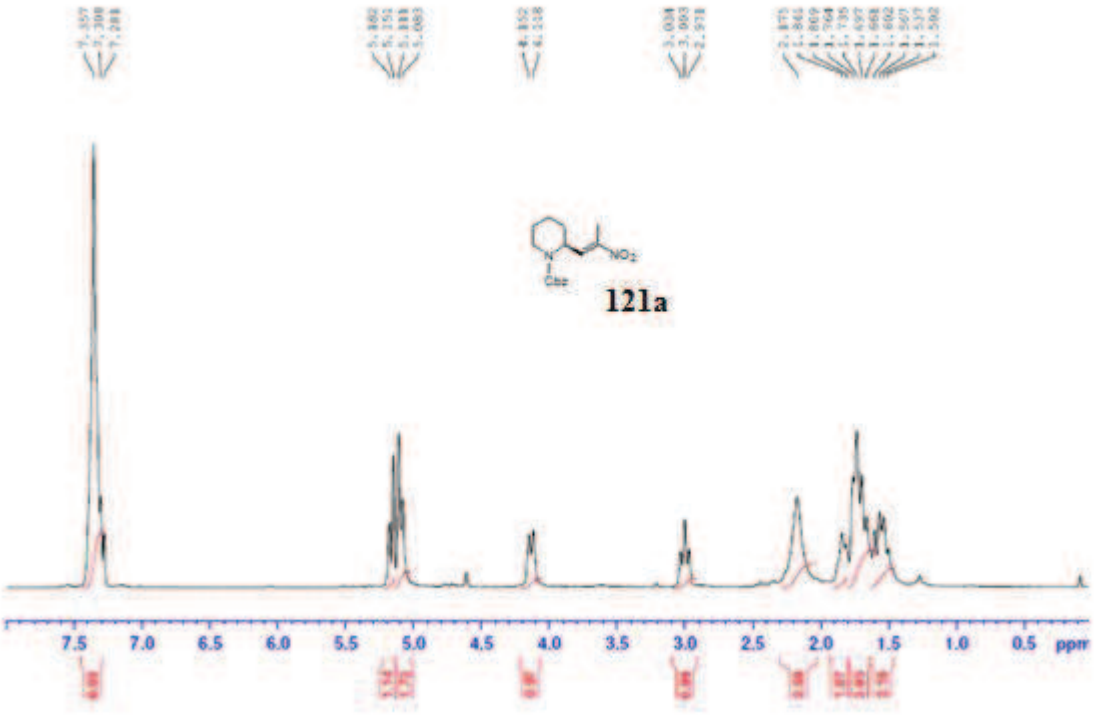
#	Name	RT	Area[μV.Sec]	%Area
1	*trans*	40.133	15561017.250	46.50

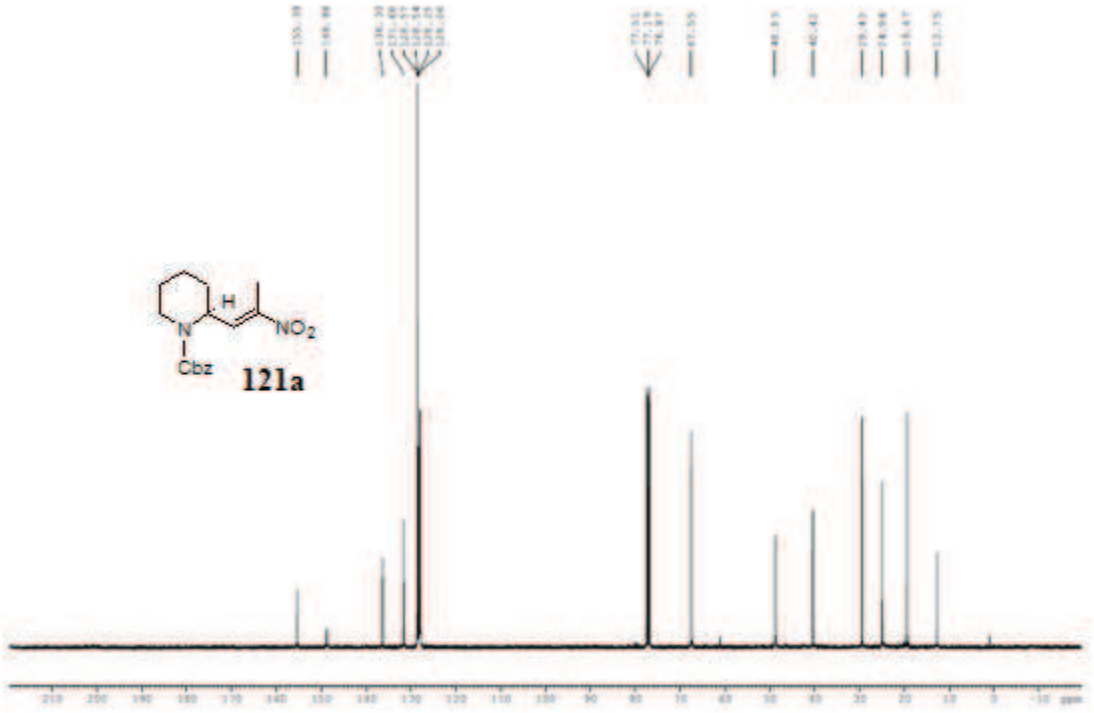
2	*cis*	44.092	17904968.099	53.50

Reduced by $Zn(BH_4)_2$

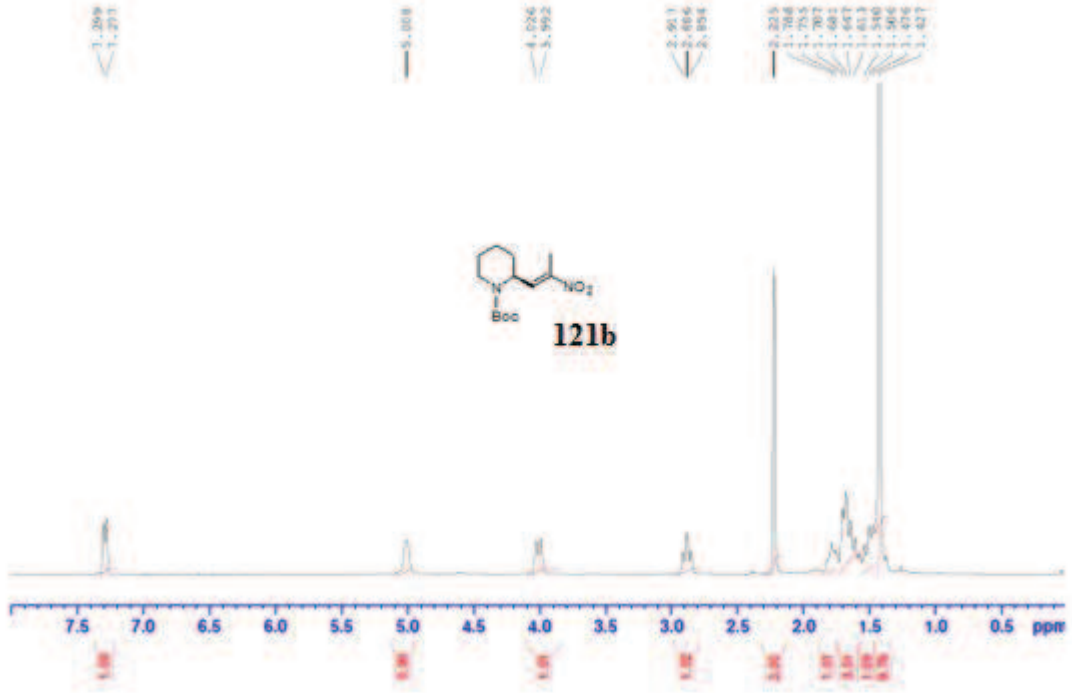
#	Name	RT	Area[μV.Sec]	%Area
1	*trans*	39.450	2640885.771	42.53
2	*cis*	43.575	3568796.269	57.47



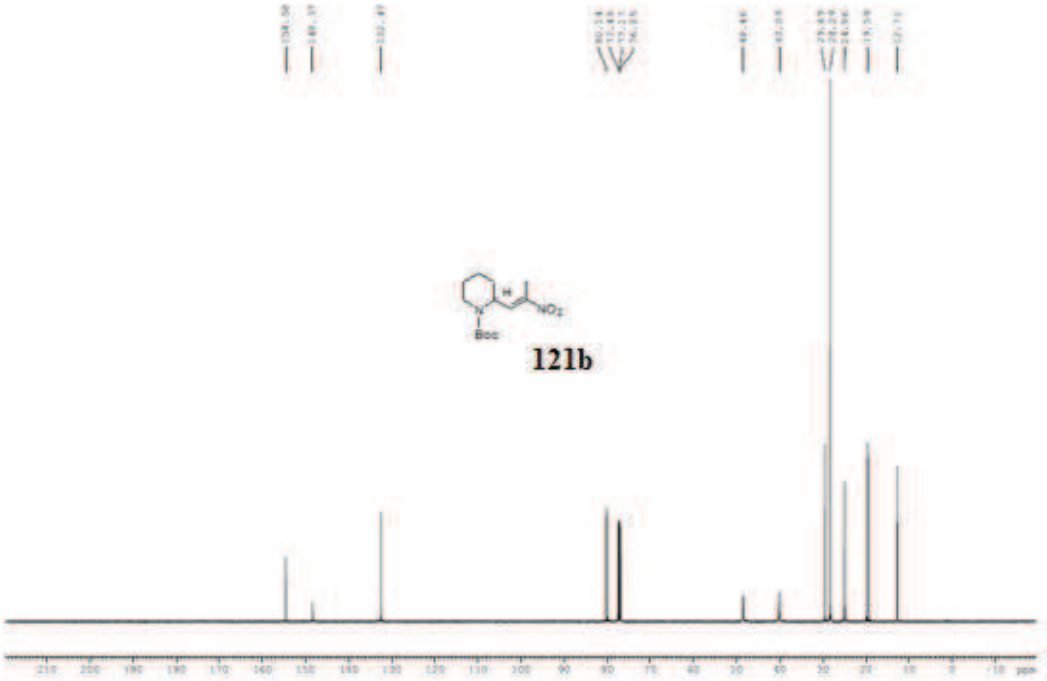

NO2
Cbz
121a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


H
N
NO2
Cbz
121a

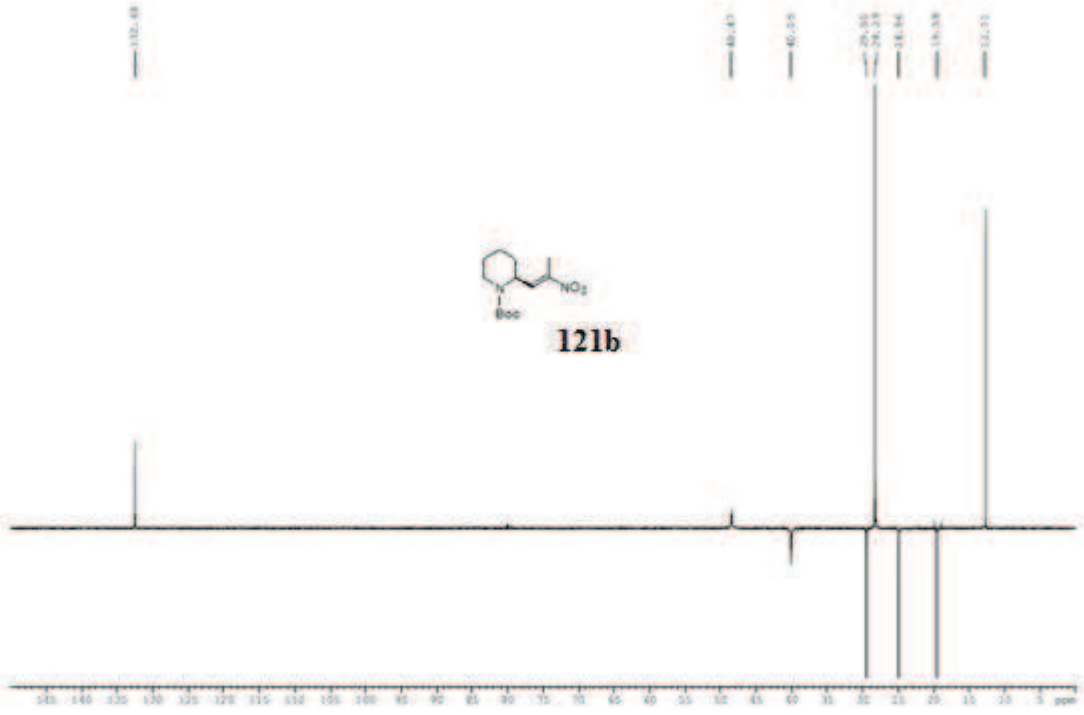
121a



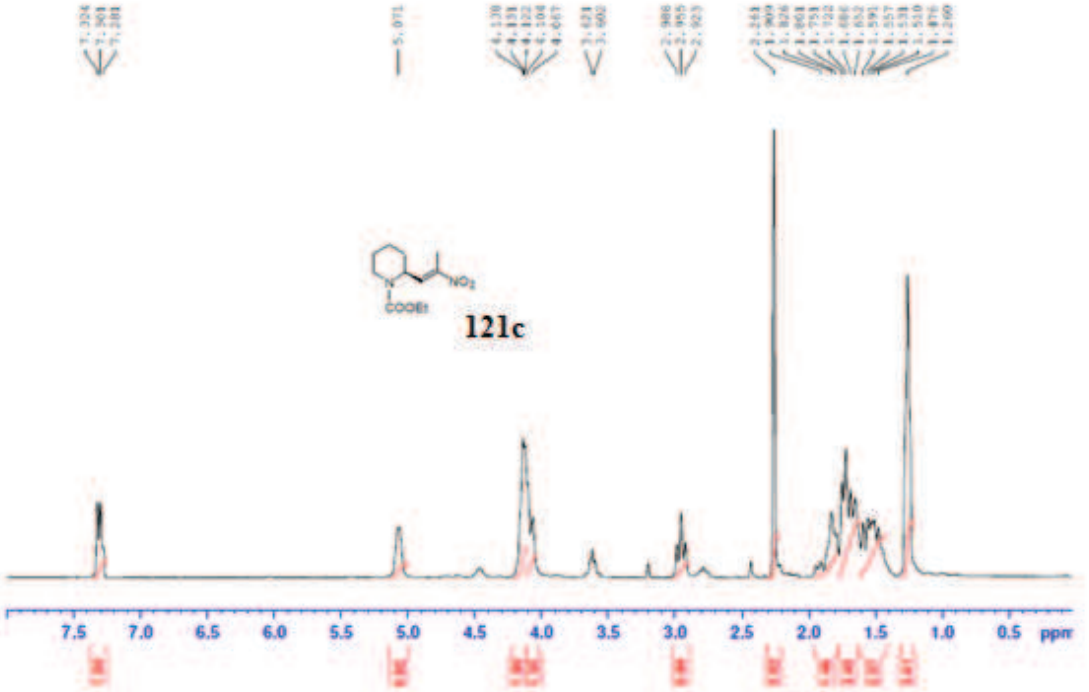
121b

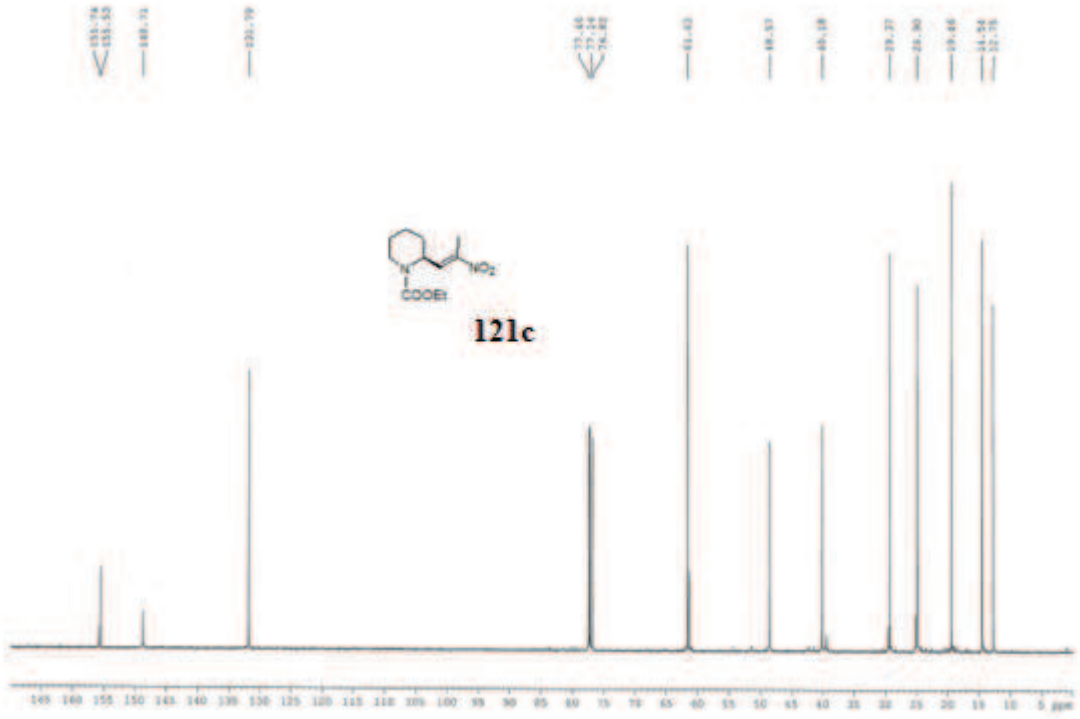


121b



121b


121c
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm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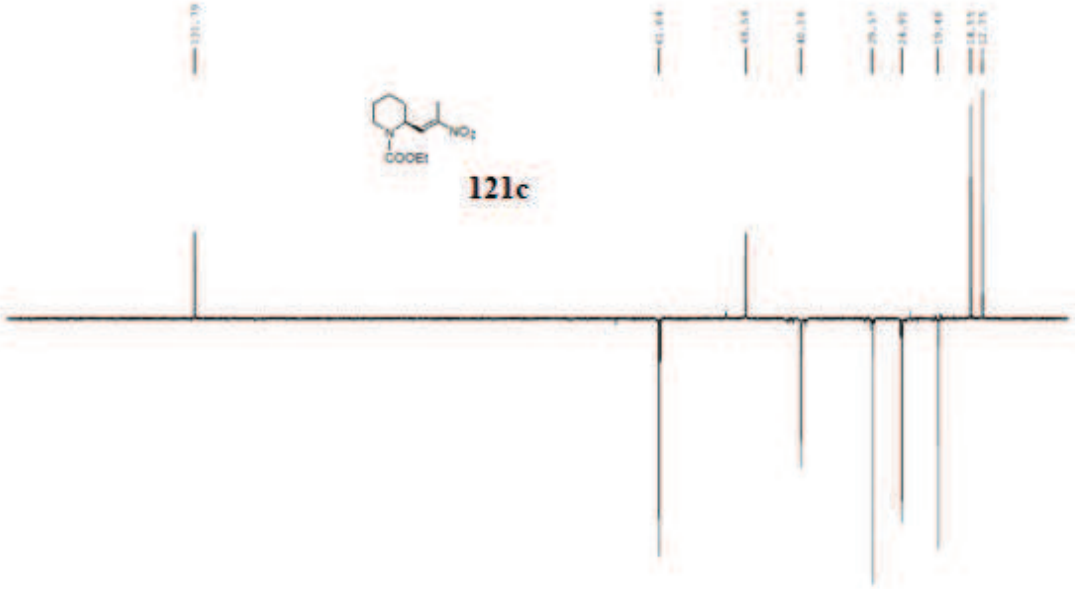
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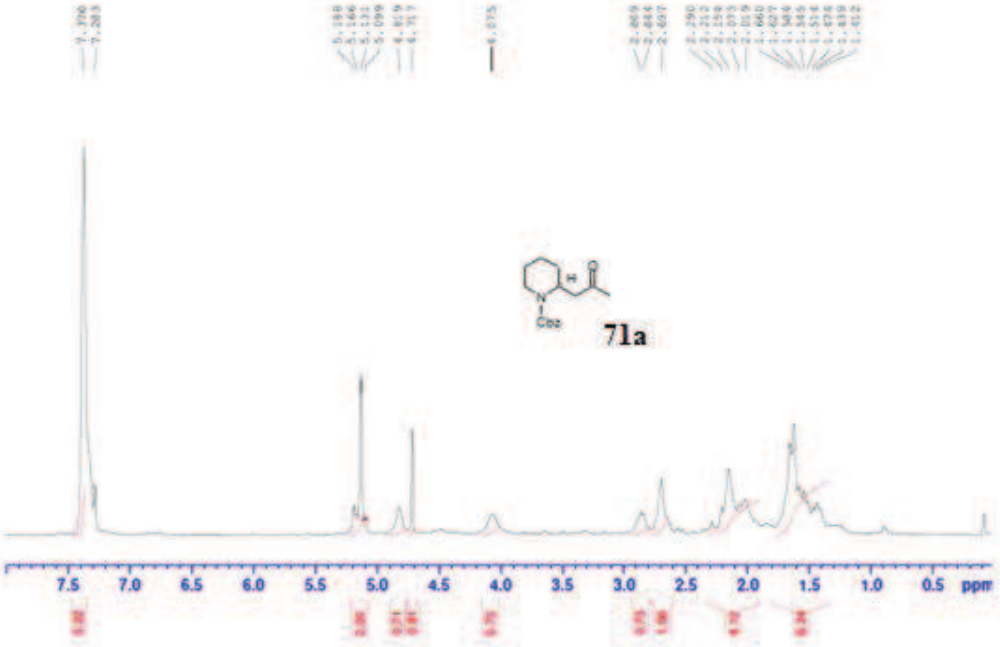
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2.0
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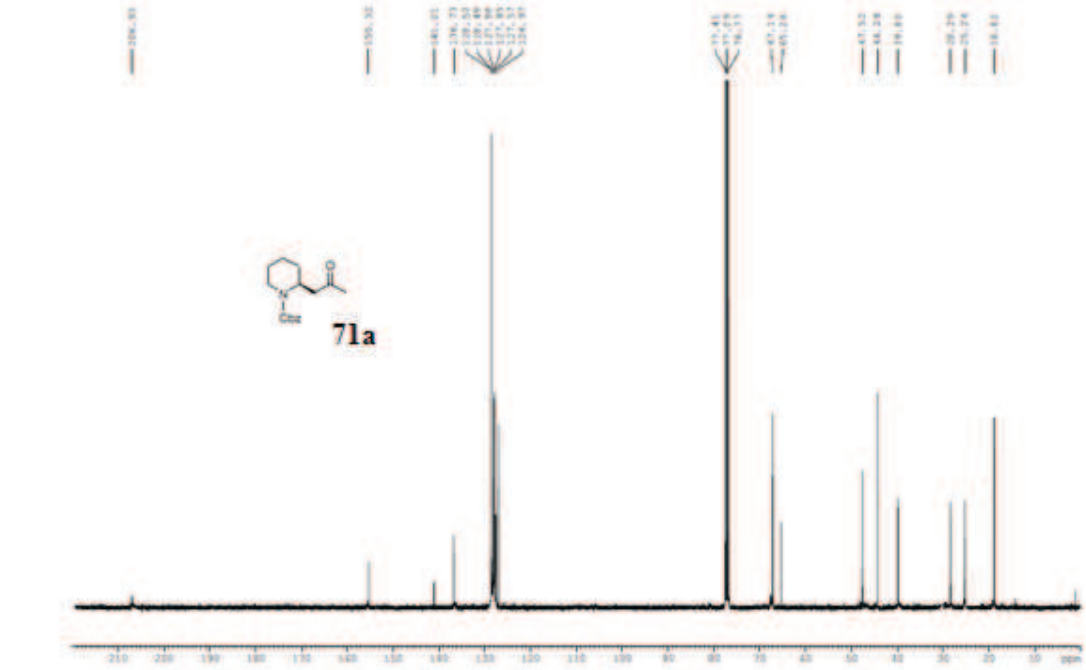
ppm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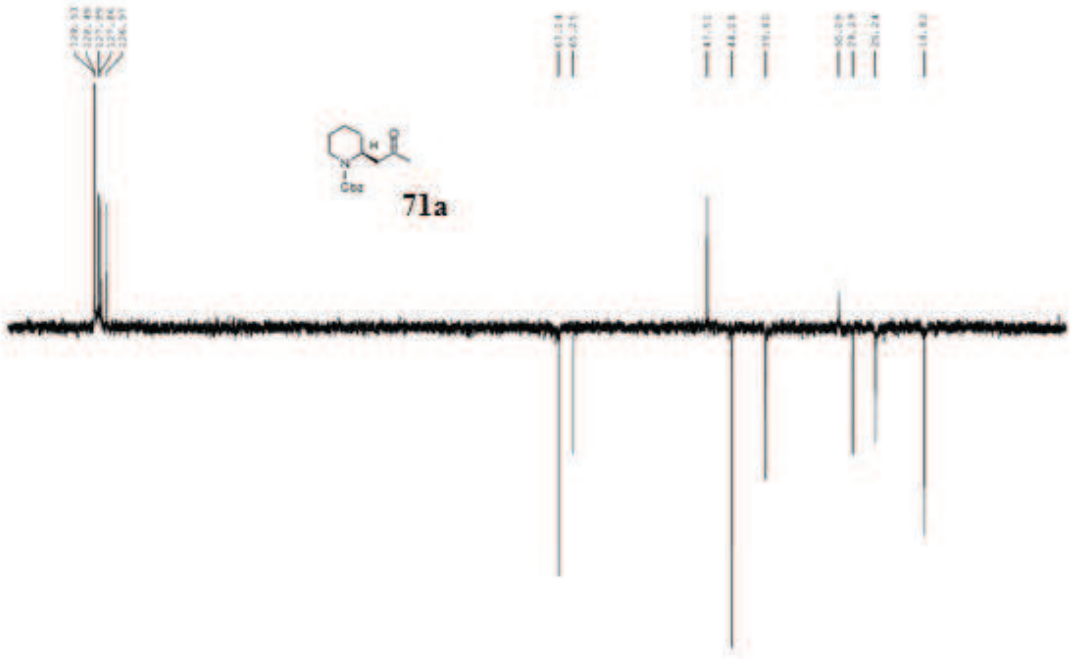
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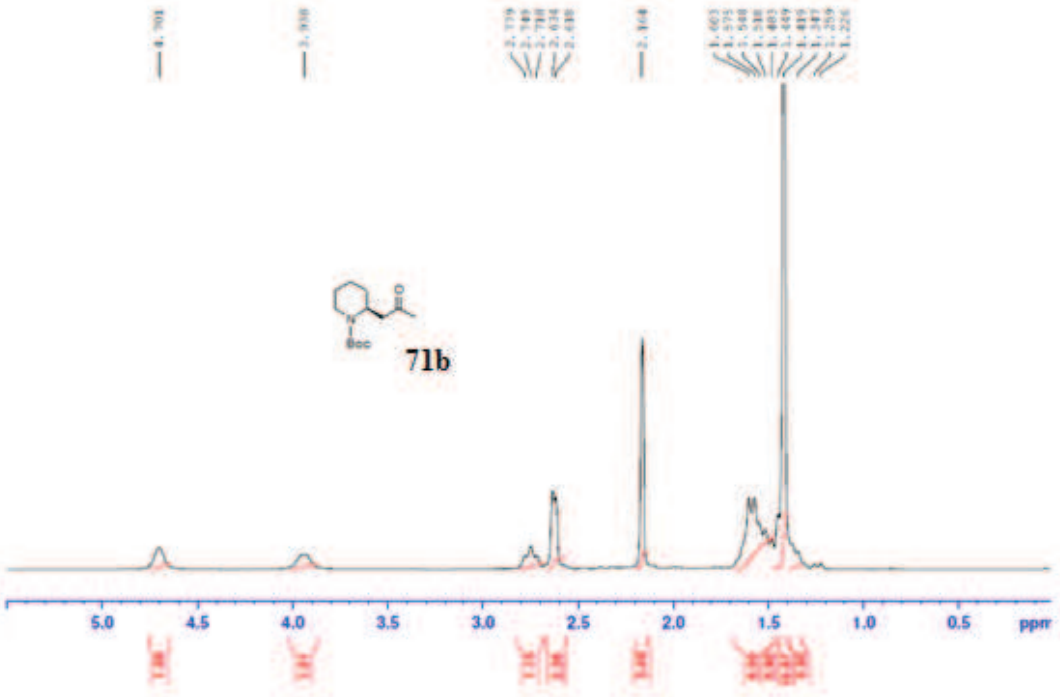
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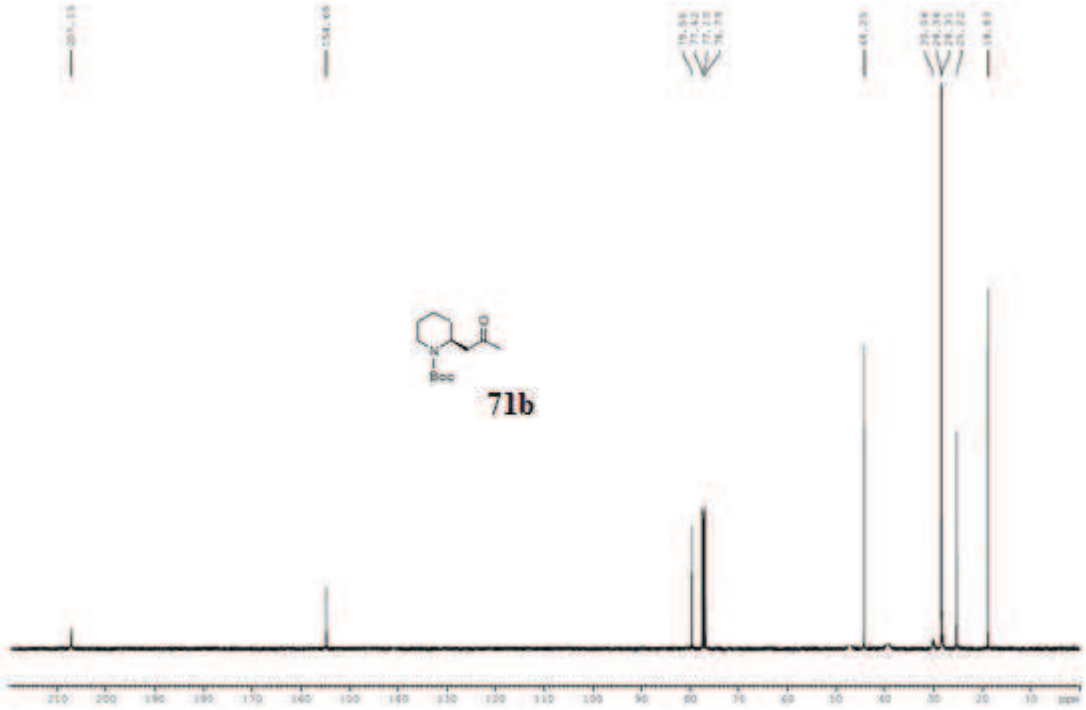
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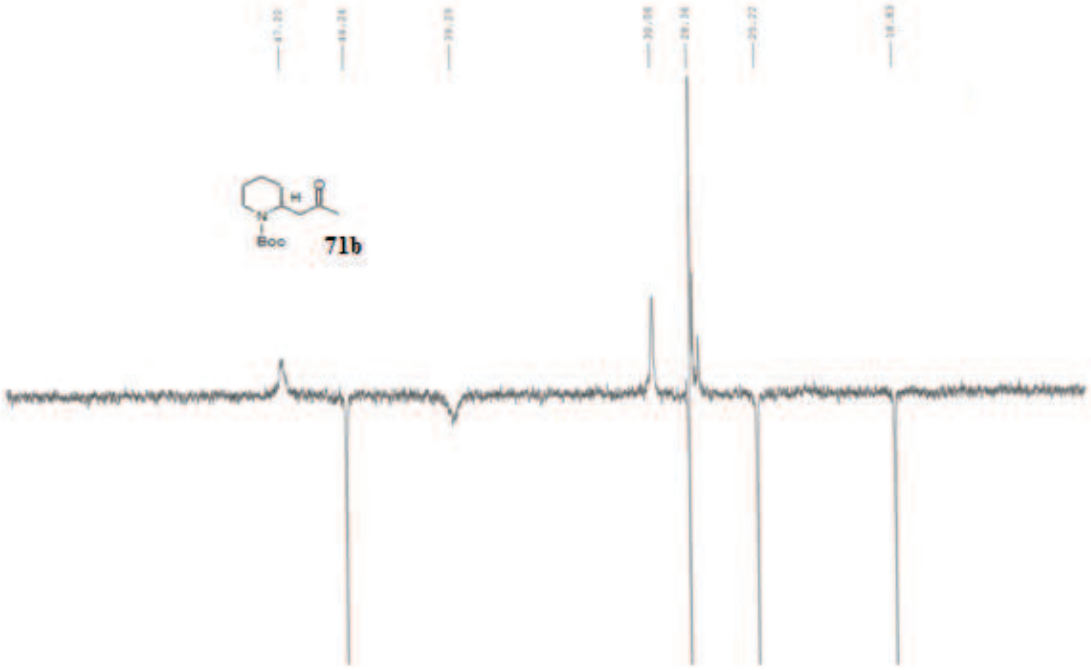
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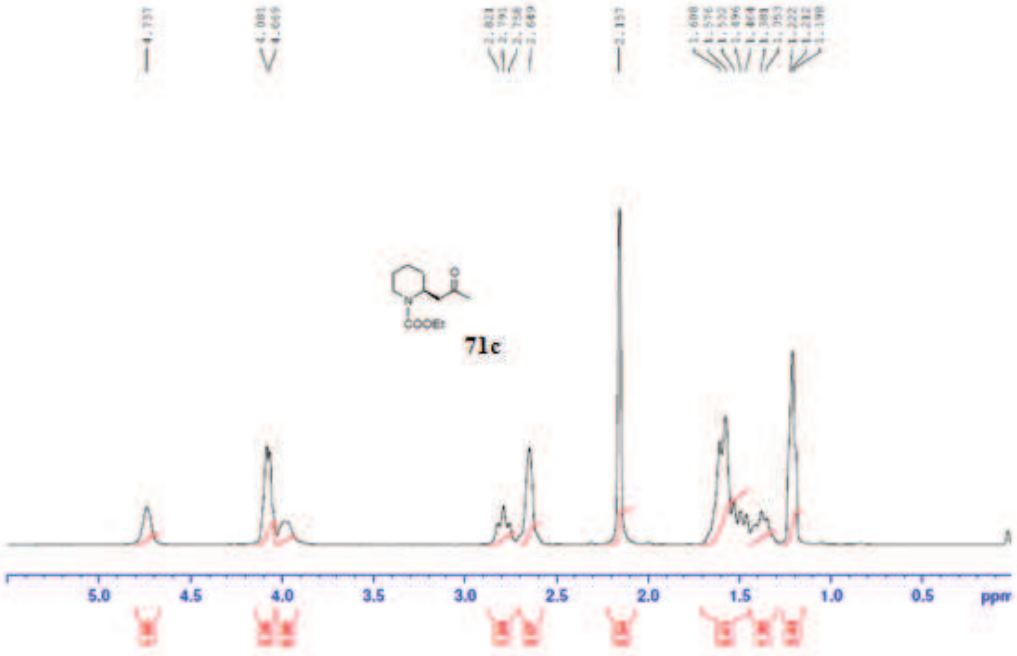
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1.0
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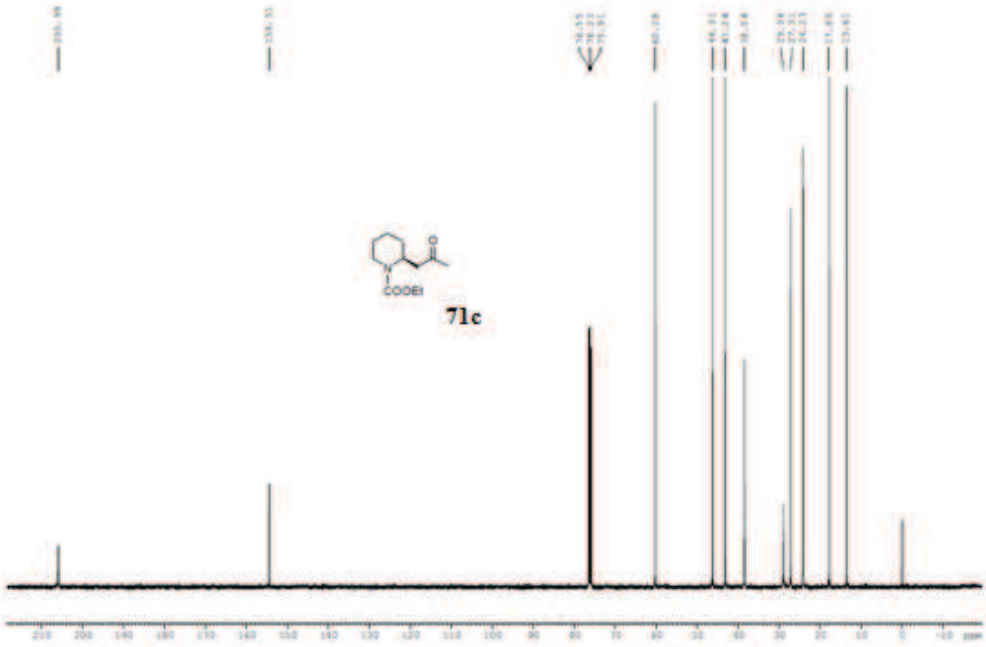
ppm



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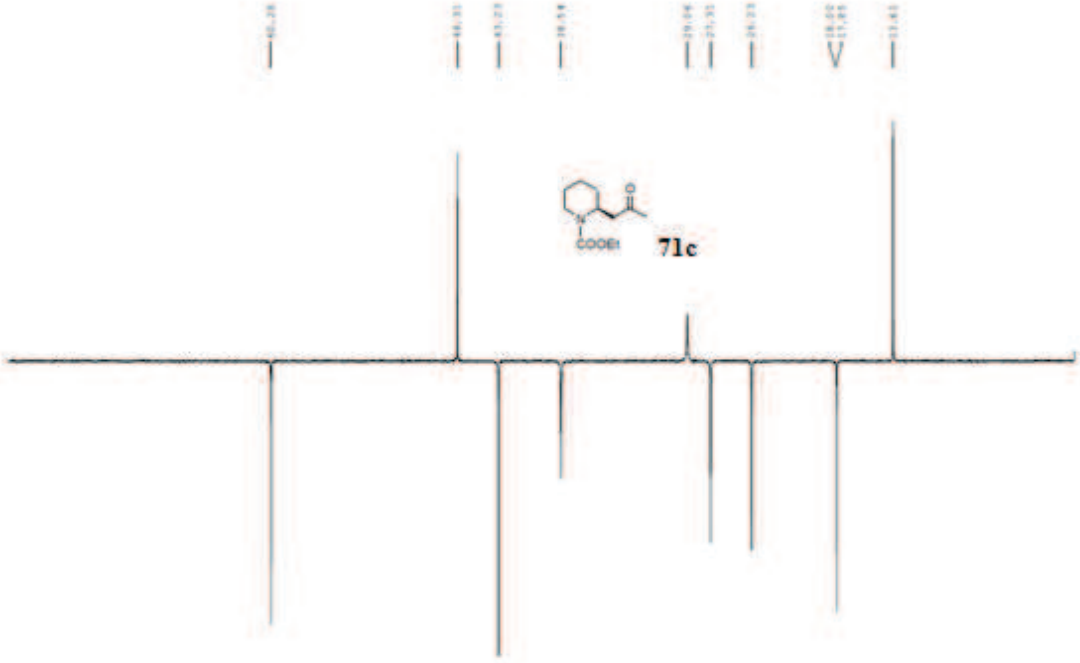

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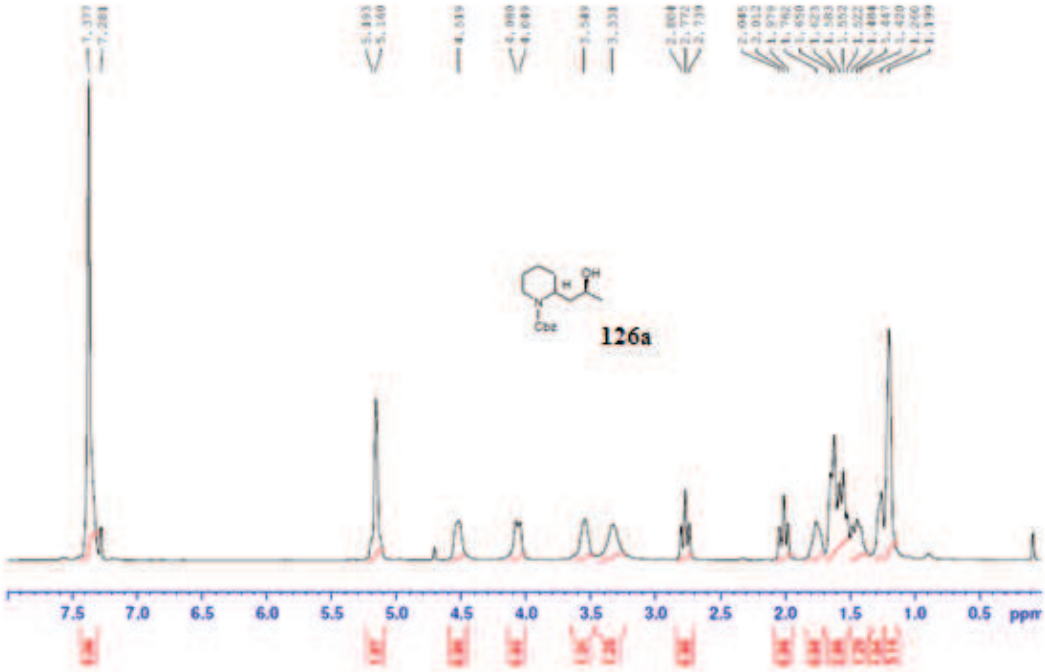
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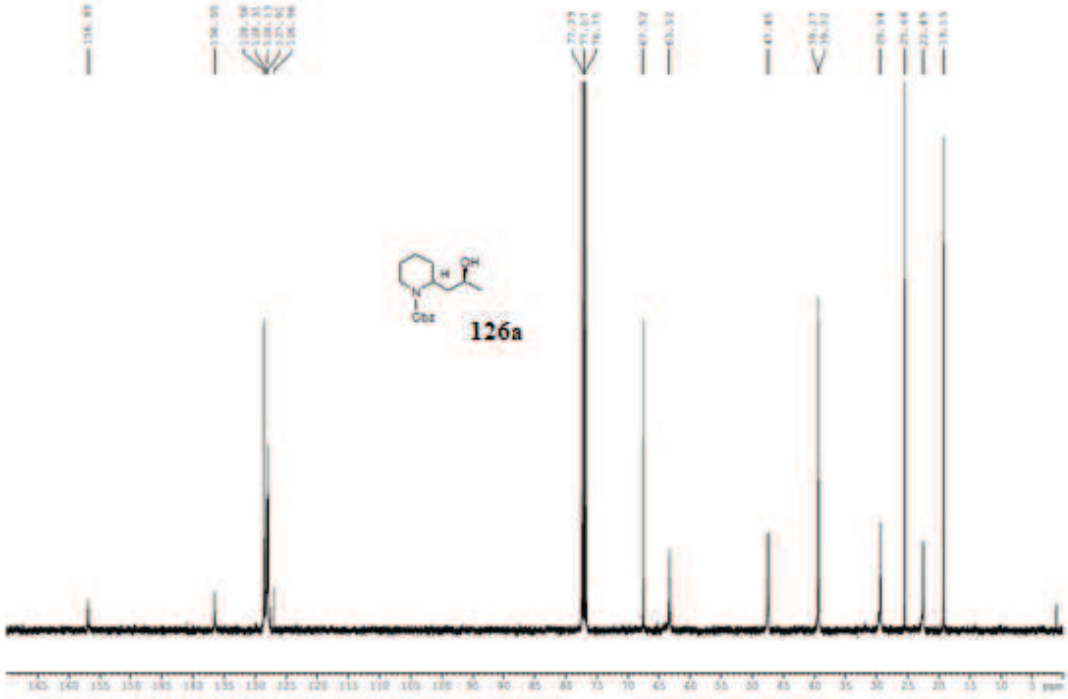
1.0
0.5
ppm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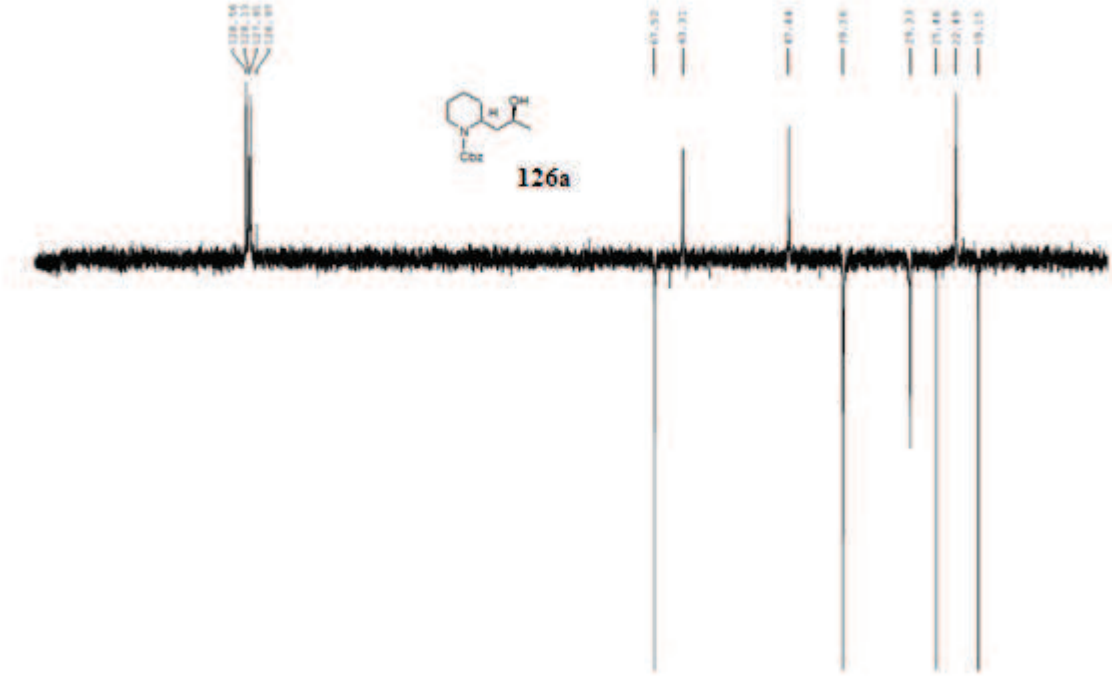
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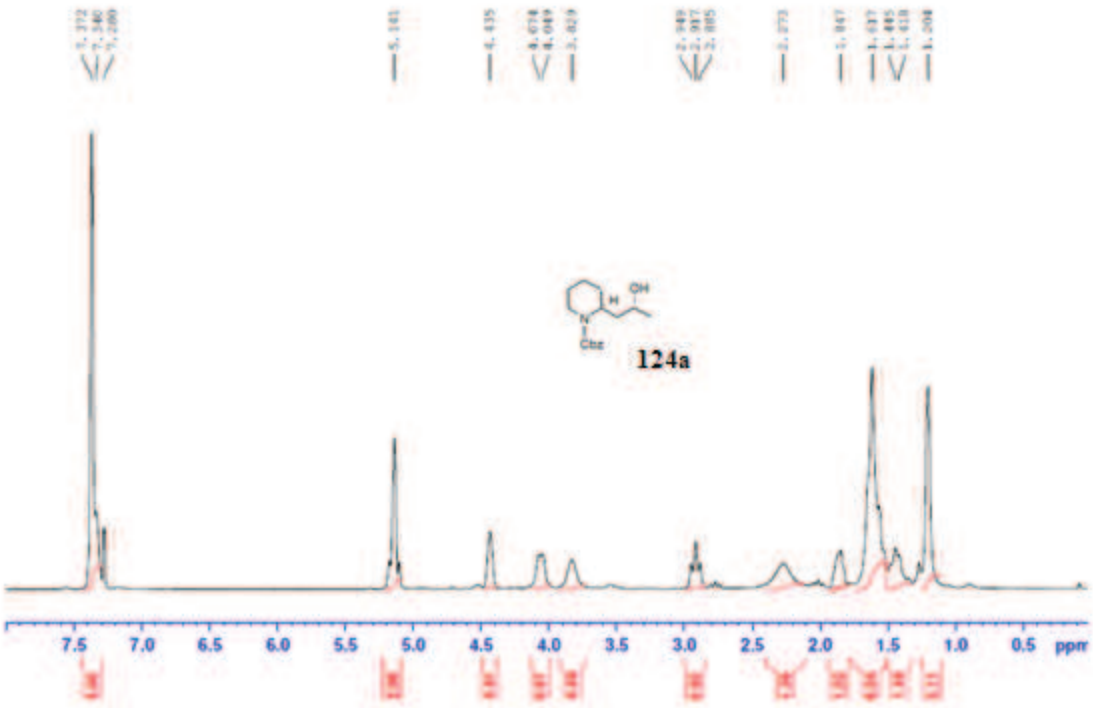
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3.0
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2.0
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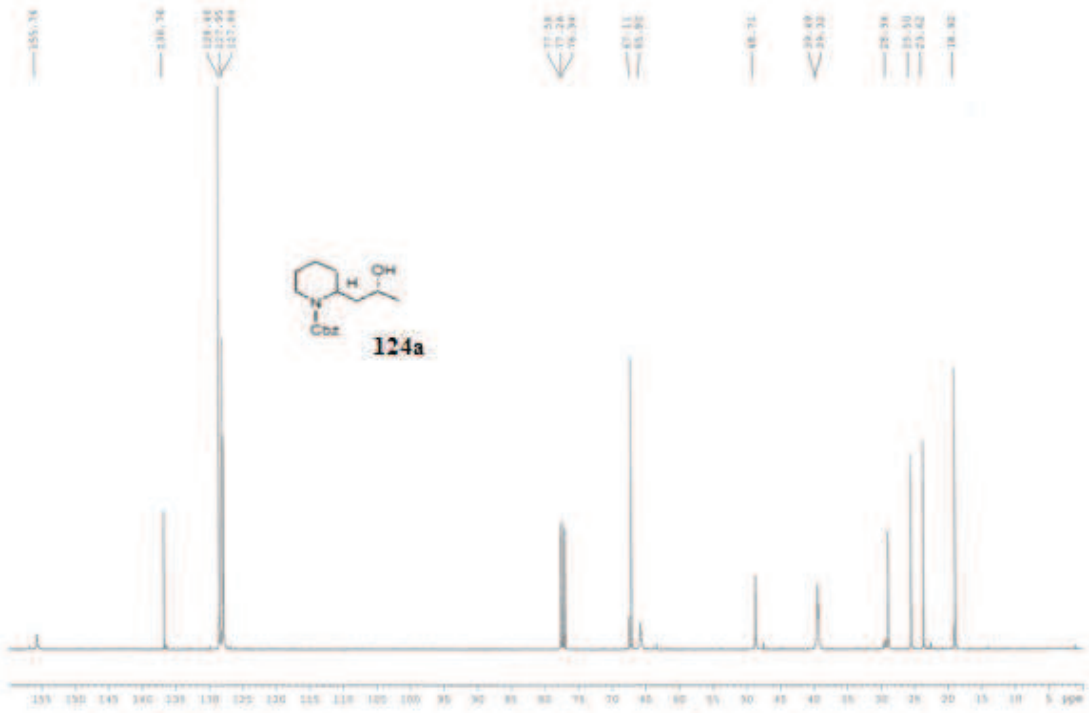
1.0
0.5
ppm



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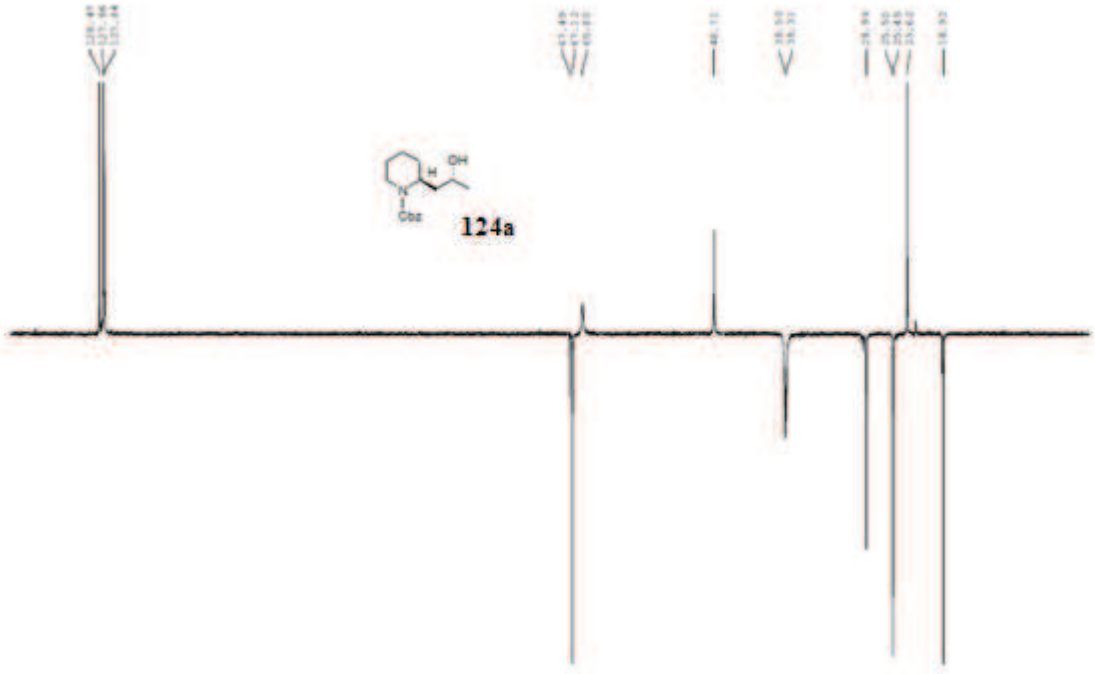

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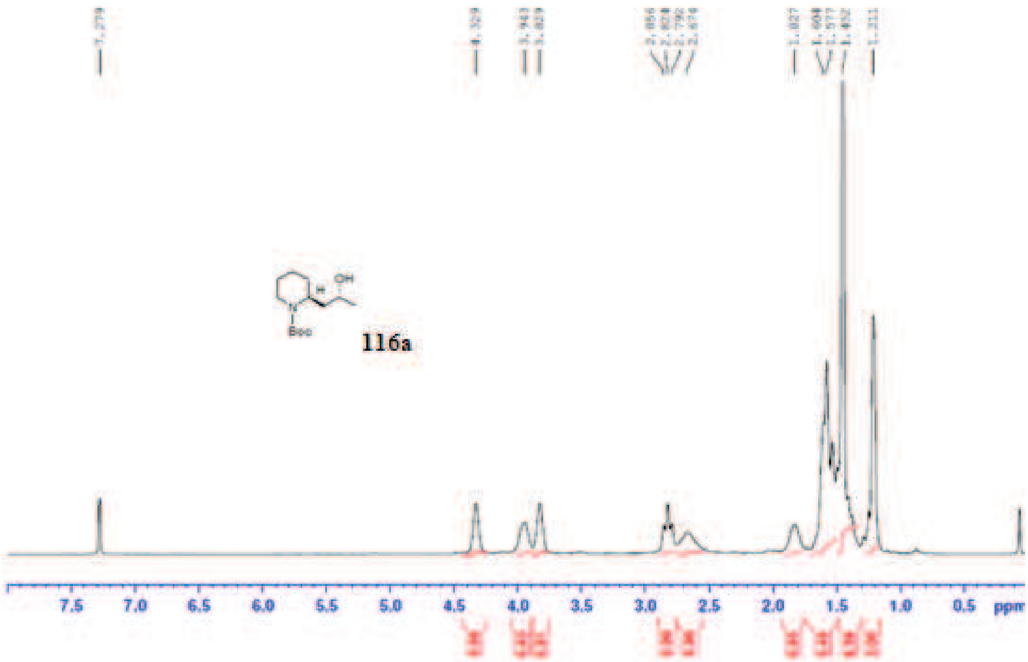
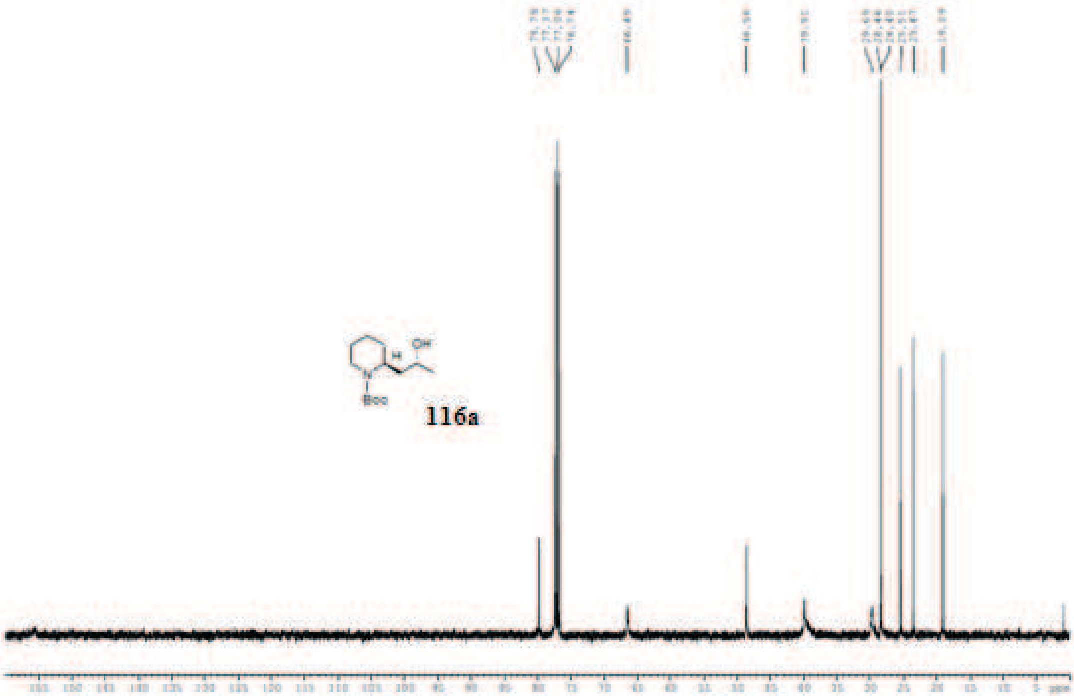
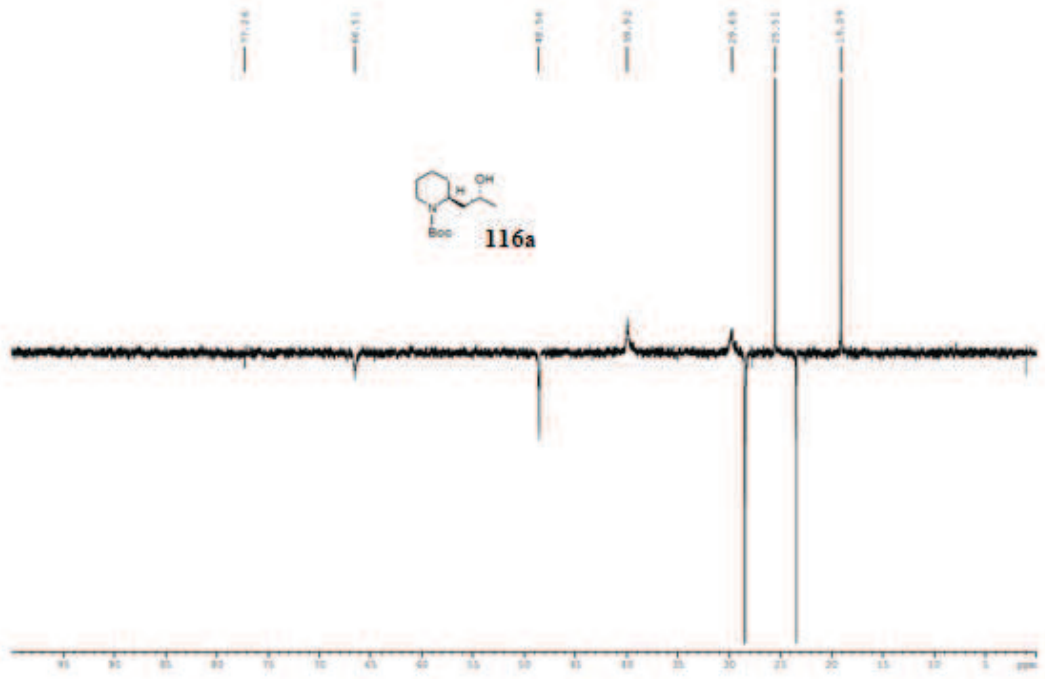


OH
Boc
116a
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm



OH
Boc
116a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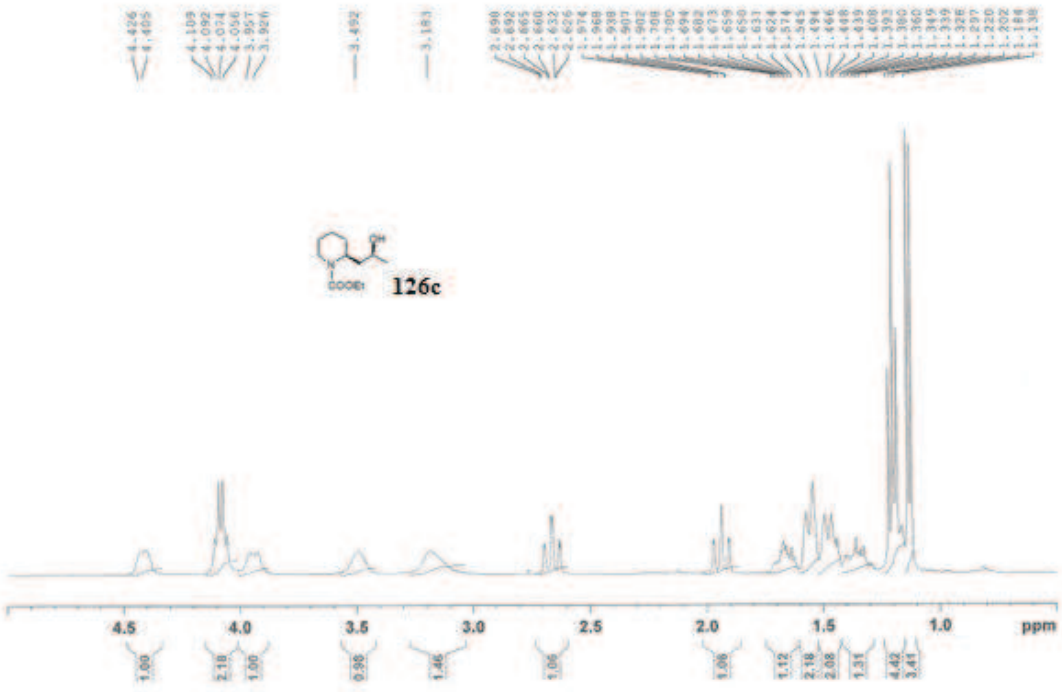
Boc
116a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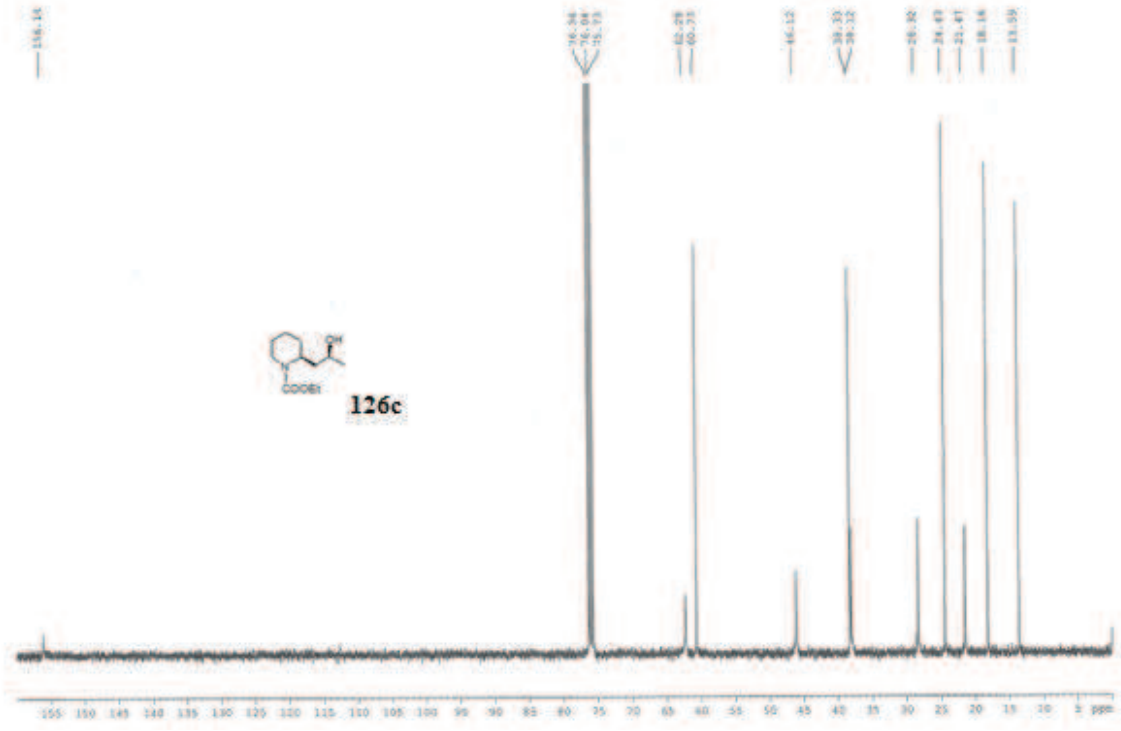
2.0
1.5
1.0
ppm



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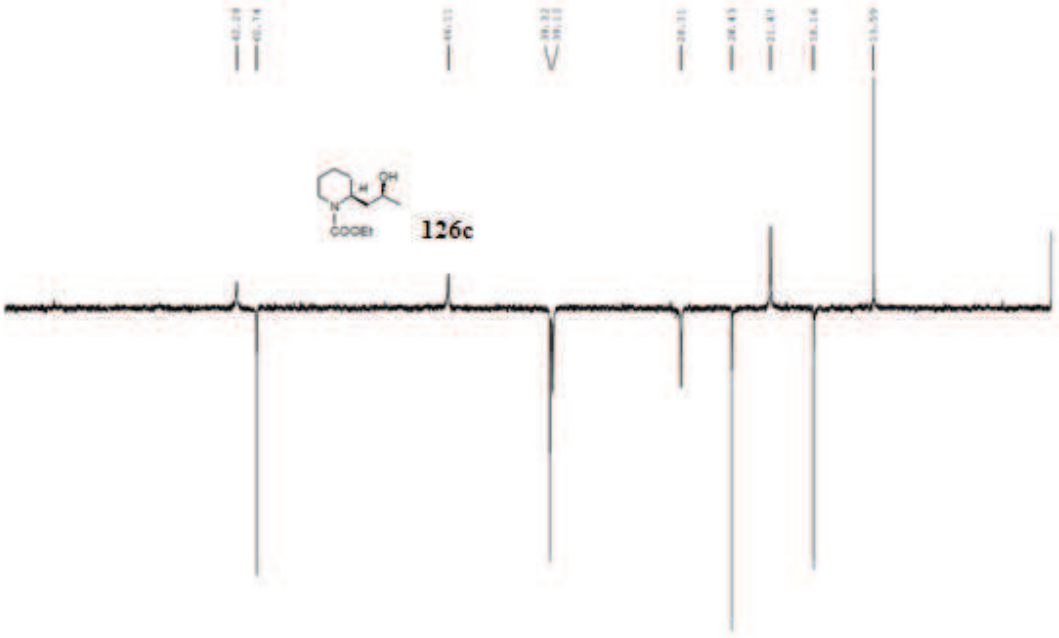

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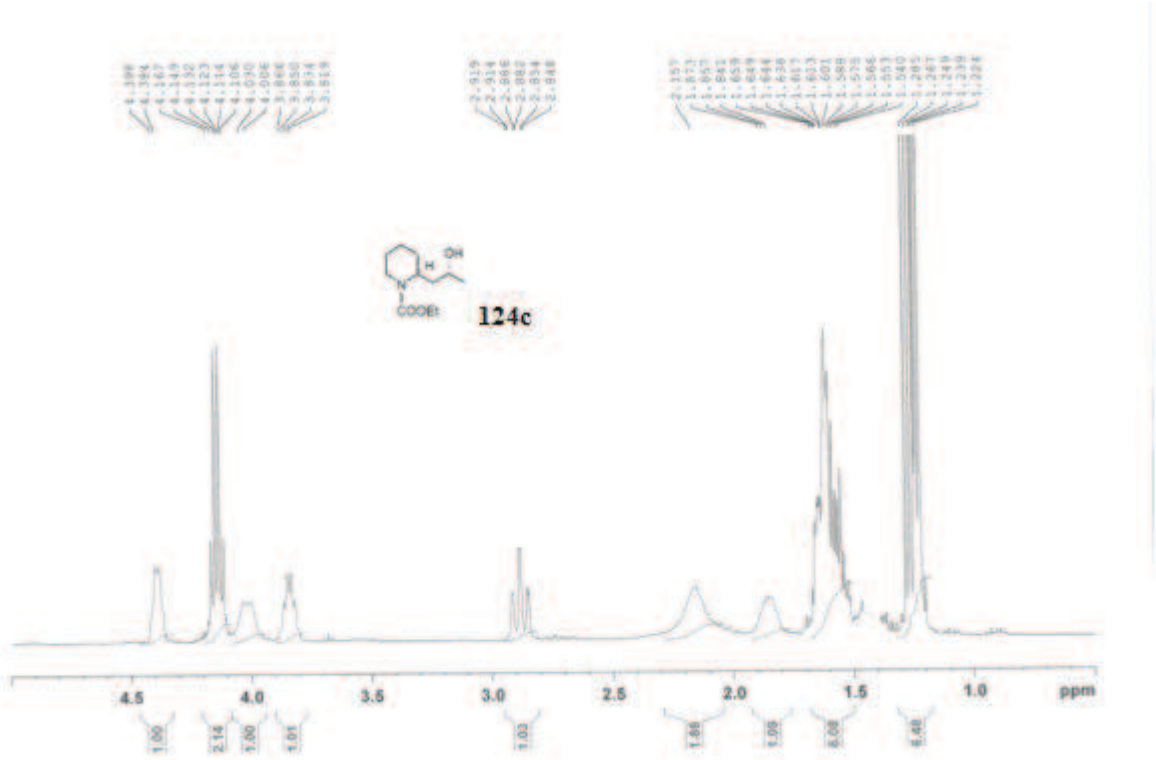
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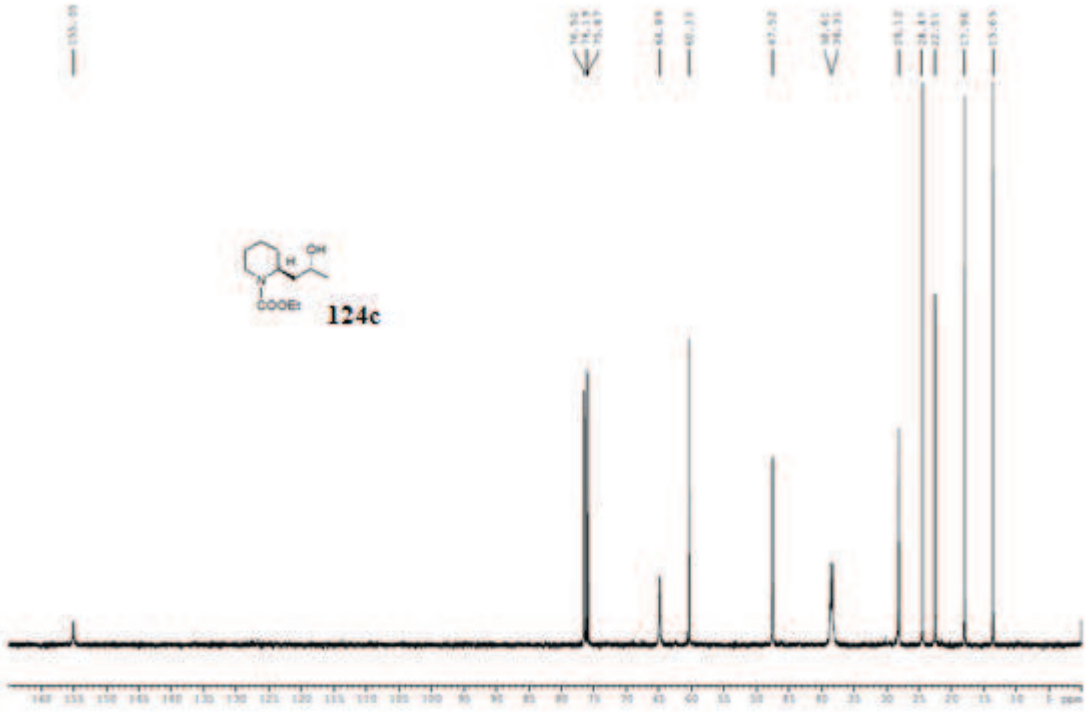
2.0
1.5
1.0
ppm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COOEt
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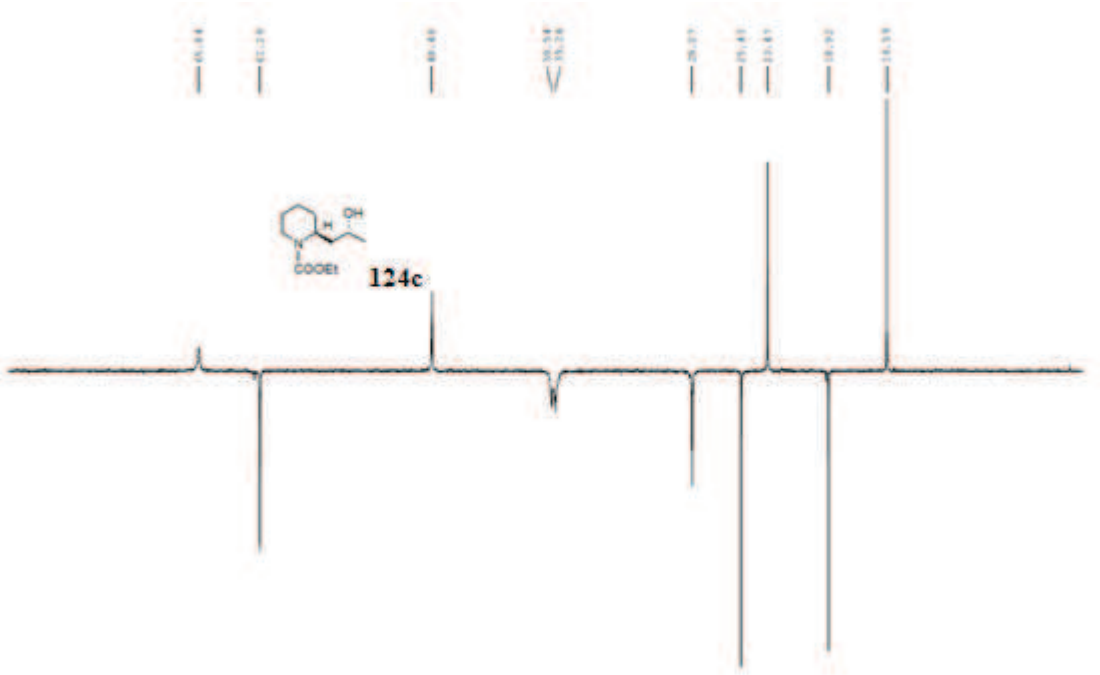
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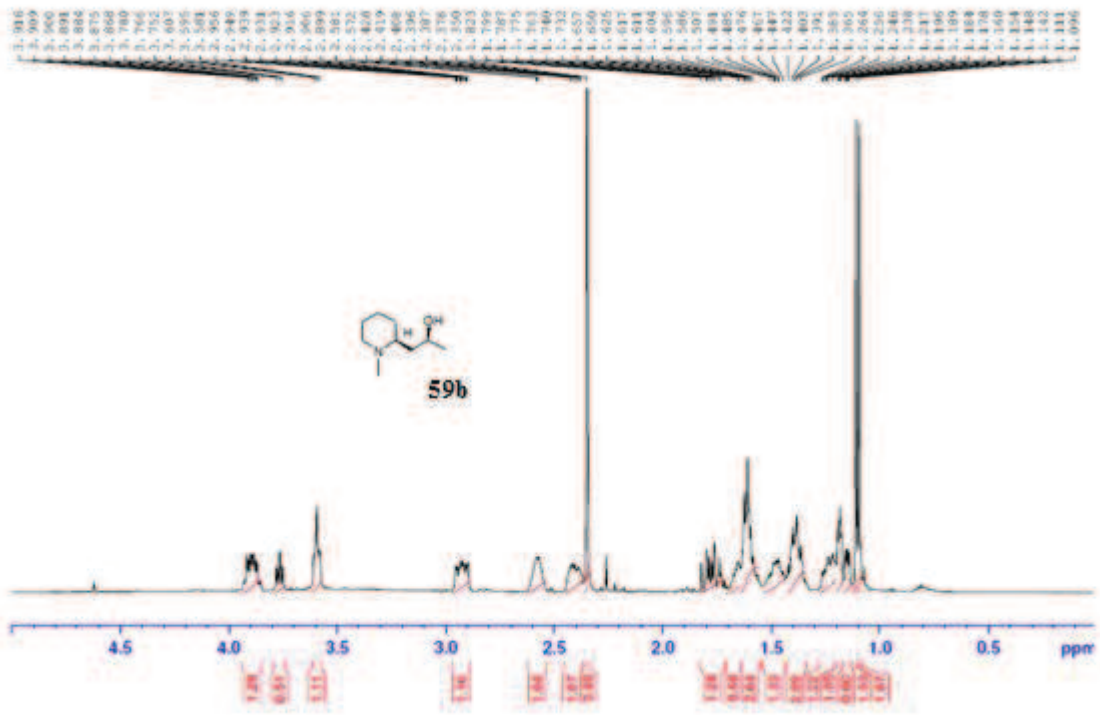
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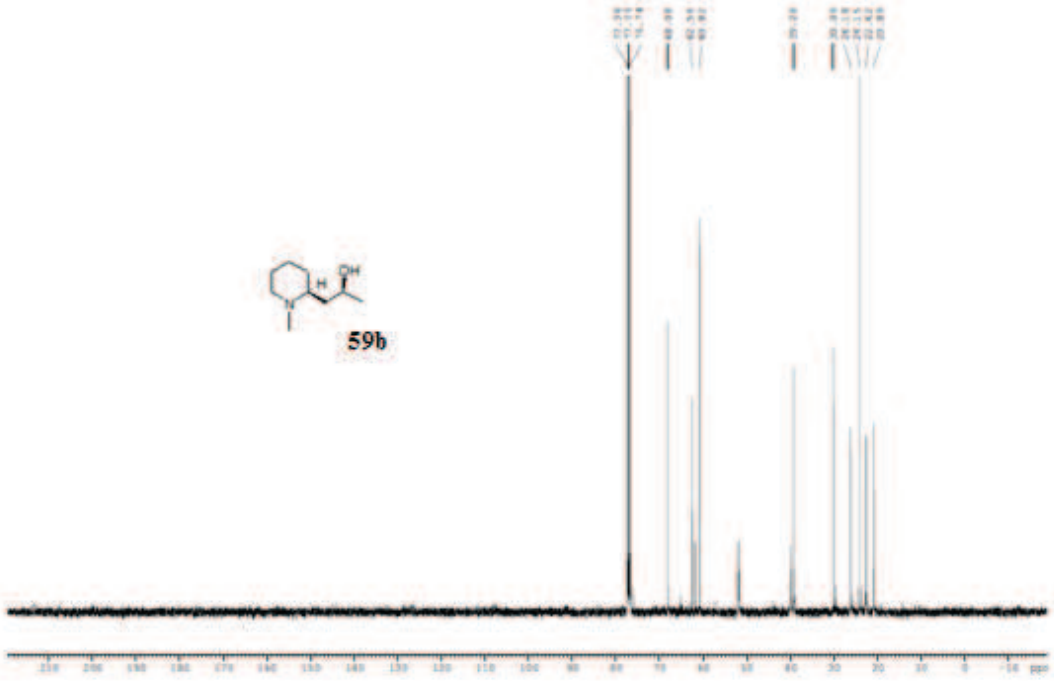

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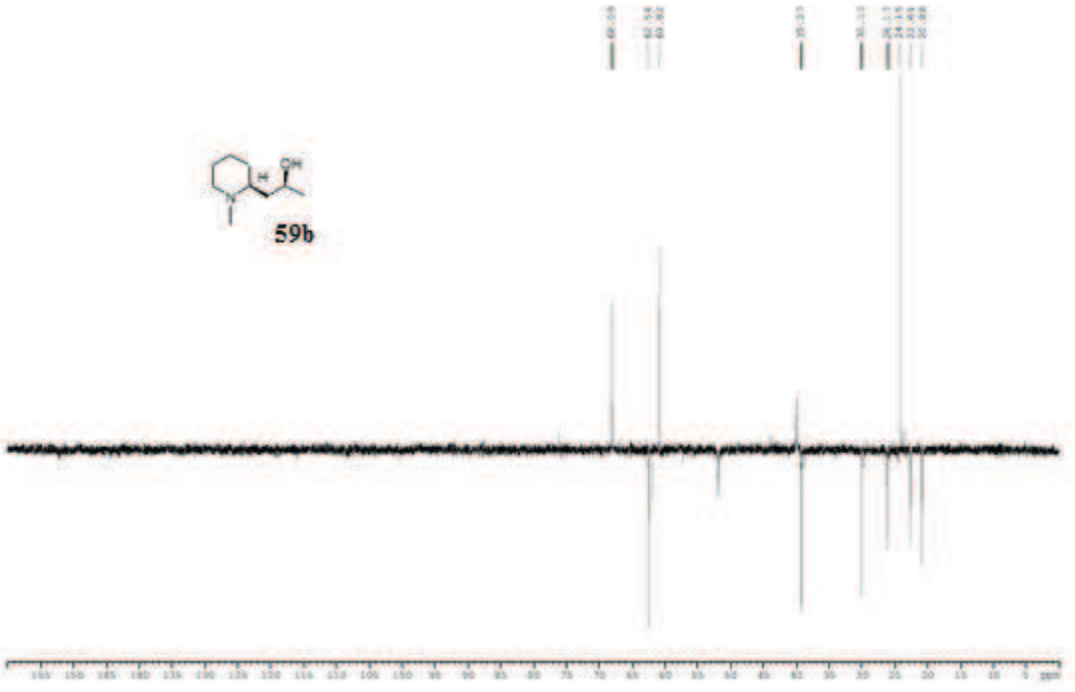

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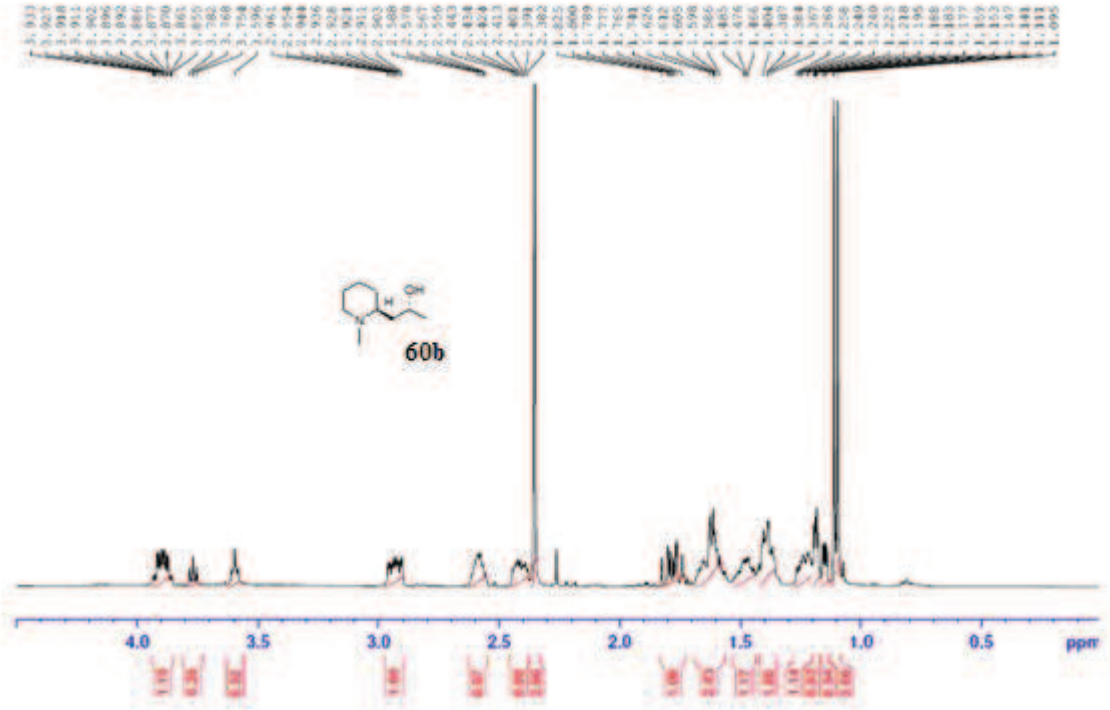
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0.5
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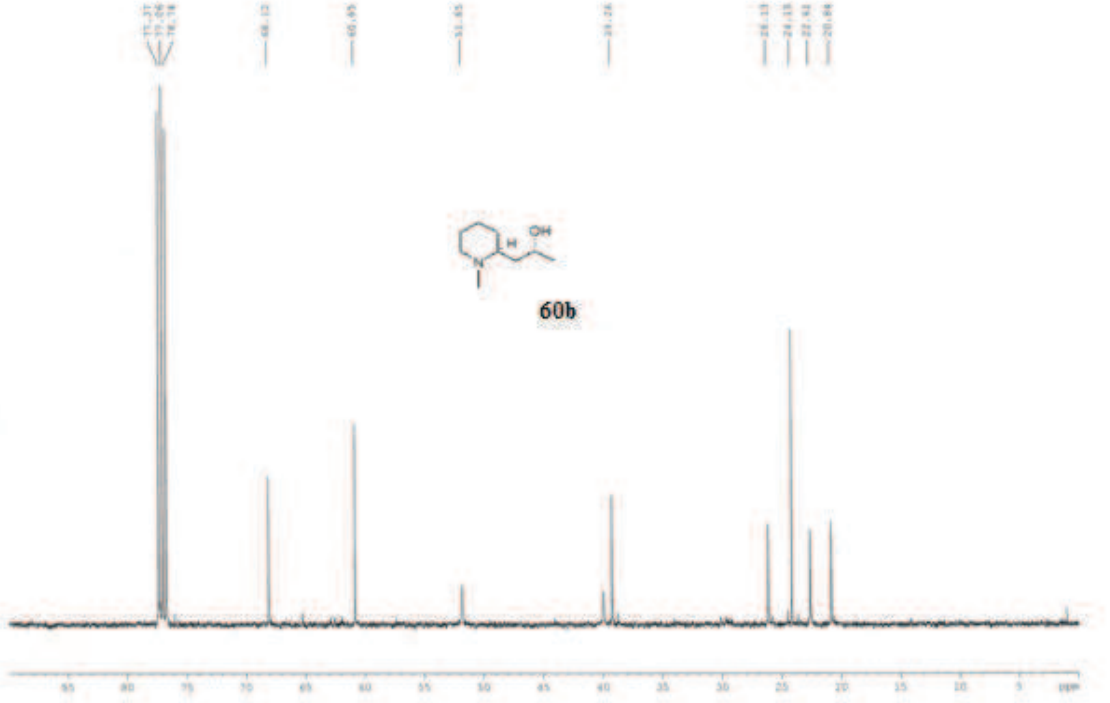
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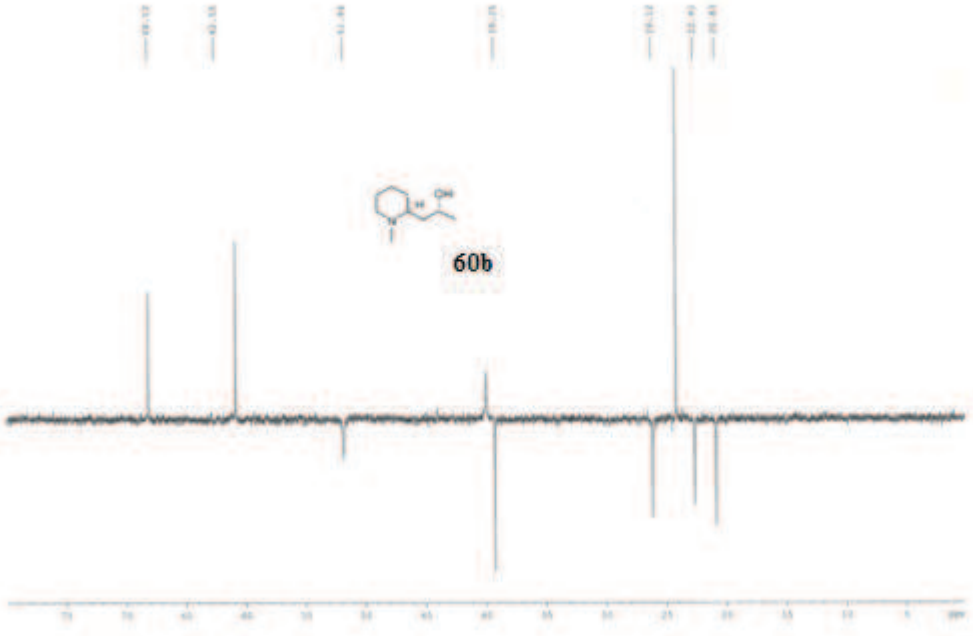
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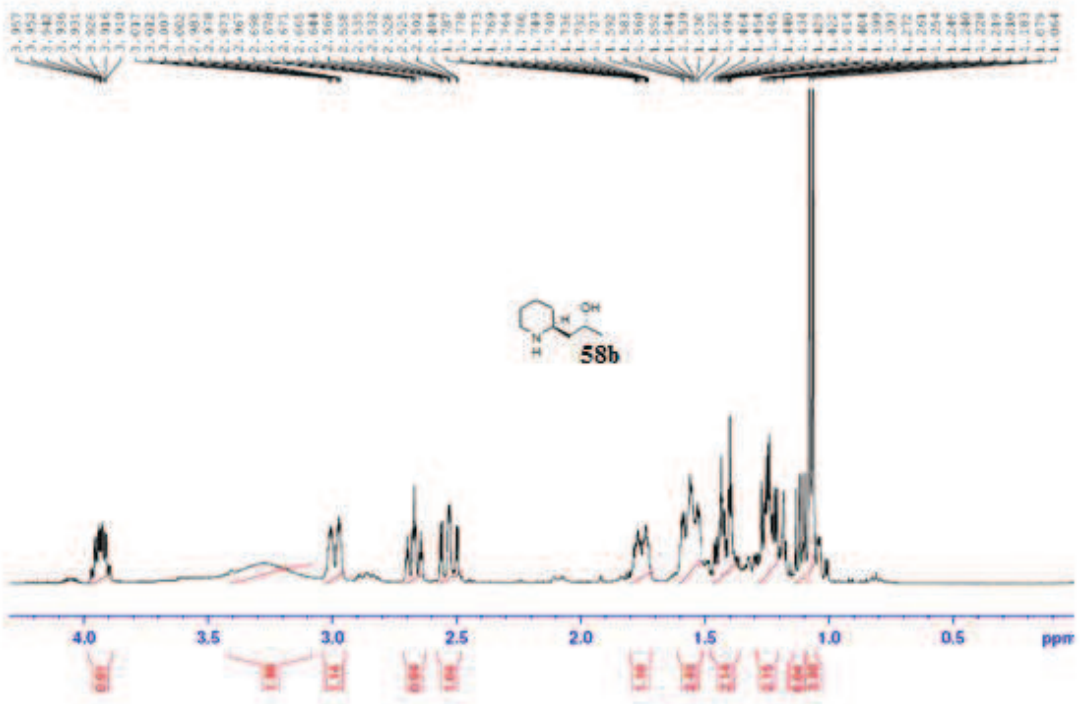
58b
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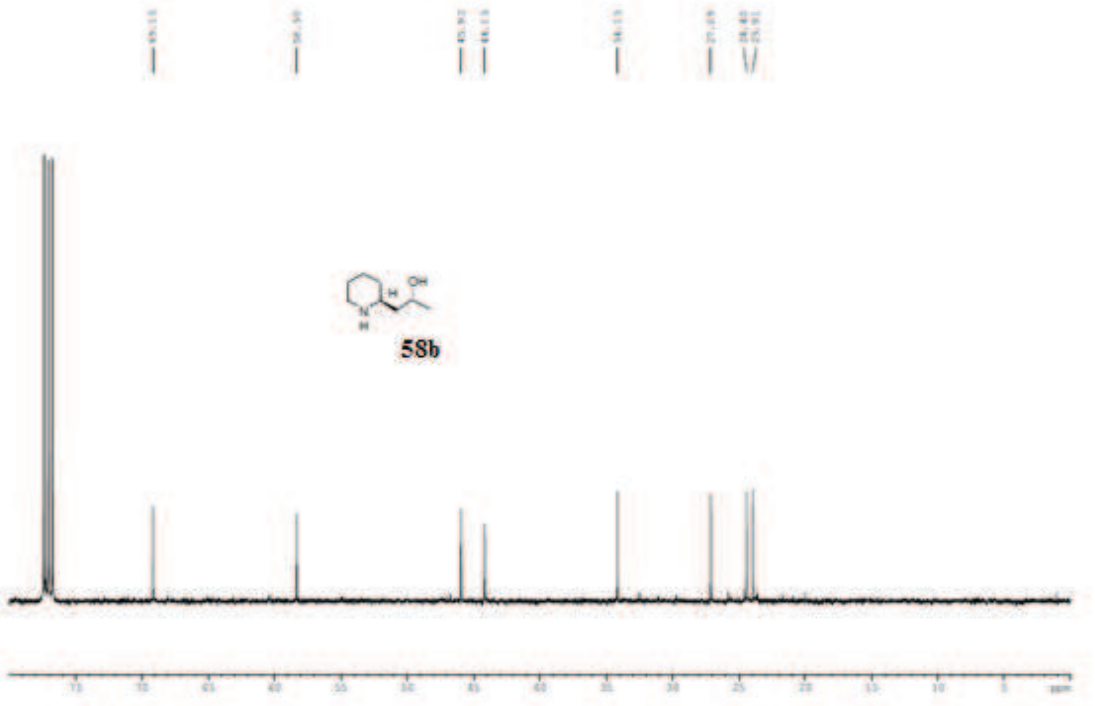
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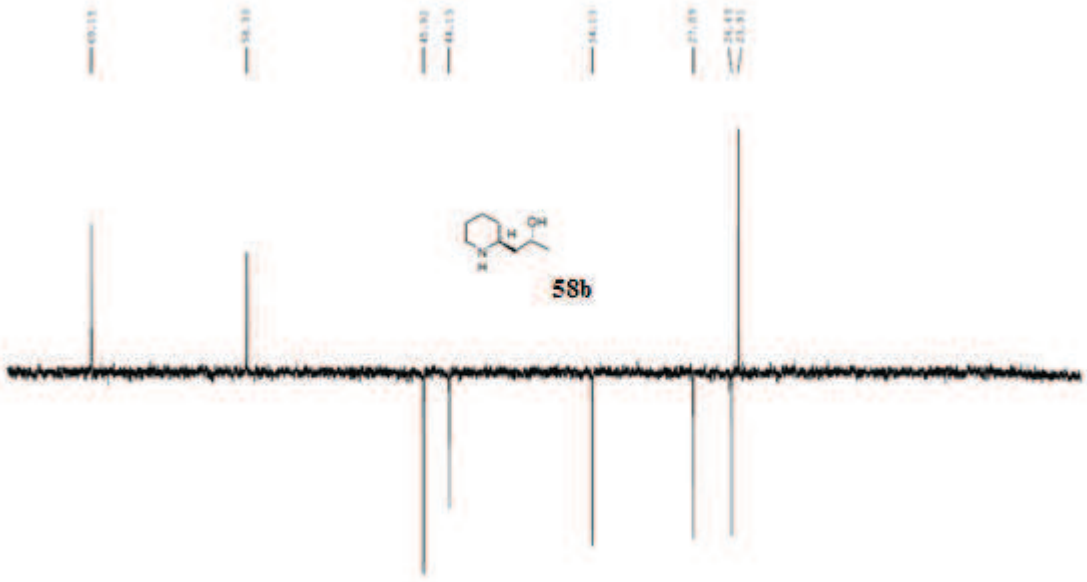
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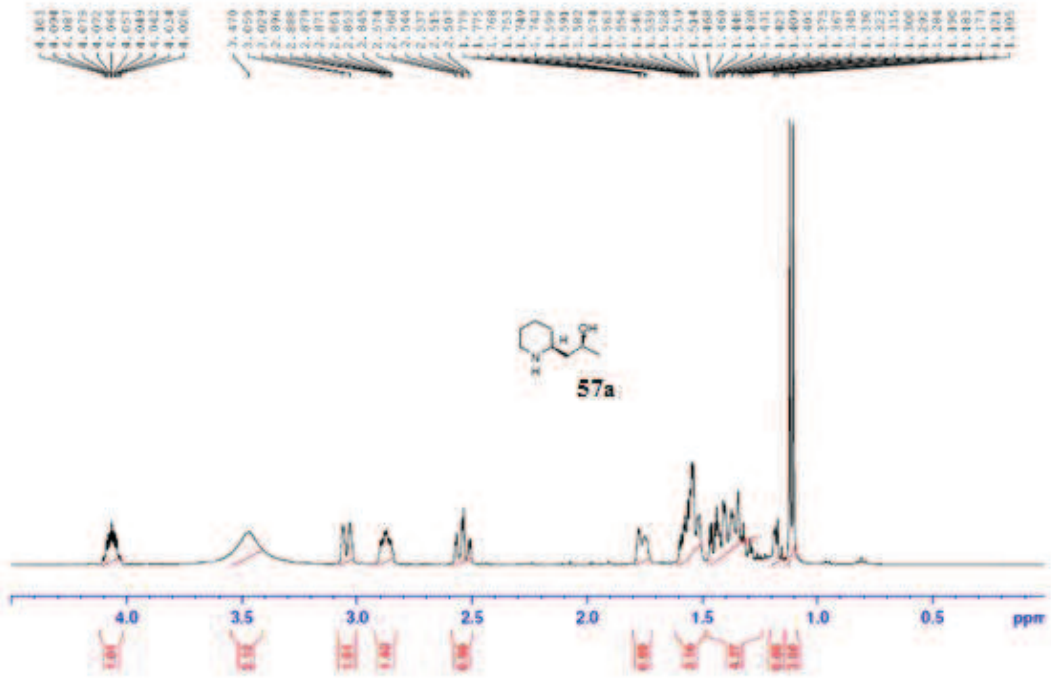
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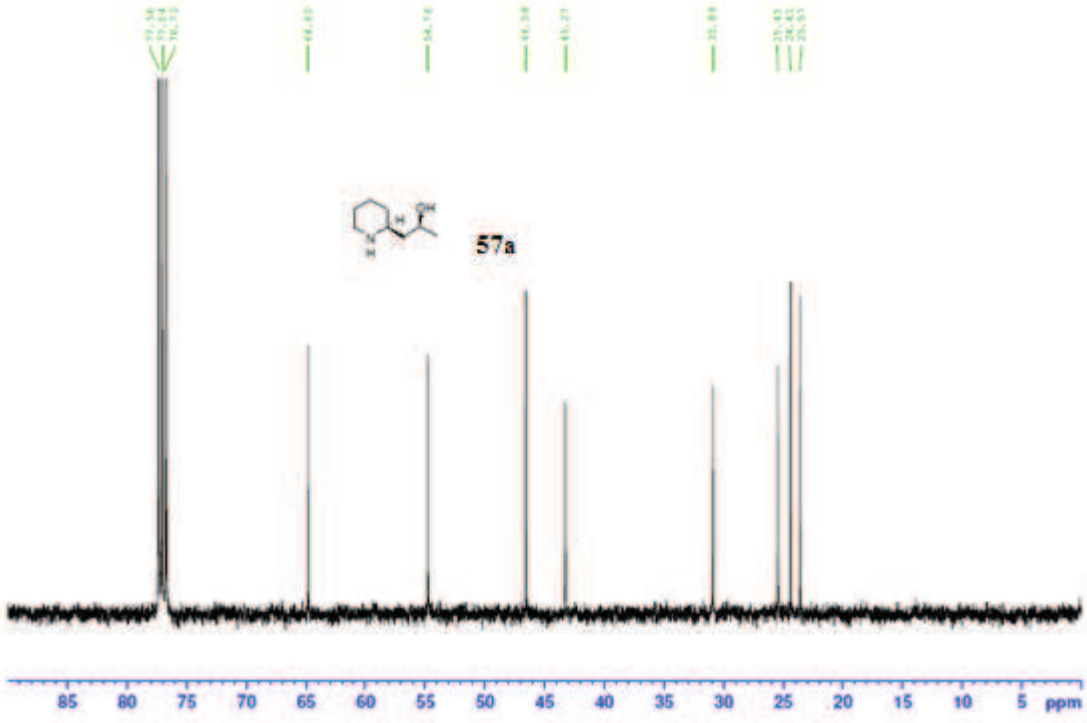
1.0
0.5
ppm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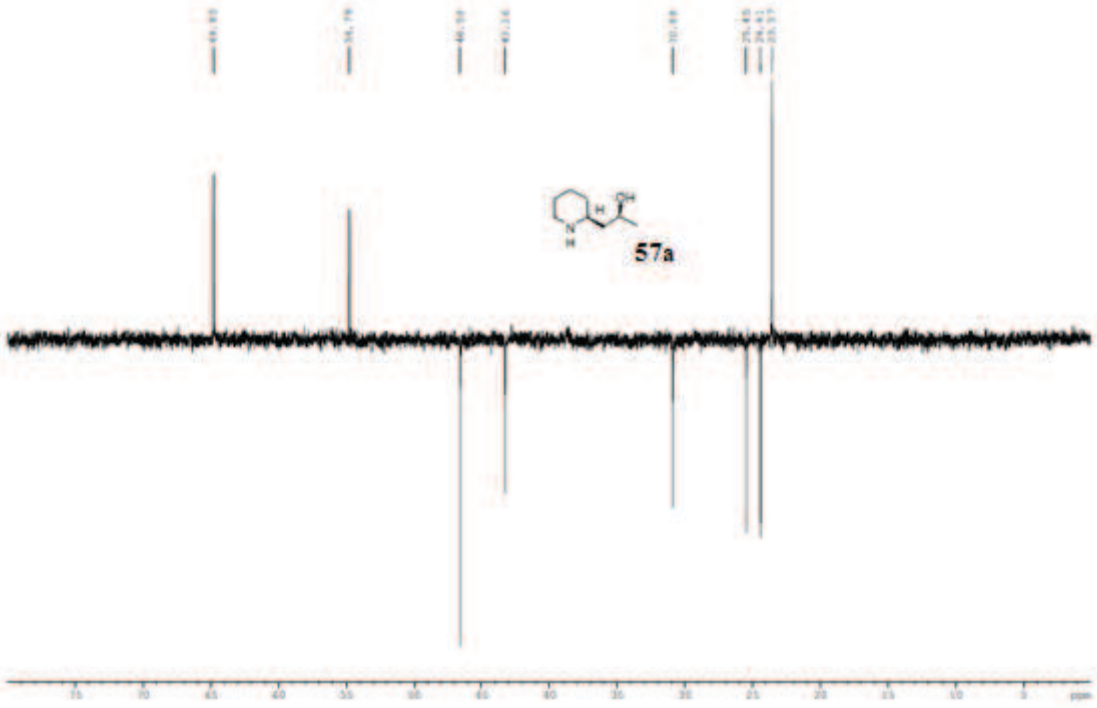
5
ppm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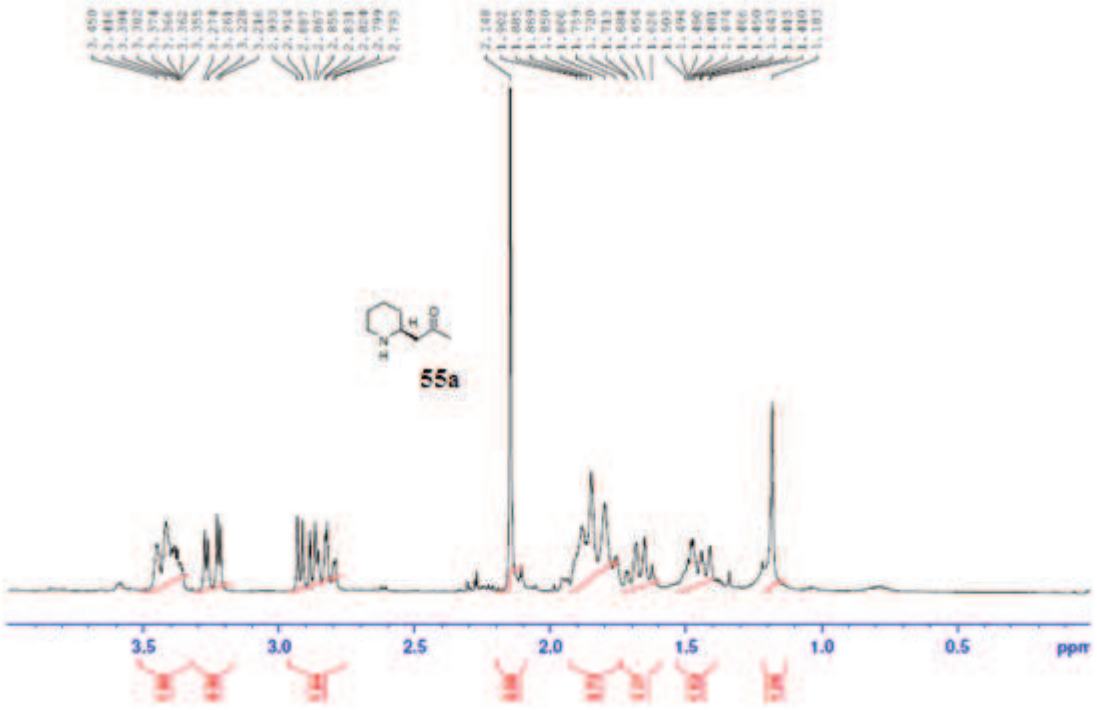
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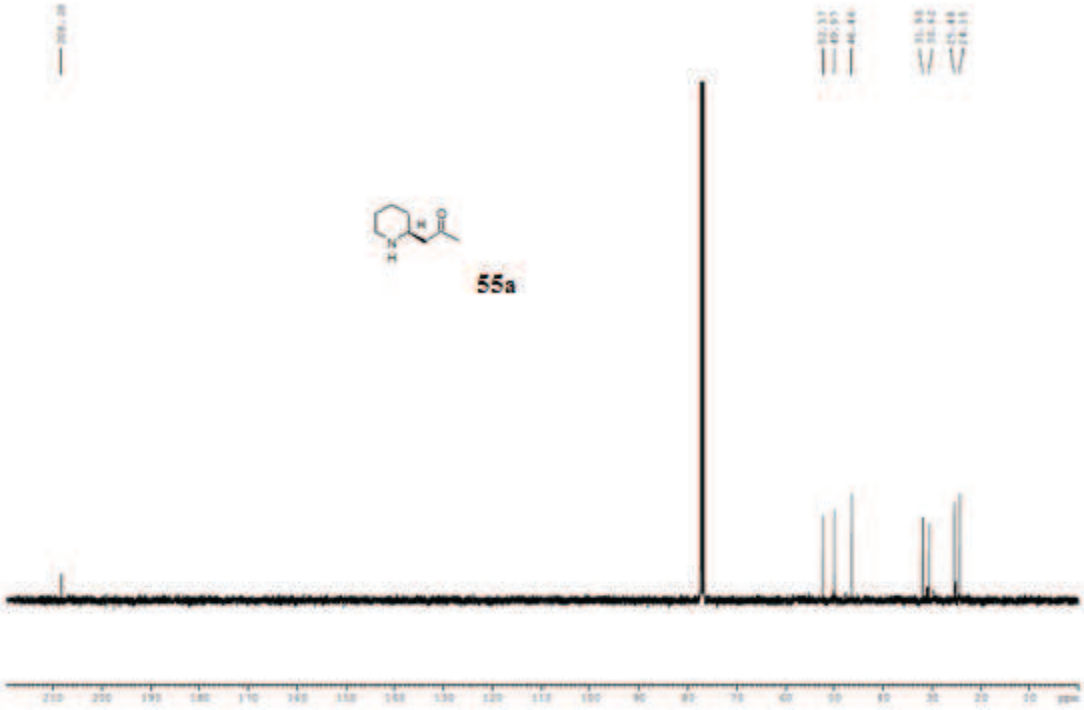
ppm



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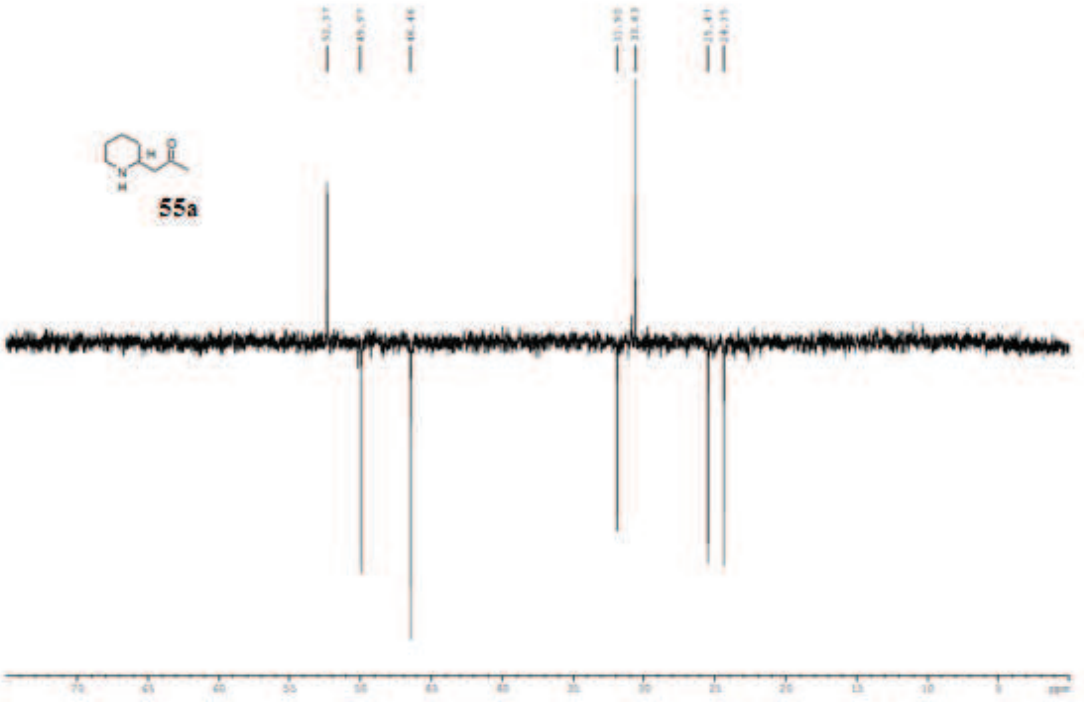

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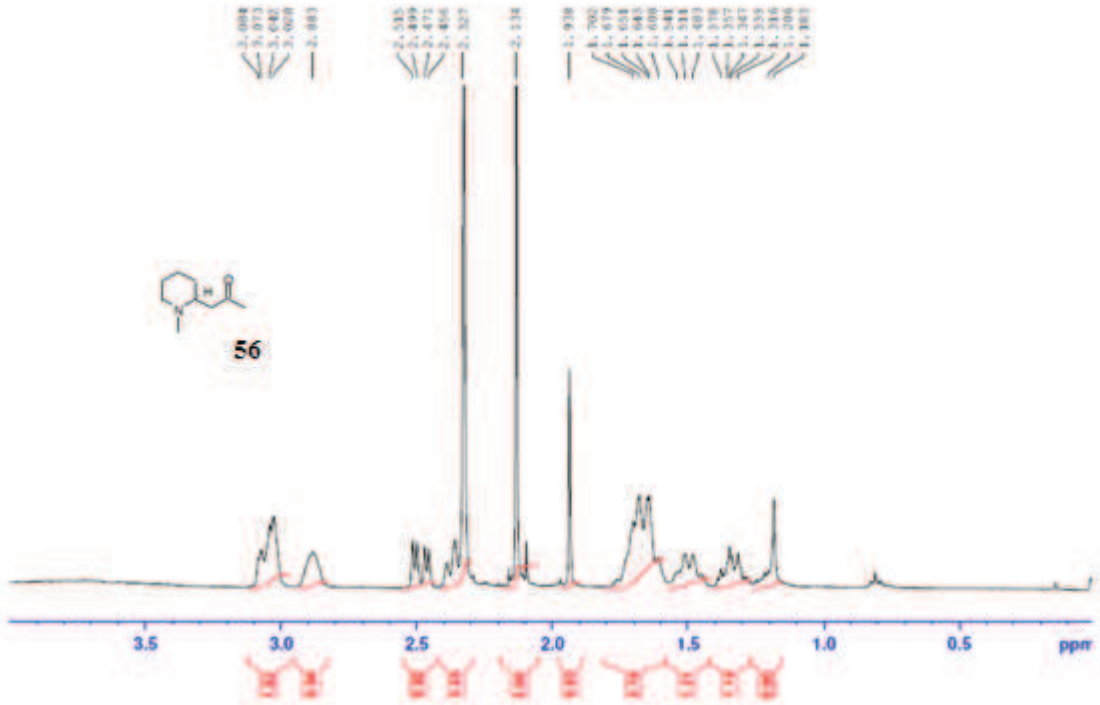
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1.5
1.0
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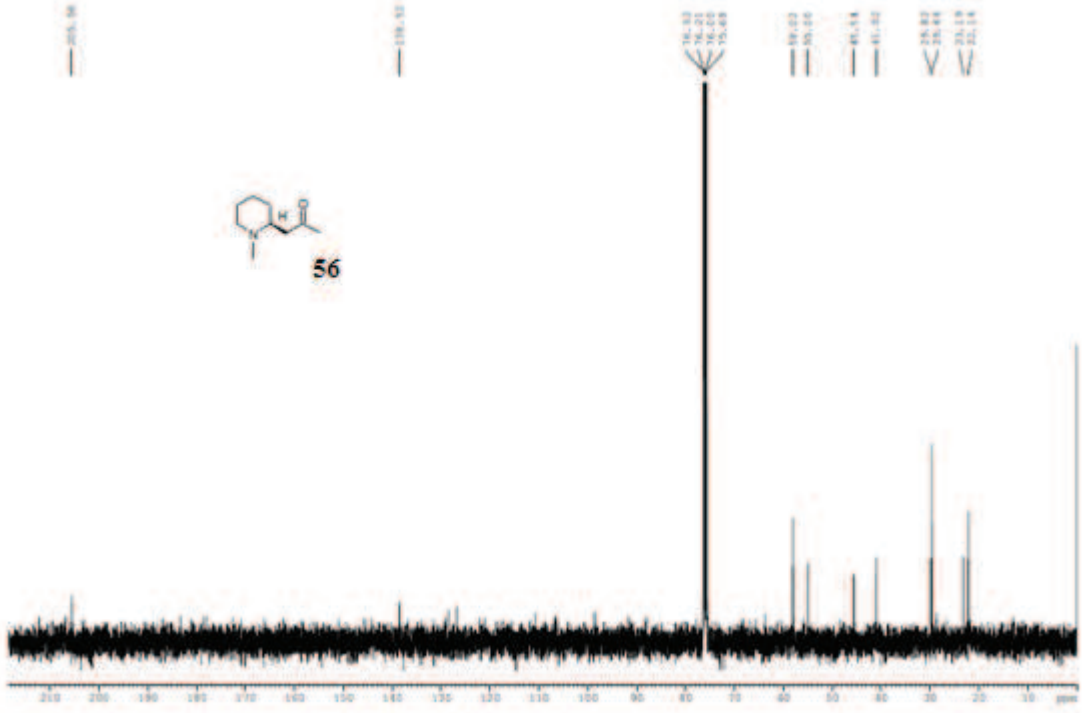
ppm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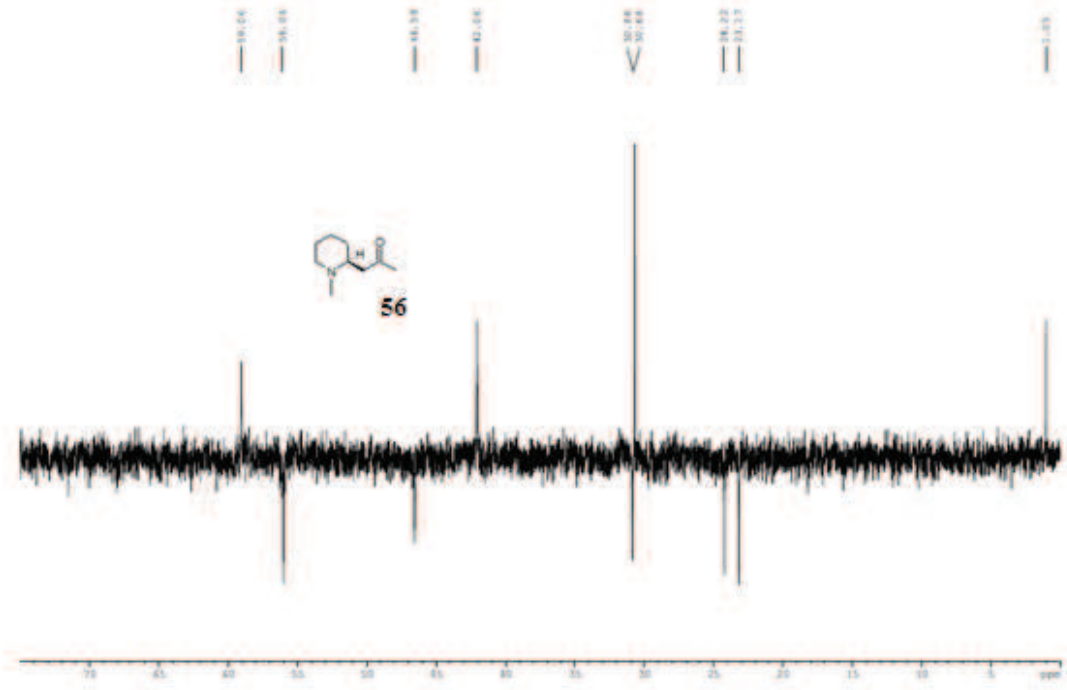
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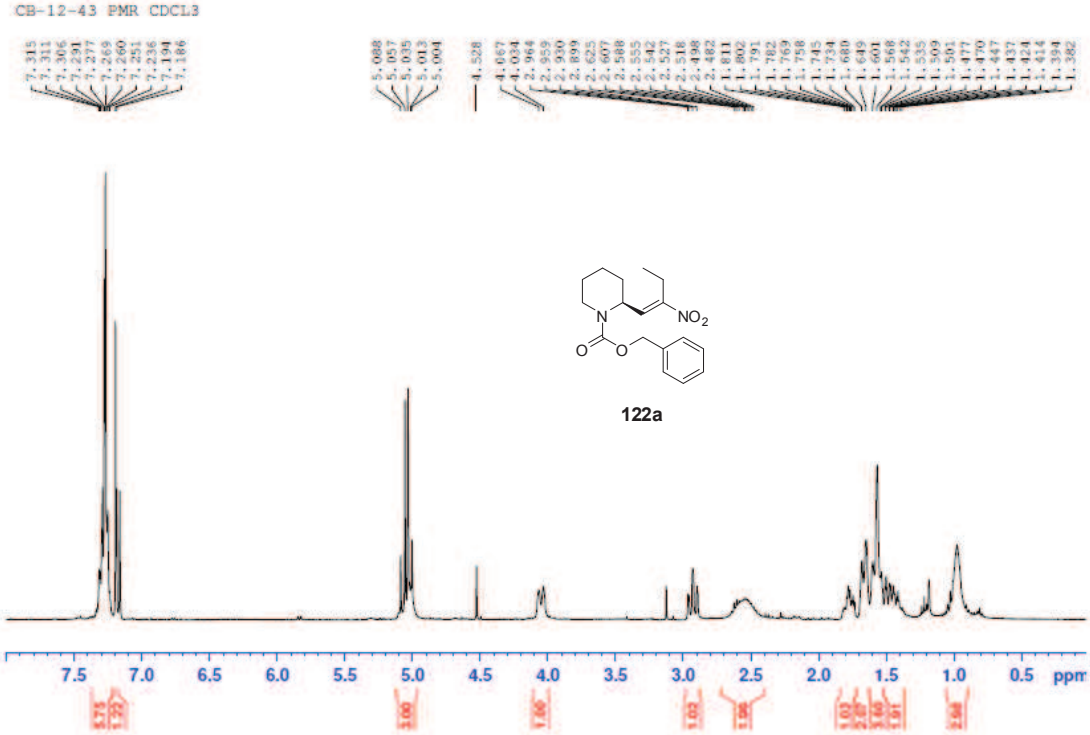
CB-12-43 PMR CDCL3
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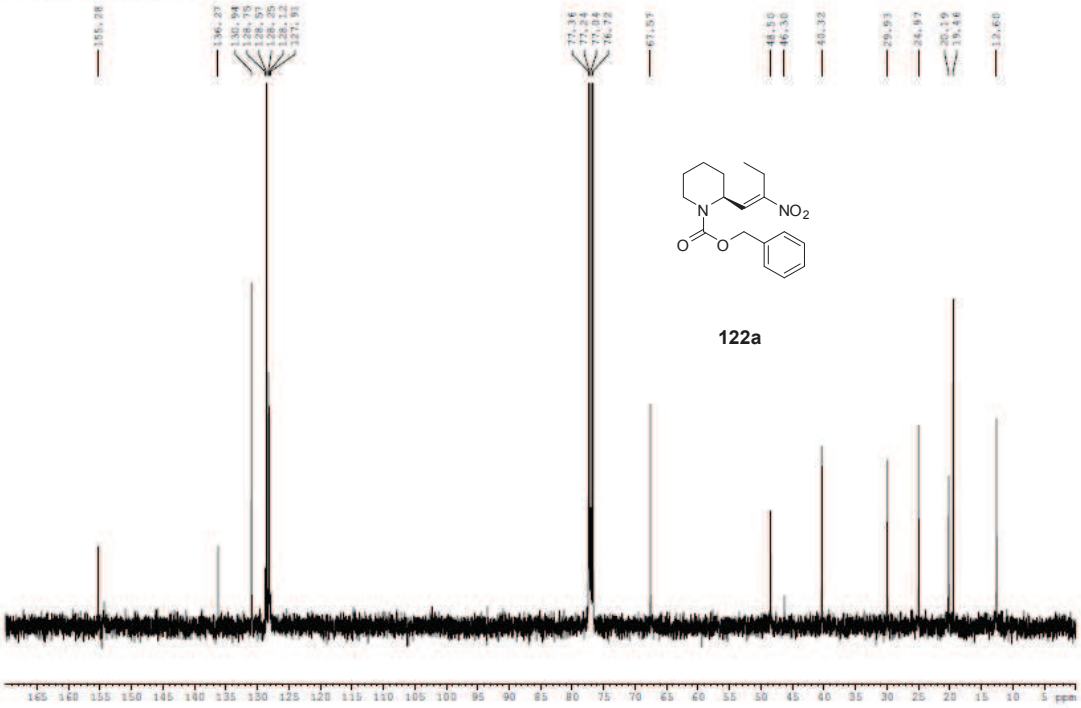
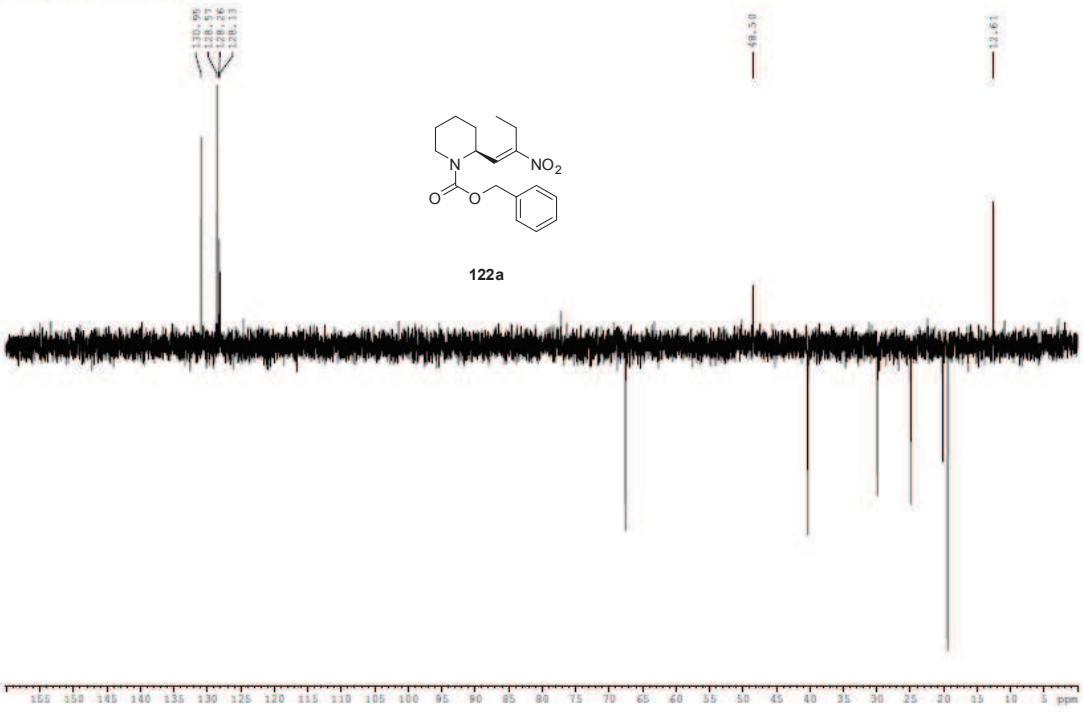
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

CB-12-43 CMR CDCL3

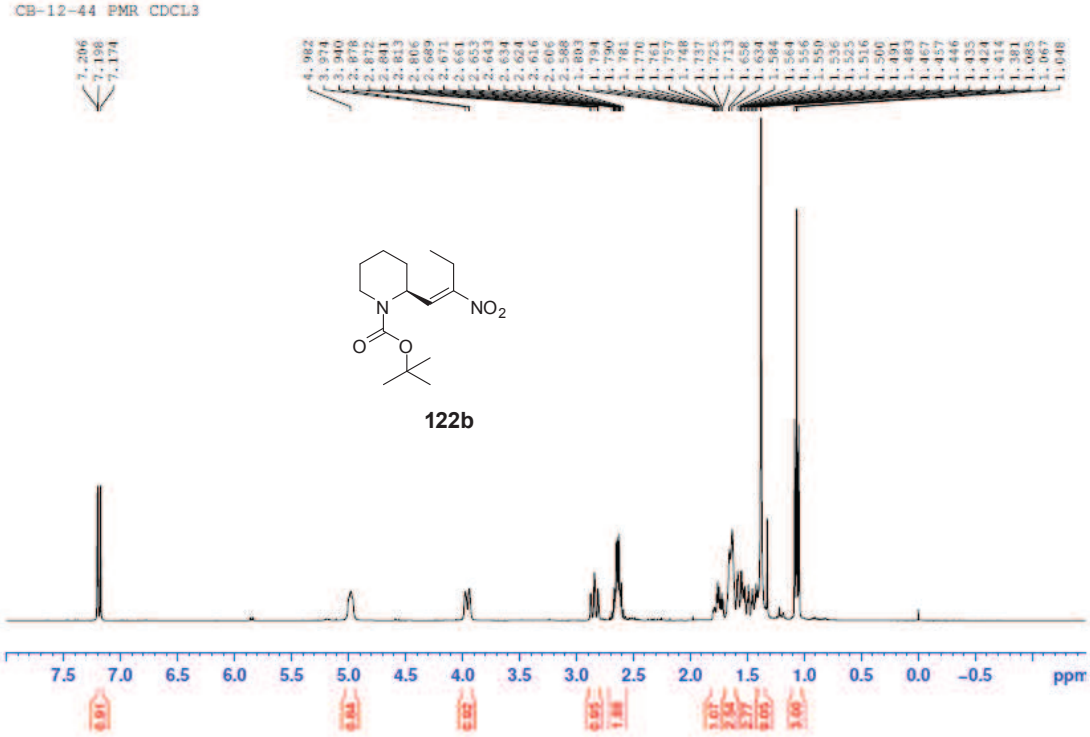


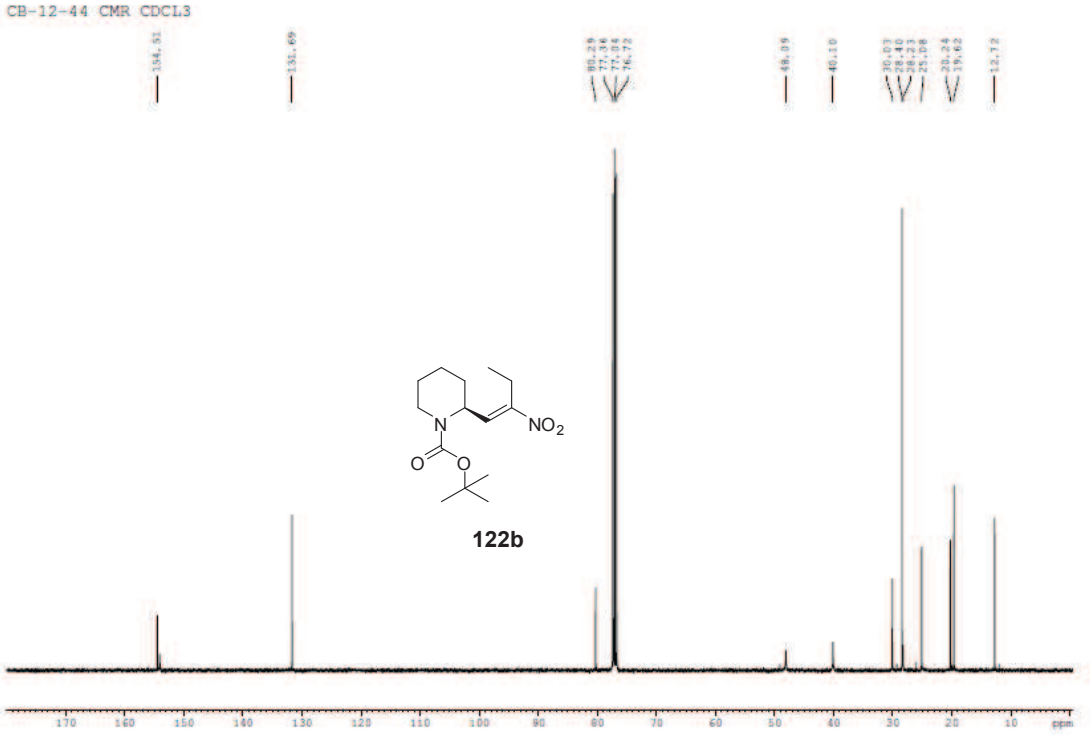
122a

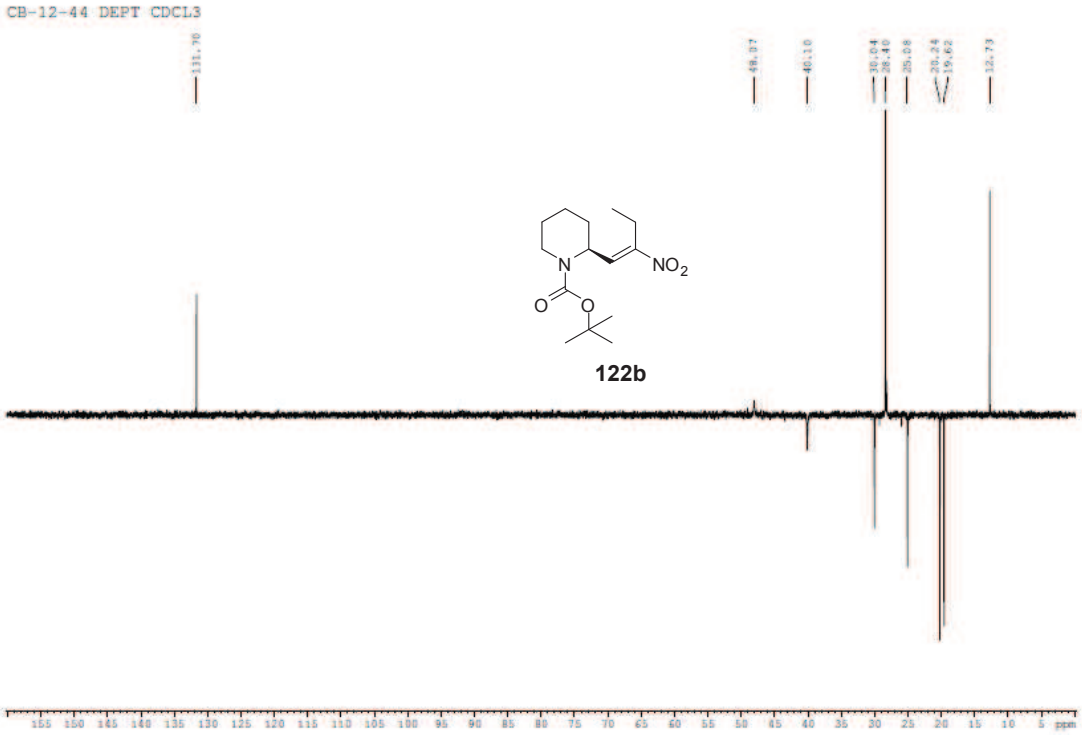
CB-12-43 DEPT CDCL3

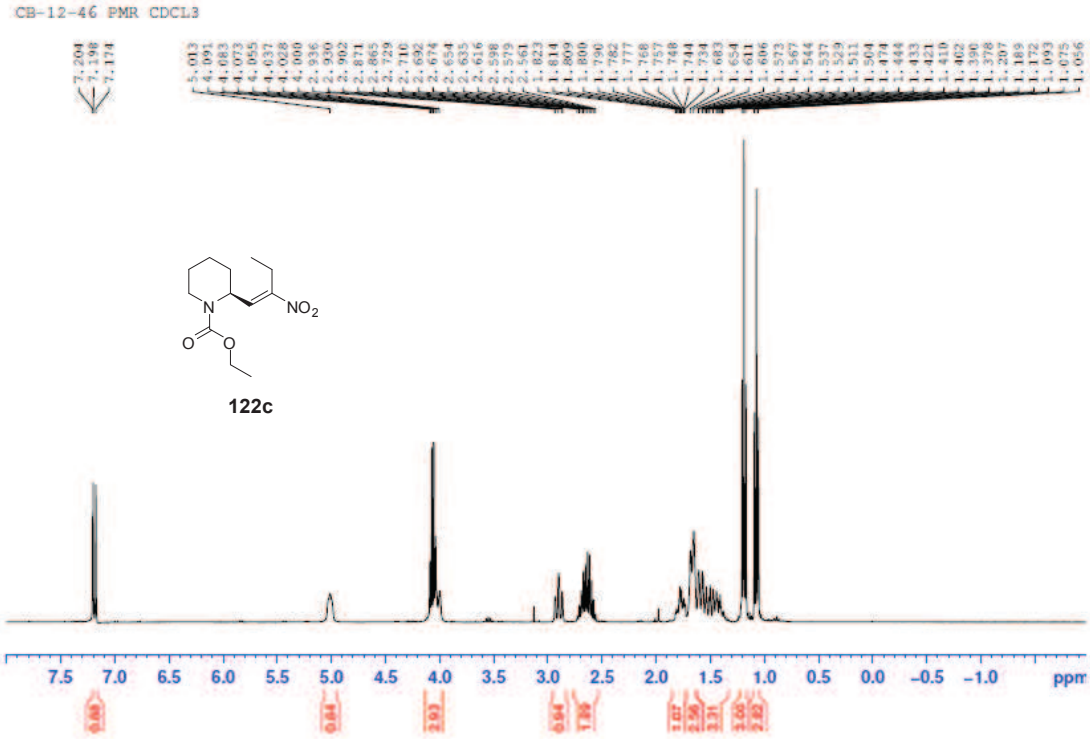


122a

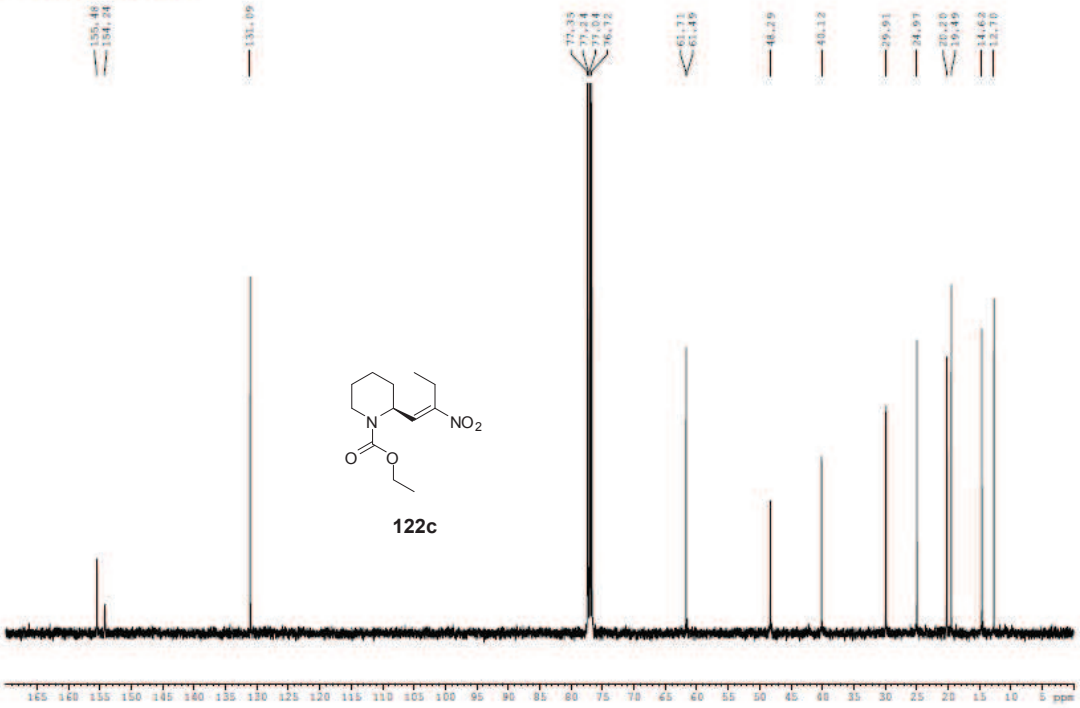

CB-12-44 PMR CDCL3
NO2
122b
ppm


CB-12-44 CMR CDCL3
NO2
122b
ppm


CB-12-44 DEPT CDCL3
131.70
48.07
40.10
30.04
28.40
25.08
20.24
19.62
12.73
N
O
O
NO2
122b

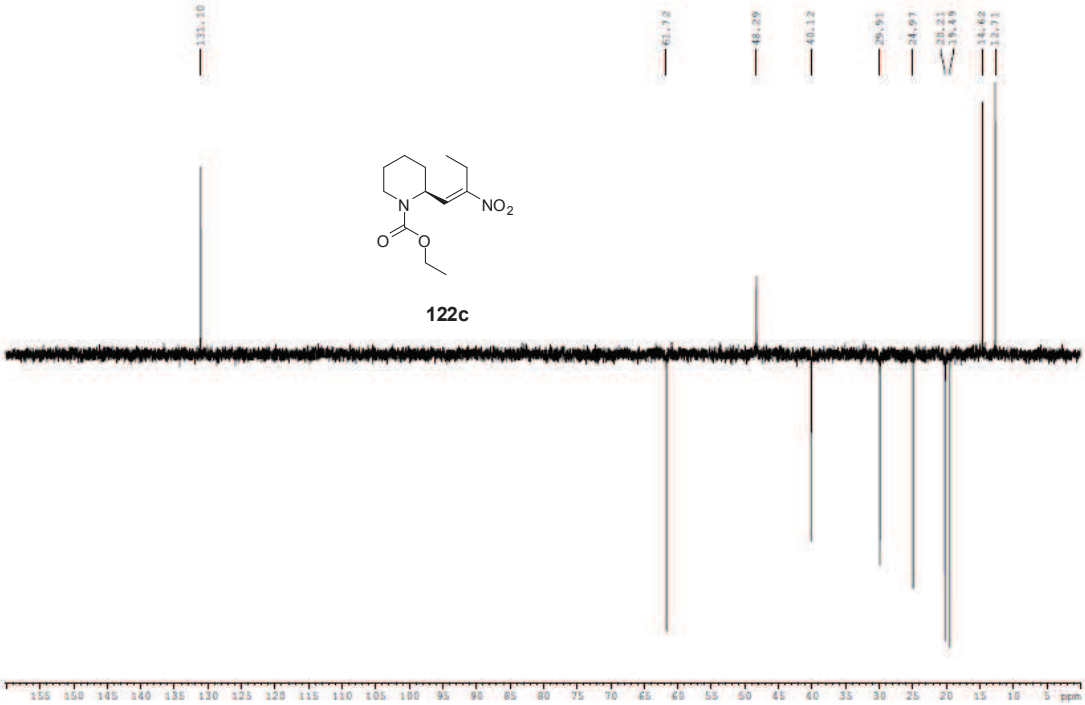

CB-12-46 PMR CDCL3
7.204
7.198
7.174
N
O
O
NO2
122c
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
ppm

CB-12-46 CDCL3 CMR

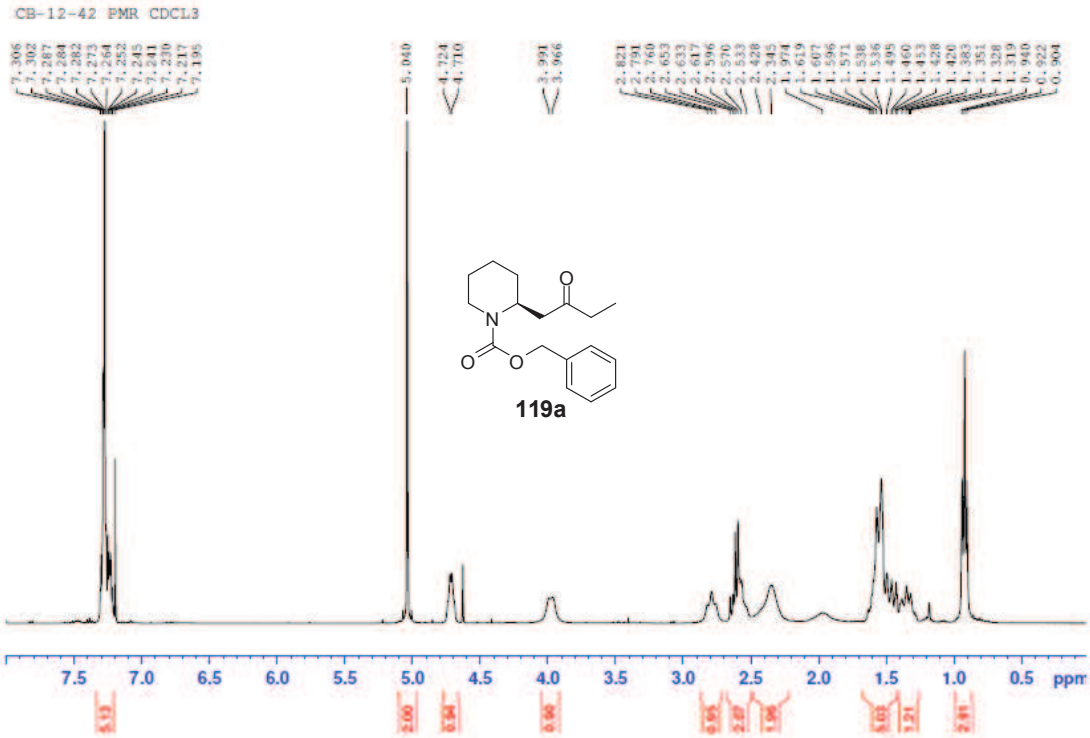


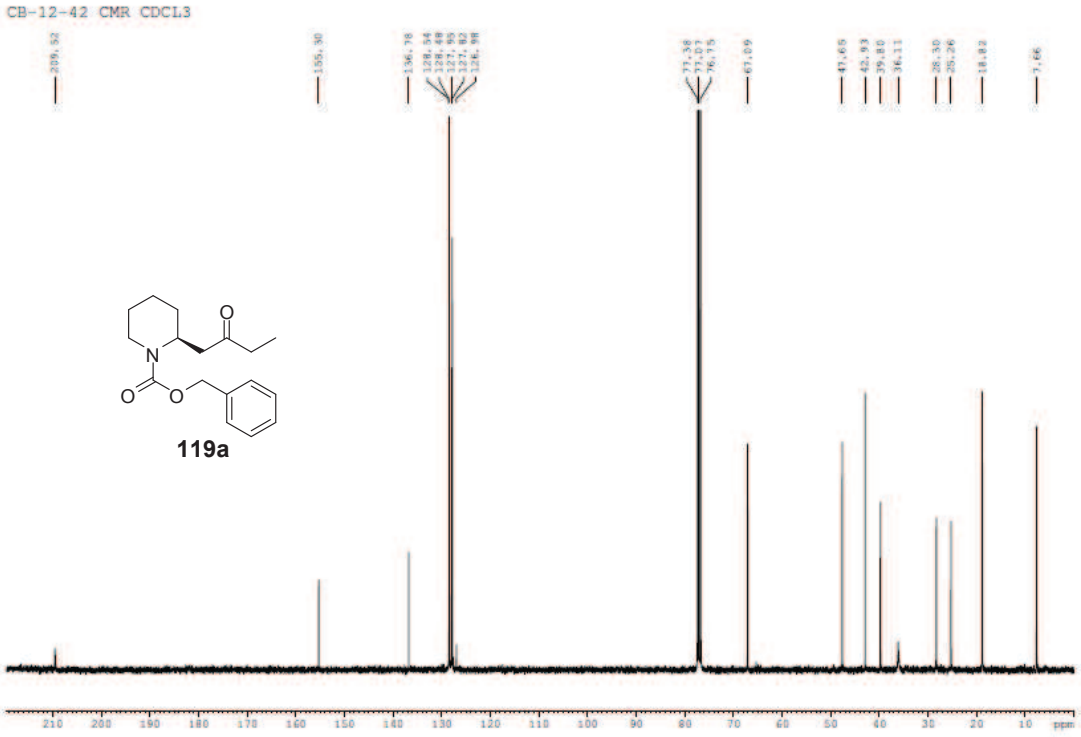
122c

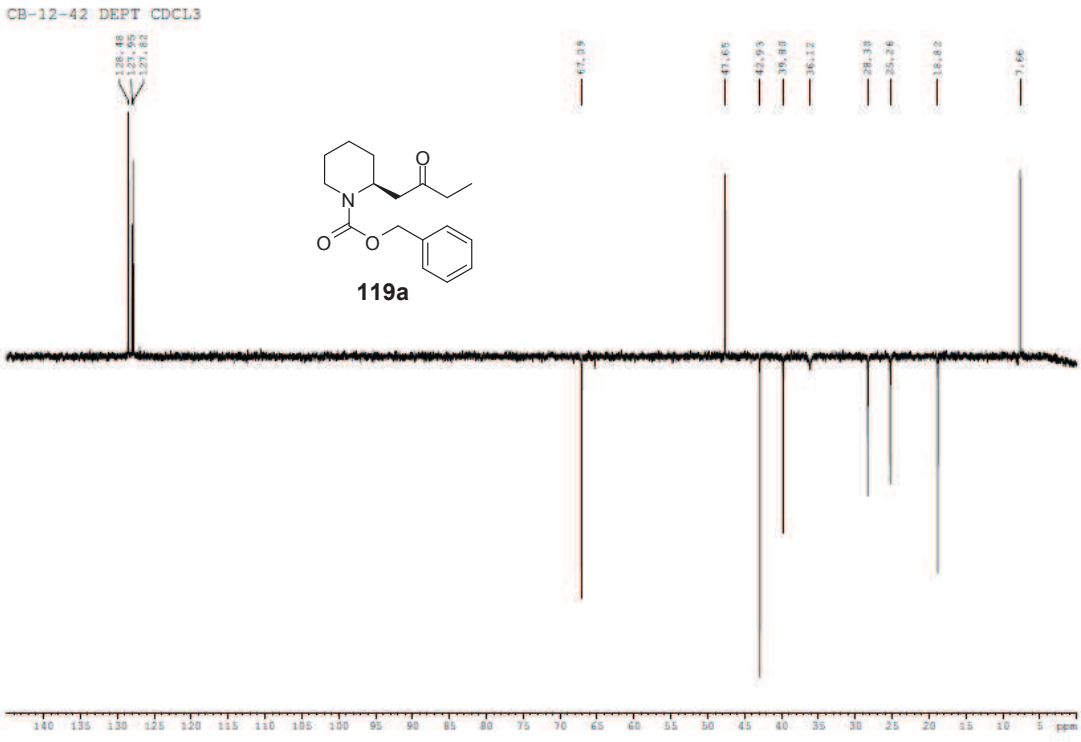
CB-12-46 CDCL3 DEPT

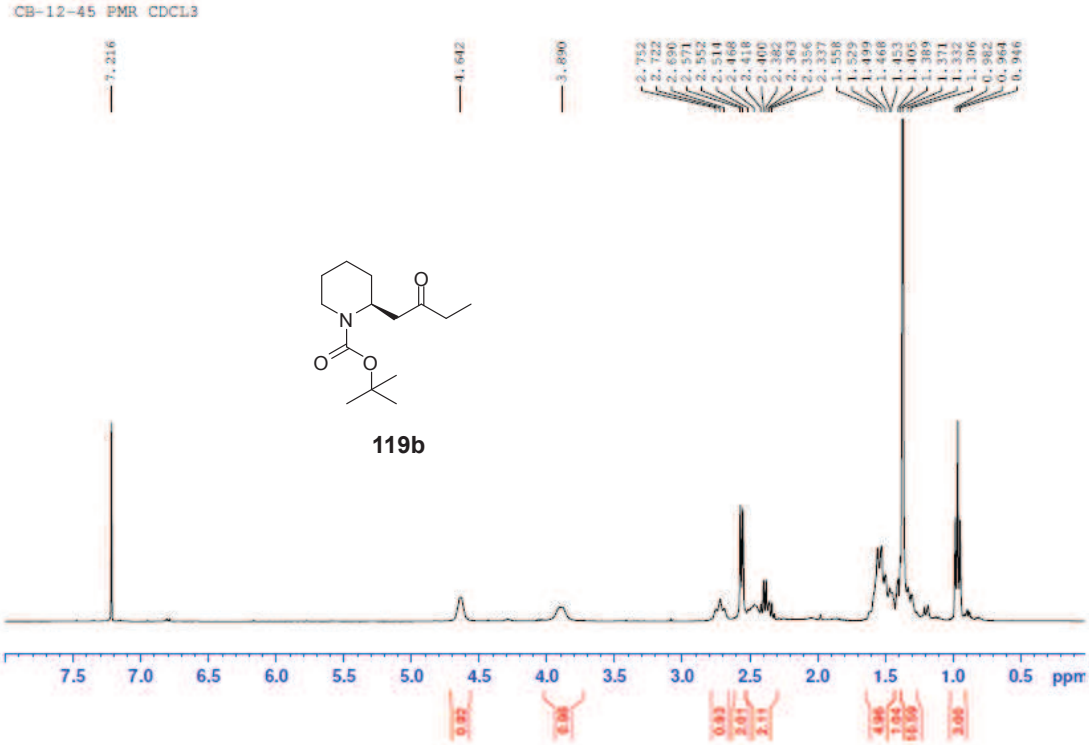


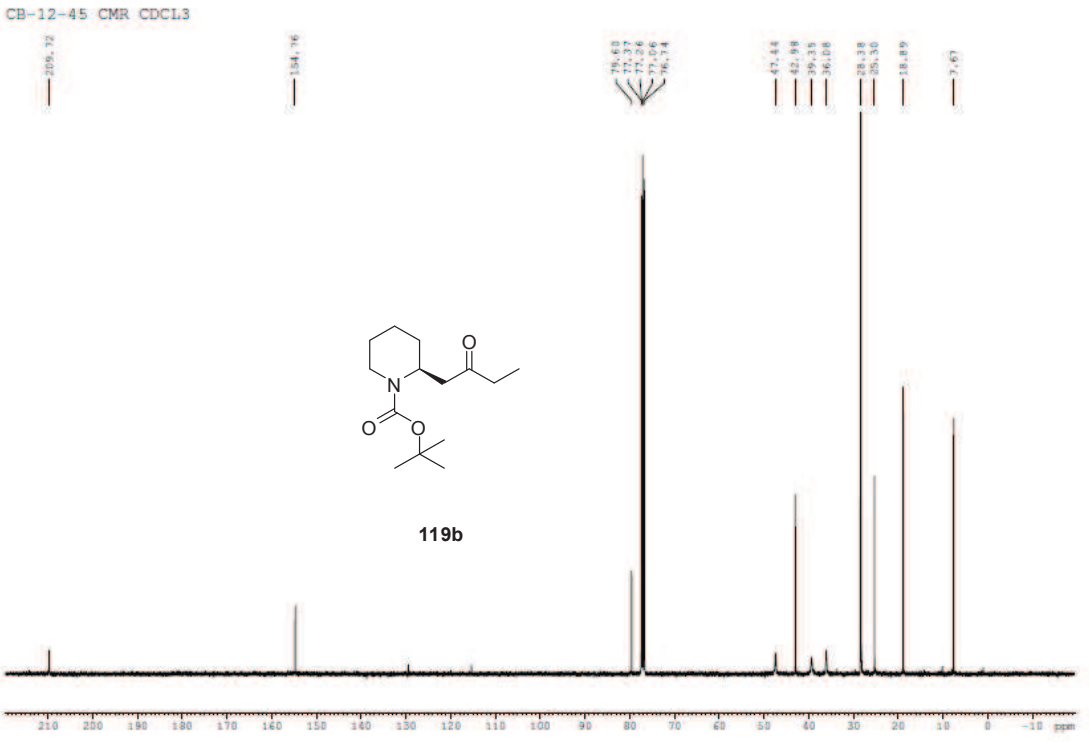
122c


CB-12-42 PMR CDCL3
7.306
7.302
7.287
7.284
7.282
7.273
7.264
7.252
7.245
7.241
7.230
7.217
7.195
5.040
4.724
4.710
3.991
3.966
2.821
2.791
2.760
2.653
2.633
2.617
2.596
2.570
2.533
2.428
2.345
1.974
1.619
1.607
1.596
1.571
1.538
1.536
1.495
1.460
1.453
1.428
1.420
1.383
1.351
1.328
1.319
0.940
0.922
0.904
O
N
O
O
119a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

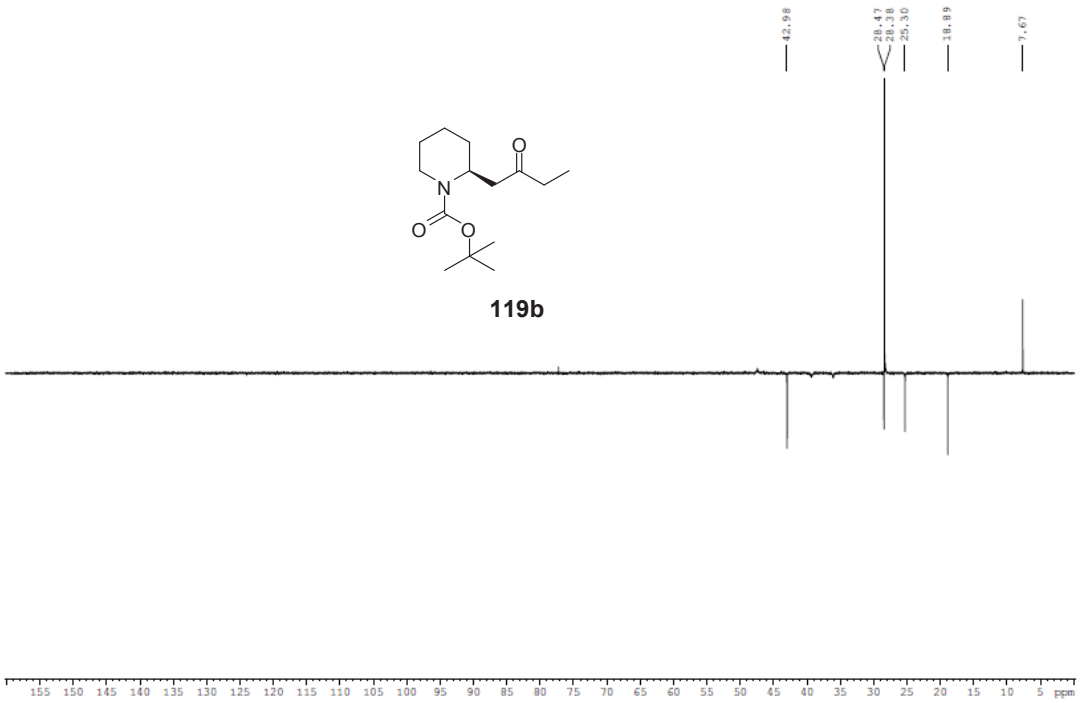

CB-12-42 CMR CDCL3
209.52
155.30
136.78
128.54
128.48
128.05
127.82
126.98
73.38
77.07
76.75
67.09
47.65
42.93
39.80
36.11
28.30
25.26
18.82
7.66
O
N
O
O
119a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


CB-12-42 DEPT CDCL3
128.48
127.99
127.82
67.09
47.65
42.93
39.80
36.12
28.30
25.26
18.82
7.66
O
N
O
O
119a
140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 ppm


CB-12-45 PMR CDCL3
119b

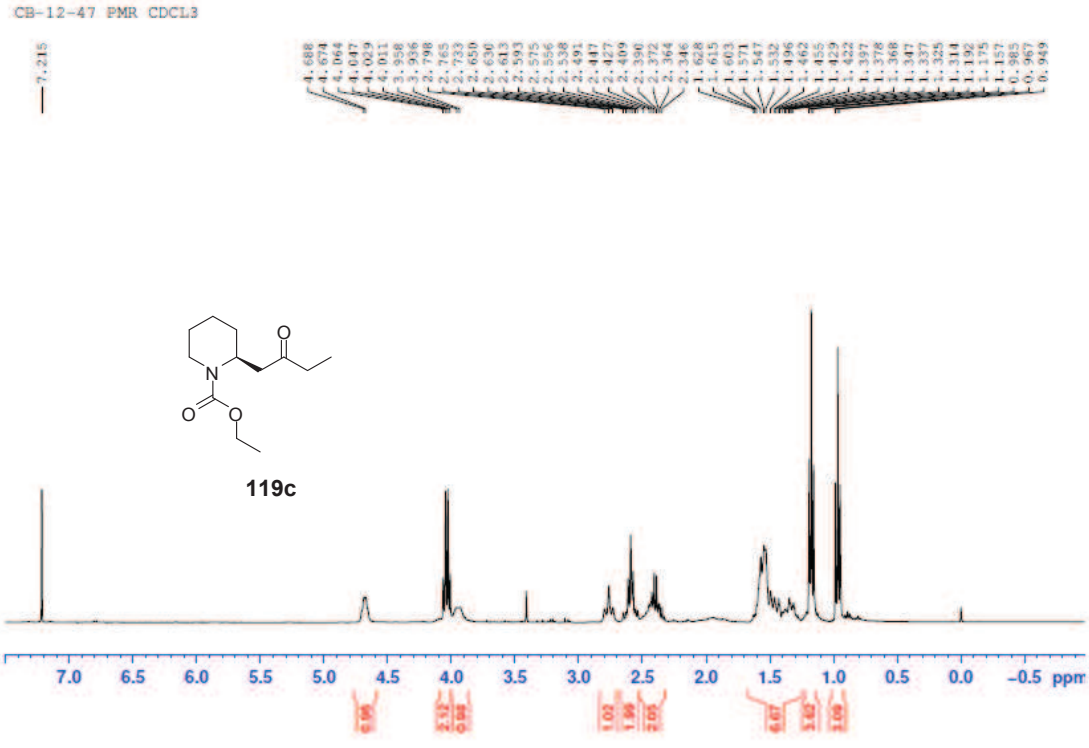

CB-12-45 CMR CDCL3
119b

CB-12-45 DEPT CDCL3



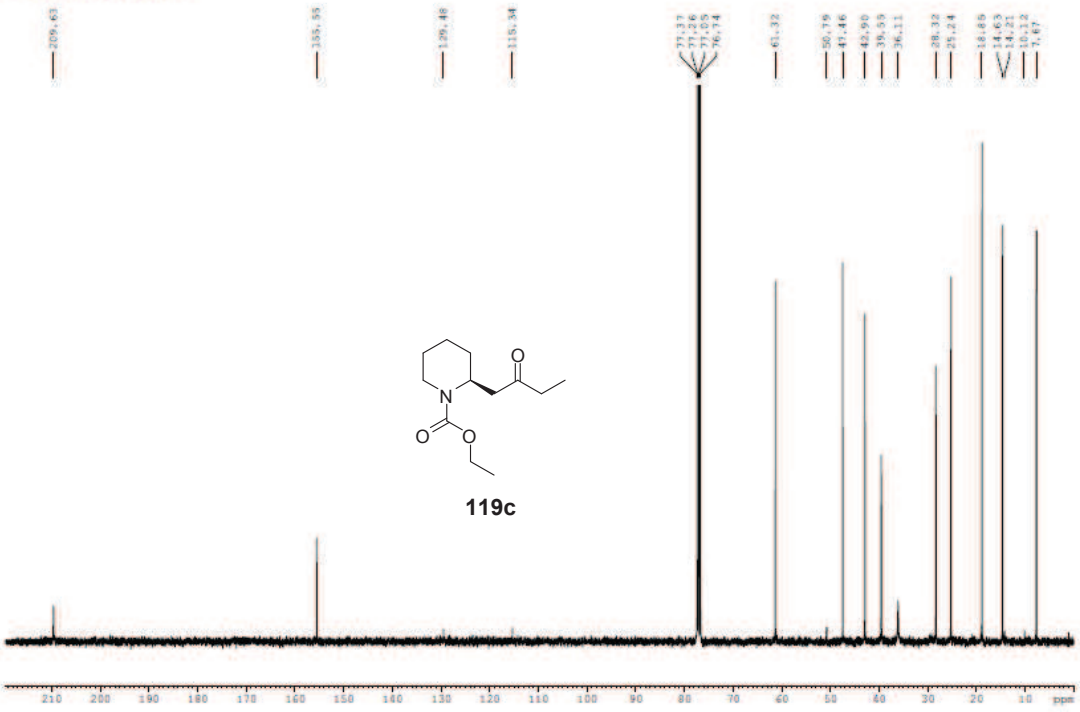
119b

CB-12-47 PMR CDCL3



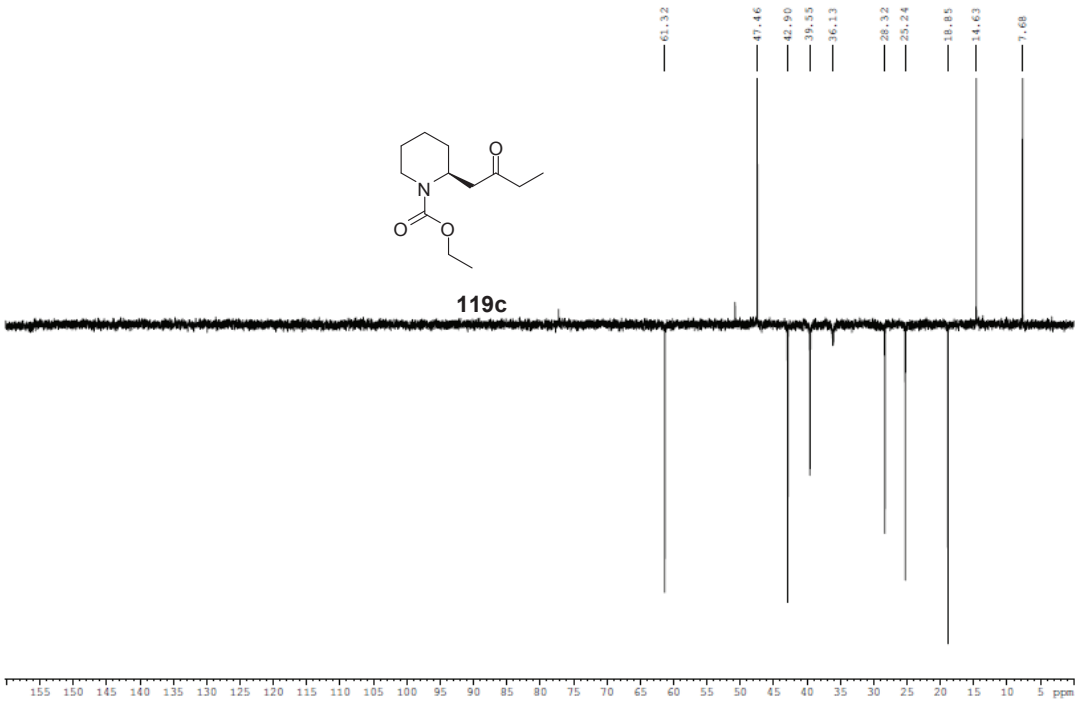
119c

CB-12-47 CMR CDCL3

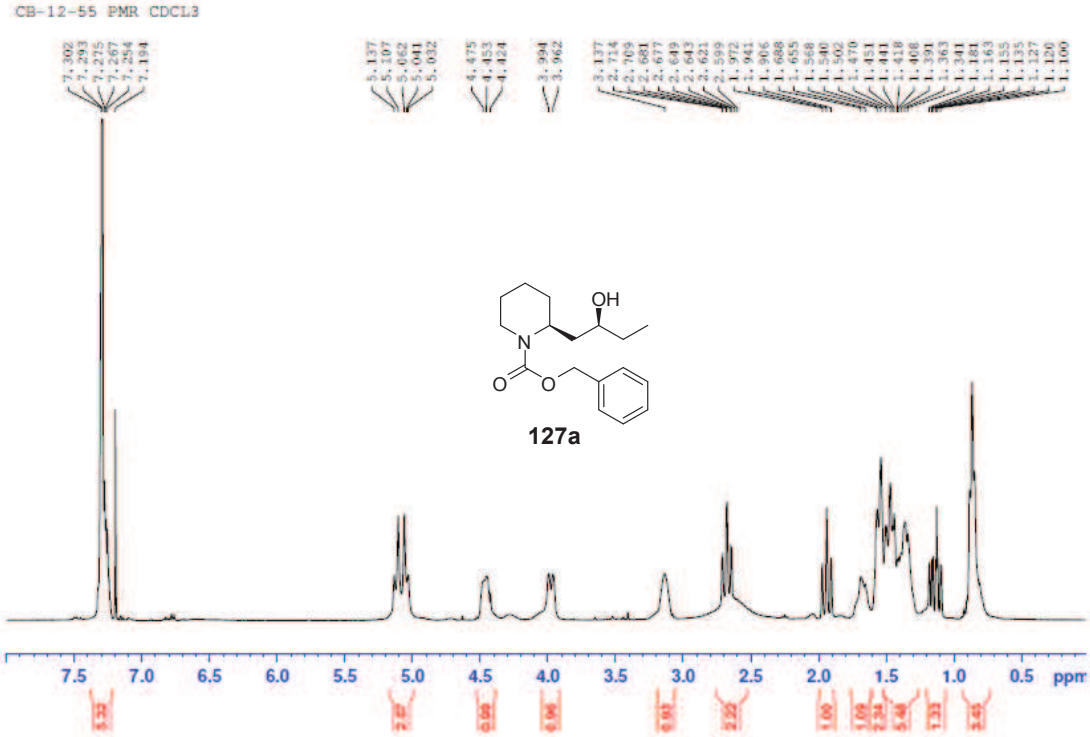


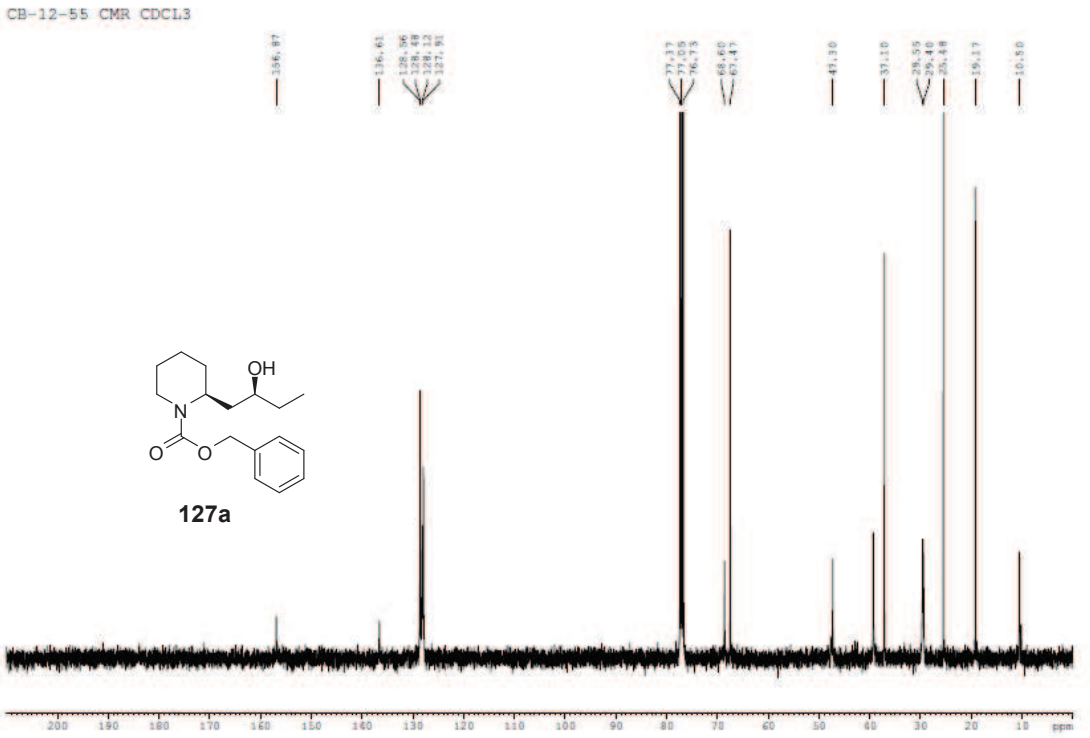
119c

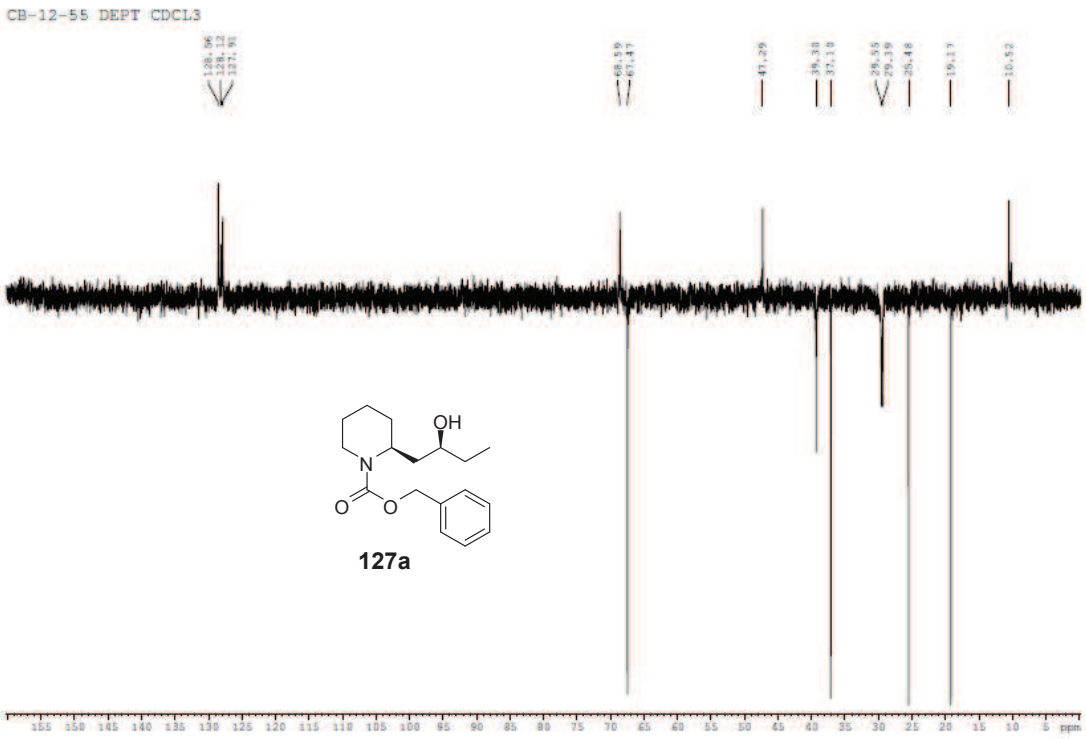
CB-12-47 DEPT CDCL3

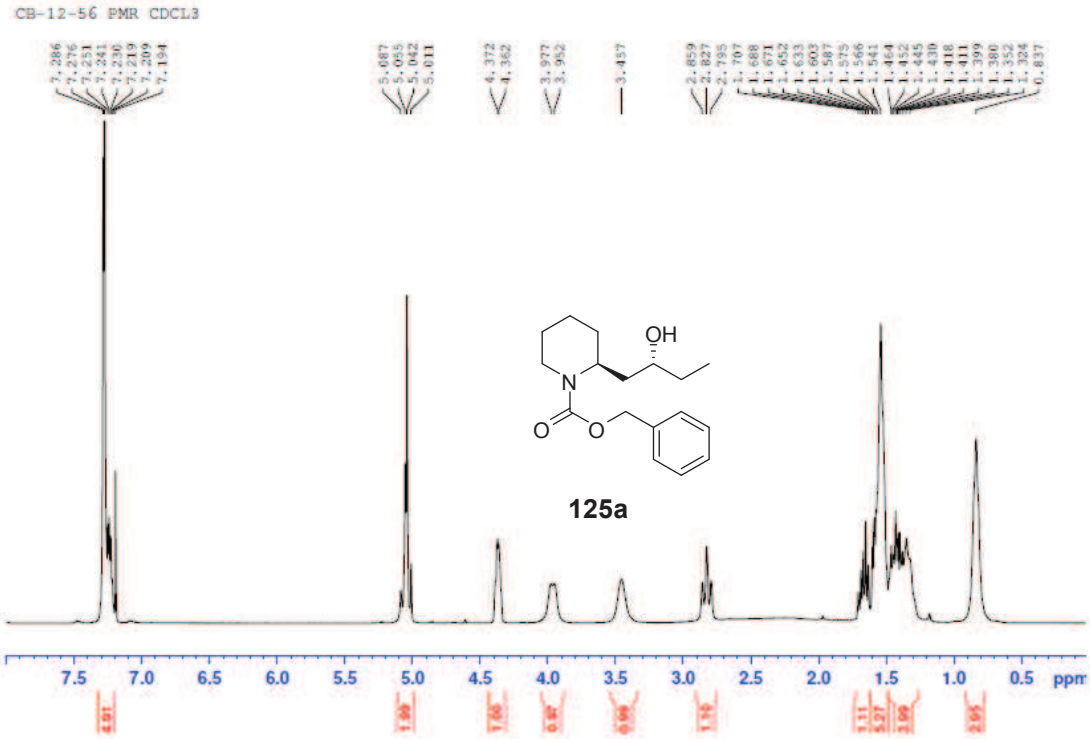


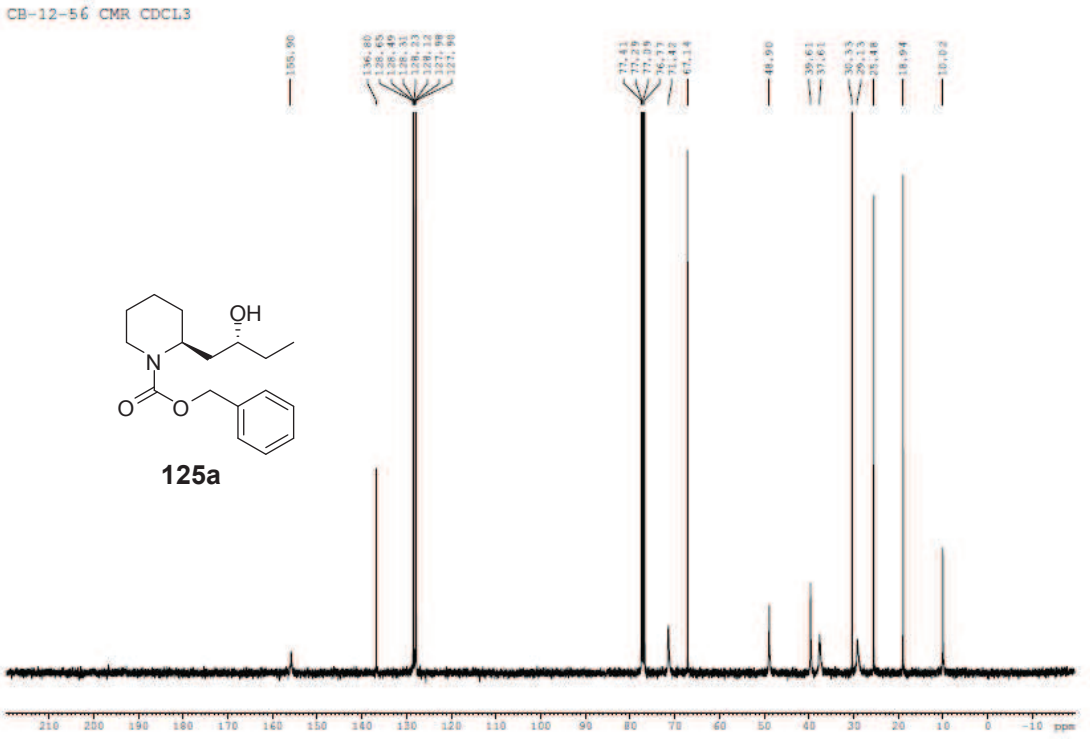
119c

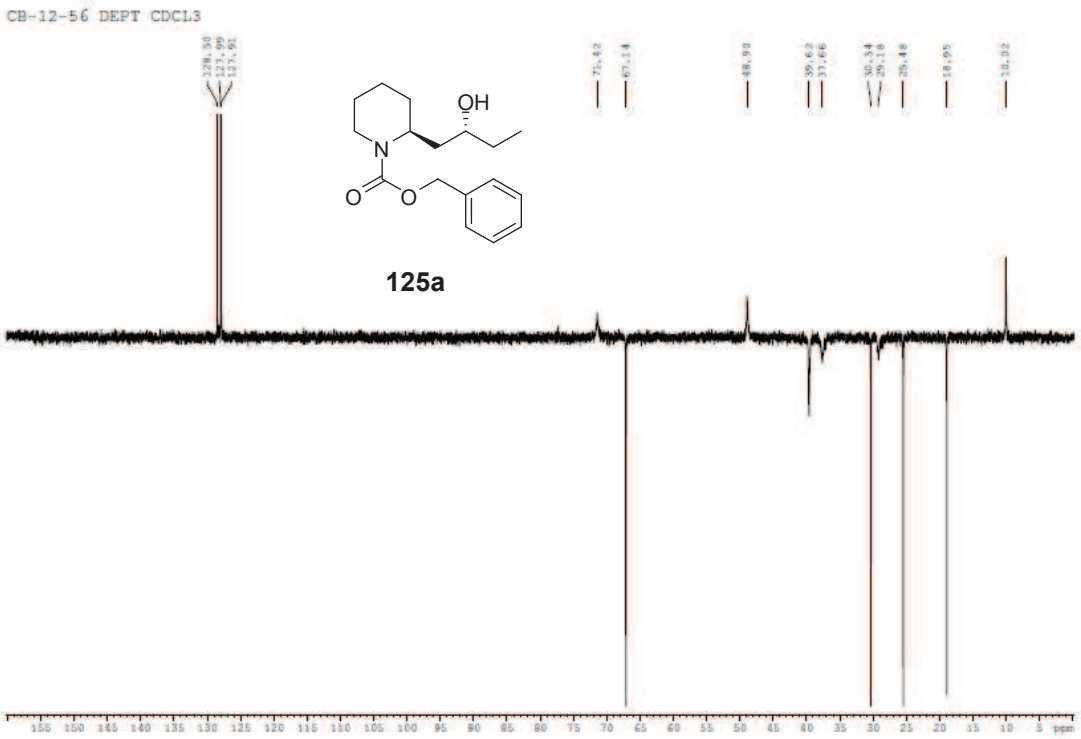

CB-12-55 PMR CDCL3
OH
N
O
O
127a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

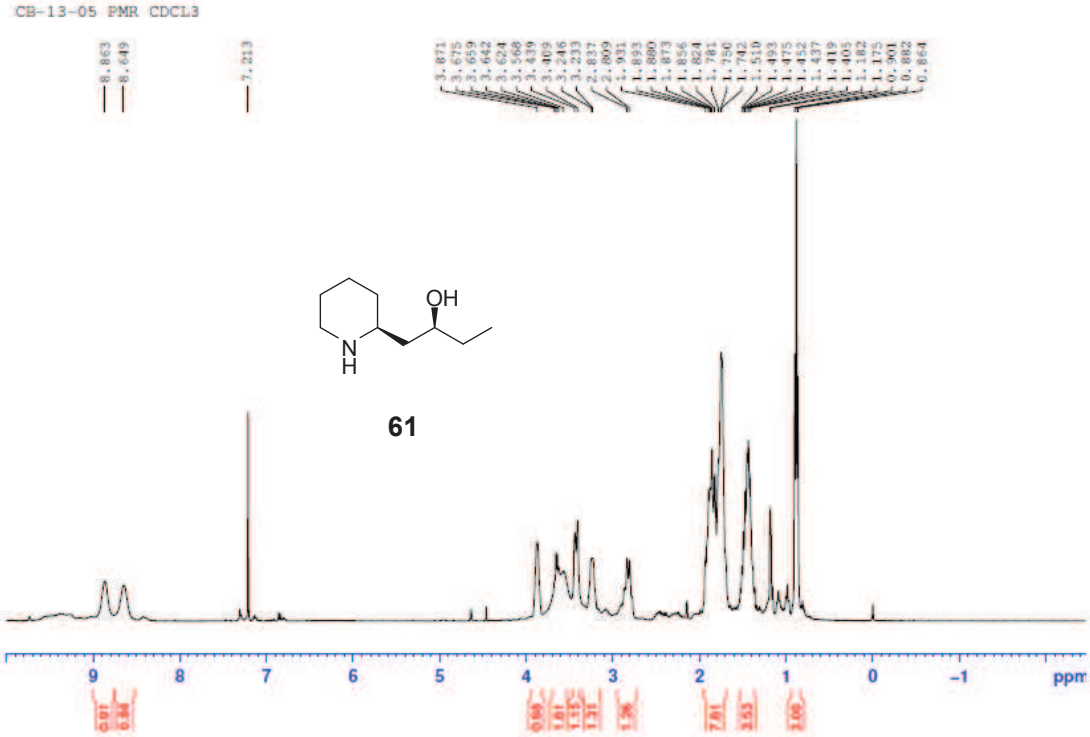

CB-12-55 CMR CDCL3
OH
N
O
O
127a
ppm

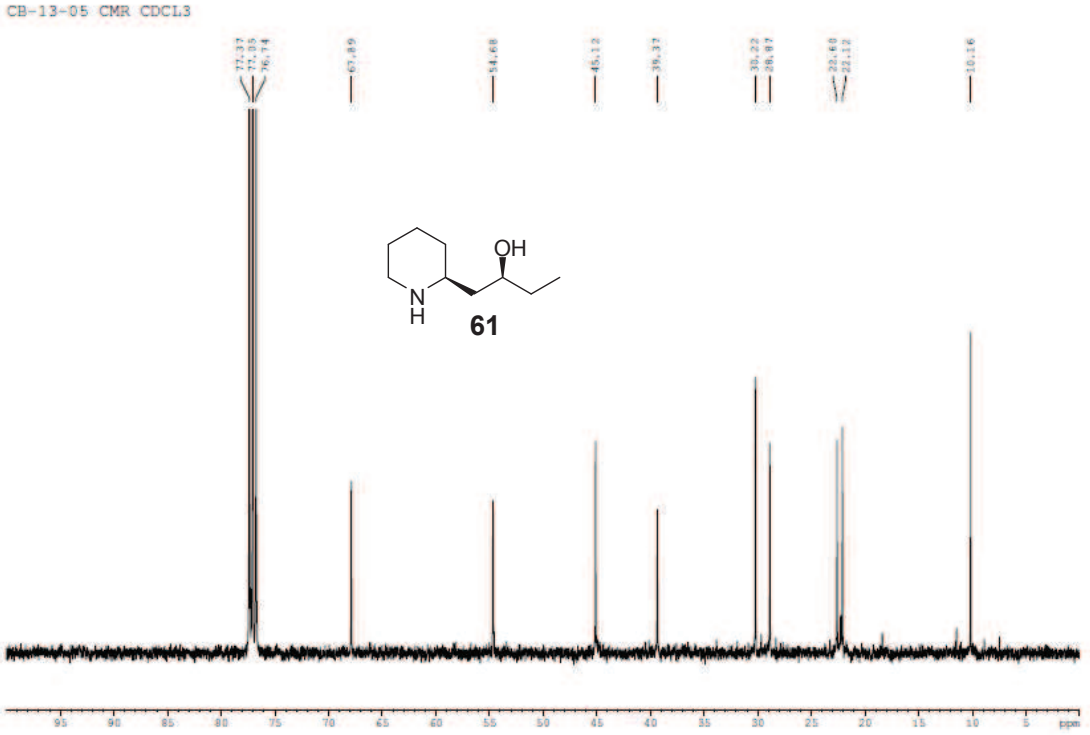

CB-12-55 DEPT CDCL3
128.06
128.12
127.93
68.59
67.47
41.29
35.38
33.10
29.55
29.39
25.48
19.17
10.52
OH
N
O
O
127a
155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 ppm


CB-12-56 PMR CDCL3
OH
N
O
O
125a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

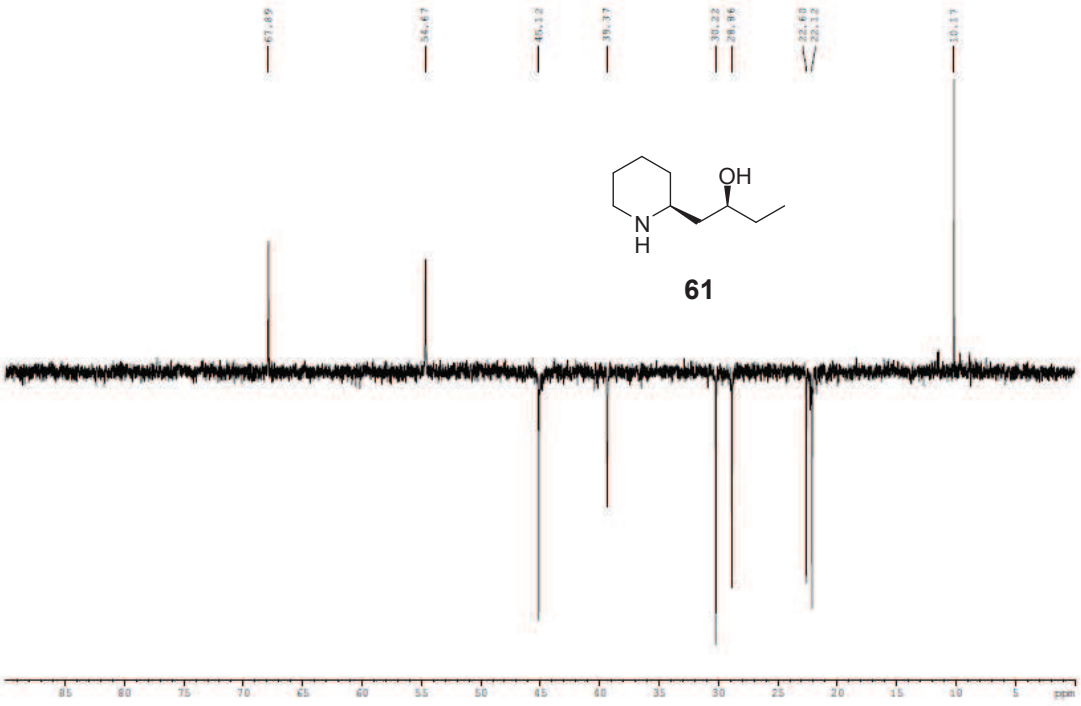

CB-12-56 CMR CDCL3
OH
N
O
O
125a
ppm


CB-12-56 DEPT CDCL3
128.50
127.99
127.91
71.42
67.14
48.90
39.62
37.66
30.34
29.18
25.48
18.95
10.02
OH
N
O
O
125a
155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 ppm


CB-13-05 PMR CDCL3
8.863
8.649
7.213
3.871
3.675
3.659
3.642
3.624
3.568
3.439
3.409
3.246
3.233
2.837
2.809
1.931
1.893
1.880
1.873
1.856
1.824
1.781
1.750
1.742
1.519
1.493
1.475
1.452
1.437
1.419
1.405
1.182
1.175
0.901
0.882
0.864
OH
N
H
61
9
8
7
6
5
4
3
2
1
0
-1
ppm

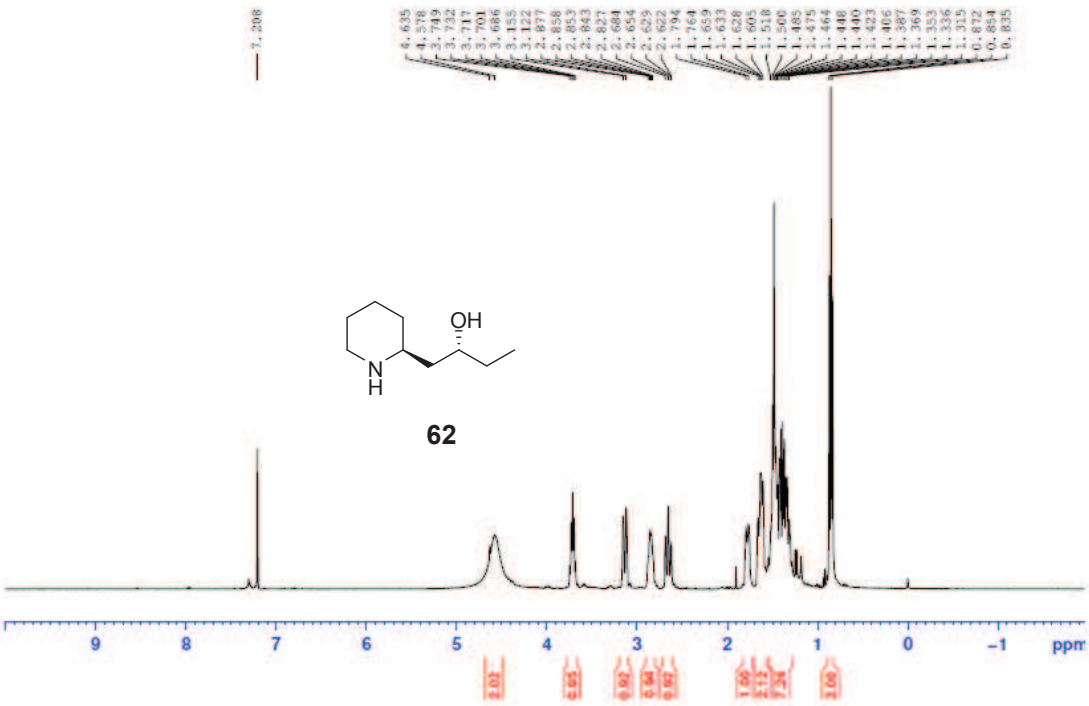

CB-13-05 CMR CDCL3
77.37
77.05
76.74
67.89
54.68
45.12
39.37
30.22
28.87
23.68
23.12
10.16
OH
N
H
61
ppm

CB-13-05 DEPT CDCL3

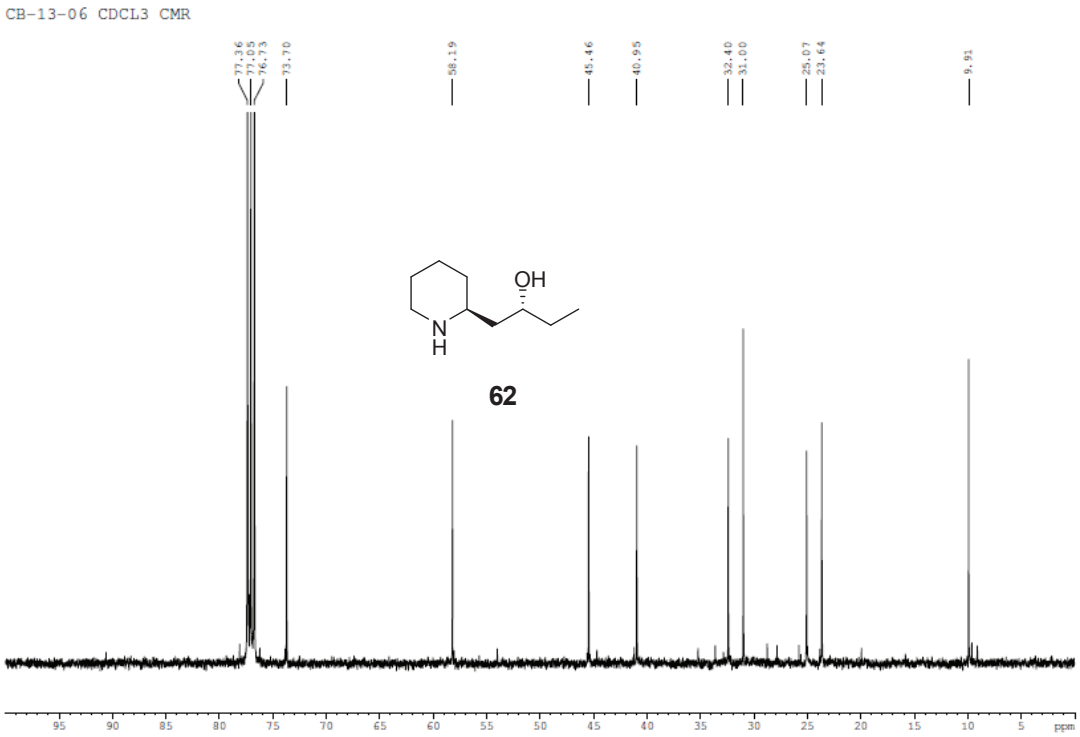


61

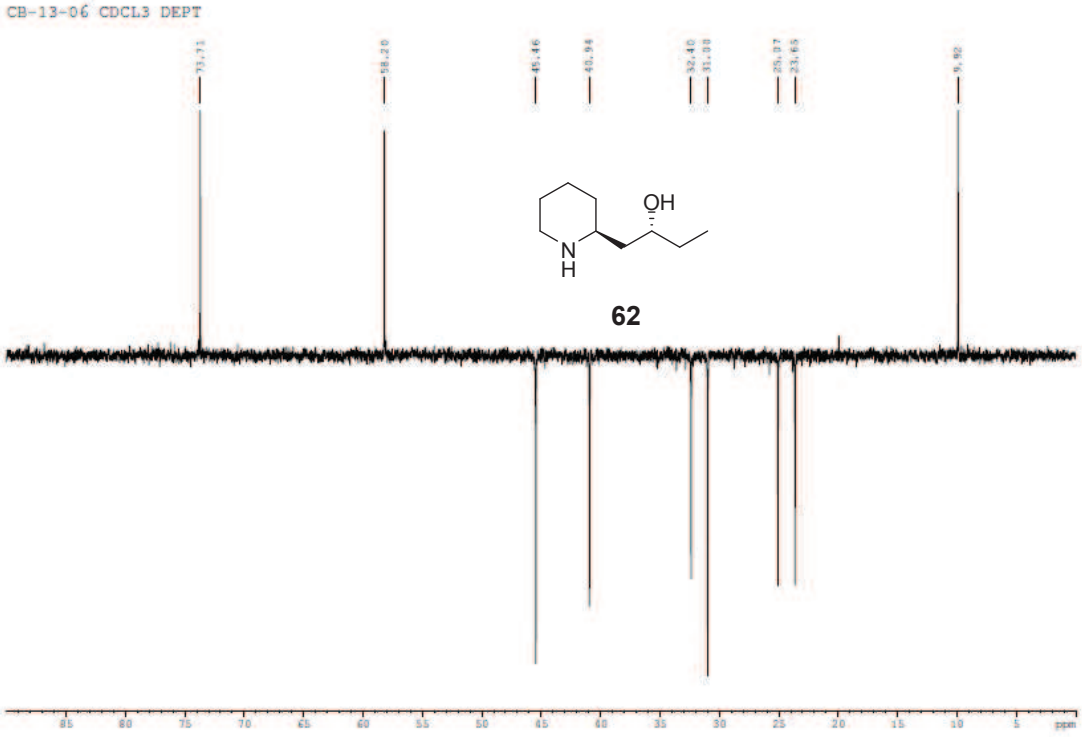
CB-13-06 PMR CDCL3

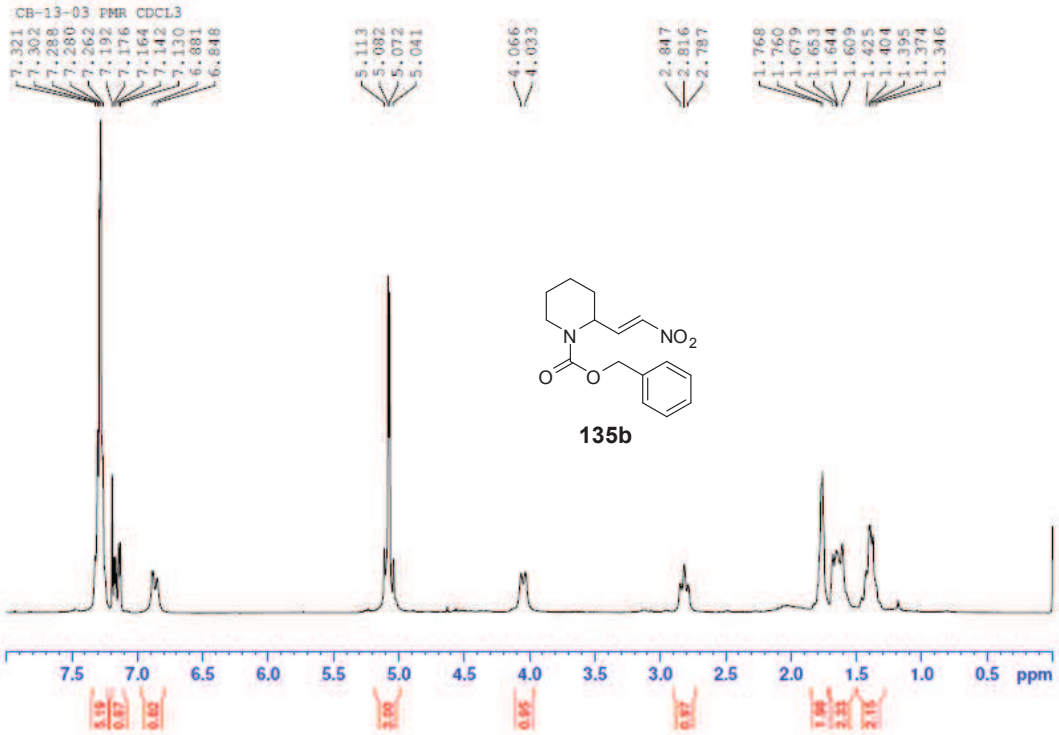


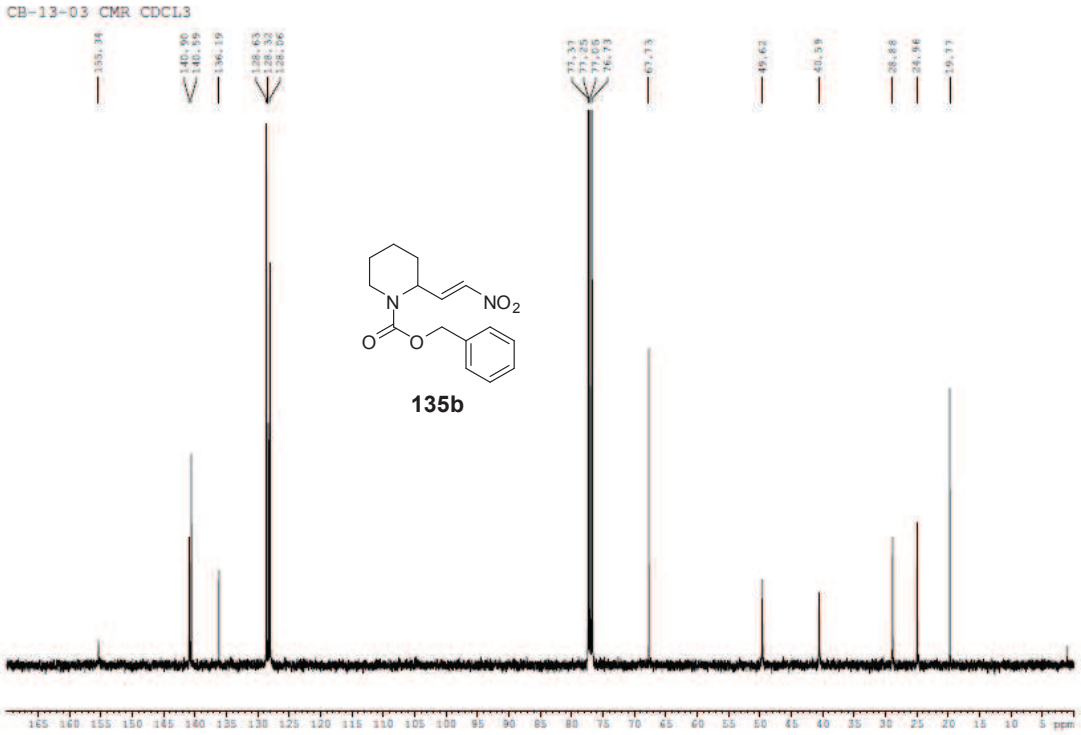
62

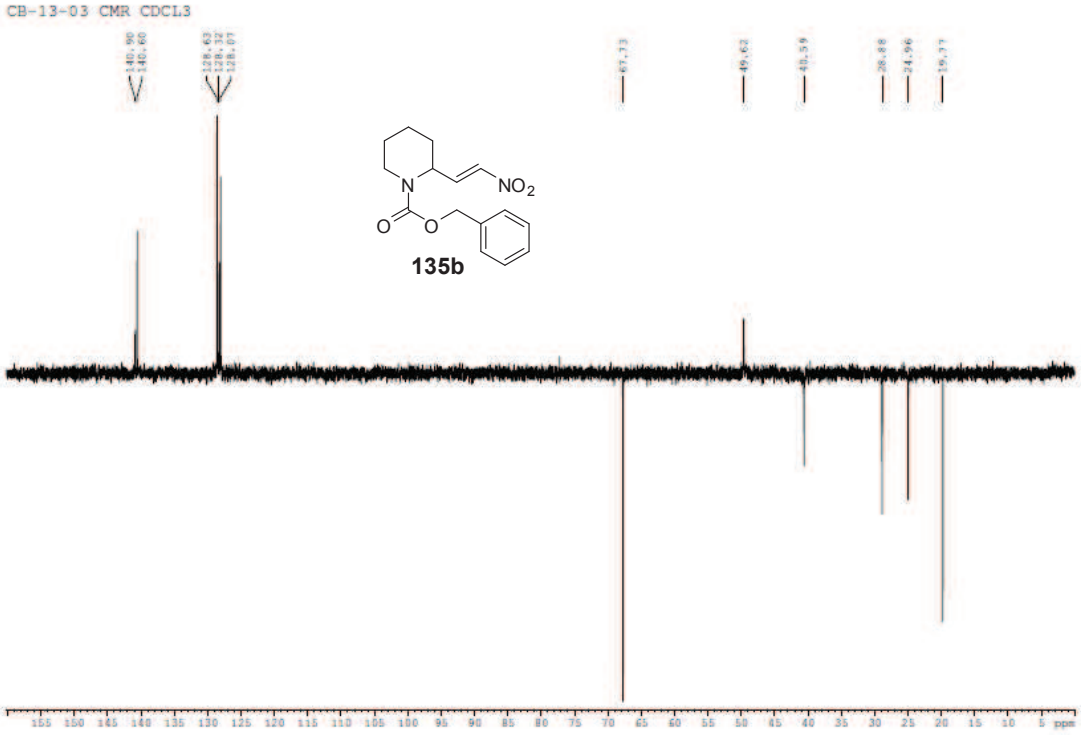

CB-13-06 CDCL3 CMR
77.36
77.05
76.73
73.70
58.19
45.46
40.95
32.40
31.00
25.07
23.64
9.91
OH
N
H
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
ppm

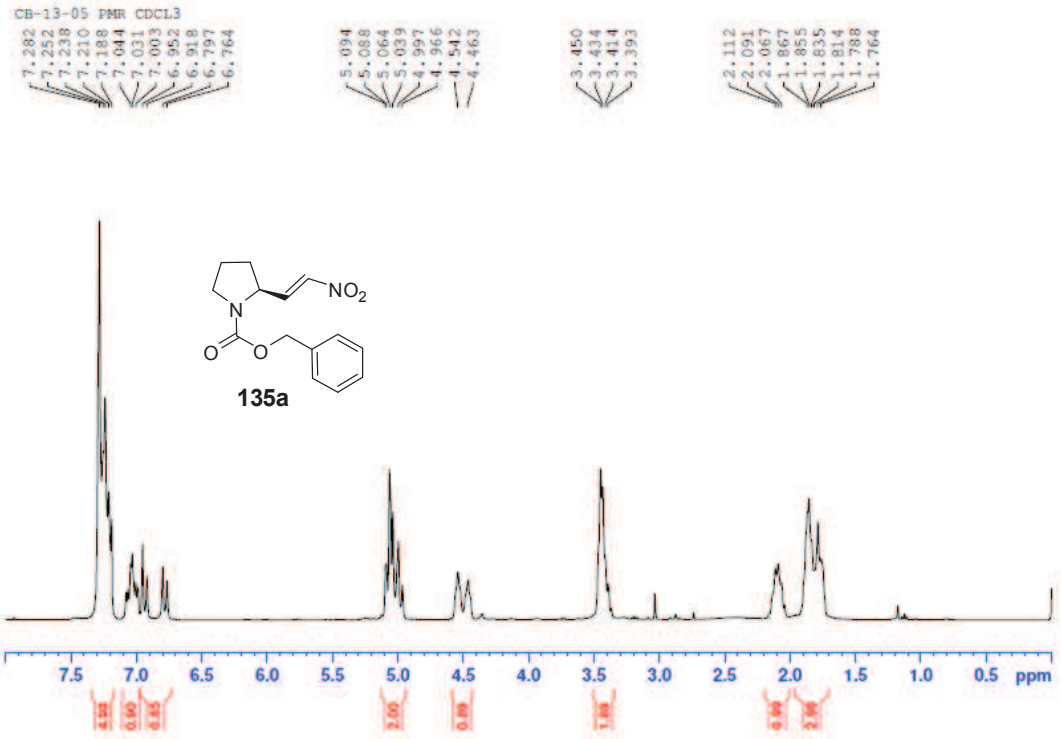
62

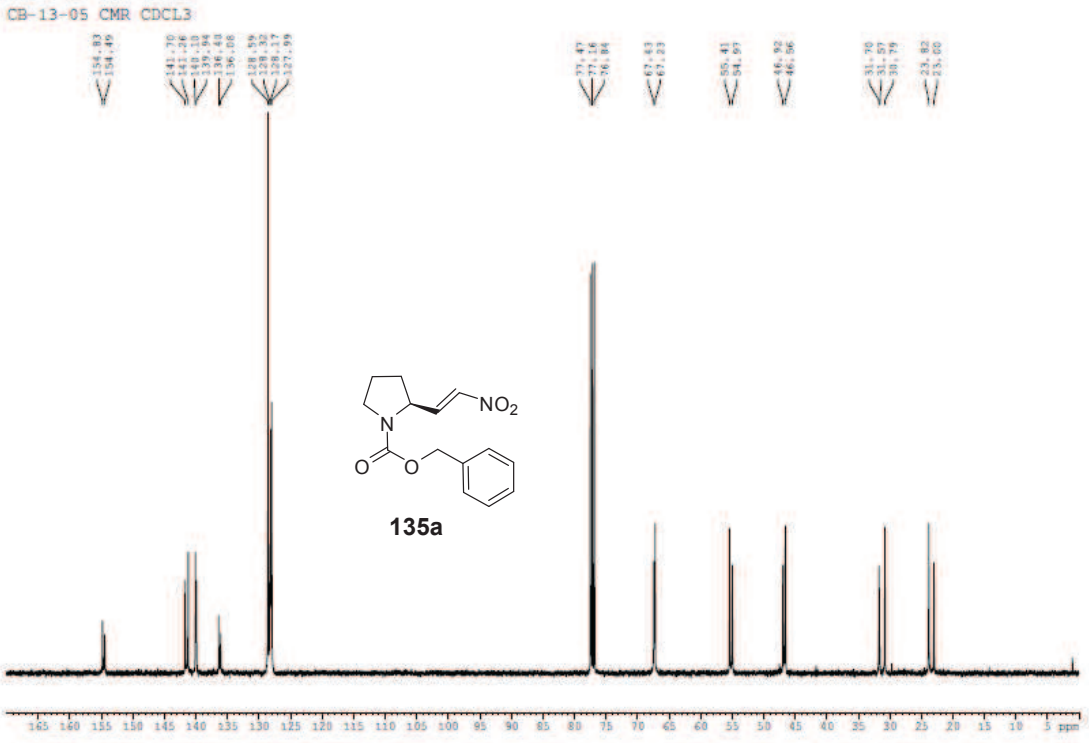

CB-13-06 CDCL3 DEPT
73.71
58.20
45.46
40.94
32.40
31.00
25.07
23.65
9.82
OH
N
H
62

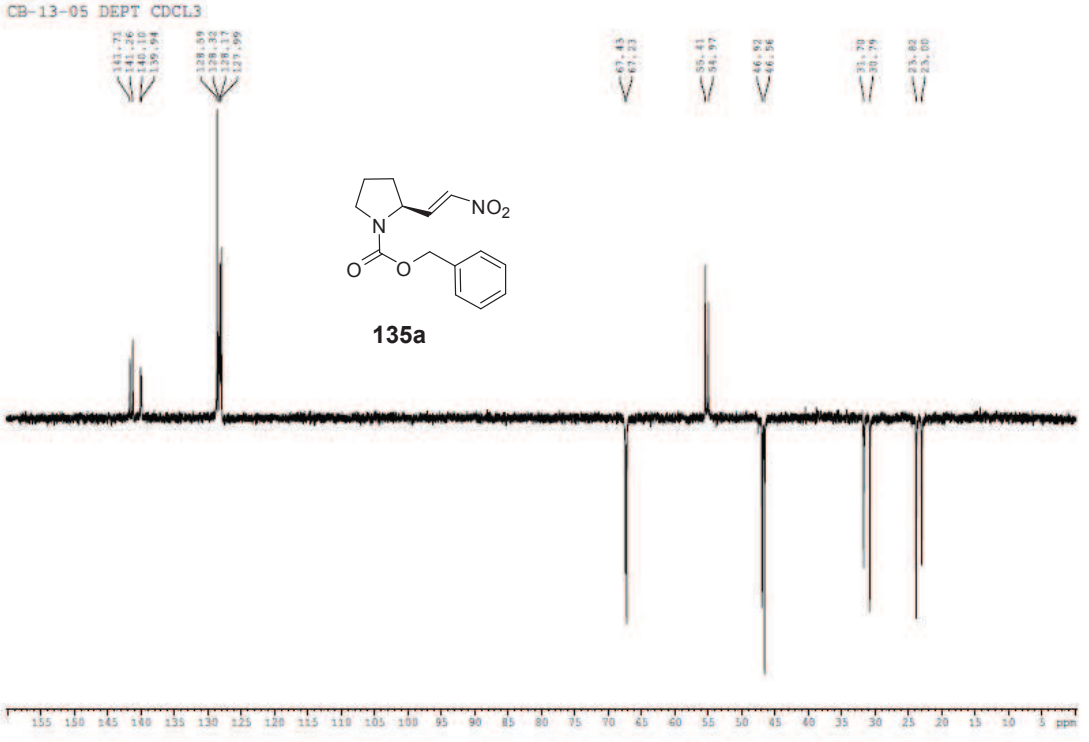

CB-13-03 PMR CDCL3
7.321
7.302
7.288
7.280
7.262
7.192
7.176
7.164
7.142
7.130
6.881
6.848
5.113
5.082
5.072
5.041
4.066
4.033
2.847
2.816
2.787
1.768
1.760
1.679
1.653
1.644
1.609
1.425
1.404
1.395
1.374
1.346
NO2
N
O
O
135b
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

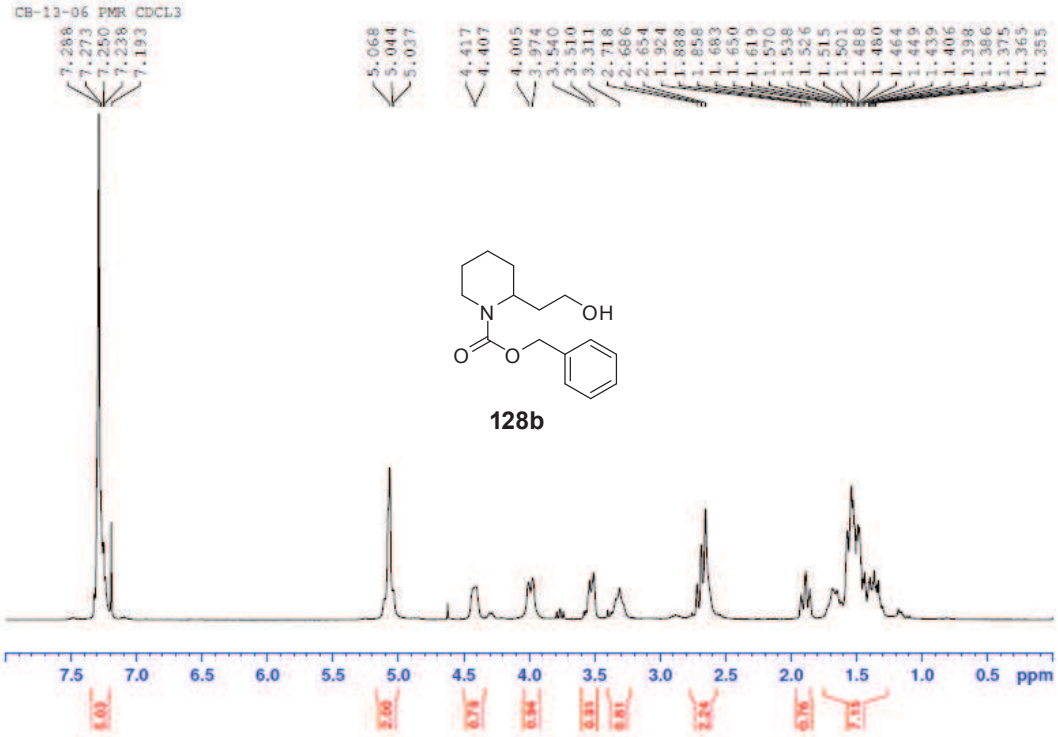

CB-13-03 CMR CDCL3
155.34
140.90
140.59
136.19
128.63
128.32
128.06
77.37
77.25
77.05
76.73
67.73
49.62
40.59
28.88
24.96
19.77
NO2
N
O
O
135b

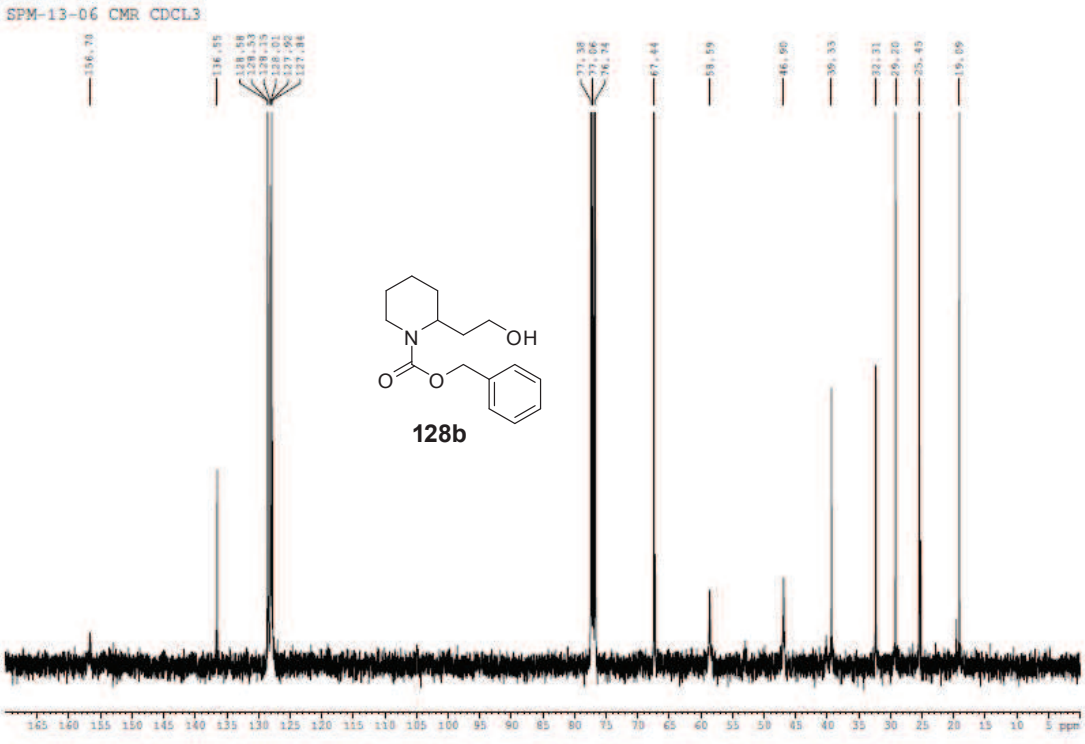

CB-13-03 CMR CDCL3
140.90
140.60
128.63
128.32
128.07
67.73
49.62
40.59
28.88
24.96
19.77
NO2
N
O
O
135b

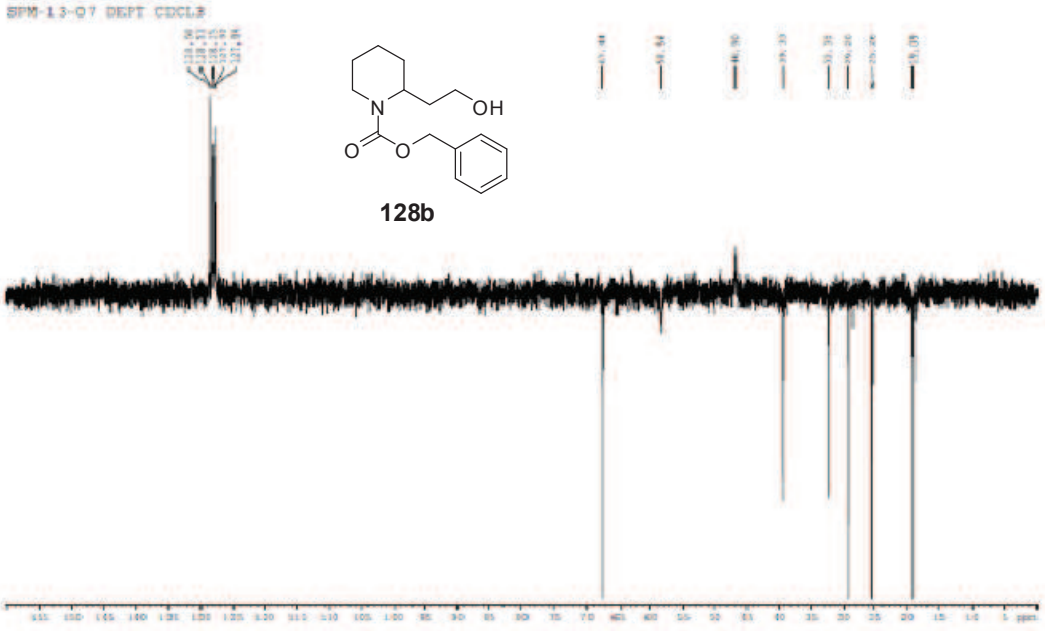

CB-13-05 PMR CDCL3
7.282
7.252
7.238
7.210
7.188
7.044
7.031
7.003
6.952
6.918
6.797
6.764
5.094
5.088
5.064
5.039
4.997
4.966
4.542
4.463
3.450
3.434
3.414
3.393
2.112
2.091
2.067
1.867
1.855
1.835
1.814
1.788
1.764
NO2
N
O
O
135a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


CB-13-05 CMR CDCL3
154.83
154.49
141.70
141.26
140.10
139.94
136.48
136.08
128.59
128.32
128.17
127.99
77.47
77.16
76.84
67.43
67.23
55.41
54.97
46.92
46.56
31.70
31.57
30.79
23.82
23.00
NO2
N
O
O
135a
ppm

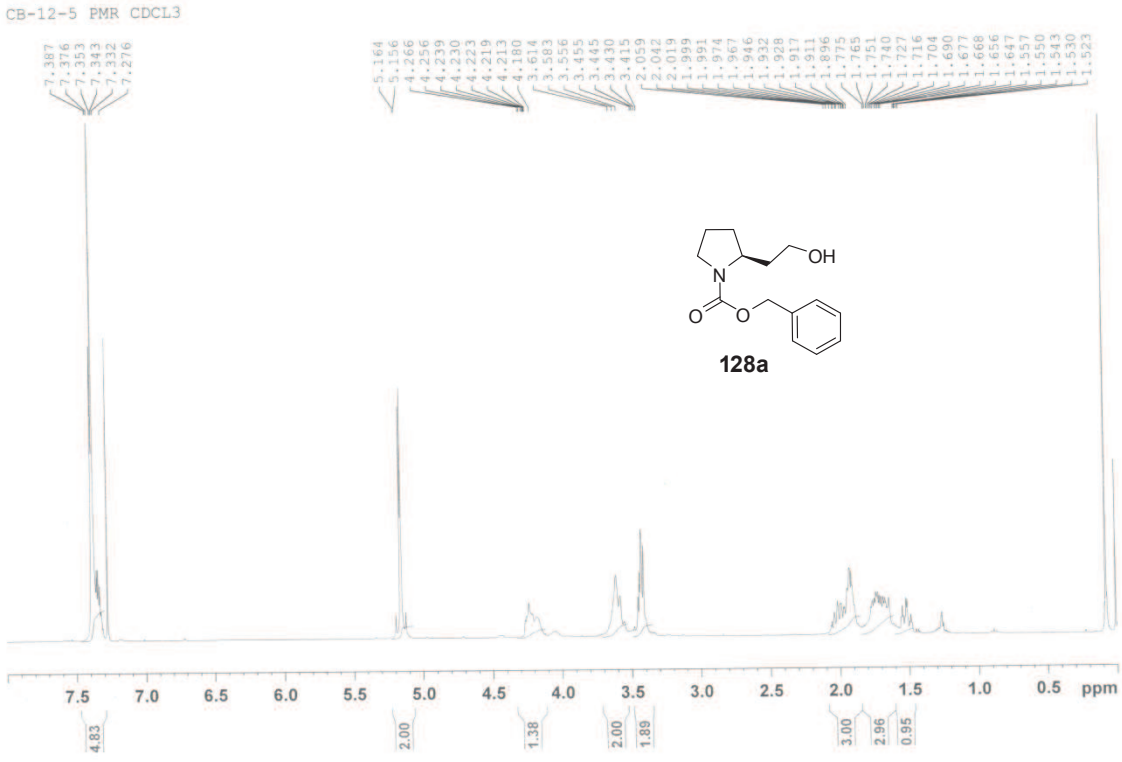

CB-13-05 DEPT CDCL3
141.71
141.26
140.10
139.94
128.59
128.32
128.17
127.99
67.43
67.23
55.41
54.97
46.92
46.56
31.70
30.79
23.82
23.00
NO2
N
O
O
135a
ppm


CB-13-06 PMR CDCL3
7.288
7.273
7.250
7.238
7.193
5.068
5.044
5.037
4.417
4.407
4.005
3.974
3.540
3.510
3.311
2.718
2.686
2.654
1.924
1.888
1.858
1.683
1.650
1.619
1.570
1.538
1.526
1.515
1.501
1.488
1.480
1.464
1.449
1.439
1.406
1.398
1.386
1.375
1.365
1.355
N
OH
O
O
128b
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

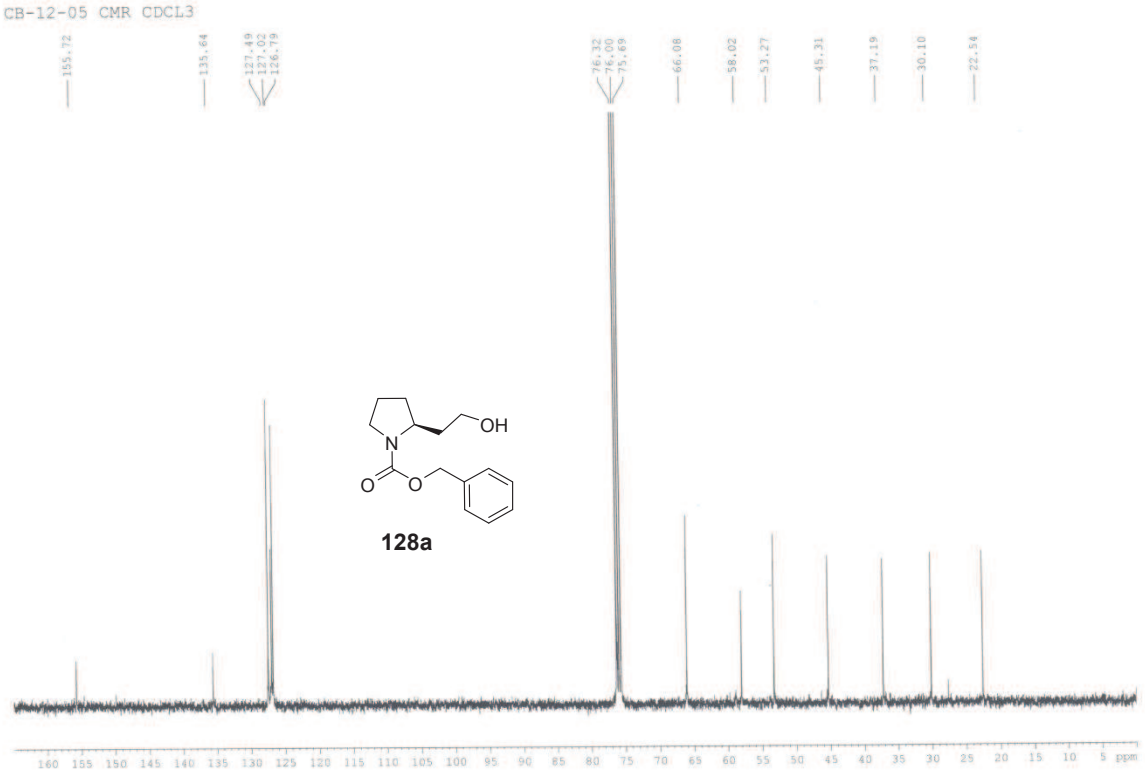

SPM-13-06 CMR CDCL3
156.78
136.55
128.58
128.53
128.15
128.01
127.92
127.84
77.38
77.06
76.74
67.44
58.59
46.90
39.33
32.31
25.20
25.49
19.09
N
OH
O
O
128b

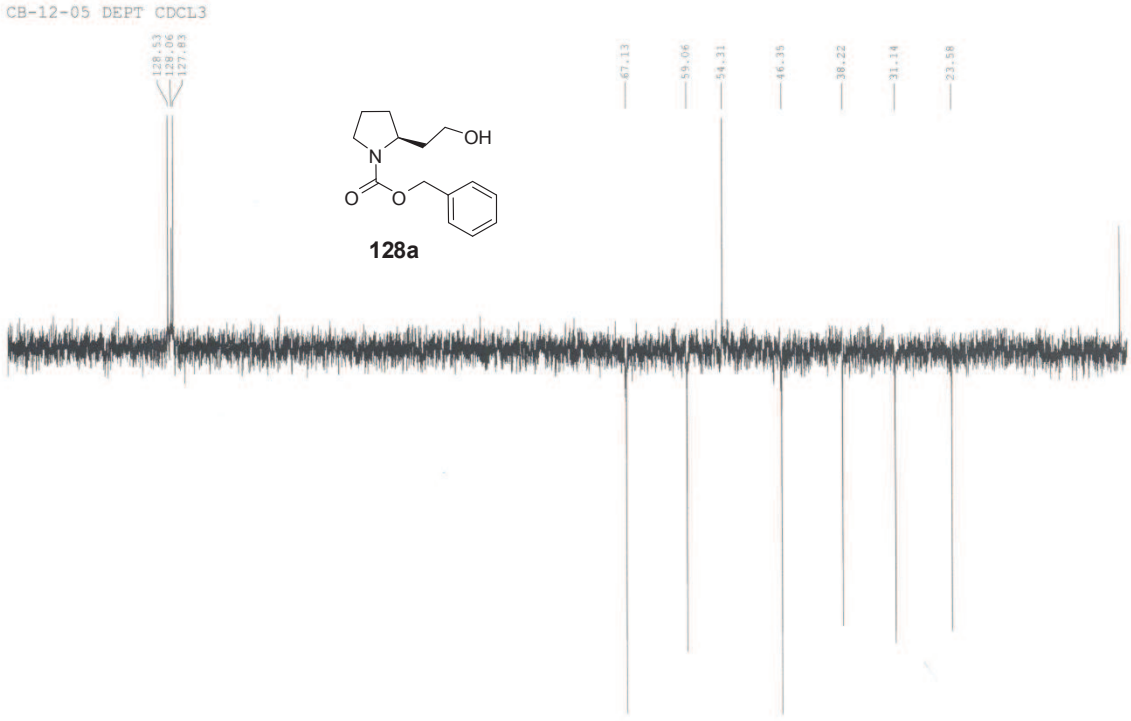

SPM-13-Q7 DEPT CDCL3
N
OH
O
O

128b

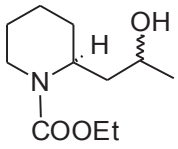

CB-12-5 PMR CDCL3
N
OH
O
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
4.83
2.00
1.38
2.00
1.89
3.00
2.96
0.95

128a


CB-12-05 CMR CDCL3
155.72
135.64
127.49
127.02
126.79
76.32
76.00
75.69
66.08
58.02
53.27
45.31
37.19
30.10
22.54
OH
N
O
O
128a
160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 ppm


CB-12-05 DEPT CDCL3
128.53
128.06
127.83
67.13
59.06
54.31
46.35
38.22
31.14
23.58
OH
N
O
O
128a

Determination of Diastereomeric ratio by HPLC Method



ZnBH4 reduction WL 210nm, FR 0.8ml, 10%IPA+hexane

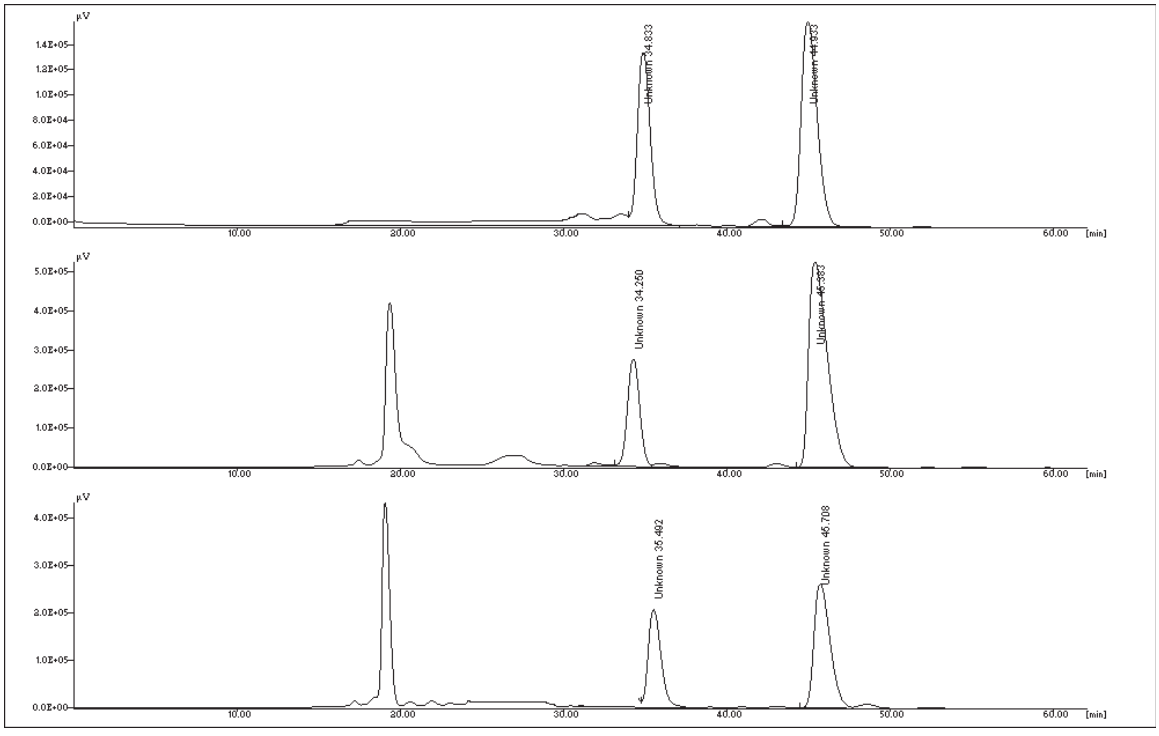
#	RT	Area[μV.Sec]	%Area
1	34.833	6945928.505	40.10
2	44.933	10375200.375	59.90

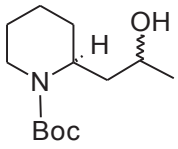
Li(t-OBu)3AlH reduction WL 210nm, FR 0.8ml, 10%IPA+hexane

#	RT	Area[μV.Sec]	%Area
1	34.250	13199004.184	25.14
2	45.383	39310079.250	74.86

NaBH4 reduction WL 210nm, FR 0.8ml, 10%IPA

#	RT	Area[μV.Sec]	%Area
1	35.492	10420770.326	38.33
2	45.708	16763138.004	61.67





NaBH4 reduction WL 220nm, FR 0.8ml, 10%IPA

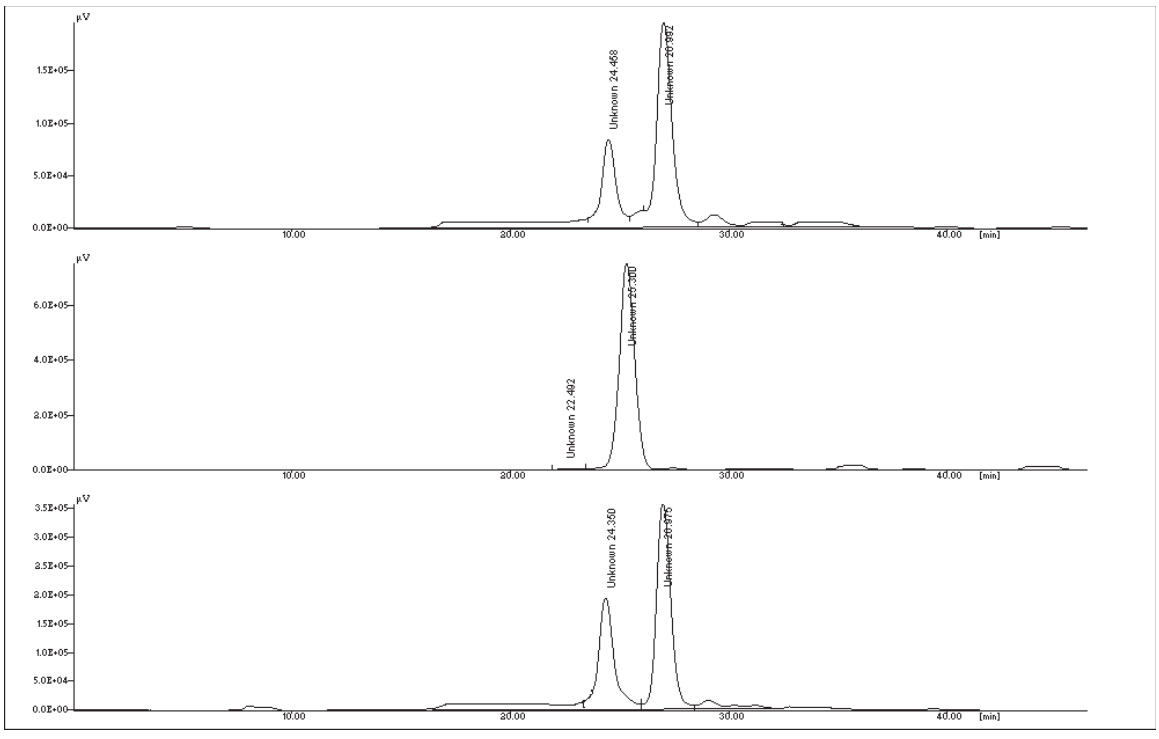
#	RT	Area[μV.Sec]	%Area
1	24.458	3555848.564	28.01
2	26.992	9139407.332	71.99

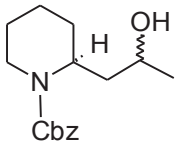
Li(t-OBu)3AlH reduction WL 220nm, FR 0.6ml, 10%IPA

#	RT	Area[μV.Sec]	%Area
1	22.492	100447.739	0.29
2	25.300	34747435.045	99.71

Zn(BH4)2 reduction WL 220nm, FR 0.8ml, 10%IPA

#	RT	Area[μV.Sec]	%Area
1	24.350	8833017.328	36.67
2	26.975	15254600.083	63.33





Zn(BH4)2 reduction WL 254nm, FR 1.0ml, 10%IPA +hexane

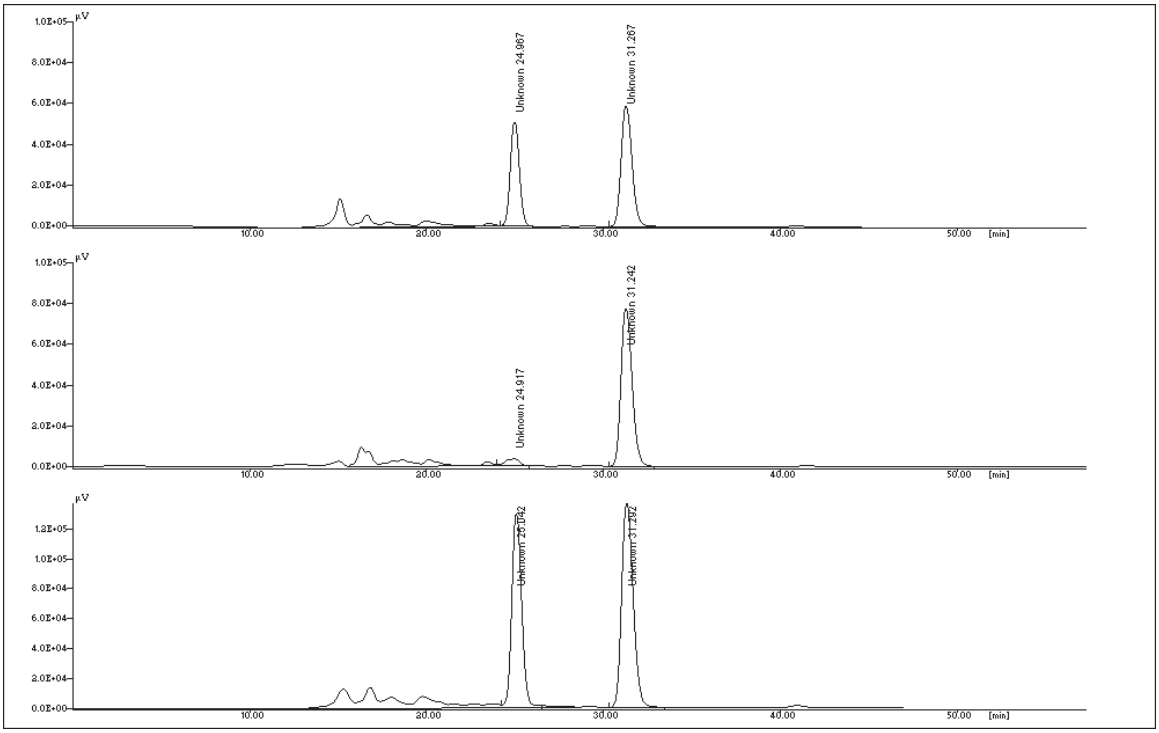
#	RT	Area[μV.Sec]	%Area
1	24.967	1637013.951	41.53
2	31.267	2305177.000	58.47

Lit(t-OBu)3AlH reduction WL 254nm, FR 1.0ml, 10%IPA+hexane

#	RT	Area[μV.Sec]	%Area
1	24.917	183898.957	5.64
2	31.242	3078425.500	94.36

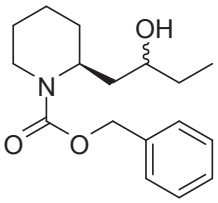
NaBH4 reduction WL 254nm, FR 1.0ml, 10%IPA +hexane

#	RT	Area[μV.Sec]	%Area
1	25.042	4530552.829	44.40
2	31.292	5673878.500	55.60

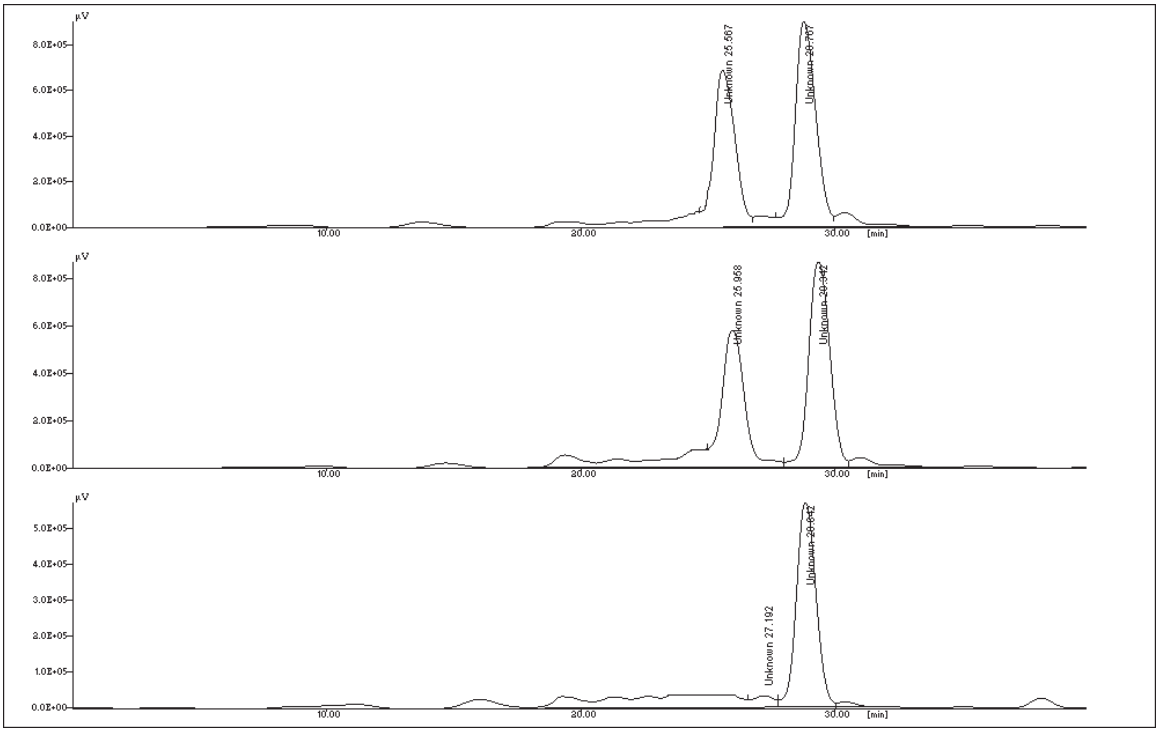


With similar specifications

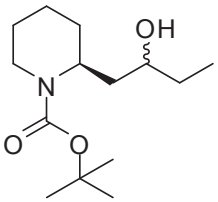
HPLC Chromatogram for



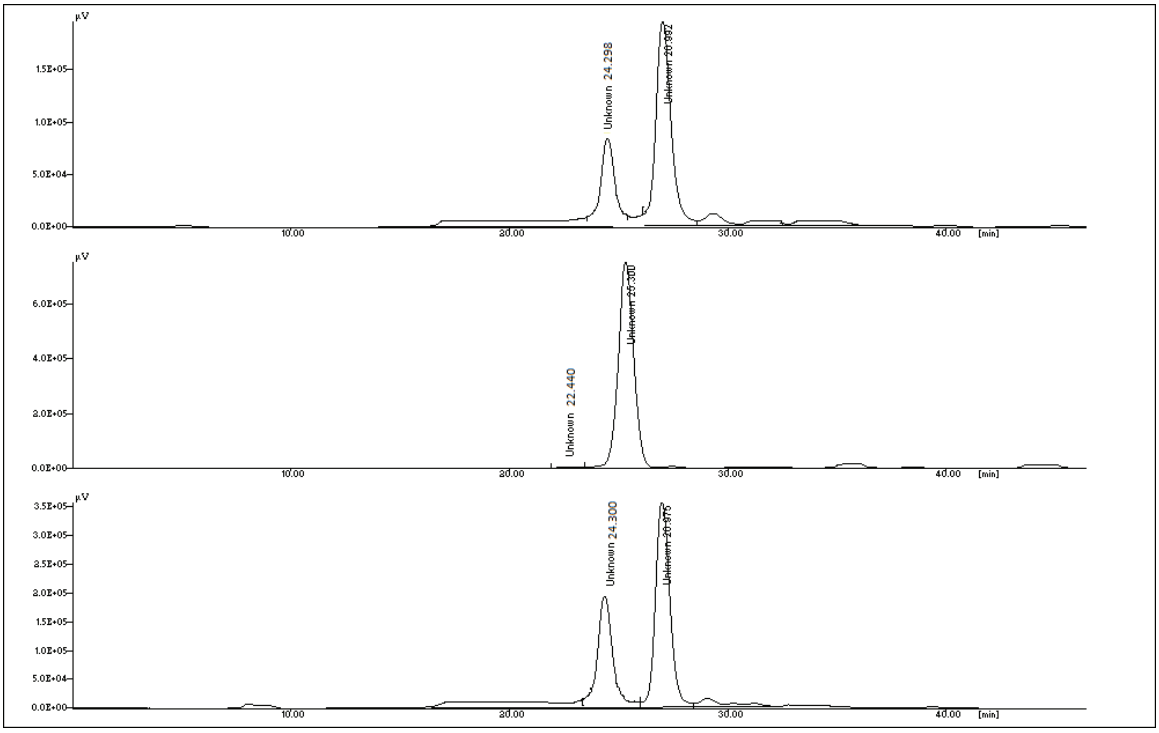
The reducing agents; $Zn(BH_4)_2$, $Li(O\text{-}^tBu)_3AlH$, NaBH4



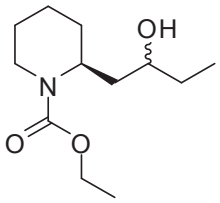
HPLC Chromatogram for



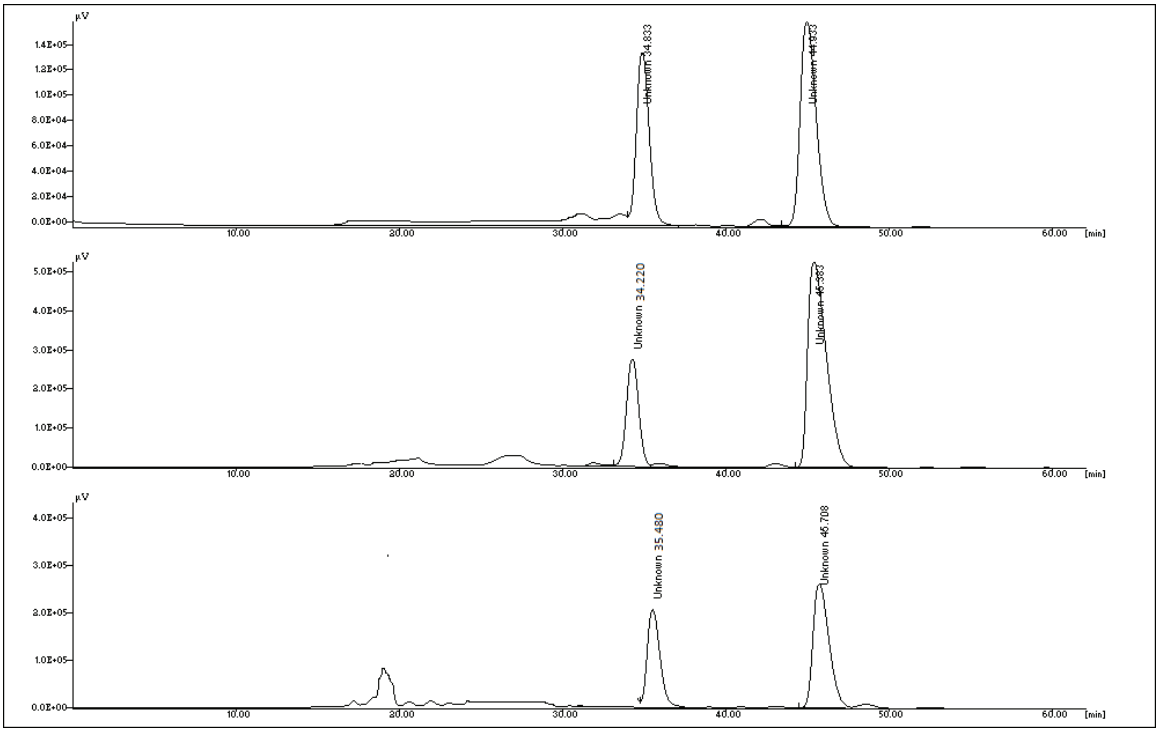
The reducing agents; $Zn(BH_4)_2$, $Li(O\text{-}^tBu)_3AlH$, NaBH4

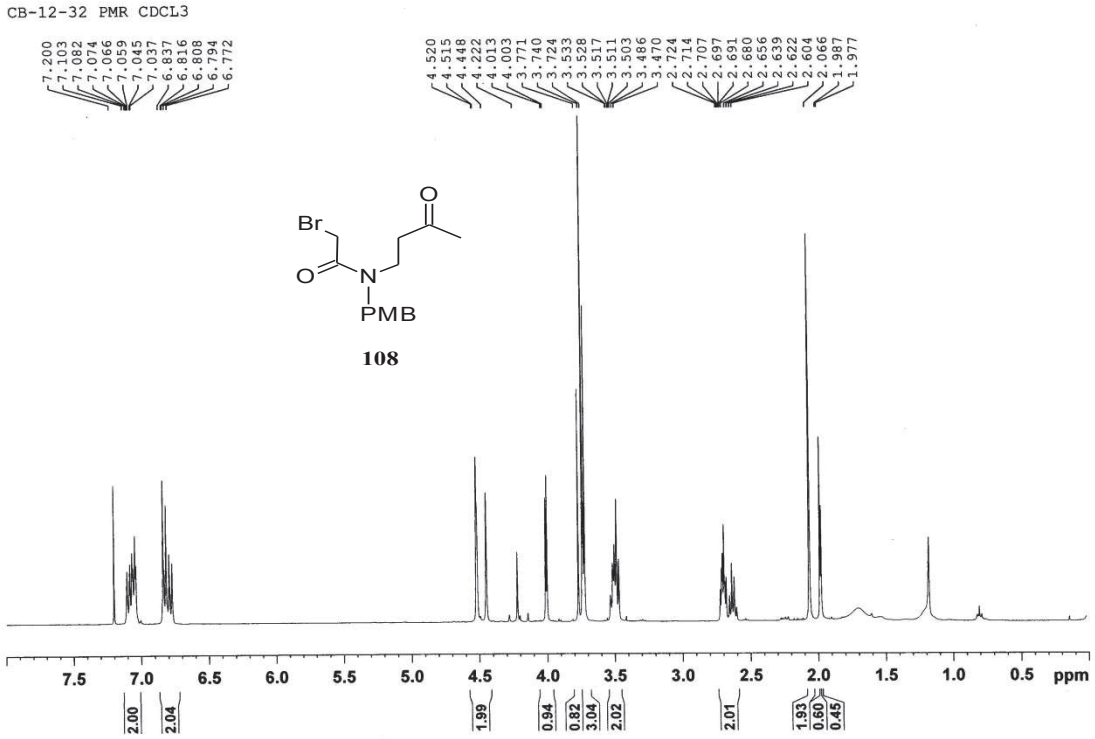


HPLC Chromatogram for

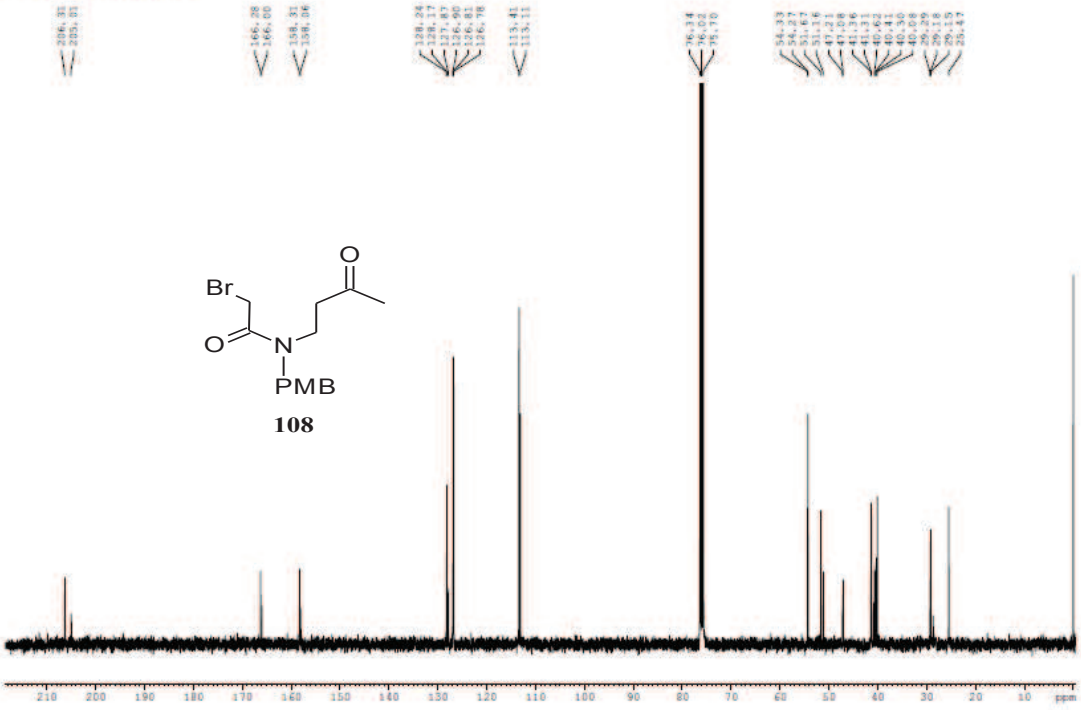


The reducing agents; $Zn(BH_4)_2$, $Li(O\text{-}^tBu)_3AlH$, NaBH4


μV
1.4E+05
1.2E+05
1.0E+05
8.0E+04
6.0E+04
4.0E+04
2.0E+04
0.0E+00
Unknown 34.833
10.00
20.00
30.00
40.00
50.00
60.00
[min]
μV
5.0E+05
4.0E+05
3.0E+05
2.0E+05
1.0E+05
0.0E+00
Unknown 34.220
10.00
20.00
30.00
40.00
50.00
60.00
[min]
μV
4.0E+05
3.0E+05
2.0E+05
1.0E+05
0.0E+00
Unknown 35.480
Unknown 45.708
10.00
20.00
30.00
40.00
50.00
60.00
[min]

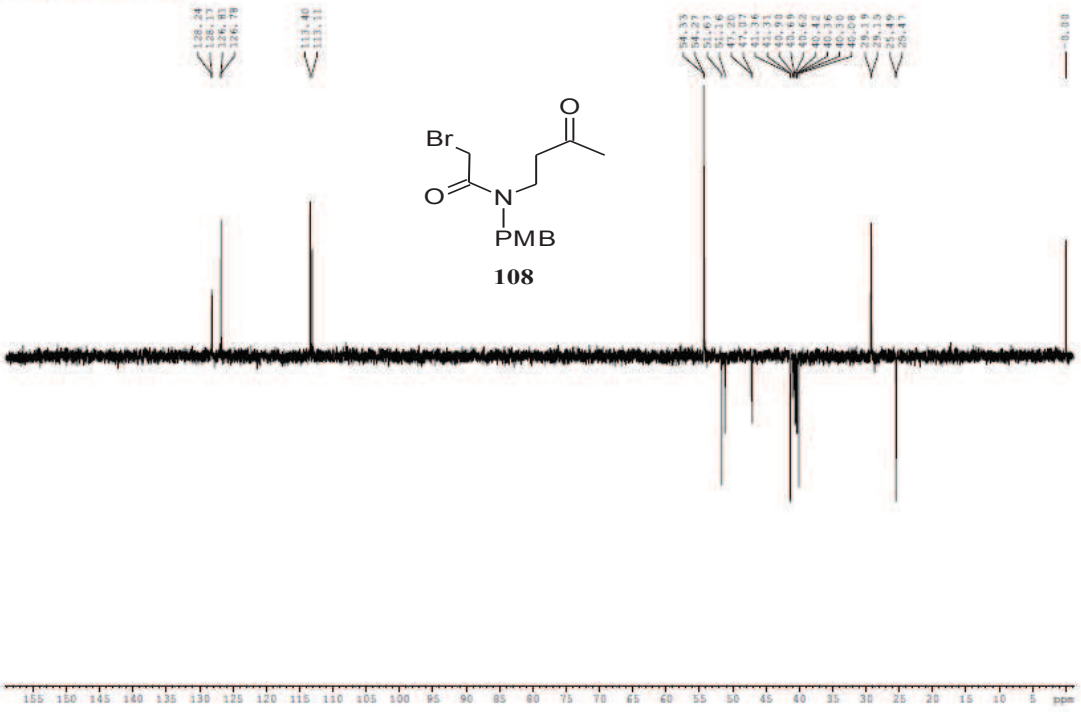

CB-12-32 PMR CDCL3
7.200
7.103
7.082
7.074
7.066
7.059
7.045
7.037
6.837
6.816
6.808
6.794
6.772
4.520
4.515
4.448
4.222
4.013
4.003
3.771
3.740
3.724
3.533
3.528
3.517
3.511
3.503
3.486
3.470
2.724
2.714
2.707
2.697
2.691
2.680
2.656
2.639
2.622
2.604
2.066
1.987
1.977
Br
O
O
N
PMB
108
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.00
2.04
1.99
0.94
0.82
3.04
2.02
2.01
1.93
0.60
0.45

CB-12-32 CMR CDCL3

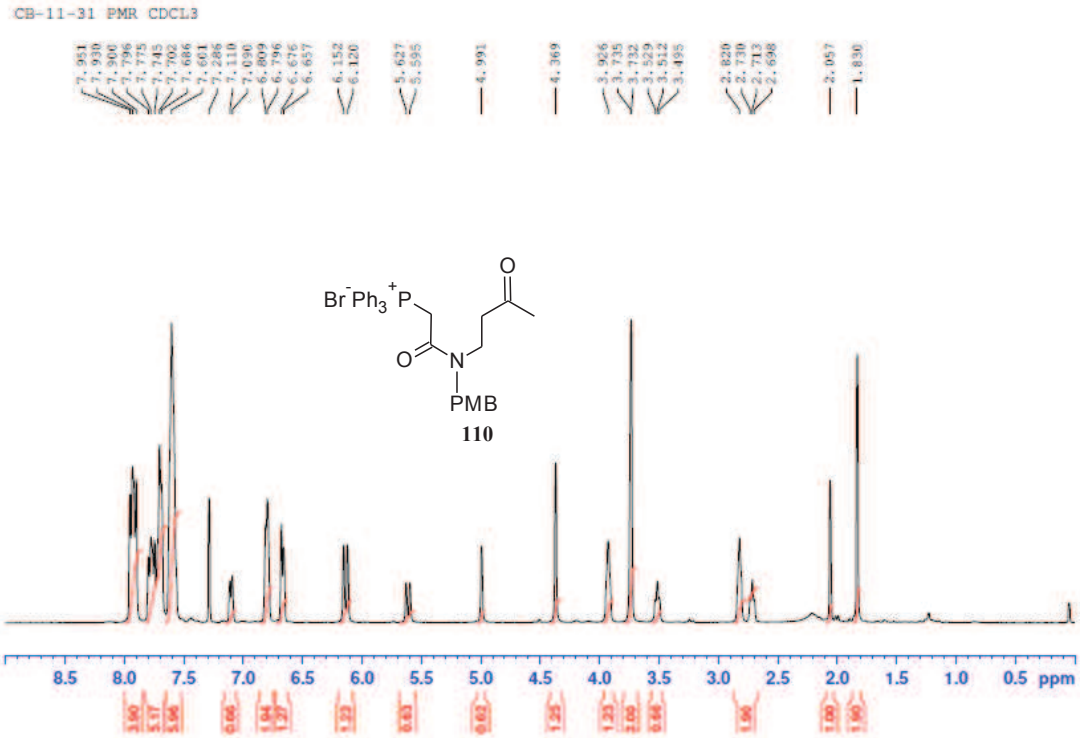


108

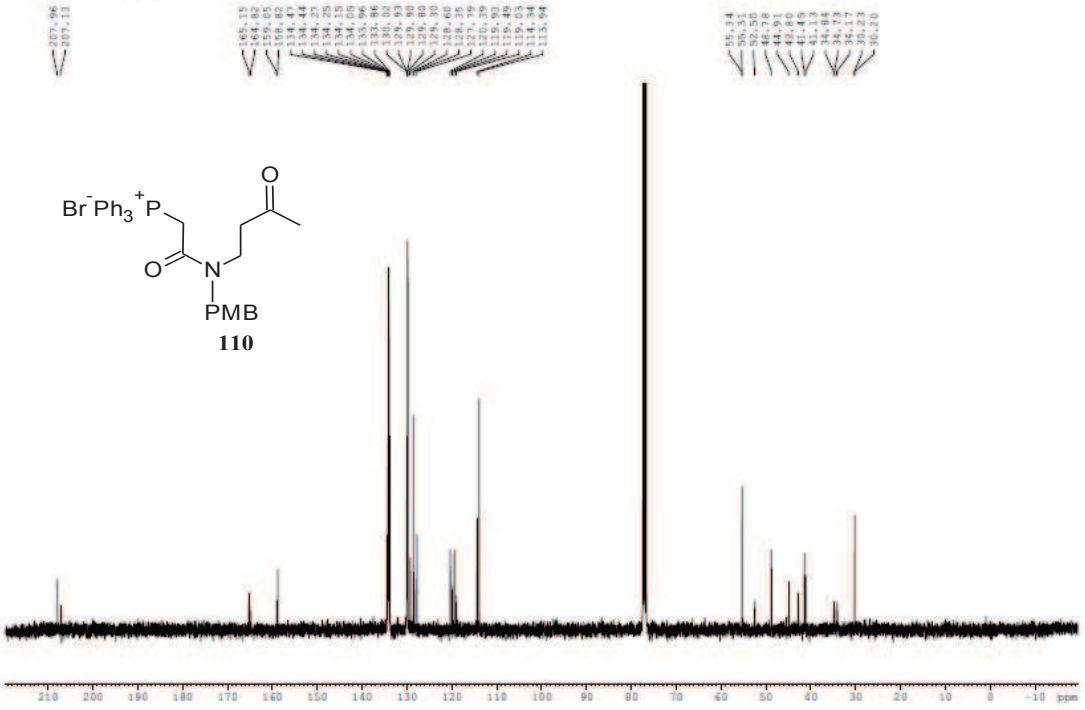
CB-12-32 DEPT CDCL3



108

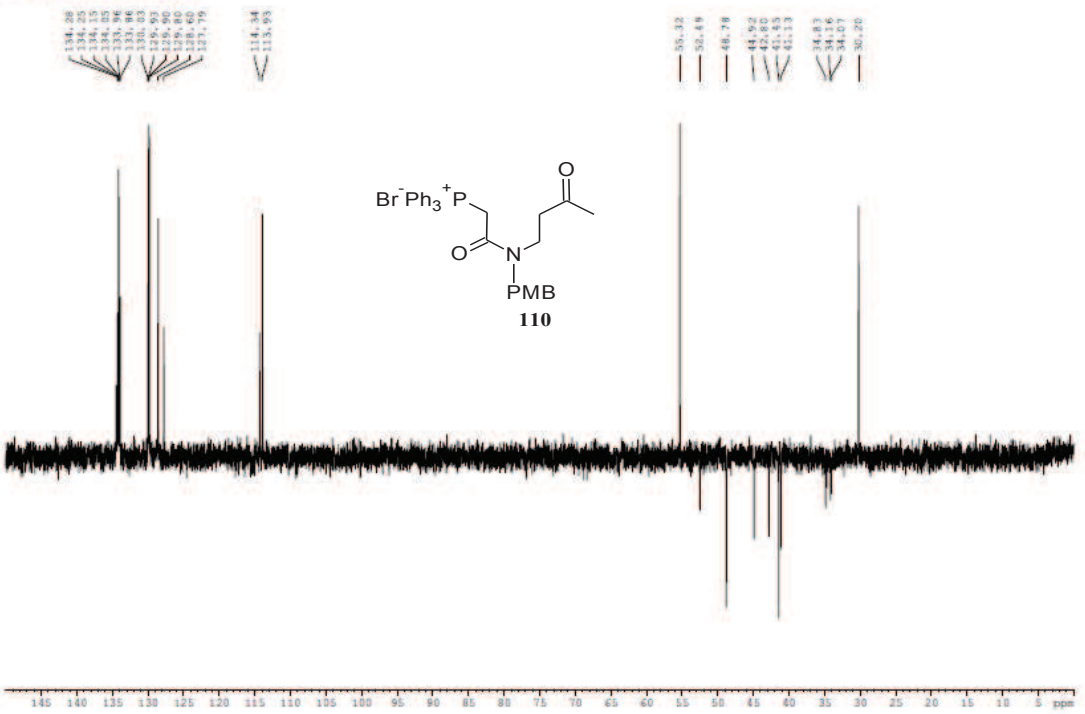

CB-11-31 PMR CDCL3
7.951
7.930
7.900
7.796
7.775
7.745
7.702
7.686
7.661
7.286
7.110
7.090
6.809
6.796
6.676
6.657
6.152
6.120
5.627
5.595
4.991
4.369
3.926
3.735
3.732
3.529
3.512
3.495
2.820
2.730
2.713
2.698
2.057
1.830
Br⁻Ph3P⁺
O
O
N
PMB
110
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

CB-12-27 CMR CDCL3

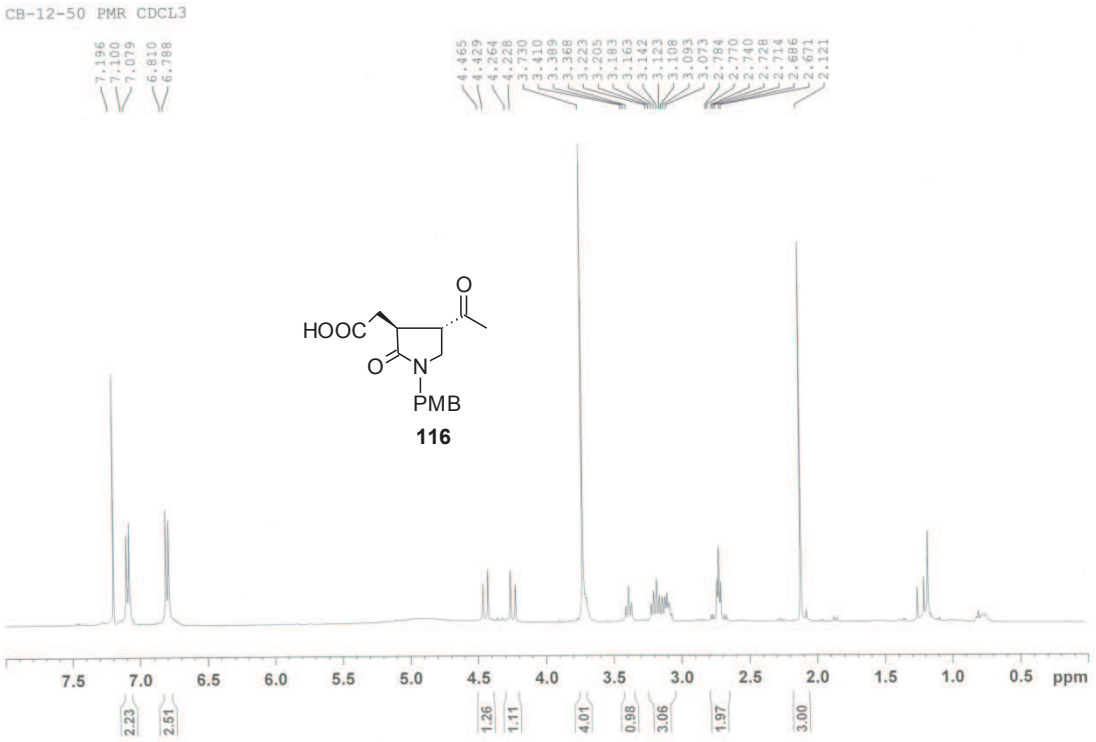


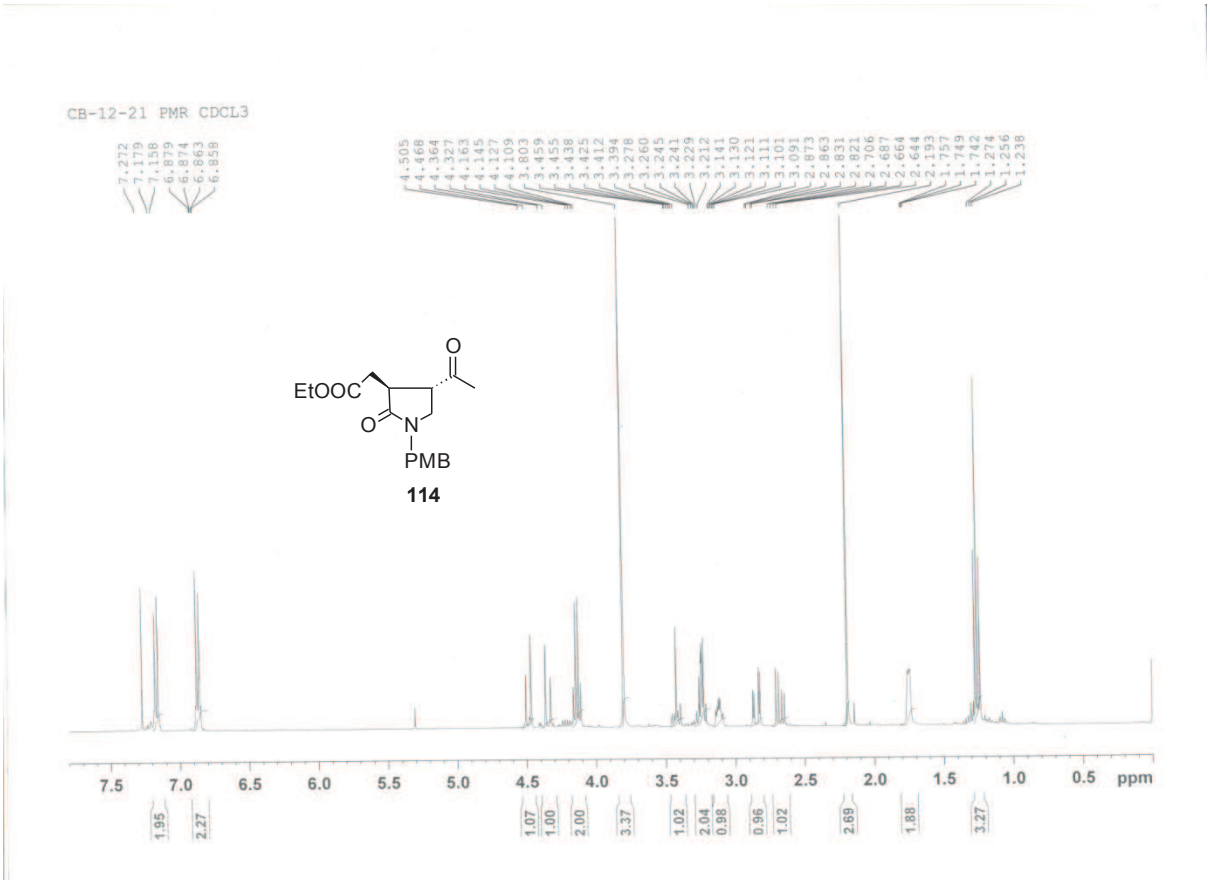
110

CB-12-27 DEPT CDCL3

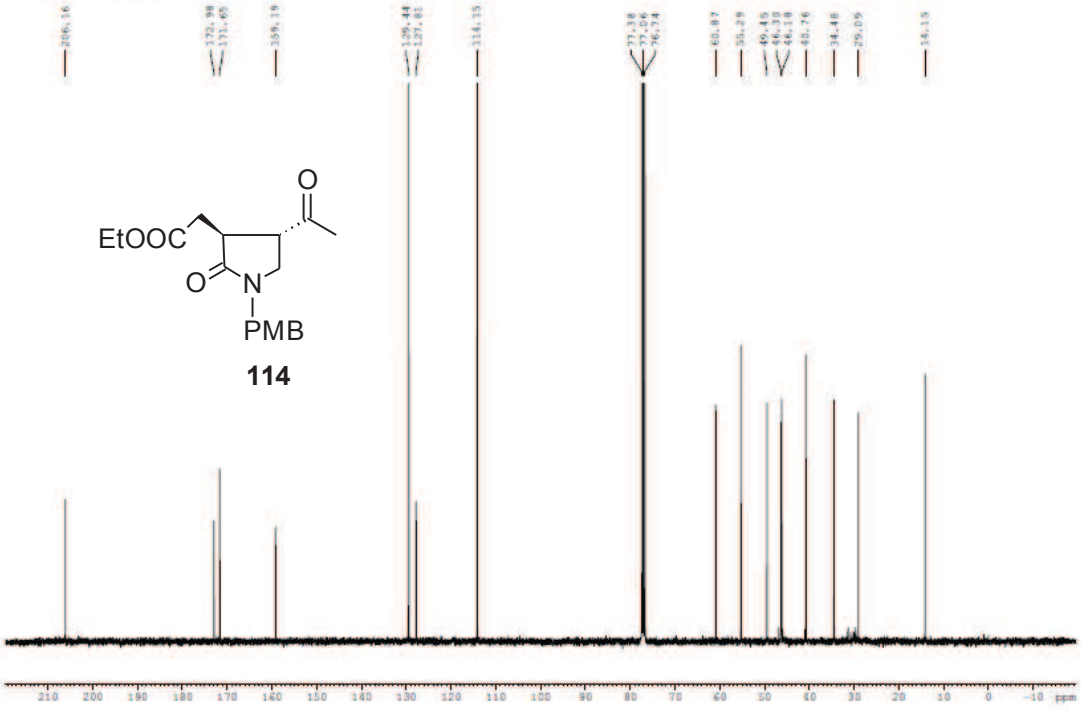


110


CB-12-50 PMR CDCL3
7.196
7.100
7.079
6.810
6.788
4.465
4.429
4.264
4.228
3.730
3.410
3.389
3.368
3.223
3.205
3.183
3.163
3.142
3.123
3.108
3.093
3.073
2.784
2.770
2.740
2.728
2.714
2.686
2.671
2.121
HOOC
O
O
N
PMB
116
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.23
2.51
1.26
1.11
4.01
0.98
3.06
1.97
3.00

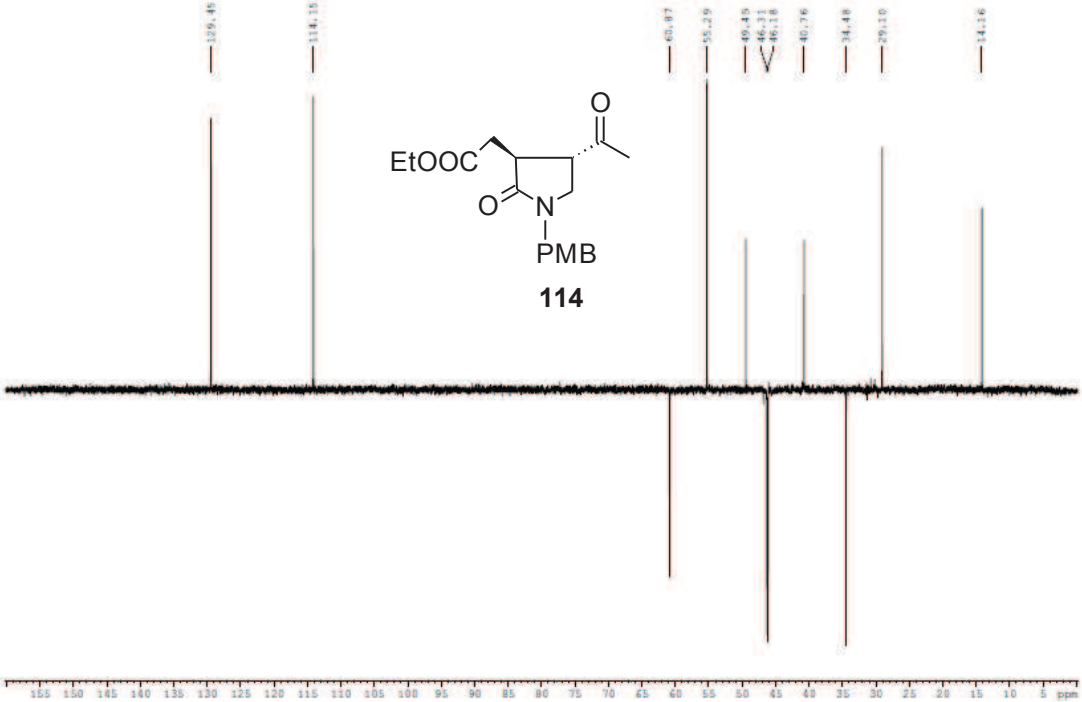

CB-12-21 PMR CDCL3
EtOOC
O
O
N
PMB
114
ppm

CB-11-35 CMR CDCL3

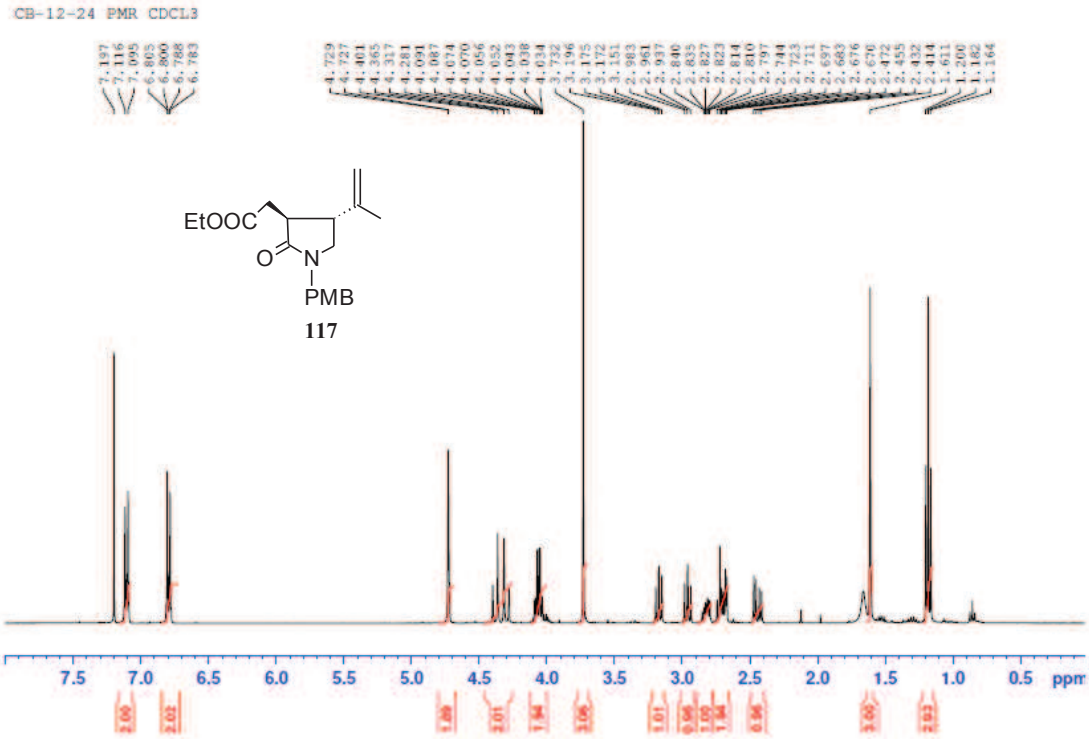


114

CB-11-35 DEPT CDCL3

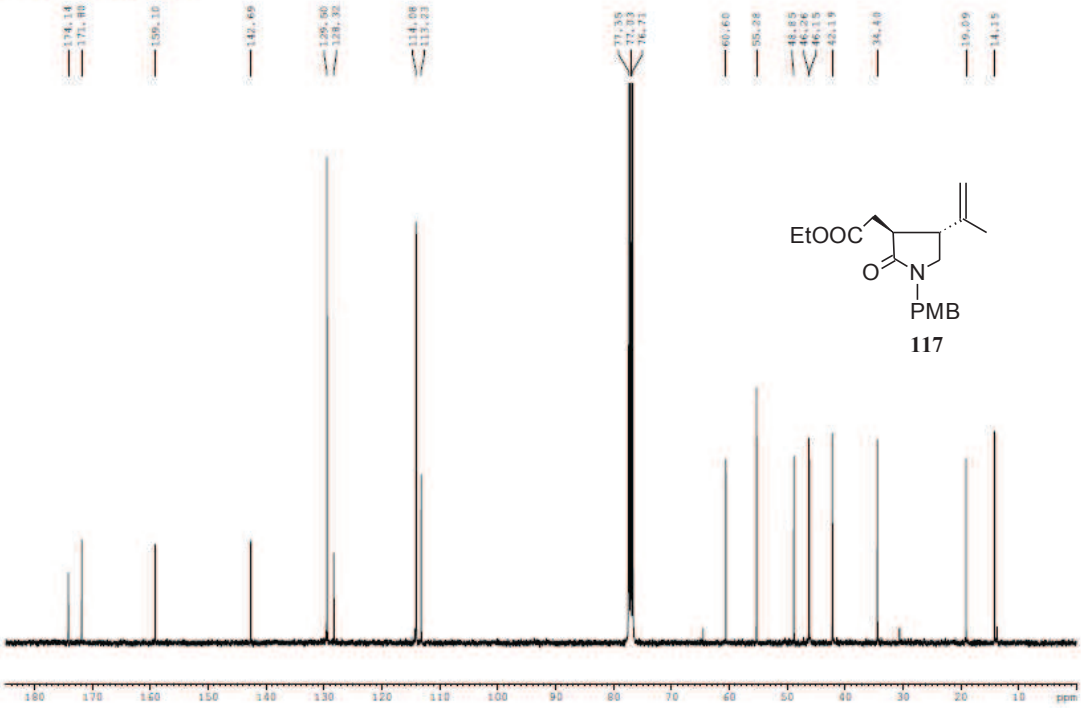


114


CB-12-24 PMR CDCL3
EtOOC
O
N
PMB
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

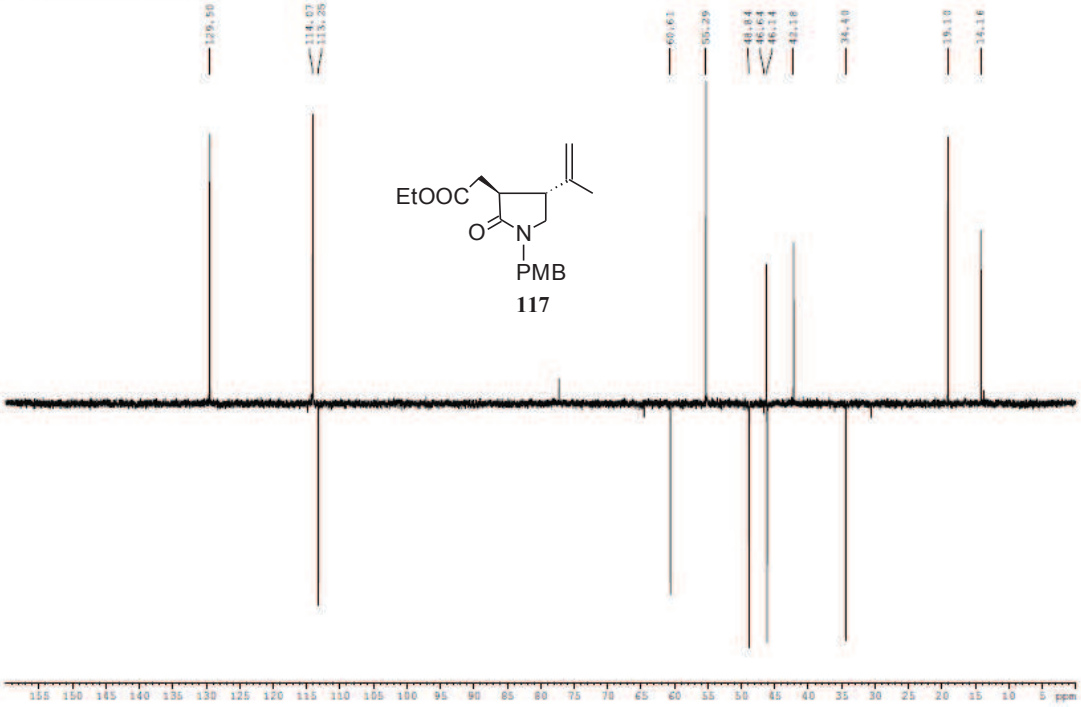
117

CB-12-24 CDCL3 CMR

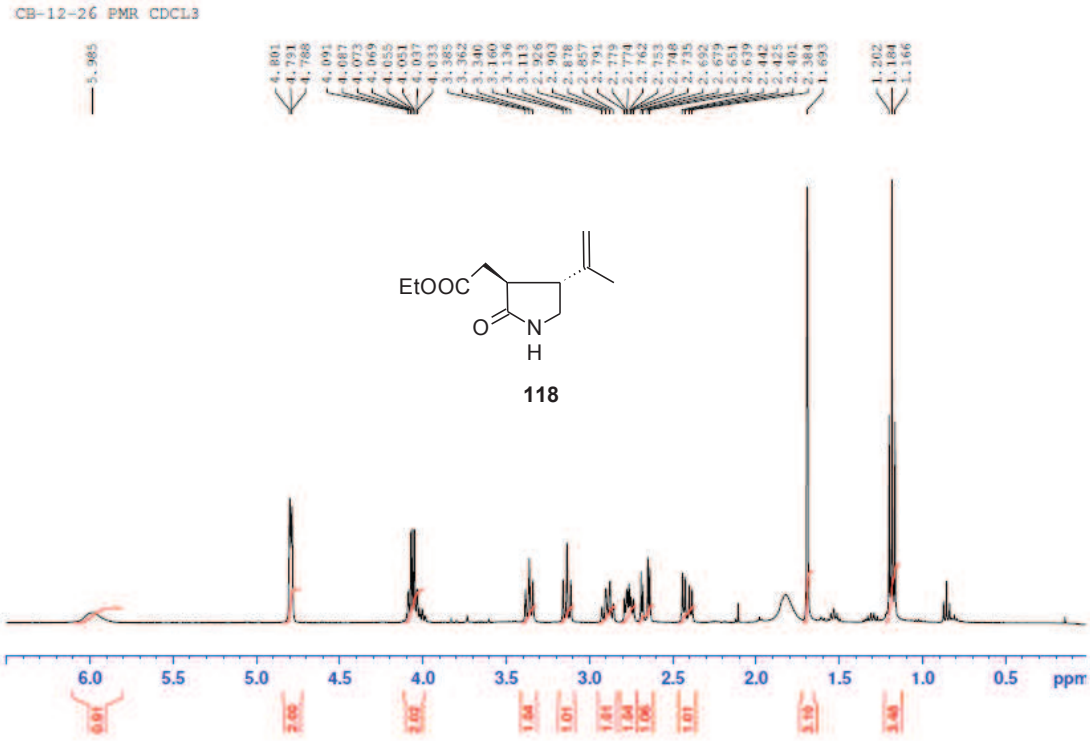


117

CB-12-24 CDCL3 DEPT

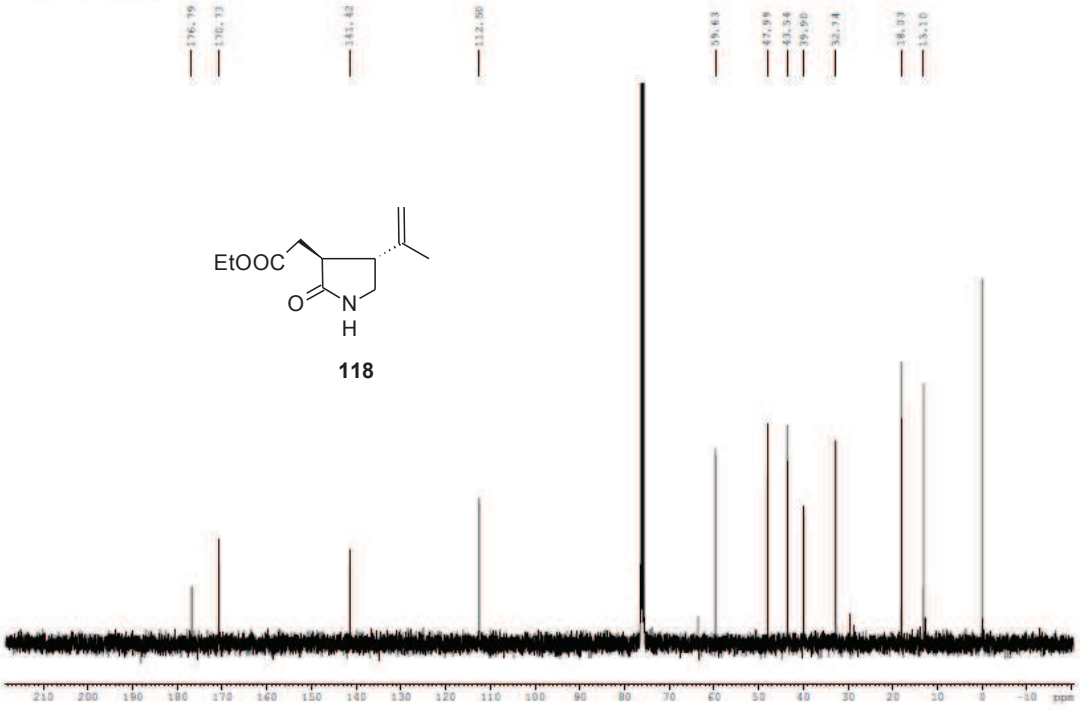


117

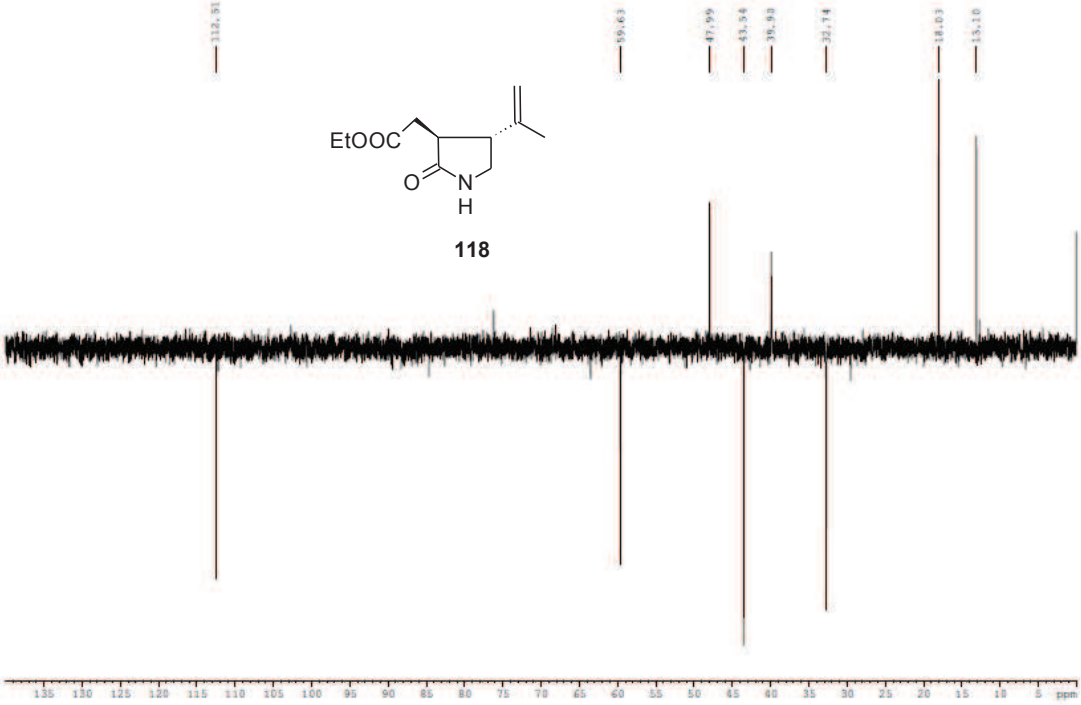


118

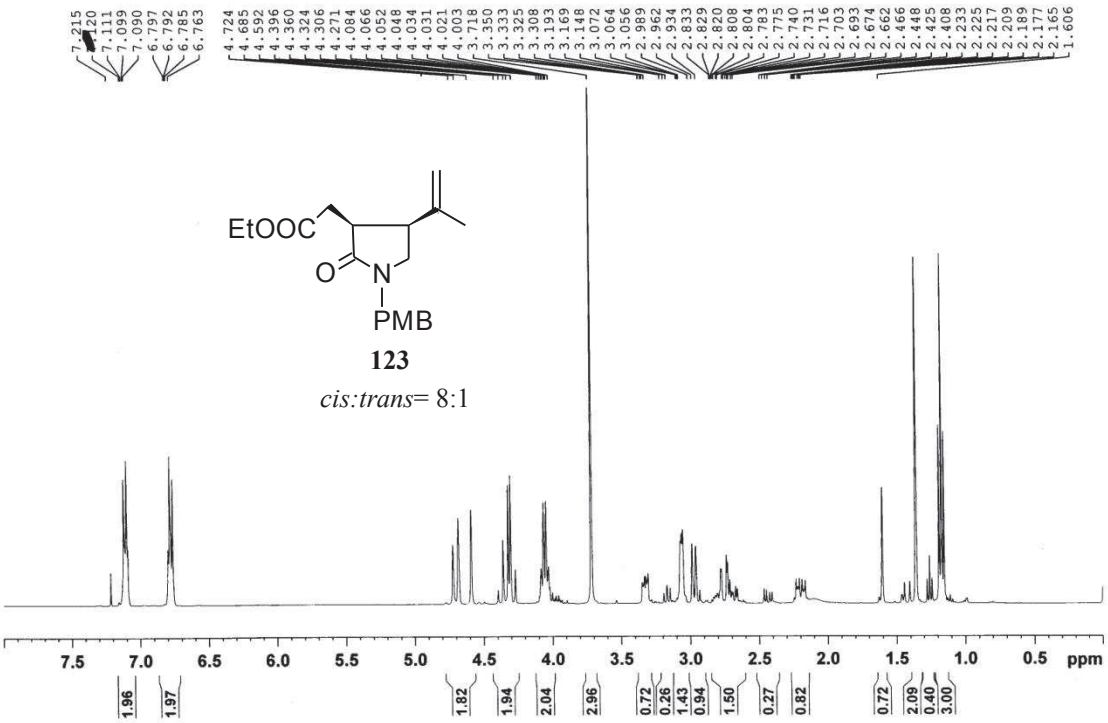
CB-12-26 CMR CDCL3



CB-12-26 DEPT CDCL3



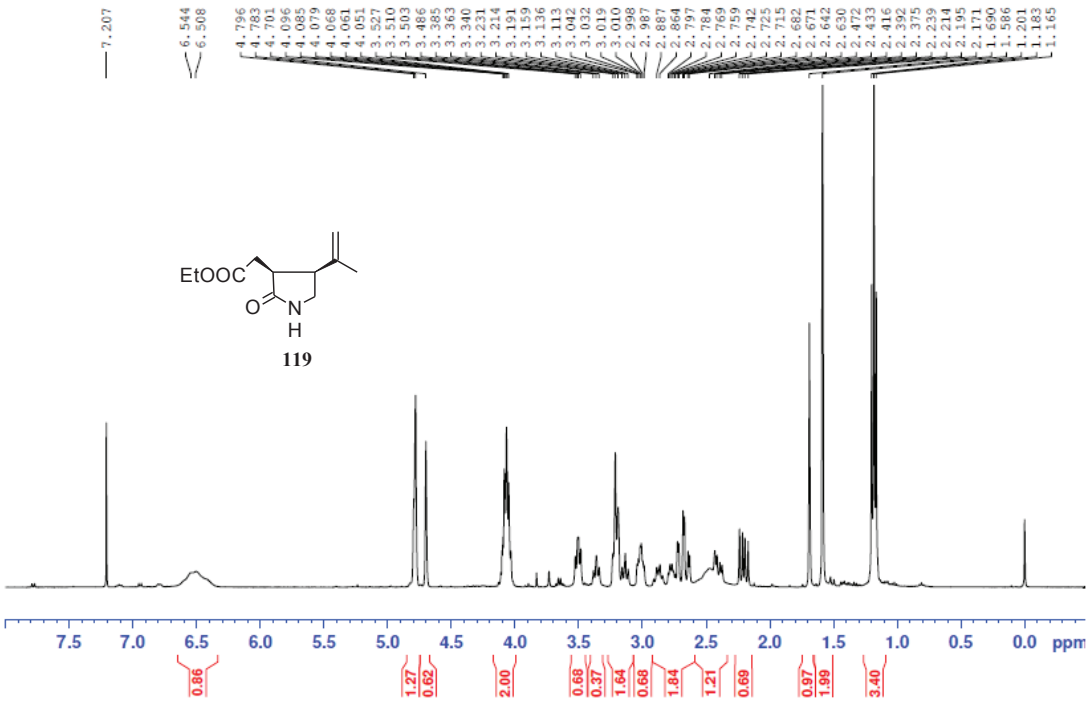
CB-12-51 PMR CDCL3



123

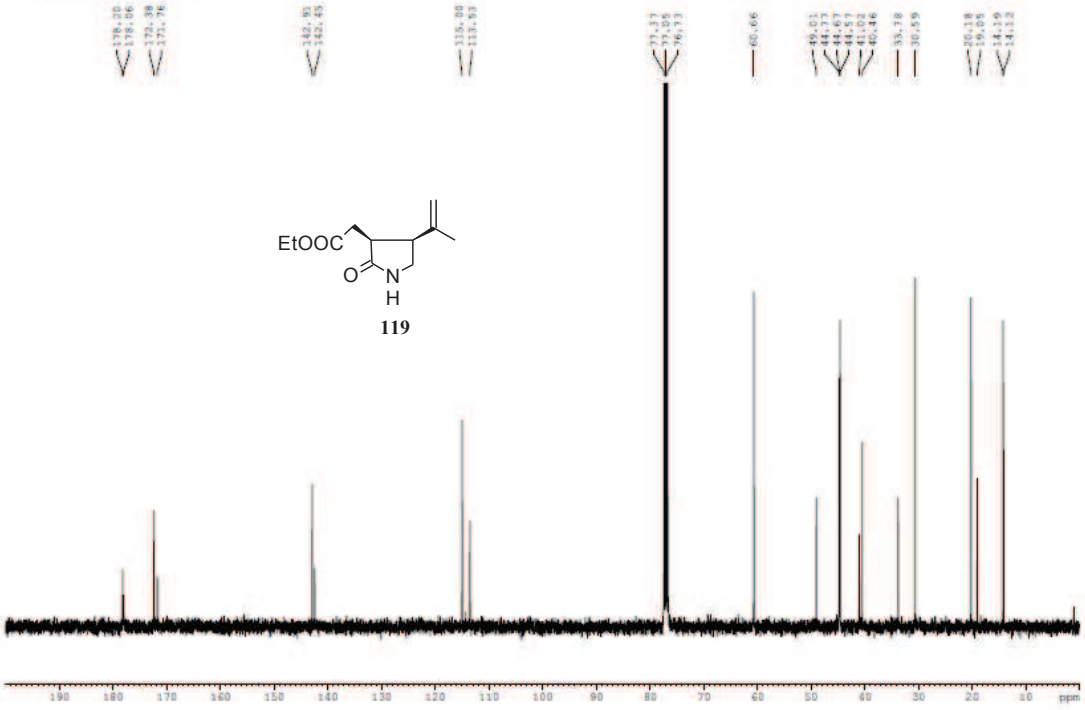
cis:trans= 8:1

CB-12-52 PMR CDCL3



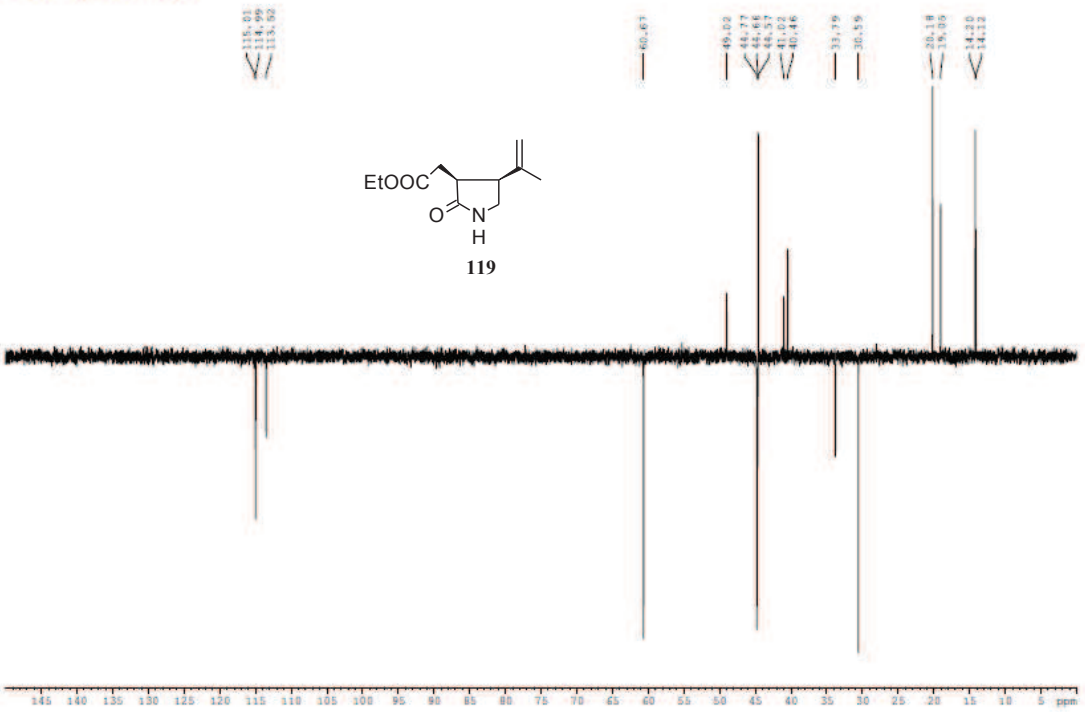
119

CB-12-52 CMR CDCL3

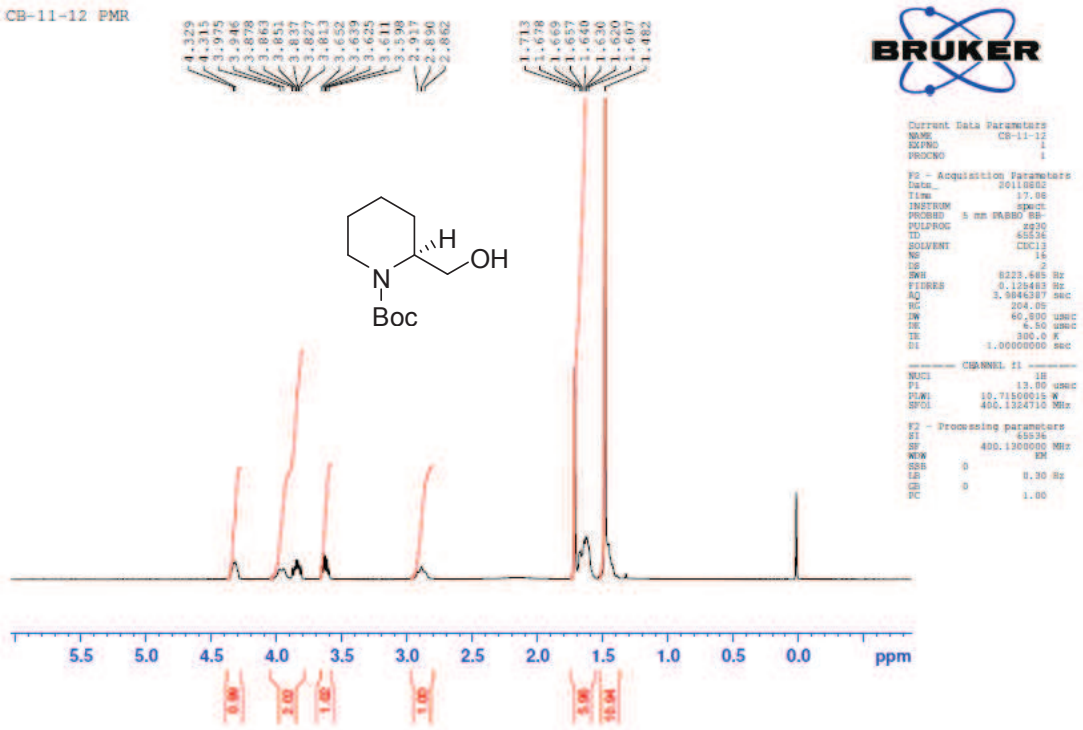


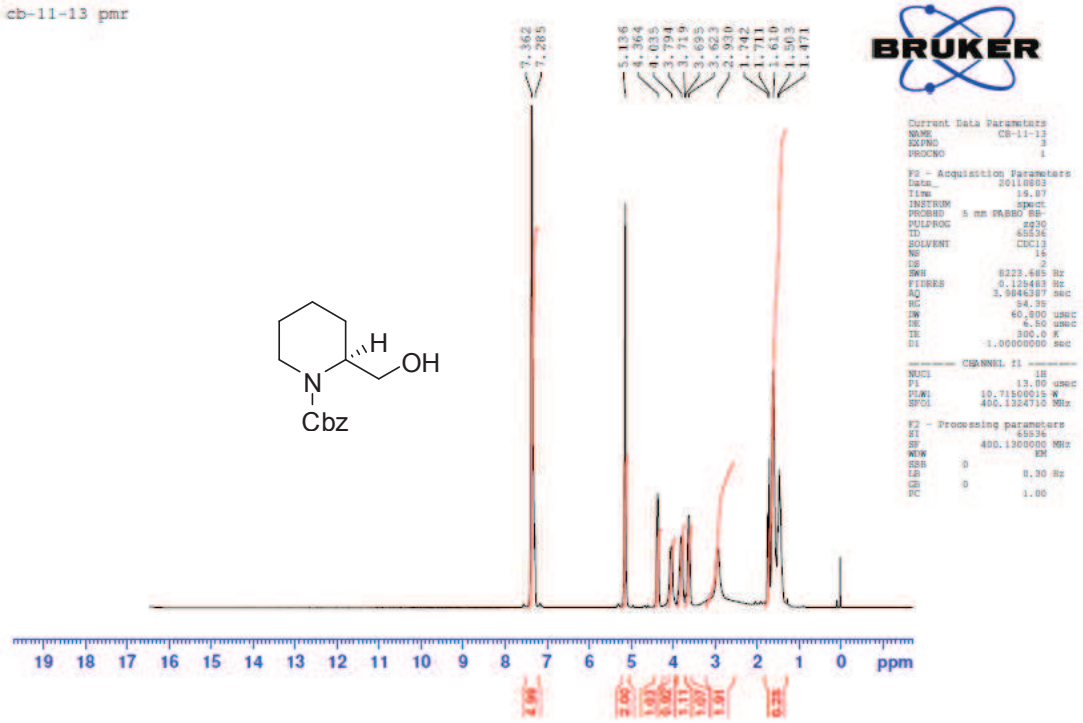
119

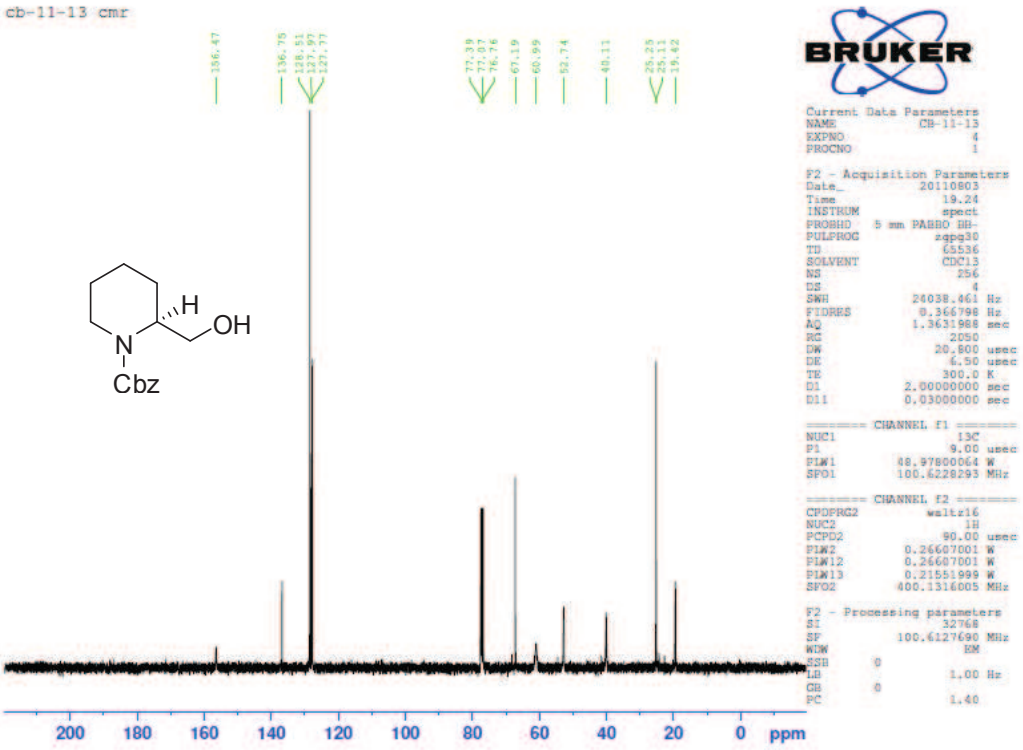
CB-12-52 DEPT CDCL3

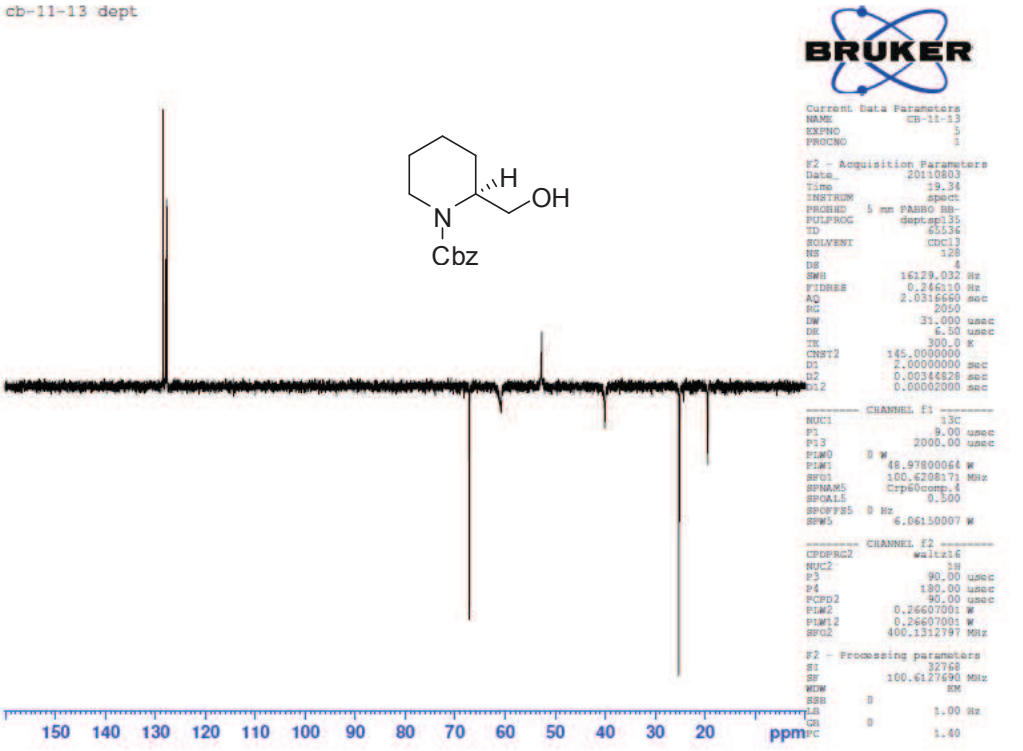


119

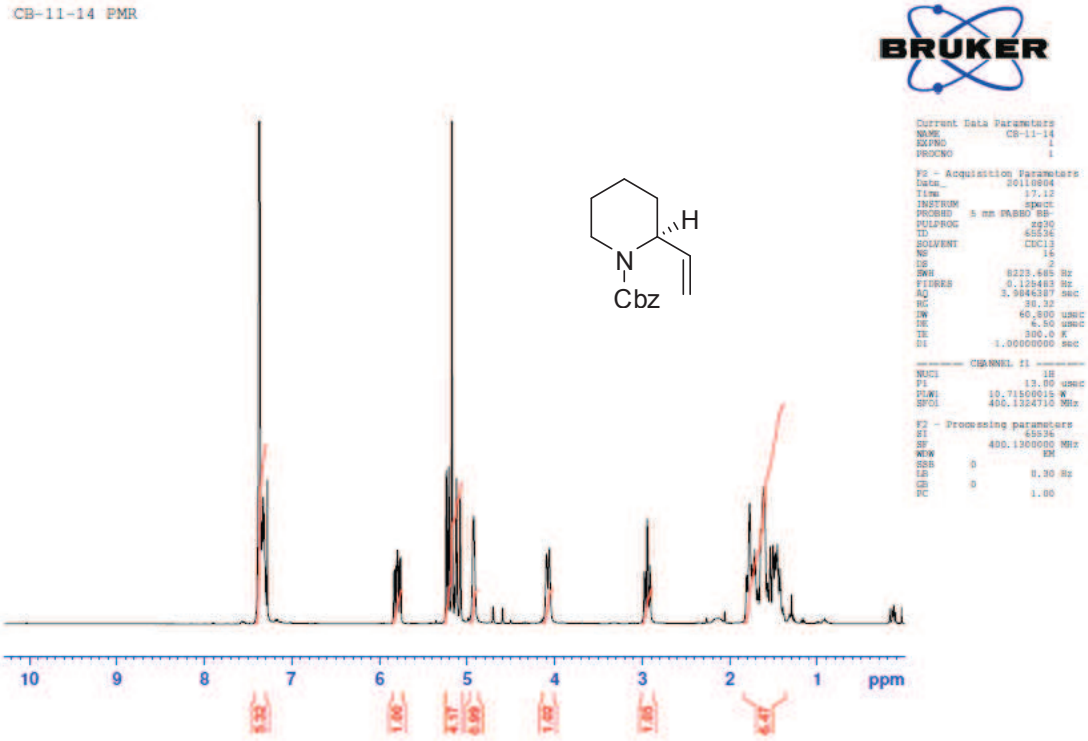

CB-11-12 PMR
BRUKER
H
OH
N
Boc
5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm


cb-11-13 pmr
BRUKER
H
OH
N
Cbz
19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm


cb-11-13 cmr
156.47
136.75
128.81
127.97
127.77
77.39
77.07
76.76
67.19
60.99
52.74
40.11
25.25
25.11
19.42
H
OH
N
Cbz
200
180
160
140
120
100
80
60
40
20
0
ppm
BRUKER
Current Data Parameters
NAME CB-11-13
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20110803
Time 19.24
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 2050
DW 20.800 usec
DE 6.50 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
CHANNEL f1
NUC1 13C
P1 9.00 usec
PLW1 48.97800064 W
SFO1 100.6228293 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PLW2 0.26607001 W
PLW12 0.26607001 W
PLW13 0.21551999 W
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

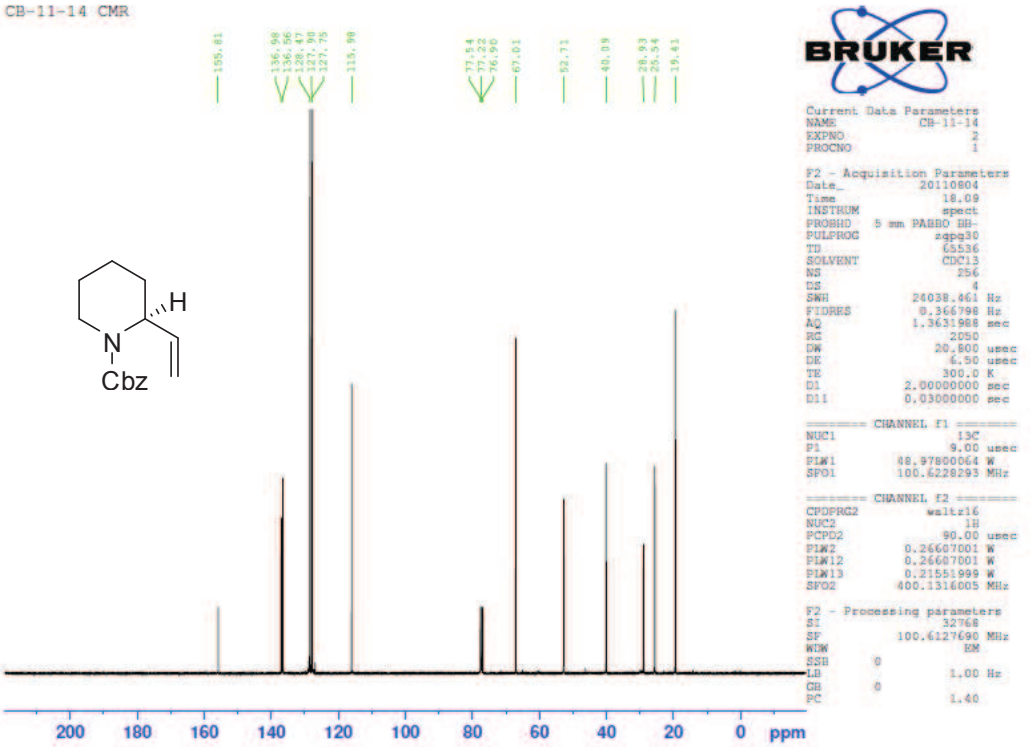

cb-11-13 dept
H
OH
N
Cbz
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm
BRUKER
Current Data Parameters
NAME CB-11-13
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20110803
Time 19.34
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG deptsp135
TD 65536
SOLVENT CDCl3
NS 128
DS 4
SWH 16129.032 Hz
FIDRES 0.246110 Hz
AQ 2.0316680 sec
RG 2050
DW 31.000 usec
DE 6.50 usec
TE 300.0 K
CNST2 145.0000000
D1 2.00000000 sec
D2 0.00344828 sec
D12 0.00002000 sec
CHANNEL f1
NUC1 13C
P1 9.00 usec
P13 2000.00 usec
PLW0 0 W
PLW1 48.97800064 W
SFO1 100.6228571 MHz
SPNAM5 Crp60comp.4
SPOAL5 0.500
SPOFFS5 0 Hz
SPW5 6.06150007 W
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
P3 90.00 usec
P4 180.00 usec
PCPD2 90.00 usec
PLW2 0.26607001 W
PLW12 0.26607001 W
SFO2 400.1312797 MHz
F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

CB-11-14 PMR



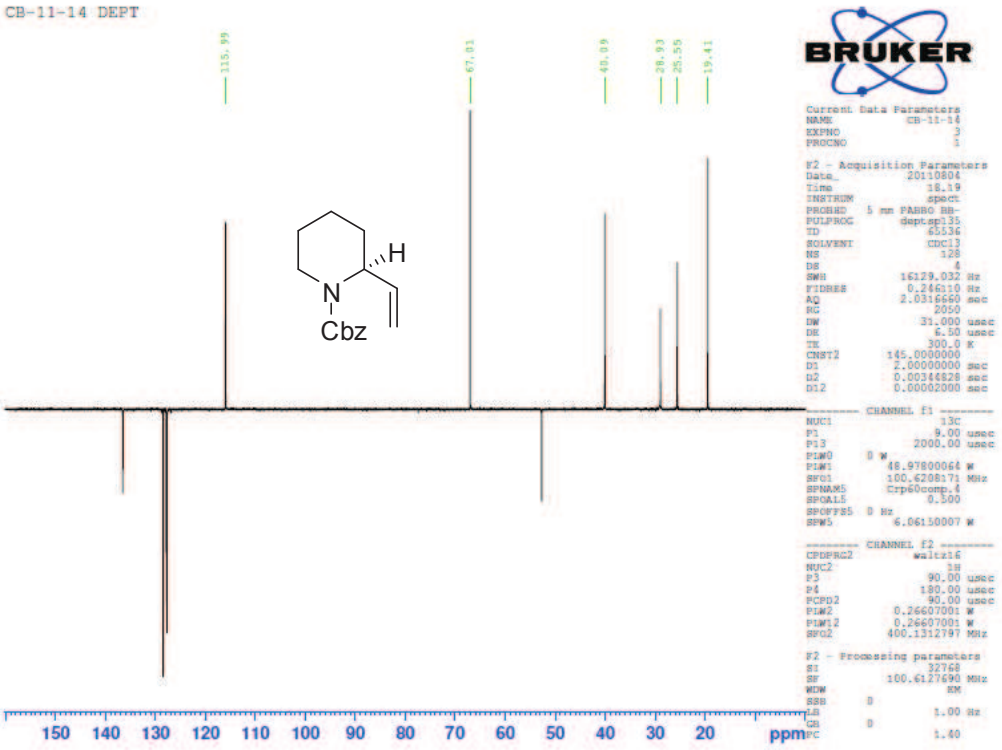

```
Current Data Parameters
NAME                  CB-11-14
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_               20110804
Time                    17.12
INSTRUM                 spect
PROBHD     5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                      30.32
DW                     60.800 usec
DE                      6.50 usec
TE                     300.0 K
D1                  1.00000000 sec

======== CHANNEL f1 ========
NUC1                       1H
P1                      13.00 usec
PLW1                10.71500015 W
SFO1               400.1324710 MHz

F2 - Processing parameters
SI                         65536
SF                 400.1300000 MHz
WDW                           EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```

CB-11-14 CMR




```
Current Data Parameters
NAME                  CB-11-14
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_               20110804
Time                    18.09
INSTRUM                 spect
PROBHD     5 mm PABBO BB-
PULPROG                 zgpg30
TD                     65536
SOLVENT                CDCl3
NS                       256
DS                         4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                      2050
DW                     20.800 usec
DE                      6.50 usec
TE                     300.0 K
D1                  2.00000000 sec
D11                 0.03000000 sec

======== CHANNEL f1 ========
NUC1                       13C
P1                       9.00 usec
PLW1                48.97800064 W
SFO1               100.6228293 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                   90.00 usec
PLW2                0.26607001 W
PLW12               0.26607001 W
PLW13               0.21551999 W
SFO2               400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF                 100.6127690 MHz
WDW                           EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

CB-11-14 DEPT



BRUKER

Current Data Parameters
NAME CB-11-14
EXPNO 3
PROCNO 1

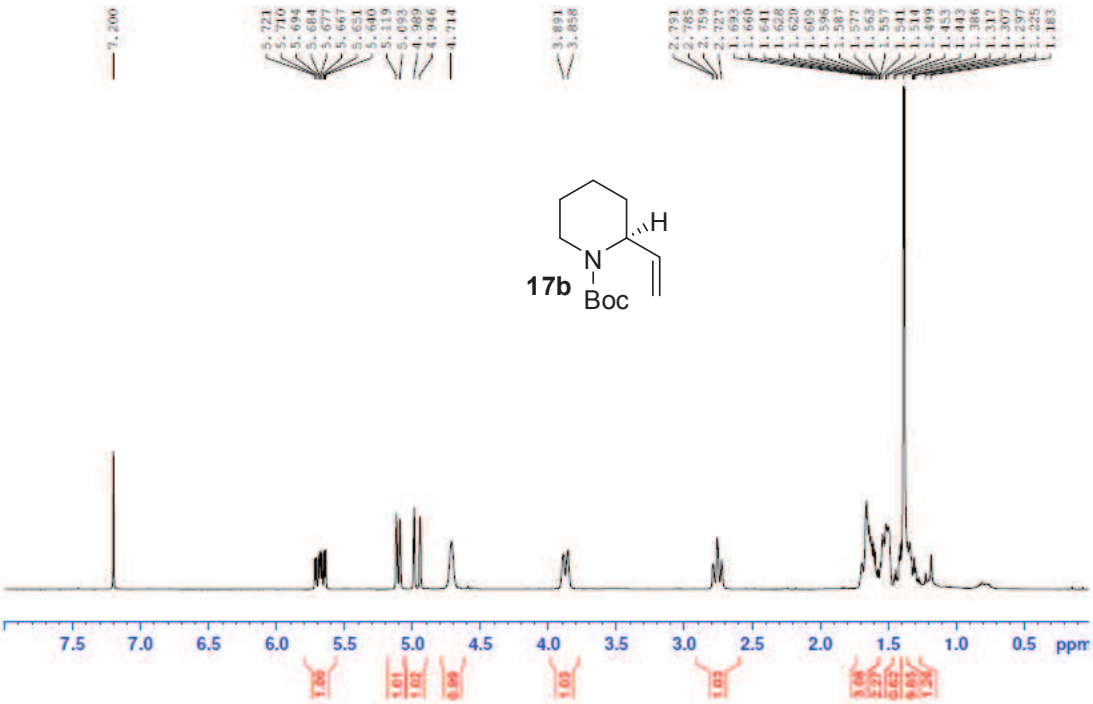
F2 - Acquisition Parameters
Date_ 20110804
Time 18.19
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG deptsp135
TD 65536
SOLVENT CDCl3
NS 128
DS 4
SWH 16129.032 Hz
FIDRES 0.246110 Hz
AQ 2.0316660 sec
RG 2050
DW 31.000 usec
DE 6.50 usec
TE 300.0 K
CNST2 145.0000000
D1 2.00000000 sec
D2 0.00344828 sec
D12 0.00002000 sec

CHANNEL f1
NUC1 13C
P1 9.00 usec
P13 2000.00 usec
PLW0 0 W
PLW1 48.97800064 W
SFO1 100.6208171 MHz
SPNAM5 Crp60comp.4
SPOAL5 0.500
SPOFFS5 0 Hz
SPW5 6.06150007 W

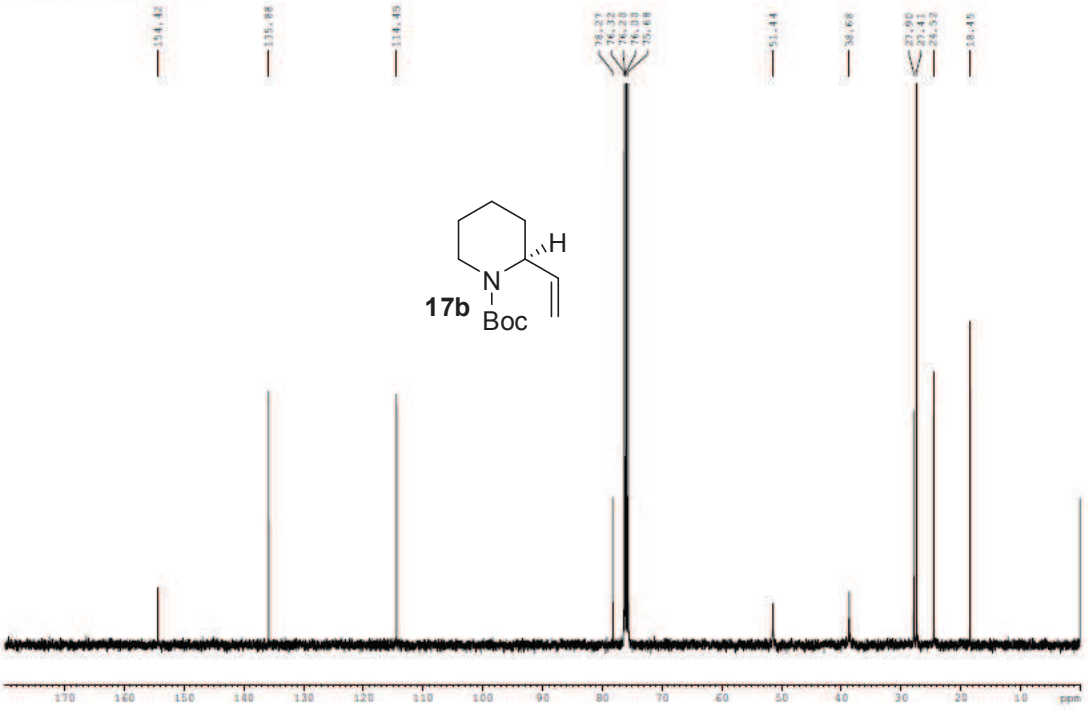
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
P3 90.00 usec
P4 180.00 usec
PCPD2 90.00 usec
PLW2 0.26607001 W
PLW12 0.26607001 W
SFO2 400.1312797 MHz

F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

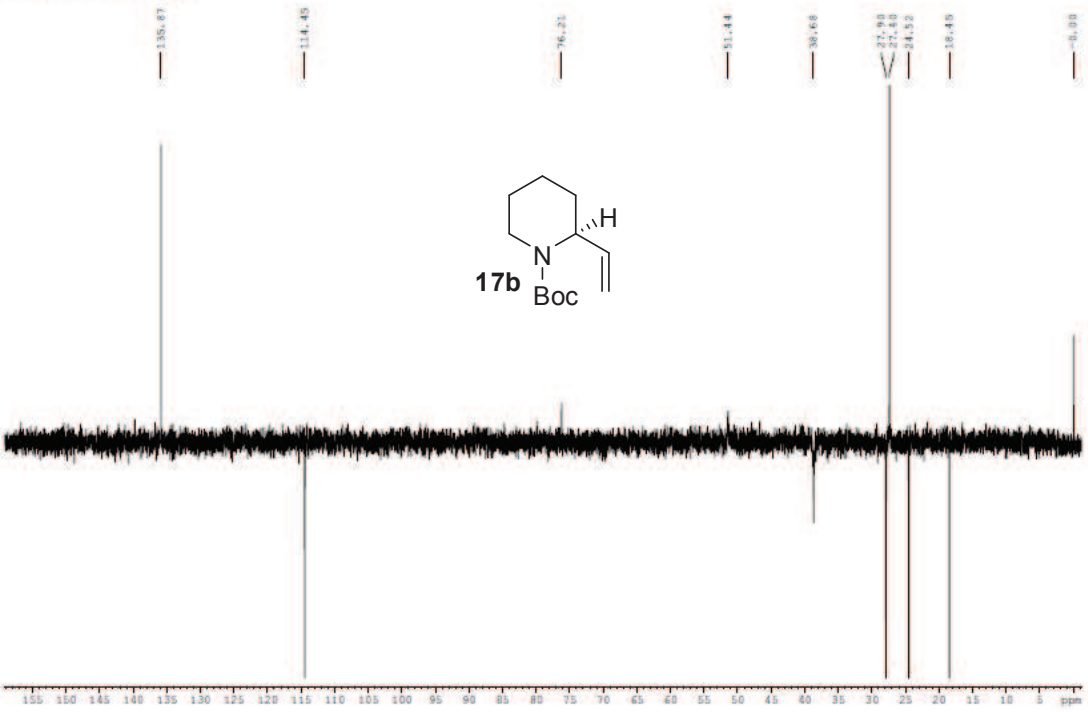
CB-12-57 PMR CDCL3

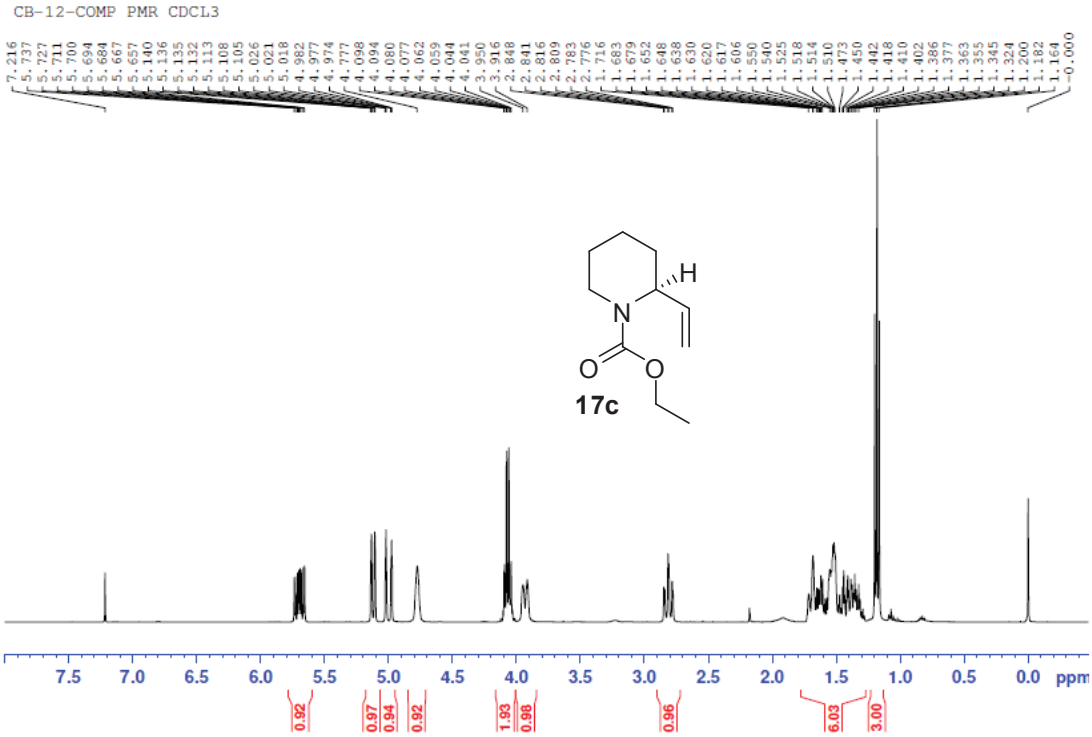


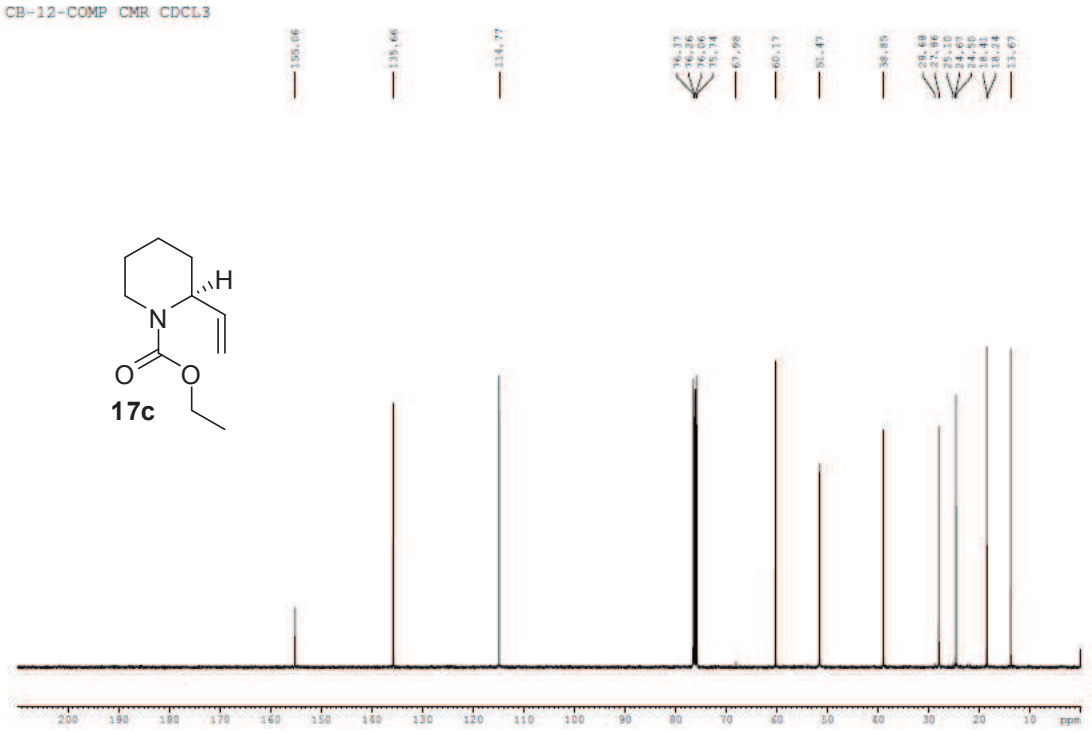
CB-12-57 CMR CDCL3



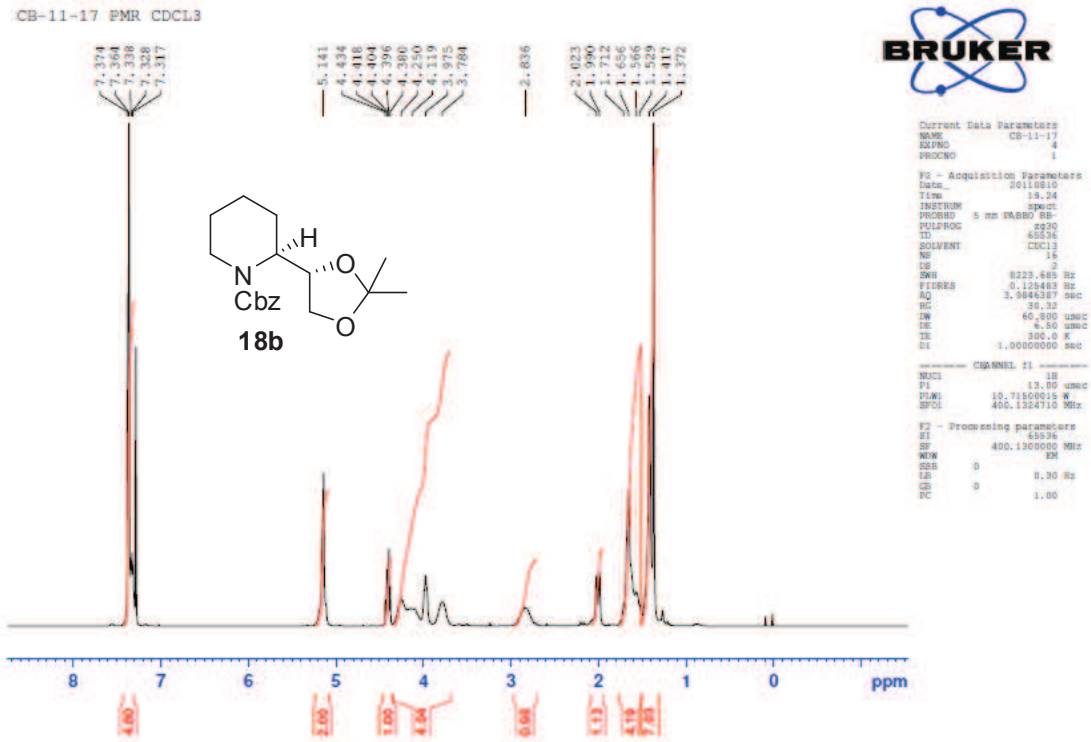
CB-12-57 DEPT CDCL3

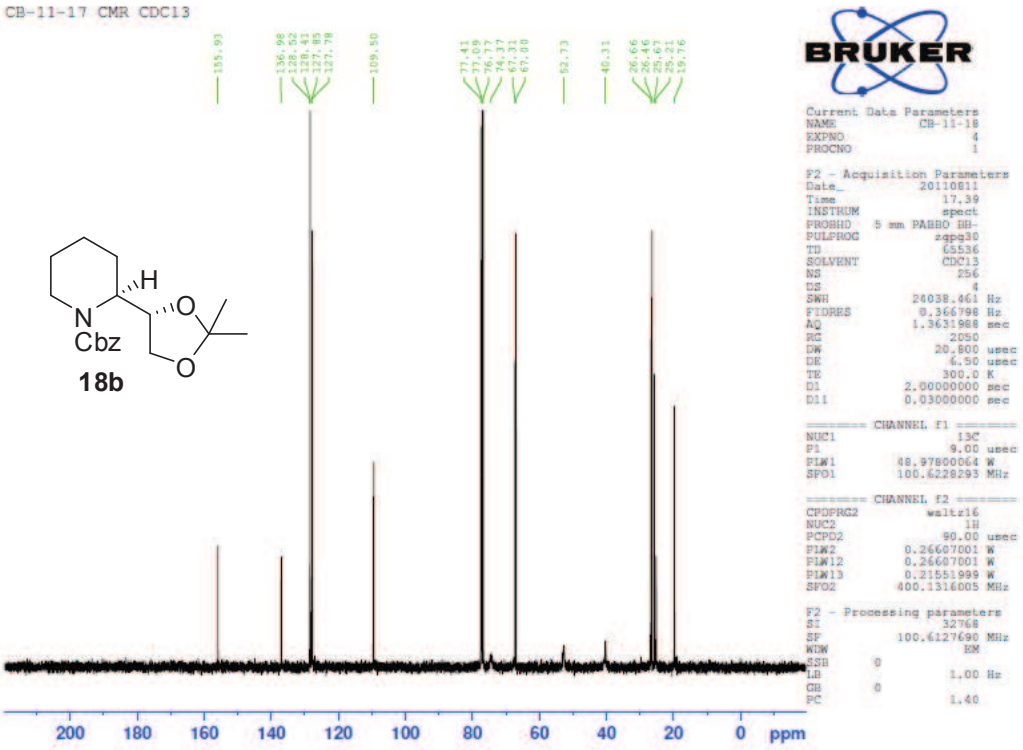


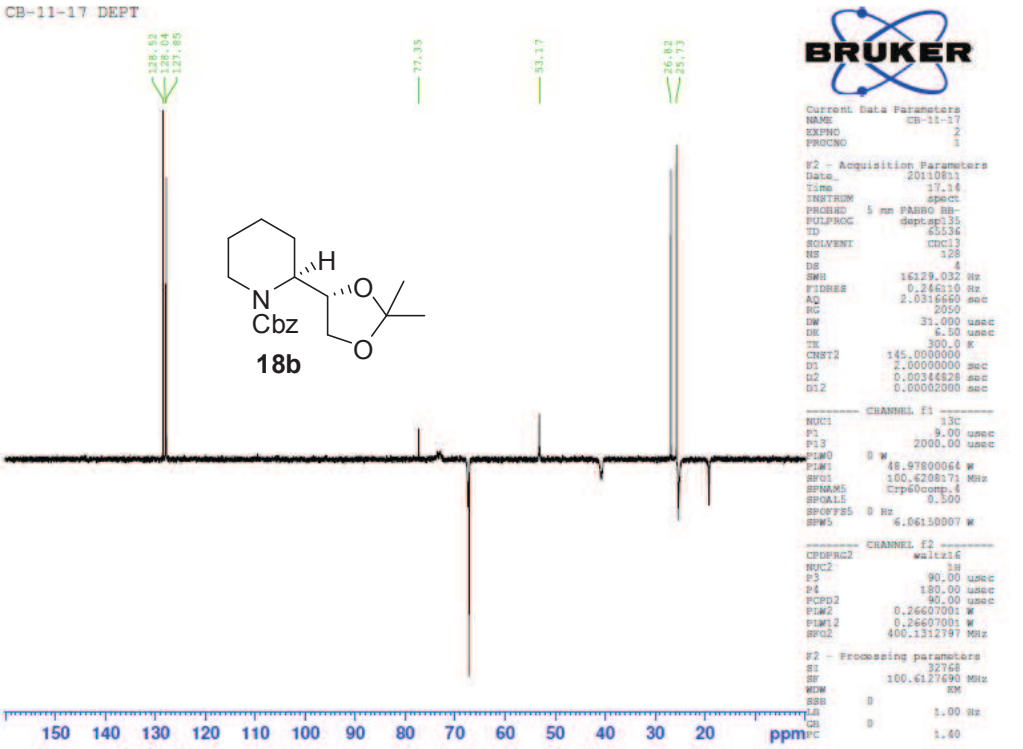

CB-12-COMP PMR CDCL3
17c
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.92 0.97 0.94 0.92 1.93 0.98 0.96 6.03 3.00


CB-12-COMP CMR CDCL3
17c
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

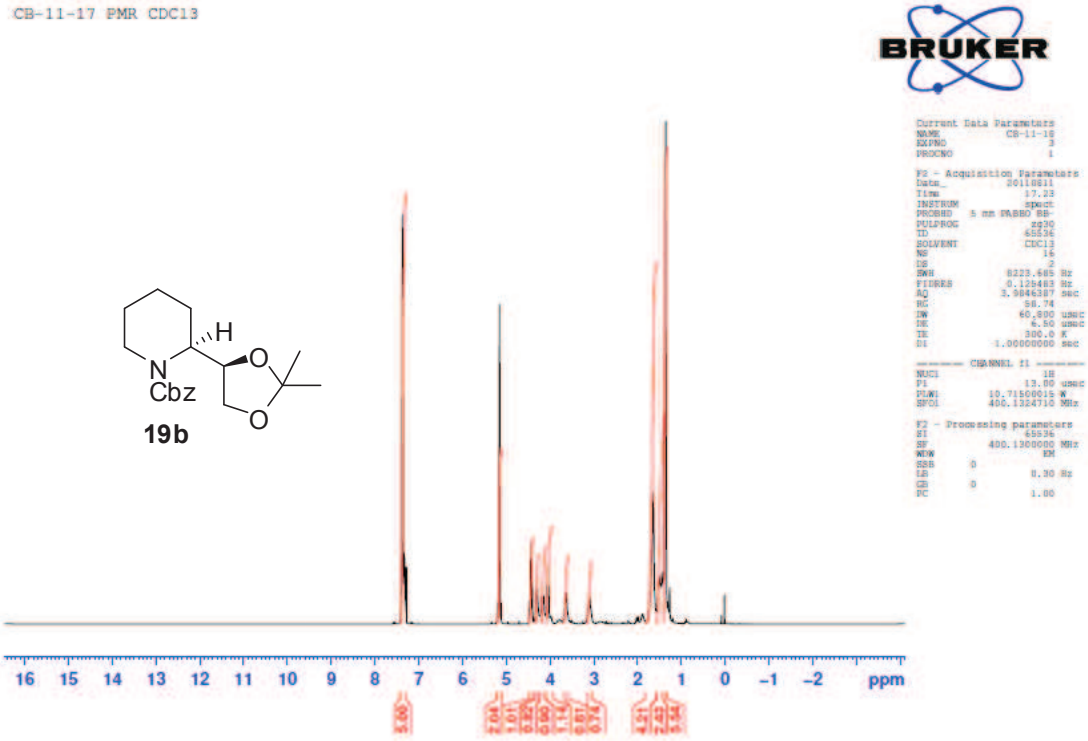

CB-12-COMP DEPT CDCL3
136.66
115.78
61.18
52.47
39.86
28.86
25.51
19.42
14.67
H
N
O
O
17c


CB-11-17 PMR CDCL3
7.374
7.364
7.338
7.328
7.317
5.141
4.434
4.418
4.404
4.396
4.380
4.256
4.119
3.975
3.784
2.836
2.023
1.990
1.712
1.656
1.566
1.529
1.417
1.372
H
N
Cbz
O
O
18b
BRUKER
Current Data Parameters
NAME CB-11-17
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20110810
Time 19.24
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125463 Hz
AQ 3.9846387 sec
RG 36.32
DW 60.800 usec
DE 6.50 usec
TE 300.0 K
D1 1.00000000 sec
CHANNEL f1
NUC1 1H
P1 13.00 usec
PLW1 10.71500015 W
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 65536
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8
7
6
5
4
3
2
1
0
ppm

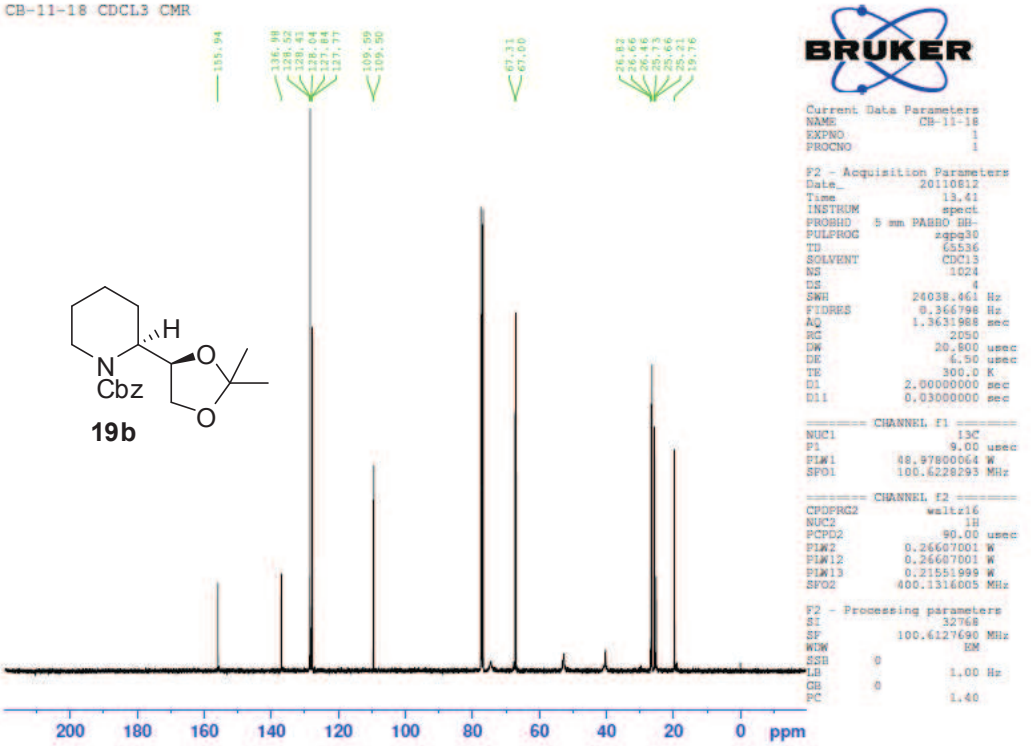

CB-11-17 CMR CDC13
155.93
136.98
128.52
128.41
127.85
127.78
109.50
77.41
77.09
76.77
74.37
67.31
67.00
52.73
40.31
26.66
26.46
25.67
25.21
19.76
H
N
Cbz
O
O
18b
200
180
160
140
120
100
80
60
40
20
0
ppm
BRUKER
Current Data Parameters
NAME CB-11-18
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20110811
Time 17.39
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 2050
DW 20.800 usec
DE 6.50 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
CHANNEL f1
NUC1 13C
P1 9.00 usec
PLW1 48.97800064 W
SFO1 100.6228293 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PLW2 0.26607001 W
PLW12 0.26607001 W
PLW13 0.21551999 W
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

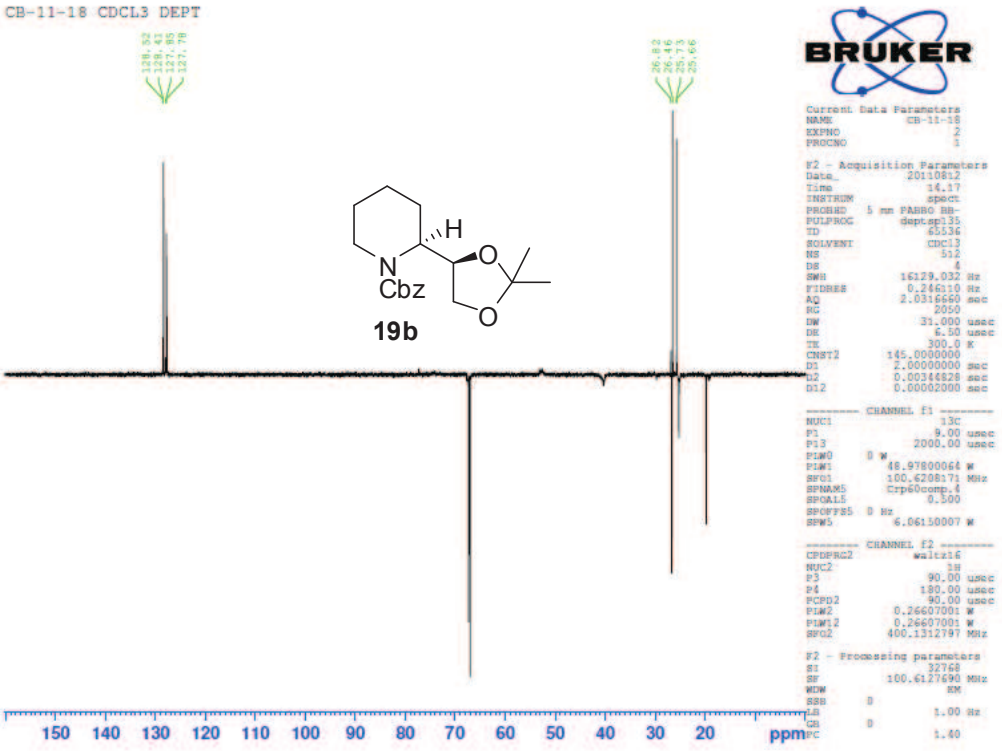

CB-11-17 DEPT
128.52
128.04
127.85
77.35
53.17
26.82
25.73
H
N
Cbz
O
O
18b
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm
BRUKER
Current Data Parameters
NAME CB-11-17
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20110811
Time 17.14
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG deptsp135
TD 65536
SOLVENT CDCl3
NS 128
DS 4
SWH 16129.032 Hz
FIDRES 0.246110 Hz
AQ 2.0316660 sec
RG 2050
DW 31.000 usec
DE 6.50 usec
TE 300.0 K
CNST2 145.0000000
D1 2.00000000 sec
D2 0.00344828 sec
D12 0.00002000 sec
CHANNEL f1
NUC1 13C
P1 9.00 usec
P13 2000.00 usec
PLW0 0 W
PLW1 48.97800064 W
SFO1 100.6208171 MHz
SPNAM5 Crp60comp.4
SPOAL5 0.500
SPOFFS5 0 Hz
SPW5 6.06150007 W
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
P3 90.00 usec
P4 180.00 usec
PCPD2 90.00 usec
PLW2 0.26607001 W
PLW12 0.26607001 W
SFO2 400.1312797 MHz
F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

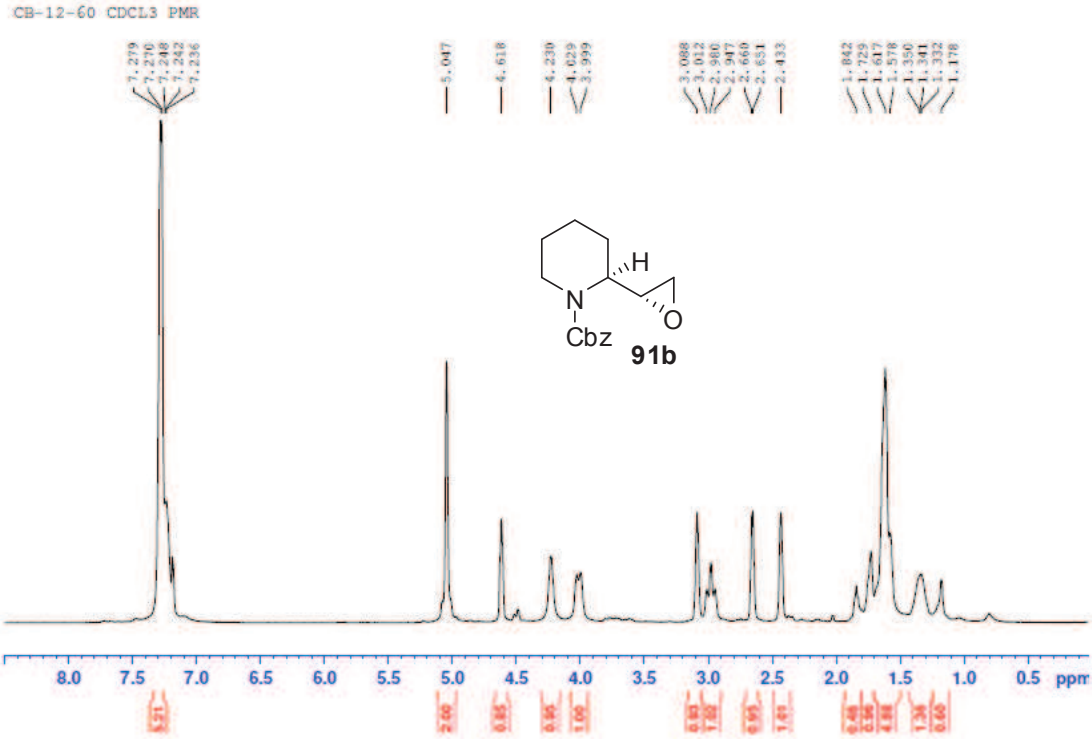
CB-11-17 PMR CDC13



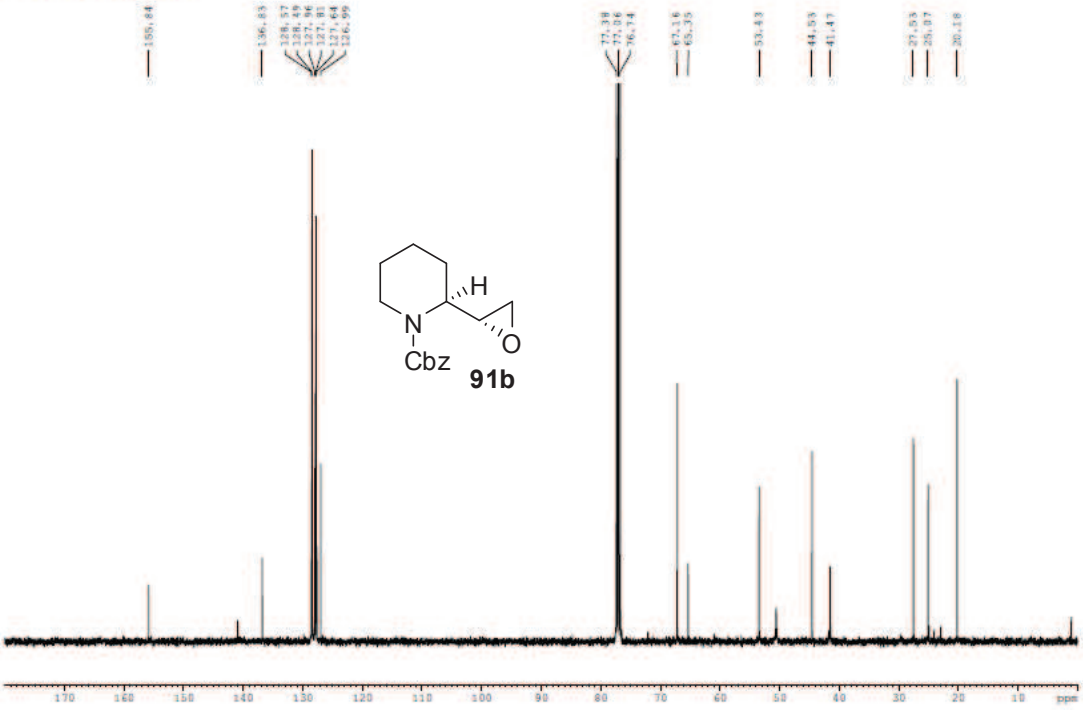
CB-11-18 CDCL3 CMR



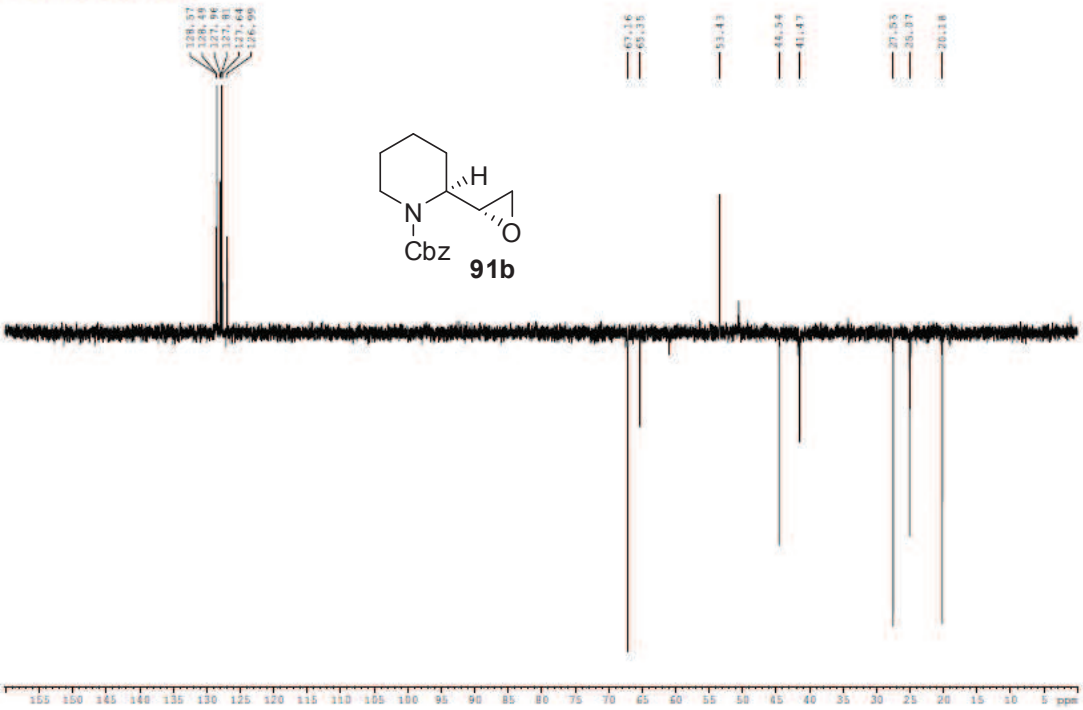

CB-11-18 CDCL3 DEPT
128.92
128.47
127.85
127.78
26.82
26.46
25.73
25.66
H
N
Cbz
O
O
19b
BRUKER
Current Data Parameters
NAME CB-11-18
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20110812
Time 14.17
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG deptsp135
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 16129.032 Hz
FIDRES 0.246110 Hz
AQ 2.0316660 sec
RG 2050
DW 31.000 usec
DE 6.50 usec
TE 300.0 K
CNST2 145.0000000
D1 2.00000000 sec
D2 0.00344828 sec
D12 0.00002000 sec
CHANNEL f1
NUC1 13C
P1 9.00 usec
P13 2000.00 usec
PLW0 0 W
PLW1 48.97800064 W
SFO1 100.6208571 MHz
SPNAM5 Crp60comp.4
SPOAL5 0.500
SPOFFS5 0 Hz
SPW5 6.06150007 W
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
P3 90.00 usec
P4 180.00 usec
PCPD2 90.00 usec
PLW2 0.26607001 W
PLW12 0.26607001 W
SFO2 400.1312797 MHz
F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

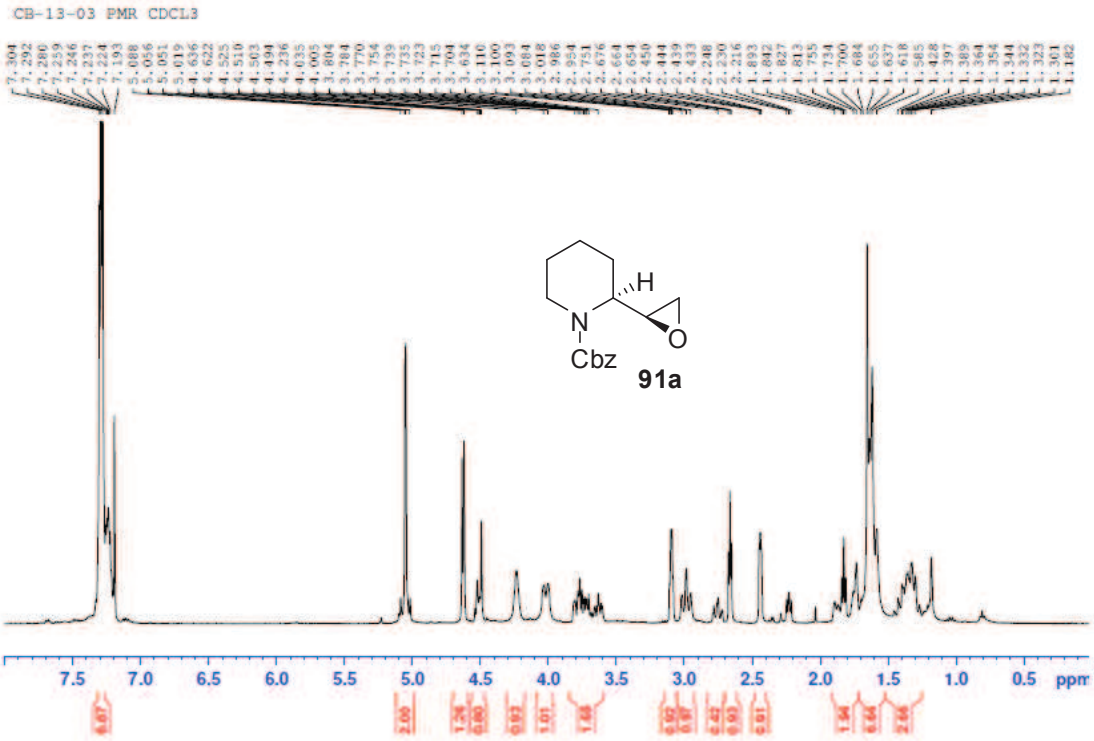

CB-12-60 CDCL3 PMR
7.279
7.270
7.248
7.242
7.236
5.047
4.618
4.239
4.029
3.999
3.088
3.012
2.980
2.947
2.660
2.631
2.433
1.842
1.729
1.617
1.578
1.350
1.341
1.332
1.178
H
N
Cbz
O
91b
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

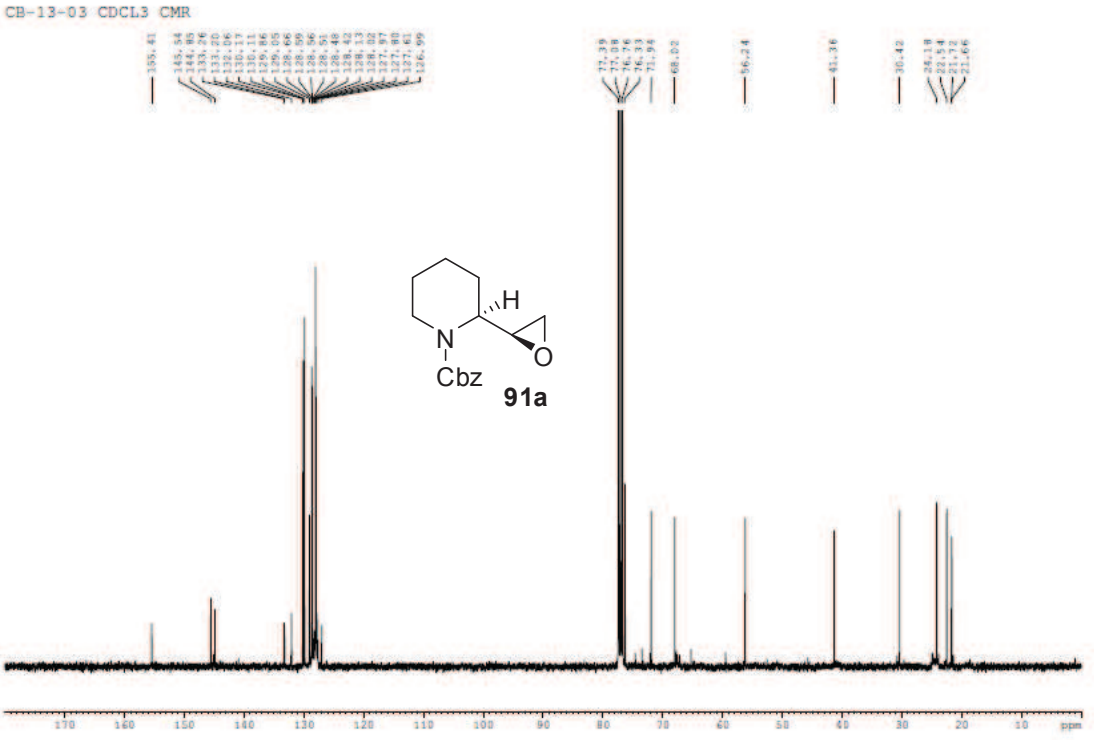
CB-12-60 CDCL3 CMR



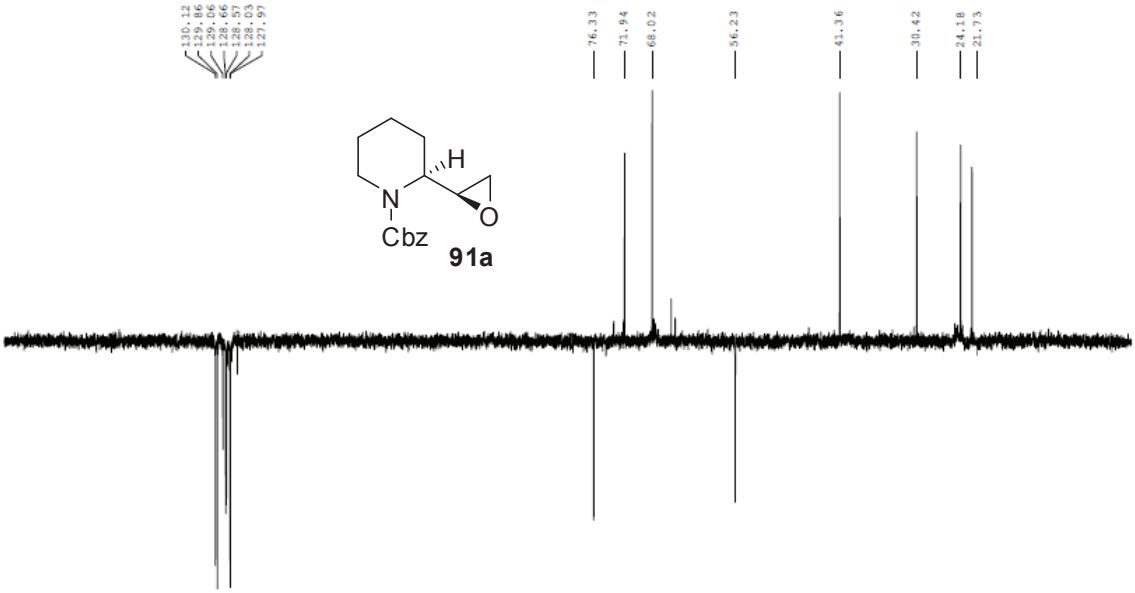
CB-12-60 CDCL3 DEPT



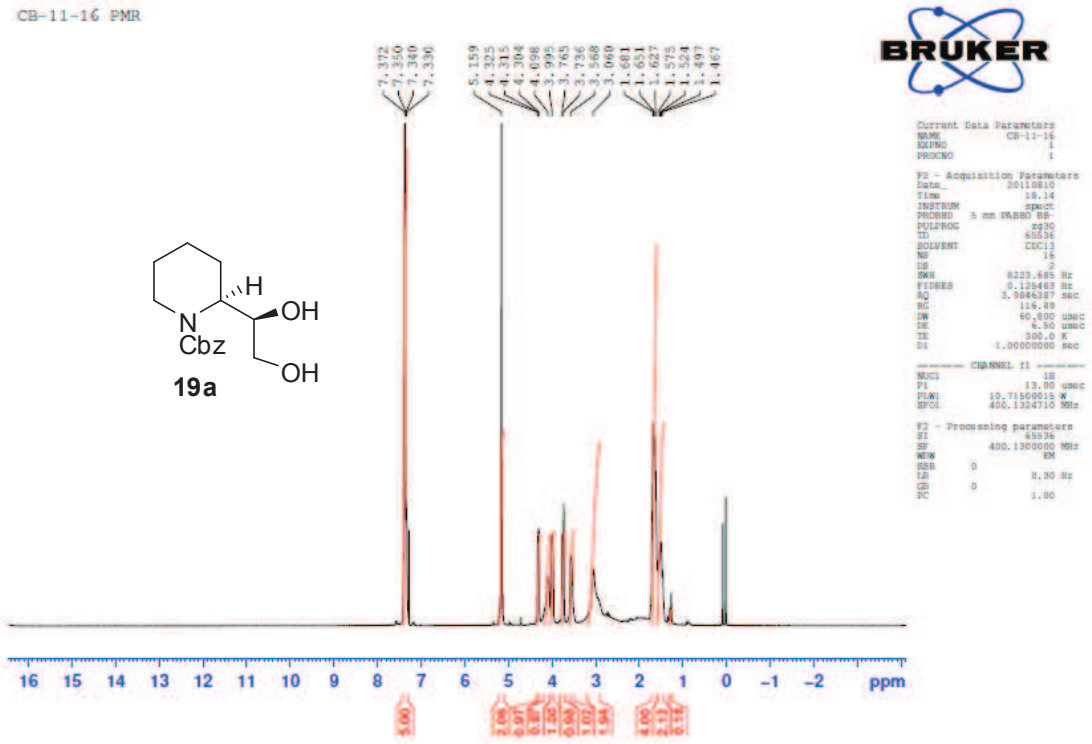

CB-13-03 PMR CDCL3
H
N
O
Cbz
91a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


CB-13-03 CDCL3 CMR
H
N
O
Cbz
91a
ppm

CB-13-03 CDCL3 DEPT



CB-11-16 PMR



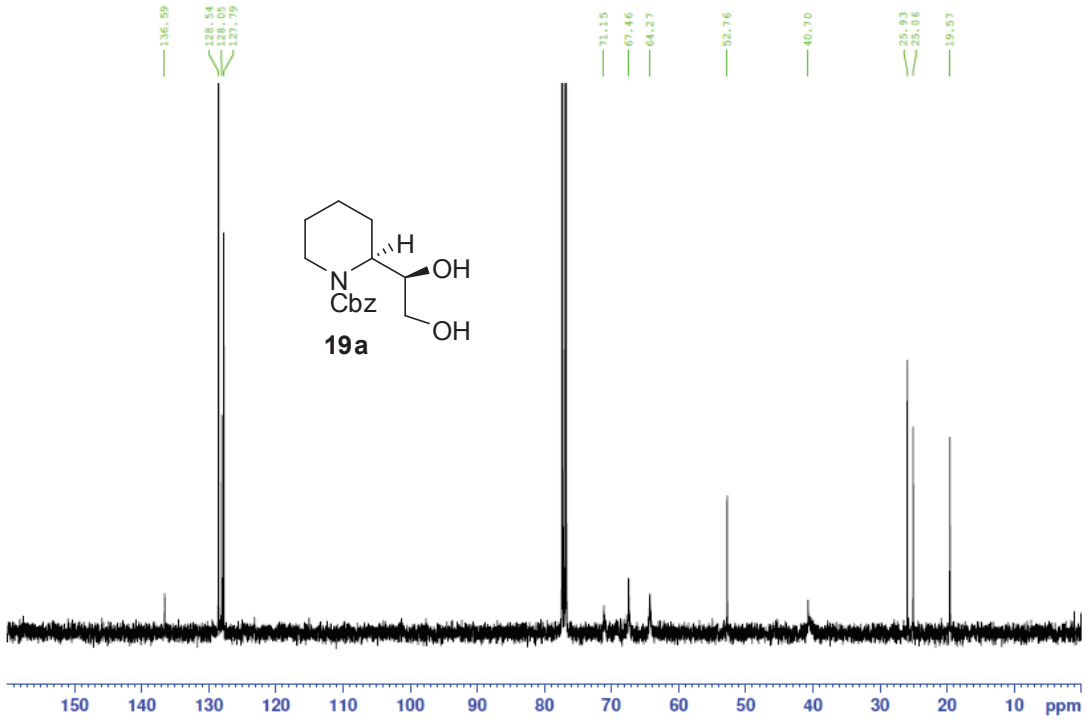
Current Data Parameters
NAME CB-11-16
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20110810
Time 18.14
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846187 sec
RG 116.49
DW 60.800 usec
DE 6.50 usec
TE 300.0 K
D1 1.00000000 sec

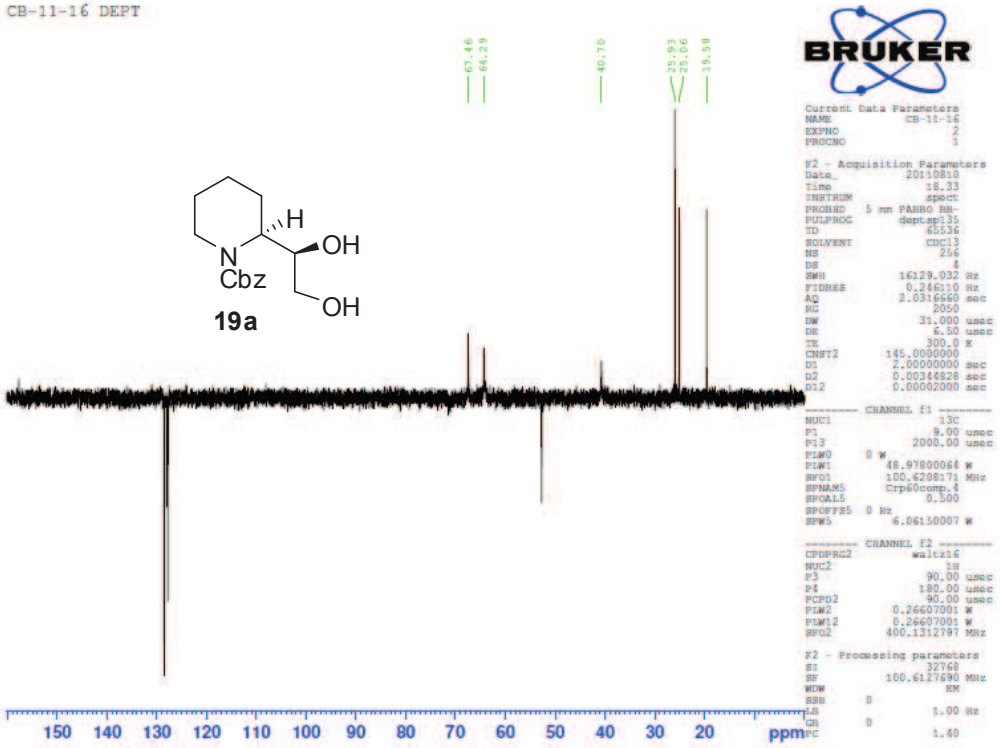
CHANNEL f1
NUC1 1H
P1 13.00 usec
PLW1 10.71500015 W
SFO1 400.1324710 MHz

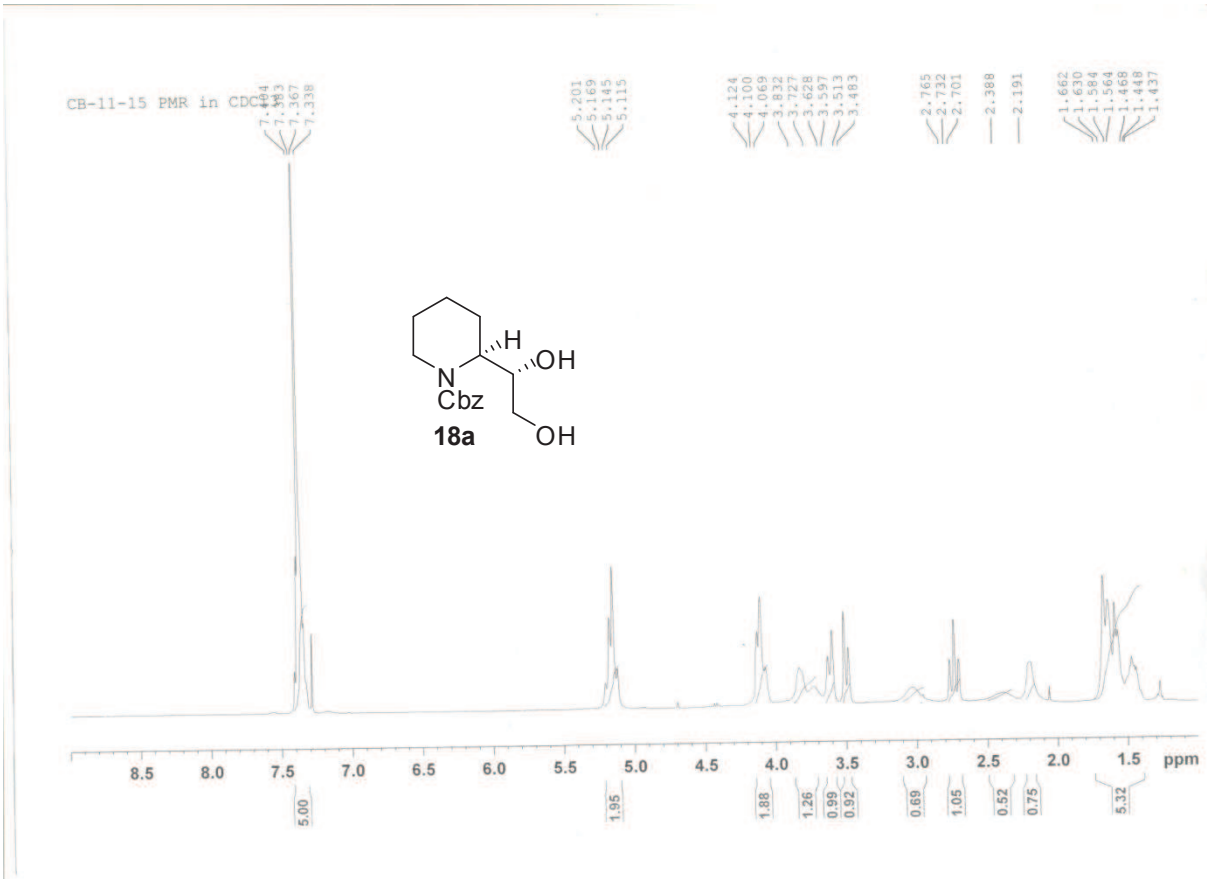
F2 - Processing parameters
SI 65536
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

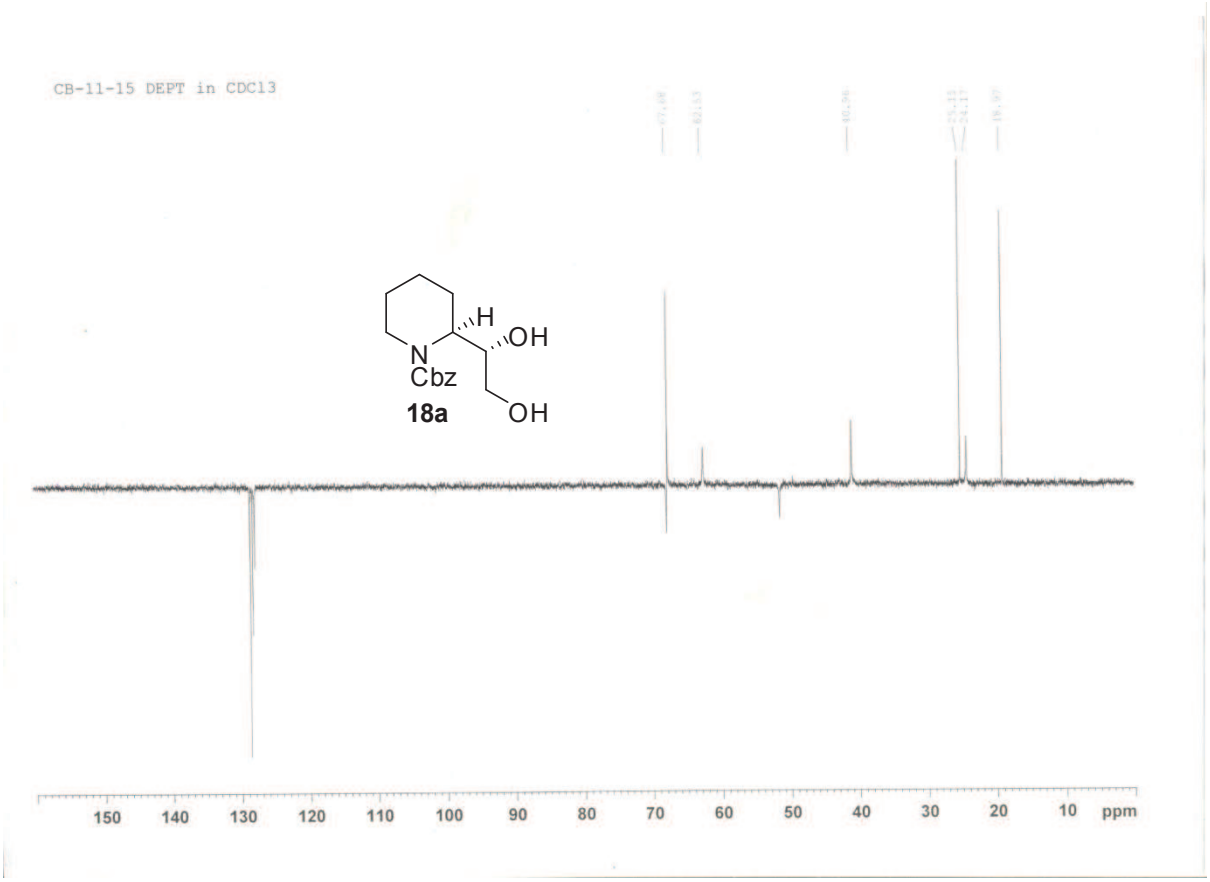
CB-11-16 CMR



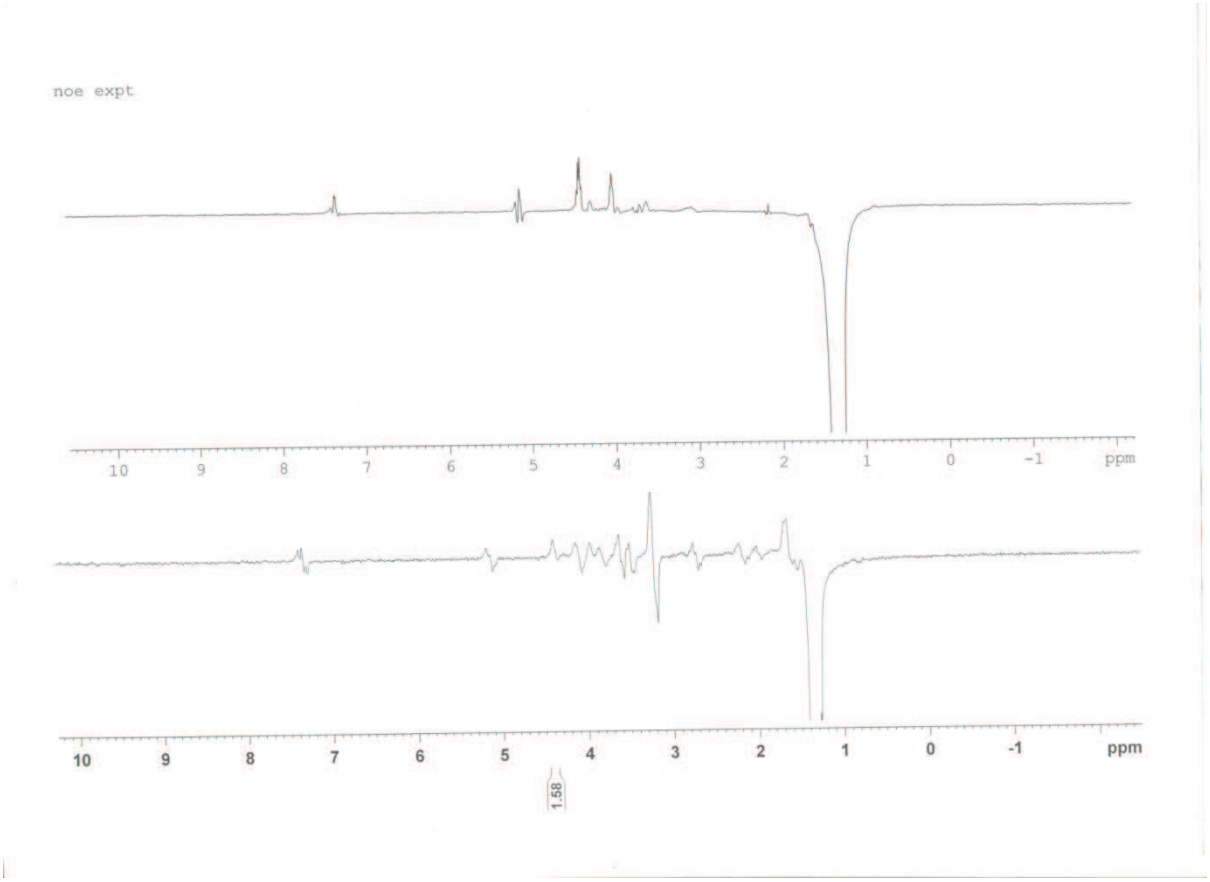
CB-11-16 DEPT




CB-11-15 PMR in CDCl3
7.404
7.383
7.367
7.338
5.201
5.169
5.145
5.115
4.124
4.100
4.069
3.832
3.727
3.628
3.597
3.513
3.483
2.765
2.732
2.701
2.388
2.191
1.662
1.630
1.584
1.564
1.468
1.448
1.437
H
OH
N
Cbz
18a
OH
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
5.00
1.95
1.88
1.26
0.99
0.92
0.69
1.05
0.52
0.75
5.32


CB-11-15 DEPT in CDCl3
H
OH
N
Cbz
18a
OH
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

NOE results



HPLC data

#	Name	RT	Area[µV.Sec]	%Area
1		22.033	503978.288	73.22
2		23.950	184365.285	26.78

Total Area of Peak = 688343.573 [µV.Sec]

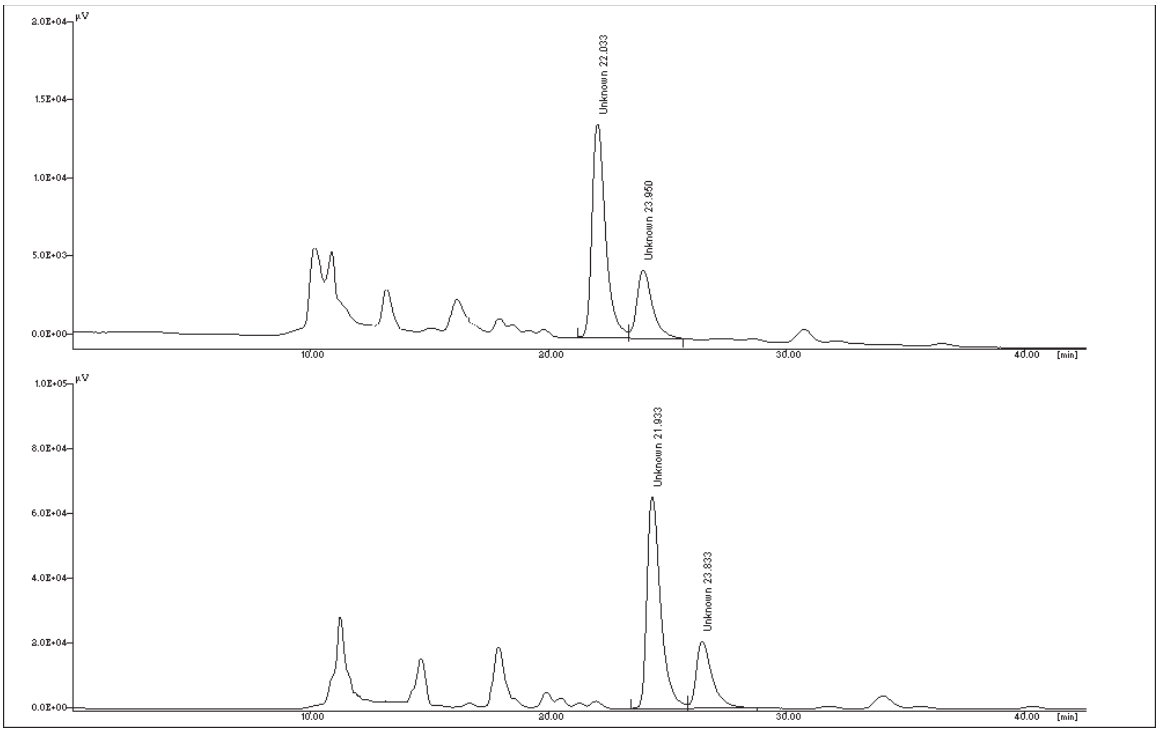
File name : 2364.CH1

Info :

N-Cbz-pipecolin-diol-(DHQD)2AQN-20%IPA+n-hex-FR 1.5ml/min at WL 254

#	Name	RT	Area[µV.Sec]	%Area
1		21.933	2194560.521	73.09
2		23.833	807852.979	26.91

Total Area of Peak = 3002413.500 [µV.Sec]



File name : 2366.CH1

Info :

N-Cbz-pipecolin-diol-(DHQ)2PYR-20%IPA+n-hex-FR 1.5ml/min at WL 254

#	Name	RT	Area[μV.Sec]	%Area
1		21.525	10206575.181	84.85
2		23.633	1822691.948	15.15

Total Area of Peak = 12029267.129 [μV.Sec]

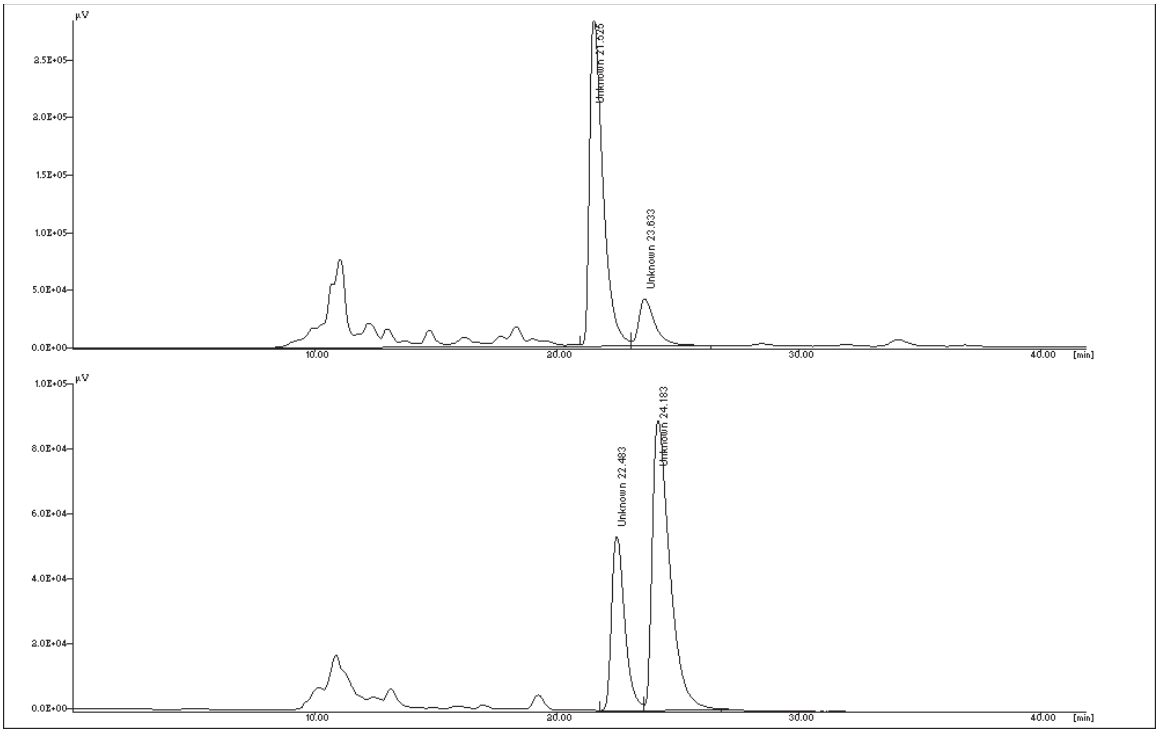
File name : 2367.CH1

Info :

N-Cbz-pipecolin-diol-(DHQD)2PYR-20%IPA+n-hex-FR 1.5ml/min at WL 254

#	Name	RT	Area[μV.Sec]	%Area
1		22.483	1890046.990	30.90
2		24.183	4226179.877	69.10

Total Area of Peak = 6116226.867 [μV.Sec]



File name : 2327.CH1

Info :

N-Cbz-pipecolin-diol-upjohn 1.5ml/min, WL 254, 20% IPA

#	Name	RT	Area[μV.Sec]	%Area	%Area	Name
1		22.433	8230273.063	59.47	59.470	
2		24.333	5609006.437	40.53	40.530	

Total Area of Peak = 13839279.500 [μV.Sec]

File name : 2329.CH1

Info :

N-Cbz-pipecolin-diol-SAD-α 1.5ml/min, WL 254, 20% IPA

#	Name	RT	Area[μV.Sec]	%Area
1		22.433	7446661.224	76.78
2		24.550	2252093.526	23.22

Total Area of Peak = 9698754.750 [μV.Sec]

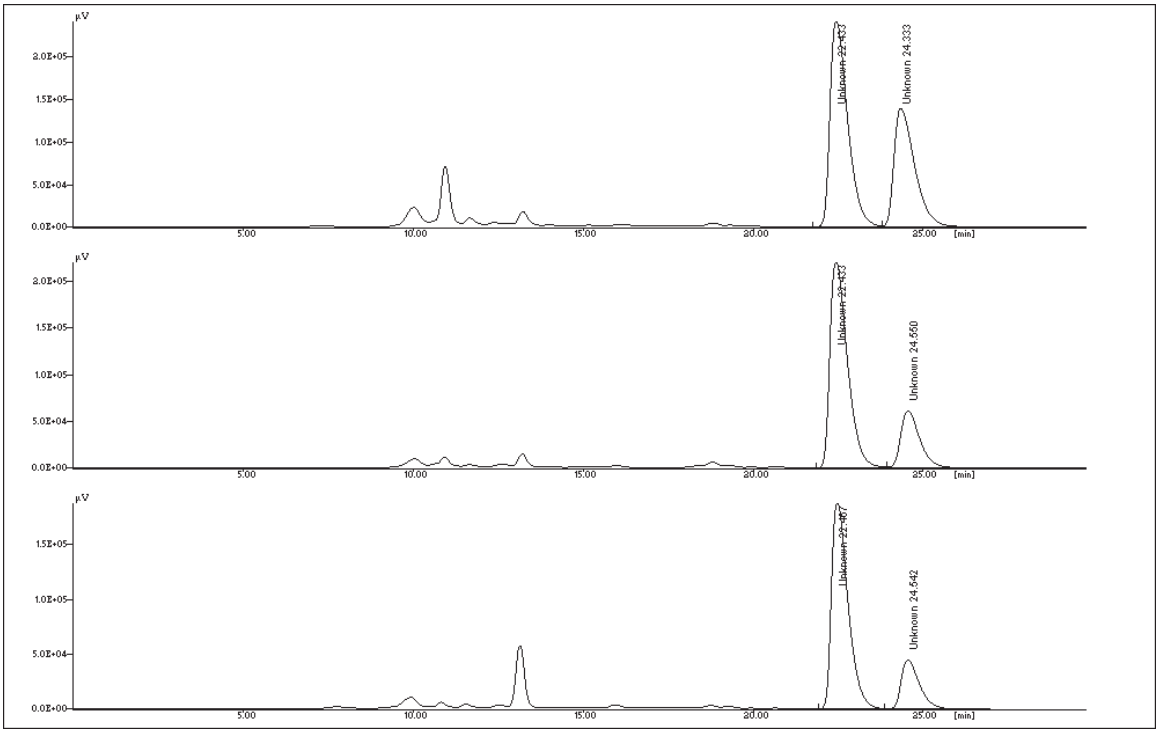
File name : 2328.CH1

Info :

N-Cbz-pipecolin-diol-SAD-β 1.5ml/min, WL 254, 20% IPA

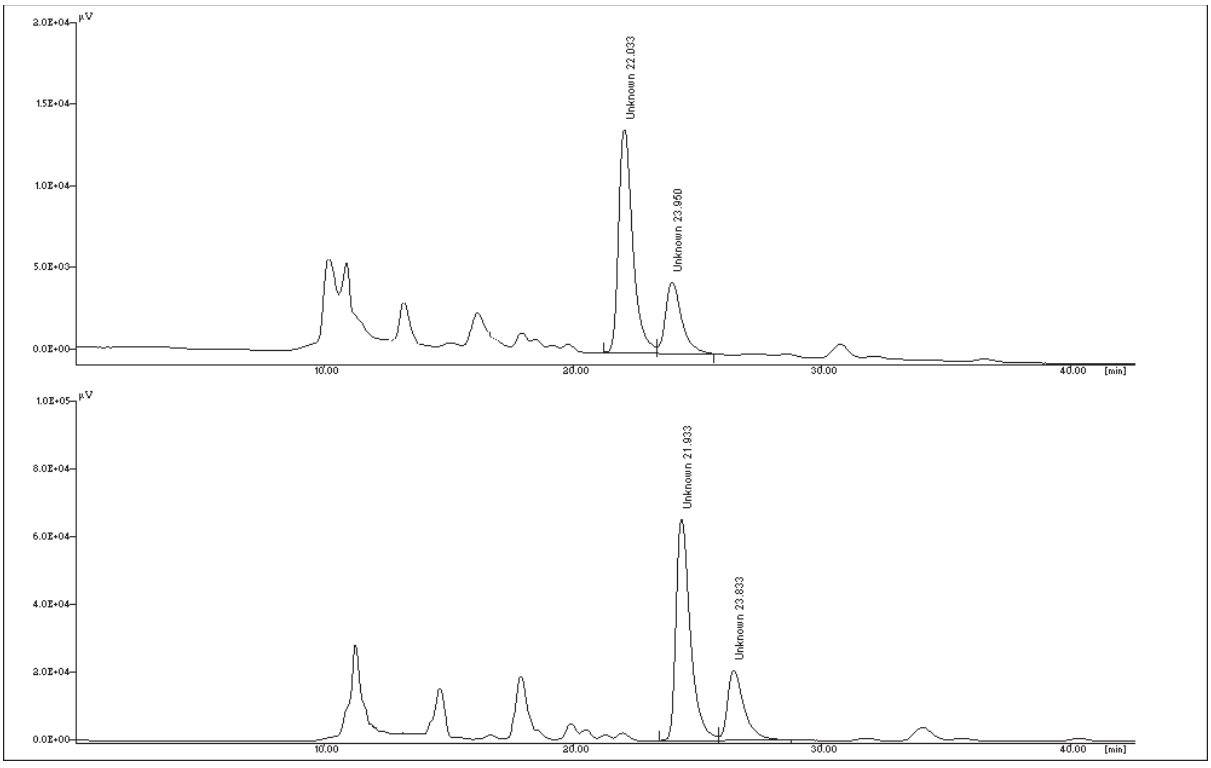
#	Name	RT	Area[μV.Sec]	%Area
1		22.467	6002576.644	79.01
2		24.542	1594237.856	20.99

Total Area of Peak = 7596814.500 [μV.Sec]

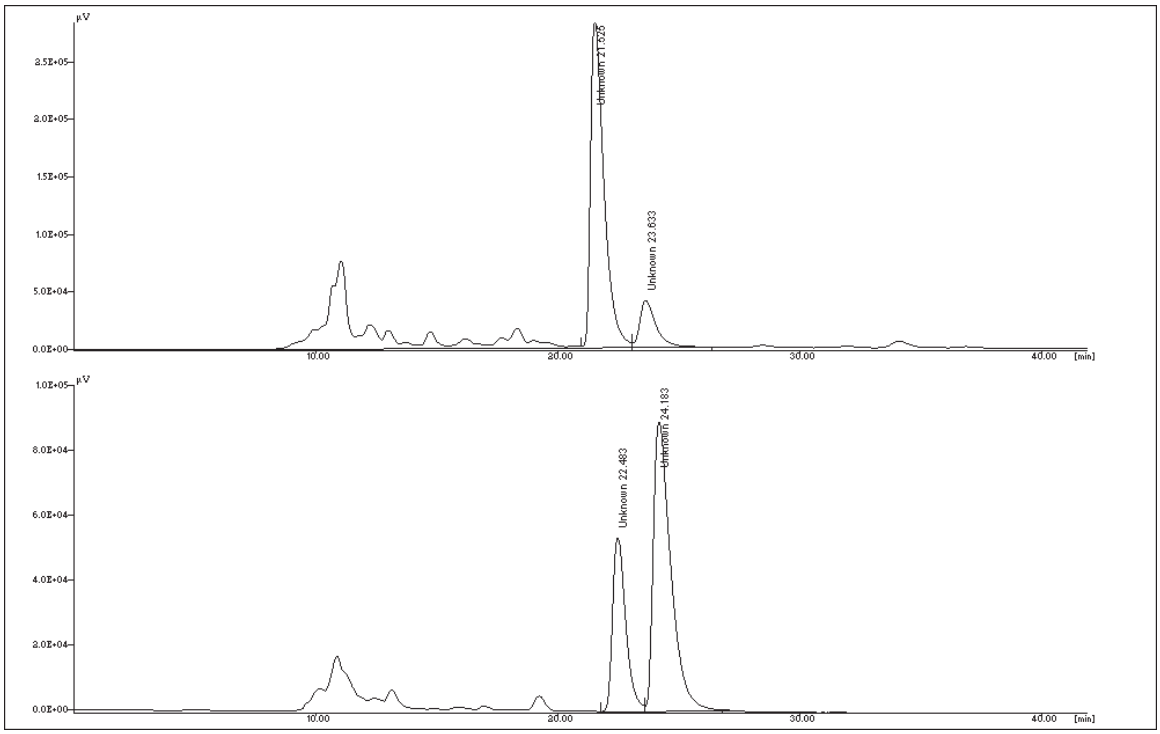


N-Cbz-diol

(DHQ)2AQN and (DHQD)2AQN

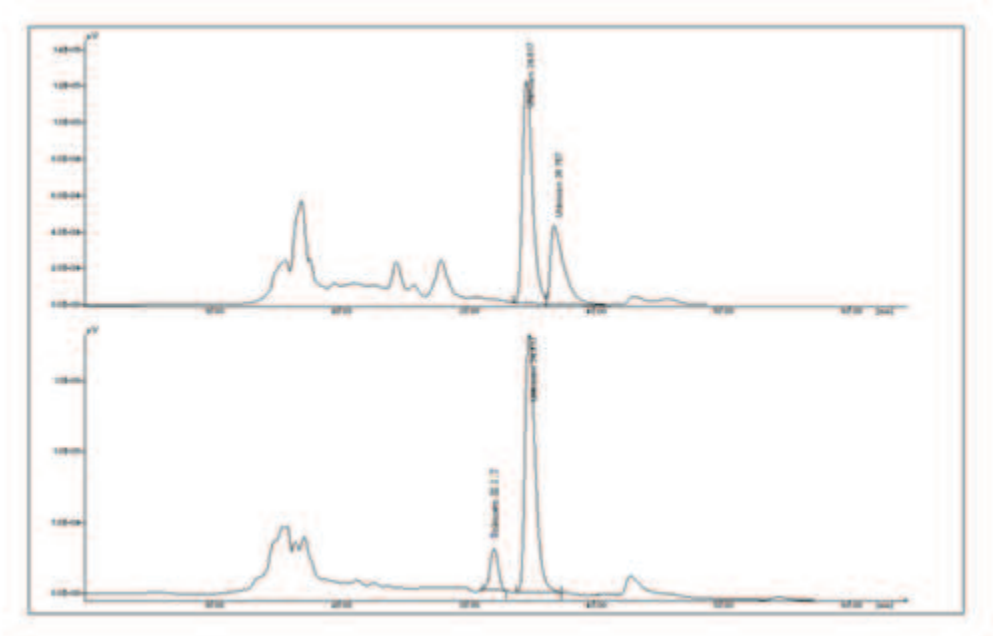


(DHQ)2PYR and (DHQD)2PYR

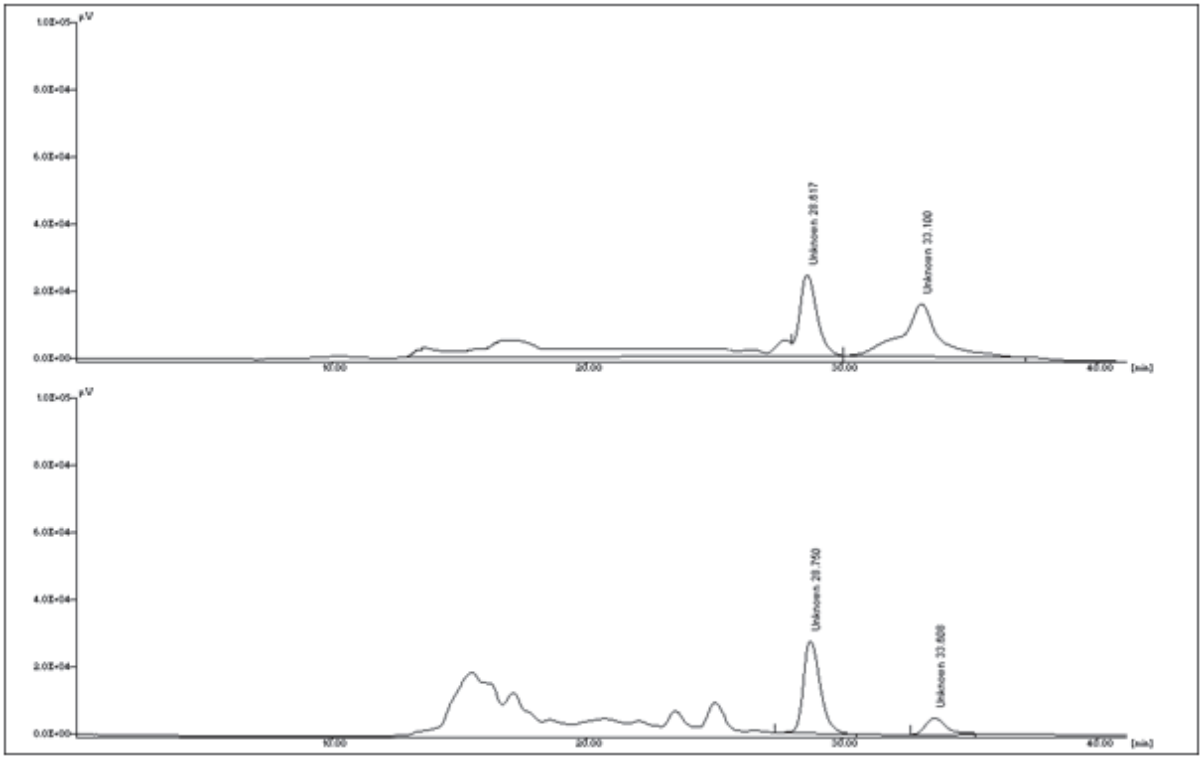


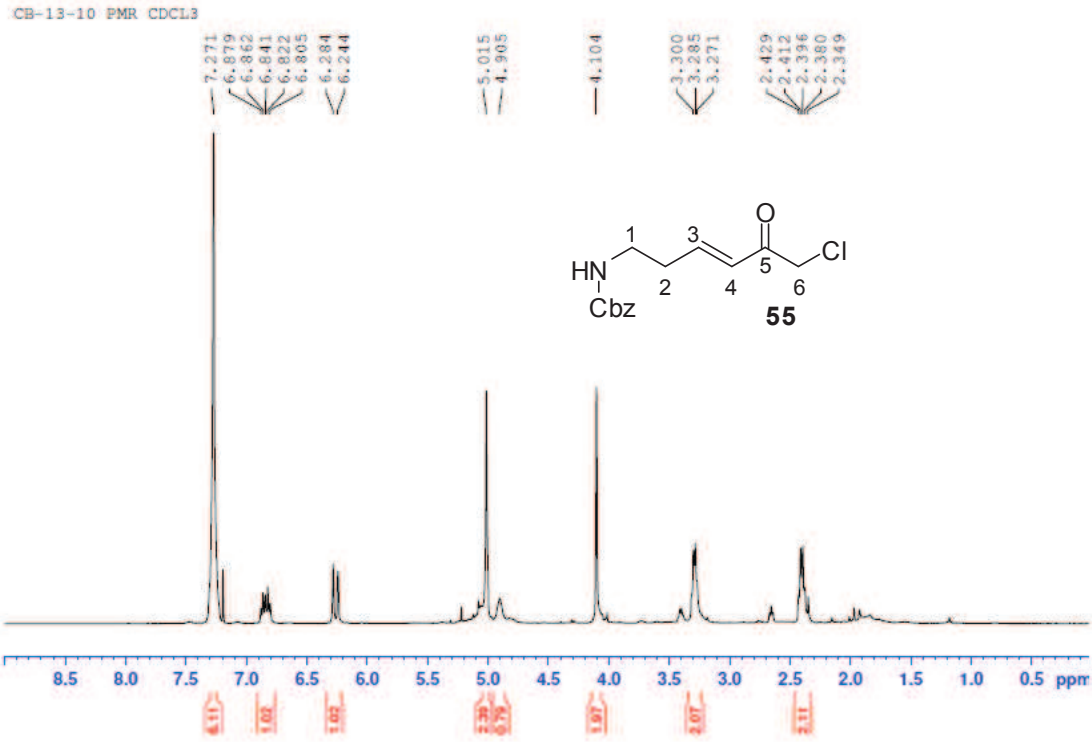
N-COOEt diol

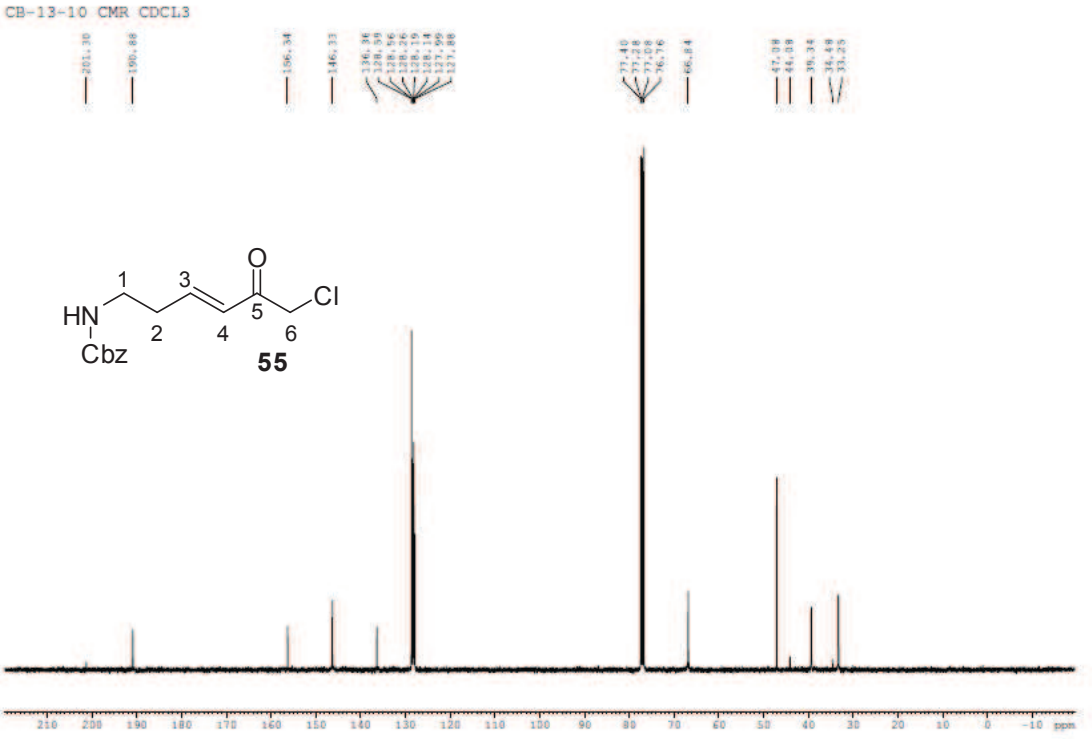
(DHQ)2PYR and (DHQD)2PYR

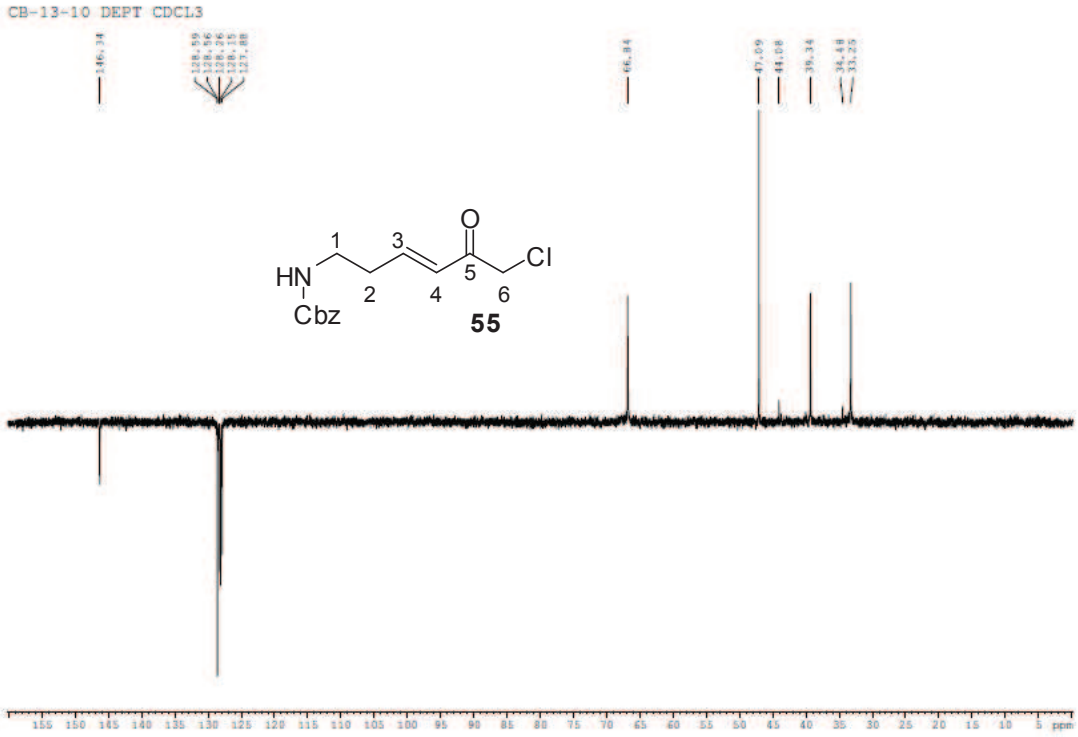


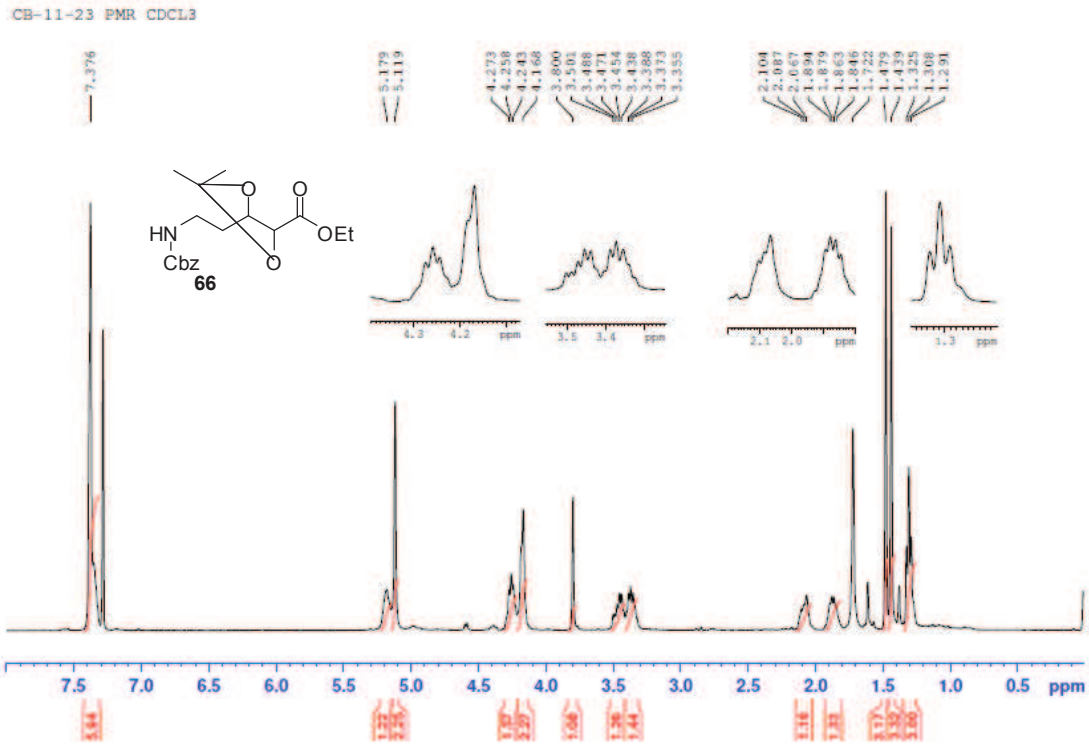
N-Boc diol (DHQD)2PYR and (DHQ)2PYR

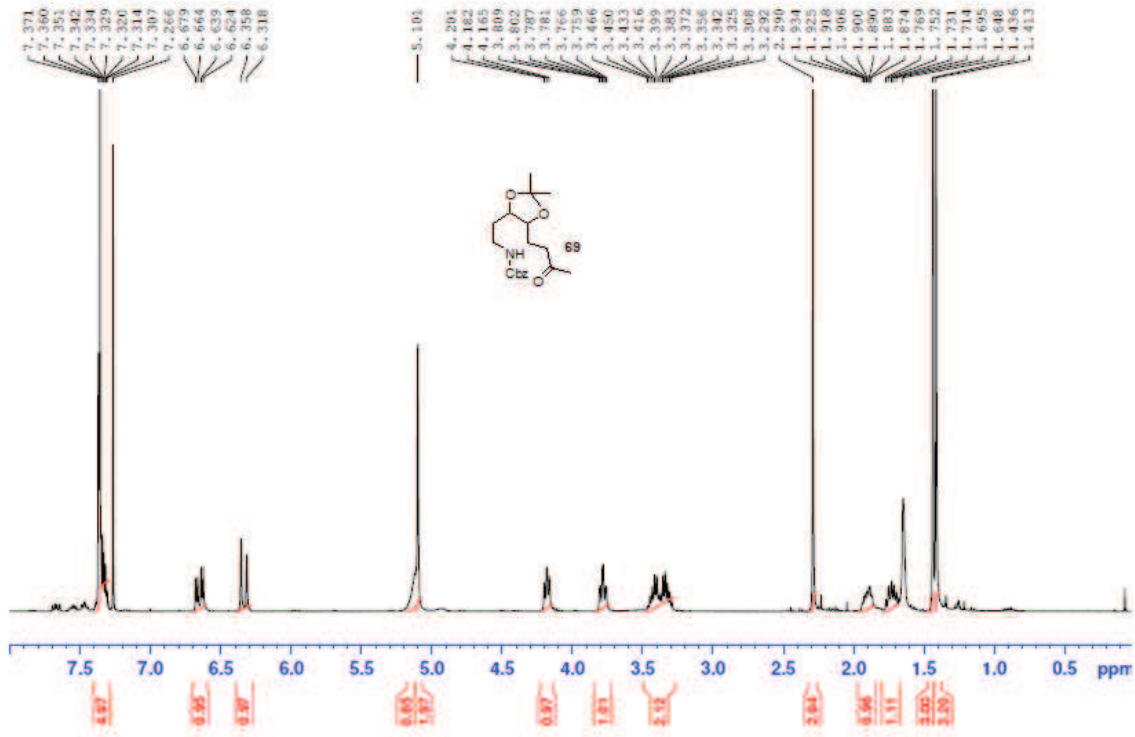


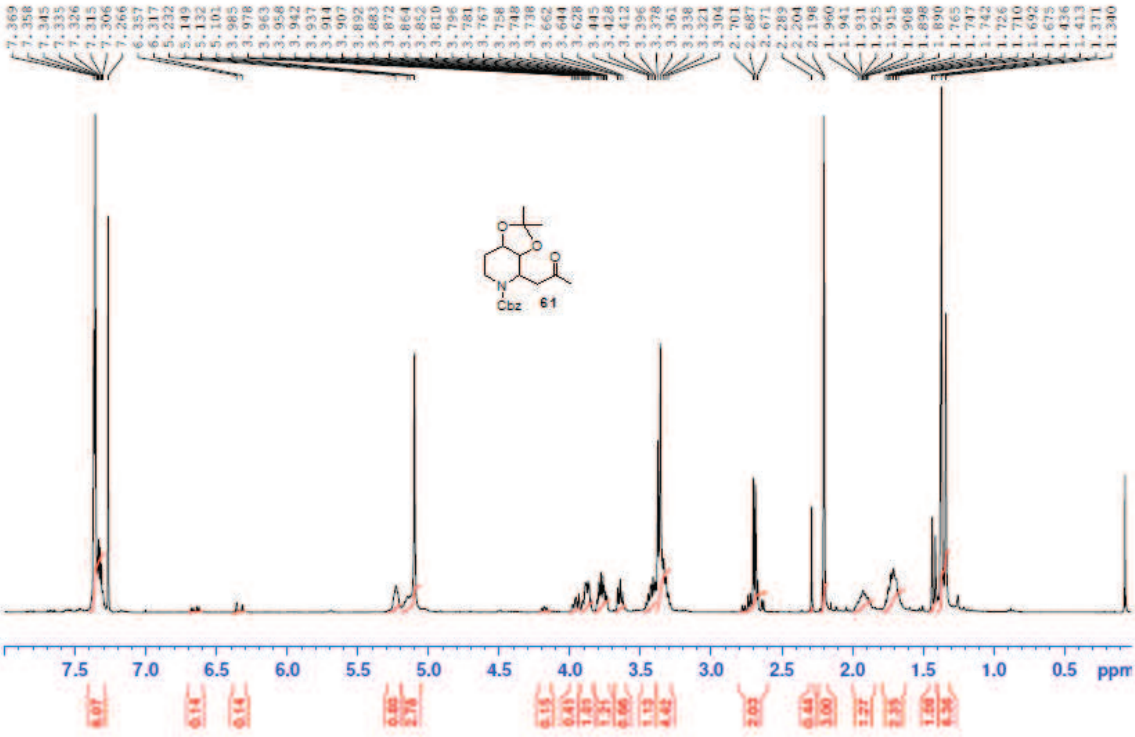

CB-13-10 PMR CDCL3
7.271
6.879
6.862
6.841
6.822
6.805
6.284
6.244
5.015
4.905
4.104
3.300
3.285
3.271
2.429
2.412
2.396
2.380
2.349
HN
Cbz
Cl
O
1
2
3
4
5
6
55
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


CB-13-10 CMR CDCL3
HN
Cbz
Cl
O
1
2
3
4
5
6
55


CB-13-10 DEPT CDCL3
HN
Cbz
Cl
O
55


CB-11-23 PMR CDCL3
HN
Cbz
OEt
66


7.371
7.360
7.351
7.342
7.334
7.329
7.320
7.314
7.307
7.266
6.679
6.664
6.639
6.624
6.358
6.318
5.101
4.201
4.182
4.165
3.809
3.802
3.787
3.781
3.766
3.759
3.466
3.450
3.433
3.416
3.399
3.383
3.372
3.356
3.342
3.325
3.308
3.292
2.290
1.934
1.925
1.918
1.906
1.900
1.890
1.883
1.874
1.769
1.752
1.731
1.714
1.695
1.648
1.436
1.413
69
NH
Cbz
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


7.369
7.358
7.345
7.335
7.326
7.315
7.306
7.266
6.357
6.317
5.232
5.149
5.132
5.101
3.985
3.978
3.963
3.958
3.942
3.937
3.914
3.907
3.892
3.883
3.872
3.864
3.852
3.810
3.796
3.781
3.767
3.758
3.748
3.738
3.662
3.644
3.628
3.445
3.428
3.412
3.396
3.378
3.361
3.338
3.321
3.304
2.701
2.687
2.671
2.289
2.204
2.198
1.960
1.941
1.931
1.925
1.915
1.908
1.898
1.890
1.765
1.747
1.742
1.726
1.710
1.692
1.675
1.436
1.413
1.371
1.340
Cbz
61
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm