SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS: CCG AND ITS DERIVATIVES, MITRALACTONINE AND DEVELOPMENT OF SYNTHETIC METHODOLOGIES

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

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DECEMBER 2006

CERTIFICATE

*Certified that the work incorporated in the thesis entitled "**Synthesis of Biologically Active Compounds: CCG And Its Derivatives, Mitralactonine And Development of Synthetic Methodologies**" submitted by Pallavi Sharma was carried out under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.*

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Research Supervisor

DECLARATION

I hereby declare that the thesis entitled " ***Synthesis of Biologically Active Compounds: CCG And Its Derivatives, Mitralactonine And Development of Synthetic Methodologies***" submitted for Ph. D. degree to the university of Pune has been carried out at Organic Chemistry Division (Technology), NCL, Pune, under the supervision of Dr. Subhash P. Chavan and the work is original and has not been submitted in part or full by me for any degree or diploma to this or any other university.

December, 2006 Pallavi Sharma

Organic Chemistry: Technology,
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……..to my parents

and lovesome memories of

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Contents

Acknowledgements

As I complete my journey to the most cherished dream it gives immense pleasure and sense of satisfaction to record my heart felt gratitude to all those persons who have made this possible for me. It's an honour rather than my duty to express my deep sense of gratitude to my mentor, Dr. Subhash P. Chavan at the first place for believing in my abilities and providing me an incredible opportunity to pursue my career as a Ph. D. student under his able guidance. His keen interest, patient listeneting and never diminishing encouragement towards the accomplishment of my work will always be highlighted in my future achievements. I would never forget the immense support and trust he bestowed on me throughout my Ph. D. carrier.

The affection and support from Dr. S. K, Kamat and Dr. U. R. Kalkote was greatly needed, deeply appreciated and will always be remembered. I am thankful to all the senior scientist and staff members of OCT division for the help extended towards the accomplishment of the work in the form of this thesis.

Words fails to extend my thanks to Dr. Bhinde, Rupesh, Sachin and Ashpaq for recording so many chiral HPLC, Dr Rajmohanan and Mr. Sathe for their timely help with NMR spectra recording, Dr. Mohan Bhadbhade and Mr. Rajesh Gonnade for the X-ray analysis. Help from microanalytical, IR and Mass facility is also acknowledged.

I am thankful to Dr. R. Sivappa for introducing and teaching me all the nitty gitty of practical chemistry and ever aspiring thoughts till date.

With much appreciation I would like to mention the crucial role of my labmates both seniors and present colleagues: Dr. Amar, Dr. Sharma, Dr. Sivshanker, Dr. Kharul, Dr. Pasupathy, Dr. Ramesh, Sambhaji, Dr. Praveen, Dushyant, Mahesh, Sanjay, Swapna, Vikas, Ashok, Sharad P., Abasaheb, Shankar, Shruti, Lalit, Kishore, Kiran and Jogdand for providing an healthy and friendly working enviroment. The help extended by all of them for accomplishing all small to big day to day lab course is heartly acknowledged.

Help from my colleague and batch mate Anamitra is gracefully and sincerely appreciated. At the same time I would like to recall all my friends from GJ hostel and NCL for providing a helping hand and cheerful moment which made my stay in NCL a memorable one. I wish to thank my friends Shubhasree, Debjani, Mrinal and Saikat for their help and encouragement during my early stages of graduation and postgraduation.

This thesis would not have been possible without the endless help and blessing of my family. I am indebted to my parents for imbibing all the good qualities, inculcating and nourishing the desire for higher studies and being patient through out my Ph. D. carrier. The healthy and inspiring environment for higher studies provided by my sisters will always be the driving force for better achievement. The love and support from my younger brother and sister is always remembered.

I am thankful to the Director, NCL and Dr. M. K. Gurjar, HOD, OCT for allowing me to carry out the research work in a prestigious and well equipped laboratory.

Finally my thanks are due to CSIR, New Delhi for financially supporting my work during my Ph. D. tenure.

Pallavi Sharma

Ac	Acetyl
Aq.	Aqueous
Bn	Benzyl
Bp	Boiling point
BuLi	Butyl Lithium
Bz	Benzoyl
CAN	Ceric ammonium nitrate
Cbz	Benzyloxy carbonyl
CSA	Camphor sulphonic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	Distortionless Enhancement by Polarisation Transfer
DHP	Dihydropyran
DIBAL	Diisobutylaluminium hydride
DMAP	4-(Dimethylamino)pyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
EtOAc, EA	Ethyl acetate
EI	Electron ionisation
ESI	Electron Spray Ionisation
GC	Gas Chromatography
h	Hour/s
HMBC	Heteronuclear multiple bond correlation
HMQC	Heteronuclear multiple quantum correlation
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography

Hz	Hertz
IPA	Isopropyl alcohol
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LiHMDS	Lithium Hexamethyldisilazide
Mp	Melting point
MPLC	Medium Pressure Liquid Chromatography
MS	Mass spectrum
MW	Micro wave
MsCl	Methanesulphonyl chloride
NBS	N-Bromosuccinimide
NMO	N-Methylmorpholine N-oxide
NMR	Nuclear Magnetic Resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
p-TSA	*p*-toluene sulphonic acid
PE, PET	Petroleum ether
PCC	Pyridinium chlorochromate
PCy_3	Tricyclohexylphosphine
Ph	Phenyl
PPTS	Pyridinium *p*-toluenesulphonate
rt	Room temperature
$TBAHSO_4$	Tetrbutylammonium hydrogen sulphate
TBDMSCl	Tetrbutyldimethylsilyl chloride
TBDPS	Tertbutyldiphenylsilyl chloride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMSCN	Trimethylsilyl cyanide
TPP	Triphenylphosphine
UV	Ultraviolet

- The compound numbers, scheme numbers and reference numbers given in each section refers to that particular section only.
- ^{1}H and ^{13}C NMR spectra were recorded on AC-200/50 MHz, MSl-300/75 MHz, DRX-400/100 MHz and DRX 500/125 MHz spectrometers using tetramethylsilane as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- EI mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using direct inlet system. ESI mass spectra were recorded on API Q STAR PULSAR.
- IR spectra were obtained on Perkin-Elmer infrared spectrometer model 681 or model 1605 FT-IR ($\tilde{\nu}$ max is expressed in cm^{-1}).
- Optical rotations were recorded on JASCO P-1020 polarimeter in the solvents specified.
- Melting points were recorded on Büchi 535 melting point apparatus. All melting points and boiling points are uncorrected.
- Elemental analyses were carried out in the Carol Erba Instument, CHNS-O EA 1108 Elemental analyzer.
- X-Ray was obtained on Bruker SMART APEX CCD diffractometer.
- Progress of the reactions were monitored by Thin Layer Chromatography (TLC) using 0.25 mm E-Merck silica gel 60 F254 precoated plates and visualized by flourescence quenching, I_2, or charring after treatment with p-anisaldehyde/ phosphomolybdic acid/ninhydrine.
- All the solvents were purified and dried according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under Nitrogen or Argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogenous materials unless otherwise stated.
- In case where chromatographic purification was done unless mentioned SiO_2 (60-120) was used as stationary phase.

The thesis entitled **"Synthesis of Biologically Active Compounds: CCG And Its Derivatives, Mitralactonine And Development of Synthetic Methodologies"** is divided into three chapters.

Chapter 1: deals with a brief review on the title compound and the present synthetic studies towards L-CCG-I and is divided into two sections.

Chapter 2: constitutes of the synthesis of mitralactonine in both racemic as well as asymmetric fashion and is divided into two sections.

Chapter 3: deals with synthesis of mitralactonine employing RCM and development of iodine as an efficient catalyst for ionic Diels-Alder reaction.

Chapter 1

Section 1: This section deals with a brief introduction to the literature methods for stereoselective cyclopropane ring construction leading to synthesis of carboxycycopropyl glycine (CCG). Among the other conformationally constrained analogs of L-glutamic acid, the four isomeric CCG-I to CCG-IV (carboxycyclopropylglycine) were known to restrict the conformation of L-glutamic acid either in extended or folded form and were found to be agonist of either the *N*-methyl D-aspartic acid (NMDA) or metabotropic glutamate receptor (m-GluR) (Figure 1).

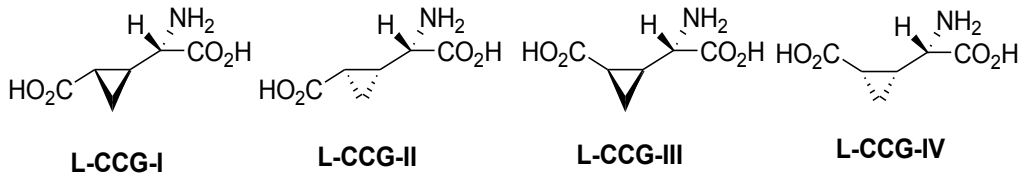


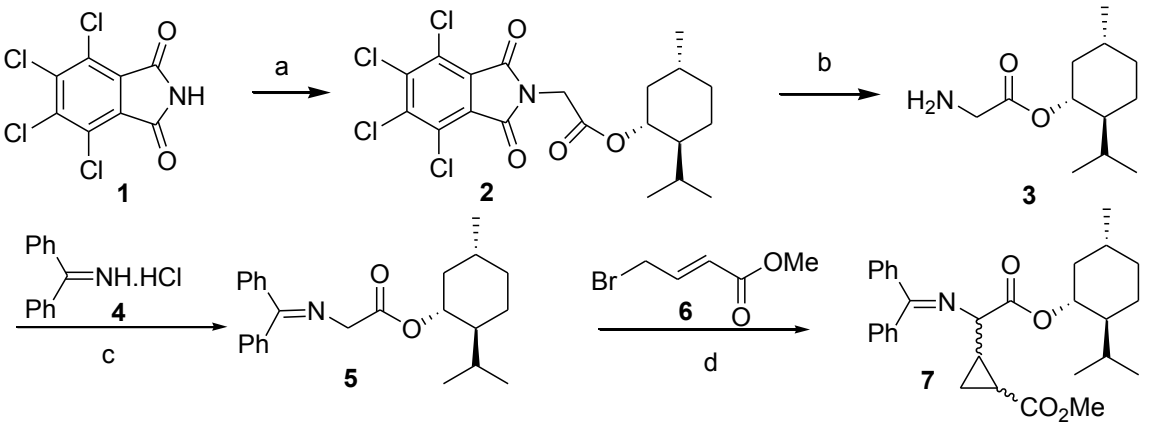
Figure 1

Section 2: Enantioselective synthesis of L-CCG-I

Based on the preliminary results from this group for diastereoselective synthesis of *rac*-CCG-I, it was decided to pursue its chiral synthesis. The present challenge was the control of the absolute stereochemistry of the three contiguous stereocenters in a single step. This section describes the asymmetric synthesis of L-CCG-I by efficiently utilising chiral auxiliary at either the amine or acid part of either of the starting materials to control the stereochemistry of the three newly generated centers.

Chiral Azomethine Ylide

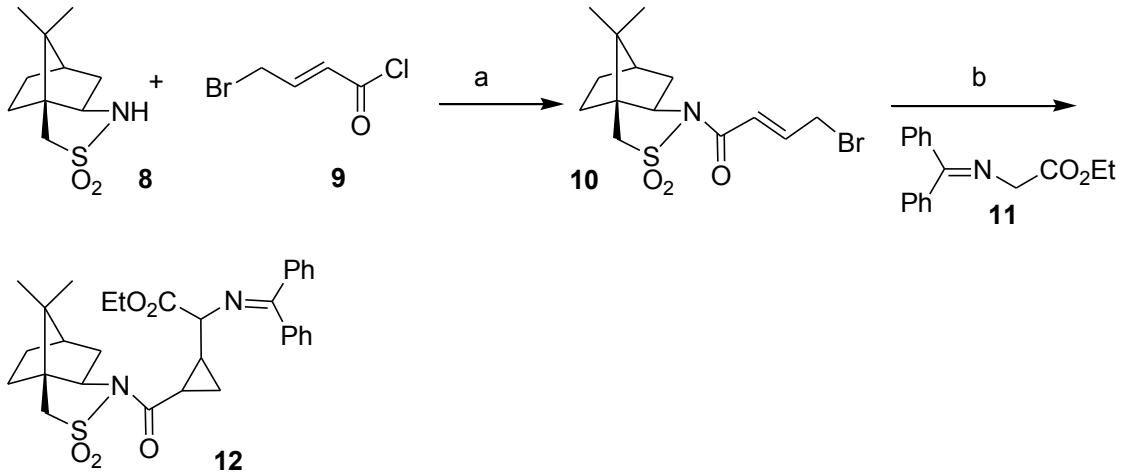
The readily available *l*-menthol as chiral auxiliary was envisaged for stereoselective cyclopropanation reaction. The chiral Schiff base **5** was obtained by tethering the *l*-menthol in the *N*-protected glycine and subsequent replacement of the protecting group with diphenylimine. The cyclopropanation reaction was carried out by dropwise addition of triethylamine to the mixture of Schiff base (**5**), 4-bromomethylcrotonate (**6**) and LiBr taken in THF. The proton NMR of **7** revealed a poor diastereoselectivity.



Scheme 1: **Reagents and conditions:** *a) i. glycine, DMF, N-methyl morphine, MW, 90 s, 70%, ii. $SOCl_2$, reflux, 10 h, iii. l-menthol, Et_3N, DCM, rt, 95%; b) ethylenediamine, rt, 0.5 h; c) DCM, rt, 12 h, 82%; d) LiBr, Et_3N, rt, 16 h, 68%.*

Chiral Michael Acceptor

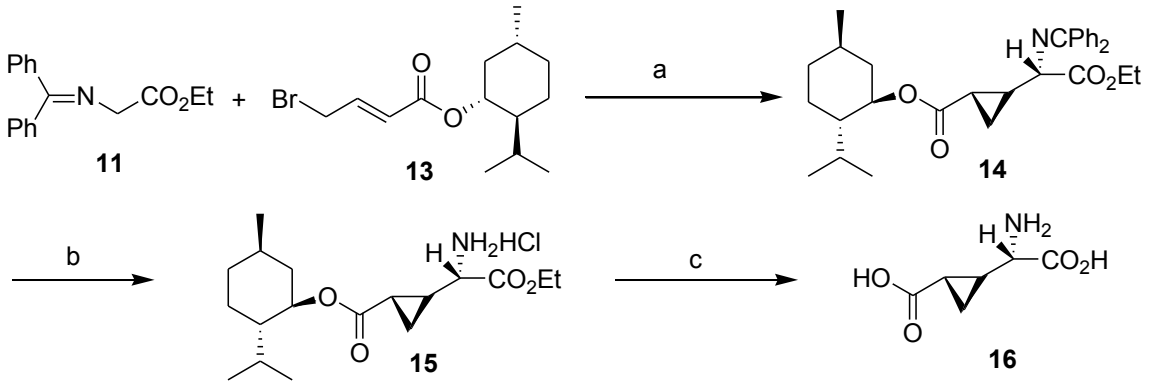
As the selectivity was not appreciable using a chiral Schiff base, we tried to prepare the chiral Michael acceptor. Accordingly, the *l*-menthol and 10,2 camphor sultam substrates were prepared and scanned for the stereoselective reaction.



Scheme 2: Reagents and conditions: *a) NaH, benzene, rt, 5 h, 60%; b) LiBr, Et_3N, THF, rt, 16 h, 60%*

The required 4-bromocrotonyl sultam **10** was prepared starting from bromocrotonyl chloride **9**. This substrate was subjected to react with diphenylimine glycinate (**11**) as per the standard conditions to render the cyclised product **12**. Unfortunately the diastereoselectivity in this case also remained poor as evident from proton NMR analysis.

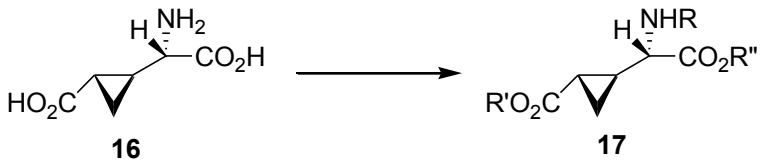
In another endeavor the *l*-menthol was introduced in the unsaturated ester part. The required substrate **13** was obtained according to literature procedure. It was then subjected to react with diphenylimine glycinate (**11**) following the standard conditions to give the cyclised product **14** in 92% diastereoselectivity as revealed by proton NMR analysis. It was further subjected to acid hydrolysis to render the amine hydrochloride salt **15**. Saponification of **15** and proper workup rendered the CCG **16** in 87% yield.



Scheme 3: Reagents and conditions: *a) LiBr, Et_3N, THF, rt, 16 h, 72%; b) 2N HCl, rt, 0.5 h, 60%; c) LiOH, MeOH: H_2O, rt, 0.5 h, DOWEX-H^+, 87%*

To confirm the stereochemistry of the three centers and to determine the enantioselectivity, a number of derivatives of the crude product were prepared of which the Boc protected methy ester **17** could be analysed easily both by chiral HPLC as well as single X-ray study (Scheme 4). A high enantioselectivity of 94% was realized which rendered optically pure compound on single recrystallisation.

Scheme 4



R = COAr, COAr', Boc

R' = menthyl, ethyl, methyl

R" = methyl, ethyl

Chapter 2

Section 1: Synthesis of (±)-Mitralactonine

Mitragyna speciosa Korth is a tropical plant indigenous to Thailand and Malay Peninsula. The leaves of this plant are known to produce narcotic like action when chewed or smoked. The investigation of the constituents of the leaves of *M. speciosa* of Malaysia led to the extraction of a new alkaloid (**18**) along with six known corynanthe-type indole alkaloids. The structure elucidation of the monoterpenoid indole alkaloid by means of spectroscopic analysis as well as racemic and asymmetric total synthesis was accomplished by Takayama *et al* in the year 1999.

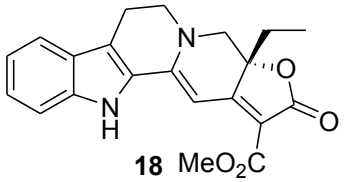
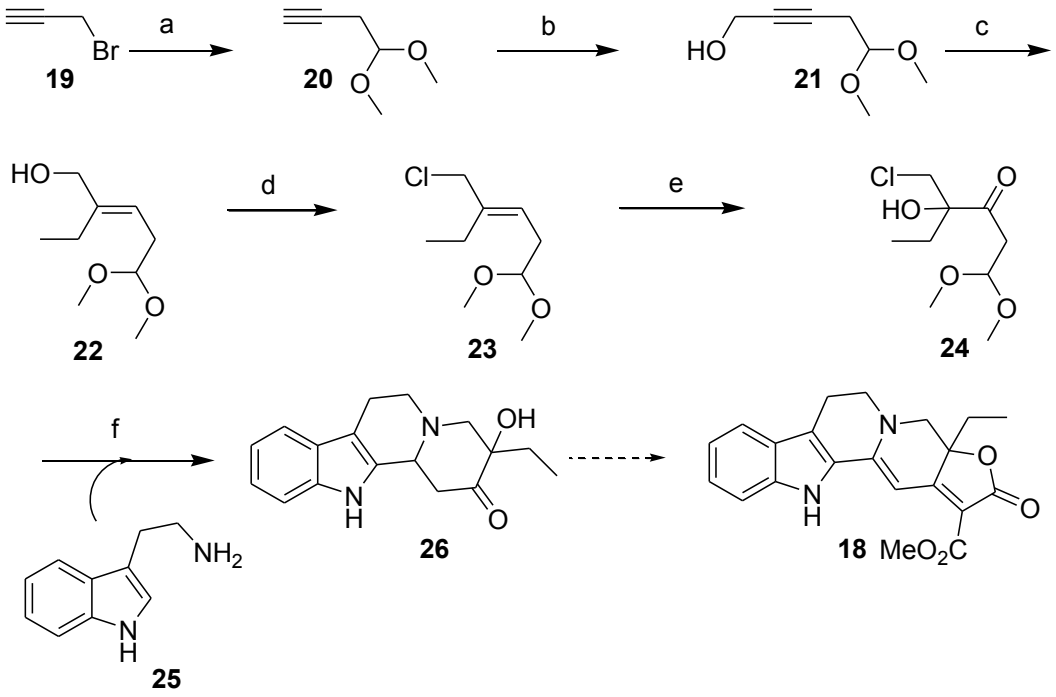


Figure 2

The present section describes a novel approach to the target molecule, which involved Pictet-Spengler cyclisation-alkylation as the key ring construction reaction leading to the tetracyclic intermediate in one-pot procedure.



Scheme 5: **Reagents and conditions:** *a) Al, $HgCl_2$, ether, rt-reflux, 3 h, -78 ^oC, 1 h, trimethylorthoformate, -45 ^oC, 1 h; b) n-BuLi, THF, -78 ^oC, $(CH_2O)_n$, reflux, 3 h, 80%; c) EtMgBr, ether, reflux, 10 h, 75%; d) MsCl, Et_3N, DCM, rt, 12 h; e) $KMnO_4$, AcOH, acetone:H_2O, 0.5 h, -10 ^oC, 84%; f) 2M HCl (EtOH), rt, 12 h, 55%.*

The key coupling fragment **24** was synthesised in five steps starting from propargyl bromide **19**. Thus treating propargyl bromide with aluminum followed by quenching with trimethyl ortho formate gave the acetal **20** which was further subjected to react with paraformaldehyde to give the corresponding propargyl alcohol **21**. Addition of ethyl Grignard gave the desired alkylated product **22** which was transformed into compound **23** on treating with MsCl and was further subjected to oxidation to give ketol **24.** The ketol **24** obtained was subjected to react with tryptamine **25** under acidic condition to render the corresponding tetracyclic compound **26** in 55% yield (Scheme 5). It was elaborated further to mitralactonine as per the literature procedure.

In conclusion, total synthesis of (±) mitralactonine was accomplished starting from propargyl bromide in a highly facile fashion.

Section 2: Formal Synthesis of (-)-Mitralactonine

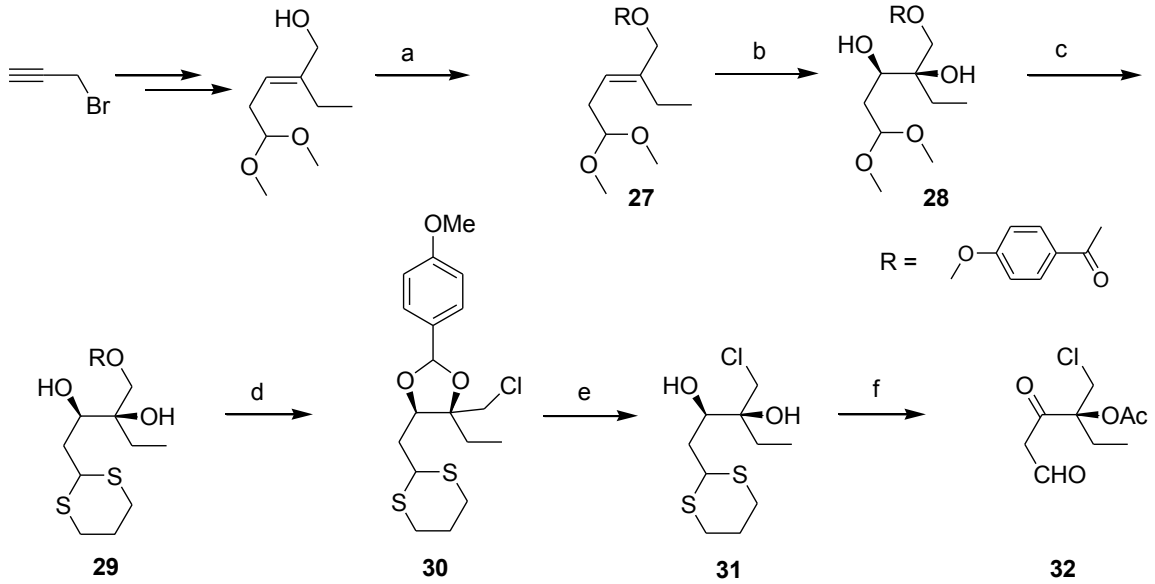
The successful synthesis of racemic mitralactonine employing Pictet-Spengler cyclisation paved the way for its asymmetric synthesis employing asymmetric dihydroxylation as the source of chirality. In the present section the studies towards the synthesis of (-)-mitralactonine is described.

Accordingly, the allylic chloro compound **23** was subjected to asymmetric dihydroxylation under standard conditions with α-AD mix as the reagent of choice. The selectivity obtained was not good enough to carry forward. A few more ligands were screened but none could provide better selectivity.

To improve the selectivity, Corey's protocol was implied wherein a benzoate moiety is introduced in place of chloro to enhance the selectivity during dihydroxylation. With this modified protocol, diol **28** was obtained in enhanced enantioselectivity of 89% ee when **27** was subjected to standard dihydroxylation condition. The secondary hydroxy group was oxidised, benzoate was removed with K_2CO_3 in methanol but the product thus obtained was not stable enough to carry forward for converting it into the corresponding chloro compound.

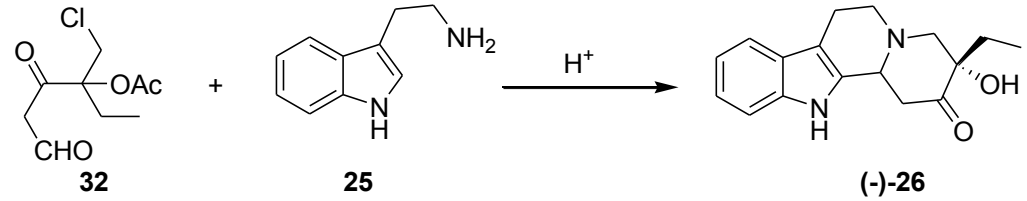
Owing to unstability of the hydrolysed product, an alternative route was sought and optimized. In this modified scheme the dimethyl acetal protection of **28** was changed to a dithiane protection **29** to enhance the stability of the substrate. Further modification according to the previous scheme provided the ketol where the tertiary hydroxy group

was protected as its acetate followed by removal of dithiane group rendering the corresponding aldehyde **32**.



Scheme 6: Reagents and conditions: *a) p-methoxybenzoyl chloride, Et_3N, DCM, rt, 85%; b) $K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2PHAL$, OsO_4, t-BuOH:H_2O, 0 ^oC, 24 h, 90%; c) propane 1,3 diol, BF_3..OEt_2, DCM, rt, 0.5 h, 70%; d) i. dimethyl acetal anisaldehyde, p-TSA, DCM, rt, 0.5 h, 88%; ii. K_2CO_3, MeOH, rt, 12 h; iii. PPh_3, CCl_4, reflux, 3 h, 86%; e) p-TSA, MeOH, rt, 0.5 h, 87%; f) i. DMP, DCM, 0-5 ^oC, 3 h, 40 %; ii. Ac_2O, DMAP, rt, 2 h, 87%,; iii MeI, acetonitrile, H_2O, reflux 24 h.*

Scheme 7



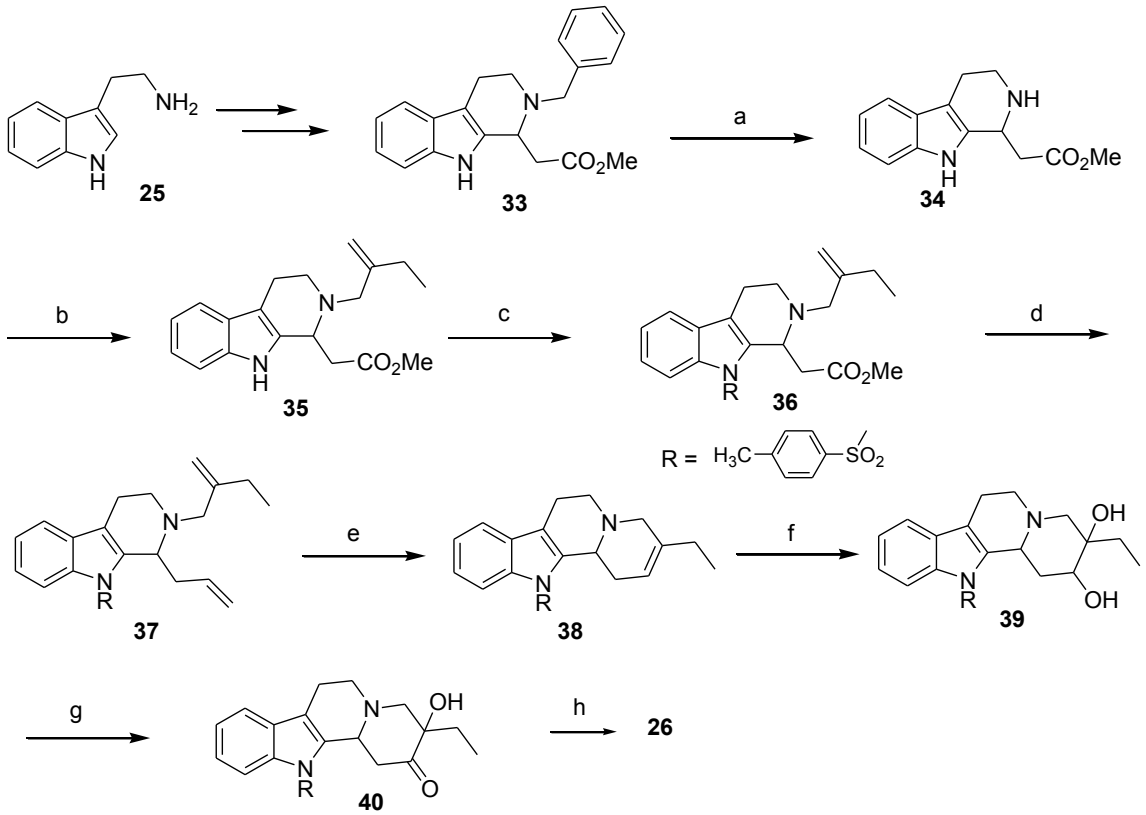
The aldehyde **32** obtained was subjected to react with tryptamine **25** under acidic condition followed by basic workup to render the tetracyclic keto-hydroxy compound **26**.

In conclusion, the asymmetric synthesis of mitralactonine was realised starting from propargyl bromide in highly convergent way using asymmetric dihydroxylation (SAD) as the key chirality inducing factor.

Chapter 3

Section 1: Formal Synthesis of (±)-Mitralactonine: RCM Approach.

A totally different approach of synthesis of (**±**)-mitralactonine was explored using ring-closing metathesis as the key ring construction reaction which will be discussed in this section.



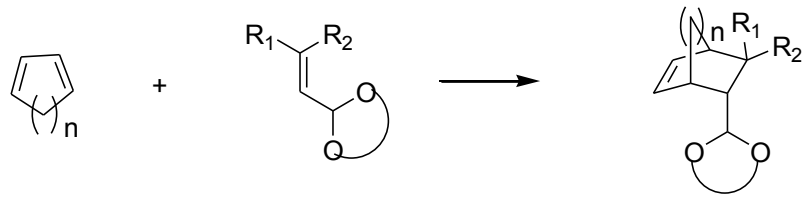
Scheme 8: Reagents and conditions: *a) H_2, Pd/C, 60 psi, rt, 10 h; b) $CH_3CH_2C(=CH_2)CH_2OMs$, K_2CO_3, rt, 70%; c) p-TsCl, $TBAHSO_4$, benzene, NaOH, rt, 20 min, 85%; d) DIBAL-H, DCM, -78 ^oC, 2 h, $Ph_3P=CH_2$, THF, rt, 12 h, 68%; e) Grubbs' 2nd gen. cat., toluene, 80 ^oC, 3 h, 87%; f) $K_3Fe(CN)_6$, K_2CO_3, OsO_4, t-BuOH:H_2O, rt, 24 h, 50%; g) DMSO, oxalyl chloride, Et_3N, DCM, -60 ^oC, 0.5 h, 40%; h) TBAF, THF, reflux 1.5 h, 63%.*

The benzyl protected tryptamine was subjected to react with propiolate ester in presence excess of TFA, gave the Pictet-Spengler cyclised compound **33**. The benzyl group was removed under hydrogenolysis conditions to provide **34** which was further condensed with the suitable alkylating moiety to render **35**. Owing to high reactivity of the indole nucleus, the indole-N was protected as tosyl derivative **36**. The aldehyde obtained by treating **36** with DIBAL-H was subjected to one carbon Wittig homologation to give the required substrate **37** for RCM reaction. Thus treating the substrate **37** with Grubbs' second-generation catalyst rendered the required RCM product **38**. Dihydroxylation

under standard two phase conditions gave the diol **39** which was further converted into keto-hydroxy compound **40** under Swern oxidation conditions (Scheme 8).
Deprotection of **40** provided the required intermediate for mitralactonine thereby completing the formal total synthesis of the same.

Section 2: I_2 as an efficient catalyst in the ionic Diels-Alder reaction of α,β-unsaturated acetals.

This section describes iodine as a catalyst for a variety of masked α,β-unsaturated dienophiles bearing no activating group towards cycloaddition. It was observed that the Diels-Alder reactions of acrolein acetal were efficiently catalysed by iodine to furnish the adducts in 15 to 30 minutes, with high selectivity in almost all the cases.



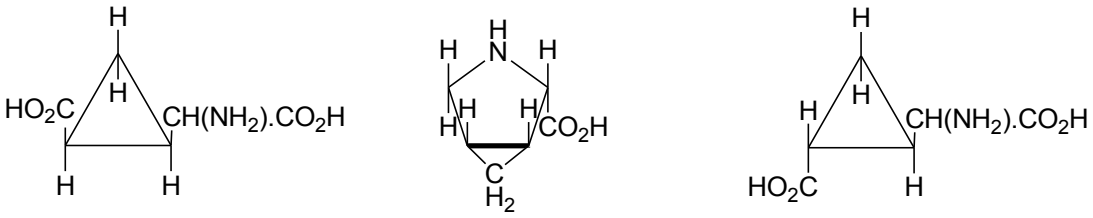
In conclusion, the study clearly demonstrates the efficiency of I_2 to catalyse ionic Diels-Alder reaction of protected dienophiles as well as those of unprotected dienophiles with dienes for cycloadduct formation with high selectivity and good yield at short reaction time.

Chapter 1 Section 1

Carboxycyclopropyl glycine (CCG): A Brief Review

1.1.1. Introduction

Carboxycyclopropyl glycines (CCG's) are conformationally constrained analogues of glutamate receptors, which are useful pharmacological tools for analysis of glutamate neurotransmitter system. The *cis* **1** and the *trans* **3** CCG's were isolated along with *Exo*-3,4-methanoproline (**2**) from immature fruits of *Aesculus parviflora* and *Blighia sapida*.[1] Both the plants are assigned to the family Sapindaceae, and both amino acid cause hypoglycaemic symptoms in animals. The *cis* isomer is known as potent growth inhibitor in mung bean seedlings (fig.1).



Cis-CCG
1

3,4-methanoproline
2

Trans-CCG
3

Figure 1

1.1.2. Structure Elucidation

The assignment of structure of *cis* and *trans* isomer isolated from *Aesculus parviflora* and *Blighia sapida* was based mainly on the studies of their behaviour towards hydrogenation and mass spectral study.[1]

The elementary analysis revealed the empirical formula as $C_6H_9NO_4$. The NMR studies showed complex pattern at high field region thereby supporting the presence of cyclopropane ring. The similarity in the NMR of **1** and **3** was in line with diastereomeric relation between them.

Mass spectral study of **1** and **3** showed markedly different behaviour of fragment peaks thereby exemplifying different disposition on the ring. Though the molecular ion peaks was absent in both the compounds against the expectation, **1** showed peak at 141 and 114, that of 114 readily decreasing with time indicating it to be parent ion of another molecular species presumably lactam whereas no such behaviour was noticed in the spectrum of **3**.

The compound **1** though stable on prolonged heating with strong mineral acid but readily formed the lactam when autoclaved at pH 3 at 120 ^{o}C, a behaviour characteristic of substituted derivative of glutamic acid. On the other hand the compound **3** was stable to mineral acid and did not yield the lactam.

The crucial evidence in support of the presence of a cyclopropane came from hydrogenation study. The compound **1** furnished *Erythro*-γ-methyl glutamic acid on exposing it to hydrogenation condition under weakly acidic condition as major product by 1,3 fission whereas 1,2 fission provided the minor compound α-amino adipic acid. The mixture of compounds could not have arisen from any other alternative structure than proposed with a cyclopropyl ring. The *Erythro* configuration of the γ-methyl glutamate indicated that **1** is the *cis* isomer of α-(carboxylcyclopropyl) glycine (assuming an L-configuration at the α-carbon based on specific rotation values). The *cis* relation of the carboxyl and glycine moiety in **1** is consistent with the observed lactam formation, and coexistence of **1** and **2** in the same species.

Unequivocal confirmation of the *cis* configuration was provided by the degradation of **1** into *cis*-cyclopropane-1,2-dicarboxylic acid using *N*-bromosuccinimide and silver oxide as oxidants.

The other isomer **3** on hydrogenation yielded a different pattern of cyclopropyl ring. No reductive 1,2 fission was observed, but equal amount of *threo*-γ-methyl glutamic acid by 1,3 fission and erythro-β-methylglutamic acid by 2,3 split were produced. The configurations of the methyl-susbstituted glutamic acids are those expected from *trans* -L-isomer of α-(carboxylcyclopropyl) glycine. Specific optical rotation and the failure to produce a lactam from **3** supported this isomeric assignment.

Oxidative degradation of **3** using *N*-bromosuccinimide followed by silver oxide oxidation gave *trans*-cyclopropane -1,2-dicarboxylic acid.

Carboxycyclopropyl glycine has three stereogenic centers and thus can exits in eight isomeric forms. As mentioned, it is regarded as conformationally constrained analogue of glutamic acid. A closer look reveals that presence of a cyclopropane ring in 3,4 position of glutamic acid restricts its conformation either in the extended or folded form there by giving rise to *cis* or *trans* form.

Thus L-Glutamic would give a set of four L- CCG's and another four D-CCG's could be realised from D-Glutamic acid (fig. 2).

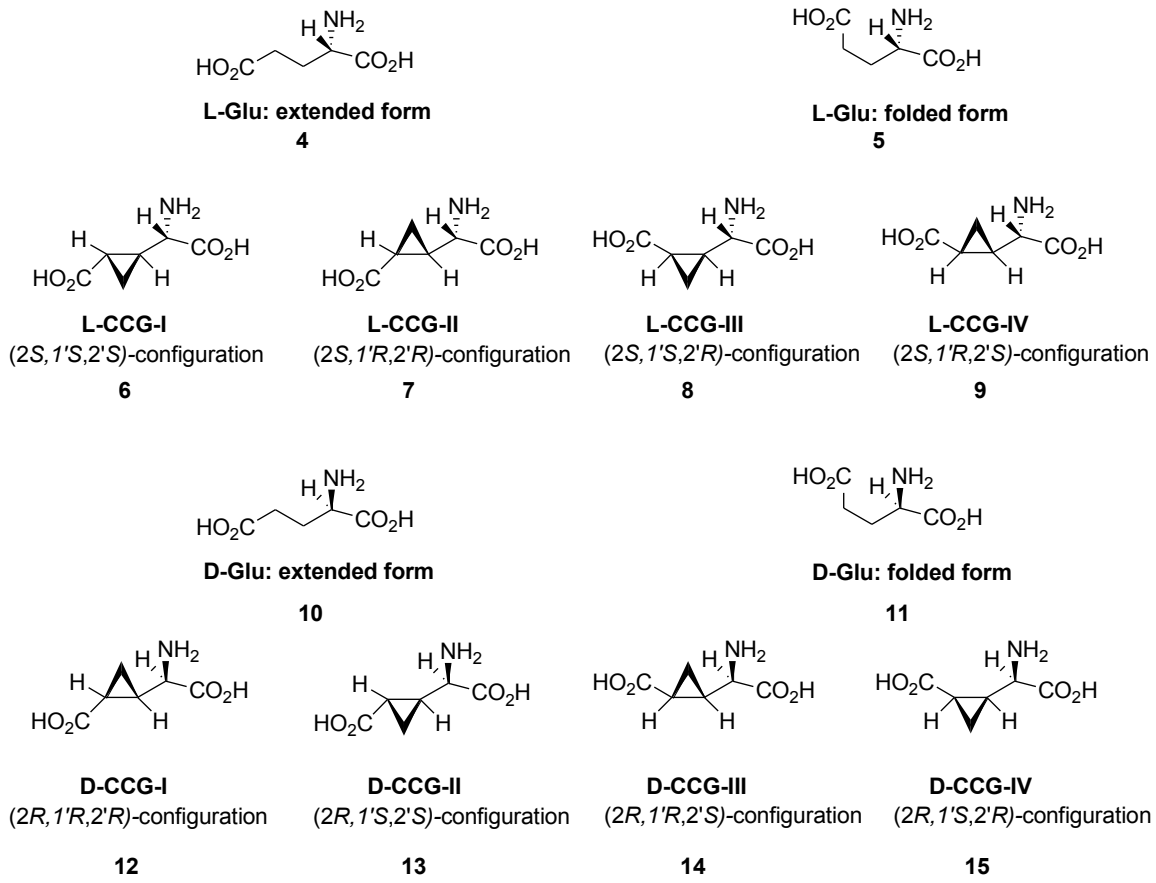


Figure 2

1.1.3. Pharmacology

L-Glutamic acid is known to function at many synapses in the mammalian central nervous system as an excitatory neurotransmitter and is implicated in the construction of memory and early learning's as well as pathogenesis of neuron damage to cause various neuronal diseases.[2] The glutamate receptors are classified as ionotropic type (iGluR's) and metabotropic type (mGluR's). mGlu's are further subdivided into *N*-methyl D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and kainic acid (KA) receptors according to their selective action as agonist. A structure activity study has revealed that the alternation of any of the functional groups of L-Glu results in significant decrease or even loss of its excitatory capability. Thus it was hypothesised that each glutamate subtype requires a particular conformation of glutamate for its selective activation *i.e.* conformational requirement for activity of receptors. In this regard CCG plays a crucial role. Presence of a cyclopropane ring restricts the conformation of glutamic acid either in the extended form or folded form and thus effects

induced by each CCG's will provide information about the steric requirements of the receptors.

Among the four diastereomers of CCG, the extended type was identified as potent and selective agonist of mGluRs. On the other hand, CCG-IV, one of the folded forms exhibited affinity to NMDA receptors. CCG-II and CCG-III are not potent agonist but were inhibitor of glutamate transport system at the excitatory synapses.

1.1.4. Literature Survey

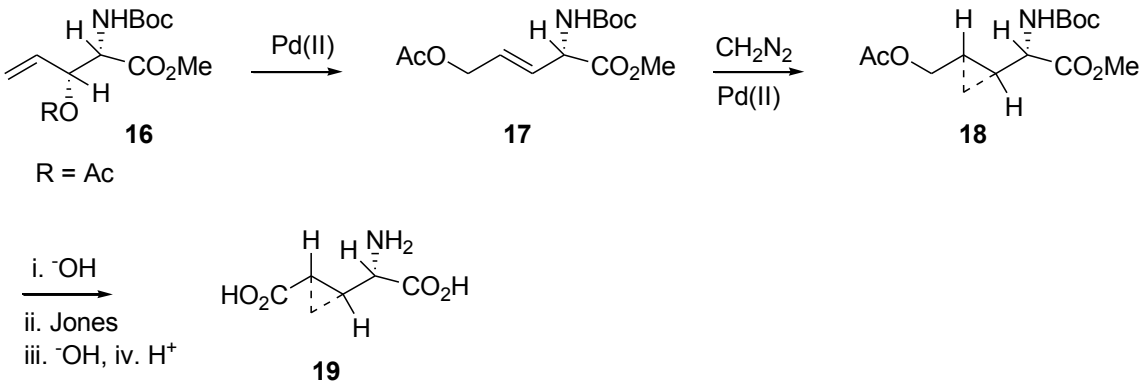
CCGs are useful tools for the investigation of the mechanism underlying the glutamate function as well as the design of useful therapeutic drugs of various neuronal diseases. To study the effect of chemical modification in these compounds will have towards the glutamate receptors as more potent agonist or antagonist behaviour at the synapses, a variety of synthetic protocols have been developed to meet the increasing demand. Obviously the key factor in building these molecules and its derivatives has been the stereocontrolled construction of cyclopropane ring. Here the reported methods have been broadly categorised into different approaches based on cyclopropanation techniques towards the total synthesis of CCG both in racemic as well as chiral form.

1.1.4.1. Metal Catalysed Cyclopropanation

Ohfune's Approach-1

Ohfune et al.[3] reported one of the first syntheses of CCG in 1985 where they efficiently utilised Pd catalysed cyclopropanation of allylic double bond with diazomethane to render the racemic *trans* CCG (**19**).

Scheme 1: Ohfune et al. (*Tetrahedron Lett*. **1985**, *26*, 83-84)

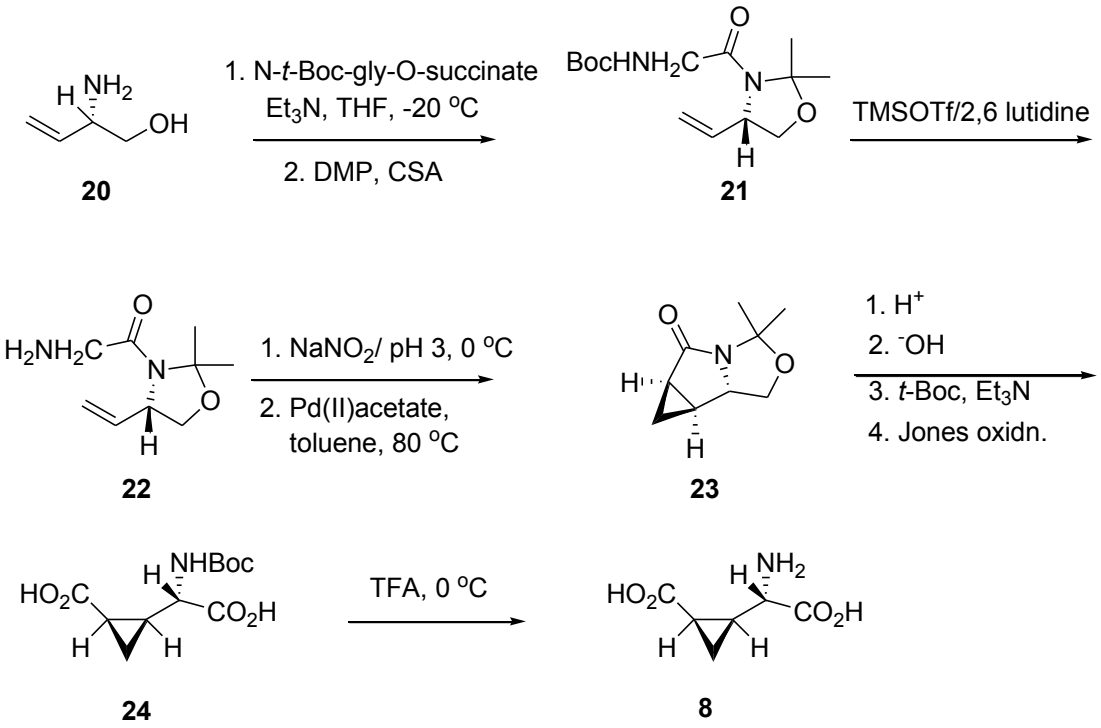


Thus, Pd (II) catalysed [3,3] sigmatropic rearrangement of allylic acetate **16** followed by cyclopropanation by using excess of diazomethane in the presence of same catalyst gave **18**, which on, saponification, oxidation and deprotection furnished *trans* (±) CCG (**19**) (Scheme 1).

Ohfune's Approach 2

In continuation of their effort to construct the cyclopropane ring catalysed by Pd, all the four diastereomers of α-(carboxycyclopropyl) glycine were realised starting from (2*S*)-2-amino-3-butenol *via* inter and intra molecular cyclopropanation with diazocarbonyl compounds.[4]

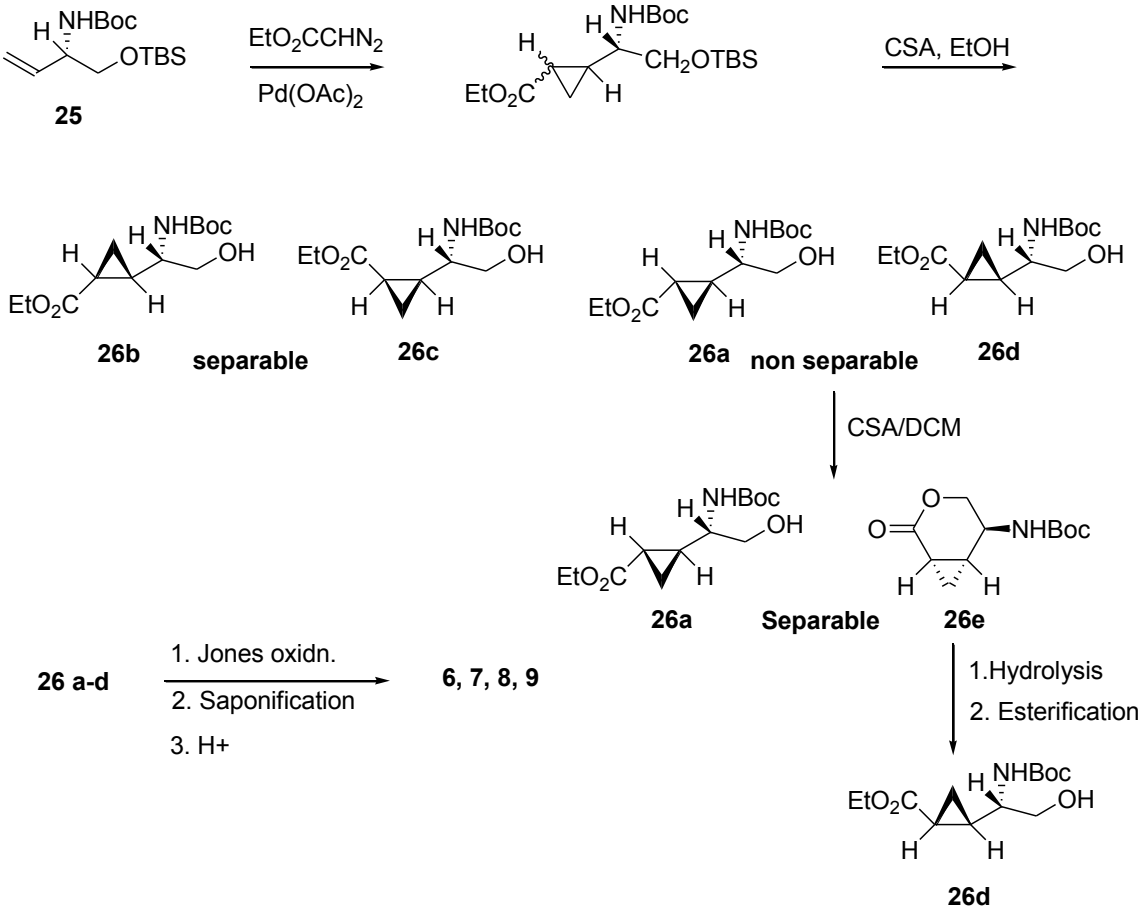
Scheme 2: Ohfune et al. (*Tetrahedron Lett.* **1988**, *29,* 1181-1184)



Accordingly, synthesis of *cis* CCG was accomplished through intramolecular cyclopropanation of the diazoamide. (2*S*)-2-Amino-3-butenol was subjected to react with *N*-*t*-Boc-glycl-*O*-succinate followed by protection with DMP in the presence of CSA to furnish the *t*-Boc protected compound **21**. Removal of Boc with TMSOTf/2,6-lutidine gave the desired amine **22**. Sequential treatment of amine with $NaNO_2$/pH 3 buffer and catalytic palladium (II) acetate yielded the mixture of cycloadduct in 6:1 ratio. The required major isomer was isolated and subjected to acetonide removal followed by

hydrolysis of amide and its protection as *t*-Boc. Jones oxidation of hydroxy group and final removal of amine protection furnished the L-CCG-II (**8**) (Scheme 2).

Scheme 3: Ohfune et al. (*Tetrahedron Lett*. **1988**, *29*, 1181-1184)

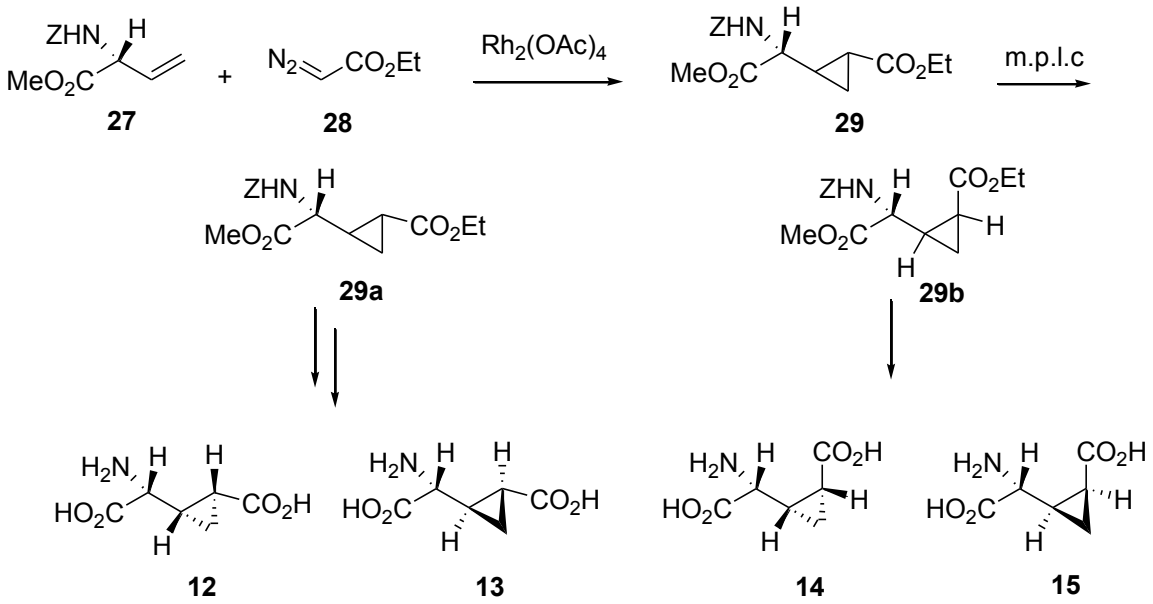


Intermolecular cycloaddition of ethyl diazoacetate catalysed by $Pd(OAc)_2$ was performed over protected compound of **20** to furnish a mixture of protected cyclopropane products in 41 % yield. Two of them, **26b** & **26c**, could easily be separated by medium pressure column chromatography after the removal of silyl protection with CSA. While the other two, **26a** & **26d** having almost same R_f were treated with CSA/DCM to give a separable mixture of **26a** and δ-lactone (**26e**), which were separated by column. Hydrolysis and esterification of **26e** provided **26d**. Jones oxidation of **26a-d** followed by saponification and acid treatment rendered all the four diasteromers of CCG's (**6, 7, 8, 9**) (Scheme 3).

Pellicciari's Approach

Pellicciari introduced a dirhodium (II) tetraacetate catalysed cyclopropanation of *N*-protected-D-vinyl glycine ester with ethyl diazoacetate to give mixture of all four diastereomers of cyclopropane, with the *trans* isomer predominating.[5] MPLC and/derivatisation technique led to the separation of all these isomers of D-CCG's (Scheme 4).

Scheme 4: Pellicciari et al. (*Tetrahedron Lett.* **1990**, *31*, 139-142)

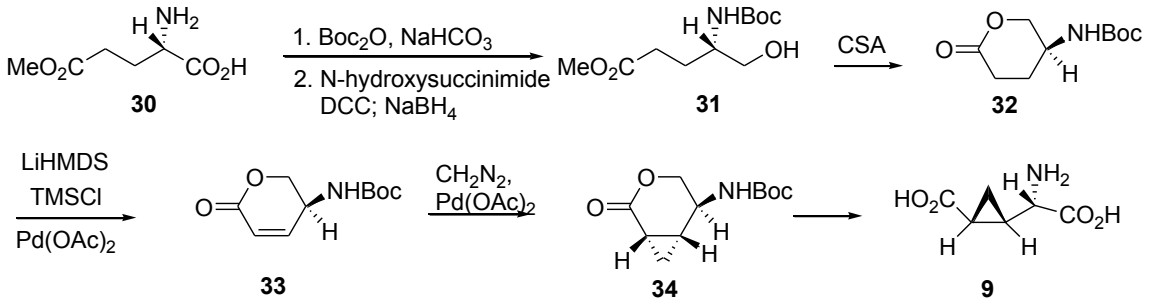


Ohfune's Approach 3

Though the Pd (II) catalysed addition of diazomethane to the carbon-carbon double bond of *E*-olefin provided *trans* CCG in good yield, the addition to *Z*-olefins rendered extremely low yield. Thus cyclopropanation on the cyclic intermediate with diazomethane was examined.

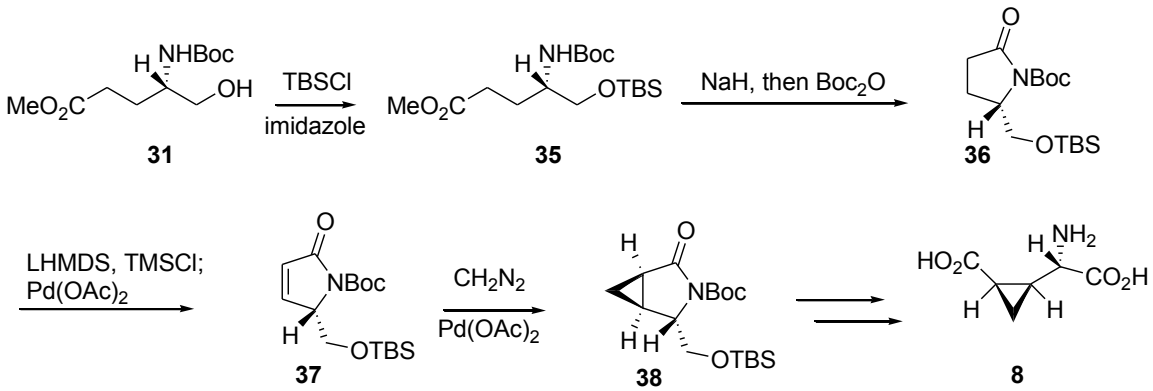
Amine protection of L-glutamic acid γ-methyl ester, followed by cyclisation gave the δ-lactone **32**. The corresponding α, β-unsaturated lactone **33** was prepared by Saegusa oxidation. Reaction of **33** with diazomethane catalysed by Pd (II) acetate gave **34** in good diastereoselectivity. The major isomer arises *via* addition to the face remote to the bulky NHBoc substituent. The bicyclic cyclopropyl lactone was taken forward to L-CCG-IV[6] (Scheme 5).

Scheme 5: Ohfune et al. (*J. Org. Chem.* **1991**, *56*, 4167-4176)



L-CCG-III was realised starting from glutamic acid. Protection of hydroxy group of **31** as the OTBS derivative **35** followed by cyclisation on treatment with NaH rendered the γ-lactam **36** on which the Boc protection was reintroduced. The required double bond was introduced by selenylation-deselenylation protocol.

Scheme 6: Ohfune et al. (*J. Org. Chem.* **1991**, *56*, 4167-4176)



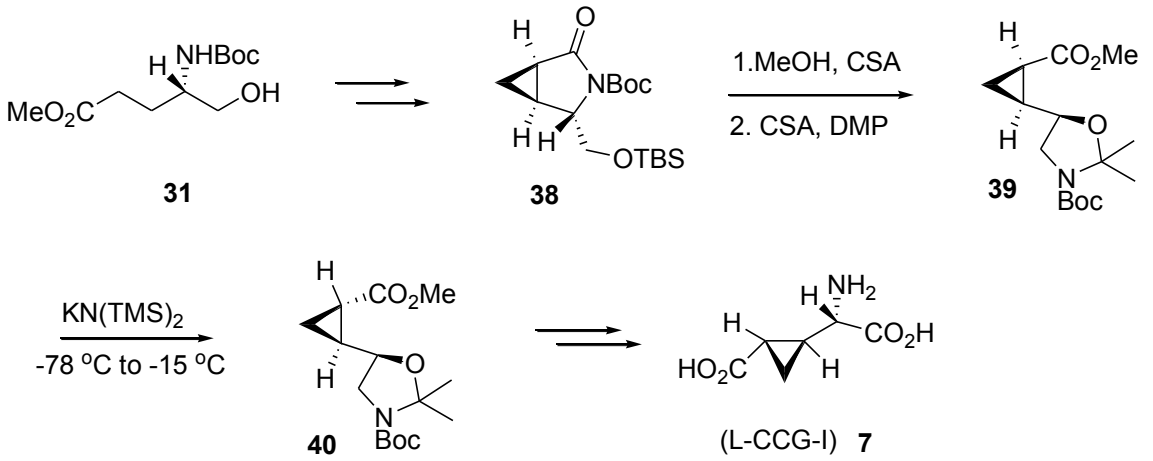
Cyclopropanation of **37** by treatment with diazomethane in the presence of Pd $(OAc)_2$ gave quantitative yield of cycloproduct **38** in 9:1 diastereomeric mixture. The predominant product arised due to approach of the Pd-carbene species on the face opposite to the bulky *t*-butyldimethylsilyloxymethylene substituent. Hydrolysis, Jones oxidation and cleavage of the protecting group gave L-CCG-III (**8**)[6] (Scheme 6).

Ohfune's Approach 4

The study of action of $[KN(TMS)_2]$ on cyclopropyl ester anion generated from *cis* ester to deliver the *trans* isomer quantitavely paved the path to yet another synthesis of L-CCG-II. Thus the bicyclic lactam **38** obtained from glutamic acid was subjected to methanolysis followed by acetonide protection to furnish the *cis* ester **39**. Deprotonation

with bis(trimethylsilyl)amide (-78 ^{o}C to -15 ^{o}C) followed by treatment with acetic acid gave the *trans* isomer exclusively. This *trans* ester was transformed into **7** through routine organic transformations[7] (Scheme 7).

Scheme 7: Ohfune et al. (*Synlett.* **1993**, 919-920)

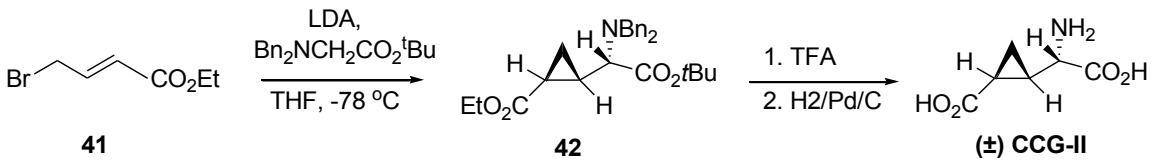


1.1.4.2. Cyclopropanation *via* MIRC

Yamaguchi's Approach

A concise and stereoselective synthesis of (±)-CCG-II was accomplished by Yamaguchi et al. wherein they have employed a Michael type addition of lithium enolate of *N*,*N*-dibenzylglycinate to β-substituted α,β-unsaturated ester previously described by Joucla et al.[8] to construct the cyclopropyl derivative. Thus the anion generated from glycine equivalent at –78 ^{o}C employing LDA as the base was subjected to react with 4-bromoethylcrotonate **41** to render the *threo* selective formation of cyclopropane **42**. Further functional group transformation led to (±)-CCG-II[9] (Scheme 8).

Scheme 8: Yamaguchi et al. (*Chem. Lett.* **1990**, 377-380)



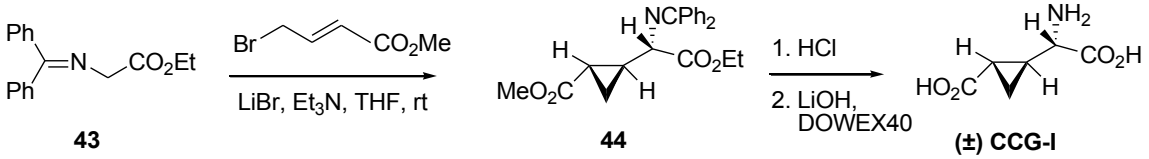
Chavan's Approach

Chavan et al. made a keen study towards the reactivity profile of Schiff's base **43** with crotonate and bromocrotonate, which take different reaction course depending upon the

substituent on the imine. This study led to one of the mildest condition of cyclopropane construction leading to the synthesis of (±)-CCG-I.[10]

Generation of a glycine anion equivalent by treating the diphenylimine Schiff's base **43** of glycine with LiBr/Et_3N in THF and subjecting it to react with 4-bromomethylcrotonate at room temperature led to formation of cyclopropane *via* Michael induced ring closure pathway. Further removal of amine protection, saponification and passage through a H^+ resin rendered (±)-CCG-I (Scheme 9).

Scheme 9: Chavan et al. (*Tetrahedron Lett.* **1996**, *37*, 2857-2858)

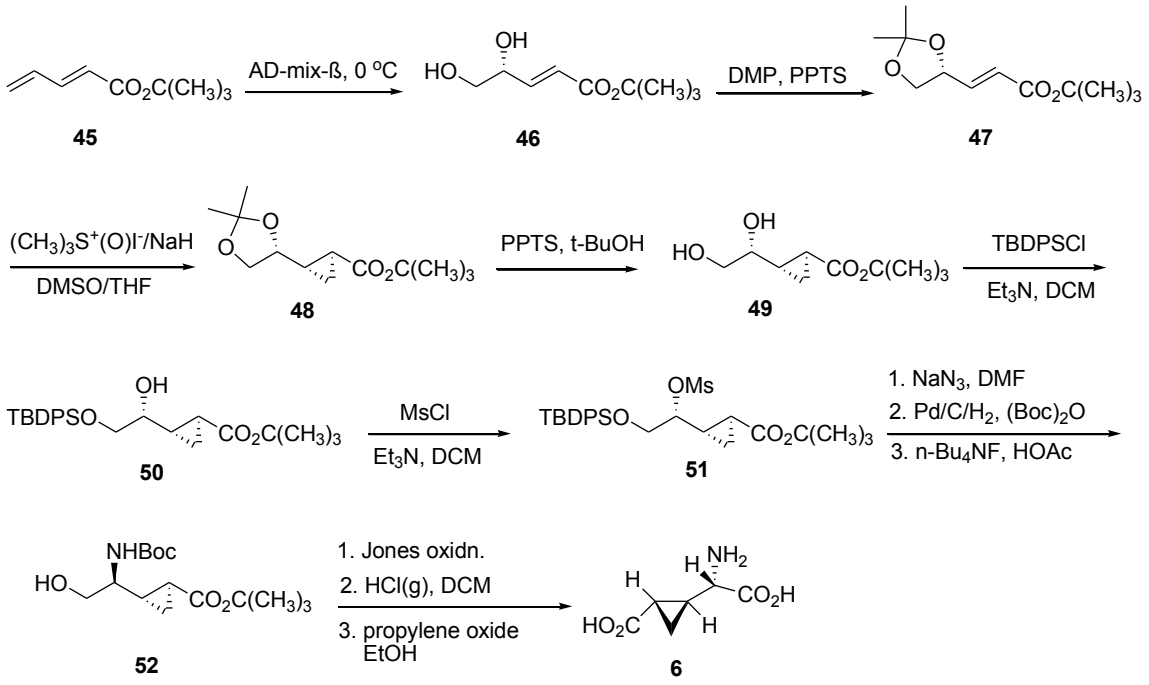


1.1.4.3. Sulfoxonium Ylide Cyclopropanation

Ma's Approach

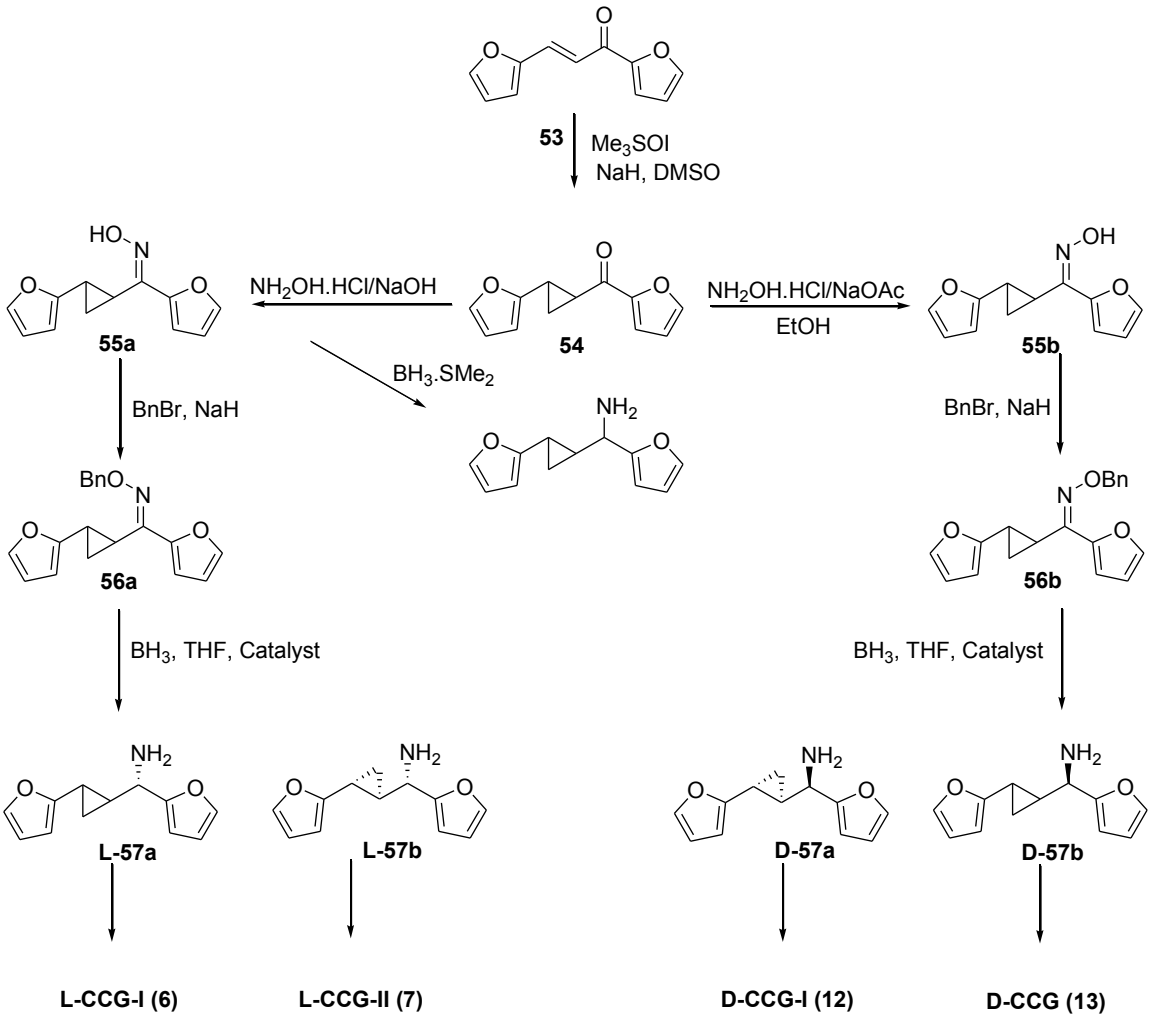
Ma and coworkers designed a dimethysulfoxonium ylide mediated cyclopropantion of a chiral electron deficient alkene towards the synthesis of L-CCG-I.

Scheme 10: Ma et al. (*Tetrahedron Lett.* **1997**, *43*, 7599)



The diene **45** obtained from coupling of acrolien and Wittig Horner reagent, was subjected to asymmetric dihydroxylation to furnish the diol **46**. The diasteroselective addition of dimethylsufoxonium methylide to protected alkene **47** afforded the cyclopropane **48** in 1:19 ratio. Removal of isopropylidene, and selective protection of primary hydroxy group followed by activation of secondary hydroxy group and its subsequent replacement, with inversion of configuration, with azide rendered the product corresponding to azide. Reduction of azide into amine and its protection as Boc followed by removal of TBDPS group and Jones oxidation and other functional group manipulation provided L-CCG-I in 14% overall yield[11] (Scheme 10).

Scheme 11: Demir et al. (*Tetrahedron: Asymmetry* **1998**, *9*, 1035-1042)



Demir's Approach

Demir et al. described a sulfoxonium ylide mediated cyclopropanation and enantioselective oxime reduction towards the synthesis of CCG. Treatment of *trans*-1,3-

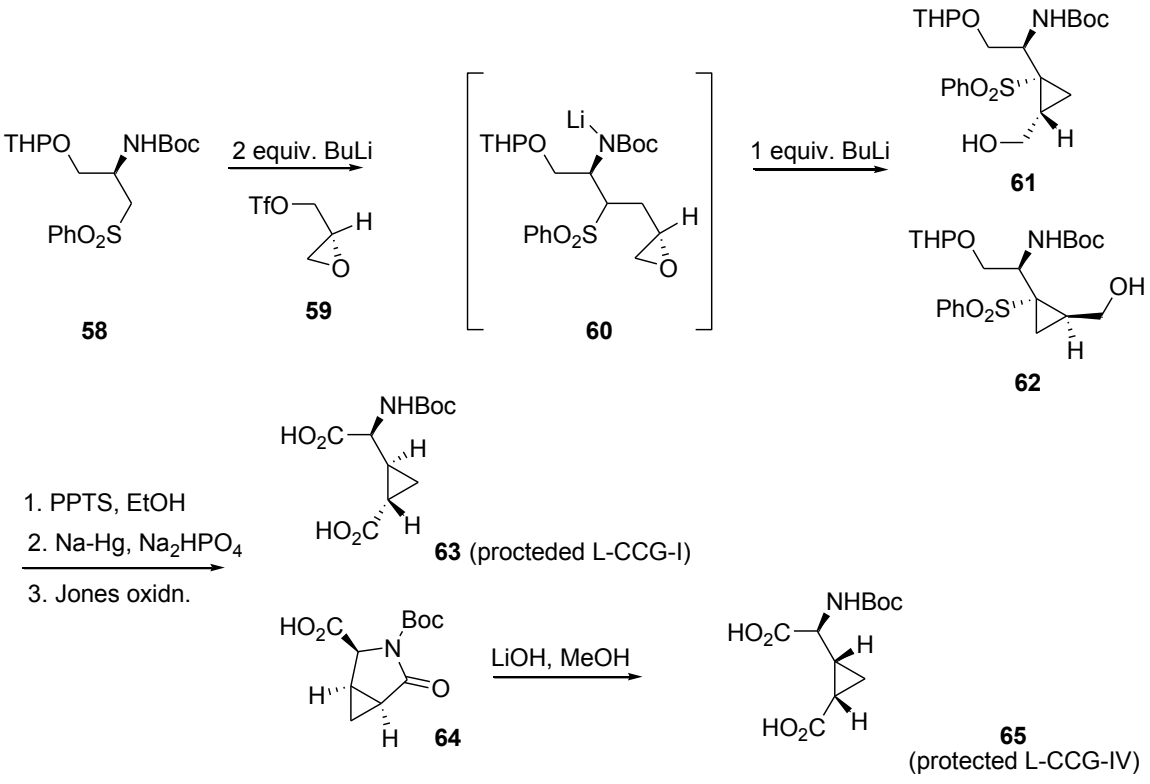
di(2-furyl) propenone with trimethylsulfoxonium iodide gave the cyclopropylketone **54** in good yield. It was converted predominantly into *E* (**55a**) or *Z* (**55b**) oxime selectively by reacting either with $NH_2OH.HCl/NaOH$ or $NH_2OH.HCl/NaOAc$-EtOH respectively. The oxime reduction with $BH_3.SMe_2$ in THF afforded the *rac*-amine. For the synthesis of optically active amino acids the oximes were converted to *O*-benzyloxime ethers using NaH and benzyl bromide in high yields. Enantioselective reduction of *E*-oxime was achieved by $BH_3.SMe_2$ in the presence of oxaborolidine catalyst prepared from chiral amino alcohols. The reduced products were separated by flash column chromatography and the oxidations of furan rings were carried out with ozone at –78 ^oC to furnish amino acids L-CCG-I and L-CCG-II[12] (Scheme 11).

1.1.4.4. Miscellaneous Approaches

Sasaki's Approach

Central to their synthesis was the generation of cyclopropyl moiety by addition of excess of BuLi to already generated β-epoxy sulfone, which undergoes an intramolecular epoxide ring opening.

Scheme 12: Sasaki et al. (*Tetrahedron Lett.* **1995**, *36*, 3149-3152)

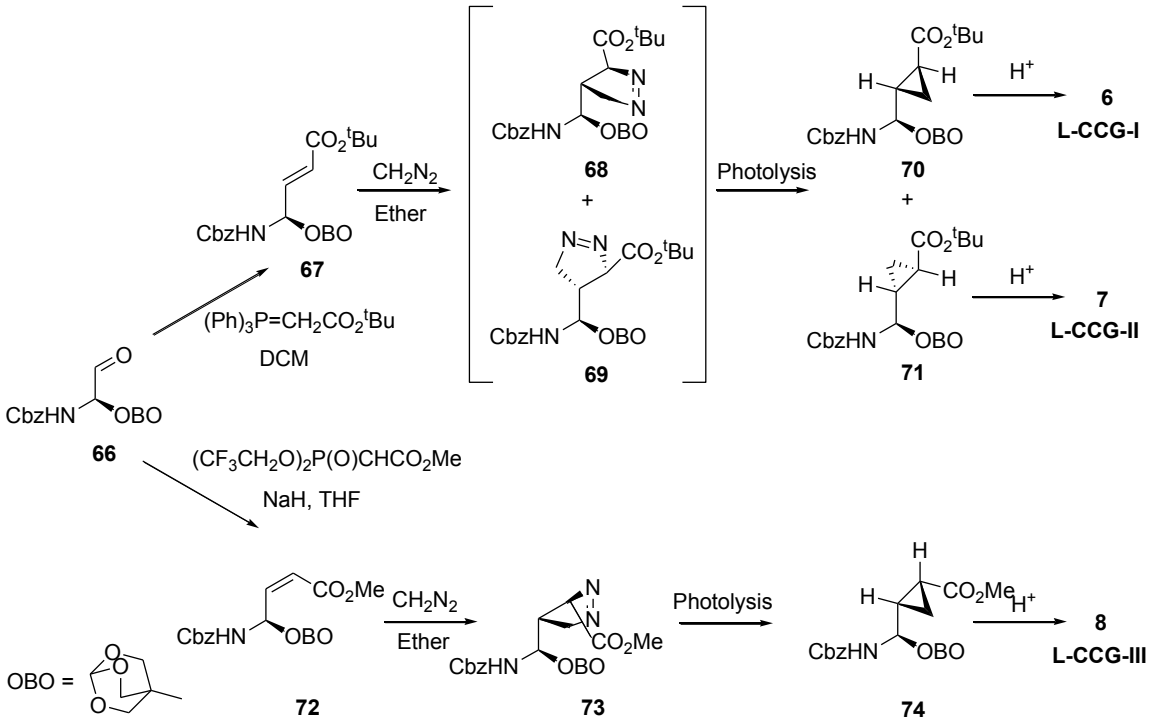


Thus the compound **60** obtained from the reaction of dilithiated species of sulfone **58** with (2*R*)-glycidyl triflate **59** was treated further with one more equivalent of BuLi to generate a new sulfonyl carbanion which led to cyclopropyl carbinols **61** and **62**. Hydrolysis of THP ether, reductive desulfonylation and Jones oxidation gave a mixture of Boc protected (2*S*,1'*R*,2'*S*) **63** and lactam **64**. Base hydrolysis of lactam gave the Boc protected *cis* isomer **65**[13] (Scheme 12).

Ortuño and Lajoie's Approach

Lajoie et al. described a non catalysed stereocontrolled 1,3-dipolar cycloaddition of diazomethane on the chiral *E* or *Z*-3,4-L-didehydroglutamate. The stereochemical control was provided by the presence of the bulky OBO function.

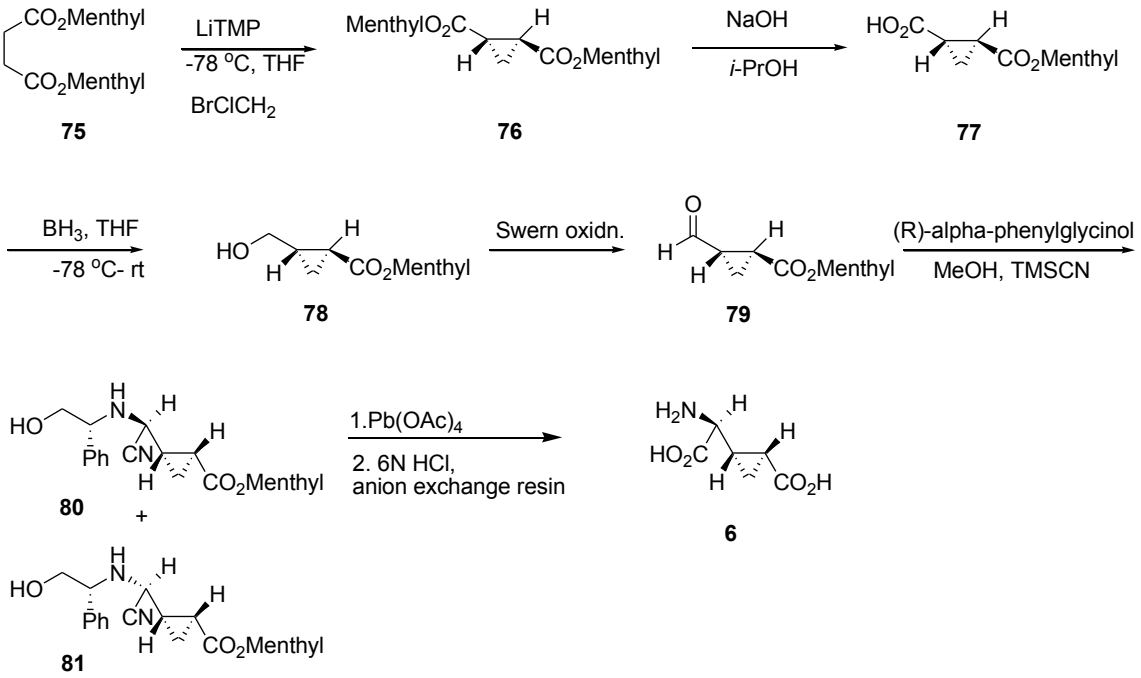
Scheme 13: Lajoie et al. (*J. Org. Chem.* **1999**, *64*, 8958-8961)



The *E*-3,4-L-didehydroglutamte was obtained by the olefination of the Cbz-L-Ser-aldehyde-OBO **66** with Wittig Horner reagent. Addition of ethereal diazomethane gave a mixture of highly unstable pyrazone **68** and **69**, which was subjected to photolysis condition to give 6:1 mixture of *syn*-and *anti-trans* cyclopropane derivatives, **70** and **71**, which were separated by chromatography and recrystallisation. Removal of all the protecting groups with HCl rendered the cyclopropane CCG-I (**6**) and CCG-II (**7**).

Similarly the *Z*-3,4-didehydroglutamate was obtained by treatment of serine aldehyde with $Na(CF_3\text{-}CH_2O)_2P{=}CHCO_2Et$ as 9:1 *Z*:*E* mixture. Here treatment with ethereal diazomethane rendered the pyrazoline **73** exclusively, which was further, converted to CCG-III (**8**) through same sequence of reactions[14] (Scheme 13).

Scheme 14: Pajouhesh et al. (Tetrahedron*: Asymmetry* **2000**, *11*, 4537)



Pajouhesh's Approach

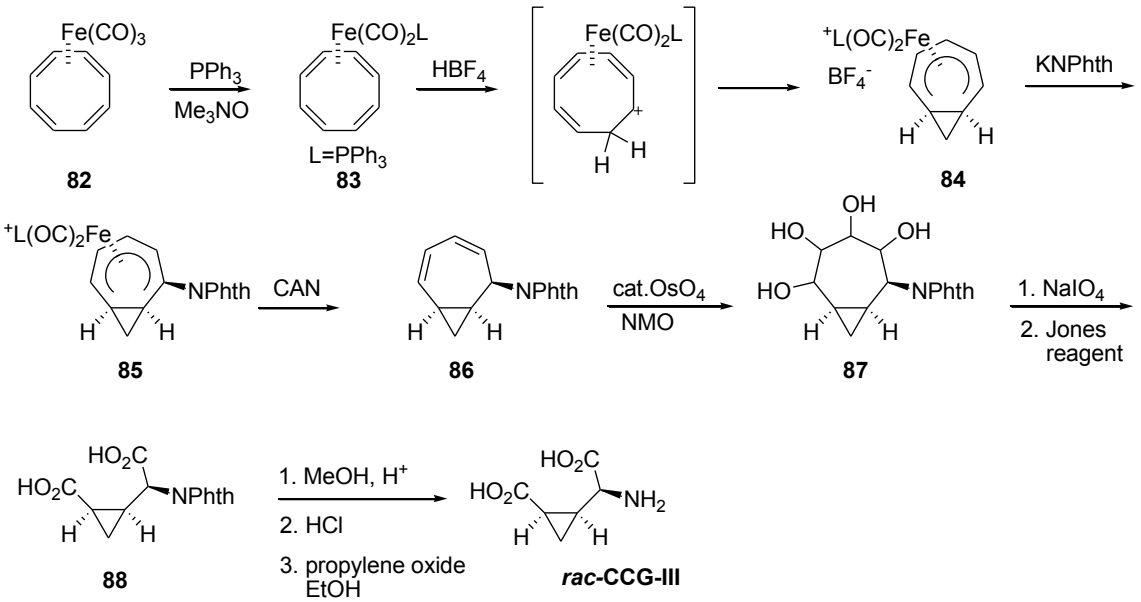
A very convenient synthesis of L-CCG-I was achieved starting from readily available (-)-dimenthyl (1*S*,2*S*)-cyclopropane-1,2-dicarboxylate **76**. Cyclopropyl ester **76** was obtained by alkylation of (-)-dimenthyl succinate **75** with $BrClCH_2$. The diester of **76** was partially hydrolysed, reduced and oxidized to aldehyde **79** under Swern oxidation conditions. Asymmetric Strecker reaction of aldehyde using (*R*)-α-phenylglycinol followed by treatment of the Schiff's base with TMSCN delivered the α-aminonitrile derivates **80** and **81** (9:1), which were separated by column chromatography. Major isomer **80** was subjected to oxidative cleavage followed by hydrolysis, which completed the synthesis of L-CCG-I[15] (Scheme 14).

Donaldsons's Approach

An organoiron methodology was developed by Donaldson et al. for the stereoselective route to *cis* CCG. Substitution of one of the carbonyl of (cyclooctatetarene)$Fe(CO)_3$ **82**

with triphenylphosphine in the presence trimethyl amine *N*-oxide furnished **83** which on protonation afforded the bicyclic cation **84**. Regioselective addition of potassium phthalimide in ether to **84** gave **85** which on oxidative decomplexation with CAN gave bicyclo[5.1.0]octa-2,4-diene (**86**). Cleavage of cycloheptadiene ring was accomplished by exhaustive hydroxylation with cat. OsO_4/NMO to give a mixture of partially separable diastereomeric tetrols **87**. Glycol cleavage of the mixture of tetrols rendered the aldehyde, which was subjected to further oxidation with Jones reagent to furnish the diacid **88**. The acid was purified by esterification, as the diacid was difficult to purify in column and then was subjected to hydrolysis with HCl followed by treatment of HCl salt with propylene oxide to give *rac*-CCG-III[16] (Scheme 15).

Scheme 15: Donaldson et al. (*Tetrahedron Lett.* **2002,** *43***,** 4541)



A modest diastereoselective nucleophilic addition of phthalimide was achieved using a chiral phosphine ligated (bicyclo[5.1.0]octadienyl)-iron cation which was carried forward to CCG-III in 38% ee.[17]

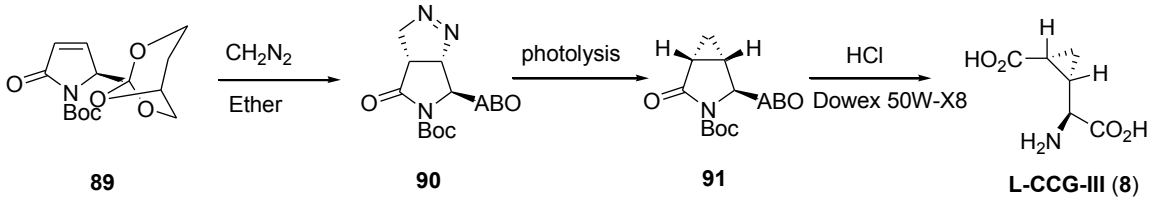
Oba's Approach

A stereocontrolled approach to L-CCG was described using 3,4-didehydro-L-pyroglutamate as the chiral template and bulky 2,7,8-trioxabicyclo[3.2.1]octyl group (ABO ester) as the stereodirecting carboxyl-protecting group during cyclopropanation with diazomethane. Stereospecific cyclopropanation was carried out by 1,3-dipolar

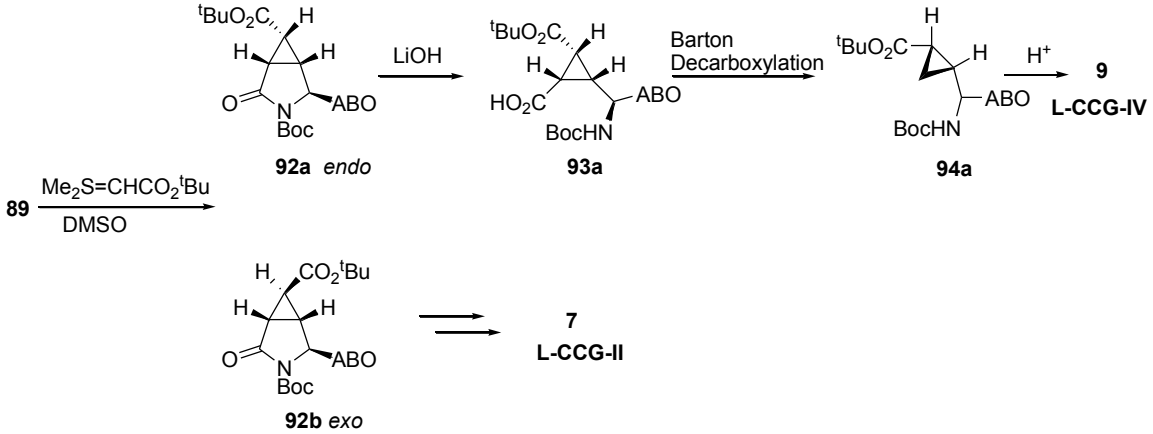
cycloaddition of diazomethane to the unsaturated orthoglutamate **89** followed by photolysis of pyrazoline **90** resulting in exclusive formation of cycloadduct **91**. Exclusive formation of one product indicates the addition of diazomethane to the olefin opposite to bulky ABO ester. Acidic hydrolysis of the cyclopropane and ion exchange treatment rendered L-CCG-III (**8**)[18] (Scheme 16).

An alternation in the 3,4 methanoglutamic acid framework by change in cyclopropanation of the olefin in **89** with sulfur ylide to render the γ-carboxyl group in the cyclopropane ring followed by decarboxylation of the original carboxyl group included in the pyroglutamate framework delivered L-CCG-IV and L-CCG-II.

Scheme 16: Oba et al. (*Tetrahedron* **2005**, *61*, 8456-8464)



Scheme 17: Oba et al. (*Tetrahedron* **2005**, *61*, 8456-8464)



Thereby, treatment of **89** with *tert*-butyl dimethylsulfuranylidene acetate gave slightly excess of *endo* product, giving 67:33 mixtures of **92a** and **92b**. The compounds were separated by column chromatography and chemoselective ring opening of lactam **92a** with LiOH gave crude **93a**. Barton decarboxylation of **93a** using mercaptopyridine *N*-oxide rendered the fully protected cylopropane **94a**. Final deprotection on treatment with HCl gave the L-CCG-IV (**9**). On the other hand the extended form of CCG (**7**) was realised by treatment of the *exo* product **92b** under similar conditions (Scheme 17).

1.1.5. References

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Chapter 1 Section 2

Enantioselective Synthesis of L-CCG-I

1.2.1. Introduction

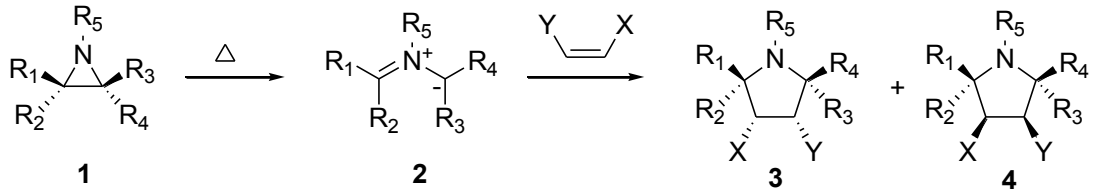
Since the present work deals with the reaction of azomethine ylides, it is pertinent to discuss the methods of their generation and activity of these compounds.

Azomethine ylides are the class of 1,3-dipoles, which has attracted considerable interest in the scientific arena due to its ability to deliver diverse products. It can have different fate depending on the reaction conditions, stereo chemical congestion and the stability of the ylide. In the absence of dipolarophile/acceptor it readily undergoes cyclisation to render the aziridine whereas in the presence of dipolarophile relatively unstable ylieds could be trapped as its cycloadducts, which has been successfully utilised in the synthesis of various complex organic molecules. Sometimes high steric congestion leads to simple alkylated product or take a diverse route depending on the electrophile.
Azomethine ylides are planar 1,3-dipoles consisting of a nitrogen and two sp^2 carbon. Owing to its high synthetic utility numerous methods have been developed for its generation.

1.2.1.1 Generation of Azomethine Ylides

Among others one of the earliest approach of generation of azomethine ylides was through the opening of aziridines.[1] Huisgen et al.[2] described the generation of azomethine ylide *via* thermolysis or photolysis of aziridines. Thermolysis gives *anti* ylide *via* a conrotatory opening whereas under photolytic condition disrotatory opening furnishes *syn* ylide. The limiting factor being the presence of effective anion stabilising group next to the nitrogen functionality for the ring opening to take place (Scheme1).

Scheme 1

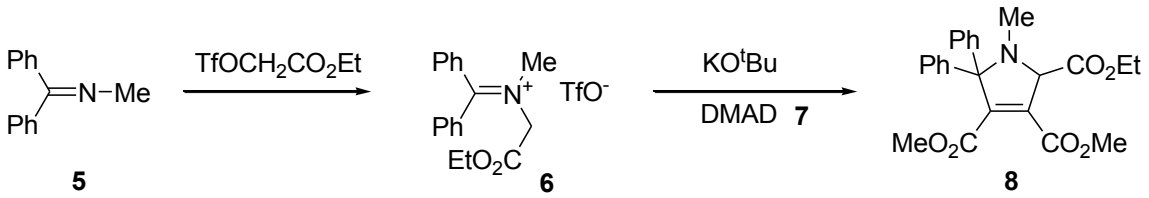


1 **2** **3** **4**

One of the most straightforward approaches to these ylides is the one involving base deprotonation of iminium salt. Deyrup[3] extensively utilised this technique for generation of azomethine ylides. Alkylation of benzophenone imine with methyl fluorosulfonate gave the iminiun salt, which was deprotonated with a variety of base to render the electrocyclic closure product but could not be trapped with any dipolarophiles

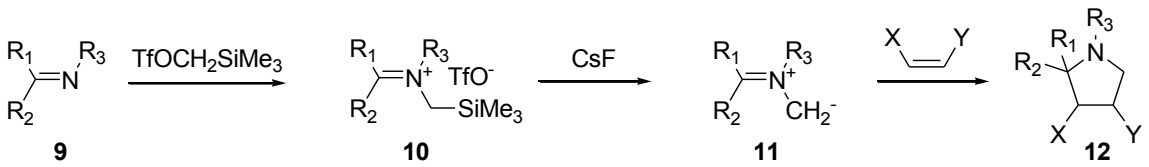
to deliver the cycloadduct. In the same line ester substituted iminium salt **6** on deprotonation with NaH or KO*t*-Bu rendered the azomethine ylide, which was successfully trapped by dimethylacetylene dicarboxylate (**7**) (DMAD) resulting in *N*-methyl pyrrolidine **8** (Scheme 2). This methodology was extended to aliphatic amines too.[3b]

Scheme 2



Desilylation[4] is especially useful for generation of non-stabilized azomethine ylides, which can be trapped by dipolarophiles. Sequential alkylation of imine **9** with $CF_3SO_3CH_2SiMe_3$ followed by transient ylide **11** generation from the immonium salt **10** with fluoride ion and its subsequent trapping with dipolarophiles render the cycloadduct **12** (Scheme 3).

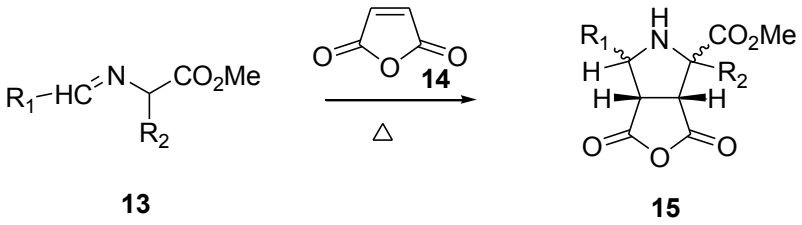
Scheme 3



This method is applicable where regiochemically different ylides could result in presence of base or the decomposition of dipolarophiles results under extreme conditions. It permits *in situ* trapping of unstable ylides by sensitive acceptor.

Amino acid derived imines undergo 1,2-prototropy under thermal condition to generate azomethine ylide[5] (Scheme 4). The formation of ylide is sensitive to the *p*Ka of the α hydrogen and the basicity of the imine nitrogen and thus on the imine structure. Thus imine **13** undergoes 1,3-dipolar cycloaddition on heating in a non-polar solvent, such as benzene, with maleic anhydride (**14**).

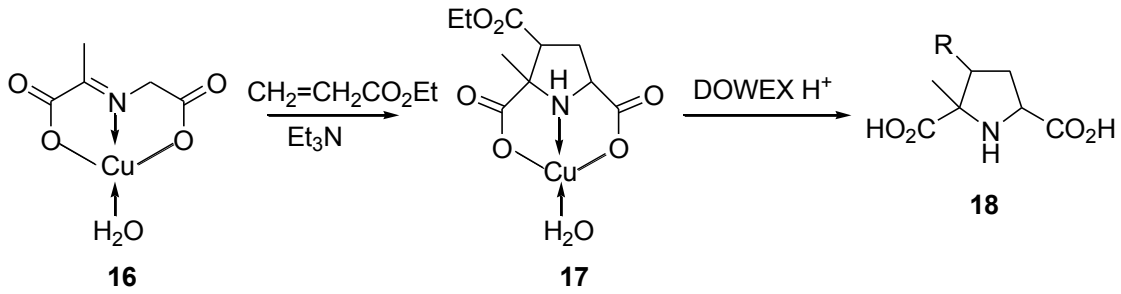
Scheme 4



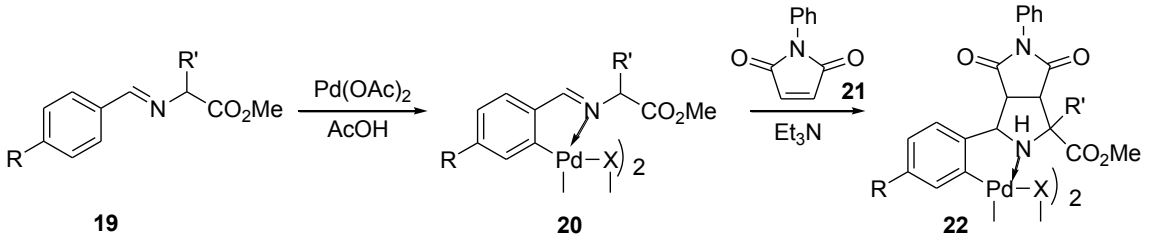
Related to 1,2-prototropy processes for the generation of azomethine ylide are the process in which metallo-azomethine ylides are formed the only difference being a metal ion in place of H atom. It was demonstrated that metal complexes of imine of amino acids and ketone/aldehyde possessing an additional coordinating group when treated with Lewis acid/metals and weak base leads to the generation of metallo-azomethine ylides which can take different reaction course depending on the conditions employed.

Casella[6] generated azomethine ylide from copper complex **16** using triethylamine as the base and trapped it with dipolarophile to furnish the cycloadduct **17** as single diastereomer (Scheme 5).

Scheme 5: Casella et al. (*Synthesis* **1979**, 150)



Scheme 6: Grigg et al. (*J. Chem. Soc., Chem. Comm*. **1982**, 384)

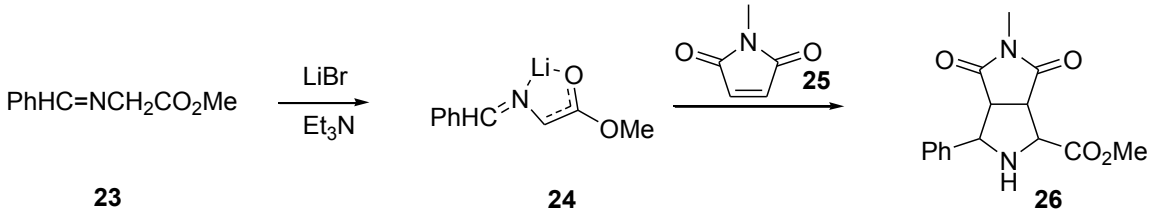


Grigg[7] generated ylide from palladium complex **20** prepared from substituted benzaldehyde Schiff's base **19** and palladium acetate, using Et_3N as the base. Trapping the azomethine with *N*-phenylmaleimide (**21**) furnished cycloadduct **22** (Scheme 6).

Subsequently various Lewis acid such as Ag, Tl, Li, Mg, Co, Ti, Zn, Sn in conjunction with bases as Hunig's base (DIEA), Et_3N, DBU, TMEDA, guanidine derived bases have been studied for metallo-azomethine generation.

Tsuge et al.[8] reported the generation of azomethine ylide of Schiff's base **23** with LiBr as the Lewis acid and Et_3N as the base in THF which was captured by *N*-methylmaleimide (**25**) to lead to an excellent yield of the cycloadduct **26** in exclusive *syn* and *endo* selectivity as a result of Li chelation which was evident from loss of selectivity in the absence of LiBr (Scheme 7).

Scheme 7: Tsuge et al. (*J. Org. Chem.* **1988,** *53*, 1384)



Initially it was proposed that the reaction proceeds through either of the two approaches (i) the concerted cycloaddition of *N*-lithiated azomethine ylide or (ii) tandem Michael-imine addition of lithium enolate (fig. 1).

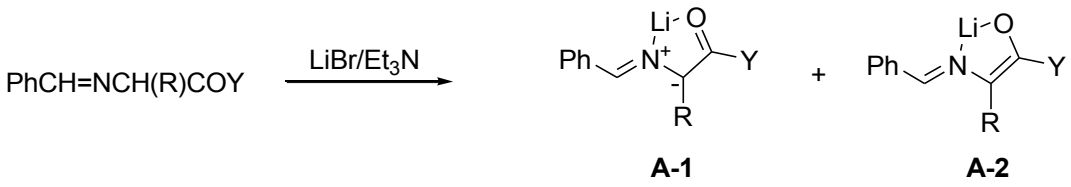
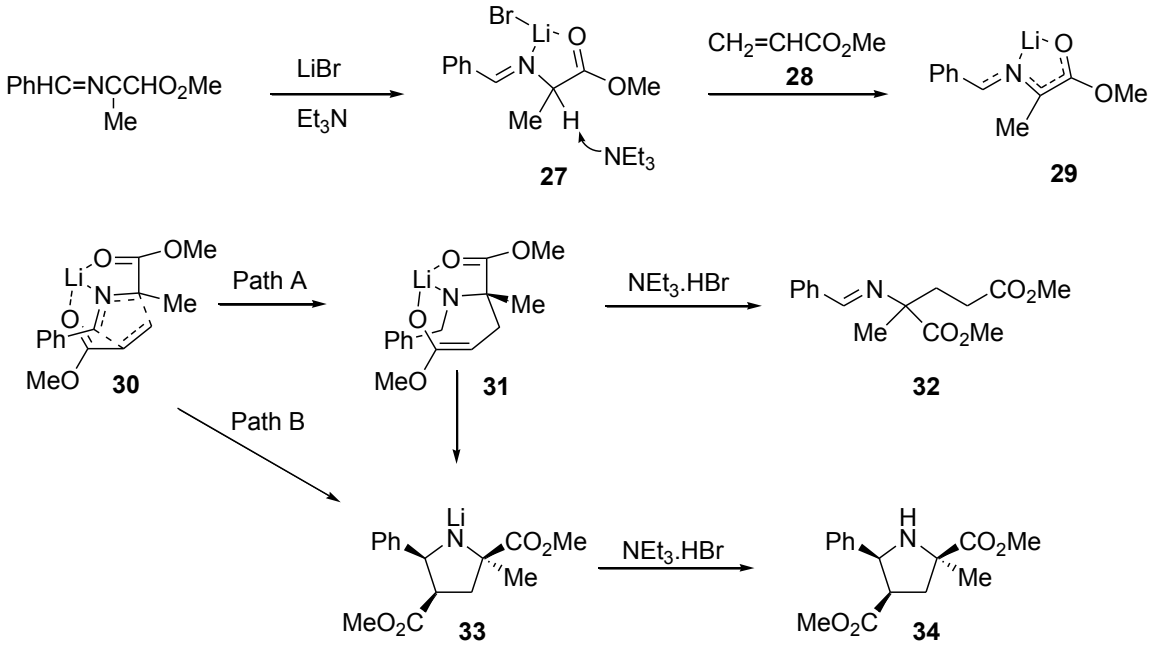


Figure 1

Later on an alternative mechanism was proposed on investigating the reaction of methyl 2-(benzylideneamino) propanoate and methyl acrylate (**28**) as the substrate of choice in the presence of Et_3N and LiBr.[9] It was observed that a 5:1 mixture of cycloadduct **34** and Michael adduct **32** were produced under variety of reaction time and temperature. Even in the midst of the reaction the ratio was same exemplifying kinetically controlled formation of transition state. On the basis of above result it was hypothesised that lithium bromide coordinates with imine nitrogen so that the α-hydrogen of **27** can be easily deprotonated with a weak base such as triethylamine to generate lithiated intermediate. This intermediate equilibrates between structure **A-1** and **A-2** (fig. 1) the only difference

being the lithium-heteroatom bond indicating little if any energy difference between them. An intermediate structure **29** could be proposed which exhibit properties both of *N*-lithiated azomethine ylide and ester enolate.

Scheme 8: Tsuge et al. (*Bull. Chem. Soc. Jpn.* **1989**, *62*, 869)



This intermediate structure could be thought to be involved in interaction with the acceptor **28** giving rise to structure **30** which could collapse through path A where formation of bond at β carbon precedes that at α carbon (**31**). Ready quenching gives to predominant Michael adduct **32,** which competes with cycloadduct formation *via* intramolecular cyclisation. The direct formation of **33** may also be involved (Path B) (Scheme 8).

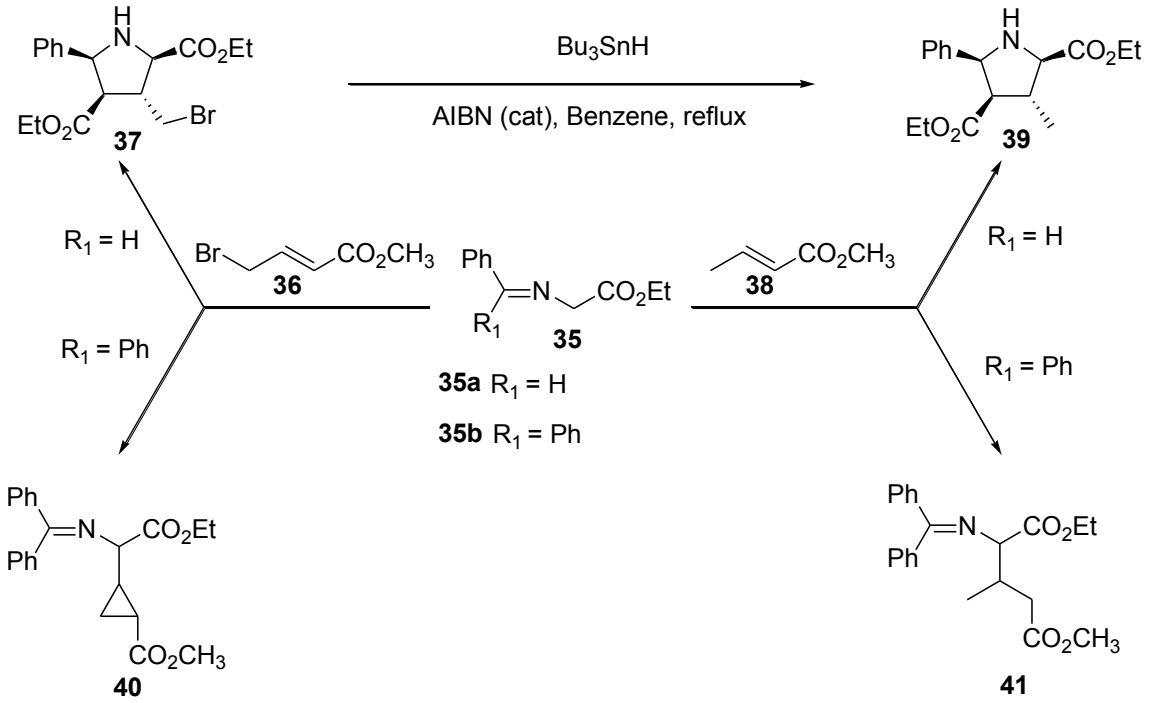
The reaction condition such as catalyst concentration, base employed, dilution effect or availability of proton source determine the final course of reaction leading to Michael adduct or cycloadduct.

Chavan et al.[10] during their study towards alkylation of glycine Schiff's base with methyl bromocrotonate illustrated the different reactivity profile of differently substituted imine towards generation of azomethine ylide and its subsequent reaction with the acceptor.

When methyl 4-bromocrotonate (**36**) was subjected to react with 1,3-dipole generated by the action of $LiBr/Et_3N$ on benzaldehyde Schiff's base **35a**, it led to cycloadduct **37**, which was confirmed by its reduction into **39** with Bu_3SnH. Similarly pyrolidine **39** was obtained by 1,3-dipolar cycloaddition with methylcrotonate **38** and **35a**. However when

methyl 4-bromocrotonate (**36**) was subjected to react with diphenylimine Schiff's base **35b** using LiBr/Et_3N, 1,3-dipolar cycloaddition was not observed, instead a product corresponding to cyclopropane **40** was realised. A subtle change in imine functionality in the Schiff's base of glycine and its subsequent reaction has a pronounced effect on the reaction pathway. On further investigation the reaction of Schiff's base **35b** with methylcrotonate **38** under the reaction condition furnished only the Michael adduct **41** (Scheme 9).

Scheme 9: Chavan et al. (*Tetrahedron Lett*. **1996**, *37***,** 2857)

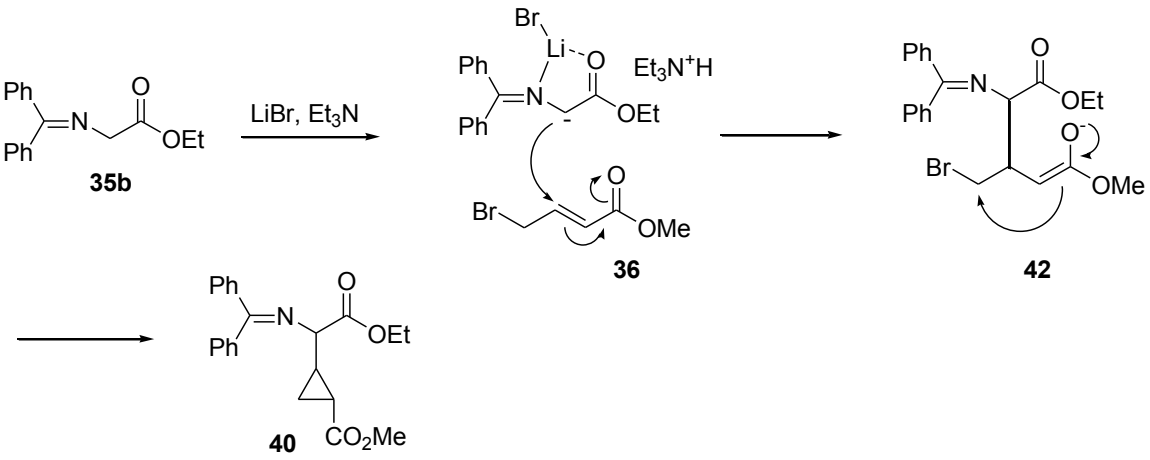


The reaction of Schiff's base with γ-substituted α,β-unsaturated acid leading to cyclopropyl product could be termed as Michael Induced Ring Closure (MIRC) reaction. MIRC is defined as " a general set of transformations which are initiated by a conjugate addition to an α,β-unsaturated ester or ketone to produce an enolate which subsequently undergoes intramolecular ring closure".[11]

The tight chelation of LiBr with imine nitrogen and carbonyl oxygen renders the proton acidic enough to be knocked off using weak base such Et_3N. The generated anion can remain as an enolate or as azomethine ylide. An in between structure could be defined as proposed by Kanamesa[9] which posses characteristic of both. When this is subjected to react with γ-bromo α,β-unsaturated ester, the anion attacks the neucleophilic β-carbon to

initially gives rise to the Michael adduct **42**. Due to the steric congestion imposed by the presence of an extra phenyl group, the moiety could not go for 1,3-dipolar cycloaddition instead in presence of a good leaving group when the electon pair returns back it kicks off the bromo to furnish the cyclised product **40**. Schematic presentation of the reaction pathway is described in scheme 10.

Scheme 10



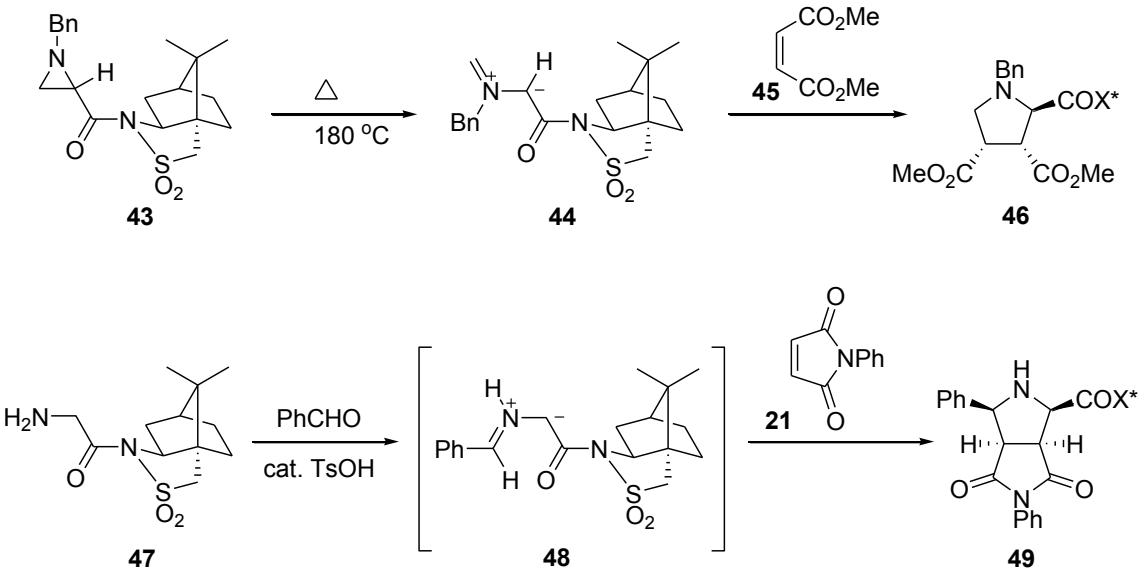
1.2.1.2. Asymmetric Induction in Cycloaddition/Michael Addition

Stereoselectivity in the reaction of an azomethine ylide with dipolarophile /acceptor can be achieved in various ways (i) chiral azomethine ylide (ii) chiral dipolarophile/acceptor or (iii) chiral catalyst. A number of reports are available in literature where moderate to good stereoselectivity has been achieved in cycloaddtion reaction utilising chiral dipole, but the field of chiral acceptor is less explored.

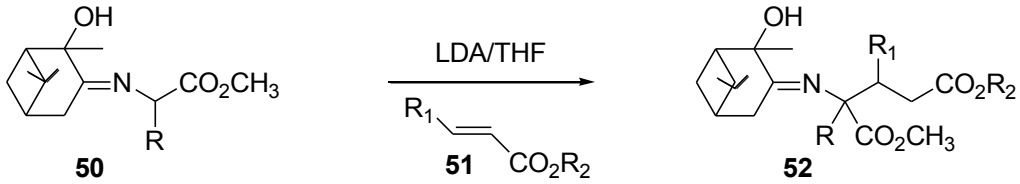
Garner[12] illustrated thermodynamically generated chiral auxiliary based chiral azomethine ylide **44** towards cycloaddition with dimethylmaleate (**45**) in good facial selectivity of 9:1. Similar study of ylide **48** obtained by imine tautomerisation and its reaction with dipolarophile resulted in good selectivity due to *endo* approach to the *E,E* ylide resulting in pyrrolidine **49** wherein all the substituents were *cis* (Scheme 11).

In the context of chiral *N*-lithiated azomethine ylide, Viallefont[13] described the effect of 2-hydroxy-3-pinane as the chrial auxiliary in the Schiff's base **50** towards it's coupling with Michael acceptor **51** to furnish the higher analogue of amino acid in moderate selectivity (Scheme 12).

Scheme 11: Garner et al. (*J. Org. Chem.* **1994**, *59*, 4)

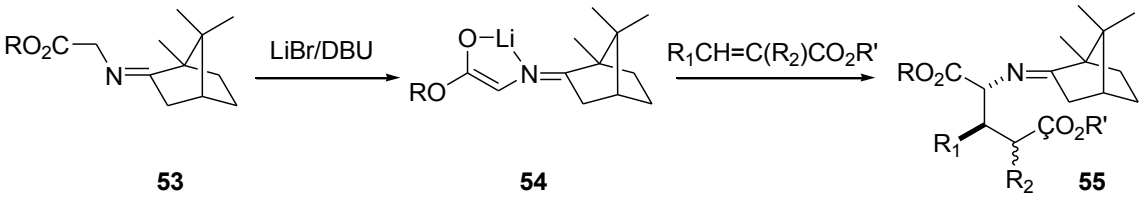


Scheme 12: Viallefont et al. (*Tetrahedron* **1988**, *44*, 5319)

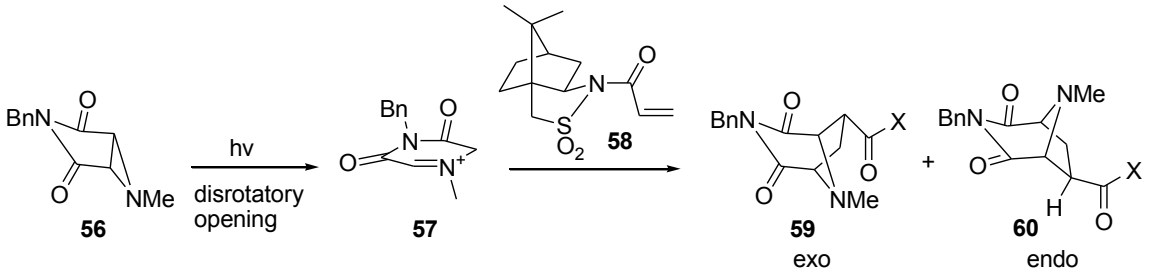


Kanamesa[14] studied the highly diastereoselective Michael addition of α,β-unsaturated ester to camphor imine of glycine **53**. The tight chelated structure of the *Z,E*-enolate and selective approach of the unsaturated ester to the *re* face of the enolates was responsible for high selectivity (Scheme 13).

Scheme 13: Kanamesa et al. (*J. Org. Chem.* **1991**, *56*, 2875)



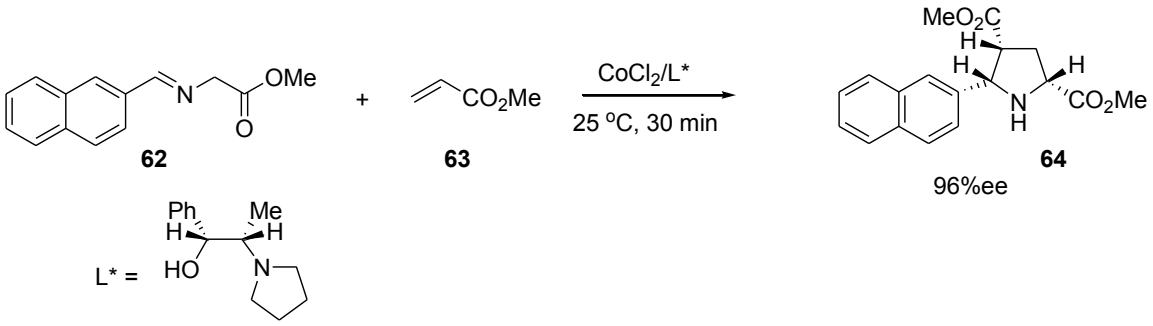
Scheme 14: Garner et al. (*J. Org. Chem.* **1990**, *55*, 3973)



Garner et al[15] described stereoselective addition of a photochemically generated azomethine ylide **57** to chiral acryloyl sultam **58** to give the substituted 3,8-diazabicyclo [3.2.1] octane moiety of quinocarcin (Scheme 14).

In addition to these two approaches, use of chiral catalyst has also proven useful in stereoselective generation of cycloadduct/Michael addition.

Scheme 15: Grigg et al. (*Tetrahedron: Asymmetry* **1995**, *6*, 2475)



Grigg[16] demonstrated the chiral metal catalyst for imine-metalloazomethine-cycloaddition pathway. Mn(II) and Co(II) salts in combination with chiral ligands furnished cycloadduct in moderate to excellent selectivity. The pre-transition state chelate result in effective shielding of one face of the metallo-dipole (Scheme 15).

1.2.2. Present Work

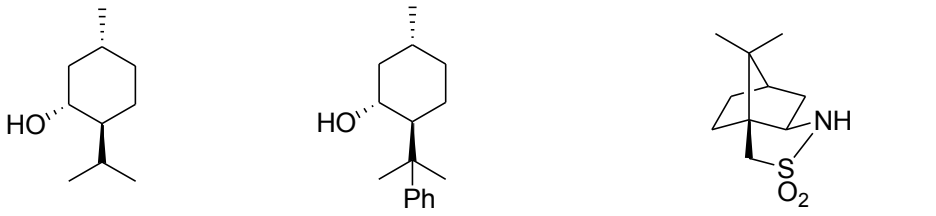
In the modern synthetic methodology, asymmetric induction has become one of the powerful tools for the generation of enantiomerically enriched compounds. Use of chiral auxiliary to induce biased stereochemical changes has now become an indispensable tactic in synthetic organic chemistry. The use of a particular auxiliary in asymmetric synthesis is subjected to some consideration such as i) availability of the

auxiliary ii) excellent stereochemical bias it can induce iii) easy to put on and iv) easy recovery/removal.

The high pharmacological demand[17] and challenging structural features wherein three contiguous stereocenters are present in the C6 moiety of carboxylcyclopropyl glycine[18] was the reason to undertake its enantioselective synthesis. The present concern was to introduce chirality in the Michael induced ring closure reaction to already standardised reaction condition of previous work[10] from this group wherein a Schiff's base reacted with the electrophile in the presence of Et_3N and LiBr to generate a cyclopropane product. As described earlier, under the reaction condition employed for cyclopropanation, one can force stereochemical bias using i) chiral azomethine ylide, ii) chiral acceptor or iii) chiral catalyst.

With knowledge of high stereochemical outcome of chiral auxiliary based azomethine ylide or acceptor towards Michael addition or cycloaddition it was planned to append some traditionally used chiral auxiliary towards MIRC leading to the synthesis of the target molecule in enantiomerically enriched form.

A few simple and traditionally used auxiliaries were sorted out which were easily available or could be easily synthesised, to study its effect in inducing chirality during cyclopropanation (fig. 2). It was planned to tag the auxiliaries both in the Schiff's base part as well as in the α,β unsaturated activated alkene part, depending on the convenience of synthesis, as shown in scheme 16.



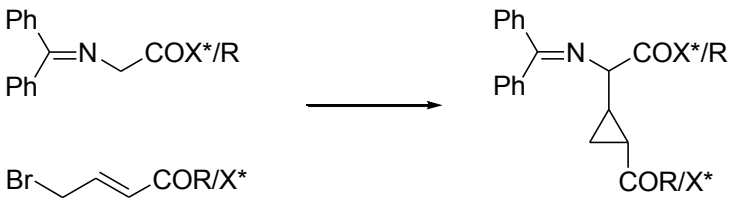
65 (-)- menthol

66 (-)-8-phenylmenthol

67 (-)-10,2-camphorsultam

Figure 2

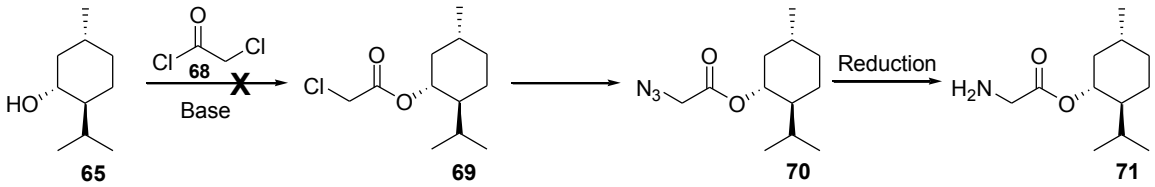
Scheme 16



1.2.2.1. Part A: Chiral Azomethine Ylide

At the onset of this endeavor it was planned to utilise readily available *l*-menthol as the chiral auxiliary of choice, which could be appended to the Schiff's base so as to generate the chiral azomethine ylide. Accordingly, the first task was to obtain the menthyl glycinate, which could be further transformed into its Schiff's base by transimination with diphenyl ketiminium chloride.

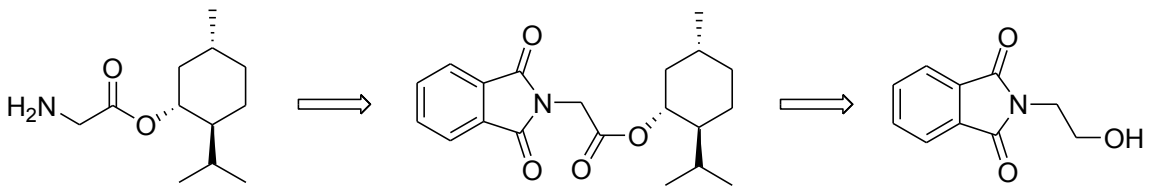
Acylation of menthol (**65**) with chloroacetyl chloride (**68**) followed by replacement of chloro by azide (**70**) and its subsequent reduction would have afforded the required menthyl glycinate (**71**). Surprisingly the reaction of menthyl with chloro acetyl chloride using variety of bases did not furnish the required acylated product.



65 **69** **70** **71**

Scheme 17

Failing to acylate menthol the focus was shifted to a totally different approach. The ready availability of phthalimido ethanol (**73**) prompted to utilise it as the starting material as delineated in the reterosynthetic path (Scheme 18) wherein the ring nitrogen was envisioned as the protected amine.

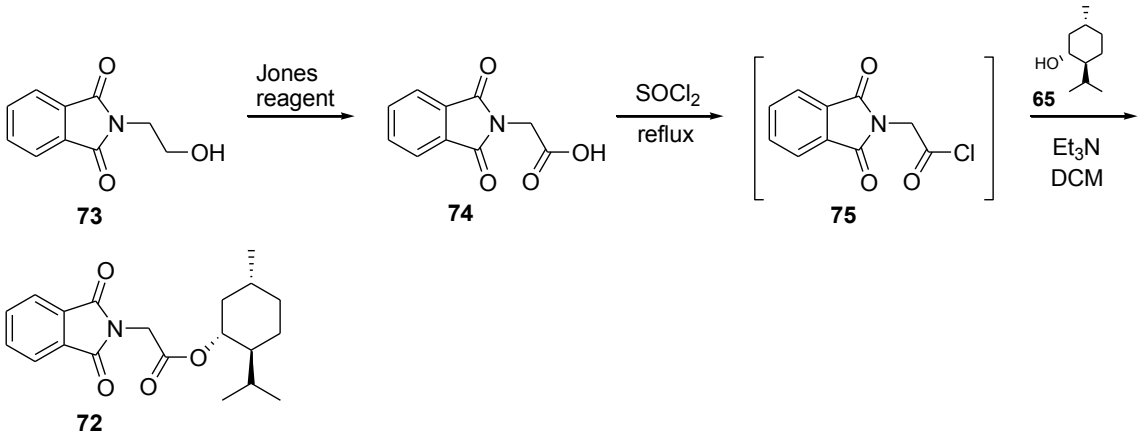


71 **72** **73**

Scheme 18: *Retrosynthetic analysis*

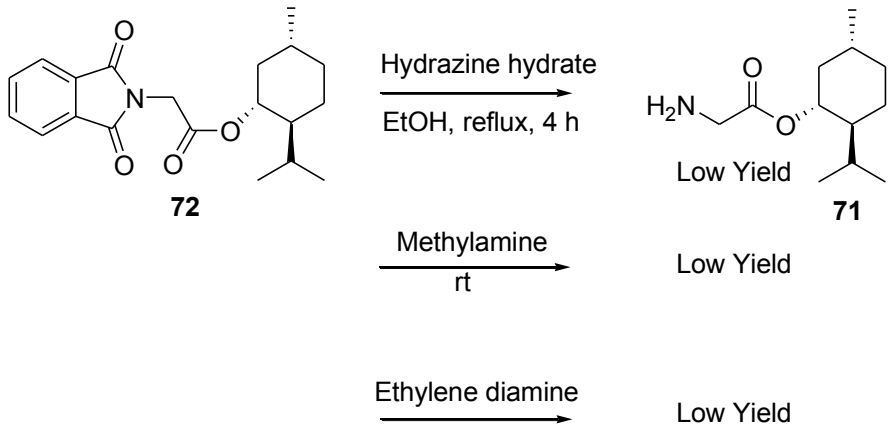
Thus, phthalimido ethanol was oxidised conveniently into its acid **74** with Jones reagent in good yield. The corresponding acid chloride **75** was obtained by treating the acid with thionyl chloride followed by heating to reflux for 10 hour. The unreacted thionyl chloride was removed by co-distillation with benzene and the crude acid chloride was used as such in the next step. *l*-Menthol was subjected to react with acid chloride in the

presence of triethylamine in DCM at room temperature to afford the pure menthyl ester **72** after chromatographic purification (Scheme 19).



Scheme 19

Removal of amine protection would have rendered the required substrate but treatment of **72** with a variety of reagents did not furnish the amine in good yield and purity (Scheme 20). Perhaps the electrophilicity of the phthalimido carbonyl group was the deciding factor.

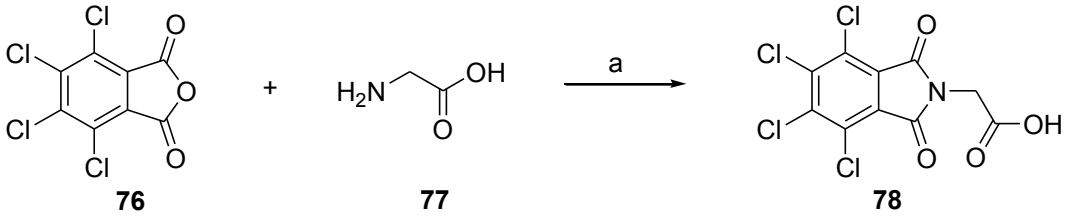


Scheme 20: *Removal of phthalimido group*

To increase the electrophilicity of the phthalimide carbonyl carbon thereby facilitating easy removal of amine protection it was thought appropriate to replace the phthalimido group with its tetrachloro phthalimido derivative. Hence the route was modified and accordingly tetrachlorophthalic anhydride (**76**) was chosen as the starting material.

Bose et al.[19] have reported a convenient microwave-assisted transformation of amino acid to its phthalimido derivative. Employing the same strategy with tetrachlorophthalic

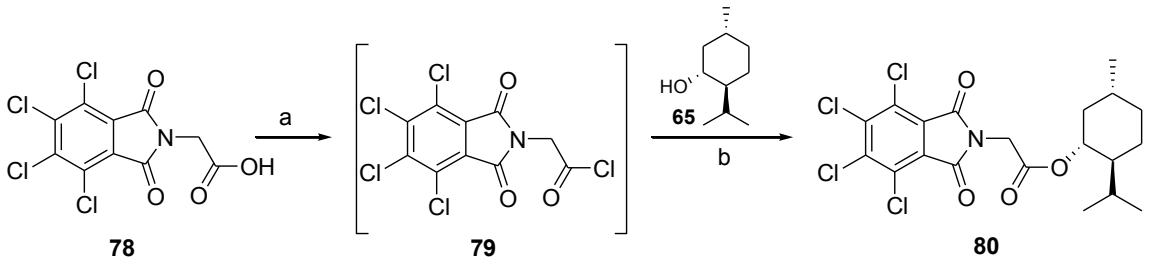
anhydride (TCPA) derivative it was possible to get the required substrate. Hence thoroughly mixing equimolar quantity of TCPA (**76**) and glycine (**77**) in DMF in presence of *N*-methylmorpholine and exposing it to microwave irradiation for 90 s afforded the required *N*-protected glycine **78**, which was recrystallised from ethanol to get the pure product in 70% yield (Scheme 21).



Scheme 21: Reagents and conditions: *a) DMF, N-methyl morpholine, MW, 90 s, 70%.*

The ^{1}H NMR spectrum of **78** showed the presence of single singlet at δ 3.94 which could be attributed to the only methylene protons present of glycine part. ^{13}C NMR spectrum along with the DEPT spectrum revealed the presence of a methylene carbon resonating at δ 39.9 apart from the quaternary aromatic carbons characteristic of tetrachlorophthalimido group thereby justifying the formation of compound **78**.

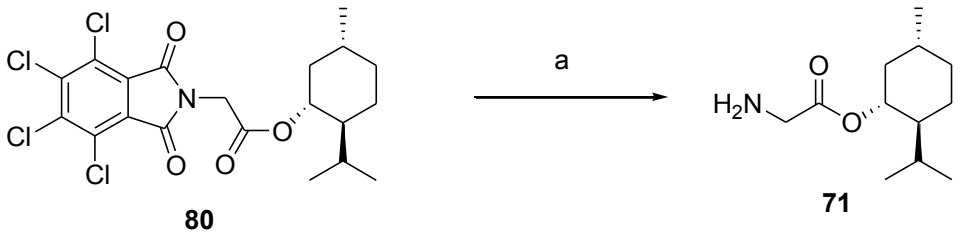
The protected glycine was converted into its acid chloride **79** by treating it with thionyl chloride and refluxing the mixture for 10 hour. Co-distillation of excess of thionyl chloride with benzene rendered the crude acid chloride, which was used, in the next step without further characterisation or purification. Treatment of *l*-menthol with the acid chloride in the presence of three equivalent of triethylamine in DCM at room temperature for 1 h furnished the acylated product **80** in 95% yield after column chromatographic purification (Scheme 22).



Scheme 22: Reagents and conditions: *a) $SOCl_2$, reflux, 10 h; b) Et_3N, DCM, rt, 6 h, 95%.*

The formation of **80** was confirmed by its spectral study. IR spectrum of **80** showed strong absorptions at 1787 cm^{-1} and 1729 cm^{-1} corresponding to two different carbonyl groups. In the ^{1}H NMR spectrum presence of dt at δ 4.73 integrating for one proton, characteristic of menthyl –C*H*OH proton, confirmed that the menthyl part has been appended. Apart from this, presence of bunch of peaks at upfield region corresponding to the menthyl moiety further revealed the presence of menthyl group in the compound. The methylene proton of glycine resonated as a singlet integrating for two protons at comparatively upfield at δ 3.41. The ^{13}C NMR spectrum displayed peaks at δ 165.7 and 162.4 corresponding to the ester carbonyl and phthalimido carbonyl along with presence of four methylene carbons at δ 40.7, 39.5, 34.2 and 23.6 corresponding to N*C*H_2 and three menthyl methylenes. The peak at δ 76.5 corresponds to the menthyl –*C*HOH.

Having obtained the ester **80** in fairly good yield attention was focused on removing the amine protection. In the present case the deprotected compound was easily isolated in good yield and purity by exposing the ester to ethylenediamine.[20] Thus the ester **80** was mixed thoroughly with ethylenediamine at room temperature and left for 0.5 h till the completion of reaction. The mixture was diluted with water and chloroform wherein some solid precipitated out which was filtered. The residue was washed thoroughly with chloroform. Separation of the organic layer and removal of the same furnished the crude product **71** pure enough to be used as such in next step (Scheme 23).

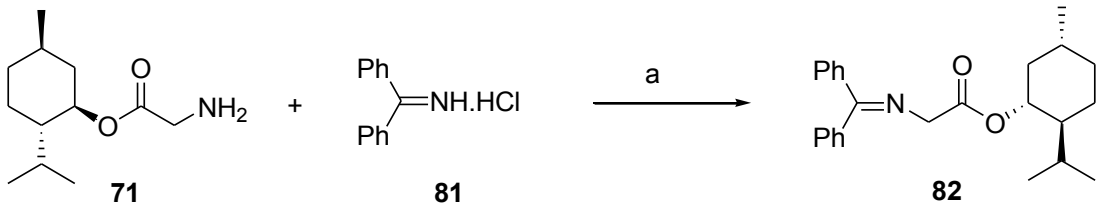


80 **71**

Scheme 23: Reagents and conditions: *a) ethylenediamine, rt, 0.5 h.*

IR spectrum of **71** showed absorption at 3274 cm^{-1} thereby confirming the presence of free amine. Absence of peak corresponding to aromatic carbon in ^{13}C NMR spectrum further emphasised the removal of the phthalimido moiety. The methylene proton of **71** next to amine resonated at comparatively upfield at δ 3.35 as a singlet integrating for two proton apart from the presence of other characteristic peaks of menthyl moiety in ^{1}H NMR spectrum.

The successful removal of *N*-protection in good yield furnished the substrate for further manipulations. Literature precedents[21] are there wherein the trans-imination has been successfully carried out by just stirring the amine with the diphenyl ketiminium chloride in DCM. So mixing an equivalent amount of menthyl glycinate (**71**) and diphenyl ketiminium chloride (**81**), obtained in two steps from phenylmagnesium bromide and benzonitrile, taken in DCM and stirring for 24 h rendered the pure product **82** in 75% yield after column chromatographic purification (Scheme 24).

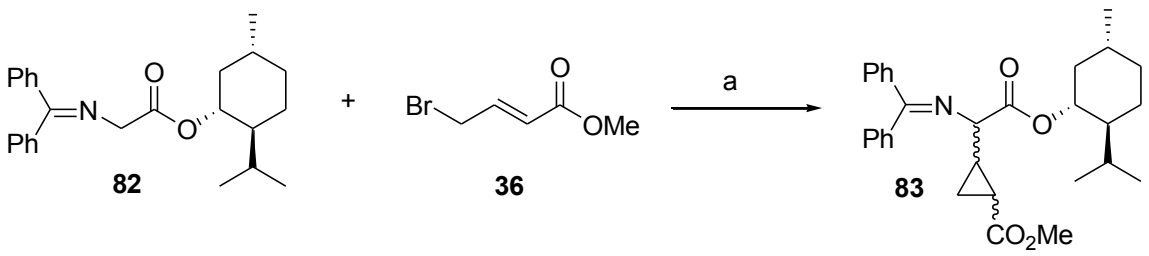


71 **81** **82**

Scheme 24: Reagent and conditions: *a) DCM, rt, 24 h, 75 %.*

^{1}H NMR spectrum of **82** revealed the presence of multiplets at δ 7.68-7.17 integrating for 10 protons thereby confirming the incorporation of diphenyl moiety. The methylene proton moved downfield to δ 4.18. ^{13}C NMR spectrum showed the presence of aromatic carbons along with a quaternary carbon corresponding to imine moiety at δ 170.1. It was further confirmed by elemental analysis.

With the successful synthesis of the required Schiff's base in good yield and purity it was subjected to Michael induced ring closure reaction. Thus to an equimolar mixture of Schiff's base **82** and methyl 4-bromocrotonate (**36**) in THF was added LiBr followed by addition of Et_3N and left to stir at room temperature for 16 h till the completion of the reaction. The cyclised product **83** was obtained in 72% yield after column chromatographic purification (Scheme 25).



82 **36** **83**

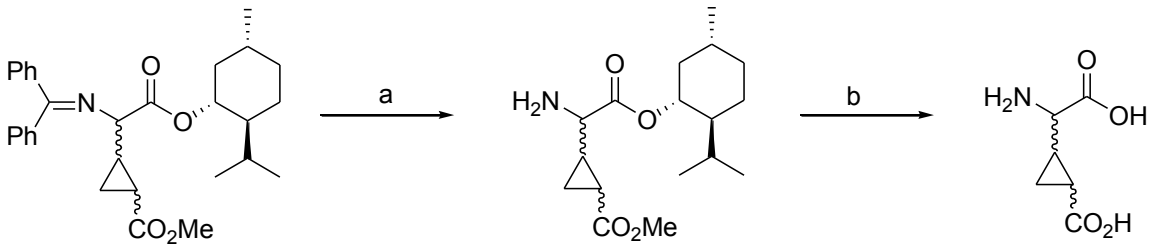
Scheme 25: Reagents and conditions: *a) Et_3N, LiBr, THF, rt, 16 h, 72%.*

The IR spectrum showed strong absorption at 1719 cm^{-1}. The formation of cyclopropane ring was exemplified by the presence of a doublet at δ 3.87 integrating for one proton characteristic of cyclopropane glycine –C*H* next to the imine in the ^{1}H NMR spectrum. Further, presence of additional upfield peaks in the ^{1}H NMR spectrum apart from the menthyl protons revealed the presence of cyclopropane. ^{13}C NMR spectrum showed the presence of methylene carbon peak at δ 11.6 characteristic of cyclopropane –$\underline{C}H_2$. Peak at δ 51.2 was attributed to cyclopropane glycine methine carbon next to imine (N$\underline{C}HCO_2R$*). Elemental analysis further revealed the formation of compound **83**.

Though the cyclopropanation was achieved in good yield with the modified Schiff's base the spectral studies revealed it to be a diastereomeric mixture. The peak at δ 3.87, characteristic of cyclopropane glycine –C*H* next to imine, in the ^{1}H NMR spectrum appeared as a set of two doublets instead of one in the ratio of 60:40. Even the ^{13}C NMR confirms the presence of diastereomeric mixture as almost all the peak appeared as a set of two peaks.

Thus the results clearly indicated that appending menthol in the Schiff's base part could not induce appreciable enough selectivity during its reaction with Michael acceptor in the formation of the cyclopropane.

Though the selectivity was not good yet it was thought to remove the imine and take it forward to the target molecule.



83 **84** **85**

Scheme 26: Reagents and conditions: *a) 2N HCl, 0.5 h, rt, 80%; b) LiOH, MeOH: H_2O, rt, 0.5 h, DOWEX-H^+, 85%.*

Exposing the imine **83** to dil HCl led to the removal of imine, which was isolated from the aqueous solution by basifying it with sodium bicarbonate and extracting with organic solvent in 80% yield (Scheme 26).

The IR spectrum showed absorption at 3350 cm^{-1} thereby justifying the presence of free amine. The ^{1}H NMRspectrum of **84** revealed the absence of aromatic protons in the

downfield region of δ 7.60-7.10. The methine proton of glycine (-NC*H*) moved upfield and resonated at δ 3.64, which was in accordance with the removal of the imine moiety. It was further exemplified by ^{13}C NMR spectrum wherein absence of aromatic carbons as well as disappearance of quaternary carbon peak at δ 169.9 was in line with the removal of imine moiety.

Further treatment of compound **84** with LiOH in aqueous methanol rendered the lithium salt of the CCG which when passed through DOWEX-H^+ resin furnished the pure CCG **85**.

The ^1H NMR spectrum of **85** was in full agreement with the formation of the target molecule. The optical rotation showed very little optical purity present if any.

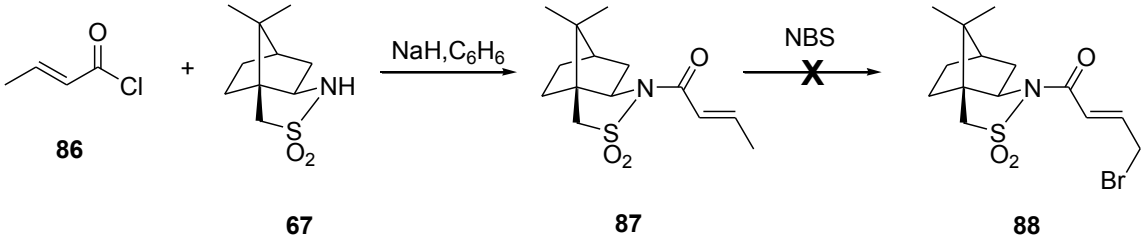
Thus the above study demonstrates the inefficiency of menthol chiral auxiliary when appended to the glycine Schiff's base to deliver enantiomerically enriched cyclopropanation product under the condition employed.

1.2.2.2. Part B: Chiral Michael Acceptor

Failing to achieve appreciable selectivity by appending the chiral auxiliary in the Schiff's base part it was thought worthwhile to prepare chiral acceptor using a few chiral auxiliaries.

Camphor sultam (**67**) has been widely studied as an effective chiral auxiliary in a variety of reactions including Michael acceptor.[22] The next target was to prepare γ-bromo crotonyl sultam (**88**) and set it for the cyclopropanation reaction with ethyl diphenylimine gylcinate (**92**) under standardised reaction condition.

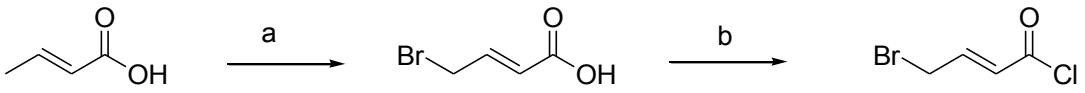
Accordingly, 10,2-camphor sultam (**67**) was made to react with crotonyl chloride (**86**) in presence of NaH in benzene to give the crotonyl sultam **87** in good yield. Allylic bromination would have rendered the required substrate but all attempts of allylic bromination failed to achieve the desired transformation (Scheme 27).



Scheme 27

So, alternatively, it was thought to prepare 4-bromocrotonylchloride **89** and condense it with sultam. Thus treating crotonic acid (**90**) with *N*-bromosuccinimide under reflux condition in CCl_4 afforded us the brominated compound **91**,[23] which was confirmed by its ^{1}H NMR spectrum study. Appearance of peak δ 10.54 integrating for one proton indicated the presence of acid functionality. A multiplet at δ 7.19-7.04 and a doublet at δ 6.05 integrating for one proton each were attributed to the two alkenes protons. The peak at δ 4.04 integrating for two protons was assigned to the only methylene group –C$\underline{H_2}$Br present.

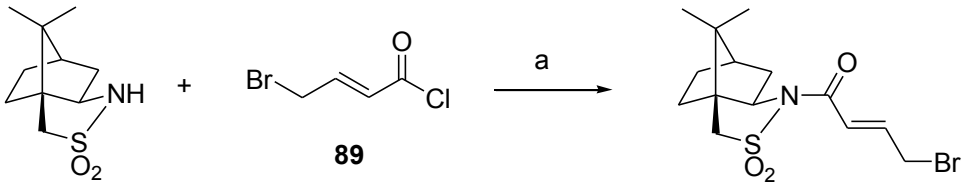
Addition of thionyl chloride to the bromocrotonic acid **91** and refluxing it for 10 h furnished the acid chloride **89** after the removal of the excess of thionyl chloride by co-distillation with benzene (Scheme 28).



90 **91** **89**

Scheme 28: Reagents and conditions: *a) NBS, CCl_4, reflux, 94%; b) $SOCl_2$, reflux, 10 h*

The required bromocrotonyl sultam **88** was obtained by treating the camphor sultam (**67**) with the bromocrotonyl chloride (**89**) in presence of NaH in benzene at room temperature in 60% yield after column chromatographic purification (Scheme 29).



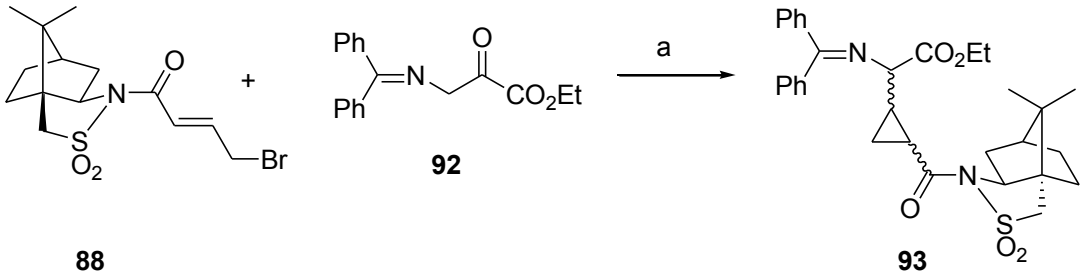
67 **89** **88**

Scheme 29: Reagents and conditions: *a) NaH, benzene, 5 h, rt, 60%*

The formation of compound **88** was confirmed by spectral analysis. EI mass spectra showed the presence of 1:1 peak at (*m/z*) 362 and 366 corresponding to molecular ion (M^+) peak and molecular ion + 4 (M^++4) peak characteristic of bromine containing compound. Thus it was confirmed the compound contains bromine in it. The IR spectrum showed absorption at 1683 cm^{-1}. Further the ^{1}H NMR spectrum revealed multiplet at δ 7.15-7.00 and a doublet at δ 6.72 integrating for one proton each which

were assigned to the alkene protons. The presence of sultam moiety was confirmed by the presence of its characteristic proton peaks as a triplet at δ 3.92 and a doublet at δ 3.47 which were assigned to NC*H* and -C*H*$_2$SO$_2$ respectively. Apart from this, methylene protons resonated at δ 2.17-2.07, 1.99-1.84 and 1.50-1.35. The only bridgehead proton appeared as a multiplet at δ 1.99-1.84 along with the methylene protons. ^{13}C NMR spectrum showed the presence of carbonyl carbon at δ 162.6. Three methine carbons corresponding to the alkene and N*C*H resonated at δ 142.3, 123.5 and 64.9 respectively. The bridgehead carbons appeared at δ 48.4 (C) and δ 44.5 (CH). DEPT spectrum revealed the presence of five methylene carbons at δ 52.9 (*C*H$_2$SO$_2$), δ 38.2 (CH$_2$Br), δ 32.7 (CH$_2$), δ 28.9 (CH$_2$) and δ 26.3 (CH$_2$) in accordance with the proposed transformation.

With the sultam based chiral acceptor in hand the crucial cyclopropantion reaction was carried out according to the standardised reaction conditions. Diphenylimnine Schiff's base (**92**) was prepared by O'Donnell's[24] procedure from diphenylimine and glycine ester hydrochloride. Thus treating the equimolar mixture of the bromo alkene **88** and diphenylimine Schiff's base **92** in THF with LiBr and Et$_3$N furnished the cyclised product **93** (single spot on TLC) in 70% yield after column chromatographic purification (Scheme 30).



88 **92** **93**

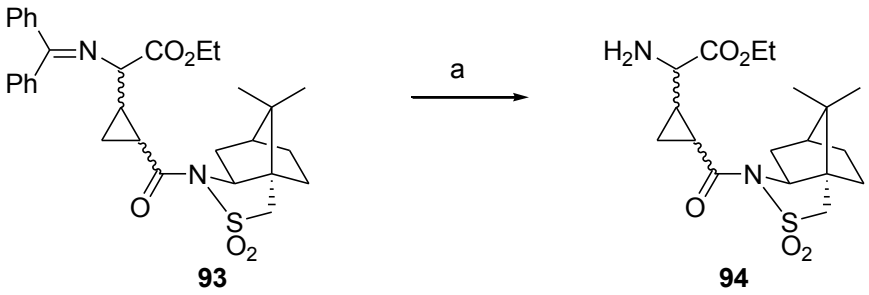
Scheme 30: Reagents and conditions: *a) LiBr, Et$_3$N, THF, rt, 16 h, 70%.*

The formation of cyclopropane **93** was confirmed by the spectral study. IR spectrum showed absorption at 1733 cm^{-1}and 1683 cm $^{-1}$ corresponding to the ester and amide carbonyl respectively. In the ^{1}H NMR spectrum the characteristic doublet of cyclopropane glycine C*H* next to imine appeared at δ 3.64 integrating for one proton. Other protons of cyclopropane ring appeared in the upfield region apart from those of sultam. Alongwith this appearance of aromatic protons at δ 7.57-7.13 and q at δ 4.11 integrating for two protons ascribed to ethyl –C*H*$_2$ justifies the condensation of the imine

glycine to the alkene moiety. ^{13}C NMR spectrum confirmed the presence of cyclopropane by the appearance of upfield methylene carbon at δ 14.04. EI mass spectra showed peak at *m/z* 548 (M^+) along with other fragment peak at 475 (M^+-CO_2Et), 334 (M^+- sultam), 311, 232, 182, 165, 105 thereby confirming the formation of the compound. Though the required cyclopropanation went smoothly the spectral study revealed it to be a diastereomeric mixture. The cyclopropane glycine –C*H* next to imine appeared as a set of two doublets in the ratio 1:1 at δ 3.64 and δ 3.57, which clearly indicates the presence of two diastereomers. Further ^{13}C NMR spectrum analysis showed almost all the peaks appearing as a set of two peaks.

Hence, once again surprisingly it was not possible to induce chirality to appreciable extent using a chiral unsaturated activated alkene towards the Michael induced ring closure reaction with Schiff's base in presence of $LiBr/Et_3N$.

Though the substrate **93** was subjected further to imine removal but there was no improvement or enrichment of either diastereomers or any improvement in TLC pattern for chromatographic separation of the diastereomers (Scheme 31).

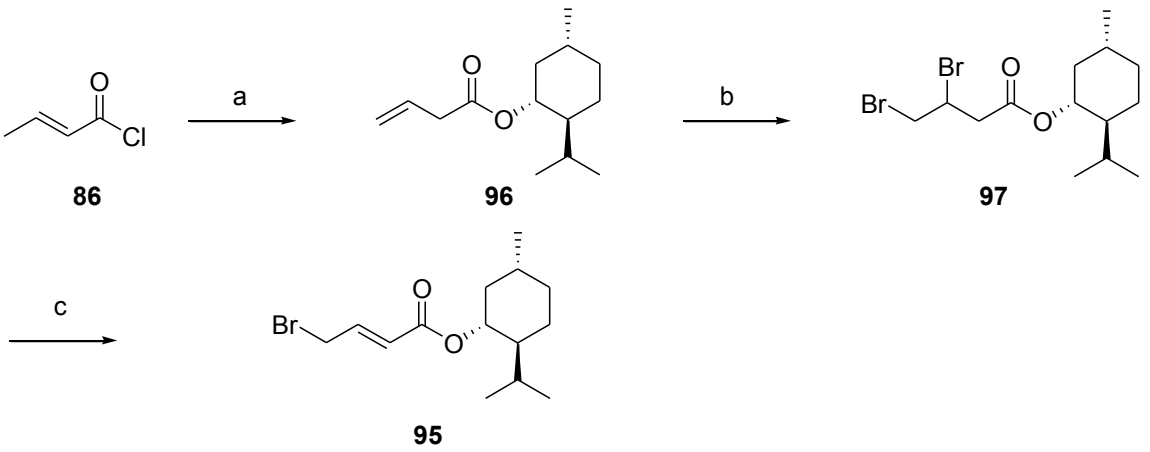


Scheme 31: Reagents and conditions: *a) 2N HCl, rt, 0.5 h, 80%.*

The results so far indicate a very inferior stereo bias in terms of diastereoselectivity in the MIRC using menthol and camphor sultam as chiral auxiliaries in the azomethine part or the unsaturated activated alkene part respectively. From the comparative point of view *l*-menthol seems to induce marginally better selectivity as compare to sultam in the key reaction. Hence, it was decided to study the effect of *l*-menthol as the stereo directing group when adhered to the Michael acceptor.

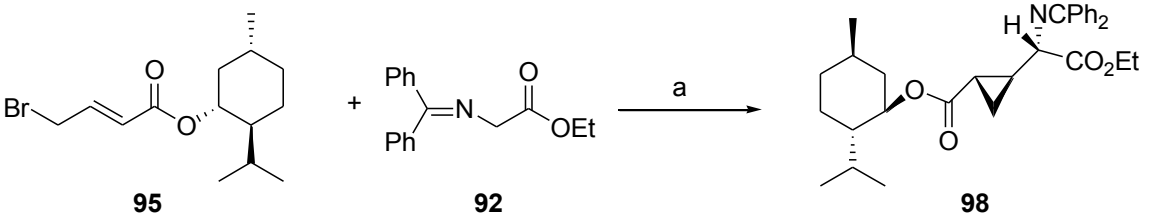
Accordingly, the immediate concern was to obtain menthyl 4-bromocrotonate (**95**) and subject it to react with Schiff's base **92.** Hudlicky et al.[25] have described a convenient route to both 2-bromo and 4-bromo menthylcrotonate starting from menthol and crotonyl

chloride. Hence the same scheme was followed and the required substrate was obtained in good yield and optical purity as revealed by the spectral data (Scheme 32).



Scheme 32: Reagents and conditions: a) *l-menthol, Et_3N, DCM, 0 ^oC-rt, 90%; b) Br_2, CCl_4, 0 ^oC-rt, quantitative; c) DBU, DME, 0 ^oC, 80%.*

Thus subjecting an equimolar quantity of Schiff's base **92** and unsaturated ester **95** in THF to react under standardised reaction conditions in presence of LiBr/Et_3N rendered the cyclised product **98** in 72% yield after column chromatographic purification (Scheme 33).



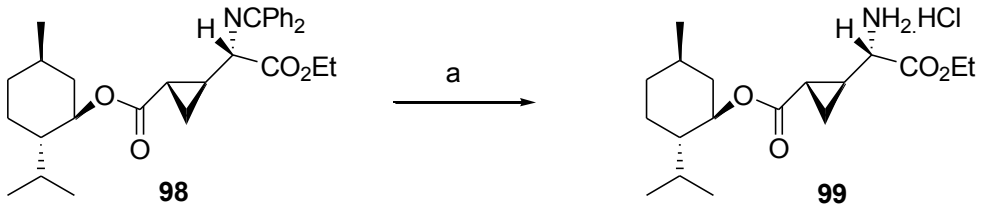
Scheme 33: Reagents and conditions: *a) LiBr, Et_3N, THF, rt, 16 h, 72%.*

IR spectrum showed sharp absorption at 1722 cm^{-1}. Appearance of a doublet at δ 3.92 integrating for one proton characteristic of cyclopropane glycine –C*H* proton next to imine in the ^1H NMR spectrum signifies the formation of cyclopropane. Further, presence of other upfield protons peaks apart from menthyl protons exemplified the said transformation.^1H NMR spectrum further revealed a dt at δ 4.66 integrating for one proton characteristic of menthyl –C*H*OH. Multiplet at δ 7.63-7.16 and multiplet at δ 4.17 integrating for ten and two protons respectively indicated the condensation of the Schiff's base to the alkene moiety. ^{13}C NMR spectrum along with DEPT confirmed the presence of methylene carbon at δ 11.5 characteristic of cyclopropane –CH_2, alongwith

other methylene carbons resonating at δ 60.7, 40.8, 34.2, 23.3 assigned to ester –$\underline{C}H_2$ and three menthyl methylenes respectively. The peak at δ 64.6 was attributed to glycine -$\underline{C}$H next to imine. The two-carbonyl carbons resonating at δ 170.9 and 170.7 were ascribed to two ester carbonyl carbons whereas peak at δ 173 was attributed to the quaternary imine carbon. The elemental analysis and mass spectra (*m/z* 489.01) further emphasised the formation of cyclopropane product.

The percentage diastereomeric excess was determined from its ^{1}H NMR spectrum study. The appearance of a set of two doublets at δ 3.92 in the ratio of 96:4 clearly signified a *de* of 92%. Menthol therefore when appended to the activated alkene part was able to render appreciably good selectivity in terms of diastereoselection.

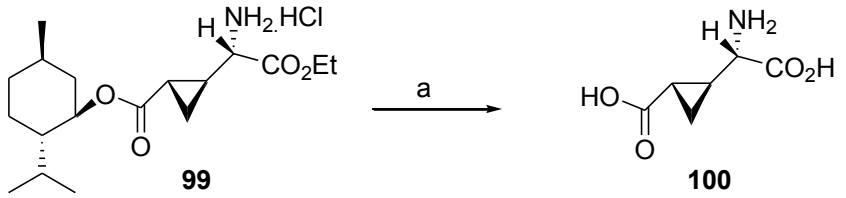
With this gratifying result the synthesis of CCG was completed by few functional group manipulations. The imine moiety was removed readily by exposing the substrate **98** to 2N HCl. The product was obtained as the hydrochloride salt **99** of the corresponding free amine (Scheme 34).



Scheme 34: Reagents and conditions: *a) 2N HCl, 0.5 h, rt, 60%.*

IR spectrum recorded in KBr showed absorption at 2902 cm^{-1} signifying the formation of amine in line with the said transformation. ^{1}H NMR spectrum showed a downfield shift of the glycine C$\underline{H}$ to δ 3.65 and absence of aromatic protons peak from downfield region. Disappearance of aromatic carbon peaks from ^{13}C NMR spectrum was indicative of the removal of the diphenyl groups, further absence of quaternary carbon at δ 173 shows the absence of imine moiety in **99**. Other characteristic peaks of cyclopropane appeared at their expected positions. Mass (*m/z* 252, 114, 96, 68) and elemental analysis further confirmed the same. Presence of a single doublet at δ 3.65 in the ^{1}H NMR spectrum signified enrichment of major isomer with the concomitant loss of trace of minor diastereomer.

Saponification of the amine salt **99** with aqueous LiOH rendered the lithium salt of the acid which when passed through DOWEX-H$^+$ resin and eluting with aqueous ammonia furnished the pure CCG **100** (Scheme 35).



Scheme 35: Reagents and conditions: *a) LiOH, MeOH: H_2O, rt, 0.5 h, 87%*

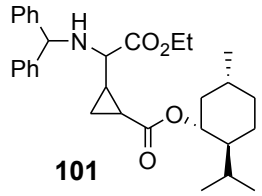
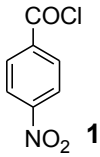
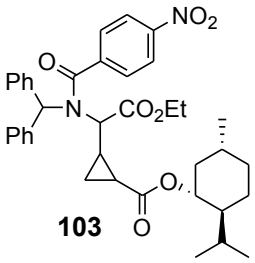
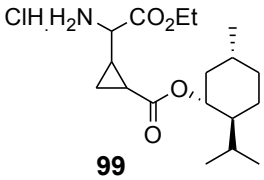
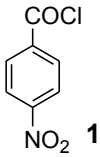
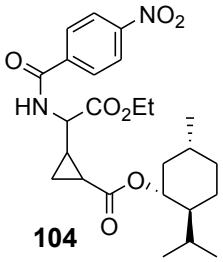
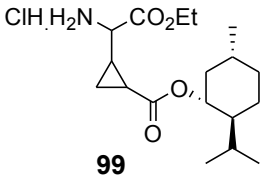
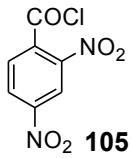
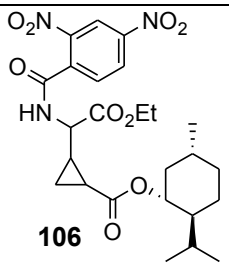
The ^{1}H NMR study revealed absence of peaks corresponding to the menthyl and the ethyl moiety thereby signifying the removal of both. The doublet appearing at δ 3.22 integrating for one proton was attributed to the cyclopropane glycine –C*H.* The four cyclopropane protons appeared as ddd at δ 1.71, dddd at δ 1.63, ddd at δ 1.28 and ddd at δ 1.17. ^{13}C NMR spectrum along with DEPT spectrum showed the presence of single methylene carbon resonating at δ 13.1 was ascribed to the cyclopropane –*C*H_2 while other carbon peaks appeared at δ 57.6 (CH), δ 21.4 (CH), δ 20.4 (CH). The carbonyl carbon peaks of free acid resonated at δ179.5 and δ 172.9.

Further mass spectrum showed peak at *m/z* 114, 96, 79, 68 in accordance with the presence of cyclopropane glycine. Absence of peak at *m/z* 141 signifies the synthesised CCG is *trans* as there is no lactone formation as expected from *cis* CCG.[18]

Though the diastereoselectivity was established beyond doubt by the ^{1}H NMR study the determination of enantioselectivity and the absolute configuration of the three chiral centers was an uphill task. The optical rotation of the recrystallised product showed $[\alpha]_D^{25}$ +106, which could be either L-CCG I [lit. $[\alpha]_D^{25}$ +102] or D-CCG IV [lit. $[\alpha]_D^{25}$ +86.7] though the D-CCG-IV could be eliminated on the basis of no appearance of peak at *m/z* 140 corresponding to *cis* CCG in mass spectral analysis but it was difficult to tell conclusively that the synthesised compound was L-CCG-I. There is little if any difference in the appearance of their NMR spectra to discriminate them. Thus to prove beyond doubt the relative and absolute stereochemical disposition of subsituent as well as the ring, it was required to prepare some derivatives of the CCG or any other cyclopropane intermediate which could render good crystalline solid for X-ray study or good enough to be resolved in chiral HPLC column.

Accordingly few derivatives of the cyclopropane intermediates were prepared with bulky subsituent with a view of absolute stereochemistry determination as described in table 1 but were found to be fruitful.

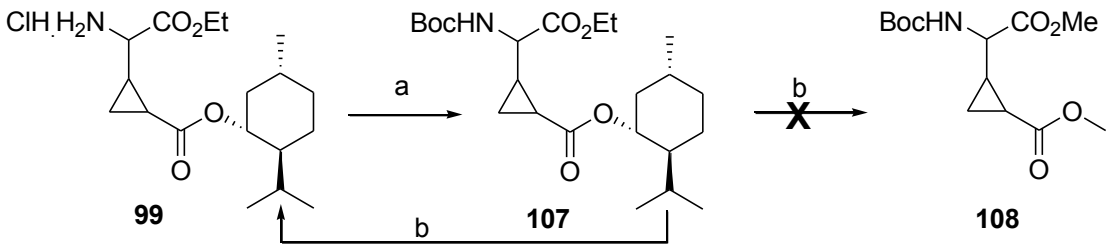
Table 1

Sr. No.	Substrate	Reagents and conditions	Product	Nature of the solid
1.	 **101**	 **102** K_2CO_3, DCM	 **103**	Thread like solid
2.	 **99**	 **102** K_2CO_3, DCM	 **104**	Thread like solid
3.	 **99**	 **105** K_2CO_3, DCM	 **106**	Thread like solid

Reports are there wherein chiral HPLC of Boc protected methyl ester of compound similar to **108** has been achieved.[26] Thus attention was focused to obtain such a derivative from any of the cyclopropane intermediate so as to ascertain at least the extent of enantioselectivity induced.

For this purpose a number of attempts were made which are summarised below:

a) Boc protection of ester **99** followed by transesterification

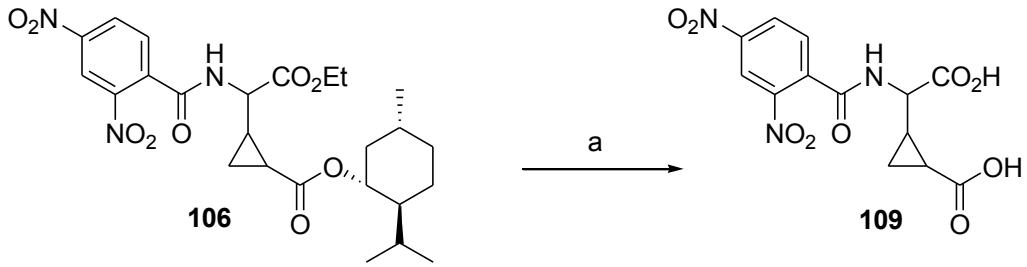


Scheme 36: Reagents and conditions: *a) $(Boc)_2$, Et_3N, DCM, rt, 2 h; b) p-TSA, dry MeOH, rt, 24 h.*

Though the Boc protected compound was obtained easily, subjecting it to trans esterification condition with cat. *p*-TSA and dry MeOH did not render the required methyl ester, instead Boc deprotected starting compound was isolated.

Due to the instability of the Boc group under acidic condition a differently protected amine compound was synthesised.

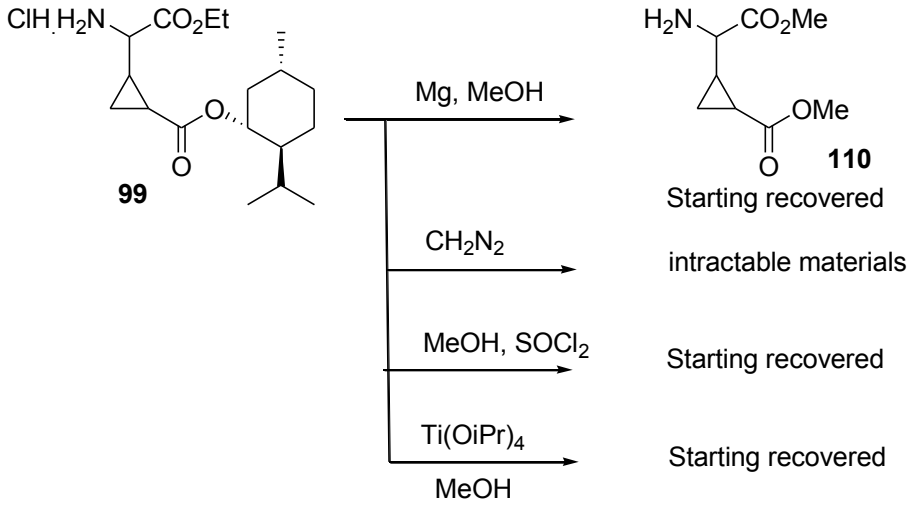
b) Ester hydrolysis of **106** followed by methylation and Boc protection of amine.



Scheme 37: Reagents and conditions: *a) LiOH, MeOH: H_2O, 0.5 h, rt.*

In this case though the TLC showed the disappearance of the starting material the product could not be isolated from aqueous medium.

c) Transesterification of **99** followed by Boc protection

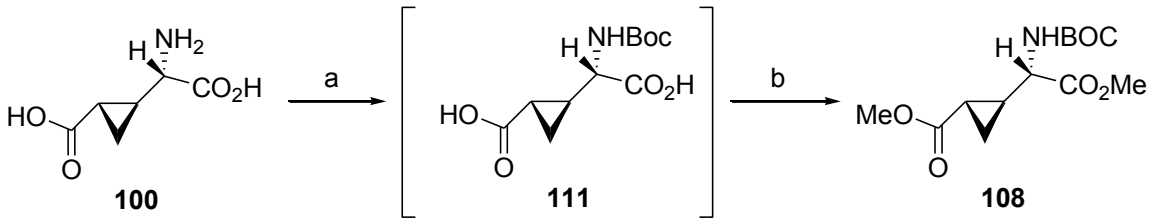


Scheme 38

Under different conditions employed for trans esterification the required compound could not be isolated.

Failing to obtain the required substrate from any of the cyclopropane intermediates, attention was shifted to the esterification and boc protection of the unrecrystallised final product **100** itself.

Subjecting the CCG **100** to react with Boc anhydride in presence of triethylamine did not furnish the protected compound. So more basic condition were tried using NaOH as the base.[27] Thus treating the substrate with Boc anhydride taking it in a mixed solvent of aq NaOH and *t*-BuOH at room temperature furnished the Boc protected CCG **111**. The crude compound was subjected to methylation with diazomethane generated *in situ* by action of KOH on *N*-methylnitroso urea (NMU). Column chromatographic (SiO_2) purification resulted in the pure product **108** in 48% yield (Scheme 39).



100 **111** **108**

Scheme 39: **Reagents and conditions**: *a) Boc_2O, NaOH, t-BuOH, rt, 24 h, 50%; b) CH_2N_2, diethyl ether, 48%.*

Delightfully the isolated compound **108** was found to be solid. Recrystallisation from diethyl ether: pet ether furnished clear crystalline solid, which was analysed for single X-ray crystallography. The ORTEP diagram (fig. 5) clearly established the trans disposition of the H-atom in C2, C1', and C2' carbons thereby clarifying that the CCG obtained is the either enantiomer of CCG-I. This along with optical rotation of the final product proved beyond doubt that the synthesised compound was L-CCG-I.

The enantioselectivity was determined by chiral HPLC analysis on chiralcel-OD of the unrecrystallised product **108**, which proved the stereo biasing to be 97% ee by using menthol as the chiral auxiliary. Single recrystalisation of **100** from water furnished the optically pure L-CCG-I.

The stereochemical out come can be rationalised by taking the *Z*-enolate into consideration. It can interact with the α,β-unsaturated ester in either of the two possible ways as shown in the fig 3.

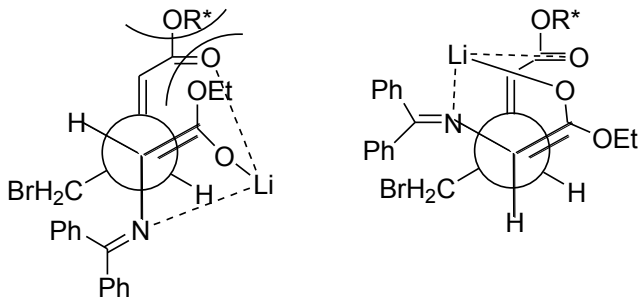


Figure 3: Plausible transition state

The transition state 1 (TS 1) is disfavoured due to high steric repulsion between the two bulky groups, ester and the ethoxide moiety. Hence the enolate undergoes addition through transition state II (TS II) leading to erythro adduct in the initial conjugate Michael addition.

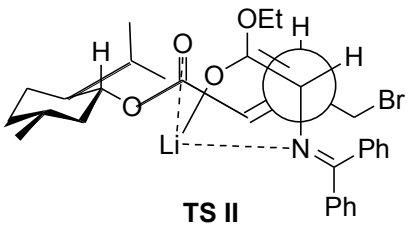


Figure 4: Plausible transition state

A different view of the transition state II (fig. 4) explains the restricted approach of the enolate towards the alkene. Because of the bulky isopropyl group which completely blocks one of the faces of the alkene and forces the enolate to approach through the other face leading to high diastereoselection. The final cyclisation to cyclopropane is always trans selective as explained by Enders et al.,[28] thereby leading to high selectivity of the constructed cyclopropane.

In conclusion, the study demonstrate the efficacy of differently placed chiral auxiliary towards the Michael induced ring closure reaction leading to the stereo controlled synthesis of carboxylcyclopropyl glycine. In this regard a new approach to diphenylimine menthyl glycinate **82** and 4-bromocrotonyl sultam **88** was achieved starting from tetrachlorophthalic anhydride and crotonic acid respectively.

The three contiguous stereocenters in the constrained glutamic acid analog L-CCG-I were established in a single step by a Michael induced ring closure reaction of a chiral,

nonracemic electrophile derivative of *l*-menthol with a glycine anion equivalent. The ready availability of *l*-menthol together with the mild reagents and reaction conditions auger well for the application of this strategy to the stereo selective synthesis of this and related products.

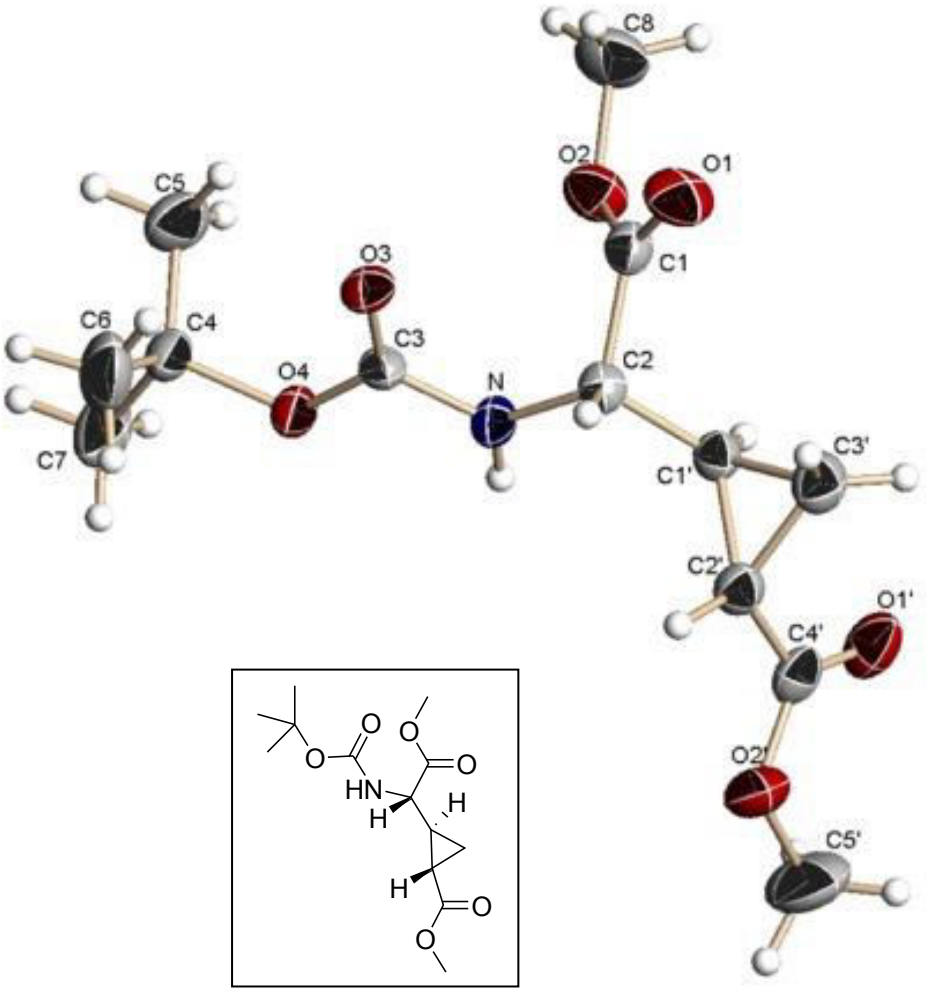
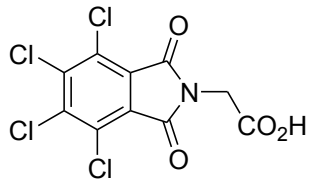


Figure 5: ORTEP View of compound 108

1.2.3. Experimental

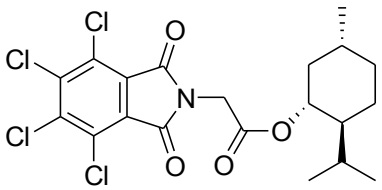
2-(4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl)acetic acid (78)



Tetrachlorophthalic anhydride **76** (19 g, 66.6 mmol) and glycine **77** (5 g, 66.6 mmol) was mixed thoroughly in motar and transferred into a glass conical. 30 ml of dry DMF was added followed by *N*-methylmorpholine (1.65 mL, 300 mmol). The mixture was irradiated under MW (medium power setting) for 90 s in domestic microwave oven. After cooling, water was added. Solid compound precipitated out which was filtered and recrystallised from boiling ethanol to furnish the pure **78** (16.2 g, 46.6 mmol).

Mol. Formula	**:** $C_{10}H_3Cl_4NO_4$
Yield	**:** 70%
Mp	**:** > 250 ^oC
^{1}H NMR (200 MHz, DMSO-d$_6$)	**:** δ 3.94 (s, 2H).
^{13}C NMR (50 MHz, DMSO-d$_6$)	**:** δ 168.5 (C), 163 (C), 138.9 (C), 128.7 (C), 128.1 (C), 39.9 (CH_2).

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl-2-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl) acetate (80)



Tetrachlorophthaloyl glycine **78** (16.15g, 46.6mmol) was taken in benzene (30mL) and cooled to 0 ^oC. Freshly distilled thionyl chloride (10.3mL, 141.6mmol) was added slowly. After completion of addition the reaction mixture was heated to reflux for 10 h. The excess of thionyl chloride was co distilled out with benzene and the acid chloride (17 g crude) was used as such without further purification.

To a well stired mixture of *l*-menthol (**65)** (17 g, 47.2 mmol) and triethyl amine (8.74 mL, 62.6 mmol) in DCM (50 mL) under argon atmosphere was added acid chloride (17 g) dropwise at 0 ^{o}C. After completion of addition the reaction mixture was stirred for additional 1 h at room temperature till the completion of reaction (TLC). The reaction mixture was washed with dil HCl, aqueous sodium bicarbonate solution and brine. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish the crude product **80**. The compound was purified by column chromatography (SiO_2) (14 g, 29.1 mmol). R_f 0.5 PE: EA 90:10.

Mol. Formula : $C_{20}H_{21}Cl_4NO_4$

Yield : 95%

Mp : >250 ^{o}C

$[\alpha]_D^{25}$: -23.55 (c 1.3, $CHCl_3$)

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3025, 2598, 1787, 1729, 1417.

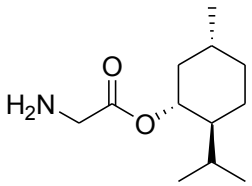
^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.73 (dt, *J* = 10.8, 4.3 Hz, 1H), 3.41 (br d, 2H), 2.01-1.98 (m, 1H), 1.86-1.80 (m, 1H), 1.74-1.61 (m, 3H), 1.56-1.46 (m, 1H), 1.40-1.34 (m, 1H), 1.12-1.03 (m, 1H), 1.01-0.94 (m, 1H), 0.93-0.91 (m, 3H), 0.90-0.89 (m, 3H), 0.78-0.76 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 165.7 (C), 162.4 (2C), 140.2 (2C), 129.8 (2C), 127.8 (2C), 76.5 (CH), 47.1 (CH), 40.7 (CH_2), 39.5 (CH_2), 34.2 (CH_2), 31.4 (CH), 26.4 (CH), 23.6 (CH_2), 21.9 (CH_3), 20.6 (CH_3), 16.4 (CH_3).

Mass (ESI) : *m/z* 502.8 (M^++Na).

Analysis : Calculated C 49.92, H 4.40, Cl 29.47, N 2.91%
Found C 49.70, H 4.32, Cl 29.29, N 2.85%

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-aminoacetate (71)



The protected glycine menthyl ester compound **80** (14 g, 29.1 mmol) and ethylenediamine (5.8 mL, 87.5 mmol) were mixed well with pestle in mortar and the

reaction mixture was left at room temperature for 0.5 h. After completion of reaction (TLC), water was added to dissolve slight excess of amine and then chloroform was added. The mixture was filtered and the residue was washed thoroughly with chloroform. The chloroform layer separated, dried over anhydrous sodium sulphate, filtered and concentrated under reduce pressure to furnish the crude amine which was used in the next step without further purification (5.6 g crude). R_f 0.2 PE: EA 80:20

Mol. Formula **:** $C_{12}H_{23}NO_2$

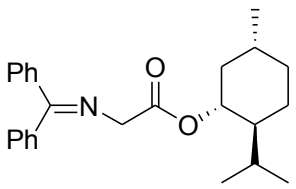
Yield **:** 90% (crude)

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) **:** 3247, 3019, 1728, 1655, 1561.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 4.70 (dt, *J* = 10.8, 4.3 Hz, 1H), 3.35 (s, 2H), 2.0-1.90 (m, 1H), 1.84-1.76 (m, 1H), 1.72-1.57 (m, 2H), 1.52-1.26 (m, 4H), 1.02-0.94 (m, 1H), 0.90-0.88 (m, 3H), 0.86-0.84 (m, 3H), 0.74-0.71 (m, 3H)

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 173.3 (C), 74.2 (CH), 46.7 (CH), 43.6 (CH_2), 40.6 (CH_2), 33.9 (CH_2), 31.1 (CH), 25.9 (CH), 23.2 (CH_2), 21.7 (CH_3), 20.4 (CH_3), 16.1 (CH_3).

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(diphenylmethyleneamino)acetate (82)



The menthyl glycinate **71** (5.6 g, 26.3 mmol) and diphenyl ketiminum chloride **81** (5.7 g, 26.3 mmol) was taken in dry DCM under nitrogen atmosphere and stirred at room temperature for 24 h. On completion of reaction the solid was filtered off, residue was washed with DCM. Combined organic layer was washed with water, dried over anhydrous sodium suphate, filtered and concentrated under reduced pressure. Column chromatography over SiO_2 (pretreated with Et_3N) rendered the pure product **82** (7.9 g, 20.9 mmol). R_f 0.5 PE: EA 95:5

Mol. Formula **:** $C_{25}H_{31}NO_2$

Yield **:** 75%

$[\alpha]_D^{25}$ **:** -42.49 (c 0.6, $CHCl_3$)

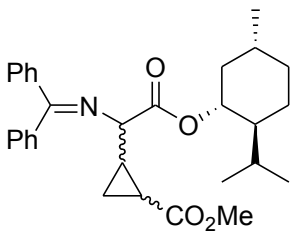
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) **:** 1736, 1659, 1599, 1447.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 7.68-7.63 (m, 2H), 7.52-7.40 (m, 4H), 7.38-7.31 (m, 2H), 7.24-7.17 (m, 2H), 4.76 (dt, *J* = 10.8, 4.2 Hz, 1H), 4.18 (s, 2H), 2.05-1.97 (m, 1H), 1.86-1.75 (m, 2H), 1.70-1.63 (m, 2H), 1.54-1.24 (m, 3H), 1.04-0.99 (m, 1H), 0.93-0.86 (m, 6H), 0.78-0.75 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 171.8 (C), 170.1 (C), 139 (C), 135.9 (C), 130.4 (CH), 129.9 (CH), 128.7 (2CH), 128.5 (2CH), 127.9 (2CH), 127.6 (2CH), 74.6 (CH), 55.7 (CH_2), 46.9 (CH_2), 40.8 (CH_2), 34.1 (CH_2), 31.3 (CH), 26.1 (CH), 23.3 (CH_2), 21.9 (CH_3), 20.7 (CH_3), 16.3 (CH_3).

Analysis **:** Calculated C 79.54, H 8.28, N 3.71%
Found C 79.21, H 8.21, N 3.66%

Methyl-2-[1-(diphenylmethyleneamino)-2-{(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl}-2-oxoethyl]cyclopropanecarboxylate (83)



To Schiff base **82** (2 g, 5.3 mmol) and methyl-4-bromocrotonate **36** (0.96 g, 5.3 mmol) in dry THF (25 mL) under argon was added lithium bromide (0.668 g, 7.6 mmol) taken into dry THF (5 mL). To this mixture was added triethylamine (0.92 mL, 6.6 mmol) taken into dry THF (10 mL) dropwise over a period of 0.5 h and the mixture was left to stir for 16 h at room temperature. After completion of the reaction (as per TLC), the reaction mixture was poured into saturated ammonium chloride solution and the aqueous layer extracted with ethyl acetate (2 x 25 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to

give crude cyclopropane **83**. Column chromatography over silica gel (pretreated with Et_3N) provided **83** (1 g, 32 mmol) as viscous liquid. R_f 0.5 PE: EA 90:10

Mol. Formula **:** $C_{30}H_{37}NO_4$

Yield **:** 72%

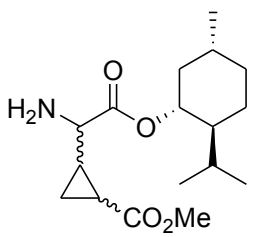
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) **:** 1719, 1622, 1441

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 7.60-7.56 (m, 2H), 7.47-7.37 (m, 4H), 7.35-7.25 (m, 2H), 7.13-7.09 (m, 2H), 4.68 (dt, *J* = 10.8, 4.2 Hz, 1H), 3.87 (d, *J* = 5.5 Hz, 1H), 3.64 (s, 4H), 2.10-1.80 (m, 4H), 1.74-1.58 (m, 3H), 1.44-1.37 (m, 1H), 1.31-1.24 (m, 1H), 1.21-1.12 (m, 1H), 1.04-0.95 (m, 2H), 0.89-0.86 (3H), 0.81-0.77 (m, 3H), 0.72-0.69 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 173.7 (C), 170.6 (C), 169.9 (C), 139.1 (C), 136.1 (C), 130.2 (CH), 128.6 (2CH), 128.4 (CH), 128.3 (2C), 127.7 (2CH), 127.5 (2CH), 74.5 (CH), 64.5 (CH_3), 51.2 (CH), 46.9 (CH), 40.6 (CH_2), 34.1 (CH_2), 31.2 (CH), 26.1 (CH), 24.6 (CH), 23.4 (CH_2), 21.8 (CH_3), 20.4 (CH_3), 16.5 (CH_3), 16.2 (CH), 11.6 (CH_2).

Analysis **:** Calculated C 75.76, H 7.84, N 2.94%
Found C 75.42, H 7.78, N 2.89%

Methyl-2-[1-amino-2-{(1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy}-2-oxoethyl) cyclopropanecarboxylate (84)



The well stirred mixture of cyclopropane **83** (1.8 g**,** 3.7 mmol) in methanol was treated with 2N HCl and stirred further for 0.5 h at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate (3 x 25 mL). The aqueous layer was neutralised by the addition of solid $NaHCO_3$ and extracted with ethyl acetate (3 x 25

mL). Organic layer washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to furnish **84** (1 g, 3.2 mmol).

Mol. Formula : $C_{17}H_{29}NO_4$

Yield : 80%

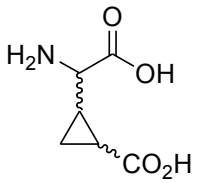
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3350, 1732.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.86 (br s, 2H), 4.78 (m, 1H), 3.64 (s, 4H), 2.35 (m, 1H), 2.17-1.82 (m, 3H), 1.79-1.60 (m, 2H), 1.55-1.18 (m, 4H), 1.13-1.01 (m, 3H), 0.93-0.86 (m, 6H), 0.75-0.73 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 173.1 (C), 167.5 (C), 77.6 (CH), 55.1 (CH), 51.9 (CH_3), 46.5 (CH), 40.2 (CH_2), 33.8 (CH_2), 31.2 (CH), 25.8 (CH), 23.1 (CH_2), 21.7 (CH_3), 20.6 (CH_3), 19.2 (CH), 16.1 (CH_3), 15.6 (CH), 13.8 (CH_2).

Analysis: : Calculated C 65.57, H 9.39, N 4.50%
Found C 65.29, H 9.32, N 4.45%

2-[Amino (carboxy) methyl] cyclopropanecarboxylic acid (85)



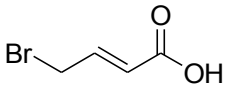
The amino ester **84** (1 g, 3.2 mmol) was treated with LiOH (0.22 g, 9.5 mmol) taken in 20 mL of methanol: water (1:1) and was allowed to stir for 6 h at room temperature. The methanol was removed on rotary evaporator and the aqueous layer extracted with ethyl acetate (3 x 25 mL). The aqueous layer was concentrated to 5 mL in rotary evaporator and loaded onto Dowex 50 x 8 (20-60, H^+ form) ion exchange resin. The column was eluted first with distilled water (2 x 100 mL) and then with 100 mL of 10% ammonia solution. The eluate was concentrated under reduced pressure and the crude product recrystallised from water to furnish colourless crystals of amino acid **85** (0.43 g, 2.7 mmol).

Mol. Formula : $C_6H_9NO_4$

$[\alpha]_D^{25}$: +14 (c 0.5, H_2O)

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 3.08 (d, *J* = 9.8 Hz, 1H), 1.60-1.41 (m, 2H), 1.17-0.97 (m, 2H).

(*E*)-4-Bromobut-2-enoic acid (91)



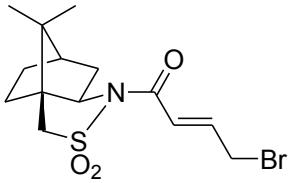
To a well-stirred mixture of crotonic acid (5 g, 58.1 mmol) in CCl_4 (60 mL) was added recrystallised N-bromosuccinimide (10 g, 58.1 mmol) and catalytic amount of benzoyl peroxide under nitrogen and heated to reflux for 5 h. On completion of reaction the mixture was cooled to ambient temperature. Solid succinimide precipitated out which was removed by filtration. The filtrate was concentrated under reduced pressure to furnish the crude bromocrotonic acid (8 g, 48.7 mmol), which was used as such with out further purification.

Mol. Formula **:** $C_4H_5BrO_2$

Yield **:** 94% (crude)

^{1}H (200 MHz, $CDCl_3$) **:** δ 10.54 (br s, 1H), 7.19-7.04 (m, 1H), 6.05 (d, *J* = 15.6 Hz, 1H), 4.04 (d, *J* = 7.3 Hz, 2H).

4-Bromocrotonylsultam (88)



Bromocrotonic acid **91** (4 g, 24.3 mmol) was taken in benzene (20 mL) and cooled to 0 ^oC. Freshly distilled thionyl chloride (3.6 mL, 48.6 mmol) was added slowly. After completion of addition the reaction mixture was heated to reflux for 10 h. The excess of thionyl chloride was co-distilled out with benzene and the acid chloride was used as such without further purification.

Weighed amount of NaH (0.98 g, 60 %, 48.3 mmol) in dry benzene was taken in a two neck round bottom flask under argon atmosphere. 10,2-Camphor sultam (2.6 g, 12.2 mmol) dissolved in dry benzene (20 mL) was added slowly to it at room temperature. After completion of addition the mixture was left to stir at room temperature for 1h. The freshly prepared bromocrotonyl chloride **89** (4.4 g, 24.1 mmol) was added drop wise. The mixture was left to stir at room temperature till the completion of the reaction

(TLC). The reaction was quenched by addition of ice cold water. The organic layer separated and the aqueous layer extracted with ethyl acetate (3 x 25 mL). The combined organic layer was washed with aqueous saturated sodium bicarbonate solution, brine, dried over anhydrous sodium sulphate and filtered. Removal of solvent under reduced pressure furnished the crude product, which was purified by column chromatography to render the pure product (3.1 g, 8.5 mmol) in 60% yield. R_f 0.6 (PE: EA 70:30)

Mol. Formula **:** $C_{14}H_{20}BrNO_3S$

Yield **:** 60%

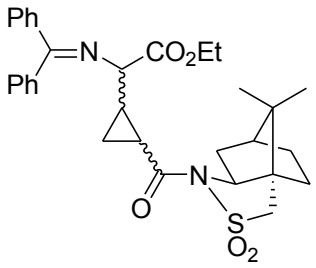
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) **:** 1683.

^{1}H (200 MHz, $CDCl_3$) **:** δ 7.15-7.00 (m, 1H), 6.72 (d, *J* = 14.8 Hz, 1H), 4.05 (d, *J* = 7.8 Hz, 2H), 3.92 (t, *J* = 6.7 Hz, 1H), 3.47 (d, *J* = 4.7 Hz, 2H), 2.17-2.07 (m, 2H), 1.99-1.84 (m, 3H), 1.50-1.35 (m, 2H), 1.17 (s, 3H), 0.98 (s, 3H).

^{13}C (50 MHz, $CDCl_3$) **:** δ 162.6 (C), 142.3 (CH), 123.5 (CH), 64.9 (CH), 52.9 (CH_2), 48.4 (C), 47.7 (C), 44.5 (CH_3), 38.2 (CH_2), 32.7 (CH_2), 28.9 (CH_2), 26.3 (CH_2), 20.7 (CH_3), 19.8 (CH_3).

Mass (EI) **:** *m/z* 366 (M^++4), 362 (M^+), 298, 134, 108, 93, 69.

Compound 93



To Schiff's base **92** (1.48 g, 5.5 mmol) and bromocrotonyl sultam **88** (2 g, 5.5 mmol) in dry THF (25 mL) under argon was added lithium bromide (0.72 g, 8.2 mmol) taken into dry THF (5 mL). To this mixture was added triethyl amine (0.7 g, 6.9 mmol) taken into dry THF (10 mL) drop wise over a period of 0.5 h and the mixture was left to stir for 16 h at room temperature. After completion of the reaction (as per TLC), the reaction mixture was poured into saturated ammonium chloride solution and the aqueous layer extracted with ethyl acetate (2 x 25 mL). The combined organic layer was dried over

anhydrous sodium sulphate and concentrated under reduced pressure to give crude cyclopropane that was purified by column chromatography (SiO_2) (2.1 g, 3.8 mmol) to render **93**.R_f 0.4 (PE: EA 90:10)

Mol. Formula : $C_{31}H_{36}N_2O_5S$

Yield : 70%.

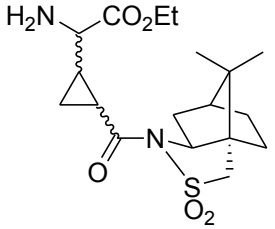
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 1733, 1683.

^{1}H (200 MHz, $CDCl_3$) : δ 7.57-7.48 (m, 2H), 7.37-7.32 (m, 3H), 7.30-7.13 (m, 5H), 4.11 (q, *J* = 7.3 Hz, 2H), 3.80 (t, *J* = 7.3 Hz, 1H), 3.64, 3.57 (2d, *J* = 7.0, 1H, 45:55), 3.36 (br s, 2H), 2.30-2.12 (m, 2H), 2.08-1.94 (m, 2H), 1.89-1.72 (m, 4H), 1.39-1.26 (m, 2H), 1.20 (t, *J* = 7.3 Hz, 3H), 1.17 (m, 1H), 1.07 (s, 3H), 0.88 (s, 3H).

^{13}C (50 MHz, $CDCl_3$) : Mixture of diastereomers

Mass (EI) : *m/z* 548 (M^+), 475 (-CO_2Et), 334(-sultam), 311, 232, 182, 165, 105.

Compound 94



The well-stirred mixture of cyclopropane **93** (2 g, 3.8 mmol) in methanol (5 mL) was treated with 2N HCl and stirred further for 0.5 h at room temperature. The reaction mixture was diluted with water (5 mL) and extracted ethyl acetate (3 x 25 mL). The aqueous layer was neutralized by the addition of solid $NaHCO_3$ (pH 10) and extracted with ethyl acetate (3 x 25 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish **94** in 80% crude yield (1.12 g, 2.9 mmol).

Mol. Formula : $C_{18}H_{28}N_2O_5S$

Yield : 80%

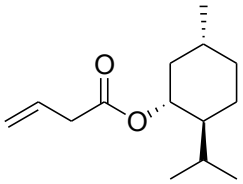
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3018, 1732, 1685.

1H (200 MHz, $CDCl_3$) **:** δ 4.19 (q, *J* = 7.3 Hz, 2H), 3.90-3.78 (m, 1H), 3.48 (br s, 2H), 3.16-3.00 (m, 1H), 2.33-2.23 (m, 1H), 2.12-2.00 (m, 2H), 1.96-1.74 (m, 6H), 1.42-1.35 (m, 2H), 1.28 (t, *J* = 7.3 Hz, 3H), 1.18 (s, 3H), 0.98 (s, 3H).

13C (50 MHz, $CDCl_3$) **:** mixture of diastereomers

Mass (ESI) **:** *m/z* 385.57 (M^++1).

***l*-Menthyl 3-Butenoate (96)**



To a well-stirred, cooled solution of *l*-menthol (5 g, 32 mmol) and triethyl amine was added crotonyl chloride (5.02 g, 48 mmol) dropwise. The pasty mass was stirred till the completion of reaction (TLC). It was quenched with the addition of 3N HCl (until acidic) and diluted with ether. The organic layer was separated and the aqueous layer extracted with ethyl ether. Combined organic layers were washed with 10% KOH, 3N HCl, brine and dried over anhydrous sodium sulphate and filtered. Concentration under reduced pressure afforded the crude compound (6.48 g, 28.8 mmol), which was used in the next step without purification. R_f 0.6 (PE: EA 95:5)

Mol. Formula **:** $C_{14}H_{24}O_2$

Yield **:** 90%

$[\alpha]_D^{25}$ **:** –80 (c 3, EtOH) [lit. –76.2 (c 6.76, EtOH)]

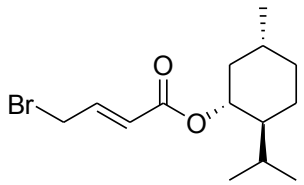
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) **:** 3020, 2958, 2871,1722.

^{1}H NMR (200MHz, $CDCl_3$) **:** δ 5.92-5.71 (m, 1H), 5.07 (br d, 1H), 5.00 (brd, 1H), 4.58 (dt, *J* = 10.8, 4.2, Hz, 1H), 2.95 (d, *J* = 7.0 Hz, 2H), 1.96-1.86 (m, 1H), 1.81-1.69 (m, 1H), 1.61-1.54 (m, 2H), 1.45-1.32 (m, 1H), 1.28-1.22 (m, 1H), 0.99-0.89 (m, 3H), 0.83-0.81 (m, 3H), 0.79-0.78 (m, 3H), 0.67 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) **:**δ 170.5 (C), 130.5 (CH), 118.1 (CH_2), 74.2 (CH), 47.0 (CH_3), 40.8 (CH_2), 39.4 (CH_2), 34.3 (CH_2),

31.4 (CH_3), 26.3 (CH_3), 23.5 (CH_2), 21.9 (CH_3), 20.6 (CH_3), 16.4 (CH_3).

***l*-Menthyl-4-bromocrotonate (95)**



The crude compound **96** (5 g, 22.3 mmol) was dissolved in 50 mL of CCl_4 and stirred at 0 ^oC. Bromine (5.6 g, 35.6 mmol) was added dropwise under cooling condition. After the addition was complete the volatile solvent was removed under vacuum and the dibromide was used as such for next step.

Dibromide was taken in freshly dried dimethoxyethane (30 mL) and DBU (5 g, 33.3 mmol) was added dropwise at 0 ^oC. After completion of reaction (TLC), it was quenched by addition of 3N HCl and diluted with ether. Organic layer was separated and the aqueous layer was extracted with ether (3 x 50 mL). Combined organic layers were washed with 3N HCl, 10% KOH, brine, dried over anhydrous sodium sulphate and filtered. Concentration under reduced pressure rendered the crude product, which was purified by column chromatography (SiO_2) to furnish the pure product (5.4 g, 17.9 mmol) in 80% yield. R_f 0.6 PE: EA (95:5)

Mol. Formula : $C_{14}H_{23}BrO_2$

Yield : 80%

$[\alpha]_D^{25}$: –62.2 (c 3.5, EtOH) [lit. [α] –60.2, c 3.32, EtOH]

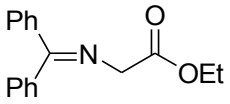
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 2954, 2869, 1719, 1655.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.05-6.88 (m, 1H), 6.13-5.96 (br d, 1H), 4.74 (dt, *J* = 10.8, 4.2 Hz, 1H), 4.00 (dd, *J* = 7.5, 1.5 Hz, 1H) 2.06-1.96 (m, 1H,), 1.92-1.78 (m, 1H), 1.74-1.60 (m, 2H), 1.53-1.33 (m, 2H), 1.11-0.96 (m, 2H), 0.93-0.91 (m, 3H), 0.90-0.88 (m, 3H), 0.85-0.83 (m, 1H), 0.76 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 164.4 (C), 141.1 (CH), 124.9 (CH), 74.2 (CH), 46.9 (CH_3), 40.7 (CH_2), 34.1 (CH_2), 31.2 (CH_3),

28.7 (CH_2), 26.2 (CH_3), 23.4 (CH_2), 21.8 (CH_3), 20.5 (CH_3), 16.3 (CH_3).

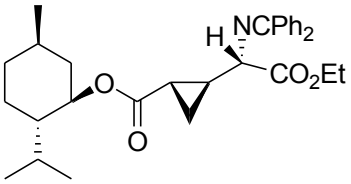
Diphenylimine ethyl glycinate (92)



Mol. Formula: **:** $C_{17}H_{17}O_2$

^{1}H NMR (200 MHz, $CDCl_3$): **:** δ 7.67-7.65 (m, 2H), 7.50-7.41 (m, 4H), 7.35-7.32 (m, 2H), 7.21-7.19 (m, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.19 (s, 2H), 1.29 (t, *J* = 7.2 Hz, 3H).

***Trans*-Ethyl-*N*-(diphenylmethylene)-α-(2-carbomenthoxycyclopropyl)-glycinate (98)**



To Schiff's base **92** (1g, 3.7 mmol) and menthyl-4-bromocrotonate **95** (1.4 g, 4.6 mmol) in dry THF (25 mL) under argon was added lithium bromide (0.48 g, 5.6 mmol) in dry THF (5 mL). To this mixture was added triethylamine (0.471 g, 4.6 mmol) in dry THF (10 mL) dropwise over a period of 0.5 h and the mixture was left to stir for 16 h at room temperature. After completion of the reaction (as per TLC), the reaction mixture was poured into saturated ammonium chloride solution and the aqueous layer extracted with ethyl acetate (2 x 25 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give crude cyclopropane **98**. Column chromatography over SiO_2 (pretreated with Et_3N) provided **98** as thick viscous liquid (1.27 g, 72% and 92% diastereomeric ratio). R_f 0.5 (PE: EA 0.5 90:10)

Mol. Formula **:** $C_{31}H_{39}NO_4$

Yield **:** 72%

$[\alpha]_D^{25}$ **:** - 23.2 (c 0.26, $CHCl_3$)

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) **:** 1722, 1446.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 7.63-7.16 (m, 10H), 4.66 (dt, *J* = 10.6, 4.4 Hz, 1H), 4.17 (m, 2H), 3.92 (d, *J* = 5.4 Hz, 1H), 2.10-

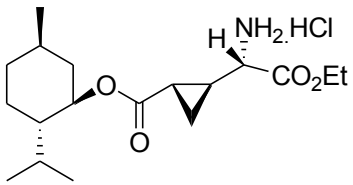
1.89 (m, 3H), 1.85-1.76 (m, 1H), 1.71 (br s, 1H), 1.65 (br s, 1H), 1.55-1.35 (m, 2H), 1.27 (t, *J* = 7.3 Hz, 3H), 1.22-1.15 (m, 1H), 1.08-1.02 (m, 1H), 0.94-0.89 (m, 9H), 0.79-0.75 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 173.0 (C), 170.9 (C), 170.7 (C), 139.1(C), 136.1 (C), 130.3 (CH), 128.8 (2CH), 128.6 (CH), 128.4 (2CH), 127.8 (2CH), 127.6 (2CH), 73.7 (CH), 64.6 (CH), 60.7 (CH_2), 46.9 (CH), 40.8 (CH_2), 34.2 (CH_2), 31.2 (CH), 26.1 (CH), 24.7 (CH), 23.3 (CH_2), 21.9 (CH_3), 20.7 (CH_3), 17.1 (CH), 16.2 (CH_3), 14.1 (CH_3), 11.5 (CH_2).

MS (ESI) **:** *m/z* 489.01, 416.

Analysis **:** Calculated C 76.04, H 8.03, N 2.86%
Found C 76.09, H 8.10, N 3.03%.

(*2S,1'S,2'*S) Ethyl α-(2-carbomenthoxycyclopropyl)-glycinate Hydrochloride (99)



The cyclopropane compound **98** (1.27g, 2.6 mmol) was treated with 2N HCl (20 mL) and the mixture was allowed to stir at room temperature for 0.5 h. The hydrochloride salt of the free amine precipitated out as a white solid on adding ethyl acetate which was filtered and washed several times with ethyl acetate to remove benzophenone. The solid was dried under vacuum to yield **99** (0.63g, 60%).

Mol. Formula **:** $C_{18}H_{32}NO_4Cl$

Yield **:** 60%

$[\alpha]_D^{25}$ **:** + 42.8 (c 0.51, Isopropanol)

Mp **:** 190-193°C

IR (KBr) $\tilde{\nu}$ (cm^{-1}) **:** 2902, 1753, 1710, 1591.

^{1}H NMR (500 MHz, $DMSOd_6$) **:** δ 8.77 (br s, 3H), 4.54 (dt, *J* = 10.7, 4.4 Hz, 1H), 4.24-4.14 (m, 2H), 3.65 (d, *J* = 9.9 Hz, 1H), 2.47

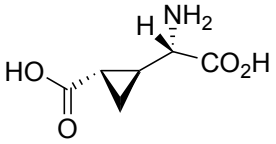
(m, 1H), 1.97-1.93 (m, 1H), 1.84-1.76 (m, 2H), 1.66-1.57 (m, 3H), 1.40 (br s, 1H), 1.35-1.30 (m, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.18-1.15 (m, 1H), 1.09-1.05 (m, 1H), 1.01-0.09 (m, 2H), 0.84 (t, *J* = 7.2 Hz , 6H), 0.67 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (125 MHz, DMSOd$_6$) **:** δ 171.7 (C), 168.3 (C), 74.0 (CH), 62.1 (CH_2), 54.0 (CH), 46.6 (CH), 40.6 (CH_2), 33.8 (CH_2), 30.9 (CH), 26.0 (CH), 23.3 (CH_2), 22.0 (CH_3), 20.8 (CH), 20.6 (CH_3), 18.8 (CH), 16.5 (CH_3), 14.0 (CH_3), 13.2 (CH_2).

MS (EI) **:** *m/z* 252, 114, 96, 68, 55.

Analysis **:** Calculated C 59.74, H 8.90, N 3.87, Cl 9.80%
Found C 59.95, H 8.65, N 3.72, Cl 9.85%

(2*S*, 1'*S*, 2'*S*)-α-(2-Carboxycyclopropyl) glycine (100)



The amino ester **99** (0.63 g, 1.55 mmol) was treated with LiOH (0.098 g, 4.65 mmol) in 20 mL of methanol: water (1:1) and was allowed to stir for 6 h at room temperature. The methanol was removed on rotary evaporator and the aqueous layer extracted with ethyl acetate (3 x 25 mL). The aqueous layer was concentrated to 5 mL in rotary evaporator and loaded onto a column packed with Dowex 50 x 8 (20-60, H^+ form) ion exchange resin. The column was eluted first with distilled water (2 x 100 mL) and then with 100 mL of 10% ammonia solution. The eluate (ammonia solution) was concentrated under reduced pressure and the crude product recrystallised from water to furnish colourless crystals of amino acid **100** (0.213 g, 87%).

Mol. Formula **:** $C_6H_9NO_4$

Yield **:** 87%

$[\alpha]_D^{25}$ **:**+106 (c 0.50, H_2O) {lit. $[\alpha]_D^{25}$ +102 (c 0.50, H_2O)}

Mp **:** 245-250°C (dec.){Mp: 243-247°C (dec.)}

IR (KBr) $\tilde{\nu}$ (cm^{-1}) **:** 2923, 1688, 1616, 1586.

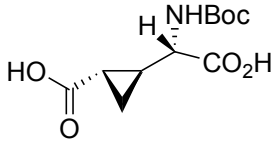
^{1}H NMR (500 MHz, D_2O) **:** δ 3.22 (d, *J* = 9.9 Hz, 1H), 1.71 (ddd, *J* = 9.0, 5.0, 4.1 Hz, 1H), 1.63 (dddd, *J* = 9.9, 9.0, 6.0, 4.1 Hz, 1H), 1.28 (ddd, *J* = 9.0, 6.0, 5.1 Hz, 1H), 1.17 (ddd, *J* = 9.0, 5.0, 5.1 Hz, 1H).

^{13}C NMR (125 MHz, D_2O) **:** δ 179.5 (C), 172.9 (C), 155.2 (C), 57.6 (CH), 21.4 (CH), 20.4 (CH), 13.1 (CH_2).

MS (EI) **:** *m/z* 114, 96, 78, 68, 55.

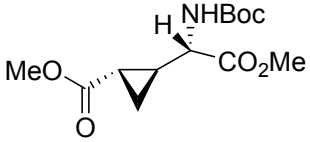
Analyis **:** Calculated C 45.28, H 5.66, N 8.80%
Found C 44.88, H 5.42, N 8.52%

(2*S*, 1'*S*, 2'*S*)*N*-Boc-α-(2-carbomethoxycyclopropyl)-glycine (111)



The unrecrystallised amino acid **100** (0.20g, 1.30 mmol) was taken in NaOH solution (0.060 g in 2 mL of water) and diluted with 1.25 mL of *tert*-butanol. To the well stirred reaction mixture was added ditert butyl dicarbonate (0.292g, 1 mmol) dropwise and left to stir overnight at room temperature. The reaction mixture was extracted with hexane (2 x 25 mL) and the organic layer was extracted with saturated sodium bicarbonate solution (3 x 25 mL). The combined aqueous layers were acidified to pH 1-1.5 with 10% $KHSO_4$ solution and extracted with diethyl ether (4 x 25 mL). The organic layer was washed with water (2 x 25 mL) and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The protected amino acid **111** was used as such without further purification.

(2*S*, 1'*S*, 2'*S*) Methyl-*N*-Boc-α-(2-carbomethoxycyclopropyl)-glycinate (108)



The crude compound **111** (0.163 g, 0.6 mmol) was taken in ether (10 mL) and cooled and then treated in portions with diazomethane, generated *in situ*, until the yellow colour persisted and then concentrated under vaccum. Purification by column chromatography (SiO_2) rendered methyl ester **108** (0.113g, 48%, 97%ee).

Mol. Formula	**:** $C_{13}H_{21}NO_6$
Yield	**:** 48%
$[\alpha]_D^{25}$	**:** +108.6 (c 0.88, $CHCl_3$)
Mp	**:** 80 ^oC
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	**:** 3440, 1720.
^1H NMR (200 MHz, $CDCl_3$)	**:** δ 5.22 (br d, 1H), 3.96 (br s, 1H), 3.76 (s, 3H), 3.65 (s, 3H), 1.77-1.70 (m, 2H), 1.42 (s, 9H), 1.27-1.19 (m, 1H), 1.09-0.99 (m, 1H).
13C NMR (50 MHz, $CDCl_3$)	**:** δ 173.6 (C), 171.6 (C), 155.2 (C), 80.2 (C), 54.8 (CH), 52.5 (CH_3), 51.9 (CH_3), 28.2 ($3CH_3$), 24.1 (CH), 17.6 (CH), 12.9 (CH_2).
MS (ESI)	**:** *m/z* 286, 188, 128, 156.
Analysis	**:** Calculated C 54.35, H 7.36, N 4.87% Found C 53.96, H 7.48, N 4.67%
HPLC	**:** Column: Chiralcel-OD, mobile phase: 10% IPA: *n*-Hex, flow rate: 0.4 ml/min, UV detection: 225 nm, t_R: minor isomer 13.5 min, $t_{R:}$ major isomer14.4 min. 97 % ee (considering the optically purity of *l*-menthol used).

Single crystals of the title compound (**108**) were crystallized from diethyl ether:pet ether and good quality crystal was selected using Leica Polarizing Microscope. X-ray intensity data were collected on a Bruker SMART APEX CCD diffractometer at room temperature.

Crystal data: Compound **108** $C_{13}H_{21}NO_6$, M = 287.31, crystal dimensions 1.26 x 0.14 x 0.10 mm, crystal system hexagonal, space group $P6_1$, a = 9.7482(7), c = 28.427(4) Å, V=2339.4(4) $Å^3$, Z = 6, D_c = 1.224 g cm^{-3}, μ (Mo-Kα) = 0.097 mm^{-1}, T = 293(2) K, 11720 reflections collected, 2512 unique [$I>2\sigma(I)$], S=1.250, R value 0.0556, $wR2$ = 0.1092 (all data R = 0.0627, $wR2$ = 0.1121). All the data were corrected for Lorentzian, polarisation and absorption effects using Bruker's SAINT and SADABS programs. SHELX-97[1] was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model.

[1] G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, university of Gottingen, Germany, 1997.

Table 1. Crystal data and structure refinement for comp.108

Identification code	compound 6
Empirical formula	C13 H21 N O6
Formula weight	287.31
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Hexagonal, P61
Unit cell dimensions	a = 9.7482(7) Å alpha = 90 deg. b = 9.7482(7) Å beta = 90 deg. c = 28.427(4) Å gamma = 120 deg.
Volume	2339.4(4) $Å^3$
Z, Calculated density	6, 1.224 Mg/m^3
Absorption coefficient	0.097 mm^{-1}
F(000)	924
Crystal size	1.26 x 0.14 x 0.10 mm
Theta range for data collection	2.41 to 25.00 deg.
Limiting indices	-11<=h<=11, -9<=k<=11, -33<=l<=33
Reflections collected / unique	11720 / 2753 [R(int) = 0.0338]
Completeness to theta = 25.00	100.0 %
Max. and min. transmission	0.9908 and 0.8878
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2753 / 1 / 186
Goodness-of-fit on F^2	1.250
Final R indices [I>2sigma(I)]	R1 = 0.0556, wR2 = 0.1092
R indices (all data)	R1 = 0.0627, wR2 = 0.1121
Absolute structure parameter	1.1(15)

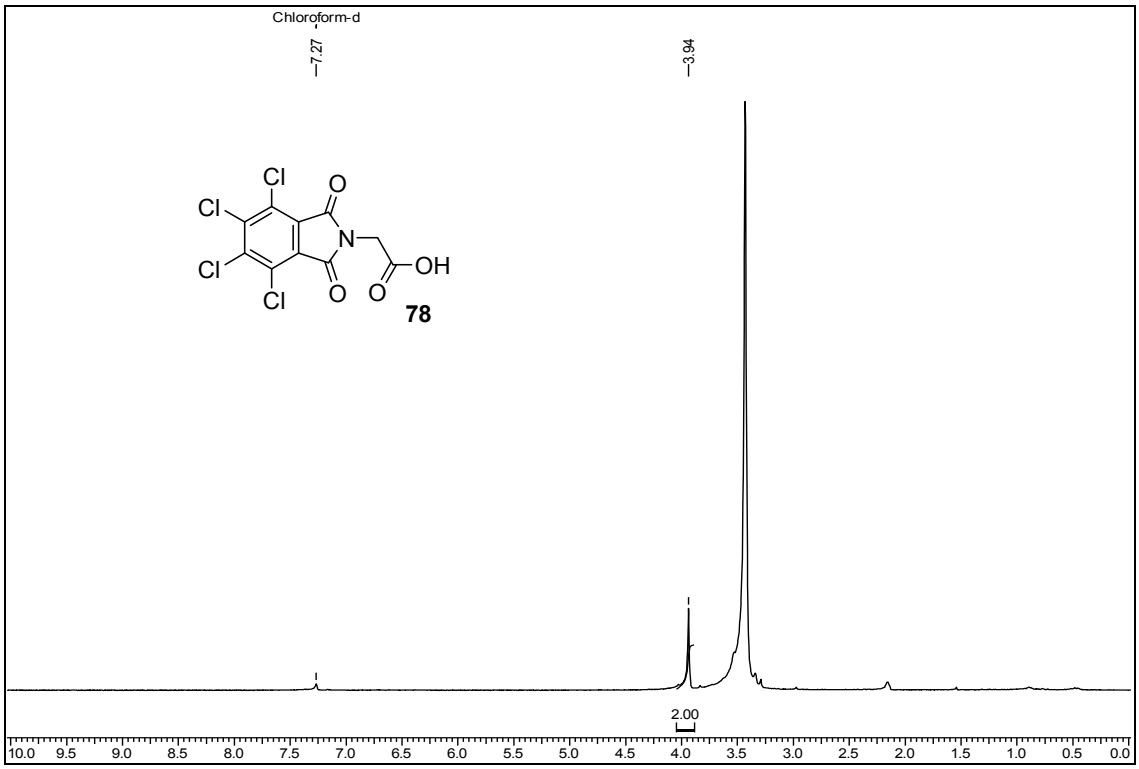
Largest diff. peak and hole 0.150 and -0.117 e.A^{-3}

Table 2. Bond lengths [Å] and angles [deg] for Comp.108

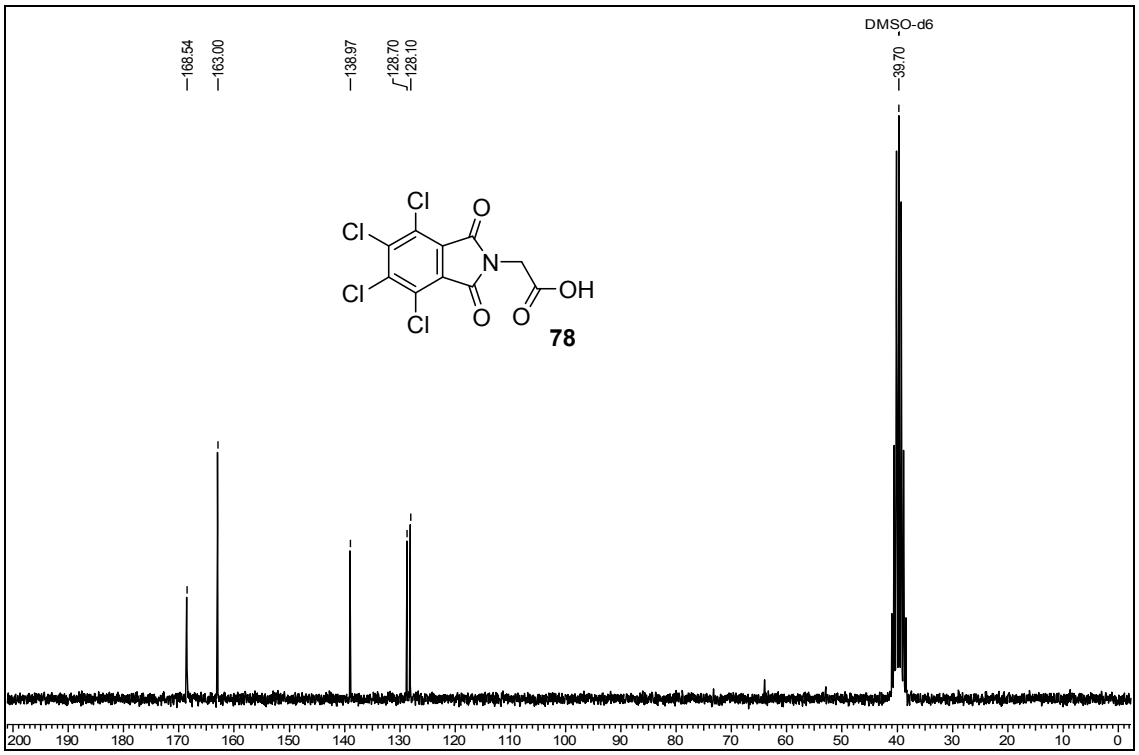
O(3)-C(3)	1.212(3)
C(3)-O(4)	1.328(3)
C(3)-N	1.340(3)
N-C(2)	1.441(4)
O(4)-C(4)	1.469(4)
C(2)-C(1')	1.503(4)
C(2)-C(1)	1.514(4)
O(2)-C(1)	1.301(4)
O(2)-C(8)	1.453(5)
C(1')-C(3')	1.473(4)
C(1')-C(2')	1.507(4)
O(1)-C(1)	1.182(4)
O(1')-C(4')	1.189(4)
C(4)-C(5)	1.478(5)
C(4)-C(7)	1.506(5)
C(4)-C(6)	1.517(6)
O(2')-C(4')	1.326(4)
O(2')-C(5')	1.440(5)
C(2')-C(4')	1.476(4)
C(2')-C(3')	1.503(5)
O(3)-C(3)-O(4)	126.0(3)
O(3)-C(3)-N	122.4(3)
O(4)-C(3)-N	111.6(2)
C(3)-N-C(2)	120.6(2)
C(3)-O(4)-C(4)	121.0(2)
N-C(2)-C(1')	110.8(2)
N-C(2)-C(1)	113.7(2)
C(1')-C(2)-C(1)	109.1(2)
C(1)-O(2)-C(8)	114.5(3)
C(3')-C(1')-C(2)	118.9(3)
C(3')-C(1')-C(2')	60.6(2)
C(2)-C(1')-C(2')	118.9(3)
O(4)-C(4)-C(5)	110.0(3)
O(4)-C(4)-C(7)	102.7(3)
C(5)-C(4)-C(7)	110.8(3)
O(4)-C(4)-C(6)	109.2(3)
C(5)-C(4)-C(6)	112.7(4)
C(7)-C(4)-C(6)	111.0(4)
O(1)-C(1)-O(2)	124.9(3)
O(1)-C(1)-C(2)	122.6(3)
O(2)-C(1)-C(2)	112.4(3)
C(4')-O(2')-C(5')	115.0(3)
C(4')-C(2')-C(3')	116.6(3)
C(4')-C(2')-C(1')	116.7(3)
C(3')-C(2')-C(1')	58.6(2)
O(1')-C(4')-O(2')	123.8(3)
O(1')-C(4')-C(2')	124.9(3)
O(2')-C(4')-C(2')	111.3(3)
C(1')-C(3')-C(2')	60.8(2)

Table 3. Torsion angles [deg] for comp.108

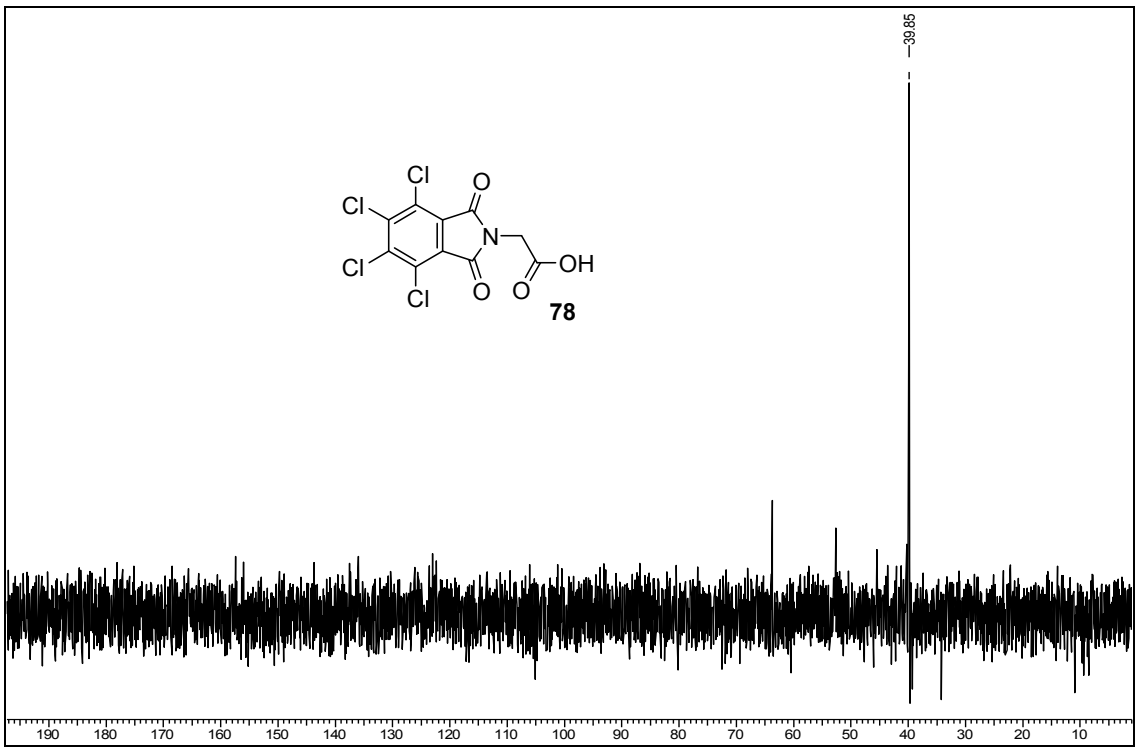
O(3)-C(3)-N-C(2)	0.2(4)
O(4)-C(3)-N-C(2)	179.9(2)
O(3)-C(3)-O(4)-C(4)	-7.8(4)
N-C(3)-O(4)-C(4)	172.5(3)
C(3)-N-C(2)-C(1')	177.4(3)
C(3)-N-C(2)-C(1)	54.0(4)
N-C(2)-C(1')-C(3')	151.8(3)
C(1)-C(2)-C(1')-C(3')	-82.2(3)
N-C(2)-C(1')-C(2')	81.5(3)
C(1)-C(2)-C(1')-C(2')	-152.6(3)
C(3)-O(4)-C(4)-C(5)	-60.7(4)
C(3)-O(4)-C(4)-C(7)	-178.6(3)
C(3)-O(4)-C(4)-C(6)	63.5(4)
C(8)-O(2)-C(1)-O(1)	6.5(5)
C(8)-O(2)-C(1)-C(2)	-176.4(3)
N-C(2)-C(1)-O(1)	-150.8(3)
C(1')-C(2)-C(1)-O(1)	84.9(4)
N-C(2)-C(1)-O(2)	32.0(3)
C(1')-C(2)-C(1)-O(2)	-92.3(3)
C(3')-C(1')-C(2')-C(4')	106.3(3)
C(2)-C(1')-C(2')-C(4')	-144.9(3)
C(2)-C(1')-C(2')-C(3')	108.8(3)
C(5')-O(2')-C(4')-O(1')	2.1(5)
C(5')-O(2')-C(4')-C(2')	-179.2(3)
C(3')-C(2')-C(4')-O(1')	33.1(5)
C(1')-C(2')-C(4')-O(1')	-33.2(4)
C(3')-C(2')-C(4')-O(2')	-145.6(3)
C(1')-C(2')-C(4')-O(2')	148.1(3)
C(2)-C(1')-C(3')-C(2')	-108.8(3)
C(4')-C(2')-C(3')-C(1')	-106.4(3)



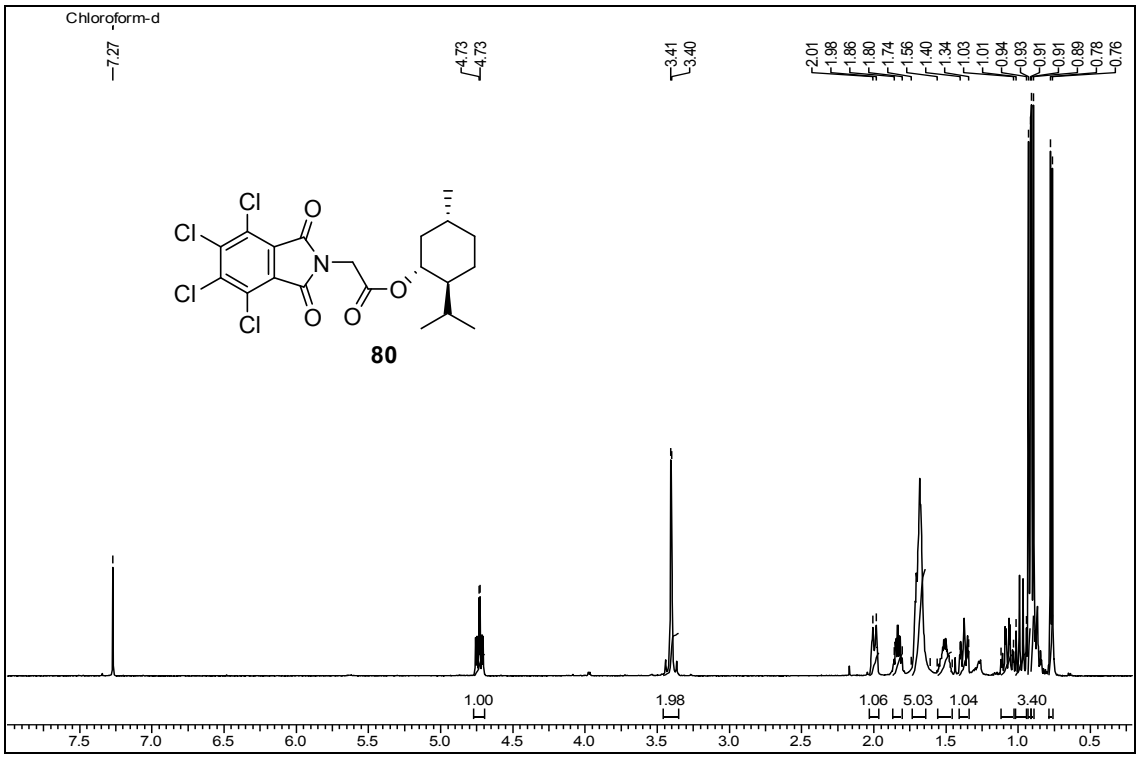
^{1}H NMR (DMSO-d_6, 200 MHz) spectrum of compound 78



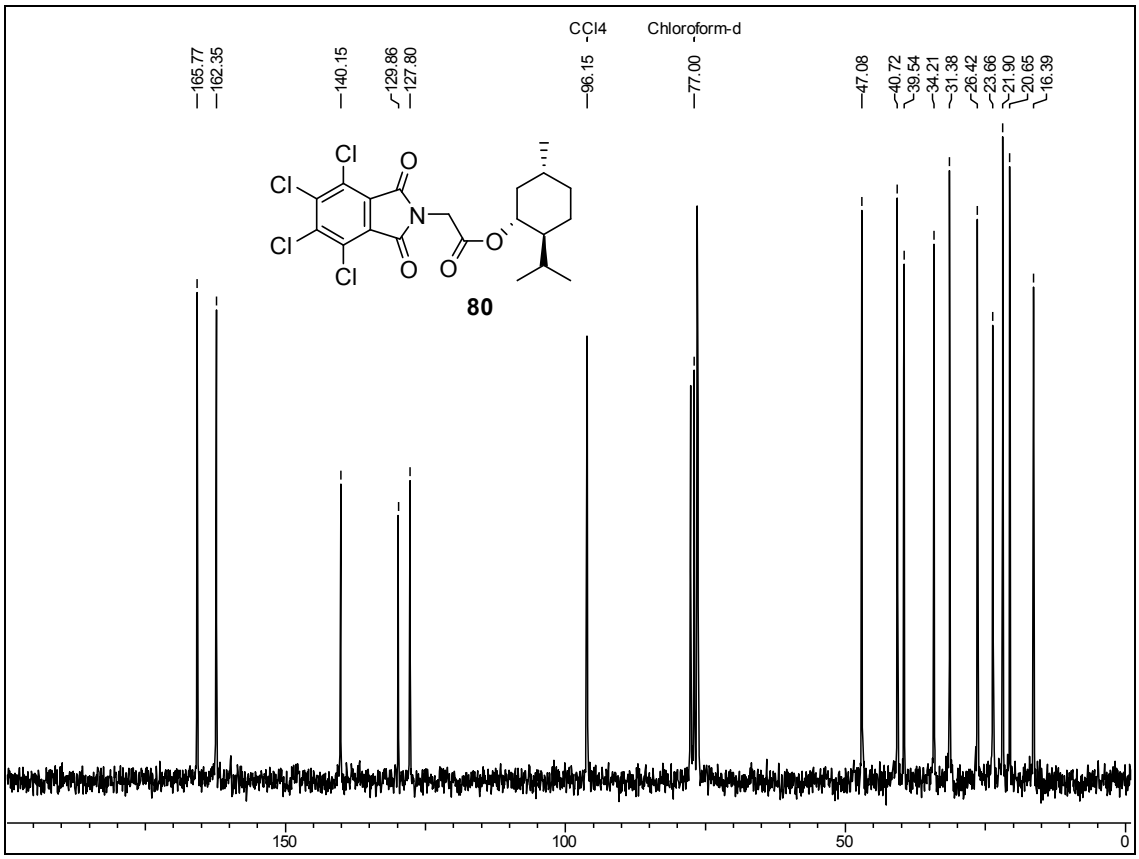
^{13}C NMR (DMSO-d$_6$, 50 MHz) spectrum of compound 78



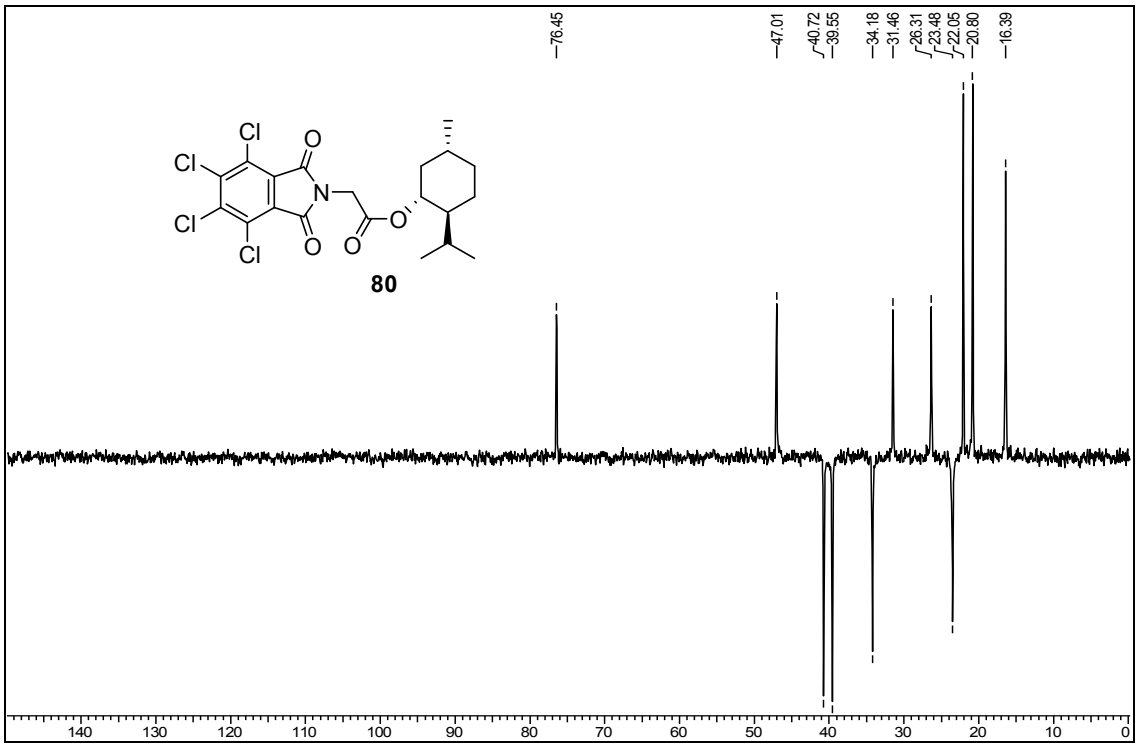
DEPT (DMSO-d$_6$, 50 MHz) spectrum of compound 78



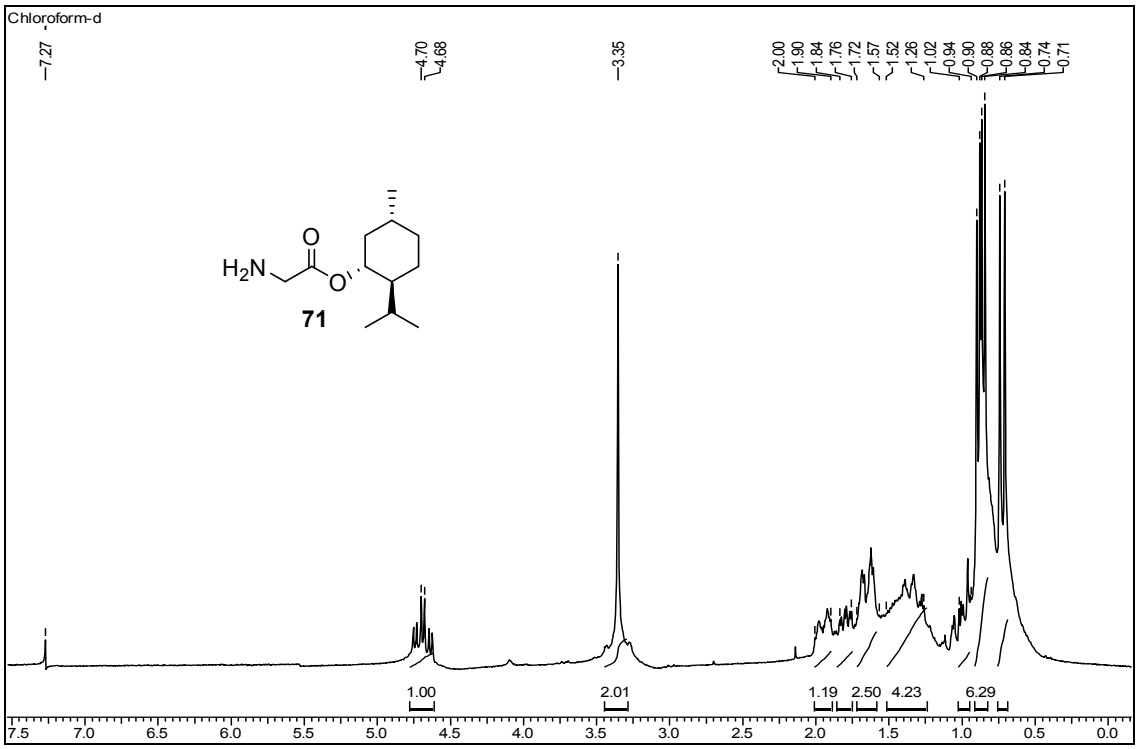
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 80



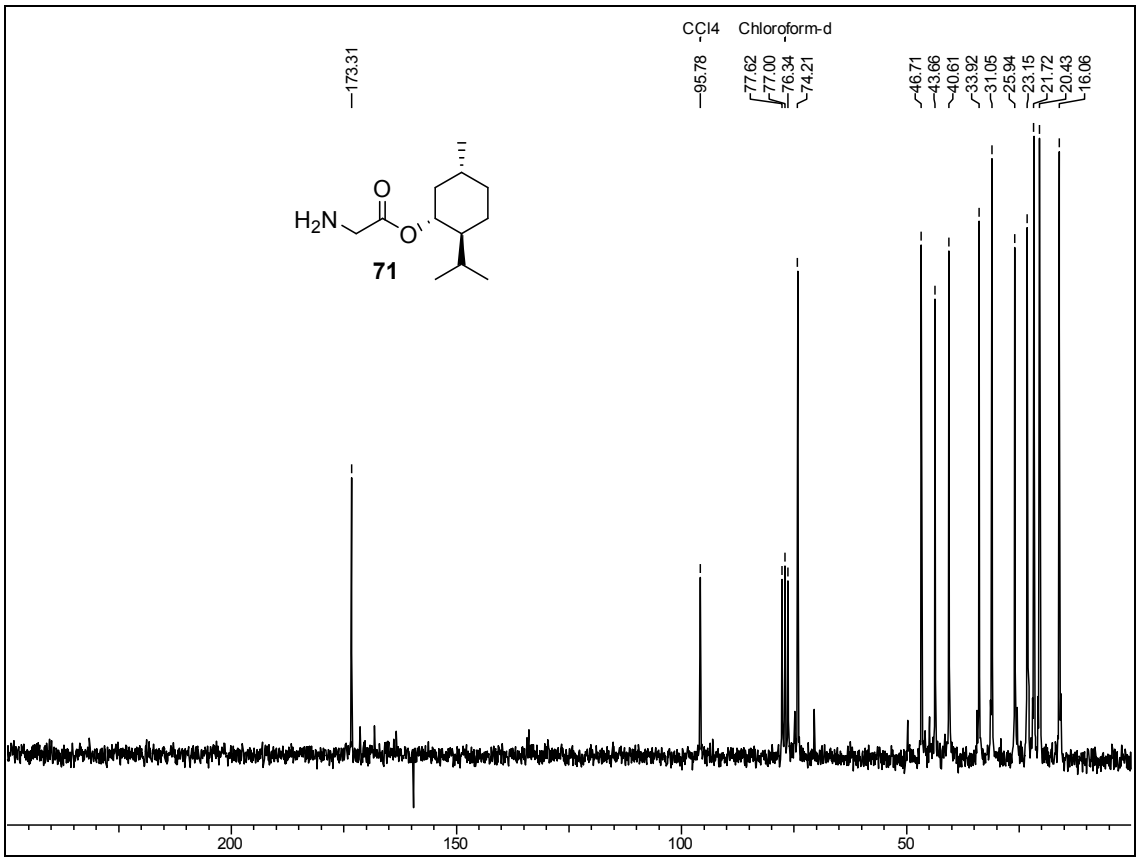
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 80



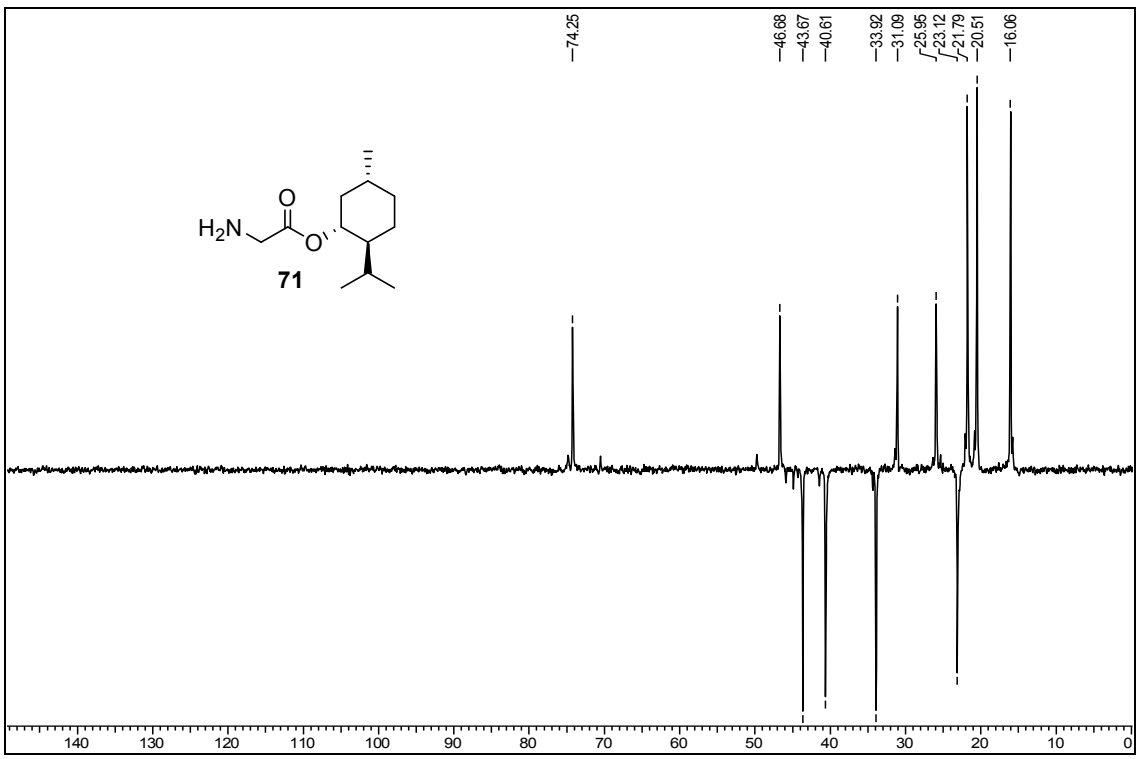
DEPT ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 80



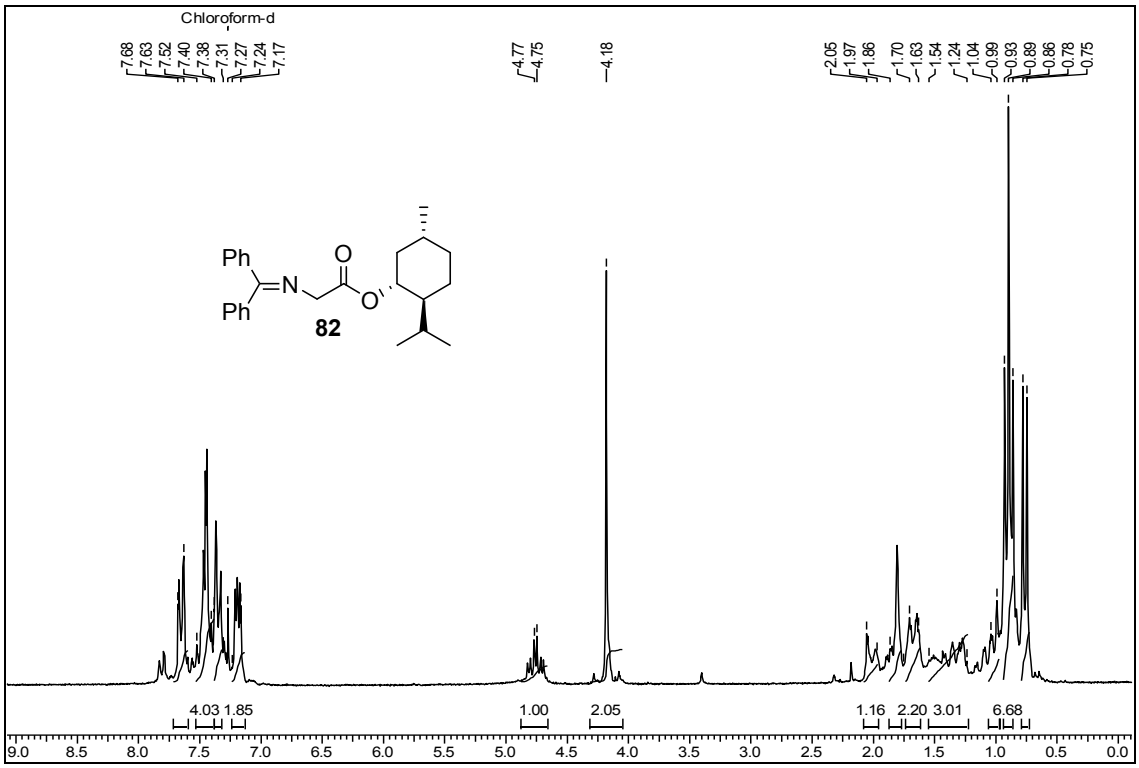
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 71



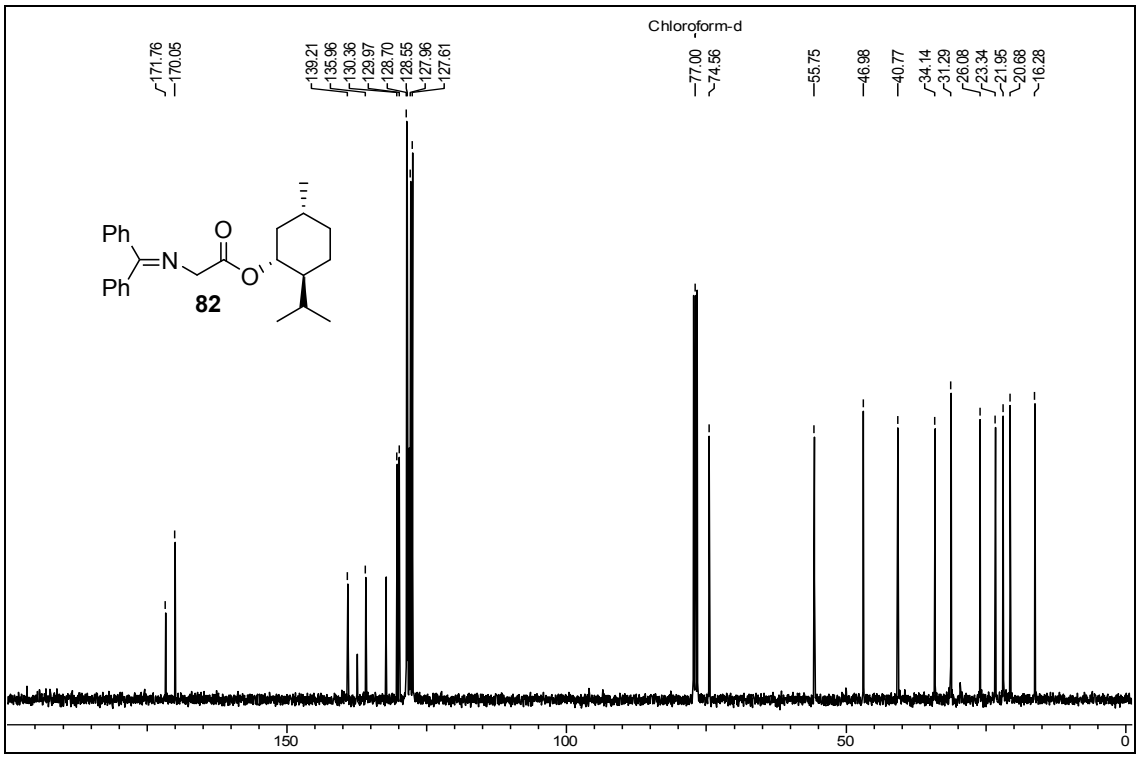
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 71



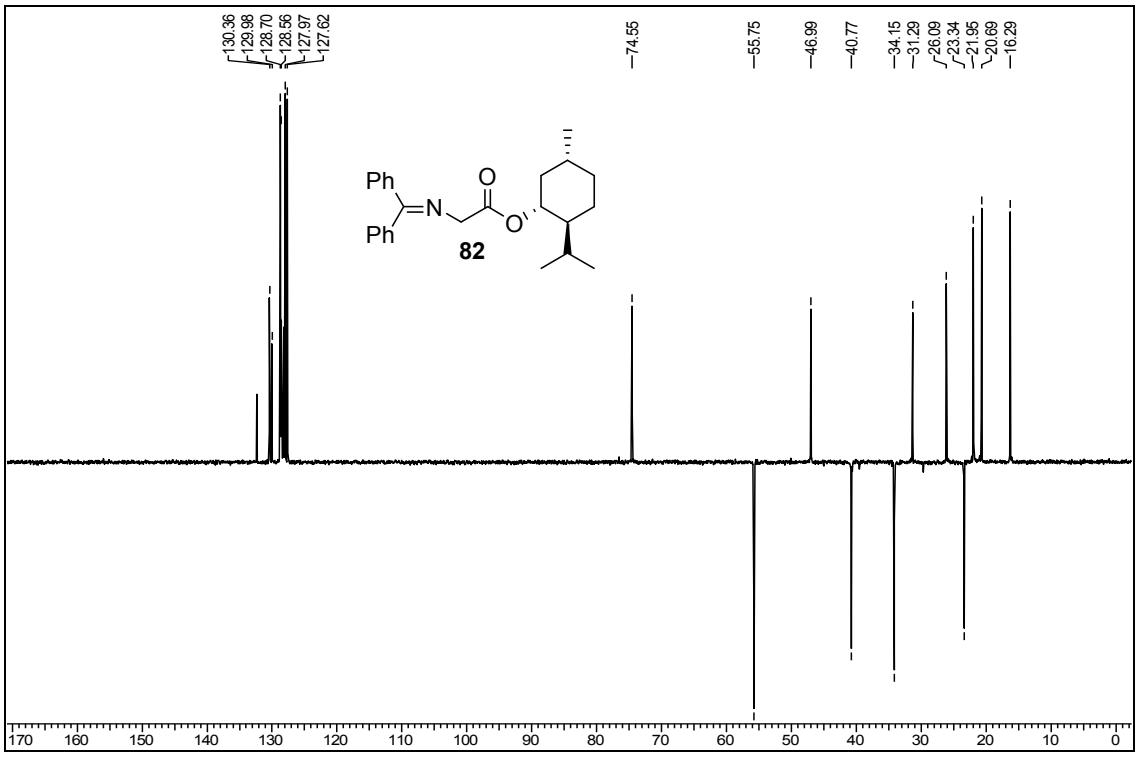
DEPT ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 71



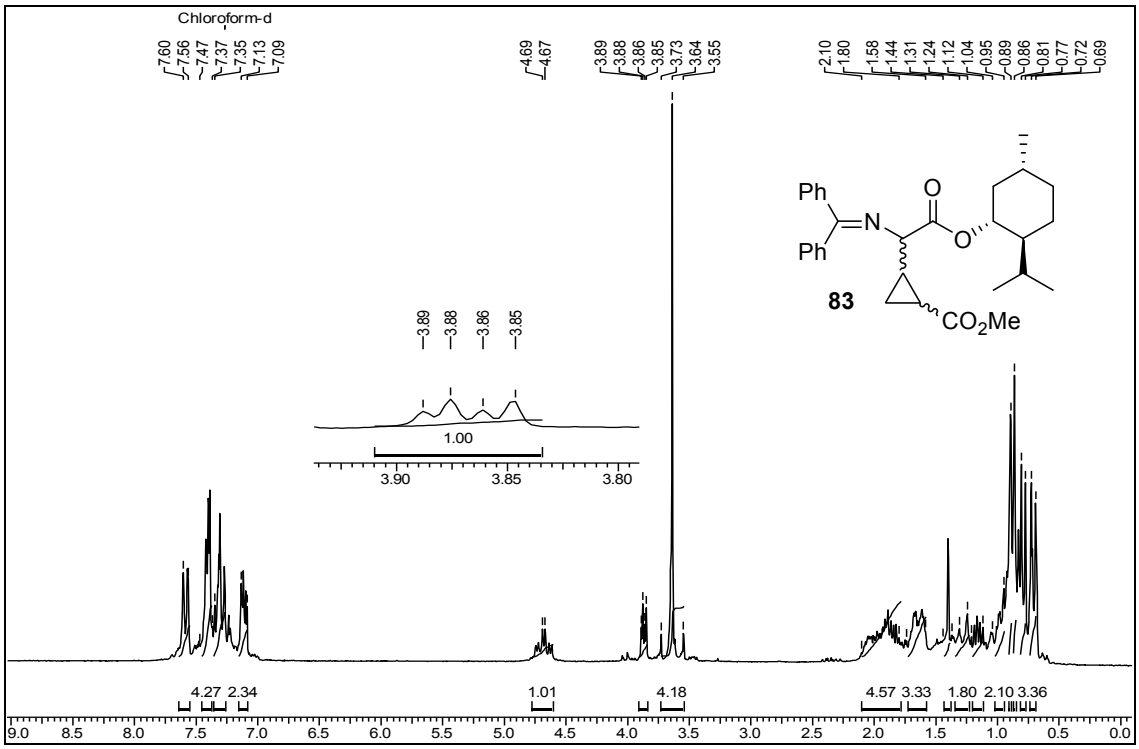
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 82



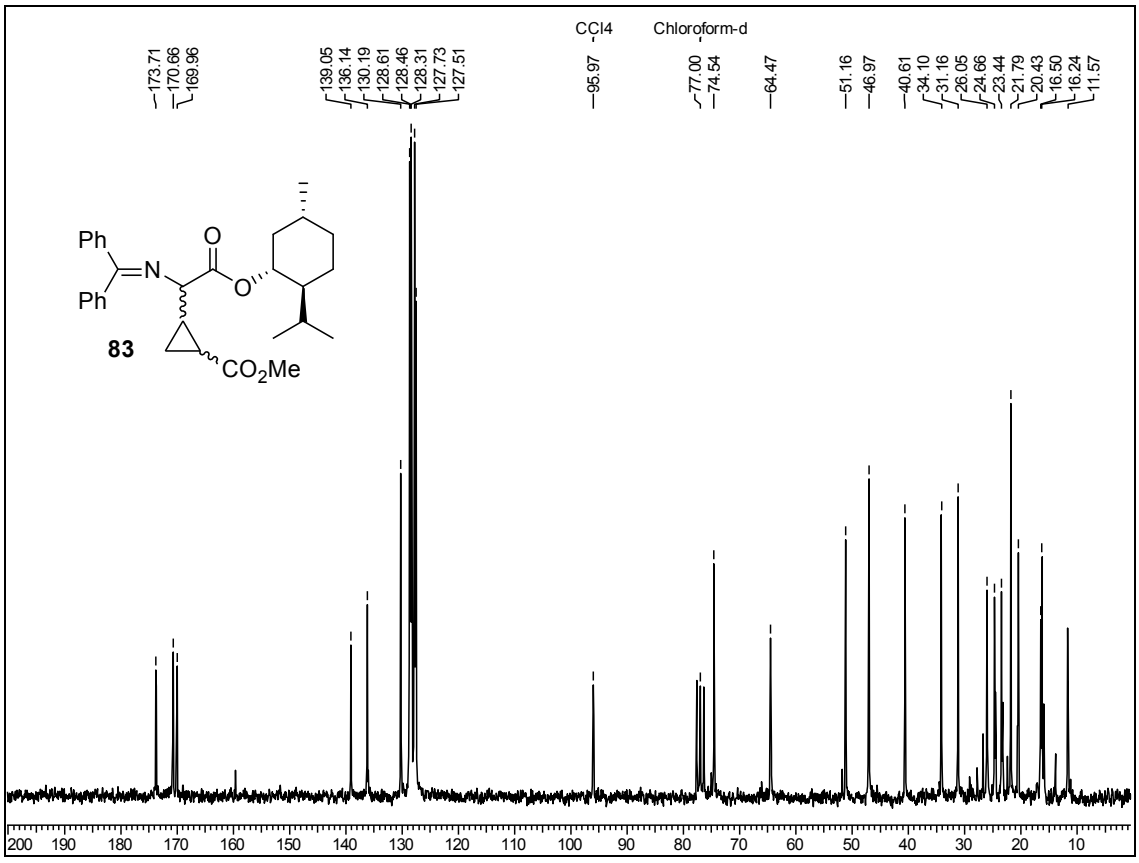
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of compound 82



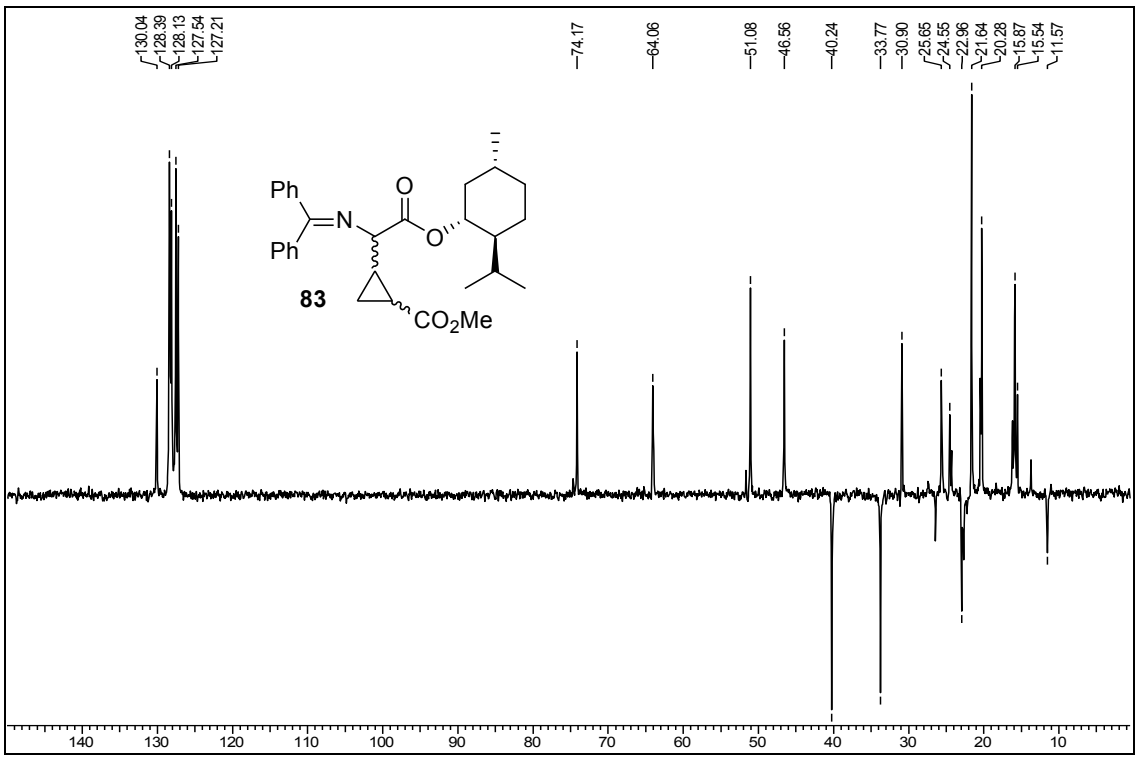
DEPT ($CDCl_3$, 50 MHz) spectrum of compound 82



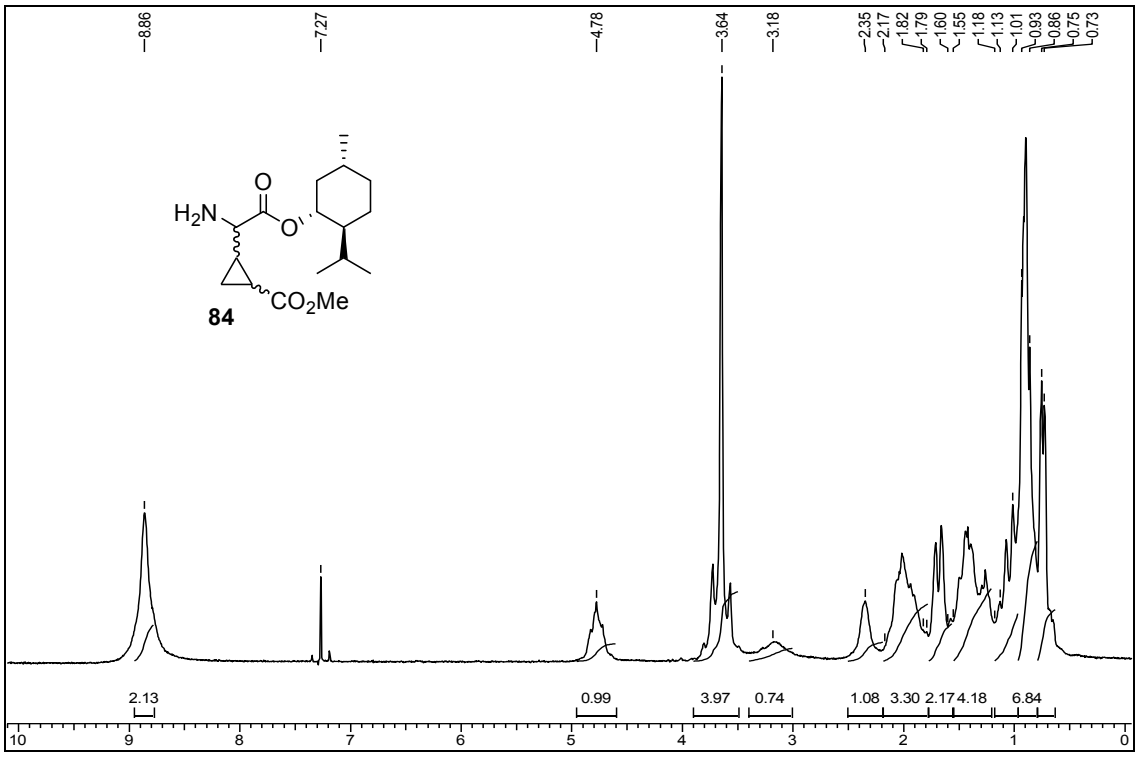
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 83



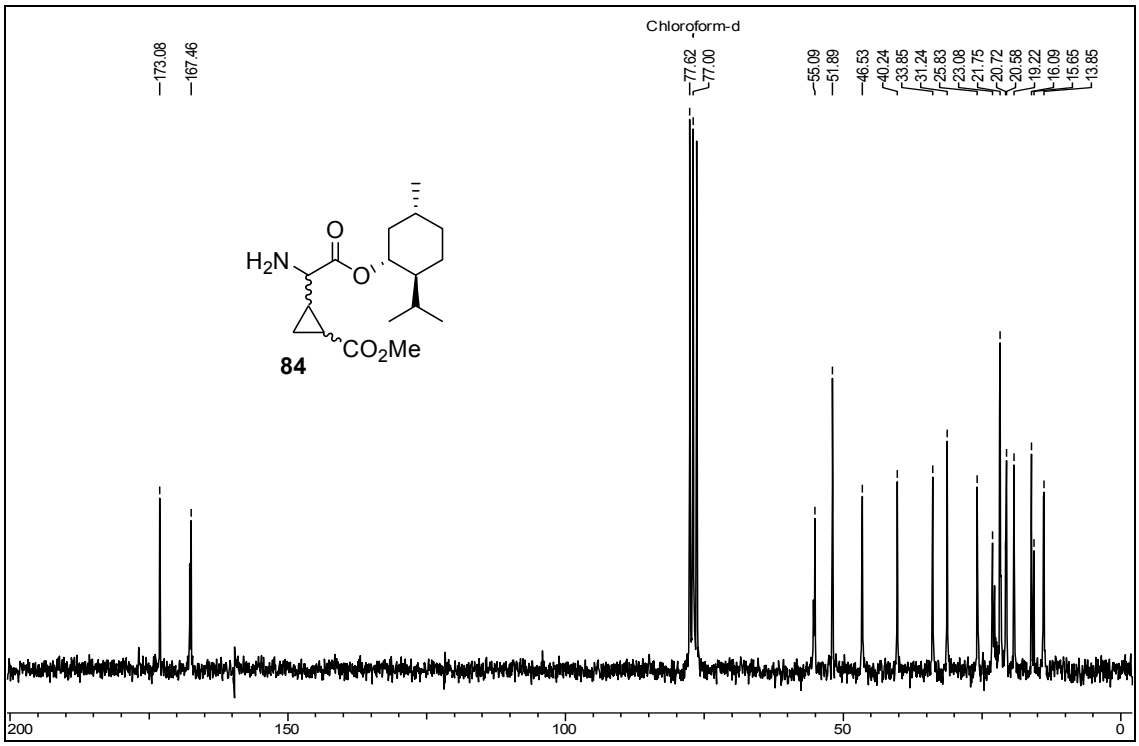
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 83



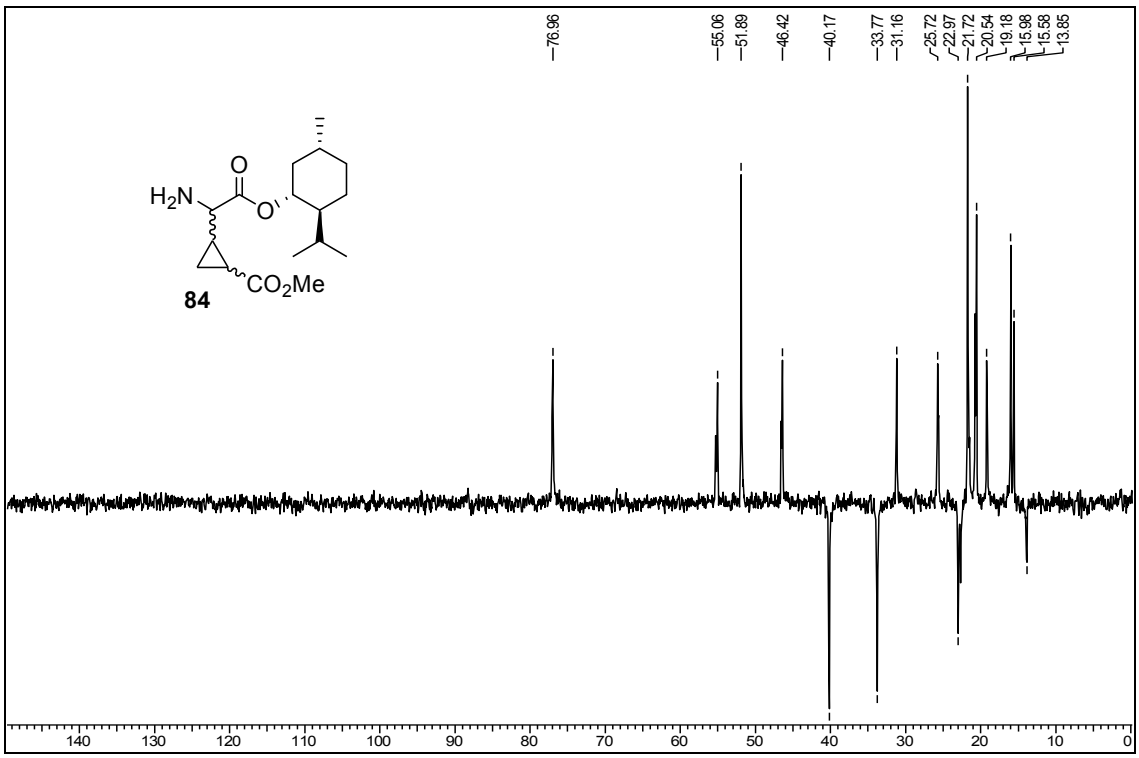
DEPT ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 83



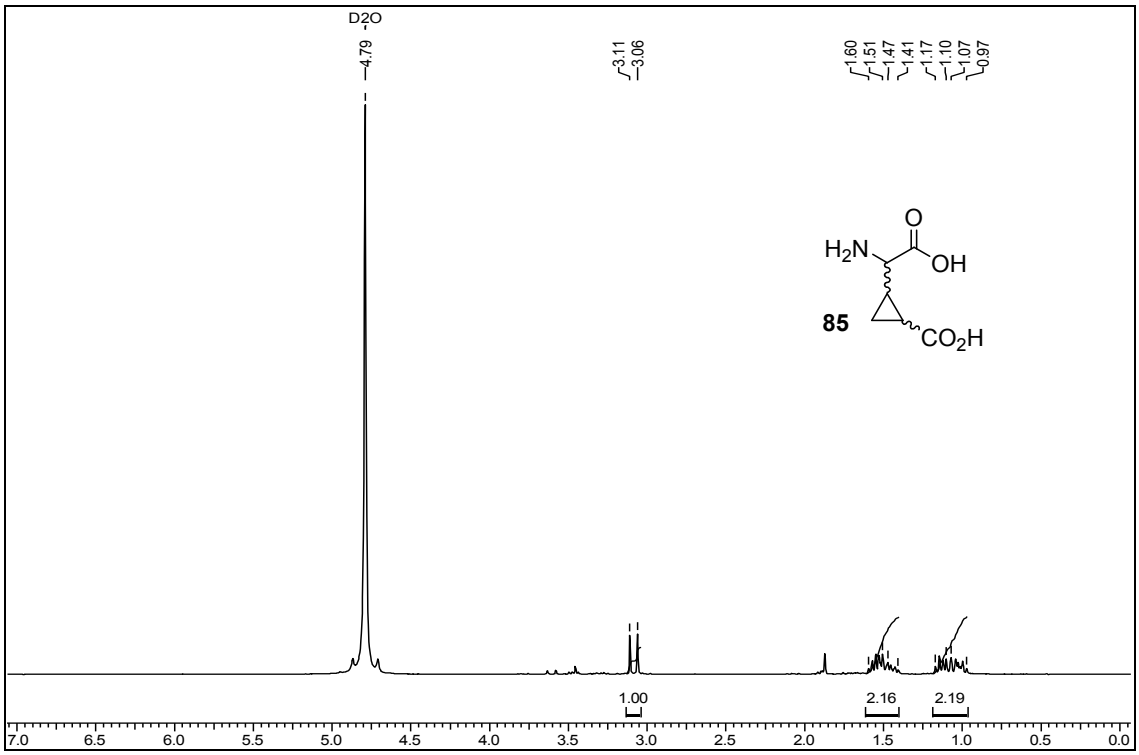
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 84



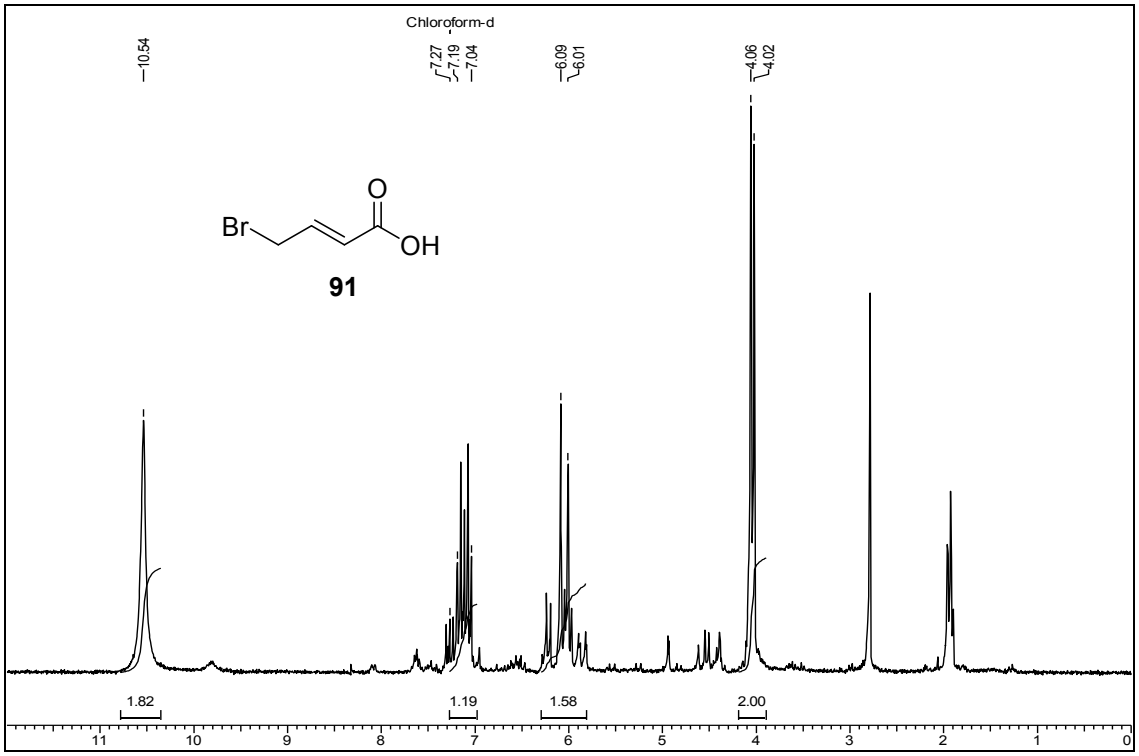
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of compound 84



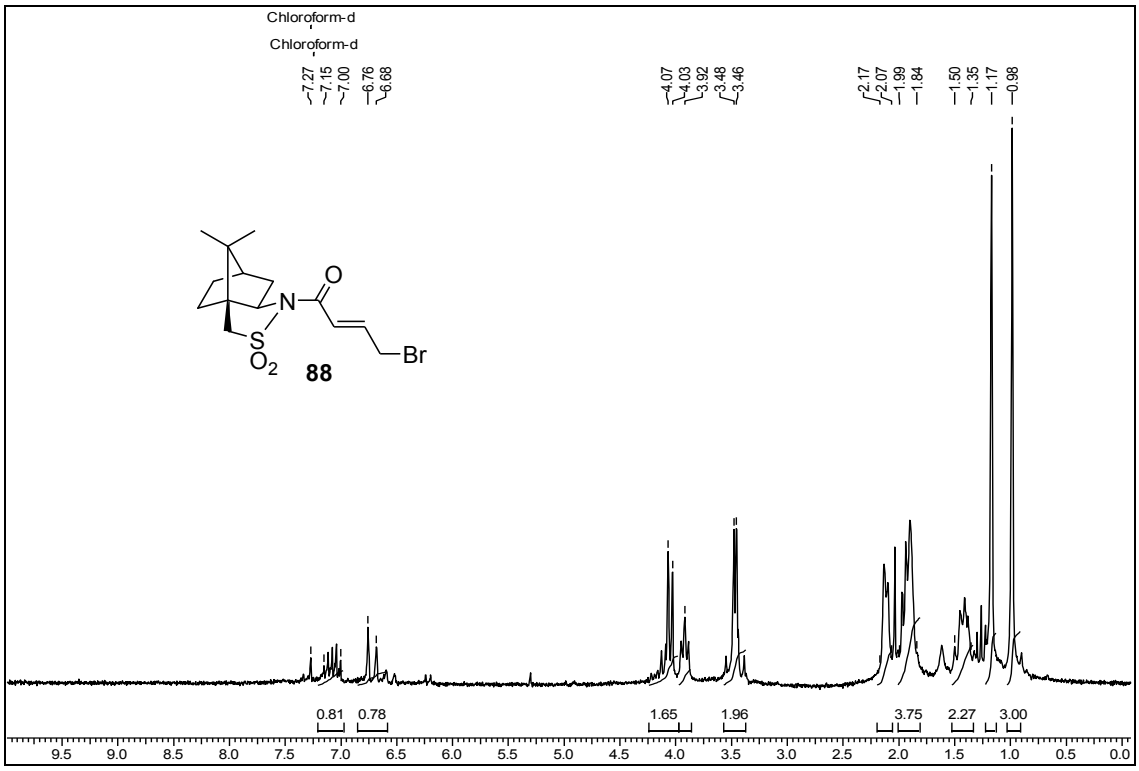
DEPT ($CDCl_3$, 50 MHz) spectrum of compound 84



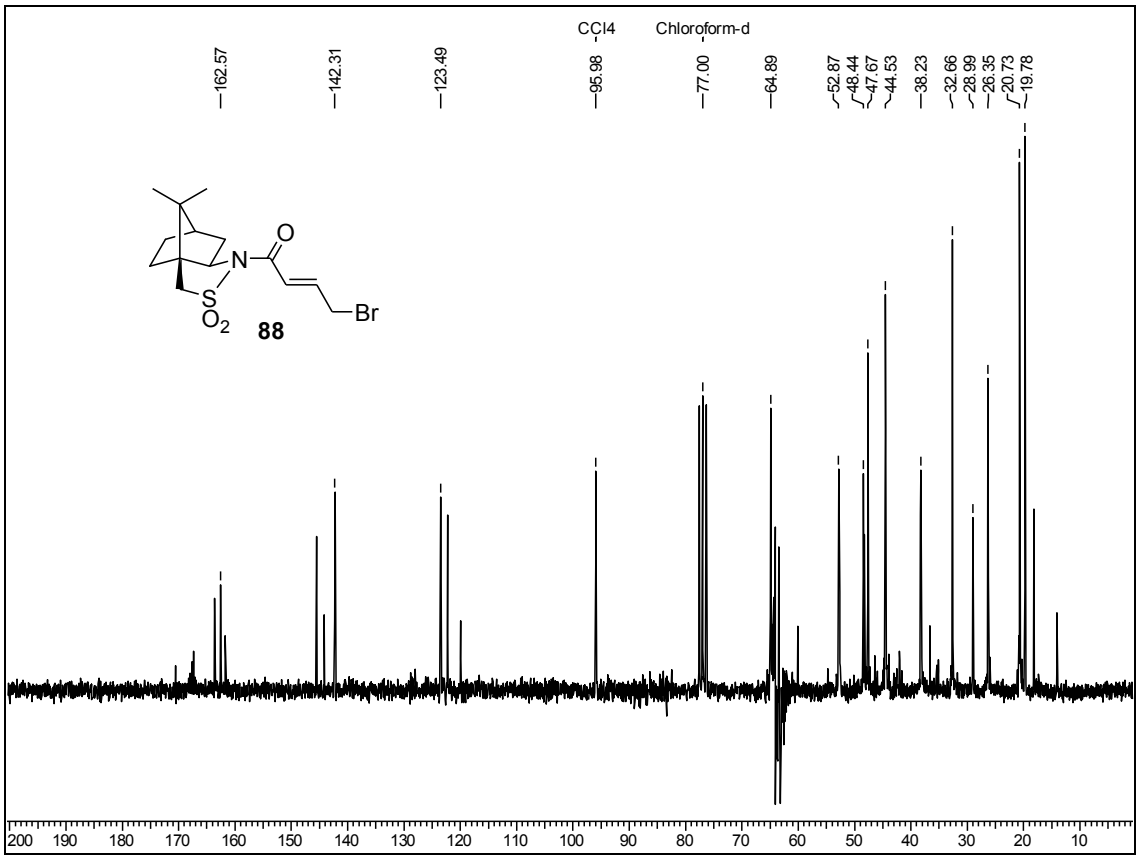
^{1}H NMR (D_2O, 200 MHz) spectrum of compound 85



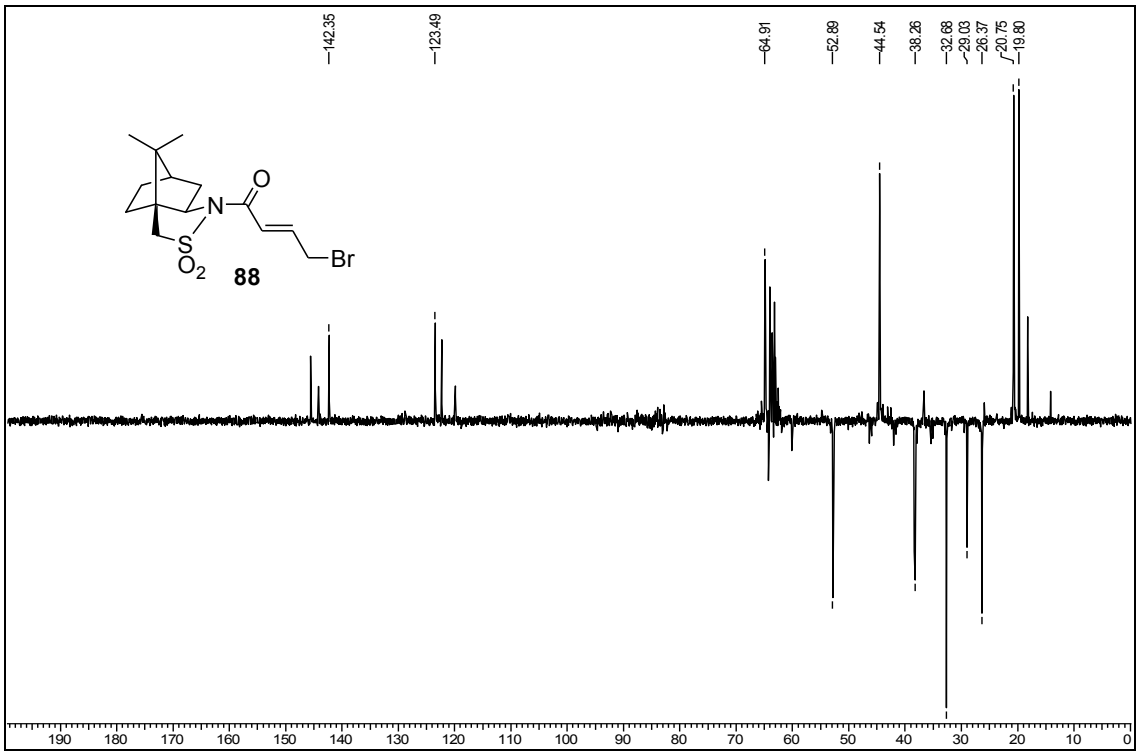
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 91



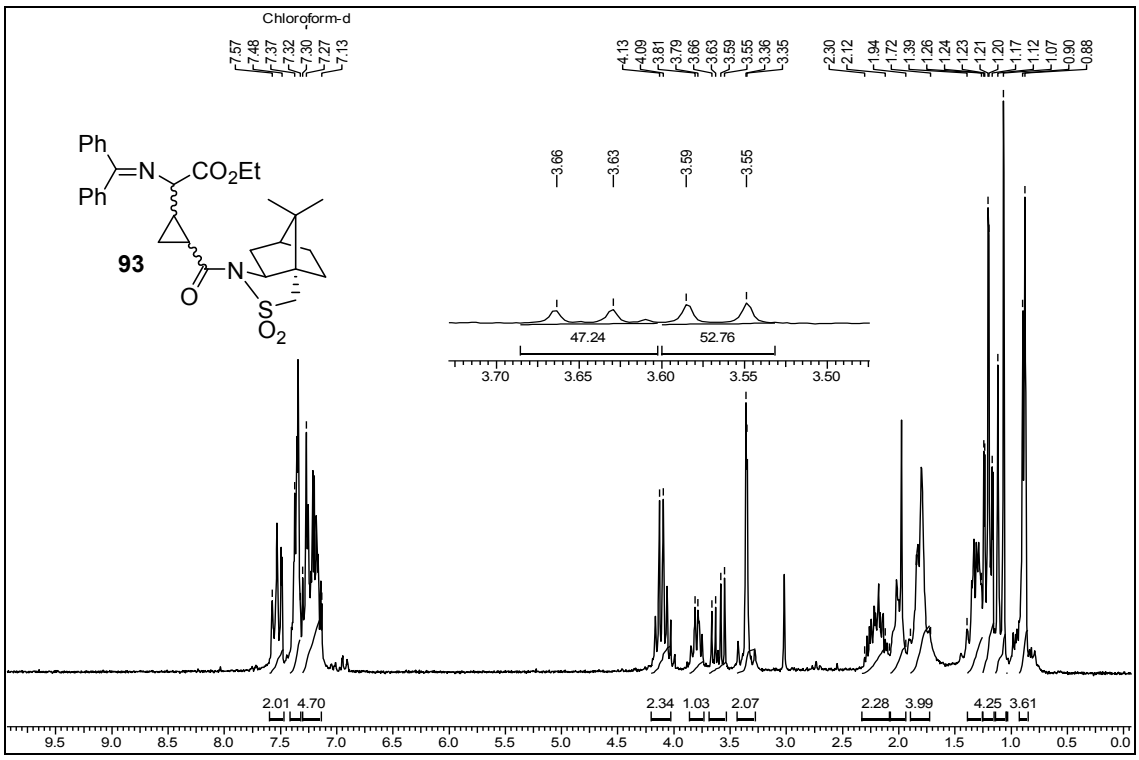
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 88



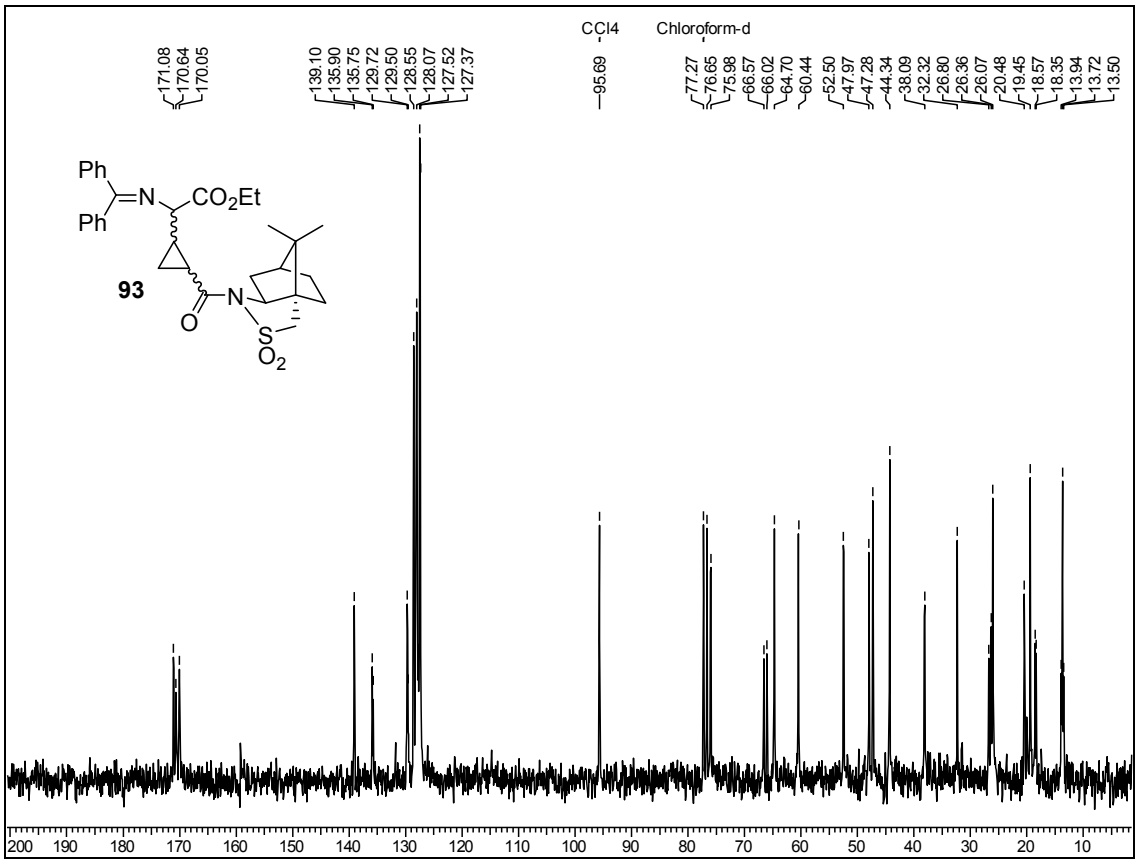
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 88



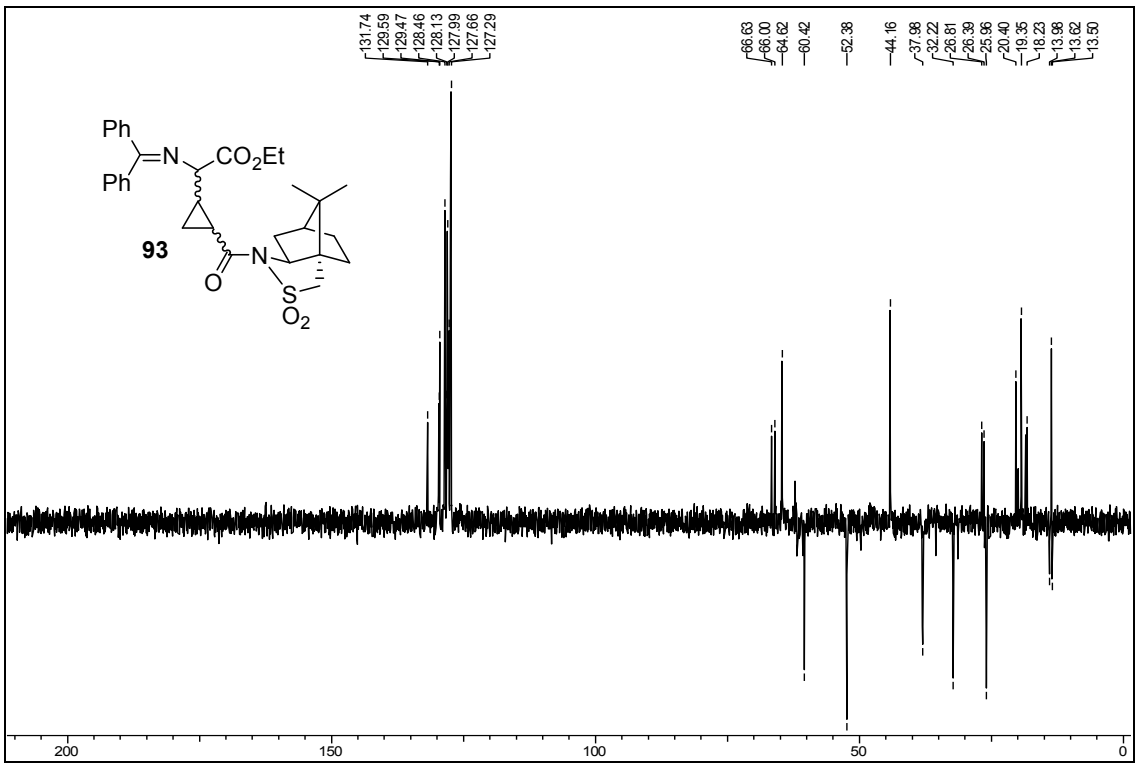
DEPT ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 88



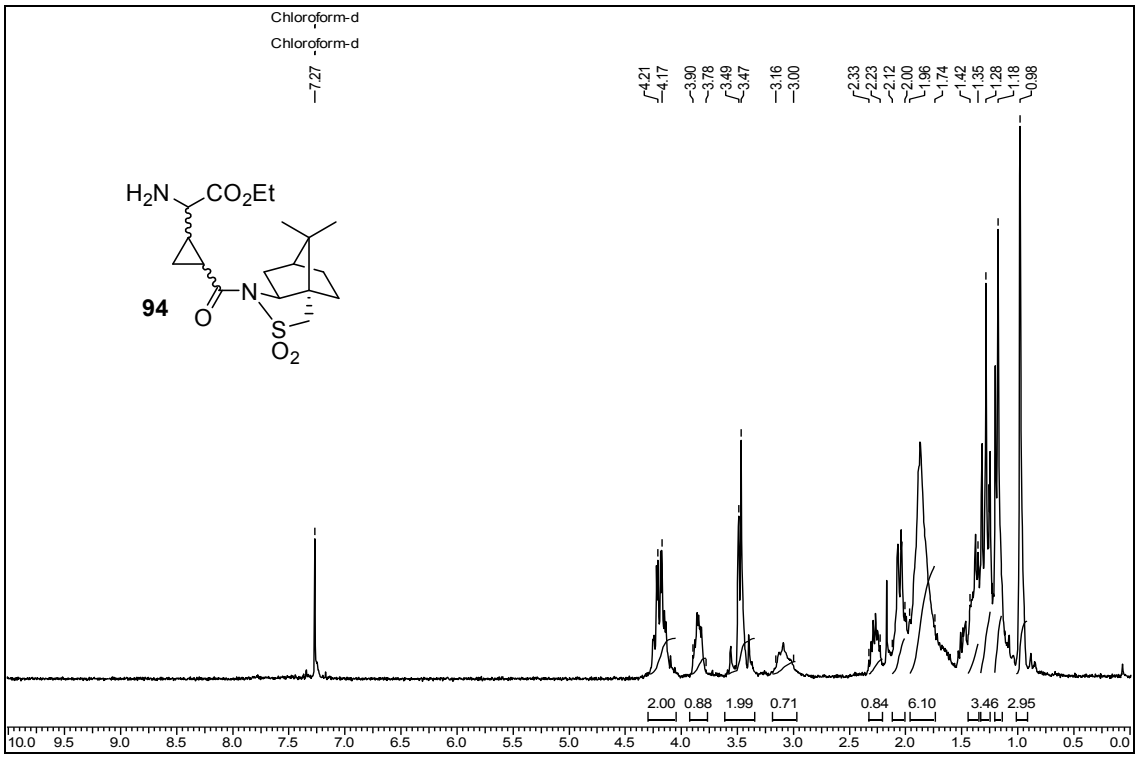
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 93



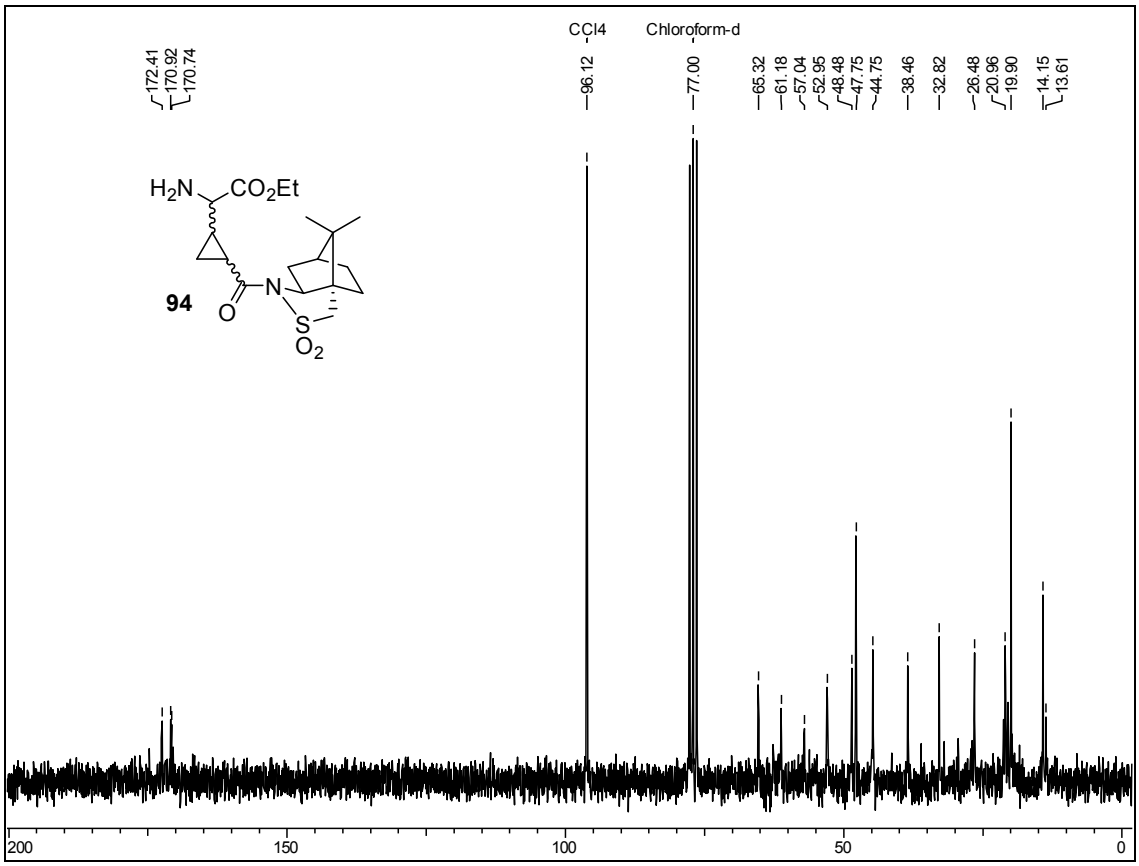
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 93



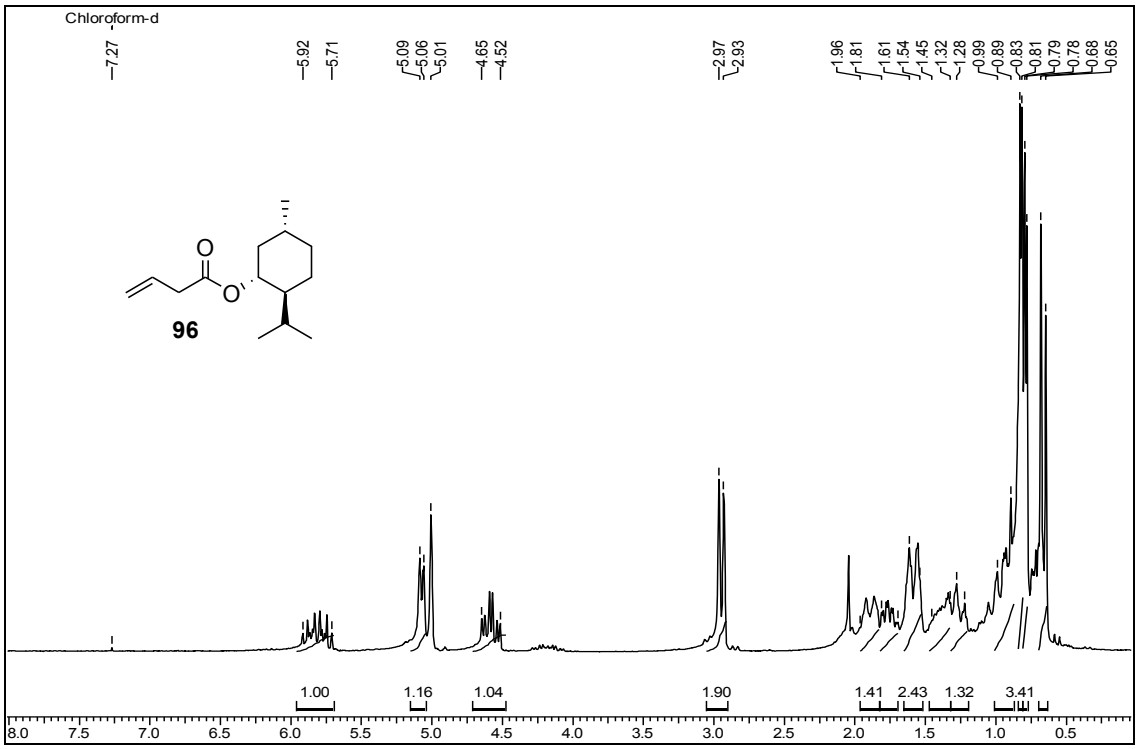
DEPT ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 93



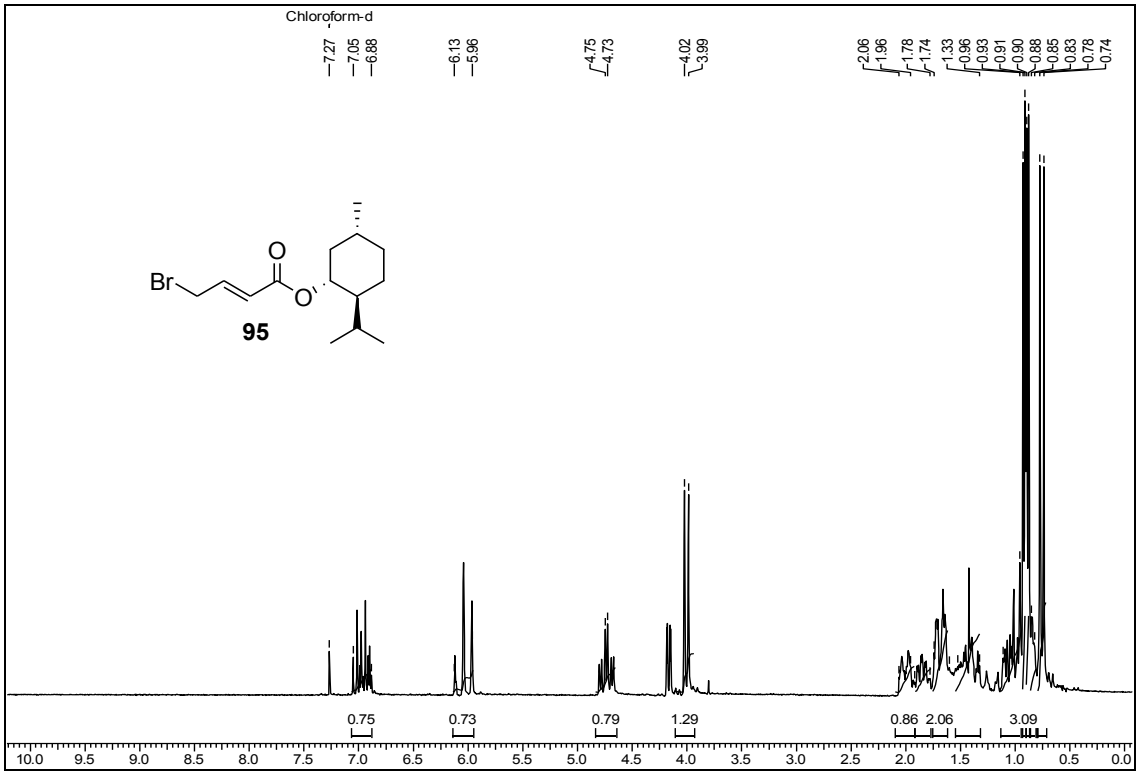
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 94



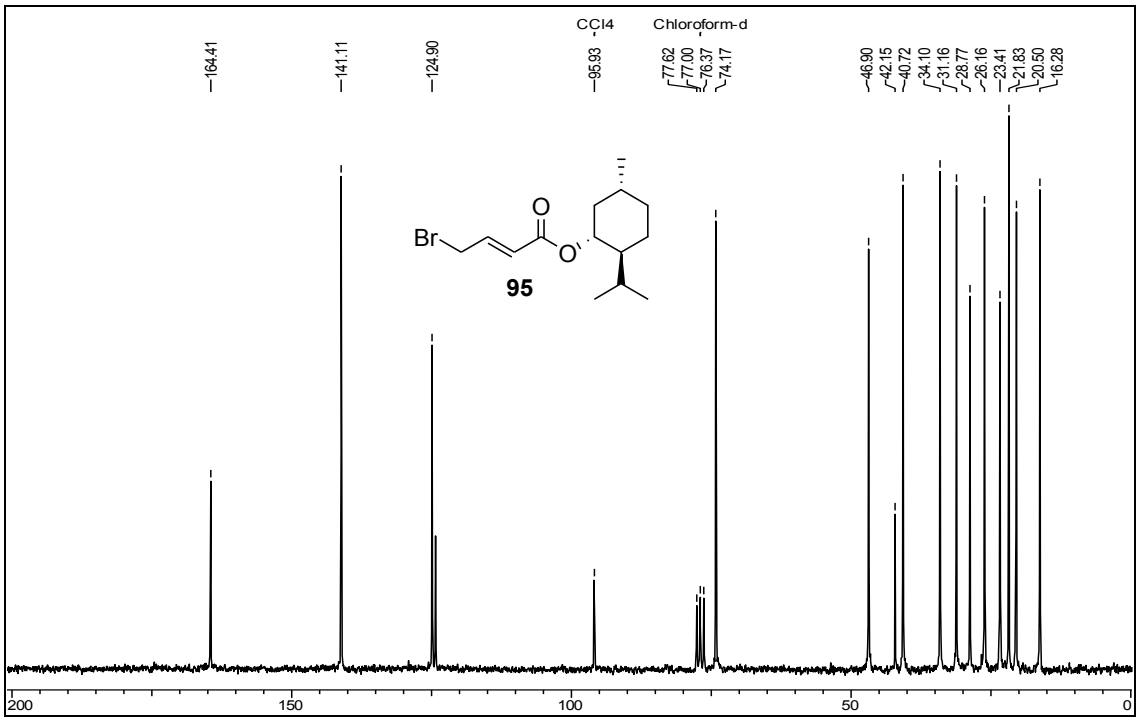
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 94



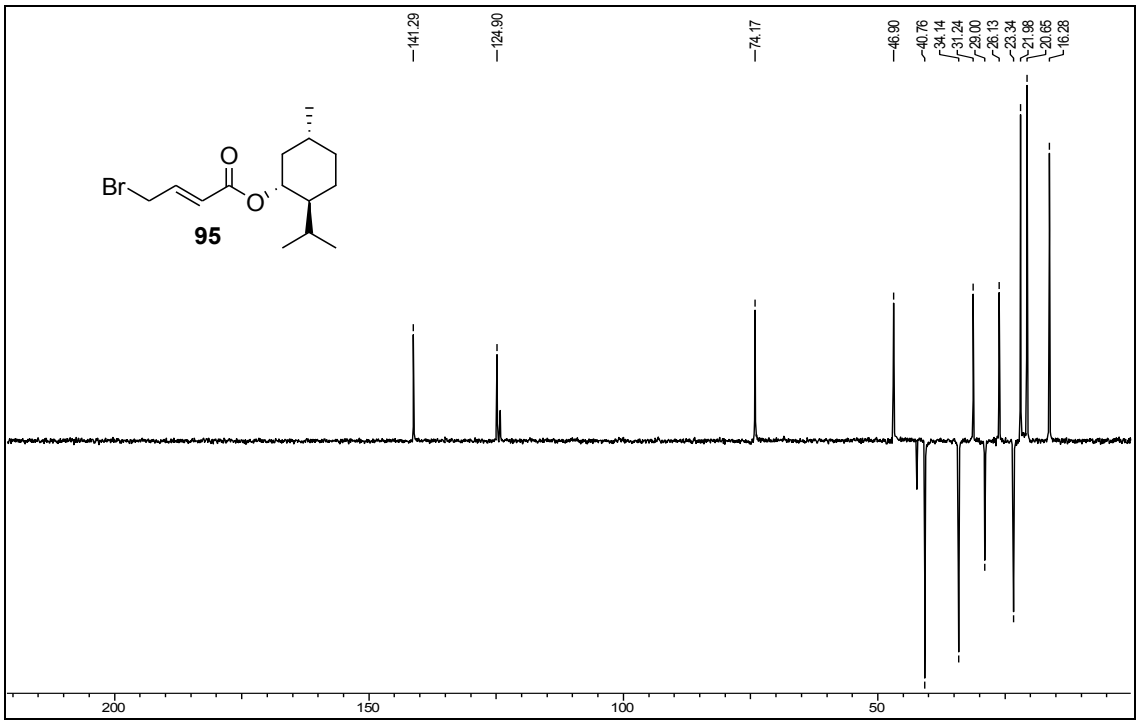
^{1}H NMR ($CDCl_3$+CCl_4, 200MHz) spectrum of compound 96



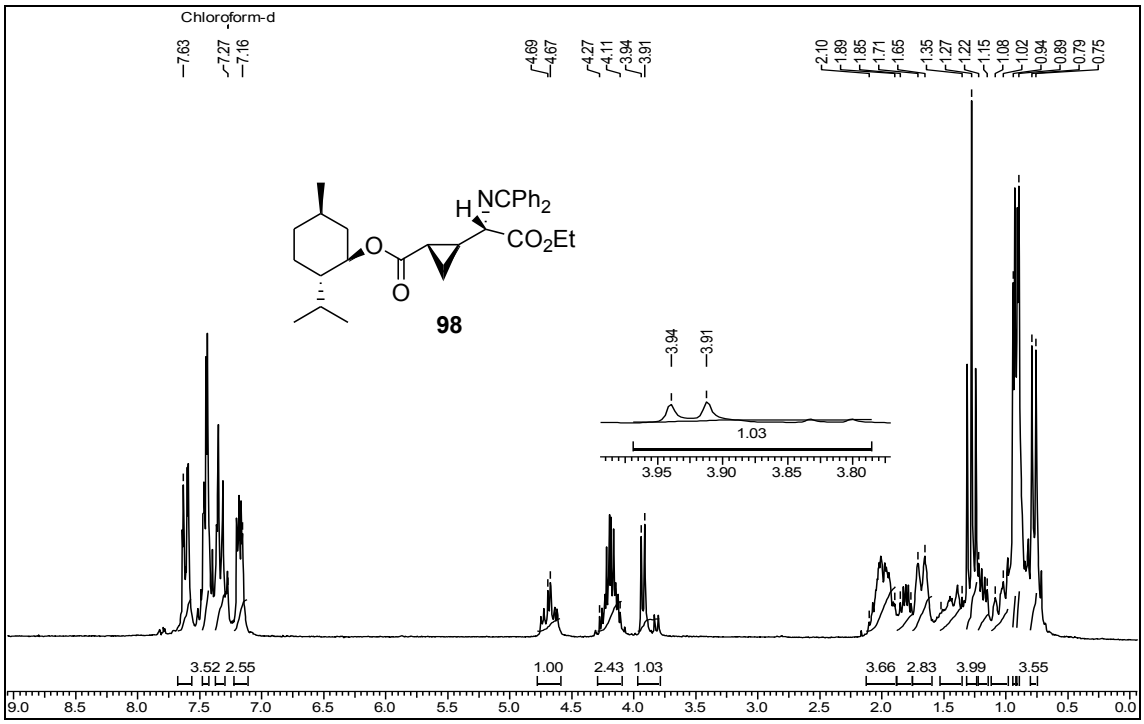
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 95



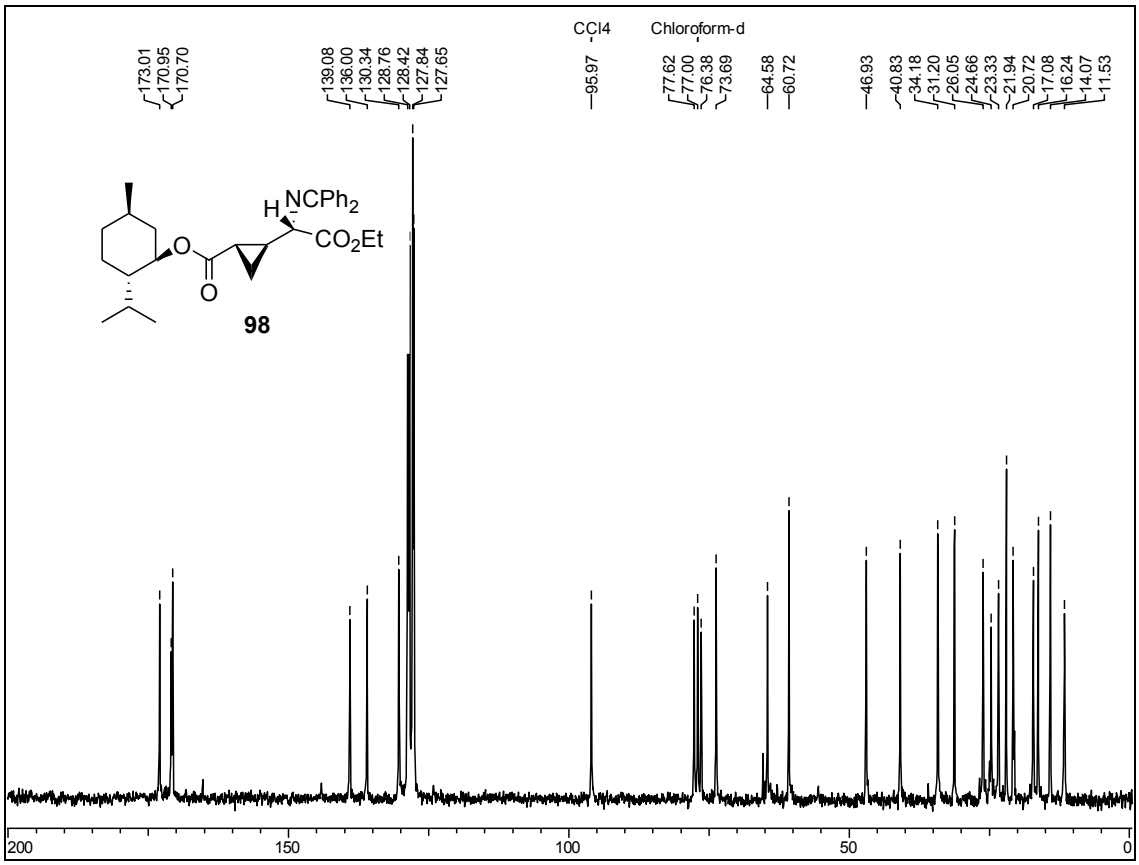
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 95



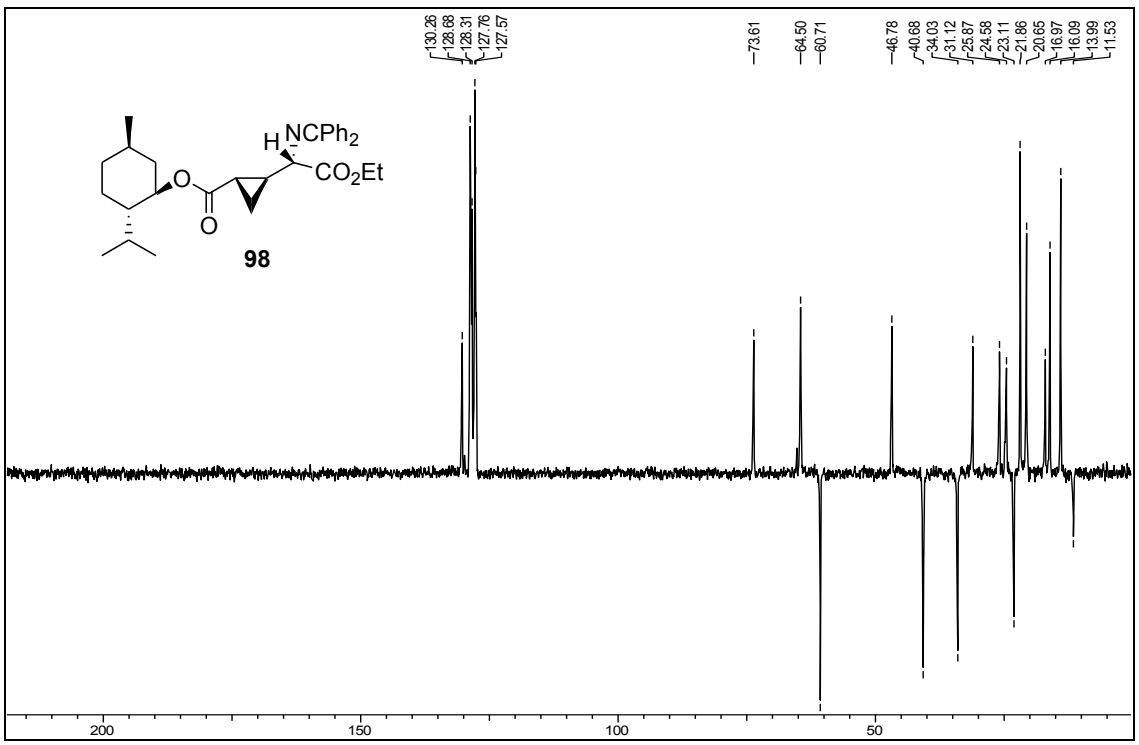
DEPT ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 95



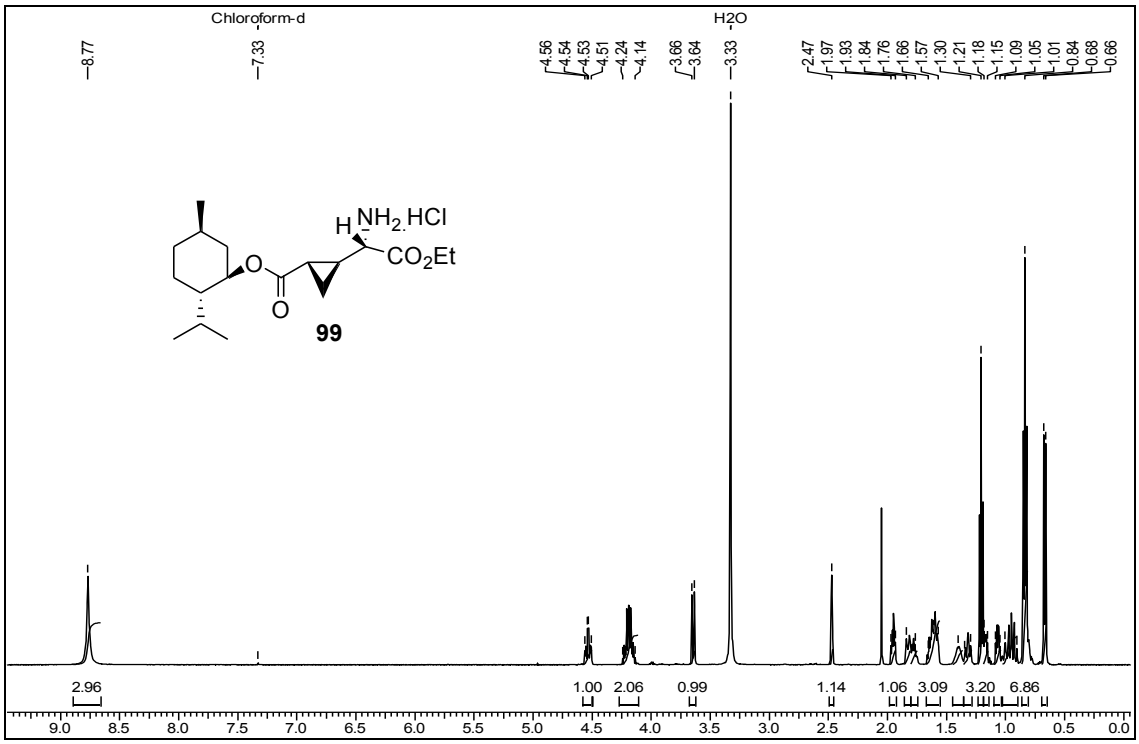
^{1}H NMR ($CDCl_3$+CCl_4, 200MHz) spectrum of compound 98



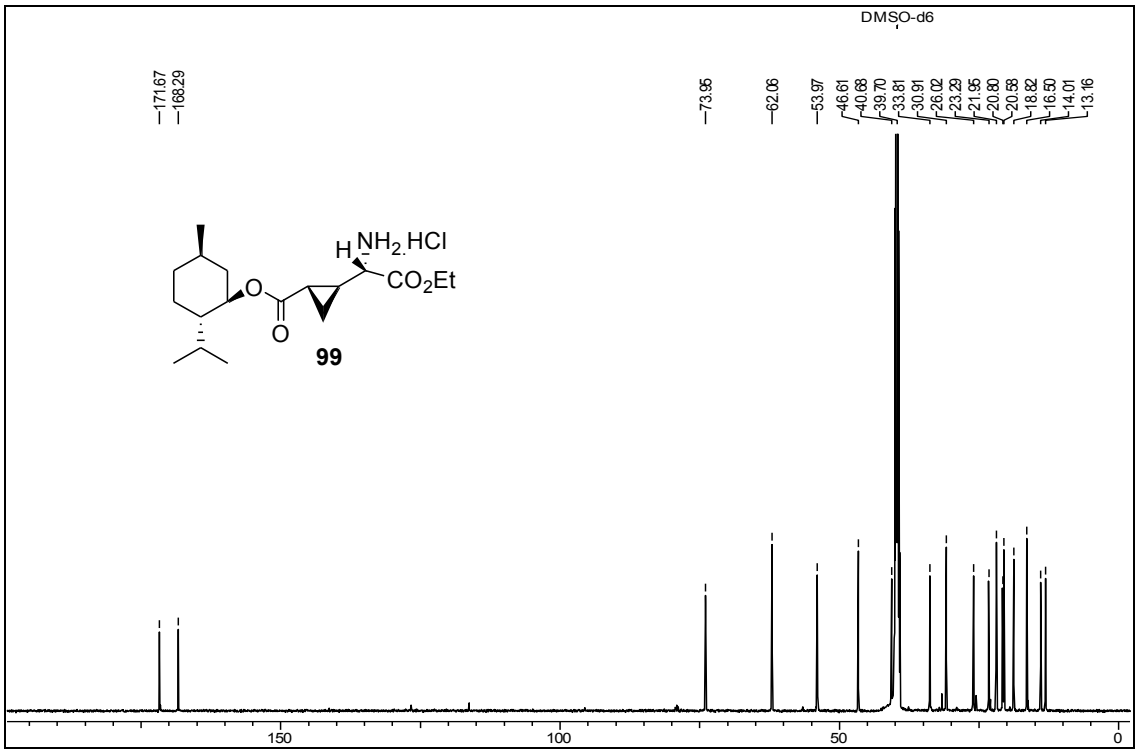
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 98



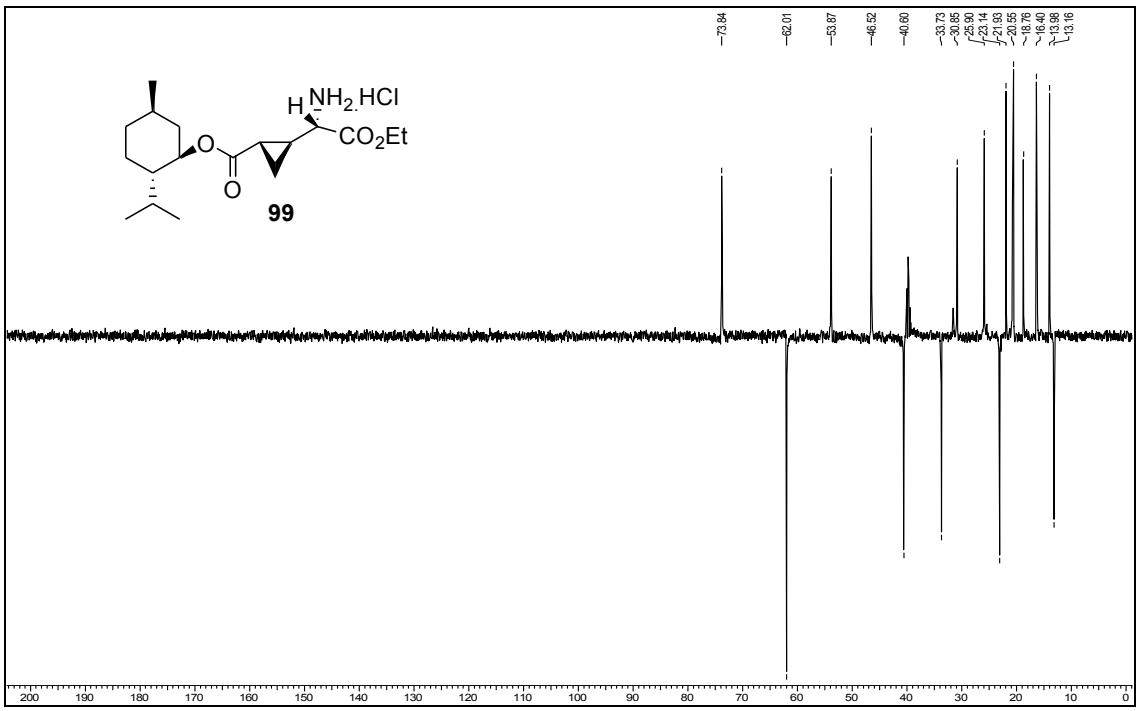
DEPT ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 98



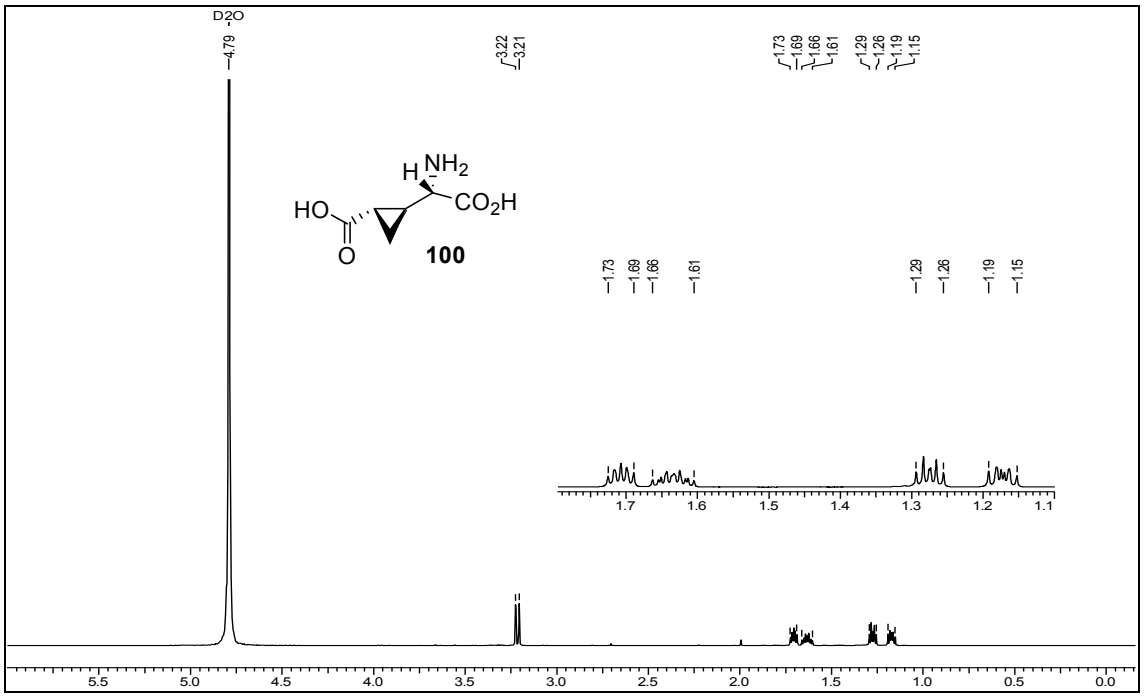
^{1}H NMR (DMSO-d_6, 500MHz) spectrum of compound 99



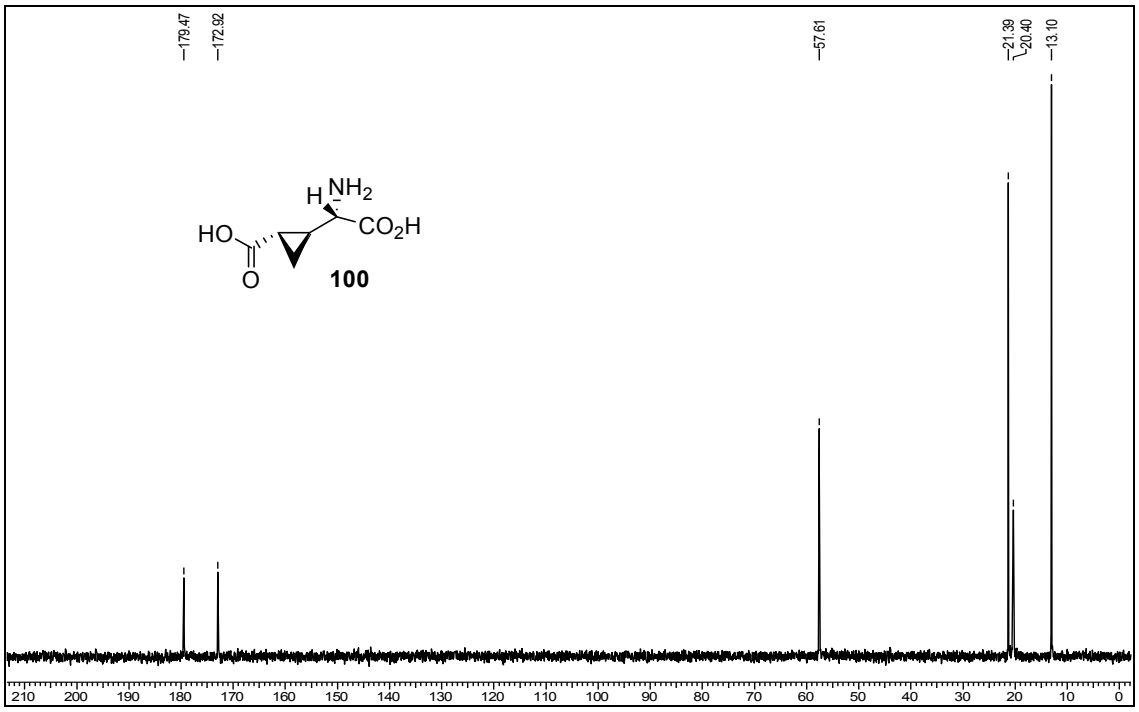
^{13}C NMR (DMSO-d$_6$, 125 MHz) spectrum of compound 99



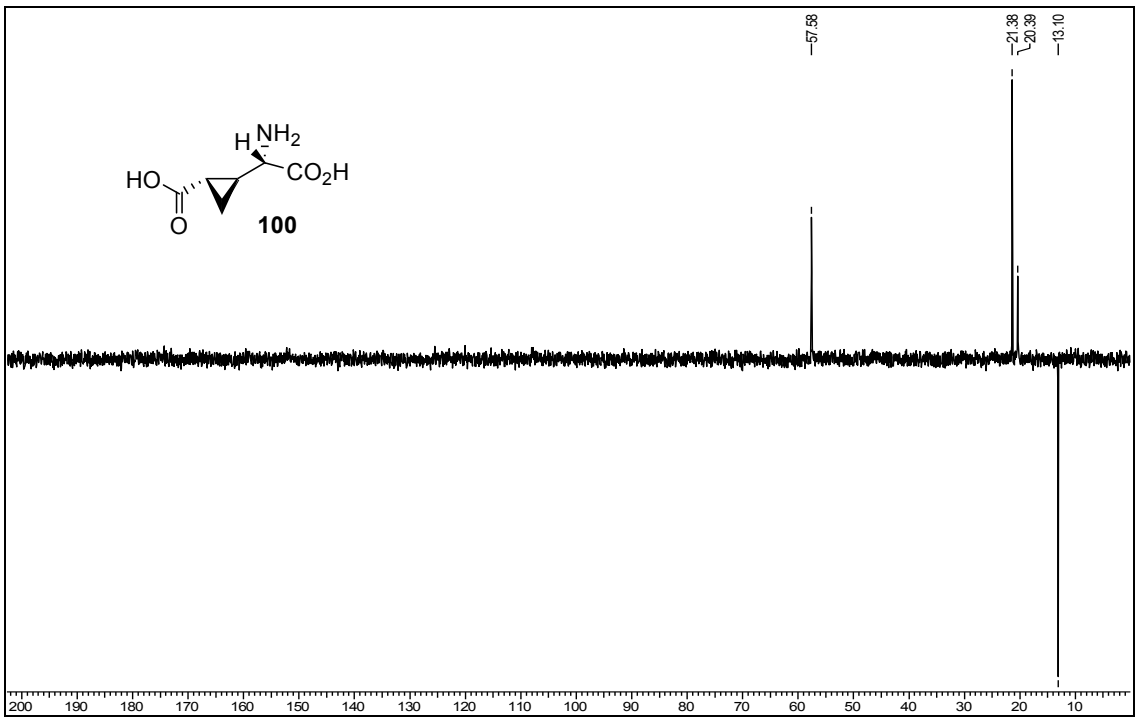
DEPT (DMSO-d$_6$, 125 MHz) spectrum of compound 99



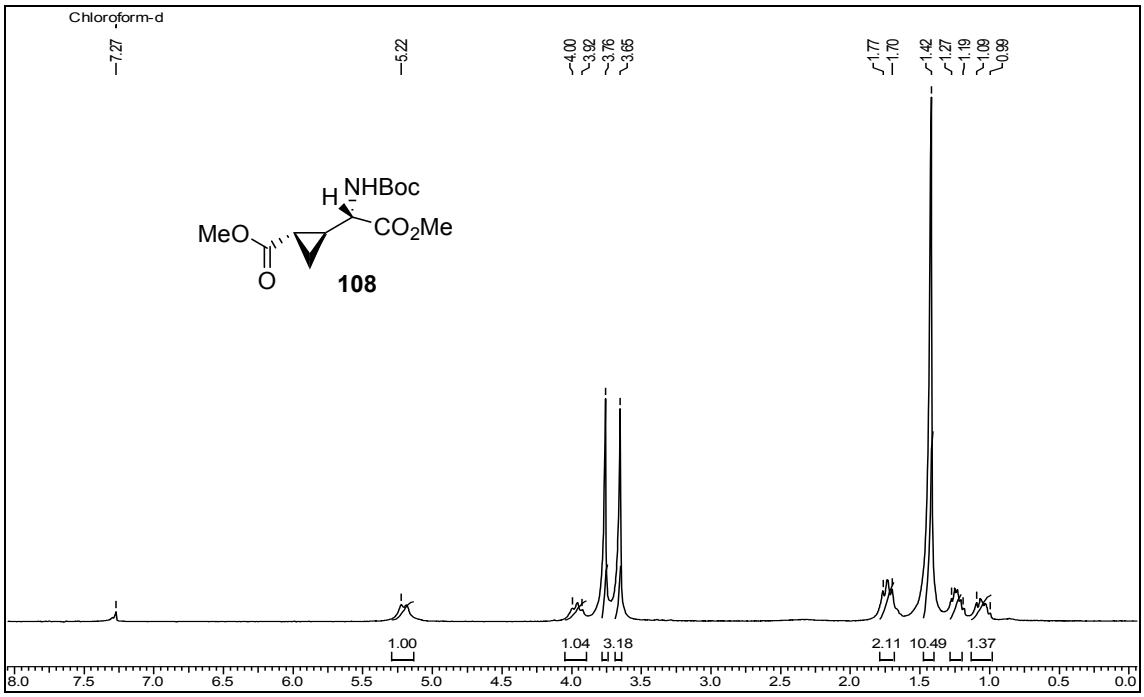
^{1}H NMR (D_2O, 500 MHz) spectrum of compound 100



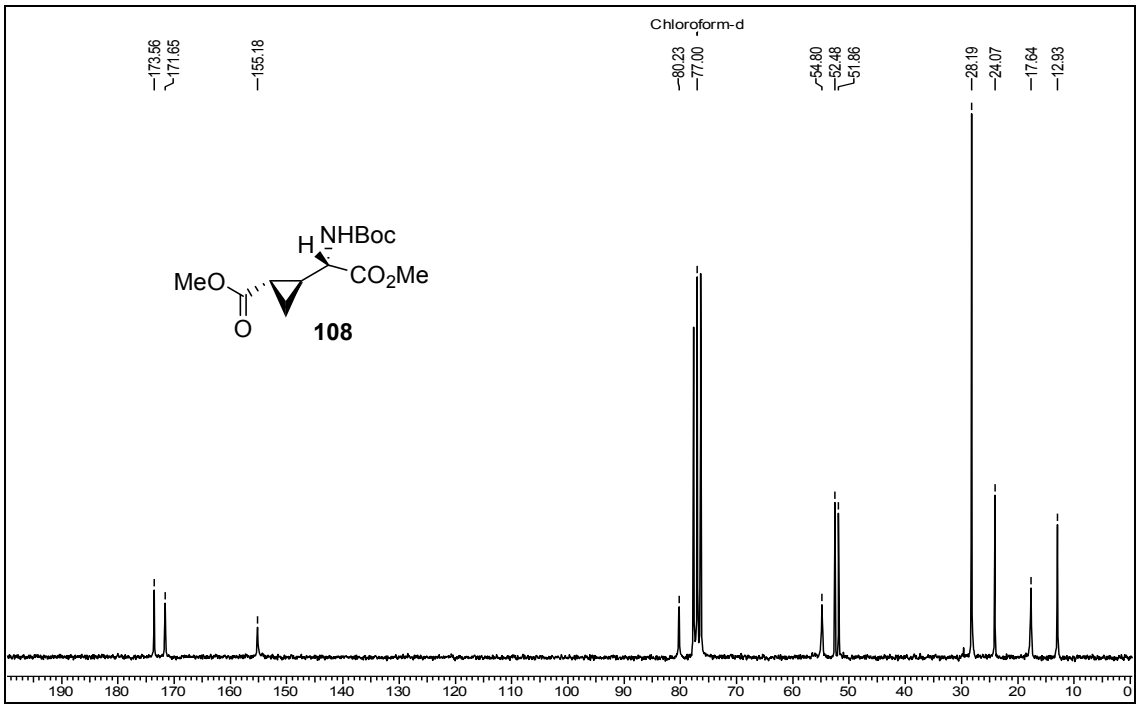
^{13}C NMR (D_2O, 125 MHz) spectrum of compound 100



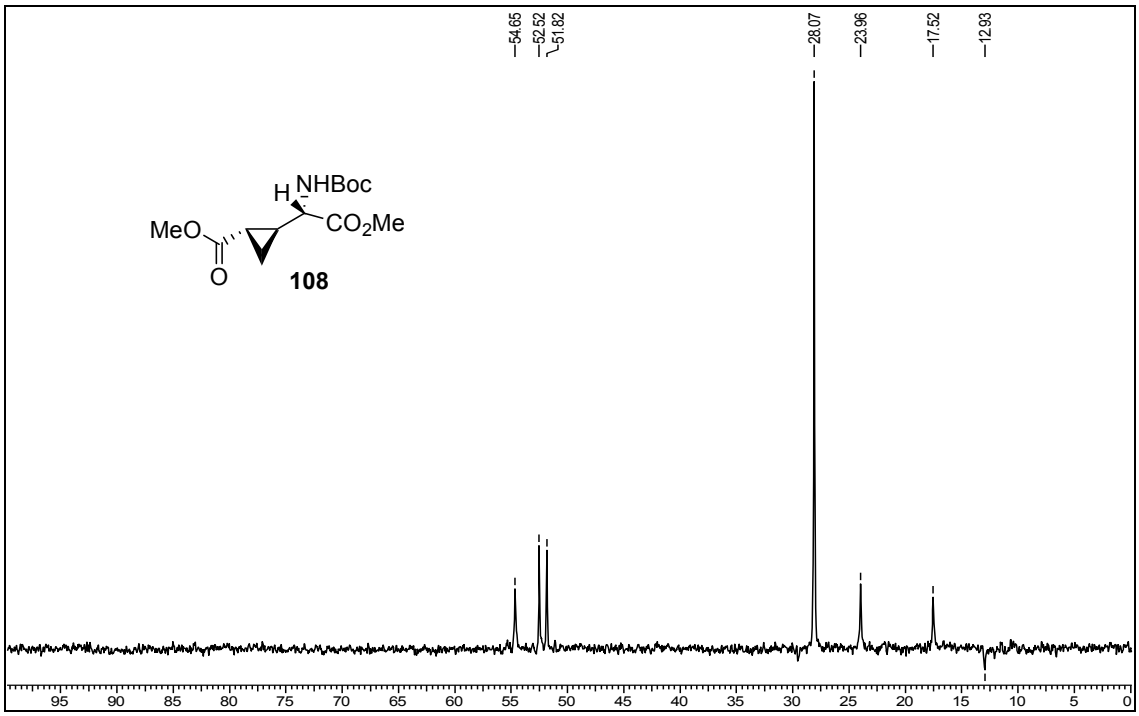
DEPT (D_2O, 125 MHz) spectrum of compound 100



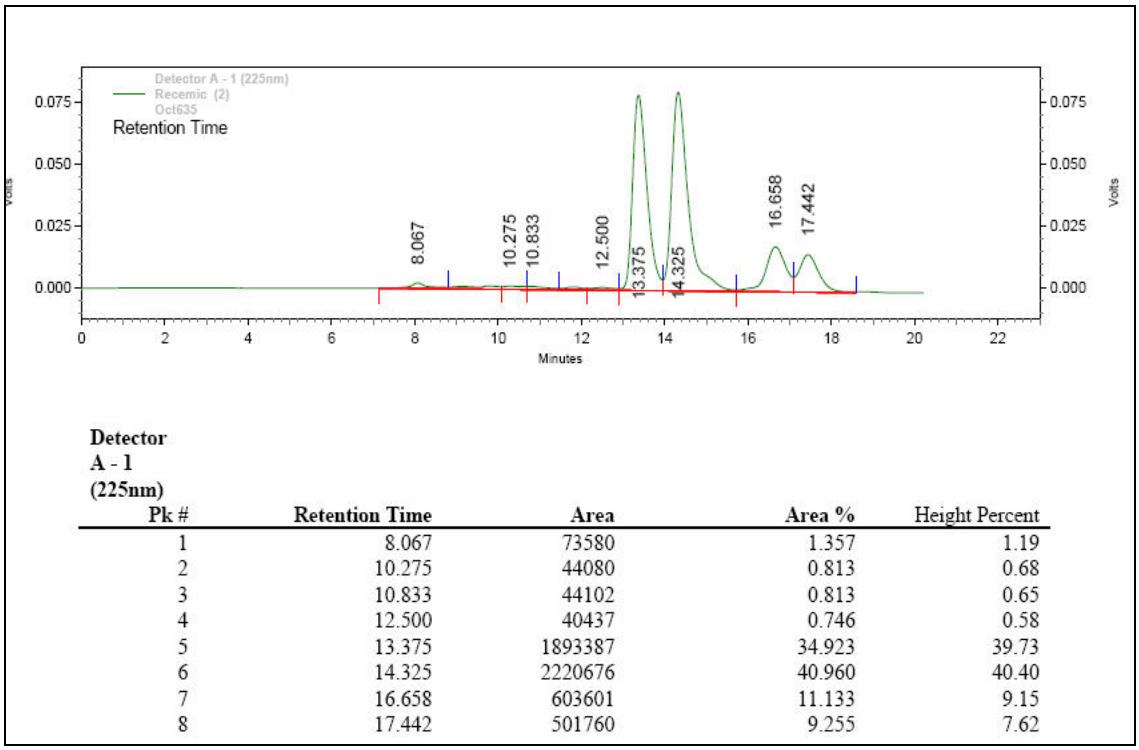
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of compound 108



^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of compound 108



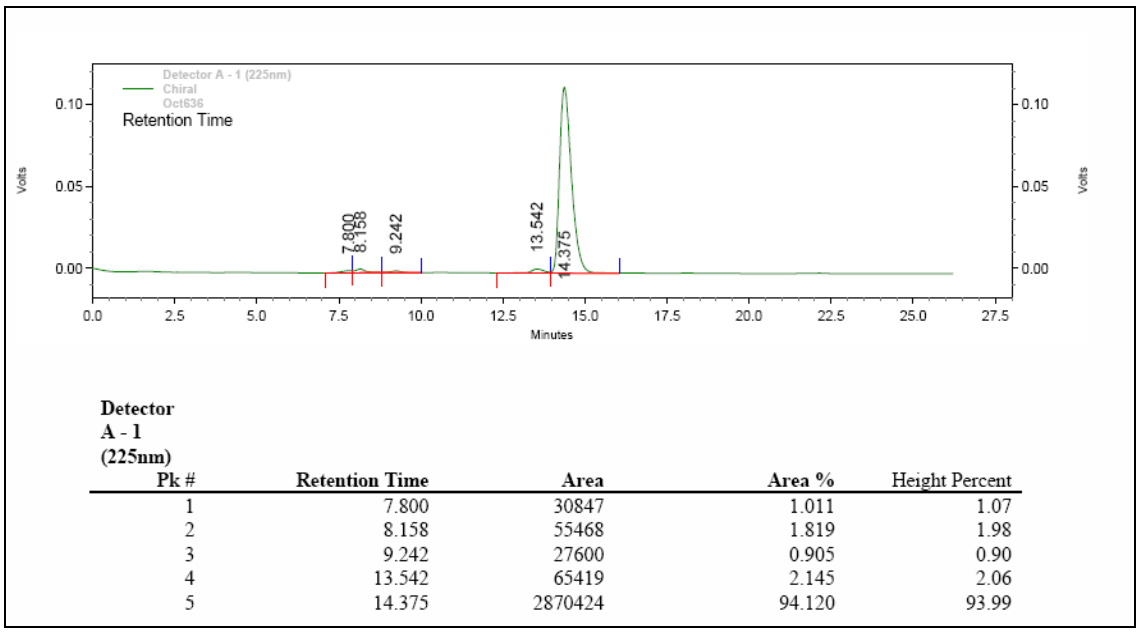
DEPT spectrum ($CDCl_3$, 50 MHz) of compound 108



Detector A - 1 (225nm)

Pk #	Retention Time	Area	Area %	Height Percent
1	8.067	73580	1.357	1.19
2	10.275	44080	0.813	0.68
3	10.833	44102	0.813	0.65
4	12.500	40437	0.746	0.58
5	13.375	1893387	34.923	39.73
6	14.325	2220676	40.960	40.40
7	16.658	603601	11.133	9.15
8	17.442	501760	9.255	7.62

Chiral HPLC analysis of compound 108 (rac); Column: Chiralcel-OD 4.6 x 25 cm, Mobile phase: n-Hex: IPA 90:10; Wavelength: 225 nm; Flow rate 0.4 mL/min



Detector A - 1 (225nm)

Pk #	Retention Time	Area	Area %	Height Percent
1	7.800	30847	1.011	1.07
2	8.158	55468	1.819	1.98
3	9.242	27600	0.905	0.90
4	13.542	65419	2.145	2.06
5	14.375	2870424	94.120	93.99

Chiral HPLC analysis of compound 108 (Optically active)

1.2.4. References

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Chapter 2 Section 1

Synthesis of (±)-Mitralactonine

2.1.1. Introduction

(-)-Mitralactonine (**1**), (-)-9-methoxymitralactonine (**11**) along with nine Corynanthe-type indole alkaloids, namely, mitragynine (**2**), speciogynine (**3**), speciociliatine (**4**), paynantheine (**5**), 7α-hydroxymitragynine (**6**), mitragynaline (**7**), corynantheidaline (**8**), corynantheidine (**9**), and isocorynoxeine (**10**) were isolated from the ethyl acetate extract of the young leaves of *M. speciosa*. Additionally, phaeophorbide a, a porphine derivative was also obtained (fig. 1).[1]

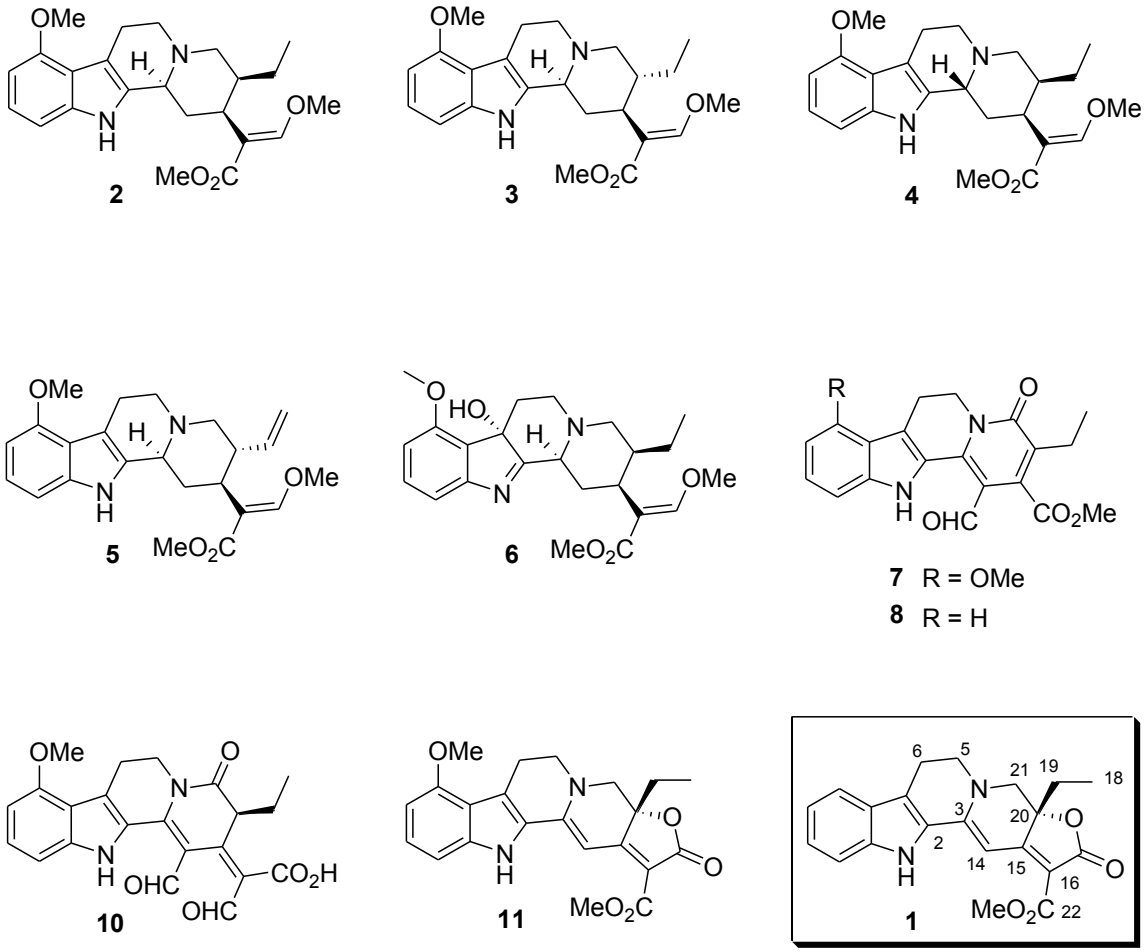


Figure 1

Mitragyna speciosa Korth. (Rubiaceae) is a tropical plant indigenous to Thailand and Malay Peninsula. It is a species of particular medicinal importance and is endemic to tropical south Asia. The plant is known as "Kartom" in Thailand and "Biak-Biak" in Malaysia. The leaves have been traditionally used by the natives for their opium like effect and cocoa like stimulant ability to combat fatigue and enhance tolerance to hard work under the scorching sun. It has also been used as a substitute for opium and for

weaning addicts off morphine. Though the plant from which it is extracted shows some medicinal properties, the pharmaceutical assay of the title compound is still in progress. This section describes the study towards the pentacyclic indole alkaloid (±)-mitralactonine (**1**).

2.1.2. Structure Elucidation

The isolated minor component **1** from the ethyl acetate extract of young leaves of *M. speciosa* was obtained as a yellow amorphous solid. The ^{1}H and ^{13}C NMR spectrum showed the presence of fundamental structural unit of common Corynanthe-type alkaloid *i.e.* an indole nucleus, an ethane bridge at C5-C6, an ethyl group at C20 and a methoxy carbonyl group. The UV spectrum exhibited a long-wavelength absorption at 460 nm, indicating a highly conjugated system *i.e*. high degree of unsaturation in the molecule. The presence of six-conjugated sp^2 carbon was revealed by the ^{13}C and HMBC spectral analysis. It further disclosed the presence of a lactone carbonyl carbon along with aromatic carbons due to indole nucleus. The characteristic proton signal at δ 6.51 appearing as a singlet was assigned to the C14 proton by HMQC spectrum and further this signal showed the HMBC conectivities between the C2, C3, C15, C16 and C20 carbons. The high resolution mass spectrum as well as the appearance of C20 carbon peak at δ 77.4 showed the presence of a lactone function constructed between the oxygen atom on C20 and the carbonyl group at the C22 position. On the basis of above findings as well as the biogenetic consideration led to determine the structure of the isolated compound to be of structural formula **1**.[2]

2.1.3. Literature Survey: Previous Work

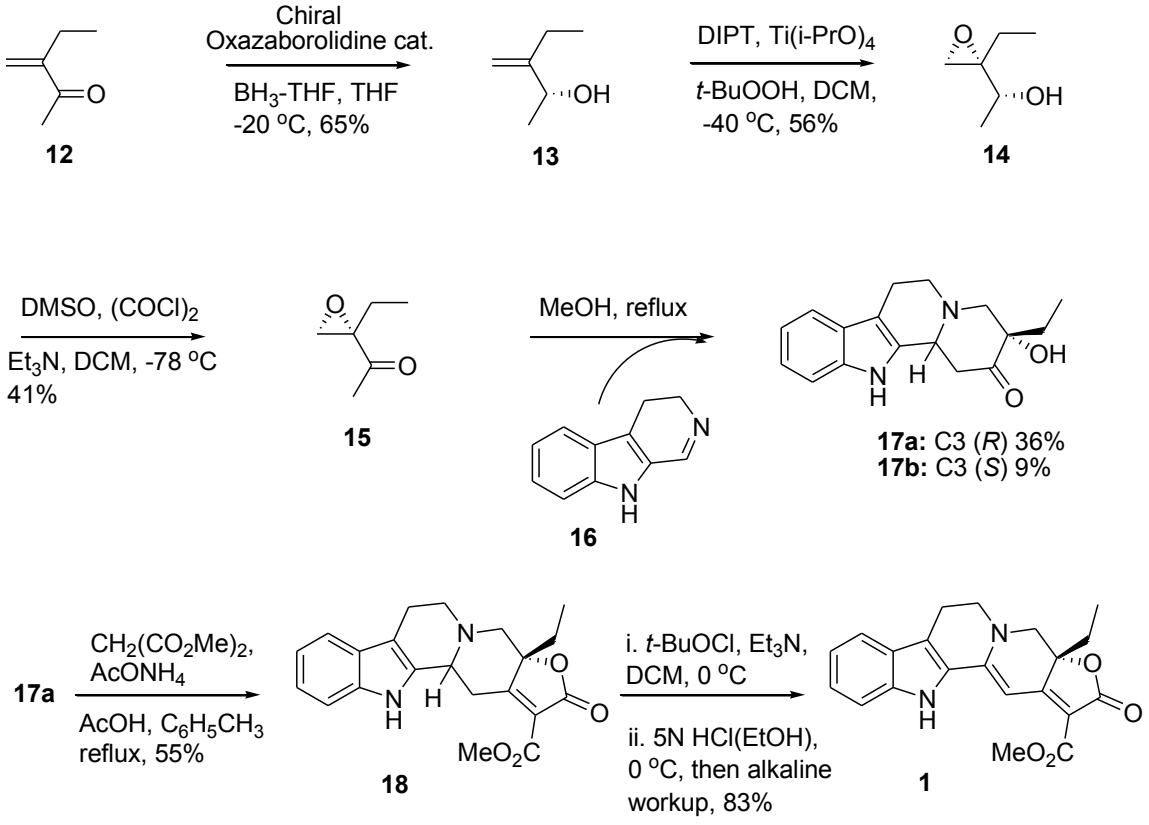
Till date only one synthesis of mitralactonine has been reported in connection with the structure elucidation of the isolated compound by Takayama et al.[2] in both racemic as well as asymmetric fashion.

The authors planned an elegant and convergent approach utilising the epoxy ketone **15** as the key synthon for the construction of highly functionalised tetracyclic intermediate **17**. The epoxy ketone **15** was obtained in step-wise manner starting from enone **12**. The chiral oxazaborolidine catalyst mediated reduction of **12** furnished the optically active alcohol **13** in 93% ee which when subjected to Sharpless asymmetric epoxidation under

the kinetic resolution condition furnished the epoxide **14** in 99% ee. The secondary carbinol was converted to ketone by Swern oxidation to give epoxy ketone **15**.

Condensation of the epoxy ketone **15** and 3,4-dihydro-β-carboline (**16**) under heating condition in methanol afforded a separable mixture of two diastereomers **17a** and **17b** in 36% and 9% yield respectively. Knoevenagel condensation on **17a** with dimethyl malonate (DMM) afforded the pentacyclic product **18** which when subjected to two step operation {(i) *t*-BuOCl, Et_3N and (ii) ethanolic HCl, then $NaHCO_3$} led to the introduction of double bond and completion of the synthesis of **1** in optically pure form (Scheme 1).

Scheme 1: Takayama et al. (*J Org. Chem.* **1999**, *64,* 1772)



2.1.4. Present Work

In continued efforts towards synthesis of naturally occuring alkaloids namely camptothecin, rutaecarpine[3] etc, synthesis of mitralactonine having a very similar skeletal framework was undertaken. Intrigued by the possibility of extending the chemistry developed in this group for the camptothecin to mitralactonine due to the

striking resemblance of D and E rings of camptothecin **19** and mitralactonine the synthesis of **1** was taken up (fig. 2).

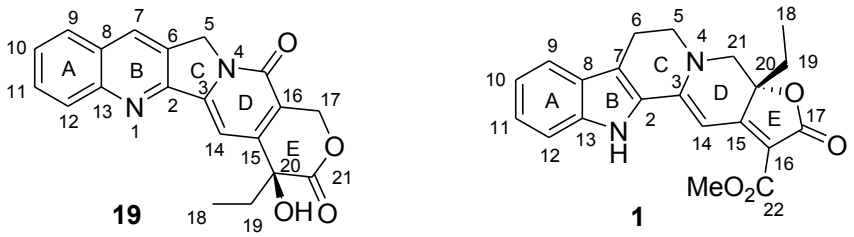
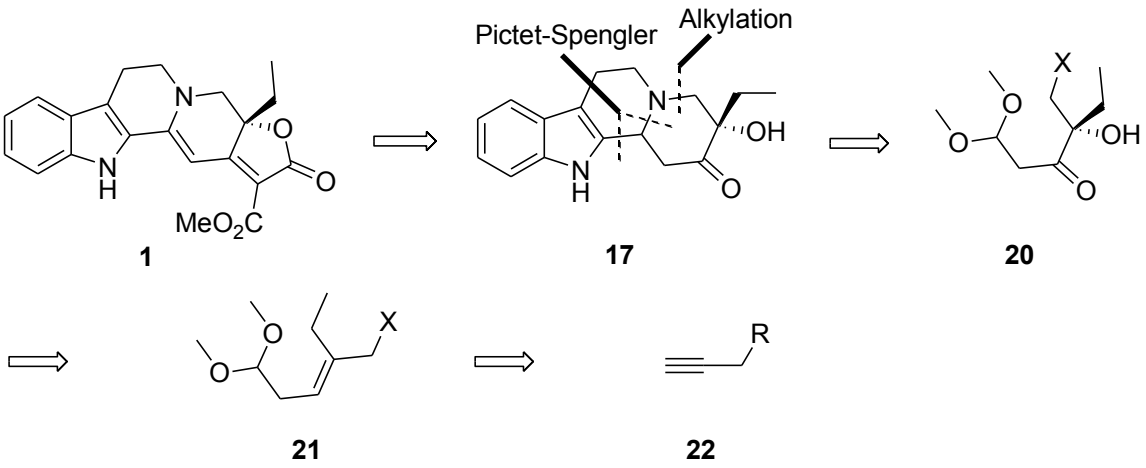


Figure 2

The biogenetic relationship of camptothecin[4] with strictosidine, an indole, provided an impetus to undertake the synthesis of mitralactonine, which could later be elaborated to other such biogenetically related alkaloids.

The retrosynthetic analysis to mitralactonine is delineated in scheme 2, which reveals a Pictet-Spengler[5] condensation-alkylation as the key step to the key intermediate **17** with requisite functionalities for further manipulation and extension. The key synthon **20** was thought to be obtained from olefin **21**, which in turn could be made from alkyne **22**.



Scheme 2: *Retrosynthetic analysis*

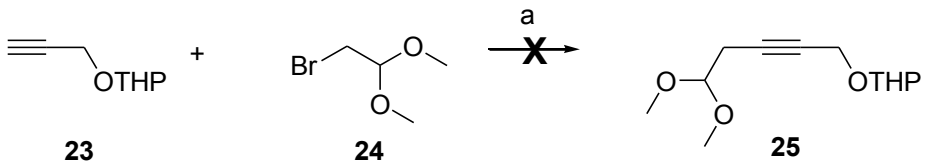
2.1.5. Results and Discussion

At the onset of the endeavor initial concern was to obtain the fragment **20** in racemic form and subject it to the crucial condensation with tryptamine. The present section describes the journey towards the racemic synthesis of the target molecule.

The keto-hydroxy fragment **20** was chosen as the key synthon as it possesses requisite functionalities for condensation as well as for further elaboration to the pentacyclic

system. As described in the retrosynthetic analysis the olefin precursor **21** to the keto-hydroxy compound **20** was thought to be obtained by ethyl Grignard addition to the functionalised alkyne, which in turn could be realised from cheaply and widely available propargyl alcohol.

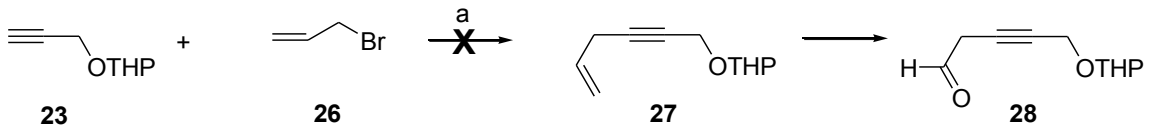
Accordingly alkylation of protected propargyl alcohol (**23**) with bromoacetaldehyde dimethyl acetal (**24**) would have rendered the substituted acetylene **25** but under conditions tried alkylated substrate **25** could not be obtained (Scheme 3).



23 **24** **25**

Scheme 3: Reagents and conditions: *a) $NaNH_2$, THF: DMSO (4:1), rt.*

A two-step strategy wherein alkylation of protected propargyl alcohol with allyl bromide (**26**) followed by its conversion into aldehyde/acetal **28** also could be not successfully realised (Scheme 4).

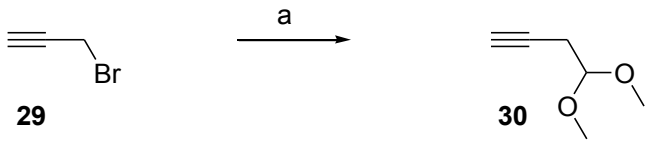


23 **26** **27** **28**

Scheme 4: Reagents and conditions: *a) $NaNH_2$, THF, rt.*

Gardiner et al.[6] described a convenient two-step approach to substituted propargyl alcohol as a versatile common achiral intermediate to carbohydrate synthesis from simple precursors. So the same strategy was adopted to obtain the required substituted propargyl alcohol starting from propargyl bromide.

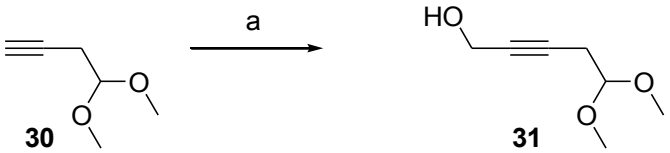
Propargyl bromide (**29**) when treated with mixture of powdered aluminum and trace of mercuric chloride in ether reacted exothermally and resulted in the formation of an organometalic substrate, which was quenched with trimethyl orthoformate at –78 ^{o}C to furnish the acetal **30** after distillation (Scheme 5).



Scheme 5: Reagents and conditions: *a) Al (powder), $HgCl_2$, diethyl ether, rt, 1 h, -78 ^oC, 1h, trimethylorthoformate, -45 ^oC, 1h.*

The ^1H NMR spectrum of **30** showed a triplet at δ 4.56 integrating for one proton ascribed to the acetal –C*H*. Peak at δ 3.39 integrating for six protons and appearing as a singlet was due to the two methoxy groups. The methylene protons appeared as dd at δ 2.54 whereas the alkyne proton resonated at δ 2.04 as a triplet. ^{13}C NMR spectrum alongwith DEPT spectrum showed the presence of single methylene carbon resonating at δ 23.6. The two methoxy carbons appeared at δ 53.2 whereas the two alkyne carbon appeared at δ 70.1 and δ 79.2. The acetal carbon resonated at δ 102.1.

Hydroxymethylation of the substrate **30** to **31** was achieved by the addition of paraformadehyde to anion generated by the action of *n*-BuLi on acetylene in THF and refluxing it for 3 h. The pure product was obtained in 80% yield after column chromatographic purification (Scheme 6).

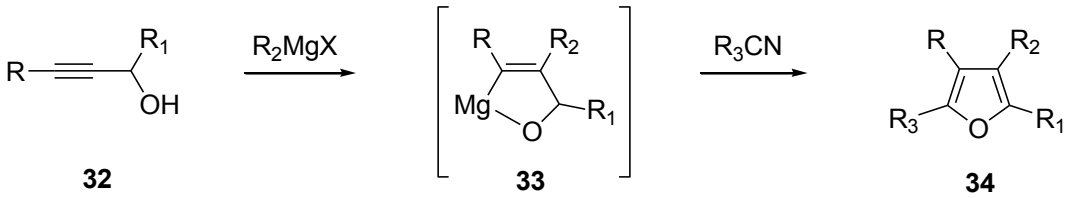


Scheme 6: Reagents and conditions: *a) n-BuLi, THF, -78 ^oC, $(CH_2O)_n$, reflux, 3 h, 80%.*

The formation of **31** was confirmed by its spectral study. IR spectrum showed absorption at 3421 cm^{-1} due to the hydroxy group. Appearance of triplet at δ 4.06 ascertained the addition of -C*H*$_2$OH group on the alkyne substrate. This alongwith disappearance of peak from δ 2.04 further exemplifies the absence of alkyne proton and hence supports the addition of hydroxymethyl group. Other peaks characteristic of the substrate appeared at their expected chemical shifts. ^{13}C NMR spectrum along with DEPT spectrum showed the presence of two methylene carbons resonating at δ 50.2 and δ 23.4 in accordance with the said transformation. Disappearance of acetylenic carbon peak from δ 79.4 in DEPT spectrum ascribed to the alkyne carbon (-*C*H-) explains the substitution at the

position. Other carbon peaks appeared at the expected positions. Formation of alcohol **31** was further confirmed by elemental analysis.

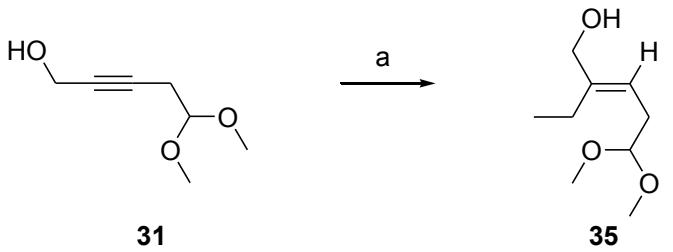
Regioselective addition of ethyl Grignard across the triple bond would furnish the tri-substituted alkene with proper disposition of substituent. Fallis et al.[7] have performed addition of vinyl and aryl Grignard reagent to propargyl alcohols **32** to generate intermediate magnesium chelate **33** wherein the regioslectivity was maintained and the alkyl group was delivered selectively to the acetylenic carbon possessing the alcoholic functionality (Scheme 7).



32 **33** **34**

Scheme 7

Keeping this in mind the substrate **31** seemed to be ideally suited to deliver the required addition product for further conversion to key synthon. Thus treating the substrate **31** with EtMgBr in diethyl ether furnished the alkylated product **35** in 75% yield (Scheme 8).



31 **35**

Scheme 8: Reagents and conditions: *a) Mg, EtBr, ether, reflux 4 h, 75%.*

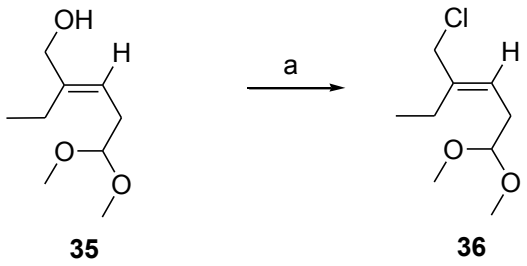
IR spectrum showed absorption at 3437 cm^{-1}. ^{1}H NMR spectrum showed the presence of alkene proton peak at δ 5.33 which appeared as a triplet. Addition of ethyl group was exemplified by the presence of peaks at δ 2.06 and δ 0.97 integrating for two and three protons and corresponding to the –C$\underline{H}_2$ and the -C$\underline{H}_3$ protons respectively. The –C$\underline{H}_2$OH proton shifted downfield to δ 4.00 and appeared as a singlet. Acetal -C$\underline{H}$ protons moved downfield to δ 4.34 and appeared as triplet whereas the –C$\underline{H}_2$ protons next to acetal appeared as triplet at δ 2.34. ^{13}C NMR spectrum showed the presence of alkene carbons

at δ 143.2 and δ 119.1 respectively for quaternary and –<u>C</u>H carbons respectively. ^{13}C NMR spectrum along with DEPT spectrum showed the presence of three methylene carbons resonating at δ 66.2, 30.8 and 21.1 which were assigned to –<u>C</u>H_2OH, -<u>C</u>H_2C= and –<u>C</u>H_2CH_3 carbons respectively. The regioselective alkylation of the substrate was proved beyond doubt by NOE study.

With the required substrate **35** in hand a quick functionalisation of the primary alcohol into a better leaving group such as mesylate, tosylate or a halide followed by conversion of alkene into keto-hydroxy functionality would furnish the key synthon.

Exposure of allylic alcohol to methanesulfonyl chloride[8] is known to furnish the corresponding chloro compound. Keeping this in mind the allylic alcohol was subjected to react with 1.5 equivalent of methanesulfonyl chloride in presence of triethylamine at 0 ^{o}C. The product was obtained as a mixture of both mesylated and chloro compound. But when the same reaction was subjected to large excess of methanesulfonyl chloride (3 eq.) and left to stir at room temperature for 12 h, it rendered the chloro compound exclusively, but the isolated chloro compound was found to be very unstable under neat condition. Hence it was prepared and was subjected for further reaction without delay.

Thus when the substrate **35** was treated with 3 eq. of methanesulfonyl chloride in presence of triethylamine in DCM for 12 h rendered the chloro compound **36** as ascertained by TLC pattern and ^{1}H and ^{13}C NMR spectral analysis. The TLC showed a very faster moving (R_f 0.8) spot in 5% ethyl acetate: Pet ether solvent system but the absence of any peak corresponding to methyl sulfonate both in ^{1}H and ^{13}C NMR spectrum confirmed the formation of corresponding primary chloro compound **36** without rearrangement rather than the mesylate (Scheme 9).



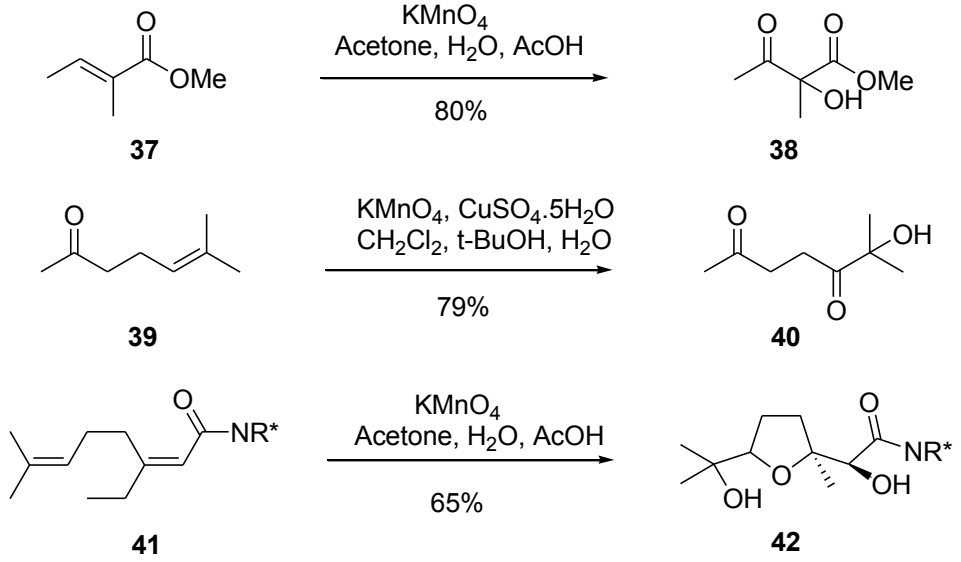
35 **36**

Scheme 9: Reagents and conditions: *a) MsCl (3 eq.), Et_3N, DCM, 0 ^{o}C-rt, 12 h.*

The ^{1}H NMR spectrum of **36** showed the disappearance of the –OH proton peak at δ 1.90. The other peaks resonated almost at the same position as in its precursor. ^{13}C NMR

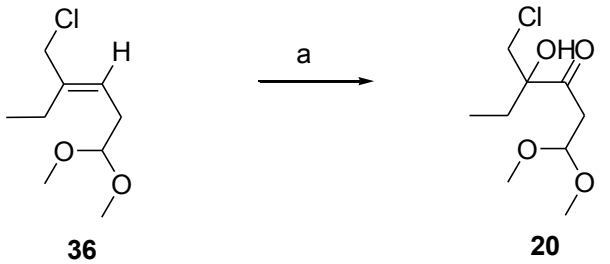
spectrum didn't show any significant change in most of the signals but one of the alkene carbons moved downfield to δ 124.6 from δ 119.

Literature precedents are there wherein the tri-substituted olefins have been converted into corresponding keto-hydroxy compound by exposing to $KMnO_4$ involving a 4e-oxidation[9] (Scheme 10).



Scheme 10

This strategy has earlier been utilised in our group for the functionalisation of such substituted alkene towards the synthesis of quinoline alkaloid. Intrigued by this possibility to obtain the ketol in a single step the crude allyl chloro compound **36** was subjected to react with $KMnO_4$ under acidic condition in acetone-water solvent system at -10 ^oC. As expected the oxidation furnished the keto-hydroxy compound **20** in 84% yield (Scheme 11).



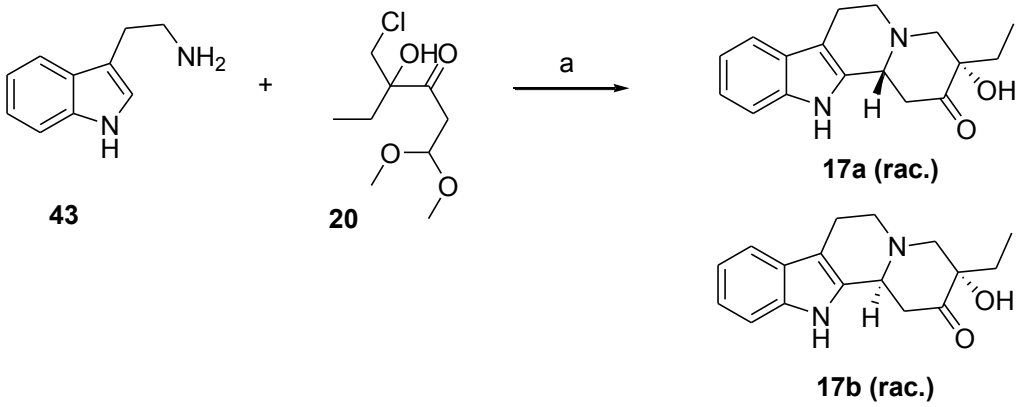
Scheme 11: Reagents and conditions: *a) $KMnO_4$, AcOH, Acetone: H_2O, -10 ^oC, 0.5 h, 84%.*

The IR spectrum of **20** showed strong absorption at 3469 cm^{-1} and 1717 cm^{-1} typical of hydroxy ketone functionality. ^1H NMR spectrum of **20** showed absence of olefinic

proton and appearance of peaks at δ 3.80 and δ 3.58 as doublets corresponding to methylene carbons adjacent to the quaternary hydroxy group. The diastereomeric behaviour of the two protons signifies the presence of adjacent chiral quaternary center. ^{13}C NMR spectrum confirmed the presence of ketone carbonyl peak at δ 208.4 and the newly formed quaternary carbon at δ 81.6 thereby exemplifying the expected conversion. Thus the key synthon **20** was thus obtained in pretty good yield and purity in five steps starting from propargyl bromide.

β-Carboline formation has been a reliable and efficient technique for the construction of alkaloid based natural and pharmaceutical products.[5] Pictet-Spengler condensation of aldehyde/ketones or equivalent has been the most successful path for tetrahydro-β-carboline syntheses. The generally accepted mechanism involves a cationic cyclisation of iminium ion on indole nucleus. Typically reaction involves reacting tryptamine with aldehyde in the presence of acid. Analogous reaction with corresponding acetals has also been equally successful. Traditionally strong acids such as acetic acid, trifluroacetic acid, HCl have been employed for the transformation.

Having synthesised the required synthon in a short sequence in racemic form stage was set to condense it with tryptamine to obtain C ring and further extend it to the required intermediate. It was decided to perform the Pictet-Spengler cyclisation first followed by alkylation. Mixing equivalent amount of tryptamine (**43**) and keto-hydroxy compound **20** in chloroform and treating with TFA followed by alkaline work up (Scheme 12) showed a very faint faster moving spot on TLC against the expected slower moving spot typical of amine compounds. Isolation of the same and characterisation surprisingly revealed the formation of tetracyclic unit **17** in single pot instead of just formation of tricyclic β-carboline unit. But the yield of the product was very discouraging. Hence, efforts were directed to standardise the conditions of condensation to improve the yield of the transformation. Under various conditions tried (entries 1, 2, 3) as shown in Table 1 results were not much very encouraging.



Scheme 12: Reagents and conditions: *a) TFA, $CHCl_3$, 0 ^oC-rt, 12 h.*

During their synthesis of indole alkaloid deplancheine, Allin et al.[10] have involved an HCl (EtOH) mediated cyclisation of bicyclic lactam into indolo quinolozine product in fairly good yield. Having failed to improve the yield with repeated trials with other acidic medium attention was shifted to this particular condition and it was thought worthwhile to apply these conditions for the formation of tetracyclic compound. Delightfully under these reaction conditions **17** was isolated in combined yield of 55% as a mixture of two diastereomers (3:1).

Table 1

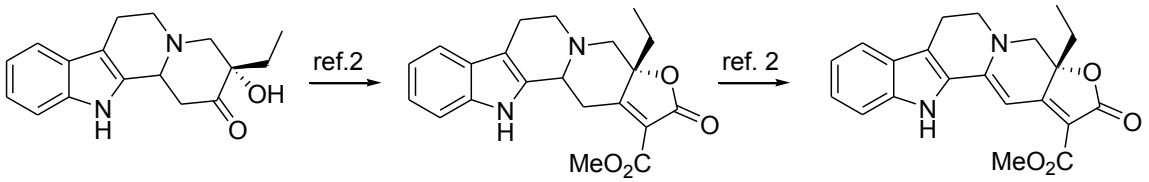
Entry	***Solvent***	***Reagent***	***Time***	***Temperature***	***Yield***
1.	$CHCl_3$	TFA	48 h	RT	10-15 %
2.	CH_3CN	TFA	48 h	RT	Trace
3.	-	Aq HCl	48 h	RT	-
4.	**EtOH**	**2M HCl (EtOH)**	**24-48 h**	**RT**	**55%**

Thus when the keto-hydroxy moiety was subjected to react with the tryptamine in presence of 2 M ethanolic HCl for 12 h at room temperature followed by alkaline work up it rendered the product **17** in 55% yield.

Reaction is typically thought to commence stepwise. Initially the acetal gets involved in Pictet-Spengler cyclisation in acidic medium and during work up under highly alkaline condition alkylation is facilitated due to rightly placed leaving group that favour the formation of six membered cycle.

The formation of **17** was confirmed by its spectral study and its comparison with already reported data. ^{1}H and ^{13}C NMR spectrum showed an array of characteristic peaks which were in full agreement with the reported compound.

Chromatographic separation (SiO_2) led to the isolation of major isomer **17a** in 42% yield whereas the minor isomer **17b** was obtained in 13% yield. The major isomer **17a** was subjected to further conversion into lactone under Knoevenegal condition with dimethyl malonate according to the reported procedure[2] and finally subjected to two-step protocol to introduce the double bond furnishing the (±) mitralactonine.



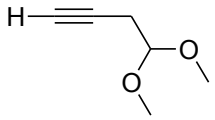
17 **18** **1**

Scheme 13

In conclusion, a very short route (5 steps) to the key synthon **20** was established in racemic form starting from propargyl bromide in good yield. An efficient one pot ring annulation under typically simple condition was achieved leading to the synthesis of highly functionalised tetracyclic key intermediate **17** to the pentacyclic indole alkaloid mitralactonine (**1**). This successful condensation paves the path to synthesis of such biogenetically related alkaoids.

2.1.6. Experimental

4,4-Dimethoxybut-1-yne (30)



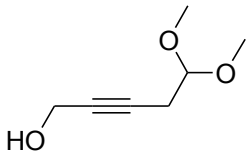
To a well-stirred mixture of powdered aluminum (4.64 g, 172.5 mmol) and $HgCl_2$ (0.6 g, 2.2 mmol) in dry ether under argon atmosphere was added propargyl bromide (17.96 g, 150.9 mmol) dropwise maintaining a gentle reflux. The mixture was stirred for an additional one hour at room temperature and then the temperature was lowered to –78 ^oC. Trimethyl orthoformate (16 g, 170.2 mmol) was added dropwise over a period of 1h and stirred additionally (2 h) at same temperature. The temperature was raised to –40 ^oC in 1 h time followed by quenching with saturated NH_4Cl solution and was allowed to come to room temperature. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was distilled out at 98 ^oC at 266 torr (mm Hg) as a solution in toluene.

Mol. Formula : $C_6H_{10}O_2$

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.56 (t, *J* = 5.6 Hz, 1H), 3.39 (s, 6H), 2.54 (dd, *J* = 5.6, 2.7 Hz, 2H), 2.04 (t, *J* = 2.7 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 102.1 (CH), 79.2 (CH), 70.1 (C), 53.2 ($2CH_3$), 23.6 (CH_2).

5,5-Dimethoxypent-2-yn-1-ol (31)



The compound **30** (2.0 g, 17.5 mmol) was taken in dry THF and cooled to –78 ^oC. *n*-BuLi (1.4 M) (12.53 ml, 17.8 mmol) was added dropwise, and the mixture stirred at –78 ^oC for 1 h. The reaction mixture was warmed to room temperature and paraformaldehyde (0.54 g, 17.9 mmol) was then added followed by reflux for 3h. The reaction mixture was cooled to room temperature and then quenched by addition of saturated aqueous NH_4Cl. The organic layer was separated, diluted with diethyl ether and washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under vacuum. Column

chromatography (SiO_2) yielded the pure product. (2.0 g, 14.0 mmol) 80%. R_f 0.2 (PE: EA 70:30)

Mol. Formula **:** $C_7H_{12}O_3$

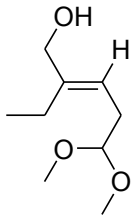
Yield **:** 80%

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) **:** 3421, 3010, 2940, 1633.

^{1}H NMR (200 MHz, $CDCL_3$) **:** δ 4.39 (t, *J* = 5.5 Hz, 1H), 4.06 (t, *J* = 2.1 Hz, 2H), 3.21 (s, 6H), 2.40 (dt, *J* = 5.5, 2.1 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 101.9 (CH), 80.3 (C), 79.8 (C), 52.8 (CH_3), 50.2 (CH_2), 23.4 (CH_2).

(*E*)-2-Ethyl-5,5-dimethoxypent-2-en-1-ol (35)



Magnesium turnings (1.77 g, 72.8 mmol) in anhydrous diethyl ether (50 mL) under argon atmosphere was treated with bromoethane (5.5 ml, 72.8 mmol) dropwise to maintain a gentle reflux and the mixture was stirred for 1 h at room temperature. To the generated Grignard was added the solution of compound **31** (3.45 g, 23.9 mmol) dissolved in 25 mL ether, dropwise again to maintain a gentle reflux and the resulting mixture stirred for additional 1 h at room temperature followed by reflux for 4 h. The reaction mixture was cooled and quenched with saturated aqueous NH_4Cl. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 25 mL). Combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Column chromatographic purification (SiO_2) furnished the allylic alcohol in 75% yield (2 g, 11.5 mmol). R_f 0.3 (PE: EA 70:30)

Mol. Formula **:** $C_9H_{18}O_3$

Yield **:** 75%

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) **:** 3437, 2967, 2936.

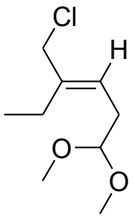
^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 5.33 (t, *J* = 7.1 Hz, 1H), 4.34 (t, *J* = 5.7 Hz, 2H), 4.01 (s, 2H), 3.29 (s, 6H), 2.34 (t, *J* = 6.4 Hz, 2H),

2.06 (q, *J* = 7.5 Hz, 2H), 1.98 (brs, 1H, -O*H*), 0.97 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 143.2 (C), 119.1 (CH), 104.1 (CH), 66.2 (CH_2), 52.8 ($2CH_3$), 30.8 (CH_2), 21.1 (CH_2), 12.9 (CH_3).

Analysis **:** Calculated C 62.04, H 10.41%
Found C 61.89, H 10.29%

(*E*)-4-(Chloromethyl)-1,1-dimethoxyhex-3-ene (36)



To a mixture of hydroxy compound **35** (2 g, 11.5 mmol) and Et_3N (4.8 mL) in 25 mL dry DCM under argon atmosphere at 0 ^oC was added MsCl (0.97 mL, 12.6 mmol) dropwise and left to stir overnight at room temperature. On completion of reaction (TLC) the reaction mixture was diluted with DCM and washed subsequently with saturated solution of $NaHCO_3$, brine, dried over anhydrous sodium sulphate, filtered and concentrated under low vacuum. The crude compound was taken forward to next step without delay due to unstability of the same. R_f 0.8 (PE: EA 95:5)

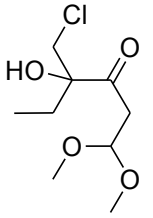
Mol. Formula **:** $C_9H_{17}ClO_2$

Yield **:** Crude (unstable)

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 5.48 (t, *J* = 7.0 Hz, 1H), 4.34 (t, *J* = 5.7 Hz, 1H), 4.04 (s, 2H), 3.03 (s, 6H), 2.36 (t, *J* = 6.5 Hz, 2H), 2.18 (q, *J* = 7.5 Hz, 2H), 1.02 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 139.7 (C), 124.6 (CH), 103.9 (CH), 52.9 ($2CH_3$), 49.4 (CH_2), 31.6 (CH_2), 21.3 (CH_2), 12.6 (CH_3).

4-(Chloromethyl)-4-hydroxy-1, 1-dimethoxyhexan-3-one (20)



To a well stirred solution of chloro olefin **36** (crude) (2.2 g, 11.5 mmol) and AcOH (1.5 mL) in 40 mL of aqueous acetone (9:1) maintained at –10 ^oC, was added $KMnO_4$ (3.1 g,

19.5 mmol)in portions such that the reaction temperature remained below –10 ^{o}C. After stirring for 0.5 h at –10 ^{o}C, the black precipitate of MnO_2 was filtered off through a celite pad and the filtrate was evaporated at reduced pressure to remove acetone and the aqueous layer was extracted with DCM (3 x 25 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish crude ketol. Column chromatoghraphy (SiO_2) rendered the pure product in 84% yield. R_f 0.5 (PE: EA 70:30)

Mol. Formula **:** $C_9H_{17}ClO_4$

Yield **:** 84%

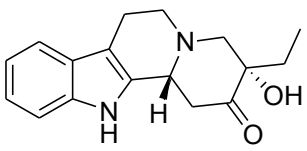
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) **:** 3469, 3018, 2940, 1717.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 4.82 (dd, *J* = 6.4, 4.4 Hz, 1H), 3.98 (br s, 1H), 3.80 (d, *J* = 11.4 Hz, 1H), 3.58 (d, *J* = 11.4 Hz, 1H), 3.39, 3.37 (2S, 6H), 3.01 (dd, *J* = 15.6, 6.6 Hz, 1H), 2.76 (dd, *J* = 15.6, 4.4 Hz, 1H), 1.84-1.63 (m, 2H), 0.87 (t, *J* = 7.5 Hz, 3H).

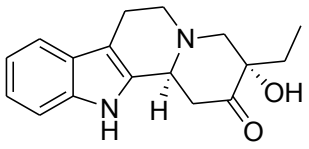
^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 208.4 (C), 101.7 (CH), 81.6 (C), 54.7 (CH_3), 53.7 (CH_3), 49.2 (CH_2), 41.5 (CH_2), 29.4 (CH_2), 7.2 (CH_3).

Analysis **:** Calculated C 48.11, H 7.63, Cl 15.78%
Found C 47.88, H 7.54, Cl 15.69%

Compound 17a and 17b



17a (rac.)



17b (rac.)

To a mixture of tryptamine (0.356g, 2.2mmol) and keto-hydroxy **20** (0.5 g, 2.2 mmol) in absolute ethanol (5mL) under nitrogen at 0 ^{o}C was added 2M ethanolic HCl drop wise (pH 1) and left to stir at room temperature for 12 h. The reaction mixture was diluted with ethyl acetate (10 mL) and water (5 mL) and made alkaline with excess of NaOH (pH 14). The organic layer was separated and aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Column

chromatographic purification rendered the two diastereomers in 55% yield. R_f 0.5 and 0.4 (PE: EA 1:1).

Mol. Formula : $C_{17}H_{20}N_2O_2$

Yield : 55% (**17a** 42 % **17b** 13%)

Mass (ESI) (17a) : *m/z* 285.33 (M^++1)

Analysis (17a) : Calculated: C 71.81, H 7.09, N 9.85 %
Found: C 71.62, H 6.95, N 9.66 %

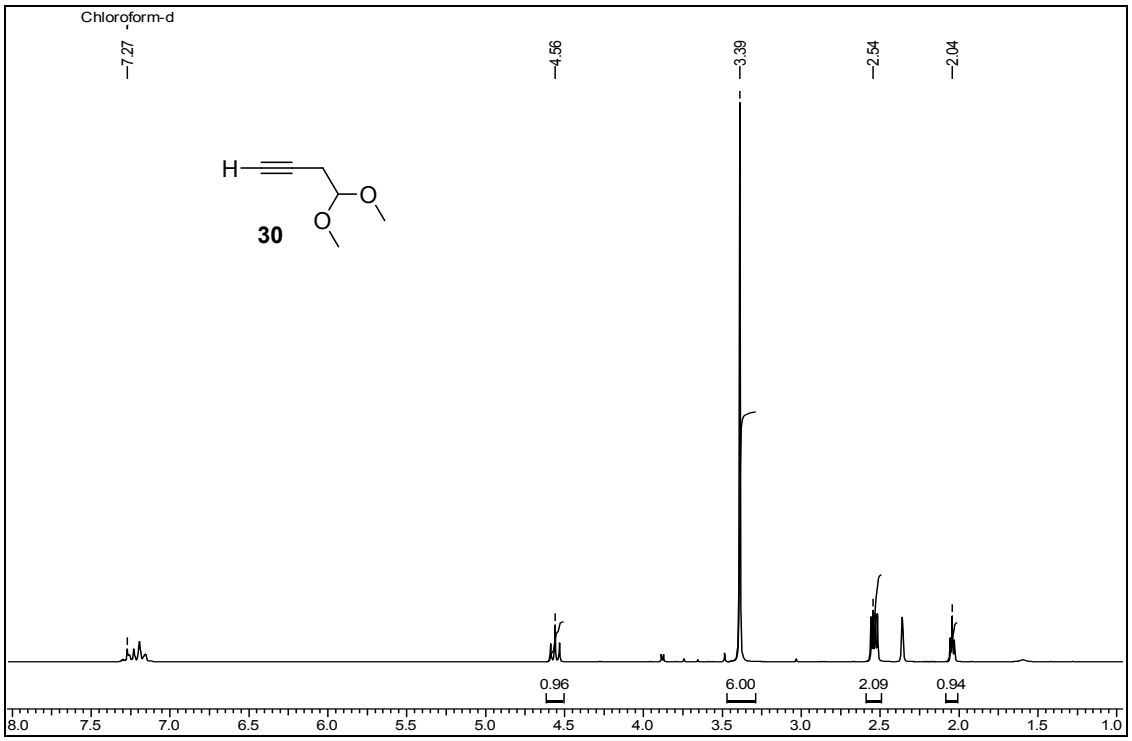
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) (17a) : 3409, 3018, 1716, 1440.

^{1}H NMR (500 MHz, $CDCl_3$) (17a) : δ 7.83 (br s, 1H, N*H*), 7.52 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* =8.0 Hz, 1H), 7.19 (m, 1H), 7.14 (m, 1H). 3.82 (br s, 1H), 3.60 (br d, 1H), 3.26 (d, *J* = 11.2 Hz, 1H), 3.18 (dd, *J* = 4.8, 11.4 Hz, 1H), 3.06-2.99 (m, 1H), 2.86 (dd, *J* = 13.2, 3.2, Hz, 1H), 2.79 (br d, *J* = 12.2 Hz, 1H), 2.70 (dd, *J* = 11.4, 3.8 Hz, 1H), 2.57 (d, *J* = 11.2 Hz, 1H), 2.31-2.23 (m, 1H), 1.91-1.84 (m, 1H), 0.84 (t, *J* = 7.6 Hz, 3H).

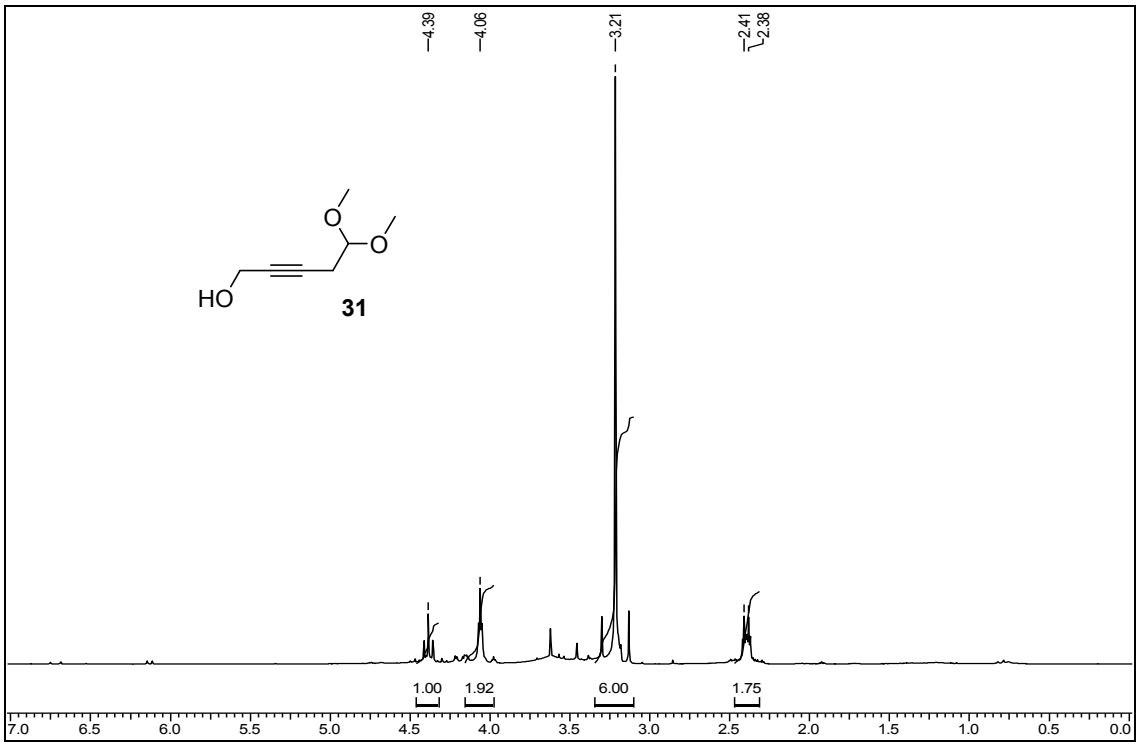
^{13}C NMR (125 MHz, $CDCl_3$) (17a) : δ 211.5 (C), 136.3 (C), 132.6 (C), 126.9 (C), 121.9 (CH), 119.6 (CH), 118.3 (CH), 111.1 (CH), 108.7 (C), 79.4 (C), 65.9 (CH_2), 59.7 (CH_3), 51.8 (CH_2), 42.8 (CH_2), 30.7 (CH_2), 21.9 (CH_2), 6.9 (CH_3).

^{1}H NMR (400 MHz, $CDCl_3$) (17b) : δ 7.82 (br s, 1H), 7.53-7.49 (m, 1H), 7.37-7.34 (m, 1H), 7.23-7.09 (m, 2H), 4.02 (br s, 1H), 3.90 (br d, 1H), 3.22-2.65 (m, 8H), 1.96 (m, 1H), 1.67 (m, 1H), 0.97 (m, 3H).

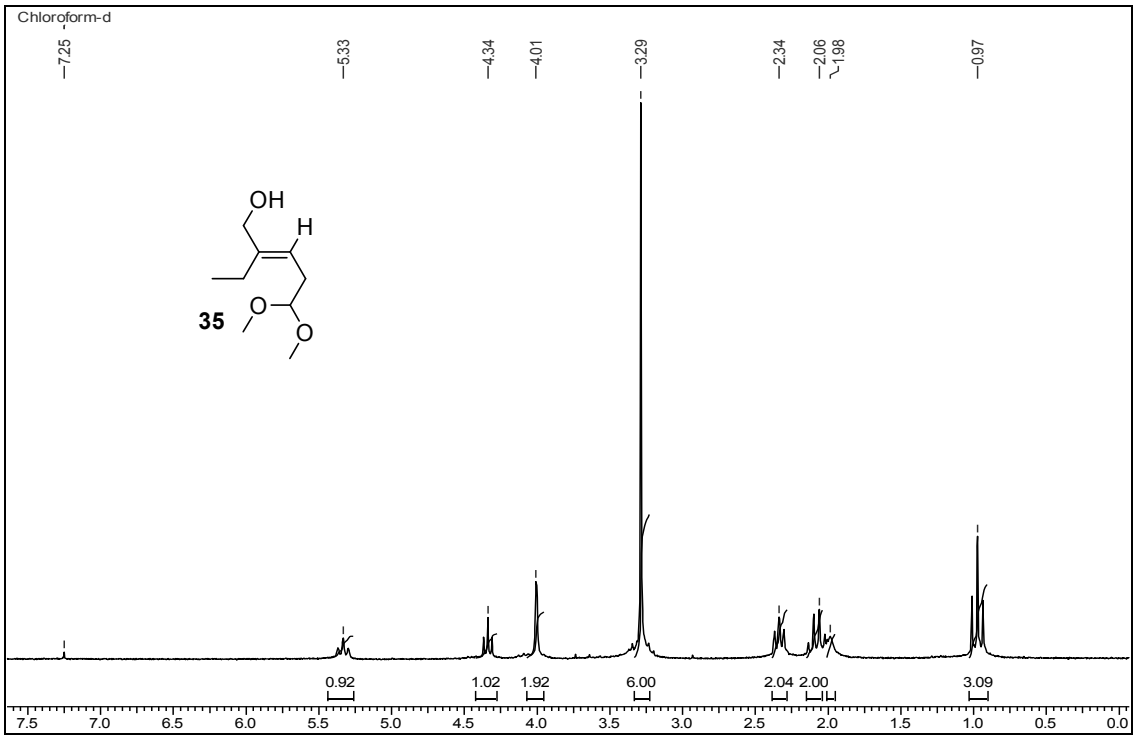
^{13}C NMR (100 MHz, $CDCl_3$) (17b) : δ 208.5 (C), 136.2 (C), 132.2 (C), 126.7 (C), 121.9 (CH), 119.6 (CH), 118.2 (CH), 111.1 (CH), 108.1 (C), 76.3 (C), 63.1 (CH_2), 58.5 (CH), 51.6 (CH_2), 41.7 (CH_2), 25.4 (CH_2), 21.1 (CH_2), 7.0 (CH_3).



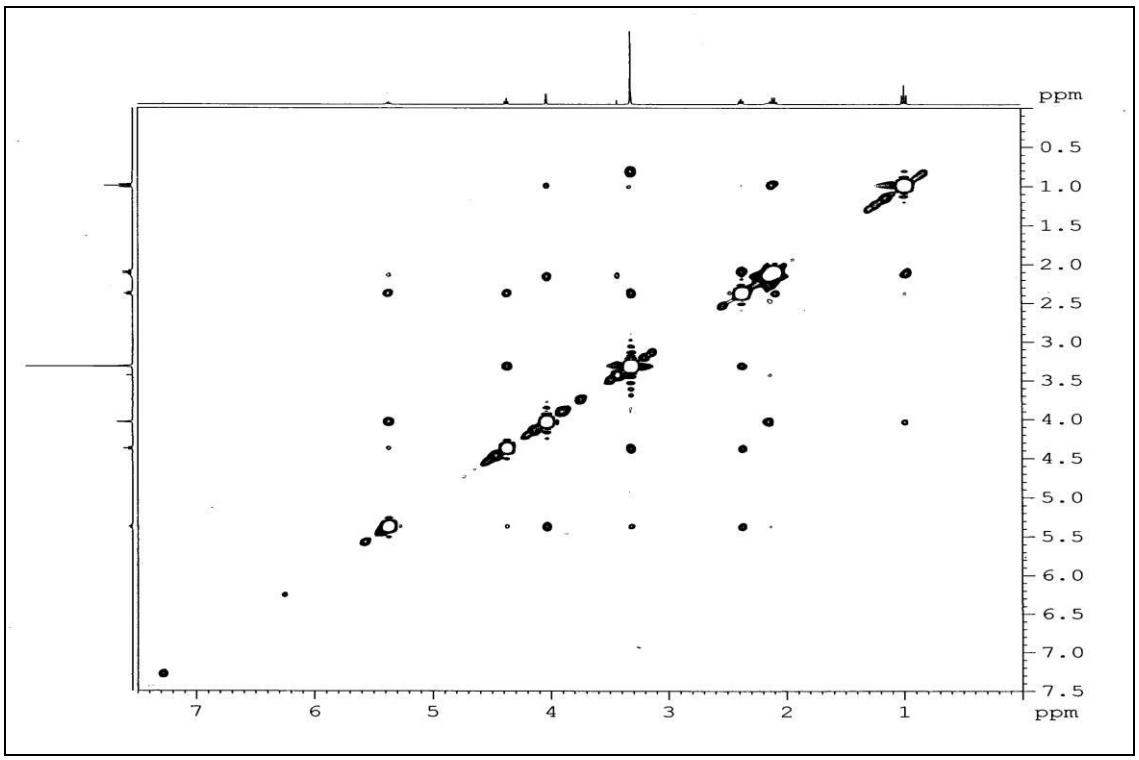
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 30



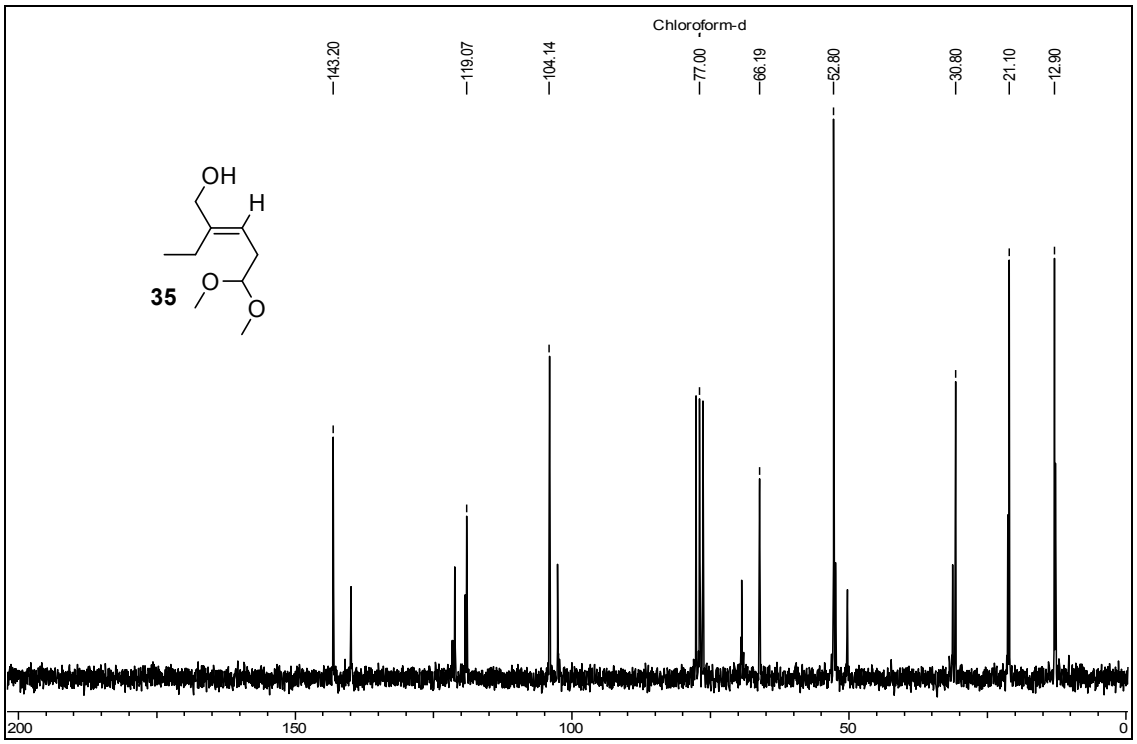
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 31



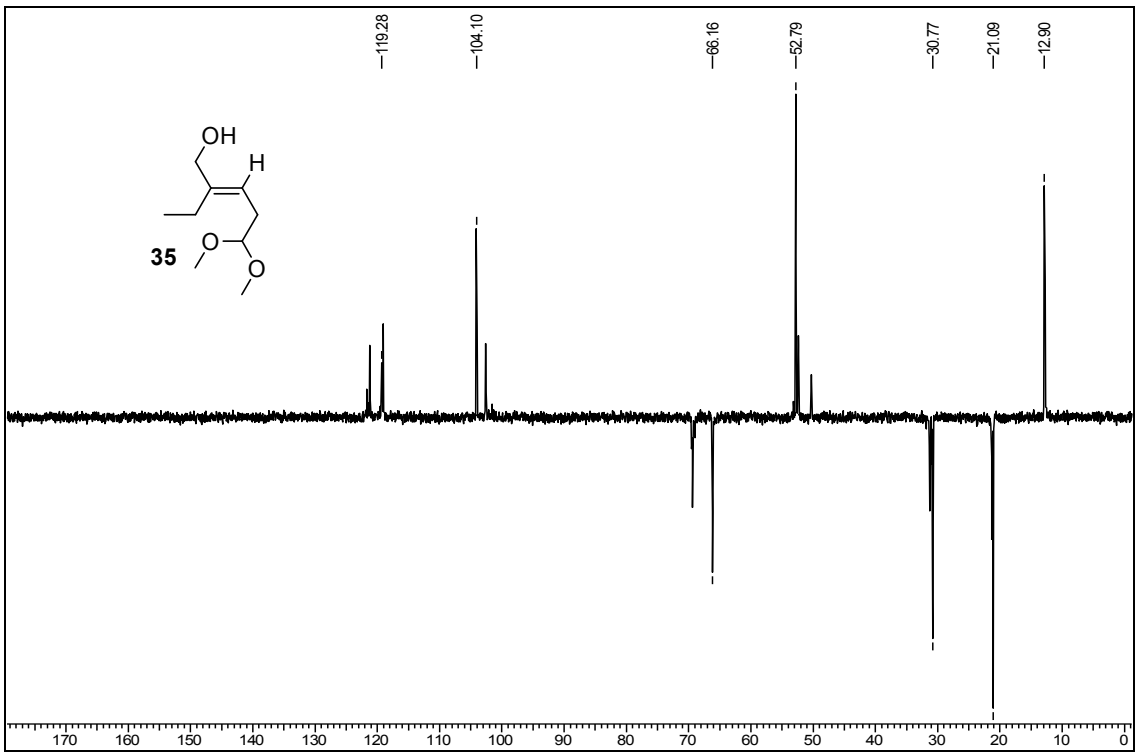
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 35



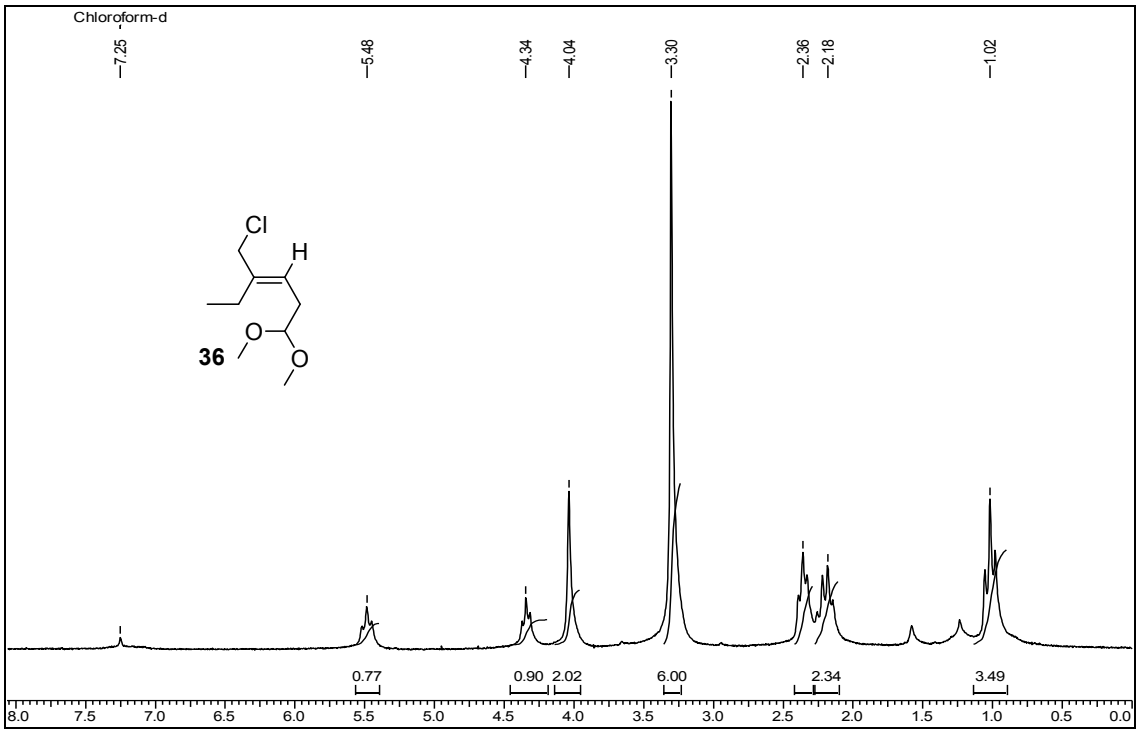
NOESY ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 35



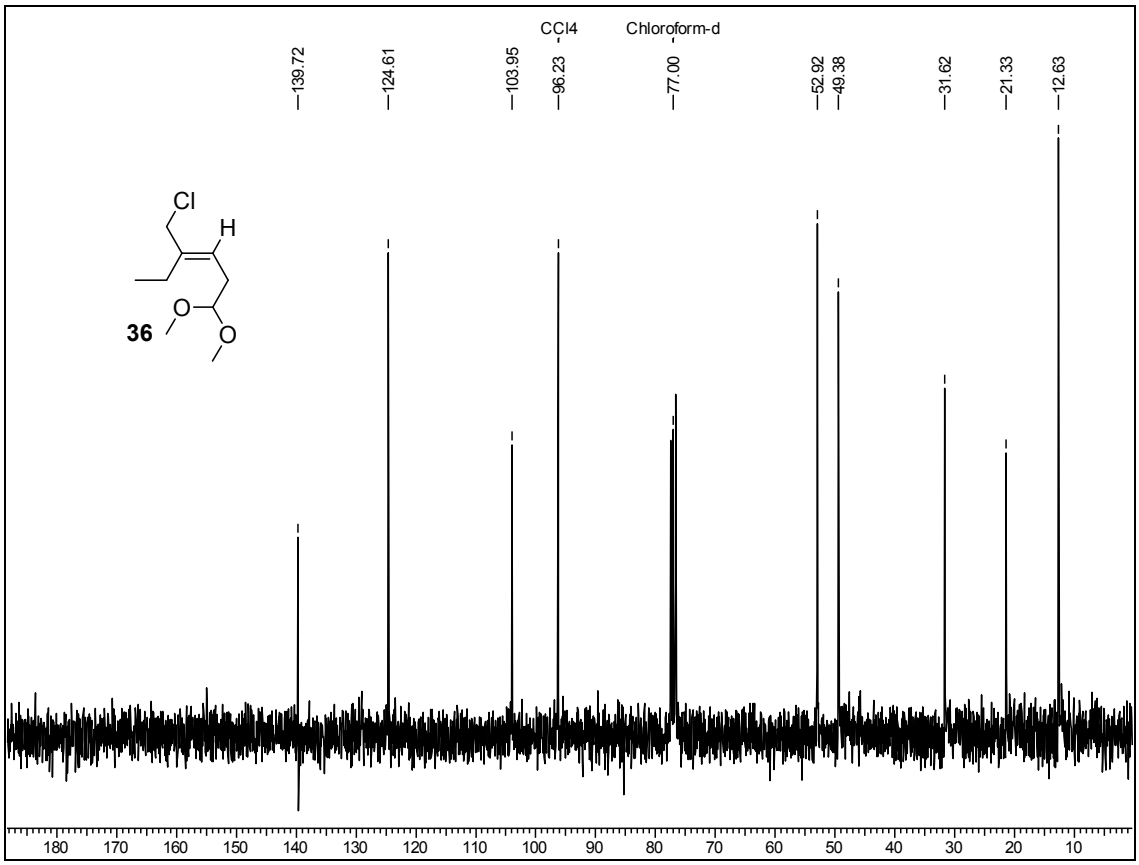
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of compound 35



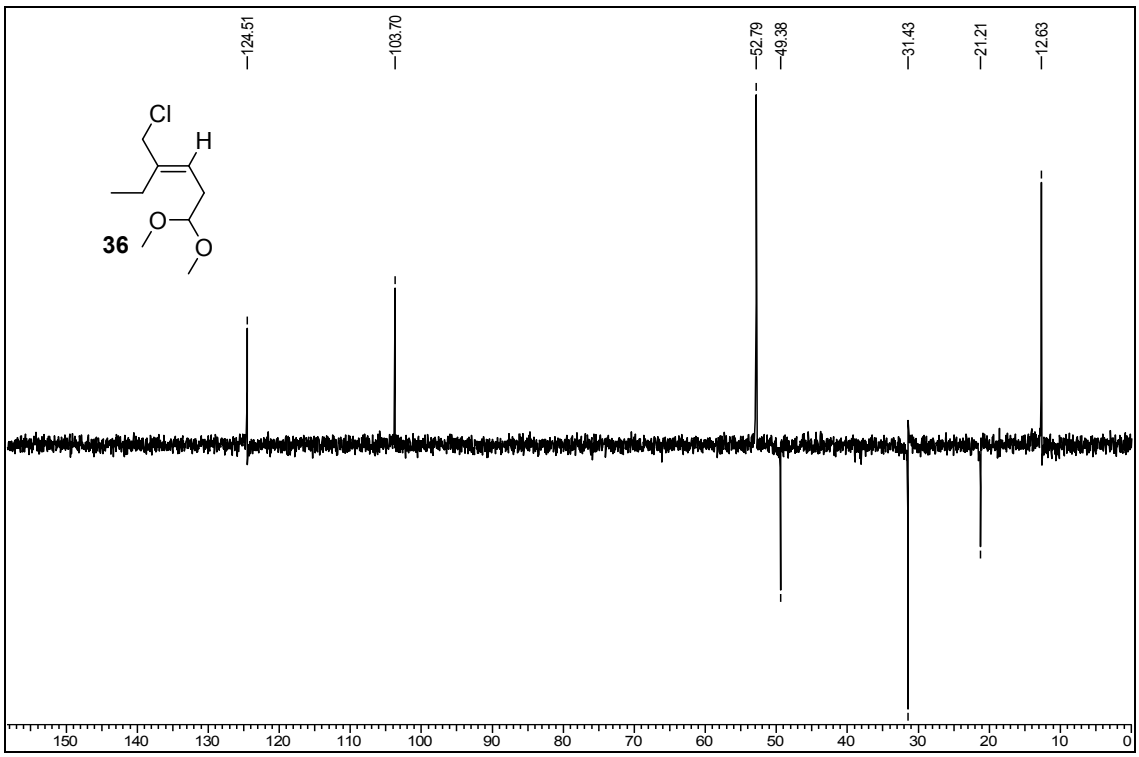
DEPT ($CDCl_3$, 50 MHz) spectrum of compound 35



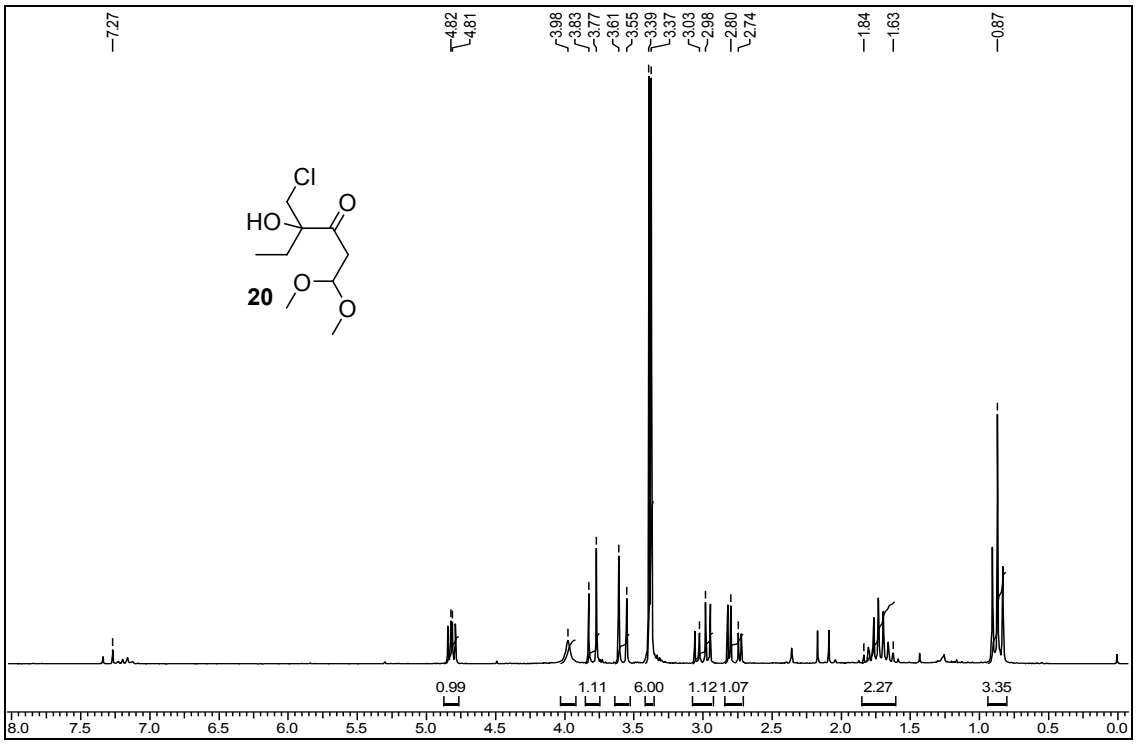
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 36



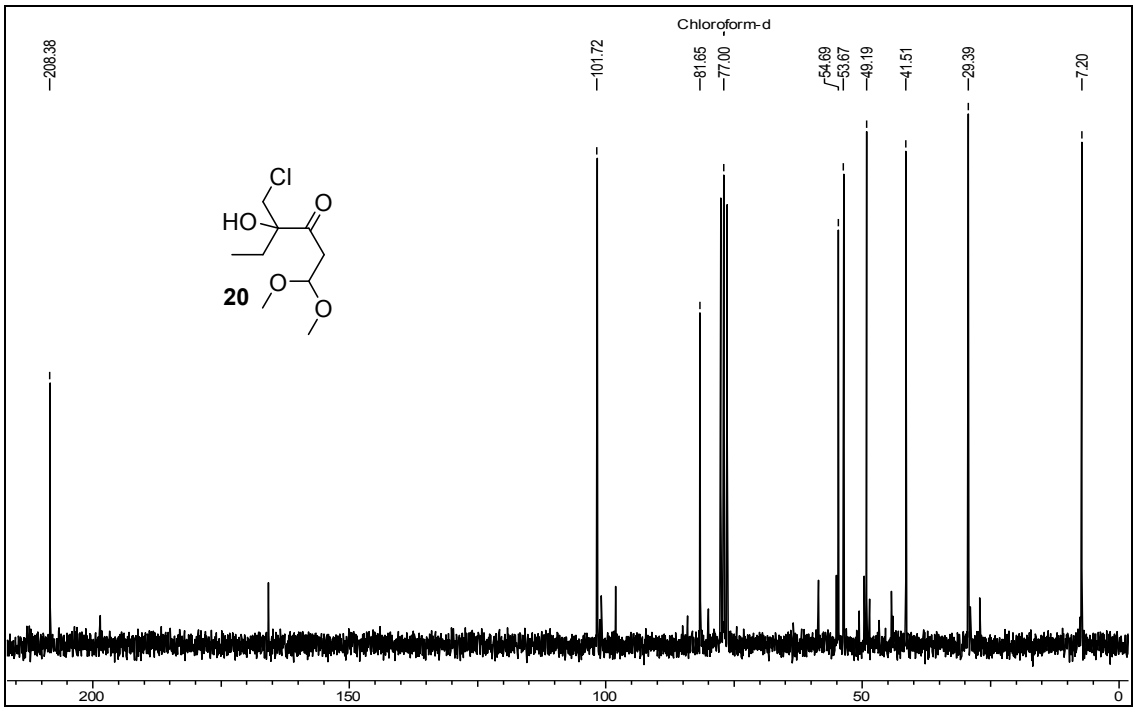
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 36



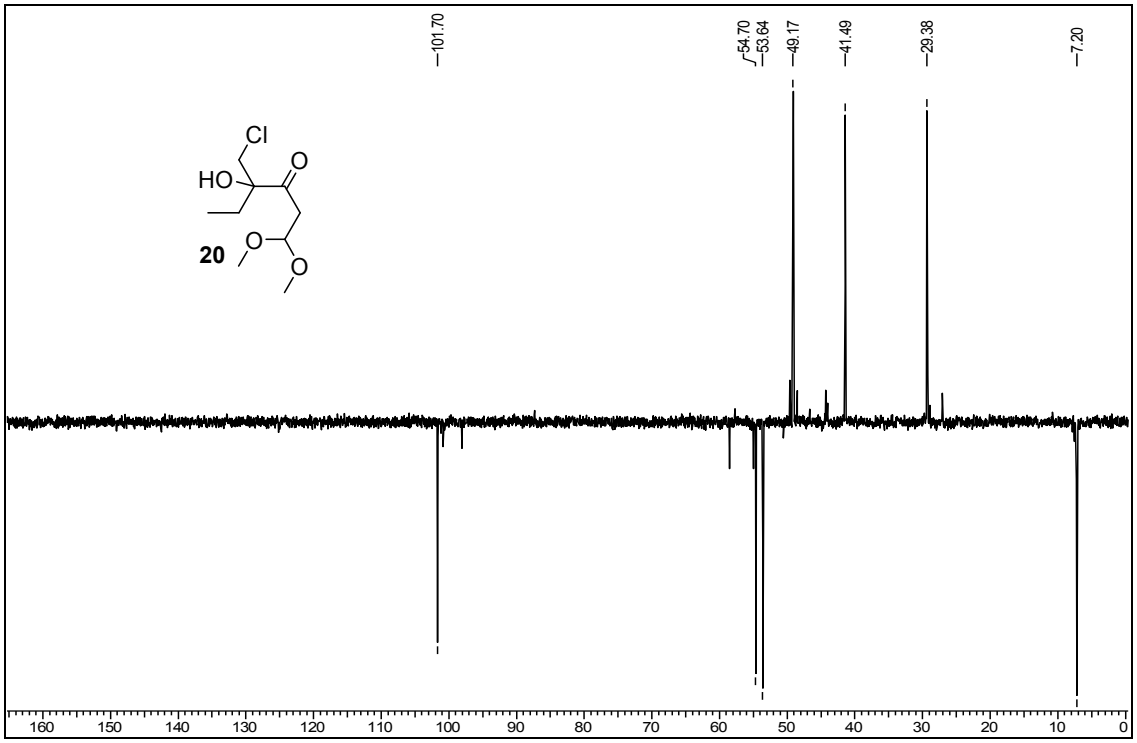
DEPT ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 36



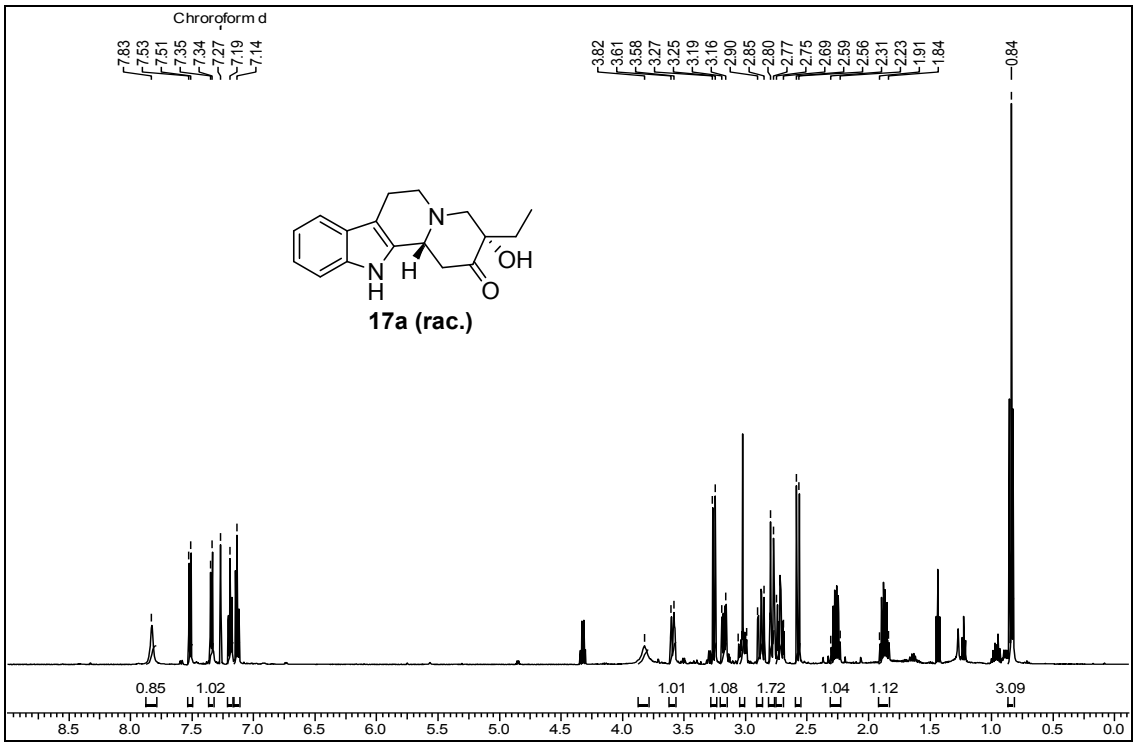
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 20



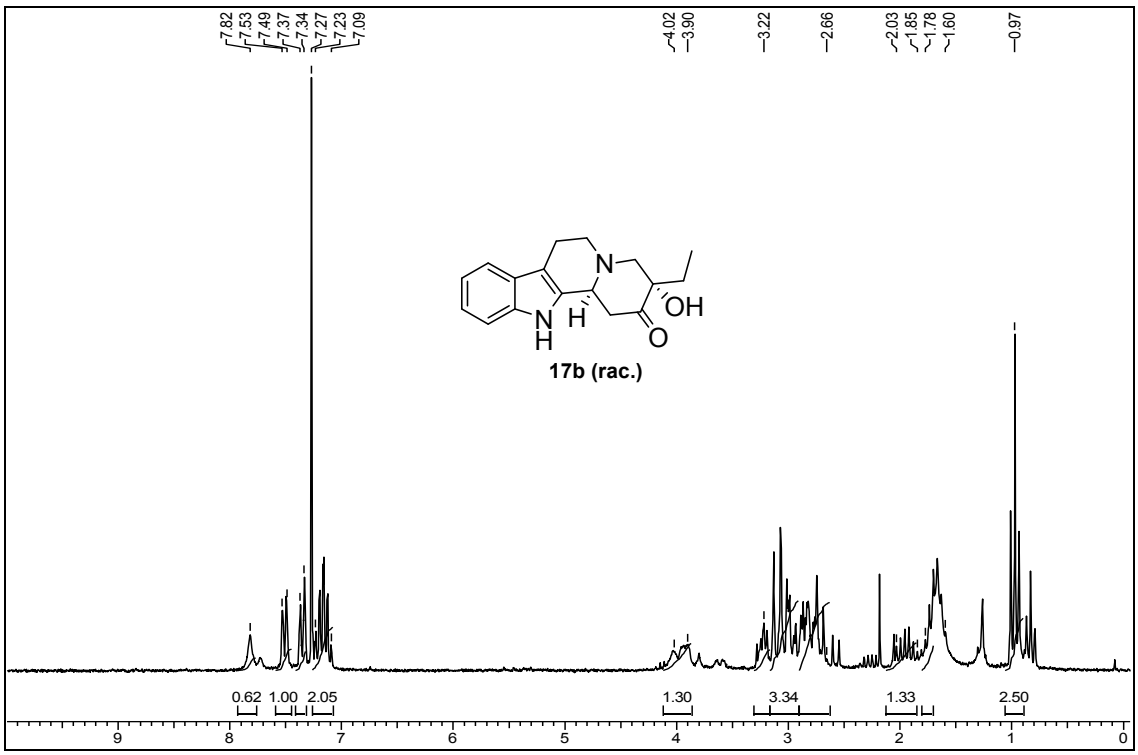
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of compound 20



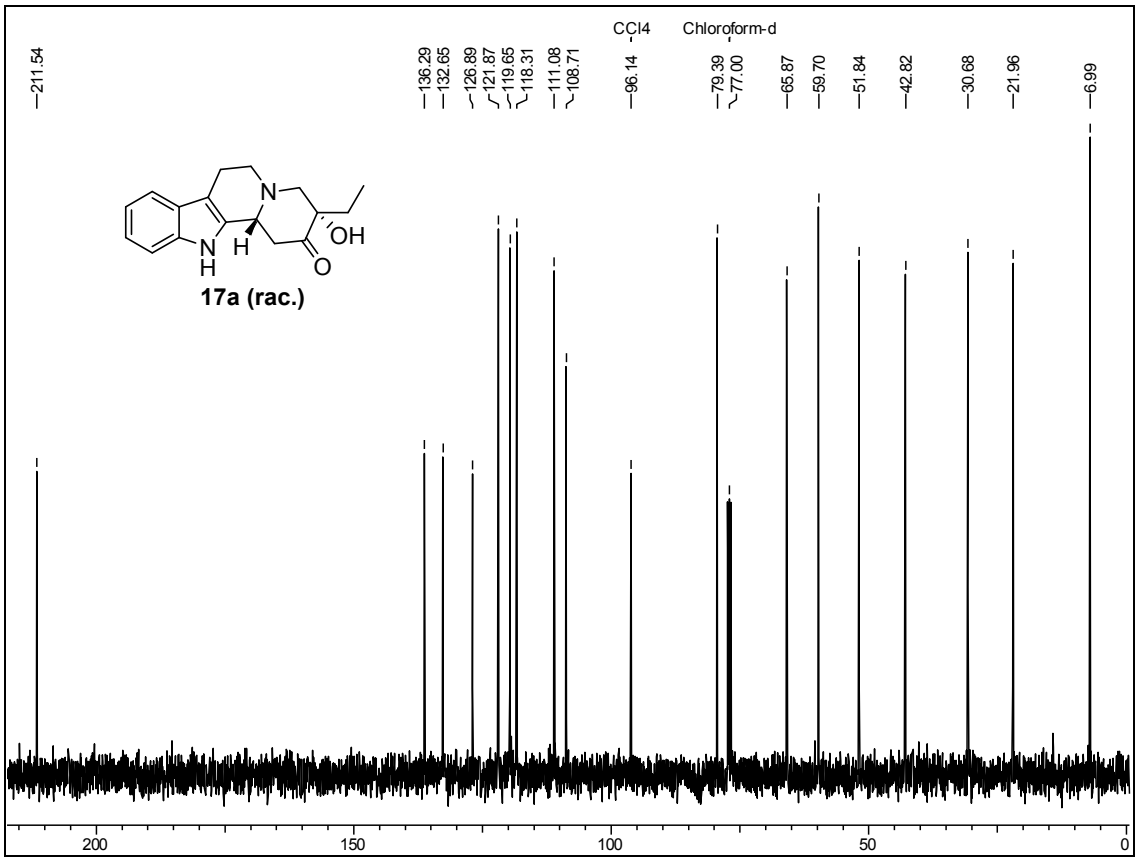
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of compound 20



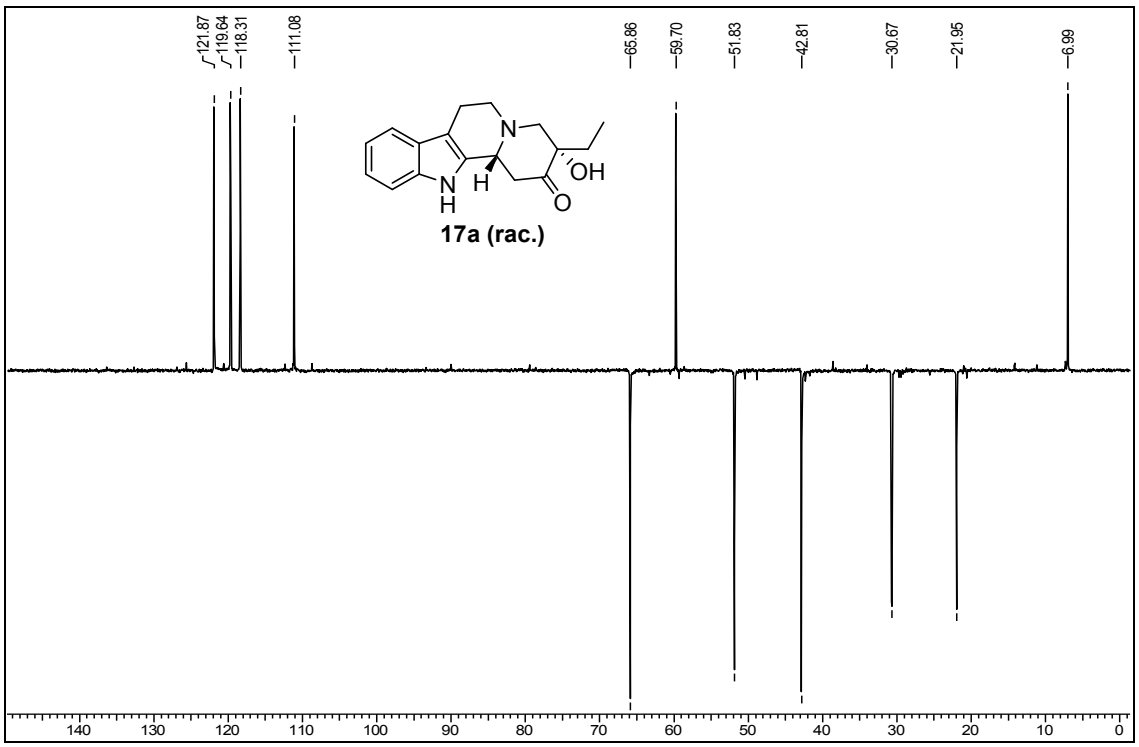
^{1}H NMR ($CDCl_3$+CCl_4, 500 MHz) spectrum of compound 17a



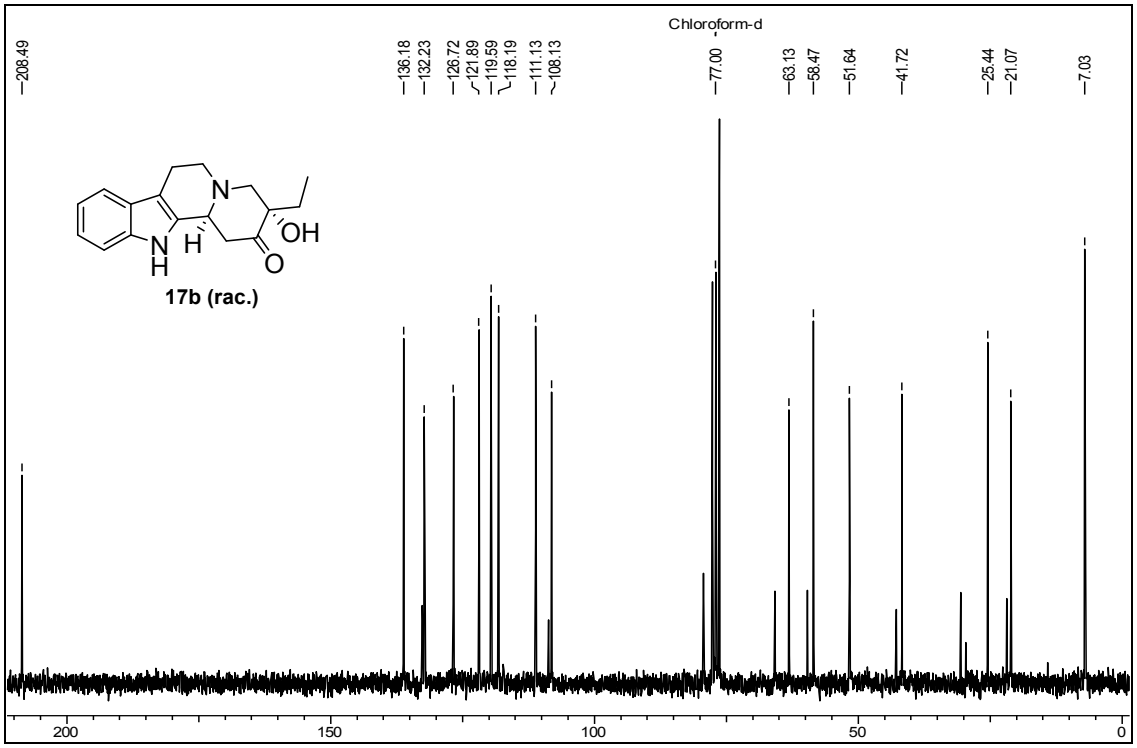
^{1}H NMR ($CDCl_3$+CCl_4, 400 MHz) spectrum of compound 17b



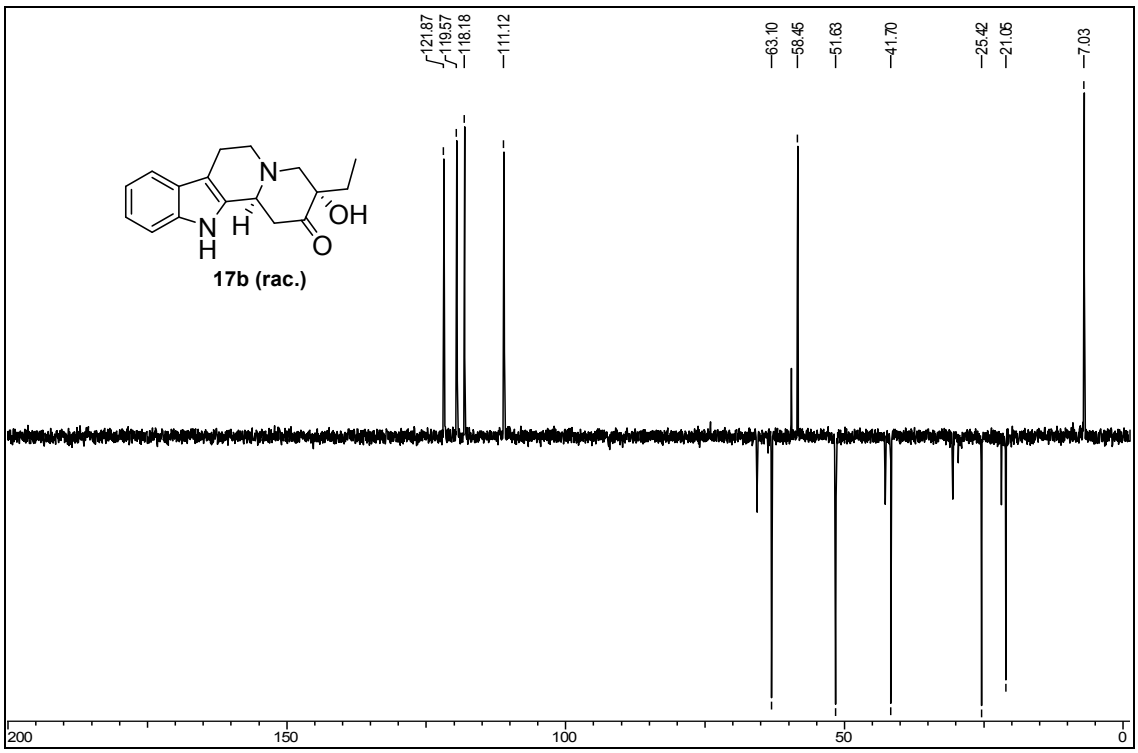
^{13}C NMR ($CDCl_3$+CCl_4, 125 MHz) spectrum of compound 17a



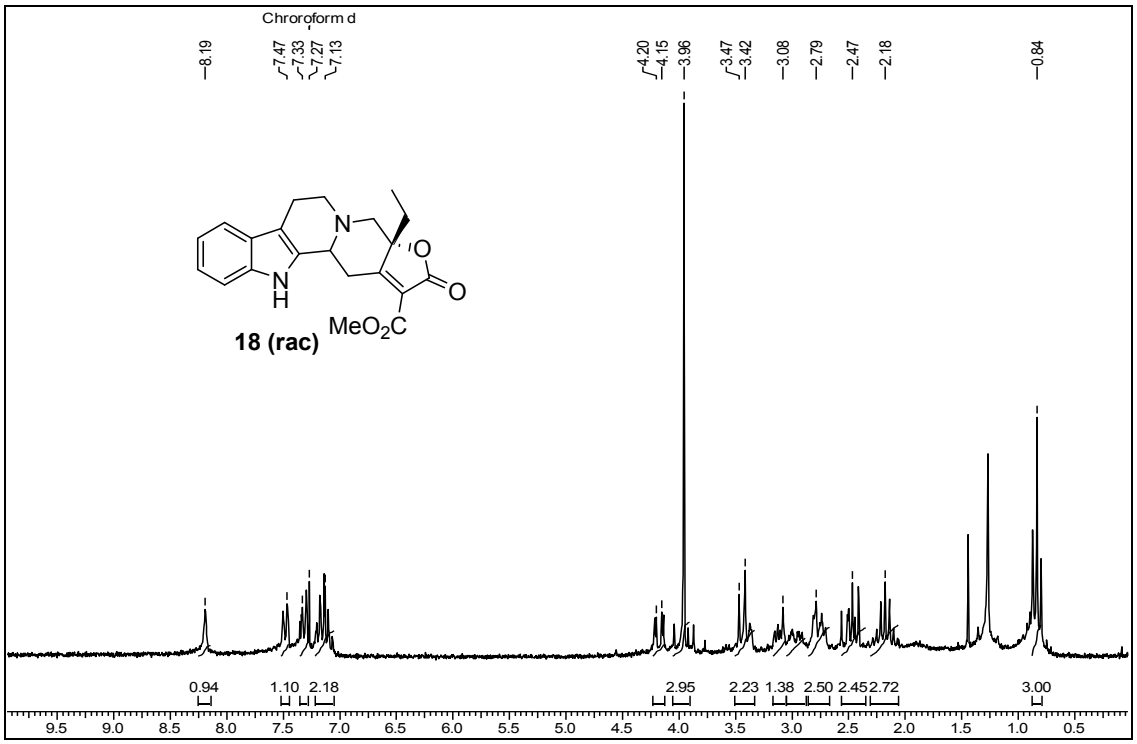
^{13}C NMR ($CDCl_3$+CCl_4, 125 MHz) spectrum of compound 17a



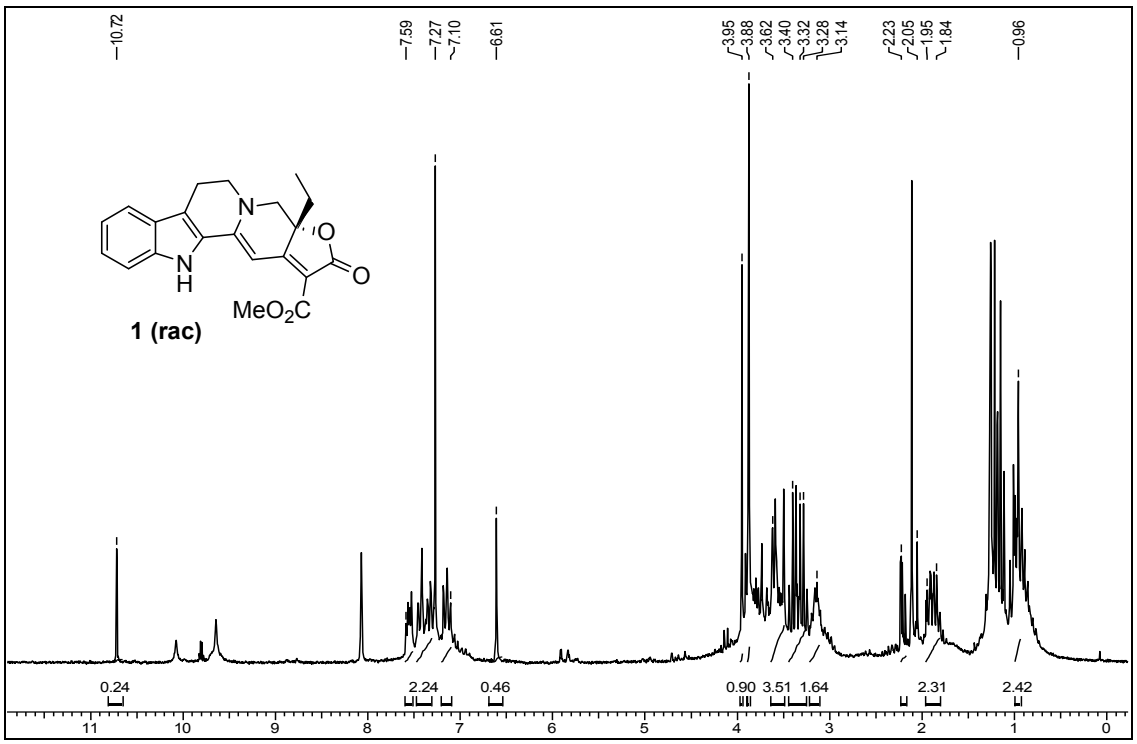
^{13}C NMR ($CDCl_3$, 100MHz) spectrum of compound 17b



DEPT ($CDCl_3$, 100MHz) spectrum of compound 17b



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



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

2.1.7. References

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Chapter 2 Section 2

Formal Synthesis of (-)-Mitralactonine

2.2.1. Introduction: A Brief Account on Sharpless Asymmetric Dihydroxylation (SAD)

As the present section deals with Sharpless asymmetric dihydroxylation (SAD) reaction as the key chirality inducing methodology it is pertinent to include a short descriptive presentation of the reaction in terms of its evolution, mechanism and selectivity.

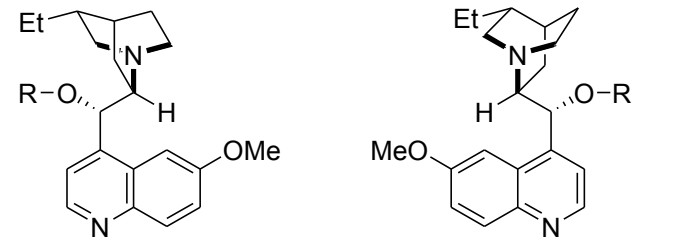
Oxidation of cabon-carbon double bond occupies an important place among the oxygen transfer reaction. Diols are easily generated by the single step transformation during the oxidation of alkene. Traditional use of OsO_4[1] and alkaline $KMnO_4$ are well documented in literature. These oxygenation reactions often use stoichiometric amounts of hazardous and poisonous oxidizing agents. Apart from this the high cost of OsO_4 demands for a more practical and economical replacement with the corresponding catalytic version. Catalytic version requires relatively inexpensive reagents for the reoxidation of the osmium (VI) glycolate product which greatly enhances the synthetic utility.[1] First to be introduced in this category was inorganic co-oxidant sodium/potassium perchlorate by Hoffmann[2] and later on usage of hydrogen peroxide by Milas.[3] These reagents lead to diminished yield due to over oxidation. Much better results were demonstrated by Sharpless et al. by the use of alkaline *t*-butyl hydrogen peroxide[4] and later on *N*-methyl morpholine *N*-oxide[5] as the co-oxidant.

Minato, Yamamoto and Tsuji demonstrated that $K_3Fe(CN)_6$ in the presence of K_2CO_3 provides powerful system for osmium catalysed dihydroxylation.[6]

The growing need to develop efficient and practical synthesis of biologically active molecule has resulted in a number of powerful asymmetric reactions. Catalytic asymmetric reactions provide an especially practical entry into chiral world due to their economical use of asymmetry inducing agents. The asymmetric dihydroxylation work arose due to the pioneering work on the stoichiometric reaction of OsO_4 with olefins, Criege[7] showed that pyridine accelerates the rate of osmium tetroxide dihydroxylation of alkenes by co-ordination to metal complexes.

Use of pyridine derivative to induce chirality in the osmylation reaction by Sharpless et al. failed due to low affinity of these ligands for OsO_4.[8] It was found that the binding constant of a ligand is extremely sensitive to the steric hindrance near the reacting center.[9] Later on Hentges[8] isolated diols with moderate to good selectivity by employing acetate ester of cinchona alkaloids as chiral ligands thereby proving the above logic correct as these have intrinsically higher affinity towards OsO_4 (fig.1, R = Ac). Use of

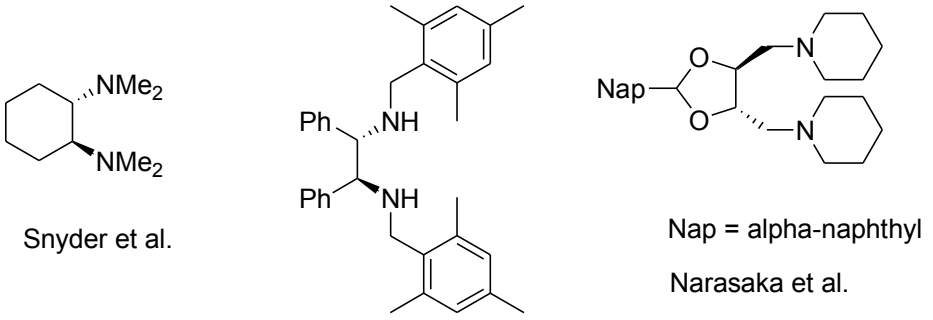
chiral diamine[10] ligands for asymmetric osmylation of olefins provide good results but a serious drawback results from their bidentate nature; they form very stable chelate complexes with the osmium (VI) gylcolate products which leads to inhibition of hydrolysis and as a consequence prevents *in situ* recycling of osmium and ligand (fig.2). Thus all the reactions with bidentate ligands are stoichiometric in both OsO_4 and the chiral ligand.



Dihydroquinidine (R = H) DHQD

Dihydroquinine (R = H) DHQ

Figure 1: *Cinchona alkaloid ligands for AD under catalytic conditions*



Snyder et al.

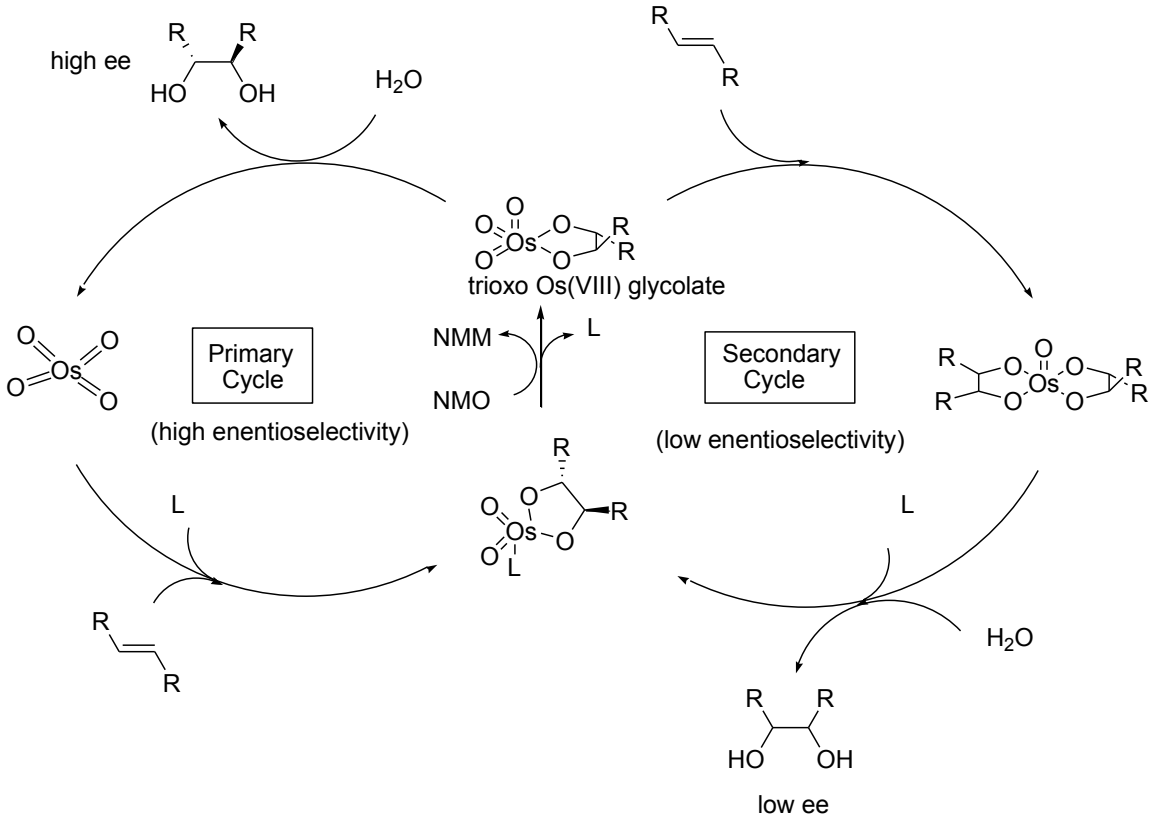
Nap = alpha-naphthyl

Narasaka et al.

Corey et al.

Figure 2: *Few chiral diamine ligands for AD under stoichiometric conditions*

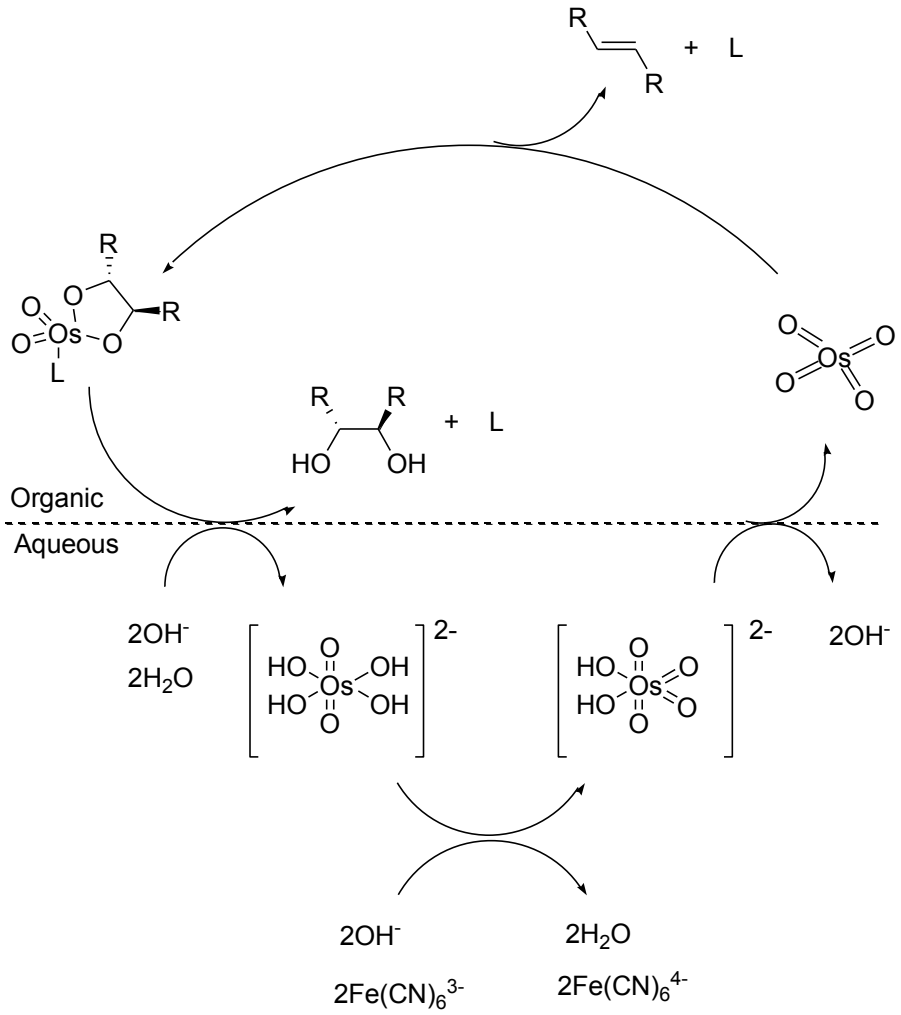
Initially all the dihydroxylation reactions using derivatives of cinchona alkaloid were performed under stoichiometric conditions, but in 1987 Marko and Sharpless found that the process became catalytic when *N*-methylmorpholine *N*-oxide was employed as the co-oxidant.[11] However, the enantiomeric excess of the diol products obtained under these catalytic conditions were initially lower than those produced by the stoichiometric reaction. The origin of the discrepancy was found to be the presence of second catalytic[12] cycle, which exhibited only or no enantioselectivity (Scheme 1). Wai discovered a partial remedy in the slow addition of the olefin.[12]



Scheme 1: *The two catalytic cycles for the asymmetric dihydroxylation using NMO as co-oxidant*

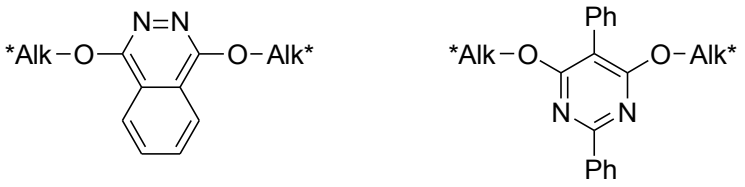
Few benchmark discoveries have led to a dramatic increase in the development of the reaction. It was found that the participation of second catalytic cycle could be virtually eliminated by performing the reaction under two-phase conditions with K_3FeCN_6 as stoichiometric reoxidant.[13] Under these conditions there is no other oxidant than OsO_4 in the organic layer, in contrast, to the homogenous NMO condition. The actual osmylation takes place in the organic layer and the resulting osmium (VI) glycolate ester undergoes hydrolysis, releasing diol and the ligand to the organic layer and the Os (VI) to the aqueous layer before its reoxidation can occur, and consequently entry of the osmium glycolate into second cycle is prevented (Scheme 2). The hydrolysis of osmium (VI) glycolate product can be accelerated considerably by $MeSO_2NH_2$. The reaction time becomes 50 times shorter and have high catalytic turnovers. Due to the "sulfonamide effect" the AD reactions can be carried out at 0 ^oC rather than room temperature, which have a beneficial effect on the enantioselectivity.[14] Though the additive enhances the

reaction rate with sterically encumbered substrates, terminal olefins react slightly slower in its presence.



Scheme 2: *Catalytic cycle of the AD reaction with $K_3Fe(CN)_6$ as the co-oxidant*

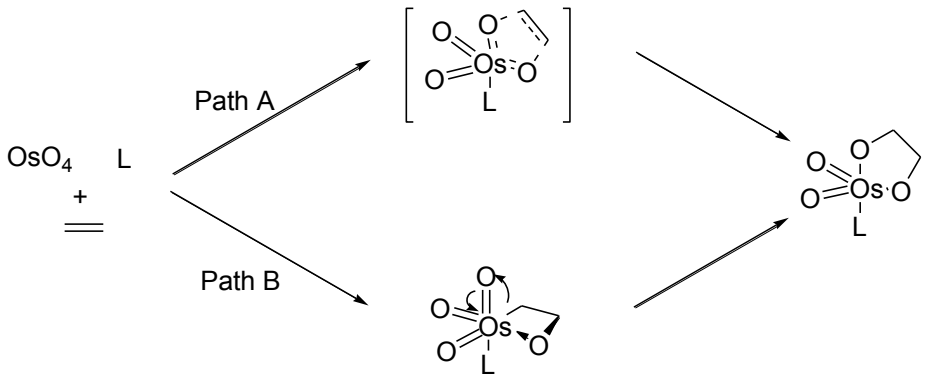
The discovery of ligands[15] with two independent cinchona alkaloid units attached to a heterocyclic spacer led to a considerable increase in both enanioselctivity and scope of the reaction (fig. 3).



Phthalazine (PHAL) Diphenylpyrimidine (PYR)

Figure 3: *Second generation of "dimeric" PHAL and PYR ligands (Alk* = DHQD or DHQ).*

Two mechanisms have been suggested for the osmium-catalysed dihydroxylation reaction: Böseken and Criegee proposed a concerted [3+2] pathway[16] (scheme 3, path A), while Sharpless *et al*. suggested a stepwise reaction which is initiated by a [2+2]-like addition[17] of the olefin across an Os=O bond (path B) followed by rearrangement of the resulting osmaoxetane intermediate to the glycolate product.



Scheme 3: *Schematic presentation of dihydroxylation mechanism*

Despite the mechanistic uncertainty, the face selectivity of the dihydroxylation can reliably be predicted using an empirical 'mnemonic device'.[18,15a] The plane of the olefin is divided into four quadrants and the substituents are placed into three quadrants according to a simple set of rules. The SE quadrant is sterically inaccessible and, with few exceptions, no substituent other than hydrogen can be placed here. The NW quadrant, lying diagonally across from the SE quadrant, is slightly more open and the NE quadrant appears to be quite spacious. The SW quadrant is special in that its preference are ligand-dependent. Even though this SW quadrant normally accepts the largest group, especially in the case of PYR ligands, it is especially attractive for aromatic groups in case of PHAL ligands.[22] An olefin, which is placed into this plane according to the above constraints, receives the two OH groups from above, i.e. from the β-face, in the case of DHQD derived ligands and from the bottom, i.e from the α-face, in the case of DHQ derivatives (fig. 4).

Predictions for 1,1-disubstituted olefins using the empirical mnemonic device are not always unambiguous;[19] since it may be difficult to judge which of the two substituent prefer the attractive, SW quadrant. Along with steric size, the properties of the substituents have also to be taken into account and compared with ligand-specific preference for the SW quadrant. PHAL ligands show the following preferences for the SW quadrant.[18b,19,20]

Aromatic group >> n-alkyl > branched alkyl > oxygenated residues

Recent studies have revealed that oxygenated residues[19] have very small preferences for ligands binding pockets (SW quadrant).[18b,20] Studies with 1,1-disubstituted olefins have shown steric size of a substituent is much more important than in the PHAL system. Thus the following preference is observed:

Branched alkyl > long *n*-alkyl (length >3) > aromatic residues > short *n*-alkyl

A few exceptions mostly for terminal olefins have appeared in recent years. The AD of certain ortho-substituted allyl benzenes in the presence of PHAL ligands have been shown to give facial selectivities opposite to those predicted by the mnemonic device.[21] Further more, trans-olefins in the same series react with the expected face selectivity even with the PHAL ligand; thereby demonstrating that exception are so far limited to the class of terminal olefins. Thus, the mnemonic device is a simple tool for predicting the facial selectivity of the AD reaction. However, reliable predictions require the intrinsic preference of each ligand to be taken into account. Thus, SW quadrant is especially attractive for aromatic groups in the PHAL systems, while aliphatic groups are preferred in the PYR systems. PYR ligands are, therefore the ligands of choice for aliphatic and/or sterically congested olefins, while PHAL ligands are better for aromatics substrates. These simple rules allow the prediction of the face selectivities even in difficult cases and very few exceptions are known.

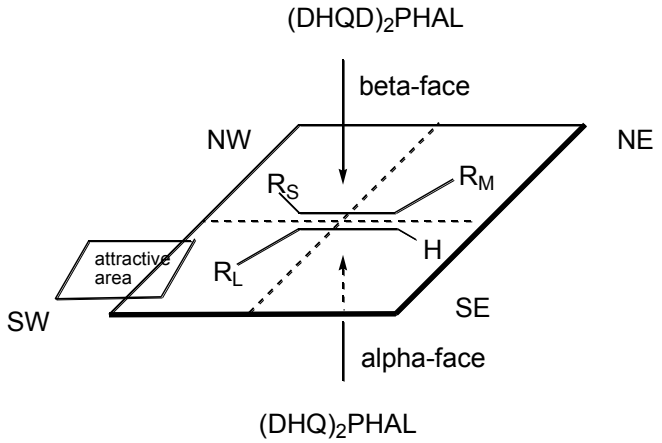


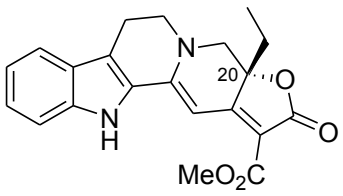
Figure 4: *Mnemonic diagram*

2.2.2. Present Work

The world is chiral and so are most of the organic compounds. Chemists from pharmaceutical world, agro and cosmetic industries require access to enantiomerically pure compounds.

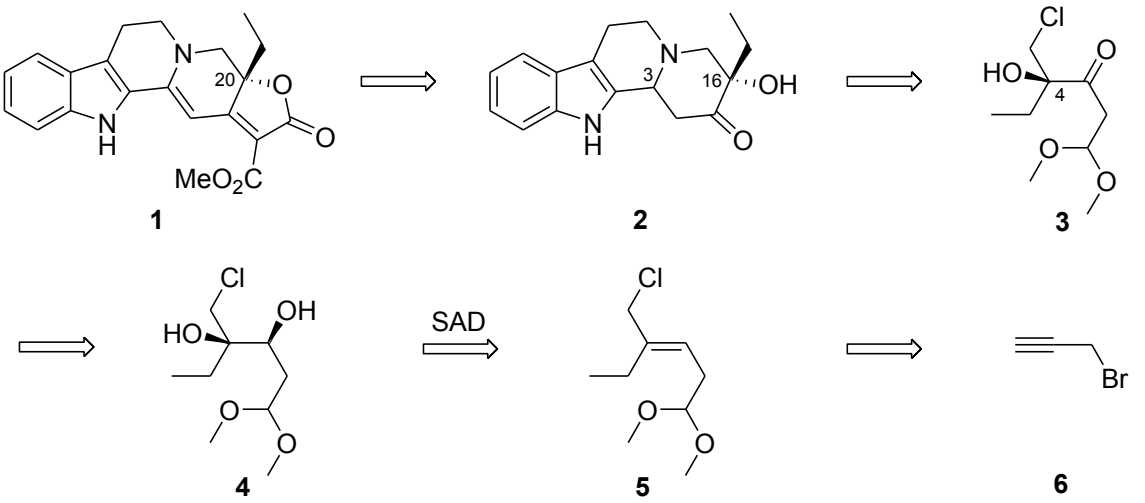
It is well known that all the biological receptors are chiral and as such can distinguish between two enantiomers of a ligand or substrate. Thus pharmacological compounds, which are chiral when screened for their activity, may behave differently in comparison to their enantiomers or racemate. Hence the quest to obtain enantiomerically pure compound has always been a challenge in the chemical world. An easy and straightforward solution is to isolate them from natural sources. Alternatively one can prepare the racemate and resolve it, plan a chiron approach for its synthesis or perform an asymmetric synthesis. The different objectives are restrained from factors such as amount of material required, the cost of starting material, length of synthetic plan etc. Resolution is restricted by the drawback that one of the enantiomers can be achieved in the maximum theoretical yield of 50 % unless the unwanted isomer is recovered and recycled. The chiron approach utilises/consumes chiral natural starting material and at best can produce a single enantiomer from a given route.

Intrigued by the above mentioned facts and with the successful accomplishment of racemic synthesis of mitralactonine **1** in short sequence it was thought worthwhile to expand the chemistry towards the asymmetric accomplishment of the target molecule, which will pave the path to other, related alkaloids.



1

The present section deals with study towards the asymmetric construction of the key synthon **3**, which was efficiently utilised in the previous section for construction of tetracyclic unit. A careful inspection of **3** reveals that the only chiral center (C4) present there in and which is further carried over to the final molecule **1** (C20) can be fixed by Sharpless asymmetric dihyroxylation[22] of alkene **5**. The retrosynthetic approach described previously can be modified in light of asymmetric synthesis as delineated in scheme 4.



Scheme 4: *Retrosynthetic plan 1*

The chiral keto-hydroxy moiety **3** could be realised by oxidation of secondary hydroxy group of chiral diol **4**, which in turn could be efficiently synthesised by selective dihydroxylation of alkene **5** obtained from propargyl bromide (**6**).

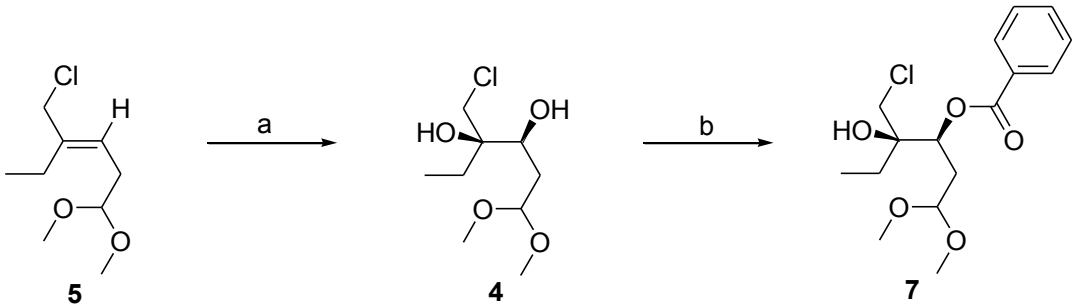
2.2.3. Results and Discussion

At the onset of the journey towards asymmetric synthesis was to perform Sharpless asymmetric dihydroxylation (SAD) of already syntheised alkene **5** in hand. Normally the reaction is carried out under basic condition but with base sensitive substrate, such as the allylic halide **5** which can readily undergo epoxide formation once the diol is generated under highly alkaline medium,[22] the reaction is buffered by the addition of $NaHCO_3$ in equivalent amount of K_2CO_3 utilised so as to eliminate the possibility of epoxide formation by maintaining the pH of the system.

Taking in the account of the well established enantioselective principle and mnemonic device for asymmetric dihydroxylation[22] of trisubstitued alkene it was concluded that $(DHQ)_2PHAL$ would be the right ligand of choice to render the C (4)-*R* isomer.

Thus when the substrate **5** was subjected to buffered solution of *t*-BuOH: H_2O (1:1) in presence of α-AD mix as the premixed ligand source, the dihydroxylated compound **4** was obtained in quantitative yield. The ^1H NMR showed absence of alkene proton peak at δ 5.48 and appearance of a triplet at δ 4.15 corresponding to the -C*H*OH proton. IR spectrum showed absorption at 3465 cm^{-1}.

Though the product was obtained in very good yield disappointingly the chiral HPLC analysis of the corresponding benzoyl derivative **7** on Chiralcel-OD revealed very poor enantioselectivity <10% (Scheme 5).



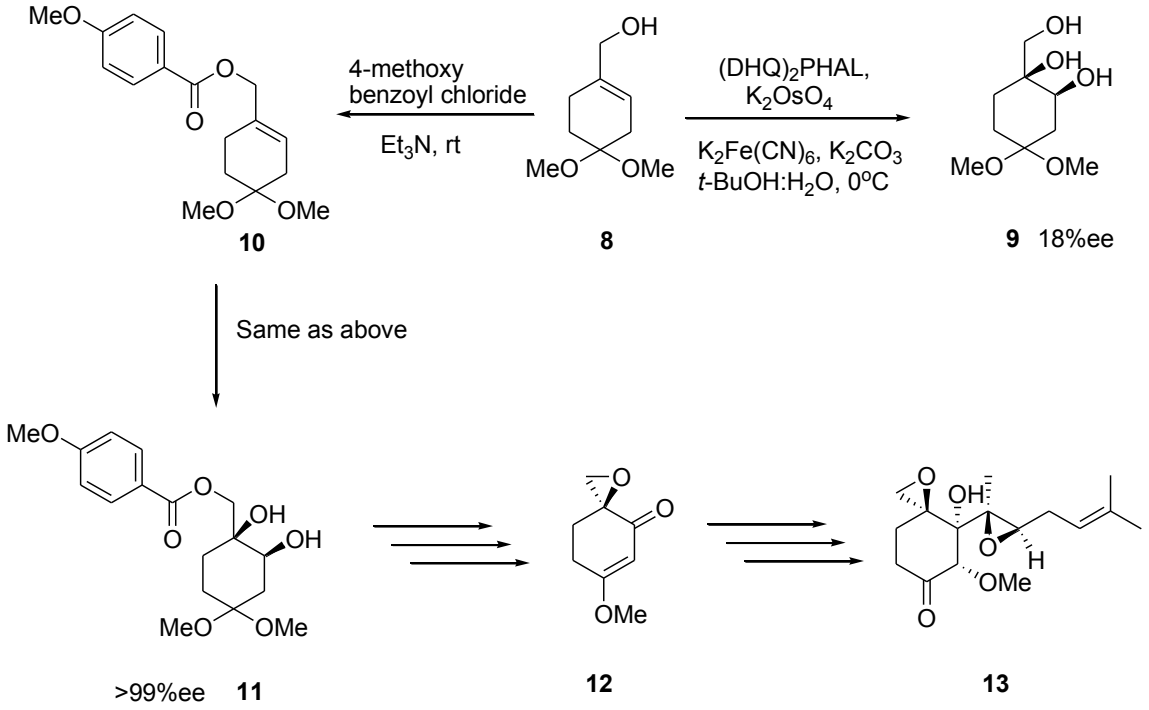
Scheme 5: Reagents and conditions: *a) α-AD mix, $NaHCO_3$, t-BuOH: H_2O 1:1, 0 ^oC, 24 h, quantitative; b) benzoyl chloride, Et_3N, DCM, rt, 3 h, 85%.*

Failing to establish an appreciable selectivity with ligand $(DHQ)_2PHAL$, a few more ligands were screened for the dihydroxylation reaction. As described in the table 1 no better ee was obtained under any of the conditions applied.

Table 1

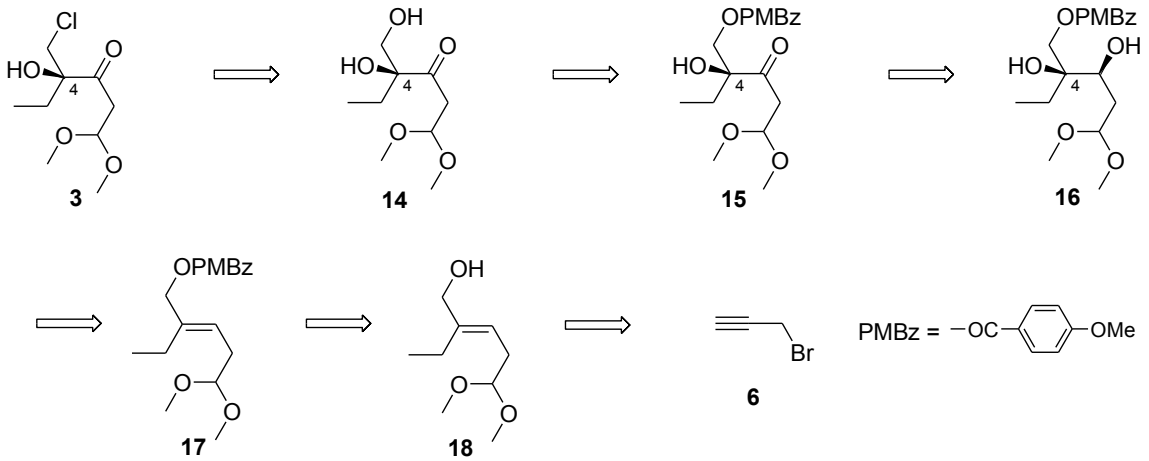
Entry	Substrate	Ligand	Reacn. Condn.	Yield	*er*
1.	**5**	α-AD mix	0 ^{o}C, 24 h	Quantitative	55:45
2.	**5**	$(DHQD)_2PYR$	0 ^{o}C, 24 h	Quantitative	55:45
3.	**5**	β-AD mix	0 ^{o}C, 24 h	Quantitative	55:45

Corey et al. has introduced a substrate modification as an effective strategy to circumvent the problem of low ee and to obtain high enantioselectivity in the asymmetric dihydroxylation of allylic alcohols towards their synthesis of (-)-Ovalicin (**13**) (Scheme 6).[23a] The elegant work efficiently demonstrated that although the Sharpless asymmetric dihydroxylation proceeds with poor selectivity in the case of various allylic alcohols, the dihydroxylation of the corresponding 4-methoxybenzoates esters affords products of high enantiomeric purity. A detailed study of variously substituted allylic, homoallylic, bishomoallylic alcohols etc revealed a uniformly excellent selectivity when derivatised as 4-methoxybenzoates.[23b] In contrast to this result a very poor selectivity was recorded for benzyl, triisopropylsilyl ethers, or pivalate ethers. Selectivity was also found to be sensitive to the length of the aliphatic chain connecting the 4-methoxybenzoyl groups to the olefin. All these results are consistent with the proposed transition state assembly for the face selective dihydroxylation of allyl 4-methoxybenzoate.[23c]



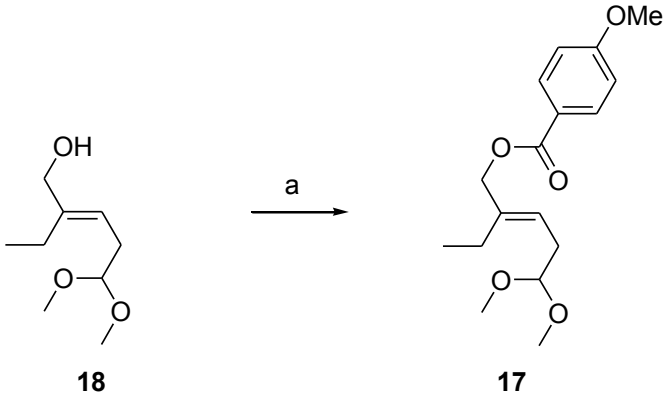
Scheme 6: *Corey's synthesis of (-)- Ovalicin (**13**)*

With the poor result of the asymmetric dihydroxylation on the allylic chloro compound **5** in terms of enantioselectivity, attention was focused towards this modified substrate controlled enhancement of selectivity. The precursor to the chloro compound **5** is an allylic alcohol **18**, which could be readily converted into its 4-methoxybenzoate derivative **17** and then can be subjected to asymmetric dihydroxylation. Hence the retro path was modified as shown in scheme 7.



Scheme 7: *Retrosynthetic plan 2*

The allylic alcohol **18** obtained from propargyl bromide (**6**) in three steps as described in previous section was subjected to react with 4-methoxybenzoyl chloride in the presence of triethylamine at room temperature for 3 h. The isolated product **17** was obtained in 85% yield after column chromatography (Scheme 8).

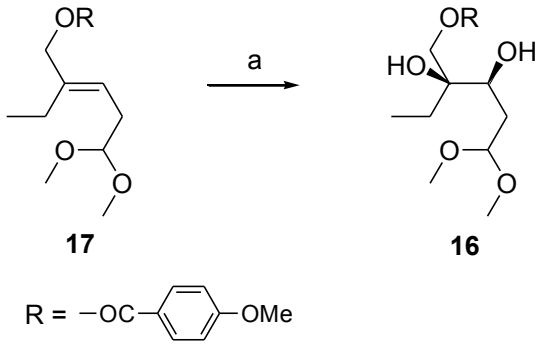


18 **17**

Scheme 8: Reagents and conditions: *a) 4-methoxybenzoyl chloride, Et_3N, rt, 3 h, 85%.*

IR spectrum showed strong absorption at 1707 cm^{-1}. ^1H NMR spectrum showed downfield shift of –C$\underline{H_2}$ protons and appearing at δ 4.75 integrating for two protons. Apart from this appearance of aromatic protons as well as a singlet at δ 3.87 integrating for three protons assigned to the methoxy group signifies the condensation of 4-methoxbenzoyl moiety. ^{13}C NMR spectrum showed presence of aromatic carbons. The –$\underline{C}H_2$ carbon moved downfield to δ 68.2 whereas the methoxy carbon appeared at δ 55.3 in line with the expected transformation. Mass (ESI) established a peak at *m/z* 309.16 (M^++1) and was further confirmed by elemental analysis.

With the required modified substrate in hand it was subjected for the crucial asymmetric dihydroxylation under standard biphasic condition (Scheme 9).



17 **16**

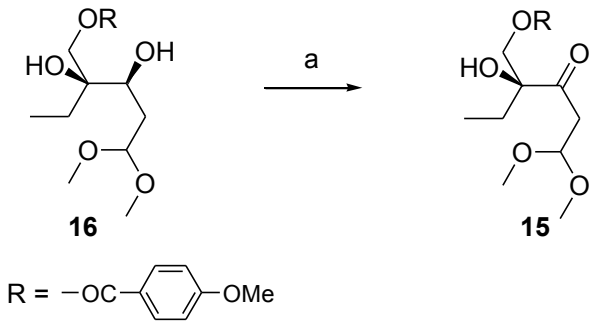
Scheme 9: Reagents and conditions: *a) $K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2PHAL$, t-BuOH:H_2O 1:1, 0 ^oC, 24 h, 90%.*

Thus to an equimolar mixture of $K_3Fe(CN)_6$ and K_2CO_3 in 1:1 *t*-BuOH: H_2O and $(DHQ)_2PHAL$ as the ligand of choice at 0 ^oC was added the alkene **17** followed by catalytic amount of OsO_4 and stirred for 24 h. The reaction time was cut short to reduce the chance of formation of benzoyl migrated side product. The isolated product **16** was obtained in 90% yield after column chromatography (SiO_2).

IR spectrum showed strong absorption at 3431 cm^{-1} in accordance with the proposed introduction of hydroxy functionality. ^1H NMR spectrum showed disappearance of olefin proton peaks from δ 5.53. The –C*H*OH peak appeared as a triplet integrating for one proton at δ 3.82. The other characteristic peaks appeared at their expected positions. ^{13}C NMR spectrum showed absence of quaternary alkene peak as well as the =C*H* peak. Appearance of peaks for the –C*H*OH and the new quaternary -C*O*H carbons was observed at δ 70.1 and δ 74.9 respectively. It was further confirmed by elemental analysis.

The enantiomeric excess was found to be 89% as determined by chiral HPLC analysis on Chiralcel-OD. Thus with the modified substrate the dihydroxylated product was isolated in fairly good optical purity if not excellent.

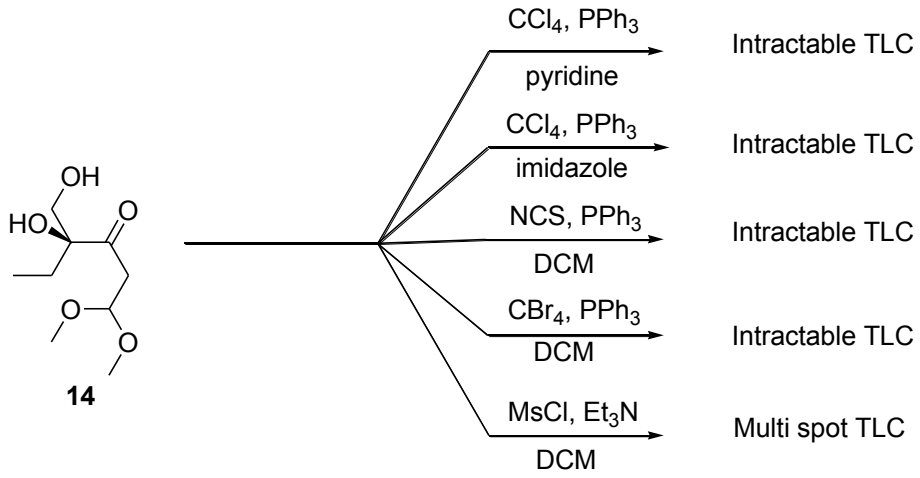
With this gratifying result the next task was to oxidise the secondary hydroxy group. The oxidised product **15** was obtained in high yields when the substrate was treated with 2 eq. of *Dess-Martin* periodinane[24] taken in DCM at room temperature. The isolated product **15** showed a strong absorption at 1715 cm^{-1} and 1707 cm^{-1} in the IR spectrum thereby signifying the presence of ketone as well as ester carbonyl in the product. ^1H NMR spectrum showed absence of –C*H*OH protons peaks whereas all other protons peaks appeared at their expected positions.



Scheme 10: Reagents and conditions: *a) DMP, DCM, rt, 3 h, 80%.*

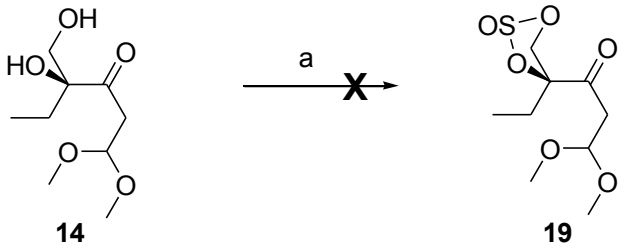
A ready removal of benzoate protection and conversion of the primary hydroxy into chloro would render the required moiety **3** in optically active form for further

condensation. Treating the compound **15** with K_2CO_3 in methanol did render the deprotected substrate **14** as revealed by ^1H NMR and IR spectrum study, but conversion of it into corresponding chloro **3** was an uphill task. Subjecting the substrate **14** to react with CCl_4 in presence of PPh_3 under reflux condition resulted in intractable reaction mixture. A number of other methods were tried such as performing the reaction in presence of base or use of different chlorinating agents but were unsuccessful on the substrate. Similar results were obtained in presence of mesylating agent or brominating agents too as described in scheme 11.



Scheme 11

Having failed to chlorinate or mesylate the hydroxy group it was thought worthwhile to convert the diol **14** into its cyclic sulfate[25] and then subject it to condensation. But here too the results were same. The expected product could not be obtained on exposing the substrate to thionyl chloride (Scheme 12).

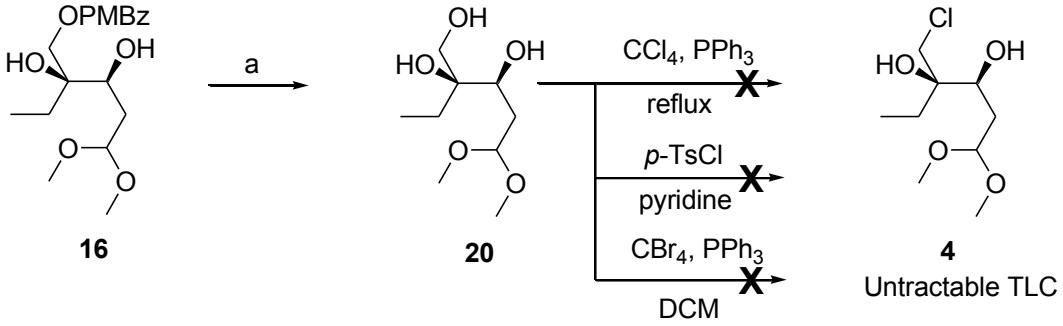


Scheme 12: Reagents and conditions: a) *$SOCl_2$, Et_3N, DCM, rt.*

It was inferred that the ketone group might be interfering with the stability of the substrate under the reaction conditions employed. Hence it was logical to protect it as its acetal alongwith conversion of the more labile acyclic dimethyl acetal into its cyclic acetal and then perform the removal of benzoate. But under the reaction conditions

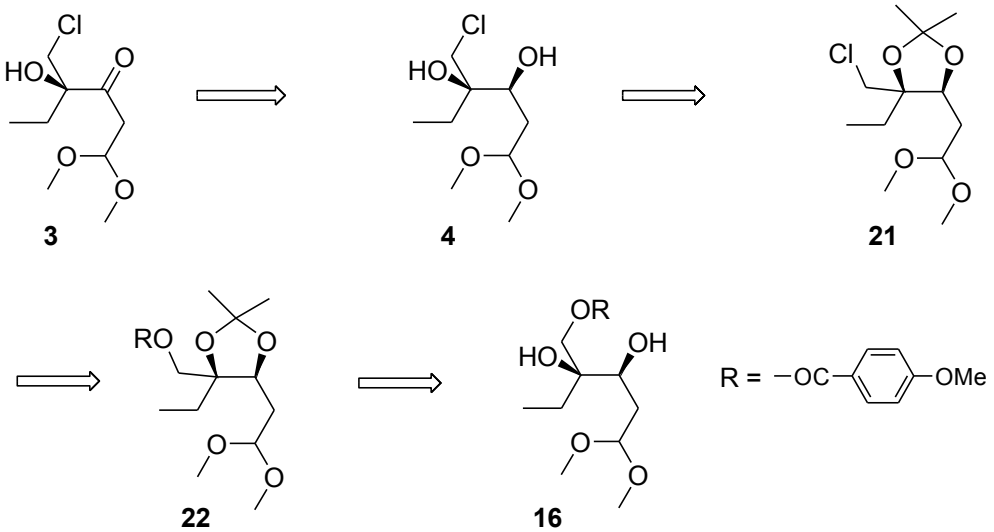
employed for acetal protection with 2,2-dimethyl propane 1,3-diol in presence of catalytic *p*-TSA under Dean-Stark reflux conditions the expected product couldn't be obtained instead a multi spot TLC was realised.

Selective conversion of the primary hydroxy group of the triol **20** obtained after the removal of benzoate from the diol **16** into corresponding chloro or tosylate was also not realised. (Scheme 13)



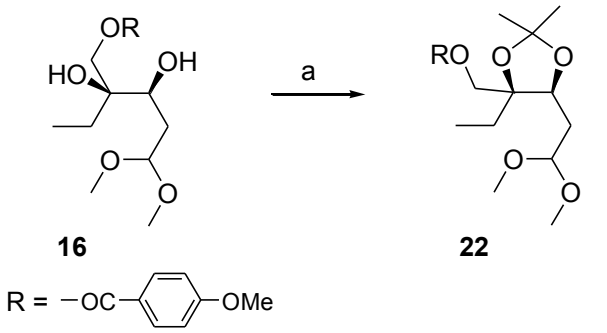
Scheme 13

It was reasoned that the inability to get the primary hydroxy group functionalised was due to the presence of the hydroxy and ketone functionality on adjacent carbon atom in the substrate, which was rendering the unit highly reactive and thus unstable under the conditions employed. To overcome the problem the approach was modified as shown in the retro path (Scheme 14) wherein the diol **16** obtained after dihydroxylation was proposed to be protected as its acetonide and then other functional group transformation was to be tried on the primary hydroxy group.



Scheme 14: *Retrosynthetic plan 3*

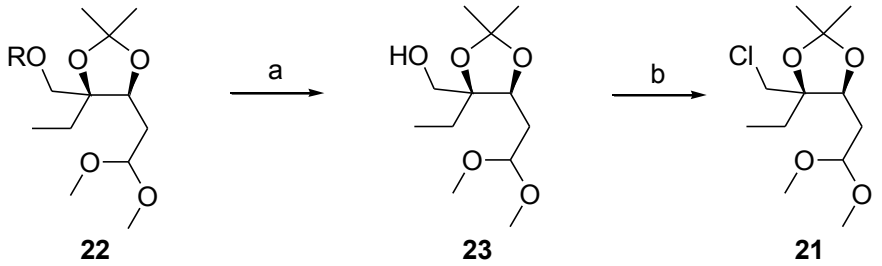
Accordingly the diol **16** was treated with dimethoxypropane under neat condition in presence of catalytic amount of *p*-TSA to render the acetonide **22** in good yield as confirmed by ^{1}H NMR study. ^{1}H NMR spectrum showed peaks at δ 1.4 and δ 1.3 integrating for three protons each corresponding to the dimethyl group. Absence of absorption in 3500 to 3000 cm^{-1} in the IR spectrum further exemplified the transformation.



Scheme 15: Reagents and conditions: *a) dimethoxypropane, p-TSA, rt, 0.5 h, 70%.*

The benzoate was removed by the action of K_2CO_3 in methanol at room temperature to furnish the alcohol **23** in 75% yield after column chromatography.

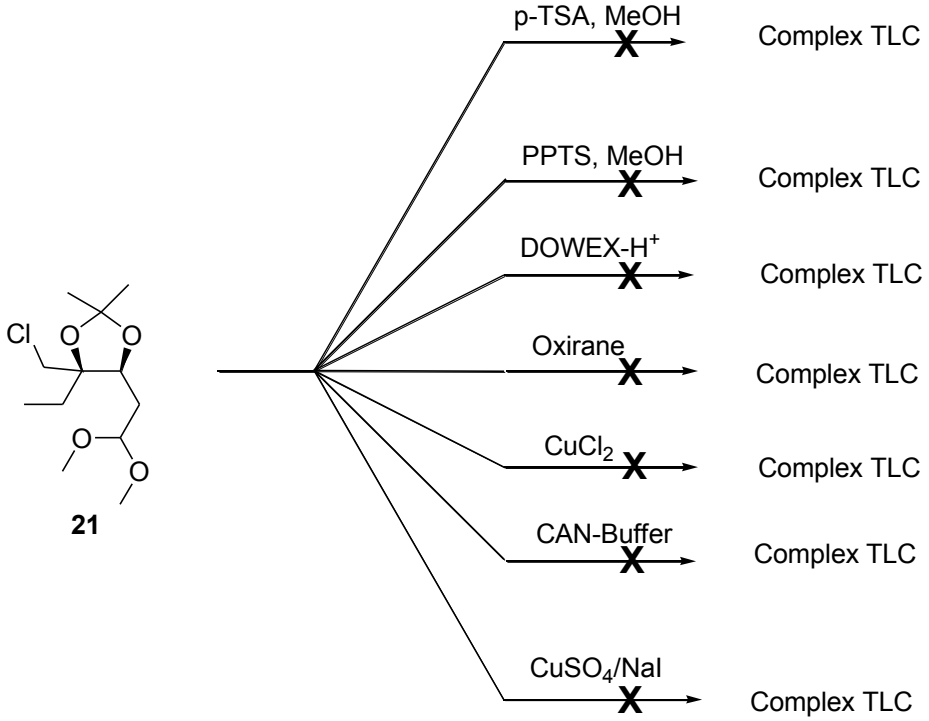
^{1}H NMR spectrum showed the absence of aromatic proton peaks as well as the methoxy proton peak at δ 3.73. The hydroxy group was converted fairly easily into its chloro **21** by the action CCl_4 and PPh_3 under reflux temperature.[26] This successful conversion clearly signifies that the presence of hydroxy group and ketone group on the adjacent carbon was rendering the substrate labile under the reaction conditions employed. Thus the problem associated with this particular transformation was eliminated by protection of the diol (Scheme 16).



Scheme 16: Reagents and conditions: *a) K_2CO_3, methanol, rt, 12 h, 75%; b) CCl_4, PPh_3, imidazole, reflux, 10 h, 88%.*

Ready removal of acetonide will furnish the diol **4**, which can be subjected for oxidation of secondary hydroxy group to deliver the key synthon **3**.

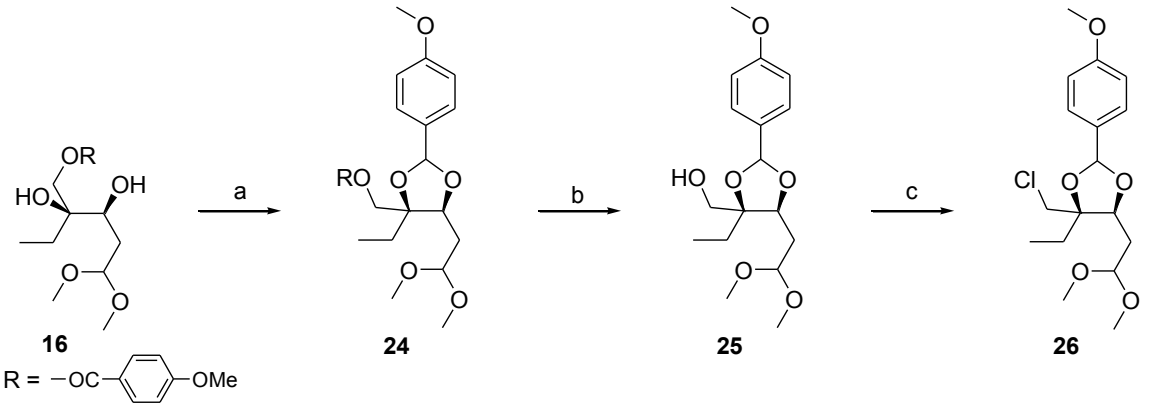
But the seemingly simple deprotection could not be realised successfully. Under various conditions[27] tried as described in scheme 17 complex pattern on TLC resulted everytime. Here again the results indicate that the deprotected compound might not be very stable under the reaction condition employed and thus resulting in multi spot TLC.



Scheme 17: *Acetonide removal*

Thus to eradicate the problem of exposing the generated deprotected compound to acidic medium it was necessary to avoid the usage of acidic catalyst during deprotection. Hence it was decided to introduce benzylidene protection instead of acetonide so that it could be removed near neutral conditions by the usage of reagents such CAN, DDQ,[28] hydogenolysis etc.

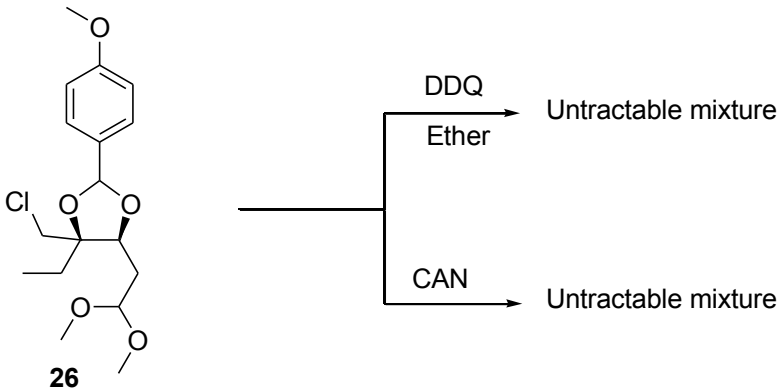
Thus the whole sequence of reaction was repeated with the corresponding 4-methoxy-benzylidene protection (Scheme 18).



Scheme 18: Reagents and conditions: *a) dimethyl acetal anisaldehyde, p-TSA, DCM, rt, 0.5 h, 70%; b) K_2CO_3, methanol, rt, 12 h, quantitative; c) CCl_4, PPh_3, imidazole, reflux, 10 h, 75%.*

The chiral diol **16** when treated with 4-methoxybenzaldehyde dimethyl acetal taken in DCM in presence of *p*-TSA offered the protected compound **24** in 70% yield after column chromatographic purification. The formation of the compound **24** was confirmed by spectral studies. The benzoate protection was removed readily on exposing the substrate to K_2CO_3 in methanol. The purified compound **25** obtained in quantitative yield was further subjected to react with CCl_4 and PPh_3 in the presence of imidazole at reflux temperature to render the corresponding chloro compound **26** in 75% yield after column chromatographic purification. The isolated compound showed characteristic change in spectral behaviour thereby confirming the transformation (Scheme 18).

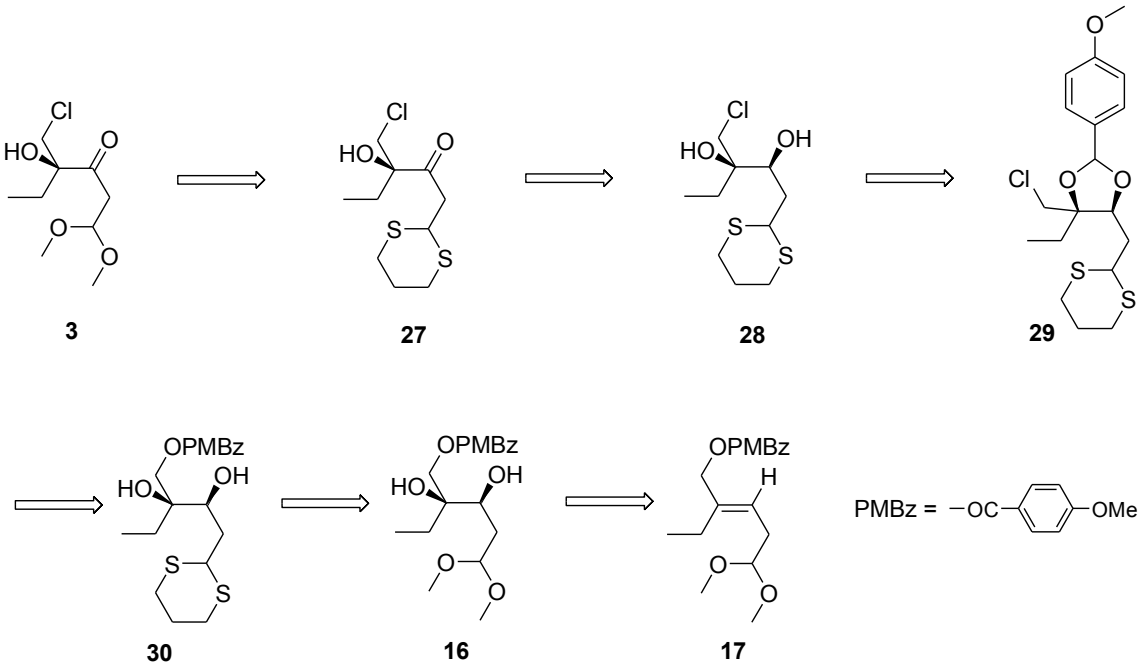
The benzylidene protected substrate **26** was subjected to deprotection with DDQ but with no better result. Here too intractable complex mixture as judged by TLC was realised. A few more conditions were tried as summarised in scheme 19.



Scheme 19: *Benzylidene removal*

All the above results signify extreme instability of the different substrates under various reaction conditions in different steps. This all can be attributed to the presence of many sensitive functional groups on consecutive carbons on a very small carbon unit. In presence of the labile acyclic dimethyl acetal generation of ketone lead to the formation of ene ether whereas the free hydroxy groups readily participate in the formation of cyclic acetal under both acidic as well as alkaline conditions.

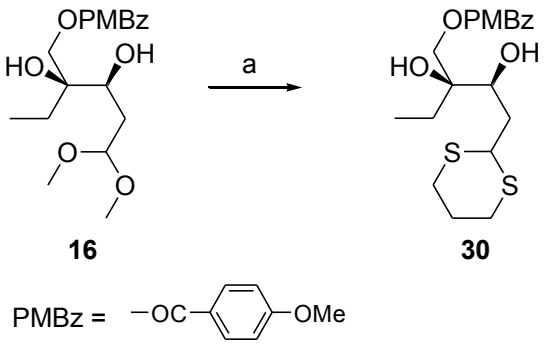
Keeping in view the entire problem associated with the substrates it was compelling to change the strategy by converting the dimethyl acetal into more stable dithiane protection so that the modified substrate could withstand highly acidic as well as alkaline conditions. The modified retro path is delineated in scheme 20.



Scheme 20: *Retrosynthetic plan 4*

As the conditions for asymmetric dihydroxylation were already standardised on substrate **17** the dithiane was proposed to be introduced on the diol **16**.

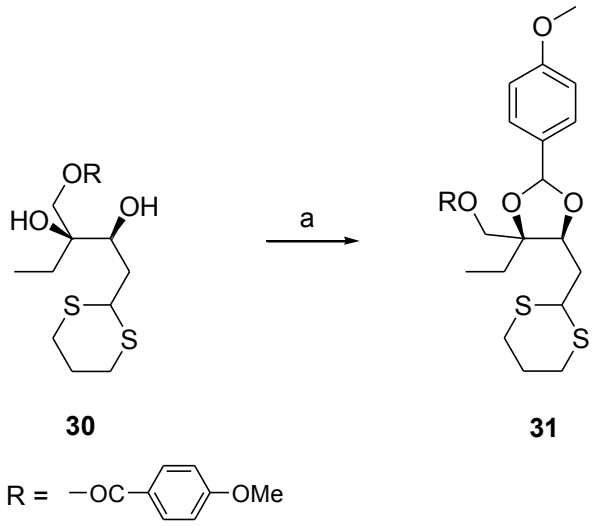
Thus chiral diol **16** when subjected to react with propane 1,3-dithiol in the presence of $BF_3.OEt_2$[29] in DCM at room temperature resulted in the formation of corresponding dithiane **30**. The isolated product was obtained in 70% yield after column chromatographic (SiO_2) purification (Scheme 21).



Scheme 21: Reagents and conditions: *a) propane 1,3-dithiol, $BF_3.OEt_2$, DCM, rt, 0.5 h, 70%.*

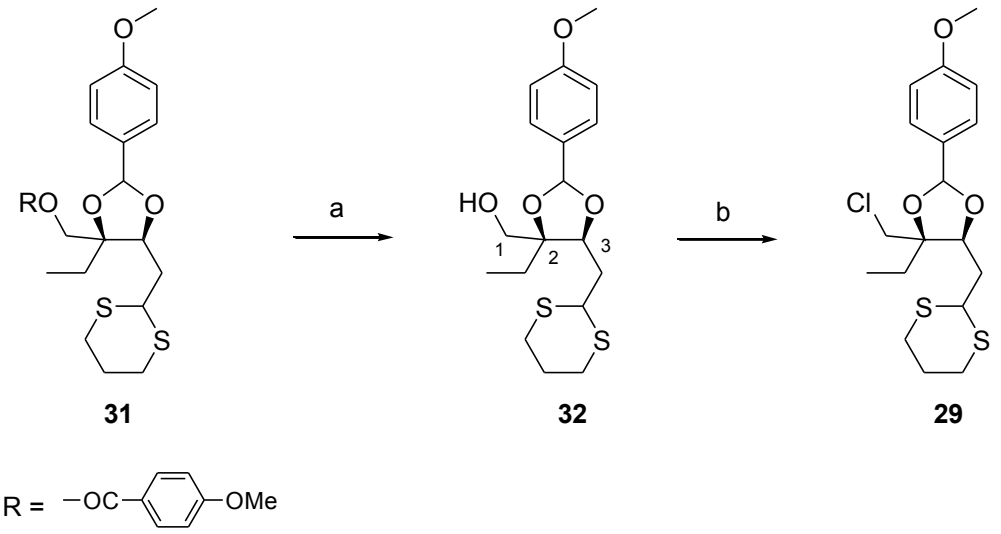
Spectral study revealed successful transformation. IR spectrum showed sharp absorption at 3427 and 1708 cm^{-1}. In the ^1H NMR spectrum the six newly introduced $–CH_2$ protons resonated at δ 2.94-2.80 and δ 2.11-1.84 integrating for four and two protons respectively and appeared as multiplets. The characteristic acetal proton of the dithiane moved upfield and appeared at δ 4.33-4.26 integrating for one proton as multiplet. ^{13}C NMR spectrum further confirmed the transformation. Alongwith DEPT spectrum it showed presence of additional three -$\underline{C}H_2$ carbons. The acetal carbon moved upfield to δ 44.2. It was further confirmed by mass (ESI) *m/z* 387.49 (M^++1) and elemental analysis.

The chiral HPLC analysis on Chiralcel-OJ-H confirmed that no racemisation occurred under the reaction condition employed and further confirmed the extent of enantioselectivity (89% ee) induced during dihydroxylation.



Scheme 22: Reagents and conditions: *a) dimethyl acetal anisaldehyde, p-TSA, DCM, rt, 0.5 h, 88%.*

The benzylidene protection of the diol **30** was successfully carried out by the addition of 4-methoxybenzaldehyde dimethyl acetal to the substrate **30** in the presence of catalytic amount of *p*-TSA in DCM at room temperature. The isolated product **31** was obtained in 88% yield and showed absence of absorption in the region 3500-3200 cm^{-1} in the IR spectrum thereby signifying absence of any hydroxy group. ^{1}H NMR spectrum showed the presence of additional aromatic protons peaks apart from the benzoate protons. The benzilydene proton appeared as a singlet at δ 5.88 (diastereomeric mixture 80:20). In addition, the additional methoxy group of benzylidene appeared as a singlet integrating for three protons at δ 3.83. The ^{13}C NMR spectrum showed the presence of extra aromatic carbons as well as the additional methoxy carbon at δ 55.2. This alongwith elemental analysis and appearance of a peak in mass (ESI) at *m/z* 505.31 (M^{+}+1) confirmed the transformation (Scheme 22).

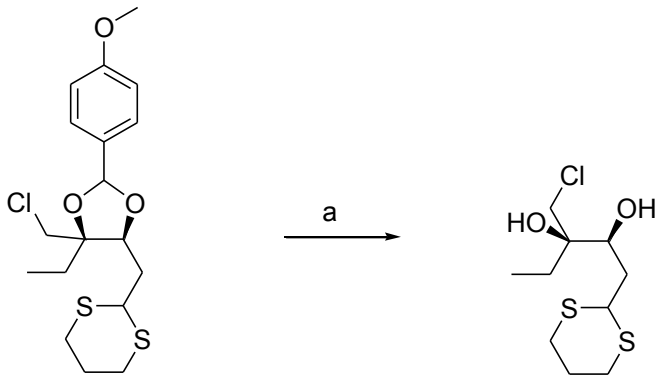


Scheme 23: Reagents and conditions: *a) K_2CO_3, MeOH, rt, 12 h, 90%; b) CCl_4, PPh_3, imidazole, reflux, 3 h, 86%.*

The benzoate group was removed by treating the substrate **31** with K_2CO_3 in methanol. It was confirmed by IR absorption at 3418 cm^{-1}. The ^{1}H NMR spectrum showed absence of peak assigned to the benzoate moiety. The isolated product **32** was found to unstable as it readily underwent benzylidene migration from 2,3 to 1,2 positions. Thus as soon it was prepared it was put forward for chlorination reaction. Accordingly in presence of PPh_3 the compound **32** was refluxed in CCl_4 to furnish the corresponding chloro **29** in 86% yield after column chromatographic purification (Scheme 23). IR showed no absorption

in the region 3500 to 3000 cm $^{-1}$ thereby signifying the absence of hydroxy group. ^{1}H NMR spectrum showed a downfield shift of –C$\underline{H_2}$ protons and appeared as two doublets at δ 3.76 and 3.58. Not much change was observed in the pattern of other peaks. It was further confirmed by mass (ESI) m/z 389.19 (M^++1) and elemental analysis.

Successful conversion of hydroxy into chloro in good yield rendered the substrate for the crucial removal of benzylidene. Gratifyingly as expected on treating the substrate **29** with catalytic amount of *p*-TSA in methanol, the diol **28** was obtained as a solid fairly easily in very good yield (87%). Thus the problem of selective benzylidene removal was overcome by changing the aldehyde protecting group from acetal to more stable dithiane.



29 **28**

Scheme 24: Reagents and conditions: *a) p-TSA. MeOH, rt, 0.5 h, 87%.*

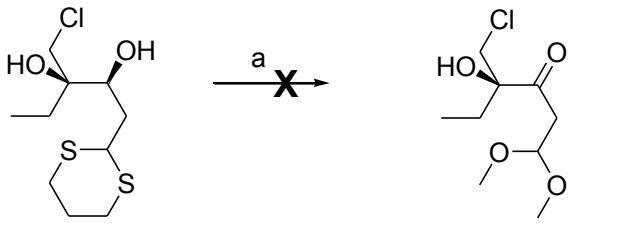
The removal of benzylidene was confirmed by its spectral study. IR spectrum showed strong absorption at 3422 cm^{-1} signifying the presence of free hydroxy group. ^{1}H NMR spectrum of **28** showed absence of aromatic proton peak as well as peak at δ 3.82 corresponding to the *p*-methoxy protons. ^{13}C NMR spectrum also showed absence of aromatic carbon and methoxy carbon. The appearance of the peak in the mass (ESI) at *m/z* 271.44 (M^++1) and elemental analysis further confirmed the transformation.

Since the isolated diol **28** was a solid it was thought that recrystalisation would lead to the enrichment of the major isomer. But the chiral HPLC analysis indicated that there was no significant increase in enantiopurity after recrystalisation. Hence this compound was carried forward for further transformations.

With the requisite diol **28** in hand a ready oxidation of secondary hydroxy group and conversion of dithiane into dimethyl acetal or aldehyde would furnish the desired keto-hydroxy compound **3**.

Literature precendents[30] are there where the dithiane protection has been successfully converted into dimethyl acetal by treating the substrate with *Dess-Martin* periodinane (DMP) in presence of dry methanol. At the same time *Dess-Martin* periodinane is known to facilitate the oxidation of the hydroxy group into corresponding aldehyde/ketone. With this knowledge it was planned to perform single pot reaction with DMP in anhydrous methanol wherein the secondary hydroxy group will be oxidized to ketone as well as the dithiane would be converted into dimethyl acetal furnishing us the required synthon **3** in a straightforward manner.

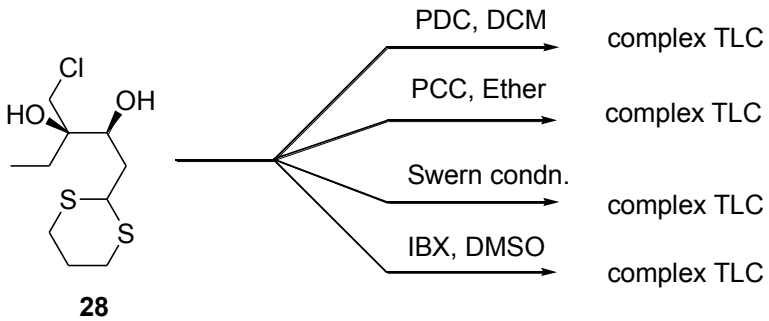
But exposing the substrate **28** in dry methanol to DMP furnished a complex TLC pattern. No desired product or starting material could be recovered from the reaction mixture.



28 **3**
complex TLC

Scheme 25: Reagents and conditions: *a) DMP, MeOH: Acetonitrile, rt, 3 h.*

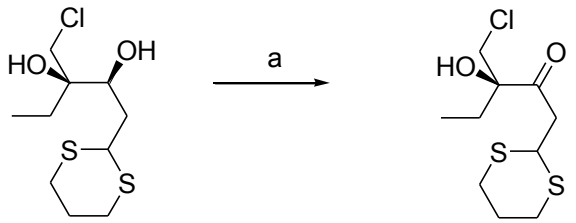
Failing to get the desired transformation in a single pot it was thought to proceed stepwise, i.e. first convert the secondary hydroxy to ketone and then look for removal of the dithiane. Since it was known that DMP facilitates dithiane removal other conditions were opted for oxidation of the secondary hydroxy group. But under various conditions[31] tried the desired transformation could not be achieved. In all the attempts the TLC showed complex pattern (Scheme 26). It was presumed that the dithiane sulphur was interfering with the reagents of the conditions applied.



28

Scheme 26: *Oxidation*

Hence it was decided to revert back to the original reagent i.e. DMP. In the reported procedure dithiane has been removed by DMP only when there is a proton source i.e in presence of protic solvent. So it was decided to perform the reaction under controlled condition i.e. in presence of highly anhydrous freshly distilled DCM over calcium hydride and maintaining the temperature at 0-5 ^{o}C. Under this condition when the substrate was subjected to react with DMP (2 eq. to be added in batches at the interval of 1 h) gratifyingly an oxidised product was isolated in 40% yield with the dithiane moiety remaining intact. It was ascertained by IR study, which revealed a strong absorption at 1718 cm^{-1} thereby signifying the presence of ketone functionality. ^{1}H NMR spectrum showed absence of –C*H*OH protons. Whereas proton peaks corresponding to the dithiane part appeared at its expected position. ^{13}C NMR spectrum revealed presence of ketone carbonyl resonating at δ 206 whereas the –*C*HOH carbon peak vanished thereby confirming the oxidation. Mass spectral analysis established a peak at (M^{+}+Na^{+}) *m/z* 291.09 thus confirming the transformation.



28 **27**

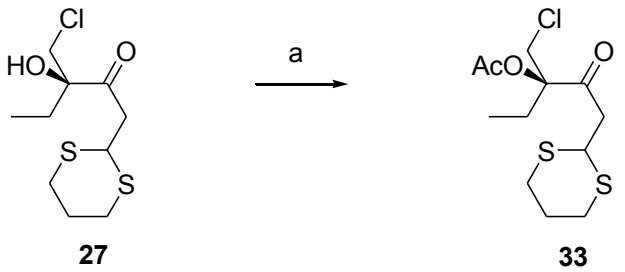
Scheme 27: Reagents and conditions: *a) DMP, dry DCM, 0-5 ^{o}C, 3 h, 40%.*

With the successful oxidation of the secondary hydroxy functionality, the only job left was to remove the dithiane protection. At this stage it was realised that removal of dithiane would render the aldehyde leading to the same substrate with highly sensitive functional groups. So it was thought appropriate to protect the tertiary hydroxy group as its acetate and then perform the removal of dithiane. Acetate could be removed later on after condensation with the tryptamine.

Hence subjecting the keto-hydroxy moiety **27** to react with acetic anhydride in presence of DMAP at room temperature furnished the acetate **33** in 87% yield after column chromatographic purification.

IR spectrum exemplified the transformation by showing a strong absorption at 1739 cm^{-1} and 1720 cm^{-1} assigned to the ester and the ketone cabonyl groups. ^{1}H NMR spectrum showed characteristic peaks of acetate functionality resonating at δ 2.19 appearing as a

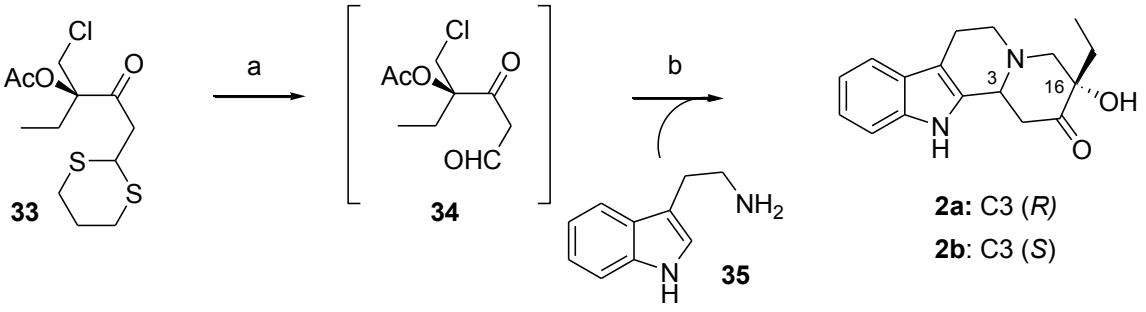
singlet and integrating for three protons corresponds to the methyl group. ^{13}C NMR spectrum also showed peak at δ 169.9 corresponding to the acetate carbonyl apart from other characteristic peaks of the substrate. Respectively the structure was further confirmed by appearance of a peak at *m/z* 311.24 in mass (ESI) and elemental analysis.



27 **33**

Scheme 28: Reagents and conditions: *a) acetic anhydride, DMAP, rt, 0.5 h, 87%.*

Plenty of reports[32] are there in literature wherein the dithianes have been successfully removed by the action of MeI. Thus following the same path the substrate **33** was subjected to react with 10 eq. of MeI in aqueous acetonitrile under reflux condition for 24 h. Proper work-up rendered the corresponding aldehyde which was put forward for condensation with tryptamine without delay owing to the lability of the aldehyde group. Under already standardised condition the tryptamine (**35**) and the keto-hydroxy synthon **34** was treated with 2 M ethanolic HCl and stirred at room temperature for 12 hours. Alkaline work up furnished the condensed product **2** with concomitant removal of the acetate group under the condition employed. Hence in the same pot Pictet-spengler[33] condensation, alkylation and removal of the acetate protection were realised.



33 **34** **35**

2a: C3 (*R*)
2b: C3 (*S*)

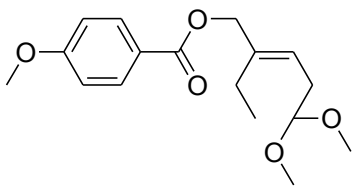
Scheme 29: Reagents and conditions: *a) MeI, acetonitrile: H_2O, reflux, 24 h; b) 2M (EtOH) HCl, rt, 12 h, 40% (over two steps).*

The condensation offered mixture the diastereomers (**2a** and **2b**) in combined yield of 40% over two steps. Preparative TLC separation rendered the pure diastereomers in 3:1 ratio. The spectral data of the isolated major compound was in full agreement with the reported one.[34] The major isomer was analysed for enantiopurity on chiral HPLC column, which showed a decline in ee from 89 % to 73 %. This alongwith the sign of the optical rotation confirms that the isolated major isomer is 3*R*, 16*S*.

In conclusion, synthesis of chiral key intermediate **2a** leading to the target molecule (-)-mitralactonine (**1**) has been achieved employing an asymmetric dihydroxylation as the key chirality inducing factor. The work demonstrates the efficacy of protecting group and other derivatisation towards the stability and enhancement of selectivity in the substrates.

2.2.4. Experimental

(*E*)-2-Ethyl-5,5-dimethoxypent-2-enyl 4-methoxybenzoate (17)



To a well stirred mixture of allylic alcohol **18** (2 g, 11.5 mmol) and triethylamine (4.8 mL, 34.4 mmol) in dry DCM (25 mL) under argon atmosphere at 0 ^{o}C was added anisyl chloride (2.93 g, 17.2 mmol) dropwise and left to stir at room temperature till the completion of reaction. The reaction mixture was diluted with water and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 25 mL). Combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. Column chromatographc purification (SiO_2) rendered the ester **17** in 85% yield (3g, 9.7 mmol). R_f 0.5 (PE: EA 90:10)

Mol. Formula : $C_{17}H_{24}O_5$

Yield : 85 %

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3016, 2966, 2936, 1707, 1607, 1511.

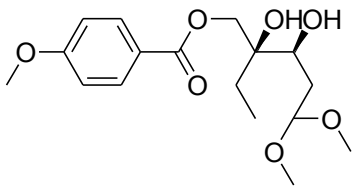
^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.00 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 5.53 (t, *J* = 7.2 Hz, 1H), 4.75 (s, 2H), 4.40 (t, *J* = 5.8 Hz, 1H), 3.87 (s, 3H), 3.34 (2s, 6H), 2.42 (t, *J* = 6.2 Hz, 2H), 2.19 (q, *J* = 7.4 Hz, 2H), 1.07 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 165.9 (C), 163.3 (C), 138.5 (C), 131.8 (2CH), 123.3 (2CH), 122.8 (C), 113.6 (CH), 104 (CH), 68.2 (CH_2), 55.3 (CH_3), 52.9 ($2CH_3$), 31.3 (CH_2), 21.7 (CH_2), 12.9 (CH_3).

Mass (ESI) : *m/z* 309.16 (M^++1)

Analysis : Calculated C 66.21, H 7.84%
Found C 65.98, H 7.78%

(2*S*,3*S*)-2-Ethyl-2,3-dihydroxy-5,5-dimethoxypentyl 4-methoxybenzoate (16)



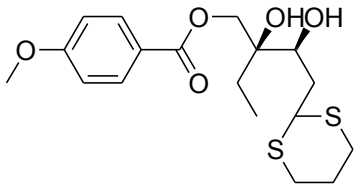
The ligand [$(DHQ)_2PHAL$] (50 mg, 1 mol%), $K_3Fe(CN)_6$ (6.4 g, 19.5 mmol), K_2CO_3 (2.7 g, 19.5 mmol) and OsO_4 (0.4 mol%) were dissolved in 1:1 mixture of water (30 mL) and *tert*-butyl alcohol (30 mL) at room temperature. $MeSO_2NH_2$ (0.62 g, 6.5 mmol) was added at this point. The vigorously stirred mixture was then cooled to 0 ^oC and the olefin **17** (2 g, 6.5 mmol) was added in one portion. After completion of reaction (24 h) it was quenched at 0 ^oC with sodium sulphite (10 eq.) and then warmed to room temperature and stirred for additional period of 30-60 min. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (5 x 50 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated on a rotary evaporator to give the crude diol which was purified through column chromatography (SiO_2) to furnish the diol **16** in 90% yield (2 g, 5.8 mmol). R_f 0.4 (PE: EA 1:1)

Mol. Formula	**:** $C_{17}H_{26}O_7$
Yield	**:** 90%
HPLC analysis	**:** Column- Chiralcel-OD, mobile phase- PET:IPA 90:10, flow rate 0.5 mL/min, t_R: major isomer: 24.80 min; t_R: minor isomer: 26.85 min. 89% ee
$[\alpha]_D^{25}$	**:** -10.38 (c 0.96, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	**:** 3431, 1706, 1606.
^1H NMR (400 MHz, $CDCl_3$)	**:** δ 7.97 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 4.61 (t, *J* = 5.1 Hz, 1H), 4.40 (d, *J* = 11.7 Hz, 1H), 4.28 (d, *J* = 11.7 Hz, 1H), 3.84 (s, 3H), 3.82 (m, 1H), 3.37, 3.33 (2s, 6H), 1.90-1.82 (m, 2H), 1.77-1.68 (m, 1H), 1.57-1.47 (m, 1H), 0.98 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$)	**:** δ 166.4 (C), 163.5 (C), 131.7 (2CH), 122.3 (C), 113.6 (2CH), 104.1 (CH), 74.9 (C), 70.1 (CH), 65.8

(CH_2), 55.3 (CH_3), 53.9 (CH_3), 52.9 (CH_3), 32.9 (CH_2), 25.9 (CH_2), 7.4 (CH_3).

Analysis **:** Calculated C 59.64, H 7.65%
Found C 59.50, H 7.55%

(2*S*,3*S*)-4-(1,3-Dithian-2-yl)-2-ethyl-2,3-dihydroxy 4-methoxybenzoate (30)



To a well stirred mixture of the diol **16** (2 g, 5.8 mmol) and propane 1,3 dithiol (0.76 g, 7 mmol) in dry DCM (20 mL) under argon atmosphere at 0 ^oC was added $BF_3.Et_2O$ (0.5eq). The reaction mixture was left to stir at room temperature till the completion of reaction (0.5 h). On completion, the temperature was lowered and the reaction quenched with excess of triethylamine. Reaction mixture was diluted with water, organic layer separated and aqueous layer extracted with DCM (3 x 25 mL). Combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude product. Column chromatographic (SiO_2) purification rendered the dithiane **30** in 70% yield (1.58 g, 4 mmol). R_f 0.5 (PE: EA 1:1).

Mol. Formula **:** $C_{18}H_{26}O_5S_2$

Yield **:** 70%

HPLC analysis **:** Chiralcel-OD-H, mobile phase-PET: IPA 90:10, flow rate 0.5 mL/min, t_R: major isomer 39.77 min, t_R: minor isomer 45.79 min. 89% ee.

$[\alpha]_D^{25}$ **:** -6.50 (c 1.13, $CHCl_3$)

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) **:** 3427, 1708, 1606.

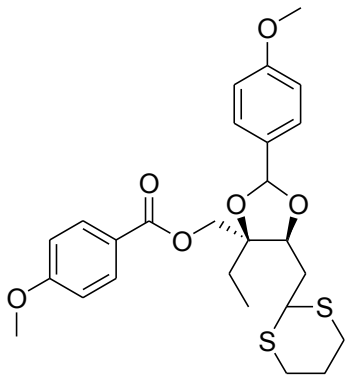
^1H NMR (200 MHz, $CDCl_3$) **:** δ 7.99 (d, *J* = 9.1 Hz, 2H), 6.93 (d, *J* = 9.1 Hz, 2H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.33-4.26 (m, 1H), 4.25 (d, *J* = 11.7 Hz, 1H), 3.99-3.92 (m, 1H), 3.88 (s, 3H), 2.94-2.80 (m, 4H), 2.11-1.84 (m, 4H), 1.80-1.66 (m, 1H), 1.62-1.43 (m 1H), 1.02 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 166.6 (C), 163.6 (C), 131.8 (2CH), 121.9 (2CH), 113.6 (C), 75.41 (C), 69.8 (CH), 66.2 (CH_2), 55.3 (CH_3), 44.2 (CH), 36.0 (CH_2), 30.3 (CH_2), 29.7 (CH_2), 25.97 (CH_2), 25.93 (CH_2), 7.56 (CH_3).

Mass (ESI) **:** *m/z* 387.49 (M^++1)

Analysis **:** Calculated C 55.93, H 6.78, S 16.59%
Found C 55.70, H 6.62, S 16.45%

[(4*S*,5*S*)-5-{(1,3-Dithian-2-yl)methyl}-4-ethyl-2-(4-methoxyphenyl)-1,3-dioxolan-4-yl]methyl 4-methoxybenzoate (31)



To a mixture of diol **30** (1.58 g, 4 mmol) and dimethyl acetal anisaldehyde (0.89 g, 5 mmol) in dry DCM (20 mL) was added catalytic amount of *p*-TSA. After the completion of reaction (0.5 h) it was quenched by addition of excess of triethylamine. The compound thus obtained was purified without further workup through column chromatography (SiO_2 pretreated with Et_3N) to render the pure protected compound **31** in 88% yield (1.8 g, 3.6 mmol). R_f 0.4 (PE: EA 80:20)

Mol. Formula **:** $C_{26}H_{32}O_6S_2$

Yield **:** 88%

$[\alpha]_D^{25}$ **:** Diastereomeric mixture

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) **:** 3018, 1710, 1606.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 8.02 (d, *J* = 9.0 Hz, 2H), 7.41 (d, *J* = 9.0 Hz, 2H), 6.97-6.88 (m, 4H), 5.88 (s, 1H), 4.52 (d, *J* = 11.5 Hz, 1H), 4.50 (dd, *J* = 9.9, 2.6, Hz, 1H), 4.36 (d, *J* = 11.5 Hz, 1H), 4.25 (dd, *J* = 10.5, 3.9 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 2.89-2.78 (m, 4H),

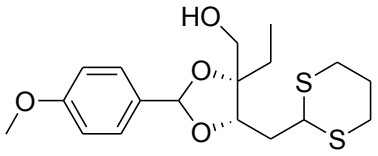
2.24-2.01 (m, 3H), 1.97-1.82 (m, 1H), 1.71 (q, *J* = 7.3 Hz, 2H), 1.07 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 165.6 (C), 163.5 (C), 160.5 (C), 131.8 (2CH), 129.5 (C), 128.3 (2CH), 122.2 (C), 113.8 (CH) 113.7 (CH), 102.8 (CH), 81.7 (C), 79.3 (CH), 65.1 (CH_2), 55.3 (CH_3), 55.2 (CH_3), 44.2 (CH), 35.8 (CH_2), 30.2 (CH_2), 29.6 (CH_2), 25.9 (CH_2), 25.2 (CH_2), 7.7 (CH_3).

Mass (ESI) **:** *m/z* 505.31 (M^++1).

Analysis **:** Calculated C 61.88, H 6.39, S 12.71%
Found C 61.66, H 6.29, S 12.65%

[(4*S*,5*S*)-5-{(1,3-Dithian-2-yl)methyl}-4-ethyl-2-(4-methoxyphenyl)-1,3-dioxolan-4-yl)methanol (32)



The protected diol **31** (1.8 g, 3.6 mmol) in methanol (10 mL) was treated with K_2CO_3 (0.98 g, 7.1 mmol) and left to stir at room temperature till the completion of reaction (12 h). The reaction mixture was diluted with water (10 mL) and extracted repeatedly with ethyl acetate (5 x 25 ml). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated to give the crude alcohol. Purification by column chromatography (SiO_2 pretreated with Et_3N) rendered the pure product **32** in 90 % yield (1.2 g, 3.2 mmol). R_f = 0.2 (PE: EA 70:30)

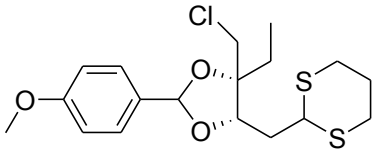
Mol. Formula **:** $C_{18}H_{26}O_4S_2$

Yield **:** 90%

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) **:** 3418, 2937, 1614, 1517.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 7.40 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.84 (s, 1H), 4.49 (dd, *J* = 10.1, 2.7 Hz, 1H), 4.26 (dd, *J* = 10.3, 4.0 Hz, 1H), 3.90 (d, *J* = 11.7 Hz, 1H,), 3.82 (s, 3H), 3.78 (d, *J* = 11.7 Hz, 1H), 2.98-2.79 (m, 4H), 2.24-2.04 (m, 2H), 2.00-1.83 (m, 2H), 1.70-1.45 (m, 3H), 0.99 (t, *J* = 7.3 Hz, 3H).

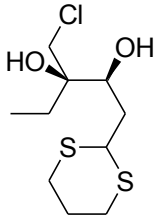
(4*S*,5*R*)-5-{(1,3-Dithian-2-yl)methyl}-4-(chloromethyl)-4-ethyl-2-(4-methoxyphenyl)-1,3-dioxolane (29)



The mixture of alcohol **32** (1.2 g, 3.2 mmol), PPh_3 (1.27 g, 4.8 mmol) and imidazole (0.33 g, 4.8 mmol) was refluxed in CCl_4 (15 mL) for 3 h. On completion of reaction (TLC) excess of solvent was removed under reduced pressure and the compound purified through column chromatography (SiO_2 pretreated with Et_3N) without further workup to give the pure product **29** in 86% yield (1.1 g, 2.8 mmol). R_f 0.3 (PE: EA 90:10)

Mol. Formula	**:** $C_{18}H_{25}ClO_3S_2$
Yield	**:** 86 %
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	**:** 3019, 1614, 1518.
^{1}H NMR (200 MHz, $CDCl_3$)	**:** δ 7.39 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.82 (s, 1H), 4.45-4.39 (m, 1H), 4.27-4.20 (m, 1H), 3.82 (s, 3H), 3.76 (d, *J* = 11.2 Hz, 1H), 3.58 (d, *J* = 11.2 Hz, 1H), 2.97-2.74 (m, 4H), 2.24-2.00 (m, 3H), 2.00-1.63 (m, 3H), 1.02 (t, *J* = 7.3 Hz, 3H)
^{13}C NMR (50 MHz, $CDCl_3$)	**:** δ 160.6 (C), 129.1 (C), 128.3 (2CH), 113.7 (2CH), 102.6 (CH), 82.3 (C), 80.6 (CH), 55.2 (CH_3), 45.9 (CH_2), 44.1 (CH), 36.3 (CH_2), 29.9 (CH_2), 29.3 (CH_2), 26.0 (CH_2), 24.6 (CH_2), 7.4 (CH_3).
Mass (ESI)	**:** *m/z* 389.19 (M^++1).
Analysis:	**:** Calculated C 55.58, H 6.48, Cl 9.11, S 16.49% Found 55.37, H 6.37, Cl 9.01, S 16.35%

(2*S*,3*R*)-3-(Chloromethyl)-1-(1,3-dithian-2-yl)pentane-2,3-diol (28)



The chloro compound **29** (1.1 g, 2.8 mmol) in methanol (10 mL) was treated with *p*-TSA and stirred at room temperature till the completion of the reaction (0.5 h). The reaction was quenched with addition of saturated aqueous sodium bicarbonate solution and the mixture extracted several times with ethyl acetate (5 x 25 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Column purification (SiO_2) rendered the pure product **28** in 87% yield (0.67 g, 2.5 mmol). R_f 0.4 (PE: EA 70:30)

Mol. Formula : $C_{10}H_{19}ClO_2S_2$

Yield : 87%

$[\alpha]_D^{25}$: -30.21(c 1.06, $CHCl_3$)

Mp : 103-104 ^oC

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3422, 3019.

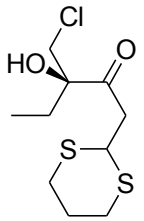
^1H NMR (200 MHz, $CDCl_3$) : δ 4.31-4.24 (m, 1H), 4.06-4.00 (m, 1H), 3.67 (s, 2H), 3.01-2.8 (m, 4H), 2.25-2.07 (m, 3H), 2.02-1.88 (m, 3H), 1.79-1.65 (m, 1H), 1.63-1.45 (m, 1H), 0.94 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 76.0 (C), 69.7 (CH), 47.3 (CH_2), 44.3 (CH), 36.3 (CH_2), 30.3 (CH_2), 29.9 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 7.4 (CH_3).

Mass (ESI) : *m/z* 271.44 (M^++1)

Analysis : Calculated C 44.35, H 7.07, Cl 13.09, S 23.68%
Found C 44.37, H 6.88, Cl 12.86, S 23.45%

(*R*)-3-(Chloromethyl)-1-(1,3-dithian-2-yl)-3-hydroxypentan-2-one (27)

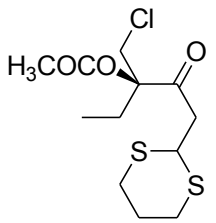


To a well-stirred solution of the diol **28** (0.67 g, 2.5 mmol) in freshly dried DCM (10 mL) at 0 ^oC was added weighed amount of *Dess-Martin* periodinane (1.5 g, 3.7 mmol) in two portions at the interval of 1 h. The mixture was stirred at 0-5 ^oC for a total period of 3 h at the end of which the reaction was quenched at 0 ^oC with addition of a mixture (1:1) of saturated aqueous solution of sodium sulphite and sodium bicarbonate. The

organic layer was separated and the aqueous layer was extracted with DCM (3 x 25 mL). Combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Column chromatographic purification (SiO_2) of the residue furnished the pure product **27** as a solid in 40% yield (0.26 g, 1 mmol). R_f 0.5 (PE: EA 70:30)

Mol. Formula	**:** $C_{10}H_{17}ClO_2S_2$
Yield	**:** 40%
$[\alpha]_D^{25}$	**:** –3.78 (c 0.58, $CHCl_3$)
Mp	**:** 57-58 ^oC
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	**:** 3458, 2923, 1718.
^1H NMR (200 MHz, $CDCl_3$)	**:** δ 4.58 (t, *J* = 6.8 Hz, 1H), 3.80 (d, *J* = 11.5 Hz, 1H), 3.62 (d, *J* = 11.5 Hz, 1H), 3.02 (d, *J* = 6.8 Hz, 1H), 2.96-2.78 (m, 4H), 2.18-2.06 (m, 1H), 1.97-1.67 (m, 4H), 0.91 (t, *J* = 7.32, 3H).
^{13}C NMR (100 MHz, $CDCl_3$)	**:** δ 206.8 (C), 81.5 (C), 49.3 (CH_2), 43.2 (CH_2), 40.4 (CH), 30.2 (CH_2), 30.1 (CH_2), 29.6 (CH_2), 25.2 (CH_2), 7.4 (CH_3).
Mass (ESI)	**:** *m/z* 291.09 (M^++Na).
Analysis	**:** Calculated C 44.68, H 6.37, Cl 13.19, S 23.86% Found C 44.45, H 6.29, Cl 13.09, S 23.72%

(*R*)-3-(Chloromethyl)-1-(1,3-dithian-2-yl)-2-oxopentan-3-yl acetate (33)

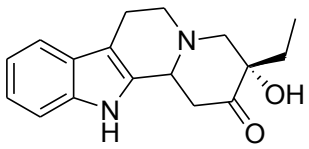


To a well stirred mixture of the ketol **27** (0.2 g, 0.7 mmol) and DMAP (0.73 g, 6 mmol) in dry DCM (7 mL) at 0 ^oC under argon was added acetic anhydride (0.3 g, 3 mmol) and left to stir at room temperature. After completion of reaction (0.5 h), the reaction mixture was diluted with water and organic layer was separated. The aqueous layer was extracted with DCM (3 x 15 mL). Combined organic layers were washed with saturated sodium bicarbonate, brine, dried over anhydrous sodium sulphate, filtered and concentrated

under reduced pressure to give the crude acetate. Column chromatographic purification (SiO_2) of the residue furnished the pure product **33** in 87% yield (0.2 g, 0.65 mmol). R_f 0.5 (PE: EA 80:20)

Mol. Formula	**:** $C_{12}H_{19}ClO_3S_2$
Yield	**:** 87%
$[\alpha]_D^{25}$	: -3.20 (c 0.74, $CHCl_3$)
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	**:** 2927, 1739, 1720.
^{1}H NMR (200 MHz, $CDCl_3$)	**:** δ 4.55 (dd, *J* = 8.6, 4.9 Hz, 1H), 4.10 (s, 2H), 3.09-2.71 (m, 6H), 2.19 (s, 3H), 2.15-1.82 (m, 4H), 0.86 (t, *J* = 7.5 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$)	**:** δ 203.2 (C), 169.9 (C), 87.7 (C), 44.0 (CH_2), 43.8 (CH_2), 40.6 (CH), 30.6 (CH_2), 30.3 (CH_2), 25.9 (CH_2), 25.3 (CH_2), 21.1 (CH), 7.2 (CH_3).
Mass (ESI)	**:** *m/z* 311.24 (M^++1).
Analysis	**:** Calculated C 46.36, H 6.16, Cl 11.40, S 20.63% Found C 46.30, H 6.10, Cl 11.31, S 20.45%

Tetracyclic ketone (2a and 2b)



A mixture of acetate **33** (0.2 g, 0.65 mmol), methyl iodide (0.9 g, 0.4 mL, 6.4 mmol) water (0.2 mL) in acetonitrile (10 mL) was refluxed for 24 h under nitrogen atmosphere. After completion of reaction most of the methyl iodide and volatile solvents were removed *in vacuo* and the residue was extracted with DCM (3 x 10 mL). The organic layer was washed with sodium bicarbonate, brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude product was used in the next reaction without further purification because of lability of the compound.

The mixture of crude aldehyde (assuming 100% conversion) and tryptamine (0.10 g, 0.6 mmol) was stirred in absolute ethanol under nitrogen atmosphere for 0.5 h. The resulting solution was acidified by the addition of 2M ethanolic HCl at 0 ^oC and the mixture was further stirred for 12 h at room temperature. After this time, the mixture was diluted with ethyl acetate and water. The aqueous solution was made alkaline by the addition of

excess of NaOH. The organic layer was separated and aqueous layer extracted with ethyl acetate (3 x 10 mL). Combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Column chromatographic purification (SiO_2) of the residue rendered the tetracyclic compound **2a** and **2b** (3:1) in 40% yield (over two steps) (0.073 g, 0.25 mmol). R_f 0.5 and 0.4 (PE: EA 60:40)

Mol. Formula **:** $C_{17}H_{20}N_2O_2$

Yield **:** 40% (2a: 30 %; 2b: 10%)

HPLC analysis (major isomer 2a) **:** Column: Chiralcel-OJ-H mobile phase: PE:IPA 90:10, flow rate: 0.5 mL/min, retention time: minor isomer: 48.67 min; major isomer: 79.04 min; Major isomer **2a**: 73 % ee.

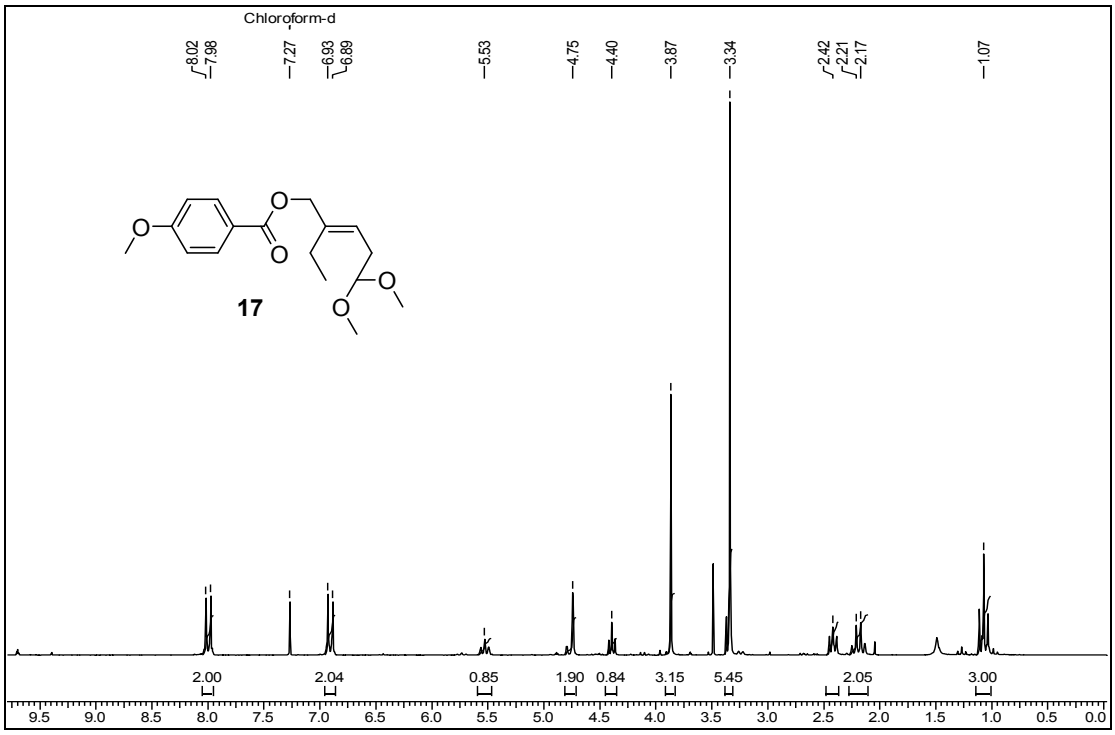
$[\alpha]_D^{25}$ (major isomer 2a) **:** -108 (c 0.13, $CHCl_3$) [lit. $[\alpha]_D^{25}$ -156, c 0.64, $CHCl_3$]

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) **:** 3409, 3018, 1716, 1440.

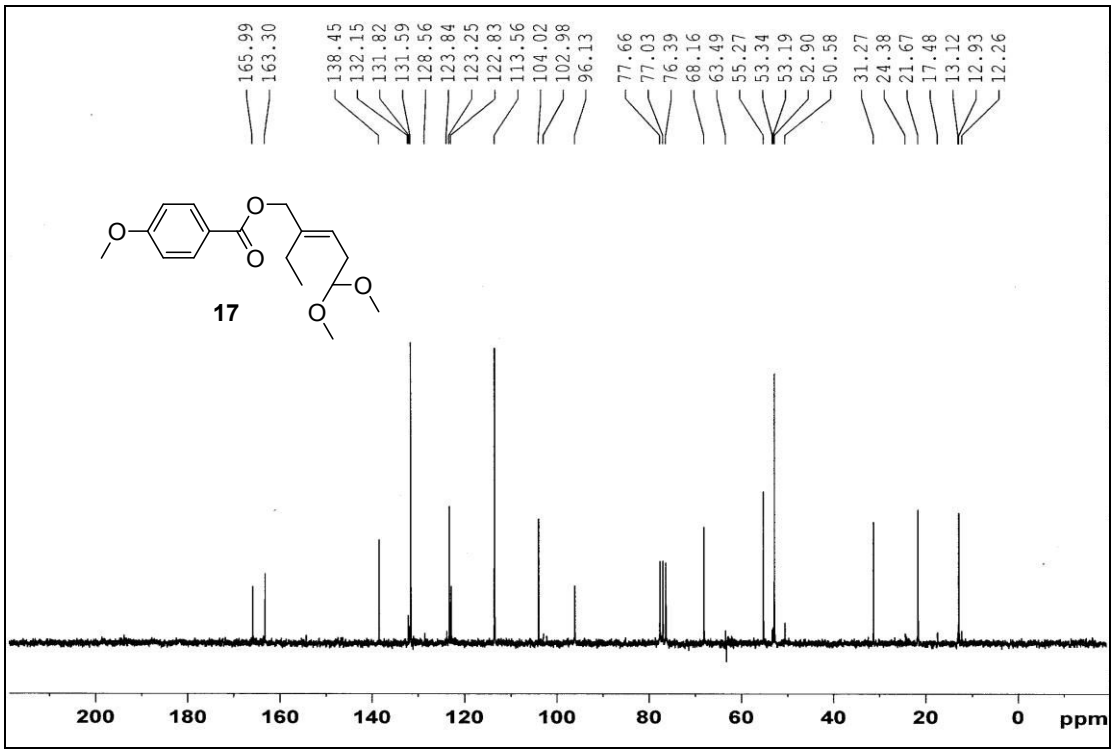
^{1}H NMR (500 MHz, $CDCl_3$) (2a) **:** δ 7.83 (br s, 1H, N*H*), 7.52 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* =8.0 Hz, 1H), 7.19 (m, 1H), 7.14 (m, 1H). 3.82 (br s, 1H), 3.60 (br d, 1H), 3.26 (d, *J* = 11.2 Hz, 1H), 3.18 (dd, *J* = 11.4, 4.8 Hz, 1H), 3.06-2.99 (m, 1H), 2.86 (dd, *J* = 3.2, 13.2 Hz, 1H), 2.79 (br d, *J* = 12.2 Hz, 1H), 2.70 (dd, *J* = 11.4, 3.8 Hz, 1H), 2.57 (d, *J* = 11.2 Hz, 1H), 2.31-2.23 (m, 1H), 1.91-1.84 (m, 1H), 0.84 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) (2a) **:** δ 211.5 (C), 136.3 (C), 132.6 (C), 126.9 (C), 121.9 (CH), 119.6 (CH), 118.3 (CH), 111.1 (CH), 108.7 (C), 79.4 (C), 65.9 (CH_2), 59.7 (CH_3), 51.8 (CH_2), 42.8 (CH_2), 30.7 (CH_2), 21.9 (CH_2), 6.9 (CH_3).

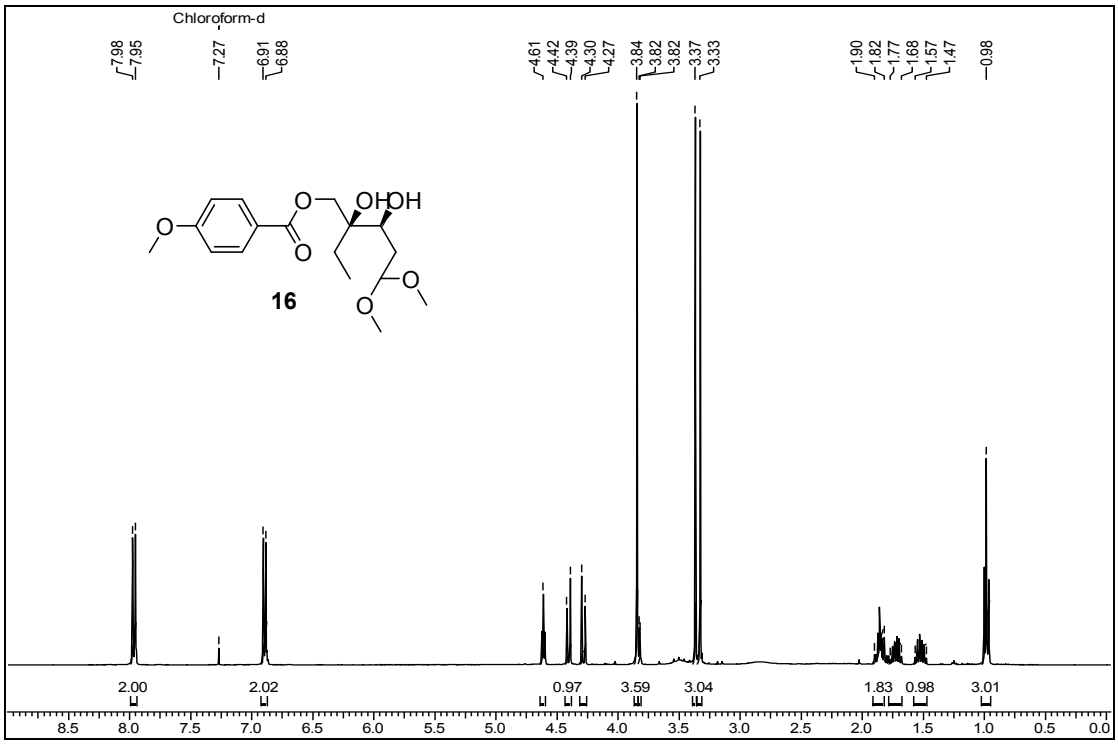
Mass (ESI) **:** *m/z* 285.33 (M^++1).



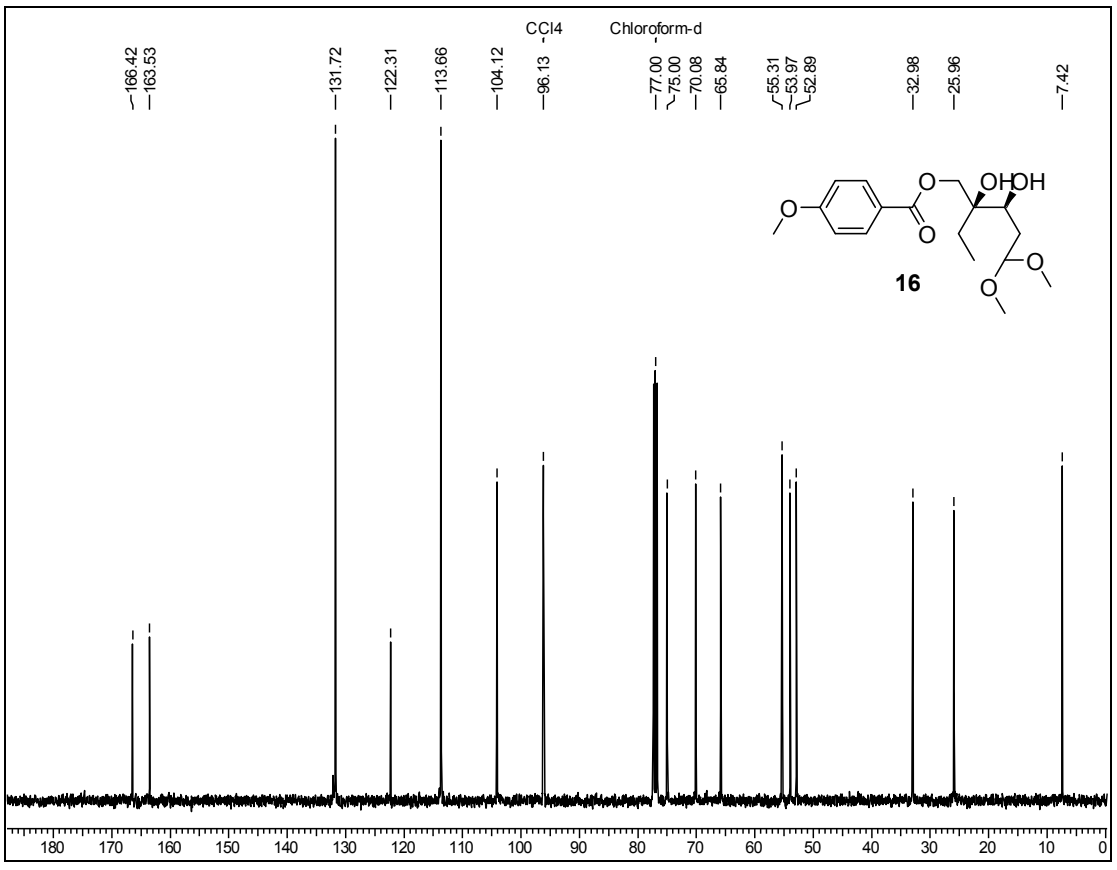
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 17



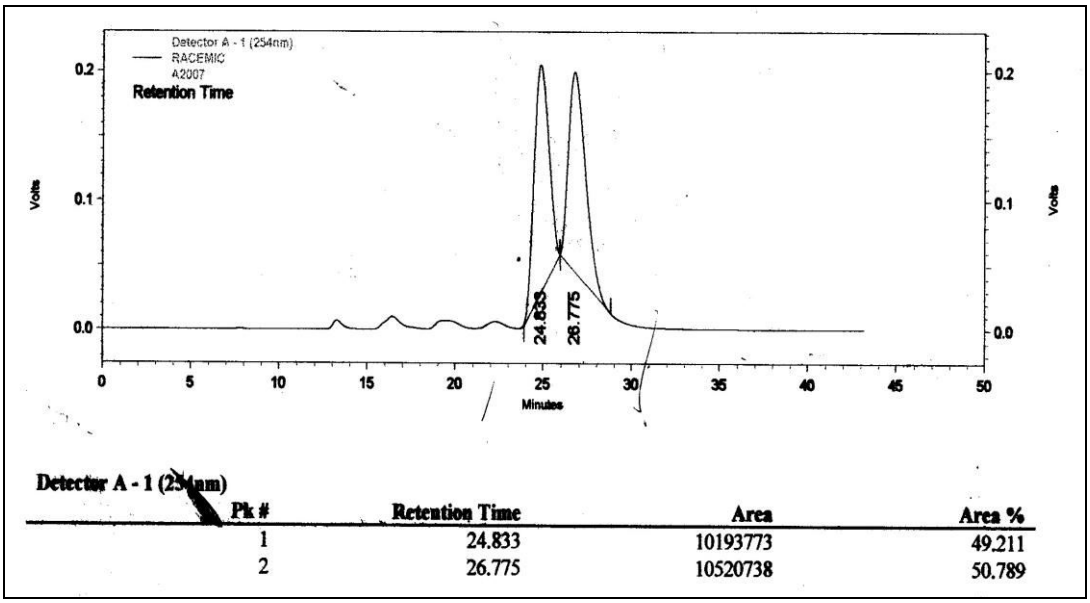
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 17



^{1}H NMR ($CDCl_3$+CCl_4, 400 MHz) spectra of compound 16



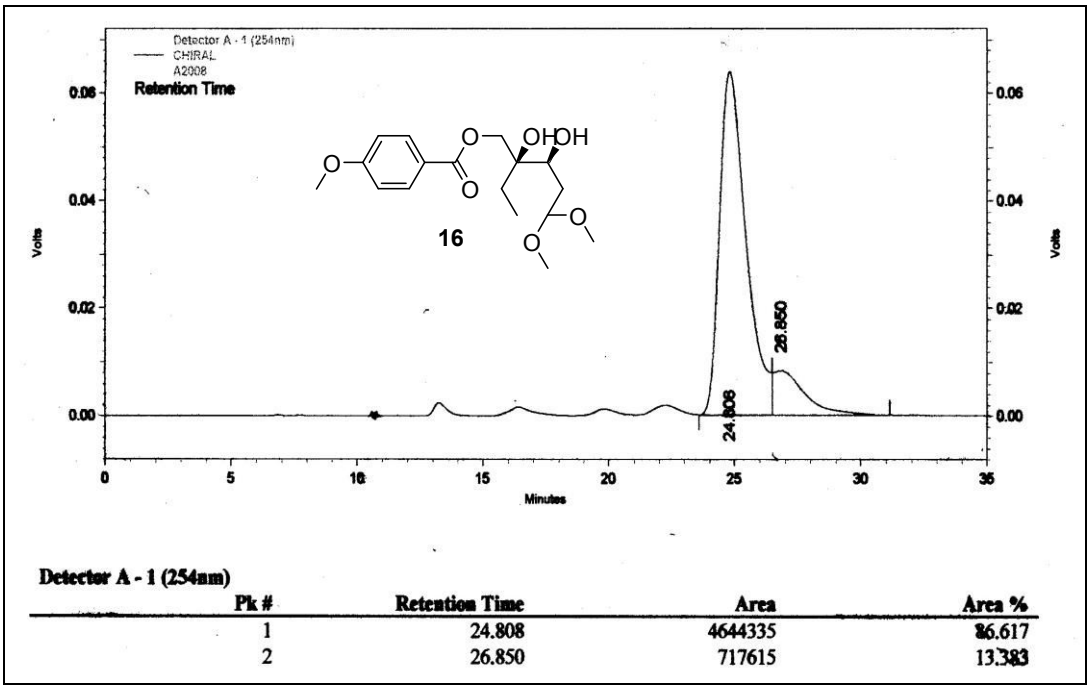
^{13}C NMR ($CDCl_3$+CCl_4, 100 MHz) spectra of compound 16



Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	24.833	10193773	49.211
2	26.775	10520738	50.789

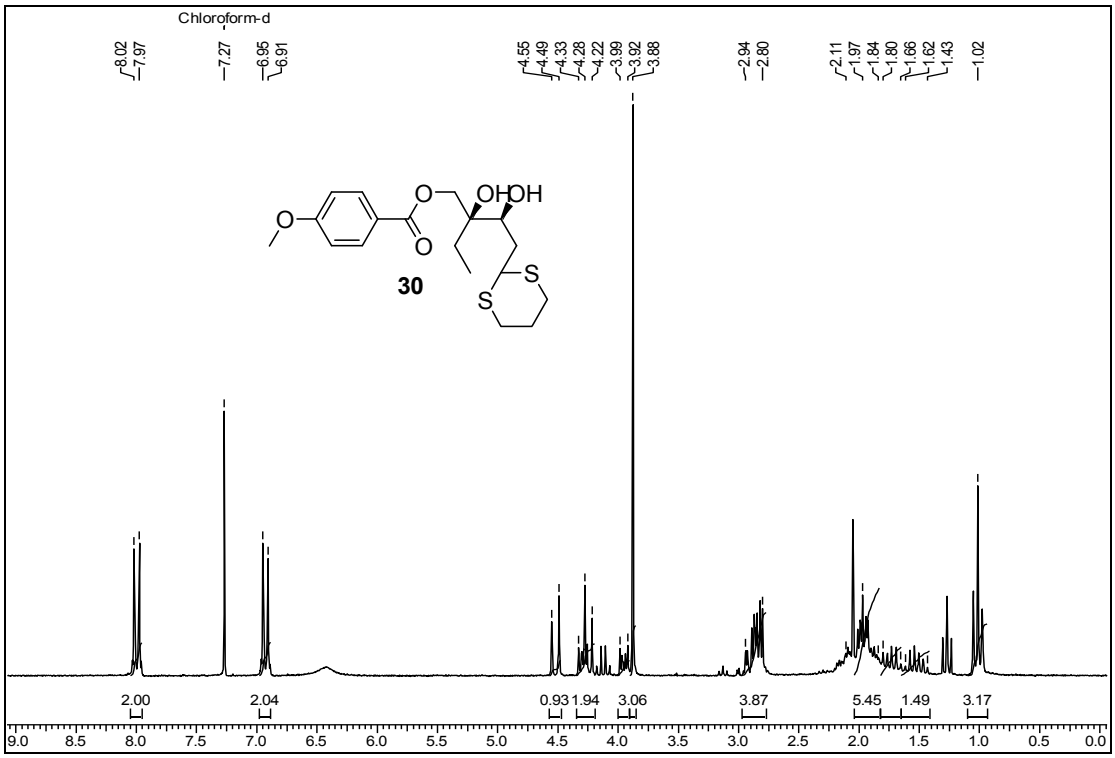
Chiral HPLC analysis of compound 16 (rac): Column: Chiralcel OD 0.25cm; Mobile phase: PE: EA 90:10; Wavelength: 254 nm; Flow rate: 0.5 mL/min



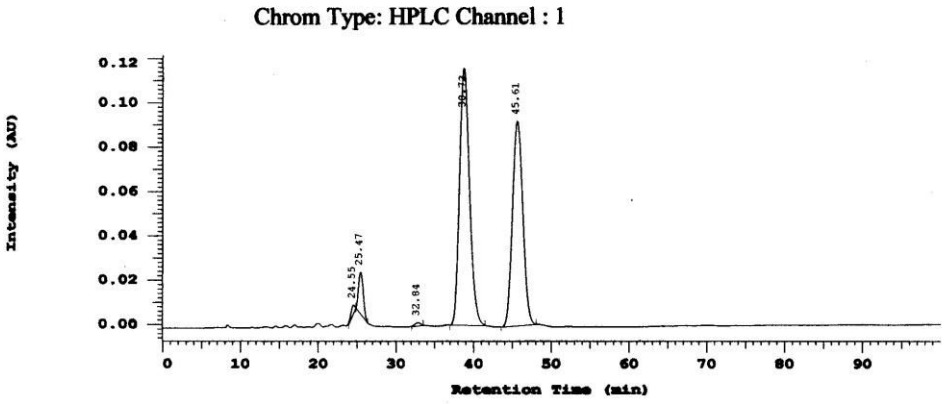
Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	24.808	4644335	86.617
2	26.850	717615	13.383

Chiral HPLC analysis of compound 16 (Optically active)



^{1}H NMR ($CDCl_3$+CCl_4, 400 MHz) spectra of compound 30



No.	RT	Area	Conc 1	BC
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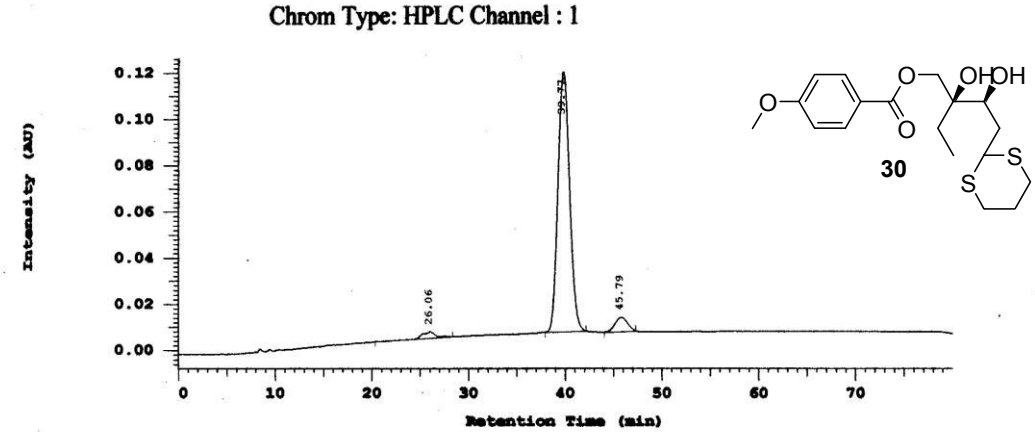
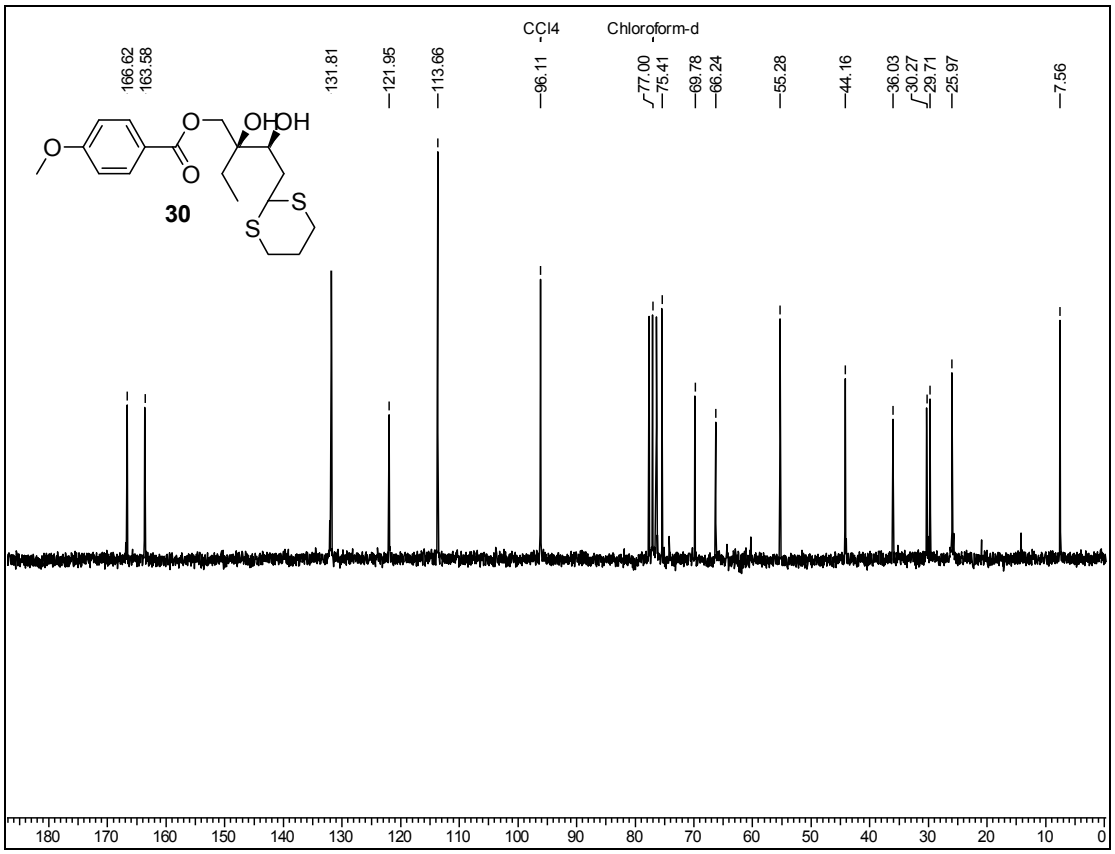
3	32.84	30297	0.310	BB
4	38.72	5095975	52.164	BB
5	45.61	4201689	43.010	BB
		9769065	100.000	

Chiral HPLC analysis of compound 30 (rac): Column:Chiralcel OD-H 250x4.6mm; Mobile phase: PE:IPA 90:10; Wavelength: 254 nm; Flow rate: 0.5 mL/min

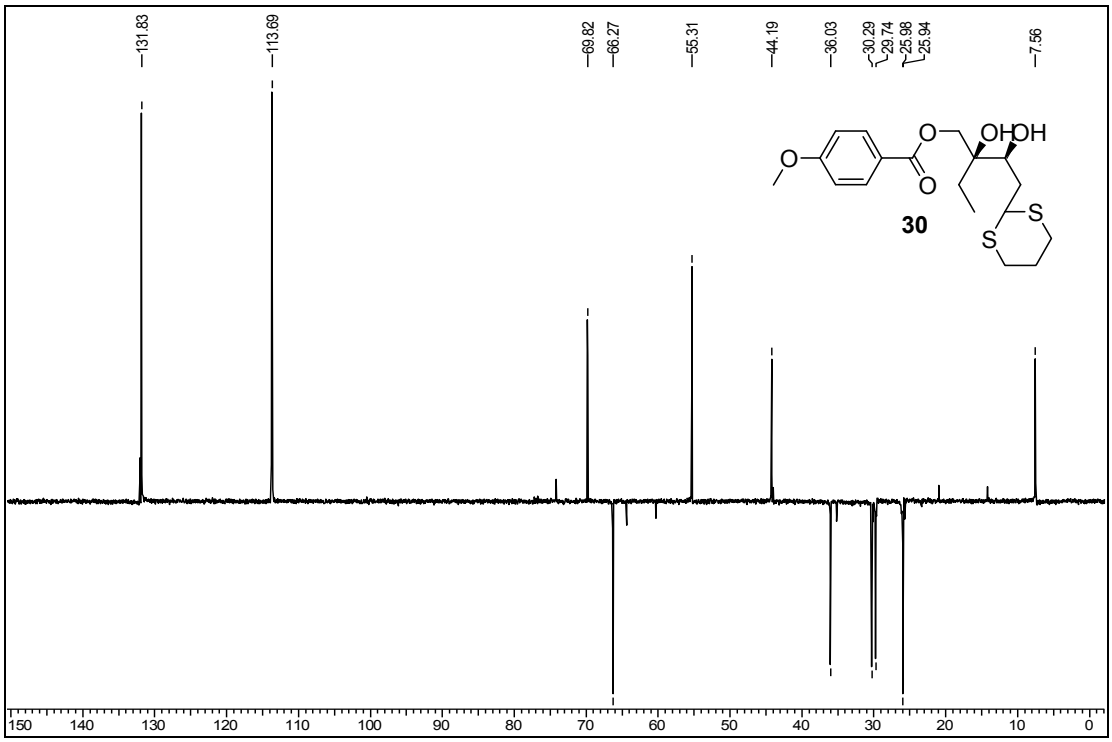


No.	RT	Area	Conc 1	BC
1	26.06	122065	2.428	BB
2	39.77	4645468	92.385	BB
3	45.79	260825	5.187	BB
		5028358	100.000	

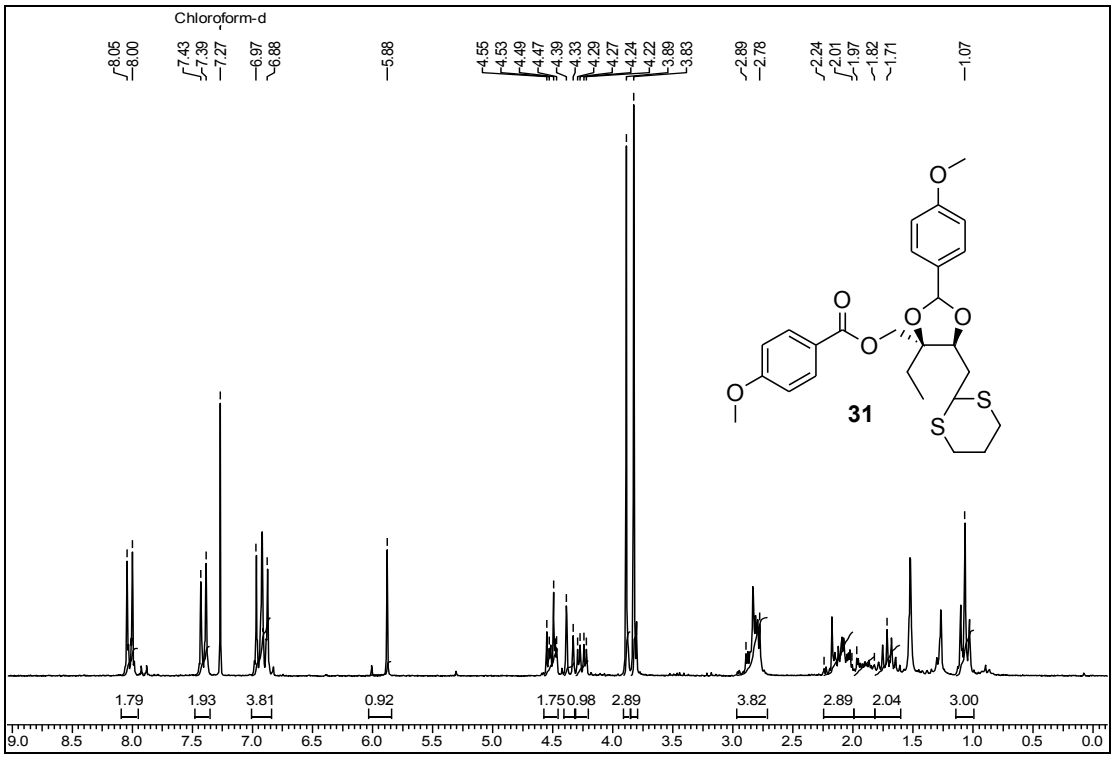
Chiral HPLC analysis of compound 30 (Optically active)



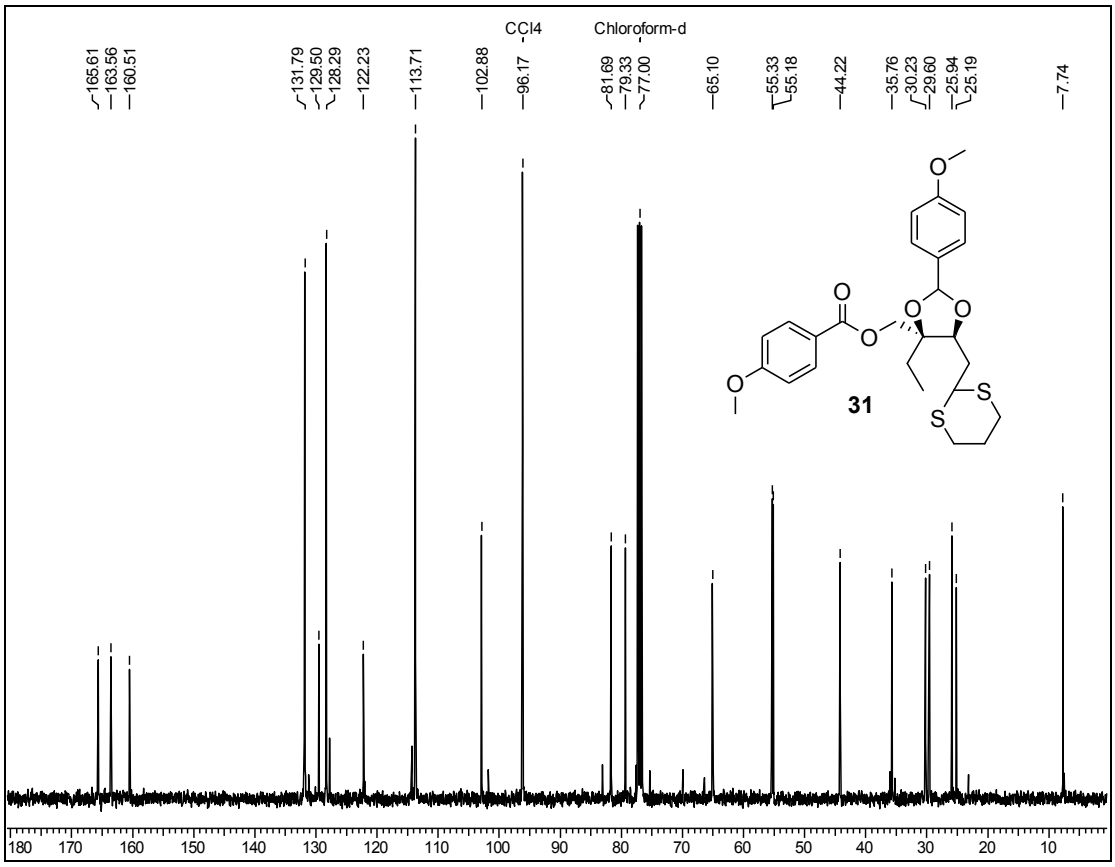
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 30



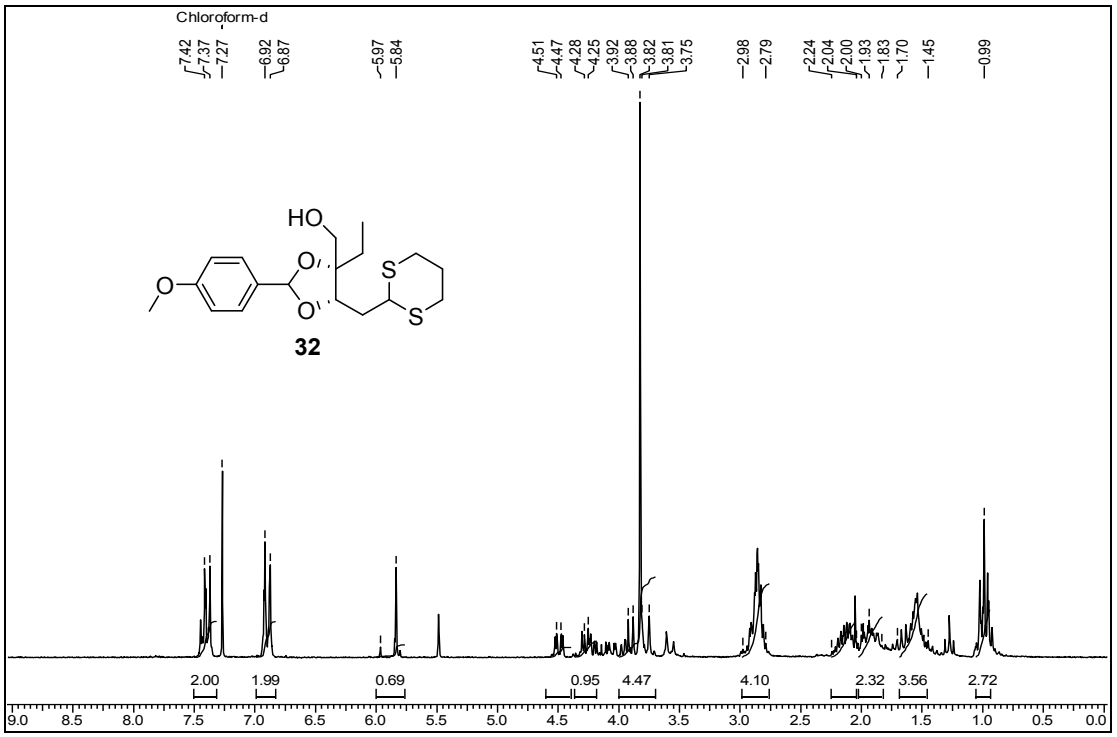
DEPT ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 30



^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 31

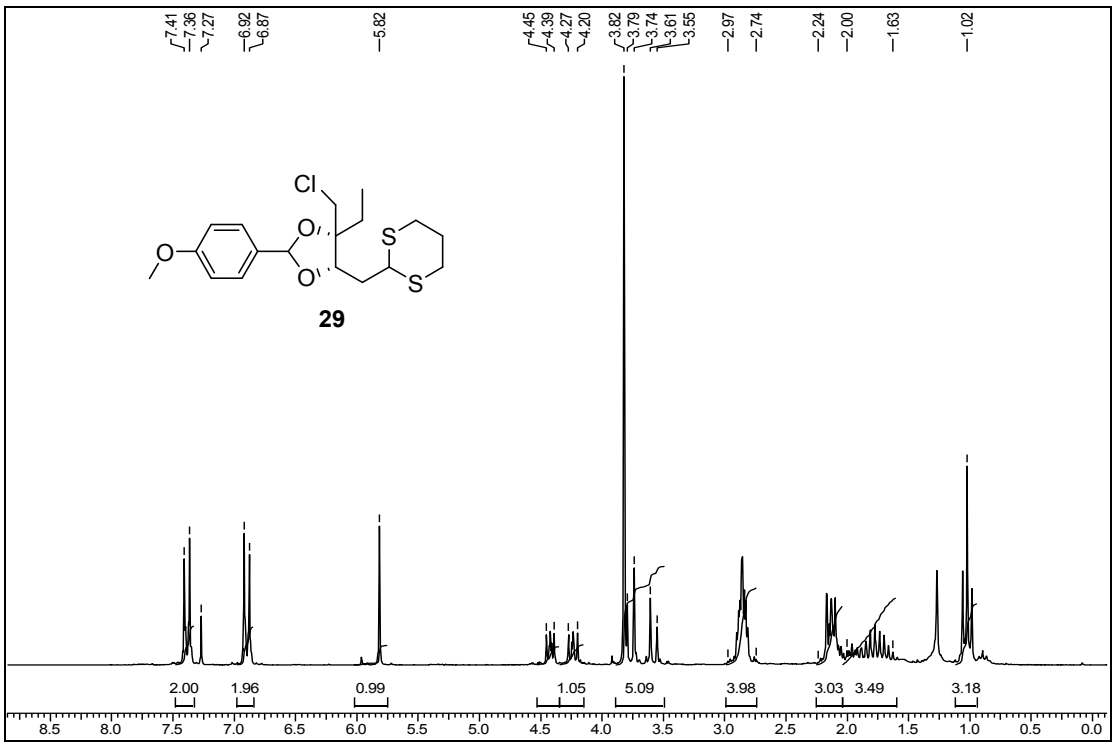


^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 31



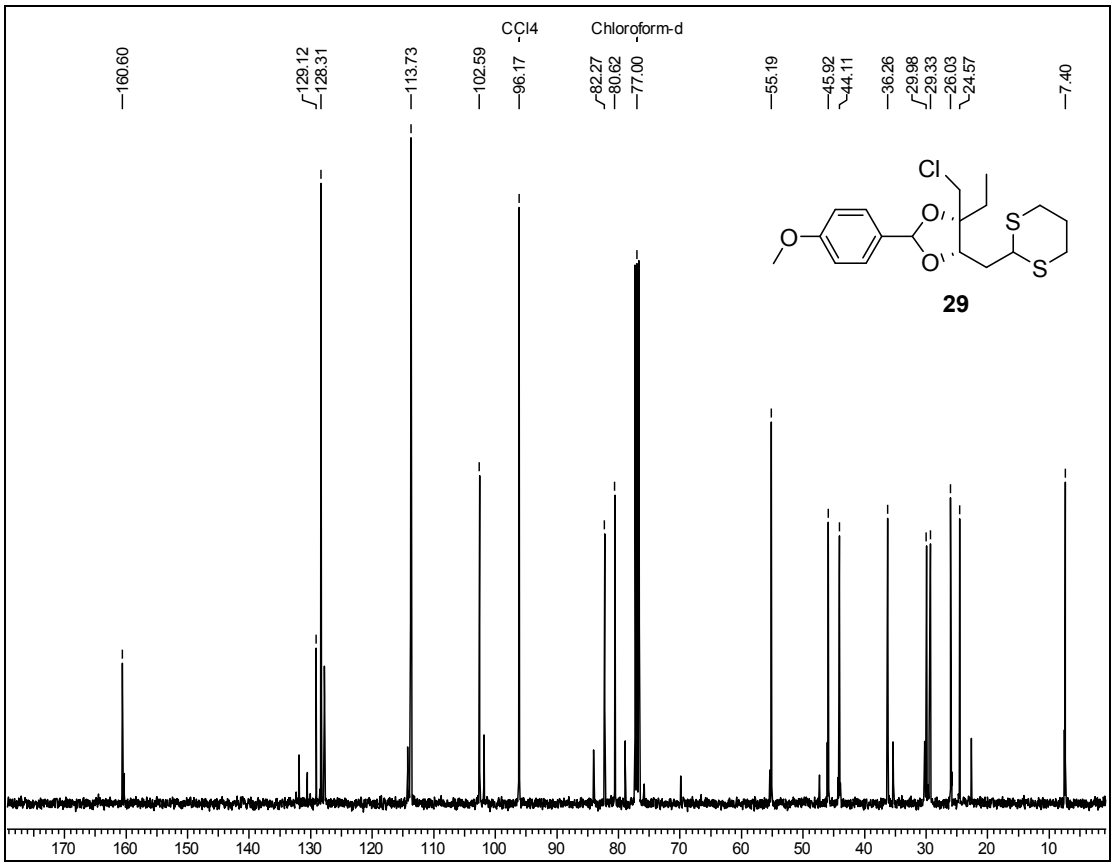
32

^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 32

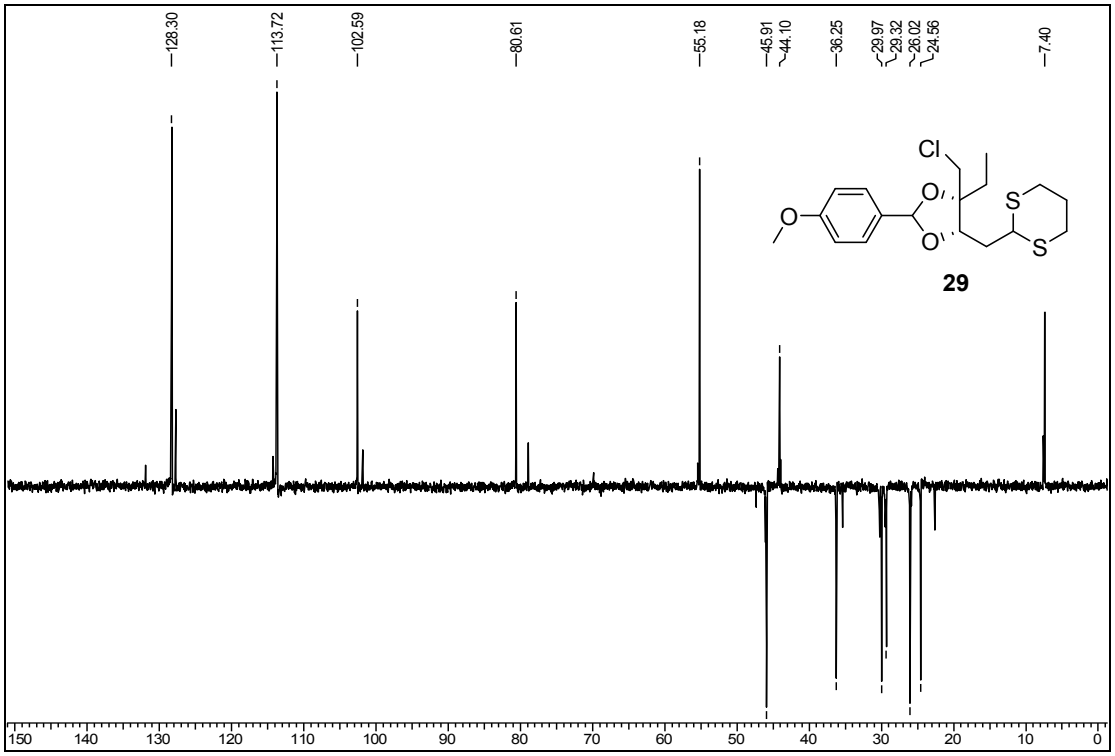


29

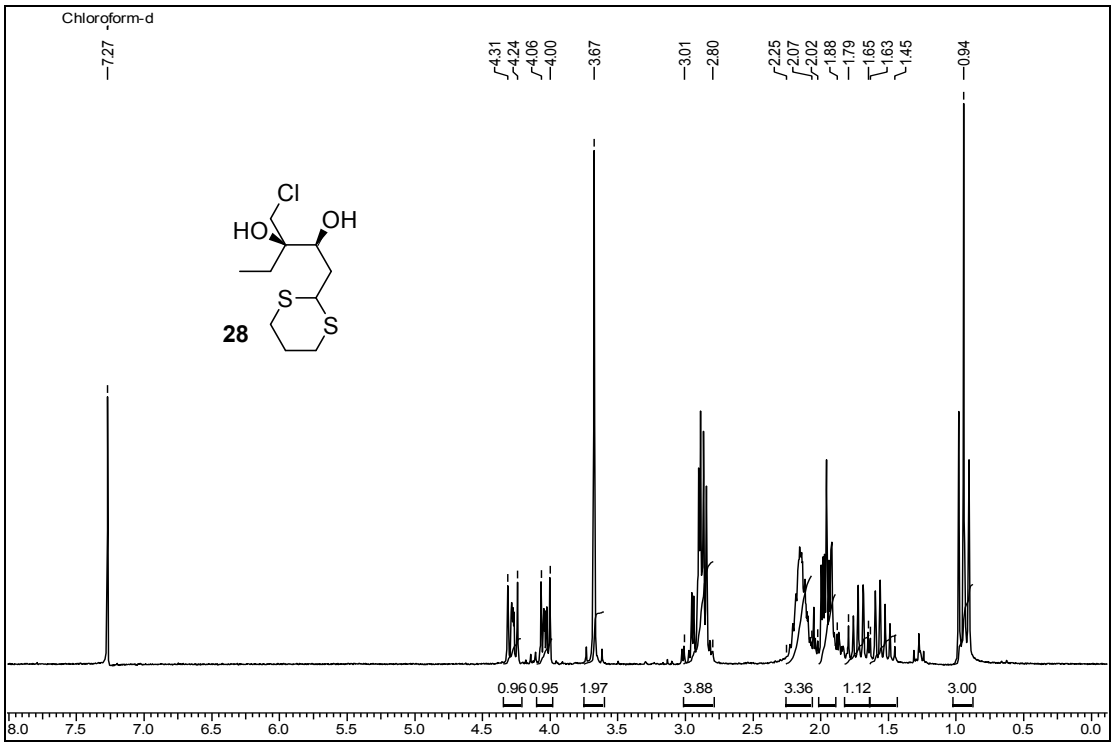
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 29



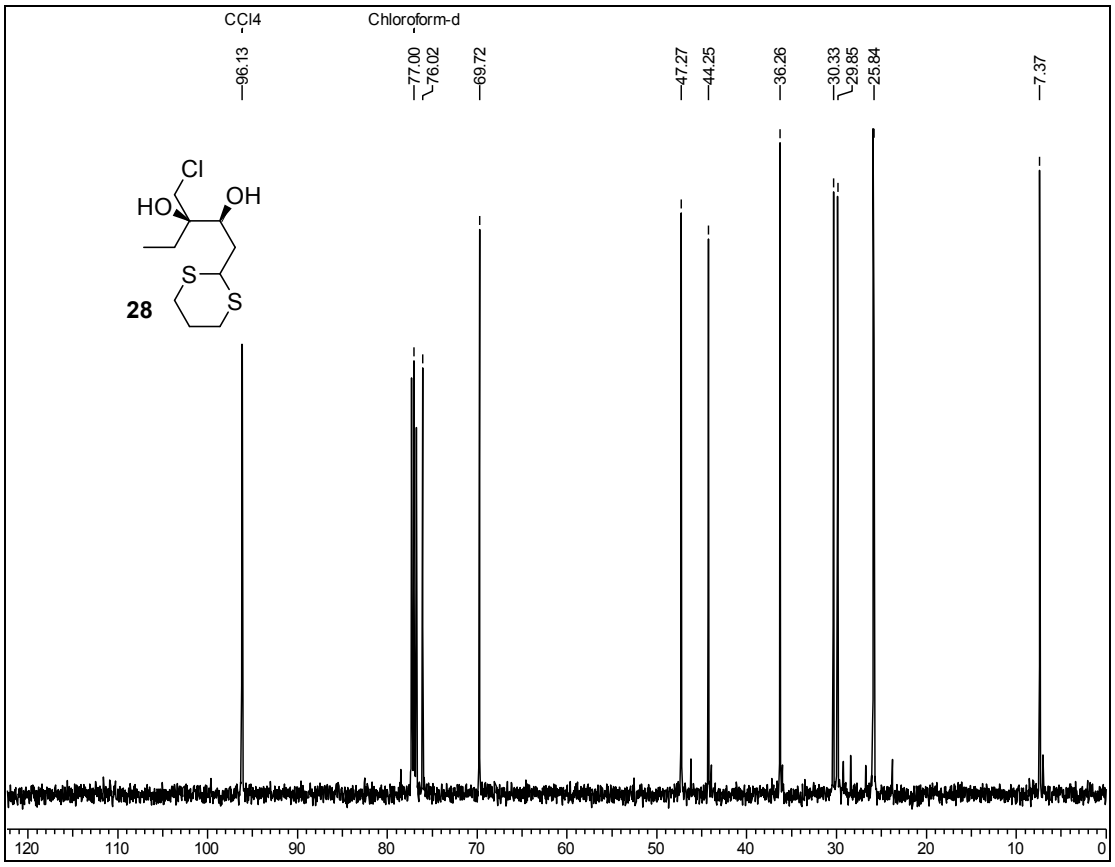
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 29



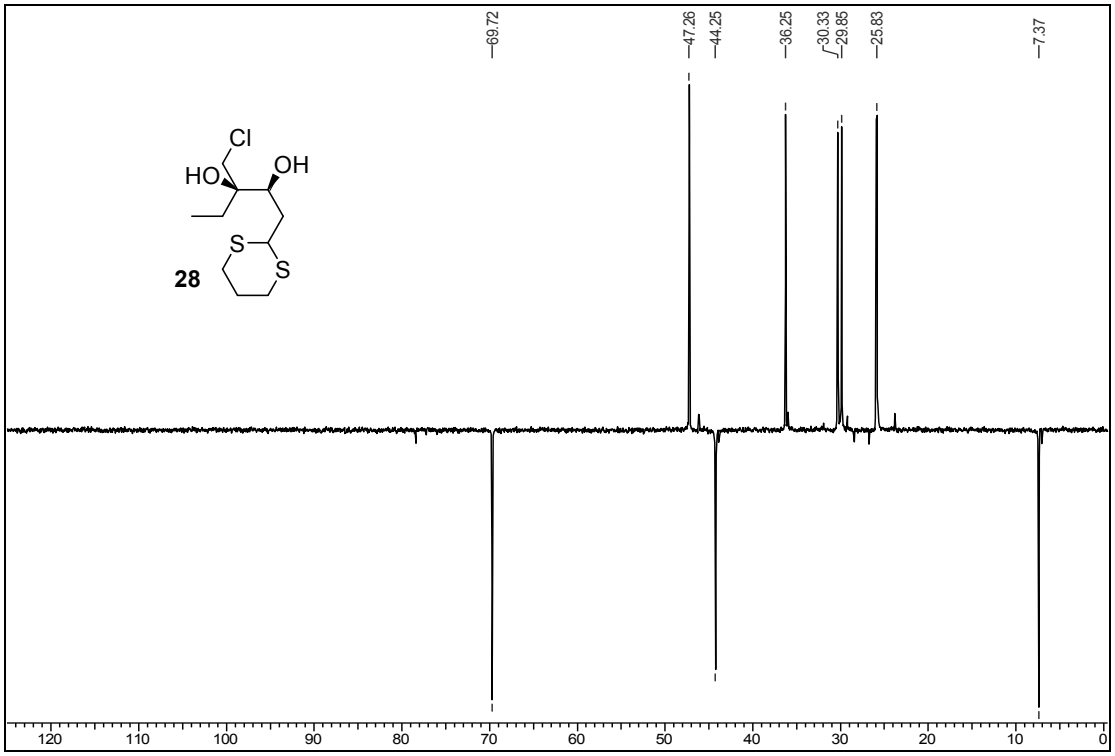
DEPT ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 29



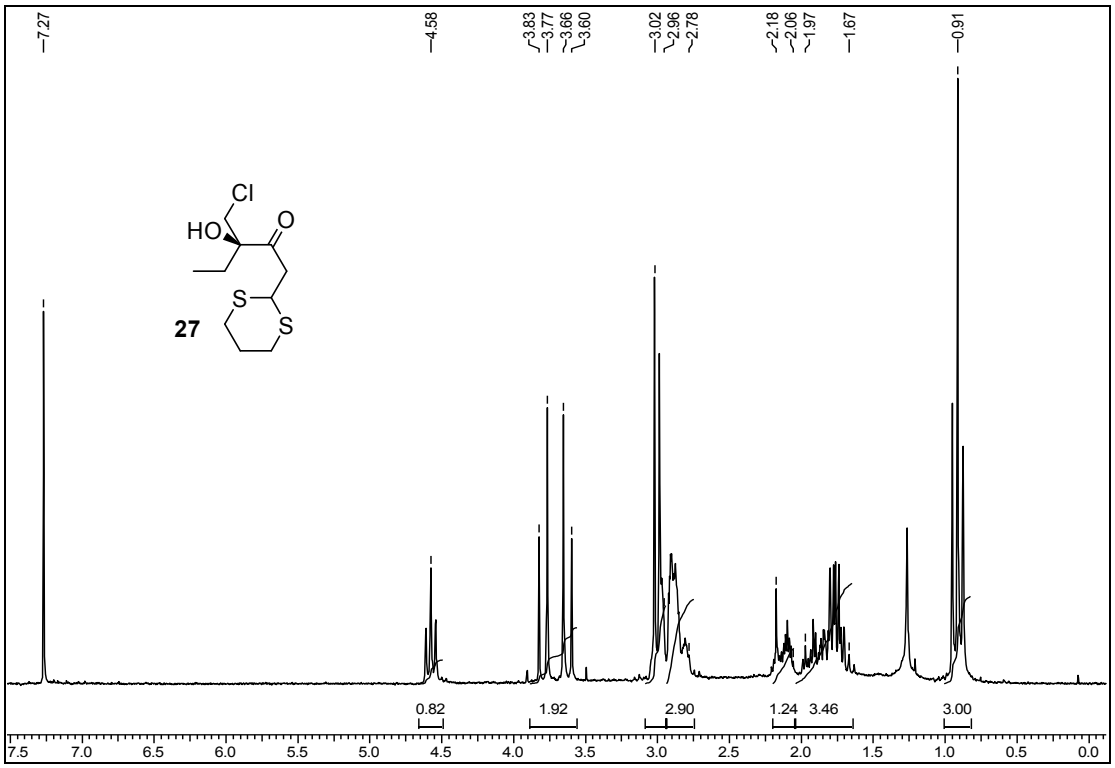
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 28



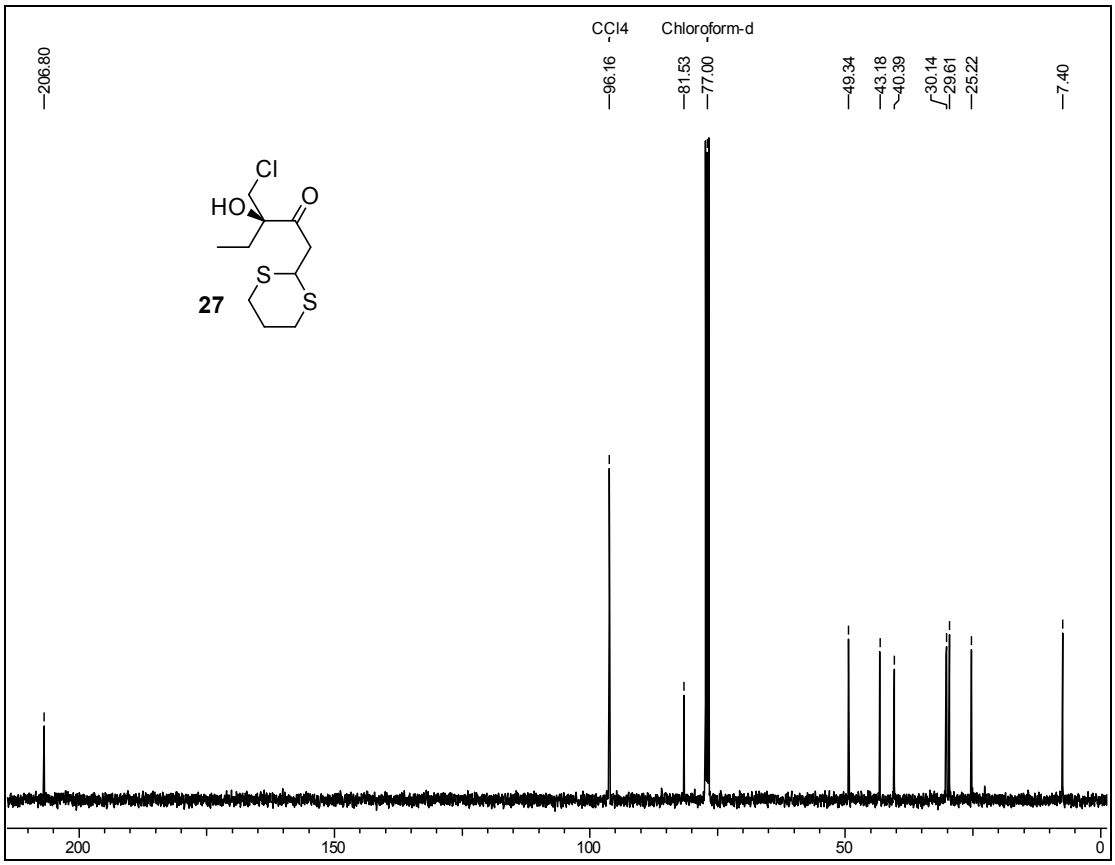
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 28



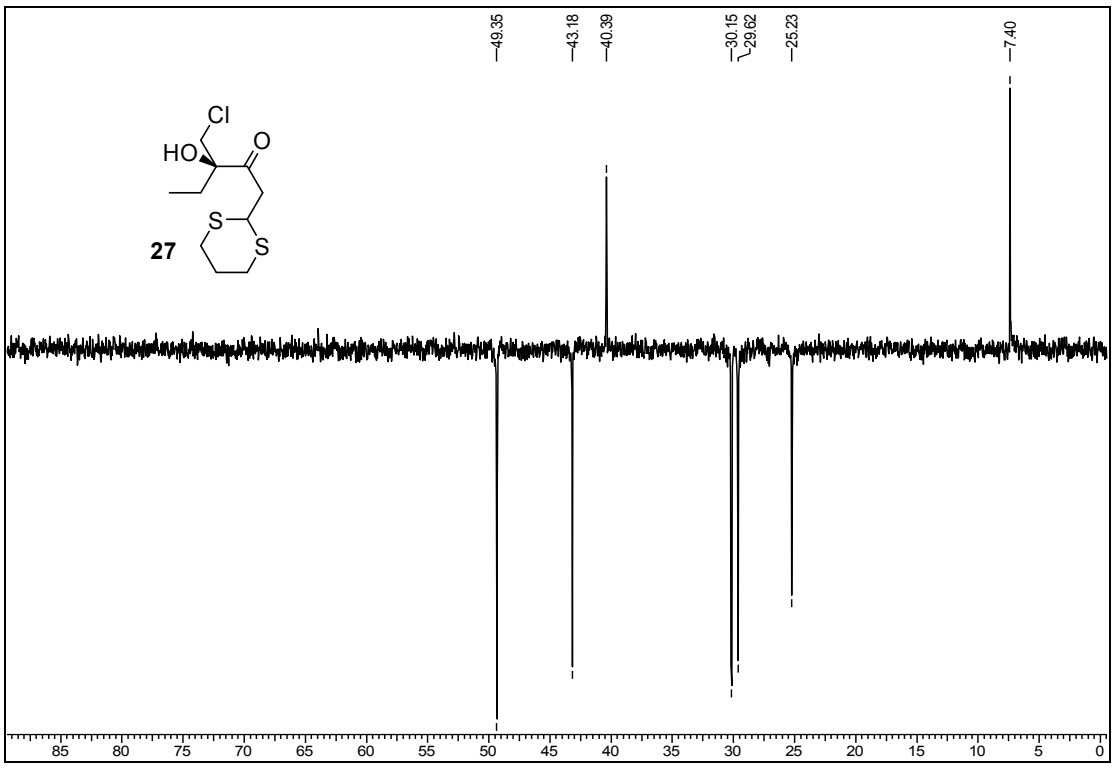
DEPT ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 28



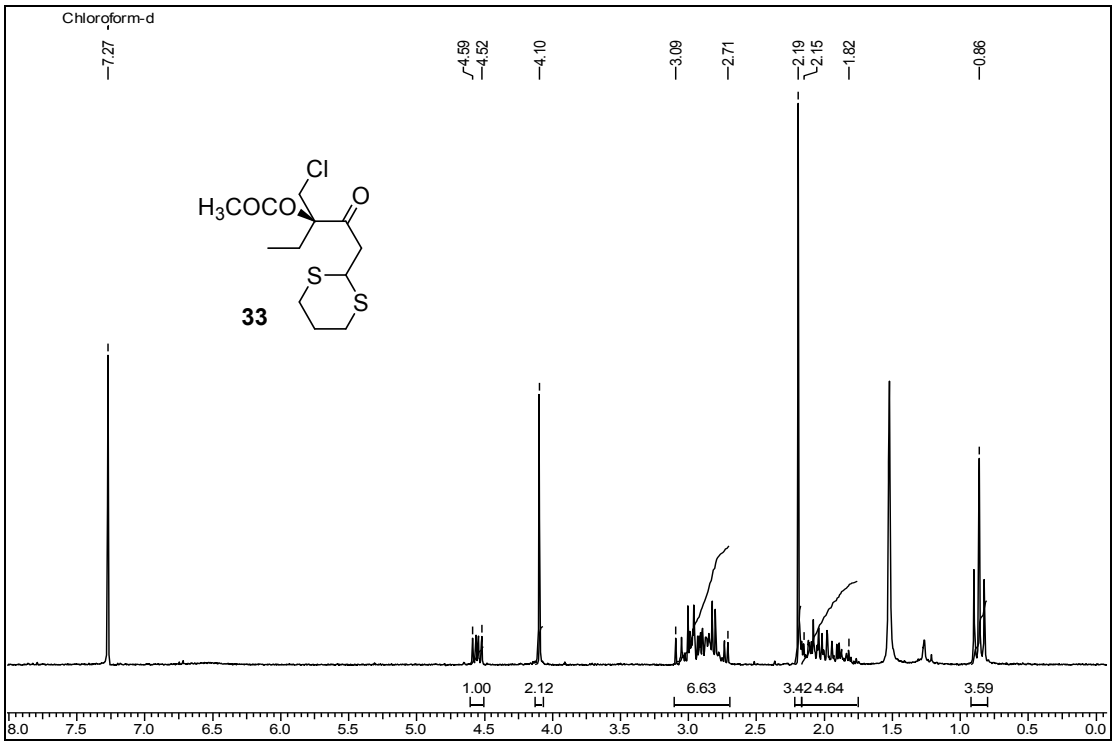
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 27



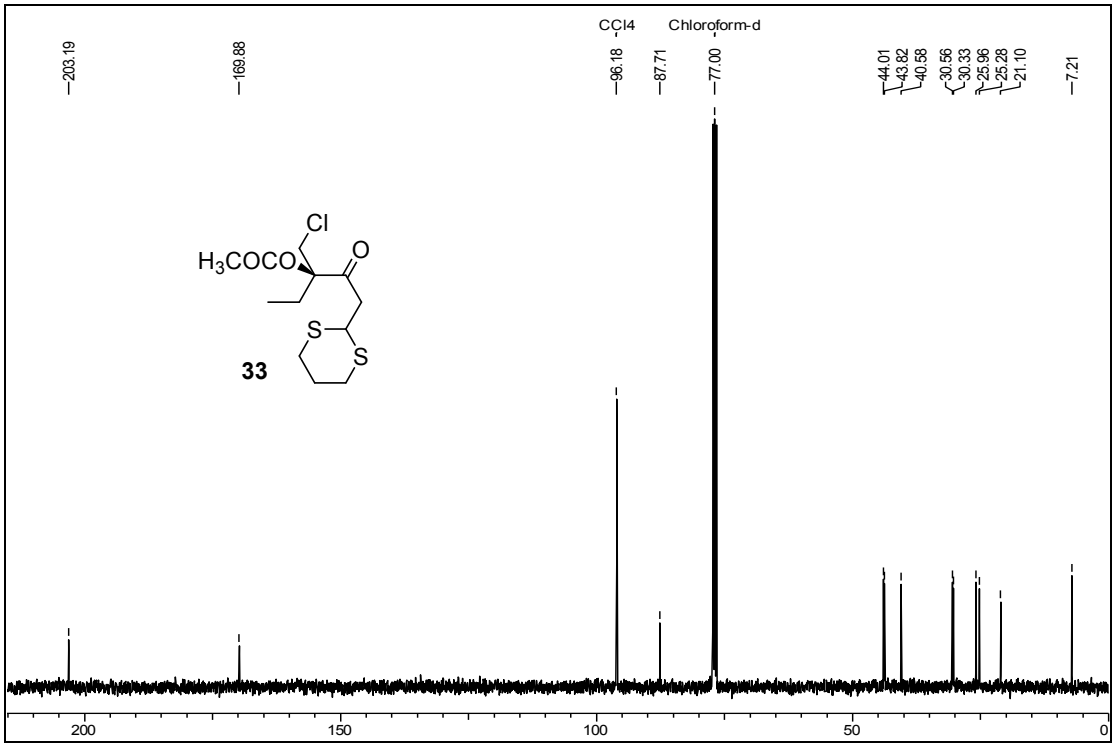
^{13}C NMR ($CDCl_3$+CCl_4, 100 MHz) spectrum of compound 27



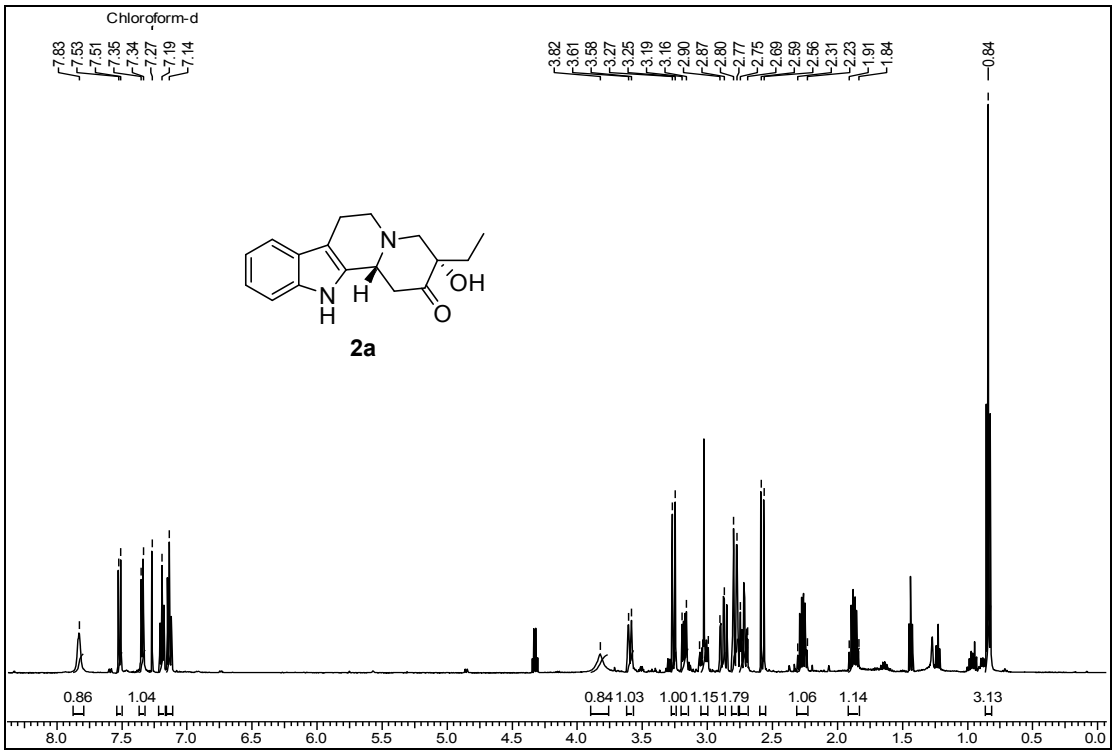
DEPT ($CDCl_3$+CCl_4, 100 MHz) spectrum of compound 27



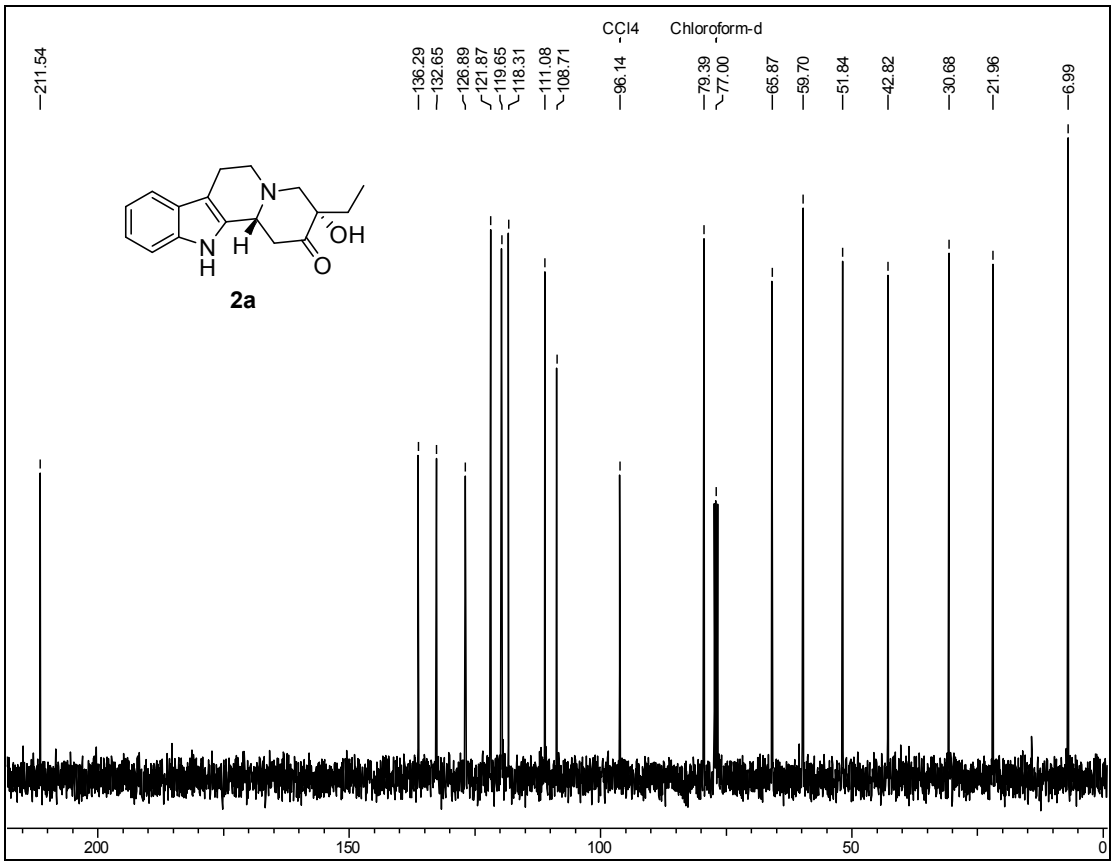
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 33



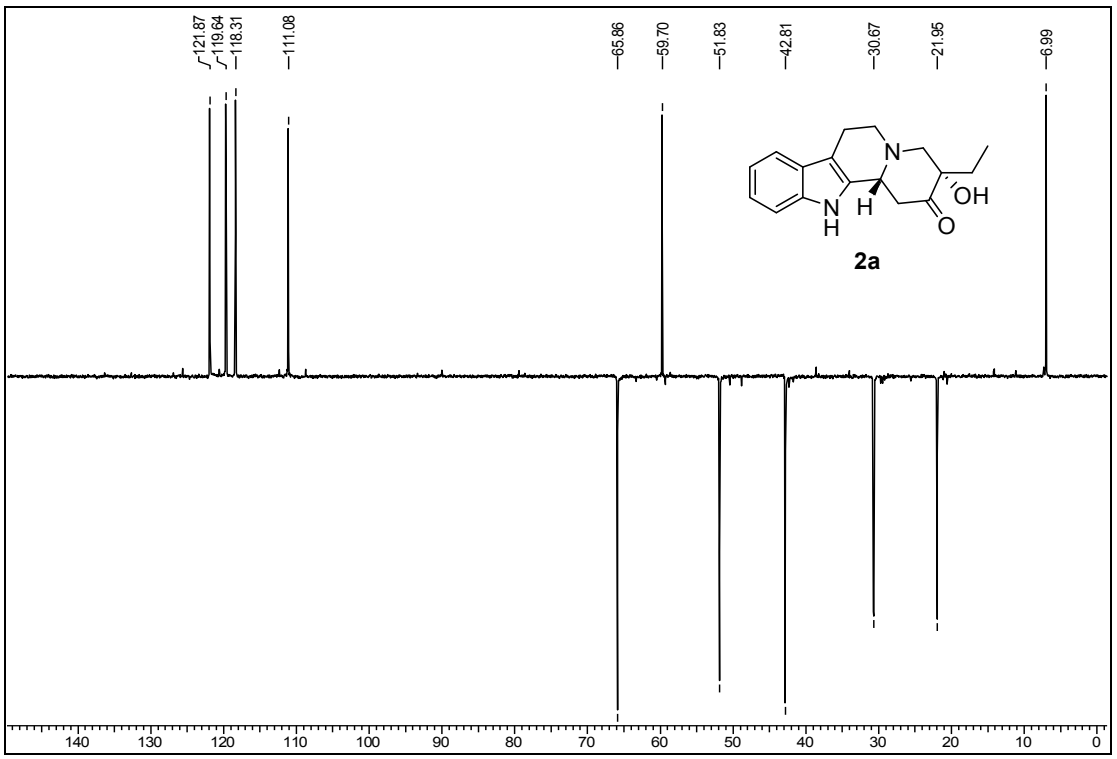
^{13}C NMR ($CDCl_3$+CCl_4, 100 MHz) spectrum of compound 33



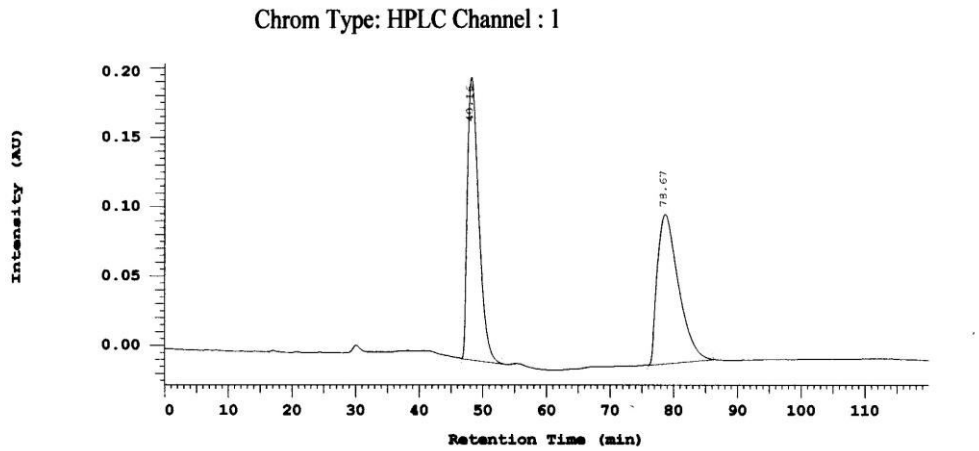
^{1}H NMR ($CDCl_3$+CCl_4, 500 MHz) spectrum of compound 2a



^{13}C NMR ($CDCl_3$+CCl_4, 125 MHz) spectrum of compound 2a

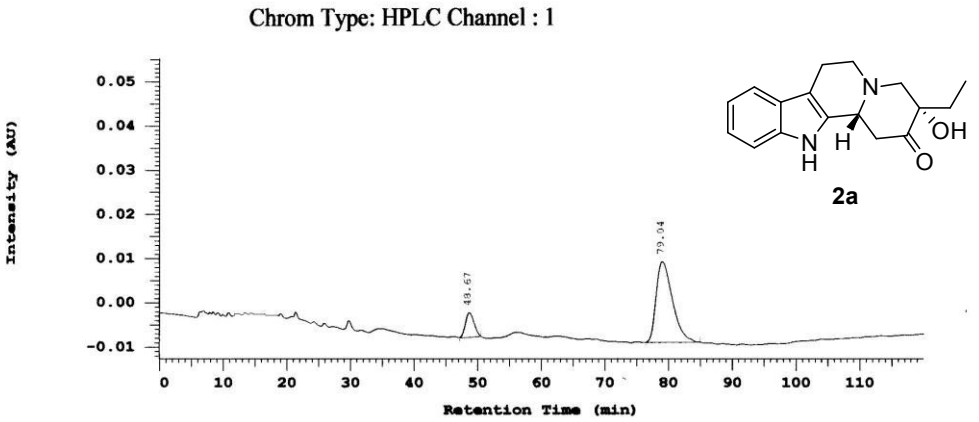


DEPT ($CDCl_3$+CCl_4, 125 MHz) spectrum of compound 2a



No.	RT	Area	Conc 1	BC
1	48.16	12407995	50.194	BB
2	78.67	12312148	49.806	BB
		24720143	100.000	

Chiral HPLC analysis of compound 2a (rac): Column:Chiralcel OJ-H 250 x 4.6mm; Mobile phase: PE:IPA 90:10; Wavelength: 254 nm; Flow rate: 0.5 mL/min



No.	RT	Area	Conc 1	BC
1	48.67	248291	13.455	BB
2	79.04	1597056	86.545	BB
		1845347	100.000	

Chiral HPLC analysis of compound 2a (Optically active)

2.2.5. References

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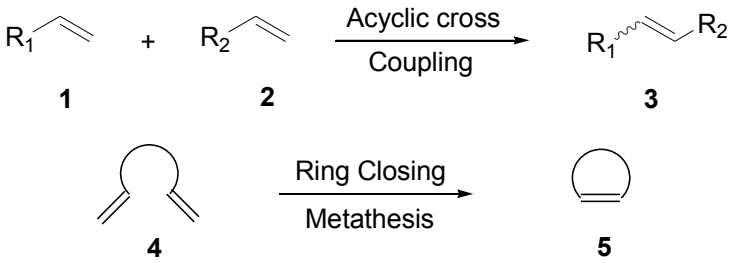
Chapter 3 Section 1

Formal Synthesis of (±)-Mitralactonine: RCM Approach

Section 1

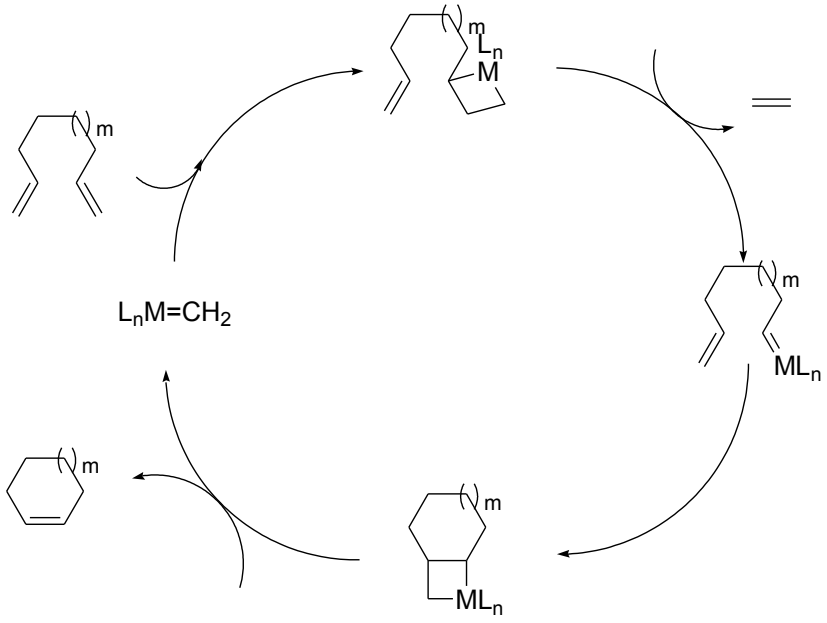
3.1.1. Introduction

Olefin metathesis is one of the most important tool in the hands of the organic chemist for the formation of C-C bond and it is gaining increasing importance due to introduction of new and efficient catalyst that are more air stable, have high functional group compatibility and active thus becoming potentially synthetically more useful.[1] Olefins by which alkylidene groups are exchanged was first reported in 1955 by Anderson and Mercking which involved the use of Ti (IV) metal for polymerization of norbornene.[2] Olefin metathesis is a disproportionation process involving bond formation, bond breakage and reorganisation (Scheme 1).



Scheme 1

The area of ring closing metathesis (RCM) is considered as the most recognised field of olefin metathesis. RCM is one of the most straightforward and reliable methods for the formation of small, medium and large ring system. The general mechanism underlying the reaction is depicted in scheme 2.



Scheme 2

Synthesis of biologically active compounds reached a new height by the introduction of air and moisture stable Mo and Ru based catalyst for RCM by Schrock[3] and Grubbs.[1] With the growing need of biologically active compounds containing *N*-heterocycles, the use of RCM have opened new vistas for the construction of such complex molecules. Grubbs et al. have described the generality of the catalytic RCM reaction for the construction of pyrroline, terahydropyridines and terahydroazapines efficiently.[4]

Some of the commonly used catalysts for olefin metathesis are presented in fig. 1.

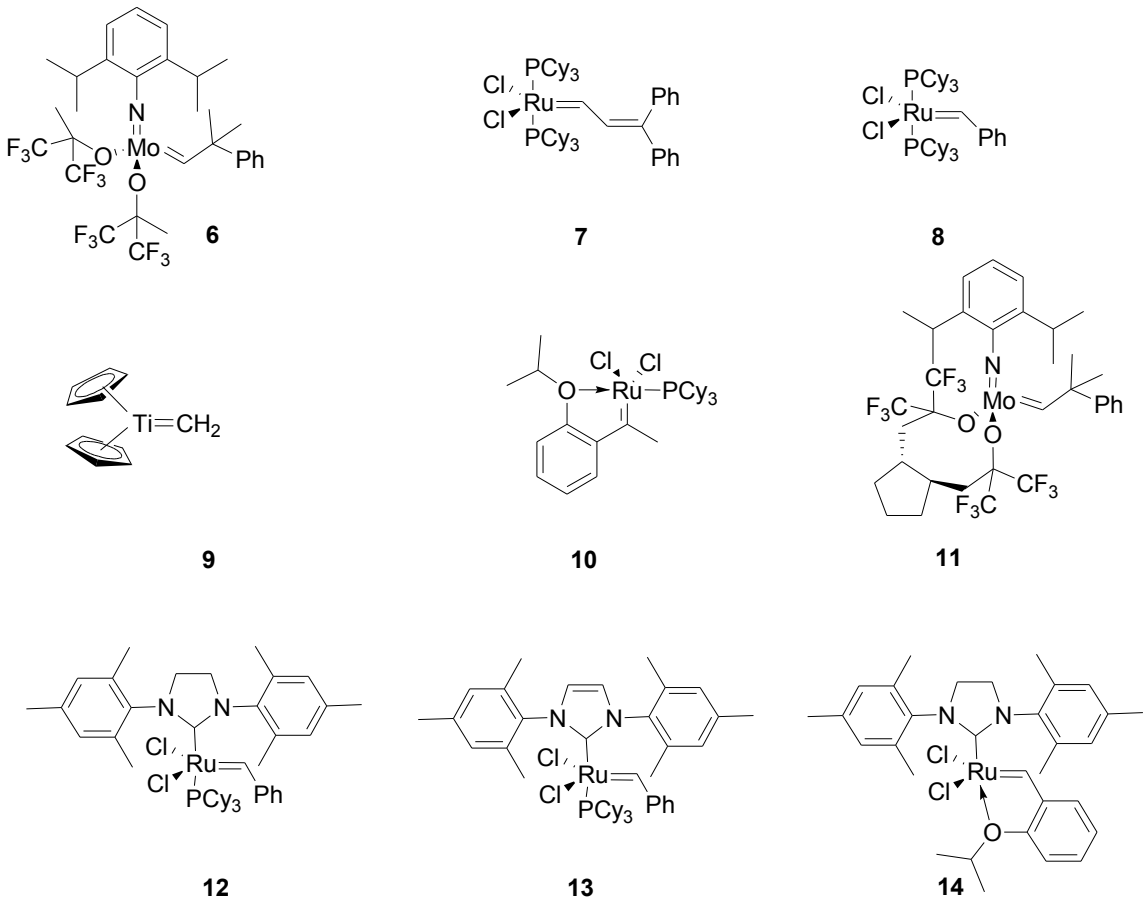
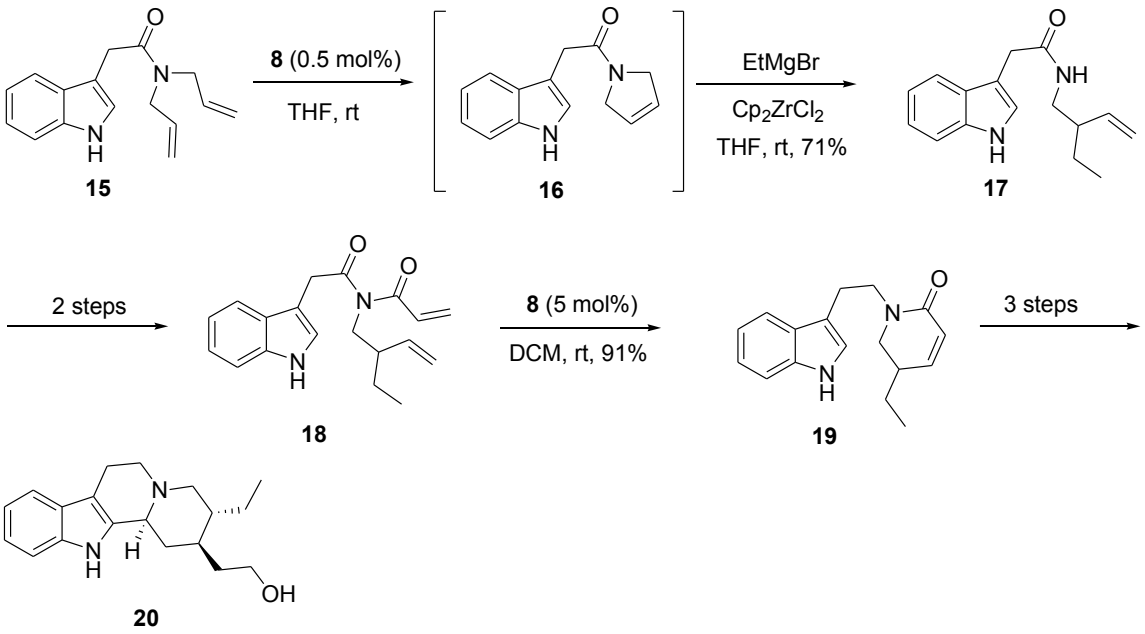


Figure 1

In the area of Corynanthe-type indole alkaloid Martin et al. reported an eight steps sequence involving two RCM reactions for a stereoselective total synthesis of dihydrocorynantheol **20**.[5] The synthesis commenced with the conversion of the diallyl amide **15** into the homoallylic amide **18** by an efficient one-pot procedure that involved the RCM of **15** to furnish an intermediate dihydropyrrole **16** that was subjected *in situ* to a carbomagnesation-elimination reaction. Compound **17** was converted in two steps into the diene **18**, which underwent a RCM reaction upon treatment with Grubbs' catalyst **8** to

deliver the α,β-unsaturated lactam **19**. Subjection of **19** to sequential diastereoselective cuprate addition, Bischler-Napieralski cyclisation, and hydroboration-oxidation then furnished **20**.

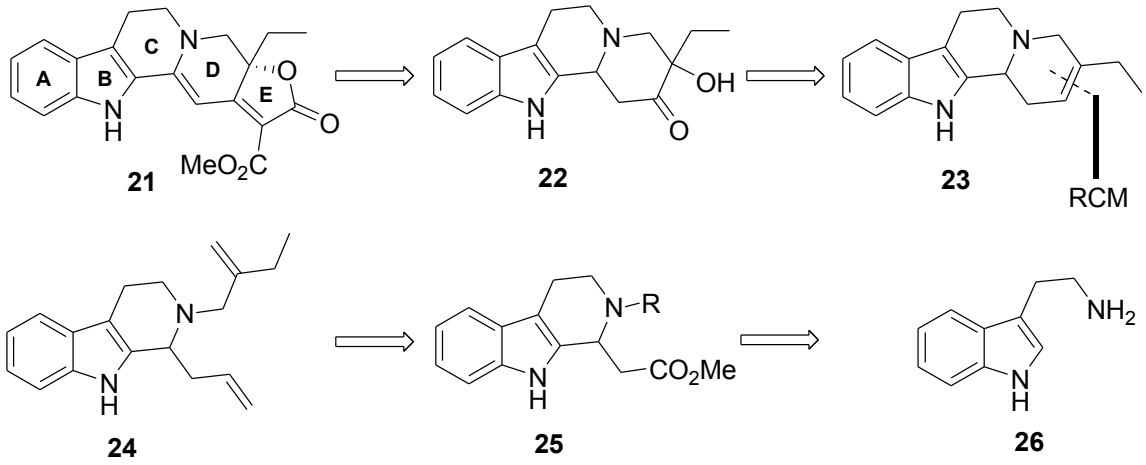


Scheme 3

3.1.2. Present Work

After successfully accomplishing the synthesis of the indole alkaloid, mitralactonine,[6] in both racemic as well as optically active form employing a Pictet-Spengler cylisation-alkylation strategy, the possibility and feasibility of a linear approach utilising tryptamine as the starting material was investigated. The present approach was based on the β-carboline chemistry[7] and D-ring construction employing ring-closing metathesis.[1]

As delineated in retrosynthetic analysis (Scheme 4) the tetracyclic alkene **23** was envisioned as the masked precursor to the functionalised key intermediate **22** which could be further elaborated to the target molecule **21**. The tetracyclic compound **23** can be realised by ring-closing of appropriately substituted β-carboline **24** which in turn could be easily accessed from tryptamine **26**.

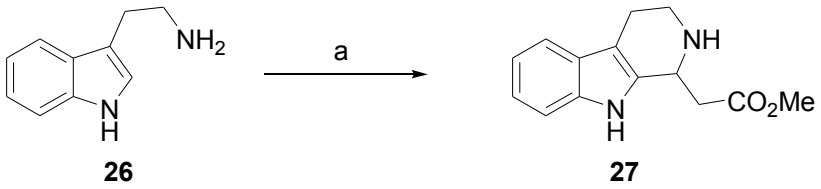


Scheme 4: *Retrosynthetic Analysis*

3.1.3. Results and Discussion

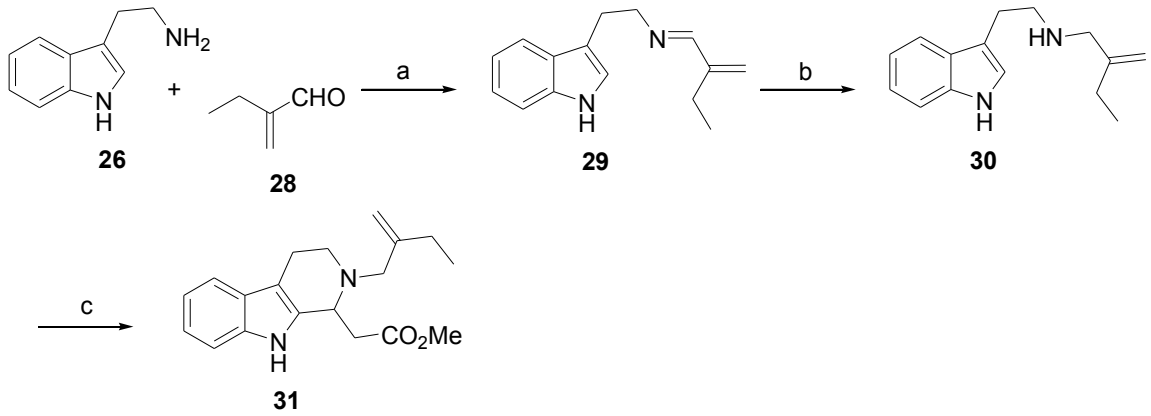
As evident from the retrosynthesis the first and the foremost task in the hand was to synthesis the dialkene compound **24** starting from tryptamine (**26**). Pictet-Spengler cyclisation of tryptamine with an aldehye equivalent was successfully exploited in the previous chapter to deliver the tetracyclic intermediate in single step. In this section the other variant of the versatile reaction was investigated. Massiot et al.[8] demonstrated the successful condensation of protected tryptamines with suitable alkynes in presence of TFA to furnish the cyclised product in very good yield. Though Massiot described the reaction with *N*-benzyl protected tryptamine analogous reaction was defined by Bailey et al.[9] on tryptamine itself.

Hence going by Bailey's methodology it was proposed to prepare the β-carboline unit first by reacting tryptamine with methyl propiolate followed by alkylation with proper substrate.



Scheme 5: Reagents and conditions: *a) methyl propiolate, TFA, $CHCl_3$, rt, 12 h, 10-15%.*

However, the β-carboline compound **27** was obtained in very poor yield even after repeated trials (Scheme 5). Hence it was decided to alkylate the tryptamine first followed by condensation with the propiolate unit. Accordingly the tryptamine (**26**) was subjected to react with ethyl acrolein (**28**) in toluene and the resulting imine **29** was in situ reduced by the action of $NaBH_4$ to furnish **30**. Pictet-Spengler condensation was carried out by reacting the synthesised compound **30** with methyl propiolate in presence of TFA. Though the product **31** was realised the yield was very discouraging in all the three steps (Scheme 6).

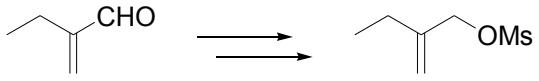


26 **28** **29** **30** **31**

Scheme 6: Reagents and conditions: *a) toluene, rt, 12 h; b) $NaBH_4$, MeOH, 0 °C, 0.5 h; c) methyl propiolate, TFA, $CHCl_3$, 0 °C-rt, 1 h.*

Failing to alkylate the tryptamine in good yields remedy was found in alkylating the corresponding *N*-Boc protected tryptamine **34**. The Boc protection was realised efficiently by subjecting the tryptamine to react with $(Boc)_2O$ in presence of K_2CO_3 as the base.

As the retrosynthetic analysis describes the nitrogen atom of tryptamine derivative is to be alkylated with an exomethylene fragment which was envisioned to be obtained from 2-ethyl acrolien (**28**) with selective conversion of aldehydic group into alcohol without effecting the double bond and converting alcohol into a proper leaving group such as mesylate, tosylate or halide as shown on the Scheme 7.

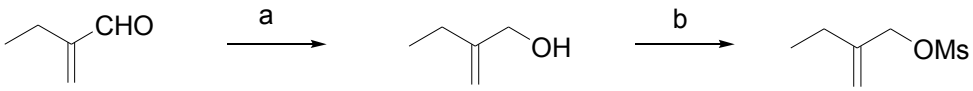


28 **32**

Scheme 7

Thus reduction of the aldehyde was realised selectively with $NaBH_4$ in methanolic $CeCl_3.7H_2O$[10] to furnish the corresponding allylic alcohol **33** in 76% yield. The formation of the product was confirmed by its spectral studies. IR spectrum showed a strong absorption at 3370 cm^{-1} signifying the presence of the hydroxy group. ^1H NMR spectrum revealed absence of aldehydic peak as well as appearance of a singlet at δ 4.04 integrating for two protons ascribed to the –C$\underline{H_2}$OH proton. Apart from this the spectrum revealed peaks corresponding to the exomethylene protons at δ 4.97 and δ 4.83 thereby confirming the selective reduction of aldehydic group only whereas the alkene functionality remained intact. ^{13}C NMR spectrum along with the DEPT spectrum showed the absence of the aldehydic carbon peak and presence of two methylene carbons at δ 65.4 and δ 25.5 corresponding to –$\underline{C}H_2OH$ and –$\underline{C}H_2CH_3$ whereas the exomethylene carbon peak appeared at δ 107.8.

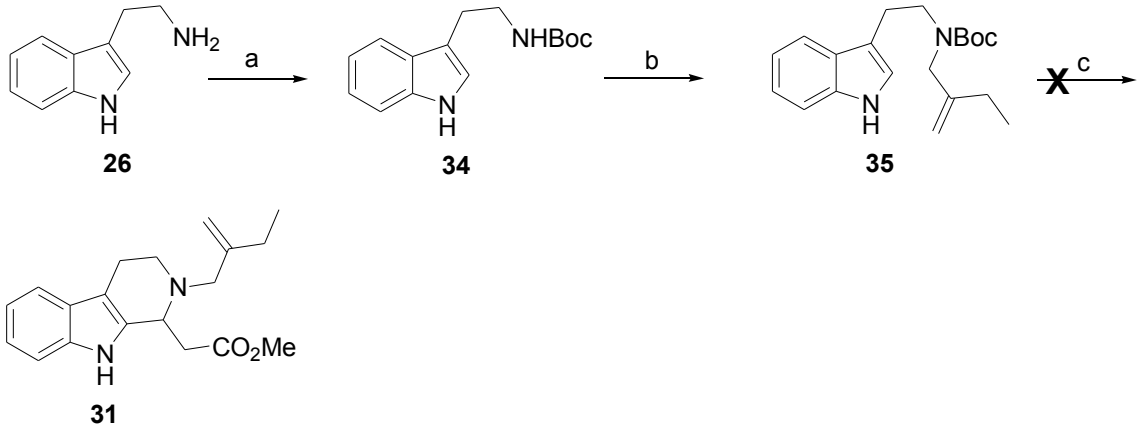
The hydroxy group was easily functionalised into corresponding mesylate **32** by exposing the substrate to methanesulfonyl chloride in presence of triethylamine at 0 °C.[11] There was no formation of corresponding chloro compound as revealed by the spectral and analytical studies. The IR spectrum showed no peak in the region 3500 to 3000 cm^{-1} justifying the absence of hydroxy group. ^1H NMR spectrum showed appearance of a singlet at δ 3.00 integrating for three protons corresponding to the methyl of the methanesulfonyl group. The –C$\underline{H_2}$ protons moved down field to δ 4.65.



28 **33** **32**

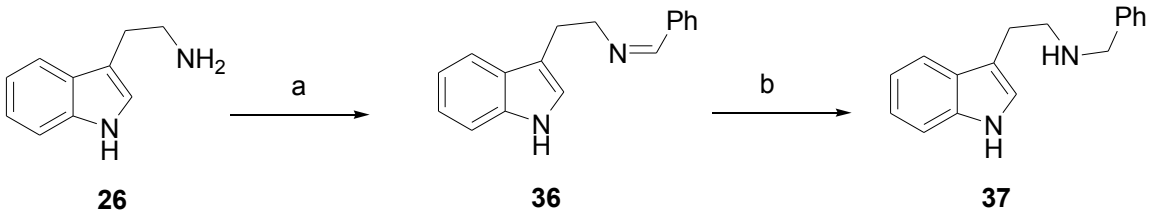
Scheme 8: Reagents and conditions: *a) $NaBH_4$, $CeCl_3.7H_2O$ (MeOH), 0 °C, 76%; b) methanesulfonyl chloride, Et_3N, 0 °C, 70%.*

The alkylation of the Boc protected tryptamine **34** was carried out in the presence of K_2CO_3 in DCM. The alkylated product **35** was obtained in good yield but all the efforts to construct the β-carboline unit **31** by reacting with methyl propiolate met with failure (Scheme 9).



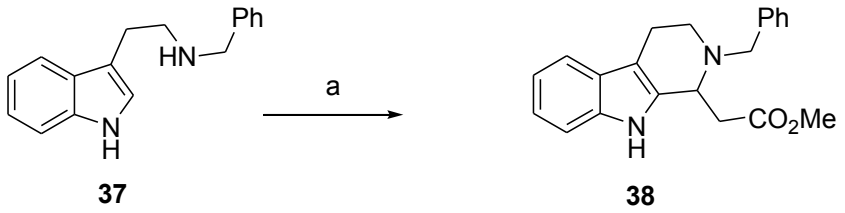
Scheme 9: Reagents and conditions: *a) $(Boc)_2O$, K_2CO_3, DCM, rt, 3 h, 85%; b) $CH_3CH_2C(=CH_2)CH_2OMs$, NaH, THF, rt, 2 h, 86%; c) methyl propiolate, TFA, $CHCl_3$, 0 ^oC-rt, 12 h.*

Being unsuccessful in constructing the β-carboline unit with proper functionality through any of the above routes in good yield and ease, attention was focused towards the formation of β-carboline as per Massiot[8] protocol from the corresponding *N*-benzyl tryptamine followed by removal of benzyl group and alkylation. Treatment of tryptamine with benzaldehyde taken in toluene furnished the imine **36** which without further purification was subjected to reduction with $NaBH_4$ to deliver the *N*-benzyl protected tryptamine **37** and was carried forward as such (Scheme 10).



Scheme 10: Reagents and conditions: *a) benzaldehyde, toluene, rt, 12 h; b) $NaBH_4$, MeOH, 0 ^oC-rt, 1 h, 94% (2 steps).*

Thus when the *N*-benzyl tryptamine **37** was subjected to react with methyl propiolate in chloroform in presence of excess of trifluroacetic acid followed by an alkaline work up furnished the cyclised product **38** in 94% yield after purification (Scheme 11).



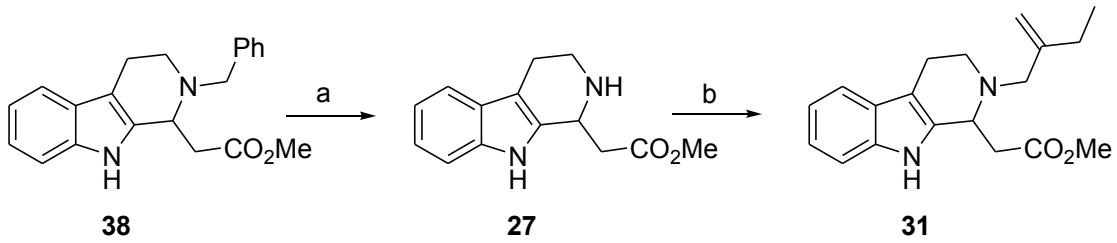
37 **38**

Scheme 11: Reagents and conditions: *a) methyl propiolate, TFA, chloroform, rt, 1 h, 94%.*

IR spectrum showed a strong absorption at 1730 cm^{-1} thereby signifying the presence of ester carbonyl. ^{1}H NMR spectrum showed the presence of the benzyl protons appearing as a singlet at δ 3.86 integrating for two protons. The –C*H* proton next to indole nucleus appeared as a broad doublet at δ 4.27 integrating for one proton whereas the –OMe protons appeared as a singlet at δ 3.71. ^{13}C NMR spectrum alongwith DEPT showed the presence of four methylene carbons resonating at δ 57.4, 44.5, 40.1 and 17.7 in accordance with the transformation. It was further confirmed by elemental analysis.

Exposing the β-carboline **38** to H_2 atmosphere under 60 psi pressure in presence of Pd/C as the catalyst rendered the pure debenzylated compound **27** in quantitative yield.

IR spectrum showed absorption at 3402 cm^{-1} signifying the presence of free amine functionality. Other peaks appeared at 1725 cm^{-1} and 1610 cm^{-1}. The ^{1}H NMR spectrum revealed the absence of benzyl protons peak at δ 3.86 and aromatic proton peaks corresponding to the phenyl group whereas rest of the proton peaks appeared at the expected position. The ^{13}C NMR spectrum alongwith the DEPT spectrum showed the disappearance of the benzyl carbon and aromatic carbon peaks associated with the phenyl ring. A peak at *m/z* 245.4 in the mass (ESI) analysis and elemental analysis further confirmed the deprotection.

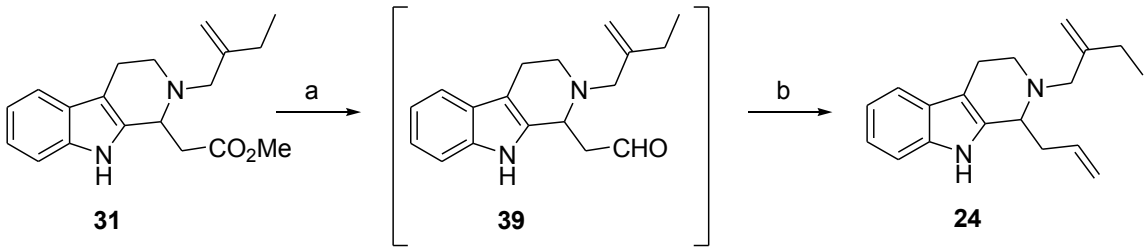


38 **27** **31**

Scheme 12: Reagents and conditions: *a) H_2, 60 psi, Pd/C, rt, 10 h, quantitative; b) $CH_3CH_2C(=CH_2)CH_2OMs$ (**32**), K_2CO_3, DCM, rt, 12 h, 70%.*

Alkylation was easily realised by mixing equimolar quantity of the compound **32** and the deprotected β-carboline compound **27** in dry DCM in presence of K_2CO_3 rendering the product **31** in 70% yield after column chromatographic (SiO_2) purification. IR spectrum showed absorption at 1723 cm^{-1}. ^1H NMR spectrum showed peaks at δ 4.90 appearing as broad doublet integrating for two protons corresponding to the exomethylene protons. The peak at δ 2.12 and δ 1.06 appearing as multiplet and triplet and integrating for two and three protons respectively corresponds to the -C$\underline{H}_2$ and -C$\underline{H}_3$ group. ^{13}C NMR spectrum alongwith DEPT spectrum showed appearance of the exomethylene carbon at δ 111.1, whereas the rest of the five methylene carbons appeared at δ 58.6, 44.3, 39.9, 26.6 and 17.6 in line with the said condensation.

After successful alkylation, the other handle of the substrate **24** was surmised through DIBAL-H reduction of the ester into aldehyde and one carbon Wittig olefination. Treating the compound **31** with DIBAL-H at –78 °C and quenching at the same temperature furnished the aldehyde **39,** which was put forward for next step without further purification. The crude aldehyde **39** was treated with $Ph_3P{=}CH_2$ which in turn was generated by action of *n*-BuLi on the corresponding salt $PPh_3^+I^-CH_3$ at 0 °C. The product **24** was isolated in 60% yield after column chromatograpy (SiO_2) over two steps.



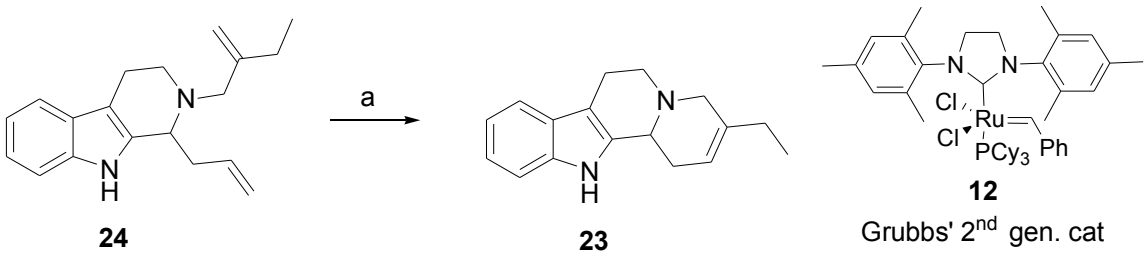
31 **39** **24**

Scheme 13: Reagents and conditions: *a) DIBAL-H, DCM, -78 °C, 1 h, (crude); b) $Ph_3P{=}CH_2$, THF, rt, 12 h, 60% (two steps).*

No absorption in the region 1750-1700 cm^{-1} in the IR spectrum confirmed the absence of ester functionality. ^1H NMR spectrum showed presence of multiplet at δ 5.96 integrating for one proton was assigned to the one of the exomethylene proton whereas the rest of the three protons appeared as a set of two multiplets at δ 5.15 and δ 4.91 integrating for one and two protons respectively. ^{13}C NMR spectrum alongwith DEPT spectrum showed the presence of two exomethylene carbons thereby confirming the transformation.

Disappearance of the ester carbonyl carbon peak from ^{13}C NMR spectrum signified the absence of ester group.

The crucial ring closing metathesis[1] reaction was achieved successfully on treating the substrate **24** in toluene with Grubbs' 2nd generation catalyst **12** (10 mol%) and heating at 80 °C (Scheme 14). The cyclised product **23** was isolated in 90% yield after column chromatography (SiO_2). The formation of **23** was confirmed by its spectral studies. ^1H NMR spectrum showed the presence of the olefin peak at δ 5.39 and integrating for one proton while all other peaks associated with the exomethylene part vanished. ^{13}C NMR spectrum alongwith DEPT spectrum showed the absence of the exomethylene carbons.



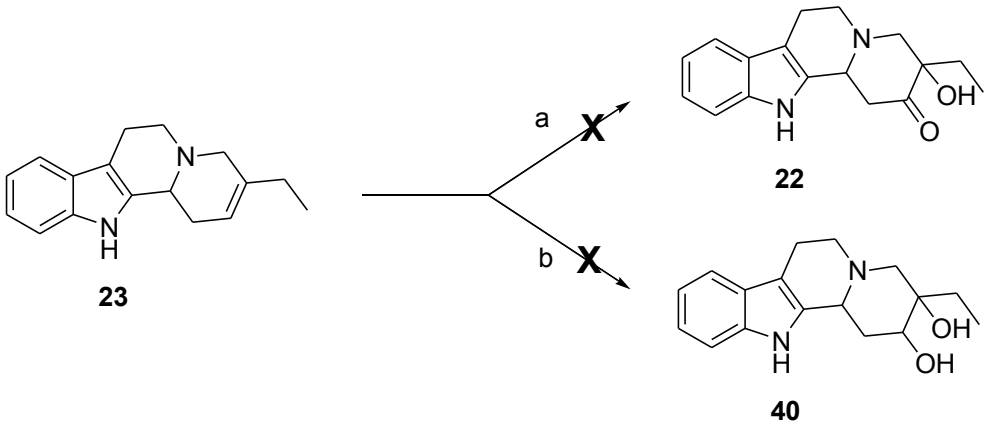
24 **23** **12**

Grubbs' 2nd gen. cat

Scheme 14: Reagents and conditions: *a) 12, toluene, 80 °C, 3 h, 90%.*

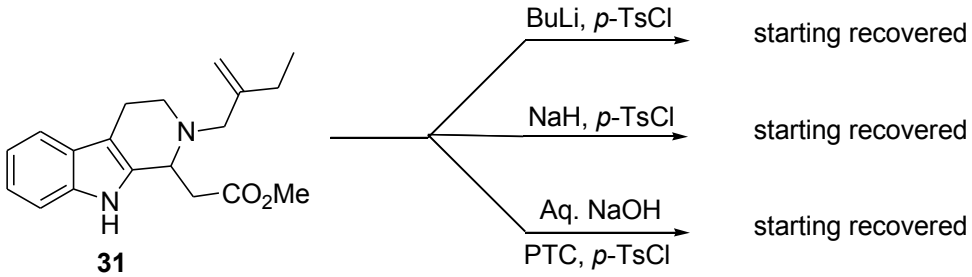
With the tetracyclic unit **23** in hand, an easy and straightforward conversion into corresponding keto-hydroxy compound can be realised by the $KMnO_4$ oxidation of the alkene.[12] Subjecting the substrate **23** to react with $KMnO_4$ in aqueous acetone under acidic condition rendered a product whose ^1H NMR analysis showed that the indole nucleus had undergone ring cleavage. It was concluded that the substrate could not withstand highly oxidising conditions. To circumvent the problem a two-step strategy employing milder condition for oxidation was sought. Use of OsO_4 in catalytic amount under biphasic condition was tried, but the end result was same (Scheme 15).

Due to the ready susceptibility of the substrate towards indole nucleus cleavage under oxidising reagents it was necessary to arrest the nucleophilicity of the indole core hence it was thought appropriate to protect the indole nitrogen as its tosylate. Since the condition of alkylation was already standardised it was thought appropriate to introduce the tosyl group at this stage only.



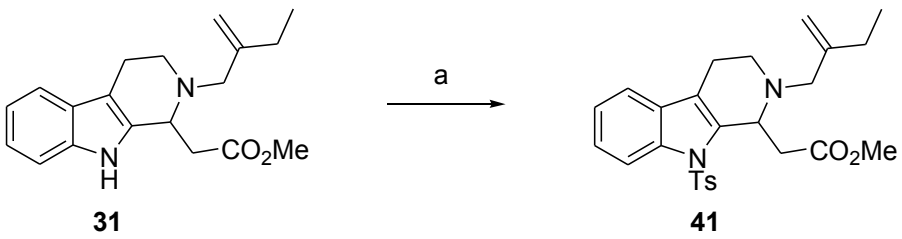
Scheme 15: Reagents and conditions: *a) $KMnO_4$, AcOH, CH_3COCH_3: H_2O, 0 °C, 0.5 h; b) OsO_4, $K_3Fe(CN)_6$, K_2CO_3, t-BuOH:H_2O, 0 °C, 24 h.*

Though large number of methods are available in the literature for this particular transformation but it could not be successfully realised to get the protected compound by any of the methods described in Scheme 16.[13]



Scheme 16

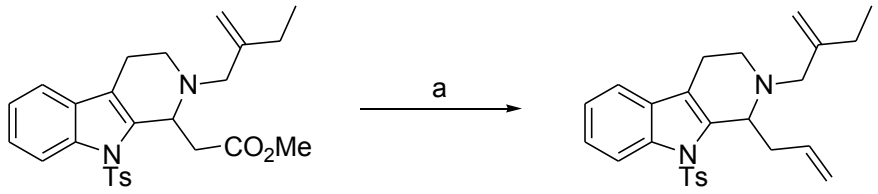
Finally, gratifyingly the transformation was achieved successfully on treating the mixture of β-carboline **31** taken in benzene under phase transfer condition in presence of crushed NaOH with *p*-tosyl chloride (Scheme 17). The reaction was complete within 20 mins, stirring for longer period renders multi spot TLC.



Scheme 17: Reagents and conditions: *a) p-TsCl, crushed NaOH, $TBAHSO_4$, benzene, rt, 20 min, 85%.*

The formation of the protected compound **41** was confirmed by its spectral study. IR spectrum showed absorption at 3019 cm^{-1}, 1735 cm^{-1} and 1366 cm^{-1}. ^{1}H NMR spectrum revealed presence of singlet integrating for three protons at δ 2.34 corresponding to the *p*-methyl group of the tosyl functionality. The broad singlet at δ 8.43 of the indole-H disappeared and additional aromatic protons peaks were visible. ^{13}C NMR spectrum showed the presence of the methyl group at δ 21.5 alongwith an increase in the number of the aromatic carbon peaks. A peak at *m/z* 467.7 (M^{+}+1) in the mass spectrum (ESI) further confirmed the product formation.

DIBAL-H reduction of the ester **41** into aldehyde at –78 °C and one carbon Wittig olefination furnished the required dialkene compound **42** in 68% yield over two steps (Scheme 18). IR spectrum showed no peak corresponding to the ester carbonyl. ^{1}H NMR spectrum showed a multiplet at δ 6.12-5.90 integrating for one proton and set of two multiplets at δ 5.17-5.02 and δ 4.85 integrating for one and two protons respectively ascribed to the exomethylene protons. ^{13}C NMR spectrum alongwith DEPT showed the presence of two exomethylene carbons resonating at δ 115.2 and δ 110.7.



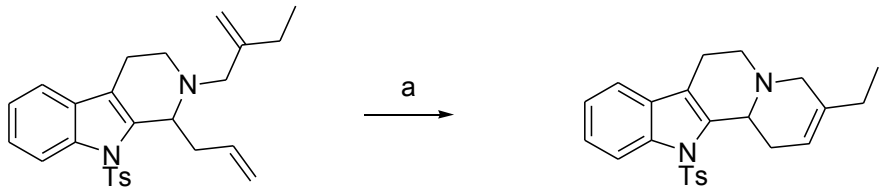
41 **42**

Scheme 18: Reagents and conditions: *a) i. DIBAL-H, DCM, -78 °C, 2 h, ii. $Ph_3P{=}CH_2$, THF, rt, 3 h, 68% (over two steps).*

With the corresponding *N*-tosyl compound the two-step conversion of ester into alkene was realised in an enhanced yield of 68% compared to the previous substrate.

The ring-closing metathesis was carried out in the presence of 10 mol% of Grubbs' 2nd generation catalyst **12** in toluene at 80 °C. The cyclised product was obtained in 87% yield (scheme 19). IR spectrum didn't show any significant changes. ^{1}H NMR spectrum showed disappearance of multiplets from δ 6.00, 5.08 and δ 4.85. An alkene peak was visible as a br d at δ 5.56 integrating for one proton corresponding to the sole alkene proton present. ^{13}C NMR spectrum alongwith DEPT spectrum showed absence of any exomethylene carbon. The alkene carbon appeared at δ 116.1 and the quaternary alkene

carbon peak resonated at δ 120.6. Appearance of a peak at *m/z* 407.5 (M^++1) in the mass spectrum (ESI) and elemental analysis confirmed the transformation.

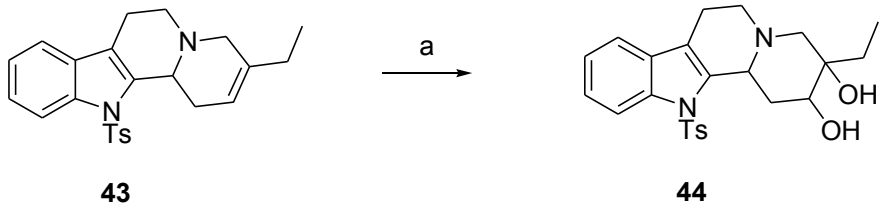


42 **43**

Scheme 19: Reagents and conditions: *a) Grubbs' 2nd generation catalyst (**12**), toluene, 80 °C, 3 h, 87%.*

The transformation was also feasible with 5 mol% catalyst loading but substantial amount of starting remained unreacted even after heating for 10 hours.

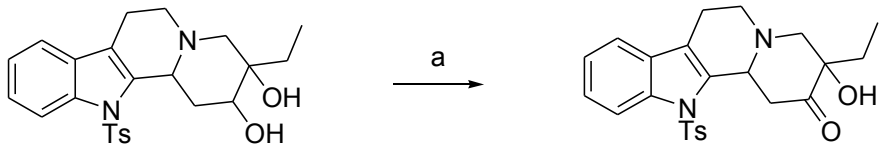
Since the indole-H was protected as its tosyl it was expected that the conversion into keto-hydroxy would be easily and conveniently facilitated under $KMnO_4$ oxidation condition. But to our dismay under both acidic as well as neutral condition the product was not realised at all. Hence once more the milder two-step strategy employing OsO_4 in catalytic amount was tried.[14] Delightfully the diol **44** was isolated on exposing the substrate **43** to biphasic system of *t*-BuOH: H_2O with $K_3Fe(CN)_6/K_2CO_3$ as the reoxidant (Scheme 20). OsO_4 was utilised in catalytic amount for the conversion. IR spectrum showed a strong absorption at 3362 cm^{-1}. ^1H NMR spectrum showed disappearance of the alkene proton. The –C*H*OH proton appeared at δ 3.71 as a multiplet. ^{13}C NMR spectrum showed peak at δ 72.1 and δ 71.3 corresponding to the –*C*HOH and –*C*OH carbons respectively. A peak at *m/z* 441.2 (M^++1) in the mass spectrum (ESI) further confirms the conversion.



43 **44**

Scheme 20: Reagents and conditions: *a) $K_3Fe(CN)_6$, K_2CO_3, t-BuOH: H_2O, OsO_4, 24 h, rt, 50%.*

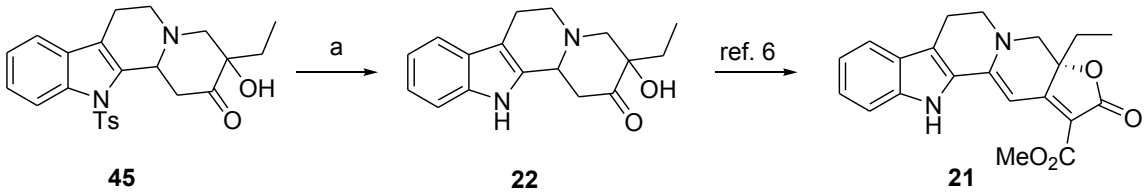
The oxidation of secondary hydroxy group and removal of the tosyl protection would furnish the required intermediate thereby concluding the formal synthesis towards mitralactonine. The oxidation was tried with *Dess-Martin* periodinane[15] without success. Under Swern oxidation condition[16] the oxidised product **45** was obtained in 40% yield. IR spectrum showed absorption at 1724 cm^{-1} signifying the presence of ketone functionality. ^{1}H NMR spectrum showed disappearance of peak corresponding to –C*H*OH thereby supporting the oxidation. ^{13}C NMR spectrum showed peak at δ 207.8 corresponding to the generated carbonyl carbon while rest of the carbon peaks associated the compound resonated at expected position. It was further proved by appearance of peak at *m/z* 439.4 (M^{+}+1) mass (ESI) spectrum and elemental analysis.



44 **45**

Scheme 21: Reagents and conditions: *a) DMSO, oxalyl chloride, Et_3N, DCM, -60 °C, 1 h, 40%.*

The tosyl protection was removed readily on treating the compound **45** with TBAF at reflux temperature for 3 h.[17] The spectral data of the isolated compound **22** were in full agreement with the reported data.[6]



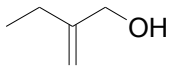
45 **22** **21**

Scheme 22: Reagents and conditions: *a) TBAF, THF, reflux, 2 h, 63%.*

In conclusion, the formal synthesis to the pentacyclic indole alkaloid was easily realised in a short and convenient strategy employing ring-closing metathesis as the key ring construction reaction and utilization of dihydroxylation reaction for the functionalisation of alkene.

3.1.4. Experimental

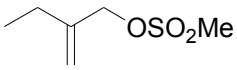
2-Methylenebutan-1-ol (33)



2-Ethyl acrolien[18] (**28**) (5 g, 60 mmol) was taken in methanolic $CeCl_3.7H_2O$ (2 g in 5 mL methanol) and temperature maintained at 0 °C. $NaBH_4$ (1.13 g, 6 mmol) was added in portions. After stirring for 0.5 h at 0 °C water was added (5 mL) and extracted with diethyl ether (4 x 25 mL). Combined organic layers were dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure at room temperature. The pure product **33** (3.9 g, 45 mmol) was distilled out at 82 °C under 220 Torr (mmHg). R_f 0.4 (PE: EA 70:30)

Mol. Formula	**:** $C_5H_{10}O$
Yield	**:** 76%
Bp	**:** 82 °C at 220 torr
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	**:** 3370, 2968, 1654, 1458.
^{1}H NMR (200 MHz, $CDCl_3$)	**:** δ 4.97 (br d, 1H), 4.83 (br d, 1H), 4.04 (s, 2H), 2.03 (q, *J* = 7.4 Hz, 2H), 1.80 (br s, 1H), 1.05 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:** δ 150.5 (C), 107.9 (CH_2), 65.4 (CH_2), 25.5 (CH_2), 11.9 (CH_3).

2-Methylenebutyl-methane sulfonate (32)



The weighed amount of the alcohol **33** (2.5 g, 29 mmol) and Et_3N (12.2 mL, 87 mmol) were taken in dry DCM (25 mL) under argon atmosphere and temperature was lowered to 0 °C. Methanesulfonyl chloride (3.6 g, 32 mmol) was added dropwise and left to stir at 0 °C till the completion of the reaction (2 h). The reaction mixture was diluted with water (10 mL) and extracted with DCM (3 x 25 mL). The combined organic layers were washed thoroughly with saturated $NaHCO_3$ solution, brine and dried over anhydrous sodium sulphate, filtered and the volatile solvent removed under reduced pressure. The

product **32** (3.3 g, 20 mmol) was obtained in 70% yield after column chromatographic (SiO_2) purification as a colour less oil. R_f 0.4 (PE: EA 70:30)

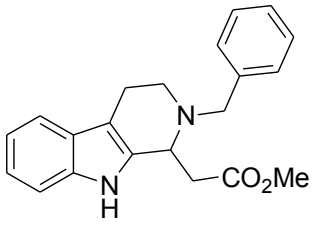
Mol. Formula : $C_6H_{12}O_3S$

Yield : 70%

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 2968, 1654, 1458.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 5.15 (m, 1H), 5.07 (m, 1H), 4.65 (s, 2H), 3.00 (s, 3H), 2.14 (q, *J* = 7.4 Hz, 2H), 1.09 (t, *J* = 7.4 Hz, 3H).

Methyl 2-(2-benzyl-2,3,4,9-tetrahydrp-1 *H*-pyrido[3,4-β]indol-1-yl)acetate (38)



To a well stirred mixture of tryptamine (**26**) (2 g, 12.5 mmol) in dry toluene (20 mL) under nitrogen was added benzaldehyde and left to stir at room temperature for 12 h. After completion of the reaction toluene was removed under reduced pressure and the residue diluted with methanol (20 mL). To this mixture was added $NaBH_4$ (in small portions at 0 °C) and left to stir at room temperature till the completion of reaction (1 h). The methanol was removed under reduced pressure and the residue diluted with water (10 mL) and extracted with ethyl acetate (3 x 25 mL). Combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The compound **37** was used as such without purification for the next step.

To a mixture of crude compound **37** (3.1 g, 12.4 mmol) and weighed amount of methyl propiolate (1.32 g, 15 mmol) in dry $CHCl_3$ (30 mL) under nitrogen atmosphere was added TFA (10.2 mL, 125 mmol) at 0 °C and left to stir at room temperature for 1 h. The reaction mixture was diluted with water (10 mL) and made alkaline with excess of 6N NaOH solution. The organic layer was separated and the aqueous layer extracted with DCM (3 x 25 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and solvent removed under reduced pressure. Purification through column chromatography (SiO_2) rendered the pure product as a pale yellow viscous oil **38** (3.9 g, 11.6 mmol) in 94 % yield. R_f 0.5 (PE: EA 90:10)

Mol. Formula : $C_{21}H_{22}N_2O_2$

Yield : 94%

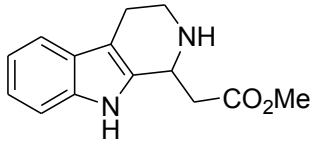
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3448, 3019, 1730.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.52 (br s, 1H), 7.53-7.25 (m, 7H), 7.22-7.06 (m, 2H), 4.27 (br d, 1H), 3.86 (s, 2H), 3.71 (s, 3H), 3.30-3.06 (m, 3H), 2.99-2.81 (m, 2H), 2.67-2.60 (br d, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 173.4 (C), 138.9 (C), 135.7 (C), 133.8(C), 128.7 (2CH), 128.3 (2CH), 127.2 (C), 126.9 (CH), 121.7 (CH), 119.3 (CH), 118.2 (CH), 110.9 (CH), 107.5 (C), 57.4 (CH_2), 52.9 (CH), 51.8 (CH_3), 44.5 (CH_2), 40.1 (CH_2), 17.7 (CH_2).

Mass (ESI) : *m/z* 335.4 (M^++1)

Methyl 2-(2,3,4,9-tetrahydro-1 *H*-pyrido[3,4-β]indol-1-yl)acetate (27)



The β-carboline **38** (3 g, 8.9 mmol) was taken in methanol: acetic acid (9:1) (20 mL) and was subjected to hydrogenation at 60 Psi H_2 pressure with Pd/C (10%) as the catalyst for 10 h. After completion of reaction, the reaction mixture was filtered through a celite bed and filtrate concentrated under reduced pressure. The residue was dissolved in ethyl acetate and thoroughly washed with saturated $NaHCO_3$ solution until neutral. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Column purification rendered the pure product **27** (2.1 g, 8.6 mmol) as a pale yellow viscous compound in quantitative yield. R_f 0.2 (PE: EA 20: 80).

Mol. Formula : $C_{14}H_{16}N_2O_2$

Yield: : Quantitative

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3402, 1725, 1610, 1438.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.69 (br s, 1H), 7.53-7.07 (m, 4H), 4.51 (t, *J* = 6.9 Hz, 1H), 3.81 (s, 3H), 3.39-3.08 (m, 2H), 2.88

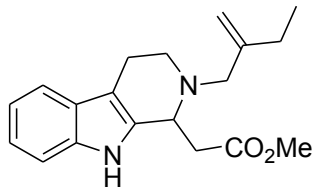
(d, J = 6.9 Hz, 2H), 2.78 (t, J = 5.4 Hz, 2H), 2.57 (br s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 173.1 (C), 135.6 (C), 134.3 (C), 127 (C), 121.5 (CH), 119.0 (CH), 117.9 (CH), 110.8 (CH), 108.7 (C), 51.7 (CH), 48.7 (CH_3), 41.4 (CH_2), 39.8 (CH_2), 22.2 (CH_2).

Mass (ESI) **:** *m/z* 245.47 (M^++1)

Analysis **:** Calculated C 68.83, H 6.6, N 11.47%
Found C 68.45, H 6.42, N 10.95%

Methyl 2-(2-(2-methylenebutyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-β]indol-1-yl)acetate (31)



To the mixture of amine **27** (2.1 g, 8.6 mmol) and compound **32** (1.4 g, 8.6 mmol) taken in dry DCM (20 mL) was added K_2CO_3 and left to stir at room temperature under nitrogen atmosphere till the completion of reaction. The reaction mixture was diluted with water and the DCM layer separated. The aqueous layer was extracted with DCM (3 x 25 mL). Combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Column chromatographic (SiO_2) purification rendered the pure product **31** (1.9 g, 6 mmol) in 70% yield as viscous pale yellow oil. R_f 0.4 (PE: EA 90: 10)

Mol. Formula **:** $C_{19}H_{24}N_2O_2$

Yield **:** 70%

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) **:** 3019, 1723.

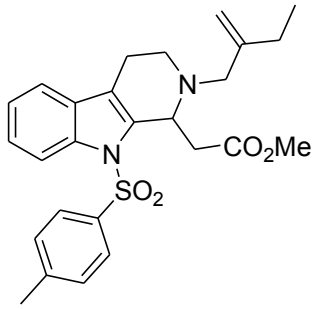
^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 8.45 (br s, 1H), 7.51-7.47 (m, 1H), 7.35-7.29 (m, 1H), 7.19-7.03 (m, 2H), 4.90 (br d, 1H), 4.22-4.10 (m, 1H), 3.74 (s, 3H), 3.20 (br s, 2H), 3.13-2.80 (m, 6H), 2.62-2.49 (m, 1H), 2.12 (q, J = 7.3 Hz, 2H), 1.06 (t, J = 7.3 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 173.8 (C), 148.7 (C), 135.6 (C), 134.1 (C), 127 (C), 121.5 (CH), 119.1 (CH), 118.1 (CH), 111.1 (CH_2), 110.8 (CH), 107.5 (C), 58.6 (CH_2), 52.8 (CH), 51.6 (CH), 44.3 (CH_2), 39.9 (CH_2), 26.6 (CH_2), 17.6 (CH_2), 12.2 (CH_3).

Mass (ESI) **:** *m/z* 312.3 (M^++1)

Analysis **:** Calculated C 73.05, H 7.74, N 8.97%
Found C 72.23, H 7.17, N 8.36%

Methyl 2-(2-(2-methylenebutyl)-9-tosyl)-9-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido [3,4-β]indol-1-yl)acetate (41)



The compound **31** (1.5 g, 4.8 mmol) was taken in benzene (20 mL) and crushed sodium hydroxide (1.0 g, 24 mmol) was added followed by the addition of catalytic amount of $TBAHSO_4$ (0.16 g, 0.5 mmol). The reaction mixture was stirred vigorously at room temperature for 15 mins followed by addition of *p*-TsCl (1.14 g, 6 mmol). It was further stirred for 20-25 mins till the completion of reaction (TLC). Water was added and organic layer separated. The aqueous layer was extracted with ethyl acetate (3 x 25 mL). Combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Column chromatographic (SiO_2) purification rendered the pure product **41** (1.9 g, 4 mmol) in 85% yield as a viscous pale yellow oil. R_f 0.6 (PE: EA 80:20)

Mol. Formula **:** $C_{26}H_{30}N_2O_4S$

Yield **:** 85%

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) **:** 3019, 1735, 1366.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 8.16 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.43-7.29 (m, 3H), 7.18 (d, *J* = 8.2 Hz, 2H), 4.92 (br s, 1H), 4.78 (br s, 2H), 3.76 (s, 3H), 3.28

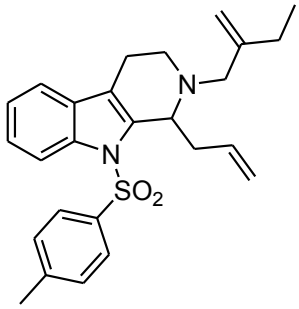
(dd, J = 15.4, 3.2 Hz, 1H), 3.18-3.03 (m, 4H), 2.90-2.66 (m, 2H), 2.59-2.44 (m, 1H), 2.34 (s, 3H), 2.27-2.09 (m, 2H), 1.08 (t, J = 7.3 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 171.6 (C), 148.9 (C), 144.6 (C), 136.6 (C), 135.4 (2C), 130.2 (C), 129.6 (2CH), 126.5 (2CH), 124.8 (CH), 123.7 (CH), 118.5 (CH), 118 (C), 115.1 (CH), 111.1 (CH_2), 58.7 (CH_2), 56.4 (CH), 51.5 (CH), 40.8 (CH_2), 39.8 (CH_2), 26.2 (CH_2), 21.5 (CH_3), 16.4 (CH_2), 12.2 (CH_3).

Mass (ESI) **:** *m/z* 467.7 (M^++1)

Analysis **:** Calcuated C 66.93 H 6.48 N 6.00 S 6.87%
Obtained C 66.54 H 6.25 N 5.85 S 6.75%

1-Allyl-2-(2-methylenebutyl)-9-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-β]indole (42)



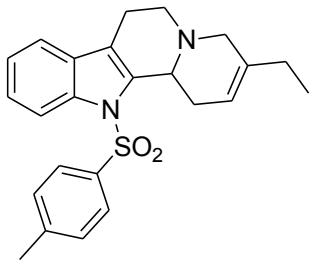
The compound **41** (1.5 g, 3.2 mmol) was taken in dry DCM (20 mL) under argon atmosphere and temperature lowered to –78 °C. DIBAL-H (2M) (2.9 mL, 5.8 mmol) was added dropwise and left to stir at same temperature till the completion of reaction (TLC). The reaction was quenched at –78 °C with the addition of methanol (3 mL) and water (3 mL) and then warmed to room temperature. The organic layer was separated and the aqueous layer was extracted with DCM (3 x 25 mL). Combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The aldehyde was used immediately as such without further purification.

To a well stirred solution of the aldehyde (1.4 g, 3.2 mmol, crude) in dry THF (15 mL) under argon atmosphere was added freshly generated one carbon ylide and left to stir at room temperature till the completion of reaction. The reaction was quenched with saturated ammonium chloride solution. Organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 25mL). Combined organic layers were washed

with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Column chromatographic (SiO_2) purification rendered the pure product **42** (0.95 g, 2.1 mmol) in 68% yield as viscous oil. (Over two steps) R_f 0.8 (PE: EA 90: 10)

Mol. Formula	**:** $C_{26}H_{30}N_2O_2S$
Yield	**:** 68%
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	**:** 3019, 1371.
^{1}H NMR (200 MHz, $CDCl_3$)	**:** δ 8.12 (d, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.33-7.20 (m, 3H), 7.12 (d, *J* = 7.1 Hz, 2H), 6.12-5.90 (m, 1H), 5.17-5.02 (m, 2H), 4.85 (m, 2H), 4.20 (br d, 1H), 3.24-2.63 (m, 6H), 2.51-2.35 (m, 2H), 2.31 (s, 3H), 2.21-2.13 (m, 2H), 1.07 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:** δ 149.2 (C), 144.4 (C), 137.3 (C), 136.8 (CH), 136.6 (C), 135.6 (C), 130.4 (C), 129.5 (2CH), 126.5 (2CH), 124.4 (CH), 123.6 (CH), 118.3 (CH), 117.3 (C), 115.8 (CH_2), 115.2 (CH), 110.7 (CH_2), 58.8 (CH_2), 58.6 (CH), 41 (CH_2), 39.7 (CH_2), 26.5 (CH_2), 21.5 (CH_3), 16.9 (CH_2), 12.2 (CH_3).
Analysis	**:** Calculated C 71.86, H 6.96, N 6.45, S 7.38% Found C 71.45, H 6.72, N 6.02, S 6.98%

3-Ethyl-12-tosyl-1,4,6,7,12,12β-hexahydroindolo[2,3-α]quinolizine (43)



The substrate **42** (0.2 g, 0.5 mmol) was taken in dry toluene (60 mL) and degassed thoroughly with argon followed by addition of Grubb's 2nd generation catalyst (0.04 g, 0.05 mmol). The mixture was heated at 80 ^oC for 3 h. The volatile solvent was removed under reduced pressure and the residue was purified through column chromatography

(SiO_2) to render the tetracyclic compound **43** (0.188 g, 0.45 mmol) in 87% yield as a brown solid. R_f 0.6 (PE: EA 20:80).

Mol. Formula : $C_{24}H_{26}N_2O_2S$

Mp : 154 °C-155 °C

Yield : 87%

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3254, 1639, 1331, 1149.

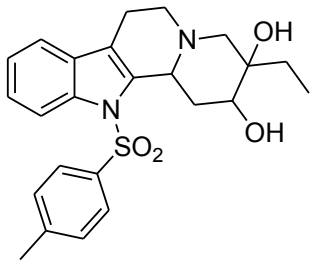
^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.07 (d, *J* = 7.9 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.32-7.20 (m, 3H), 7.10 (d, *J* = 8.3 Hz, 2H), 5.56 (br d, 1H), 4.22 (br s, 1H), 3.63-3.56 (m, 1H), 3.32-3.07 (m, 3H), 2.89-2.68 (m, 3H), 2.27 (s, 3H), 2.23-2.18 (m, 1H), 2.11-1.99 (m, 2H), 1.08 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 144.3 (C), 138.2 (C), 138 (C), 136.7 (C), 134.1 (C), 130.9 (C), 129.3 (2CH), 126.6 (2CH), 124.5 (CH), 124.1 (CH), 120.6 (C), 118.4 (CH), 118 (CH), 116.1 (CH), 57.5 (CH_2), 56.1 (CH), 48.2 (CH_2), 31.5 (CH_2), 27.6 (CH_2), 22.4 (CH_2), 21.5 (CH_3), 12.1 (CH_3).

Mass (ESI) : *m/z* 407.54 (M^++1)

Analysis : Calculated C 70.90, H 6.45, N 6.89, S 7.89%
Found C 70.72, H 6.32, N 6.54, S 7.76%

3-Ethyl-12-tosyl-1,2,3,4,6,7,12,12 β-octahydroindolo [2,3-α] quinolizine-2,3-diol (44)



To a well stirred solution of K_3FeCN_6 (0.45 g, 13.7 mmol) and K_2CO_3 (0.19 g, 13.7 mmol) in water: *t*-BuOH (5 mL) at 0 °C was added OsO_4 (0.2 mL, 0.02 M soln.) followed by addition of tetracyclic alkene **43** (0.188 g, 0.45 mmol). Methane sulfonamide (0.044 g, 0.45 mmol) was added at this point. The biphasic reaction mixture was stirred at room temperature till the completion of reaction. The reaction was quenched with addition of

sodium sulphite. The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 x 25 mL). Combined organic layers were dried over sodium sulphate, filtered and concentrated under reduced pressure. Column chromatographic purification (SiO_2) rendered the pure product **44** (0.1 g, 0.23 mmol) in 50% yield as a brown solid. R_f 0.2 (PE: EA 20: 80).

Mol. Formula : $C_{24}H_{28}N_2O_4S$

Mp :179 ºC-180 ºC

Yield : 50%

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3362, 2928.

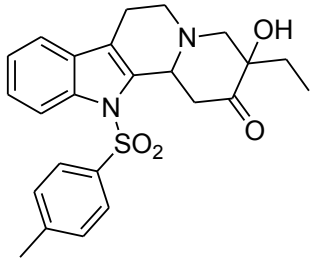
^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.04 (d, *J* = 8.3, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.31-7.20 (m, 3H), 7.05 (d, *J* = 8.3 Hz, 2H), 3.83 (br d, 1H), 3.71 (dd, *J* = 11.3, 5.2 Hz, 1H), 3.59-3.27 (m, 2H), 3.11-2.92 (m, 3H), 2.83-2.52 (m, 4H), 2.26 (s, 3H), 1.94-1.76 (m, 1H), 1.71-1.51 (m, 1H), 0.98 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 144.5 (C), 138.4 (2C), 133.2 (2C), 130.8 (C), 129.2 (2CH), 126.6 (2CH), 124.8 (CH), 124.4 (CH), 118.4 (CH), 116.4 (CH), 72.1 (C), 71.7 (CH), 61.9 (CH_2), 58.9 (CH), 49.9 (CH_2), 29.6 (CH_2), 27.6 (CH_2), 22.9 (CH_2), 21.5 (CH_3), 7.5 (CH_3).

Mass (ESI) : *m/z* 441.29 (M^++1)

Analysis : Calculated C 65.43, H 6.41, N 6.36, S 7.28%
Found C 65.02, H 6.23, N 6.02, S 7.15%

3-Ethyl-3-hydroxy-12-tosyl-1,3,4,6,7,12β-hexahydroindolo[2,3-α]quinolizin-2(12*H*)-one (45)



To a solution of oxalyl chloride (0.06 g, 0.45 mmol) in DCM (5 mL) at –60 ºC under argon atmosphere was added DMSO (0.07 mL, 0.9 mmol) dissolved in DCM (2 mL)

dropwise. After stirring for 0.5 h, alcohol **44** (0.1 g, 0.22 mmol) dissolved in DCM (2 mL) was added to the mixture. The stirring was continued for additional 1 h, triethyl amine was added and the reaction mixture was stirred for 5 min and then allowed to warm to room temperature. Water was added and the organic layer separated. Aqueous layer was extracted with DCM (3 x 10 mL). Combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Column chromatographic (SiO_2) purification rendered pure compound **45** (0.04 g, 0.09 mmol) as viscous oil in 40% yield. R_f 0.4 (PE: EA 60:40).

Mol. Formula **:** $C_{24}H_{26}N_2O_4S$

Yield **:** 40%

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) **:** 3437, 1724, 1367.

^{1}H NMR (400 MHz, $CDCl_3$) **:** δ 8.06 (d, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.32-7.20 (m, 3H), 7.08 (d, *J* = 8.5 Hz, 2H), 4.21 (br d, 1H), 3.51 (dd, *J* = 15.3, 4.5 Hz, 1H), 3.19 (d, *J* = 12.3 Hz, 1H), 3.12-3.10 (m, 1H), 3.00 (d, *J* = 12.3 Hz, 1H), 2.89-2.82 (m, 2H), 2.77-2.71 (m, 1H), 2.61-2.56 (m, 1H), 2.30 (s, 3H), 1.91-1.85 (m, 2H), 1.74-1.71 (m, 1H), 0.98 (t, *J* = 7.5, 3H).

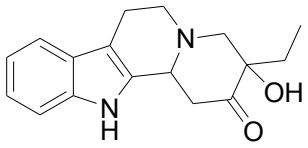
^{13}C NMR (100 MHz, $CDCl_3$) **:** δ 207.8 (C), 144.6 (C), 138.4 (C), 135.9 (C), 133.6 (C), 130.6 (C), 129.9 (CH), 129.3 (CH), 126.8 (CH), 126.7 (CH), 125.2 (CH), 124.5 (CH), 122.6 (C), 118.6 (CH), 116.5 (CH), 76.5 (C) 65.2 (CH_2), 59.4 (CH), 49.9 (CH_2), 44.3 (CH_2), 27.3 (CH_2), 22.8 (CH_2), 21.5 (CH_3), 7.3 (CH_3).

Mass (ESI) **:** *m/z* 439.39 (M^++1).

Analysis **:** Calculated C 65.73, H 5.98, N 6.39, S 7.31%

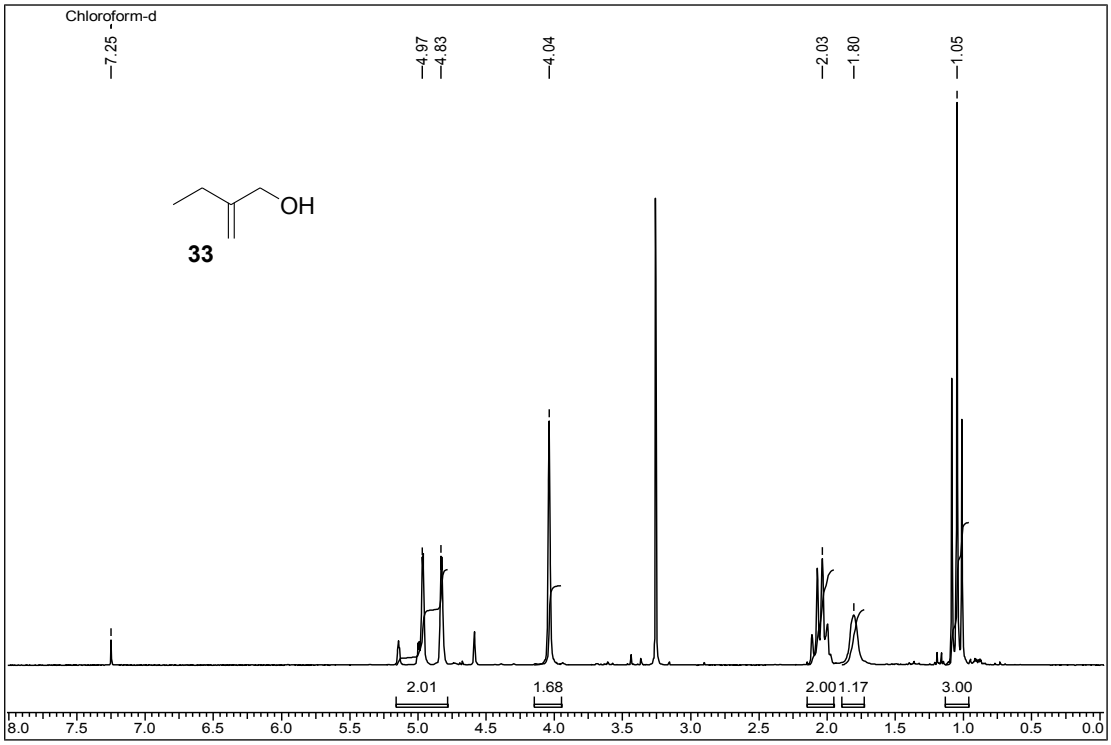
Found C 65.50, H 5.88, N 6.32, S 7.20%

3-Ethyl-3-hydroxy-1,3,4,6,7,12 β-hexahydroindolo [2,3-α] quinolizin-2(12H)-one (22)

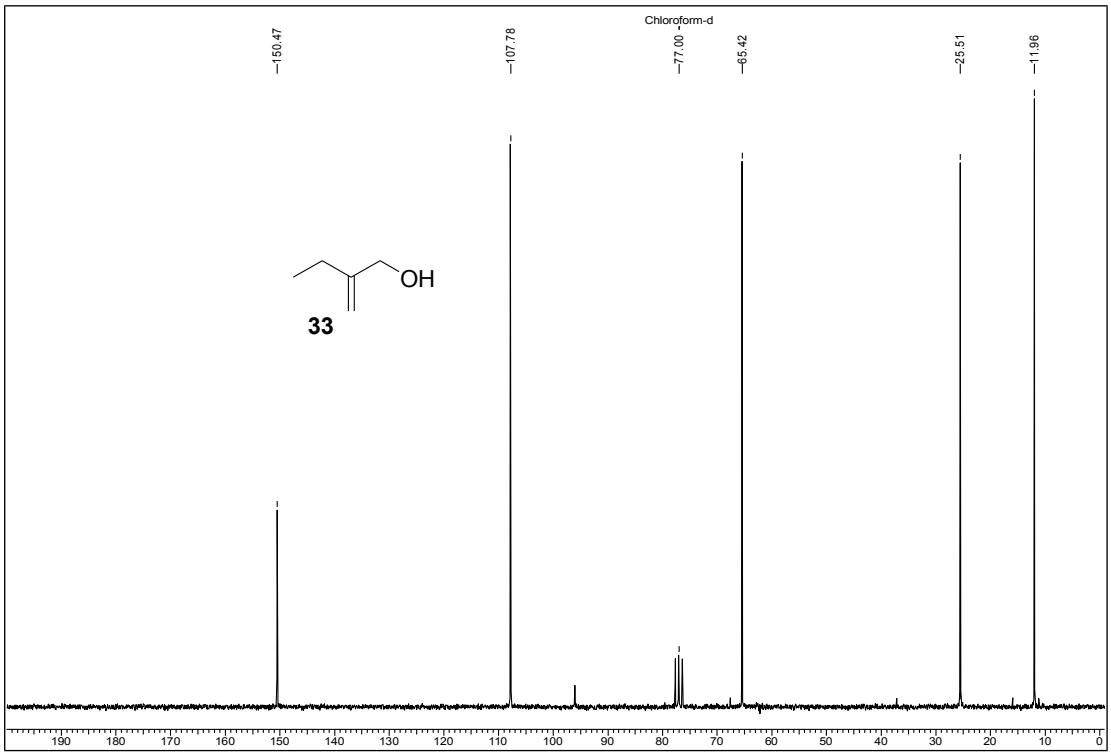


To a solution of the compound **45** (0.04 g, 0.09 mmol) in THF was added tetra-n-butylammonium fluoride (0.5 mL, 0.5 mmol) 1.0 M solution in THF at room temperature under argon atmosphere, and then the mixture was refluxed for 2 h. After completion of reaction saturated $NaHCO_3$ solution was added and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and solvent removed under reduced pressure. Chromatographic (SiO_2) purification rendered the pure product **22** (0.015 g, 0.05 mmol) in 63% yield. R_f 0.4 (PE: EA 70: 30).

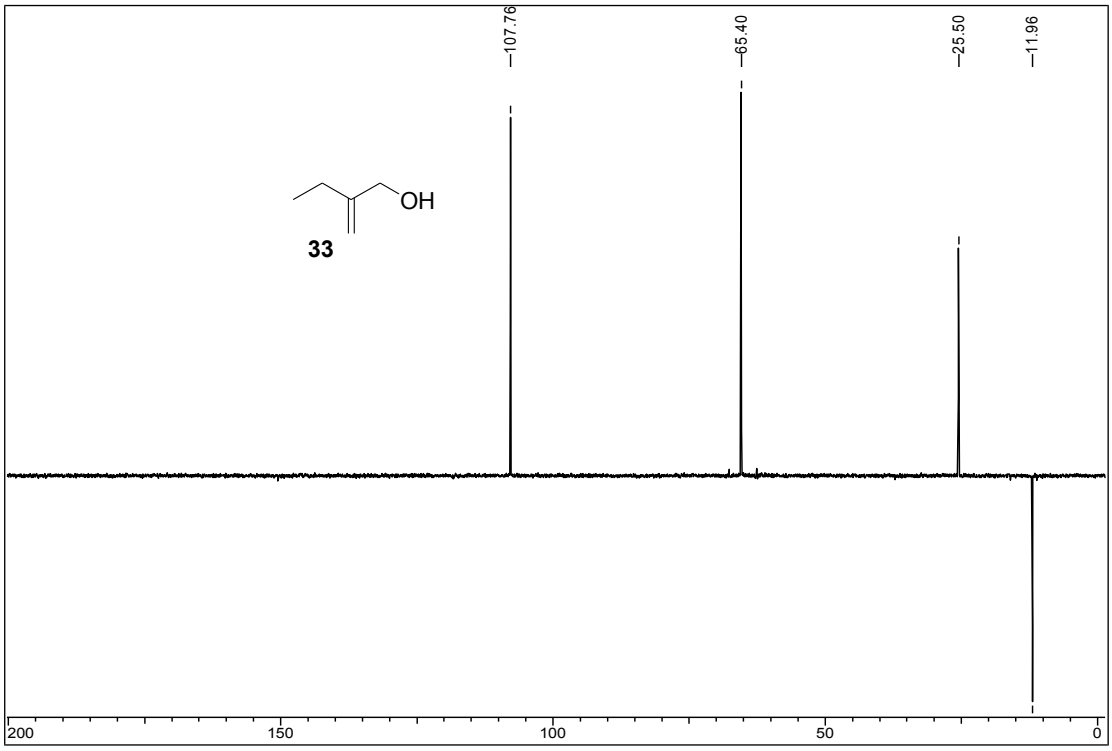
Mol. formula	**:** $C_{17}H_{20}N_2O_2$
Yield	**:** 63%
IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1})	**:** 3409, 3018, 1716, 1440.
^{1}H NMR (400 MHz, $CDCl_3$)	**:** δ 7.82 (br s, 1H), 7.53-7.49 (m, 1H), 7.37-7.34 (m, 1H), 7.23-7.09 (m, 2H), 4.02 (br s, 1H), 3.90 (br d, 1H), 3.22-2.65 (m, 8H), 1.96 (m, 1H), 1.67 (m, 1H), 0.97 (m, 3H).
^{13}C NMR (100 MHz, $CDCl_3$)	**:** δ 208.5 (C), 136.2 (C), 132.2 (C), 126.7 (C), 121.9 (CH), 119.6 (CH), 118.2 (CH), 111.1 (CH), 108.1 (C), 76.3 (C), 63.1 (CH_2), 58.5 (CH), 51.6 (CH_2), 41.7 (CH_2), 25.4 (CH_2), 21.1 (CH_2), 7.0 (CH_3).
Mass (ESI)	**:** *m/z* 285.33 (M^++1).
Analysis	**:** Calculated C 71.81, H 7.09, N 9.85% Found C 71.62, H 6.95, N 9.66%.



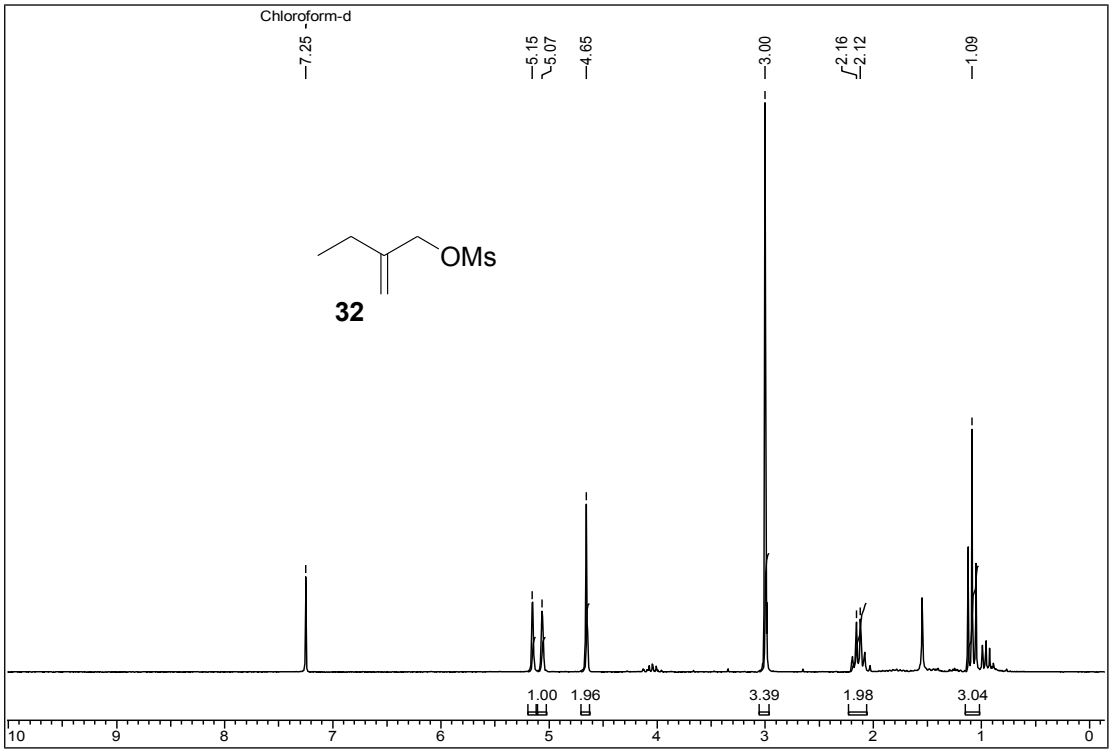
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 33



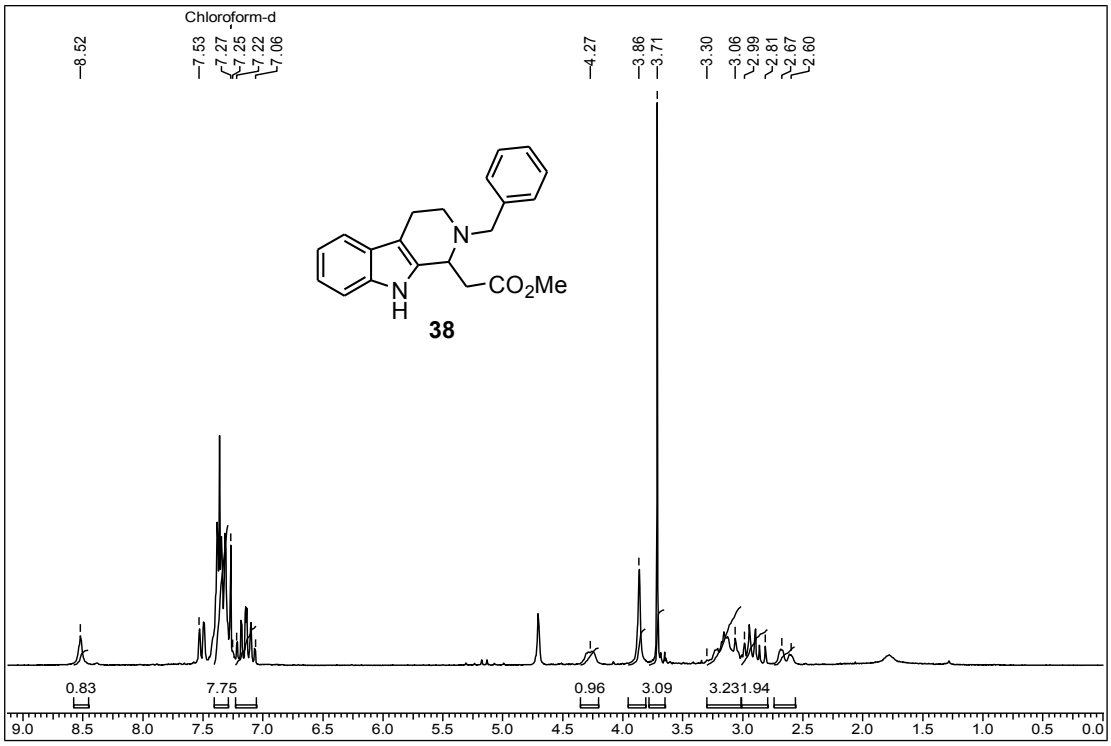
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 33



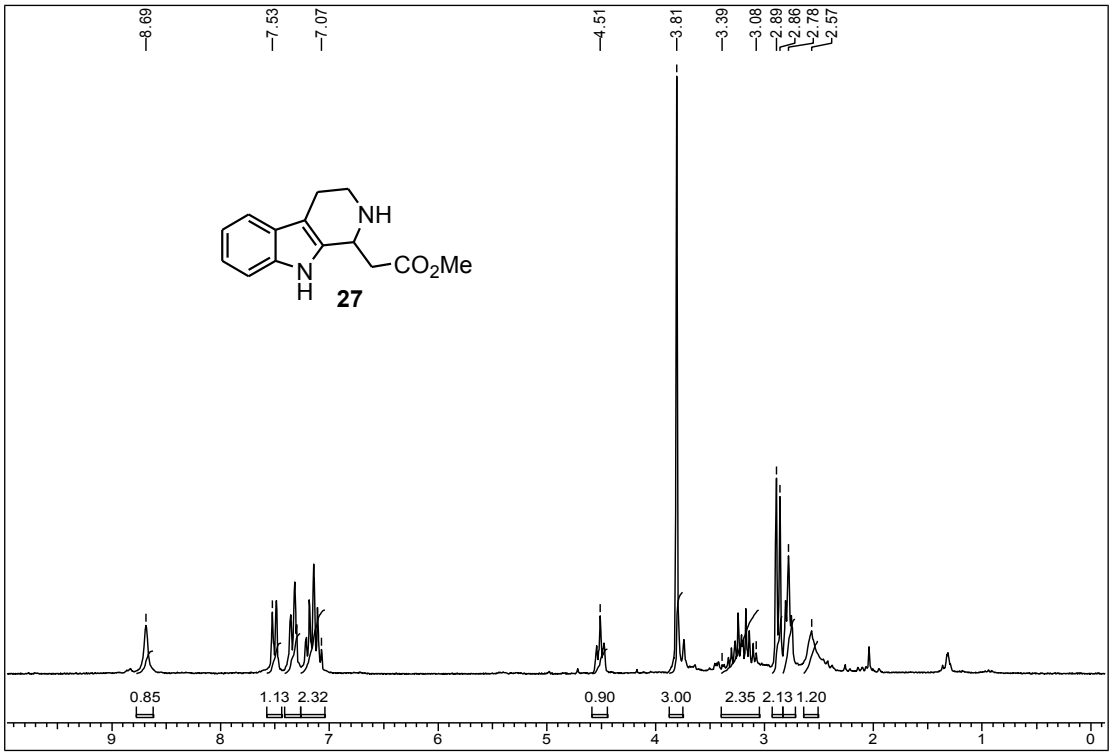
DEPT ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 33



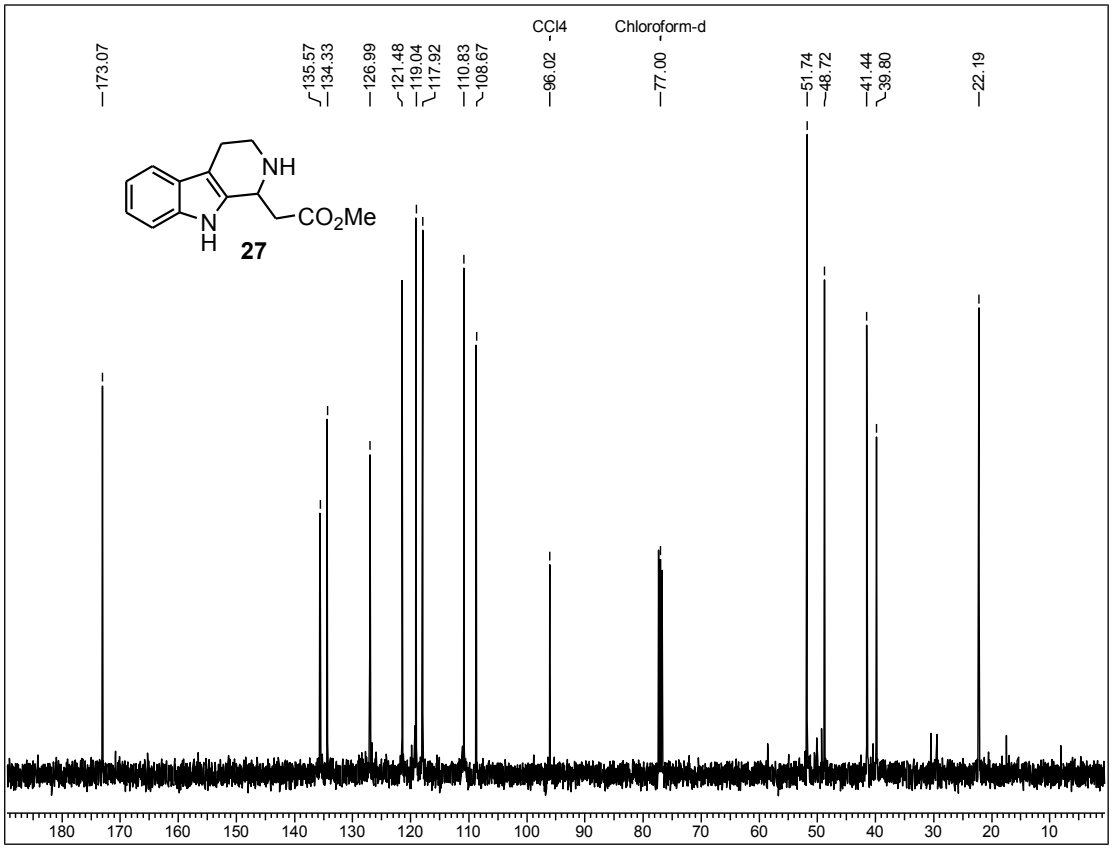
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 32



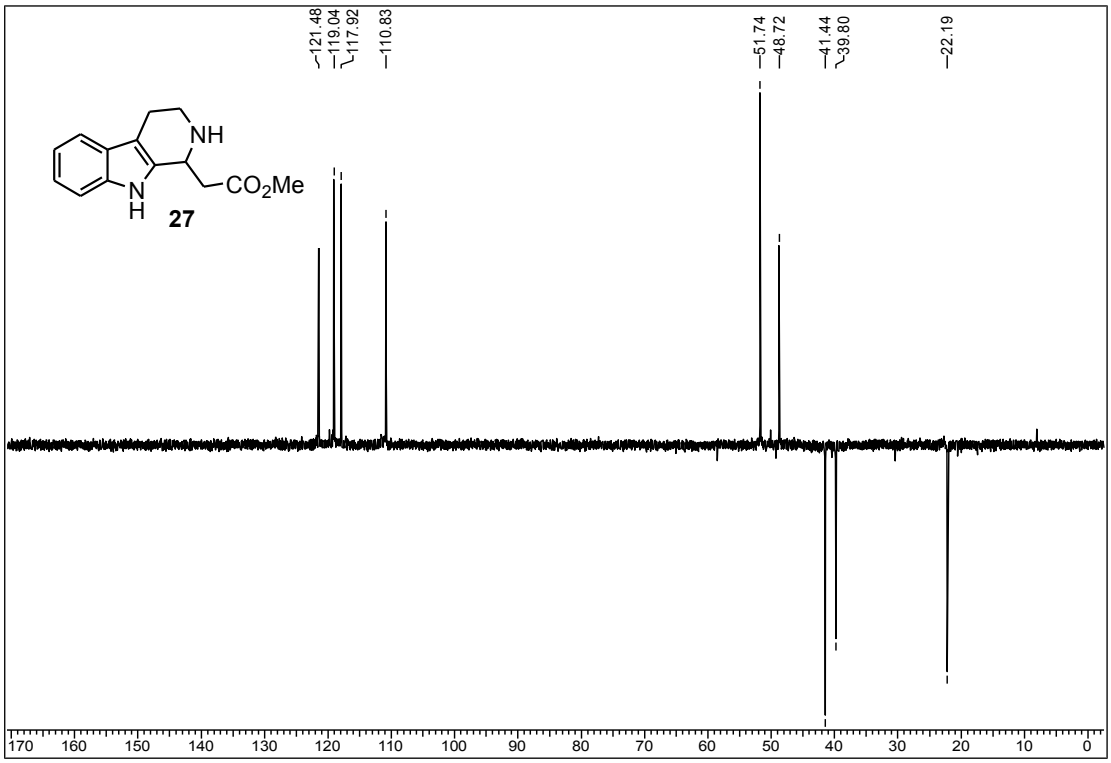
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 38



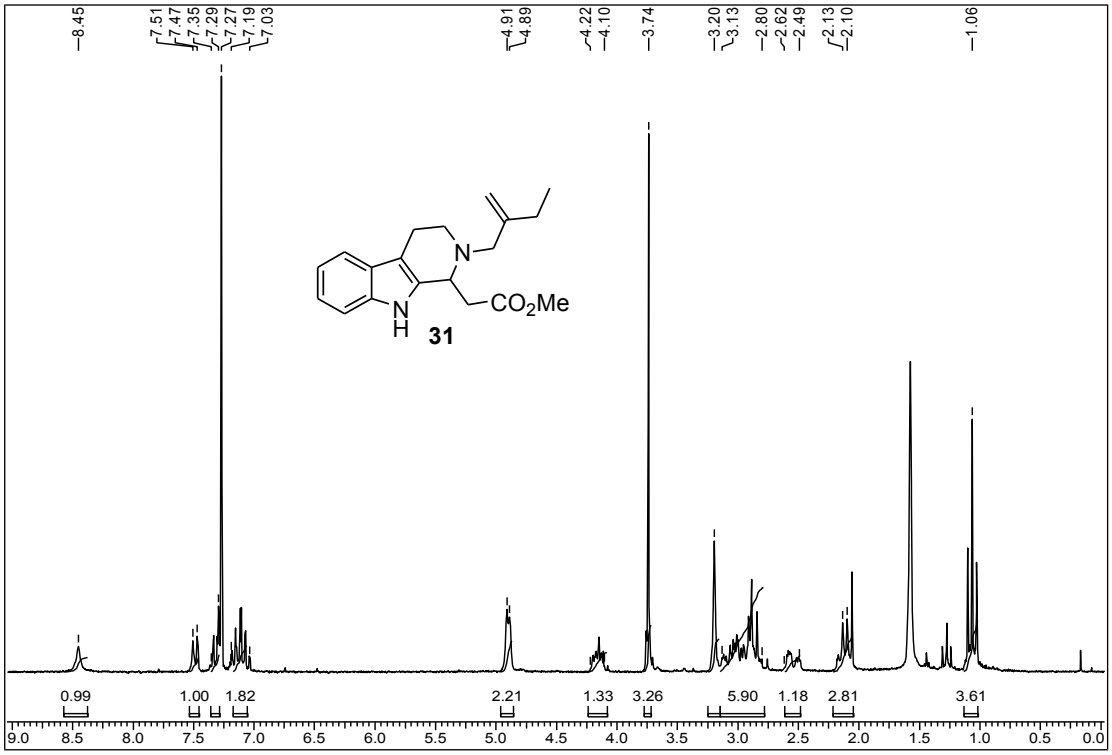
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 27



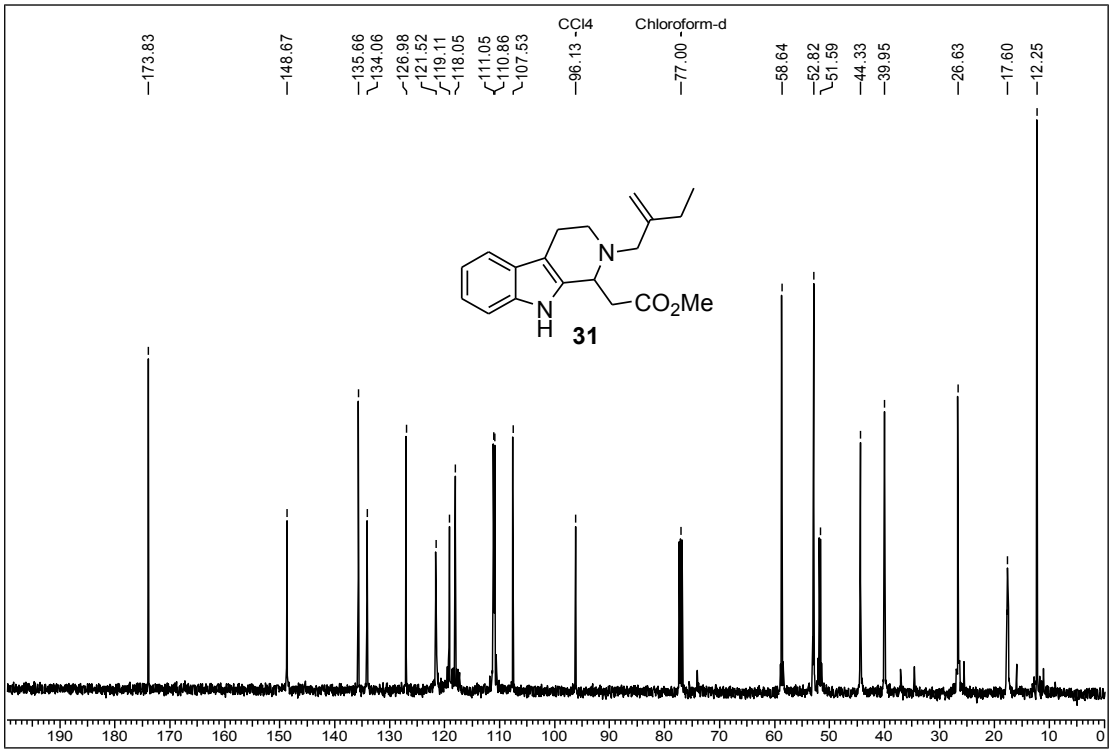
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 27



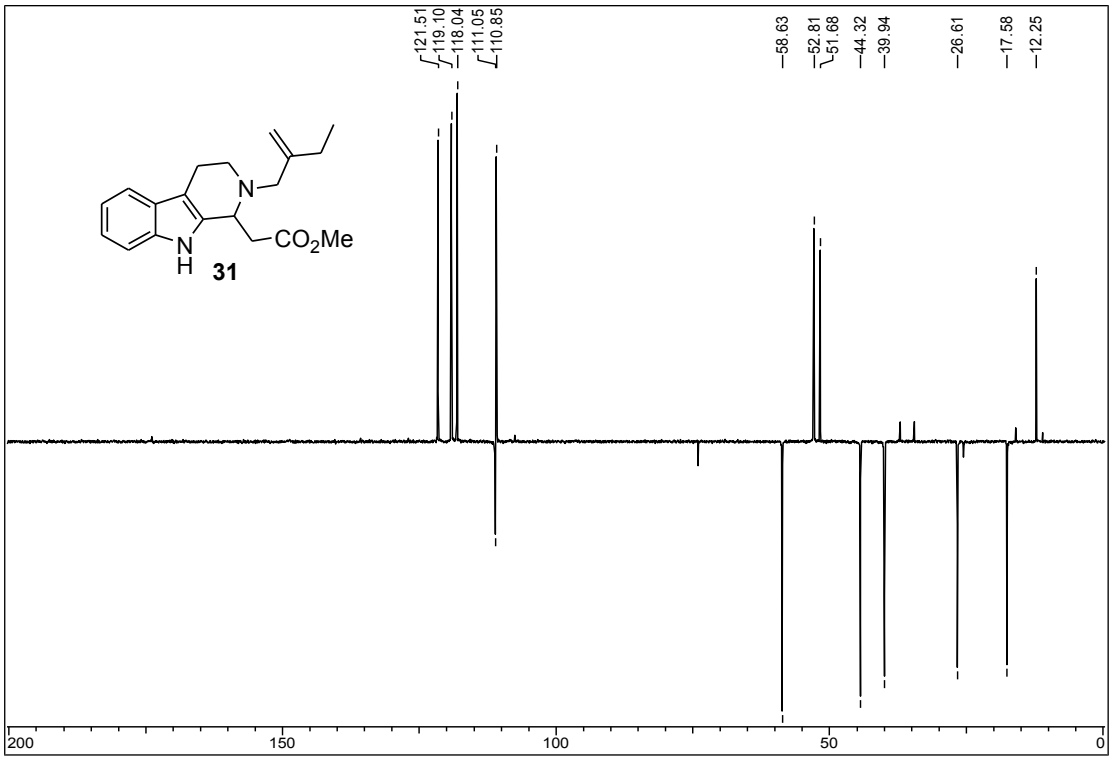
DEPT ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 27



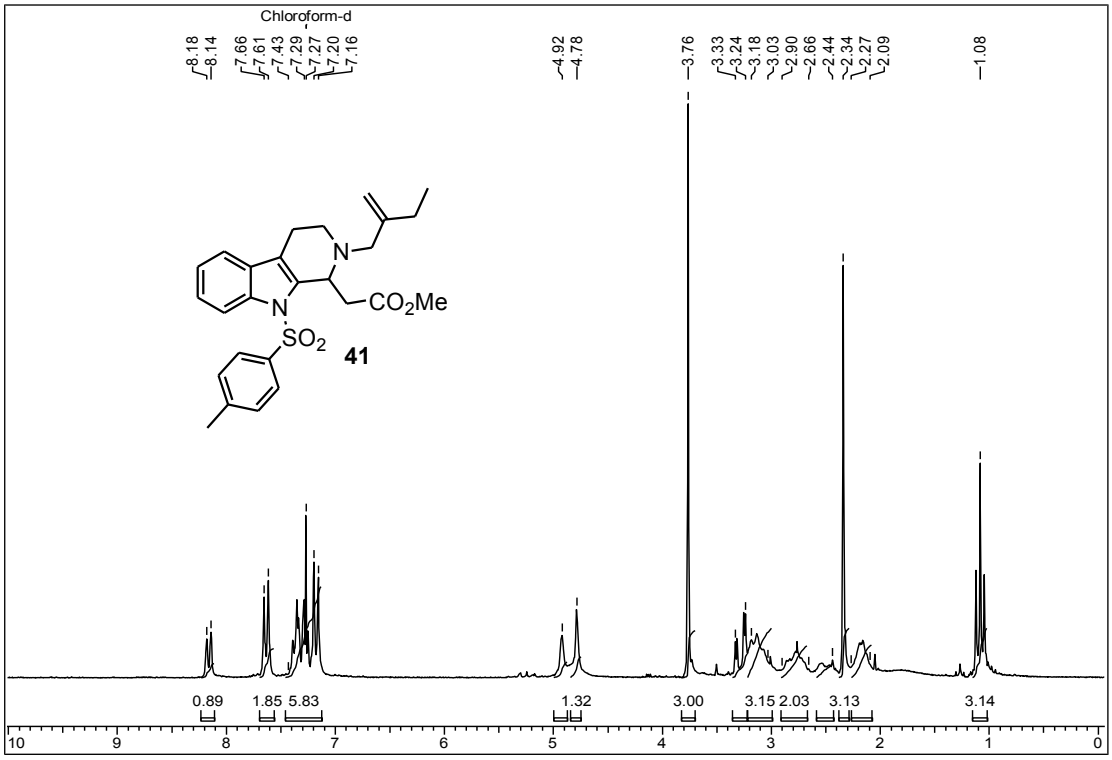
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 31



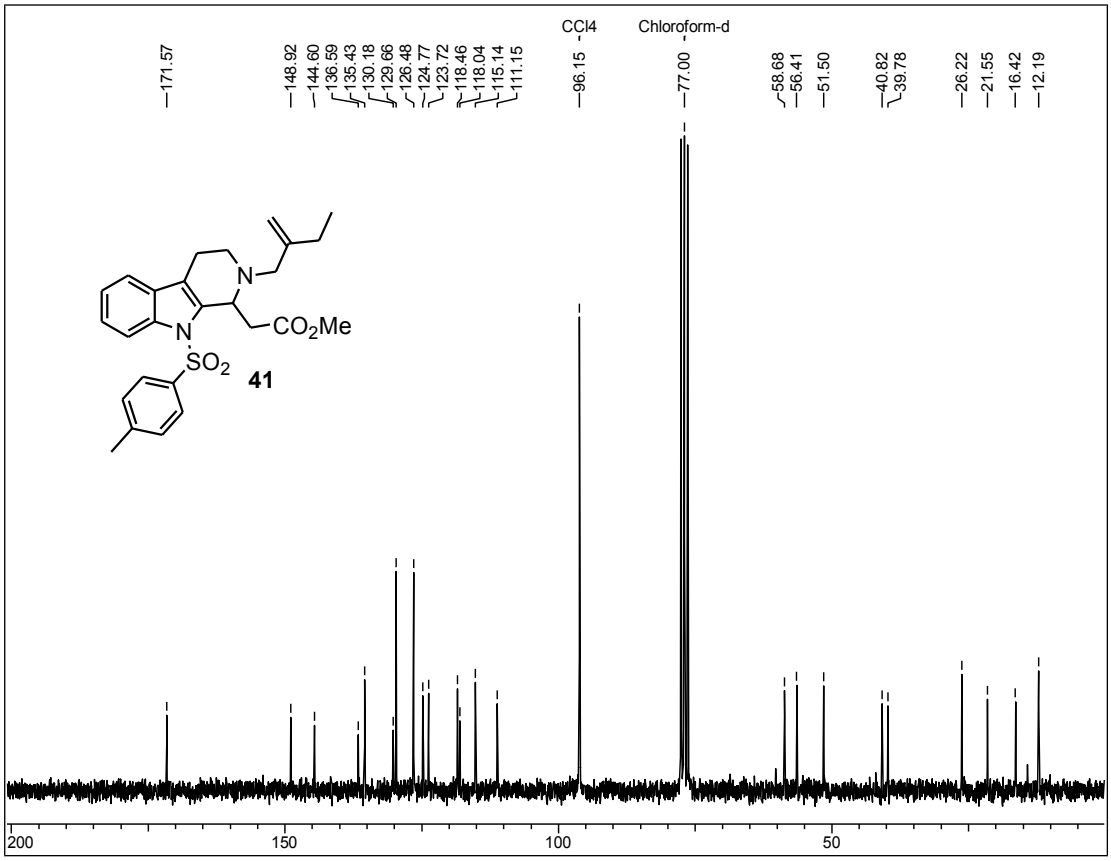
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 31



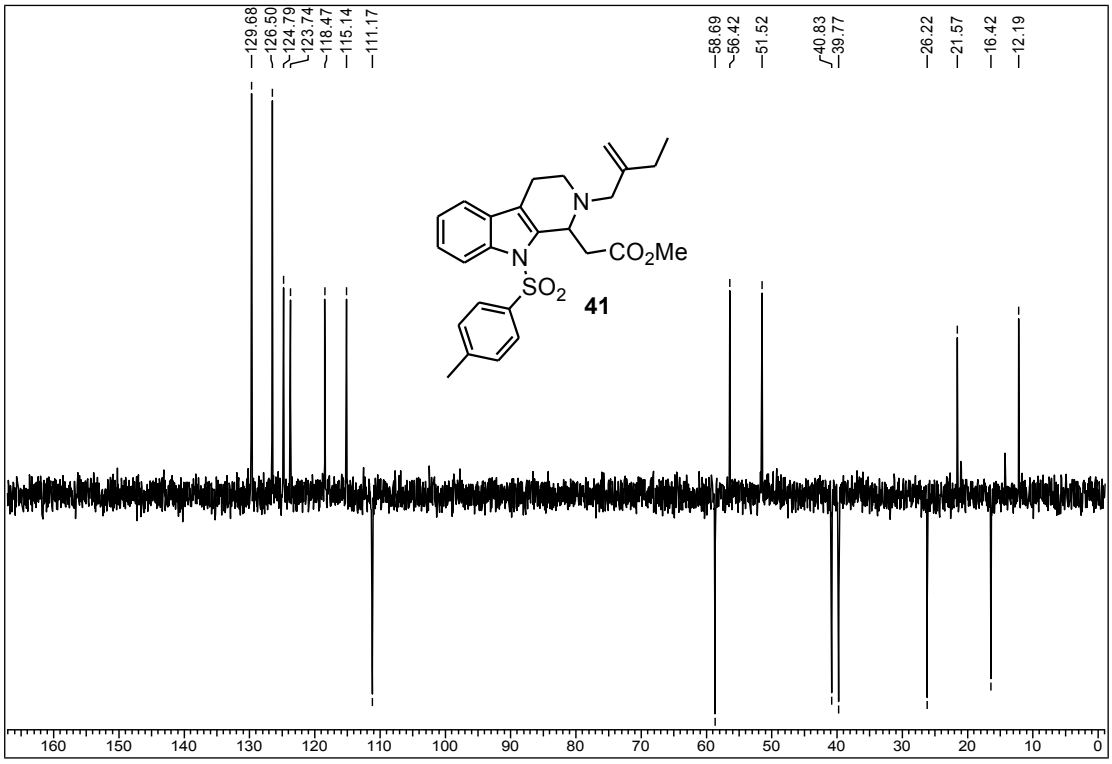
DEPT ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 31



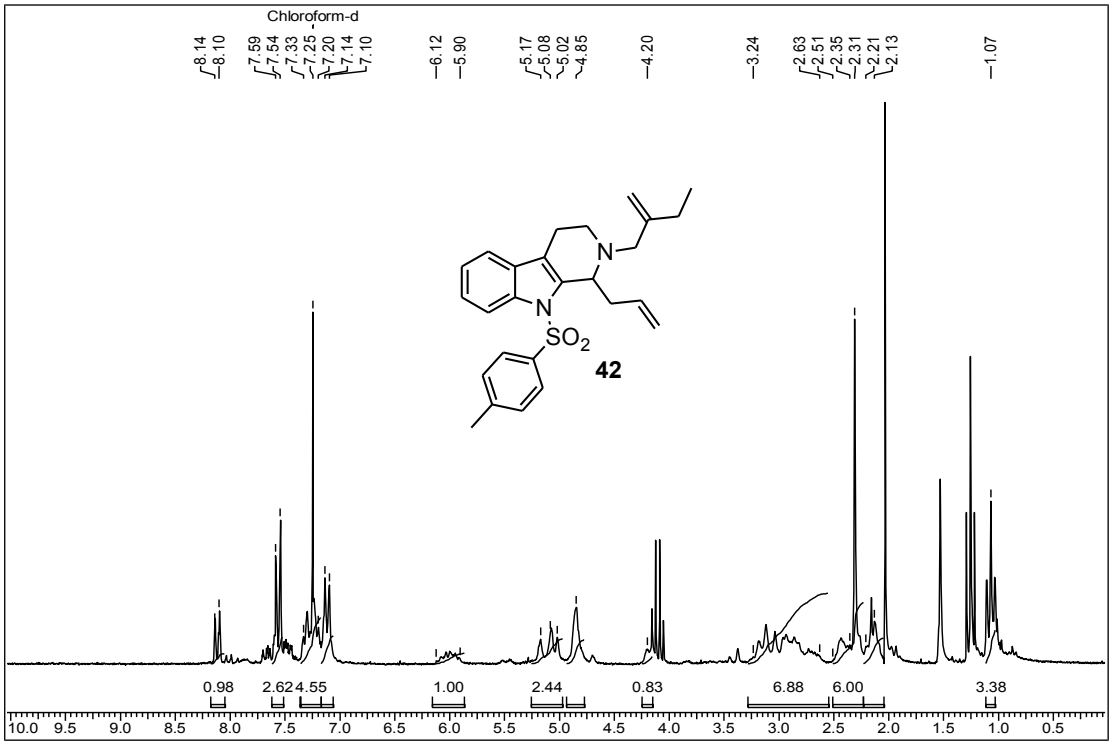
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 41



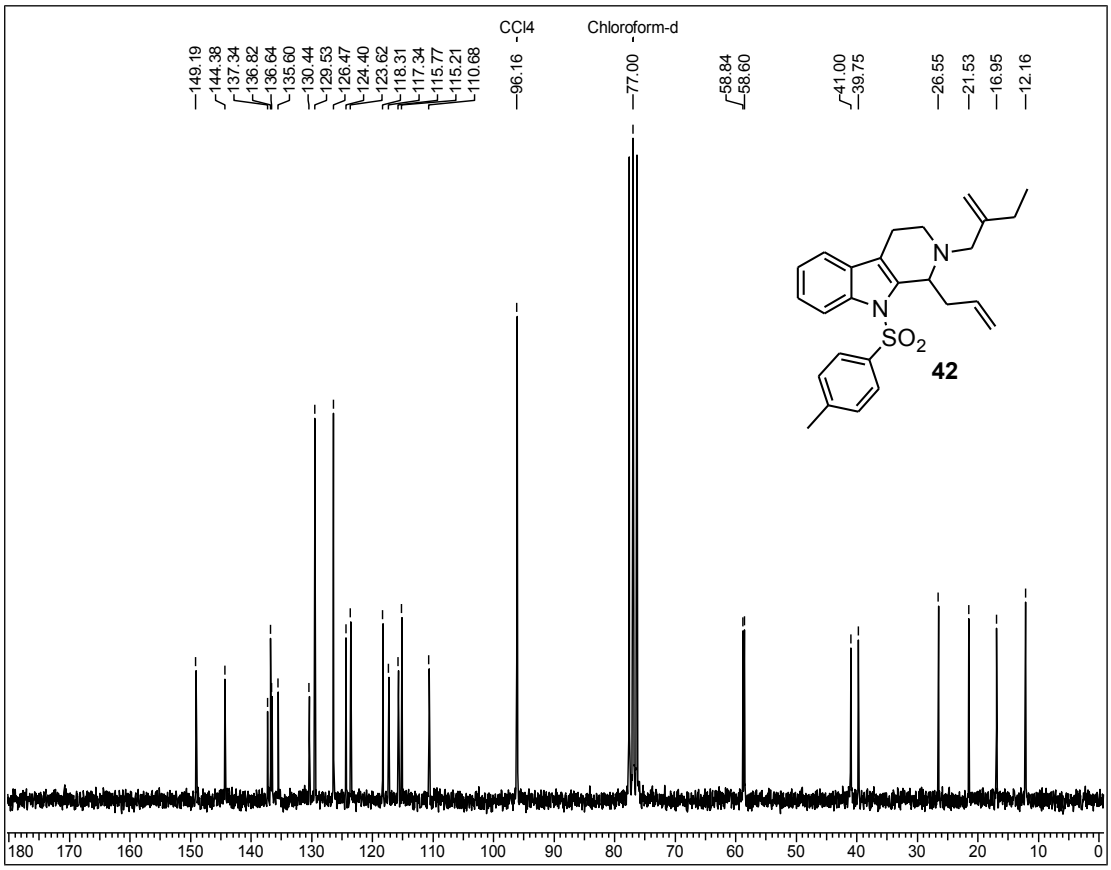
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 41



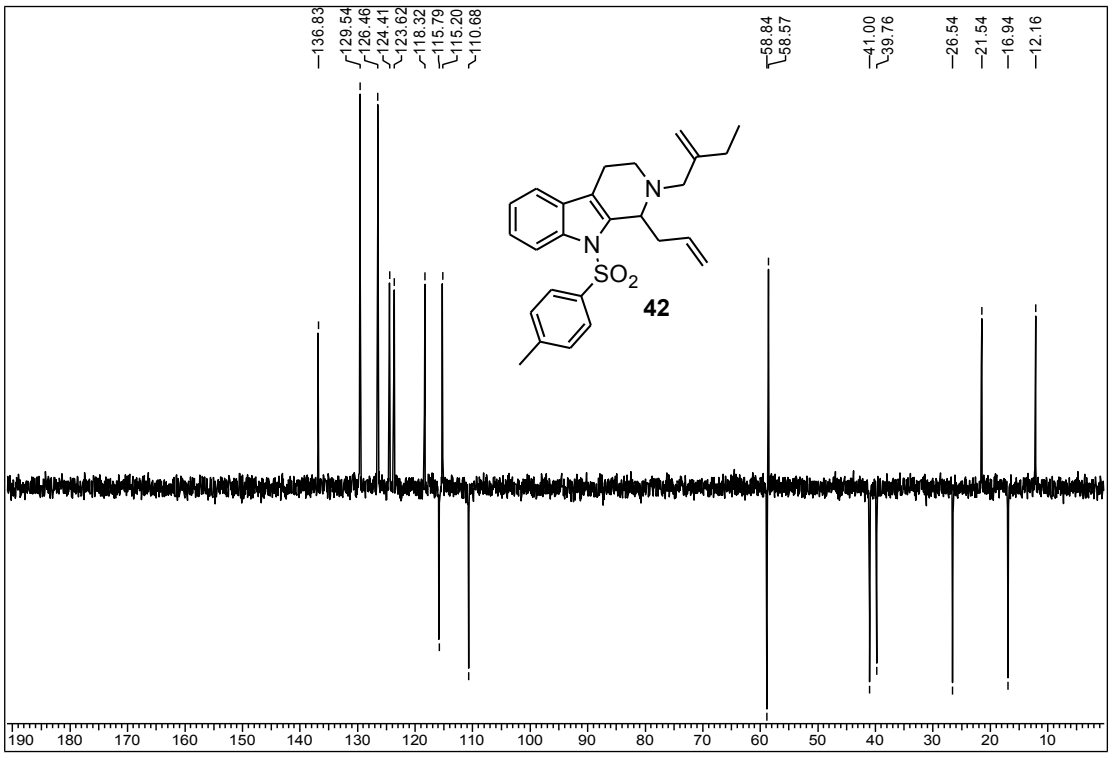
DEPT ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 41



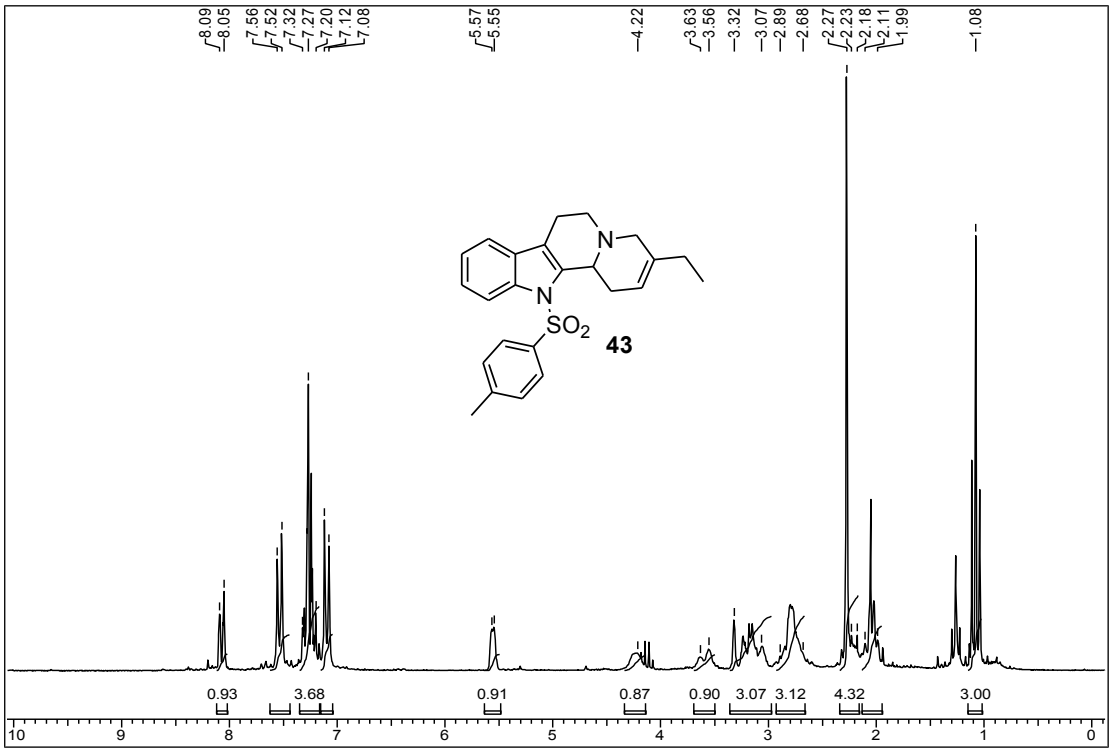
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 42



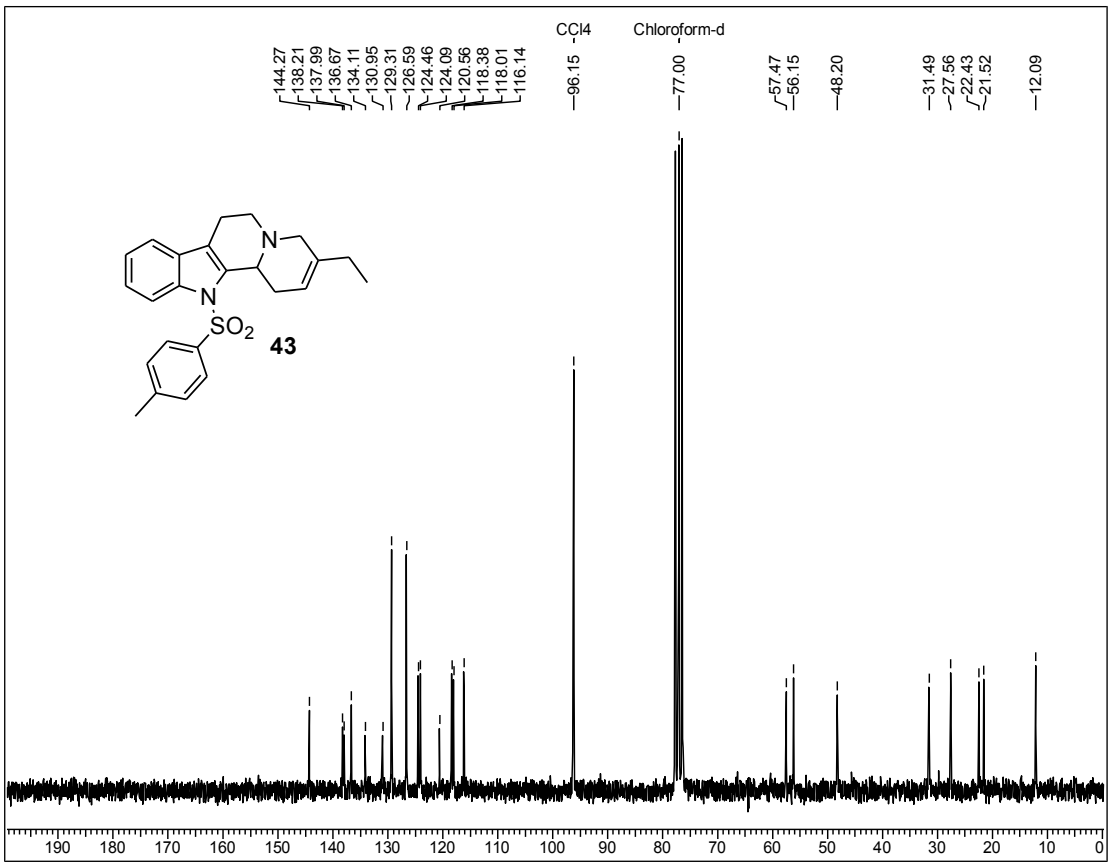
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 42



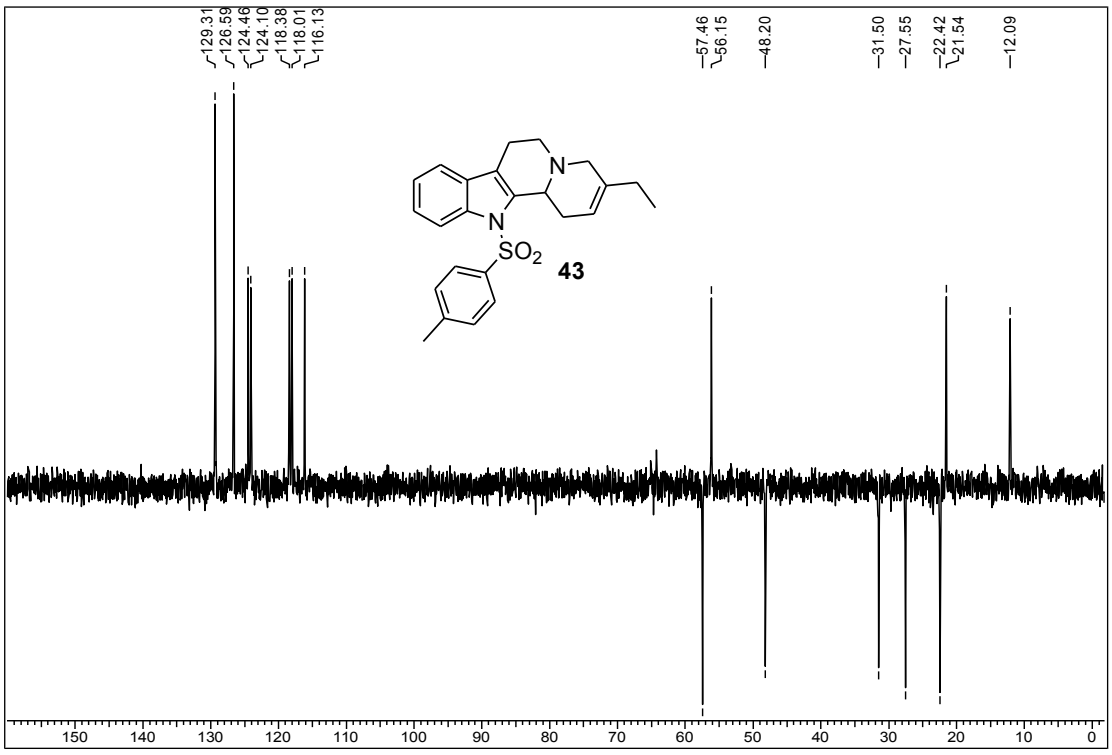
DEPT ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 42



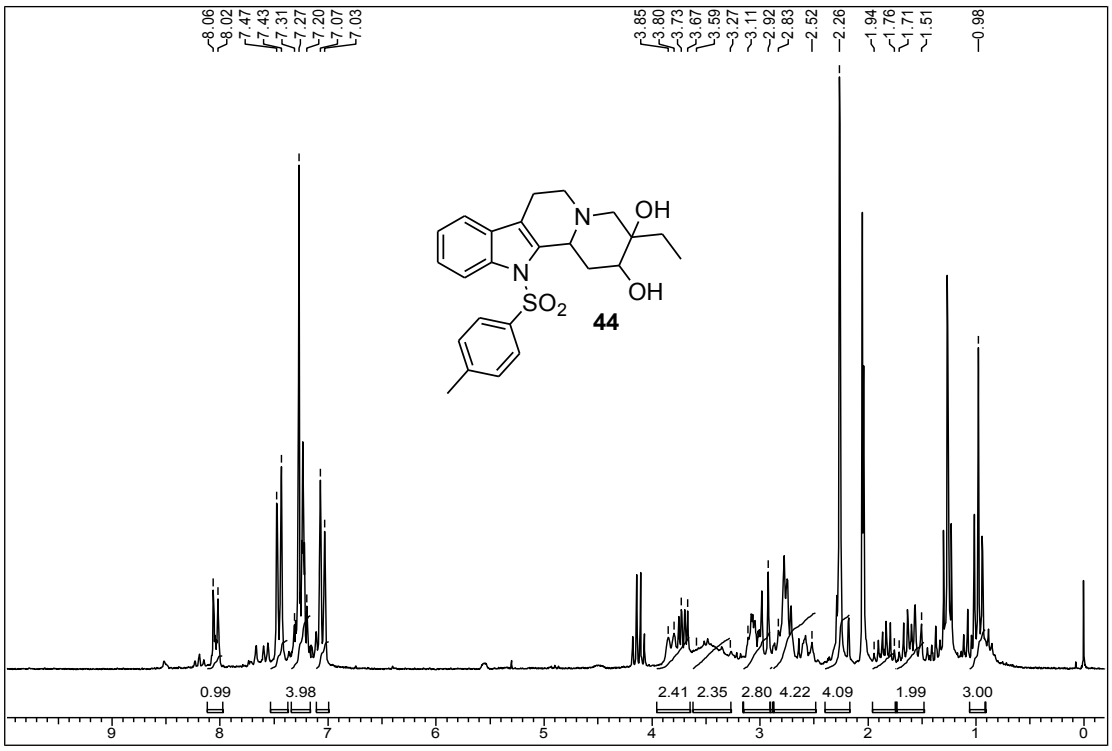
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 43



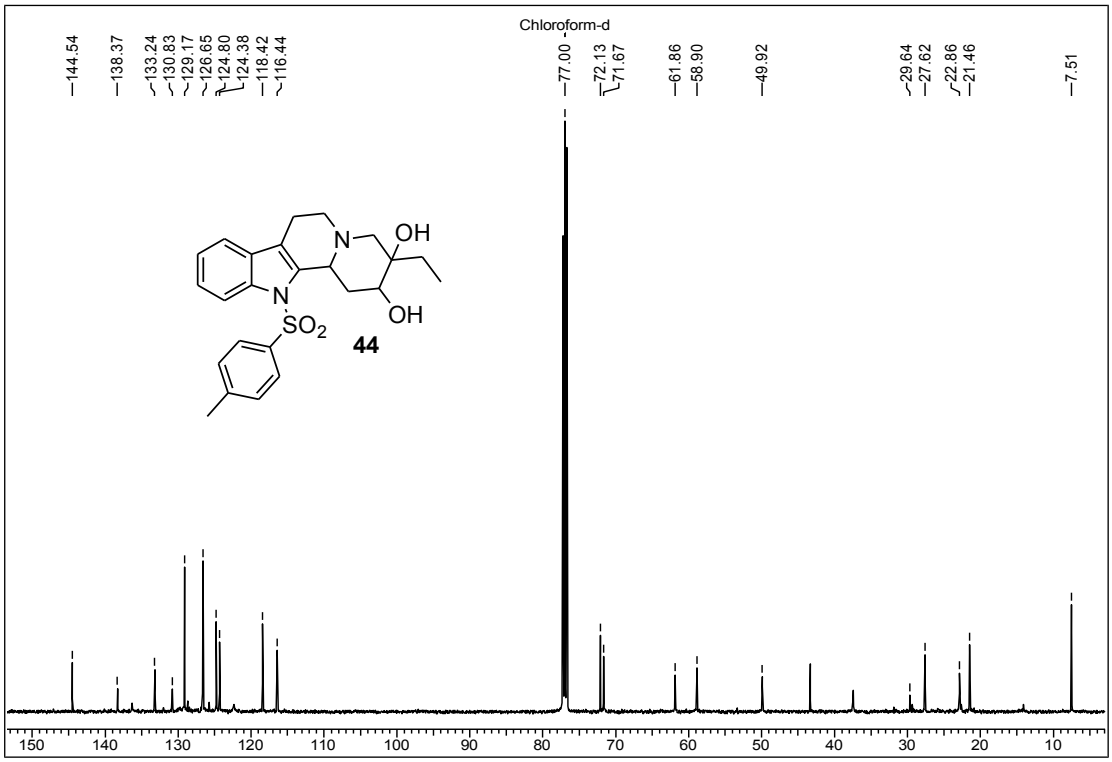
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 43



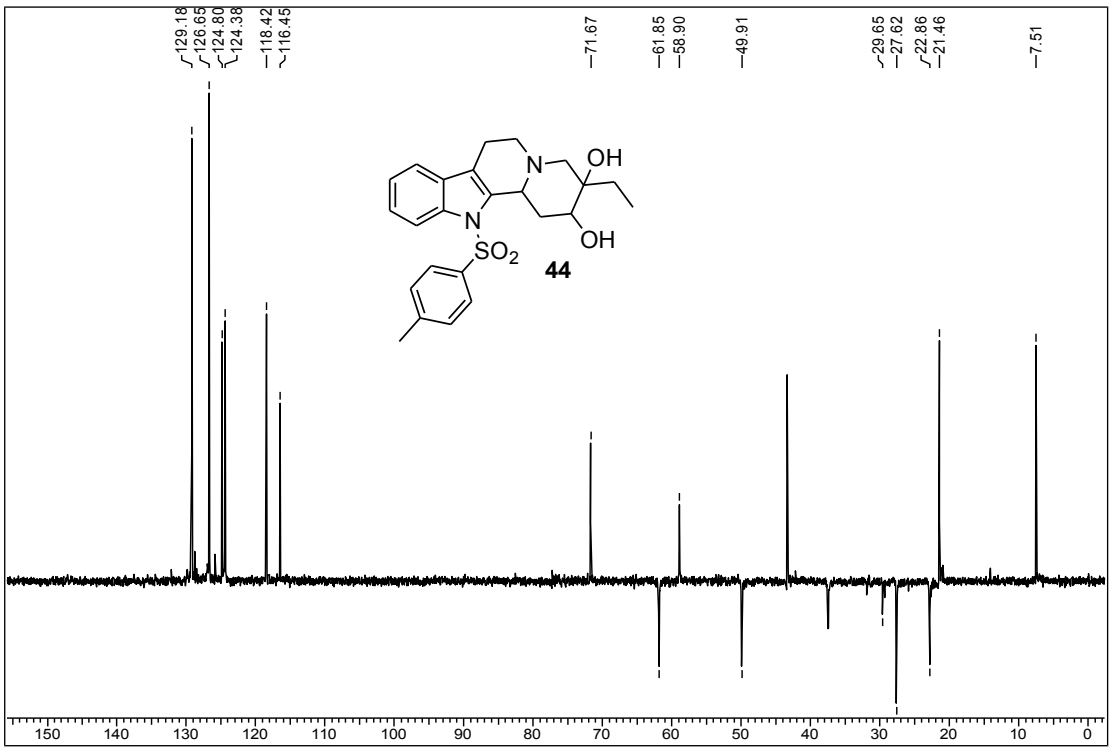
DEPT ($CDCl_3$+CCl_4, 50 MHz) spectrum of compound 43



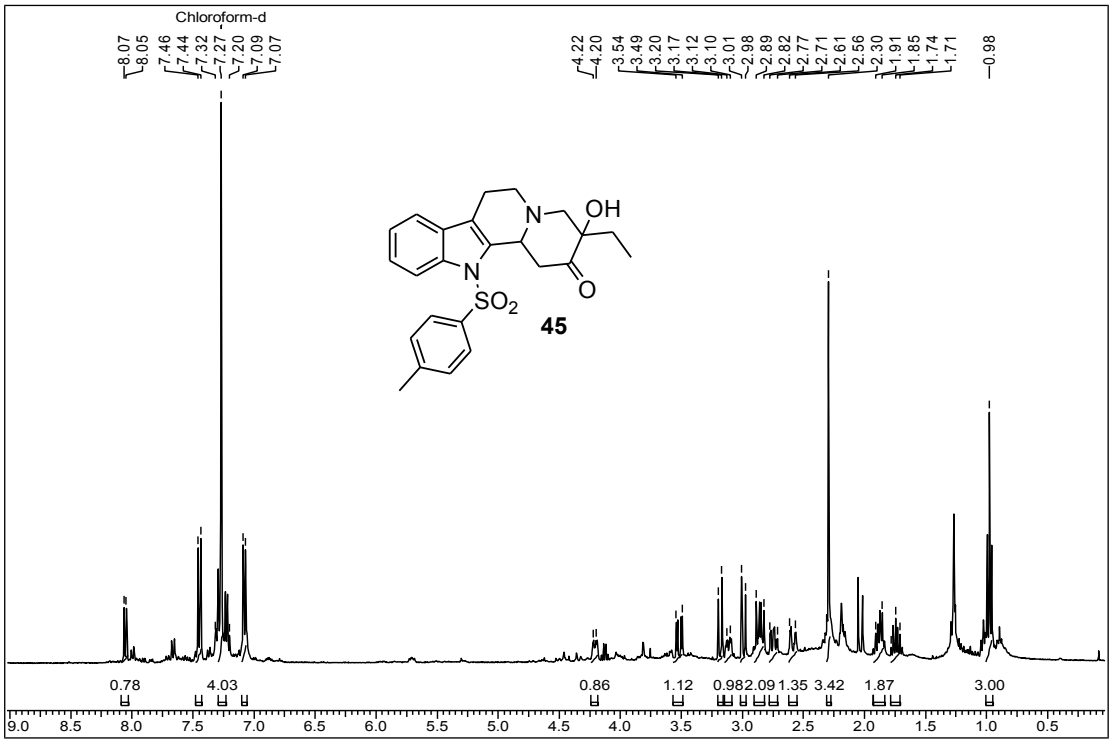
^{1}H NMR ($CDCl_3$, 200MHz) spectrum of compound 44



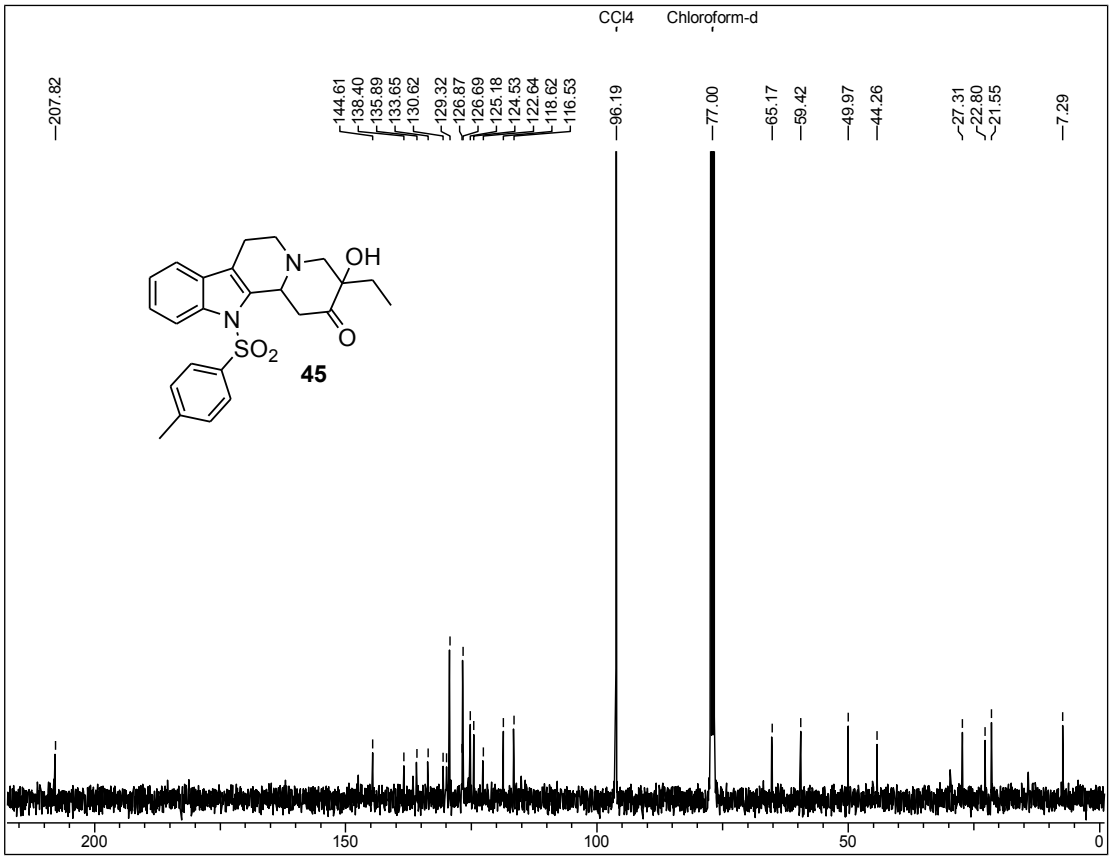
^{13}C NMR ($CDCl_3$, 125 MHz) spectrum of compound 44



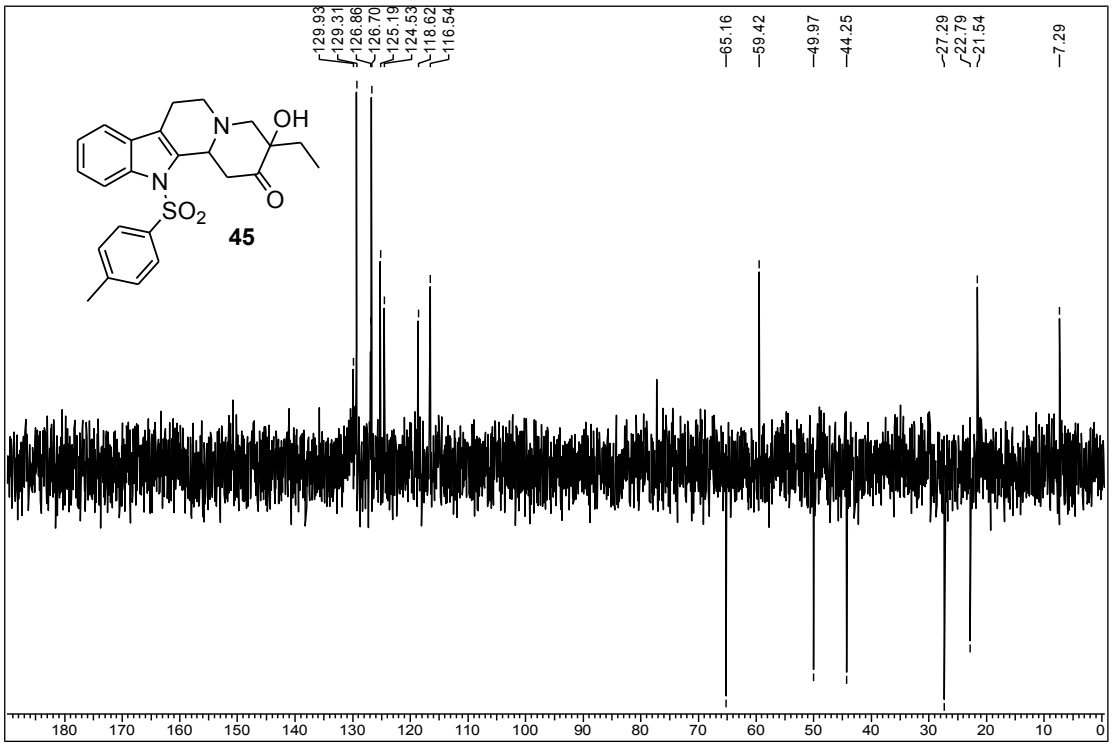
DEPT ($CDCl_3$, 125 MHz) spectrum of compound 44



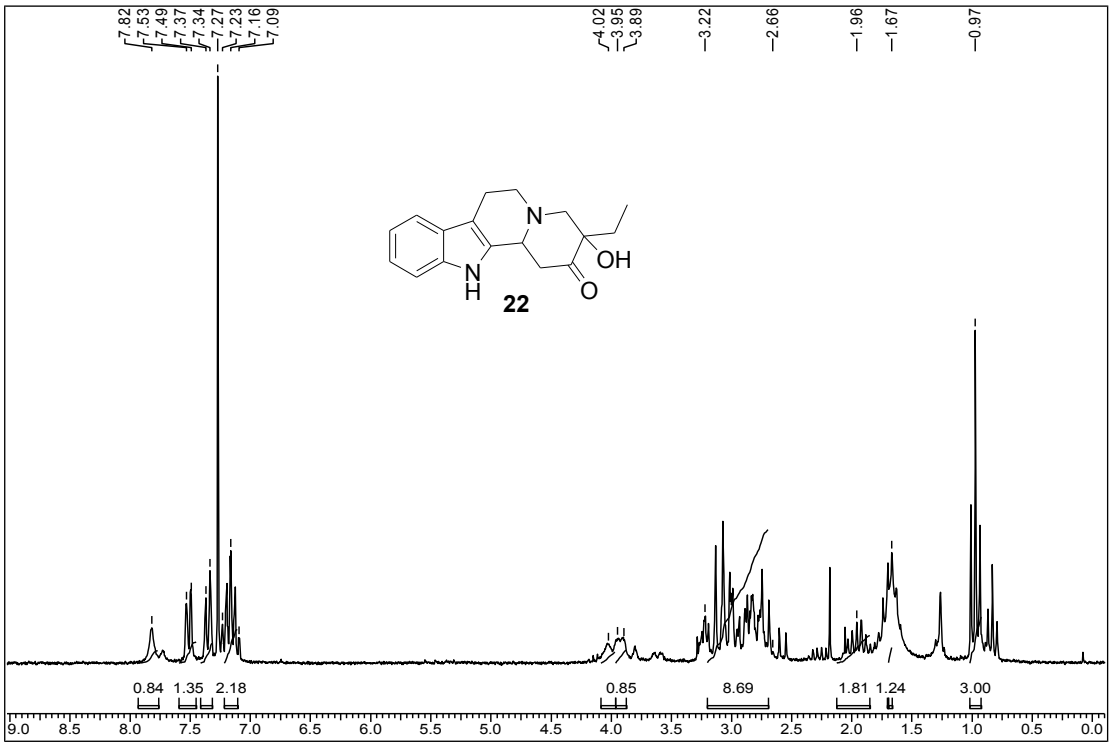
^{1}H NMR ($CDCl_3$+CCl_4, 400 MHz) spectrum of compound 45



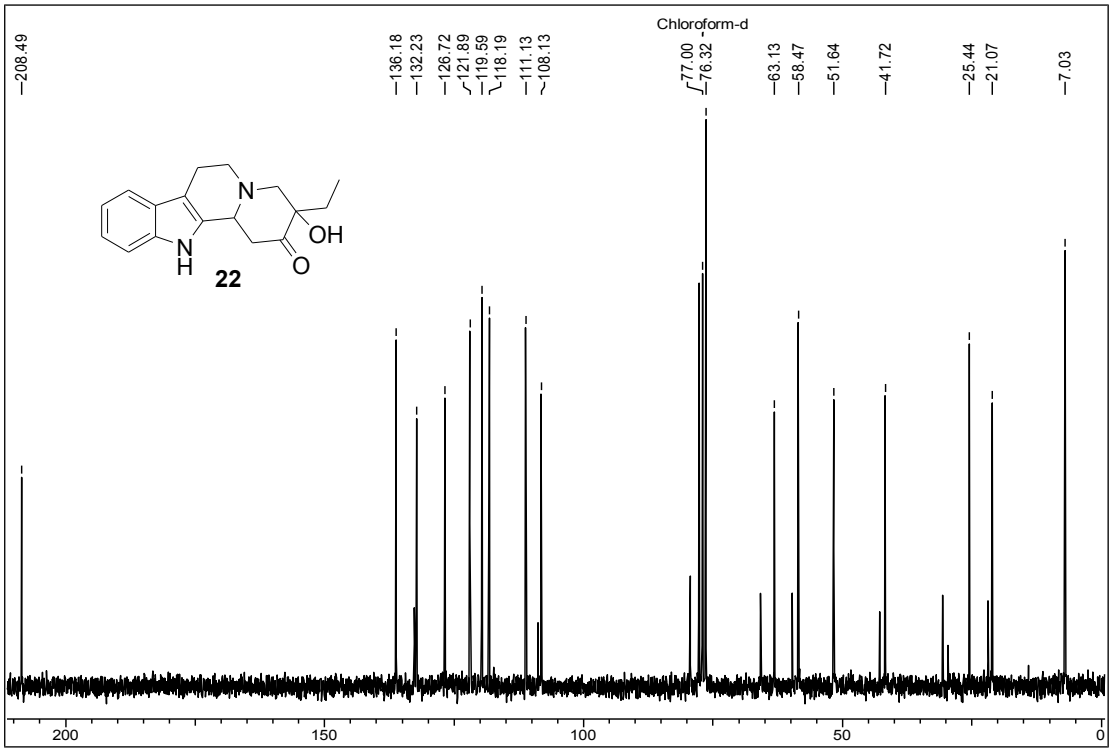
^{13}C NMR ($CDCl_3$+CCl_4, 100 MHz) spectrum of compound 45



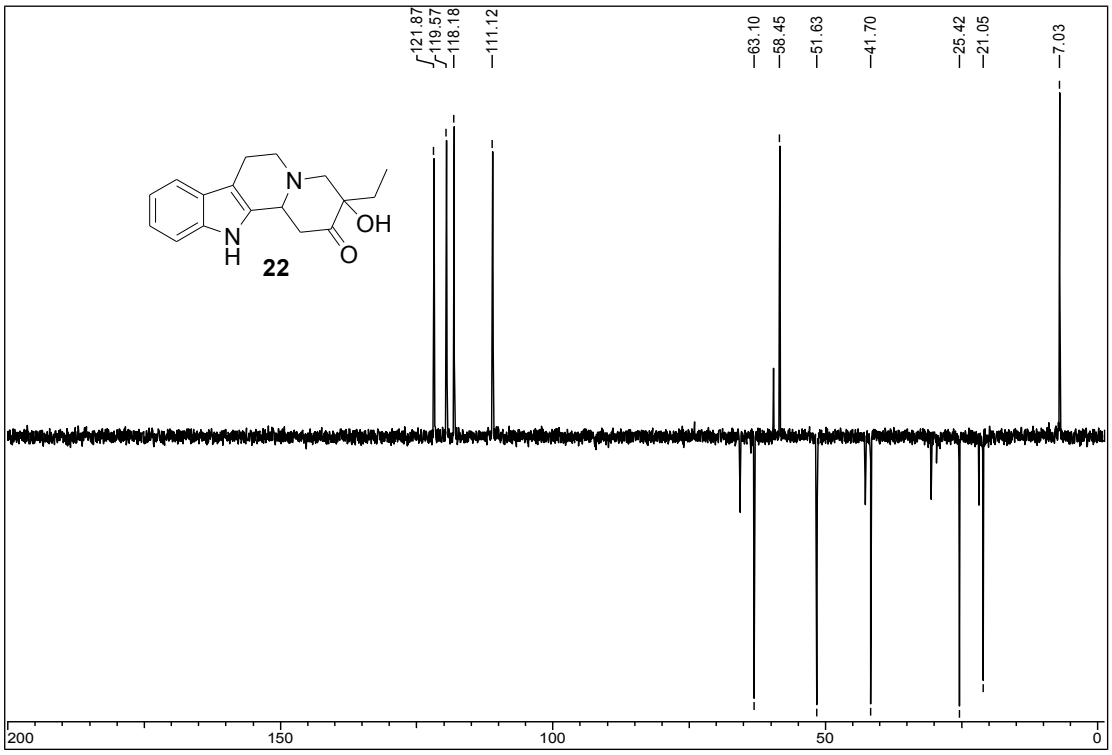
DEPT ($CDCl_3$+CCl_4, 100 MHz) spectrum of compound 45



^{1}H NMR ($CDCl_3$+CCl_4, 400 MHz) spectrum of compound 22



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



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

3.1.5. References

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Chapter 3 Section 2

I_2 as an Efficient Catalyst in the Ionic Diels-Alder Reaction of α, β-Unsaturated Acetals

3.2.1. Introduction

Diels-Alder reaction[1] finds immense utility in synthetic arena by virtue of its operational simplicity, generality and stereoselective construction of six membered rings. Although Diels-Alder reaction is a very powerful tool for six membered ring annulation, it is often marred with polymerization of diene as well as dienophiles under the reaction conditions. A useful variant of Diels-Alder reaction developed by Gassman *et.al*.[2] employs acetals or orthoesters of the α,β-unsaturated dienophile so as to avoid the problem of polymerization or isomerisation under thermal conditions. Thus in the Lewis acid catalysed ionic Diels-Alder reaction, powerful dienophiles are generated by transient formation of a carbocation, most powerful carbon based electron withdrawing group known, adjacent to the vinyl moiety which finally gives the neutral adduct. Thus the masked dienophiles furnish 4π+2π cycloadduct in high yield and under milder reaction conditions.

Till date a number of acids and Lewis acids *viz.* TfOH,[2b,e] TMSOTf,[2c] $BF_3.Et_2O$,[2d] $TiCl_4$-$Ti(O^iPr)_4$,[3] electro-generated acid,[4] $LiClO_4$,[5] Nafion-H[6a] and recently $InCl_3$[6b] have been studied as catalysts to effect 4π+2π cycloaddition reaction. A variety of protic acids are also known to catalyse the ionic Diels-Alder reactions, most of them are either very strong, employ harsh conditions as well involve hazardous reagents with unattractive reaction conditions thereby limiting their usage.

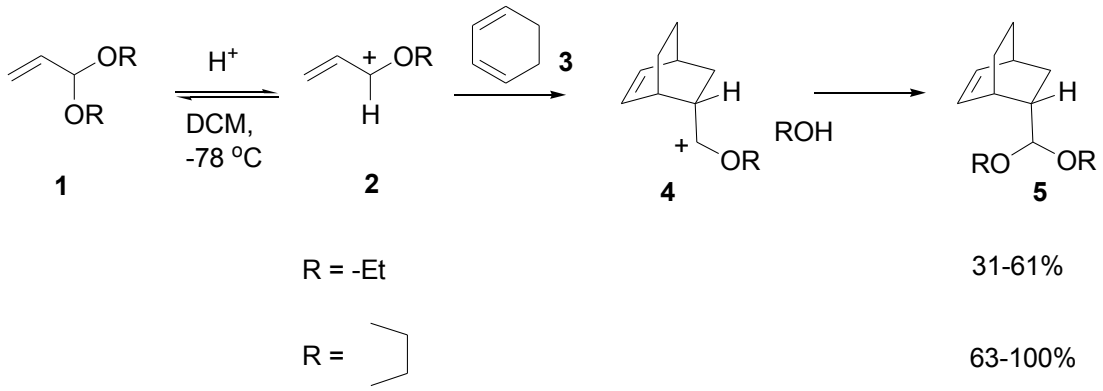
Recently our group has reported the use of $FeCl_3$ and $FeCl_3$ adsorbed on silica gel[7a] as well as $MgBr_2$[7b] as efficient catalysts for the ionic Diels Alder reaction.

3.2.2. Literature Survey

A short descriptive presentation of the work reported by different groups involving ionic Diels-Alder reaction is being presented to give a better and comparative view of the different catalyst employed so far.

Gassman et al.[2b] described for the first time the useful variant of the Diels-Alder reaction involving acetals of acrolein as a convenient precursors of the alkoxy-substituted allyl cations**,** which served as excellent dienophiles.

Scheme 1: Gassman et al. (*J. Am. Chem. Soc*. **1987**, *109*, 2182)

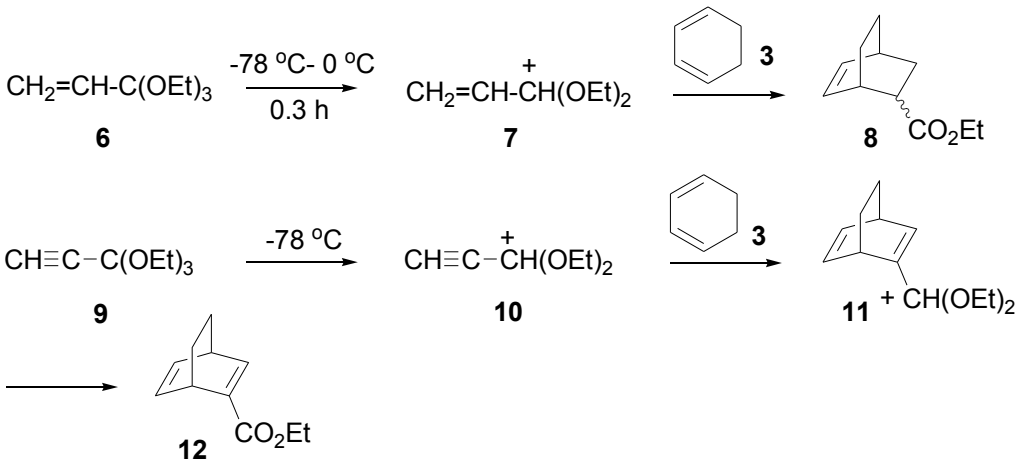


Catalyst: Triflic acid in 1,1,2-trichloro-1,2,2-trifluoro ethane

Reacting different 1,3-dienes and acetals taken in DCM at –78 °C with 2 mol% of triflic acid in 1,1,2-trichloro-1,2,2-trifluroethane gave good yields of the corresponding cycloadduct.

A dramatic increase in the yield of cycloadduct was realised by the use of corresponding cyclic acetals in place of the acyclic one (Scheme 1).

Scheme 2: Gassman et al. (*J. Org. Chem.* **1988**, *53*, 2392 and *Tetrahedron Lett*. **1988**, *29*, 3407)



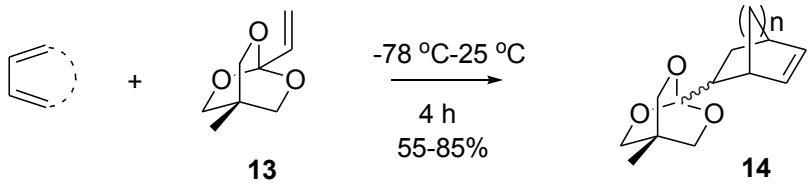
Catalyst: Trimethyl silyl triflate

The group further demonstrated the triethylortho acrylate as excellent precursor of the 1,1-diethoxyallyl cation which adds to 1,3-dienes at low temperature to produce the corresponding adducts of ethyl acrylate as the final product[2c] (Scheme 2).

Using the same catalyst a formal low temperature addition of ethyl propiolate to 1,3-diene *via* intermediacy of propargyl cation was achieved.[8]

The concept was further extended to cyclic ortho ester which underwent cycloaddition with various cyclic and acyclic diene at low temperature with boron-trifluoride-diethyl ether as catalyst to furnish the adduct with retention of the ortho ester protecting group[2d] (scheme 3).

Scheme 3: Gassman et al. (*J. Chem. Soc., Chem. Comm.* **1989**, 837)

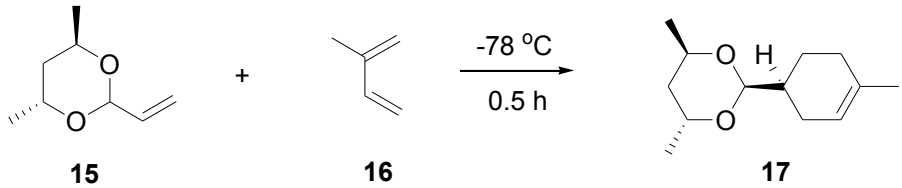


13 14

Catalyst: Boron trifluoride-diethyl ether

Chiral acetals derived from 2,4-pentanediol was shown to proceed with good diastereoselection to provide enantiomerically enriched cyclohexene carboxaldehyde derivatives catalysed by equimolar mixture of $TiCl_4$ and $Ti(O^iPr)_4$[3] (Scheme 4).

Scheme 4: Sammakia et al. (*J. Org. Chem.* **1994**, *59*, 6890)

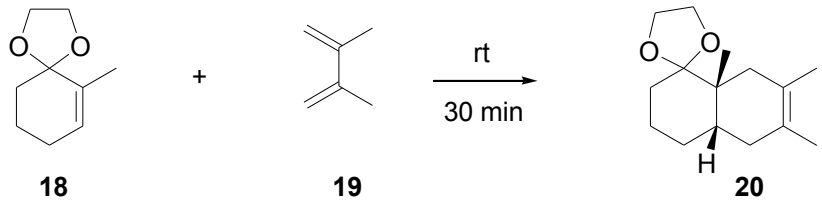


15 16 17

Catalyst: $TiCl_4$ + $Ti(O^iPr)_4$

Ketals and orthoester of unsaturated ketones and esters, respectively, undergo inter and intra molecular ionic Diels-Alder reactions in the presence of 4.0-5.0 M $LiClO_4$-diethyl ether containing a few mol% of camphor sulphonic acid[5] (Scheme 5).

Scheme 5: Grieco et al. (*Synlett.* **1995**, 1155)

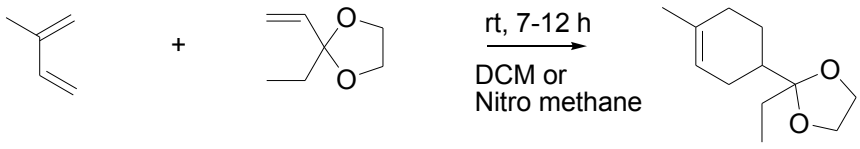


18 **19** **20**

Catalyst: 4.0 M $LiClO_4$-Et_2O; 1.0 mol% CSA

Vankar et al.[6a] demonstrated the efficiency of $LiClO_4$ in nitromethane and Nafion-H in dichloromethane to catalyse the reaction of variety of achiral olefinic acetals with isoprene and cyclopentadiene to form the cycloadducts (Scheme 6).

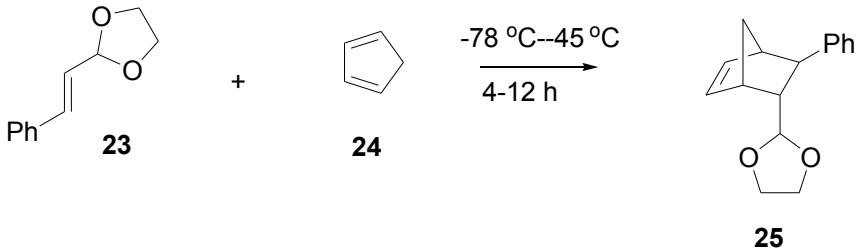
Scheme 6: Vankar et al. (*Tetrahedron* **1999**, *55*, 1099)



16 **21** **22**

Catalyst: $LiClO_4$ in Nitro methane; Nafion-H in DCM

Scheme 7: Vankar et al. (*Tetrahedron Lett*. **2000**, *41*, 10333)



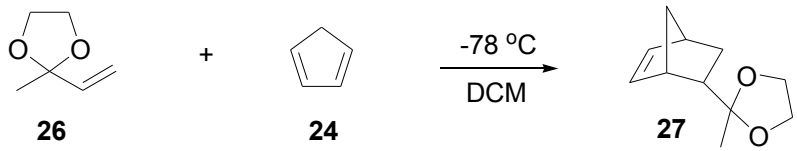
23 **24** **25**

Catalyst: $InCl_3$ (20 mol%) in nitro methane

Indium trichloride[6b] (20 mol%) in nitromethane was shown to catalyse ionic Diels–Alder reaction of a variety of 2,3-olefinic acetals to form the corresponding cycloadducts in good yields with good *endo* selectivities (Scheme 7).

Enone acetals and diene under went cycloaddition catalysed by electrogenerated acid.[4] The reaction was performed using platinum electrodes in dichloromethane containing lithium perchlorate ($LiClO_4$) and tetrabutylammonium perchlorate as a source of acid catalyst (Scheme 8).

Scheme 8: Torii et al. (*J. Org. Chem.* **1990**, *55*, 3958)

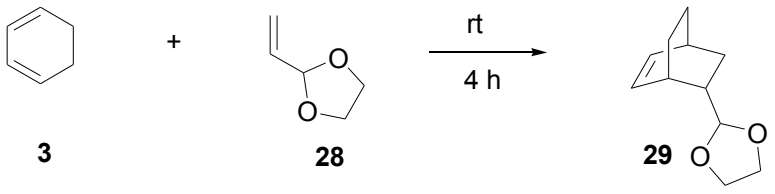


26 **24** **27**

Catalyst: Electrogenerated acid

Chavan et al.[7a] demonstrated the utility of $FeCl_3$ and $FeCl_3$ absorbed on silica gel as efficient Lewis acid catalyst for ionic Diels-Alder reaction rendering the cycloadduct in good to excellent yield and selectivity (Scheme 9). Just in another endeavor Chavan et al. exploited the oxophilic propensity of $MgBr_2$[7b] which showed efficient catalysing power to promote ionic Diels-Alder reaction to furnish the cycloadducts (Scheme 9).

Scheme 9: Chavan et al. (*Synlett*. **2001**, 667 and *Syn. Com.* **2007**)



3 **28** **29**

Catalysts: i) $FeCl_3$ or $FeCl_3$ adsorbed on silica gel
ii) $MgBr_2$

3.2.3. Present Work

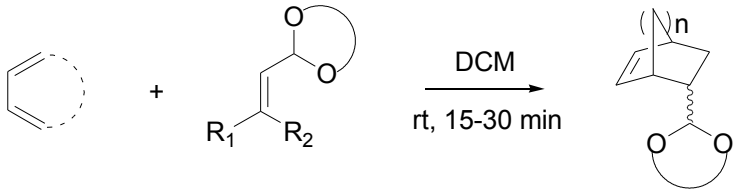
Molecular iodine is an age-old reagent which has been widely utilised in a wide variety of organic transformation due its mild Lewis acidity as well as oxidising property. It has immense utility due to its operational simplicity, low cost and less toxicity and thus becomes more important environmentally benign reagent for functional group transformation. It is especially utilised for the oxidation of alcohols and aldehydes to

esters,[9] nitriles[10] and amides, introduction of protecting groups,[11] transesterification,[12] deprotection,[11] iodocyclisation,[13] C-C bond formation[14] and formation of heterocycles.[15]

Intrigued by the special characteristic of the molecular iodine interest to study its ability to catalyse the much studied reaction of "ionic Diels-Alder reaction" was undertaken. Earlier use of $FeCl_3$[7a] and $MgBr_2$[7b] as Lewis acid has been efficiently demonstrated in the ionic Diels-Alder reaction of variously substituted dienes and masked dienophiles. It was decided to explore the propensity of I_2 to catalyse the ionic Diels-Alder reaction.

In context with Diels-Alder reaction I_2 has been reported wherein it activates substrates like *N*-allyl enamides and lactam derivatives, anilide and maleimide derivatives *via* the formation of cationic intermediates arising from iodolactonisation, to give the cycloadducts. In all the above, the presence of a suitably placed olefin is critical and crucial for the success of the reaction. Aditionally, an excess (2 eq.) of iodine has to be employed to affect the Diels–Alder reaction.[16]

In the present study I_2 was found to catalyse all kinds of masked α,β-unsaturated dienophiles bearing no activating group, with equal ease. It was observed that the Diels-Alder reactions of acrolein acetal were efficiently catalysed by iodine to furnish the adducts in 15–30 min, with high selectivity.

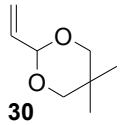
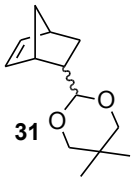
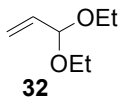
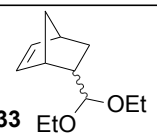
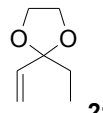
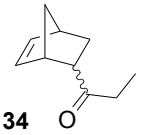
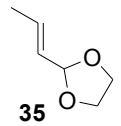
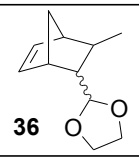
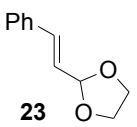
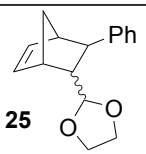


Catalyst: Iodine (I_2)

Scheme 10

When a mixture of the 2,2-dimethylpropylene acetal of acrolein **30** and cyclopentadiene (**24**) (1:2) in dry DCM at 0 °C was treated with 0.1 eq. of I_2, the adduct **31** was obtained in excellent yield after quenching the reaction with Et_3N and purification by column chromatography. The product was obtained as a mixture of *endo* and *exo* isomers 12.6:1. The characteristic doublets at δ 3.7 and δ 4.2 in the ^1H NMR spectrum indicated the ratio of *endo* and *exo* isomers respectively.

Table 1

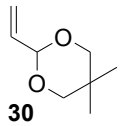
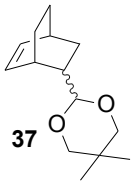
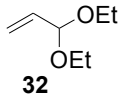
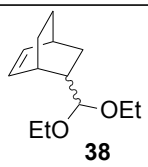
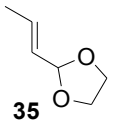
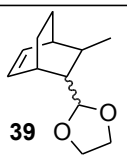
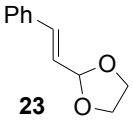
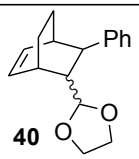
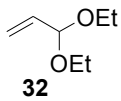
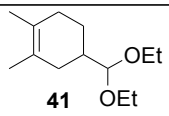
Entry	Diene	Dienophile	Product	Method	Yield *Endo: exo*[1i]
1.	 **24**	 **30**	 **31**	1a	80[1e] (12.6:1)
2.	 **24**	 **32**	 **33**	1b	70[1f] (8.34:1)
3.	 **24**	 **21**	 **34**	1d	85[1e] (10:1)
4.	 **24**	 **35**	 **36**	1a	45[1f] (3.5:1)
5.	 **24**	 **23**	 **25**	1c	67[1f] (21:1)

1a) Diene: dienophile 2:1, I_2 (0.1 eq.), 15-30 mins, DCM, 0 °C; 1b) Diene: dienophile 2:1, I_2 (<0.05 eq.), 15-30 mins, DCM, 0 °C; c) Diene: dienophile 2:1, I_2 (0.2 eq.), overnight, DCM (stored over K_2CO_3), 0 °C; d) corresponding hydrolysed product obtained; e) reported in lit. ref. 4; f) reported in lit ref. 6b; g) reported in ref. 2b; h) only endo isomer obtained; i) determined by ^1H NMR.

To demonstrate the generality of this protocol a variety of protected α,β-unsaturated dienophiles substituted at various positions were subjected to reaction with both cyclic and acyclic dienes. Moderate to excellent yields were obtained as shown in Table 1 and Table 2. As shown in Table 1, acetals of both ketones and aldehydes participated smoothly to give appreciable yields. It is noteworthy that the yield from the reaction of **30** with cyclopentadiene (**24**) in the presence of I_2 is far better than that reported using electro-generated acids. As shown in entries 2–4 in Table 2 reaction with cyclohexadiene

resulted in almost exclusive formation of *endo* isomers in all cases. The protocol developed works equally well for both acyclic and cyclic acetals. Variously substituted dienophiles react to different extents to furnish the corresponding cycloadducts in varying yields, although the selectivity remains unaffected. In most of the cases the *endo*: *exo* ratio was determined by the ^{1}H NMR spectral studies.

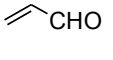
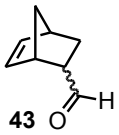
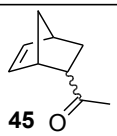
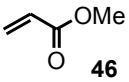
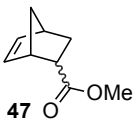
Table 2

Entry	Diene	Dienophile	Product	Method	Yield *Endo: exo*[2e]
1.	 **3**	 **30**	 **37**	1a	73
2.	 **3**	 **32**	 **38**	1a	73[2c,2d]
3.	 **3**	 **35**	 **39**	1a	61[2c,2d]
4.	 **3**	 **23**	 **40**	1c	48[2d]
5.	 **19**	 **32**	 **41**	1a	43

2a) Diene: dienophile 2:1, I_2 (0.1 eq.), 15-30 mins, DCM, 0 ^{o}C; 2b) Diene: dienophile 2:1, I_2 (0.2 eq.), overnight, DCM (stored over K_2CO_3), 0 ^{o}C; 2c) reported in ref. 2b; 2d) only endo isomer obtained; 2e) determined by ^{1}H NMR.

Interestingly, it was observed that under the above mentioned reaction conditions, I_2 also effectively catalyses the Diels–Alder reaction of unprotected dienophiles (Table 3), which are known to undergo polymerisation under most of the reported reaction conditions, in good to moderate yields. Here in few cases the *endo*: *exo* ratio was determined by GC analysis.

Table 3

Entry	Diene	Dienophile	Product	Method	Yield *Endo:exo*[3d]
1.	 **24**	 **42**	 **43**	3a	74[3c]
2.	 **24**	 **44**	 **45**	3b	77[3c]
3.	 **24**	 **46**	 **47**	3a	40

3a) Diene: dienophile (2:1), I_2, (0.05 eq.), DCM, 15-30 min; 3b) Diene: dienophile (2:1), I_2, (0.1 eq.), DCM, 15-30 min; 3c) determined by ^1H NMR; 3d) determined by GC.

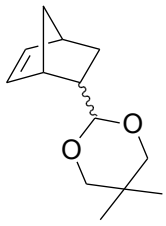
In conclusion, this study clearly demonstrates the efficiency of I_2 to catalyse ionic Diels-Alder reactions of protected dienophiles as well as those of unprotected dienophiles with dienes for cycloadduct formation with high selectivity and good yields over very short reaction times.

3.2.4. Experimental

General procedure for iodine catalysed Diels-Alder reaction

To a well-stirred mixture of the protected dienenophlie (1 eq.) and diene (2 eq.) in dichloromethane at 0 ^{o}C under nitrogen atmosphere was added 0.1 eq. of iodine and stirred at room temperature till the completion of the reaction (15-30 min). On completion (TLC), the reaction was quenched with the addition of Et_3N and the product purified through column chromatography (SiO_2) without further work up.

2-(Bicyclo[2.2.1]hept-5-en-2-yl)-5,5-dimethyl-1,3-dioxane (31)



Mol. Formula : $C_{13}H_{20}O_2$

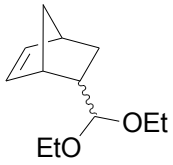
Yield : 80%

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 2956, 2869, 1734, 1470.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.15-6.10 (m, 1H), 5.93-5.89 (m, 1H), 4.21 (minor isomer), 3.72 (d, *J* = 8.3 Hz, 1H), 3.61-3.50 (m, 2H), 3.34-3.27 (m, 2H), 2.95 (br s, 1H), 2.80 (br s, 1H), 2.38-2.25 (m, 1H), 1.89-1.77 (m, 1H), 1.42-1.35 (m, 1H), 1.25 (m, 1H), 1.18 (s, 3H), 0.88-0.83 (m, 1H), 0.69 (s, 3H).

Mass (EI) : *m/z* 208, 167, 141, 128, 115, 91, 77, 66.

5-(Diethoxymethyl)bicyclo[2.2.1]hept-2-ene (33)



Mol. Formula : $C_{12}H_{20}O_2$

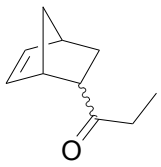
Yield : 70%

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3059, 2974, 2875, 1720, 1115.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 6.14-6.09 (m, 1H), 5.94-5.90 (m, 1H), 4.26 (minor isomer), 3.82 (d, *J* = 9.1, 1H), 3.70-3.38 (m, 5H), 2.84 (br s, 1H), 2.76 (br s, 1H), 2.44-2.31 (m, 1H), 1.85-1.72 (m, 1H), 1.41-1.30 (m, 1H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H), 0.81-0.72 (m, 1H).

Mass (EI) **:** *m/z* 210, 196, 183, 172, 167, 153, 138, 103, 91, 85, 81, 75.

1-(Bicyclo[2.2.1]hept-5-en-2-yl)propan-1-one (34)



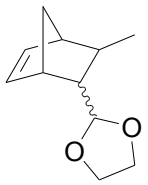
Mol. Formula **:** $C_{10}H_{14}O$

Yield **:** 85%

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) **:** 2930, 1700, 1622.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 6.14-6.09 (m, 1H), 5.81-5.77 (m, 1H), 3.20 (br s, 1H), 3.02-2.94 (m, 1H), 2.88 (br s, 1H), 2.42 (q, *J* = 7.4 Hz, 2H), 1.78-1.67 (m, 1H), 1.53-1.41 (m, 2H), 1.31-1.24 (m, 1H), 1.00 (t, *J* = 7.4 Hz, 3H).

2-(3-Methylbicyclo[2.2.1]hept-5-en-yl)-1,3-dioxolane (36)



Mol. Formula **:** $C_{11}H_{16}O_2$

Yield **:** 45%

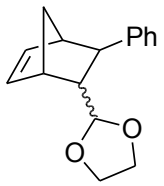
IR (neat) $\tilde{\nu}$ (cm^{-1}) **:** 3058, 2928, 2907, 2872, 1731, 1570.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 6.20-6.15 (m, 1H), 6.05-5.95 (m, 1H), 4.72 (minor isomer), 4.19 (d, *J* = 8.3 Hz, 1H), 3.96-3.89 (m, 2H), 3.86-3.73 (m, 2H), 2.86 (br s, 1H), 2.39

(br s, 1H), 1.60-1.47 (m, 2H), 1.40-1.22 (m, 2H), 1.14 (s, 3H).

Mass (EI) **:** *m/z* 180, 165, 151, 139, 113, 105, 91, 77, 73.

2-(3-Phenylbicyclo[2.2.1]hept-5-en-2-yl)-1,3-dioxolane (25)



Mol. Formula **:** $C_{16}H_{18}O_2$

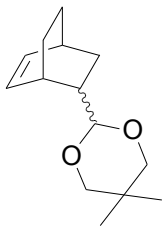
Yield **:** 67%

IR (neat) $\tilde{\nu}$ (cm^{-1}) **:** 3061, 2957, 2849, 1729, 1600.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 7.63-7.23 (m, 5H), 6.44-6.37 (m, 1H), 6.30-6.25 (m, 1H), 4.99 (minor), 4.51 (d, *J* = 8.3 Hz, 1H), 4.01-3.93 (m, 2H), 3.90-3.80 (m, 2H), 3.14 (br s, 1H), 3.04 (br s, 1H), 2.64 (br d, 1H), 2.41-2.33 (m, 1H), 1.90-1.79 (m, 1H), 1.63-1.58 (m, 1H).

Mass (EI): **:** *m/z* 242 (6), 176 (72), 104 (100), 91 (16), 66 (28).

2-(Bicyclo[2.2.2]oct-5-en-2-yl)-5,5-dimethyl-1,3-dioxane (37)



Mol. Formula **:** $C_{14}H_{22}O_2$

Yield **:** 73%

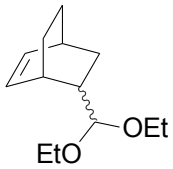
IR (neat) $\tilde{\nu}$ (cm^{-1}) **:** 3040, 2959, 2866, 2845, 1727, 1469, 1393.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 6.29-6.21 (m, 1H), 6.11-6.04 (m, 1H), 3.79 (d, *J* = 8.2 Hz, 1H), 3.60-3.49 (m, 2H), 3.34-3.20 (m, 2H), 2.69 (br s, 1H), 2.47 (br s, 1H), 1.98-1.86 (m, 1H), 1.69-1.57 (m, 1H), 1.52-1.40 (m, 1H), 1.30-

1.18 (m, 3H), 1.15 (s, 3H), 1.10-1.01 (m, 1H), 0.67 (s, 3H).

Mass (EI) **:** *m/z* 222, 193, 179, 168, 154, 141, 128, 115, 107, 91, 79.

5-(Diethoxymethyl)bicyclo[2.2.2]oct-2-ene (38)



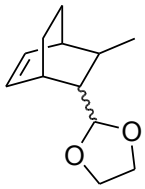
Mol. Formula **:** $C_{13}H_{22}O_2$

Yield **:** 73%

IR (neat) $\tilde{\nu}$ (cm^{-1}) **:** 3042, 2973, 2866, 2359, 1642, 1444.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 6.29-6.22 (m, 1H), 6.13-6.06 (m, 1H), 3.88 (d, *J* = 9 Hz, 1H), 3.67-3.37 (m, 4H), 2.59 (br s, 1H), 2.49 (br s, 1H), 2.03-1.90 (m, 1H), 1.68-1.55 (m, 1H), 1.51-1.37 (m, 2H), 1.31-1.22 (m, 2H), 1.19 (t, *J* = 7.3 Hz, 3H), 1.14 (t, *J* = 7.3 Hz, 3H), 1.10-0.98 (m, 1H).

2-(3-Methylbicyclo[2.2.2]oct-5-en-2-yl)-1,3-dioxolane (39)



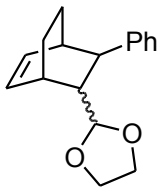
Mol. Formula **:** $C_{12}H_{18}O_2$

Yield **:** 61%

IR (neat) $\tilde{\nu}$ (cm^{-1}) **:** 2949, 2872, 1634, 1471, 1403.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 6.38-6.31 (m, 1H), 6.12-6.05 (m, 1H), 4.31 (d, *J* = 7.3 Hz, 1H), 3.94-3.85 (m, 2H), 3.83-3.74 (m, 1H), 2.55 (br s, 1H), 2.17 (br s, 1H), 1.80-1.66 (m, 1H), 1.52-1.28 (m, 3H), 1.25-1.16 (m, 2H), 1.08 (s, 3H), 1.04 (m, 1H).

2-(3-Phenylbicyclo[2.2.2]oct-5-en-2-yl)-1,1-dioxolane (40)



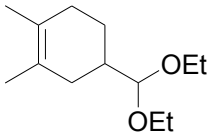
Mol. Formula : $C_{17}H_{20}O_2$

Yield : 48%

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) : 3042, 2890, 2802, 1608.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.45-7.20 (m, 5H), 6.52-6.45 (m, 1H), 6.30-6.22 (m, 1H), 4.46 (d, *J* = 7 Hz, 1H), 3.93-3.65 (m, 4H), 2.83 (br s, 1H), 2.66 (br s, 1H), 2.44 (br s, 1H), 2.22-2.16 (m, 1H), 1.76-1.56 (m, 2H), 1.46-1.27 (m, 1H), 1.09-0.87 (m, 1H).

4-(Diethyoxymethyl)-1,2-dimethylcyclohex-1-ene (41)



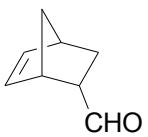
Mol. Formula : $C_{13}H_{24}O_2$

Yield : 43%

IR (neat) $\tilde{\nu}$ (cm^{-1}) : 2980, 2799, 1375, 1201, 1034.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.18 (d, *J* = 6.8 Hz, 1H), 3.71-3.58 (m, 2H), 3.56-3.40 (m, 2H), 1.92-1.73 (m, 7H), 1.59 (s, 6H), 1.20 (t, *J* = 7.3 Hz, 6H).

Bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (43)



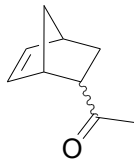
Mol. Formula : $C_8H_{10}O$

Yield : 74%

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) **:** 2960, 2930, 2870, 1720, 1452.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 9.40 (d, *J* = 2.6 Hz, 1H), 6.22-6.16 (m, 1H), 6.00-5.96 (m, 1H), 3.23 (br s, 1H), 2.97 (br s, 1H), 2.94-2.84 (m, 1H), 1.76-1.66 (m, 1H), 1.51-1.39 (m, 2H), 0.97 (m, 1H).

1-(Bicyclo[2.2.1]hept-5-en-2-yl)ethanone (45)



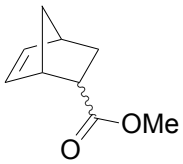
Mol. Formula **:** $C_9H_{12}O_2$

Yield **:** 77%

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) **:** 3062, 1690, 1332, 1077.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 6.10-6.06 (m, 1H), 5.81-5.76 (m, 1H), 3.18 (br s, 1H), 2.98-2.90 (m, 1H), 2.84 (br s, 1H), 2.06 (s, 3H), 1.75-1.62 (m, 1H), 1.48-1.37 (m, 2H), 1.29-1.25 (m, 1H).

Methyl bicyclo[2.2.1]hept-5-ene-2-carboxylate (47)

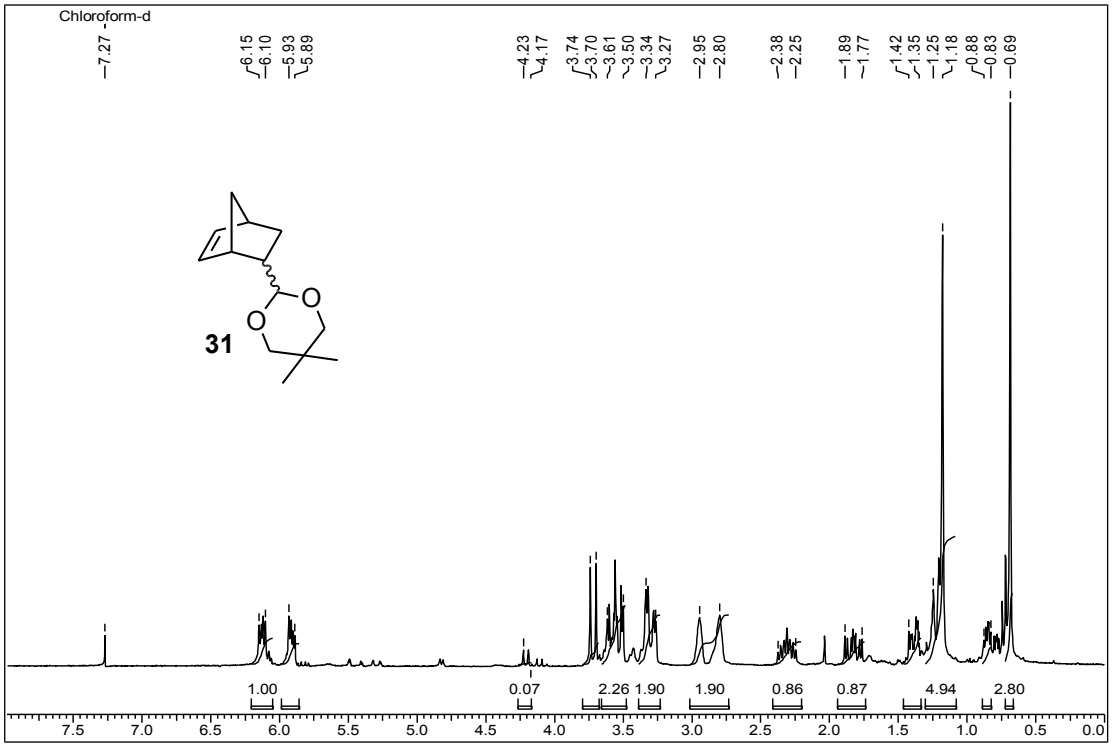


Mol. Formula **:** $C_9H_{12}O_2$

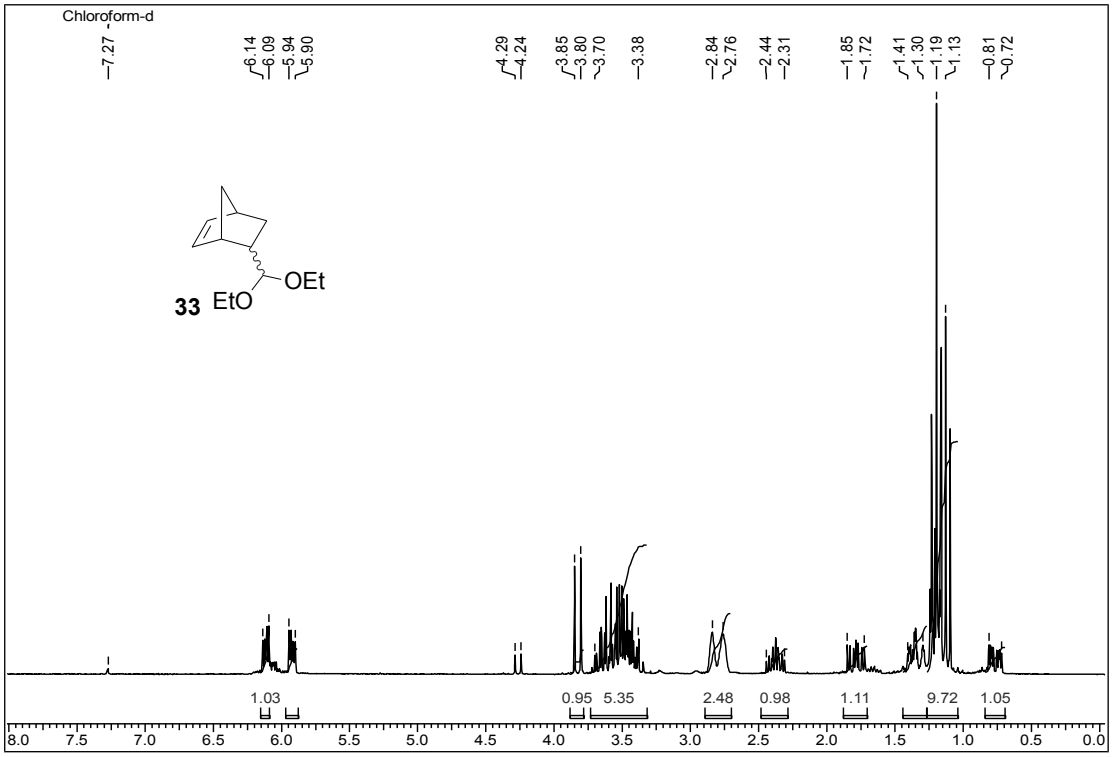
Yield **:** 40%

IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}) **:** 2990, 1740, 1690, 1340, 1070.

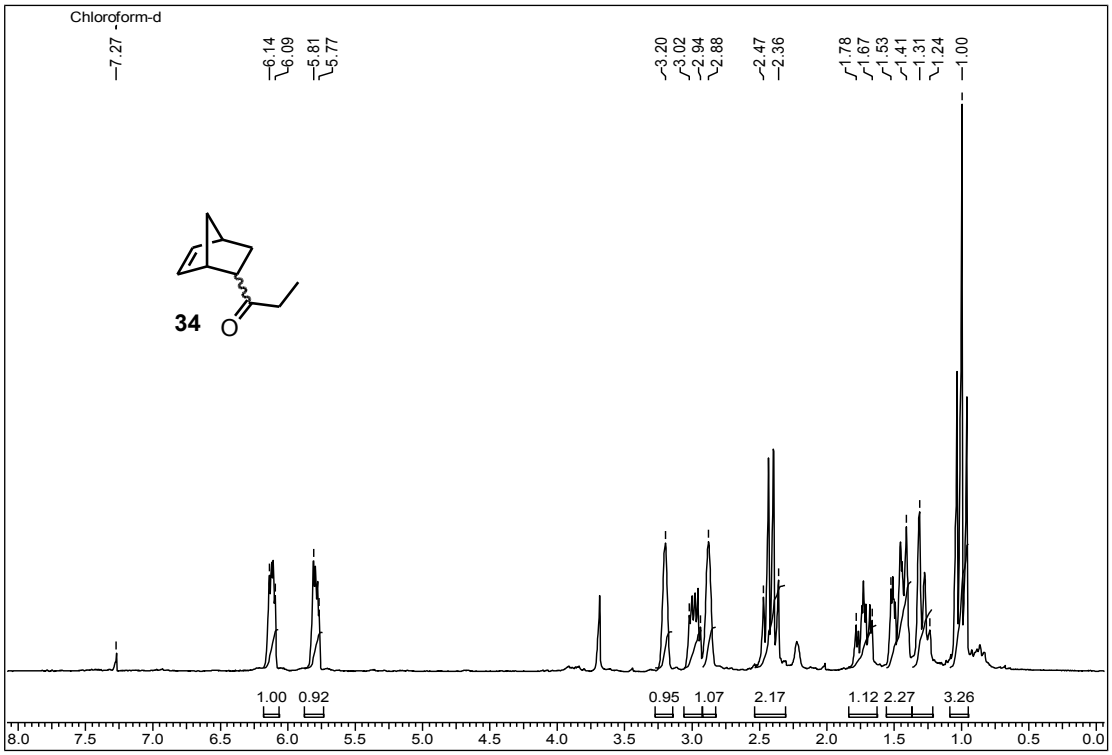
^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 6.19-6.15 (m, 1H), 5.92-5.88 (m, 1H), 3.61 (s, 3H), 3.19 (br s, 1H), 2.97-2.88 (m, 2H), 1.95-1.83 (m, 1H), 1.46-1.36 (m, 1H), 1.28-1.24 (m, 1H).



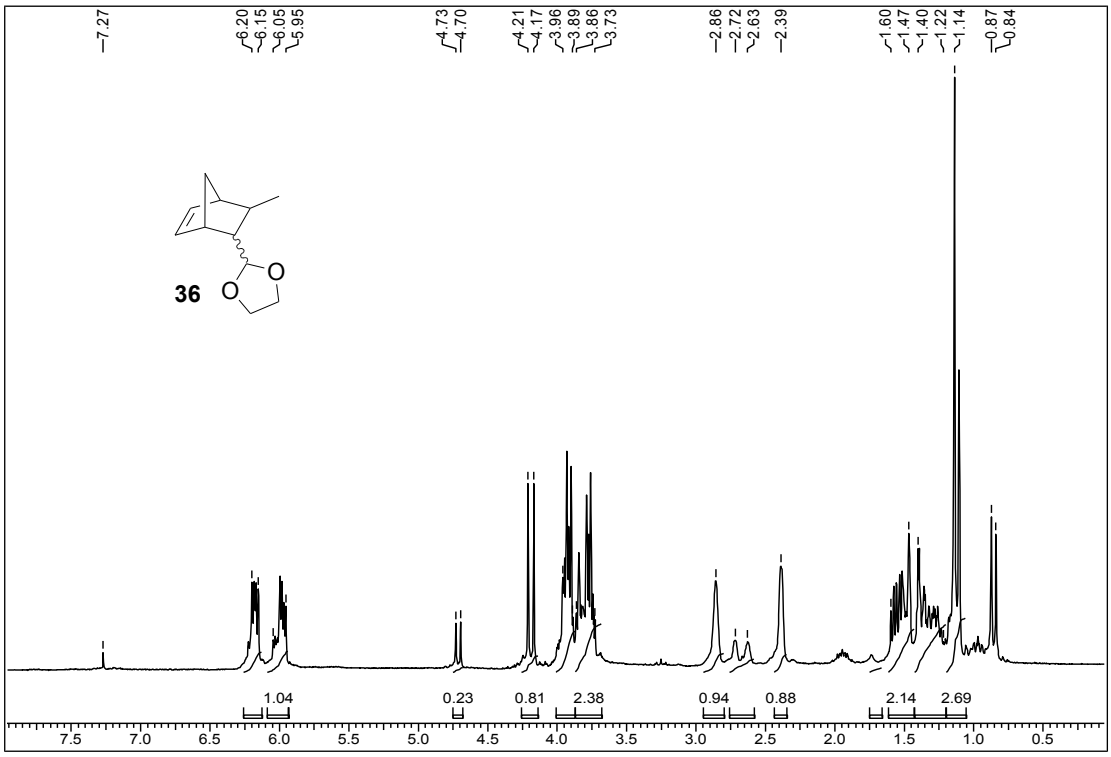
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 31



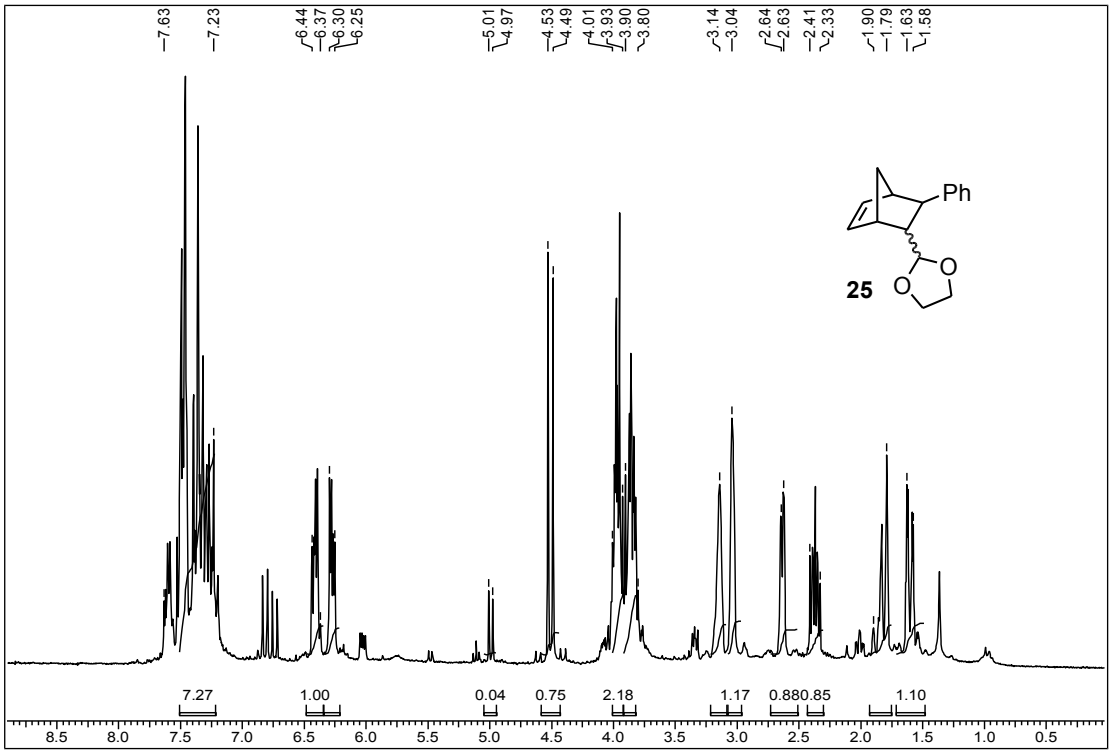
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 33



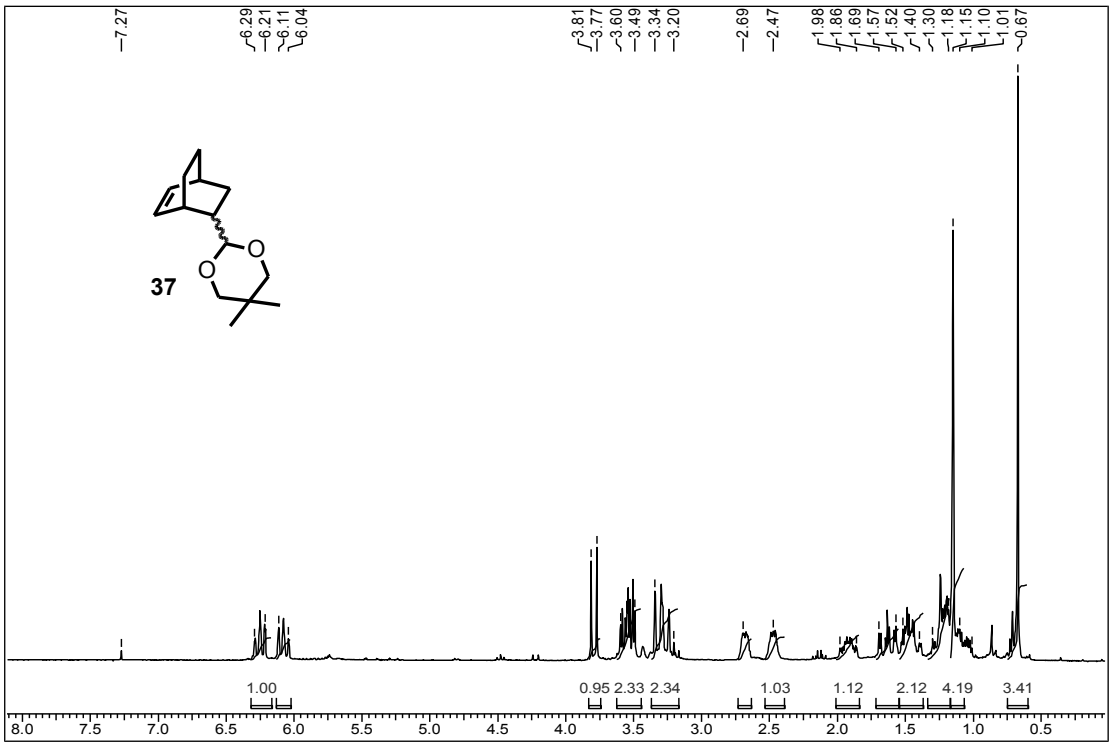
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 34



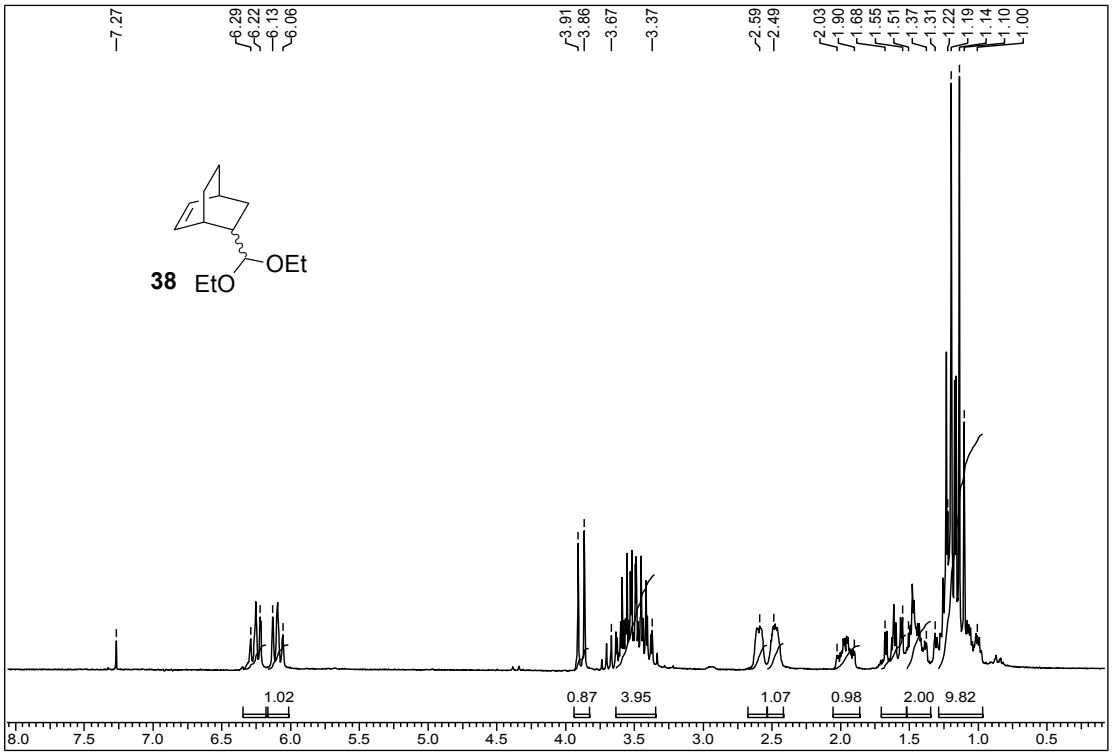
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 36



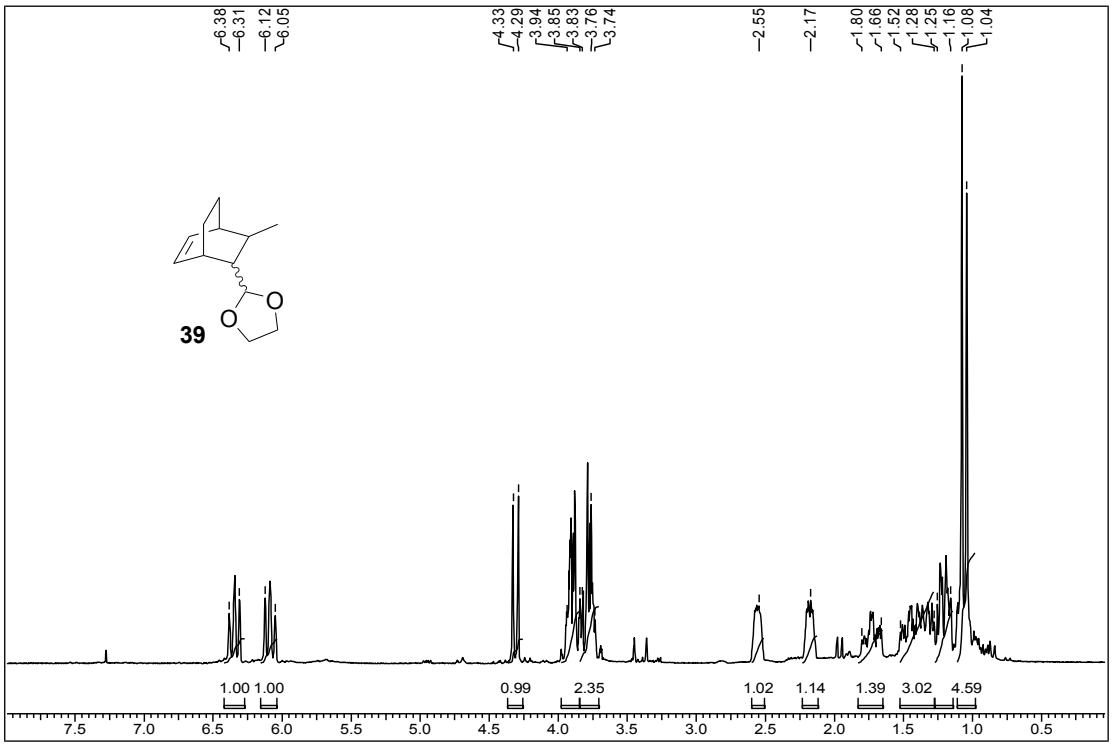
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 25



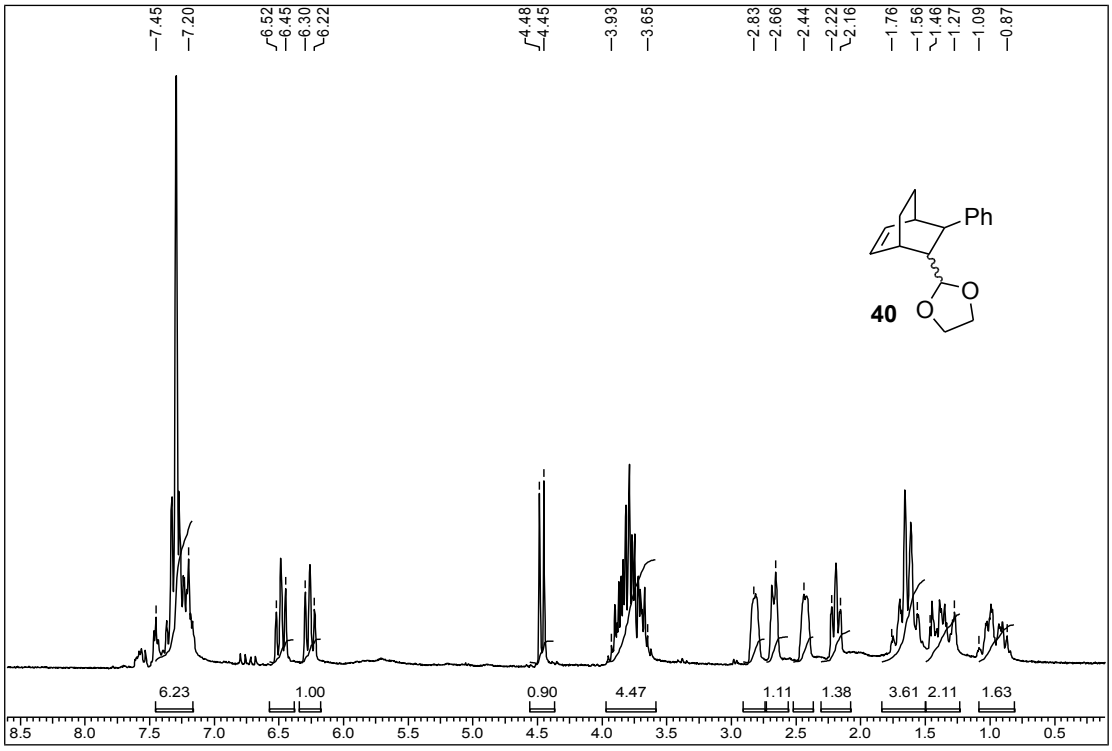
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 37



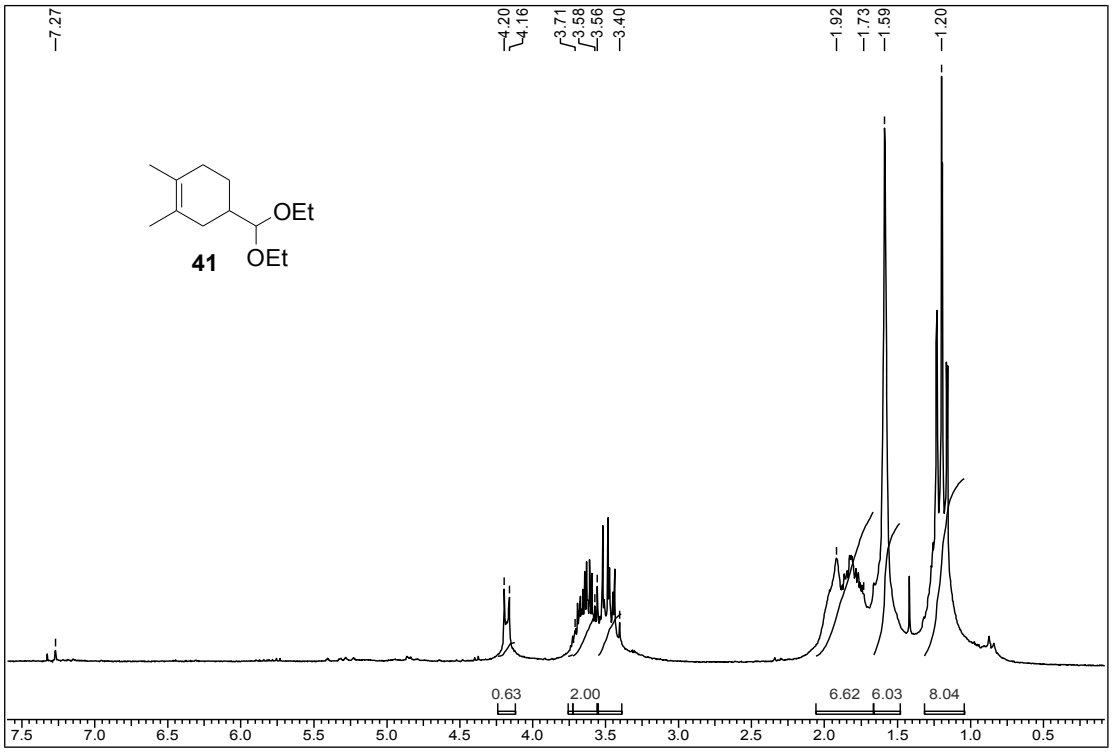
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 38



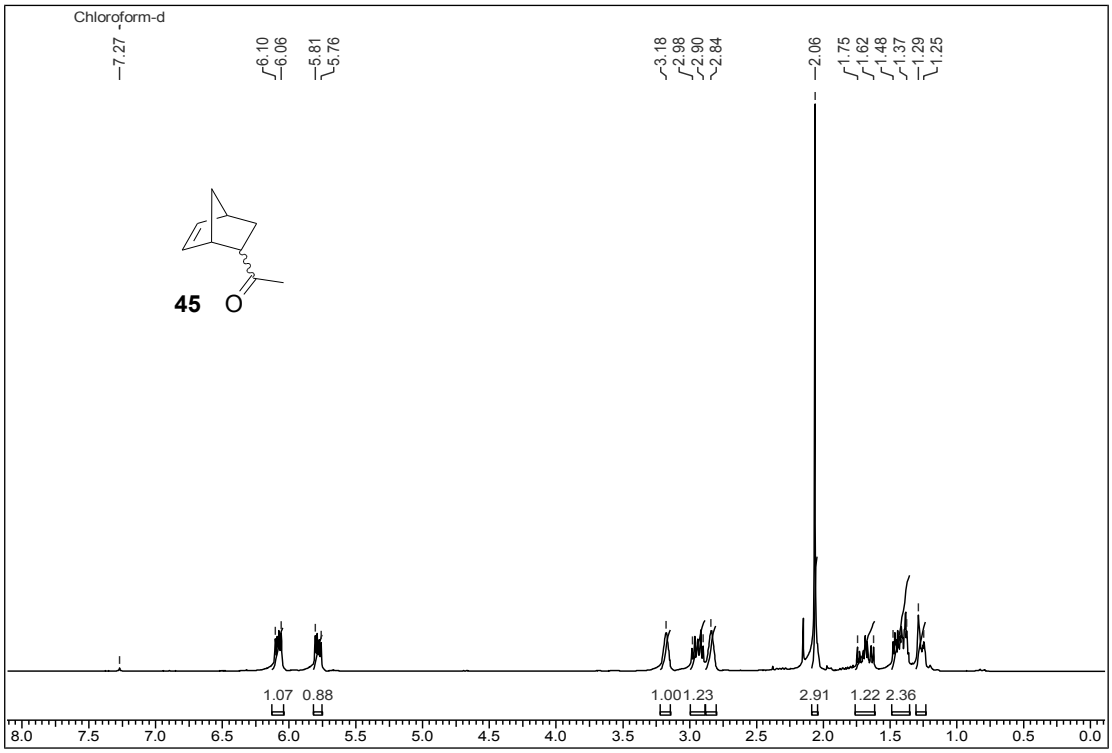
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 39



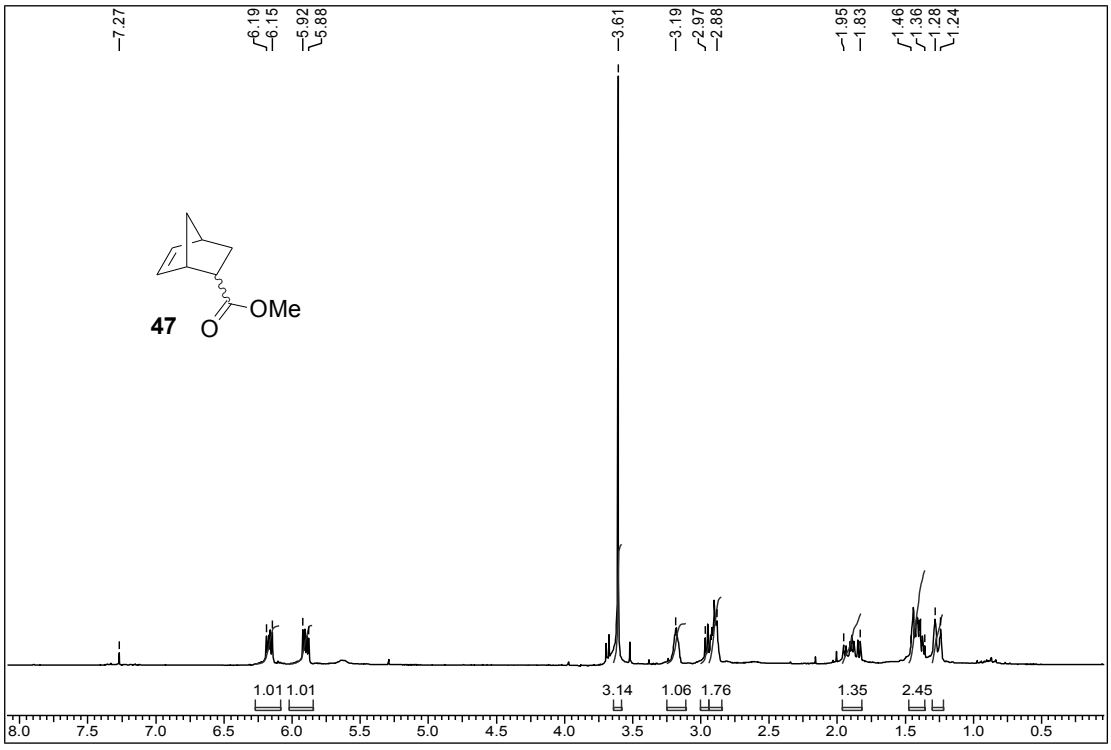
^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 40



^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 41



^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 45



^{1}H NMR ($CDCl_3$+CCl_4, 200 MHz) spectrum of compound 47

3.2.5. References

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