Design & Tactics for Total Synthesis of D_2 Receptor Agonist Quinagolide & Development and Application of On-Water Oxidation of Furan in Collective Synthesis of Bioactive Natural Products

Thesis Submitted to AcSIR

For the Award of the Degree of

DOCTOR OF PHILOSOPHY

In

CHEMICAL SCIENCES

By

Appasaheb L. Kadam
(Registration Number: 10CC12A26039)

Under the guidance of
Dr. Subhash P. Chavan

Division of Organic Chemistry,
CSIR-National Chemical Laboratory,
Pune 411 008, INDIA

November 2019

CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled **"Design & Tactics for Total Synthesis of D_2 Receptor Agonist Quinagolide & Development and Application of On-Water Oxidation of Furan in Collective Synthesis of Bioactive Natural Products"** submitted by **Mr. Appasaheb L. Kadam** to Academy of Scientific and Innovative Research (**AcSIR**) in fulfillment of the requirements for the award of the Degree of Doctor of Philosophy, embodies original research work under my supervision. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

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Appasaheb L. Kadam
(Research Student)
(Reg. No. 10CC12A26039)

Dr. Subhash P. Chavan
(Research Supervisor)

Date: 14th Nov, 2019
Place: CSIR-NCL, Pune.

Declaration by the Candidate

I hereby declare that the original research work embodied in this thesis entitled, **"Design & Tactics for Total Synthesis of D_2 Receptor Agonist Quinagolide & Development and Application of On-Water Oxidation of Furan in Collective Synthesis of Bioactive Natural Products"** submitted to Academy of Scientific and Innovative Research for the award of degree of Doctor of Philosophy (Ph.D.) is the outcome of experimental investigations carried out by me under the supervision of **Dr. Subhash P. Chavan**, Chief Scientist, Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune. I affirm that the work incorporated is original and has not been submitted to any other academy, university or institute for the award of any degree or diploma.

November 2019
CSIR-National Chemical Laboratory
Pune 411008

Appasaheb L. Kadam
(Research Student)

This dissertation is dedicated to all those people who have always given me the love, trust, and support to come to this stage of my life

-To My Family and Teachers-

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Borhade sir, Mrs. Kulkarni madam, Mrs. Suryavanshi madam and Dr. S. V. Patil sir for their sincere efforts and patience in guiding me during my graduation and post-graduation studies. I would also like to thank my mentors Dr. Jayant Kolhe, Dr. Mukul Lal, Dr. Ravindra Sonawane, Dr. Prasanna and Dr. Deshpande for their excellent guidance, constant encouragement, and sincere advice during my job at Syngenta, Goa. I wish to thank a great scientific community whose achievements are a constant source of inspiration for me.

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–Appasaheb L. Kadam

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Abbreviations

Units

°C	Degree centigrade
mg	Milligram
h	Hour
Hz	Hertz
µg	Microgram
mL	Millilitre
min	Minutes
MHz	Megahertz
mmol	Millimole
ppm	Parts per million

Chemical Notations

Ac	Acetyl
AcOH	Acetic Acid
Ar	Aryl
CH_3CN	Acetonitrile
n-BuLi	*n*-Butyl Lithium
^{t}BuOH	*tert*-Butyl alcohol
MOMCl	Chloromethyl Methyl Ether
CBS	Corey-Bakshi-Shibata catalyst
CCl_4	Carbon tetrachloride
$CDCl_3$	Deuterated Chloroform
CD_3OD	Deuterated Methanol
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Diisobutylaluminiumhydride
DMF	*N*, *N'*-Dimethylformamide
DMAP	*N*,*N'*-Dimethylaminopyridine
DIPEA	*N*, *N*-Diisopropylethylamine
Et_2O	Diethyl Ether
$(DHQ)_2PHAL$	1,4-bis(Dihydroquinin-9-*O*-yl)phthalazine
$(DHQD)_2PHAL$	1,4-bis(Dihydroquinindin-9-*O*-yl)phthalazine

DIAD	Diisopropyl azodicarboxylate
DCE	1,2-Dichloroethane
DET	Diethyl Tartrate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
EtOH	Ethanol
Et	Ethyl
EtOAc	Ethyl Acetate
HG-II	Hoveyda-Grubbs' 2nd Generation Catalyst
IBX	Iodoxybenzoic Acid
LiHMDS	Lithium Hexamethyl Disilazide
LAH	Lithium Aluminum Hydride
m-CPBA	*m*-Chloroperbenzoic Acid
MeOH	Methanol
NMO	*N*-Methyl Morpholine Oxide
Me	Methyl
MeI	Methyl Iodide
Ph	Phenyl
PMB	*para*-Methoxy Benzyl
p-TSA	*par*a-Toluenesulfonic Acid
TsCl	*p*-Toluenesulphonyl Chloride
$NaBH_4$	Sodiumborohydride
NaH	Sodium Hydride
THF	Tetrahydrofuran
TBAI	Tetra-*n*-Butylammonium Iodide
TBAF	Tetra-*n*-Butylammonium Fluoride
TBDMS	*tert*-Butyldimethyl Silyl
TBSCl	*tert*-Butyldimethyl Silyl Chloride
TIPSOTf	Triisopropylsilyl Trifluoromethanesulfonate
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
Ts	Toluenesulfonyl
TMS	Trimethylsilyl

Other Notations

calcd	Calculated
δ	Chemical shift
J	Coupling constant in NMR
RCM	Ring Clossing Metathesis
DEPT	Distortionless Enhancement by Polarization Transfer
dr	Diastereomeric excess
ee	Enantiomeric excess
equiv	Equivalents
ESI	Electrospray ionization Mass spectrometry
HPLC	High Pressure Liquid Chromatography
HMBC	Heteronuclear Multiple Bond Correlation
COSY	Homonuclear Correlation Spectroscopy
HRMS	High Resolution Mass Spectrometry
IR	Infra Red
m/*z*	Mass-to-charge ratio
M.S	Molecular sieves
Mp	Melting Point
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
ORTEP	Oak Ridge Thermal Ellipsoid Plot
rt	Room temperature

General remarks

- Deuterated solvents for NMR spectroscopic analyses were used as received. All ^{1}H NMR and ^{13}C NMR and 2D NMR analysis were obtained using a Bruker or JEOL 200 MHz, 400 MHz or 500 MHz spectrometers. Coupling constants were measured in Hertz. All chemical shifts are quoted in ppm, relative to TMS, using the residual solvent peak as a reference standard. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br =broad.
- HRMS spectra were recorded at UHPLC-MS (Q-exactive-Orbitrap Mass Spectrometer) using electron spray ionization [(ESI^{+}, +/– 5kV), solvent medium: water, acetonitrile, methanol and ammonium acetate] technique and mass values are expressed as *m*/*z*. GC-HRMS (EI) was recorded in Agilent 7200 Accurate-mass-Q-TOF.
- Infrared spectra were scanned on Bruker ALPHA spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO P-2000 digital polarimeter.
- Melting points were recorded on Buchi M-535, M-560 melting point apparatus and are uncorrected and the temperatures are in centigrade scale.
- All reactions are monitored by Thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, Iodine adsorbed on silica gel or by immersion in ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde or $KMnO_4$ followed by heating with a heat gun for ~15 sec.
- All solvents and reagents were purified and dried by 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 homogeneous materials unless otherwise stated.
- Column chromatography was performed on silica gel (100-200 or 230-400 mesh size).
- Chemical nomenclature (IUPAC) and structures were generated using ChemDraw Professional 15.1.

- Reactions were carried out in oven-dried glassware under a positive pressure of argon unless otherwise mentioned with magnetic stirring. Air sensitive reagents and solutions were transferred *via* syringe or cannula and were introduced to the apparatus *via* rubber septa.
- The compounds, scheme and reference numbers given in each section of chapter refers to that particular section of the chapter only.
- All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification.

Synopsis

AcSIR	**Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry**
Name of the Candidate	**Appasaheb L. Kadam**
AcSIR Enrolment No. & Date	**Ph. D in Chemical Sciences (10CC12A26039); August 2012**
Title of the Thesis	**Design & Tactics for Total Synthesis of D_2 Receptor Agonist Quinagolide & Development and Application of On-Water Oxidation of Furan in Collective Synthesis of Bioactive Natural Products**
Research Supervisor	**Dr. Subhash P. Chavan**

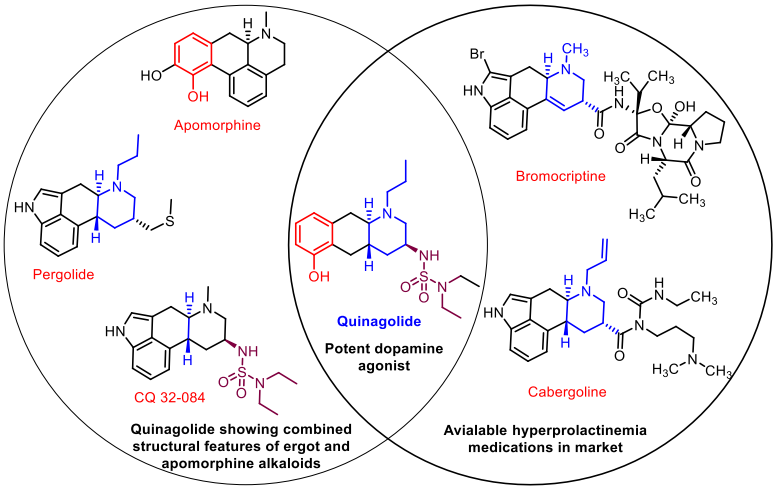
Biologically active natural products and their synthetic derivatives have found the largest contribution to drug discoveries. In that context, challenging structural features and bioactivity of natural products attracted synthetic chemists for its economic and scalable synthesis through the development of synthetic methodologies. The thesis hereby presents a unique design and state-of-art strategies for the total synthesis of D_2 receptor agonist quinagolide in racemic as well as enantioselective fashion, along with the development of on-water oxidation of furan and its application in the collective synthesis of Tamiflu, pipecolic acid and its 3-hydroxy derivatives. The work embodied in this thesis has been divided into three chapters as described below.

Chapter 1: Total Synthesis of D_2 Receptor Agonist (±)-Quinagolide.

Section 1: Introduction and Literature Review of Quinagolide.

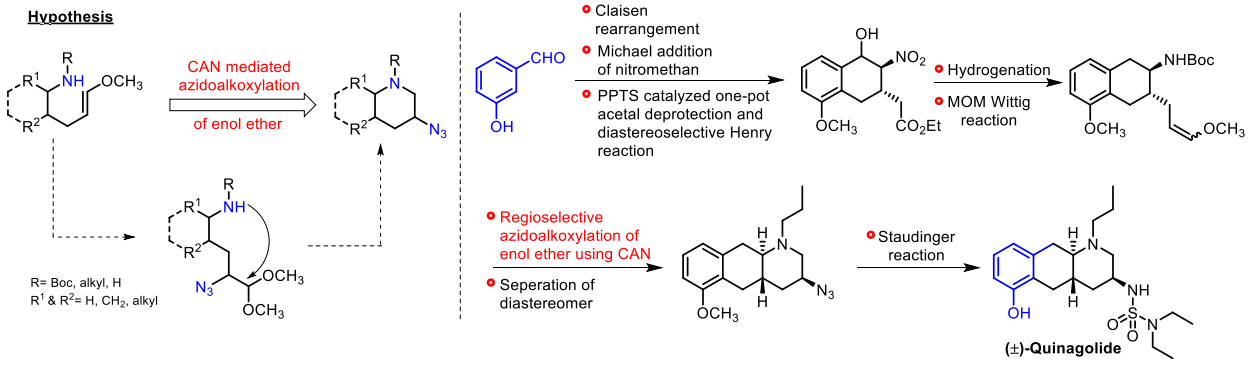
Hyperprolactinemia which is responsible for life-threatening diseases is a condition that arises because of the elevated level of prolactin in the blood. Currently, for the treatment of hyperprolactinemia, drugs such as bromocriptine, cabergoline and quinagolide are used as medications. Out of these medications available in the market, bromocriptine and cabergoline have serious side effects whereas quinagolide which is newly introduced by Ferring Pharmaceuticals under the trade name Norprolac is considered as first-line therapy in the

treatment of hyperprolactinemia. Quinagolide is a selective D_2 receptor agonist, used for the treatment of elevated levels of prolactin. It is developed by combining structural features of ergot and apomorphine alkaloids.



In 1985, Nordmann *et al*. reported the total synthesis of quinagolide in racemic form using β–tetralone as the starting material. Subsequently, the same group reported dopaminomimetic activity of quinagolide is entirely associated with (–) enantiomer through chiral resolution. Currently, quinagolide is sold in its racemic form using the modified route of Nordmann reported by Banziger *et al*.

Section 2: Total Synthesis of (±)-Quinagolide by Employing CAN Mediated Regioselective Azidoalkoxylation of Enol Ether.

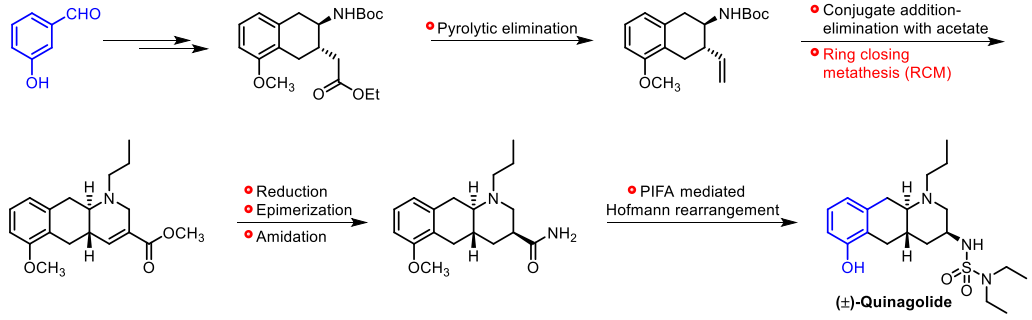


Total synthesis of (±)-quinagolide was accomplished *via* synthesis of 3-azidopiperidine skeleton by employing CAN mediated regioselective azidoalkoxylation of enol ether for the first time. During the course of synthesis, PPTS catalyzed one-pot acetal deprotection and

diastereoselective Henry reaction to fix three contiguous stereocenters on tetrahydronapthalene ring has been successfully developed. Claisen rearrangement of allyl ether derivatives of substituted benzaldehyde under microwave condition was reported for the first time.

Section 3: Total Synthesis of (±)-Quinagolide *via* RCM Approach.

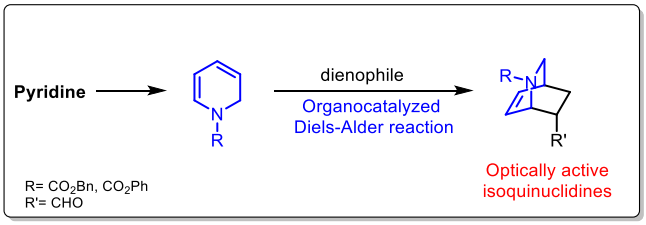
Over the last three decades, ring-closing metathesis (RCM) is found to be an important tool for the synthesis of numerous piperidine and pyrrolidine alkaloids. In an alternative approach for the total synthesis of (±)-quinagolide, RCM was used as a key step for the construction of a tricyclic 3-substituted piperidine skeleton. Other key features include pyrolytic elimination and PIFA mediated Hofmann rearrangement.



Chapter 2: Enantioselective Formal Total Synthesis of (–)-Quinagolide.

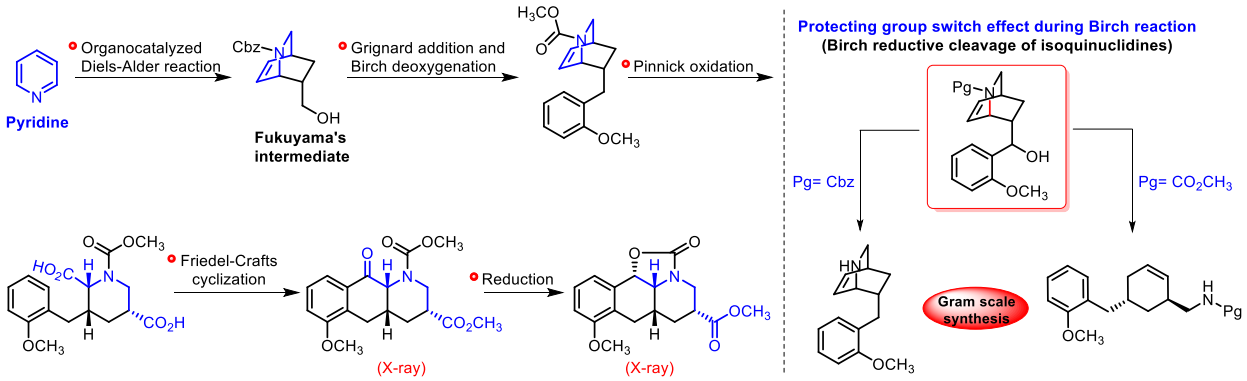
Section 1: Synthesis of Isoquinuclidine Skeleton Using Organocatalyzed Diels–Alder Reaction and its Application in Total Synthesis.

The isoquinuclidine ring system is widely found in natural products such as the alkaloids ibogaine and dioscorine. Organocatalyzed Diels–Alder reaction of 1,2-dihydropyridines derived from pyridine with acrolein is an efficient tool for the enantioselective synthesis of isoquinuclidine skeleton. The examples described in the literature using the organocatalyzed Diels–Alder reaction for the synthesis of isoquinuclidines are scarce. Enantioselective synthesis of isoquinuclidines using organocatalyzed Diels–Alder reaction was applied in the total synthesis of natural products and bioactive compounds such as Tamiflu, (+)-Luciduline and Catharanthine.

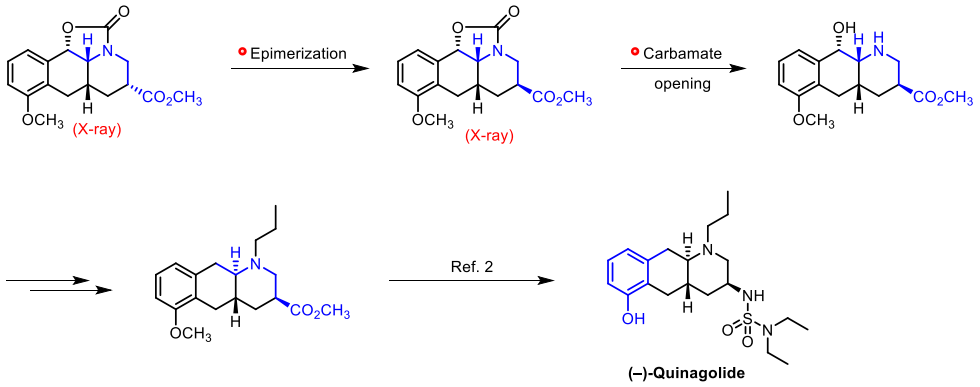


Section 2: Enantioselective Formal Total Synthesis of (–)-Quinagolide.

As discussed above, currently, quinagolide is sold in its racemic form but the dopaminomimetic activity is entirely associated with the (–)-enantiomer. Furthermore, enantioselective synthesis is not reported in the literature, we undertook the synthetic study for enantioselective synthesis of quinagolide.



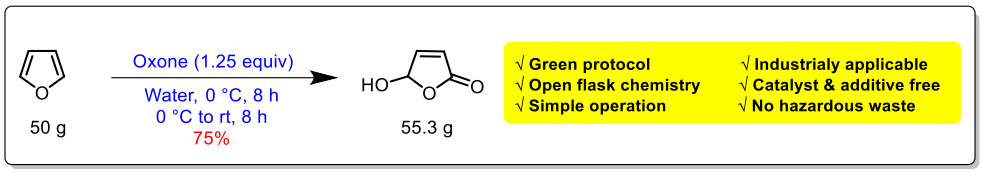
The enantioselective formal total synthesis of (–)-quinagolide has been accomplished in a linear sequence of 8 purification steps from pyridine. The key steps are (a) organocatalyzed Diels–Alder reaction for fixing all three stereocenters on piperidine ring; (b) protecting group enabled deoxygenation of isoquinuclidine skeleton under Birch reduction condition; (c) Lewis acid ($TiCl_4$) catalyzed regioselective Friedel–Crafts cyclization of dicarboxylic acid and (d) one-pot diastereoselective ketone reduction–intramolecular cyclization to form oxazolidinone which enables *trans*-geometry installation. During the course of the synthesis, an interesting reductive cleavage of the C-*N* bond in the electron-deficient isoquinuclidine skeleton under the Birch reduction condition has been observed. Endeavor towards completion of the target molecule is currently under progress.



Chapter 3: On-Water Oxidation of Furan and its Application in the Collective Synthesis of Oseltamivir Phosphate (Tamiflu), (*S*)-Pipecolic acid and its 3-Hydroxy Derivatives.

Section 1: On-Water Oxidation of Furan: Scalable Synthesis of 5-Hydroxy-2-(5*H*)-Furanone Using Oxone as a Sole Oxidant.

Simple, efficient and scalable synthesis of 5-hydroxy-2(5*H*)-furanone has been accomplished from furan. Using this green protocol, 5-hydroxy-2(5*H*)-furanone was successfully synthesized on a multigram scale. The present method paves the way for industrial-scale synthesis of 5-hydroxy-2(5*H*)-furanone on large scale using oxone as a green oxidant which has advantages like stability, simple handling, non-toxic nature, low costs, and water solubility.

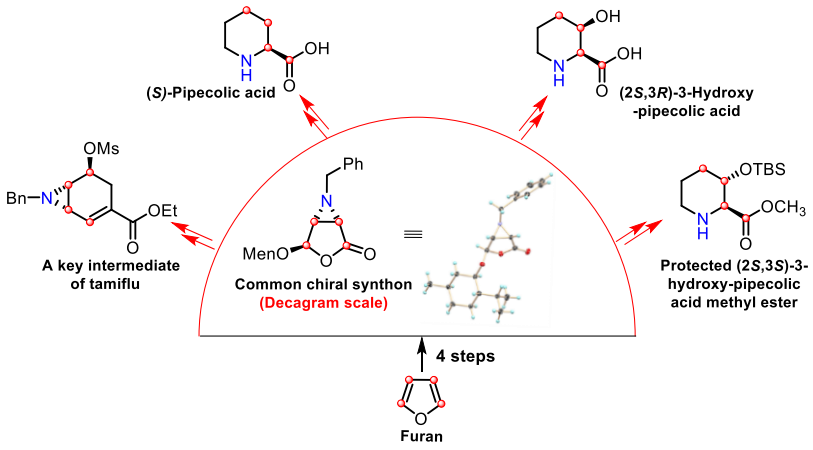


Section 2: Introduction and Literature Review of Oseltamivir Phosphate (Tamiflu), (*S*)-Pipecolic acid and its 3-Hydroxy Derivatives.

Oseltamivir phosphate (Tamiflu®) was launched in 1999 as an antiviral drug. It has been discovered in 1995 by Gilead Science (US) along with F. Hoffmann-La Roche Ltd. Pipecolic acid and its derivatives have found widespread utility as several biologically active secondary metabolites, synthetic drug candidates and as a building block in organic synthesis. This section describes the synthetic route to Tamiflu, pipecolic acid and its derivatives reported in the literature.

Section 3: Collective Synthesis of Oseltamivir Phosphate (Tamiflu), (*S*)-Pipecolic acid and its 3-Hydroxy Derivatives.

The unified synthetic strategy for the total synthesis of piperidine class of alkaloids (*S*)-pipecolic acid and (2*S*,3*R*)-3-hydroxypipecolic acid and formal total synthesis of Tamiflu from furan derived common chiral aziridino lactone synthon is described here. Key features of synthesis includes furan oxidation, decagram scale synthesis of furan derived common chiral aziridino lactone synthon and its first-ever application in total synthesis, one-pot reductive aziridine ring-opening–debenzylation and hydrogenation of unsaturated ester followed by intramolecular amidation for the synthesis of piperidine class of alkaloids and RCM using Lewis acid for the synthesis of Tamiflu framework. In addition, the synthesis of important building block aziridino lactone was achieved from a common intermediate.



Noteworthy Findings:

- Accomplished the total synthesis of (±)-quinagolide *via* two conceptually different strategies- i) CAN mediated regioselective azidoalkoxylation of enol ether and ii) RCM.
- Accomplished the first enantioselective formal total synthesis of (–)-quinagolide from pyridine. During the course of the synthesis, an interesting Birch reductive cleavage of the C-*N* bond in electron-deficient isoquinuclidine has been observed.
- Developed on-water oxidation of furan using oxone and its application in the collective synthesis of Tamiflu, pipecolic acid and its 3-hydroxy derivatives was demonstrated utilizing common chiral aziridino lactone synthon.

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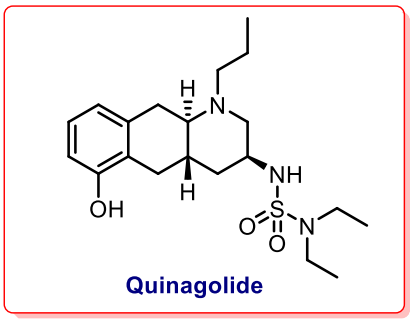
CHAPTER 1

Section 1

"Introduction and Literature Review of Quinagolide"



Quinagolide

1.1.1. Introduction

Ergot alkaloids and their synthetic derivatives are well known for their biological activities.[1] From the last few decades, increasing efforts have been directed towards the synthesis of new derivatives and partial structures with the primary goal of dissecting out specific dopaminomimetic pharmacophore after the successful use of bromocriptine, pergolide, and lisuride which are used for the treatment of hyperprolactinemia, acromegaly, and parkinsonism. Initially, it was assumed that the rigid arylethylamine moieties (**1a-d**) such as phenylethylamine, tryptamine and (aminoethyl)indole of ergolines are responsible for dopaminomimetic activity (**Figure 1**). In this context, a close comparison of well-known dopamine agonists such as ergolines CQ 32-084 (**2**) and pergolide (**3**) and apomorphine (**4)** particularly paying attention to the absolute configuration of both led to the discovery of new dopamine agonist namely quinagolide (**5)**.

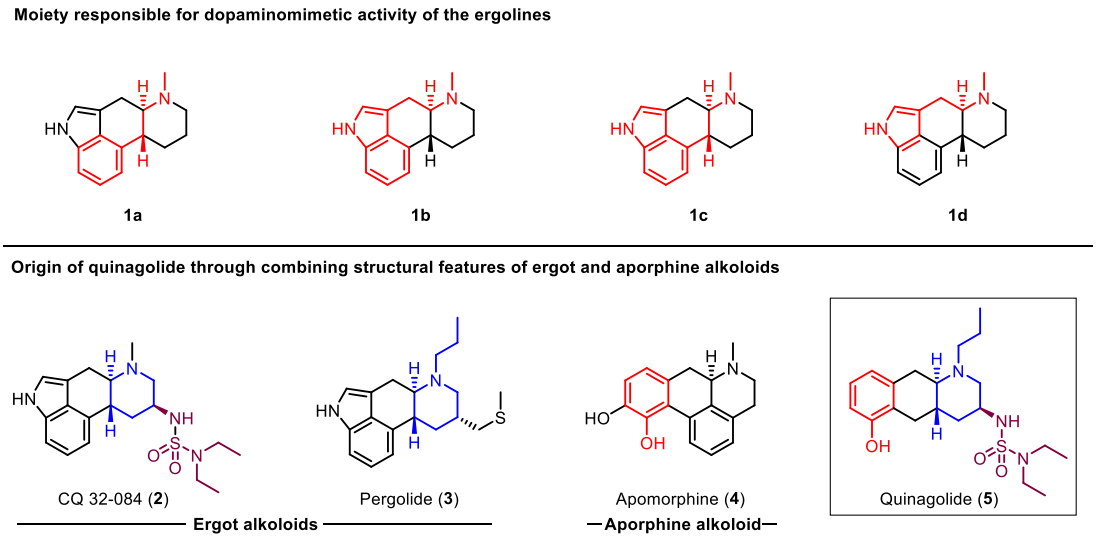
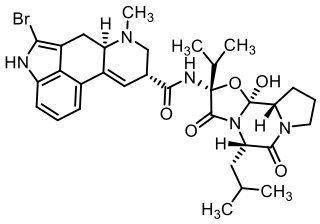


Figure 1: Discovery of quinagolide.

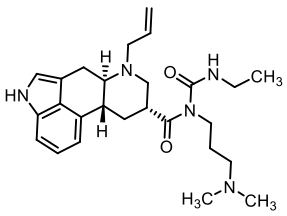
Thus, quinagolide (**5),** a selective D_2 receptor agonist that is used for the treatment of elevated levels of prolactin (called hyperprolactinemia) has the combined structural features of both ergolines and apomorphine (**Figure 2**).[2,3] Quinagolide hydrochloride is marketed under the trade name Norprolac® by Ferring Pharmaceuticals, Lausanne, Switzerland.

Hyperprolactinemia

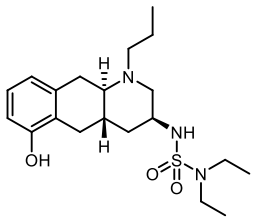
Prolactinoma is a benign tumor (adenoma) of the pituitary gland, which produces hormone prolactin and a condition that arises due to elevated prolactin levels in the blood is defined as hyperprolactinemia. Pharmacological causes such as the use of certain medications for the treatment of various diseases and physiological causes such as pregnancy and stress are the main factors behind the elevated level of prolactin. Hyperprolactinemia may also be the result of the disease of other organs such as the liver, kidneys, ovaries, and thyroid. The most common symptoms of hyperprolactinemia are hypogonadism, infertility and erectile dysfunction in men and galactorrhea and disruptions in the normal menstrual period in women. Although hyperprolactinemia is not considered a life-threatening disease, it causes severe effects on the life of patients and often leads to multiple life-threatening diseases.[4] For the treatment of hyperprolactinemia, drugs such as bromocriptine (**6**), cabergoline (**7**) and quinagolide (**5**) are used as medications (**Figure 2**).[3]



Bromocriptine (**6**)



Cabergoline (**7**)

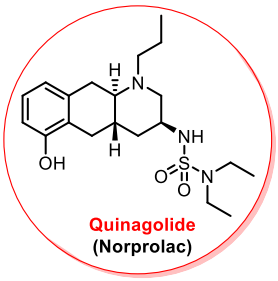


Quinagolide (**5**)

Figure 2. Available hyperprolactinemia medications bromocriptine (**6**), cabergoline (**7**) and quinagolide (**5**).

Out of these medications available in the market, bromocriptine (**6**) has serious side effects, whereas quinagolide (**5**), which may improve patient compliance to treatment due to its reduced side effect profile, has distinct advantages over cabergoline (**7**). Owing to being well-tolerated and effective therapy, with a simple dosing regimen, quinagolide (**5**), which is newly introduced by Ferring Pharmaceuticals under the trade name Norprolac, is considered as first-line therapy in the treatment of hyperprolactinemia.[1b]

Quinagolide (Norprolac)

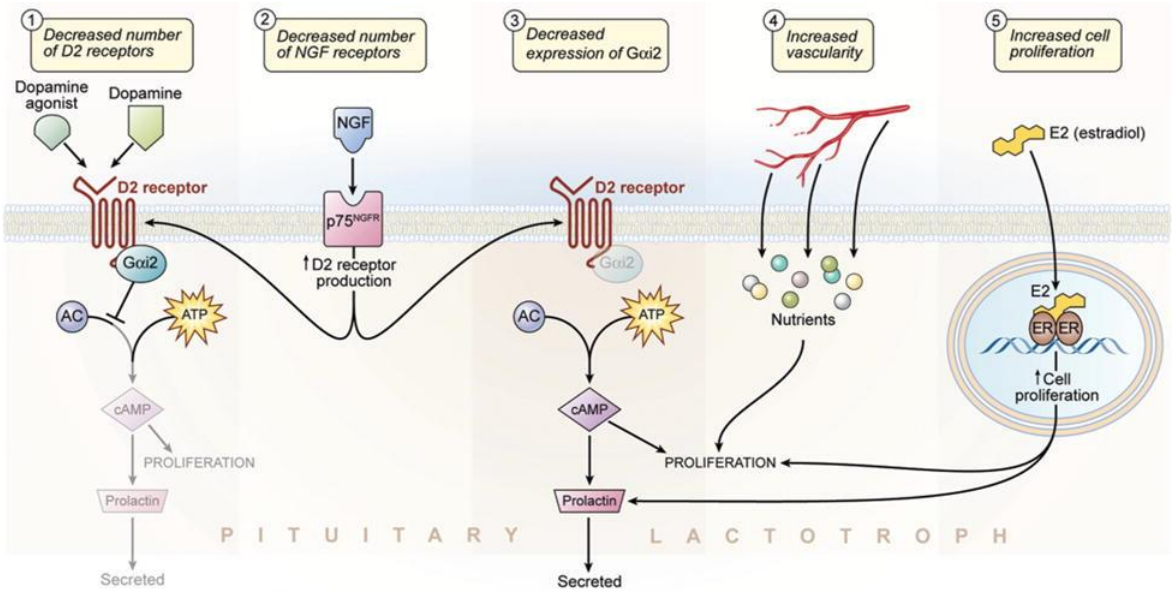


Composition

Tablets containing 0.025, 0.050, 0.075, or 0.150 mg quinagolide as the hydrochloride are available in the market.

Norprolac tablets also contain silica, magnesium stearate, hypromellose, starch-maize, cellulose, lactose, iron oxide red (0.025 mg tablet only), indigo carmine (0.050 mg tablet only) as an inactive excipient.

Pharmacology



(Figure source: Oh, M. C.; Aghi, M. K. *Journal of Neurosurgery*; DOI: https://doi.org/10.3171/2010.11.JNS101369)

Figure 3: The mode of action of quingolide.

Presently available different D_2 receptor agonists comprise of members of ergot or ergoline family, whereas quinagolide, which is a selective dopamine D_2 receptor agonist, is not an ergot

or ergoline compound. Quinagolide binds to the D_2 dopamine receptor expressed on the surface of lactotroph cells in the anterior pituitary, reduces adenylyl cyclase activity and intracellular cyclic adenosine monophosphate and thus inhibits prolactin secretion (**Figure 3**).[5]

Due to the dopaminomimetic activity of quinagolide, the secretion of the anterior pituitary hormone prolactin is strongly inhibited, but it does not reduce normal levels of other pituitary hormones, such as luteinizing hormone, follicle-stimulating hormone, thyrotropin or corticotropin. Due to its favorable tolerability profile and a prolonged duration of action, quinagolide (Norprolac), which is a specific inhibitor of prolactin secretion, is effective and suitable for once-a-day oral treatment for patients presenting with hyperprolactinemia and its clinical manifestations including those who have not responded adequately to other dopamine agonist therapy. The size and growth of prolactin-secreting pituitary macroadenomas were found to be reduced when treated with quinagolide (Norprolac) for the long-term.

Pharmacokinetics

1. Absorption

The radiolabelled drug of quinagolide is rapidly and well absorbed after the oral administration. A non-selective radio-immunoassay (RIA) of quinagolide along with some of its metabolites indicates that the plasma concentration values were close to the limit of quantification and gave no reliable information.

2. Distribution

After the single oral administration of radiolabelled quinagolide drug, the apparent volume of distribution was calculated to be approximately 100 L. The protein binding of quinagolide is non-specific and nearly 90%.

3. Metabolism and elimination

Quinagolide is extensively metabolized during its first pass. At 17 hours at steady state under single-dose conditions, the terminal half-life of 11.5 hours has been calculated for the parent drug. Quinagolide and its *N*-desethyl analogs are the bioactive but minor components in the blood whereas, their sulfate or glucuronide conjugates, which are inactive, represent the major circulating metabolites. Glucuronide and sulfate conjugates of quinagolide and it's *N*-desethyl

and *N*,*N*-bidesethyl analogs are the primary metabolites in urine. The unconjugated forms of the 3 components were found in the feces, and more than 95% of the drug is excreted as metabolites when studies performed with ^{3}H-labelled quinagolide. The total radioactivity recovered in feces and urine is equal in amounts.

Pharmacodynamics

Pharmacodynamic studies reveal a large amount of meaningful information on the pharmacokinetic nature of quinagolide and its active metabolites in which the reduction in plasma prolactin levels, a reliable sign of drug activity, has been quantified. The results show that the clinically significant prolactin-lowering effect occurs within 2 hours after the ingestion of the recommended therapeutic dose, and it reaches a maximum within 4 to 6 hours and maintains for about 24 hours. The prolactin-lowering effect of a single oral dose of 0.050 mg was close to the maximum, whereas higher doses did not result in a considerably more significant impact but give the prolonged duration of action.

Adverse reaction

With the treatment of Norprolac, the adverse reactions which are characteristic for dopamine receptor agonist therapy were reported. Most of the side effects occur mainly during the first few days of treatment, which are usually not considered as serious to require discontinuation of treatment and be likely to disappear when treatment is continued.

The most common side effects (>10%) are nausea, vomiting, headache, dizziness, and fatigue. Less common side effects (1 to 10%) include anorexia, abdominal pain, constipation or diarrhea, insomnia, nasal congestion, hypotension, and muscular weakness.

1.1.2. Literature Review

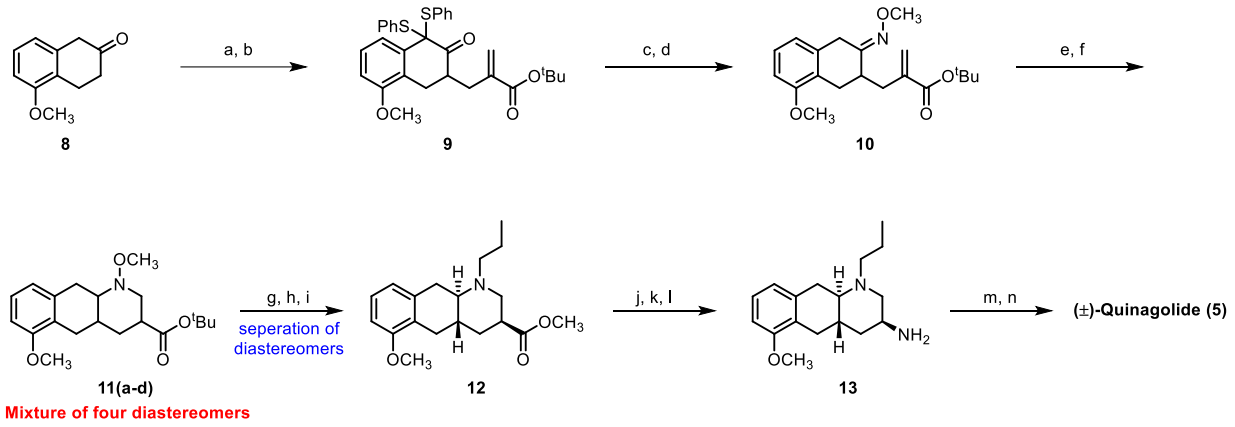
Though quinagolide is sold in its racemic form, and it is a synthetic analog of ergot family alkaloids, till date, there are only two synthetic approaches in the racemic form which include med-chem approach by Nordmann *et al*.[2,6] followed by the scalable synthetic approach of quinagolide intermediate by Banziger *et al*.[7] reported in the literature.

Here both of these synthetic approaches are discussed in detail.

Med-Chem approach (*J. Med. Chem*. **1985**, *28*, 367).[2]

In the year 1985, Nordmann *et al*. from Sandoz Ltd. reported the discovery and total synthesis of new dopamine agonist quinagolide by combining the structural features of ergot and apomorphine alkaloids. Synthesis commenced with β-tetralone **8** as the starting material (**Scheme 1**). For the synthesis of the third piperidine ring, tetralone **8** was converted to ester **9** using regioselective alkylation with *tert*-butyl 2-(bromomethyl)acrylate and LDA as a base. Compound **9** was then converted to tricyclic ring **11** as a mixture of four diastereomers through reduction and cyclization of oxime **10**. All four diastereomers were separated using silica gel column chromatography. Required diastereomer was converted to the methyl ester **12** by alkylation with propanal under hydrogenation condition.

For the construction of side chain, the Curtius rearrangement of corresponding azide derived from methyl ester **12** was used to obtain 3-amino piperidine **13**. Amine **13** was then converted to the final product by the sulfonation using *N*,*N*-diethyl sulfamoyl chloride and ether cleavage with BBr_3.

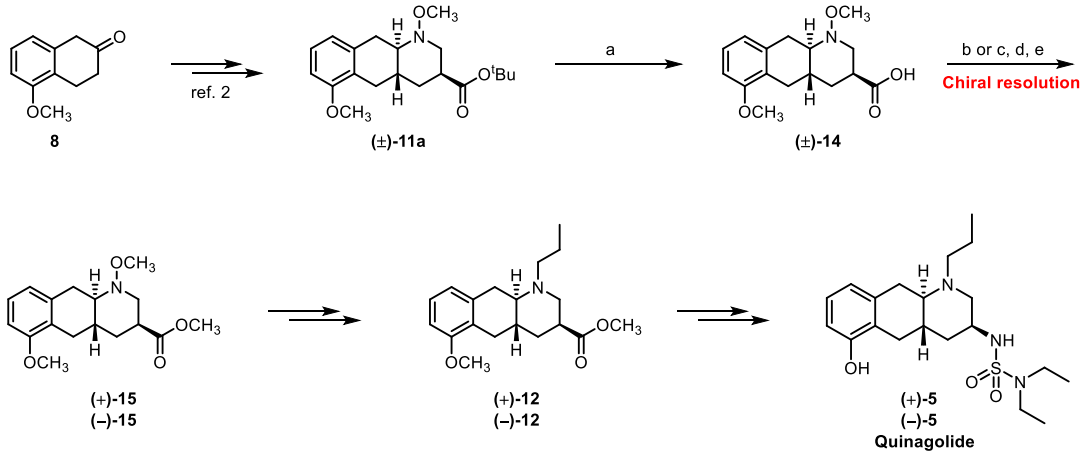


Scheme 1: Reagents and conditions: *(a) S-phenyl benzenethiosulfonate, NaOAc, MeOH, rt, 82%; (b) LDA, tert-butyl 2-(bromomethyl)acrylate, Et_2O-THF-HMPT, –78 °C, 66%; (c) Al(Hg), THF-H_2O, 50 °C, 2 h, 71%; (d) H_2NOCH_3.HCl, $Na_2HPO_4.2H_2O$, MeOH, rt, 4 h, 72%; (e) $NaCNBH_3$, MeOH, rt, 12 h; (f) MeOH, rt, 72 h; (g) H_2SO_4, MeOH, reflux, overnight, 92%; (h) Zn, AcOH, H_2O, rt, overnight, 72%; (i) Propanal, H_2, 10% Pd/C, PrOH, rt, overnight, 74%; (j) Hydrazine hydrate, MeOH, 50 °C, 20 h, 80%; (k) NOCl, THF, reflux, 1 h; (l) HCl, THF, reflux, 1 h, 61% (over 2 steps); (m) Et_2NSO_2Cl, $CHCl_3$, 50 °C, overnight, 87%; (n) BBr_3, CH_2Cl_2, –10 °C, 4 h, 89%.*

The resolution, absolute configuration and dopaminomimetic activity of quinagolide (*J. Med. Chem*. **1985**, *28*, 1540).[6]

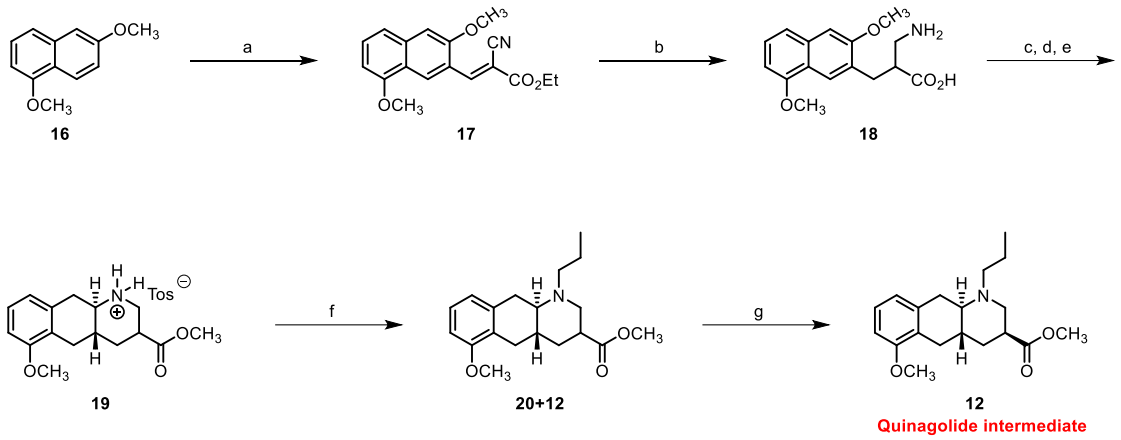
In the same year (1985), Nordmann *et al.* disclosed the absolute configuration and dopaminomimetic activity of quinagolide through the resolution of racemic intermediate (**Scheme 2**). Initially, they failed to resolve the parent compound **(±)-5**.[2] Therefore, acid (±)-**14** derived from (±)-**11a** was resolved with D-(+)-α-methylbenzylamine and L-(–)-α-methylbenzylamine. The two enantiomers were converted to the methyl esters **(+)-15** and **(–)-15** by esterification of the corresponding acids with diazomethane. Following the same reaction sequence used in **(±)-5**, compounds **(+)-15** and **(–)-15** were converted to the enantiomerically pure **(+)-5** and **(–)-5** respectively.

In comparison with the racemic quinagolide, the optical antipodes **(+)-5** and **(–)-5** were evaluated *in vivo* as well as *in vitro* for dopaminomimetic activity. These results showed that the dopaminomimetic activity is entirely associated with the (–) enantiomer of quinagolide which has the absolute configuration (3*S*,4a*S*,10a*R*) corresponding to the absolute configuration of ergoline CQ 32-084 (**2**).



Scheme 2: Reagents and conditions: *(a) TFA, rt, 45 min, 90%; (b) D-(+)-α-methylbenzylamine CH_2Cl_2-Et_2O, –20 °C, 30%; (c) L-(–)-α-methylbenzylamine, CH_2Cl_2-Et_2O, –20 °C, 28%; (d) 1 N HCl; (e) CH_2N_2, CH_2Cl_2, 98%.*

Scalable approach (*Org. Process Res. Dev*. **2000**, *4*, 460).[7]



Scheme 3: Reagents and conditions: *(a) Ethoxymethylenecyanoacetate, hexyllithium, THF, –70 °C, 2 h, 55%; (b) (i) H_2, Pt/C, H_2SO_4, EtOH, 50 °C, 4 h; (ii) NaOH, H_3O^+, 83% (over 2 steps); (c) Li, NH_3, THF-^{t}BuOH, –70 °C, 1.5 h; (d) HCl (aq), 95% (over 2 steps); (e) $NaBH_4$, CH_3OH, –70 °C, 2 h then PTSA, EtOAc, 78%; (f) n-propyl iodide, K_2CO_3, DMF, 50 °C, 2.5 h; (g) LDA, TMSCl, THF, –40 °C, 2 h, 85% (over 2 steps).*

Scalable synthesis of quinagolide intermediate was reported by Banziger *et al*. from Novartis Ltd. in the year 2000 on the similar line of med-chem approach to build the third heterocyclic piperidine ring (**Scheme 3**).

Synthesis commenced with the selective ortho-lithiation using hexyllithium followed by alkylation at the C7 position of 1,6-dimethoxynaphthalene **16** with ethoxymethylenecyanoacetate. The next step was the hydrogenation of an unsaturated nitrile system in **17** using Pt/C to obtain amino-acid **18**. Birch reduction of amino-acid **18** followed by hydrolysis of corresponding enol ether afforded tricyclic imine which was reduced using sodium cyanoborohydride to furnish compound **19**. Alkylation of amine **19** with propyl iodide furnished mixture of diastereomers **20** and **12**, which was epimerized to the single diastereomer **12** following kinetic protonation using LDA and TMSCl. Multi-kilogram scale synthesis of quinagolide intermediate **12** was achieved in 27–29% overall yield (based on 1,6-dimethoxynaphthalene **16**) in only 5 isolated steps.

1.1.3. Conclusion and Prospect

Quinagolide contains a *trans*-fused 3-aminopiperidine skeleton and has combined structural features of ergot and apomorphine alkaloids. Moreover, the synthesis of ergot alkaloids poses a challenge to the synthetic chemists due to its *trans*-fused 3-substituted piperidine scaffold. In this context, quinagolide is an attractive target due to its challenging structural features and medicinal importance. Though, quinagolide, a D_2 receptor agonist used for the treatment of hyperprolactinemia is currently sold in racemic form and Nordmann *et al*. resolved the intermediate of (±)-quinagolide and found that the dopaminomimetic activity is entirely associated with the (–)-enantiomer of quinagolide, till date, enantioselective total synthesis of (–)-quinagolide is not reported. The medicinal use of quinagolide and the necessity to make it available in enantiomerically pure form led to develop a new route for the total synthesis of quinagolide.

1.1.4. References

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(2) Nordmann, R.; Petcher, T. J. *J. Med. Chem*. **1985**, *28*, 367.

(3) Sarno, A. D.; Landi, M. L.; Marzullo, P.; Somma, C. D.; Pivonello, R.; Cerbone, R.; Lombardi, G.; Colao, A. *Clinical Endocrinology* **2000**, *53*, 53.

(4) (a) Mancini, T.; Casanueva, F. F.; Giustina, A. *Endocrinology and Metabolism Clinics of North America* **2008**, *37*, 67. (b) Barlier, A.; Jaquet, P. *European Journal of Endocrinology* **2006**, *154*, 187 and references cited therein.

(5) McDonald, W. M.; Sibley, D. R.; Kilpatrick, B. F.; Caron, M. G. *Molecular and Cellular Endocrinology* **1984**, *36*, 201.

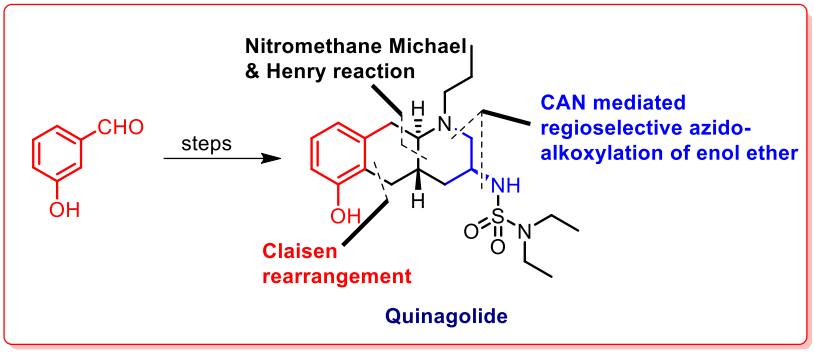
(6) Nordmann, R.; Widmer, A. *J. Med. Chem*. **1985**, *28*, 1540.

(7) Banziger, M.; Cercus, J.; Stampfer, W.; Sunay, U. *Org. Process Res. Dev*. **2000**, *4*, 460.

CHAPTER 1

Section 2

"Total Synthesis of (±)-Quinagolide by Employing CAN Mediated Regioselective Azidoalkoxylation of Enol Ether"



ABSTRACT: The total synthesis of (±)-quinagolide, a D_2 receptor agonist was accomplished *via* a CAN (ceric ammonium nitrate) mediated regioselective azidoalkoxylation of enol ether route. Key features of the synthesis include Claisen rearrangement, PPTS (pyridinium *p*-toluenesulfonate) catalyzed one-pot acetal deprotection followed by a diastereoselective Henry reaction which enables the construction of the required *trans* ring junction and CAN mediated regioselective azidoalkoxylation of enol ether. The PPTS catalyzed intramolecular diastereoselective Henry reaction to fix three contiguous stereocenters on tetrahydronaphthalene and the first-of-its-kind synthesis of the 3–azidopiperidine skeleton using a CAN mediated regioselective azidoalkoxylation of enol ether are important findings of the present work.

Reference:

Chavan, S. P.; **Kadam, A. L.**; Lasonkar, P. B.; Gonnade, R. G. *Org. Lett.* **2018**, *20*, 7011.

1.2.1. Objective

Ergot alkaloids and their synthetic derivatives are well-known for their biological activities.[1] In that context synthesis of well-known dopamine agonists such as ergolines CQ 32-084 (**1**) and pergolide (**2**), apomorphine (**3**) and quinagolide (**4**) which has the combined structural features of both ergolines and apomorphine is highly desired (**Figure 1**).[2]

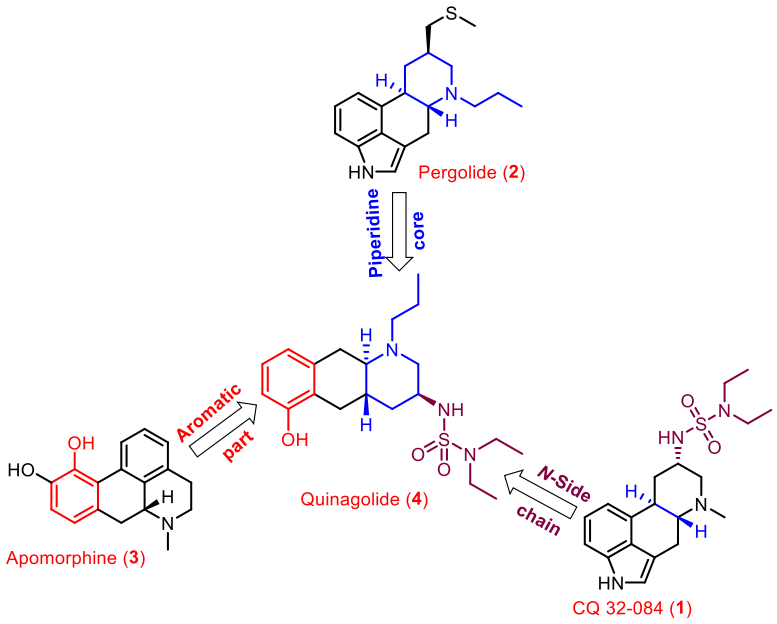


Figure 1. Quinagolide showing combined structural features of both ergolines and apomorphine.

Several natural products and biologically active compounds contain 3-aminopiperidine scaffolds as an integral part, which in turn highlighted its importance.[3] A literature survey reveals that there are many methods documented for the synthesis of 3-aminopiperidine scaffolds.

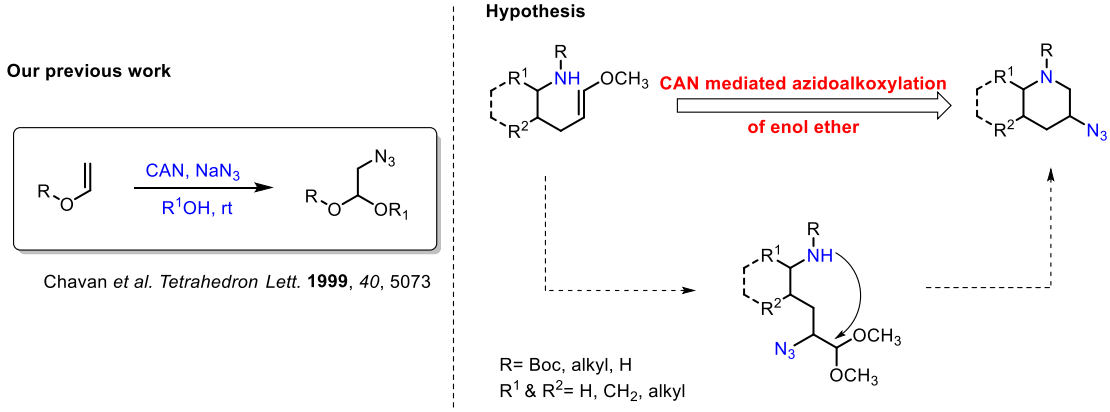
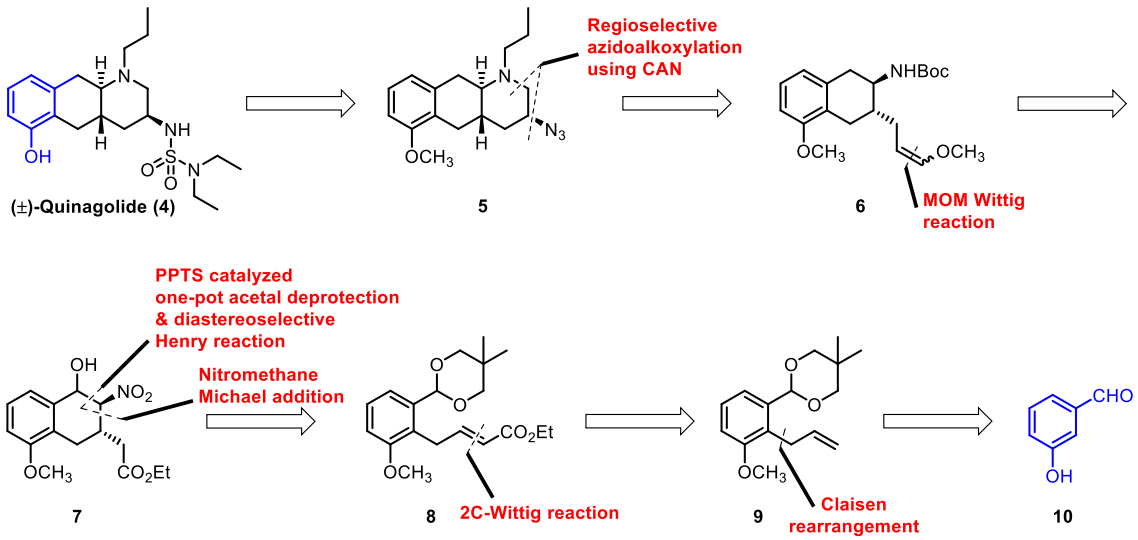


Figure 2. Initial hypothesis for 3–azidopiperidine synthesis (based on previous work from this group).

Out of the reported methods, synthesis of the 3-aminopiperidine skeleton using azidoalkoxylation of endocyclic enecarbamate is a well-established method.[4] However, there remained an urgent need for the development of the methodology for the rapid construction of a 3-aminopiperidine skeleton. In this context, this group reported a methodology of CAN mediated regioselective azidoalkoxylation of enol ethers for the synthesis of 2-azidoacetals which are synthons of α-amino acids.[5] In the present work, the idea was to utilize the methodology of CAN mediated regioselective azidoalkoxylation of enol ethers for the construction of the 3-aminopiperidine skeleton of quinagolide (**Figure 2**).

1.2.2. Present Work

1.2.2.1. Retrosynthetic analysis



Scheme 1. Retrosynthetic Analysis

To test the hypothesis for the synthesis of the 3-aminopiperidine skeleton of quinagolide using CAN mediated regioselective azidoalkoxylation, the proposed retrosynthetic analysis is shown in **Scheme 1**. Quinagolide **4** could be obtained from 3-azido piperidine **5** using Staudinger reaction as a key step which in turn could be synthesized from enol ether **6** by employing a methodology of CAN mediated regioselective azidoalkoxylation of enol ether. Enol ether **6** could be obtained from nitroester **7** by double hydrogenation and ester to enol ether conversion using a Wittig reaction. Nitroester **7** could be accessed from unsaturated ester **8** by Michael addition of nitromethane and PPTS catalyzed concomitant acetal deprotection followed by a diastereoselective Henry reaction. The unsaturated ester **8** could be obtained from *meta*-

hydroxybenzaldehyde **10** using Claisen rearrangement and two-carbon Wittig homologation on compound **9** as the key steps.

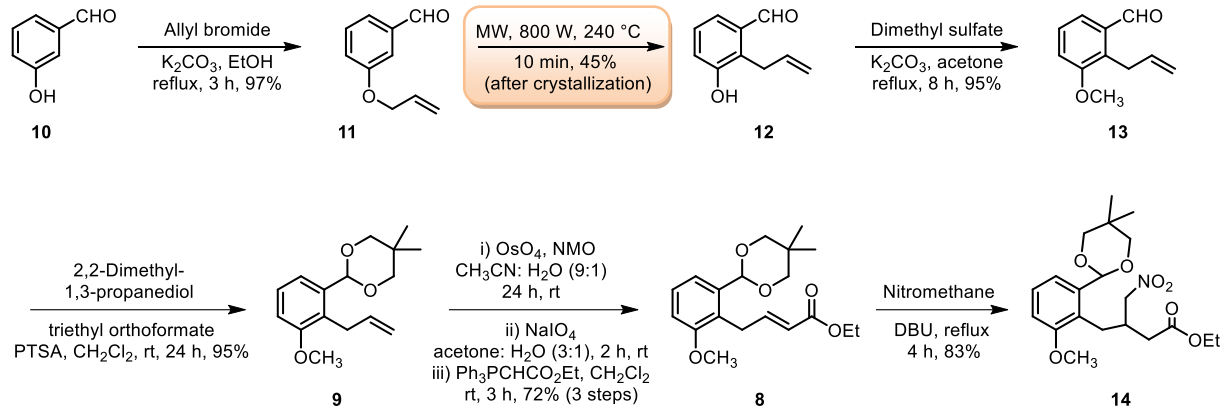
1.2.2.2. Results and discussion

Synthesis of quinagolide **4** began with the synthesis of Henry reaction precursor nitroester **14** from commercially available *meta*–hydroxybenzaldehyde as the starting material. *meta*–Hydroxybenzaldehyde **10** (**Scheme 2**) was treated with allyl bromide and K_2CO_3 under reflux conditions to obtain allyl ether **11** in 97% yield. In ^{1}H-NMR spectrum of compound **11**, peaks at 6.17–5.97 (m, 1H), 5.51–5.37 (m, 1H) and 5.37–5.27 (m, 1H) corresponding to olefin protons and distinct peak at δ 4.61 (td, J = 1.5, 5.2 Hz, 2H) for O-CH_2 protons of allyl group indicated the formation of the product. Also in the ^{13}C-NMR spectrum, signals appeared at δ 68.8 and 117.9 corresponding to O-CH_2 and olefin CH_2 carbons respectively of allyl ether group and disappearance of hydroxyl group band in IR spectrum further confirmed the product formation.

In the next step, compound **11** when irradiated neat in a microwave for 10 min, underwent Claisen rearrangement to furnish the rearranged phenol **12** in 45% yield after crystallization. The other byproduct was a *para*–allyl ether derivative which was separated by crystallization. The formation of compound **12** was confirmed by the IR spectrum, in which peak at 3219 cm^{-1} corresponded to the free hydroxyl group. In the ^{1}H-NMR spectrum, an upfield shift of distinct signals at δ 3.91 (td, J = 1.7, 5.8 Hz, 2H) corresponded to benzylic CH_2 protons of allyl group and ^{13}C-NMR signal appearing at δ 28.5 corresponded to benzylic carbon of allyl group indicating the formation of the product. It is noteworthy to mention that microwave-assisted Claisen rearrangement of substituted benzaldehyde derivatives was reported for the first time. This green protocol has advantages over conventional methods since the latter requires very high temperature, solvent and extended period of reaction time.

Then, the free hydroxyl group of **12** was methylated using dimethyl sulfate and K_2CO_3 to afford compound **13** in 95% yield. The presence of singlet at 3.87 (3H) for O-CH_3 protons in the ^{1}H-NMR spectrum indicated the formation of the product. ^{13}C-NMR signal appearing at δ 56.0 indicated the presence of methoxy carbon in the product. The formation of compound **13** was further confirmed by the disappearance of hydroxyl group signals at 3219 cm^{-1} in the IR spectrum. Aldehyde functionality of compound **13** was protected as its acetal derivative **9** using

2,2-dimethyl-1,3-propanediol, triethyl orthoformate, and PTSA in CH_2Cl_2 at room temperature in 95% yield. IR spectrum indicated the disappearance of aldehyde peak at 1705 cm^{-1} thus confirming the protection of aldehyde functionality. Also in the ^{1}H-NMR spectrum, distinct singlet at δ 5.52 (1H) corresponded to acetal proton as well as the disappearance of aldehyde proton at δ 10.27 (s, 1H) confirmed the product formation. At the same time, ^{13}C-NMR and DEPT spectra showed acetal C-H carbon at δ 99.7 and the disappearance of aldehyde carbon which confirmed the formation of the product. The structure of **9** was further confirmed by HRMS, which showed a peak at 263.1642 corresponding to the formula $C_{16}H_{23}O_3$ $[M + H]^+$ of the product.



Scheme 2. Synthesis of Henry Reaction Precursor Nitro-ester 14

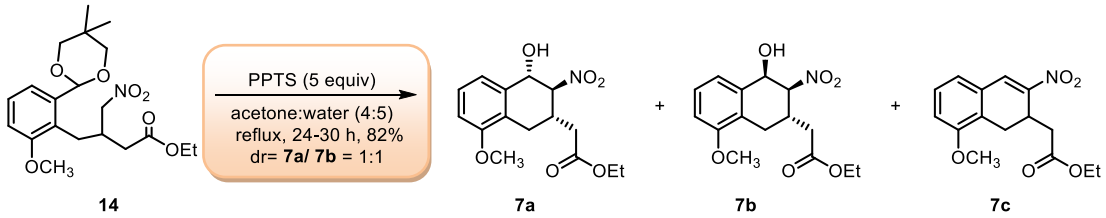
The olefin **9** was then dihydroxylated using OsO_4–NMO in CH_3CN–H_2O (9:1) followed by cleavage of corresponding diol using $NaIO_4$ and subsequent two carbon Wittig homologation on the resulting aldehyde to furnish α, β-unsaturated ester **8** in 72% yield over three steps. The formation of the product was confirmed by the peak at 1715 cm^{-1}corresponding to the carbonyl stretching frequency of ester functionality in the IR spectrum. ^{1}H-NMR spectrum showed peaks at δ 6.85 (dt, J = 2.7, 6.6, 15.6 Hz, 1H) and 5.67 (d, J = 15.6 Hz, 1H) for olefinic protons of unsaturated ester whereas presence of peak at δ 166.8 in ^{13}C-NMR spectrum corresponded to carbonyl carbon of ester functionality thus confirming the product formation. The structure of **8** was further confirmed by HRMS, which showed a peak at 335.1853 corresponding to the formula $C_{19}H_{27}O_5$ $[M + H]^+$ of the product.

Unsaturated ester **8** on Michael reaction of nitromethane under reflux conditions using DBU as the base furnished nitroester **14** in 83% yield as a Henry reaction precursor.[6] Structure of compound **14** was confirmed by ^{1}H NMR spectrum which showed the disappearance of olefinic

peaks and appearance of signals at δ 4.60–4.34 (m, 2H) and 2.46 (d, *J* = 5.6 Hz, 2H) for methylene protons. In the ^{13}C-NMR spectrum, peaks at δ 78.2 and 35.6 corresponding to methylene carbons also indicated the formation of the product. The structure of **14** was further confirmed by HRMS, which showed a peak at 396.2019 corresponding to the formula $C_{20}H_{30}NO_7$ $[M + H]^+$ of the product.

In the next crucial step, when nitroester **14** was subjected to acetal deprotection using PTSA in acetone-H_2O under reflux conditions, deprotection of acetal was observed and crude aldehyde was isolated after workup, which was subsequently treated with catalytic amount of mild base pyridine in CH_2Cl_2 to obtain nitrostyrene **7c** in 66% yield (entry 1, **Table 1**). Alternatively, when acetal deprotection was carried out using $FeCl_3$, the same aldehyde was observed, which was subjected to a Henry reaction using catalytic DBU or alumina. But unfortunately, in both cases (entries 2 and 3, **Table 1**), nitrostyrene **7c** was isolated as a major product.

Table 1. PPTS Catalyzed One-Pot Acetal Deprotection–Diastereoselective Henry Reaction



14 **7a** **7b** **7c**

entry	conditions	yield (**7a+7b+7c**)	ratio (**7a:7b:7c**)
1.	PTSA, acetone-water (1:1), reflux, 24 h then pyridine (cat.), CH_2Cl_2, rt, 1 h	66%	0:0:1
2.	i) $FeCl_3$, CH_2Cl_2, reflux, 20 min ii) DBU (cat.), CH_2Cl_2, rt, 10 min	80%	0:0:1
3.	i) $FeCl_3$, CH_2Cl_2, reflux, 20 min ii) Neutral alumina, CH_2Cl_2, rt, 2 h	86%	0:0:1
4.	PPTS (commercial, 3 equiv), acetone:water (1:1), reflux, 24 h	61%+25% (**14**)	1:1:0
5.	PPTS (commercial, 5 equiv), acetone:water (4:5), reflux, 24 h	75%	1:1:0.5
6.	PPTS (fresh, 5 equiv), acetone:water (4:5), reflux, 24–30 h	82%	1:1:0

The reduction of nitrostyrene **7c** using known literature procedures led to the inseparable mixture of *cis* and *trans*-nitro-esters in variable ratio. It was realized that when commercially available PPTS was used for the deprotection, it gave one-pot acetal deprotection followed by a diastereoselective Henry reaction in variable ratio along with recovery of starting material (entry 4, **Table 1**). An increase in PPTS amount, as well as time, resulted in the conversion of Henry reaction product into nitrostyrene **7c** (entry 5, **Table 1**). Fortunately, when freshly prepared PPTS was used for the reaction, pleasingly, nitroalcohols **7a** and **7b** were exclusively isolated in a 1:1 diastereomeric ratio in 82% combined yield (entry 6, **Table 1**). Separation of both the diastereomers was carried out by repeated silica gel column chromatography. The structure of compound **7a** was confirmed by single-crystal X-ray analysis, wherein nitro and ester groups were found to be *trans* to each other as required for quinagolide **4**. Structure of compound **7b** was confirmed by comparison of its ^{1}H NMR spectrum with that of **7a**, in which coupling constants between three contiguous stereocenters for **7a** were 9.5 and 11.6 Hz while for **7b** the corresponding coupling constants were 3.2 and 11.0 Hz indicating that in compound **7b** also, the nitro and ester groups were *trans* to each other as in case of **7a**, as required in quinagolide **4** (**Figure 3**).

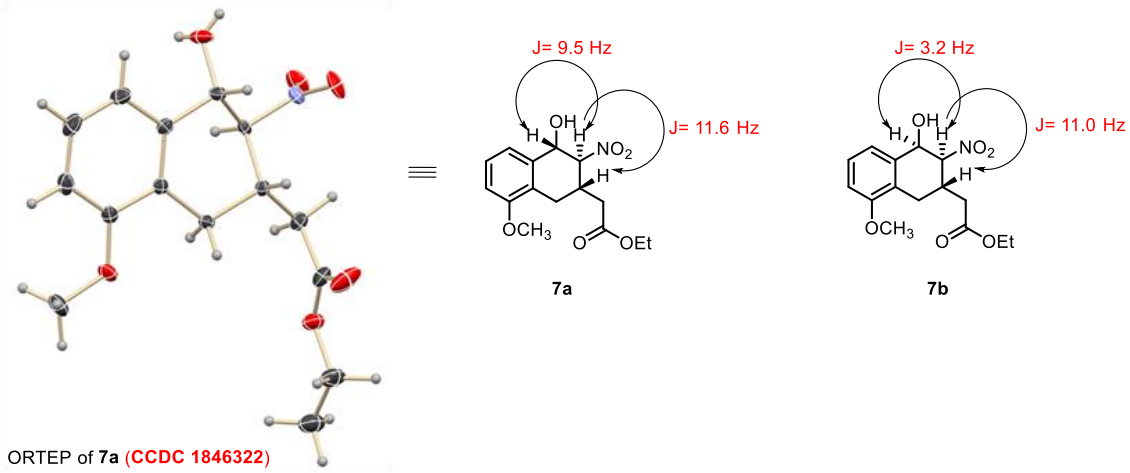


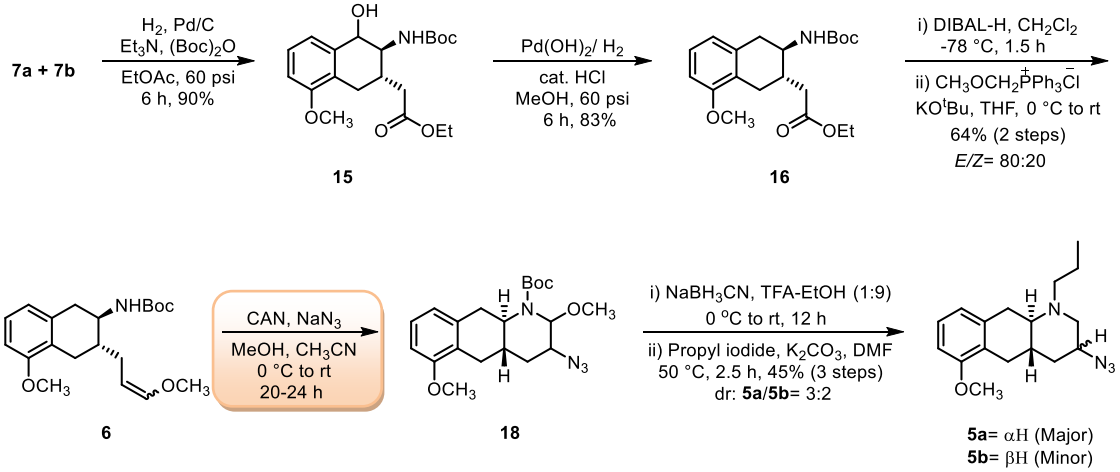
Figure 3. ORTEP diagram of **7a** and coupling constants between protons of three contiguous stereocenters for **7a** and **7b**.

It was noteworthy that acetal deprotection followed by a diastereoselective Henry reaction was carried out in one-pot in which two out of three stereocenters were incorporated into the product in the desired configuration. A literature survey revealed that the diastereoselective Henry

reaction using PPTS to fix three contiguous stereocenters on tetrahydronaphthalene was an important finding in context to the total synthesis of natural products having this structural requirement.[7]

The next aim was the synthesis of enol ether **6** for the key azidoalkoxylation reaction. To this end, reduction of the mixture of nitroesters **7a** and **7b** to corresponding amine and its concomitant Boc protection was achieved by hydrogenation using Pd/C and Boc anhydride to afford compound **15** as a mixture of diastereomers in 90% yield (**Scheme 3**). ^{1}H NMR revealed peak at δ 1.55–1.35 (br s, 9H) corresponding to Boc group protons and the presence of a peak at δ 28.30 for –CH_3 (*tert*-butyl group) in the ^{13}C-NMR spectrum indicating the formation of the product.

In the next step, benzylic deoxygenation of compound **15** was carried out using $Pd(OH)_2$ under hydrogenation condition to furnish ester **16** as a single diastereomer in 83% yield. Here, one-pot nitro reduction, concomitant protection of resulting amine and benzylic deoxygenation under hydrogenation condition could not be realized. The formation of product **16** was confirmed by the DEPT NMR spectrum, in which the presence of four methylene carbons confirmed the assigned structure of compound **16**. The peak observed at 364.2120 $[M + H]^+$ in the HRMS spectrum further confirmed the molecular formula $C_{20}H_{30}NO_5$ of compound **16**.

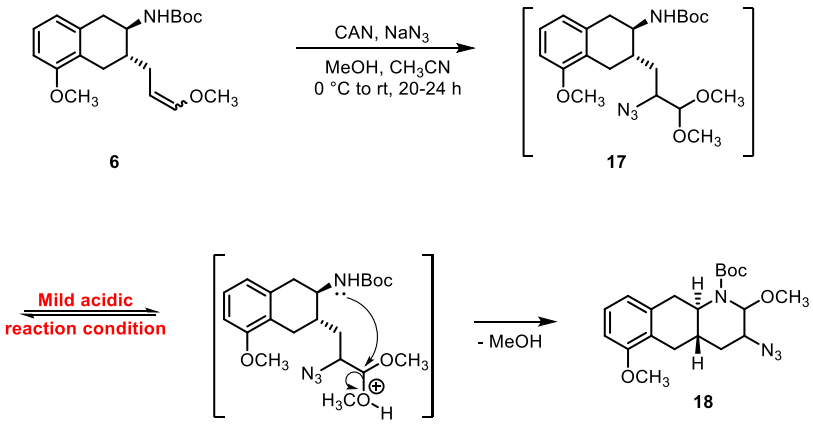


Scheme 3. CAN Mediated Azidoalkoxylation of Enol Ether

For the synthesis of enol ether **6** from ester **16**, it was reduced with DIBAL-H and the corresponding aldehyde was treated with MOM Wittig salt and potassium *t*–butoxide in THF at 0 °C to afford enol ether **6** in 64% yield (*E*/*Z*=80:20) over two steps.[8] The IR spectrum showed the disappearance of the band at 1707 cm^{-1} for carbonyl of ester indicating the product formation.

The peaks in the ^{1}H NMR spectrum at δ 6.33 (d, *J* = 12.6 Hz, 0.8H), 5.97 (d, *J* = 6.1 Hz, 0.2H) and 4.83–4.72 (m, 1H) were assigned to two protons of the double bond of enol ether. The peak at δ 55.2 in the ^{13}C-NMR spectrum indicated the presence of the methoxy carbon of enol ether. The peak observed at 370.1988 in the HRMS spectrum further confirmed the molecular formula $C_{20}H_{29}NO_4Na$ $[M + Na]^+$ of the enol ether **6**.

After enol ether **6** in hand, there was a time to test the hypothesis of 3-azidopiperidine skeleton synthesis based on the methodology of azidoalkoxylation earlier reported by this group.[9] Accordingly, enol ether **6** was treated with sodium azide, CAN (2 equiv) and MeOH (5 equiv) in CH_3CN as a solvent at 0 °C to room temperature for 20–24 h. However, instead of conventional azidoalkoxylation product **17**, the formation of tricyclic piperidine **18** was observed as a complex diastereomeric mixture. Formation of tricyclic skeleton **18** can be explained on the basis of regioselective azidoalkoxylation of the enol ether **6** followed by protonation of one of the methoxy group of acetal under slightly acidic reaction condition and nucleophilic addition of pendant amine present in **17** on the resulting acetal to obtain compound **18** as a diastereomeric mixture (**Scheme 4**).

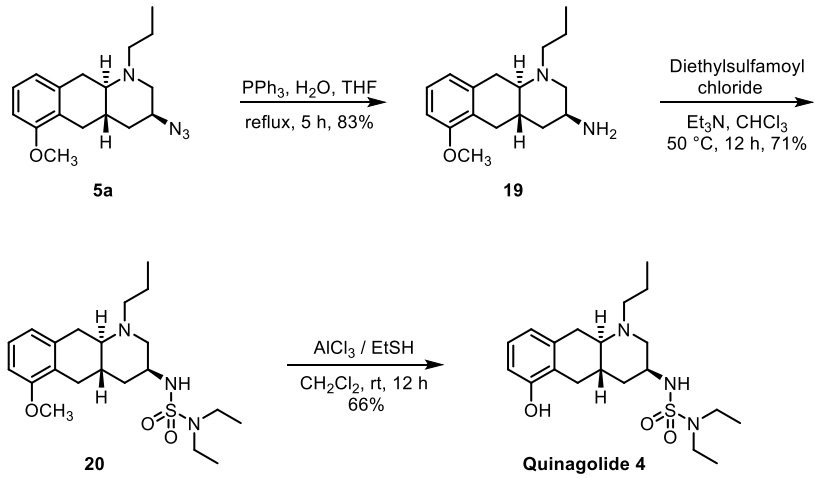


Scheme 4. Plausible Mechanism for Formation of Tricyclic Piperidine 18 from Enol Ether 6

The IR spectrum compound **18** showed the band at 2107 cm^{-1} for azide functionality. The ^{1}H NMR spectrum showed the disappearance of olefinic protons of enol ether and exhibited peaks at δ 4.37–4.26 (m, 1H) for one *N*,O-acetal proton. The ^{13}C-NMR spectrum showed the characteristic peaks at δ 95.6 and 94.9 for *N*,O-acetal carbon of diastereomeric mixture of compound **18**. The disappearance of the peaks of olefinic carbon of enol ether in DEPT NMR confirmed the formation of compound **18**. The HRMS spectrum showed the peak at 411.2001

which further confirmed the molecular formula $C_{20}H_{28}N_4O_4Na$ $[M + Na]^+$ of tricyclic skeleton **18**.

In the next step, compound **18** was treated with $NaCNBH_3$ in TFA–EtOH (1:9)[9] followed by propylation of free amine using propyl iodide and K_2CO_3 as the base in DMF as a solvent at 50 °C to afford a mixture of tricyclic ring system **5a** and **5b** (**Scheme 3**). The major diastereomer **5a**, which was found to be the required one, was separated by repeated column chromatography. Formation of tricyclic ring systems **5a** and **5b** was observed in a 3: 2 diastereomeric ratio in 45% combined yield from enol ether **6**. The appearance of a strong band at 2105 cm^{-1} in the IR spectrum indicated the presence of azide functional group. The structure of compound **5a** was confirmed by detailed 2D NMR analysis. In the NOESY spectrum of compound **5a,** there was no NOE observed between proton at azide center and βH (with respect to the azide center) at ring junction, indicating that they were *trans* to each other. The HRMS spectrum showed a peak at 301.2024 which further confirmed molecular formula $C_{17}H_{25}N_4O$ $[M + H]^+$ of compound **5a**. To the best of this author's knowledge, such type of 3-azidopiperidine synthesis using a CAN mediated regioselective azidoalkoxylation of enol ether is first-of-its-kind, which allows rapid access to piperidine based natural products and biologically active compounds containing such type of functionality.[3]



Scheme 5. Completion of the Total Synthesis

After getting the required skeleton in hand, the next step was the reduction of azide **5a** to the corresponding amine, which was carried out under the Staudinger reaction condition[10] in 83% yield (**Scheme 5**). The IR spectrum revealed a strong band at 3362 cm^{-1} for *N*-H stretching frequency of amine, thus confirming the reduction of azide **5a**. The ^1H NMR spectrum showed a

peak at δ 5.03 (br s, 2H) corresponding to amine protons. The peak at 275.2120 in the HRMS spectrum further confirmed the molecular formula $C_{17}H_{27}N_2O$ $[M + H]^+$ and the assigned structure of amine **19**.

Furthermore, amine **19** was sulfonated using diethylsulfamoyl chloride and Et_3N in $CHCl_3$ to afford compound **20** in 71% yield. The IR spectrum showed the band at 1105 cm^{-1} indicating the presence of sulfamide functional group. The ^1H NMR spectrum of compound **20** showed peaks for the sulfamide functional group at δ 3.28 (q, *J* = 6.7 Hz, 4H) and 1.18 (t, *J* = 7.0 Hz, 6H). In the ^{13}C-NMR spectrum, signals at δ 41.7 (2C) and 13.7 (2C) for sulfamide functional group confirmed the structure of compound **20**. HRMS spectrum showed a peak at 410.2477 for molecular formula $C_{21}H_{36}N_3O_3S$ $[M + H]^+$ which further confirmed the formation of compound **20**.

To complete the total synthesis, the last step was a demethylation of **20**, which was performed using $AlCl_3$–EtSH to afford quinagolide **4** in 66% yield.[11] The analytical and spectral data obtained for quinagolide **4** were in complete agreement with the reported data.[2]

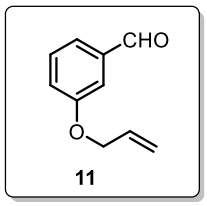
1.2.3. Conclusion

In summary, total synthesis of (±)-quinagolide was achieved from *meta*–hydroxybenzaldehyde in 14 purification steps. A PPTS catalyzed one-pot acetal deprotection followed by a diastereoselective Henry reaction which enables the construction of required *trans* geometry and CAN mediated regioselective azidoalkoxylation of enol ether which allows quick access to the piperidine ring as well as nitrogen-containing side chain of quinagolide are noteworthy features. A diastereoselective Henry reaction using PPTS to fix three contiguous stereocenters on tetrahydronaphthalene and synthesis of 3-azidopiperidines using CAN mediated regioselective azidoalkoxylation of enol ether are important findings of this synthesis.

1.2.4. Experimental Section

1.2.4.1. Experimental Procedures and Characterization Data

3-(Allyloxy)benzaldehyde (11).



11

To a magnetically stirred solution of 3-hydroxybenzaldehyde **10** (30 g, 0.24 mol, 1 equiv) in 200 mL of EtOH, K_2CO_3 (42.4 g, 0.31 mol, 1.25 equiv), NaI (3.69 g, 0.024 mol, 0.1 equiv) and allyl bromide (35.7 g, 0.29 mol, 1.2 equiv) were added and refluxed for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was allowed to cool to room temperature. The reaction mixture was filtered through simple filter paper and the residue was washed with EtOH (2 X 100 mL). The solvent was evaporated and the residue was extracted with EtOAc (3 X 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded pure allyl ether compound **11** (38.64 g, 97% yield) as a yellow oil.

R_f : 0.4 (EtOAc–PE= 10:90);

Yield: 97%;

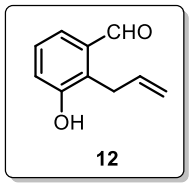
IR ($CHCl_3$): ν_{max} 2819, 1691, 1595, 1321 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.98 (s, 1H), 7.51–7.43 (m, 2H), 7.41 (d, *J* = 1.6 Hz, 1H), 7.26–7.15 (m, 1H), 6.17–5.97 (m, 1H), 5.51–5.37 (m, 1H), 5.37–5.27 (m, 1H), 4.61 (td, *J* = 1.5, 5.2 Hz, 2H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 191.9, 159.0, 137.6, 132.5, 129.9, 123.4, 121.9, 117.9, 113.0, 68.8;

HRMS (ESI) *m/z* calcd for $C_{10}H_{11}O_2$ $[M + H]^+$: 163.0754, found: 163.0755.

2-Allyl-3-hydroxybenzaldehyde (12).



12

Allyl ether compound **11** (1.5 g) was added in a glass vial, equipped with a Teflon cap. The reaction was kept for 10 min in a microwave reactor at 800 W (240 °C). The progress of the reaction was monitored by TLC. After completion, the reaction mixture was allowed to cool to room temperature and extracted with EtOAc (3 X 20 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4 and filtered. Concentration of organic layer *in vacuo*

followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded pure allyl compound as a mixture of regioisomers, which was separated by crystallization using EtOAc–PE (10:90) in deep freeze for 12 h to afford pure compound **12** as a white solid (0.68 g, 45% yield). (Note: Anton Paar, microwave synthesis reactor, model- monowave 300 was used for the reaction.).

R_f : 0.2 (EtOAc–PE =10:90);

Yield: 45%;

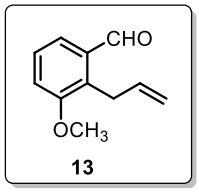
M. p.: 102 °C; IR ($CHCl_3$): ν_{max} 3219, 1672, 1599, 1281 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 10.20 (s, 1H), 7.47 (dd, *J* = 1.4, 8.0 Hz, 1H), 7.31 (t, *J* = 8 Hz, 1H), 7.12 (dd, *J* = 1.4, 8.0 Hz, 1H), 6.16–5.96 (m, 1H), 5.74 (s, 1H), 5.17–4.96 (m, 2H), 3.91 (td, *J* = 1.7, 5.8 Hz, 2H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 192.9, 154.9, 135.9, 135.2, 127.7, 127.5, 124.8, 121.5, 116.2, 28.5;

HRMS (ESI) *m/z* calcd for $C_{10}H_{11}O_2$ $[M + H]^+$: 163.0754, found: 163.0755.

2-Allyl-3-methoxybenzaldehyde (13).



13

To a magnetically stirred solution of compound **12** (14 g, 0.086 mol, 1 equiv) in anhydrous acetone (150 mL), K_2CO_3 (35.8 g, 0.26 mol, 3 equiv) and dimethyl sulfate (27.2 g, 0.22 mol, 2.5 equiv) were added and the reaction mixture was refluxed for 8 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was allowed to cool to room temperature. The reaction mixture was filtered through simple filter paper and the residue was washed with acetone (2 X 50 mL). The solvent was evaporated and the residue was diluted with 200 mL of water and stirred for 8 hrs at room temperature and extracted with EtOAc (3 X 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded pure compound **13** as a yellow oil (14.45 g, 95% yield).

R_f : 0.5 (EtOAc–PE= 10:90);

Yield: 95%;

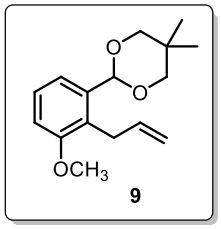
IR ($CHCl_3$): ν_{max} 1705, 1594, 1215, 756 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 10.27 (s, 1H), 7.48 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.12 (dd, *J* = 1.2, 8.0 Hz, 1H), 6.12–5.92 (m, 1H), 5.06–4.86 (m, 2H), 3.87 (s, 3H), 3.87–3.82 (m, 2H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 192.3, 157.7, 136.6, 134.9, 130.9, 127.4, 122.4, 115.8, 115.3, 56.0, 28.0;

HRMS (ESI) *m/z* calcd for $C_{11}H_{13}O_2$ $[M + H]^+$: 177.0910, found: 177.0912.

2-(2-Allyl-3-methoxyphenyl)-5,5-dimethyl-1,3-dioxane (9).



9

To a magnetically stirred solution of aldehyde **13** (14 g, 79 mmol, 1 equiv) in CH_2Cl_2 (300 mL), 2,2–dimethyl-1,3–propanediol (20.68 g, 198 mmol, 2.5 equiv), PTSA (1.5 g, 7.9 mmol, 0.1 equiv) and triethyl orthoformate (23.5 g, 159 mmol, 2 equiv) were added and stirred at room temp for 24 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3 X 100 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded pure compound **9** as a light yellow oil (19.8 g, 95% yield).

R_f : 0.6 (EtOAc–PE =10:90);

Yield: 95%;

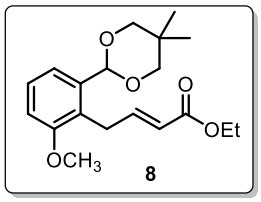
IR ($CHCl_3$): ν_{max} 2954, 1590, 1466, 1262, 1100 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.32 (dd, *J* = 1.4, 7.8 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 6.86 (dd, *J* = 1.4, 7.8 Hz, 1H), 6.07–5.86 (m, 1H), 5.52 (s, 1H), 5.01–4.87 (m, 2H), 3.80 (s, 3H), 3.76–3.57 (m, 4H), 3.55–3.48 (m, 2H), 1.30 (s, 3H), 0.78 (s, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 157.4, 137.6, 137.0, 127.3, 126.0, 118.4, 114.5, 111.2, 99.7, 77.8 (2C), 55.8, 30.2, 29.4, 23.1, 21.8;

HRMS (ESI) *m/z* calcd for $C_{16}H_{23}O_3$ $[M + H]^+$: 263.1642, found: 263.1642.

Ethyl (*E*)-4-(2-(5,5-dimethyl-1,3-dioxan-2-yl)-6-methoxyphenyl)but-2-enoate (8).



8

To a magnetically stirred solution of compound **9** (10 g, 38 mmol, 1 equiv) in CH_3CN: H_2O (9:1, 100 mL) was added NMO (6.7 g, 57 mmol, 1.5 equiv) and catalytic amount of OsO_4 (0.5 mL, 0.1 M solution in

toluene) at 25 °C, and the reaction mixture was stirred for 24 h. The reaction was quenched with a saturated solution of $Na_2S_2O_3$, further stirred for 30 min. and the reaction mixture was extracted with EtOAc (3 X 100 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The organic layer was concentrated *in vacuo*, and the obtained crude diol was directly used for the next step without further purification. For analysis purposes, a small amount was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (50:50) to afford pure diol as a colorless liquid.

R_f : 0.2 (EtOAc–PE = 50:50);

IR ($CHCl_3$): ν_{max} 3401, 2956, 1593, 1032, 755 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.27 (d, *J* = 5.8 Hz, 2H), 6.91 (t, *J* = 5.8 Hz, 1H), 5.57 (s, 1H), 4.05–3.94 (m, 1H), 3.84 (s, 3H), 3.82–3.61 (m, 6H), 3.56–3.44 (m, 1H), 3.07–2.96 (m, 2H), 2.60 (br s, 1H), 1.34 (s, 3H), 0.82 (s, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 157.8, 137.7, 127.5, 124.9, 119.4, 111.1, 101.0, 77.9, 77.8, 71.4, 66.7, 55.6, 30.2, 29.7, 23.3, 21.8;

HRMS (ESI) *m/z* calcd for $C_{16}H_{25}O_5$ $[M + H]^+$: 297.1697, found: 297.1696.

To a magnetically stirred solution of above-obtained diol in acetone–water (100 mL, 3:1), $NaIO_4$ (24.5 g, 0.11 mol, 3 equiv) was added at room temp. in 5 equal lots and stirred for 2 h at room temperature. The reaction mixture was filtered and washed with acetone (2 X 100 mL). The solvent was evaporated and the residue was diluted with 100 mL of water and then extracted with CH_2Cl_2 (3 X 100 mL). The combined organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude aldehyde which was used in the next reaction without further purification.

To a magnetically stirred solution of crude aldehyde in CH_2Cl_2 (100 mL), $Ph_3PCHCOOEt$ (19.9 g, 57 mmol, 1.5 equiv) was added and stirred for 3 h at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated under reduced pressure and residue was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (20:80) to afford compound **8** as a light yellow liquid (9.2 g, 72% yield over 3 steps).

R_f : 0.4 (EtOAc–PE = 20:80);

Yield: 72%;

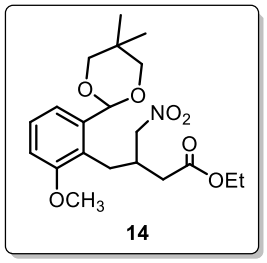
IR ($CHCl_3$): ν_{max} 1715, 1590, 1265, 1081 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.31–7.18 (m, 2H), 7.07 (td, *J* = 6.2, 15.6 Hz, 1H), 6.85 (dd, *J* = 2.7, 6.6 Hz, 1H), 5.67 (d, *J* = 15.6 Hz, 1H), 5.41 (s, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 3.75–3.53 (m, 6H), 1.27 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 3H), 0.77 (s, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 166.8, 157.4, 147.4, 137.6, 127.8, 124.0, 121.3, 118.6, 111.1, 99.9, 77.8 (2C), 60.0, 55.6, 30.1, 28.2, 23.2, 21.8, 14.2;

HRMS (ESI) *m/z* calcd for $C_{19}H_{27}O_5$ $[M + H]^+$: 335.1853, found: 335.1853.

Ethyl 3-(2-(5,5-dimethyl-1,3-dioxan-2-yl)-6-methoxybenzyl)-4-nitrobutanoate (14).



14

To a magnetically stirred solution of compound **8** (9 g, 26.9 mmol, 1 equiv) in nitromethane (36 mL), DBU (4.9 g, 32.3 mmol, 1.2 equiv) was added and refluxed for 6 h. The progress of the reaction was monitored by TLC. After completion, the solvent was carefully evaporated under reduced pressure and the crude compound was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) to afford compound **14** as a thick yellow liquid (8.85 g, 83% yield).

R_f : 0.5 (EtOAc–PE= 20:80);

Yield: 83% ;

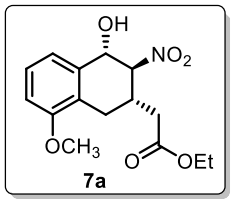
IR ($CHCl_3$): ν_{max} 2907, 1729, 1551, 1338, 1216, 757 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.33 (dd, 1.3, 7.8 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 6.87 (dd, *J* = 1.3, 7.8 Hz, 1H), 5.60 (s, 1H), 4.60–4.34 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.74–3.67 (m, 4H), 3.05–2.86 (m, 3H), 2.46 (d, *J* = 5.6 Hz, 2H), 1.32 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.82 (s, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 171.7, 157.5, 138.4, 128.1, 124.3, 119.0, 110.8, 99.2, 78.2, 77.7 (2C), 60.5, 55.4, 35.6, 34.8, 30.2, 27.1, 23.2, 21.8, 14.1;

HRMS (ESI) *m/z* calcd for $C_{20}H_{30}NO_7$ $[M + H]^+$: 396.2017, found: 396.2019.

***rac*-Ethyl 2-((2*S*,3*S*,4*S*)-4-hydroxy-8-methoxy-3-nitro-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (7a) & ethyl 2-((2*S*,3*S*,4*R*)-4-hydroxy-8-methoxy-3-nitro-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (7b).**



7a

To a magnetically stirred solution of nitro compound **14** (5 g, 12.6 mmol, 1 equiv) in acetone-water (4:5, 45 mL), freshly prepared pyridinium *p*-toluenesulfonate (PPTS) (15.9 g, 63.3 mmol, 5 equiv) was added and the

reaction mixture was refluxed for 24–30 h. The progress of the reaction was monitored by TLC. After completion, the solvent was evaporated under reduced pressure and residue was extracted with EtOAc (3 X 100 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded pure **7a** as a white solid (1.6 g, 41% yield).

R_f : 0.3 (EtOAc–PE = 30:70);

M. p.: 106–109 °C;

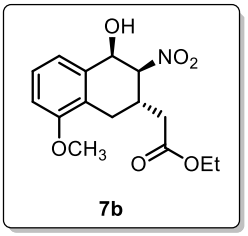
Yield: 41%;

IR ($CHCl_3$): ν_{max} 3412, 1731, 1553, 1260, 1053, 772 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.28 (t, *J* = 7.8 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.31 (t, *J* = 9.5 Hz, 1H), 4.60 (dd, *J* = 9.5, 11.6 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.20 (dd, *J* = 5.4, 17.6 Hz, 1H), 2.91–2.74 (m, 1H), 2.67 (d, *J* = 8.3 Hz, 1H), 2.57–2.33 (m, 3H), 1.28 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 170.7, 156.2, 136.7, 127.8, 122.2, 117.9, 109.2, 93.5, 71.8, 60.9, 55.4, 36.7, 33.5, 28.3, 14.1;

HRMS (ESI) *m/z* calcd for $C_{15}H_{19}NO_6Na$ $[M + Na]^+$: 332.1105, found: 332.1104.



7b

Further elution of the column with EtOAc–PE (20: 80) as eluent furnished **7b** (1.6 g, 41% yield) as a colorless liquid.

R_f : 0.25 (EtOAc–PE= 30:70);

Yield: 41%;

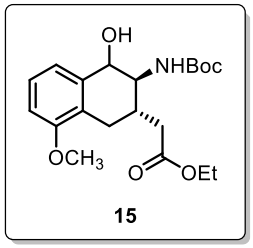
IR ($CHCl_3$): ν_{max} 3412, 1731, 1553, 1053 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.26 (t, *J* = 7.9 Hz, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 5.19 (d, *J* = 3.2 Hz, 1H), 4.88 (dd, *J* = 3.2, 11.0 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.83 (s, 3H), 3.35–3.08 (m, 2H), 2.75–2.39 (m, 4H), 1.28 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.3, 156.7, 135.3, 127.8, 123.0, 121.1, 110.0, 88.9, 69.1, 60.8, 55.4, 36.7, 28.1, 27.9, 14.1;

HRMS (ESI) *m/z* calcd for $C_{15}H_{19}NO_6Na$ $[M + Na]^+$: 332.1105, found: 332.1104.

***rac*-Ethyl 2-((2*S*,3*S*)-3-((*tert*-butoxycarbonyl)amino)-4-hydroxy-8-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (15).**



15

To a magnetically stirred mixture of nitro compounds **7a** and **7b** (3 g, 9.7 mmol, 1 equiv) in EtOAc (60 mL), Et_3N (4.1 mL, 29 mmol, 3 equiv), $(Boc)_2O$ (6.35 g, 29 mmol, 3 equiv) and Pd/C (100 mg) were added and reaction mixture was stirred at 60 *psi* under H_2 pressure for 6 h. After completion, the reaction mixture was filtered through celite, washed thoroughly with EtOAc (3 X 50 mL) and concentrated under reduced pressure. The residue thus obtained was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (30:70) to afford pure compound **15** (3.35 g, 90% yield) as a pale yellow liquid.

R_f : 0.4 (EtOAc–PE= 30:70);

Yield: 90%;

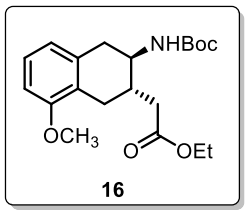
IR ($CHCl_3$): ν_{max} 3430, 2980, 1705, 1503, 1255, 768 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): (Mixture of diastereomers) δ 7.25–7.12 (m, 1.5H), 6.91 (d, *J* = 7.6 Hz, 0.5H), 6.82–6.67 (m, 1H), 5.29 (d, *J* = 9.6 Hz, 0.5H), 4.98 (d, *J* = 9.2 Hz, 0.5H), 4.71–4.44 (m, 1H), 4.25–4.07 (m, 2H), 3.80 (s, 3H), 3.57 (d, *J* = 9.5 Hz, 1H), 3.27–2.93 (m, 2H), 2.76–2.50 (m, 1H), 2.50–2.15 (m, 3H), 1.55–1.35 (br s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz): (Mixture of diastereomers) δ 173.4, 157.2, 156.7, 156.2, 155.8, 139.3, 137.8, 127.2, 127.1, 124.3, 123.0, 121.7, 118.8, 109.3, 108.3, 79.8, 79.2, 74.6, 69.8, 60.6, 60.4, 58.5, 55.2, 54.3, 38.1, 37.7, 34.0, 30.3, 29.8, 29.4, 28.35, 28.30, 14.2;

HRMS (ESI) *m/z* calcd for $C_{20}H_{30}NO_6$ $[M + H]^+$: 380.2068, found: 380.2068.

***rac*-Ethyl 2-((2*S*,3*R*)-3-((*tert*-butoxycarbonyl)amino)-8-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (16).**



16

To a magnetically stirred solution of compound **15** (3.2 g, 8.44 mmol, 1 equiv) in MeOH (30 mL), 2-3 drops of conc. HCl and $Pd(OH)_2$ (100 mg) were added and the reaction mixture was stirred at 60 *psi* under H_2 pressure for 6 h. After completion, the reaction mixture was filtered through celite, washed thoroughly with MeOH (3 X 50 mL), concentrated under reduced pressure and residue thus obtained was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (20:80) to afford pure compound **16** (2.55 g, 83% yield) as a colorless liquid.

R_f : 0.5 (EtOAc–PE= 20:80);

Yield: 83%;

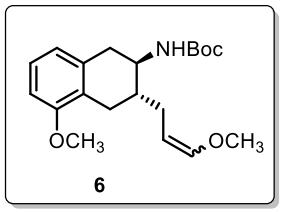
IR ($CHCl_3$): ν_{max} 2979, 1707, 1505, 1165, 768 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.10 (t, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 7.9 Hz, 2H), 4.67 (d, *J* = 9.2 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 3.78–3.69 (m, 1H), 3.19–2.96 (m, 2H), 2.73–2.55 (m, 2H), 2.49–2.24 (m, 3H), 1.45 (s, 9H), 1.28 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 173.4, 156.9, 155.4, 135.6, 126.5, 123.4, 120.9, 107.2, 79.2, 60.5, 55.1, 50.5, 38.1, 36.2, 35.6, 28.8, 28.4 (3C), 14.2;

HRMS (ESI) *m/z* calcd for $C_{20}H_{30}NO_5$ $[M + H]^+$: 364.2118, found: 364.2120.

***rac-tert*-Butyl ((2*R*,3*R*)-5-methoxy-3-(3-methoxyallyl)-1,2,3,4-tetrahydronaphthalen-2-yl)carbamate (6).**



6

To a magnetically stirred cooled solution (-78 °C) of compound **16** (1.0 g, 2.75 mmol, 1 equiv) in anhydrous CH_2Cl_2 (20 mL), was added DIBAL-H (0.86 g, 6.06 mmol, 2.2 equiv) and the resulting solution was stirred at -78 °C for 1.5 h. The solution was treated with saturated aq. sodium-potassium tartrate (10 mL) and the resulting suspension was warmed to room temperature. The mixture was stirred for 30 min, the suspension was filtered, and the solution was partitioned with CH_2Cl_2 (50 mL) and brine (20 mL). The organic layer was washed with brine (2 X 30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to provide the crude aldehyde as a clear oil which was immediately used for next reaction without further purification.

To a magnetically stirred suspension of (methoxymethyl)triphenylphosphonium chloride (2.83 g, 8.26 mmol, 3 equiv) in anhydrous THF (20 mL) at 0 °C, was added potassium *tert*-butoxide (0.77 g, 6.88 mmol, 2.5 equiv). The reaction mixture was stirred at 0 °C for 30 min and then the above-obtained aldehyde in anhydrous THF (10 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred overnight. Saturated aqueous NH_4Cl (15 mL) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 X 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded pure enol ether **6** (*E/Z* = 80:20) (0.61 g, 64% yield over 2 steps) as a thick colorless liquid.

R_f : 0.5 (EtOAc–PE= 10:90);

Yield: 64%;

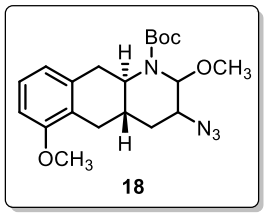
IR ($CHCl_3$): ν_{max} 2971, 1696, 1173, 758 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.10 (t, *J* = 7.8 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 6.33 (d, *J* = 12.6 Hz, 0.8H), 5.97 (d, *J* = 6.1 Hz, 0.2H), 4.83–4.72 (m, 1H), 4.66–4.51 (m, 1H), 3.82 (br s, 4H), 3.58 (s, 0.5H), 3.54 (s, 2.5H), 3.09 (dd, *J* = 3.8, 16.4 Hz, 1H), 2.93–2.80 (m, 1H), 2.63 (dd, *J* = 7.6, 16.8 Hz, 1H), 2.46 (dd, *J* = 6.5, 17.5 Hz, 1H), 2.25–2.12 (m, 1H), 2.02–1.94 (m, 1H), 1.83 (br s, 1H), 1.46 (s, 9H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.2, 155.4, 148.3, 147.4, 135.4, 126.3, 126.2, 124.0, 121.2, 107.2, 104.0, 100.0, 79.1, 59.4, 55.9, 55.2, 49.2, 38.6, 34.7, 30.7, 28.4 (3C), 26.3;

HRMS (ESI) *m/z* calcd for $C_{20}H_{29}NO_4Na$ $[M + Na]^+$: 370.1989, found: 370.1988.

***rac-tert*-Butyl (4a*S*,10a*R*)-3-azido-2,6-dimethoxy-3,4,4a,5,10,10a-hexahydrobenzo[g]quinoline-1(2H)-carboxylate (18).**



18

To a magnetically stirred solution of enol ether **6** (0.3 g, 0.86 mmol, 1 equiv) in dry acetonitrile (10 mL), NaN_3 (62 mg, 0.95 mmol, 1.1 equiv) followed by methanol (0.175 mL, 4.3 mmol, 5 equiv) were added under argon atmosphere and stirred for 15 min. CAN (0.947 g, 1.73 mmol, 2 equiv) dissolved in dry acetonitrile (10 mL) was added dropwise to it at 0 °C and the reaction mixture was gradually brought to room temperature and stirred for 20-24 h. The reaction mixture was concentrated under reduced pressure and extracted with CH_2Cl_2 (3 X 20 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was used in the next step without further purification. For analysis purposes, a small amount was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (5:95) to afford compound **18** as a colorless liquid.

R_f : 0.4 (EtOAc–PE= 5:95);

IR ($CHCl_3$): ν_{max} 2929, 2107, 1696, 1257, 1081, 759 cm^{-1};

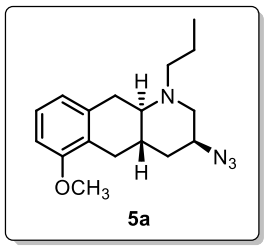
^{1}H NMR ($CDCl_3$, 400 MHz): (Mixture of diastereomers) δ 7.12 (t, *J* = 7.8 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 2H), 4.65–4.45 (m, 1H), 4.37–4.26 (m, 1H), 3.82 (s, 3H), 3.79– 3.66 (m, 1H), 3.62–3.54 (m, 3H), 3.17–2.92 (m, 2H), 2.77–2.59 (m, 1H), 2.48 (dd, *J* = 7.1, 17.4 Hz, 1H), 2.40–2.26 (m, 1H), 2.07–1.80 (m, 2H), 1.47 (br s, 9H);

^{13}C NMR ($CDCl_3$, 100 MHz): (Mixture of diastereomers) δ 157.1, 157.0, 155.6, 155.4, 135.5, 135.0, 126.7, 126.6, 123.4, 123.1, 121.1, 120.9, 107.4, 107.3, 95.6, 94.9, 79.5, 79.4, 63.8, 63.4,

62.6, 62.1, 57.7, 57.4, 55.22, 55.20, 50.1, 49.7, 35.9, 35.6, 35.3, 35.2, 34.6, 34.5, 33.4, 33.2, 32.6, 32.4, 29.6, 28.4 (3C), 27.9, 27.4;

HRMS (ESI) *m/z* calcd for $C_{20}H_{28}N_4O_4Na$ $[M + Na]^+$: 411.2003, found: 411.2001.

***rac*-(3*S*,4a*S*,10a*R*)-3-Azido-6-methoxy-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinoline (5a).**



5a

To a magnetically stirred cooled (0 °C) solution of above crude compound **18** in EtOH (3 mL), sodium cyanoborohydride (163 mg, 2.6 mmol, 3 equiv) was added. After stirring for 20 min at that temperature, trifluoroacetic acid (0.3 mL) was added dropwise. The resulting solution was stirred for 12 h while warming to room temperature. The mixture was then concentrated *in vacuo* and redissolved in EtOAc (20 mL) and treated with saturated $NaHCO_3$ (5 mL). The layers were then separated and the aqueous layer was extracted with EtOAc (3 X 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was used for next reaction without further purification.

To a magnetically stirred solution of above-obtained amine in DMF (5 mL), pulverized K_2CO_3 (179 mg, 1.3 mmol, 1.5 equiv) was added and the reaction mixture was heated to 50 °C. After stirring for 20 min at that temperature, *n*-propyl iodide (0.44 g, 2.6 mmol, 3 equiv) was added and the reaction mixture was stirred for an additional 2.5 h at 50 °C. The reaction mixture was cooled to room temperature and extracted with EtOAc (3 X 10 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by repeated silica gel (230–400 mesh) column chromatography using EtOAc–PE (5:95) afforded pure product **5a** (55 mg, 21% yield) as a white solid.

R_f : 0.5 (EtOAc–PE= 10:90);

M. p.: 84–86 °C;

Yield: 21%;

IR ($CHCl_3$): ν_{max} 2930, 2105, 1202, 759 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.12 (t, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 3.86–3.83 (m, 1H), 3.82 (s, 3H), 3.17 (dd, *J* = 5.0, 16.4 Hz, 1H), 3.10 (td, *J* = 2.4, 12.4 Hz, 1H), 2.95 (dd, *J* = 4.8, 17.4 Hz, 1H), 2.81–2.72 (m, 2H), 2.59–2.51 (m, 2H), 2.27 (dt, *J*

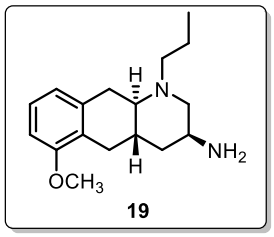
= 5.0, 10.5 Hz, 1H), 2.18–2.07 (m, 2H), 2.03–1.93 (m, 1H), 1.56–1.47 (m, 2H), 1.47–1.40 (m, 1H), 0.93 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.7, 136.5, 126.3, 124.2, 121.3, 106.9, 60.6, 56.2, 55.2, 54.9, 54.7, 35.6, 34.5, 32.6, 30.4, 17.5, 11.9;

HRMS *m/z* (ESI) calcd for $C_{17}H_{25}N_4O$ $[M + H]^+$: 301.2023, found: 301.2024.

(Note: Minor isomer **5b** was contaminated with major isomer **5a** and **5b** could not be isolated in pure form. The ^{1}H NMR spectrum of mixture of **5a** and **5b** is enclosed.)

***rac*-(3*S*,4a*S*,10a*R*)-6-Methoxy-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinolin-3-amine (19).**



19

To a magnetically stirred solution of azide **5a** (50 mg, 0.17 mmol, 1 equiv) in THF (5 mL), PPh_3 (66 mg, 0.25 mmol, 1.5 equiv) and H_2O (0.021 mL, 1.16 mmol, 7 equiv) were added at room temperature. The mixture was heated under reflux for 5 h. After evaporation of the solvent under reduced pressure, the residue was purified by silica gel (230–400 mesh) column chromatography using MeOH–$CHCl_3$ (10:90) to afford pure amine **19** (38 mg, 83% yield) as a thick yellow liquid.

R_f : 0.2 (MeOH–$CHCl_3$ = 10:90);

Yield: 83%;

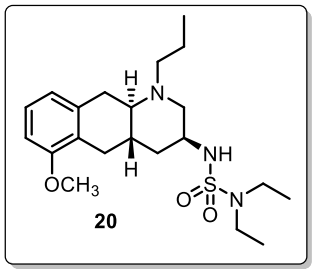
IR ($CHCl_3$): ν_{max} 3362, 2958, 1588, 1253, 1076, 766 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.08 (t, *J* = 7.8 Hz, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 5.03 (br s, 2H), 3.79 (s, 3H), 3.37 (br s, 1H), 3.11 (dd, *J* = 4.8, 16.2 Hz, 1H), 3.01 (d, *J* = 11.8 Hz, 1H), 2.89 (dd, *J* = 4.8, 17.4 Hz, 1H), 2.75–2.64 (m, 2H), 2.56–2.44 (m, 2H), 2.24 (dt, *J* = 5.0, 10.5 Hz, 1H), 2.15–2.04 (m, 2H), 1.95–1.81 (m, 1H), 1.52–1.33 (m, 3H), 0.87 (t, *J* = 7.4 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.7, 136.4, 126.2, 124.4, 121.3, 106.9, 60.9, 56.6, 55.2, 54.4, 46.2, 37.0, 34.6, 32.1, 30.5, 17.5, 11.9;

HRMS (ESI) *m/z* calcd for $C_{17}H_{27}N_2O$ $[M + H]^+$: 275.2118, found: 275.2120.

***rac*-*N*,*N*-Diethyl-*N*'-(3*S*,4a*S*,10a*R*)-6-methoxy-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinolin-3-sulfamide (20).**



To a magnetically stirred solution of amine **19** (30 mg, 0.11 mmol, 1 equiv) in $CHCl_3$ (5 mL), triethylamine (0.08 mL, 0.55 mmol, 5 equiv) and diethylsulfamoyl chloride (47 mg, 0.27 mmol, 2.5 equiv) were added and the mixture was stirred for 12 h at 50 °C. Ice and 1 N $NaHCO_3$ (2 mL) were added and stirring continued for 10 min at room temperature. The mixture was extracted with CH_2Cl_2 (3 X 10 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using MeOH–CH_2Cl_2 (1:99) afforded pure product **20** (32 mg, 71% yield) as a white solid.

R_f : 0.5 (MeOH–CH_2Cl_2 = 1:99);

M. p.: 86–88 °C;

Yield: 71%;

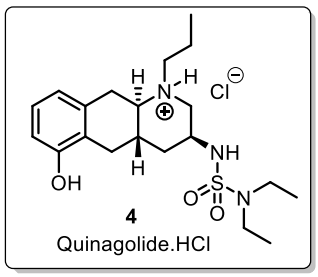
IR ($CHCl_3$): ν_{max} 3383, 3019, 1215, 1105, 757 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.10 (t, *J* = 7.9 Hz, 1H), 6.71 (d, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 7.9 Hz, 1H), 3.80 (s, 3H), 3.68 (br s, 1H), 3.28 (q, *J* = 6.7 Hz, 4H), 3.14 (dd, *J* = 3.7, 15.3 Hz, 2H), 2.95 (d, *J* = 14.0 Hz, 2H), 2.86 (br s, 1H), 2.67 (br s, 2H), 2.48 (br s, 1H), 2.23–2.03 (m, 3H), 1.57 (br s, 2H), 1.39 (t, *J* = 11.6 Hz, 1H), 1.18 (t, *J* = 7.0 Hz, 6H), 0.94 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.6, 135.2, 126.5, 123.7, 121.1, 107.1, 61.7, 56.5, 55.2, 54.3, 47.9, 41.7 (2C), 36.5, 33.4, 31.9, 30.2, 17.3, 13.7 (2C), 11.6;

HRMS (ESI) *m/z* calcd for $C_{21}H_{36}N_3O_3S$ $[M + H]^+$: 410.2472, found: 410.2477.

***rac*-*N*,*N*-Diethyl-*N*'-(3*S*,4a*S*,10a*R*)-6-hydroxy-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinolin-3-sulfamide (4) hydrochloride**.



To a magnetically stirred mixture of ethanethiol (1 mL) in dry CH_2Cl_2 (1 mL) was added aluminum chloride (49 mg, 0.36 mmol, 5 equiv) at 0 °C. The resulting solution was warmed to room temperature and compound **20** (30 mg, 0.07 mmol, 1 equiv) was added with stirring. After being stirred for 12 h, the reaction mixture was poured into

water, basified with 1N $NaHCO_3$, and extracted with CH_2Cl_2 (3 X 5 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The obtained residue was passed through a small bed of silica gel (230–400 mesh) using MeOH–$CHCl_3$ (10:90) and the solvent was evaporated under reduced pressure. The obtained product was dissolved in CH_2Cl_2 (2 mL) and precipitated by the addition of HCl in Et_2O. The precipitated product was filtered and washed with CH_2Cl_2 to yield pure quinagolide **4** (19 mg, 66%) as hydrochloride.

M. p. 228–232 °C (lit. M. p. 234–236 °C)[1];

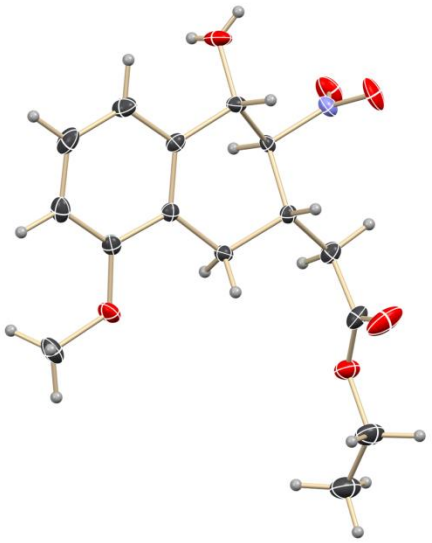
Yield: 66%;

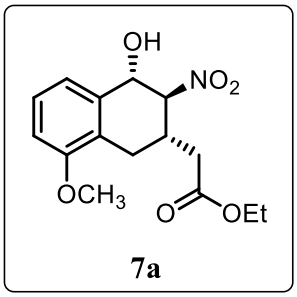
^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.08 (br s, 1H), 9.52 (br s, 1H), 7.72 (br s, 1H), 6.95 (t, *J* = 8.0 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 3.66 (br s, 1H), 3.32-3.07 (m, 11H), 2.86 (d, *J* = 14.6 Hz, 1H), 2.22- 2.12 (m, 2H), 1.98 (d, *J* = 12.2 Hz, 1H), 1.68 (br s, 3H), 1.10 (t, *J* = 8.0 Hz, 6H), 0.95 (t, *J* = 8.0 Hz, 3H);

^{13}C NMR (DMSO-d_6, 100 MHz): δ 154.4, 133.9, 126.7, 121.1, 119.3, 112.1, 62.1, 54.2, 53.5, 46.5, 41.2 (2C), 33.6, 29.8, 29.8, 29.7, 15.9, 13.7 (2C), 11.0;

HRMS (ESI) *m/z* calcd for $C_{20}H_{34}N_3O_3S$ $[M]^+$: 396.2315, found: 396.2320.

1.2.4.2. X-ray crystallography details of compound 7a





7a

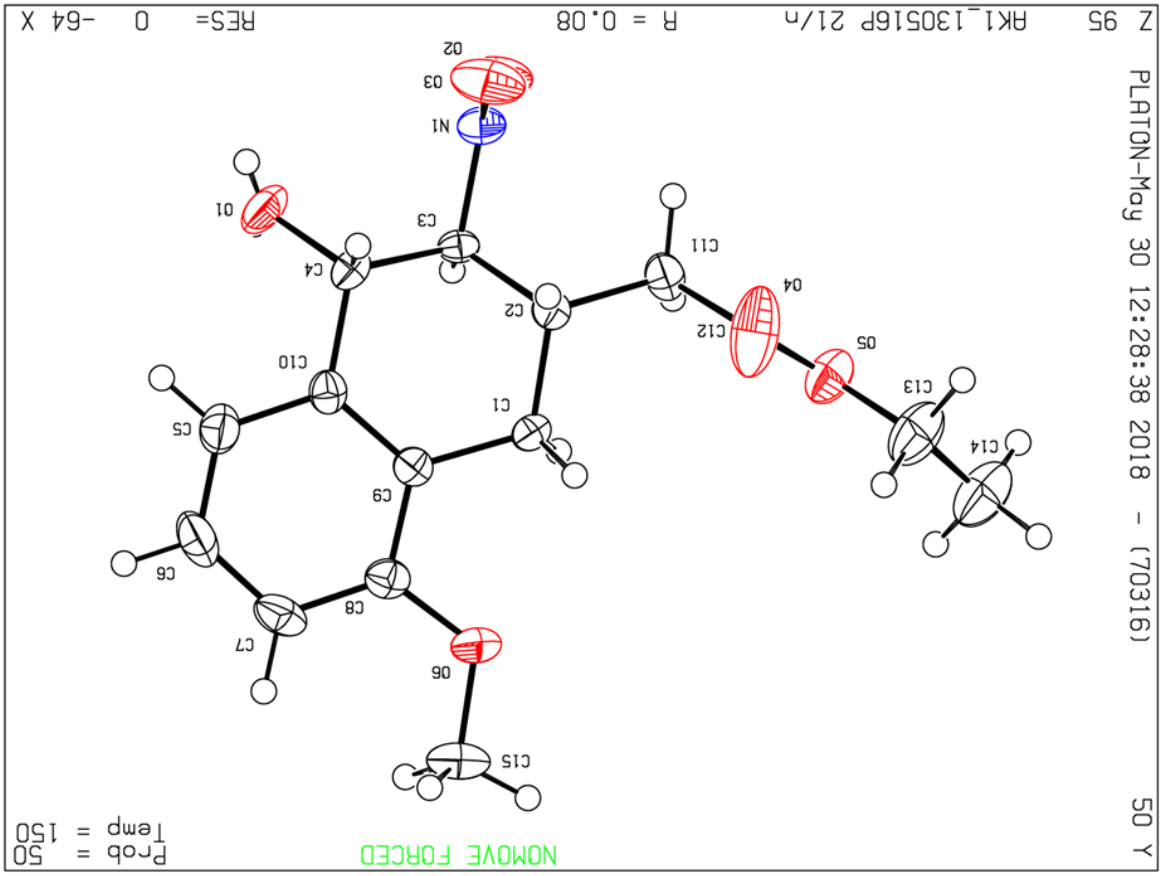


Table 1: Crystallographic Information for compound **7a**

Crystal Data	**AK1_130516**
Formula	$C_{15}H_{19}NO_6$
M_r	309.31
Crystal Size, mm	0.360 x 0.300 x 0.220
Temp. (K)	150(2)
Crystal Syst.	Monoclinic
Space Group	$P2_1/n$
a/Å	5.2381(2)
b/Å	16.3038(6)
c/Å	17.8354(5)
α/°	90
β/°	94.761(2)
γ/°	90
V/Å^3	1517.90(9)
Z	4
D_{calc}/g cm^{-3}	1.354
μ/mm^{-1}	0.105
F(000)	656
Ab. Correct.	multi-scan
T_{min}/ T_{max}	0.977/0.963
$2\theta_{max}$	59.37
Total reflns.	15151
Unique reflns.	4171
Obs. reflns.	2795
h, k, l (min, max)	(-7, 7), (-22, 22), (-24, 24)
R_{int}	0.0701
No. of parameters	210
R1 [$I > 2\sigma(I)$]	0.0793
wR2[$I > 2\sigma(I)$]	0.1595
R1 [all data]	0.1208
wR2 [all data]	0.1796
goodness-of-fit	1.058
$\Delta\rho_{max}$, $\Delta\rho_{min}$(eÅ^{-3})	+0.518, -0.275

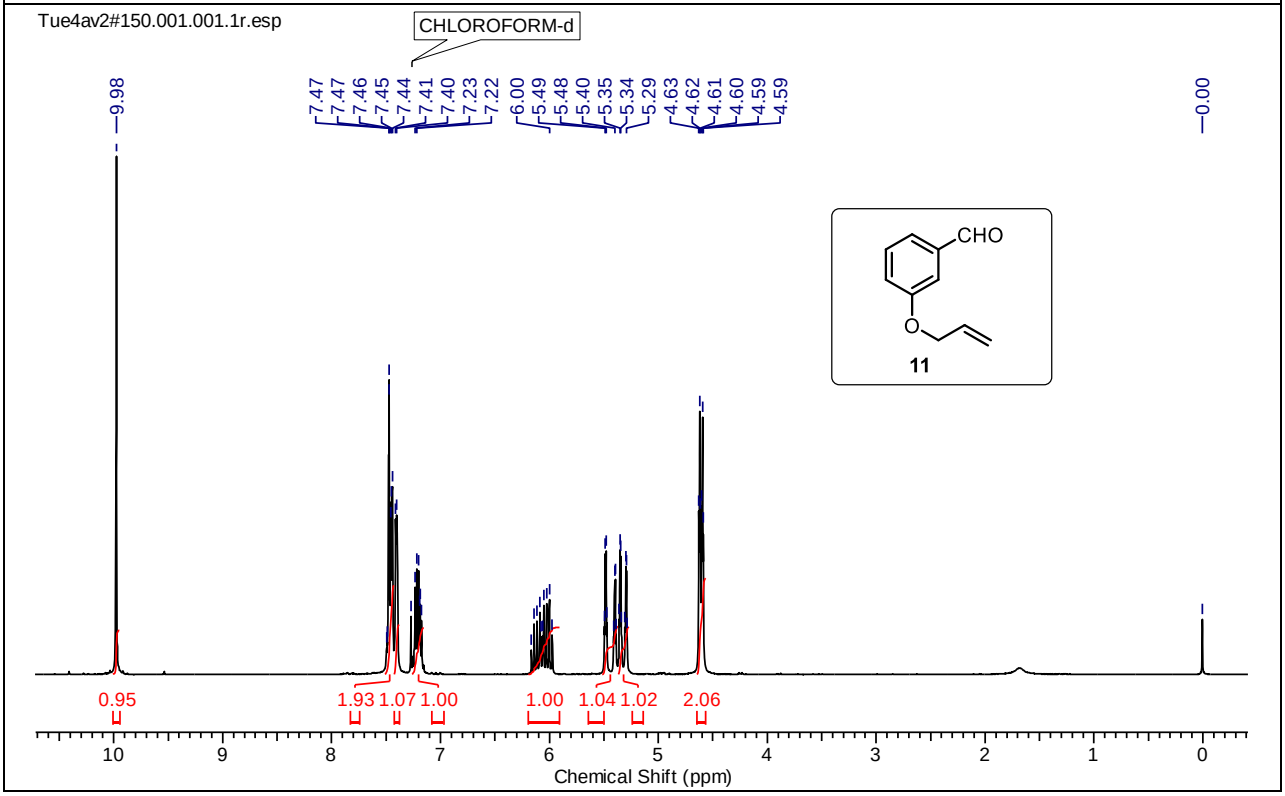
X-ray intensity data measurements of compounds **7a** were carried out on a Bruker SMART APEX II CCD diffractometer with graphite monochromatized (MoKα= 0.71073 Å) radiation at 150(2) K. The X-ray generator was operated at 50 kV and 30 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 12 frames (total 36 frames). Data were collected with ω scan width of 0.5° at eight different settings of φ and 2θ keeping the sample-to-detector distance fixed at 5.00 cm for **7a**. The unit-cell measurements, data collection, integration, scaling, and absorption corrections for these crystals were performed by using Bruker APEX2 Program suite.[1] The diffraction images were integrated by using Bruker SAINT Programs.[2] The data were corrected for Lorentz-polarization and absorption effects by using the multi-scan method by using SADABS[3] with the transmission coefficients. Using APEX2 program suite, the structure was solved with the ShelXS-97 (Sheldrick, 2008)[4] structure solution program, using direct methods. The model was refined with a version of ShelXL-2013 (Sheldrick, 2015)[5] using Least Squares minimization based on F^2. All the H-atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms by using the HFIX command in SHELX-TL. A check of the final CIFs by using PLATON[6] did not show any missing symmetry. An *ORTEP* III[7] view of compounds was drawn with 50% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii.

References

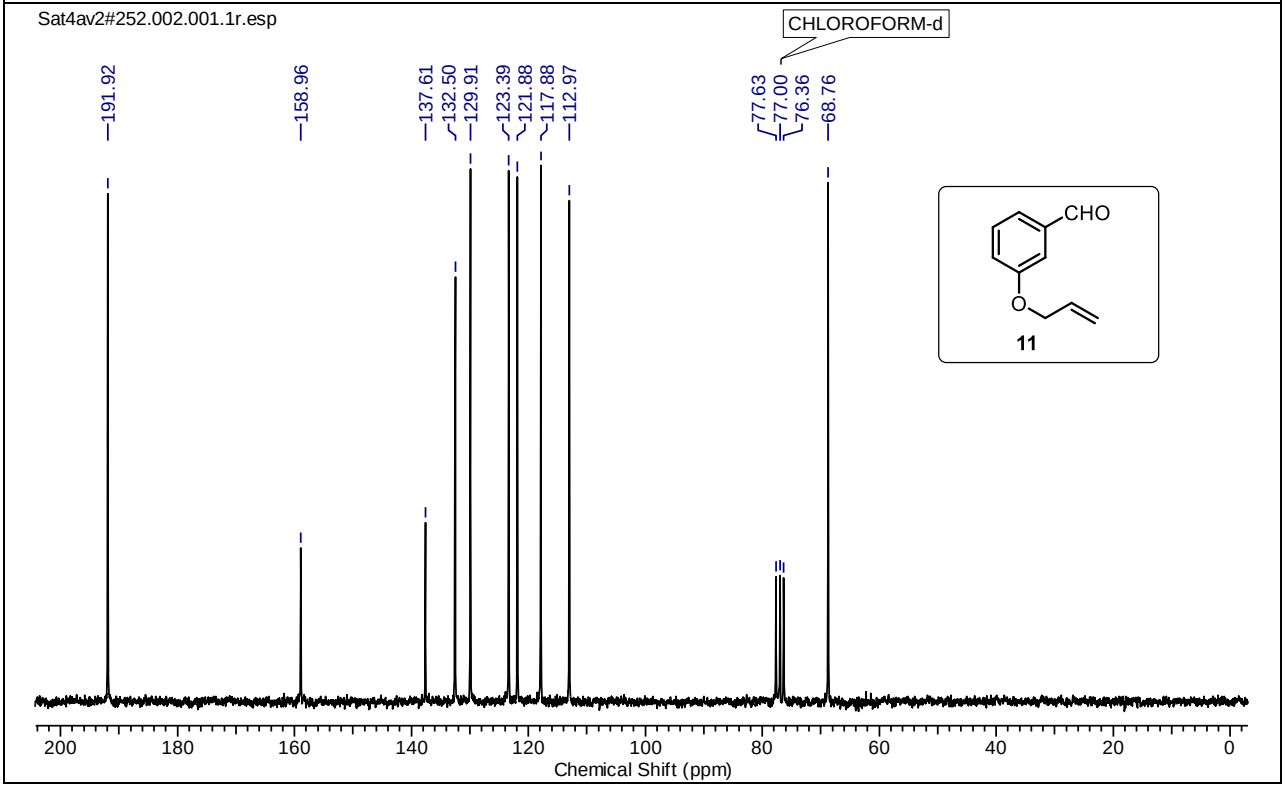
1. Bruker (2006). *APEX2*, *SAINT* and *SADABS*. Bruker AXS Inc., Madison, USA.
2. Bruker 2006b. SAINT, Version 7.60a. Bruker AXS Inc., Madison, Wisconsin, USA.
3. Bruker 2006a. SADABS, Version 2.05. Bruker AXS Inc., Madison, Wisconsin, USA.
4. G. M. Sheldrick, *Acta Crystallogr*., **2008**, *A64*, 112.
5. G. M. Sheldrick, *Acta Crystallogr*., **2015**, *C71*, 3–8.
6. a) A. L. Spek, PLATON, A Multipurpose Crystallographic Tool; Utrecht University: Utrecht, Netherland, 2002; b) A. L. Spek, *J. Appl. Crystallogr.* **2003**, *36*, 7–13.
7. L. J. Farrugia, *J. Appl. Crystallogr.* **2012**, *45*, 849–854.

1.2.5. Spectral Data

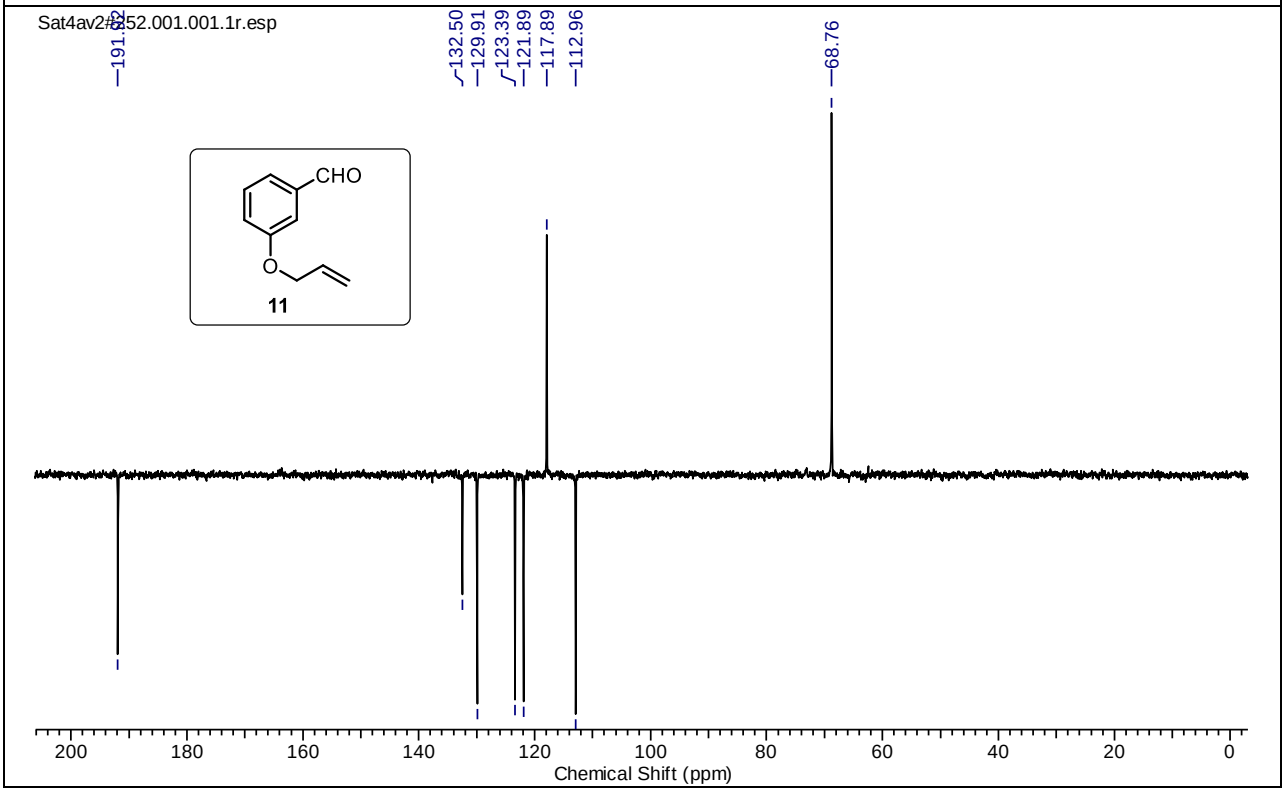
^{1}H-NMR spectrum of compound 11 ($CDCl_3$, 200 MHz)



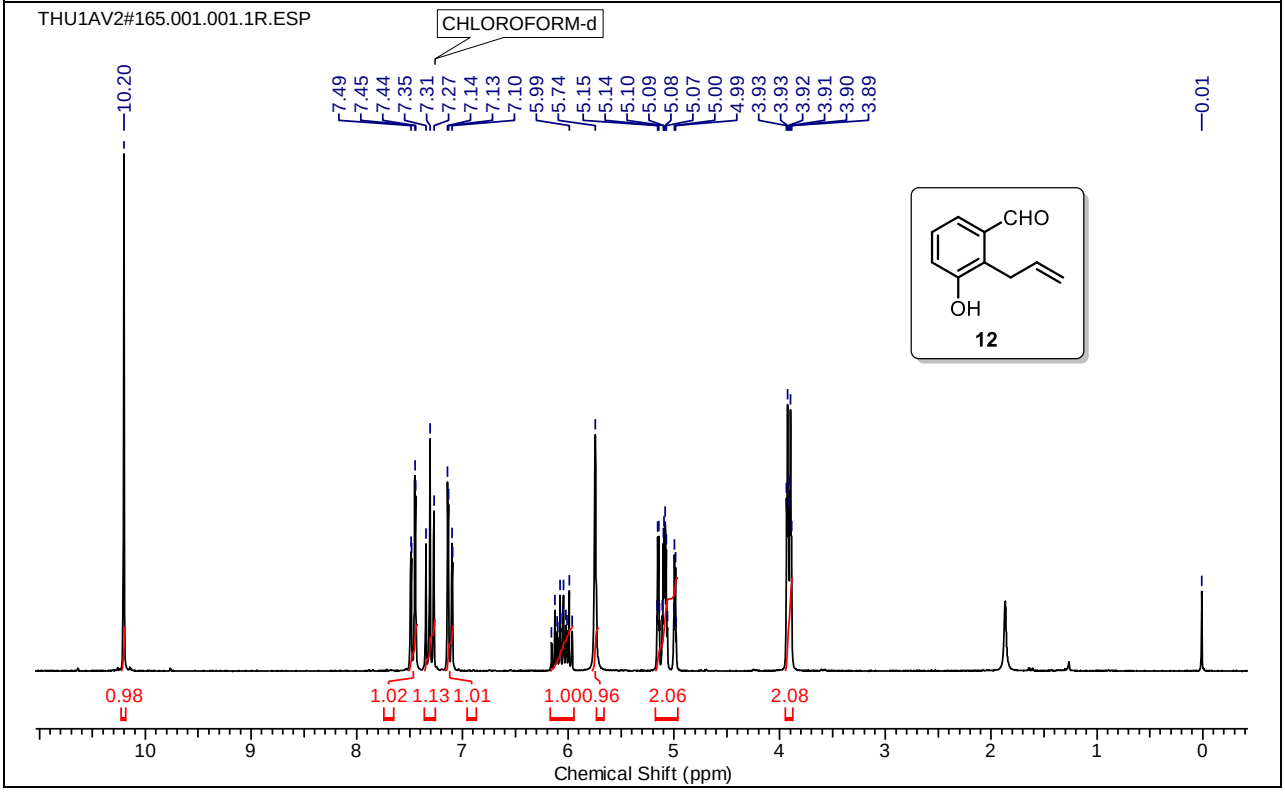
^{13}C-NMR spectrum of compound 11 ($CDCl_3$, 50 MHz)



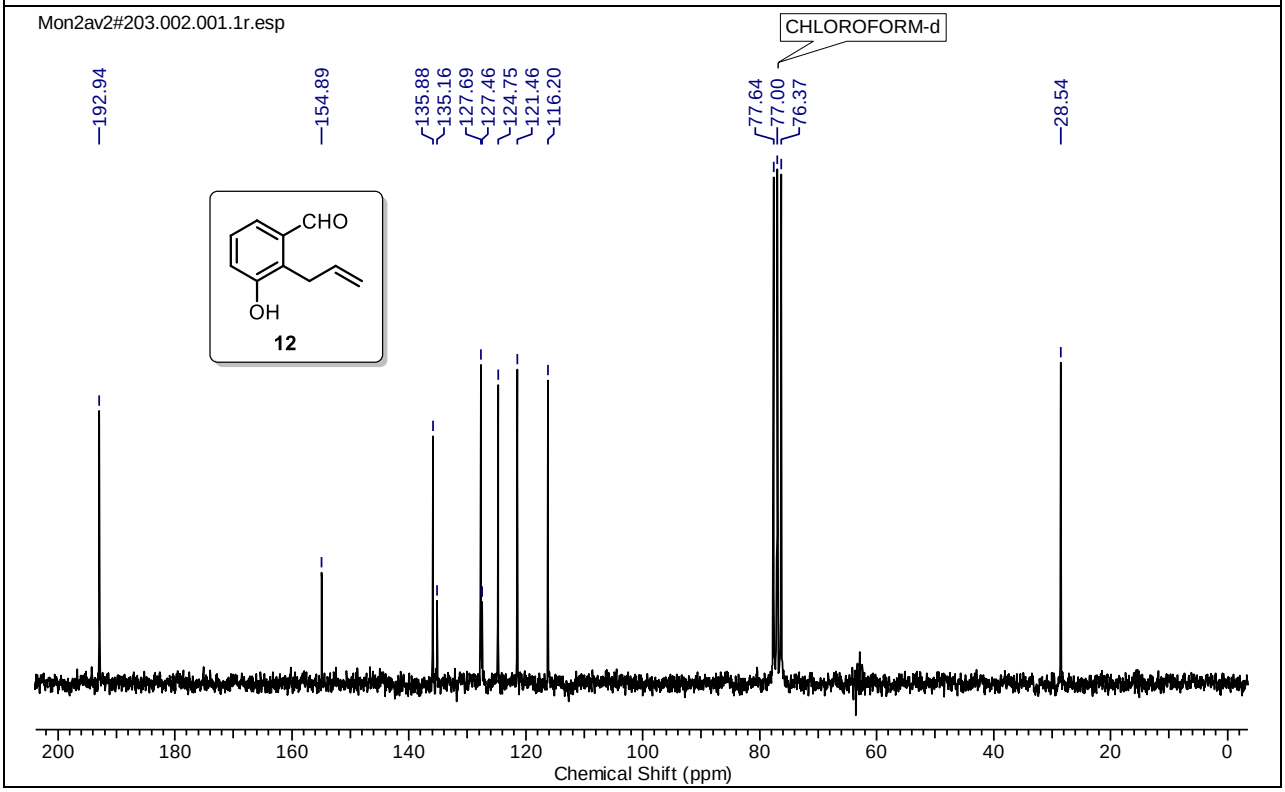
DEPT NMR spectrum of compound 11 ($CDCl_3$, 50 MHz)



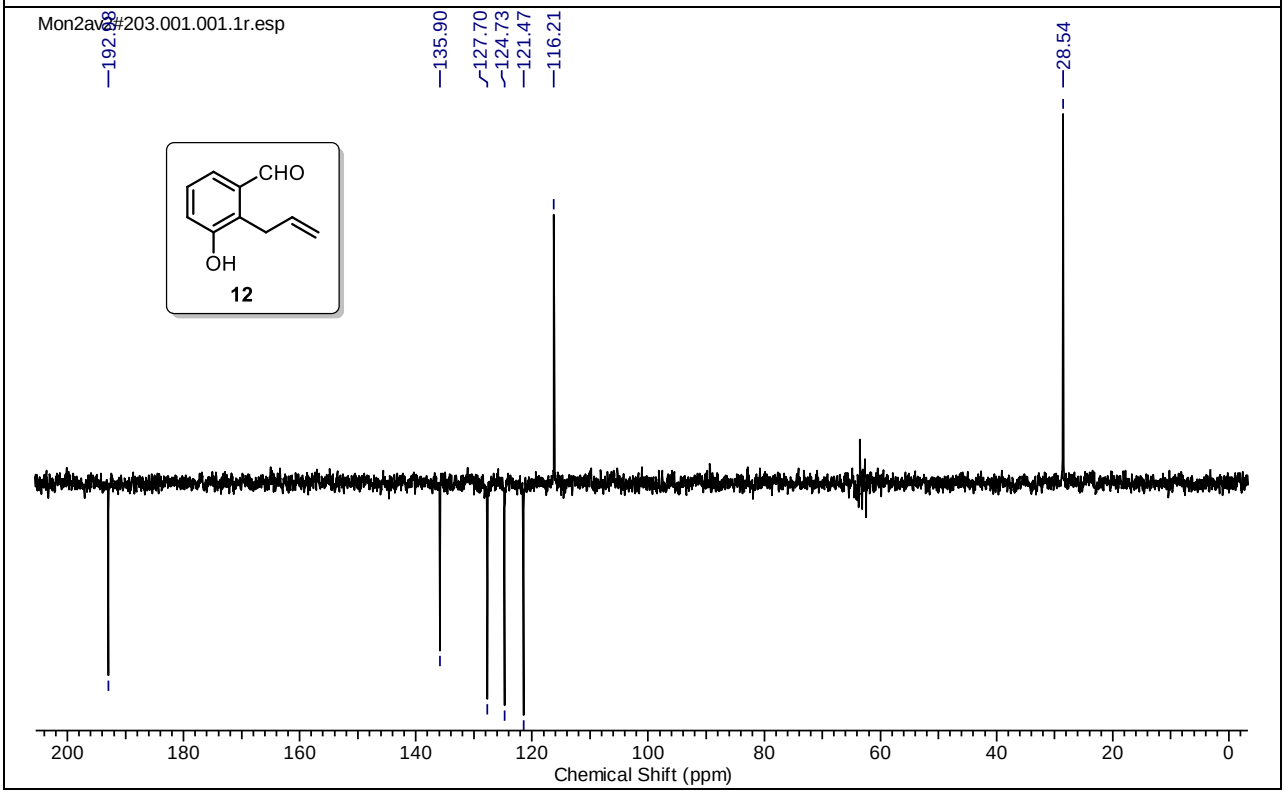
^{1}H-NMR spectrum of compound 12 ($CDCl_3$, 200 MHz)



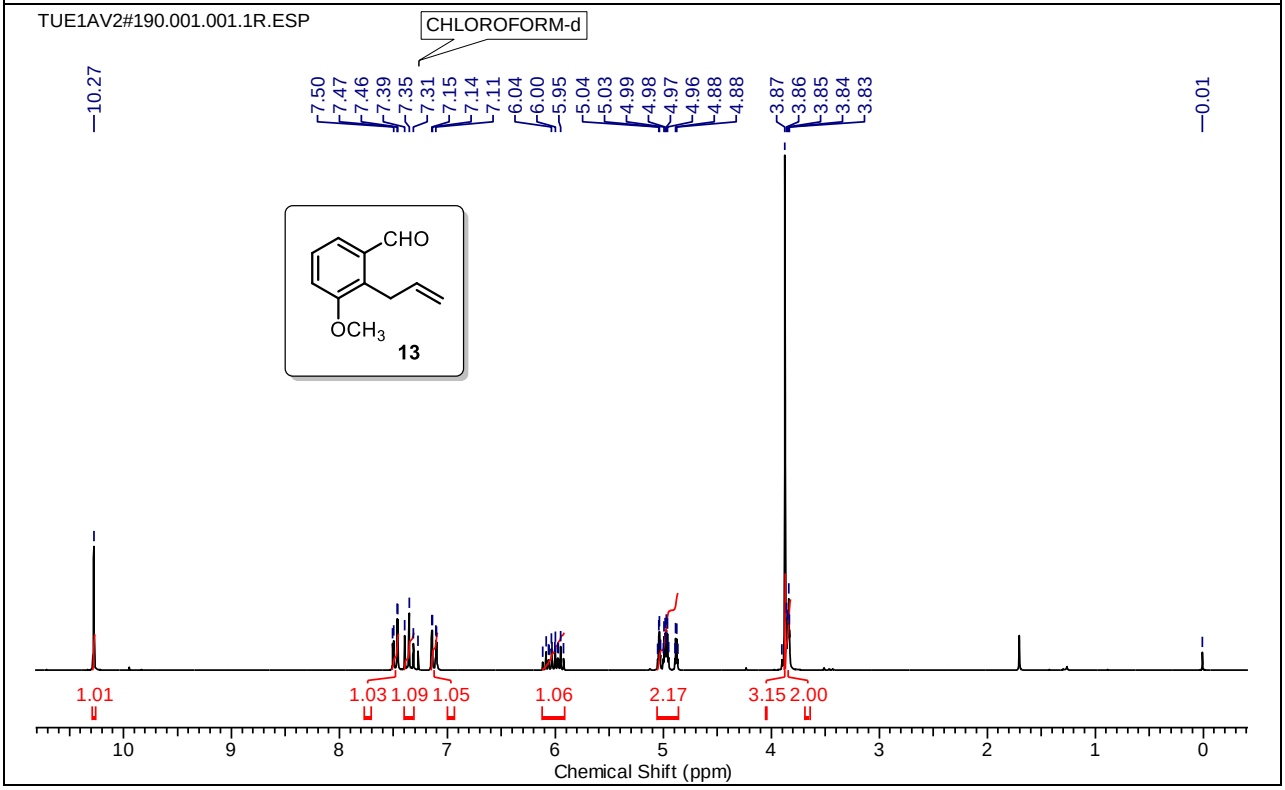
^{13}C-NMR spectrum of compound 12 ($CDCl_3$, 50 MHz)



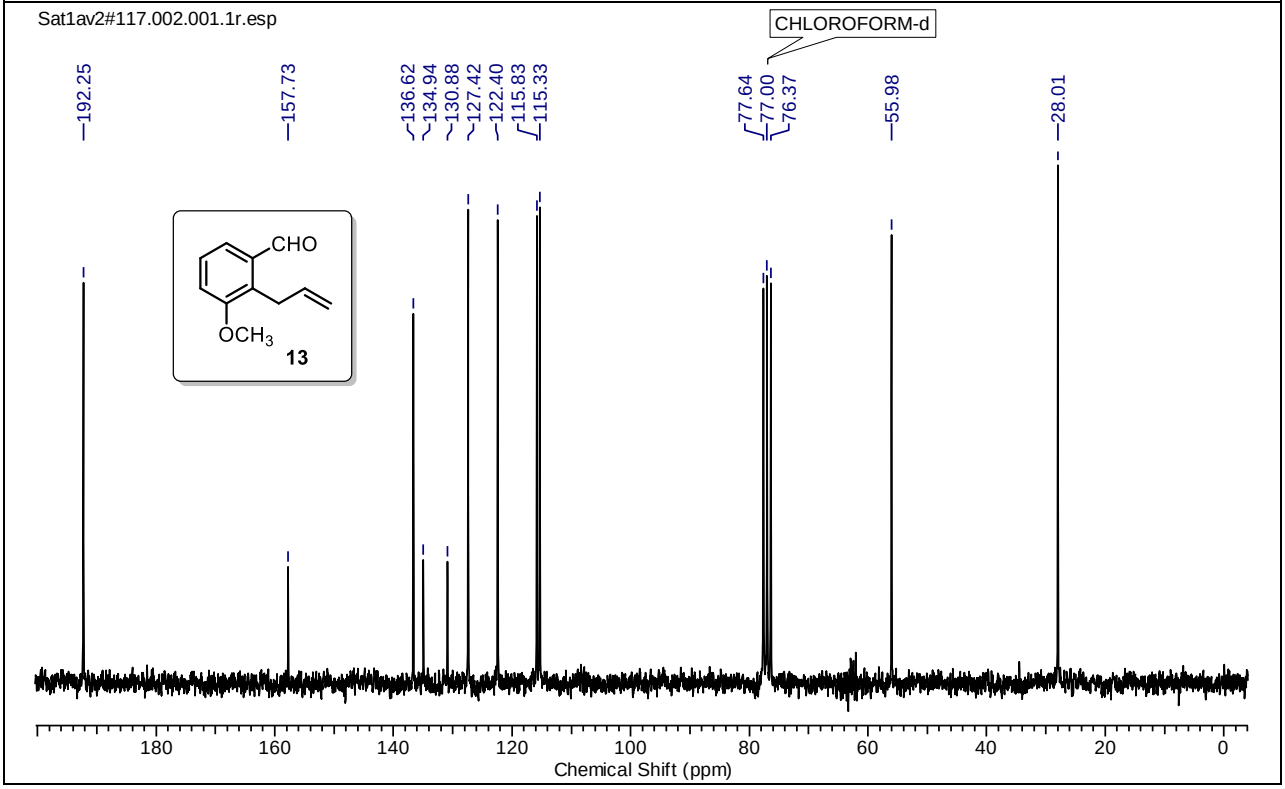
DEPT NMR spectrum of compound 12 ($CDCl_3$, 50 MHz)



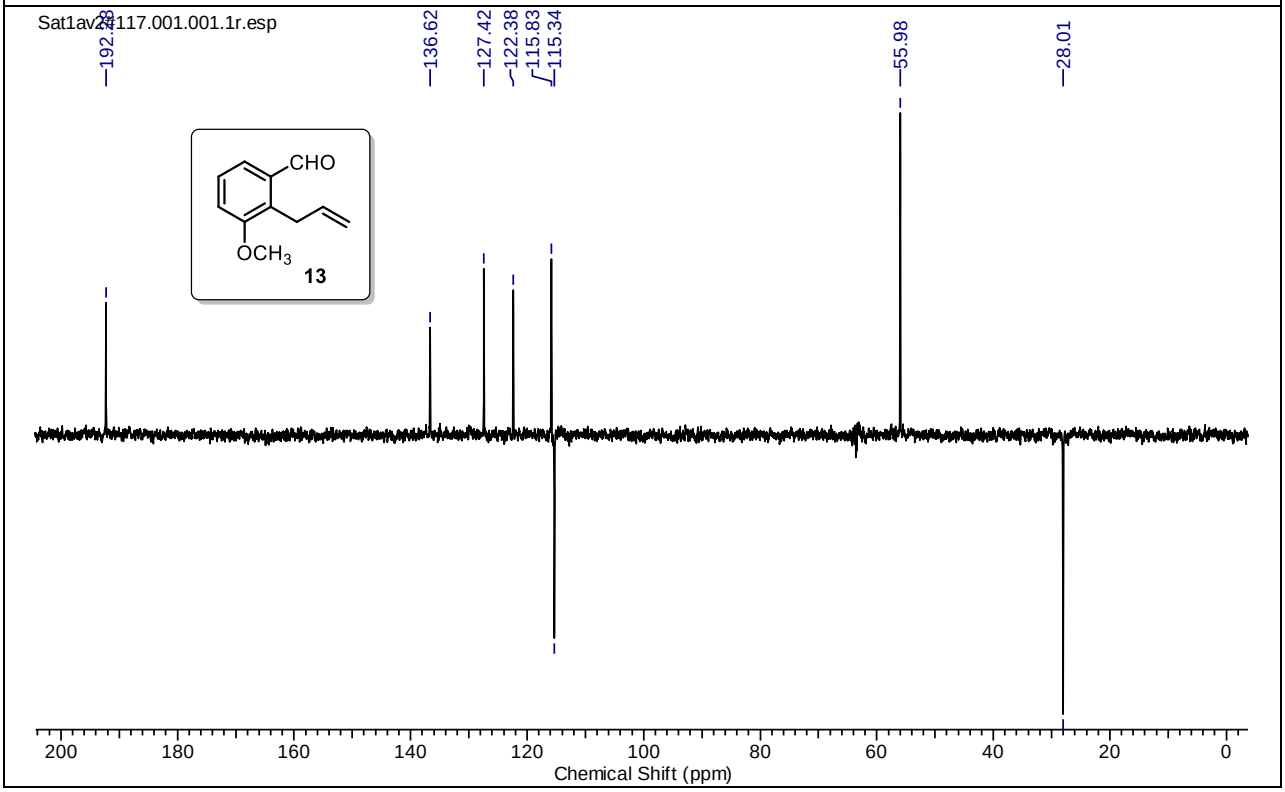
^{1}H-NMR spectrum of compound 13 ($CDCl_3$, 200 MHz)



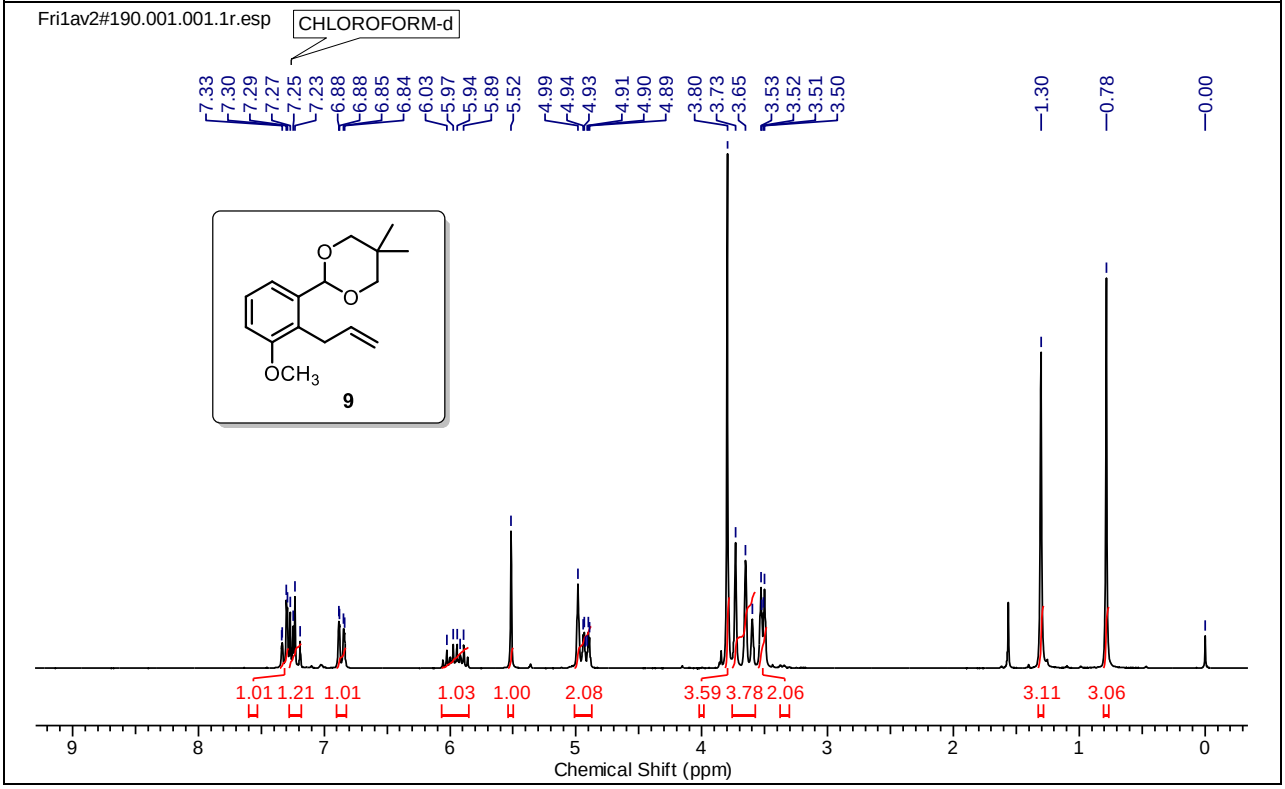
^{13}C-NMR spectrum of compound 13 ($CDCl_3$, 50 MHz)



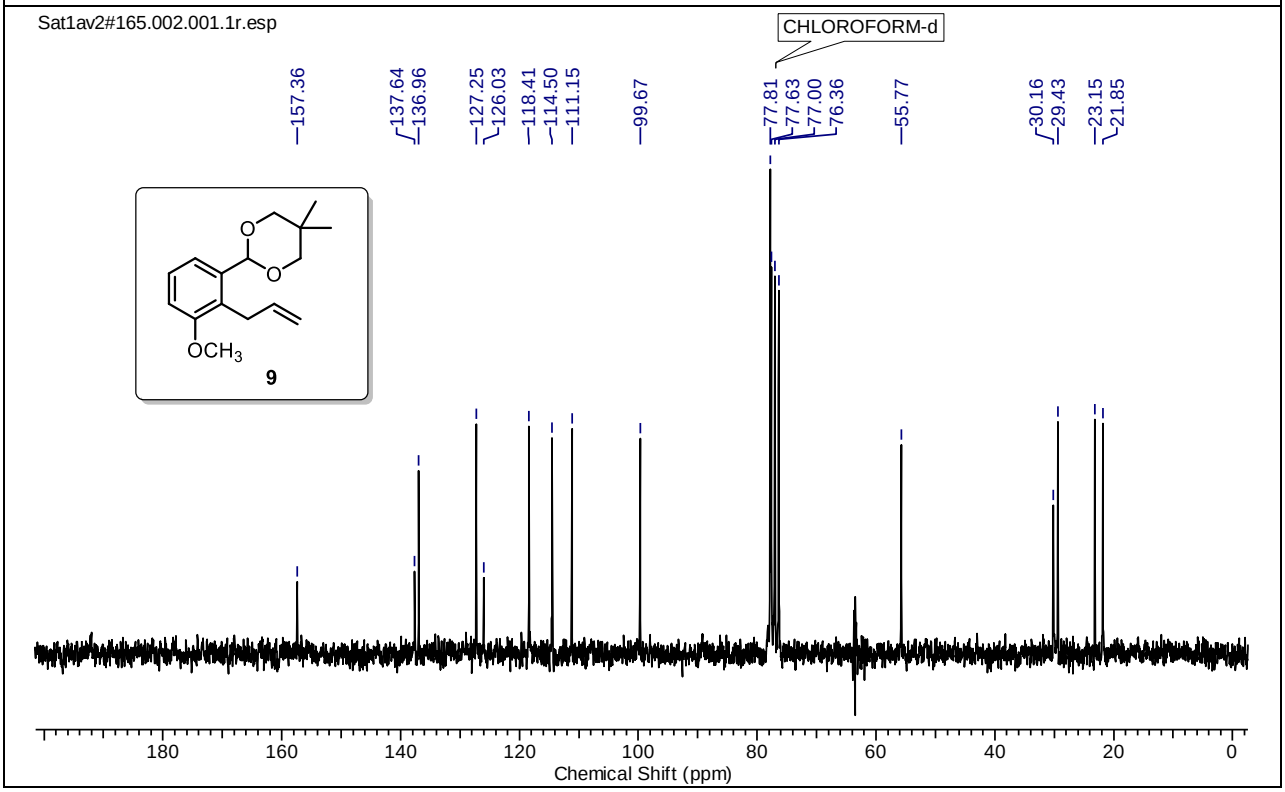
DEPT NMR spectrum of compound 13 ($CDCl_3$, 50 MHz)



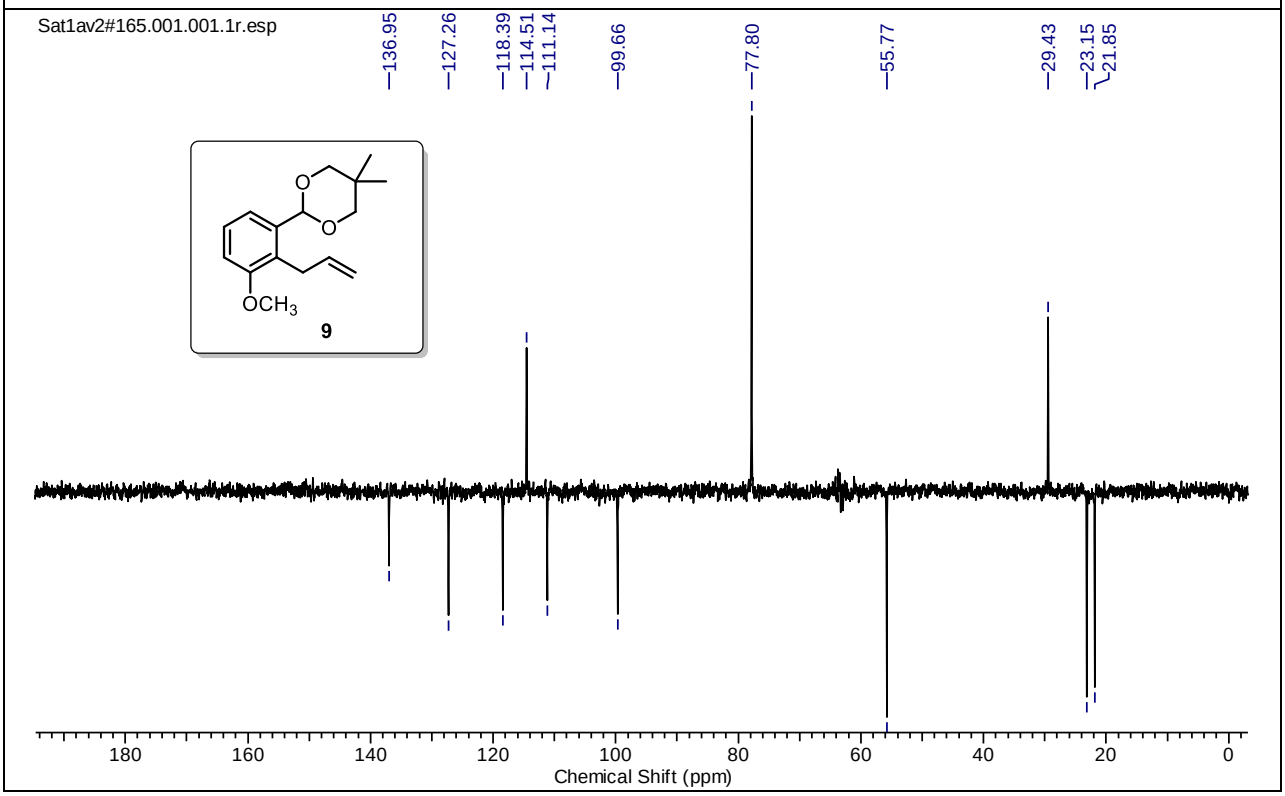
^{1}H-NMR spectrum of compound 9 ($CDCl_3$, 200 MHz)



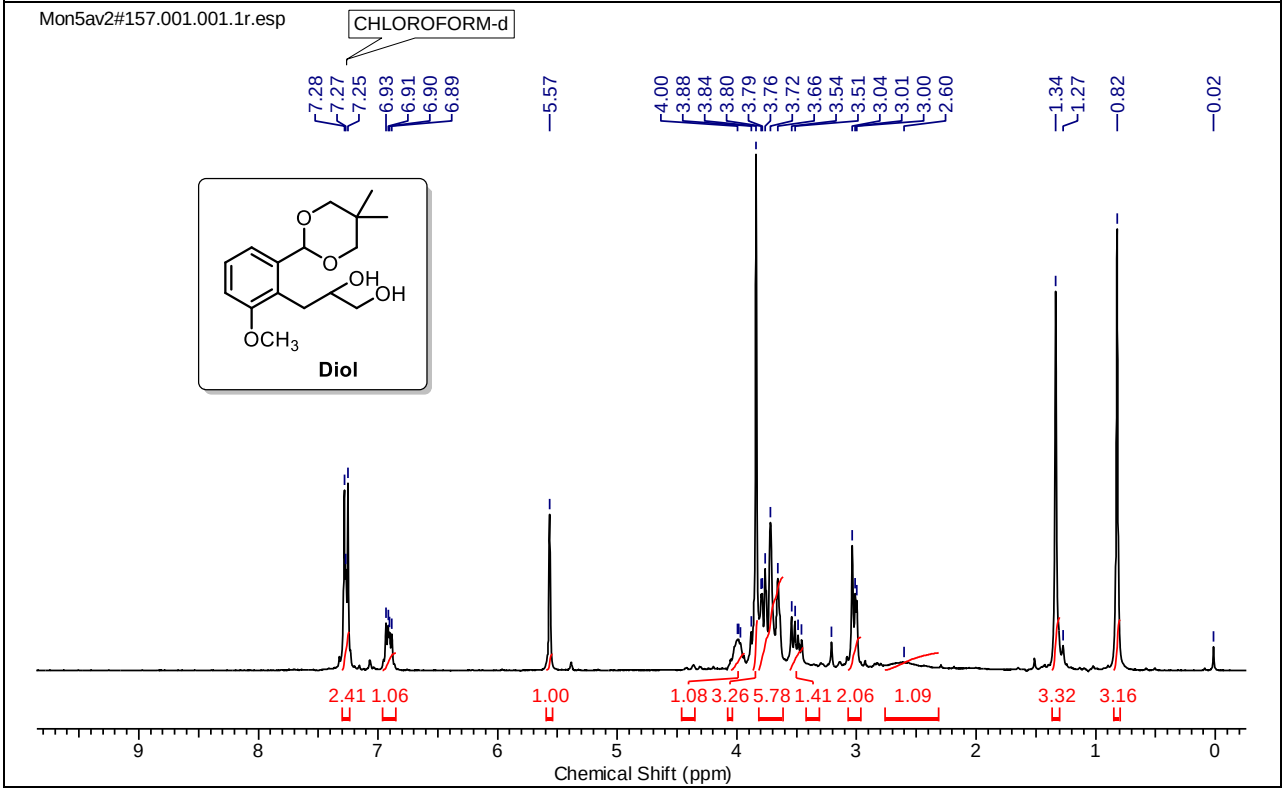
^{13}C-NMR spectrum of compound 9 ($CDCl_3$, 50 MHz)



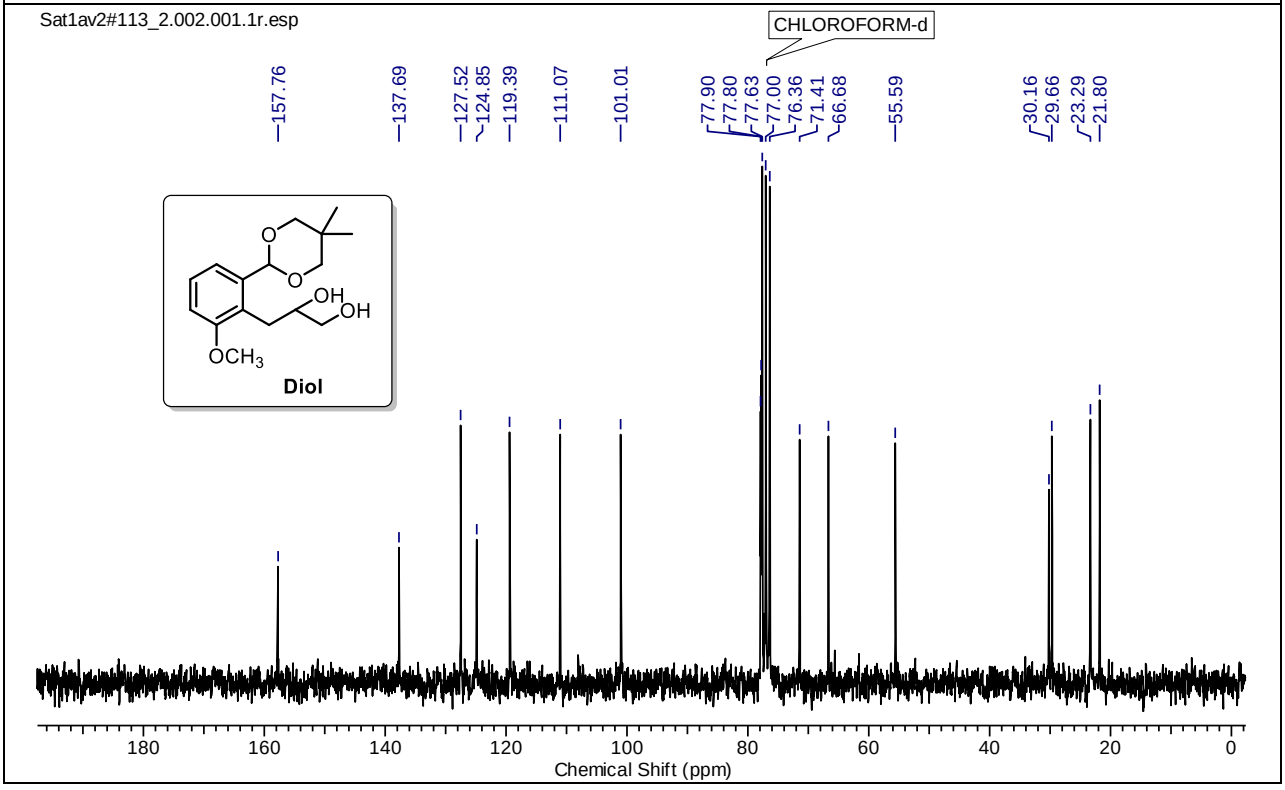
DEPT NMR spectrum of compound 9 ($CDCl_3$, 50 MHz)



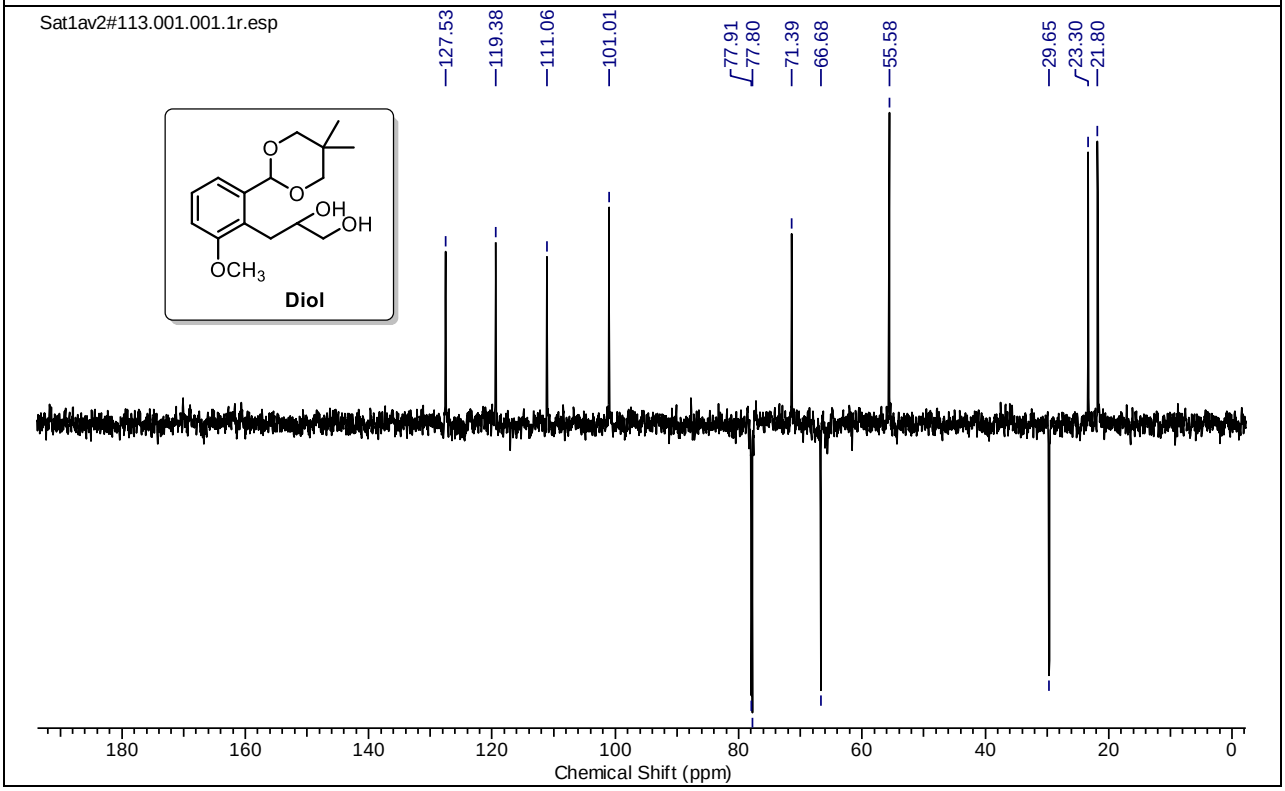
^{1}H-NMR spectrum of Diol ($CDCl_3$, 200 MHz)



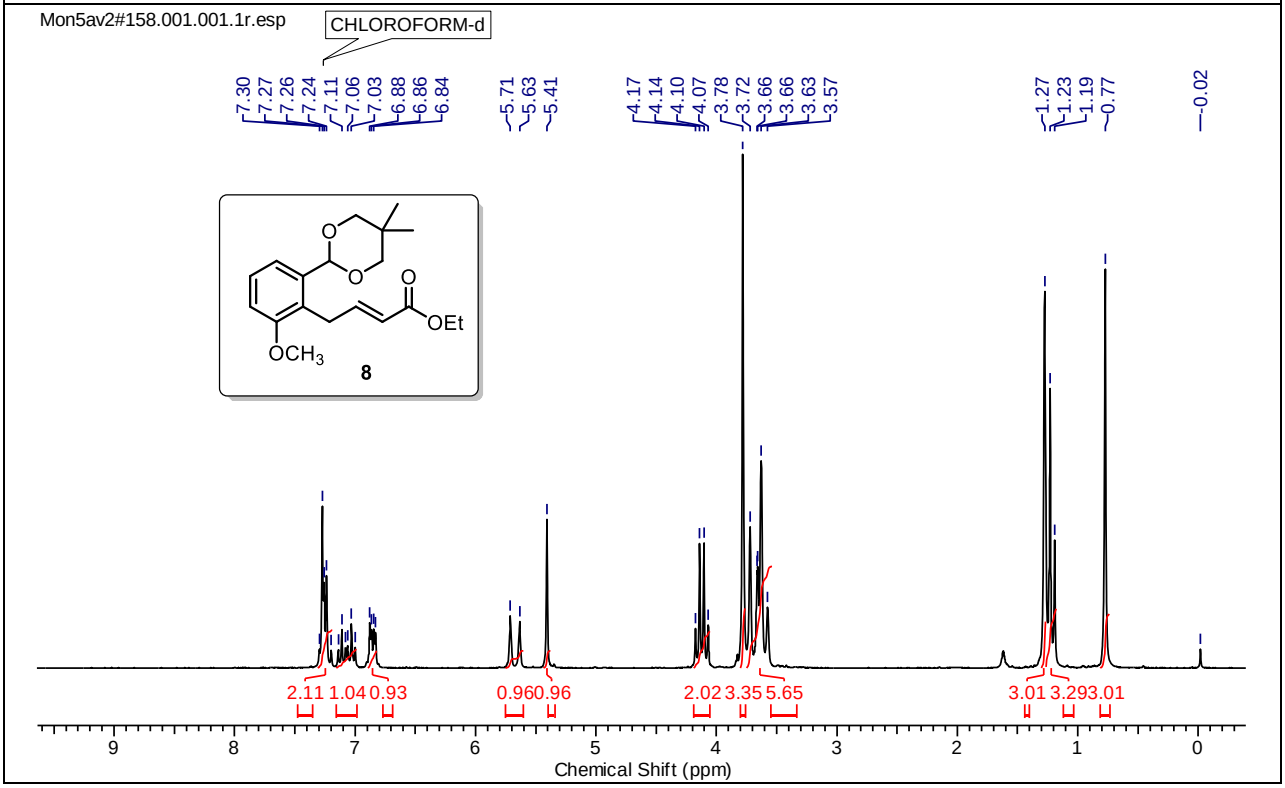
^{13}C-NMR spectrum of Diol ($CDCl_3$, 50 MHz)



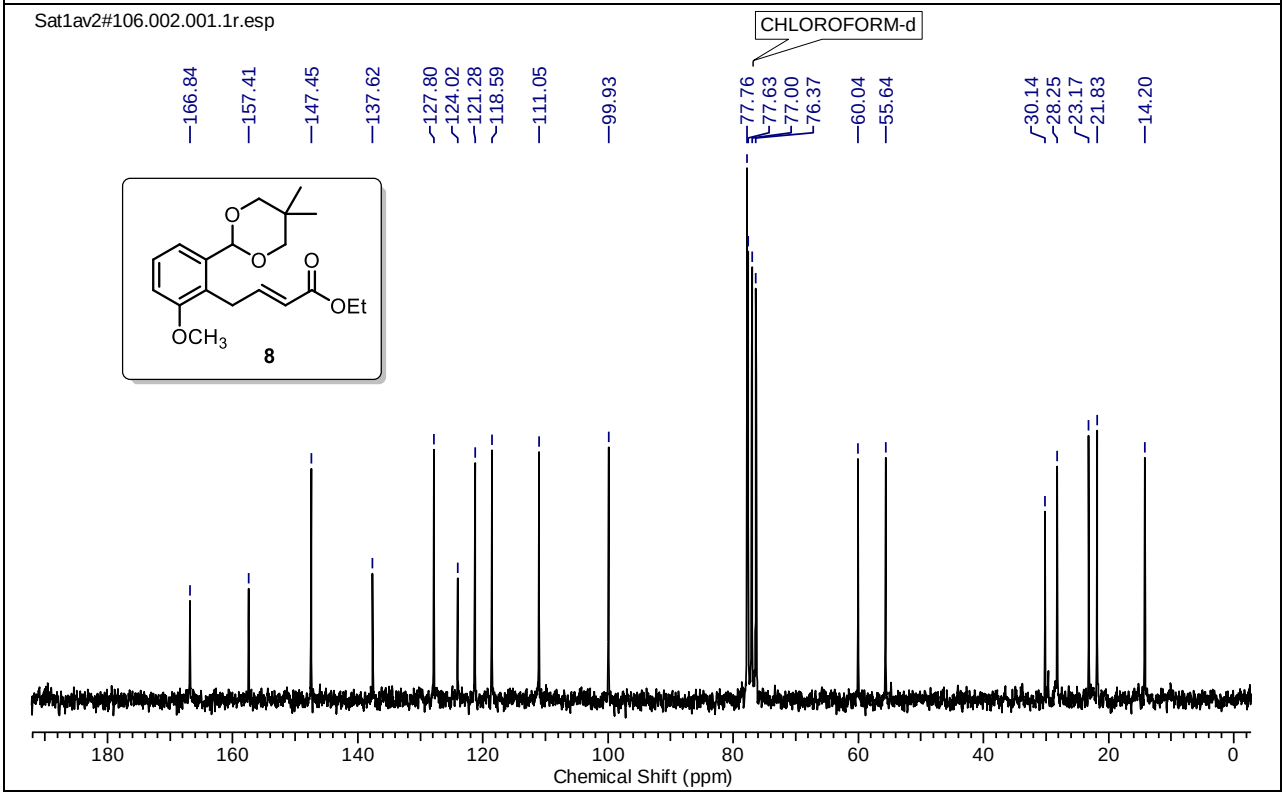
DEPT NMR spectrum of Diol ($CDCl_3$, 50 MHz)



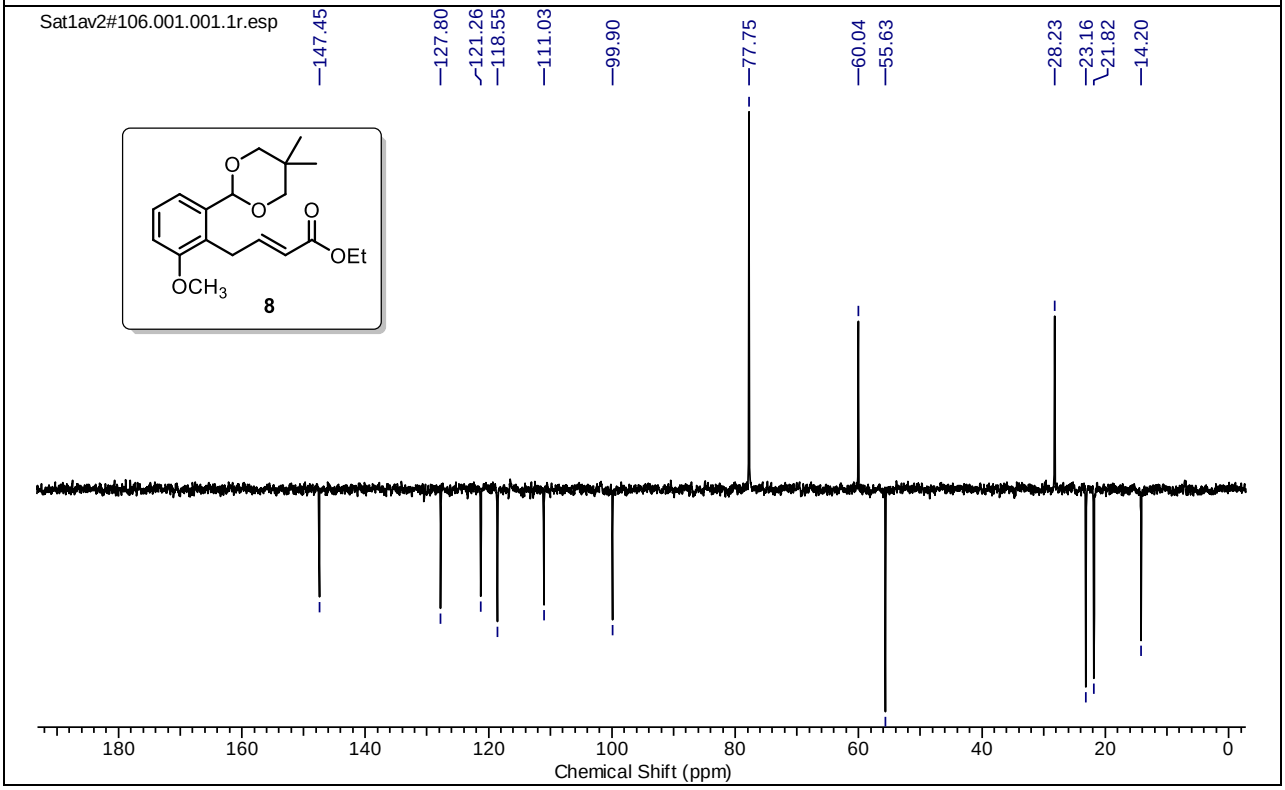
^{1}H-NMR spectrum of compound 8 ($CDCl_3$, 200 MHz)



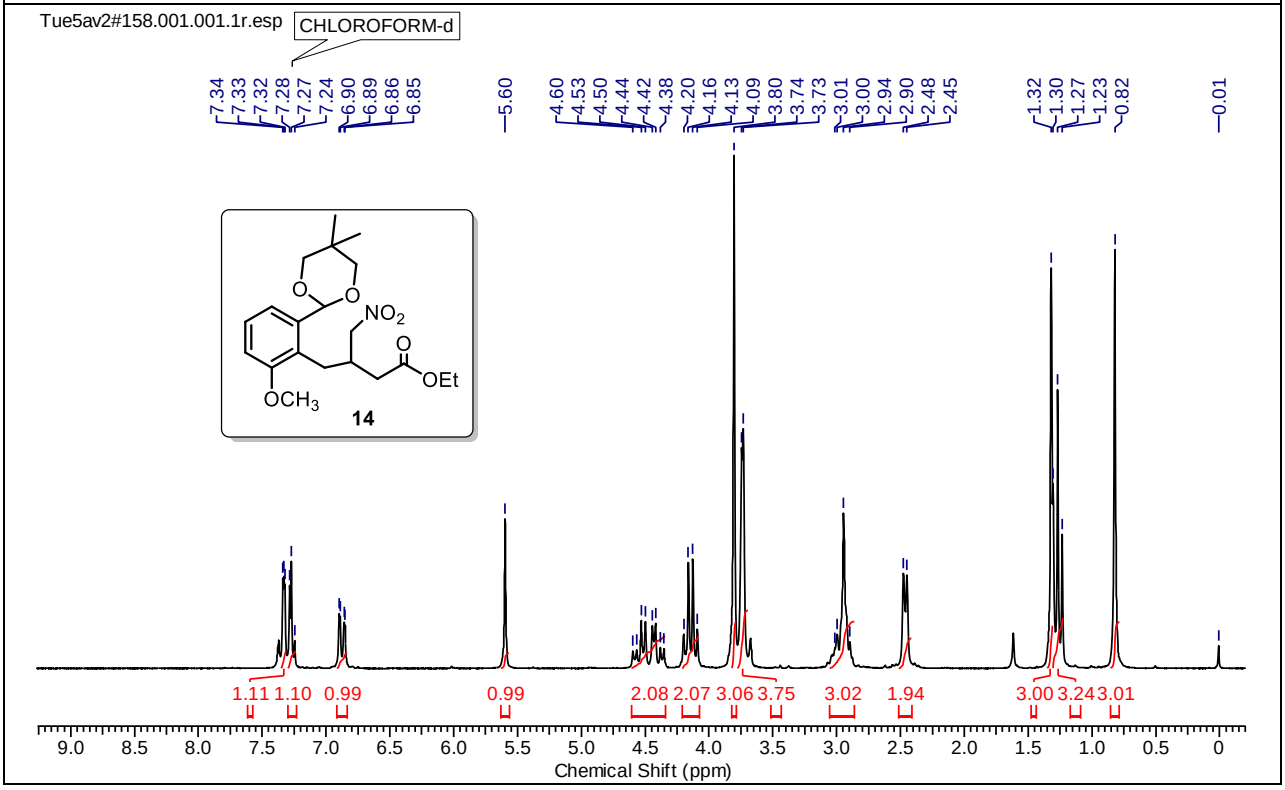
^{13}C-NMR spectrum of compound 8 ($CDCl_3$, 50 MHz)



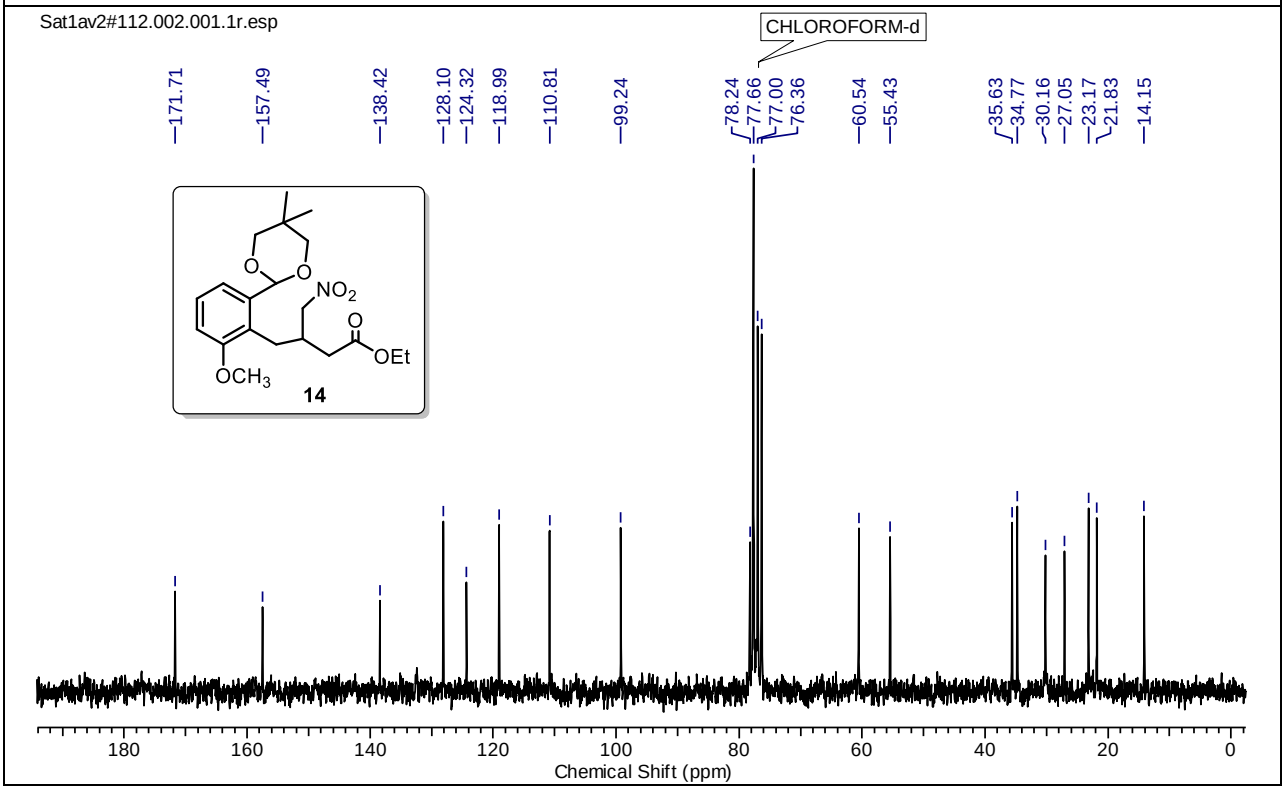
DEPT NMR spectrum of compound 8 ($CDCl_3$, 50 MHz)



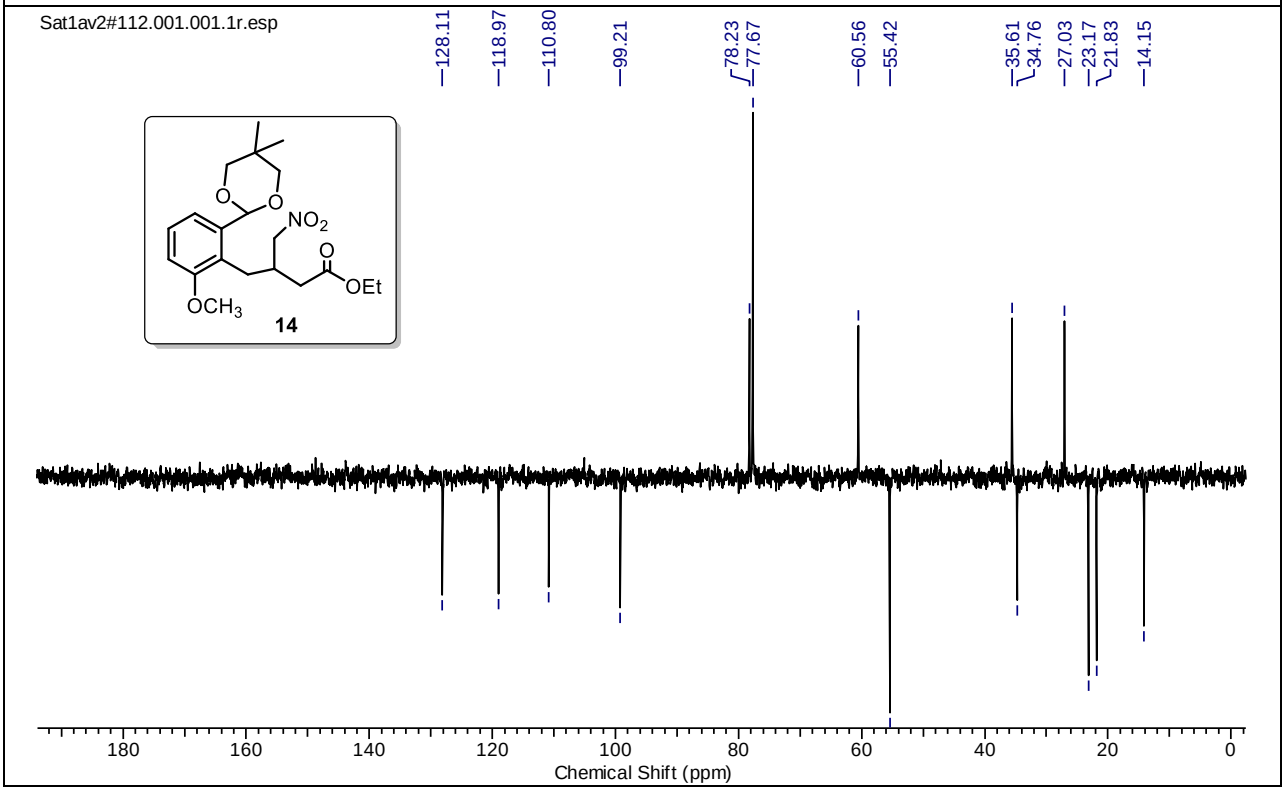
^{1}H-NMR spectrum of compound 14 ($CDCl_3$, 200 MHz)



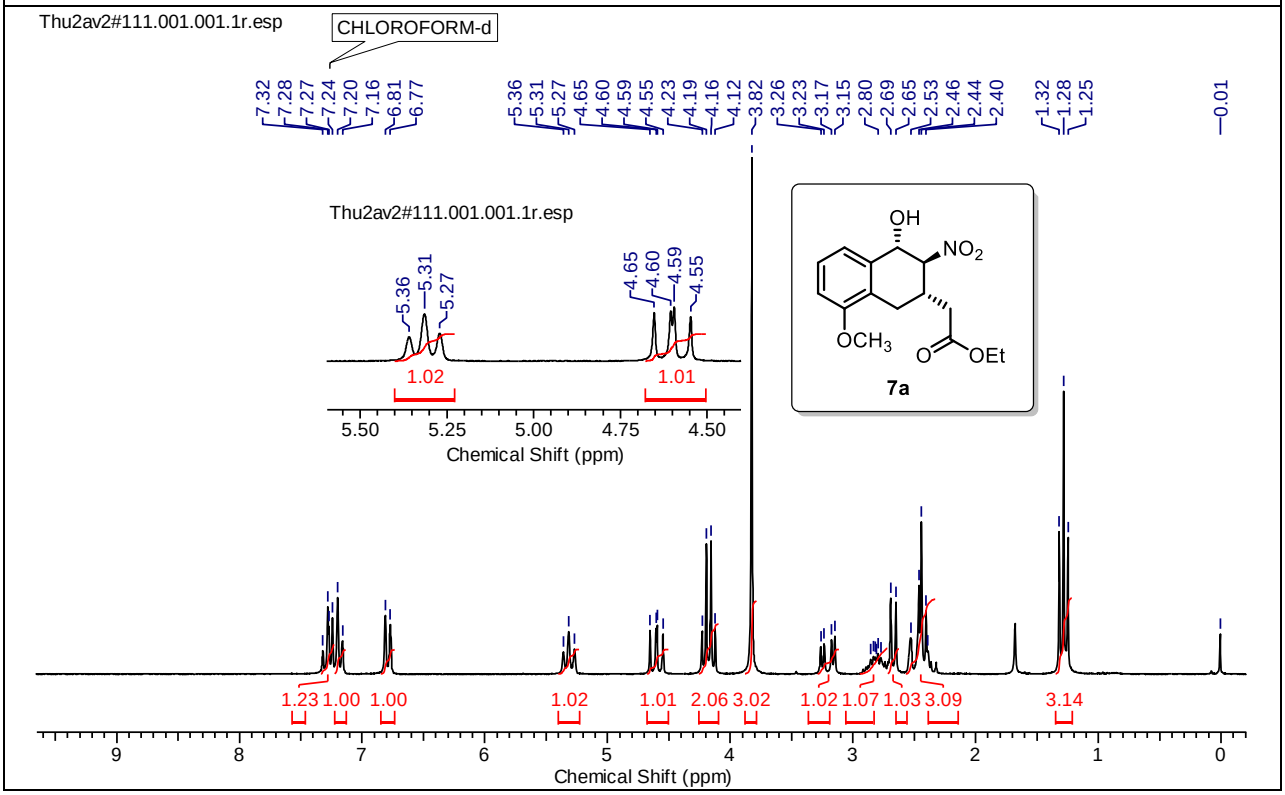
^{13}C-NMR spectrum of compound 14 ($CDCl_3$, 50 MHz)



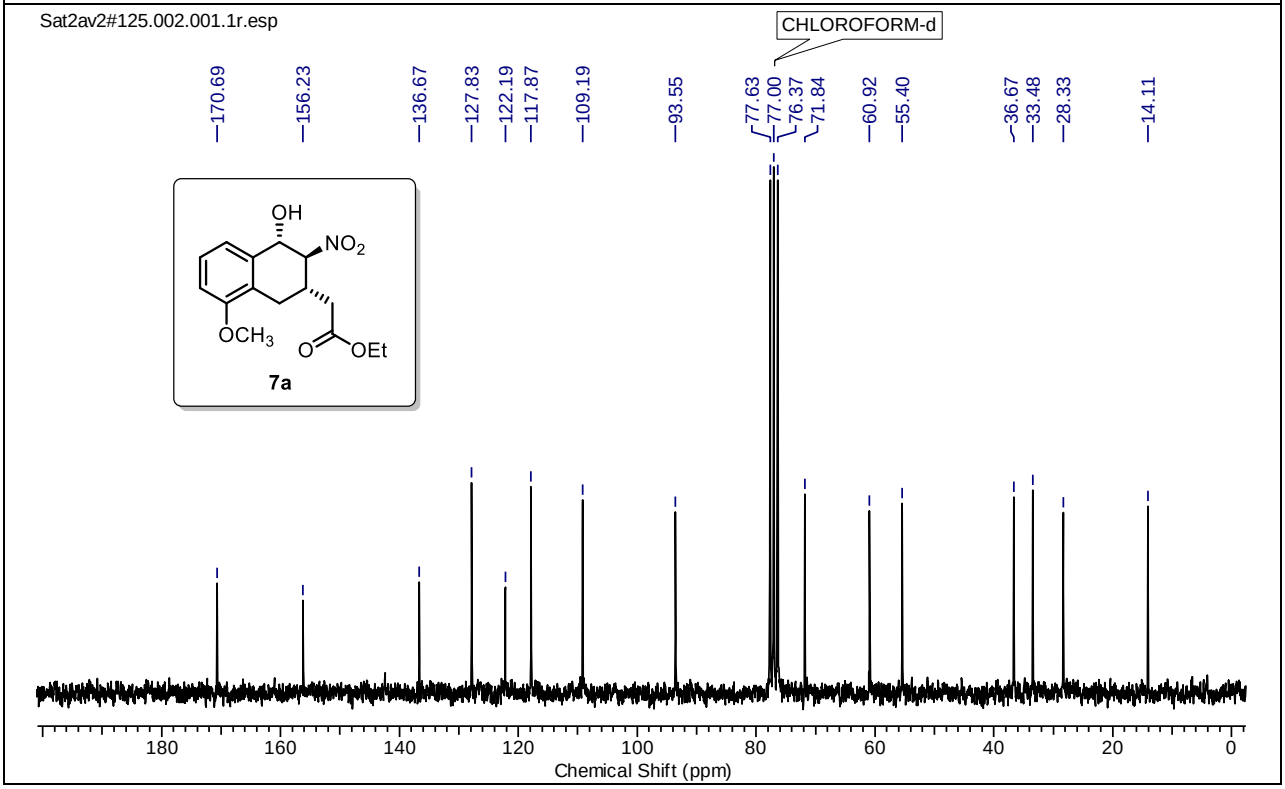
DEPT NMR spectrum of compound 14 ($CDCl_3$, 50 MHz)



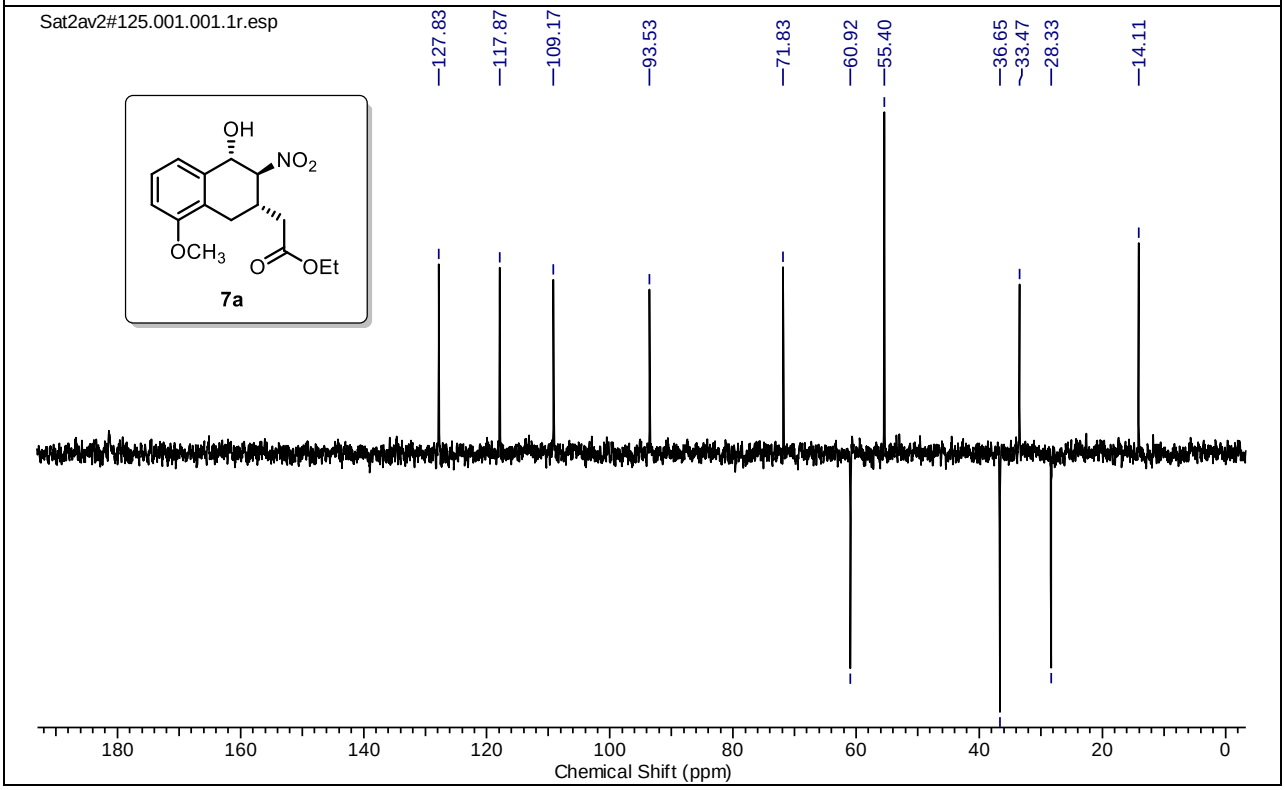
^{1}H-NMR spectrum of compound 7a ($CDCl_3$, 200 MHz)



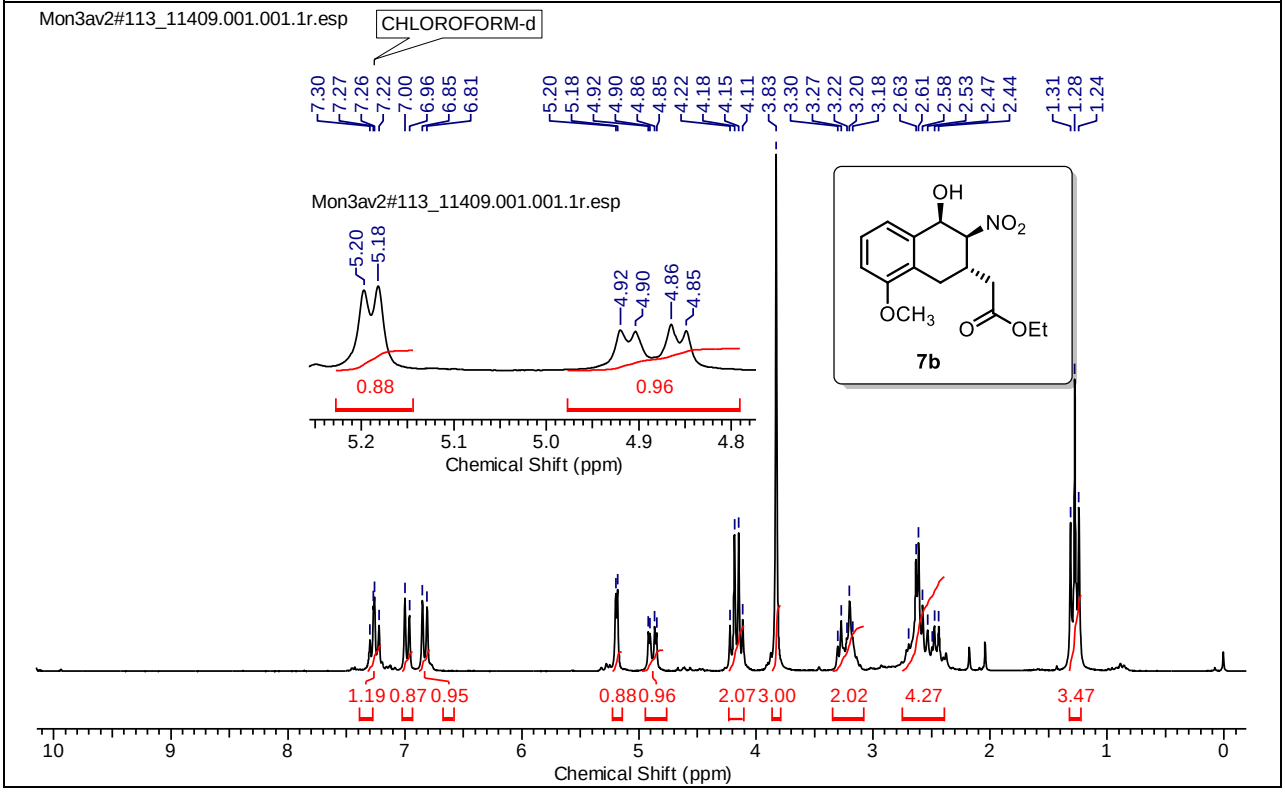
^{13}C-NMR spectrum of compound 7a ($CDCl_3$, 50 MHz)



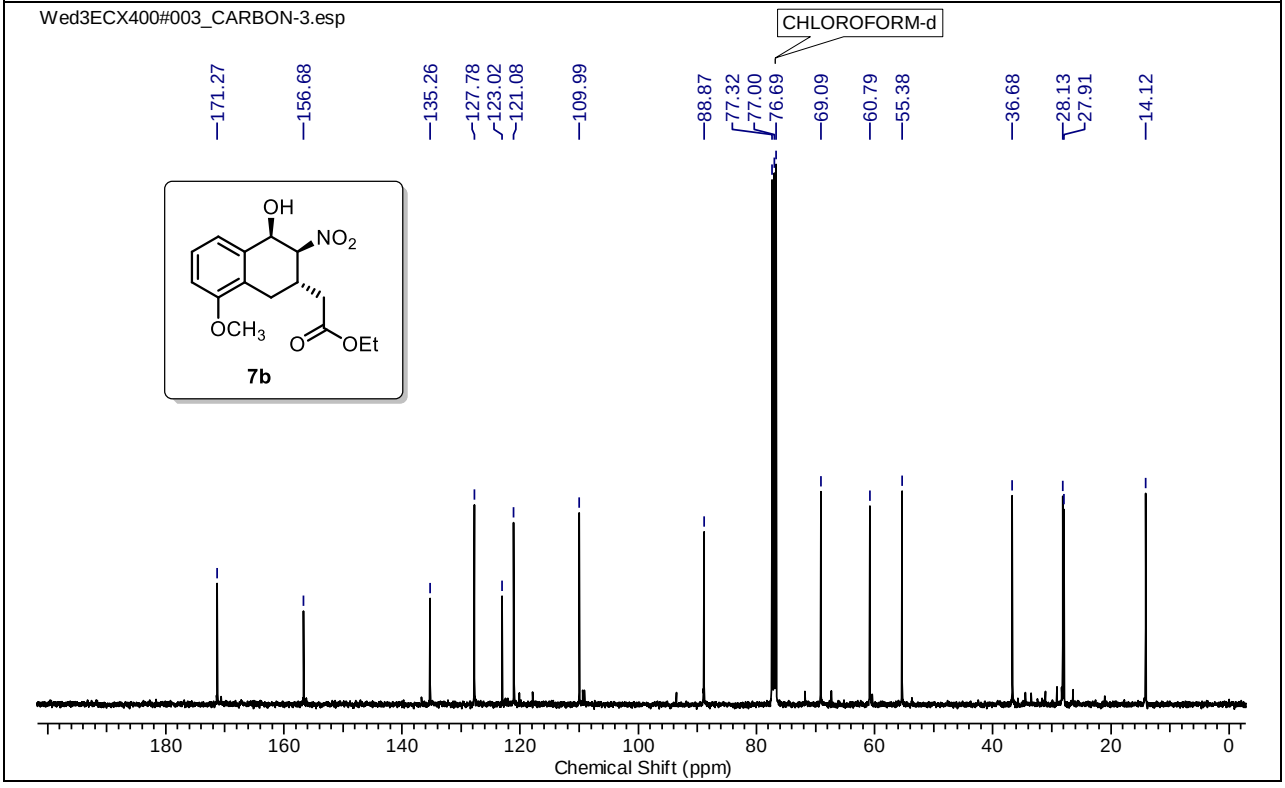
DEPT NMR spectrum of compound 7a ($CDCl_3$, 50 MHz)



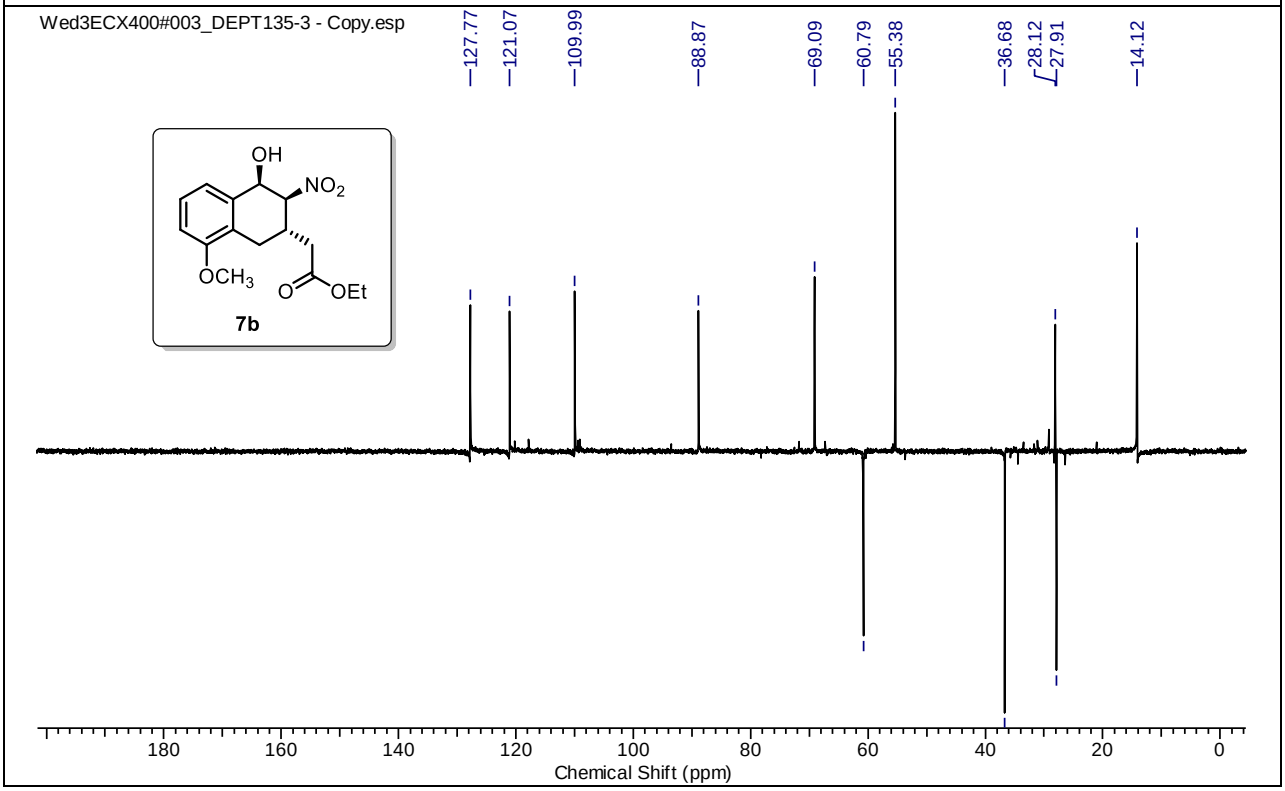
^{1}H-NMR spectrum of compound 7b ($CDCl_3$, 200 MHz)



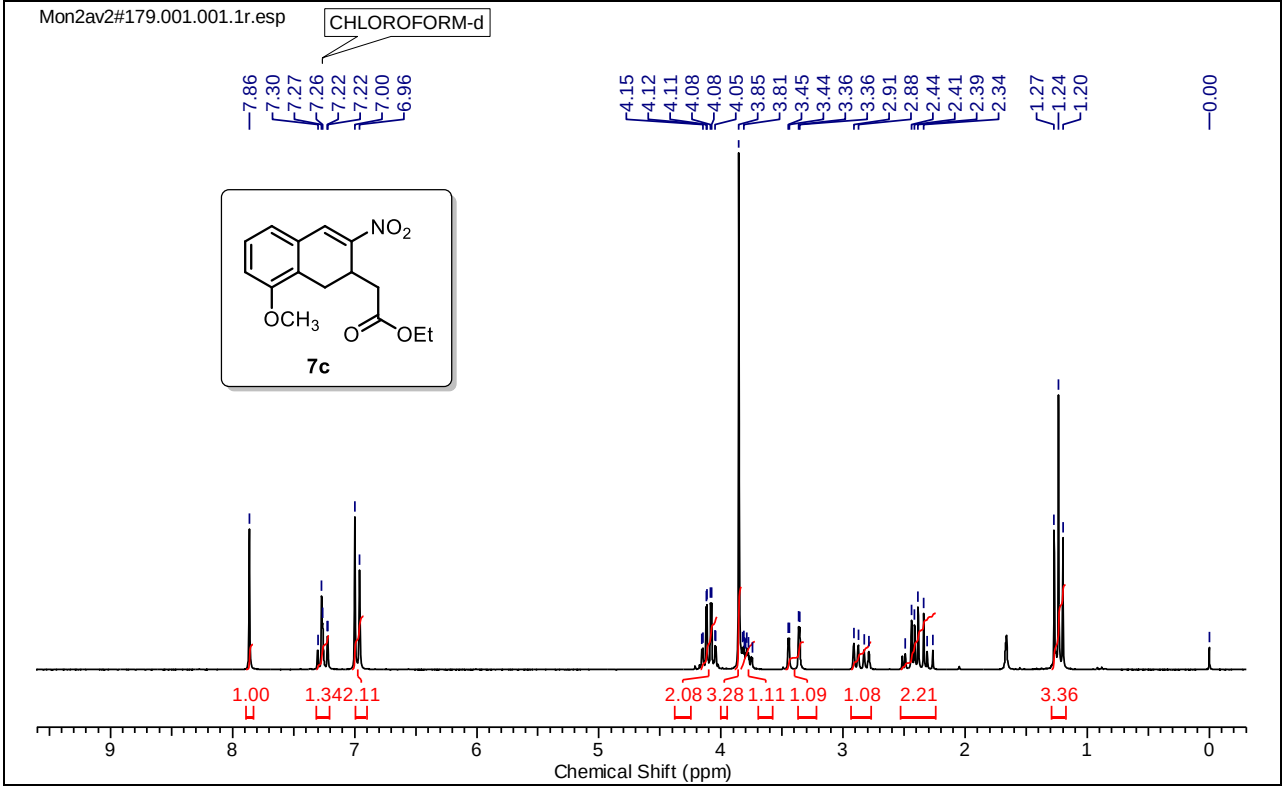
^{13}C-NMR spectrum of compound 7b ($CDCl_3$, 100 MHz)



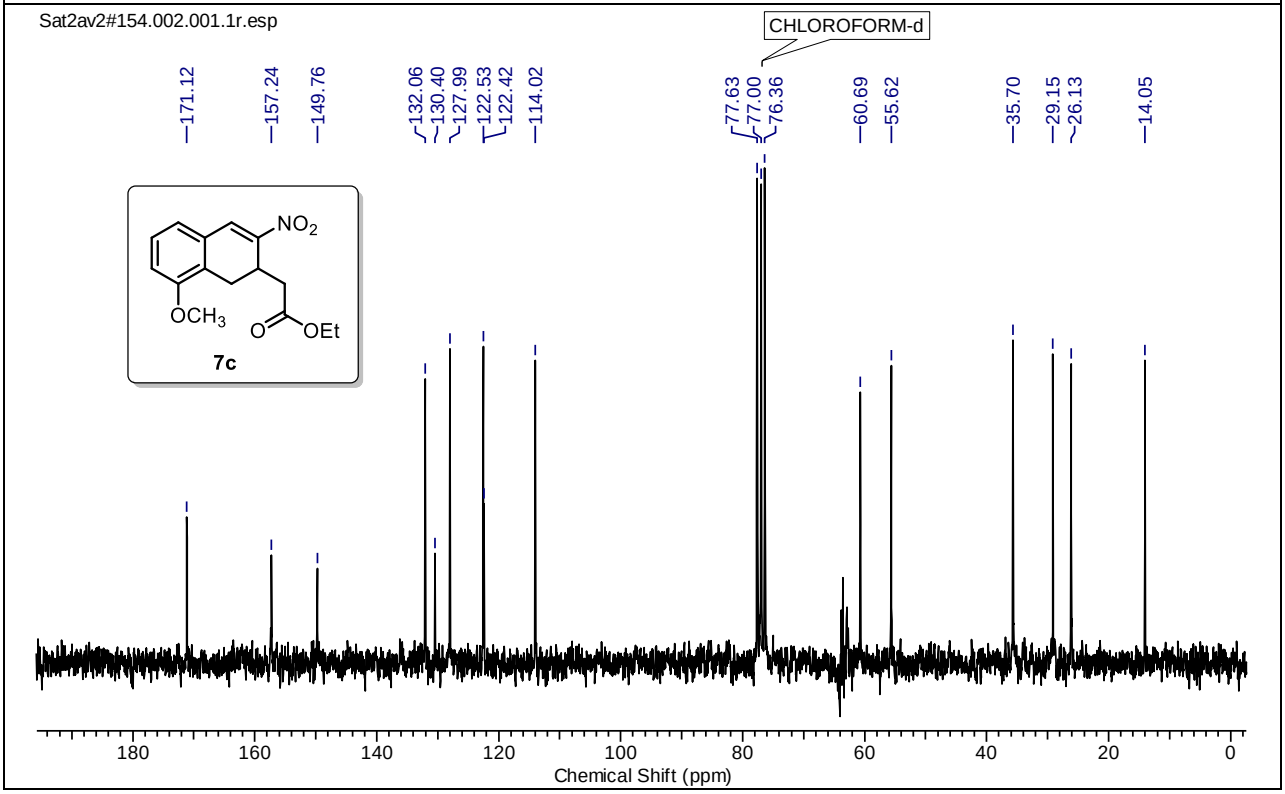
DEPT NMR spectrum of compound 7b ($CDCl_3$, 100 MHz)



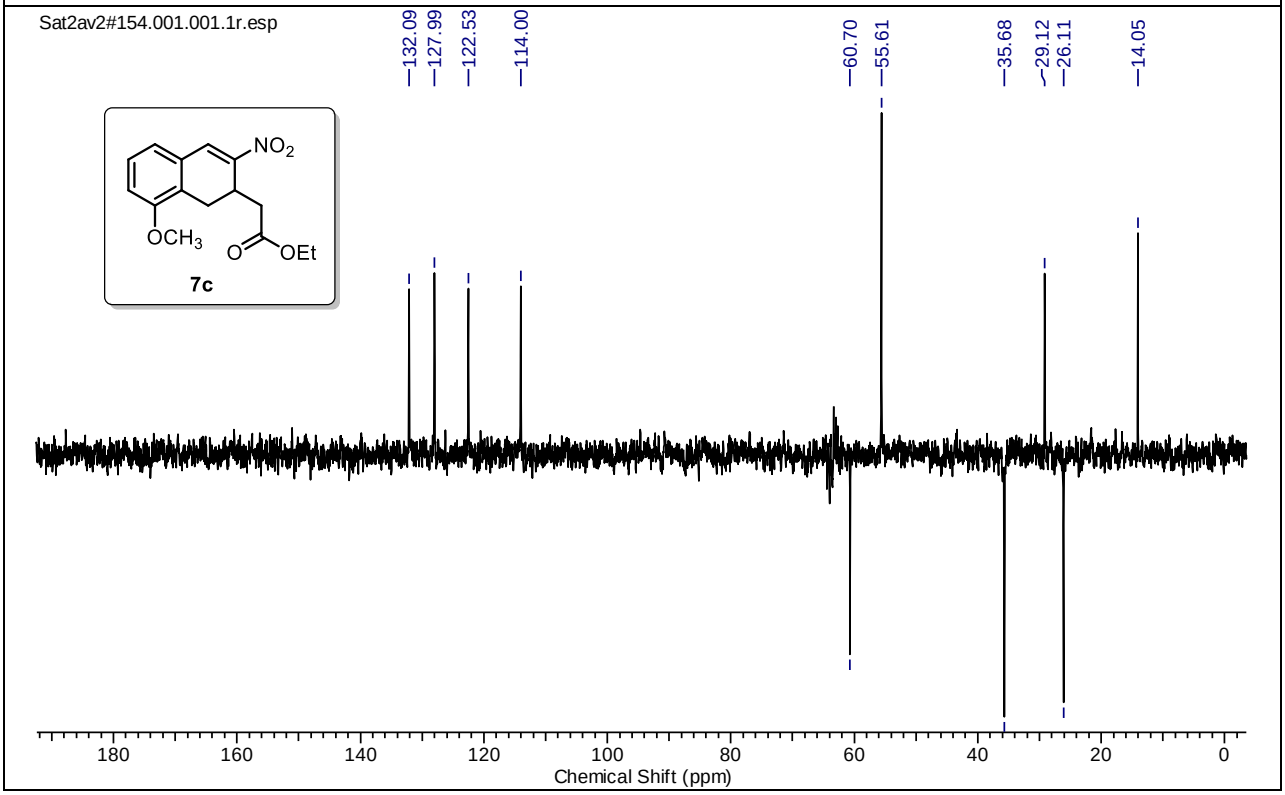
^{1}H-NMR spectrum of compound 7c ($CDCl_3$, 200 MHz)



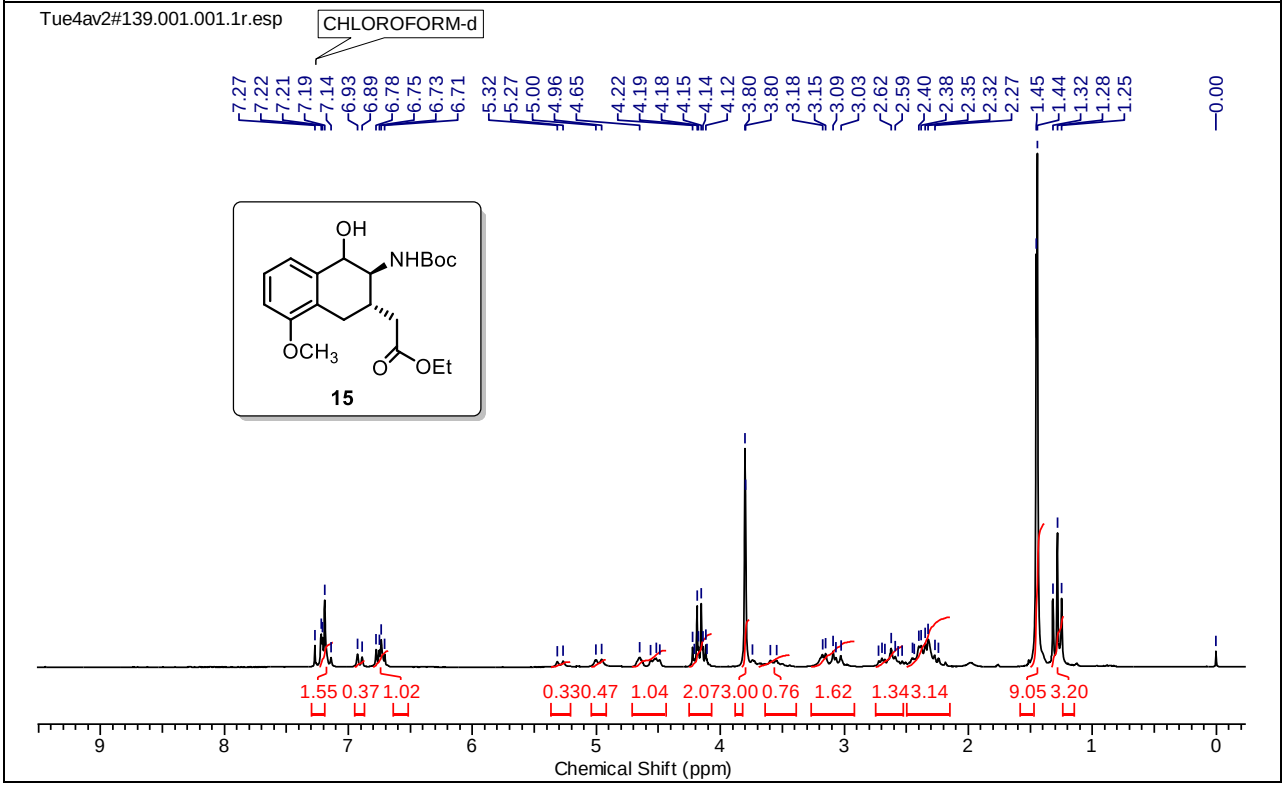
^{13}C-NMR spectrum of compound 7c ($CDCl_3$, 50 MHz)



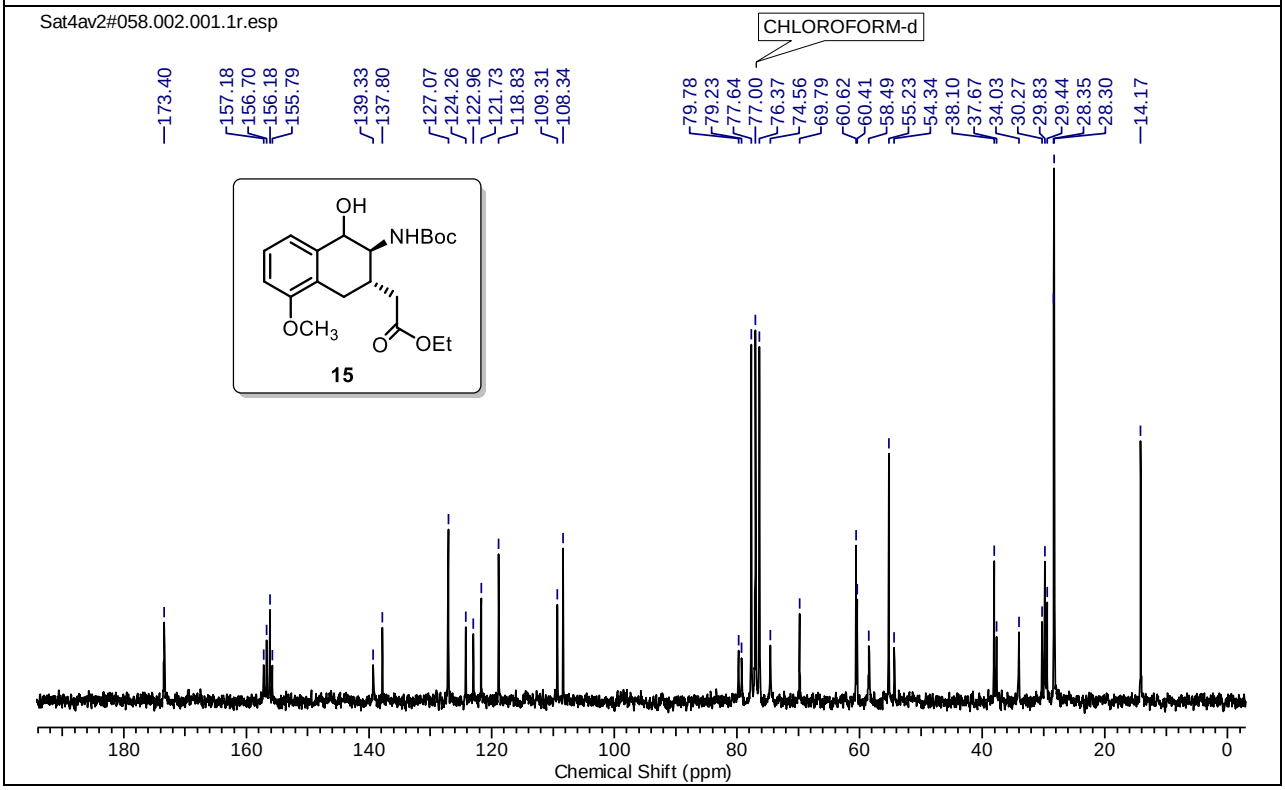
DEPT NMR spectrum of compound 7c ($CDCl_3$, 50 MHz)



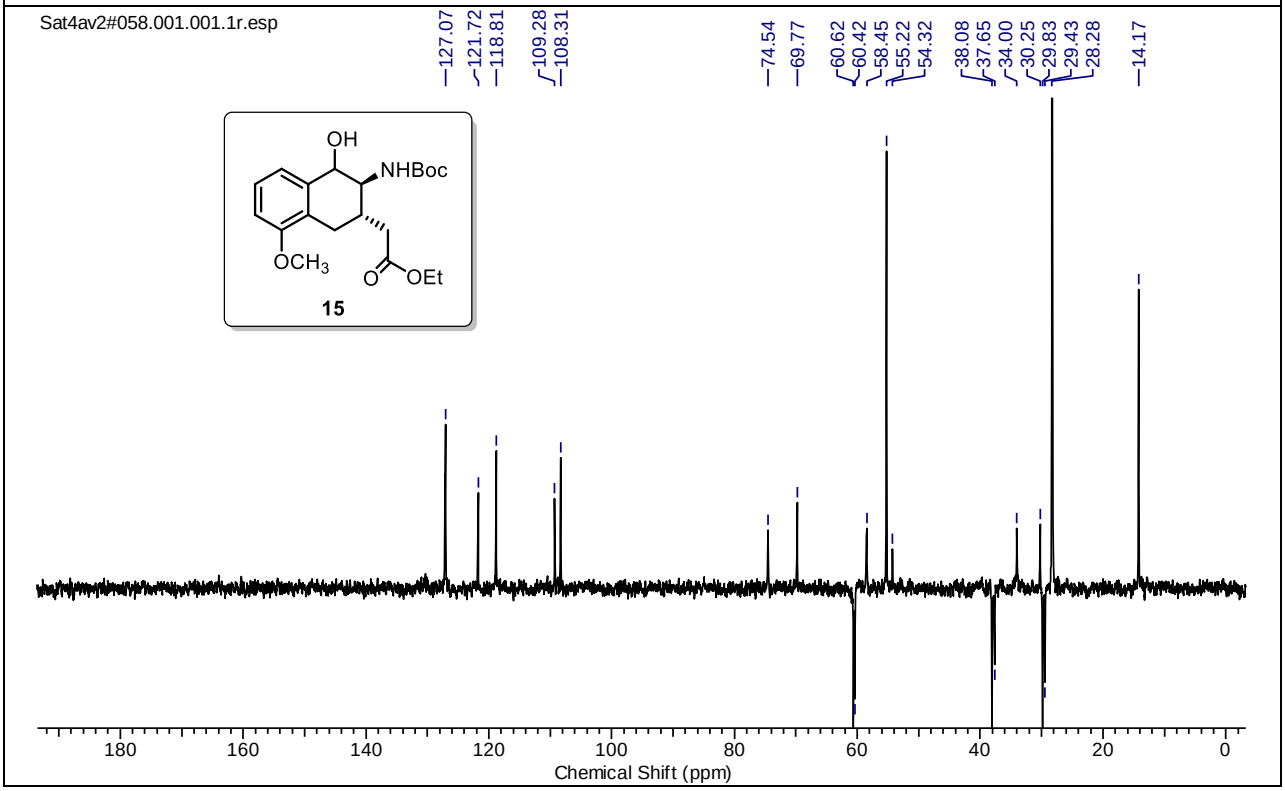
^{1}H-NMR spectrum of compound 15 ($CDCl_3$, 200 MHz)



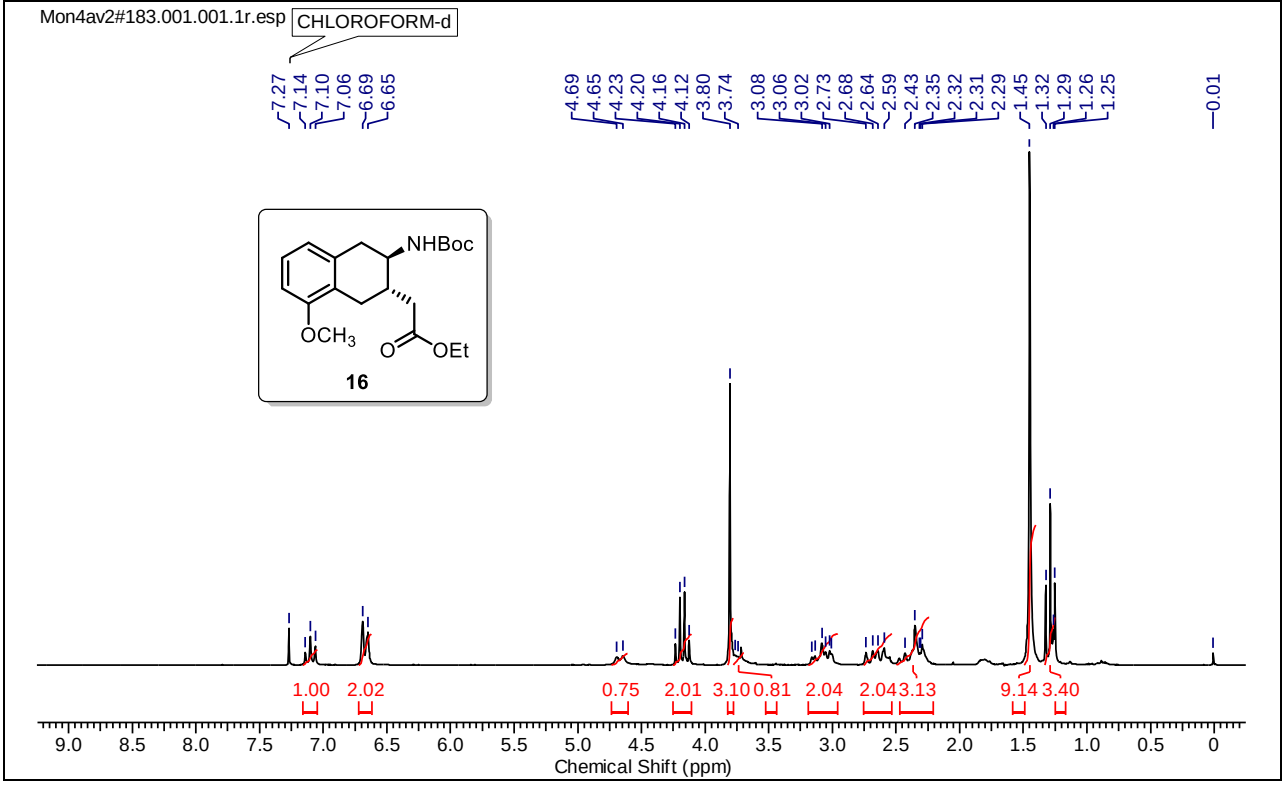
^{13}C-NMR spectrum of compound 15 ($CDCl_3$, 50 MHz)



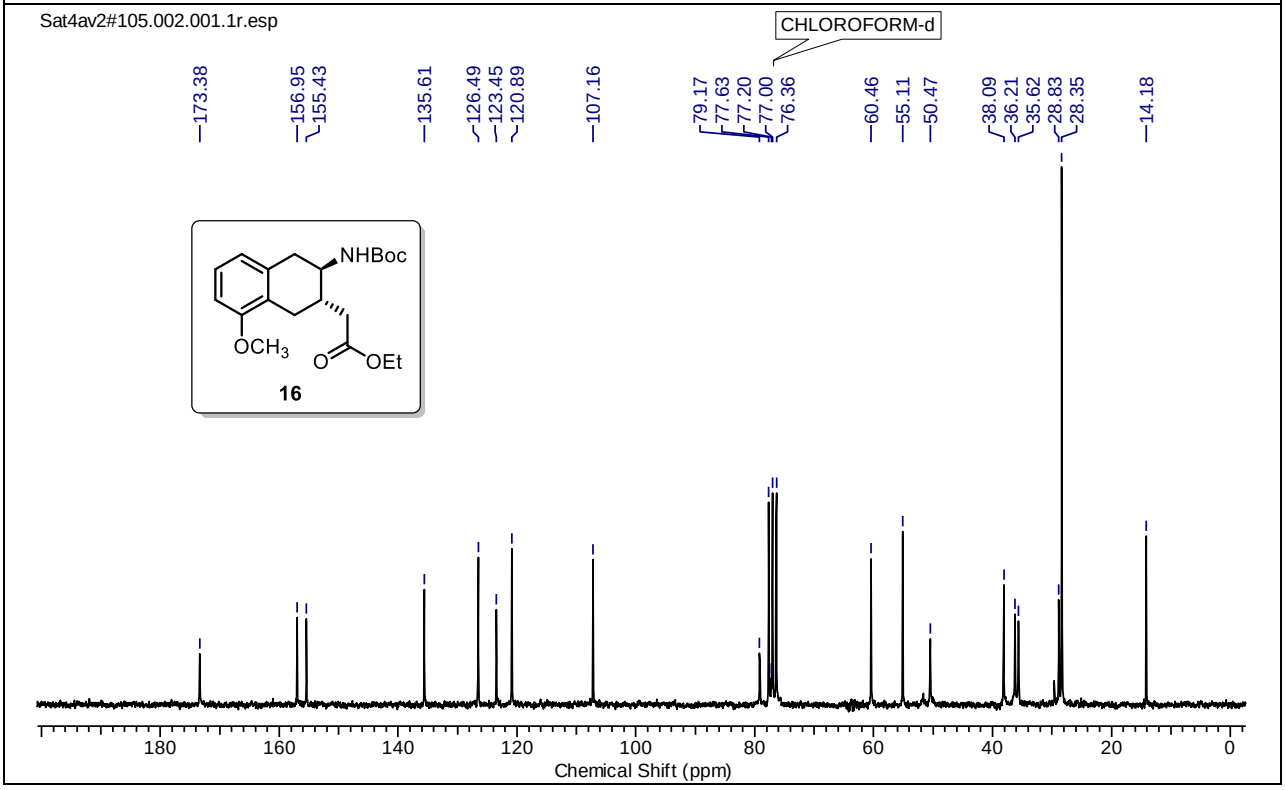
DEPT NMR spectrum of compound 15 ($CDCl_3$, 50 MHz)



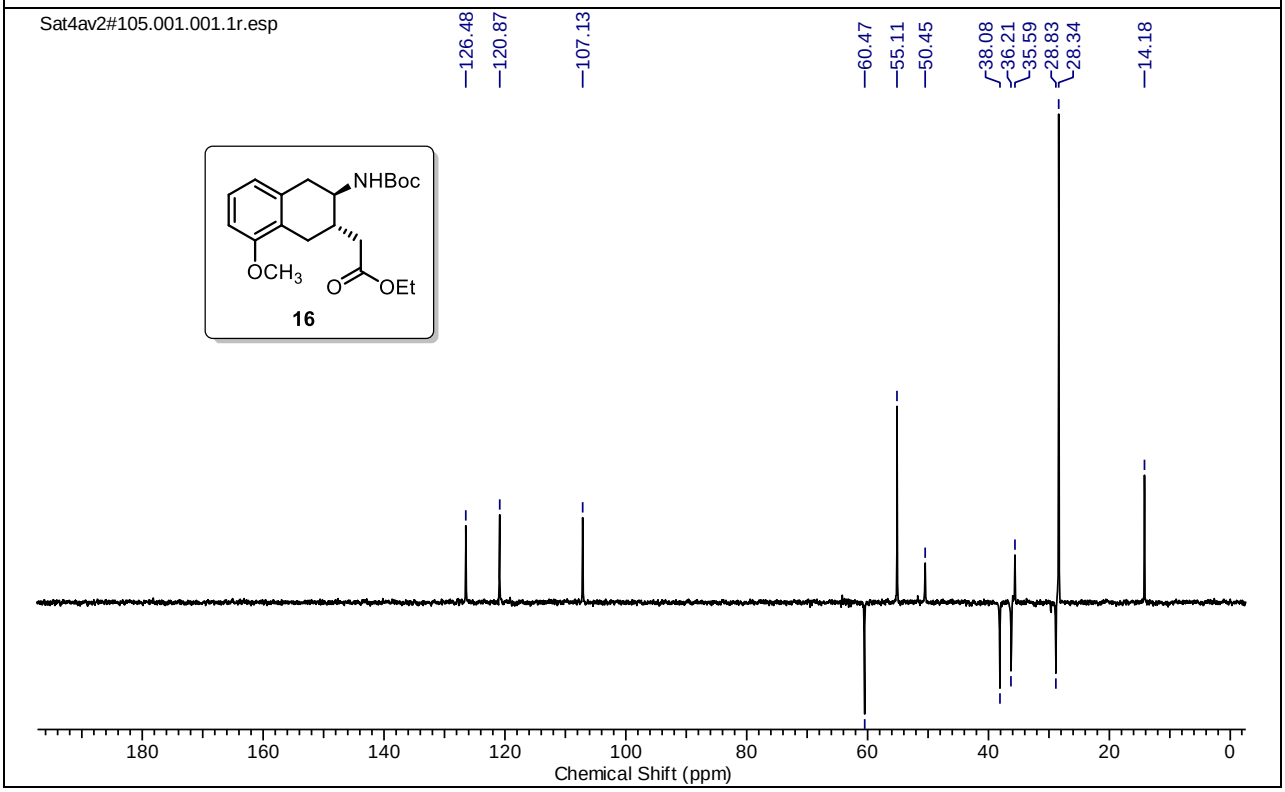
^{1}H-NMR spectrum of compound 16 ($CDCl_3$, 200 MHz)



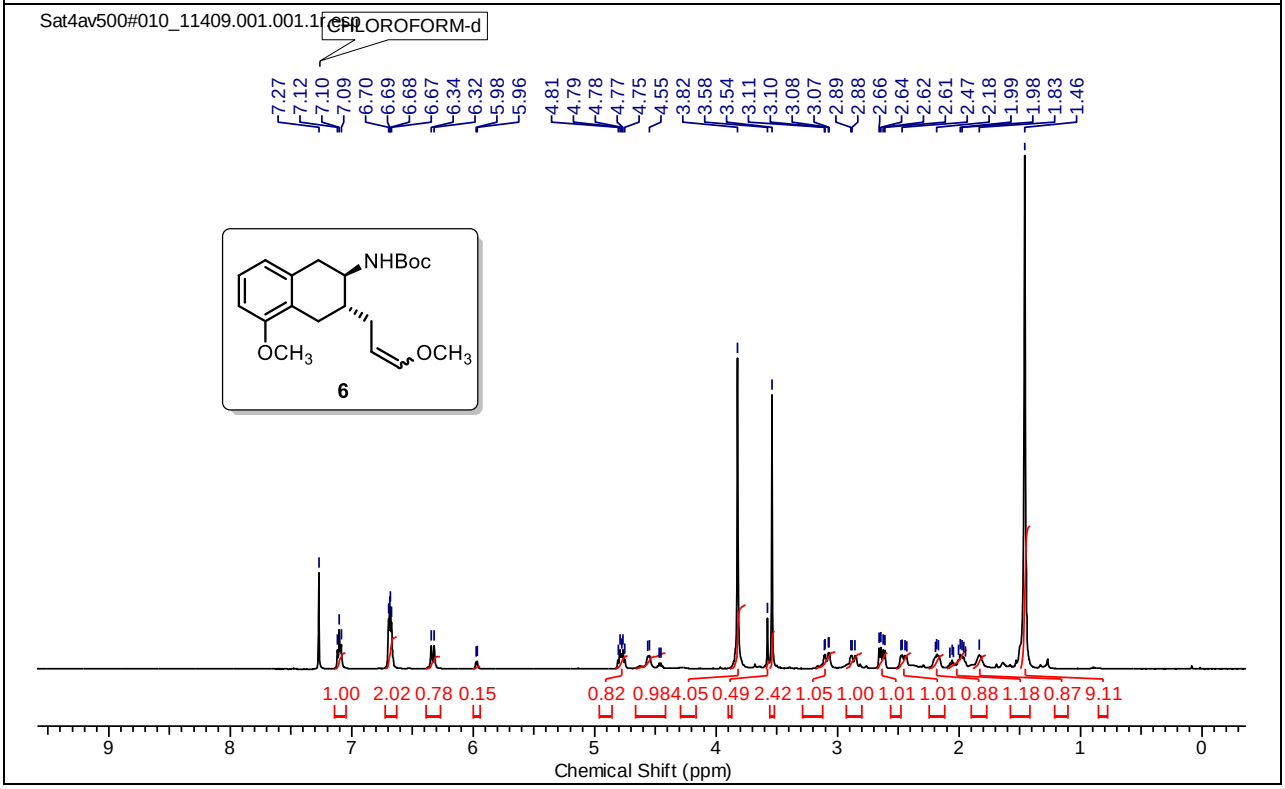
^{13}C-NMR spectrum of compound 16 ($CDCl_3$, 50 MHz)



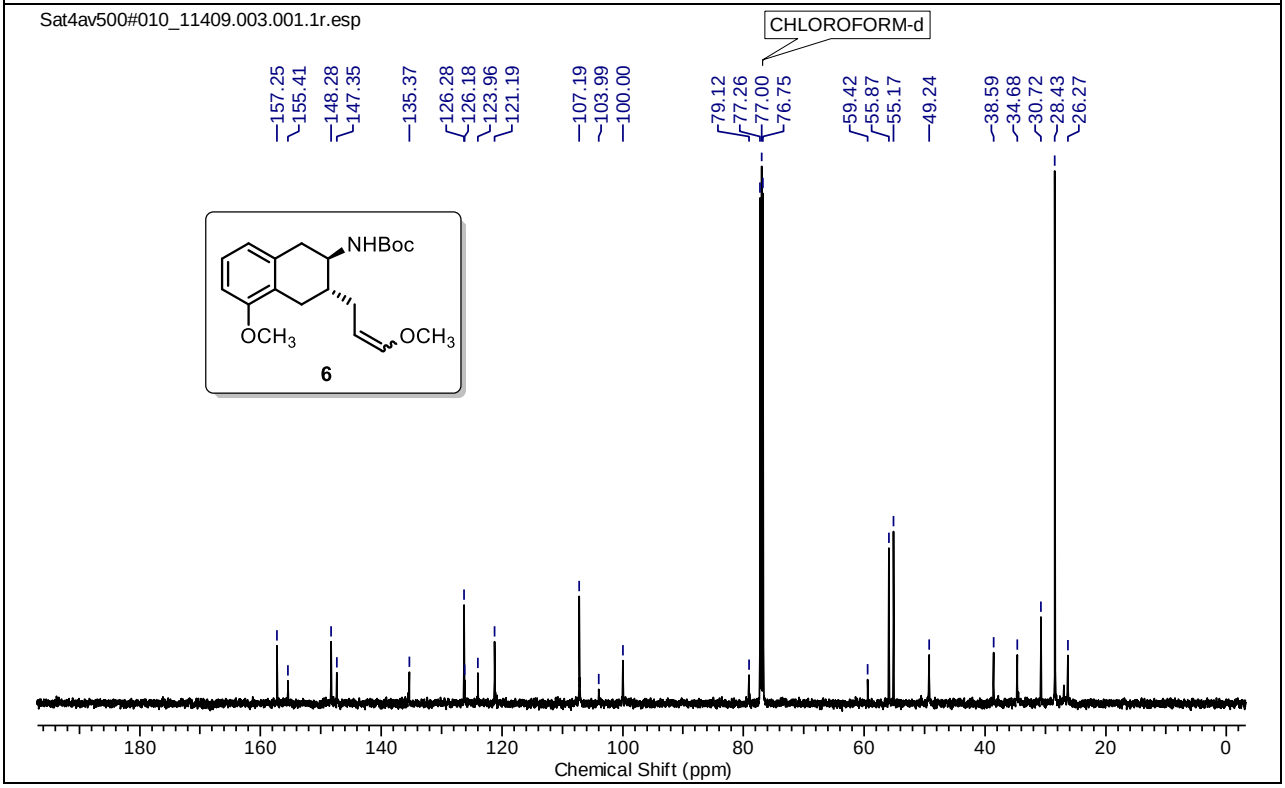
DEPT NMR spectrum of compound 16 ($CDCl_3$, 50 MHz)



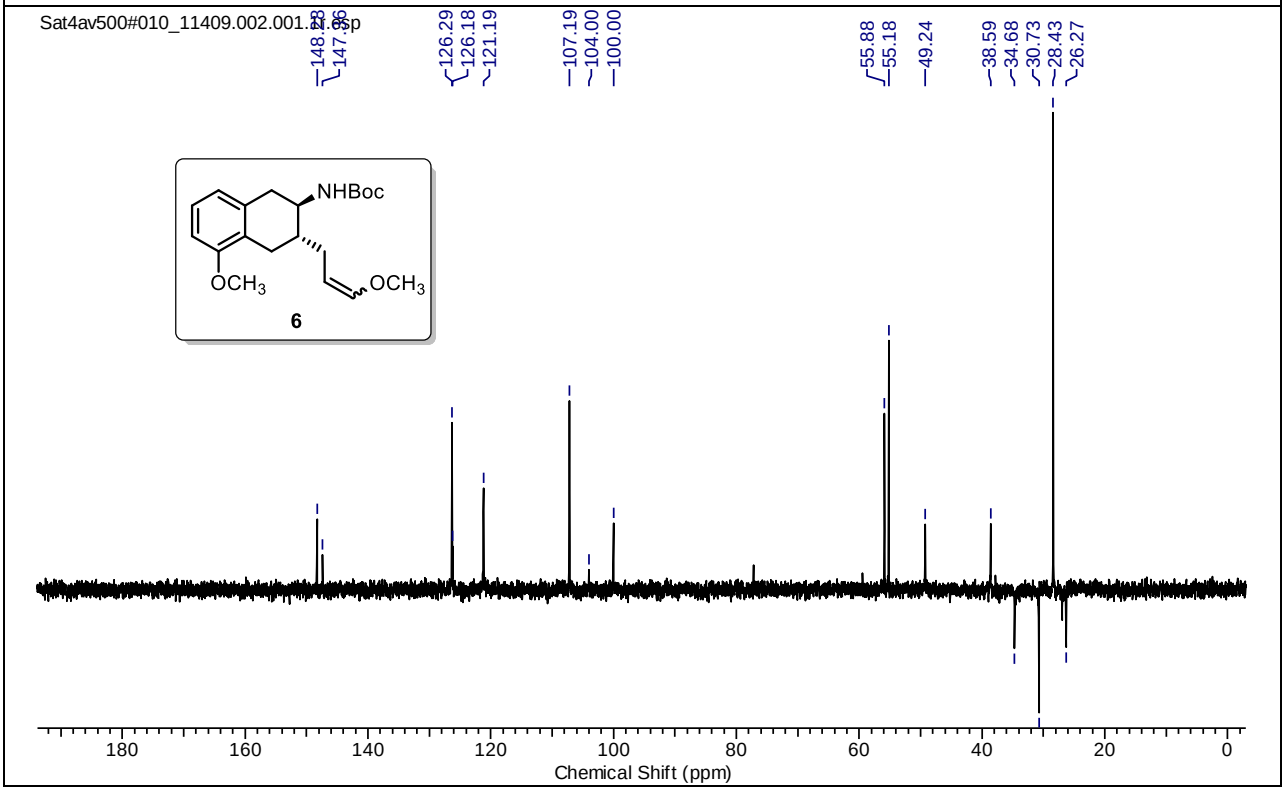
^{1}H-NMR spectrum of compound 6 ($CDCl_3$, 500 MHz)



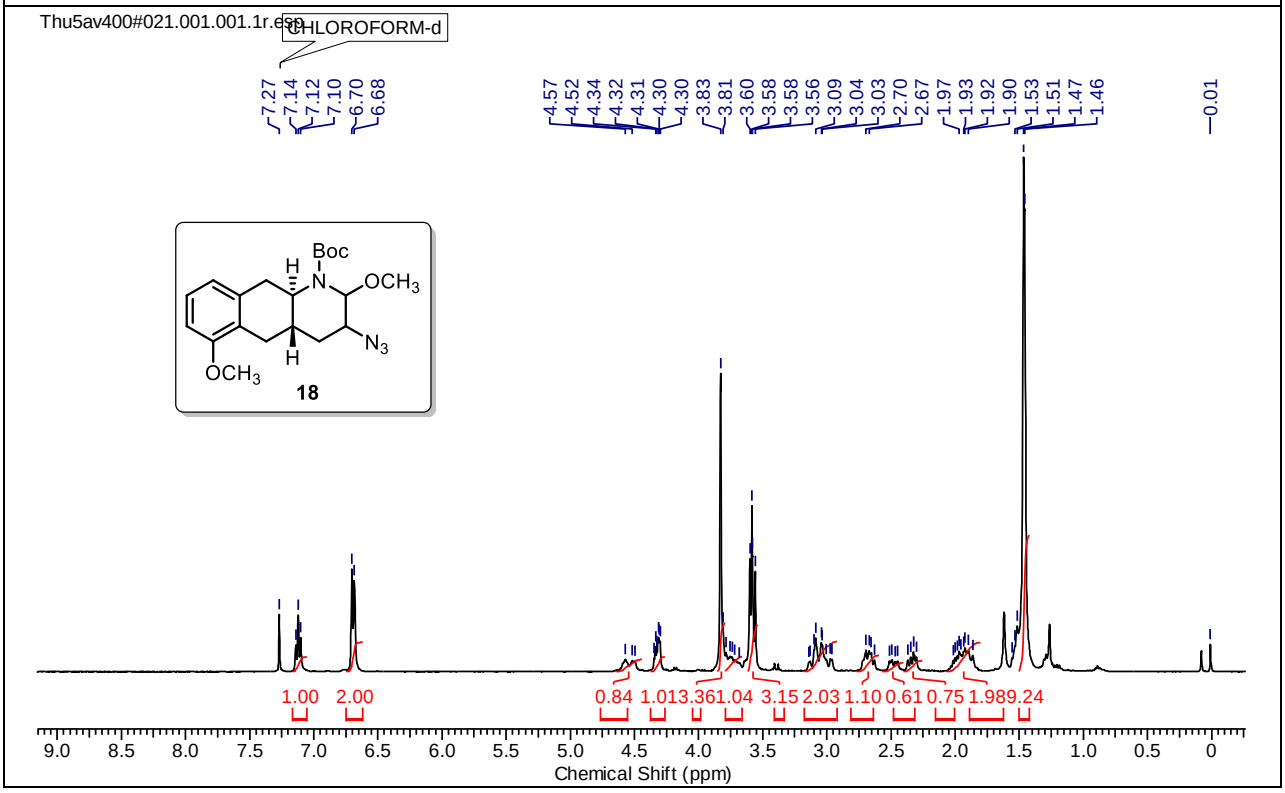
^{13}C-NMR spectrum of compound 6 ($CDCl_3$, 125 MHz)



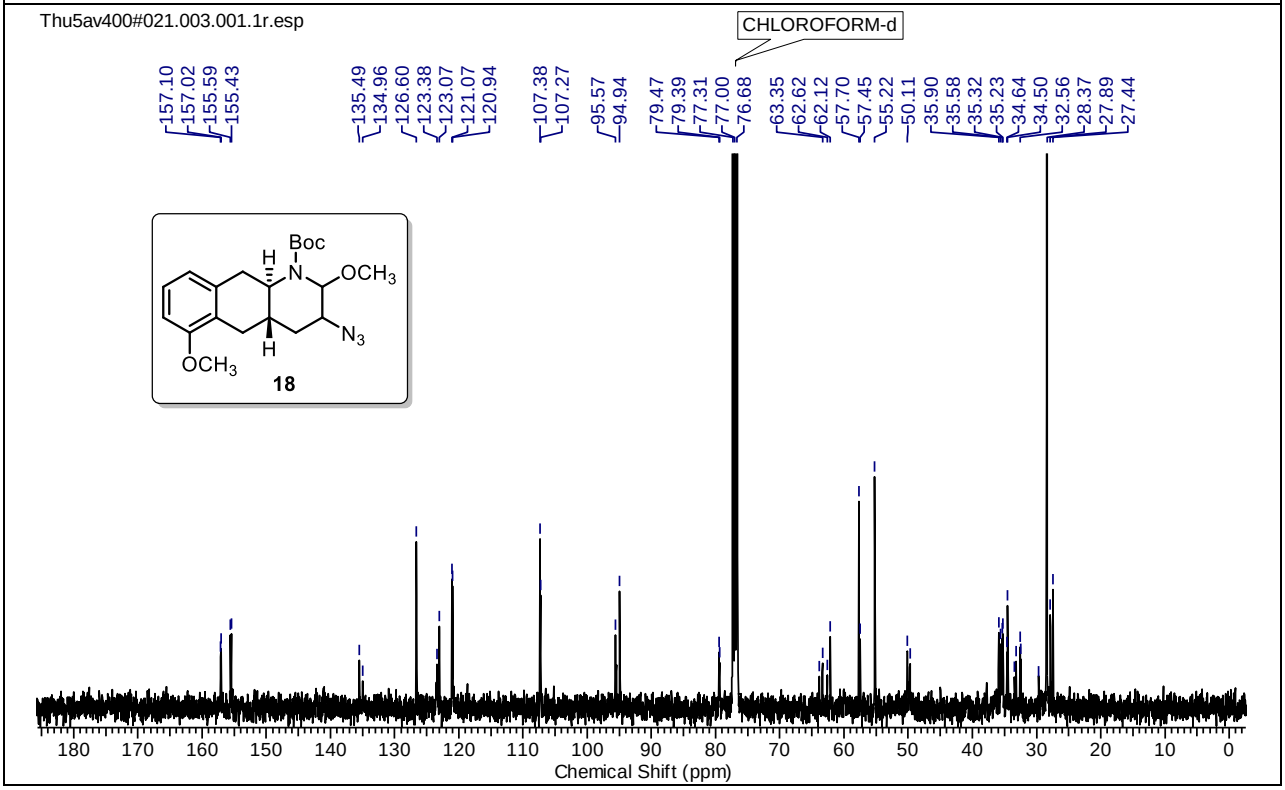
DEPT NMR spectrum of compound 6 ($CDCl_3$, 125 MHz)



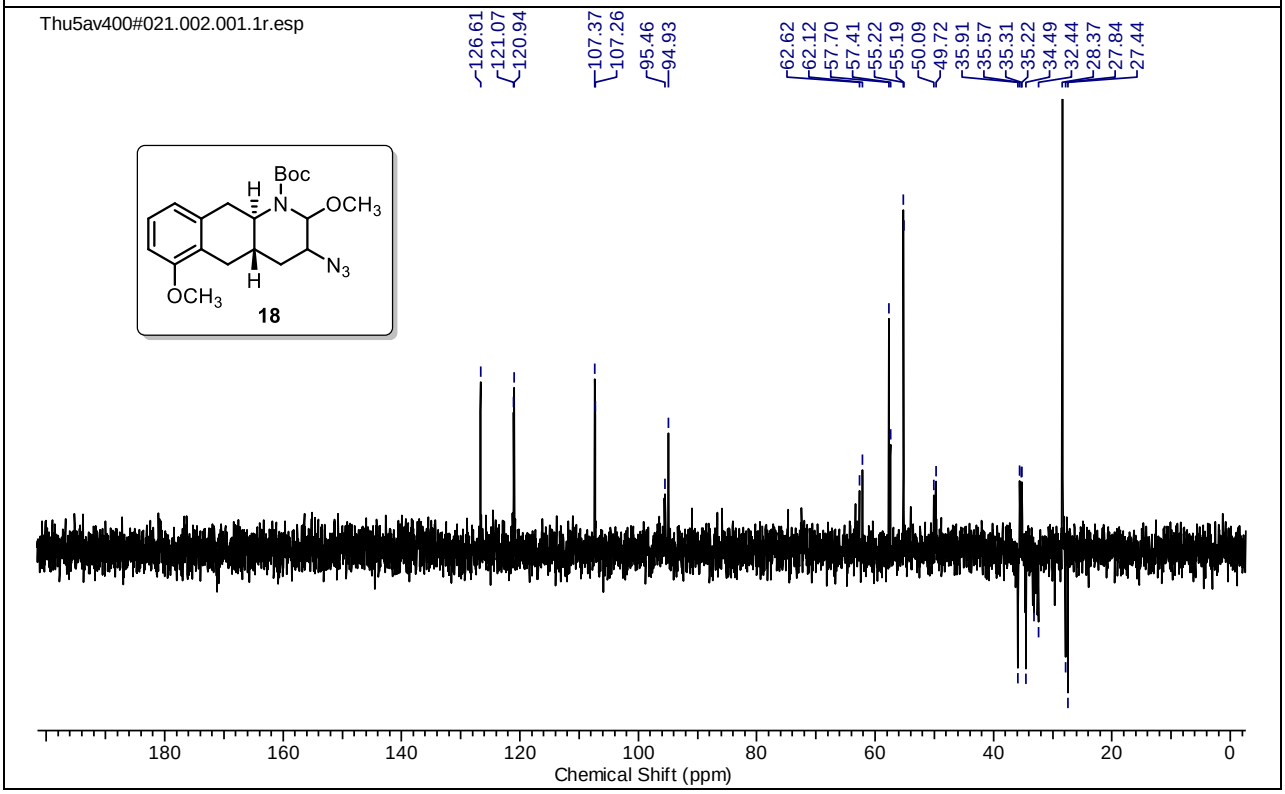
^{1}H-NMR spectrum of compound 18 ($CDCl_3$, 400 MHz)



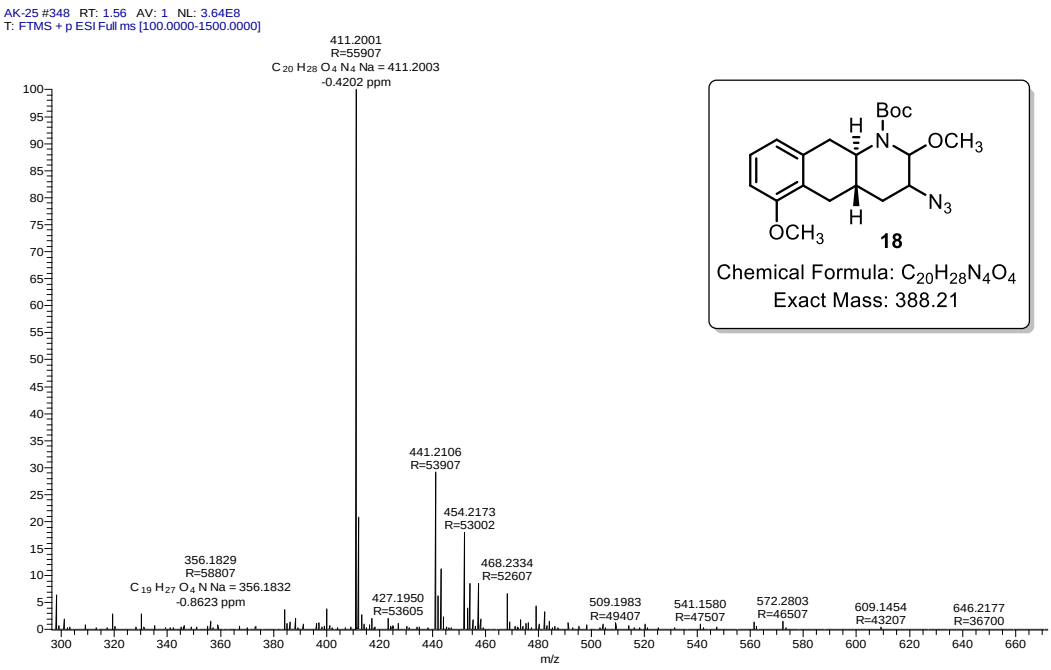
^{13}C-NMR spectrum of compound 18 ($CDCl_3$, 100 MHz)



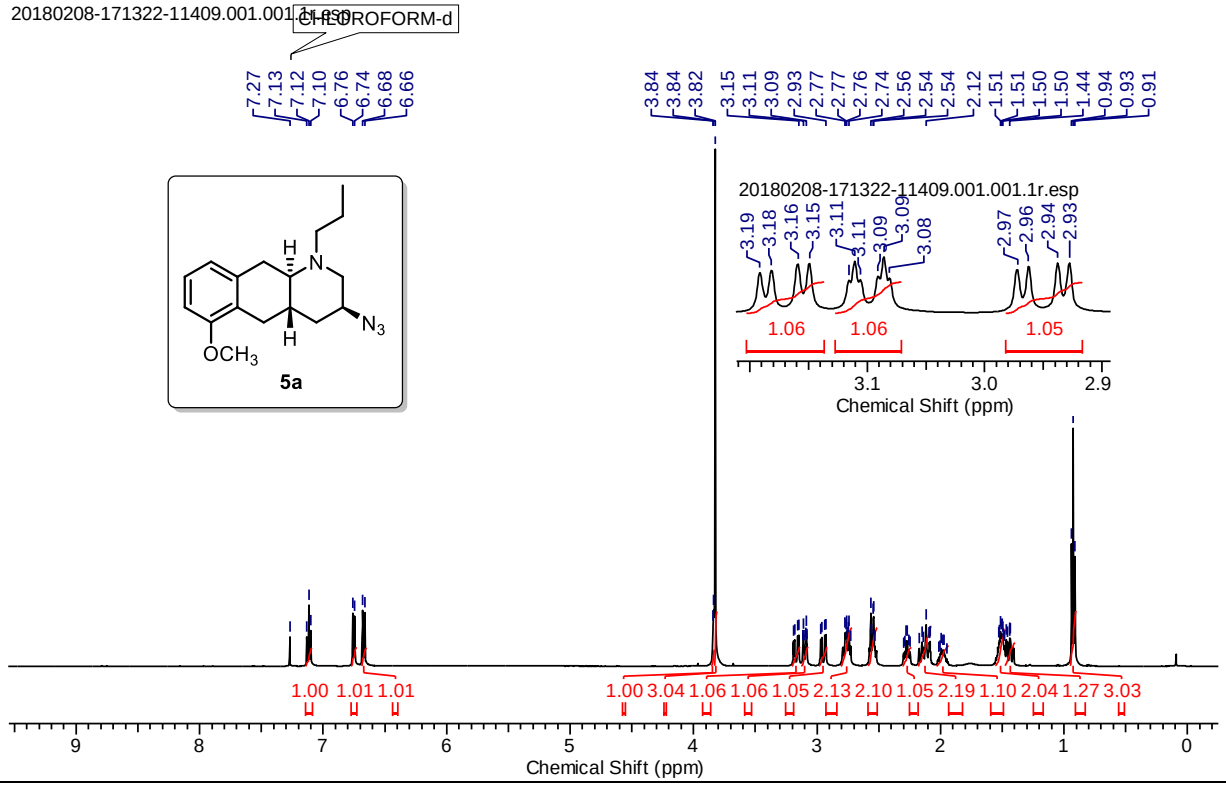
DEPT NMR spectrum of compound 18 ($CDCl_3$, 100 MHz)



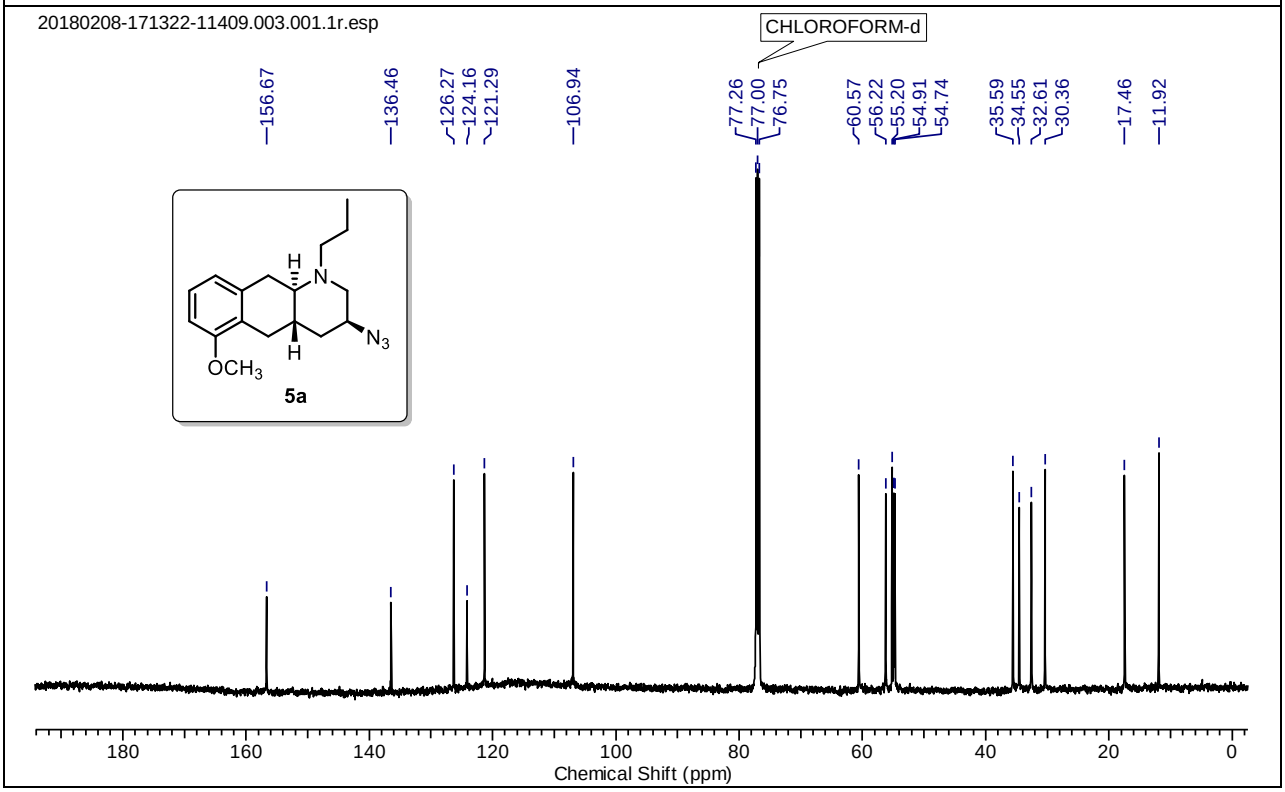
HRMS spectrum of compound 18



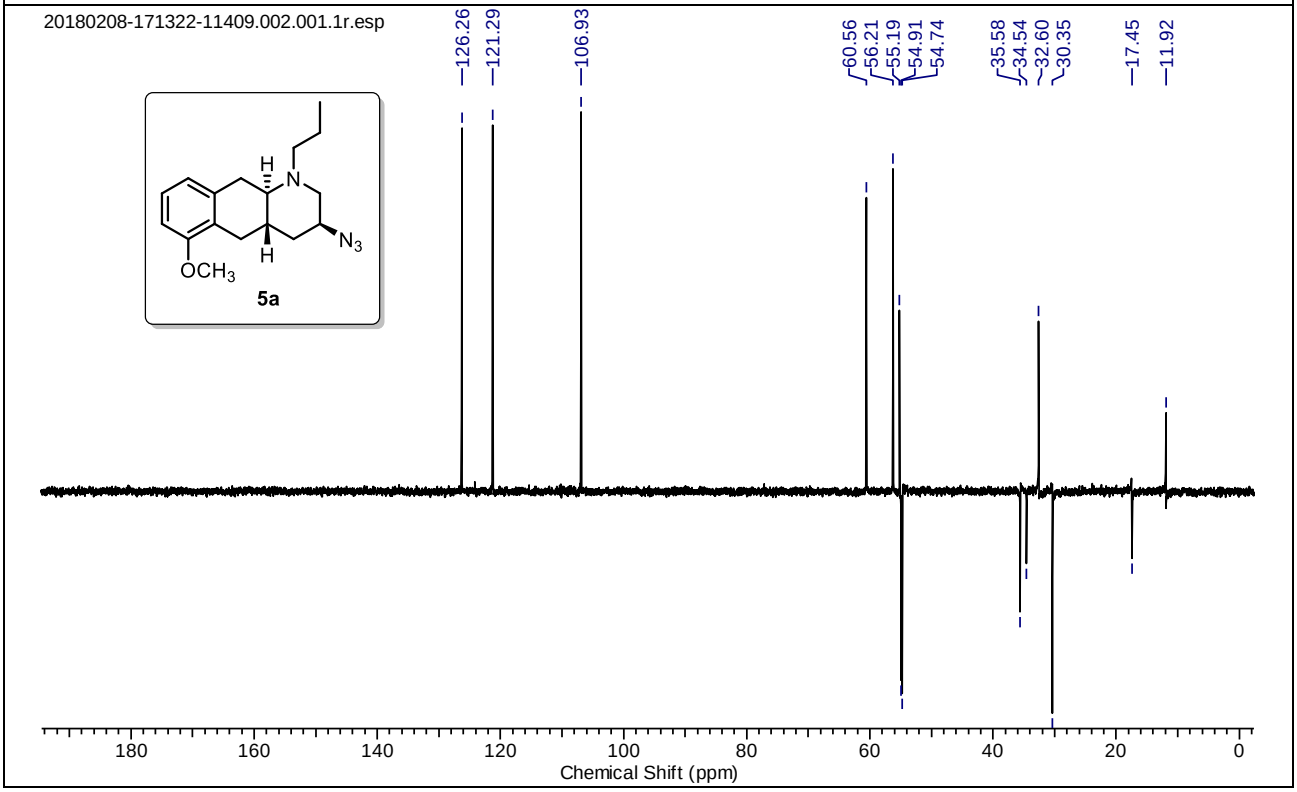
^{1}H-NMR spectrum of compound 5a ($CDCl_3$, 500 MHz)



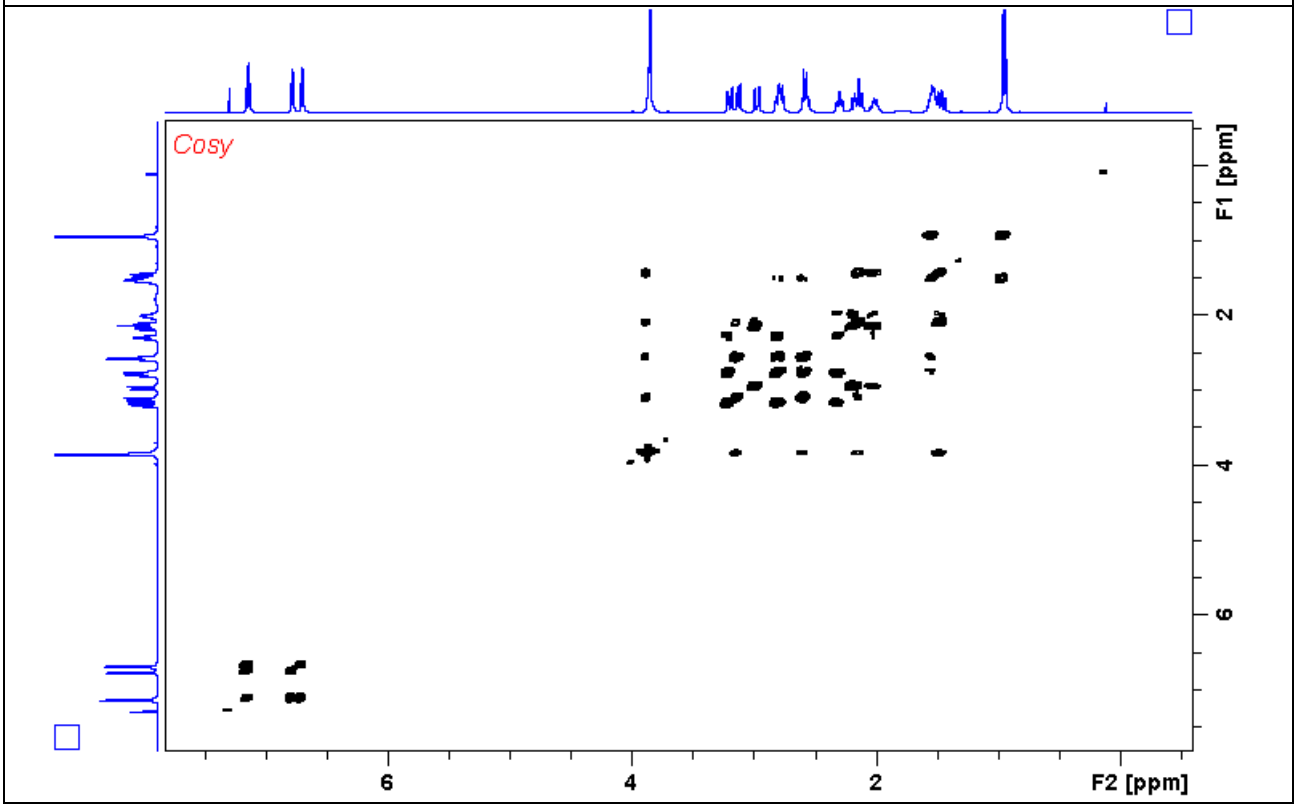
^{13}C-NMR spectrum of compound 5a ($CDCl_3$, 125 MHz)



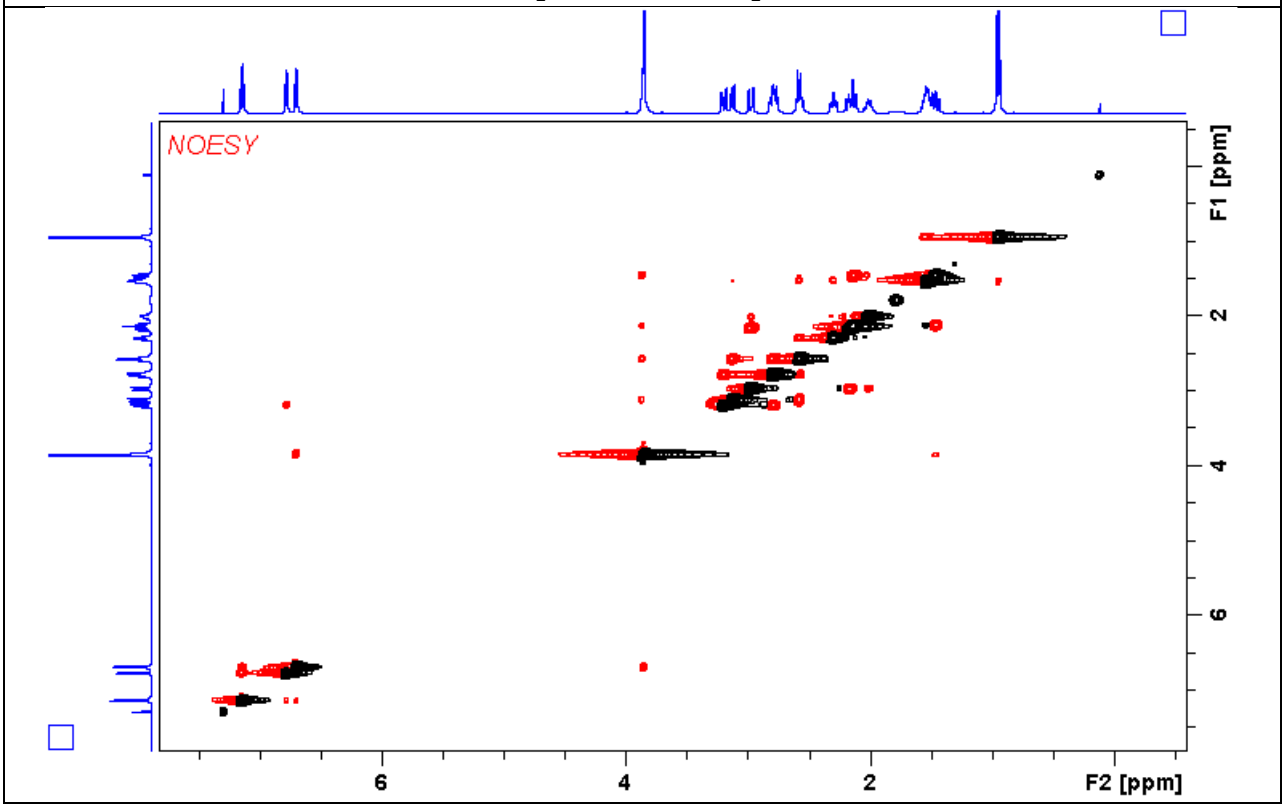
DEPT NMR spectrum of compound 5a ($CDCl_3$, 125 MHz)



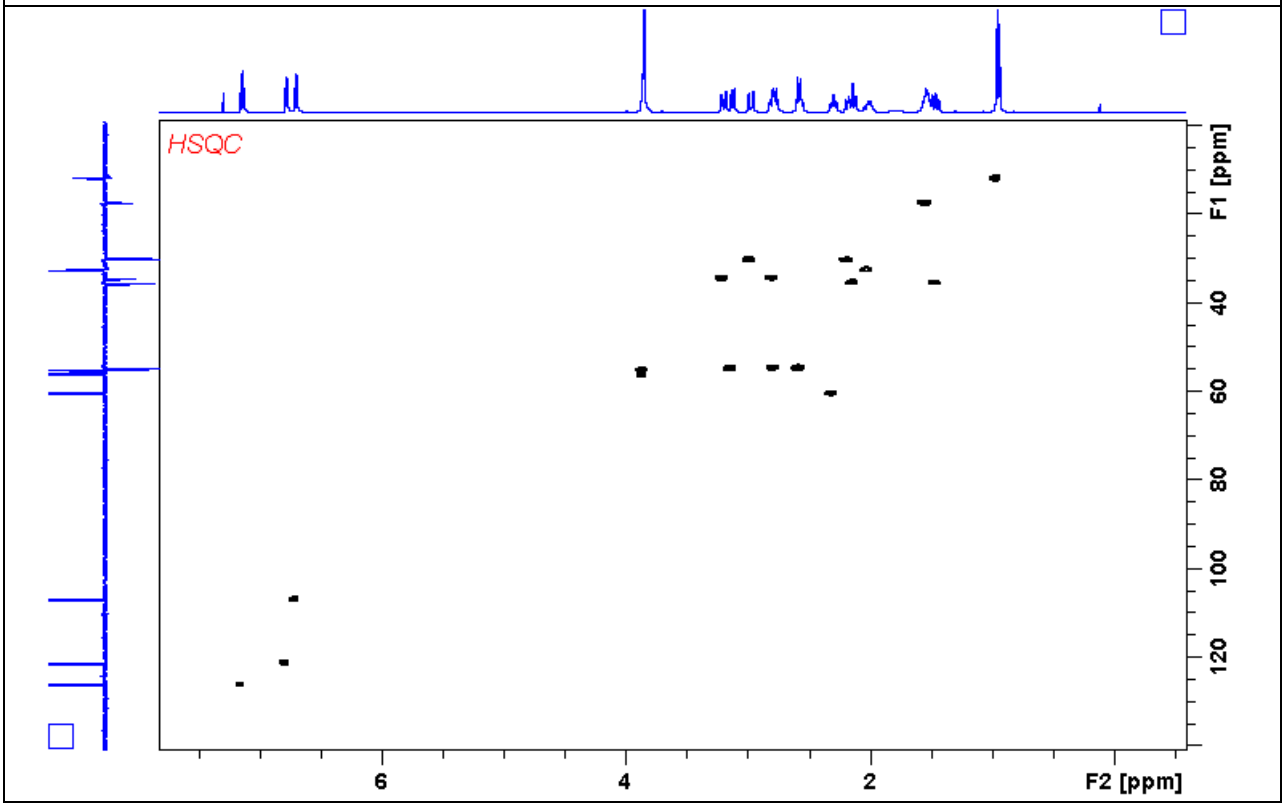
COSY spectrum of compound 5a



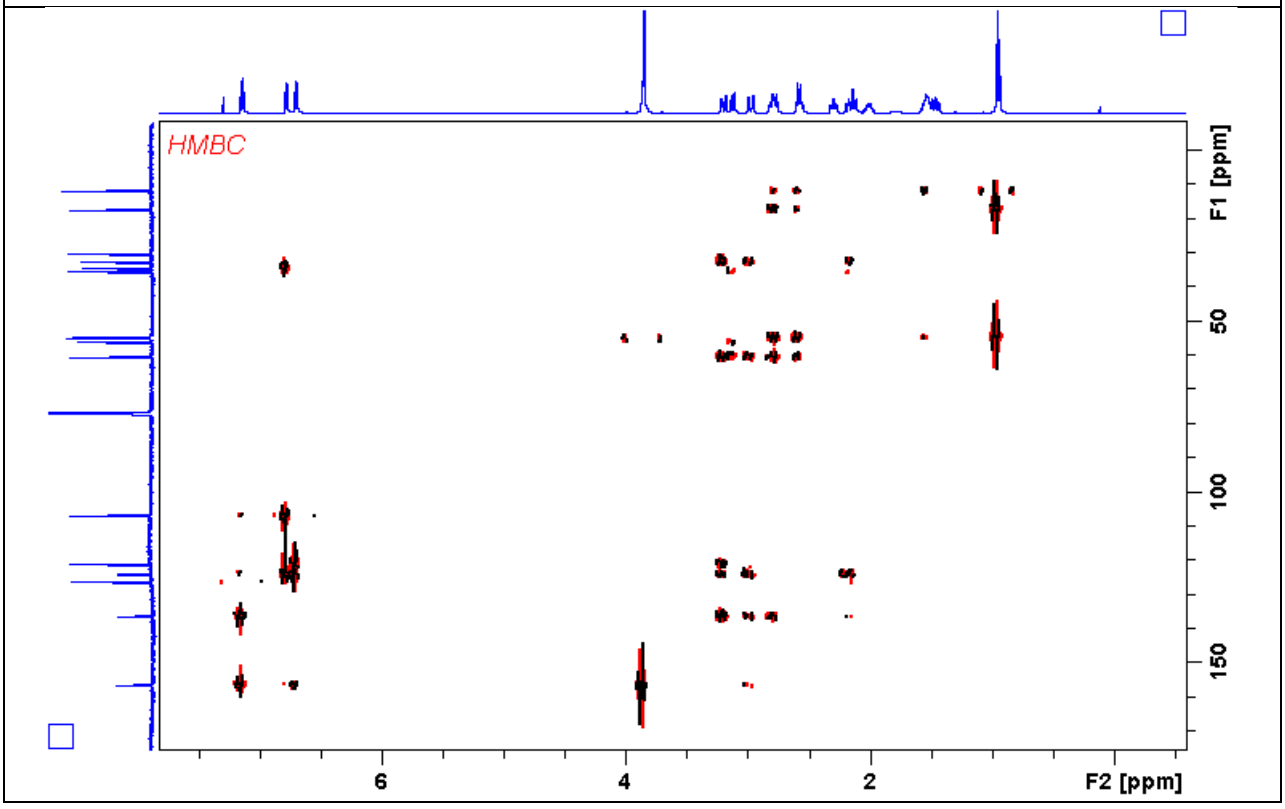
NOESY spectrum of compound 5a



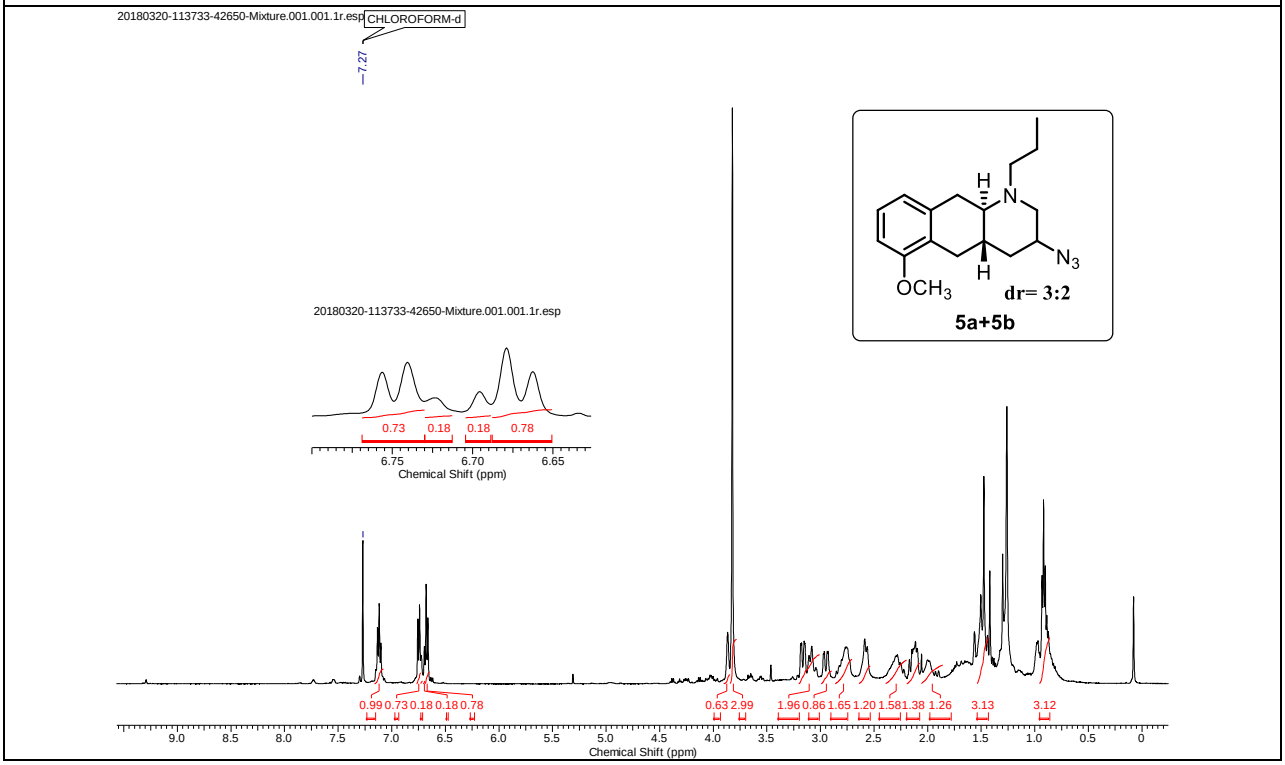
HSQC spectrum of compound 5a



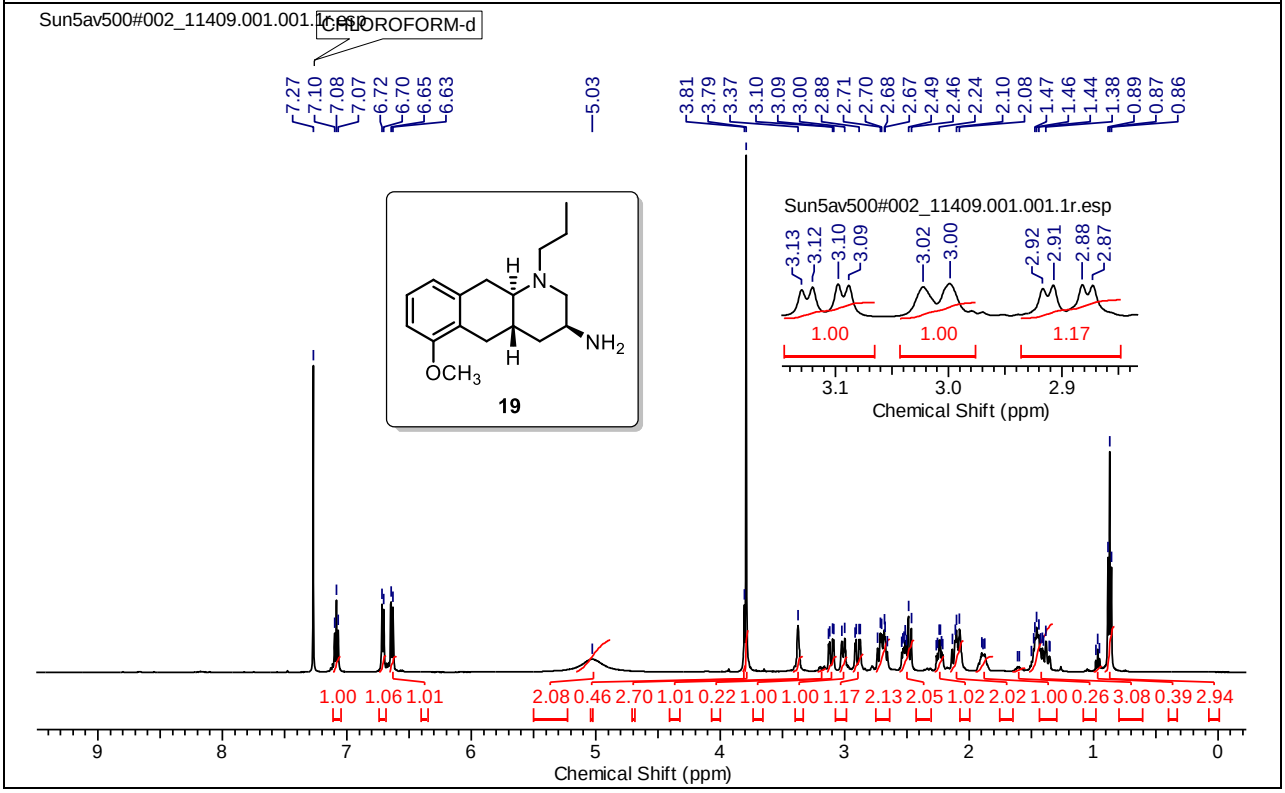
HMBC spectrum of compound 5a



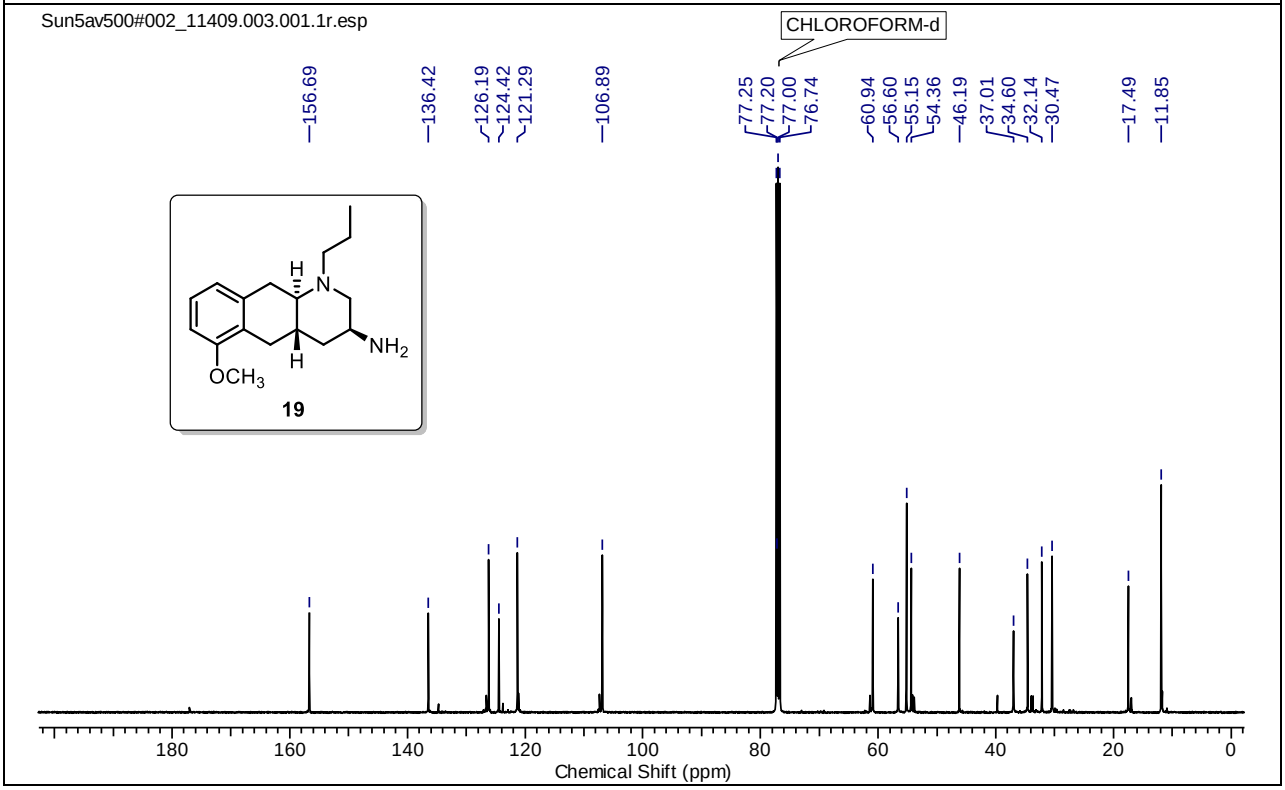
^{1}H-NMR spectrum of compound 5a+5b ($CDCl_3$, 500 MHz)



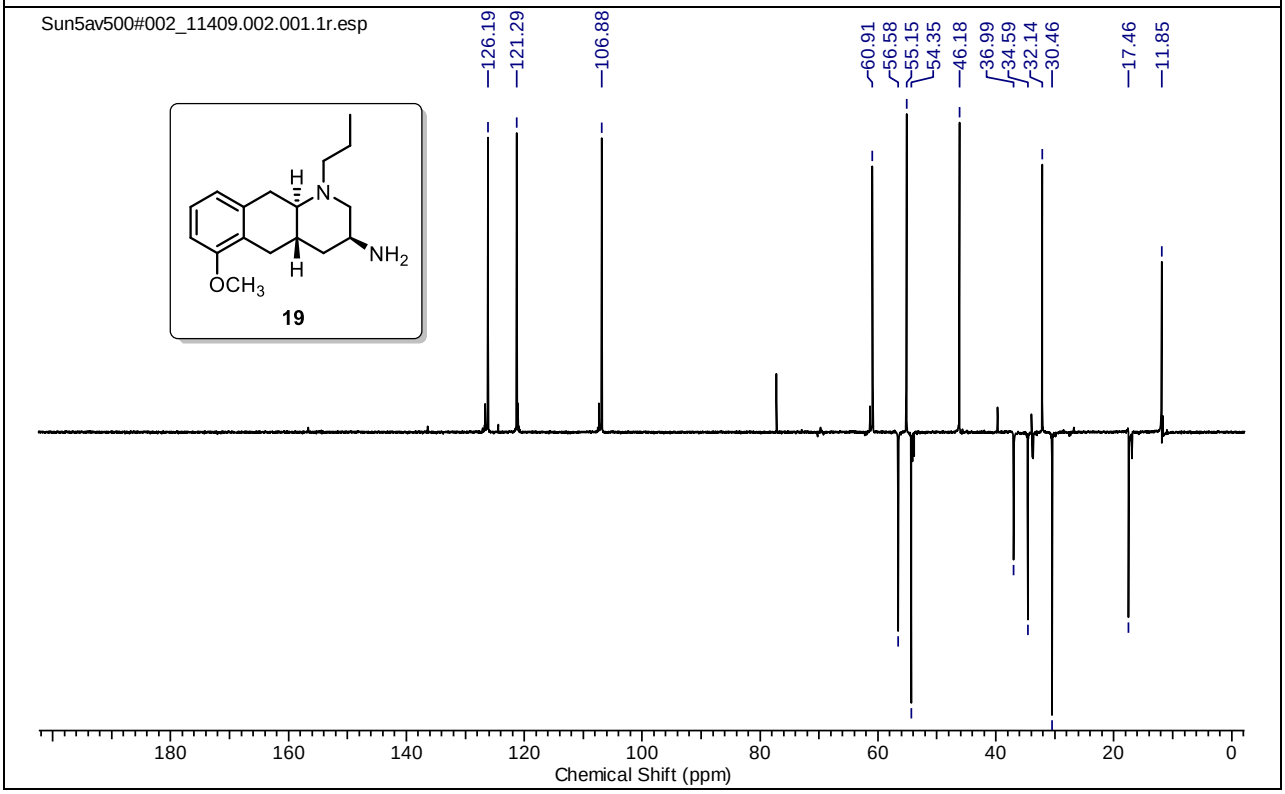
^{1}H-NMR spectrum of compound 19 ($CDCl_3$, 500 MHz)



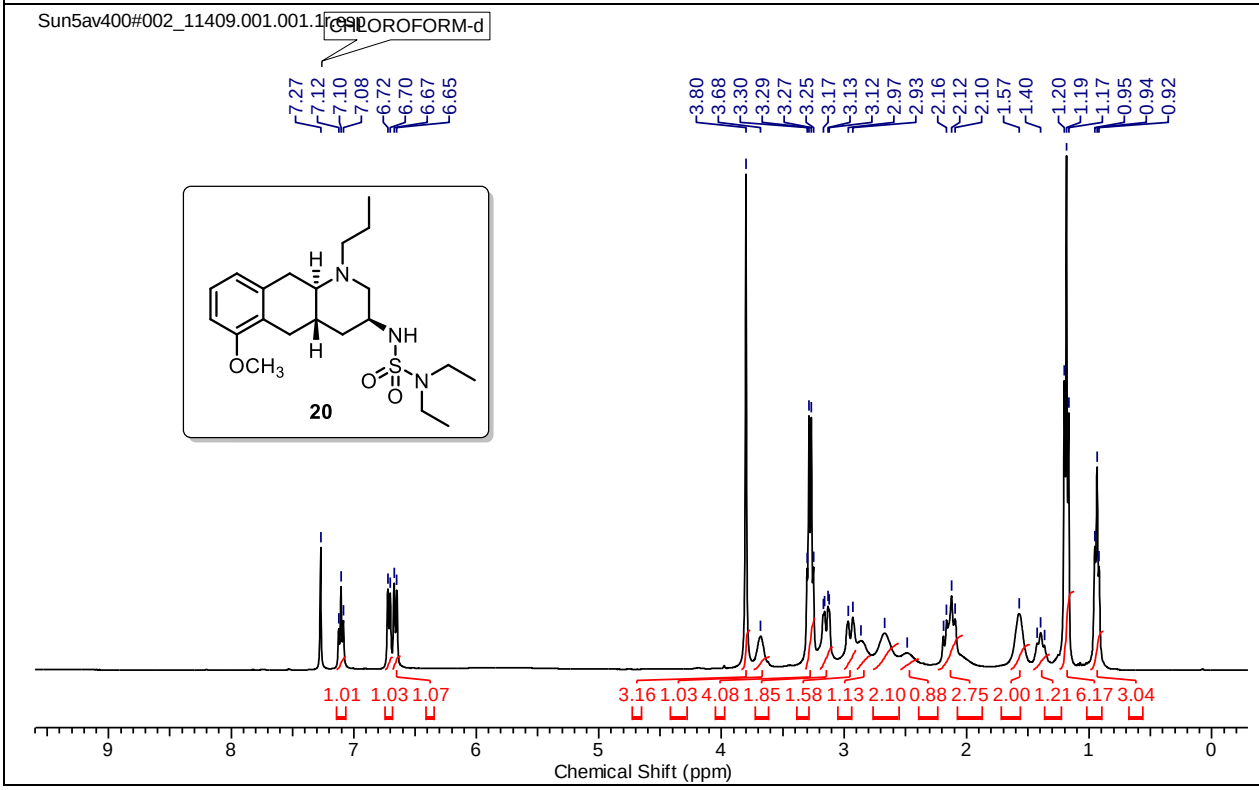
^{13}C-NMR spectrum of compound 19 ($CDCl_3$, 125 MHz)



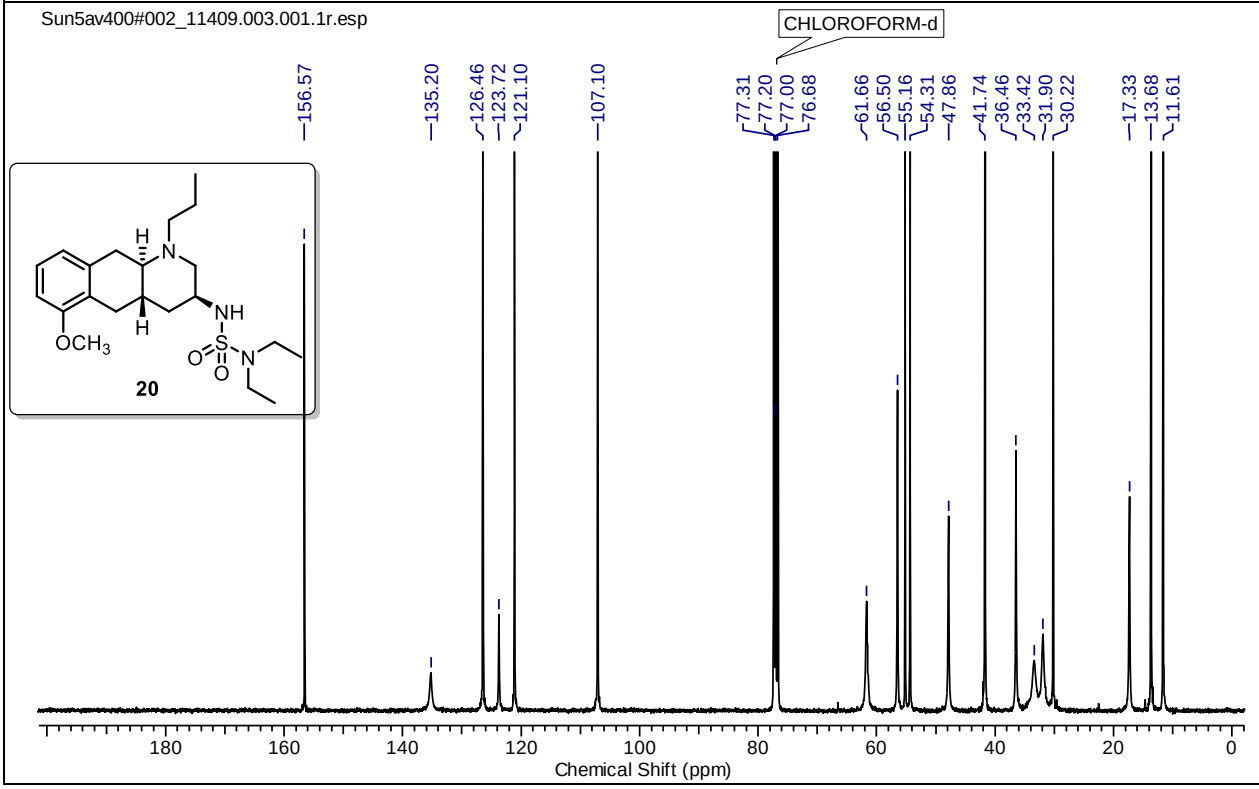
DEPT NMR spectrum of compound 19 ($CDCl_3$, 125 MHz)



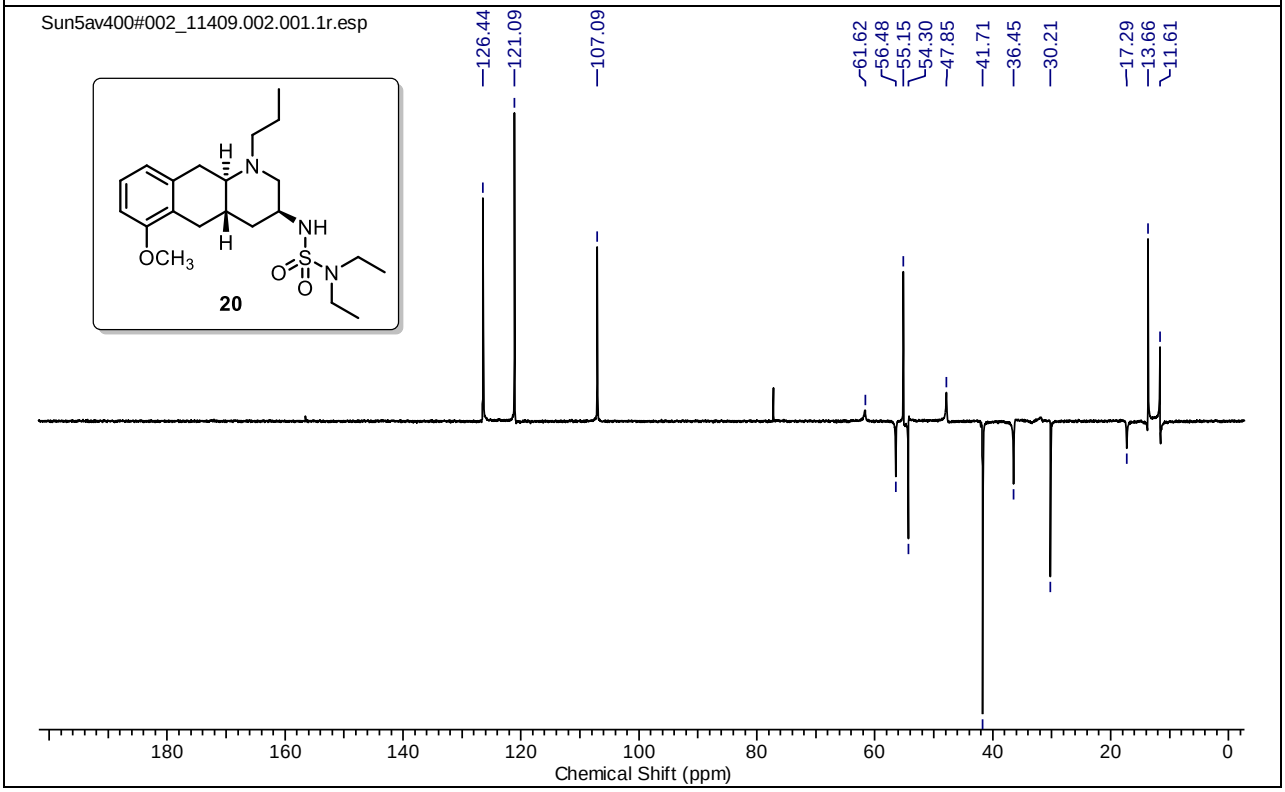
^{1}H-NMR spectrum of compound 20 ($CDCl_3$, 400 MHz)



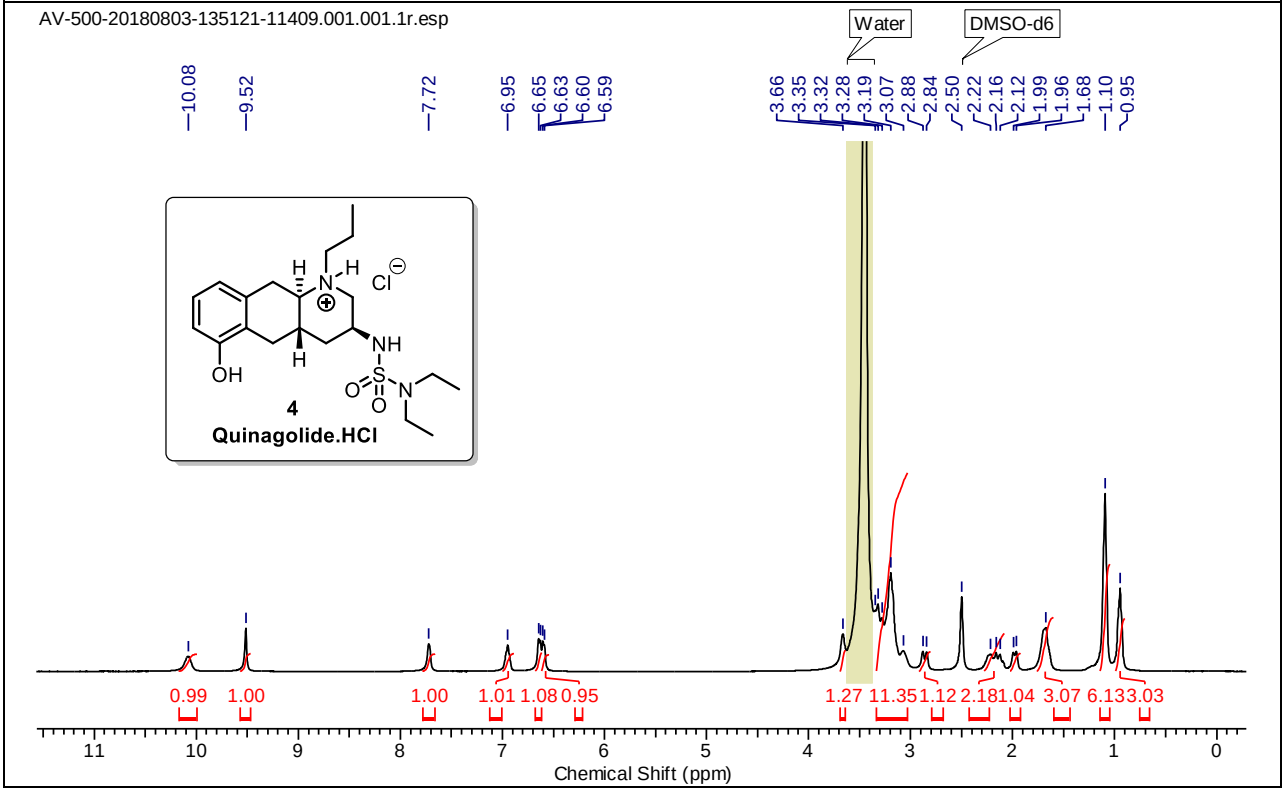
^{13}C-NMR spectrum of compound 20 ($CDCl_3$, 100 MHz)



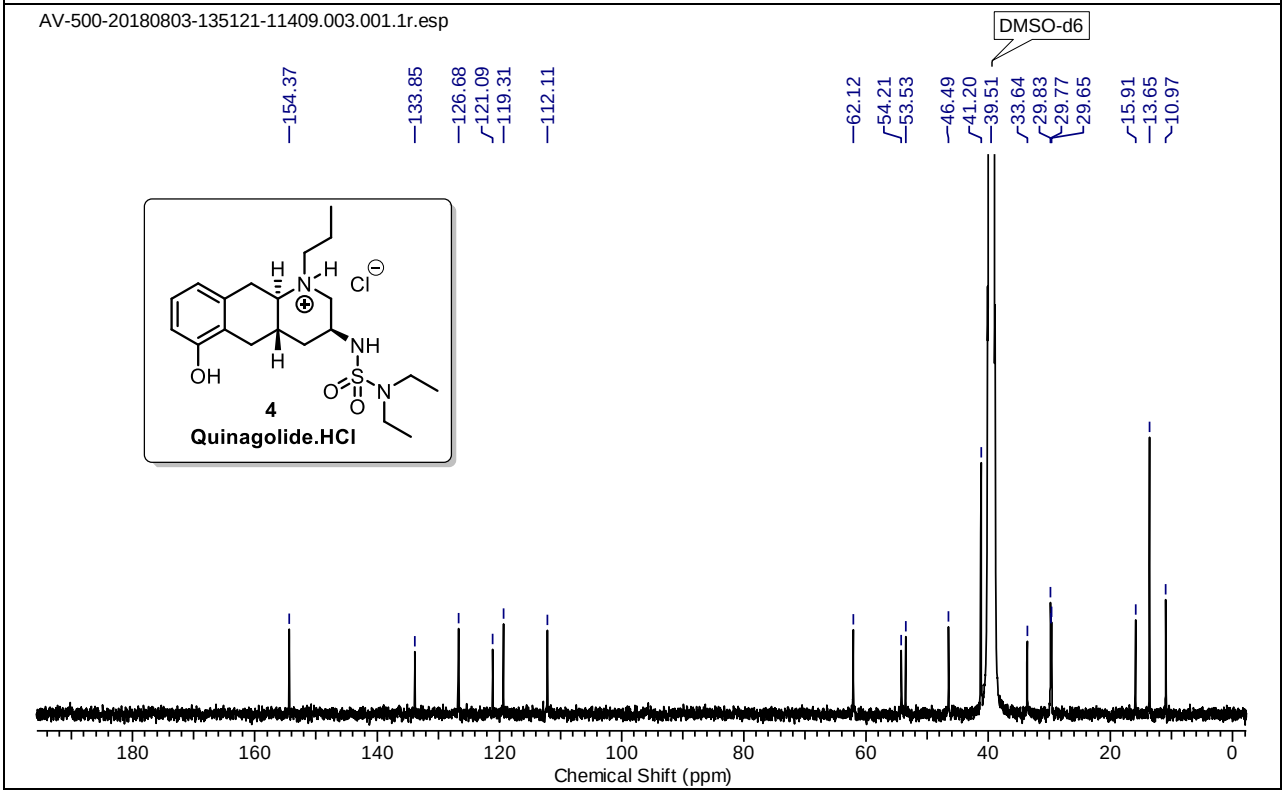
DEPT NMR spectrum of compound 20 ($CDCl_3$, 100 MHz)



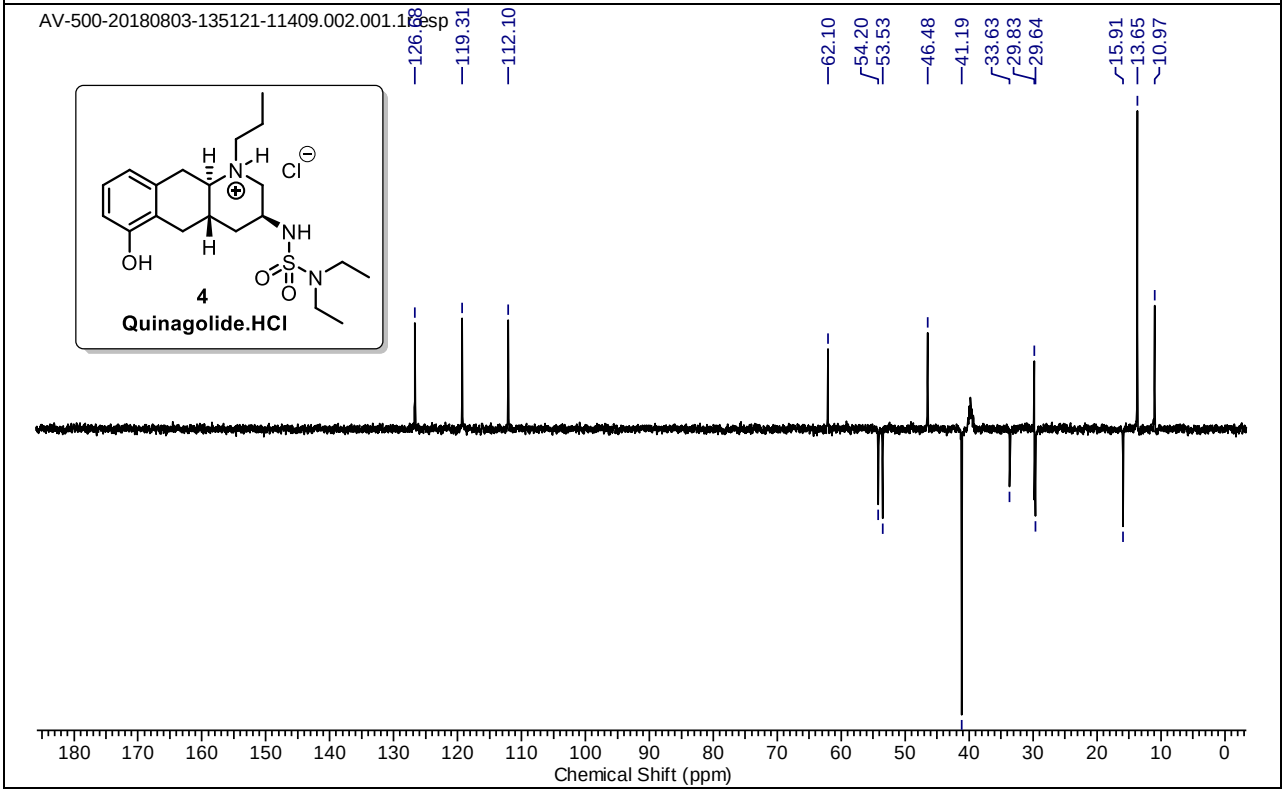
^{1}H-NMR spectrum of compound 4 (DMSO-d_6, 400 MHz)



^{13}C-NMR spectrum of compound 4 (DMSO-d$_6$, 100 MHz)



DEPT NMR spectrum of compound 4 (DMSO-d$_6$, 100 MHz)



1.2.6. References

(1) (a) Somei, M.; Yokoyama, Y.; Murakami, Y.; Ninomiya, I.; Kiguchi, T.; Naito, T. Recent Synthetic Studies on the Ergot Alkaloids and Related Compounds. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 2000, vol. *54*, pp 191. (b) Krogsgaard-Larsen, N.; Jensen, A. A.; Schrøder, T. J.; Christoffersen, C. T.; Kehler, J. *J. Med. Chem*. **2014**, *57*, 5823. (c) Sinz, A. *Pharm. Unserer Zeit* **2008**, *37*, 306.

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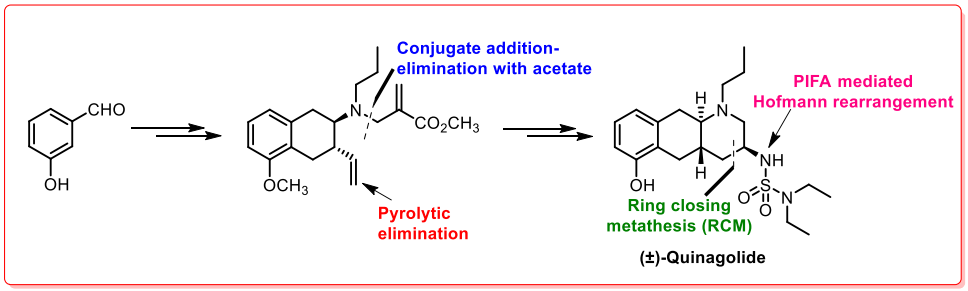
CHAPTER 1

Section 3

"Total Synthesis of (±)-Quinagolide *via* RCM approach"



ABSTRACT: A potent dopamine (D_2) receptor agonist (±)-quinagolide which is used for the treatment of hyperprolactinemia was synthesized using a ring-closing metathesis (RCM) approach from *meta*-hydroxybenzaldehyde as the starting material. Key features of this synthesis are pyrolytic elimination, late-stage expedient synthesis of functionalized *trans*-fused tetrahydropyridine-3-carboxylate from olefin **6**, *via* conjugate addition–elimination upon acetate **11**, followed by ring-closing metathesis and phenyliodine bis(trifluoroacetate) (PIFA) mediated Hofmann rearrangement of piperidine-3-carboxamide, which enables the synthesis of a 3-aminopiperidine skeleton of quinagolide. For the total synthesis of natural products like ergot alkaloids, late-stage synthesis of functionalized *trans*-fused tetrahydropyridine-3-carboxylates using ring-closing metathesis is the main achievement of the present work.

Reference:

Chavan, S. P.; **Kadam, A. L.**; Kawale, S. A. *ACS Omega* **2019**, *4*, 8231.

1.3.1. Objective

Although hyperprolactinemia is not considered as a life-threatening disease, it causes severe effects on the life of patients and often leads to multiple life-threatening diseases.[1] For the treatment of hyperprolactinemia, drugs such as bromocriptine (**1**), cabergoline (**2**) and quinagolide (**3**) are used as medications (**Figure 1**).[2] Out of these medications available in the market, bromocriptine (**1**) and cabergoline (**2**) have serious side effects whereas quinagolide (**3**) which is newly introduced by Ferring Pharmaceuticals under the trade name Norprolac is considered as the first-line therapy in the treatment of hyperprolactinemia. In this context, the development of the practical route to this potent dopamine agonist in a less number of steps is highly desired.

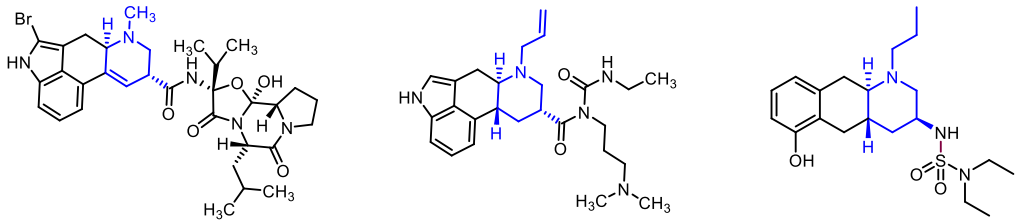


Figure 1. Available hyperprolactinemia medications bromocriptine (**1**), cabergoline (**2**) and quinagolide (**3**).

Over the last three decades, ring-closing metathesis (RCM) is found to be an important tool for the synthesis of numerous piperidine and pyrrolidine alkaloids.[3] In that context, this group effectively utilized the ring-closing metathesis (RCM) as an important synthetic tool for the total synthesis of natural products.[4]

The synthesis of alkaloids using RCM generally requires either *N*-protecting groups (especially electron-withdrawing) or Lewis acid, so that lone pair of basic amine does not adversely interfere in the reaction through chelation with the catalyst. Furthermore, synthesis of functionalized 3-substituted tetrahydropyridine scaffolds which are an integral part of many biologically active natural products such as ergot alkaloids using ring-closing metathesis (RCM) is considered as a challenging task.[5,6] To the best of this author's knowledge, in literature, there are only a few reports in which late-stage synthesis of functionalized tetracyclic 3-substituted tetrahydropyridine scaffolds using ring-closing metathesis (RCM) is documented (**Figure 2**).[7,8]

After the seminal work by Martin and co-workers for the synthesis of functionalized tetracyclic tetrahydropyridine scaffolds using ring-closing metathesis,[9] the late-stage synthesis of tetracyclic 3-substituted tetrahydropyridine for the total synthesis of (+)-isolysergol was reported by the same group in the year 2010 (eq. 1 **Figure 2**).[7] Also, recently (2017), Jia and co-workers reported late-stage synthesis of tetracyclic 3-substituted tetrahydropyridine for the total synthesis of (–)-agroclavine and (–)-elymoclavine using ring-closing metathesis (eq. 2 **Figure 2**).[8]

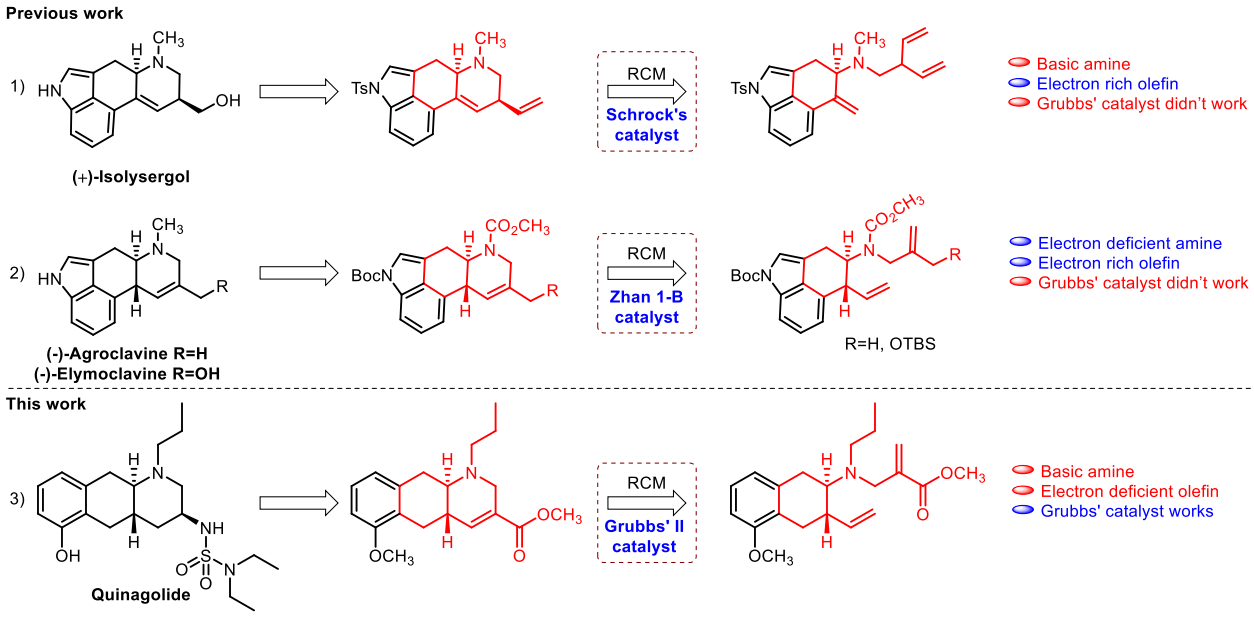


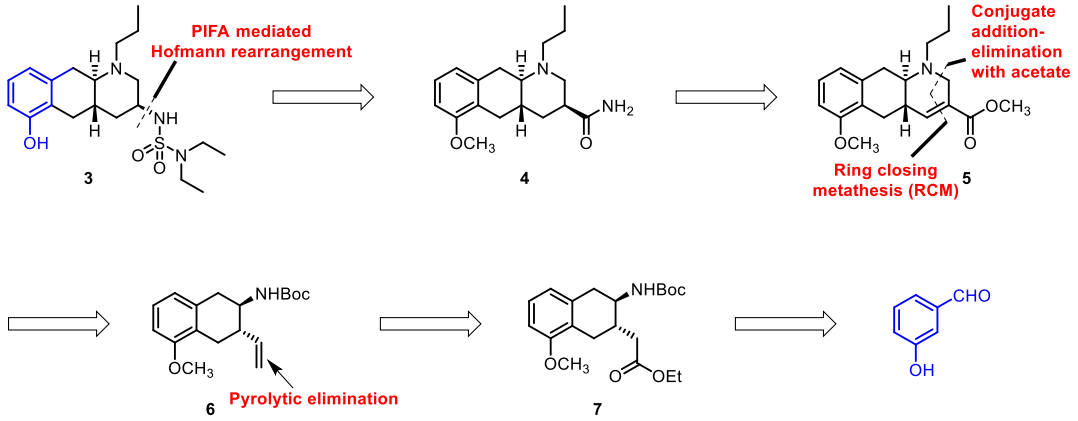
Figure 2. Late-stage synthesis of functionalized tri or tetracyclic 3-substituted tetrahydro-pyridines using the RCM approach.

Here, in the case of the first synthesis, preparation of functionalized tetrahydropyridine scaffolds using ring-closing metathesis of basic amine-containing electron-rich olefins was achieved using Schrock's catalyst, whereas in the latter synthesis, Zhan 1-B catalyst was used for the construction of functionalized tetrahydropyridine scaffolds using ring-closing metathesis of electron-deficient amine-containing electron-rich olefins. Reportedly, in both of these elegant syntheses, Grubbs' I, II and Grubbs-Hoveyda catalyst didn't work. In that context, late-stage synthesis of tricyclic *trans*-fused tetrahydropyridine-3-carboxylates using ring-closing metathesis could be more challenging, as the basic amine and the electron-deficient olefin are the main deciding factors.[3] Here, it was thought that the construction of tetrahydropyridine-3-carboxylate using RCM can fulfill the requirements for the rapid assembly of a 3-aminopiperidine core of quinagolide.

1.3.2. Present Work

1.3.2.1. Retrosynthetic Analysis

The retrosynthetic plan for (±)-quinagolide is shown in **Scheme 1**. It was thought that quinagolide could be accessed from inexpensive and commercially available starting material *meta*-hydroxybenzaldehyde.



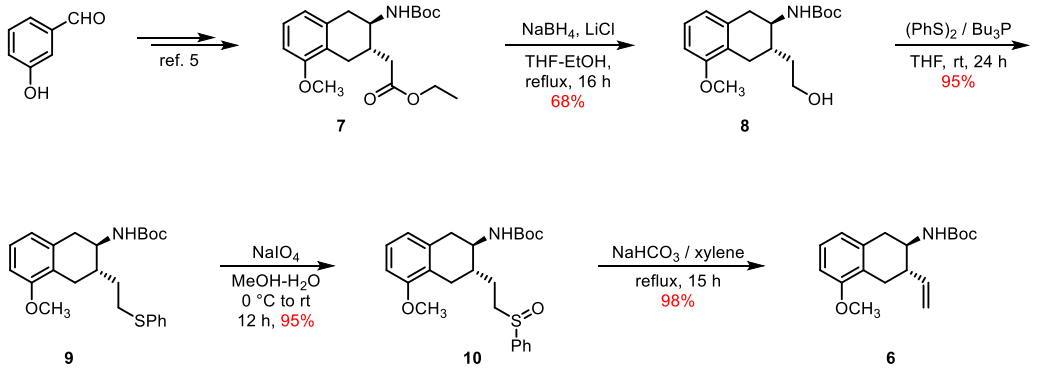
Scheme 1. Key Retrosynthetic Disconnections for Quinagolide

As per the retrosynthetic plan, quinagolide **3** could be obtained from tricyclic tetrahydropyridine-3-carboxylate **5** using phenyliodine bis(trifluoroacetate) (PIFA) mediated Hofmann rearrangement on the corresponding carboxamide **4** followed by sulfonation and demethylation. Tricyclic *trans*-fused tetrahydropyridine-3-carboxylate **5** could be obtained from olefin **6** upon conjugate addition–elimination with required acetate followed by ring-closing metathesis. Olefin **6** could be obtained from ester **7** by reduction to alcohol, corresponding sulfoxide synthesis and pyrolytic elimination as key steps. Ester **7**, in turn, could be accessed from *meta*-hydroxybenzaldehyde using PPTS catalyzed one-pot acetal deprotection followed by diastereoselective Henry reaction as a key step, which is reported in the previous section.

1.3.2.2. Results and Discussion

Synthesis commenced with the goal of conversion of ester functionality in compound **7** into corresponding olefin **6** through pyrolytic elimination (**Scheme 2**). To this end, ester **7** was reduced to the corresponding alcohol **8** using $NaBH_4$-LiCl in THF-EtOH (1:1) under reflux condition in 68% yield. The disappearance of O-CH_3 of ester in the ^1H NMR spectrum and the peak corresponding to ester carbonyl carbon in the ^{13}C NMR spectrum confirmed the formation of the product. The structure of **8** was further confirmed by the HRMS spectrum which showed a

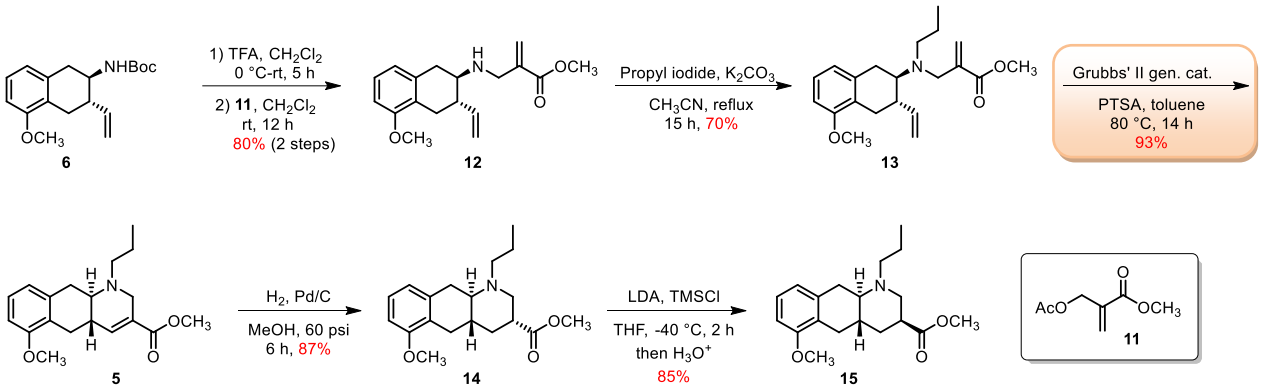
peak at 322.2014 corresponding to the formula $C_{18}H_{28}O_4N$ $[M + H]^+$ of the product. Alcohol **8** was then converted into sulfide **9** by the combined action of diphenyl disulfide and tributyl phosphine in 95% yield.[10] Signals at δ 7.33–7.00 (m, 5H) in the ^1H NMR spectrum corresponding to the aromatic protons of the S-Ph group indicated the formation of the product. HRMS spectrum showed a peak at 414.2100 corresponding to the formula $C_{24}H_{32}O_3NS$ $[M + H]^+$ which further confirmed the formation of the product. Oxidation of the sulfide **9** to the corresponding sulfoxide **10** was achieved using $NaIO_4$ in 95% yield.[11] Pyrolytic elimination of sulfoxide **10** under refluxing xylene condition afforded olefin **6** in 98% yield.[12] Peaks at δ 5.93–5.72 (m, 1H) and 5.23–5.05 (m, 2H) in ^1H NMR spectrum for olefinic protons and δ 116.2 and 107.2 in ^{13}C NMR spectrum corresponding to olefinic carbons clearly indicated the formation of the product. The formation of the product was further confirmed by the HRMS spectrum which showed a peak at 304.1906 corresponding to the formula $C_{18}H_{26}O_3N$ $[M + H]^+$ of the product. Here, pyrolytic elimination was found to be a clean and high yielding reaction and it is a good alternative reaction sequence for the construction of a vinyl group over other reduction-elimination sequences in terms of overall yield and cost-effectiveness of the process.



Scheme 2. Synthesis of Olefin 6 from Ester 7 by Pyrolytic Elimination

After the successful synthesis of olefin **6**, the next task was the synthesis of diene for ring-closing metathesis (**Scheme 3**). At this stage, few conditions for the *N*-alkylation using methyl 2-(bromomethyl)acrylate and acetate **11** were attempted, but all of them failed to provide the desired product. In most cases, the starting material was recovered. So, it was decided to remove the *N*-Boc protecting group and then attempt alkylation. Accordingly, olefin **6** was treated with TFA (10 equiv) in CH_2Cl_2 for 5 h and the corresponding amine was treated with acetate **11** in CH_2Cl_2 at room temperature by applying the protocol described by Ramachandran *et al.*[13] Pleasingly, the crude amine upon conjugate addition-elimination with acetate **11**, smoothly

provided the desired *N*-alkylated product **12** in 80% yield over two steps. The formation of the product was confirmed by the presence of signals at δ 6.26 (s, 1H) and 5.74 (s, 1H) in ^{1}H NMR spectrum and δ 126.3 in ^{13}C NMR spectrum corresponding to the characteristic exocyclic methylene protons and carbon respectively of the newly added acrylate group. The structure of **12** was further confirmed by the HRMS spectrum which showed the signal at 302.1738 corresponding to the formula $C_{18}H_{24}O_3N$ $[M + H]^+$ of the product. Here, it was observed that the concentration of reaction mixture affects the rate of the reaction and 0.05 M concentration gives the optimum yield. In the next step, *N*-propylation was carried out using propyl iodide and K_2CO_3 in acetonitrile under reflux condition for 15 h to afford the corresponding diene **13** in 70% yield.

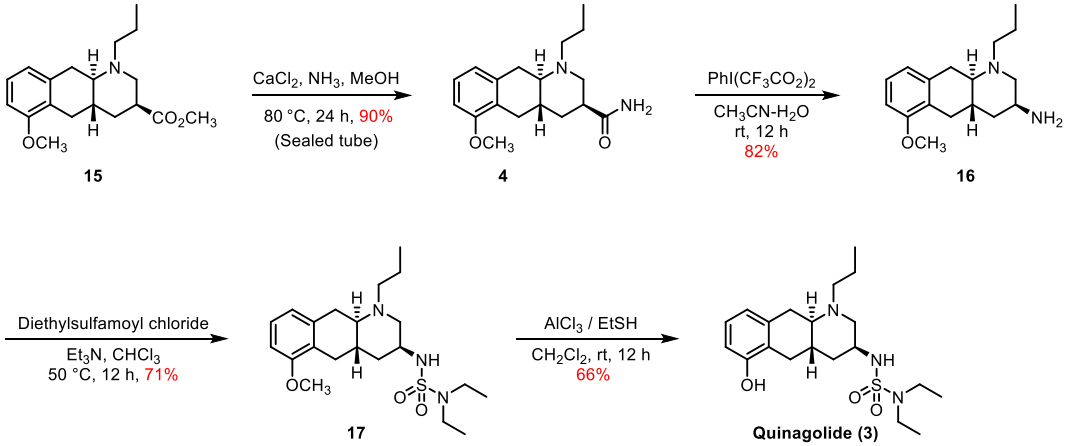


Scheme 3. Synthesis of Tricyclic Core of Quinagolide using RCM

With the diene **13** in hand, the next step was the evaluation of crucial ring-closing metathesis reaction for the synthesis of the *trans*-fused tricyclic skeleton. Though, it is reported in the literature that for the synthesis of tetracyclic skeleton using ring-closing metathesis, Grubbs' catalysts didn't work,[7,8] ring-closing metathesis (RCM) reaction of diene **13** using Grubbs' II generation catalyst and PTSA (1.1 equiv) in toluene at 80 °C for 14 h smoothly provided the required tricyclic core **5** of the quinagolide in 93% yield. The disappearance of exocyclic olefinic protons and carbons of the starting material in the ^{1}H and ^{13}C NMR spectra and appearance of a characteristic signal at δ 6.95 (br s, 1H) corresponding to the newly formed olefinic proton of unsaturated ester in the ^{1}H NMR spectrum clearly confirmed the formation of RCM product. The structure of **5** was further confirmed by the HRMS spectrum which showed a peak at 316.1903 corresponding to the formula $C_{19}H_{26}O_3N$ $[M + H]^+$ of the product. It is noteworthy to mention that the solvent has a great influence on the rate of reaction. When the reaction was carried out in

CH_2Cl_2 as the solvent under reflux condition for 24 h, less than 30% conversion was observed along with recovery of starting material, while toluene turned out to be the best solvent for metathesis. Also, it was observed that the reaction was completely homogeneous in toluene at 80 °C and precipitation of ammonium salt was not observed when formed.

After crucial intermediate in hand, the next aim was the synthesis of the amino side chain of quinagolide. To this end, the reduction of the double bond of **5** was achieved using Pd/C under hydrogenation condition to afford the compound **14** in 87% yield. The stereochemistry of the newly generated center was confirmed by comparison of the spectrum of compound **14** prepared by a different route.[14,15] Furthermore, epimerization at ester center of **14** was achieved using the known protocol to afford piperidine-3-carboxylate **15** in 85% yield.[14] Compound **15** showed ^1H and ^{13}C NMR spectra, identical with the data reported by Banziger *et al*.[14]



Scheme 4. Completion of the Total Synthesis

Towards the completion of the total synthesis of quinagolide, the next aim was the construction of the side chain. To this end, ester **15** was converted into the corresponding carboxamide **4** using NH_3/MeOH and $CaCl_2$ in 90% yield (**Scheme 4**).[16] Formation of the product was confirmed by the disappearance of peaks corresponding to methyl ester and appearance of signals at δ 8.63 (d, J = 4.3 Hz, 1H) and 6.02 (d, J = 4.3 Hz, 1H) corresponding to the -NH_2 protons of amide in ^1H NMR spectrum. The structure of **4** was further confirmed by the HRMS spectrum which showed a peak at 303.2069 corresponding to the formula $C_{18}H_{27}O_2N_2$ $[M + H]^+$ of the product. Carboxamide **4** was subjected for phenyliodine bis(trifluoroacetate) (PIFA) mediated Hofmann rearrangement to obtain the corresponding amine **16** in 82% yield.[17] Amine **16** showed ^1H and ^{13}C NMR spectra, consistent with the data reported in the previous section. Furthermore, amine **16** was converted to the quinagolide (**3**) in two steps as shown in **Scheme 4**

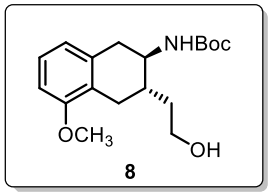
using the sequence discussed in the previous section. All the spectral data of quinagolide **3** were in complete agreement with the reported data.[18]

1.3.3. Conclusion

To conclude, the total synthesis of (±)-quinagolide was achieved using a ring-closing metathesis approach. Pyrolytic elimination, late-stage synthesis of functionalized *trans*-fused tetrahydropyridine-3-carboxylate from olefin **6** upon conjugate addition–elimination with acetate **11** followed by ring-closing metathesis and phenyliodine bis(trifluoroacetate) (PIFA) mediated Hofmann rearrangement of piperidine-3-carboxamide, which enables the synthesis of the 3-aminopiperidine skeleton of quinagolide, are key features of this synthesis. The present synthetic route allows late-stage synthesis of *trans*-fused tetrahydropyridine-3-carboxylates using ring-closing metathesis reaction, which could serve as an important example in the context of the total synthesis of natural products having this structural motif such as ergot alkaloids and PIFA mediated Hofmann rearrangement of piperidine-3-carboxamide allowing quick access to the 3-aminopiperidine skeleton, which poses a challenge to synthetic chemists, are the main achievements of the present work.

1.3.4. Experimental Section

***rac-tert*-Butyl ((2*R*,3*S*)-3-(2-hydroxyethyl)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)carbamate (8).**



8

To a stirred solution of ester **7** (1 g, 2.75 mmol, 1 equiv) in EtOH-THF (1:1, 50 mL), $NaBH_4$ (0.416 g, 11.0 mmol, 4 equiv) followed by LiCl (0.467 g, 11.0 mmol, 4 equiv) were added at room temperature. The resulting suspension was refluxed for 16 h. After completion of the reaction, the solvent was evaporated under reduced pressure and the residue was treated with 1 N HCl (20 mL) and extracted with EtOAc (3 X 100 mL). The organic layer was separated, washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (30:70) to yield alcohol **8** (0.6 g, 68%) as a thick colorless liquid.

R_f : 0.5 (EtOAc–PE = 50:50);

Yield: 68%;

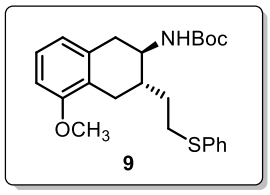
IR ($CHCl_3$): ν_{max} 3435, 1702, 1587, 1215, 771 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.10 (t, *J* = 8.1 Hz, 1H), 6.68 (d, *J* = 8.1 Hz, 2H), 4.63 (br s, 1H), 3.91–3.65 (m, 6H), 3.18–2.87 (m, 2H), 2.73–2.32 (m, 2H), 2.15–1.70 (m, 4H), 1.45 (s, 9H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 157.1, 155.7, 135.3, 126.4, 123.7, 121.1, 107.2, 79.3, 60.5, 55.2, 49.6, 35.2, 34.8, 28.4 (3C), 26.8;

HRMS (ESI) *m/z* calcd for $C_{18}H_{28}O_4N$ $[M + H]^+$: 322.2013, found: 322.2014.

***rac-tert*-Butyl ((2*R*,3*S*)-5-methoxy-3-(2-(phenylthio)ethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)carbamate (9).**



9

To a stirred solution of alcohol **8** (0.6 g, 1.86 mmol, 1 equiv) and diphenyl disulfide (1.224 g, 5.60 mmol, 3 equiv) in THF (15 mL), tri-*n*-butylphosphine (1.38 mL, 5.60 mmol, 3 equiv) was added and the reaction mixture was stirred for 24 h at room temperature. After completion of the reaction, the solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) to yield the sulfide **9** (0.735 g, 95% yield) as a white solid.

R_f : 0.6 **(**EtOAc–PE=10:90);

Yield: 95%;

M. p.: 98–99 °C;

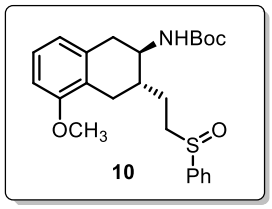
IR ($CHCl_3$): ν_{max} 3435, 1698, 1504, 771 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.33–7.00 (m, 6H), 6.63 (d, *J* = 8.0 Hz, 2H), 4.45 (d, *J* = 8.3 Hz, 1H), 3.77 (s, 3H), 3.75–3.61 (m, 1H), 3.18–2.82 (m, 4H), 2.66–2.18 (m, 2H), 2.06–1.75 (m, 2H), 1.64–1.50 (m, 1H), 1.36 (s, 9H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 157.1, 155.5, 136.5, 135.3, 129.1 (2C), 128.9 (2C), 126.5, 125.8, 123.4, 121.1, 107.2, 79.2, 55.2, 49.6, 37.3, 34.9, 31.9, 31.2, 28.4 (3C), 26.7;

HRMS (ESI) *m/z* calcd for $C_{24}H_{32}O_3NS$ $[M + H]^+$: 414.2097, found: 414.2100.

***rac-tert*-Butyl ((2*R*,3*S*)-5-methoxy-3-(2-(phenylsulfinyl)ethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)carbamate (10).**



To a stirred solution of sulfide **9** (0.7 g, 1.69 mmol, 1 equiv) in MeOH-H_2O (9:1, 120 mL), $NaIO_4$ (0.399 g, 1.86 mmol, 1.1 equiv) was added at 0 °C and the reaction mixture was stirred at room temperature for 12 h. The crude reaction mixture was diluted with CH_2Cl_2 (100 mL) and H_2O (100 mL), the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 X 50 mL). The combined organic layer was washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (40:60) to yield the sulfoxide **10** (0.69 g, 95%) as a thick colorless liquid.

R_f : 0.3 (EtOAc–PE=40:60);

Yield: 95%;

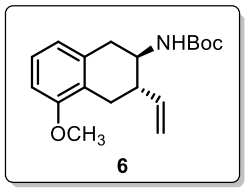
IR ($CHCl_3$): ν_{max} 3298, 1698, 1526, 1168, 752 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): (Mixture of diastereomers) δ 7.69–7.57 (m, 2H), 7.57–7.45 (m, 3H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 4.83–4.49 (m, 1H), 3.80 (s, 1.5H), 3.79 (s, 1.5H), 3.77–3.63 (m, 1H), 3.15–2.75 (m, 4H), 2.72–2.50 (m, 1H), 2.44–2.25 (m, 1H), 2.14–1.79 (m, 3H), 1.45 (s, 9H);

^{13}C NMR ($CDCl_3$, 50 MHz): (Mixture of diastereomers) δ 157.0, 155.4, 143.9, 143.6, 135.2, 135.1, 130.9, 129.2, 126.5, 124.0, 123.96, 123.1, 123.0, 121.0, 107.2, 79.4, 55.1, 54.7, 54.3, 49.7, 49.2, 37.8, 37.3, 35.2, 35.0, 28.4 (3C), 27.1, 26.9, 25.3, 24.6;

HRMS (ESI) *m/z* calcd for $C_{24}H_{32}O_4NS$ $[M + H]^+$: 430.2047, found: 430.2047.

***rac-tert*-Butyl ((2*R*,3*S*)-5-methoxy-3-vinyl-1,2,3,4-tetrahydronaphthalen-2-yl)carbamate (6).**



To a stirred solution of sulfoxide **10** (0.67 g, 1.56 mmol, 1 equiv) in xylene (40 mL), sodium bicarbonate (0.262 g, 3.12 mmol, 2 equiv) was added and the resulting mixture was refluxed for 15 h. After completion of the reaction, the reaction mixture was cooled to room temperature, water (20 mL) was added and extracted with EtOAc (3 X 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The obtained residue was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) to yield the olefin **6** (0.465 g, 98%) as a white solid.

R_f : 0.5 (EtOAc–PE=10:90);

Yield: 98%;

M. p.: 73–75 °C;

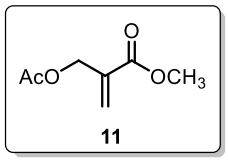
IR ($CHCl_3$): ν_{max} 3438, 1706, 1040, 770 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.11 (t, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 5.93–5.72 (m, 1H), 5.23–5.05 (m, 2H), 4.56 (br s, 1H), 3.82 (s, 3H), 3.74 (br s, 1H), 3.24 (dd, *J* = 5.0, 16.4 Hz, 1H), 2.98 (dd, *J* = 5.4, 17.4 Hz, 1H), 2.73–2.32 (m, 3H), 1.46 (s, 9H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 157.0, 155.5, 140.0, 135.6, 126.4, 123.5, 121.1, 116.2, 107.2, 79.2, 55.2, 49.7, 44.2, 35.4, 29.6, 28.4 (3C);

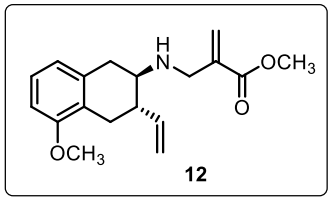
HRMS (ESI) *m/z* calcd for $C_{18}H_{26}O_3N$ $[M + H]^+$: 304.1907, found: 304.1906.

Methyl 2-(acetoxymethyl)acrylate (11).



Acetate **11** was prepared according to the previously reported literature procedure.[19] Known compound; spectroscopic data matched with those in the literature.[19]

***rac*-Methyl 2-((((2*R*,3*S*)-5-methoxy-3-vinyl-1,2,3,4-tetrahydronaphthalen-2-yl)amino)methyl)acrylate (12).**



To a stirred solution of olefin **6** (0.45 g, 1.48 mmol, 1 equiv) in CH_2Cl_2 (15 mL), trifluoroacetic acid (1.13 mL, 14.8 mmol, 10 equiv) was added at 0 °C. After stirring for 5 h at room temperature, the mixture was treated with saturated $NaHCO_3$ and extracted with

CH_2Cl_2 (3 X 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield crude amine which was used in the next reaction without further purification.

To a stirred solution of the above crude amine in CH_2Cl_2 (10 mL), acetate **11** (0.235 g, 1.48 mmol, 1 equiv) was added and the mixture was stirred for 12 h at room temperature. After completion of the reaction, the solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (30:70) to yield the *N*-alkylated compound **12** (0.36 g, 80% yield) as a colorless liquid.

R_f : 0.2 (EtOAc–PE =30:70);

Yield: 80%;

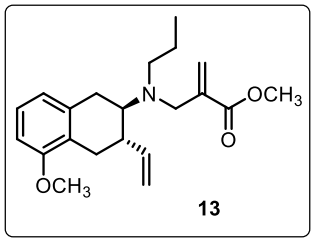
IR ($CHCl_3$): ν_{max} 3435, 1702, 1587, 1215, 771 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.11 (t, *J* = 7.8 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.26 (s, 1H), 5.74 (s, 1H), 5.66 (dd, *J* = 8.4, 9.8 Hz, 1H), 5.36–5.08 (m, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.67 (d, *J* = 14.8 Hz, 1H), 3.47 (d, *J* = 14.8 Hz, 1H), 3.22–2.87 (m, 2H), 2.79–2.24 (m, 5H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 167.0, 157.0, 140.5, 138.4, 136.2, 126.3 (2C), 123.9, 121.1, 117.3, 107.1, 55.2, 54.6, 51.8, 47.6, 44.8, 35.2, 29.0;

HRMS (ESI) *m/z* calcd for $C_{18}H_{24}O_3N$ $[M + H]^+$: 302.1751, found: 302.1738.

***rac*-Methyl 2-((((2*R*,3*S*)-5-methoxy-3-vinyl-1,2,3,4-tetrahydronaphthalen-2-yl)(propyl)amino)methyl)acrylate (13).**



13

To a stirred solution of compound **12** (0.35 g, 1.16 mmol, 1 equiv) in dry acetonitrile (15 mL), pulverized K_2CO_3 (0.482 g, 3.48 mmol, 3 equiv) was added and the reaction mixture was heated to 50 °C. After stirring for 20 min at that temperature, *n*-propyl iodide (0.34 mL, 3.48 mmol, 3 equiv) was added and the reaction mixture was refluxed for the next 15 h. The reaction mixture was then cooled to room temperature, filtered and concentrated under reduced pressure. The residue thus obtained was extracted with EtOAc (3 X 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The obtained residue was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) to yield the diene **13** (0.28 g, 70%) as a colorless liquid.

R_f : 0.6 (EtOAc–PE=10:90);

Yield: 70%;

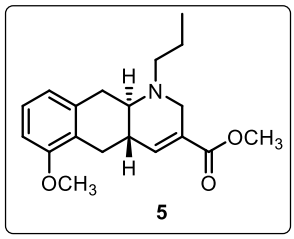
IR ($CHCl_3$): ν_{max} 3019, 1710, 1601, 1216, 769 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.10 (t, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.20 (br s, 1H), 6.11–5.81 (m, 2H), 5.15–4.92 (m, 2H), 3.81 (s, 3H), 3.75 (s, 3H), 3.56–3.24 (m, 2H), 3.07–2.72 (m, 4H), 2.68–2.31 (m, 4H), 1.53–1.35 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 167.8, 157.0, 142.4, 139.2, 137.8, 126.2, 125.6, 124.5, 121.2, 113.7, 106.9, 59.5, 55.2, 51.9, 51.6, 50.8, 42.5, 30.8, 29.3, 21.9, 11.8;

HRMS (ESI) *m/z* calcd for $C_{21}H_{30}O_3N$ $[M + H]^+$: 344.2220, found: 344.2227.

***rac*-Methyl (4a*S*,10a*R*)-6-methoxy-1-propyl-1,2,4a,5,10,10a-hexahydrobenzo[g]quinoline-3-carboxylate (5).**



5

To a degassed solution of the diene **13** (0.25 g, 0.73 mmol, 1 equiv) in toluene (100 mL), PTSA (152 mg, 0.80 mmol, 1.1 equiv) was added and the reaction mixture was heated to 50 °C for 30 min. Then, the Grubbs' II catalyst (10 mol%) was added in three equal parts at the intervals of 2 h and the reaction mixture was stirred for 14 h at 80 °C. After completion of the reaction, it was cooled to room temperature, treated with a saturated Na_2CO_3 solution and the resulting mixture was extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) to yield the tricyclic compound **5** (214 mg, 93%) as a colorless liquid.

R_f : 0.5 (EtOAc–PE =30:70);

Yield: 93%;

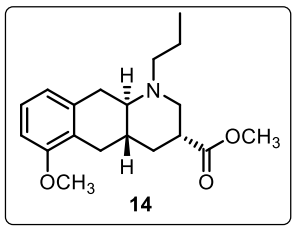
IR ($CHCl_3$): ν_{max} 1714, 1620, 1175, 756 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.14 (t, *J* = 8.0 Hz, 1H), 6.95 (br s, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.71 (s, 1H), 3.27–3.00 (m, 3H), 2.98–2.68 (m, 2H), 2.56–2.14 (m, 4H), 1.69–1.53 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 166.4, 157.1, 140.7, 136.5, 128.2, 126.6, 124.3, 121.6, 107.2, 58.6, 55.3, 53.9, 51.6, 50.4, 38.5, 34.4, 28.9, 18.6, 12.0;

HRMS (ESI) *m/z* calcd for $C_{19}H_{26}O_3N$ $[M + H]^+$: 316.1907, found: 316.1903.

***rac*-Methyl (3*R*,4a*R*,10a*R*)-6-methoxy-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinoline-3-carboxylate (14).**



14

To a stirred solution of compound **5** (200 mg, 0.63 mmol, 1 equiv) in dry MeOH (10 mL), 10% Pd/C (20 mg) was added and the reaction mixture was stirred under H_2 atmosphere at 60 *psi* pressure for 6 h. The reaction mixture was then filtered through celite, washed thoroughly with EtOAc (3 X 50 mL) and concentrated under reduced pressure. The obtained residue was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (15:85) to yield the pure compound **14** (175 mg, 87% yield) as a pale yellow liquid.

R_f : 0.4 (EtOAc–PE =20:80);

Yield: 87%;

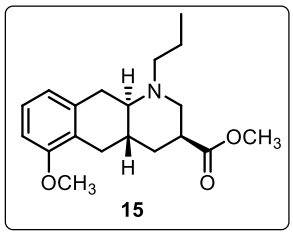
IR ($CHCl_3$): ν_{max} 3019, 1728, 1253, 771 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.11 (t, *J* = 7.8 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 3.27–3.12 (m, 2H), 2.98 (dd, *J* = 4.9, 17.6 Hz, 1H), 2.82–2.52 (m, 4H), 2.39 (t, *J* = 11.5 Hz, 1H), 2.28–2.14 (m, 3H), 1.74–1.61 (m, 1H), 1.60–1.46 (m, 2H), 1.37–1.28 (m, 1H), 0.91 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 174.5, 156.7, 136.3, 126.3, 124.2, 121.2, 107.0, 60.2, 55.2, 55.1, 54.2, 51.7, 41.6, 36.7, 34.7, 34.6, 30.5, 17.5, 11.9;

HRMS (ESI) *m/z* calcd for $C_{19}H_{28}O_3N$ $[M + H]^+$: 318.2064, found: 318.2065.

***rac*-Methyl (3*S*,4a*R*,10a*R*)-6-methoxy-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinoline-3-carboxylate (15).**



15

To a cooled (-78 °C) solution of diisopropylamine (0.22 mL, 1.56 mmol, 3.1 equiv) in anhydrous THF (5 mL), *n*-BuLi (1.6 M in hexane, 0.95 mL, 1.51 mmol, 3 equiv) was added dropwise and reaction mixture was allowed to come to 0 °C and stirred for 30 min. It was again cooled to -40 °C and a solution of compound **14** (160 mg, 0.50 mmol, 1 equiv) in anhydrous THF (5 mL) was added dropwise. After stirring for 1 h at -40 °C, TMSCl (0.135 mL, 1.05 mmol, 2.1 equiv) was added dropwise and the reaction mixture was stirred for another 1 h at -40 °C. After completion of the reaction, the reaction mixture was poured on the ice-

cooled solution of 1N HCl (5 mL), followed by the addition of a 1N Na_2CO_3 (10 mL) solution. The reaction mixture was then extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) to yield the *N*-propyl ester **15** (136 mg, 85%) as a white solid.

R_f : 0.5 (EtOAc–PE=20:80);

Yield: 85%;

M. p.: 96–98 °C;

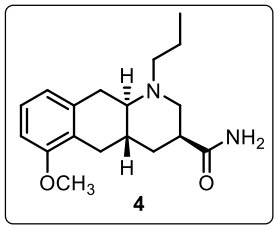
IR ($CHCl_3$): ν_{max} 1718, 1263, 775 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.09 (t, *J* = 7.8 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 3.47 (d, *J* = 11.5 Hz, 1H), 3.13 (dd, *J* = 4.9, 16.0 Hz, 1H), 2.98 (dd, *J* = 4.6, 17.1 Hz, 1H), 2.85–2.52 (m, 3H), 2.47–2.28 (m, 3H), 2.26–2.01 (m, 2H), 1.98–1.73 (m, 1H), 1.58–1.40 (m, 2H), 1.38–1.20 (m, 1H), 0.90 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 174.4, 156.7, 136.7, 126.1, 124.6, 121.3, 106.8, 61.5, 55.2, 54.5, 53.6, 51.6, 39.9, 34.8, 34.2, 32.3, 30.7, 18.2, 11.8;

HRMS (ESI) *m/z* calcd for $C_{19}H_{28}O_3N$ $[M + H]^+$: 318.2064, found: 318.2065.

***rac*-(3*S*,4a*R*,10a*R*)-6-Methoxy-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinoline-3-carboxamide (4).**



4

To a stirred solution of compound **15** (120 mg, 0.38 mmol, 1 equiv) in MeOH (5 mL) in a sealed tube, $CaCl_2$ (88 mg, 0.79 mmol, 2.1 equiv) was added followed by NH_3 in MeOH (1:1, 5 mL) and the reaction mixture was stirred at 80 °C for 24 h. The solvents were then evaporated under reduced pressure, the obtained residue was treated with a saturated solution of $NaHCO_3$ and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel (230–400 mesh) column chromatography using MeOH–EtOAc (1:99) to yield the amide **4** (103 mg, 90%) as a white solid.

R_f: 0.3 (MeOH–EtOAc=1:99);

Yield: 90%;

M. p.: 179–181 °C;

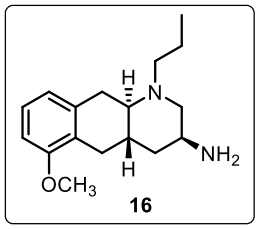
IR ($CHCl_3$): ν_{max} 3465, 1665, 1216, 758 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.63 (d, *J* = 4.3 Hz, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.02 (d, *J* = 4.3 Hz, 1H), 3.80 (s, 3H), 3.34–3.07 (m, 2H), 3.03–2.53 (m, 4H), 2.53–2.01 (m, 5H), 2.00–1.70 (m, 1H), 1.70–1.34 (m, 3H), 0.93 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 178.5, 156.6, 135.9, 126.2, 124.2, 121.0, 107.0, 61.2, 55.1, 54.8, 53.3, 41.0, 35.0, 34.0, 33.8, 30.4, 18.3, 12.0;

HRMS (ESI) *m/z* calcd for $C_{18}H_{27}O_2N_2$ $[M + H]^+$: 303.2067, found: 303.2069.

***rac*-(3*S*,4a*S*,10a*R*)-6-Methoxy-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinolin-3-amine (16).**

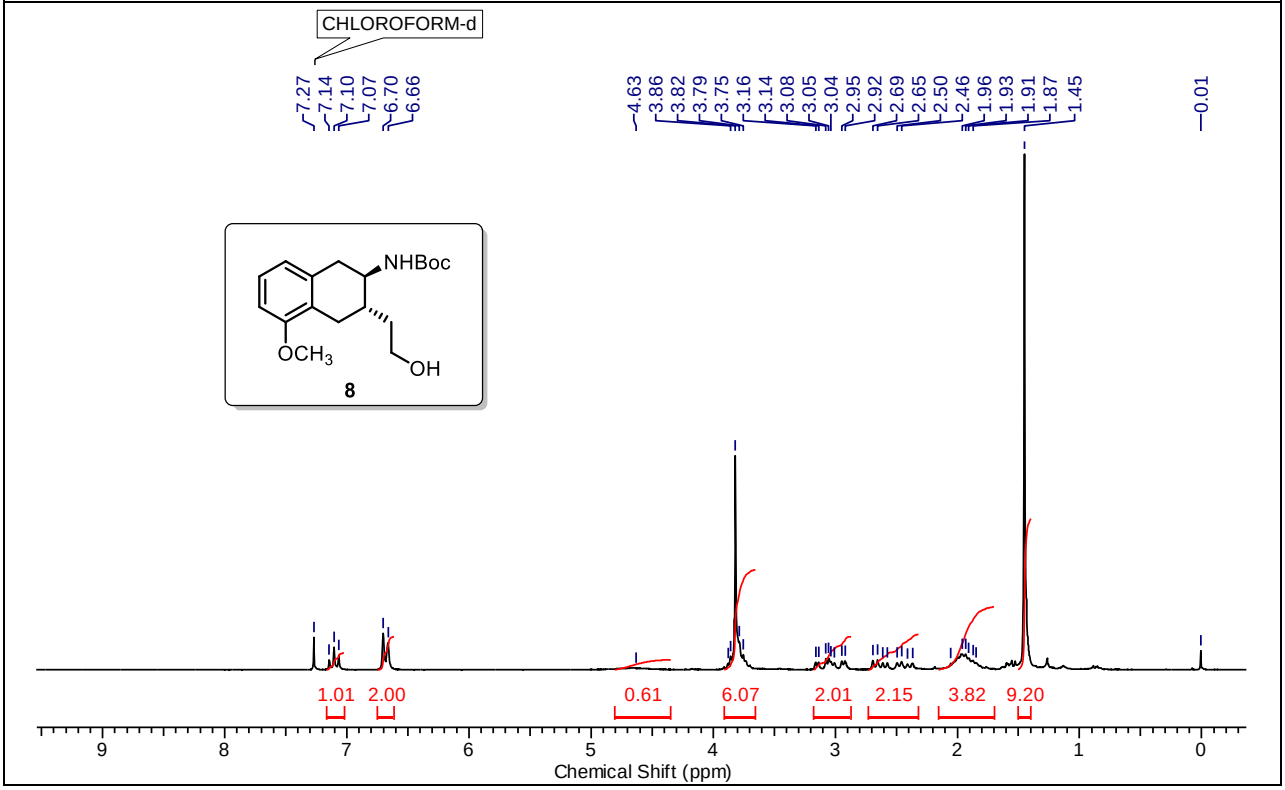


16

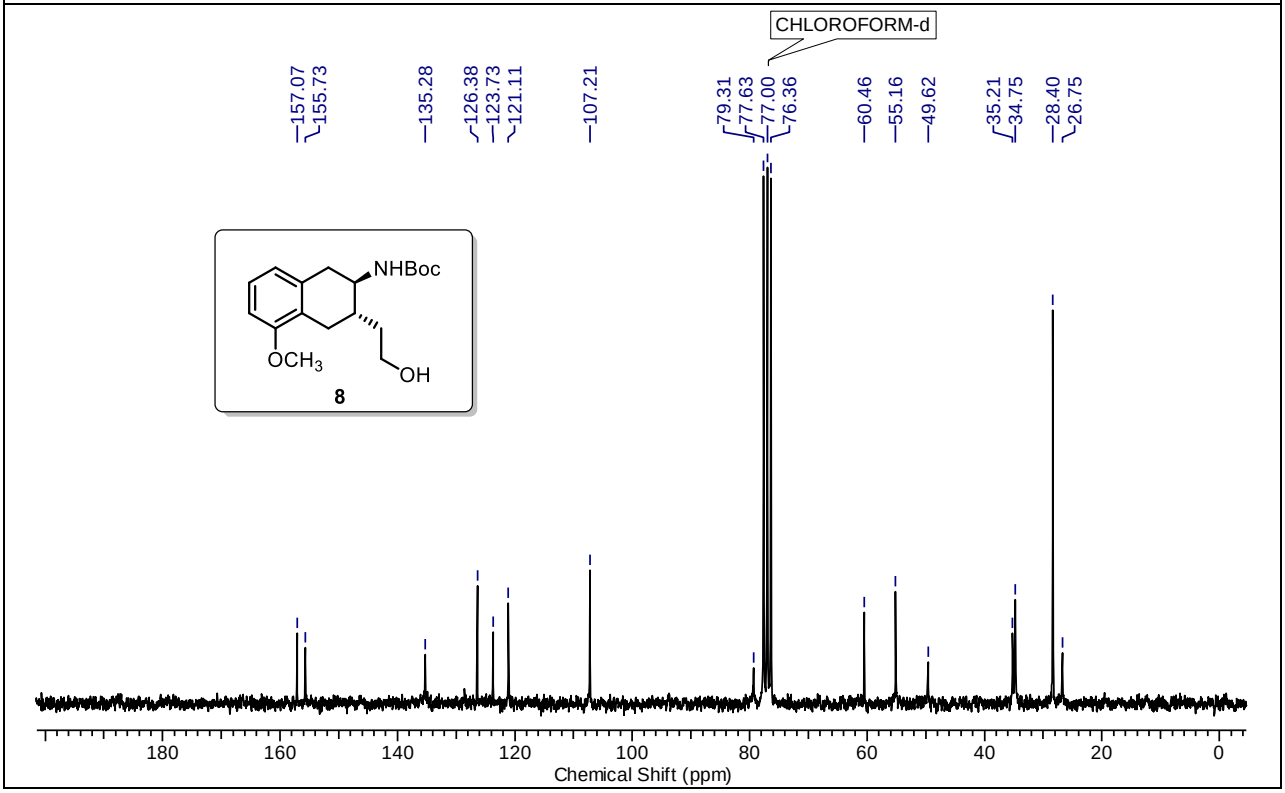
To a stirred solution of PIFA (0.171 g, 0.39 mmol, 1.5 equiv) in acetonitrile-water (deionized) (10 mL, 1:1 v/v) in round-bottomed flask covered with aluminum foil, amide **4** (80 mg, 0.26 mmol, 1 equiv) was added at room temperature. Stirring was continued at room temperature for 12 h. The reaction mixture was then concentrated under reduced pressure, the obtained residue was dissolved in water (10 mL), acidified with concentrated HCl (3 mL), and extracted with Et_2O. The ether layer was washed with 10% aq. HCl, the combined aqueous layers were basified with $NaHCO_3$, extracted with EtOAc (3 X 50 mL) and concentrated under reduced pressure. The obtained residue was purified by silica gel (230–400 mesh) column chromatography using MeOH–$CHCl_3$ (10:90) to yield the pure compound **16** (60 mg, 82% yield) as a thick yellow liquid (For spectral details, see page no. 35).

1.3.5. Spectral Data

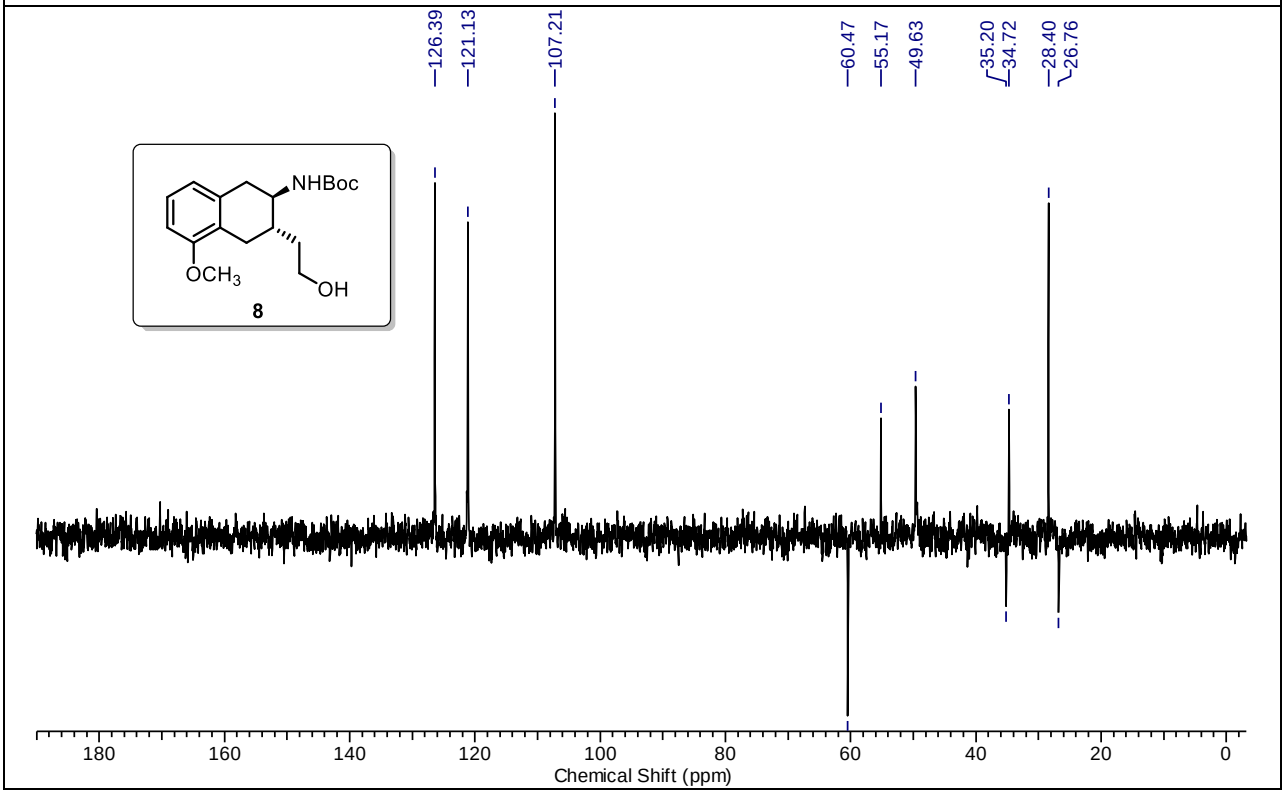
^{1}H-NMR spectrum of compound 8 ($CDCl_3$, 200 MHz)



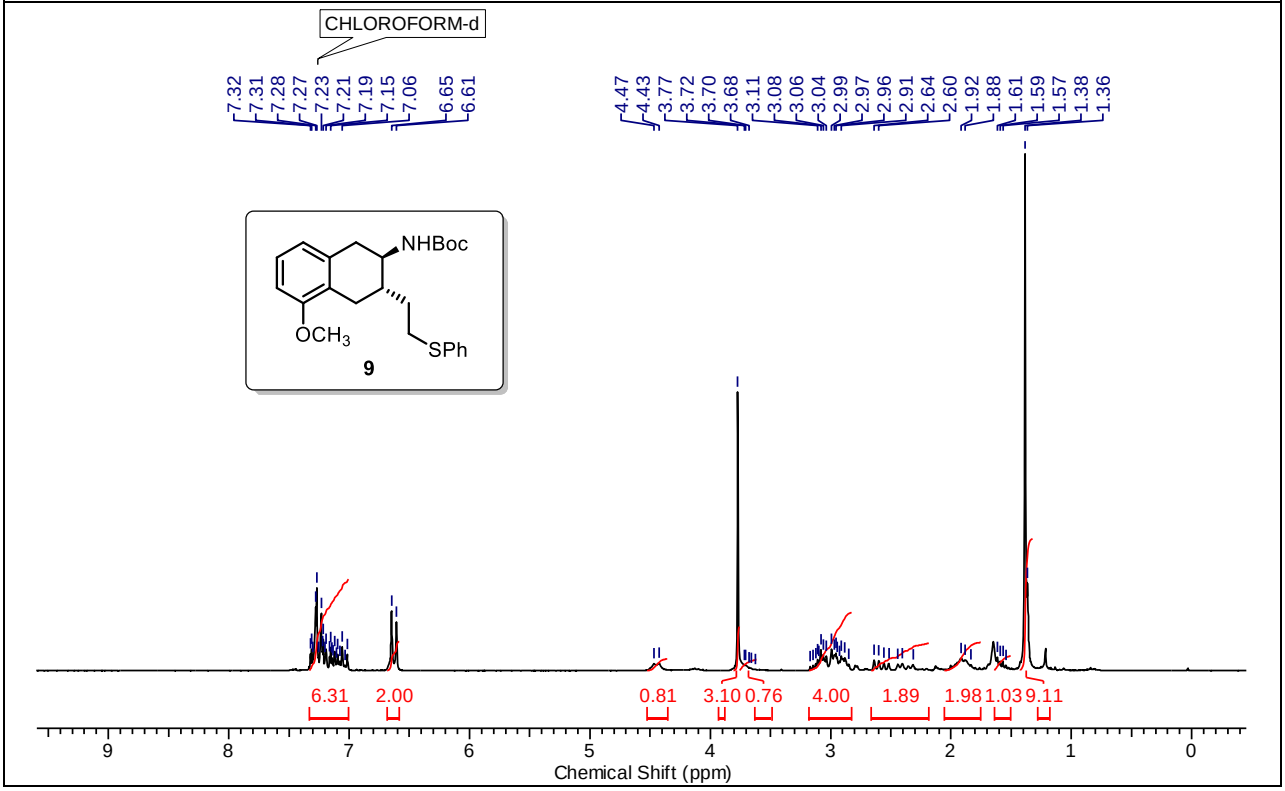
^{13}C-NMR spectrum of compound 8 ($CDCl_3$, 50 MHz)



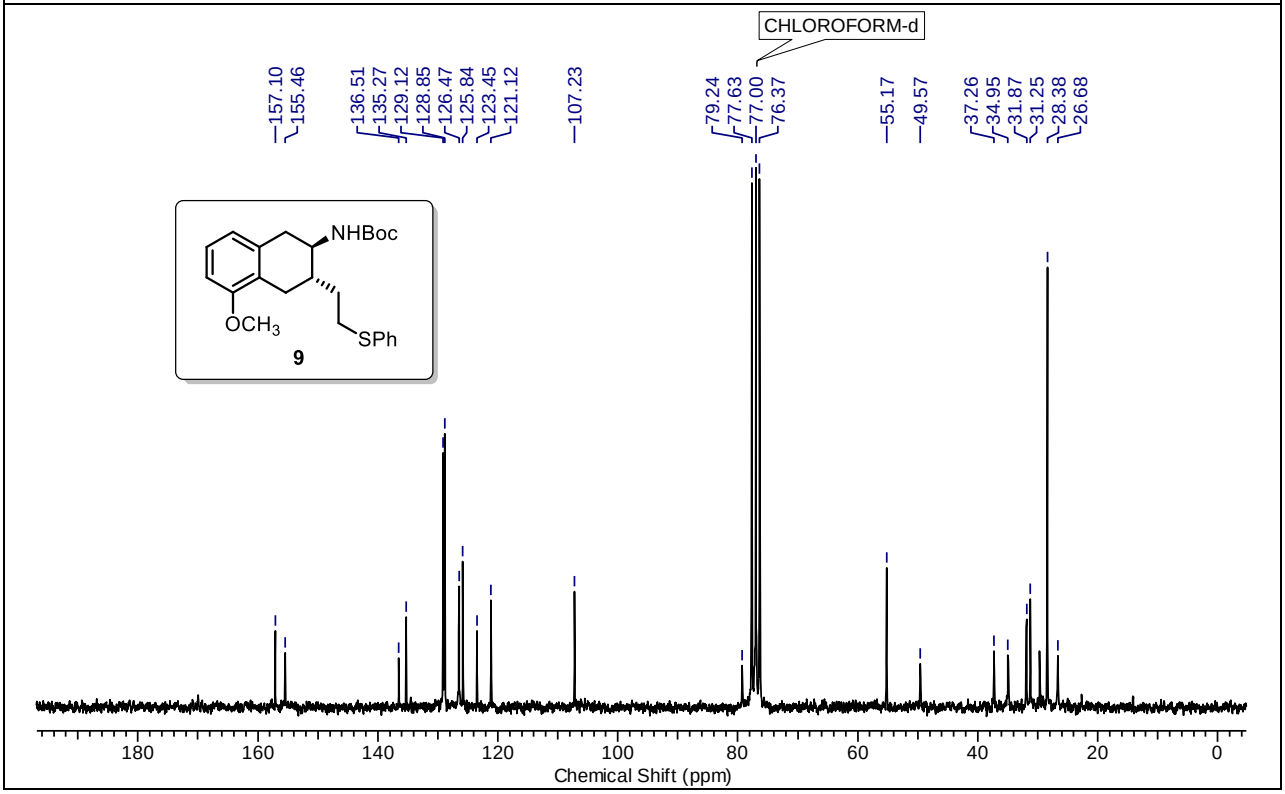
DEPT NMR spectrum of compound 8 ($CDCl_3$, 50 MHz)



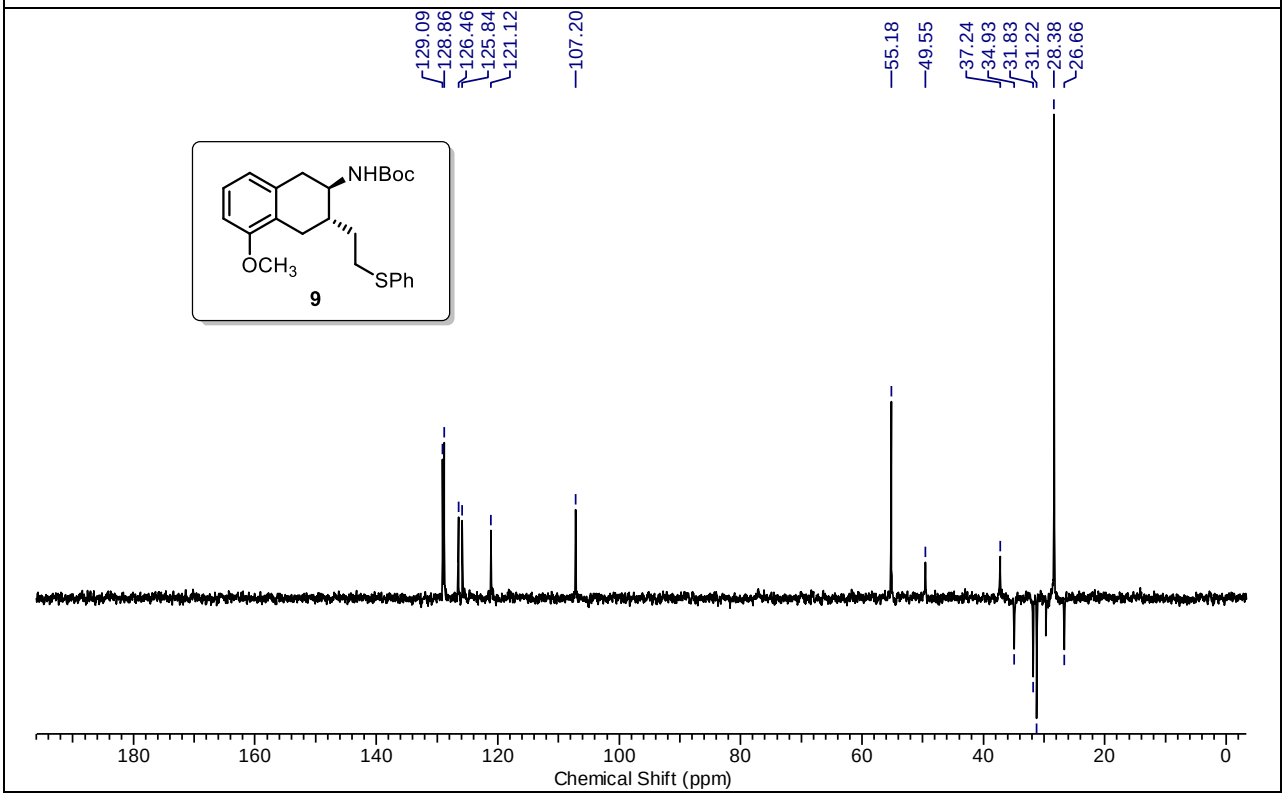
^{1}H-NMR spectrum of compound 9 ($CDCl_3$, 200 MHz)



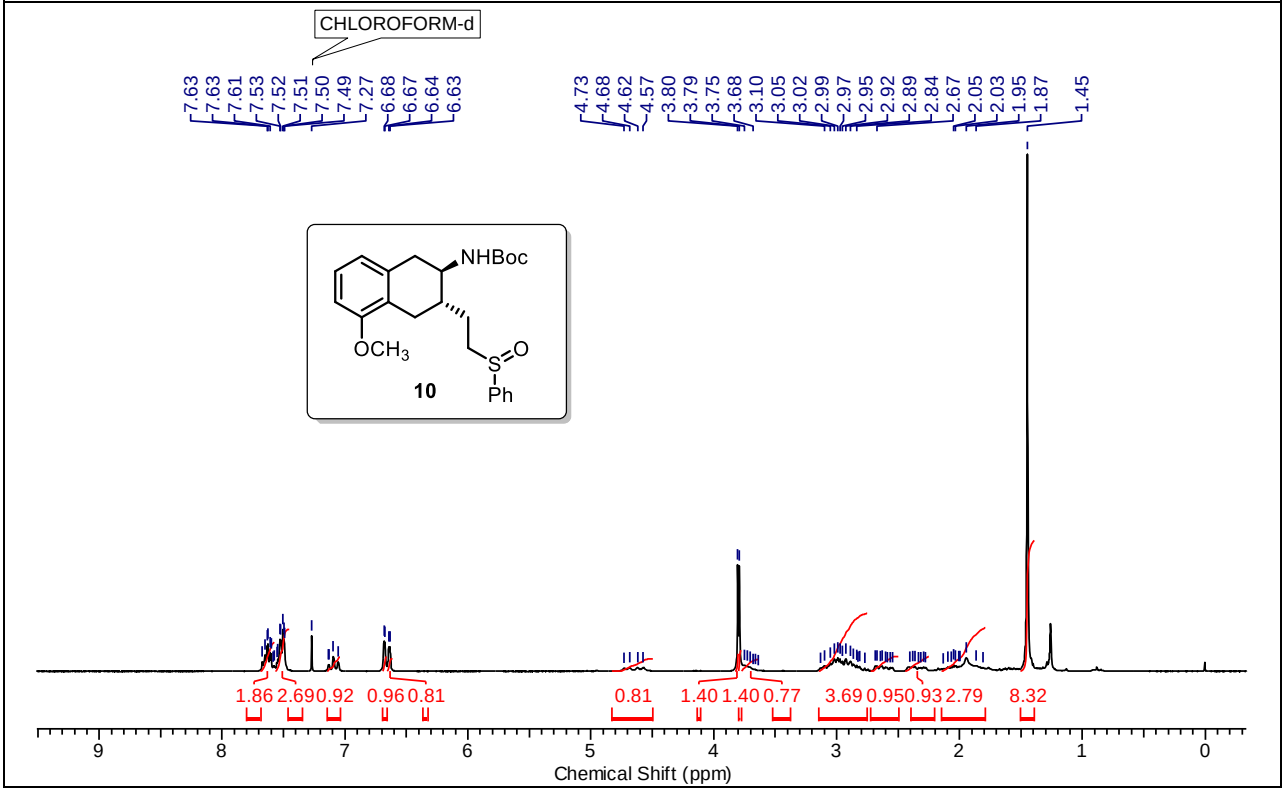
^{13}C-NMR spectrum of compound 9 ($CDCl_3$, 50 MHz)



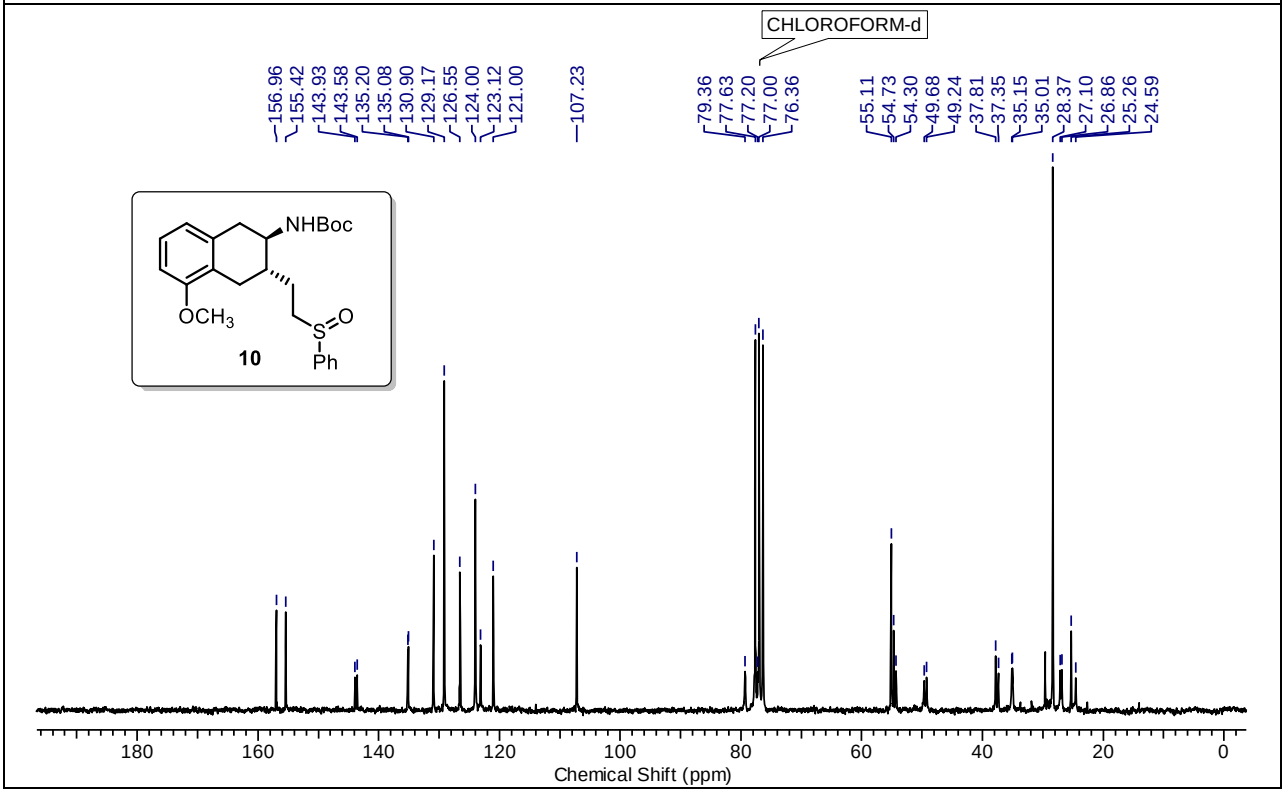
DEPT NMR spectrum of compound 9 ($CDCl_3$, 50 MHz)



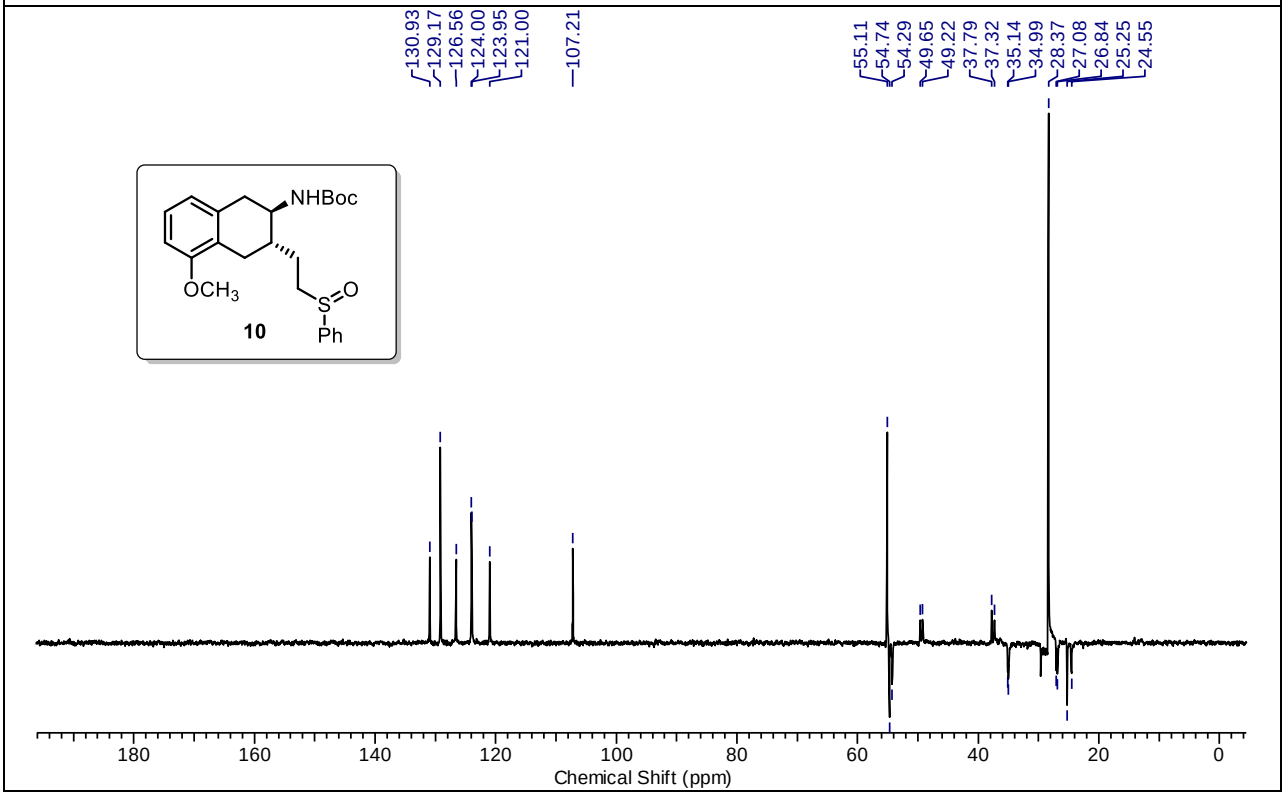
^{1}H-NMR spectrum of compound 10 ($CDCl_3$, 200 MHz)



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



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



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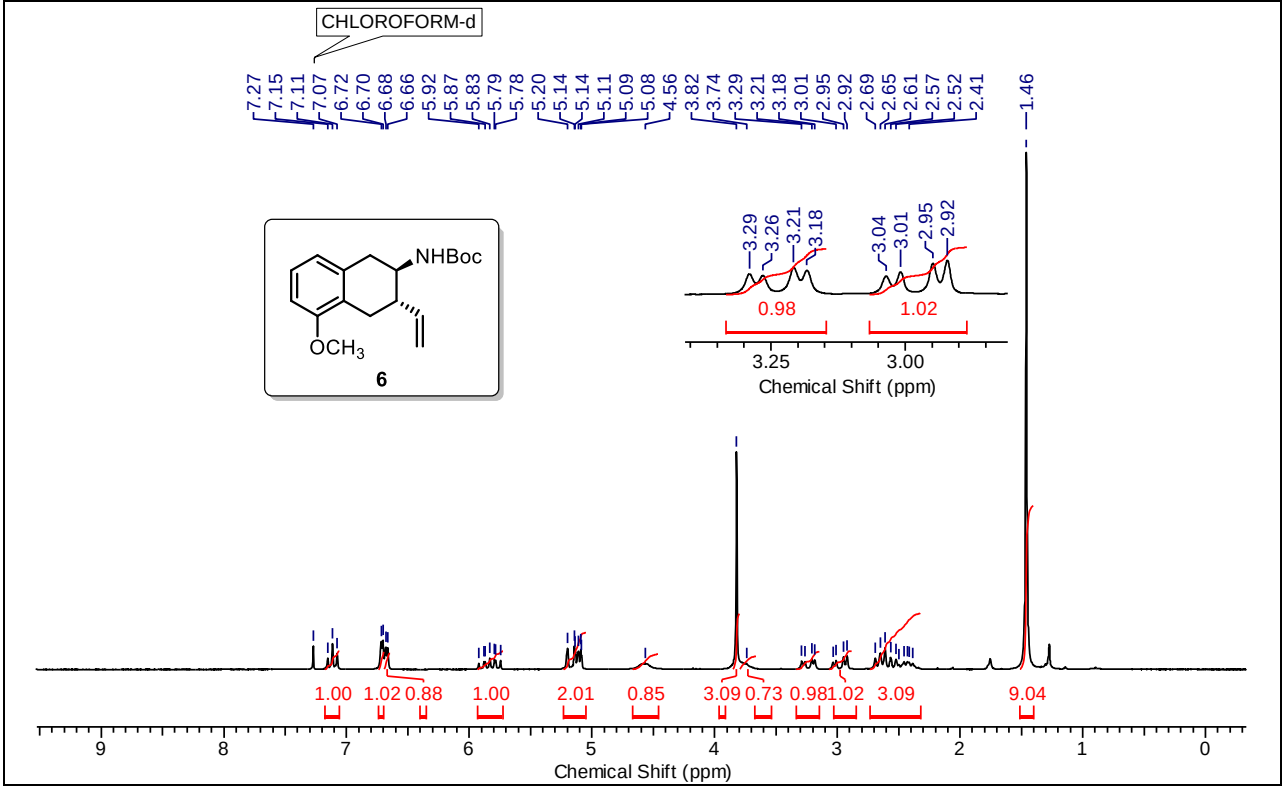

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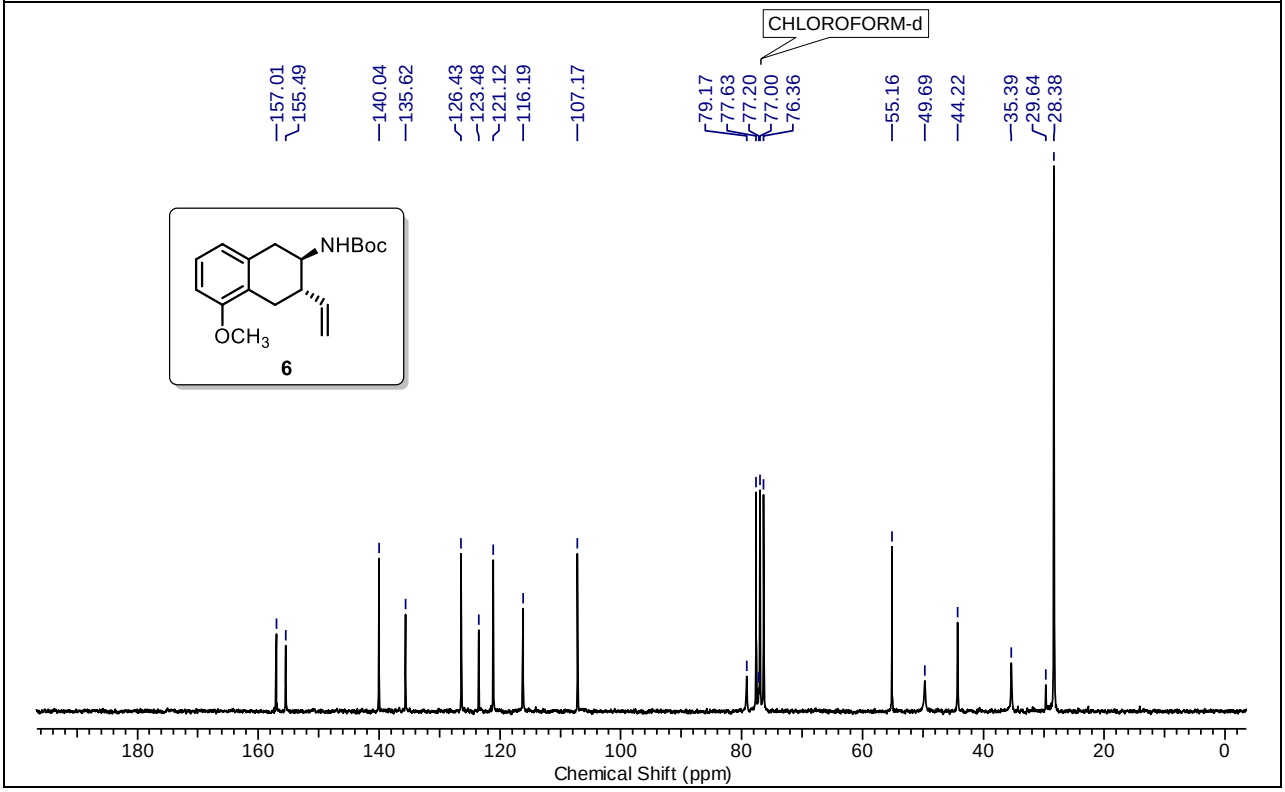

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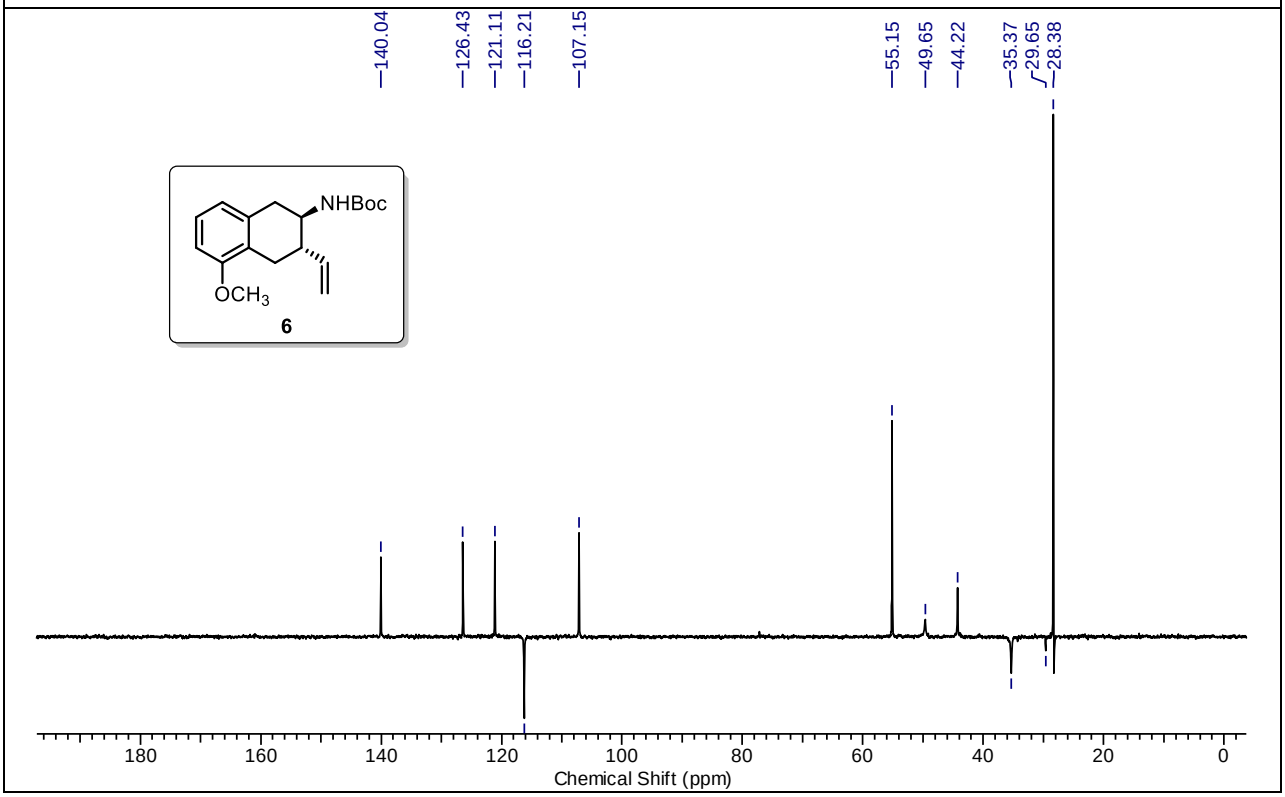

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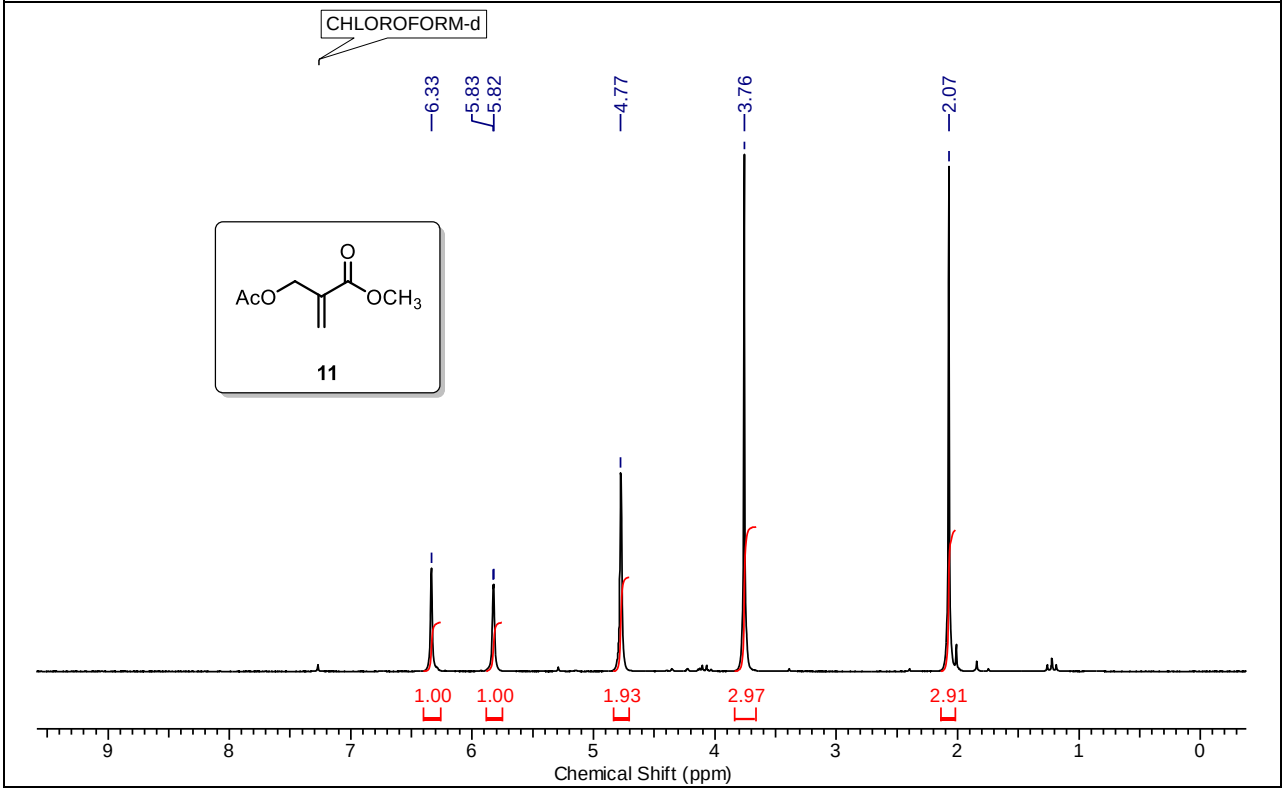

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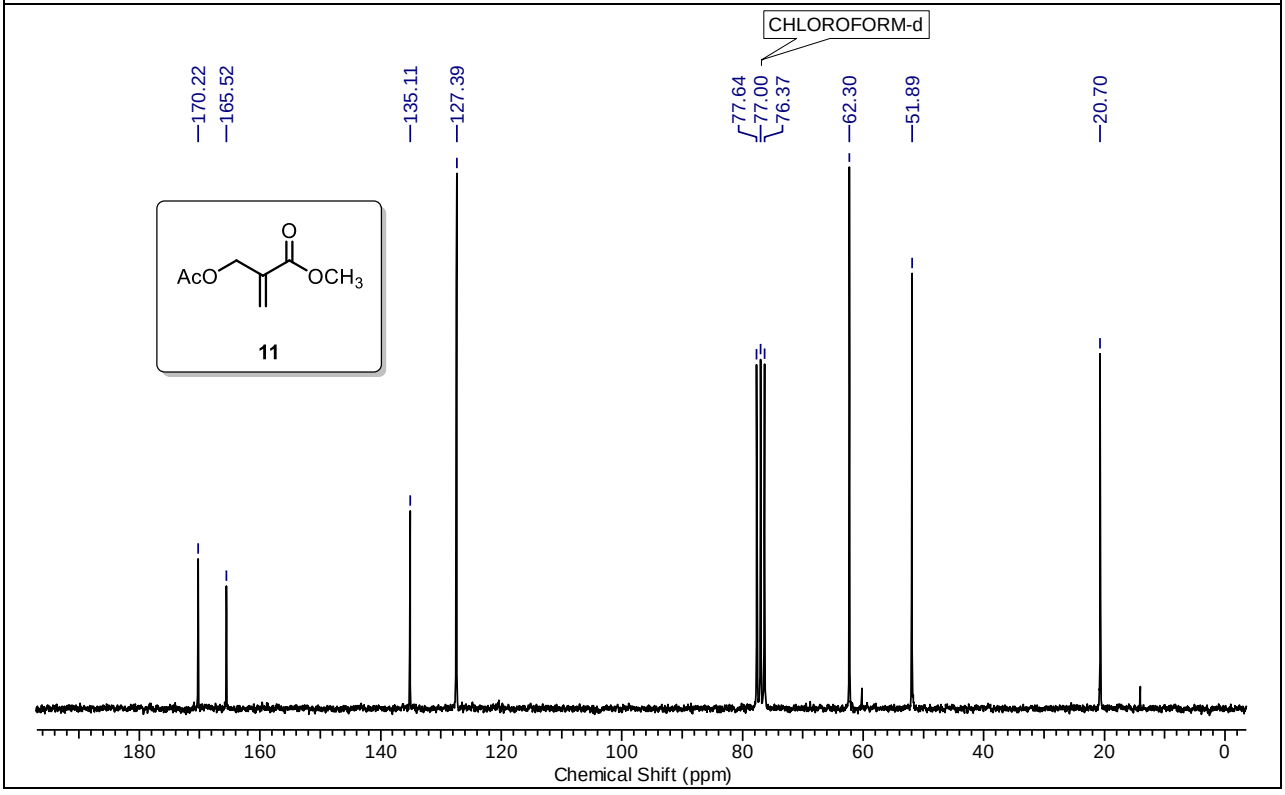
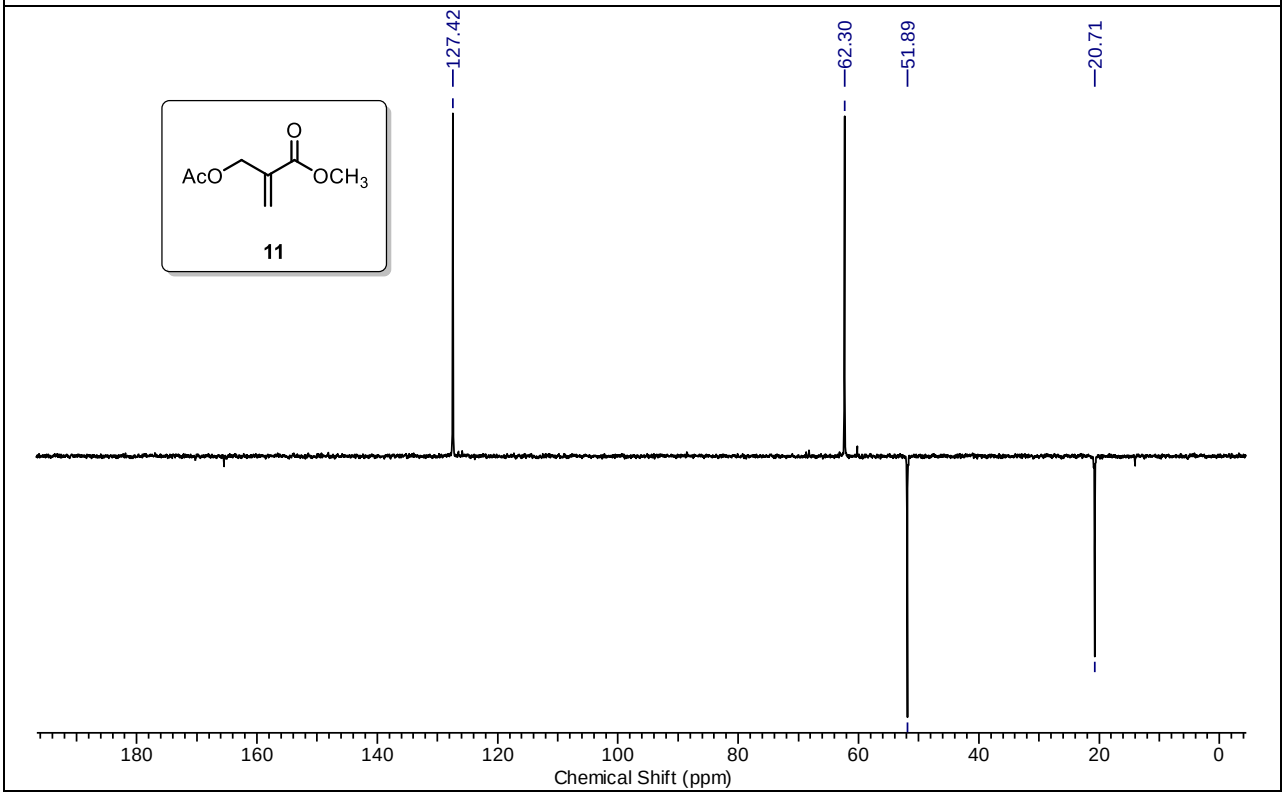


DEPT NMR spectrum of compound 11 ($CDCl_3$, 50 MHz)



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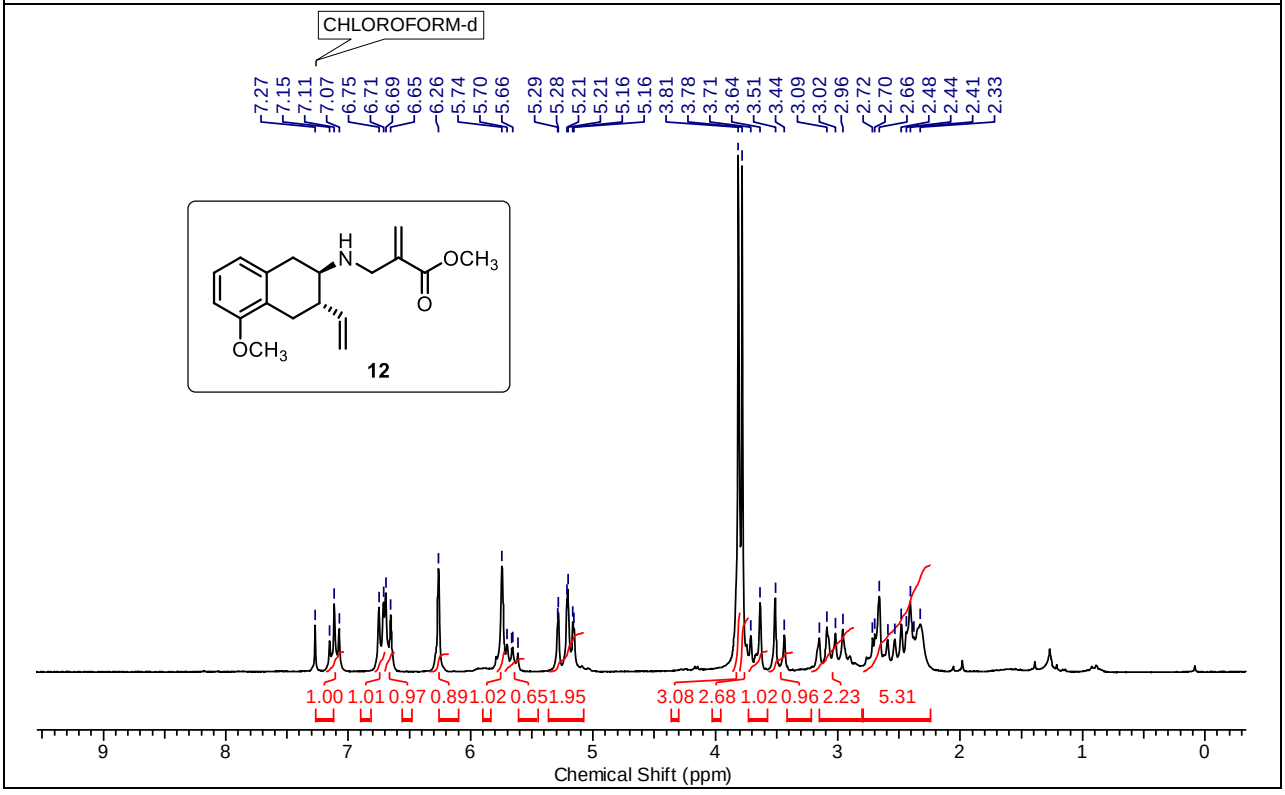

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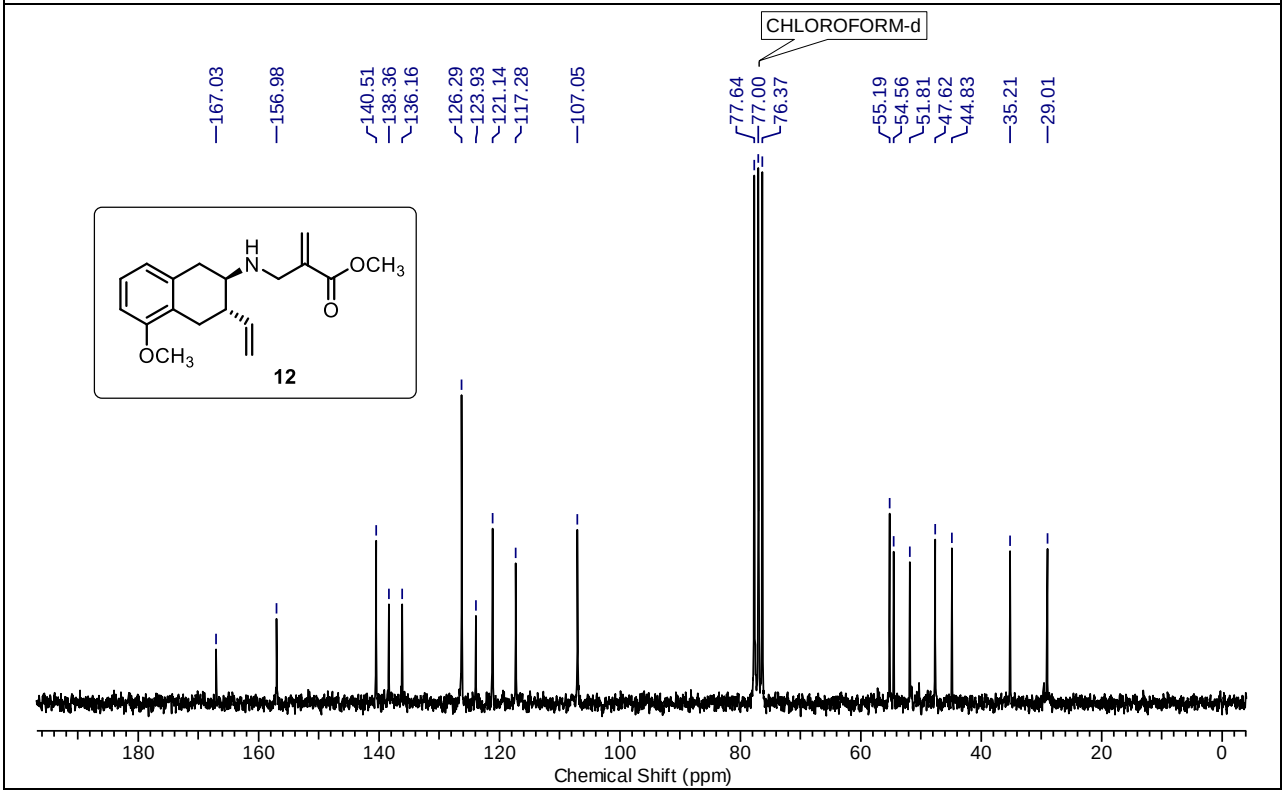

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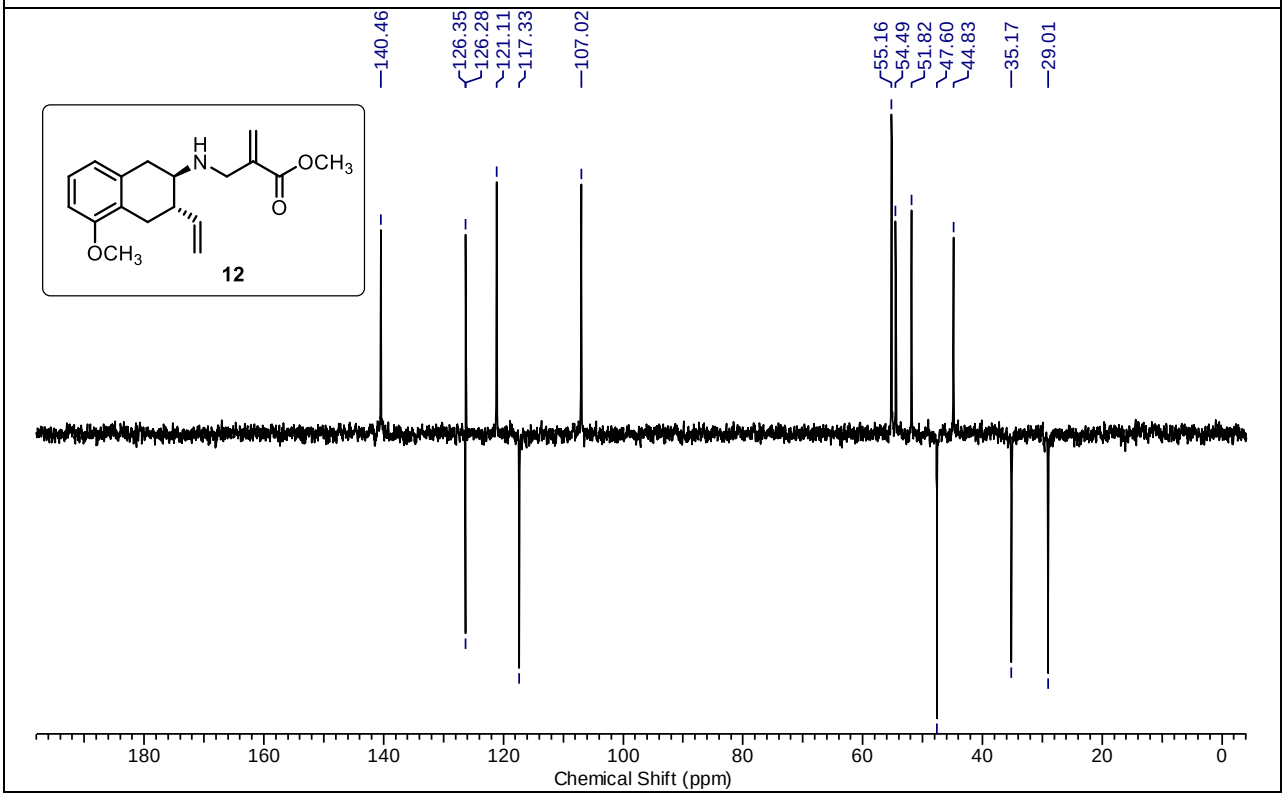

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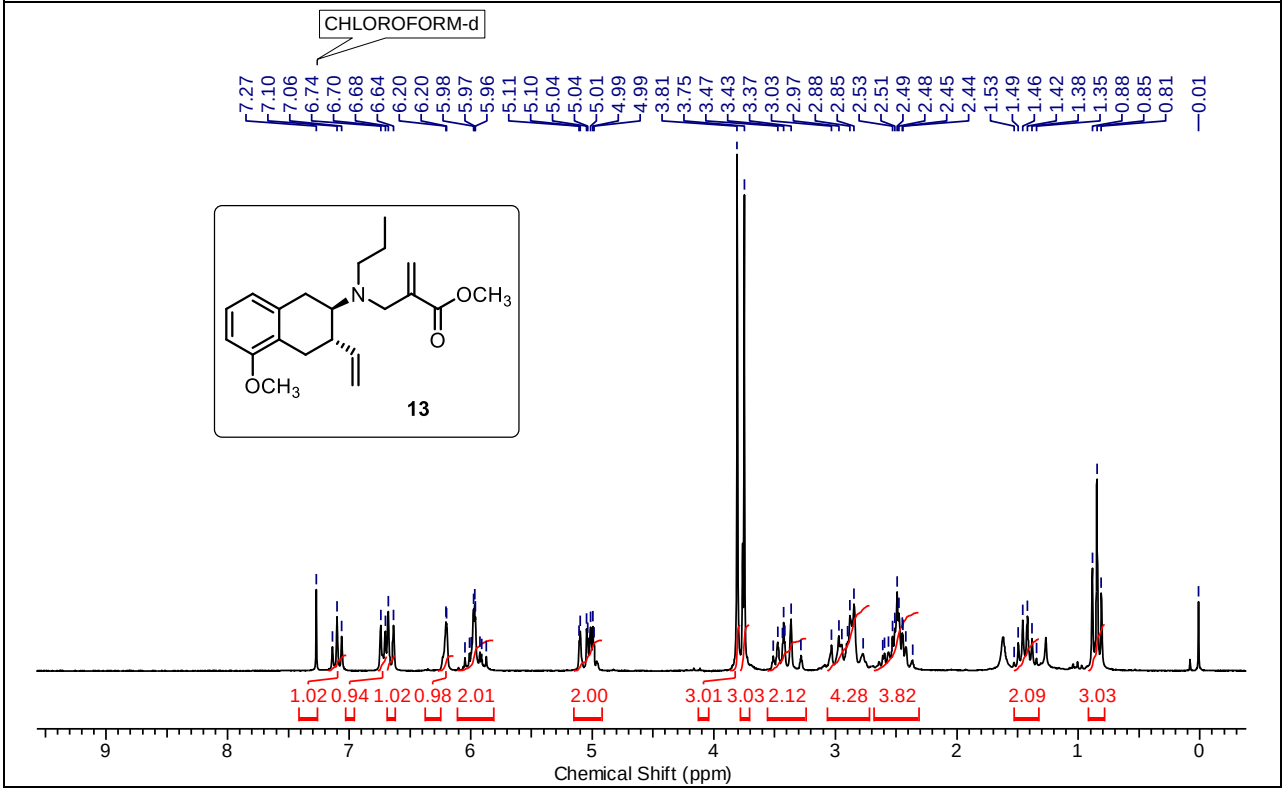

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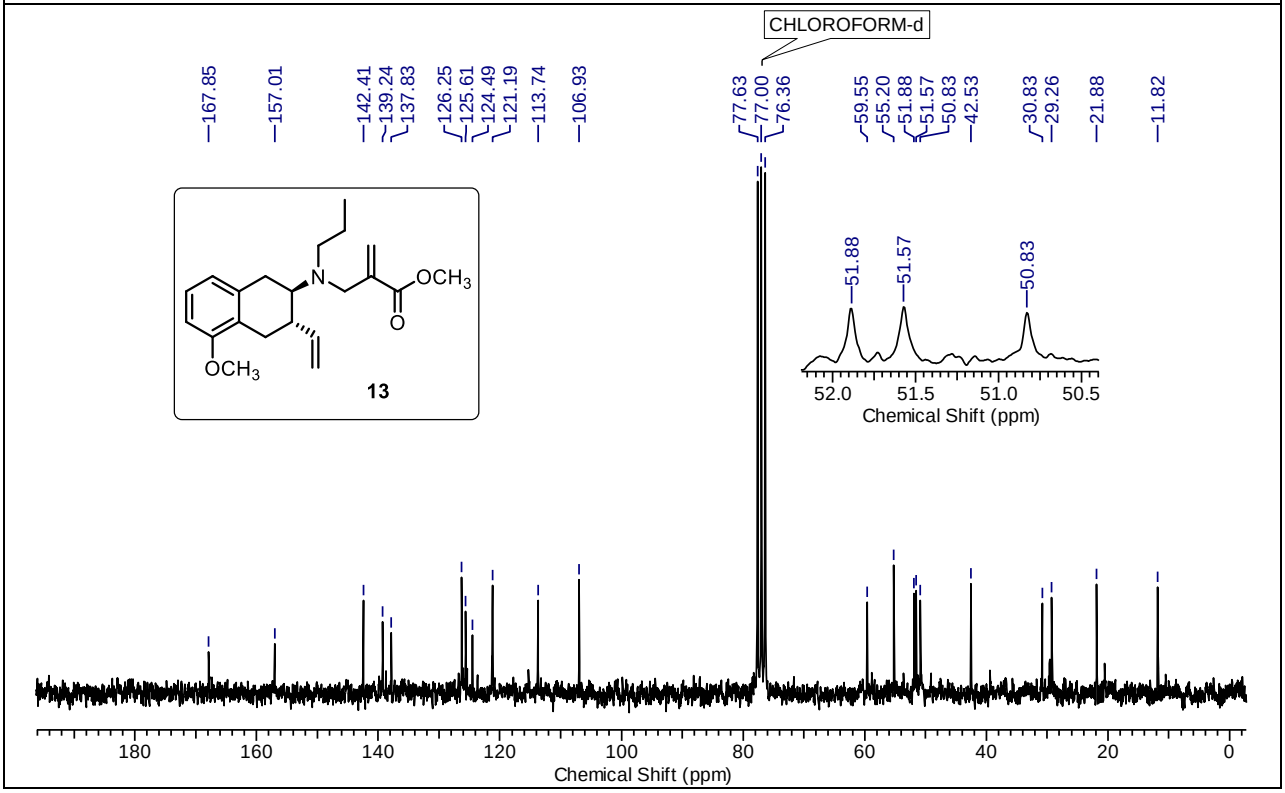
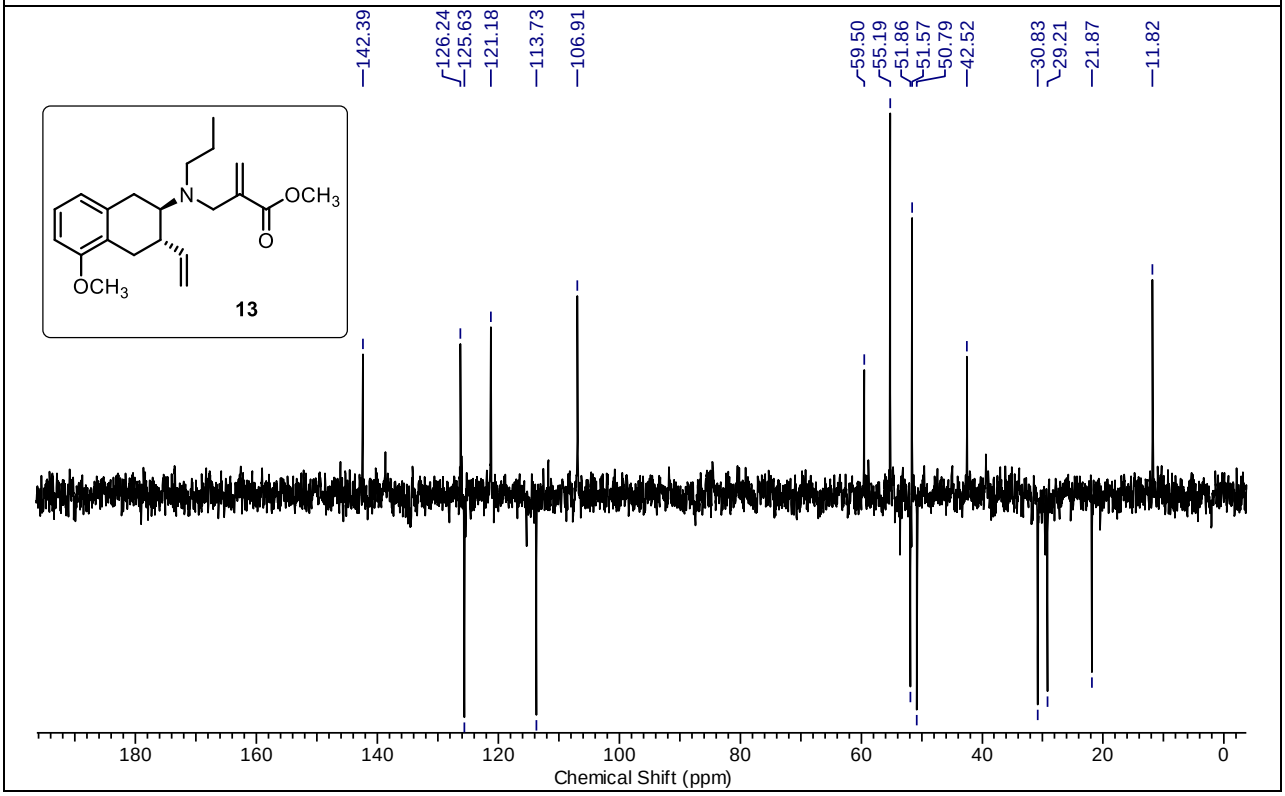
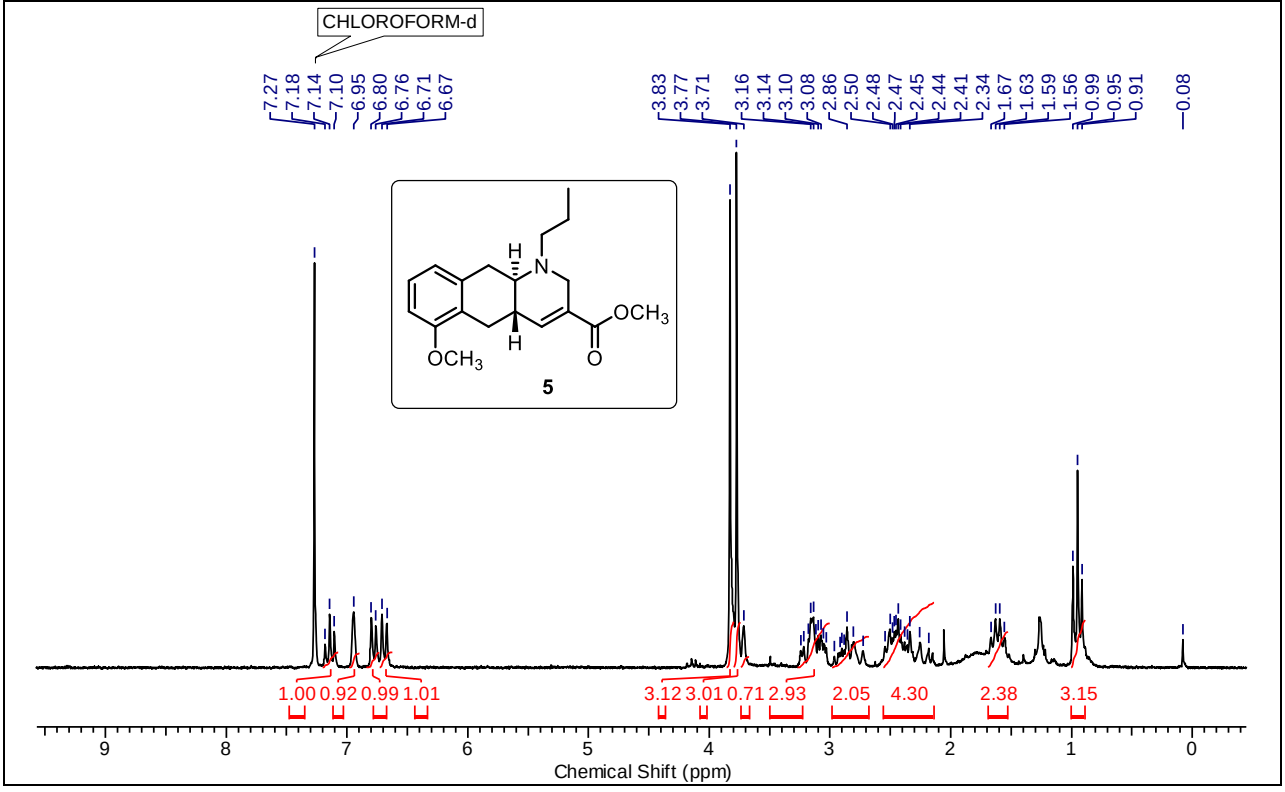


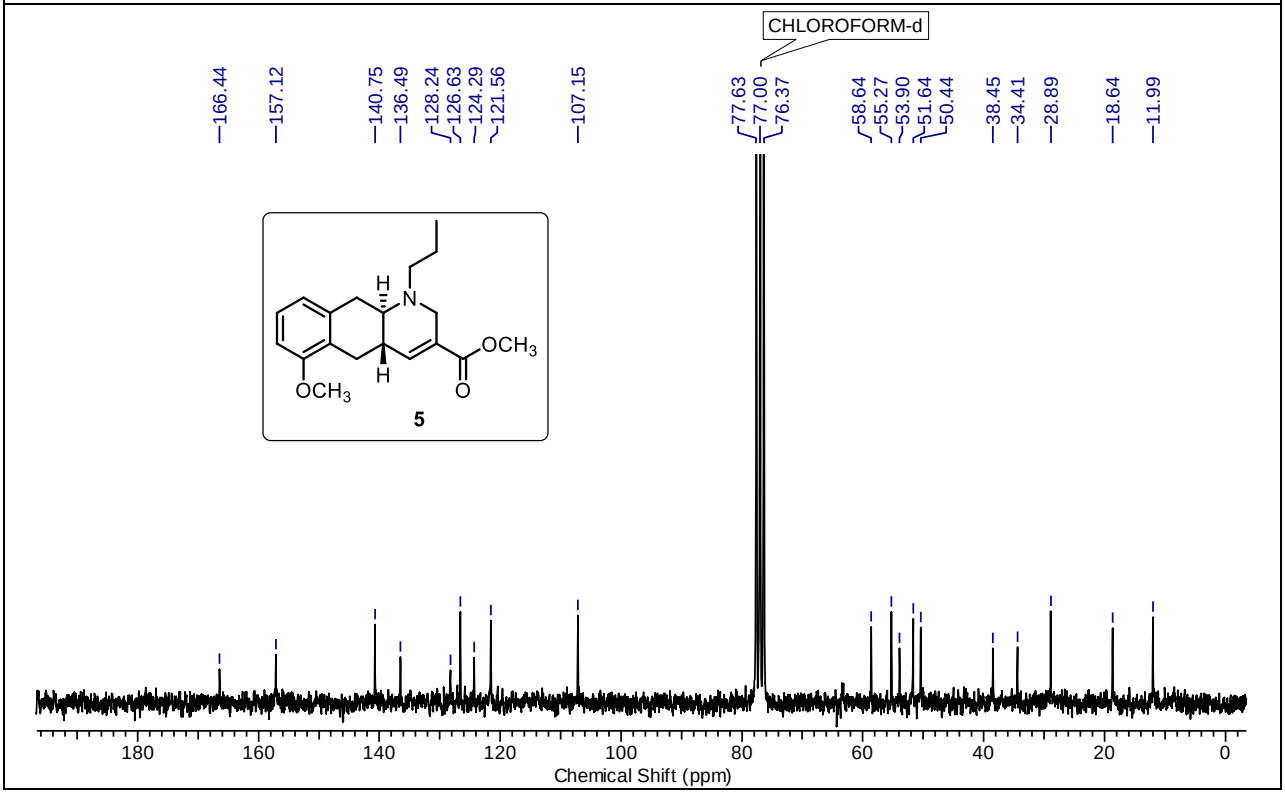
DEPT NMR spectrum of compound 13 ($CDCl_3$, 50 MHz)



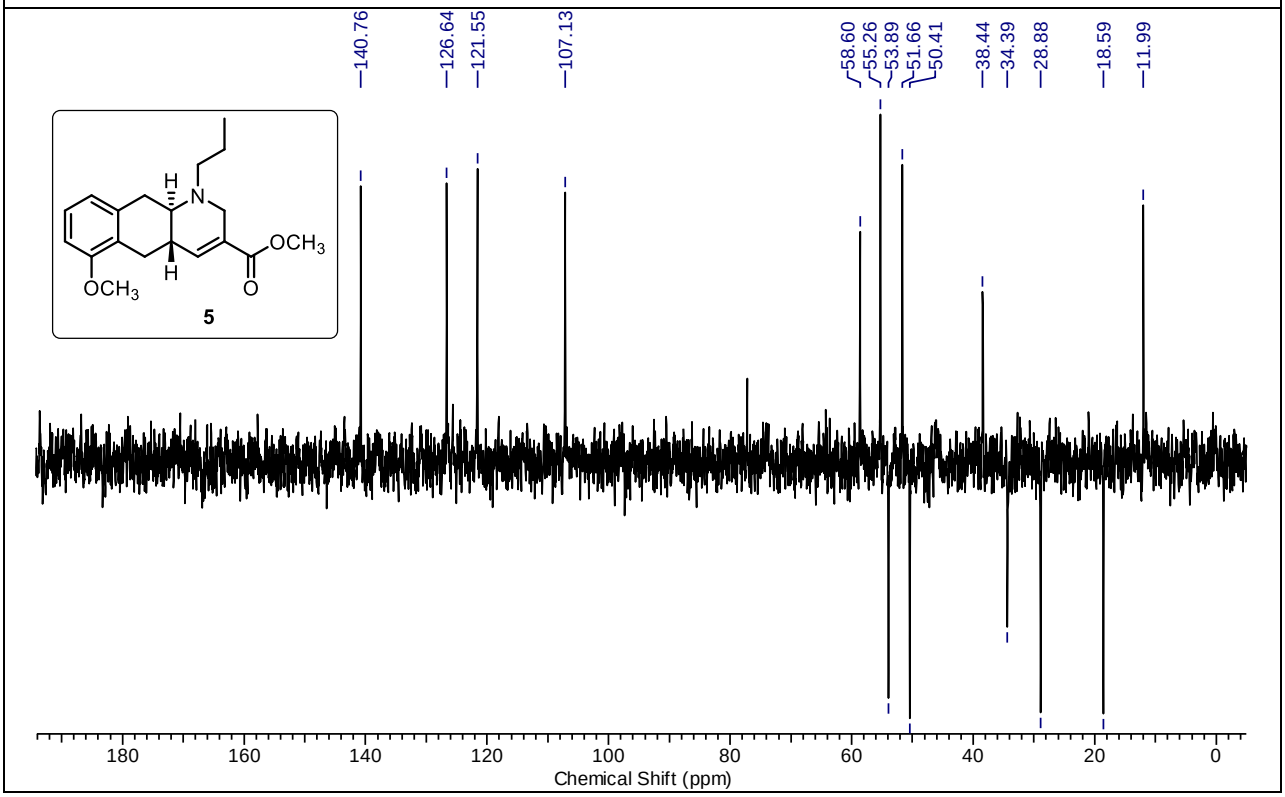
^{1}H-NMR spectrum of compound 5 ($CDCl_3$, 200 MHz)



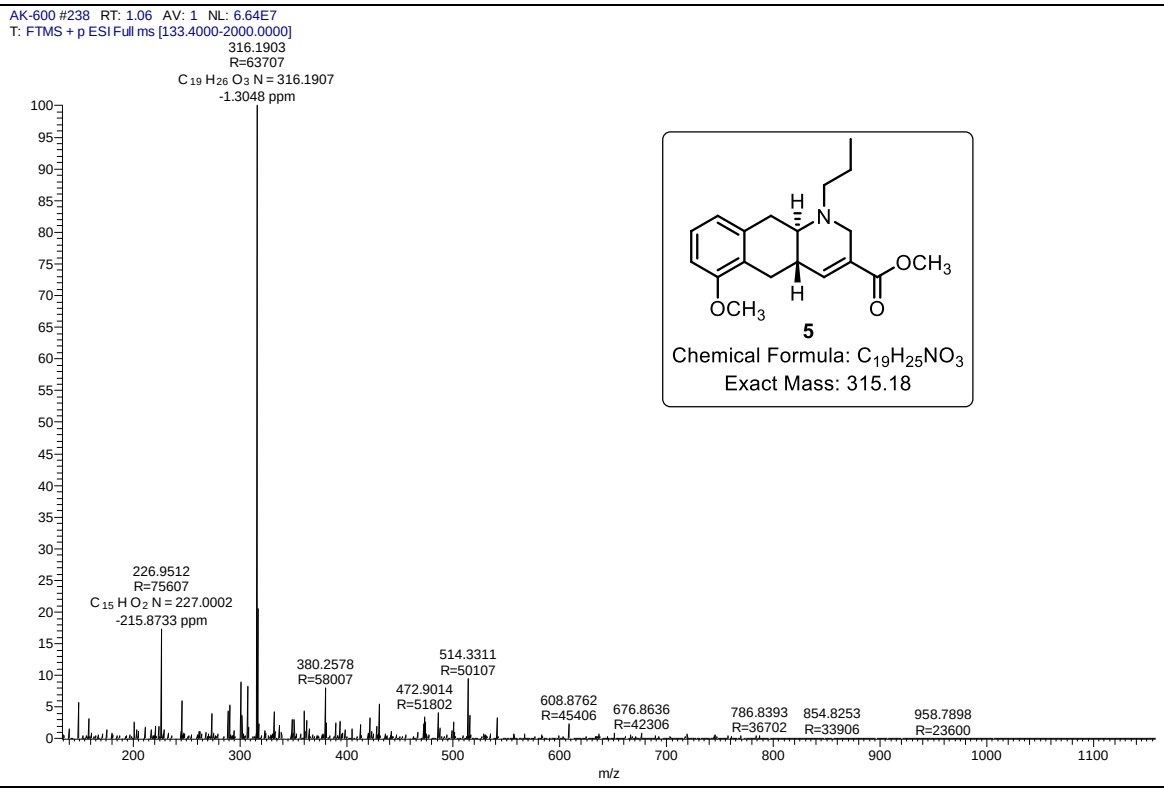
^{13}C-NMR spectrum of compound 5 ($CDCl_3$, 50 MHz)



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



HRMS spectrum of compound 5



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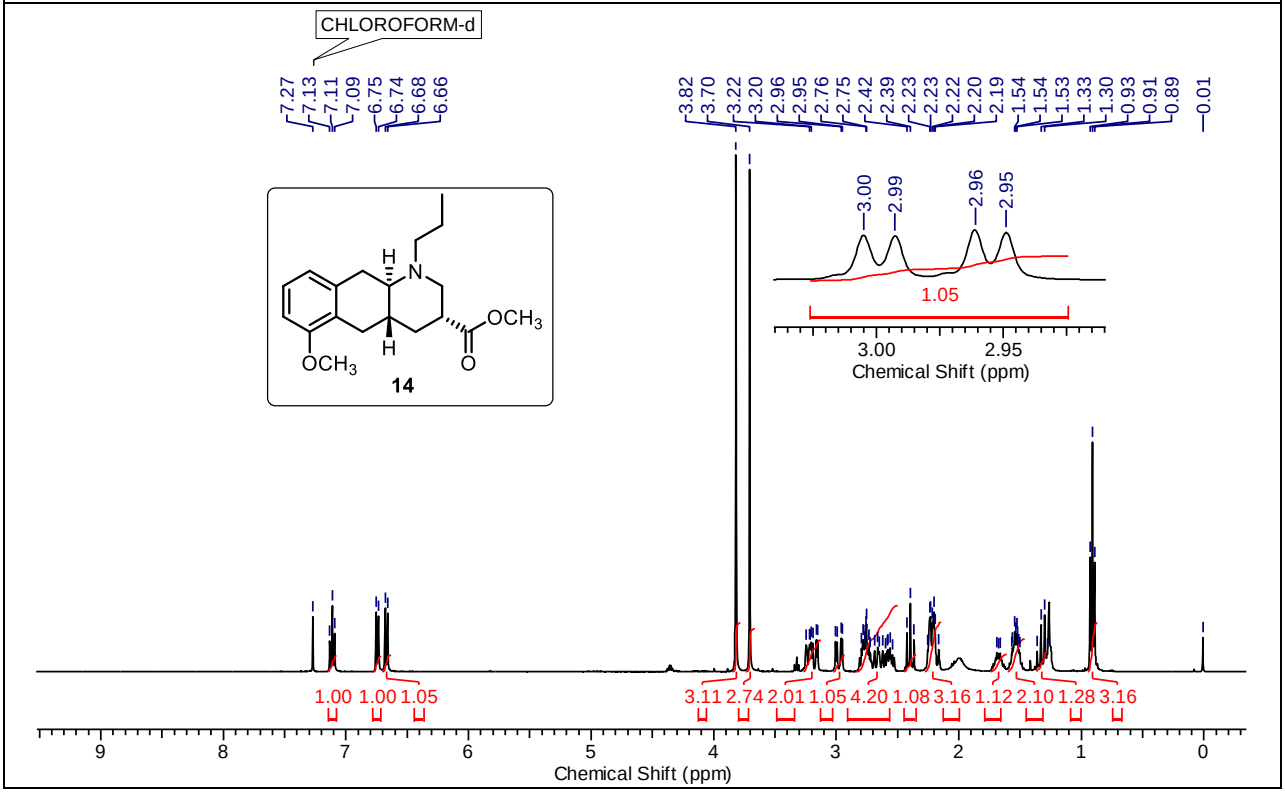

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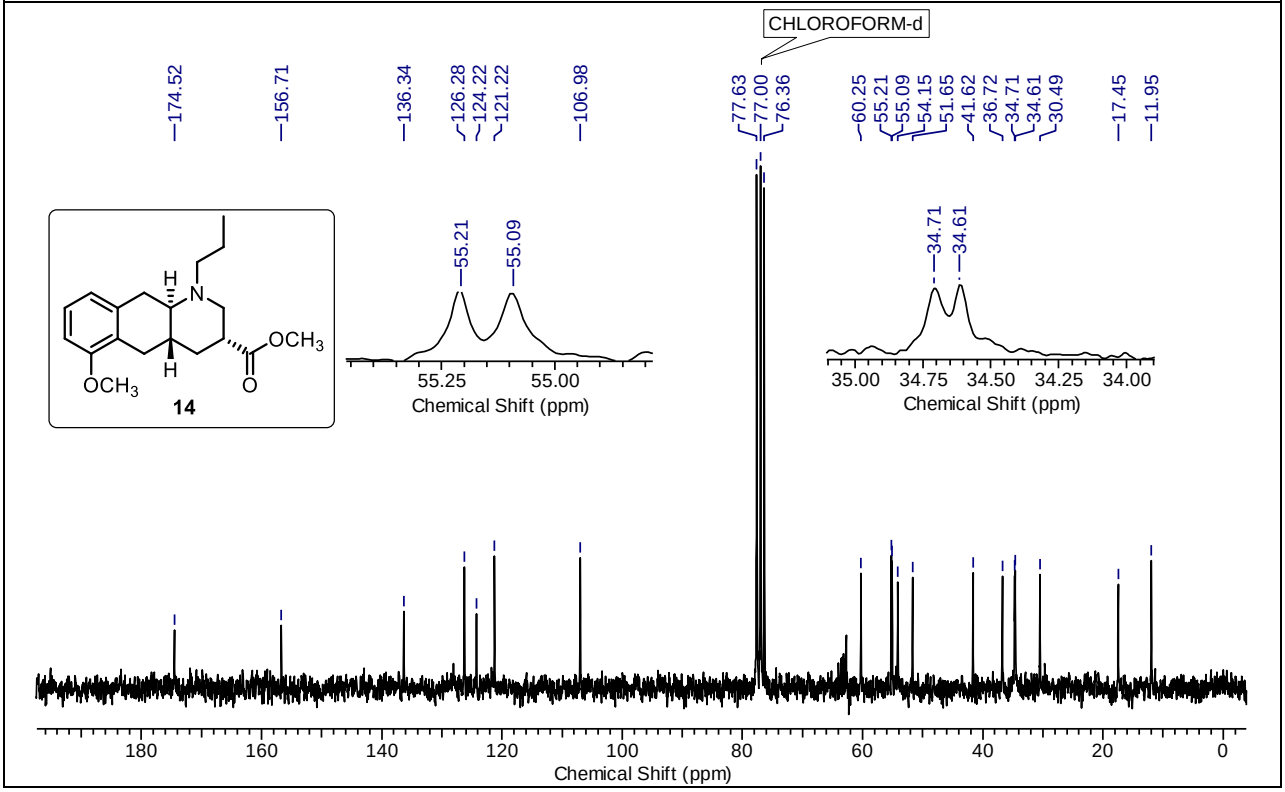
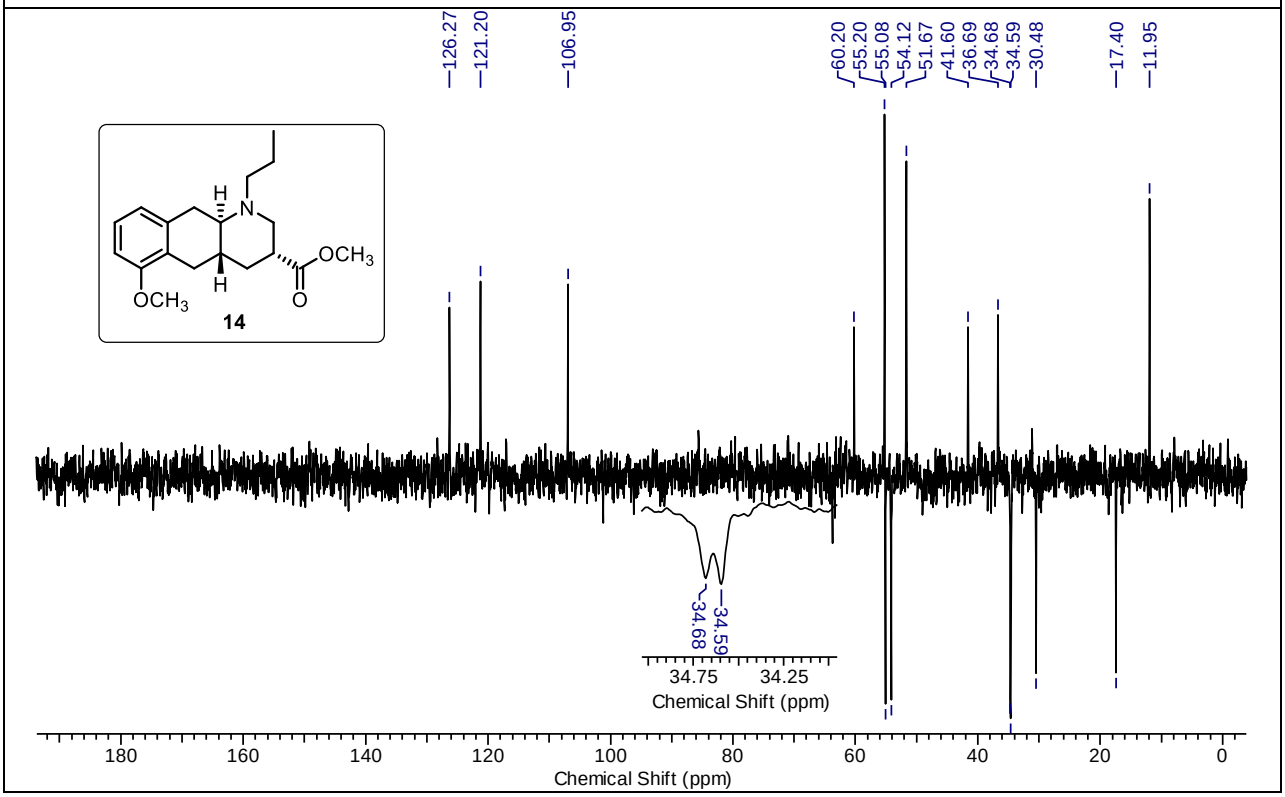


DEPT NMR spectrum of compound 14 ($CDCl_3$, 50 MHz)



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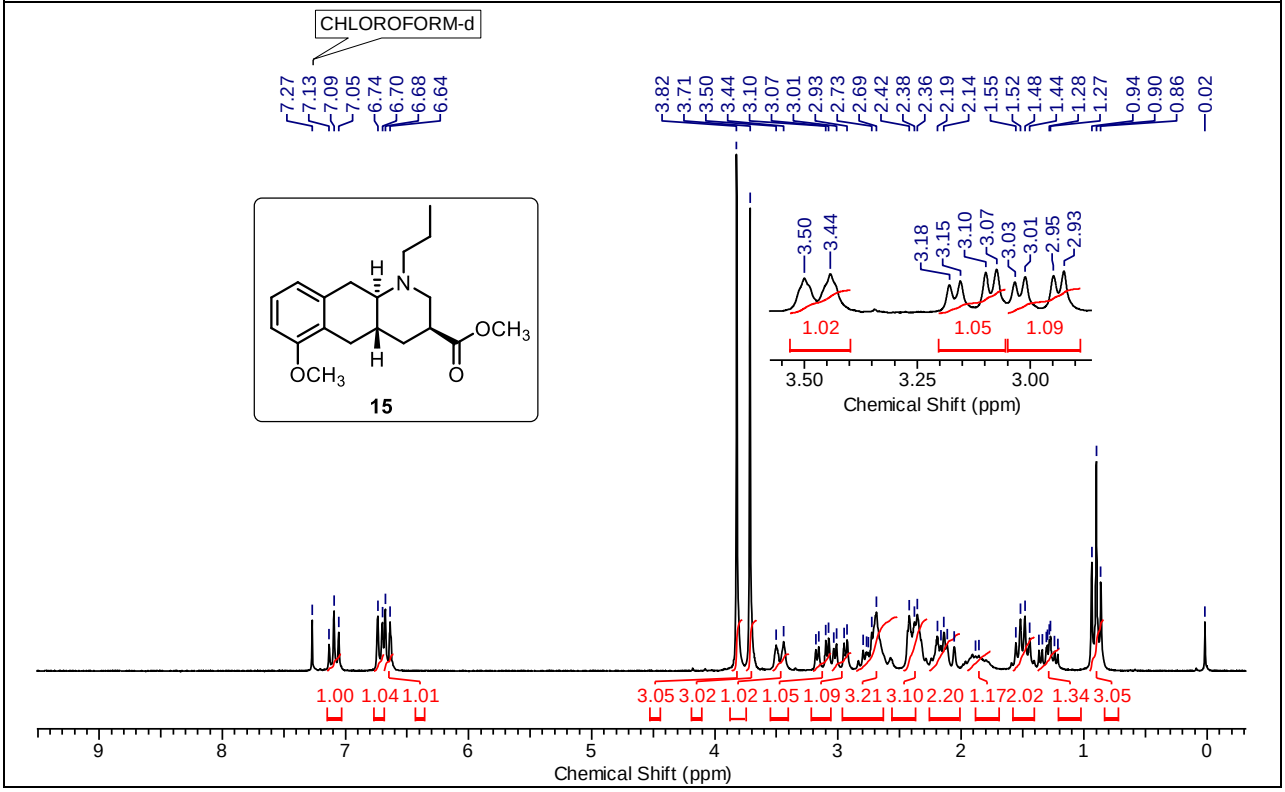

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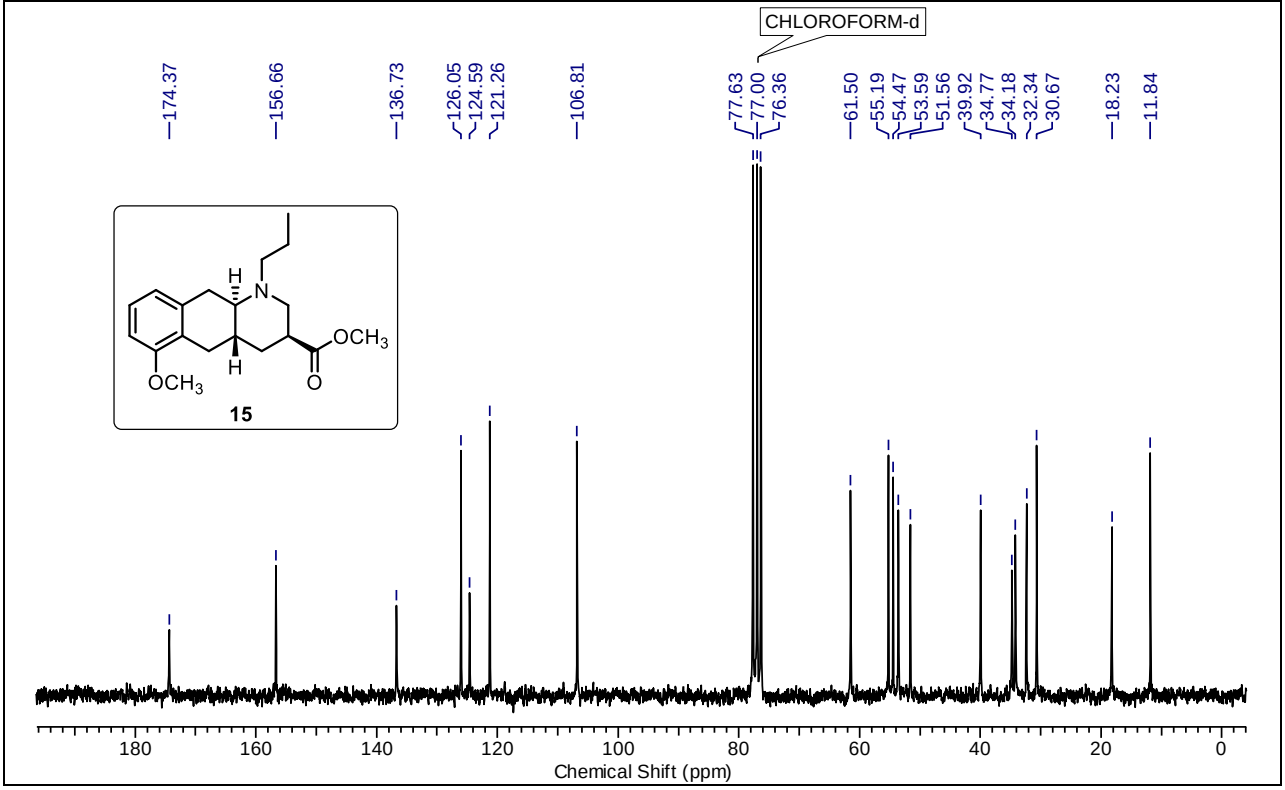

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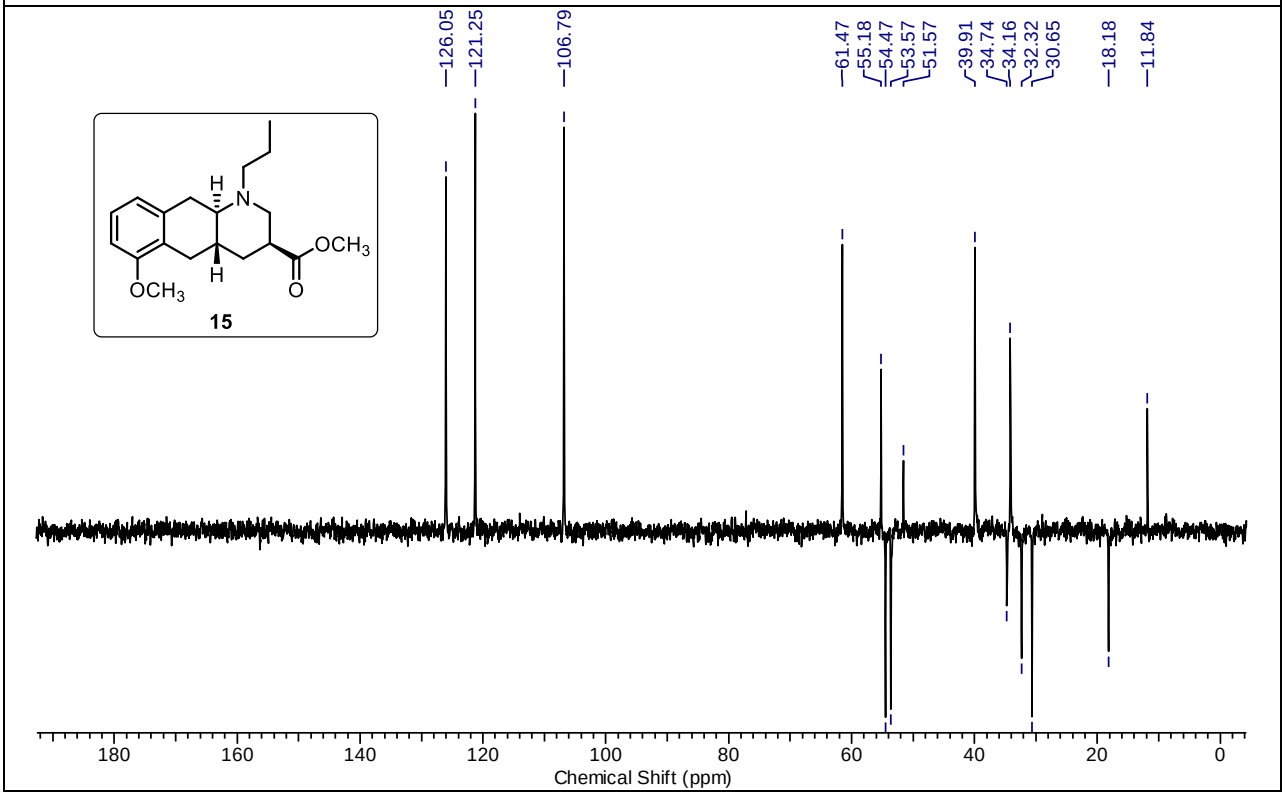

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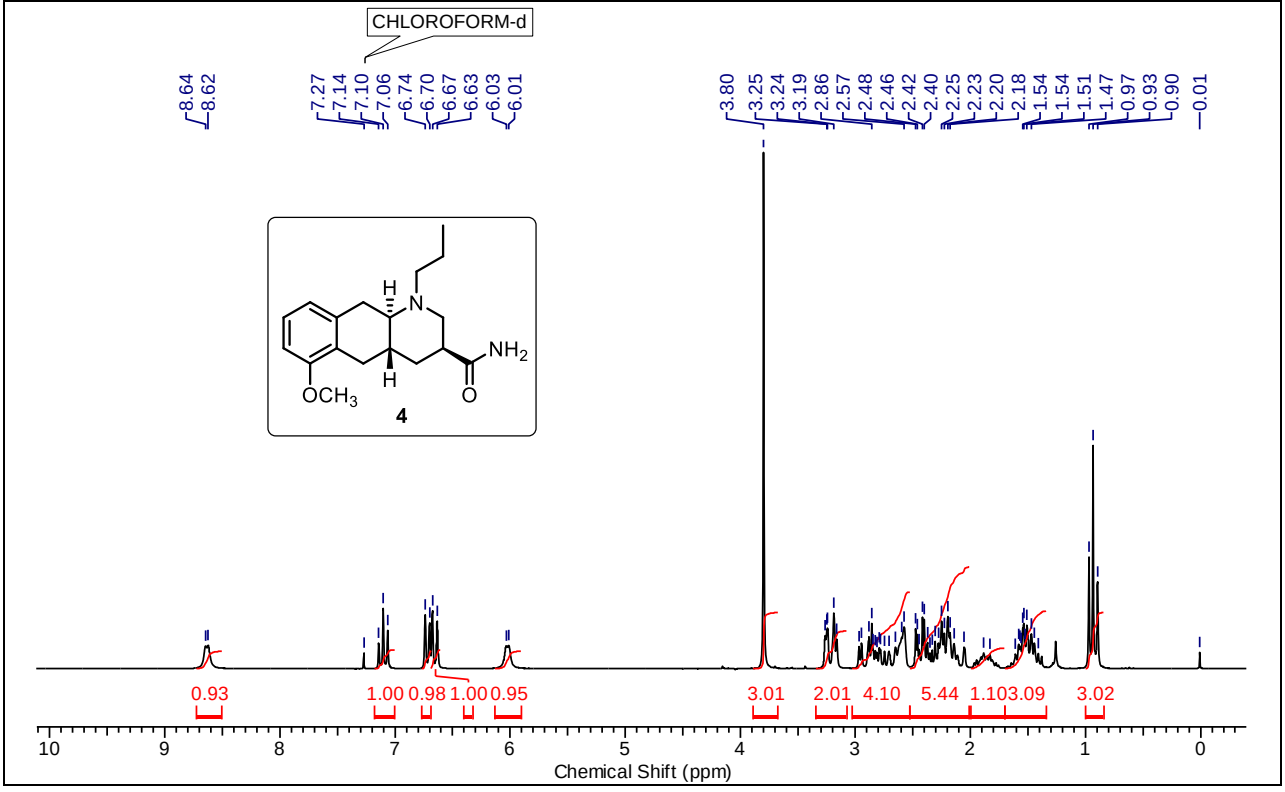

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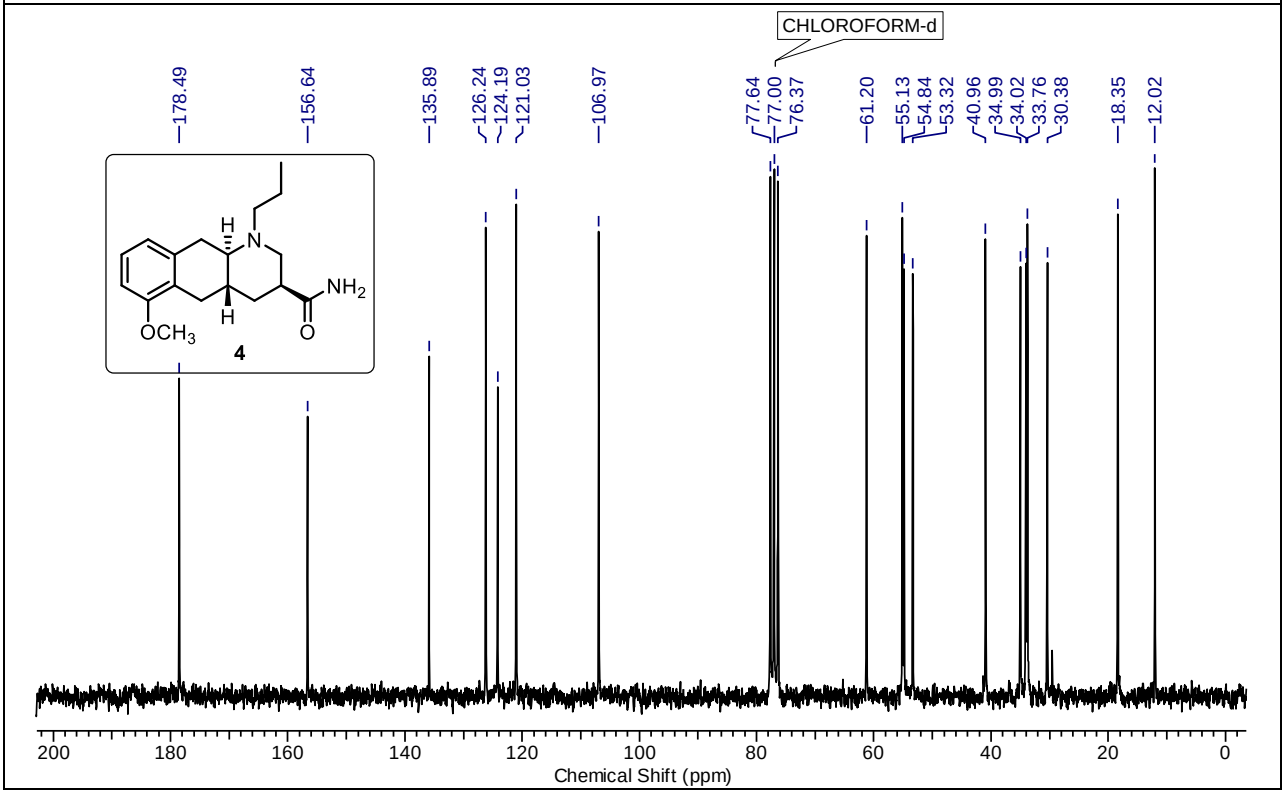
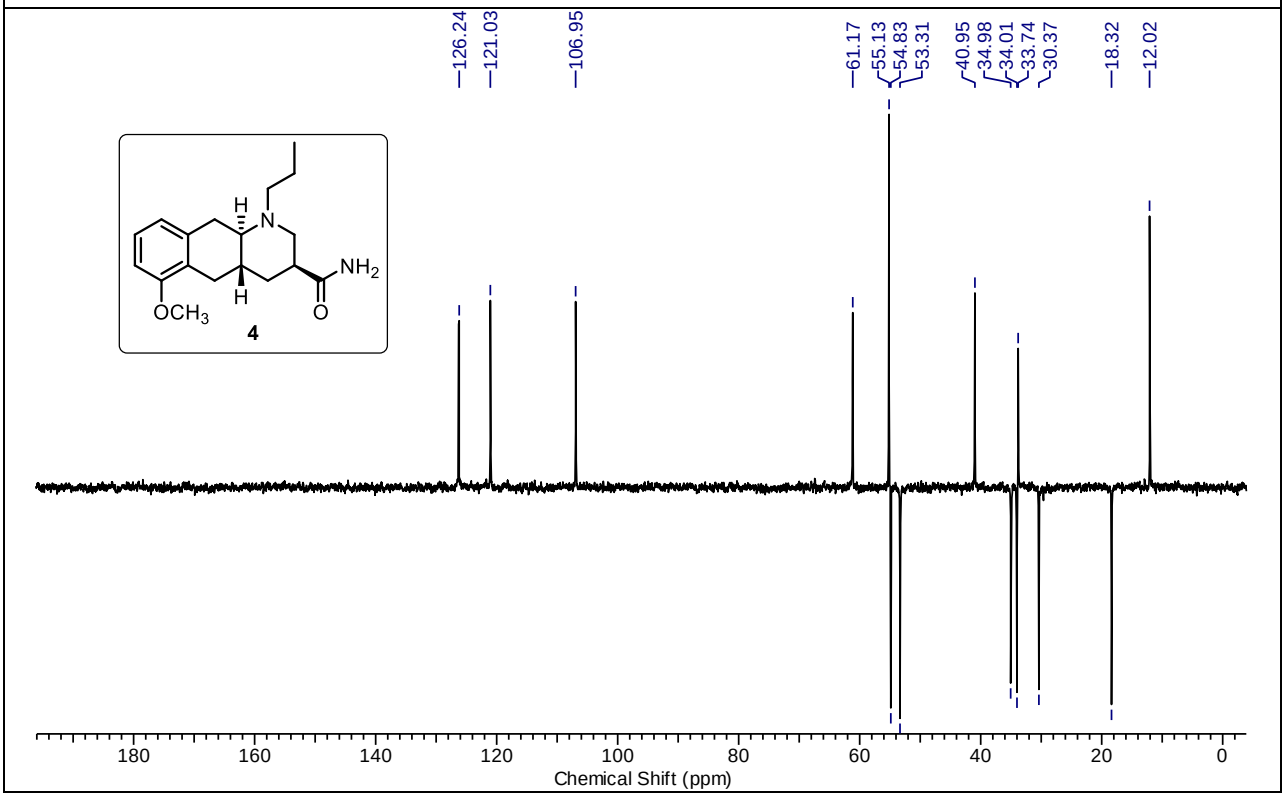


DEPT NMR spectrum of compound 4 ($CDCl_3$, 50 MHz)



1.3.6. References

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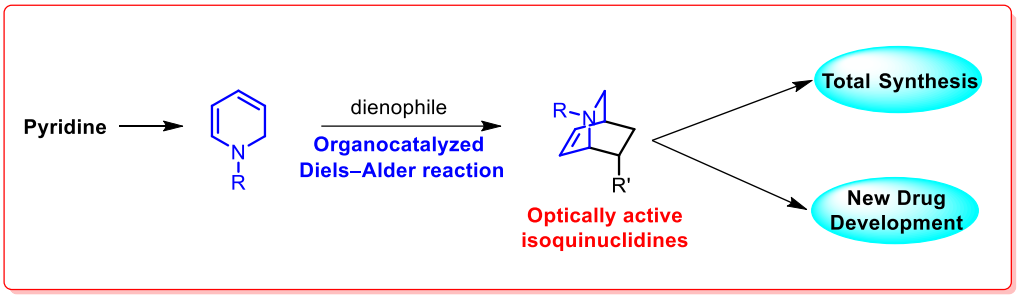
CHAPTER 2

Section 1

"Synthesis of Isoquinuclidine Skeleton Using Organocatalyzed Diels–Alder Reaction and its Application in Total Synthesis"



2.1.1. Introduction

The isoquinuclidine (2-azabicyclo[2.2.2]octane) skeleton is widely found in natural products such as ibogaine (**1**), dioscorine (**2**), mearsine (**3**) and cannivonine (**4**) (representative examples of each class of alkaloids) which have a large spectrum of interesting pharmacological properties (**Figure 1**).[1] Ibogaine (**1**) which was isolated more than 100 years ago, is an alkaloid found in leaves, stem, root, and root-bark of the African shrub *Tabernanthe iboga*. It was recently indicated that ibogaine could be used as an anti-addictive and anti-craving agent due to its reducing properties of cravings for alcohol and other drugs. Dioscorine (**2**) has been shown to be a central nervous system depressant and a modulator of the nicotinic acetylcholine receptor. Biological properties of mearsine (**3**) are not explored to that extent and little has been reported in the literature whereas New Brunswick cranberry alkaloids such as cannivonine (**4**) have been used as a folk medicine for the treatment of tumor (chemotherapy).

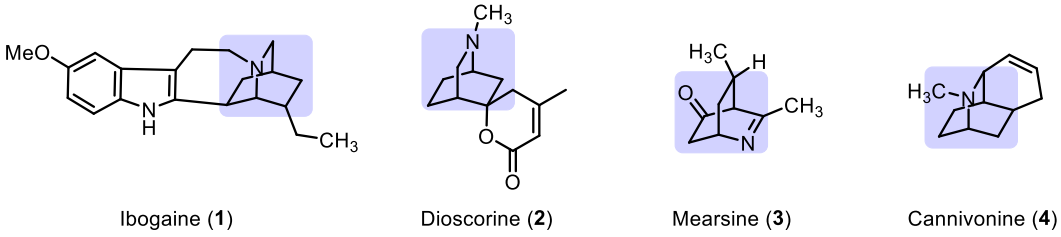
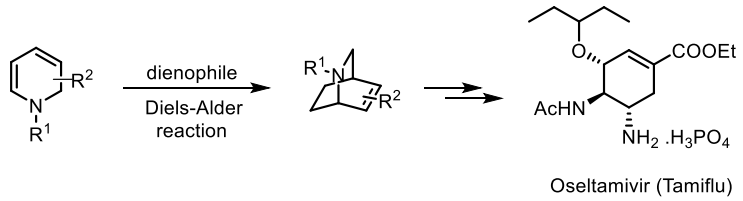


Figure 1: Representative natural products consisting of an isoquinuclidine skeleton.

It was also recently shown that isoquinuclidines can be used as synthetic intermediates for the synthesis of oseltamivir phosphate (Tamiflu) which is an important anti-influenza drug. Elegant methods for the synthesis of chiral isoquinuclidines have been developed, especially since Fukuyama's synthesis of oseltamivir using organocatalyzed Diels–Alder reaction (**Scheme 1)**.[2]



Scheme 1: Fukuyama's Synthesis of Oseltamivir

Methods for the enantioselective synthesis of isoquinuclidines can be divided into following two types based on the catalytic system used such as-

Enantioselective synthesis of isoquinuclidines using (a) organocatalysis and (b) organometallic catalysts.

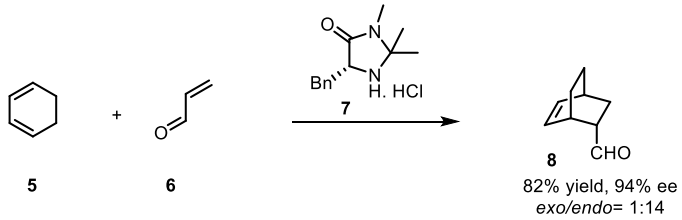
As part of the synthetic interest of this group, a brief review of the enantioselective synthesis of isoquinuclidines using organocatalysis is presented in this section.

2.1.2. Literature

2.1.2.1. Synthesis of isoquinuclidine skeleton employing Organocatalyzed Diels–Alder reactions

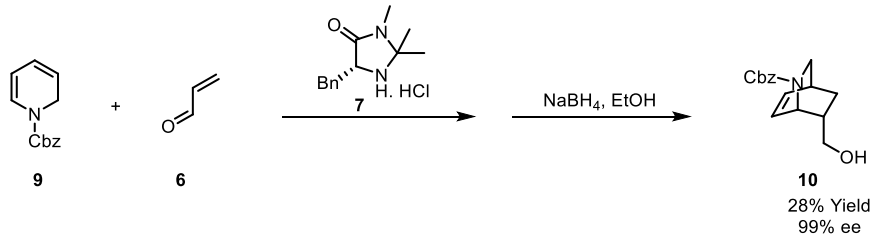
MacMillan's catalyst[3]

In the year 2000, MacMillan and co-workers reported for the first time that the chiral amines could be used as an organocatalyst for the enantioselective Diels–Alder reaction.[3] High enantioselectivity (94%) and good yield (82%) was observed for the Diels–Alder reaction of cyclohexadiene **5** with acrolein **6** using organocatalyst **7** (**Scheme 2**). Furthermore, they have developed the first highly enantioselective Diels–Alder reaction and demonstrated its general applications with various dienes and dienophiles.



Scheme 2: MacMillan's First Enantioselective Diels–Alder Reaction using Organocatalyst

Fukuyama and co-workers in 2007 reported the first example of the enantioselective synthesis of isoquinuclidine employing MacMillan's catalyst for the total synthesis of oseltamivir (Tamiflu).[2] The modest yield (28%) and high enantioselectivity (99% ee) of the chiral isoquinuclidine skeleton **10** were achieved using asymmetric Diels–Alder reaction of *N*-Cbz dihydropyridine **9** with acrolein **6** employing MacMillan's catalyst **7** (**Scheme 3**).[2b]

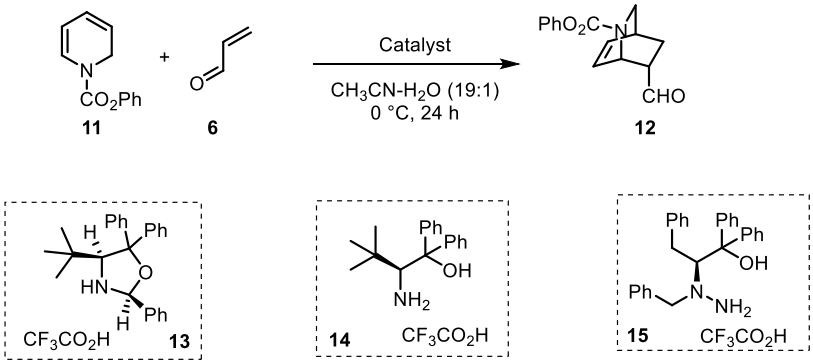


Scheme 3: Fukuyama's Synthesis of Isoquinuclidine using MacMillan's Organocatalyst

Nakano's catalyst[4]

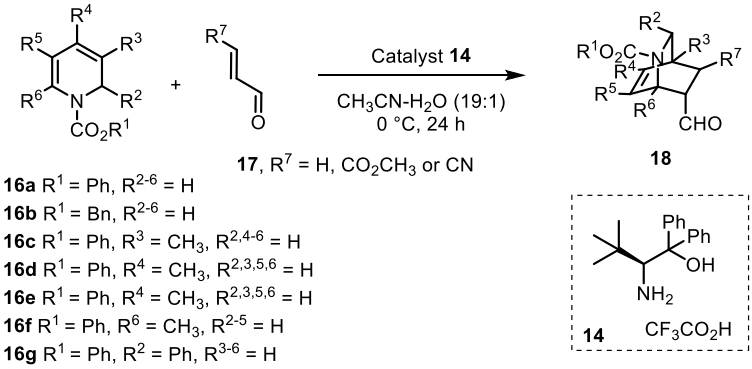
Nakano, Takeshita, and co-workers developed a series of novel oxazolidine-based organocatalysts for the enantioselective synthesis of isoquinuclidines (**Scheme 4**).[4a] Out of the tested organocatalysts, the high enantioselectivity (*endo* only, 99% ee) and good yield (71%) of adduct **12** were reported for the Diels–Alder reaction of dihydropyridine **11** with acrolein **6** employing catalyst **13**.

Subsequently, Nakano and co-workers developed several β-amino alcohol catalysts for the asymmetric Diels–Alder reaction of 1,2-dihyropyridines (1,2-DHP) **11** with acrolein **6** (**Scheme 4**).[4b] Catalyst **14** was found to be the most efficient organocatalyst for the enantioselective synthesis of isoquinuclidines. The organocatalyst **14** which significantly enhances the selectivity (*endo* only, 96% ee) and yield (98%) of the isoquinuclidine **12** also revealed the importance of bulky substituents such as phenyl and *tert*-butyl groups.[4c]



Scheme 4: Developments in the Organocatalyzed Diels–Alder Reaction of 1,2-DHPs

Recently, Nakano and co-workers also reported the hydrazine-based organocatalyst **15** for the asymmetric synthesis of isoquinuclidines (**Scheme 4**).[4d] Moderate enantioselectivity was observed using this catalyst and did not provide better results for the Diels–Alder reaction.



Scheme 5: Organocatalyzed Diels–Alder Reaction of Substituted 1,2-DHPs with Dienophile

The scope of the catalyst **14** was also examined in the reactions of substituted dihydropyridines **16** with dienophiles **17** (**Scheme 5**).[4e] The excellent yield (96%) and enantioselectivity (98%) for the substituted *endo*-adduct **18** were observed for the reaction of **16a** with **17** (R^7= CO_2CH_3) using organocatalyst **14**. The enantioselectivity of the above products was determined by converting Diels–Alder adduct into the corresponding alcohols by reduction with sodium borohydride.

The structural and electronic properties of the organocatalysts control the enantioselectivity of the Diels–Alder reaction (**Figure 2**). The iminium ion intermediate formed by organocatalyst on reaction with acrolein either exerts steric influences or forms hydrogen bond interactions or both that resulted in the reaction outcome. For the amino alcohol as the organocatalysts, the approach of diene was controlled by the presence of the bulky substituent at α- and β-positions of the catalyst. Whereas, in the case of oxazolidine organocatalysts, the approach of diene was controlled by the presence of the steric influence of the substituents present on the catalyst.

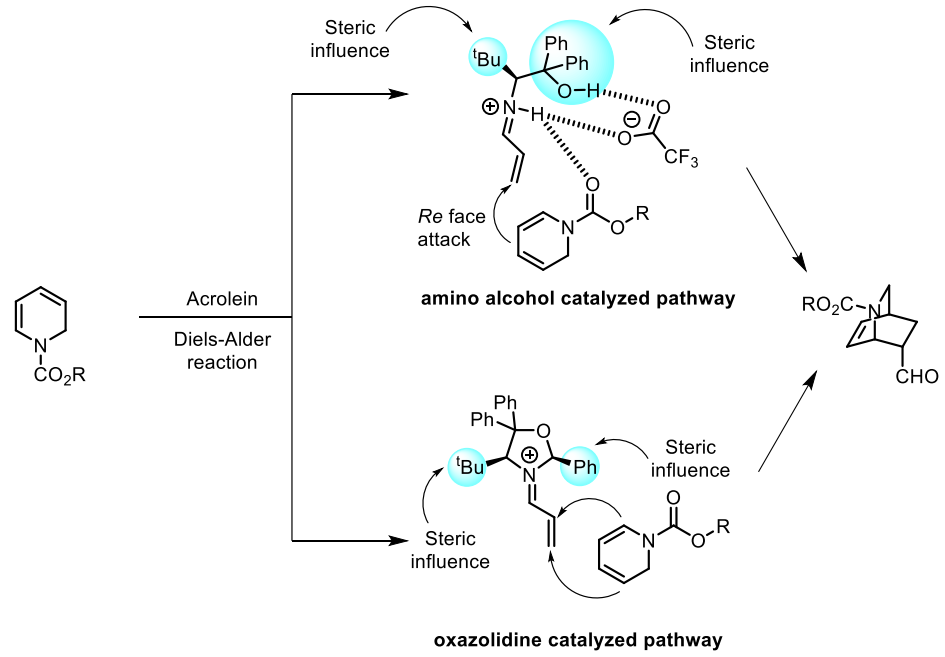
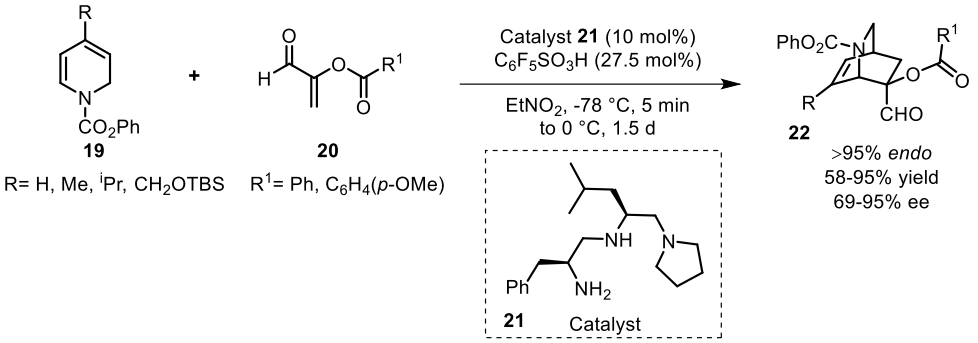


Figure 2: Function of organocatalysts in asymmetric Diels–Alder reaction.

Ishihara's catalyst[5]

In the year 2014, Ishihara *et al.* reported the asymmetric Diels–Alder reaction of 1,2-DHPs **19** with α-(acyloxy)acroleins **20** using chiral primary ammonium salts derived *in situ* from

organocatalyst **32** (**Scheme 6**).[5] The formation of bicyclic *endo*-adduct **22** was observed in good to high yield (58-95%) and in high enantioselectivity (69-95% ee).



Scheme 6: Ishihara's Organocatalyst in the Asymmetric Diels–Alder Reaction of 1,2-DHPs

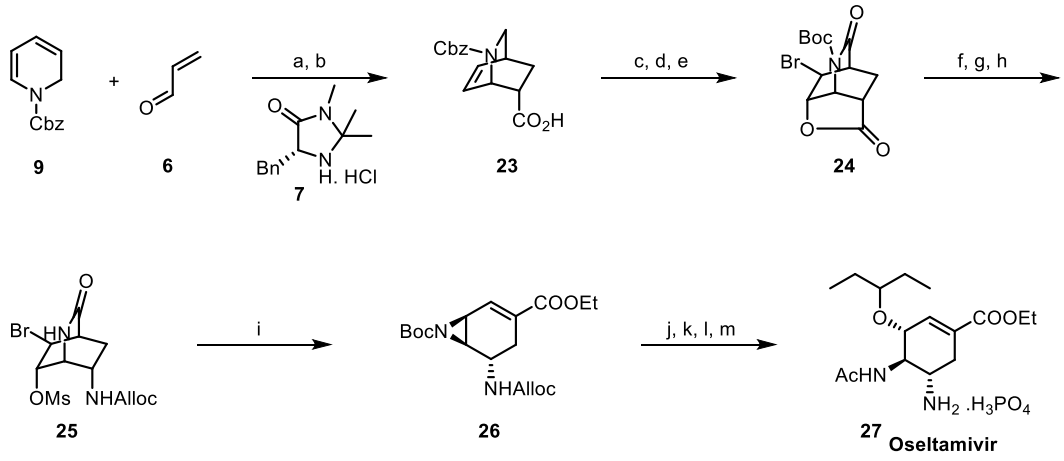
2.1.2.2. Applications of Isoquinuclidine Skeleton in Total Synthesis

To date, there are only three synthetic approaches (total synthesis of oseltamivir by Fukuyama[2] and (+)-luciduline by Charette,[6] and formal synthesis of catharanthine by Batey[7]) reported in the literature in which application of chiral isoquinuclidine skeleton constructed *via* organocatalyzed Diels–Alder reaction has been demonstrated.

Here, each approach is discussed in detail.

Fukuyama's Approach towards the Synthesis of Oseltamivir (Tamiflu)

(*Angew. Chem. Int. Ed.* **2007**, *46*, 5734).[2]



Scheme 7: Reagents and conditions: *(a) **7** (10 mol%), $CH_3CN–H_2O$, rt, 12 h; (b) $NaClO_2$, $NaHPO_4.2H_2O$, 2-methyl-2-butene, t-BuOH–H_2O, 0 °C-rt, 1 h; (c) Br_2, aq.$NaHCO_3$, CH_2Cl_2, rt, 26% (4 steps from pyridine); (d) H_2, Pd/C, $(Boc)_2O$, EtOH–THF, rt, 2 h, 92%; (e) $RuO_2.nH_2O$, $NaIO_4$, DCE–H_2O, 80 °C, 1.5 h, 86%; (f) NH_3, t-BuOH, THF, 0 °C, 95%; (g) MsCl, Et_3N, CH_2Cl_2, rt, 1 h, 91%; (h) allyl alcohol, $PhI(OAc)_2$, M.S. 4 Å , toluene, 60 °C, 10 h, 88%; (i) NaOEt, EtOH, 0 °C, 87%; (j) $BF_3.OEt_2$, 3-pentanol, –20 °C, 62%; (k) i) TFA, CH_2Cl_2, 0 °C-rt; ii) Ac_2O, pyridine, 88% (2 steps); (l) Pd/C, Ph_3P, 1,3-dimethyl-barbituric acid; (m) EtOH, reflux, 40 min, H_3PO_4, 76%.*

Fukuyama and co-workers reported the total synthesis of the oseltamivir phosphate **27** which is highlighted in **Scheme 7**. Synthesis commenced with the pyridine as a starting material. The Diels–Alder reaction of dihydropyridine **9** derived from pyridine and acrolein **6** as a dienophile in the presence of MacMillan's catalyst **7** furnished bicyclic adduct, which was treated under Pinnick oxidation condition to obtain bicyclic acid **23**. Acid **23** on bromolactonisation and oxidation with $RuO_2/NaIO_4$ furnished imide **24**. Hofmann rearrangement using iodobenzene diacetate was used as a key step for the introduction of the amino group to furnish intermediate **25**. The compound **25** was transformed into aziridine **26** following the series of domino reactions which was regioselectively opened with 3-pentanol in presence of Lewis acid followed by necessary functional group manipulations to furnish oseltamivir phosphate **27**.

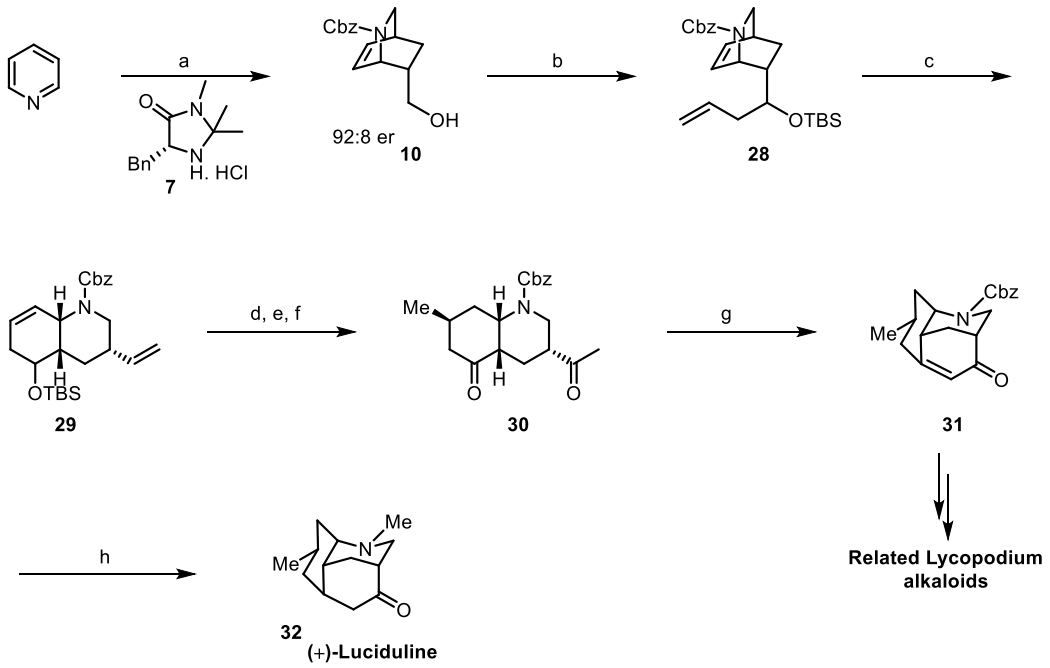
Charette's Approach towards the Asymmetric Total Synthesis of (+)-Luciduline

(*J. Org. Chem*. **2011**, *76*, 5354–5362).[6]

Charette and co-workers reported the asymmetric total synthesis of (+)-luciduline and general approach towards the related lycopodium alkaloids (**Scheme 8**). The synthesis commenced with the preparation of Fukuyama's intermediate **10** using asymmetric Diels–Alder reaction catalyzed by MacMillan's catalyst **7**. The next key step was the tandem metathesis reaction for the synthesis of precursor **29** from intermediate **28**. For the tandem metathesis reaction, Grubbs' second generation catalyst was used, to obtain desired hydroquinoline **29** in 81% yield. Dess-Martin oxidation, alumina-induced alkene migration and 1,4-addition with methylcuprate followed by Wacker oxidation were used to obtain intermediate **30**. The next step was aldol condensation, which was achieved with LiHMDS to furnish the core skeleton **31** of lycopodium

alkaloids. Concomitant hydrogenation and *in situ* reductive amination of intermediate **31** was carried out to complete the synthesis of (+)-luciduline **32**.

Also, the potential of intermediate **31** was explored to enable the divergent synthesis of other lycopodium alkaloids.



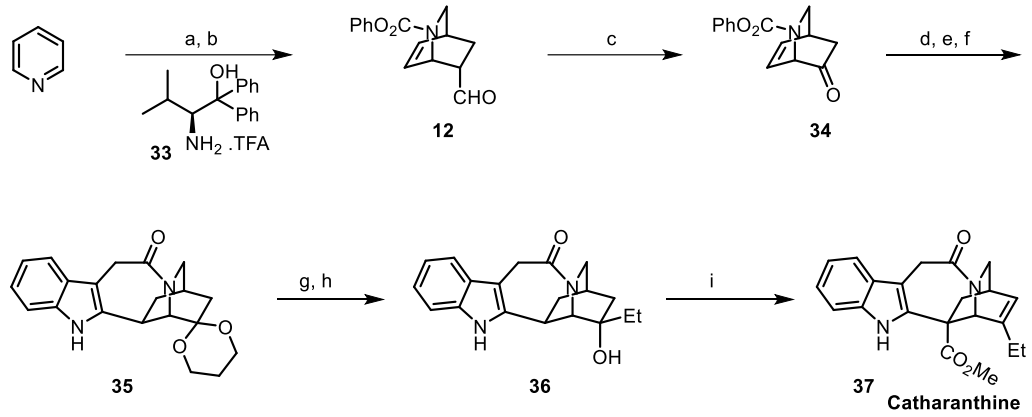
Scheme 8: Reagents and conditions: *(a) i) Cbz-Cl, $NaBH_4$, MeOH, –78 °C to rt, 45 min; ii) Acrolein, **7** (10 mol%), $CH_3CN–H_2O$, rt, 24 h; iii) $NaBH_4$, EtOH, 0 °C, 24 h, 33% (3 steps); (b) i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C to rt, 45 min; ii) AllylMgBr, CH_2Cl_2, –78 °C to rt, 1 h; iii) TBSCl, imidazole, CH_2Cl_2, rt, 24 h, 61% (3 steps); (c) Grubbs' 2nd gen. cat., CH_2Cl_2, 17 h, rt, 81%; (d) i) TBAF, THF, rt, 20 h, 92%; ii) Dess-Martin periodinane, CH_2Cl_2, rt, 2 h; iii) Basic Al_2O_3, EtOAc, rt, 20 h; (e) Me_2CuLi, Et_2O, –78 °C, 3 h, 81% (3 steps), d.r. >20:1; (f) O_2 (1 atm), $PdCl_2$ (20 mol%), $THF–H_2O$, rt, 24 h, 78%; (g) LiHMDS, THF, –78 °C to rt, 62%; (h) Formalin, Pd/C, H_2, EtOH, rt, 2 h, 75%;*

Batey's Approach towards the Formal Synthesis of Catharanthine

(*Org. Chem. Front.* **2018**, *5*, 2934).[7]

Recently (2018), Batey *et al*. reported the formal synthesis of catharanthine *via* enantioselective isoquinuclidine synthesis using sequential Diels–Alder/visible–light photoredox C–C bond cleavage (**Scheme 9**). Synthesis of required isoquinuclidine skeleton **34** was achieved in three

steps from pyridine *viz.* (a) ketene equivalent Diels–Alder reaction using amino alcohol **33** as an organocatalyst to obtain bicyclic aldehyde **12** in two steps and (b) conversion of **12** to ketone **34** using visible–light photoredox catalyst. Conversion of **34** to core skeleton of catharanthine **35** was achieved by amidation with 3-indole acetic acid and Trost cyclization condition with stoichiometric $AgBF_4$ and $(CH_3CN)_2PdCl_2$ as key steps. The next step was the reaction of **35** with ethynyl magnesium bromide followed by the hydrogenation using PtO_2 to afford intermediate **36** to complete the formal synthesis of catharanthine **37**.



Scheme 9: Reagents and conditions: *(a) $NaBH_4$, phenyl chloroformate, MeOH, –78 °C to rt; (b)* ***33*** *(10 mol%), acrolein, CH_3CN–H_2O, 1–2 °C, 8 d, 71% (er= 97:3); (c) $Ru(bpy)_3Cl_2(H_2O)_6$ (5 mol%), piperidine, CH_3CN, SiO_2, AcOH, Blue LED light, O_2 (1 atm), CH_3CN, 14 h, 83%; (d) 1,3-propanediol, PTSA, benzene, reflux, 96%; (e) (i) hydrazine hydrate, KOH, MeOH–H_2O, reflux; (ii) 3-indole acetic acid, EDC, NEt_3, CH_2Cl_2, 63% (2 steps); (f) $AgBF_4$, $(CH_3CN)_2PdCl_2$, CH_3CN, 75 °C, 59%; (g) PTSA, acetone–H_2O, 60 °C, 85%; (h) (i) ethynyl magnesium bromide, THF; (ii) H_2, PtO_2 (cat.), MeOH, 80% (2 steps); (i) 6 steps from ref. 8*

2.1.3. Conclusion and Prospect

From the last decade, increasing efforts have been directed towards the development of a new catalytic system for the synthesis of chiral isoquinuclidine skeleton *via* organocatalyzed Diels–Alder reaction due to its potential to construct the complex natural products and drug molecules in enantioselective fashion. Despite the high functionalization ability of isoquinuclidine skeleton to provide complex scaffolds in chiral fashion, its applications for the synthesis of bioactive compounds and medicinally important drug molecules are scarce. Since

chiral isoquinuclidine skeleton could be synthesized with ease *via* organocatalyzed Diels–Alder reaction in high enantioselectivity and good yield, there is great potential as well as opportunity to develop interesting chemistry in context to the total synthesis of natural products utilizing this highly functional chiral scaffold.

2.1.4. References

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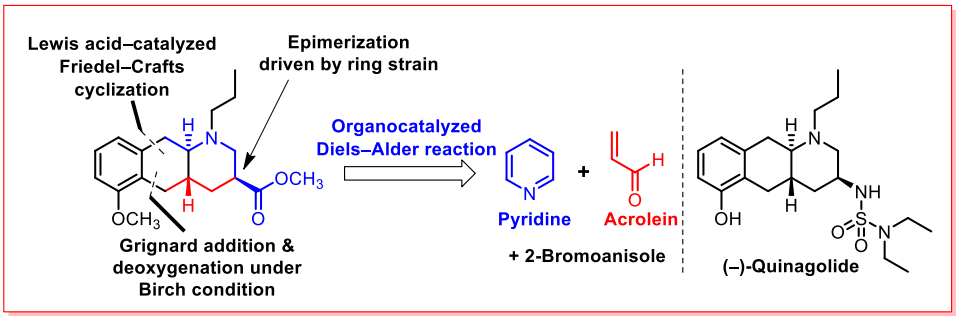
CHAPTER 2

Section 2

"Enantioselective Formal Total Synthesis of (–)-Quinagolide"



ABSTRACT: The enantioselective formal total synthesis of (–)-quinagolide has been accomplished in a linear sequence of 8 purification steps from pyridine. The key steps are (a) organocatalyzed Diels–Alder reaction for fixing all three stereocenters on piperidine ring; (b) protecting group enabled deoxygenation of isoquinuclidine skeleton under Birch reduction condition; (c) Lewis acid ($TiCl_4$) catalyzed intramolecular Friedel–Crafts cyclization of dicarboxylic acid and (d) one-pot diastereoselective ketone reduction–intramolecular cyclization to form oxazolidinone which enables *trans*-geometry installation. During the course of the synthesis, an interesting reductive cleavage of the C-*N* bond in the electron-deficient isoquinuclidine skeleton under the Birch reduction condition has been observed. This is the first synthetic effort to access the core skeleton of (–)-quinagolide.

Reference:

Chavan, S. P.; **Kadam, A. L.**; Gonnade, R. G. *Org. Lett.* **2019**, *accepted.*
(DOI: 10.1021/acs.orglett.9b03477)

2.2.1. Objective

Quinagolide (**1**), which is a selective D_2 receptor agonist used for the treatment of elevated levels of prolactin, has combined structural features of well-known dopamine agonists namely ergolines CQ 32-084 (**2**) and pergolide (**3**) and apomorphine (**4**) (**Figure 1**).

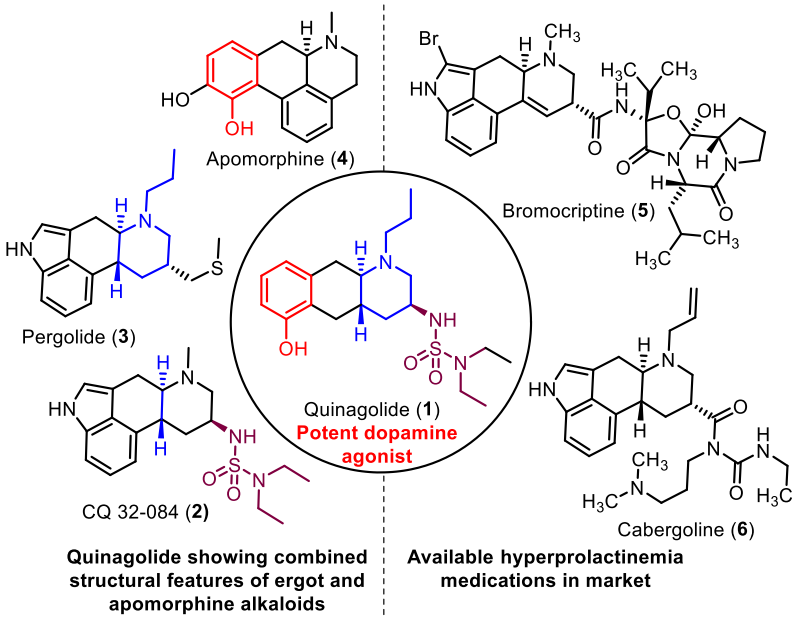


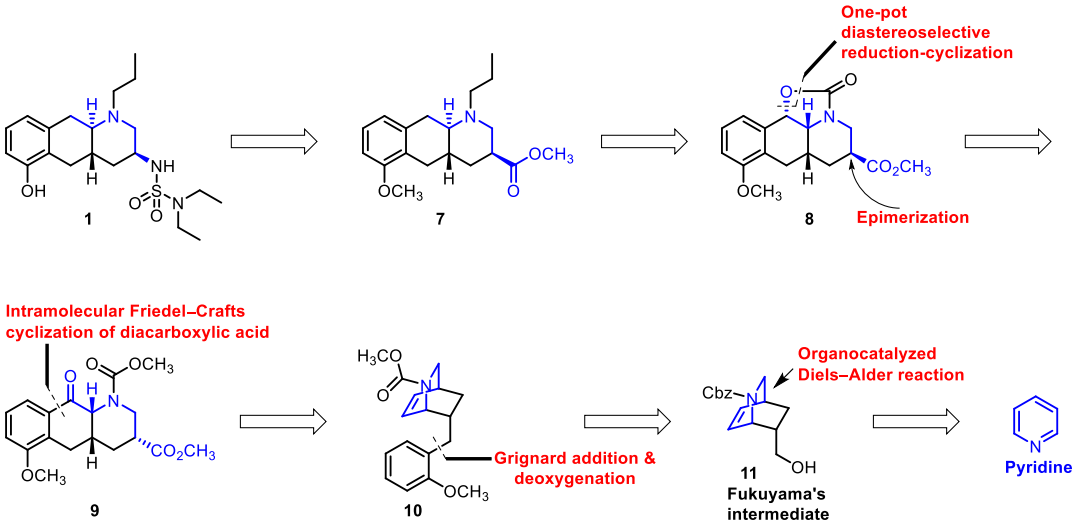
Figure 1. Available hyperprolactinemia medications in the market and structural features of quinagolide **1**.

Furthermore, quinagolide (**1**) has distinct advantages over the bromocriptine (**5**) and cabergoline (**6**), which are currently available medications for the treatment hyperprolactinemia. [1] Quinagolide hydrochloride as its racemate is marketed by Ferring Pharmaceuticals, Switzerland under the trade name Norprolac. Though there are four total syntheses of (±)-quinagolide reported in literature,[2,3,4] and Nordmann *et al*. resolved the intermediate of (±)-quinagolide and found that the dopaminomimetic activity is entirely associated with the (–)-enantiomer,[2b] to date, enantioselective total synthesis of (–)-quinagolide is not reported in the literature. In this context, the development of a new synthetic route for the enantioselective total synthesis of (–)-quinagolide is highly desirable.

2.2.2. Present Work

2.2.2.1. Retrosynthetic Analysis

From the last few decades, pyridine has served as an ideal choice of starting material for the effective total synthesis of alkaloids in enantioselective fashion while also providing the basic nitrogen atom as well.[5] In this context, the nitrogen atom and the three necessary stereocenters on the piperidine ring of quinagolide could be introduced from pyridine *via* organocatalyzed Diels–Alder reaction of the corresponding dihydropyridine and acrolein.[6] Also, the tricyclic ring skeleton of quinagolide could be constructed by the Grignard reaction followed by Friedel–Crafts cyclization.

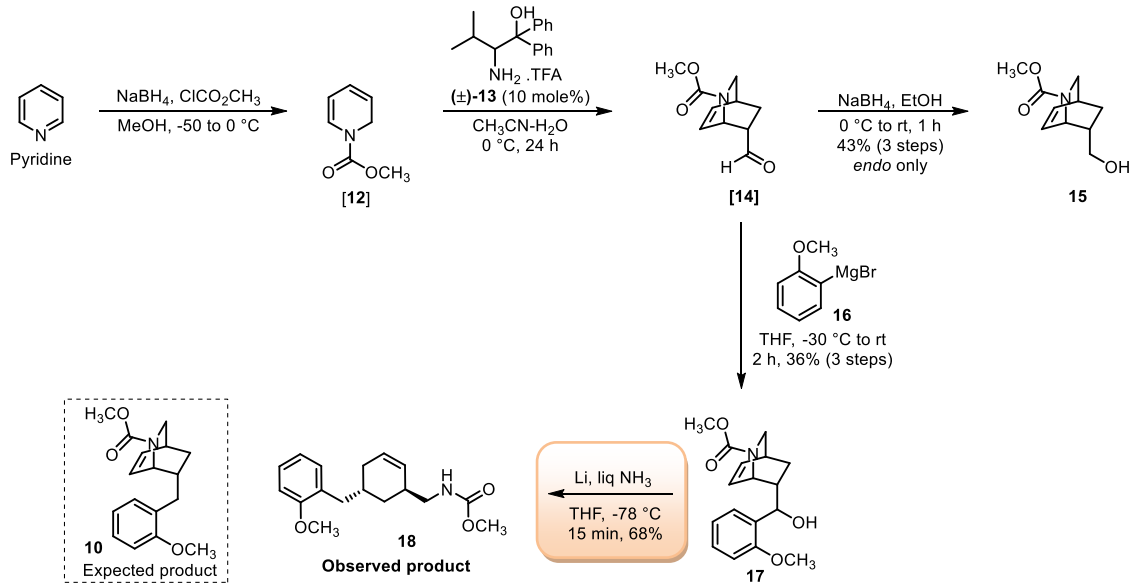


Scheme 1. Retrosynthetic Analysis for (–)-Quinagolide 1

On the basis of these deliberations, retrosynthetic analysis for target molecule **1** is outlined in **Scheme 1**. It was envisioned that bicyclic precursor **10** could be effectively converted to tricyclic skeleton **7** of quinagolide (**1**) *via* functionalization of olefin part of bicyclic precursor **10** into keto-ester **9**. The steps involved could be Lewis acid–catalyzed intramolecular Friedel–Crafts cyclization of dicarboxylic acid followed by epimerization at tetracyclic intermediate **8**, which in turn could be synthesized from keto-ester **9** through one-pot reductive cyclization. Bicyclic precursor **10** could be successively constructed *via* Grignard addition on bicyclic aldehyde corresponding to Fukuyama's intermediate **11**,[5f] which in turn could be synthesized using organocatalyzed Diels–Alder reaction followed by benzylic deoxygenation under Birch reduction condition.

2.2.2.2. Results and Discussion

In initial attempts to establish a synthetic strategy toward **7**, The synthesis commenced with pyridine, acrolein, and racemic beta-amino alcohol **13**[6] as an organocatalyst (**Scheme 2**).

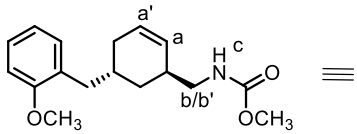


Scheme 2. Initial Attempts

Pyridine was treated with methyl chloroformate and $NaBH_4$ in MeOH at –45 °C to afford dihydropyridine **12** in quantitative yield. The Diels–Alder reaction of dihydropyridine **12** with acrolein using (±)-β–amino alcohol **13** as an organocatalyst furnished the desired bicyclic adduct **14**. For the characterization purpose, aldehyde **14** was reduced to corresponding bicyclic alcohol **15** (*endo* only) in 43% yield over 3 steps. The formation of the product was confirmed by the presence of a signal at 3432 cm^{-1} in the IR spectrum corresponding to O-H stretching frequency and a peak at δ 65.40 in the ^{13}C NMR spectrum for O-CH_2 carbon. The structure of **15** was further confirmed by the HRMS spectrum which showed a peak at 220.0945 corresponding to the formula $C_{10}H_{15}O_3NNa$ $[M + Na]^+$ of the product. In the next step, the resulting crude aldehyde **14** was subjected for addition reaction of Grignard reagent **16** derived from 2-bromo anisole to provide the inseparable mixture of diastereomeric alcohol **17** in 36% yield over 3 steps. The presence of a strong peak at 3429 cm^{-1} in the IR spectrum for O-H stretching frequency and peaks at δ 7.33–7.07 (m, 2H) and 7.02–6.79 (m, 2H) in ^1H NMR spectrum corresponded to aromatic region confirming the formation of the product. At this stage, deoxygenation of **17** would have provided bicyclic alkene **10**. For deoxygenation of **17**, literature known reaction conditions were screened, but either complex reaction mixture or disappointingly

desired product formation in very poor yield was observed. Under the Birch reaction condition, instead of obtaining bicyclic alkene **10** as an expected product, ring-opened carbamate **18** was isolated as a major product in 68% yield. The formation of the product was confirmed by the presence of a peak at δ 4.78 (br s, 1H) corresponding to *N*-H proton in ^{1}H NMR spectrum and peaks appearing at δ 35.9 and 35.7 in ^{13}C NMR spectrum corresponding to newly formed methylene carbon of CH_2-C=C group. The peak at 312.1568 in the HRMS spectrum corresponding to the formula $C_{17}H_{23}O_3NNa$ $[M + Na]^+$ further confirmed the formation of the product.

The structure of compound **18** was fully confirmed by 2D NMR spectral analysis. In the NOESY spectrum of compound **18**, a strong correlation between olefinic proton **a** was observed with methylamine protons **b** as well as *N*-H proton **c**, indicating the position of olefin. It was further supported by HMBC confirming the structure of compound **18**.



18

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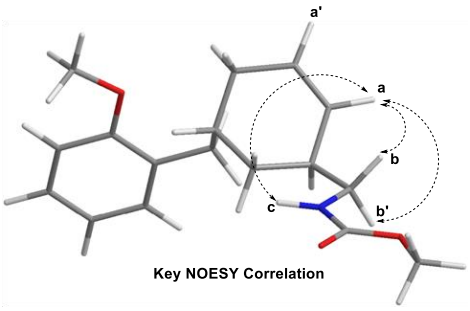
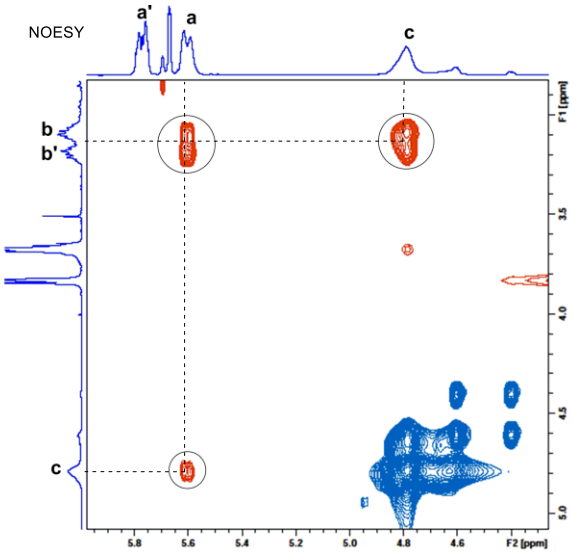
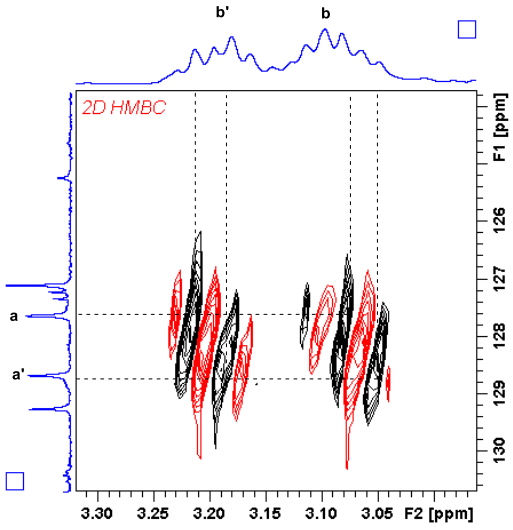
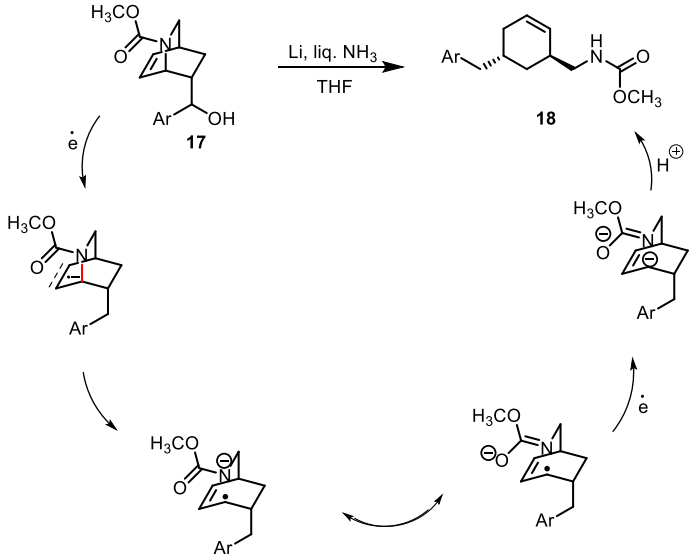






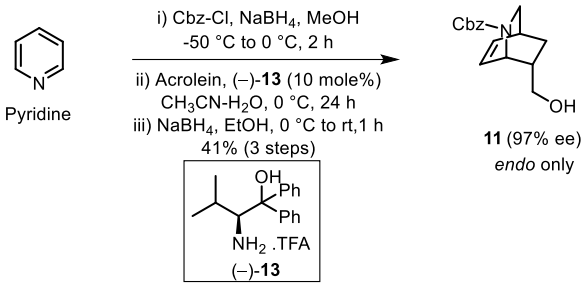
Ring-opening of isoquinuclidine **17** under the Birch reduction condition could be explained on the basis of the mechanism proposed in **Scheme 3**.[7] It is noteworthy to mention that such type of

ring-opening of isoquinuclidine under the Birch reduction condition is first-of-its-kind and hopefully will find more applications in context to the total synthesis of alkaloids and drug development.



Scheme 3. Plausible Reaction Pathway for Ring Opening of Isoquinuclidine 17

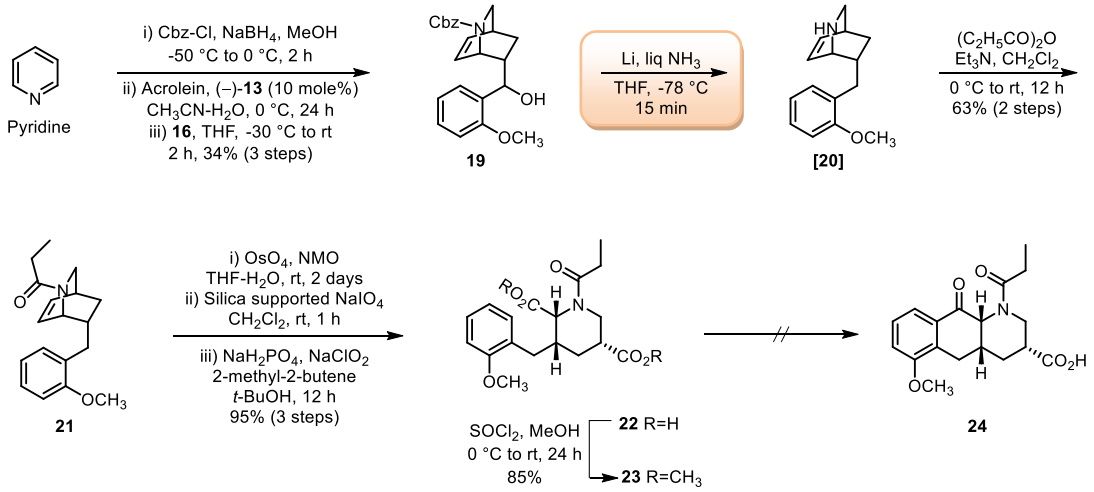
It was thought that the methylcarbamate protecting group played a vital role in the opening of bicyclic intermediate **17** under the Birch reduction condition. It was surmised that synthesis of a bicyclic amine having a protecting group like *N*-Cbz would solve the problem as *N*-Cbz will be easily deprotected under Birch reduction condition and thus ring opening will be prevented. Thus, Fukuyama's intermediate **11** was successfully synthesized on a gram scale and in high enantiomeric excess (97% ee) following Nakano type Diels–Alder reaction using (–)-**13** derived from L-valine as an organocatalyst (**Scheme 4**).[6]



Scheme 4. Synthesis of Fukuyama's Intermediate 11

In the next step, the bicyclic aldehyde obtained from Diels–Alder reaction was subjected for addition reaction of Grignard reagent **16** derived from 2-bromoanisole, to obtain bicyclic intermediate **19** in 34% yield over 3 steps (**Scheme 5**). The strong peak at 3430 cm^{-1} in the IR

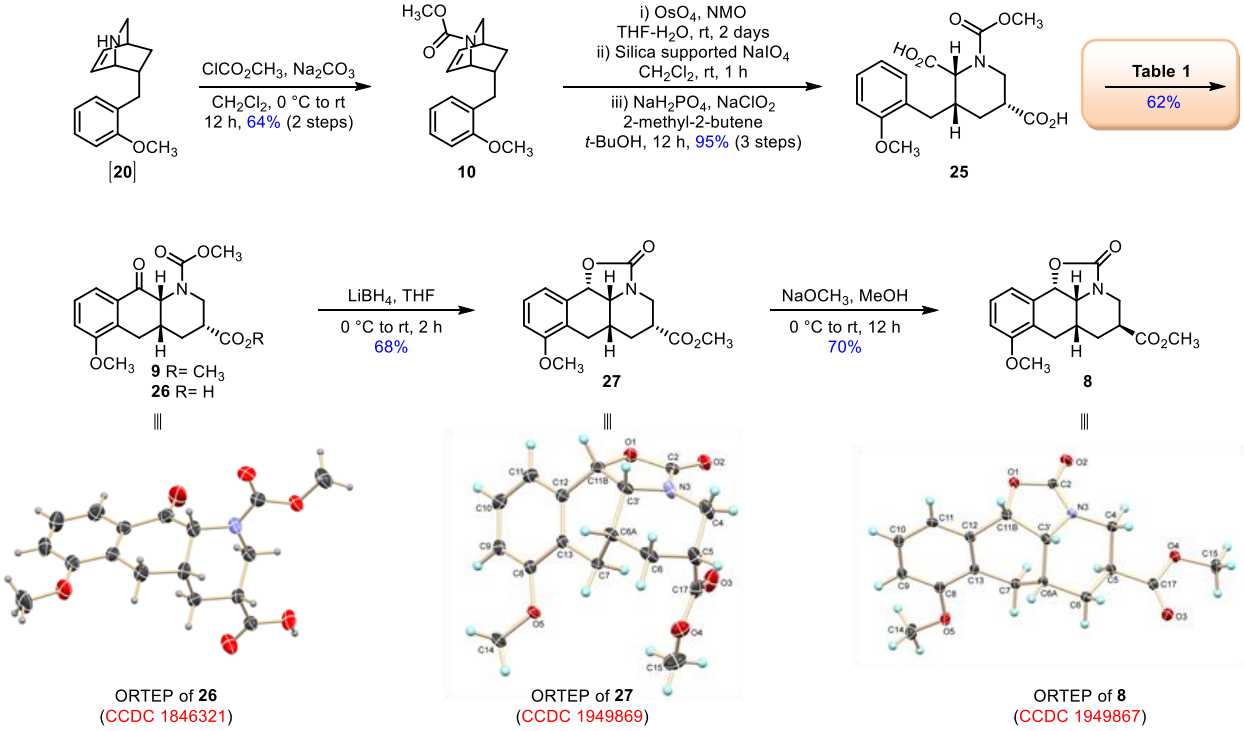
spectrum for O-H stretching frequency and peaks at δ 6.98–6.81 (m, 2H) and 6.60–6.39 (m, 2H) in ^{1}H NMR spectrum corresponding to aromatic region confirmed the formation of the product. The peak at 380.1851 in the HRMS spectrum corresponding to the formula $C_{23}H_{26}O_4N$ $[M + H]^+$ further confirmed the formation of the product. At this stage, as anticipated, pleasingly, deoxygenation of bicyclic intermediate **19** under the Birch reduction condition worked well, to furnish bicyclic amine **20**. The next step was the protection of bicyclic amine with a suitable group, which can be easily converted to tertiary propylamine in the final product. Accordingly, bicyclic amine **20** was protected as its amide derivative **21** using propionic anhydride in 63% yield over 2 steps. Signals at δ 171.7 and 171.6 (mixture of rotamers) in ^{13}C NMR corresponded to amide carbonyl carbon confirming the formation of the product. The structure of **21** was further supported by the HRMS spectrum in which the appearance of a peak at 286.1801 corresponding to the formula $C_{18}H_{24}O_2N$ $[M + H]^+$ of the product was observed. The amide **21** was then dihydroxylated using OsO_4-NMO in THF-water for 2 days and the crude diol was subjected to cleavage using silica-supported $NaIO_4$ in CH_2Cl_2 to provide the corresponding dialdehyde. The crude dialdehyde was then subjected to a Pinnick oxidation reaction to afford dicarboxylic acid **22** in 95% yield over 3 steps.[8]



Scheme 5. Successful Synthesis of Bicyclic Amine 20 and Attempted Synthesis of Tricyclic Skeleton

For the characterization purpose, dicarboxylic acid **22** was converted into the corresponding methyl diester **23** in 85% yield. Presence of signals at δ 3.80 (s, 3H), 3.75 (s, 3H) and 3.67 (s, 3H) in ^{1}H NMR spectrum were due to the three –OCH_3 groups and peaks at δ 173.4, 173.2, 172.9, 171.0 and 169.6 (mixture of rotamers) corresponding to three carbonyl carbons present in

the structure confirmed the formation of product. At this stage, intramolecular Friedel–Crafts cyclization of dicarboxylic acid **22** using Lewis acid would have provided tricyclic keto-acid **24**. But unfortunately, several attempts failed to cyclize dicarboxylic acid **22** into tricyclic core **24**.



Scheme 6. Successful Synthesis of the Core Skeleton of Quinagolide

Detailed literature analysis revealed that the methylcarbamate protection of alpha-amino acid might be essential for its intramolecular Friedel–Crafts cyclization.[9] Accordingly, bicyclic amine **20** was protected as it's methylcarbamate derivative **10** using methyl chloroformate in 64% yields (**Scheme 6**). Peaks at δ 3.82 (s, 1.2H), 3.81 (s, 1.8H), 3.64 (s, 1.8H) and 3.63 (s, 1.2H) (mixture of rotamers) in ^{1}H NMR spectrum and δ 157.5 and 155.7 (mixture of rotamers) corresponding to carbonyl carbon of methylcarbamate in ^{13}C NMR spectrum confirmed the formation of product. HRMS spectrum showed a peak at 310.1414 corresponding to formula $C_{17}H_{21}O_3NNa$ $[M + Na]^+$ which further confirmed the product formation. Dihydroxylation of olefin **10** using OsO_4-NMO in THF-H_2O for 2 days afforded the corresponding diol. The crude diol was subjected for cleavage using silica-supported $NaIO_4$ in CH_2Cl_2 to afford dialdehyde, which was converted into dicarboxylic acid **25** under Pinnick oxidation condition in 95% yield. ^{1}H NMR spectrum showed a peak at δ 8.62 (br s, 2H) corresponding to –OH protons of dicarboxylic acid and presence of signals at δ 178.9 and 176.3 corresponding to the carbonyl carbon of dicarboxylic acid in ^{13}C

NMR spectrum confirmed the formation of the product. The disappearance of olefinic signals in ^{1}H and ^{13}C NMR spectrum also indicated the formation of the product. HRMS spectrum showed signal at 374.1210 corresponding to formula $C_{17}H_{21}O_7NNa$ $[M + Na]^+$ (calculated value 374.1210) which further confirmed the product formation.

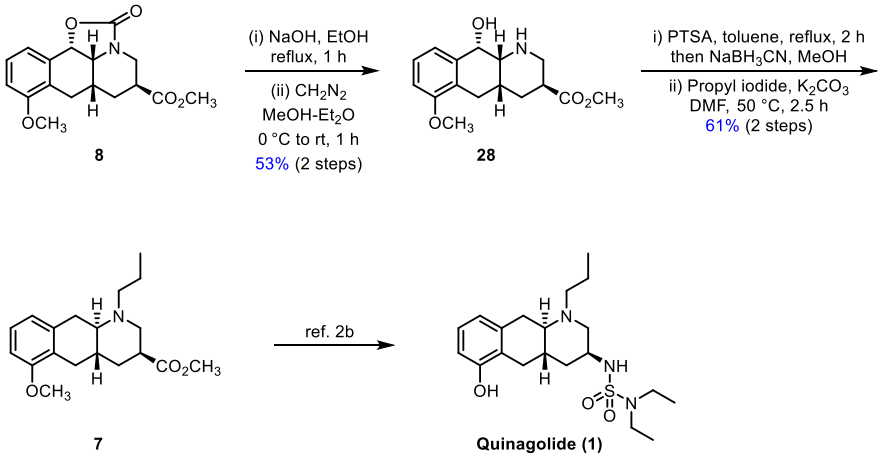
The seemingly simple intramolecular Friedel–Crafts cyclization was found to be the crucial step in this synthesis and posed several problems. Several attempts for the intramolecular Friedel–Crafts cyclization of the dicarboxylic acid **25** were made to arrive at an optimized condition as shown in **Table 1**.

Table 1: Intramolecular Friedel–Crafts Cyclization of Dicarboxylic Acid 25

Entry	Reagents	Equiv	Temp (°C)	Time (h)	Yield (%)[a,b]
01	CF_3SO_2H	0.2	45	1.5	-[c]
02	TFA/TFAA	2.4	rt	3	N.R.[d]
03	PPA	5	80	2	-[c]
04	BF_3.OEt	2.5	0	3.5	N. R.[d]
05	TFAA/BF_3.OEt	5	40	4	-[c]
06	$FeCl_3.MeNO_2$	3.1	0	2	-[c]
07	$SnCl_4$	2.2	0	1	-[c]
08	$AlCl_3$	4.0	0	0.5	25%
09	$AlCl_3$	4.0	0	2	37%
10	$TiCl_4$	4.0	0	0.5	40%
11	$TiCl_4$	4.0	0	2	52%
12	**$TiCl_4$**	**5**	**0** °C	**2**	**62%**

[a]Isolated yield of compound **9**, [b]Corresponding acid chloride was used, [c]Complex reaction mixture, [d]No reaction.

The same was accomplished by converting dicarboxylic acid **25** into corresponding acid chloride and $TiCl_4$ mediated cyclization of acid chloride in CH_2Cl_2 to afford tricyclic keto-ester **9** in 62% yield. The relative stereochemistry of **9**, which was found to be *cis* was unambiguously determined by single-crystal X-ray analysis of the corresponding acid **26**. At this stage, the plan was the double epimerization at the tricyclic core **9** to get desired stereochemistry. Many attempts for the epimerization of **9** failed. Also, the deprotection of methyl carbamate was not realized mainly because of either the aromatization of B ring or decomposition of starting material. When ketone **9** was subjected to reduction using $LiBH_4$ in THF, tetracyclic carbamate **27** was isolated as a single diastereomer in 68% yield (**Scheme 6**). The structure and absolute stereochemistry of compound **27** were confirmed by single-crystal X-ray analysis. In the next step, interestingly, epimerization at the ester center of compound **27** was performed using relatively mild base *viz*. $NaOCH_3$ in MeOH to obtain tetracyclic skeleton **8** in 70% yield with required stereochemistry. This may be attributed to the rigid shape and release of strain during epimerization. At this stage also, the structure and absolute stereochemistry of compound **8** were confirmed by single-crystal X-ray analysis.



Scheme 7. Completion of the Formal Synthesis of (–)-Quinagolide

The next task was the installation of a *trans*-ring junction. To the end, the opening of tetracyclic carbamate **8** was performed by refluxing in ethanolic NaOH[10] and subsequent esterification with diazomethane in MeOH: Et_2O (1:1) furnished corresponding tricyclic amino-alcohol **28** in 53% yield (**Scheme 7**). Strong signal at 3426 cm^{-1} in the IR spectrum corresponding to O-H stretching frequency indicated the formation of the product. The disappearance of a signal at δ 156.2 in the ^{13}C NMR spectrum corresponding to oxazolidinone carbonyl carbon confirmed the formation of

the product. HRMS spectrum showed a peak at 292.1541 corresponding to formula $C_{16}H_{22}O_4N$ $[M + H]^+$ (calculated value 292.1543) which further confirmed the formation of the product.

In the next step, amino-alcohol **28** was treated with PTSA under reflux in toluene[11] in order to form intermediate enamine followed by its reduction with $NaBH_3CN$ and *N*-alkylation using propyl iodide to afford compound **7** in 61% yield over two steps. Compound **7** showed ^1H and ^{13}C NMR spectra, identical with those of a racemic sample reported in the literature[3,4b] and since the synthesis of (–)-quinagolide (**1**) from compound **7** was reported by Nordmann *et al.*,[2b] the present work constitutes the formal total synthesis of (–)-quinagolide.

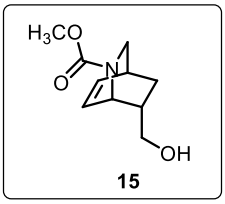
2.2.3. Conclusion

In summary, the enantioselective formal total synthesis of (–)-quinagolide in a linear sequence of 8 purification steps from pyridine has been accomplished. The key steps used in the synthesis were organocatalyzed Diels–Alder reaction for fixing all three stereocenters on piperidine ring, Birch deoxygenation, Lewis acid ($TiCl_4$) catalyzed intramolecular Friedel–Crafts cyclization of a dicarboxylic acid, and one-pot diastereoselective ketone reduction-intramolecular cyclization to form tetracyclic oxazolidinone which provides required *trans*-geometry. The reductive cleavage of C-*N* bond in electron-deficient isoquinuclidine skeleton under Birch reduction conditions to access substituted cyclohexenes was an important finding and hopefully will find more applications in total synthesis and drug development programs in the near future.

2.2.4. Experimental Section

2.2.4.1. Experimental Procedures and Characterization Data

Methyl (1*S*,4*S*,7*S*)-7-(hydroxymethyl)-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (15).



15

To a stirred solution of pyridine (10 g, 126 mmol, 1 equiv) in methanol (200 mL) at –40 °C, was added sodium borohydride (5.02 g, 132 mmol, 1.05 equiv). To this was added methyl chloroformate (9.3 mL, 120 mmol, 0.95 equiv) dropwise through the dropping funnel over a period of 30 min at such a rate that inner temperature was maintained between –47 to –35 °C. After stirring for 20 min, the resulting solution was gradually warmed to 0 °C. Water (200 mL) was added and the reaction mixture was extracted with Et_2O (3 X 200 mL). The combined organic extracts were washed with 1 N HCl (200 mL), 1 N NaOH (200 mL), water (100 mL), and brine (100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude dihydropyridine as a pale yellow oil, which was immediately used for the next reaction without further purification.

To a stirred solution of above obtained dihydropyridine (16.5 g, 118 mmol, 1 equiv) and catalyst (±)-**13** (4.38 g, 11.8 mmol, 0.1 equiv) in CH_3CN:H_2O (190 mL: 10 mL) at –25 °C, was added distilled acrolein (23.8 mL, 356 mmol, 3 equiv) and the solution was stirred at 0 °C for 24 h. The reaction mixture was diluted with water (200 mL) and extracted with Et_2O (3 X 300 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude aldehyde which was used for the next reaction without further purification.

To a solution of crude aldehyde (20 g, 102 mmol, 1 equiv) in EtOH (200 mL), was added $NaBH_4$ (3.87 g, 102 mmol, 1 equiv) portion-wise at 0 °C and the mixture was stirred for 1 h while warming to room temperature. The reaction was quenched with 1 N HCl, the solvent was evaporated under reduced pressure and the reaction mixture was extracted with CH_2Cl_2 (3 X 200 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (30:70) afforded pure product **15** (10.7 g, 43% yield over 3 steps) as a colorless viscous oil.

R_f : 0.3 (EtOAc–PE =50:50);

Yield: 43% over 3 steps;

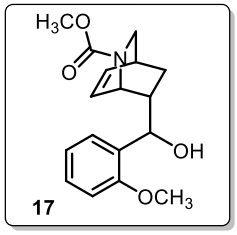
IR ($CHCl_3$): ν_{max} 3432, 1670, 1458, 1121 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): (mixture of rotamers) δ 6.47–6.21 (m, 2H), 4.92–4.68 (m, 1H), 3.68 (s, 1H), 3.66 (s, 2H), 3.37–3.06 (m, 3H), 2.96 (tt, *J* = 2.6, 9.8 Hz, 1H), 2.80–2.66 (m, 1H), 2.49–2.19 (m, 2H), 1.76 (ddd, *J* = 2.5, 9.7, 12.5 Hz, 1H), 0.90–0.70 (m, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz): (mixture of rotamers) δ 156.0, 155.5, 134.9, 134.6, 130.4, 130.0, 65.4, 52.4, 47.2, 47.1, 46.9, 46.8, 41.5, 30.8, 30.5, 26.1;

HRMS (ESI) *m/z* calcd for $C_{10}H_{15}O_3NNa$ $[M + Na]^+$: 220.0944, found: 220.0945.

Methyl 7-(hydroxy(2-methoxyphenyl)methyl)-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (17).



To a cooled (–30 °C) solution of crude aldehyde obtained from two steps as in the preparation of **15** described above (20 g, 102 mmol, 1 equiv) in dry THF (500 mL), was added 2-methoxyphenylmagnesium bromide **16** (102.5 mL of a 1 M solution in THF, 102 mmol, 1 equiv) dropwise through the dropping funnel and the thick reaction mixture was brought to room temperature over a period of 2 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution carefully at 0 °C. The reaction mixture was extracted with EtOAc (3 X 300 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (30:70) afforded pure product **17** (13.8 g, 36% yield over 3 steps) as a colorless viscous oil.

R_f : 0.4 (EtOAc–PE =50:50);

Yield: 36% over 3 steps;

IR ($CHCl_3$): ν_{max} 3429, 1682, 1455 cm^{-1};

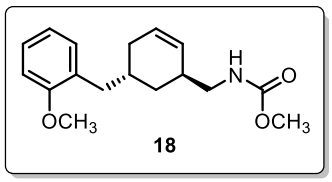
^{1}H NMR ($CDCl_3$, 400 MHz): (mixture of rotamers) δ 7.33–7.07 (m, 2H), 7.02–6.79 (m, 2H), 6.55–6.38 (m, 1.4H), 6.30–6.18 (m, 0.4H), 5.21–5.07 (m, 0.5H), 4.27–3.99 (m, 1.4H), 3.86 (s, 1H), 3.85 (s, 2H), 3.73–3.55 (m, 3H), 3.28–3.13 (m, 1H), 3.04–2.86 (m, 1H), 2.81–2.56 (m, 2H), 1.95–1.74 (m, 1H), 1.58–1.37 (m, 1H), 0.79 (t, *J* = 10.4 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz): (mixture of rotamers) δ 157.3, 156.7, 155.9, 155.6, 135.4, 135.0, 134.8, 134.6, 131.1, 130.8, 130.5, 130.2, 129.9, 129.4, 129.3, 129.0, 128.9, 128.8, 128.6, 128.1,

128.0, 121.0, 120.9, 120.6, 120.5, 111.0, 110.9, 110.7, 75.4, 74.9, 74.4, 55.3, 52.3, 52.2, 52.1, 48.1, 47.6, 47.4, 47.3, 47.14, 47.07, 46.9, 46.8, 45.5, 44.5, 31.2, 31.0, 30.7, 27.5, 26.7;

HRMS (ESI) *m/z* calcd for $C_{17}H_{21}O_4NNa$ $[M + Na]^+$: 326.1363, found: 326.1361.

Methyl (((1*S*,5*R*)-5-(2-methoxybenzyl)cyclohex-2-en-1-yl)methyl)carbamate (18).



18

To a cooled (–78 °C) solution of liquid NH_3 (30 mL) in anhydrous THF (30 mL) was added Li (0.35 g, 49.5 mmol, 5 equiv). The reaction mixture was stirred for 15 min at that temperature, followed by dropwise addition of **17** (3 g, 9.9 mmol, 1 equiv) in THF (10 mL). The reaction mixture was stirred at –78 °C for the next 15 min, then quenched with solid NH_4Cl (30 g) and the NH_3 was allowed to evaporate over a period of 12 h by gradually warming it to room temperature. The resultant mixture was filtered, solid was washed with EtOAc and water (50 mL) was added to the organic layer. The layers were separated and the aqueous layer was extracted with EtOAc (3 X 100 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded pure product **18** (1.95 g, 68% yield) as a colorless viscous oil.

R_f : 0.6 (EtOAc–PE =30:70);

Yield: 68%;

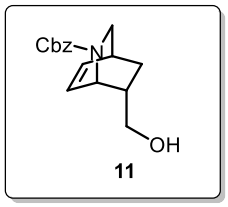
IR ($CHCl_3$): ν_{max} 3336, 2917, 1704, 1586, 1242 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): (mixture of rotamers) δ 7.23–7.15 (m, 1H), 7.11–7.05 (m, 1H), 6.92–6.82 (m, 2H), 5.80–5.72 (m, 0.8H), 5.68–5.66 (m, 0.4H), 5.59 (d, *J* = 9.8 Hz, 0.8H), 4.78 (br s, 1H), 3.83 (s, 0.6H), 3.81 (s, 2.4H), 3.70–3.62 (m, 3H), 3.25–3.01 (m, 2H), 2.68–2.53 (m, 2H), 2.42–2.28 (m, 1H), 2.13–1.94 (m, 2H), 1.81–1.65 (m, 1H), 1.62–1.40 (m, 2H);

^{13}C NMR ($CDCl_3$, 100 MHz): (mixture of rotamers) δ 157.6, 157.2, 157.0, 131.6, 130.8, 130.6, 129.2, 128.6, 127.5, 127.2, 127.1, 127.0, 125.1, 120.2, 120.1, 110.4, 110.2, 55.3, 55.2, 51.9, 46.1, 45.6, 38.4, 35.9, 35.7, 34.1, 34.0, 31.2, 31.1, 30.3, 30.1, 29.3;

HRMS (ESI) *m/z* calcd for $C_{17}H_{23}O_3NNa$ $[M + Na]^+$: 312.1570, found: 312.1568.

Benzyl (1*S*,4*S*,7*S*)-7-(hydroxymethyl)-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (11).



11

To a stirred solution of pyridine (10 g, 126 mmol, 1 equiv) in methanol (200 mL) at –40 °C was added sodium borohydride (5.02 g, 132 mmol, 1.05 equiv). To this was added benzyl chloroformate (17.2 mL, 120 mmol, 0.95 equiv) dropwise through the dropping funnel over a period of 30 min at such a rate that inner temperature was maintained between –47 to –35 °C. After stirring for 20 min, the resulting solution was gradually warmed to 0 °C. Water (200 mL) was added and the reaction mixture was extracted with Et_2O (3 X 200 mL). The combined organic extracts were washed with 1 N HCl (200 mL), 1 N NaOH (200 mL), water (100 mL), and brine (100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude dihydropyridine as a pale yellow oil, which was immediately used in the next reaction without further purification.

To a stirred solution of above obtained dihydropyridine (25 g, 116 mmol, 1 equiv) and catalyst (–)-**13** (4.3 g, 11.6 mmol, 0.1 equiv) in CH_3CN:H_2O (285 mL: 15 mL) at –25 °C was added distilled acrolein (23.3 mL, 348 mmol, 3 equiv) and the solution was stirred at 0 °C for 24 h. The reaction mixture was diluted with water (200 mL) and extracted with Et_2O (3 X 500 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude aldehyde which was used for the next reaction without further purification.

To a solution of crude aldehyde (28 g, 103 mmol, 1 equiv) in EtOH (300 mL), was added $NaBH_4$ (3.9 g, 103 mmol, 1 equiv) portion-wise at 0 °C and the mixture was stirred for 1 h while warming to room temperature. The reaction was quenched with 1 N HCl, and the solvent was evaporated under reduced pressure. The reaction mixture was extracted with CH_2Cl_2 (3 X 200 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (30:70) afforded pure product **11** (14.2 g, 41% yield over 3 steps) as a colorless viscous oil. [ee= 97%, HPLC conditions: Chiralcel OD-H (250 mm X 4.6 mm), 1.0 mL/min, IPA: *n*-Hexane (6: 94)].

R_f : 0.2 (EtOAc–PE =50:50);

Yield: 41% over 3 steps;

IR ($CHCl_3$): ν_{max} 3425, 1685, 1420, 1111 cm^{-1};

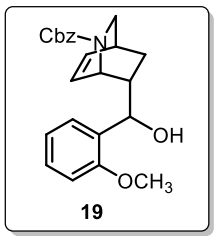
$[\alpha]_D^{25}$ +70.2 (*c* 1.09, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 200 MHz): (mixture of rotamers) δ 7.43–7.24 (m, 5H), 6.49–6.24 (m, 2H), 5.20–5.05 (m, 2H), 4.92–4.79 (m, 1H), 3.36–3.09 (m, 3H), 3.08–2.95 (m, 1H), 2.73 (br s, 1H), 2.46–2.23 (m, 2H), 1.85–1.68 (m, 1H), 0.86–0.80 (m, 1H);

^{13}C NMR ($CDCl_3$, 50 MHz): (mixture of rotamers) δ 155.2, 154.8, 136.9, 134.9, 134.6, 130.4, 130.0, 128.4, 127.8, 127.6, 66.7, 65.5, 47.3, 47.2, 46.9, 46.8, 41.5, 30.8, 30.5, 26.1;

HRMS (ESI) *m/z* calcd for $C_{16}H_{20}O_3N$ $[M + H]^+$: 274.1438, found: 274.1435.

Benzyl (1*S*,4*S*,7*S*)-7-(hydroxy(2-methoxyphenyl)methyl)-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (19).



19

To a cooled (–30 °C) solution of crude aldehyde obtained from two steps as in the preparation of **11** described above (28 g, 103 mmol, 1 equiv) in dry THF (500 mL), was added 2-methoxyphenylmagnesium bromide **16** (103.3 mL of a 1 M solution in THF, 103 mmol, 1 equiv) dropwise through the dropping funnel and the thick reaction mixture was brought to room temperature over a period of 2 h. The reaction mixture was carefully quenched with a saturated aqueous NH_4Cl solution at 0 °C. The reaction mixture was extracted with EtOAc (3 X 300 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (20:80) afforded **19** as a mixture of diastereomers in 1:1 ratio (16.3 g, 34% combined yield over 3 steps) as a colorless viscous oil.

First diastereomer-

R_f : 0.5 (EtOAc–PE =50:50);

Yield: 17% over 3 steps;

IR ($CHCl_3$): ν_{max} 3430, 2946, 1688, 1424, 1113, 753 cm^{-1};

$[\alpha]_D^{25}$ –26.6 (*c* 1, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz): (mixture of rotamers) δ 7.44–7.27 (m, 6H), 7.18–7.06 (m, 1H), 6.98–6.81 (m, 2H), 6.60–6.39 (m, 2H), 5.26–5.14 (m, 3H), 4.14–4.04 (m, 1H), 3.86 (s, 1.5H), 3.83 (s, 1.5H), 3.25 (d, *J* = 9.8 Hz, 1H), 3.02 (d, *J* = 10.4 Hz, 1H), 2.82–2.65 (m, 2H), 1.82–1.67 (m, 1H), 1.50–1.35 (m, 1H), 0.82 (d, *J* = 12.8 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz): (mixture of rotamers) δ 157.4, 157.3, 155.2, 155.0, 137.2, 137.1, 135.2, 134.6, 131.1, 130.5, 129.33, 129.29, 129.1, 128.9, 128.8, 128.7, 128.5, 128.4, 127.8, 127.7, 127.6, 120.6, 120.5, 110.7, 75.2, 74.8, 66.61, 66.56, 55.3, 47.4, 47.2, 47.1, 46.9, 44.5, 44.4, 31.0, 30.8, 26.9, 26.7;

HRMS (ESI) *m/z* calcd for $C_{23}H_{26}O_4N$ $[M + H]^+$: 380.1856, found: 380.1851.

Second diastereomer-

R_f : 0.4 (EtOAc–PE =50:50);

Yield: 17% over 3 steps;

IR ($CHCl_3$): ν_{max} 3430, 2946, 1688, 1424, 1113, 753 cm^{-1};

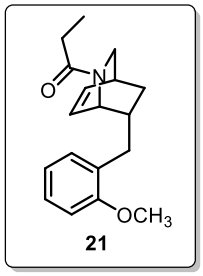
$[\alpha]_D^{25}$ +60.9 (*c* 1.4, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz): (mixture of rotamers) δ 7.42–7.28 (m, 5H), 7.19 (t, *J* = 6.1 Hz, 1H), 7.12–7.00 (m, 1H), 7.00–6.80 (m, 2H), 6.57–6.40 (m, 1H), 6.35–6.16 (m, 1H), 5.21–4.88 (m, 3H), 4.27–4.13 (m, 2H), 3.87 (s, 1.5H), 3.74 (s, 1.5H), 3.29 (d, *J* = 9.8 Hz, 1H), 2.98 (d, *J* = 10.4 Hz, 1H), 2.83 (d, *J* = 17.7 Hz, 1H), 2.73–2.64 (m, 1H), 1.98–1.80 (m, 1H), 1.58 (d, *J* = 12.8 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz): (mixture of rotamers) δ 156.7, 154.9, 154.3, 137.0, 136.8, 135.5, 134.7, 130.8, 130.3, 130.1, 129.8, 128.9, 128.8, 128.5, 128.34, 128.30, 128.0, 127.7, 127.6, 127.5, 127.0, 121.03, 120.95, 111.1, 110.9, 75.6, 75.5, 66.5, 66.4, 55.3, 55.1, 48.0, 47.7, 47.2, 47.0, 45.9, 45.5, 31.1, 31.0, 27.6, 27.5;

HRMS (ESI) *m/z* calcd for $C_{23}H_{26}O_4N$ $[M + H]^+$: 380.1856, found: 380.1851.

1-((1*R*,4*S*,7*R*)-7-(2-Methoxybenzyl)-2-azabicyclo[2.2.2]oct-5-en-2-yl)propan-1-one (21).



21

To a cooled (–78 °C) solution of liquid NH_3 (200 mL) in anhydrous THF (200 mL), was added Li (1.46 g, 211 mmol, 5 equiv). The reaction mixture was stirred for 15 min at that temperature, followed by dropwise addition of **19** (16 g, 42.2 mmol, 1 equiv) in THF (100 mL). The reaction mixture was stirred at –78 °C for the next 15 min, then quenched with solid NH_4Cl (100 gm) and the NH_3 was allowed to evaporate over a period of 12 h by gradually warming it to room temperature. The resultant mixture was filtered, solid was washed with EtOAc, and water (100 mL) was added to the organic layer. The layers were separated and the aqueous layer was extracted with EtOAc (3 X 300 mL). The combined organic layer was washed with brine, dried

over anhydrous Na_2SO_4 and filtered. The concentration of the organic layer *in vacuo* afforded product **20** as a yellow viscous oil which was used for the next reaction without further purification.

To a stirred, cooled (0 °C) solution of amine **20** (9.4 g, 41 mmol, 1 equiv) in anhydrous CH_2Cl_2 (100 mL), were added triethylamine (6.9 mL, 49.2 mmol, 1.2 equiv) and DMAP (1.5 g, 12.3 mmol, 0.3 equiv) followed by propionic anhydride (15.85 mL, 123 mmol, 3 equiv) and the reaction mixture was stirred for 12 h while gradually warming to room temperature. After completion, the reaction mixture was diluted with water (100 mL) and extracted with CH_2Cl_2 (3 X 200 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (30:70) afforded pure bicyclic amide **21** (7.56 g, 63% yield over 2 steps) as a colorless viscous oil.

R_f : 0.3 (EtOAc–PE =50:50);

Yield: 63% over 2 steps;

IR ($CHCl_3$): ν_{max} 2939, 1625, 1432, 1244, 755 cm^{-1};

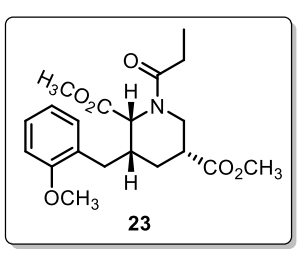
$[\alpha]_D^{25}$ +57.5 (*c* 4, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz): (mixture of rotamers) δ 7.19 (td, *J* = 8.0, 20.0 Hz, 1H), 7.10–7.02 (m, 1H), 6.95–6.77 (m, 2H), 6.53–6.31 (m, 2H), 5.11 (br s, 0.5H), 4.04 (d, *J* = 5.5 Hz, 0.5H), 3.82 (s, 1.5H), 3.80 (s, 1.5H), 3.29–3.21 (m, 1H), 3.06–2.96 (m, 1H), 2.77 (br s, 1H), 2.51–2.27 (m, 3H), 2.21–1.95 (m, 3H), 1.90–1.74 (m, 1H), 1.09 (t, *J* = 7.3 Hz, 1.5H), 0.99 (t, *J* = 7.6 Hz, 1.5H);

^{13}C NMR ($CDCl_3$, 100 MHz): (mixture of rotamers) δ 171.7, 171.6, 157.6, 157.4, 135.7, 133.9, 131.5, 130.4, 130.3, 129.2, 128.0, 127.6, 127.2, 120.4, 120.3, 110.30, 110.28, 55.15, 55.12, 50.7, 47.6, 46.8, 46.5, 39.2, 38.0, 36.3, 35.8, 31.5, 31.0, 30.5, 30.1, 27.2, 27.1, 9.3, 8.9;

HRMS (ESI) *m/z* calcd for $C_{18}H_{24}O_2N$ $[M + H]^+$: 286.1802, found: 286.1801.

Dimethyl (2*R*,3*R*,5*R*)-3-(2-methoxybenzyl)-1-propionylpiperidine-2,5-dicarboxylate (23).

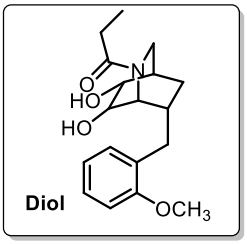


23

To a stirred solution of amide **21** (5 g, 17.5 mmol, 1 equiv) in THF: H_2O (700 mL: 20 mL), were added NMO (2.46 g, 21.05 mmol, 1.2 equiv) and OsO_4 (3 mL, 0.1 M in toluene) at room temperature and the reaction mixture was stirred for next 2 days at that temperature. The

mixture was then quenched with saturated aqueous $Na_2S_2O_3$ (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 X 100 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of the organic layer *in vacuo* afforded crude diol as a thick liquid which was used for the next reaction without further purification.

For analysis purpose, small amount was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (50:50) to afford pure **diol** as a colorless viscous liquid.



R_f : 0.3 (EtOAc–PE =70:30);

IR ($CHCl_3$): ν_{max} 3368, 2936, 1606, 1453, 1243, 1036 cm^{-1};

$[\alpha]_D^{25}$ +47.4 (*c* 1, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz): (mixture of rotamers) δ 7.25–7.15 (m, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 6.95–6.79 (m, 2H), 4.36–4.20 (m, 1.5H), 3.98–3.90 (m, 1H), 3.83 (s, 3H), 3.81–3.74 (m, 1H), 3.50 (s, 0.5H), 3.18–3.08 (m, 1H), 2.86 (br s, 1H), 2.72 (dd, *J* = 7.8, 13.5 Hz, 1H), 2.66–2.52 (m, 2H), 2.36–2.16 (m, 3H), 2.12 (br s, 1H), 2.10–2.00 (m, 0.5H), 1.94 (br s, 0.5H), 1.89–1.79 (m, 0.5H), 1.20–1.15 (m, 1H), 1.12 (t, *J* = 7.4 Hz, 1.5H), 0.92 (t, *J* = 7.4 Hz, 1.5H);

^{13}C NMR ($CDCl_3$, 125 MHz): (mixture of rotamers) δ 175.7, 174.2, 157.5, 157.3, 130.3, 130.2, 127.8, 127.7, 127.5, 120.6, 120.5, 110.5, 110.4, 66.7, 66.6, 65.6, 64.9, 55.3, 55.2, 51.3, 42.5, 40.6, 37.2, 36.1, 34.2, 34.0, 33.3, 33.0, 29.2, 28.4, 26.5, 26.4, 9.1, 8.9;

HRMS (ESI) *m/z* calcd for $C_{18}H_{26}O_4N$ $[M + H]^+$: 320.1856, found: 320.1855.

To a vigorously stirred suspension of silica gel supported $NaIO_4$ (35 g) in CH_2Cl_2 (120 mL), was added a solution of the diol (5.6 g, 17.5 mmol, 1 equiv) in CH_2Cl_2 (120 mL) at room temperature and a heterogeneous mixture was stirred for next 1 h. The mixture was filtered, and the silica gel was thoroughly washed with CH_2Cl_2 (200 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of the organic layer *in vacuo* afforded crude dialdehyde as a thick liquid which was used as such in the next reaction without further purification.

To a cooled (0 °C) solution of dialdehyde (5.56 g, 17.5 mmol, 1 equiv) in *t*-BuOH (450 mL), was added 2-methyl-2-butene (11.15 mL, 105 mmol, 6 equiv) followed by simultaneous dropwise addition of aqueous solution (15 mL each) of $NaClO_2$ (7.3 g, 80.6 mmol, 4.6 equiv) and

$NaH_2PO_4.2H_2O$ (10.94 g, 70.2 mmol, 4 equiv). The reaction mixture was stirred at room temperature for 12 h. *t*-BuOH was removed *in vacuo* and the resulting solution was treated with 0.1 N aqueous NaOH solution (150 mL) and washed with CH_2Cl_2 (3 X 100 mL). The remaining aqueous phase was acidified with HCl to adjust pH ca. 1 and extracted with EtOAc (4 X 200 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of the organic layer *in vacuo* afforded dicarboxylic acid **22** (5.8 g, 95% yield over 3 steps) as a white foam.

Dicarboxylic acid **22** (1 g, 2.86 mmol, 1 equiv) was dissolved in a mixture of $SOCl_2$ (0.52 mL, 7.16 mmol, 2.5 equiv) and anhydrous MeOH (20 mL) at 0 °C. The resulting solution was allowed to reach room temperature and was stirred for 24 h. The reaction mixture was then concentrated *in vacuo*, treated with a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc (3 X 100 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (20:80) afforded compound **23** as a thick colorless liquid (920 mg, 85% yield).

R_f : 0.5 (EtOAc–PE =50:50);

Yield: 85%;

IR ($CHCl_3$): ν_{max} 2948, 1735, 1653, 1430, 1244, 756 cm^{-1};

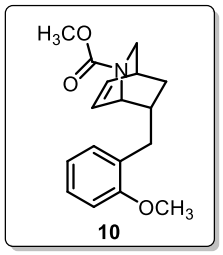
$[\alpha]_D^{25}$ +16.5 (*c* 2, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz): (mixture of rotamers) δ 7.25–7.16 (m, 1H), 7.08 (d, *J* = 6.7 Hz, 1H), 6.95–6.76 (m, 2H), 5.41 (d, *J* = 4.9 Hz, 0.7H), 4.82–4.80 (m, 0.3H), 4.41–4.40 (d, *J* = 4.0 Hz, 0.3H), 3.95 (dd, *J* = 3.5, 13.3 Hz, 0.7H), 3.80 (s, 3H), 3.75 (s, 3H), 3.67 (s, 3H), 3.57 (t, *J* = 12.8 Hz, 0.7H), 3.04 (dd, *J* = 4.3, 13.1 Hz, 0.7H), 2.95–2.91 (m, 0.3H), 2.86–2.81 (m, 0.3H), 2.62–2.57 (m, 0.3H), 2.48–2.35 (m, 3H), 2.34–2.21 (m, 0.7H), 2.06–1.92 (m, 2.3H), 1.70 (q, *J* = 12.7 Hz, 0.7H), 1.14 (t, *J* = 7.3 Hz, 2H), 1.08 (t, *J* = 7.2 Hz, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz): (mixture of rotamers) δ 173.4, 173.2, 172.9, 171.0, 169.6, 157.5, 157.4, 131.0, 130.8, 127.9, 127.7, 127.5, 127.3, 120.4, 120.2, 110.3, 58.0, 55.2, 54.3, 52.0, 51.9, 51.75, 51.68, 43.6, 42.0, 41.3, 39.5, 38.8, 37.7, 33.6, 33.4, 28.8, 28.4, 27.0, 26.5, 9.3, 9.1;

HRMS (ESI) *m/z* calcd for $C_{20}H_{27}O_6NNa$ $[M + Na]^+$: 400.1731, found: 400.1730.

Methyl (1*R*,4*S*,7*R*)-7-(2-methoxybenzyl)-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (10).



10

To a stirred, cooled (0 °C) solution of amine **20** (9.4 g, 41 mmol, 1 equiv) in anhydrous CH_2Cl_2 (100 mL), was added sodium carbonate (13 g, 123 mmol, 3 equiv) followed by dropwise addition of methyl chloroformate (4.75 mL, 61.5 mmol, 1.5 equiv) and the reaction mixture was stirred for 12 h while gradually warming to room temperature. After completion, the reaction mixture was diluted with water (100 mL) and extracted with CH_2Cl_2 (3 X 200 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (15:85) afforded bicyclic alkene **10** (7.75 g, 64% yield over 2 steps) as a thick colorless liquid.

R_f : 0.5 (EtOAc–PE= 30:70);

Yield: 64% over 2 steps;

IR ($CHCl_3$): ν_{max} 2947, 1692, 1453, 1246, 1116 cm^{-1};

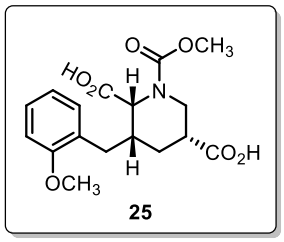
$[\alpha]_D^{25}$ +26.5 (*c* 2, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz): (mixture of rotamers) δ 7.22–7.14 (m, 1H), 7.07 (d, *J* = 7.2 Hz, 1H), 6.91–6.80 (m, 2H), 6.47–6.33 (m, 2H), 4.59 (br s, 0.6H), 4.39 (br s, 0.4H), 3.82 (s, 1.2H), 3.81 (s, 1.8H), 3.64 (s, 1.8H), 3.63 (s, 1.2H), 3.24–3.14 (m, 1H), 3.02–2.88 (m, 1H), 2.76–2.66 (m, 1H), 2.54–2.38 (m, 2H), 2.38–2.26 (m, 1H), 1.83–1.71 (m, 1H), 1.03 (d, *J* = 12.6 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz): (mixture of rotamers) δ 157.5, 155.7, 155.4, 134.5, 134.0, 131.1, 130.3, 130.23, 130.18, 128.0, 127.9, 127.2, 120.2, 110.2, 55.0, 52.14, 52.05, 49.3, 48.9, 47.0, 46.6, 38.4, 35.9, 35.8, 31.1, 30.9, 30.0, 29.9;

HRMS (ESI) *m/z* calcd for $C_{17}H_{21}O_3NNa$ $[M + Na]^+$: 310.1414, found: 310.1414.

(2*R*,3*R*,5*R*)-3-(2-Methoxybenzyl)-1-(methoxycarbonyl)piperidine-2,5-dicarboxylic acid (25).

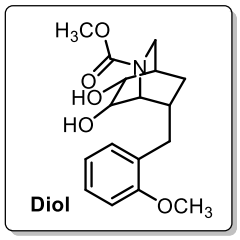


25

To a stirred solution of compound **10** (6.5 g, 22.6 mmol, 1 equiv) in THF: H_2O (875 mL: 25 mL), were added NMO (3.18 g, 27.2 mmol, 1.2 equiv) and OsO_4 (4 mL, 0.1 M in toluene) at room temperature and the reaction mixture was stirred for next 2 days at that temperature. The mixture was then quenched with saturated aqueous $Na_2S_2O_3$ (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 X 200 mL).

The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of the organic layer *in vacuo* afforded crude diol as a thick liquid which was used for the next reaction without further purification.

For analysis purposes, a small amount was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (50:50) to afford pure **diol** as a colorless viscous liquid.



R_f : 0.4 (EtOAc–PE =70:30);

IR ($CHCl_3$): ν_{max} 3402, 2943, 1680, 1458 cm^{-1};

$[\alpha]_D^{25}$ +11.0 (*c* 2, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz): (mixture of rotamers) δ 7.20 (t, *J* = 6.7 Hz, 1H), 7.11 (d, *J* = 6.9 Hz, 1H), 6.94–6.81 (m, 2H), 4.28–4.18 (m, 1H), 3.93 (br s, 2H), 3.83 (s, 3H), 3.73–3.65 (m, 4H), 3.16–3.05 (m, 1H), 2.91 (br s, 2H), 2.75–2.61 (m, 1H), 2.60–2.50 (m, 1H), 2.37 (br s, 1H), 2.04 (br s, 1H), 1.91–1.79 (m, 1H), 1.16 (dd, *J* = 6.1, 13.0 Hz, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz): (mixture of rotamers) δ 157.8, 157.4, 130.2, 130.0, 127.6, 127.5, 120.5, 110.4, 66.6, 65.2, 64.9, 55.2, 53.7, 53.2, 52.6, 52.5, 41.4, 41.3, 36.4, 36.3, 34.0, 33.2, 33.0, 29.0, 28.7;

HRMS (ESI) *m/z* calcd for $C_{17}H_{23}O_5NNa$ $[M + Na]^+$: 344.1468, found: 344.1467.

To a vigorously stirred suspension of silica gel supported $NaIO_4$ (45 g) in CH_2Cl_2 (150 mL), was added a solution of the diol (7 g, 21.8 mmol, 1 equiv) in CH_2Cl_2 (150 mL) at room temperature and a heterogeneous mixture was stirred for next 1 h. The mixture was filtered, and the silica gel was thoroughly washed with CH_2Cl_2 (200 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of the organic layer *in vacuo* afforded crude dialdehyde as a thick liquid which was used for the next reaction without further purification.

To a cooled (0 °C) solution of dialdehyde (6.9 g, 21.6 mmol, 1 equiv) in *t*-BuOH (600 mL), was added 2-methyl-2-butene (13.75 mL, 129 mmol, 6 equiv) followed by simultaneous dropwise addition of aqueous solution (20 mL each) of $NaClO_2$ (9 g, 99.5 mmol, 4.6 equiv) and $NaH_2PO_4.2H_2O$ (13.5 g, 86.5 mmol, 4 equiv). The reaction mixture was stirred at room temperature for 12 h. *t*-BuOH was removed *in vacuo* and the resulting solution was treated with 0.1 N aqueous NaOH solution (200 mL) and washed with CH_2Cl_2 (3 X 100 mL). The remaining aqueous phase was acidified with HCl to adjust pH ca. 1 and extracted with EtOAc (4 X 200

mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of the organic layer *in vacuo* afforded dicarboxylic acid **25** (7.55 g, 95% yield over 3 steps) as a white solid.

R_f : 0.3 (EtOAc);

Yield: 95% over 3 steps;

M. p.: 65–67°C;

IR ($CHCl_3$): ν_{max} 3435, 1711 (broad), 1457, 1243 cm^{-1};

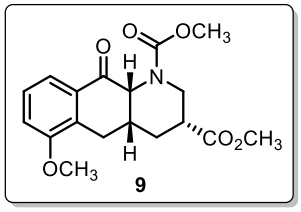
$[\alpha]_D^{25}$ +7.1 (*c* 2, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz): (mixture of rotamers) δ 8.62 (br s, 2H), 7.21 (t, *J* = 6.7 Hz, 1H), 7.14 (d, *J* = 7.3 Hz, 1H), 6.96–6.79 (m, 2H), 4.99 (br s, 0.6H), 4.81 (br s, 0.4H), 4.42–4.26 (m, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.43–3.25 (m, 1H), 3.15–2.96 (m, 1H), 2.57 (dd, *J* = 9.5, 13.1 Hz, 1H), 2.52–2.40 (m, 1H), 2.11 (br s, 1H), 1.99 (d, *J* = 13.4 Hz, 1H), 1.76–1.60 (m, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz): (mixture of rotamers) δ 178.9, 176.3, 157.5, 156.7, 131.1, 127.8, 127.3, 120.4, 110.4, 57.0, 56.8, 55.2, 53.3, 42.0, 41.8, 41.3, 37.9, 33.4, 28.2;

HRMS (ESI) *m/z* calcd for $C_{17}H_{21}O_7NNa$ $[M + Na]^+$: 374.1210, found: 374.1210.

Dimethyl (3*R*,4a*R*,10a*R*)-6-methoxy-10-oxo-3,4,4a,5,10,10a-hexahydrobenzo[g]quinoline-1,3(2*H*)-dicarboxylate (9).



9

To a cooled (0 °C) solution of dicarboxylic acid **25** (2 g, 5.69 mmol, 1 equiv) in anhydrous CH_2Cl_2 (20 mL), were added anhydrous *N*,*N*-dimethylformamide (2–3 drops) and oxalyl chloride (1.03 mL, 11.96 mmol, 2.1 equiv) dropwise and the reaction mixture was stirred at room temperature for 1 h. The acid chloride thus formed was used immediately for the next reaction.

To a cooled (0 °C) solution of $TiC1_4$ (3.18 mL, 28.5 mmol, 5 equiv) in anhydrous CH_2C1_2 (20 mL) was added acid chloride solution over a period of 15 min and the reaction mixture was stirred at 0 °C for 2 h. Anhydrous MeOH (10 mL) was carefully added to the reaction mixture at –30 °C and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was then poured into a rapidly stirred mixture of ice (~50 g), 35% HC1 (10 mL) and CH_2C1_2 (50 mL) and the mixture was stirred for 15 min. The organic layer was separated, and the aqueous layer was extracted with CH_2C1_2 (3 X 100 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo*

followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded pure tricyclic keto-ester **9** as a thick colorless liquid (1.23 g, 62% yield).

R_f : 0.5 (EtOAc–PE =30:70);

Yield: 62%;

IR ($CHCl_3$): ν_{max} 1717, 1699, 1644, 1450, 1263 cm^{-1};

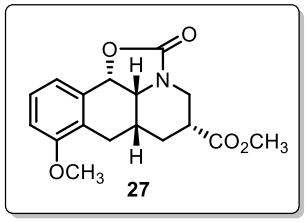
$[\alpha]_D^{25}$ +7.5 (*c* 2, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz): (mixture of rotamers) δ 7.62 (dd, *J* = 3.4, 7.6 Hz, 1H), 7.31–7.25 (m, 1H), 7.05 (dd, *J* = 4.4, 7.8 Hz, 1H), 5.20 (d, *J* = 5.0 Hz, 0.6H), 5.01 (d, *J* = 5.0 Hz, 0.4H), 4.39 (dd, *J* = 4.2, 13.4 Hz, 0.4H), 4.26 (dd, *J* = 4.2, 13.7 Hz, 0.6H), 3.86 (s, 3H), 3.79 (s, 2H), 3.72 (s, 1H), 3.62 (s, 3H), 3.15–3.06 (m, 2H), 2.88 (t, *J* = 12.8 Hz, 0.6H), 2.79 (t, *J* = 12.8 Hz, 0.4H), 2.64–2.53 (m, 2H), 2.00–1.90 (m, 1H), 1.54–1.43 (m, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz): (mixture of rotamers) δ 193.9, 172.8, 172.7, 157.2, 157.13, 157.10, 156.8, 132.3, 132.2, 129.6, 129.5, 127.35, 127.28, 118.81, 118.78, 115.0, 114.9, 60.9, 60.4, 55.65, 55.61, 53.0, 52.9, 51.80, 51.77, 42.0, 41.9, 41.7, 41.5, 35.3, 35.1, 29.3, 29.2, 27.6;

HRMS (ESI) *m/z* calcd for $C_{18}H_{21}O_6NNa$ $[M + Na]^+$: 370.1261, found: 370.1259.

Methyl (3^1*R*,5*R*,6a*R*,11b*S*)-8-methoxy-2-oxo-3^1,5,6,6a,7,11b-hexahydro-2*H*,4*H*-benzo[g]oxazolo[5,4,3-*ij*]quinoline-5-carboxylate (27).



27

To a cooled (0 °C) solution of compound **9** (650 mg, 1.87 mmol, 1 equiv) in anhydrous THF (10 mL), was added $LiBH_4$ (41 mg, 1.87 mmol, 1 equiv) and the reaction mixture was stirred for 2 h while warming to room temperature. The reaction mixture was quenched with 1 N HCl at 0 °C and stirred for 2 h at room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 X 50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (50:50) afforded tetracyclic carbamate **27** (405 mg, 68% yield) as a white solid.

R_f : 0.2 (EtOAc–PE =70:30);

Yield: 68%;

M. p.: 203–205 °C;

IR ($CHCl_3$): ν_{max} 1741, 1642, 1442, 756 cm^{-1};

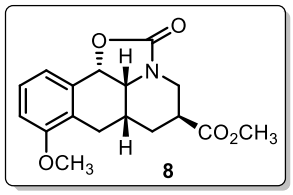
$[\alpha]_D^{25}$ –152.1 (*c* 1.2, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.21 (t, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 5.59 (d, *J* = 9.2 Hz, 1H), 4.54 (d, *J* = 13.4 Hz, 1H), 4.10 (dd, *J* = 3.6, 9.0 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.12 (dd, *J* = 4.8, 13.5 Hz, 1H), 2.97 (dd, *J* = 3.1, 15.6 Hz, 1H), 2.65 (br s, 1H), 2.55 (d, *J* = 14.5 Hz, 1H), 2.17 (t, *J* = 13.0 Hz, 1H), 2.09 (td, *J* = 5.5, 14.6 Hz, 1H), 1.91 (td, *J* = 3.4, 12.7 Hz, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.7, 156.4, 156.1, 132.0, 127.9, 127.3, 122.8, 111.1, 74.1, 55.6, 55.3, 52.4, 40.9, 35.7, 32.6, 29.3, 21.2;

HRMS (ESI) *m/z* calcd for $C_{17}H_{19}O_5NNa$ $[M + Na]^+$: 340.1155, found: 340.1154.

Methyl (3^1*R*,5*S*,6a*R*,11b*S*)-8-methoxy-2-oxo-3^1,5,6,6a,7,11b-hexahydro-2*H*,4*H*-benzo[g]oxazolo[5,4,3-*ij*]quinoline-5-carboxylate (8).



8

To a cooled (0 °C) solution of compound **27** (350 mg, 1.10 mmol, 1 equiv) in anhydrous MeOH (10 mL), was added $NaOCH_3$ (72 mg, 1.32 mmol, 1.2 equiv) and the reaction mixture was stirred for 12 h while warming to the room temperature. The reaction mixture was quenched with 1 N HCl at 0 °C. The solvent was evaporated under reduced pressure and the reaction mixture was extracted with EtOAc (3 X 50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (30:70) afforded tetracyclic carbamate **8** (245 mg, 70% yield) as a white solid.

R_f : 0.4 (EtOAc–PE =50:50);

Yield: 70%;

M. p.: 175–177 °C;

IR ($CHCl_3$): ν_{max} 1741, 1642, 1442, 757 cm^{-1};

$[\alpha]_D^{25}$ –118.8 (*c* 0.5, $CHCl_3$);

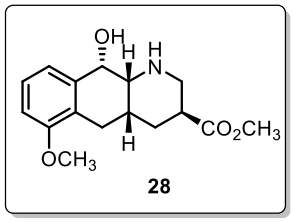
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (t, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 5.62 (d, *J* = 9.2 Hz, 1H), 4.23 (dd, *J* = 3.8, 13.0 Hz, 1H), 4.13 (dd, *J* = 3.4, 8.8 Hz,

1H), 3.84 (s, 3H), 3.73 (s, 3H), 3.07–2.94 (m, 2H), 2.86–2.75 (m, 1H), 2.44 (dd, *J* = 13.0, 16.0 Hz, 1H), 2.27 (d, *J* = 15.3 Hz, 1H), 2.05–1.91 (m, 2H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.3, 156.5, 156.2, 131.9, 127.5, 127.3, 122.8, 111.1, 74.2, 55.6, 54.9, 52.1, 42.3, 35.4, 32.0, 31.2, 20.7;

HRMS (ESI) *m/z* calcd for $C_{17}H_{20}O_5N$ $[M + H]^+$: 318.1336, found: 318.1333.

Methyl (3*S*,4a*R*,10*S*,10a*R*)-10-hydroxy-6-methoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinoline-3-carboxylate (28).



28

A stirred solution of **8** (225 mg, 0.71 mmol, 1 equiv) in 10% ethanolic NaOH (10 mL) was heated under reflux for 1 h. After evaporation of the solvent *in vacuo*, the residue was dissolved in water (5 mL) and treated with 6 N HCl at 0 °C to adjust the pH 6.5–7. The reaction mixture was extracted with EtOAc (5 X 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and filtered. The concentration of the organic layer *in vacuo* afforded amino–acid as a sticky yellow solid.

To a cooled (0 °C) solution of the above crude compound in MeOH (10 mL), was added 10% solution of CH_2N_2 in Et_2O (10 mL) dropwise and the reaction mixture was stirred for 1 h while warming to room temperature. The solvent was evaporated under reduced pressure and the reaction mixture was extracted with EtOAc (3 X 50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (50:50) afforded amino–alcohol **28** (110 mg, 53% yield over 2 steps) as a sticky yellow liquid.

R_f : 0.5 (EtOAc);

Yield: 53% over 2 steps;

IR ($CHCl_3$): ν_{max} 3426, 1715, 1263, 758 cm^{-1};

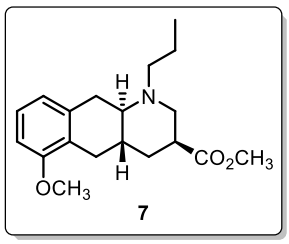
$[\alpha]_D^{25}$ –61.1 (*c* 1, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.25–7.13 (m, 2H), 6.72 (dd, *J* = 1.6, 7.1 Hz, 1H), 4.79 (d, *J* = 4.4 Hz, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 3.32 (d, *J* = 8.3 Hz, 1H), 2.93–2.49 (m, 6H), 2.29–1.70 (m, 4H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 174.8, 156.5, 138.1, 126.8, 122.8, 118.6, 108.1, 69.6, 57.9, 55.2, 51.7, 48.1, 37.8, 32.2, 29.4, 22.7;

HRMS (ESI) *m/z* calcd for $C_{16}H_{22}O_4N$ $[M + H]^+$: 292.1543, found: 292.1541.

Methyl (3*S*,4a*R*,10a*R*)-6-methoxy-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinoline-3-carboxylate (7).



7

To a stirred solution of compound **28** (80 mg, 0.27 mmol, 1 equiv) in toluene (10 mL), was added PTSA (157 mg, 0.82 mmol, 3 equiv) and the reaction mixture was refluxed for 2 h using Dean-Stark apparatus. The reaction mixture was cooled to 0 °C, MeOH (10 mL) and $NaBH_3CN$ (52 mg, 0.82 mmol, 3 equiv) were added and the reaction mixture was stirred at room temperature for 12 h. After completion, the solvent was evaporated under reduced pressure. The residue was treated with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 X 10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of the organic layer *in vacuo* afforded amine which was used for the next reaction without further purification.

To a solution of crude amine (70 mg, 0.25 mmol, 1 equiv) in anhydrous DMF (5 mL) was added pulverized K_2CO_3 (53 mg, 0.38 mmol, 1.5 equiv) and the reaction mixture was heated to 50 °C. After stirring for 20 min at that temperature, *n*-propyl iodide (0.13 g, 0.76 mmol, 3 equiv) was added and the reaction mixture was stirred for an additional 2.5 h at 50 °C. The reaction mixture was cooled to room temperature and extracted with EtOAc (3 X 10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded ester **7** (53 mg, 61% yield over 2 steps) as a yellow solid.

R_f : 0.5 (EtOAc–PE =20:80);

Yield: 61% over 2 steps;

M. p.: 96–97 °C;

IR ($CHCl_3$): ν_{max} 1718, 1263, 775 cm^{-1};

$[\alpha]_D^{25}$ –105.2 (*c* 1, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.09 (t, *J* = 7.8 Hz, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 3.46 (td, *J* = 2.3, 11.6 Hz, 1H), 3.12 (dd, *J* = 5.0, 16.0 Hz, 1H), 2.97 (dd, *J* = 4.6, 17.2 Hz, 1H), 2.84–2.54 (m, 3H), 2.46–2.27 (m, 3H), 2.26–2.02 (m, 2H), 1.99–1.80 (m, 1H), 1.60–1.42 (m, 2H), 1.37–1.29 (m, 1H), 0.89 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 174.4, 156.7, 136.7, 126.1, 124.6, 121.3, 106.8, 61.5, 55.2, 54.5, 53.6, 51.6, 39.9, 34.8, 34.2, 32.3, 30.7, 18.2, 11.8;

HRMS (ESI) *m/z* calcd for $C_{19}H_{28}O_3N$ $[M + H]^+$: 318.2064, found: 318.2065.

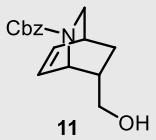
2.2.4.2. HPLC chromatograms of 11

D-7000 HPLC System Manager Report

Analyzed: 06/06/17 01:12 PM
Reported: 06/06/17 02:33 PM
Processed: 06/06/17 02:33 PM

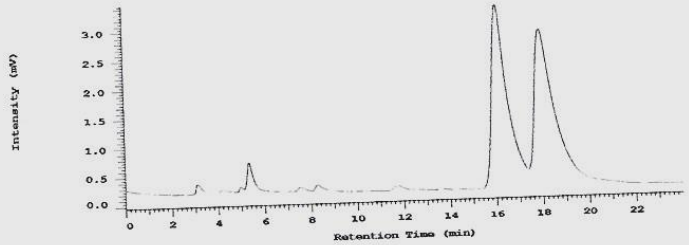
Data Path: C:\WIN32APP\HSM\HPLC\DATA\9511\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: AK-788 (Rac)
Injection from this vial: 1 of 1
Sample Description: IPA:n-Hexane (6:94)

Series:9511
Volume: 10.0 ul



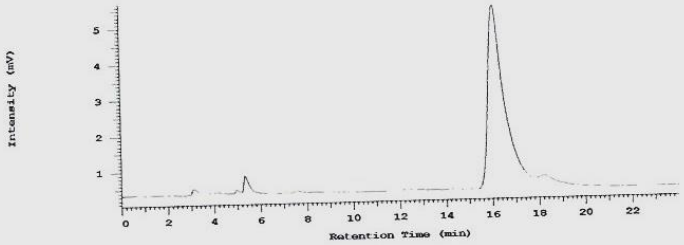
11

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	16.09	147948	49.501	BV
2	17.97	150929	50.499	VB
		298877	100.000	

Chrom Type: HPLC Channel : 1



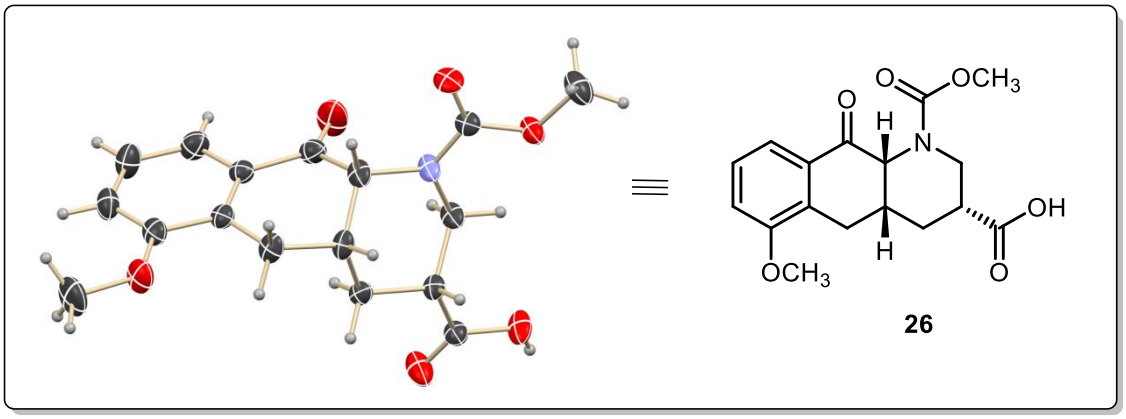
No.	RT	Area	Conc 1	BC
1	16.09	249355	98.769	BV
2	18.23	3108	1.231	TBB
		252463	100.000	

Peak rejection level: 0

Project Leader: Dr.S.P.Chavan
Column : Chiralcel OD-H (250 mmx4.6mm)
Mobile Ph : IPA:n=Hexane(6:94)
Wavelength : 254nm
Flow : 1.0 ml/min.
Inject vol: 2ul

2.2.4.3. X–ray crystallography details of compounds 26, 27 and 8

X–ray crystallography details of compound **26**



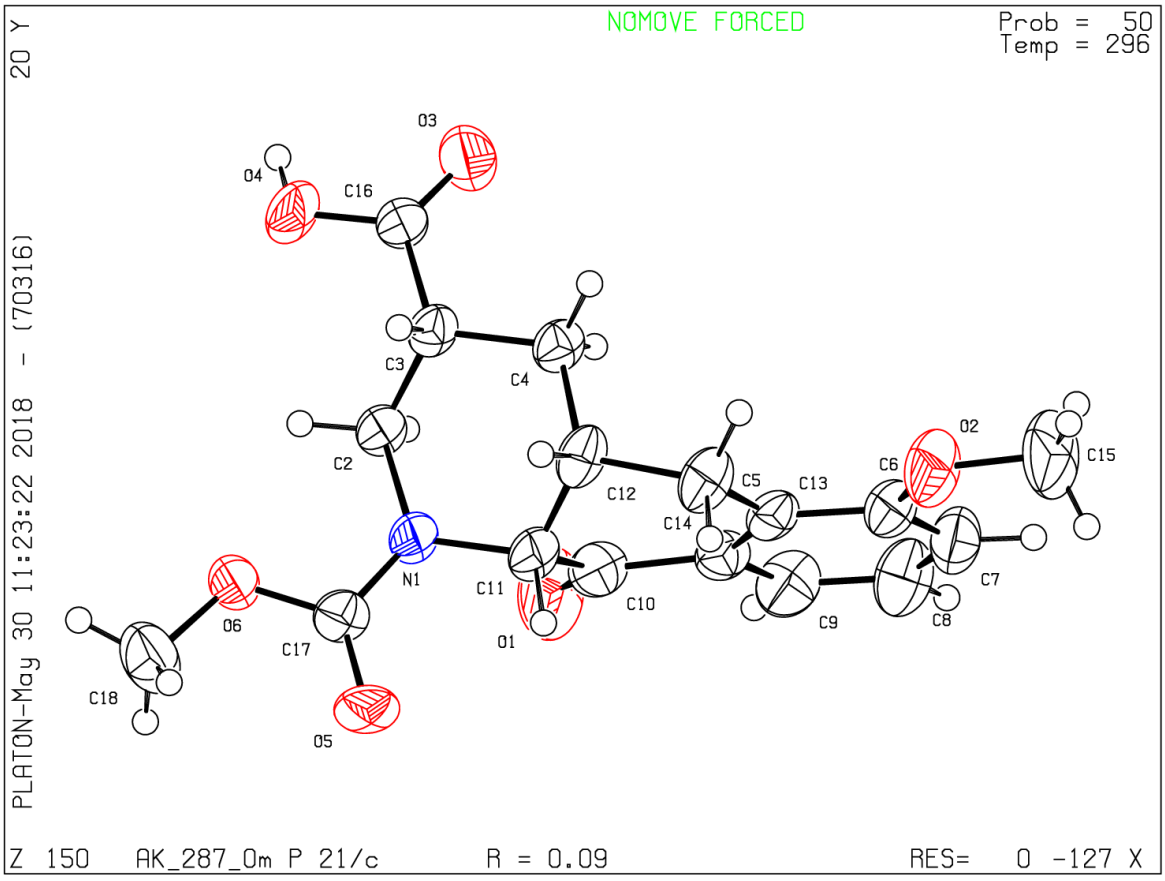
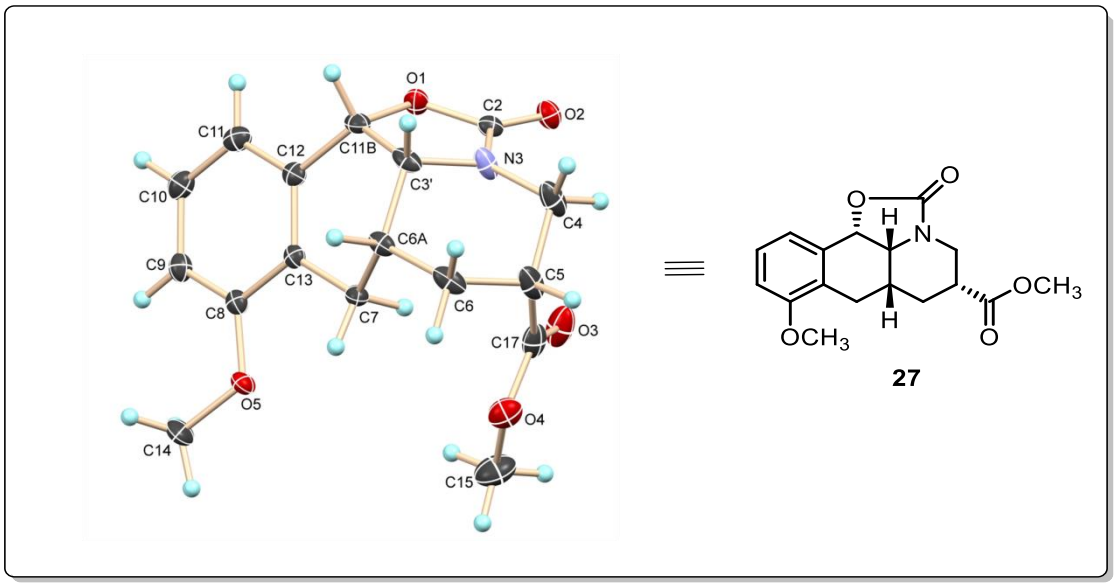


Table 1: Crystallographic Information for compound **26**

Crystal Data	**AK_287**
Formula	$C_{17}H_{19}NO_6$
M_r	333.33
Crystal Size, mm	0.520 x 0.490 x 0.420
Temp. (K)	296(2)
Crystal Syst.	Monoclinic
Space Group	$P2_1/c$
a/Å	15.7499(16)
b/Å	7.0810(9)
c/Å	15.9588(15)
α/°	90
β/°	113.883(7)
γ/°	90
V/Å^3	1627.4(3)
Z	4
D_{calc}/g cm^{-3}	1.360
μ/mm^{-1}	0.104
F(000)	704
Ab. Correct.	multi-scan
T_{min}/ T_{max}	0.948/0.958
$2\theta_{max}$	51
Total reflns.	11405
Unique reflns.	3026
Obs. reflns.	2203
h, k, l (min, max)	(-19, 18), (-8, 8), (-19, 19)
R_{int}	0.0626
No. of parameters	220
R1 [$I > 2\sigma(I)$]	0.0870
wR2[$I > 2\sigma(I)$]	0.1982
R1 [all data]	0.1167
wR2 [all data]	0.2161
goodness-of-fit	1.148
$\Delta\rho_{max}$, $\Delta\rho_{min}$(eÅ^{-3})	+0.289, -0.279

X–ray crystallography details of compound **27**



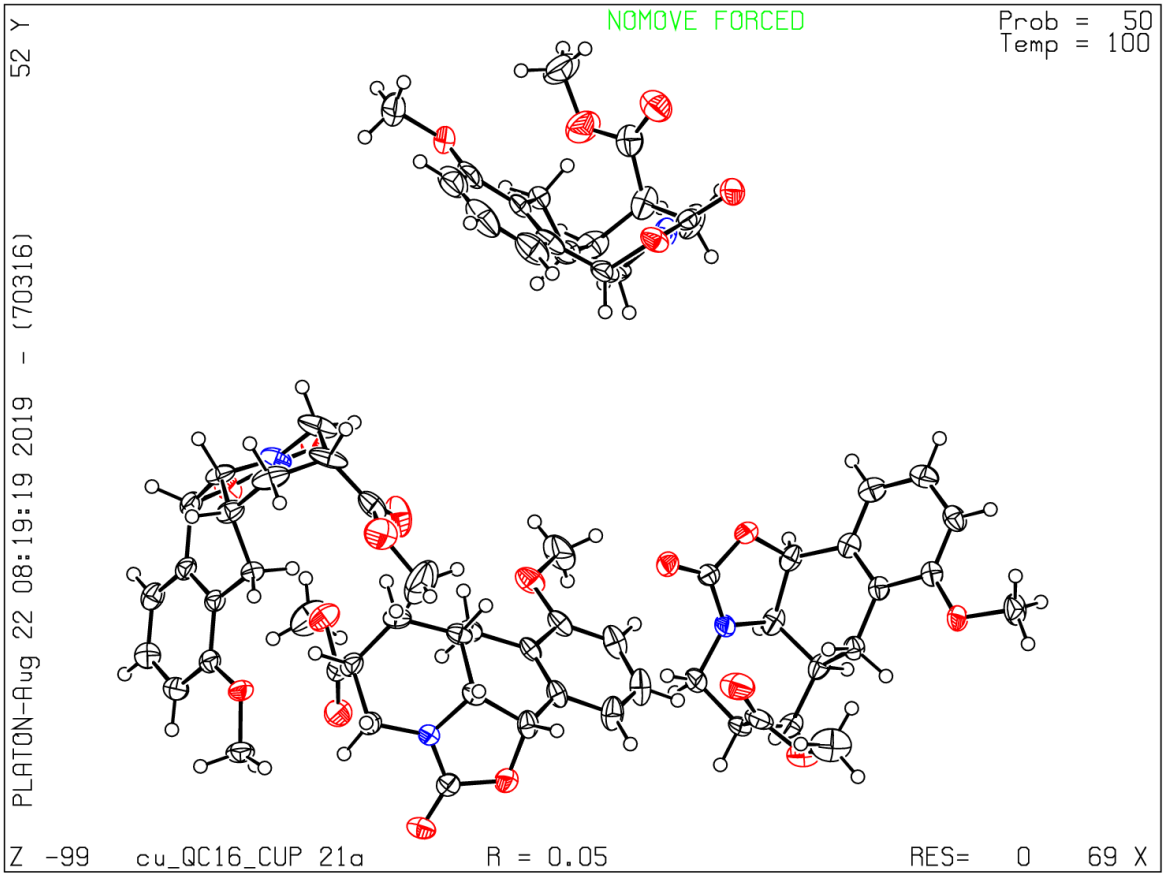
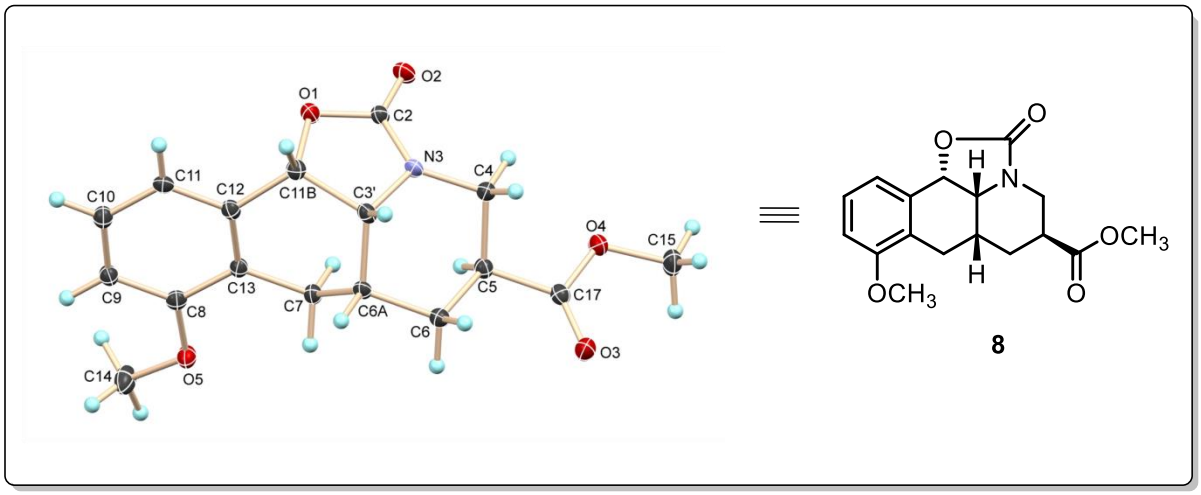


Table 2: Crystallographic Information for compound **27**

Crystal Data	**QC_16**
Formula	$C_{17}H_{19}NO_5$
M_r	317.33
Crystal Size, mm	0.326 x 0.119 x 0.080
Temp. (K)	100(2)
Crystal Syst.	Monoclinic
Space Group	$P2_1$
a/Å	11.3888(8)
b/Å	15.4213(10)
c/Å	17.6145(11)
α/°	90
β/°	90.411(3)
γ/°	90
V/Å^3	3093.6(4)
Z	8
D_{calc}/g cm^{-3}	1.363
μ/mm^{-1}	0.836
F(000)	1344
Ab. Correct.	multi-scan
T_{min}/ T_{max}	0.772/0.936
$2\theta_{max}$	140
Total reflns.	56759
Unique reflns.	11003
Obs. reflns.	10321
h, k, l (min, max)	(-13, 13), (-18, 18), (-21, 21)
R_{int}	0.0548
No. of parameters	837
R1 [$I > 2\sigma(I)$]	0.0503
wR2[$I > 2\sigma(I)$]	0.1137
R1 [all data]	0.0541
wR2 [all data]	0.1162
goodness-of-fit	1.130
$\Delta\rho_{max}$, $\Delta\rho_{min}$(eÅ^{-3})	+0.364, -0.235

X–ray crystallography details of compound **8**



8

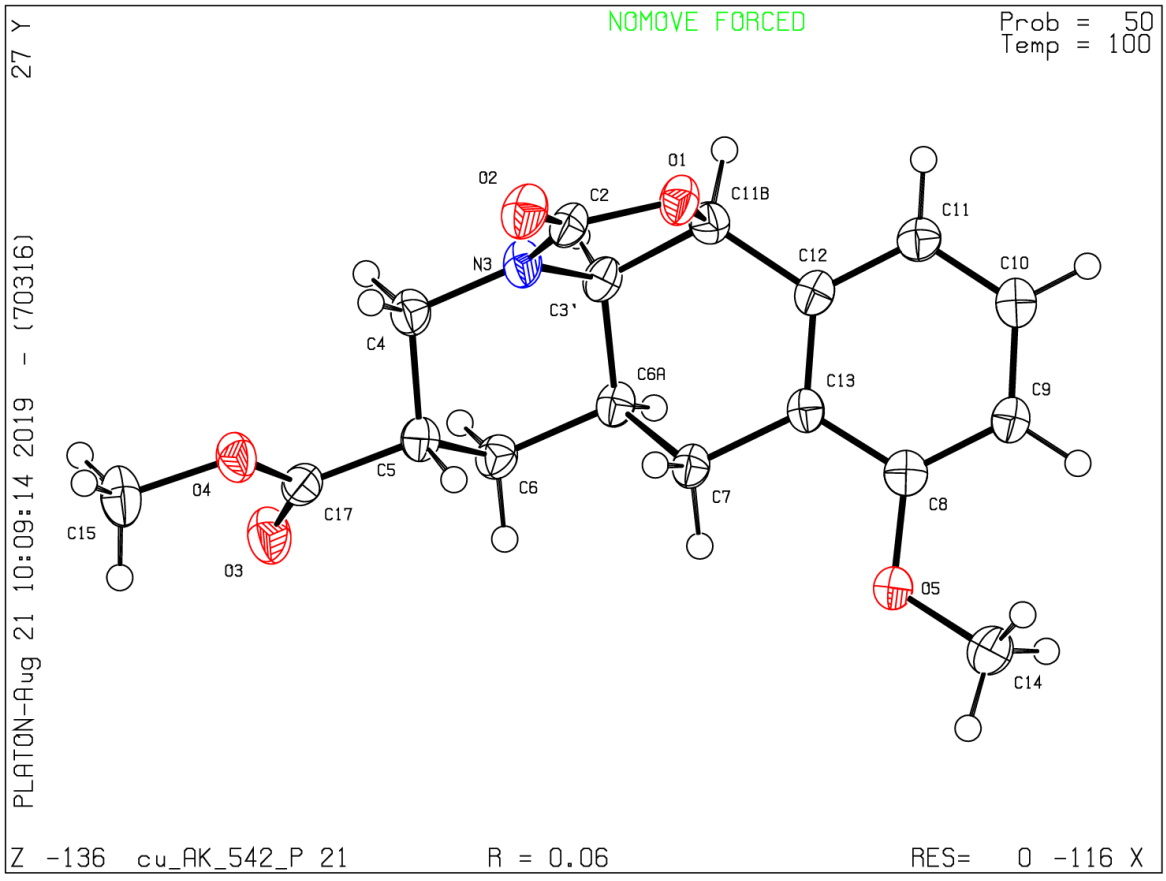


Table 3: Crystallographic Information for compound **8**

Crystal Data	**AK_542**
Formula	$C_{17}H_{19}NO_5$
M_r	317.33
Crystal Size, mm	0.300 x 0.090 x 0.030
Temp. (K)	100(2)
Crystal Syst.	Monoclinic
Space Group	$P2_1$
a/Å	11.5760(3)
b/Å	5.99210(10)
c/Å	12.1748(3)
α/°	90
β/°	114.2320(10)
γ/°	90
V/Å^3	770.09(3)
Z	2
D_{calc}/g cm^{-3}	1.369
μ/mm^{-1}	0.840
F(000)	336
Ab. Correct.	multi-scan
T_{min}/ T_{max}	0.787/0.975
$2\theta_{max}$	149.4
Total reflns.	29023
Unique reflns.	3074
Obs. reflns.	2639
h, k, l (min, max)	(-14, 14), (-7, 6), (-15, 15)
R_{int}	0.0897
No. of parameters	210
R1 [$I > 2\sigma(I)$]	0.0611
wR2[$I > 2\sigma(I)$]	0.1274
R1 [all data]	0.0750
wR2 [all data]	0.1390
goodness-of-fit	1.054
$\Delta\rho_{max}$, $\Delta\rho_{min}$(eÅ^{-3})	+0.298, -0.285

X-ray intensity data measurements of compound **26** were carried out on a Bruker SMART APEX II CCD diffractometer with graphite monochromatized (MoKα= 0.71073 Å) radiation at 297(2) K. The X-ray generator was operated at 50 kV and 30 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 12 frames (total 36 frames). Data were collected with ω scan width of 0.5° at eight different settings of φ and 2θ keeping the sample-to-detector distance fixed at 5.00 cm. The unit-cell measurements, data collection, integration, scaling, and absorption corrections for these crystals were performed by using Bruker APEX2 Program suite.[1] The diffraction images were integrated by using Bruker SAINT Programs.[2] The data were corrected for Lorentz-polarization and absorption effects by using the multi-scan method by using SADABS[3] with the transmission coefficients. Using APEX2 program suite, the structure was solved with the ShelXS-97 (Sheldrick, 2008)[4] structure solution program, using direct methods. The model was refined with a version of ShelXL-2013 (Sheldrick, 2015)[5] using Least Squares minimization based on F^2. All the H-atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms by using the HFIX command in SHELX-TL. A check of the final CIFs by using PLATON[6] did not show any missing symmetry. An *ORTEP* III[7] view of compound **26** was drawn with 50% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii.

X-ray intensity data measurements of compounds **27** and **8** were carried out on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatech multilayer mirrors optics. The intensity measurements were carried out with Cu micro-focus sealed tube diffraction source (Cu-Kα = 1.54178 Å) at 100(2) K temperature. The X-ray generator was operated at 50 kV and 1.4 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 12 frames. Data were collected with ω scan width of 0.5º at different settings of φ and ω with a frame time of 15-20 secs keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX3 program (Bruker, 2016). All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2016).[8] SHELX-97 was used for structure solution and full-matrix least-squares refinement on F^2.[4] Positions of the H-atoms were calculated as per the

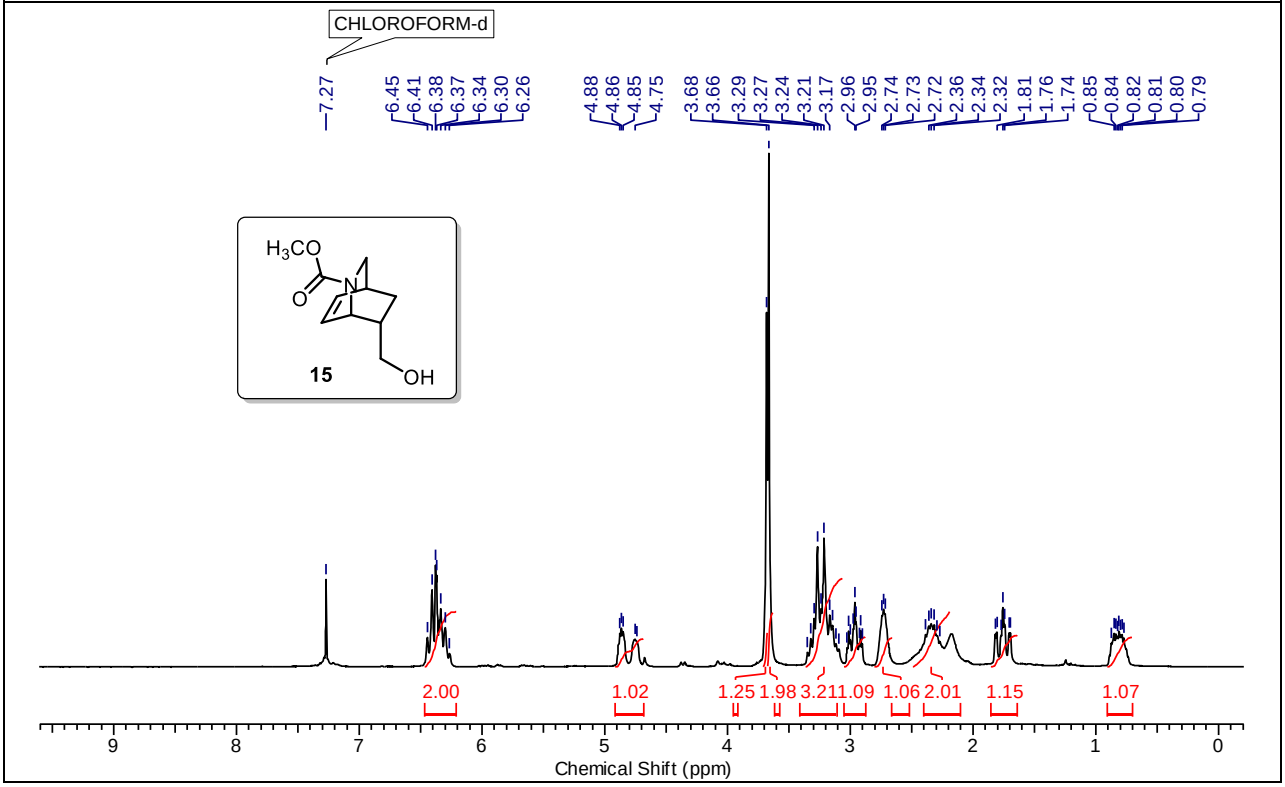
hybridization and constrained to ride on their parent atoms. Single crystal-XRD data of samples **27** and **8** are summarized in table 2 and table 3 respectively. An *ORTEP* III[7] of compounds was drawn at the 30% probability displacement ellipsoids level and H atoms are shown as small spheres of arbitrary radii.

References

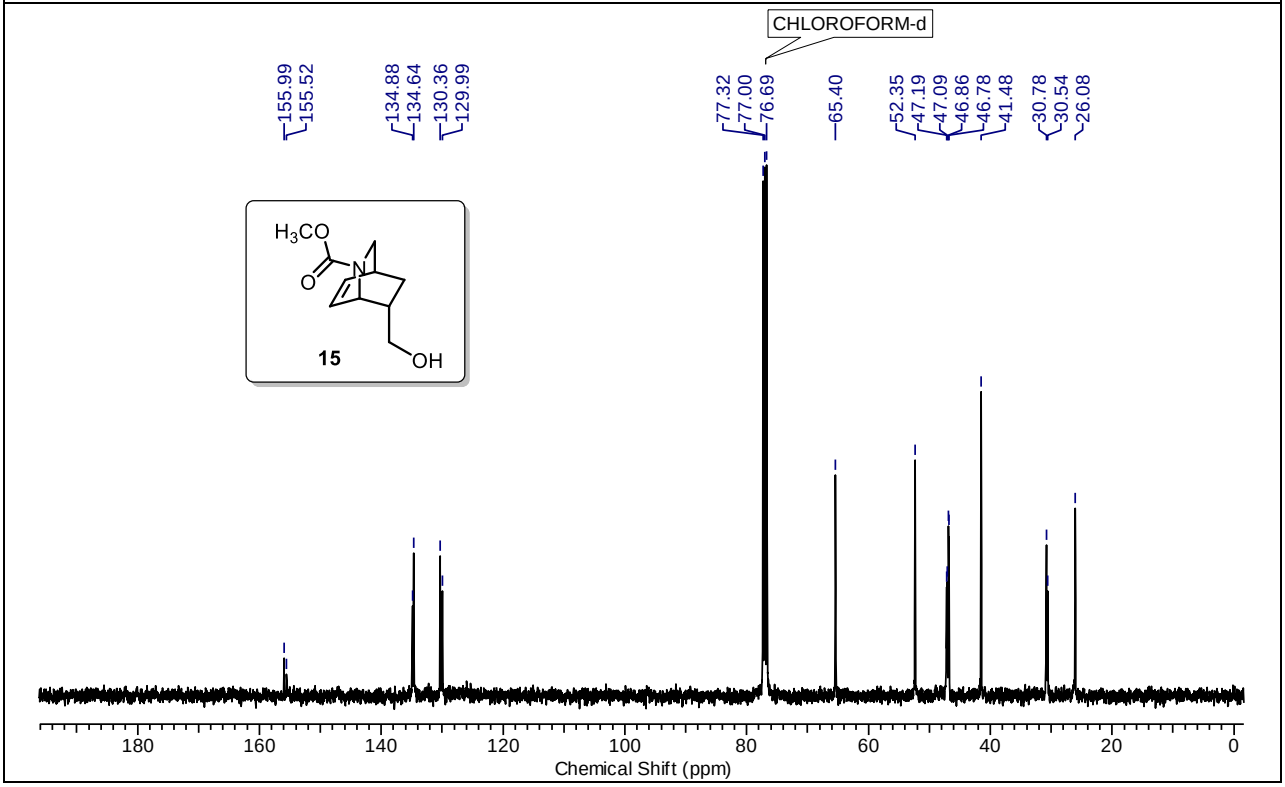
1. Bruker (2006). *APEX2*, *SAINT* and *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA.
2. Bruker 2006b. SAINT, Version 7.60a. Bruker AXS Inc., Madison, Wisconsin, USA.
3. Bruker 2006a. SADABS, Version 2.05. Bruker AXS Inc., Madison, Wisconsin, USA.
4. G. M. Sheldrick, *Acta Crystallogr*., **2008**, *A64*, 112.
5. G. M. Sheldrick, *Acta Crystallogr*., **2015**, *C71*, 3–8.
6. a) A. L. Spek, PLATON, A Multipurpose Crystallographic Tool; Utrecht University: Utrecht, Netherland, 2002; b) A. L. Spek, *J. Appl. Crystallogr.* **2003**, *36*, 7–13.
7. L. J. Farrugia, *J. Appl. Crystallogr.* **2012**, *45*, 849–854.
8. Bruker (**2016**). *APEX3*, *SAINT* and *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA.

2.2.5. Spectral Data

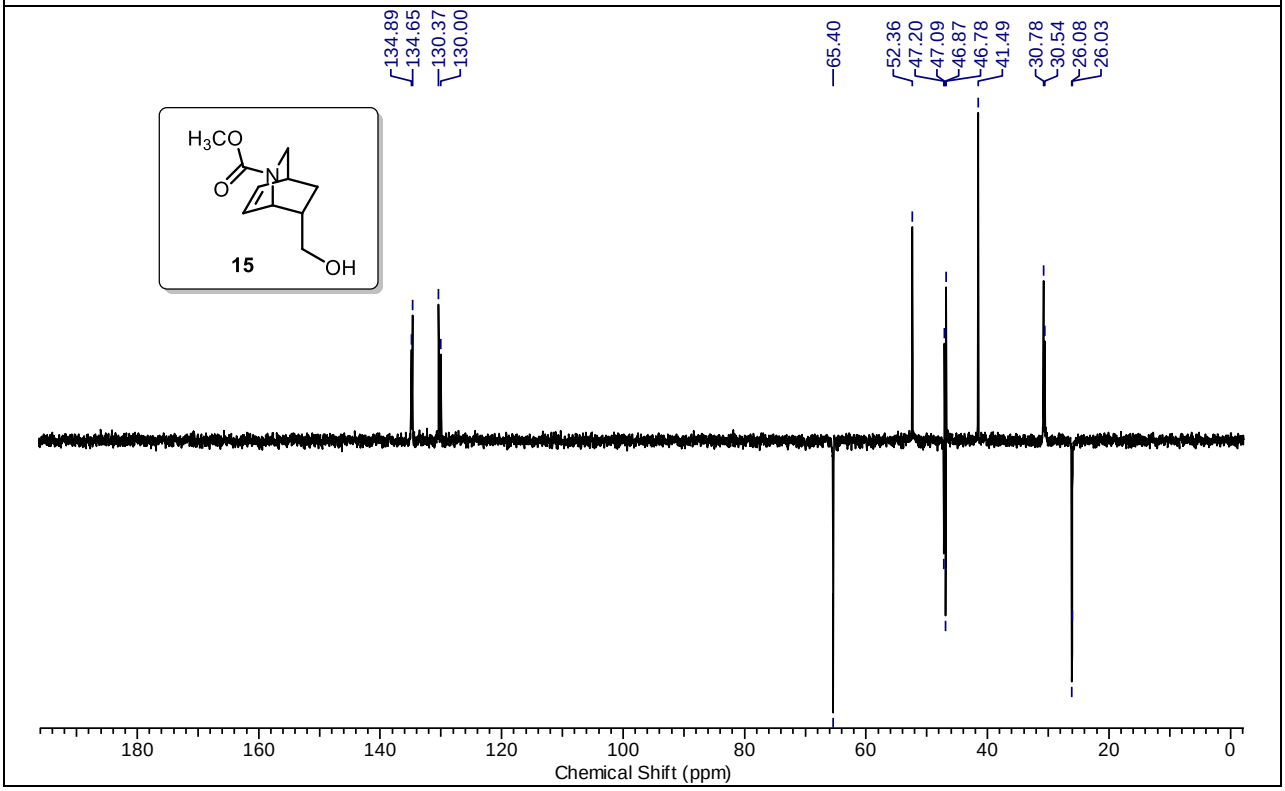
^{1}H-NMR spectrum of compound 15 ($CDCl_3$, 200 MHz)



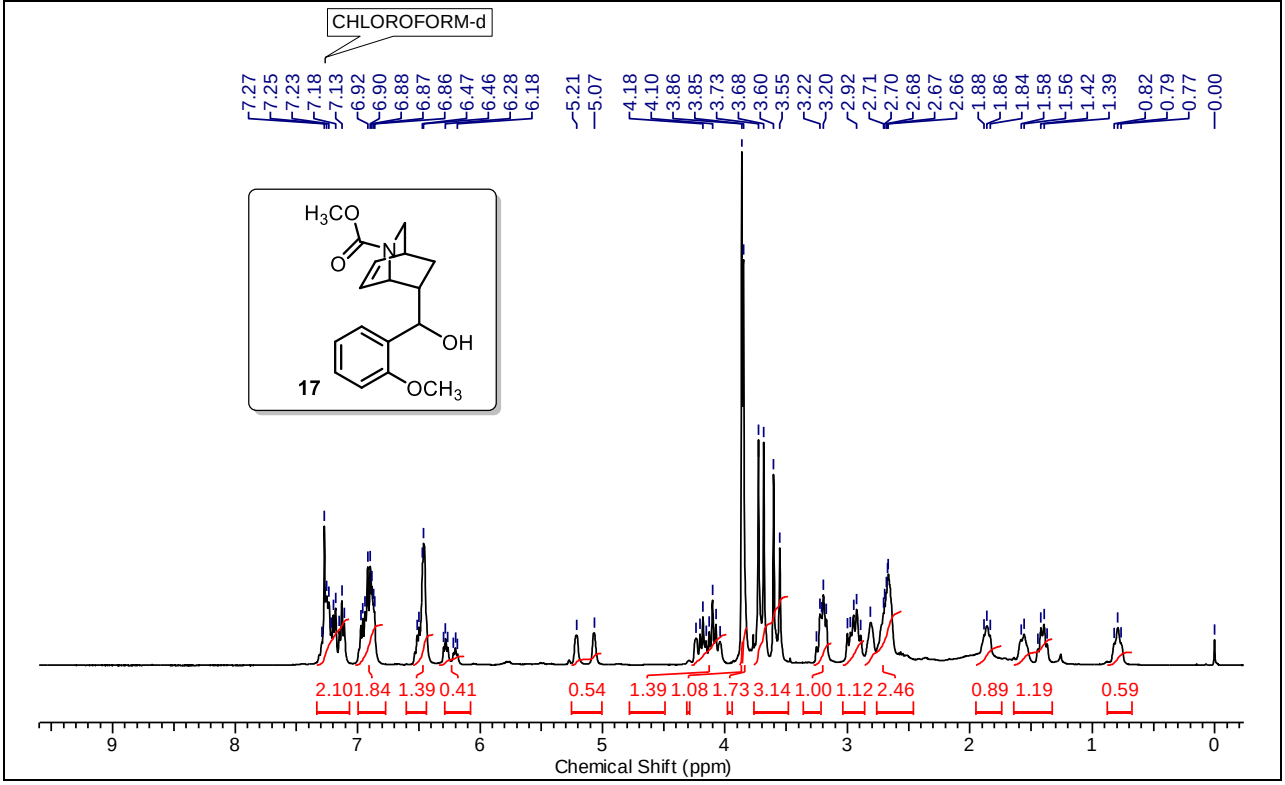
^{13}C-NMR spectrum of compound 15 ($CDCl_3$, 100 MHz)



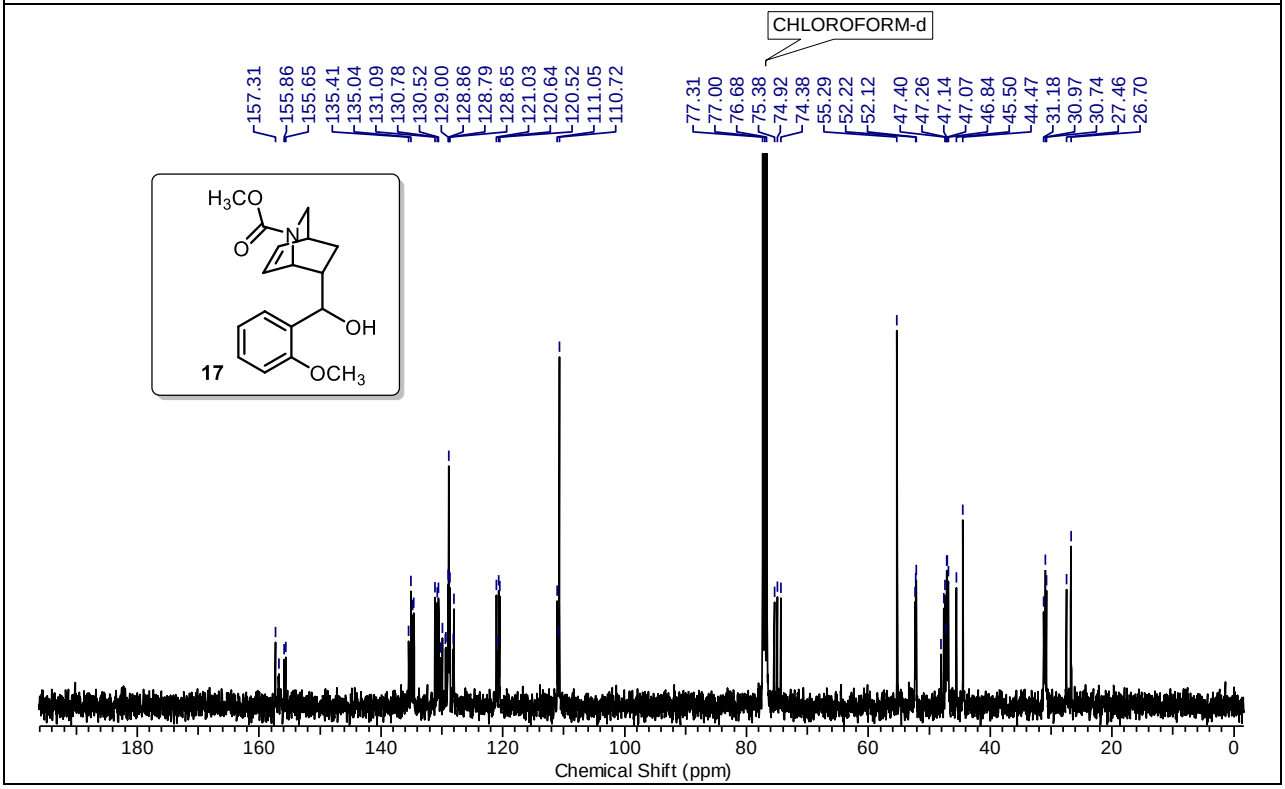
DEPT NMR spectrum of compound 15 ($CDCl_3$, 100 MHz)



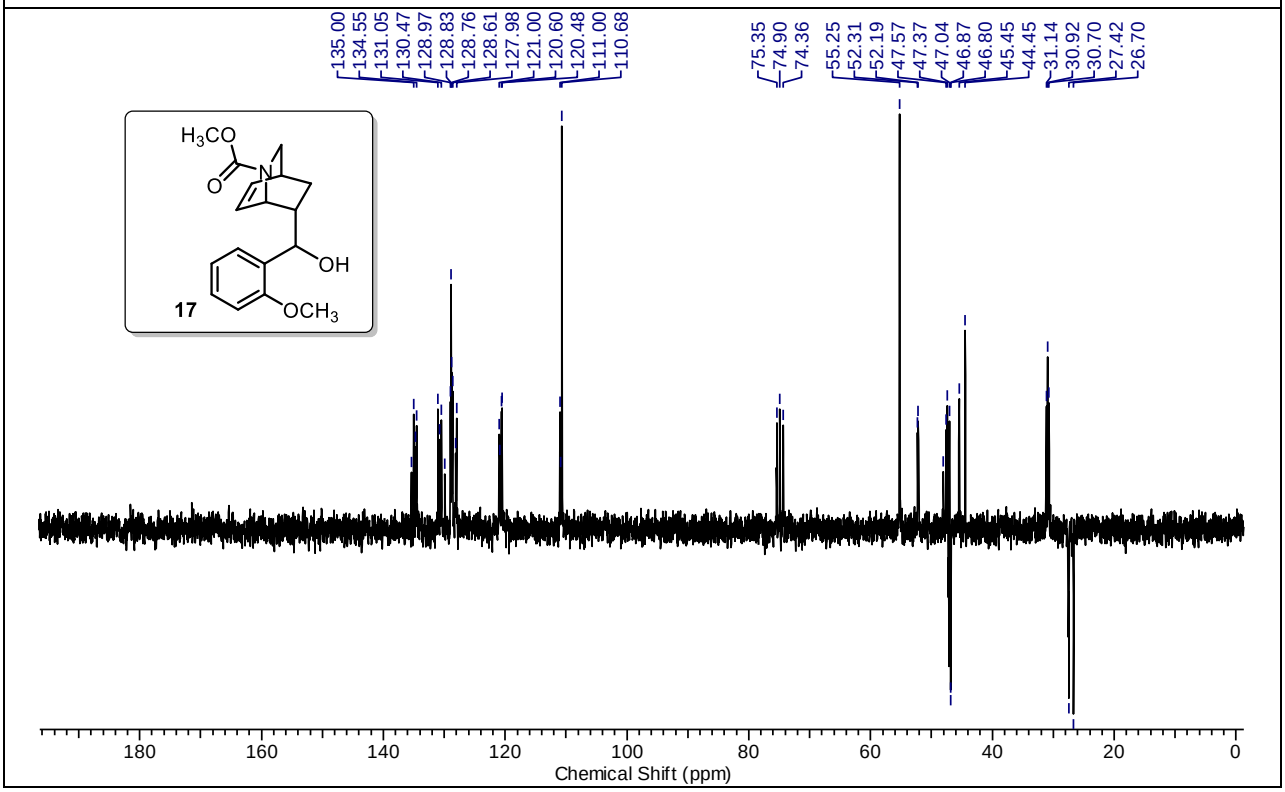
^{1}H-NMR spectrum of compound 17 ($CDCl_3$, 400 MHz)



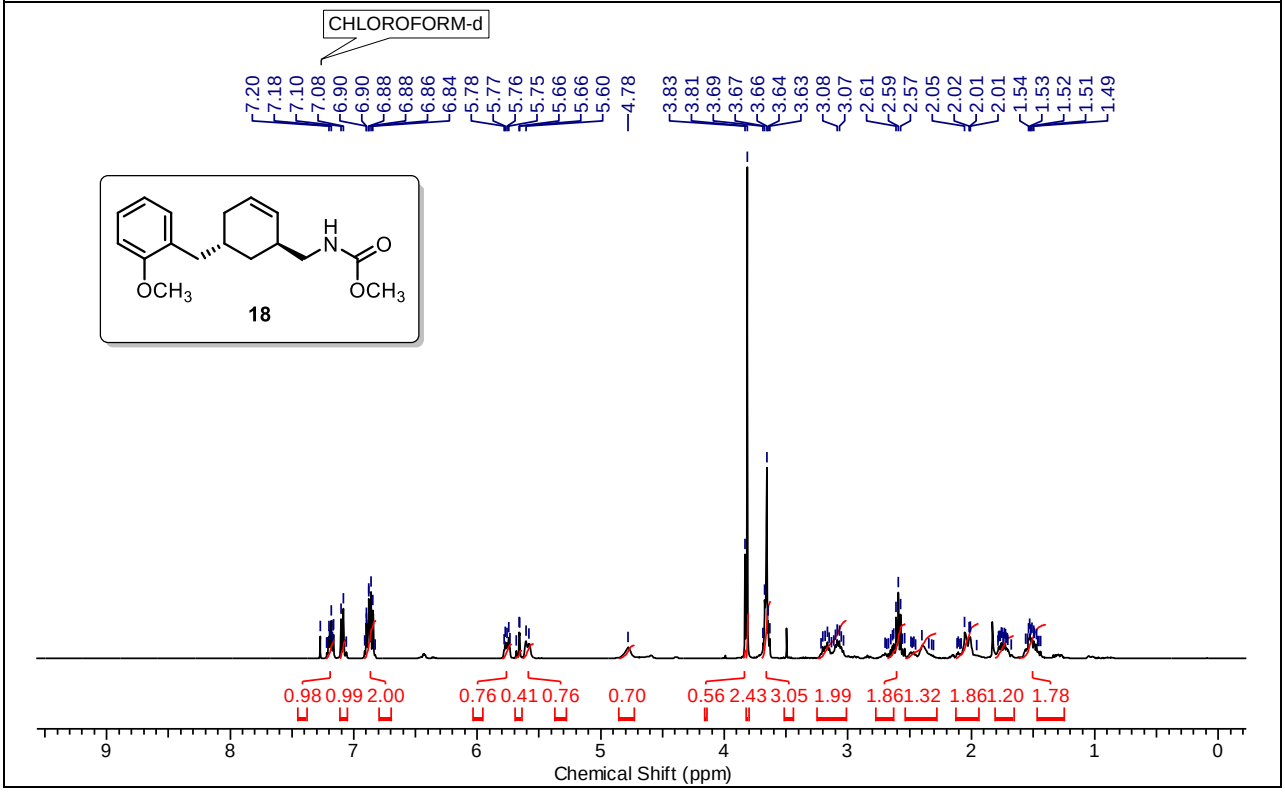
^{13}C-NMR spectrum of compound 17 ($CDCl_3$, 100 MHz)



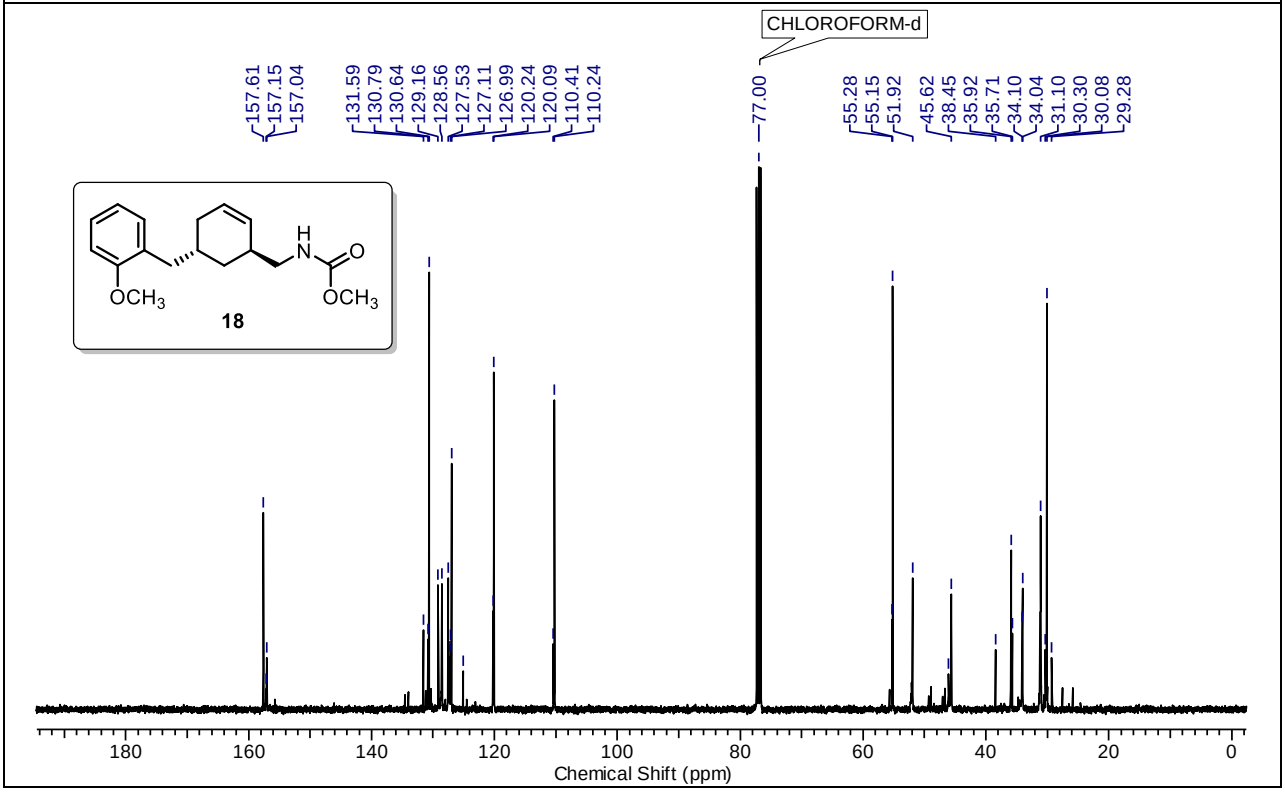
DEPT NMR spectrum of compound 17 ($CDCl_3$, 100 MHz)



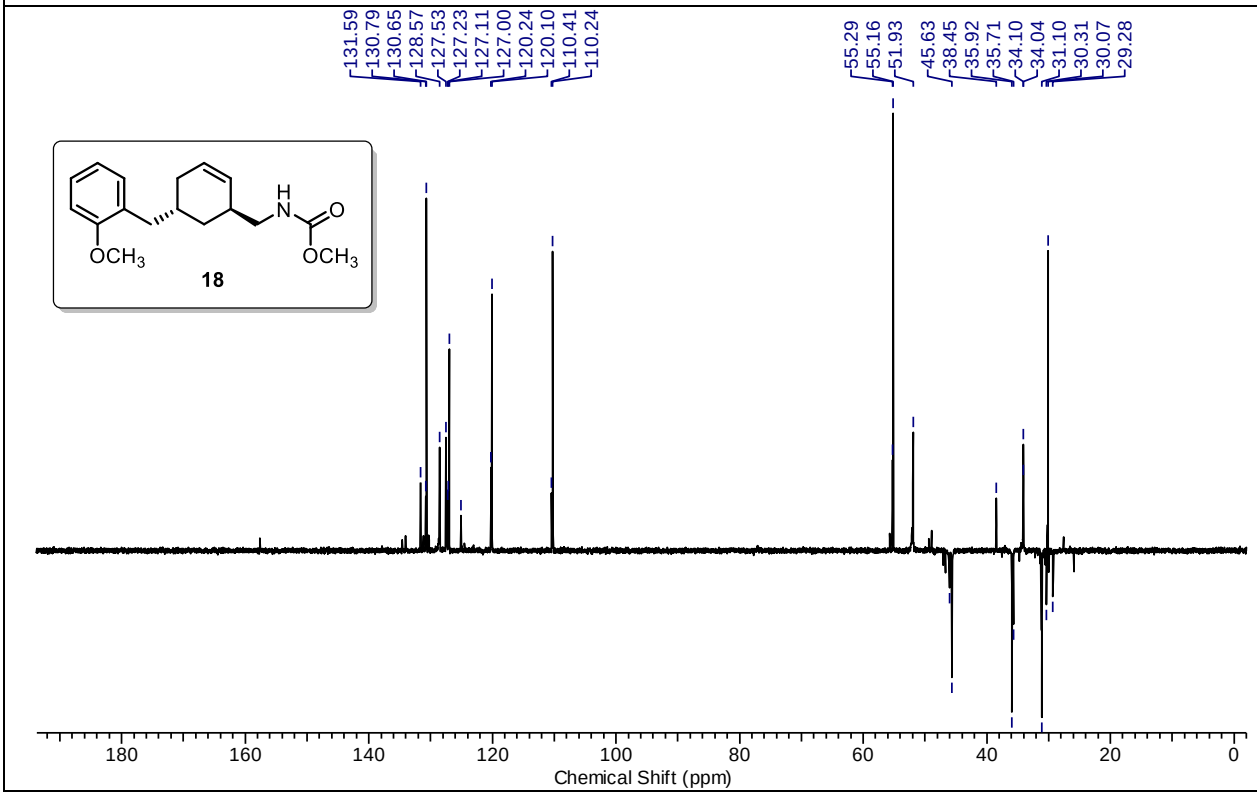
^{1}H-NMR spectrum of compound 18 ($CDCl_3$, 400 MHz)



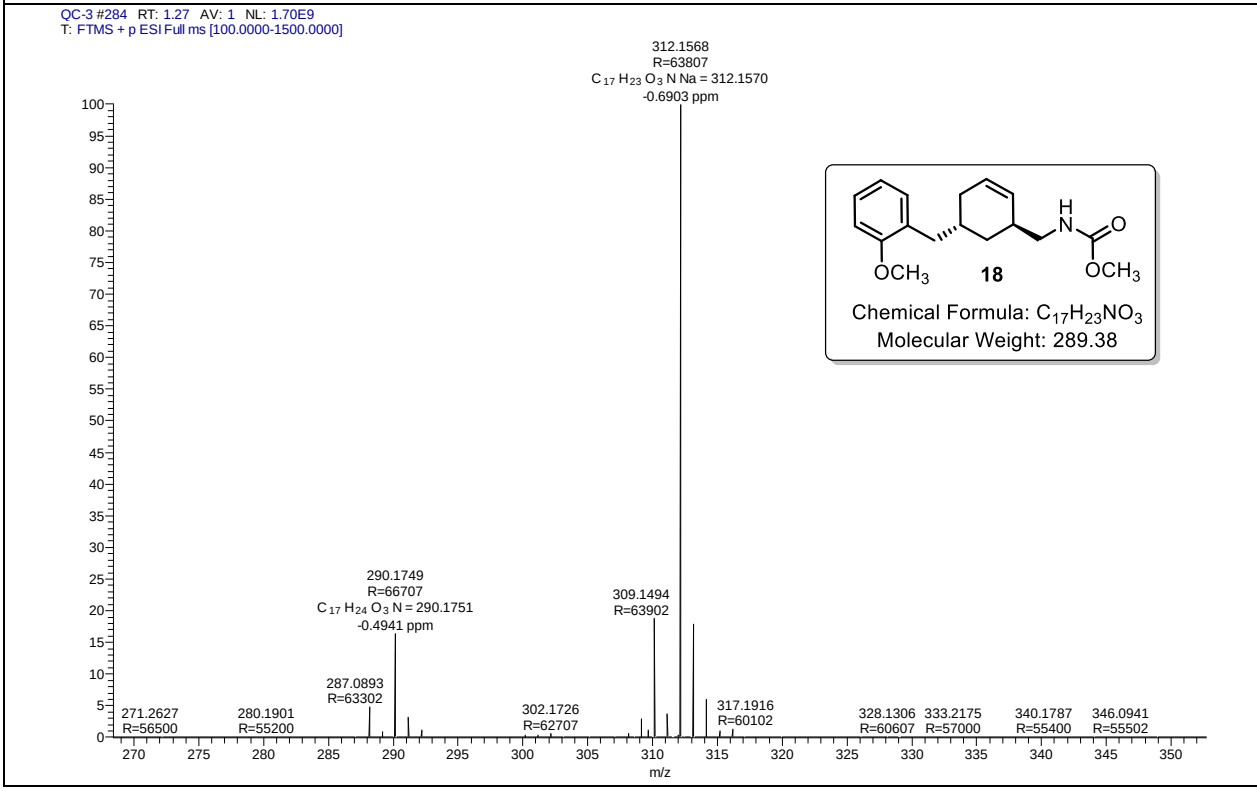
^{13}C-NMR spectrum of compound 18 ($CDCl_3$, 100 MHz)



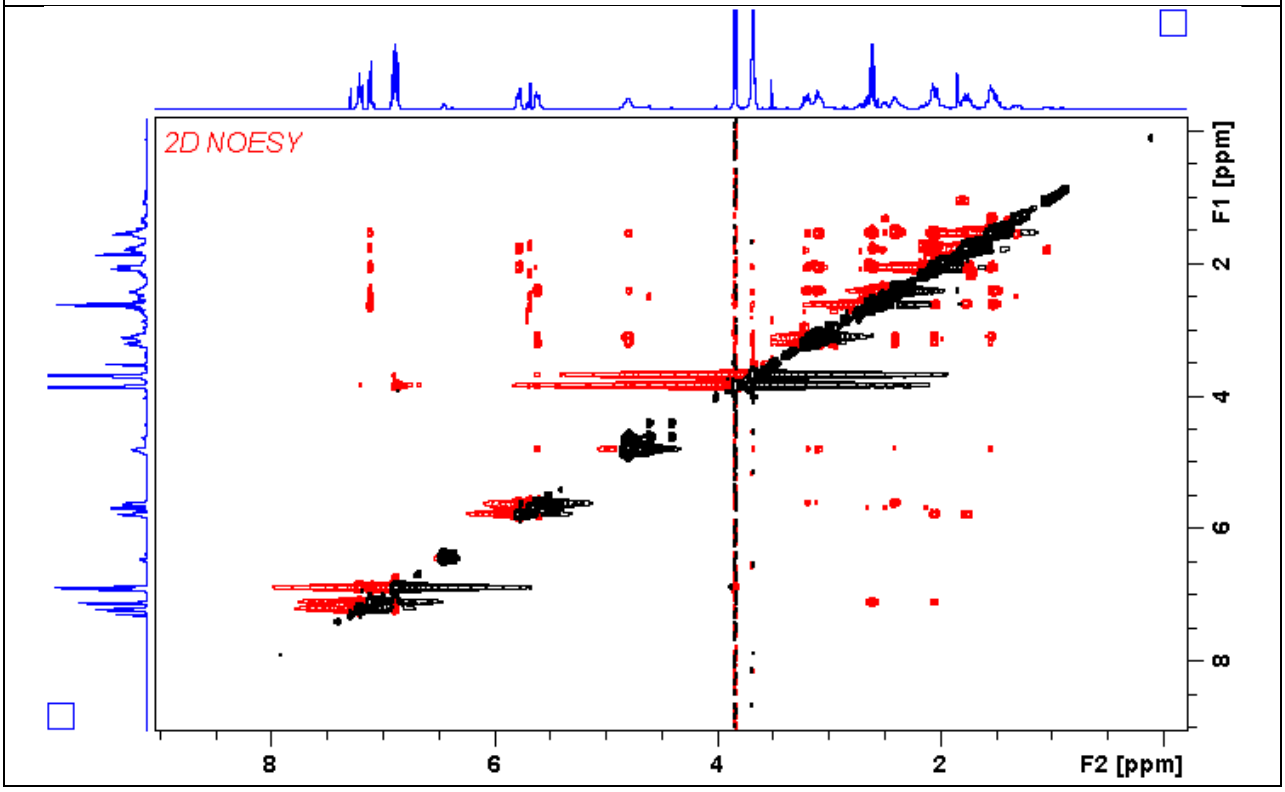
DEPT NMR spectrum of compound 18 ($CDCl_3$, 100 MHz)



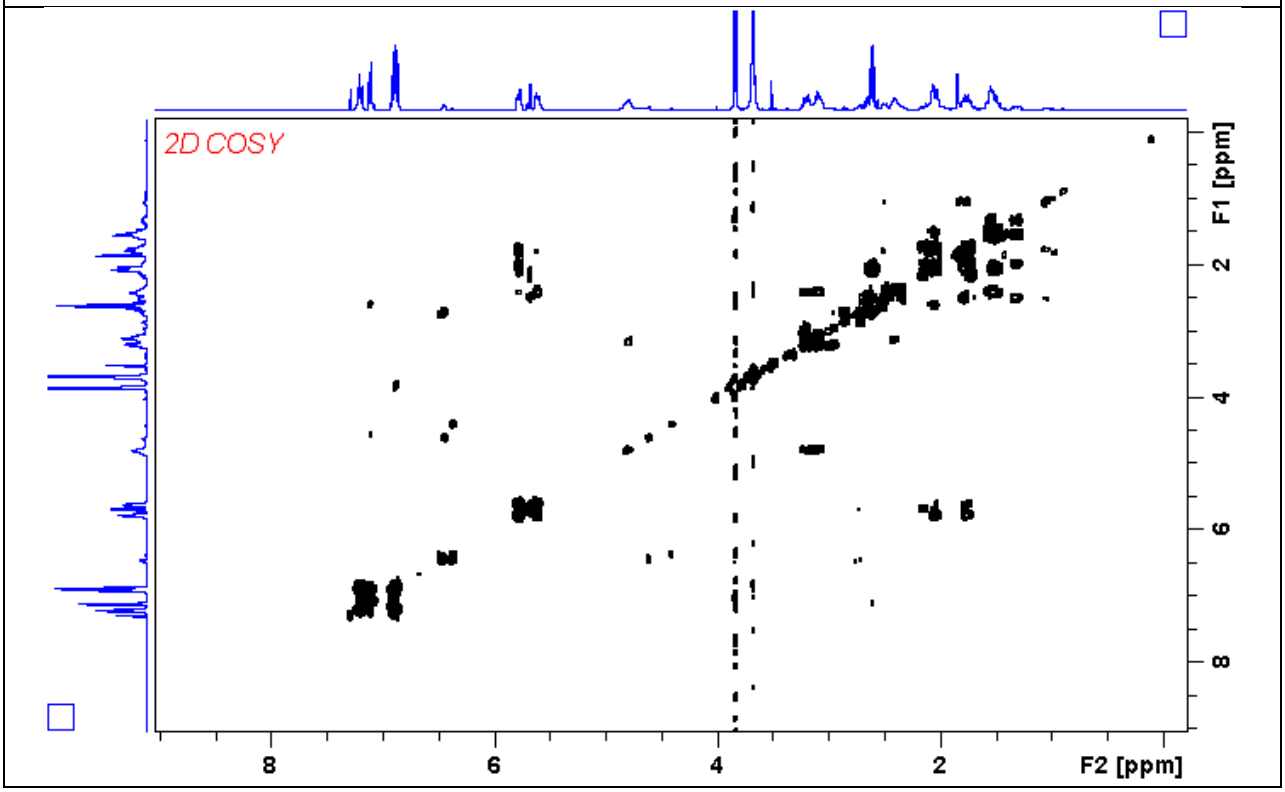
HRMS spectrum of compound 18



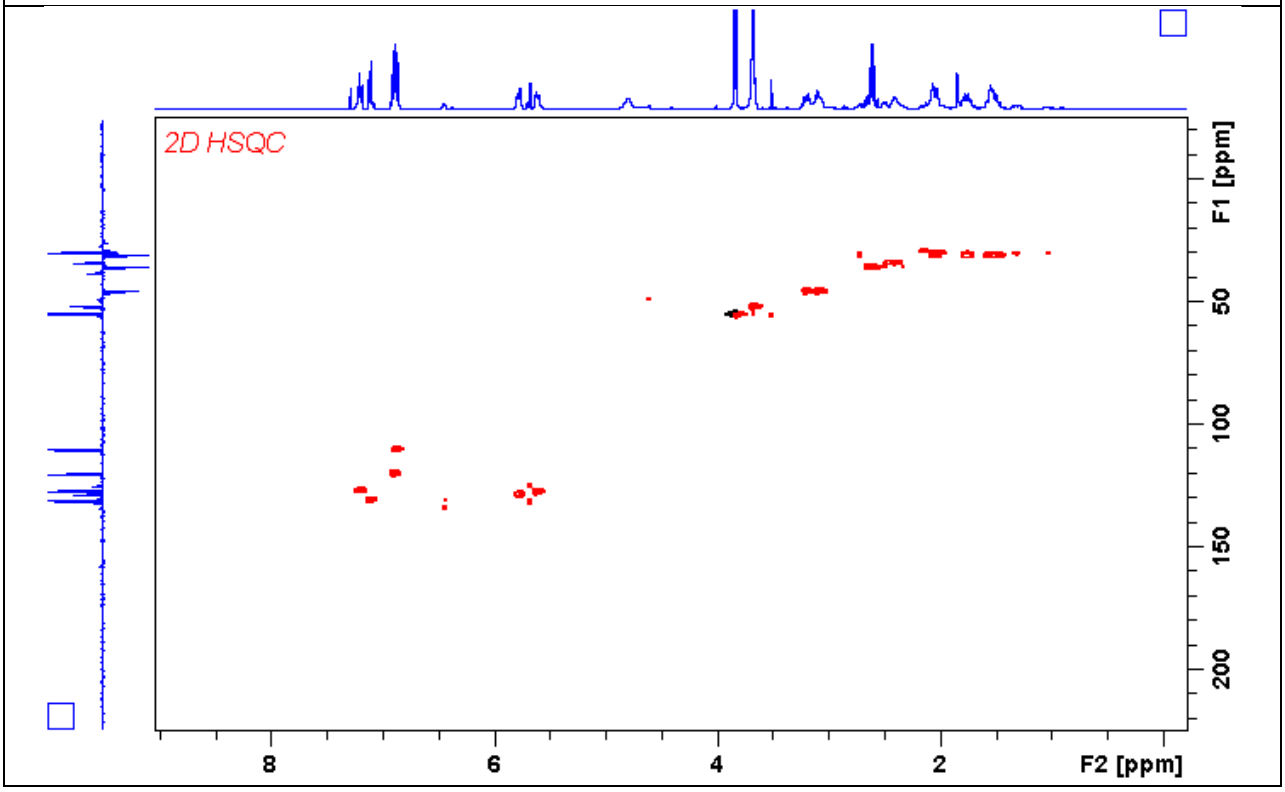
NOESY spectrum of compound 18 ($CDCl_3$, 400 MHz)



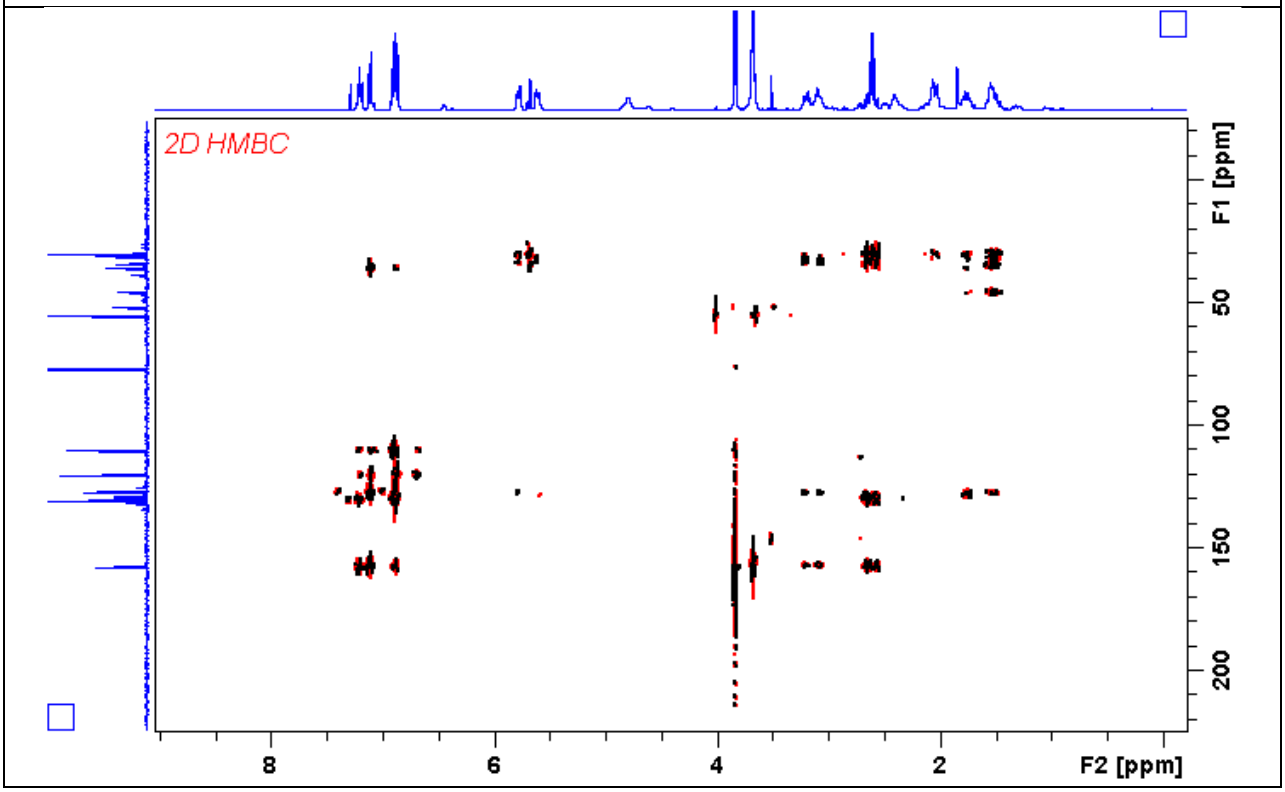
COSY spectrum of compound 18 ($CDCl_3$, 400 MHz)



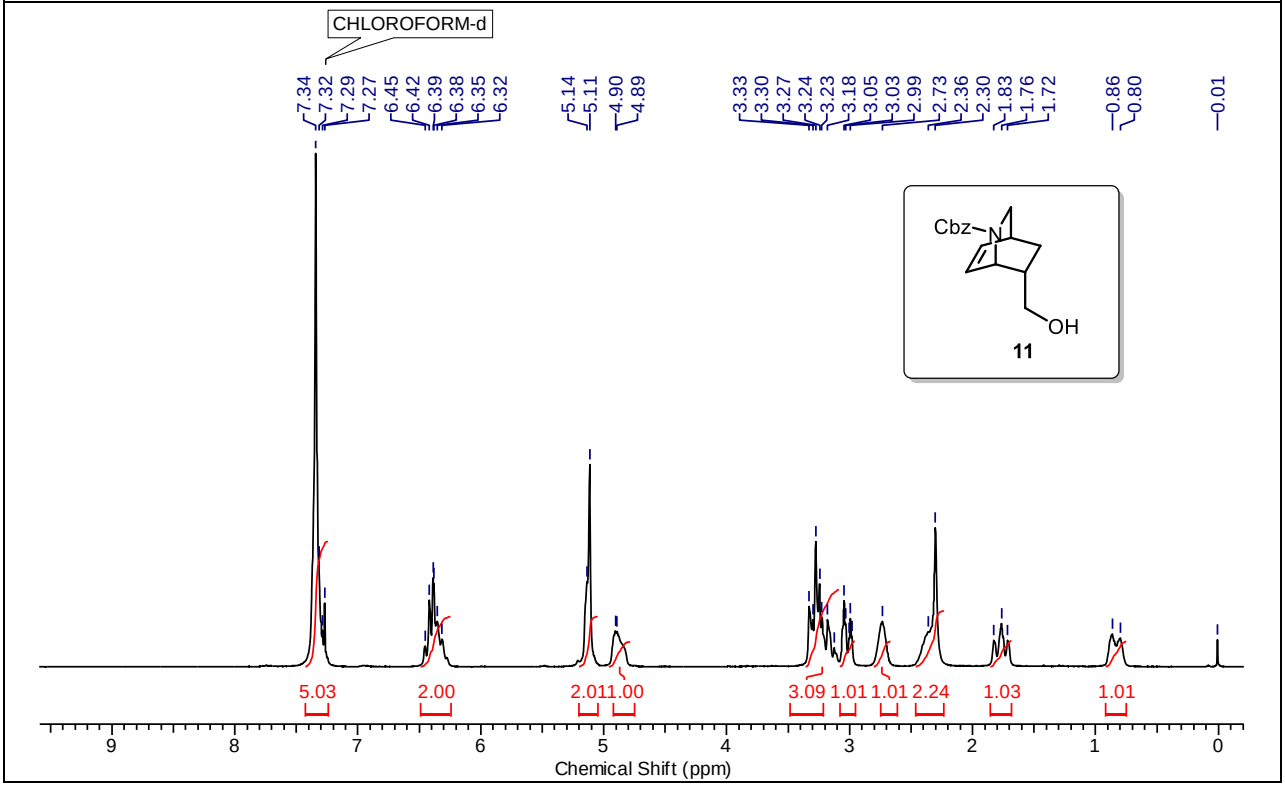
HSQC spectrum of compound 18 ($CDCl_3$, 400 MHz)



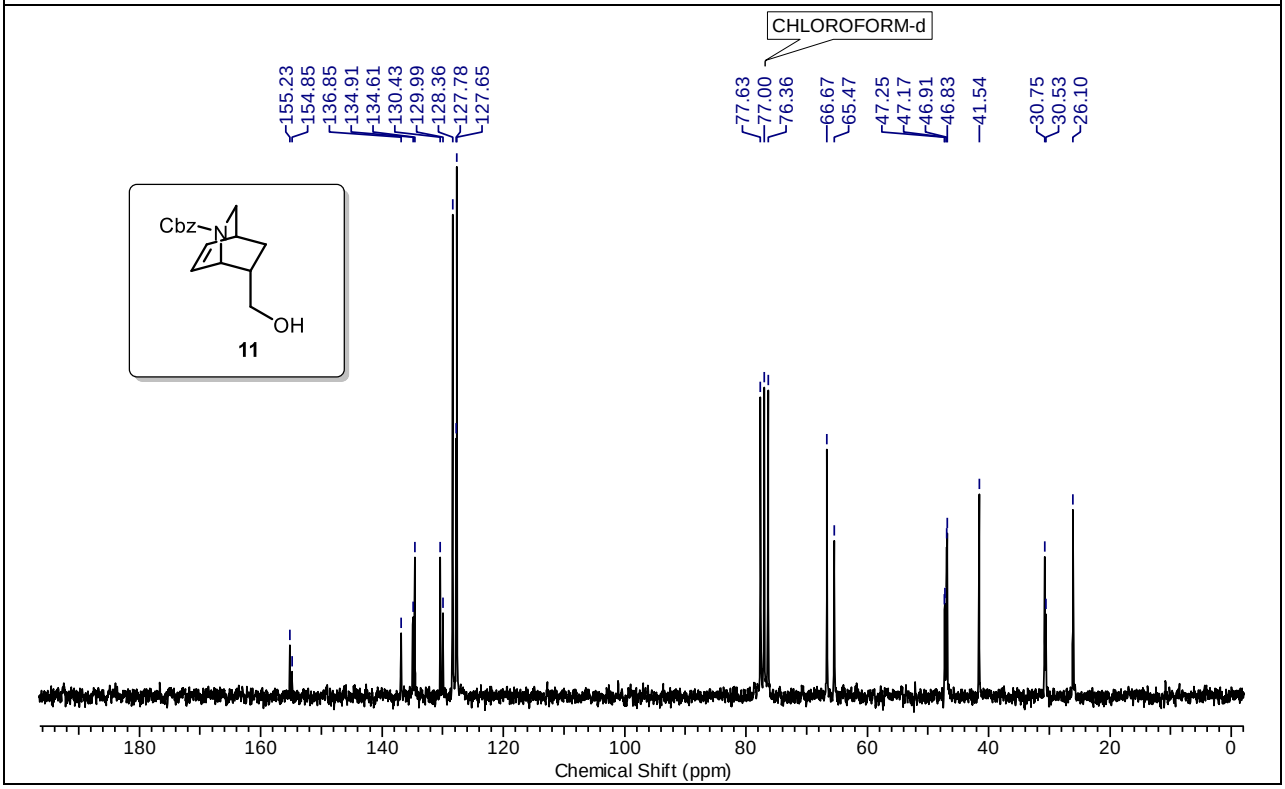
HMBC spectrum of compound 18 ($CDCl_3$, 400 MHz)



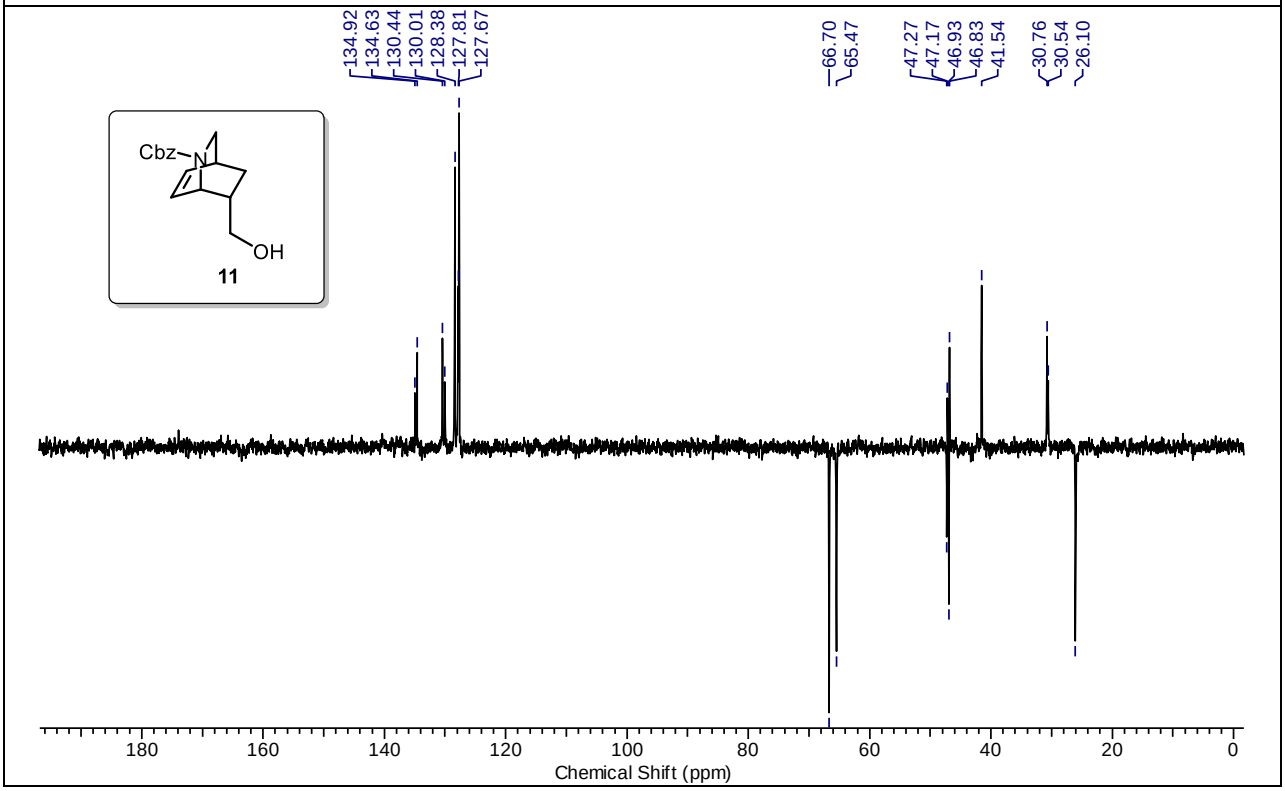
^{1}H-NMR spectrum of compound 11 ($CDCl_3$, 200 MHz)



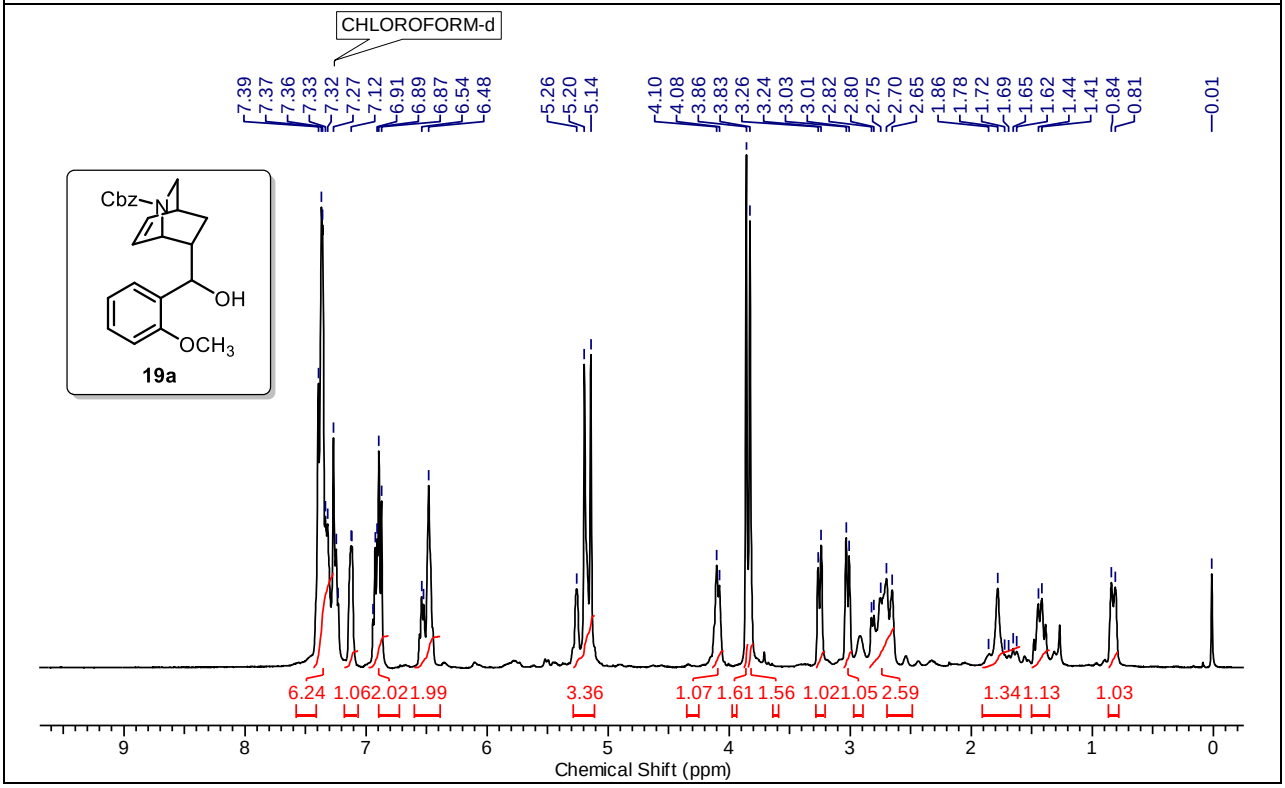
^{13}C-NMR spectrum of compound 11 ($CDCl_3$, 50 MHz)



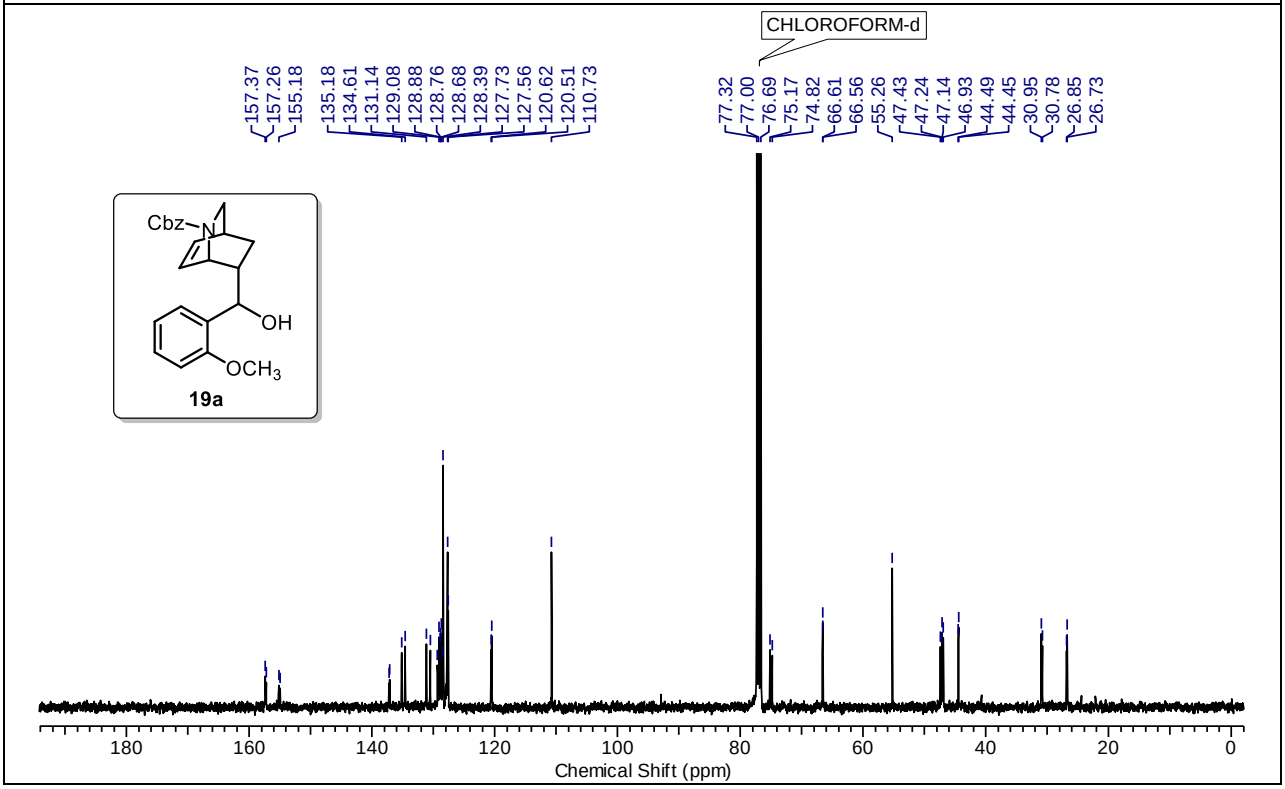
DEPT NMR spectrum of compound 11 ($CDCl_3$, 50 MHz)



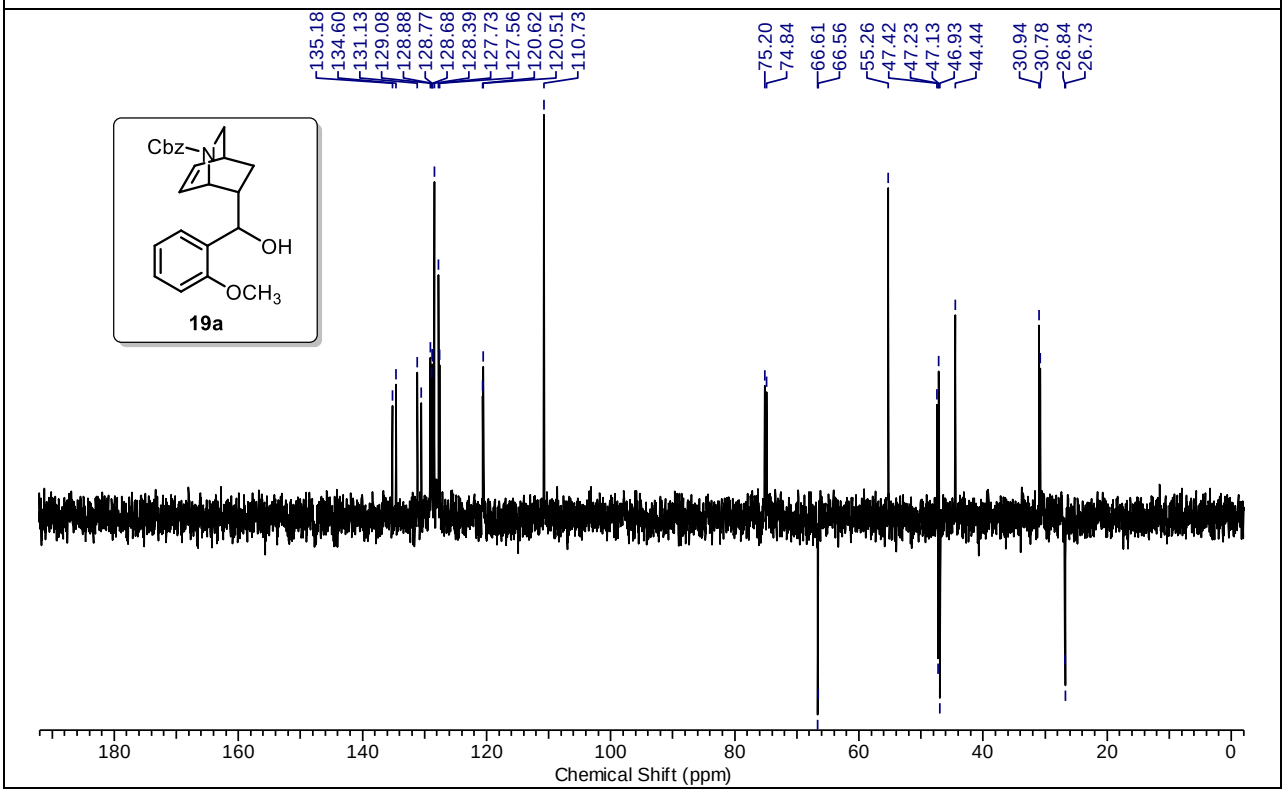
^{1}H-NMR spectrum of compound 19a ($CDCl_3$, 400 MHz)



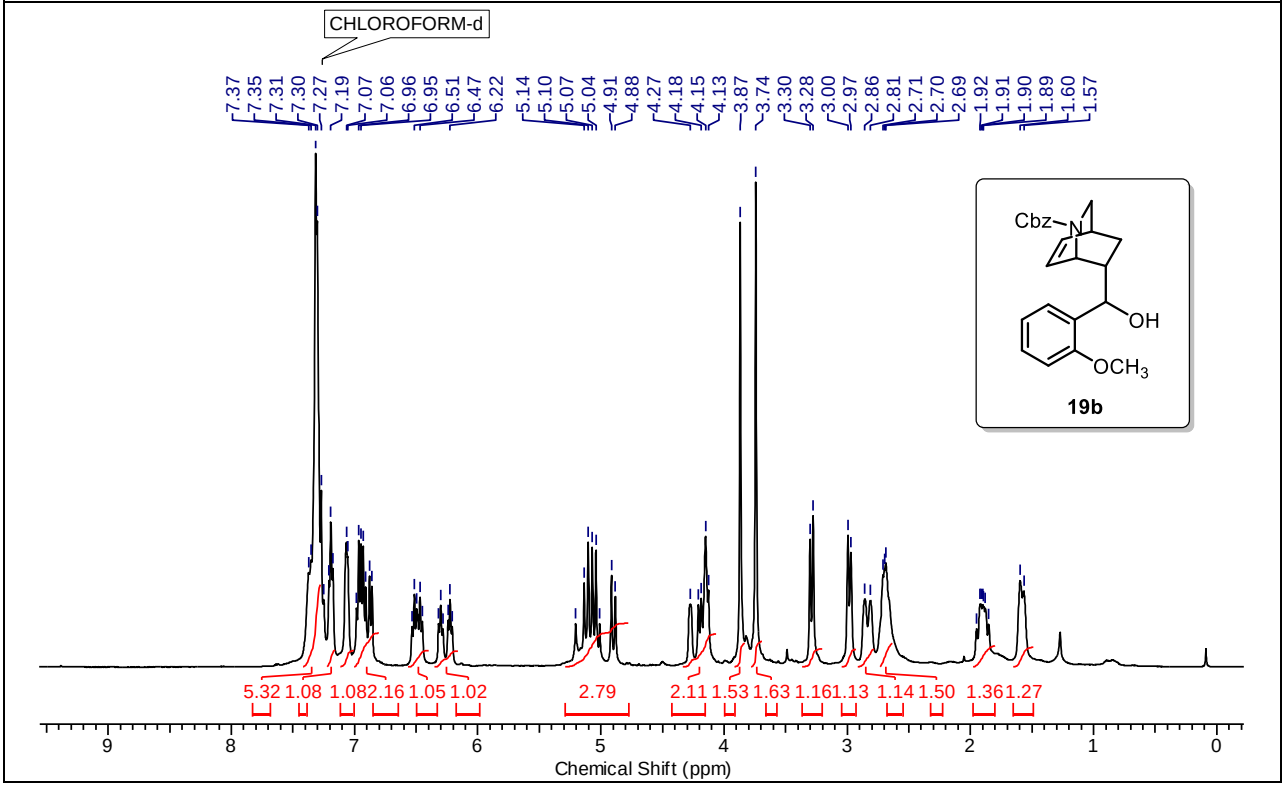
^{13}C-NMR spectrum of compound 19a ($CDCl_3$, 100 MHz)



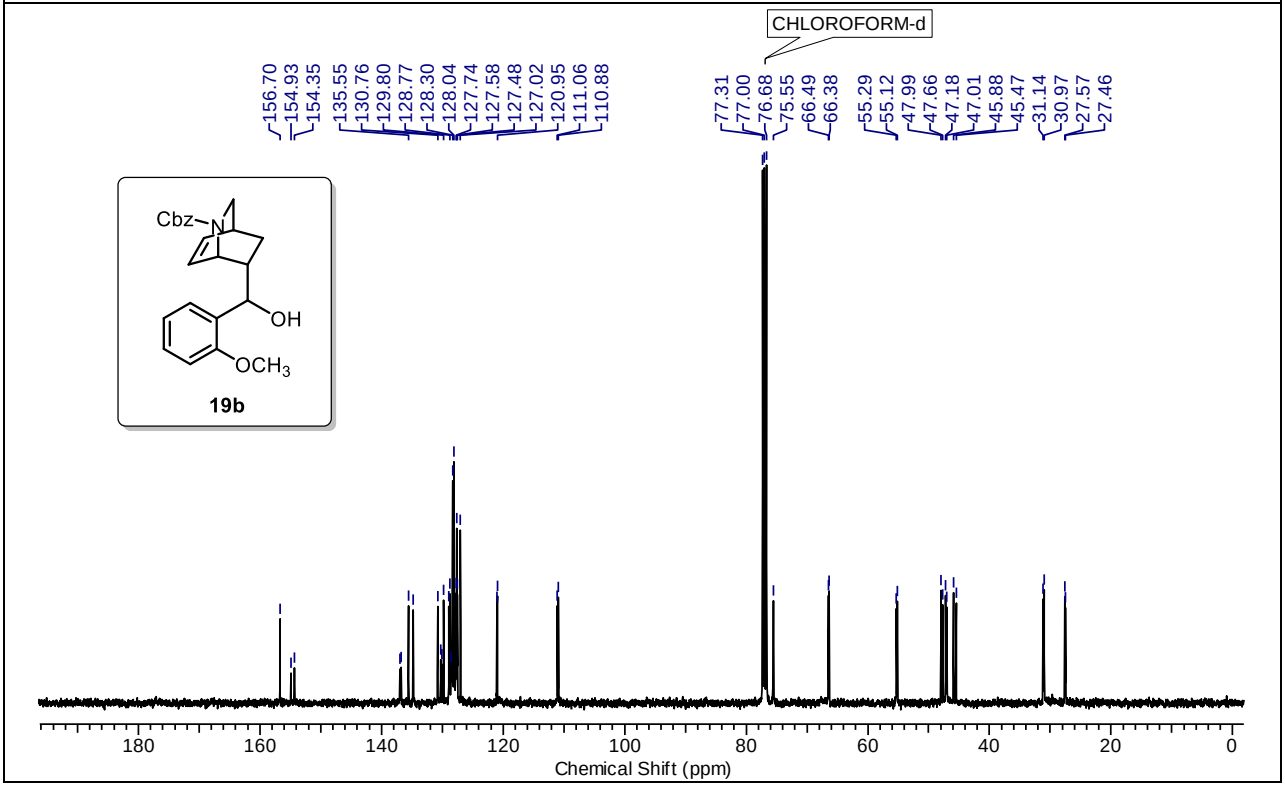
DEPT NMR spectrum of compound 19a ($CDCl_3$, 100 MHz)



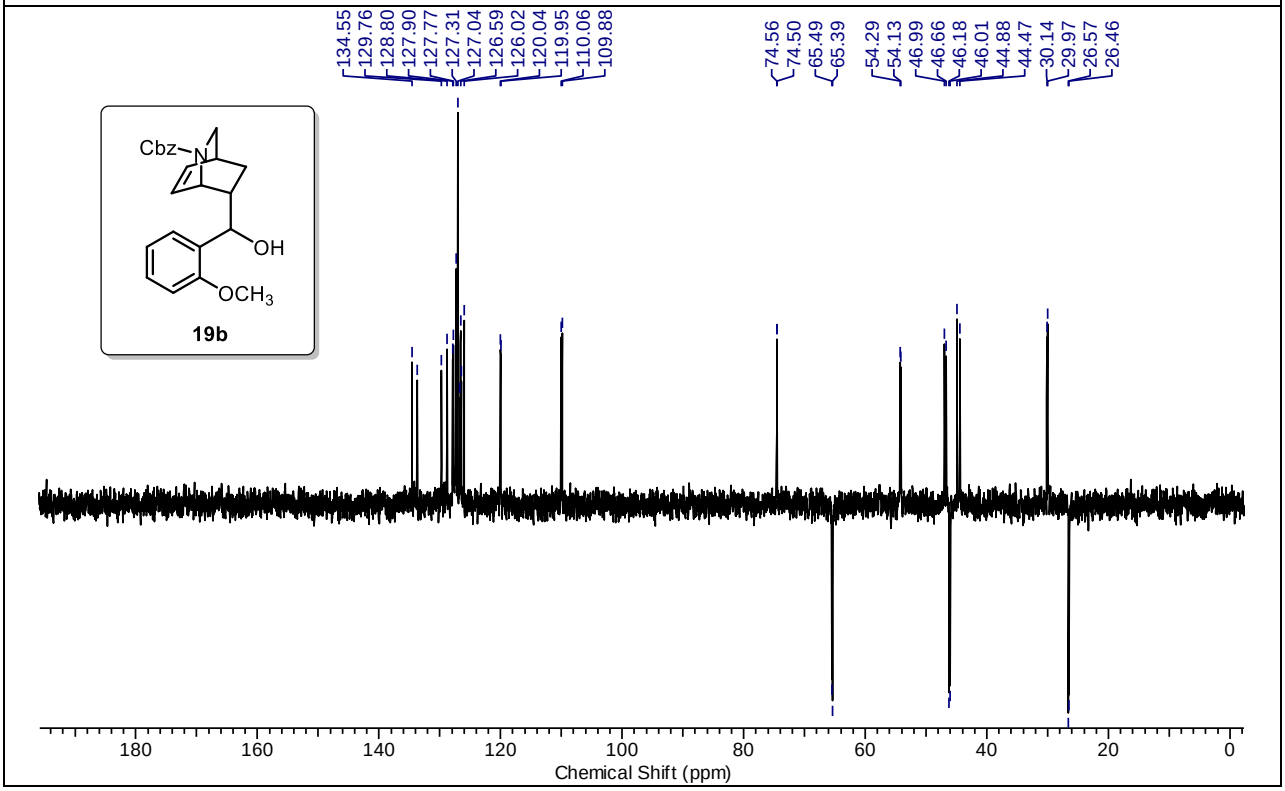
^{1}H-NMR spectrum of compound 19b ($CDCl_3$, 400 MHz)



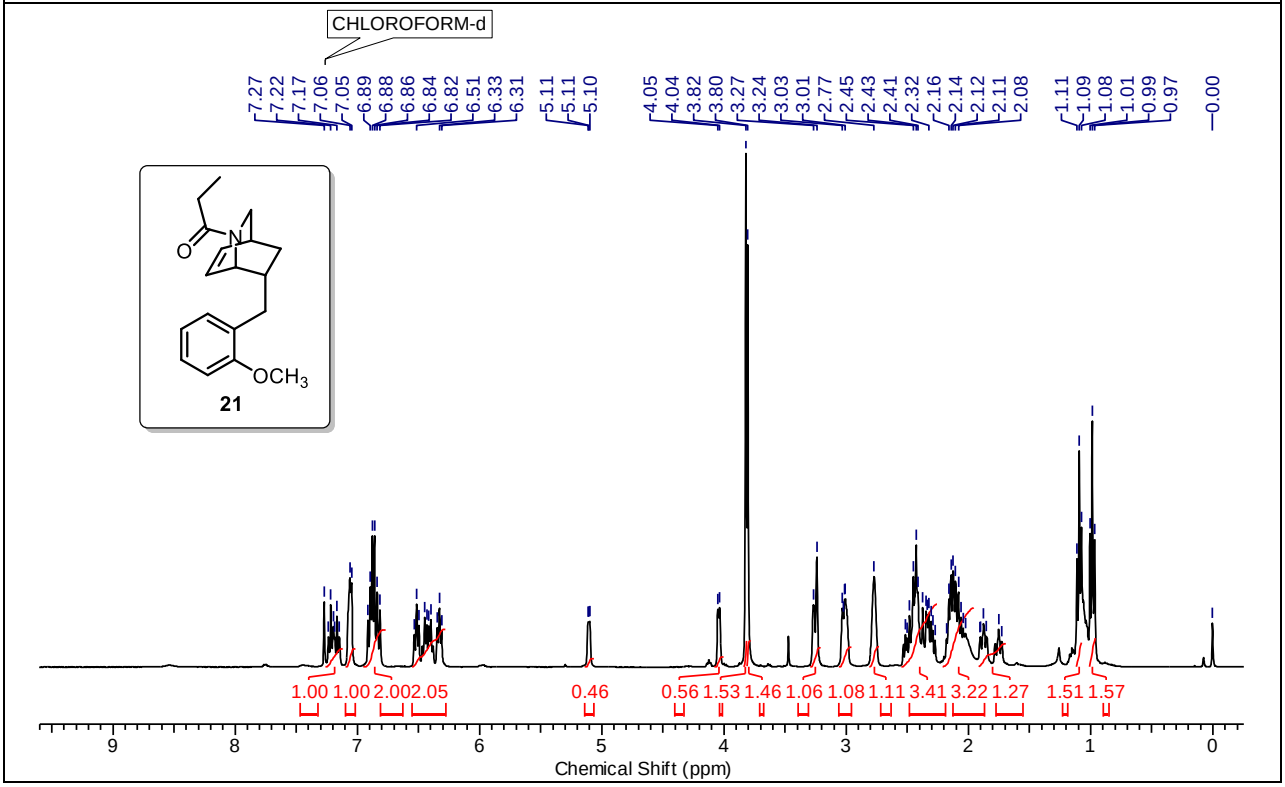
^{13}C-NMR spectrum of compound 19b ($CDCl_3$, 100 MHz)



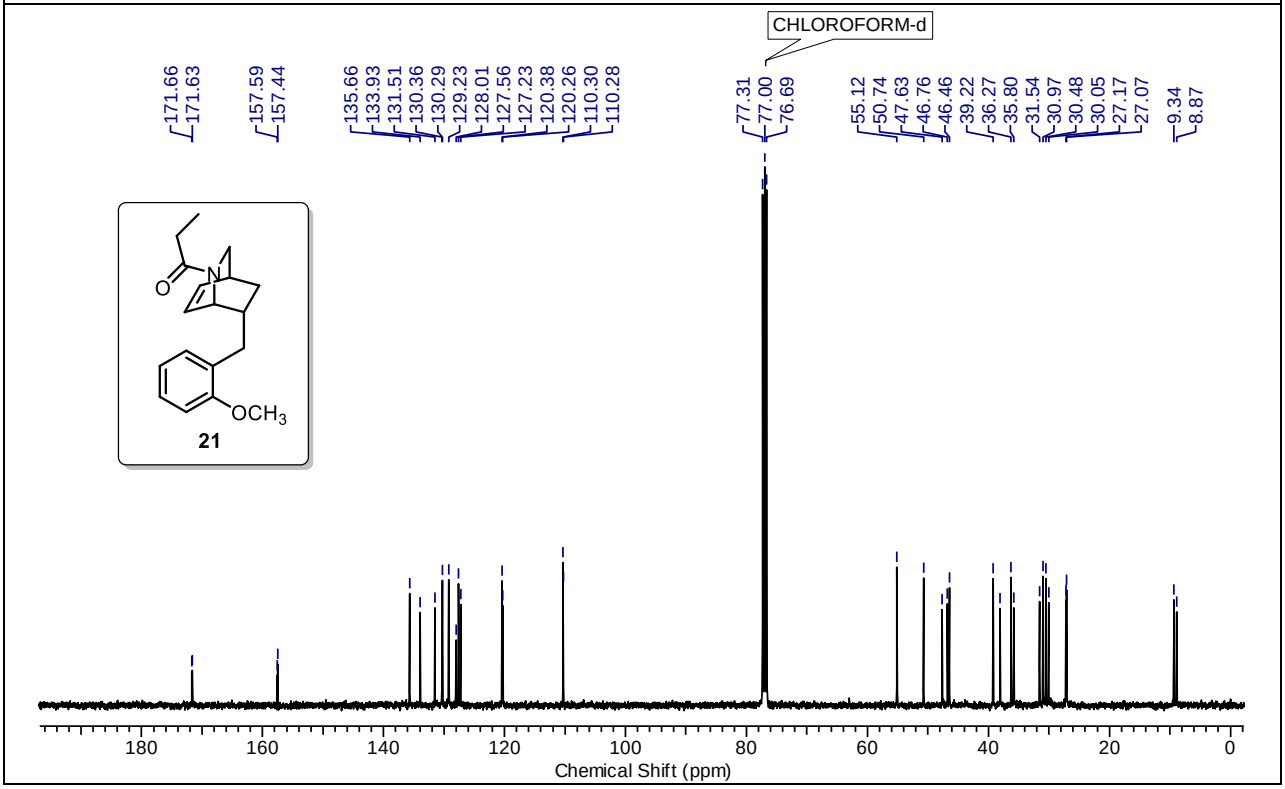
DEPT NMR spectrum of compound 19b ($CDCl_3$, 100 MHz)



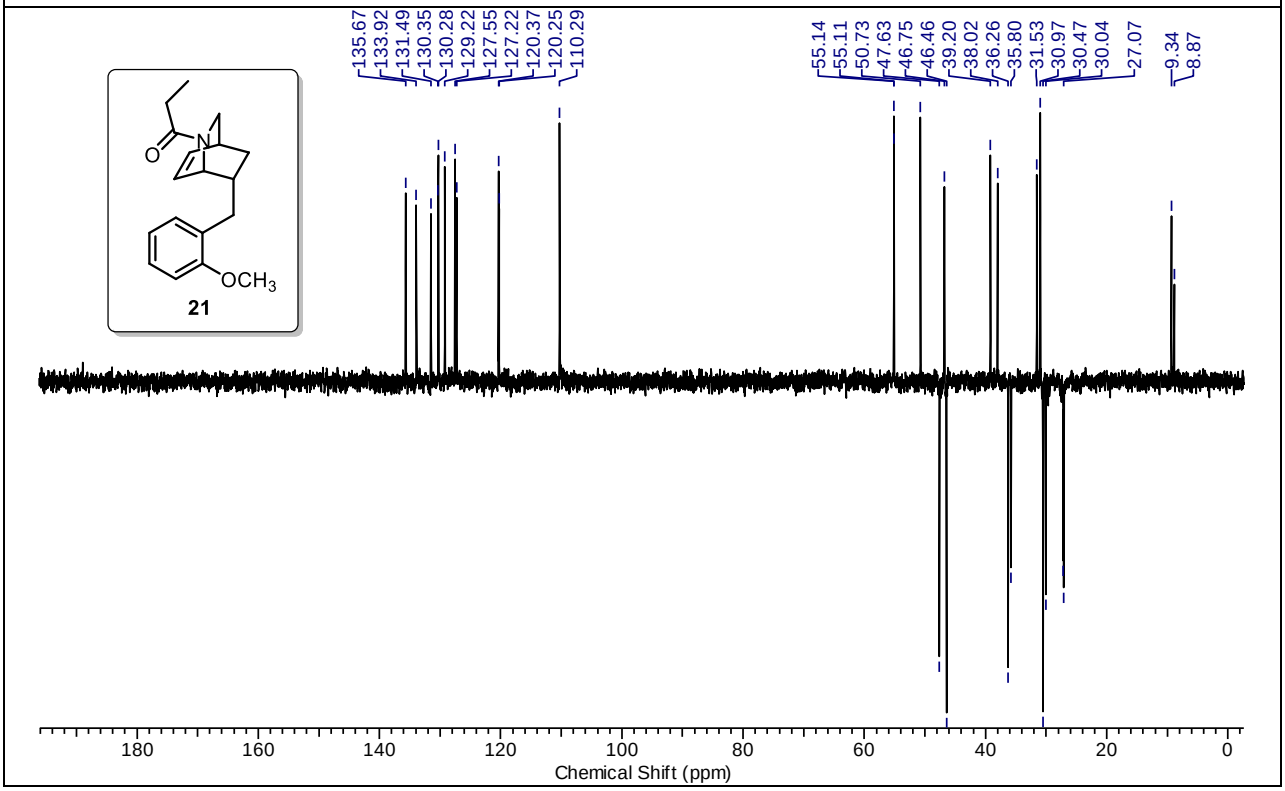
^{1}H-NMR spectrum of compound 21 ($CDCl_3$, 400 MHz)



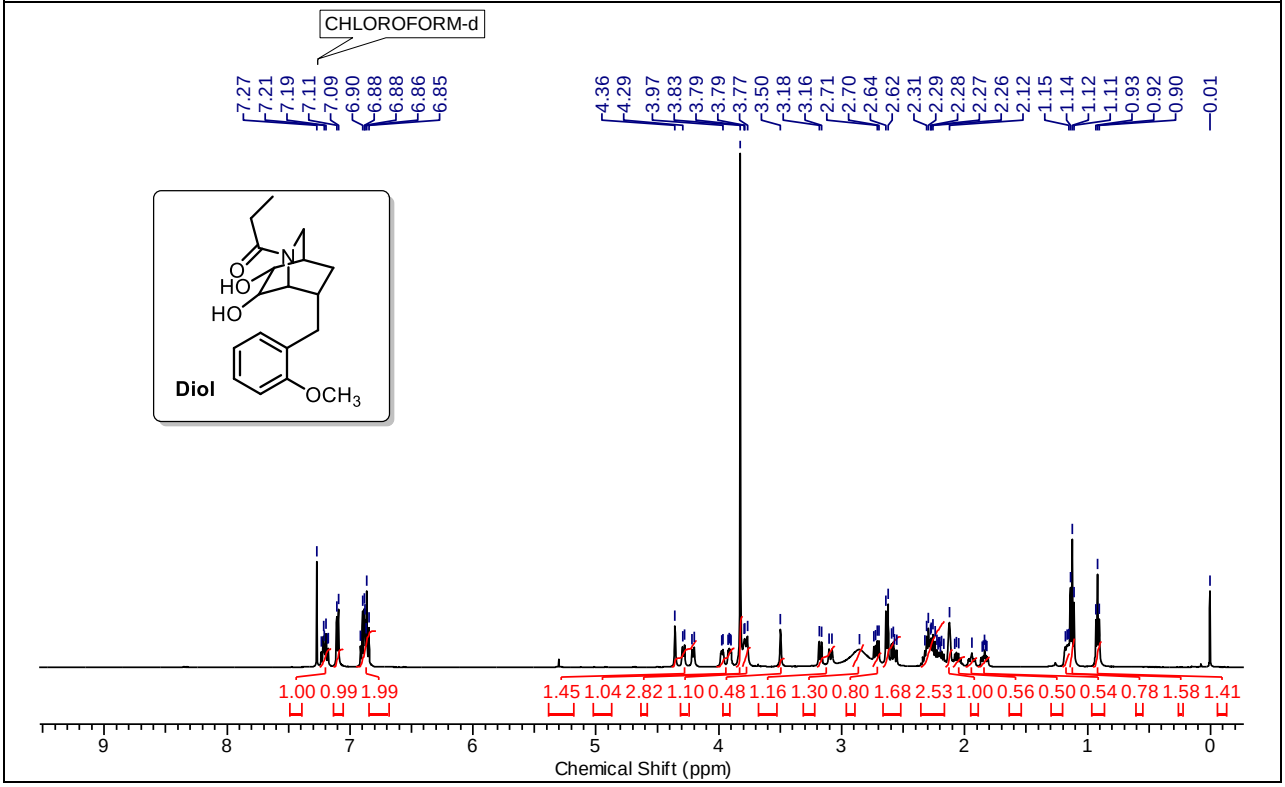
^{13}C-NMR spectrum of compound 21 ($CDCl_3$, 100 MHz)



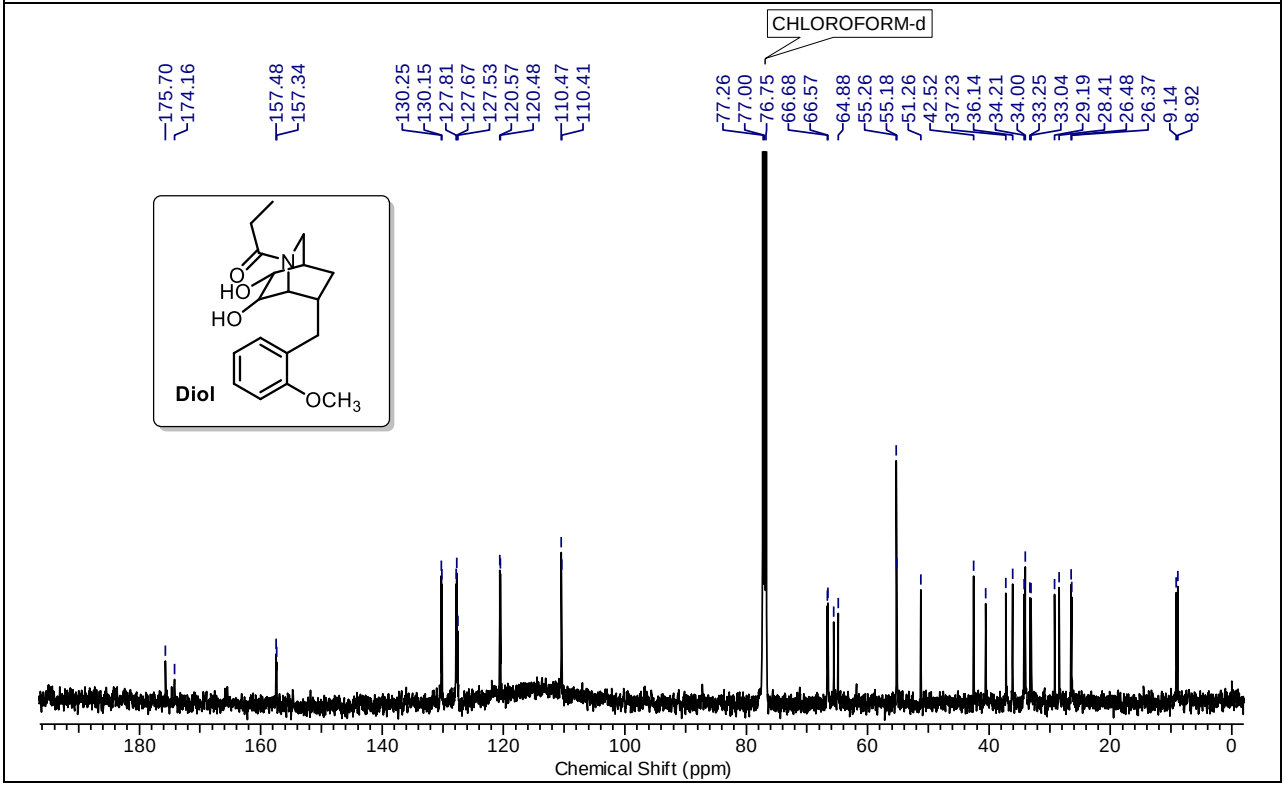
DEPT NMR spectrum of compound 21 ($CDCl_3$, 100 MHz)



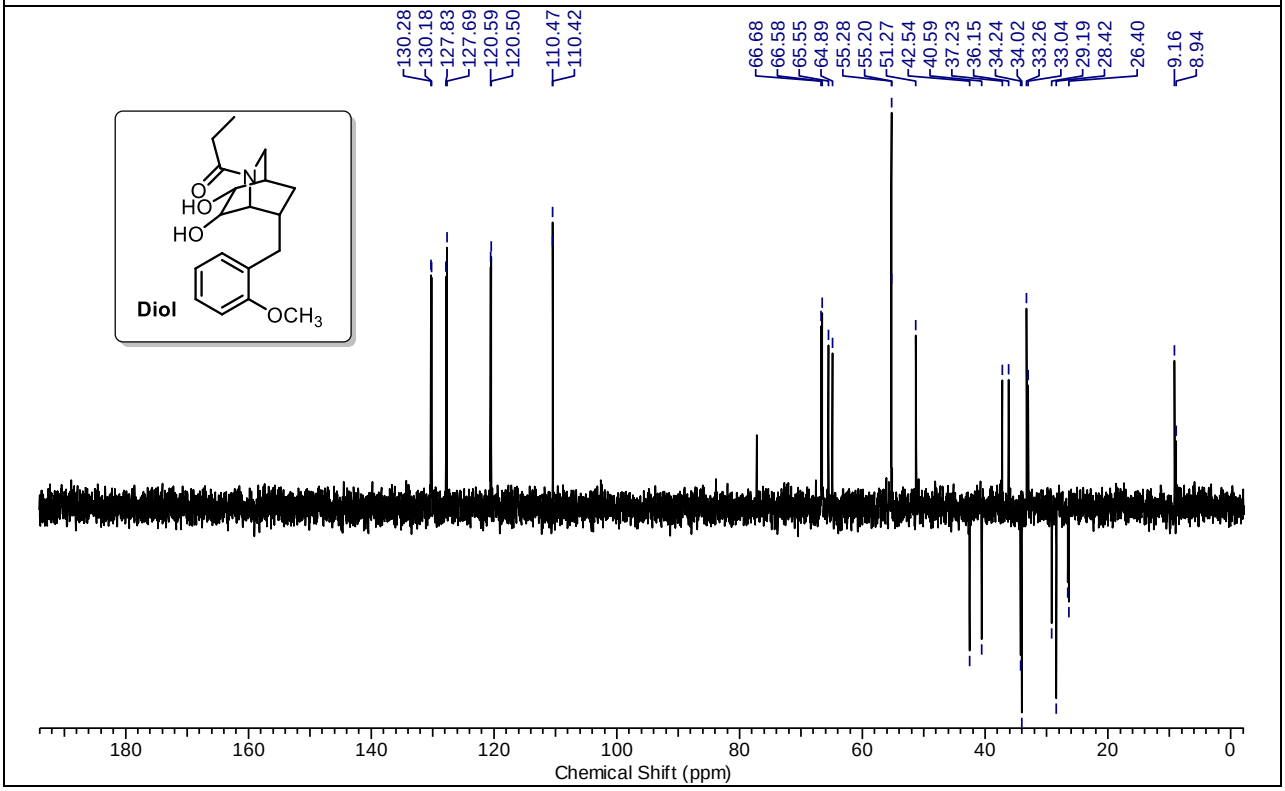
^{1}H-NMR spectrum of Diol ($CDCl_3$, 500 MHz)



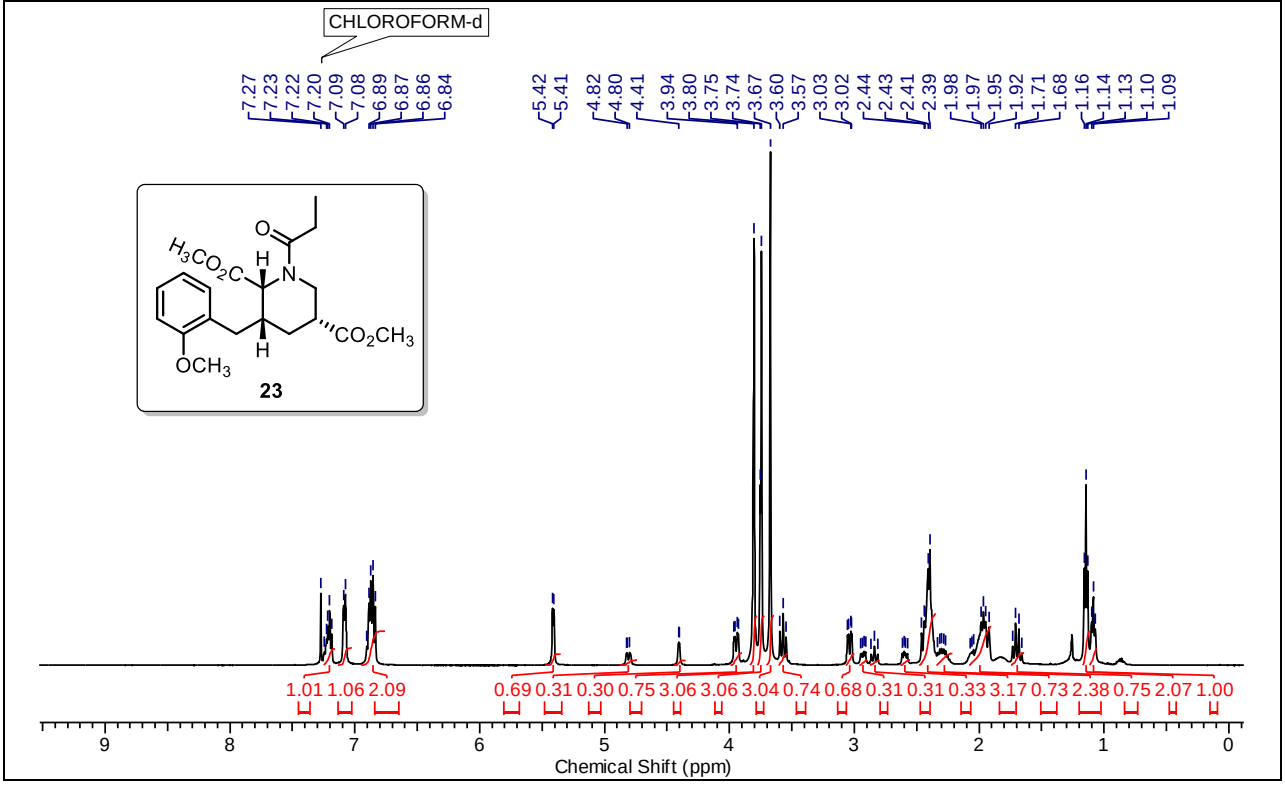
^{13}C-NMR spectrum of Diol ($CDCl_3$, 125 MHz)



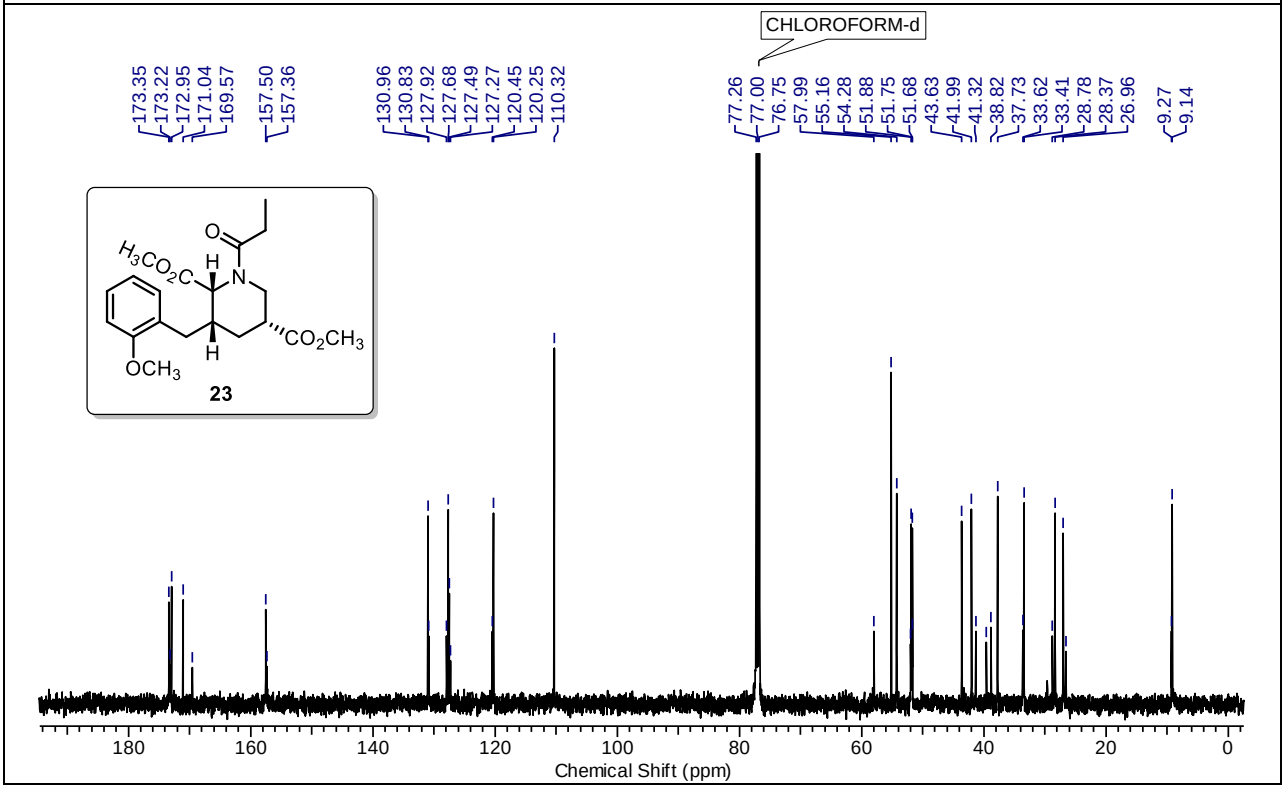
DEPT NMR spectrum of Diol ($CDCl_3$, 125 MHz)



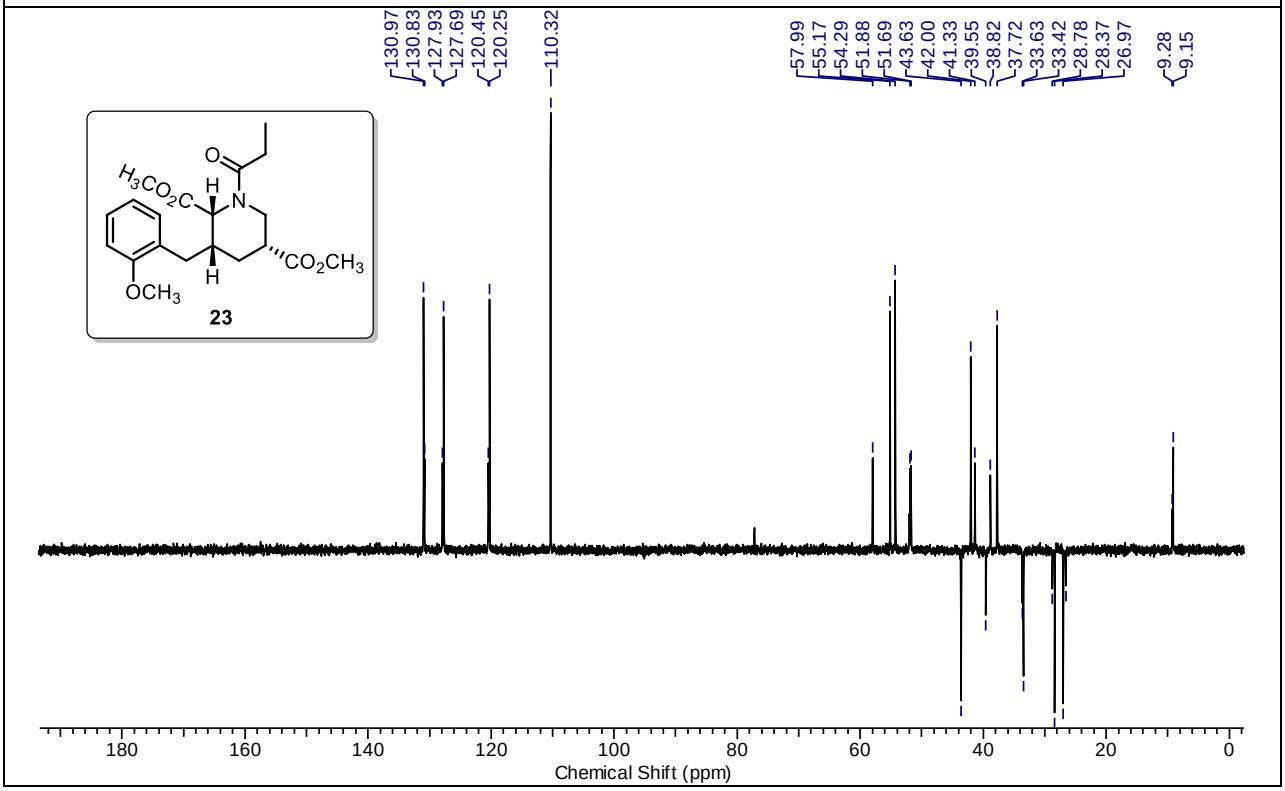
^{1}H-NMR spectrum of compound 23 ($CDCl_3$, 500 MHz)



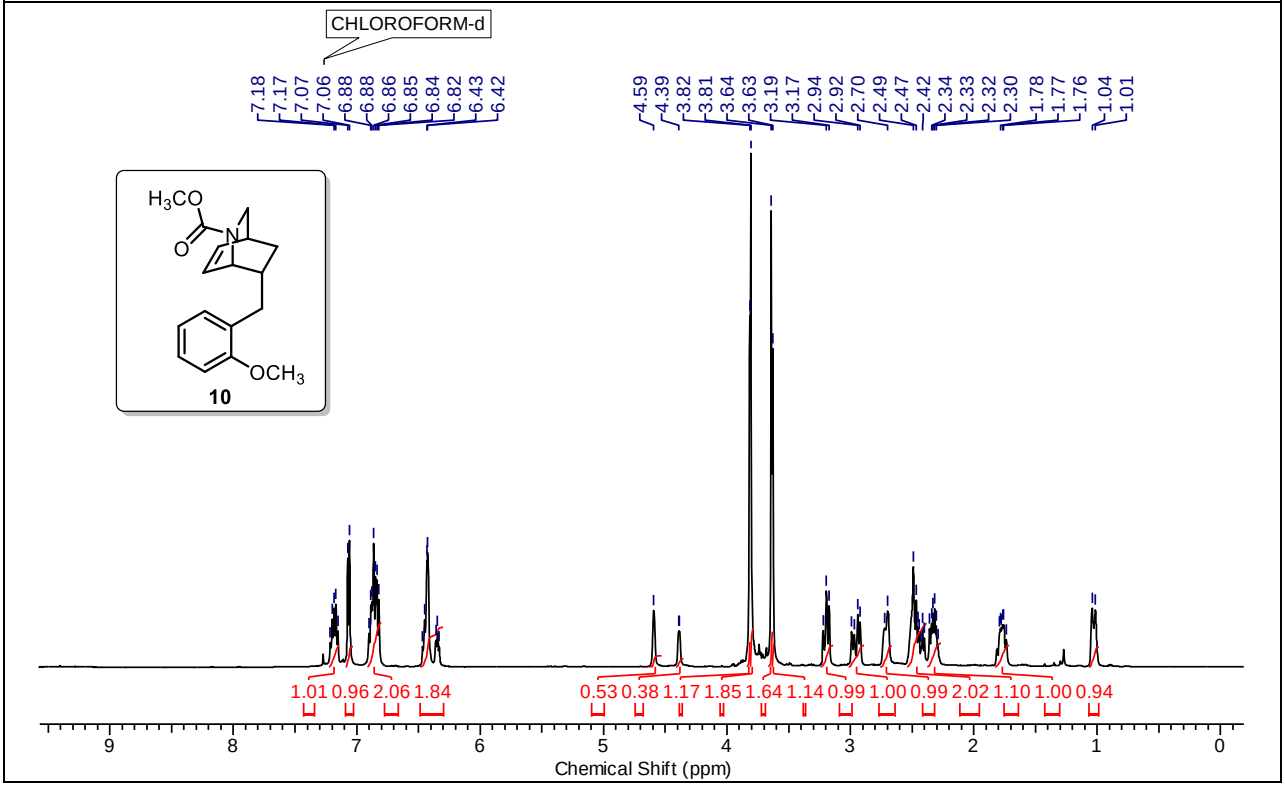
^{13}C-NMR spectrum of compound 23 ($CDCl_3$, 125 MHz)



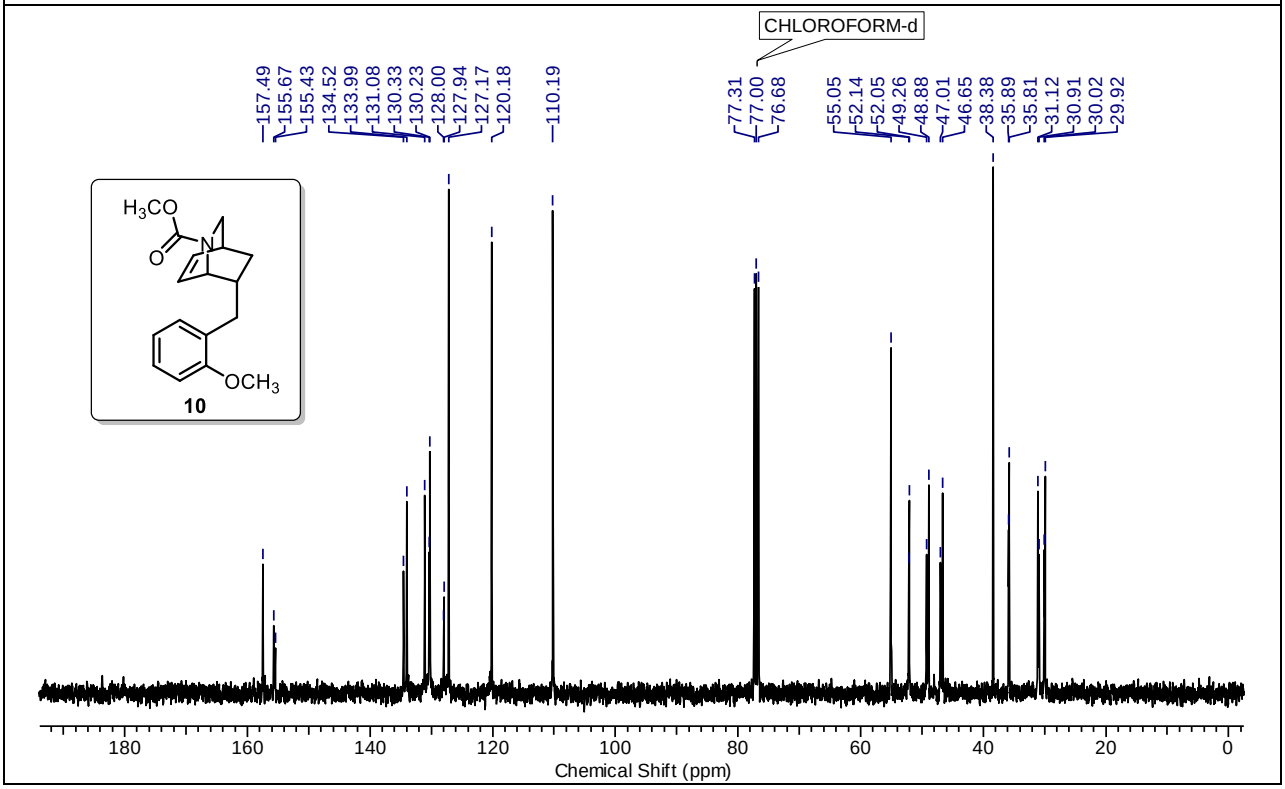
DEPT NMR spectrum of compound 23 ($CDCl_3$, 125 MHz)



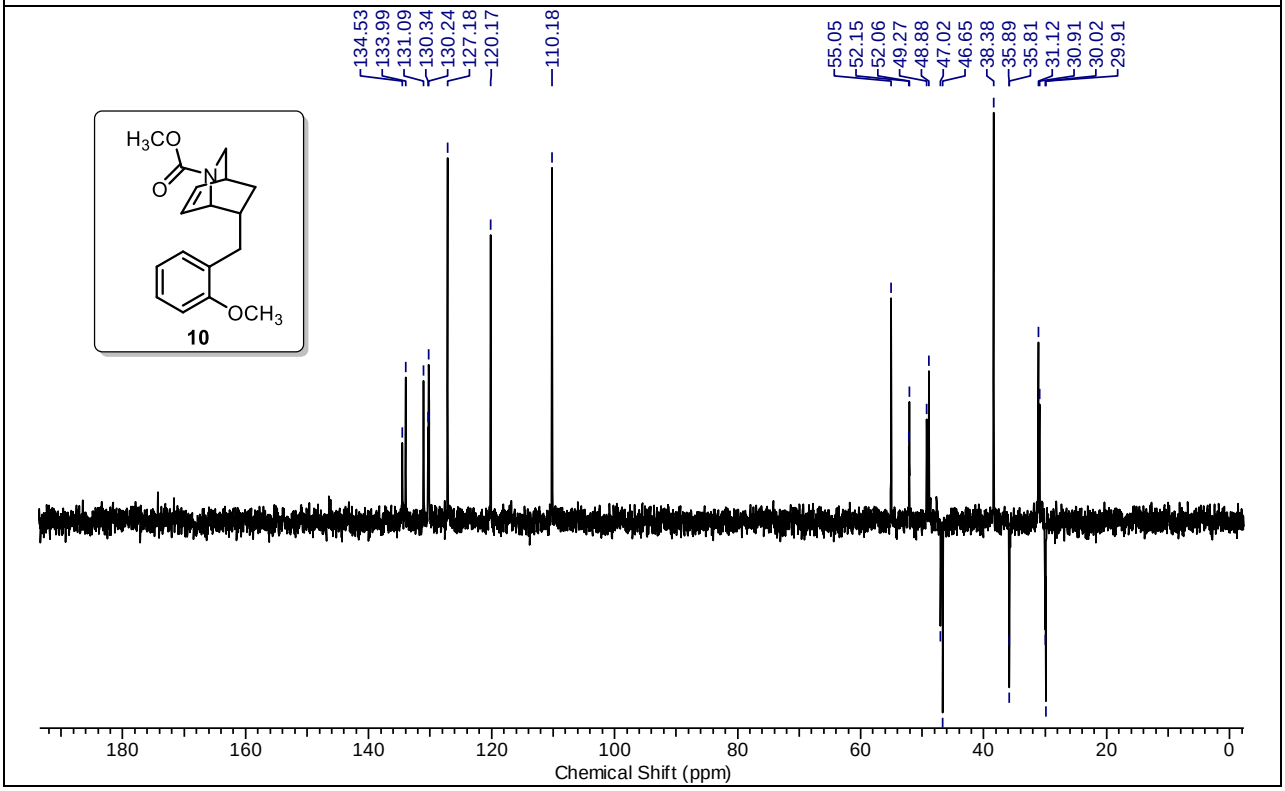
^{1}H-NMR spectrum of compound 10 ($CDCl_3$, 500 MHz)



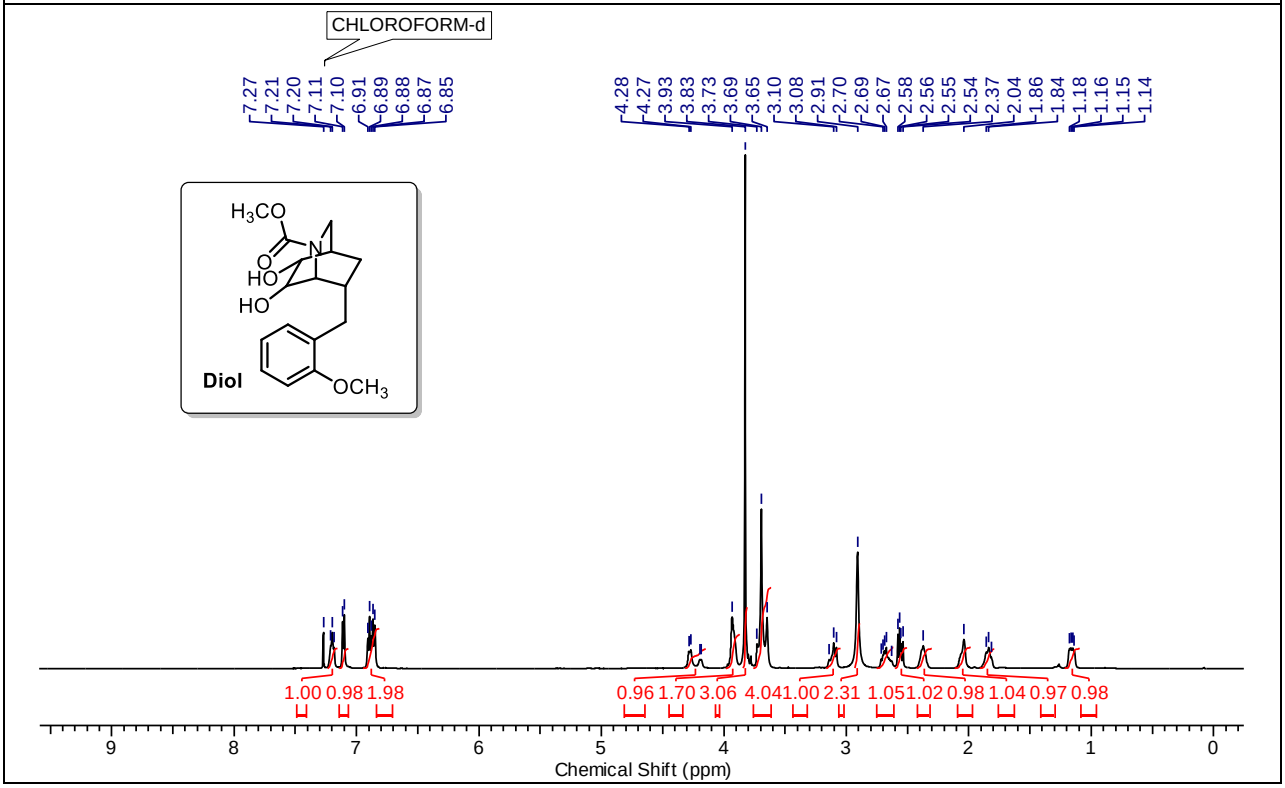
^{13}C-NMR spectrum of compound 10 ($CDCl_3$, 100 MHz)



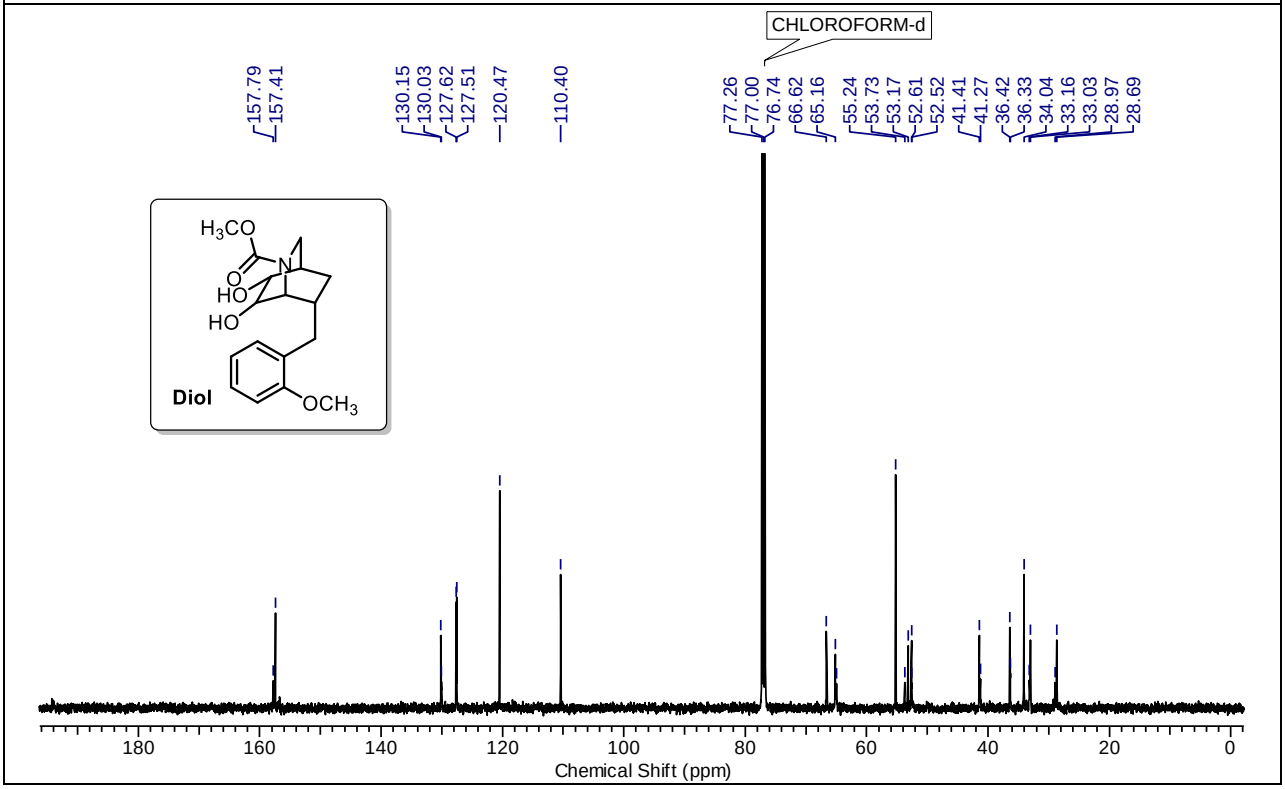
DEPT NMR spectrum of compound 10 ($CDCl_3$, 100 MHz)



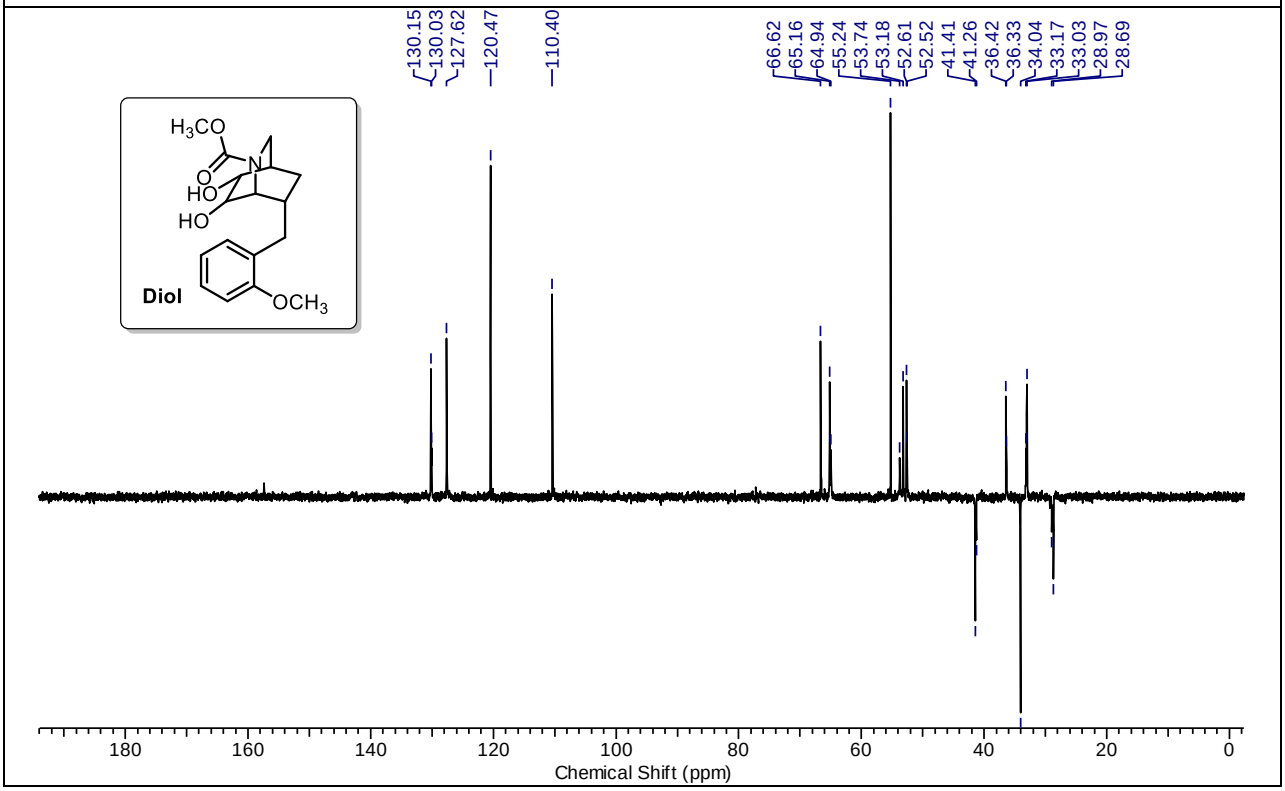
^{1}H-NMR spectrum of Diol ($CDCl_3$, 500 MHz)



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



DEPT NMR spectrum of Diol ($CDCl_3$, 125 MHz)



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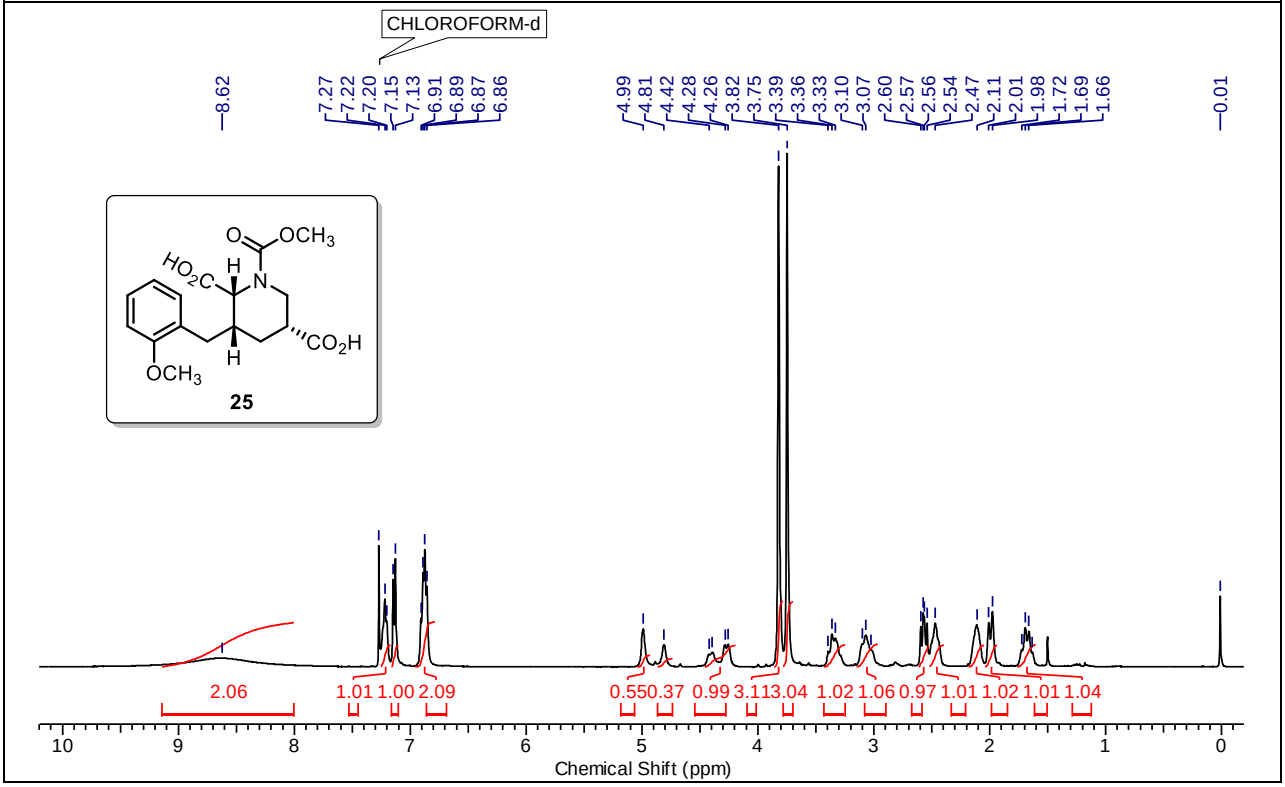

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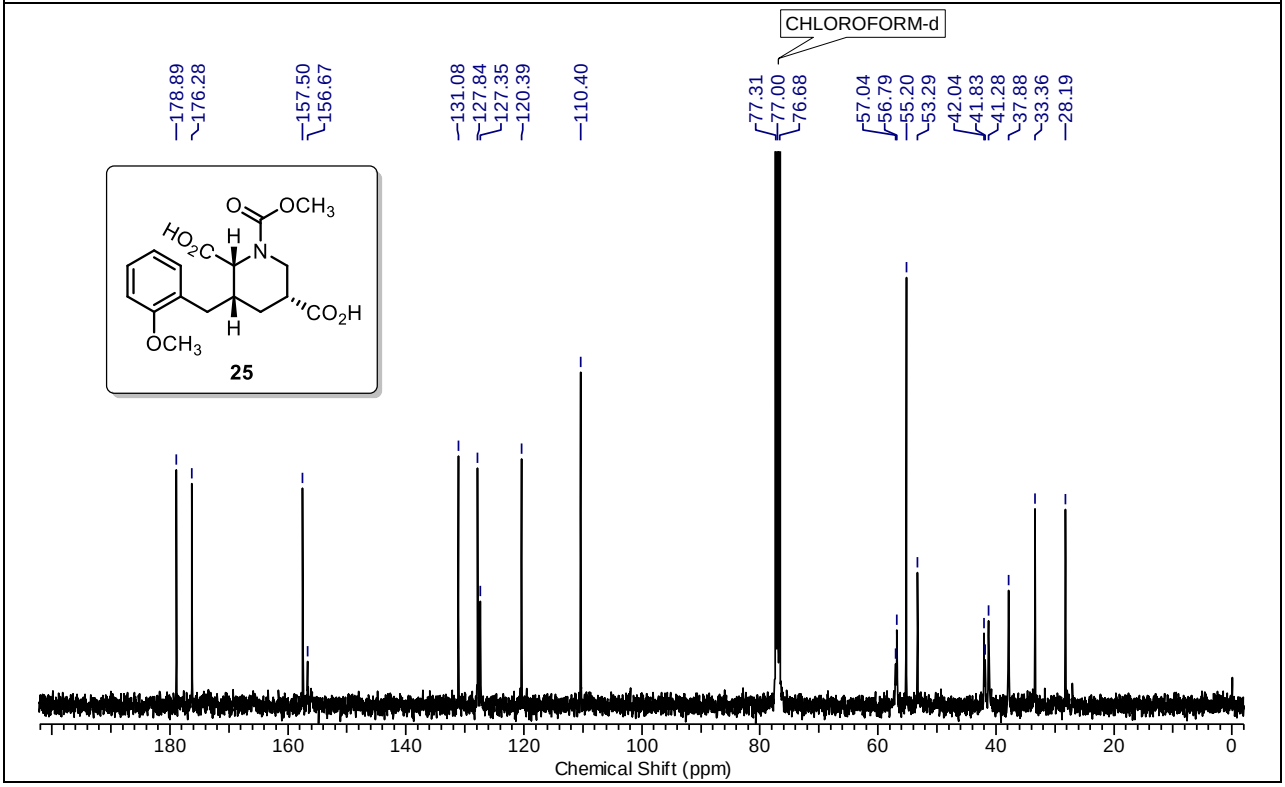

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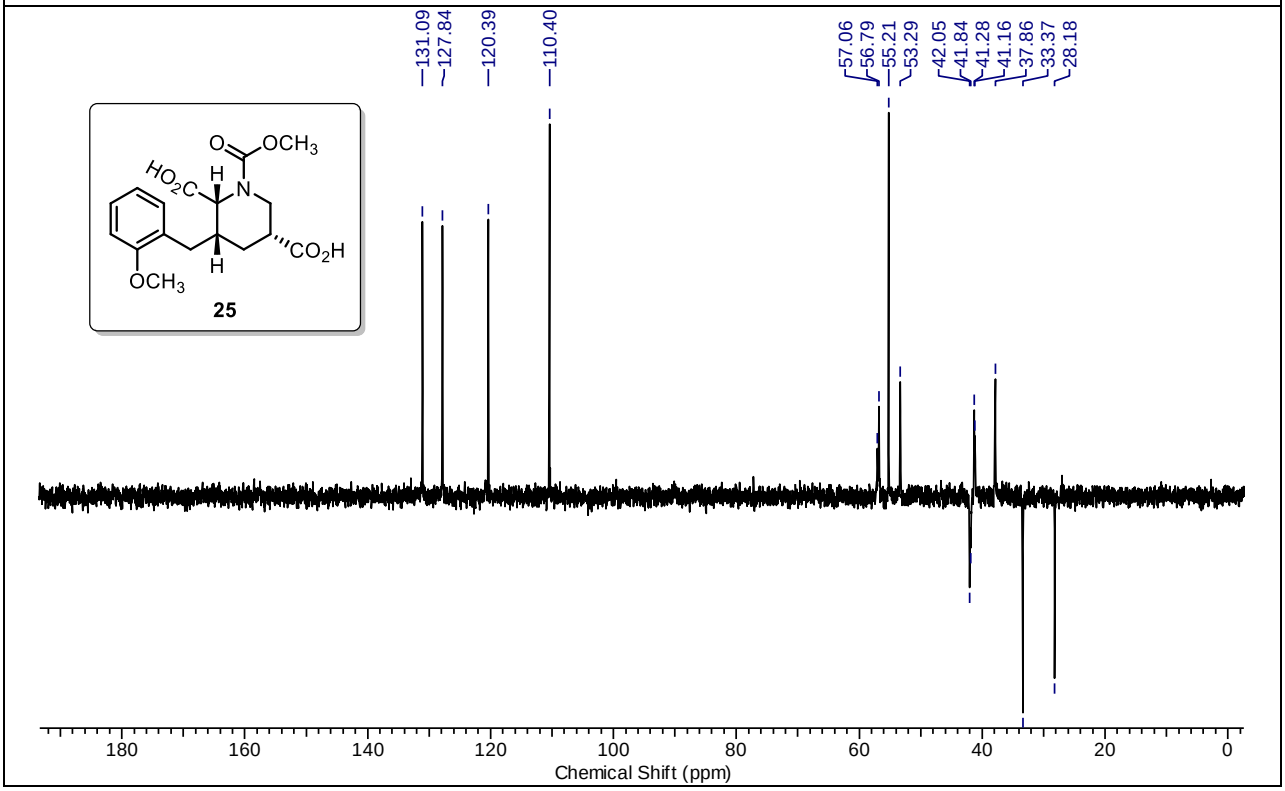

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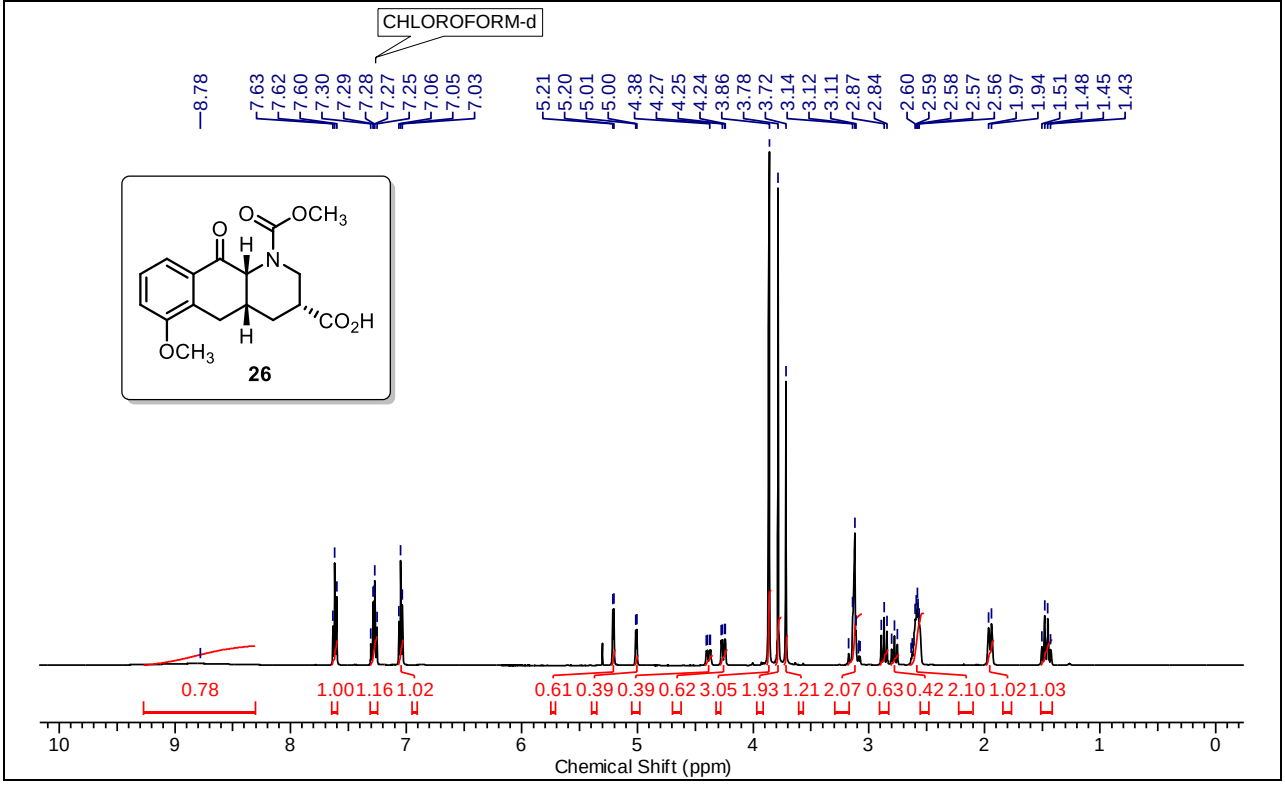

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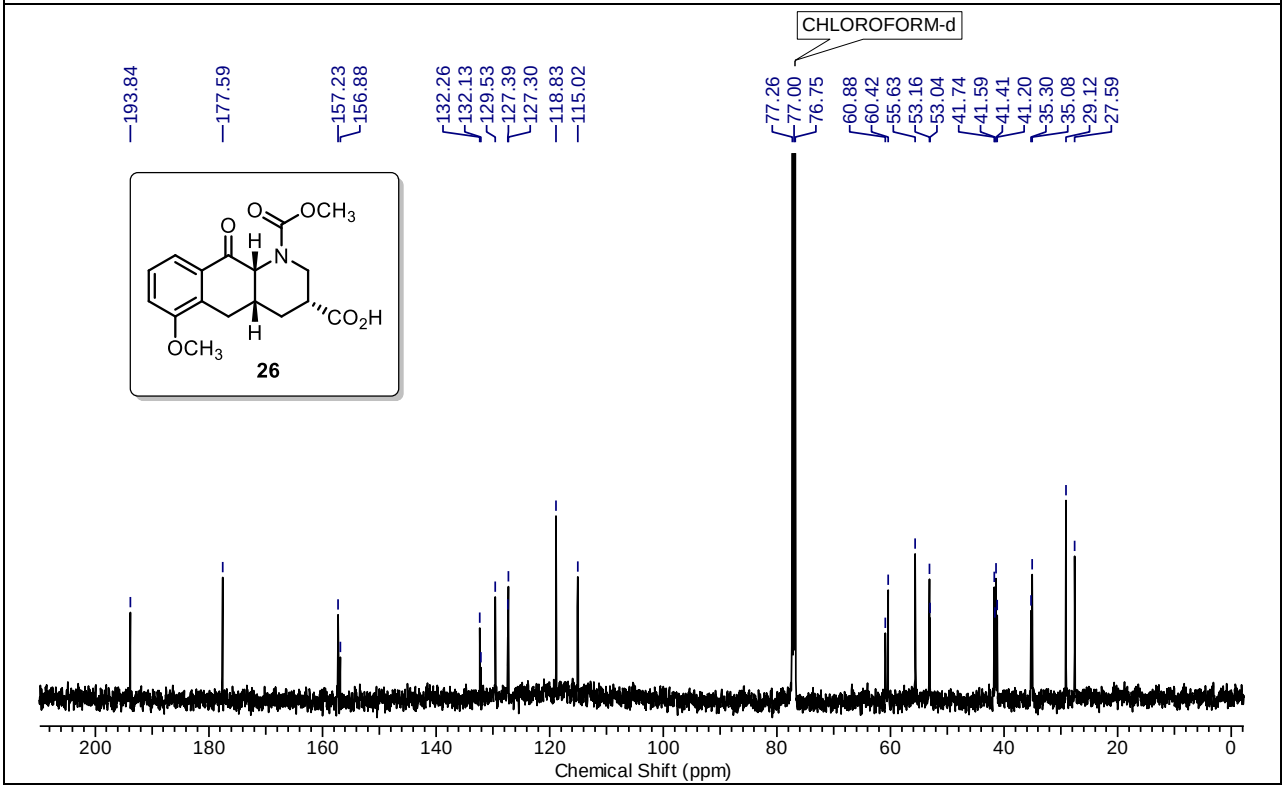
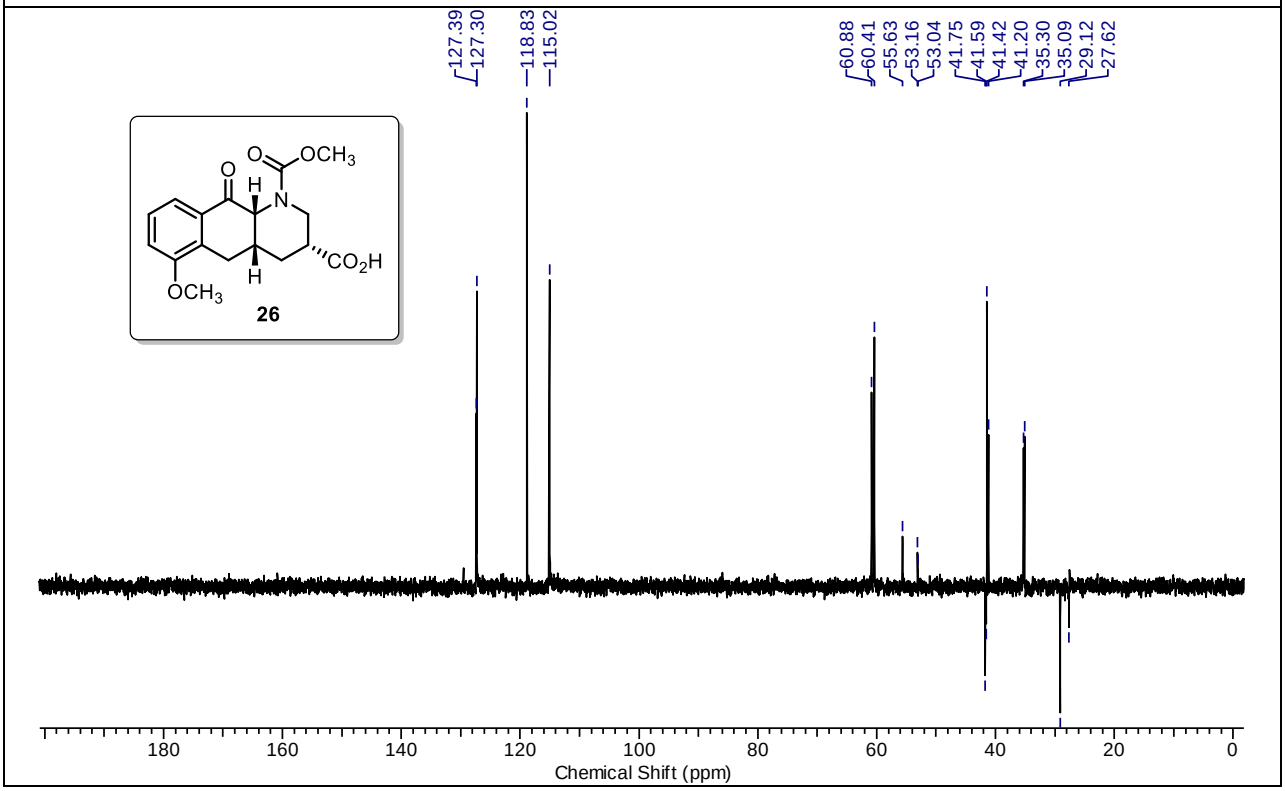
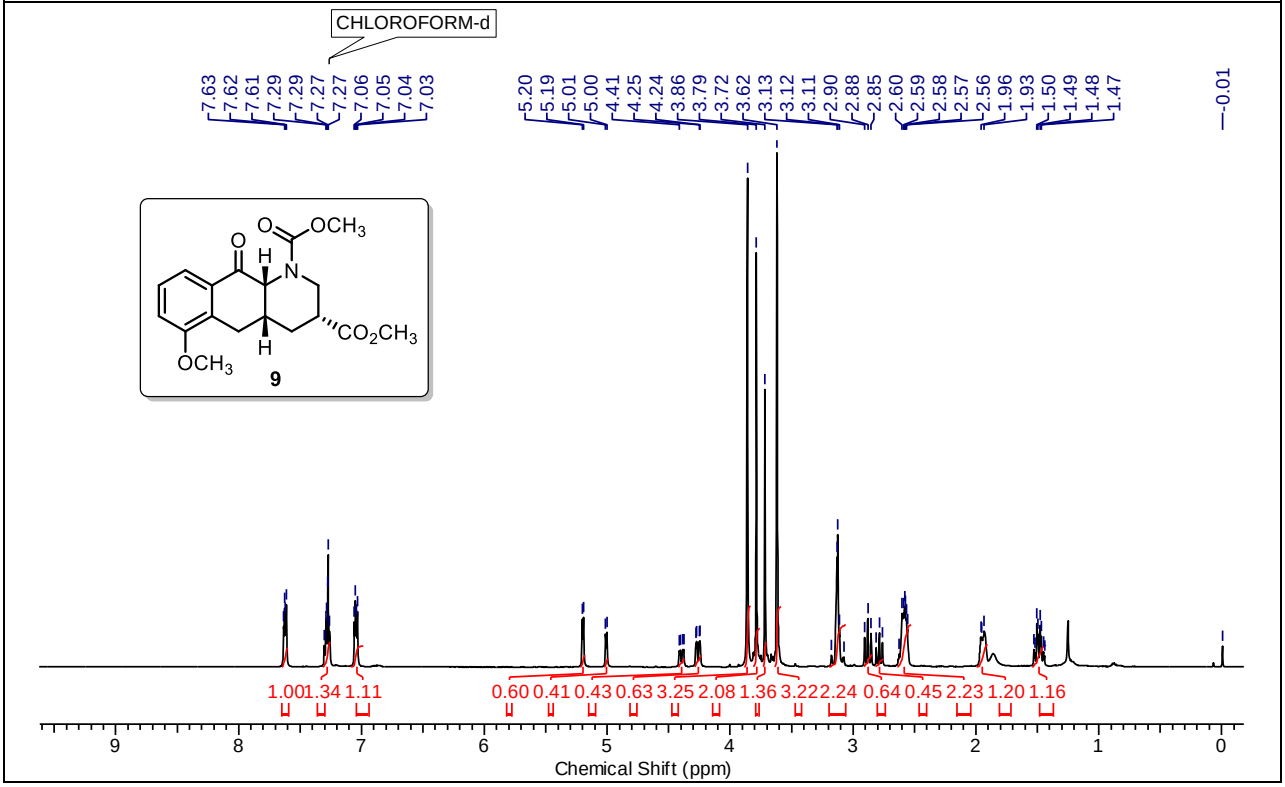


DEPT NMR spectrum of compound 26 ($CDCl_3$, 125 MHz)



^{1}H-NMR spectrum of compound 9 ($CDCl_3$, 500 MHz)



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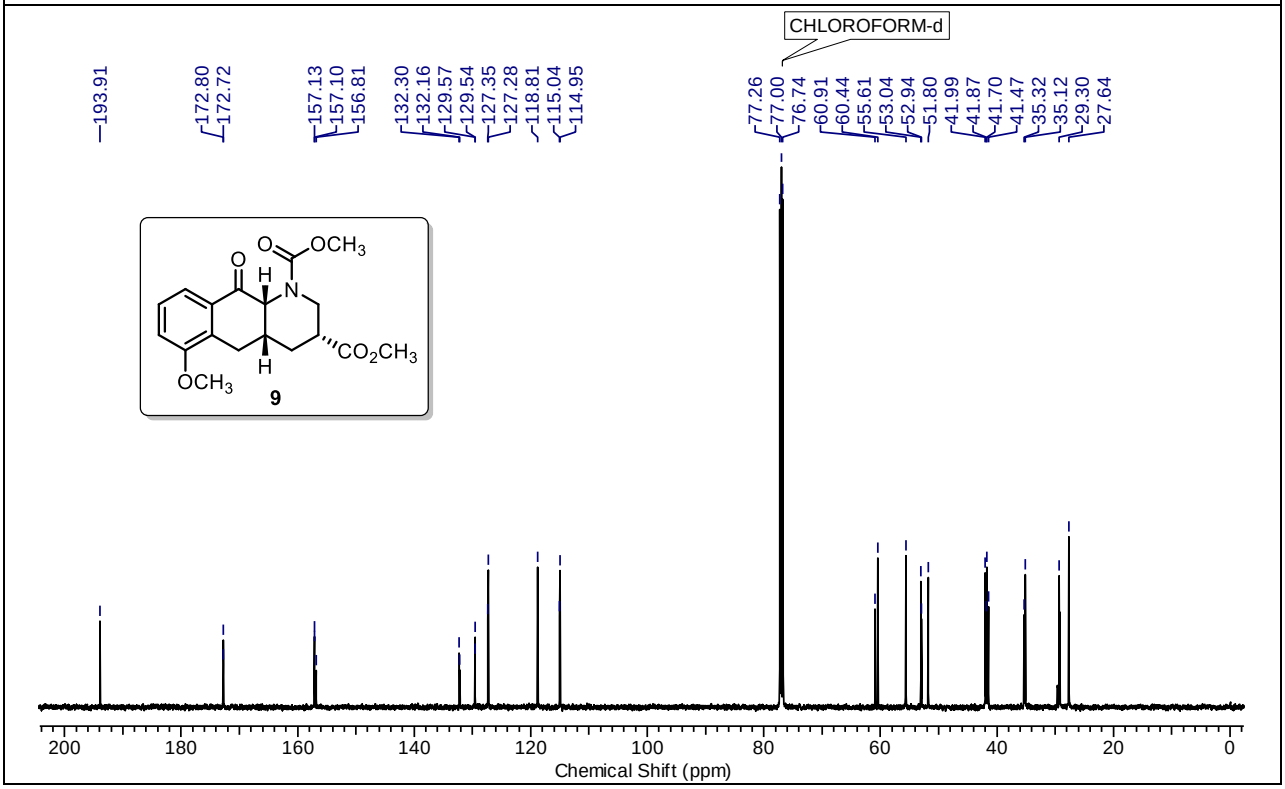
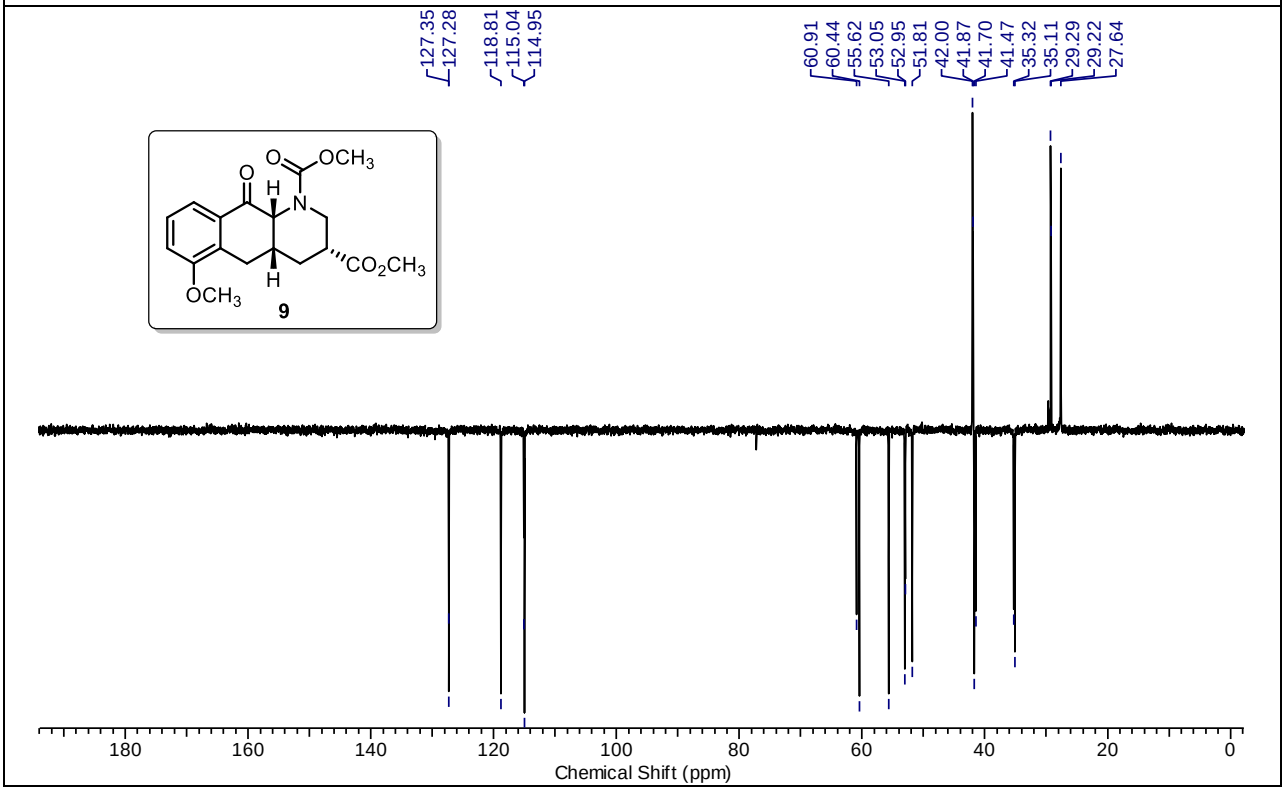


DEPT NMR spectrum of compound 9 ($CDCl_3$, 125 MHz)



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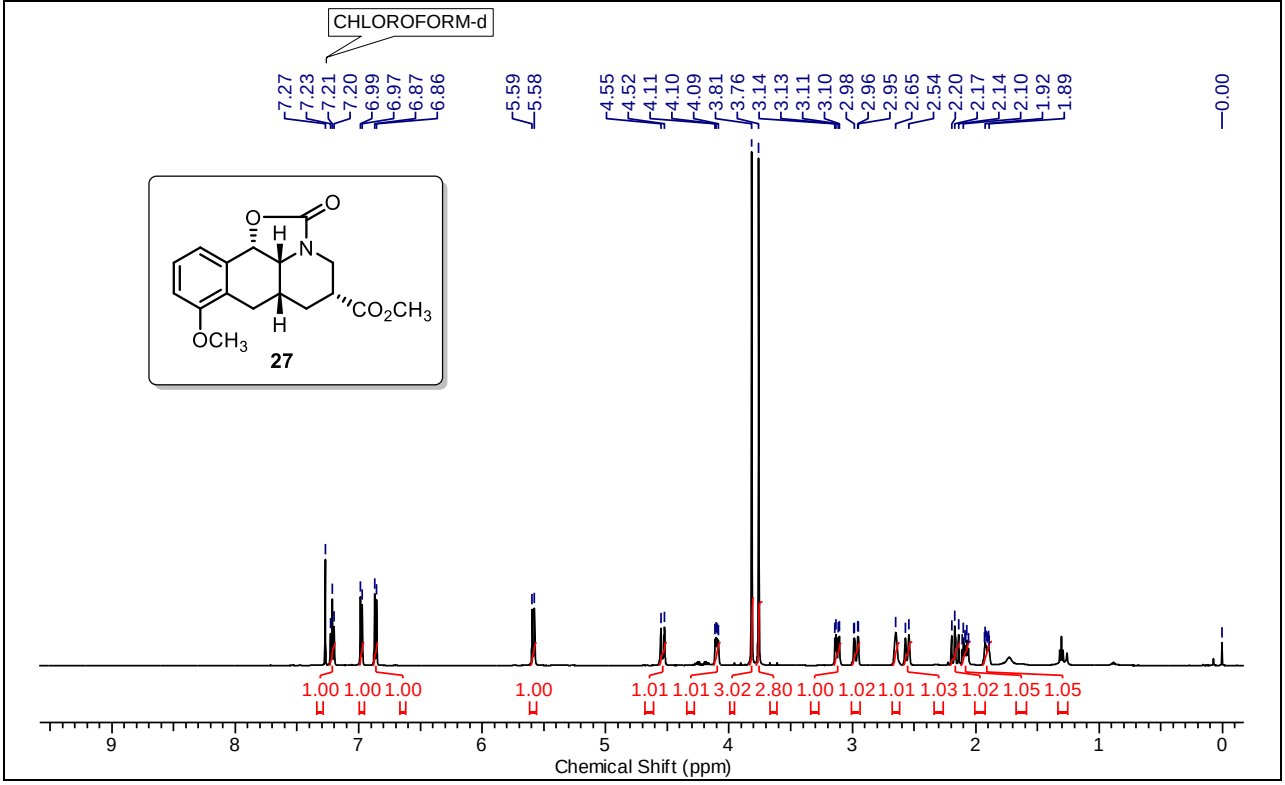

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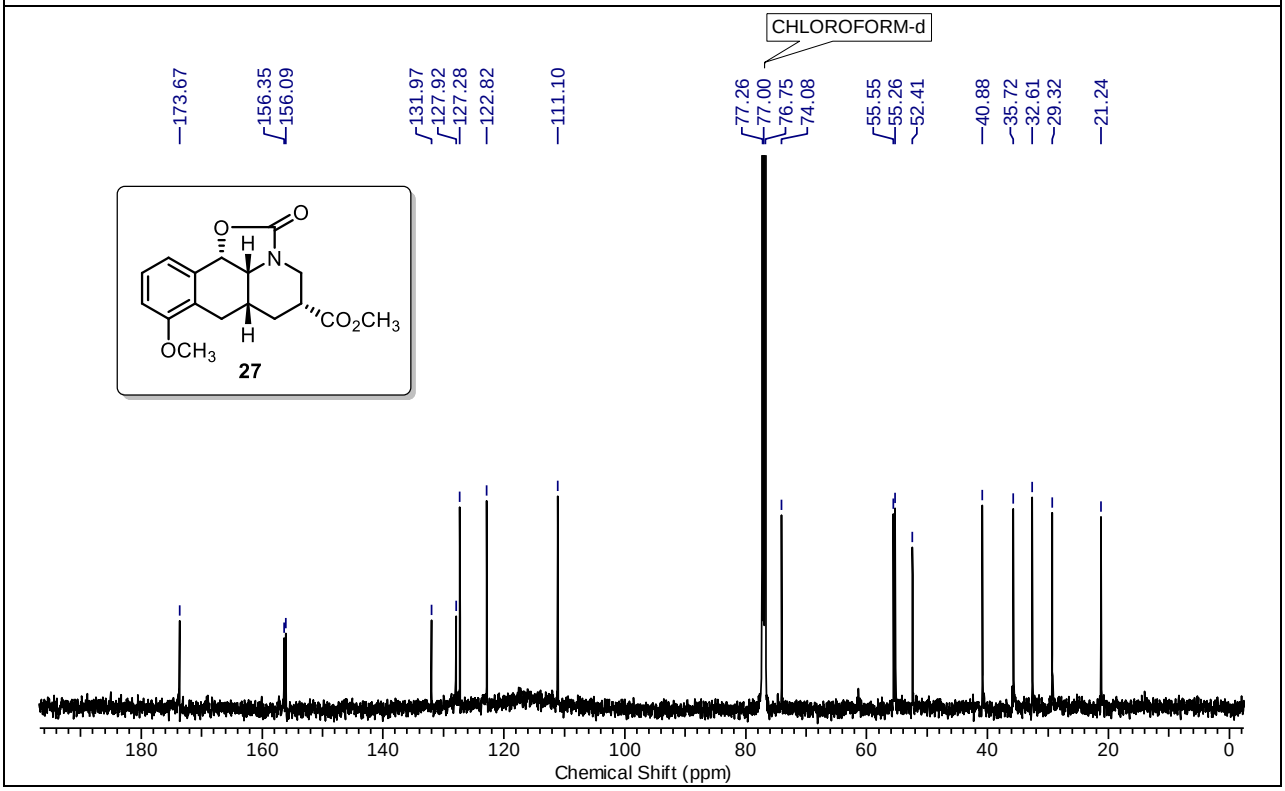
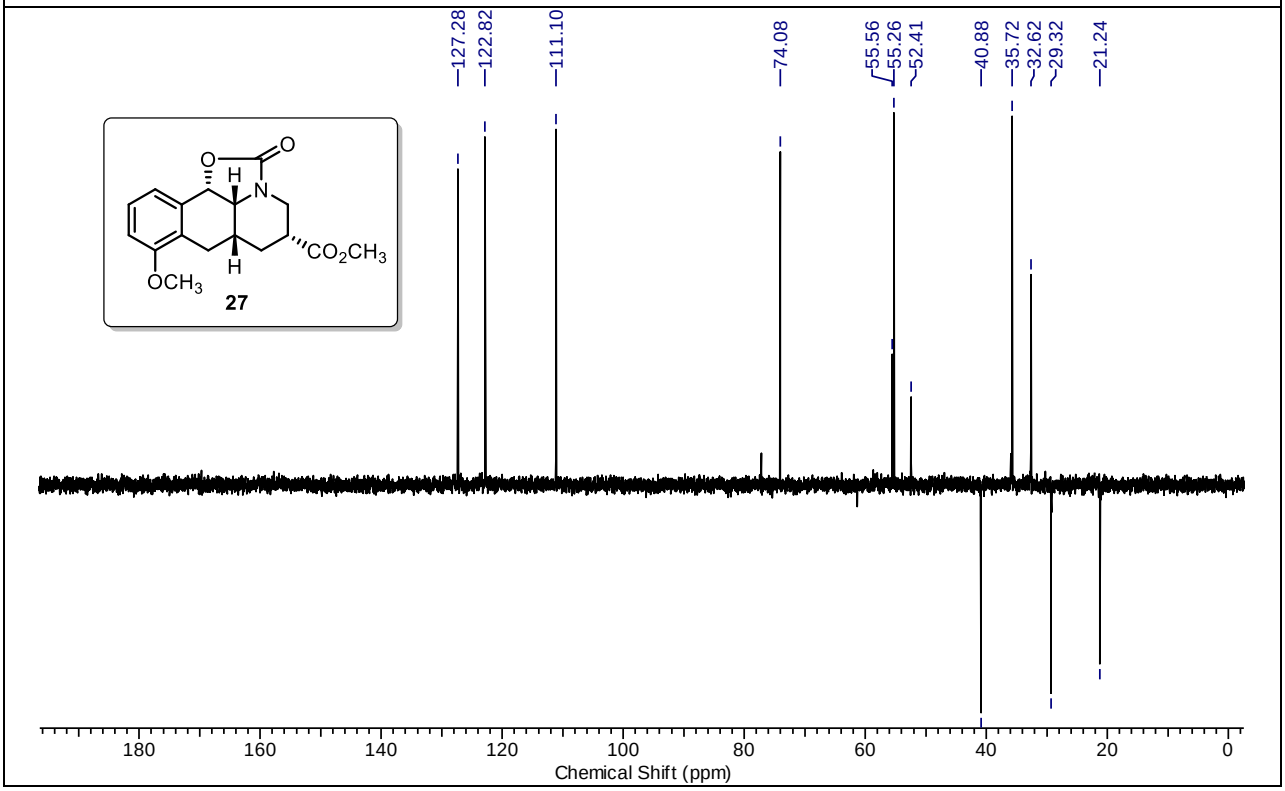


DEPT NMR spectrum of compound 27 ($CDCl_3$, 125 MHz)



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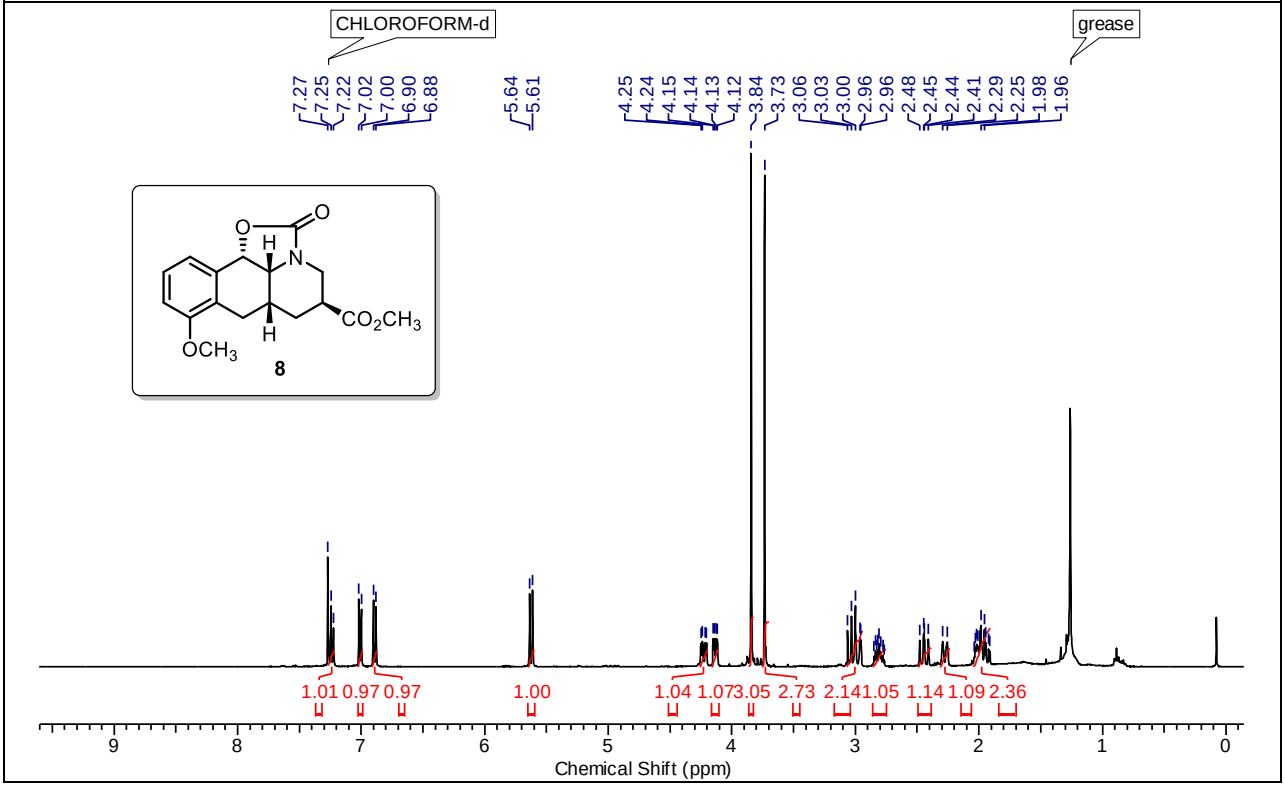
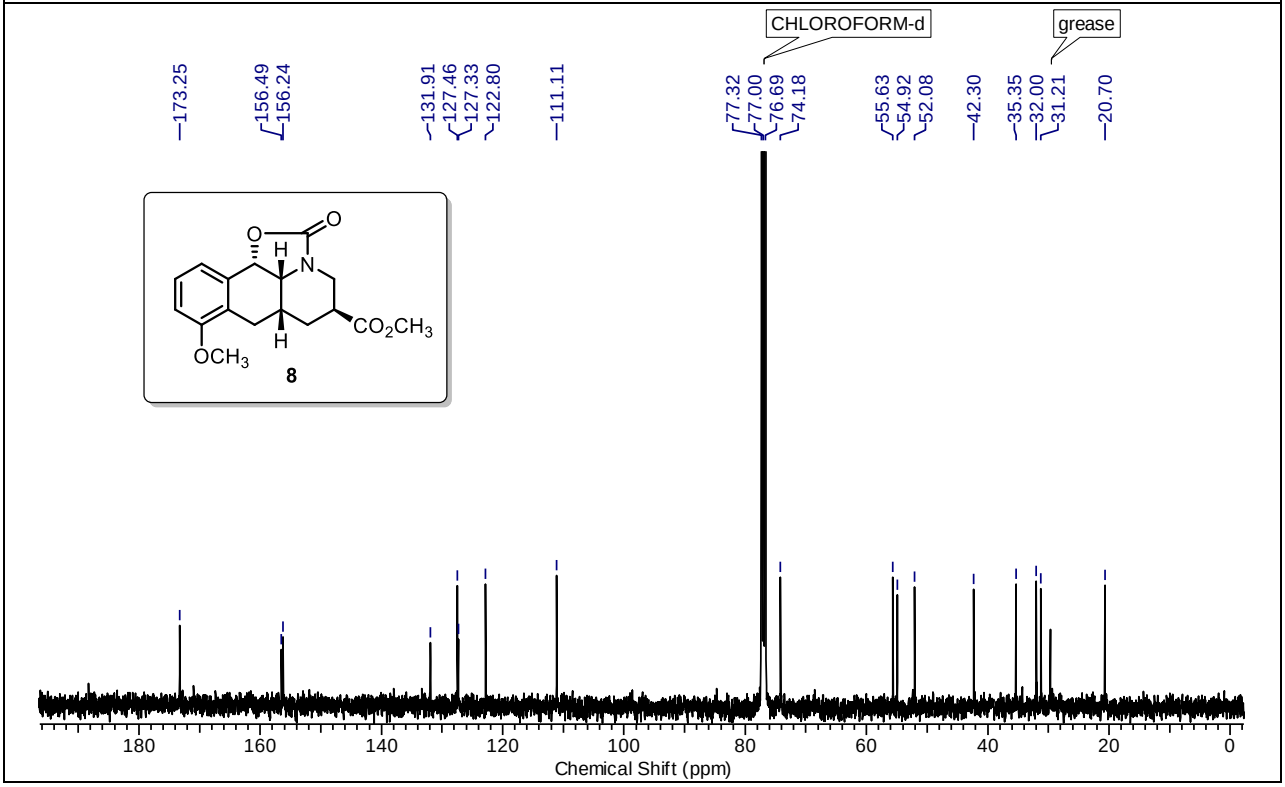
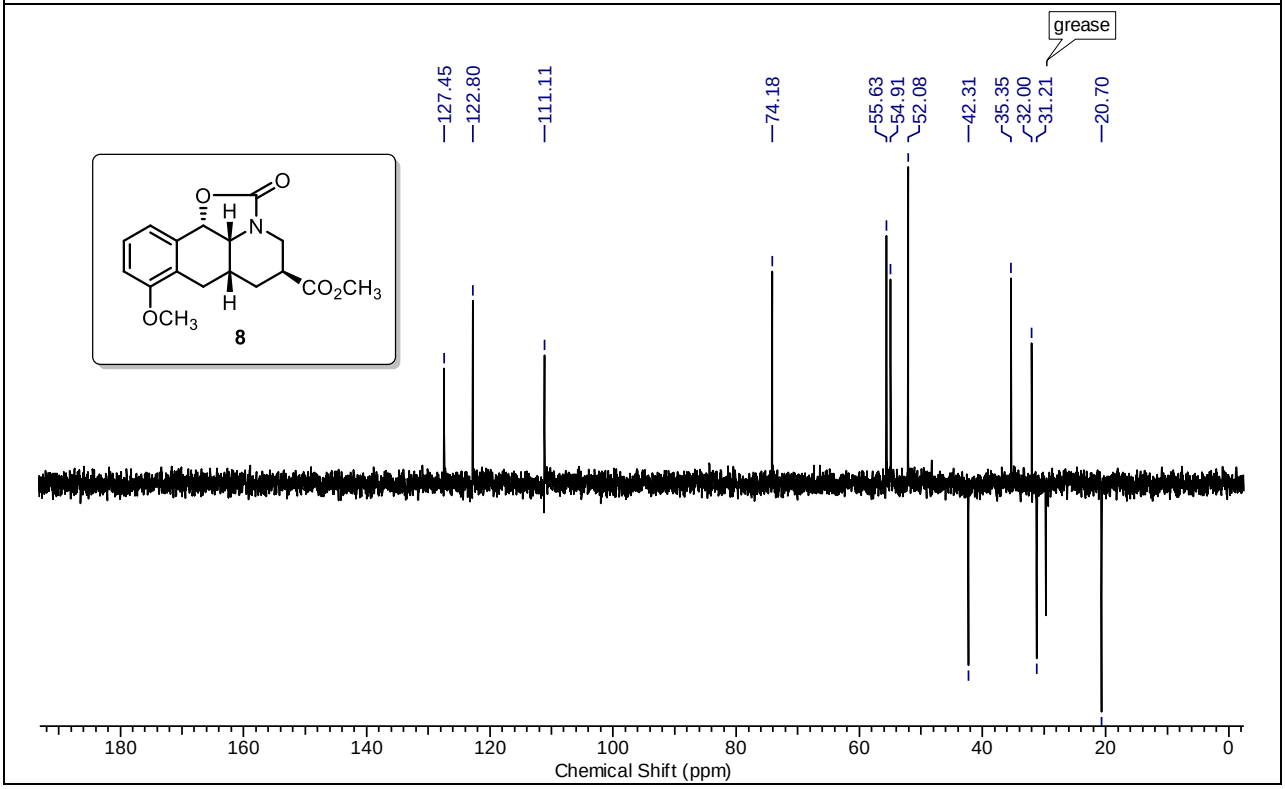


^{13}C-NMR spectrum of compound 8 ($CDCl_3$, 100 MHz)



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



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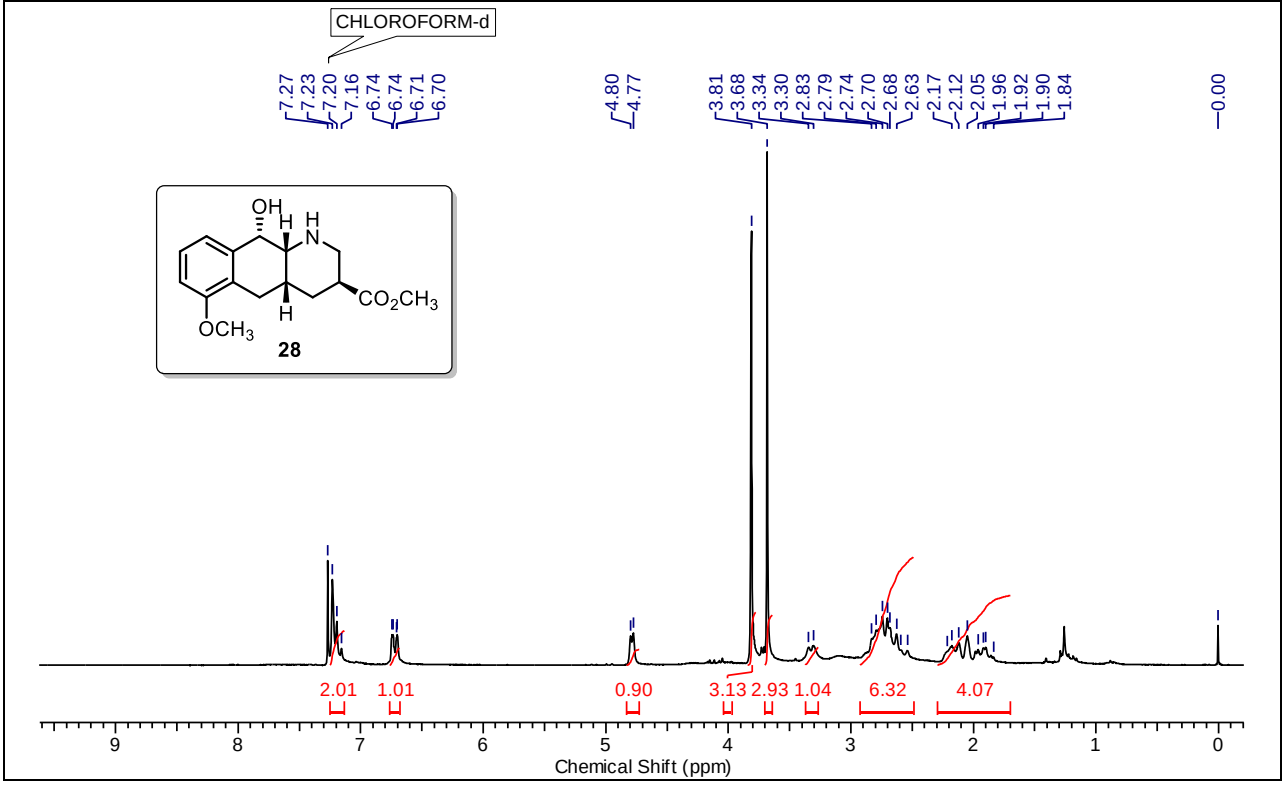

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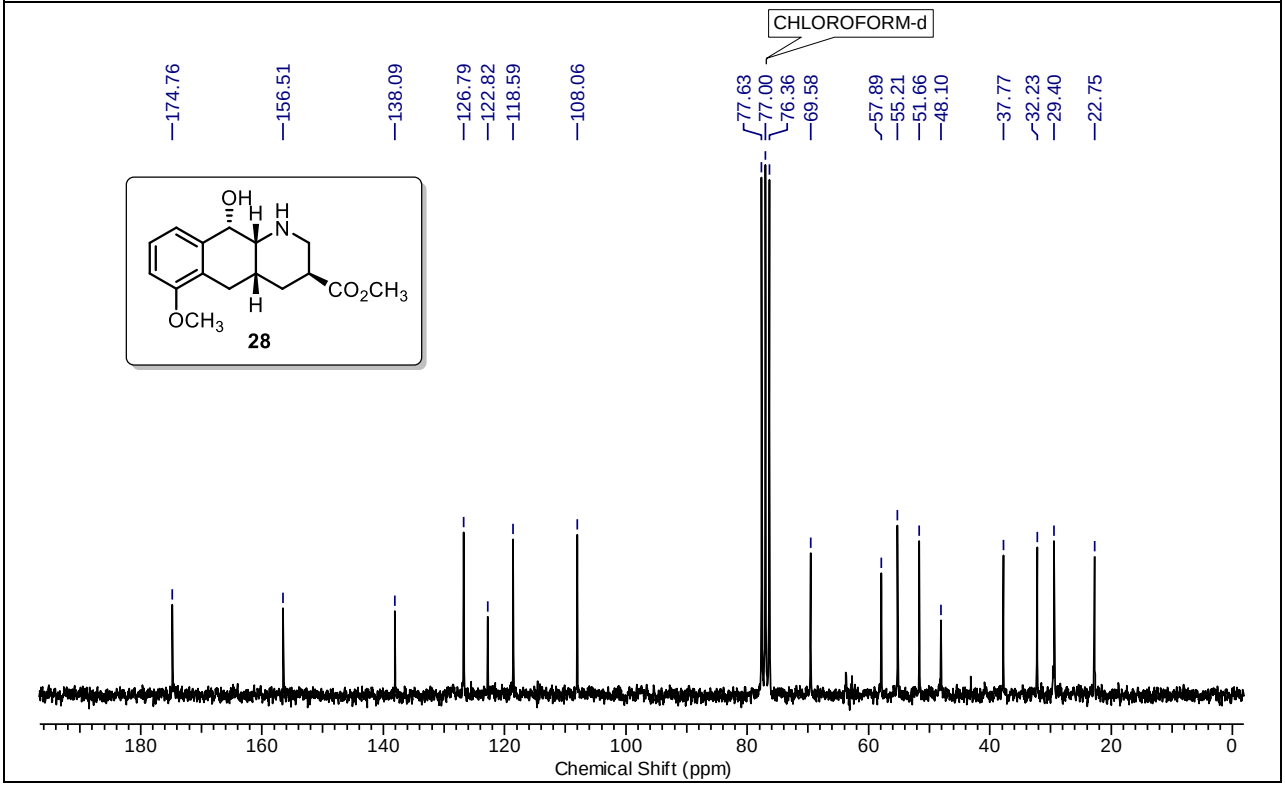
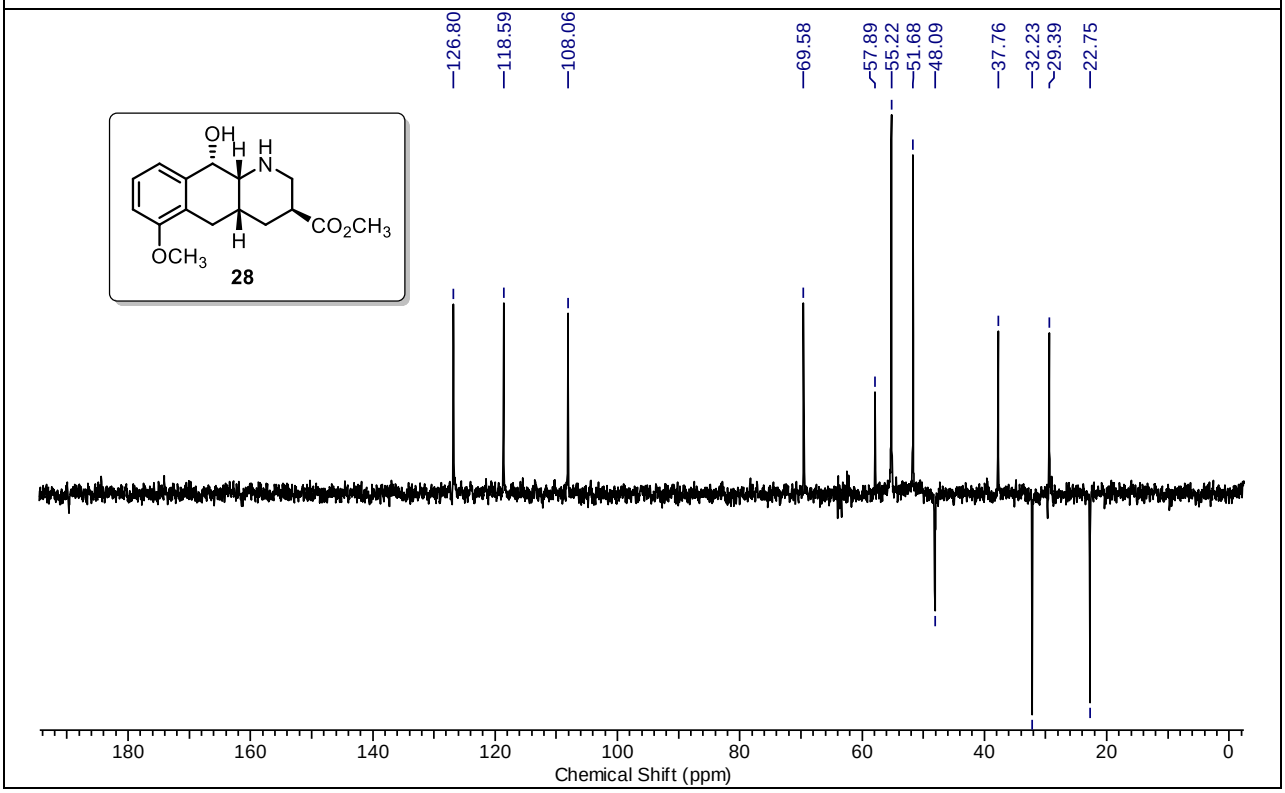
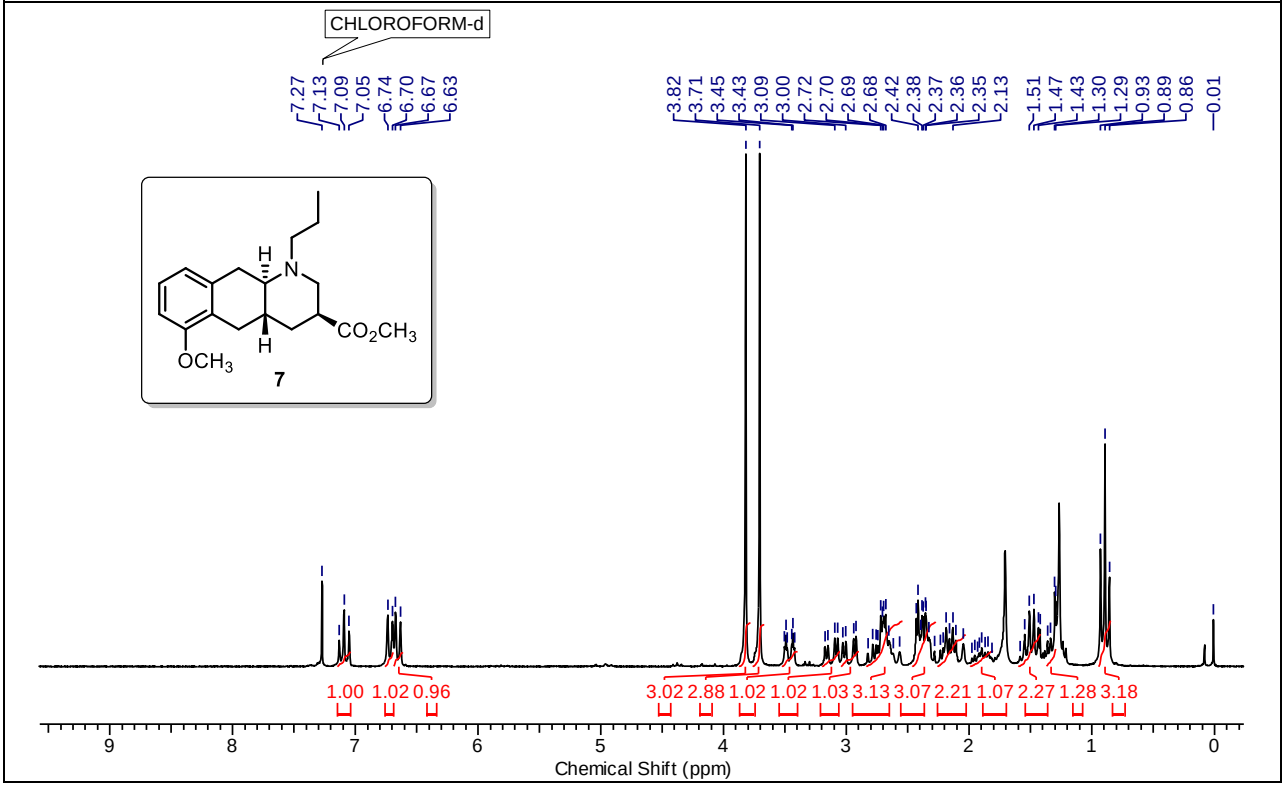


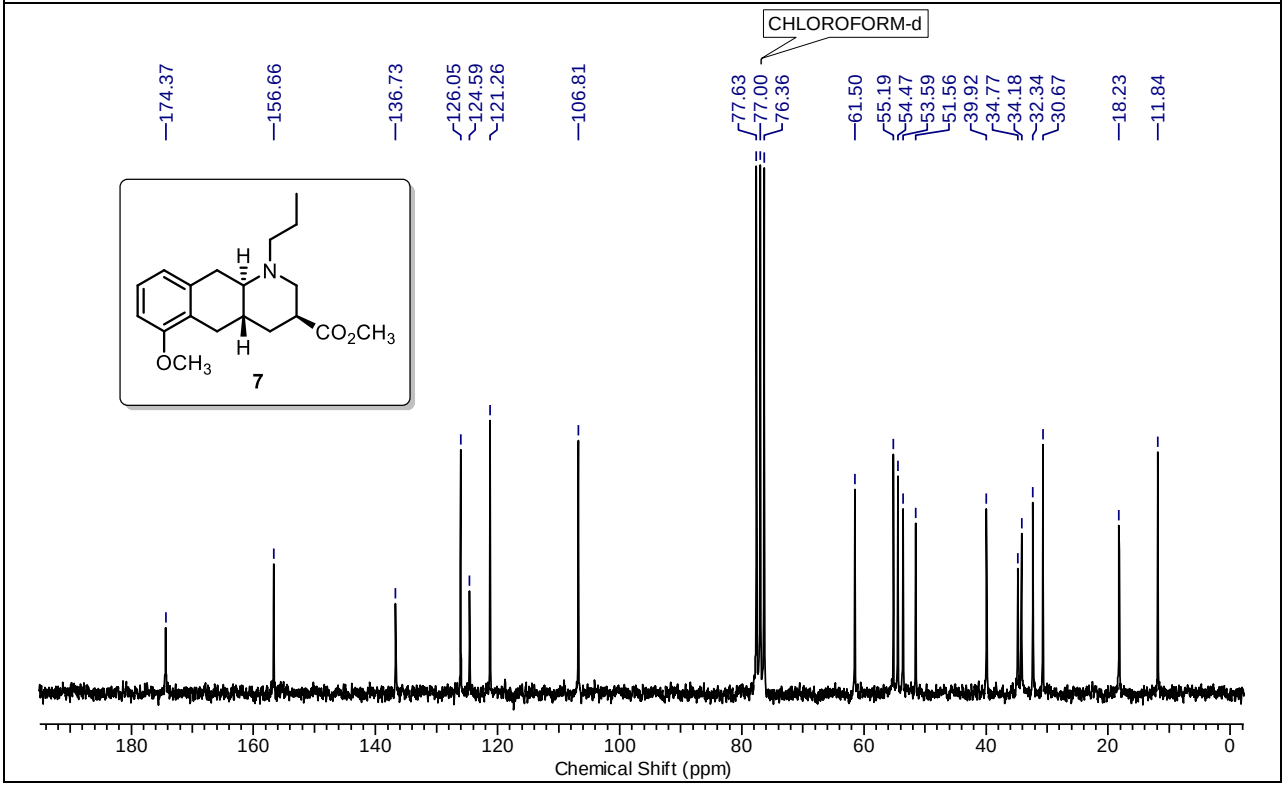
DEPT NMR spectrum of compound 28 ($CDCl_3$, 50 MHz)



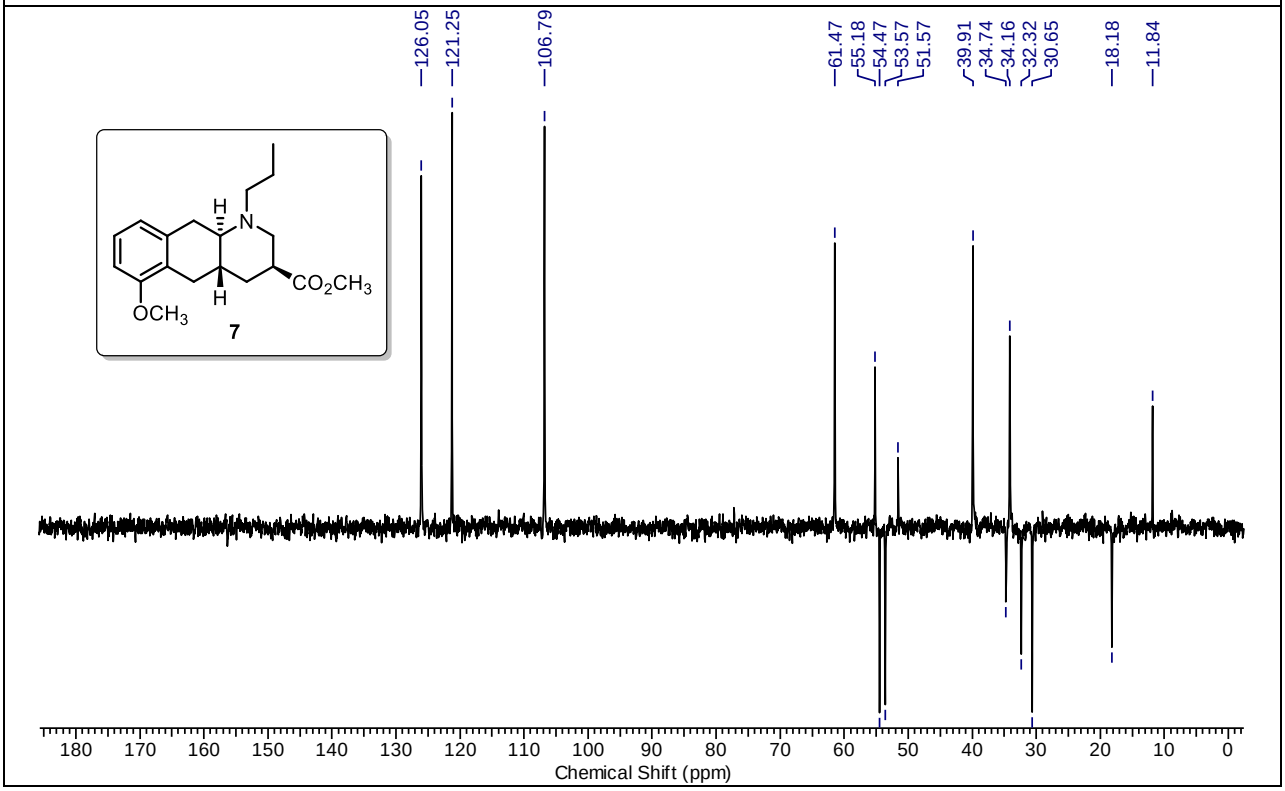
^{1}H-NMR spectrum of compound 7 ($CDCl_3$, 200 MHz)



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



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



2.2.6. References

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(7) Compound **18** (major) showed complex ^{1}H and ^{13}C NMR spectra due to the presence of rotamers and minor olefin regioisomer. For similar types of ring opening of 7-azabenzonorbornenes under Birch reaction conditions, see: Hodgson, D. M.; Winning, L. H. *Beilstein J. Org. Chem*. **2008**, *4*, 38. doi:10.3762/bjoc.4.38

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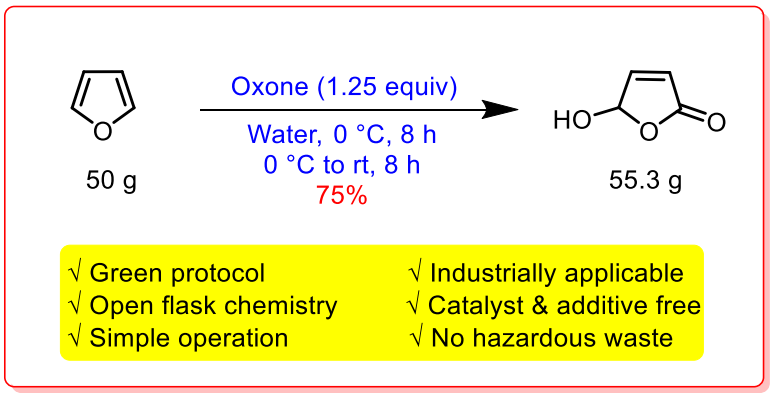
Chapter 3: On-Water Oxidation of Furan and its Application in the Collective Synthesis of Oseltamivir Phosphate (Tamiflu), (*S*)-Pipecolic acid and its 3-Hydroxy Derivatives

CHAPTER 3

Section 1

"On-Water Oxidation of Furan: Scalable Synthesis of 5-Hydroxy-2(5*H*)-Furanone Using Oxone as a Sole Oxidant"



ABSTRACT: Simple, efficient and scalable method for the synthesis of 5-hydroxy-2(5*H*)-furanone has been developed on a multigram scale from furan. Oxidation of furan was performed using oxone as the sole oxidant and water as a solvent, which makes this protocol green and industrially applicable.

3.1.1. Introduction

Water is environmentally clean, most inexpensive and abundantly available solvent on earth, but its applications in organic synthesis are very much limited.[1] Since, it was reported that instead of organic solvents, Diels-Alder reaction could be accelerated by water, much attention was directed towards the development of organic reactions in water.[2] The main criterion to carry out organic transformations in water is the solubility of reagents. But in 2005, Sharpless and co-workers used the term "on water" reaction as the reaction is benefited by stirring insoluble reactant(s) in aqueous emulsion without the addition of any organic co-solvents.[3] Also in recent years, much attention has been directed towards the oxidation of small molecules for the synthesis of natural products and bioactive drug molecules, but its application at the industrial level is not successful to a greater extent as the expensive reagents, special setups, and hazardous byproducts are the main limitations of such conversions. The development of industrially applicable organic transformations using water as an environmentally safe solvent has great potential.

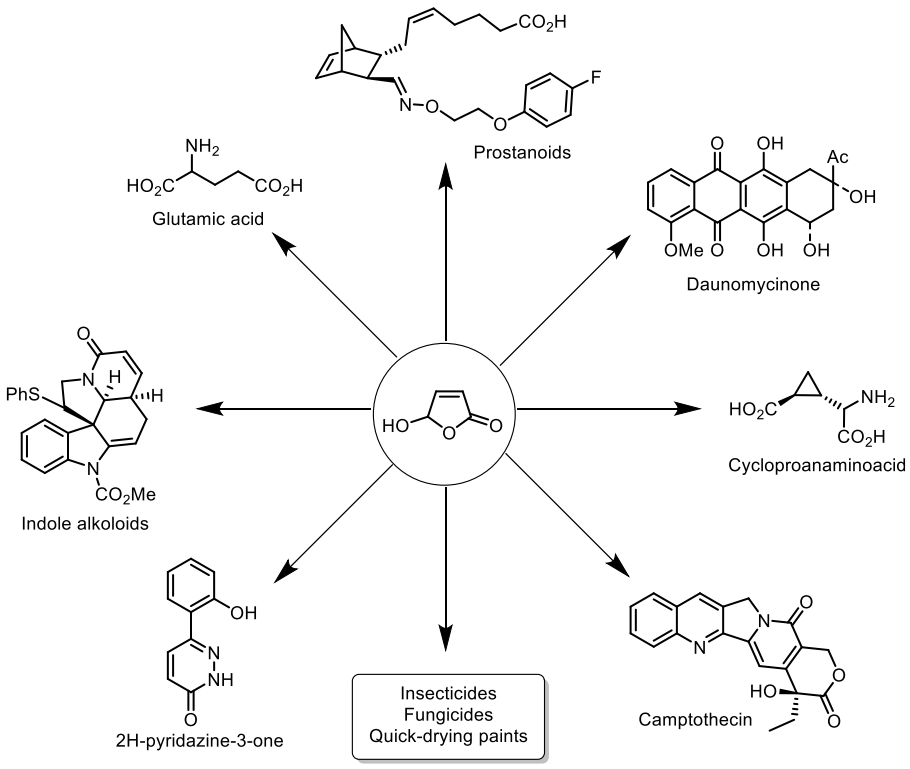


Figure 1: Application of 5-hydroxy-2(5*H*)-furanone.

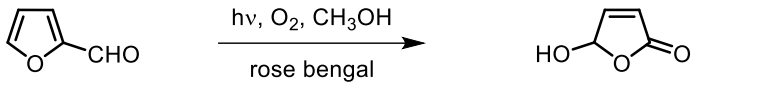
In this context, large scale synthesis of 5-hydroxy-2(5*H*)-furanone (**2**) has attracted much attention as it finds wide applications for the synthesis of insecticides, pesticides, quick-drying paints, prostanoids, alkaloids, *etc*. A long list of applications of 5-hydroxy-2(5*H*)-furanone (**2**) is found in the literature [4] as 5-hydroxy-2(5*H*)-furanone (**2**) has been used as a key synthon in the total synthesis of natural products and biologically active compounds (**Figure 1**).

3.1.2. Literature

Importance of 5-hydroxy-2(5*H*)-furanone has been demonstrated in the literature, in the form of development of various methods for its synthesis. The methods for the synthesis of 5-hydroxy-2(5*H*)-furanone are photocatalytic,[5] thermo-catalytic[6] and electrocatalytic [7] oxidation of furan and its derivatives (*i.e.*, furfuryl alcohol, furfural, and furoic acid).

Each method for the synthesis of 5-hydroxy-2(5*H*)-furanone is discussed in detail below.

Photocatalytic Oxidation[5]

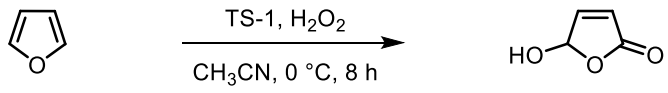


Furfural 5-hydroxy-2(5*H*)-furanone

Willette *et al*. in the year 1973 reported the photo-oxidation of furfural to 5-hydroxy-2(5*H*)-furanone as a major product in 43% yield using rose bengal as a photosensitizer.[5a] The same method was successfully demonstrated at the decagram scale by Moradei *et al.* in the year 2003 in 81–85% yield.[5b] Furthermore, Fukuyama and coworkers in 2005 found that the photo-oxidation of furfural to 5-hydroxy-2(5*H*)-furanone proceeded with bubbling air under sunlight, instead of bubbling oxygen under irradiation with a high-pressure mercury lamp.[5c] Recently in the year 2012, energy-efficient photo-oxidation of furfural to 5-hydroxy-2(5*H*)-furanone in 98% yield using 5-mm light-emitting diodes and photosensitizers was reported by Carney *et al.*[5d]

In the case of photocatalytic oxidation, although progress has been made, synthesis of 5-hydroxy-2(5*H*)-furanone mainly depends on environmentally hazardous photosensitizers. Moreover, poor recyclability of photosensitizers and the potential risk of explosion of reaction mixture severely limited the applications of photocatalytic methods.

Thermocatalytic Oxidation[6]

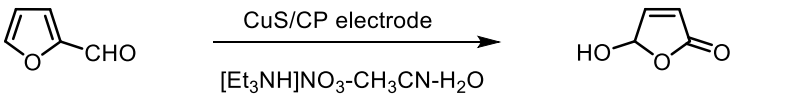


Furan 5-hydroxy-2(5*H*)-furanone

In the year 1999, Kumar *et al.*[6a] reported the thermocatalytic oxidation of furan to the 5-hydroxy-2(5*H*)-furanone in 98.3% yield using titanium silicate molecular sieves (TS-1) catalyst and H_2O_2 as an oxidant. The reaction was performed using 20 weight% TS-1 with respect to furan in CH_3CN as a solvent.

In comparison to the photocatalytic oxidation, thermo-catalytic oxidation of furan for the synthesis of 5-hydroxy-2(5*H*)-furanone is highly desired. However, great difficulty in obtaining the selectivity in thermo-catalytic oxidation of furan and its derivatives, where 5-hydroxy-2(5*H*)-furanone is easily oxidized into maleic acid under reaction condition and problems associated with synthesis and accessibility of catalyst (*i.e.* TS-1) mainly limited its application for the large scale synthesis.[6b,c]

Electrocatalytic Oxidation[7]



Furfural 5-hydroxy-2(5*H*)-furanone

More recently (2019), Wu *et al.*[7] reported the elegant method of electrocatalytic oxidation of biomass-derived furfural for the synthesis of 5-hydroxy-2(5*H*)-furanone. The method used H_2O as the oxygen source and metal chalcogenides (CuS, ZnS, PbS, etc.) as electrocatalysts. Using CuS nanosheets, high selectivity (83.6%) and conversion (70.2%) of furfural were achieved. Though this method has advantages over other literature reported methods for the synthesis of 5-hydroxy-2(5*H*)-furanone, electrocatalysis is mainly limited to the academic purpose.

3.1.3. Objective

By taking the literature reports into consideration which uses an expensive and stoichiometric amount of reagents, multiple steps, long reaction time, tedious workup and catalyst preparation,

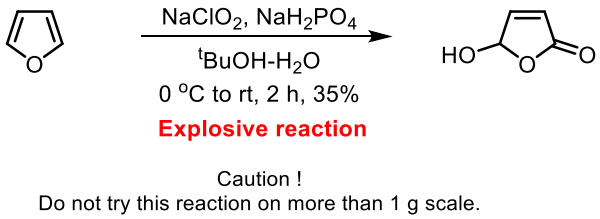
there is a challenging but long-standing need to develop a simple, green, and selective method for the scalable and industrially applicable synthesis of 5-hydroxy-2(5*H*)-furanone.

3.1.4. Present Work

3.1.4.1. Results and Discussion

The research program in the Chavan group directed towards the total synthesis of biologically active compounds[8,9] required a large quantity of 5-hydroxy-2(5*H*)-furanone as a synthon. Initially, the method reported by Kumar *et al*. for the synthesis of 5-hydroxy-2(5*H*)-furanone[6a] using the TS-1 catalyst was explored. But it was almost impossible to maintain the good quality and ready availability of the TS-1 catalyst, as its preparation itself was a challenging task and scale-up was another issue.

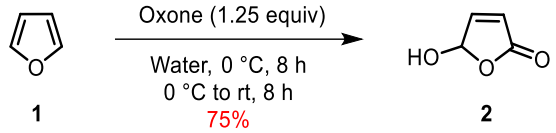
While searching for an appropriate oxidizing agent for the oxidation of furan which allows simple reaction conditions at ambient temperature in high yields, it was decided to screen bench table oxidizing reagents. Furthermore, oxidation of 2-alkyl furan to the corresponding keto-acid was reported in good yields using $NaClO_2$ as an oxidizing agent (**Scheme 1**).[10] Oxidation of furan under the above-mentioned condition was not reported in the literature. Here, initially, the same reaction condition for the oxidation of furan was attempted. When oxidation of furan using $NaClO_2$ was tried at 0 °C, high exotherm was observed giving product 5-hydroxy-2(5*H*)-furanone in ~35% yield. When the same reaction was carried out on a 5 g scale, the explosive nature of the reaction mixture was observed. So with this result, it was quickly realized that it is almost impossible to scale up the reaction, which was necessary for the total synthesis program of this group. Ultimately, it forced to look towards other oxidizing agents, which would give smooth conversion and high yield at ambient conditions.



Scheme 1. Oxidation of Furan using $NaClO_2$

While searching for an alternative oxidant for the oxidation of furan, attention was directed towards the oxone which is considered to be an ideal oxidant having advantages like stability, simple handling, non-toxic nature, and the low cost.[11]

Considering the literature precedents and oxidation properties of oxone,[11] the oxidation of furan was performed using oxone as an oxidant in the water at room temperature. Pleasingly 5-hydroxy-2(5*H*)-furanone (**2**) was isolated in good yields (**Scheme 2**).[12]



Scheme 2. On-Water Oxidation of Furan

Initially, when furan (**1)** was treated with oxone (1 equiv) in acetonitrile-H_2O (1:1) at 0 °C and allowed to warm to room temperature for 12 h, the corresponding 5-hydroxy-2(5*H*)-furanone (**2**) was isolated in 37% yield (**Table 1**). Increase in oxone/furan mole ratio from 1 to 1.25 increased yields up to 48%. A further increase in oxone/furan mole ratio up to 1.5 did not improve the yields further, and over-oxidation of the product formed was observed. Also, changing the solvent system from acetonitrile-H_2O (1:1) to acetone-water (1:1) with 1.25 equiv of oxone didn't improve the yield. Here, in both of these solvent systems, a dark yellow colored product formation was observed along with over oxidation of the product formed.

Table 1- Oxidation of Furan

Sr. no.	Solvents	Solvents ratio	Oxone/Furan (Mole ratio)	Reaction condition	Yields[a, b]
1	Acetonitrile-H_2O	1:1	1.0	0 °C to rt, 12 h	37%
2	Acetonitrile-H_2O	1:1	1.25	0 °C to rt, 12 h	48%
3	Acetonitrile-H_2O	1:1	1.5	0 °C to rt, 12 h	45%
4	Acetone-H_2O	1:1	1.25	0 °C to rt, 12 h	43%
5	Water	-	1.25	0 °C to rt, 12 h	58%
6	**Water**	**-**	**1.25**	**0 °C, 8 h then rt, 8 h**	**75%**

[a] reaction carried out on 5 g scale, [b]isolated yields

Furthermore, when the reaction was carried in water as a solvent, the desired product formation was observed in 58% yield. Here also, over-oxidation of the product was observed. But, when the reaction was carried out at 0 °C for 8 h, the desired product formation was observed in 75% yield. In this reaction, a thick colorless liquid was isolated after workup, which solidified upon overnight standing. Thus, temperature and the time-dependent study indicated that 0 °C and 8 h

reaction time were the best suitable parameters for the high conversion. Thus, the solvent and temperature effect was found to be the deciding factor for the high conversion in the oxidation of furan in water.

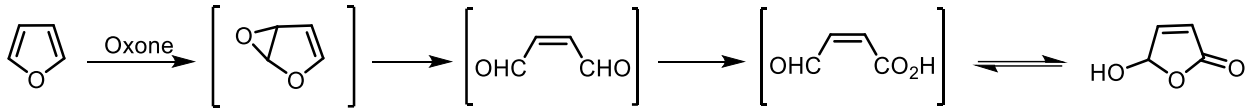
After optimization, it was found that 1.25 equiv of oxone in the water at 0 °C for 8 h was the optimum condition for smooth conversion and high yield. Thus the oxidation of furan to 5-hydroxy-2(5*H*)-furanone has been achieved using oxone as a sole oxidant in water, and to the best of this author's knowledge, such type of transformation is not reported in the literature.

The main objective while starting this project was to develop the scalable synthesis of 5-hydroxy-2(5*H*)-furanone using mild reaction conditions. Thus after getting optimized reaction condition in hand, oxidation of furan was scaled up to 50 gram using oxone as an oxidant in high yield. It was noted that the workup of the reaction mixture was the challenging task as the product formed was soluble in water and requires multiple extractions with ethyl acetate for efficient isolation of the product. It was noteworthy that during the scale-up of the furan oxidation on a gram scale (50 g), exotherm was not observed while delivering the product in high yield at 0 °C.

In a typical experimental procedure, to a mechanically stirred, cooled (0 °C) solution of furan (**1**) (50 g, 0.735 mol) in water (1000 mL) was added oxone (564 g, 1.83 mol) portion-wise and stirred at 0 °C for 8 h. The mixture was allowed to warm to room temperature and stirred for the next 8 h. The reaction mixture was filtered, solid was thoroughly washed with ethyl acetate, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 X 500 mL). Additionally, the aqueous layer was saturated with NaCl and extracted with ethyl acetate (3 X 500 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated at a temperature below 40 °C under reduced pressure to give crude 5-hydroxy-2(5*H*)-furanone as a clear liquid which solidified on cooling. The solid was recrystallized at -78 °C from $CHCl_3$ (300 mL) to afford 55.3 g (75% yield) of 5-hydroxy-2(5*H*)-furanone (**2**). The physical and spectroscopic data were in full agreement with the literature data.[5b]

The possible reaction mechanism is based on the oxidation properties of oxone.[11] It is proposed that the oxidation of furan with oxone proceeds *via* epoxidation of one of the double bonds of furan ring (**Scheme 3**). The unstable epoxide formed is thought to rearrange immediately to *cis*-2-butene-1,4-*dial* followed by oxidation of one of the aldehyde groups leading to the formation

of 5-hydroxy-2(5*H*)-furanone. A similar mechanism has been proposed for the oxidation of furan and alkyl-substituted furan using peracids, dioxiranes, and TS-1/H_2O_2.[13]



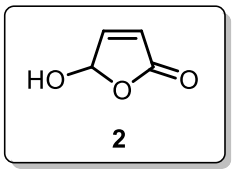
Scheme 3. Possible Reaction Mechanism

3.1.5. Conclusion

Simple, efficient and scalable synthesis of 5-hydroxy-2(5*H*)-furanone has been accomplished. Using this green protocol, 5-hydroxy-2(5*H*)-furanone was successfully synthesized on a multigram scale. The present method paves the way for the industrial-scale synthesis of 5-hydroxy-2(5*H*)-furanone using oxone as a green oxidant which has advantages like stability, simple handling, non-toxic nature, low costs, and water solubility.

3.1.6. Experimental Section

5-Hydroxy-2(5*H*)-furanone (2).



To a mechanically stirred, cooled (0 °C) solution of furan (**1**) (50 g, 0.735 mol) in water (1000 mL) was added oxone (564 g, 1.83 mol) portion-wise and stirred at 0 °C for 8 h. The mixture was allowed to warm to room temperature and stirred for the next 8 h. The reaction mixture was filtered, solid was thoroughly washed with ethyl acetate, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 X 500 mL). Additionally, the aqueous layer was saturated with NaCl and extracted with ethyl acetate (3 X 500 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated at a temperature below 40 °C under reduced pressure to give crude 5-hydroxy-2(5*H*)-furanone as a clear liquid which solidified on cooling. The solid was recrystallized at -78 °C from $CHCl_3$ (300 mL) to afford 55.3 g (75% yield) of 5-hydroxy-2(5*H*)-furanone (**2**).

Yield: 75 %;

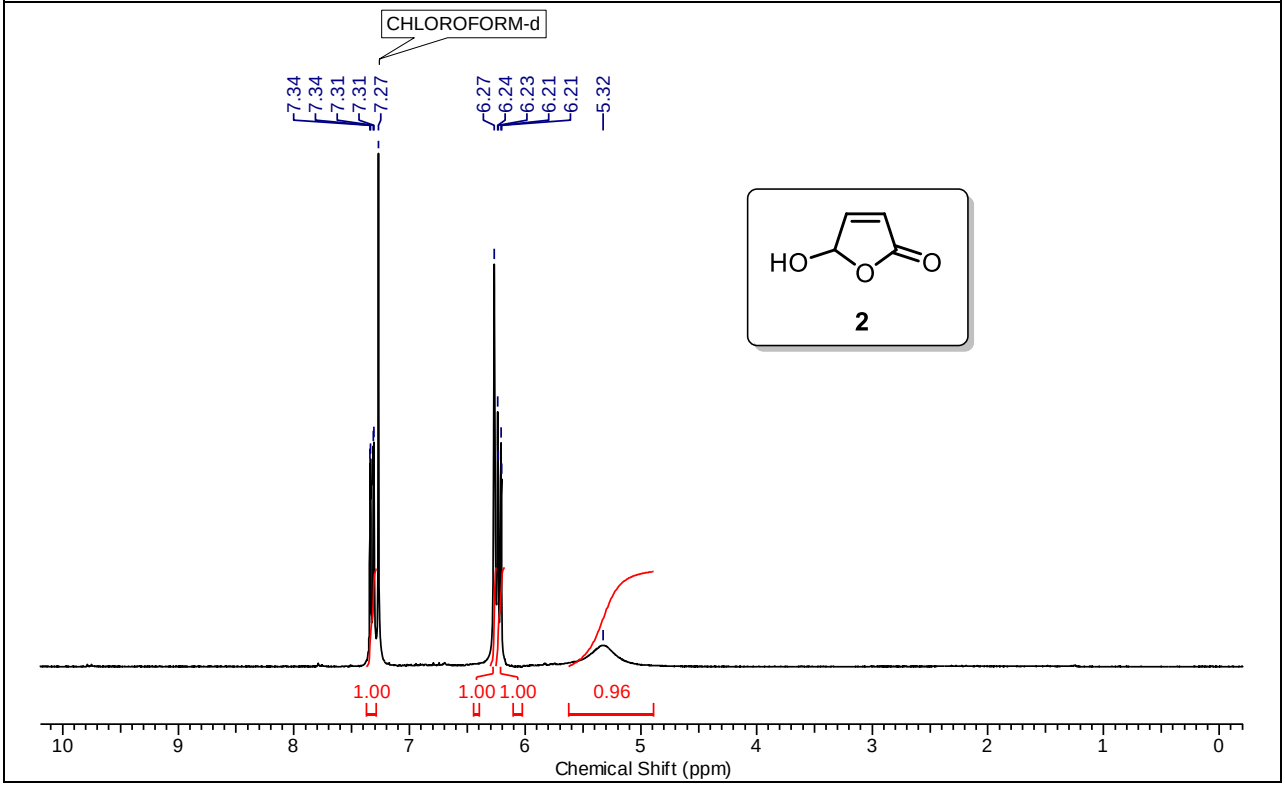
M. P.: 53–55 °C (lit.[5b] Mp = 52 °C);

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.33 (dd, *J* = 1.1, 5.6 Hz, 1H), 6.27 (s, 1H), 6.22 (dd, *J* = 1.1, 5.6 Hz, 1H), 5.33 (br s, 1H);

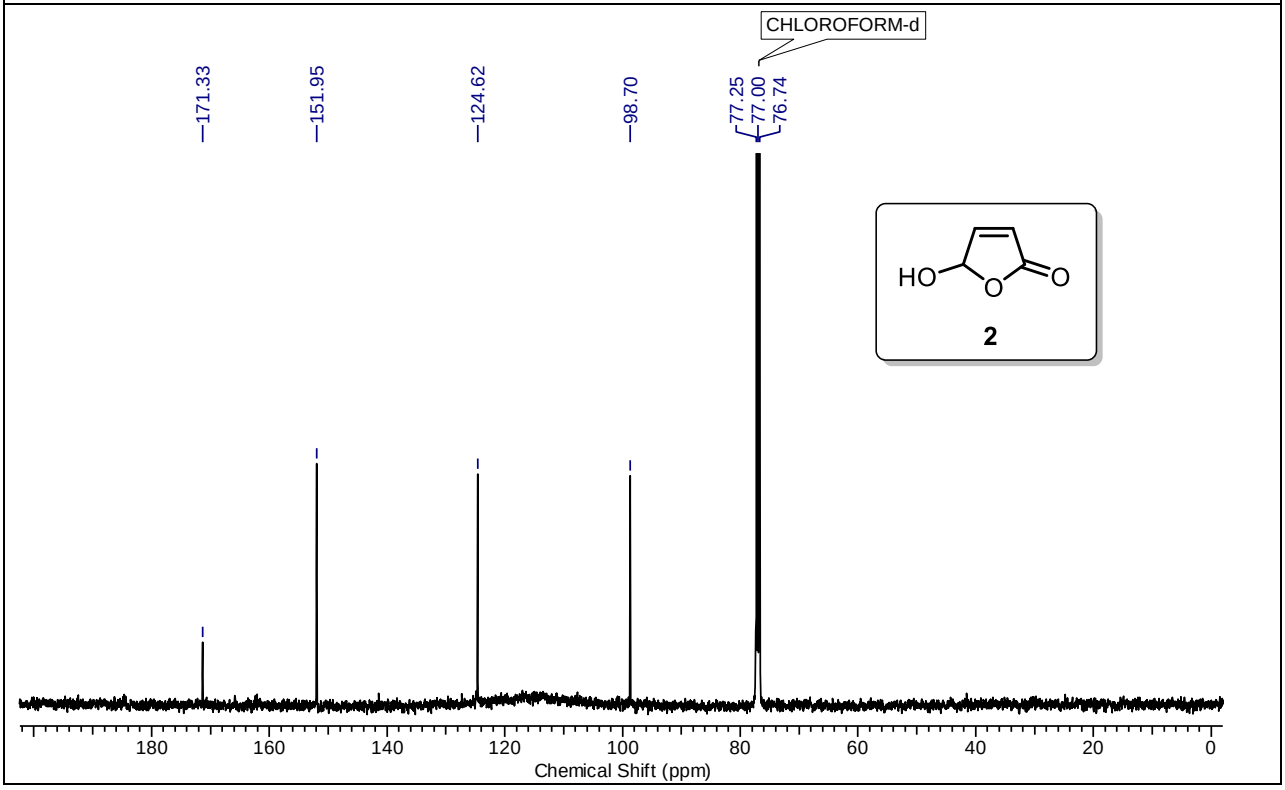
^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.3, 152.0, 124.6, 98.7.

3.1.7. Spectral Data

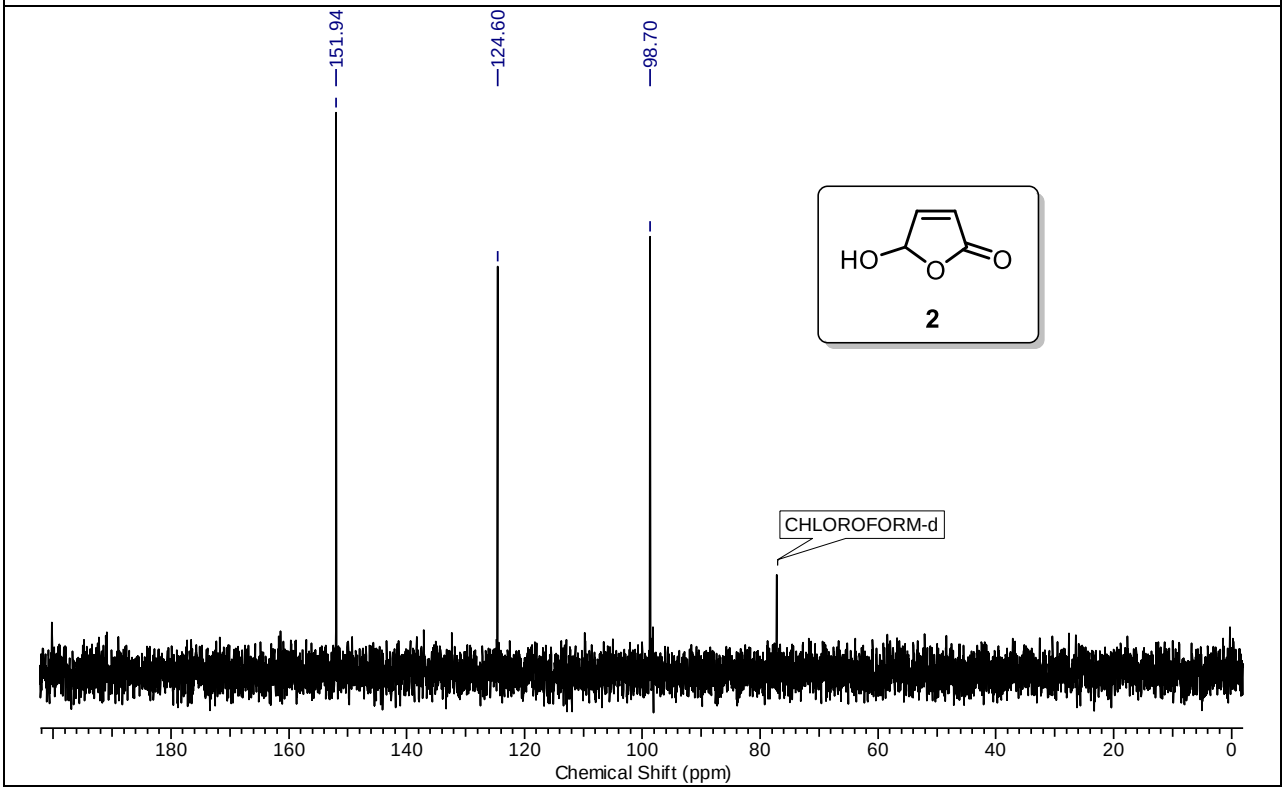
^{1}H-NMR spectrum of compound 2 ($CDCl_3$, 200 MHz)



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



DEPT NMR spectrum of compound 2 ($CDCl_3$, 125 MHz)



3.1.8. References

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(8) This research group focuses mainly on total synthesis of biologically active compounds including natural products. Current total synthesis targets include 7-epi-deoxypancratastatin, vitamin H D-(+)-Biotin, Quinagolide, antihistaminic drug Olopatadine, synthetic route towards Tamiflu, antidepressant drug Venlafaxine etc.

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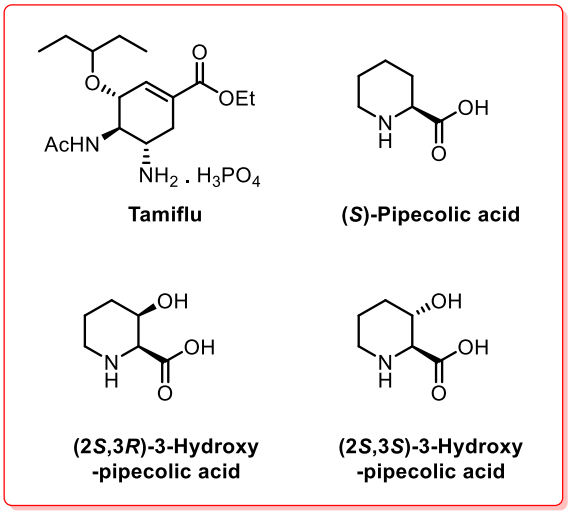
Chapter 3: On-Water Oxidation of Furan and its Application in the Collective Synthesis of Oseltamivir Phosphate (Tamiflu), (*S*)-Pipecolic acid and its 3-Hydroxy Derivatives

CHAPTER 3

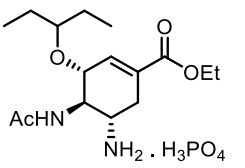
Section 2

"Introduction and Literature Review of Oseltamivir Phosphate (Tamiflu), (*S*)-Pipecolic acid and its 3-Hydroxy Derivatives"



3.2.1. Introduction and Literature Review of Oseltamivir Phosphate (Tamiflu)

3.2.1.1. Introduction



Oseltamivir phosphate (Tamiflu®)

Oseltamivir phosphate has been discovered in 1995 by Gilead Science (US) and marketed along with F. Hoffmann-La Roche Ltd.[1] Oseltamivir phosphate was launched in 1999 as an antiviral drug under the trade name Tamiflu®. Oseltamivir phosphate which is an orally active prodrug is used for the treatment of H5N1 influenza. Kim *et al.* from Gilead Science reported discovery chemistry synthesis of oseltamivir phosphate utilizing (–)-quinic acid as a starting material. The commercial route of oseltamivir phosphate (Tamiflu) was developed by Gilead Science (US) along with F. Hoffmann-La Roche Ltd. starting from (–)-shikimic acid.

Neuraminidase inhibitor

The occurrences of an influenza pandemic is a worldwide concern due to its mortality and morbidity caused. Four influenza pandemics or epidemics *viz.* Spanish flu (1918), Asian flu (1957), Hong Kong flu (1968) and Swine flu (2009) have occurred in the last century. The mutation of influenza virus proteins which was observed in the avian H5N1 influenza virus originated in Hong Kong in the year 1997, in which the virus is allowed to evade the human immune system is a characteristic of influenza pandemics. Avian influenza has a more than 50% lethality rate. Every year approx. 250,000 to 500,000 deaths occurred worldwide due to the outbreak of the influenza spreads.

Hemagglutinin and neuraminidase are the two glycoproteins found on the surface envelope of the influenza virus (**Figure 1**). Influenza virus attaches to the terminal sialic acid residue present on the host cell surface glycoprotein receptor through hemagglutinin. On the other hand, the neuraminidase which is anchored on the viral membrane cleaves glycoside bond of sialic acid to that of hemagglutinin hydrolytically in order to release the progeny viruses from the host

(infected) cell surface. This process releases budding virion from the infected (host) cell which is crucial for the spreading of the infection.

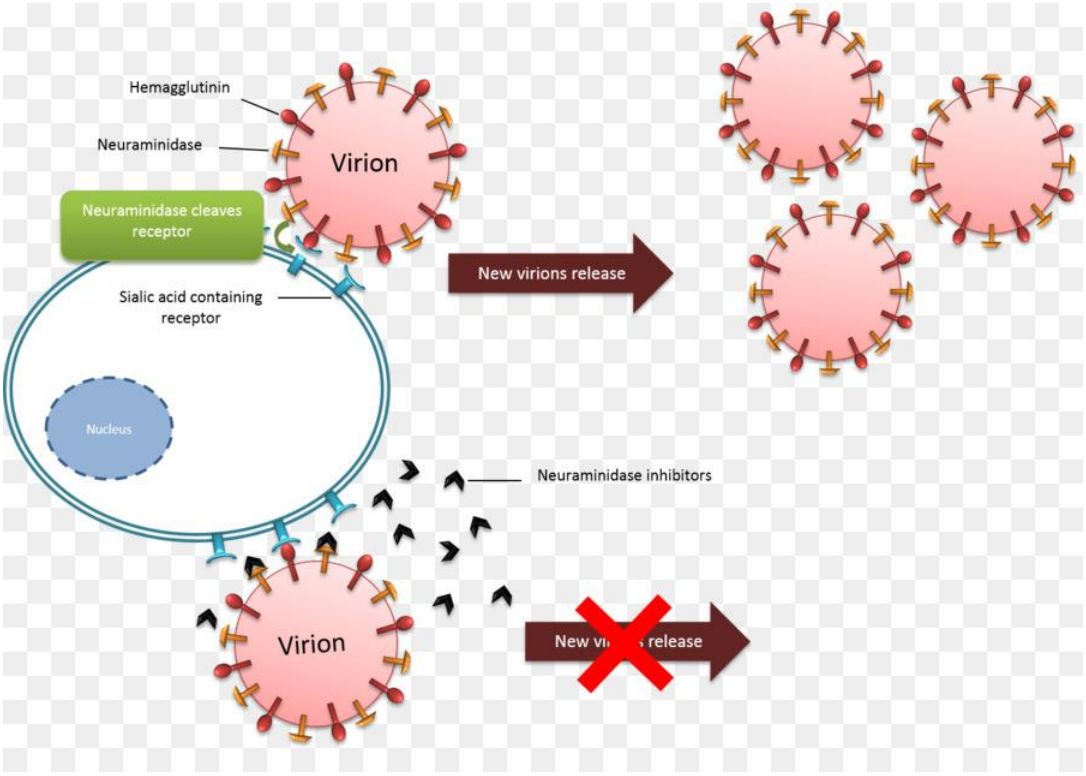
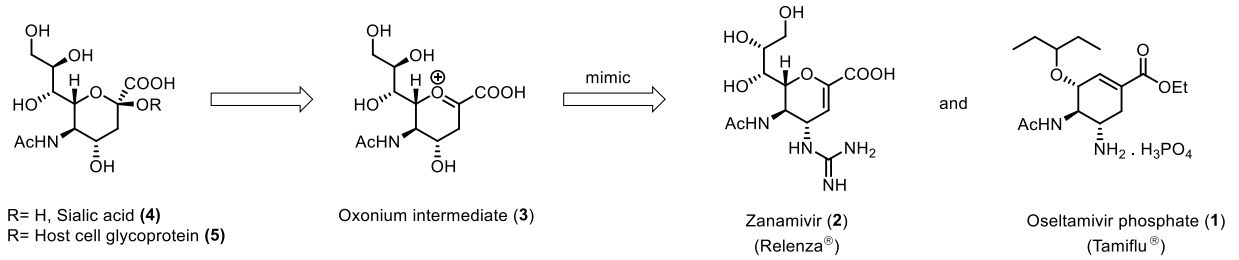


Figure 1: Replication pathway of influenza virus and the mode of action of neuraminidase inhibitors (figure source: internet).

The sialic acid (**4**) of the host cell glycoprotein (**5**) shows stable chair conformation of the pyran ring in water and is converted into the boat conformation when attached to the active site of neuraminidase of the influenza virus (**Scheme 1**).[2] The carboxylic acid of the sialic acid residue (**4**) forms acid-base interactions with arginine residue of neuraminidase glycoprotein of the influenza virus, thus stabilizing the boat conformation. The boat conformation of sialic acid residue is stereochemically essential for the glycoside bond cleavage between neuraminidase glycoprotein of the influenza virus and sialic acid residue of the host cell glycoprotein resulting in the spreading of the infection. The oxonium intermediate (**3**) is released after the cleavage of the glycoside bond. The neuraminidase inhibitors target the essential and specific fundamental molecular processes of the virus in which fundamental proteins (neuraminidase) of the virus or mutant viruses are conserved.



Scheme 1: Discovery of the Influenza Neuraminidase Inhibitors

Two neuraminidase inhibitors (anti-influenza drugs) zanamivir (**2**, GSK's Relenza®, marketed in July 1999)[3] and oseltamivir phosphate (**1**, Gilead's Tamiflu®, marketed in October 1999 by Roche)[1] strongly bind to the active site of the neuraminidase glycoprotein of the influenza virus as a stable analogues of **4** and thus inhibit its activity (**Scheme 1**). These anti-influenza drugs were designed as a mimic of oxonium intermediate **3**, which on enzymatic hydrolysis gives sialic acid (**4**).

Tamiflu (**1**) is a white crystalline solid prodrug that is hydrolyzed to its carboxylate active form in the gastrointestinal tract. It is the first orally active neuraminidase inhibitor that is used to treat the influenza virus.

3.2.1.2. Literature review

Several elegant synthetic approaches for the total synthesis of oseltamivir phosphate (Tamiflu) have been reported in the literature.[4] These can be broadly divided into six different retrosynthetic strategies as shown in **Figure 2**.

a) (–)-Shikimic acid or other six-membered rings used as a starting material.

b) Diels–Alder reaction using acrylic acid as a dienophile.

c) Core six-membered ring construction through intramolecular ring-closing metathesis.

d) Core six-membered ring construction *via* a Horner-Wadsworth-Emmons (HWE) reaction or aldol condensation.

e) Synthesis from nitroalkenes by Curtius rearrangement.

f) Synthesis from D-glucal by Claisen rearrangement.

As part of this group's interest in the total synthesis of Tamiflu employing ring-closing metathesis as a key step, the related metathesis approaches for the total synthesis of tamiflu[5–11] documented in the literature have been discussed in this section.

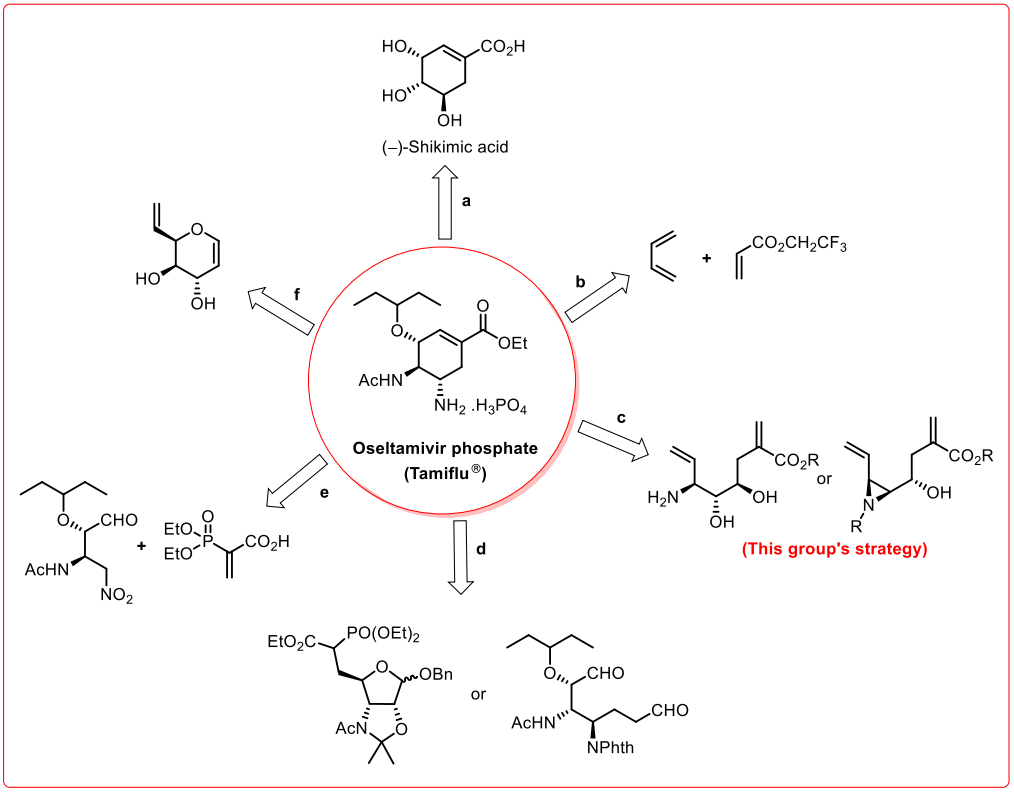
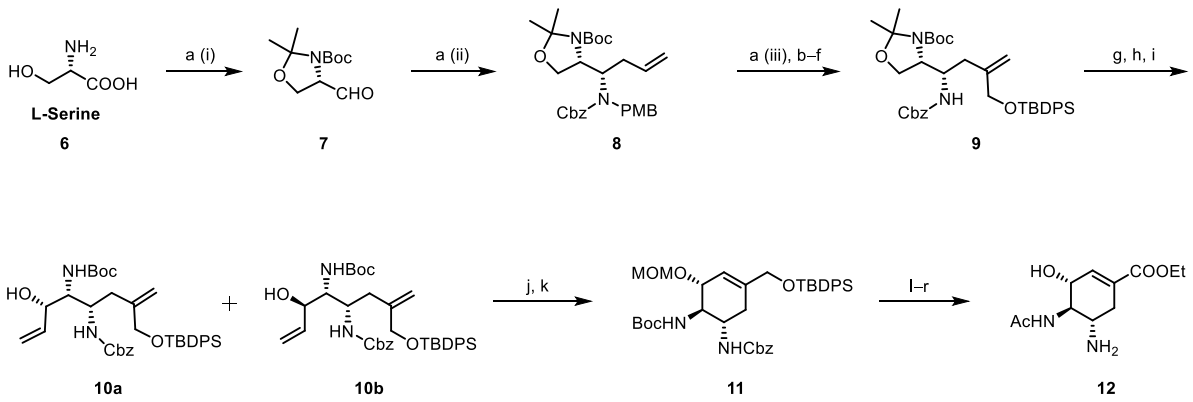


Figure 2: Different retrosynthetic strategies for the synthesis of oseltamivir phosphate (Tamiflu)

Yao's approach (*J. Org. Chem.* **2006**, *71*, 5365)[5a]

In 2006, Yao and coworkers reported the synthesis of Tamiflu intermediate by employing ring-closing metathesis (RCM) as a key step (**Scheme 2**). Synthesis endeavor started with the synthesis of olefin **8** from Garner aldehyde **7** following the procedure previously reported, which in turn was obtained from the L-serine (**6**). Olefin **8** was converted to compound **9** *via* dihydroxylation, protection-deprotection, and oxidation followed by Wittig olefination sequence. The compound **9** was converted to a diastereomeric mixture of vinyl alcohols **10a** and **10b** in three steps using *N-O* acetal deprotection and Swern oxidation of primary hydroxy group to aldehyde followed by addition reaction of vinyl magnesium bromide. The required diene **10b** was subjected to RCM using Grubbs' Ist generation catalyst after the protection of secondary alcohol as MOM ether to furnish functionalized cyclohexene **11**. The cyclohexene **11** was then converted to Tamiflu intermediate **12** by following the standard procedure of protection-deprotection and oxidation. Functionalized cycloalkene skeleton **12** of Tamiflu was achieved in 13 steps and 19% overall yield from known intermediate **8**.

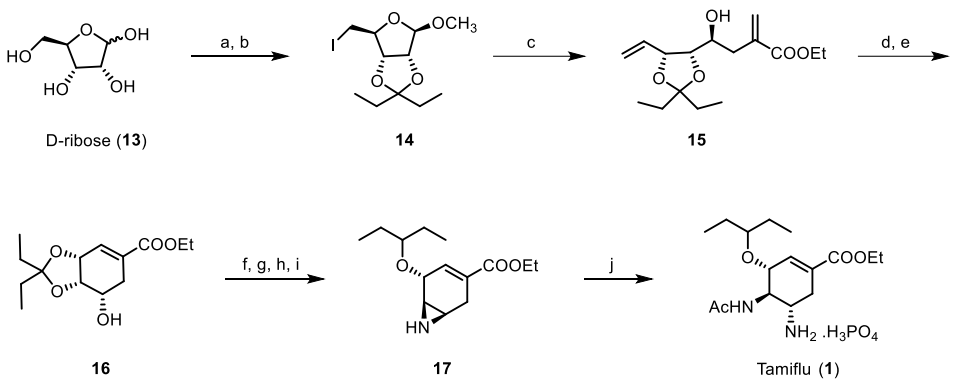


Scheme 2: Reagents and conditions: *(a) (i) ref 5b; (ii) ref 5c; (iii) OsO_4, NMO, acetone-water (5:1), 89%; (b) H_2, Pd/C, MeOH, 35 °C; (c) CbzCl, $NaHCO_3$, H_2O-EtOAc (1:1), 86% (2 steps); (d) TBDPSCl, imidazole, CH_2Cl_2, rt, 96%; (e) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, –78 °C; (f) PPh_3CH_3Br, n-BuLi, THF, 86% (2 steps); (g) $BiBr_3$, CH_3CN, rt, 89%; (h) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, –78 °C; (i) VinylMgBr, $ZnBr_2$, THF, –78 to –30 °C,* ***10a*** *(19%) +* ***10b*** *(56%); (j) MOMCl, DIPEA, Et_3N, 98%. (k) Grubbs-Hoveyda catalyst (10 mol %), CH_2Cl_2, rt, 98%; (l) TBAF, THF, rt, 96%. (m) PCC, 4 Å MS, CH_2Cl_2, rt; (n) $NaClO_2$, K_2HPO_4, 2,3-dimethylbuta-1,3-diene, t-BuOH-THF-H_2O (1:1:1), 10 °C to rt, 88% (2 steps); (o) EtOH, HOBT, EDCI, DIPEA, CH_2Cl_2, rt, 85%; (p) 5% HCl-EtOH, 0 °C to rt; (q) AcCl, Na_2CO_3, EtOH, 0 °C to rt, 83% (2 steps); (r) $Pd(OAc)_2$, Et_3SiH, Et_3N, CH_2Cl_2, 0 °C to rt, 92%.*

Chai's approach (*Org. Lett.* **2010**, *12*, 60)[6a]

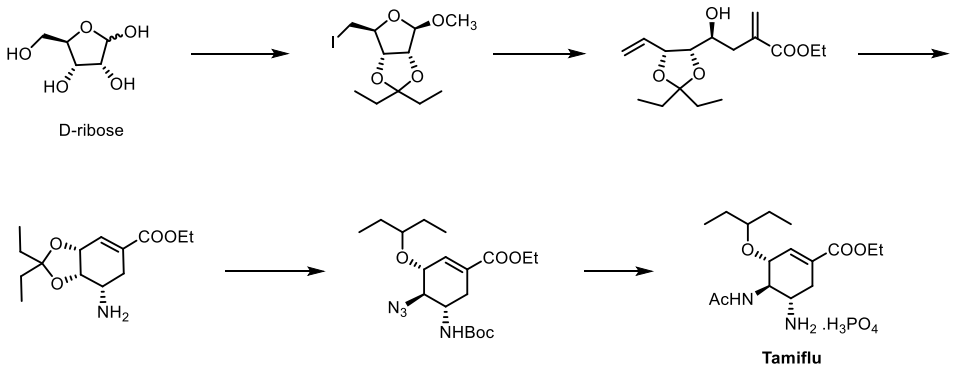
Chai and coworkers in 2010 reported the formal synthesis of Tamiflu employing RCM as a key step and D-ribose (**13**) as a inexpensive and renewable starting material (**Scheme 3**). The D-ribose (**13**) was subjected for protection of diol as pentanide followed by conversion of alcohol to iodide under Appel reaction condition to afford iodo compound **14**. Bernet–Vasella reaction of iodo compound **14** furnished aldehyde, which without isolation was subjected to Reformatsky type allylation using ethyl 2-(bromomethyl)acrylate to afford diene **15**. The diene **15** was subjected for RCM using the Grubbs-Hoveyda catalyst to afford core six-membered cyclohexene ring **16**. The functionalized cyclohexene ring **16** was successively converted to the known intermediate **17** of Tamiflu by employing selective opening of the 3-pentylidene ketal to install 3-pentyl ether moiety, selective protection of alcohols and azidation followed by Staudinger

reduction of azide and *in situ* aziridation as key steps. Synthesis of advanced intermediate **17** of Tamiflu (**1**) was achieved in 9 steps in 28% overall yield from D-ribose.



Scheme 3: Reagents and conditions: *(a) 3-Pentanone, HCl (1 M in MeOH), $HC(OMe)_3$, reflux, 6 h, 89%; (b) I_2, Ph_3P, PhMe-CH_3CN (1:1), reflux, 5 min, 90%; (c) (i) Zn, THF-H_2O (2:1), ethyl 2-(bromomethyl)acrylate, reflux, 3 h; (ii) reflux, 4 h, 78%, dr = 5.2:1; (d) Grubbs-Hoveyda catalyst (2 mol%), DCE, reflux, 2 h, 99%; (e) (i) $AlCl_3$,$CHCl_3$, sonication, 0 ^oC; (ii) Et_3SiH, –50 ^oC, 4 h; then 0 ^oC, 16 h, 67%; (f) MsCl, Et_3N, CH_2Cl_2, –20 ^oC, 40 min; then rt, 1 h, 92%; (g) Tf_2O, pyridine, CH_2Cl_2, –10 ^oC, 30 min; then 0 ^oC, 20 min; (h) NaN_3, acetone-H_2O (9:1), rt, 4 h, 86% (2 steps); (i) Ph_3P, Et_3N, THF, rt, 17 h, 84%; (j) ref 6b and 6c.*

Kongkathip's 1st approach (*Tetrahedron Lett.* **2010**, *51*, 3208)[7]

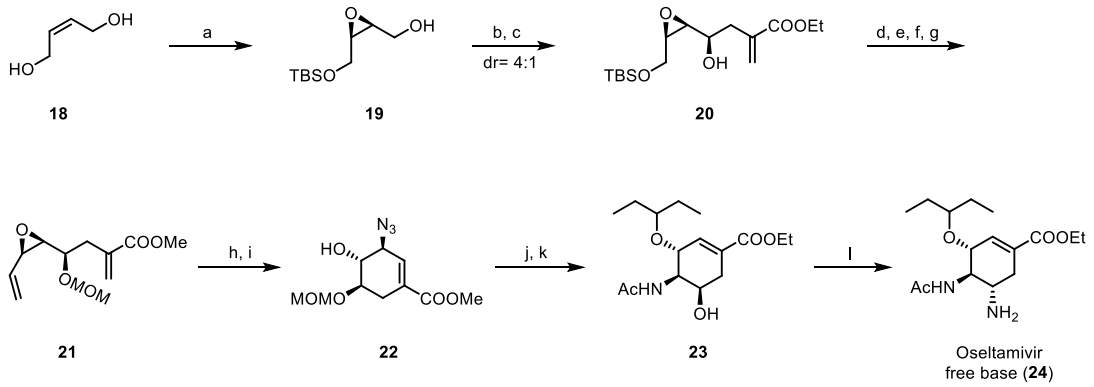


Scheme 4: Kongkathip's 1st approach for Tamiflu

Shortly after the Chai's approach, Kongkathip and coworkers independently reported a similar synthetic strategy for the total synthesis of Tamiflu from D-ribose (**Scheme 4**).

Sudalai's approach (*Org. Biomol. Chem.* **2012**, *10*, 3988)[8a]

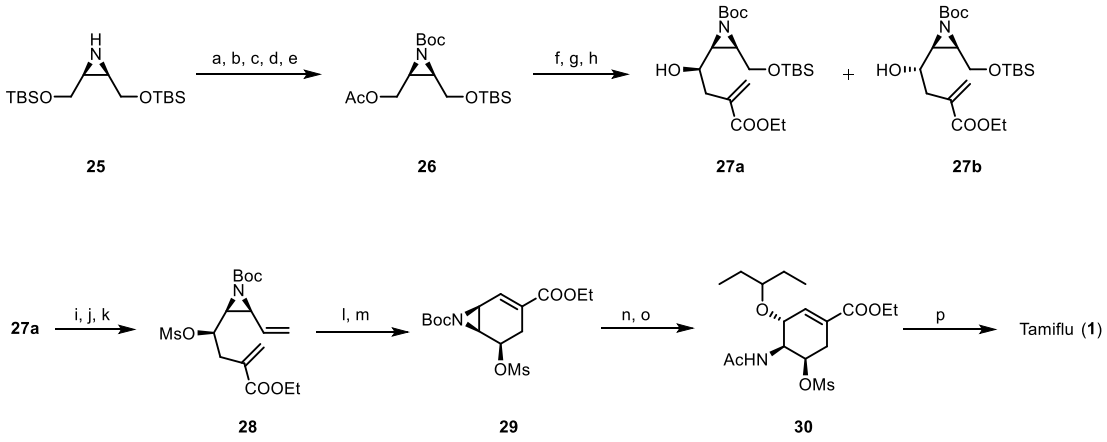
In 2012, Sudalai and coworkers reported the enantioselective synthesis of oseltamivir free base **24** from the *cis*-2-butene-1,4-diol (**18**) as starting material (**Scheme 5**). The *cis*-2-butene-1,4-diol (**18**) was subjected to the protection of alcohol as mono TBS ether followed by the Sharpless asymmetric epoxidation using (–)-DET to afford epoxide **19** in 96% ee. Epoxide **19** was converted into alcohol **20** using the oxidation of alcohol to aldehyde followed by a Barbier allylation (dr= 4:1). After the protection of newly formed secondary alcohol and deprotection of primary alcohol of **20**, it was subjected to the oxidation using IBX followed by the addition of Bestman-Ohira reagent and selective alkyne reduction to obtain diene **21**. The RCM of diene **21** using Grubbs' 2nd generation catalyst, followed by the opening of epoxide with azide were used as key steps for the construction of cyclohexene core **22**. Formation of aziridine followed by its protection and ring-opening of aziridine with 3-pentanol using Lewis acid were employed as key steps for the construction of functionalized cyclohexene skeleton **23**. Finally, cyclohexene skeleton **23** was converted to the oseltamivir free base **24** by following the procedure previously reported.



Scheme 5: Reagents and conditions: *(a) (i) TBSCl, imidazole, CH_2Cl_2, 0 °C, 73%; (ii) (+)-DET, $Ti(^iPrO)_4$, TBHP, 4 Å MS, 96% ee; (b) TEMPO, $PhI(OAc)_2$, 75%; (c) Ethyl 2-(bromomethyl)acrylate, Zn, aq. sat. NH_4Cl, THF, 10 h, (dr = 4:1), 64%; (d) MOMCl, DIPEA, 90%; (e) TBAF, THF, 0 °C, 2 h, 88%; (f) (i) IBX, DMSO, 25 °C, 1 h; (ii) K_2CO_3, MeOH, Bestman-Ohira reagent, 82%; (g) H_2, pyridine/1-octene/EtOAc, Lindlar's catalyst, 95%; (h) Grubbs' 2nd gen. catalyst, CH_2Cl_2, 90%; (i) NaN_3, NH_4Cl, DMF-EtOH-H_2O, 83%; (j) (i) PPh_3, PhMe, reflux, 3 h; (ii) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 81% (2 steps); (k) (i) 3-Pentanol, $BF_3.OEt_2$; (ii) 2 N HCl, EtOH, 64%; (l) Ref 8b.*

Kang's approach (*J. Org. Chem.* **2012**, *77*, 8792)[9]

Kang *et al.* in 2012 reported the total synthesis of Tamiflu (**1**) starting from the meso *cis*-aziridine **25** (**Scheme 6**). The *cis*-aziridine **25** was prepared from the *cis*-2-butene-1,4-diol following the procedure previously reported. The meso *cis*-aziridine **25** was transformed into enantiopure aziridine **26** by enzymatic desymmetrization using amino lipase followed by TBS protection. The acetate side of the aziridine **26** was converted into a diastereomeric mixture of alcohols **27a** and **27b** (dr= 3:1) using the oxidation of alcohol to aldehyde followed by a Barbier allylation using ethyl 2-(bromomethyl)acrylate. After the protection of newly formed secondary alcohol and deprotection of primary alcohol of major isomer **27a**, it was subjected to the oxidation using DMP followed by the one-carbon Wittig homologation to afford diene **28**. The RCM of diene **28** in presence of Grubbs' 2nd generation catalyst was employed as a key step for the construction of aziridine containing cyclohexene core **29**. Opening of aziridine **29** with 3-pentanol using Lewis acid followed by protection-deprotection of amine afforded compound **30**. Azidation on compound **30** followed by the reduction of azide and salt formation with phosphoric acid were used as key steps for the completion of the total synthesis of Tamiflu (**1**). It should be noted that Kang's approach for the total synthesis of Tamiflu closely follows a similar synthetic strategy as previously reported by Sudalai and coworkers.

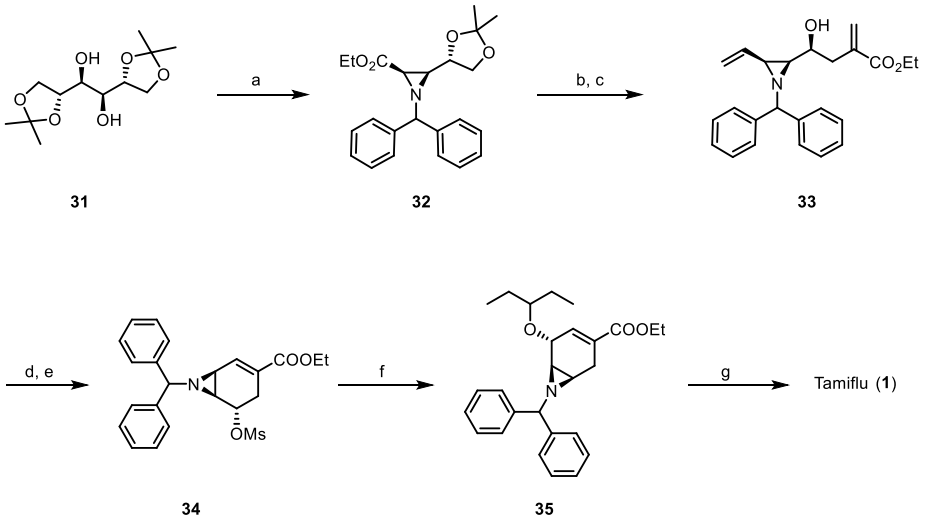


Scheme 6: Reagents and conditions: *(a) Boc_2O, Et_3N, CH_2Cl_2, 88%. (b) TBAF, THF, 76%; (c) Amino lipase PS, vinyl acetate, n-hexane-THF, 68%; (d) BzCl, Et_3N, DMAP, 75%; (e) TBSCl, imidazole, CH_2Cl_2, 94%; (f) K_2CO_3, MeOH, 87%; (g) DMP, CH_2Cl_2, 87%; (h) Ethyl 2-(bromomethyl)acrylate, Zn, THF: aq. NH_4Cl (1:1),* ***27a*** *(71%) +* ***27b*** *(25%); (i) MsCl, CH_2Cl_2,*

DMAP, 84%; (j) TBAF, THF, 72%; (k) DMP, CH_2Cl_2, 91%; (l) KHMDS, PPh_3MeBr, THF, 63%; (m) Grubbs' 2nd gen. cat., CH_2Cl_2, 68%; (n) 3-Pentanol, $BF_3.Et_2O$, 84%; (o) (i) TFA ; (ii) Ac_2O, Et_3N, CH_2Cl_2, 93% (2 steps); (p) (i) NaN_3; (ii) H_2, Lindlar catalyst; (iii) H_3PO_4, 80% (3 steps).

Chavan's approach (*RSC Adv.* **2014**, *4*, 11417)[10a]

This lab in 2014 reported the concise synthesis of Tamiflu starting from D-mannitol (**Scheme 7**). The synthesis started with the conversion of D-mannitol acetonide **31** to *cis* aziridine synthon **32** following the procedure previously reported. Ester side of *cis* aziridine **32** was transformed into a vinyl group using two-step protocol *i.e.* DIBAL-H reduction of ester followed by one carbon Wittig homologation of the corresponding aldehyde whereas acetonide side of *cis* aziridine **32** was functionalized to diastereomeric mixture of allyl alcohol using Barbier reaction with ethyl 2-(bromomethyl)acrylate as a key step to afford diene **33** after separation of diastereomers. The diene **33** was subjected to ring-closing metathesis in the presence of Grubbs' 2nd generation catalyst to afford core cyclohexane skeleton **34**. One-pot opening of aziridine **34** with 3-pentanol using Lewis acid and formation of rearranged aziridine **35** were used as key steps to complete the formal synthesis of Tamiflu (**1**).

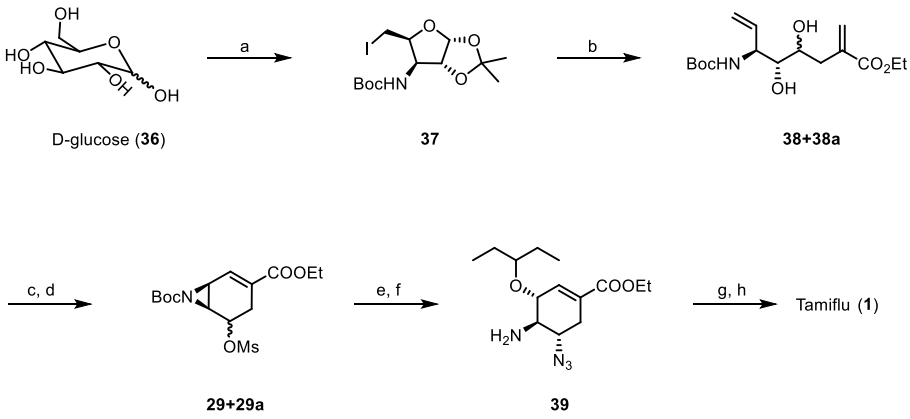


Scheme 7: Reagents and conditions: *(a) Ref. 10b; (b) (i) DIBAL-H, CH_2Cl_2, –78 °C; (ii) $Ph_3P^+CH_3Br^-$, KO^tBu, toluene, rt, 65% (2 steps); (c) (i) TMSOTf, CH_2Cl_2, 0 °C, 2 h, 85%; (ii) $NaIO_4$, CH_2Cl_2, rt; (iii) Ethyl 2-(bromomethyl)acrylate, Zn, THF: aq. NH_4Cl, 10 min, 94%; (d)*

Grubbs' 2nd gen. cat., Ti(O^{i}Pr)$_4$, CH_2Cl_2, reflux, 12 h, 74%; (e) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 2 h, 79%; (f) 3-Pentanol, $BF_3.Et_2O$, CH_2Cl_2, 3 h then Et_3N, 1 h, rt, 80%; (g) Ref. 10c.

Kongkathip's 2nd approach (*Tetrahedron* **2015**, *71*, 2393)[11a]

Kongkathip and coworkers in 2015 reported the modified approach for the total synthesis of Tamiflu starting from D-glucose (**Scheme 8**). Five-membered intermediate **37** was synthesized from D-glucose (**36**) following the procedure previously reported followed by conversion of alcohol to iodide under Appel condition. Zn and In mediated domino reaction of compound **37** with ethyl 2-(bromomethyl)acrylate afforded a diastereomeric mixture of dienes **38** and **38a**. After separation of both the diastereomers, they were subjected to protection, aziridination using NaH as a base followed by ring-closing metathesis (RCM) in presence of Grubbs' 2nd generation catalyst to afford cyclohexene skeletons **29** and **29a** respectively. Both the diastereomers **29** and **29a** were separately converted into the Tamiflu (**1**) through intermediate **39** following the similar procedure previously reported in the literature.



Scheme 8: Reagents and conditions: *(a) (i) Ref. 11b; (ii) Boc_2O, MeOH, rt, 83%; (iii) I_2, PPh_3, imidazole, toluene-CH_3CN, reflux, 64%; (b) Zn, AcOH, THF-H_2O, sonication, 40 °C, 1 h then In, ethyl 2-(bromomethyl)acrylate, 40 °C, (**38a**, 39%; **38**= 43%); (c) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C; (ii) NaH, CH_2Cl_2-DMSO, rt, 8 h; (d) Grubbs' 2nd gen. cat., CH_2Cl_2, 0 °C, (**29a**, 60%; **29**= 49%); (e) **29a:** (i) $BF_3.OEt_2$, 3-pentanol, –10 °C, 2 h, 91%; (ii) NaH, CH_2Cl_2-DMSO, rt, 8 h, 87%; (iii) NaN_3, NH_4Cl, DMF, 90 °C, 89%; (f) **29:** (i) $BF_3.OEt_2$, 3-pentanol, –10 °C, 2 h, 95%; (ii) NaN_3, DMF-H_2O, 90 °C, 68%; (g) (i) TFA, CH_2Cl_2, 4 h, then Ac_2O, 1 h, 78%; (h) (i) H_2, Lindlar catalyst, EtOH, 10 h, 88%; (ii) H_3PO_4, EtOH, 60 °C, 3 h, 78%.*

3.2.2. Introduction and Literature Review of (*S*)-Pipecolic acid and its 3-Hydroxy Derivatives

3.2.2.1. Introduction

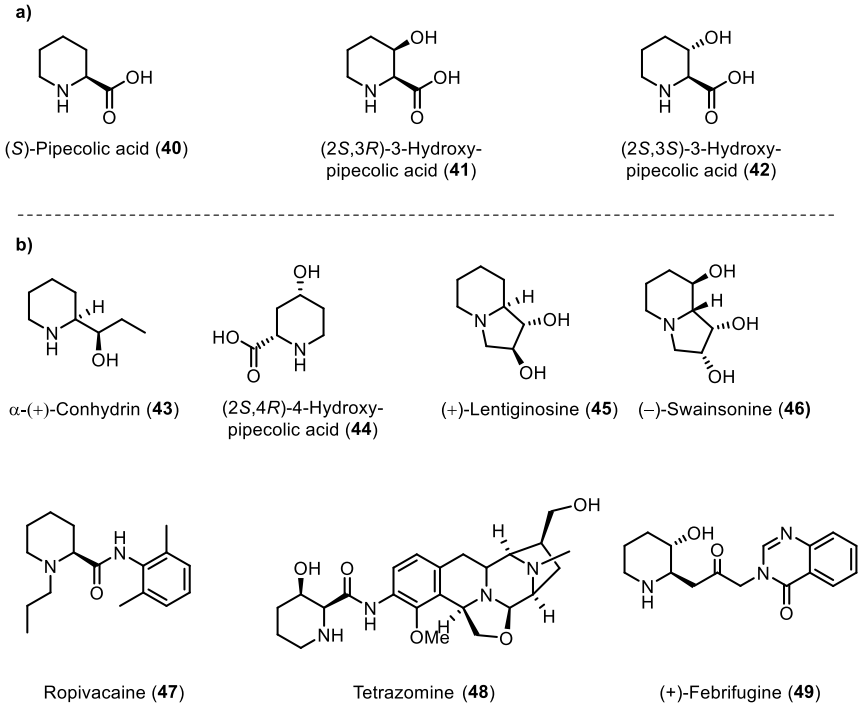


Figure 3: (a) Structure of (*S*)-pipecolic acid and its 3-hydroxy derivatives. (b) Bioactive natural products and pharmacologically active compounds consisting of pipecolic acid and its 3-hydroxy derivatives as a key element.

(*S*)-Pipecolic acid (**40**) is a nonproteinogenic α-amino acid.[12] It is a metabolite of lysine. Pipecolic acid is an integral part of several secondary metabolites in plants and fungi, and also found in the human physiological fluid. (*S*)-Pipecolic acid (**40**) and its 3-hydroxy derivatives *viz*. (2*S*,3*R*)-3-hydroxypipecolic acid (**41**) and (2*S*,3*S*)-3-hydroxypipecolic acid (**42**) have wide spectrum of biological activities. In addition, (*S*)-Pipecolic acid and its 3-hydroxy derivatives are constituent of several bioactive natural products and pharmacologically active compounds such as (+)-Conhydrin (**43**, poisonous alkaloid), (2*S*,4*R*)-4-hydroxypipecolic acid (**44**, constituent of synthetic HIV protease inhibitor palinavir), (+)-lentiginosine (**45**), and (–)-swainsonine (**46**, α-D-mannosidase inhibitor) and ropivacaine (**47**, local anaesthetic agent), tetrazomine (**48**, antitumour antibiotic) and (+)-febrifugine (**49**, potent antimalarial agent).[13]

3.2.2.2. Literature

Several elegant synthetic approaches for the asymmetric total synthesis of pipecolic acid and its 3-hydroxy derivatives have been reported in the literature.[14] These can be broadly divided into the following three types based on the synthetic strategy used.

1. Chiral pool approaches.
2. Chiral induction approaches.

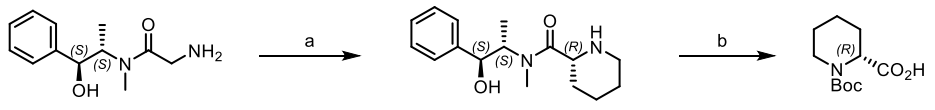
(a) Chiral auxiliary based approaches; (b) Catalytic asymmetric methods

3. Chemoenzymatic approaches (enzymatic kinetic resolution).

Out of the above approaches, chiral pool and chiral induction using catalytic asymmetric methods are extensively studied. As part of this group's interest in the development of a synthetic strategy for pipecolic acid and its 3-hydroxy derivatives utilizing chiral auxiliary and aziridine chemistry, the related approaches documented in the literature have been discussed in this section.

Myer's approach (*J. Am. Chem. Soc.* **1995**, *117*, 8488)[15]

Myer *et al*. reported the protective group free, practical synthesis of (*R*)-pipecolic acid employing diastereoselective alkylation of pseudoephedrine glycinamide **50** (**Scheme 9**). The enolate derived from **(*S*,*S*)-(+)-50** was treated with l-chloro-4-iodobutane followed by heating of the crude reaction product to induce cyclization of the chloroalkylamine to form the (*R*)-pipecolic acid amide **51** in 72% yield (96% *de*). Hydrolysis of the pseudoephedrine auxiliary under mild conditions followed by acylation of the crude product with $(Boc)_2O$, and recrystallization afforded *N*-Boc-(*R*)-pipecolic acid **52** in 77% yield.

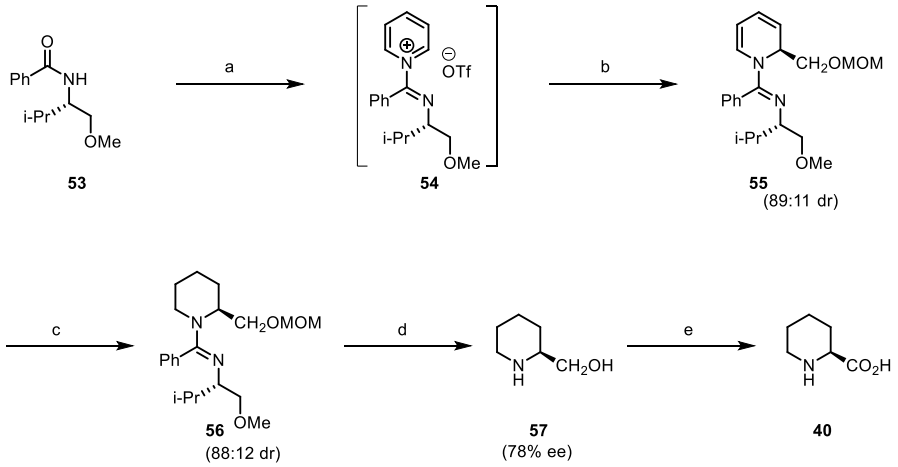


50 **51** **52**

Scheme 9: Reagents and conditions: *(a) i) n-BuLi, LiCl; ii) $Cl(CH_2)_4I$, 72%; (b) i) NaOH; ii) $(Boc)_2O$, 77%.*

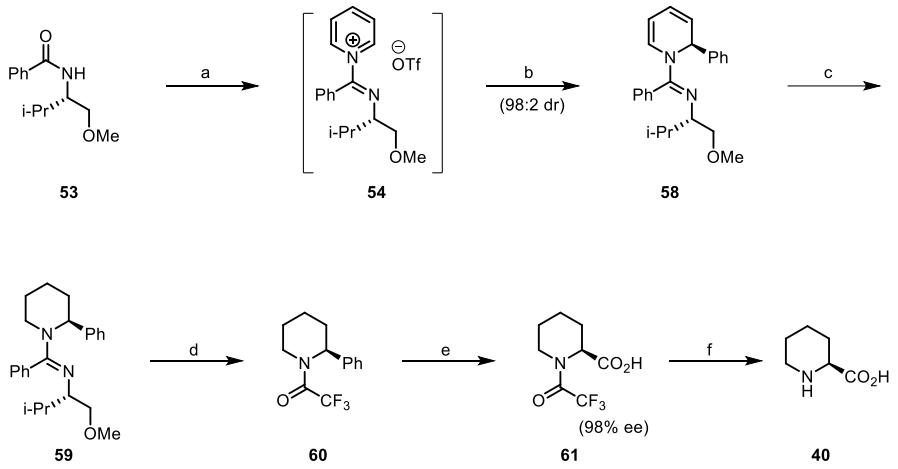
Charette's approach (*J. Org. Chem.* **2010**, *75*, 2077)[16a]

Charette *et al*. reported the stereoselective synthesis of (*S*)-pipecolic acid **(Scheme 10)** employing L-valinol (**53**) as a chiral auxiliary. The synthesis started with the preparation of dihydropyridine **55** by regio- and diastereoselective umpolung type addition of nucleophile $LiCH_2OMOM$ to the chiral pyridinium salt **54**. Hydrogenation of dihydropyridine **55** to piperidine **56** followed by cleavage of chiral auxiliary and MOM ether under acidic conditions afforded enantioenriched (*S*)-2-piperidine methanol **57**, thereby completing a formal synthesis of (*S*)-pipecolic acid (**40**) as shown in **Scheme 10**.



Scheme 10: Reagents and conditions: *(a) Tf_2O, pyridine, CH_2Cl_2, –40 °C to rt; (b) $MOMOCH_2CuCNLi.2HCl$, THF, –78 °C, 72%; (c) H_2 (1 atm), Pd/C, THF, rt, 63%; (d) (i) HCl, MeOH, reflux; (ii) 6M HCl, reflux, 63%; (e) ref. 16b*

In an alternative route, Charette and co-workers introduced phenyl substituent at the 2-position of the chiral pyridinium salt **54** derived from L-valinol (**53**) which could be easily oxidized to a carboxylic acid with the aid of Sharpless procedure (**Scheme 11**). Thus, synthesis started with the preparation of dihydropyridine **58** by regio- and diastereoselective addition of phenylmagnesium bromide to chiral pyridinium salt **54**. Hydrogenation of **58** led to the *N*-iminopiperidine **59**. The chiral auxiliary was next removed by alane reduction, followed by protection of the piperidine nitrogen as a trifluoroacetamide **60**. Oxidation of the phenyl substituent to the carboxylic acid **61** followed by the deprotection of *N*-trifluoroacetyl group afforded (*S*)-pipecolic acid **40** in 40% yield (6 steps) from **53**.

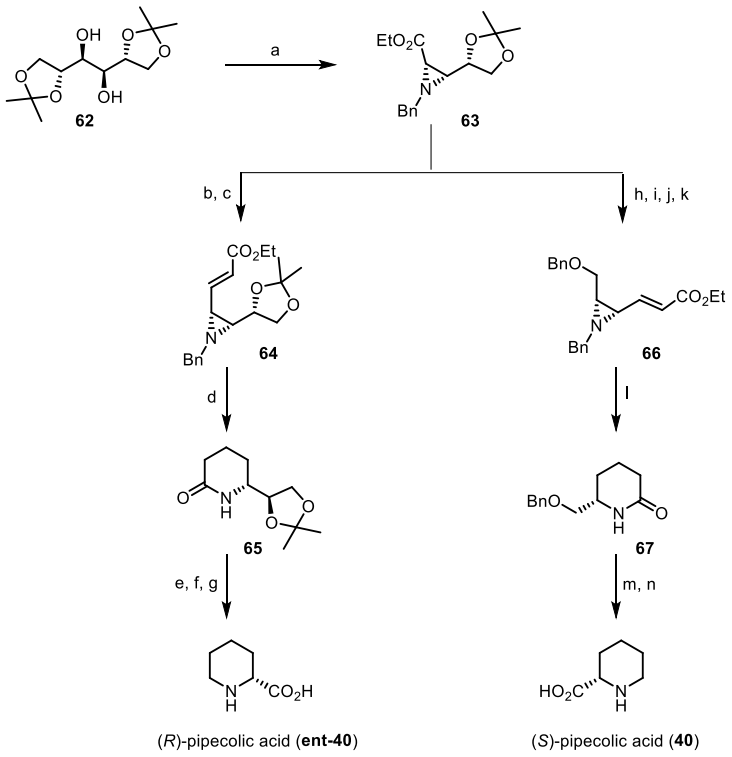


Scheme 11: Reagents and conditions: *(a) Tf_2O, pyridine, CH_2Cl_2, –40 °C to rt; (b) PhMgBr.LiBr, Et_2O, –20 °C, 89%; (c) H_2 (300 psi), Pd/C, MeOH, rt, 80%; (d) (i) AlH_3, Et_2O, 0 °C; (ii) TFAA, Et_2O, –20 °C, 79%; (e) $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O, rt; (f) K_2CO_3, MeOH, rt, 72%*

Chavan's approach (*Tetrahedron: Asymmetry* **2014**, *25*, 1246)[17]

Chavan *et al*. in the year 2014 reported the efficient total synthesis of both the antipodes of pipecolic acid from aziridine synthon (**Scheme 12**). The synthesis started with the *cis* aziridine-2-carboxylate **63** derived from D-mannitol diacetonide **62** using a known literature procedure. *cis* Aziridine-2-carboxylate **63** was converted into α,β-unsaturated ester **64** in two steps by DIBAL-H reduction of the ester to the corresponding aldehyde followed by 2-carbon Wittig homologation. For the synthesis of piperidine ring **65**, concomitant regioselective ring-opening, olefin reduction and cyclization of α,β-unsaturated ester **64** under hydrogenation condition were used in key steps. Reduction of lactam **65** using BH_3.DMS followed by protection of amine and oxidative cleavage of acetonide functionality afforded (*R*)-pipecolic acid (**ent-40**). The (*R*)-pipecolic acid (**ent-40**) was achieved in 5 purification steps in 31% overall yield from *cis* aziridine-2-carboxylate **63**.

Synthesis of (*S*)-pipecolic acid (**40**) was achieved by the functionalization of acetonide side of *cis* aziridine-2-carboxylate **63** to α,β-unsaturated ester **66** followed by its concomitant regioselective hydrogenation and reduction-oxidation sequence on lactam **67**. The (*S*)-pipecolic acid **40** was achieved in 7 purification steps in 28% overall yield from *cis* aziridine-2-carboxylate **63**.

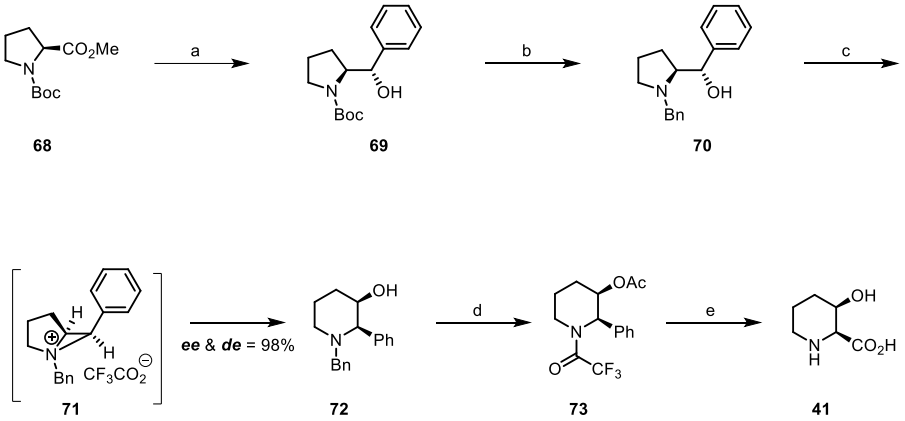


Scheme 12: Reagents and conditions: *(a) i) $NaIO_4$, CH_2Cl_2, rt, 2 h; (ii) ethyl 2-bromo-2-(triphenyl-λ^5-phosphanylidene)acetate, CH_2Cl_2, rt, 84% over two steps; (iii) $BnNH_2$, Et_3N, EtOH, 0 ºC to rt, 72 h, 77%; (b) DIBAL-H (1M in toluene), CH_2Cl_2, –78˚C, 1 h; (c) Ph_3PCHCO_2Et, cat. $PhCO_2H$, toluene, reflux, 5 h, 82% over two steps; (d) Pd/C (10%), HCO_2NH_4, MeOH, 60 ˚C, 3 h, 90%; (e) i) BH_3·DMS, THF, 0˚C to rt, 6 h then 6N HCl, reflux, 3h; ii) Cbz-Cl, $NaHCO_3$, THF:H_2O (1:1), 75% over two steps; (f) $RuCl_3·6H_2O$, $NaIO_4$, CH_3CN:CCl_4:H_2O (1:1:3), rt, 1 h, 60%; (g) H_2, Pd/C (10%), MeOH, 95%. (h) LAH, THF, 0° C, 1h, 90%; (i) BnBr, NaH, DMF, 95%; (j) PTSA, MeOH, 85%; (k) i) $NaIO_4$, acetone:water (2:1), rt, 0.25h; ii) Ph_3PCHCO_2Et, cat. $PhCO_2H$, toluene, Δ, 85% over two steps; (l) Pd/C (10%), H_2, 3h, 88 %; (m) i) LAH, THF, 0 °C to rt, 6h; ii) Pd/C (10%), H_2, $(Boc)_2O$, MeOH, 75% over two steps; (n) i) TFA, CH_2Cl_2; ii) $KMnO_4$, 3N H_2SO_4, 69% over two steps*.

Cossy's approach (*Synlett* **2009**, *13*, 2157)[18]

Cossy *et al*. reported the efficient synthesis of 3-hydroxypipecolic acid using enantioselective ring expansion of prolinols (**Scheme 13**). The two key steps (a) a one-pot diastereoselective

DIBAL-H reduction /Grignard addition sequence applied to proline ester **68** and (b) a ring expansion applied to the corresponding prolinol **69** were used. The synthesis started with the commercially available *N*-Boc-L-proline methyl ester **68**, which was converted into the corresponding amino alcohol **69** using DIBAL-H followed by the addition of phenylmagnesium bromide (dr= 99:1). Compound **69** was treated with TFA followed by *N*-benzylation to afford prolinol **70**. Prolinol **70** treated under standard conditions, underwent regioselective ring expansion *via* aziridinium intermediate **71** to furnish piperidin-3-ol **72**. The substituted piperidin-3-ol **72** was hydrogenated followed by trifluoroamidation using TFAA to afford piperidine **73**. Treatment of compound **73** with $RuCl_3 \cdot 3H_2O/NaIO_4$ followed by saponification furnished the desired 3-hydroxypipecolic acid **41**.

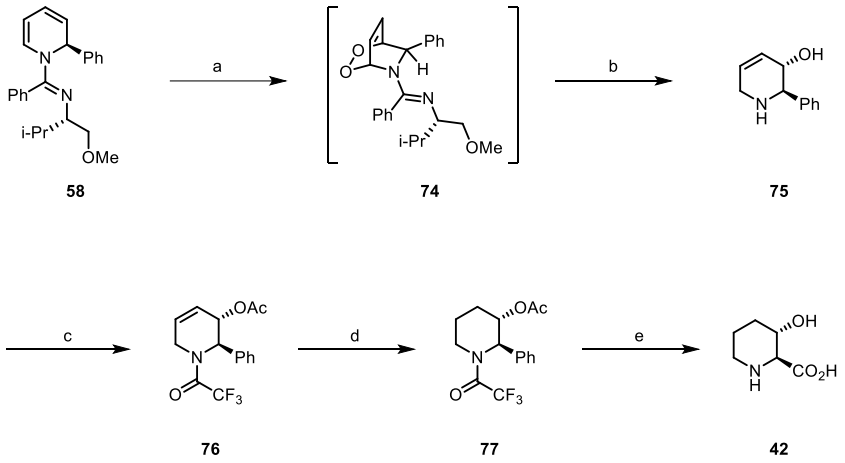


Scheme 13: Reagents and conditions: *(a) DIBAL-H, –78 °C, 30 min then PhMgBr, –78 °C to rt, 57%; (b) (i) TFA, CH_2Cl_2, rt, 2 h, 87%; (ii) BnCl, K_2CO_3, CH_2Cl_2, reflux, 4 h, 73%; (c) TFAA, Et_3N, THF, 3 h, MW, 100 °C then NaOH (aq), quantitative; (d) (i) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 16 h, 98%; (ii) H_2, $Pd(OH)_2$, 45 °C, EtOH, H-Cube, 77%; (iii) DMAP, TFAA, Et_3N, CH_2Cl_2, rt, 16 h, 98%; (e) (i) $NaIO_4$, $RuCl_3/H_2O$, CH_3CN, H_2O, CCl_4, rt, 18 h; (ii) K_2CO_3, MeOH, rt, 15 h, 67% (2 steps).*

Charette's approach (*J. Org. Chem.* **2010**, *75*, 2077)[16a]

Charette *et al*. reported the formal synthesis of 3-hydroxypipecolic acid **42** using an intermediate **58** obtained by the diastereoselective addition of phenylmagnesium bromide on *N*-pyridinium salt derived from chiral auxiliary L-valinol and pyridine (**Scheme 14**). The 3-hydroxy substituent of the (2*S*,3*S*)-3-hydroxypipecolic acid (**42**) was introduced by hetero-Diels–Alder reaction of oxygen with the 1,2-dihydropyridine **58**. The endoperoxide was effectively reduced aluminum

hydride to furnish piperidine derivative **75**. The protection of amine, as well as alcohol, gave **76** which on hydrogenation led to known intermediate **77**. This constitutes the formal synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid (**42**). The synthesis of intermediate **77** required 6 steps from dihydropyridine **58** (30% yield) or 8 steps (20% overall yield) from L-valinol.



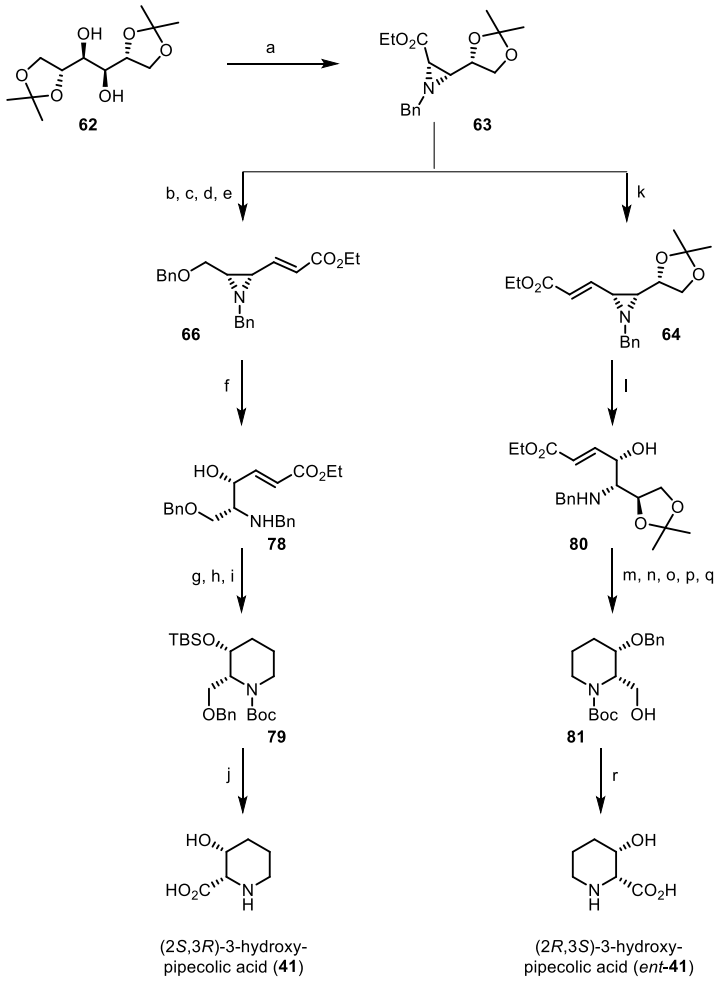
Scheme 14: Reagents and conditions: *(a) O_2, hv, methylene blue, CH_2Cl_2, –78 °C; (b) AlH_3, Et_2O, –78 °C to rt, 61%; (c) (i) TFAA, Et_2O, –20 °C; (ii) NaOAc, Ac_2O, pyridine, rt, 89%; (d) H_2, Pd/C, CH_3CN, rt, 93%; (e) ref. 16c*

Chavan's approach (*Tetrahedron Lett*. **2014**, *55*, 6423)[19a]

In the year 2014, this group reported the formal synthesis of both the antipodes of *cis* 3-hydroxy pipecolic acid utilizing *cis* aziridine-2-carboxylate **63** as a chiral synthon (**Scheme 15**). Synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid (**41**) started with the functionalization of acetonide side of *cis* aziridine-2-carboxylate **63** derived from D-mannitol (**62**) to α,β-unsaturated ester **66** in 5 steps. The α,β-unsaturated ester **66** was converted into the piperidine ring **79** through regioselective aziridine opening using H_2O as a nucleophile followed by concomitant reduction and cyclization of resultant compound **78** under hydrogenation condition. Synthesis of intermediate **79** constitutes the formal synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid (**41**) in 8 purification steps in 24% overall yield starting from *cis* aziridine-2-carboxylate **63**.

Synthesis of (2*R*,3*S*)-3-hydroxypipecolic acid (**ent-41**) started with the *cis* aziridine-2-carboxylate **63** which was converted into α,β-unsaturated ester **64** in two steps by using DIBAL-H reduction of the ester to the corresponding aldehyde followed by 2-carbon Wittig

homologation (**Scheme 15**). For the synthesis of piperidine ring **81**, regioselective aziridine opening of α,β-unsaturated ester **64** using H_2O as a nucleophile followed by concomitant olefin reduction and cyclization of compound **80** under hydrogenation condition was used as a key step. Synthesis of intermediate **81** constitutes the formal synthesis of (2*R*,3*S*)-3-hydroxypipecolic acid (**ent-41**) in 9 purification steps in 12% overall yield starting from *cis* aziridine-2-carboxylate **63**.



Scheme 15: Reagents and conditions: *(a) i) $NaIO_4$, CH_2Cl_2, rt, 2 h; (ii) ethyl 2-bromo-2-(triphenyl-λ^5-phosphanylidene)acetate, CH_2Cl_2, rt, 84% over two steps; (iii) $BnNH_2$, Et_3N, EtOH, 0 ºC to rt, 72 h, 77%; (b) LAH, THF, 0 °C, 1 h, 90%; (c) BnBr, NaH, DMF, 95%; (d) PTSA, CH_3OH, 85%; (e) i) $NaIO_4$, $(CH_3)_2CO:H_2O$ (2:1); ii) Ph_3PCHCO_2Et, cat. $PhCO_2H$, toluene, reflux, 85% (over two steps); (f) TFA, $CH_3CN:H_2O$ (9:1), 85%; (g) TBSCl, imidazole, cat. DMAP, CH_2Cl_2, reflux, 90%; (h) H_2, 10% $Pd(OH)_2/C$, EtOH, 88%; (i) i) BH_3·DMS, THF; ii) $(Boc)_2O$, CH_2Cl_2, Et_3N, 80% over two steps; (j) Ref. 19b; (k) i) DIBAL-H, CH_2Cl_2, –78 °C; ii) Ph_3PCHCO_2Et, cat. $PhCO_2H$, toluene, reflux, 82%, (over two steps); (l) TFA, $CH_3CN:H_2O$,*

(9:1), 75%; (m) 10% Pd/C, HCO_2NH_4, MeOH, 60 °C, 90%; (n) BnBr, NaH, cat. TBAI, DMF, 85%; (o) 80% (aq.) AcOH; (p) i) $NaIO_4$, $(CH_3)_2CO$:H_2O, (2:1); ii) BH_3·DMS, THF, 65%, over 3 steps; (q) i) H_2, (10 %) $Pd(OH)_2/C$, EtOH; ii) $(Boc)_2O$, Et_3N, CH_2Cl_2, 80% over 2 steps; (r) Ref. 19c.

3.2.3. References

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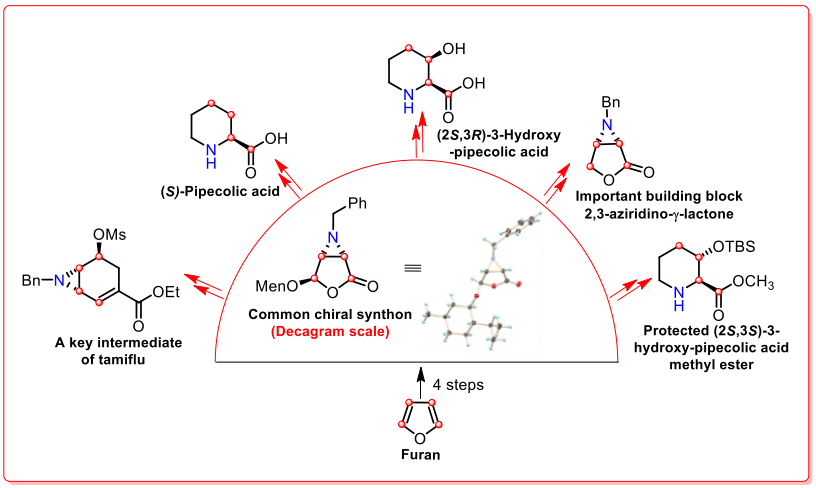
Chapter 3: On-Water Oxidation of Furan and its Application in the Collective Syntheses of Oseltamivir Phosphate (Tamiflu), (*S*)-Pipecolic acid and its 3-Hydroxy Derivatives

CHAPTER 3

Section 3

"Collective Syntheses of Oseltamivir Phosphate (Tamiflu), (*S*)-Pipecolic acid and its 3-Hydroxy Derivatives"



ABSTRACT: The unified synthetic strategy for oseltamivir phosphate (tamiflu), (*S*)-pipecolic acid and its 3-hydroxy derivatives from furan derived common chiral bicycloaziridino lactone synthon is described here. Key features are short (4-steps), enantiopure, and decagram scale synthesis of common chiral synthon from furan and its first-ever application in the total synthesis of biologically active compounds by taking the advantages of high functionalization ability of chiral synthon.

3.3.1. Objective

Oseltamivir phosphate (**1**, Tamiflu) which is neuraminidase inhibitor was first developed by Gilead Sciences for the treatment of swine flu (H5N1 human flu), whereas pipecolic acid and its 3-hydroxy derivatives (**2**, **3**, and **4**) are important building blocks for the synthesis of various biologically active compounds (**Figure 1**). To date, there are many synthetic approaches for the synthesis of tamiflu, pipecolic acid and its 3-hydroxy derivatives reported in the literature.[1,2] Out of these, there are only a few reports in which chiral aziridines were used as the starting material. Of note, in literature reports, there is a lack of scalable route for the synthesis of a common aziridine building block in less number of steps for the collective synthesis of bioactive compounds using simple reagents and reaction conditions.[3] In that context, the development of synthetic methodologies for the scalable asymmetric synthesis of the aziridine building block in less number of steps using simple reagents and reaction conditions is highly desirable.

Furthermore, due to the continued interest of this group in the synthesis of biologically active compounds which are having societal importance using chiral aziridine as a building block,[4] synthetic studies towards tamiflu, D-(+)-biotin, pipecolic acid, and its 3-hydroxy derivatives were initiated.

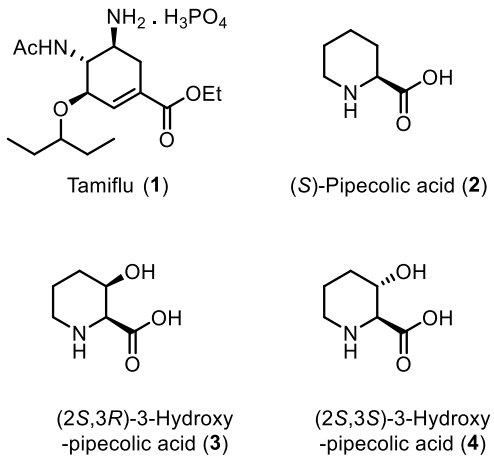
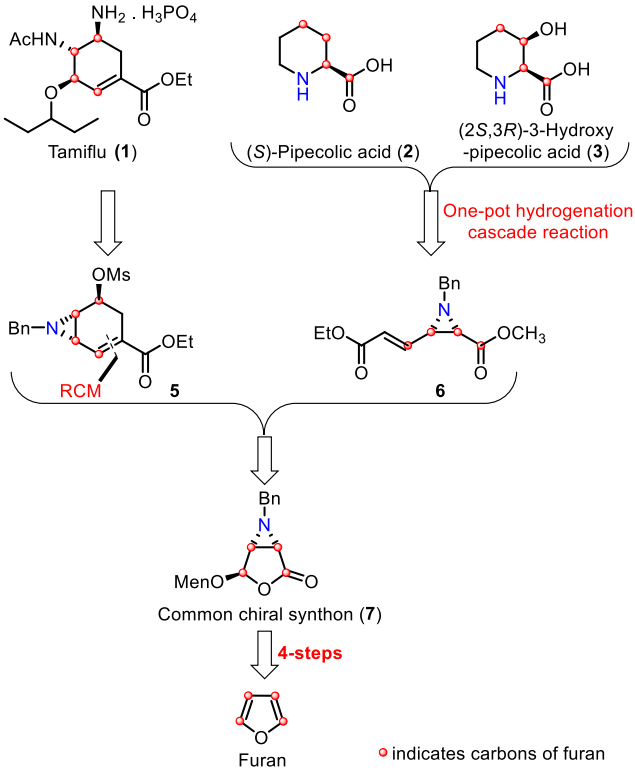


Figure 1. Structure of tamiflu and piperidine alkaloids.

3.3.2. Present Work

3.3.2.1. Retrosynthetic Analysis

The retrosynthetic plan is outlined in **Scheme 1**. It was envisioned that the common chiral synthon **7** could be an ideal choice for the collective synthesis of tamiflu and piperidine class of alkaloids in enantioselective fashion. Core skeleton **5** of tamiflu (**1**) could be synthesized by using ring-closing metathesis (RCM) of diene derived from common chiral synthon **7**, whereas piperidine alkaloids (*S*)-pipecolic acid (**2**) and (2*S*,3*R*)-3-hydroxypipecolic acid (**3**) could be constructed through regioselective ring-opening and reductive cyclization of functionalized vinyl aziridine **6** derived from common chiral synthon **7**. The common chiral synthon bicycloaziridino lactone **7** in turn, could be obtained from a non-chiral starting material furan by taking the advantages of chiral resolution of bromo-butenolide using menthol as a chiral auxiliary.



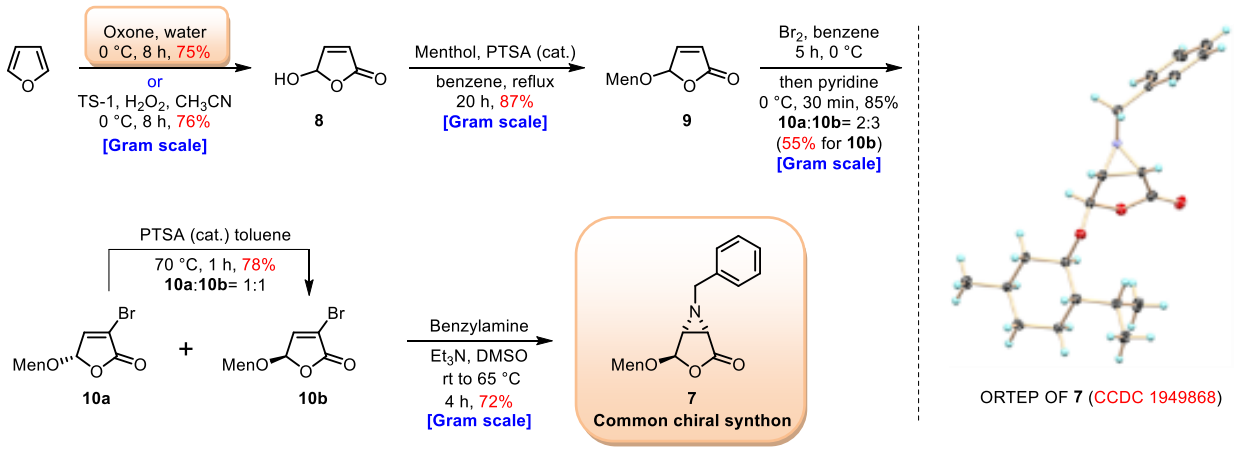
Scheme 1. Retrosynthetic Analysis

3.3.2.2. Results and Discussion

Synthesis commenced with the commercially available starting material furan (**Scheme 2**). Synthesis of hydroxy lactone **8** from furan was achieved by using a method developed in the previous section. Alternatevly, oxidation of furan was achieved by using a method developed by Kumar *et al.*[5] in which, furan on treatment with catalytic amount of titanium silicate molecular sieve (TS-1) catalyst and H_2O_2 in acetonitrile at 0 ^oC underwent oxidation to furnish 5-hydroxy-2(5*H*)-furanone **8** in 76% yield. The hydroxy-butenolide **8** was then refluxed with (–)-menthol in benzene in the presence of a catalytic amount of PTSA with azeotropic removal of water formed during the reaction to obtain product **9** containing a mixture of diastereomers in 87% combined yield.[6] Compound **9** was then treated with bromine in benzene at 0 ^oC for 5 h followed by treatment with pyridine at 0 °C to provide bromo-butenolides **10a** and **10b** as a mixture of diastereomers (ratio 2: 3) in 85% yield.[7] The major diastereomer **10b** was obtained in an enantiomerically pure form by recrystallization from *n*-hexane at –18 °C. The filtrate from recrystallization containing compound **10a** as a major diastereomer was treated with PTSA in toluene at 70 °C to obtain a mixture of **10a** and **10b** in a 1:1 ratio in 78% yield and an additional amount of **10b** was obtained by the repetitions of the process of crystallization. The global yield obtained for the enantiomerically pure diastereomer **10b** was 55% from compound **9**. In the next step, bromo-butenolide **10b** was treated with benzylamine and triethylamine in DMSO for 30 min at room temperature followed by heating at 65 ^oC for 4 h to furnish *cis*–aziridine **7** in 72% yield. The characteristic peak at δ 5.49 (s, 1H) in ^1H NMR spectrum and δ 99.1 in ^{13}C NMR spectrum corresponded to proton of acetal functionality of butenolide, and peaks at δ 2.91 (d, J = 4.1 Hz, 1H) and 2.74 (d, J = 4.1 Hz, 1H) corresponded to *cis*-aziridine protons in ^1H NMR spectrum which confirmed the formation of product. It was further confirmed by the peak at 366.2037 corresponding to the formula $C_{21}H_{29}O_3NNa$ $[M + Na]^+$ of the product in the HRMS spectrum. Moreover, the structure and absolute stereochemistry of synthon **7** were unequivocally confirmed by single-crystal X-ray analysis. Synthesis of common chiral bicycloaziridino lactone synthon **7** was achieved in four steps in 26% overall yield.

The main advantages of this methodology are decagram scale synthesis, less number of reaction steps and enantiopure synthesis of aziridine skeleton from the non-chiral starting material. Here, it is noteworthy to mention that unlike other aziridine synthons, bicycloaziridino lactone synthon **7** is a crystalline solid and has remarkably high stability at room temperature (bicycloaziridino

lactone **7** was stable for more than a year at room temperature without either decomposition or formation of side products).



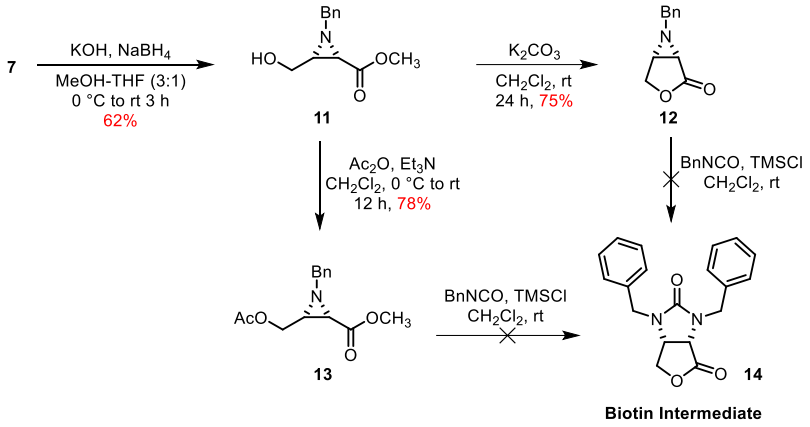
Scheme 2. Synthesis of Common Chiral Bicycloaziridino Lactone Synthon 7 from Furan

To the best of this author's knowledge, the application of chiral bicycloaziridino lactone synthon **7** for the total synthesis of natural products is not reported in the literature. However, very closely related elegant work was reported by Dodd *et al.* involving the 3-step preparation of a similar chiral aziridino-γ-lactone synthon from ribonolactone and its application in natural product synthesis.[8] It may also be noted that Dodd *et al*. employed a chiral pool strategy against the current method which describes a recyclable chiral auxiliary strategy to incorporate chirality. Moreover, using the current method, it is possible to synthesize opposite enantiomer of common bicycloaziridino lactone synthon **7** by utilizing the bromo-butenolide **10a** or by employing D-menthol as the chiral auxiliary.

Synthesis of D-(+)-biotin, tamiflu, (*S*)-pipecolic acid and its 3-hydroxy derivatives were undertaken to showcase the accessibility of diverse skeletons of bioactive molecules from bicycloaziridino lactone synthon **7**. To this end, bicycloaziridino lactone **7** was treated with KOH and $NaBH_4$ in MeOH-THF (3:1) at 0 °C to furnish alcohol **11** in 62% yield. As expected, the stereochemistry of aziridine **11** was found to be *cis* and was subsequently confirmed by ^{1}H NMR spectroscopy (coupling constants of aziridine protons are 6.9 and 6.1 Hz, which are found to be in accordance with the literature values).[4c]

Alcohol **11** was then treated with K_2CO_3 in CH_2Cl_2 to afford 2,3-aziridino-γ-lactone **12** in 75% yield. The formation of the product was confirmed by the disappearance of O-CH_3 protons of methyl ester and appearance of characteristic peaks at δ 4.33 (d, J = 9.9 Hz, 1H) and 4.21 (d, J = 9.9 Hz, 1H) corresponding to O-CH_2 of lactone in ^{1}H NMR spectrum. The peak at 190.0862

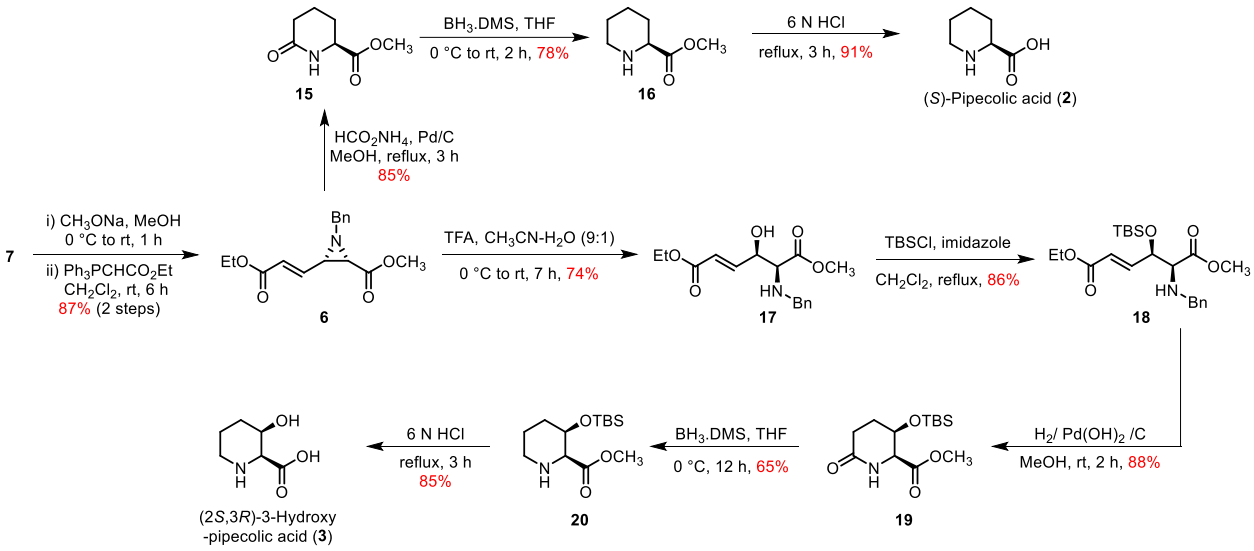
corresponding to the formula $C_{11}H_{12}O_2N$ $[M + H]^+$ in the HRMS spectrum further confirmed the formation of the product. The next crucial step was the synthesis of a five-membered urea ring of D-(+)-biotin. For the synthesis of the five-membered urea ring, it was decided to use the protocol reported by Ha *et al*.[9] Accordingly, 2,3-aziridino-γ-lactone **12** was treated with benzyl isocyanate and TMSCl in CH_2Cl_2 at room temperature. However, the formation of the desired product was not observed. Here, the opening of aziridine by chloride ion was observed and confirmed by LCMS, which is expected to be the first step, but many attempts to cyclize the chloro-amine further to get required five-membered urea met with failure. Here, it was thought that the ring strain in 2,3-aziridino-γ-lactone **12** might hinder the cyclization. To overcome that, compound **13** was prepared from alcohol **11** in 78% yield. Unfortunately, at this stage also, the formation of the desired product was not observed. The major outcome of this study is the synthesis of 2,3-aziridino-γ-lactone **12**, which is used as an important building block for the synthesis of several natural products.[10]



Scheme 3. Attempted Synthesis of D-(+)-Biotin from Common Chiral Synthon 7

Towards the goal of utilizing bicycloaziridino lactone **7** in total synthesis, bicycloaziridino lactone **7** was treated with $NaOCH_3$ in MeOH and the crude aldehyde obtained was subjected for two carbon Wittig homologation to obtain vinyl aziridine **6** in 87% yield over 2 steps (**Scheme 4**). Peaks at δ 6.86 (dd, J = 8.5, 15.9 Hz, 1H) and 6.11 (d, J = 15.9 Hz, 1H) in the ^{1}H NMR spectrum and δ 142.4 and 125.2 in the ^{13}C NMR spectrum corresponding to the olefin functionality of unsaturated ester indicated the formation of the product. HRMS spectrum showed a signal at 290.1382 corresponding to the formula $C_{16}H_{20}O_4N$ $[M + H]^+$ further confirming the structure of the product.

In the next step, vinyl aziridine **6** was subjected to transfer hydrogenation condition using ammonium formate and Pd/C in MeOH under reflux condition, to provide methyl-6-oxopipecolate **15** in 85% yield. The disappearance of olefin and *N*-benzyl protons and appearance of signals at δ 6.59 (br s, 1H) and 171.6 for proton and carbon of amide group in ^{1}H and ^{13}C NMR spectrum respectively indicated the formation of the product. The structure of **15** was further confirmed by the analysis of HRMS spectrum in which signal at 180.0630 corresponded to the formula $C_7H_{11}O_3NNa$ $[M + Na]^+$ of the product. Here, one-pot aziridine opening, olefin reduction, debenzylation, and cyclization were observed under hydrogenation condition.[11] Lactam **15** was reduced using BH_3.DMS to the corresponding amine **16** in 78% yield. In the last step, amino-ester **16** was treated with 6 N HCl under reflux condition to obtain (*S*)-pipecolic acid **2** in 91% yield. The spectral and analytical data obtained for (*S*)-pipecolic acid **2** were in complete agreement with the reported data.[4b]



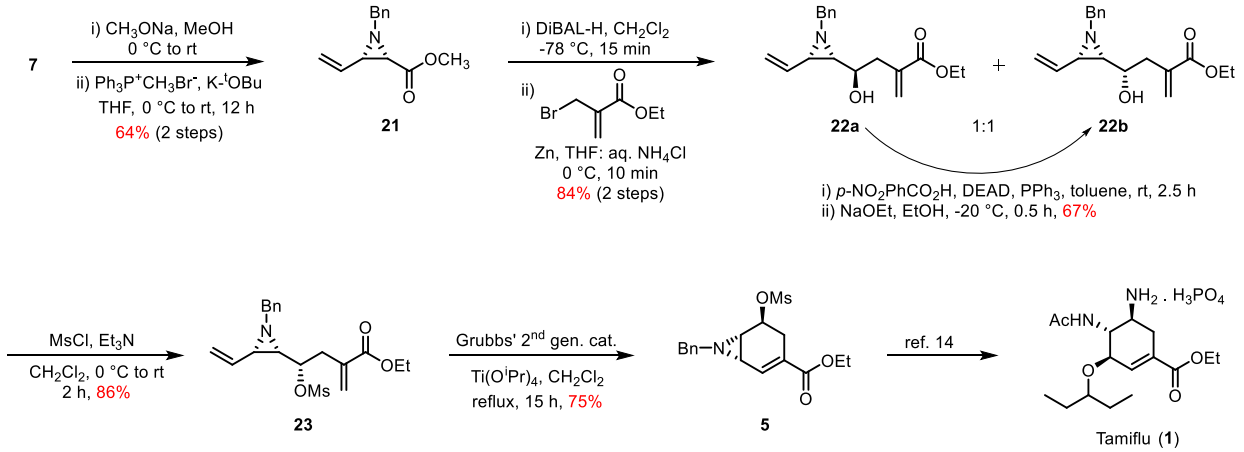
Scheme 4. Total Synthesis of (*S*)-Pipecolic acid and (2*S*,3*R*)-3-Hydroxypipecolic acid from Common Chiral Synthon 7

For the total synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid, vinyl aziridine **6** was regioselectively opened using TFA in CH_3CN-H_2O (9:1) to obtain amino-alcohol **17** in 74% yield (**Scheme 4**). The disappearance of characteristic aziridine protons and the appearance of a signal at δ 4.36–4.32 (m, 1H) for CH-O in ^{1}H NMR spectrum indicated the formation of the product. The peak at 308.1491 corresponding to the formula $C_{16}H_{22}O_5N$ $[M + H]^+$ in the HRMS spectrum further confirmed the formation of the product. Amino-alcohol **17** was then treated with TBSCl

and imidazole in CH_2Cl_2 to obtain TBS protected alcohol **18** in 86% yield. In the next step, compound **18** was subjected to hydrogenation using $Pd(OH)_2$ to afford lactam **19** in 88% yield. The disappearance of olefin and *N*-benzyl protons and appearance of signals at δ 6.21 (br s, 1H) and 169.2 for proton and carbon of amide group in ^1H and ^{13}C NMR spectrum respectively indicated the formation of the product. It was further confirmed by the HRMS spectrum in which signal at 310.1441 corresponded to the formula $C_{13}H_{25}O_4NNaSi$ $[M + Na]^+$ of the product. Lactam **19** was reduced using BH_3.DMS to the corresponding amine **20** in 65% yield. The formation of the product was confirmed by the disappearance of signal related to the amide group in ^1H and ^{13}C NMR spectrum and appearance of one extra methylene carbon at δ 45.2 corresponding to *N*-CH_2 in DEPT NMR spectrum. In the last step, amine **20** was subjected to ester hydrolysis and deprotection of the TBS group using 6 N HCl under reflux condition to furnish (2*S*,3*R*)-3-hydroxypipecolic acid **3** in 85% yield. The spectral and analytical data obtained for (2*S*,3*R*)-3-hydroxypipecolic acid **3** were in complete agreement with the reported data. [12]

After successful completion of the total synthesis of (*S*)-pipecolic acid and (2*S*,3*R*)-3-hydroxypipecolic acid, attention was turned towards the synthesis of tamiflu (**1**) using bicycloaziridino lactone **7** as a key intermediate. Here, it was thought that the aziridine part of synthon **7** could be easily converted into 1,2-*trans*-diamine of the target molecule whereas lactone moiety could be converted into a six-membered core skeleton of tamiflu (**Scheme 5**). To this end, bicycloaziridino lactone **7** was treated with $NaOCH_3$ in MeOH and the corresponding aldehyde was subjected to one carbon Wittig homologation to afford vinyl aziridine **21** in 64% yield over 2 steps. The formation of vinyl aziridine **21** was indicated by the presence of olefinic signals at δ 5.88–5.65 (m, 1H), 5.35 (dd, *J* = 1.5, 17.3 Hz, 1H) and 5.19 (dd, *J* = 1.5, 10.3 Hz, 1H) in ^1H NMR spectrum and corresponding carbons at δ 133.2 and 119.5 in ^{13}C NMR spectrum. The product formation was further confirmed by HRMS which showed a peak at 218.1173 corresponding to the formula $C_{13}H_{16}O_2N$ $[M + H]^+$ with the calculated value of 218.1176. In the next step, ester **21** was reduced to the corresponding aldehyde using DiBAL-H at –78 °C followed by allylation using addition of allyl zinc reagent prepared by the reaction of zinc and ethyl 2-(bromomethyl)acrylate to the crude aldehyde to successfully produce the homoallyl alcohols **22a** and **22b** in 84% yield over 2 steps in the 1:1 ratio.

At this stage, it was assumed that the compound **22b** had the relative stereochemistry as shown in **Scheme 5**, although the relative stereochemistry was not confirmed until after it was converted into the known intermediate for tamiflu prepared by a different route. Nonetheless, the undesired diastereomer **22a** was effectively converted into the desired compound **22b** in 67% yield using Mitsunobu inversion followed by hydrolysis.[13] The formation of product was confirmed by the presence of signals at δ 6.17 (d, *J* = 1.4 Hz, 1H) and 5.55 (d, *J* = 1.4 Hz, 1H) in ^{1}H NMR spectrum and δ 127.6 in ^{13}C NMR spectrum corresponding to the characteristic exocyclic methylene protons and carbon of the newly added acrylate group respectively. The structure of **22b** was further confirmed by the HRMS spectrum which showed the signal at 302.1752 corresponding to the formula $C_{18}H_{24}O_3N$ $[M + H]^+$ of the product. The compound **22b** was treated with mesyl chloride to obtain mesylate **23** in 86% yield. The signal at δ 2.65 (s, 3H) corresponding to the methyl protons of the mesylate group in ^{1}H NMR spectrum indicated the formation of the product. HRMS spectrum showed a peak at 380.1527 corresponding to the formula $C_{19}H_{26}O_5NS$ $[M + H]^+$ which further confirmed the formation of the product.

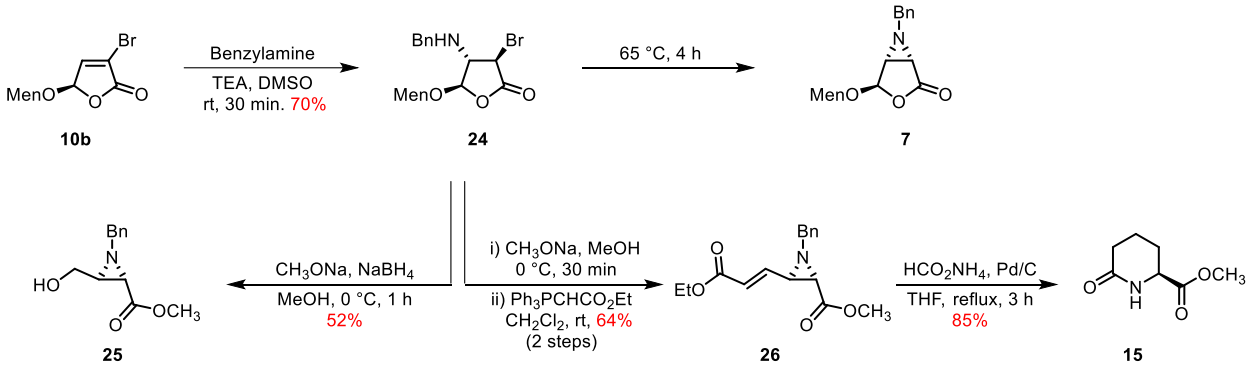


Scheme 5. Formal Total Synthesis of Tamiflu from Common Chiral Synthon 7

After getting required diene **23** in hand, the next task was the construction of tamiflu skeleton using ring-closing metathesis (RCM). Towards this, diene **23** was subjected for RCM using Grubbs' 2nd generation catalyst and titanium tetraisopropoxide as a Lewis acid to obtain tamiflu skeleton **5** in 75% yield. The spectral and analytical data of compound **5** were in good agreement with the reported data.[14] This constitutes the formal total synthesis of tamiflu (**1**) from furan in 10 steps in 7.5% overall yield.

Furthermore, during the synthesis of bicycloaziridino lactone synthon **7** from bromo-butenolide **10b**, after the reaction with benzylamine, the formation of amino-lactone **24** at room temperature

in 30 min in 70% isolated yield was observed (**Scheme 6**). The signal at δ 4.29 (d, *J* = 5.8 Hz, 1H) corresponding to the proton of CH-Br indicated the formation of the product. The stereochemistry of Br substituent with respect to amine in compound **24** was found to be *trans* as shown in **Scheme 6** and confirmed by ^{1}H NMR analysis (J= 5.8 Hz), which is found to be in accordance with the literature values.[15] The formation of the compound was further confirmed by the HRMS spectrum which showed a peak at 424.1479 corresponding to the formula $C_{21}H_{31}O_3NBr$ $[M + H]^+$ of the product. To check the synthetic utility of amino-lactone **24** for the synthesis of chiral aziridine, amino-lactone **24** was treated with $NaOCH_3$ followed by $NaBH_4$ in MeOH at 0 °C to furnish aziridine **25** in 52% yield. The stereochemistry of aziridine **25** was found to be *trans* (by ^{1}H NMR) as shown in **Scheme 6**.

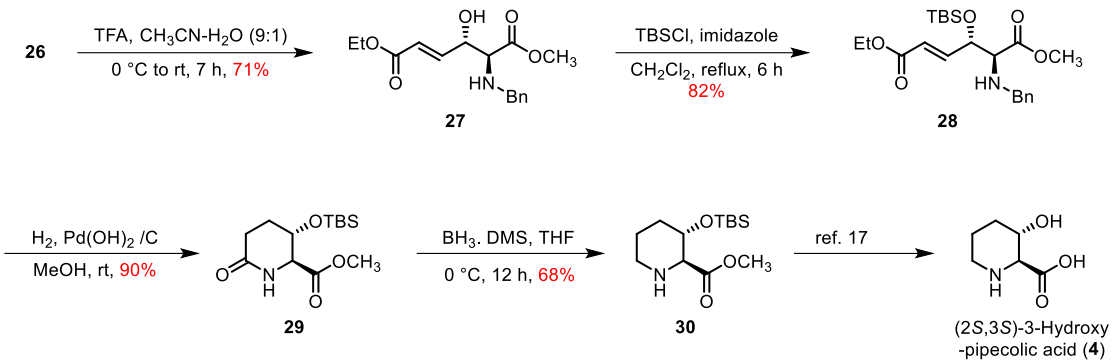


Scheme 6. Synthesis of Vinyl Aziridine 26 and Methyl-6-oxopipecolate 15

Furthermore, aldehyde obtained from amino-lactone **24** was subjected for two carbon Wittig homologation to obtain *trans*-vinyl aziridine **26** in 64 % yield over 2 steps. Peaks at δ 6.99–6.56 (m, 1H) and 6.33–6.00 (m, 1H) in ^{1}H NMR spectrum corresponding to the olefin functionality of unsaturated ester indicated the formation of the product. HRMS spectrum showed a signal at 290.1384 corresponding to the formula $C_{16}H_{20}O_4N$ $[M + H]^+$ further confirming the structure of the product. To demonstrate the synthetic utility, *trans*-vinyl aziridine **26** under transfer hydrogenation condition was converted into the methyl-6-oxopipecolate **15** in 85% yield. The methyl-6-oxopipecolate **15** derived from *cis*-vinyl aziridine **6** and *trans*-vinyl aziridine **26** has the same spectral and analytical data along with specific rotation,[16] which in turn confirmed the assigned relative and absolute stereochemistry of *trans*-vinyl aziridine **26**.

Subsequently, *trans*-vinyl aziridine **26** was effectively converted into amino-ester **30** using the same sequence used in the synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid (**3**) (**Scheme 7**). Since the last step for the synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid (**4**) from amino-ester **30** is well

documented in the literature,[17] this constitutes the formal total synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid (**4**).



Scheme 7. Formal Total Synthesis of (2*S*,3*S*)-3-Hydroxypipecolic acid (4)

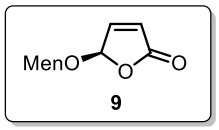
3.3.3. Conclusion

To conclude, a unified synthetic strategy for the synthesis of tamiflu, (*S*)-pipecolic acid and its 3-hydroxy derivatives from common chiral bicycloaziridino lactone synthon **7** derived from furan has been accomplished. Common chiral bicycloaziridino lactone synthon **7** was synthesized in only 4 steps on decagram scale quantity from furan. Moreover, the synthesis of bicycloaziridino lactone synthon **7** was achieved using simple reagents and reaction conditions in an enantiomerically pure form. Other key features are the first-ever application of bicycloaziridino lactone synthon **7** in total synthesis tamiflu and piperidine class of alkaloids, successful functionalization of bicycloaziridino lactone **7** to vinyl aziridine **6** and Lewis acid-catalyzed RCM of aziridine containing diene for the construction of tamiflu framework. Scalable synthesis of enantiomerically pure bicycloaziridino lactone **7** in less number of steps using easily available and inexpensive reagents and high stability of this aziridine synthon at room temperature makes this protocol attractive and hopefully will find more applications in the total synthesis of natural products.

3.3.4. Experimental Section

3.3.4.1. Experimental Procedures and Characterization Data

(*R*)-5-(((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)oxy)furan-2(5*H*)-one (9).



9

To the stirred solution of 5-hydroxy-2-(5*H*)-furanone (**8**) (30 g, 0.3 mol, 1 equiv) in benzene, (–)-menthol (29.6 g, 0.19 mol, 0.95 equiv) and catalytic amount of *p*-TSA (190 mg, 1 mmol, 0.1 equiv) were added and the reaction mixture was refluxed for 20 h with azeotropic removal of water. After completion, the reaction mixture was cooled to room temperature and washed with water and brine, dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (02:98) afforded the mixture of diastereomers in the ratio 60:40 as a viscous solid (62 g, 87 % yield). The mixture of diastereomers was used in the next reaction without further separation.

For analytical purposes, the mixture of diastereomers was subjected to recrystallization using light petroleum ether at –23 °C to obtain enantiomerically pure **9** as a white crystalline solid.

R_f : 0.4 (EtOAc–PE= 10:90);

Yield: 87%;

M. p.: 70 °C (lit.[6] Mp = 70.5–70.7 °C);

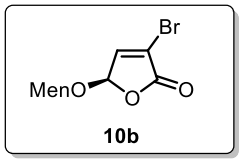
$[\alpha]_D^{25}$: –136 (*c* 1, EtOH). {lit.[6] $[\alpha]_D$ –136.4, (*c* 1, EtOH)};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.16 (dd, *J* = 1.0, 5.7 Hz, 1H), 6.20 (dd, *J* = 1.1, 5.7 Hz, 1H), 6.08 (s, 1H), 3.65 (dt, *J* = 4.4, 10.6 Hz, 1H), 2.21–2.00 (m, 2H), 1.75–1.59 (m, 2H), 1.53–1.33 (m, 1H), 1.33–1.15 (m, 1H), 1.15–0.96 (m, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 170.7, 150.9, 124.7, 100.4, 79.1, 47.7, 40.3, 34.1, 31.4, 25.3, 23.1, 22.2, 20.8, 15.7;

HRMS (ESI) *m/z* calcd for $C_{14}H_{22}O_3Na$ $[M + Na]^+$: 261.1461, found: 261.1460.

(*R*)-3-Bromo-5-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)furan-2(5*H*)-one (10b).



10b

To a stirred, ice-cold (0 °C) solution of mixture of diastereomers of **9** (30 g, 0.126 mol, 1 equiv) in dry benzene (300 mL), was added solution of bromine (6.5 ml, 0.126 mol, 1 equiv) in benzene dropwise and the reaction

mixture was stirred at same temperature for 6 h. The progress of the reaction was monitored by TLC. After that pyridine (12.2 ml, 0.151 mol, 1.2 equiv) was added dropwise at 0 °C and the reaction mixture was stirred for 30 min. After completion, the reaction mixture was treated with water and extracted with EtOAc (3 X 500 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (02:98) afforded a diastereoisomeric mixture of **10a** and **10b** as a yellow oil. Pure **10b** was separated as a white crystalline solid by crystallization with *n*-hexane at -18 °C. An additional amount of pure **10b** was recovered from the remaining filtrate from crystallization by successive epimerization at 70 °C in toluene using PTSA as a catalyst, followed by the above-mentioned method of purification and recrystallization (22 g, 55% yield).

R_f : 0.5 (EtOAc–PE= 10:90);

Yield: 55%;

M. p.: 88–90 °C (lit.[7] Mp = 70.5–70.7 °C) ;

IR ($CHCl_3$): ν_{max} 1770, 1624 cm^{-1};

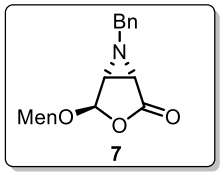
$[\alpha]_D^{25}$ –121.6 (*c* 3, $CHCl_3$), {lit.[7] $[\alpha]_D$ –121.1 (*c* 1.82, $CHCl_3$)};

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.23 (s, 1H), 6.02 (s, 1H), 3.66 (dt, *J* = 4.2, 10.7 Hz, 1H), 2.16–2.05 (m, 2H), 1.72–1.63 (m, 2H), 1.47–1.35 (m, 1H), 1.30–1.22 (m, 1H), 1.07–0.97 (m, 2H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 7.2 Hz, 3H), 0.86–0.82 (m, 1H), 0.79 (d, *J* = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.1, 147.5, 117.7, 99.7, 79.4, 47.7, 40.3, 34.1, 31.4, 25.2, 23.0, 22.1, 20.8, 15.6;

HRMS (ESI) *m/z* calcd for $C_{14}H_{21}O_3BrNa$ $[M + Na]^+$: 339.0566, found: 339.0567.

(1*S*,4*R*,5*R*)-6-Benzyl-4-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (7).



7

To a stirred solution of bromolactone **10b** (15 g, 0.047 mol, 1 equiv) in DMSO (150 mL), triethylamine (7.32 mL, 0.052 mol, 1.1 equiv) followed by benzylamine (5.18 mL, 0.047 mol, 1 equiv) was added at room temperature. The reaction mixture was stirred at room temperature for 30 min and then heated at 65 °C for 4 h. The progress of the reaction was monitored by TLC. After completion,

the reaction mixture was treated with cold water (150 mL) and extracted with EtOAc (3 X 200 mL). The combined organic layer was washed with water (2 X 200 mL) and brine (100 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded pure product **7** as a white solid (11.73 g, 72% yield).

R_f : 0.3 (EtOAc–PE= 15:85);

Yield: 72%;

M. p.: 149–151 °C;

IR ($CHCl_3$): ν_{max} 3022, 1779, 1216, 765 cm^{-1};

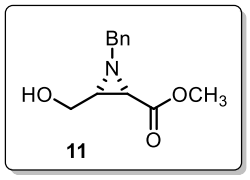
$[\alpha]_D^{25}$ –227.6 (*c* 1, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.28 (m, 5H), 5.49 (s, 1H), 3.67 (d, *J* = 13.3 Hz, 1H), 3.56 (dt, *J* = 4.1, 10.8 Hz, 1H), 3.49 (d, *J* = 13.3 Hz, 1H), 2.91 (d, *J* = 4.1 Hz, 1H), 2.74 (d, *J* = 4.1 Hz, 1H), 2.12–2.02 (m, 2H), 1.71–1.61 (m, 2H), 1.44–1.31 (m, 1H), 1.27–1.18 (m, 1H), 1.06–0.94 (m, 2H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 7.3 Hz, 3H), 0.85–0.80 (m, 1H), 0.78 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.5, 136.7, 128.6 (2C), 127.9 (2C), 127.7, 99.1, 77.4, 60.7, 47.7, 45.5, 39.9, 38.7, 34.2, 31.3, 25.3, 23.0, 22.2, 20.8, 15.6;

HRMS (ESI) *m/z* calcd for $C_{21}H_{29}O_3NNa$ $[M + Na]^+$: 366.2040, found: 366.2037.

Methyl (2*S*,3*R*)-1-benzyl-3-(hydroxymethyl)aziridine-2-carboxylate (11).



To a stirred, cooled (0 °C) solution of compound **7** (1 g, 2.9 mmol, 1 equiv) in MeOH-THF (3:1) (40 mL), KOH (169 mg, 2.9 mmol, 1 equiv) was added followed by $NaBH_4$ (110 mg, 2.9 mmol, 1 equiv) and the reaction mixture was stirred for 3 h while gradually warming to room temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was treated with 1 N HCl to adjust the pH to 7 and extracted with EtOAc (3 X 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (30:70) afforded pure product **11** as a colorless liquid (0.4 g, 62% yield).

R_f : 0.2 (EtOAc–PE= 50:50);

Yield: 62%;

IR ($CHCl_3$): ν_{max} 3417, 1730, 1216, 768 cm^{-1};

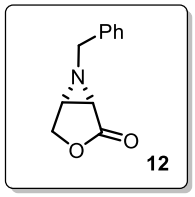
$[\alpha]_D^{25}$ –59.2 (*c* 3.5, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37 - 7.25 (m, 5H), 3.75 (dd, *J* = 4.0, 5.1 Hz, 2H), 3.73 (s, 3H), 3.63 (dd, *J* = 13.4, 13.7 Hz, 2H), 2.39 (d, *J* = 6.9 Hz, 1H), 2.26 (q, *J* = 6.1 Hz, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.9, 137.4, 128.5 (2C), 128.0 (2C), 127.4, 63.4, 60.0, 52.2, 46.5, 41.7;

HRMS (ESI) *m/z* calcd for $C_{12}H_{16}O_3N$ $[M + H]^+$: 222.1125, found: 222.1124.

(1*S*,5*R*)-6-Benzyl-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (12).



To a stirred solution of compound **11** (0.2 g, 0.9 mmol, 1 equiv) in CH_2Cl_2 (10 mL), K_2CO_3 (250 mg, 1.8 mmol, 2 equiv) was added and the reaction mixture was stirred for 24 h at room temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was filtered and extracted with CH_2Cl_2 (3 X 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (30:70) afforded pure product **12** as a colorless thick liquid (128 mg, 75% yield).

R_f : 0.4 (EtOAc–PE= 50:50);

Yield: 75%;

IR ($CHCl_3$): ν_{max} 1774 cm^{-1};

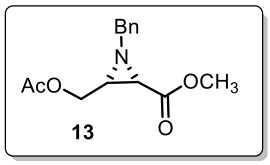
$[\alpha]_D^{25}$ –1.3 (*c* 0.5, $CHCl_3$), {lit.[10] $[\alpha]_D$ –1.6 (*c* 0.9, $CHCl_3$)};

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39–7.28 (m, 5H), 4.33 (d, *J* = 9.9 Hz, 1H), 4.21 (d, *J* = 9.9 Hz, 1H), 3.71 (d, *J* = 13.7 Hz, 1H), 3.47 (d, *J* = 13.7 Hz, 1H), 2.97 (t, *J* = 4.2 Hz, 1H), 2.72 (d, *J* = 4.2 Hz, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.3, 137.0, 128.6 (2C), 127.8 (2C), 127.6, 69.5, 61.0, 42.0, 39.6;

HRMS (ESI) *m/z* calcd for $C_{11}H_{12}O_2N$ $[M + H]^+$: 190.0863, found: 190.0862.

Methyl (2*S*,3*R*)-3-(acetoxymethyl)-1-benzylaziridine-2-carboxylate (13).



To a stirred, cooled (0 °C) solution of compound **11** (0.13 g, 0.58 mmol, 1 equiv) in anhydrous CH_2Cl_2 (5 mL), triethylamine (0.25 mL, 1.76 mmol, 3 equiv) and DMAP (cat.) followed by acetic anhydride (90 mg, 0.88 mmol, 1.5 equiv) were added. The reaction mixture was stirred for 1 h while gradually warming to room temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was treated with saturated aq. $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (3 X 10 mL). The combined organic layer was washed with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (30:70) afforded pure product **13** as a colorless liquid (120 mg, 78% yield).

R_f : 0.4 (EtOAc–PE= 30:70);

Yield: 78%;

IR ($CHCl_3$): ν_{max} 1739, 1642 cm^{-1};

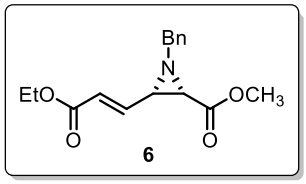
$[\alpha]_D^{25}$ –51.5 (*c* 2.5, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37–7.23 (m, 5H), 4.28–4.18 (m, 2H), 3.77 (d, *J* = 13.7 Hz, 1H), 3.74 (s, 3H), 3.50 (d, *J* = 13.7 Hz, 1H), 2.40 (d, *J* = 6.5 Hz, 1H), 2.29 (q, *J* = 6.5 Hz, 1H), 1.96 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.7, 169.3, 137.2, 128.4 (2C), 128.1 (2C), 127.4, 63.3, 62.2, 52.2, 43.2, 41.4, 20.6;

HRMS (ESI) *m/z* calcd for $C_{14}H_{18}O_4N$ $[M + H]^+$: 264.1230, found: 264.1231.

Methyl (2*S*,3*S*)-1-benzyl-3-((*E*)-3-ethoxy-3-oxoprop-1-en-1-yl)aziridine-2-carboxylate (6).



To a stirred solution of bicyclolactone **7** (1.5 g, 4.37 mmol, 1 equiv) in anhydrous MeOH (15 mL), was added NaOMe (236 mg, 4.37 mmol, 1 equiv) at 0 °C and the reaction mixture was stirred for 1 h while gradually warming to room temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was treated with saturated aq. NH_4Cl and extracted with EtOAc (3 X 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of the organic layer

in vacuo afforded crude aldehyde which was used in the next reaction without further purification.

To a stirred solution of aldehyde in CH_2Cl_2 (30 mL) was added (carbethoxymethylene) triphenylphosphorane (1.83 g, 5.24 mmol, 1.2 equiv) and the reaction mixture was stirred for 6 h at room temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was concentrated to dryness and residue was extracted with EtOAc (3 X 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded pure product **6** as a yellow solid (1.1 g, 87% yield).

R_f : 0.5 (EtOAc–PE= 30:70);

Yield: 87%;

M. p.: 71–73 °C;

IR ($CHCl_3$): ν_{max} 1716, 1651, 1215, 770 cm^{-1};

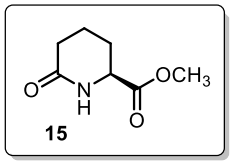
$[\alpha]_D^{25}$ +12.7 (*c* 1.5, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.28 (m, 5H), 6.86 (dd, *J* = 8.5, 15.9 Hz, 1H), 6.11 (d, *J* = 15.9 Hz, 1H), 4.22–4.13 (m, 2H), 3.76 (d, *J* = 14.0 Hz, 1H), 3.73 (s, 3H), 3.64 (d, *J* = 14.0 Hz, 1H), 2.62 (d, *J* = 6.7 Hz, 1H), 2.57 (t, *J* = 7.3 Hz, 1H), 1.27 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.6, 165.4, 142.4, 136.9, 128.5 (2C), 127.8 (2C), 127.4, 125.2, 63.2, 60.4, 52.3, 45.7, 44.9, 14.1;

HRMS (ESI) *m/z* calcd for $C_{16}H_{20}O_4N$ $[M + H]^+$: 290.1387, found: 290.1382.

Methyl (*S*)-6-oxopiperidine-2-carboxylate (15).



15

To a stirred solution of compound **6** (0.5 g, 1.73 mmol, 1 equiv) in MeOH (10 mL), were added ammonium formate (1.09 g, 17.3 mmol, 10 equiv) and 10% Pd/C (50 mg) and refluxed for 3 h under nitrogen atmosphere. The reaction mass was filtered through celite, the organic layer was concentrated *in vacuo* and the obtained residue was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (90:10) to afford pure product **15** as a pale yellow liquid (231 mg, 85% yield).

R_f : 0.2 (EtOAc–PE= 100:00);

Yield: 85%;

IR ($CHCl_3$): ν_{max} 3019, 1739, 1666 cm^{-1};

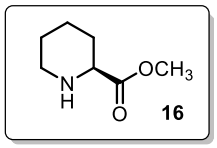
$[\alpha]_D^{25}$ –9.0 (*c* 0.5, $CHCl_3$), {lit.[16] $[\alpha]_D$ –9.6 (*c* 1.06, $CHCl_3$)};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.59 (br s, 1H), 4.16–4.01 (m, 1H), 3.77 (s, 3H), 2.43–2.29 (m, 2H), 2.27–2.02 (m, 1H), 1.96–1.67 (m, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 171.6 (2C), 54.6, 52.6, 30.9, 25.3, 19.3;

HRMS (ESI) *m/z* calcd for $C_7H_{11}O_3NNa$ $[M + Na]^+$: 180.0631, found: 180.0630.

Methyl (*S*)-piperidine-2-carboxylate (16).



To a stirred, cooled (0 °C) solution of amide **15** (0.2 g, 1.27 mmol, 1 equiv) in anhydrous THF (5 mL), BH_3·DMS (0.36 mL, 3.82 mmol, 3 equiv) was added dropwise. The resulting reaction mixture was further stirred at 5 °C for 20 h. Methanol (excess) was added to the reaction mixture, stirred for 4 h and concentrated under reduced pressure. Water (10 mL) was added and the reaction mixture was extracted using CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (40:60) afforded pure product **16** as a colorless thick liquid (142 mg, 78% yield).

R_f : 0.2 (EtOAc–PE= 50:50);

Yield: 78%;

IR ($CHCl_3$): ν_{max} 3414, 1730 cm^{-1};

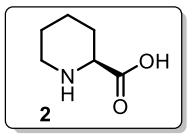
$[\alpha]_D^{25}$ –1.25 (*c* 0.5, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.02 (br s, 1H), 3.80 (s, 3H), 3.46–3.25 (m, 2H), 2.81–2.57 (m, 1H), 2.12–1.99 (m, 1H), 1.86–1.48 (m, 5H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 171.7, 64.1, 52.6, 52.1, 27.9, 23.9, 21.7;

HRMS (ESI) *m/z* calcd for $C_7H_{13}O_2NNa$ $[M + Na]^+$: 166.0838, found: 166.0836.

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



A mixture of amine **15** (100 mg, 0.69 mmol, 1 equiv) and 6 N HCl (10 mL) was kept at 120 ºC for 3 h. The solvent was removed under reduced pressure and the residue was dissolved in H_2O (50 mL). The mixture was loaded on an ion-exchange column (DOWEX 50W X8) and eluted with H_2O and then with aq. NH_3 solution. The

eluate of aq. NH_3 was concentrated to dryness under reduced pressure to give **2** (82 mg, 91%) as a white solid.

R_f : 0.4 (CH_2Cl_2–MeOH–NH_4OH= 9:1:1);

Yield: 91%;

M. p.: 270–272 °C, (lit.[1b] 271–274 °C);

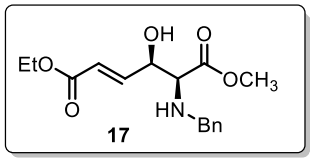
$[\alpha]_D^{25}$ –25.5 (*c* 1, H_2O), {lit.[1b] $[\alpha]_D$ –25.9 (*c* 1, H_2O)};

^{1}H NMR (D_2O, 400 MHz): δ 3.85 (dd, *J* = 3.4, 11.7 Hz, 1H), 3.44–3.36 (m, 1H), 3.03–2.93 (m, 1H), 2.23 (dd, *J* = 3.1, 13.9 Hz, 1H), 1.89–1.78 (m, 2H), 1.73–1.51 (m, 3H);

^{13}C NMR (D_2O, 100 MHz): δ 172.1, 57.1, 43.8, 25.8, 21.4, 21.3;

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

1-Ethyl 6-methyl (4*R*,5*S*,*E*)-5-(benzylamino)-4-hydroxyhex-2-enedioate (17).



17

To a stirred solution of ester **6** (1.1 g, 3.80 mmol, 1 equiv) in CH_3CN:H_2O (9:1, 20 mL), was added TFA (0.58 mL, 7.61 mmol, 2 equiv) dropwise at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred until complete disappearance of starting material (~ 7 h). The reaction mixture was quenched by excess $NaHCO_3$, water (10 mL) was added and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (30:70) afforded pure product **17** as a thick yellow liquid (865 mg, 74% yield).

R_f : 0.3 (EtOAc–PE= 30:70);

Yield: 74%;

IR ($CHCl_3$): ν_{max} 3422, 1721, 1659 cm^{-1};

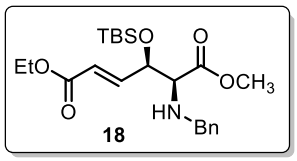
$[\alpha]_D^{25}$ +2.9 (*c* 2, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35–7.31 (m, 2H), 7.30–7.26 (m, 3H), 6.90 (dd, *J* = 4.6, 15.6 Hz, 1H), 6.14 (dd, *J* = 1.5, 15.6 Hz, 1H), 4.36–4.32 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.84 (d, *J* = 13.0 Hz, 1H), 3.75 (d, *J* = 13.0 Hz, 1H), 3.73 (s, 3H), 3.28 (d, *J* = 6.1 Hz, 1H), 2.70 (br s, 2H), 1.30 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.8, 166.1, 146.0, 138.7, 128.5 (2C), 128.3 (2C), 127.5, 122.3, 71.0, 64.6, 60.5, 52.6, 52.3, 14.2;

HRMS (ESI) *m/z* calcd for $C_{16}H_{22}O_5N$ [M + H]$^+$: 308.1492, found: 308.1491.

1-Ethyl 6-methyl (4*R*,5*S*,*E*)-5-(benzylamino)-4-((*tert*-butyldimethylsilyl)oxy)hex-2-enedioate (18).



18

To a stirred solution of hydroxyl amino ester **17** (0.85 g, 2.76 mmol, 1 equiv), imidazole (376 mg, 5.53 mmol, 2 equiv) and DMAP (34 mg, 0.27 mmol, 0.1 equiv) in CH_2Cl_2 (20 mL), was added TBSCl (0.83 g, 5.53 mmol, 2 equiv) dissolved in CH_2Cl_2 (10 mL) slowly at 0 °C after which reaction was heated to reflux for 6 h until completion of reaction. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was concentrated to dryness and residue was extracted with CH_2Cl_2 (3 X 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded TBS ether **18** as a thick colorless liquid (1 g, 86% yield).

R_f : 0.5 (EtOAc–PE= 20:80);

Yield: 86%;

IR ($CHCl_3$): ν_{max} 3417, 3023, 1720, 1655 cm^{-1};

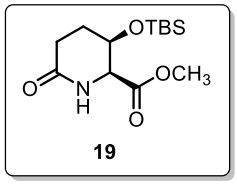
$[\alpha]_D^{25}$ –5.0 (*c* 3, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz): (mixture of invertomers) δ 7.38–7.31 (m, 4H), 7.31–7.24 (m, 1H), 7.08–7.00 (m, 1H), 6.00 (d, *J* = 16.0 Hz, 1H), 4.68–4.62 (m, 1H), 4.27 (q, *J* = 6.9 Hz, 2H), 4.00 (dd, *J* = 2.9, 13.5 Hz, 1H), 3.77–3.76 (m, 3H), 3.66 (dd, *J* = 2.7, 13.4 Hz, 1H), 3.34 (br s, 1H), 2.18 (br s, 1H), 1.39–1.33 (m, 3H), 0.92–0.91 (m, 9H), 0.05–0.03 (m, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.8, 166.1, 147.9, 139.7, 128.2 (2C), 128.1 (2C), 127.0, 121.8, 73.4, 64.9, 60.4, 51.82, 51.78, 25.6 (3C), 18.0, 14.2, -4.5, -5.4;

HRMS (ESI) *m/z* calcd for $C_{22}H_{36}O_5NSi$ [M + H]$^+$: 422.2357, found: 422.2361.

Methyl (2*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-6-oxopiperidine-2-carboxylate (19).



19

The amino ester **18** (0.85 g, 2.01 mmol, 1 equiv) was dissolved in methanol (10 mL) and to that was added catalytic amount of palladium hydroxide over carbon (10%, 20 mg). The resulting reaction mixture was stirred under a hydrogen atmosphere using balloon pressure for 2 h. The reaction mixture

was filtered through Celite and the filtrate was concentrated *in vacuo*. Purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (90:10) afforded TBS ether **19** as white solid (0.51 g, 88% yield).

R_f : 0.2 (EtOAc–PE= 90:10);

Yield: 88%;

M. p.: 70–72 °C;

IR ($CHCl_3$): ν_{max} 3410, 1741, 1664, 1216 cm^{-1};

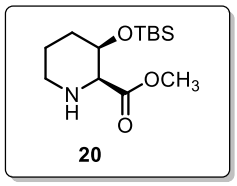
$[\alpha]_D^{25}$ –47.3 (*c* 0.8, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.21 (br s, 1H), 4.56–4.52 (m, 1H), 4.11 (d, *J* = 2.7 Hz, 1H), 3.77 (s, 3H), 2.62–2.51 (m, 1H), 2.38–2.29 (m, 1H), 2.03–1.87 (m, 2H), 0.82 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 169.2, 64.8, 60.5, 52.5, 27.6, 25.8, 25.4 (3C), 17.8, -4.5, -5.5;

HRMS (ESI) *m/z* calcd for $C_{13}H_{25}O_4NNaSi$ $[M + Na]^+$: 310.1445, found: 310.1441.

Methyl (2*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)piperidine-2-carboxylate (20).



20

To the stirred solution of amide **19** (0.4 g, 1.39 mmol, 1 equiv) in anhydrous THF (20 mL), was added BH_3·DMS (0.39 mL, 4.18 mmol, 3 equiv) dropwise at 0 ºC. The resulting reaction mixture was further stirred at 5 ºC for 20 h. Methanol (excess) was added to the reaction mixture, stirred for 4 h and concentrated under reduced pressure. Water (10 mL) was added and the reaction mixture was extracted using CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (30:70) afforded TBS ether **20** as a thick colorless liquid (247 mg, 65% yield).

R_f : 0.2 (EtOAc–PE= 50:50);

Yield: 65%;

IR ($CHCl_3$): ν_{max} 3420, 1730 cm^{-1};

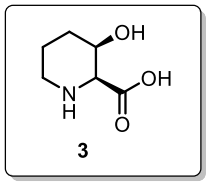
$[\alpha]_D^{25}$ –10.2 (*c* 0.4, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.16 (br s, 1H), 3.67 (s, 3H), 3.43 (d, *J* = 1.5 Hz, 1H), 3.14–3.07 (m, 1H), 2.61–2.54 (m, 1H), 2.15 (br s, 1H), 1.87–1.81 (m, 1H), 1.75–1.57 (m, 2H), 1.33–1.26 (m, 1H), 0.84 (s, 9H), 0.03 (s, 3H), -0.04 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.9, 66.6, 63.4, 51.6, 45.2, 31.8, 25.6 (3C), 20.2, 17.9, -4.6, -5.4;

HRMS (ESI) *m/z* calcd for $C_{13}H_{28}O_3NSi$ $[M + H]^+$: 274.1833, found: 274.1832.

(2*S*,3*R*)-3-Hydroxypiperidine-2-carboxylic acid (3).



3

A mixture of amine **20** (100 mg, 0.36 mmol, 1 equiv) and 6 N HCl (10 mL) was kept at 120 ºC for 3 h. The solvent was removed under reduced pressure and the residue was dissolved in H_2O (50 mL). The mixture was loaded on an ion-exchange column (DOWEX 50W X8) and eluted with H_2O and then with aq. NH_3 solution. The eluate of aq. NH_3 was concentrated to dryness under reduced pressure to give **3** (45 mg, 85%) as a white solid.

R_f : 0.2 ($CHCl_3$-MeOH-30% NH_4OH= 3:5:2);

Yield: 85%;

M. p.: 235–238 °C (decomp);

IR (neat): ν_{max} 3357, 1625, 1405 cm^{-1};

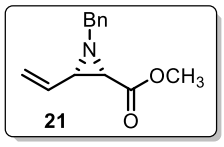
$[\alpha]_D^{25}$ –53.6 (*c* 0.6, H_2O), {lit.[12] $[\alpha]_D$ –52.8 (*c* 0.6, H_2O)};

^{1}H NMR (D_2O, 400 MHz): δ 4.44 (br s, 1H), 3.61 (s, 1H), 3.35 (d, *J* = 10.4 Hz, 1H), 2.99–2.89 (m, 1H), 1.98–1.86 (m, 2H), 1.78–1.62 (m, 2H);

^{13}C NMR (D_2O, 100 MHz): δ 172.3, 64.1, 62.2, 43.6, 28.7, 15.8;

HRMS (ESI) *m/z* calcd for $C_6H_{12}O_3N$ $[M + H]^+$: 146.0812, found: 146.0811.

Methyl (2*S*,3*S*)-1-benzyl-3-vinylaziridine-2-carboxylate (21).



21

To a stirred solution of bicyclolactone **7** (1.5 g, 4.37 mmol, 1 equiv) in anhydrous MeOH (15 mL), was added NaOMe (236 mg, 4.37 mmol, 1 equiv) at 0 °C and the reaction mixture was stirred for 1 h while gradually warming to room temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was treated with saturated aq. NH_4Cl and extracted with EtOAc (3 X 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and

filtered. The concentration of the organic layer *in vacuo* afforded crude aldehyde which was used in the next reaction without further purification.

To a stirred solution of methyl triphenylphosphonium bromide (5.46 g, 15.3 mmol, 3.5 equiv) in THF (30 mL) was added potassium *tert*-butoxide (1.57 g, 13.99 mmol, 3.2 equiv) at 0 °C and stirred for 1 h. To this, the above-obtained solution of aldehyde in THF (10 mL) was added dropwise at 0 °C and the reaction mixture was stirred for 6 h while warming to room temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was treated with saturated aq. NH_4Cl and extracted with EtOAc (3 X 100 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded pure product **21** as a pale yellow liquid (610 mg, 64% yield).

R_f : 0.5 (EtOAc–PE= 10:90);

Yield: 64%;

IR ($CHCl_3$): ν_{max} 1738, 1646 cm^{-1};

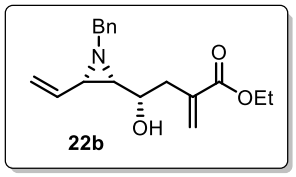
$[\alpha]_D^{25}$ +12.5 (*c* 4, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.31–7.15 (m, 5H), 5.88–5.65 (m, 1H), 5.35 (dd, *J* = 1.5, 17.3 Hz, 1H), 5.19 (dd, *J* = 1.5, 10.3 Hz, 1H), 3.66 (s, 3H), 3.61 (s, 2H), 2.47–2.37 (m, 2H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 169.3, 137.4, 133.2, 128.3 (2C), 127.7 (2C), 127.2, 119.5, 63.2, 52.0, 47.9, 44.1;

HRMS (ESI) *m/z* calcd for $C_{13}H_{16}O_2N$ $[M + H]^+$: 218.1176, found: 218.1173.

Ethyl (*S*)-4-((2*S*,3*S*)-1-benzyl-3-vinylaziridin-2-yl)-4-hydroxy-2-methylenebutanoate (22b).



22b

To a stirred solution of *cis*-vinylaziridine-2-carboxylate **21** (0.5 g, 2.30 mmol, 1 equiv) in dry CH_2Cl_2 (15 mL) was added DIBAL-H (4.6 mL, 1 M solution in toluene, 4.60 mmol, 2 equiv) at -78 °C slowly over period of 10 min and the reaction mixture was stirred at same temperature for 30 min. The reaction was quenched by the careful addition of pre-cooled MeOH (2 mL) and allowed to warm to 0 °C. Roche's salt (saturated solution of sodium potassium tartrate, 5 mL) was added and stirred for 0.5 h. The compound was extracted with CH_2Cl_2 (3 X 20 mL) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under

reduced pressure to furnish crude aldehyde which was used for the next reaction without further purification.

To the solution of crude aldehyde obtained from the above reaction in THF (10 mL), was added ethyl 2-(bromomethyl)acrylate (0.53 g, 2.76 mmol, 1.2 equiv), activated zinc powder (0.45 g, 6.91 mmol, 3 equiv) and saturated aq. solution of NH_4Cl (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for additional 10 min. The reaction mixture was filtered through a simple filter paper and thoroughly washed with ethyl acetate (3 X 10 mL). Water was added to the filtrate and the organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated to give a crude residue that was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (15:85) to afford pure product **22a** as a colorless syrup (290 mg, 42% yield).

Further elution of the column with EtOAc–PE (20:80) as eluent furnished **22b** (290 gm, 42% yield) as a thick colorless liquid.

To the solution of **22a** (100 mg, 3.32 mmol, 1 equiv) in toluene (10 mL), were added triphenylphosphine (217 mg, 0.83 mmol, 2.5 equiv), *p*-nitrobenzoic acid (138 mg, 0.83 mmol, 2.5 equiv) and DEAD (0.13 mL, 0.83 mmol, 2.5 equiv) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 2.5 h and the progress of the reaction was monitored by TLC. To the reaction mass, water (5 mL) was added and the compound was extracted with EtOAc (3 X 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a crude product which was used for the next reaction without further purification.

The above crude product was dissolved in absolute ethanol (5 mL) and to the solution was added NaOEt (25 mg, 0.36 mmol, 1.1 equiv) at -20 °C. The reaction mixture was stirred further for 0.5 h at the same temperature. Drops of acetic acid were added to the reaction mixture to adjust the pH to 7. The solution was diluted with water (5 mL) and extracted with EtOAc (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (20:80) to afford pure product **22b** as a thick colorless liquid (67 mg, 67% yield over two steps).

R_f : 0.2 (EtOAc–PE= 50:50);

Yield: 67%;

IR ($CHCl_3$): ν_{max} 3425, 1709, 1634 cm^{-1};

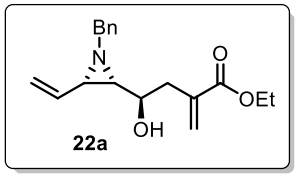
$[\alpha]_D^{25}$ +27.3 (*c* 3.5, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.35–7.14 (m, 5H), 6.17 (d, *J* = 1.4 Hz, 1H), 5.74–5.57 (m, 1H), 5.55 (d, *J* = 1.4 Hz, 1H), 5.35–5.07 (m, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.63–3.41 (m, 3H), 2.54 (br s, 1H), 2.45–2.29 (m, 2H), 2.20 (t, *J* = 7.2 Hz, 1H), 1.79 (t, *J* = 6.8 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 167.1, 138.6, 136.7, 134.3, 128.4 (2C), 128.0 (2C), 127.6, 127.2, 118.3, 68.0, 63.9, 60.7, 50.0, 46.4, 37.8, 14.1;

HRMS (ESI) *m/z* calcd for $C_{18}H_{24}O_3N$ $[M + H]^+$: 302.1751, found: 302.1752.

Ethyl (*R*)-4-((2*S*,3*S*)-1-benzyl-3-vinylaziridin-2-yl)-4-hydroxy-2-methylenebutanoate (22a).



22a

R_f: 0.25 (EtOAc–PE= 50:50);

Yield: 42%;

IR ($CHCl_3$): ν_{max} 3425, 1709, 1634 cm^{-1};

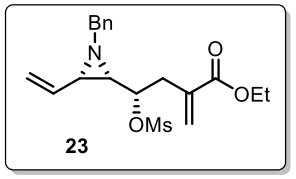
$[\alpha]_D^{25}$ +16.5 (*c* 4, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.31–7.17 (m, 5H), 6.16 (d, *J* = 1.4 Hz, 1H), 5.90–5.69 (m, 1H), 5.53 (d, *J* = 1.1 Hz, 1H), 5.39–5.12 (m, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.72–3.62 (m, 2H), 3.45 (d, *J* = 13.3 Hz, 1H), 2.83 (br s, 1H), 2.51–2.29 (m, 2H), 2.21 (t, *J* = 7.1 Hz, 1H), 1.77 (t, *J* = 6.9 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 167.9, 138.6, 137.2, 134.7, 128.3 (2C), 128.1 (2C), 127.6, 127.1, 118.1, 68.8, 63.7, 61.0, 49.0, 46.0, 37.9, 14.1;

HRMS (ESI) *m/z* calcd for $C_{18}H_{24}O_3N$ $[M + H]^+$: 302.1751, found: 302.1752.

Ethyl (*S*)-4-((2*S*,3*S*)-1-benzyl-3-vinylaziridin-2-yl)-2-methylene-4-((methylsulfonyl)oxy)butanoate (23).



23

To a stirred solution of alcohol **22b** (0.15 g, 0.49 mmol, 1 equiv) in CH_2Cl_2 (15 mL), was added triethylamine (0.24 mL, 1.74 mmol, 3.5 equiv) followed by mesyl chloride (0.11 mL, 1.49 mmol, 3 equiv) at 0 °C. The reaction mixture was allowed to stir at room temperature for 2 h under nitrogen atmosphere. The completion of the reaction was monitored by TLC and the reaction mixture was poured in cold water. The compound was extracted with CH_2Cl_2 (3 X 10 mL) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated

under reduced pressure to furnish a residue which was purified by silica gel (230–400 mesh) column chromatography using EtOAc–PE (20:80) to afford pure product **23** as a yellow liquid (163 mg, 86% yield).

R_f : 0.5 (EtOAc–PE= 30:70);

Yield: 86%;

IR ($CHCl_3$): ν_{max} 1711, 1637, 1206 cm^{-1};

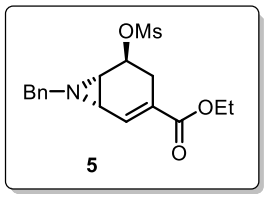
$[\alpha]_D^{25}$ +32.8 (*c* 3, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.26 (m, 5H), 6.33 (s, 1H), 5.73 (s, 1H), 5.72–5.64 (m, 1H), 5.40 (d, *J* = 17.1 Hz, 1H), 5.28 (d, *J* = 10.4 Hz, 1H), 4.48 (dt, *J* = 4.6, 8.7 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.54 (s, 2H), 2.78–2.72 (m, 1H), 2.65 (s, 3H), 2.64–2.59 (m, 1H), 2.30 (t, *J* = 6.7 Hz, 1H), 2.07 (dd, *J* = 7.0, 9.5 Hz, 1H), 1.30 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.2, 138.0, 134.5, 133.2, 129.5, 128.5 (2C), 128.4 (2C), 127.5, 119.2, 82.3, 64.0, 60.8, 47.8, 45.6, 38.0, 36.6, 14.1;

HRMS (ESI) *m/z* calcd for $C_{19}H_{26}O_5NS$ $[M + H]^+$: 380.1526, found: 380.1527.

Ethyl (1*S*,5*S*,6*S*)-7-benzyl-5-((methylsulfonyl)oxy)-7-azabicyclo[4.1.0]hept-2-ene-3-carboxylate (5).



5

To the solution of the olefin compound **23** (100 mg, 0.26 mmol, 1 equiv) in dry CH_2Cl_2 (100 mL), were added titanium tetraisopropoxide (0.04 mL, 0.13 mmol, 0.5 equiv) and Grubbs' 2nd generation catalyst (22 mg, 0.026 mmol, 0.1 equiv). The reaction mixture was refluxed for 15 h and the completion of the reaction was monitored with TLC. The reaction mixture was filtered through celite bed and thoroughly washed with CH_2Cl_2 (3 X 50 mL). The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (15:85) afforded compound **5** as a yellow liquid (69 mg, 75% yield).

R_f : 0.4 (EtOAc–PE= 30:70);

Yield: 75%;

IR ($CHCl_3$): ν_{max} 1707, 1641, 1358, 1217 cm^{-1};

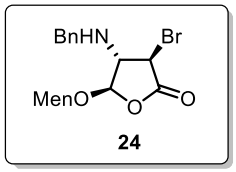
$[\alpha]_D^{25}$ –65.6 (*c* 0.5, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.28 (m, 6H), 5.45–5.41 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.65 (d, *J* = 13.4 Hz, 1H), 3.57 (d, *J* = 13.4 Hz, 1H), 3.02 (s, 3H), 2.97 (t, *J* = 1.9 Hz, 1H), 2.61 (td, *J* = 2.5, 5.7 Hz, 1H), 2.50 (td, *J* = 3.8, 17.5 Hz, 1H), 2.31 (t, *J* = 5.3 Hz, 1H), 1.30 (t, *J* = 6.9 Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.0, 137.9, 136.4, 128.5 (2C), 127.7 (2C), 127.4, 126.8, 73.6, 62.7, 60.9, 44.0, 38.8, 35.6, 27.6, 14.2;

HRMS (ESI) *m/z* calcd for $C_{17}H_{22}O_5NS$ $[M + H]^+$: 352.1213, found: 352.1213.

(3*R*,4*S*,5*R*)-4-(Benzylamino)-3-bromo-5-(((1*R*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl)oxy)dihydrofuran-2(3*H*)-one (24).



24

To a stirred solution of bromolactone **10b** (10 g, 0.031 mol, 1 equiv) in DMSO (100 mL), were added triethylamine (4.88 mL, 0.035 mol, 1.1 equiv) followed by benzylamine (3.45 mL, 0.031 mol, 1 equiv) at room temperature. The reaction mixture was stirred at room temperature for 30 min. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was treated with cold water (100 mL) and extracted with EtOAc (3 X 100 mL). The combined organic layer was washed with water (2 X 50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded pure product **24** as a pale yellow liquid (9.37 g, 70% yield).

R_f : 0.3 (EtOAc–PE= 10:90);

Yield: 70%;

IR ($CHCl_3$): ν_{max} 3427, 1770 cm^{-1};

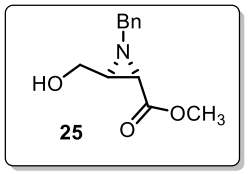
$[\alpha]_D^{25}$ –104.5 (*c* 2.5, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.39–7.29 (m, 5H), 5.51 (d, *J* = 3.3 Hz, 1H), 4.29 (d, *J* = 5.8 Hz, 1H), 3.92 (s, 2H), 3.65–3.49 (m, 2H), 2.32–2.05 (m, 2H), 1.98 (br s, 1H), 1.74–1.62 (m, 2H), 1.50–1.17 (m, 3H), 0.97–0.87 (m, 8H), 0.79 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 170.1, 138.5, 128.7 (2C), 128.2 (2C), 127.7, 104.1, 78.4, 68.0, 51.6, 47.6, 41.4, 39.5, 34.2, 31.3, 25.1, 22.8, 22.2, 20.9, 15.5;

HRMS (ESI) *m/z* calcd for $C_{21}H_{31}O_3NBr$ $[M + H]^+$: 424.1482, found: 424.1479.

Methyl (2*S*,3*S*)-1-benzyl-3-(hydroxymethyl)aziridine-2-carboxylate (25).



To a stirred, cooled (0 °C) solution of compound **24** (1 g, 2.36 mmol, 1 equiv) in MeOH (40 mL), were added $NaOCH_3$ (127 mg, 2.36 mmol, 1 equiv) followed by $NaBH_4$ (89 mg, 2.36 mmol, 1 equiv) and the reaction mixture was stirred for 1 h at 0 °C. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was treated with 1 N HCl to adjust the pH to 7 and extracted with EtOAc (3 X 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (30:70) afforded pure product **25** as a colorless liquid (0.27 g, 52% yield).

R_f : 0.2 (EtOAc–PE= 50:50);

Yield: 52%;

IR ($CHCl_3$): ν_{max} 3417, 1730 cm^{-1};

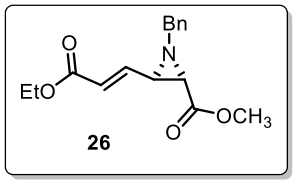
$[\alpha]_D^{25}$ +72.2 (*c* 3, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.40–7.26 (m, 5H), 4.03 (d, *J* = 13.4 Hz, 1H), 3.93 (d, *J* = 13.4 Hz, 1H), 3.82–3.72 (m, 1H), 3.70 (s, 3H), 3.59–3.41 (m, 1H), 2.75 (d, *J* = 2.9 Hz, 1H), 2.60 (q, *J* = 3.2 Hz, 1H), 2.41 (br s, 1H);

^{13}C NMR ($CDCl_3$, 50 MHz): δ 169.3, 138.7, 128.4 (2C), 128.2 (2C), 127.2, 61.0, 54.5, 52.2, 46.9, 37.4;

HRMS (ESI) *m/z* calcd for $C_{12}H_{16}O_3N$ $[M + H]^+$: 222.1125, found: 222.1124.

Methyl (2*S*,3*R*)-1-benzyl-3-((*E*)-3-ethoxy-3-oxoprop-1-en-1-yl)aziridine-2-carboxylate (26).



To a stirred solution of compound **24** (1.5 g, 3.54 mmol, 1 equiv) in anhydrous MeOH (15 mL), was added NaOMe (191 mg, 3.54 mmol, 1 equiv) at 0 °C and the reaction mixture was stirred for 30 min at that temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was treated with saturated aq. NH_4Cl and extracted with EtOAc (3 X 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of the organic layer *in vacuo* afforded crude aldehyde which was used in the next reaction without further purification.

To a stirred solution of aldehyde in CH_2Cl_2 (30 mL) was added (carbethoxymethylene) triphenylphosphorane (1.48 g, 4.25 mmol, 1.2 equiv) and the reaction mixture was stirred for 6 h at room temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was concentrated to dryness and residue was extracted with EtOAc (3 X 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded pure product **26** as a pale yellow liquid (0.66 g, 64% yield).

R_f : 0.5 (EtOAc–PE= 30:70);

Yield: 64%;

IR ($CHCl_3$): ν_{max} 1716, 1651, 1215, 770 cm^{-1};

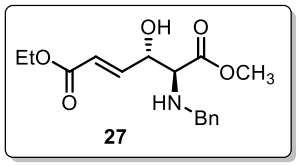
$[\alpha]_D^{25}$ +29.41 (*c* 1, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 200 MHz): (mixture of invertomers) δ 7.41–7.22 (m, 5H), 6.99–6.56 (m, 1H), 6.33–6.00 (m, 1H), 4.31–4.13 (m, 2H), 4.13–3.79 (m, 2H), 3.72 (s, 3H), 3.20–2.92 (m, 1H), 2.76–2.61 (m, 1H), 1.29 (t, *J* =7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz): (mixture of invertomers) δ 168.6, 165.7, 145.3, 140.2, 138.4, 137.6, 128.4, 128.0, 127.8, 127.2, 123.5, 60.6, 60.5, 56.5, 54.7, 54.6, 52.4, 46.2, 45.7, 44.5, 42.8, 14.2;

HRMS (ESI) *m/z* calcd for $C_{16}H_{20}O_4N$ $[M + H]^+$: 290.1387, found: 290.1384.

1-Ethyl 6-methyl (4*S*,5*S*,*E*)-5-(benzylamino)-4-hydroxyhex-2-enedioate (27).



27

To a stirred solution of ester **26** (0.6 g, 2.07 mmol, 1 equiv) in CH_3CN:H_2O (9:1, 20 mL), was added TFA (0.32 mL, 4.15 mmol, 2 equiv) dropwise at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred until complete disappearance of starting material (~ 7 h). The reaction mixture was quenched by excess $NaHCO_3$, water (10 mL) was added and extracted with EtOAc (3 X 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (30:70) afforded pure product **27** as a yellow solid (452 mg, 71% yield).

R_f : 0.3 (EtOAc–PE= 30:70);

Yield: 71%;

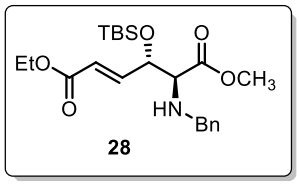
M. p.: 77–79 °C;

IR ($CHCl_3$): ν_{max} 3427, 3021, 1722, 1651 cm^{-1};

$[\alpha]_D^{25}$ +35.35 (*c* 1.7, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37–7.27 (m, 5H), 6.78 (dd, *J* = 4.2, 15.6 Hz, 1H), 6.11 (dd, *J* = 1.9, 15.6 Hz, 1H), 4.57–4.53 (m, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.93 (d, *J* = 13.0 Hz, 1H), 3.76 (s, 3H), 3.68 (d, *J* = 13.0 Hz, 1H), 3.57 (d, *J* = 5.3 Hz, 1H), 2.34 (br s, 2H), 1.28 (t, *J* = 7.2 Hz, 3H);
^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.2, 165.9, 145.1, 138.8, 128.5 (2C), 128.4 (2C), 127.5, 122.8, 70.1, 64.2, 60.5, 52.5, 52.2, 14.1;
HRMS (ESI) *m/z* calcd for $C_{16}H_{22}O_5N$ $[M + H]^+$: 308.1492, found: 308.1491.

1-Ethyl 6-methyl (4*S*,5*S*,*E*)-5-(benzylamino)-4-((*tert*-butyldimethylsilyl)oxy)hex-2-enedioate (28).



28

To a stirred solution of amino alcohol **27** (0.35 g, 1.14 mmol, 1 equiv), imidazole (155 mg, 2.28 mmol, 2 equiv) and DMAP (14 mg, 0.11 mmol, 0.1 equiv) in CH_2Cl_2 (20 mL), was added TBSCl (342 mg, 2.28 mmol, 2 equiv) dissolved in CH_2Cl_2 (10 mL) slowly at 0 °C after which reaction was heated to reflux for 6 h until completion of reaction. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was concentrated to dryness and residue was extracted with CH_2Cl_2 (3 X 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (10:90) afforded TBS ether **28** as a thick yellow liquid (393 mg, 82% yield).

R_f : 0.5 (EtOAc–PE= 20:80);

Yield: 82%;

IR ($CHCl_3$): ν_{max} 3426, 1719, 1656 cm^{-1};

$[\alpha]_D^{25}$ –6.4 (*c* 2.4, $CHCl_3$);

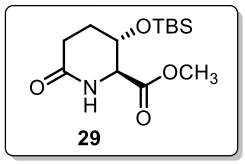
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33–7.28 (m, 4H), 7.27–7.21 (m, 1H), 6.98 (dd, *J* = 5.3, 15.6 Hz, 1H), 6.00 (dd, *J* = 1.3, 15.4 Hz, 1H), 4.51–4.46 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.86 (d, *J*

= 13.4 Hz, 1H), 3.71 (s, 3H), 3.68 (d, *J* = 13.4 Hz, 1H), 3.35 (d, *J* = 5.7 Hz, 1H), 1.98 (br s, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.8, 166.1, 147.3, 139.3, 128.3 (2C), 128.2 (2C), 127.1, 121.9, 73.5, 66.0, 60.4, 52.2, 51.7, 25.6 (3C), 18.0, 14.2, -4.5, -5.2;

HRMS (ESI) *m/z* calcd for $C_{22}H_{36}O_5NSi$ $[M + H]^+$: 422.2357, found: 422.2358.

Methyl (2*S*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)-6-oxopiperidine-2-carboxylate (29).



29

The amino ester **28** (0.35 g, 0.83 mmol, 1 equiv) was dissolved in methanol (10 mL) and to that was added catalytic amount of palladium hydroxide over carbon (10%, 20 mg). The resulting reaction mixture was stirred under a hydrogen atmosphere using balloon pressure for 2 h. The reaction mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. Purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (50:50) afforded TBS ether **29** as off white solid (215 mg, 90% yield).

R_f : 0.3 (EtOAc–PE= 50:50);

Yield: 90%;

M. p.: 87 °C;

IR ($CHCl_3$): ν_{max} 3404, 1743, 1666 cm^{-1};

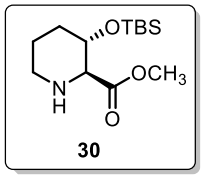
$[\alpha]_D^{25}$ –56.0 (*c* 1, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.62 (br s, 1H), 4.32 (d, *J* = 3.1 Hz, 1H), 4.02 (br s, 1H), 3.75 (s, 3H), 2.59 (td, *J* = 8.8, 17.2 Hz, 1H), 2.30 (td, *J* = 4.6, 17.7 Hz, 1H), 1.86–1.76 (m, 2H), 0.87 (s, 9H), 0.09 (s, 6H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.5, 170.7, 65.4, 62.2, 52.6, 26.5, 26.4, 25.5 (3C), 17.9, -4.9, -5.1;

HRMS (ESI) *m/z* calcd for $C_{13}H_{25}O_4NNaSi$ $[M + Na]^+$: 310.1445, found: 310.1442.

Methyl (2*S*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)piperidine-2-carboxylate (30).



30

To the stirred solution of amide **29** (0.2 g, 0.69 mmol, 1 equiv) in anhydrous THF (20 mL), was added BH_3·DMS (0.2 mL, 2.09 mmol, 3 equiv) dropwise at 0 ºC. The resulting reaction mixture was further stirred at 5 °C for 20 h. Methanol (excess) was added to the reaction mixture, stirred for 4 h and concentrated under reduced pressure. Water (10 mL) was added and the reaction mixture was

extracted using CH_2Cl_2 (3 X 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. The concentration of organic layer *in vacuo* followed by purification of the obtained residue by silica gel (230–400 mesh) column chromatography using EtOAc–PE (50:50) afforded TBS ether **30** as a thick yellow liquid (129 mg, 68% yield).

R_f : 0.2 (EtOAc–PE= 50:50);

Yield: 68%;

IR ($CHCl_3$): ν_{max} 3422, 1737, 1216 cm^{-1};

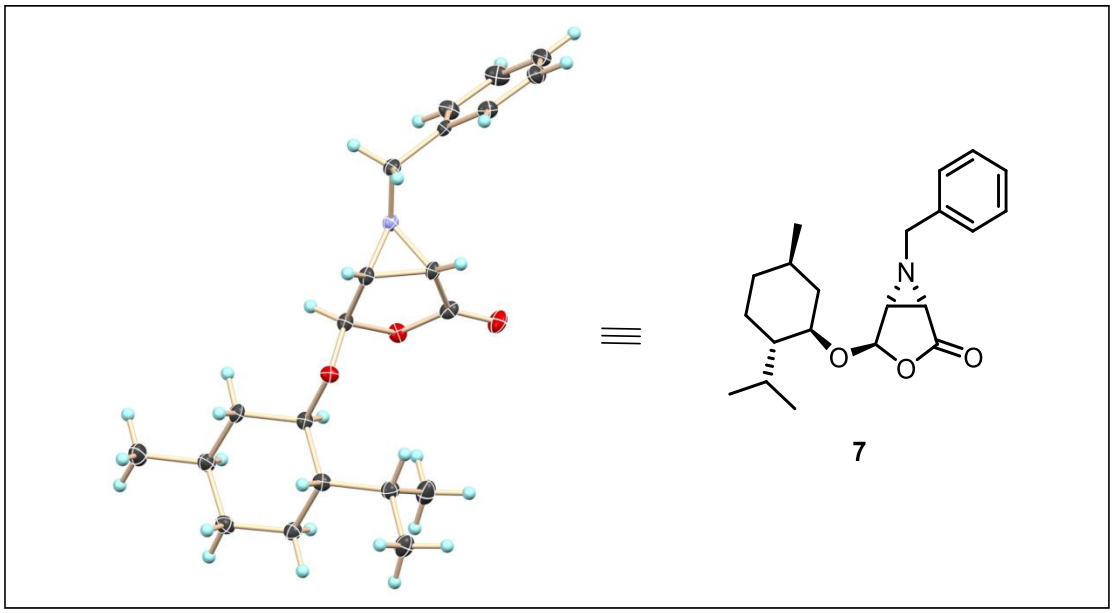
$[\alpha]_D^{25}$ –12.2 (*c* 1.2, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.71 (s, 3H), 3.71–3.66 (m, 1H), 3.20 (d, *J* = 8.4 Hz, 1H), 3.02–2.95 (m, 1H), 2.57–2.49 (m, 1H), 2.01–1.95 (m, 1H), 1.84 (br s, 1H), 1.75–1.70 (m, 1H), 1.52–1.39 (m, 2H), 0.85 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.2, 70.8, 66.2, 51.8, 44.9, 33.8, 25.7, 25.6 (3C), 17.8, -4.3, -5.2;

HRMS (ESI) *m/z* calcd for $C_{13}H_{28}O_3NSi$ $[M + H]^+$: 274.1833, found: 274.1833.

3.3.4.2. X–ray crystallography details of compound 7



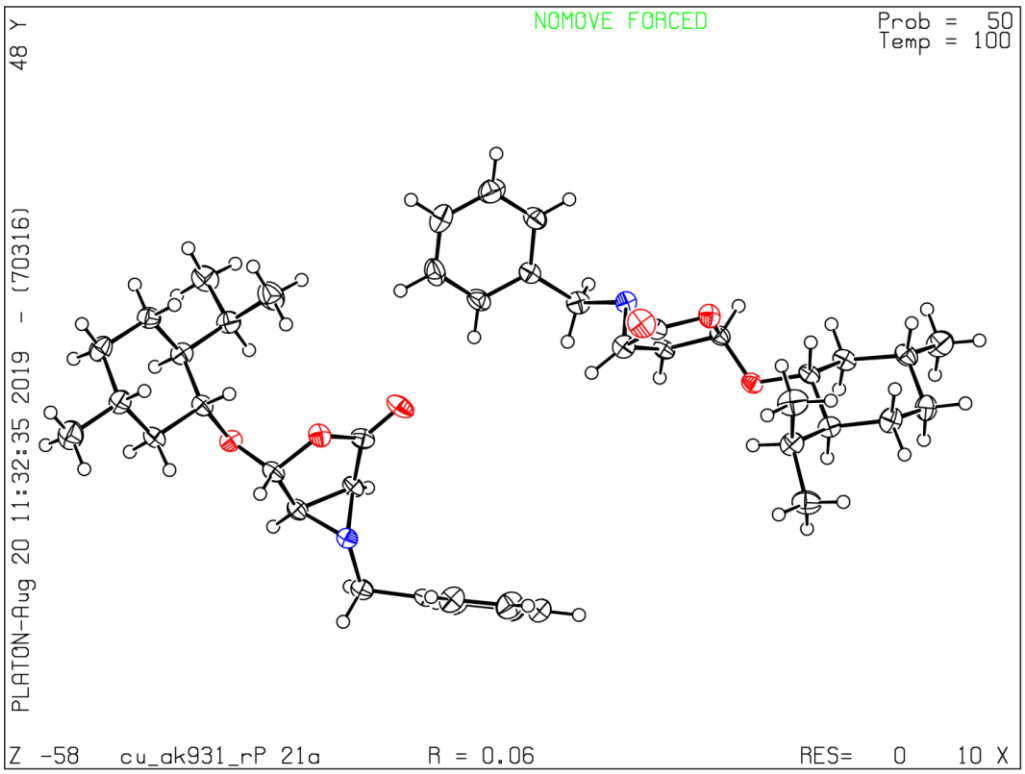


Table 1: Crystallographic Information for compound **7**

Crystal Data	**AK_931**
Formula	$C_{21}H_{29}NO_3$
M_r	343.45
Crystal Size, mm	0.101 x 0.050 x 0.010
Temp. (K)	100(2)
Crystal Syst.	Monoclinic
Space Group	$P2_1$
a/Å	5.4948(2)
b/Å	36.7789(16)
c/Å	10.1107(4)
α/°	90
β/°	105.460(2)
γ/°	90
V/Å^3	1969.37(14)
Z	4
D_{calc}/g cm^{-3}	1.158
μ/mm^{-1}	0.608
F(000)	744
Ab. Correct.	multi-scan
T_{min}/ T_{max}	0.941/0.994
$2\theta_{max}$	149.8
Total reflns.	41795
Unique reflns.	7996
Obs. reflns.	7221
h, k, l (min, max)	(-6, 5), (-45, 45), (-12, 12)
R_{int}	0.0870
No. of parameters	457
R1 [$I > 2\sigma(I)$]	0.0620
wR2[$I > 2\sigma(I)$]	0.1519

R1 [all data]	0.0683
wR2 [all data]	0.1554
goodness-of-fit	1.074
$\Delta\rho_{max}$, $\Delta\rho_{min}$(eÅ^{-3})	+0.310, -0.279

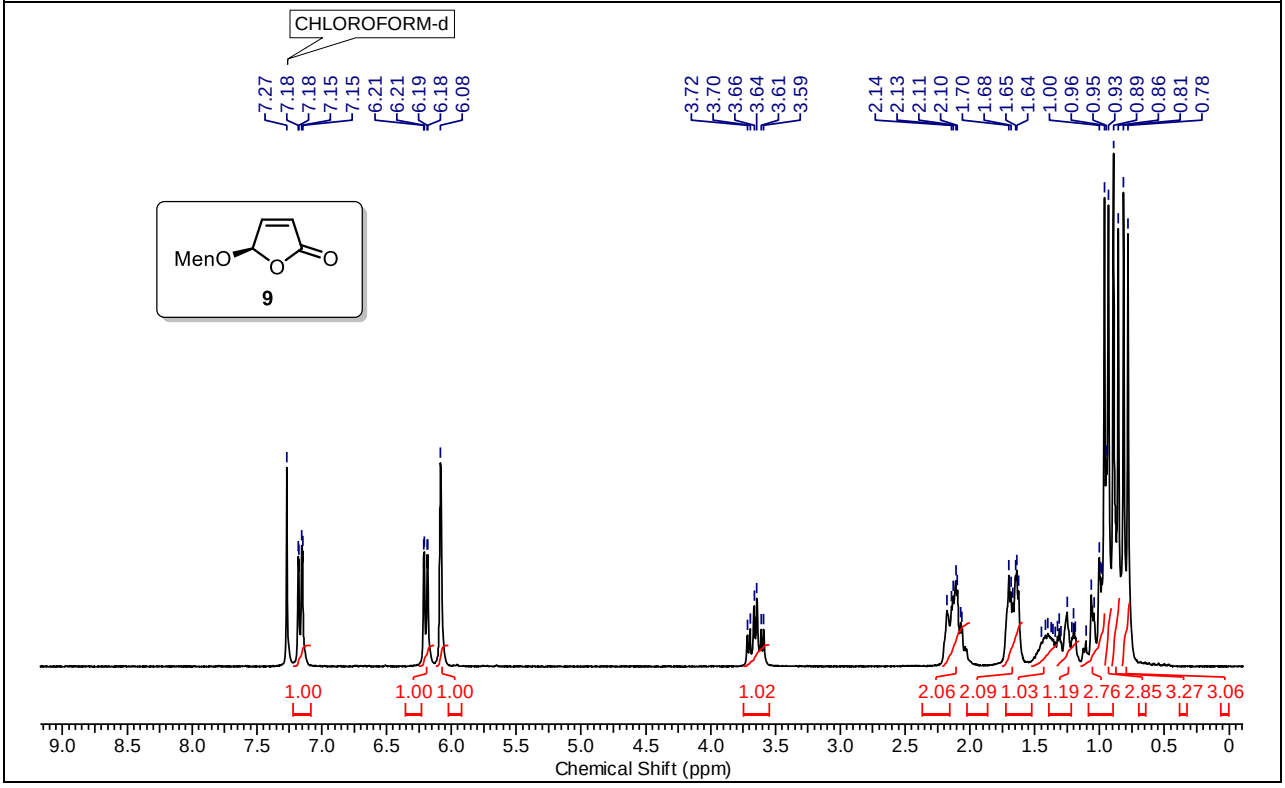
X-ray intensity data measurement of compound **7** was carried out on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatech multilayer mirrors optics. The intensity measurements were carried out with Cu micro-focus sealed tube diffraction source (Cu-Kα = 1.54178 Å) at 100(2) K temperature. The X-ray generator was operated at 50 kV and 1.4 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 12 frames. Data were collected with ω scan width of 0.5º at different settings of φ and ω with a frame time of 15-20 secs keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX3 program (Bruker, 2016). All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2016).[1] SHELX-97 was used for structure solution and full-matrix least-squares refinement on F^2.[2] Positions of the H-atoms were calculated as per the hybridization and constrained to ride on their parent atoms. Single crystal-XRD data of sample **7** are summarized in table 1. An *ORTEP* III[3] of compound **7** was drawn at the 30% probability displacement ellipsoids level and H atoms are shown as small spheres of arbitrary radii.

References

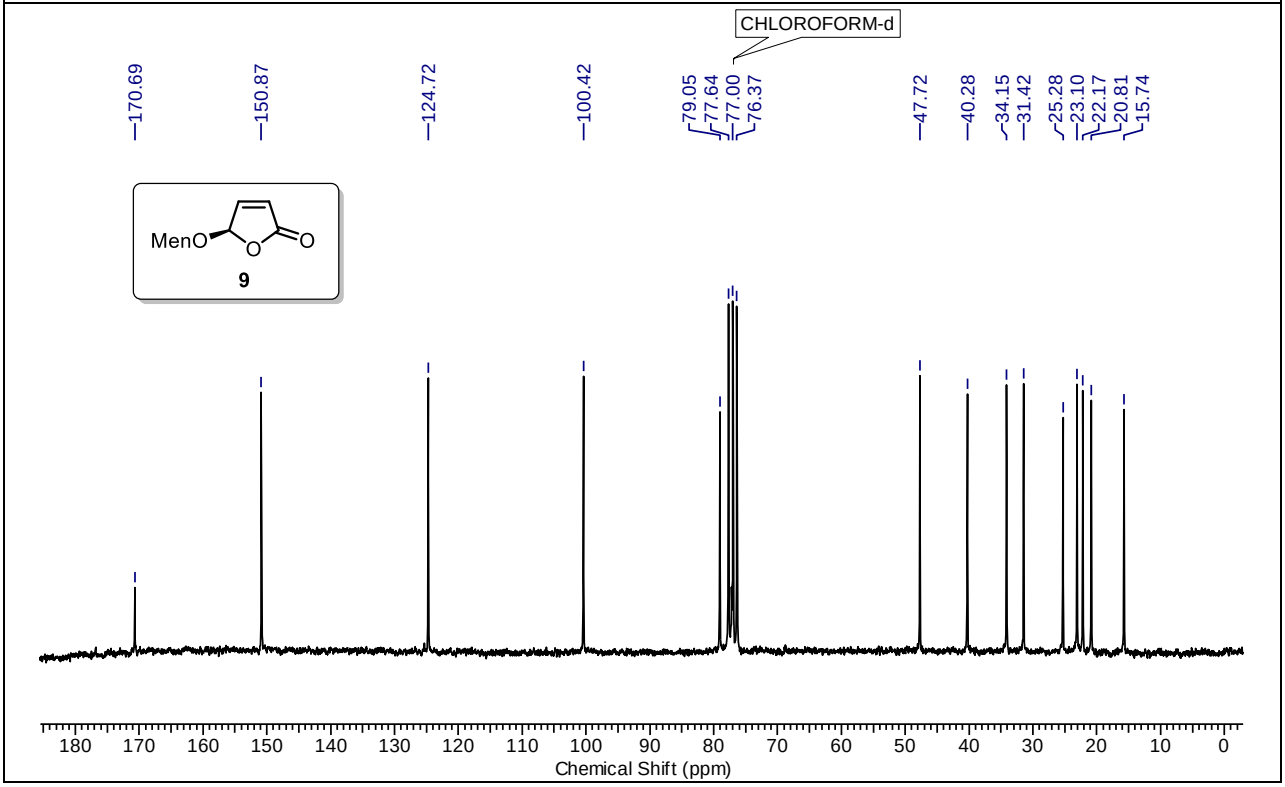
1. Bruker (**2016**). *APEX3, SAINT* and *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA.
2. Sheldrick, G. M. *Acta Cryst.* **2008**, A64, 112.
3. Farrugia, L. J. *J. Appl. Cryst.* **2012**, 45, 849.

3.3.5. Spectral Data

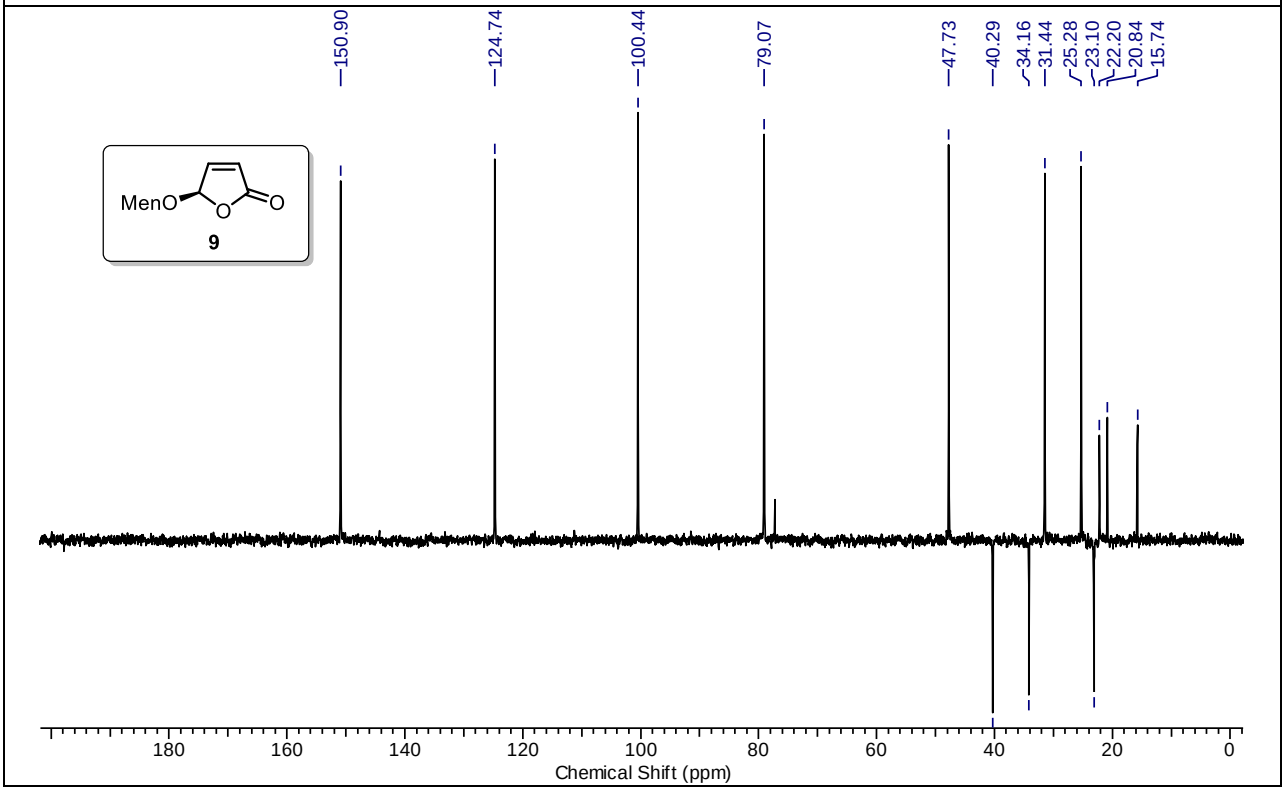
^{1}H-NMR spectrum of compound 9 ($CDCl_3$, 200 MHz)



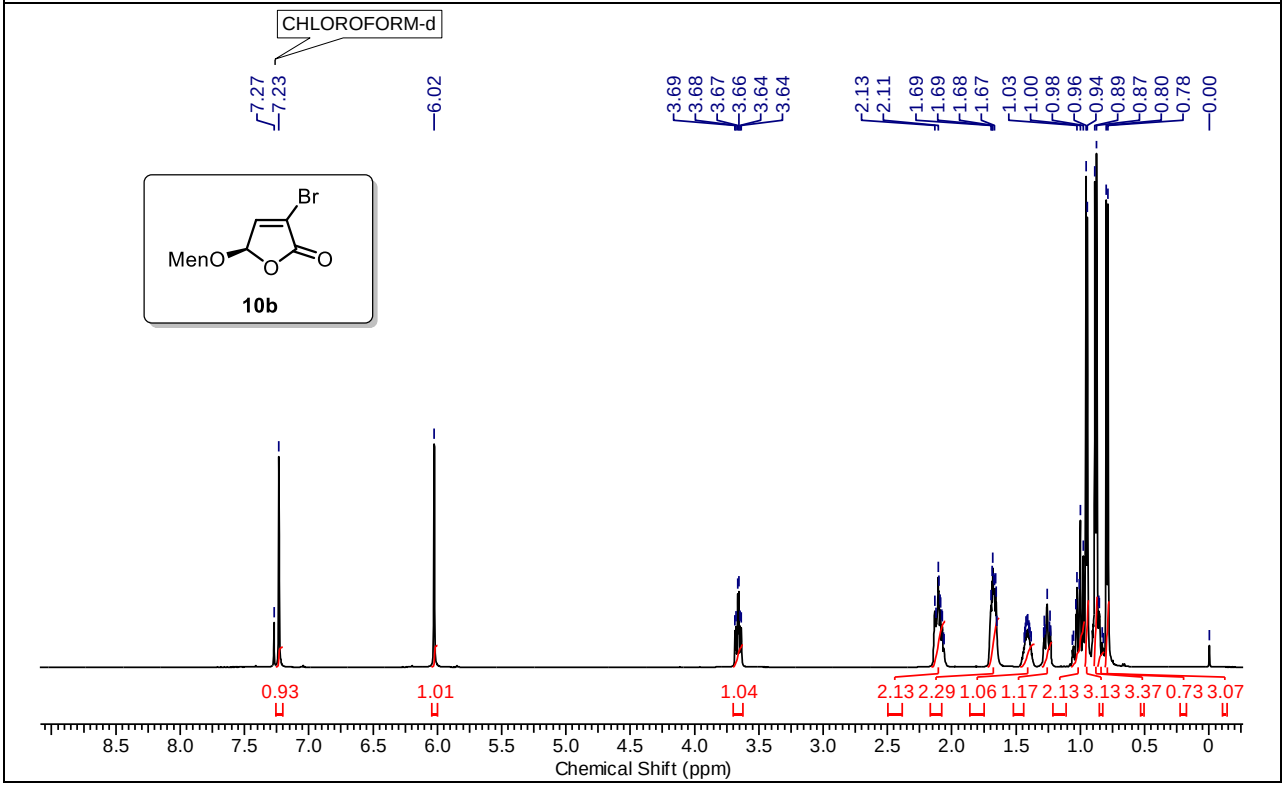
^{13}C-NMR spectrum of compound 9 ($CDCl_3$, 50 MHz)



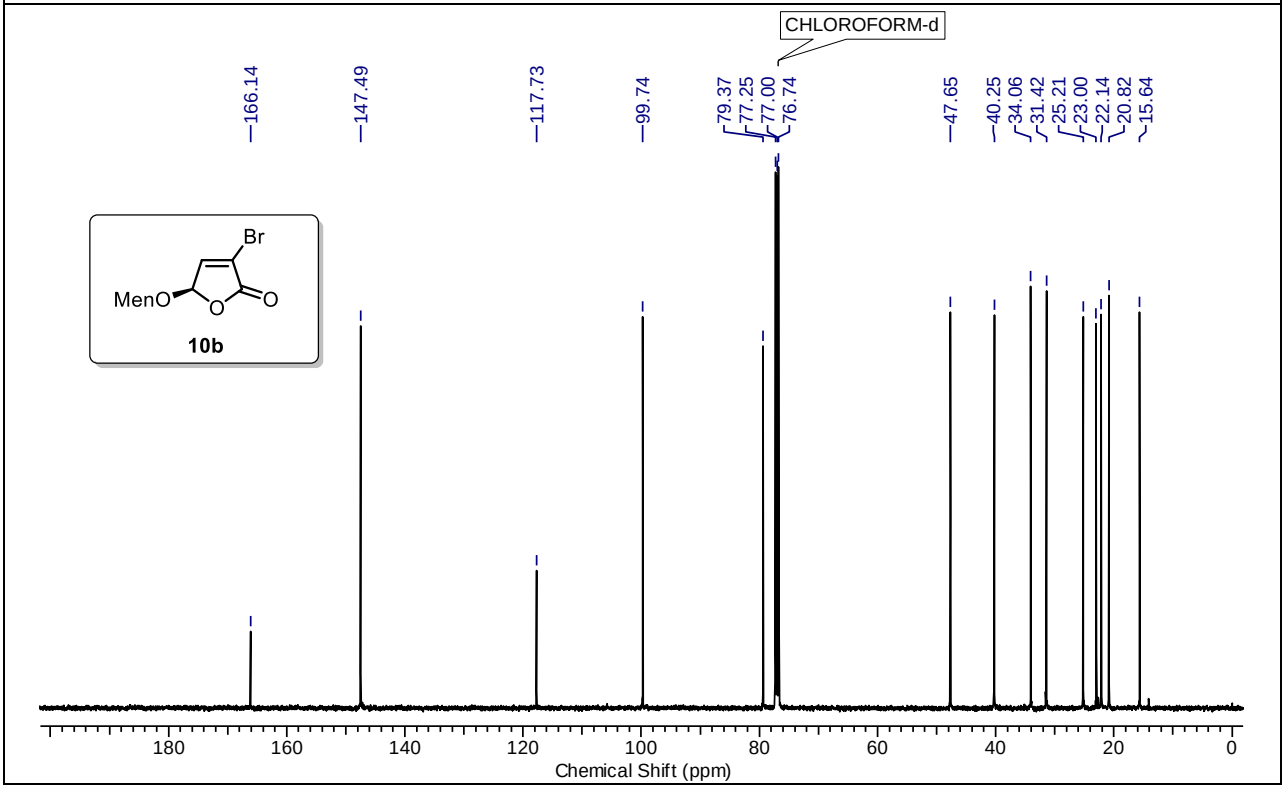
DEPT NMR spectrum of compound 9 ($CDCl_3$, 50 MHz)



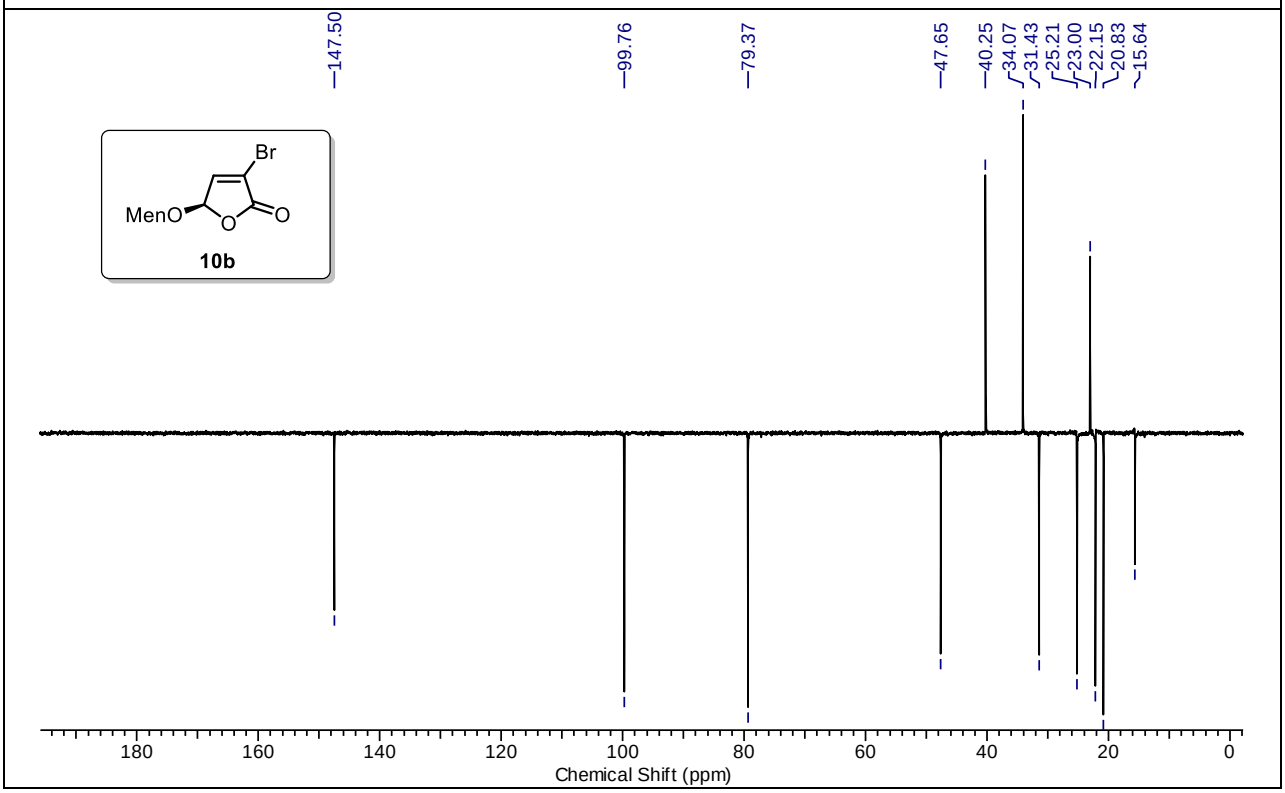
^{1}H-NMR spectrum of compound 10b ($CDCl_3$, 500 MHz)



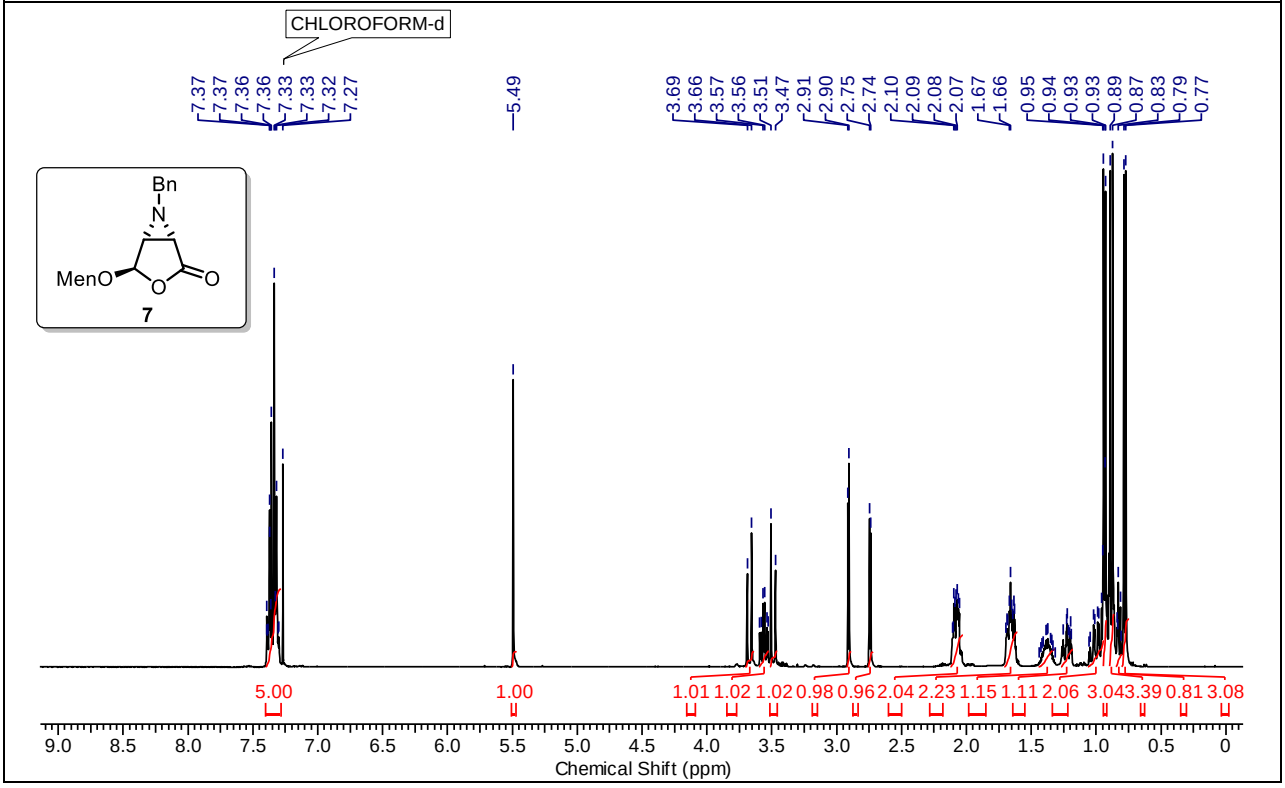
^{13}C-NMR spectrum of compound 10b ($CDCl_3$, 125 MHz)



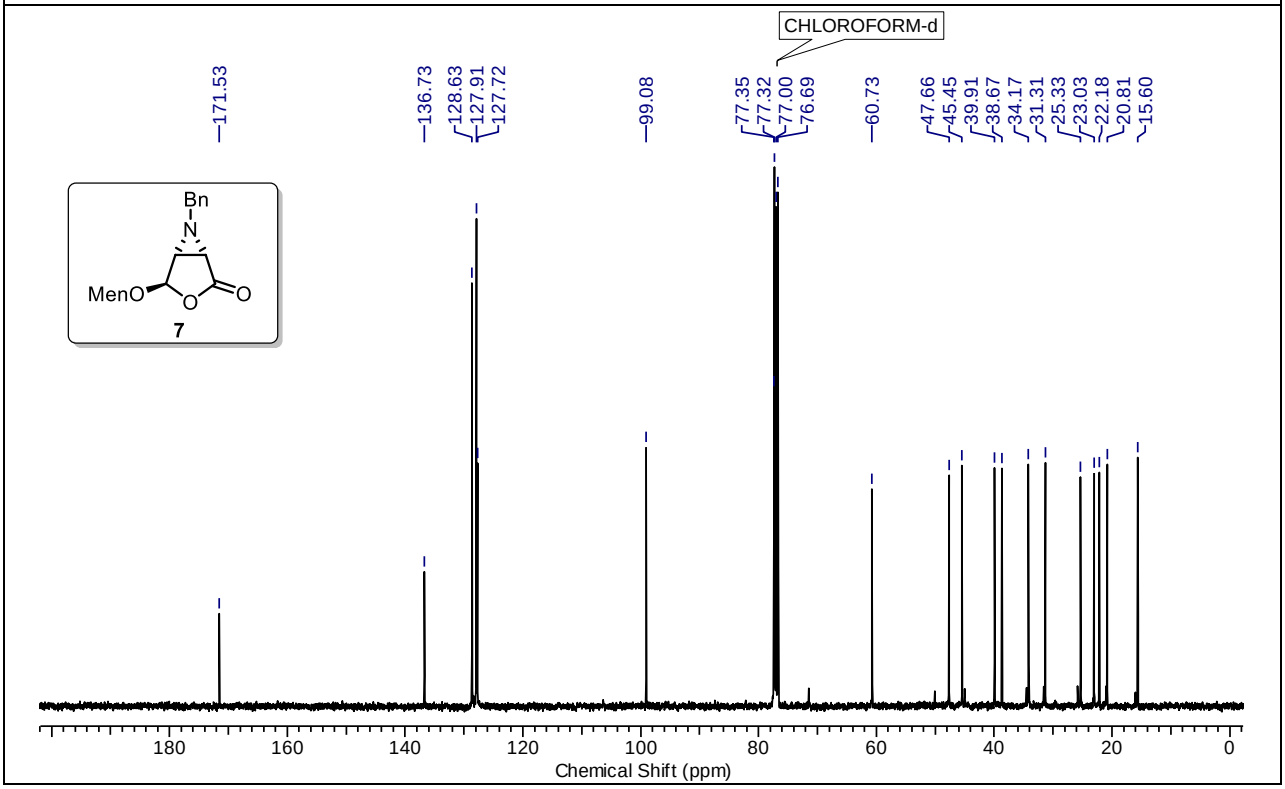
DEPT NMR spectrum of compound 10b ($CDCl_3$, 125 MHz)



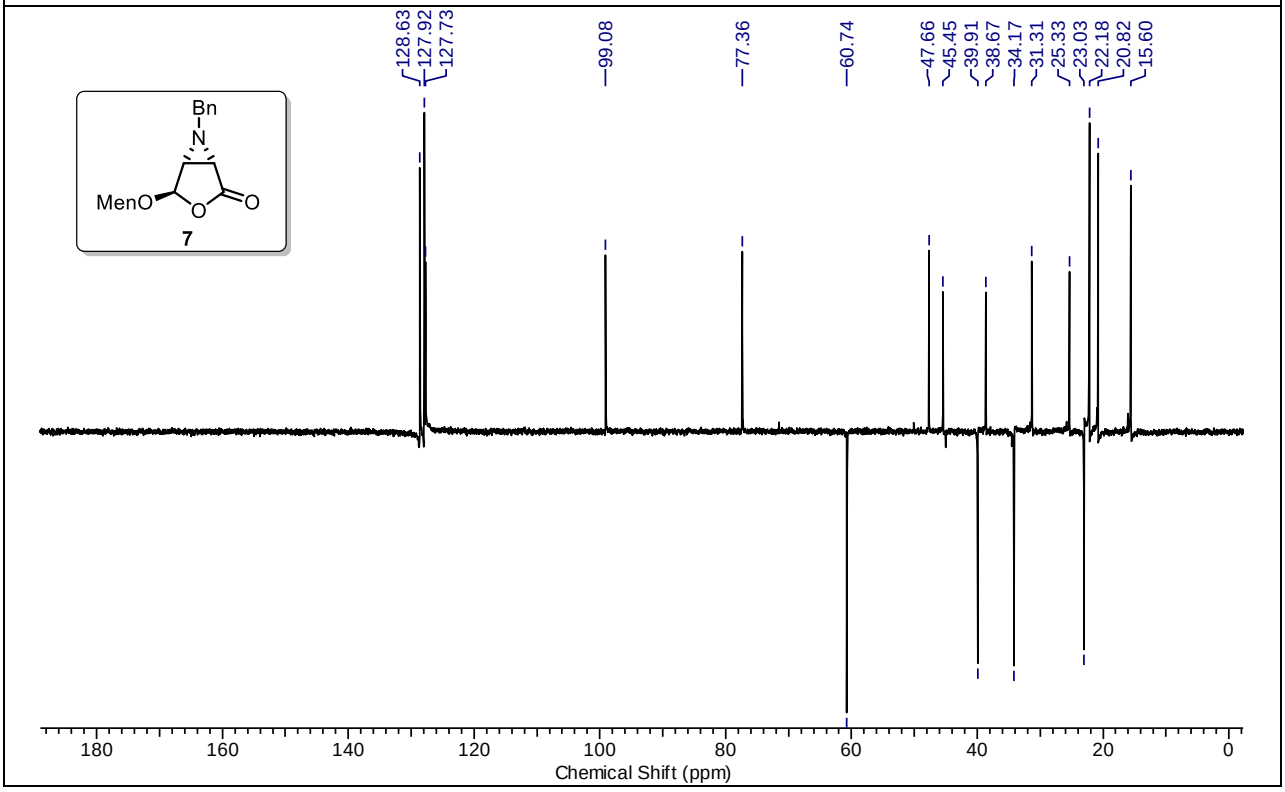
^{1}H-NMR spectrum of compound 7 ($CDCl_3$, 400 MHz)



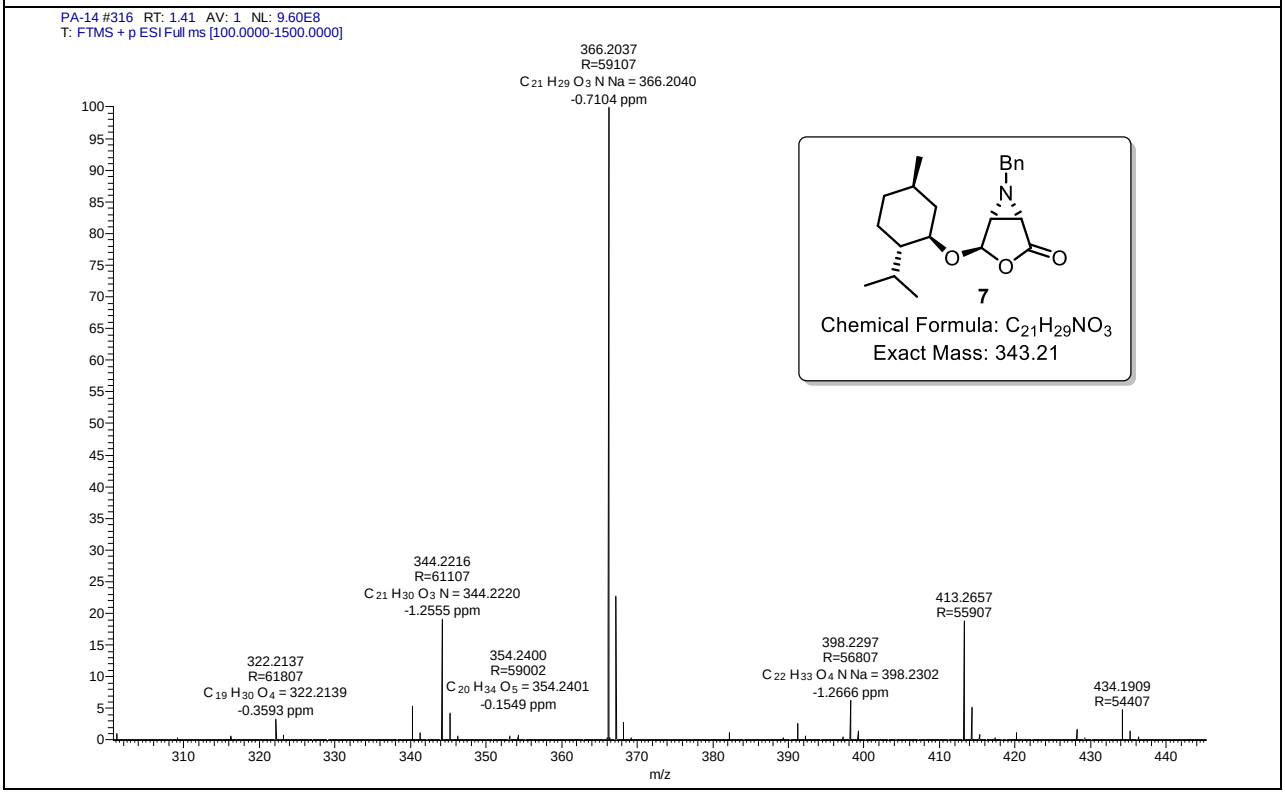
^{13}C-NMR spectrum of compound 7 ($CDCl_3$, 100 MHz)



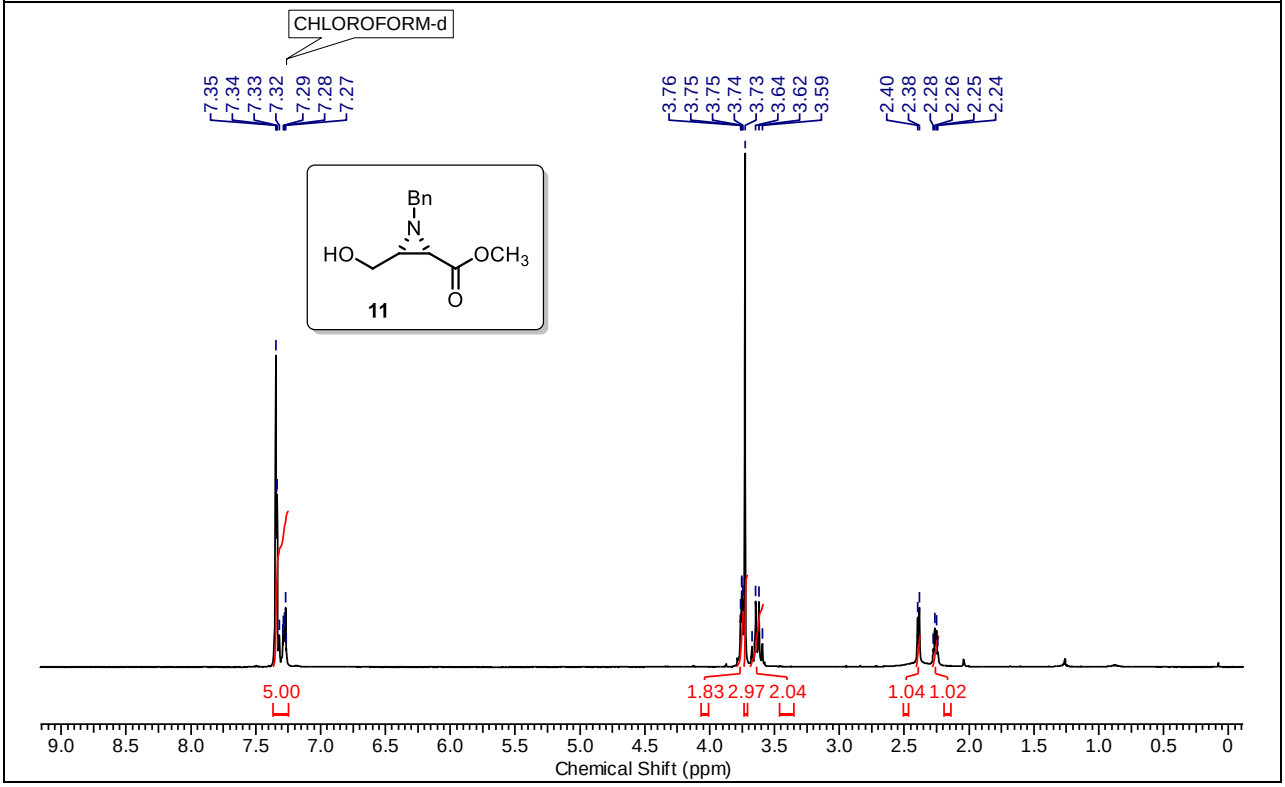
DEPT NMR spectrum of compound 7 ($CDCl_3$, 100 MHz)



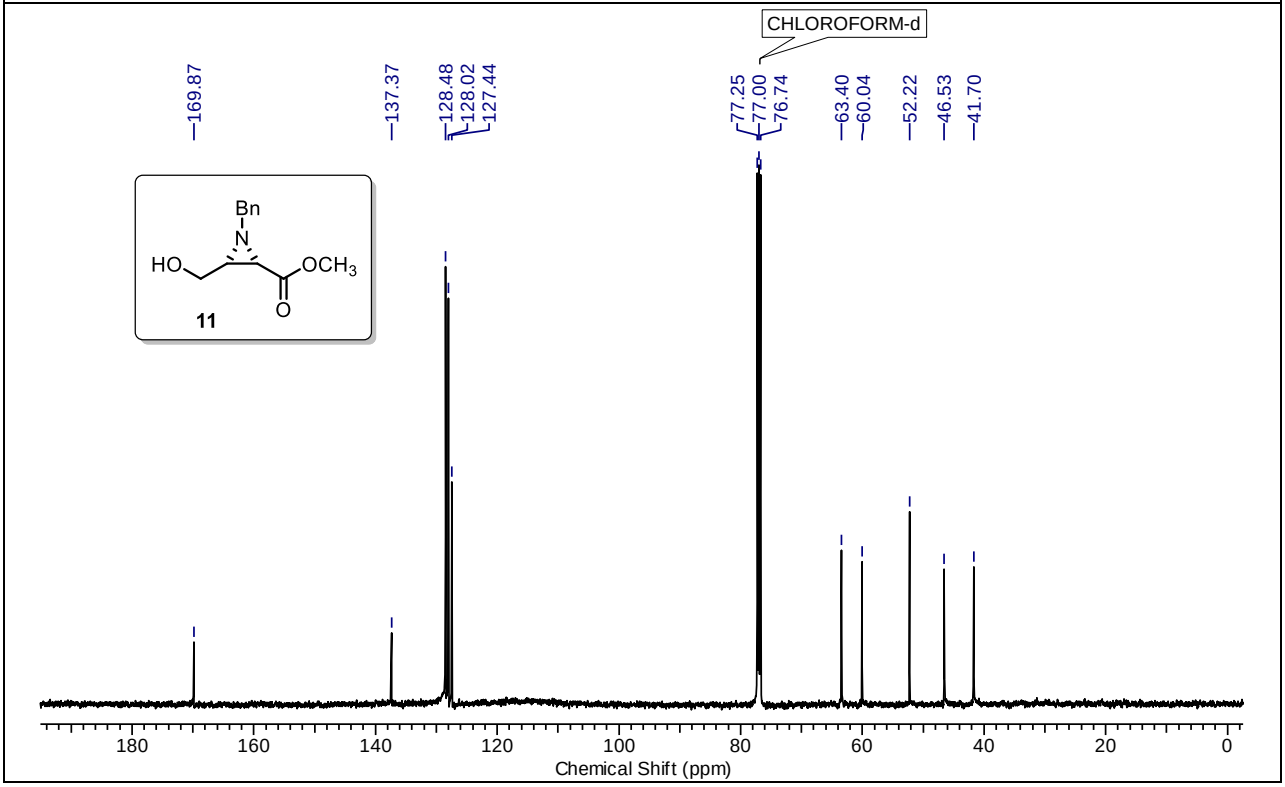
HRMS spectrum of compound 7



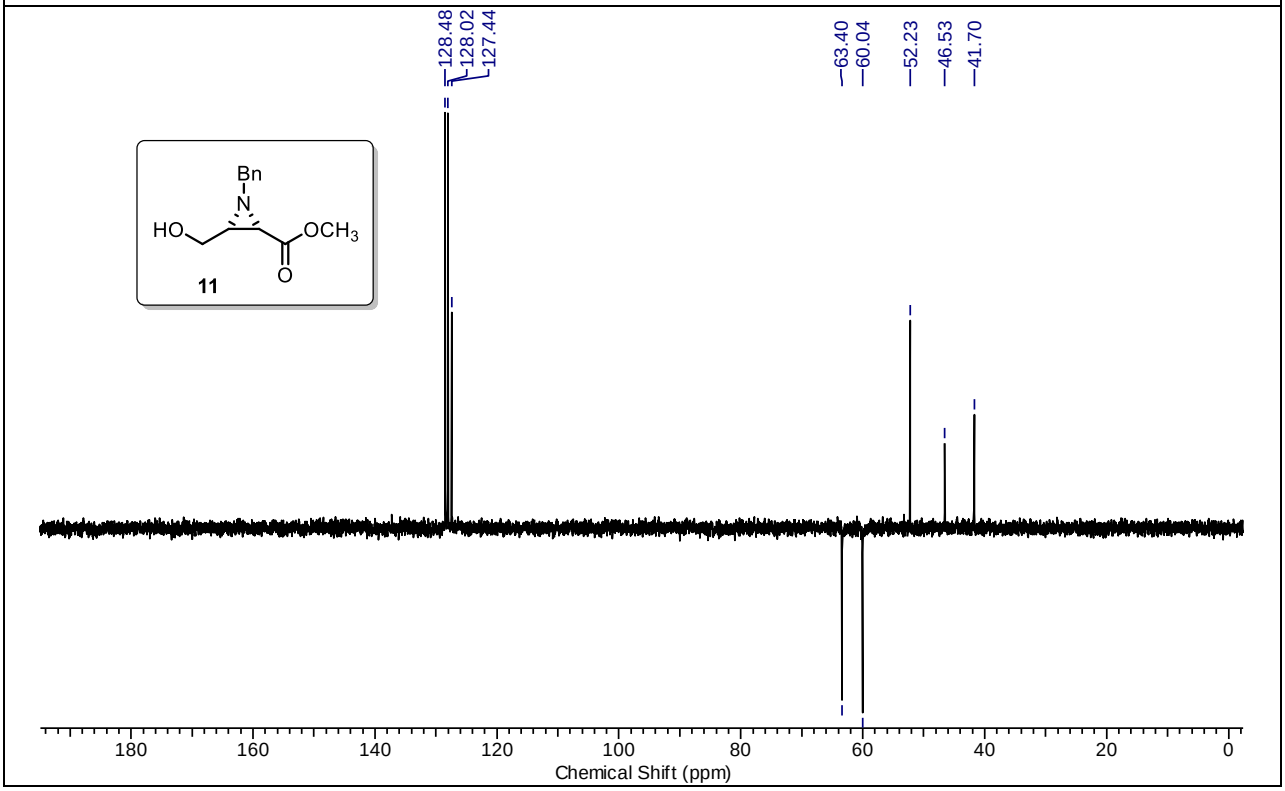
^{1}H-NMR spectrum of compound 11 ($CDCl_3$, 500 MHz)



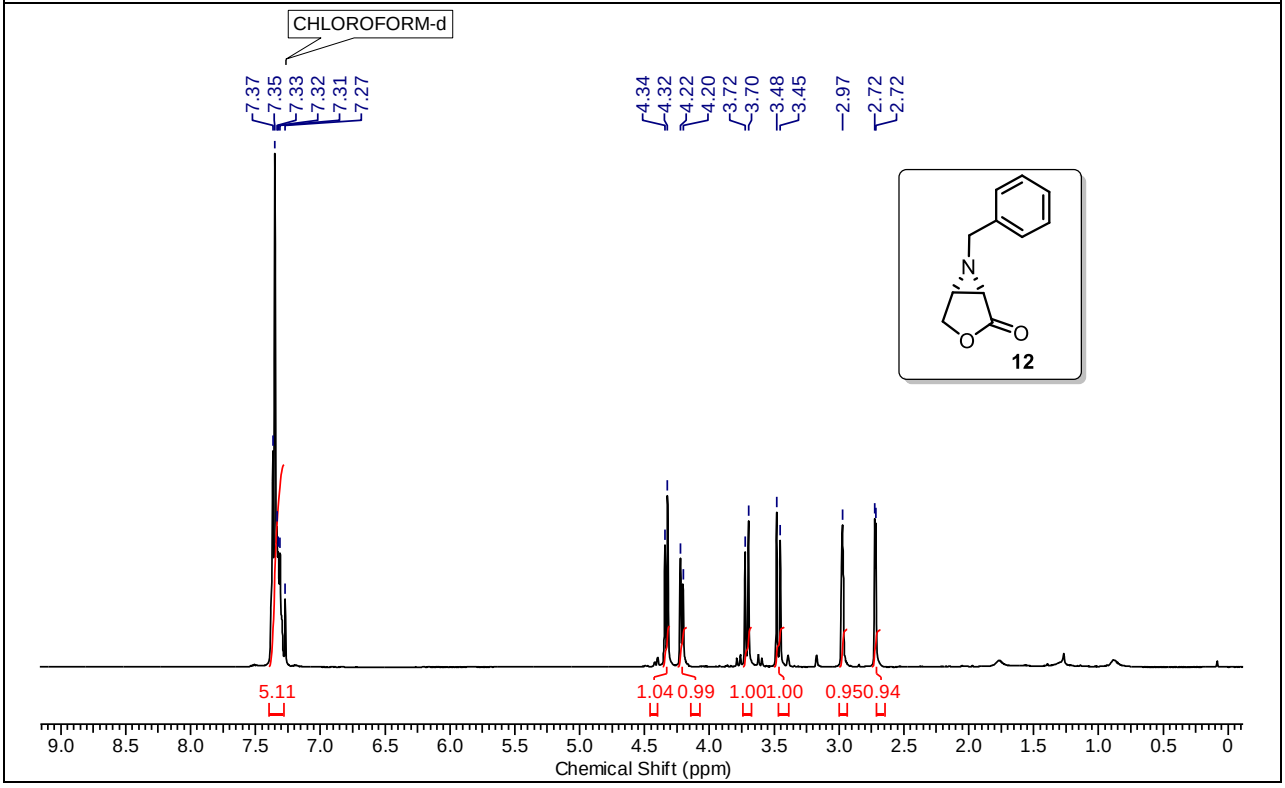
^{13}C-NMR spectrum of compound 11 ($CDCl_3$, 125 MHz)



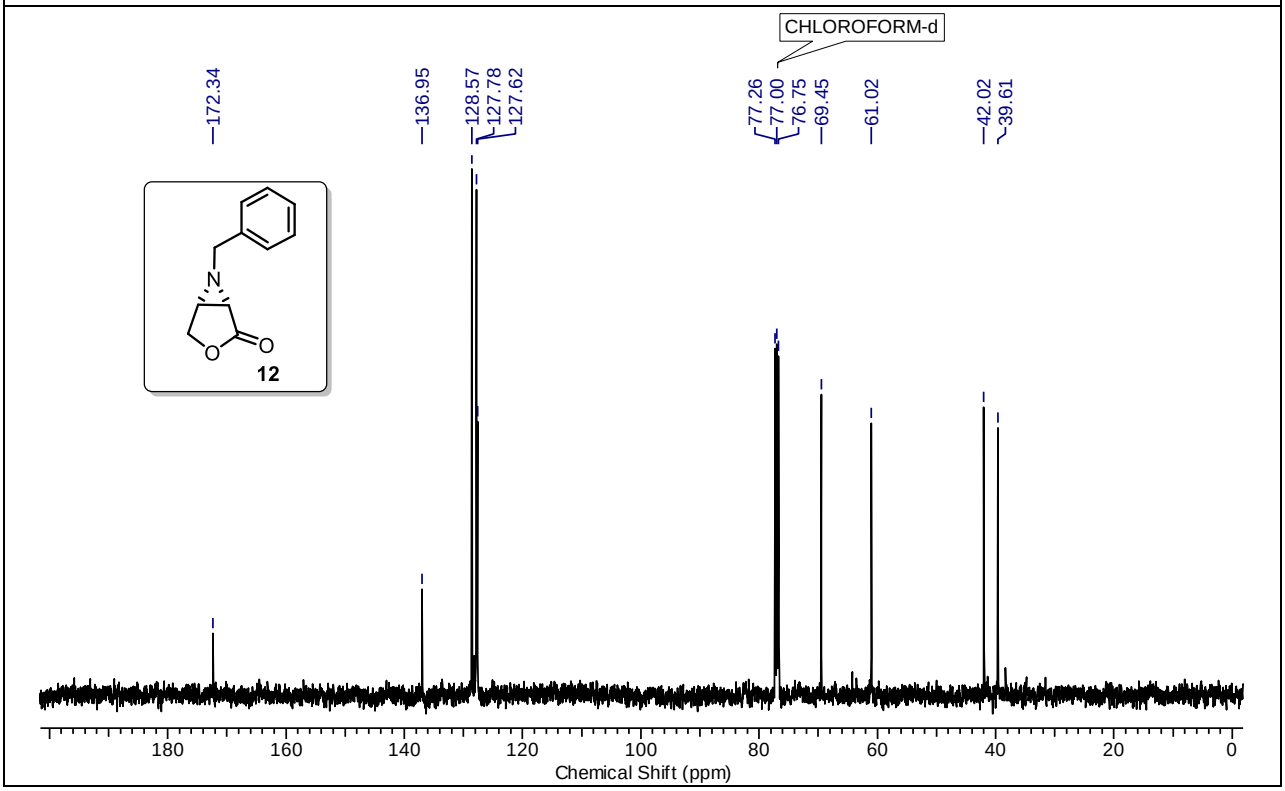
DEPT NMR spectrum of compound 11 ($CDCl_3$, 125 MHz)



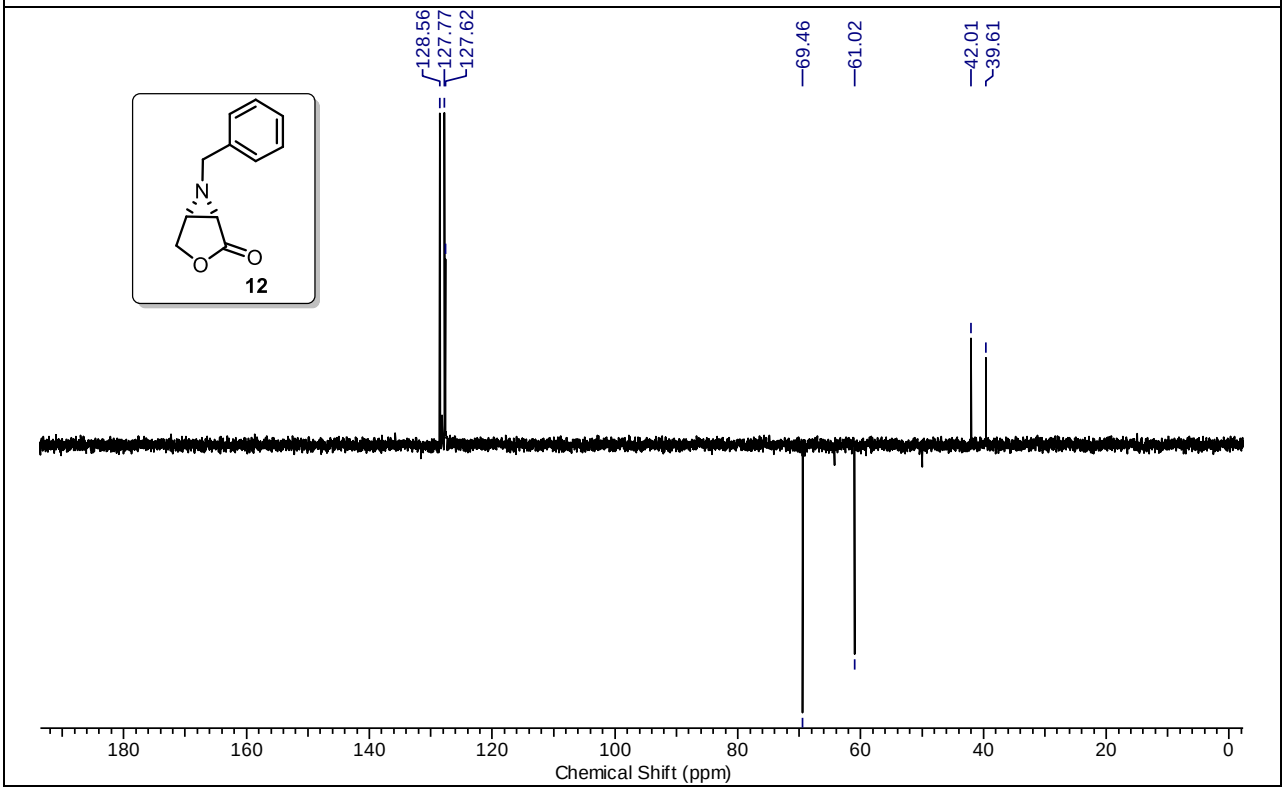
^{1}H-NMR spectrum of compound 12 ($CDCl_3$, 500 MHz)



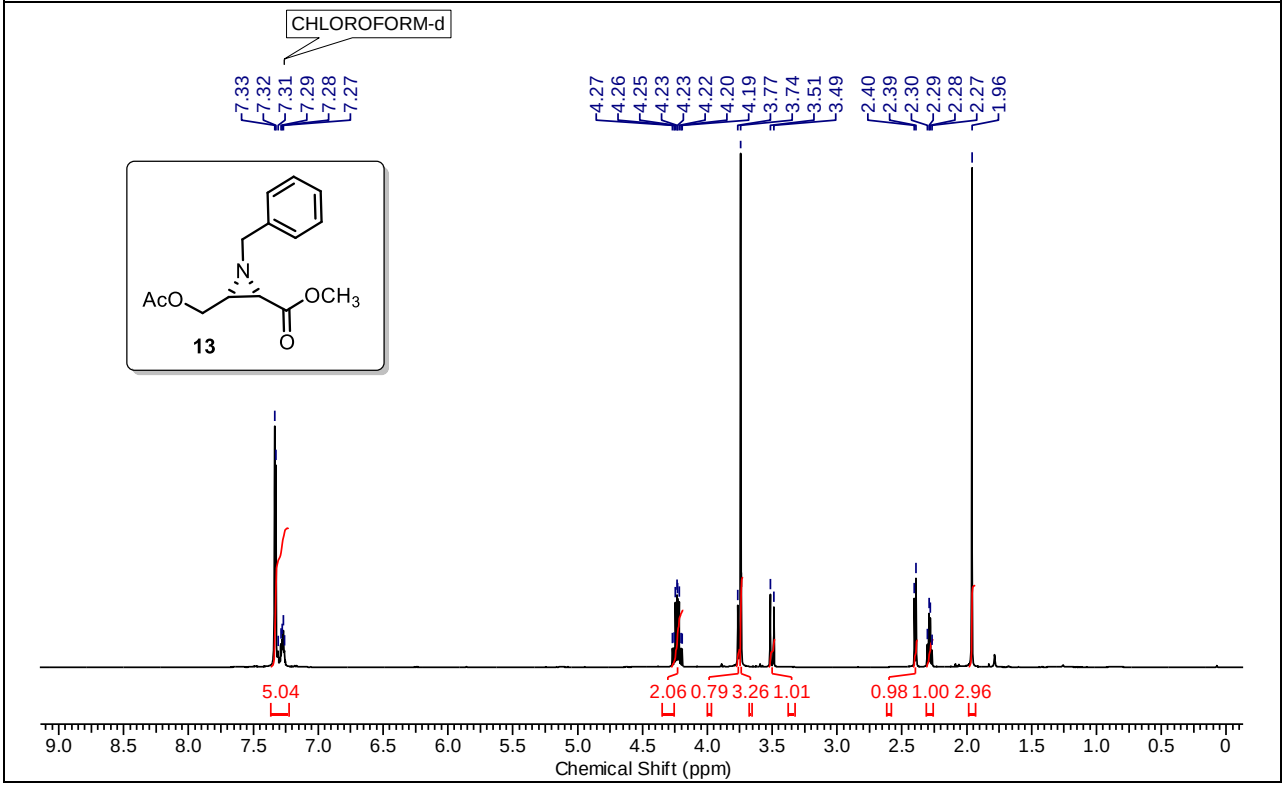
^{13}C-NMR spectrum of compound 12 ($CDCl_3$, 125 MHz)



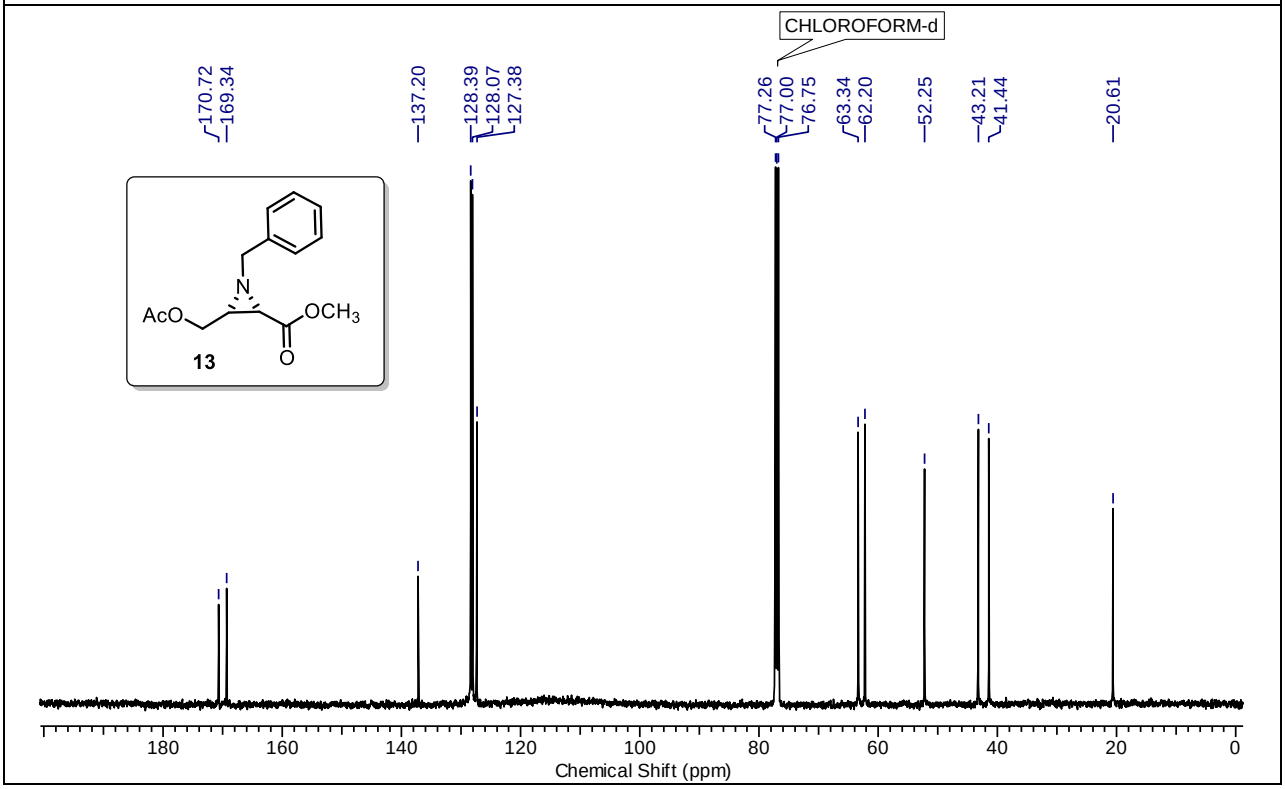
DEPT NMR spectrum of compound 12 ($CDCl_3$, 125 MHz)



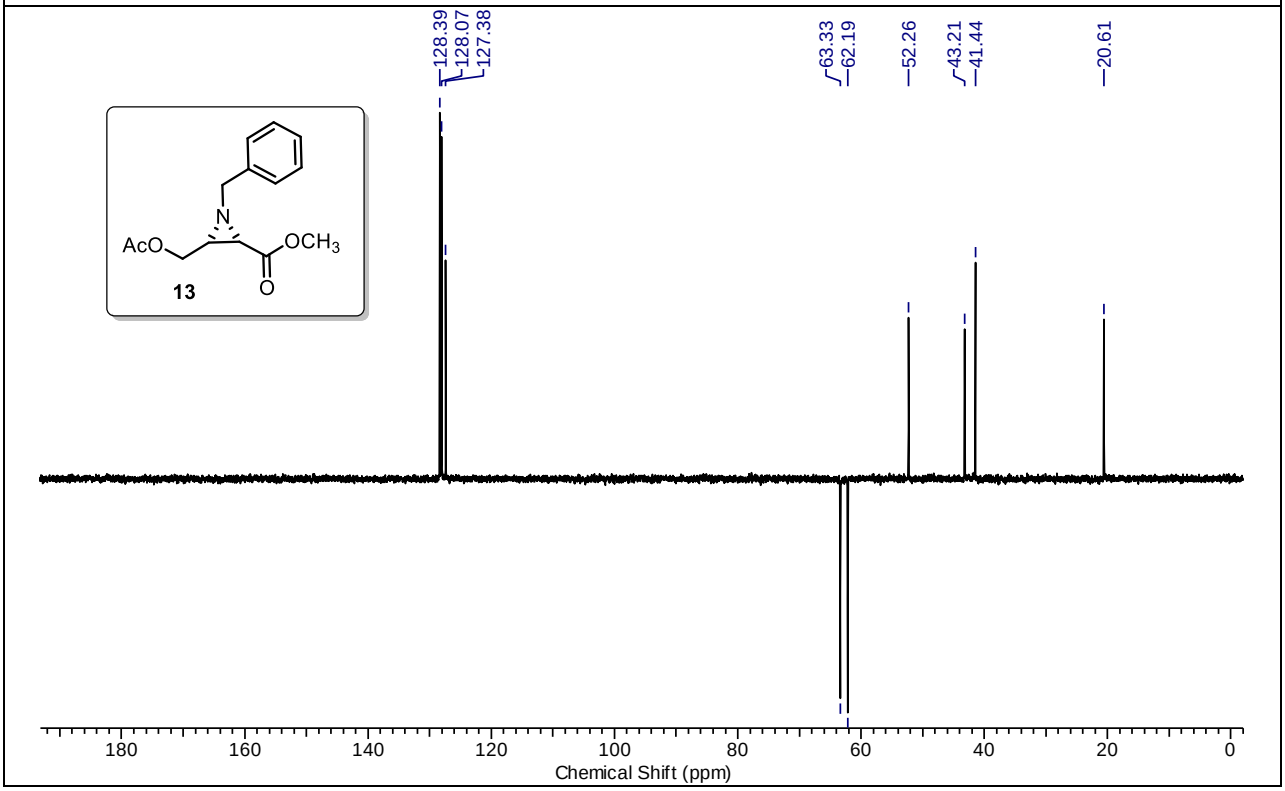
^{1}H-NMR spectrum of compound 13 ($CDCl_3$, 500 MHz)



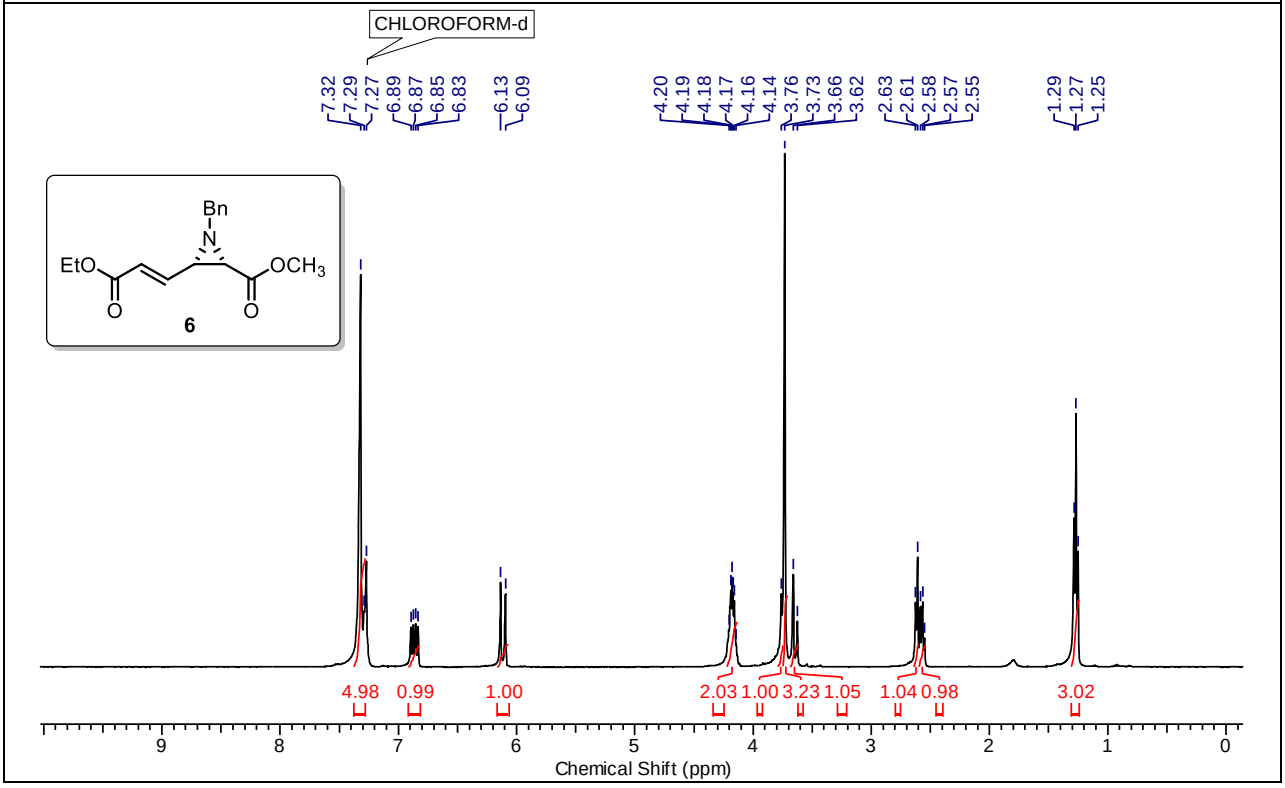
^{13}C-NMR spectrum of compound 13 ($CDCl_3$, 125 MHz)



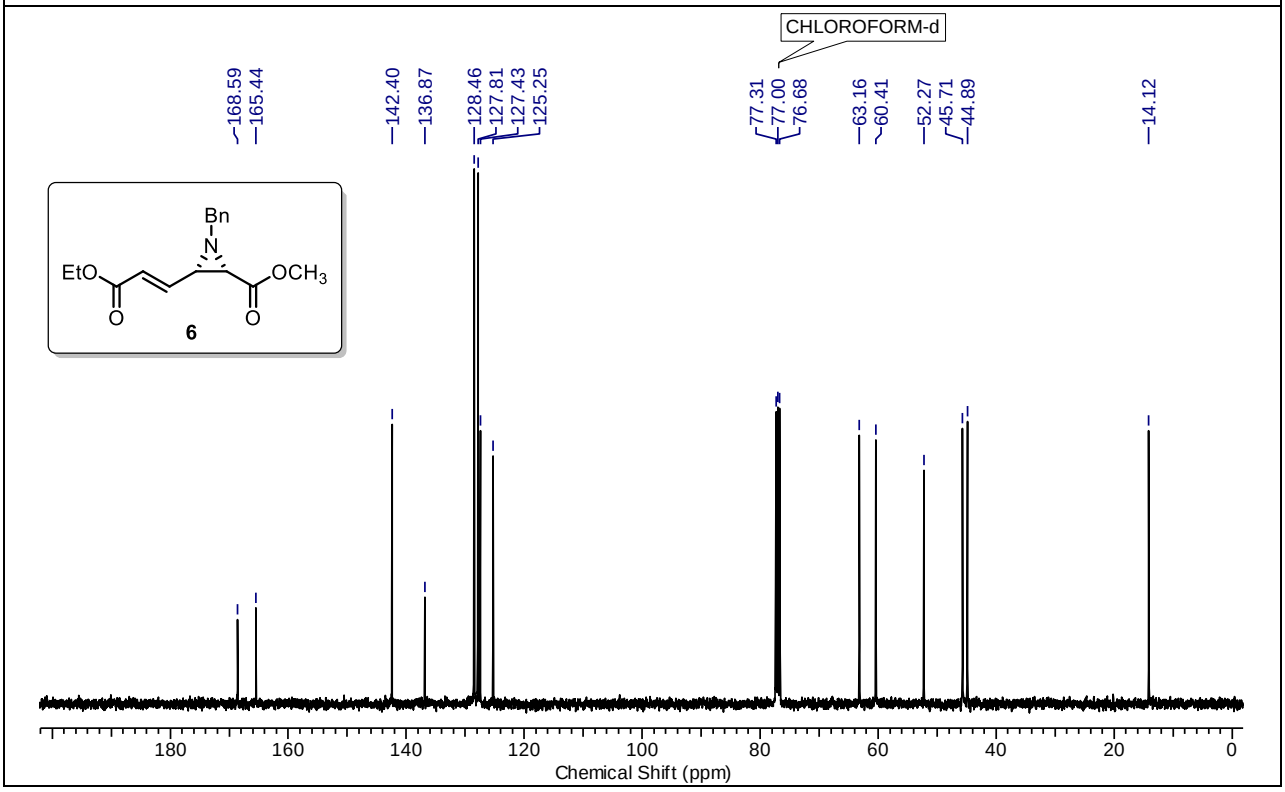
DEPT NMR spectrum of compound 13 ($CDCl_3$, 125 MHz)



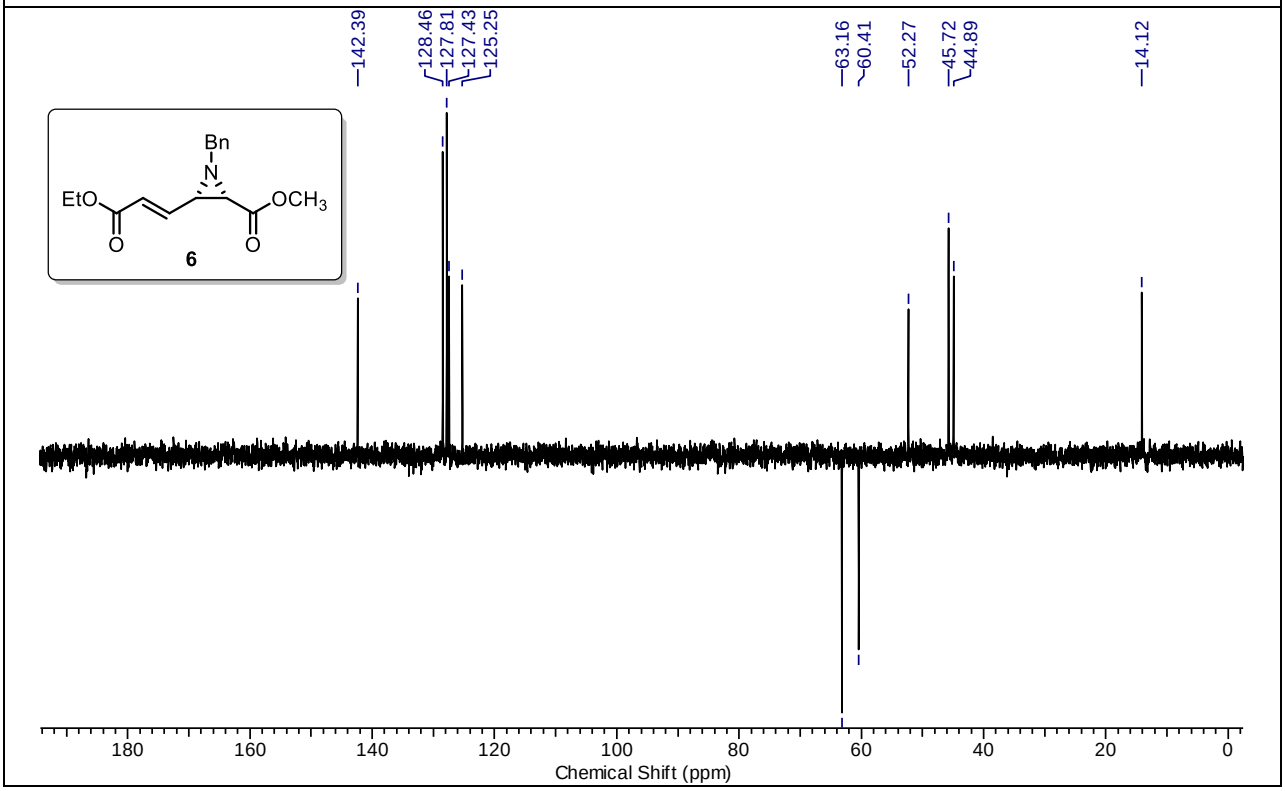
^{1}H-NMR spectrum of compound 6 ($CDCl_3$, 400 MHz)



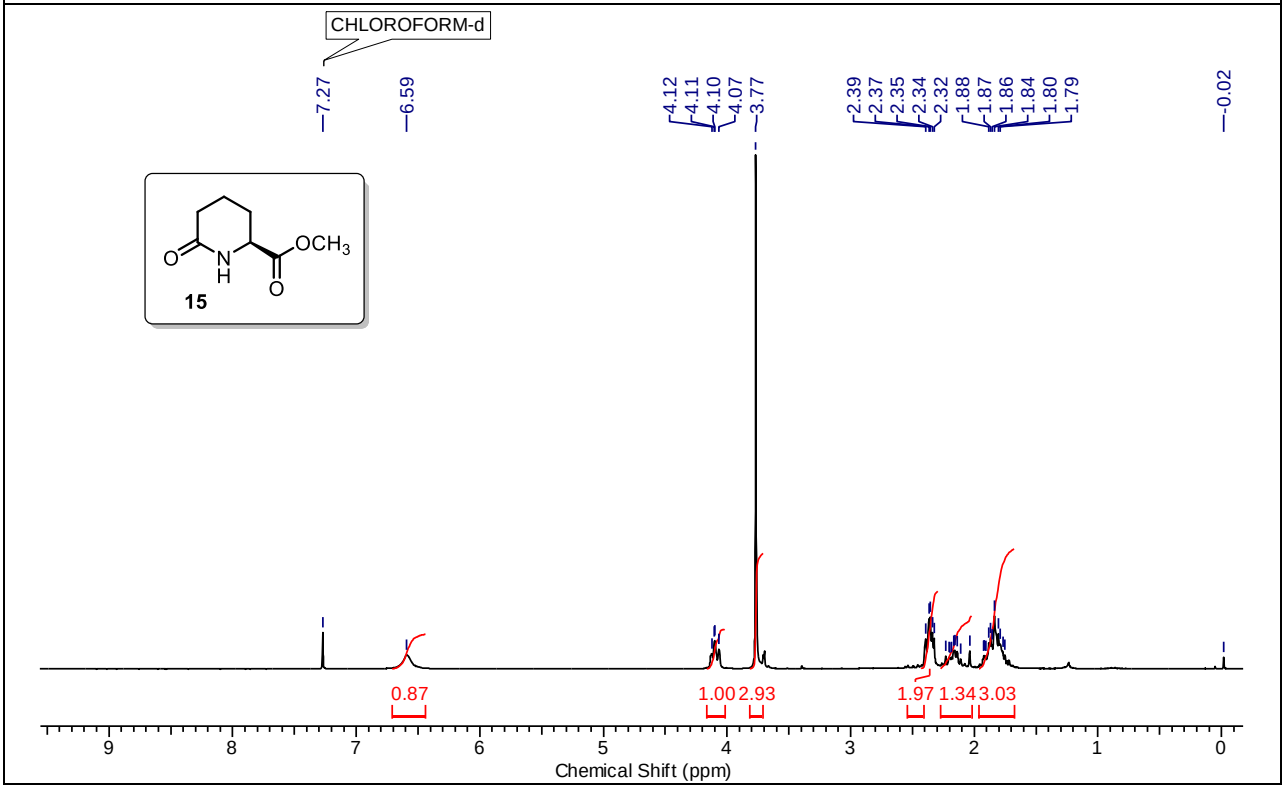
^{13}C-NMR spectrum of compound 6 ($CDCl_3$, 100 MHz)



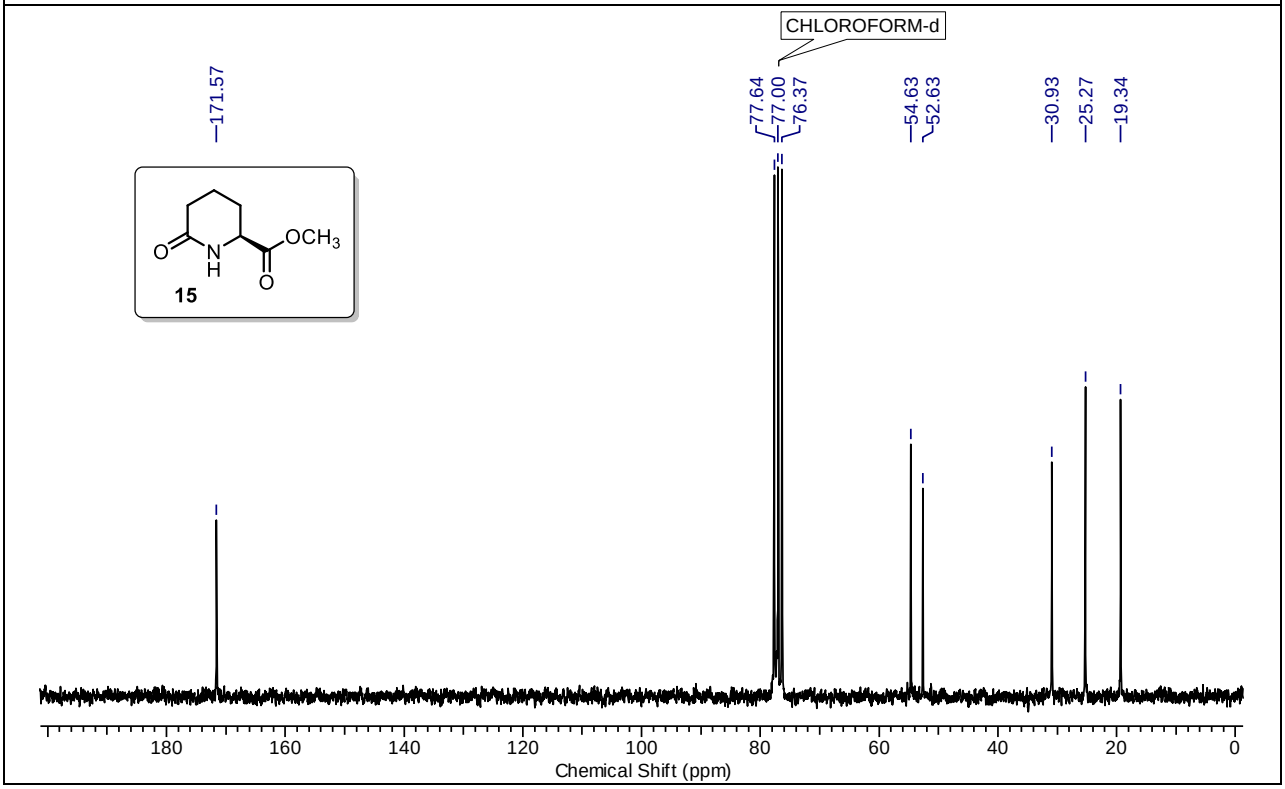
DEPT NMR spectrum of compound 6 ($CDCl_3$, 100 MHz)



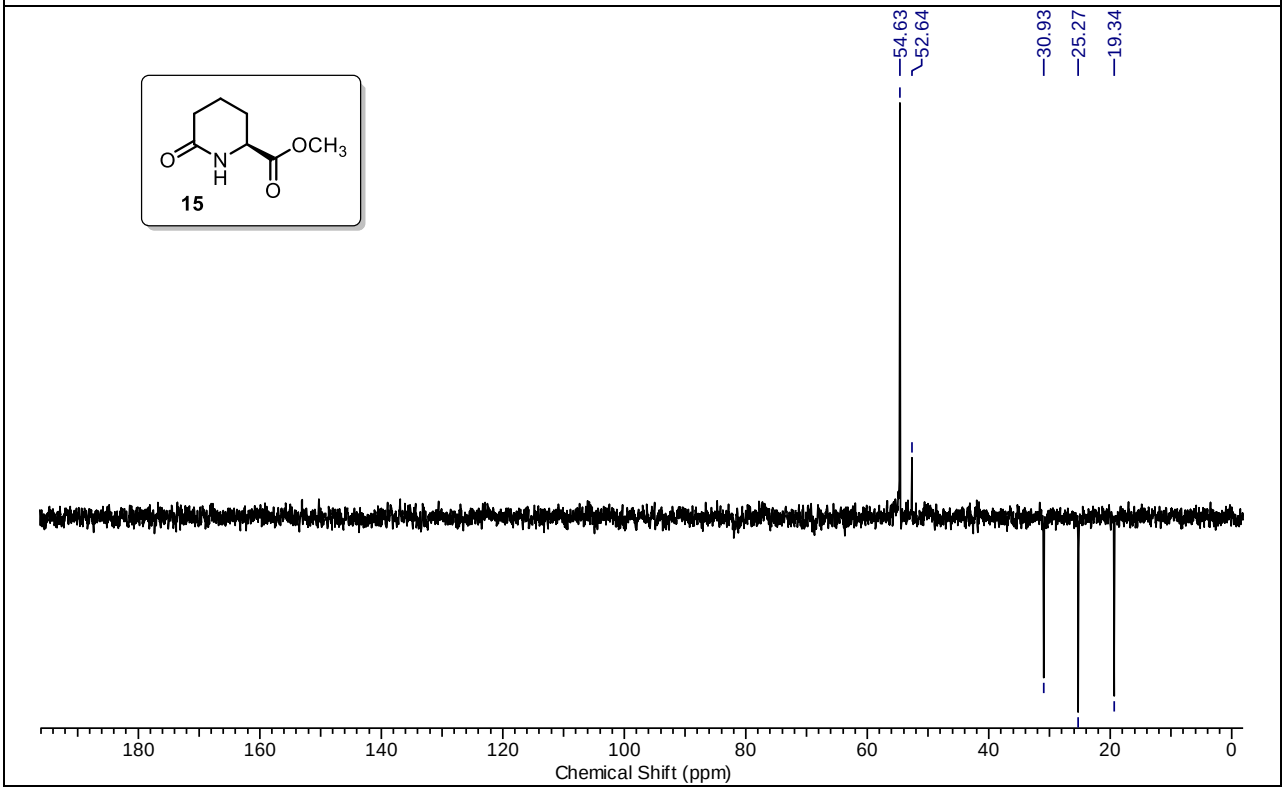
^{1}H-NMR spectrum of compound 15 ($CDCl_3$, 200 MHz)



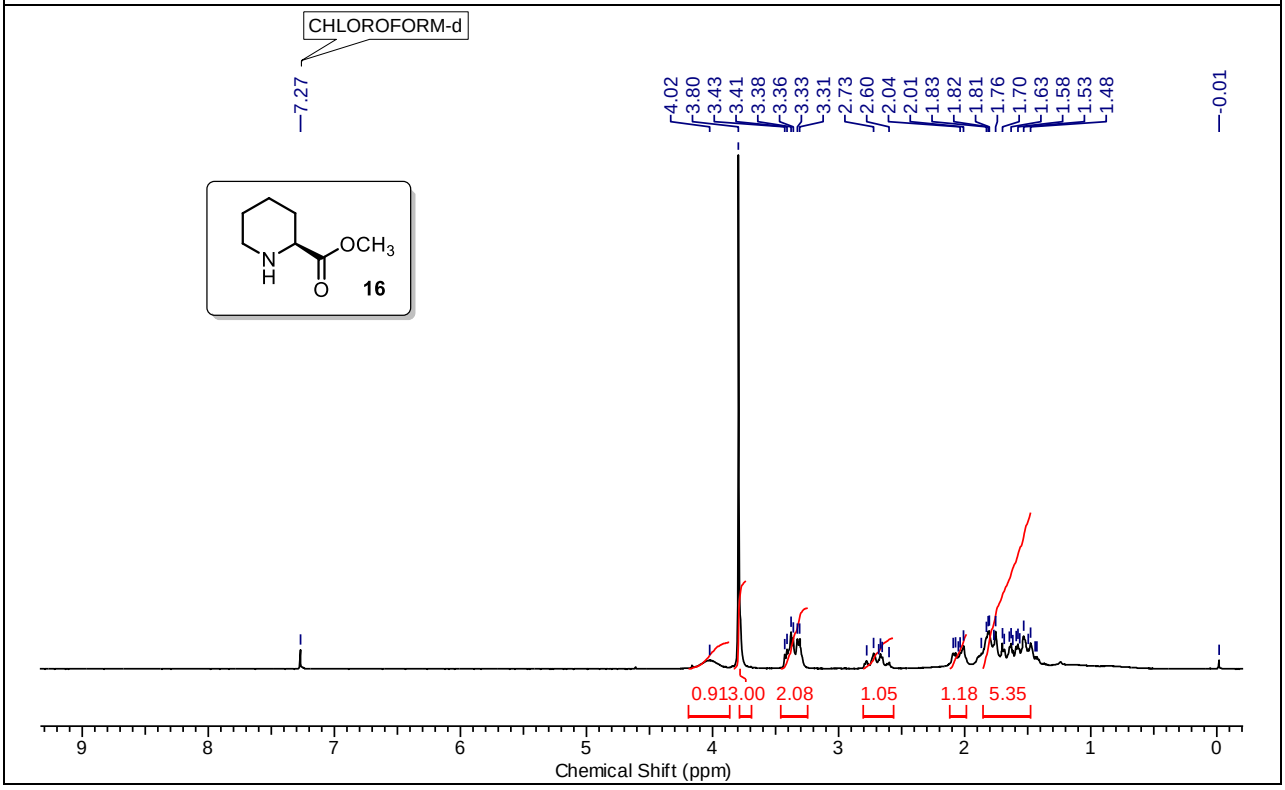
^{13}C-NMR spectrum of compound 15 ($CDCl_3$, 50 MHz)



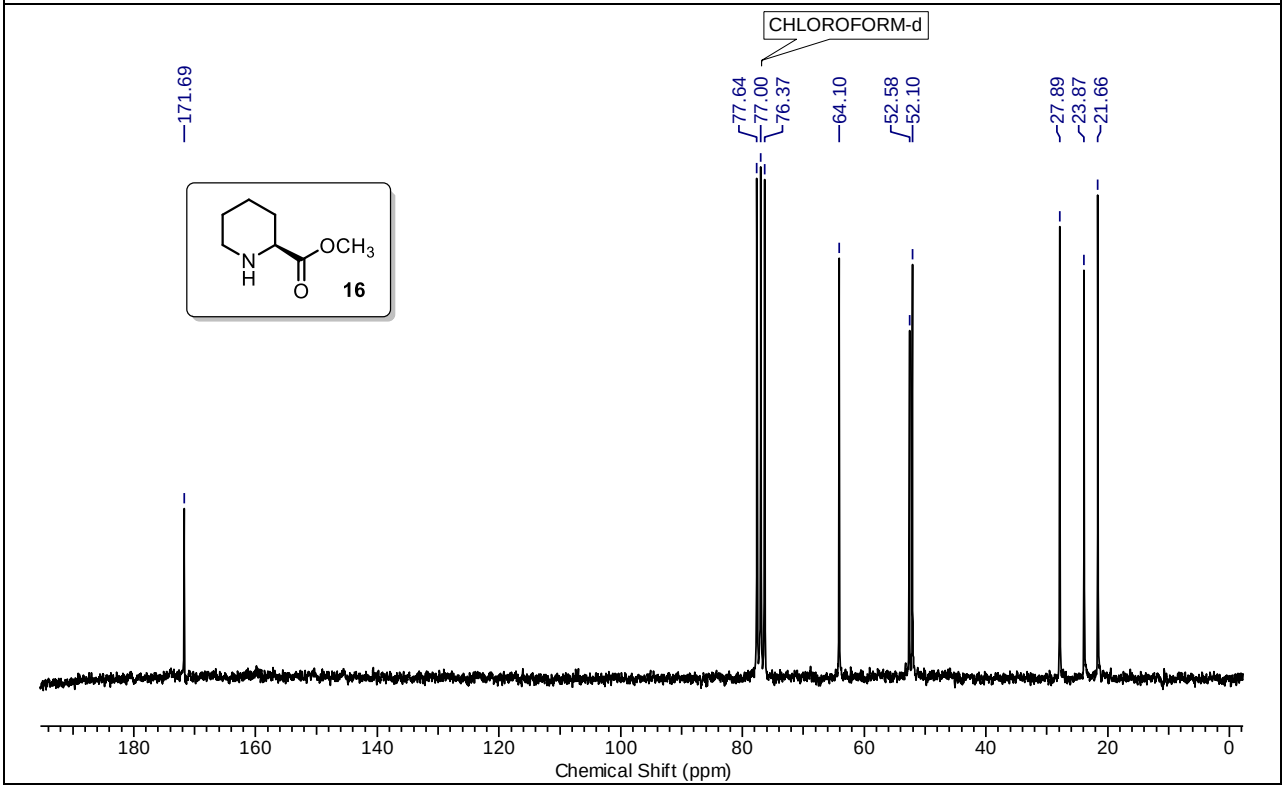
DEPT NMR spectrum of compound 15 ($CDCl_3$, 50 MHz)



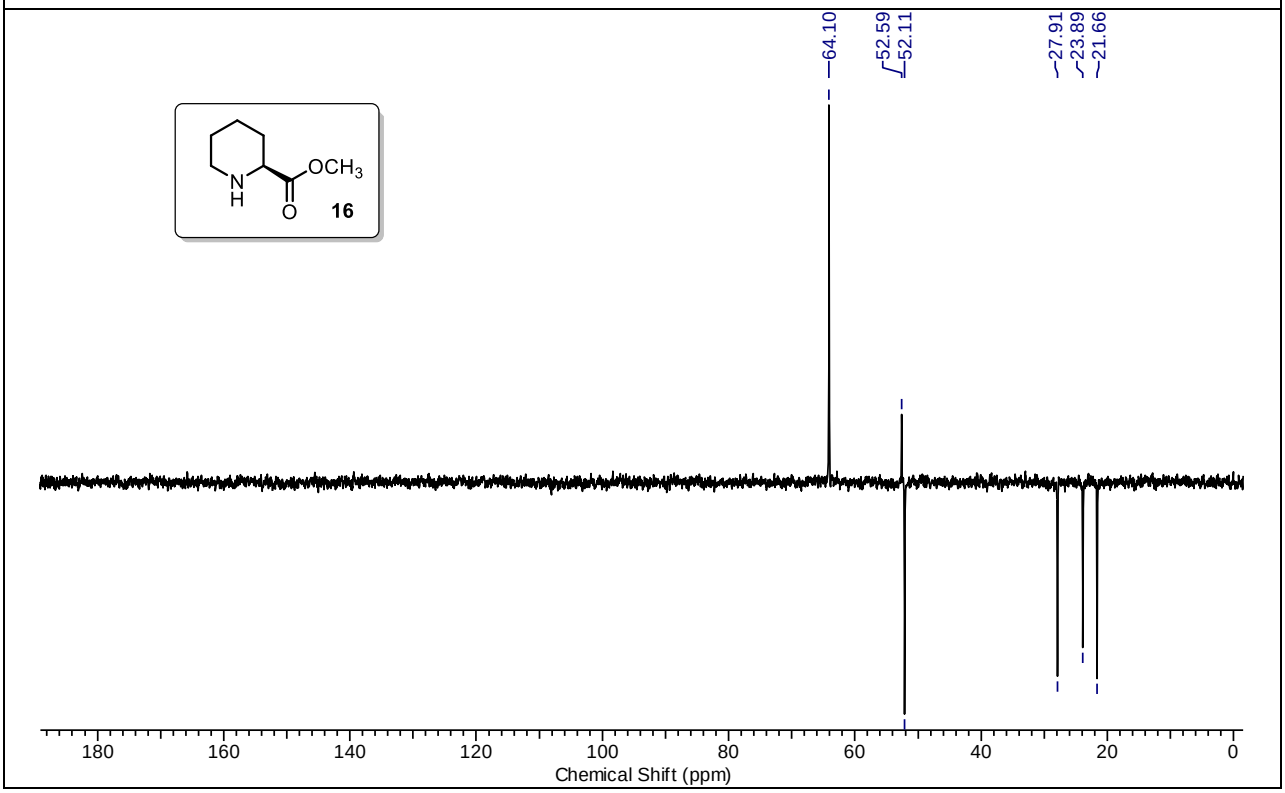
^{1}H-NMR spectrum of compound 16 ($CDCl_3$, 200 MHz)



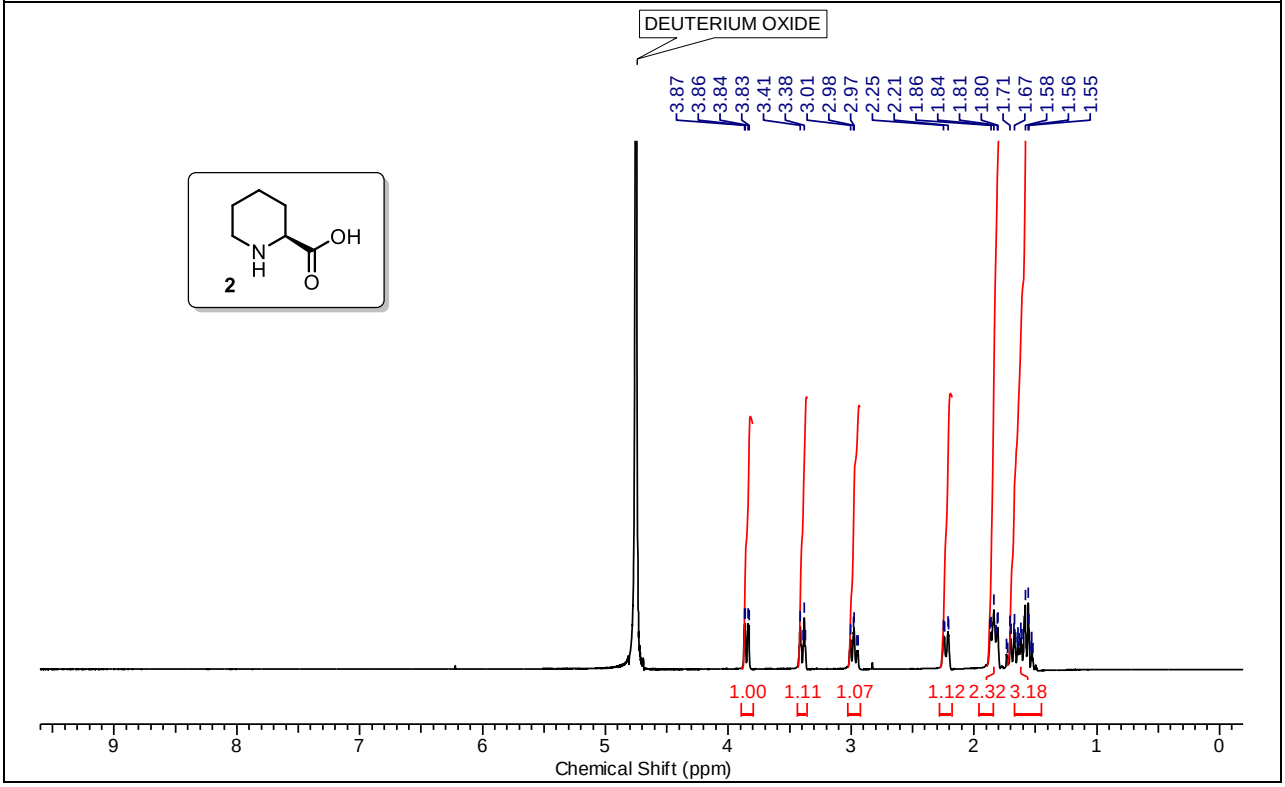
^{13}C-NMR spectrum of compound 16 ($CDCl_3$, 50 MHz)



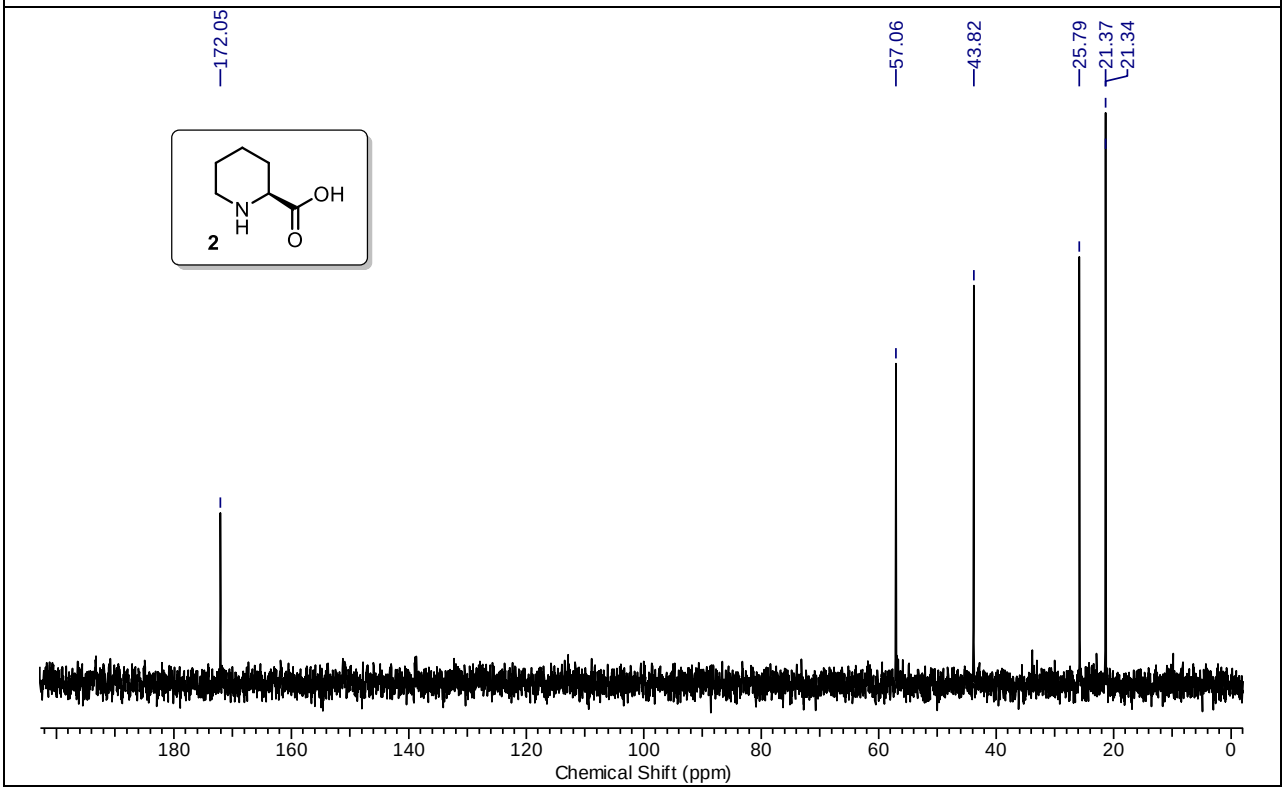
DEPT NMR spectrum of compound 16 ($CDCl_3$, 50 MHz)



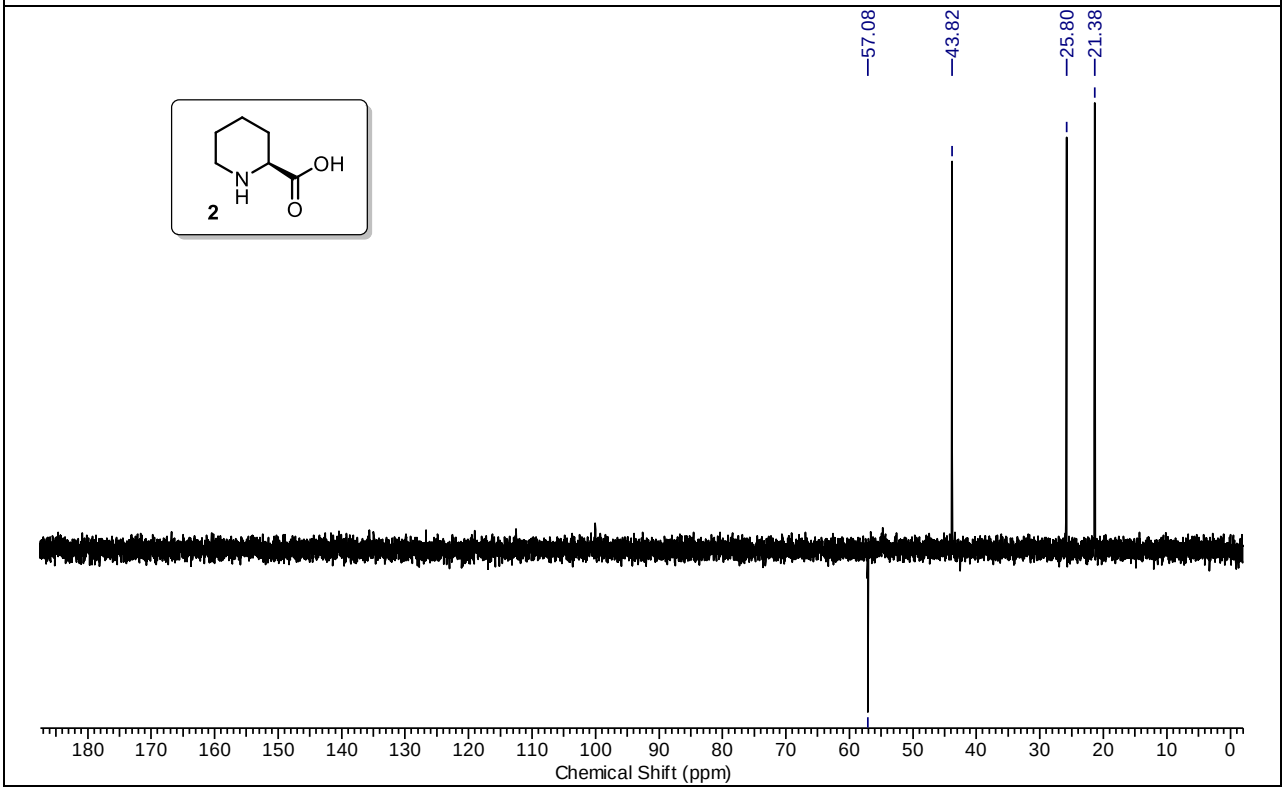
^{1}H-NMR spectrum of compound 2 (D_2O, 400 MHz)



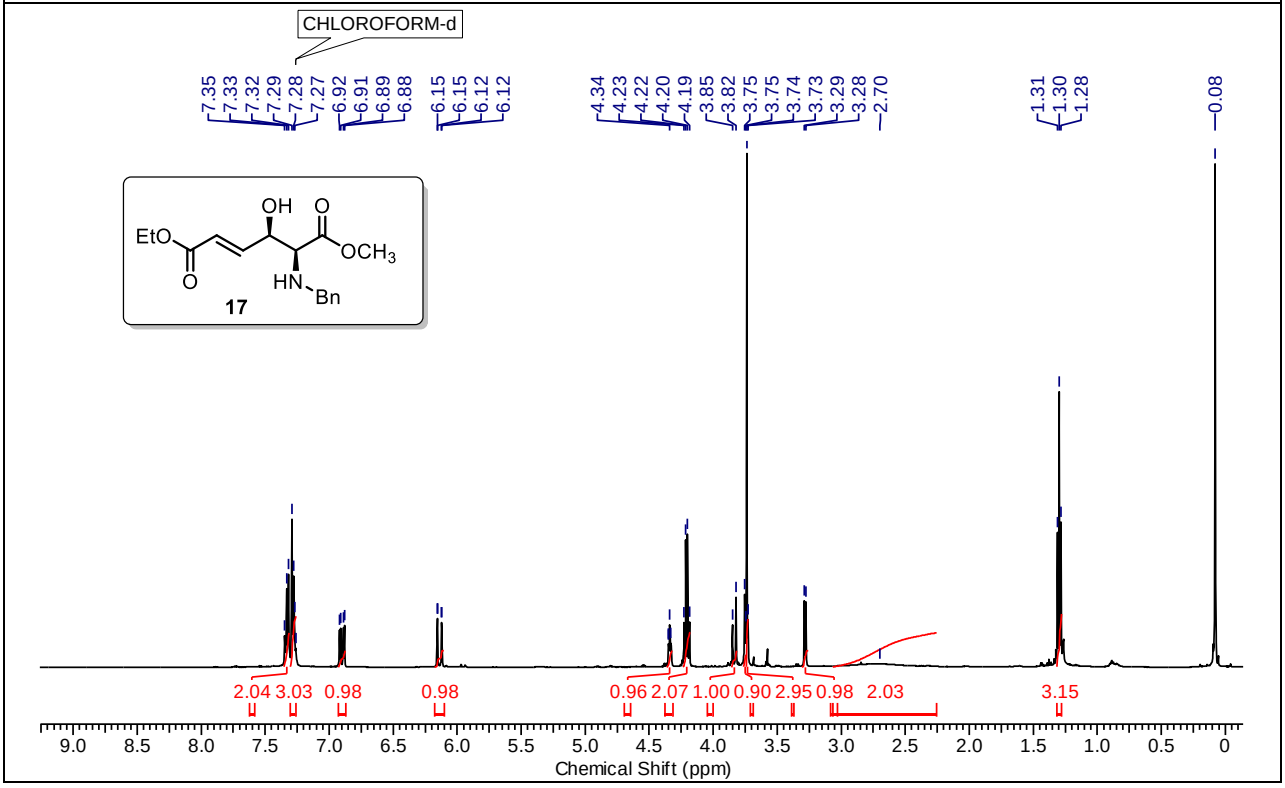
^{13}C-NMR spectrum of compound 2 (D_2O, 100 MHz)



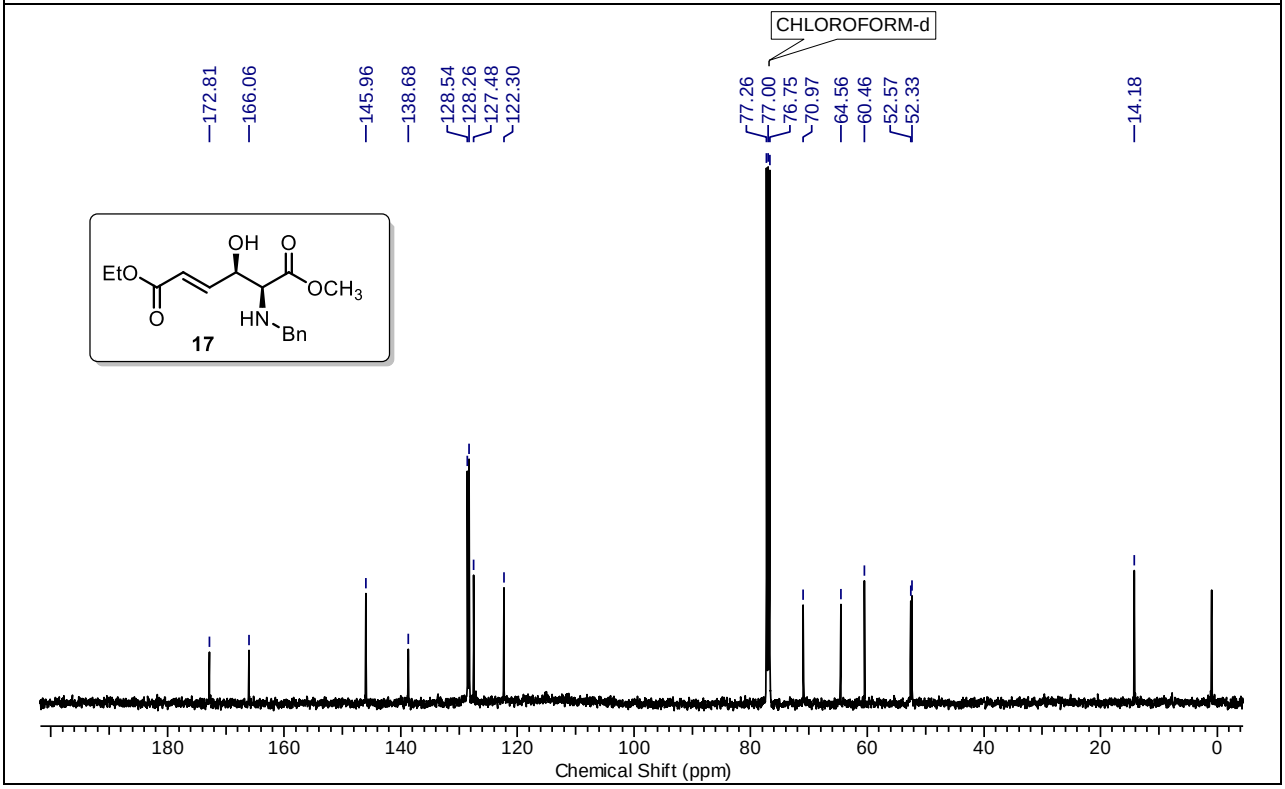
DEPT NMR spectrum of compound 2 (D_2O, 100 MHz)



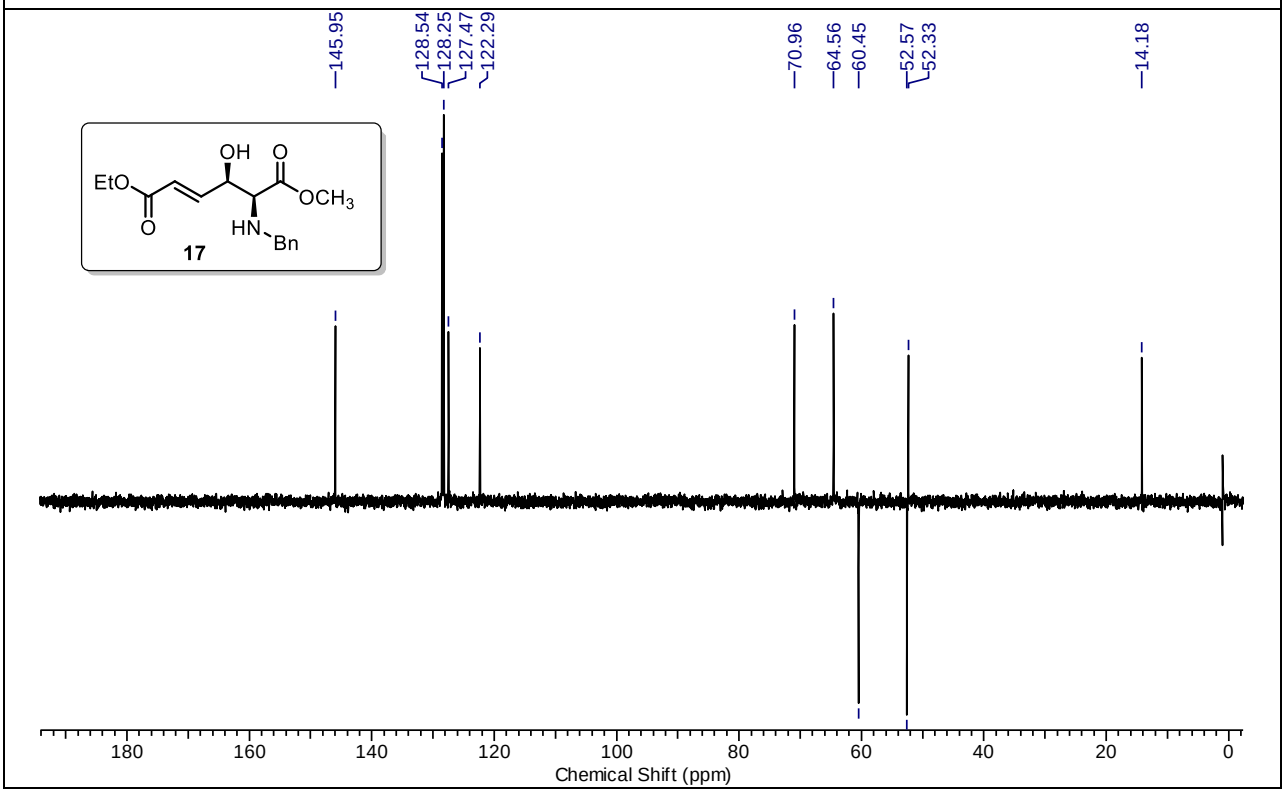
^{1}H-NMR spectrum of compound 17 ($CDCl_3$, 500 MHz)



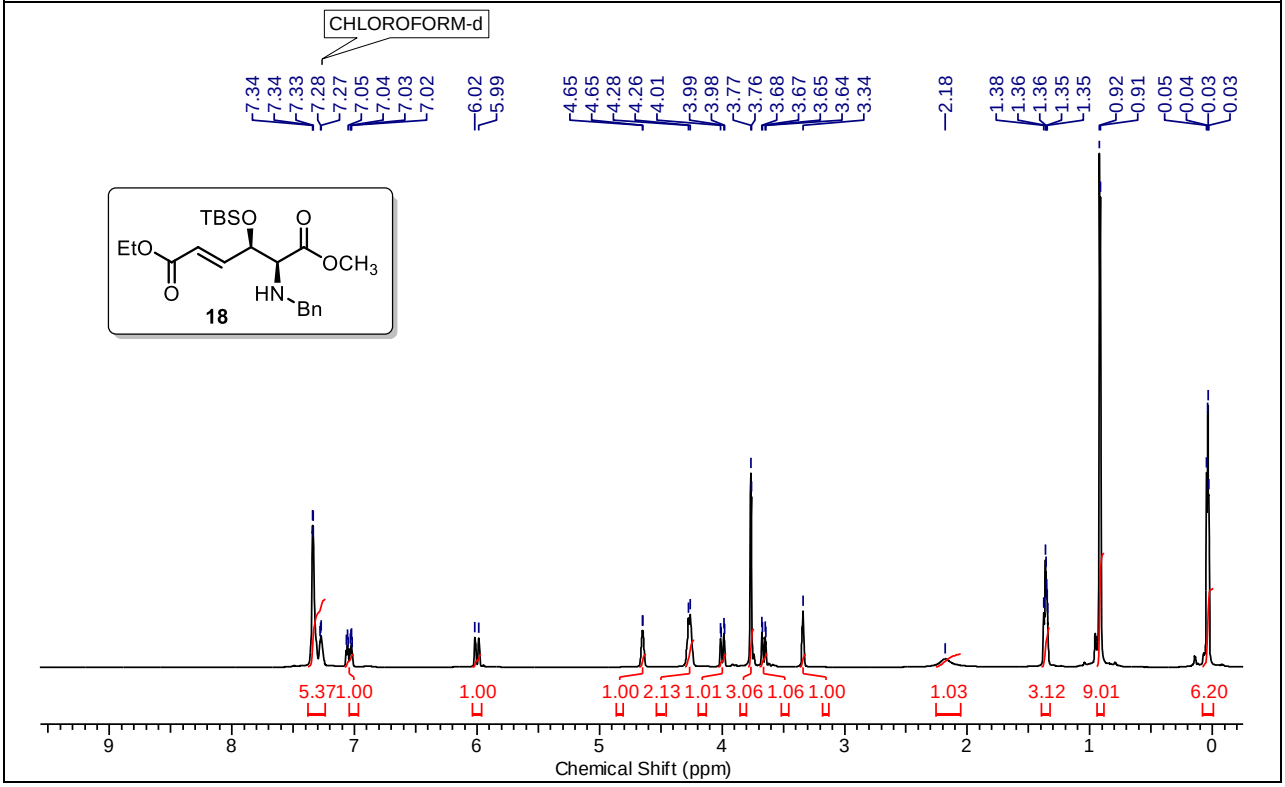
^{13}C-NMR spectrum of compound 17 ($CDCl_3$, 125 MHz)



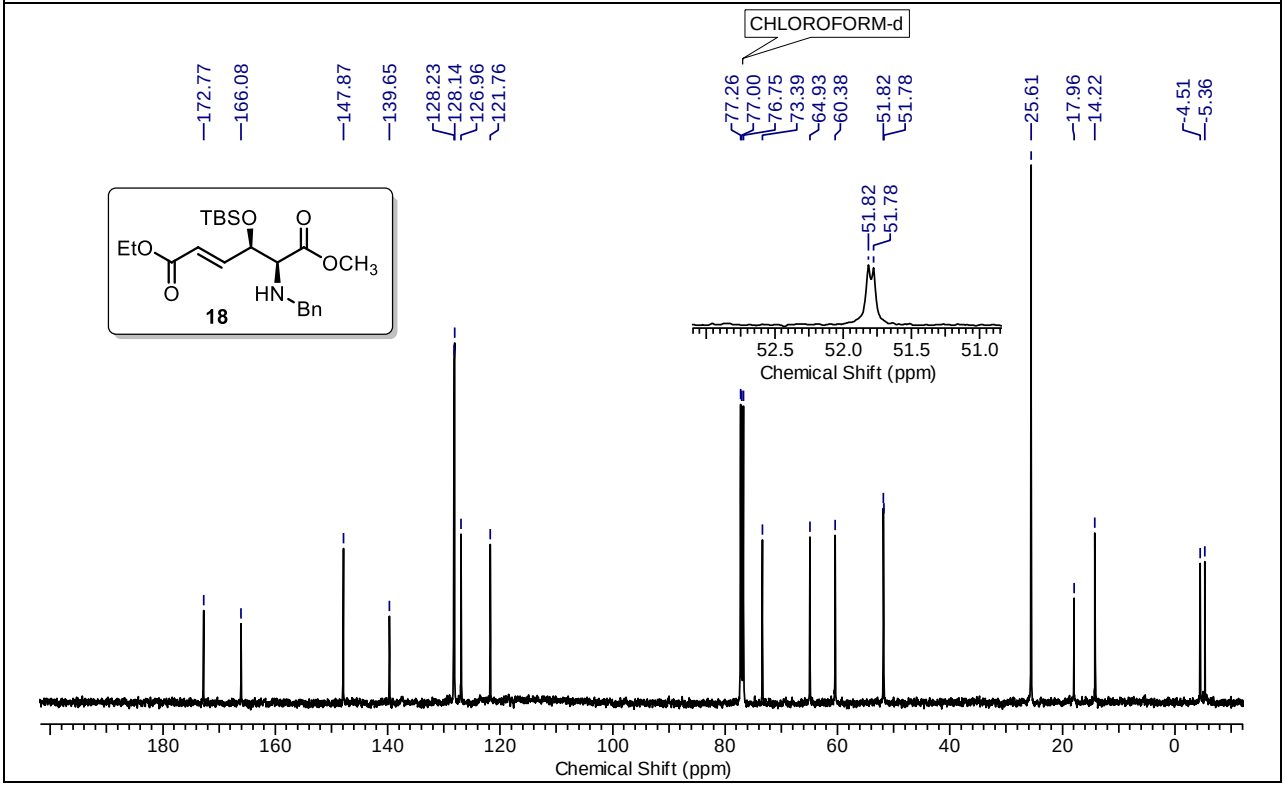
DEPT NMR spectrum of compound 17 ($CDCl_3$, 125 MHz)



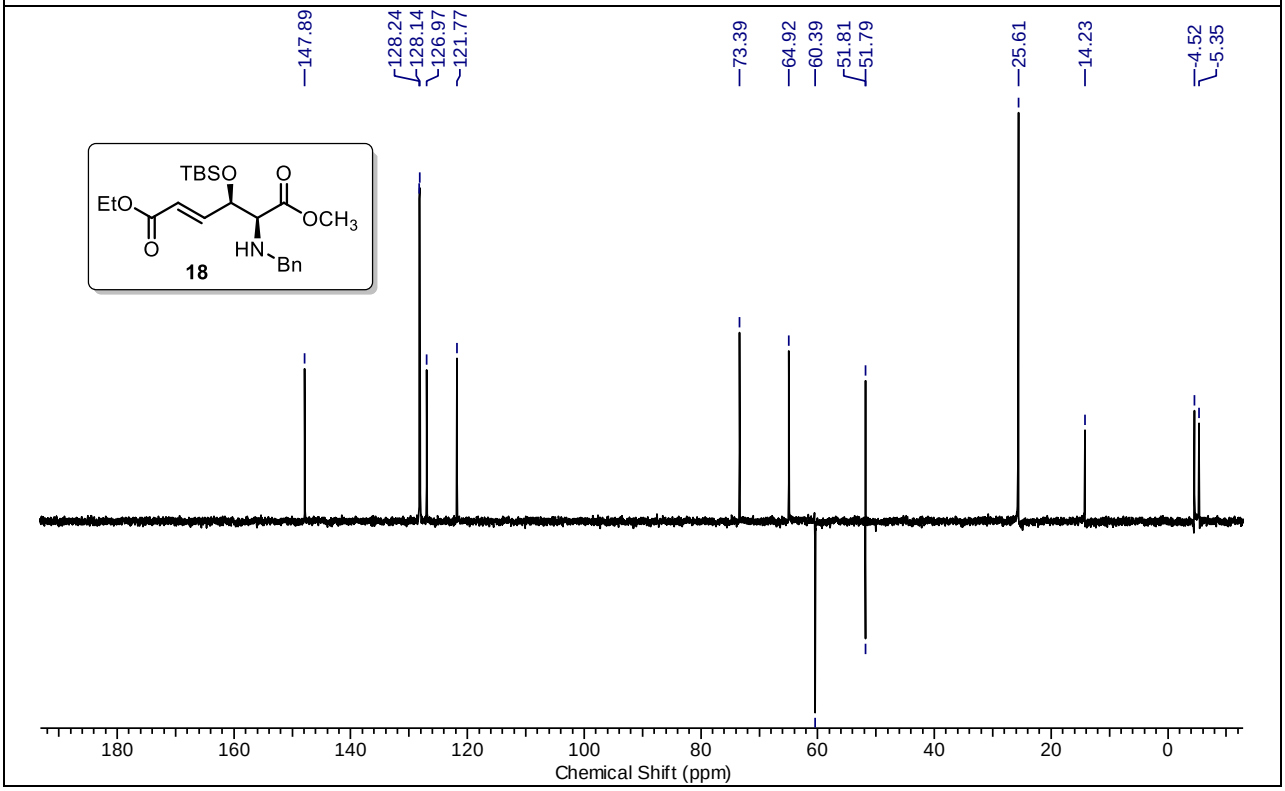
^{1}H-NMR spectrum of compound 18 ($CDCl_3$, 500 MHz)



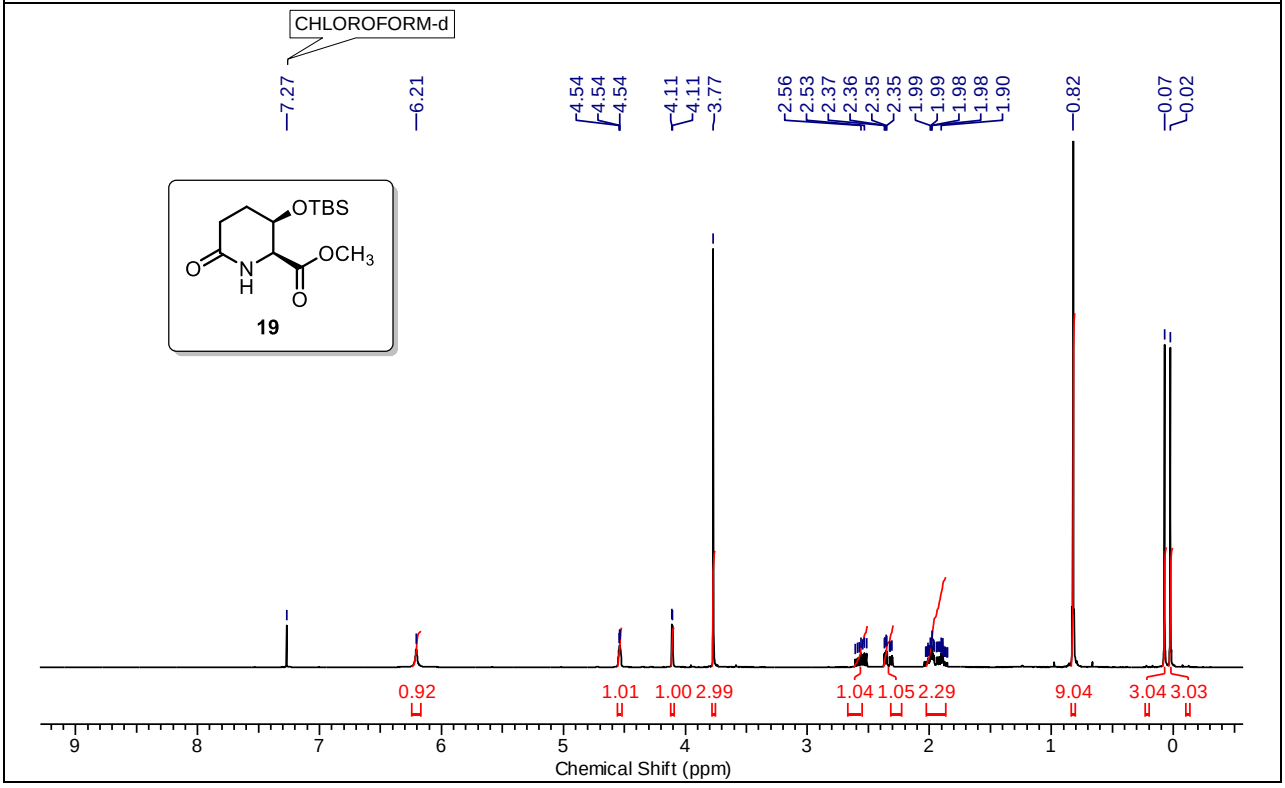
^{13}C-NMR spectrum of compound 18 ($CDCl_3$, 125 MHz)



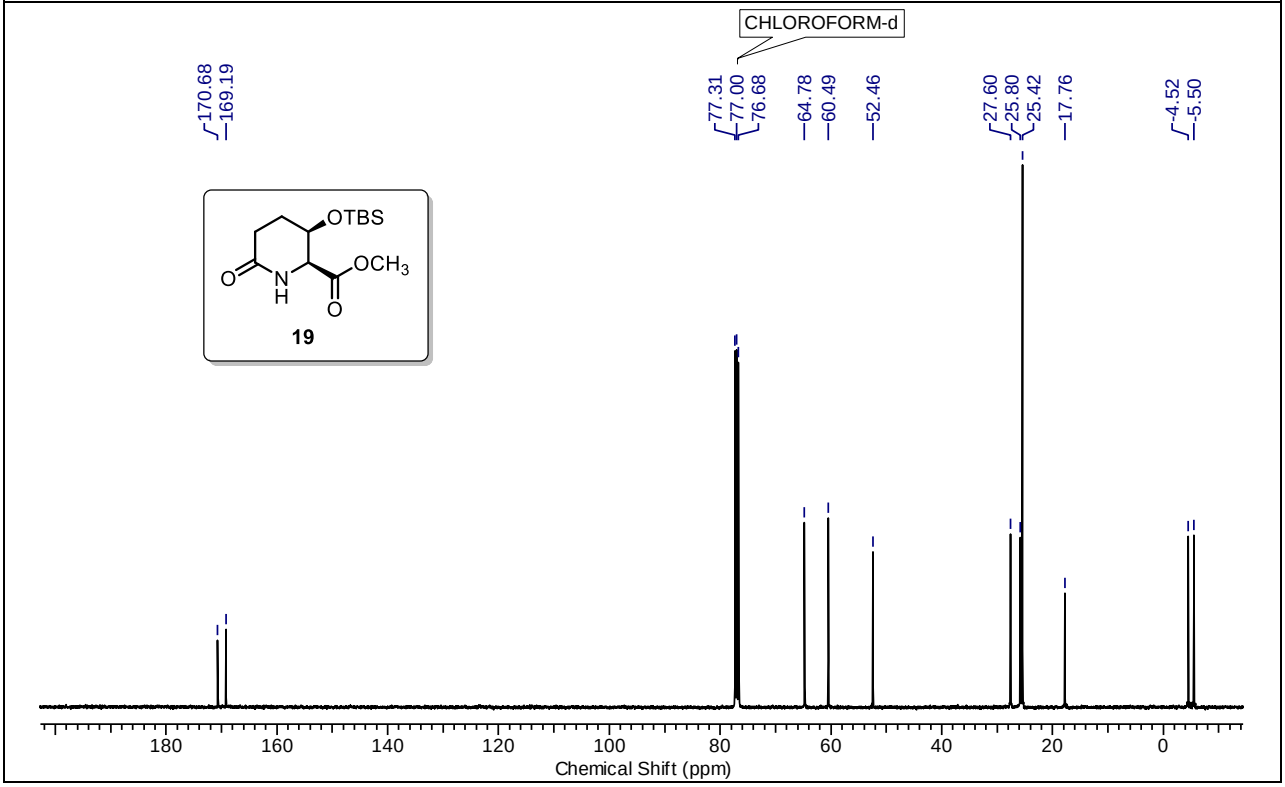
DEPT NMR spectrum of compound 18 ($CDCl_3$, 125 MHz)



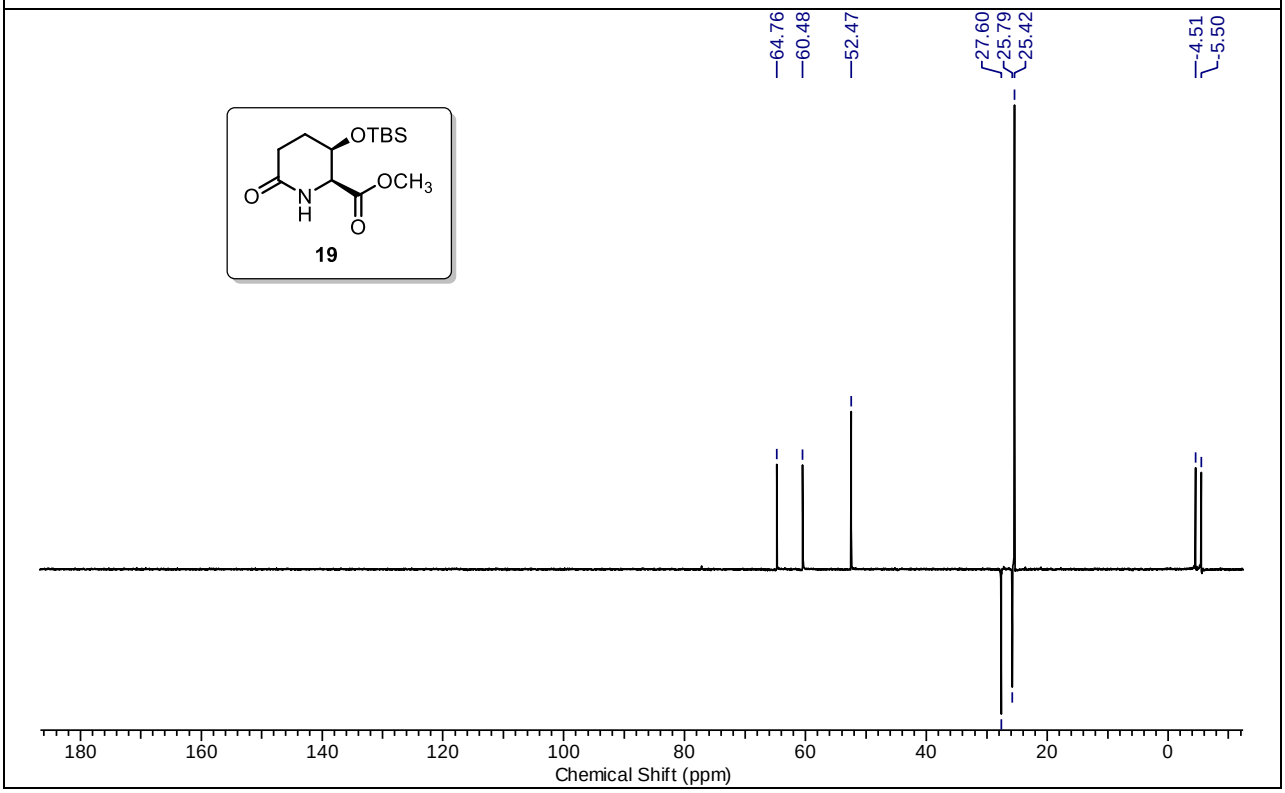
^{1}H-NMR spectrum of compound 19 ($CDCl_3$, 400 MHz)



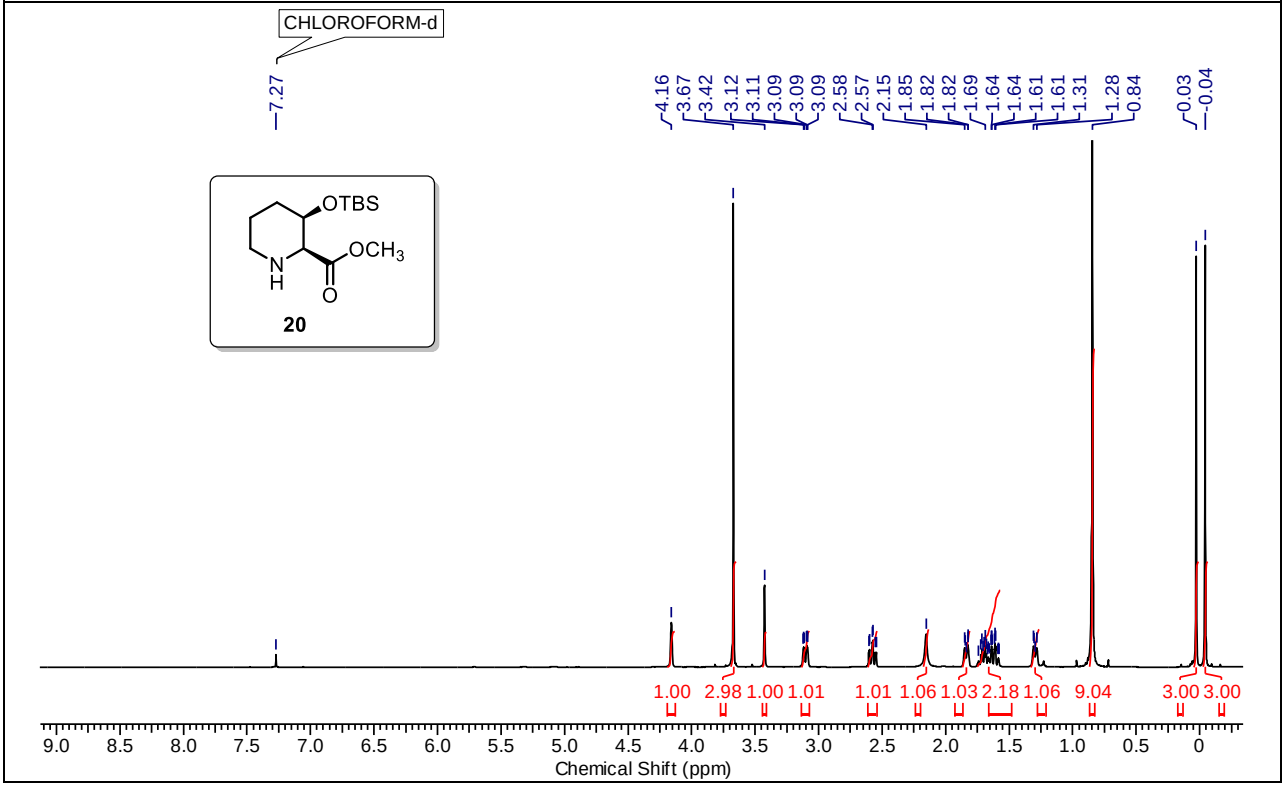
^{13}C-NMR spectrum of compound 19 ($CDCl_3$, 100 MHz)



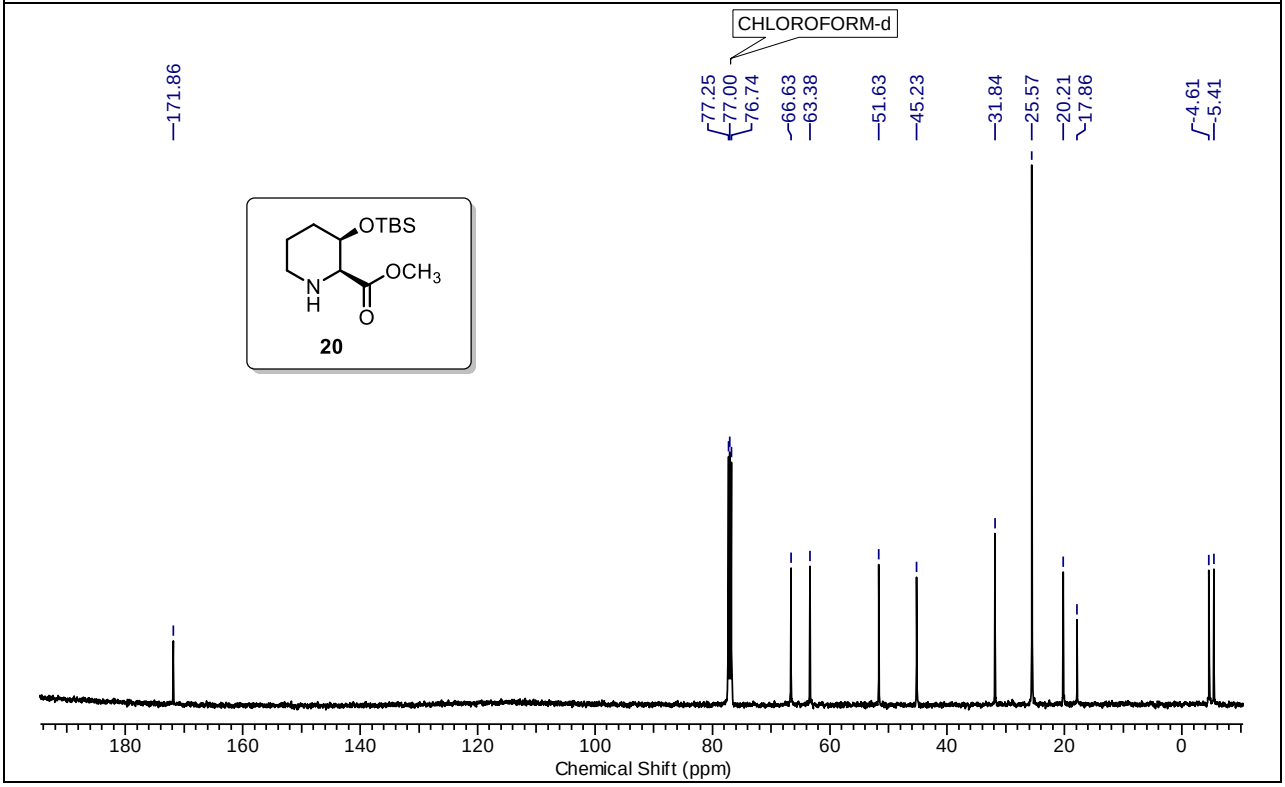
DEPT NMR spectrum of compound 19 ($CDCl_3$, 100 MHz)



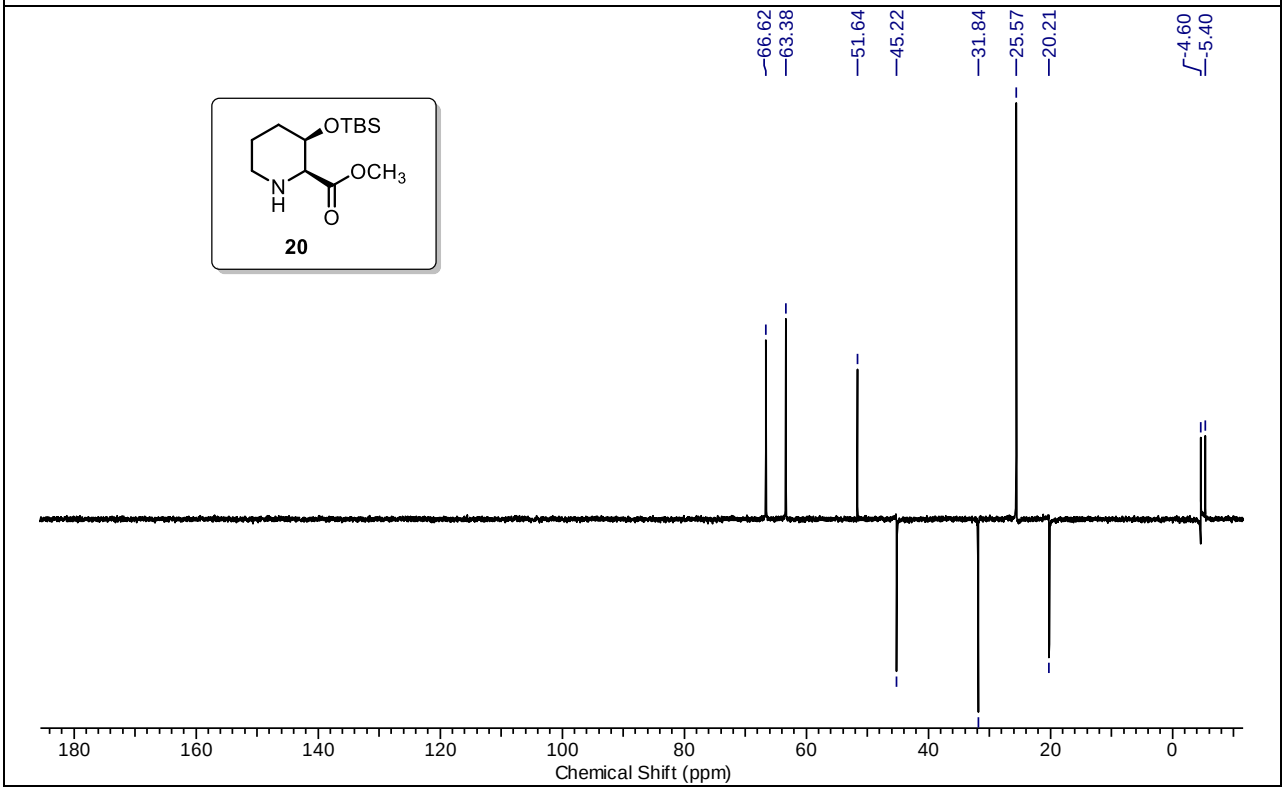
^{1}H-NMR spectrum of compound 20 ($CDCl_3$, 500 MHz)



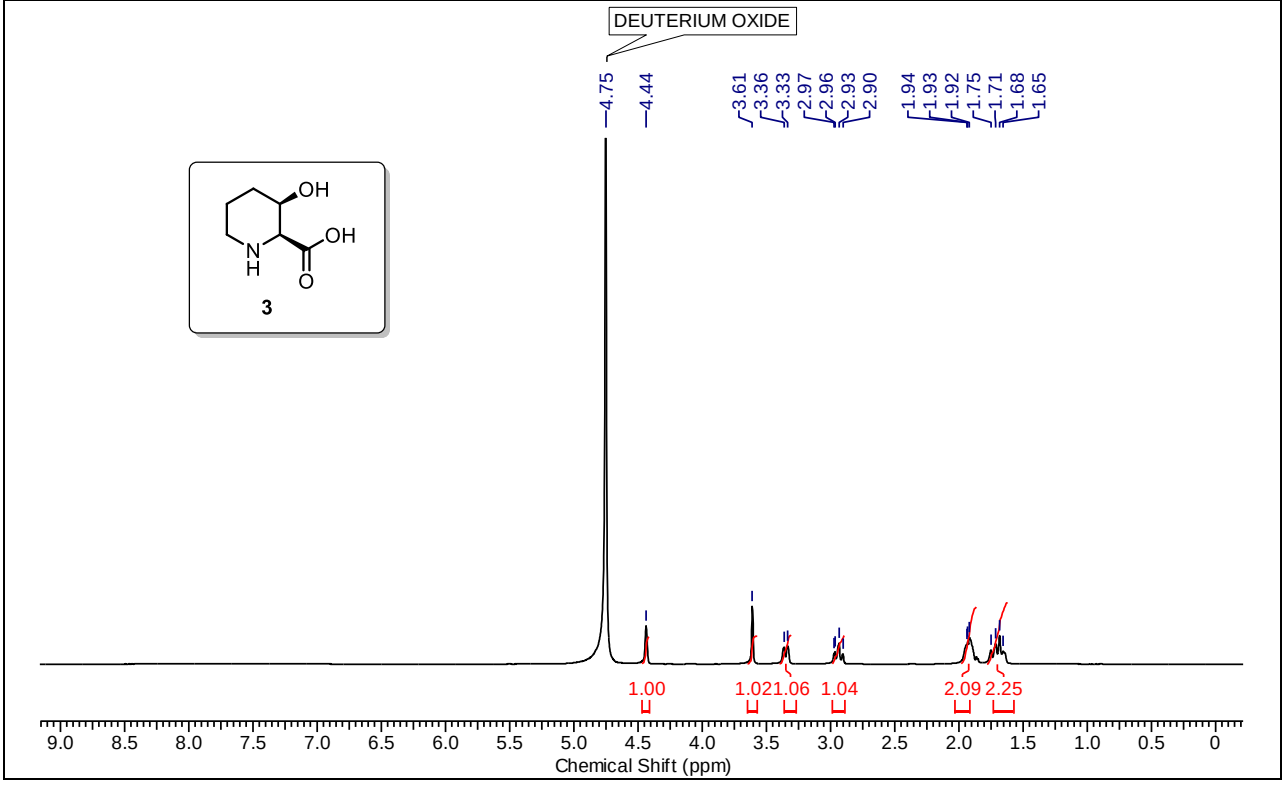
^{13}C-NMR spectrum of compound 20 ($CDCl_3$, 125 MHz)



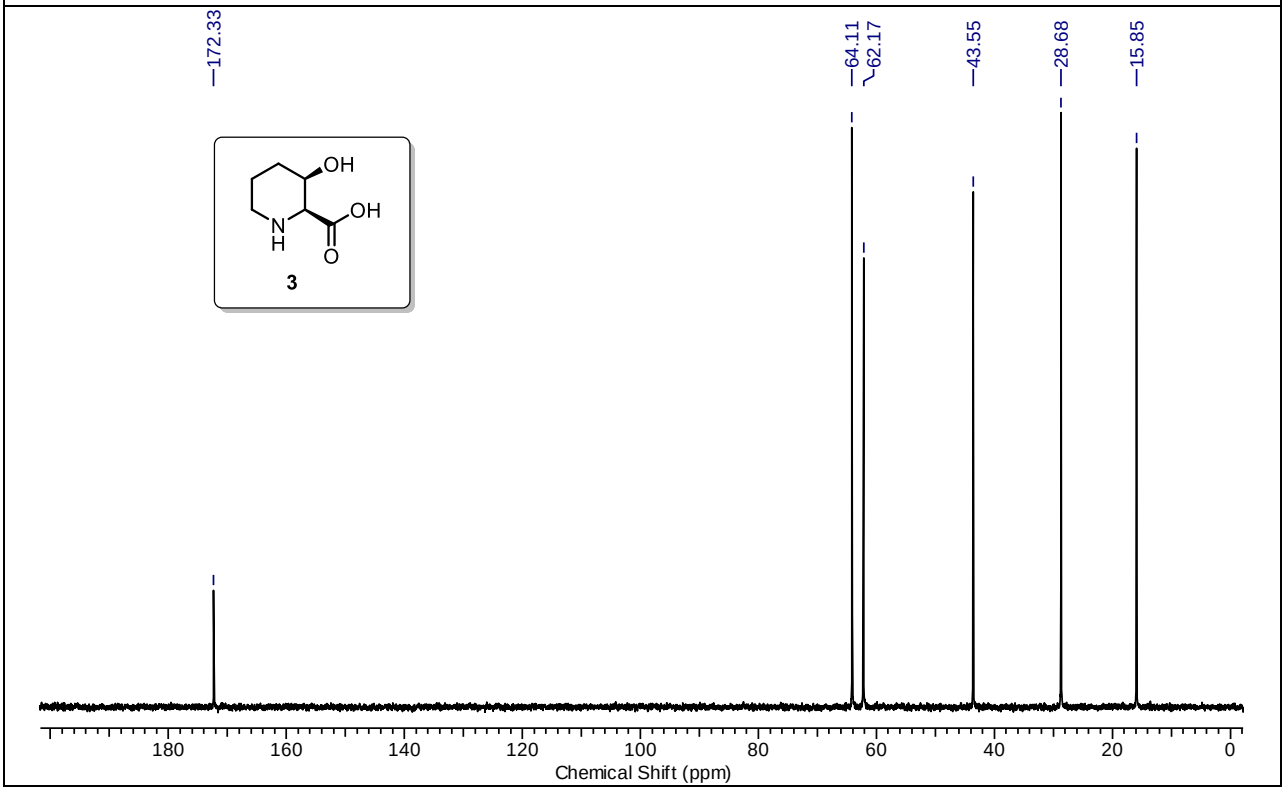
DEPT NMR spectrum of compound 20 ($CDCl_3$, 125 MHz)



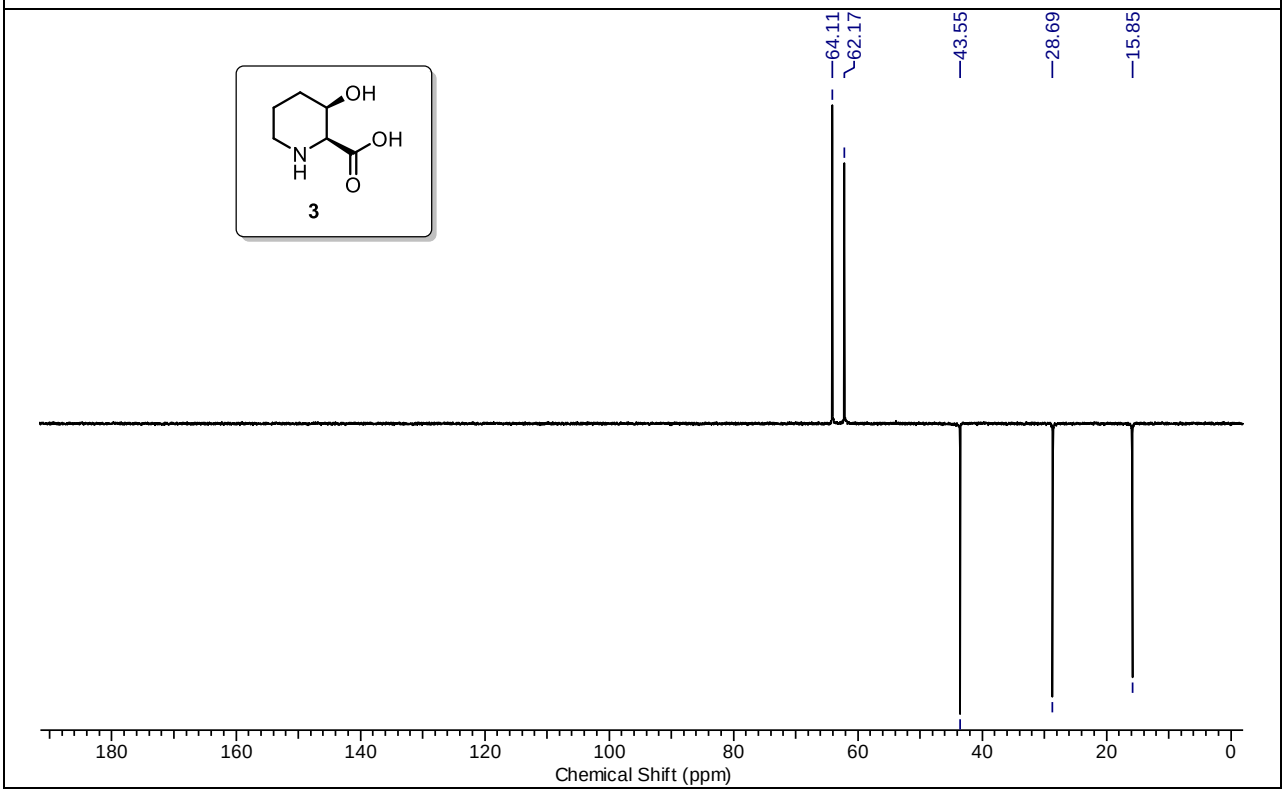
^{1}H-NMR spectrum of compound 3 (D_2O, 400 MHz)



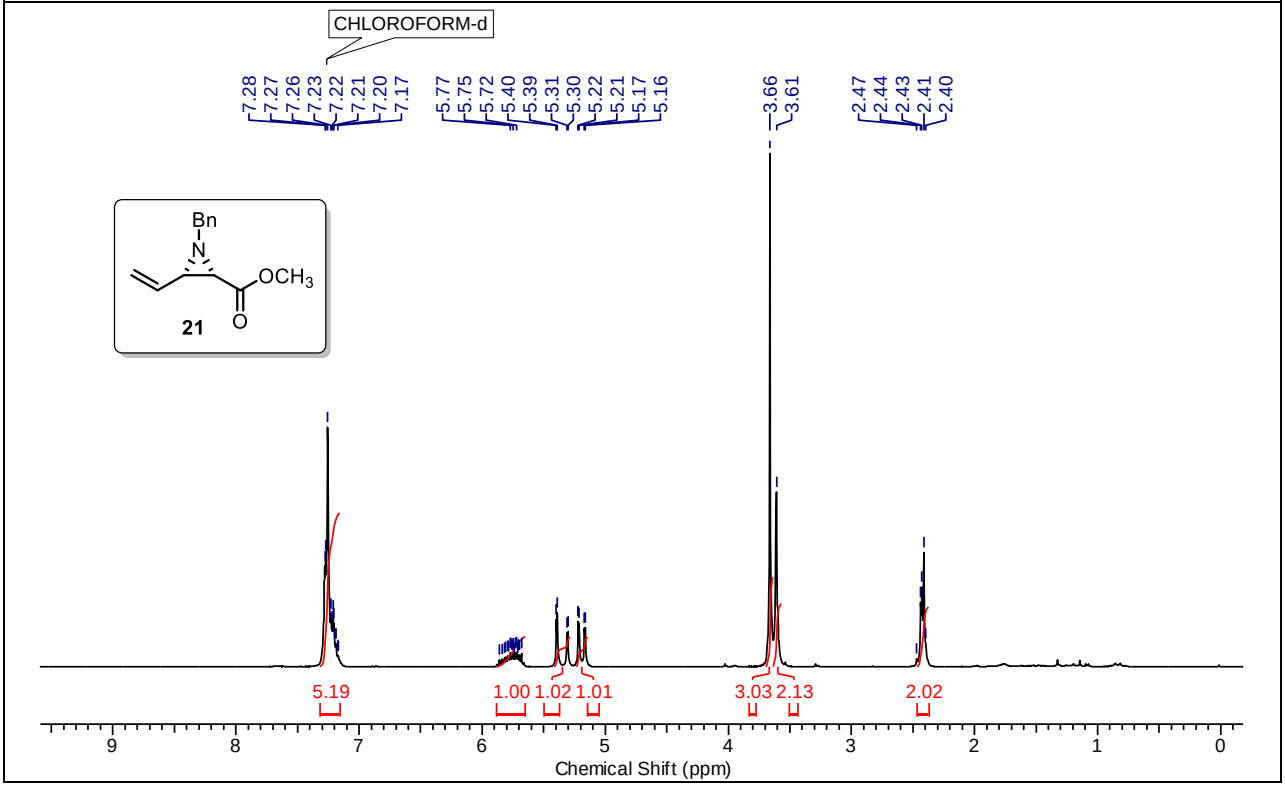
^{13}C-NMR spectrum of compound 3 (D_2O, 100 MHz)



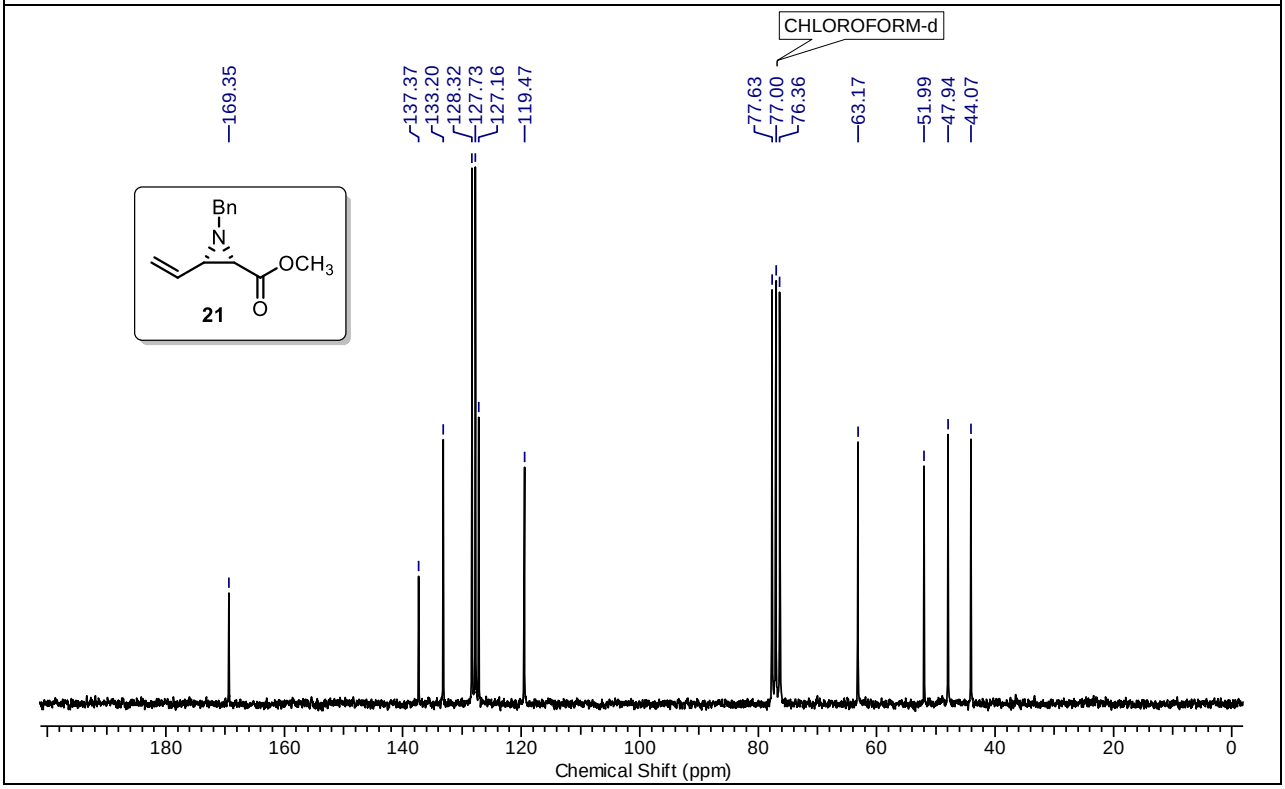
DEPT NMR spectrum of compound 3 (D_2O, 100 MHz)



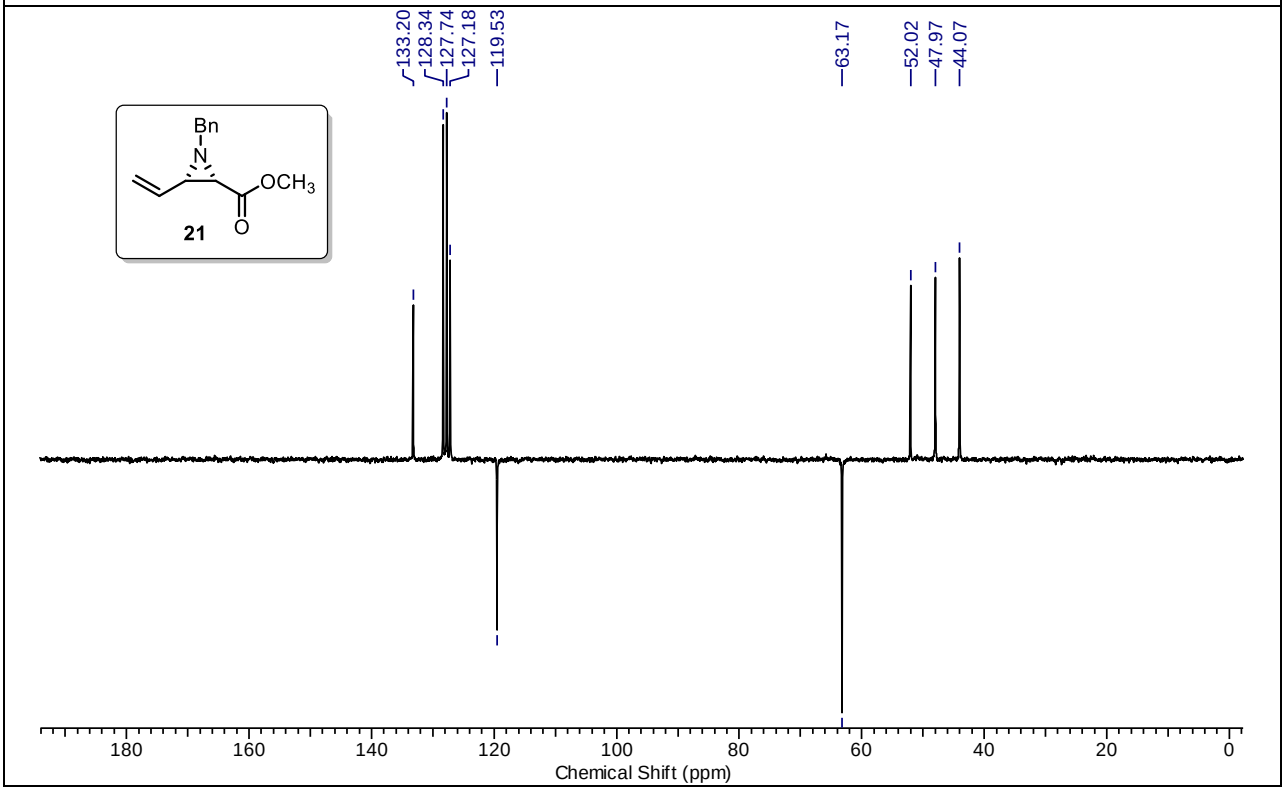
^{1}H-NMR spectrum of compound 21 ($CDCl_3$, 200 MHz)



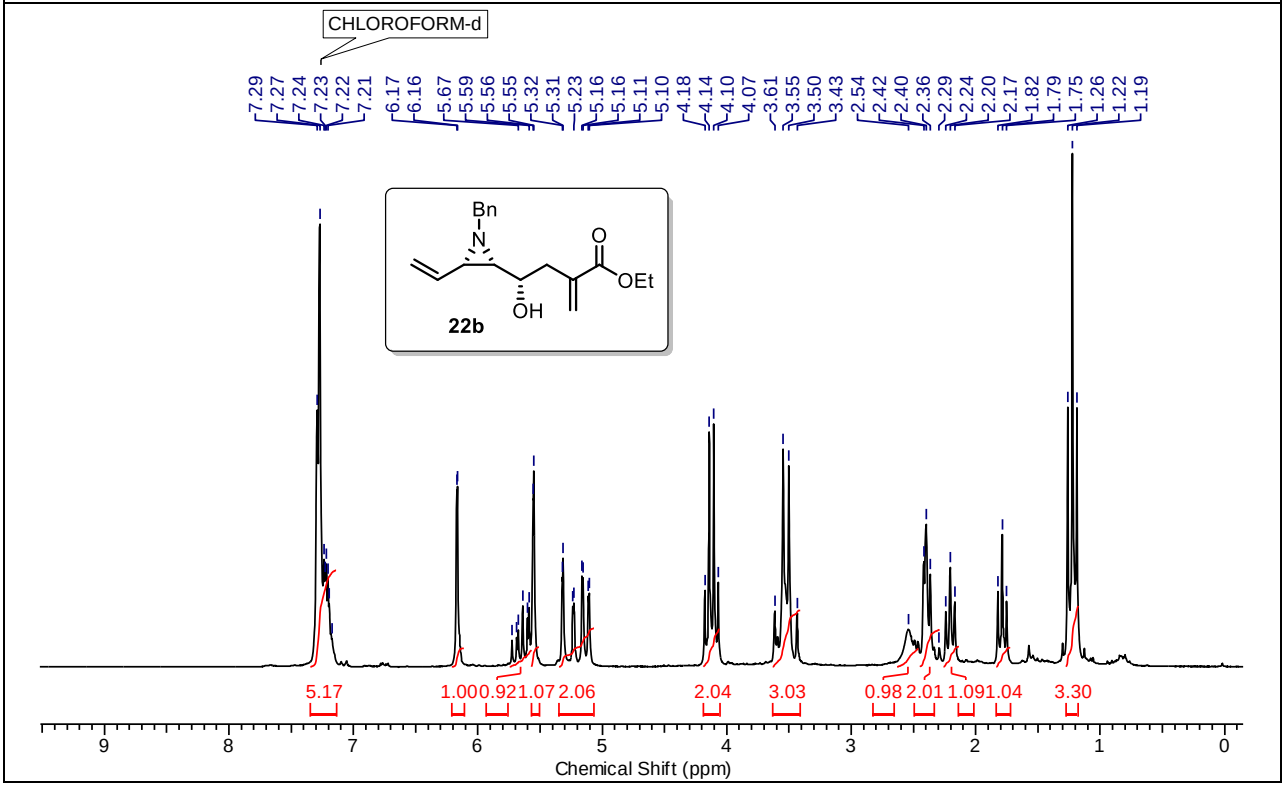
^{13}C-NMR spectrum of compound 21 ($CDCl_3$, 50 MHz)



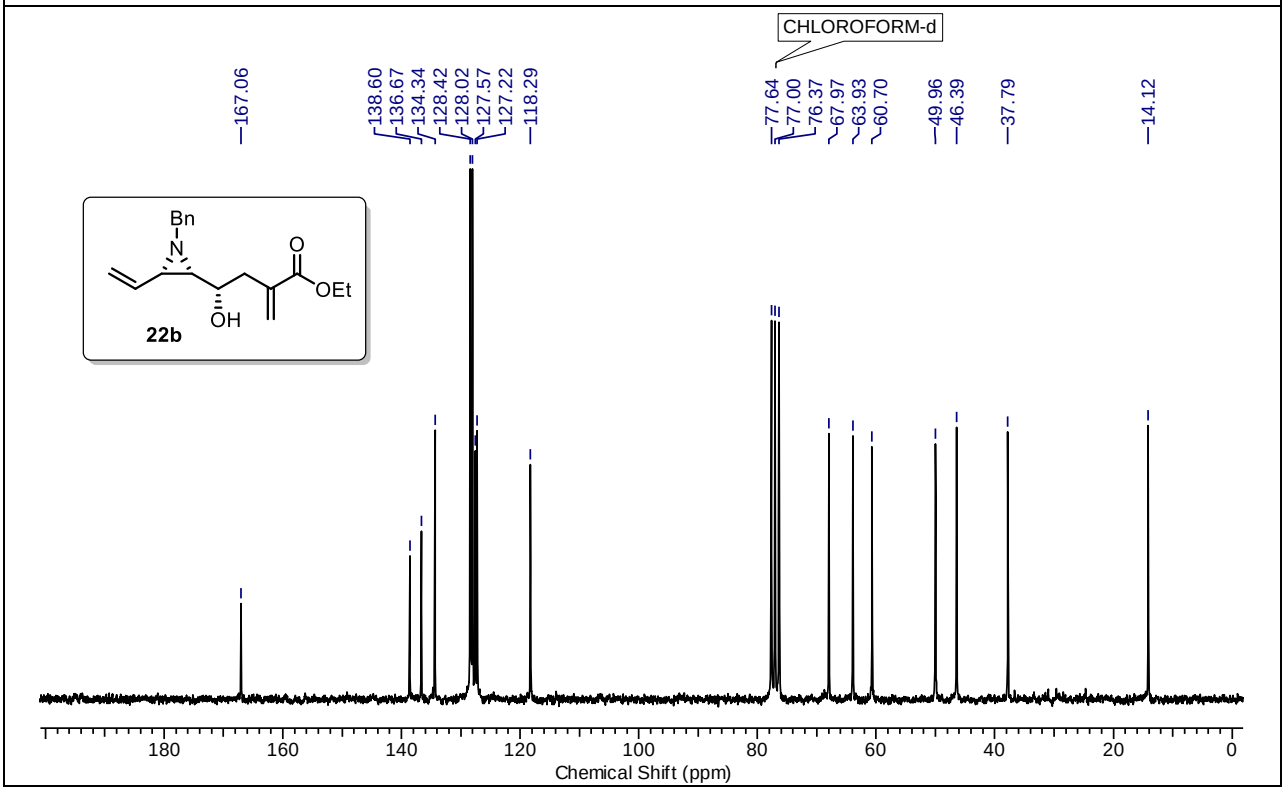
DEPT NMR spectrum of compound 21 ($CDCl_3$, 50 MHz)



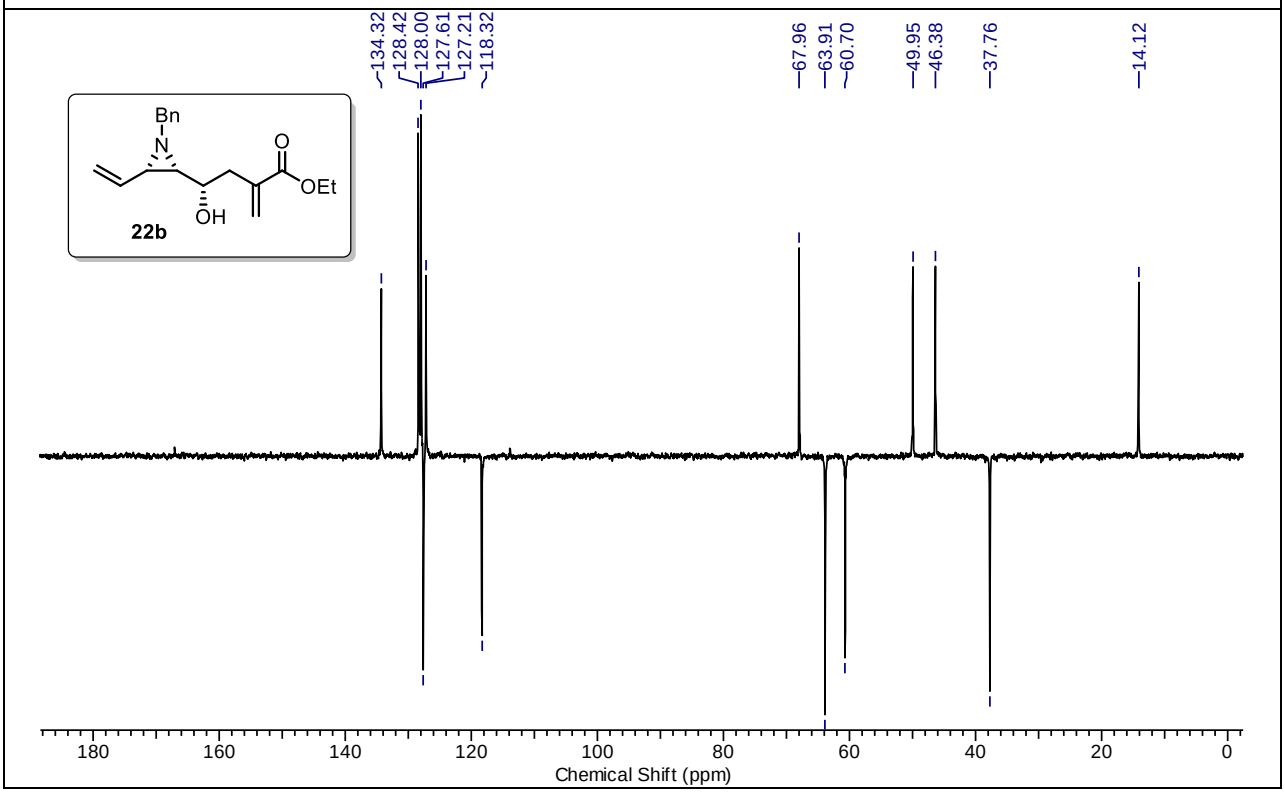
^{1}H-NMR spectrum of compound 22b ($CDCl_3$, 200 MHz)



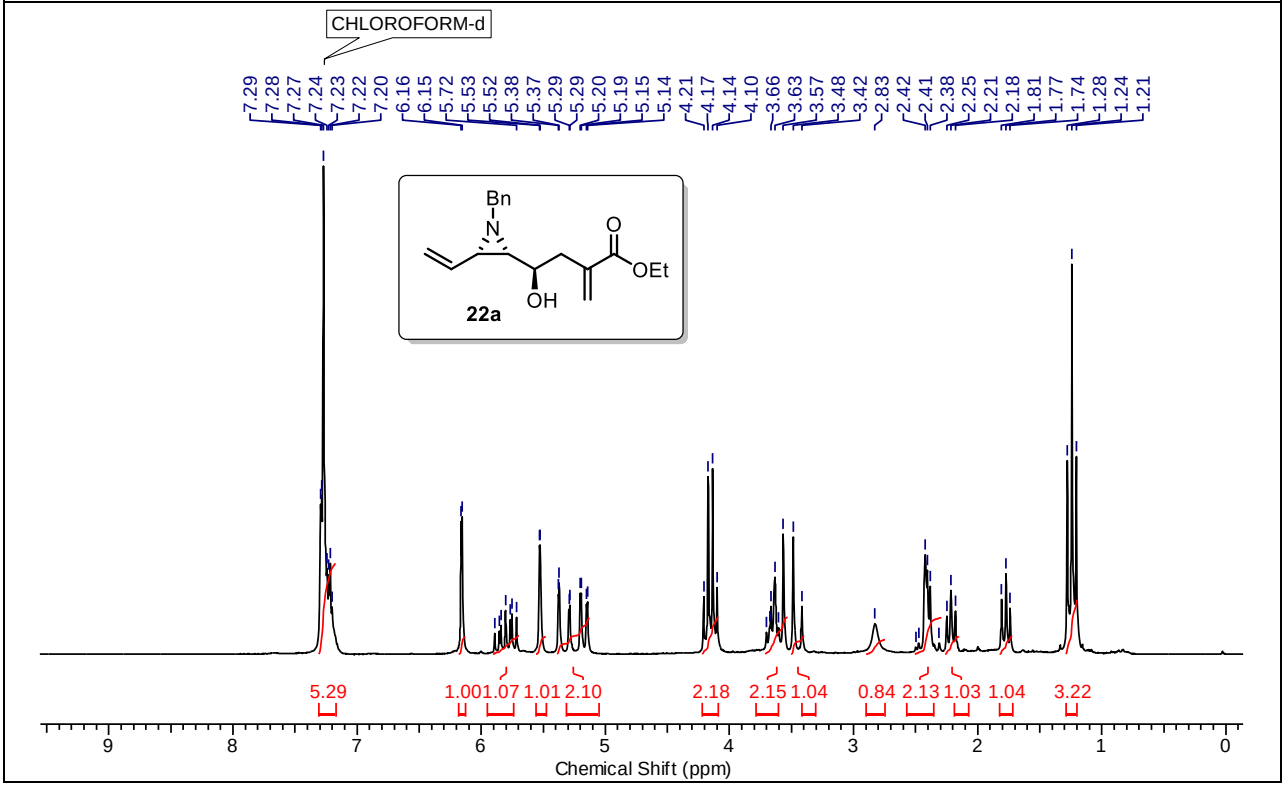
^{13}C-NMR spectrum of compound 22b ($CDCl_3$, 50 MHz)



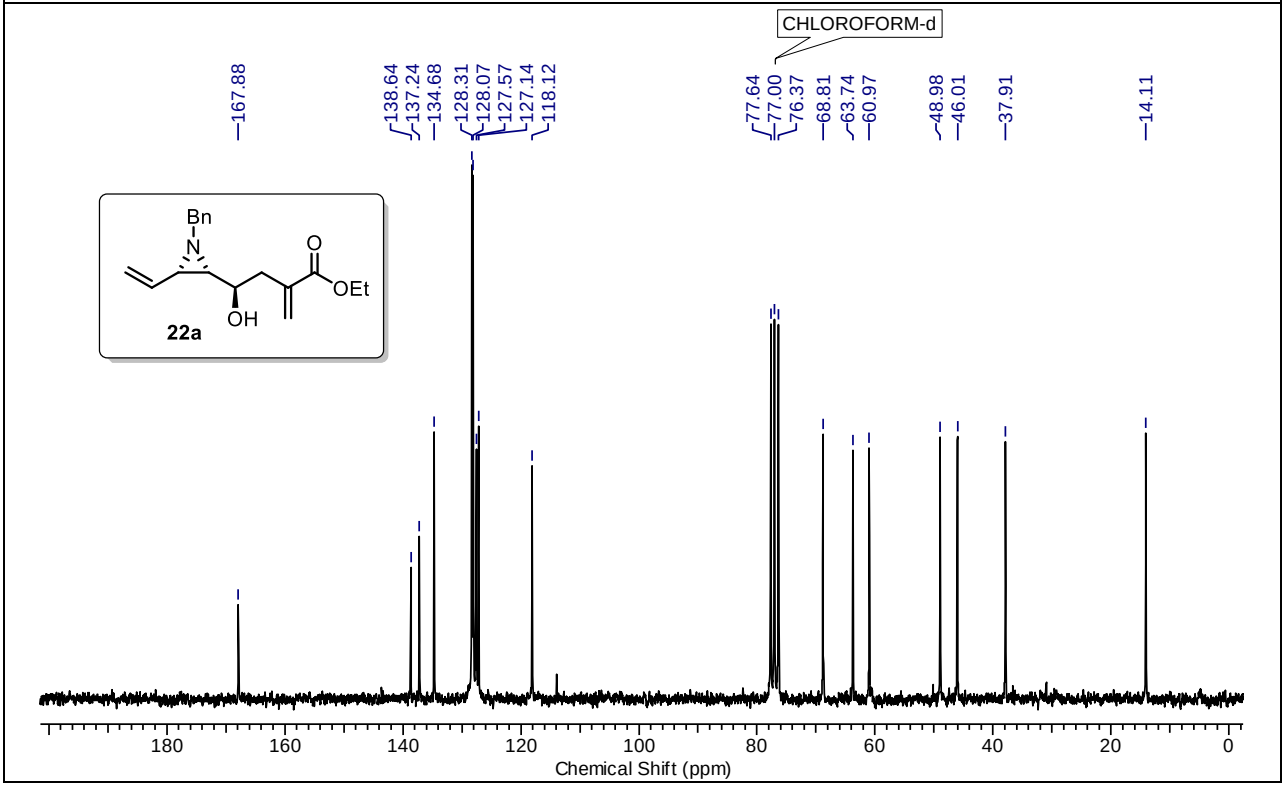
DEPT NMR spectrum of compound 22b ($CDCl_3$, 50 MHz)



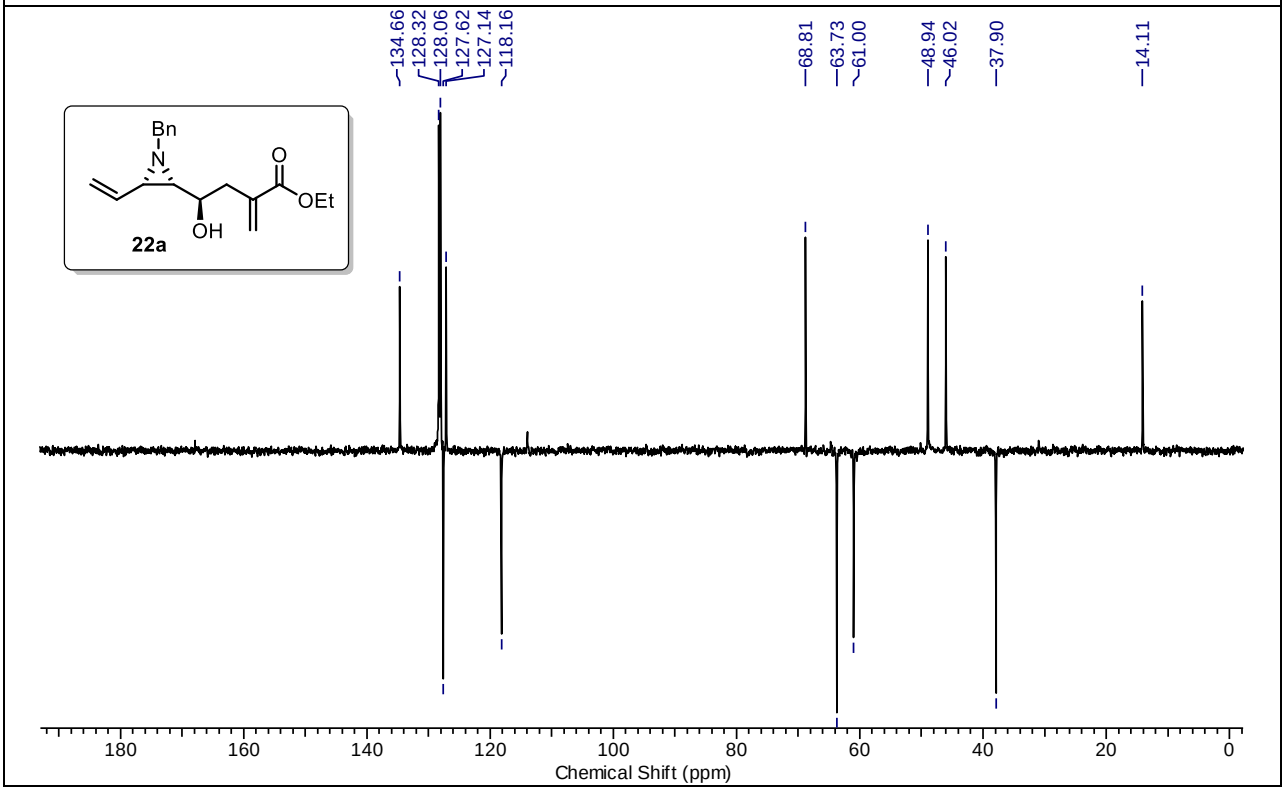
^{1}H-NMR spectrum of compound 22a ($CDCl_3$, 200 MHz)



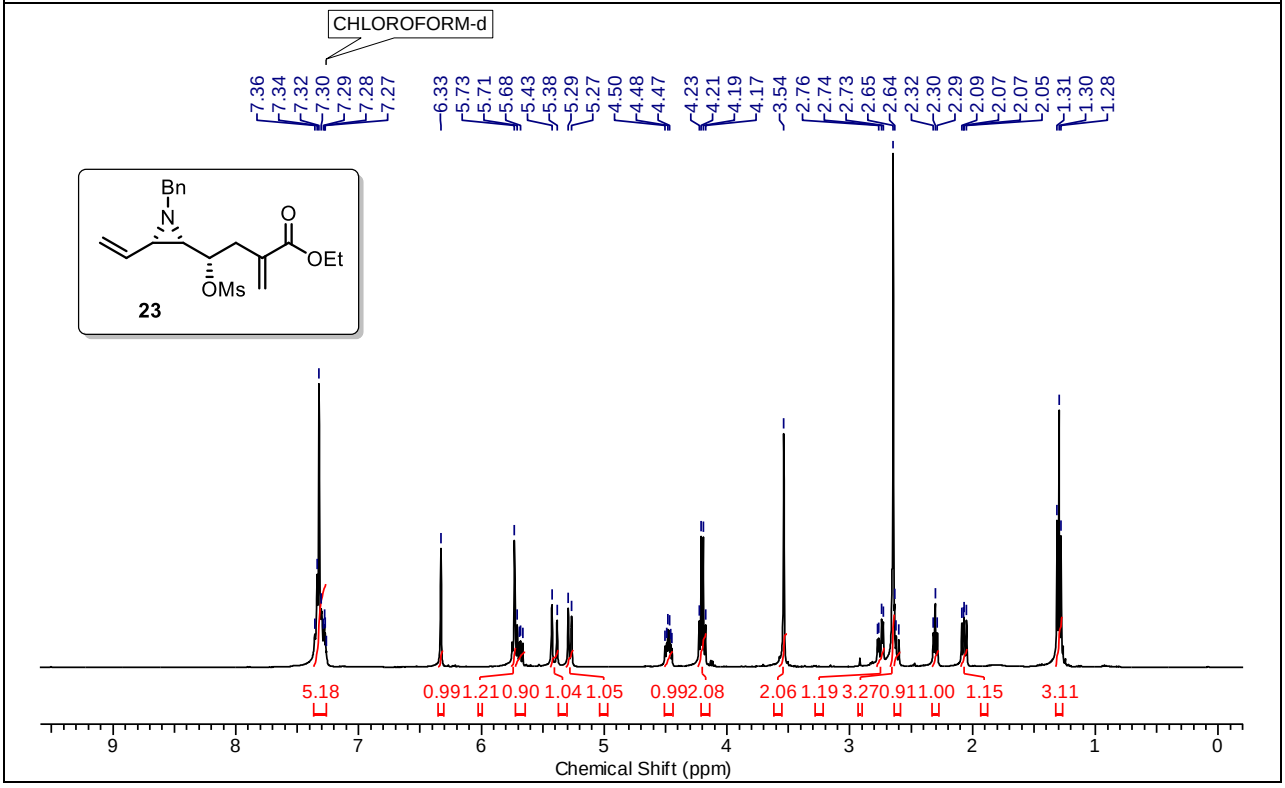
^{13}C-NMR spectrum of compound 22a ($CDCl_3$, 50 MHz)



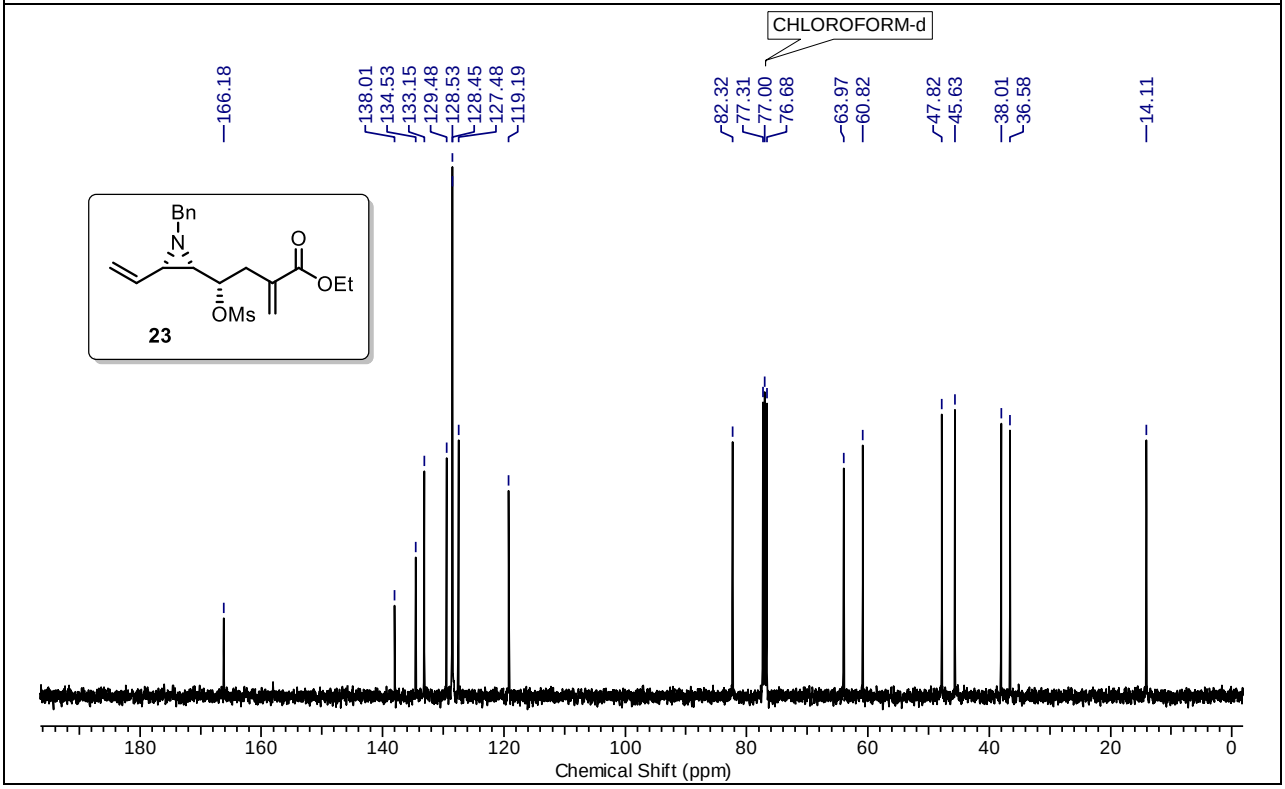
DEPT NMR spectrum of compound 22a ($CDCl_3$, 50 MHz)



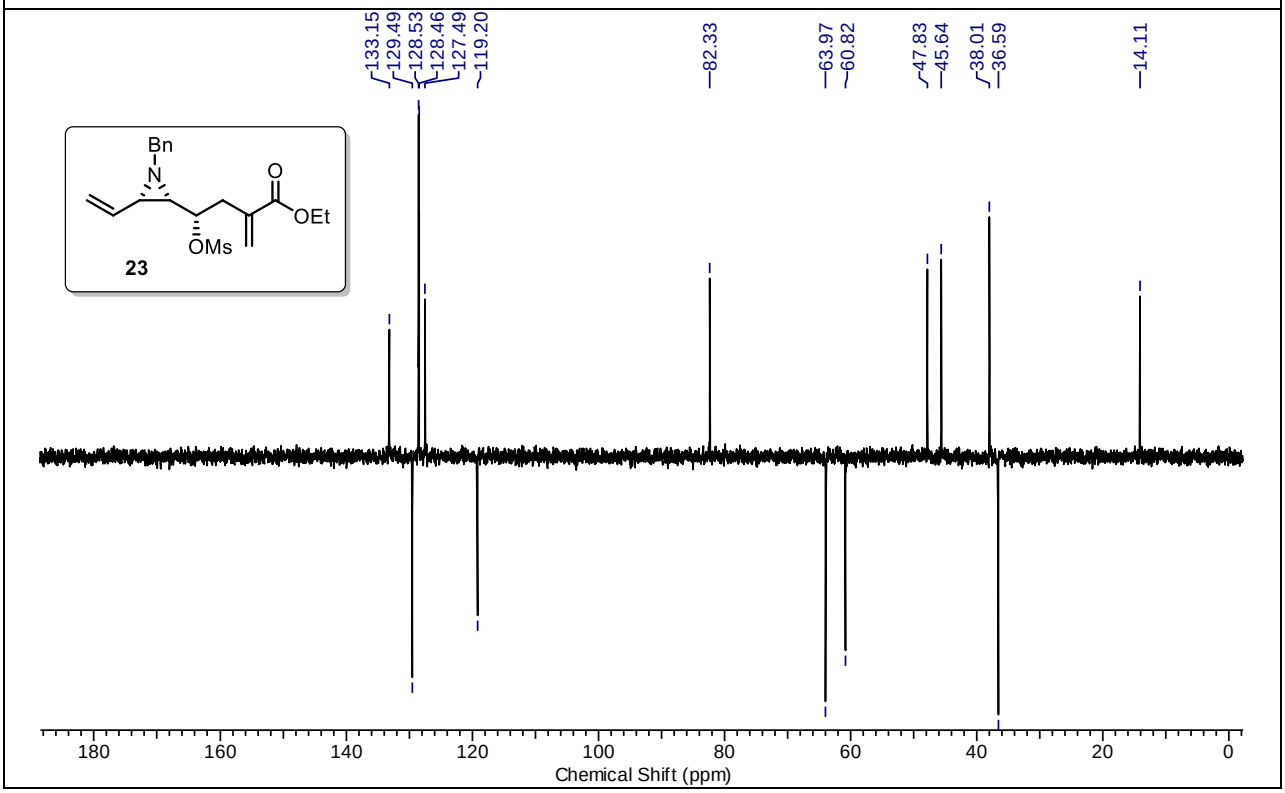
^{1}H-NMR spectrum of compound 23 ($CDCl_3$, 400 MHz)



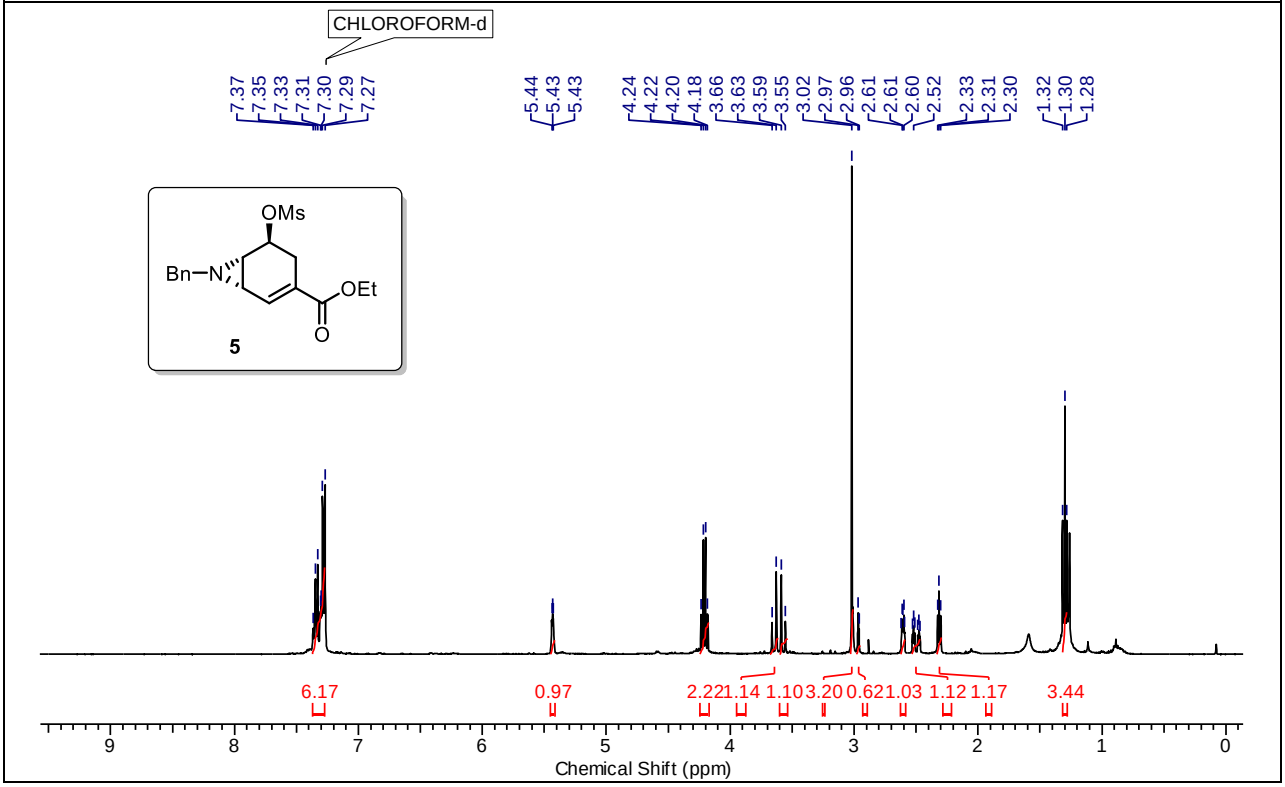
^{13}C-NMR spectrum of compound 23 ($CDCl_3$, 100 MHz)



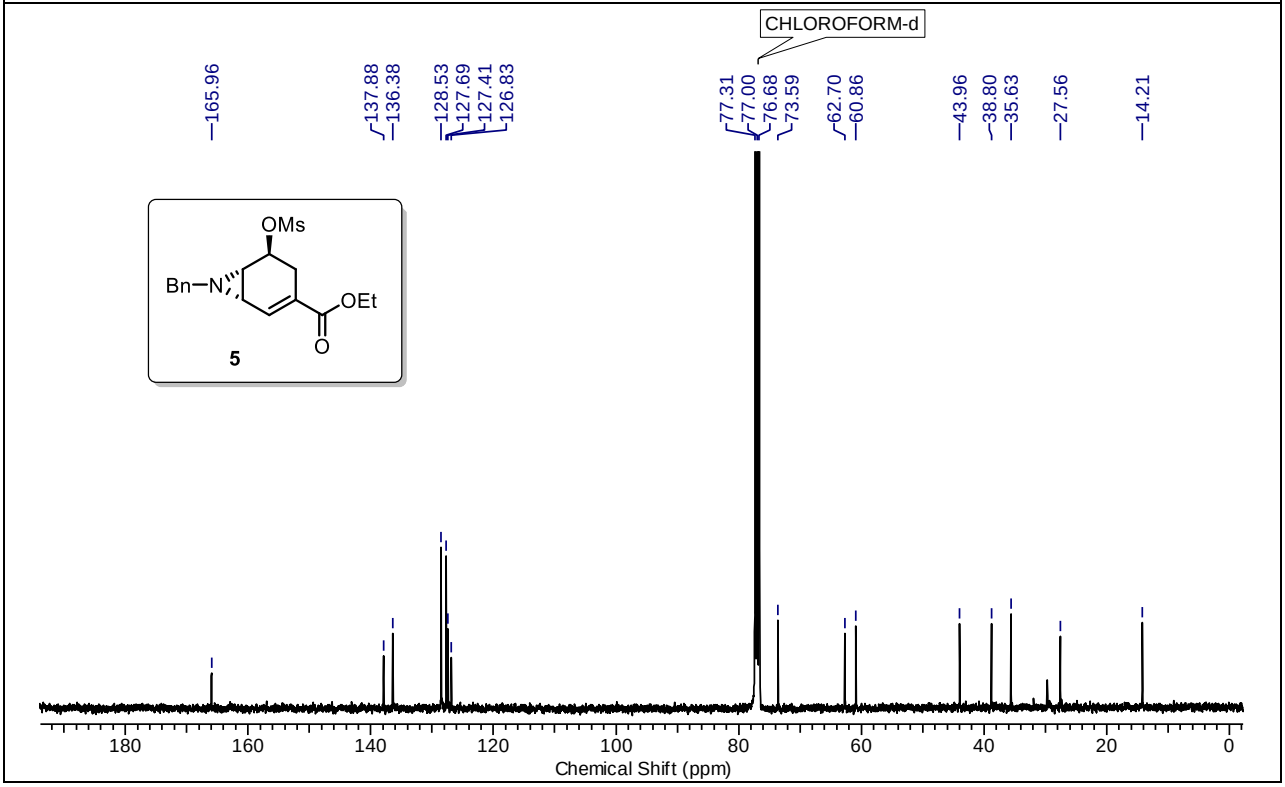
DEPT NMR spectrum of compound 23 ($CDCl_3$, 100 MHz)



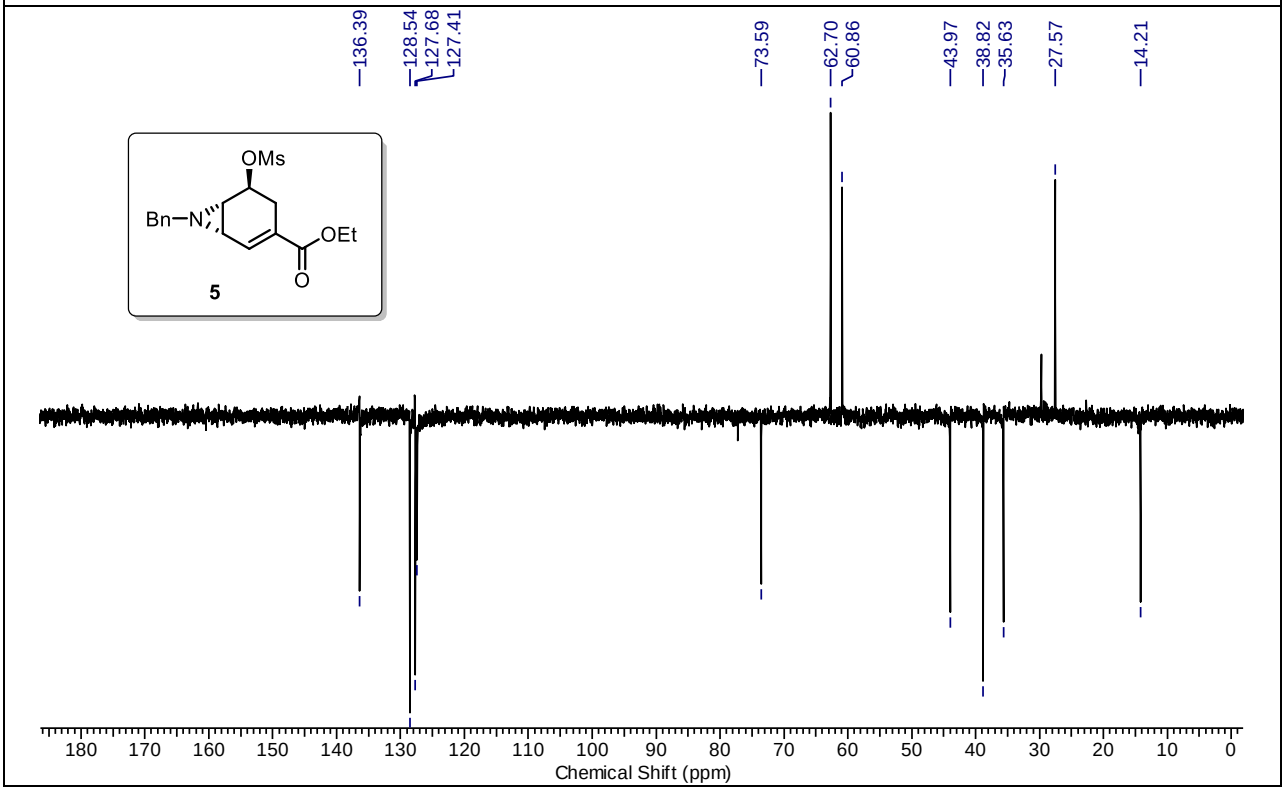
^{1}H-NMR spectrum of compound 5 ($CDCl_3$, 400 MHz)



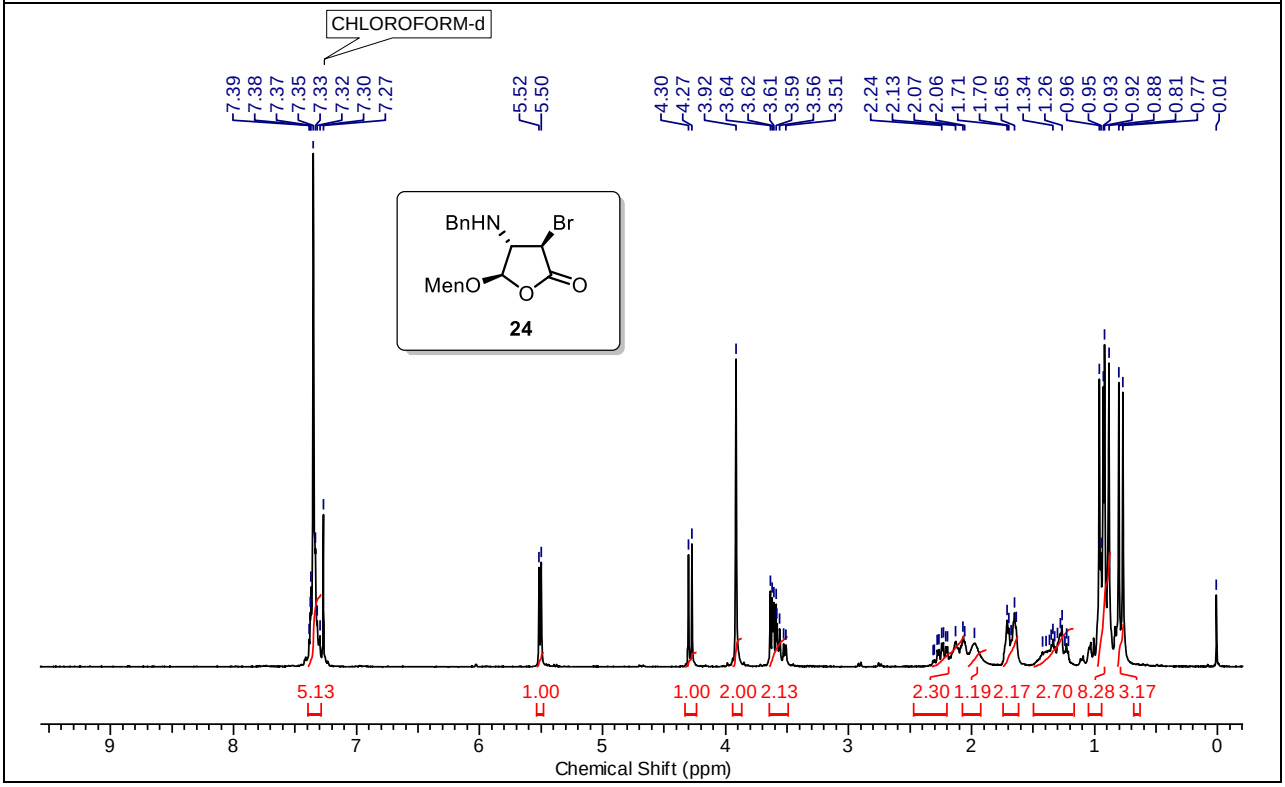
^{13}C-NMR spectrum of compound 5 ($CDCl_3$, 100 MHz)



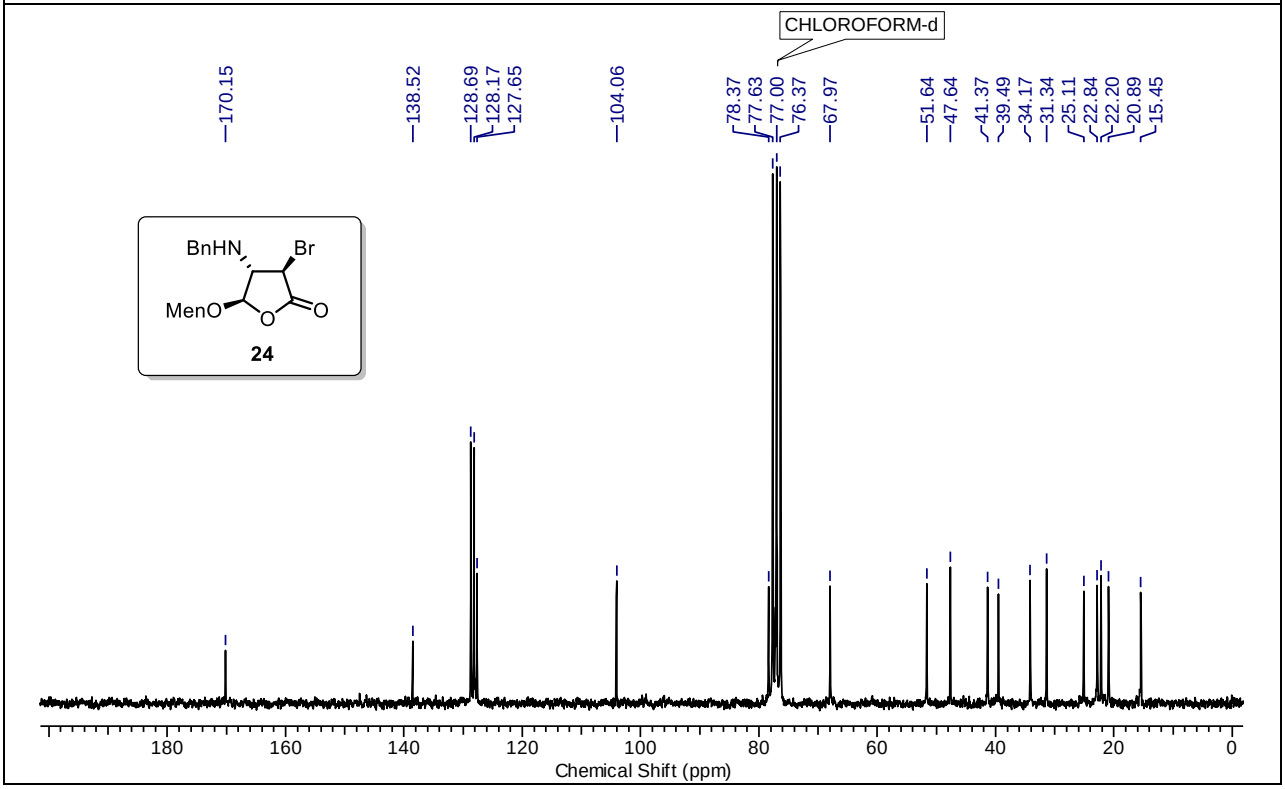
DEPT NMR spectrum of compound 5 ($CDCl_3$, 100 MHz)



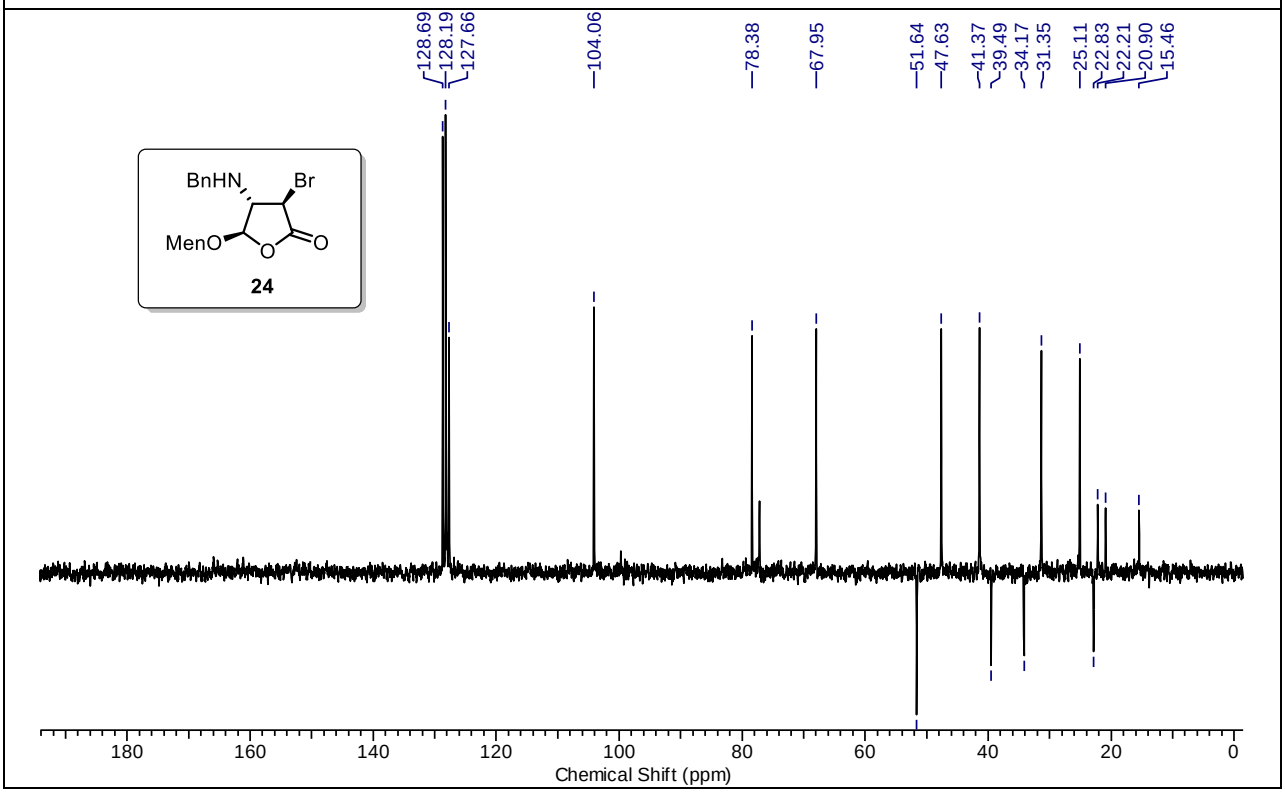
^{1}H-NMR spectrum of compound 24 ($CDCl_3$, 200 MHz)



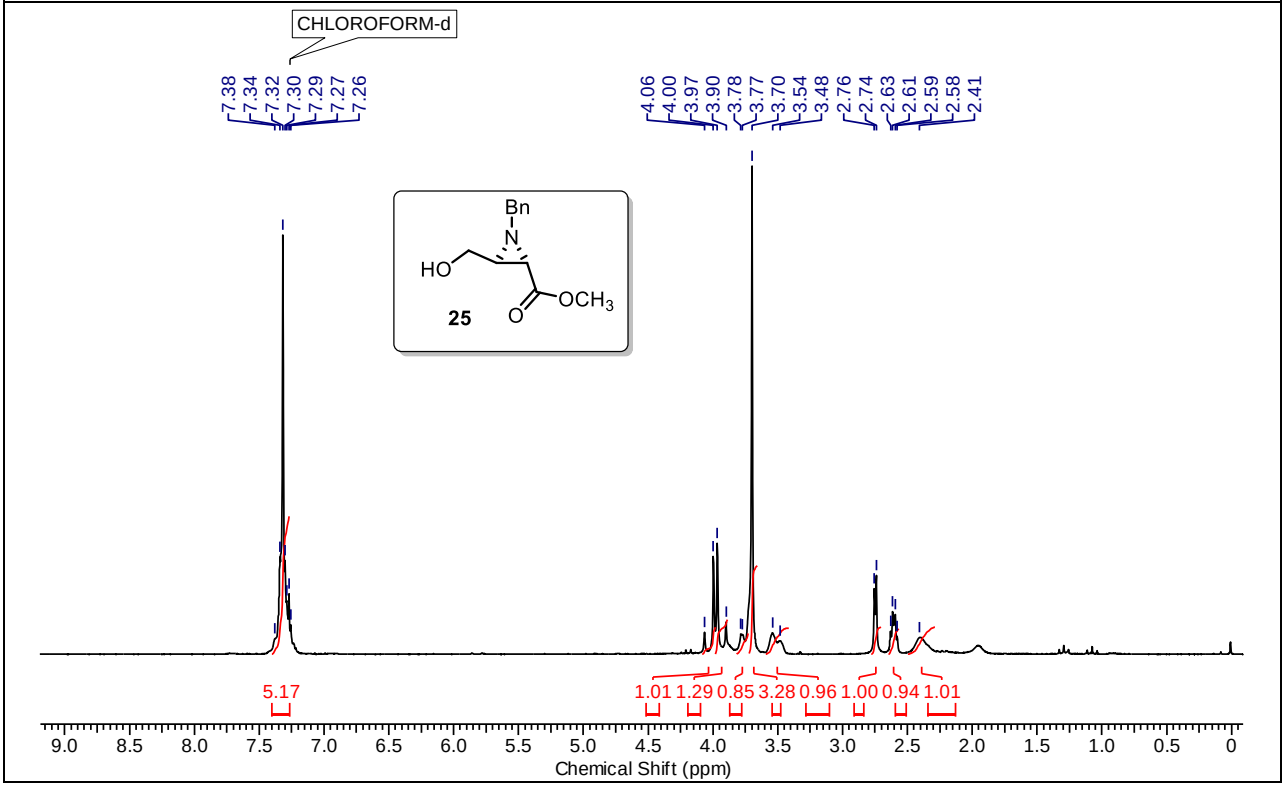
^{13}C-NMR spectrum of compound 24 ($CDCl_3$, 50 MHz)



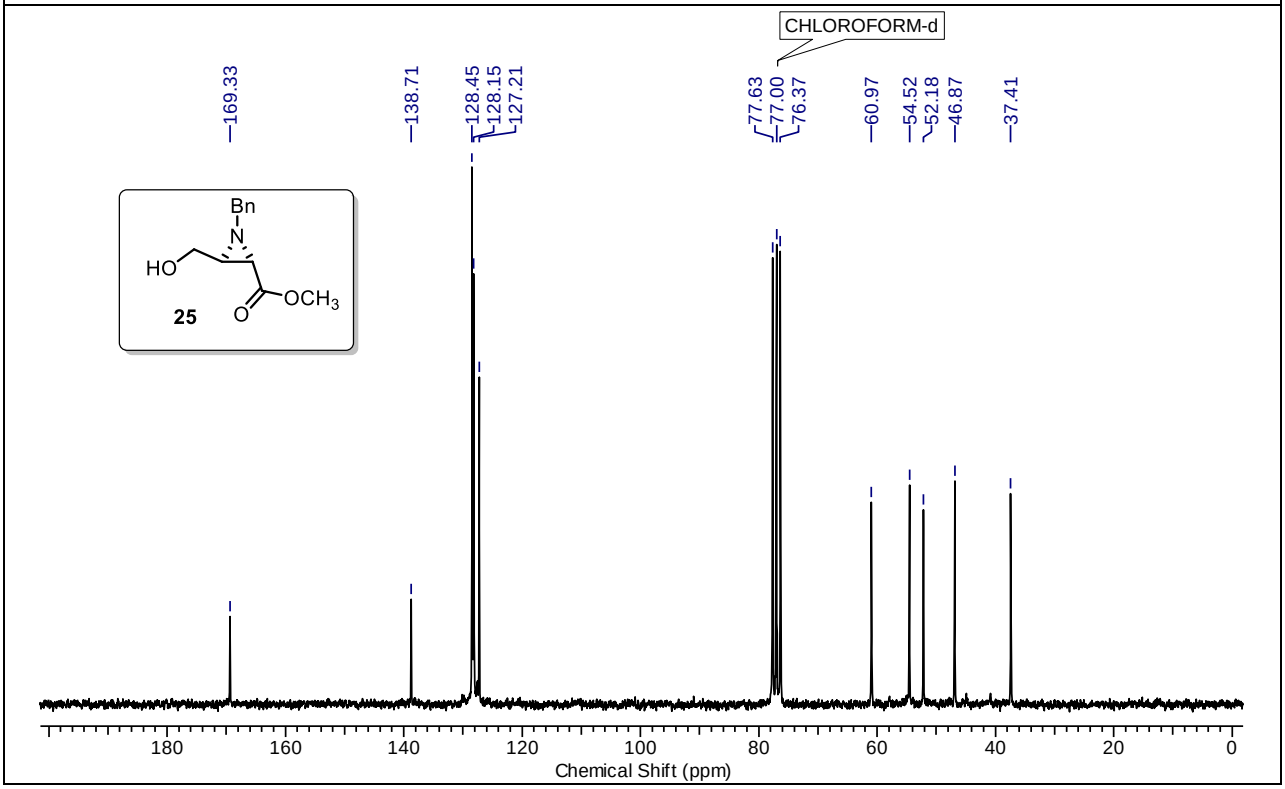
DEPT NMR spectrum of compound 24 ($CDCl_3$, 50 MHz)



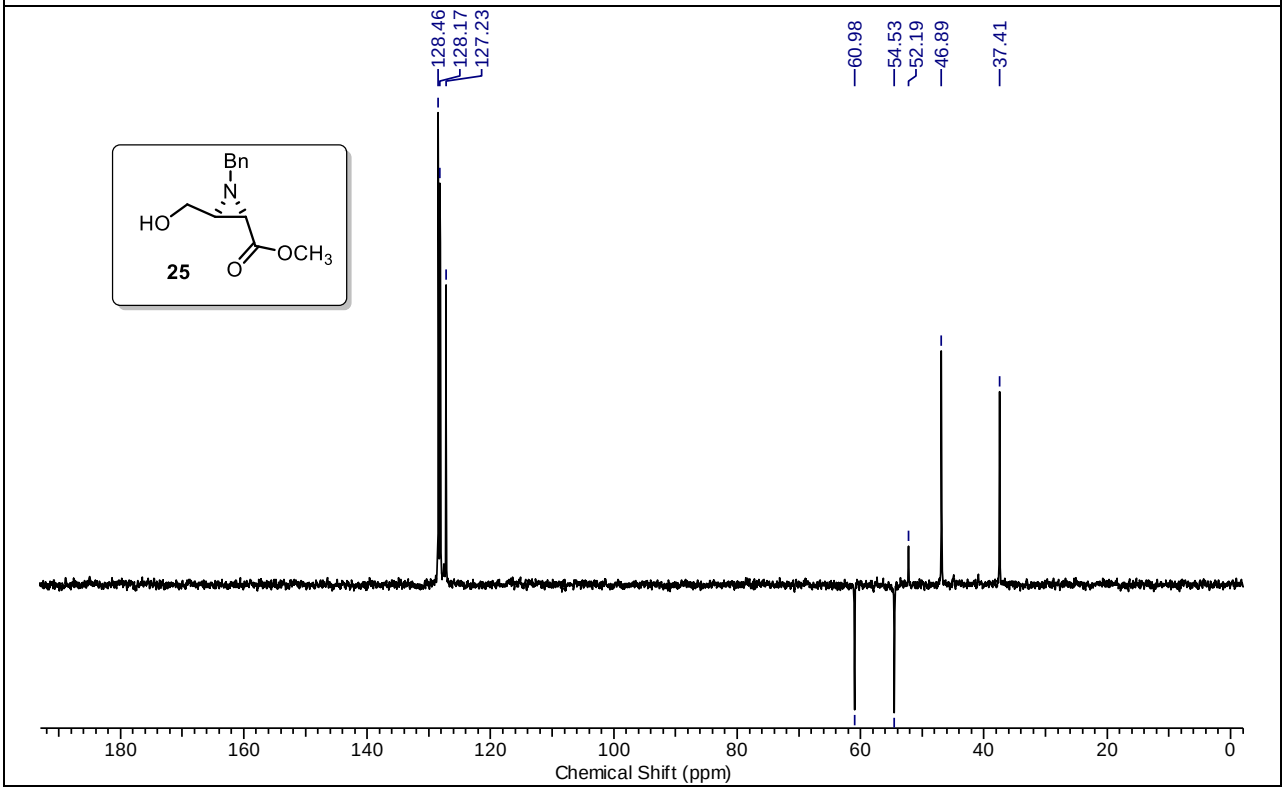
^{1}H-NMR spectrum of compound 25 ($CDCl_3$, 200 MHz)



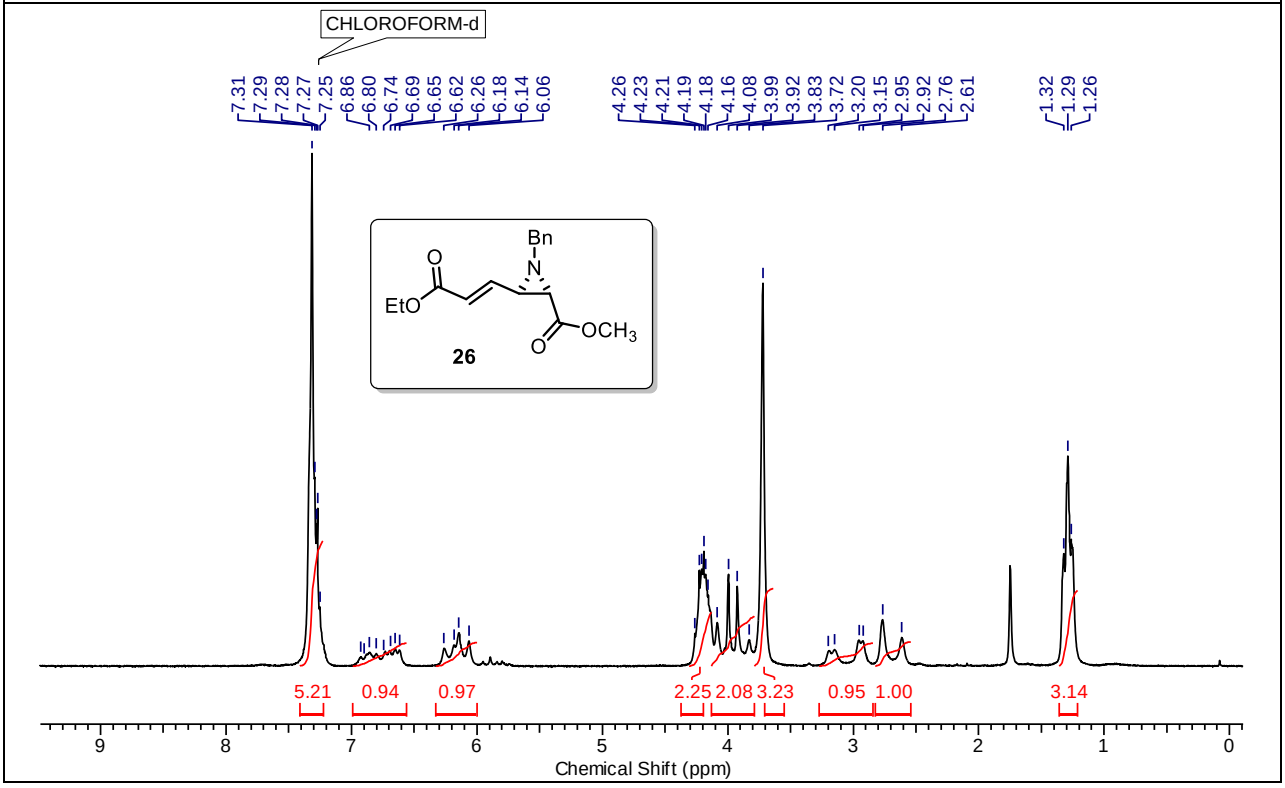
^{13}C-NMR spectrum of compound 25 ($CDCl_3$, 50 MHz)



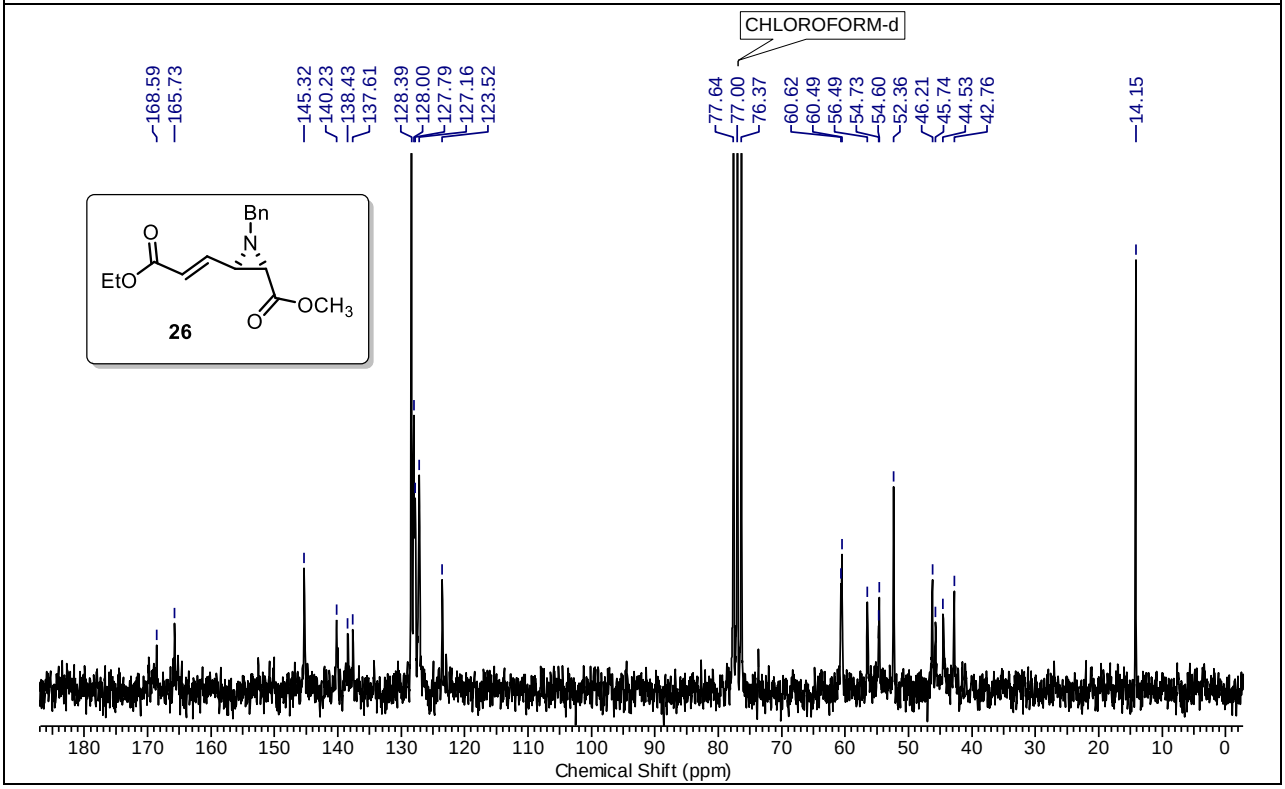
DEPT NMR spectrum of compound 25 ($CDCl_3$, 50 MHz)



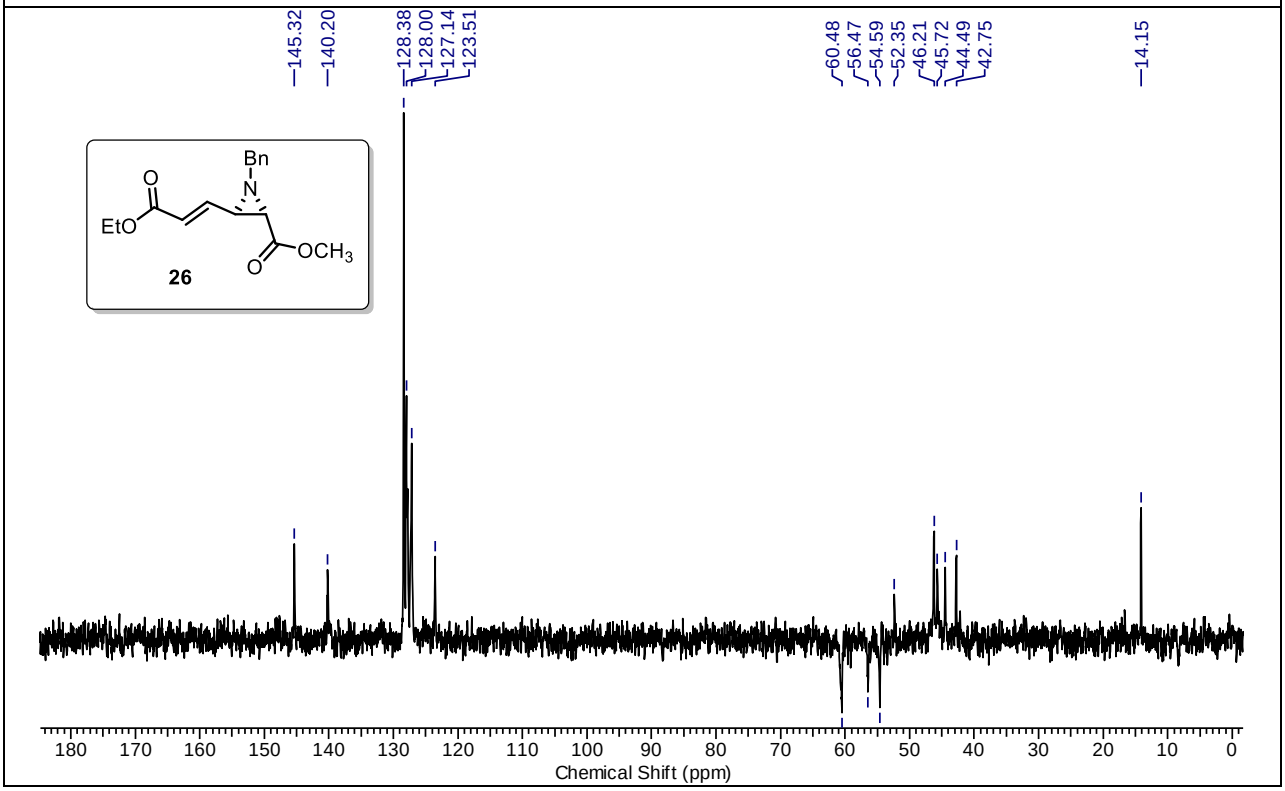
^{1}H-NMR spectrum of compound 26 ($CDCl_3$, 200 MHz)



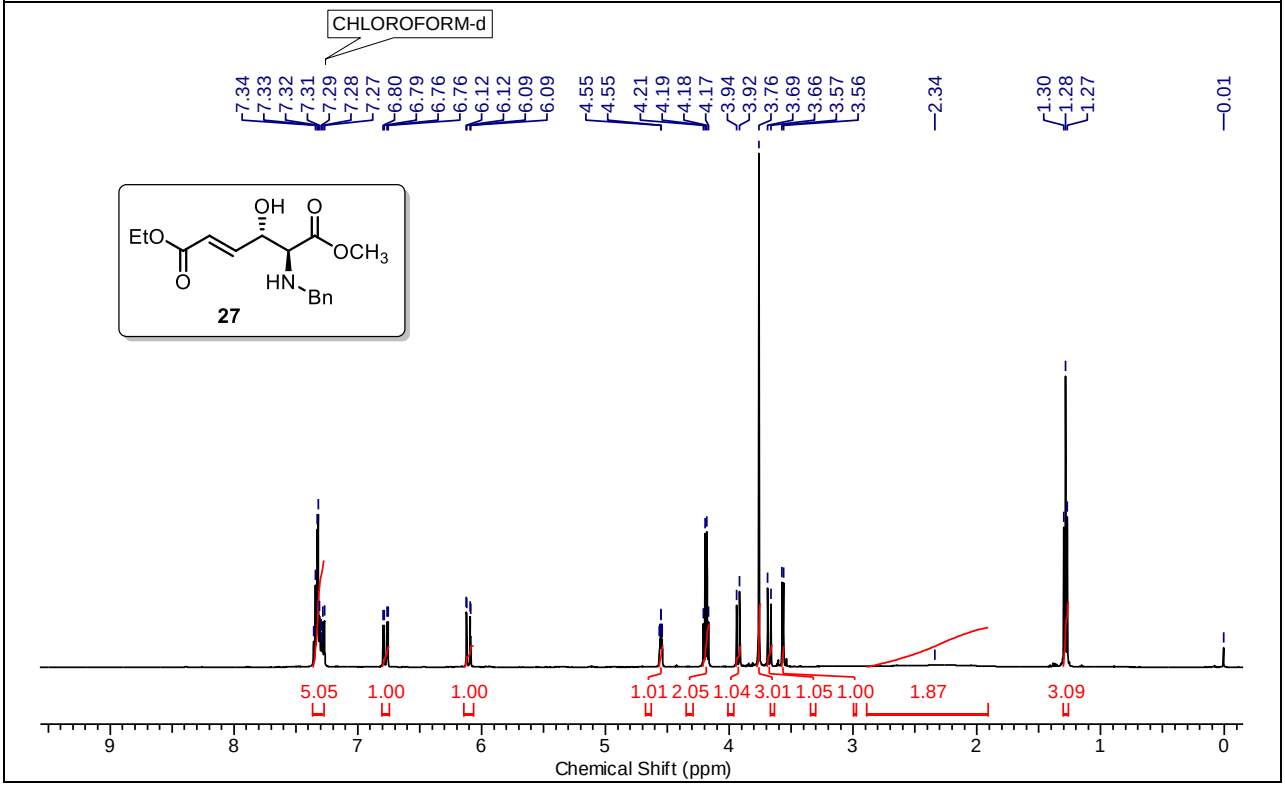
^{13}C-NMR spectrum of compound 26 ($CDCl_3$, 50 MHz)



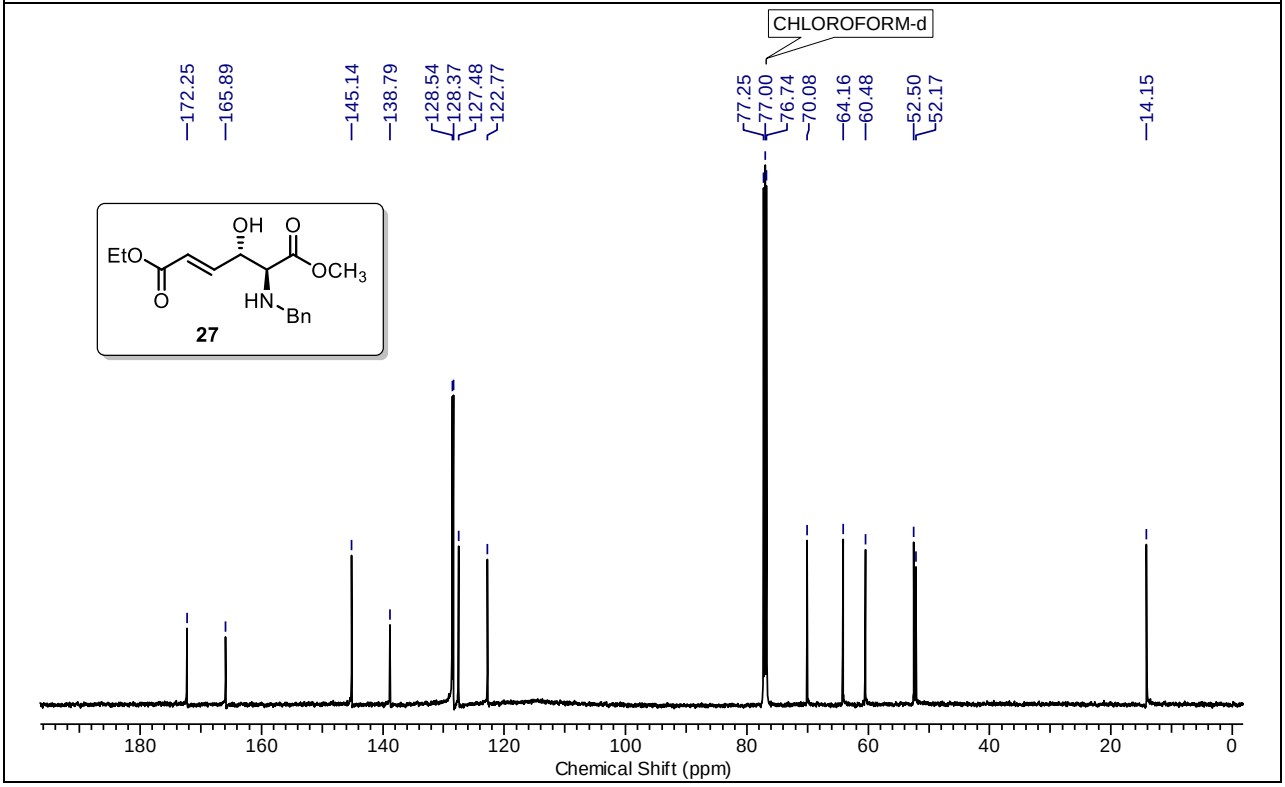
DEPT NMR spectrum of compound 26 ($CDCl_3$, 50 MHz)



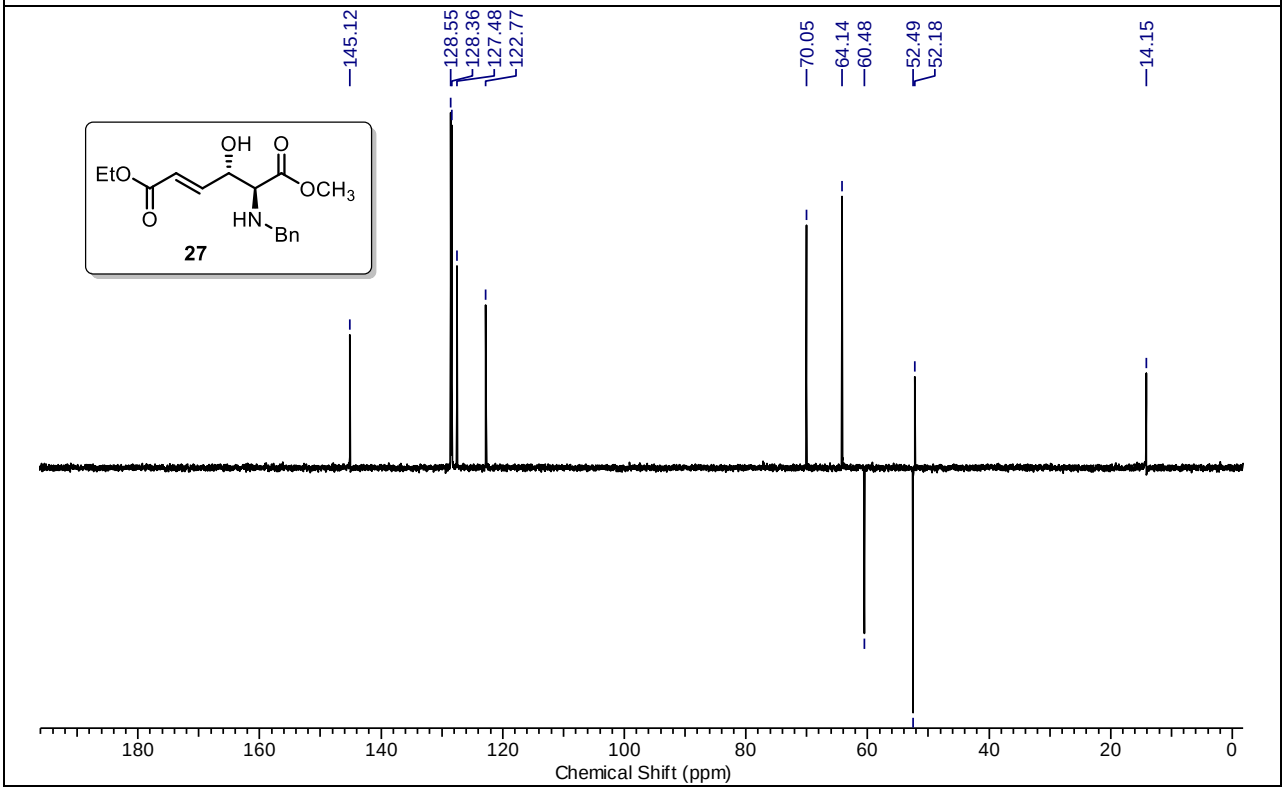
^{1}H-NMR spectrum of compound 27 ($CDCl_3$, 500 MHz)



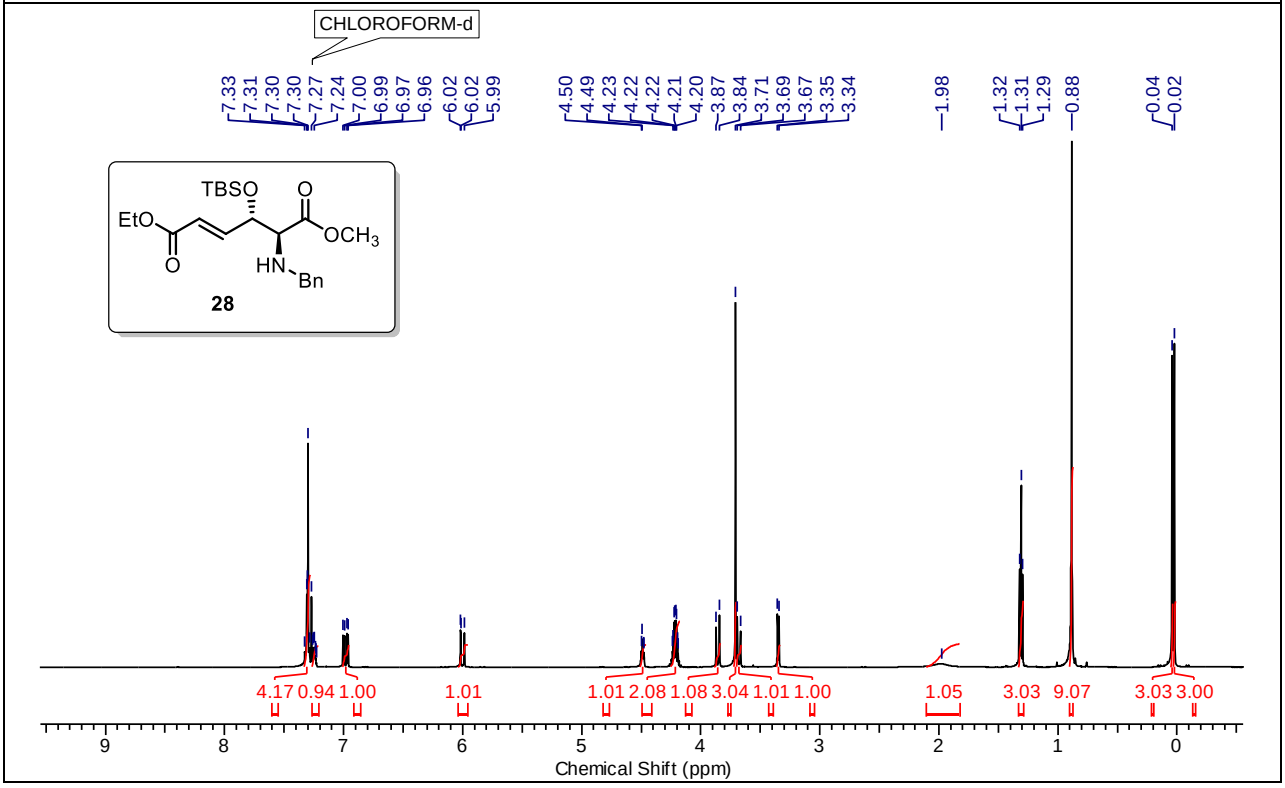
^{13}C-NMR spectrum of compound 27 ($CDCl_3$, 125 MHz)



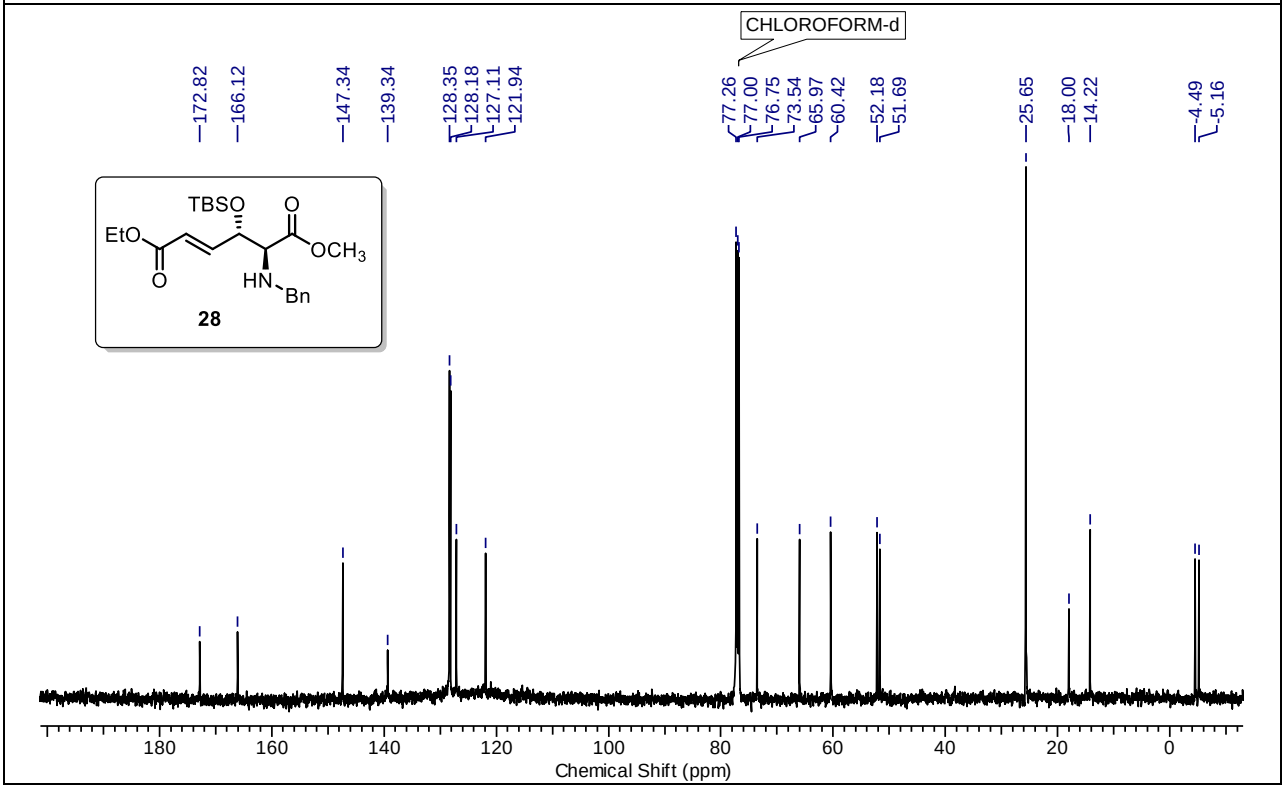
DEPT NMR spectrum of compound 27 ($CDCl_3$, 125 MHz)



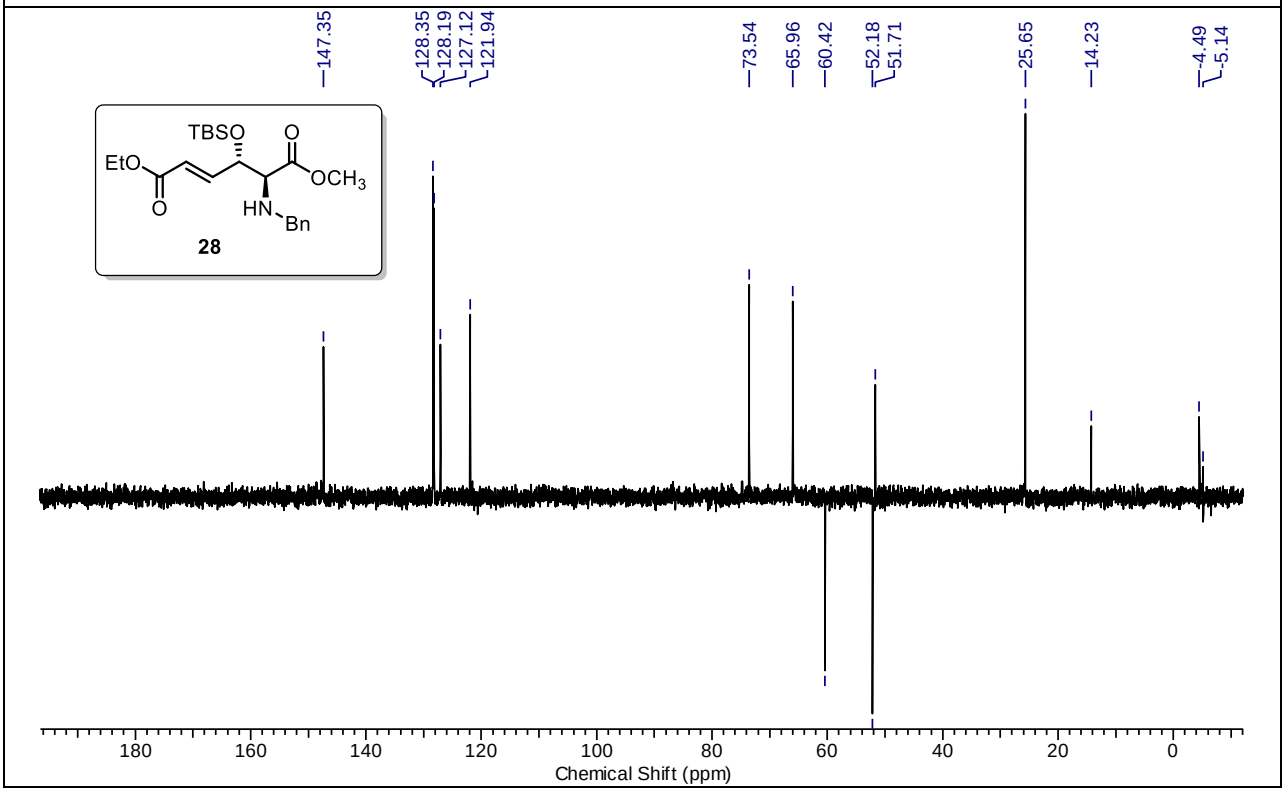
^{1}H-NMR spectrum of compound 28 ($CDCl_3$, 500 MHz)



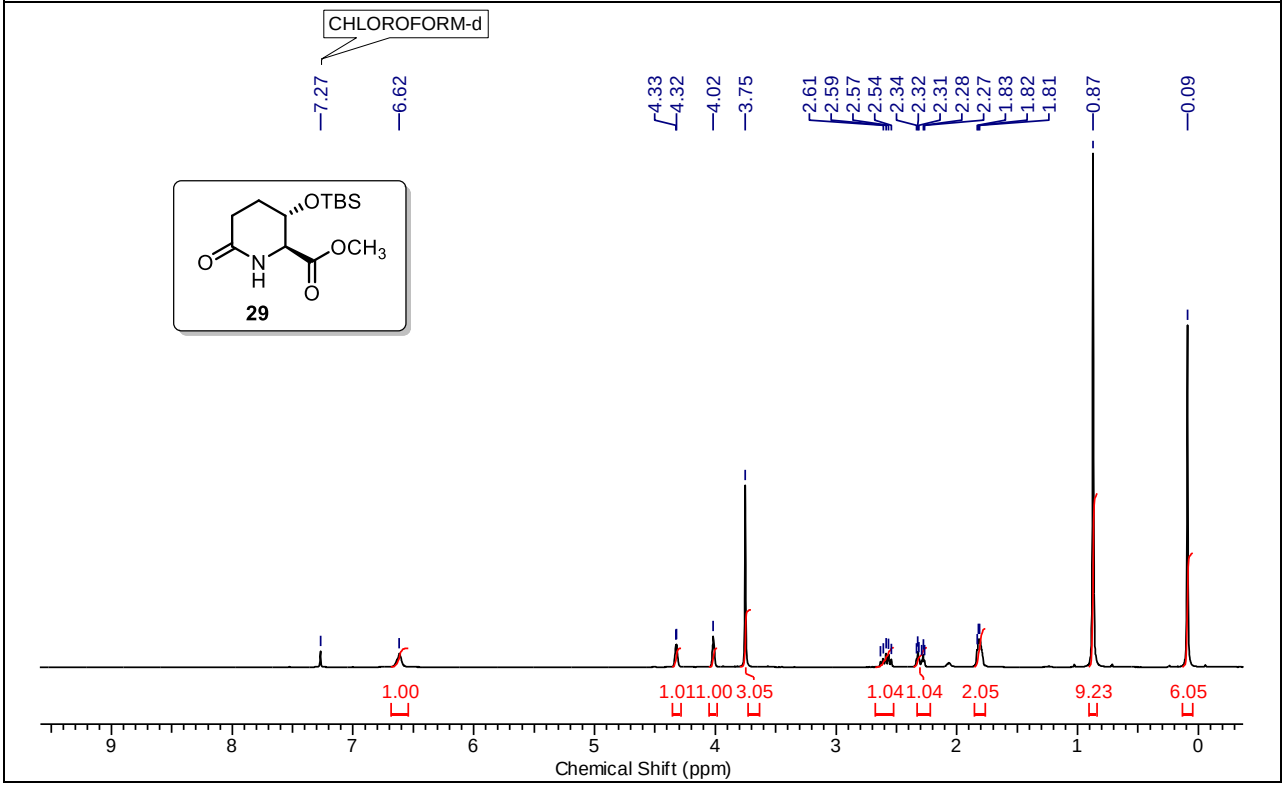
^{13}C-NMR spectrum of compound 28 ($CDCl_3$, 125 MHz)



DEPT NMR spectrum of compound 28 ($CDCl_3$, 125 MHz)



^{1}H-NMR spectrum of compound 29 ($CDCl_3$, 400 MHz)



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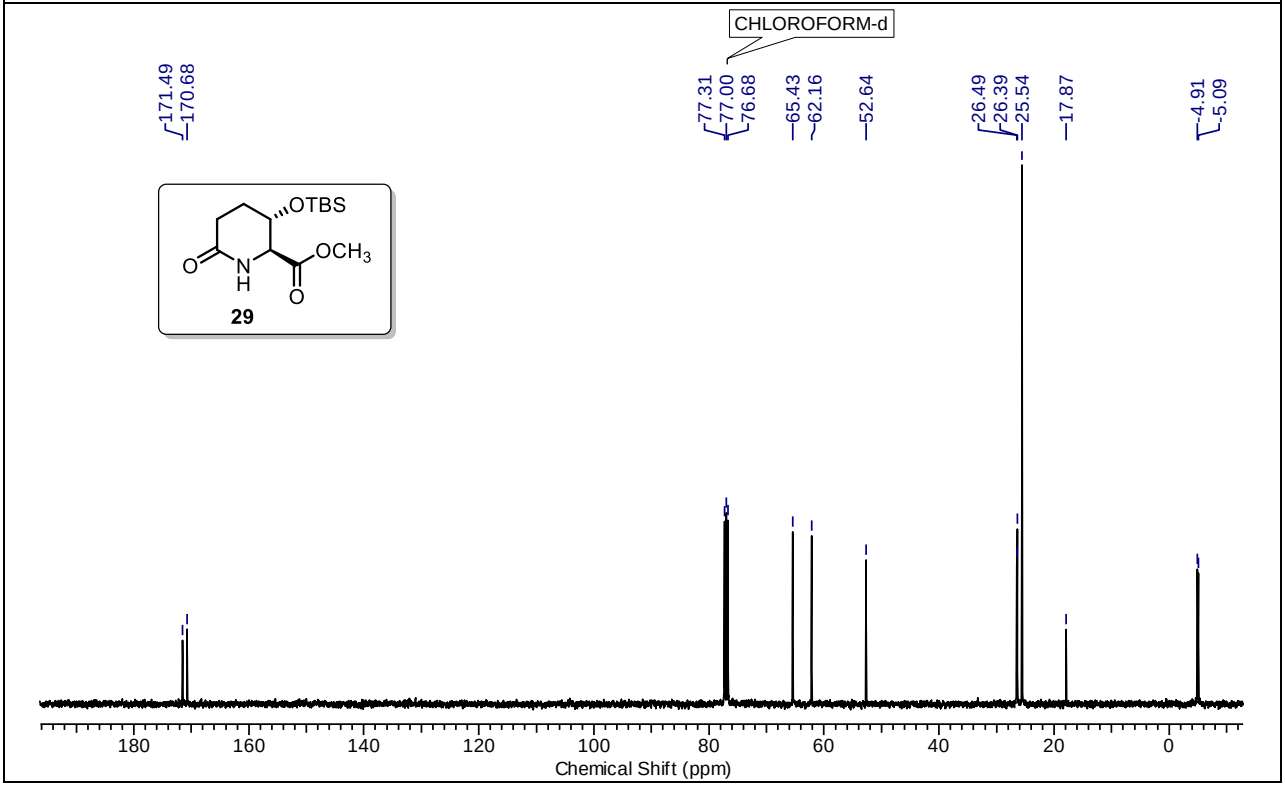
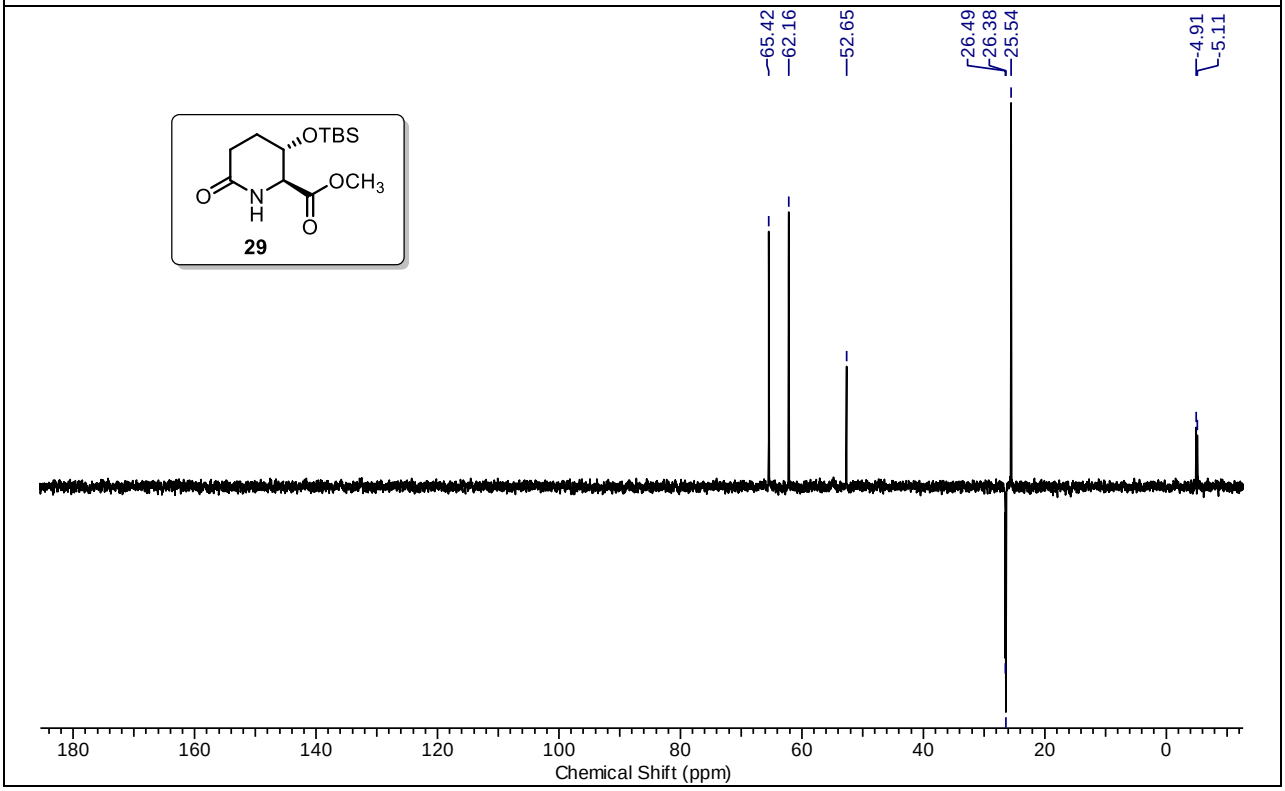


DEPT NMR spectrum of compound 29 ($CDCl_3$, 100 MHz)



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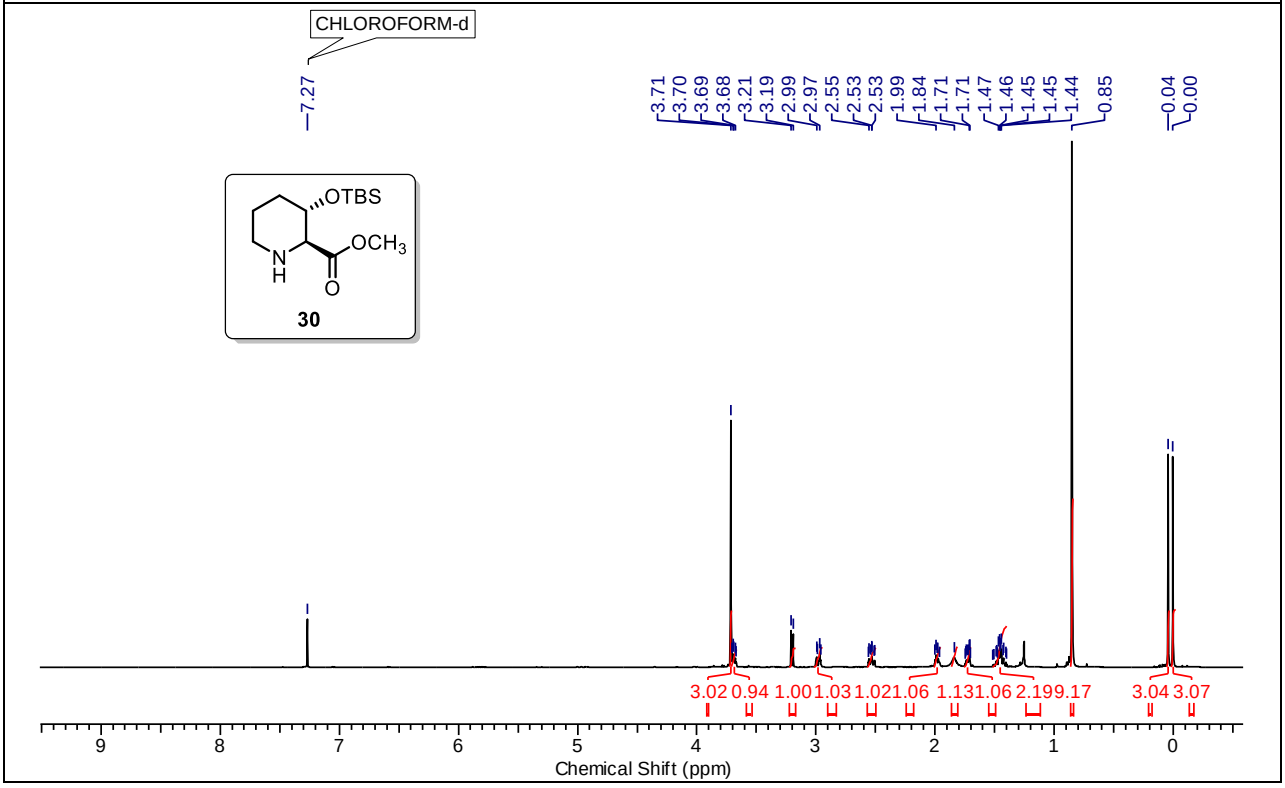
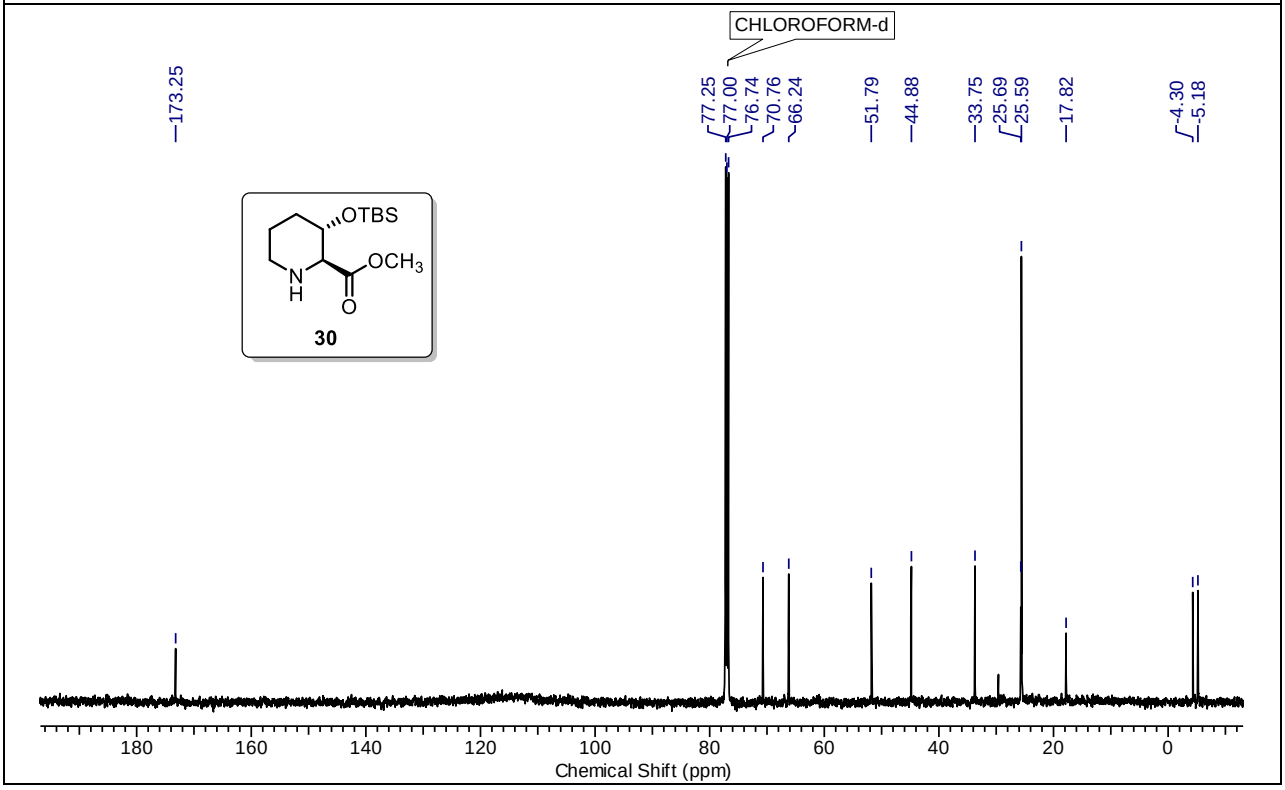
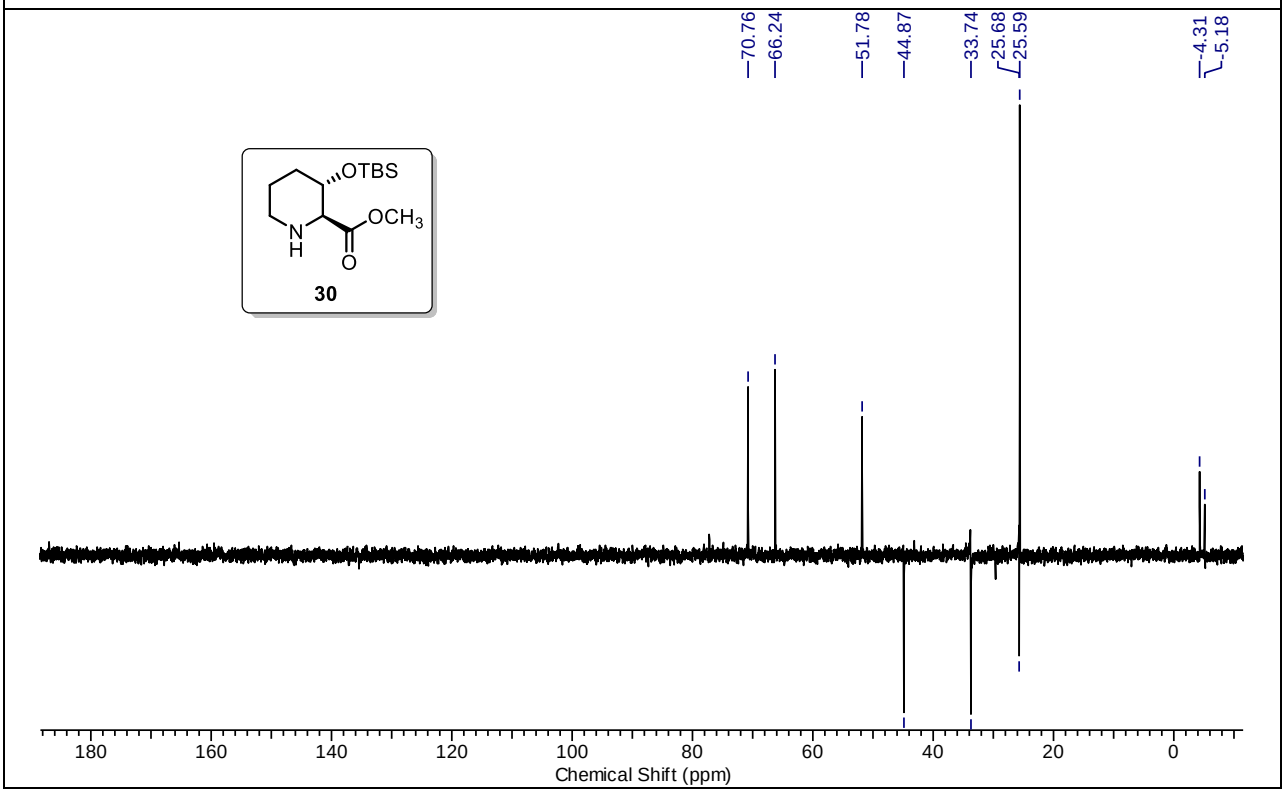


^{13}C-NMR spectrum of compound 30 ($CDCl_3$, 125 MHz)



DEPT NMR spectrum of compound 30 ($CDCl_3$, 125 MHz)



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1. Enantioselective Formal Total Synthesis of (–)-Quinagolide. *Chavan, S. P.; **Kadam, A. L.**; Gonnade, R. G. *Org. Lett.* **2019,** ASAP, DOI: 10.1021/acs.orglett.9b03477.

2. Total Synthesis of (±)-Quinagolide, a Potent D_2 Receptor Agonist for the Treatment of Hyperprolactinaemia. *Chavan, S. P.; **Kadam, A. L.**; Kawale, S. A. *ACS Omega* **2019**, *4*, 8231.

3. Synthesis of 3-Azidopiperidine Skeleton Employing Ceric Ammonium Nitrate (CAN)-Mediated Regioselective Azidoalkoxylation of Enol Ether: Total Synthesis of D_2 Receptor Agonist (±)-Quinagolide. *Chavan, S. P.; **Kadam, A. L.**; Lasonkar, P. B.; Gonnade, R. G. *Org. Lett.* **2018,** *20*, 7011.

4. A Facile and Convenient Synthesis of (±)-Biotin via $MgCl_2/Et_3N$-Mediated C–C Coupling and Mitsunobu Reaction. *Chavan, S. P.; Chavan, P. N.; Lasonkar, P. B.; Khairnar, L. B.; **Kadam, A. L.** *Synlett* **2014**, *25*, 2879.

5. Furan Derived Bicycloaziridino Lactone Synthon: Collective Synthesis of Tamiflu, (*S*)-Pipecolic acid and its 3-Hydroxy Derivatives. *Chavan, S. P.; **Kadam, A. L.**; Shinde, S. S.; Gonnade, R. G. (*Communicated*).

6. On-Water Oxidation of Furan: Scalable Synthesis of 5-Hydroxy-2(5*H*)-Furanone Using Oxone as a Sole Oxidant. *Chavan, S. P. and **Kadam, A. L.** (*To be communicated*).

7. Unusual metal free auto-oxidation of electron-deficient cyclohexenes by air: Synthesis of *meta*- hydroxybenzaldehydes and cyclohexenones. *Chavan, S. P.; Lasonkar, P. B.; **Kadam, A. L.** (*To be communicated*).

8. Scalable Synthesis of 3-Ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one: A antidiabetic drug Glimepiride Intermediate. *Chavan, S. P.; Pawar, A. A.; Patil, N. B.; **Kadam, A. L.**; Shinde, S. S. (*To be communicated*).

9. Process for the Preparation of 5-Hydroxy-2(5*H*)-Furanone from Furan. *Chavan, S. P.; **Kadam, A. L.** IN Patent App. 201,911,033,067.

10. Process for the Preparation of Glimepiride intermediate. *Chavan, S. P.; Pawar, A.

A.; Patil, N. B.; **Kadam, A. L.**; Shinde, S. S. IN Patent App. 201,911,040,874.

11. Process for the Preparation of Sacubitril Intermediates. *Kontham, R.; *Chavan, S. P. Thorat, S.; **Kadam, A. L.** IN Patent App. 201,911,043,858.

12. Process for the Preparation of Penflufen intermediate. *Chavan, S. P.; Muthukrishnan, M.; **Kadam, A. L.**; Kumar, V. (*Under Filing*).

Appasaheb L. Kadam

Division of Organic Chemistry

National Chemical Laboratory

Dr. Homi Bhabha Road

Pune 411 008, India.

Mobile No.: +91 9922332787

Email ID: kadamappasaheb85@gmail.com

Google Scholar: https://scholar.google.co.in/citations?user=pcXbiwIAAAAJ&hl=en

LinkedIn Profile: https://www.linkedin.com/in/appasaheb-kadam-b85863172

Appasaheb L. Kadam was born in Neurgaon (village), Yeola (tehsil), Nashik (dist), Maharashtra, India. He did his primary schooling in Swami Vivekanand High School, Erandgaon, Yeola (10^{th} standard, 1^{st} ranking in the class). He finished intermediate education at Janata Vidyalaya, Yeola (12^{th} standard). Then he completed B.Sc. chemistry (1^{st} ranking in the class) from S. M. Science College Yeola, in the year 2008. He received M.Sc in Organic Chemistry (1^{st} ranking in the class) from H.P.T. Arts & R.Y.K. Science College, Nashik (affiliated to SP Pune University) in 2010 after which he joined research chemistry at Syngenta, Goa (06/2010–07/2012). He has been awarded a National fellowship for pursuing his doctoral studies in CSIR-National Chemical Laboratory under the supervision of Dr. Subhash P. Chavan. His research interest centers around the total synthesis of biologically active natural products and drugs such as Quinagolide, oseltamivir phosphate (Tamiflu), (*S*)-pipecolic acid and its 3-hydroxy derivatives and, development of a methodology for on-water oxidation of furan and its applications in the total synthesis. During his Ph.D. tenure, he has actively involved in several industrial as well as government projects related to the synthesis and development of a process for Sitagliptin, Sacubitril, Glimepiride, Brivaracetam and Penflufen under the guidance of Dr. Subhash P. Chavan at CSIR-NCL, Pune. He trained & supervised 12 bachelor and master's degree students during that period.

Reprint of Publications

Organic LETTERS

Letter

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Synthesis of 3-Azidopiperidine Skeleton Employing Ceric Ammonium Nitrate (CAN)-Mediated Regioselective Azidoalkoxylation of Enol Ether: Total Synthesis of D_2 Receptor Agonist (±)-Quinagolide

Subhash P. Chavan,*[,†,‡] Appasaheb L. Kadam,[†,‡] Pradeep B. Lasonkar,[†] and Rajesh G. Gonnade[‡,§]

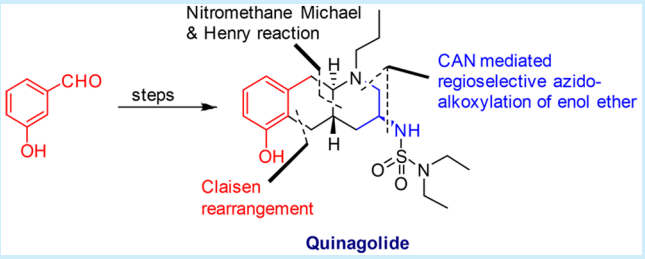
[†]Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune 411008, India

[‡]Academy of Scientific and Innovative Research (AcSIR), New Delhi 110025, India

[§]Physical and Materials Chemistry Division, CSIR-National Chemical Laboratory, Pune 411008, India

Supporting Information

ABSTRACT: The total synthesis of (±)-quinagolide, which is a D_2 receptor agonist, was accomplished via a ceric ammonium nitrate (CAN)-mediated regioselective azidoalkoxylation of enol ether route. Key features of the synthesis include Claisen rearrangement, PPTS (pyridinium *p*-toluenesulfonate)-catalyzed one-pot acetal deprotection, followed by a diastereoselective Henry reaction, which enables construction of the required *trans* ring junction and CAN-mediated regioselective azidoalkoxylation of enol ether. The PPTS-catalyzed intramolecular diastereoselective Henry reaction to fix three contiguous stereocenters on tetrahydronaphthalene and the first-of-its-kind synthesis of the 3-azidopiperidine skeleton, using a CAN-mediated regioselective azidoalkoxylation of enol ether, are important findings of the present work.



Ergot alkaloids and their synthetic derivatives are well-known for their biological activities.[1] Ergolines CQ 32-084 (**1**), pergolide (**2**), and apomorphine (**3**) are well-known dopamine agonists. Quinagolide (**4**), which is a selective D_2 receptor agonist that is used for the treatment of elevated levels of prolactin has the combined structural features of both ergolines and apomorphine (see Figure 1).[2,3] Quinagolide hydrochloride is marketed by Ferring Pharmaceuticals (Lausanne, Switzerland) under the trade name Narprolac. The synthesis and biological activity of quinagolide was first reported by Nordmann et al. in racemic form, using *β*-tetralone[2] as the starting material and, subsequently, in the year 2000, Banziger et al. reported the large-scale synthesis of a quinagolide intermediate.[4]

Although quinagolide is sold in its racemic form, the dopaminomimetic activity is entirely associated with the (−) enantiomer[5] and it would be desirable to use the (−) enantiomer for medicinal use. Also, the synthesis of the *trans*-fused amino piperidine skeleton poses a challenge to synthetic chemists. The medicinal use of quinagolide and necessity to make it available in enantiomerically pure form prompted us to undertake its synthesis under our research program, directed toward the expedient synthesis of drug molecules[6] having societal importance.

3-Aminopiperidine scaffolds constitute an integral part of several natural products and biologically active compounds.[7] For the synthesis of 3-aminopiperidine scaffolds, azidoalkoxylation of endocyclic enecarbamate is a well-established method.[8] In this context, a methodology of CAN-mediated azidoalkoxylation of enol ethers was previously reported by our group.[9] In the present work, the idea was to utilize this methodology for the synthesis of the 3-aminopiperidine

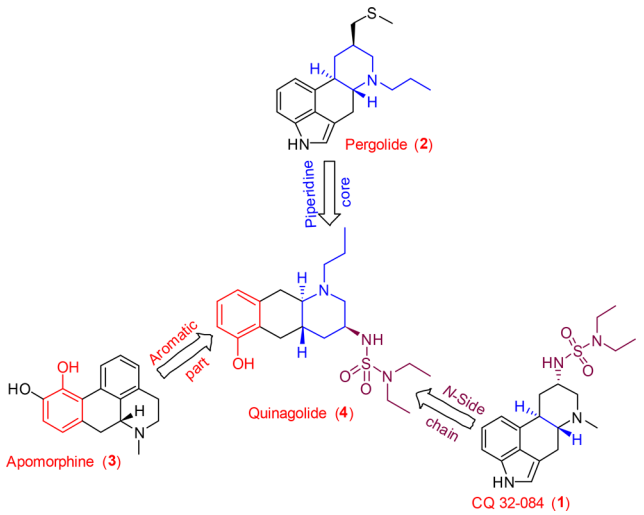


Figure 1. Quinagolide (**4**) showing combined structural features of both ergolines and apomorphine.

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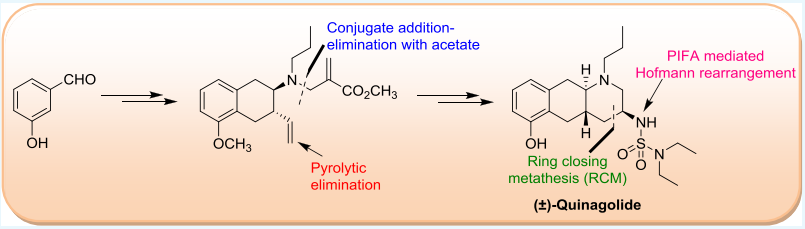
Total Synthesis of (±)-Quinagolide: A Potent D_2 Receptor Agonist for the Treatment of Hyperprolactinemia

Subhash P. Chavan,*[,†,‡] Appasaheb L. Kadam,[†,‡] and Sanket A. Kawale[†,‡]

[†]Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune 411008, India

[‡]Academy of Scientific and Innovative Research (AcSIR), New Delhi 110025, India

Supporting Information



ABSTRACT: A potent dopamine (D_2) receptor agonist (±)-quinagolide, which is used for the treatment of hyperprolactinemia, was synthesized using the ring closing metathesis (RCM) approach from *meta*-hydroxybenzaldehyde as the starting material. The key features of this synthesis are pyrolytic elimination, late-stage expedient synthesis of functionalized trans-fused tetrahydropyridine-3-carboxylates from olefin **6**, via conjugate addition−elimination upon acetate **11**, followed by RCM and phenyliodine bis(trifluoroacetate) (PIFA)-mediated Hofmann rearrangement of piperidine-3-carboxamide, which enables the synthesis of 3-aminopiperidine skeleton of quinagolide. For the total synthesis of natural products such as ergot alkaloids, late-stage synthesis of functionalized trans-fused tetrahydropyridine-3-carboxylates using RCM and PIFA-mediated Hofmann rearrangement of piperidine-3-carboxamide, which allows quick access to the synthetically challenging 3-aminopiperidine skeleton, are the main achievements of the present work.

INTRODUCTION

Prolactinoma is a benign tumor (adenoma) of the pituitary gland, which produces hormone prolactin, and a condition that arises because of elevated prolactin levels in blood is defined as hyperprolactinemia. Pharmacological causes such as use of certain medications for the treatment of various diseases and physiological causes such as pregnancy and stress are the main factors behind the elevated level of prolactin. Hyperprolactinemia may also be the result of disease of other organs such as the liver, kidneys, ovaries, and thyroid. The most common symptoms of hyperprolactinemia are hypogonadism, infertility, and erectile dysfunction in men and galactorrhea and disruptions in the normal menstrual period in women. Although hyperprolactinemia is not considered as a life-threatening disease, it causes severe effects on the life of patients and often leads to multiple life-threatening diseases.[1] For the treatment of hyperprolactinemia, drugs such as bromocriptine (**1**), cabergoline (**2**), and quinagolide (**3**) are used as medications (see Figure 1).[2]

Out of these medications available in the market, bromocriptine (**1**) and cabergoline (**2**) have serious side effects, whereas quinagolide (**3**) which is newly introduced by Ferring Pharmaceuticals under the trade name NORPROLAC is considered as a first-line therapy in the treatment of hyperprolactinemia.[1b]

The potent dopamine (D_2) receptor agonist quinagolide is developed by combining structural features of both ergot and apomorphine alkaloids.[3] Quinagolide was first synthesized in racemic form, and subsequently, its biological activity was reported by Nordmann et al.[3] Later in the year 2000, scalable synthesis of quinagolide intermediate was reported by Bänziger et al.[4] Though the dopaminomimetic activity is completely

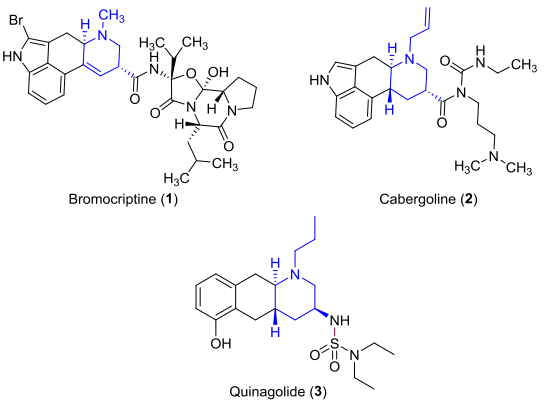


Figure 1. Available hyperprolactinemia medications bromocriptine (**1**), cabergoline (**2**), and quinagolide (**3**).

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Enantioselective Formal Total Synthesis of (−)-Quinagolide

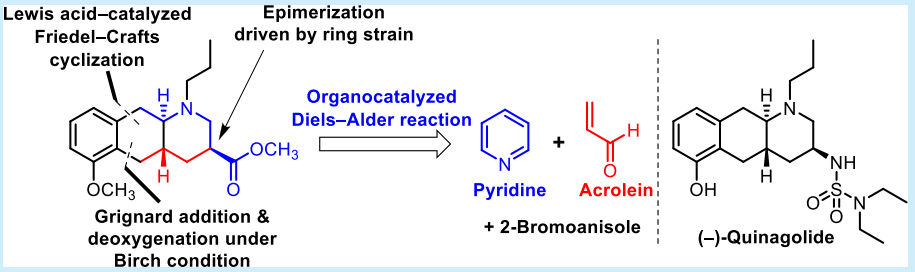
Subhash P. Chavan,*[,†,‡] Appasaheb L. Kadam,[†,‡] and Rajesh G. Gonnade[‡,§]

[†]Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune 411008, India

[‡]Academy of Scientific and Innovative Research (AcSIR), New Delhi 110025, India

[§]Physical and Materials Chemistry Division, CSIR-National Chemical Laboratory, Pune 411008, India

Supporting Information



ABSTRACT: The enantioselective formal total synthesis of (−)-quinagolide has been accomplished in a linear sequence of 8 purification steps from pyridine. The key steps are (a) organocatalyzed Diels−Alder reaction for fixing all three stereocenters on piperidine ring; (b) protecting group enabled deoxygenation of isoquinuclidine skeleton under Birch reduction condition; (c) Lewis acid ($TiCl_4$) catalyzed intramolecular Friedel−Crafts cyclization of dicarboxylic acid; and (d) one-pot diastereoselective ketone reduction−intramolecular cyclization to form oxazolidinone which enables *trans*-geometry installation. During the course of the synthesis, an interesting reductive cleavage of the C−N bond in the electron-deficient isoquinuclidine skeleton under the Birch reduction conditions has been observed. This is the first synthetic effort to access the core skeleton of (−)-quinagolide.

The isoquinuclidine (2-azabicyclo[2.2.2]octane) ring system is found in a wide number of natural products, namely iboga-type alkaloids.[1] Elegant methods for the synthesis of chiral isoquinuclidines have been developed, especially since Fukuyama's synthesis of oseltamivir using organocatalyzed Diels−Alder reaction.[2] Despite the high functionalization ability of isoquinuclidine to provide complex scaffolds in chiral fashion, its applications for the synthesis of natural products and bioactive compounds are scarce.[1] To date, there are only three synthetic approaches (total synthesis of oseltamivir by Fukuyama[2] and (+)-luciduline by Charette[3] and formal synthesis of catharanthine by Batey[4]) reported in the literature in which application of the chiral isoquinuclidine skeleton constructed via organocatalyzed Diels−Alder reaction has been demonstrated.

Due to our continued interest in the synthesis of biologically active compounds, we were interested in the enantioselective synthesis of (−)-quinagolide (**1**) by taking advantage of the chiral isoquinuclidine skeleton. Quinagolide (**1**), a selective D_2 receptor agonist used for the treatment of elevated levels of prolactin, has combined structural features of well-known dopamine agonists, namely ergolines CQ 32-084 (**2**), pergolide (**3**), and apomorphine (**4**) (Figure 1). Furthermore, quinagolide (**1**) has distinct advantages over bromocriptine (**5**) and cabergoline (**6**), which are currently available medications for the treatment of hyperprolactinemia.[5] Quinagolide hydrochloride as its racemate is marketed by

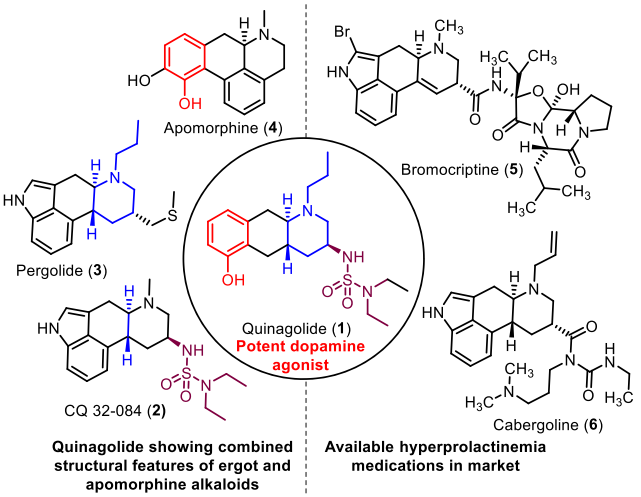


Figure 1. Available hyperprolactinemia medications on the market and structural features of quinagolide (**1**).

Ferring Pharmaceuticals, Switzerland, under the trade name Norprolac.

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NOSTALGIA

With Dr. S. P. Chavan Sir

21st International Conference on Organic Synthesis (ICOS-21)

IIT Bombay, Mumbai, India

December 11–16, 2016