SYNTHETIC STUDIES TOWARDS HERITOL, (−)-VENLAFAXINE, 7-DEOXYPANCRATISTATIN AND DEVELOPMENT OF IMPORTANT SYNTHETIC METHODOLOGIES

A THESIS

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Synthetic Studies towards Heritol, (−)-Venlafaxine, 7-Deoxypancratistatin and Development of Important Synthetic Methodologies"** submitted by Mr. Sumanta Garai was carried out by him under my supervision at National Chemical Laboratory, Pune. Material that has been obtained from other sources is duly acknowledged in this thesis.

February, 2013

Dr. Subhash P. Chavan
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DECLARATION

I hereby declare that the thesis entitled **"Synthetic Studies towards Heritol, (−)-Venlafaxine, 7-Deoxypancratistatin and Development of Important Synthetic Methodologies"** submitted for Ph. D. degree to the University of Pune has been carried out at National Chemical Laboratory, under the supervision of Dr. Subhash P. Chavan. This work is original and has not been submitted in part or full by me for any degree or diploma to this or any other university.

February, 2013 Sumanta Garai
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Dedicated to

……my beloved Parents

Acknowledgements

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My family is always source of inspiration and great moral support for me in perceiving my education, it is impossible to express my sense of gratitude for my family, ***Ma*** *and* ***Baba****. Whatever I am and whatever I will be in future is because of their enormous blessings, hard work, commitments to my ambitions, and their selfless sacrifices. It was their single minded pursuit of the cause of my education that gave me the strength and will continue to guide my future. Although this eulogy is insufficient, I preserve an everlasting gratitude for them. Words fall short to thank my sisters* ***Mithu*** *and* ***Tumpa*** *who made me strong, and for their never ending encouragement and support. My special thanks to my brother in law* ***Gopal*** *for his sacrifice, support and encouragement. The love and affection of my nieces* ***Diyu*** *and* ***Puchku*** *which made my gloomy days shine, is acknowledged.*

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NCL, Pune

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General Remarks

1. All the melting points are uncorrected and the temperatures are in the centigrade scale.
2. The compound numbers, Scheme numbers and reference numbers given in each section refer to that section only.
3. All the solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80 ºC.
4. Organic layers were dried over anhydrous sodium sulfate.
5. TLC analysis was carried out using thin layer plates pre-coated with silica gel 60 F254 (Merck) and visualized by fluorescence quenching or Iodine or by charring after treatment with *p*-anisaldehyde.
6. In cases where chromatographic purification was done, silica gel (200-400 mesh) was used as the stationary phase or otherwise as stated.
7. IR spectra were recorded on **Perkin-Elmer Infrared Spectrophotometer Model 68B** or on **Perkin-Elmer 1615 FT Infrared Spectrophotometer.**
8. ^{1}H NMR and ^{13}C NMR were recorded on **Bruker AV-200** (50 MHz) or **Bruker AV-400** (100 MHz) or **Bruker DRX-500** (125 MHz). Figures in the parentheses refer to ^{13}C frequencies. Tetramethyl silane was used as the internal standard.
9. Mass spectra were recorded at an ionization energy of 70 eV on **Finnigan MAT-1020**, automated GC/MS instrument and on **API Q STARPULSAR** using electron spray ionization [(ESI), solvent medium: a mixture of water, acetonitrile and ammonium acetate] technique and mass values are expressed as *m/z*. HRMS were recorded on a micromass Q-T of micro with spray source (ESI^{+}) mode.
10. Starting materials were obtained from commercial sources or prepared using known procedures.
11. Microanalysis data were obtained using a **Carlo-Erba CHNS-O EA 1108** elemental analyzer within the limits of accuracy (± 0.4%).

Ac	Acetyl
ADD	(Azodicarbonyl)dipiperidine
AIBN	2,2-Azobis(*iso*-butyronitrile)
Ar	Aryl
Aq.	Aqueous
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BMS	Borane dimethyl sulfide
Bn	Benzyl
Boc	*tert*-butoxy carbonyl
Bu	Butyl
s-Bu	*sec*-butyl
t-Bu	*tert*-butyl
CAN	Cerric ammonium nitrate
Cat.	Catalytic
Cbz	Carbobenzyloxy
m-CPBA	*meta*-chloroperbenzoic acid
CSA	Camphor sulfonic acid
DBDMH	1,3-Dibromo-5,5-dimethylhydantoin
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCB	1,2-Dichlorobenzene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEPT	Distortionless Enhancement by Polarization Transfer
DIAD	Diisopropylazodicarboxylate
DIBAL	Diisobutyl aluminium hydride
DIPT	Diisopropyltartrate
DMAP	4-Dimethylamino pyridine
DME	1,2-dimethoxyethane

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

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

The thesis entitled, **"Synthetic Studies towards Heritol, (-)-Venlafaxine, 7-Deoxypancratistatin and Development of Important Synthetic Methodologies"** is divided into three chapters.

Chapter 1 deals with the introduction and synthetic studies towards heritol, heritonin and vallapin and devolopement of a methodology for Friedel-Crafts acylation reaction using esters and is divided into four sections.

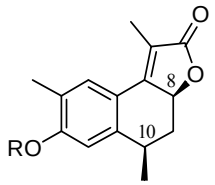
Chapter 2 deals with a brief review on venlafaxine and its asymmetric total synthesis using an organocatalyst and is divided into two sections.

Chapter 3 deals with the introduction and synthesis of epimer of 7-deoxypancratistatin and a methodology for retro-Reformatsky reaction and is divided into three sections.

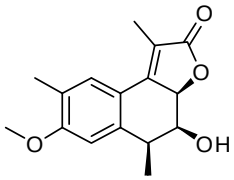
Chapter 1: Diastereoselective total synthesis of (±)-heritol and (±)-heritonin, attempted synthesis towards vallapin and Friedel- Crafts acylation reaction using esters

Section 1: Introduction to heritol, heritonin and vallapin.

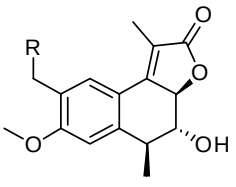
Miles and co-workers have isolated cadinane sesquiterpene lactones *viz.* heritol **(1)**, heritonin **(2)**, vallapin **(3)**, vallapianin **(4)** and heritianin **(5)** from the sap of the mangrove plant *Heritiera littoralis* of Philippines and other tropical countries (Figure 1). These compounds were shown to possess ichthyotoxicity in *ppm* quantities to



1, R=H, Heritol
2, R= CH_3, Heritonin



3, Vallapin



4, R= OH, Vallapianin
5, R= H, Heritianin

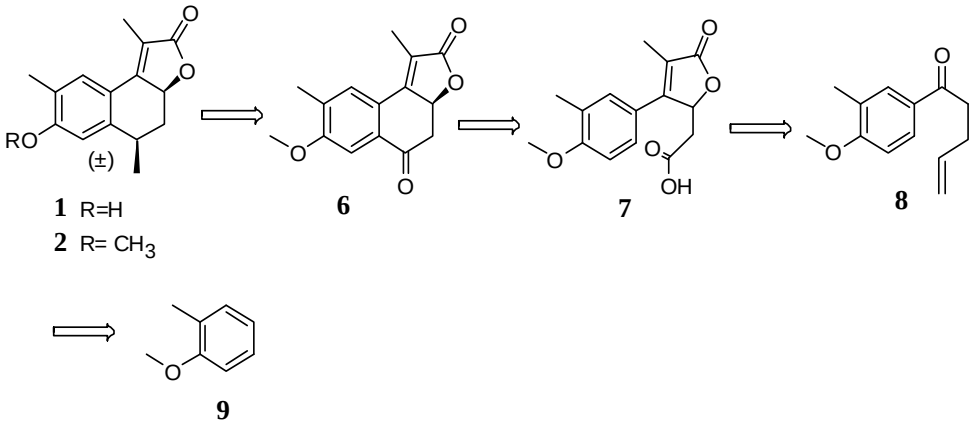
Figure 1. Structures of heritol (**1**), heritonin (**2**), vallapin (**3**), vallapianin (**4**), heritianin (**5**).

Tilapia nilotica fingerlings and this plant drew attention of scientists because it had beenutilized by natives of the Philippine islands as a fish poison.

Toxicity towards fish is often used as a measure of pesticidal activity. These compounds represent a new and novel class of sesquiterpene and possess unusual oxygenation pattern not generally encountered in cadinane family.

Section 2: Diastereoselective total synthesis of (±)-heritol and (±)-heritonin

A highly diastereoselective synthesis of heritol and heritonin by intramolecular cyclisation on a preformed sensitive butenolide functionality is described. Retrosynthetic analysis of heritol **1** and heritonin **2** (Scheme 1) revealed that heritol **1** and heritonin **2** can be obtained from tetralone unit **6**, which in turn could be obtained from acid **7** *via* intramolecular Friedel-Crafts acylation. The acid **7** having *α, β*-unsaturated lactone can be synthesized from keto compound **8**. The keto compound **8** can be accessed from cheap and commercially available starting material **9**.

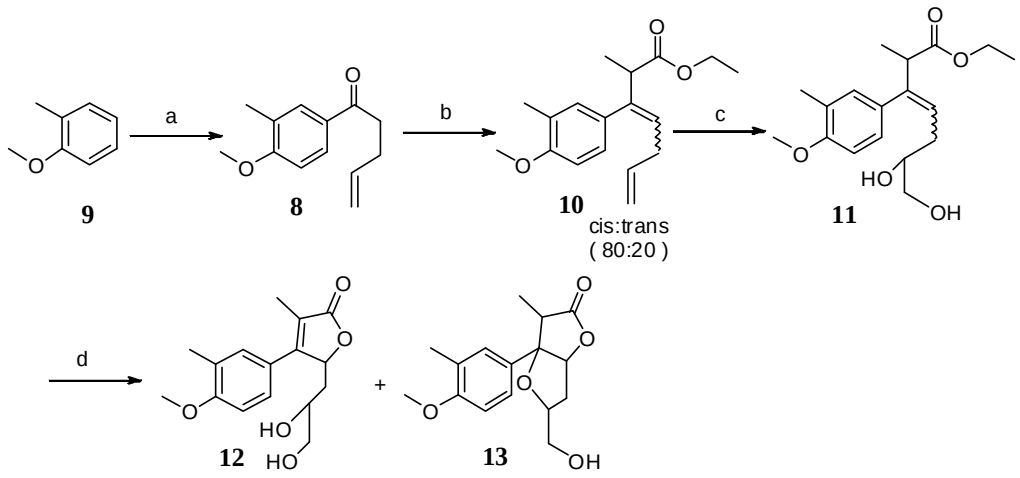


Scheme 1. Retrosynthetic analysis of (±)-heritonin **2** and (±)-heritol **1**.

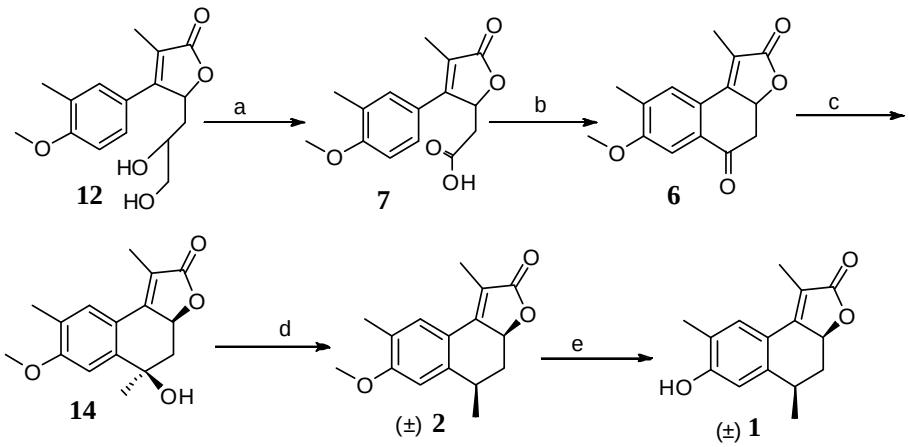
Thus as shown in the retrosynthetic plan (Scheme 1), the butenolide **12** can be obtained from keto compound **8** by using Reformatsky reaction followed by dihydroxylation and cyclization (Scheme 2).

After successful synthesis of compound **12** having butenolide ring in place, next task was to construct the tetralin unit of heritol *via* cyclization. The compound **12** was subjected to oxidative cleavage by using $NaIO_4$ to afford aldehyde which was subjected to oxidation to afford acid **7**. Acid **7** was converted to its acid chloride and

then treated with triflic acid to furnish the key tetralone intermediate **6**. Grignard reaction of **6** with methyl magnesium bromide furnished the corresponding hydroxy compound **14** in 97% yield as a single diastereomer. The hydroxy compound **14** was



Scheme 2. Reagents and conditions: *a) Allylacetyl chloride, CF_3SO_3H, DCM, rt, 4 h, 95%; b) i) Ethyl 2-bromopropionate, activated Zn, benzene:ether (1:1), reflux, 3 h; ii) PTSA, DCM, rt, 12 h, 85% (over two steps); c) OsO_4, NMO, acetonitrile:water (9:1), 30 min, 99%; d) OsO_4, NMO, acetonitrile:water (9:1), 3 days; ii) $BF_3.OEt_2$, DCM, rt, 1 h, 76% (**12**), 8% (**13**).*

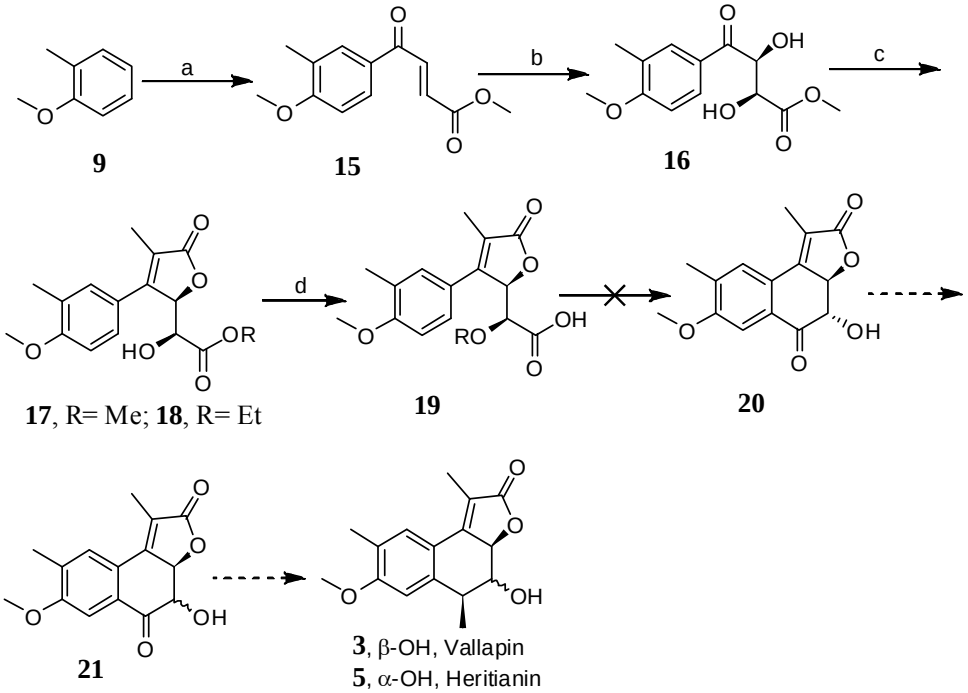


Scheme 3. Reagents and conditions: *a) i) $NaIO_4$, acetone:H_2O (3:1), 0 ºC-rt, 15 min.; ii) $NaClO_2$, NaH_2PO_4, H_2O_2, acetonitrile, rt, 4 h, 78% (over two steps); b) i) Oxalyl chloride, DCM, overnight; ii) CF_3SO_3H, DCM, reflux, 3 h, 95% (after two steps, based on starting material recovered); c) MeMgBr (1.5 eq), THF, -78 ºC-0 ºC, 5 h, 97%; d) Et_3SiH, $BF_3.OEt_2$, DCM, -78 ºC, 96%; e) $AlCl_3$, EtSH, DCM, rt, 12 h, 80%.*

subjected to deoxygenation using triethylsilane, $BF_3.OEt_2$ in DCM. Interestingly and gratifyingly it afforded only one diastereomer, heritonin **2**, in 96% yield. Finally the compound **2** was subjected to demethylation with $AlCl_3$-EtSH at room temperature to afford heritol **1** (Scheme 3).

Section 3: Attempted synthesis towards vallapin

This section describes attempted synthesis of vallapin. The synthetic strategy towards vallapin began with *o*-cresol methyl ether **9** as the starting material. Ester **15** was synthesized by Friedel-Crafts acylation reaction. The olefin ester **15** was subjected to chiral dihydroxylation to furnish enantiomerically pure diol **16** in good yield with 97% enantiomeric excess. Butenolide ring was constructed by Reformatsky reaction followed by dehydration reaction (Scheme 4). When acid **19** was subjected to cyclisation, in some cases starting material was recovered or dehydration occurred.



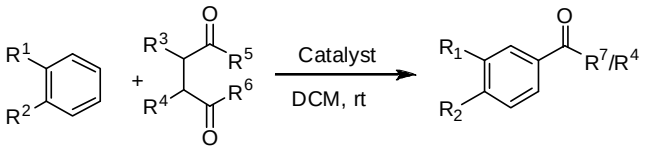
Scheme 4. Reagents and conditions: *a) i) maleic anhydride, $AlCl_3$, DCM, rt, 4 h, 95%; ii) Me_2SO_4, K_2CO_3, acetone, 99%; b) OsO_4, $(DHQD)_2PHAL$, K_2CO_3, $K_3[Fe(CN)_6]$, $MeSO_2NH_2$, ^tBuOH: water (1:1), 2 days , 95%, 97% ee; c) i) Ethyl-2-bromopropionate, activated Zn, benzene:ether (1:1), reflux, 3 h; ii) PTSA, toluene, reflux, 6 h; d) $LiOH.H_2O$, THF: H_2O (3:1), rt, overnight, 80%.*

Although the synthesis of vallapin (**3**) and heritianin (**5**) could not be achieved by this route, an advanced intermediate, bearing the hydroxyl butenolide was obtained in good yields which under proper choice of reagents and conditions can be converted to vallapin (**3**) and heritianin (**5**).

Section 4: Unprecedented, mild, efficient and simple Friedel-Crafts acylation reaction using esters

Inter- and intramolecular Friedel-Crafts acylation of aromatic ring is one of the most fundamental, important and useful C-C bond forming reaction in organic and industrial chemistry for the synthesis of aromatic ketones and important synthetic intermediates. Conventionally unstable and sensitive acylating reagents such as acid chlorides, anhydrides and acids are employed for acylation agent with appropriate Lewis acid or appropriate protocol. Hence development of a stable, ready to use and easy to handle reagents is very important for Friedel-Crafts acylation reaction. Esters are more stable, less expensive, easily purified by distillation, recrystallisation or by column chromatography and easier to handle than conventional acylating agents. Hence, ester would be ideal choice which may be used as a substitute for the

Intermolecular:



Reaction Time: 10 min-6 h

Yeilds: 60-74%

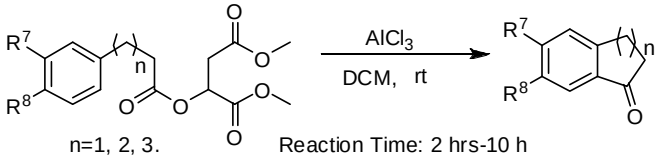
Catalyst= $AlCl_3$, $BF_3.OEt_2$, CF_3SO_3H

R^1= -H, $-CH_3$; R^2 = -H, $-CH_3$, $-OCH_3$, -Cl, $-SCH_3$; R^3= $-OCOR^7$; R^7= -Me,- Et, $-CH_2Cl$,- Ph, -vinyl, -allyl

R^4= -H; R^5=R^6= -OMe, -OEt, , N-Allyl

Aromatic Partner:furan, napthalene

Intramolecular:



n=1, 2, 3. Reaction Time: 2 hrs-10 h

R^7 = $-CH_3$, $-OCH_3$ Yields= 70-85%

R^8 = $-OCH_3$

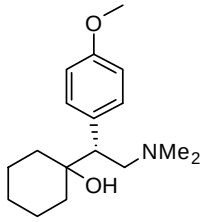
conventional acylating agents but because of its low reactivity, its utilization as acylating agent remains a challenging problem.

A very simple, efficient, new and mild intermolecular and intramolecular F-C acylation reaction of various aliphatic and aromatic esters under very simple reaction condition is described. The detailed mechanistic pathway was studied by DFT calculation and with experimental evidence.

Chapter 2: Asymmetric total synthesis of (−)-venlafaxine

Section 1: Introduction to venlafaxine

This section describes the biological activity and reported synthetic routes to venlafaxine (**22**) (Figure 2). Venlafaxine (**22**) is a new generation antidepressant drug developed by Wyeth-Ayerst company in 1993. Venlafaxine is a phenylethylamine compound, which exhibits a unique pharmacological profile with antidepressant properties. Although venlafaxine is sold as a racemate, (−)-venlafaxine is a more potent inhibitor of norepinephrine synaptosomal uptake while (+)-venlafaxine is more selective in serotonin uptake. It is different from other antidepressants and has no or little activity on a variety of neuroreceptors (e. g. α or β-adrenergic receptors, muscarinic receptors, cholin receptors, histaminic receptors etc.).

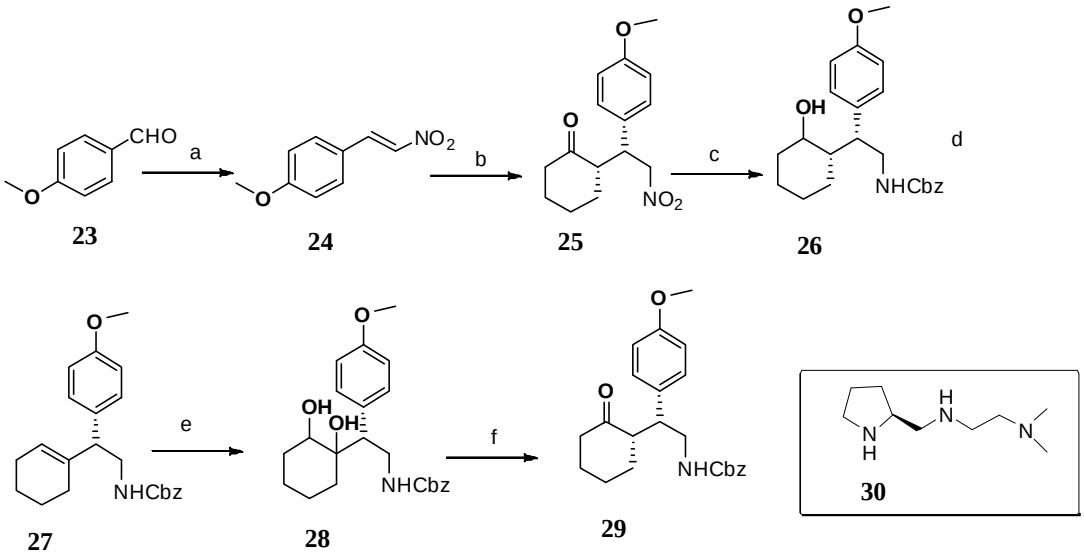


(-)-venlafaxine, **22**

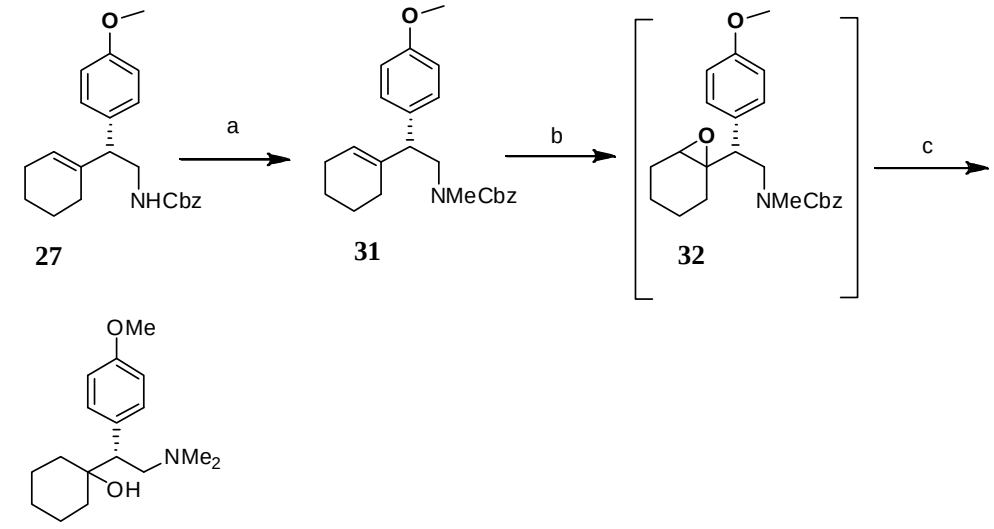
Figure 2. Structure of (−)-venlafaxine (**22**)

Section 2: Asymmetric total synthesis of (−)-venlafaxine using organocatalyst

The present section describes the total synthesis of **(−)**-venlafaxine using organocatalyst. The synthesis started from readily available anisaldehyde **23**, which was converted into *p*-methoxynitrostyrene **24** by employing Henry reaction conditions. Michael addition of *p*-methoxynitrostyrene **24** with cyclohexanone was done in the presence of catalyst **30** to yield nitro ketone compound **25** in 80% yield



Scheme 5. Reagents and conditions: *a) CH_3NO_2, AcOH, NH_4OAc, sonication, 4 h; b) Cyclohexanone,* ***30****, DMF, PTSA, 48 h, rt, 99% ee, 80%; c) i) $NaBH_4$, THF: H_2O (9:1); ii) $NiCl_2$, $6H_2O$, $NaBH_4$, MeOH, CbzCl, Et_3N, 60%; d) i) MsCl, Et_3N, DCM, rt then reflux; ii) DBU, CH_3CN, reflux, 90% e) i) OsO_4, NMO, acetonitrile:H_2O (9:1), 97%; f) i) MsCl, Et_3N, DCM, rt then reflux; ii) Zn, NaI, DME, reflux.*



venlafaxine, **22**

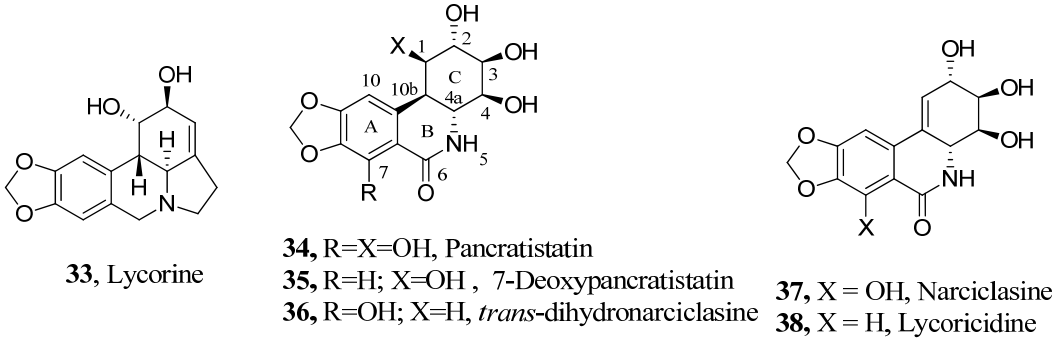
Scheme 6. Reagents and conditions: *a) NaH, MeI, overnight, rt, 90%; b) m-CPBA, $NaHCO_3$, 30 min, rt, 75%; c) $LiAlH_4$, THF, reflux, 80%, ≥ 99% ee.*

and in ≥99% enantiomeric excess. Then the keto compound **25** was converted into hydroxyl carbamate compound **26** by reduction of keto and nitro functional groups followed by *in situ* amine protection. The hydroxy compound **26** was mesylated followed by demesylation to give dehydrated compound **27**. Compound **27** was dihydroxylated by catalytic amount of OsO_4 and NMO to yield diol **28**. The secondary hydroxyl group was selectively mesylated by methanesulphonyl chloride, Et_3N in DCM to yield monomesylated product. But interestingly, when mesylated compound was subjected to deoxygentaion (Zn, NaI), a rearranged product **29** was obtained as a major product. Then the strategy was changed and it was thought to introduce tertiary hydroxy from epoxide. So compound **27** was subjected to *N*-methylation to get compound **31**. Then compound **31** was subjected to epoxidation to get epoxide **32**. After getting the epoxy compound **32** in hand, it was immediately treated with lithium aluminum hydride to get the desired product (−)-venlafaxine **22** in 80% yield with ≥99% enantiomeric ratio (Scheme-6).

Chapter 3: Synthetic studies towards 7-deoxypancratistatin and retro-Reformatsky reaction

Section 1: Introduction to pancratistatin class of *Amaryllidaceae* alkaloids

This section describes the biological activity and reported synthetic routes to pancratistatin (**34)** and 7-deoxypancratistatin (**35)**. Pancratistatin (**34)** and structurally related naturally occurring materials such as lycorine (**33**), 7-deoxypancratistatin (**35)**, *trans*-dihydronarciclasine (**36**), narciclasine (**37)** and lycoricidine (**38)** (Figure 3) have attracted considerable synthetic attention because of interest in the biological activity



33, Lycorine

34, R=X=OH, Pancratistatin
35, R=H; X=OH , 7-Deoxypancratistatin
36, R=OH; X=H, *trans*-dihydronarciclasine

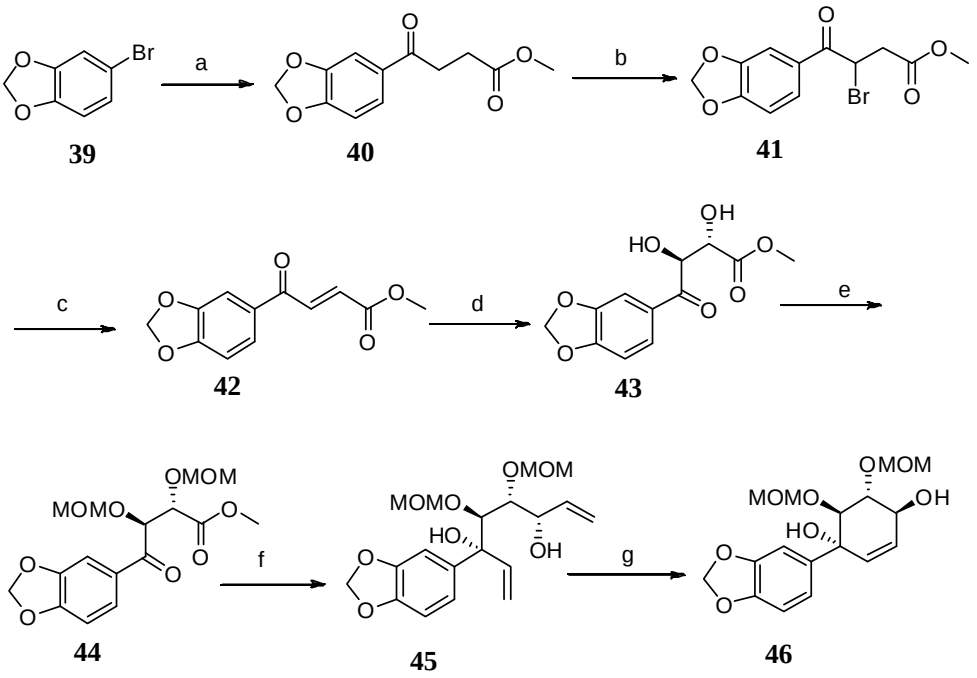
37, X = OH, Narciclasine
38, X = H, Lycoricidine

Figure 3. Few representatives of Amaryllidaceae alkaloids

of these compounds and their novel structural aspects. In 1984, Pettit and co-workers reported the isolation and structure of the highly oxygenated phenanthridone alkaloid designated pancratistatin **34** and the 7-deoxy compound **35**, isolated by Ghosal and co-workers. This alkaloid exhibits high levels of *in vitro* and *in vivo* cancer cell growth inhibitory activity and antiviral activity. Pancratistatin possesses six contiguous stereogenic centers in the C ring of a phenanthridone skeleton and a trans-fused BC ring junction.

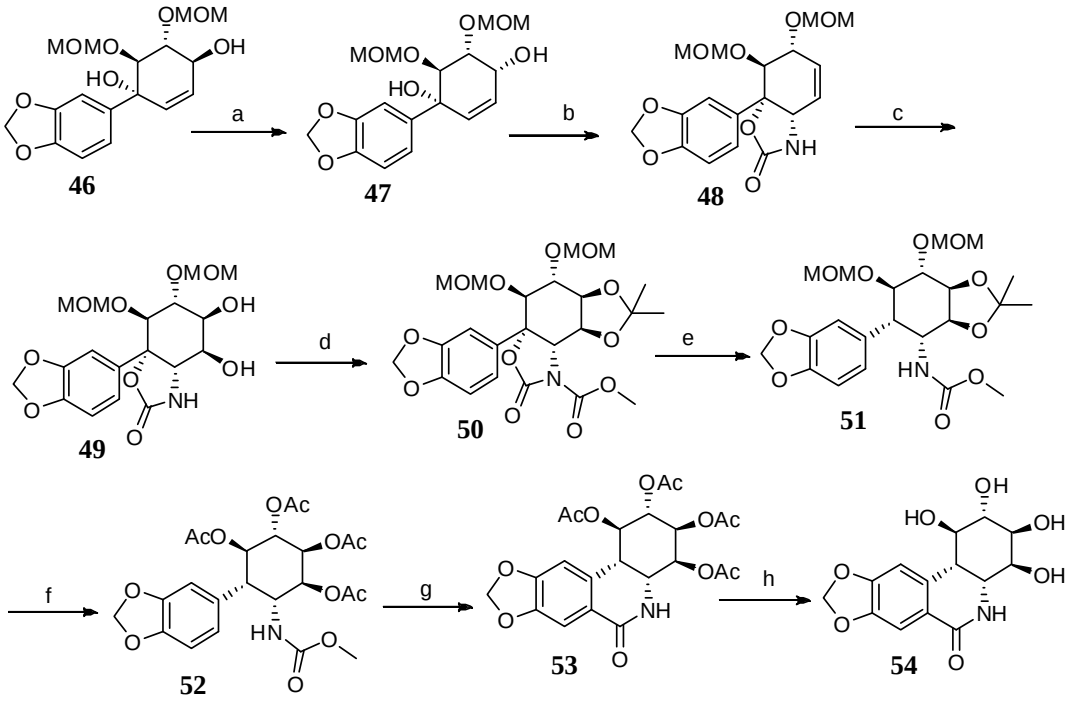
Section 2: A highly stereocontrolled asymmetric total synthesis of epimer *of* 7-deoxypancratistatin

Synthesis of epimer of 7-deoxypancrastatin was started from commercially available cheap starting material 1, 2-methylenedioxybenzene **39**. This key intermediate **46** was synthesized *via* dihydroxylation, Grignard and ring closing metathesis reaction (Scheme 7).



Scheme 7. Reagents and conditions: *a) i) Mg, succinic anhydride, THF, 0 °C, 2 h; ii) Me_2SO_4, K_2CO_3, acetone, reflux, 3 h, 85%; b) NBS, NH_4OAc, CCl_4, reflux, 10 h, 98%; c) Et_3N, DCM, overnight, quant; d) $(DHQD)_2PHAL$, OsO_4, $K_3[Fe(CN)_6]$, K_2CO_3, $^tBuOH:H_2O$(1:1), 4 days, 85%, ≥99% ee; e) MOMCl, DIPEA, DCM, reflux, 3 h, 99%; f) i) vinylmagnesium bromide, THF, 0 °C, 6 h; ii) $CeCl_3.6H_2O$, $NaBH_4$, 0 °C, 15 min, 65%; g) Grubbs' 1st gen. catalyst, DCM, reflux, overnight, 92%.*

After successful construction of cyclohexene ring, nitrogen was installed *via* Overmann rearrangement to get compound **48**. After dihydroxylation followed by deoxygenation it gave compound **51**. B-ring was constructed by Bischler-Napieralski reaction then finally after acetate deprotection it gave epimer of 7-deoxypancratistatin, **54** (Scheme 8).



Scheme 8. Reagents and conditions: *a) i) Bu_3P, DEAD, p-$NO_2C_6H_5CO_2H$, toluene, rt, 3 h; ii) NaOMe, MeOH, 0 °C, 30 min, 65%; b) i) Cl_3CCN, DBU, DCM, 0 °C, 45 min ii) K_2CO_3, xylene, reflux, 4 h, 98%; c) OsO_4, NMO, CH_3CN:H_2O (9:1), rt, 99%; d) i) 2,2-Dimethoxypropane, cat. PTSA, DCM, 0 °C, 1 h; ii) Dimethyldicarbonate, Et_3N, DMAP, DCM, 1 h, rt, 97%; e) $Pd(OH)_2$, 1 drop CH_3COOH, EtOH, H_2, rt, 10 h, 95%; f) i) 2-3 Drops conc. HCl, MeOH, rt, 4 h; ii) Ac_2O, pyridine, rt, overnight, 97%; g) Tf_2O, DMAP, DCM, -5 °C, 16 h, 70%; h) K_2CO_3, MeOH, rt, overnight, 85%.*

Section 3: A simple and straightforward retro-Reformatsky reaction

The Reformatsky reaction is an organic reaction which involves a reaction of aldehydes (or ketones) **55**, with α-halo esters **56**, using metallic zinc to form β-hydroxy-esters **57**. It was discovered by Sergey Nikolaevich Reformatsky

As compared to well known and popular C-C bond forming Reformatsky reaction (Path I), the reverse C-C bond breaking retro-Reformatsky reaction (Path II) has been less attractive to organic chemist due to the unavailability of simple, efficient and direct method for such type of transformation (Figure 4).

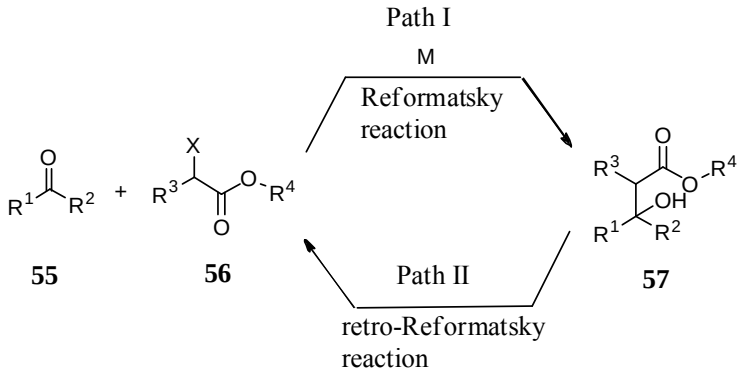
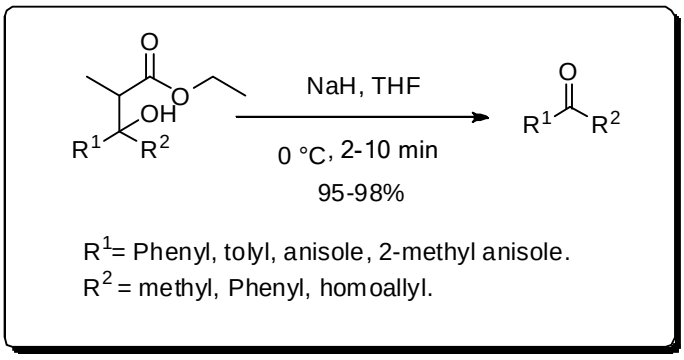


Figure 4. A Reformatsky and retro-Reformatsky reaction.

It was observed that Reformatsky product (β-aryl-β-hydroxy ester) undergoes very facile C-C bond cleavage (retro-Reformatsky reaction) to give keto compound in very short time with excellent yield. A wide variety substrates were subjected to retro-Reformatsky reaction and it found to be general in nature.



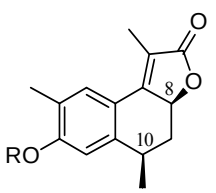
Chapter 1: Diastereoselective total synthesis of (±)-heritol and (±)-heritonin, attempted synthesis towards vallapin and Friedel-Crafts acylation reaction using esters

Section 1

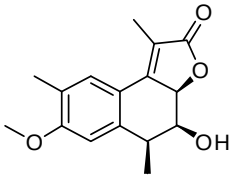
Section 1: Introduction to heritol, heritonin and vallapin

1.1.1. Introduction

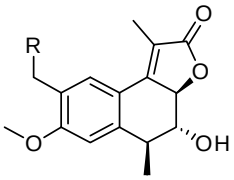
Miles and co-workers have isolated cadinane sesquiterpene lactones heritol **(1)**[1], heritonin **(2)**[2], vallapin **(3)**[3], vallapianin **(4)**[3] and heritianin **(5)**[4] (Figure 1) from the sap of the mangrove plant *Heritiera littoralis* of Philippines and other tropical countries. These compounds were shown to possess ichthyotoxicity in *ppm* quantities to *Tilapia nilotica* fingerlings and this plant drew attention of scientists because it had been utilized by natives of the Philippine islands as a fish poison. Toxicity towards fish is often used as a measure of pesticidal activity.[5] These compounds represent a new and novel class of sesquiterpene and possess unusual oxygenation pattern not generally encountered in cadinane family.



1, R=H, Heritol
2, R= CH_3, Heritonin



3, Vallapin



4, R= OH, Vallapianin
5, R= H, Heritianin

Figure 1. Structures of heritol (**1**), heritonin (**2**), vallapin (**3**), vallapianin (**4**), heritianin (**5**).

1.1.2. Structure Elucidation

Heritol and heritonin:

Miles *et al.* have established the structure and relative stereochemistry of heritol **(1)** from its spectral data and confirmed it by its single crystal X-ray analysis. Pure heritol **(1)** was crystallized from methanol as white needles (mp 271-272 ^oC, $[\alpha]^{25}_D$ +261.3) and analyzed for $C_{15}H_{16}O_3$ by HRMS, which indicated eight degree of unsaturation. The presence of aromaticity in the molecule was suggested by the fact that the molecular ion at m/e 244 was the base peak. Also, fragmentations at m/e 216 $(M\text{-}CO)^+$ and m/e 215 $(M\text{-}CHO)^+$ were typical of a phenol moiety.

The IR spectrum revealed absorptions at 3450 cm^{-1} and 1750 cm^{-1}, indicating the presence of a hydroxyl group and an α, β-unsaturated γ-lactone moiety. This was further supported by the UV (cyclohexane) absorption at 228 nm (ε 11950), characteristic of butenolide moiety. The ^1H NMR spectrum revealed resonances at δ 6.85 (s, 1H) and 7.42 (s, 1H), for two isolated protons on an aromatic ring, which was

further supported by UV spectrum that gave absorptions at 217, 285 and 305 nm. Moreover, ^{1}H NMR spectrum provided evidence of the three nonequivalent methyl groups, by revealing resonances at δ 1.42 (d, *J* = 10.0 Hz, 3H), 2.18 (s, 3H) and 2.30 (s, 3H). Two of these resonances were singlets, indicating their attachment to the quaternary carbons. The third methyl group exhibiting doublet was assigned to be attached to a methine carbon. The ^{1}H NMR spectrum also gave signal for a methylene proton at δ 2.62 (m, 1H); a benzylic proton at δ 3.10 (m, 1H); a proton on a carbon bearing oxygen at δ 4.90 (dd, *J* = 10.0, 3.0 Hz) and a hydroxyl proton at δ 5.22 (s, 1H). On acetylation of heritol, signal at δ 5.22 disappeared, which further confirmed its assignment as a hydroxylic proton.

Due to solubility problem with heritol, ^{13}C NMR spectrum was recorded for its acetate, which gave 17 resonances, indicating a molecule with no symmetry. Six aromatic resonances were observed at δ 121.1, 126.5, 129.2, 130.2, 141.9 and 151.0 ppm. The intensity ratios of these lines and the presence of two lines of the same intensity at δ 121.1 and 130.2 suggested the symmetric *ortho* tetra substitution with two protons located in the *para* position. The two additional deshielded carbon resonances at δ 118.5 and 155.8 were assigned to the α, β-carbons of the butenolide moiety. A resonance at δ 79.3 was assigned to the methine carbon attached to the oxygen involved in the lactone functional group. On the basis of the above spectroscopic data and a single crystal X-ray analysis, structure **1** was assigned to heritol. Although, the absolute stereochemistry at the centers C-8 and C-10 could not be ascertained rigorously even by X-ray analysis, they were tentatively assigned to be ***S*** and ***R*** respectively, based on their biosynthetic origin.

Structure of heritonin was elucidated by comparison of its spectroscopic data with that of heritol and assigned structure **2**, a methyl ether of heritol.

Vallapin:

In 1991 Miles *et al.* have established the structure and relative stereochemistry of **3** from its spectral data and confirmed it by its single crystal X-ray analysis. Pure vallapin **(3)** was crystallized from methanol as white needles (mp 269 ^{o}C, $[\alpha]^{25}_{D}$ −289.5°) and molecular formula of $C_{16}H_{18}O_4$ was established by HRMS ($[M]^+$ m/z found 274.1203, calcd 274.1204), which indicated eight degree of unsaturation. The presence of aromaticity in the molecule was suggested by the fact that the molecular

ion at m/e 274 was also the base peak. Also, fragmentations at m/e 246 $(M\text{-}CO)^+$ and m/e 245 $(M\text{-}CHO)^+$ were typical of a phenol and fragmentations at m/e 77 and m/e 128 indicated aromatic and napthalenic functionalities respectively.

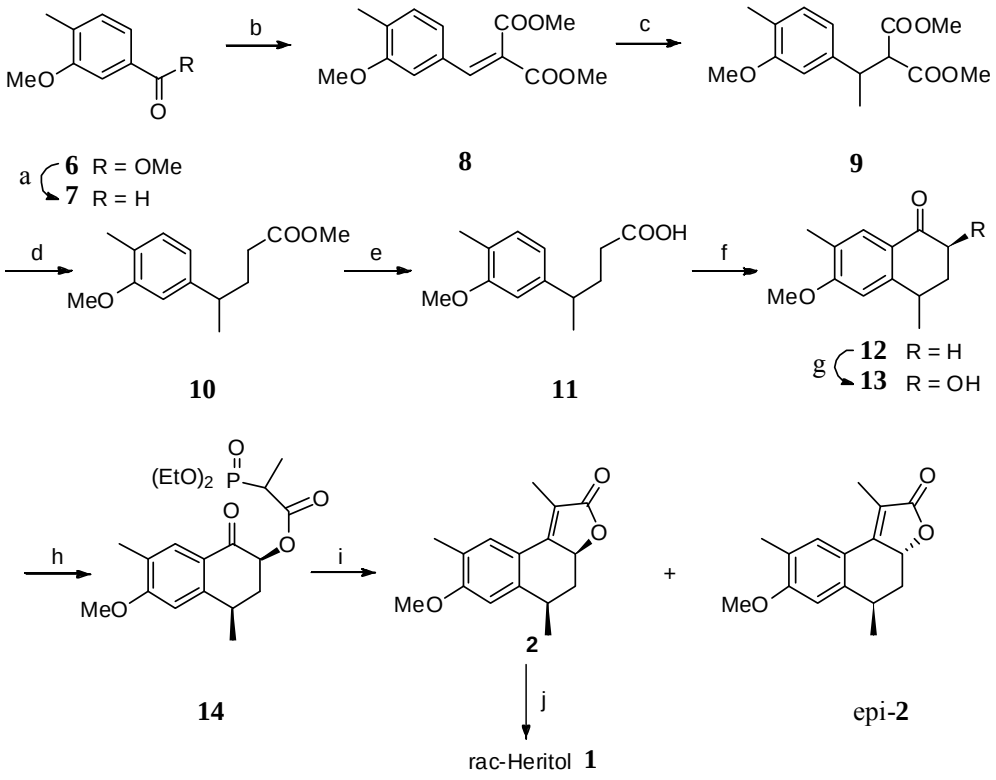
The IR spectrum revealed absorptions at 3450 cm^{-1} and 1750 cm^{-1}, indicating the presence of a hydroxyl group and an α, β-unsaturated γ-lactone moiety. This was further supported by the UV (cyclohexane) absorption at 228 nm (ε 11950), characteristic of butenolide moiety. The ^1H NMR ($CDCl_3$, 200 MHz) spectrum gave resonances at δ 6.74 (s, 1H) and 7.48 (s, 1H), for two isolated protons on an aromatic ring, which was further supported by UV spectrum that gave absorptions at 217, 286 and 310 nm. Moreover, ^1H NMR spectrum provided evidence of the three nonequivalent methyl groups, by revealing resonances at δ 1.45 (d, J = 10.0 Hz, 3H) and 2.31 (s, 3H). Two of these resonances were singlets, indicating their attachment to the quaternary carbons. The third methyl group with double multiplicity was assigned to be attached to a methine carbon. The ^1H NMR spectrum also gave signal for a methine proton at δ 3.06 (m, 1H); a proton on a carbon bearing oxygen at δ 5.22 (s**,** lH), a proton at δ 4.42 (s**,** lH), and a methoxy group at δ 3.95 (s**,** 3H). The basic skeleton of vallapin was assigned by consideration of the spectral data and the isoprene rule. Further structure and stereochemical relationship was confirmed by single-crystal X-ray diffraction study.

1.1.3. Literature Review

There are only three racemic syntheses and one enantioselective synthesis of heritol **(1)** and heritonin **(2)** reported in literature. The first synthesis, reported by Irie *et al.*,[6] employed intramolecular Wittig-Horner reaction as the key step for the construction of butenolide moiety. The other synthesis was reported by Chavan *et al.*,[7] where dihydroxylation of β, γ-unsaturated ester and elimination-lactonisation under basic conditions, were used as the key steps. Apart from these two syntheses, three methodologies have been developed by Chavan *et al.* for the butenolide ring construction, using which synthesis of heritonin has been achieved. One of the methodology used *p*-toluenesulfonic acid for cyclisation of β, γ-dihydroxy ester[8] to the butenolide; which was later on modified by the same authors, where instead of *p*TSA, Amberlyst-15 was used for similar cyclisations.[9] The third methodology used ceric ammonium nitrate[10] for one step oxidative cyclisation of β, γ-unsaturated acid to

the butenolide rings. The racemic synthesis of heritonin **(2)** was reported by Silveira *et al.*[11] in 2004, where Lewis acid catalyzed reaction of various arylacetic acids with allylsilanes provided 4-alkyl-2-tetralone, which was further elaborated for the synthesis of heritonin **(2)** and its C-8 epimer. The first enantiospecific synthesis was reported by Chavan *et al.*[12] by using (*R*)-(+)-citronellal as the key synthon which is abundantly available both from plants and synthetically. The correct absolute configuration of natural (+)-heritol **(1)** was assigned to be (*S*, *R*) configuration at C10 and C8 respectively.

Irie's Approach[6] (*Chem. Pharm. Bull.* **1990**, *38,* 1852)



Scheme 1. Reagents and conditions ***:*** *a) (i) LAH; (ii) MnO_2; b) $CH_2(COOMe)_2$, C_6H_5COOH, piperidine; c) Me_2CuLi, ether; d) (i) KOH, H^+, 150-170 ^oC; (ii) $(COCl)_2$; (iii) CH_2N_2; (iv) $C_6H_5CO_2Ag$, Et_3N; e) KOH; f) $(COCl)_2$, $AlCl_3$, 35% (over 10 steps); g) $PhI(OAc)_2$, 67%; h) $CH_3CH[C(O)Cl]P(O)(OEt)_2$; i) NaH, benzene, 1.5%; j) BCl_3.*

In 1990, the first total synthesis of (±)-heritol (**1)** was reported by Irie *et al.* utilizing tetralone **12**. For the construction of the butenolide moiety, they had used intramolecular Wittig reaction (Wadsworth-Emmons modification) as the key step on tetralone intermediate **12**. Tetralone **12** was prepared from methyl 3-methoxy-4-methylbenzoate **6** as the starting material. Accordingly, reduction of **6** was carried out with LAH followed by MnO_2 oxidation of the resulting alcohol which gave aldehyde **7** (Scheme 1).

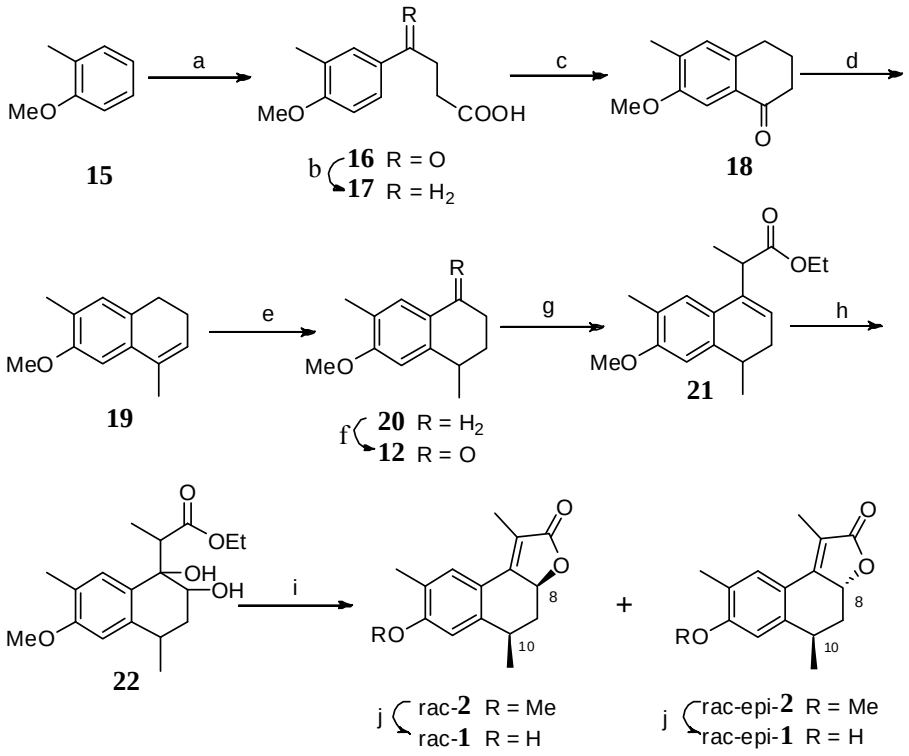
Condensation of aldehyde **7** with diethyl malonate provided the benzal malonate **8**. The diester **9** was synthesized by introduction of methyl group by 1, 4-addition using lithium dimethylcuprate on **8**. Alkaline hydrolysis of the diester **9** and concomitant decarboxylation at 150-170 ^{o}C, followed by Arnt-Eistert one carbon homologation of the corresponding acid gave ester **10**. The ester **10** was hydrolyzed to the corresponding acid **11**, which was converted to the corresponding acid chloride by treatment with oxalyl chloride followed by intramolecular Friedel-Crafts acylation reaction using anhydrous aluminium chloride in CH_2Cl_2 to furnish the tetralone **12**.

The overall yield of tetralone **12** from the methyl benzoate **3** was reported to be 35%. Oxidation of **12** was carried out with iodosobenzene diacetate to give stereoisomeric α-hydroxy ketone **13**, which on **e**sterification with α-(diethylphosphono) propionylchloride gave the phosphonate **14** in good yield. Intramolecular Emmons-Wadsworth reaction of phosphonate **14** with various bases in different solvents was slow and yielded inseparable mixture, consisting of heritonin **(2)** and its C-8 epimer (10: 1 ratio respectively) in 1.5% overall yield. Demethylation of the heritol methyl ether **(2)** was carried out with boron trichloride to afford heritol **(1)** as a *racemic* mixture. The synthetic *rac*-heritol had mp 245-246 ^{o}C, lower than that of optically active (+)-heritol **(1)**. Spectral data of heritol synthesized by above sequence of reactions matched with the natural product.

Chavan' s Approach[7] *(Tetrahedron* **1991** *47*, 5759)

The second synthesis of *rac*-heritol **(1)** was reported by Chavan *et al.* in 1991 by using same tetralone intermediate **12** (previously reported by Irie *et al.*[6]), where butenolide ring was constructed by a different route in high yields in respect to the previous one.

Accordingly, tetralone **12** was synthesized from *o*-cresol methyl ether **15** as a starting material by using standard high yielding reaction sequences. At first Friedel-Crafts acylation of **15** was carried out using succinic anhydride to provide the keto acid **16** in 85% yield, which was subjected to Clemmensen reduction to give butyric acid derivative **17**. On treatment with trifluoroacetic anhydride, acid **17** underwent cyclisation to furnish tetralone **18** in 80% yield. 1,4-Ketone transposition followed by introduction of methyl group was achieved as shown in the Scheme-2 using standard functional group transformations to furnish intermediate tetralone **12** in 40% overall yield starting form *o*-cresol methyl ether **15**.



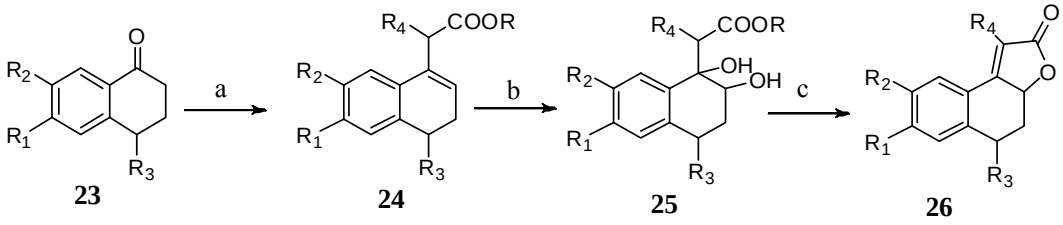
Scheme 2. *Reagents and conditions* **:** *a) Succinic anhydride, $AlCl_3$, $C_6H_5NO_2$, 0 ^oC to rt, 24 h, 85%; b) Zn(Hg), HCl, reflux; c) $(CF_3CO)_2O$, 0 ^oC, 10 min, 80%; d) MeMgI, Et_2O, H^+; e) H_2, 10% Pd/C; f) CrO_3, AcOH: EtCOOH (1: 3), 40% (over 3 steps); g) Ethyl-α-bromopropionate, I_2, Zn, Et_2O, H^+, 80%; h) OsO_4 (cat), NMO, CH_3CN: H_2O (9: 1), 85%; (i) MsCl, Et_3N, DMAP, benzene, reflux, 15 h, 77%; j) EtSH, $AlCl_3$, CH_2Cl_2.*

This tetralone **15** was subjected to Reformatsky reaction with ethyl-2-bromopropionate, followed by acidic work-up, to give selectively β, γ-unsaturated ester **21** as a mixture of diastereomers; which on dihydroxylation using catalytic osmium tetroxide gave diol **22**. Diol **22** was treated with mesyl chloride in the presence of base to provide 3: 2 diastereomeric mixture of heritonin **(2)** and its C-8 epimer, which were separated by crystallization and demethylation was carried out using aluminium chloride-ethanethiol to give racemic heritol **(1)** and its C-8 epimer as the sole product, respectively.

Other butenolide ring construction protocols used for the synthesis of heritol[8-10]

Chavan's Approach [8-9] (*Tetrahedron Lett.* **1992**, *33*, 4605; *Green Chem.* **2002**, *4*, 194).

For the construction of butenolide ring Chavan *et al.*[8] reported the first methodology where *p*-toluenesulfonic acid was used for one-pot dehydration as well as lactonisation purpose. Accordingly, tetralone **23** was subjected to Reformatsky



23 **24** **25** **26**

R^1, R^2 = H/ Me/ OMe; R^3, R^4 = H/ Me and R = Me/ Et.

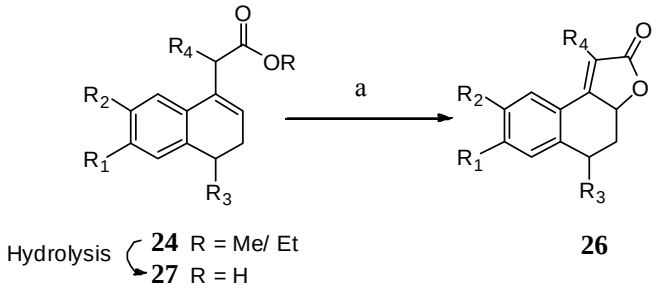
Scheme 3. Reagents and conditions: ***a)*** *$R_4CHBrCO_2R$, Zn; b) Cat. OsO_4, NMO; c) PTSA, benzene, reflux.*

reaction to get β, γ-unsaturated ester **24** which was dihydroxylated to give diol **25**, which was then subjected to catalytic amount of *p*-toluenesulfonic acid under refluxing condition in benzene to yield the required butenolide moiety **26** in high yield (Scheme 3). Heritonin **(2)** and its C-8 epimer have been synthesized using this methodology, in 90% overall yield. This group (Chavan *et al.*[9]) also used Amberlyst-

15 instead of *p*TSA for the green synthesis of heritonin **(2)**, heritol **(1)** and their analogs.

Chavan's Approach[10] (*J. Chem. Soc., Chem. Comm.* **1994**, 1101)

Ceric ammonium nitrate mediated oxidative cyclisation was used by this group (Chavan *et al.*[10]) for cyclisation of the β, γ-unsaturated acid **27** to butenolide ring. Accordingly, β, γ-unsaturated ester **24** was subjected for alkaline hydrolysis to give β, γ-unsaturated acid **27**, which on treatment with CAN in acetonitrile yielded butenolide **26** in good to excellent yield (Scheme 4). Heritonin **(2)** was prepared using this procedure from the corresponding acid in 36% yield.



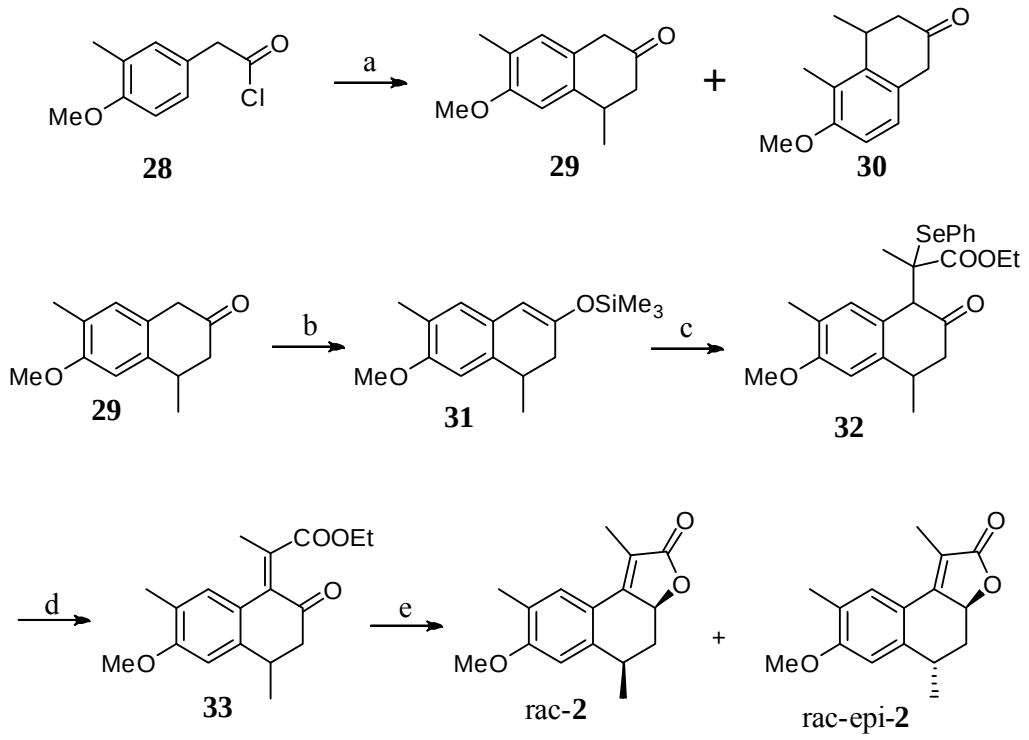
R^1, R^2 = H/ Me/ OMe and R^3, R^4 = H/ Me

Scheme 4. Reagents and conditions: *a) CAN, CH_3CN, $NaHCO_3$, rt.*

Silveira's Approach[11] (*Tetrahedron Lett.* **2004**, *45*, 4077)

The approach by Silveira *et al.* differs from the others in butenolide ring construction. They have mainly used two key steps, (i) Friedel-Crafts reaction of aromatic acyl chlorides with allyltrimethylsilanes by using $AlCl_3$ for the formation of β-tetralones.[13]; (ii) Alkylation of the silylenolethers with *α*-halo-*α*-phenylselenoesters by using Lewis acid.[14]

Accordingly, aryl acid chloride **28** was treated with allyltrimethylsilane in the presence of anhydrous aluminium chloride to give β-tetralone **29**, along with isomeric tetralone **30** in 41% overall yield. They were separated by repeated crystallization to give **29** in 25% isolated yield.



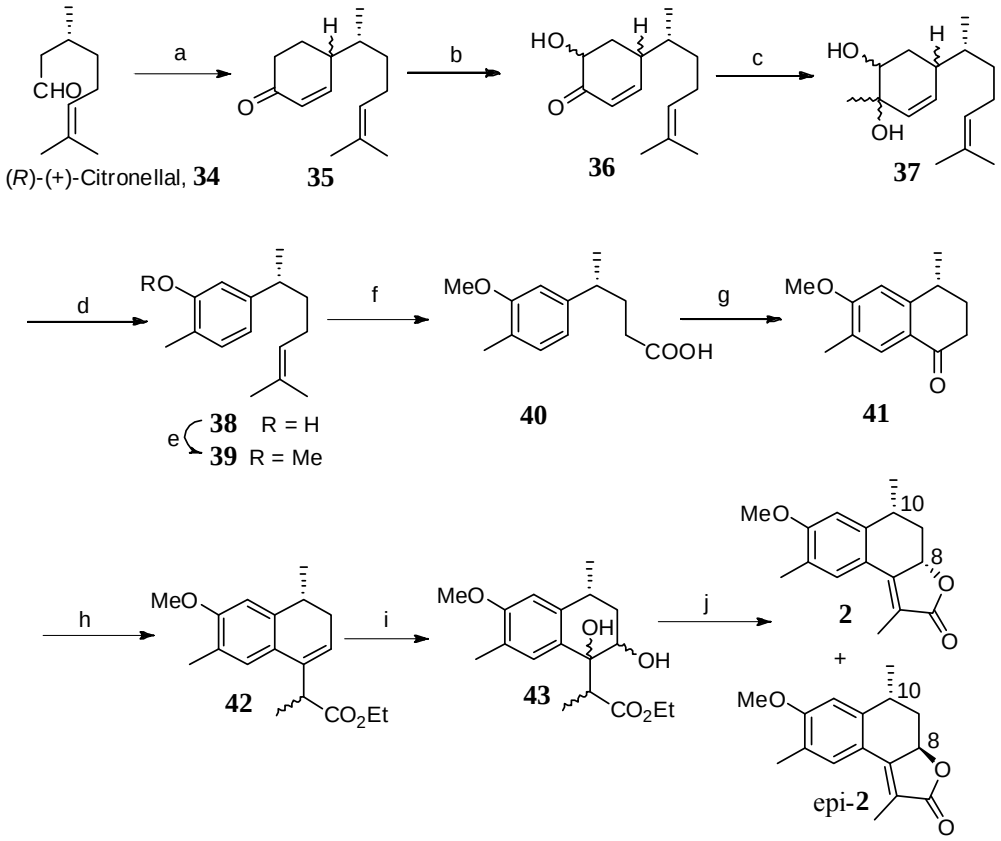
Scheme 5. Reagents and conditions: *a) $AlCl_3$, allyltrimethyl silane, CH_2Cl_2, -20 ^oC to reflux, 90 min, 41%; b) LDA, THF, -78 ^oC, TMSCl, 76%; c) $ZnBr_2$, α-chloro-α-phenylseleno-ethylpropionate, CH_2Cl_2, 0 ^oC to rt; d) mCPBA, CH_2Cl_2, -78 ^oC to rt, 41% (over two steps); e) (i) $NaBH_4$, EtOH, 0 ^oC, 5 min, rt, 1 h; (ii) 12 N HCl, 60 ^oC, 40 min, 75% (over two steps).*

Enol ether **31** was prepared from β-tetralone **29** which was treated with *α*-chloro-*α*-phenylseleno-ethylpropionate in the presence of $ZnBr_2$ to furnish γ-ketoester **32**. Oxidation was carried out with *m*-CPBA at -78 ^oC to provide α, β-unsaturated ester **33** in 41% yield, together with 16% of its isomeric *trans*-ester. Finally, ester **33** was cyclised upon reduction with $NaBH_4$ followed by acid hydrolysis to give *rac*-heritonin **2** and its C-8 epimer as a 3: 2 diastereomeric mixture in 75% overall yield (Scheme 5).

Chavan's Approach[12] (*Tetrahedron Lett.* **2007**, *48*, 643)

The first enantiospecific total synthesis of (−)-heritol **(1)** and correct absolute configuration was reported by this group (Chavan *et al.*) from (*R*)-(+)-citronellal as the key synthon which is abundantly available both from plants and synthetically.

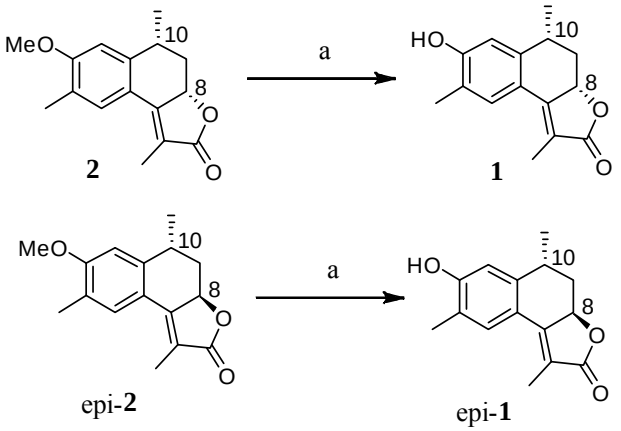
Accordingly, (*R*)-(+)-citronellal **34** was converted to corresponding enone **35** by following the reported procedure.[15] α-Hydroxylation of ketone was carried out by using Rubottom Oxidation protocol to provide α-hydroxy enone **36**. The enone **36**



Scheme 6. Reagents and conditions: *a) i) Formalin (35%), piperidine acetate, 110 ^{o}C, 4 h; ii) NaOMe (cat), methyl acetoacetate, MeOH, reflux, 5 h, 45% (over two steps); b) (i) LDA, THF, -78 ^{o}C, 1.5 h, TMSCl, -78 ^{o}C to rt, 5 h; (ii) mCPBA, CH_2Cl_2, 0 ^{o}C to rt, 10 h; (iii) Dilute HCl, CH_2Cl_2, rt, 12 h, 70% (over three steps); c) MeMgI, diethyl ether, 0 ^{o}C to rt, 12 h, 95%; d) (i) Oxalyl chloride, DMSO, CH_2Cl_2, -78 ^{o}C, then diol* ***37****, 30 min, Et_3N, -78 ^{o}C to rt, 5 h; (ii) Methanesulfonyl chloride, Et_3N, CH_2Cl_2, 0 ^{o}C to rt, 3 h, reflux, 5 h; (iii) KOH, methanol, reflux, 7 h, 47% (over three steps); e) K_2CO_3 dimethyl sulfate, acetone, reflux, 12 h, 86%; f) OsO_4 (cat), Jones' reagent, acetone, rt, 7 h, 82%; g) Trifluoroacetic anhydride, trifluoroacetic acid, 0 ^{o}C, 3 h, 80%; h) Zn, ethyl-2-bromopropionate, iodine, ether, reflux, 3 h, H^+, 80%; i) OsO_4 (cat), NMO, CH_3CN-H_2O, rt, 24 h, 95%; j) pTSA, benzene, reflux, 1 h, 90% (over two steps).*

was treated with methyl magnesium iodide followed by Swern oxidation of diol which gave α-hydroxy ketone. The crude α-hydroxy ketone was subjected for mesylation followed by hydrolysis to give phenolic intermediate **38**. The double bond of the anisole derivative **39** was oxidatively cleaved[16] by using Jones' reagent in the presence of osmium tetroxide (catalytic) to furnish the acid intermediate **40**. For the synthesis of key chiral tetralone intermediate **41**, acid **40** was treated with triflouroacetic anhydride in triflouroacetic acid. For the construction of butenolide ring, tetralone **41** was subjected to Reformatsky reaction condition followed by dehydration to give selectively β,γ-unsaturated ester **42** (Scheme 6). Double bond was converted to corresponding diol followed by cyclisation and dehydration which gave mixture of heritonin **(2)** and C-8 epi-heritonin in 3:2 ratio.

Finally, heritol **(1)** was obtained by demethylation of **2** using anhydrous aluminium chloride in the presence of ethanethiol[17] and under identical reaction conditions, pure *epi*-heritol (*epi*-**1**) (C-8 epimer of **1**) was obtained (Scheme 7).



Scheme 7. Reagents and conditions: a*) $AlCl_3$, EtSH, CH_2Cl_2, rt, 12 h, 80%.*

To the best of knowledge, no report of a total synthesis vallapin (3), vallapianin (4) and heritianin (5) exists in the literature.

1.1.4. References

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Chapter 1: Diastereoselective total synthesis of (±)-heritol and (±)-heritonin, attempted synthesis towards vallapin and Friedel-Crafts acylation reaction using esters

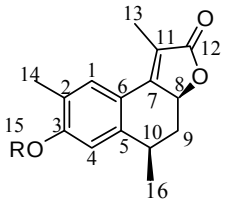
Section 2

Diastereoselective total synthesis of (±)-heritol and (±)-heritonin

1.2.1. Present Work

1.2.1.1. Objective

Literature survey revealed that herirol (**1**) and heritonin (**2**) have attracted many organic chemists towards their synthesis due to the potential interesting biological activity and unique structural features. These compounds represent a new and novel class of sesquiterpene and possess unusual oxygenation pattern not generally encountered in cadinane family. Most of the reported syntheses have drawbacks involving lengthy routes, expensive starting materials, hazardous reagents or harsh reaction conditions and/or low overall yields and all reported syntheses end with mixture of heritol and its epimer. To overcome these problems there still exists a need to develop a simple, practical, efficient and diastereoselective synthesis of heritol (**1**) and heritonin (**2**) (Figure 1).



1 R=H
2 R= CH_3

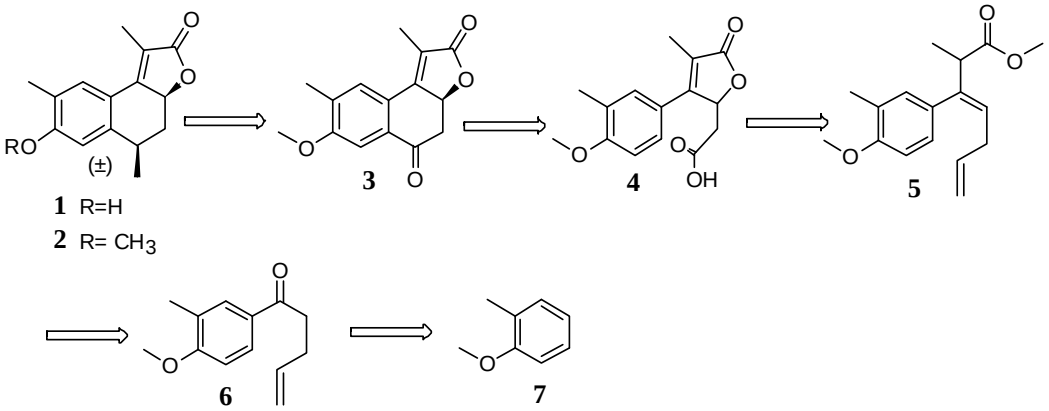
Figure 1. Structure of heritol and heritonin.

This group is engaged in the synthesis of biologically active compounds and earlier this group has developed a practical and efficient protocol for the synthesis of different biologically active terpenes.[1] In continuation of search for practical routes for such molecules, synthesis of heritol and heritonin was undertaken.

All reported syntheses involved first construction of tetralin unit of heritol followed by the installation of the sensitive butenolide ring at a later stage[2] or begin with substituted tetralone as the starting material and then involved the synthesis of butenolide ring.[3] The current novel route involves the diastereoselective total synthesis of heritol and heritonin, where the key reaction is the formation of tetralone on preformed sensitive butenolide functionality.

1.2.1.2. Retrosynthetic analysis

Retrosynthetic analysis of heritonin (**2**) and heritol (**1**) (Scheme 1) revealed that heritonin (**2**) and heritol (**1**) can be obtained from tetralone unit **3**, which in turn could be obtained from acid **4** *via* intramolecular Friedel-Crafts acylation. The acid **4** having α,β-unsaturated lactone can be synthesized from diene **5**. The diene **5** could be accessed from the keto compound **6** *via* Reformatsky reaction followed by dehydration. The keto compound **6** can be accessed from cheap and commercially available starting material **7**.



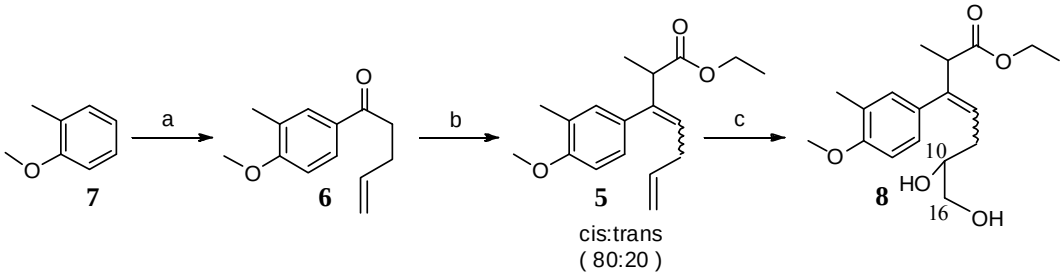
Scheme 1. Retrosynthetic analysis of (±)-heritonin **2** and (±)-heritol **1**.

1.2.1.3. Results and discussion

As discussed in the retrosynthetic approach, the diastereoselective total synthesis of (±)-heritol and (±)-heritonin was started from 2-methylanisole **7** which is commercially available and inexpensive starting material. The aryl ketone **6** was prepared by the Friedel-Crafts acylation of 2-methylanisole **7** with allylacetyl chloride and triflic acid in DCM at room temperature to furnish the corresponding allylic keto compound **6** in 95% yield. The IR spectrum of **6** showed strong band at 1676 cm^{-1}, characteristic of conjugated ketone functionality. The ^{1}H NMR spectrum showed multiplet at δ 5.80-6.00 for one proton and δ 4.97-5.13 for two protons, which are characteristic peaks for the presence of olefinic double bond (-CH=CH_2) which clearly suggested the formation of ketone **6**. This was further confirmed by its ^{13}C NMR and DEPT NMR spectra, which showed a quaternary carbon singlet at δ 197.77 for the carbonyl carbon. Elemental analysis and mass spectrum finally ascertained the formation of ketone **6**.

Reformatsky reaction on **6** with ethyl 2-bromopropionate using activated Zn in benzene:diethylether (1:1) as the solvent at reflux condition gave β-hydroxy ester, which without further purification was treated with PTSA in DCM at room temperature to afford selectively β,γ-unsaturated ester **5** as an inseparable mixture of geometrical isomers (82:18) in 85% yield (over two steps).

Formation of **5** was confirmed by using spectroscopic methods. IR spectrum showed strong absorption band at 1732 cm^{-1} indicating the presence of ester functionality. ^{1}H NMR spectrum of **5** revealed a quartet at δ 4.11 (-O<u>CH</u>$_2$CH$_3$) and triplet at δ 1.26 (-OCH$_2$<u>CH</u>$_3$) for ethyl ester moiety. The quartet δ 1.27 (CH$_3$<u>CH</u>CO-) was merged in to the triplet of ethyl ester. The triplet which appeared at δ 5.57 integrating for one proton confirmed the presence of olefinic *γ*-proton of *β, γ*-unsaturated ester. ^{13}C and DEPT spectra showed doubling of signals for carbonyl, olefinic and ethyl ester carbon revealing it to be mixture of isomers which was also further confirmed by GC and GC-MS analysis. GC spectrum of compound **5** showed two peaks at 12.2 and 12.6 min. retention times with 80% and 20% area respectively. GC-MS spectrum showed a molecular ion peak at 288 (M^+) and both compounds showed same fragmentation pattern which indicated that both are diastereomers. Its mass spectrum showed



Scheme 2. Reagents and conditions: *a) Allylacetyl chloride, CF_3SO_3H, DCM, rt, 4 hrs, 95%; b) i) Ethyl 2-bromopropionate, activated Zn, benzene:ether (1:1), reflux, 3 hrs; ii) PTSA, DCM, rt, 12 hrs, 85% (over two steps); c) OsO_4, NMO, acetonitrile:water (9:1), 30 min, 99%.*

molecular ion peaks at m/z 289 $(M+H)^+$ and 311 $[M+Na]^+$. Finally the structure was confirmed by the elemental analysis.

The β,γ-unsaturated ester **5** was subjected to exhaustive dihydroxylation of both the double bonds with OsO_4. It was observed that the reaction did not go to completion

even after five to six days and also after sequential or portion wise addition of OsO_4 over 2-3 days due to the presence of tri-substituted highly sterically congested double bond. The exact reason as to why the reaction did not go to completion was not clear but it was believed that the active dihydroxylation catalyst gets "poisoned" and is not available for further dihydroxylation. So it was decided to perform stepwise dihydroxylation.

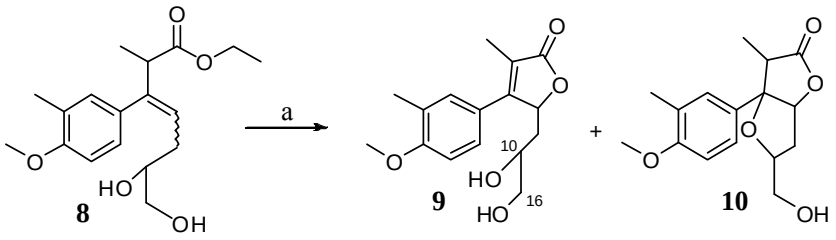
Thus selective dihydroxylation of monosubstituted olefin of β,γ-unsaturated ester **5** by using cat. amount OsO_4 and NMO as a co-oxidant in acetonitrile:water (9:1) as solvent system furnished the diol **8** in 99% yield. IR spectrum of compound **8** showed strong bands at 3444 and 1732 cm^{-1}, characteristic peaks for free hydroxyl group and ester moiety. In the ^1H NMR spectrum of compound **8** showed multiplet at δ 5.80-6.00 for one proton and multiplet at δ 4.97-5.13 for two protons were absent indicating the conversion of olefinic bond to diol. ^{13}C NMR and DEPT NMR spectra of compound **8** showed doubling of peaks due to the mixture of diastereomers. The mass spectrum of compound **8** showed peaks at m/z 323 and 345 corresponding to $[M+H]^+$ and $[M+Na]^+$. Finally the structure was confirmed by elemental analysis (Scheme 2).

Further dihydroxylation of sterically crowded trisubstituted olefin of diol **8** was successfully carried out under the same reaction conditions for three days. The crude tetrol mixture on treatment with PTSA furnished the desired α,β-unsaturated lactone **9** along with undesired bicyclic product **10** in 1:1.2 ratio.

In an attempt to get the desired compound **9** as the sole product, the crude mixture was treated with different stoichiometric amounts of $BF_3.OEt_2$, PTSA in DCM at room temperature (Table 1). Gratifyingly, use of excess $BF_3.OEt_2$ proved to be an ideal condition which furnished compound **9** and **10** in 9.5:1 ratio (Scheme 3).
In the presence of Lewis acid, due to complexation **8** leads to the formation of benzylic carbocation which can either undergo i) *β*-proton elimination to furnish α,β-unsaturated lactone **9** (desired product) or ii) C10-OH can attack on benzylic cation and form bicyclic compound **10** (undesired product).

The excess $BF_3.OEt_2$ used may be complexing as a monodentate Lewis acid with both C10-OH and C16-OH separately or one BF_3 molecule may be complexing as a bidentate Lewis acid with both C10-OH and C16-OH. Usually $BF_3.OEt_2$ acts as a

monodentate ligand. In literature there are few isolated reports available where BF_3 acts as a bidentate Lewis acid. People have also isolated and characterised 1:1 complex of boron halide and β-dicarbonyl campound[4] and have also invoked the formation of BF_3 complex in deprotection of silyl ethers with *o*-hydroxy benzaldehydes which has been isolated and well characterized.[5] Therefore in presence of excess $BF_3.OEt_2$ the lone pair of oxygen gets locked due to the chelation. So the possibility of C10-OH attack on the benzylic cation is very less. β-Proton elimination occours predominantly under this situation leading to the formation of compound **9** as the major product.



Scheme 3. Reagents and conditions: *a) OsO_4, NMO, acetonitrile:water (9:1), 3 days; ii) $BF_3.OEt_2$, DCM, rt, 1 h, 76% (**9**), 8% (**10**).*

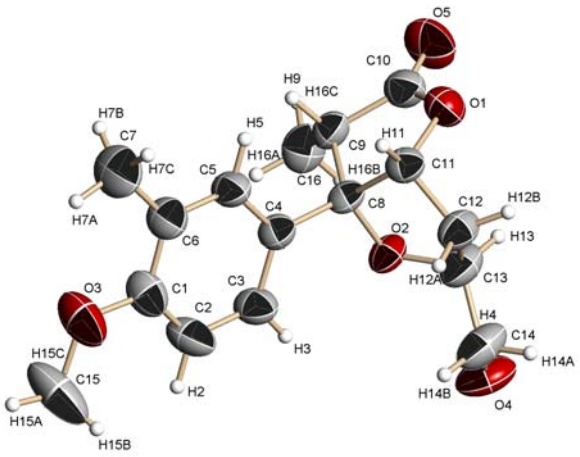
Table 1. Optimization for butenolide synthesis.

Entry No	Conditions	Ratio **9**:**10**
1	PTSA	1:1.2
2	$BF_3.OEt_2$ (2.5 eq.)	1.02:1
3	$BF_3.OEt_2$ (excess)	9.5:1

The formation of compounds **9** and **10** was confirmed by spectral techniques. The IR spectrum of **9** showed strong bands at 3421 and 1741 cm^{-1}, indicating the presence of free hydroxyl group and butenolide ring. From its ^1H NMR and ^{13}C NMR spectra it was evident that it is a diastereomeric mixture. Presence of a singlet at δ 2.23 and multiplet at δ 5.62 indicated the formation of α,β-unsaturated-γ-lactone.^{13}C NMR

spectrum of compound **9** showed it to be a diastereomeric mixture. Peaks at δ 175.33 and 175.09 indicated the presence of unsaturated lactone. The mass spectrum of compound **9** showed peaks at m/z 293 and 315 corresponding to $[M+H]^+$ and $[M+Na]^+$. Finally the structure of compound **9** was confirmed by the elemental analysis.

The IR spectrum of compound **10** showed strong bands at 3444 cm^{-1} and 1774 cm^{-1} indicating the presence of free hydroxyl group and five membered saturated lactone ring. From its ^1H NMR and ^{13}C NMR spectra, it was evident that it is a diastereomeric mixture. Doublets at δ 1.21 and δ 5.16 indicated the formation of five membered saturated lactone ring. The ^{13}C NMR spectrum of compound **10** showed signals at δ177.39 and 177.08 corresponding to carbonyl group of saturated lactone and peaks at δ 91.79 and 90.82 disappeared in DEPT NMR spectrum which indicated them to be quaternary carbons at the bridge head. The mass spectrum of compound **10** showed peaks at m/z 315 corresponding to $[M+Na]^+$. The structure of undesired bicyclic compound was further confirmed by single crystal XRD[6] spectroscopy (Figure 2). Finally the structure of compound **10** was confirmed by the elemental analysis.



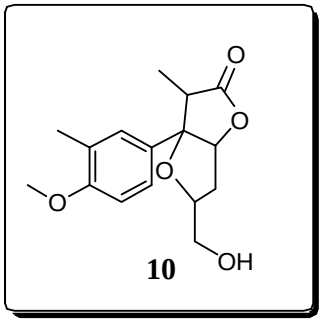
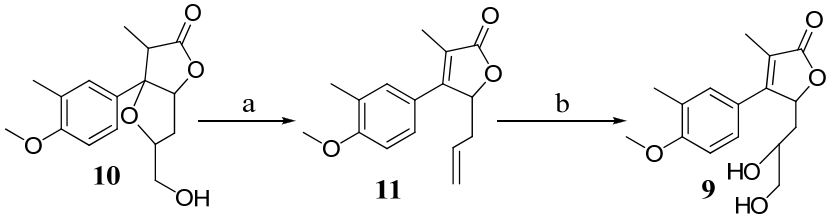


Figure 2. ORTEP diagram of the bicyclic compound **10**

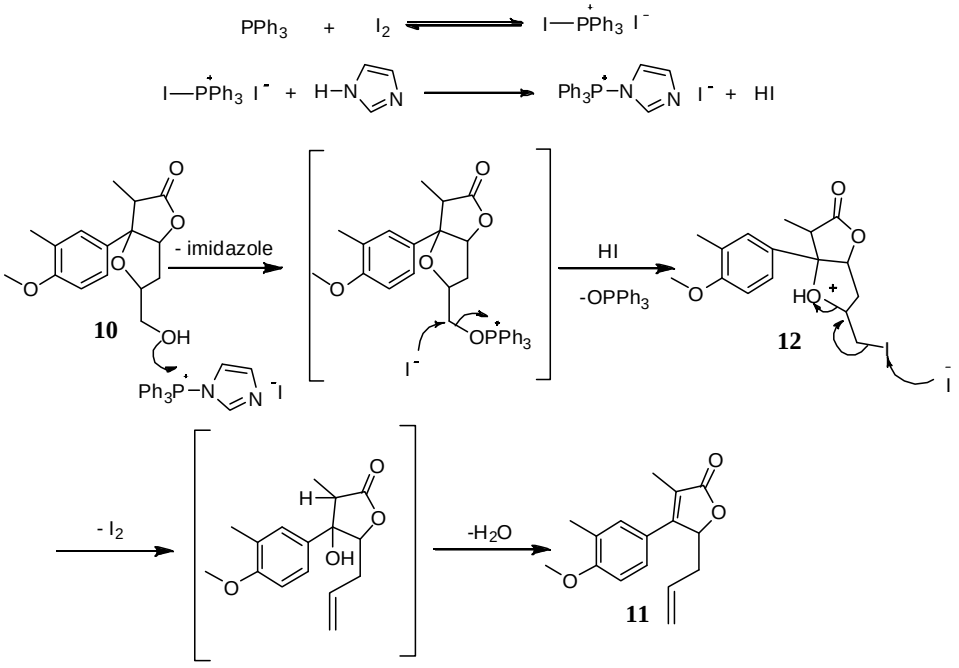
The undesired bicyclic compound **10** was subjected to standard iodination reaction conditions, but surprisingly it was observed that the allylic lactone **11** was formed under the reaction conditions (Scheme 4). The formation of compound **11** was confirmed by the spectral techniques. The IR spectrum of compound **11** showed strong band at 1741 cm^{-1} which indicated the presence of butenolide ring. The ^1H NMR spectrum showed multiplet at δ 5.33-5.37 for one proton and singlet at δ 2.27

for three protons indicating the formation of butenolide ring. Multiplets at δ 5.56-5.76 for one proton and at δ 4.96-5.09 for two protons indicated the presence of vinylic (CH_2=CH-) group. ^{13}C NMR spectrum of compound **11** showed peak at δ 174.61 which indicated the butenolide ring. The mass spectrum of compound **11** showed peaks at m/z 259 and 281 corresponding to $[M+H]^+$ and $[M+Na]^+$. Finally the structure of compound **11** was confirmed by the elemental analysis.



Scheme 4. Reagents and conditions: *a) PPh_3, I_2, imidazole, toluene, reflux, 6 h, 95%; b) OsO_4, NMO, acetonitrile:water (9:1), 24 h, 75%.*

Several attempts were made to cyclize the allylic lactone **11** to achieve target molecule **2** *via* acid catalyzed cyclisation and *via* epoxide formation but unfortunately those efforts were unsuccessful. The allylic lactone **11** was then converted to desired diol **9** in very good yield by treatment with OsO_4 using NMO as a co-oxidant in acetonitrile:water (9:1) as solvent (Scheme 4).



Scheme 5. Proposed mechanism for transformation of compound **10** to compound **11.**

The mechanism of this reaction is uncertain and is under investigation. The proposed mechanism leading to the formation of **11** is depicted in Scheme 5. It seems likely that similar to the iodo-epoxide opening by Zn[7] and I_2, PPh_3[8] specifically, iodolactone **12** was formed in this case as an intermediate. On iodine elimination followed by dehydration, it gave rise to allylic lactone **11**.

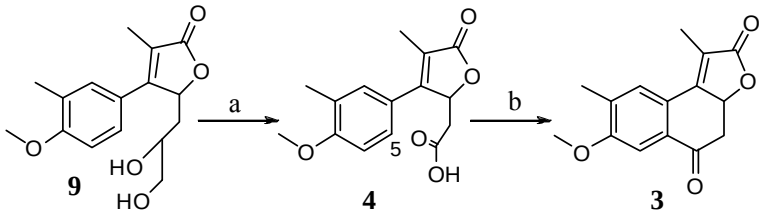
After successful synthesis of compound **9** having butenolide ring, next task was to construct the tetralin unit of heritol *via* cyclization. Towards this end, the efforts to cyclise compound **9** to get tetralin unit using a variety of conditions involving acid catalysed cyclisation of diol, and also *via* epoxide formation, were not successful. Thisresult illustrated that the meta position (C5 position, heritol numbering) of the ring is deactivated due to the long conjugation of ring electron with the butenolide ring.

This finding, however allowed to attempt the cyclisation by Friedel-Crafts acylation because the intermediate acyl cation would be highly electrophilic, thus facilitating cyclisation at the deactivated C5 position. Based on this hypothesis, the compound **9** was subjected to oxidative cleavage by using $NaIO_4$ to afford aldehyde. The crude aldehyde was subjected to oxidation[9] using $NaClO_2$ to afford acid **4** in 78% yield (over two steps).

The IR spectrum of **4** showed strong bands at 1708 and 1741 cm^{-1}, indicating the presence of carbonyl groups of acid derivative and butenolide ring. Broad peak at 3456 cm^{-1} indicated the presence of carboxylic acid group. In the ^1H NMR spectrum of **4**, doublet of doublet at δ 2.83 for one proton and δ 2.41 for one proton indicated the presence of two diastereomeric protons α-to acid group (-$\underline{CH_2}CO_2H$). Further, absence of multiplets at δ 3.30-3.39 and δ 3.50-361 in the ^1H NMR spectrum of the isolated product clearly suggested the formation of acid **4**. This was further confirmed by its ^{13}C NMR spectrum which displayed a peak at δ 171.36 for carbonyl group of acid derivative **4**. The mass spectrum of compound **4** showed peaks at m/z 277 and 299 corresponding to $[M+H]^+$ and $[M+Na]^+$. Finally the structure of compound **4** was confirmed by the elemental analysis.

Acid **4** was converted to its acid chloride using oxalyl chloride in DCM at room temperature. After distillation of excess oxalyl chloride and solvent, the crude acid chloride was treated with triflic acid[10] in DCM at reflux condition to furnish the key

intermediate **3** in 95% yield (over two steps, based on recovered starting acid **4** , 36% conversion from acid **4**) (Scheme 6).



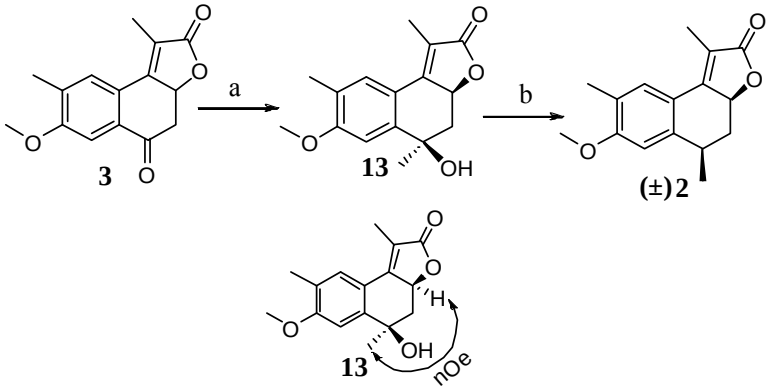
Scheme 6. Reagents and conditions: *a) i) $NaIO_4$, acetone:H_2O (3:1), 0 ºC-rt, 15 min.; ii) $NaClO_2$, NaH_2PO_4, H_2O_2, acetonitrile, rt, 4 h, 78% (over two steps); b) i) Oxalyl chloride, DCM, overnight; ii) CF_3SO_3H, DCM, reflux, 3 h, 95% (over two steps, based on starting material recovered)*

The key intermediate tetralone **3** was completely characterized by its spectral data. The IR spectrum of compound **3** revealed the absorptions at 1745 and 1702 cm^{-1}, characteristic of a butenolide ring and a carbonyl group. The ^1H NMR spectrum exhibited singlets at δ 7.56 and δ 7.53 which were assigned to the two *para* disubtituted aromatic protons. Also ^{13}C NMR spectrum showed signals for four quaternary carbons at δ 159.83, 152.65, 135.35, 131.88 which were attributed to the four aromatic quaternary carbon atoms; and the one at δ 192.61 was assigned to the carbonyl carbon. This suggested successful cyclisation of the acid side chain over aromatic ring. The mass spectrum of compound **3** showed peaks at m/z 259 and 281 corresponding to $[M+H]^+$ and $[M+Na]^+$. Finally the structure of compound **10** was confirmed by the elemental analysis.

Having key intermediate tetralone **3** in hand, the remaining task was the introduction of methyl group. Grignard reaction of **3** with methyl magnesium bromide furnished the corresponding hydroxy compound **13** in 97% yield as a single diastereomer.

The compound **13** was completely characterized by its spectral data. The IR spectrum of compound **13** showed a broad peak at 3528 cm^{-1}, characteristic of a free hydroxyl group. The ^1H NMR spectrum exhibited a singlet at δ 1.63 for three protons and was attributed to the methyl group [Ar-C($\underline{CH_3}$)OH-]. Also, ^{13}C NMR spectrum showed absent of peak at δ 192.61 corresponding to aromatic ketone group and appearance of a new peak at δ 31.65 which supported the newly generated carbon centre. The

relative stereochemistry of the compound **13** was confirmed by 2D NOESY spectral analysis The mass spectrum of compound **13** showed peaks at m/z 275 and 297 corresponding to $[M+H]^+$ and $[M+Na]^+$. Finally the structure of compound **13** was confirmed by elemental analysis.



Scheme 7. Reagents and conditions: *a) MeMgBr (1.5 eq), THF, -78 ºC-0 ºC, 5 h, 97%; b) Et_3SiH, $BF_3.OEt_2$, DCM, -78 ºC, 96%.*

The hydroxy compound **13** was subjected to deoxygenation using triethylsilane,[11] $BF_3.OEt_2$ in DCM. Interestingly and gratifyingly, it afforded only the desired diastereomer **2** in 96% yield (Scheme 7). This may be attributed to the steric hindrance of the butenolide moiety which directs the hydride from the face opposite to it thereby resulting in *cis* stereochemistry (Figure 3).

This result indicates that the stereochemistry at the C8 position directs the stereochemistry at the C10 position because the beta face is sterically crowded by lactone ring.

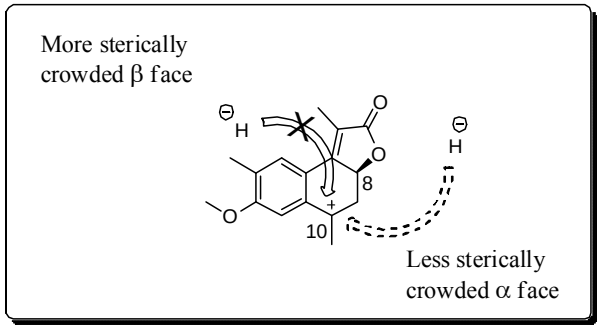
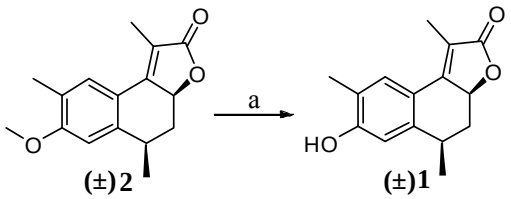


Figure 3. Face selectivity of deoxygenation reaction.

The compound **2** was completely characterized by its spectral data. The ^{1}H NMR spectrum exhibited a doublet at δ 1.47 for three protons and was attributed to the methyl group (Ar-CH<u>CH$_3$</u>-). The mass spectrum of compound **2** showed peaks at m/z 259 and 281corresponding to $[M+H]^+$ and $[M+Na]^+$. Finally the structure of compound **2** was confirmed by elemental analysis.

Finally, compound **2** was subjected to demethylation with $AlCl_3$-EtSH at room temperature to afford heritol **1** in 80% yield (Scheme 8). Spectral data for heritol **1** was in complete agreement with data reported by this group and others eariler.[2b, 2c]



Scheme 8. Reagents and conditions: *a) $AlCl_3$, EtSH, DCM, rt, 12 h, 80%.*

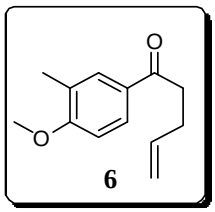
Formation of heritol was established by its IR and ^{1}H NMR spectral data comparison with literature values[2] and was found to be in good agreement. Presence of an absorption frequency at 3595 cm^{-1}, characteristic of a phenolic hydroxyl group in the IR spectrum, and absence of a three proton singlet at δ 3.89 in its ^{1}H NMR spectrum, were indicative of the deprotection. Further, its ^{1}H NMR spectrum showed only one multiplet signal, corresponding to the proton at C-8, at δ 4.91-4.95, which indicated that no epimerisation had occurred under the reaction conditions. In ^{13}C NMR spectrum of heritol (**1**) peak at 55.31 was absent which also supported the deprotection.

1.2.2. Conclusion

In conclusion, the highly distereoselective total synthesis of racemic heritonin **2** and heritol **1** by using intramolecular Friedel-Crafts acylation as a key step, from cheap and commercially available starting materials in eight and nine purification operation in 43% and 33% overall yield respectively which is highest overall yield reported so far has been achieved.

1.2.3. Experimental

1-(4-Methoxy-3-methylphenyl)-pent-4-en-1-one (6)



6

To a cold (0 ºC), magnetically stirred solution of *o*-cresol methyl ether **7** (1 g, 8.2 mmol) and freshly prepared allylacetyl chloride (1 ml, 9.02 mmol) in anhydrous DCM (10 mL) was added catalytic amount (0.1 mL) of trifluoromethanesulphonic acid and stirred for 4 h at room temperature. The reaction was quenched with saturated $NaHCO_3$ solution (10 mL) and extracted with DCM (3×10 mL). The combined organic layer was washed with brine (10 mL) and dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent under reduced pressure and purification of the resultant residue on a silica gel column using ethyl acetate/hexane (0.5:9.5) as eluent furnished the keto compound **6** (1.54 g, 95%) as colorless oil. R_f (10% EtOAc/hexane): 0.6

Molecular formula: $C_{13}H_{16}O_2$

Yield: 95%

IR ($CHCl_3$): 2924, 1676, 1640, 1602, 1503 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.25 (s, 3H), 2.42-2.54 (m, 2H), 3.02 (t, *J*=7.1 Hz, 2H), 3.90 (s, 3H), 4.97-5.14 (m, 2H), 5.80-6.01 (m, 1H), 6.84 (d, *J*=8.9 Hz, 1H), 7.78 (d, *J*=2.5 Hz, 1H), 7.83 (dd, *J*=2.3, 8 Hz, 1H).

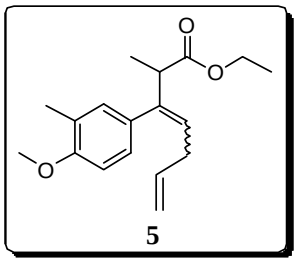
^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 16.21, 28.37, 37.19, 55.32, 109.06, 115.04, 126.55, 128.04, 129.47, 130.52, 137.51, 161.56, 197.77.

MS (ESI) (m/z): 205 $[M+H]^+$, 227 $[M+Na]^+$.

Elemental analysis: Calculated C, 76.44; H, 7.90 %; Found C, 76.31; H, 8.04 %.

(*E*) and (*Z*)-Ethyl 3-(4-methoxy-3-methylphenyl)-2-methylhepta-3,6-dienoate (5)

To a magnetically stirred solution of allylic keto compound **6** (1 g, 4.9 mmol) and activated Zn (961 mg, 14.7 mmol) in the presence of catalytic amount of iodine in anhydrous diethyl ether and benzene (1:1) (5 mL), was slowly added a solution of ethyl 2-bromopropionate (0.96 mL, 7.35 mmol) in anhydrous diethyl ether and benzene (1:1) (5 mL) over a period of 15 min and further refluxed (80 °C) for 3 h in



5

an argon atmosphere. The reaction mixture was cooled to 0ºC and quenched with 10% HCl (10 mL) and extracted with ethyl acetate (3×8 mL). The combined organic layer was washed with brine (7 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude alcohol was used as such in the next reaction without further purification.

Catalytic amount of PTSA was added to a magnetically stirred solution of β-hydroxy ester (1.45 g, 4.7 mmol) obtained above in dry DCM (15 mL) and stirred for 12 h at rt in an argon atmosphere. Saturated $NaHCO_3$ solution (10 mL) was added to the reaction mixture and extracted with DCM (3×10 mL). The organic layer was washed with brine (10 mL) and dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate/hexane (0.2:9.8) as eluent furnished the mixture of geometrical isomers (80:20, confirmed by GC and GC-mass analysis) of **5** (1.19 g, 85%) as colorless oil, which were found to be inseparable by column chromatography on silica gel as well as on silver nitrate impregnated silica gel.[12] R_f (10% EtOAc/hexane): 0.6

Molecular formula: $C_{18}H_{24}O_3$

Yield: 85%

IR ($CHCl_3$): 2986, 2837, 1731, 1607, 1504 cm^{-1}.

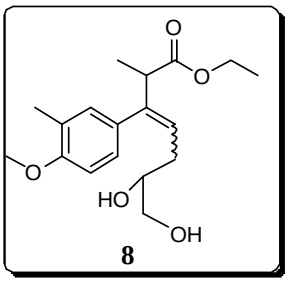
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.16-1.31 (m, 6H), 2.20 (s, 3H), 2.63-2.70 and 2.93-3.10 (m, 2H), 3.39 (q, *J*=7.1 Hz, 1H), 3.82 and 3.83 (s, 3H), 4.06-4.16 (m, 2H), 4.94-5.07 (m, 2H), 5.53-5.88 (m, 2H), 6.70-6.78 (m, 1H), 6.89-7.07 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 14.07, 14.15, 15.86, 16.24, 16.53, 32.06, 33.15, 40.83, 47.69, 55.04, 55.10, 60.26, 60.48, 109.22, 114.70, 115.18, 125.49, 125.58, 125.86, 125.92, 126.93, 127.73, 127.75, 130.85, 131.19, 134.19, 136.25, 137.06, 140.17, 141.02, 156.69, 156.77, 174.31, 174.36.

MS (ESI) (m/z): 289 $[M+H]^+$, 311 $[M+Na]^+$.

Elemental analysis: Calculated C, 74.97; H, 8.39 %; Found C, 75.03; H, 8.34 %.

(*E*) and (*Z*)-Ethyl 6, 7-dihydroxy-3-(4-methoxy-3-methylphenyl)-2-methylhept-3-enoate (8)



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To a cold (0 ^{0}C), magnetically stirred solution of β,γ-unsaturated ester **5** (1 g, 3.5 mmol) in acetonitrile: water (9:1) (10 mL) , catalytic amount OsO_4 (0.1 mL, 0.1 M solution in toluene) was added in presence of *N*-methylmorpholine-*N*-oxide (NMO) (472 mg, 3.5 mmol) as a co-oxidant and stirred for 30 min at rt. The reaction was quenched with saturated Na_2SO_3 (10 mL) solution and again stirred for 30 min. The solvent was evaporated and the residue was extracted with ethyl acetate (3×10 mL). The combined organic layer was washed with brine (7 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue on a silica gel column using ethyl acetate/hexane (5:5) as eluent furnished the diol **8** (1.11 g, 99%) as yellowish oil. R_f (100% EtOAc): 0.8

Molecular formula: $C_{18}H_{26}O_5$

Yield: 99%

IR ($CHCl_3$): 3444, 2939, 1732, 1605, 1502 cm^{-1}.

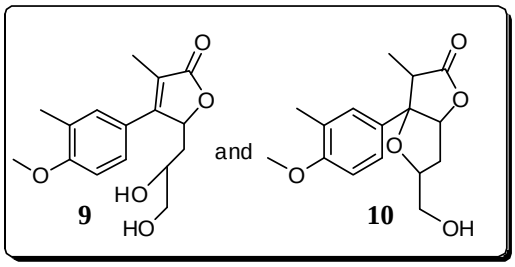
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.18-1.26 (m, 6H), 2.05-2.17 (m, 2H), 2.19 (s, 3H), 3.36-3.71 (m, 2H), 3.81 and 3.82 (s, 3H), 4.05-4.16 (m, 2H), 5.57-5.69 (m, 1H), 6.68-6.76 (m, 1H), 6.84-6.98 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 14.13, 14.18, 16.29, 33.01, 47.91, 47.95, 55.04, 55.11, 60.30, 60.53, 66.15, 71.97, 72.00, 109.35, 124.29, 124.32, 126.09, 127.04, 130.85, 130.95, 131.00, 142.09, 142.16, 156.67, 174.70, 174.75.

MS (ESI) (m/z): 323 $[M+H]^+$, 345 $[M+Na]^+$.

Elemental analysis: Calculated C, 67.06; H, 8.13%; Found C, 67.36; H, 8.18 %

5-(2, 3-Dihydroxypropyl)-4-(4-methoxy-3-methylphenyl)-3-methylfuran-2(5*H*)-one (9) and 5-(hydroxymethyl)-3a-(4-methoxy-3-methylphenyl)-3-methyltetrahydrofuro[3,2-b]furan-2(5H)-one (10)



To a cold (0 ºC), magnetically stirred solution of diol **8** (1 g, 3.1 mmol) in acetonitrile: water (9:1) (10 mL), catalytic amount of OsO_4 (0.1 mL, 0.1 M solution in toluene) was added in presence of *N*-methylmorpholine-*N*-oxide (NMO) (838 mg, 6.2 mmol) as a co-oxidant and stirred for 3 days at rt. The reaction was quenched with saturated Na_2SO_3 solution (10 mL) and again stirred for 30 min. Evaporation of the solvent furnished a residue which was extracted with ethyl acetate (3×8 mL). The combined organic layer was washed with brine (7 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude reaction mixture was used as such in the next reaction without further purification.

Catalytic amount of PTSA was added to a magnetically stirred solution of tetrol (300 mg, 0.96 mmol) in dry DCM (3 mL) and stirred for 12 h at rt in an argon atmosphere. Saturated $NaHCO_3$ solution (10 mL) was added to the reaction mixture and extracted with CH_2Cl_2 (3×8 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent under reduced pressure and purification of the residue thus obtained on a silica gel column gave mixture of lactone **9** (120 mg, 42%) and bicyclic compound **10** (146 mg, 52%) in 0.82: 1 ratio.

To a magnetically stirred solution of tetrol (2.1 g, 6.77 mmol) in dry DCM (20 mL), excess $BF_3.OEt_2$ (4.2 mL) was added and the reaction mixture was stirred for 12 h at room temperature in an argon atmosphere. Saturated $NaHCO_3$ solution (10 mL) was added to the reaction mixture and extracted with CH_2Cl_2 (3×8 mL). The organic layer was washed with brine (10 mL) and dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent under reduced pressure furnished a residue. Purification of the residue on a silica gel column gave mixture of lactone **9** (1.5 gm, 76% yield) and bicyclic compound **10** (0.15 gm, 8%) in 9.5: 1 ratio.

Compound 9:

Molecular formula: $C_{16}H_{20}O_5$

Yield: 76%

Melting Point: 102-105 °C

IR ($CHCl_3$): 3421, 3019, 2927, 1741, 1647, 1607, 1508 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.77-1.89 (m, 1H), 2.02 (s, 3H), 2.17-2.20 (m, 1H), 2.23 (s, 3H), 3.30-3.39 (m, 1H), 3.50-3.61 (m, 2H), 3.85 (s, 3H), 5.48-5.65 (m, 1H), 6.87 (d, *J*=8.6 Hz, 1H), 7.18-7.24 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 9.99, 10.05, 16.15, 37.11, 37.54, 55.25, 65.74, 66.61, 68.71, 69.33, 78.69, 79.36, 110.01, 120.41, 120.68, 122.89, 122.99, 127.11, 127.28, 130.08, 158.93, 160.23, 160.28, 175.09, 175.33.

MS (ESI) (m/z): 293 $[M+H]^+$, 315 $[M+Na]^+$.

Elemental analysis: Calculated C, 65.74; H, 6.90 %; Found C, 65.84; H, 6.86 %.

Compound 10:

Molecular formula: $C_{16}H_{20}O_5$

Yield: 8%

Melting Point: 90-116 °C (mixture of diastereomers)

IR ($CHCl_3$): 3444, 2978, 1774, 1610, 1504 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.18 and 1.21 (d, *J*=7.2 Hz, 1H), 1.90-2.30 (m, 2H), 2.24 (s, 3H), 2.92 (q, *J*=7.2 Hz, 1H), 3.58-3.70 (m, 2H), 3.84 and 3.85 (s, 3H), 4.34-4.41 (m, 1H), 5.08-5.17 (m, 1H), 6.82 and 6.86 (d, *J*=8 Hz, 1H), 7.17-7.25 (m, 2H).

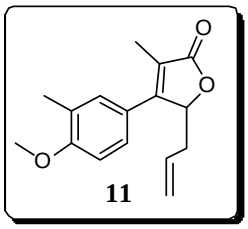
^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 7.40, 7.65, 16.19, 32.45, 32.59, 47.57, 48.56, 55.12, 64.04, 65.00, 79.56, 80.10, 86.58, 87.49, 90.82, 91.79, 109.60, 109.76, 123.56, 123.58, 126.67, 126.84, 127.01, 127.15, 128.74, 131.09, 157.16, 157.32, 177.08, 177.39.

MS (ESI) (m/z): 315 $[M+Na]^+$.

Elemental analysis: Calculated C, 65.74; H, 6.90 %; Found C, 65.59; H, 6.95 %.

5-Allyl-4-(4-methoxy-3-methylphenyl)-3-methylfuran-2(5*H*)-one (11)

A mixture of bicyclic lactone **10** (146 mg, 0.5 mmol), PPh_3 (262 mg, 1.0 mmol), imidazole (34 mg, 0.5 mmol) and iodine (262 mg, 1.0 mmol) in anhydrous toluene (5 mL) was stirred and refluxed under nitrogen atmosphere for 6 h. After completion of reaction, it was diluted with water and extracted with ethyl acetate (3×5 mL). Combined organic layers were then washed with saturated solution of $Na_2S_2O_3$ (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford a residue which was purified by silica gel column chromatography using ethyl acetate/hexane (2:8) as eluent to furnish the allylic lactone **11** (96 mg, 95% yield) as yellowish white semisolid compound. R_f (30% EtOAc/hexane): 0.7.



11

Molecular formula: $C_{16}H_{18}O_3$

Yield: 95%

IR ($CHCl_3$): 3020, 2800, 1750, 1646, 1606, 1508 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4) : δ 1.92-2.09 (m, 4H), 2.15-2.24 (m, 1H), 2.27 (s, 3H), 3.90 (s, 3H), 4.95-5.09 (m, 2H), 5.34-5.39 (m, 1H), 5.56-5.76 (m, 1H), 6.91 (d, *J*=8.2 Hz, 1H), 7.14-7.24 (m, 2H).

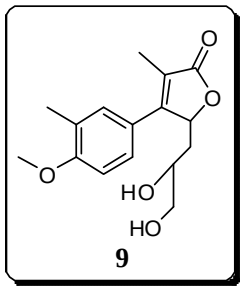
^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) : δ 10.06, 16.38, 37.02, 55.37, 80.53, 110.04, 119.07, 122.22, 123.41, 126.91, 127.64, 129.97, 131.15, 158.46, 158.93, 174.61.

MS (ESI) (m/z): 259 $[M+H]^+$, 281 $[M+Na]^+$.

Elemental analysis: Calculated C, 74.39; H, 7.02%; Found C, 74.54; H, 7.09%.

5-(2,3-Dihydroxypropyl)-4-(4-methoxy-3-methylphenyl)-3-methylfuran-2(5*H*)-one (9) from 5-allyl-4-(4-methoxy-3-methylphenyl)-3-methylfuran-2(5*H*)-one (11)

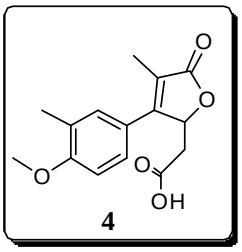
To a cold (0 ºC), magnetically stirred solution of allylic lactone **11** (100 mg, 0.4 mmol) in acetonitrile: water (9:1) (10 mL), catalytic amount of OsO_4 (0.1 mL, 0.1 M



9

solution in toluene) was added in presence of *N*-methylmorpholine-*N*-oxide (NMO) as a co-oxidant and stirred for 1 h at rt. The reaction was quenched with saturated Na_2SO_3 solution (5 mL) and again stirred for 0.5 h. Evaporation of the solvent furnished the residue which was extracted with ethyl acetate (3×8 mL). The combined organic layer was washed with brine (7 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue on a silica gel column using ethyl acetate/hexane (1:1) as eluent furnished the diol compound **9** (85 mg, 75% yield) as white solid. All data matched with previous compound.

2-(3-(4-Methoxy-3-methylphenyl)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)acetic acid (4)



4

To a magnetically stirred solution of lactone **9** (270 mg, 0.92 mmol) in acetone: water (3:1), $NaIO_4$ (556 mg, 2.6 mmol) was added portion wise and stirred for 15 min at room temperature. The solid residue was separated by filtration. The filtrate was extracted with DCM (3×5 mL). The combined organic layer was washed with brine (7 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude aldehyde was used in the next reaction without further purification.

A solution of $NaClO_2$ (230 mg, 2.5 mmol) in water (2 mL) was added dropwise to a stirred mixture of crude aldehyde (210 mg, 0.81 mmol) in acetonitrile (5 mL) and NaH_2PO_4 (324 mg, 2.13 mmol) in water (2 mL) and 2.13 mL of 35% H_2O_2, keeping the temperature at 10 ºC with water cooling. Oxygen evolved from the solution and the reaction was monitored by TLC until the end of the reaction (about 4 h). A small amount (100 mg) of Na_2SO_3 was added to destroy the unreacted HOCl and H_2O_2. After acidification with 10% aqueous HCl (3 mL), it was extracted with ethyl acetate (3×5 mL). The combined organic layer was washed with brine (3 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue was done on a silica gel column using ethyl acetate/hexane (5:5) as eluent to furnish the acid **4** (200 mg, 78%) as white solid. R_f (80% EtOAc/hexane): 0.6 (long tail).

Molecular formula: $C_{15}H_{16}O_5$

Yield: 78%

Melting Point: 135-137 °C

IR ($CHCl_3$): 3456, 3020, 2950, 1747, 1651, 1606, 1507 cm^{-1}.

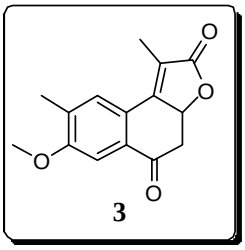
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.07 (d, *J*=1.5 Hz, 3H), 2.27 (s, 3H), 2.41 (dd, *J*=9.6, 18 Hz, 1H), 2.83 (dd, *J*=2.5, 17 Hz, 1H), 3.90 (s, 3H), 5.75 (m, 1H), 6.93 (d, *J*= 8.4 Hz, 1H), 7.17 (d, *J*=2 Hz, 1H), 7.23 (dd, *J*=8, 2 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$ +C_2D_6SO): δ 10.05, 16.20, 38.68, 55.33, 77.75, 110.20, 121.33, 122.44, 127.02, 127.26, 129.79, 158.18, 158.96, 171.36, 174.13.

MS (ESI) (m/z): 277 $[M+H]^+$, 299 $[M+Na]^+$.

Elemental analysis: Calculated C, 65.21; H, 5.84%; Found C, 65.31; H, 5.89%.

7-Methoxy-1,8-dimethyl-3a,4-dihydronaphtho[2,1-*b*]furan-2,5-dione (3)



3

To a magnetically stirred solution of acid **4** (110 mg, 0.4 mmol) in DCM (3 mL), was added dropwise excess oxalyl chloride (1.0 mL) and stirred overnight at room temperature. Excess oxalyl chloride and solvent was distilled out at 120 ºC (oil bath temp.). The crude acid chloride was used in the next reaction without further purification.

To the stirred solution of crude acid chloride (100 mg) in DCM (3 mL) under reflux was added catalytic amount (0.02 mL) of trifluoromethanesulphonic acid. The reaction mixture was stirred under reflux for 3 h and it was diluted with water and extracted with DCM (3×3 mL). Combined organic layers were then washed with brine (3 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford a residue which was purified by silica gel column chromatography using ethyl acetate/hexane (1.5:8.5) as eluent to furnish the tetralone **3** (40 mg, 95% based on the recovery 54 mg of acid **4**) as white solid. R_f(15% EtOAc/hexane): 0.7.

Molecular formula: $C_{15}H_{14}O_4$

Yield: 95%

Melting Point: 203-205 °C

IR ($CHCl_3$): 2923, 2853, 1745, 1702, 1636, 1602, 1508 cm^{-1}.

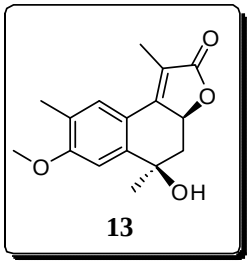
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.21 (d, *J* = 2 Hz, 3H), 2.36 (s, 3H), 2.62 (dd, *J* = 16, 12 Hz, 1H), 3.51 (dd, *J* = 16, 6 Hz, 1H), 3.95 (s, 3H), 5.17-5.31 (m, 1H), 7.53 (s, 1H), 7.56 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 9.82, 16.94, 45.24, 55.80, 76.76, 107.67, 120.86, 125.25, 129.23, 131.88, 135.35, 152.65, 159.83, 174.17, 192.61.

MS (ESI) (m/z): 259 $[M+H]^+$, 281 $[M+Na]^+$.

Elemental analysis: Calculated C, 69.76; H, 5.46%; Found C, 69.44; H, 5.39%.

5-Hydroxy-7-methoxy-1,5,8-trimethyl-4,5-dihydronaphtho[2,1-b]furan-2(3a*H*)-one (13)



13

To a dry round bottom flask under argon was added tetralone **3** (100 mg, 1.4 mmol) in dry THF (2 mL). The solution was cooled to -78 ºC and MeMgBr (1.4 M, Aldrich make, 0.43 mL, 0.6 mmol) was added dropwise. The reaction was stirred at same temperature for 1 hour, then slowly allowed to come room temperature and further stirred at room temperature for 5 h. The reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate (3×3 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (20% EtOAc/hexane) to provide the product **13** (103 mg, 97% yield) as white semisolid compound. R_f (50% EtOAc/hexane): 0.5.

Molecular formula: $C_{16}H_{18}O_4$

Yield: 97%

IR (nujol): 3529, 2925, 2855, 1739, 1646, 1613 cm^{-1}.

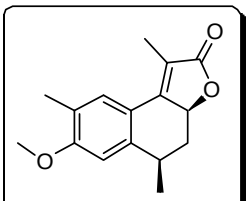
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.63 (s, 3H), 1.85 (t, *J* = 11.4 Hz, 1H), 2.12 (d, *J* = 2 Hz, 3H), 2.26 (s, 3H), 2.81 (dd, *J* = 11, 4 Hz, 1H), 3.93 (s, 3H), 4.88-4.97 (m, 1H), 7.19 (s, 1H), 7.39 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 9.84, 16.16, 29.68, 31.65, 46.32, 55.48, 71.57, 77.11, 96.11, 107.66. 116.92, 118.74, 127.26, 129.00, 145.15, 155.74, 160.09, 175.21.

MS (ESI) (m/z): 275 $[M+H]^+$, 297 $[M+Na]^+$.

Elemental analysis: Calculated C, 70.06; H, 6.61%; Found C, 70.26; H, 6.69%.

(3a*S*, 5*R*)-7-Methoxy-1,5,8-trimethyl-4,5-dihydronaphtho[2,1-*b*]furan-2(3*aH*)-one [heritonin, 2]



2

To a magnetically stirred solution of hydroxy compound **13** (30 mg, 0.11 mmol) in DCM (3 mL) at -78 ºC was added $BF_3.OEt_2$ (0.07 mL, 0.55 mmol) and Et_3SiH (0.1 mL, 0.66 mmol) dropwise. The reaction was allowed to warm up to room temperature over 30 min and stirred at room temperature for 3 h and quenched by adding saturated $NaHCO_3$ solution (3 mL) and extracted with DCM (3×5 mL). The organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent and purification of the residue on silica gel (5% EtOAc/hexane) provided the product heritonin **2** (27 mg, 96% yield) as white solid.

Molecular formula: $C_{16}H_{18}O_3$

Yield: 96%

Melting Point: 115-117 ^{0}C (lit. 115-116 ^{0}C)

IR (nujol): 2926, 2854, 1747, 1659, 1611 cm^{-1}.

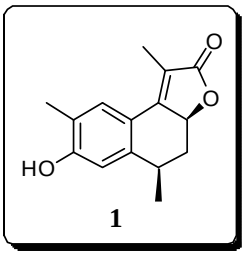
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (d, *J* = 7 Hz, 3H), 1.36-1.64 (m, 1H), 2.14 (d, *J* = 1.6 Hz, 3H), 2.25 (s, 3H), 2.58-2.69 (m, 1H), 3.04-3.22 (m, 1H), 3.89 (s, 3H), 4.85-4.94 (m, 1H), 6.84 (s, 1H), 7.41 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 9.88, 15.98, 21.70, 31.95, 38.62, 55.32, 78.14, 108.32, 115.86, 125.70, 129.57, 142.21, 156.71, 159.53, 175.63.

MS (ESI) (m/z): 259 $[M+H]^+$, 281 $[M+Na]^+$.

Elemental analysis: Calculated C, 74.39; H, 7.02%; Found C, 74.55; H, 7.10%.

(3*aS*, 5*R*)-7-Hydroxy-1,5,8-trimethyl-4,5-dihydronaphtho[2,1-*b*]furan-2(3*aH*)-one [heritol, 1]



1

Ethanethiol (1 mL) was added to a magnetically stirred solution of methyl ether **2** (20 mg, 0.078 mmol) and anhydrous aluminum chloride (50 mg, 0.375 mmol) in DCM (1 mL) at room temperature. The reaction mixture was allowed to stir for 12 h. Water was added to the reaction mixture and the separated solid was extracted with DCM (3×5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to furnish a white solid. Purification of the solid by flash column chromatography using 20% ethyl acetate/hexane as an eluent afforded heritol **1** (18 mg, 94% yield) as white solid.

Molecular formula: $C_{15}H_{16}O_3$

Yield: 94%

Melting Point: 270-271 ^{0}C (lit. 271-272 ^{0}C).

IR (nujol): 3595, 2960, 2360, 1749, 1654, 1559 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$+CD_3OD): δ 1.41 (d, *J*= 7 Hz, 3H), 1.43-1.48 (m, 1H), 2.11 (d, *J*=1.5 Hz, 3H), 2.26 (s, 3H), 2.58-2.62 (m, 1H), 3.04-3.10 (m, 1H), 4.91-4.95 (m, 1H), 6.88 (s, 1H), 7.40 (s, 1H).

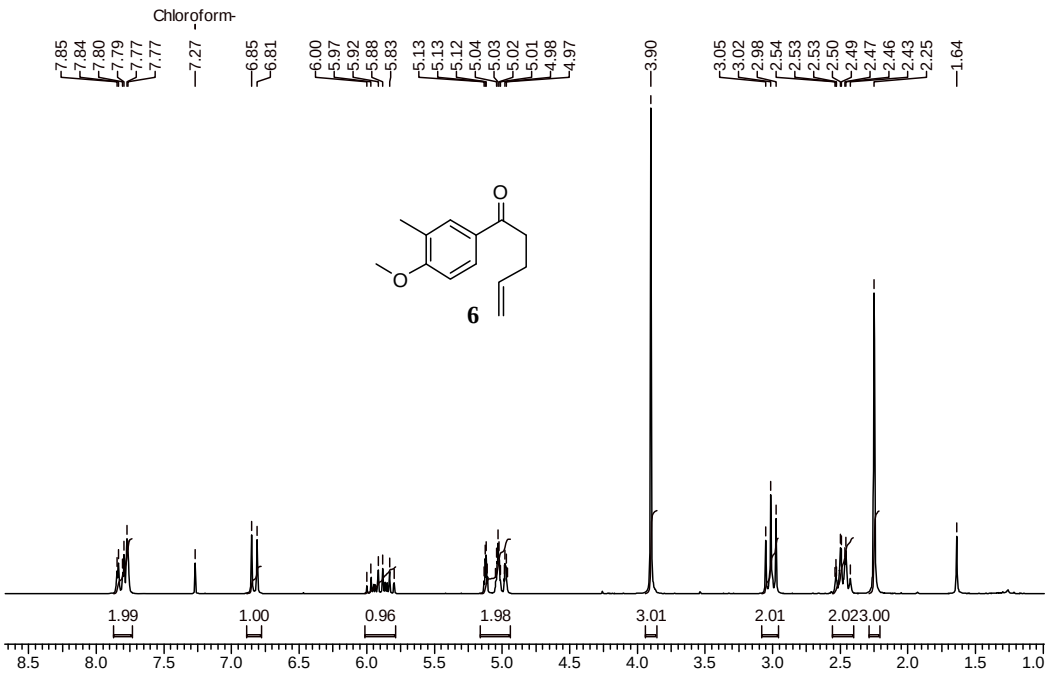
^{13}C NMR (125 MHz, $CDCl_3$+CD_3OD): δ 9.38, 15.36, 21.00, 31.39, 38.34, 78.57, 113.01, 114.41, 120.65, 119.58, 123.59, 130.00 142.16, 157.63, 157.95, 175.53.

MS (ESI) (m/z): m/z 245 $[M+H]^+$, 267 $[M+Na]^+$

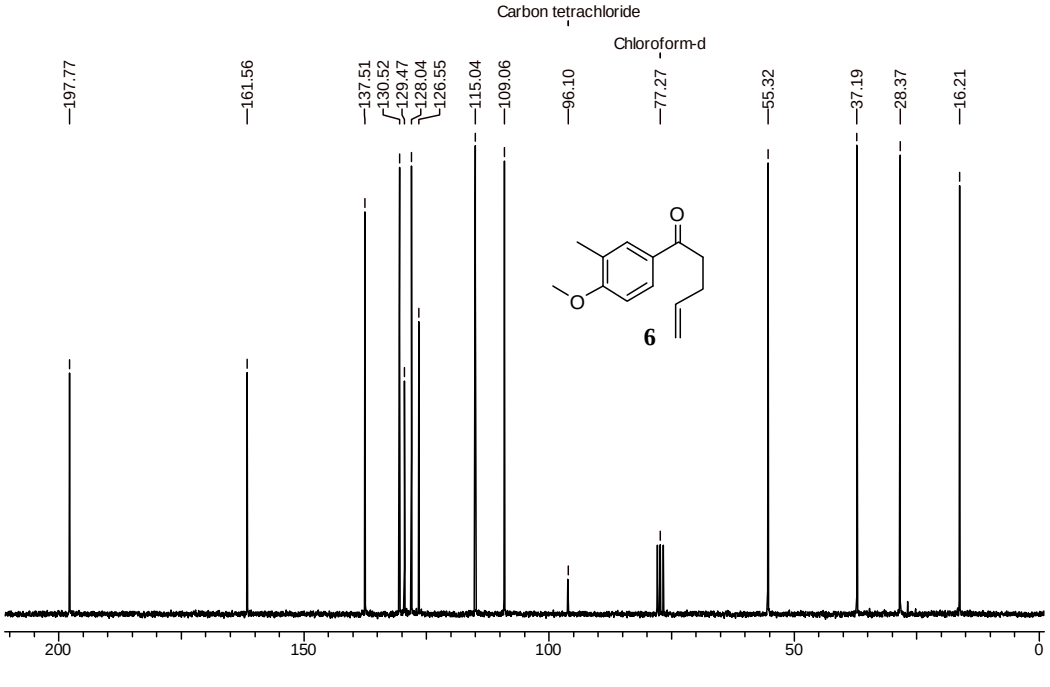
Elemental analysis: Calculated C, 73.75; H, 6.60%; Found C, 73.89; H, 6.49%.

1.1.4. NMR Spectra

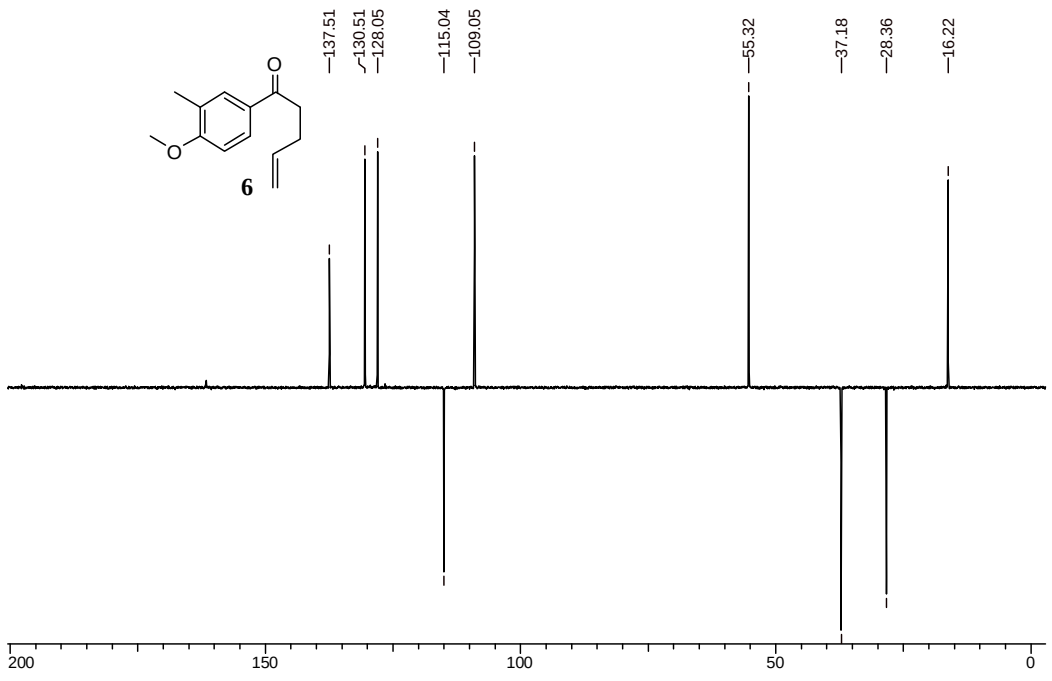
^{1}H NMR spectrum of compound **6** ($CDCl_3$+CCl_4, 200 MHz)



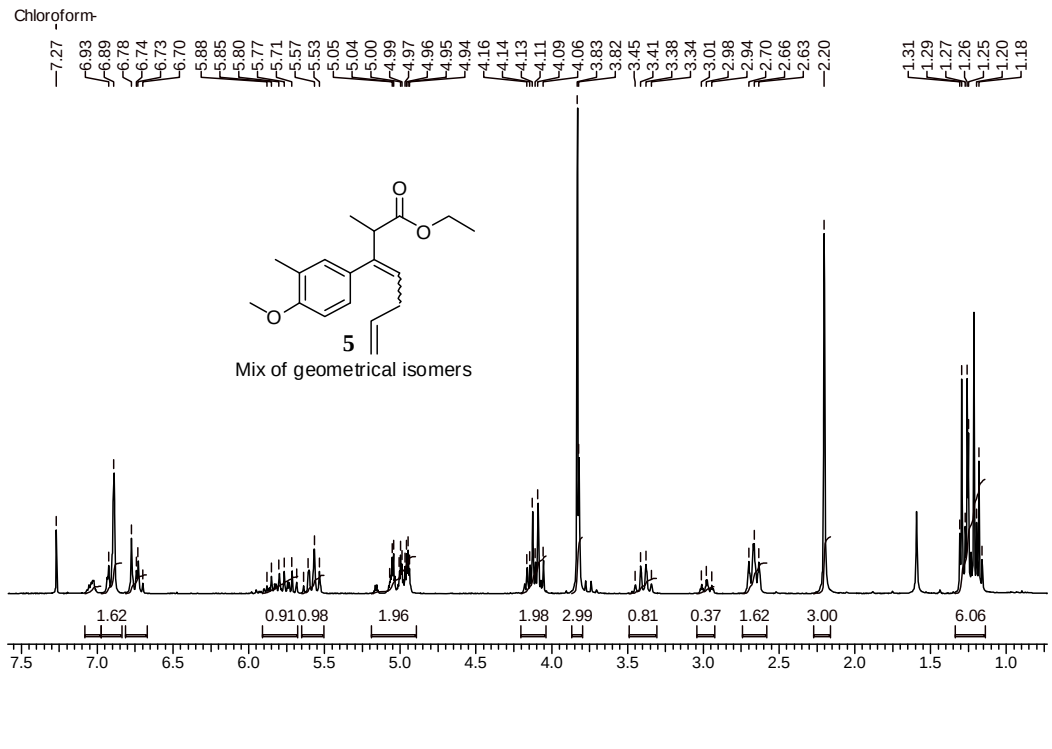
^{13}C NMR spectrum of compound **6** ($CDCl_3$ + CCl_4, 50 MHz)



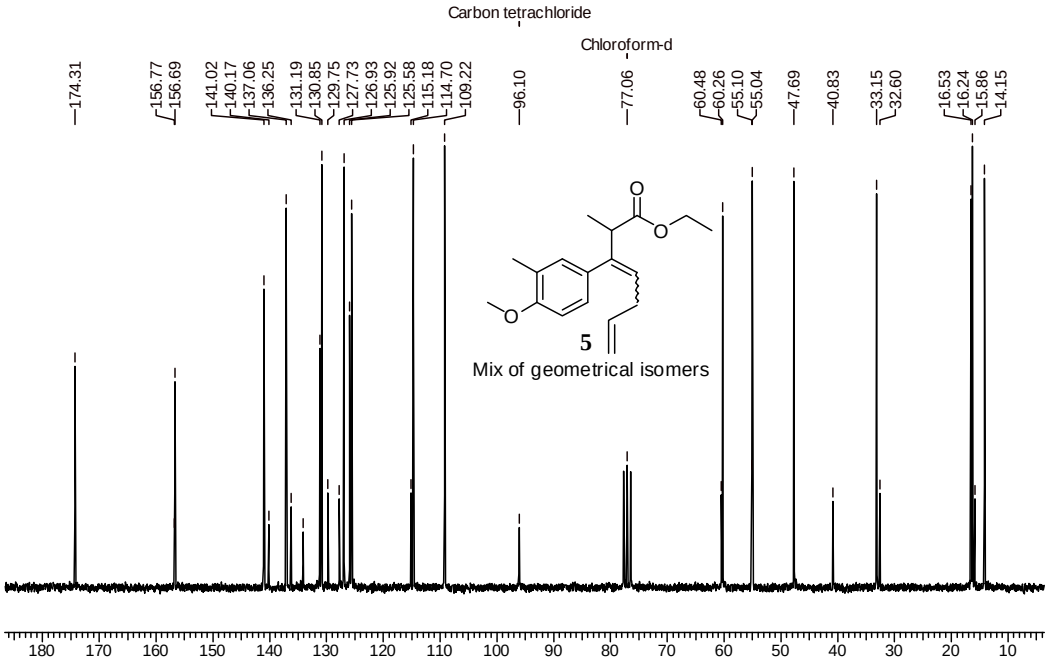
DEPT spectrum of compound **6** ($CDCl_3$ + CCl_4, 50 MHz)



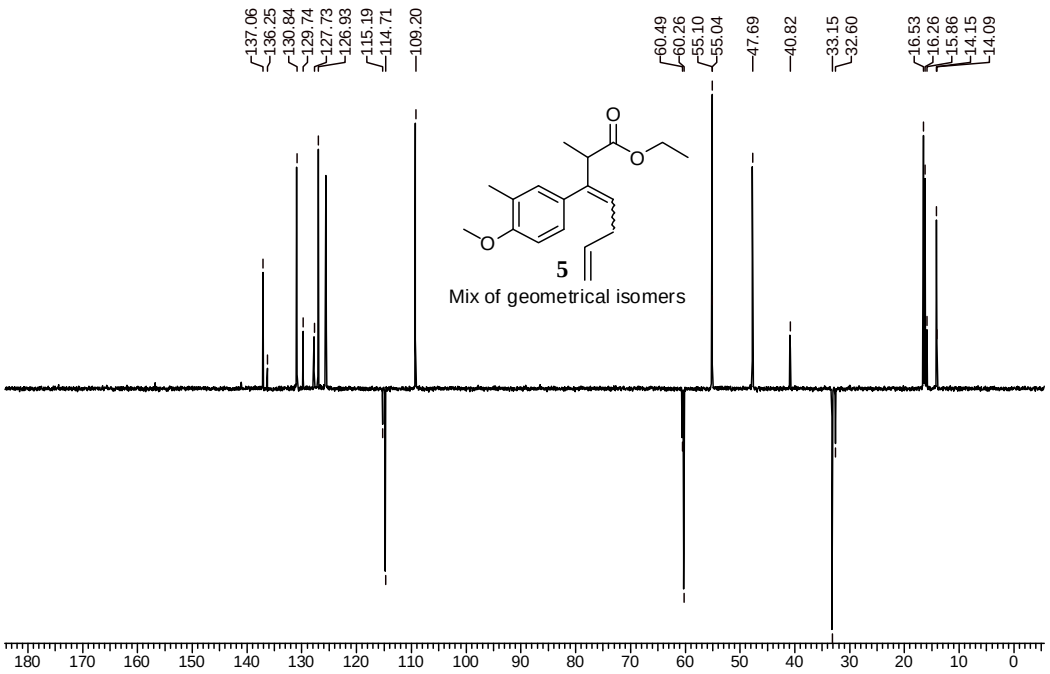
^{1}H NMR spectrum of compound **5** ($CDCl_3$+CCl_4, 200 MHz)



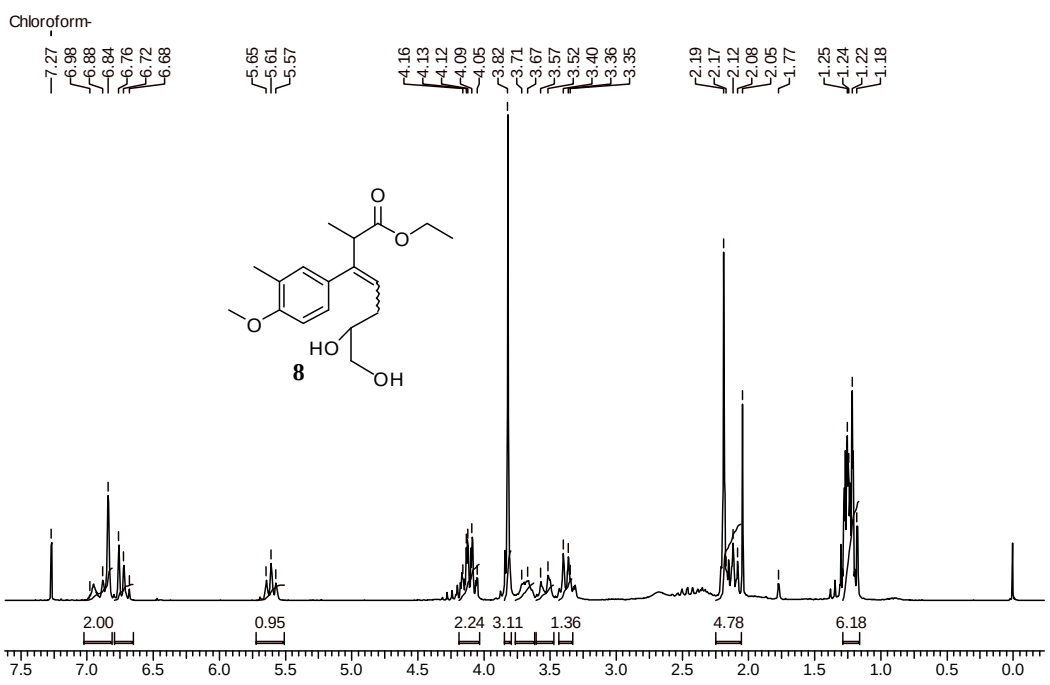
^{13}C NMR spectrum of compound **5** ($CDCl_3$ + CCl_4, 50 MHz)



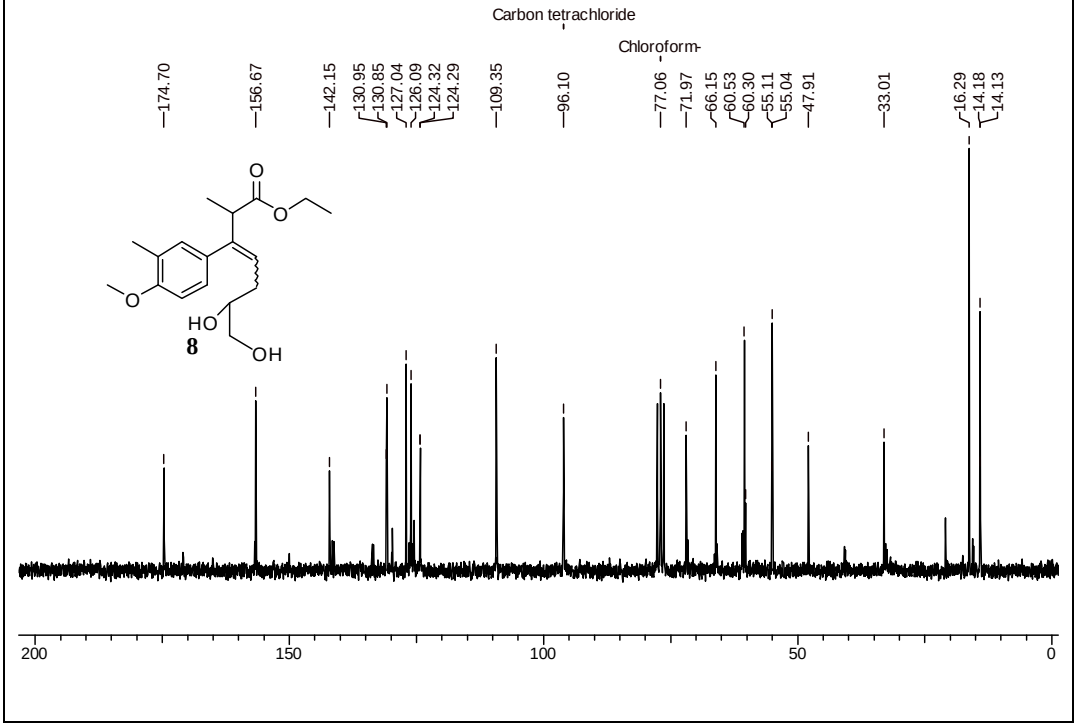
DEPT spectrum of compound **5** ($CDCl_3$ + CCl_4, 50 MHz)



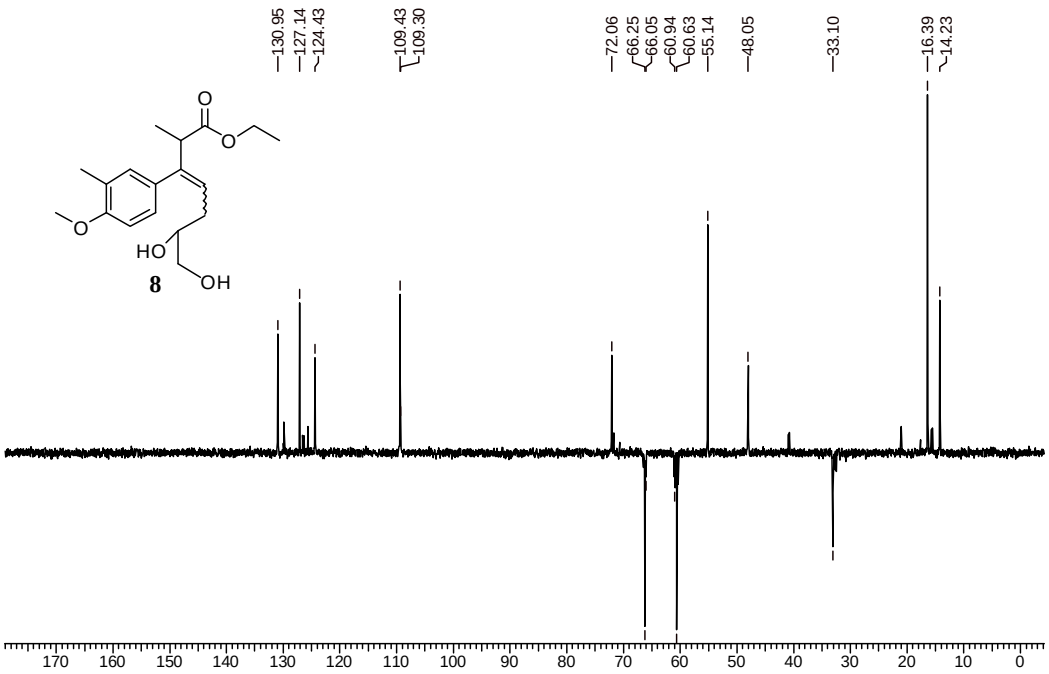
^{1}H NMR spectrum of compound **8** ($CDCl_3$+CCl_4, 200 MHz)



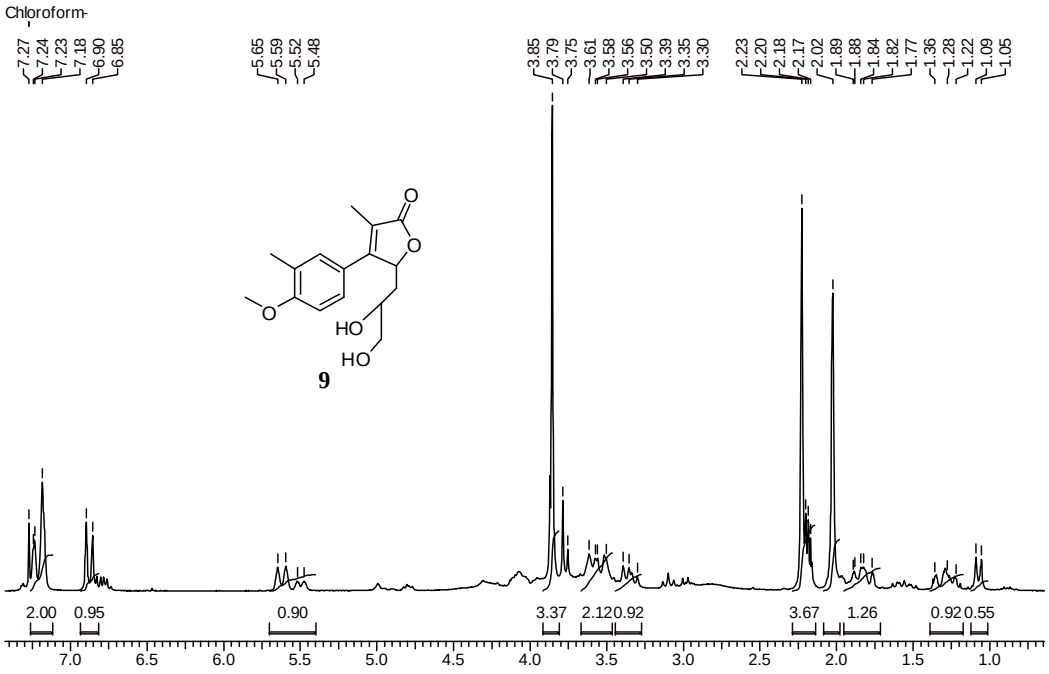
^{13}C NMR spectrum of compound **8** ($CDCl_3$ + CCl_4, 50 MHz)



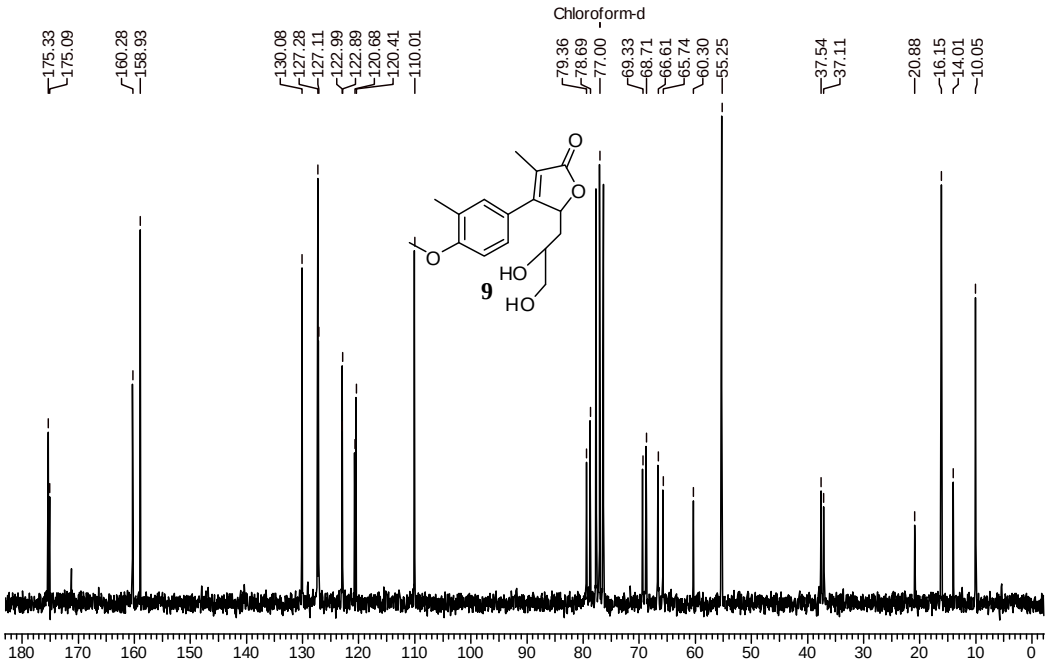
DEPT spectrum of compound **8** ($CDCl_3$ + CCl_4, 50 MHz)



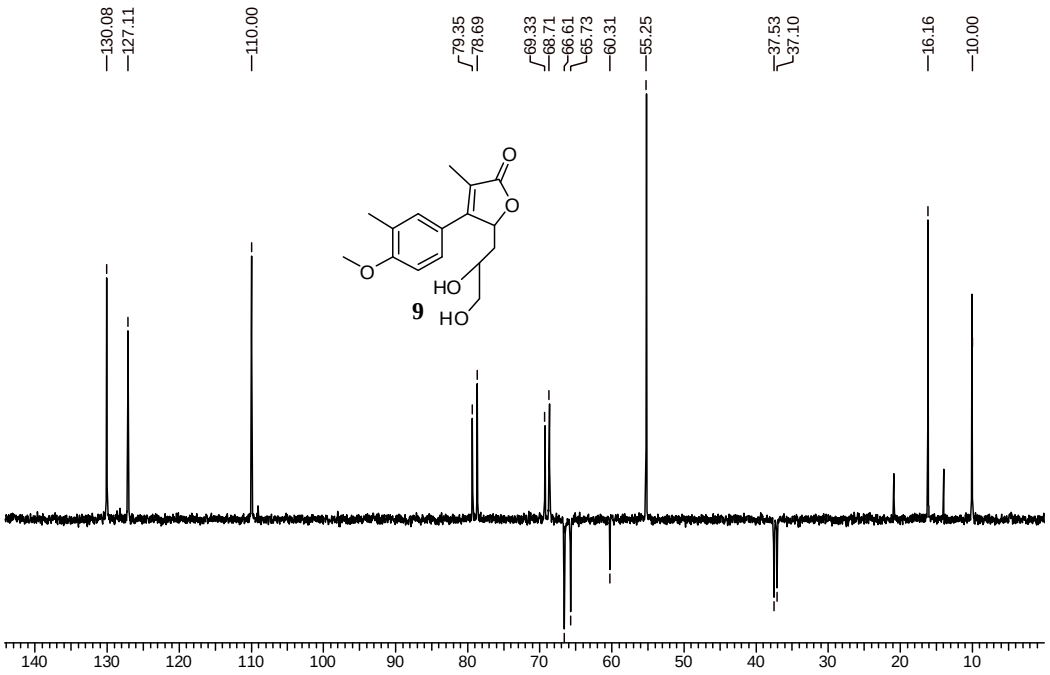
^{1}H NMR spectrum of compound **9** ($CDCl_3$, 200 MHz)



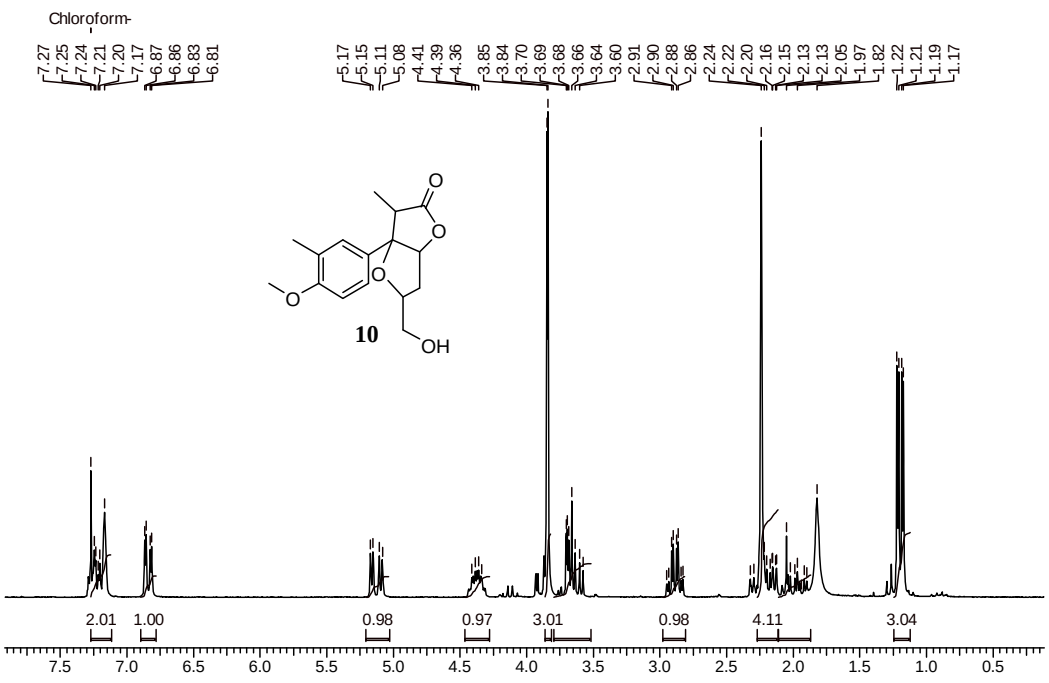
^{13}C NMR spectrum of compound **9** ($CDCl_3$, 50 MHz)



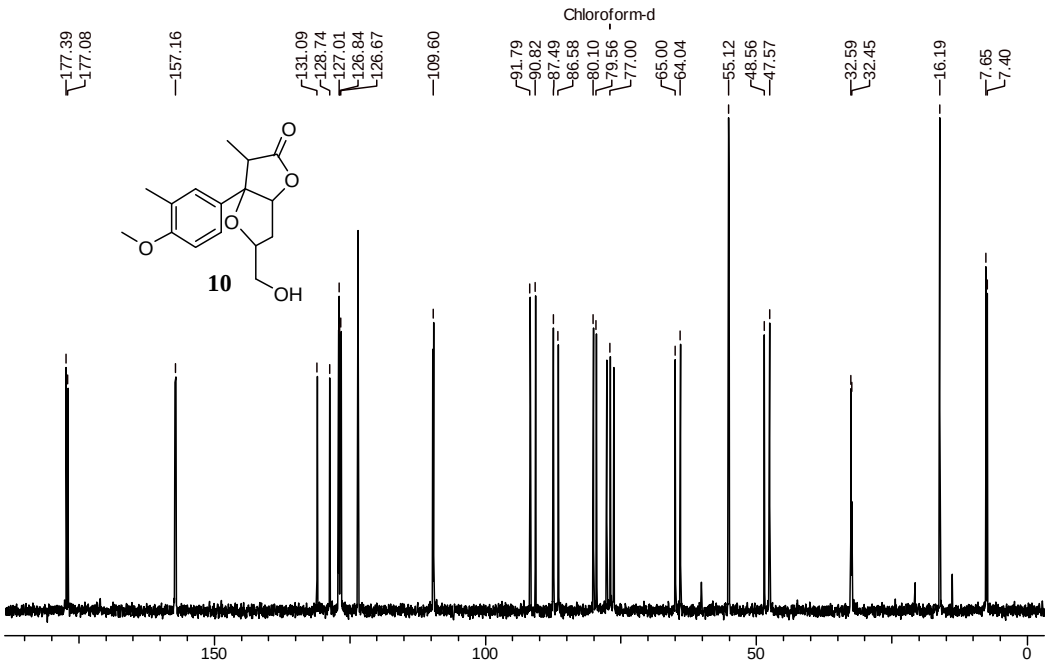
DEPT spectrum of compound **9** ($CDCl_3$, 50 MHz)



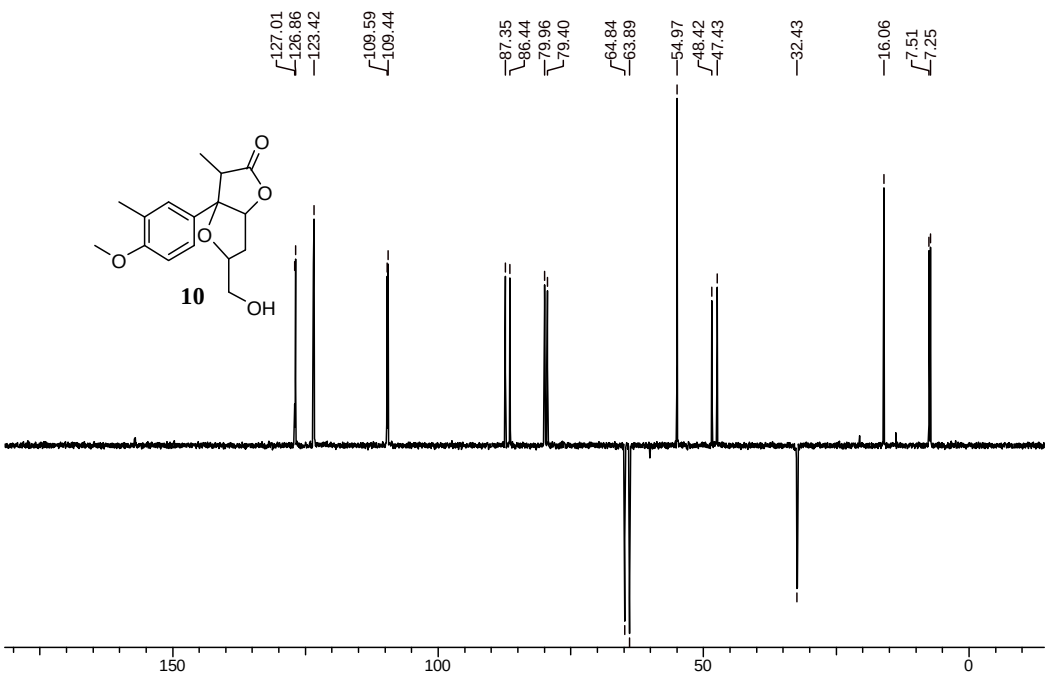
^{1}H NMR spectrum of compound **10** ($CDCl_3$, 200 MHz)



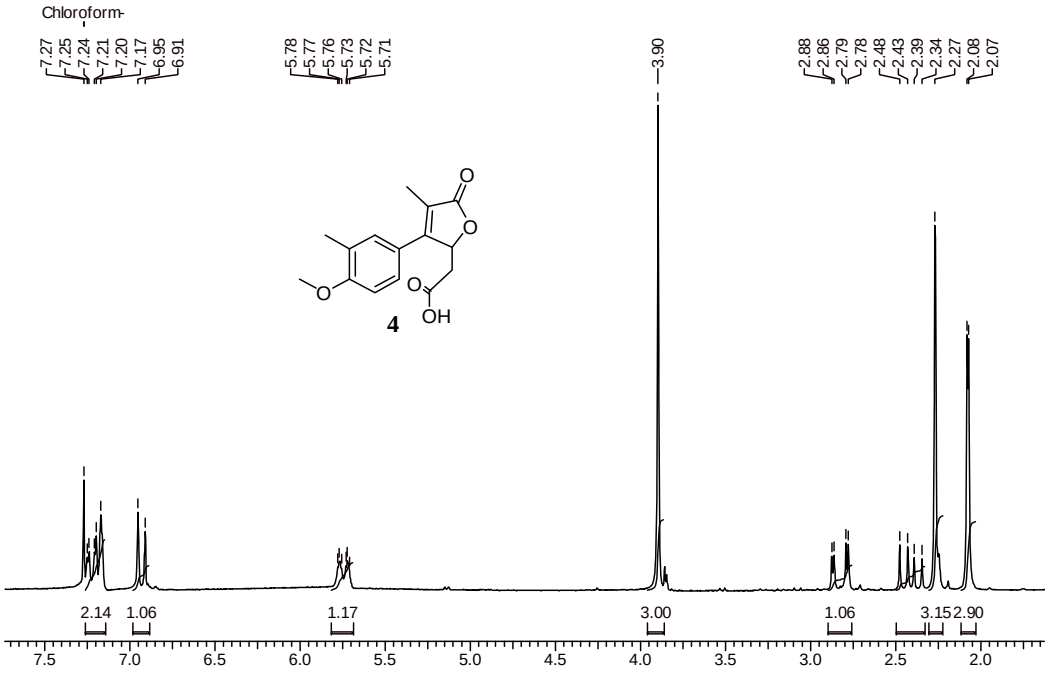
^{13}C NMR spectrum of compound **10** ($CDCl_3$, 50 MHz)



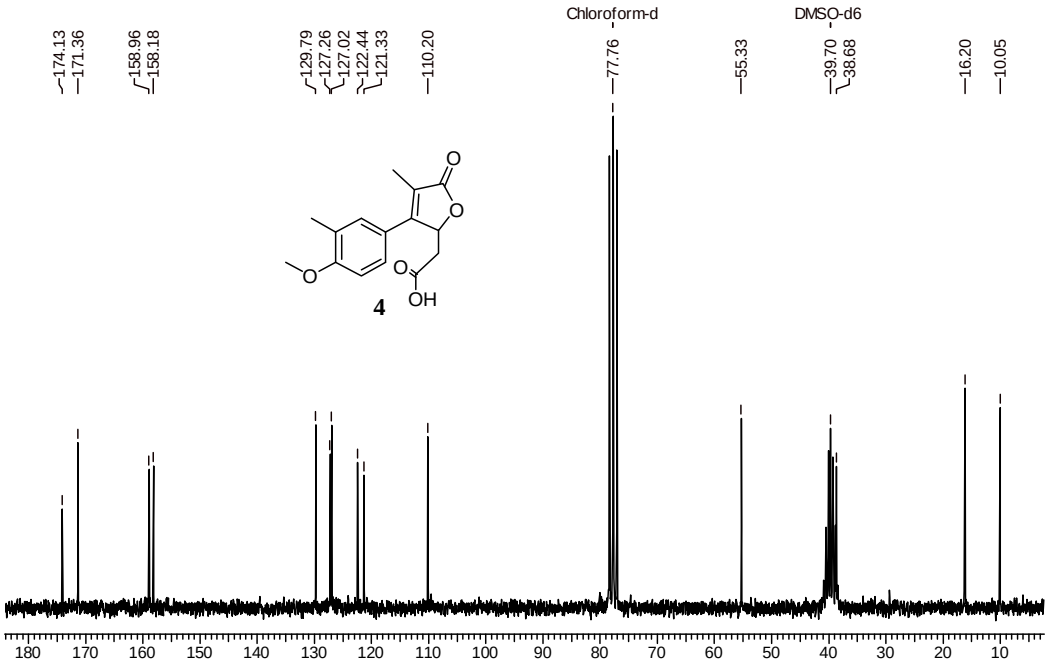
DEPT spectrum of compound **10** ($CDCl_3$, 50 MHz)



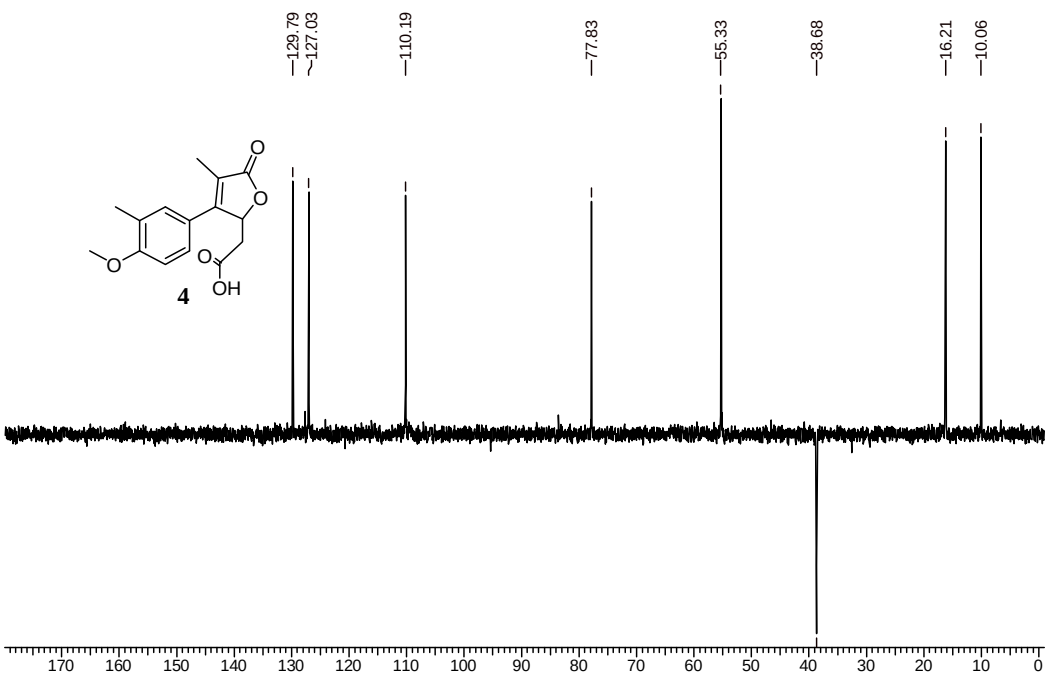
^1H NMR spectrum of compound **4** ($CDCl_3 + CCl_4$, 200 MHz)



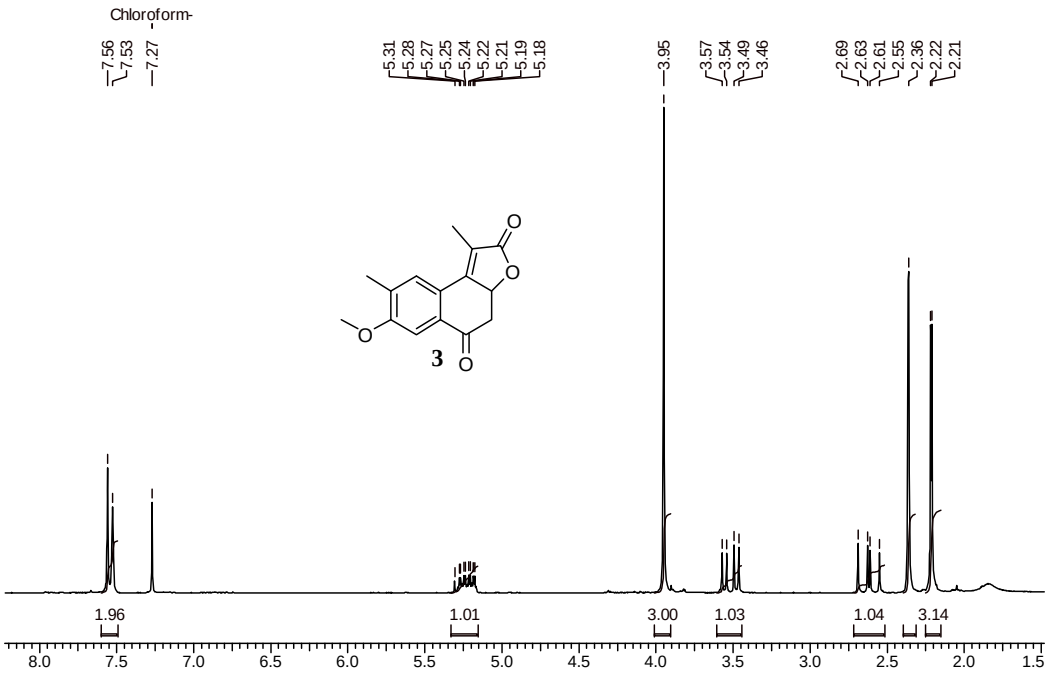
^{13}C NMR spectrum of compound **4** ($CDCl_3$ + C_2D_6SO, 50 MHz)



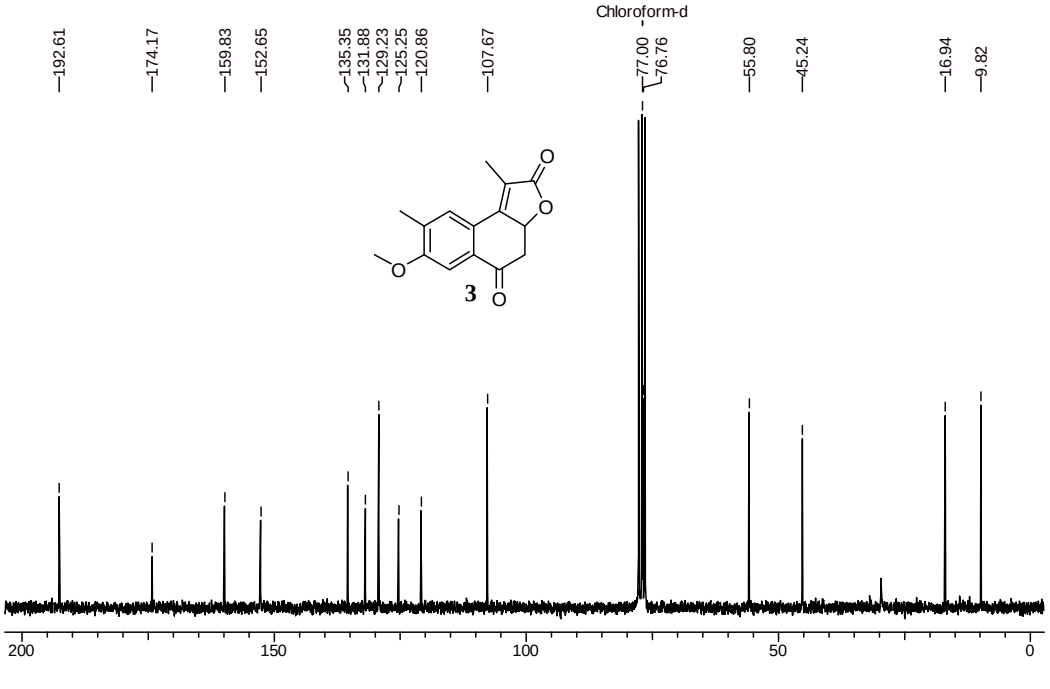
DEPT spectrum of compound **4** ($CDCl_3$ + C_2D_6SO, 50 MHz)



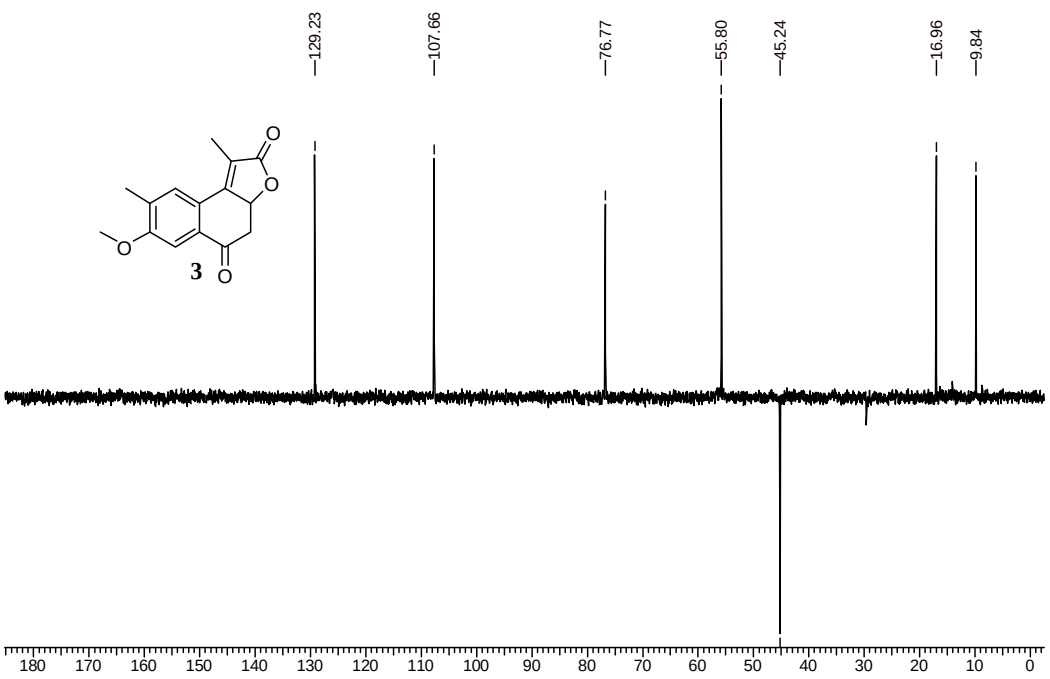
^{1}H NMR spectrum of compound **3** ($CDCl_3 + CCl_4$, 200 MHz)



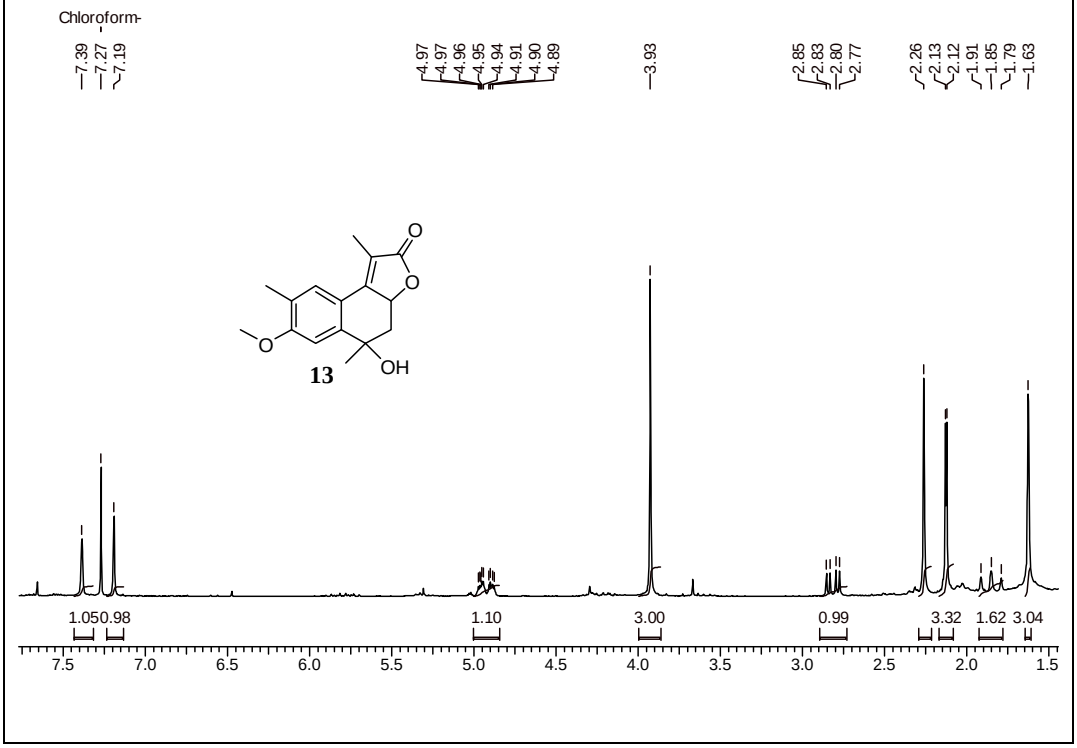
^{13}C NMR spectrum of compound **3** ($CDCl_3$, 50 MHz)



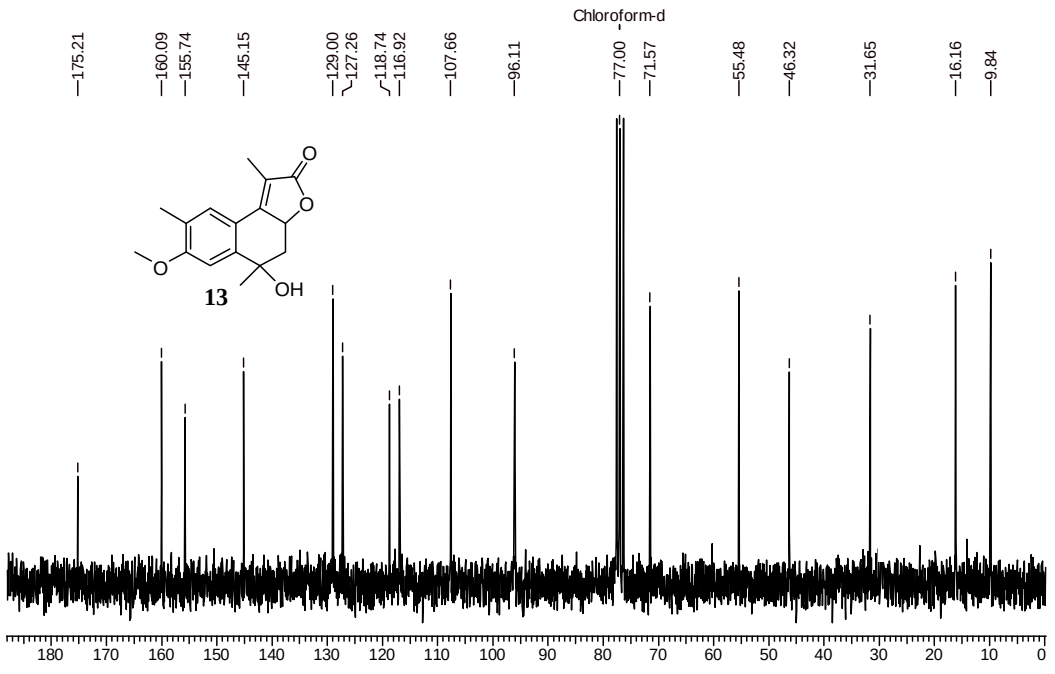
DEPT spectrum of compound **3** ($CDCl_3$, 50 MHz)



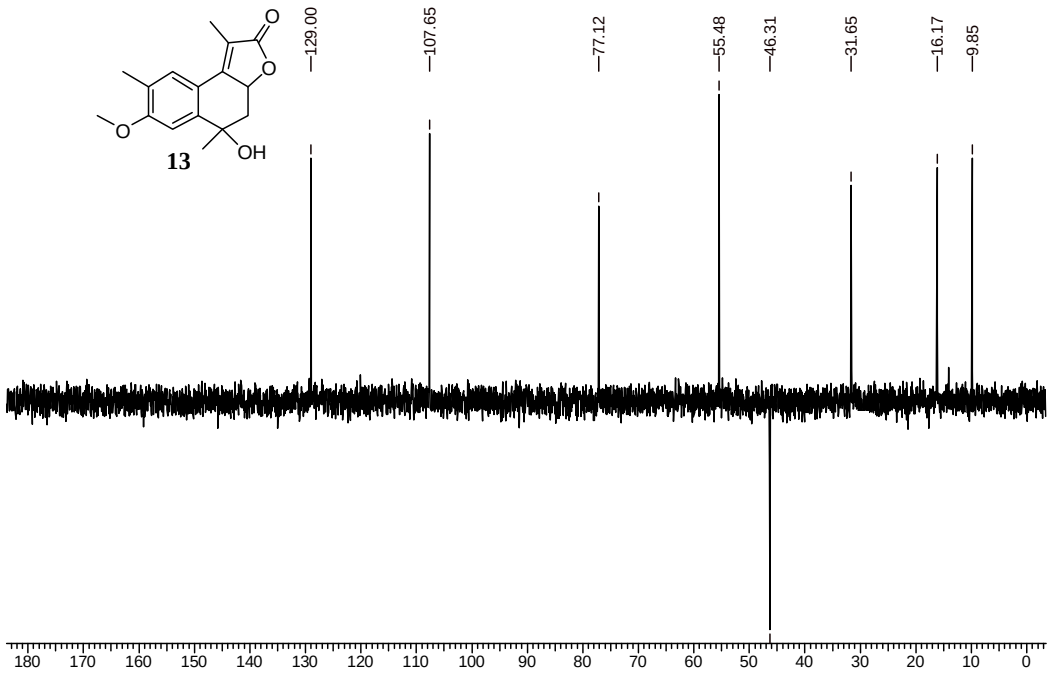
^1H NMR spectrum of compound **13** ($CDCl_3$ + CCl_4, 200 MHz)



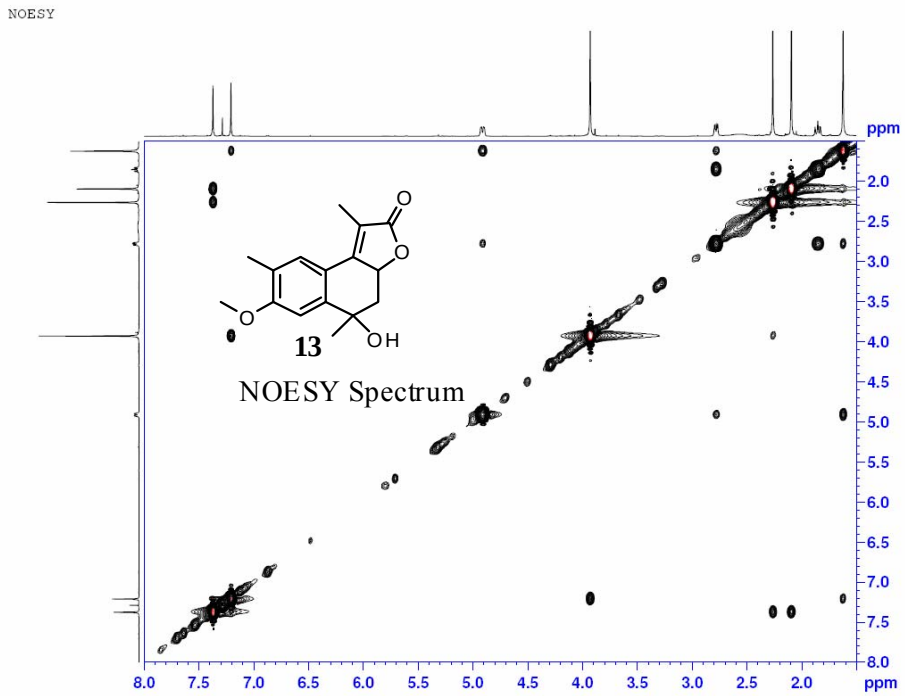
^{13}C NMR spectrum of compound **13** ($CDCl_3$, 50 MHz)



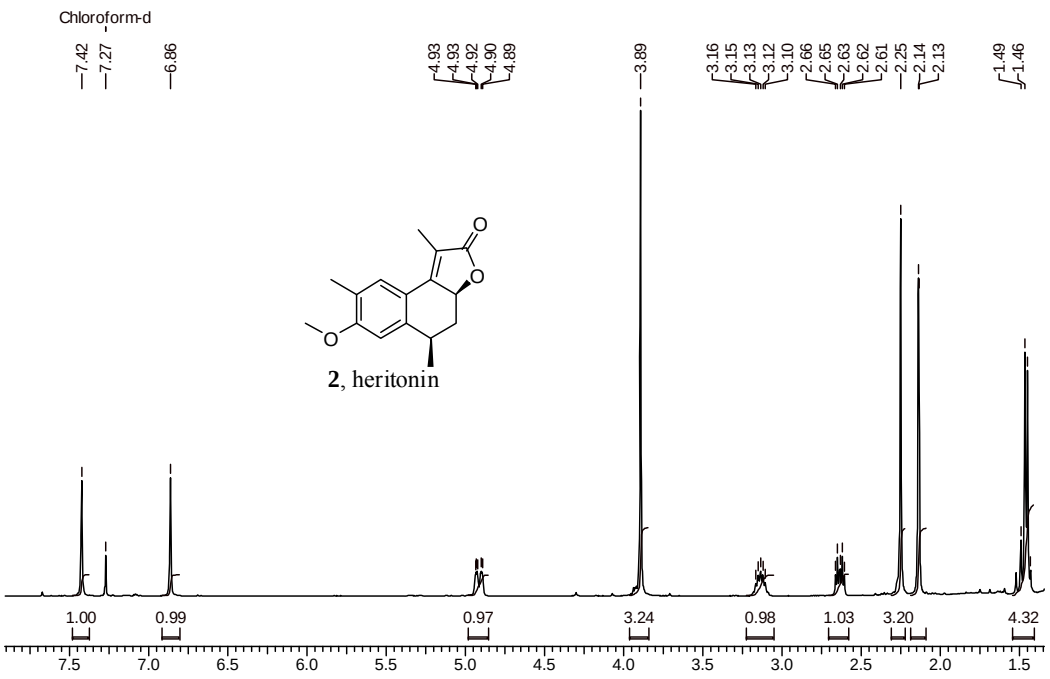
DEPT spectrum of compound **13** ($CDCl_3$, 50 MHz)



NOESY NMR Spectrum of compound **13** ($CDCl_3$ + CCl_4, 200 MHz)

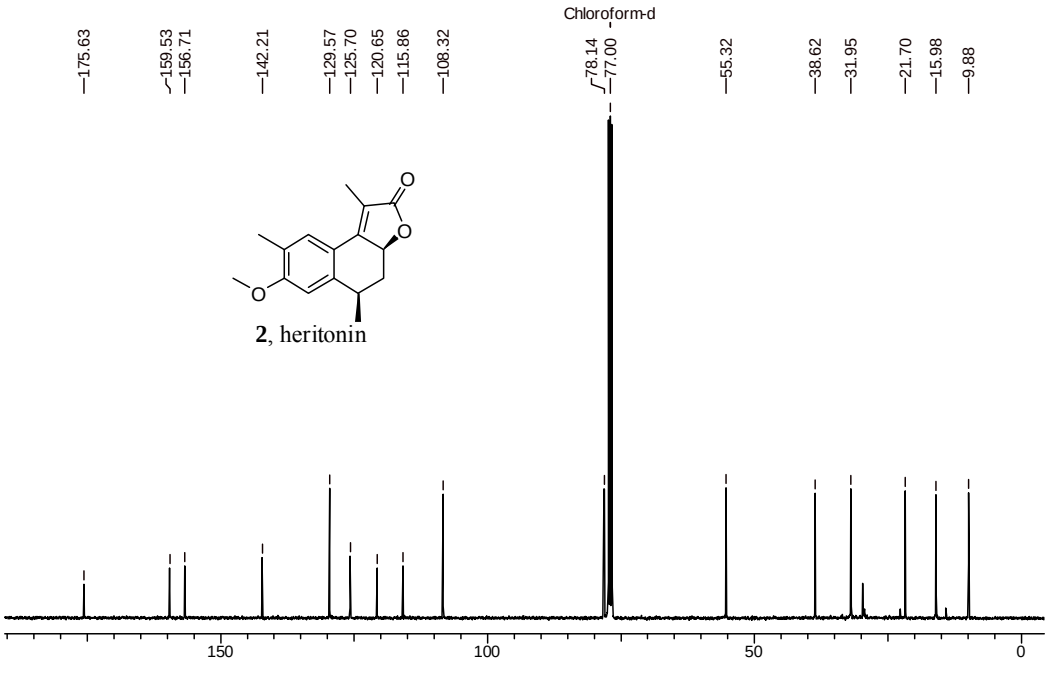


^{1}H NMR spectrum of compound **2** ($CDCl_3$, 200 MHz)



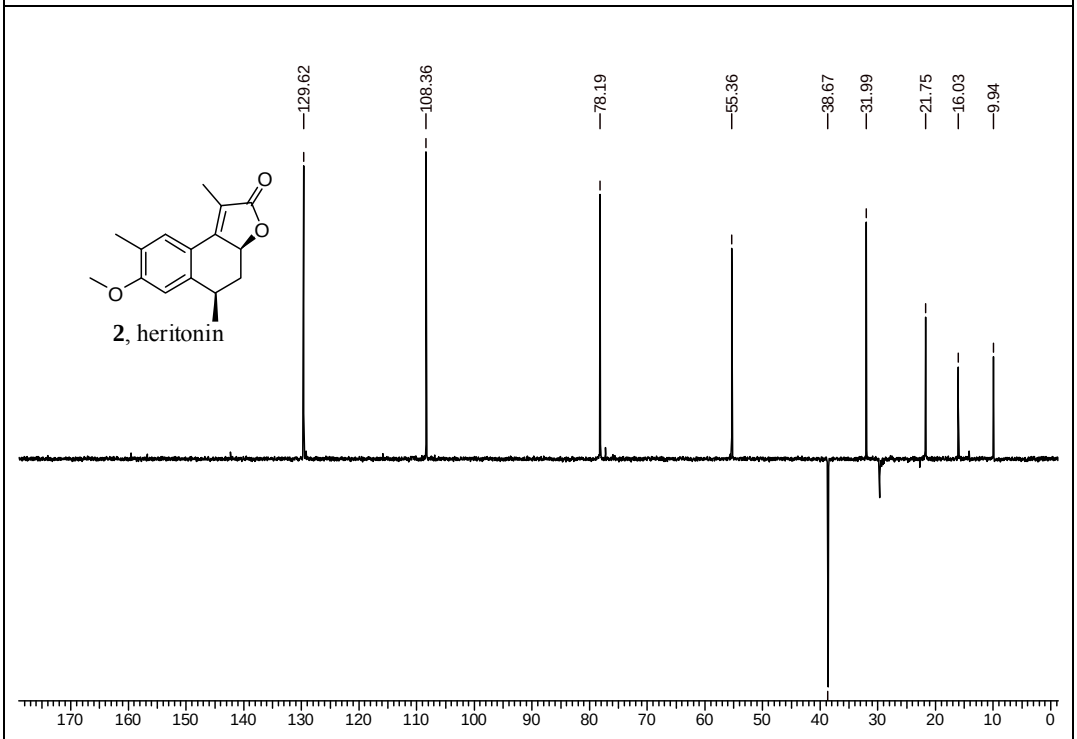
2, heritonin

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



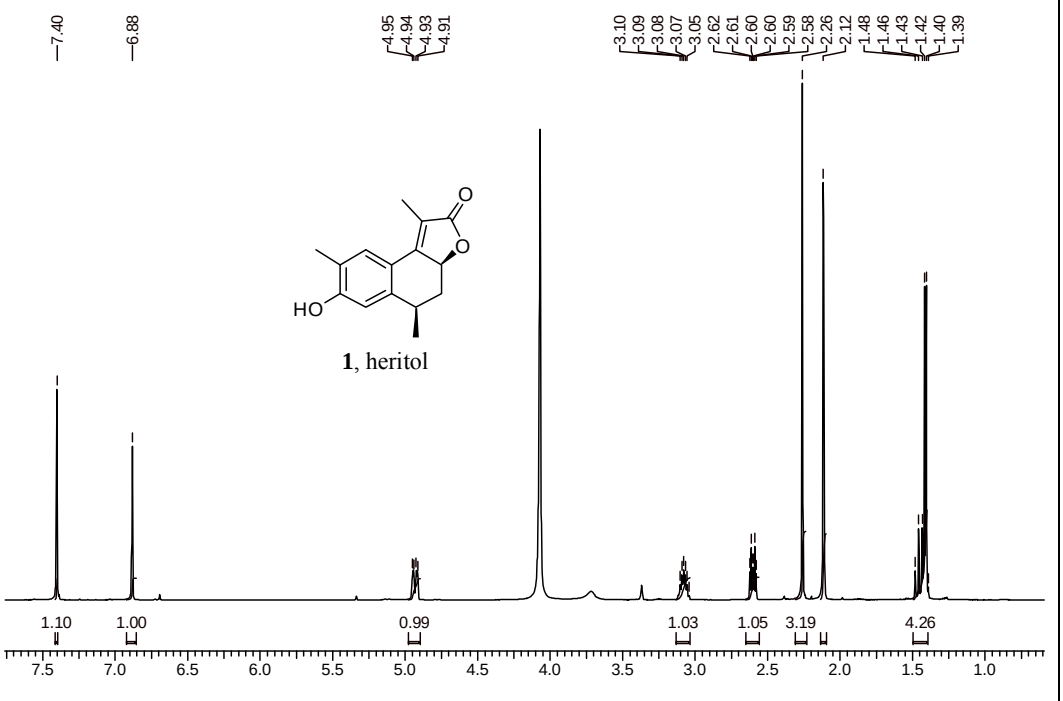
2, heritonin

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



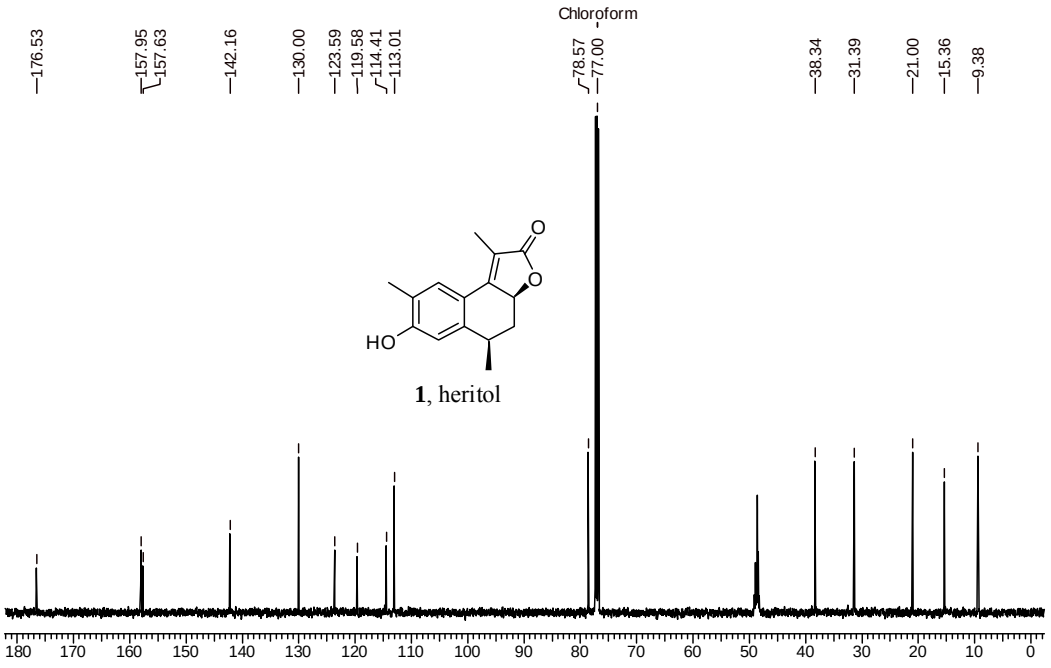
2, heritonin

^1H NMR spectrum of compound **1** ($CDCl_3$, 200 MHz)



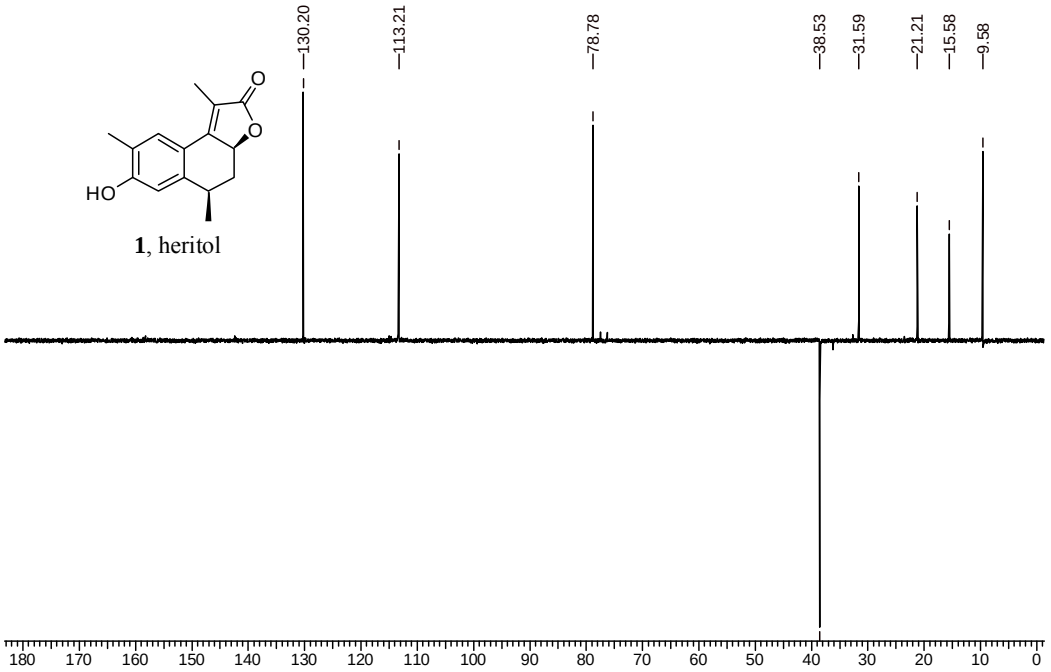
1, heritol

^{13}C NMR spectrum of compound **1** ($CDCl_3$, 50 MHz)



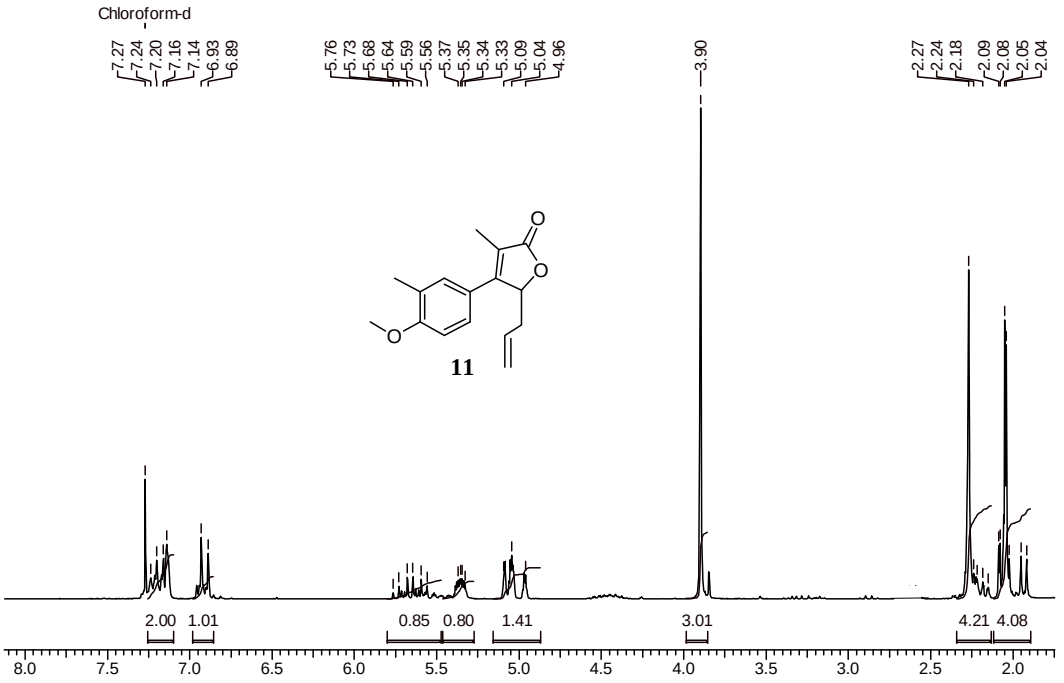
1, heritol

DEPT spectrum of compound **1** ($CDCl_3$, 50 MHz)

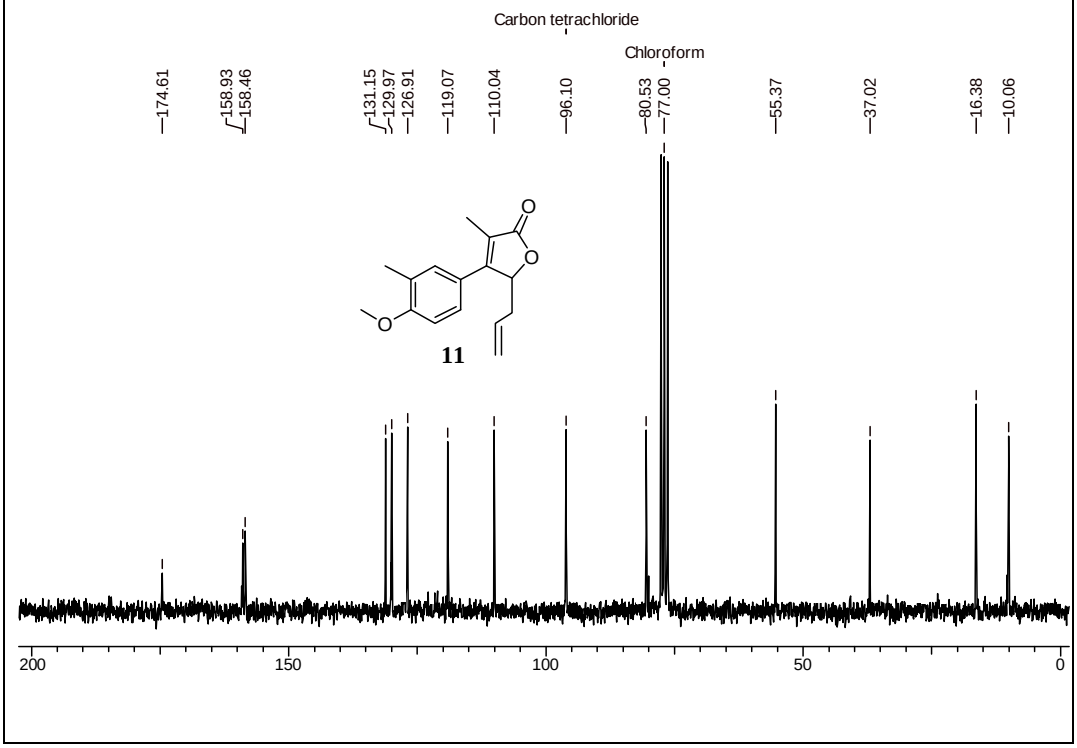


1, heritol

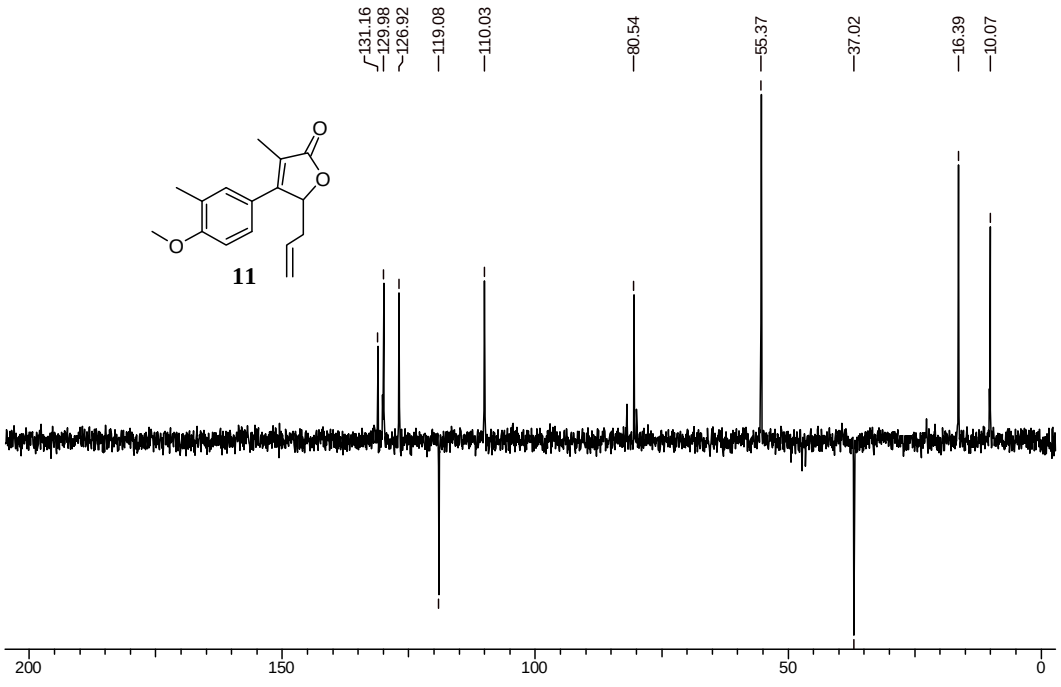
^{1}H NMR spectrum of compound **11** ($CDCl_3$ + CCl_4, 200 MHz)



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



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



1.2.5. References

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10. Epple, G.; Effenberger, F. *Angew Chem. Int. ed.* **1972**, *11*, 300.
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Chapter 1: Diastereoselective total synthesis of (±)-heritol and (±)-heritonin, attempted synthesis towards vallapin and Friedel-Crafts acylation reaction using esters

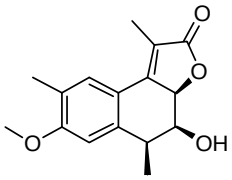
Section 3

Attempted synthesis towards vallapin

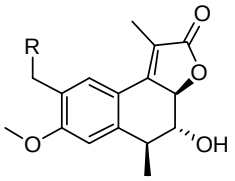
1.3.1. Present Work

1.3.1.1. Objective

Vallapin (**1**), vallapianin (**2**) and heritianin (**3**) (Figure 1) have attracted organic chemists towards their synthesis due to their potentially interesting biological activity and unique structural features involving three contiguous stereocentre. It is very challenging for a synthetic organic chemist to install of three contiguous stereocentres. These compounds represent a new and novel class of sesquiterpenes and possess unusual oxygenation pattern not generally encountered in cadinane family.



1, Vallapin



2, R= OH, Vallapianin
3, R= H, Heritianin

Figure 1. Structures of vallapin (**1**), vallapianin (**2**), heritianin (**3**).

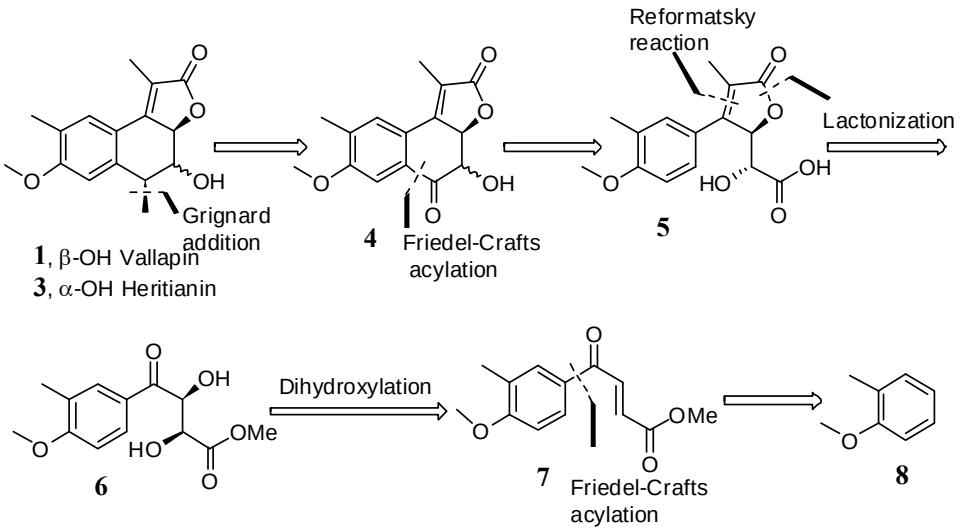
In literature there are no reports on the total synthesis of these structurally complex natural products. In this context, there is a need of convenient and efficient route for the synthesis of these natural products.

This group is engaged in the synthesis of biologically active compounds and earlier this group has developed a practical and efficient protocol for the synthesis of different biologically active terpenes.[1] In continuation of search for practical routes for such molecules, synthesis of vallapin and heritianin was undertaken.

1.3.1.2. Retrosynthetic analysis

Retrosynthetic analysis of vallapin (**1**) and heritianin (**3**) (Scheme 1) revealed that vallapin (**1**) and heritianin (**3**) can be obtained from α-hydoxy tetralone unit **4**, which in turn could be obtained from α-hydoxy acid **5** *via* intramolecular Friedel-Crafts acylation. The α-hydoxy acid **5** having α, β-unsaturated lactone can be synthesized from the keto compound **6** *via* Reformatsky reaction followed by dehydration. The two hydroxyl functional groups of keto-compound **6** can be installed *via* Sharpless asymmetric dihydroxylation of the unsaturated ketone compound **7**. Unsaturated

ketone compound **7** can be accessed from inexpensive and commercially available starting material **8**.



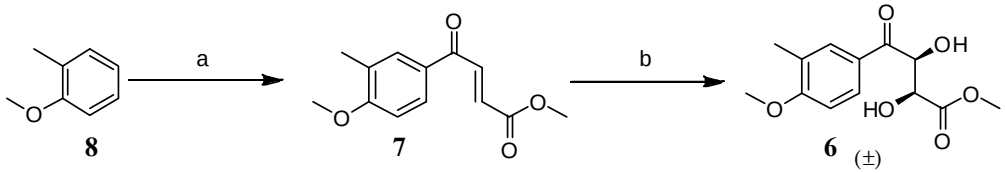
Scheme 1. Retrosynthetic analysis of vallapin (**1**) and heritianin (**3**).

1.3.1.3. Results and discussion

As discussed in the retrosynthetic approach, the total synthesis of vallapin (**1**) and heritianin (**3**) was started from 2-methylanisole **8** which is commercially available and inexpensive starting material. The unsaturated ketone **7** was prepared by the Friedel-Crafts acylation reaction of 2-methylanisole **8** (Scheme 2). 2-Methylanisole **8** was treated with maleic anhydride to give acid[2] and the crude acid thus obtained was directly treated with Me_2SO_4 to give corresponding ester **7** in 95% yield over two steps. The IR spectrum of compound **9** showed strong absorption bands at 1729 and 1667 cm^{-1} for corresponding α,β-unsaturated ester and ketone. ^1H NMR spectrum of compound **7** showed peaks at δ 6.82 and 7.90 as doublets corresponding to the protons of double bond of unsaturated ketone compound **7**. The coupling constant of the two protons of the double bond was 15.0 Hz which revealed that the double bond is in *trans* geometry. ^{13}C and DEPT NMR spectra of compound **7** showed peaks at δ 136.88 and 131.39 corresponding to the double bond of unsaturated ketone compound **7**. The mass spectrum of compound **7** showed peak at m/z 257 corresponding to $[M+Na]^+$. Finally the structure of compound **7** was confirmed by elemental analysis.

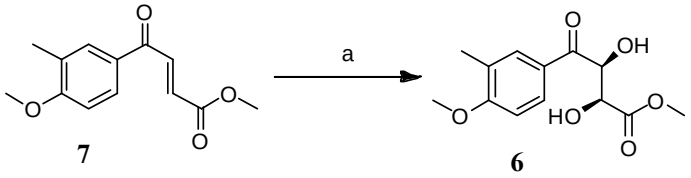
The olefin **7** was treated with catalytic amount of OsO_4 and NMO as a co-oxidant in acetonitrile:water (9:1) as solvent system to furnish the racemic mixture of diol **6** in

99% yield. The IR spectrum of compound **6** showed strong bands at 3450, 1748 and 1681 cm^{-1} for free hydroxyl group, ester and ketone functional groups respectively. The ^{1}H NMR spectrum of compound **6** showed that the doublets at δ 6.82 and δ 7.90 were absent indicating the conversion of conjugated double bond into diol. ^{13}C NMR and DEPT NMR spectra of compound **6** showed peaks at δ 72.68 and 73.79 for corresponding methine carbons [-CH(OH)-CH(OH)-]. The mass spectrum of compound **6** showed peak at m/z 291 corresponding to $[M+Na]^{+}$. Finally the structure of compound **6** was confirmed by elemental analysis (Scheme 2).



Scheme 2. Reagents and conditions: *a) i) Maleic anhydride, $AlCl_3$, DCM, rt, 4 h, 95%; ii) Me_2SO_4, K_2CO_3, acetone, 99%; b) OsO_4, NMO, $CH_3CN:H_2O$ (9:1), 30 min, 99%.*

Chiral diol could be synthesized from enone **7** by using Sharpless asymmetric dihydroxylation. Accordingly, the prochiral enone **7** was subjected to Sharpless asymmetric dihydroxylation (SAD)[3] reaction conditions with $(DHQD)_2PHAL$ as a chiral catalyst to yield chiral diol **6** in 85% yield with 97% *ee*[4]. All spectral data of chiral diol **6**, matched with the racemic diol **6** (Scheme 3).

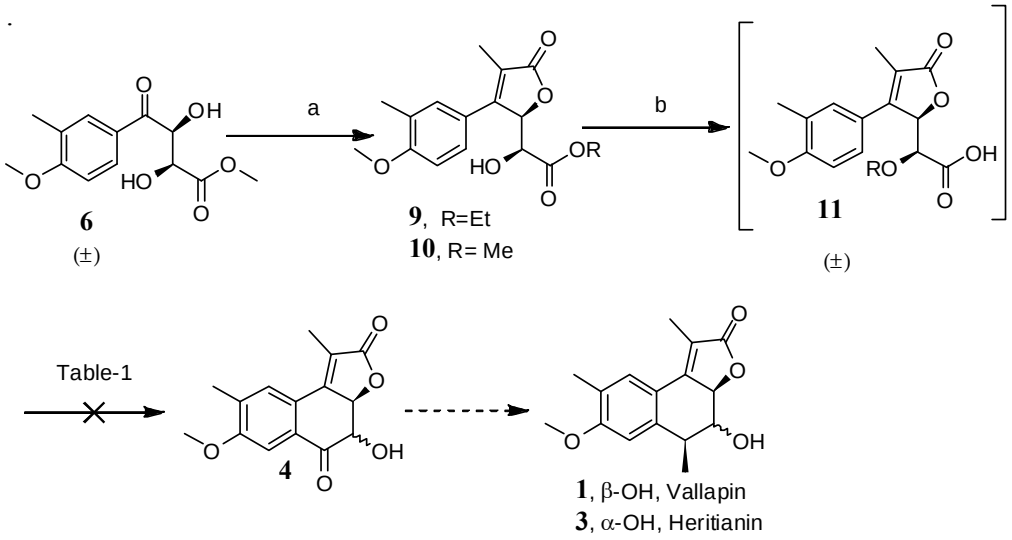


Scheme 3. Reagents and conditions: *a) $(DHQD)_2PHAL$, OsO_4, $K_3[Fe(CN)_6]$, K_2CO_3, $^{t}BuOH:H_2O$(1:1), 2 days, 85%, 97% ee.*

Reformatsky reaction on (±)-**6** with ethyl 2-bromopropionate using activated Zn in benzene:diethylether (1:1) as the solvent under reflux conditions furnished β-hydroxy ester, which without further purification was treated with PTSA in DCM at room temperature to afford ethyl ester **9** which was formed by transesterification of methyl ester as a major product and methyl ester **10** as a minor product.

Formation of compounds **9** and **10** was confirmed by using spectroscopic methods. The IR spectrum of **9** showed strong bands at 1748 and 1741 cm^{-1}, indicating the presence of carbonyl functional group of ester and butenolide ring respectively. Presence of a doublet at δ 2.07 and multiplet at δ 5.57-5.60 in its ^{1}H NMR spectrum indicated the formation of α, β-unsaturated-*γ*-lactone **9** and quartet at δ 4.36 and a triplet at δ 1.38 indicated it to be an ethyl ester. ^{13}C NMR and DEPT NMR spectra showed peaks at δ 171.27 corresponding to the presence of unsaturated lactone and at δ 62.69 (for $–O\underline{C}H_2$) and 10.17 (for $–\underline{C}H_3$) also confirmed the formation of ethyl ester. The mass spectrum of compound **9** showed peaks at m/z 343 $[M+Na]^+$. Finally the structure of compound **9** was confirmed by the elemental analysis.

The IR spectrum of methyl ester **10** showed strong bands at 1750 and 1740 cm^{-1}, indicating the presence carbonyl functional groups of ester and butenolide ring. Presence of a singlet at δ 2.08 and multiplet at δ 5.58-5.60 in its ^{1}H NMR spectrum indicated the formation of α, β-unsaturated-*γ*-lactone **10** and a singlet at δ 3.92 indicated it to be the methyl ester. The mass spectrum of compound **10** showed peaks at m/z 329 $[M+Na]^+$. Finally the structure of compound **10** was confirmed by the elemental analysis (Scheme 4).



Scheme 4. Reagents and conditions: *a) i) Ethyl-2-bromopropionate, activated Zn, benzene: ether (1:1), reflux, 3 h; ii) PTSA, toluene, reflux, 6 h, 55%; b) LiOH.H_2O, THF: H_2O (3:1).*

Compound **9** was treated for ester hydrolysis with LiOH to give acid **11**, which without further purification was subjected for cyclization but it failed to furnish the desired tetralone **4**. Then it was thought that free hydroxyl group might be creating problems. Accordingly, free hydroxy group was protected with different protecting groups and the corresponding acids were treated for cyclization (Table 1) but unfortunately it was not possible to obtain the desired tetralone **4**.

Table 1

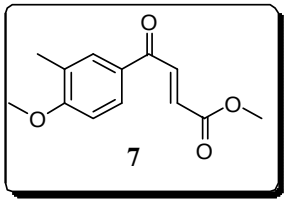
SN	R	**Reaction condition**	Observation	SN	R	**Reaction condition**	Observation
1	-H	i) $(COCl)_2$, DCM; ii) Triflic acid	SM recovered	8	-Ac	i) $(COCl)_2$, DCM; ii) $AlCl_3$	Dehydration
2	-H	PPA	Dehydration	9	-Ac	PPA	Dehydration
3	-H	i) $(COCl)_2$, DCM; ii) $AlCl_3$	Dehydration	10	-Bn	Triflic anhydride	Dehydration
4	-H	Cynuric chloride, $AlCl_3$	SM recovered	11	-Bn	PPA	Dehydration
5	-H	Triphosgene, $AlCl_3$	SM recovered	12	-Bn	Cynuric chloride, $AlCl_3$	Dehydration
6	-Ac	TFAA, TFA	SM recovered	13	-Bn	i) $(COCl)_2$, DCM; ii) $AlCl_3$	Dehydration
7	-Ac	MeOCOCl, $AlCl_3$	Dehydration	14	-Ts	Ag_2O/ In presence of base	Dehydration

1.3.2. Conclusion

In conclusion, although the synthesis of vallapin (**1**) and heritianin (**3**) could not be achieved by this route, a advanced intermediates, bearing the hydroxy butenolide (**9** and **10**) were obtained in good yields which under proper choice of reagents and conditions can be converted to vallapin or heritianin.

1.3.3. Experimental

(*E*)-Methyl 4-(4-methoxy-3-methylphenyl)-4-oxobut-2-enoate (7)



7

To a cold (0 ºC), magnetically stirred solution of *o*-cresol methyl ether **8**(10 g, 0.082 mol) and maleic anhydride (9.65 g, 0.0984 mol) in anhydrous DCM (100 mL) was added anhydrous $AlCl_3$ (37.2 g, 0.328 mol) and stirred for 4 h at room temperature. The reaction was quenched with 10% aq. HCl and extracted with DCM (3× 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude acid was used in the next reaction without further purification.

To a solution of crude acid (20 g, 0.10 mol) in dry acetone (400 mL), K_2CO_3 (32 g, 0.24 mol) was added followed by Me_2SO_4 (21.6 mL, 0.24 mol) and stirred at rt for 45 min. The reaction mixture was cooled and quenched with water and extracted with ethyl acetate (3× 60 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (20% EtOAc/pet ether) to provide the product **7** (18.14 g, 95% yield over two steps) as white solid. R_f (30% EtOAc/pet ether): 0.5.

Molecular formula: $C_{13}H_{14}O_4$

Yield: 95%

Melting Point: 108-110 °C

IR ($CHCl_3$): 2940, 2851, 1729, 1669, 1592, 1505, 1458 cm^{-1}.

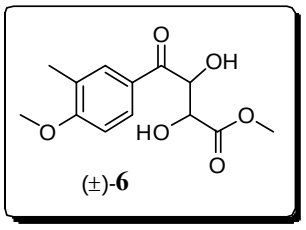
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.22 (s, 3H), 3.81 (s, 3H), 3.87 (s, 3H), 6.82 (d, *J*= 15.4 Hz, 1H), 6.84 (d, *J*=9.0 Hz, 1H), 7.79-7.86 (m, 2H), 7.90 (d, *J*= 15.4 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 16.11, 52.13, 55.49, 109.36, 127.29, 129.04, 129.21, 130.90, 131.28, 136.77, 162.46, 166.25, 187.50.

MS (ESI) (m/z): 257 $[M+Na]^+$.

Elemental analysis: Calculated C, 66.66; H, 6.02%; Found C, 66.82; H, 6.15%.

Methyl 2,3-dihydroxy-4-(4-methoxy-3-methylphenyl)-4-oxobutanoate (6)



(±)-**6**

To a cold (0 ^{0}C), magnetically stirred solution of enone **7** (2 g, 8.5 mmol) in acetonitrile: water (9:1) (20 mL), catalytic amount of OsO_4 (0.1 mL, 0.1 M solution in toluene) was added in presence of *N*-methylmorpholine-*N*-oxide (NMO) (3.46 g, 25.5 mmol) as a co-oxidant and stirred for 30 min at rt. The reaction was quenched with saturated Na_2SO_3 (10 mL) solution and again stirred for 30 min. The solvent was evaporated and the residue was extracted with ethyl acetate (3×10 mL). The combined organic layer was washed with brine (7 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue on a silica gel column using ethyl acetate/hexane (3.5:6.5) as eluent furnished the diol compound (±)-**6** (2.25 g, 98%) as white solid. R_f (60% EtOAc): 0.8.

Molecular formula: $C_{13}H_{16}O_6$

Yield: 98%

Melting Point: 94-96 °C

IR ($CHCl_3$): 2955, 1747, 1675, 1601, 1505, 1441 cm^{-1}.

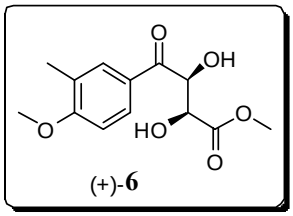
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.26 (s, 3H), 3.01 (d, *J*=8.2 Hz, 1H), 3.91 (s, 3H), 4.12 (d, *J*=6.7 Hz, 1H), 4.55 (d, *J*=6.9 Hz, 1H), 5.33-5.37 (m, 1H), 6.89 (d, *J*=8.4 Hz, 1H), 7.78-7.86 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 16.20, 53.04, 55.59, 72.68, 73.79, 109.58, 125.18, 127.68, 128.80, 131.04, 162.77, 172.04, 195.52.

MS (ESI) (m/z): 291 $[M+Na]^+$.

Elemental analysis : Calculated C, 58.20; H, 6.01%; Found C, 58.38; H, 6.11%.

(2*S*,3*S*)-Methyl 2,3-dihydroxy-4-(4-methoxy-3-methylphenyl)-4-oxobutanoate (6)


(+)-**6**

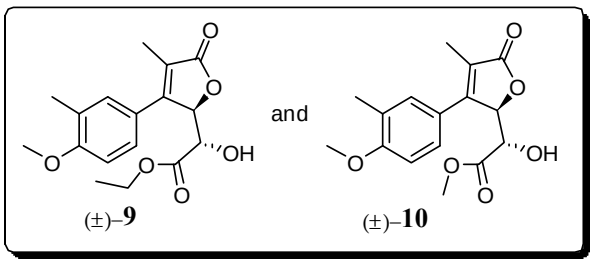
To a mixture of $K_3Fe(CN)_6$ (2.1 g, 6.3 mmol), K_2CO_3 (0.87 g, 6.3 mmol) and $(DHQD)_2PHAL$ (0.016 g, 0.021 mmol) in ^tBuOH-H_2O (1:1, 10 mL) cooled at 0 ^oC was added osmium tetroxide (0.08 mL, 0.1 M solution in toluene, 0.4 mol %) followed by methane sulfonamide (2.0 g, 2.1 mmol). After stirring for 5 min at 0 ^oC, the olefin **7** (0.5 g, 2.1 mmol) was added in one portion. The reaction mixture was stirred at 0 ^oC for 2 days and then quenched with solid sodium sulfite (0.5 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (35% EtOAc/pet ether) to provide the product (+)-**6** (0.517 g, 90% yield) as white solid.

Molecular formula: $C_{13}H_{16}O_6$

Yield: 90%

$[\alpha]_D^{25}$: +41.41 (*c* 0.55, $CHCl_3$)

Methyl 2-hydroxy-2-(-3-(4-methoxy-3-methylphenyl)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)acetate (9) and ethyl 2-hydroxy-2-(3-(4-methoxy-3-methylphenyl)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)acetate (10)


(±)–**9** and (±)–**10**

To a magnetically stirred solution of hydroxy ketone compound **6** (1 g, 4.0 mmol) and activated Zn (1 g, 12.0 mmol) in the presence of catalytic amount of iodine in anhydrous diethylether and benzene (1:1) (10 mL), was slowly added a solution of ethyl 2-bromopropionate (1.0 mL, 6.0 mmol) in anhydrous diethylether and benzene (1:1) (10 mL) over a period of 15 min and further refluxed (80 °C) for 3 h in an argon atmosphere. The reaction mixture was cooled to 0 ºC and quenched with 10% HCl (10 mL) and extracted with ethyl acetate (3×10 mL). The combined organic layer was washed with brine (7 mL) and dried over

anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude alcohol was used as such in the next reaction without further purification.

Catalytic amount of PTSA was added to a magnetically stirred solution of β-hydroxy ester (1.45 g, 4.7 mmol) obtained above in dry DCM (15 mL) and stirred for 12 h at rt in an argon atmosphere. Saturated aq. $NaHCO_3$ solution (10 mL) was added to the reaction mixture and extracted with DCM (3×10 mL). The organic layer was washed with brine (10 mL) and dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate/hexane (2:8) as eluent furnished the ethyl ester as a major product (0.773 g, 65%) and methyl ester as a minor product (0.171 g, 15%). R_f (40% EtOAc/hexane): 0.5 (for ethyl ester) and 0.4 (for methyl ester).

Compound 9:

Molecular formula: $C_{17}H_{20}O_6$

Yield: 65%

IR ($CHCl_3$): 3421, 2986, 2837, 1748, 1741, 1504 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.38 (t, *J*=7.07 Hz, 3H), 2.07 (d, *J*=1.6 Hz, 3H), 2.27 (s, 3H), 3.89 (s, 3H), 4.25-4.45 (m, 3H), 5.57-5.60 (m, 1H), 6.92 (d, *J*=8.0 Hz, 1H), 7.22-7.28 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 10.11, 14.21, 16.38, 55.32, 62.64, 69.09, 81.26, 110.14, 122.72, 123.66, 126.84, 127.64, 129.93, 155.06, 159.11, 171.27, 174.08.

MS (ESI) (m/z): 343 $[M+Na]^+$.

Elemental analysis: Calculated C, 63.74; H, 6.29 %; Found C, 63.94; H, 6.35 %

Compound 10:

Molecular formula: $C_{16}H_{18}O_6$

Yield: 15%

IR ($CHCl_3$): 3421, 2986, 2837, 1752, 1740, 1504 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4) : δ 2.08 (d, *J*=1.8 Hz, 3H), 2.27 (s, 3H), 2.83 (d, *J*= 6.9 Hz, 1H), 3.90 (s, 3H), 3.92 (s, 3H), 5.58-5.60 (m, 1H), 6.92 (d, *J*= 8.2 Hz, 1H), 7.21-7.24 (m, 2H).

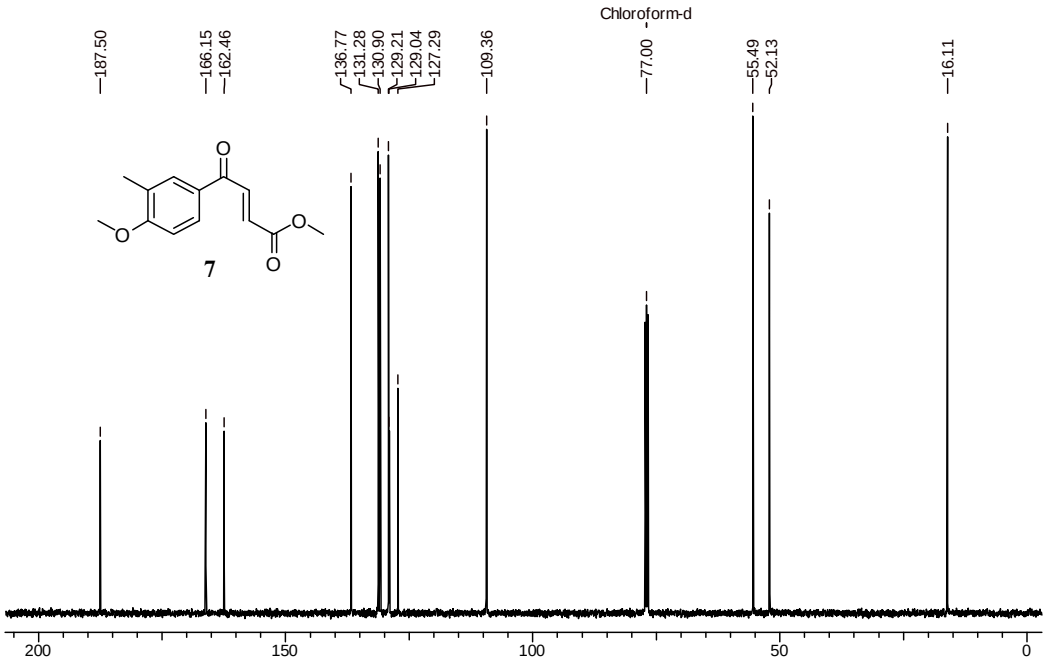
MS (ESI) (m/z): 329 $[M+Na]^+$.

Elemental analysis: Calculated C, 62.74; H, 5.92 %; Found C, 62.83; H, 5.97 %.

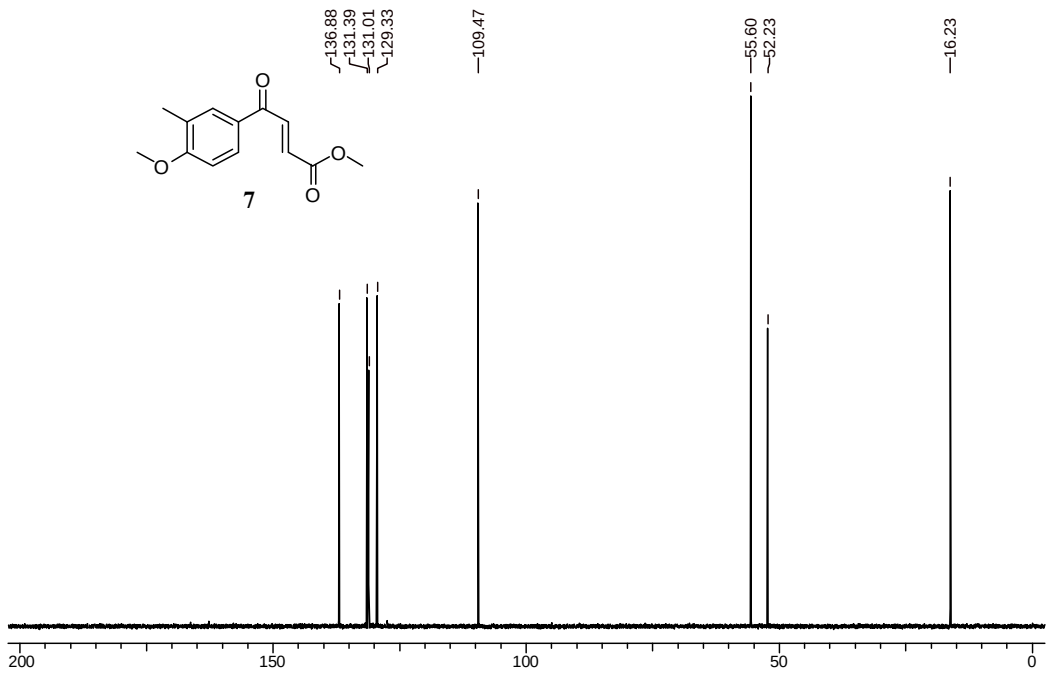
1.3.4. NMR Spectra

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

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

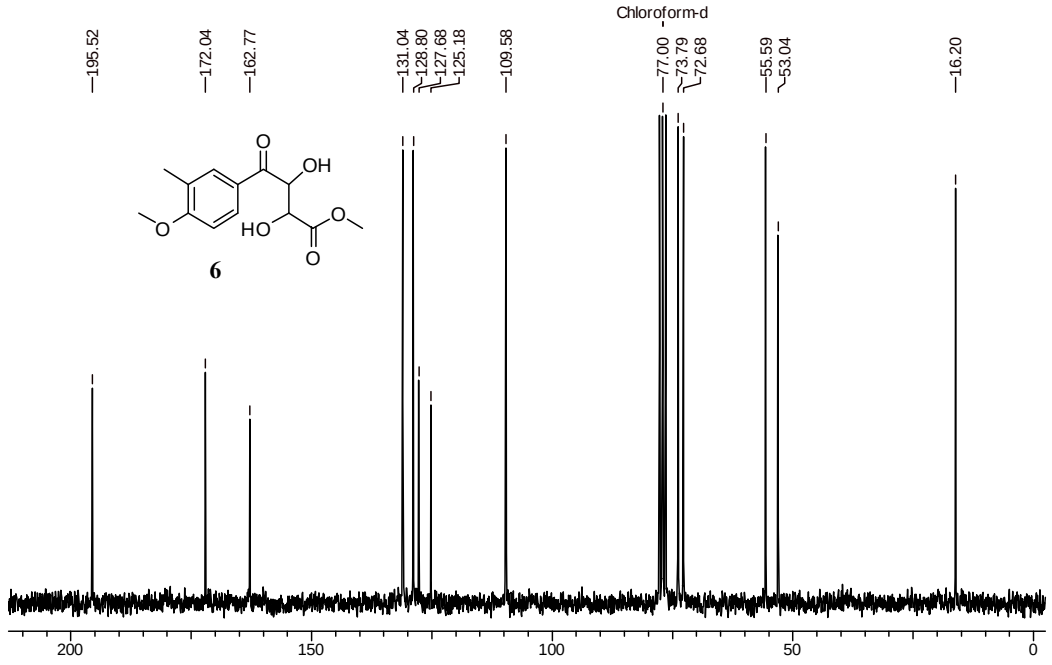


DEPT spectrum of compound **7** ($CDCl_3$, 50 MHz)

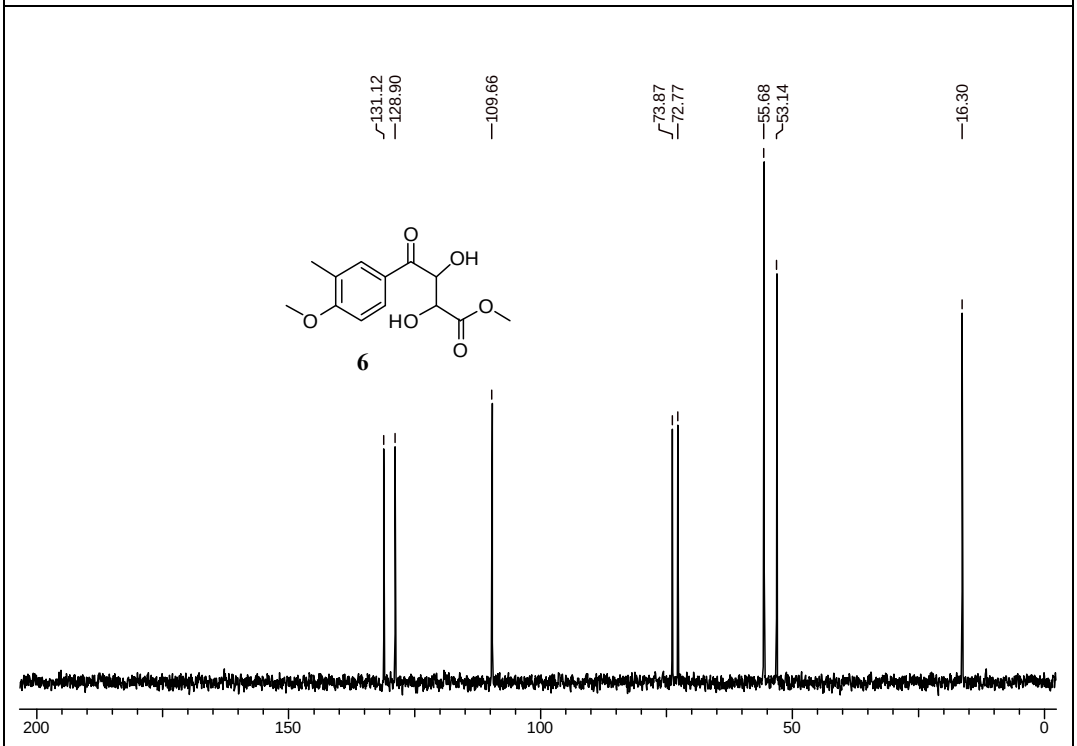


^1H NMR spectrum of compound **6** ($CDCl_3$, 200 MHz)

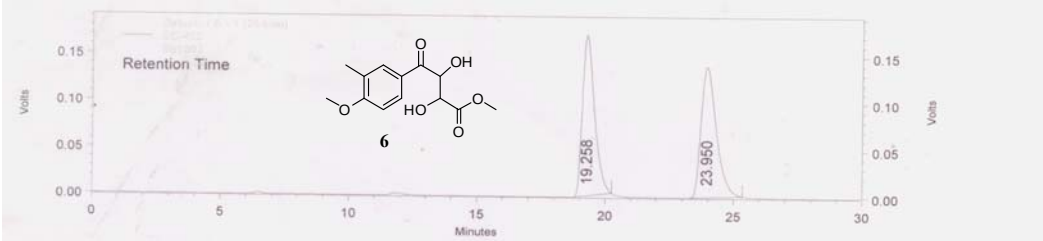
^{13}C NMR spectrum of compound **6** ($CDCl_3$, 50 MHz)



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



HPLC chromatogram of racemic diol **6**

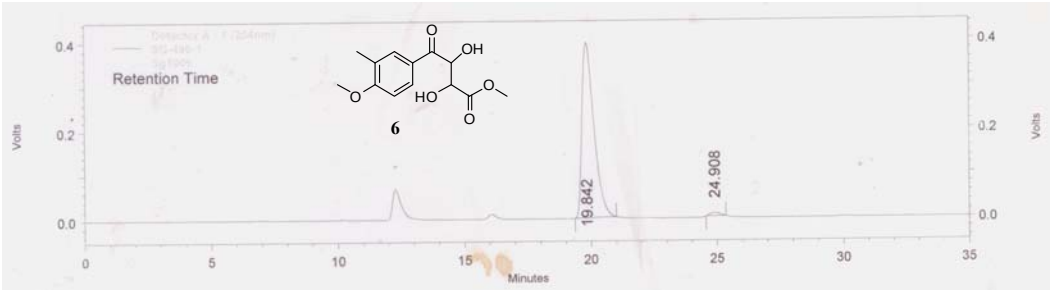


Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	19.258	5642713	49.338
2	23.950	5794194	50.662
Totals		11436907	100.000

Grp Leader : Dr.S. P. CHAVAN
Column :Chiralcel OJ-H (4.6x250mm)
Mobile Phase IPA:Pet Ether (40:60)
Wavelength : 254nm
Flow Rate : 0.5ml/min 43kgf
Sample Con :1mg/1.5ml Inj vol-5ul

HPLC chromatogram of chiral diol **6**



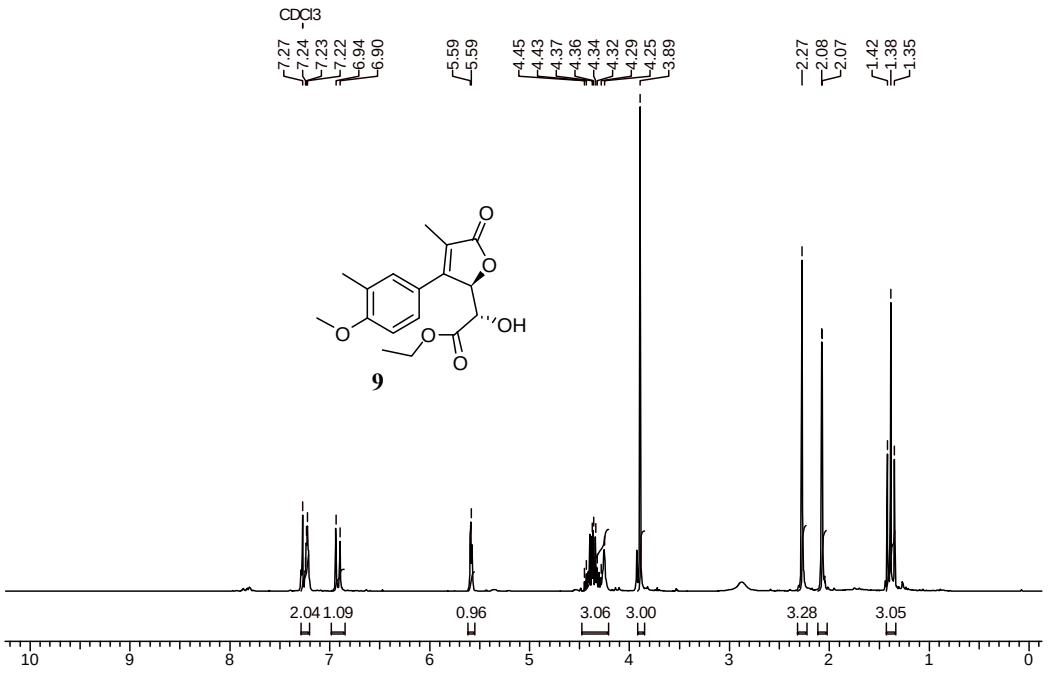
Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	19.842	12993649	98.408
2	24.908	210245	1.592
Totals		13203894	100.000

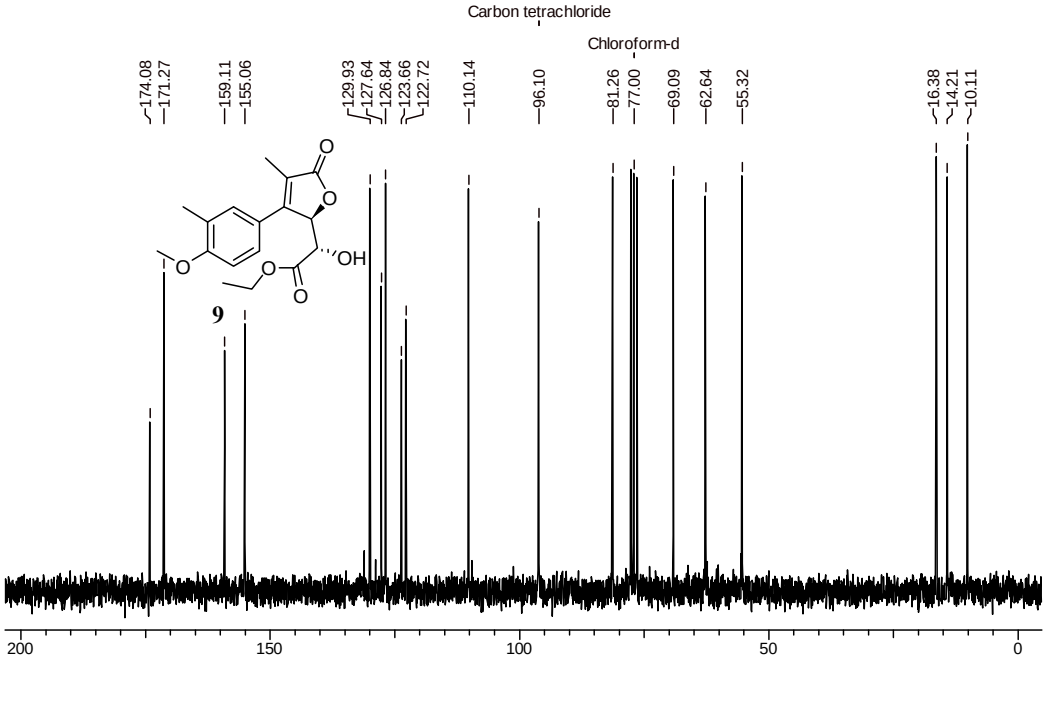
Project Leader :- Dr .S. P. Chavan
Column :-Chiralcel OJ-H (250x4.6mm)
M.P. : IPA:PE:(40:60)
Wavelength :- 254nm
Flow :- 0.5ml/min(390psi)
conc. :- 1.3mg/ 1ml
Injection vol : Inj Vol- 5ul Kunte

%ee = 97%

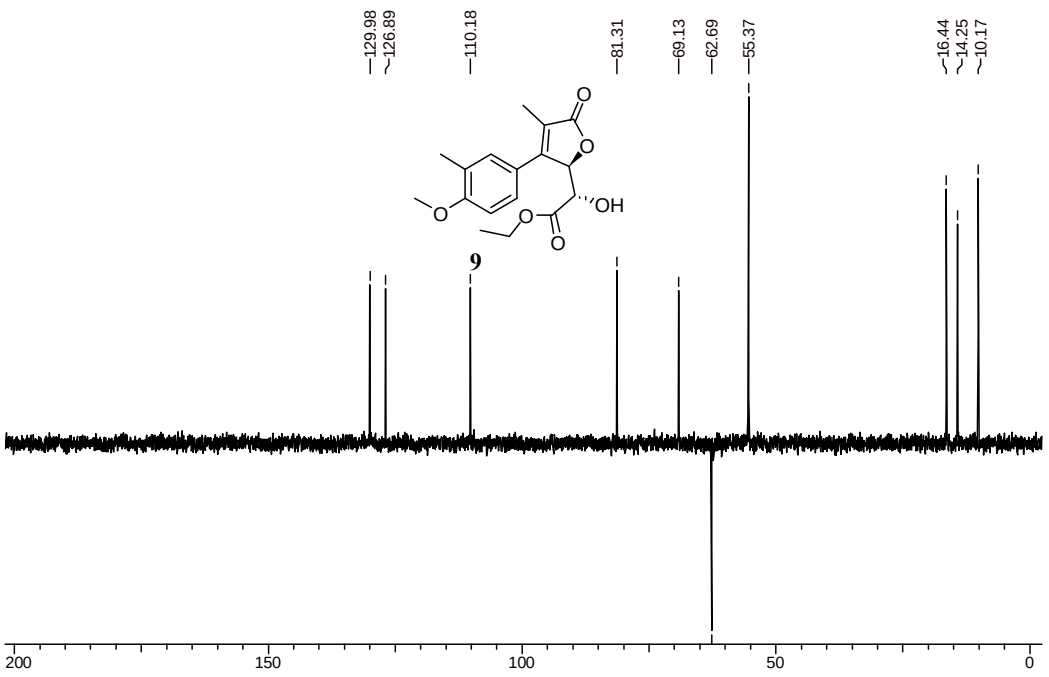
^{1}H NMR spectrum of compound **9** ($CDCl_3$+CCl_4, 200 MHz)



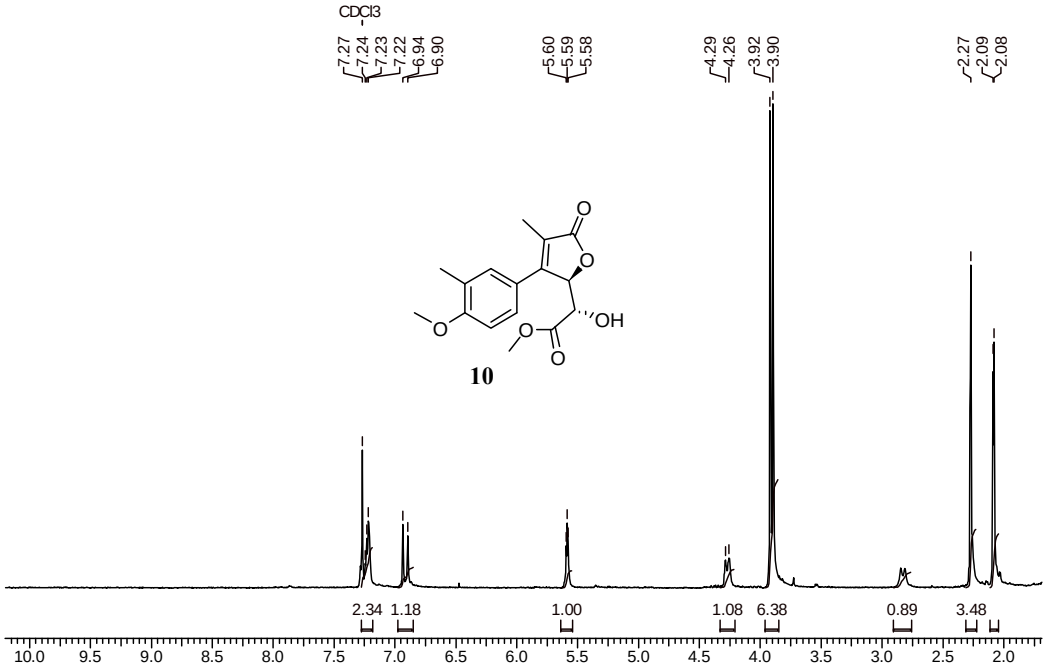
^{13}C NMR spectrum of compound **9** ($CDCl_3$ + CCl_4, 50 MHz)



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



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



1.2.5. References

1. a) Chavan, S. P.; Ravindranathan, T.; Patil, S. S.; Dhondge, V.; Dantale, S. W. *Tetrahedron Lett*. **1996**, *37*, 2629–2630. b) Chavan, S. P.; Ravindranathan, T.; Patil, S. S. *Tetrahedron* **1999**, *40*, 4733–4734. c) Chavan, S. P.; Thakkar, M.; Kharul, R. K.; Pathak, A. B.; Bhosekar, G. V.; Bhadbhade, M. M. *Tetrahedron* **2005**, *61*, 3873–3879. d) Chavan, S. P.; Kharul, R. K.; Kale, R. R.; Khobragade, D. A. *Tetrahedron* **2003**, *59*, 2737–2741. () Chavan, S. P.; Dhawane, A. N.; Kalkote, U. R. *Tetrahedron Lett.* **2007**, *48*, 965-966. () Chavan, S. P.; Dhawane, A. N.; Kalkote, U. R. *Synthesis* **2007**, 3827-3830. g) Chavan, S. P.; Garai, S.; Kalkote, U. R. *Tetrahedron* **2012**, *68*, 8509.
2. a) Kameo, K.; Asami, Y.; Ogawa, K.; Matsunaga, T.; Saito, S.; Tomisawa, K.; Sota, K. *Chem. Pharm. Bull.* **1989**, *37*, 1260. b) Aprahamian, I.; Preda, D. V.; Bancu, M.; Belanger, A. P.; Sheradsky, T.; Scott, L. T.; Rabinovitz, M. *J. Org. Chem.* **2005**, *71*, 290.
3. a) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483 and references therein.
4. Enantiomeric excess (*% ee*) was determined by Chiral HPLC analysis (Chiralcel OJ-H (250×4.6 mm), mobile phase: isopropanol: pet ether= 40:60, wave length= 254 nm, flow rate= 0.5 ml/min).

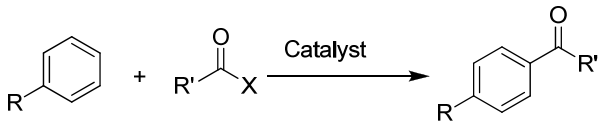
Chapter 1: Diastereoselective total synthesis of (±)-heritol and (±)-heritonin, attempted synthesis towards vallapin and Friedel-Crafts acylation reaction using esters

Section 4

Unprecedented, mild, efficient and simple Friedel-Crafts acylation reaction using esters

1.4.1 Introduction

The **Friedel–Crafts reaction** was developed by Charles Friedel and James Crafts in 1877 to attach substituents to an aromatic ring. There are two main types of Friedel–Crafts reactions: alkylation reactions and acylation reactions, both proceeding by electrophilic aromatic substitution. The general reaction scheme is shown below (Scheme 1).



Scheme 1. The general Frieldel-Carfts reaction.

Friedel–Crafts alkylation involves the alkylation of an aromatic ring with an alkyl halide using a strong Lewis acid reagent. Friedel–Crafts acylation is the acylation of aromatic rings with acetyl chloride using a strong Lewis acid reagent. Friedel–Crafts acylation is also possible with acid anhydrides. This reaction has several advantages over the alkylation reaction. Due to the electron-withdrawing effect of the carbonyl group, the ketone product is always less reactive than the original molecule, so multiple acylations do not occur.

Inter- and intramolecular Friedel-Crafts acylation of aromatic ring is one of the most fundamental, important and useful C-C bond forming reactions in organic and industrial chemistry for the synthesis of aromatic ketones and important synthetic intermediates.[1] Conventionally unstable and sensitive acylating reagents such as acid chlorides,[2] and anhydrides,[3] are employed as acylating agents with suitable Lewis acid following appropriate protocol. Acids[4] also have been shown to undergo Friedel-Crafts acylation reaction under harsh conditions. Hence, development of a stable, ready to use and easy to handle reagent is very important for Friedel-Crafts acylation reactions.

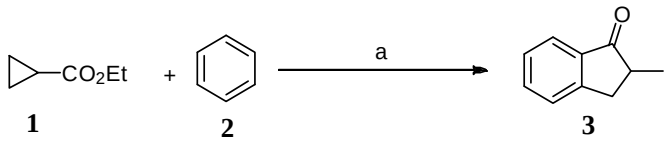
Esters are more stable, less expensive, easily purified, and easier to handle than conventional acylating agents. Hence, esters would be ideal choice if they could substitute the conventional acylating agents but because of their low reactivity, their utilization as acylating agents in Friedel-Crafts reaction remains a challenging problem.

1.4.2 Ester as an acylating agent: A review

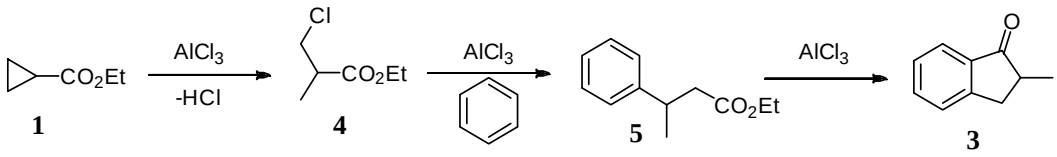
A short descriptive presentation of the work reported by other groups is being presented to give a better comparative view of the different methods for Friedel-Crafts acylation reaction of esters. In literature, there are only few isolated reports available on the Frieldel-Crafts acylation reaction of esters.

Pinnick's Approach[5] *(J. Org. Chem.***1981**, *46*, 3758)

Pinnick *et al.* have reported an intramolecular Friedel-Crafts acylation reaction of benzene with ethyl cyclopropanecarboxylate **1** in the presence of anhydrous $AlCl_3$ to furnish 2-methyl-1-indanone **3** in excellent yield. The plausible reaction mechanism as proposed by author is ring opening of the cyclopropane ring to yield the chloro ester **4** which then alkylates with benzene and gives **5**. Further intramolecular acylation of ester **5** led to the indanone product **3** (Scheme 2).



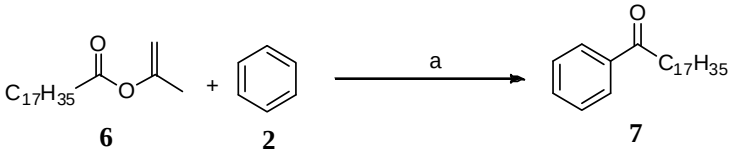
Plausible mechanism:



Scheme 2. Reagents and conditions: *a) $AlCl_3$, heat, 93%.*

Rothman's Approach[6] (*J. Org. Chem.* **1970**, *35*, 2351)

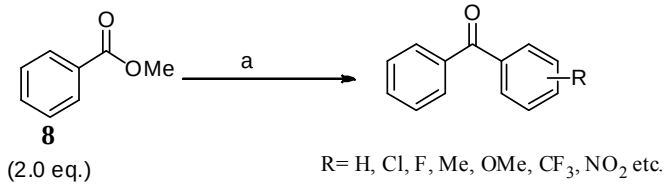
Rothman *et al.* have reported a very simple method for Friedel-Crafts acylation reaction of benzene **2** with isopropenyl ester **6** (enol ester derivative) in presence of anhydrous $AlCl_3$ to yield stearophenone **7** in good yield (Scheme 3).



Scheme 3. Reagents and conditions: *a) $AlCl_3$.*

Olah's Approach[7] **(***Tetrahedron* **2000**, *56*, 7199)

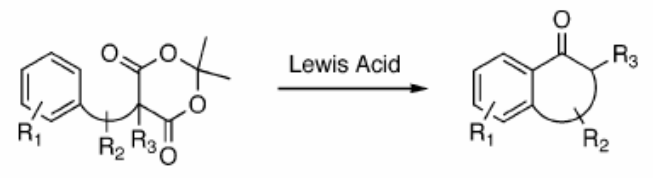
Olah *et al.* have reported intermolecular Friedel-Crafts acylation reaction of different aromatic compounds with methyl benzoate **8** in the presence of stiochiometric amount of triflic acid in good yields (70-93%) (Scheme 4).



Scheme 4. Reagents and conditions: *a) CF_3SO_3H (5.0 eq.), Ph-R, 85 °C, 0.5-8 h, 70-93%.*

Fillion's Approach[8] *(J. Org. Chem.* **2005**, *70*, 1316)

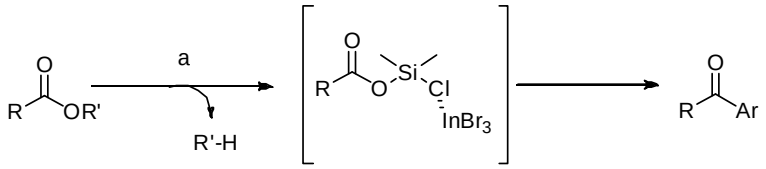
Fillion *et al.* reported the intramolecular Friedel-Crafts acylation reaction of different aromatic compounds with Meldrum's acid derivatives. The advantages of these derivatives are that they are easily prepared, functionalized, handled, and purified and can be readily cyclised in the presence of metal trifluoromethanesulfonates as catalysts in nitromethane solvent under reflux conditions with good yield (Scheme 5).



Scheme 5

Baba's Approach[9] *(J. Org. Chem.* **2008**, *73*, 9465)

Recently Baba *et al.* reported indium tribromide catalysed inter and intramolecular Friedel-Crafts acylation reaction using ester but there are some drawbacks in their protocol such as their utility is restricted to a narrow range of substrates and it involves utilisation of very costly reagents like dimethylchlorosilane and indium tribromide. The key intermediate $RCOOSi(Cl)Me_2$ is generated during the reaction from alkoxy esters with the evolution of the corresponding alkanes (Scheme 6).



Scheme 6. Reagents and conditions: *a) Cat. $InBr_3$, Me_2HSiCl, ArH.*

1.4.3 Results and discussion

Since esters are more stable, less expensive, easily purified, and easier to handle than conventional acylating agents, esters would be ideal choice if they could substitute the conventional acylating agents. So, by properly choosing the activating group which can activate the ester for the Friedel-Crafts acylation reaction it can be used as acylating agent.

In literature there are some isolated reports on the Friedel-Crafts acylation reaction of α-acetoxybutanendioic anhydride **11a**. Pevarello *et al.*[10] and Mi *et al.*[11] reported Friedel-Crafts acylation of **11a** with 1, 2-dichlorobenzene and benzene respectively at reflux conditions, where anhydride cabonyl group participated in acylation reaction and formed the corresponding α-hydroxy keto acid **9**. Interestingly, when **11a** was treated with different aromatic compounds it was pleasing to note that the acylation reaction goes through the ester carbonyl group in very short time and at room temperature where anhydride group acts as an activating group (Figure 1) and also it was observed

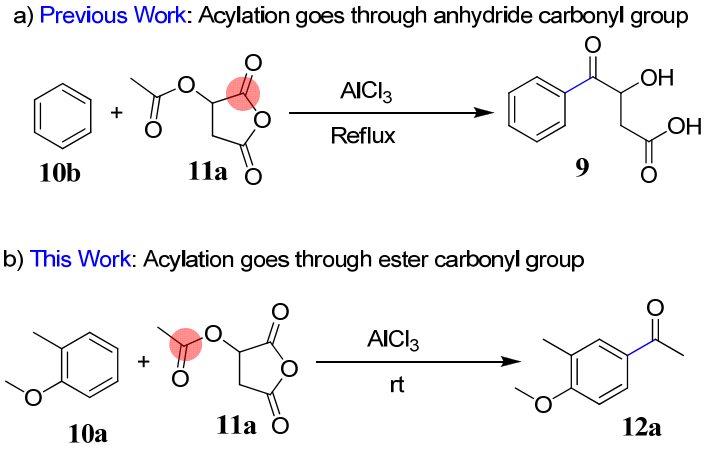


Figure 1. Friedel-Crafts acylation reaction of α-acetoxybutanedioic anhydride.

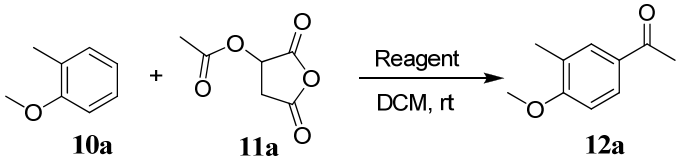
that tartaric anhydride, methyl or ethyl ester of malic acid and tartaric acid also act as activating groups. It is worth noting that these alcohols which activate the esters in Friedel-Crafts acylation reaction are commercially readily available, stable, inexpensive and can be easily prepared in the laboratory.

In literature there is no report of direct Friedel-Crafts acylation reaction using such activated esters in the presence of $AlCl_3$. Herein, the facile Friedel-Crafts acylation reaction of esters that occur at room temperature in very short time, in good yields and with high regio-selectivity is described.

Thus, as a test case the intermolecular acylation of electron rich 2-methylanisole **10a** with 2, 5-dioxotetrahydrofuran-3-yl acetate **11a**[12] was studied in search for effective reagent and reaction conditions. Accordingly, Friedel- Crafts acylation of **10a** with **11a** in the presence of $AlCl_3$ at room temperature furnished aromatic ketone **12a** in 74% yield. When $BF_3.OEt_2$[13] and triflic acid[14] were used as reagents the yield was 60% and 50% respectively (Table 1, entries 2 and 3). Attempts to improve yields with other Lewis acids failed (Table 1).

Next, the different reagents, which have been previously reported to catalyze the Friedel-Crafts acylation reaction of activated aromatic compounds with acid chloride,

Table 1. Effect of reagents on the acylation of 2-methyl anisole.



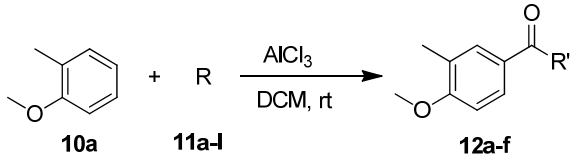
10a **11a** **12a**

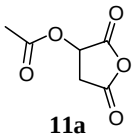
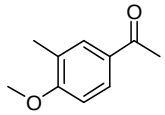
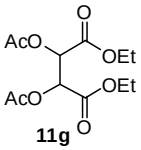
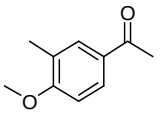
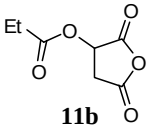
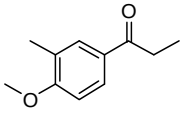
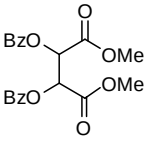
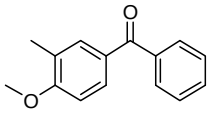
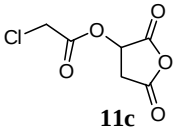
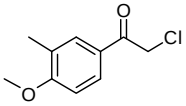
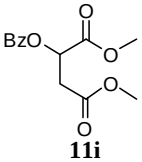
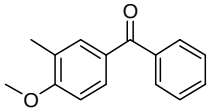
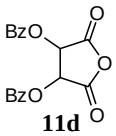
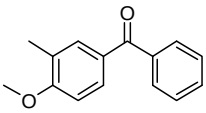
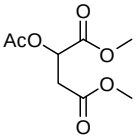
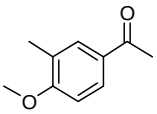
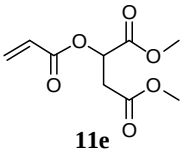
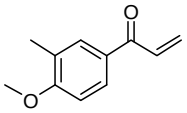
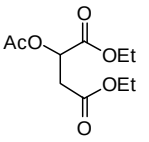
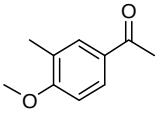
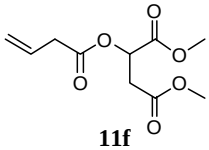
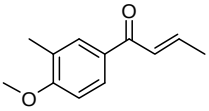
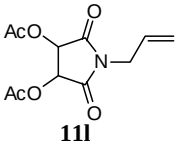
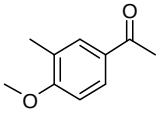
Entry	Reagent	Time	Yield (%)
1	$AlCl_3$	10 min	74
2	$BF_3.OEt_2$	12 hrs	60
3	CF_3SO_3H	20 hrs	50
4	$ZnCl_2$	overnight	SM[a] was recovered
5	ZnO	overnight	SM was recovered
6	$FeCl_3$	2 hrs	SM decomposed

[a] SM=Starting material

anhydride and acids were examined. But when the Friedel-Crafts acylation of activated esters were tried, surprisingly starting material was recovered when $ZnCl_2$ and ZnO[15] were used as reagents while the starting material decomposed when $FeCl_3$[16] was used as reagent (entries 4-6).

Table 2. Acylation of 2-methyl anisole with different acylating agents.



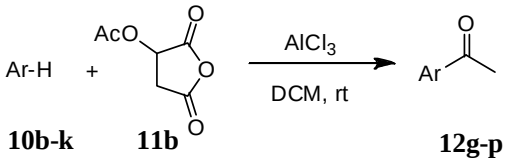
SN	R[a]	Product	SN	X	Product
1	 **11a**	 **12a, 10 min, 74%**	7	 **11g**	 **12a, 15 min, 74%**
2	 **11b**	 **12b, 10 min, 72%**	8	 **11h**	 **12d, 10 min, 75%**
3	 **11c**	 **12c, 6 h, 49%**	9	 **11i**	 **12d, 10 min, 75%**
4	 **11d**	 **12d, 10 min, 74%**	10	 **11j**	 **12a, 20 min, 70%**
5	 **11e**	 **12e, overnight, 74%**	11	 **11k**	 **12a, 20 min, 69%**
6	 **11f**	 **12f[b], 12 h, 70%**	12	 **11l**	 **12a, 2 h, 70%**

[a]Some esters were prepared by following literature procedure while others are commercially available. [b]Only isomerised product was isolated

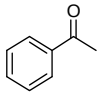
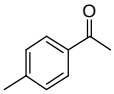
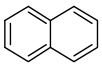
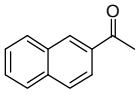
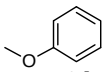
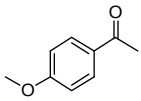
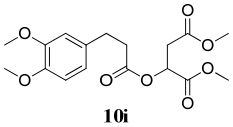
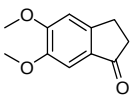
After establishing the optimum reaction conditions, in order to examine the scope of this reaction, the Friedel-Crafts acylation reactions of various types of esters were studied and the results are summarized in Table 2.

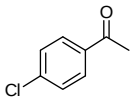
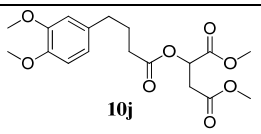
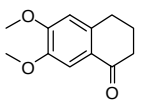
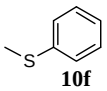
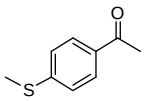
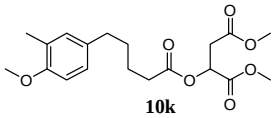
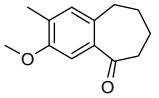
The influence of activating group and the side chain of the ester on the acylation efficiency were examined using $AlCl_3$ with 2-methylanisole **10a** as a model substrate at room temperature as the standard reaction conditions (Table 2). Increase in the number of carbons in the acid part of ester *i.e.* acetate ester **11a**, propionate ester **11b**, 2-chloroacetate ester **11c,** benzoate ester **11d**, acryloyl ester **11e** and allyl ester **11f** had no adverse effect on the efficiency of Friedel-Crafts acylation reactions, furnishing corresponding ketones in similar yields (72-74%). The activating group was also varied to study the effect on the efficiency of the reaction. Accordingly, when the activating group was changed from malic anhydride to ethyl or methyl ester of malic acid and tartaric acid (**11g-11k**) there was hardly any effect on the yield and reaction time (70-75%, 10-20 min) and also acylation smoothly proceeded with ester when imide **11l** was the activating group (Table 2).

Table 3. Acylation of different aromatic compounds with same acylating agent:



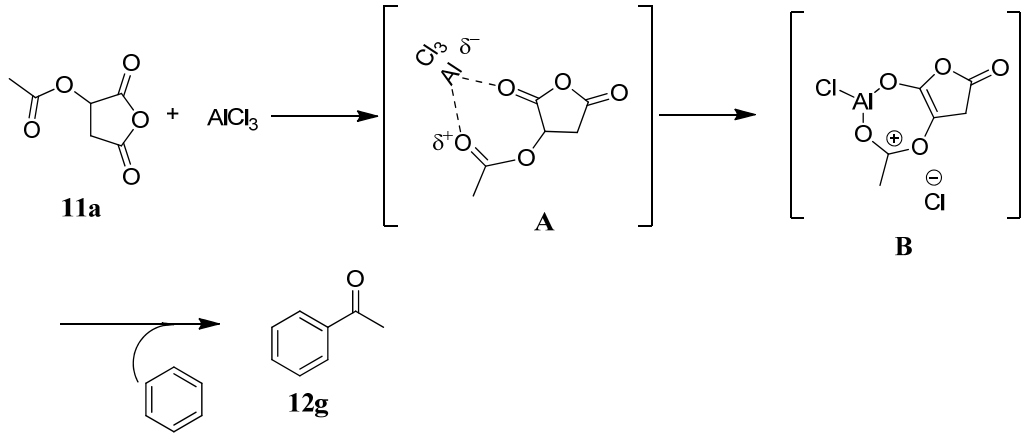
10b-k **11b** **12g-p**

SN	Ar-H	Product	SN	Ar-H	Product
1	 **10b**	 **12g, overnight, 49%**	6	 **10g**	 **12l, 6 h, 40%**
2	 **10c**	 **12h, 6 h, 70%**	7	 **10h**	 **12m, overnight, 55%**
3	 **10d**	 **12i, 15 min, 70%**	8	 **10i**	 **12n, 2 h, 70%**

4	 **10e**	 **12j, 6 h, 60%**	9	 **10j**	 **12o, 2 h, 70%**
5	 **10f**	 **12k, overnight, 69%**	10	 **10k**	 **12p, 30 min, 65%**

Having established the reactivity of variety of esters with aromatic ring in the presence of $AlCl_3$, this protocol was also be applied for inter- and intramolecular acylation of different activated and deactivated aromatic rings. Different aromatic rings (**10b-f**) gave corresponding ketone in very short time and in good yields at room temperature (Table 3, entries 1-5). Heterocyclic compound **10g** and polycyclic compound **10h** also participated in the Friedel-Crafts acylation reaction and gave moderate yields (entries 6-7). The efficiency and simple reaction conditions led us to investigate intramolecular Friedel-Crafts acylation reactions. This methodology was equally efficient in the preparation of 1-tetralone, 1-indanone and seven membered ring as well (entries 8-10).

A plausible reaction pathway for the inter- and intramolecular Friedel-Crafts acylation reaction of ester is illustrated in Scheme 7. Activation of carbonyl group of ester occurs by chelation of the Lewis acid with the adjacent carbonyl group of the



Scheme 7. Proposed mechanism for the $AlCl_3$ mediated Friedel-Crafts acylation of ester.

(intermediate **A)** to form seven membered ring. Due to the chelation it forms ionic intermediate **B** in which carbonyl carbon bears positive charge and gets activated and participates in the Friedel-Crafts acylation reaction (Scheme 7).

Comprehensive theoretical calculations were performed to rationalize these unusual and unexpected experimental observations and presumptions regarding formation of activated adduct, which result in chemoselective acylation. Density functional theory (DFT) and Fukui function analysis has emerged as a standard tool for investigation of pathways of organic reactions. Fukui function[17] are known as reactivity indices, and they can give information about the atom in a molecule to either lose or accept electron. In other words, nucleophilicity or electrophilicity of an atom can be estimated from their atom condensed Fukui function. The proposed adduct (Figure 2) was first optimized in DFT-B3LYP method in 6-31G^{*++} basis set with PCM model to incorporate the solvent effect, preceded by calculation of Fukui functions[18].

From atom condensed Fukui function of the activated adduct we observed that electrophilic Fukui function ($f_a^{+)}$ at position C-5 has the highest index, depicting that

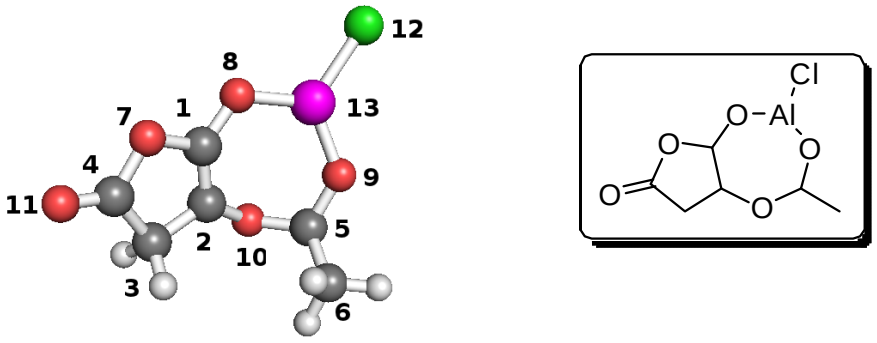


Figure 2. Activated adduct for the acylation reaction.

Table 4. Presents the condensed eletrophilic Fukui functional (f_a^+) for the adduct.

Carbon No	C1	C2	C3	C4	C5	C6
F_a^+	0.0247	0.019	0.009	0.009	0.242	0.053

ester carbonyl carbon center is more prone to act as an electrophilic center than anhydride carbonyl carbon, which possesses a smaller value (Table 4).

The presumptions are further confirmed by transition state calculations[19]. It has been observed that transition state (TS1) for the unexpected ester carbonyl centered product is 36.67 kcal/mole more stable than that (TS2) of the expected anhydride carbonyl centered product, which results in the preferential formation of the former, confirming the inference from the Fukui function analysis (Figure 4).

a) b)

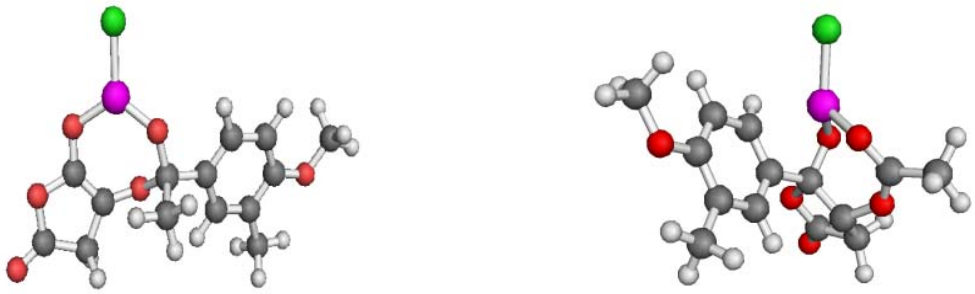


Figure 3. a) Optimized transition state for the unexpected product (TS1); b) Optimized transition state for the expected product (TS2).

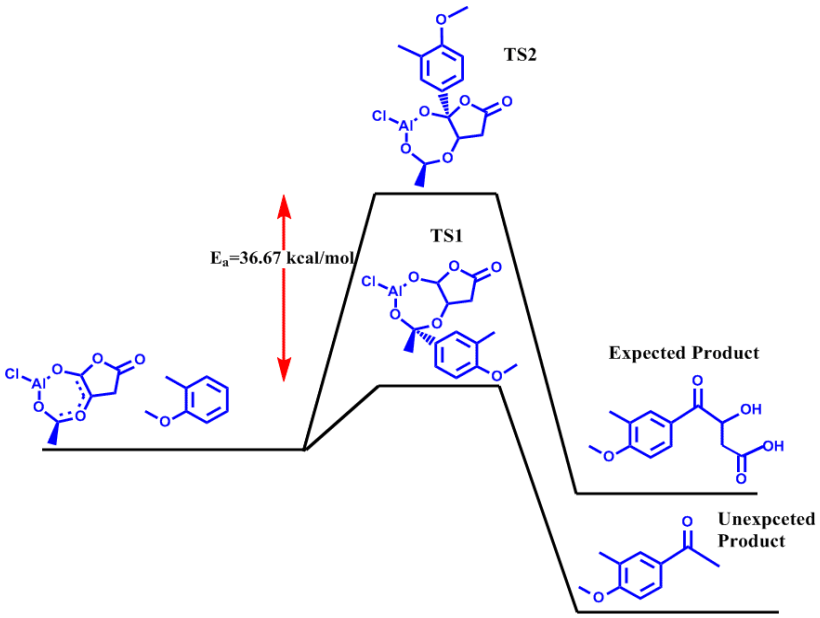
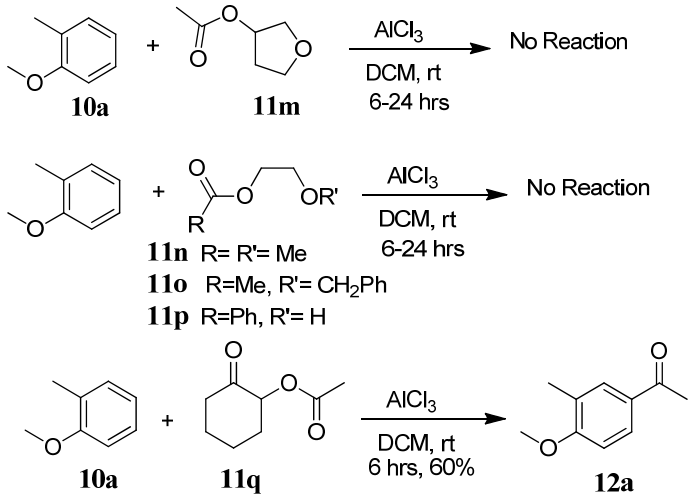


Figure 4. Energy profile diagram for unexpected and expected product.

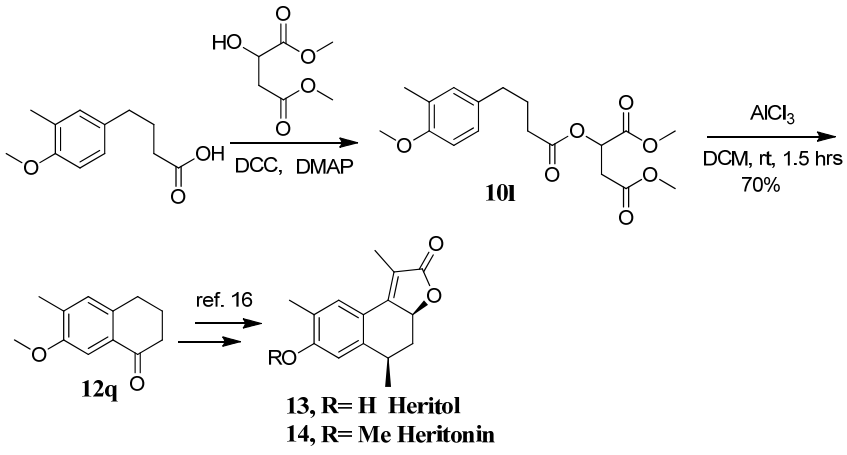
To gain mechanistic insight, further experiments were carried out. Tetrahydrofuran acetate ester **11m** lacking a carbonyl group was synthesized. Accordingly when the

substrate **11m** was subjected to reaction with **10a** under the optimized reaction conditions, starting materials were recovered even after stirring for 24 hours at room



Scheme 8. Studies on the Friedel-Crafts acylation reaction pathway.

temperature as well as under reflux conditions. In order to ascertain whether the presence of only the oxygen of lactone or ester activates the ester, compounds **11n-p** were synthesized. However when substrates **11n-p** were subjected to the optimized reaction conditions, all cases resulted in the recovery of the starting materials. The activated ester **11q** bearing a ketone was synthesized**,** which also underwent facile Friedel-Crafts acylation with aromatic compound **12a** (Scheme 8).



Scheme 9. Direct synthesis of 1-tetralone intermediate **12q** of heritol and heritonin.

Advantages of this acylation methodology were demonstrated by the synthesis of 1-tetralone intermediate **12q**[20] of heritol and heritonin from highly stable ester **10l** (Scheme 9). The same transformation from acid was earlier reported by this group by using trifluoroacetic anhydride and CF_3CO_2H.

1.4.4. Conclusion

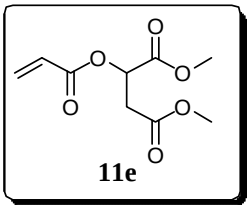
In conclusion, a simple, efficient, new and mild Friedel-Crafts acylation reaction using various aliphatic and aromatic esters was developed and the detailed mechanistic pathway was studied by DFT calculation and supported with experimental evidence. This methodology was also extended to intramolecular Friedel-Crafts acylation reaction to synthesize 1-indanone, 1-tetralone and seven membered ring in good yields. The advantages of this methodology are: (i) very simple reaction conditions and simple reagents, (ii) the use of very stable esters which can be stored at room temperature for a long period of time, (iii) the activating groups are very simple, commercially readily available, cheap and can also be easily prepared in the laboratory, (iv) the reaction proceeds with equal efficiency in inter- and intramolecular Friedel-Crafts acylation reactions, (v) high yield, selectivity, (vi) applicable for both aliphatic as well as aromatic esters, (vii) it can be easily scaled up. It is believed that, this protocol owing to its robustness, simplicity and efficiency should find widespread usage amongst practicing synthetic organic chemists.

1.4.5. Experimental

General procedure for preparation of esters (A):

To a cold (0 ^{0}C), magnetically stirred solution of acid (1 molar equiv), alcohol (1.5 molar equiv) and 4-dimethylaminopyridine (0.8 molar equiv) in anhydrous DCM, was added dicyclohexylcarbodiimide (1.2 molar equiv) over 5 min period under nitrogen. After a further 5 min at 0 ^{0}C, the reaction mixture was stirred at room temperature until the completion of reaction. The dicyclohexylurea that had precipitated was removed by filtration. The filtrate was washed with ice cooled 10% aqueous HCl followed by saturated solution of sodium bicarbonate. The aqueous layer was extracted with DCM. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was purified by flash silica gel column chromatography using pet ether/ethyl acetate as eluent.

Dimethyl 2-(acryloyloxy)succinate (11e)


11e

Following the general procedure **A**, acrylic acid (0.5 g, 7 mmol), dimethyl 2-hydroxysuccinate (1.7 g, 10.4 mmol) and dimethylaminopyridine (0.683 g, 5.6 mmol) in CH_2Cl_2 (5 mL) were treated with dicyclohexylcarbodiimide (1.734 g, 8.4 mmol) at 0 ^{0}C and stirred at room temperature for 5 h. Purification by flash column chromatography (silica gel, 8:2 pet ether/ethyl acetate) afforded the colorless oily liquid compound (1.23 g, 82% yield). R_f (30% Ethyl acetate/pet ether): 0.6.

Molecular formula: $C_9H_{12}O_6$

Yield: 82%

IR ($CHCl_3$): 2957, 2925, 1736, 1637 cm^{-1}.

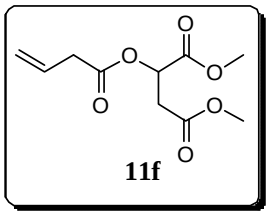
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.93 (d, *J*= 6 Hz, 2H), 3.73 (s, 3H), 3.79 (s, 3H), 5.54 (t, *J*=6 Hz, 1H), 5.92 (dd, *J*=10, 2 Hz, 1H), 6.17 (dd, *J*=16, 10 Hz, 1H), 6.49 (dd, *J*=16, 2 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 35.9, 52.1, 52.6, 68.2, 127.3, 132.2, 164.7, 169.0, 169.3.

MS (ESI) (m/z): 239 $[M+Na]^+$.

HRMS (ESI): Calculated 239.05261 $(M+Na)^+$; Found 239.05252

Dimethyl 2-(but-3-enoyloxy)succinate (11f)


11f

Following the general procedure **A**, vinylacetic acid (2 g, 19.2 mmol), dimethyl 2-hydroxysuccinate (4.67 g, 28.8 mmol) and dimethylaminopyridine (1.874 g, 15.3 mmol) in CH_2Cl_2 (20 mL) were treated with dicyclohexylcarbodiimide (4.74 g, 23 mmol) at 0 ^{0}C and stirred overnight at room temperature. Purification by flash column chromatography (silica gel, 8:2 pet ether/ethyl acetate) afforded the colorless oily liquid compound (3.36 g, 76% yield). R_f (30% Ethyl acetate/pet ether): 0.7.

Molecular formula: $C_{10}H_{14}O_6$

Yield: 76%

IR ($CHCl_3$): 2957, 1745, 1643 cm^{-1}.

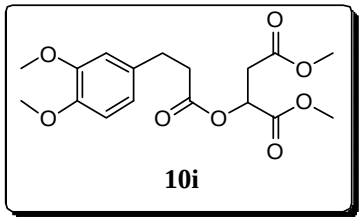
^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): δ 2.89 (d, *J*=6.4 Hz, 2H), 3.16-3.19 (m, 2H), 3.73 (s, 3H), 3.78 (s, 3H), 5.19-5.23 (m, 2H), 5.47 (t, *J*=6.1 Hz, 1H), 5.87-5.95 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 35.8, 38.4, 51.9, 52.5, 68.2, 118.8, 129.4, 168.9, 169.2, 170.0.

MS (ESI) (m/z): 253 $[M+Na]^+$.

HRMS (ESI): Calculated 253.06826 $(M+Na)^+$; Found 253.06814.

Dimethyl 2-((3-(3,4-dimethoxyphenyl)propanoyl)oxy)succinate (10i)



10i

Following the general procedure **A**, 3-(3,4-dimethoxyphenyl)propanoic acid (0.1 g, 0.476 mmol), dimethyl 2-hydroxysuccinate (0.116 g, 0.714 mmol) and dimethylaminopyridine (0.046 g, 0.38 mmol) in CH_2Cl_2 (5 mL) were treated with dicyclohexylcarbodiimide (0.118 g, 0.571 mmol) at 0 ^{0}C and stirred overnight at room temperature. Purification by flash column chromatography (silica gel, 7:3 pet ether/ethyl acetate) afforded the colorless oily liquid compound (143 mg, 85% yield). R_f (50% Ethyl acetate/pet ether): 0.6.

Molecular formula: $C_{17}H_{22}O_8$

Yield: 85%

IR ($CHCl_3$): 2930, 2850, 1746, 1590, 1517 cm^{-1}.

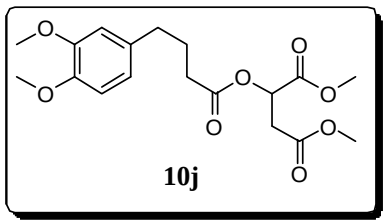
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4) : δ 2.64-2.73 (m, 2H), 2.85-2.96 (m, 4H), 3.70 (s, 3H), 3.76 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 5.47 (t, *J*=6 Hz, 1H), 6.70-6.80 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 30.2, 35.5, 35.7, 52.0, 52.5, 55.6, 55.7, 68.0, 111.2, 111.6, 120.0, 132.7, 147.5, 148.8, 169.1, 169.3, 171.5.

MS (ESI) (m/z): 377 $[M+Na]^+$.

HRMS (ESI): Calculated 377.12069 $(M+Na)^+$; Found 377.12029.

Dimethyl 2-((4-(3,4-dimethoxyphenyl)butanoyl)oxy)succinate (10j)


10j

Following the general procedure, 4-(3,4-dimethoxyphenyl)butanoic acid (0.2 g, 0.89 mmol), dimethyl 2-hydroxysuccinate (0.216 g, 1.335 mmol) and dimethylaminopyridine (0.087 g, 0.38 mmol) in CH_2Cl_2 (5 mL) were treated with dicyclohexylcarbodiimide (0.220 g, 1.07 mmol) at 0 ^{0}C and stirred at room temperature for 3 h. Purification by flash column chromatography (silica gel, 6:4 pet ether/ethyl acetate) afforded the colorless oily liquid compound (213 mg, 65% yield). R_f (50% Ethyl acetate/pet ether): 0.5.

Molecular formula: $C_{18}H_{24}O_8$

Yield: 65%

IR ($CHCl_3$): 2953, 2853, 1746, 1612, 1506 cm^{-1}.

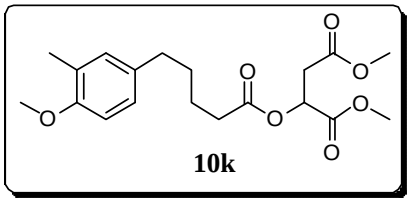
^{1}H NMR (500 MHz, $CDCl_3$+CCl_4) : δ 1.94-1.98 (m, 2H), 2.36-2.43 (m, 2H), 2.62 (t, *J*=7.5 Hz, 2H), 2.88 (d, *J*=6 Hz, 2H), 3.72 (s, 3H), 3.79 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 5.48 (t, *J*=6 Hz, 1H), 6.69-6.71 (m, 2H), 6.78 (d, *J*=8.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 26.5, 32.9, 34.4, 35.8, 51.9, 52.4, 55.7, 55.8, 67.9, 111.3, 111.9, 120.3, 133.8, 147.3, 148.9, 169.1, 169.2, 172.1.

MS (ESI) (m/z): 391 $[M+Na]^+$.

HRMS (ESI): Calculated 391.13634 $(M+Na)^+$; Found 391.13630.

Dimethyl 2-((5-(4-methoxy-3-methylphenyl)pentyl)oxy)succinate (10k):


10k

Following the general procedure, 5-(3,4-dimethoxyphenyl)pentanoic acid (0.3 g, 1.27 mmol), dimethyl 2-hydroxysuccinate (0.310 g, 2 mmol) and dimethylaminopyridine (1.24 g, 1 mmol) in CH_2Cl_2 (5 mL) were treated with dicyclohexylcarbodiimide (0.314 g, 1.5 mmol) at 0 ^{0}C and stirred at room temperature

for 3 h. Purification by flash column chromatography (silica gel, 7:3 pet ether/ethyl acetate) afforded the colorless oily liquid compound (381 mg, 79% yield). R_f (30% Ethyl acetate/pet ether): 0.5.

Molecular formula: $C_{19}H_{26}O_7$

Yield: 79%

IR ($CHCl_3$): 2950, 2857, 1745, 1610 cm^{-1}

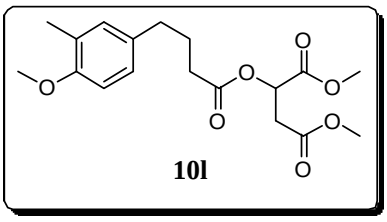
^{1}H NMR (400 MHz, $CDCl_3$+CCl_4) : δ 1.60-1.70 (m, 4H), 2.20 (s, 3H), 2.20-2.44 (m, 2H), 2.54 (t, *J*=7.5 Hz, 2H), 2.88 (d, *J*=6.2 Hz, 2H), 3.71 (s, 3H), 3.77 (s, 3H), 3.81(s, 3H), 5.47 (t, *J*=6.2 Hz, 1H), 6.72 (d, *J*=8.8 Hz, 1H), 6.94 (d, *J*=6 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 16.2, 24.3, 30.9, 33.6, 34.5, 35.8, 52.0, 52.5, 55.2, 67.9, 109.7, 126.2, 130.7, 133.6, 155.8, 169.2, 169.3, 172.3.

MS (ESI) (m/z): 389 $[M+Na]^+$.

HRMS (ESI): Calculated 389.15707 $(M+Na)^+$; Found 389.15719.

Dimethyl 2-((4-(4-methoxy-3-methylphenyl)butaNo.yl)oxy)succinate (10l)



10l

Following the general procedure, 4-(4-methoxy-3-methylphenyl)butanoic acid (0.14 g, 0.7 mmol), dimethyl 2-hydroxysuccinate (0.17 g, 1.05 mmol) and dimethylaminopyridine (0.068 g, 0.56 mmol) in CH_2Cl_2 (5 mL) were treated with dicyclohexylcarbodiimide (0.173 g, 0.84 mmol) at 0 ^{0}C and stirred at room temperature for 3 h. Purification by flash column chromatography (silica gel, 8.5:1.5 pet ether/ethyl acetate) afforded the colorless oily liquid compound (142 mg, 60% yield). R_f (40% Ethyl acetate/pet ether): 0.7.

Molecular formula: $C_{18}H_{24}O_7$

Yield: 60%

IR ($CHCl_3$): 2954, 2853, 1745, 1610, 1500 cm^{-1}.

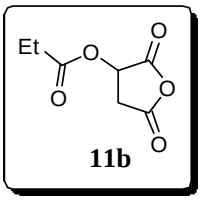
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4) : δ 1.91 (q, *J*=7 Hz, 2H), 2.20 (s, 3H), 2.36-2.44 (m, 2H), 2.58 (t, *J*=8 Hz, 2H), 2.88 (d, *J*=6 Hz, 2H), 3.72 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 5.48 (t, *J*=6 Hz, 1H), 6.72 (d, *J*=8 Hz, 1H), 6.95 (d, *J*=6 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 16.0, 26.5, 32.8, 33.8, 35.6, 51.8, 52.3, 55.0, 67.8, 109.5, 126.1, 126.3, 130.6, 132.6, 155.8, 169.2, 172.0.

MS (ESI) (m/z): 375 $[M+Na]^+$.

HRMS (ESI) : Calculated 375.14142 $(M+Na)^+$; Found 375.14126.

2,5-Dioxotetrahydrofuran-3-yl propionate (11b)



11b

L-malic acid (2 g, 15 mmol) were dissolved in propionyl chloride (7 mL). The solution was refluxed for 8 hrs .The excess propionyl chloride and propionic acid formed were distilled off *in vacuo*. The viscous residue was crystallized in chloroform /pet ether mixture to give a quantitative yield. This anhydride was recrystallized from chloroform- pet ether mixture.

Molecular formula: $C_7H_8O_5$

Yield: 100%

Melting Point: 87-88 °C

IR ($CHCl_3$): 1794, 1751, 1715 cm^{-1}

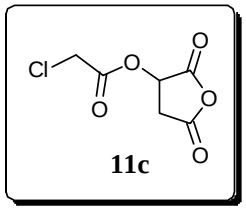
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.20 (t, *J*=8 Hz, 3H), 2.48 (q, *J*= 8 Hz, 2H), 3.00 (dd, *J*=18, 6.4 Hz, 1H), 3.38 (dd, *J*=18, 9.6 Hz, 1H), 5.53 (dd, *J*=10, 6.4 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 8.6, 26.8, 35.0, 67.4, 166.4, 167.9, 173.2

MS (ESI) (m/z): 195 $[M+Na]^+$.

HRMS (ESI): Calculated 195.02639 $(M+Na)^+$; Found 195.02659.

2,5-Dioxotetrahydrofuran-3-yl 2-chloroacetate (11c)



11c

L-malic acid (5 g, 37 mmol) were dissolved in 2-chloroacetyl chloride (15 mL). The solution was refluxed for 6 h .The excess 2-chloroacetyl chloride and 2-chloroacetic acid formed were removed *in vacuo*. The viscous residue was crystallized in chloroform /pet ether mixture to give a quantitative yield. This anhydride was recrystallized from chloroform- pet ether mixture.

Molecular formula: $C_6H_5ClO_5$

Yield: 100%

Melting Point: 82-85 °C

IR ($CHCl_3$): 1791, 1770, 1717 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 3.10 (dd, *J*= 8, 20 Hz, 1H), 3.46 (dd, *J*= 10, 20 Hz, 1H), 4.26 (s, 2H), 5.71 (dd, *J*=6, 10 Hz, 1H).

MS (ESI) (m/z): 215 $[M+Na]^+$.

HRMS (ESI): Calculated 215.5431 $(M+Na)^+$; Found 215.5442.

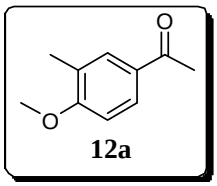
General procedure for the intermolecular Friedel-Crafts acylation reaction (B)

To a cold (0 ºC), magnetically stirred solution of aromatic compound (1 molar equiv) and the corresponding anhydride or ester (1.2 molar equiv) in anhydrous DCM, was added anhydrous crystalline aluminum chloride (4 molar equiv[2]) in one portion under nitrogen. The resulting mixture was warmed to room temperature and the red-orange reaction mixture was stirred at room temperature until the completion of reaction. The reaction mixture was then poured into an ice cooled 10% aqueous HCl and the aqueous layer was extracted with DCM. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was purified by flash silica gel column chromatography using pet ether/ethyl acetate as eluent.

General procedure for the intramolecular Friedel-Crafts acylation reaction (C):

To a cold (0 ºC), magnetically stirred solution of ester (1 molar equiv) in anhydrous DCM, was added anhydrous crystalline aluminum chloride (4 molar equiv) in one portion under nitrogen. The resulting mixture was warmed to room temperature and the red-orange reaction mixture was stirred at room temperature until the completion of reaction. The reaction mixture was then poured into an ice cooled 10% aqueous HCl and the aqueous layer was extracted with DCM. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* The crude product was purified by flash silica gel column chromatography using a pet ether/ethyl acetate eluent.

1-(4-Methoxy-3-methylphenyl)ethaNo.ne (12a)


12a

Compound **12a** was prepared following the general procedure **B**. The crude product was purified by flash column chromatography (silica gel, 9:1 pet ether/ethyl acetate) to afford the colorless oily liquid.

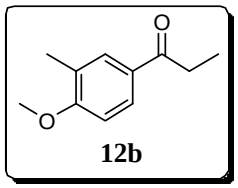
Molecular formula: $C_{10}H_{12}O_2$

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.25 (s, 3H), 2.55 (s, 3H), 3.90 (s, 3H), 6.83 (d, *J*=10 Hz, 1H), 7.77-7.84 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 16.0, 25.9, 55.1, 108.7, 126.3, 128.2, 129.5, 130.5, 161.3, 196.1.

CAS Registry No.: [10024-90-5].

1-(4-Methoxy-3-methylphenyl)propan-1-one (12b)


12b

Compound **12b** was prepared following the general procedure **B**. The crude product was purified by flash column chromatography (silica gel, 9:1 pet ether/ethyl acetate) to afford the colorless oily liquid.

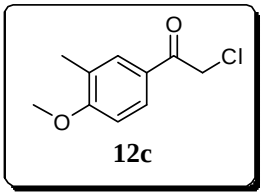
Molecular formula: $C_{11}H_{14}O_2$

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.20 (t, *J*=8 Hz, 3H), 2.24 (s, 3H), 2.93 (q, *J*=8 Hz, 2H), 3.88 (s, 3H), 6.82 (d, *J*=8 Hz, 1H), 7.77-7.84 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 8.5, 16.6, 31.3, 55.4, 109.0, 126.6, 127.9, 129.4, 130.6, 161.5, 199.6.

CAS Registry No.: [76805-57-7].

2-Chloro-1-(4-methoxy-3-methylphenyl)ethaNo.ne (12c)



12c

Compound **12b** was prepared following the general procedure **B**. The crude product was purified by flash column chromatography (silica gel, 9:1 pet ether/ethyl acetate) to afford the colorless oily liquid.

Molecular formula: $C_{10}H_{11}ClO_2$

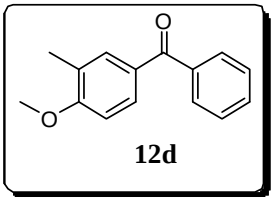
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4) : δ2.26 (s, 3H), 3.12 (s, 3H), 4.63 (s, 2H), 6.86 (d, *J*=10 Hz, 1H), 7.77-7.85 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ16.37, 45.43, 55.54, 109.37, 126.82, 127.29, 128.91, 131.23, 162.38, 189.62.

MS (ESI) (m/z): 221 $[M+Na]^+$.

HRMS (ESI): Calculated 221.6354 $(M+Na)^+$; Found 221.6365.

(4-Methoxy-3-methylphenyl)(phenyl)methaNo.ne (12d)



12d

Compound **12c** was prepared following the general procedure **B**. The crude product was purified by flash column chromatography (silica gel, 9:1 pet ether/ethyl acetate) to afford the colorless oily liquid.

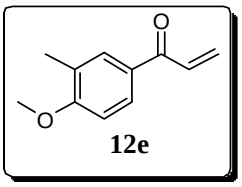
Molecular formula: $C_{15}H_{14}O_2$

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.27 (s, 3H), 3.92 (s, 3H), 6.86 (d, *J*=8 Hz, 1H), 7.42-7.78 (m, 7H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 16.2, 55.4, 108.8, 126.6, 128.0, 129.6, 130.5, 131.6, 132.6, 138.4, 161.4, 195.5.

CAS Registry No.: [30090-97-2].

1-(4-Methoxy-3-methylphenyl)prop-2-en-1-one (12e)



12e

Compound **12d** was prepared following the general procedure **B**. The crude product was purified by flash column chromatography (silica gel, 8:2 pet ether/ethyl acetate) to afford the colorless oily liquid.

Molecular formula: $C_{11}H_{12}O_2$

IR ($CHCl_3$): 2927, 1676, 1503 cm^{-1}.

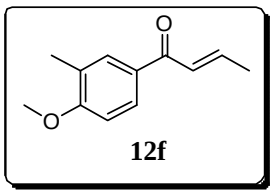
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.26 (s, 3H), 3.91 (s, 3H), 5.85 (dd, *J*= 10, 2 Hz, 1H), 6.40 (dd, *J*=16, 2 Hz, 1H), 6.85 (d, *J*=10 Hz, 1H), 7.17 (dd, *J*=16, 10 Hz, 1H), 7.79-7.85 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 16.2, 55.3, 109.1, 126.8, 128.1, 128.8, 129.7, 131.3, 132.1, 161.7, 189.0.

MS (ESI) (m/z): 199 $[M+Na]^+$.

HRMS (ESI): Calculated 199.07295 $(M+Na)^+$; Found 199.07315.

(*E*)-1-(4-Methoxy-3-methylphenyl)but-2-en-1-one (12f)



12f

Compound **12e** was prepared following the general procedure **B**. The crude product was purified by flash column chromatography (silica gel, 8.5:1.5 pet ether/ethyl acetate) to afford the colorless oily liquid.

Molecular formula: $C_{12}H_{15}O_2$

IR ($CHCl_3$): 2925, 1666, 1621, 1600, 1503 cm^{-1}.

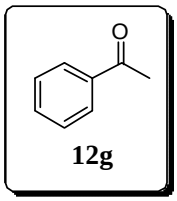
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.00 (d, *J*=5.3 Hz, 3H), 2.26 (s, 3H), 3.90 (s, 3H), 6.82-7.07 (m, 3H), 7.78-7.84 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 16.2, 18.4, 55.4, 109.1, 126.7, 127.1, 128.5, 130.1, 131.1, 143.5, 161.5, 189.1.

MS (ESI) (m/z): 191 $[M+Na]^+$.

HRMS (ESI): Calculated 191.10666 $(M+Na)^+$; Found 191.10667

Acetophenone (12g)



Compound **12g** was prepared following the general procedure **B**. The crude product was purified by flash column chromatography (silica gel, 9:1 pet ether/ethyl acetate) to afford the colorless oily liquid.

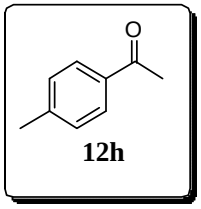
Molecular formula: C_8H_8O

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.61 (s, 3H), 7.42-7.57 (m, 3H), 7.93-7.98 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 26.4, 128.2, 128.5, 132.9, 137.0, 197.6.

CAS Registry No.: [1260026-11-6].

1-*p*-Tolylethanone (12h)



Compound **12h** was prepared following the general procedure **B**. The crude product was purified by flash column chromatography (silica gel, 9:1 pet ether/ethyl acetate) to afford the colorless oily liquid.

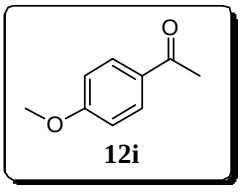
Molecular formula: $C_9H_{10}O$

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.41 (s, 3H), 2.56 (s, 3H), 7.23 (d, *J*= 8 Hz, 2H), 7.84 (d, *J*=8 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 21.1, 25.9, 128.0, 128.7, 134.3, 143.1, 196.7.

CAS Registry No.: [122-00-9].

1-(4-Methoxyphenyl)ethanone (12i)



Compound **12i** was prepared following the general procedure **B**. The crude product was purified by flash column chromatography (silica gel, 9:1 pet ether/ethyl acetate) to afford the colorless oily liquid.

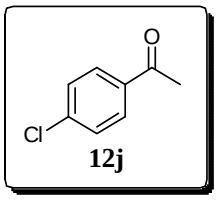
Molecular formula: $C_9H_{10}O_2$

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.55 (s, 3H), 3.87 (s, 3H), 6.92 (d, *J*=10 Hz, 2H), 7.92 (d, *J*=10 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 26.1, 55.2, 113.5, 130.2, 130.4, 163.3, 196.0.

CAS Registry No.: [100-06-1].

1-(4-Chlorophenyl)ethanone (12j)



12j

Compound **12j** was prepared following the general procedure **B**. The crude product was purified by flash column chromatography (silica gel, 9:1 pet ether/ethyl acetate) to afford the colorless oily liquid.

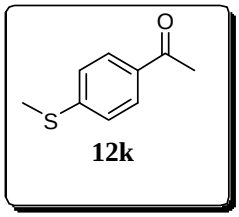
Molecular formula: C_8H_7ClO

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4) : δ 2.60 (s, 3H), 7.44 (d, *J*=8.7 Hz, 2H), 7.90 (d, *J*=8.7 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 26.5, 128.8, 129.7, 135.3, 139.5, 196.6.

CAS Registry No.: [99-91-2].

1-(4-(Methylthio)phenyl)ethanone (12k)



12k

Compound **12k** was prepared following the general procedure **B**. The crude product was purified by flash column chromatography (silica gel, 8:2 pet ether/ethyl acetate) to afford the colorless oily liquid.

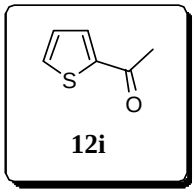
Molecular formula: $C_9H_{10}OS$

^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 2.55 (s, 3H), 2.59 (s, 3H), 7.26 (d, *J*=8.5 Hz, 2H), 7.88 (d, *J*=8.5 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): 14.7, 26.3, 124.8, 128.6, 133.4, 145.7, 196.6.

CAS Registry No.: [1778-09-2].

1-(Thiophen-2-yl)ethanone (12l)



12i

Compound **12l** was prepared following the general procedure **B**. The crude product was purified by flash column chromatography (silica gel, 8:2 pet ether/ethyl acetate) to afford the colorless oily liquid.

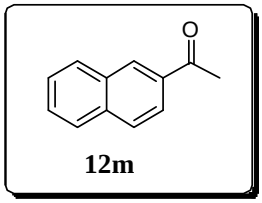
Molecular formula: C_6H_6OS

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.58 (s, 3H), 7.13 (dd, *J*=6, 4 Hz, 1H), 7.63-7.71 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 26.2, 127.8, 132.1, 133.4, 144.2, 190.0.

CAS Registry No.: [88-15-3].

1-(Naphthalen-2-yl)ethanone (12m)



12m

Compound **12m** was prepared following the general procedure **B**. The crude product was purified by flash column chromatography (silica gel, 9:1 pet ether/ethyl acetate) to afford the colorless oily liquid.

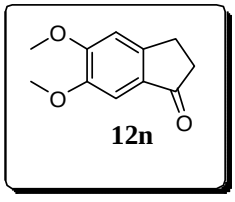
Molecular formula: $C_{12}H_{10}O$

^{1}H NMR (400 MHz, $CDCl_3$+CCl_4) : δ 2.74 (s, 3H), 7.56-7.61 (m, 2H), 7.87-8.05 (m, 4H), 8.47 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): 26.5, 123.9, 126.6, 127.7, 128.3, 129.5, 130.1, 132.5, 134.4, 135.5, 197.6.

CAS Registry No.: [93-08-3].

5,6-Dimethoxy-2,3-dihydro-1*H*-inden-1-one (12n)



12n

Compound **12n** was prepared following the general procedure **C**. The crude product was purified by flash column chromatography (silica gel, 5:5 pet ether/ethyl acetate) to afford the white solid.

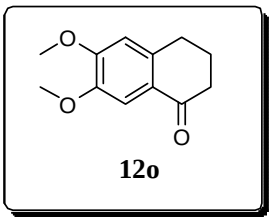
Molecular formula: $C_{11}H_{12}O_3$

^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 2.66-2.69 (m, 2H), 3.04-3.07 (m, 2H), 3.91 (s, 3H), 3.97 (s, 3H), 6.88 (s, 1H), 7.17 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): 25.5, 36.4, 55.9, 56.0, 104.1, 107.3, 129.9, 149.3, 150.1, 155.3, 205.3.

CAS Registry No.: [2107-69-9].

6,7-Dimethoxy-3,4-dihydronaphthalen-1(2*H*)-one (12o)


12o

Compound **12o** was prepared following the general procedure **C**. The crude product was purified by flash column chromatography (silica gel, 7:3 pet ether/ethyl acetate) to afford the white solid.

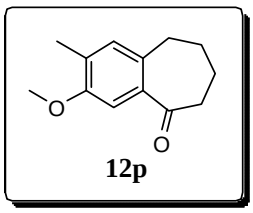
Molecular formula: $C_{12}H_{14}O_3$

^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 2.07 (q, *J*=6.2 Hz, 2H), 2.53 (t, *J*=6.7 Hz, 2H), 2.84 (t, *J*=6 Hz, 2H), 3.86 (s, 3H), 3.88 (s, 3H), 6.60 (s, 1H), 7.44 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): 23.6, 29.4, 38.4, 55.8, 108.5, 110.0, 125.8, 139.0, 147.9, 153.4, 196.6.

CAS Registry No.: [13575-75-2].

3-Methoxy-2-methyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one (12p)


12p

Compound **12p** was prepared following the general procedure **C**. The crude product was purified by flash column chromatography (silica gel, 9:1 pet ether/ethyl acetate) to afford the colorless oily liquid.

Molecular formula: $C_{13}H_{16}O_2$

IR ($CHCl_3$): 2924, 1700, 1640, 1602, 1503 cm^{-1}.

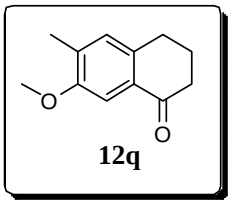
^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 1.79-1.87 (m, 4H), 2.23 (s, 3H), 2.71-2.74 (m, 2H), 2.85-2.88 (m, 2H), 3.86 (s, 3H), 6.96 (s, 1H), 7.24 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 16.2, 20.7, 25.2, 31.6, 40.7, 55.3, 109.40, 131.5, 132.2, 134.0, 136.7, 156.3, 204.7.

MS (ESI) (m/z): 191 $[M+Na]^+$.

HRMS (ESI): Calculated 227.10425 $(M+Na)^+$; Found 227.10447.

7-Methoxy-6-methyl-3,4-dihydronaphthalen-1(2*H*)-one (12q)



12q

Compound **3q** was prepared following the general procedure **C**. The crude product was purified by flash column chromatography (silica gel, 9:1 pet ether/ethyl acetate).

Molecular formula: $C_{12}H_{14}O_2$

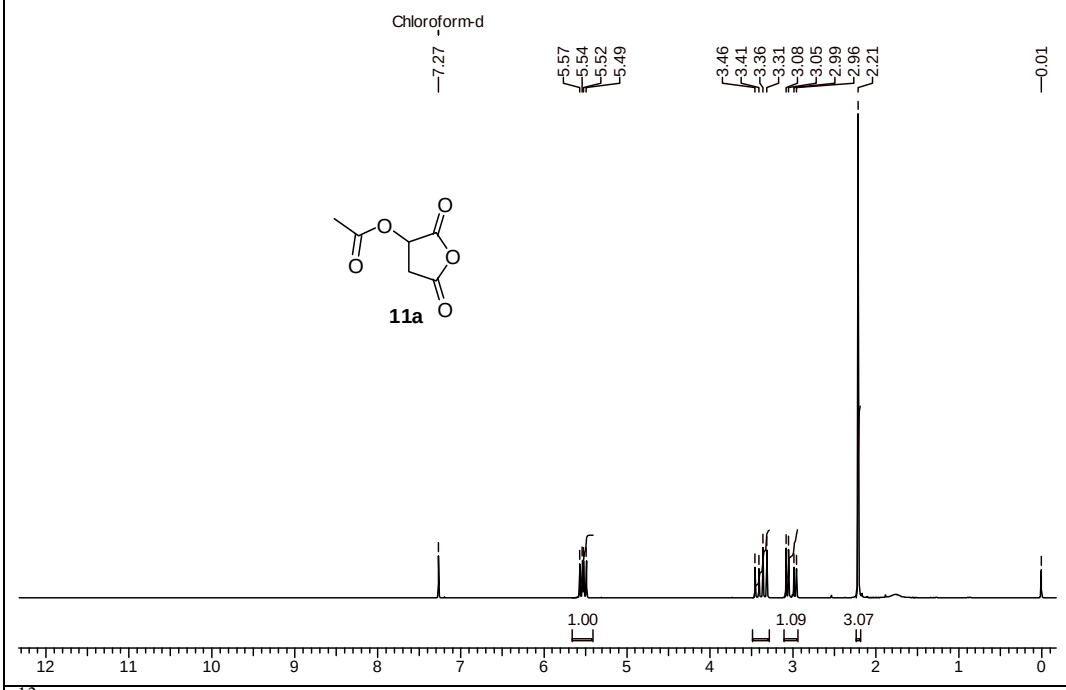
^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): δ 2.07 (q, *J*=6.2 Hz, 2H), 2.53 (t, *J*=6.7 Hz, 2H), 2.84 (t, *J*=6 Hz, 2H), 3.86 (s, 3H), 3.88 (s, 3H), 6.60 (s, 1H), 7.44 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): 23.6, 29.4, 38.4, 55.8, 108.5, 110.0, 125.8, 139.0, 147.9, 153.4, 196.6.

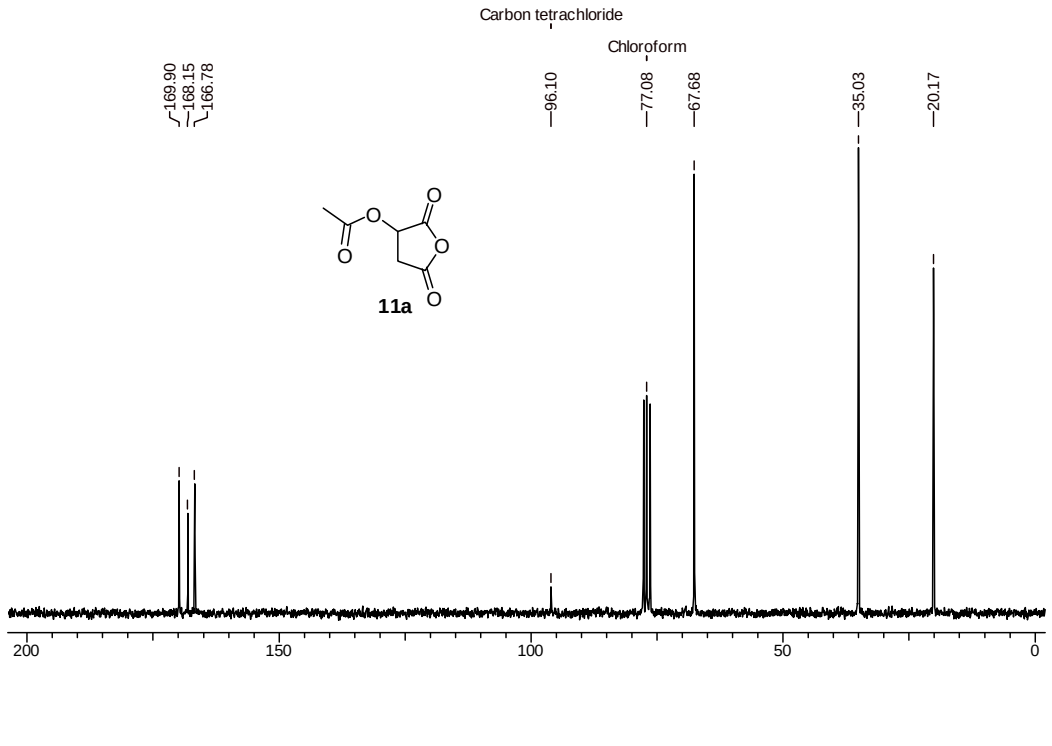
CAS Registry No. : [13575-75-2].

1.4.6. NMR Spectra

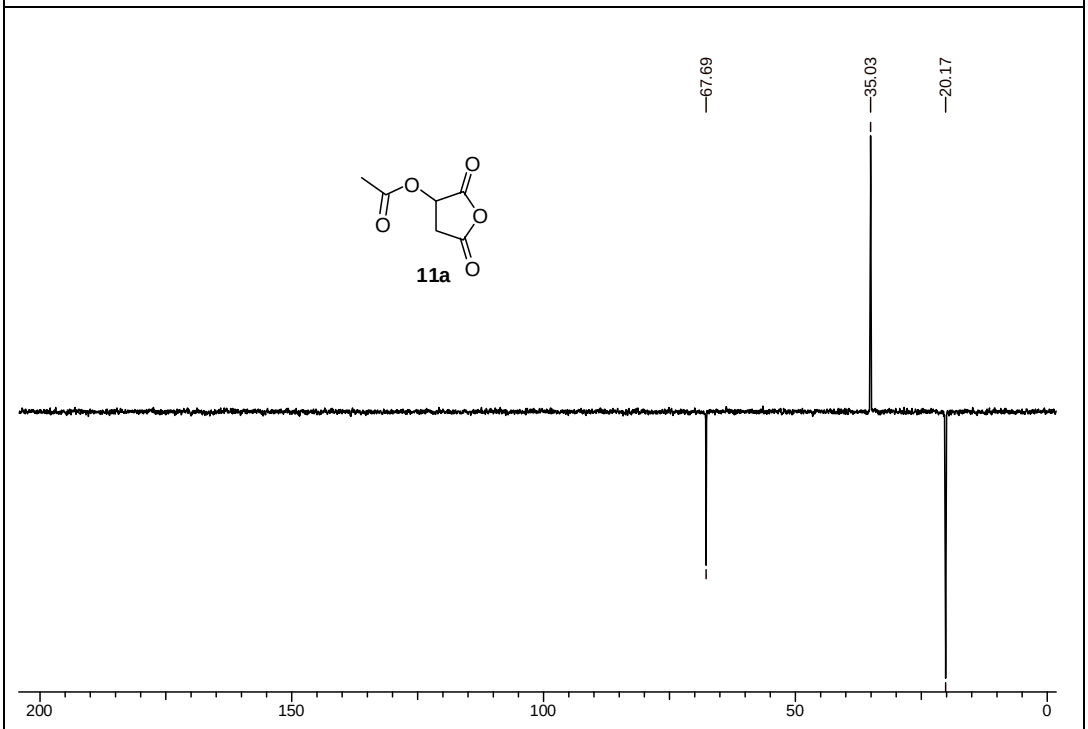
^{1}H NMR spectrum of compound **11a** ($CDCl_3$ + CCl_4, 200 MHz)



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

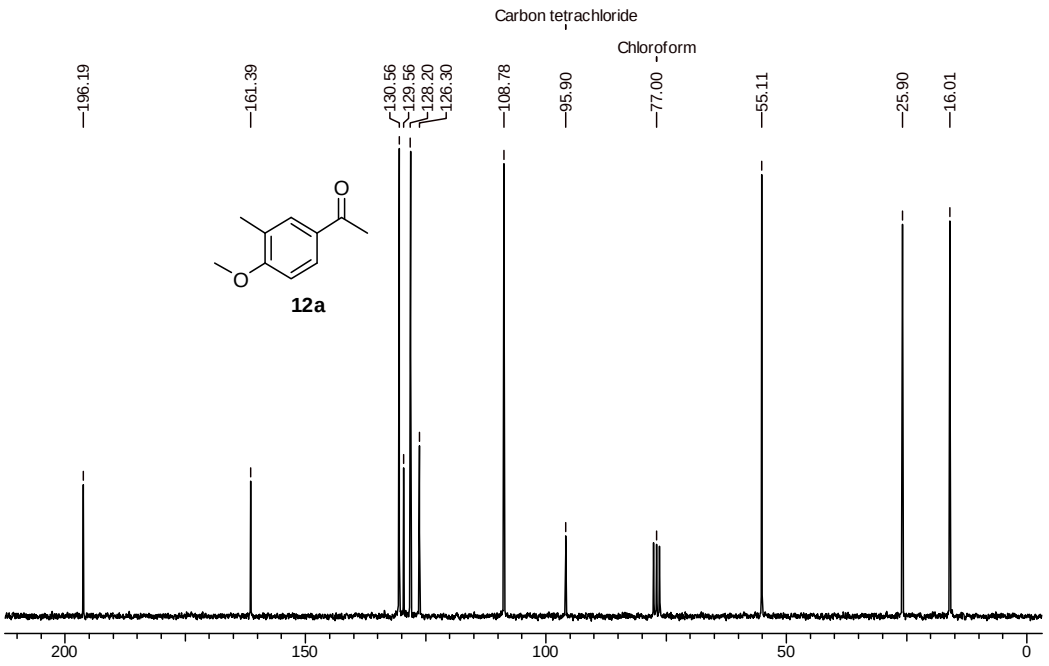


DEPT spectrum of compound **11a** ($CDCl_3 + CCl_4$, 50 MHz)

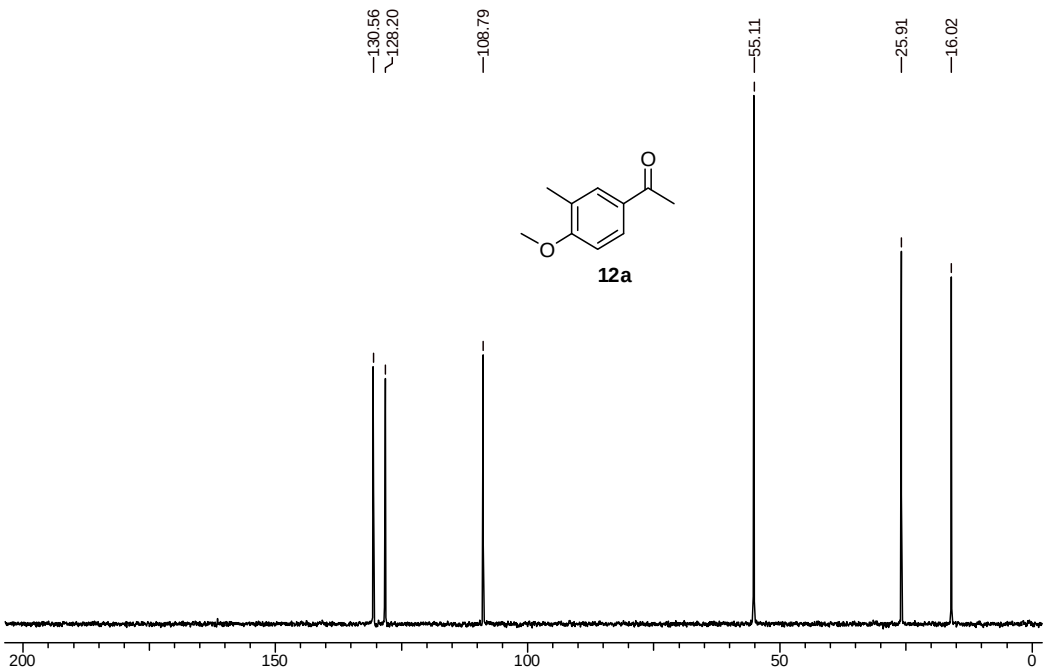


^{1}H NMR spectrum of compound **12a** ($CDCl_3 + CCl_4$, 200 MHz)

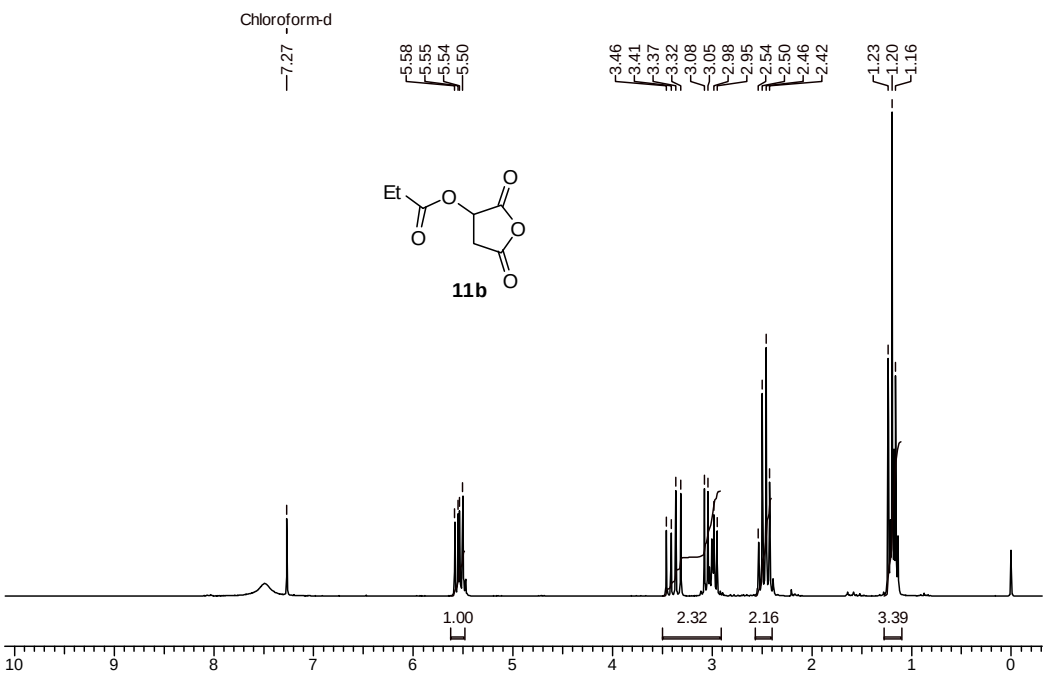
^{13}C NMR spectrum of compound **12a** ($CDCl_3 + CCl_4$, 50 MHz)



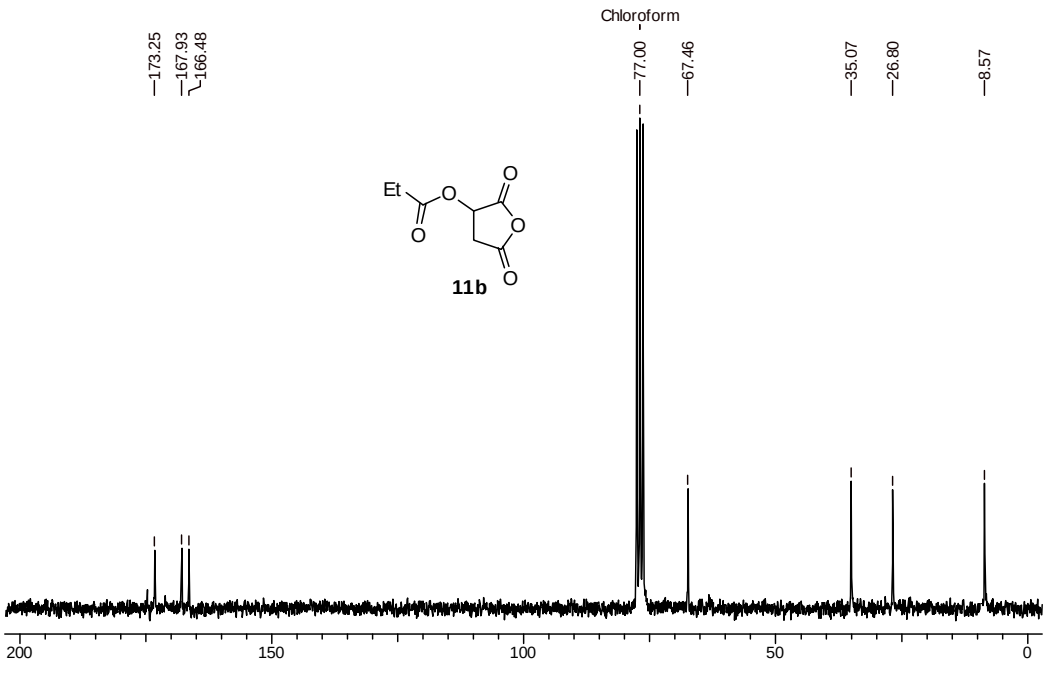
DEPT spectrum of compound **12a** ($CDCl_3 + CCl_4$, 50 MHz)



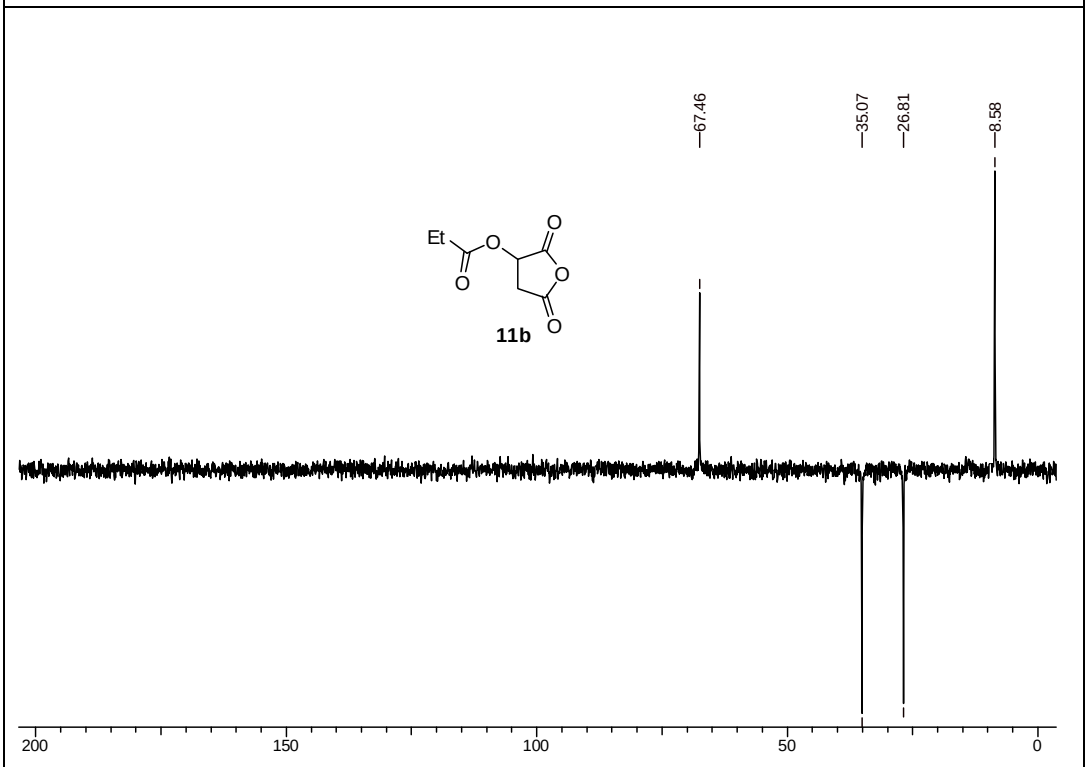
^{1}H NMR spectrum of compound **11b** ($CDCl_3$ + CCl_4, 200 MHz)



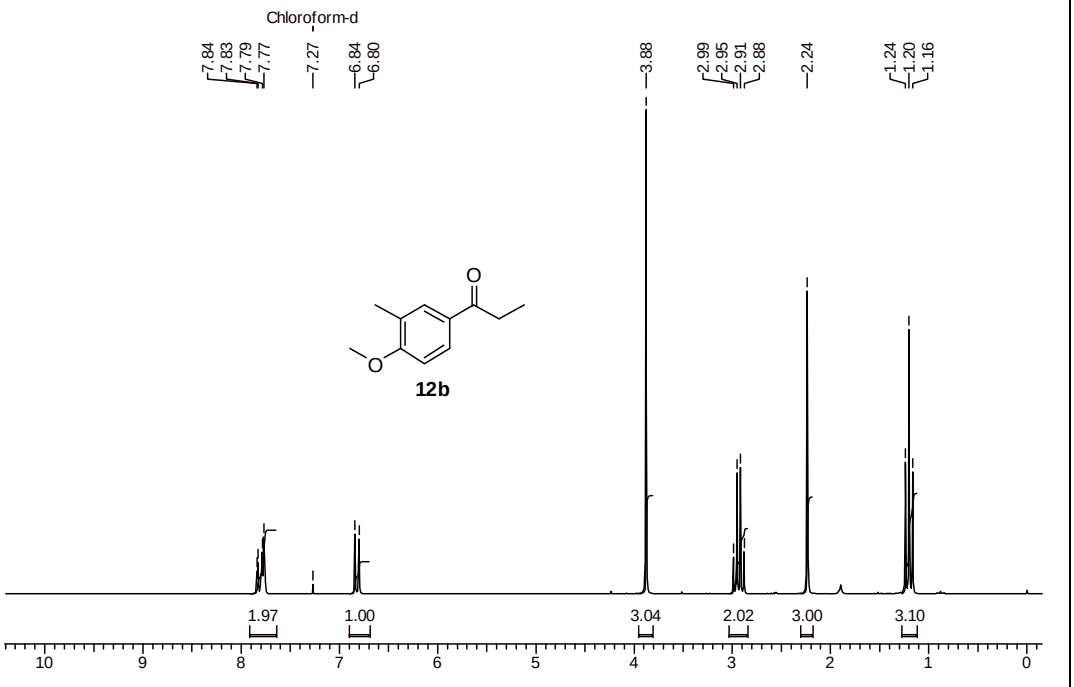
^{13}C NMR spectrum of compound **11b** ($CDCl_3$, 50 MHz)



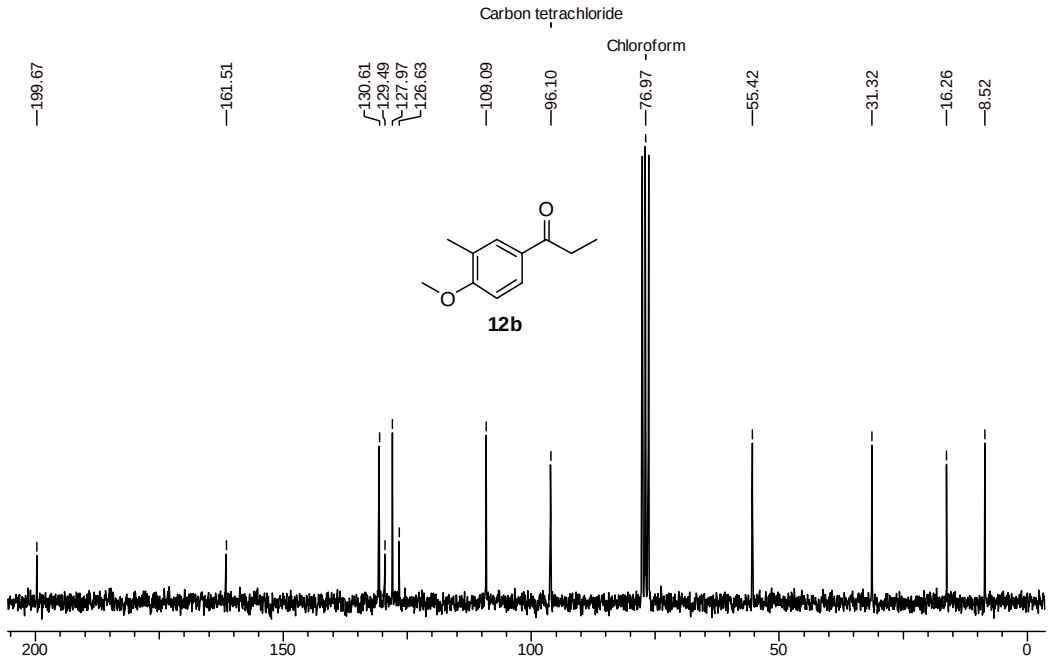
DEPT spectrum of compound **11b** ($CDCl_3$, 50 MHz)



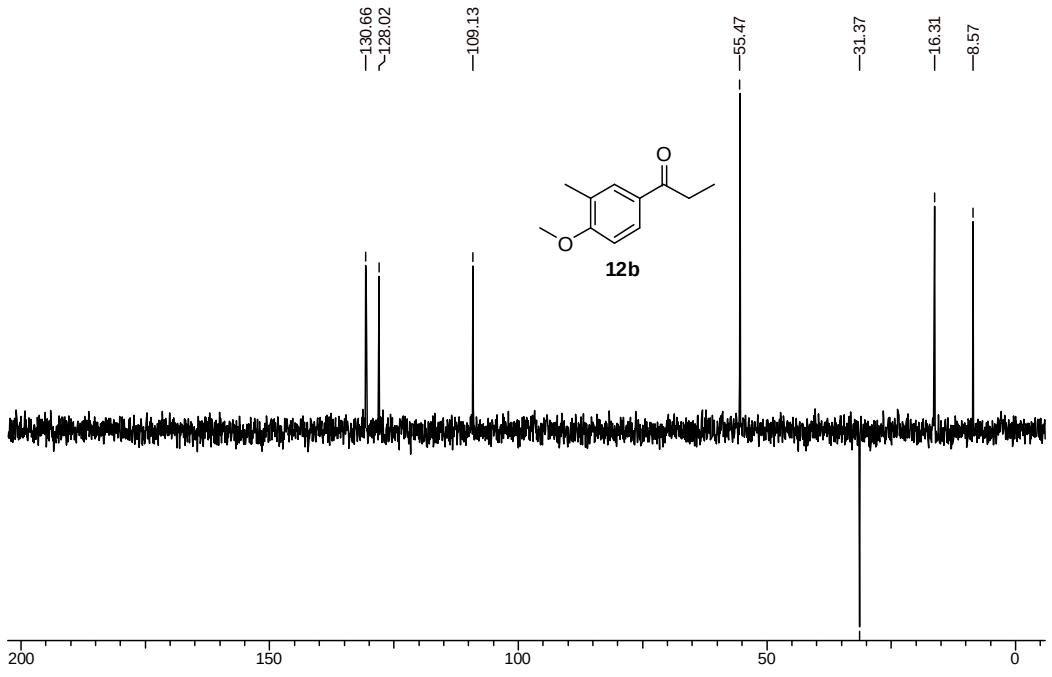
^1H NMR spectrum of compound **12b** ($CDCl_3$ + CCl_4, 200 MHz)



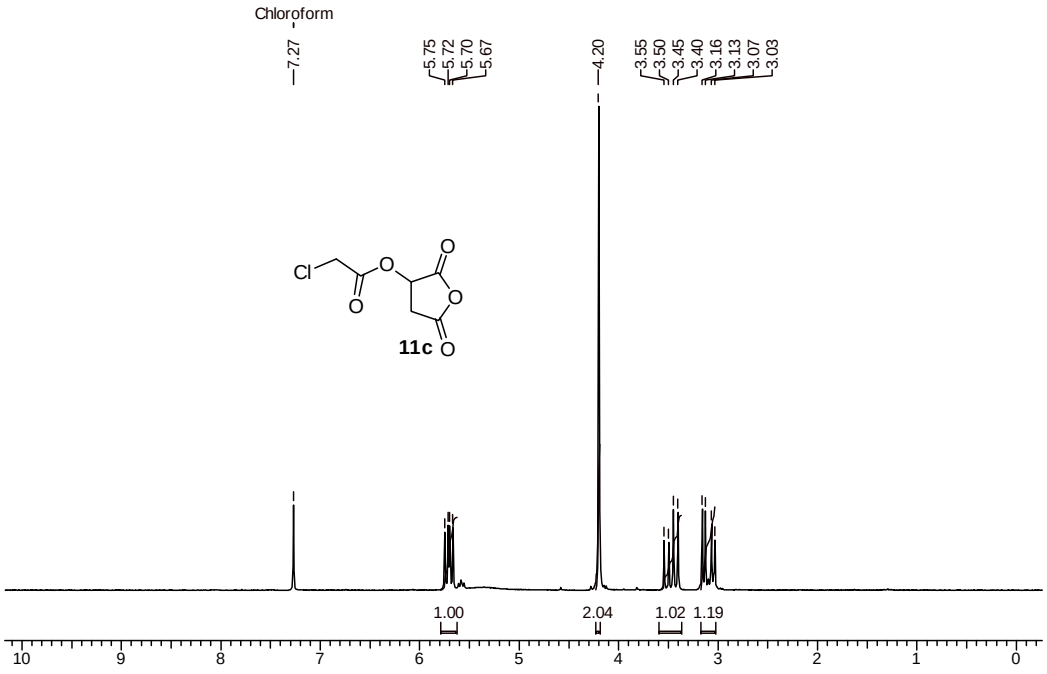
^{13}C NMR spectrum of compound **12b** ($CDCl_3 + CCl_4$, 50 MHz)



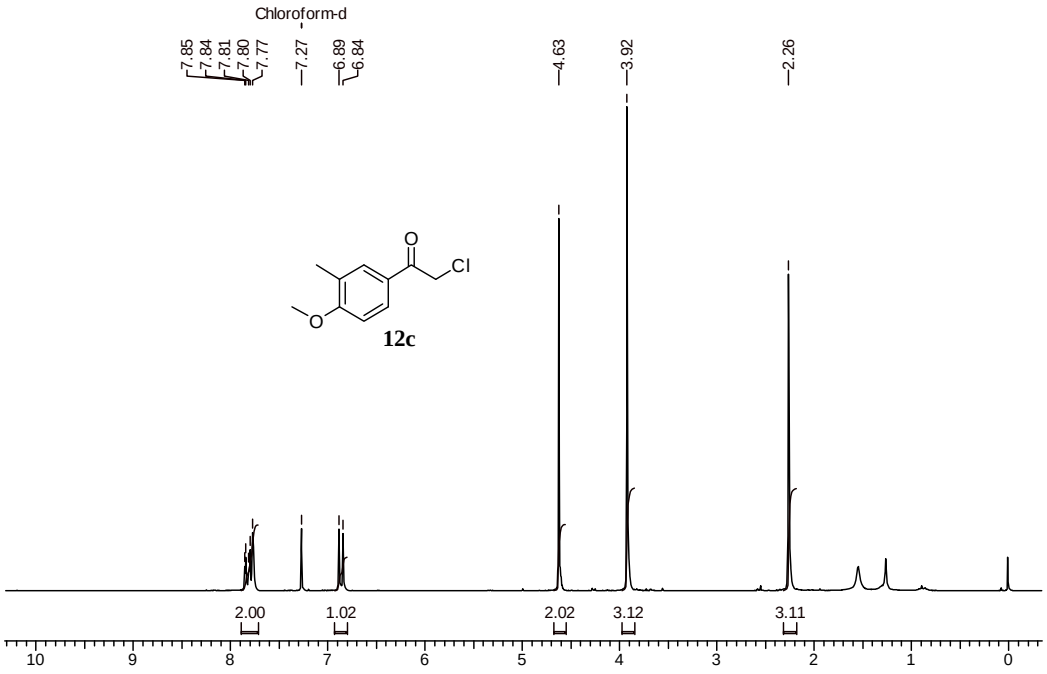
DEPT spectrum of compound **12b** ($CDCl_3 + CCl_4$, 50 MHz)



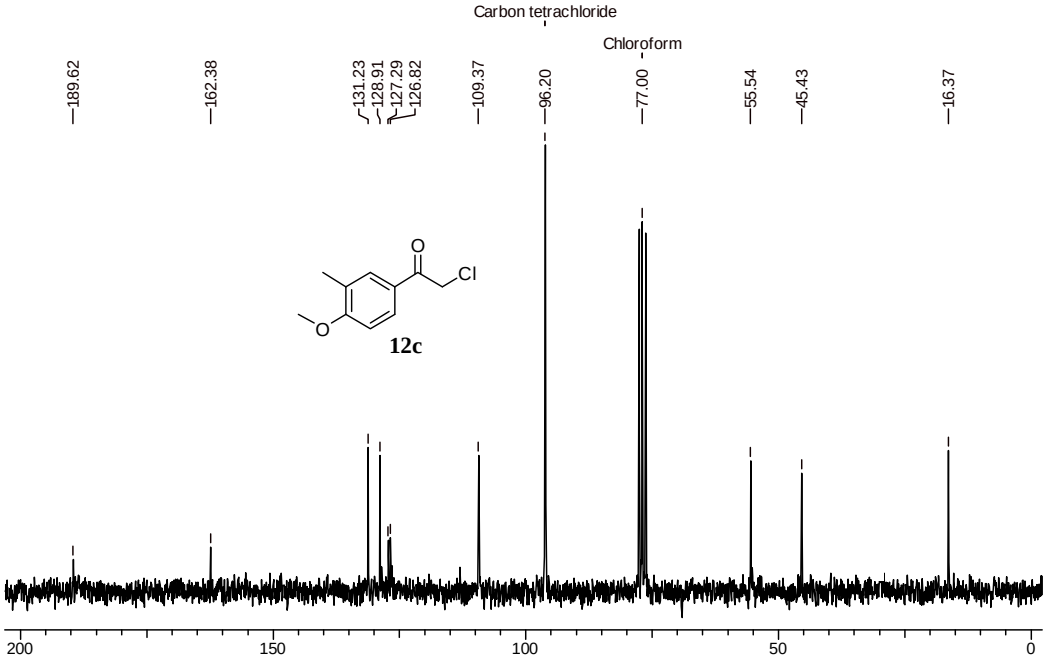
^{1}H NMR spectrum of compound **11c** ($CDCl_3$ + CCl_4, 200 MHz)



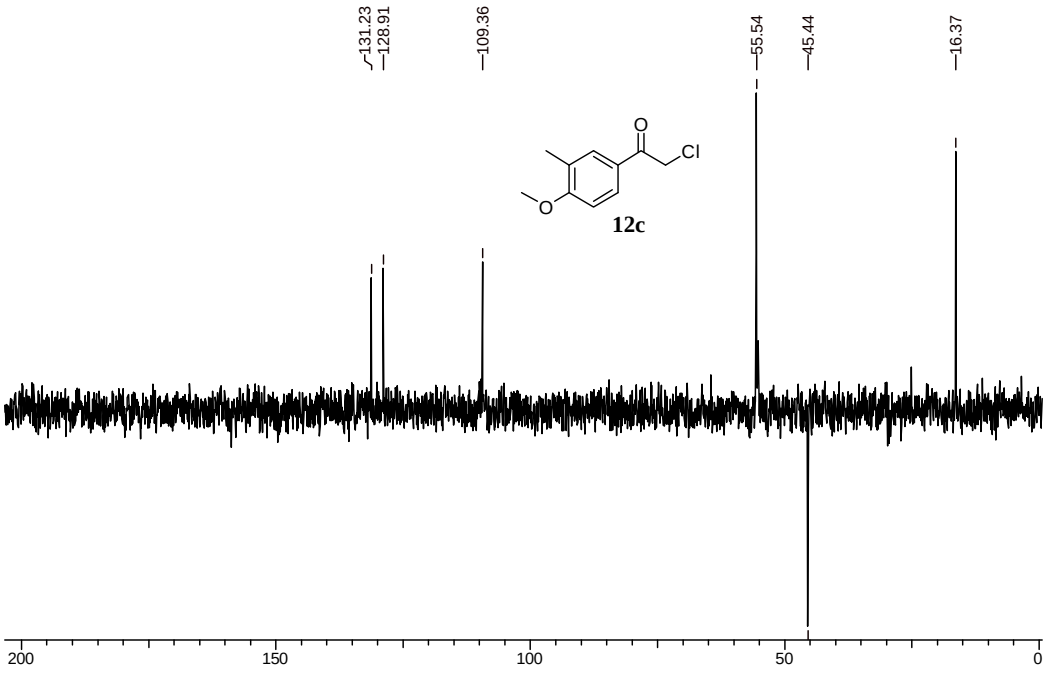
^{1}H NMR spectrum of compound **12c** ($CDCl_3$ + CCl_4, 200 MHz)



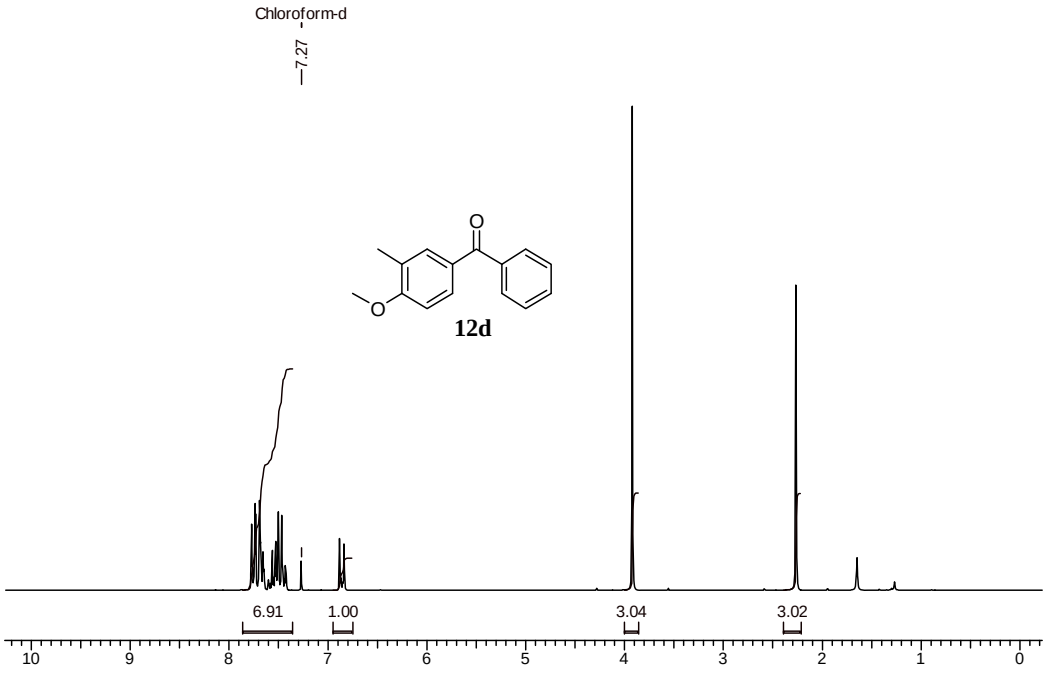
^{13}C NMR spectrum of compound **12c** ($CDCl_3 + CCl_4$, 50 MHz)



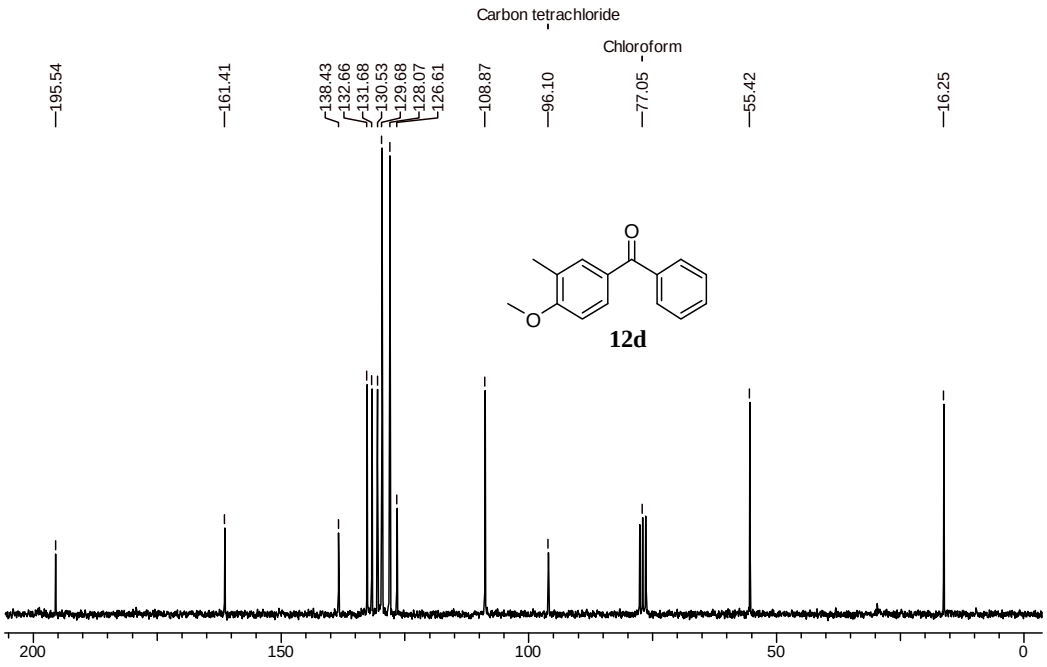
DEPT spectrum of compound **12c** ($CDCl_3 + CCl_4$, 50 MHz)



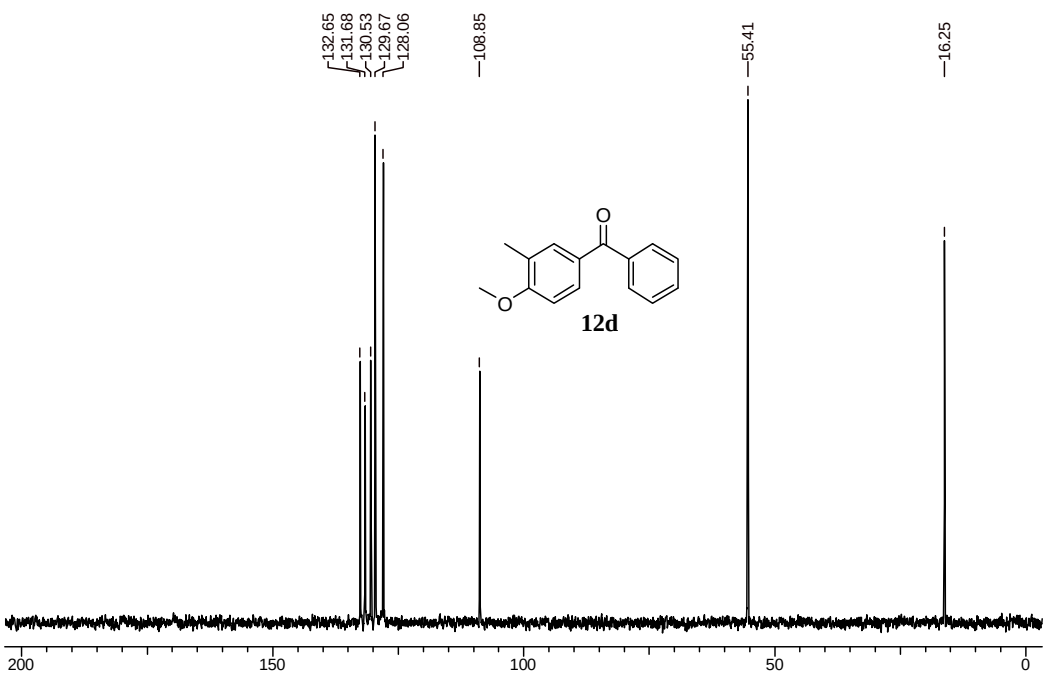
^{1}H NMR spectrum of compound **12d** ($CDCl_3$ + CCl_4, 200 MHz)



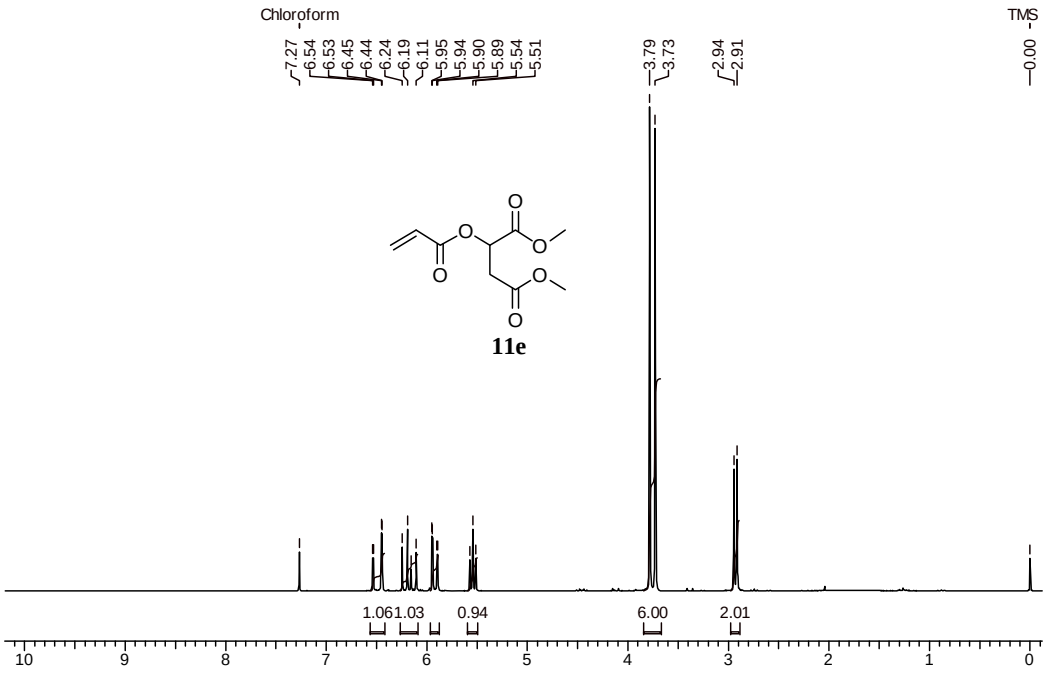
^{13}C NMR spectrum of compound **12d** ($CDCl_3$ + CCl_4, 50 MHz)



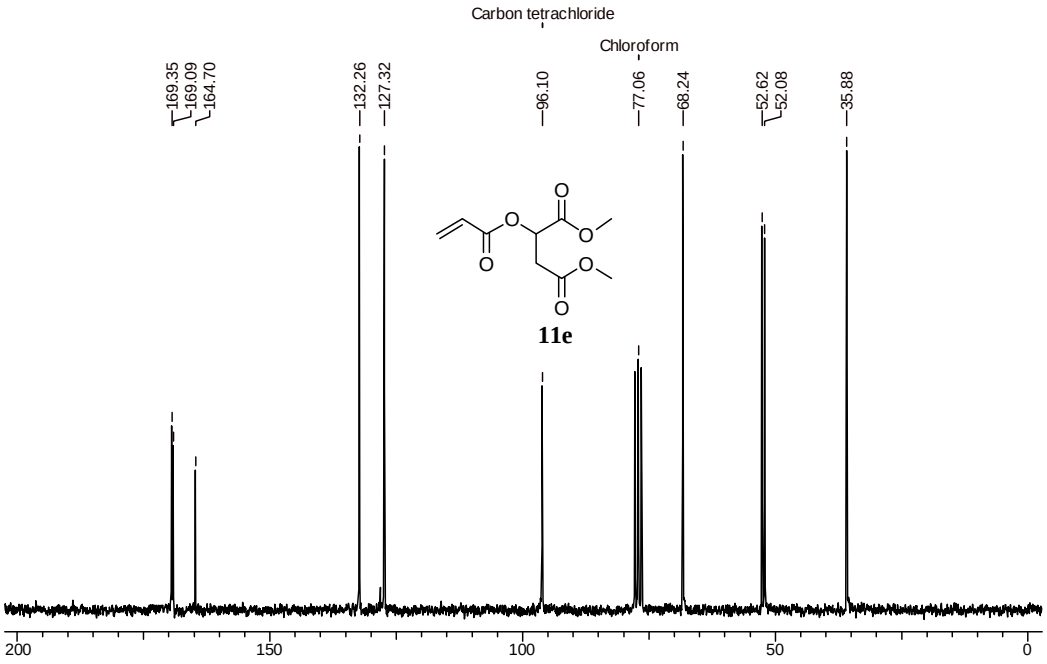
DEPT spectrum of compound **12d** ($CDCl_3 + CCl_4$, 50 MHz)



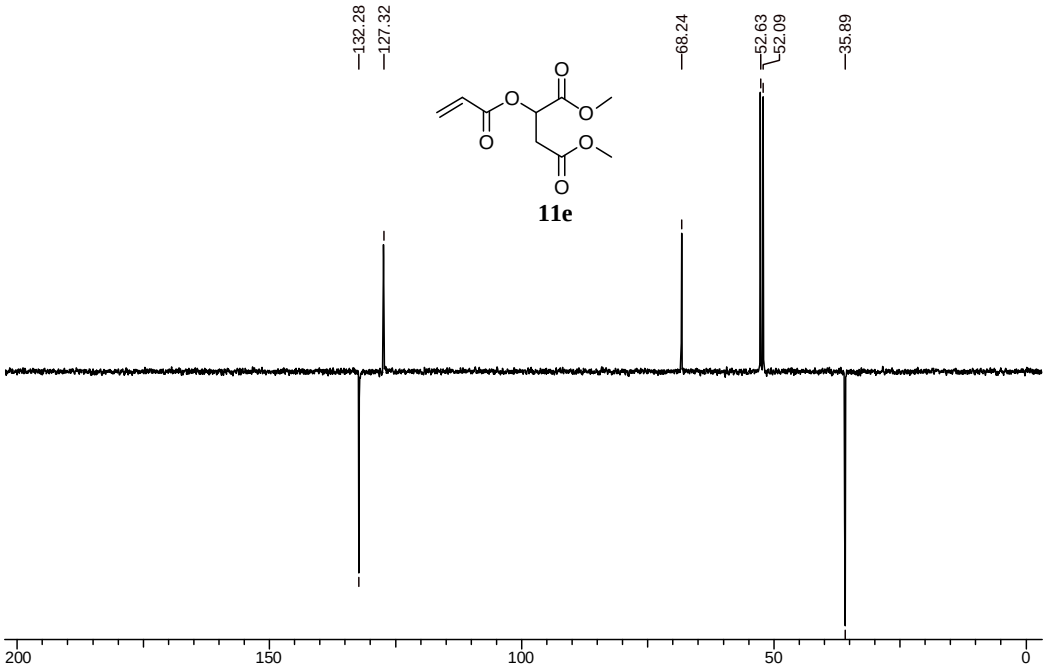
^{1}H NMR spectrum of compound **11e** ($CDCl_3 + CCl_4$, 200 MHz)



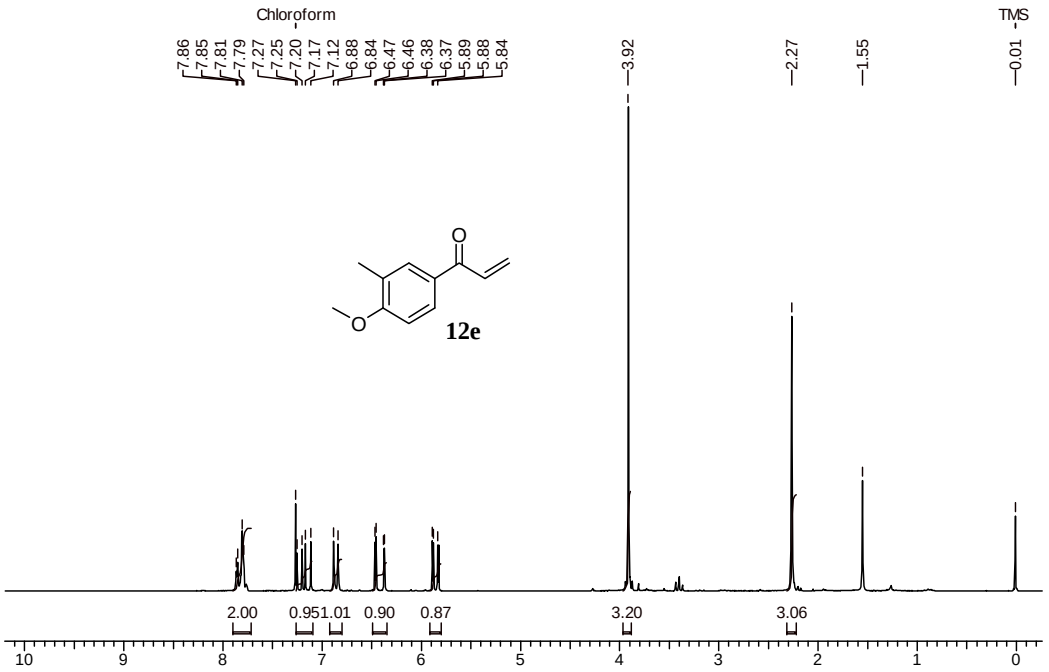
^{13}C NMR spectrum of compound **11e** ($CDCl_3 + CCl_4$, 50 MHz)



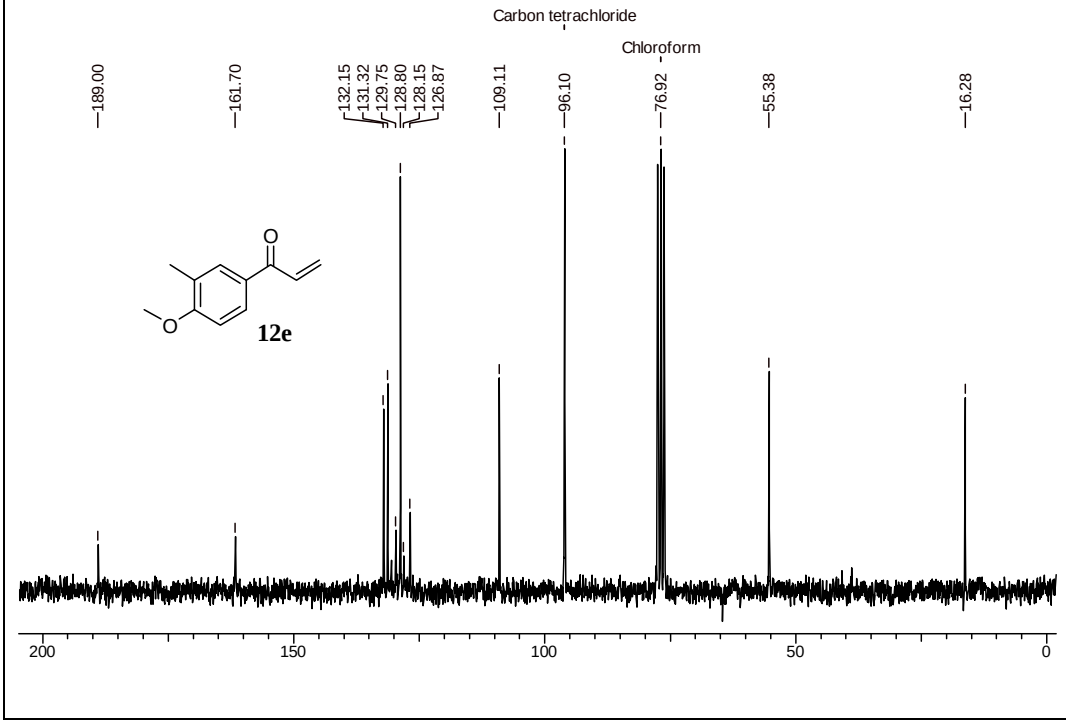
DEPT spectrum of compound **11e** ($CDCl_3 + CCl_4$, 50 MHz)



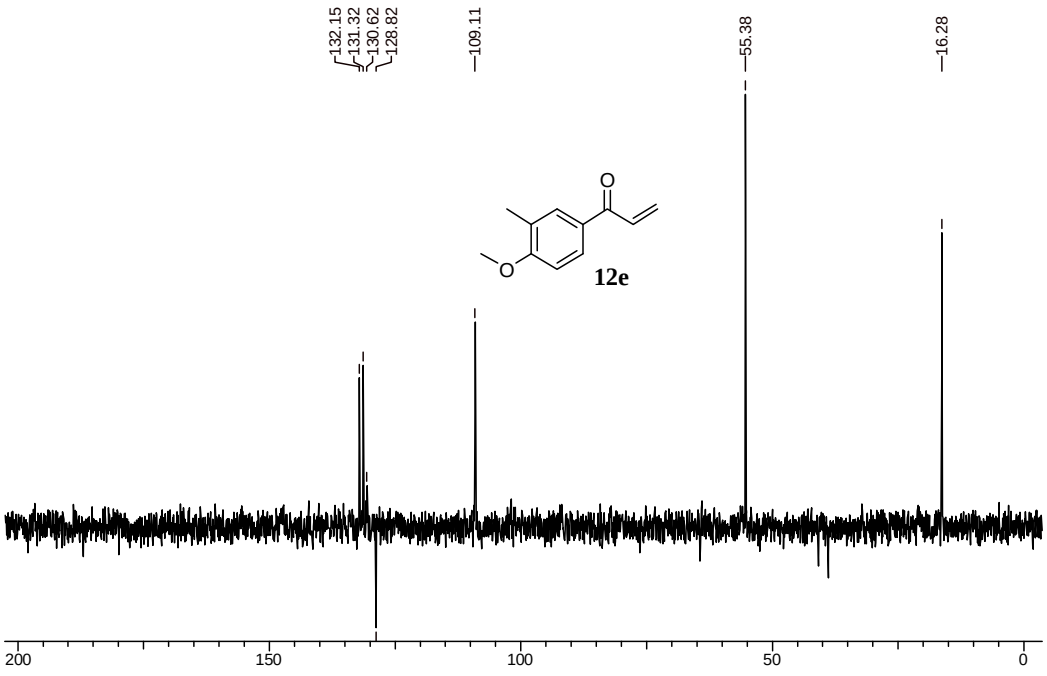
^{1}H NMR spectrum of compound **12e** ($CDCl_3$ + CCl_4, 200 MHz)



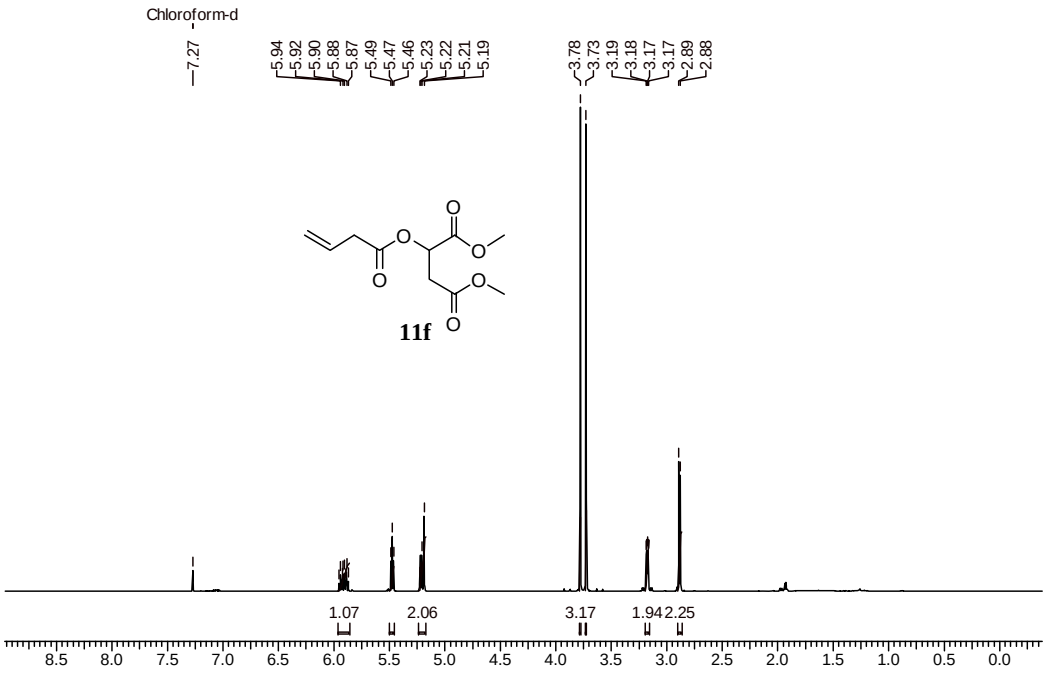
^{13}C NMR spectrum of compound **12e** ($CDCl_3$ + CCl_4, 50 MHz)



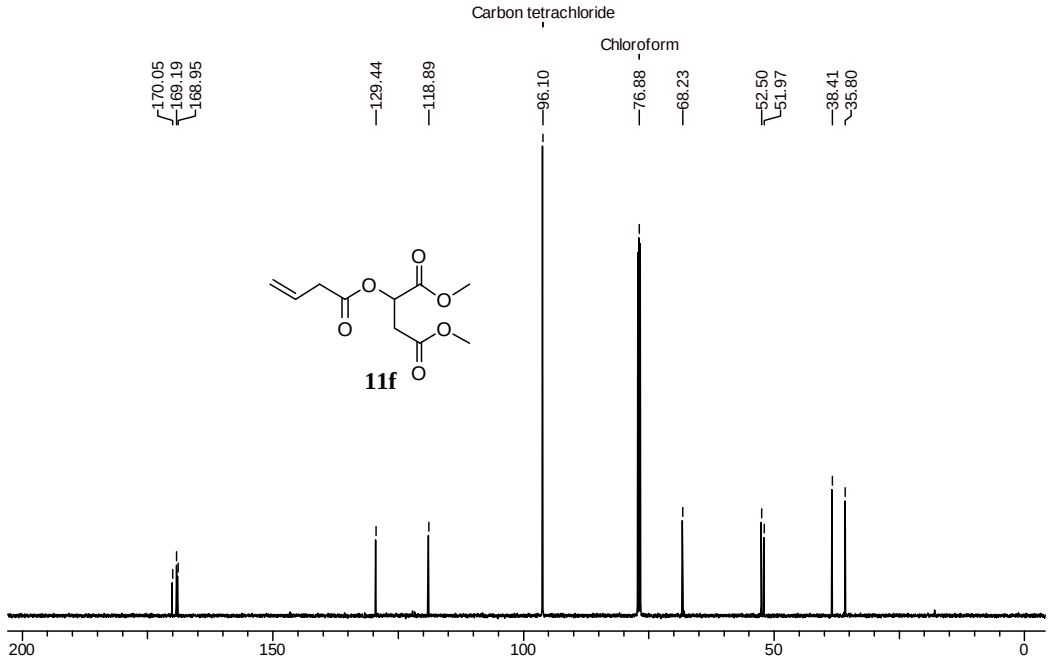
DEPT spectrum of compound **12e** ($CDCl_3 + CCl_4$, 50 MHz)



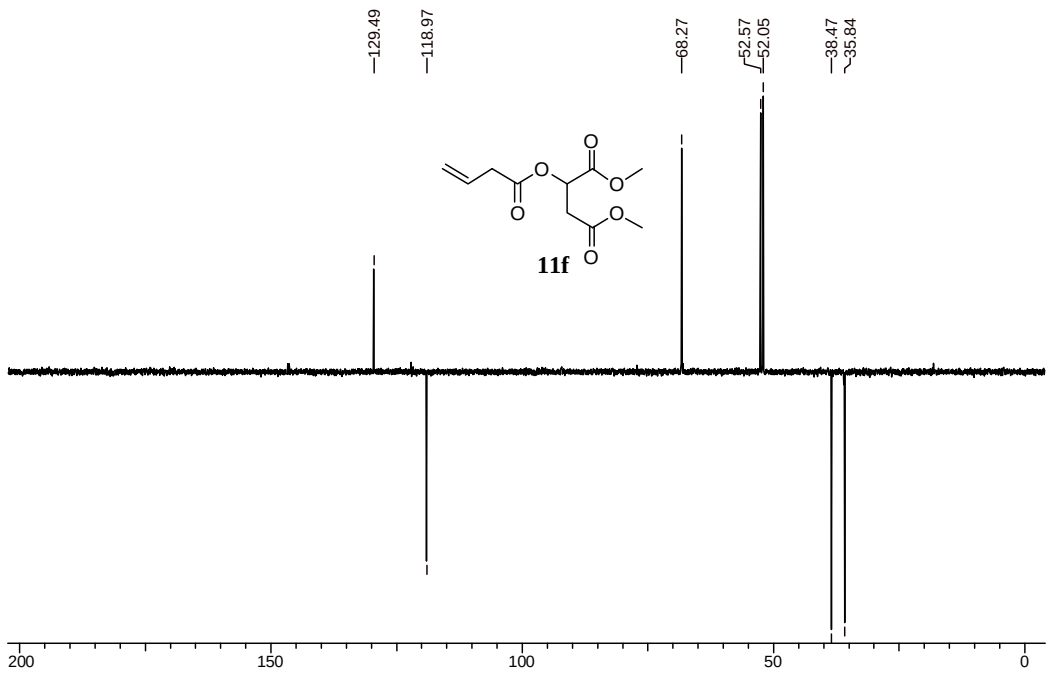
^{1}H NMR spectrum of compound **11f** ($CDCl_3 + CCl_4$, 500 MHz)



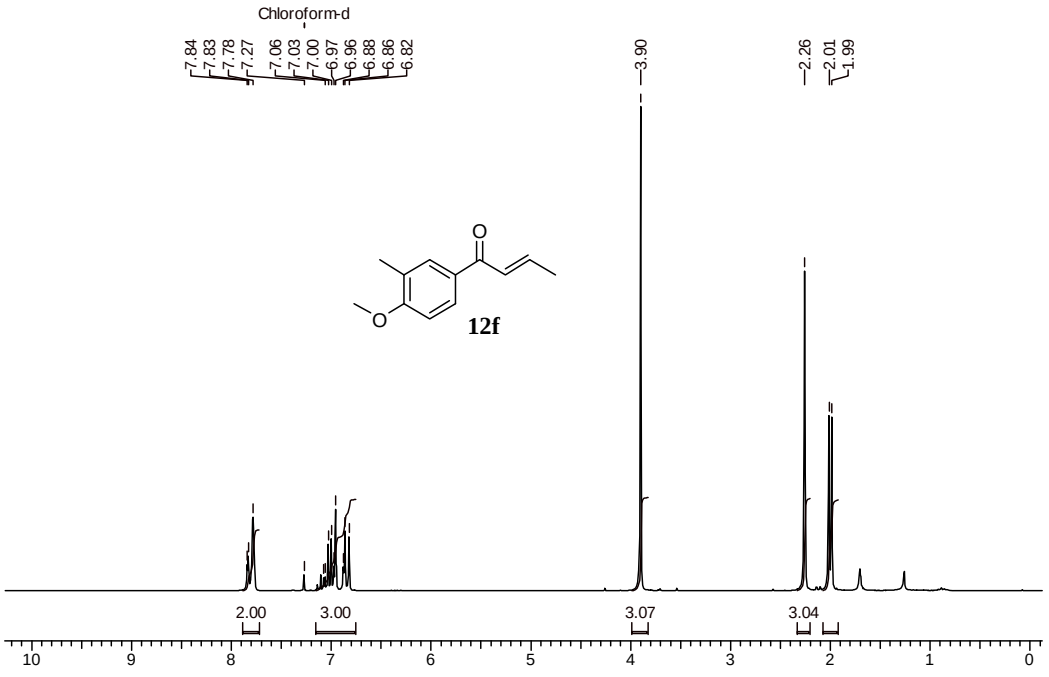
^{13}C NMR spectrum of compound **11f** ($CDCl_3$ + CCl_4, 125 MHz)



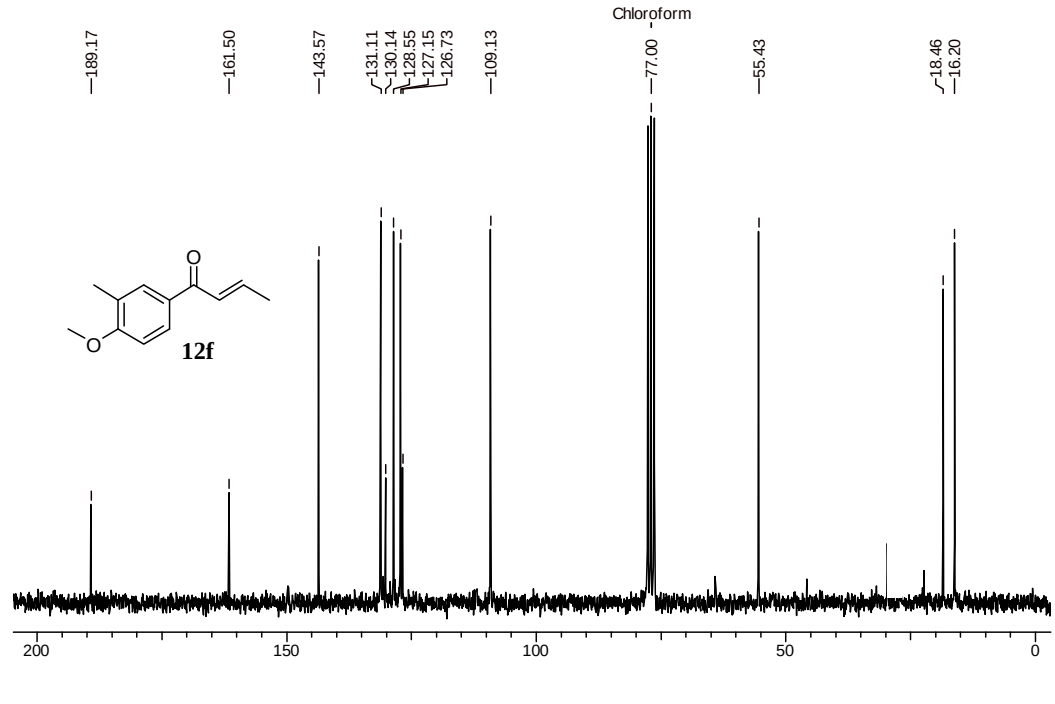
DEPT spectrum of compound **11f** ($CDCl_3$ + CCl_4, 125 MHz)



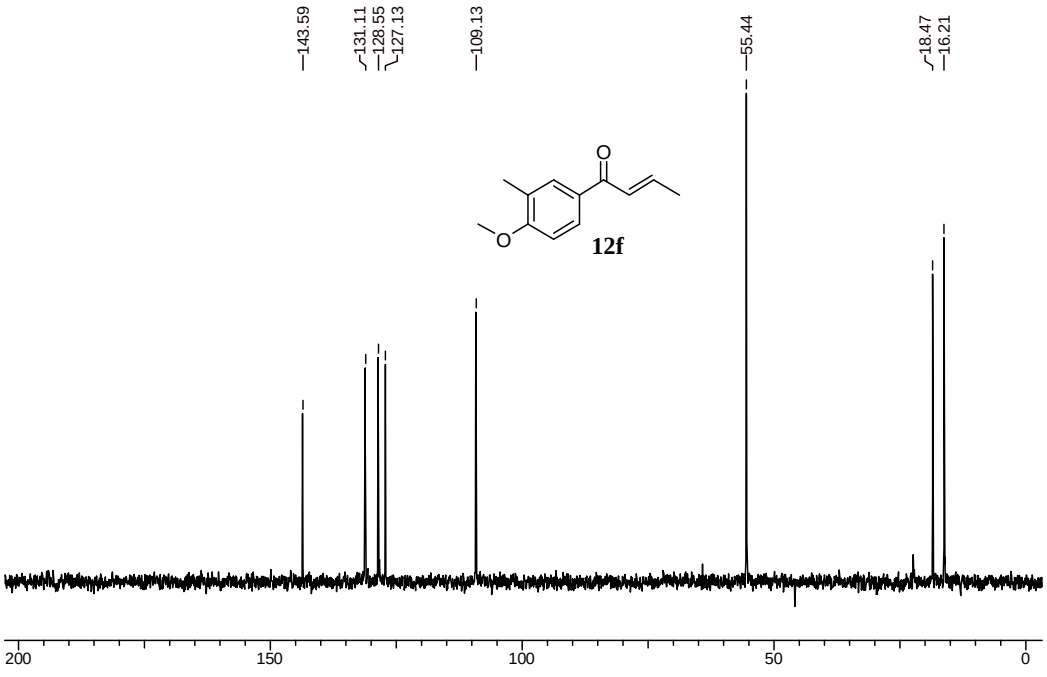
^{1}H NMR spectrum of compound **12f** ($CDCl_3$ + CCl_4, 200 MHz)



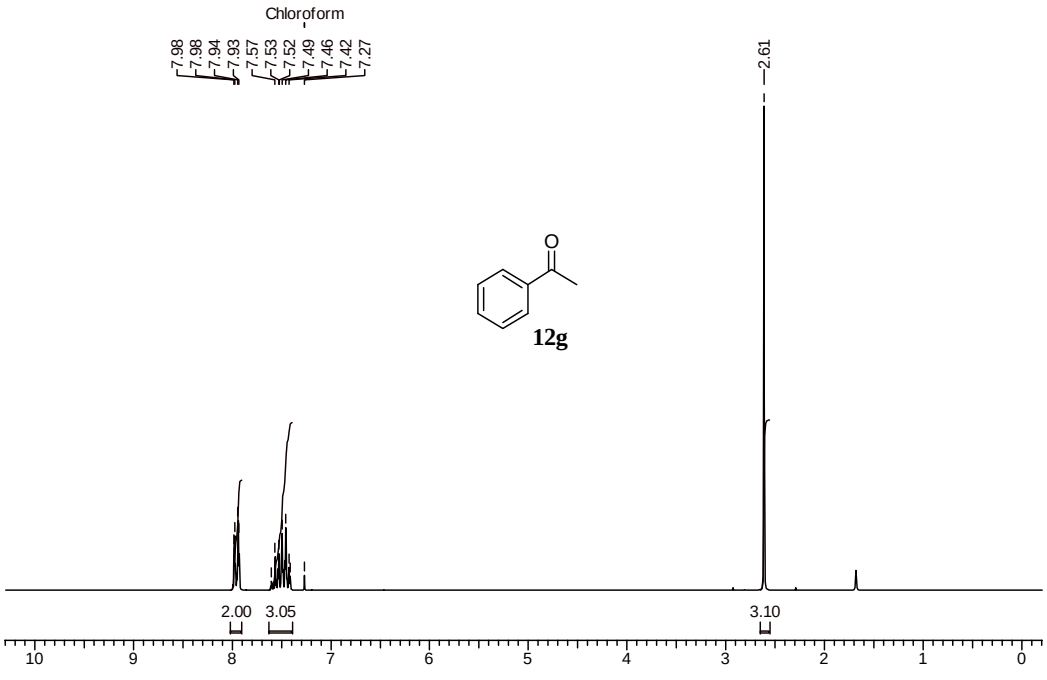
^{13}C NMR spectrum of compound **12f** ($CDCl_3$ + CCl_4, 50 MHz)



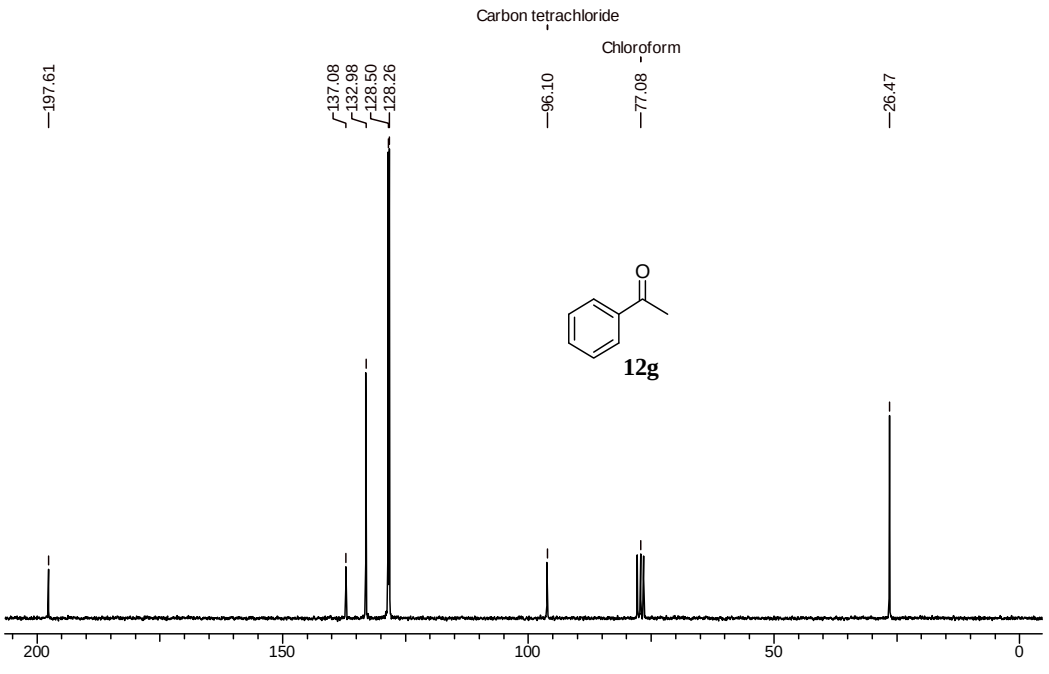
DEPT spectrum of compound **12f** ($CDCl_3$ + CCl_4, 50 MHz)



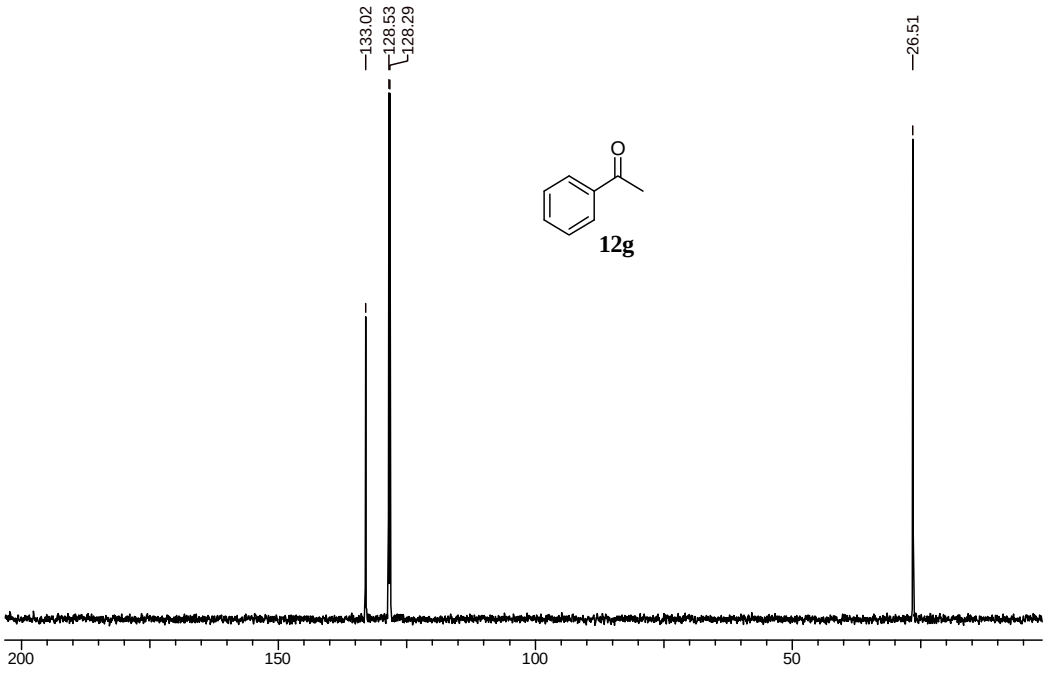
^{1}H NMR spectrum of compound **12g** ($CDCl_3$ + CCl_4, 200 MHz)



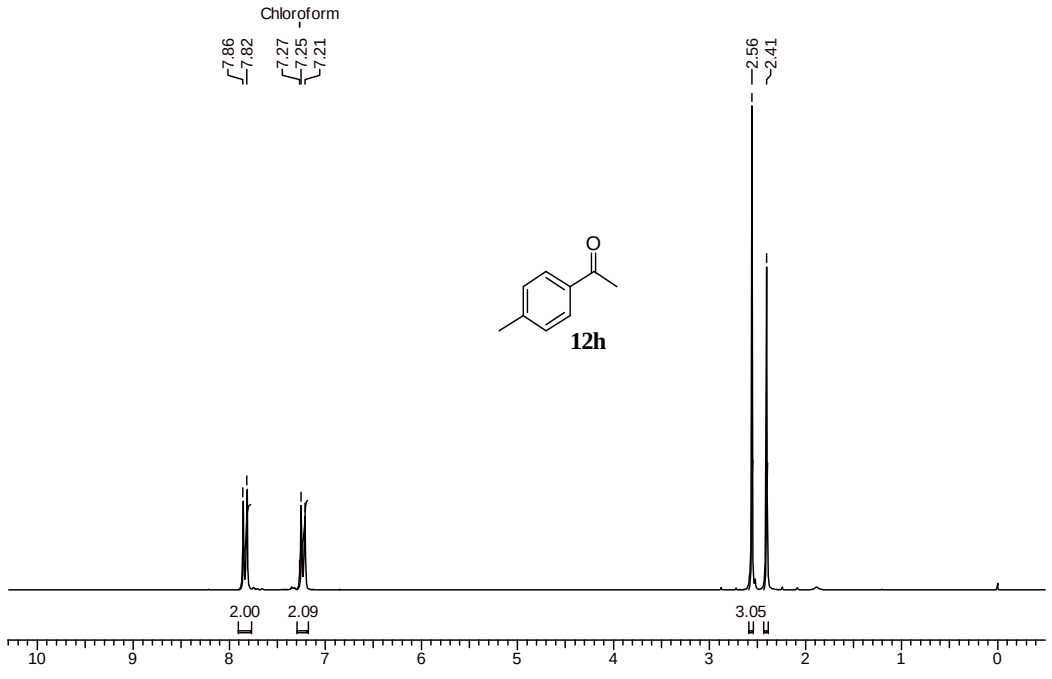
^{13}C NMR spectrum of compound **12g** ($CDCl_3 + CCl_4$, 50 MHz)



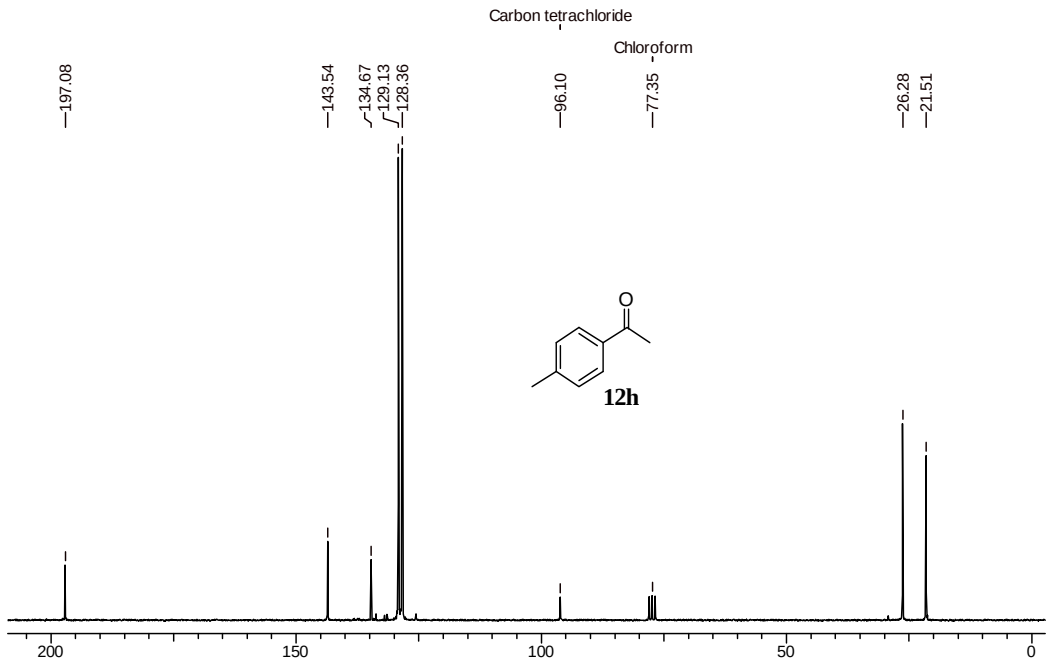
DEPT spectrum of compound **12g** ($CDCl_3 + CCl_4$, 50 MHz)



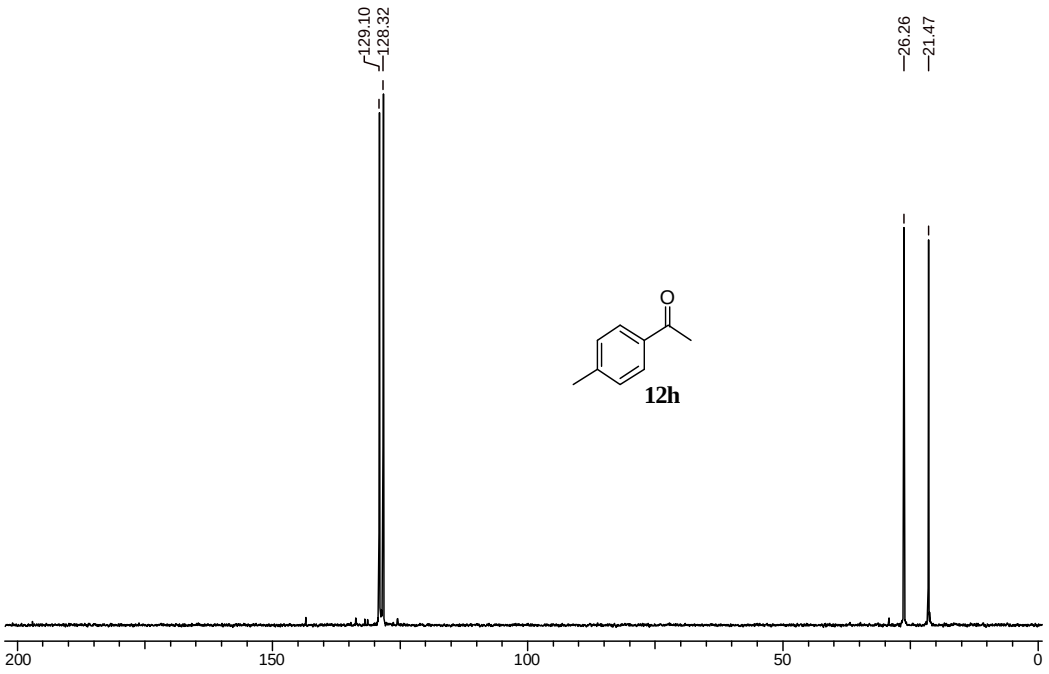
^{1}H NMR spectrum of compound **12h** ($CDCl_3$ + CCl_4, 200 MHz)



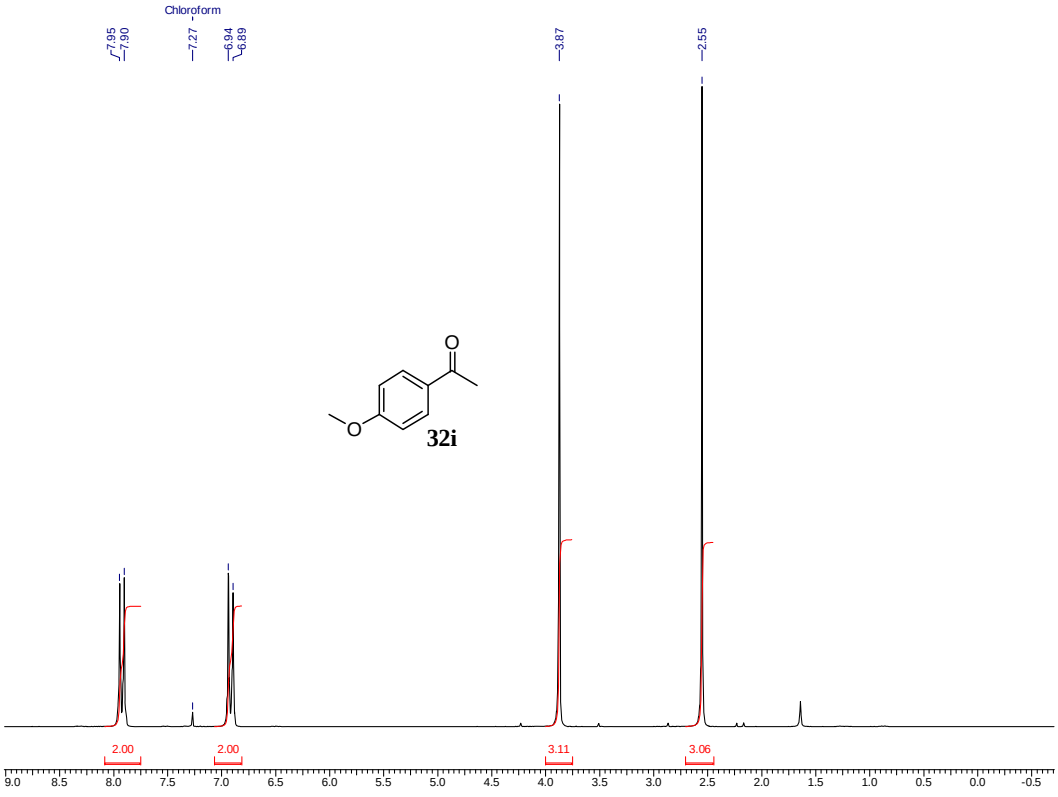
^{13}C NMR spectrum of compound **12h** ($CDCl_3$ + CCl_4, 50 MHz)



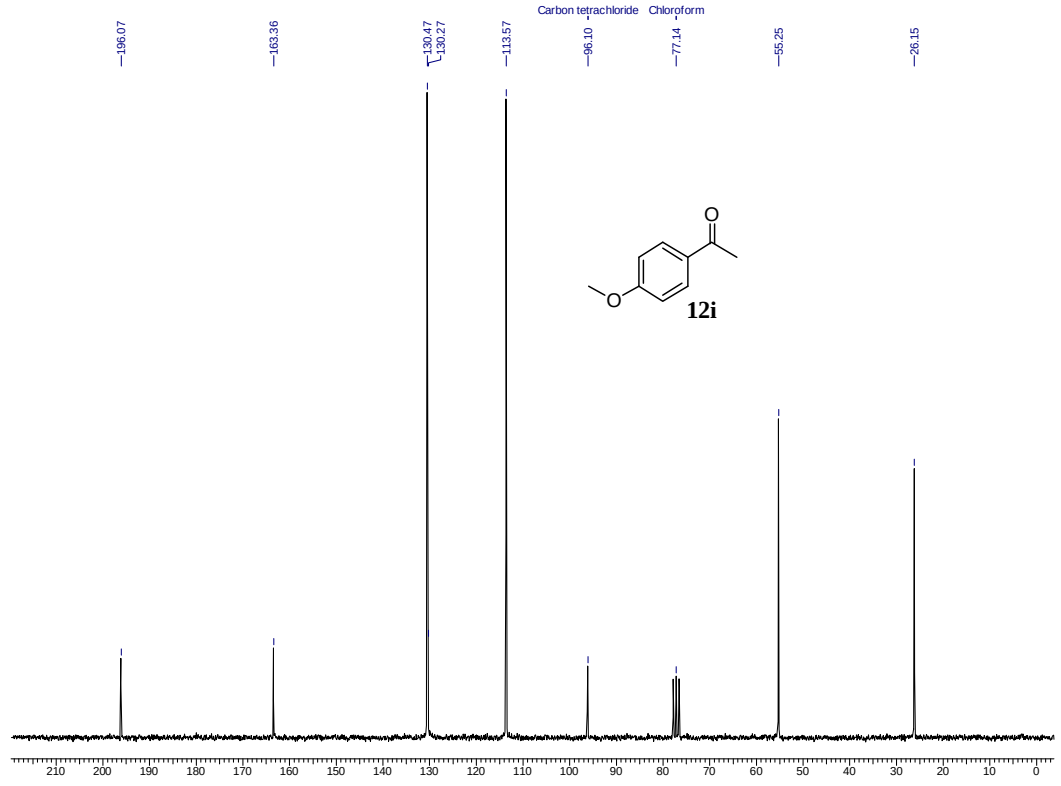
DEPT spectrum of compound **12h** ($CDCl_3 + CCl_4$, 50 MHz)



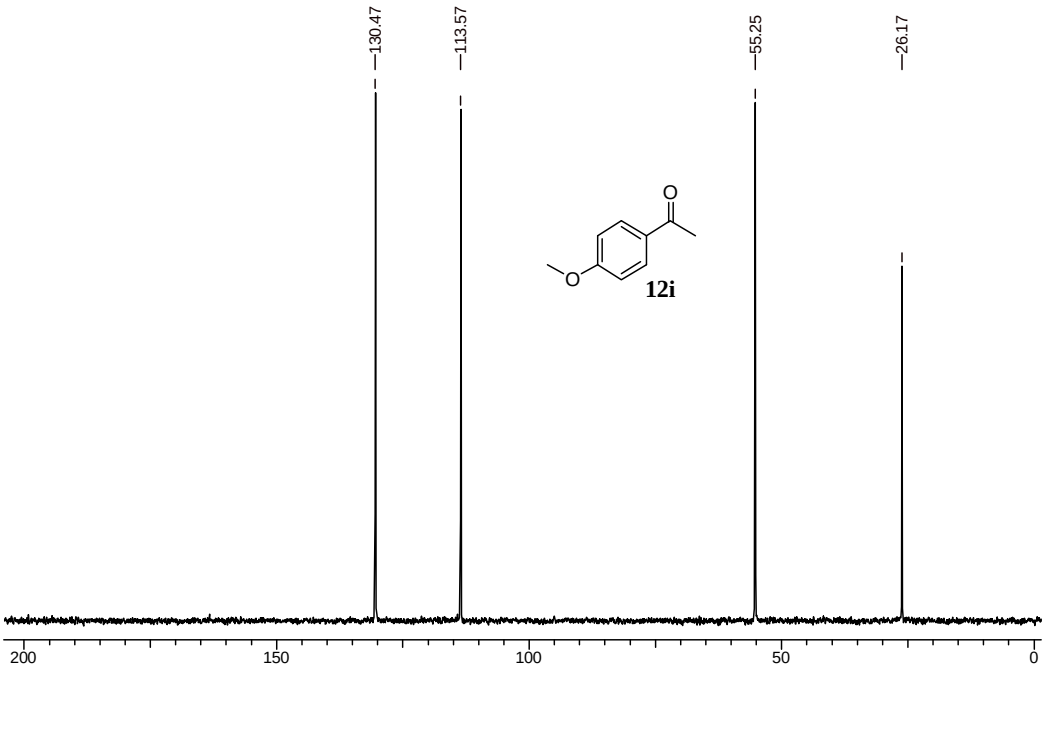
^1H NMR spectrum of compound **12i** ($CDCl_3 + CCl_4$, 200 MHz)



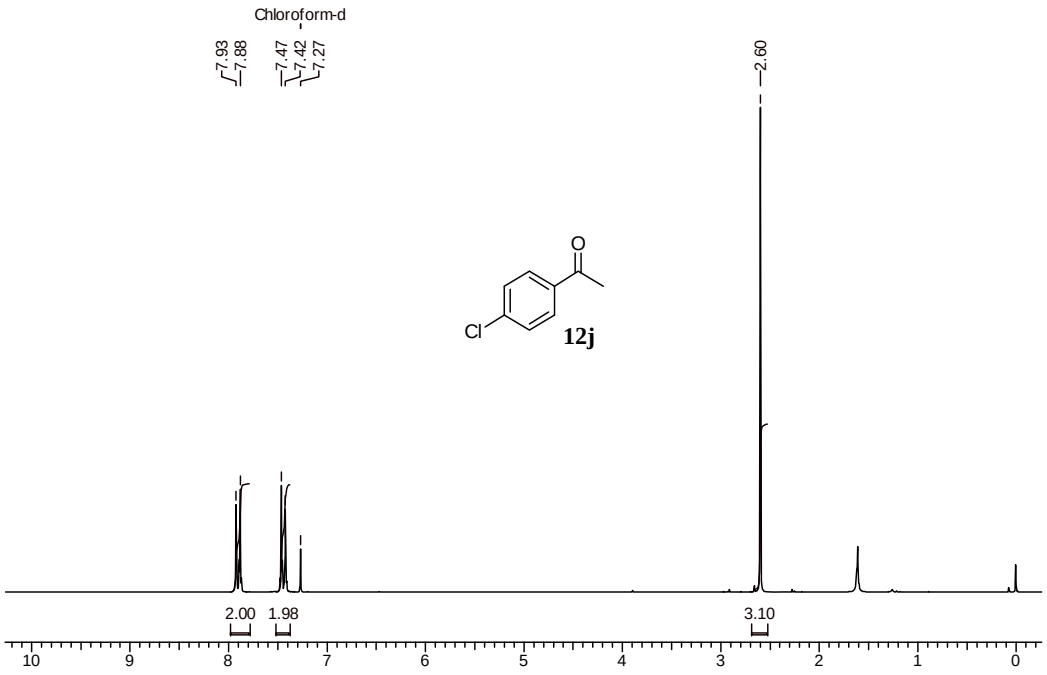
^{13}C NMR spectrum of compound **12i** ($CDCl_3 + CCl_4$, 50 MHz)



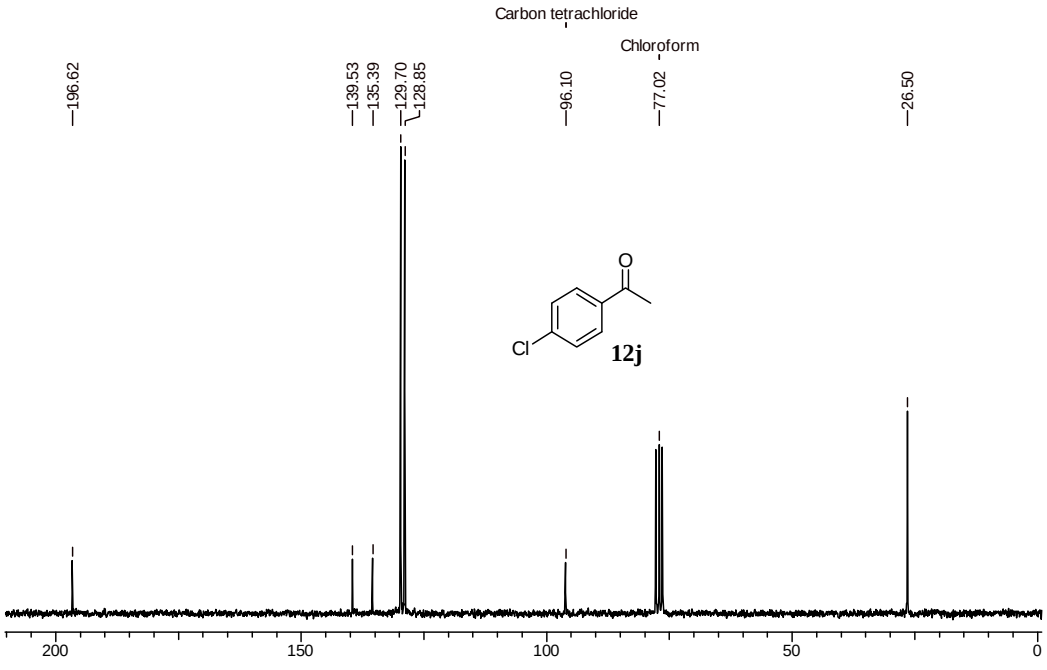
DEPT spectrum of compound **12i** ($CDCl_3 + CCl_4$, 50 MHz)



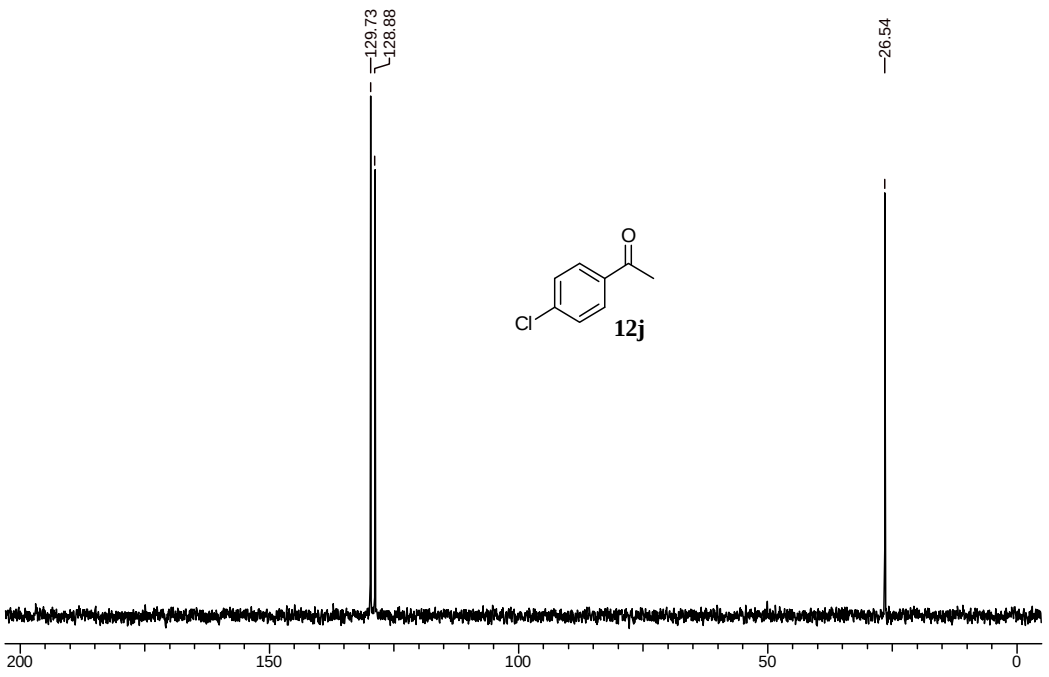
^{1}H NMR spectrum of compound **12j** ($CDCl_3$ + CCl_4, 200 MHz)



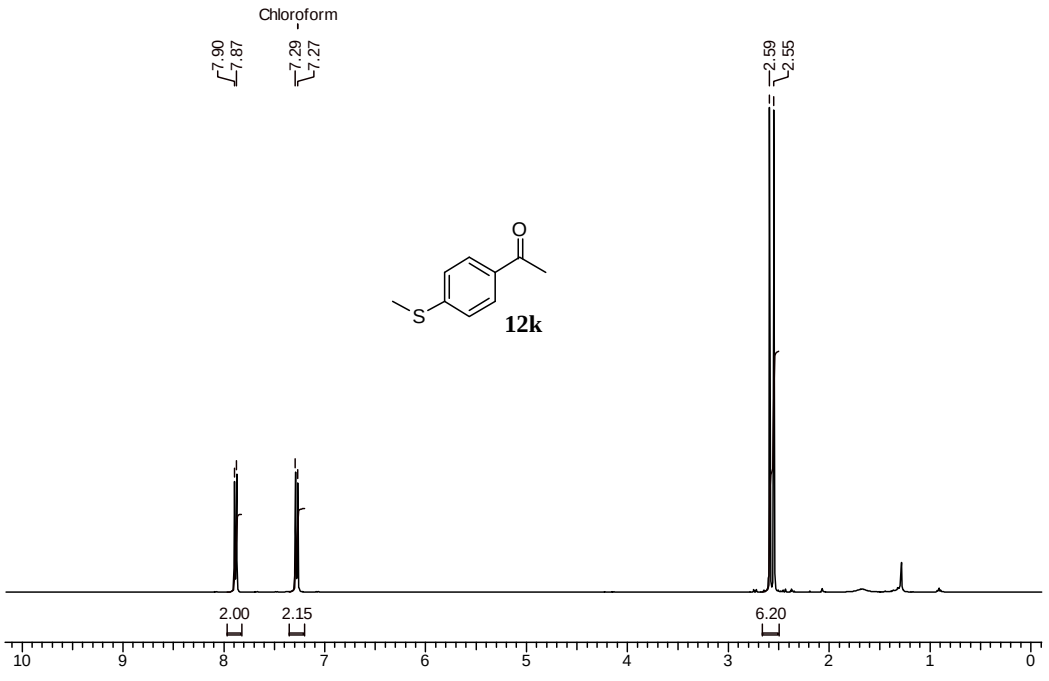
^{13}C NMR spectrum of compound **12j** ($CDCl_3$ + CCl_4, 50 MHz)



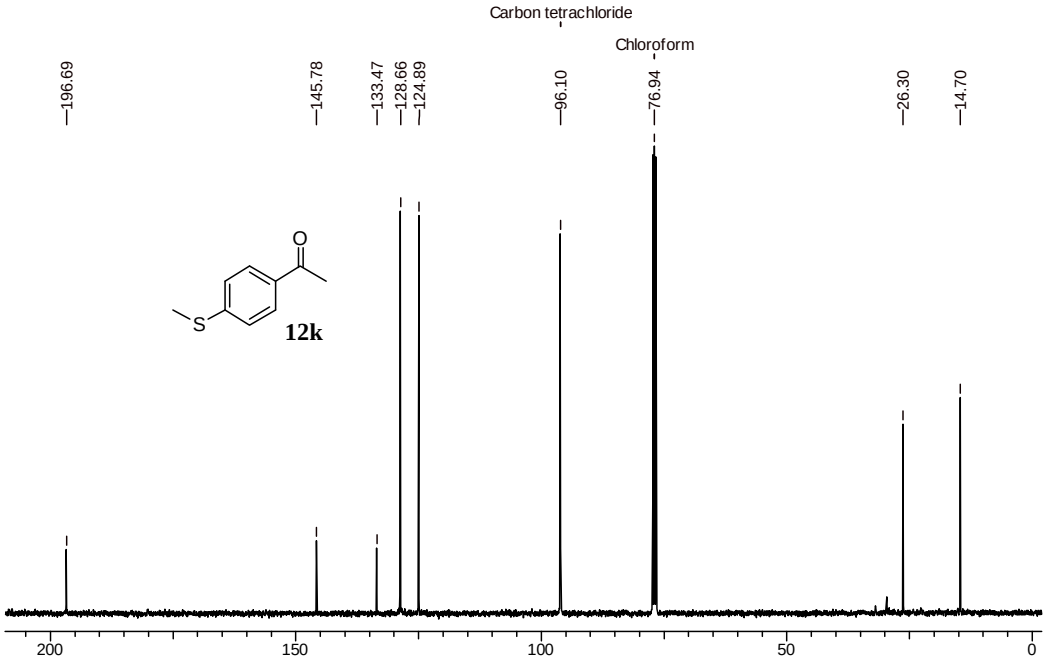
DEPT spectrum of compound **12j** ($CDCl_3$ + CCl_4, 50 MHz)



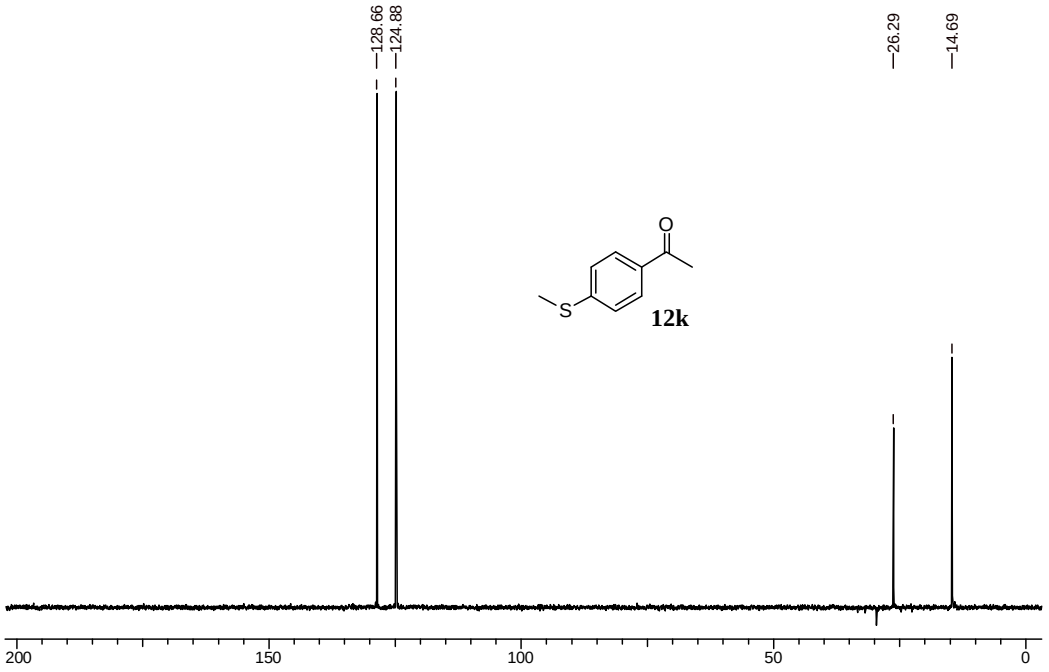
^{1}H NMR spectrum of compound **12k** ($CDCl_3$ + CCl_4, 400 MHz)



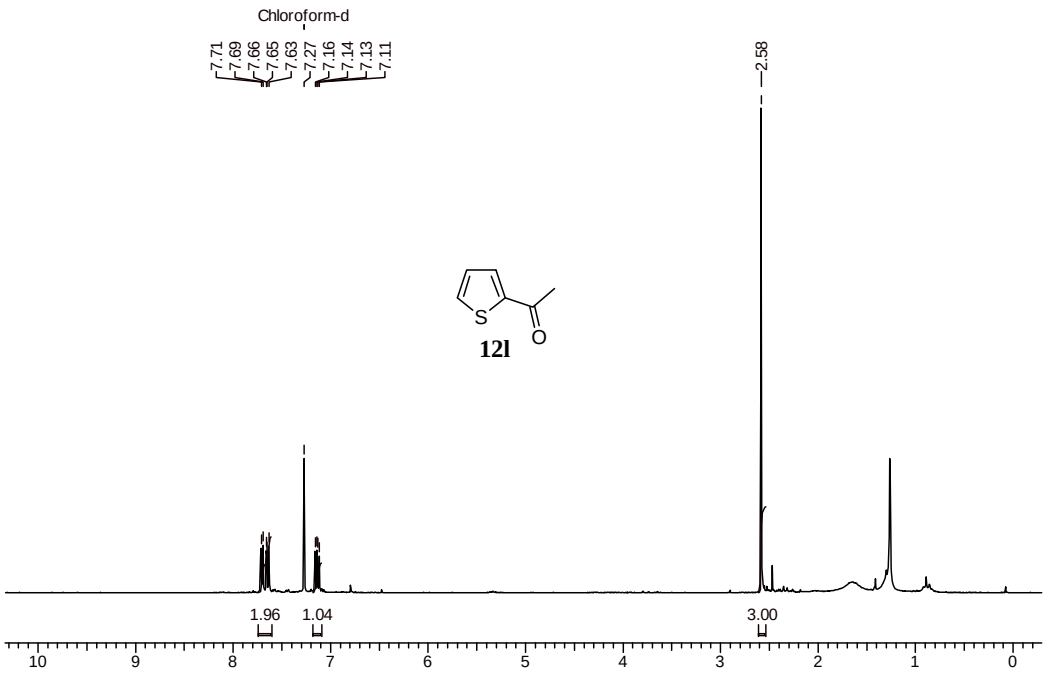
^{13}C NMR spectrum of compound **12k** ($CDCl_3 + CCl_4$, 100 MHz)



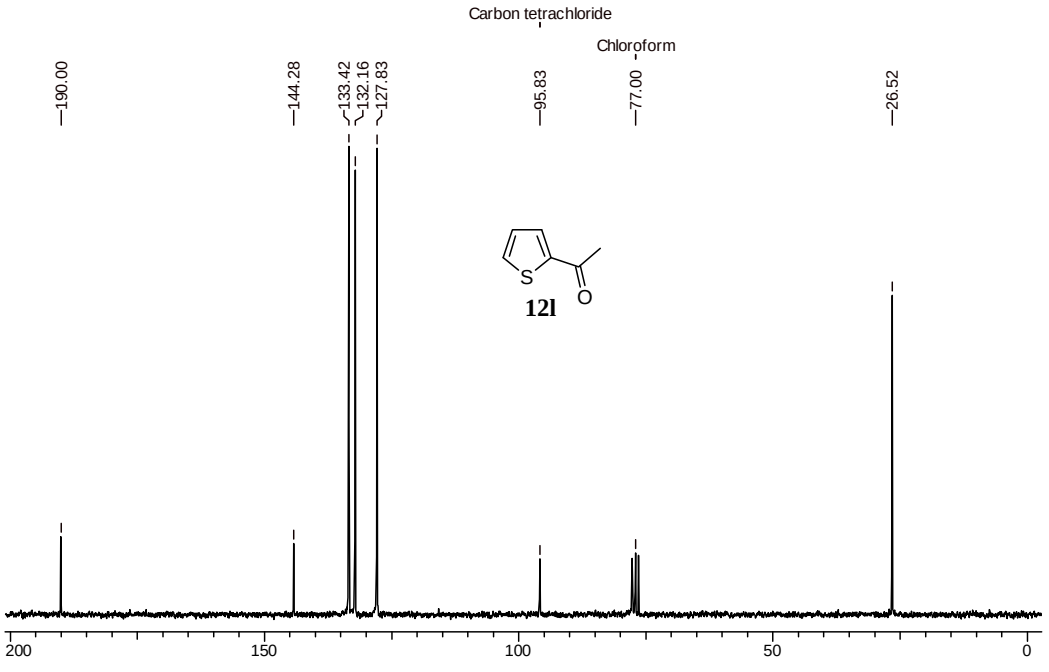
DEPT spectrum of compound **12k** ($CDCl_3 + CCl_4$, 100 MHz)



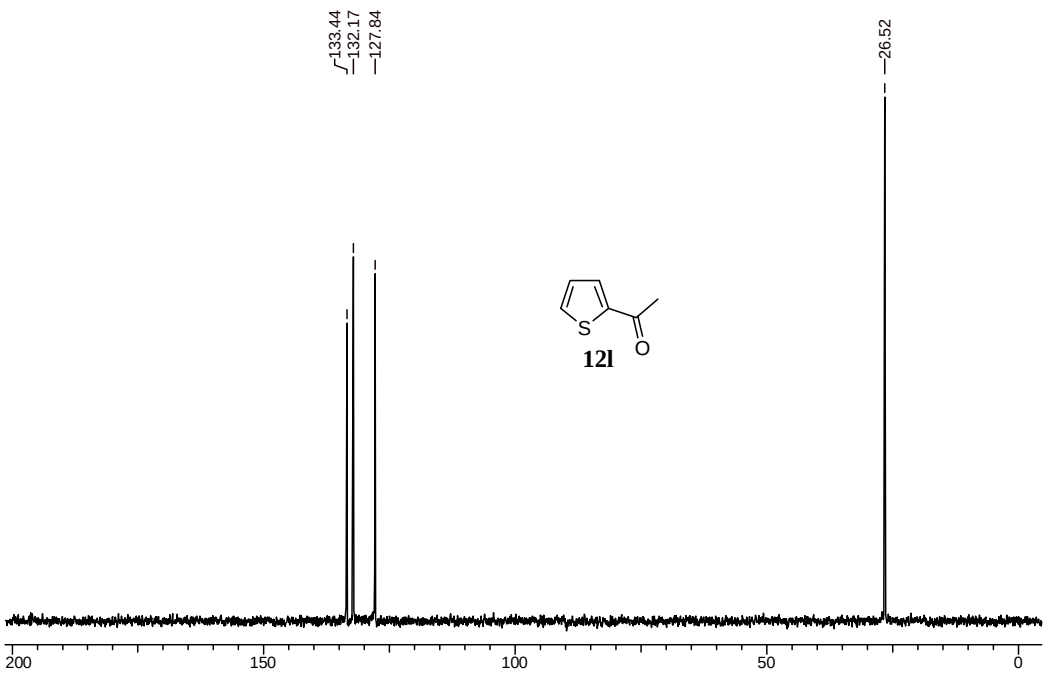
^{1}H NMR spectrum of compound **12l** ($CDCl_3$ + CCl_4, 200 MHz)



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

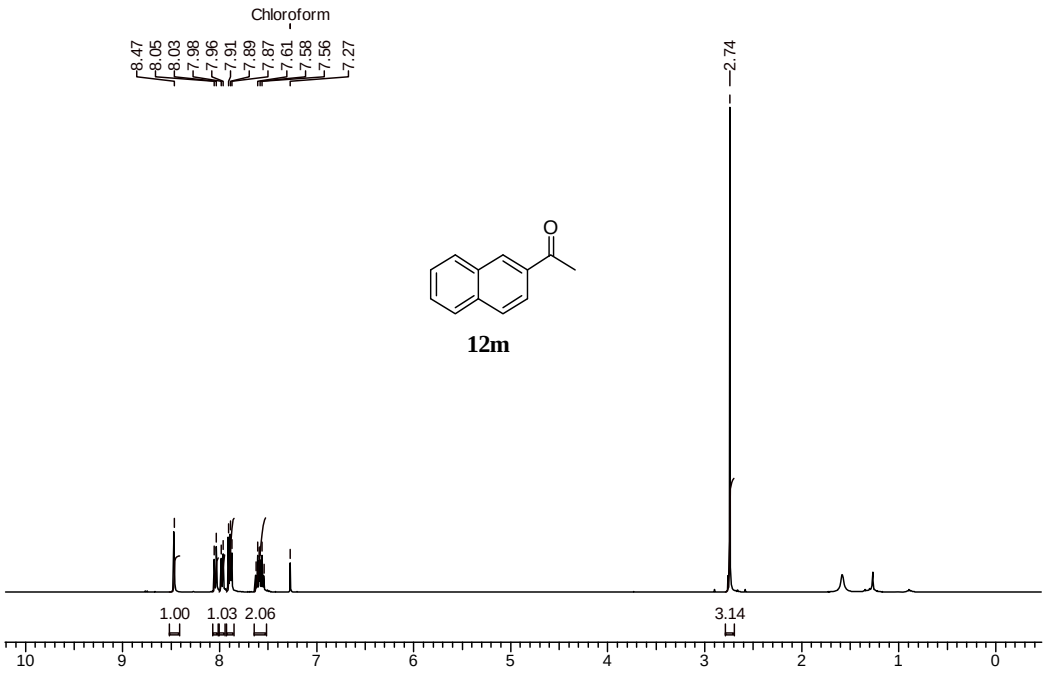


DEPT spectrum of compound **12l** ($CDCl_3$ + CCl_4, 50 MHz)



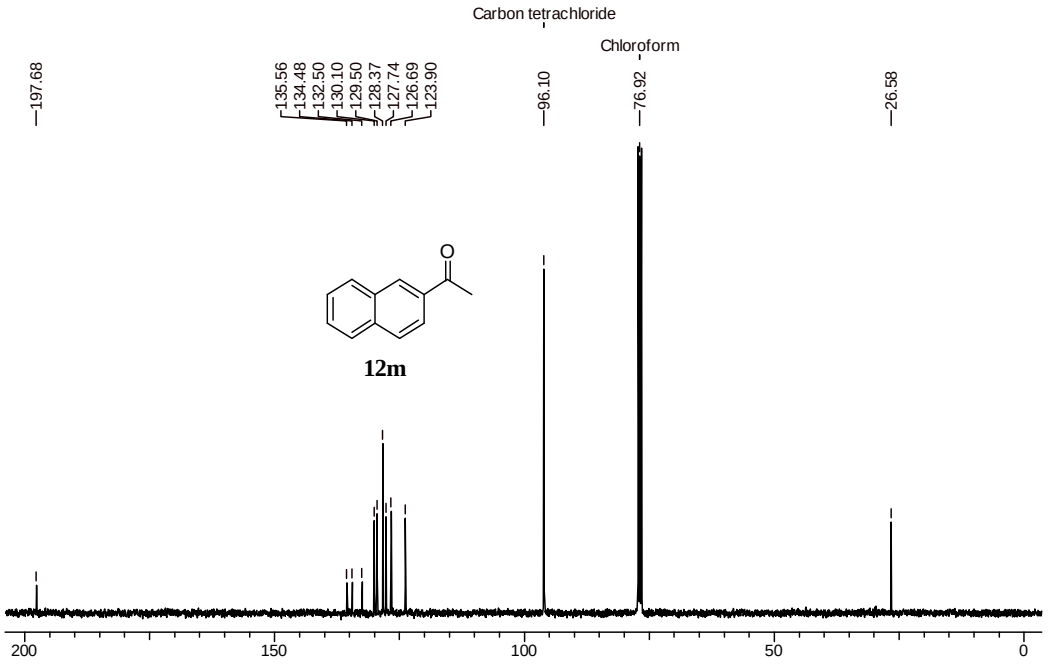
12l

^{1}H NMR spectrum of compound **12m** ($CDCl_3$ + CCl_4, 400 MHz)

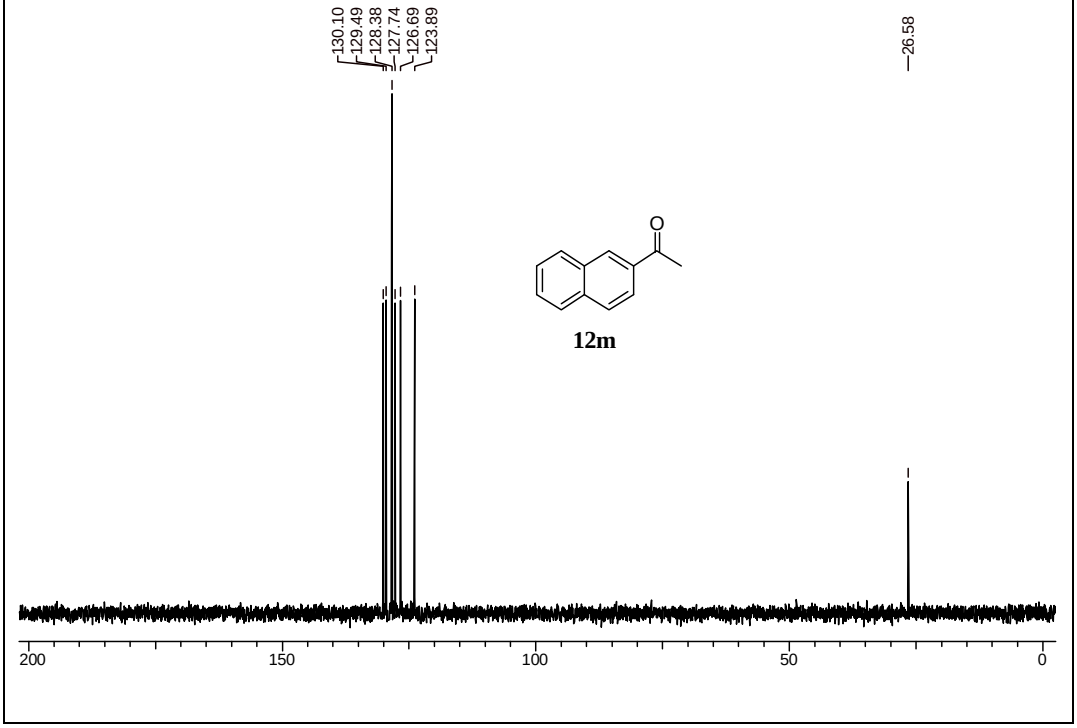


12m

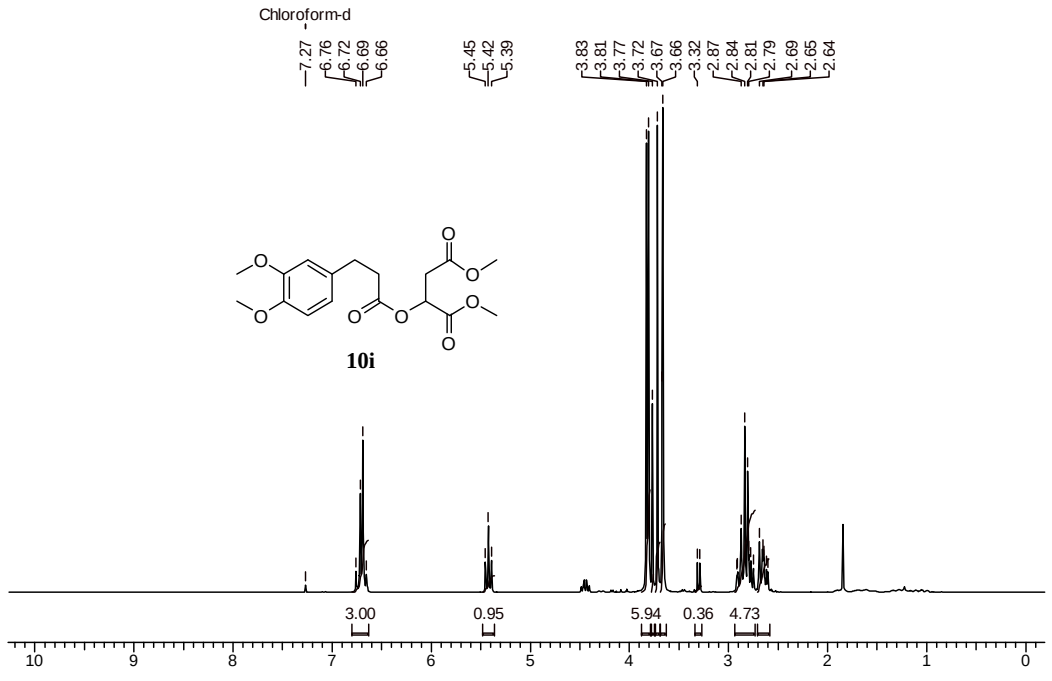
^{13}C NMR spectrum of compound **12m** ($CDCl_3 + CCl_4$, 100 MHz)



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

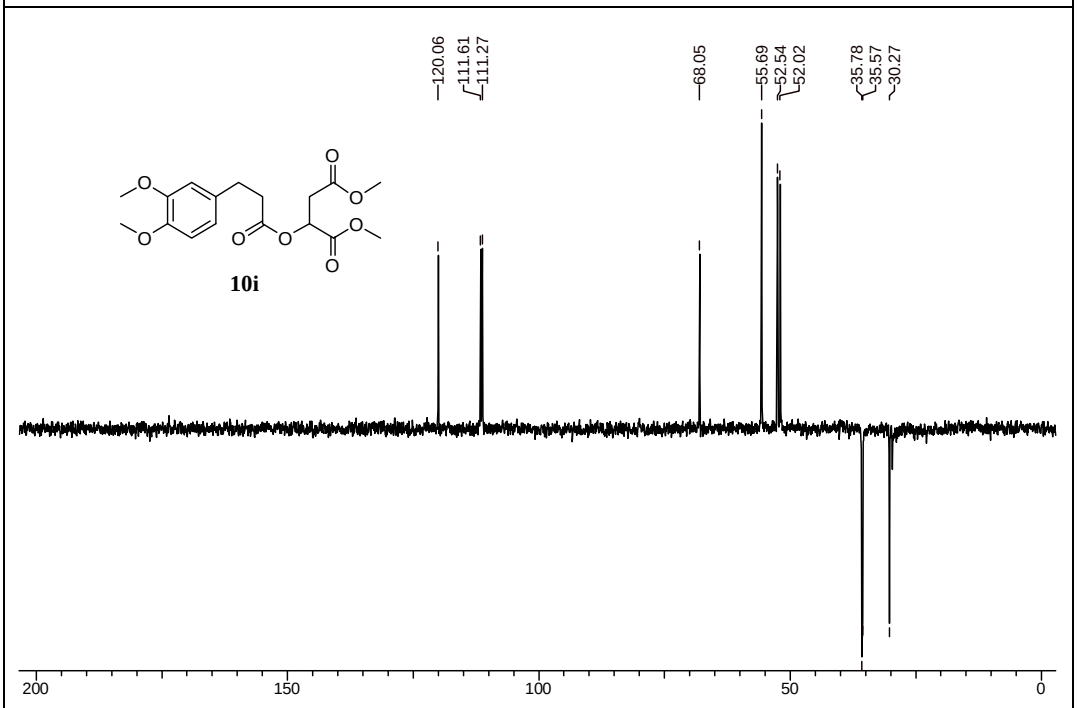


^{1}H NMR spectrum of compound **10i** ($CDCl_3$ + CCl_4, 200 MHz)

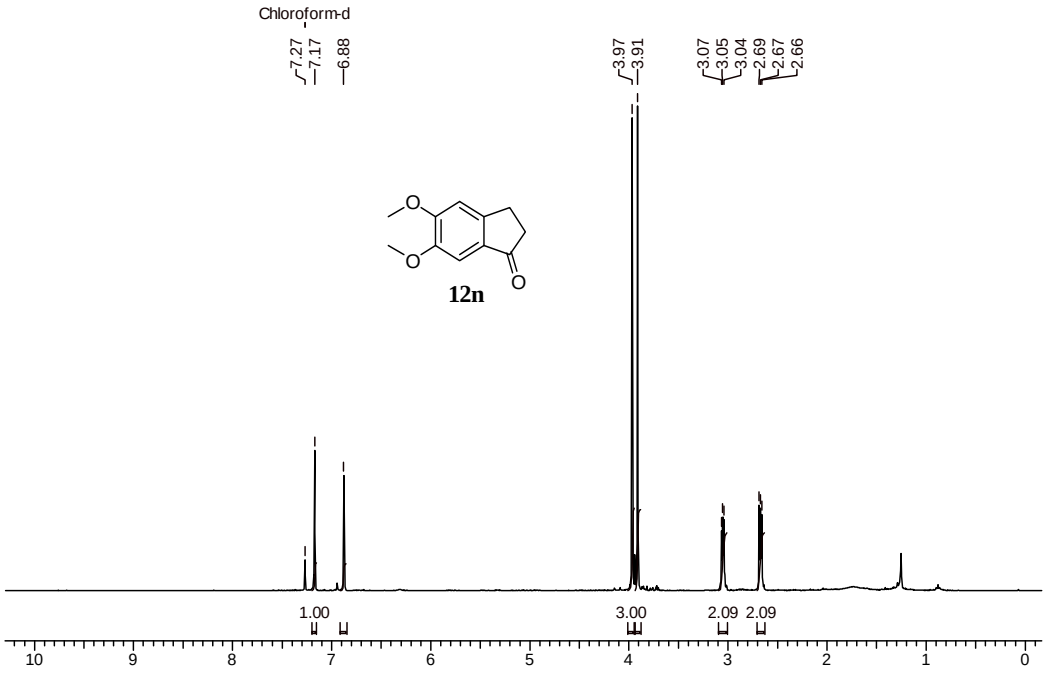


^{13}C NMR spectrum of compound **10i** ($CDCl_3$ + CCl_4, 50 MHz)

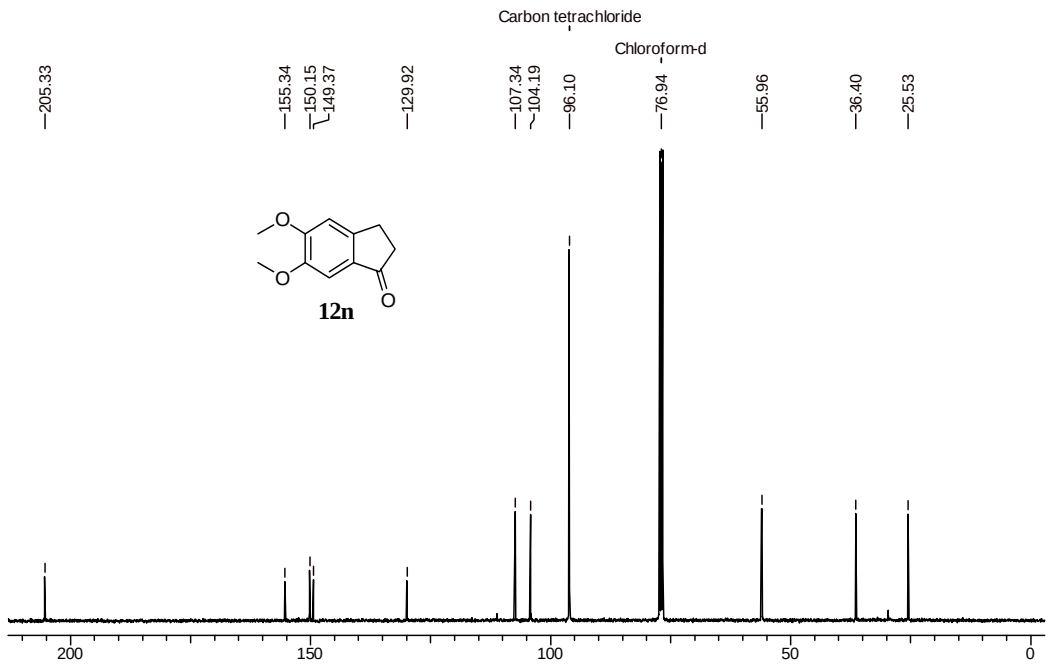
DEPT spectrum of compound **10i** ($CDCl_3$ + CCl_4, 50 MHz)



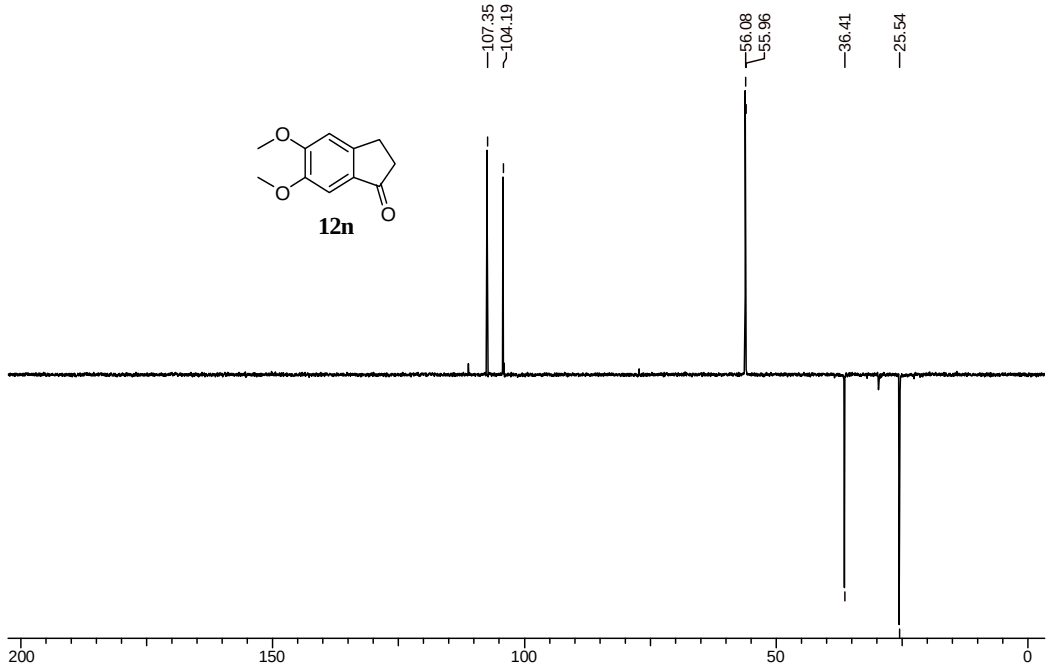
^{1}H NMR spectrum of compound **12n** ($CDCl_3$ + CCl_4, 400 MHz)



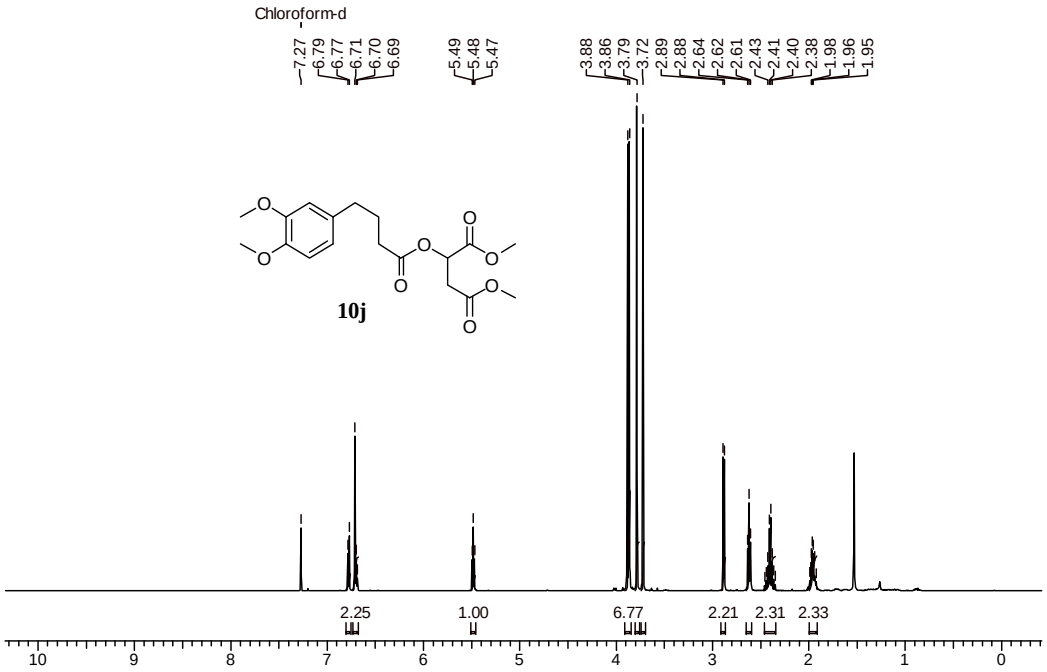
^{13}C NMR spectrum of compound **12n** ($CDCl_3 + CCl_4$, 100 MHz)



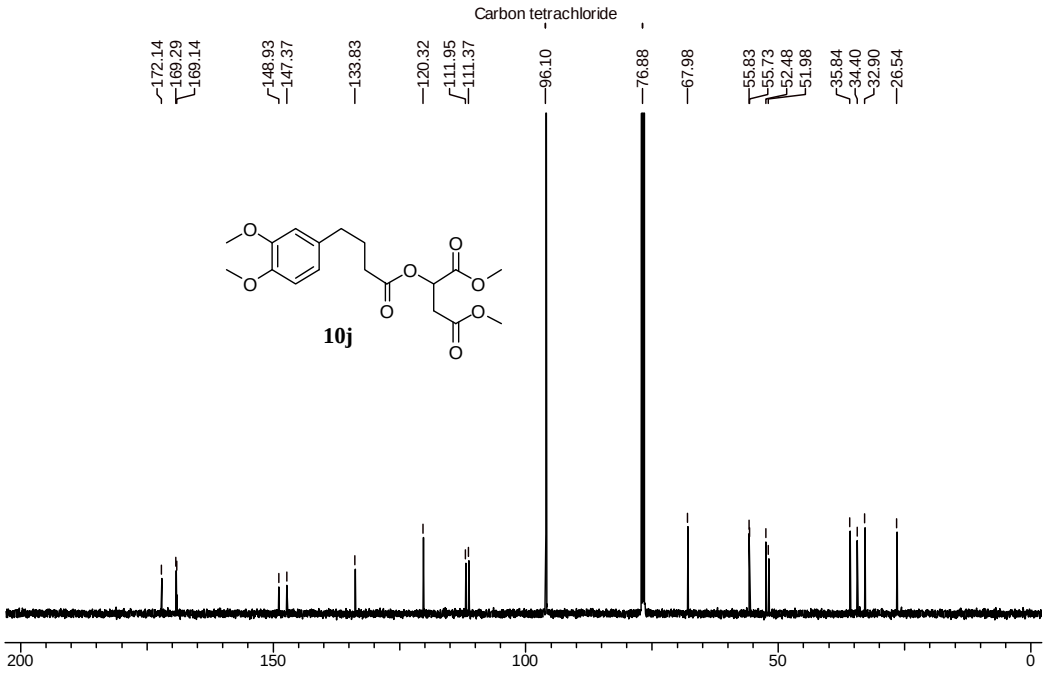
DEPT spectrum of compound **12n** ($CDCl_3 + CCl_4$, 100 MHz)



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



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



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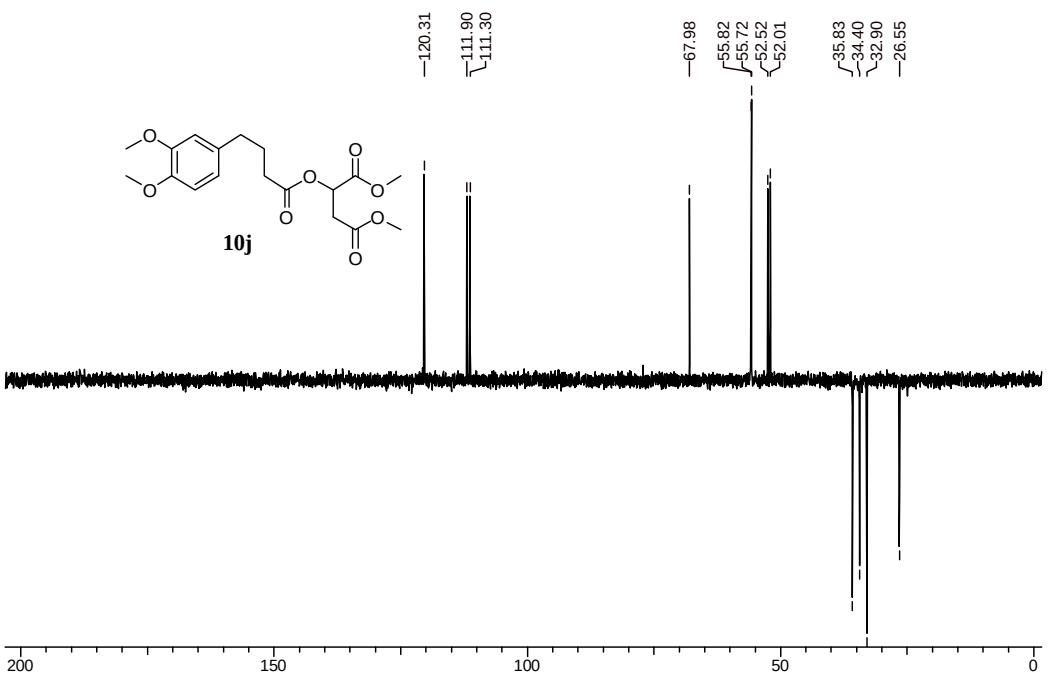

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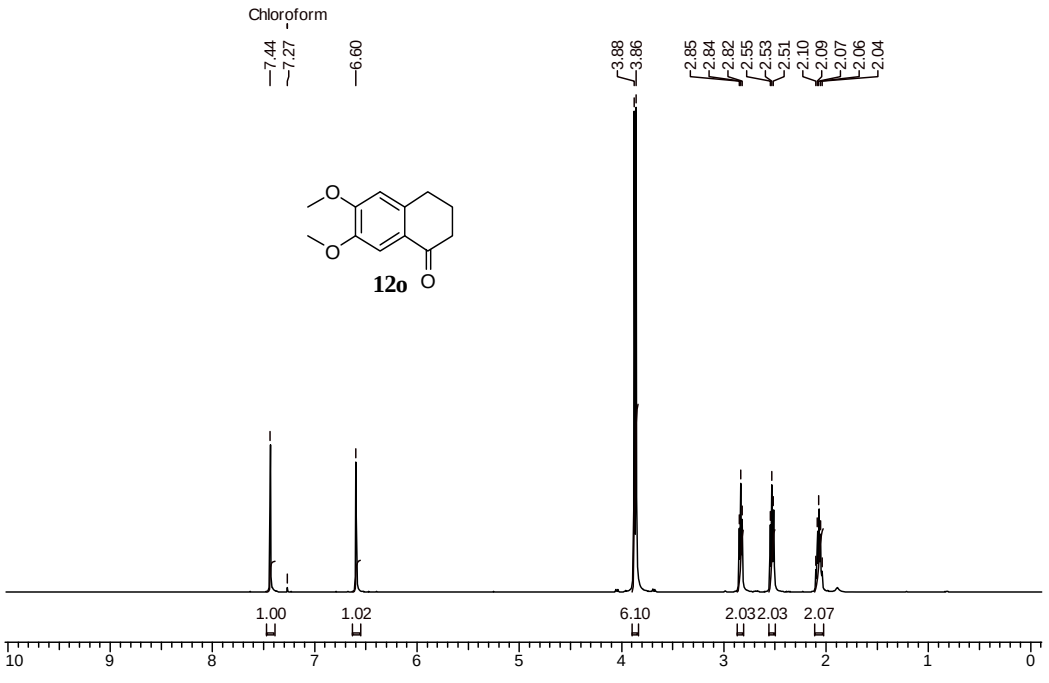

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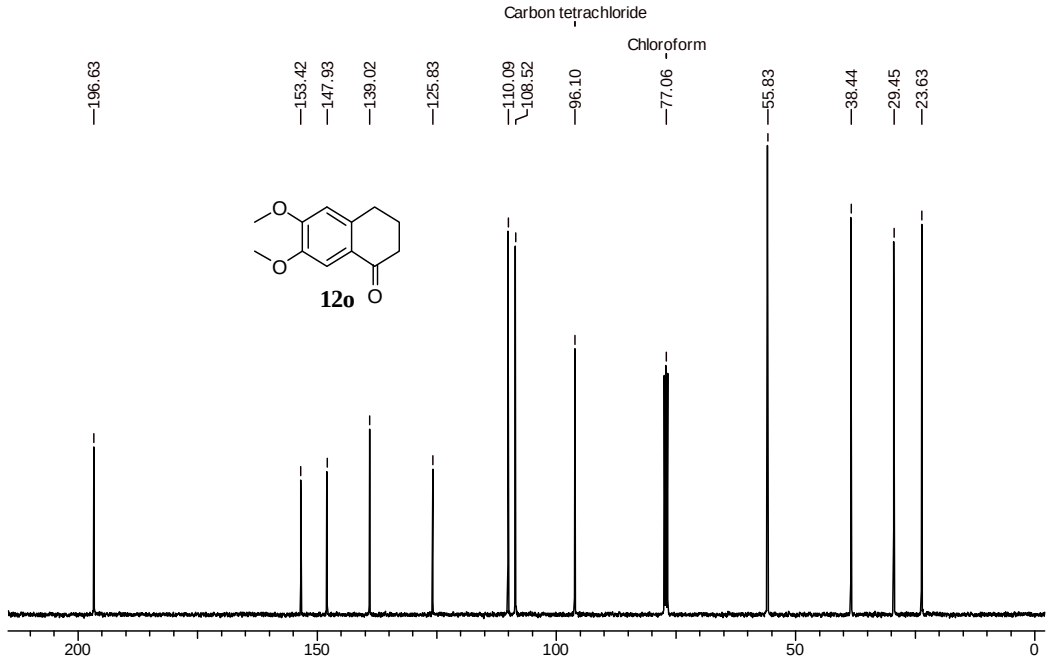

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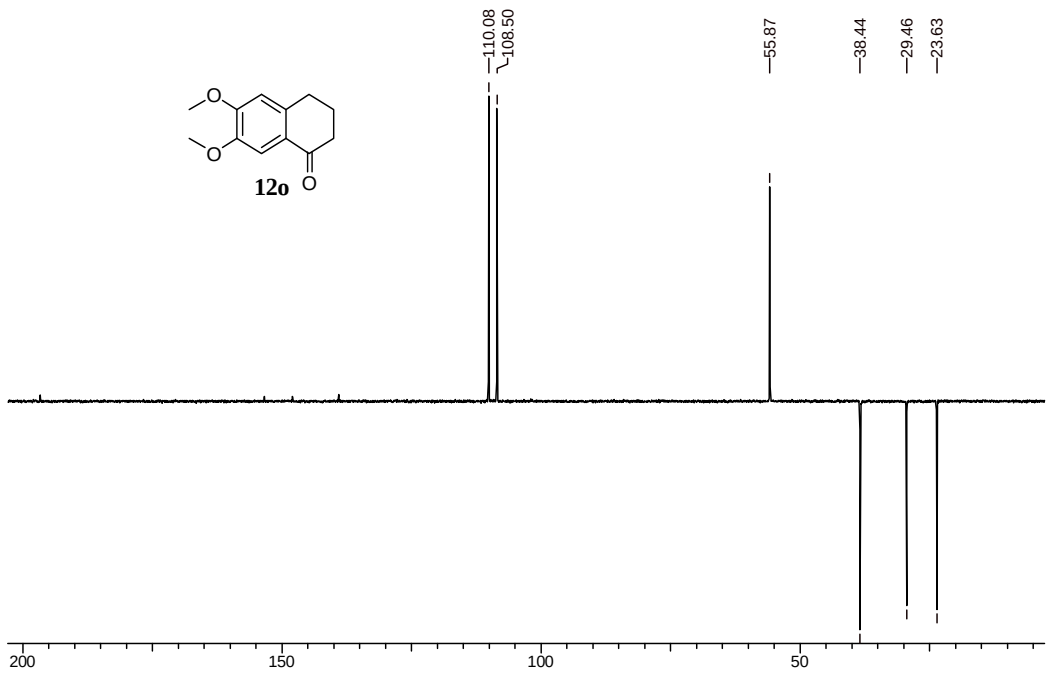

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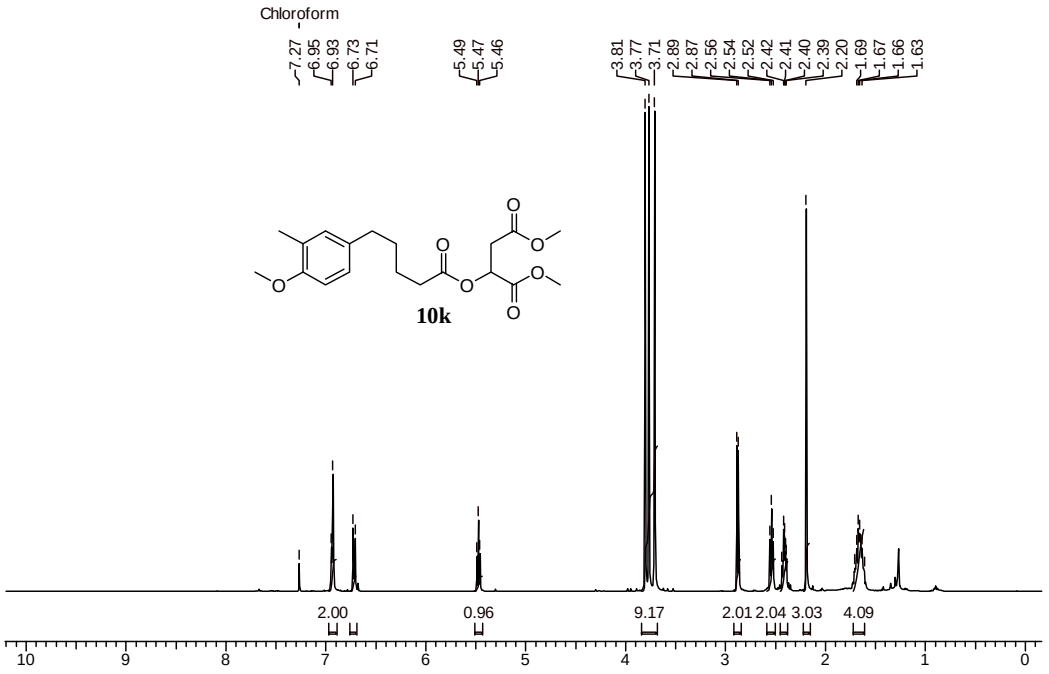

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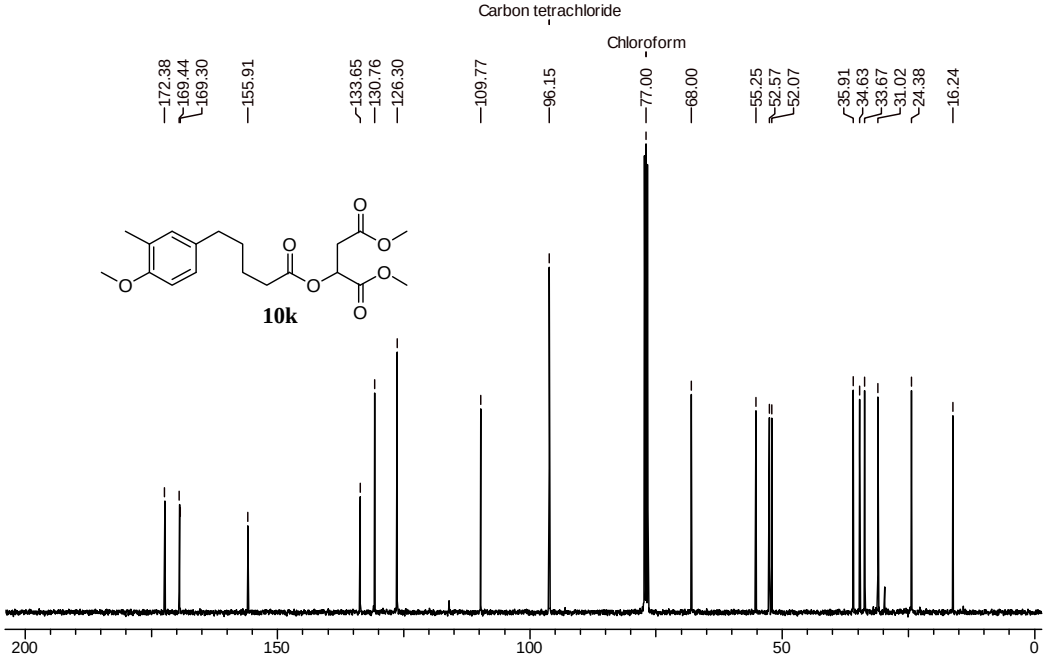

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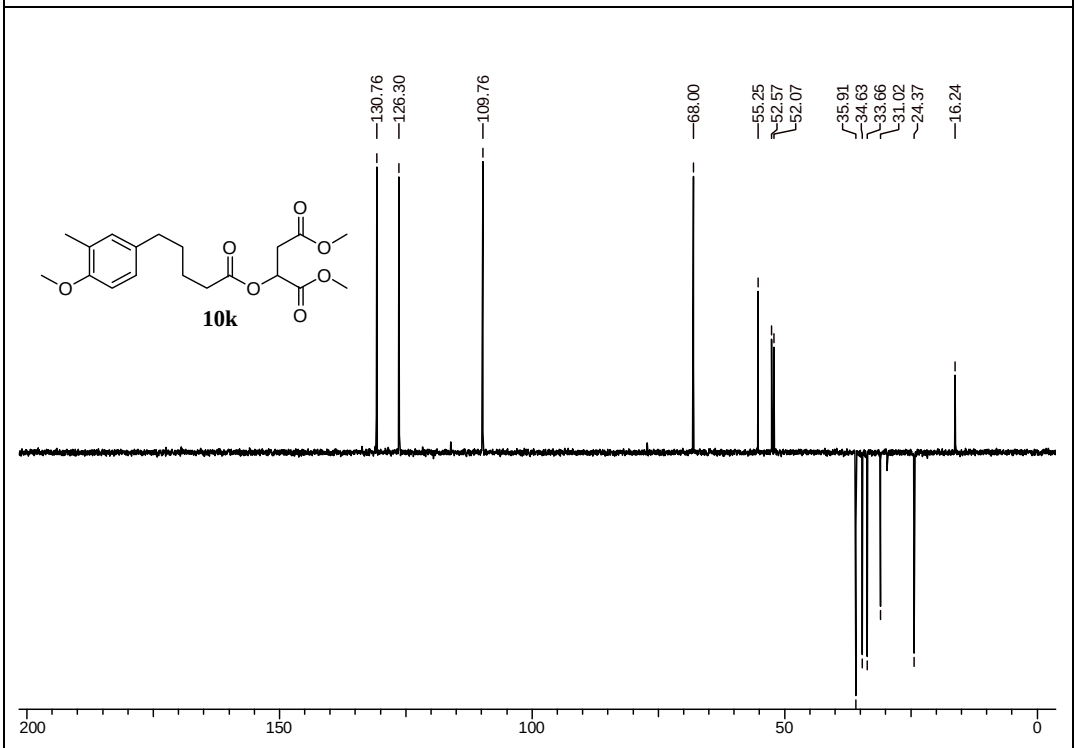

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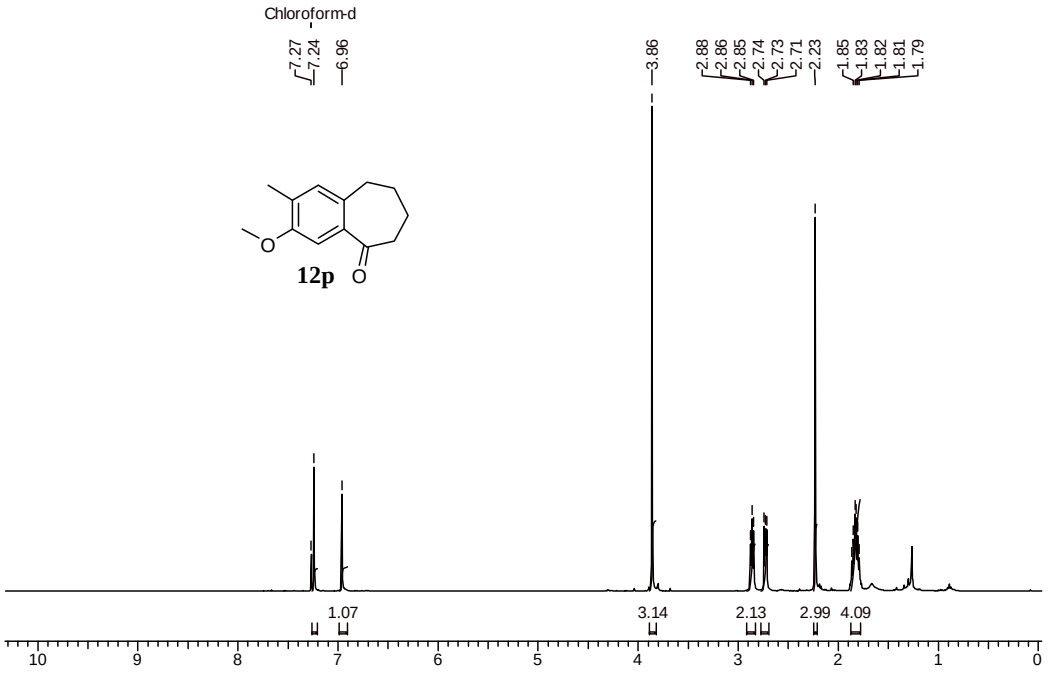

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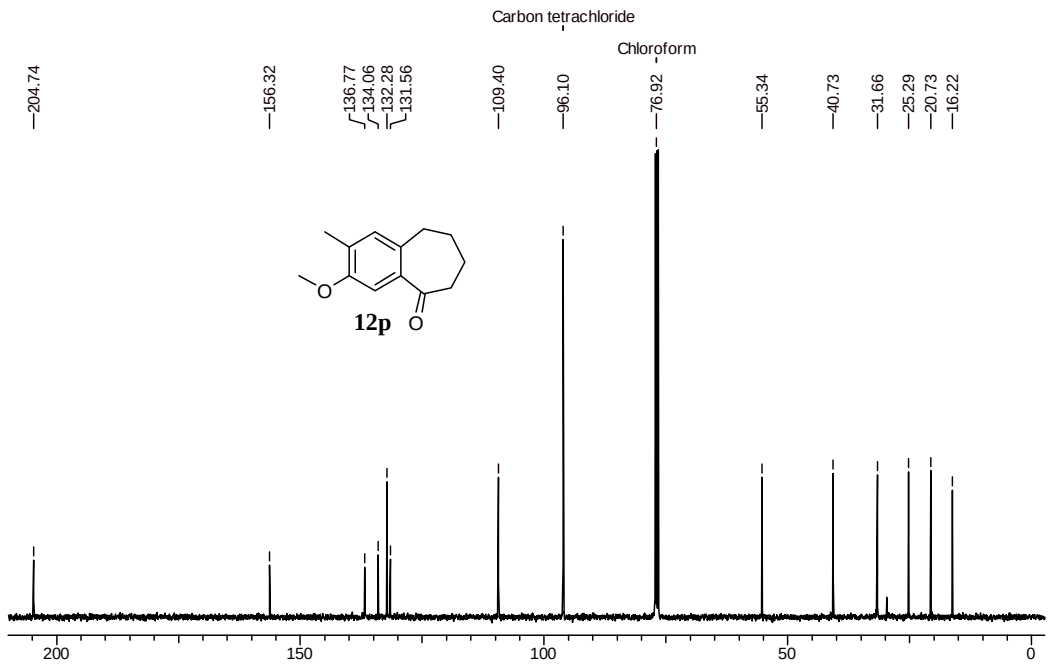

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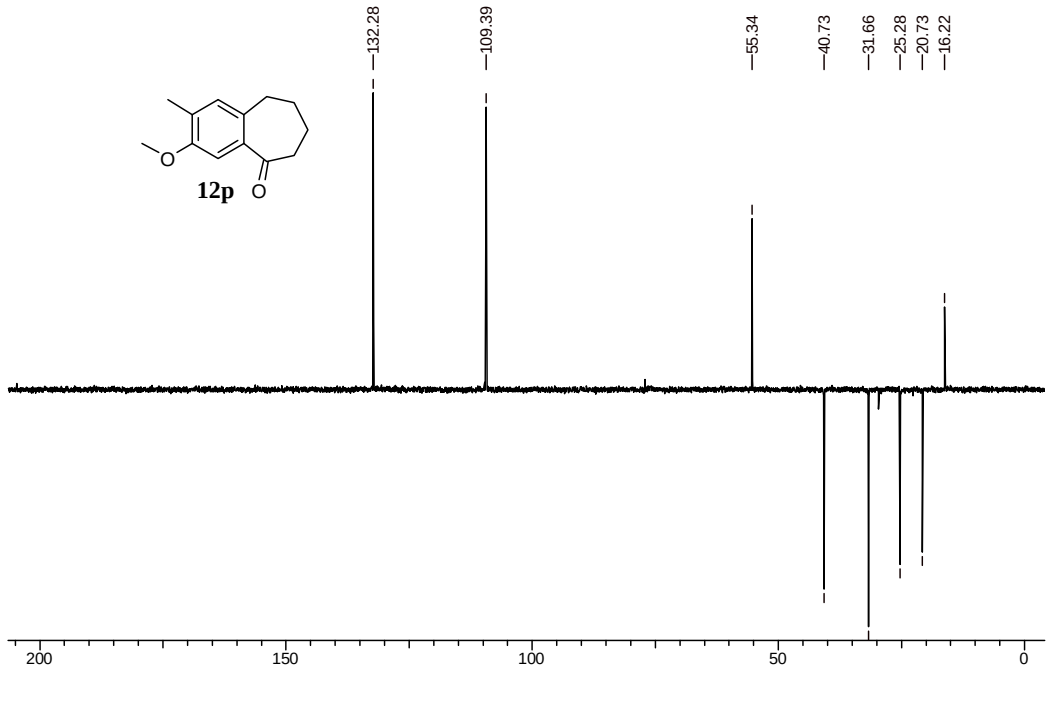

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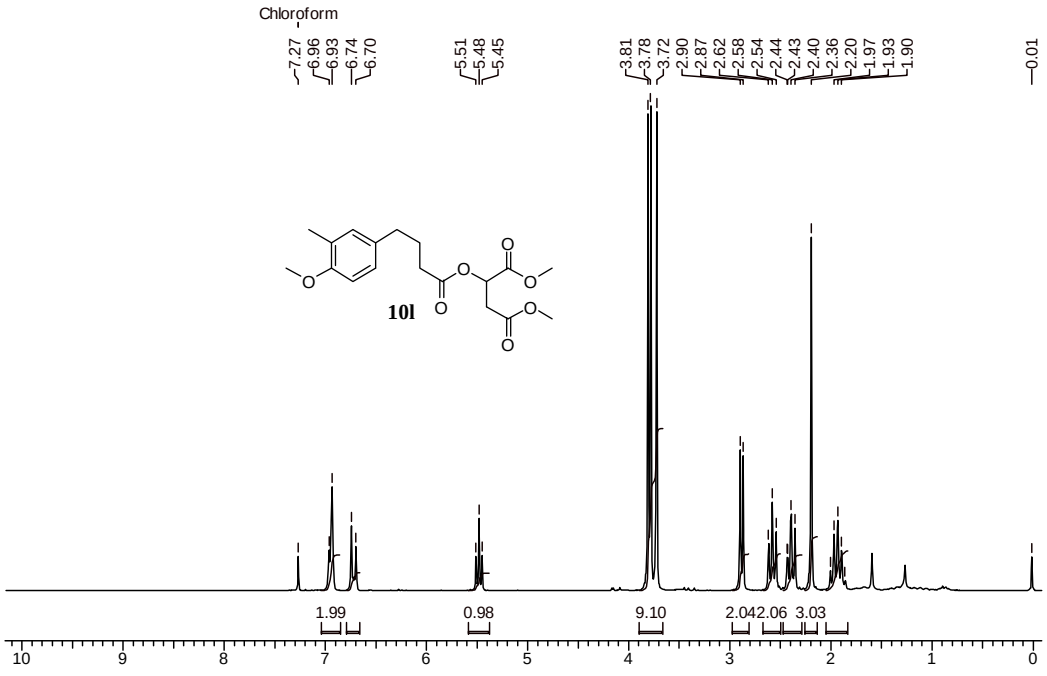

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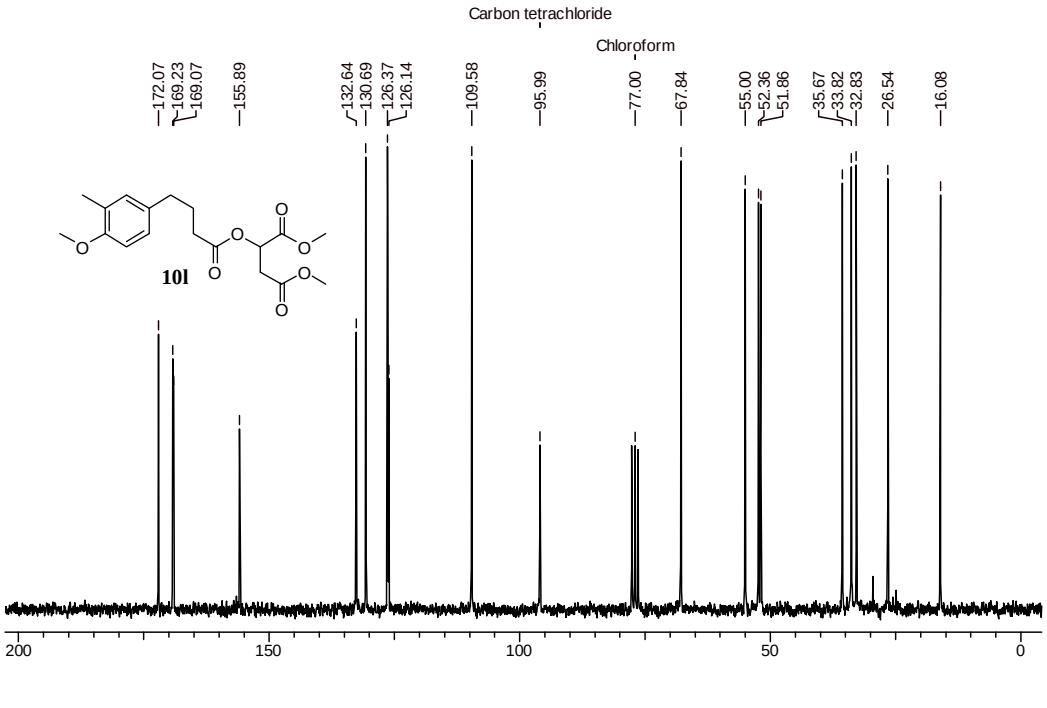

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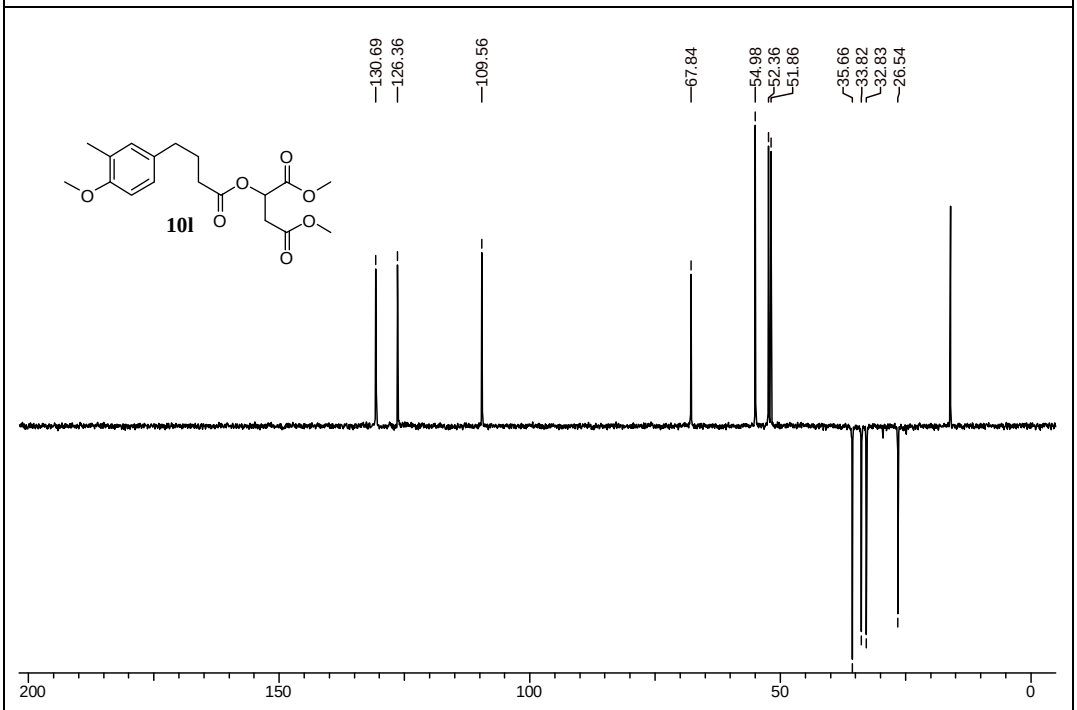

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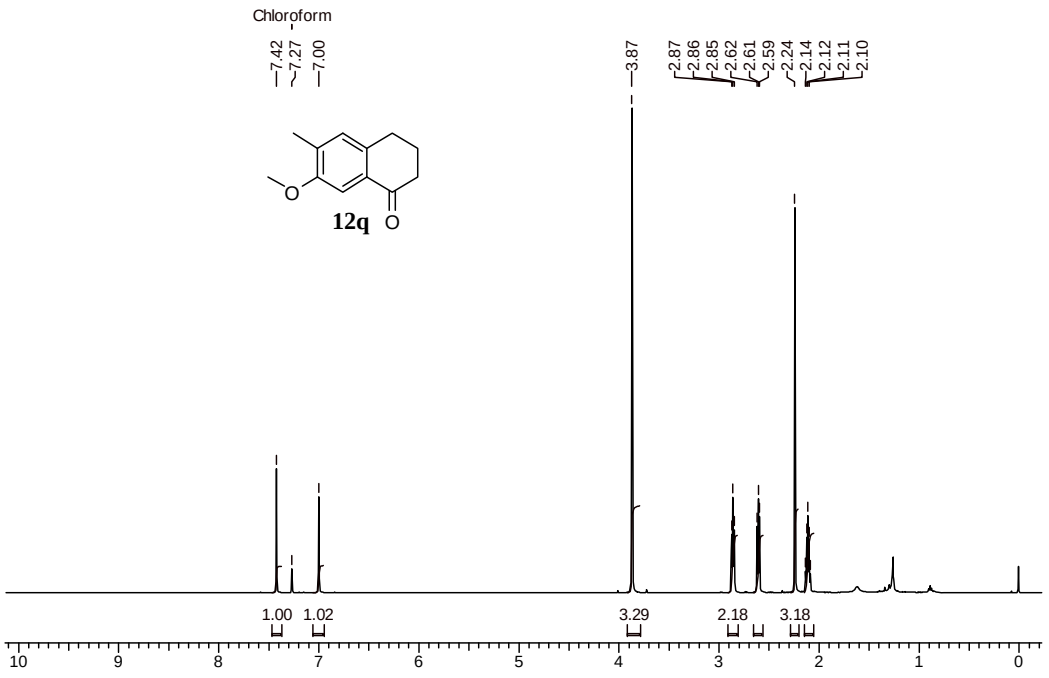

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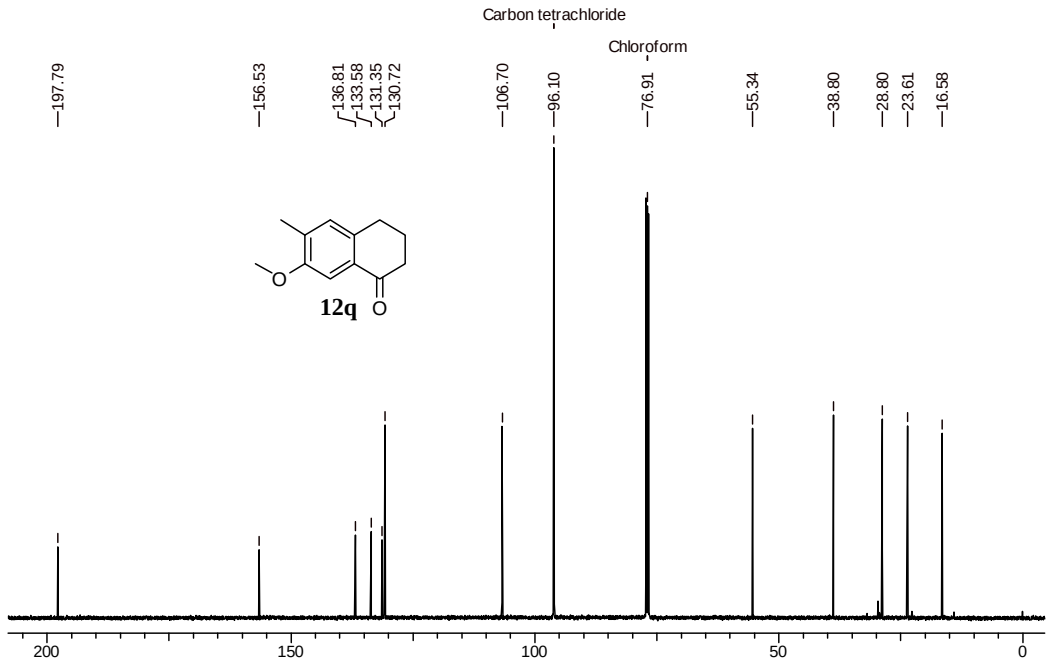
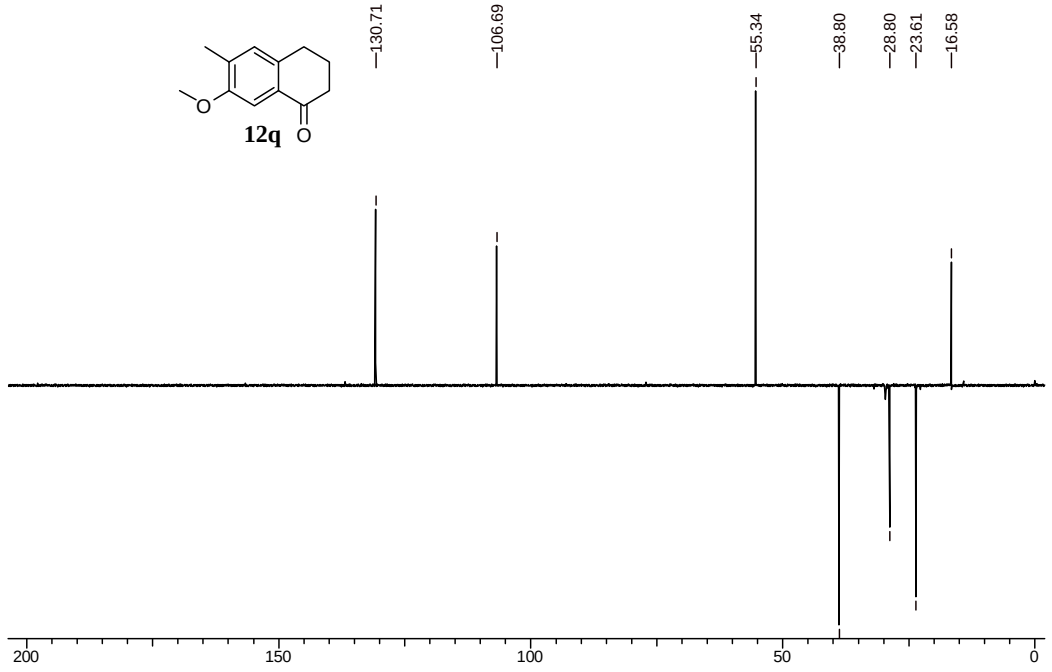


DEPT spectrum of compound **12q** ($CDCl_3 + CCl_4$, 125 MHz)



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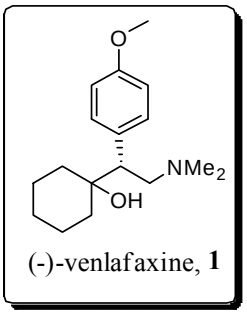
Chapter 2: Asymmetric total synthesis of (−)-venlafaxine

Section 1

Introduction to venlafaxine

2.1.1. Introduction



(-)-venlafaxine, **1**

Figure 1. Structure of (–)-venlafaxine.

Introduction of Selective serotonin re-uptake inhibitors (SSRIs) proved to be a major advancement in the pharmacotherapy of depression, both from a practical and theoretical basis. Venlafaxine (**1**) (Figure 1) is a new generation antidepressant drug[1] developed by Wyeth-Ayerst Company in 1993 and it is marketed by Pfizer with the trade name of EffexorXR®. Recently, generic version of venlafaxine has been approved by USFDA. It is a white to off-white crystalline solid phenylethylamine compound, which exhibits a unique pharmacological profile with antidepression properties. Venlafaxine is structurally and pharmacologically related to the atypical opioid analgesic tramadol, and more distantly to the newly released opioid tapentadol, but not to any of the conventional antidepressant drugs. In 2007, venlafaxine was the sixth most commonly prescribed antidepressant in the U.S. retail market; with 17.2 million prescriptions. Although venlafaxine is sold as a racemate, (–)-venlafaxine is a more potent inhibitor of norepinephrine synaptosomal uptake while (+)-venlafaxine is more selective in serotonin uptake. It is different from other antidepressants in that it has no or little activity on a variety of neuroreceptors[1a] (e. g. α or β-adrenergic receptors, muscarinic receptors, cholinergic receptors, histaminic receptors etc.). Like TCAs it has no activity at the fast sodium channels of cardiac cells, therefore devoid of cardiotoxicity. It does not inhibit MAO activity. It is unique among other antidepressants in that it downregulates β-receptors after a single dose and causes rapid onset of clinical antidepressant activity. It inhibits dopamine reuptake at high dosage. The absence of other significant sites of pharmacological action gives it a wide therapeutic window. Coadministration of two drugs, which inhibit individually either serotonin or norepinephrine uptake, has been shown to shorten the treatment time. Likewise, combination of two drugs inhibiting both serotonin and

norepinephrine uptake appears to produce a more rapid onset of clinical antidepressant activity than either mechanism alone.

2.1.2 Mechanism of Action

Venlafaxine (**1**), a bicyclic antidepressant, is usually known as a serotonin-norepinephrine reuptake inhibitor (SNRI), but it has been referred to as a serotonin-norepinephrine-dopamine reuptake inhibitor (SNDRI).[2] The mode of action is by blocking the transporter "reuptake" proteins for key neurotransmitters affecting mood, thereby leaving more active neurotransmitters in the synapse. In high doses it weakly inhibits the reuptake of dopamine,[3] with recent evidence showing that the norepinephrine transporter also transports some dopamine as well, since dopamine is inactivated by norepinephrine reuptake in the frontal cortex, which largely lacks dopamine transporters: therefore, venlafaxine can increase dopamine neurotransmission in this part of the brain.[4,5] Venlafaxine interacts with opioid receptors (mu-, kappa1- kappa3- and delta-opioid receptor subtypes) as well as alpha2-adrenergic receptor, and was shown to increase pain threshold in mice. When mice were tested with a hotplate analgesia meter, both venlafaxine and mirtazapine induced a dose-dependent, naloxone-reversible antinociceptive effect following intraperitoneal injection. These findings suggest venlafaxine's seemingly superior efficacy in severe depression.[6]

2.1.3 Asymmetric Organocatalysis

The extensive utility of synthetic chiral molecules as single-enantiomers in pharmaceuticals, optical and electronic devices, as components in polymers with novel properties and as probes of biological function, has made asymmetric catalysis an important area of research.[9]

Previously, organometallic complexes were usually used in the maximum asymmetric reactions but nowadays this picture is changing, and organic catalysis is becoming an increasingly popular part of organic chemistry, having a large number of advantages over metal-based and bioorganic methods. The handling simplicity and easy availability of these mostly inexpensive, bench-stable catalysts which are incomparably more robust than enzymes or other bioorganic catalysts which make

organocatalysis a powerful and attractive method for the synthesis of structurally complex chiral organic molecules.[7]

Organocatalysis is the catalysis of chemical transformations using a purely organic molecule, which is composed of mainly carbon, hydrogen, nitrogen, sulfur, and phosphorus, and does not contain any metals.[8]

At least 1,500 research papers describing the use of organocatalysts in more than 130 different reaction types were published in between 1998 and 2008 (Figure 2). Surprisingly, in the year of 1995 there was no report on the use of such catalysts. Now, it is widely accepted that organocatalysis is one of the principal branches of asymmetric synthesis.[8]

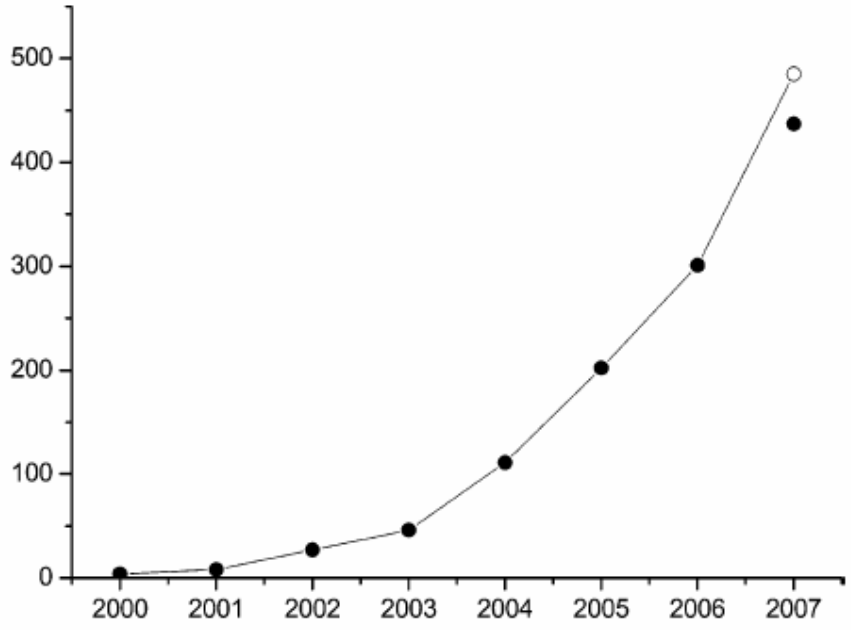
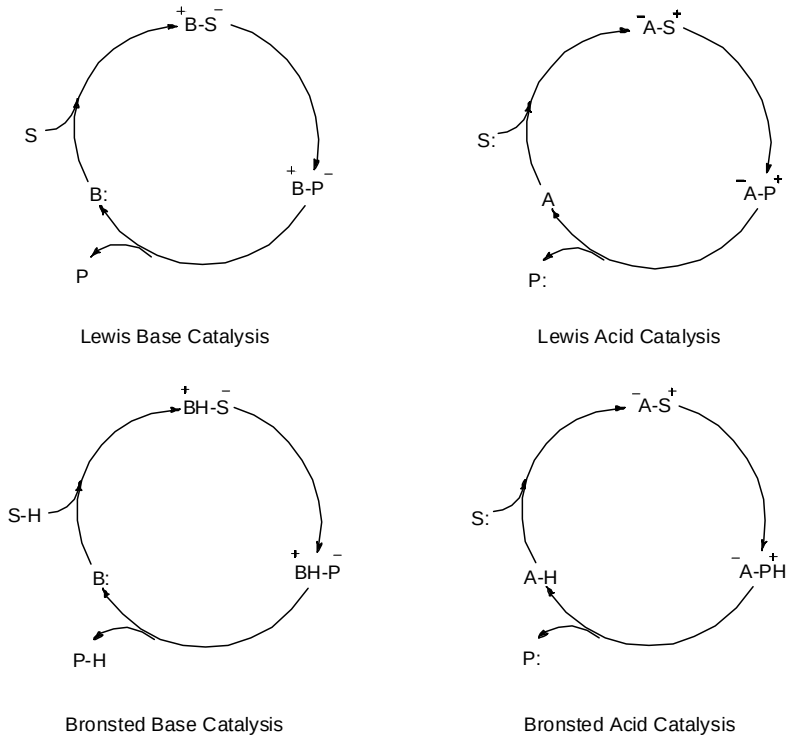


Figure 2. Number of publications using the term "organocatalysis" in the title or abstract since the year 2000.

Organic chemists have found a lot of advantages of organocatalysis over metal catalyst with the advancement of organocatalysis research. It saves money, time and energy; with simple experimental procedure and decreases the chemical waste. The profits of organocatalysis arise from three factors:[9] **1.** Organic molecules are generally stable to oxygen and moisture in the atmosphere, so, there is no need for special reaction vessels, storage containers and experimental techniques, or for ultra-dry

reagents and solvents, no need for glove boxes, inert gases, ultra-dry solvents or even high levels of experimental expertise. **2.** A large number of organic reagents like amino acids, carbohydrates and hydroxy acids are naturally available as single enantiomers. Therefore, simple organocatalysts are usually cheap to prepare and readily accessible in a range of quantities, suitable for small-scale reactions to industrial-scale reactions. **3.** Small organic molecules are generally non-toxic and environmental friendly, increasing the safety of catalysis in both biological research and chemical research, including industry and academic institutions.

Recently, List and co-workers[10] introduced a system for the classification of organocatalysis based on the mechanism of catalysis (Scheme 1). The four categories are Lewis base, Lewis acid, Bronsted base and Bronsted acid catalysis. Accordingly, Lewis base catalysts (B:) initiate the catalytic cycle *via* nucleophilic addition to the substrate (S). The resulting complex undergoes a reaction and then releases the product (P) and the catalyst for further turnover. Lewis acid catalysts (A) activate nucleophilic substrates (S:) in a similar manner. Brønsted base and acid catalytic cycles are initiated via a (partial) deprotonation or protonation, respectively.



Scheme 1. Organocatalytic cycles.

Not all but some natural products like cinchona alkaloids and their derivatives act as good catalysts.[11] Also some amino acids like proline and phenylalanine[12] (Figure 3) and their derivatives have been used in asymmetric reaction as catalysts for a long time. The peptides derived from these amino acids also show good activity as organocatalysts.

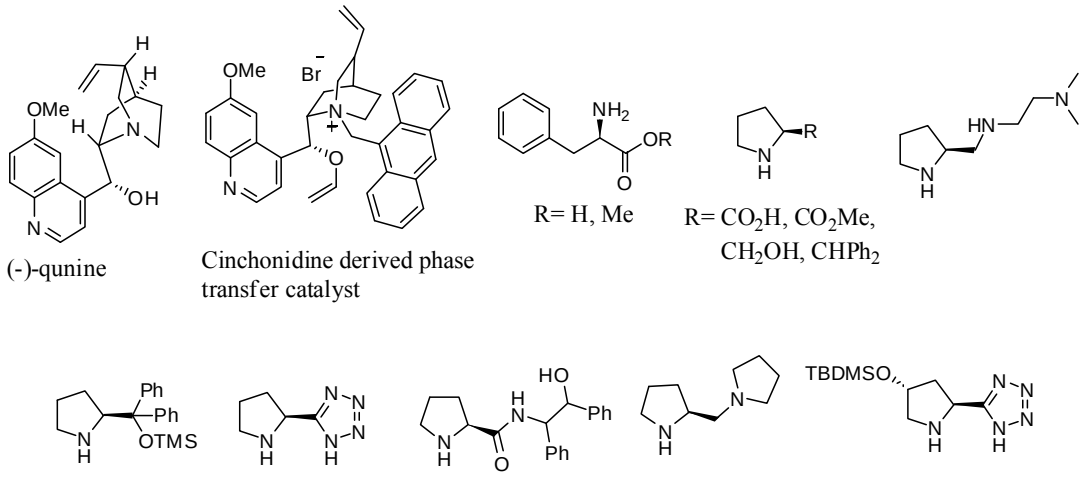
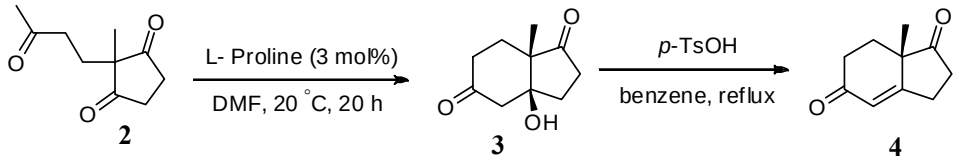


Figure 3. Some examples of organocatalysts derived from cinchona alkaloids and amino acids.

The history of organocatalytic reactions has a rich past; such catalysis has in the past played a determinant role in the formation of prebiotic key building blocks such as sugars. In this way, the reactions have led to the introduction and widespread use of homochirality in the living world.[13] In early 1970 two groups independently reported Robinson annulation of meso triones **2** by using L-proline (3 mol %). Hajos and Parrish isolated ketol **3**[14] while Wiechert and co-workers reported the synthesis of enone **4** (Scheme 2).[15]



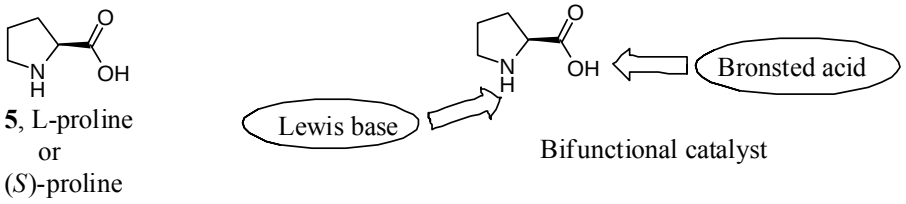
Scheme 2. Proline catalyzed asymmetric Robinson annulation.

Till early 2000, very few groups were actively working in this topic and the field was very narrow. In 2000, List and Barbas *et al.* have reported proline catalysed asymmetric aldol reaction[16] and after that, world has witnessed tremendous growth of

organocatalysis field. Simple amino acid like proline and its derivatives have been used as organocatalysts for the asymmetric aldol reaction,[16,17] the Robinson annulation,[14,18] Michael reaction,[19] Mannich reaction,[20] Diels-Alder reaction,[21] α-halogenation,[22] and epoxidation reaction.[23]

2.1.4. Proline: a universal catalyst

Proline has been defined as a "universal catalyst" because of its high usefulness in variety of asymmetric organic transformations. Although the natural L-form is normally used, proline is available in both enantiomeric forms,[24] this is being more advantageous when compared to enzymatic catalysis. Proline is the only natural amino acid with a secondary amine functionality, which raises the pKa value and better nucleophilicity as compared to other amino acids. It can be regarded as a bifunctional catalyst as the secondary amine acts as Lewis base and the acid group acts as Brønsted acid (Figure 4).



5, L-proline
or
(*S*)-proline

Figure 4. Proline and its bifunctional nature.

Proline is able to act as a nucleophile, in particular with carbonyl compounds or Michael acceptors, to form either an iminium ion or enamine (Figure 5).

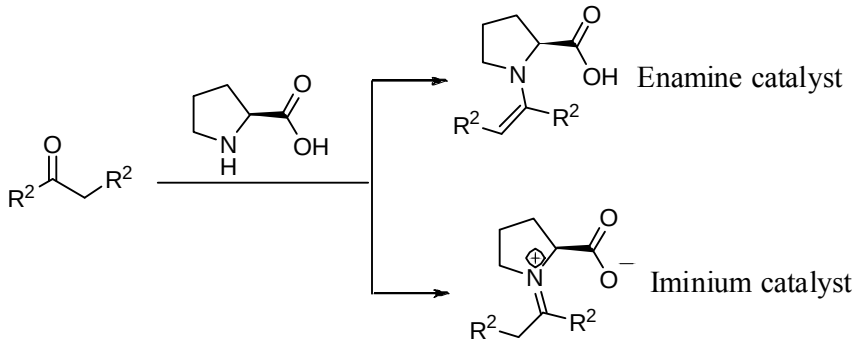
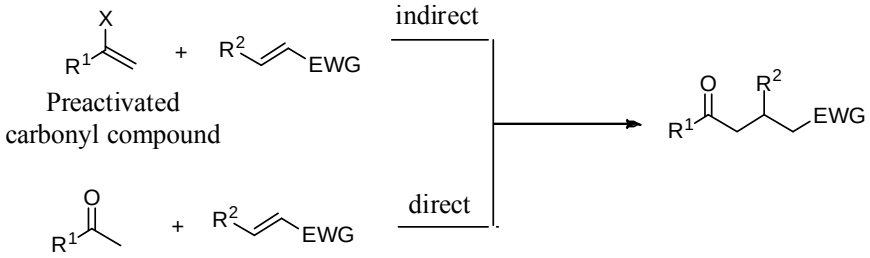


Figure 5. Modes of proline catalysis.

The high, and often exceptional, enantioselectivity of proline-mediated reactions can be rationalized by the capacity of the molecule to orchestrate highly organized transition states by an extensive hydrogen-bonding network.

2.1.5. Proline catalysed asymmetric Michael Reactions (review)

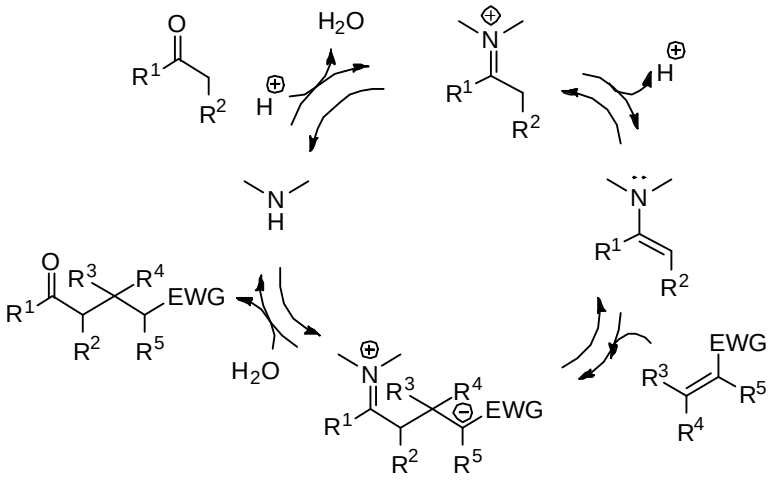
Michael reaction is the C-C bond formation by conjugate addition of nucleophiles to the *β*-position of α, β-unsaturated carbonyl compounds and this reaction is frequently used in organic synthesis (Scheme 3).[25] Since stereogenic centers can be created in the course of the Michael reaction, this reaction has found widespread application in synthesis of optically active compounds.



Scheme 3. Indirect and direct Michael reaction.

The use of preformed enamines in the Michael reaction has been initiated by Stork *et al.*[26] and then, several non asymmetric as well as asymmetric examples have been reported. For example, Seebach *et al.* have extensively studied asymmetric Michael additions of preformed enamines derived from chiral amines to conjugated nitroalkenes and alkylidene malonates.[27] Early examples of the asymmetric Michael addition of (*S*)-proline-derived preformed enamines to acrylonitriles, acrylates and methyl vinyl ketone was reported by Yamada *et al.*[28] Enamines can also be formed reversibly from amines and carbonyl compounds and used as intermediates in a catalytic cycle (Scheme 4).

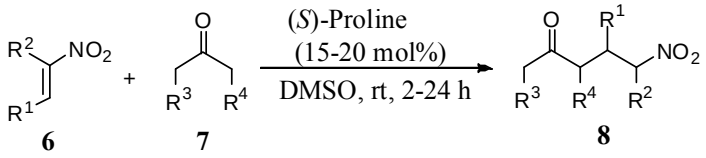
For the preparation of ν-nitrocarbonyl compounds, enamine-catalytic Michael addition reaction of carbon nucleophiles to nitroalkenes is a useful synthetic method. ν-Nitrocarbonyl compounds are important precursors in organic synthesis[29] due to the various possible transformations, for example to aminocarbonyl compounds, aminoalkanes, or pyrrolidines. In organocatalysis, a number of different Michael



Scheme 4. Enamine-catalyzed Michael reaction.

acceptors have already been used. Among them, nitroalkenes are the most prominent ones, because of their high acceptor reactivity and the possible conversion into other useful functionalities.[30]

The first enamine-catalytic asymmetric intermolecular Michael reaction using nitroalkene was developed by List *et al.* in 2001.[31] The addition of unactivated symmetric ketones **7** to nitroolefins **6** was found to proceed in the presence of (*S*)-proline to furnish the desired *v*-nitro ketones **8** in generally high yields and good diastereoselectivities but only low enantioselectivities (%*ee* = 23%) (Scheme 5).



Scheme 5. Proline-Catalyzed Michael Addition of unmodified Ketones to Nitroolefins.

In literature there are several reports on organocatalytic Michael reaction using different proline based and other catalysts.[32]

2.1.6. Literature review on synthesis of venlafaxine

Till date there are number of racemic syntheses reported by others and by this group. In literature there are only two asymmetric syntheses reported. Recently Nanda *et al.*

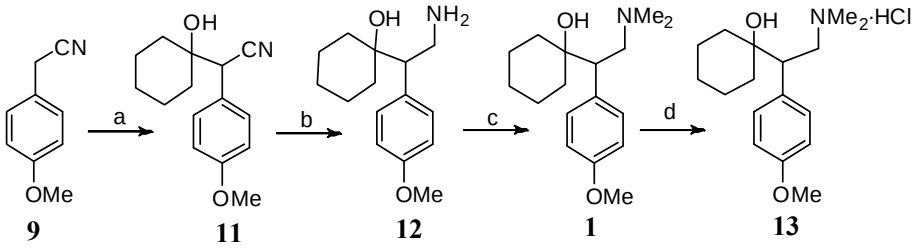
reported asymmetric synthesis of both isomers of venlafaxine by using enzymetic resolution as the key step but there are some drawbacks like loss of 50% unwanted enantiomer and lengthy route. Davies *et al.* [5] reported asymmetric synthesis of (+)-venlafaxine by using Rh-catalysed Mannich reaction as a key step where they used environmentally hazardous, expensive, costly metal catalyst and tedious reaction conditions.

a) Racemic synthesis

Though in literature there are number of racemic syntheses of venlafaxine, here some selected racemic syntheses are described.

Yardley's Approach[33] (*J. Med. Chem.* **1986**, *33*, 2899; US Patent No. 4, 535, 186, **1985**)

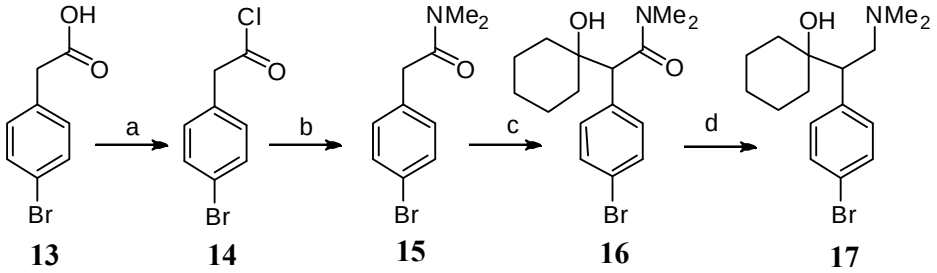
p-Methoxyphenylacetonitrile **9** was condensed with cyclohexanone **10** using LDA at –78 ^{o}C to yield cyanoalcohol **11**. Under hydrogenation reaction condition with 5% Rh/Al_2O_3 in NH_3/EtOH system compound **11** gave aminoalcohol **12**. For *N,N*-dimethylation of the primary amine, compound **12** was subjected with modified Eschweiler-Clarke reaction to afford venlafaxine **1**. Hydrochloride salt of venlafaxine, **13** was prepared using 20% HCl in isopropanol (Scheme 6).



Scheme 6. Reagents and conditions: *a) LDA, THF, –78 ^{o}C then cyclohexanone **10**, 2 h, 83%; b) H_2, 5% Rh/Al_2O_3, NH_3-EtOH (2:8), 57%; c) HCHO, HCO_2H, H_2O reflux, overnight; d) HCl (20% in iPrOH) 80% (over 2 steps).*

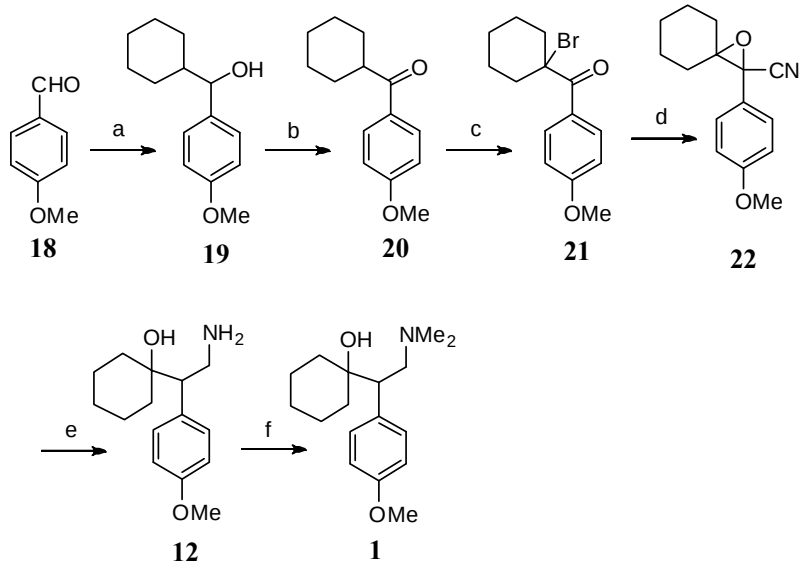
Tetrahydroisoquinolines and trace amount of oxazines were formed during the Eschweiler-Clarke reaction. This problem was circumvented in a modified route (Scheme 7), where acid chloride **14** was prepared from corresponding *p*-bromophenylacetic acid **13** by using $(COCl)_2$ in the presence of DMF. Acid chloride

14 was treated with Me_2NH to give corresponding acetamide **15**. Condensation of cyclohexanone **10** with acetamide **15** at –78 ^oC using LDA furnished amidoalcohol **16**, which was further reduced using AlH_3 to yield venlafaxine analog **17**. A small library of several analogues of venlafaxine has been prepared by these methods.



Scheme 7. Reagents and conditions: *a) $(COCl)_2$, DMF, DCM, r t, 4 h; b) Me_2NH, DCM, r t, overnight, 97% (over 2 steps); c) LDA, THF, –78 ^oC, then cyclohexanone **10**, 50 min, 44%; d) $LiAlH_4$, conc. H_2SO_4, THF, 0 ^oC, 1 h, 40%.*

Rathod's approach[34] (EP 1249447, **2001**)

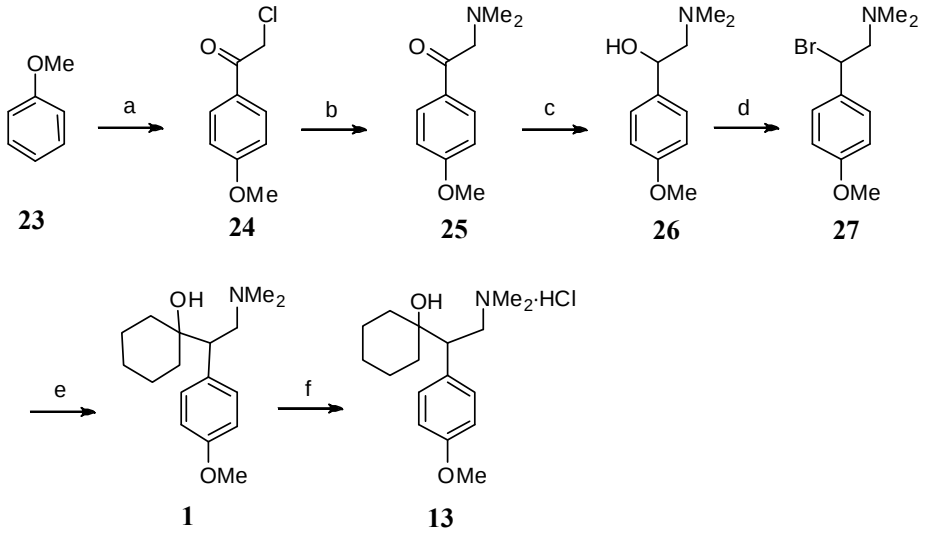


Scheme 8. Reagents and conditions: *a) Cyclohexyl magnesium bromide, THF, 10 ^oC to r t, 6 h, 80%; b) CrO_3, H_2O, r t, 3 h, 76%; c) PTAB, THF, reflux, 3 h, 82%; d) NaCN, MeOH, r t, 2 h, 64%; e) H_2, Raney Ni, NH_3-EtOH, 500 kPa, r t, 7 h, 78%; f) HCHO, HCO_2H, H_2O, reflux, 6 h, 75%.*

Rathod *et al.* patented a protocol for the synthesis of venlafaxine **1** involving Grignard reaction of cyclohexyl magnesium bromide with *p*-anisaldehyde **18** to yield alcohol **19**. The alcohol was subjected with CrO_3 to give corresponding ketone **20**, which was again treated with PTAB to give α-bromoketone **21**. α-Bromoketone **21** was treated with NaCN to yield spiroepoxide **22** in moderate yield. Opening of epoxide ring and reduction of cyanide was performed in one pot with Raney nickel to afford aminoalcohol **12**, which was converted into venlafaxine **1** by a known procedure (Scheme 8).

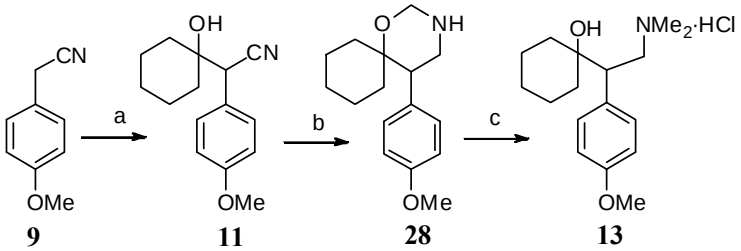
Jinpei's approach[35] (*J. China Pharm. Univ*. **1999**, *30*, 249)

Anisole **23** was treated with chloroacetyl chloride under Friedel-Crafts acylation reaction condition to yield chloroketone **24**, which upon treatment with Me_2NH afforded aminoketone **25**. Reduction of ketone functional group of compound **25** with KBH_4 gave aminoalcohol **26**, which was further transformed into the corresponding bromide **27** by using PBr_3. Grignard reaction of the bromide **27** with cyclohexanone **10** gave venlafaxine (**1**) which was further treated with conc. HCl to give its hydrochloride salt **13** (Scheme 9).



Scheme 9. Reagents and conditions: *a) $ClCO_2CH_2Cl$, $AlCl_3$, PhH, reflux, 4 h, 70%; b) 33% aq. Me_2NH, EtOH, r t, 15 h; c) KBH_4, EtOH, r t, 8 h, 64%; d) PBr_3, $CHCl_3$, 0 ^oC then reflux, 15 h, 53%; e) Mg, THF, reflux, then 0 ^oC, cyclohexanone* ***10*** *then reflux, 1 h; f) conc. HCl, 47% (over 2 steps).*

Rangappa's approach[36] (*Bioorg. Med. Chem. Lett.* **2004**, *14*, 3279)

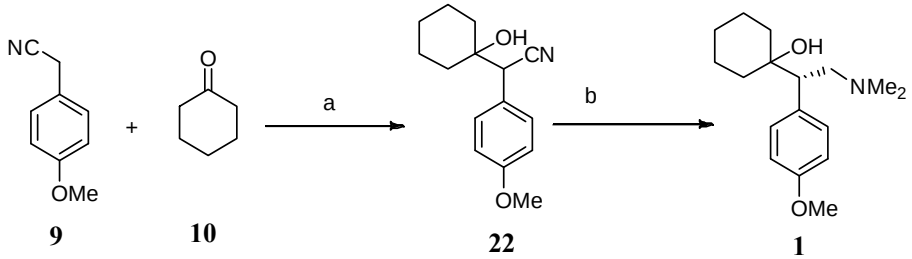


Scheme 10. Reagents and conditions: *a) Cyclohexanone* ***10****, NaOH, Bu_4NBr, H_2O-MeOH, r t, 15 h, 96%; b) Raney Ni, H_2 (10 atm), anhydrous NH_3-MeOH, 35-40 ^oC, then formalin, 25-30 ^oC, 3 h, 83%; c) HCO_2H, HCHO, reflux, 25-30 h, then HCl in iPrOH (pH = 2), 85%.*

Just after the grant of US patent[37] filed by chavan *et al.*, Rangappa *et al.* published their work, where they used condensation of *p*-methoxyphenylacetonitrile **9** with cyclohexanone **10**, using NaOH in MeOH-H_2O (1:1) medium. Cyanoalcohol **11** with Raney nickel followed by reaction with formalin gave oxazine **28**, which was further subjected to Eschweiler-Clarke reaction conditions to obtain venlafaxine free base **1**. Treatment of **1** with ^{i}PrOH/HCl gave its hydrochloride salt **13** (Scheme 10).

Chavan's approach[37] (US 6,504,044B2, **2003,** *Tetrahedron Lett.* **2004**, *45*, 7291, *Synthtic Communications* **2007**, *37*, 2007)

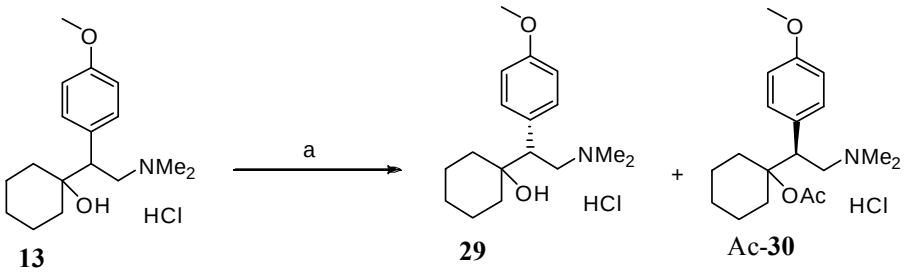
Chavan *et al.* reported a green, novel and mild method for condensation of phenylacetonitrile **9** with cyclohexanone **10** to give cycloalkanol **22**. By using this protocol this group reported the practical synthesis of venlafaxine **1** (Scheme 11).



Scheme 11. Reagents and conditions: *a)10% aqueous NaOH, $TBAHSO_4$, 0-15 °C, 30 min-1 h, quantitative yield; (b) H_2, 280 psi, formalin, MeOH, 100 °C, 30% (60% cycloalkanol is recovered).*

Kochetkov's approach[38] (*Mendeleev Commun.* **2010**, *20*, 314)

Kochetkev *et al.* separated both enantiomers of venlafaxine from racemic mixture of venlafaxine by using enzymatic kinetic resolution. The racemic mixture of venlafaxine (**13**) was treated with vinyl acetate in presence of porcine pancreatic lipase (PPL) in chloroform at 20 °C which gave its (*R*)-enantiomer (**29**) and (*S*)-acetate of **30** wherein the *ee* value of (*S*)-acetate venlafaxine (**30**) was > 99% (Scheme 12).



13 **29** Ac-**30**

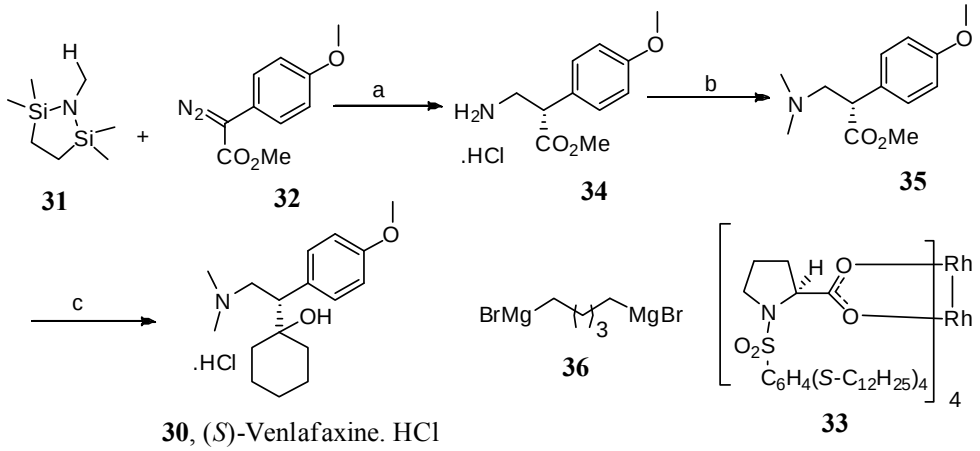
Scheme 12. Reagents and conditions: *a) Vinyl acetate, PPL, $CHCl_3$.*

b) Asymmetric synthesis

In literature only two asymmetric syntheses are reported.

Davies' approach[39] **(***Chem. Commun.* **2006**, 3110)

Davies *et al.* developed a method for the synthesis chiral β-amino esters **34** from the



31 **32** **34** **35**

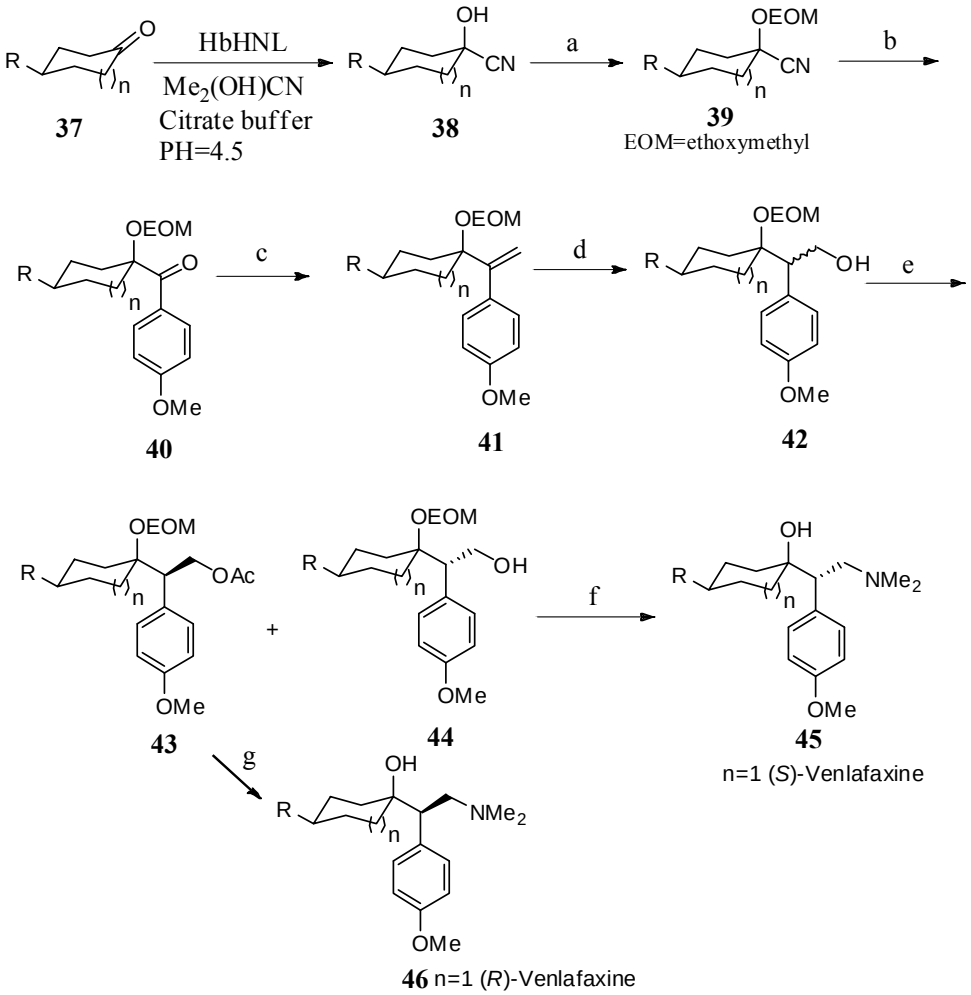
36 **33**

30, (*S*)-Venlafaxine. HCl

Scheme 13. Reagents and conditions: *a) i)* ***33****, -40 °C; ii) HCl/ether; b) HCHO/NaBH(OAc)$_3$, DCM ; c) i)* ***36****; ii) HCl/ether.*

Rhodium (II) prolinate **33** catalyzed intermolecular C–H insertion between methyl aryldiazoacetates **32** and a bis-silyl protected methylamine **31**. Using their own methodology they synthesized chiral amino ester **34** in moderate yield with 93% *ee*. Amine functional group of compound **34** was converted to corresponding *N,N*-dimethyl functional group **35** by treatment with formaldehyde and $NaBH(OAc)_3$. Finally Grignard reaction of the **36** with ester **35** gave venlafaxine **1** which was further treated with conc. HCl to give its hydrochloride salt **30** (Scheme 13).

Nanda's Approach[40] (*Tetrahedron Lett.* **2012**, *53*, 1990–1992)



Scheme 14. Reagents and conditions: *(a) EOM-Cl, DIPEA, 90%; (b) p-$MeOC_6H_4MgBr$, 85%; (c) Ph_3P^+MeI, KO^tBu, 82%; (d) $BH_3.SMe_2$, KOH, H_2O_2, 84%; (e) CH_2=CHOAc, Lipase PS-D, MS 4 Å, 48%; (f) (i) p-TSCl, Et_3N, DMAP, 88%; (ii) Me_2NH, 80 °C, 48 h; (iii) PTSA, MeOH, 65% (over two steps); (g) (i) K_2CO_3, MeOH; then same reaction sequences as in f.*

Nanda *et al.* synthesized both the enantiomers of venlafaxine (**1**) and some of its analogues by using chemoenzymatic kinetic resolution as a key step. Cyclohexanone **37** was converted to its corresponding cyanohydrin **38** by an enzymatic transcyanation reaction with acetonecyanohydrin and HbHNL as the enzyme. The free hydroxyl group of compound **38** was protected as its EOM ether to afford EOM-protected cyanohydrin **39**. Addition of Grignard reagent of 4-bromoanisole on compound **39** followed by acidic work-up gave ketone **40**. For one carbon homologation, ketone **40** was treated with methyl triphenylphosphonium iodide in the presence of KO^tBu to yield olefin **41**. Hydroboration of the double bond of compound **41** with $BH_3.SMe_2$ afforded the corresponding racemic hydroxymethylated compound **42**. Compound **42** was subjected for lipase catalyzed enzymatic kinetic resolution with vinyl acetate to give optically pure compounds **43** and **44**. Compound **43** was converted to its tosylate derivative followed by treatment with dimethyl amine and then EOM protecting group was removed by treatment with PTSA, to afford (*S*)-venlafaxine **45**. Compound **43** was deacetylated with K_2CO_3–MeOH and by following the similar reaction sequences as described above (*R*)-venlafaxine **46** was obtained (Scheme 14).

2.1.7. References

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Chapter 2: Asymmetric total synthesis of (-)-venlafaxine

Section 2

Asymmetric total synthesis of (−)-venlafaxine using organocatalyst

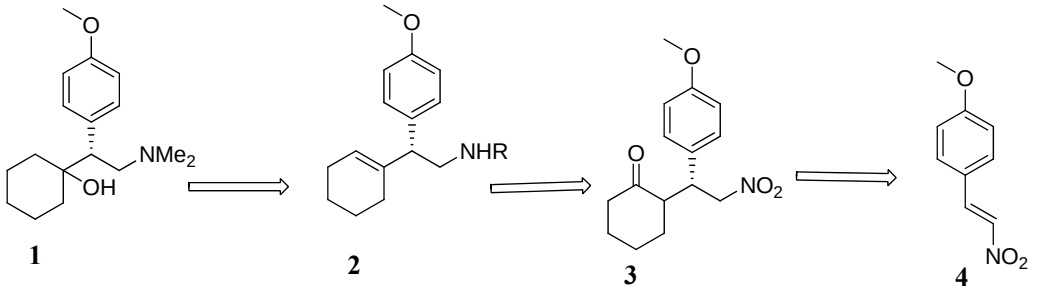
2.2.1. Present Work

2.2.1.1. Objective

There are a number of racemic syntheses reported in the literature[1] including a few reports from this group.[2] The resolution of racemic venlafaxine by kinetic enzymatic resolution has been recently reported in the literature.[3] However only two asymmetric syntheses have been reported so far. Davies *et al*.[4] have reported an asymmetric synthesis of (+)-venlafaxine by using a Rh-catalyzed Mannich reaction as a key step while Nanda *et al*.[5] have very recently reported an asymmetric synthesis of both enantiomers of venlafaxine by using an enzymatic resolution as the key step. The aforementioned two asymmetric syntheses have delivered venlafaxine in chiral form but the Rh-catalyzed Mannich reaction involved use of environmentally hazardous, expensive Rh-catalyst while there is loss of 50% material in the form of unwanted enantiomer in case of kinetic enzymatic resolution because the (−) and (+) enantiomers of venlafaxine exhibit different biological activities.

To overcome these problems, as both the different enantiomers have different biological activity and as a part of our continued interest in antidepressant agents, it was thought to develop an efficient, simple and practical strategy for the asymmetric synthesis of (–)-venlafaxine (**1**) by using an organocatalyst wherein by switching the stereocenter of the catalyst one could synthesize both the enantiomers of venlafaxine and there would be no loss of material in the form of unwanted enantiomer.

2.2.1.2. Retrosynthetic analysis



Scheme 1. Retrosynthetic analysis of (–)-venlafaxine.

The retrosynthetic analysis is outlined in Scheme 1. In principle, the tertiary hydroxyl group in venlafaxine could be installed by epoxidation of **2** followed by selective epoxide ring opening. The required intermediate **2** could be obtained from nitroketone **3** by reduction followed by selective dehydration. The ketone compound **3** in turn could be accessed from nitro styrene **4** through organocatalytic asymmetric Michael reaction[6] with cyclohexanone.

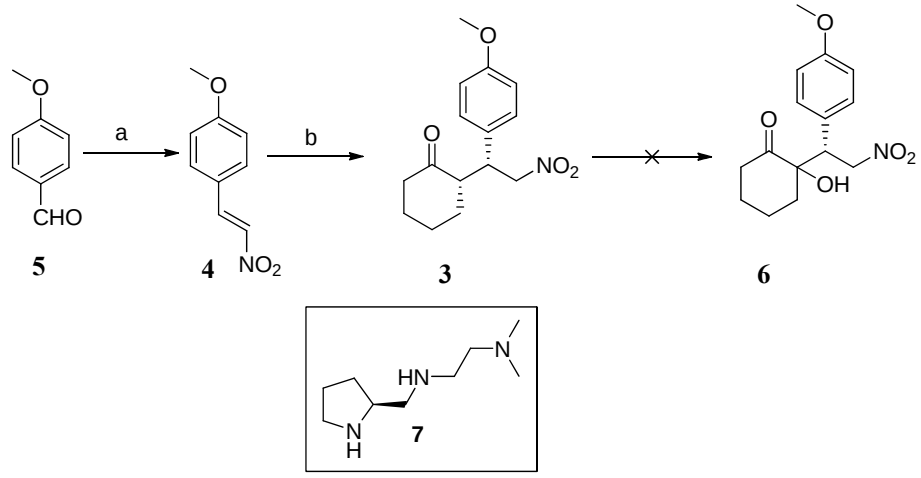
2.2.1.3. Results and discussion

Accordingly, the synthesis of (–)-venlafaxine began with the Henry reaction of inexpensive and easily available starting material *viz*. anisaldehyde (**5**) with nitromethane in the presence of ammonium acetate in glacial acetic acid under sonication at room temperature to furnish the nitrostyrene **4**[7] in 95% yield. IR spectrum of compound **4** showed absence of peak at 1689 cm^{-1} for corresponding carbonyl functional group of compound **5** and appearance of new peaks at 1620 and 1600 cm^{-1}. The ^{1}H NMR spectrum showed doublets at δ 7.5 for one proton and δ 7.96 for one proton with *J*= 14 Hz, which are characteristics peaks for the presence of α, β unsaturated *trans* double bond (-C<u>H</u>=C<u>H</u>-NO_2). This was further confirmed by its ^{13}C and DEPT NMR spectra, which showed peaks at δ 138.7 and 135.1 for the olefinic carbons.

Michael addition of nitrostyrene **4** with cyclohexanone in the presence of proline based organocatalyst **10**[8] (20 mol%) furnished the nitroketone **3** in 79% yield with ≥ 99% *ee* after stirring for 24 h at room temperature, in the presence of PTSA as an additive, in DMF as the solvent. The IR spectrum showed a strong absorption at 1713 cm^{-1} indicating the presence of a ketone functionality. The ^{1}H NMR spectrum of compound **3** revealed doublet of doublets at δ 4.57 for one proton and at δ 4.88 for one proton, indicating the presence of two diastereomeric protons α to the nitro group (-CH-<u>CH_2</u>-NO_2). The ^{13}C NMR spectrum showed peak at δ 211.6 corresponding to carbonyl group and DEPT NMR spectrum showed four peaks for CH_2 group at δ 42.6, 33.1, 28.5 and 25.03 respectively which confirmed the presence of mono substituted cyclohexanone ring.

After construction of the main framework of (–)-venlafaxine, the remaining tasks were installation of the tertiary hydroxyl group and introduction of the *N,N*- dimethyl group. At this stage, the seemingly simple installation of the tertiary hydroxyl group

was attempted under a variety of reaction conditions without success due to the competing highly acidic nature of the proton α- to the nitro group (Scheme 2).

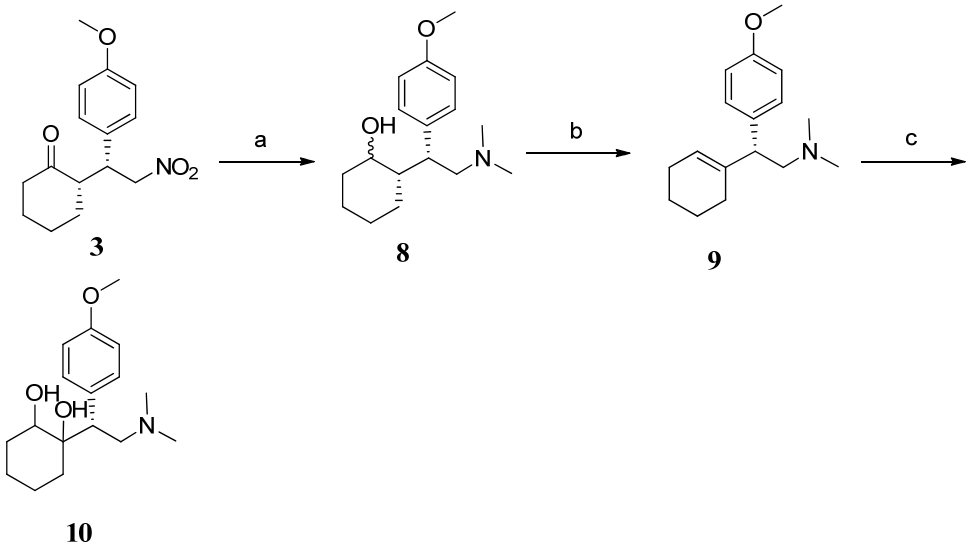


Scheme 2. Reagents and conditions: *a) CH_3NO_2, NH_4OAc, glacial acetic acid, sonication, 3 h, 95%; b) Cyclohexanone,* ***7****, PTSA, DMF, 24 h, 79%, 99% ee*.

The reduction of both the ketone and nitro functional groups in intermediate **3** in one pot was attempted but a complex reaction mixture was obtained. Therefore, it was decided to perform stepwise reduction. Thus, selective reduction of ketone functionality of compound **3** was achieved by using $NaBH_4$ in THF:H_2O (9:1) as the solvent system to afford the corresponding nitroalcohol. The crude nitroalcohol was subjected to reduction[9] of nitro group by $NiCl_2.6H_2O$ and $NaBH_4$ in MeOH as a solvent and the amine functional group was converted into *N,N*-dimethyl functional group by *in situ* treatment with formaldehyde to give **8** in 55% yield.

The absence of band at 1714 cm^{-1} in compound **8** corresponding to ketone functional group and appearance of a new broad band at 3300 cm^{-1} indicated the reduction of carbonyl group. ^{1}H NMR spectrum showed singlet at δ 2.30 for six protons which was attributed to the presence of NMe_2 group. ^{13}C NMR spectrum showed absence of peak at δ 211.6 corresponding to carbonyl group and a new peak at δ 65.9 appeared which also supported the reduction of carbonyl group. New peak at δ 45.3 appeared which supported the presence of NMe_2 group in compound **8**. The mass spectrum of compound **8** showed peak at m/z 278 corresponding to $[M+H]^+$. Finally the structure of compound **8** was confirmed by elemental analysis.

The hydroxyl group of compound **8** was converted into the corresponding mesyl derivative by using mesyl chloride (MsCl) in the presence of Et_3N as a base in DCM as the solvent under reflux conditions. The crude mesylated product on treatment with DBU in acetonitrile, selectively furnished the more substituted olefin **9** in 60% yield. The IR spectrum of compound **9** showed absence of a broad band at 3300 cm^{-1} which indicated the absence of free hydroxyl functional group. Multiplet at δ 5.58 for one proton in ^1H NMR spectrum revealed the formation of more substituted double bond. ^{13}C NMR spectrum showed peaks at δ 138.5 and 122.2 corresponding to double bond. The peak at δ 138.5 vanished in DEPT NMR spectrum which indicated the presence of a quaternary centre of the double bond. The mass spectrum of compound **9** showed peak at m/z 260 corresponding to $[M+H]^+$. Finally the structure was confirmed by elemental analysis (Scheme 3).



Scheme 3. Reagents and conditions: *a) i) $NaBH_4$, THF:H_2O (9:1), 2 h; ii) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, 1.5 h, 0 °C then HCHO, rt overnight, 55% (over two steps); b) i) MsCl, Et_3N, reflux, 14 h; ii) DBU, CH_3CN, 24 h, reflux, 60% (over two steps); c) OsO_4, NMO, CH_3CN:H_2O (9:1), 24 h.*

Compound **9** was subjected to dihydroxylation with OsO_4 and NMO as a co-oxidant in CH_3CN:H_2O (9:1) as a solvent system, but purification and isolation of the product proved very difficult due to presence of free hydroxyl and amine functional groups. So, it was decided to install at first tertiary hydroxyl group with protected amine functional group and then install *N,N*-dimethyl functional group at the late stage.

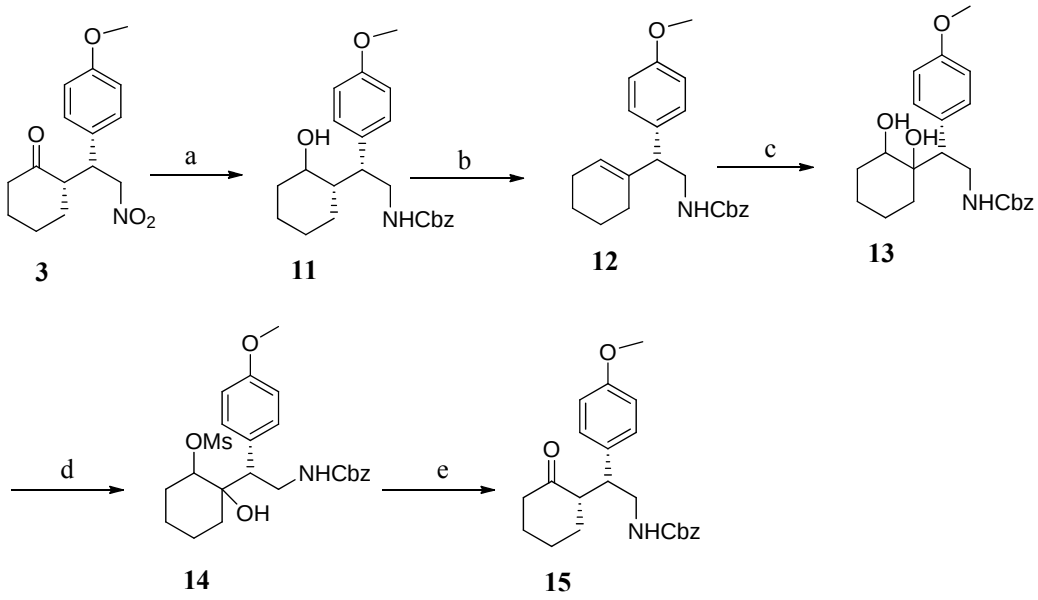
Accordingly, ketone functional group of compound **3** was selectively reduced as discussed above. The crude nitroalcohol was subjected to reduction of nitro group by $NiCl_2.6H_2O$ and $NaBH_4$ in MeOH as a solvent and the amine thus obtained was protected *in situ* by benzyl chloroformate (Cbz-Cl) in the presence of Et_3N as the base to furnish Cbz protected amino alcohol **11** in 60% yield.

The IR spectrum showed strong bands at 3433 and 1701 cm^{-1}, characteristics peaks for free hydroxyl group and carbamate moiety. The ^1H NMR spectrum showed multiplet at δ 7.20-7.32 for five protons and singlet at δ 5.04 for two protons which indicated the presence of *N*-Cbz group. ^{13}C NMR spectrum was also in good agreement with the structure of **11**. The mass spectrum of compound **11** showed peak at m/z 406 corresponding to $[M+Na]^+$. Finally the structure of compound **11** was confirmed by HRMS analysis.

The hydroxyl group of compound **11** was converted into the corresponding mesyl derivative by using mesyl chloride (MsCl) in the presence of Et_3N as a base and DCM as the solvent under reflux conditions. The crude mesylated product on treatment with DBU in acetonitrile, selectively furnished the more substituted olefin **8** in 68% yield. The IR spectrum of compound **12** showed absence of a broad band at 3433 cm^{-1} indicating the absence of free hydroxyl group. Multiplet at δ 5.58-5.61 for one proton in ^1H NMR spectrum revealed the formation more substituted double bond. ^{13}C NMR spectrum showed peaks at δ 138.3 and 122.9 for double bond. The peak at 138.5 vanished in DEPT spectrum which indicated it to be the quaternary centre of the double bond. The mass spectrum of compound **12** showed peak at m/z 388 corresponding to $[M+Na]^+$. Finally the structure of compound **12** was confirmed by HRMS analysis.

The compound **12** was subjected to dihydroxylation with OsO_4 and NMO as a co-oxidant in acetonitrile:water (9:1) as solvent system, furnishing the diol **13** in 97% yield. The IR spectrum of compound **13** showed a broad band at 3400 cm^{-1} indicating the presence of free hydroxyl group. The multiplet δ 5.58-5.61 was absent in ^1H NMR spectrum which indicated the conversion of double bond to diol. ^{13}C NMR spectrum showed peaks at 74.7 and 71.4. The peak at 74.7 vanished in DEPT spectrum therefore it indicated the presence of carbon corresponding to CHOH-COH. The mass

spectrum of compound **13** showed peak at m/z 400 corresponding to $[M+H]^+$. Finally the structure of compound **13** was confirmed by HRMS analysis.

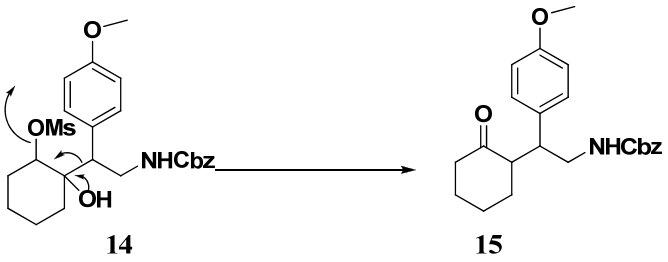


Scheme 4. Reagents and conditions: *a) i) $NaBH_4$, THF: H_2O (9:1); ii) $NiCl_2$, $6H_2O$, $NaBH_4$, MeOH, CbzCl, Et_3N, 60%; b) i) MsCl, Et_3N, DCM, rt then reflux; ii) DBU, CH_3CN, reflux, 90% c) i) OsO_4, NMO, acetonitrile:H_2O (9:1), 97%; d) MsCl, Et_3N, DCM, rt then reflux, 67%; e) Zn, NaI, DME, reflux 45%.*

The secondary hydroxyl group of diol **13** was selectively mesylated by methanesulphonyl chloride, Et_3N in DCM to yield monomesylated product **14** in 67% yield. The ^1H NMR spectrum showed a singlet at δ 3.00 for three protons corresponding to the methyl group ($\underline{C}H_3SO_2$-). ^{13}C NMR spectrum showed peak at δ 38.4 which is a characteristic peak for mesyl (CH_3SO_2-) group. The mass spectrum of compound **14** showed a peak at m/z 478 corresponding to $[M+H]^+$. Finally the structure of the compound **14** was confirmed by HRMS analysis (Scheme 4).

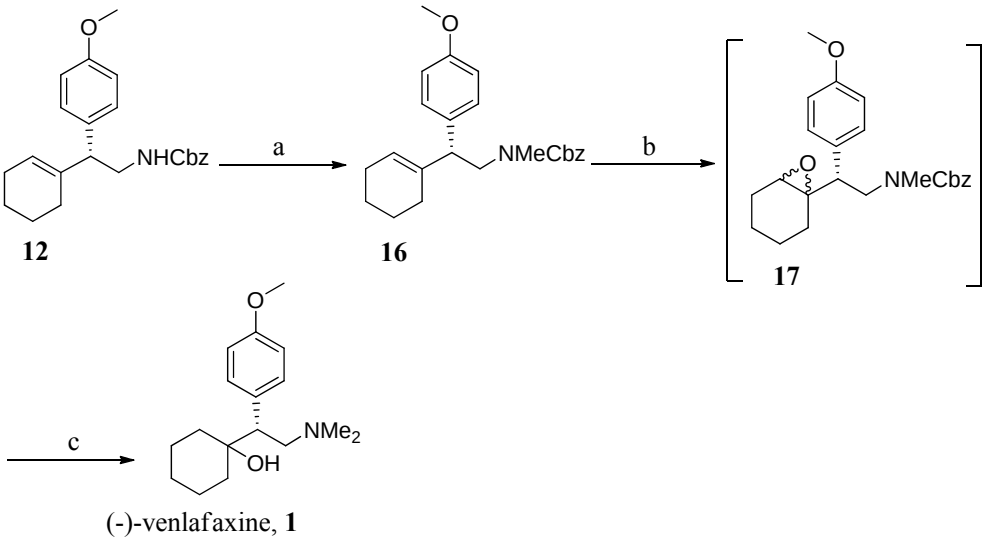
Interestingly, when mesylated compound was subjected to deoxygentaion reaction (Zn, NaI)[10], a rearranged product **15** was obtained as a major product in 45%. Structure of the rearranged product **15** was confirmed by spectral analysis. The IR spectrum showed a strong absorption at 1713 cm^{-1} indicating the presence of a ketone functionality. In ^1H NMR spectrum, the singlet at δ 3.00 for three protons was absent and a new peak appeared at δ 212.5 in the ^{13}C NMR spectrum corresponding to carbonyl group, indicating the formation of rearranged product. Finally, HRMS

analysis and mass spectrum confirmed the formation of **15**. The plausible mechanism for rearrangement is given below (Scheme-5)



Scheme 5. Plausible mechanism.

Therefore for the installation of tertiary hydroxyl group, it was decided to carry out epoxidation followed by reductive epoxide ring opening. Thus, the compound **12** was subjected to methylation with NaH and MeI in dry THF to afford the compound **16** in 92% yield. From its ^{1}H NMR and ^{13}C NMR spectra it was evident that it existed as rotameric mixture. Singlets at δ 2.74 and 2.71 in ^{1}H NMR spectrum were attributed to the methyl group (-N<u>Me</u>Cbz). ^{13}C NMR spectrum of compound **16** showed signals at δ 35.2 and 34.5 which clearly indicated the *N*-methylation of carbamate functional group. The mass spectrum of compound **16** showed peak at m/z 402 corresponding to $[M+Na]^{+}$. Finally the structure of compound **16** was confirmed by HRMS analysis.



Scheme 6. Reagents and conditions: *a) MeI, NaH, THF, overnight, rt, 92%; b) m-CPBA, $NaHCO_3$, DCM, 2 h, rt; c) $LiAlH_4$, THF, 5 h, reflux, 60% , ≥99% ee.*

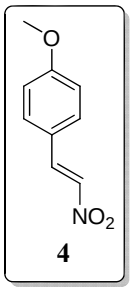
The compound **16** was subjected to epoxidation with *m*-CPBA in the presence of $NaHCO_3$ in DCM to afford the epoxide **17**. The crude epoxide was subjected to selective epoxide opening as well as carbamate reduction in one pot using lithium aluminum hydride under reflux in THF as the solvent to afford (−)-venlafaxine (**1**) in 60% yield with ≥99% *ee*[11] (Scheme 6). A broad band at 3323 cm^{-1} in its IR spectrum indicated the presence of free hydroxyl functional group. The disappearance of multiplet at δ 7.27-7.33 for five protons in its ^1H NMR spectrum and appearance of a peak at δ 2.38 for six protons for NMe_2 group clearly indicated the reduction of carbamate functional group to NMe_2 functional group. The ^{13}C NMR and DEPT NMR spectra of compound **1** showed a new peak at 31.2 which was attributed to CH_2 group, clearly indicating that the epoxide was selectively opened from less hindered side to furnish target compound venlafaxine (**1**). The mass spectrum of compound **1** showed peak at m/z 278 corresponding to $[M+H]^+$.

2.2.2. Conclusion

In conclusion, the asymmetric total synthesis of (−)-venlafaxine has been achieved in a very efficient manner from commercially available, cheap starting material by using an environmentally friendly proline-based catalyst. By using different enantiomers of proline-based catalyst one can access both the eanantiomers of venlafaxine in a very concise manner.

2.2.3. Experimental

(*E*)-1-Methoxy-4-(2-nitrovinyl)benzene (4)



4

A mixture of anisaldehyde **5** (20 g, 0.147 mol), nitromethane (94 mL, 1.741 mol), glacial acetic acid (24 mL, 0.419 mol) and ammonium acetate (24 g, 0.311 mol) was sonicated (33 KHz, Enertech) for 3 h. After removal of nitromethane, it was partitioned between dichloromethane (DCM) (3×100 mL) and water, organic layer was washed with water followed by brine, dried over anhydrous Na_2SO_4 and filtered. Removal of the DCM under reduced pressure and purification of the residue on a silica gel column using ethyl acetate/ pet ether (5:95) gave nitrostyrene **4** (24.7 g, 95%) as yellow solid. R_f (10% EtOAc/hexane): 0.5.

Molecular formula: $C_9H_9NO_3$

Yield: 95%

Melting Point: 80-82 ^{0}C (lit[7] 78-79 ^{0}C)

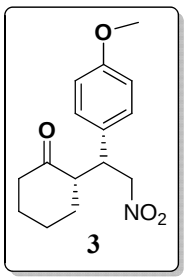
IR ($CHCl_3$): 3021, 2950, 1702, 1554, 1255 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 3.88 (s, 3H), 6.95 (d, *J*=8.8 Hz, 2H), 7.50 (d, *J*=13.7 Hz, 1H), 7.51 (d, *J*=8.8 Hz, 2H), 7.96 (d, *J*=13.7, 1H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 55.33, 114.84, 122.53, 131.03, 135.05, 138.67, 162.82.

MS (ESI) (m/z): 202 $[M+Na]^+$.

(*S*)-2-((*R*)-1-(4-Methoxyphenyl)-2-nitroethyl)cyclohexanone (3)



3

To a solution of the amine catalyst **7** (115 mg, 0.67 mmol), *p*-toluene sulfonic acid monohydrate (127 mg, 0.67 mmol) and the nitrostyrene **4** (3 g, 16.8 mmol) in DMF (1 mL) was added cyclohexanone (8.2 g, 84 mmol), and the solution was stirred at ambient temperature for 24 h. The solution was then concentrated under reduced pressure and the residue was extracted with ethyl acetate (3×100 mL), washed with water followed by brine, dried over anhydrous Na_2SO_4 and filtered. Removal of the ethyl acetate under reduced pressure and purification of the residue on a silica gel column using ethyl acetate/ pet ether (2:8) gave nitroketo compound **3** (6.1 g, 79%) as white solid. R_f (20% EtOAc/hexane): 0.4.

Molecular formula: $C_{15}H_{19}NO_4$

Yield: 79%

$[\alpha]_D^{25}$: -26 (*c* 1.0, $CHCl_3$)

Melting Point: 135-137 ^{0}C

IR ($CHCl_3$): 3020, 2939, 1708, 1555, 1216 cm^{-1}.

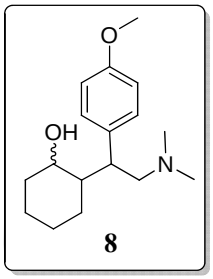
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.15-1.33 (m, 1H), 1.56-1.66 (m, 1H), 2.07-2.12 (m, 1H), 2.36-2.71 (m, 3H), 3.69 (dt, *J*=4.5, 10 Hz, 1H), 3.78 (s, 3H), 4.57 (dd,

J=9.9, 12.2 Hz, 1H), 4.88 (dd, *J*=4.5, 12.2 Hz, 1H), 6.83 (d, *J*=8.7 Hz, 2H), 7.07 (d, *J*=8.6 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 25.01, 28.49, 33.09, 42.62, 43.17, 52.06, 55.05, 78.99, 114.27, 129.10, 129.49, 158.94, 211.60.

MS (ESI) (m/z): 300 $[M+Na]^+$.

2-(2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl)cyclohexanol (8)



8

To a cold (0 °C), magnetically stirred solution of keto nitro compound **3** (2 g, 7.2 mmol) in THF: H_2O (9:1) (20 mL), $NaBH_4$ (1.09 g, 28.0 mmol) was added portion wise and stirred for 2 h at the same temperature. The reaction was quenched by addition of saturated aq. NH_4Cl solution at 0 °C and the reaction mixture was again stirred for 10 min. Evaporation of the solvent furnished a residue which was extracted with ethyl acetate (3×8 mL). The combined organic layer was washed with brine (7 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude reaction mixture was used as such in the next reaction without further purification.

The crude reaction mixture (1.30 g, 4.65 mmol) was dissolved in distilled methanol and cooled to 0 °C. $NiCl_2.6H_2O$ (2.75 g, 11.6 mmol) was added under N_2 atmosphere. $NaBH_4$ (4.5 g, 0.116 mol) was added portion wise very slowly, the reaction mixture turned into black colored solution and was stirred for 1.5 h at 0 °C. Then 37% aq. HCHO solution (19 mL, 0.2325 mmol) was added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was cooled to 0 °C and quenched with saturated NH_4Cl solution (10 mL) and again stirred for 10 min. Evaporation of the solvent furnished a residue which was extracted with ethyl acetate (3× 20 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue on a silica gel column using ethyl acetate/hexane (4:6) as eluent furnished amine compound **8** (1.10 g, 55%) as a colorless liquid. R_f (50% EtOAc/hexane): 0.2.

Molecular formula: $C_{17}H_{27}NO_2$

Yield: 55%

IR ($CHCl_3$): 3430, 2931, 1610, 1511 cm^{-1}.

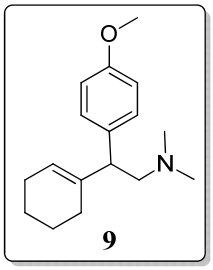
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 0.98-1.06 (m, 1H), 1.16-1.31 (m, 2H), 1.37-1.62 (m, 5H), 1.93-1.98 (m, 1H), 2.09 (dd, *J*= 1.0, 12.5 Hz, 1H), 2.30 (s, 6H), 2.51 (t, *J*=10.0 Hz, 1H), 2.96 (dd, *J*=12.8, 10.0 Hz, 1H), 3.77 (s, 3H), 4.03-4.10 (m, 1H), 6.79 (d, *J*=8.7 Hz, 2H), 6.98 (d, *J*=8.7 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 20.62, 25.76, 26.72, 32.72, 45.27, 45.99, 48.29, 55.00, 64.94, 65.93, 113.61, 128.33, 137.27, 157.72.

MS (ESI) (m/z): 277 $[M+Na]^+$.

Elemental analysis: Calculated C, 73.61; H, 9.81; N, 5.05 %; Found C, 73.41; H, 9.89; N, 5.10 %.

2-(Cyclohex-1-en-1-yl)-2-(4-methoxyphenyl)-N,N-dimethylethanamine (9)



9

To the stirred solution of amine **8** (800 mg, 3.0 mmol) in anhydrous DCM (10 mL) was added Et_3N (2.5 mL, 18.0 mmol) followed by mesyl chloride (0.7 mL, 9.0 mmol) at 0 °C. The reaction mixture was refluxed for 1 h. The reaction was quenched by addition of saturated aq. $NaHCO_3$ solution and evaporation of the solvent furnished a residue which was extracted with DCM (3× 8 mL). The combined organic layer was washed with brine (7 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude reaction mixture was used as such in the next reaction without further purification.

To the crude mesylated product (850 mg) in dry acetonitrile, was added DBU (1 mL) at room temperature. The reaction mixture was refluxed for 8 h. The solvent was evaporated to furnish a residue which was extracted with ethyl acetate (3×8 mL). The combined organic layer was washed with brine (10 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue on a silica gel column using 100% ethyl acetate as eluent furnished the olefin product **9** (0.449 mg, 60% yield) as a colorless liquid. R_f (50% EtOAc/hexane): 0.6.

Molecular formula: $C_{17}H_{25}NO$

Yield: 60%

IR ($CHCl_3$): 2931, 1610, 1511 cm^{-1}.

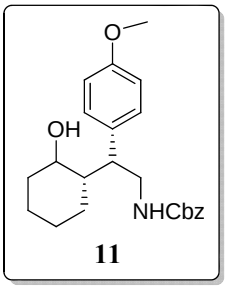
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.51-1.57 (m, 4H), 1.75-1.90 (m, 2H), 1.97-2.12 (m, 2H), 2.22 (s, 6H), 2.61 (dd, *J*=4.8, 7.1 Hz, 2H), 3.30 (t, *J*=7.5 Hz, 1H), 3.79 (s, 3H), 5.54-5.62 (m, 1H), 6.80 (d, *J*=8.7 Hz, 2H), 7.10 (d, *J*=8.7 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 22.31, 22.82, 25.26, 26.88, 45.17, 48.96, 54.96, 61.86, 113.77, 122.17, 128.71, 133.83, 138.46, 158.19.

MS (ESI) (m/z): 260 $[M+H]^+$.

Elemental analysis: Calculated C, 78.72; H, 9.71; N, 5.40 %; Found C, 78.92; H, 9.61; N, 5.30 %.

Benzyl ((2*R*)-2-((1*S*)-2-hydroxycyclohexyl)-2-(4-methoxyphenyl) ethyl)carbamate (11)



11

Ketone functional group of compound **3** (2 g) was reduced by the same procedure as above. The crude hydroxyl compound (2.06 g, 7.4 mmol) was dissolved in distilled methanol and cooled to 0 °C. Then $NiCl_2.6H_2O$ (4.4 g, 18.5 mmol) was added in N_2 atmosphere. $NaBH_4$ (7.03 g, 0.185 mol) was added portion wise very slowly, then reaction mixture turned into black colored solution and was stirred for 1.5 h at 0 °C. Then Et_3N (4 mL, 29.6 mmol) was added followed by addition of benzylchloroformate (3.7 mL, 22.2 mmol) and the reaction mixture was stirred overnight at room temperature. The reaction mixture was cooled to 0 °C and quenched with saturated aq. NH_4Cl solution (10 mL) and again stirred for 10 min. Evaporation of the solvent furnished a residue which was extracted with ethyl acetate (3× 20 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue on a silica gel column using ethyl acetate/hexane (2.5:7.5) as eluent furnished the Cbz protected amine compound **11** (2.07 g, 75%) as white solid. R_f (40% EtOAc/hexane): 0.5.

Molecular formula: $C_{23}H_{29}O_4N$

Yield: 75%

$[\alpha]_D^{25}$: +62 (*c* 0.28, $CHCl_3$)

Melting Point: 110-112 ^{0}C.

IR ($CHCl_3$): 3433, 2930, 1701, 1610, 1511, 1454 cm^{-1}.

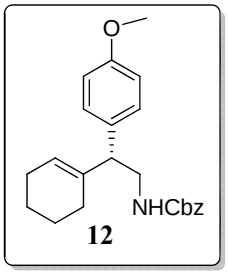
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.03-1.27 (m, 3H), 1.46-1.62 (m, 5H), 1.89-1.94 (m, 1H), 2.68-2.80 (m, 2H), 3.10-3.21 (m, 1H), 3.79 (s, 3H), 3.85-3.91 (m, 1H), 4.26 (bs, 1H), 5.04 (s, 2H), 6.83 (d, *J*= 8.7 Hz, 2H), 7.04 (d, *J*=8.6 Hz, 2H), 7.27-7.37 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 19.93, 25.11, 26.10, 33.74, 44.06, 45.04, 47.70, 55.06, 65.75, 66.50, 114.04, 127.95, 128.41, 129.28, 134.33, 136.67, 156.59.

MS (ESI) (m/z): 384 $[M+H]^+$.

HRMS (ESI): Calculated 384.2169 $(M+H)^+$; Found 384.2160.

(*R*)-Benzyl (2-(cyclohex-1-en-1-yl)-2-(4-methoxyphenyl)ethyl)carbamate (12)



12

To the stirred solution of Cbz protected amine **11** (100 mg, 0.26 mmol) in anhydrous DCM, was added Et_3N (0.22 mL, 1.56 mmol) followed by mesyl chloride (0.06 mL, 0.78 mmol) at 0 °C. The reaction mixture was refluxed for 14 h. The reaction was quenched by addition of saturated aq. $NaHCO_3$ solution and evaporation of the solvent furnished a residue which was extracted with DCM (3× 8 mL). The combined organic layer was washed with brine (7 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude reaction mixture was used as such in the next reaction without further purification.

To the crude mesylated product (120 mg) in dry acetonitrile, was added DBU (1 mL) at room temperature. The reaction mixture was refluxed for 24 h. The solvent was evaporated to furnish a residue which was extracted with ethyl acetate (3×8 mL). The combined organic layer was washed with brine (10 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue on a silica gel column using ethyl acetate/hexane (1:9) as eluent furnished the olefinic product **12** (64.6 mg, 68% yield) as a colorless liquid. R_f(10% EtOAc/hexane): 0.6.

Molecular formula: $C_{23}H_{27}O_3N$

Yield: 68%

$[\alpha]_D^{25}$: +45.4 (*c* 0.64, $CHCl_3$)

IR ($CHCl_3$): 2930, 1701, 1610, 1511, 1454 cm^{-1}.

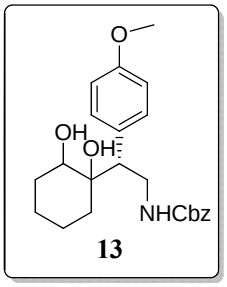
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.48-1.60 (m, 4H), 1.71-1.83 (m, 2H), 2.00-2.13 (m, 2H), 3.20-3.63 (m, 3H), 3.79 (s, 3H), 4.57-4.71 (m, 1H), 5.03-5.18 (m, 2H), 5.56-5.64 (m, 1H), 6.82 (d. *J*=10 Hz, 2H), 7.09 (d, *J*=10 Hz, 2H), 7.27-7.36 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 22.84, 23.25, 25.69, 27.35, 43.83, 52.10, 55.51, 66.91, 114.25, 122.88, 128.43, 128.86, 129.25, 133.62, 137.11, 138.29, 156.55, 158.76.

MS (ESI) (m/z): 388 $[M+H]^+$.

HRMS (ESI): Calculated 388.1883 $(M+Na)^+$; Found 388.1869.

Benzyl (2-(1,2-dihydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl)carbamate (13)



13

To a cold (0 °C), magnetically stirred solution of **12** (90 mg, 0.25 mmol) in acetonitrile: water (9:1) (10 mL), catalytic amount of OsO_4 (0.1 mL, 0.1 M solution in toluene) was added in the presence of *N*-methylmorpholine-*N*-oxide (NMO) (99 mg, 0.74 mmol) as a co-oxidant and stirred overnight at rt. The reaction was quenched with saturated aq. Na_2SO_3 (5 mL) solution and again stirred for 30 min. The solvent was evaporated and the residue was extracted with ethyl acetate (3×5 mL). The combined organic layer was washed with brine (3 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue on a silica gel column using ethyl acetate/hexane (4:6) as eluent furnished the diol compound **13** (95 mg, 97%) as yellowish oil. R_f (40% EtOAc/hexane): 0.2.

Molecular formula: $C_{23}H_{29}NO_5$

Yield: 97%

IR ($CHCl_3$): 3433, 2930, 1701, 1610, 1511 cm^{-1}.

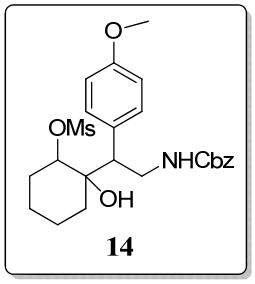
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.56-1.68 (m, 5H), 1.75-2.00 (m, 3H), 3.07-3.14 (m, 1H), 3.41-3.62 (m, 2H), 3.80 (s, 3H), 3.85-3.97 (m, 1H), 4.67-4.72 (m, 1H), 5.04 (d, *J*=2 Hz, 2H), 6.85 (d, *J*=8.0 Hz, 2H), 7.18 (d, *J*=8.0 Hz, 2H), 7.26-7.32 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 20.79, 23.19, 30.32, 32.55, 41.66, 52.27, 55.04, 60.29, 66.56, 71.38, 74.68, 113.84, 127.96, 128.38, 130.32, 130.88, 136.44, 156.47, 158.67.

MS (ESI) (m/z): 400 $[M+H]^+$.

HRMS (ESI): Calculated 400.4875 $(M+H)^+$; Found 400.4885.

2-(2-(((Benzyloxy)carbonyl)amino)-1-(4-methoxyphenyl)ethyl)-2-hydroxycyclohexyl methanesulfonate (14)



14

To the stirred solution of diol **13** (70 mg, 0.20 mmol) in anhydrous DCM was added Et_3N (0.04 mL, 0.30 mmol) followed by mesyl chloride (0.02 mL, 0.24 mmol) at 0 °C. The reaction mixture was refluxed for 4 h. The reaction was quenched by addition of saturated $NaHCO_3$ solution and evaporation of the solvent furnished a residue which was extracted with DCM (3× 8 mL). The combined organic layer was washed with brine (7 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue on a silica gel column using ethyl acetate/hexane (4:6) as eluent furnished the diol compound **14** (55 mg, 67%) as colorless oil. R_f (50% EtOAc/hexane): 0.3.

Molecular formula: $C_{24}H_{31}NO_7S$

Yield: 67%

IR ($CHCl_3$): 3443, 2933, 1701, 1615, 1511 cm^{-1}.

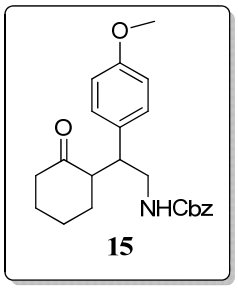
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4) : δ 1.50-2.00 (m, 8H), 3.05 (s, 3H), 3.14-3.21 (m, 1H), 3.50 (dt, *J*= 4.5, 10.5 Hz, 1H), 3.86 (s, 3H), 3.90-4.00 (m, 1H), 4.45-4.57 (m, 1H), 4.60-4.70 (m, 1H), 5.08 (s, 2H), 6.91 (d, *J*=8.7 Hz, 2H), 7.30-7.48 (m, 7H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4) : 21.29, 28.10, 32.19, 38.38, 41.56, 55.04, 66.45, 73.78, 83.29, 127.88, 127.97, 128.38, 129.22, 130.86, 136.49, 156.27, 158.92.

MS (ESI) (m/z): 478 $[M+H]^+$.

HRMS (ESI): Calculated 478.5778 $(M+H)^+$; Found 478.5796

Benzyl (2-(4-methoxyphenyl)-2-(2-oxocyclohexyl)ethyl)carbamate (15)



15

To the mesylate compound **14** (30 mg, 0.063 mmol) in 1,2-dimethoxyethane (4 mL), was added NaI (45 mg, 0.3 mmol) and powdered Zn (42 mg, 0.65 mmol) and the mixture was refluxed for 24 h. Zn powder was filtered off and the filtrate was evaporated to dryness. Purification of the residue on a silica gel column using ethyl acetate/hexane (3:7) as eluent furnished the keto compound **15** (11 mg, 45%) as colorless oil. R_f (40% EtOAc/hexane): 0.7.

Molecular formula: $C_{23}H_{27}NO_4$

Yield: 45%

IR ($CHCl_3$): 2925, 1710, 1701, 1610, 1511 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.42-1.67 (m, 8H), 2.72-2.85 (m, 1H), 3.45-3.57 (m, 2H), 3.80 (s, 3H), 4.04 (dd, *J*= 6.0, 8.0 Hz, 1H), 5.08 (s, 2H), 6.84 (d, *J*=8.7 Hz, 2H), 7.09 (d, *J*=8.6 Hz, 2H), 7.30-7.40 (m, 5H).

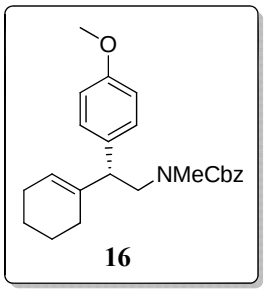
^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 25.94, 26.03, 28.38, 30.24, 43.25, 50.35, 55.03, 56.91, 66.45, 114.42, 127.90, 127.99, 128.39, 129.51, 136.55, 156.16, 159.07, 212.51.

MS (ESI) (m/z): 404 $[M+Na]^+$.

HRMS (ESI): Calculated 404.4540 $(M+Na)^+$; Found 404.4530.

(*R*)-Benzyl(2-(cyclohex-1-en-1-yl)-2-(4-methoxyphenyl) ethyl) (methyl) carbamate (16)

To a cold (0 ºC), magnetically stirred solution of olefin **12** (100 mg, 0.274 mmol) in dry THF (5 mL), NaH (22 mg, 0.55 mmol, 60%) was added followed by dropwise addition of MeI (0.034 mL, 0.55 mmol) and the reaction mixture was stirred at rt for overnight. The reaction mixture was cooled to 0 °C and quenched with saturated



16

NH_4Cl solution (10 mL) and again stirred for 10 min. Evaporation of the solvent furnished a residue which was extracted with ethyl acetate (3× 20 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue on a silica gel column using ethyl acetate/hexane (1:9) as eluent furnished the *N*-methylCbz compound **16** (95 mg, 92%) as colorless liquid. R_f (10% EtOAc/hexane): 0.7.

Molecular formula: $C_{24}H_{29}O_3N$

Yield: 92%

$[\alpha]_D^{25}$: +46.09 (*c* 1.4, $CHCl_3$)

IR ($CHCl_3$): 2928, 1701, 1609, 1510, 1456, 1402 cm^{-1}.

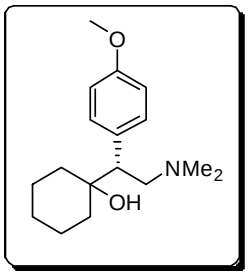
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.45-1.58 (m, 5H), 1.68-1.90 (m, 2H), 1.97-2.13 (m, 2H), 2.71 and 2.74 (s, 3H), 3.37-3.55 (m, 2H), 3.69-3.90 (m, 4H), 4.95-5.10 (m, 2H), 5.54-5.58 (m, 1H), 6.74-6.82 (m, 2H), 6.99-7.13 (m, 2H), 7.27-7.33 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 22.40, 22.85, 25.31, 26.66, 27.08, 34.46, 35.16, 49.79, 50.26, 51.89, 54.89, 66.56, 66.83, 113.55, 122.03, 127.53, 127.67, 127.80, 127.95, 128.29, 128.94, 133.34, 136.89, 137.16, 137.96, 138.11, 156.00, 158.19.

MS (ESI) (m/z): 402 $[M+Na]^+$.

HRMS (ESI): Calculated 402.2040 $(M+Na)^+$; Found 402.2025.

(*R*)-1-(2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl)cyclohexanol [(−)-venlafaxine, 1]



To a cold (0 °C), magnetically stirred solution of N-methylCbz compound **9** (235 mg, 0.6 mmol) in distilled DCM (5 mL), $NaHCO_3$ (126 mg, 1.5 mmol) was added followed by 60% *m*-CPBA (348 mg, 1.2 mmol) added portion wise and stirred for 2 h at room temperature. The reaction was quenched with solid $NaHCO_3$ and stirred for further 15 min. The reaction mixture

was extracted with DCM (3 × 5 mL) and the combined organic layer was washed with brine (7 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude reaction mixture was used as such in the next reaction without further purification.

To a cold (0 °C), magnetically stirred suspension of lithium aluminium hydride (100 mg, 2.5 mmol) in dry THF (5 mL), crude epoxide (100 mg, 0.25 mmol) was added dropwise and refluxed for 5 h. The reaction mixture was cooled to 0 °C and excess lithium aluminium hydride was quenched with ethyl acetate and then by addition of water and stirred for 2 h. Evaporation of the solvent furnished a residue which was extracted with ethyl acetate (3× 20 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue on a silica gel column using ethyl acetate as eluent furnished the (−)-venlafaxine (**1**) (103 mg, 60% over two steps) as white solid. R_f (100% EtOAc): 0.2 (long tail).

Molecular formula: $C_{17}H_{27}NO_2$

Yield: 60% (over two steps)

$[\alpha]_D^{25}$: −24.285 (*c* = 1.04, EtOH) Literature[12] *R*-(-)-venlafaxine $[\alpha]_D^{25}$ = - 27.1 (c = 1.04, EtOH).

IR ($CHCl_3$): 3164, 2982, 2938, 2860, 2782, 1610 cm^{-1}.

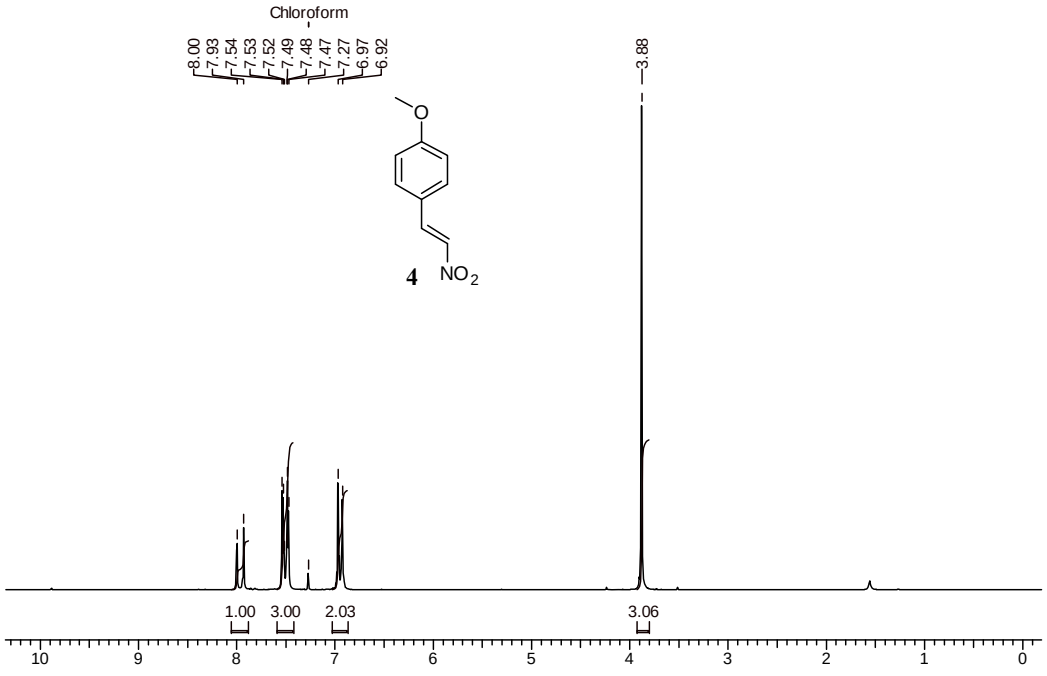
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 0.83-1.00 (m, 2H), 1.23-1.76 (m, 8H), 2.28 (dd, *J*=12.2, 2.9 Hz, 1H), 2.33 (s, 6H), 2.93 (dd, J= 12.2, 2.9 Hz, 1H), 3.28 (t, *J*=12.2 Hz, 1H), 3.79 (s, 3H), 6.79 (d, *J*=8.8 Hz, 2H), 7.03 (d, *J*=8.79 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 20.70, 21.05, 25.55, 30.72, 37.53, 44.89, 51.20, 54.36, 60.74, 73.48, 112.75, 129.43, 132.00, 157.72.

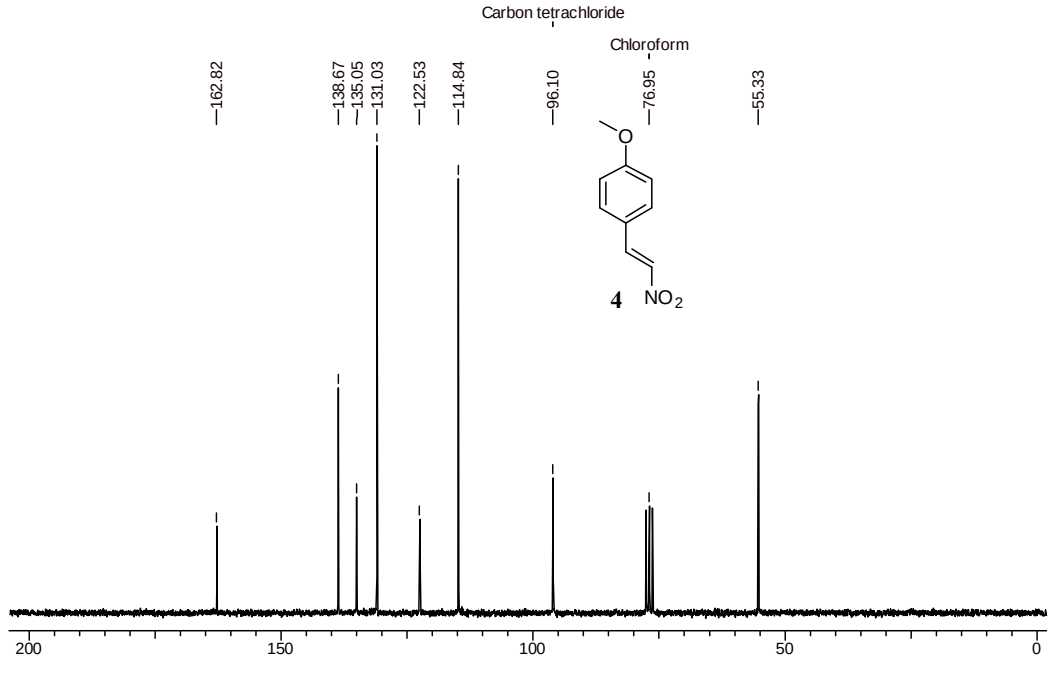
MS (ESI) (m/z): 278 $[M+H]^+$.

2.2.4. NMR Spectra

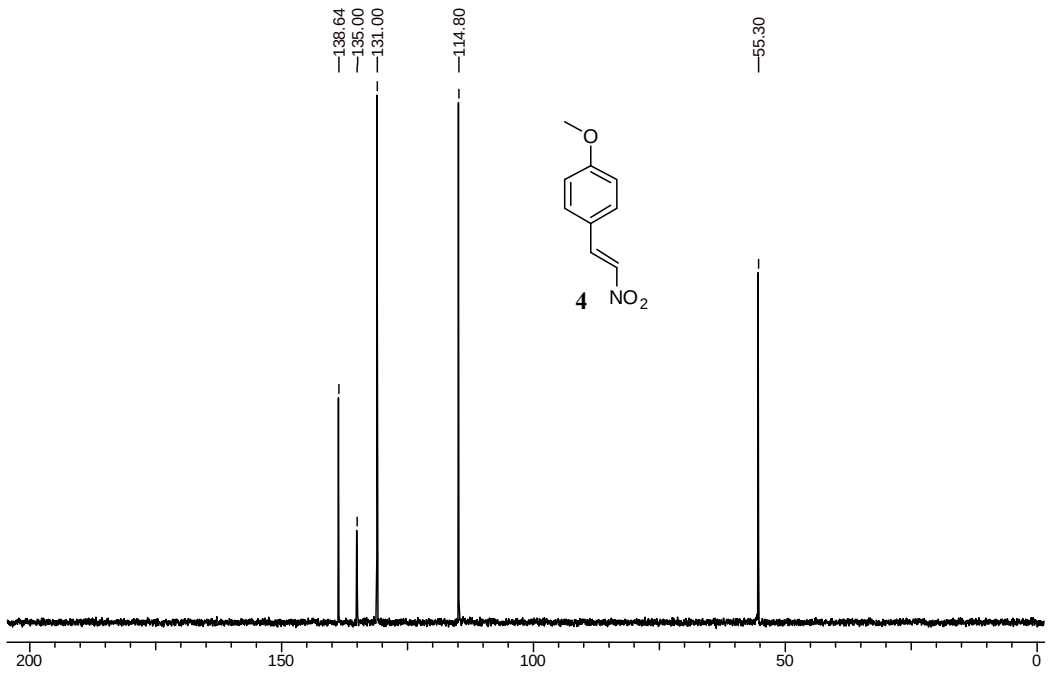
^{1}H NMR spectrum of compound **4** ($CDCl_3$+CCl_4, 200 MHz)



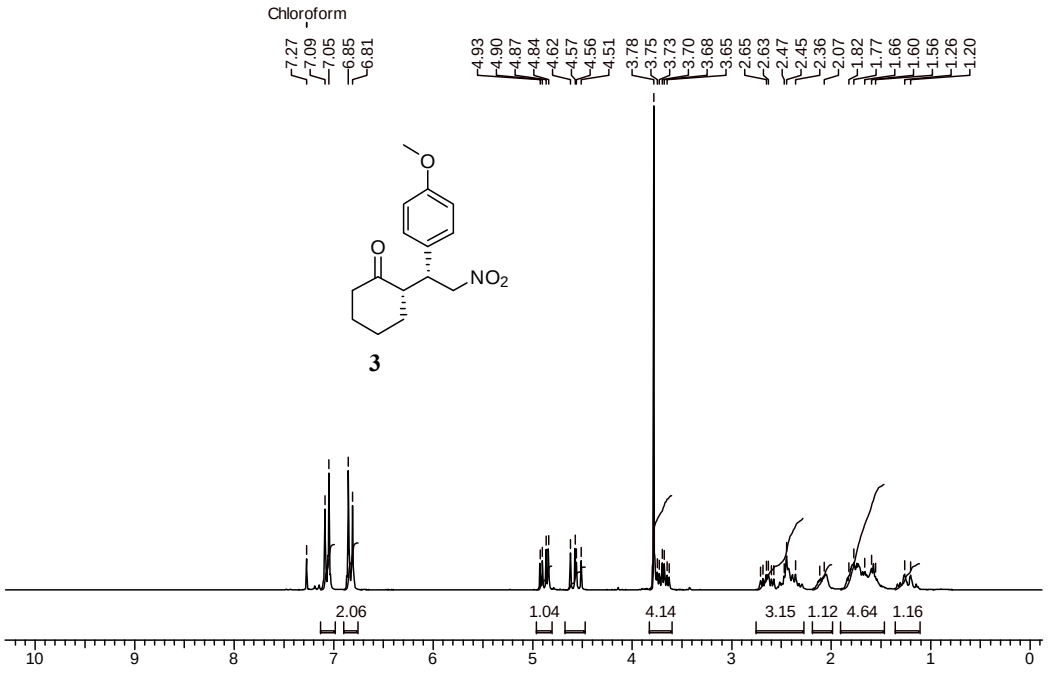
^{13}C NMR spectrum of compound **4** ($CDCl_3$ + CCl_4, 50 MHz)



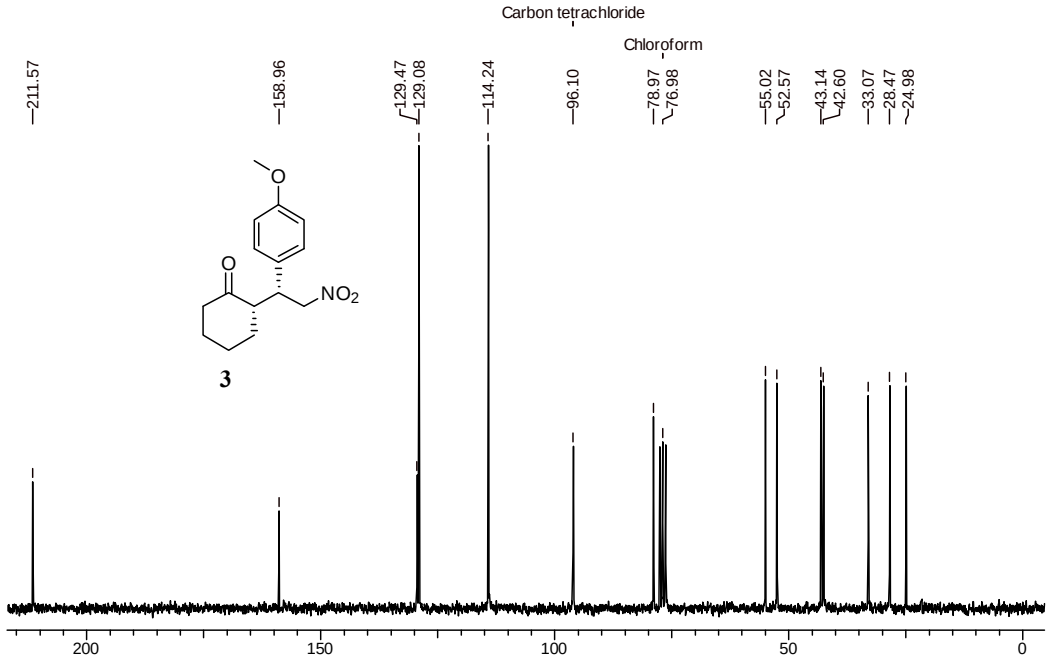
DEPT spectrum of compound **4** ($CDCl_3$ + CCl_4, 50 MHz)



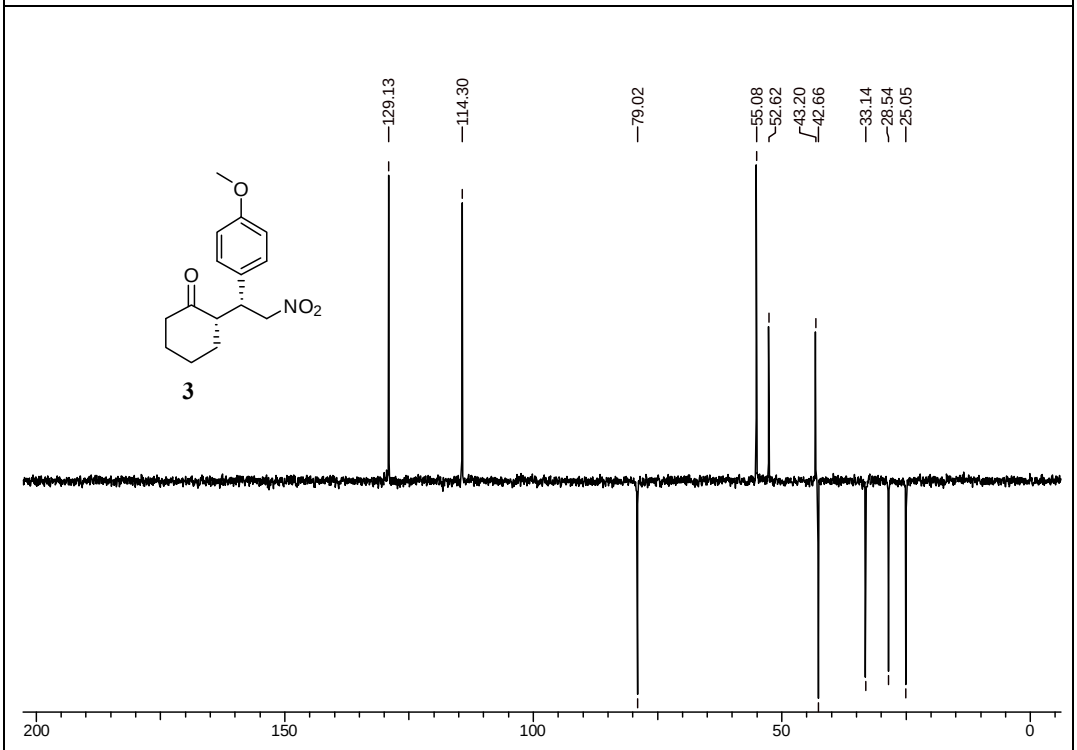
^{1}H NMR spectrum of compound **3** ($CDCl_3$+CCl_4, 200 MHz)



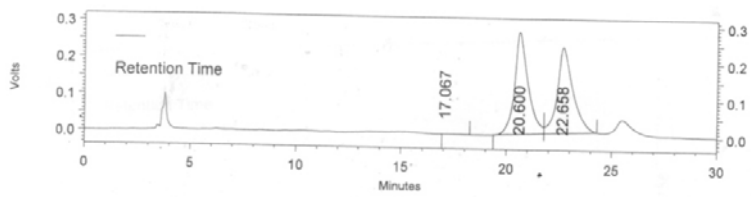
^{13}C NMR spectrum of compound **3** ($CDCl_3$ + CCl_4, 50 MHz)

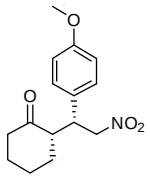


DEPT spectrum of compound **3** ($CDCl_3$ + CCl_4, 50 MHz)



HPLC chromatogram of racemic compound **3**





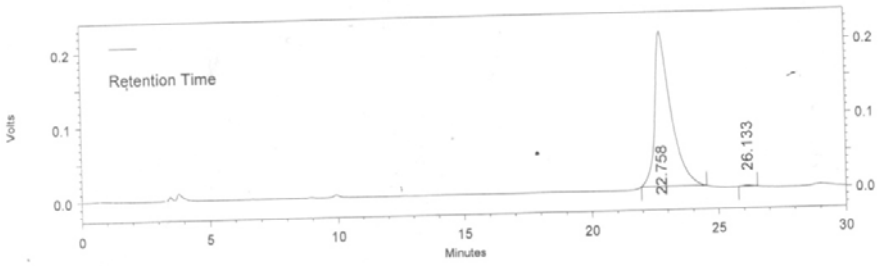
3

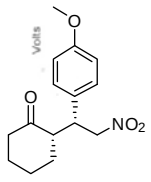
Detector A - 1
(220nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	17.067	8501	0.035	87	0.02
2	20.600	12501574	50.755	278474	54.31
3	22.658	12121303	49.211	234158	45.67
Totals		24631378	100.000	512719	100.00

Grp Leader :Dr
Column :Chiralcel OD-H (250x4.6mm)
Mobile Phase : IPA: PE:
Wavelength : 280 nm
Flow Rate : 0.7mL/min(21Kgf)
Sample Con :1mg/ 2mL

HPLC chromatogram of Chiral compound **3**





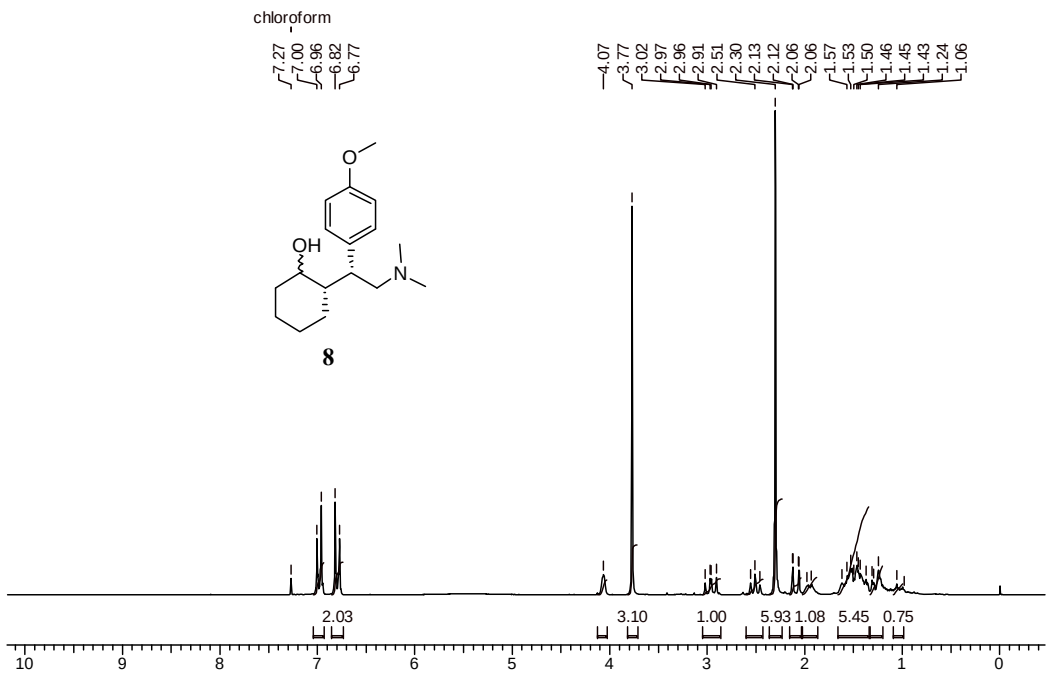
3

Detector A - 1
(220nm)

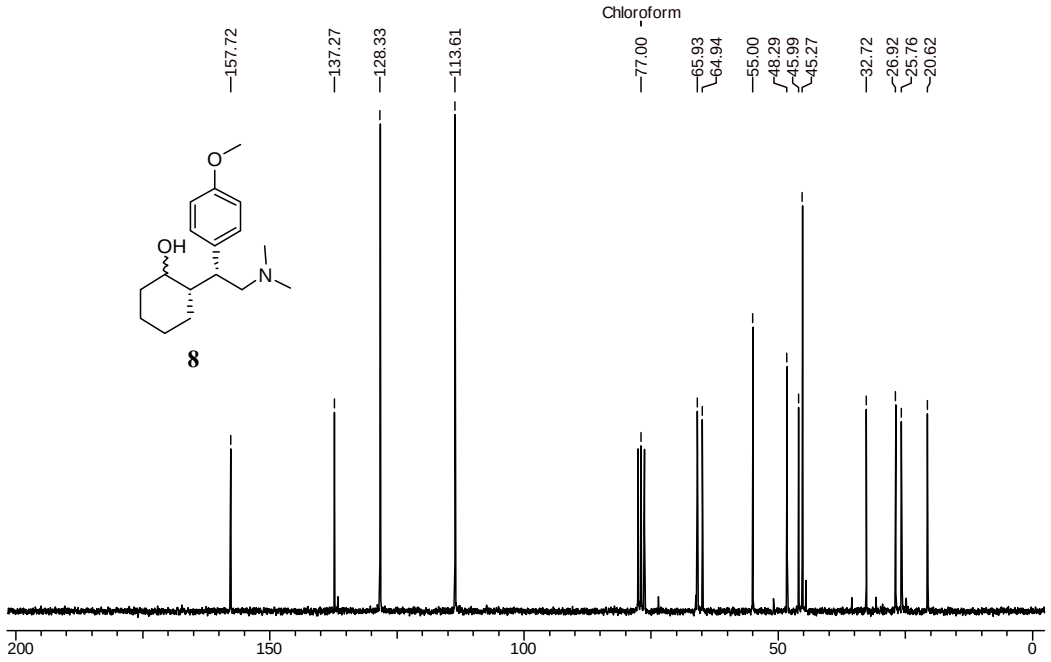
Pk #	Retention Time	Area	Area %	Height	Height Percent
1	22.758	9301149	99.660	208405	99.43
2	26.133	31770	0.340	1201	0.57
Totals		9332919	100.000	209606	100.00

Grp Leader :Dr S.P.Chavan
Column :Whelke-O1(R,R) (250x4.6mm)
Mobile Phase : IPA: PE: (3:97)
Wavelength : 280 nm
Flow Rate : 0.7mL/min(21Kgf)
Sample Con :1mg/ 2mL

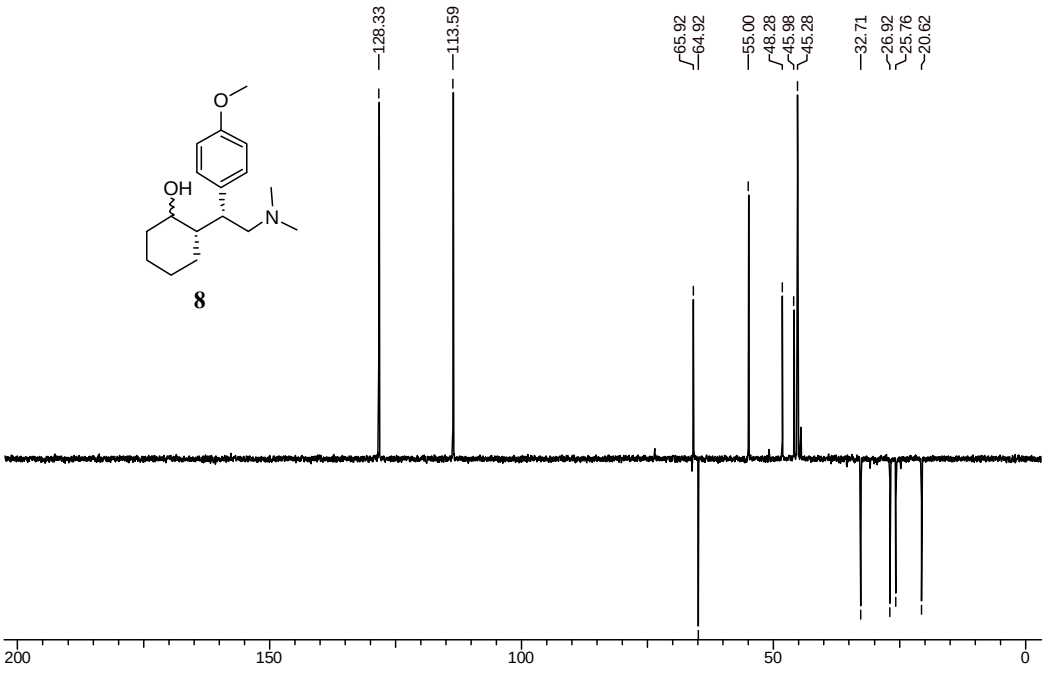
^{1}H NMR spectrum of compound **8** ($CDCl_3$, 200 MHz)



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

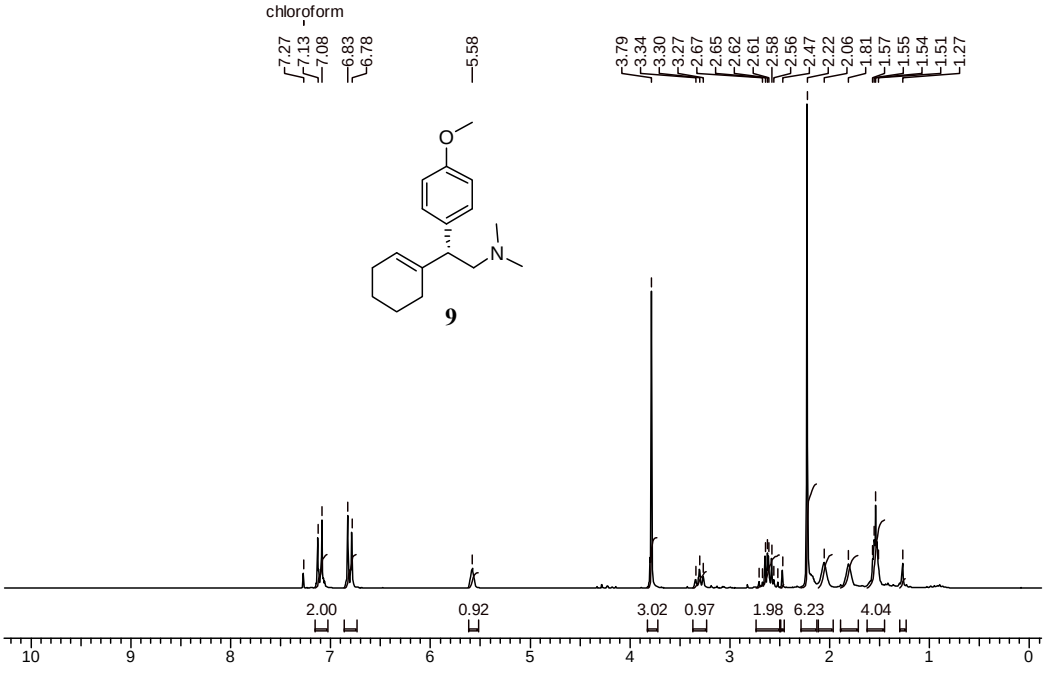


DEPT spectrum of compound **8** ($CDCl_3$, 50 MHz)



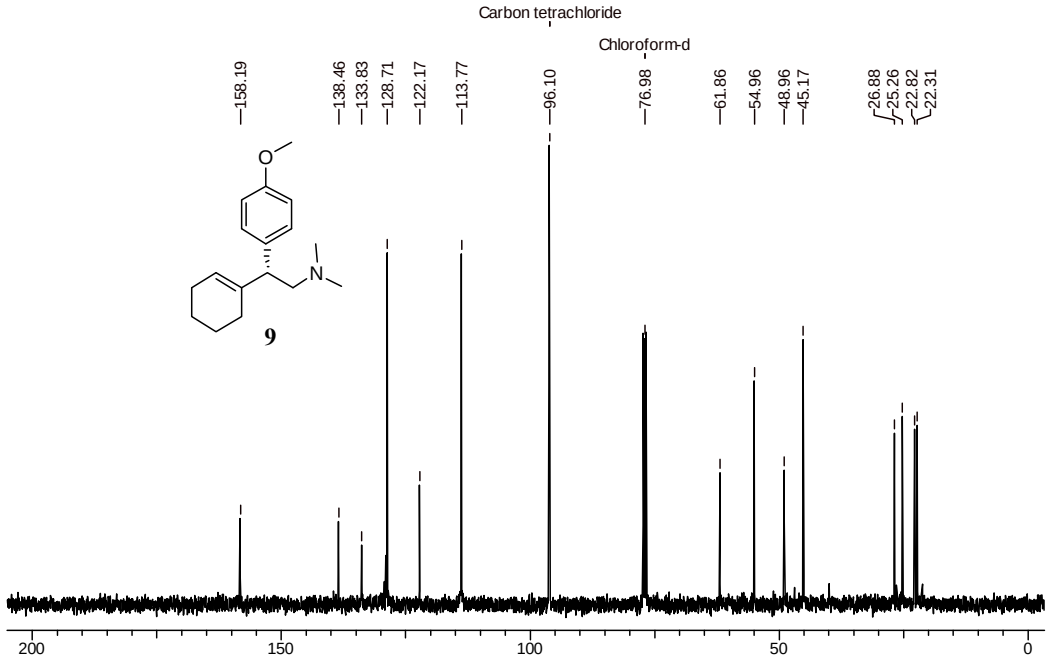
8

^1H NMR spectrum of compound **9** ($CDCl_3$+CCl_4, 200 MHz)

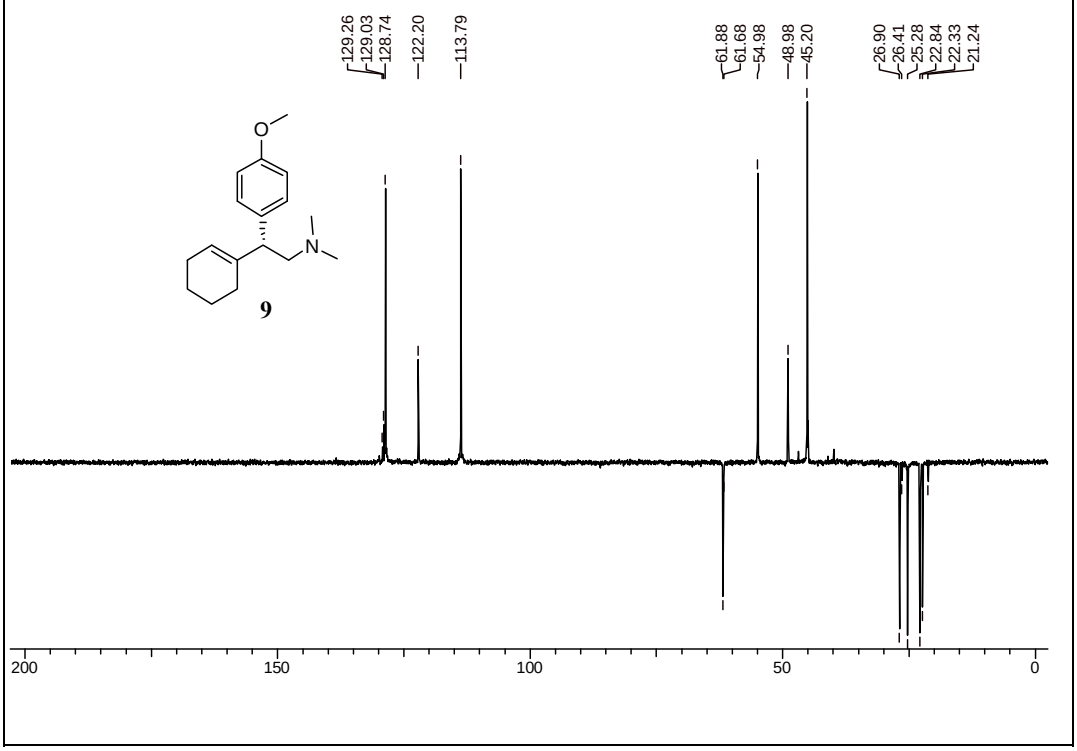


9

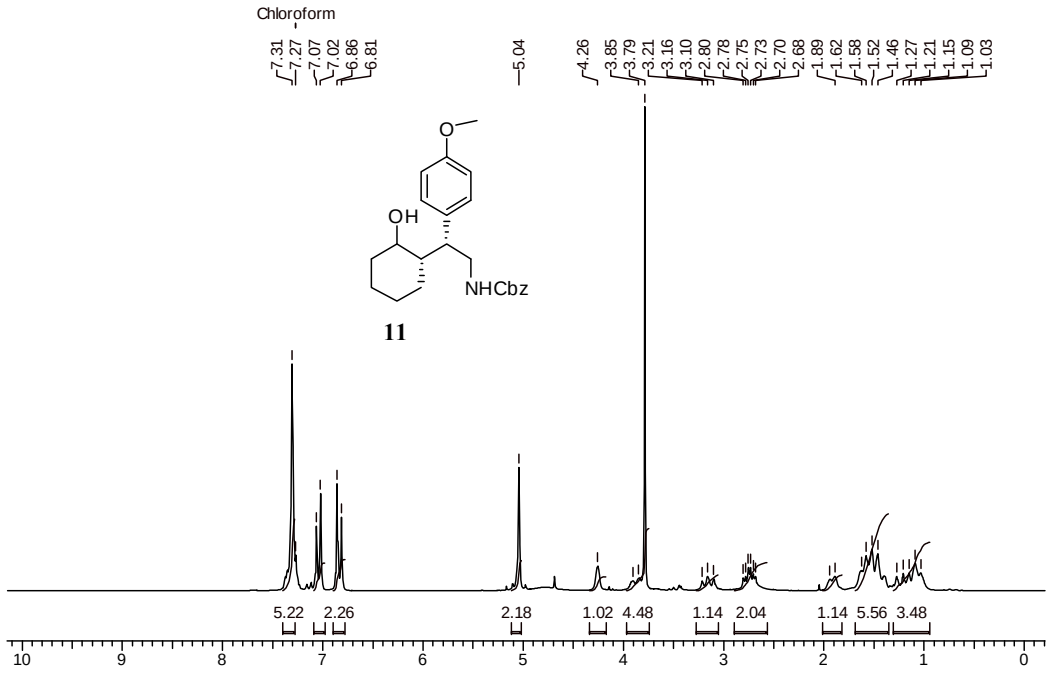
^{13}C NMR spectrum of compound **9** ($CDCl_3 + CCl_4$, 50 MHz)



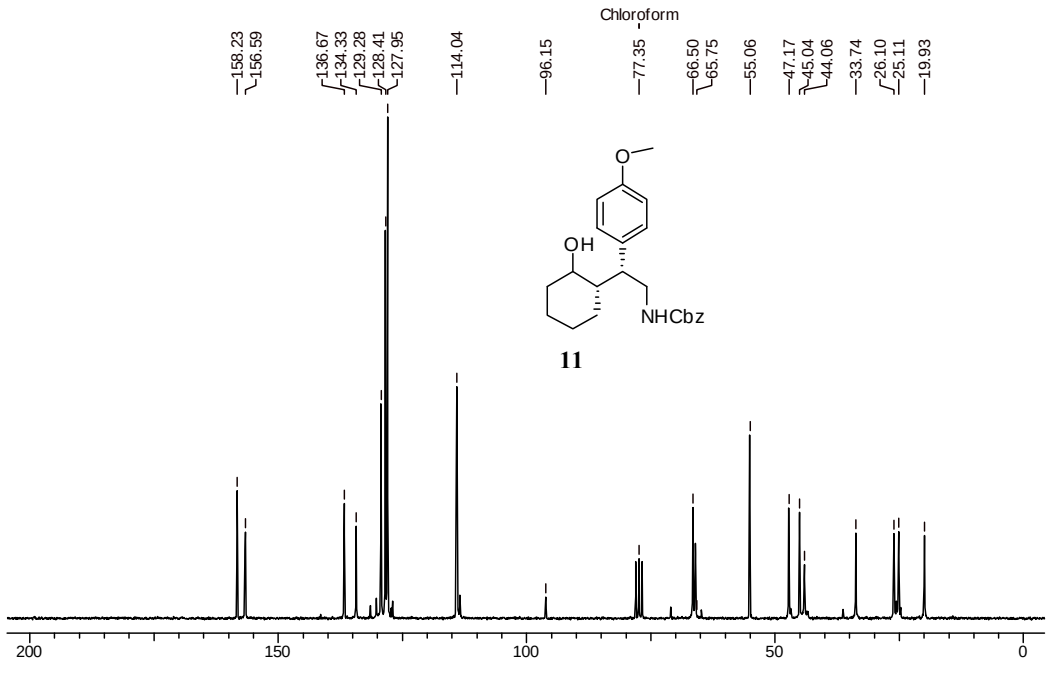
DEPT spectrum of compound **9** ($CDCl_3 + CCl_4$, 50 MHz)



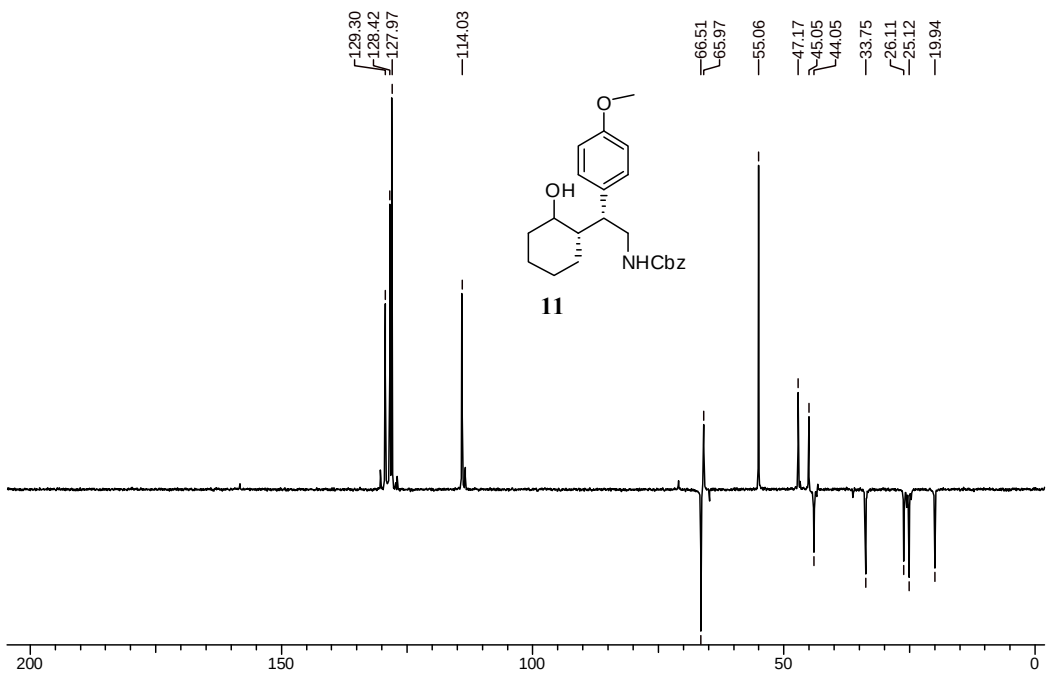
^{1}H NMR spectrum of compound **11** ($CDCl_3$, 200 MHz)



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

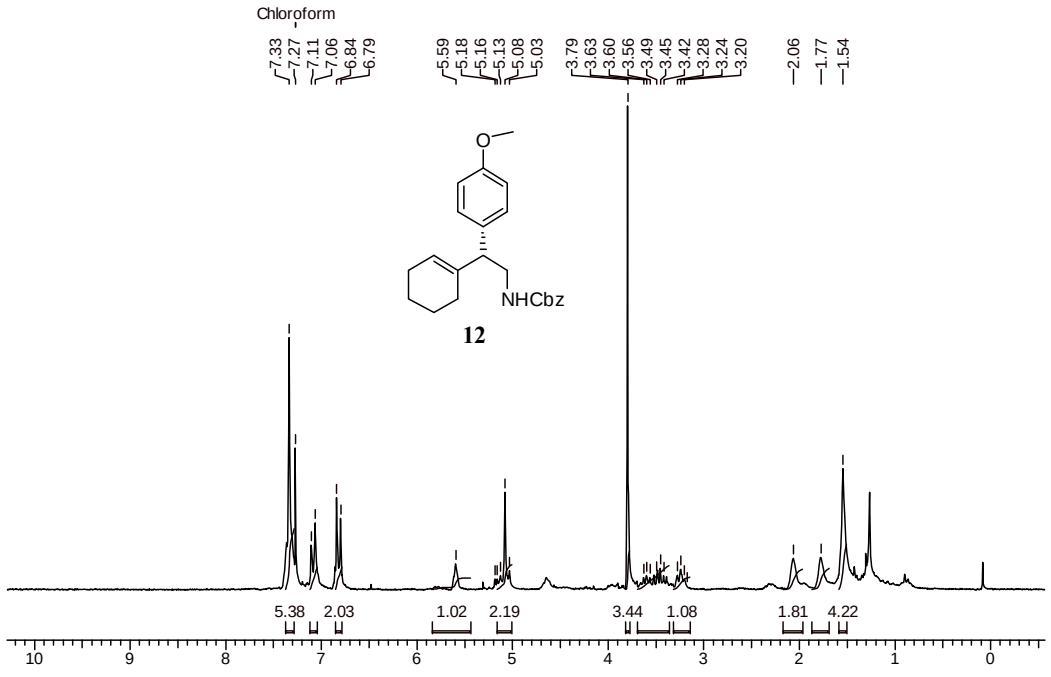


DEPT spectrum of compound **11** ($CDCl_3$, 50 MHz)



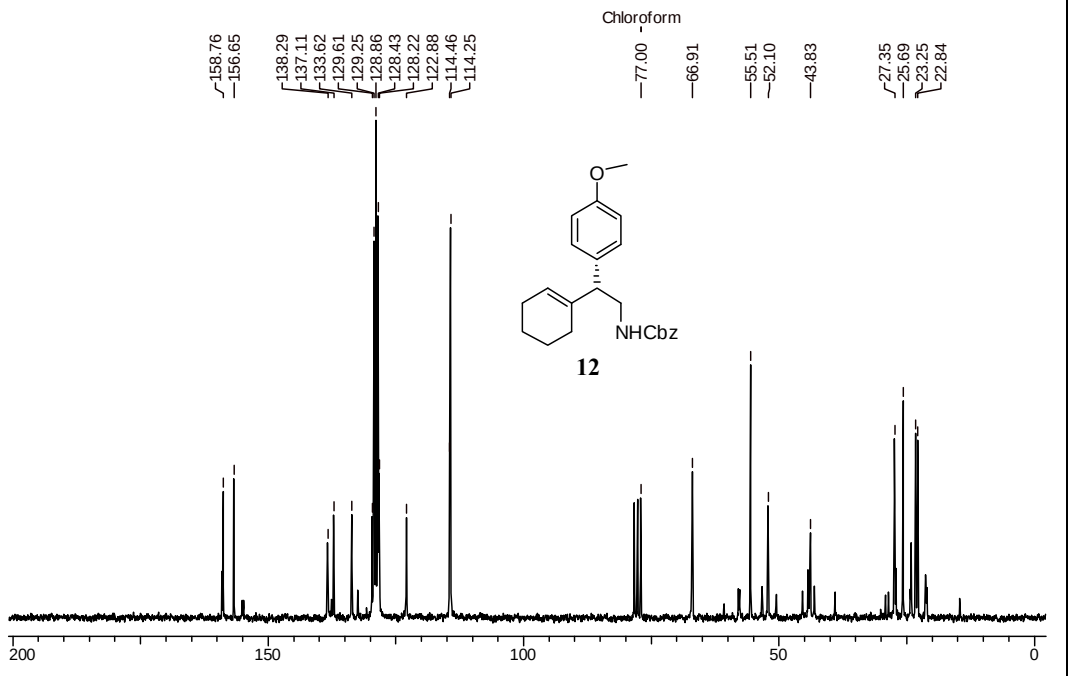
11

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

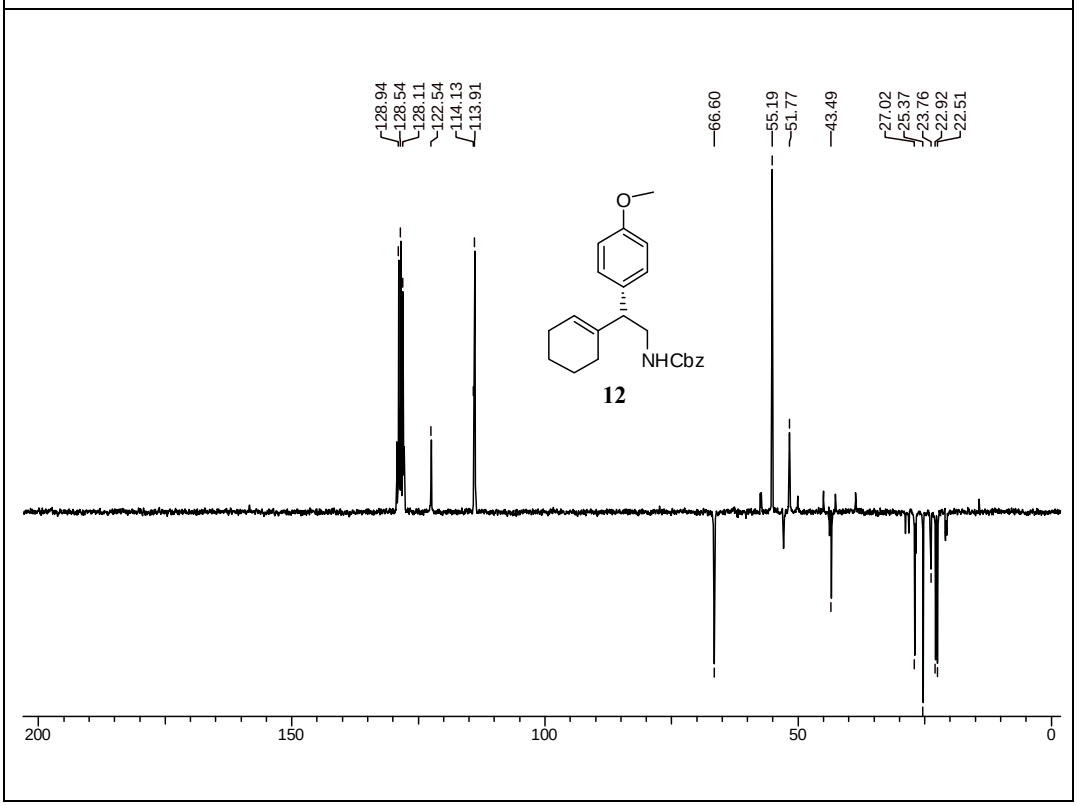


12

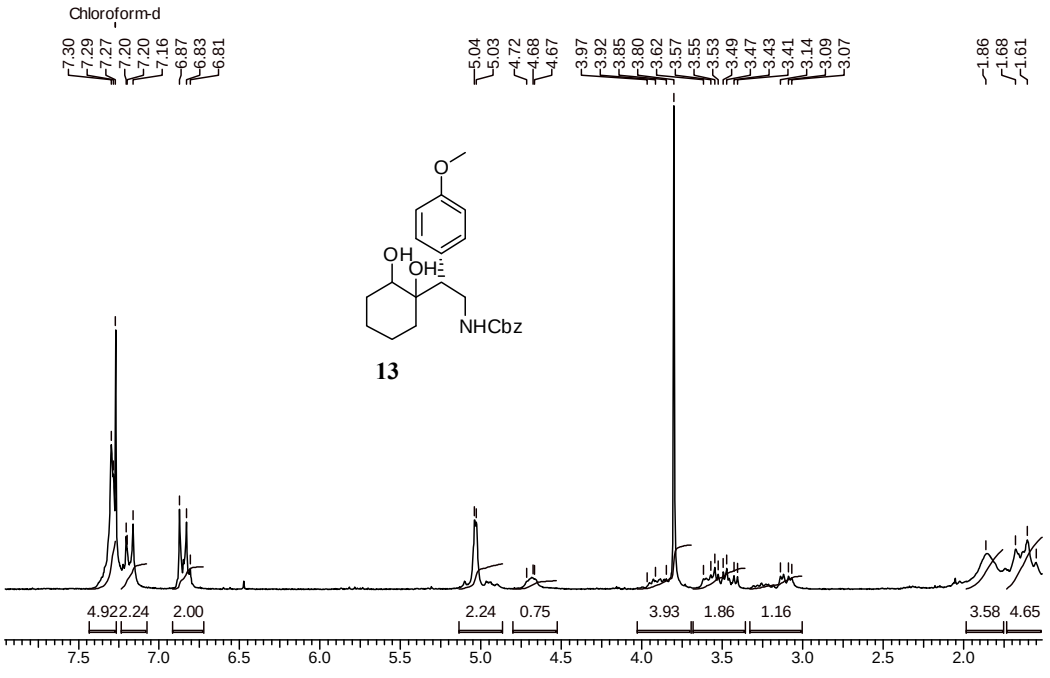
^{13}C NMR spectrum of compound **12** ($CDCl_3$, 50 MHz)



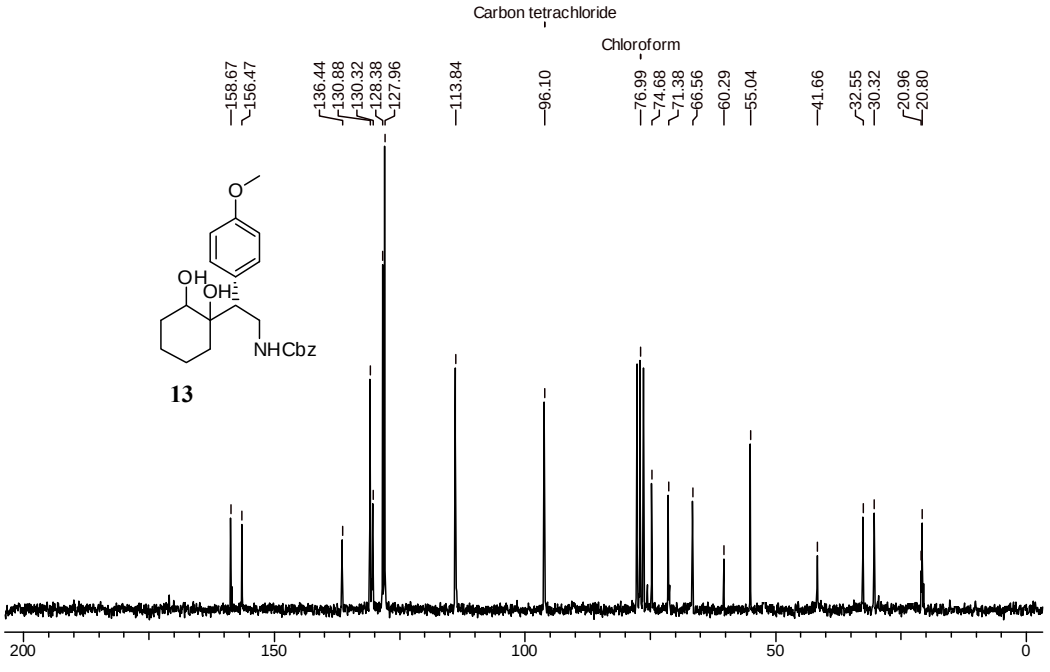
DEPT spectrum of compound **12** ($CDCl_3$, 50 MHz)



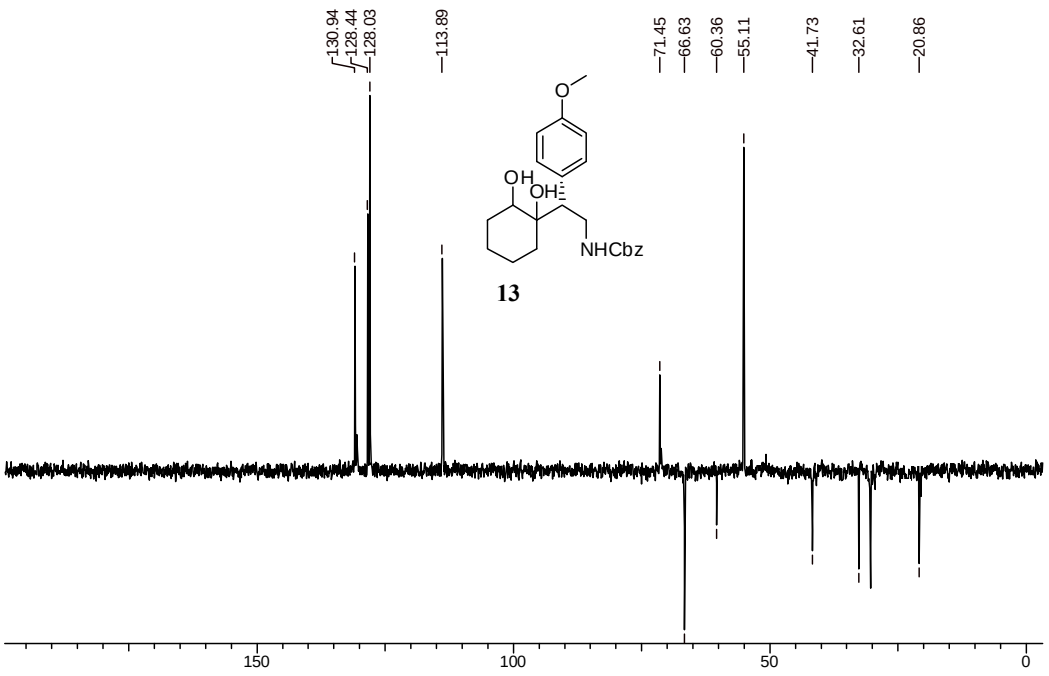
^{1}H NMR spectrum of compound **13** ($CDCl_3$+CCl_4, 200 MHz)



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

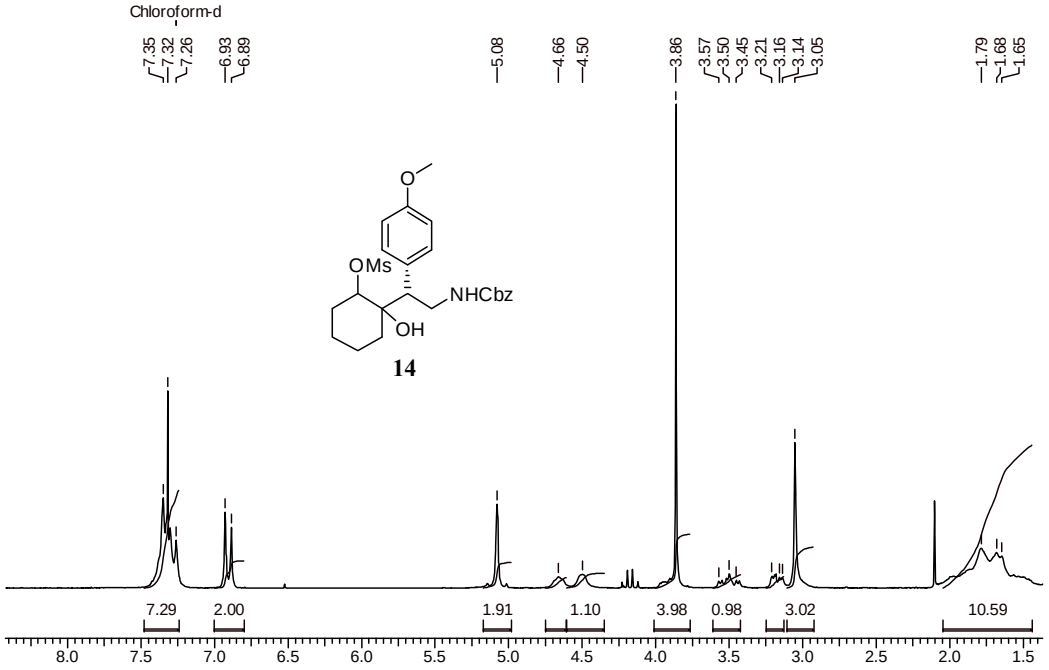


DEPT spectrum of compound **13** ($CDCl_3$ + CCl_4, 50 MHz)



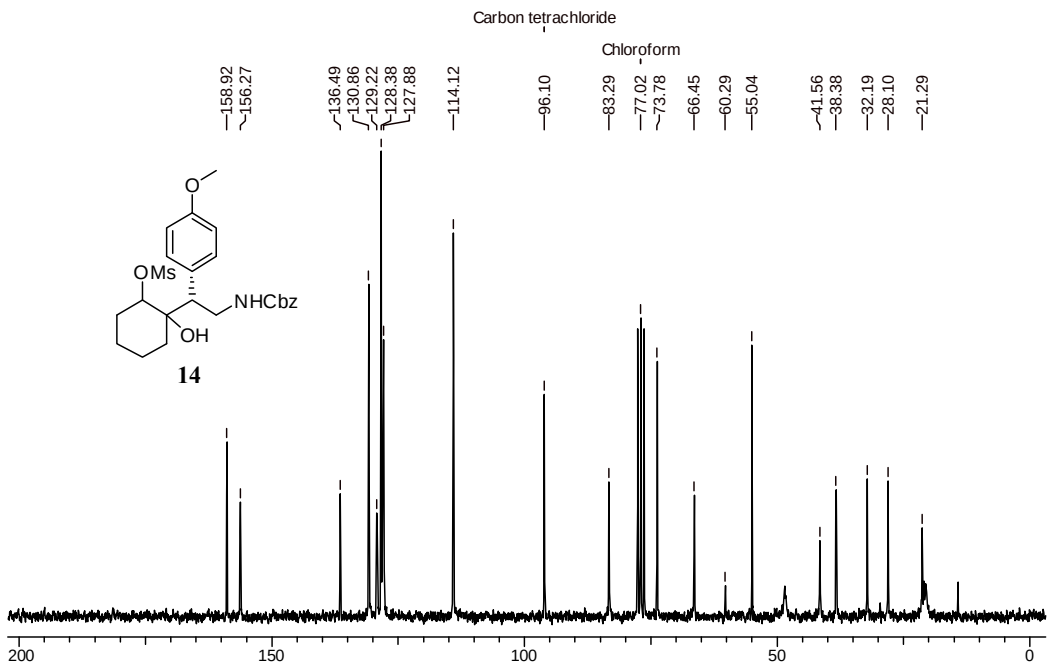
13

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

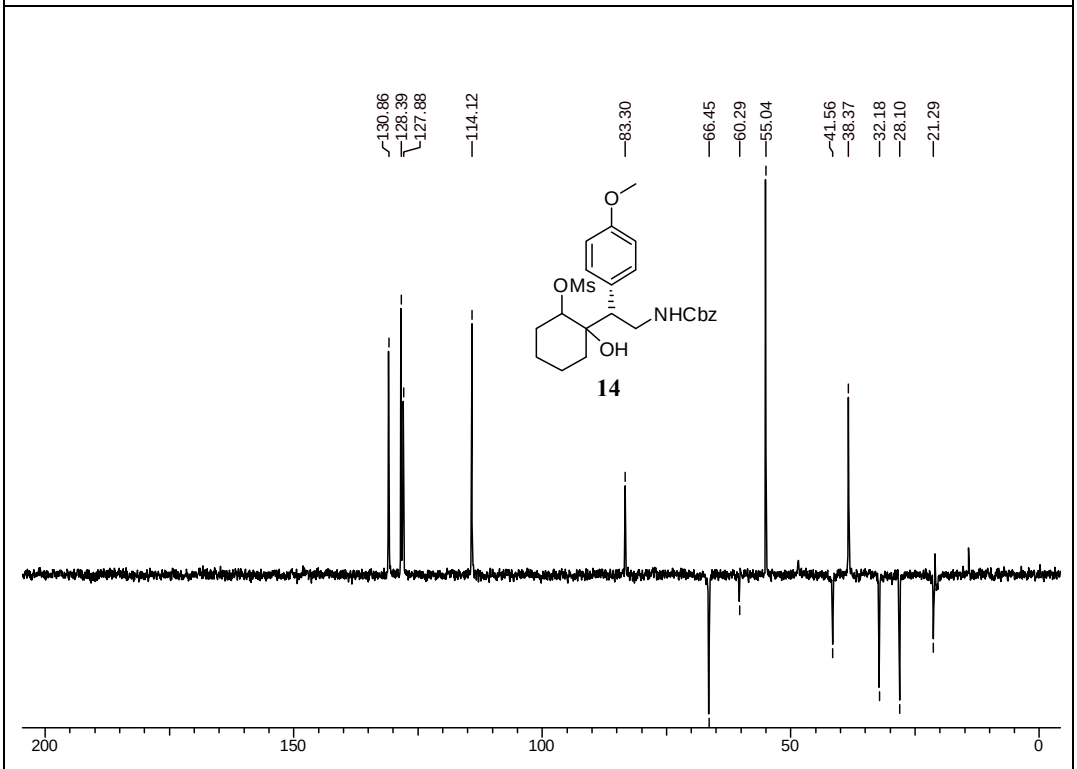


14

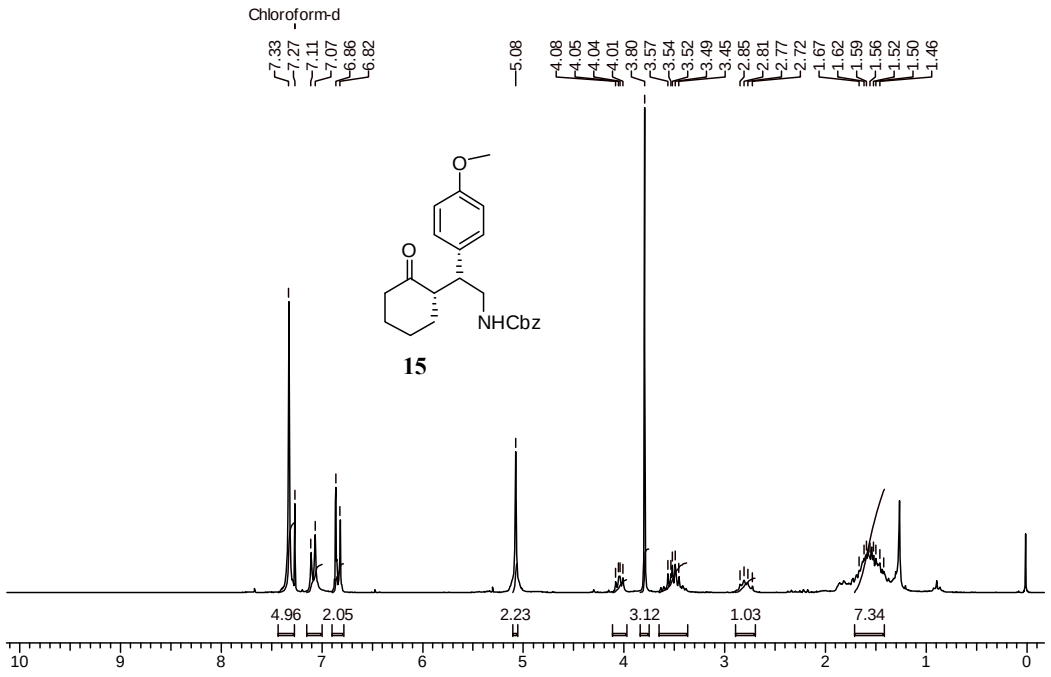
^{13}C NMR spectrum of compound **14** ($CDCl_3 + CCl_4$, 50 MHz)



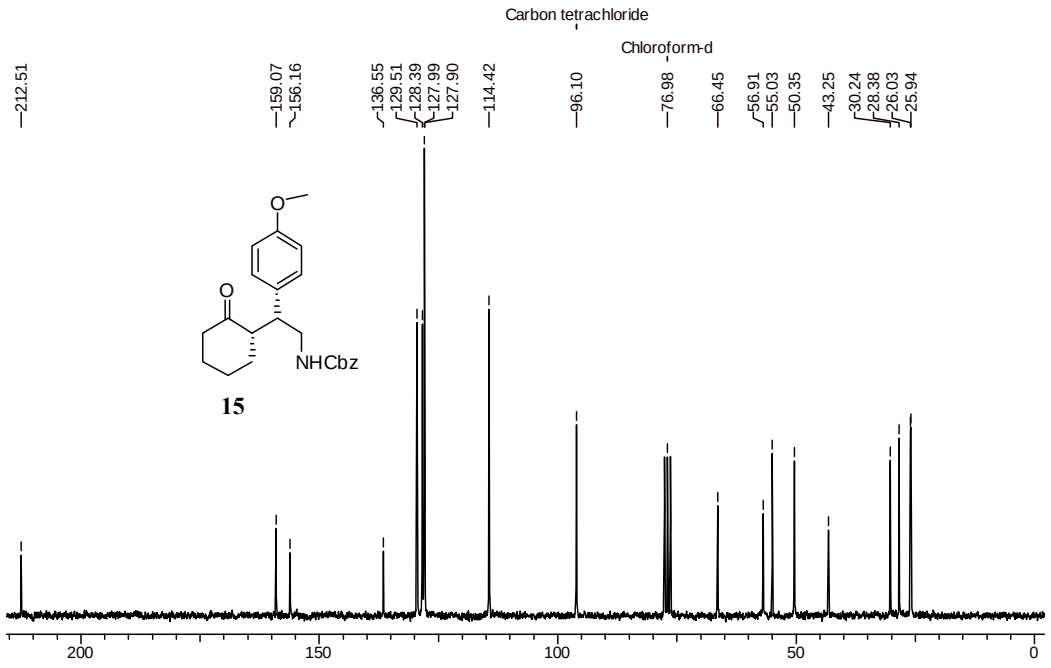
DEPT spectrum of compound **14** ($CDCl_3 + CCl_4$, 50 MHz)



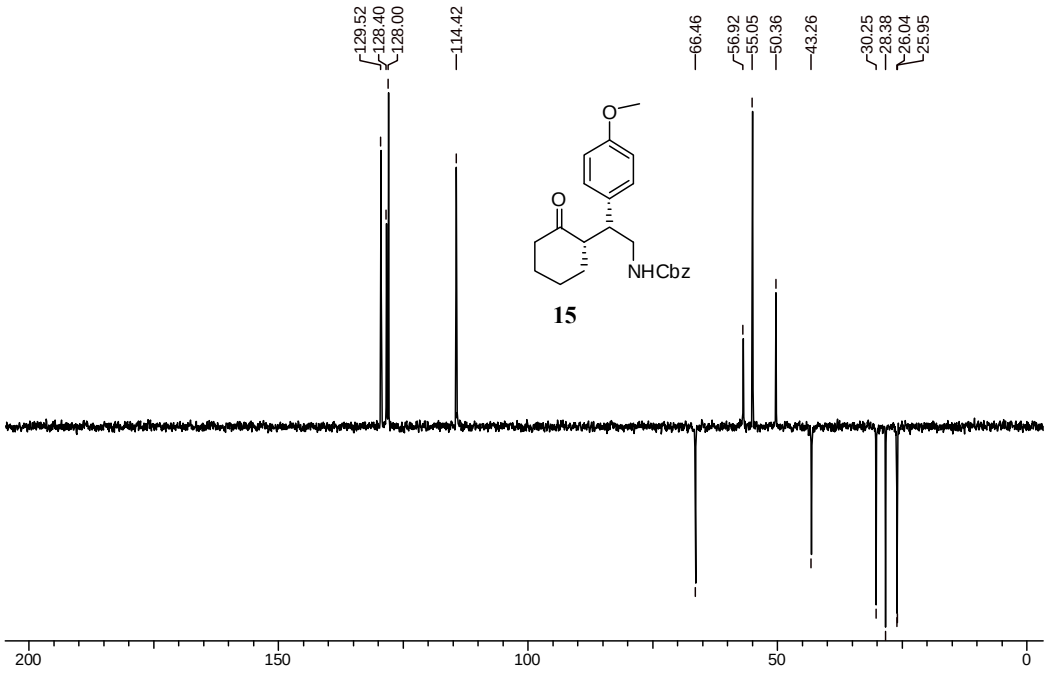
^{1}H NMR spectrum of compound **15** ($CDCl_3$+CCl_4, 200 MHz)



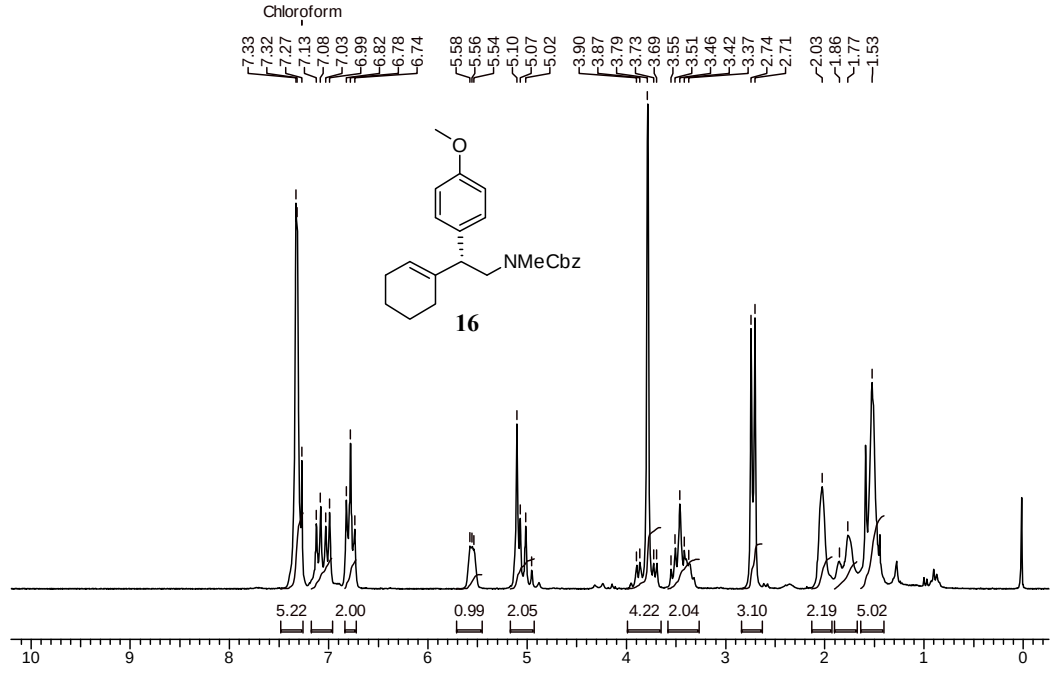
^{13}C NMR spectrum of compound **15** ($CDCl_3$ + CCl_4, 50 MHz)



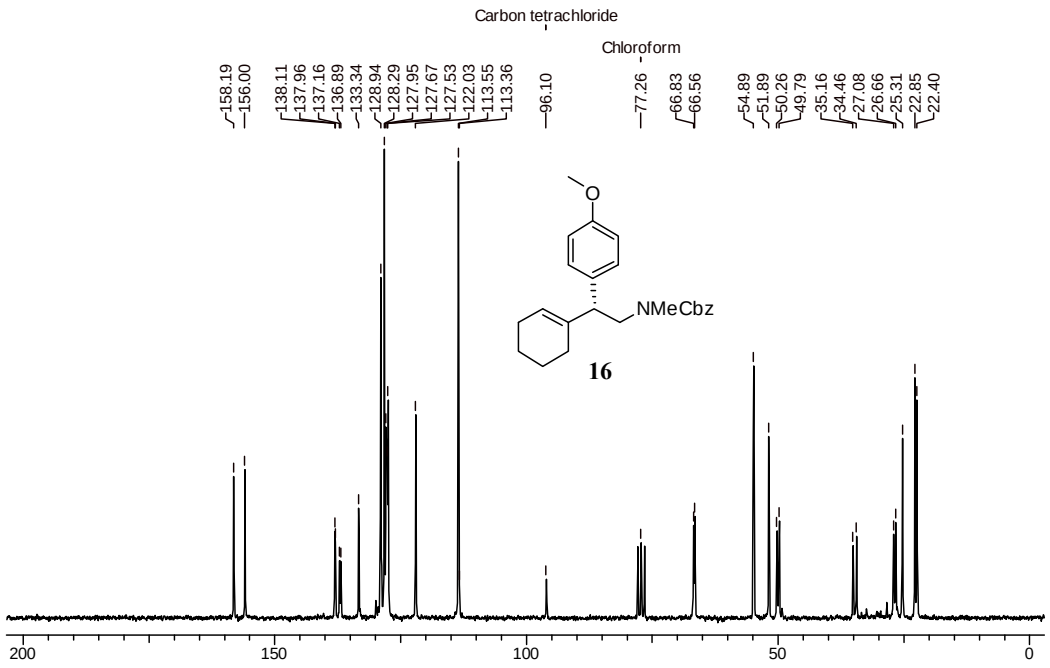
DEPT spectrum of compound **15** ($CDCl_3$ + CCl_4, 50 MHz)



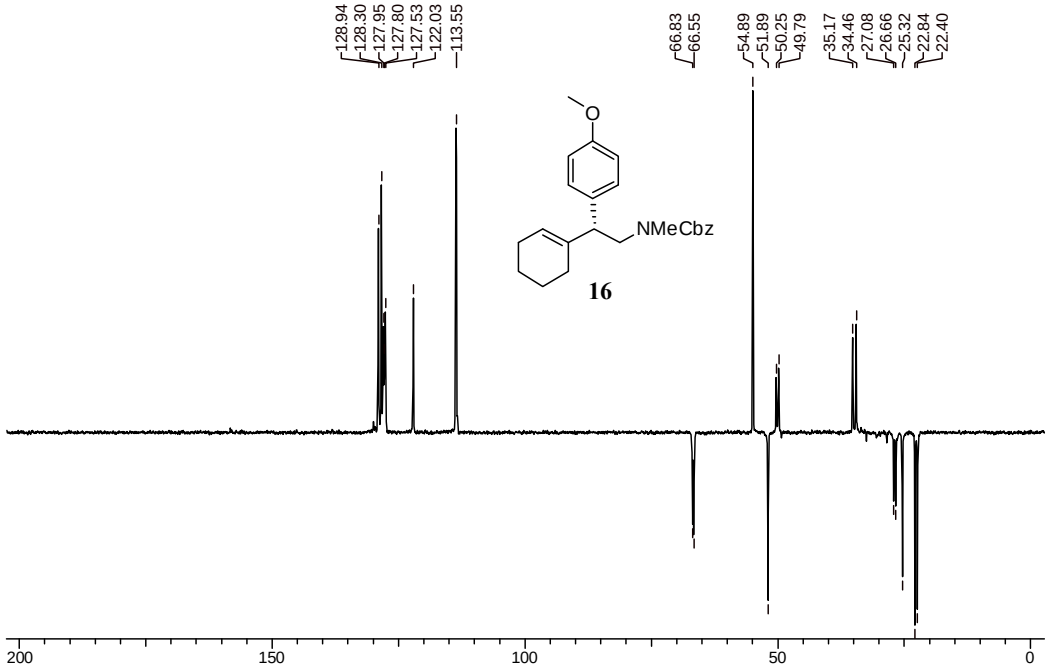
^{1}H NMR spectrum of compound **16** ($CDCl_3$+CCl_4, 200 MHz)



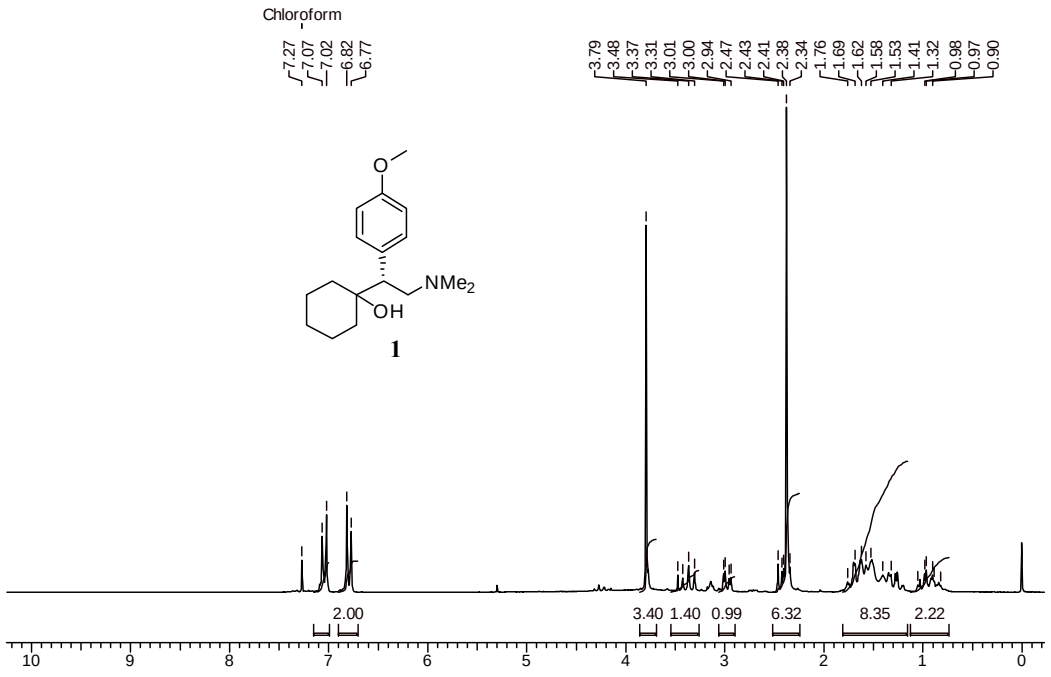
^{13}C NMR spectrum of compound **16** ($CDCl_3 + CCl_4$, 50 MHz)



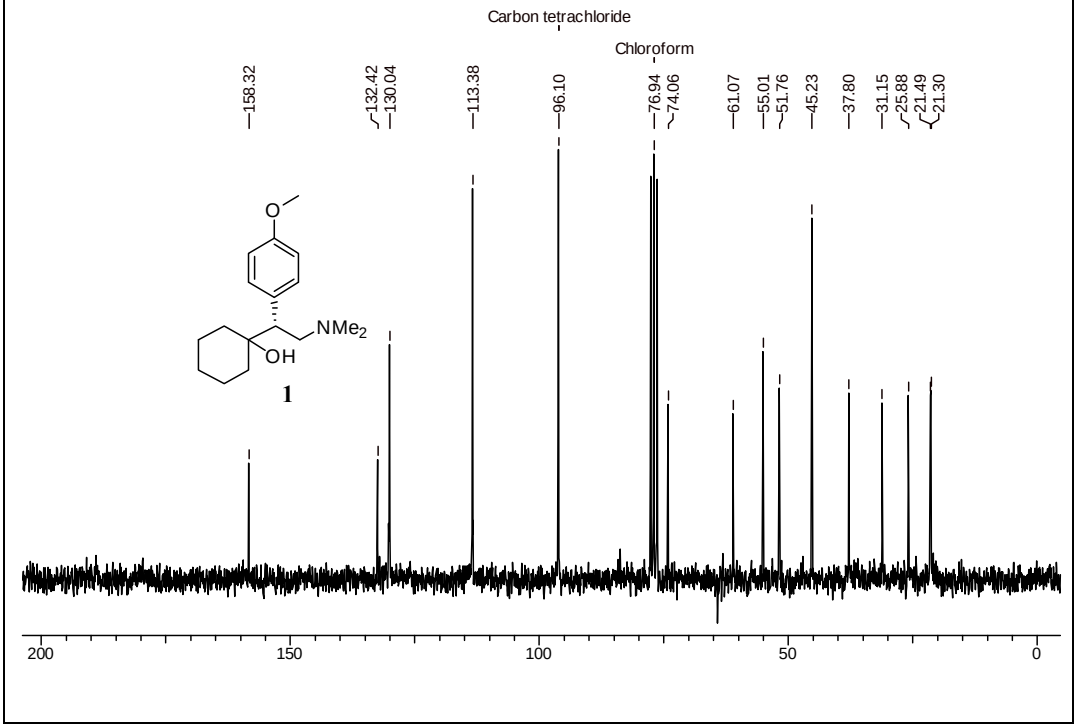
DEPT spectrum of compound **16** ($CDCl_3 + CCl_4$, 50 MHz)



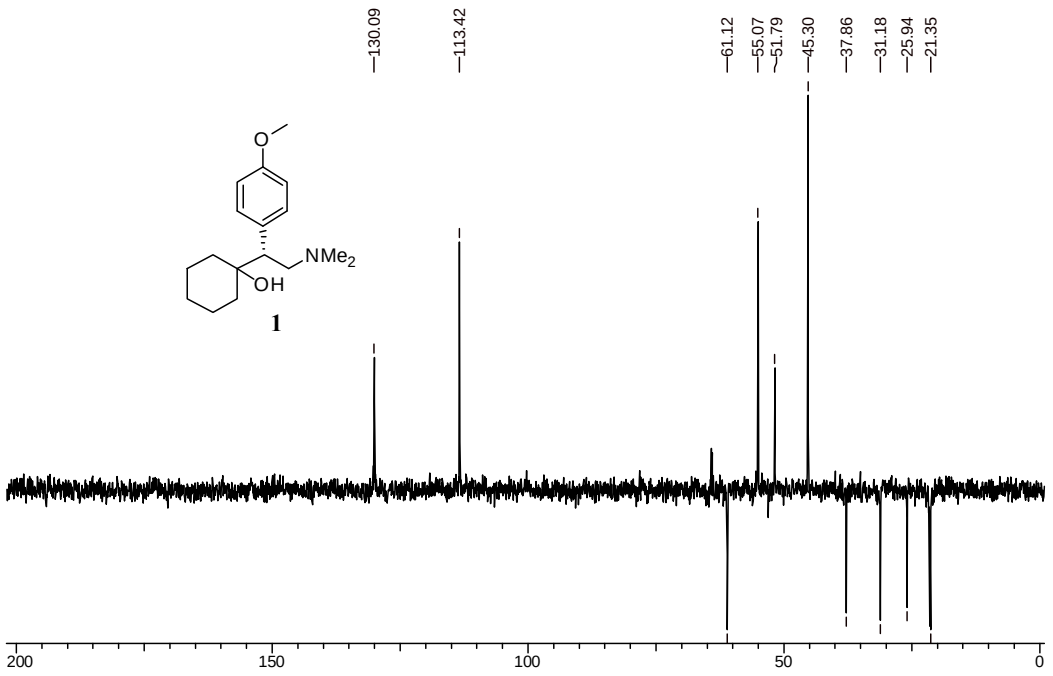
^{1}H NMR spectrum of compound **1** ($CDCl_3$+CCl_4, 200 MHz)



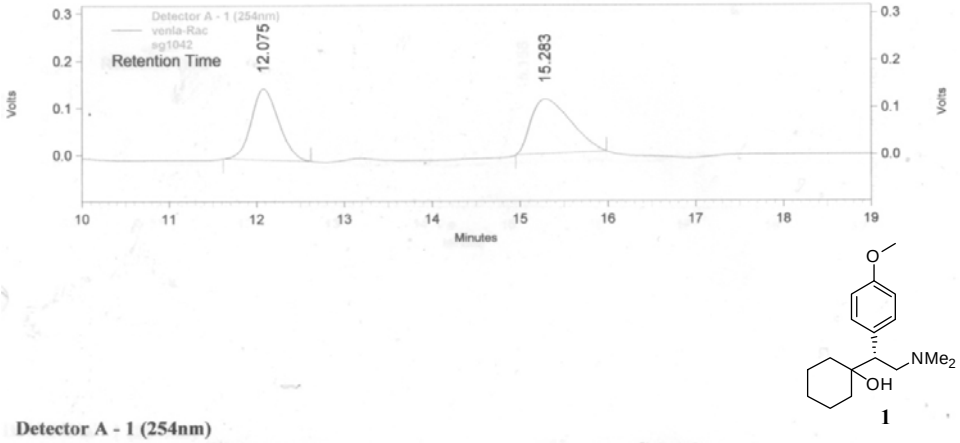
^{13}C NMR spectrum of compound **1** ($CDCl_3$ + CCl_4, 50 MHz)



^{1}H NMR spectrum of compound **1** ($CDCl_3$+CCl_4, 50 MHz)



HPLC chromatogram of racemic venlafaxine **1**

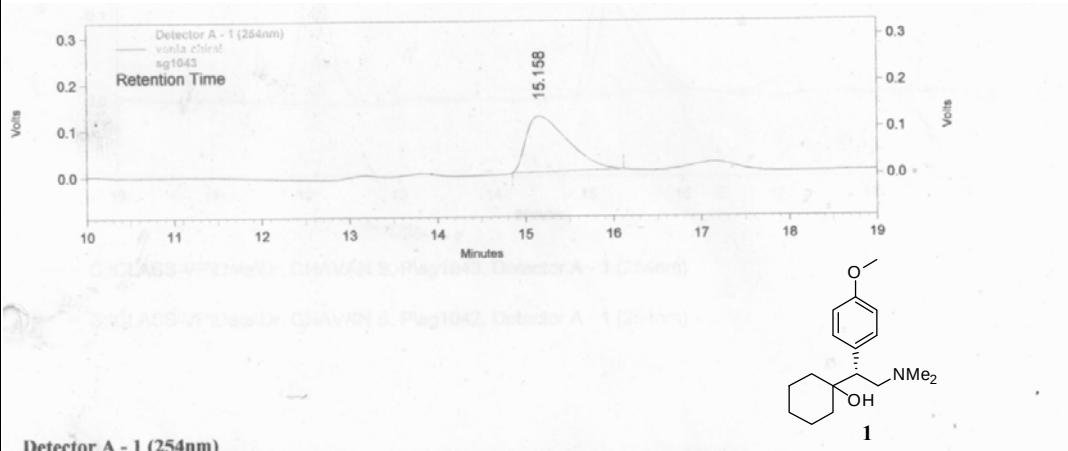


Detector A - 1 (254nm)

Retention Time	C Area	Area %
12.075	3291874	47.587
15.283	3625754	52.413
Totals	6917628	100.000

Project Leader : Dr. S. P. Chavan
Column :Kromasil 5-Amy Coat (250x4.6 mm)
Mobile Phase :EtOH: pet ether:DEA (05:95:0.5)
Wavelength :254nm
Flow Rate :0.5ml/min (25Kgf)
conc. :1 mg/1mL
Inj vol- :10 ul

HPLC chromatogram of chiral (−)-venlafaxine **1**



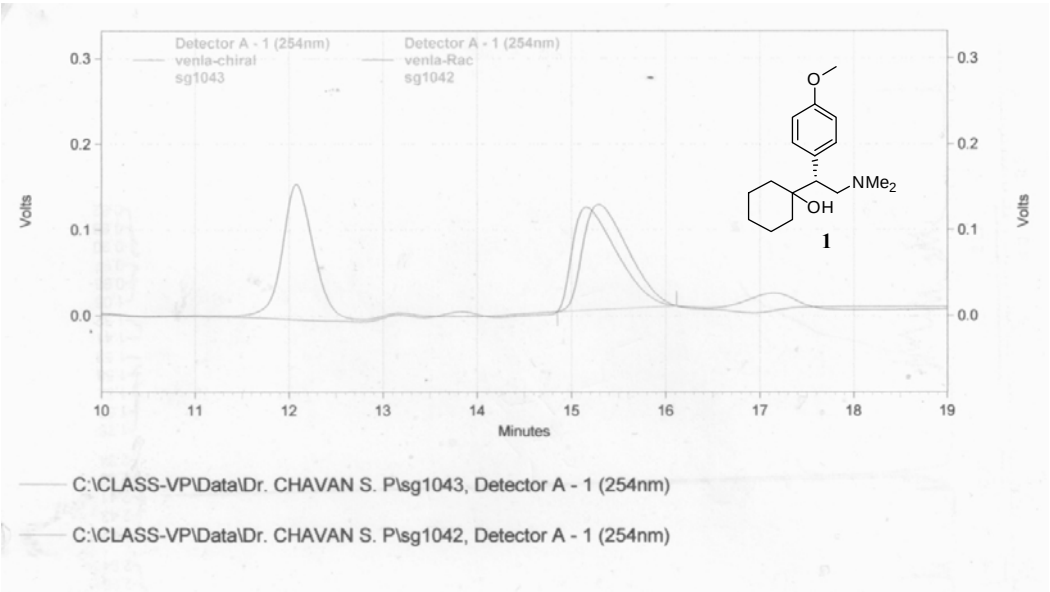
1

Detector A - 1 (254nm)

Retention Time	C Area	Area %
15.158	3923335	100.000
Totals	3923335	100.000

Project Leader : Dr. S. P. Chavan
Column :Kromasil 5-Amy Coat (250x4.6 mm)
Mobile Phase :EtOH: pet ether:DEA (05:95:0.5)
Wavelength :254nm
Flow Rate :0.5ml/min (25Kgf)
conc. :1 mg/1mL
Inj vol- :10 ul

HPLC chromatogram of both racemic venlafaxine **1** and chiral (−)-venlafaxine **1**



1

2.2.5. References

1. For selected examples, see a) Jinpei, Z.; Huibin, Z.; Xuezhen, H.; Wenlong, H. *J. China Pharm. Univ.* **1999**, *30*, 249. b) Yardley, J. P.; Husbands, G. E. M.; Stack, G.; Butch, J.; Moywe J. A.; Muth, E. A.;Andree, T.; Fletcher, H.; James, N. M. G.; Sielecki, A. *J. Med. Chem.* **1986**, *33*, 2899. c) Husbands, G. E. M.; Yardley, J. P.; Mills, G.; Muth, E. A. US Patent No. 4, 535, 186, **1985**. d) Rathod, D. M.; Rangaraju, S. G.; Moreshwar, M.; Patel, N.; Deodhar, M.; Mandar, M. EP 1249447, **2001**. e) Kavitha, B. C. V; Rangappa, K. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3279. f) Saigal, J.; Gupta, R.; Pandit, V. V.; Desai, A. J.; Mehta, N. V.; Rane, S. H. US Patent No. 7,026,513, **2006**. g) Dolitzky, B.-Z.; Aronhime, J.; Wizel, S.; Nisnevich, G. A. US Patent No. 6, 924, 393, **2005**.
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Chapter 3: Synthetic studies towards 7-deoxypancratistatin and retro-Reformatsky reaction

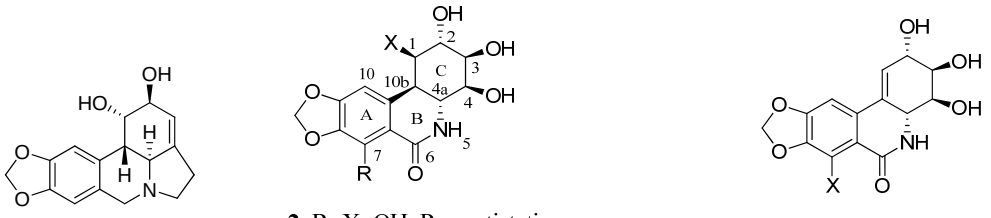
Section 1

Introduction to pancratistatin class of Amaryllidaceae alkaloids

3.1.1. Introduction

The *Amaryllidaceae* alkaloids are richly represented in the tropics and have pronounced centers of diversity in South-Africa and the Andean region. Some forms are also found in the Mediterranean area and temperate regions of Asia. The *Amaryllidaceous* alkaloids are a diverse group of structurally complex natural products which are used for medicinal purposes dating back to at least the fourth century[1] and these alkaloids possess a wide spectrum of biological activities.

A particular characteristic of *Amaryllidaceae* alkaloids is a consistent presence of an exclusive group of alkaloids, which has been isolated from the plants of all the genera of this family. The Amaryllidaceae alkaloids represent a large and still expanding group of isoquinoline alkaloids, the majority of which are not known to occur in any other family of plants. Since the isolation of the first alkaloid, lycorine (**1**), from *Narcissus pseudonarcissus* in 1877,[2] substantial progress has been made in examining the *Amaryllidaceae* plants, although they still remain a relatively untapped phytochemical source.[3] At present, over 300 alkaloids have been isolated from plants of this family [4] and, although their structures vary considerably, these alkaloids are considered to be biogenetically related (Figure 1). Over the past three decades many of these compounds have been isolated, screened for different biological activities, and synthesized by a number of research groups.



1, Lycorine

2, R=X=OH, Pancratistatin
3, R=H; X=OH , 7-Deoxypancratistatin
4, R=OH; X=H, *trans*-Dihydronarciclasine

5, X = OH, Narciclasine
6, X = H, Lycoricidine

Figure 1. Few representatives of *Amaryllidaceae* alkaloids.

In 1984, Pettit and co-workers[5] reported isolation of pancratistatin (**2**), which was shown to display promising antineoplastic and antiviral activity. In 1989, Ghosal and co-workers[6] isolated the 7-deoxy compound (**3**), which has been shown in *in vitro* antiviral assays to exhibit a better therapeutic index than pancratistatin (**2)** due to decreased toxicity.[7]

Narciclasine (**5**) and lycoricidine (**6**) were extracted from different bulbs of narcissi and daffodils.[8] These particular compounds have attracted considerable attention because of their spectrum of antineoplastic activities.[9] Pettit and co-workers isolated yet another constituent, *trans*-dihydronarciclasine (**4**) from the Chinese medicinal plant *Zephyranthes candida* in 1990[10] and it exhibited even higher potency (two to ten folds higher) than pancratistatin against selected human cancer cell lines.[11]

The cytotoxic effects are ascribed to the capacity of these compounds (**2**−**6**) to inhibit protein synthesis in eukaryotic ribosomes.[12] In the case of **3**, this effect is exerted by blocking of peptide bond formation on the 60-S ribosome unit.[12a] Recent studies in this area have revealed that pancratistatin (**2**) induces apoptosis, or programmed cell death, selectively in cancer cells, with minimal effect on normal cells, and that the mitochondria in cancerous cells are the site of action.[13] In addition to the antitumor activity, pancratistatin (**2**) also displays a reasonable antiviral profile, most likely because of its aminoinositol moiety, which would effectively serve to act as an inhibitor of common glucosidases. Although the mode of action of these compounds remains to be elucidated, they are being the subject of preclinical development studies as agents for the treatment of certain cancers.

The potent biological activity and unique yet challenging structural features of these molecules possessing phenanthridone skeleton with four or six contiguous stereogenic centres in the C ring and *trans*-fused BC- ring (C10b-C4a) have rendered them an attractive target for synthetic organic chemists.

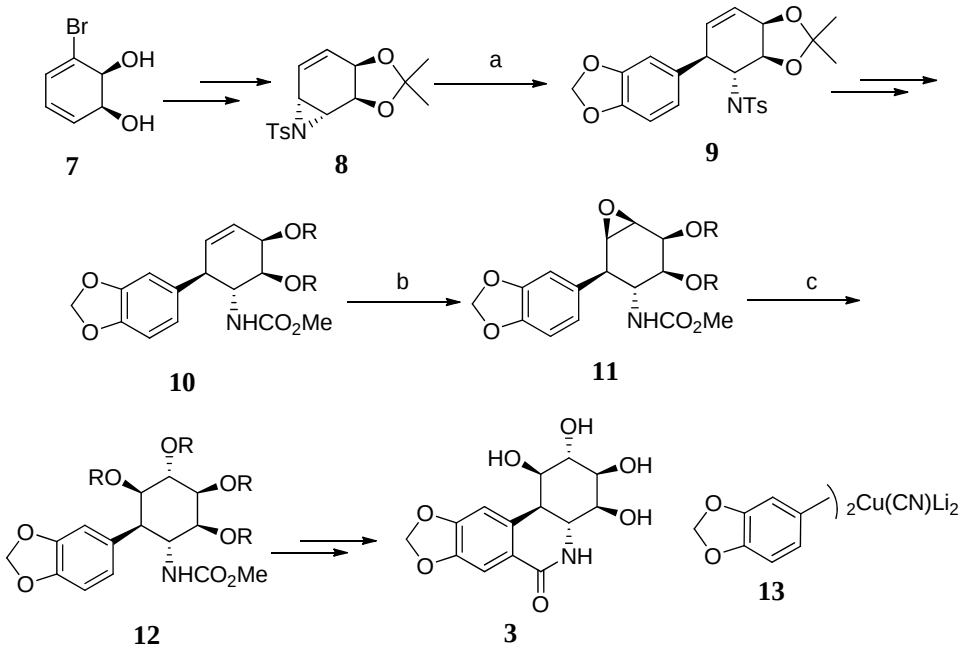
3.1.2. Literature review on synthesis of 7-deoxypancratistatin

In literature, several syntheses of 7-deoxypancrastistatin are reported but some selected syntheses are described here.

Hudlicky's Approach[14] (*Synlett* **1995**, 1125)

Hudlicky *et al.* reported an asymmetric synthesis of 7-deoxypancratistatin (**3**) in 2.6% overall yield starting from enantiopure diol **7** which is prepared from bromobenzene by toluene dioxygenase-mediated whole cell fermentation. The key steps involved regioselective opening of tosylaziridine **8** with a higher order cuprate **13** derived from 6-bromo-1,3-benzodioxol in presence of $BF_3.OEt_2$ to give *trans* substituted tosylamide **9**. Deprotection to free diol followed by epoxide ring opening with water

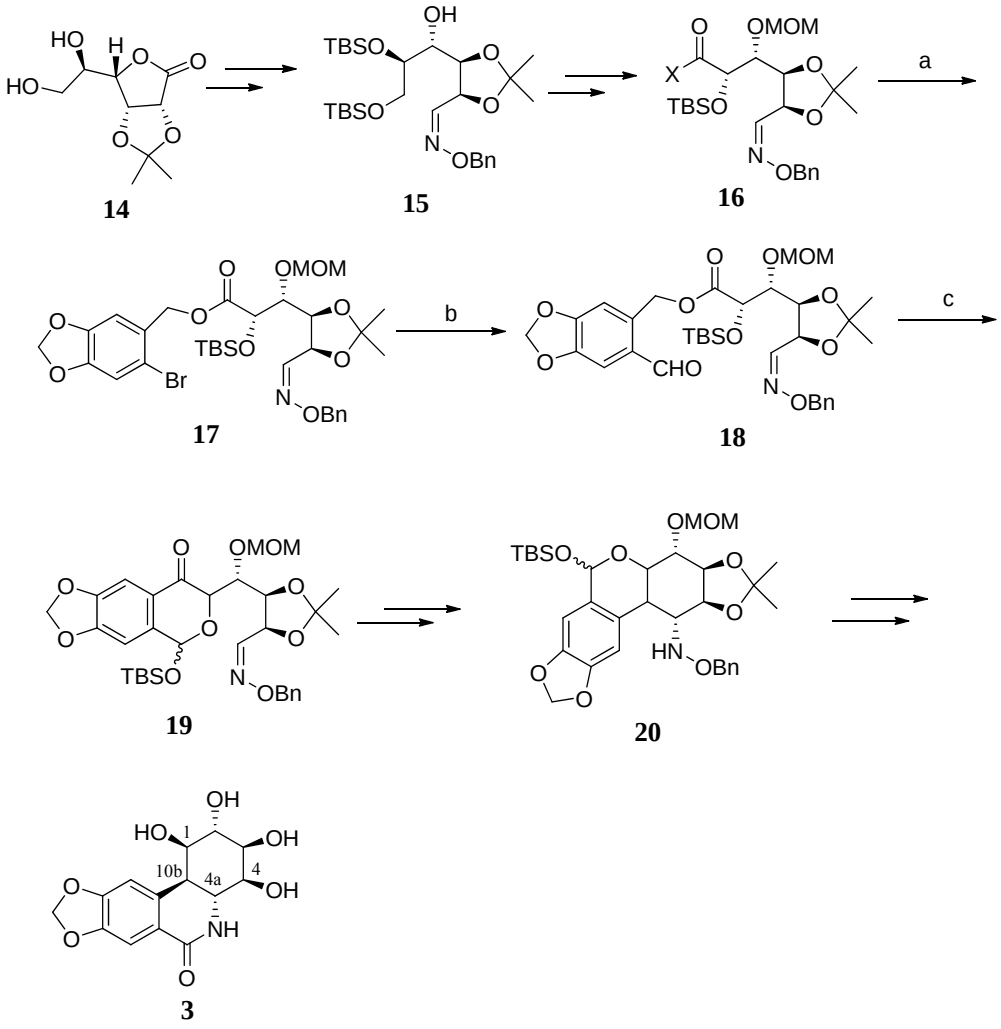
and finally cyclisation of urethane **12** and deprotection of acetate group gave 7-deoxypancratistatin (**3**) (Scheme 1).



Scheme 1. Reagents and conditions: *a)* ***13****, $BF_3.OEt_2$, -78 °C to rt; b) ^tBuOOH, $VO(acac)_2$, benzene, 70 °C; c) H_2O, BzONa, 100 °C.*

Keck's approach[15] (*J. Am. Chem. Soc.* **1995**, *117*, 7289; *J. Org. Chem.* **1999**, *64*, 4465)

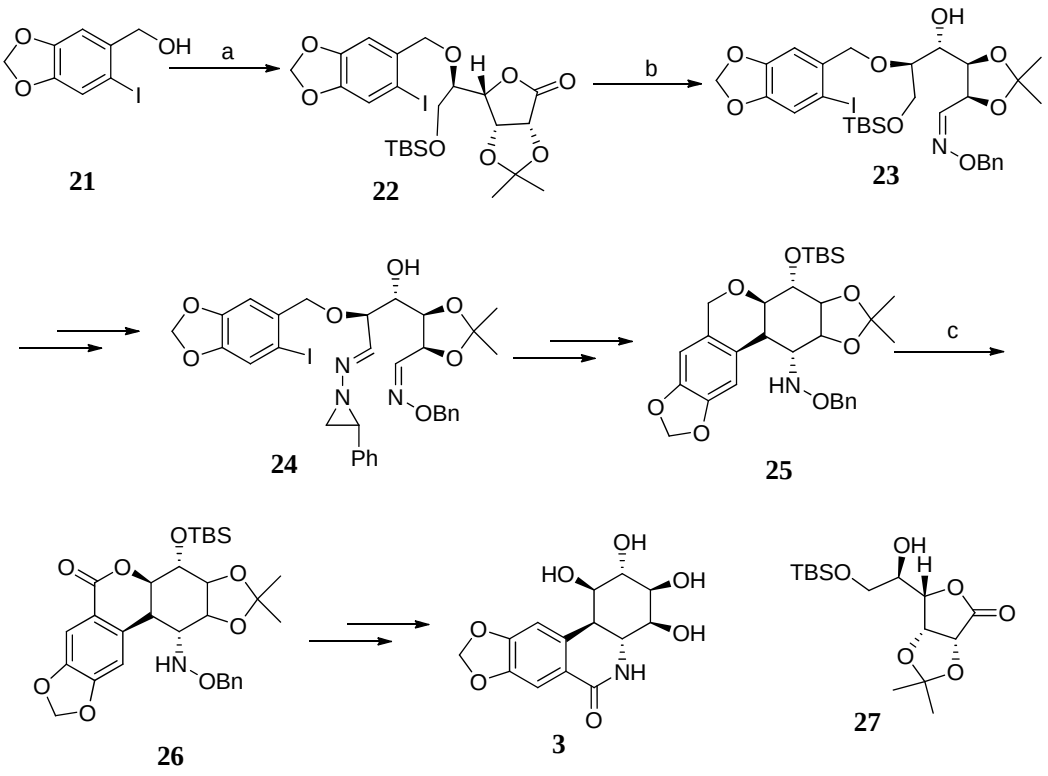
Keck *et al.* reported the total synthesis of 7-deoxypancratistatin (**3**) where the key step is the 6-exo cyclization between a benzylic radical and an oxime ether to construct the highly functionalized cyclohexane ring **20** of pancratistatin. Their synthesis started from D-gulonolactone **14**, which furnishes carbons 4a-10b with the desired absolute configurations at C1-C4 (Scheme 2).



Scheme 2. Reagents and conditions: *a) Ph_3P. DEAD, 4-bromo-5-(hydroxymethyl)-1, 2-(methylenedioxy)benzene; b) i) n-BuLi; ii) TPAP; c) i) HF-Pyr; ii) Dess-Martin, 60%.*

Keck's approach[16] (*J. Org. Chem.* **1998**, *63*, 9164)

An efficient total synthesis of 7-deoxypancratistatin (**3**) was accomplished by Keck *et al.* in 13 steps and in 21 % overall yield by employing a radical cascade strategy involving 6-exo radical cyclization of phenyl radical **24** with *N*-aziridinylimine as the key step to construct the highly functionalized cyclohexane nucleus **26** (Scheme 3).

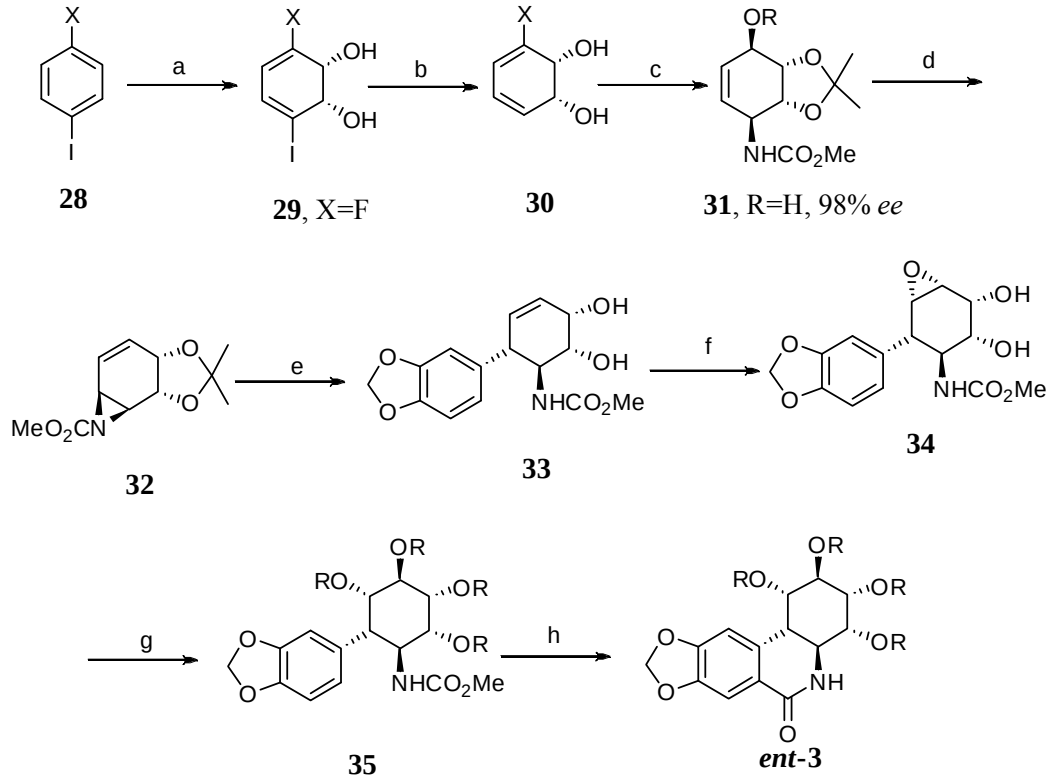


Scheme 3. Reagents and conditions: *a) i) NaH, Cl_3CCN, 0 °C; ii) TfOH, THF, 0 °C; iii)* ***27****, 75% (over two steps); b) i) L-Selectride, CH_2Cl_2, -78 °C; ii) HCl.H_2NOBn, pyr; c) PCC, 83%.*

Hudlicky's Approach[17] (*Tetrahedron Lett.* **1999**, *40*, 3081)

In 1990 Hudlicky *et al.* reported the total synthesis of *ent*-conduramine A and enantiomer of 7-deoxypancratistatin (**3**). The diene diol **30** was synthesized by employing *Pseudomonas putida* strains UV4 and NCIMB 8859 in sequence with ~20% *ee* and 88% yield followed by dehalogenation. Compound **30** then subjected to fermentation with the PPL lipase, which selectively digests the *S,S*-enantiomer and provides the desired *R,R* enantiomer. Half of the total mass is carried forward for the synthesis of protected ent-conduramine A, **31**. The protected *ent-conduramine* A **31** was subjected to the Mitsunobu protocol leading to formation of aziridine compound **32**. The regioselective opening of aziridine ring with aryl cuprate followed by deprotection of acetonide group gave diol **33**. Compound **33** was subjected for vanadium oxide catalyzed epoxidation to yield epoxide **34.** The epoxide **34** was subjected to regioselective ring opening followed by *O*-acylation to give tetraacetate **35**. Finally 'B'ring was constructed by modified Bischler-Napieralski reaction

conditions to give target molecule enantiomer of 7-deoxypancratistatin (**ent-3**) (Scheme 4).

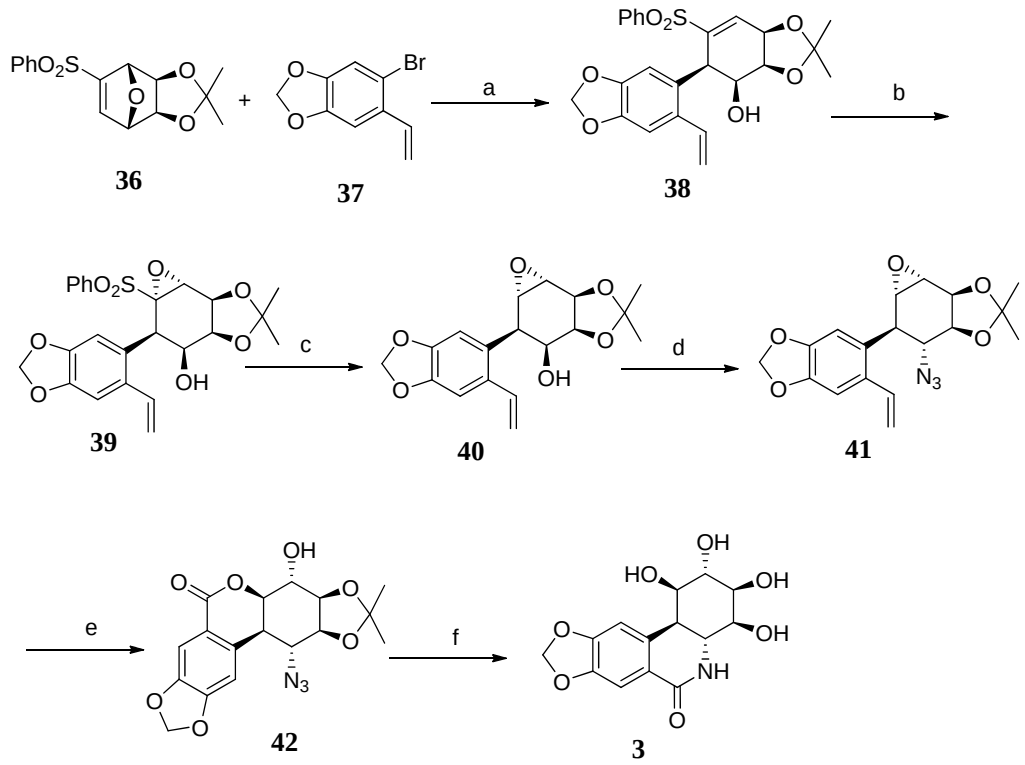


Scheme 4. Reagents and conditions: *a) E. coli JM109 (DTG601); b) Bu_3SnH, AIBN, THF; c) i) DMP, p-TsOH; then $HONHCO_2Me$, $NaIO_4$, H_2O, MeOH; ii) Al(Hg), THF, H_2O; iii) Ac_2O, pyr; iv) PPL lipase, pH 7; d) PPh_3, DEAD, THF; e) i) (3,4-Methylenedioxy)bromobenzene, n-BuLi, Cu, $BF_3.Et_2O$, -78 °C; ii) Dowex-50W, MeOH; f) $VO(acac)_2$, ^tBuOH, PhH, 70 °C; g) i) BzONa, H_2O, 100 °C; ii) Ac_2O, pyr; h) i) Tf_2O, DMAP, CH_2C1_2, 0 °C; ii) K_2CO_3, MeOH.*

Plumet's Approach[18] (*Org. Lett.* **2000**, *2*, 3683)

Plumet *et al.* reported total synthesis of (+)-7-deoxypancratistatin (**3**) in 19 steps in 8% overall yield from two readily available compounds, furan and *trans*-1,2-bis(phenylsulfonyl)ethylene. Their synthesis started from vinyl sulfone **36** which was prepared from furan. Vinyl sulfone **36** was treated with aryl bromide **37** in the presence of BuLi to afford the desired cyclohexenol **38**. Compound **38** was converted into epoxide **39** by treatment with ^{t}BuOOLi. Desulfonation was carried out with Na-Hg to give compound **40**. Cyclohexenol **40** was converted into the azido derivative **41**

by a two-step sequence wherein hydroxyl group was converted to corresponding triflate by using Tf_2O and pyridine followed by treatment with Bu_4NN_3 to provid **41**. The treatment of **41** with $NaIO_4$ and $RuCl_3.H_2O$ in a $CCl_4/CH_3CN/H_2O$ mixture afforded lactone **42** in 79% yield. Treatment of **42** under hydrogenolysis condition afforded amine which was converted to the corresponding triol by removal of the acetonide with trifluoroacetic acid. Finally, this triol was treated with K_2CO_3 in dry MeOH affording the natural product (+)-7-deoxypancratistatin (**3**) (Scheme 5).

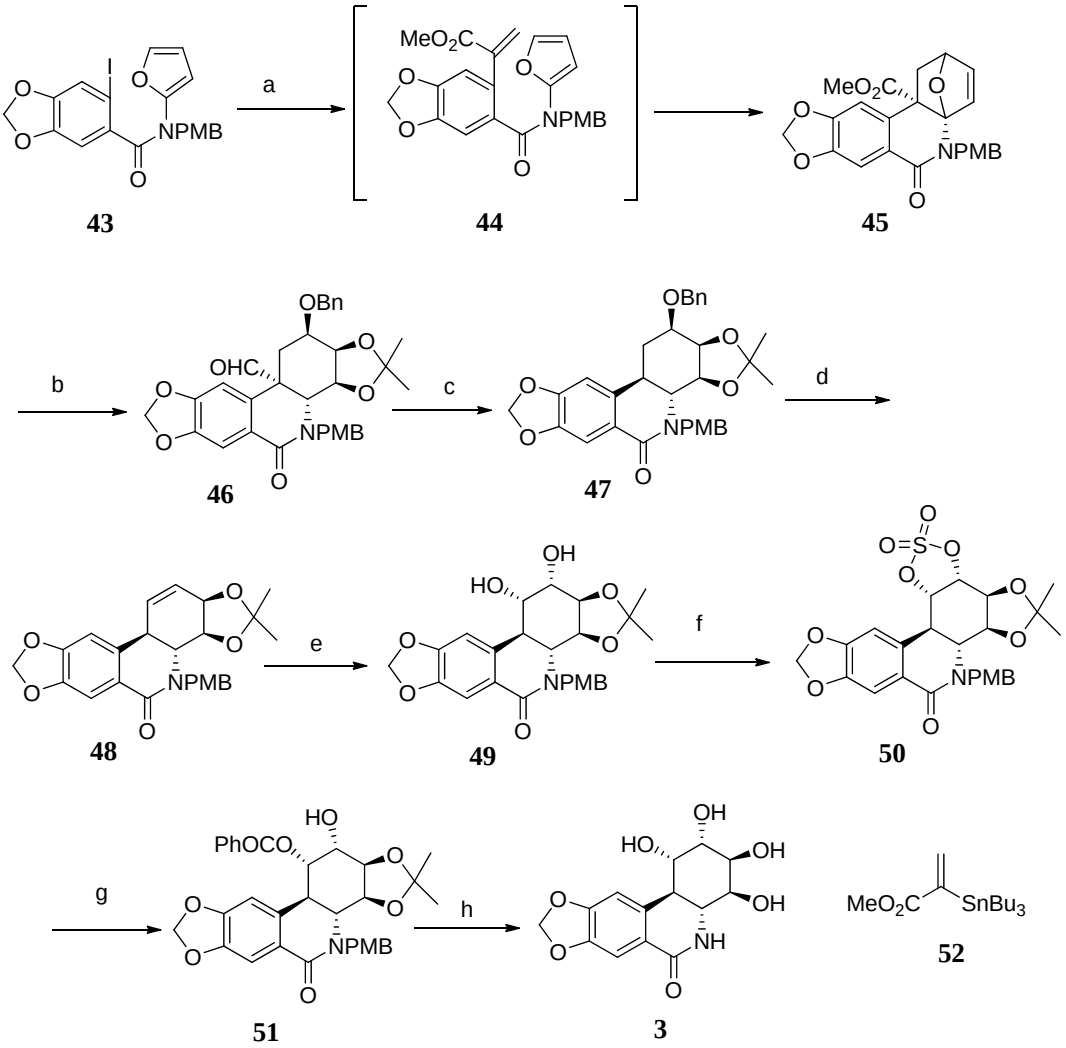


Scheme 5. Reagents and conditions: *a) BuLi, THF/toluene, -78 °C, 96%; b) ^tBuOOH, BuLi, THF, -78 °C, 84%; c) Na-Hg, MeOH/THF, -23 °C, 81%; d) i) Tf_2O, pyr, DCM, 0 °C; ii) Bu_4NN_3, benzene, 80% (over two steps); e) $NaIO_4/RuCl_3$, $CH_3CN/CCl_4/H_2O$, 79%; f) i) H_2 (40 psi), 10% Pd(C), MeOH, 88%; ii) CF_3COOH, 0 °C; iii) K_2CO_3, MeOH, Δ, 82%.*

Padwa's Approach[19] (*Tetrahedron Lett.* **2006**, *47*, 3905)

Padwa *et al.* reported a highly efficient total synthesis of 7-deoxypancratistatin (**3**) wherein the key feature of the synthesis is the ready preparation of the phenanthridone skeleton **45** by a Stille- intramolecular Diels– Alder furan (IMDAF) cycloaddition

cascade reaction and the resulting cycloadduct is converted into a key aldehydic intermediate **46**, which is then induced to undergo a stereospecific decarbonylation reaction using Wilkinson's catalyst to set the trans B–C ring junction of the target molecule. Double



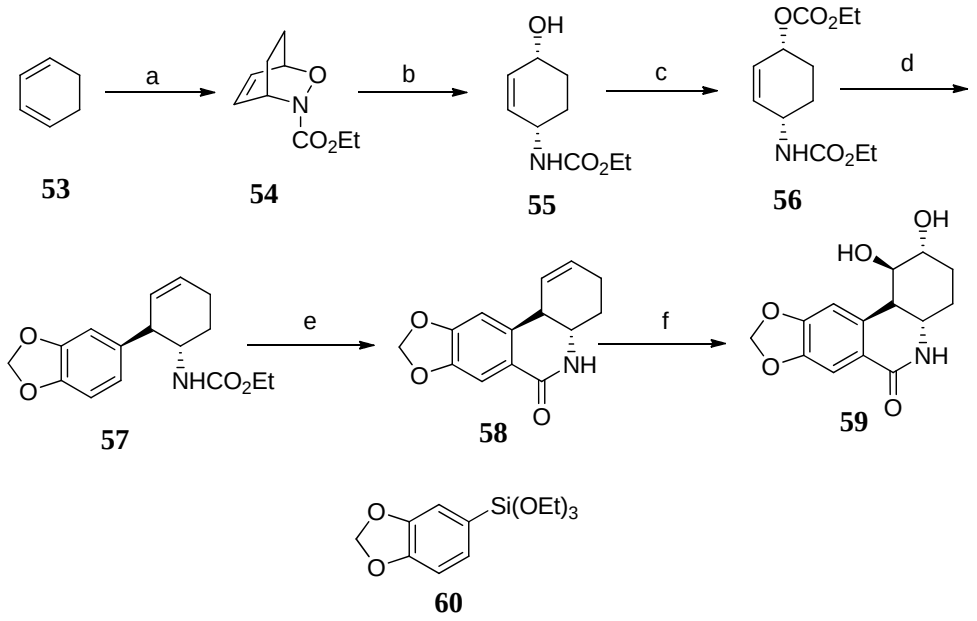
Scheme 6. Reagents and conditions: *a) Pd (0),* ***52****, 82 %; b) i) OsO_4, NMO, 98%; ii) 2,2-Dimethoxypropane, PPTS, 80%; iii) TMSOTf, $Zn(BH_4)_2$, 74%; iv) NaH, $PhCH_2Br$; v) LiOH/THF; vi) $(COCl)_2$, $Zn(BH_4)_2$; vii) NMO, TPAP; c) $RhCl(PPh_3)_3$, heat; d) i) H_2, $Pd(OH)_2$; ii) NaH, CS_2, MeI; iii) heat; e) Cat. OsO_4, NMO; f) i) $SOCl_2$; ii) $NaIO_4$; g) i) $PhCO_2Cs$; ii) H^+; h) i) LiOH; ii) H_2, $Pd(OH)_2$, 80 %.*

bond between C1 and C2 of compound **48** was installed by carrying out a debenzylation under hydrogenolysis conditions, followed by a Chugaev elimination of

the xanthate ester. Compound **48** was subjected to dihydroxylation to give diol **49**. Treatment of diol **49** with thionyl chloride, followed by oxidation of the resulting sulfite with $NaIO_4$ in the presence of catalytic $RuCl_3$, furnished sulfate **50**. Reaction of sulfate **50** with cesium benzoate, followed by acid hydrolysis, resulted in the formation of triol. The final ester hydrolysis and amide deprotection gave the target molecule 7-deoxypancratistatin (**3**) in 80% yield (Scheme 6).

DeShong's Approach[20] (*Org. Lett.* **2006**, *8*, 4183)

DeShong *et al.* reported the synthesis of 7-deoxypancratistatin analogue by using palladium catalyzed allylic arylation. Their synthesis started by Diels-Alder reaction



Scheme 7. Reagents and conditions: *a) EtCONHOH, $Bu_4N^+IO_4^-$, $CHCl_3$/DMF, 0 °C to rt, 71%; b) $Mo(CO)_6$, CH_3CN/H_2O, reflux, 62%; c) $ClCO_2Et$, pyr, DCM, rt, 83 °C; d)* ***60****, Pd(dba)2, TBAF, THF, 65 °C, 81%; d) $POCl_3/Me_3SiOSiMe_3$, P_2O_5, 85 °C, 56%; f) i) H_2O_2, HCO_2H, rt; ii) NaOH, 90 °C, 51%.*

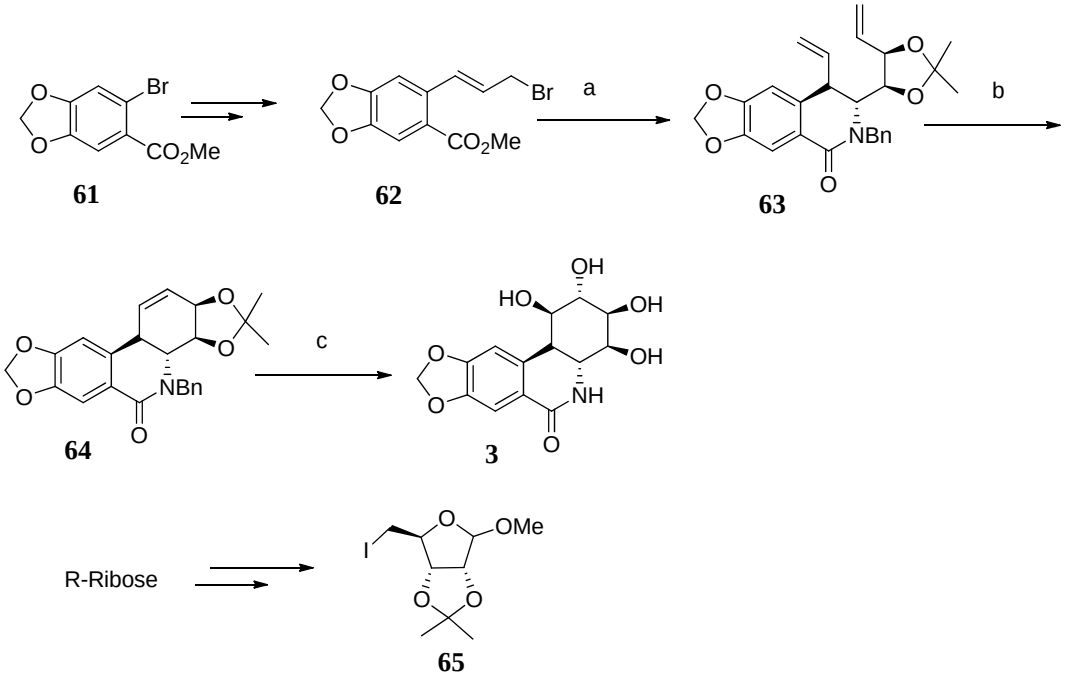
of cyclohexadiene **53** with the acyl nitroso dienophile which gave hydroxamate **54**. The hydroxamate **54** was subjected to reductive N-O bond cleavage with molybdenum hexacarbonyl to form allylic alcohol-carbamate **55**, followed by acylation with ethyl chloroformate to give carbonate-carbamate **56**. Coupling of carbonate **56** with electron-rich aryl siloxane **60** in the presence of TBAF and a Pd(0) catalyst gave the allylic arylated coupling product **57**. Carbamate **57** was subjected to

Bischler-Napieralski cyclization using P_2O_5 and $POCl_3/Me_3SiOSiMe_3$ (1:1), which gave lactam **58**. One-pot *trans*-dihydroxylation with hydrogen peroxide in formic acid gave diol **59** in 51% yield (Scheme 7).

Madsen's Approaches[21] (*Chem. Eur. J.* **2006**, *12*, 3243)

Approach-1

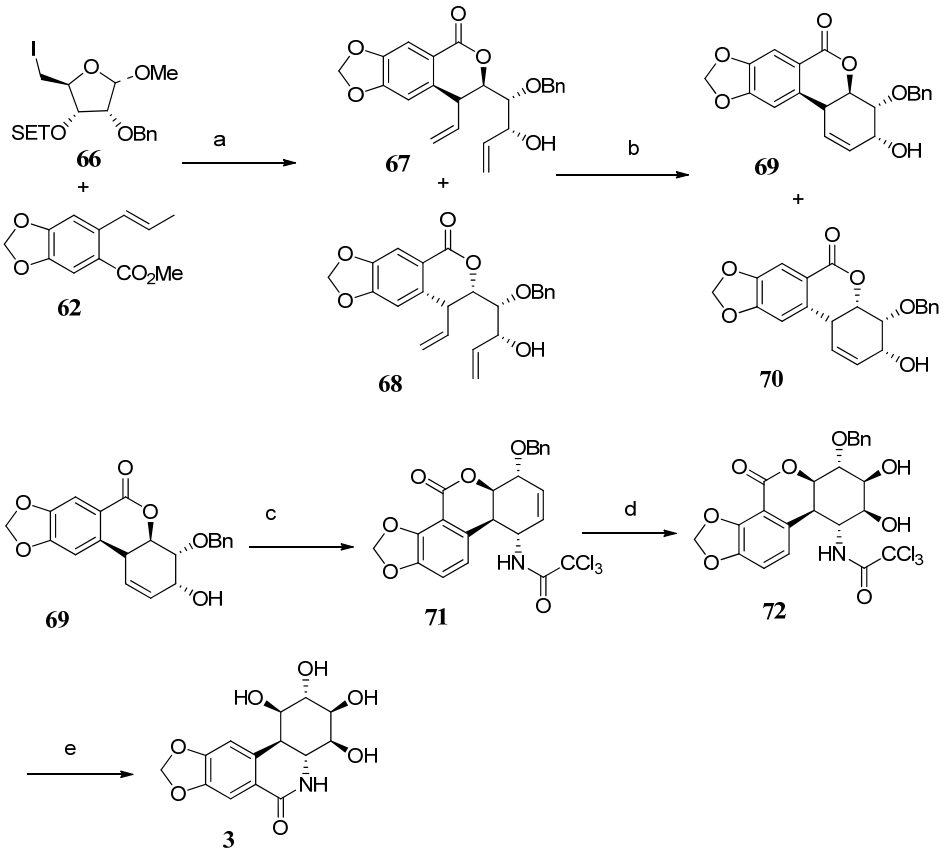
The utility of olefin metathesis was explored in the elaboration of C-ring of 7-deoxypancratistatin (**3**) by Madsen *et al.* in total 13 steps in 1.4 % overall yield. In their synthesis, the diene **63** was subjected to metathesis with Grubbs' first-generation catalyst to afford cyclohexene **64** which was oxygenated to complete the synthesis of the natural product **3**. The derivation of chiral diene **63** from D-ribose included zinc mediated tandem reactions (Scheme 8).



Scheme 8. Reagents and conditions: *a) i)* **65***, Zn, THF, H_2O, 40 °C, ultrasound; ii) Zn, $BnNH_2$, THF, 40 °C, ultrasound; b) [Ru(=CHPh)$(PCy_3)_2(Cl)_2$], CH_2Cl_2; c) i) H^+ resin, MeOH, 65 °C; ii) m-CPBA, CH_2Cl_2 ; iii) BzONa, H_2O, 100 °C; iv) H_2, Pd/C, AcOH.*

Approach-2

In this second strategy, reaction between ribofuranoside **66** (derived from D-xylose) and compound **62** in the presence of zinc followed by ring-closing metathesis yielded **69** and **70** in 2:1 ratio. Subsequent Overman rearrangement of **69**, dihydroxylation and deprotection afforded the **3** in 23 steps in 4.3 % overall yield (Scheme-9).

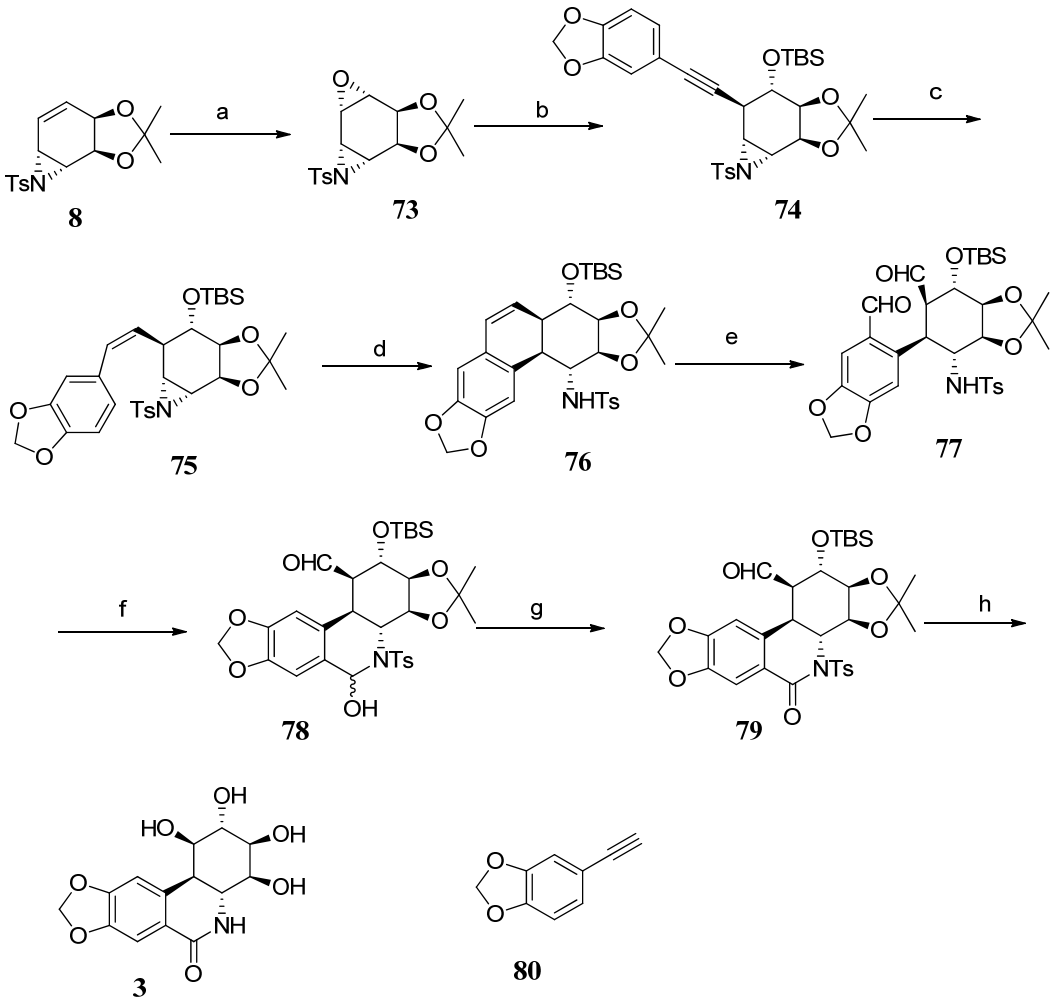


Scheme 9. Reagents and conditions: *a) i) Zn, THF, H_2O, 40 ^oC, ultrasound, then H^+ resin, MeOH, 50 ^oC, b) Grubbs' 1st generation catalyst, CH_2Cl_2, 40 ^oC; c) CCl_3CN, DBU, CH_2Cl_2, -45 ^oC to -20 ^oC, then 1 mm Hg, neat, 120 ^oC; d) OsO_4, NMO, THF; e) i) K_2CO_3, MeOH, 65 ^oC, ii) H_2, $Pd(OH)_2$/C, EtOAc.*

Hudlicky's Approach[22] (*J. Org. Chem.* **2010**, *75*, 3069)

In 2010 Hudlicky *et al.* reported the synthesis of 7-deoxypancratistatin (**3**) and its analogues. The synthesis of aziridine **8** was described in previous Scheme 1. Vinyl aziridine **8** was treated with *m*-CPBA for epoxidation to furnish epoxy aziridine **73** in 96% yield. Epoxy aziridine **73** was treated with alane, which was derived from aryl acetylene **80** (n-BuLi, Me_2AlCl, -50 to 0 °C), to produce an intermediate acetylenic

alcohol that was immediately protected to give its silyl ether **74**. Silyl ether **74** was subjected to the Lindlar hydrogenation protocol to afford the required *cis*-alkene **75**. Adsorption of the aziridine **75** on activated silica followed by heating at 120 °C, yielded the key phenanthrene skeleton **76** in 74% yield. Direct ozonolysis of phenanthrene **76** followed by oxidative workup gave di-aldehyde compound **77** which on standing at rt gave compound **78**. Compound **78** was subjected to oxidation with

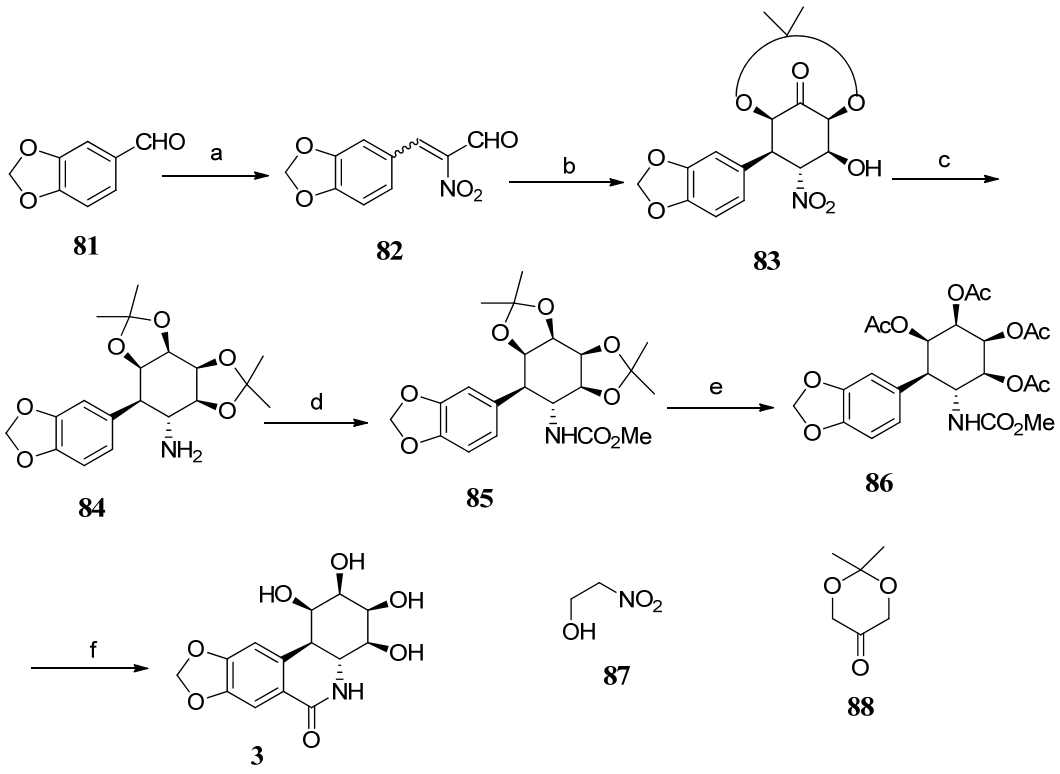


Scheme 10. Reagents and conditions: *a) m-CPBA, DCE, reflux, 96%; b) i)* ***80****, n-BuLi, Me_2AlCl, toluene, -50 to -20 °C; ii) TBDMSOTf, Et_3N, DCM, -78 °C-rt, 77%; c) Lindlar's catalyst, quinoline, H_2, Pd/C, MeOH, 95%; d) Silica gel, 120 °C, 24 h, 74%; e) O_3, Me_2S, MeOH, -78 °C; f) rt; g) IBX, DMF, rt, 61%; h) i) Et_3N, THF, TMSCl, 80 °C then O_3, DCM, Me_2S, -78 °C; ii) TBAF, THF, rt; $NaBH_4$, EtOH, 0 °C; deprotection.*

IBX to yield compound **79**. After functional group manipulations and deprotection of protecting groups of compound **79** the target molecule 7-deoxypancratistatin (**3**) was obtained (Scheme 10).

Alonso's Appraoch[23] (*Org. Biomol. Chem.* **2012**, *10*, 825)

Alonso *et al.* reported the synthesis of (±)-7-deoxy-pancratistatin (**3**) and its 2-*epi*- and 2,4-di *epi*- unnatural analogues and studied their cytotoxic activity against the human lung tumoral cell line NCI-H460. Their synthesis started with Henry-type condensation between **81** and **87** followed by oxidation of the terminal hydroxyl group to give β-aryl-α-nitro-α,β-enals **82**. Annulation of enals **82** with dioxanone **88** furnished protected nitrocyclitols **83** in good yield. Treatment of **83** with nickel boride and then with 2,2-dimethoxypropane led to the isolation of the diacetonide **84** as a single diastereoisomer. Amine was converted to corresponding carbamate **85** with



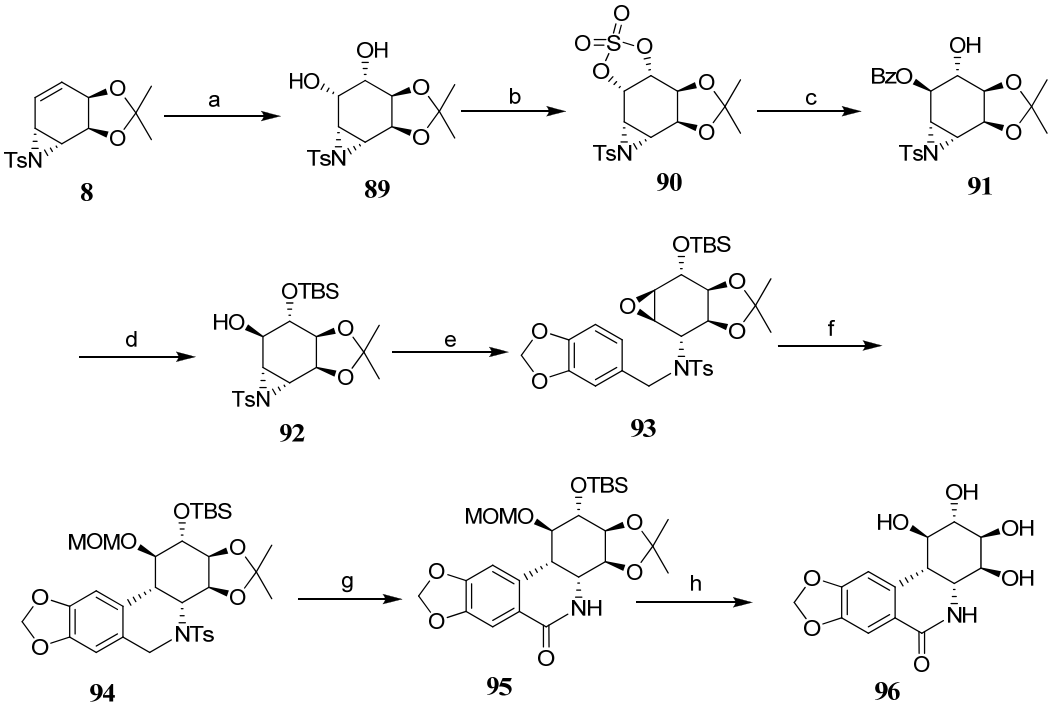
Scheme 11. Reagents and conditions: *a) Condensation with **87**, IBX; b) Annulation with **88**; c) i) $NiCl_2$, $NaBH_4$, MeOH; ii) 2,2-DMP, p-TsOH.H_2O, acetone; d) $ClCO_2Me$, DMAP, DCM, 80%; e) i) p-TsOH.H_2O, MeOH, DCM; ii) Py, Ac_2O; f) Tf_2O, DMAP, DCM.*

methyl chloroformate in 80% yield. Deprotection and protection of hydroxyl group followed by construction of 'B' ring using Bischler-Napieralsky protocol and finally deprotection of acetate group led to the target molecule **3** (Scheme 11).

3.1.3. Literature review on synthesis of epimer of 7-deoxypancratistatin

Hudlicky's Approach[24] (*Org. Lett.* **2001**, *4*, 115; *J. Org. Chem.* **2002**, *67*, 8726)

In 2001 Hudlicky *et al.* reported the total synthesis of *epi*-7-deoxypancratistatin (**96**) in 12 steps from bromobenzene. Key steps of their synthesis were the enzymatic oxidation of bromobenzene with toluene dioxygenase, selective opening of a cyclic sulfate over an aziridine with oxygen nucleophile, and an intramolecular Lewis acid-



Scheme 12. Reagents and conditions: *a) $RuCl_3.H_2O$, $NaIO_4$, EtOAc. H_2O, 15 sec., 85%; b) SO_2Cl_2, Et_3N, DCM, 93%; c) i) $BzONH_4$, DMF; ii) THF, H_2O, H_2SO_4, 90%; d) i) TBSCl, imidazole, DMF, rt; ii) NaOMe, THF, rt, (63% over two steps); e) i) t-BuLi, THF, -30 °C; ii) Piperonyl bromide, NBu_4I; f) i) Me_2AlCl, DCM, -30 °C, 68%; ii) MOMCl, $^iPr_2EtN$, rt, 97% g) i) $RuCl_3.H_2O$, $NaIO_4$, CH_3CN, CCl_4, H_2O, rt, 50%; ii) Na/naphthalene, DME, -50 °C, 75%; h) HCl, MeOH, rt, 68%.*

catalyzed cyclization onto an epoxy conduramine derived *via* aza-Payne rearrangement. They started their synthesis from aziridine which was synthesized from bromobenzene. The aziridine **8** was dihydroxylated and converted to the cyclic sulfate **90** with sulfuryl chloride. The sulfate **90** was treated with $PhCO_2NH_4$ in DMF followed by hydrolysis of the sulfate with dilute H_2SO_4 to give compound **91** in 90% yield. Protection of the free alcohol, hydrolysis of the benzoate, and alkylation of **13** with piperonyl bromide furnished *N*-alkylated amino oxirane **93**. Epoxyconduramine **93** was treated with Me_2AlCl for a smooth cyclization to furnish the phenanthridone core **94** of the alkaloid with α-stereochemistry at 10b. Then free hydroxyl group was protected with MOM-Cl to give compound **94** in 97% yield over two steps. Compound **94** was treated with $RuCl_3/NaIO_4$ followed by reductive detosylation, and finally hydrolyzed to furnish the *cis*-epimer of 7-deoxypancratistatin (**96**) (Scheme 12).

3.1.4. References

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Chapter 3: Synthetic studies towards 7-deoxypancratistatin and retro-Reformatsky reaction

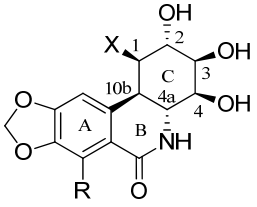
Section 2

A highly stereocontrolled asymmetric total synthesis of epimer of 7-deoxypancratistatin

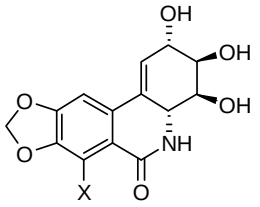
3.2.1. Present Work

3.2.1.1. Objective

The potent biological activity and unique yet challenging structural features of *Amaryllidaceae* alkaloids (**1-4**) (Figure 1) possessing phenanthridone skeleton with four or six contiguous stereogenic centres in the C ring and *trans*-fused BC- ring (C10b-C4a) have rendered it an attractive target for synthetic organic chemists.



1, R=X=OH, Pancratistatin
2, R=H; X=OH , 7-Deoxypancratistatin



3, X = OH, Narciclasine
4, X = H, Lycoricidine

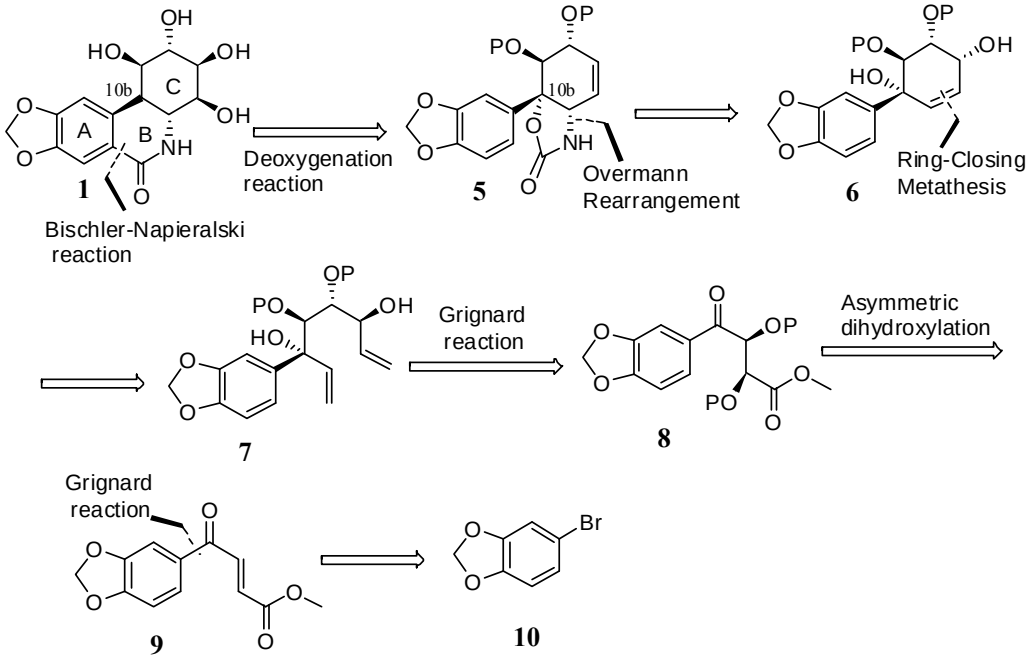
Figure 1. Structures of pancratistatin (**1**), 7-deoxypancratistatin (**2**), narciclasine (**3**) and lycoricidine (**4**).

The potent biological activity of these compounds having novel framework coupled with their low natural abundance/availability was the impetus to undertake the synthesis of these classes of compounds which should provide these compounds in a practical way. Here a new, highly stereo-controlled asymmetric total synthesis of epimer of (+)-7-deoxypancratistatin is described.

3.2.1.2. Retrosynthetic analysis

Scheme 1 highlights the overall retrosynthetic strategy towards (+)-7-deoxypancratistatin (**1**). The B ring of 7-deoxypancratistatin could be constructed by Bischler-Napieralski reaction and C10b centre could be fixed *via* deoxygenation of tertiary, protected benzylic alcohol of intermediate **5**. Allylic nitrogen group could be installed *via* Overmann rearrangement of allylic alchol **6**. It was envisioned that the requisite precursor **6**, which contains four stereocenters in the C ring, could be stereoselectively synthesized from diene **7** *via* ring closing metathesis. The diene **7** in turn could be obtained from diol **8** taking advantage of the existing chiral centers to direct the other two chiral centers to be installed. Further analysis indicated that the diol compound **8** could be synthesized from the unsaturated ketone compound **9** by

using Sharpless asymmetric dihydroxylation (SAD). The unsaturated ketone **9** could be obtained from easily available, inexpensive starting material **10** *via* Grignard reaction (Scheme1).



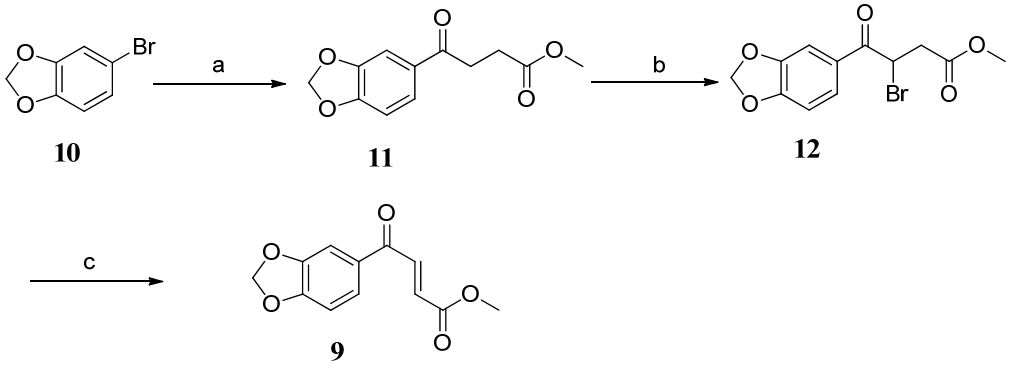
Scheme 1. Retrosynthetic analysis of 7-deoxypancratistatin.

3.2.1.3. Results and discussion

Accordingly, the synthesis began with the Grignard reaction of 4-bromo-1,2-(methylenedioxy)benzene **10** with succinic anhydride. Aryl Grignard reagent was prepared from **10** and it was quenched with succinic anhydride to give acid and the crude acid thus obtained was directly treated with Me_2SO_4 to give corresponding ester **11** in 85% yield over two steps. The IR spectrum of compound **11** showed strong bands at 1737 and 1678 cm^{-1} indicating the presence of ester and aromatic ketone functionalities. The ^1H NMR spectrum of compound **11** showed singlet at δ 3.71 for three protons indicating the presence of methyl ester and two triplets at δ 2.74 and 3.23 for two protons each which indicated the presence $–CH_2-CH_2-$ moiety. The ^{13}C NMR spectrum showed peaks at δ 173.18 and 195.69 corresponding to ester and ketone functional groups. Its DEPT NMR spectrum showed presence of two CH_2 groups respectively. The mass spectrum of compound **11** showed peak at m/z 259 corresponding to $[M+Na]^+$. Finally, the structure of compound **11** was confirmed by HRMS analysis.

Attempts to install the double bond in one pot under IBX/DMSO[1] reaction condition was unsuccessful leading to recovery of starting materials. Then it was decided to introduce the olefin by stepwise addition and elimination operation. Accordingly, α-bromination[2] of ketone **11** was carried out with NBS to give selectively mono α-bromoketone **12** in 98% yield. The ^{1}H NMR spectrum showed a double doublet at 5.40 for one proton and was attributed to the α-protons of carbonyl group. Two diastereomeric α-proton of the ester appeared at 3.07 and 3.46 as double doublet. ^{13}C NMR and DEPT NMR spectra showed peak at 39.11 for corresponding methine carbon. The mass spectrum of compound **12** showed peak at m/z 336 and 338 corresponding to $[M+Na]^{+}$ and $[(M+2)+Na]^{+}$ with equal intensity which further confirmed the formation of bromo compound **12**. Finally, the structure of compound **12** was confirmed by HRMS analysis.

Treatment of compound **12** with Et_3N furnished exclusively the *trans* olefin **9** in quantitative yield. The IR spectrum of compound **9** showed strong absorption bands at



Scheme 2. Reagents and conditions: *a) i) Mg, succinic anhydride, THF, 3 h, 0 °C-rt; ii) Me_2SO_4, K_2CO_3,acetone, 3 h, 85%(over two steps); b) NBS, NH_4OAc, CCl_4, reflux, 98%; c) Et_3N, DCM, 10 min. quant.*

1727 and 1661 cm^{-1} corresponding to α,β-unsaturated ester and ketone, which supported the dehydrohalogenation of compound **12**. ^{1}H NMR spectrum showed the absence of peaks at δ 5.40, 3.07 and 3.46 and appearance of new peaks at δ 6.87 and 7.89 as doublet corresponding to the protons of double bond of unsaturated ketone compound **9**. The coupling constant of the two protons of the double bond was 15 Hz which revealed that the double bond had *trans* geometry. ^{13}C NMR and DEPT NMR

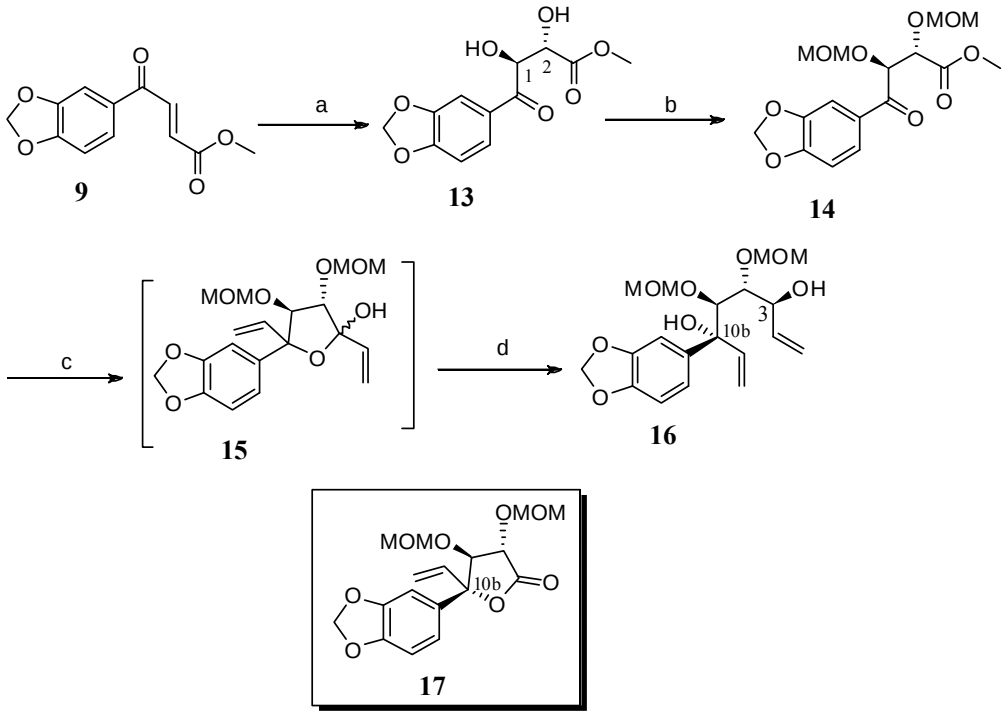
spectra showed the absence of two peaks at δ 39.11 and 38.46 corresponding to methine and methylene group and appearance of new peaks at δ 136.48 and 131.47 corresponding to the double bond of unsaturated ketone compound **9**. The mass spectrum of compound **9** showed peak at m/z 257 corresponding to $[M+Na]^+$. Finally, the structure of compound **9** was confirmed by HRMS analysis (Scheme 2).

This prochiral enone **9** was deemed to be a suitable substrate for the installation of the chiral centers. The compound **9** was subjected to Sharpless asymmetric dihydroxylation (SAD)[3] reaction conditions with $(DHQD)_2PHAL$ as a chiral catalyst to yield chiral diol **13** in 85% yield with ≥98% *ee*.[4] The IR spectrum of compound **13** showed strong bands at 3456, 1747 and 1675 cm^{-1} for free hydroxyl, ester and ketone functional groups respectively. In ^1H NMR spectrum of compound **13**, doublets at δ 6.87 and 7.89 were absent indicating the conversion of conjugated double bond into diol. ^{13}C NMR and DEPT NMR spectra of compound **13** showed the peaks at δ 72.62 and 74.03 for corresponding methine carbons [-CH(OH)-CH(OH)-]. The mass spectrum of compound **13** showed a peak at m/z 291 corresponding to $[M+Na]^+$. Finally the structure of compound **13** was confirmed by HRMS analysis. The enantiomeric excess of diol **13** was determined by chiral HPLC analysis.

After screening various literature reports on SAD it was observed that surprisingly SAD on such type of double bond is not reported in the literature. MOM protection of diol in **13** occoured smoothly with MOMCl to afford di-MOM protected diol **14** in 92% yield without epimerization.[5] The broad band at 3456 cm^{-1} was absent in IR spectrum of compound **14** which indicateed the MOM protection of free hydroxyl group. The ^1H NMR spectrum of compound **14** showed multiplet at δ 4.53-4.69 for four protons and two singlets at δ 3.27 and 3.11 corresponding to two MOM groups. ^{13}C NMR and DEPT NMR spectra of compound **14** showed peaks at δ 95.78 and 96.08 for two CH_2 carbons and at δ 51.93 and 55.74 for two CH_3 carbons for the corresponding MOM group. The mass spectrum of compound **14** showed peak at m/z 379 corresponding to $[M+Na]^+$. Finally the structure of compound **14** was confirmed by HRMS analysis. The enantiomeric excess of MOM protected diol **14** was determined by chiral HPLC analysis.

Ketone **14** was subjected to the 2 equiv. vinyl magnesium bromide to give lactol **15** in 60% yield, which was found to be unstable at room temperature (under controlled

experiment lactone intermediate **17** was isolated). The diastereoselectivity of the Grignard reaction of **15** can be accounted for by the Cram's chelation model[6] (**a**, Figure 2). So after purification, it was immediately treated under Luche reduction[7] with $CeCl_3.7H_2O$ and $NaBH_4$ to yield diene **16** in 95% yield as a sole observable diastereomer (determined by ^1H NMR and ^{13}C NMR).



Scheme 3. Reagents and conditions: *a) i) $(DHQD)_2PHAL$, OSO_4, $K_3[Fe(CN)_6]$, K_2CO_3, $^tBuOH:H_2O$ (1:1), 4 days, 85%, ≥98% ee; b) MOM-Cl, DIPEA, DCM, reflux, 92%; c) Vinyl magnesium bromide (2 eqiv.), THF, 0 °C, 60%; d) $CeCl_3.7H_2O$, $NaBH_4$, MeOH, 0 °C, 15 min, 95%.*

The IR spectrum of compound **16** showed absence of strong bands at 1759 and 1675 cm^{-1} corresponding to ester and ketone functional groups respectively and the appearance of a broad band at 3451 cm^{-1} indicated the presence of free hydroxyl functional group. ^1H NMR spectrum of compound **16** showed a double doublet at δ 6.28 for one proton and a multiplet at δ 5.36-5.45 for two protons which were assigned to the three protons of double bond (-CH=CH_2) attached to C10b centre. Multiplets at δ 5.15-5.30 for one proton and δ 5.63-5.80 for two protons were assigned to the three protons of the double bond (-CH=CH_2) attached to C3 centre.

The ^{13}C NMR and DEPT NMR spectra of compound **16** showed peaks at δ 113.69 and 117.68 for CH_2 carbons and at δ 137.21 and 142.12 for CH carbons corresponding to two double bonds (-CH=CH_2). The mass spectrum of compound **16** showed peak at m/z 405 corresponding to $[M+Na]^+$. Finally, the structure of compound **16** was confirmed by HRMS analysis (Scheme 3).

The stereochemistry at the C3 centre was surprisingly controlled by Felkin-Anh model.[8] It is well known in the literature that Ce^{+3} have good affinity towards chelation and hence it was assumed that Luche reduction should furnish the product as predicted by Cram's chelation model. Although the exact reason for the observation remains unclear, it can be surmised that due to the bulky size of Ce^{+3} ion

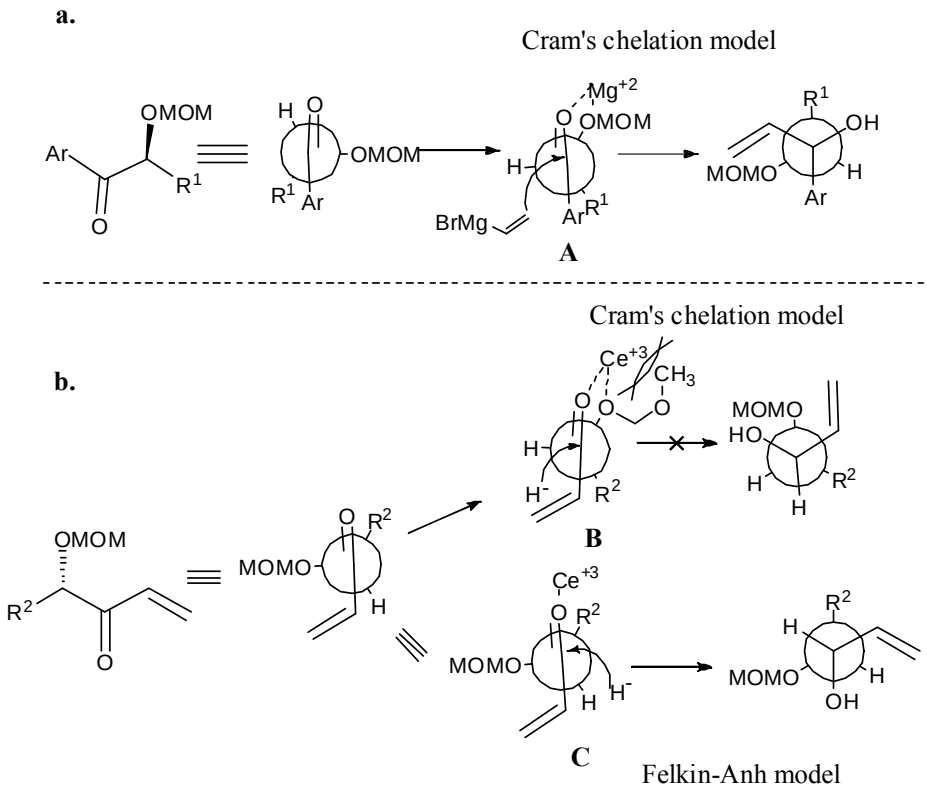


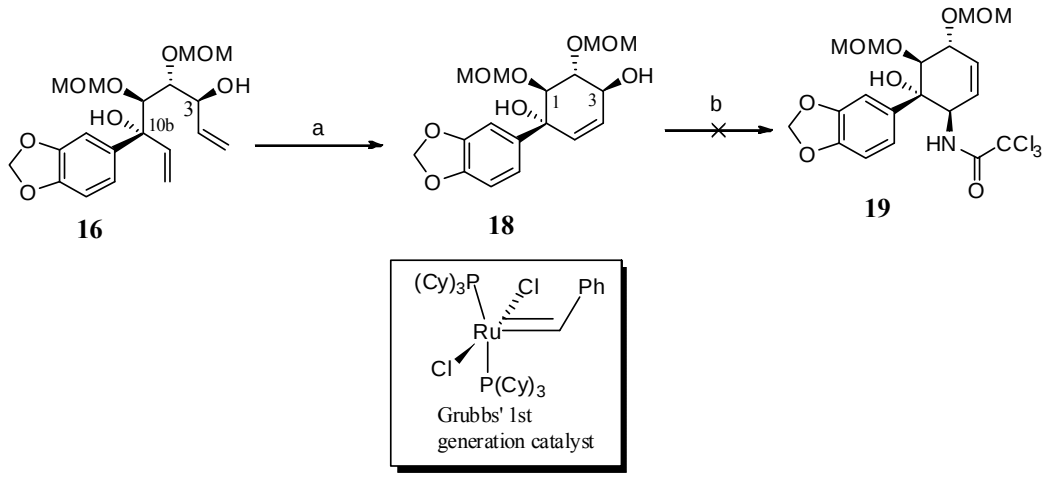
Figure 2. Felkin-Anh and Cram's chelation model transition state.

and MOM group chelation is not favourable. Cram's chelation transition state (**B**) was more sterically congested as compared to Felkin-Ahn transition state (**C**), which resulted in the hydride attack on the less hindered face of the non-chelated transition state (**C**). Having accomplished the assembling of requisite carbon atoms and appropriately placed functionalities, the stage was set for the construction of

cyclohexene ring. Accordingly the resultant diene **16** was subjected for ring closing metathesis using Grubbs' 1st generation catalyst to gratifyingly afford substituted cyclohexene advanced intermediate **18** in 96% yield.

The ^{1}H NMR spectrum of compound **18** showed the absence of double doublet at δ 6.28 and all multiplets at δ 5.36-5.45, 5.15-5.30 and 5.63-5.80 corresponding to two double bonds of compound **16** and the appearance of double doublets at δ 5.72 and 5.91 for one proton each indicating the formation of cyclohexene ring. ^{13}C NMR spectrum of compound **18** showed peaks at δ 127.53 and 131.99 for the double bond. The mass spectrum of compound **18** showed peak at m/z 377 corresponding to $[M+Na]^{+}$. Finally, the structure of compound **18** was confirmed by HRMS analysis.

It should be emphasized that the synthesis of **18** is operationally simple and the intermediate **18** can be synthesized in gram scale. Selectively, secondary hydroxyl group in allylic alcohol **18** was converted to corresponding imidate with Cl_3CCN for the ensuing Overman rearrangement.[9] Unfortunately, imidate did not undergo the anticipated rearrangement to give product **19**, instead the reaction led to recovery of the starting imidate (Scheme 4).



Scheme 4. Reagents and conditions: *a) Grubbs' Ist gen.catalyst, DCM, reflux, 4 h, 96%; b) i) CCl_3CN, DBU, DCM, 0 °C, 30 min; ii) K_2CO_3, xylene, reflux.*

The failure of the rearrangement might be attributed to the influence of the bulky MOM group for which the *β* face of double bond was sterically congested which prevented the migration of the imidate group (**E**). At this stage, it was decided to invert the C3 stereo-centre where *α* face was less sterically congested (**F**) (Figure 3).

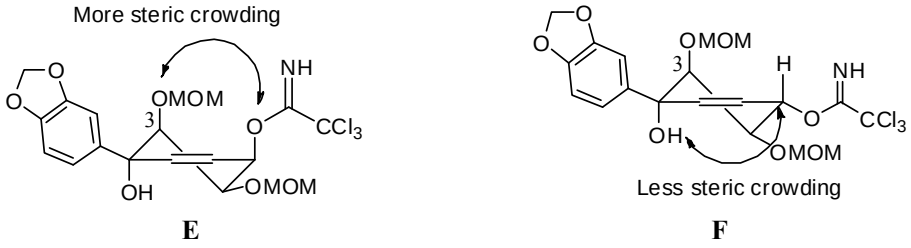


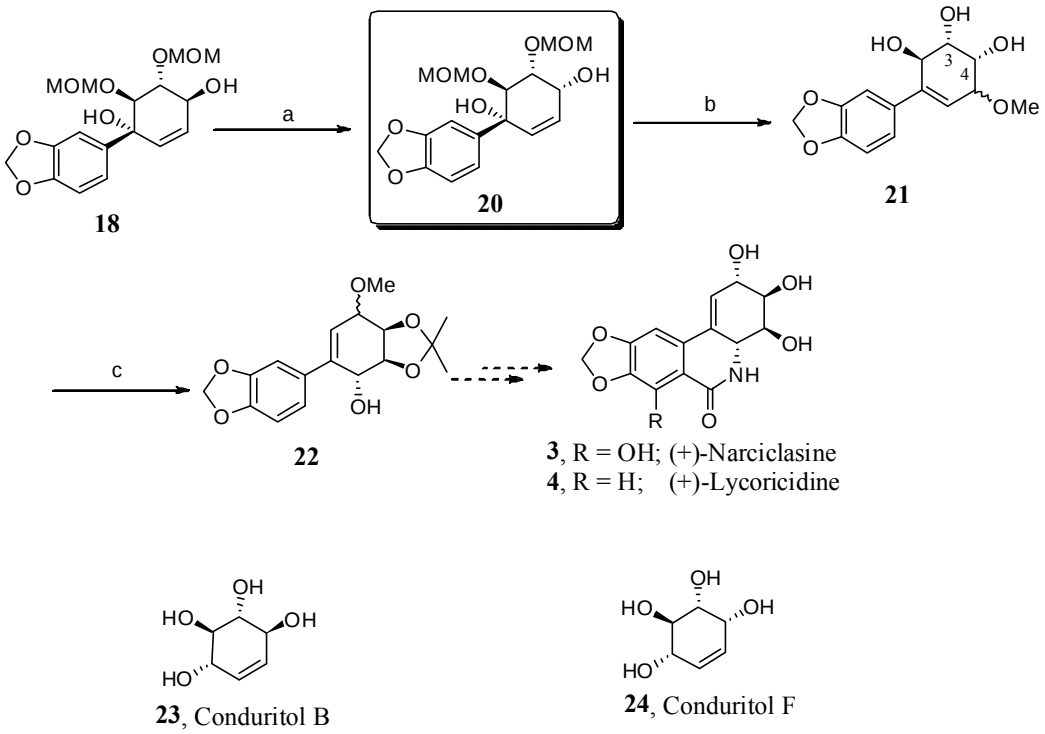
Figure 3. Effect of MOM group on Overman rearrangement.

In view of the unfavorable steric effect of MOM group on the rearrangement of allylic alcohol **18,** it was subjected to Mitsunobu reaction[10] condition with *p*-nitrobenzoic acid to afford crude nitrobenzoate ester which was hydrolyzed with NaOMe to afford the advanced intermediate **20** in 65% yield. TLC analysis showed different R_f values of compound **18** and **20**. ^{1}H NMR spectrum of compound **20** showed multiplet at δ 5.78-5.90 corresponding to two protons of the double bond. ^{13}C NMR and DEPT NMR spectra were also in good agreement with the structure of compound **20**. The mass spectrum of compound **20** showed a peak at m/z 377 corresponding to $[M+Na]^+$. Finally, the structure of compound **20** was confirmed by HRMS analysis.

It should be noted that 1-arylconduritols B and F[11] have very close structural resemblance with compounds **18** and **20** respectively, and can be potentially readily synthesized on multi-gram scale from these compounds **18** and **20**. Similarly the acid catalyzed rearrangement of the tertiary hydroxyl group of compound **20** gave rearranged product **21** in 85% yield as a single isomer (^{1}H NMR and ^{13}C NMR). The IR spectrum of compound **21** showed a broad band at 3410 cm^{-1} for the corresponding free hydroxyl functional group. ^{1}H NMR spectrum of compound **21** showed multiplet at δ 5.91-5.92 for one proton corresponding to the double bond; and the peak at δ 3.42 for three protons corresponding to OMe group. ^{13}C NMR and DEPT NMR spectra showed a new peak at δ 57.03 for the corresponding OMe group. The mass spectrum of compound **21** showed peak at m/z 303 corresponding to $[M+Na]^+$. Finally, the structure of compound **21** was confirmed by HRMS analysis.

Selectively two *cis* hydroxyl (C3OH and C4OH) functional groups of triol **21** were protected as acetonide with 2,2-dimethoxypropane to afford acetonide protected diol **22** in 95% yield. ^{1}H NMR spectrum of compound **22** showed two singlets at δ 1.29 and 1.34 for total six protons corresponding to acetonide group. ^{13}C and DEPT NMR spectra showed peaks at δ 24.38 and 26.27 for the corresponding two methyl groups;

and at δ 108.39 for the quaternary carbon of the acetonide group. The mass spectrum of compound **22** showed peak at m/z 343 corresponding to $[M+Na]^+$. Finally, the structure of compound **22** was confirmed by HRMS analysis. The main framework of lycoricidine (**4**) has very close structural similarity with the compound **22.** By doing some simple functional group transformations, intermediate **22** can be easily transformed into lycoricidine (**4**) (Scheme 5).

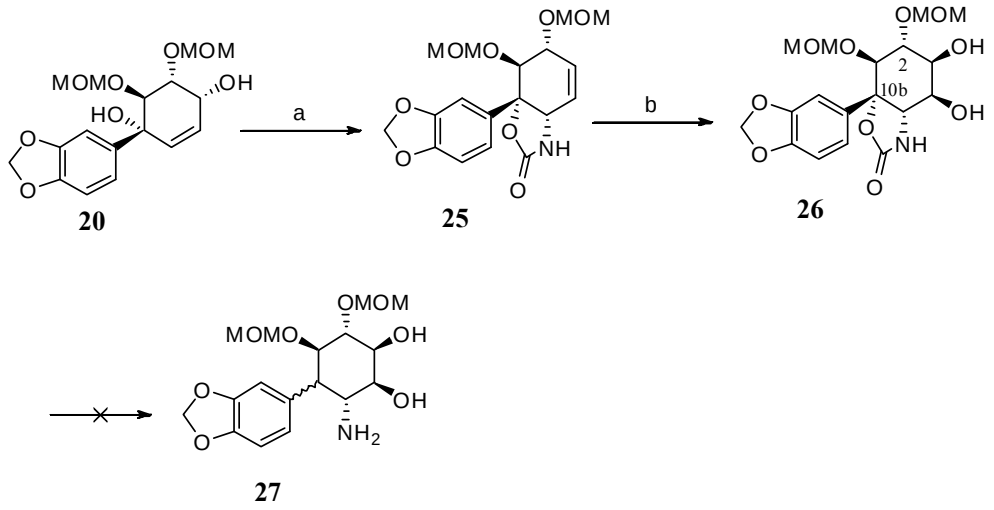


Scheme 5. Reagents and conditions: *a) i) Bu_3P, DEAD, p-$NO_2C_6H_4CO_2H$, toluene, 0 °C, 5 h; b) Cat. H_2SO_4, MeOH, rt, 4 h, 85%; c) 2,2-Methoxypropane, PTSA, DCM, rt, 30 min., 95%.*

The secondary hydroxyl group of alcohol **20** was selectively converted to the corresponding imidate by treating with Cl_3CCN. With this imidate in hand, the Overman rearrangement[9] was tried with K_2CO_3 in xylene under the reflux condition and it was gratifying to find that it worked very well as per hypothesis. After 3 h, the desired rearranged product **25** was obtained as a single isomer in 98% yield giving credence to the hypothesis. The IR spectrum of compound **25** showed a strong band at 1759 cm^{-1} for the carbonyl group of the carbamate ring, which supported the

formation of carbamate ring after rearrangement. The ^{1}H NMR spectrum of compound **25** showed multiplet at δ 5.89-5.92 for one proton and a doublet at δ 6.04 for one proton corresponding to double bond. ^{13}C NMR and DEPT NMR spectra showed peak at δ 157.42 for the corresponding carbonyl group of carbamate ring. The mass spectrum of compound **25** showed a peak at m/z 402 corresponding to $[M+Na]^{+}$. Finally, the structure of compound **25** was confirmed by HRMS analysis.

Treatment of this bicyclic compound **25** with OsO_4 afforded diol **26** as a sole isolable diastereomer in 99% yield and the relative stereochemistry was confirmed by 2D NMR study and finally, by a single crystal XRD analysis[12] (Figure 4). The IR spectrum showed a broad band at 3403 cm^{-1} for the corresponding free hydroxyl group. The ^{1}H NMR spectrum showed multiplet at δ 5.89-5.92 and the doublet at δ 6.04 was

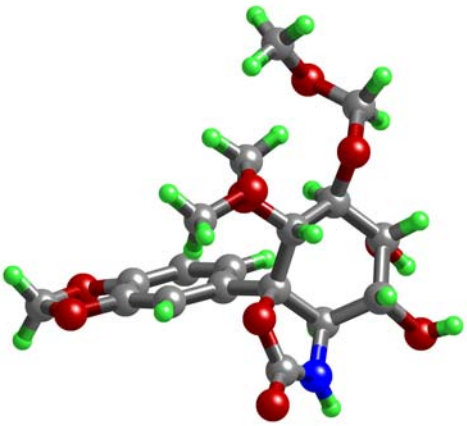


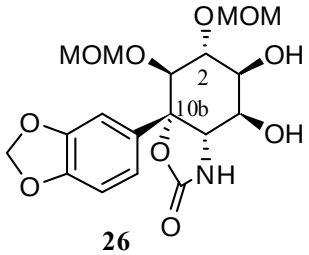
Scheme 6. Reagents and conditions: *a) i) CCl_3CN, DBU, DCM, 0 °C, 30 min; ii) K_2CO_3, xylene, reflux, 3 h, 98%; b) OsO_4, NMO; CH_3CN: H_2O, (9:1), rt, 3 days, 99%.*

absent indicating the conversion of double bond into diol. ^{13}C NMR and DEPT NMR spectra of compound **26** showed peaks at δ 72.12 and 69.53 for the corresponding methine carbons [-CH(OH)-CH(OH)-]. The mass spectrum of compound **26** showed a peak at m/z 436 corresponding to $[M+Na]^{+}$. Finally, the structure of compound **26** was confirmed by HRMS analysis.

This stereochemical outcome can be attributed to the approach of the reagent from the β-face of the double bond because the nearby carbamate ring and the bulky MOM

group at C2 position provided steric bias for α-face of the double bond. After successful installation of all functional groups around the cyclohexane ring with the desired stereochemistry, next task was deoxygenation of teriary, benzylic protected C10b hydroxyl group. Towards this end, despite the significant efforts, it was not possible to get the desired deoxygenated product[13] under different reaction conditions like hydrogenolysis (Pd/C[14], $Pd(OH)_2/C$[15] and Raney Ni[16]), ionic hydrogenation[17] ($Et_3SiH/BF_3.OEt_2$ and Et_3SiH/TFA) and Birch reduction[18] (Scheme 6).





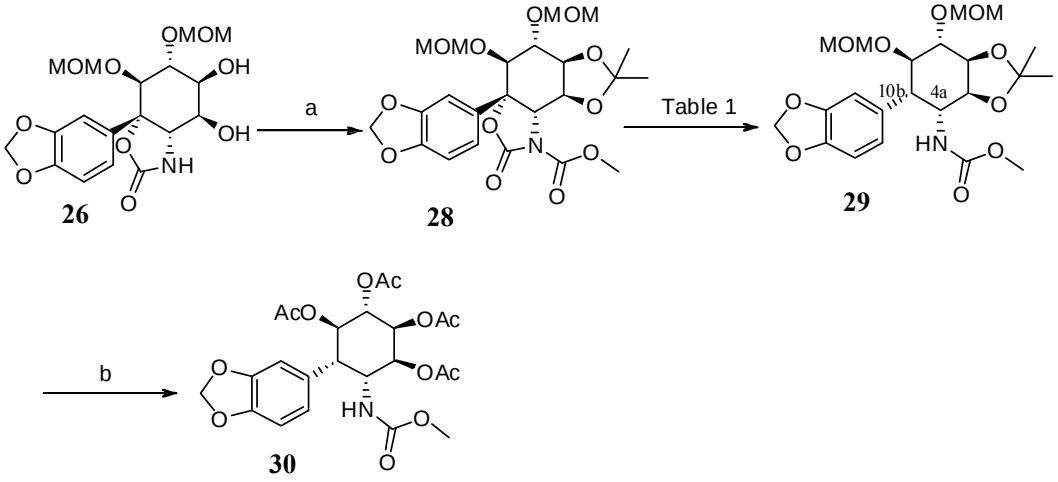
26

Figure 4. ORTEP diagram of the bicyclic compound **26.**

The above results indicated that the carbamate ring is very stable and is highly resistant under the above reaction conditions. This finding, however led to activate the carbamate ring. Accordingly, the diol of compound **26** was protected as its acetonide followed by treatment with dimethyldicarbonate to furnish compound **28** where the carbamate ring was activated. The IR spectrum of compound **28** showed strong bands at 1827 and 1735 cm^{-1} for corresponding carbonyl groups of cyclic carbamate and acyclic methyl carbamate; and absence of broad band at 3403 cm^{-1} indicated the protection of diol as acetonide. The ^1H NMR spectrum of compound **28** showed singlets at δ 1.58 and δ 1.40 for total six protons corresponding to acetonide group and singlet at δ 3.87 for three protons corresponding to methyl carbamate ($\underline{CH_3}OCO$-). ^{13}C NMR and DEPT NMR spectra were also in good agreement with the structure of compound **28**. The mass spectrum of compound **28** showed peak at m/z 534 corresponding to $[M+Na]^+$. Finally, the structure of compound **28** was confirmed by HRMS analysis.

With the activated compound **28** in hand, next aim was to carry out deoxygenation reaction in order to fix the desired stereochemistry at C10b centre (Table-1). Hydrogenolysis of compound **28** gratifyingly furnished the deoxygenated compound as a single isomer, however, with the *cis* stereochemistry leading to formation of product **29** (Table 1, entry 1-4). The IR spectrum of compound **29** showed the absence of band at 1735 cm^{-1} for cyclic carbamate ring and the appearance of a new band at 1718 cm^{-1} indicating the deoxygenation reaction of **28**. ^{1}H NMR spectrum showed multiplet at δ 3.27-3.30 for one proton corresponding to benzylic proton (C10B). ^{13}C NMR and DEPT NMR spectrum of compound **29** showed peak at δ 44.29 for the corresponding C10b carbon. The mass spectrum of compound **29** showed peak at m/z 492 corresponding to $[M+Na]^{+}$. Finally, the structure of compound **29** was confirmed by HRMS analysis.

The ionic hydrogenation and Birch reduction conditions resulted in complex reaction mixture (entry 5-6). Under Raney nickel reaction conditions, the deoxygenated product could not be obtained (entry 7). Although the desired *trans* stereochemistry at C4a-C10B centre as required to obtain (+)-7-deoxypancratistatin (**1**) could not be achieved under these reaction conditions, an advanced intermediate



Scheme 7. Reagents and conditions: *a) i) $Me_2C(OMe)_2$, cat. PTSA, DCM, 0 °C, 1 h; ii) Dimethyldicarbonate, Et_3N, DMAP, DCM, 1 h, rt, 97%; b) i) con. HCl (2-3 drops), MeOH, rt, 4 h; ii) Ac_2O, pyridine, rt, overnight, 97%.*

Table-1. Deoxygenation of activated carbamate.

Entry	Reaction Conditions	Product[a]
1	$Pd(OH)_2$, CH_3COOH, H_2, EtOH	*Cis* stereochemistry
2	$Pd(OH)_2$, H_2, EtOH	*Cis* stereochemistry
3	Pd/C, CH_3COOH, H_2, EtOH	*Cis* stereochemistry
4	Pd/C, H_2, EtOH	*Cis* stereochemistry
5	Li, liq. NH_3, THF	Complex reaction mixture
6	$BF_3.OEt_2$/TFA, Et_3SiH, DCM	Complex reaction mixture
7	Raney Ni, H_2, EtOH, reflux	SM[b] was recovered

[a] relative stereochemistry at C4a-C10b centres; [b] Starting Material.

26, bearing the exact required stereochemistry for the synthesis of (+)-7-deoxypancratistatin (**1**) was obtained in good yields and it is believed that by proper choice of reagents and reaction conditions, it can be converted to (+)-7-deoxypancratistatin (**1**).

With *cis* deoxygenated product **29** in hand, it was carried forward towards the total synthesis of epimer of 7-deoxypancratistatin. Accordingly, acetonide and MOM groups were globally deprotected in one pot by addition of 2-3 drops of con. HCl in MeOH. Then free hydroxyl groups were protected with acetic anhydride to yield tetraacetate **30** in 97% yield (Scheme 7). The IR spectrum of compound **30** showed a strong absorption band at 1752 cm^{-1} for the corresponding acetate functional group. ^1H NMR spectrum of compound **30** showed the absence of singlets at δ 1.40, 1.58, 3.23 and 3.38 for the corresponding methyl groups of acetonide and MOM groups and appearance of four singlets at δ 2.22, 2.02, 1.99 and 1.86 which supported the formation of tetraacetate compound **30**. ^{13}C NMR and DEPT NMR spectra showed peak at δ 170.31 for the corresponding carbonyl group of acetate; and peaks at δ

20.98, 20.53, 20.43 and 10.39 for the corresponding methyl group of acetate ($\underline{CH_3}CO$-). The mass spectrum of compound **30** showed peak at m/z 532 corresponding to $[M+Na]^+$. Finally, the structure of compound **30** was confirmed by HRMS analysis. The relative stereochemistry and structure of compound **30** was confirmed by single crystal XRD analysis[19] (Figure 5).

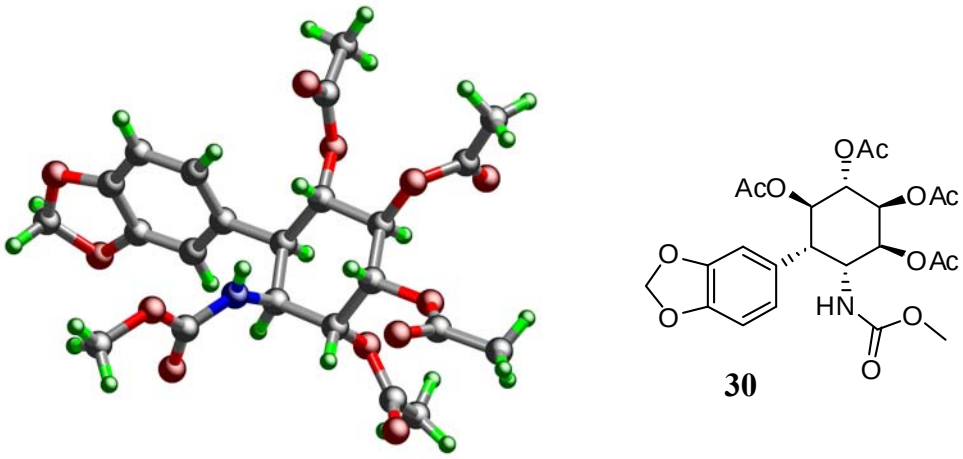
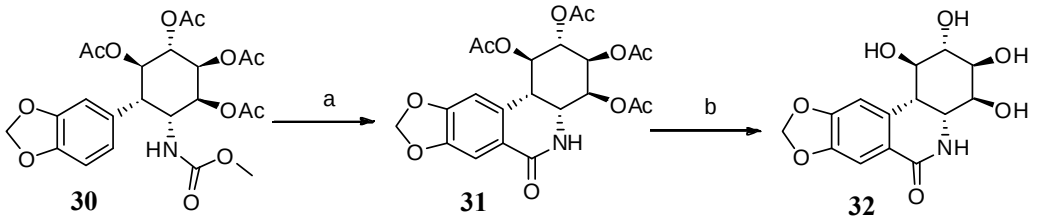


Figure 5. ORTEP diagram of the bicyclic compound **30**.

The carbamate **30** was treated with Tf_2O and DMAP under modified Bischler-Napieralski protocol[20] for the construction of B ring to afford compound **31**. The IR spectrum of compound **31** showed a strong band at 1661 cm^{-1} indicating the formation of lactam **31**. The ^1H NMR spectrum exhibited singlets at δ 7.56 and δ 6.65 which were assigned to the two *para* aromatic protons indicating the formation of 'B' ring. ^{13}C NMR and DEPT NMR spectra showed signals for four quaternary carbons at δ 151.11, 148.10, 132.51and 122.23 which were attributed to the four aromatic quaternary carbon atoms. The mass spectrum of compound **31** showed peak at m/z 477corresponding to $[M+Na]^+$. Finally, the structure of compound **31** was confirmed by HRMS analysis.

Finally, global removal of all four acetate groups of compound **31** was achieved by treatment with K_2CO_3 in MeOH to furnish epimer of (+)-7-deoxypancratistatin **32** (Scheme 8). The IR spectrum of compound **32** showed the absence of peak at 1752 cm^{-1} for the corresponding carbonyl group of acetate indicating the global deprotection of all four acetate groups. ^1H NMR spectrum of compound **32** showed the absence of four singlets at δ 2.20, 2.03, 2.00 and 1.97 for the corresponding

acetate group which also supported the deprotection of all four acetate groups. ^{13}C and DEPT NMR spectra were also in good agreement with the structure of **32**. The mass spectrum of compound **32** showed a peak at m/z 332 corresponding to $[M+Na]^+$. The absolute stereochemistry of **32** was assigned by the comparison of the reported optical rotations.[21]



Epimer of (+)-7-deoxypancratistatin

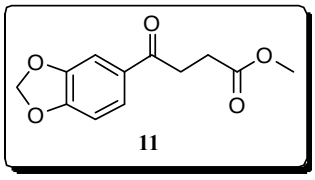
Scheme 8. Reagents and conditions: *a) Tf_2O, DMAP, DCM, -5 °C, 16 h, 70%; b) K_2CO_3, MeOH, rt, overnight, 85%.*

3.2.2. Conclusions

In summary, a new, scalable and potentially practical synthetic route to the epimer of (+)-7-doxypancratistatin **32** has been accomplished, starting from inexpensive, commercially and easily available starting materials in 15% overall yield after 15 purification steps which is the highest overall yield reported so far. An advanced intermediate **20** was synthesized in multi-gram scale which can be elaborated for the efficient synthesis of different 1-arylconduritols and lycrocidine (**4**).

3.2.3. Experimental

Methyl 4-(benzo[1,3]dioxol-5-yl)-4-oxobutanoate (11)



In a 250 mL round bottom flask were placed freshly activated Mg turnings (4.8 g, 0.2 mol) and freshly distilled THF (10 mL) under nitrogen atmosphere. After the addition of a little iodine, 4-bromo-1, 2-methylenedioxybenzene **10** (16.2 g, 0.13 mol) was added drop wise to maintain gentle reflux. After the addition, which takes about 30 min, the reaction mixture was stirred for additional 1 h at that temperature. Then aryl Grignard reagent was formed as brown liquid which was further diluted by addition of 250 mL additional dry THF.

To cold (0 °C) stirred solution of succinic anhydride (17 g, 0.168 mol) in dry THF, the freshly generated Grignard solution was added drop wise by syringe and further stirred for 2 h at 0 °C. The reaction mixture was cooled and quenched with saturated aqueous solution of NH_4Cl and extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude acid was used in the next reaction without further purification.

To a solution of crude acid (20 g, 0.09 mol) in dry acetone (200 mL), K_2CO_3 (28 g, 0.2 mol) was added followed by Me_2SO_4 (20 mL, 0.21 mol) and refluxed for 3 h. The reaction mixture was cooled and quenched with water and extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (20% EtOAc/pet ether) to provide the product **11** (16.5 g, 85% yield over two steps) as white solid, melting point. R_f (20% EtOAc/pet ether): 0.4.

Molecular formula: $C_{12}H_{12}O_5$

Yield: 85% (over two steps)

Melting Point: 62-64 °C.

IR ($CHCl_3$): 2912, 1737, 1678, 1443 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.74 (t, *J*=6.7 Hz, 2H), 3.23 (t, *J*=6.7 Hz, 2H), 3.71 (s, 3H), 6.05 (s, 2H), 6.85 (d, *J*=8.2 Hz, 1H), 7.44 (d, *J*=1.6 Hz, 1H), 7.59 (dd, *J*=1.6, 8.2 Hz, 1H).

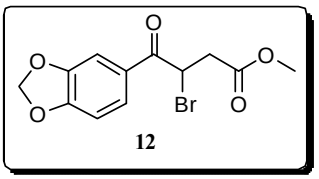
^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 28.03, 33.03, 51.68, 101.74, 107.81, 124.18, 131.39, 148.13, 151.76, 173.18, 195.69.

MS (ESI) (m/z): 259 $[M+Na]^+$

HRMS (ESI): Calculated 237.0757 $(M+H)^+$; Found 237.0751.

Methyl 4-(benzo[1,3]dioxol-5-yl)-3-bromo-4-oxobutanoate (12)

To a mixture of keto ester **11** (16 g, 0.068 mol) and *N*-bromosuccinimide (13.27 g, 0.073 mol) in bottle grade CCl_4 (200 mL) was added NH_4OAc (0.52 g, 0.007 mol).



12

The reaction mixture was refluxed for 10 h and then cooled to room temperature. The mixture was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (20% EtOAc/pet ether) to provide the product **12** (21 g, 98% yield) as white solid. R_f (30% EtOAc/pet ether): 0.6.

Molecular formula: $C_{12}H_{11}O_5Br$

Yield: 98%

Melting Point: 82-84 °C.

IR ($CHCl_3$): 2923, 1734, 1675, 1604, 1504, 1444 cm^{-1}.

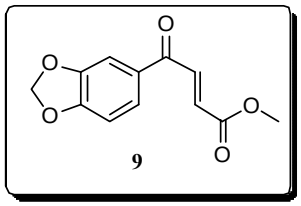
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 3.07 (dd, *J*=5.6, 17.2 Hz, 1H), 3.46 (dd, *J*=8.7, 17.2 Hz, 1H), 3.70 (s, 3H), 5.40 (dd, *J*=5.9, 8.7 Hz, 1H), 6.07 (s, 2H), 6.89 (d, *J*=8.2 Hz, 1H), 7.49 (d, *J*=1.8 Hz, 1H), 7.66 (dd, *J*=1.8, 8.3 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 38.44, 39.04, 52.02, 101.98, 108.03, 108.76, 125.48, 128.38, 148.33, 152.43, 170.63, 190.15.

MS (ESI) (m/z): 336 $[M+Na]^+$

HRMS (ESI) : Calculated 336.9682 $[M+Na]^+$, 338.9667$[(M+2)+Na]^+$; Found 336.9676, 338.9649

(*E*)-Methyl 4-(benzo[1,3]dioxol-5-yl)-4-oxobut-2-enoate (9)



9

To a magnetically stirred solution of bromo compound **12** (15 g, 0.048 mol) in dry DCM, excess triethylamine (45 mL) was added and stirred overnight at room temperature. Evaporation of the solvent under reduced pressure furnished a residue. The residue was purified by flash column chromatography (20% EtOAc/pet ether) to provide the product **9** (11.1 g, quantitative yield) as white solid. R_f (30% EtOAc/pet ether): 0.6.

Molecular formula: $C_{12}H_{10}O_5$

Yield: Quantitative

Melting Point: 123-124 °C

IR ($CHCl_3$): 2945, 2851, 1727, 1661, 1592, 1505, 1458 cm^{-1}.

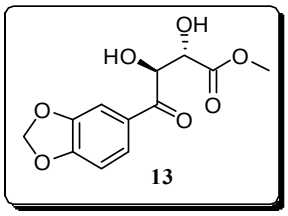
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4) : δ 3.85 (s, 3H), 6.09 (s, 2H), 6.87 (d, *J*=15.4 Hz, 1H), 6.90 (d, *J*=8.2 Hz, 1H), 7.49 (d, *J*=1.8 Hz, 1H), 7.63 (dd, *J*=1.6, 8.1 Hz, 1H), 7.89 (d, *J*=15.4 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4) : 25.17, 102.03, 107.99, 108.29, 125.64, 131.43, 131.55, 136.46, 148.59, 152.58, 165.94, 186.79.

MS (ESI) (m/z): 257 $[M+Na]^+$

HRMS (ESI): Calculated 235.0601 $[M+H]^+$; Found 235.0596

(2*S*,3*S*)-Methyl 4-(benzo[1,3]dioxol-5-yl)-2,3-dihydroxy-4-oxobutanoate (13)



13

To a mixture of $K_3Fe(CN)_6$ (63 g, 0.19 mol), K_2CO_3 (26.1 g, 0.19 mol) and $(DHQD)_2PHAL$ (0.48 g, 0.60 mmol) in ^{t}BuOH-H_2O (1:1, 480 mL) cooled at 0 ^{o}C was added osmium tetroxide (4.8 mL, 0.1 M solution in toluene, 0.4 mol %) followed by methane sulfonamide (6.0 g, 0.06 mol). After stirring for 5 min at 0 ^{o}C, the olefin **9** (15 g, 0.065 mol) was added in one portion. The reaction mixture was stirred at 0 ^{o}C for 3 days and then quenched with solid sodium sulfite (30 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (3 × 150 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (55% EtOAc/pet ether) to provide the product **13** (14.6 g, 85% yield) as white solid. R_f (60% EtOAc/pet ether): 0.5.

Molecular formula: $C_{12}H_{12}O_7$

Yield: 85%

$[\alpha]_D^{25}$: +57.0 (*c* 0.26, $CHCl_3$)

Melting Point: 86-89 °C

IR ($CHCl_3$): 3456 (broad), 2955, 1747, 1675, 1601, 1505, 1441 cm^{-1}.

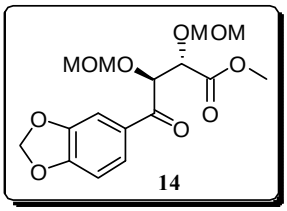
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 3.90 (s, 3H), 4.55 (s, 1H), 5.32 (s, 1H), 6.08 (s, 2H), 6.90 (d, *J*=8.2 Hz, 1H), 7.43 (d, *J*=1.6 Hz, 1H), 7.56 (dd, *J*=1.6, 8.2 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 52.99, 72.57, 73.99, 102.07, 108.27, 124.87, 127.62, 148.56, 152.77, 171.83, 194.82.

MS (ESI) (m/z): 291 $[M+Na]^+$

HRMS (ESI): Calculated 290.0475 $[M+Na]^+$; Found 291.0465.

(2*S*,3*S*)-Methyl 4-(benzo[1,3]dioxol-5-yl)-2,3-bis(methoxymethoxy)-4-oxobutanoate (14)



14

To a stirred solution of the diol **13** (12.5 g, 0.042 mol) in dry DCM (125 mL) was successively added diisopropylethylamine (37.5 mL, 0.215 mol) and MOMCl (12.5 mL, 0.168 mol) drop-wise at 0 °C. The yellow solution was warmed to room temperature and stirred for 3 h under reflux condition. The reaction mixture was cooled and quenched with water and extracted with DCM (3×75 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (60% EtOAc/pet ether) to provide the product **14** (15.05 g, 92% yield) as a colorless liquid. R_f (40% EtOAc/pet ether): 0.6;

Molecular formula: $C_{16}H_{20}O_9$

Yield: 92%

$[\alpha]_D^{25}$: -76.46 (*c* 0.21, $CHCl_3$)

IR ($CHCl_3$): 2924, 1759, 1675, 1604, 1489, 1442 cm^{-1}.

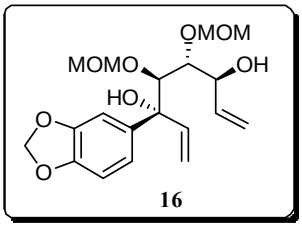
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 3.11 (s, 3H), 3.27 (s, 3H), 3.79 (s, 3H), 4.53-4.73 (m, 5H), 5.26 (d, *J*=3.3 Hz, 1H), 6.07 (s, 2H), 6.87 (d, *J*=8.2 Hz, 1H), 7.53 (d, *J*=1.6 Hz, 1H), 7.72 (dd, *J*=1.7, 8.2 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 51.93, 55.75, 75.21, 79.19, 95.79, 101.68, 107.65, 108.43, 125.16, 129.64, 147.85, 151.82, 169.29, 193.92.

MS (ESI) (m/z): 379 $[M+Na]^+$

HRMS (ESI): Calculated 379.1000 $[M+Na]^+$; Found 379.0987.

(3*R*,4*S*,5*R*,6*S*)-3-(Benzo[1,3]dioxol-5-yl)-4,5-bis(methoxymethoxy)octa-1,7-diene-3,6-diol (16)



16

To a dry round bottom flask under argon was added ketone **14** (11.08 g, 31.08 mmol) in dry THF (200 mL). The solution was cooled to 0 ºC and vinyl magnesium bromide (1M solution in THF) (92 mL, 92.00 mmol) was added dropwise. The reaction was stirred at same temperature for 5 h. The reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate (3×40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by passing through short column (25% EtOAc/pet ether) to provide the lactol **15** (7.08 g, 60% yield) as a brown liquid. R_f (30% EtOAc/pet ether) 0.4. The lactol **15** was immediately subjected to further reduction.

To a stirred solution of lactol **15** (6.2 g, 16.32 mmol) and cerium chloride heptahydrate (27.12 g, 72.92 mmol) in methanol (60 mL) was added sodium borohydride (1.45 g, 38.04 mmol) portionwise at 0 °C. The reaction mixture was stirred for 15 min at that temperature, after which acetone was added to destroy residual sodium borohydride. All volatiles were evaporated *in vacuo* and the residue was partitioned between water and ethyl acetate. The aqueous phase was extracted with ethyl acetate (3×50 mL), the combined organic phase washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (50% EtOAc/pet ether) to provide the product **16** (5.92 g, 95%) as a colorless liquid. R_f (40% EtOAc/pet ether): 0.4.

Molecular formula: $C_{19}H_{26}O_8$

Yield: 95%

$[\alpha]_D^{25}$: +78.62 (*c* 0.57, $CHCl_3$)

IR ($CHCl_3$): 3451, 2927, 2950, 1640, 1540, 1488, 1438 cm^{-1}.

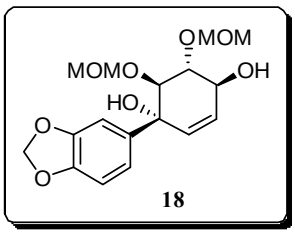
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.35 (s, 3H), 3.40 (s, 3H), 3.49 (dd, *J*=3.2, 6.1 Hz, 1H), 3.95 (t, *J*=5.9 Hz, 1H), 4.02 (d, *J*=3 Hz, 1H), 4.57-4.70 (m, 4H), 5.15-5.45 (m, 4H), 5.63-5.80 (m, 1H), 5.96 (s, 2H), 6.28 (dd, *J*=10.6, 17.0 Hz, 1H), 6.76 (d, *J*=8.1 Hz, 1H), 6.85 (dd, *J*=1.6, 8.2 Hz, 1H), 6.94 (d, *J*=1.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): 56.33, 72.99, 78.56, 80.76, 81.91, 98.17, 98.62, 101.07, 106.31, 108.11, 113.62, 117.60, 118.85, 137.16, 142.06, 146.57, 147.82.

MS (ESI) (m/z): 405 $[M+Na]^+$

HRMS (ESI): Calculated 405.1520 $[M+Na]^+$; Found 405.1507.

(1*R*,4*S*,5*R*,6*S*)-1-(Benzo[1,3]dioxol-5-yl)-5,6-bis(methoxymethoxy)cyclohex-2-ene-1,4-diol (18)



18

To a stirred homogeneous solution of **16** (4 g, 10.52 mmol) in anhydrous DCM (1.6 lit.) was added Grubbs' 1st generation catalyst (0.436 mg, 5 mol %) and the solution was refluxed overnight. The reaction mixture was concentrated *in vacuo* and the residue obtained was purified by flash column chromatography (70% EtOAc/pet ether) to provide the product **18** (3.56 g, 96% yield) as a colorless liquid. R_f (60% EtOAc/pet ether): 0.4.

Molecular formula: $C_{17}H_{22}O_8$

Yield: 96%

$[\alpha]_D^{25}$: -18.89 (*c* 0.66, $CHCl_3$)

IR ($CHCl_3$): 3410 (broad), 2900, 1640, 1487 cm^{-1}.

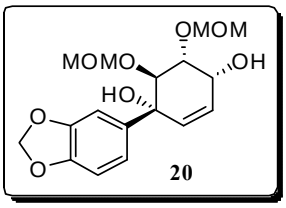
^{1}H NMR (500 MHz, $CDCl_3$) : δ 3.43 (s, 3H), 3.45 (s, 3H), 3.53 (dd, *J*=5.8, 9.8 Hz, 1H), 3.81 (d, *J*=9.5 Hz, 1H), 4.24-4.26 (m, 1H), 4.60-4.65 (m, 3H), 4.70 (d, *J*=6.7 Hz, 1H), 5.72 (dd, *J*=1.8, 10.1 Hz, 1H), 5.91 (dd, *J*=3.0, 10.1 Hz, 1H), 5.95 (s, 2H), 6.77 (d, *J*=8.2 Hz, 1H), 6.88 (dd, *J*=1.8, 8.2 Hz, 1H), 7.03 (d, *J*=1.5 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): 55.91, 56.05, 71.20, 76.07, 82.79, 84.12, 98.05, 98.22, 101.02, 107.33, 108.32, 120.93, 127.47, 131.93, 135.24, 146.93, 147.37.

MS (ESI) (m/z): 377 $[M+Na]^+$

HRMS (ESI): Calculated 377.1207 $[M+Na]^+$; Found 377.1203.

(1*R*,4*R*,5*R*,6*S*)-1-(Benzo[1,3]dioxol-5-yl)-5,6-bis(methoxymethoxy)cyclohex-2-ene-1,4-diol (20)



To a solution of alcohol **18** (3 g, 8.48 mmol) in dry toluene (40 mL), PBu_3 (6.32 mL, 25.44 mmol) and *p*-nitrobenzoic acid (4.52 g, 27.16 mmol) were added at 0 °C and stirred for 15 min, followed by addition of DEAD (5.12 mL, 29.68 mmol) and the reaction mixture was allowed to stir at that temperature for 1 h and then for an additional 2 h at room temperature. The reaction mixture was quenched by adding water and extracted with ethyl acetate (3×20 mL). The combined organic phases were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude ester (3.2 g) was used as such for the next reaction without further purification.

A solution of ester (3.2 g, 6.36 mmol) and NaOMe (0.516 g, 9.32 mmol) in MeOH (40 mL) was stirred at 0 °C for 0.5 h. Several drops of CH_3COOH were added to the reaction mixture to adjust the pH to 7. The solution was diluted with water (80 mL) and extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (60% EtOAc/pet ether) to provide the product **20** (1.952 g, 65% yield over two steps) as semisolid compound. R_f (60% EtOAc/pet ether): 0.3.

Molecular formula: $C_{17}H_{22}O_8$

Yield: 65% (over two steps)

$[\alpha]_D^{25}$: -79.99 (*c* 0.48, $CHCl_3$)

IR ($CHCl_3$): 3410, 2900, 1640, 1487 cm^{-1}.

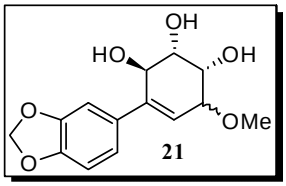
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 3.22 (s, 3H), 3.48 (s, 3H), 3.93-4.03 (m, 2H), 4.15 (d, *J*=6.6 Hz, 1H), 4.34 (d, *J*=6.7 Hz, 1H), 4.49-4.61 (m, 1H), 4.80 (s, 2H), 5.81 (d, *J*=10.4 Hz, 1H), 5.89 (d, *J*=2.0 Hz, 1H), 5.94 (s, 2H), 6.74 (d, *J*=8.2 Hz, 1H), 6.87 (dd, *J*=1.6, 8.2 Hz, 1H), 6.97 (d, *J*=1.4 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 55.76, 56.27, 65.75, 74.13, 78.32, 79.84, 97.19, 97.79, 100.89, 107.39, 108.05, 120.51, 128.87, 133.22, 135.85, 146.85, 147.32.

MS (ESI) (m/z): 377 $[M+Na]^+$

HRMS (ESI): Calculated 377.1207 $[M+Na]^+$; Found 377.1210.

(1*S*,2*S*,3*R*)-4-(benzo[1,3]dioxol-5-yl)-6-methoxycyclohex-4-ene-1,2,3-triol (21)



21

To a stirred solution of **20** (30 mg, 0.085 mmol) in distilled MeOH (5 mL) was added 2-3 drops of con H_2SO_4. The reaction mixture was stirred at room temperature for overnight. The reaction mixture was quenched with saturated aq. $NaHCO_3$ solution. The solvent was evaporated and the separated aqueous layer was extracted with ethyl acetate (3×5 mL) and the combined organic fractions were then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude reaction mixture was residue was purified on a silica gel column using 100% MeOH and DCM as eluent furnished the compound **21** (20 mg, 85%) as a colorless semi-solid compound. R_f (100% EtOAc): 0.2.

Molecular formula: $C_{14}H_{16}O_6$

Yield: 85%

^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 3.42 (s, 3H), 3.98 (bs, 3H), 4.08 (bs, 2H), 4.56 (bs, 1H), 5.91 -5.92 (m, 3H), 6.69-6.73 (m, 1H), 6.89-6.93 (m, 2H).

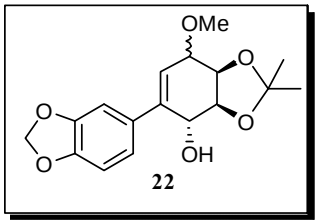
^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): 57.03, 69.71, 70.37, 73.72, 78.47, 101.06, 107.19, 108.12, 120.36, 123.23, 132.56, 138.87, 147.26, 147.65.

MS (ESI) (m/z): 303 $[M+Na]^+$

HRMS (ESI): Calculated 303.2625 $[M+Na]^+$; Found 303.2642

(3a*S*,4*R*,7a*R*)-7-methoxy-2,2-dimethyl-3a,4,7,7a-tetrahydro-[5,5'-bibenzo [1,3]dioxol]-4-ol (22)

To a solution of triol **21** (0.03 g, 0.0107 mmol) in dry DCM (10 mL) was added 2,2-dimethoxy propane (0.016 mL, 0.13 mmol) and catalytic amount *p*-TsOH. The reaction mixture was stirred at 0 °C to room temperature for 1 h. A pinch of $NaHCO_3$



22

was added and stirred for 15 min. The separated aqueous layer was extracted with DCM (3×5 mL) and the combined organic fractions were then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude reaction mixture was residue was purified on a silica gel column using 30% ethyl acetate and pet ether as eluent furnished the compound **22** (33 mg, 95%) as a colorless liquid compound. R_f (50% EtOAc/pet ether): 0.7.

Molecular formula: $C_{17}H_{20}O_6$

Yield: 95%

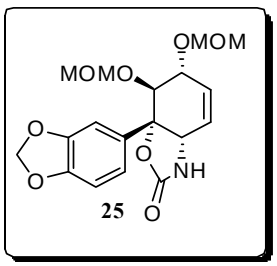
^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 1.29 (s, 3H), 1.34 (s, 3H), 3.45 (s, 3H), 4.05 (d, *J*=8.0 Hz, 1H), 4.47 (d, *J*=12.0 Hz, 1H), 4.64-4.71 (m, 2H), 5.96 (d, *J*=4.0 Hz, 2H), 6.29 (d, *J*=4.0 HZ, 1H), 6.81 (d, *J*=8.0 Hz, 1H), 6.99-7.01 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): 24.38, 26.27, 56.99, 68.82, 74.59, 74.73, 78.49, 101.10, 106.51, 108.27, 108.39, 119.83, 123.20, 134.25, 147.52, 147.85.

MS (ESI) (m/z): 343 $[M+Na]^+$

HRMS (ESI): Calculated 343.3263 $[M+Na]^+$; Found 343.3233.

(3*aS*,6*R*,7*S*,7a*S*)-7a-(Benzo[1,3]dioxol-5-yl)-6,7-bis(methoxymethoxy)-3,3a,7,7a-tetrahydrobenzooxazol-2(6*H*)-one (25)



25

A magnetically stirred solution of compound **20** (1.2 g, 3.38 mmol) in dry DCM (20 mL) maintained under an atmosphere of nitrogen was cooled to 0 °C and then treated with DBU (1.0 mL, 6.76 mmol) and trichloroacetonitrile (1.0 mL, 10.16 mmol). The reaction mixture was stirred at 0 °C for 0.5 h, then diluted with DCM (10 mL) and treated with NH_4Cl (10 mL of a saturated aqueous solution). The separated aqueous layer was extracted with DCM (3×10 mL) and the combined organic fractions were then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by passing through a short column of SiO_2 (15% EtOAc/pet ether) to provide the trichloroacetimidate as a colorless liquid. R_f (20% EtOAc/pet ether) 0.4. trichloroacetimidate was put for further reaction.

A solution of trichloroacetimidate (1.6 g), in xylene (10 mL) solid K_2CO_3 (1.6 g) was added and heated to reflux for 4 h. The solvent was removed, and the residue was purified by flash column chromatography (70% EtOAc/pet ether) to provide the product **25** (1.26 g, 98% yield) as a semisolid compound. R_f (70% EtOAc/pet ether): 0.3.

Molecular formula: $C_{18}H_{21}O_8N$

Yield: 98% (over two steps)

$[\alpha]_D^{25}$: -33.15 (*c* 0.26, $CHCl_3$)

IR ($CHCl_3$): 2924, 1760, 1505, 1442 cm^{-1}.

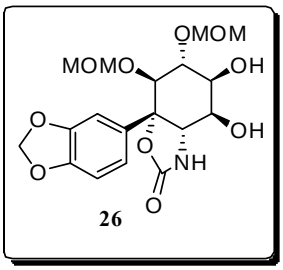
^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 3.37 (s, 3H), 3.46 (s, 3H), 3.91 (d, *J*=8.3 Hz, 1H), 4.07 (d, *J*=8.8 Hz, 1H), 4.47 (d, *J*=3.01, 1H), 4.68 (q, *J*=6.8 Hz, 2H), 4.75 (d, *J*=6.5 Hz, 1H), 4.84 (d, *J*=6.5 Hz, 1H), 5.89-5.92 (m, 1H), 5.97 (s, 2H), 6.04 (d, *J*=10 Hz, 1H), 6.70 (dd, *J*=1.5, 8.3 Hz, 1H), 6.77 (d, *J*=8 Hz, 1H), 6.86 (d, *J*=1.2 Hz, 1H), 6.97 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): 55.52, 56.20, 58.59, 75.55, 77.78, 85.89, 97.20, 97.63, 101.13, 107.16, 107.90, 118.60, 123.67, 131.48, 133.02, 147.59, 147.64, 157.42.

MS (ESI) (m/z): 402 $[M+Na]^+$

HRMS (ESI): Calculated 402.1159 $[M+Na]^+$; Found 402.1149.

(3a*S*,4*S*,5*S*,6*R*,7*S*,7a*S*)-7a-(Benzo[1,3]dioxol-5-yl)-4,5-dihydroxy-6,7-bis(methoxymethoxy)hexahydrobenzo[d]oxazol-2(3*H*)-one (26)



26

To a cold (0 °C), magnetically stirred solution of carbamate **25** (1.2 g, 3.16 mmol) in acetonitrile: water (9:1) (20 mL), catalytic amount of OsO_4 (0.1 mL, 0.1 M solution in toluene) was added in presence of *N*-methylmorpholine-*N*-oxide (NMO) (1.28 g, 948 mmol) as a co-oxidant and stirred for 4 days at rt. The reaction was quenched with saturated aq. Na_2SO_3 (10 mL) solution and again stirred for 30 min. The solvent was evaporated and the residue was purified by flash column chromatography (100% EtOAc) to

provide the diol compound **26** (1.31 g, 99%) as white solid, melting point 68-69 °C. R_f (100% EtOAc): 0.2.

Molecular formula: $C_{18}H_{23}O_{10}N$

Yield: 99%

$[\alpha]_D^{25}$: -7.10 (*c* 0.16, $CHCl_3$)

Melting Point: 68-69 °C

IR ($CHCl_3$): 3403, 2925, 1744, 1492, 1442 cm^{-1}.

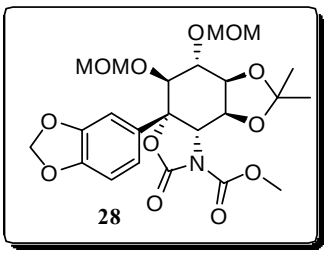
^{1}H NMR (400 MHz, DMSO-d_6): δ 3.19 (s, 3H), 3.24 (s, 3H), 3.65 (dd, *J*=3.8, 9.3 Hz, 1H), 3.78-3.87 (m, 3H), 3.99 (d, *J*=9.3 Hz, 1H), 4.55 (s, 2H), 4.57 (d, *J*=6.8 Hz, 1H), 4.74 (d, *J*=6.8 Hz, 1H), 6.01 (s, 2H), 6.91 (d, *J*=8.3 Hz, 1H), 7.06 (dd, *J*=1.8, 8.3 Hz, 1H), 7.13 (d, *J*=1.5 Hz, 1H)

^{13}C NMR (100 MHz, DMSO-d_6): 55.26, 55.43, 61.65, 69.80, 72.37, 78.44, 79.04, 86.11, 95.31, 95.95, 101.24, 106.91, 107.67, 119.58, 134.31, 146.77, 147.10, 156.61.

MS (ESI) (m/z): 436 $[M+Na]^+$

HRMS (ESI): Calculated 436.1214 $[M+Na]^+$; Found 436.1209.

(3a*S*,4*R*,5*S*,5a*S*,8a*S*,8b*S*)-methyl-5a-(benzo[1,3]dioxol-5-yl)-4,5-bis(methoxymethoxy)-2,2-dimethyl-7-oxohexahydro-[1,3]dioxolo[4',5':5,6]benzo[1,2-d]oxazole-8(7H)-carboxylate (28)



28

To a solution of diol **26** (0.9 g, 2.18 mmol) in dry DCM (10 mL) was added 2,2-dimethoxypropane (0.3 mL, 2.61 mmol) and catalytic amount of *p*-TsOH. The reaction mixture was stirred at 0 °C to room temperature for 1 h. A pinch of $NaHCO_3$ was added and stirred for 15 min. The separated aqueous layer was extracted with DCM (3×10 mL) and the combined organic fractions were then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude reaction mixture was used in the next reaction without further purification.

To a stirred solution of crude acetonide protected diol (0.9 g) in dry DCM (10 mL) was added triethylamine (3 mL) and catalytic amount of DMAP. Then dimethyldicarbonate (0.6 mL) was added and stirred for 1 h at room temperature. The solvent was evaporated and the crude residue was purified by flash column chromatography (50% EtOAc/pet ether) to provide the compound **28** (1.08 g, 97%) as colorless liquid. R_f (50% EtOAc/pet ether): 0.5.

Molecular formula: $C_{23}H_{29}O_{12}N$

Yield: 97%

$[\alpha]_D^{25}$: -14.4 (*c* 0.18, $CHCl_3$)

IR ($CHCl_3$): 2923, 2853, 1827, 1805, 1735, 1441 cm^{-1}.

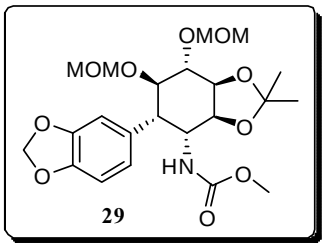
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 3.19 (s, 3H), 3.24 (s, 3H), 3.65 (dd, *J*=3.8, 9.3 Hz, 1H), 3.78-3.87 (m, 3H), 3.99 (d, *J*=9.3 Hz, 1H), 4.55 (s, 2H), 4.57 (d, *J*=6.8 Hz, 1H), 4.74 (d, *J*=6.8 Hz, 1H), 6.01 (s, 2H), 6.91 (d, *J*=8.3 Hz, 1H), 7.06 (dd, *J*=1.8, 8.3 Hz, 1H), 7.13 (d, *J*=1.5 Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 24.92, 26.30, 54.03, 55.70, 55.85, 62.00, 72.61, 73.19, 75.03, 76.37, 83.26, 95.69, 96.40, 101.28, 107.35, 107.80, 109.58, 119.49, 132.19, 147.76, 149.76, 151.33.

MS (ESI) (m/z): 534 $[M+Na]^+$

HRMS (ESI): Calculated 534.1582 $[M+Na]^+$; Found 534.1569.

Methyl((3a*S*,4*R*,5*S*,6*R*,7*S*,7a*S*)-6,7-bis(methoxymethoxy)-2,2-dimethyl-3a,4,5,6,7,7a-hexahydro-[5,5'-bibenzo [1,3]dioxol]-4-yl)carbamate (29)



29

A mixture of **28** (0.2 g, 0.39 mmol), catalytic amount of 10% palladium hydroxide on charcoal and 2-3 drops of CH_3CO_2H in absolute ethanol EtOH (5 mL) was hydrogenated overnight at 35 *psi,*. After filtration and evaporation of the solvent, the crude residue was purified by flash column chromatography (60% EtOAc/pet ether) to provide the deoxygenated product **29** (0.182 g, 99%) as a colourless liquid. R_f (50% EtOAc/pet ether): 0.7.

Molecular formula: $C_{22}H_{31}O_{10}N$

Yield: 99%

$[\alpha]_D^{25}$: + 16.4 (*c* 0.39, $CHCl_3$)

IR ($CHCl_3$): 2927, 1717 (broad), 1491, 1444 cm^{-1}.

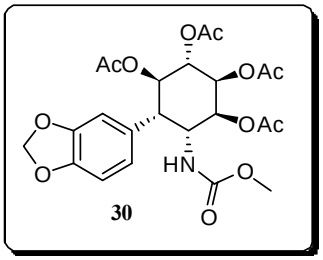
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.26 (s, 3H), 1.36 (s, 3H), 2.95 (s, 3H), 3.25-3.27 (m, 1H), 3.47 (s, 3H), 3.60 (bs, 2H), 4.02-4.25 (m, 4H), 4.38 (d, *J*=7 Hz, 1H), 4.45-4.47 (m, 1H), 4.67 (d, *J*= 7 Hz, 1H), 4.83 (s, 2H), 5.93 (s, 2H), 6.75-6.79 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 24.07, 26.67, 44.31, 52.16, 53.46, 55.29, 56.11, 75.21, 75.65, 76.35, 76.70, 95.25, 95.99, 100.88, 108.13, 108.90, 121.94, 133.75, 146.46, 147.63, 156.47.

MS (ESI) (m/z): 492 $[M+Na]^+$

HRMS (ESI): Calculated 492.1840 $[M+Na]^+$; Found 492.1835.

(1*S*,2*S*,3*S*,4*R*,5*S*,6*R*)-5-(Benzo[1,3]dioxol-5-yl)-6-((methoxycarbonyl)amino)cyclohexane-1,2,3,4-tetrayl tetraacetate (30)



30

To a stirred solution of **29** (0.180 g, 0.384 mmol) in distilled MeOH (5 mL) was added 2-3 drops of con HCl. The reaction mixture was stirred at room temperature for 4 h. The solvent was evaporated and the crude reaction mixture was used in the next reaction without further purification.

To a flask charged with crude tetrol (0.160 g, 0.14 mmol) and pyridine (1.5 mL), was added acetic anhydride (1.5 mL) at room temperature. After overnight stirring at room temperature, the reaction mixture was concentrated under reduced pressure and was purified by flash column chromatography (50% EtOAc/pet ether) to provide the compound **30** (0.174 g, 99%) as colourless crystals. R_f (50% EtOAc): 0.8.

Molecular formula: $C_{23}H_{27}O_{12}N$

Yield: 99%

$[\alpha]_D^{25}$: -8.92 (*c* 0.16, $CHCl_3$).

Melting Point: 199-202 °C

IR ($CHCl_3$): 2923, 1752 (broad), 1445 cm^{-1}.

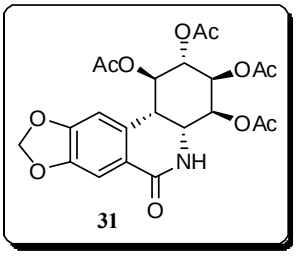
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.86 (s, 3H), 1.99 (s, 3H), 2.02 (s, 3H), 2.22 (s, 3H), 3.48 (s, 3H), 3.53 (dd, *J*=3.5, 12.5 Hz, 1H), 5.43-5.50 (m, 3H), 5.90 (s, 2H), 5.95-6.00 (m, 1H), 5.50 (d, *J*=10 Hz, 1H), 6.69-6.70 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 20.39, 20.43, 20.53, 20.98, 45.17, 52.21, 53.75, 68.88, 70.06, 70.52, 71.83, 100.93, 108.23, 108.63, 121.19, 146.77, 147.65, 156.25, 169.25, 170.31.

MS (ESI) (m/z): 532 $[M+Na]^+$

HRMS (ESI): Calculated 532.1425 $[M+Na]^+$; Found 532.1419.

(1*R*,2*S*,3*S*,4*S*,4a*R*,11b*S*)-6-Oxo-1,2,3,4,4a,5,6,11b-octahydro-[1,3]dioxolo[4,5-j]phenanthridine-1,2,3,4-tetrayl tetraacetate (31)



31

To a solution of tetraacetate **30** (0.03 g, 0.059 mmol) in CH_2Cl_2 (3 mL) were added trifluoromethanesulfonic anhydride (0.035 mL, 0.19 mmol) and DMAP (0.022 g, 0.177 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 16 h (total consumption of starting material), and then the solvent was removed in *vacuo*. THF (2 mL) and 2 N aq. HCl (0.2 mL) were added, and the mixture was stirred at room temperature for 6 h. The reaction mixture was quenched with saturated aq. $NaHCO_3$. The solvent was evaporated and the crude reaction mixture was purified by flash column chromatography (70% EtOAc/pet ether) to provide the compound **31** (0.02 g, 70%) as a colorless semi-solid compound. R_f (60% EtOAc\pet ether): 0.4.

Molecular formula: $C_{23}H_{27}O_{12}N$

Yield: 70%

$[\alpha]_D^{25}$: + 62.62 (*c* 0.25, $CHCl_3$)

IR ($CHCl_3$): 2924, 1752 (broad), 1660, 1465 cm^{-1}.

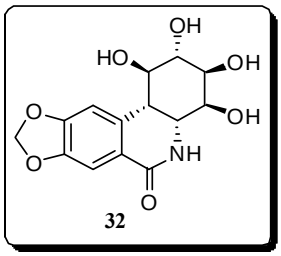
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.98 (s, 3H), 2.02 (s, 3H), 2.05 (s, 3H), 2.21 (s, 3H), 3.18 (dd, *J*=3.0, 10.7 Hz, 1H), 4.04 (t, *J*=3.7 Hz, 1H), 5.31 (t, *J*=10.1 Hz, 1H), 5.38 (dd, *J*=3.0, 10.7 Hz, 1H), 5.52 (t, *J*= 10.1 Hz, 1H), 5.57 (t, *J*= 3.4 Hz, 1H), 6.05 (s, 2H), 6.30 (s, 1H), 6.65 (s, 1H), 7.56 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): 20.51, 20.55, 20.62, 20.76, 39.89, 53.06, 68.71, 69.14, 70.13, 72.42, 101.90, 107.99, 108.81, 122.23, 132.51, 148.10, 151.11, 165.21, 168.97, 169.39, 169.97, 170.23.

MS (ESI) (m/z): 500 $[M+Na]^+$

HRMS (ESI): Calculated 500.1163 $[M+Na]^+$; Found 500.1161.

(1*R*,2*S*,3*S*,4*S*,4a*R*,11b*S*)-1,2,3,4-Tetrahydroxy-1,3,4,4a,5,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-6(2H)-one (32)



32

To a suspension of K_2CO_3 (0.075 g) in methanol (5 mL) was added compound **31** (0.015 g, 0.048 mmol). The reaction mixture was stirred at room temperature until total consumption of the starting material (15 h), and then the precipitate was removed by filtration. The solvent was evaporated and the residue was purified on a silica gel column affording **32** (0.008 g, 85%). R_f (20% MeOH/DCM): 0.2.

Molecular formula: $C_{14}H_{15}NO_7$

Yield: 85%

$[\alpha]_D^{25}$: + 5.9 (*c* 0.49, MeOH)

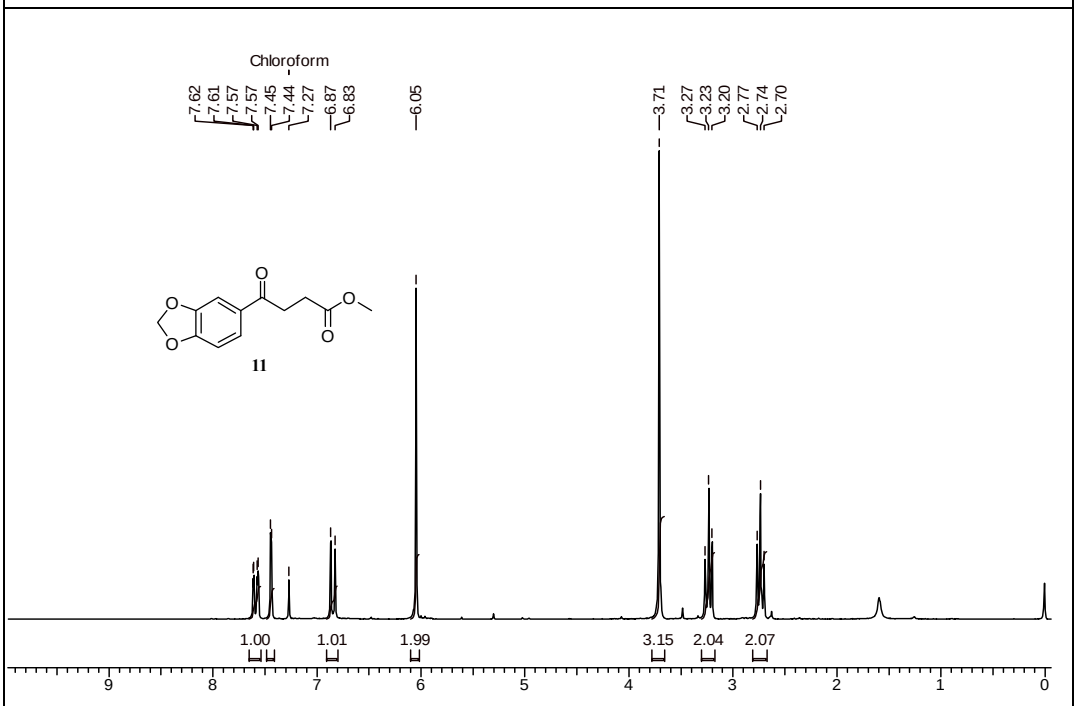
^{1}H NMR (500 MHz, DMSO-d_6): δ 2.72 (dd, *J*=4.0, 10.4 Hz, 1H), 3.07 (dd, *J*=8.2, 10.1 Hz, 1H), 3.43-3.48 (m, 3H), 3.92 (m, 1H), 6.03 (d, *J*=7.6 Hz, 2H), 6.82 (s, 1H), 7.24 (s, 1H).

^{13}C NMR (125 MHz, DMSO-d_6): 41.16, 55.50, 70.07, 71.14, 73.85 (two CH merged), 101.97, 106.84, 110.65, 122.65, 137.44, 147.00, 149.94, 165.07.

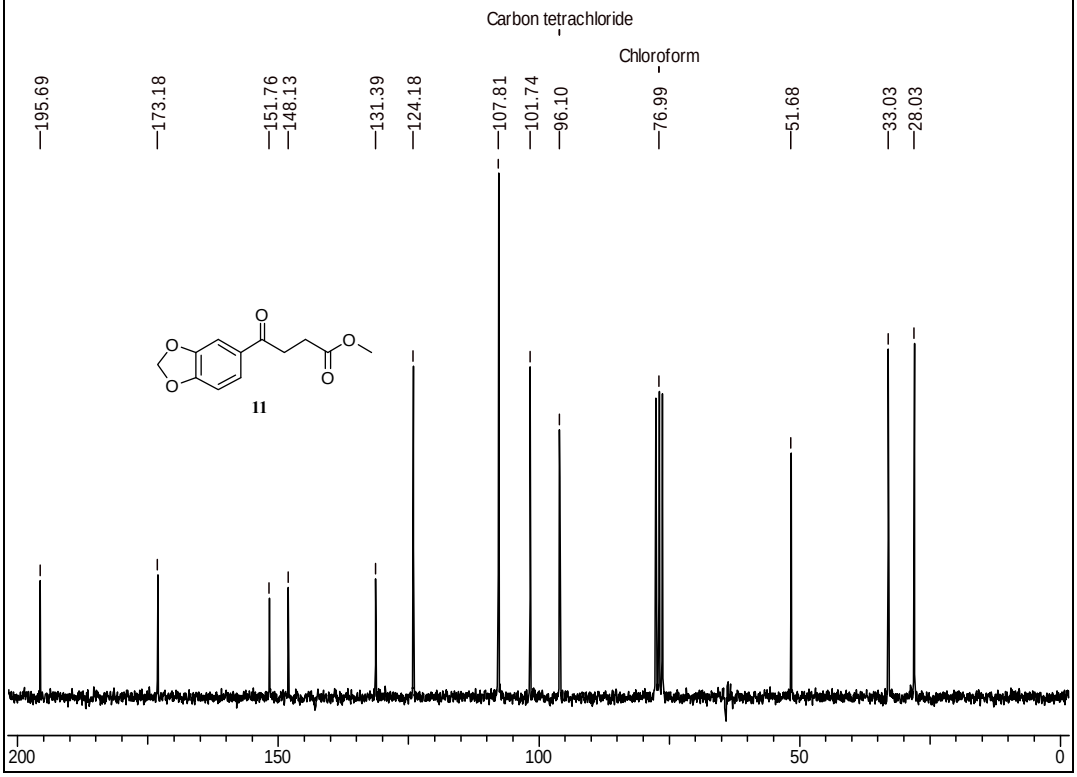
MS (ESI) (m/z): 332 $[M+Na]^+$

3.2.4. NMR Spectra

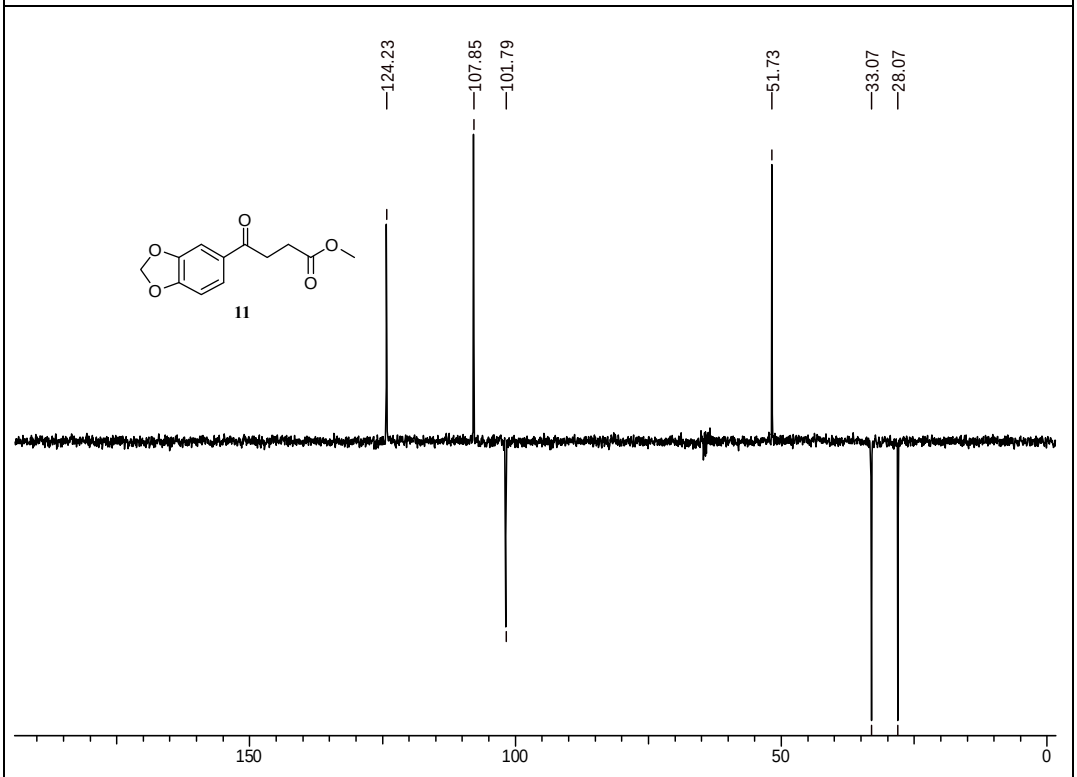
^{1}H NMR spectrum of compound **11** ($CDCl_3$ + CCl_4, 200 MHz)



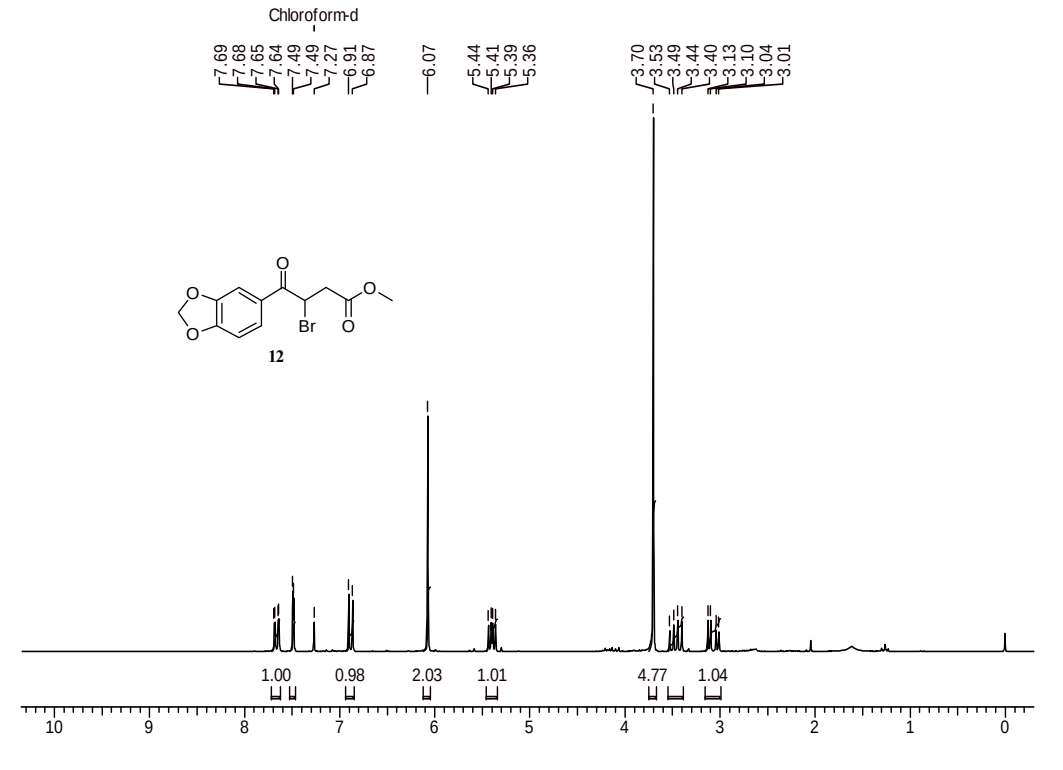
^{13}C NMR spectrum of compound **11** ($CDCl_3$ + CCl_4, 50 MHz)



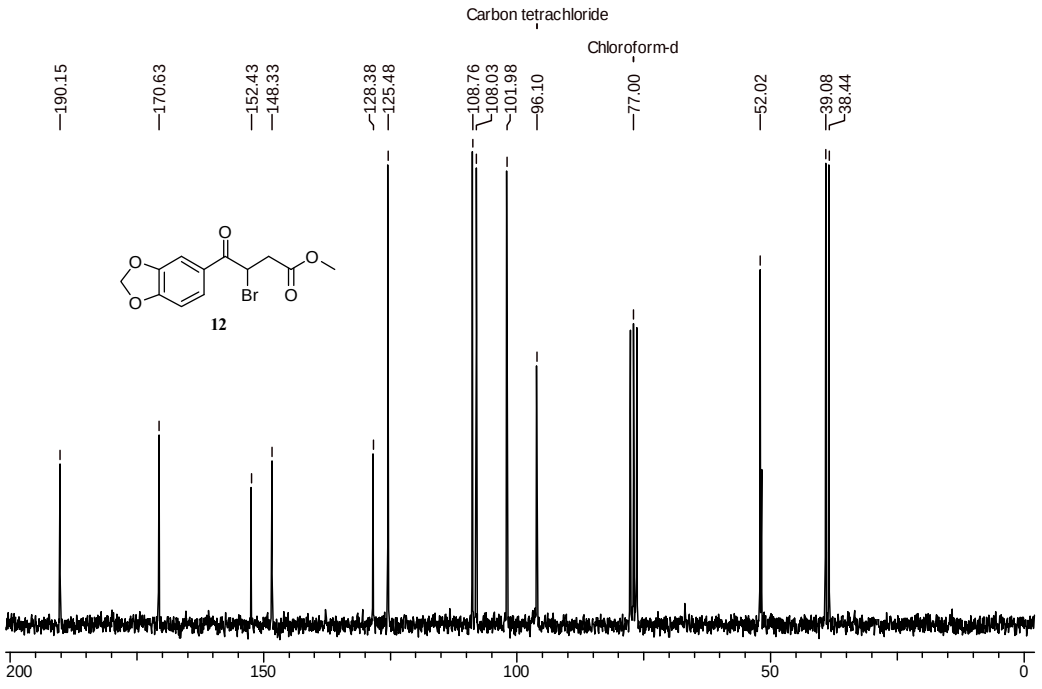
DEPT NMR spectrum of compound **11** ($CDCl_3$ + CCl_4, 50 MHz)



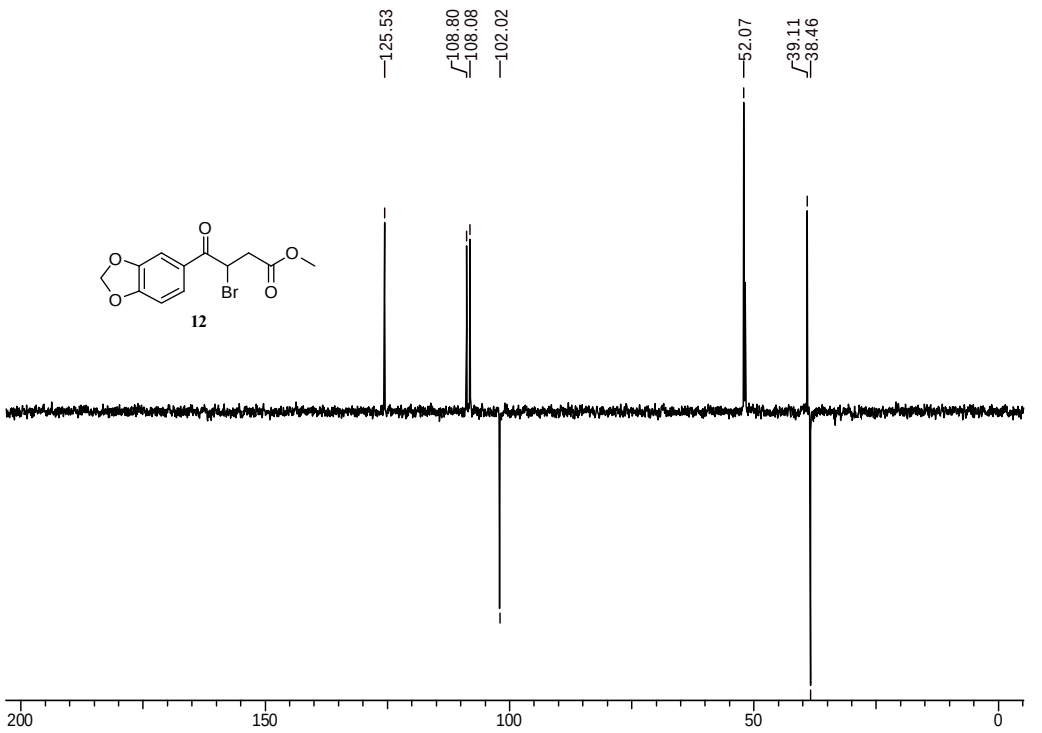
^{1}H NMR spectrum of compound **12** ($CDCl_3$ + CCl_4, 200 MHz)



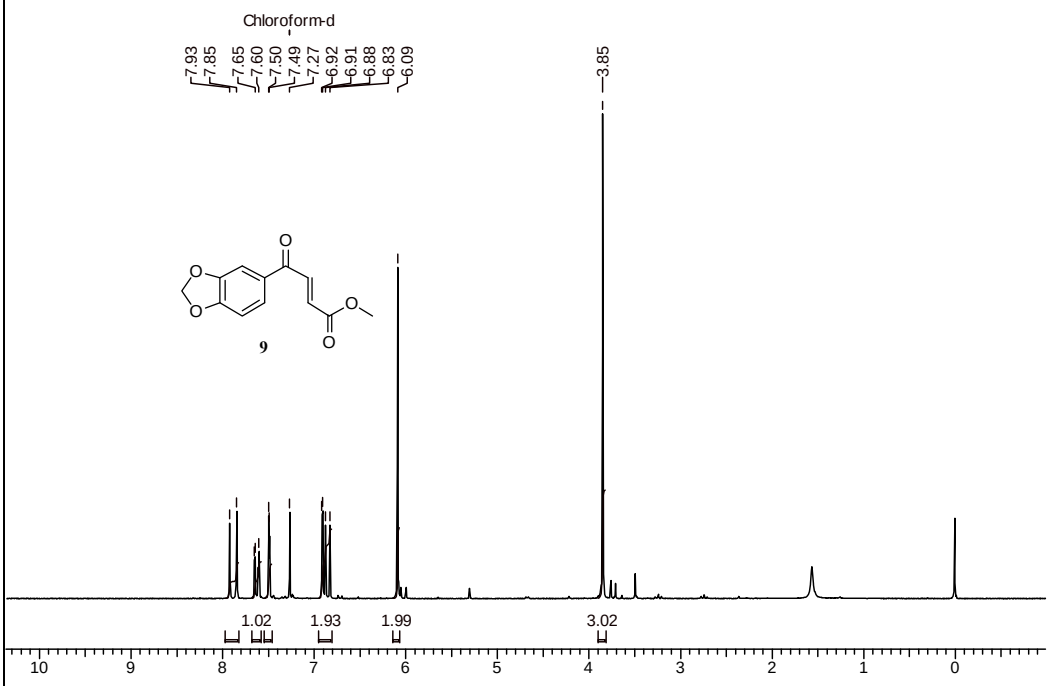
^{13}C NMR spectrum of compound **12** ($CDCl_3$ + CCl_4, 50 MHz)



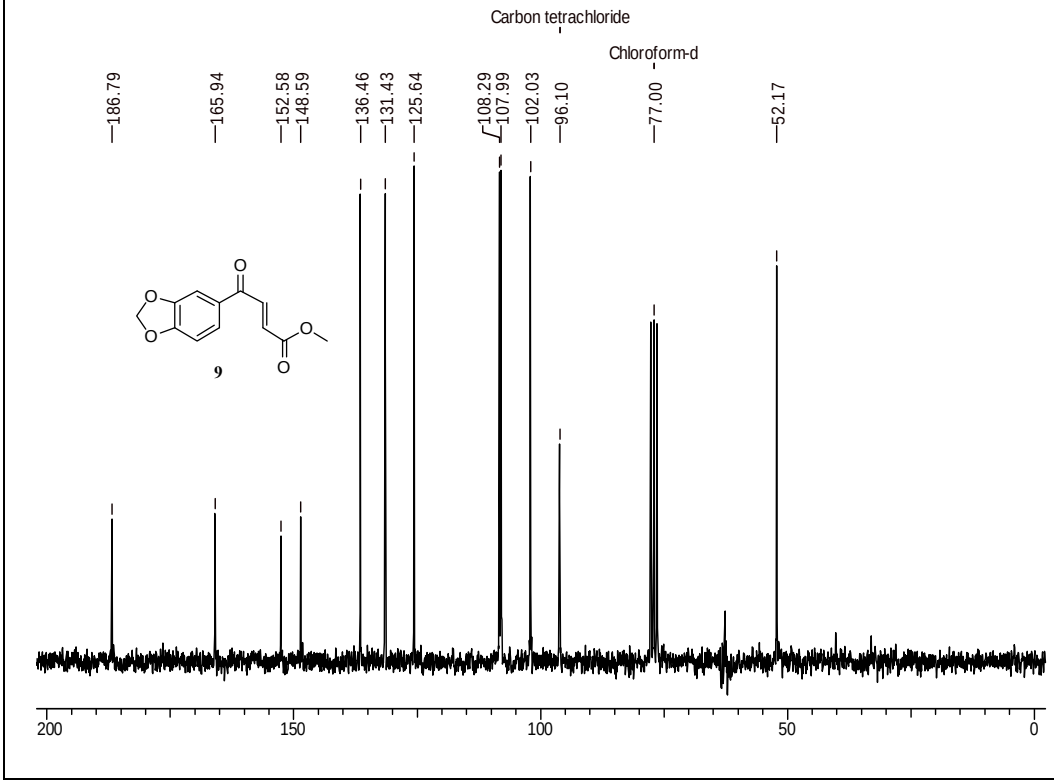
DEPT spectrum of compound **12** ($CDCl_3$ + CCl_4, 50 MHz)



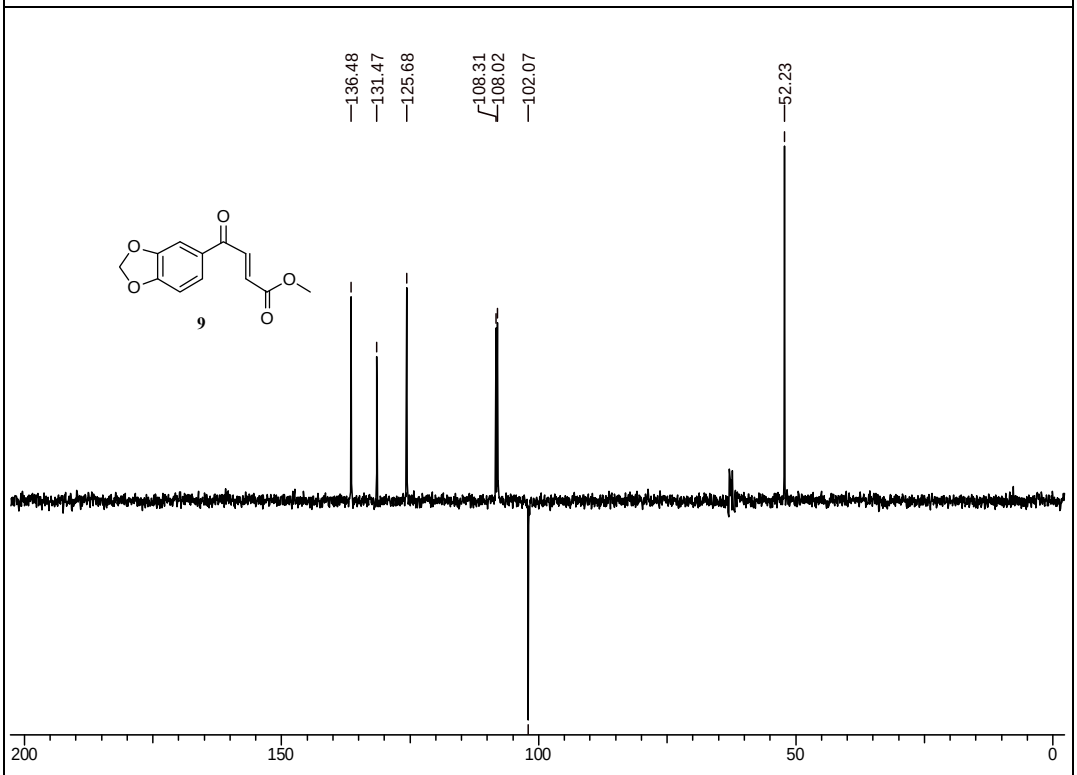
^{1}H NMR spectrum of compound **9** ($CDCl_3$ + CCl_4, 200 MHz)



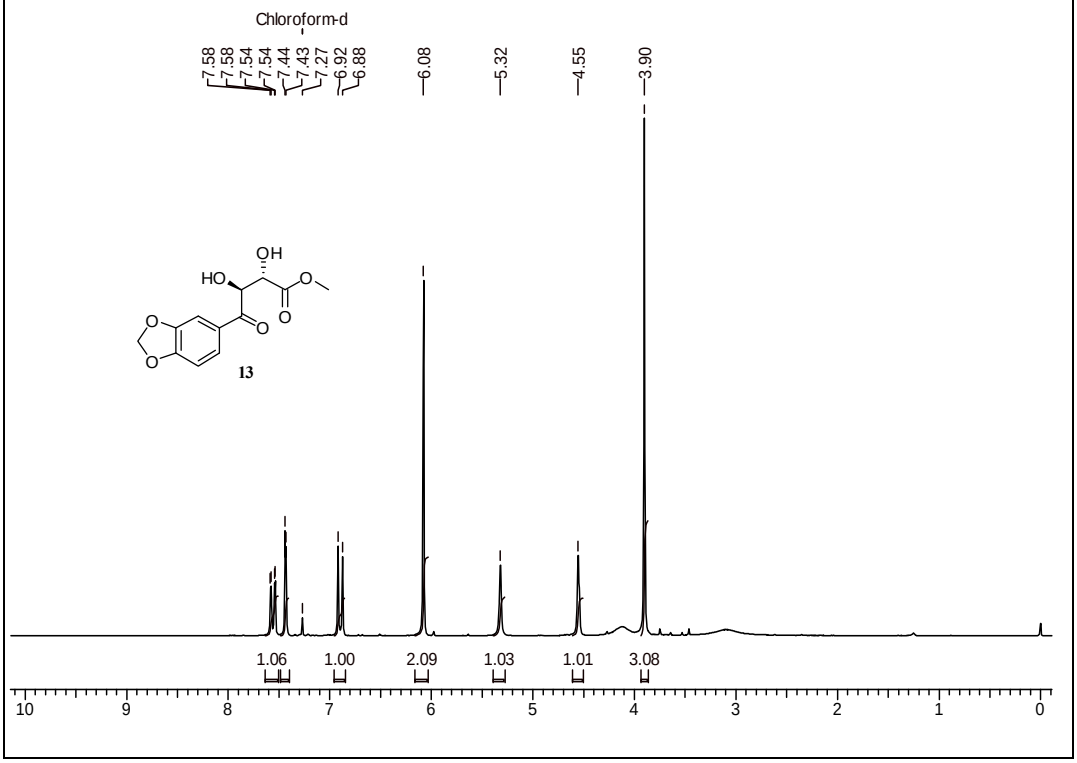
^{13}C NMR spectrum of compound **9** ($CDCl_3$ + CCl_4, 50 MHz)



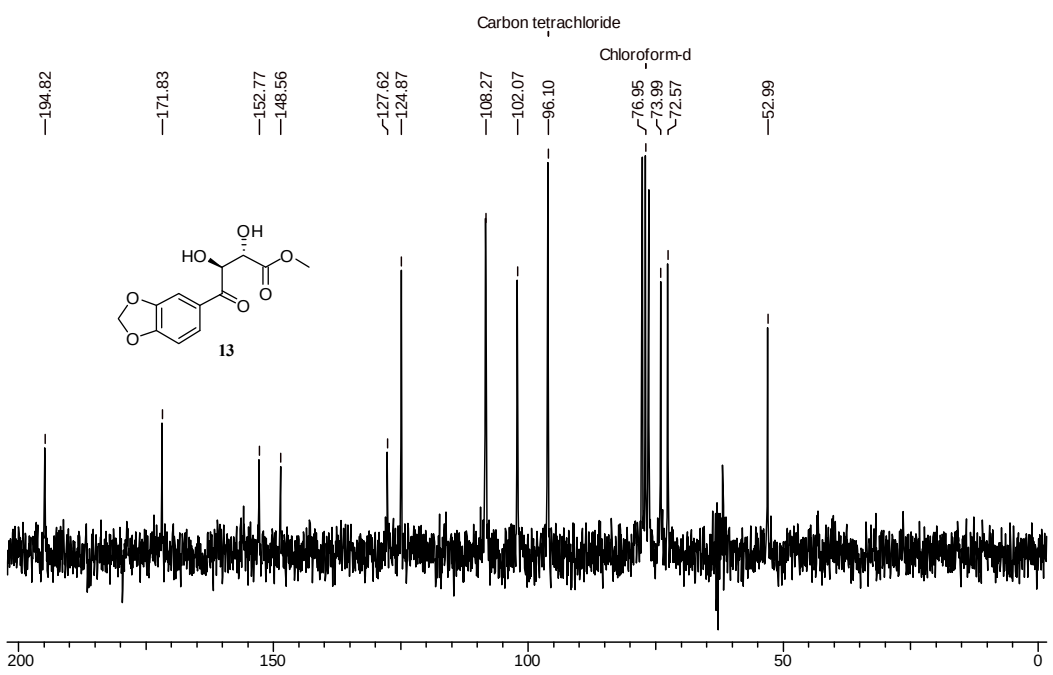
DEPT spectrum of compound **9** ($CDCl_3$ + CCl_4, 50 MHz)



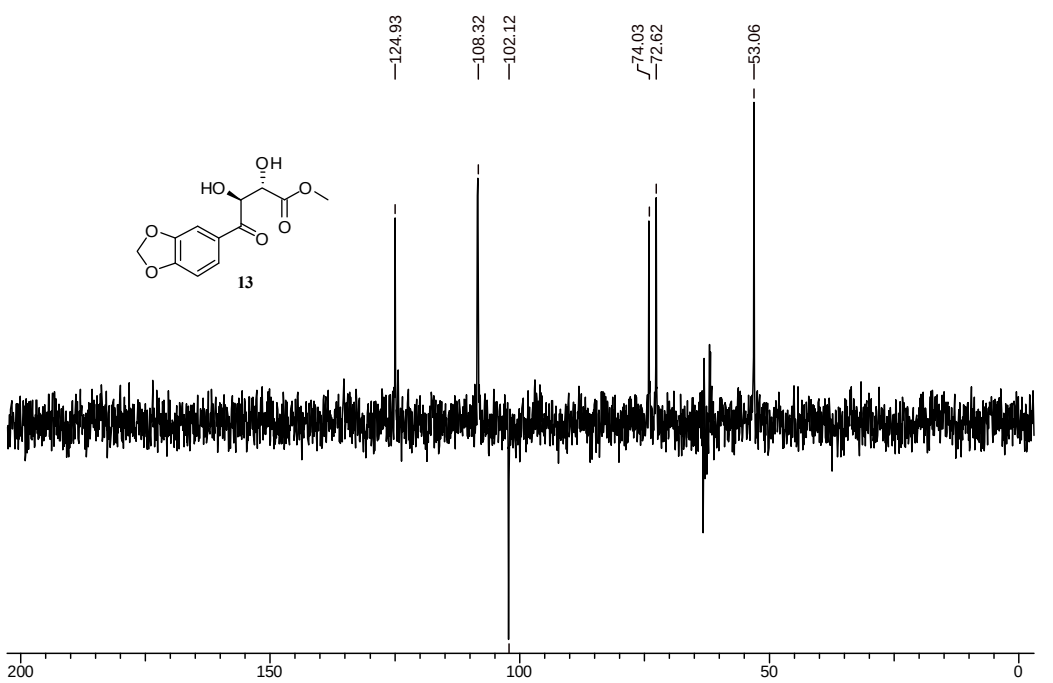
^{1}H NMR spectrum of compound **13** ($CDCl_3$ + CCl_4, 200 MHz)



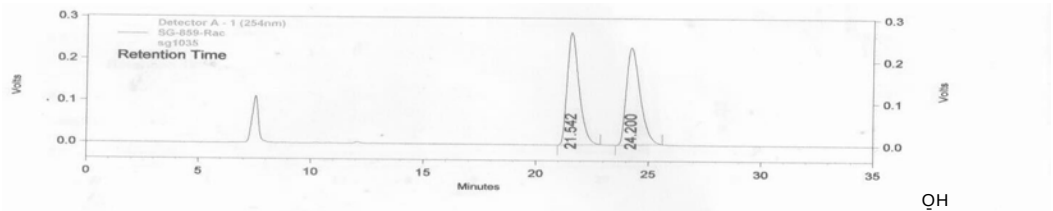
^{13}C NMR spectrum of compound **13** ($CDCl_3$ + CCl_4, 50 MHz)

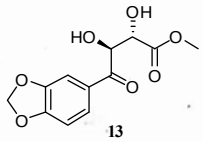


DEPT spectrum of compound **13** ($CDCl_3$ + CCl_4, 50 MHz)



HPLC chromatogram of racemic diol **13**





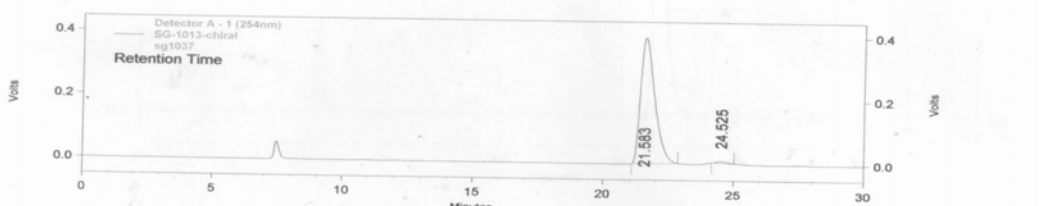
13

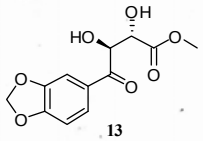
Detector A - 1 (254nm)

Retention Time	C Area	Area %
21.542	9793533	49.954
24.200	9811615	50.046
Totals	19605148	100.000

Project Leader : Dr. S. P. Chavan
Column :Chiralcel OJ-H (250x4.6 mm)
Mobile Phase :IPA: pet ether (40:60)
Wavelength :254nm
Flow Rate :0.5ml/min (515psi)
conc. :1. mg/1mL
Inj vol- :10 ul

HPLC chromatogram of chiral diol **13**





13

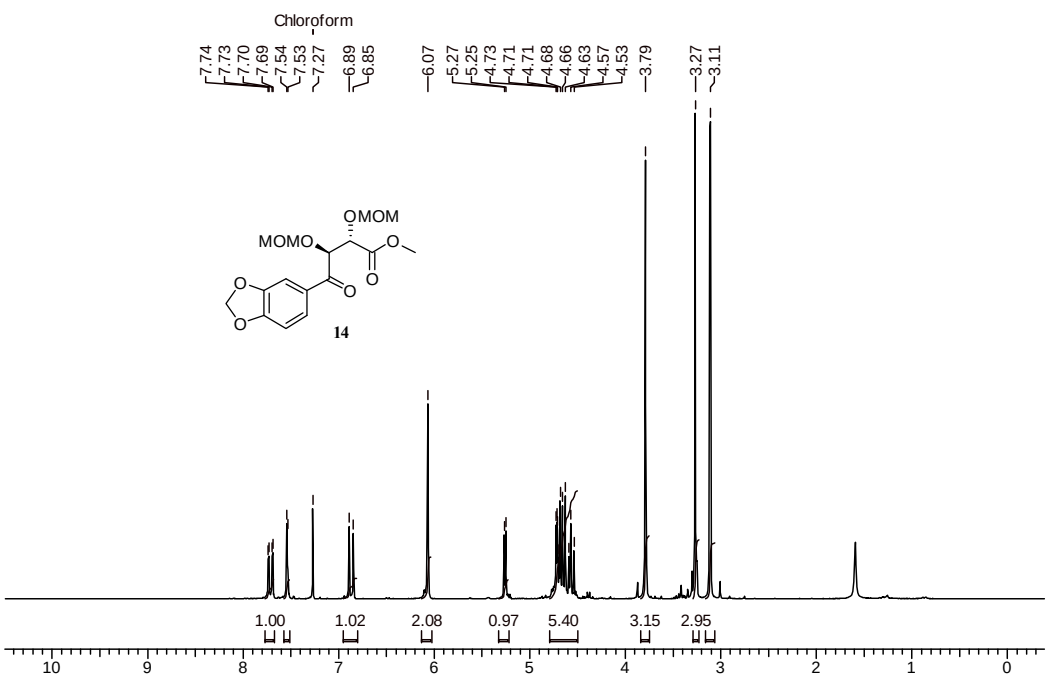
Detector A - 1 (254nm)

Retention Time	C Area	Area %
21.583	14952892	99.164
24.525	126055	0.836
Totals	15078947	100.000

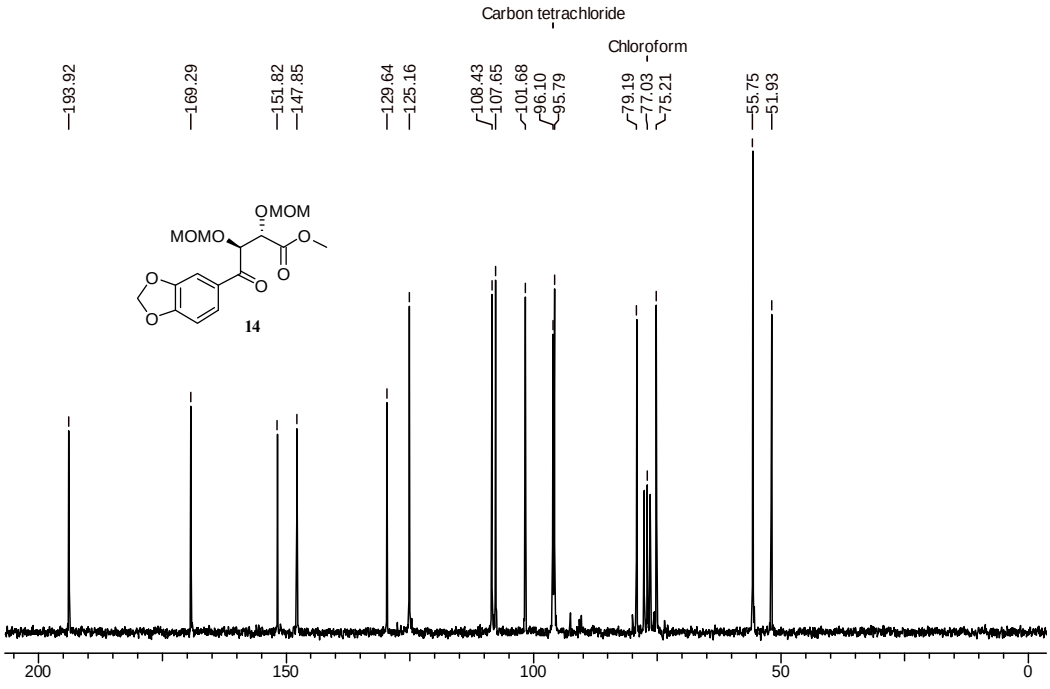
Project Leader : Dr. S. P. Chavan
Column :Chiralcel OJ-H (250x4.6 mm)
Mobile Phase :IPA: pet ether (40:60)
Wavelength :254nm
Flow Rate :0.5ml/min (515psi)
conc. :1. mg/1mL
Inj vol- :10 ul

"1.ee - 98.328

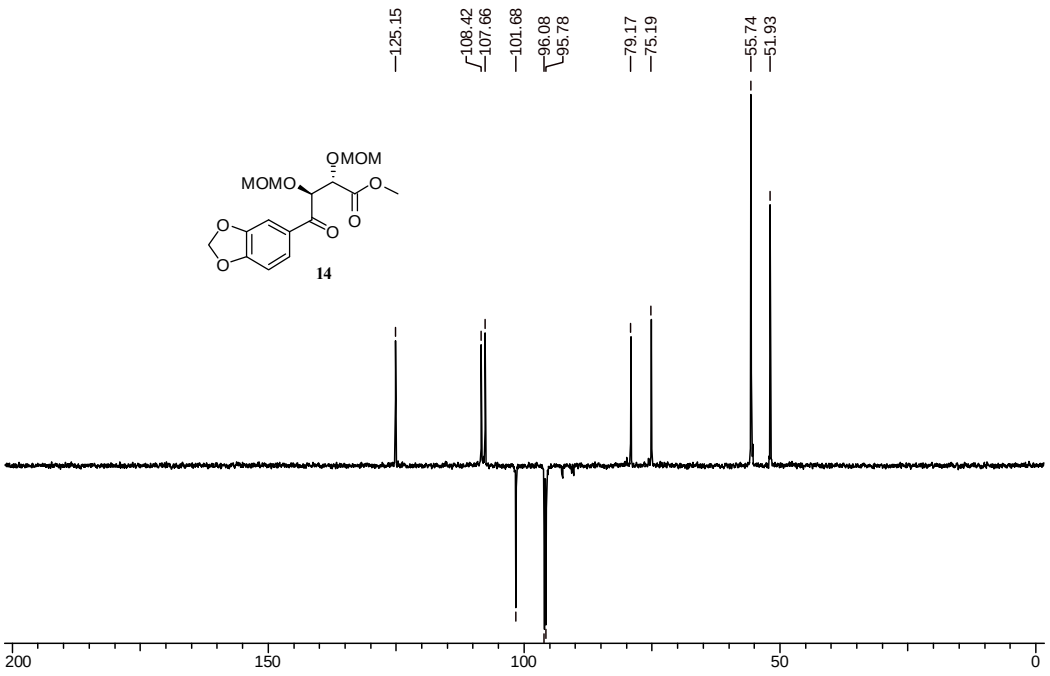
^{1}H NMR spectrum of compound **14** ($CDCl_3$ + CCl_4, 200 MHz)



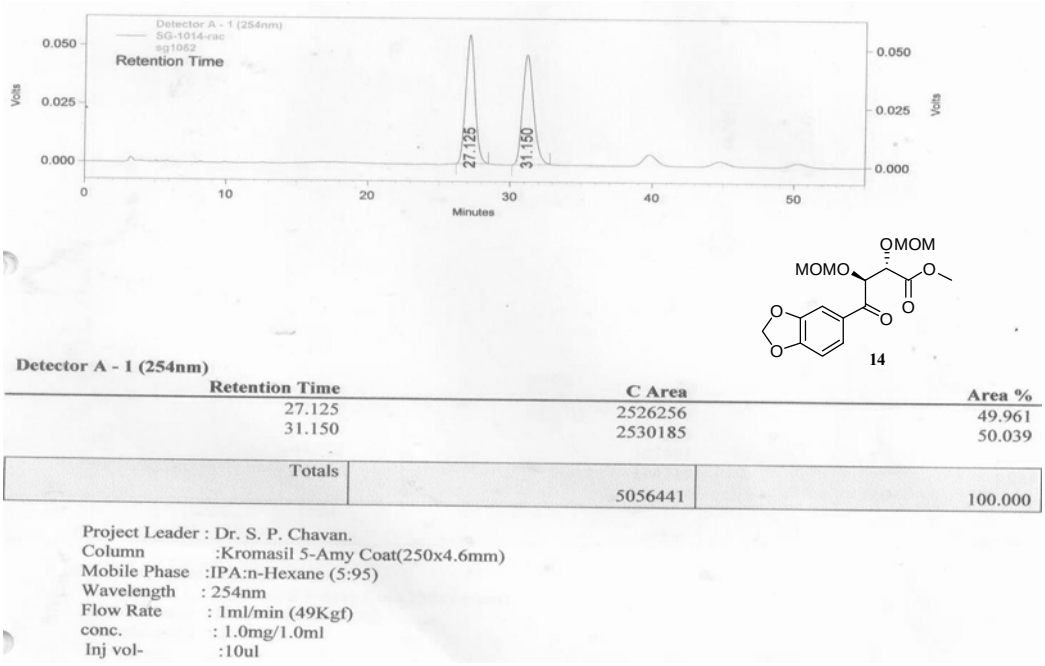
^{13}C NMR spectrum of compound **14** ($CDCl_3$ + CCl_4, 50 MHz)



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



HPLC chromatogram of racemic diol **14**

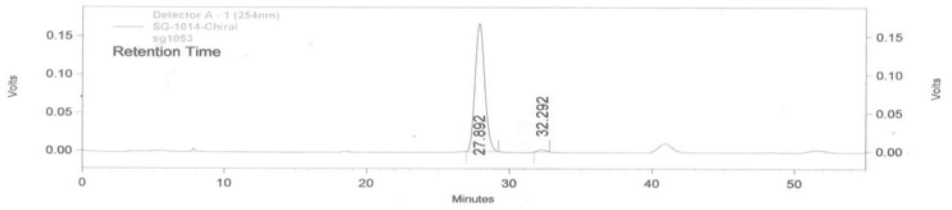


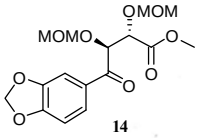
Detector A - 1 (254nm)

Retention Time	C Area	Area %
27.125	2526256	49.961
31.150	2530185	50.039
Totals	5056441	100.000

Project Leader : Dr. S. P. Chavan.
Column :Kromasil 5-Amy Coat(250x4.6mm)
Mobile Phase :IPA:n-Hexane (5:95)
Wavelength : 254nm
Flow Rate : 1ml/min (49Kgf)
conc. : 1.0mg/1.0ml
Inj vol- :10ul

HPLC chromatogram of chiral diol **14**





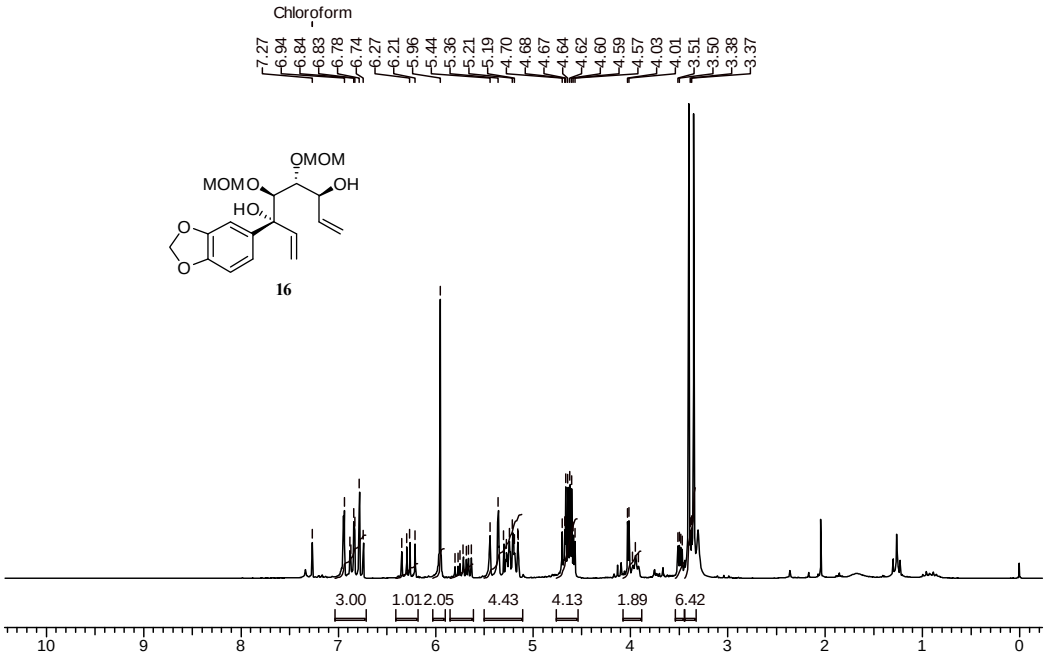
14

Detector A - 1 (254nm)

Retention Time	C Area	Area %
27.892	7859571	98.815
32.292	94277	1.185
Totals	7953848	100.000

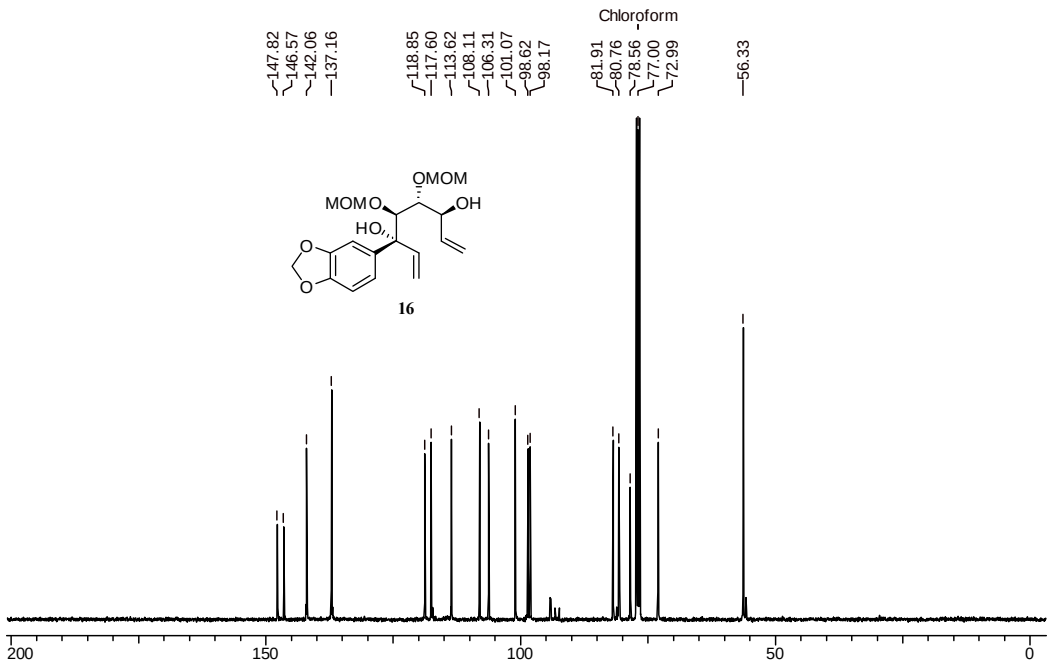
Project Leader : Dr. S. P. Chavan.
Column :Kromasil 5-Amy Coat(250x4.6mm)
Mobile Phase :IPA:n-Hexane (5:95)
Wavelength : 254nm
Flow Rate : 1ml/min (49Kgf)
conc. : 1.0mg/1.0ml
Inj vol- :10ul

^{1}H NMR spectrum of compound **16** ($CDCl_3$, 400 MHz)

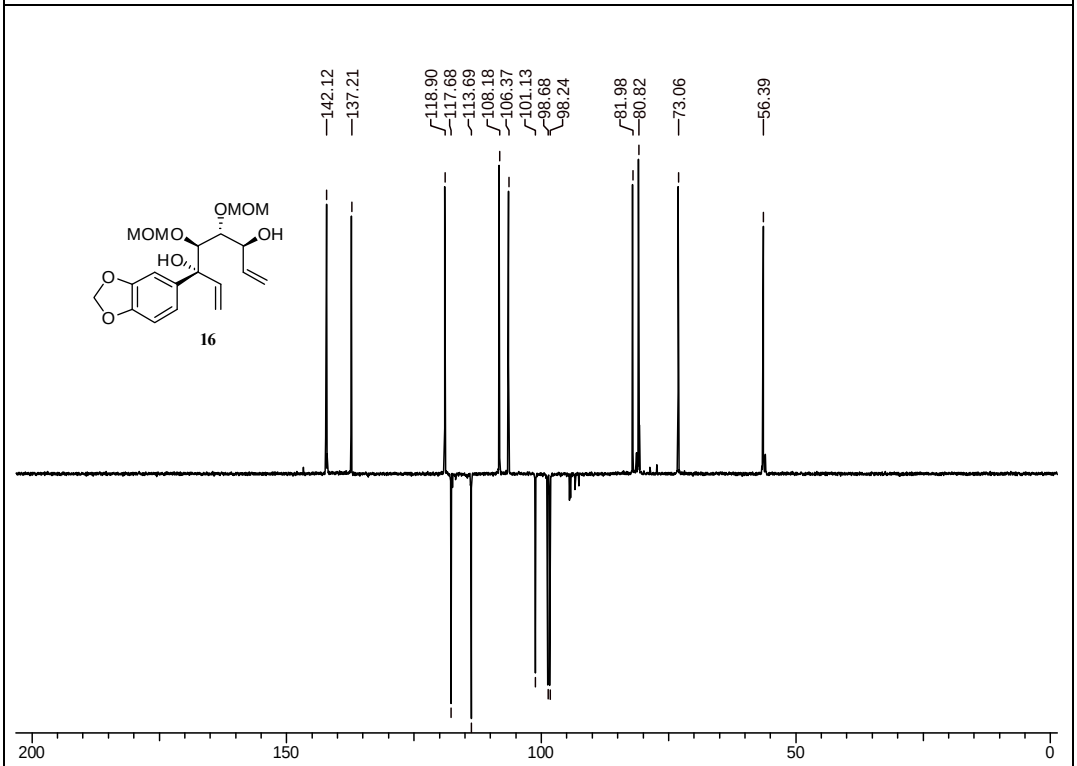


16

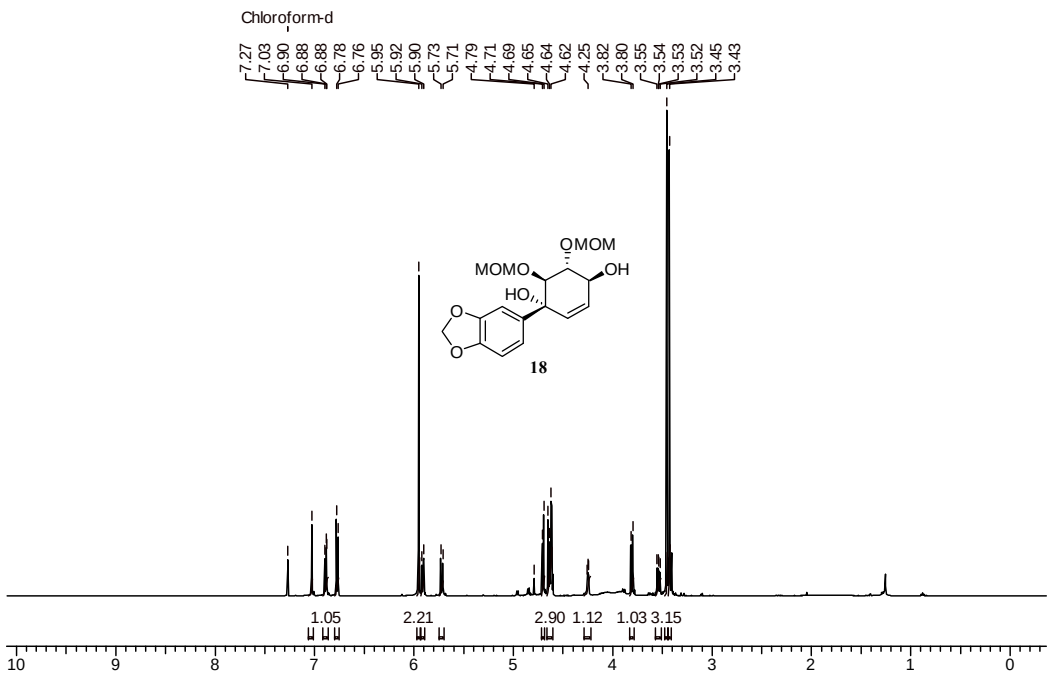
^{13}C NMR spectrum of compound **16** ($CDCl_3$, 100 MHz)



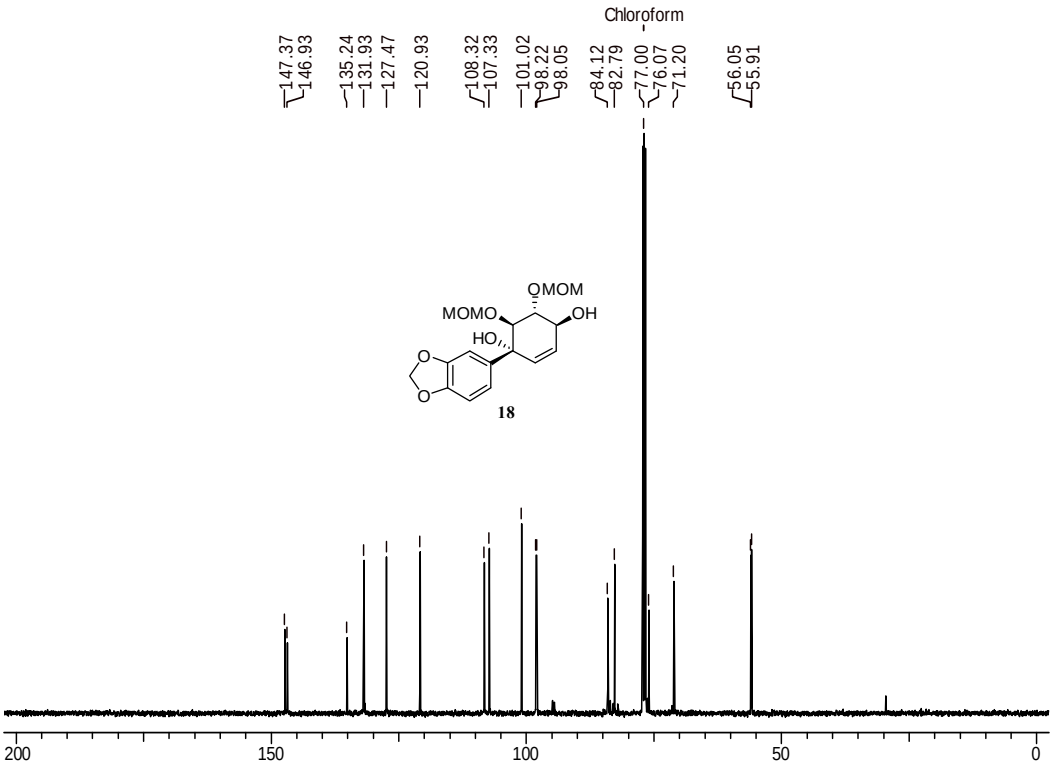
DEPT spectrum of compound **16** ($CDCl_3$, 100 MHz)



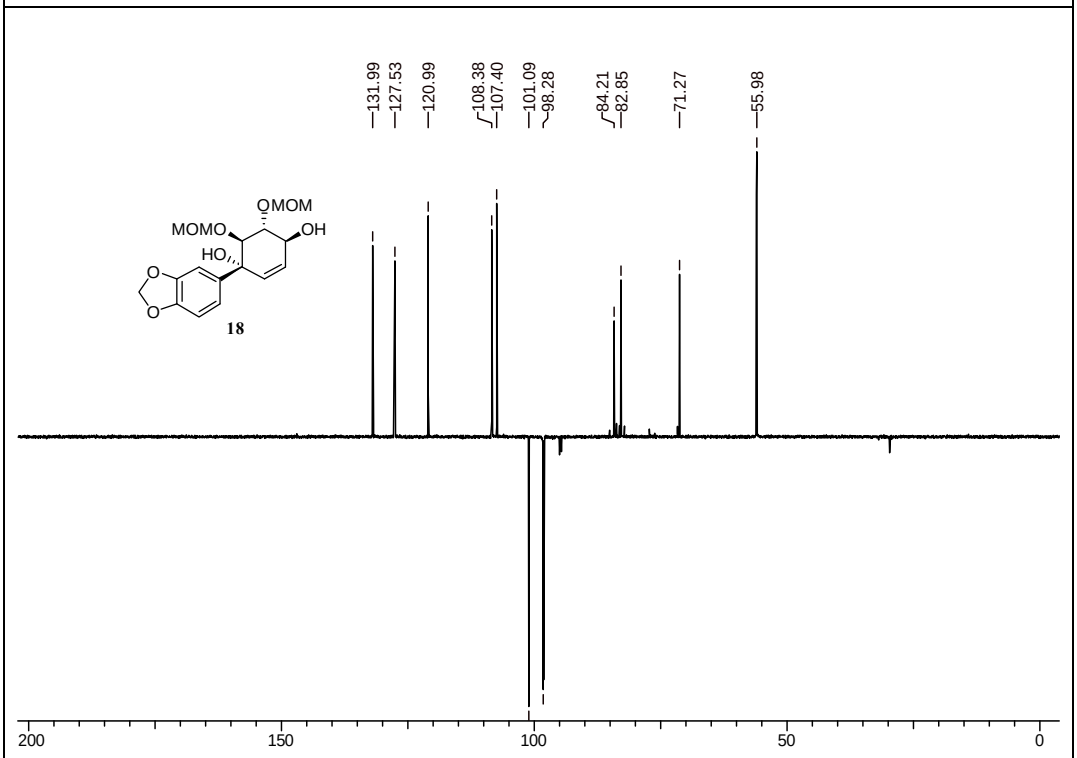
^{1}H NMR spectrum of compound **18** ($CDCl_3$, 500 MHz)



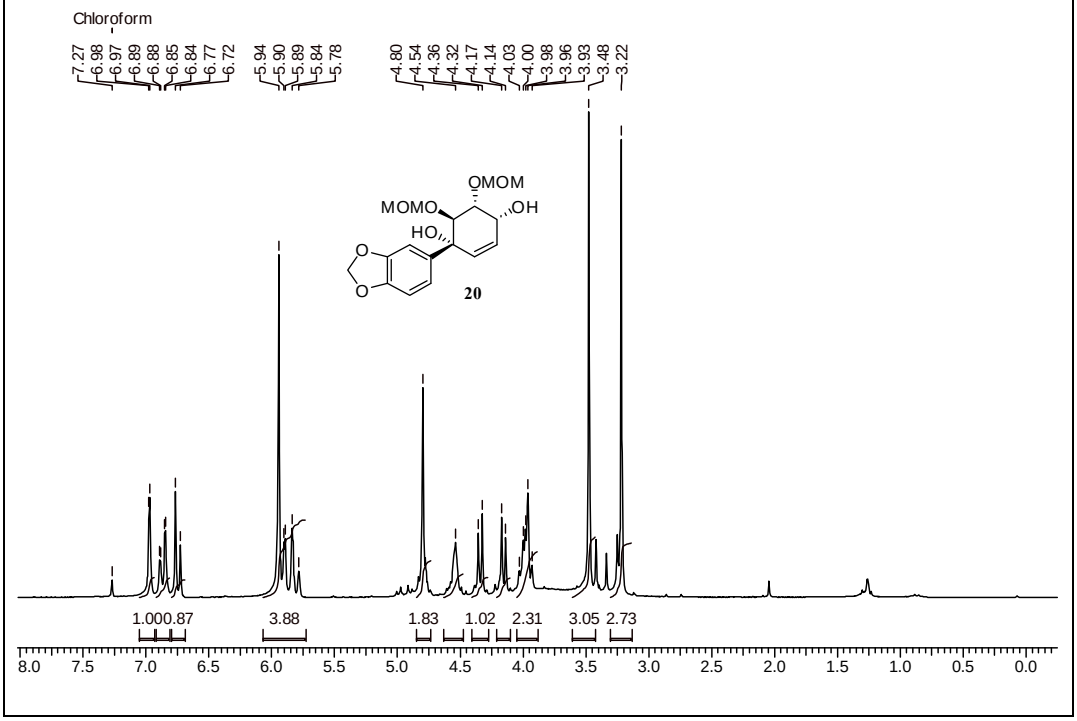
^{13}C NMR spectrum of compound **18** ($CDCl_3$, 125 MHz)



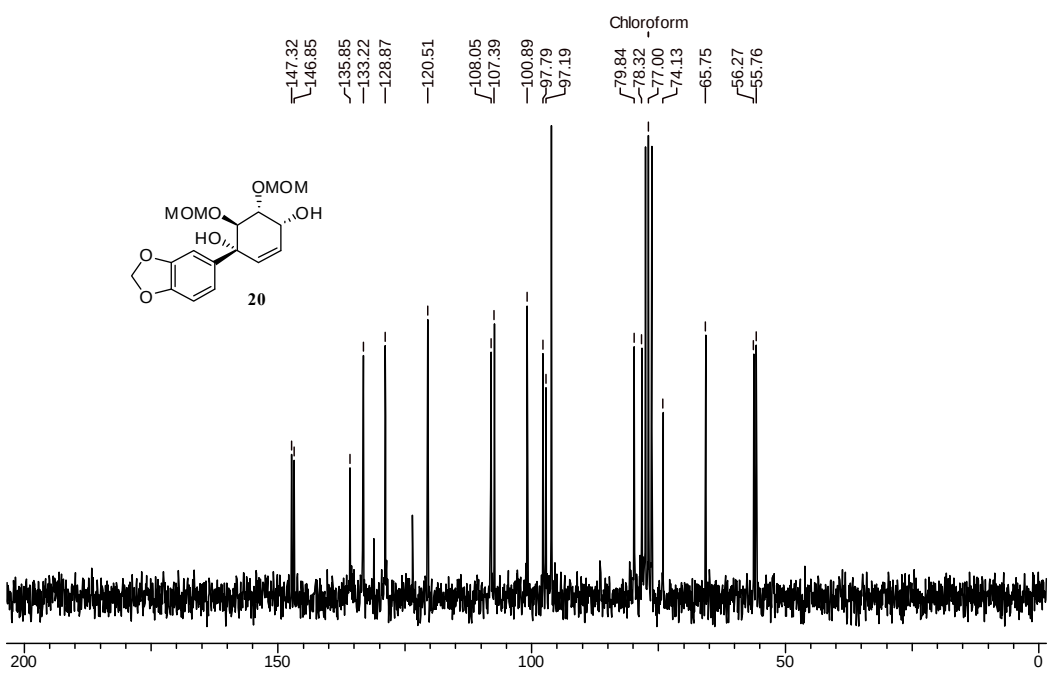
DEPT spectrum of compound **18** ($CDCl_3$, 125 MHz)



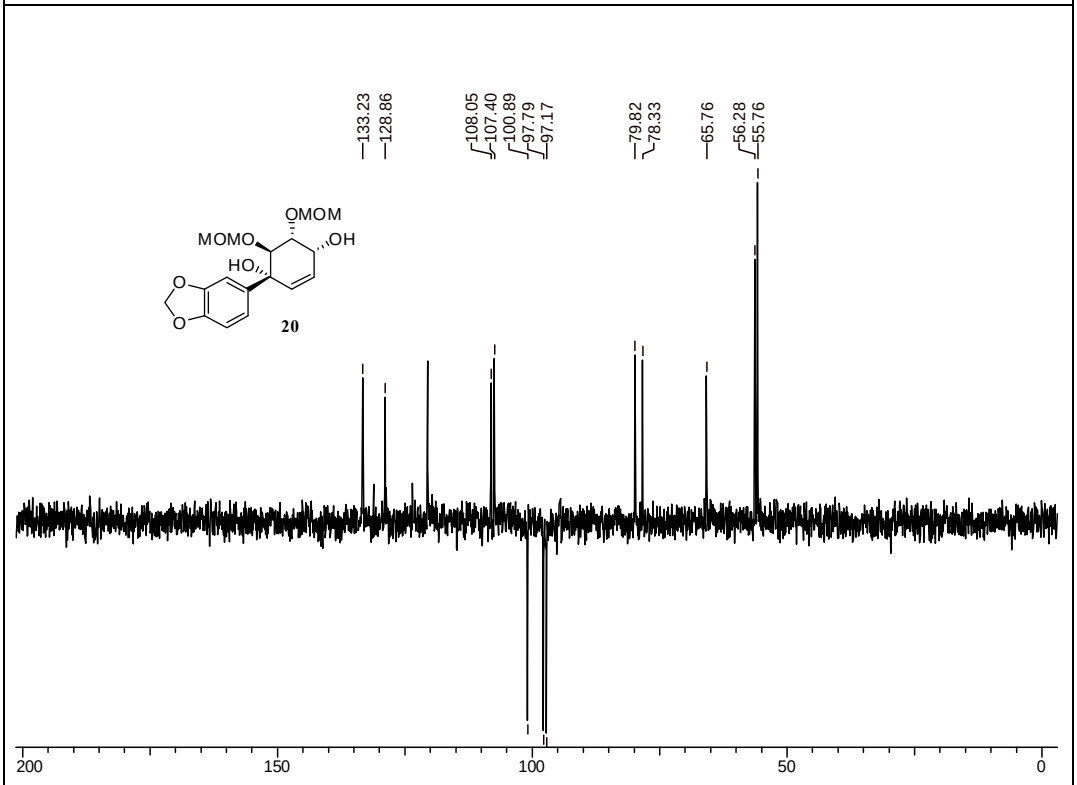
^1H NMR spectrum of compound **20** ($CDCl_3$ + CCl_4, 200 MHz)



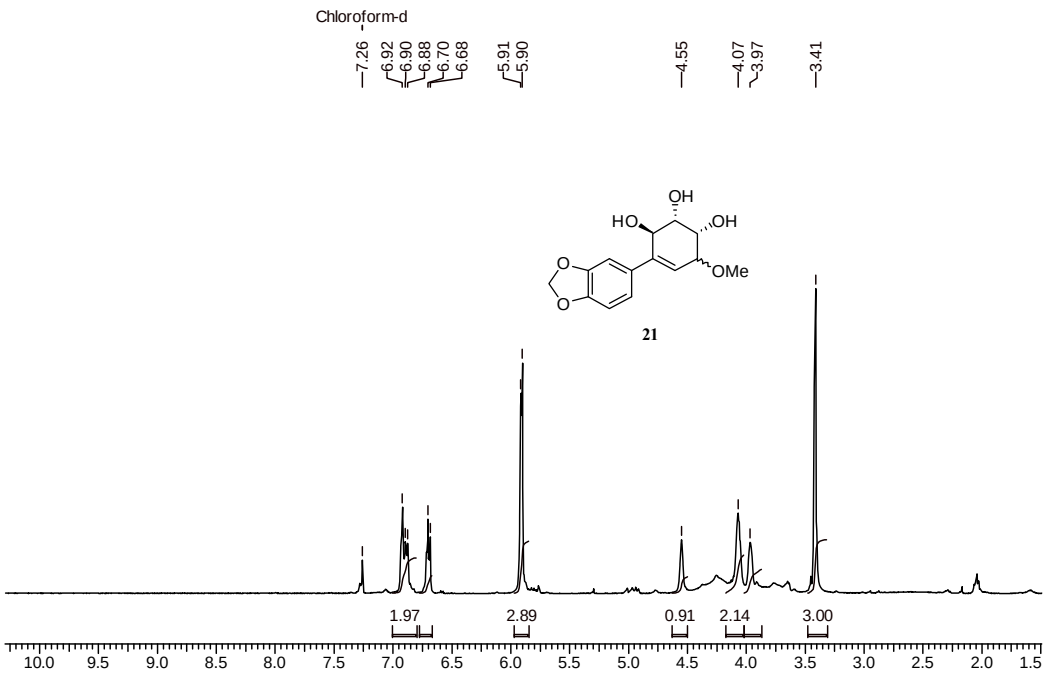
^{13}C NMR spectrum of compound **20** ($CDCl_3$ + CCl_4, 50 MHz)



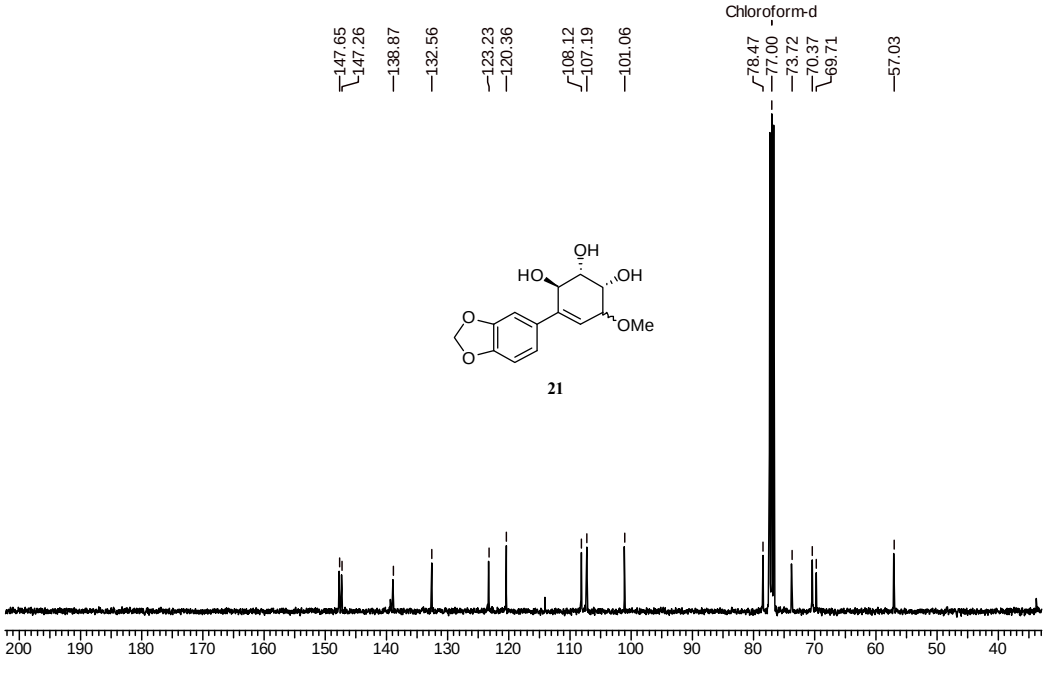
DEPT spectrum of compound **20** ($CDCl_3$ + CCl_4, 50 MHz)



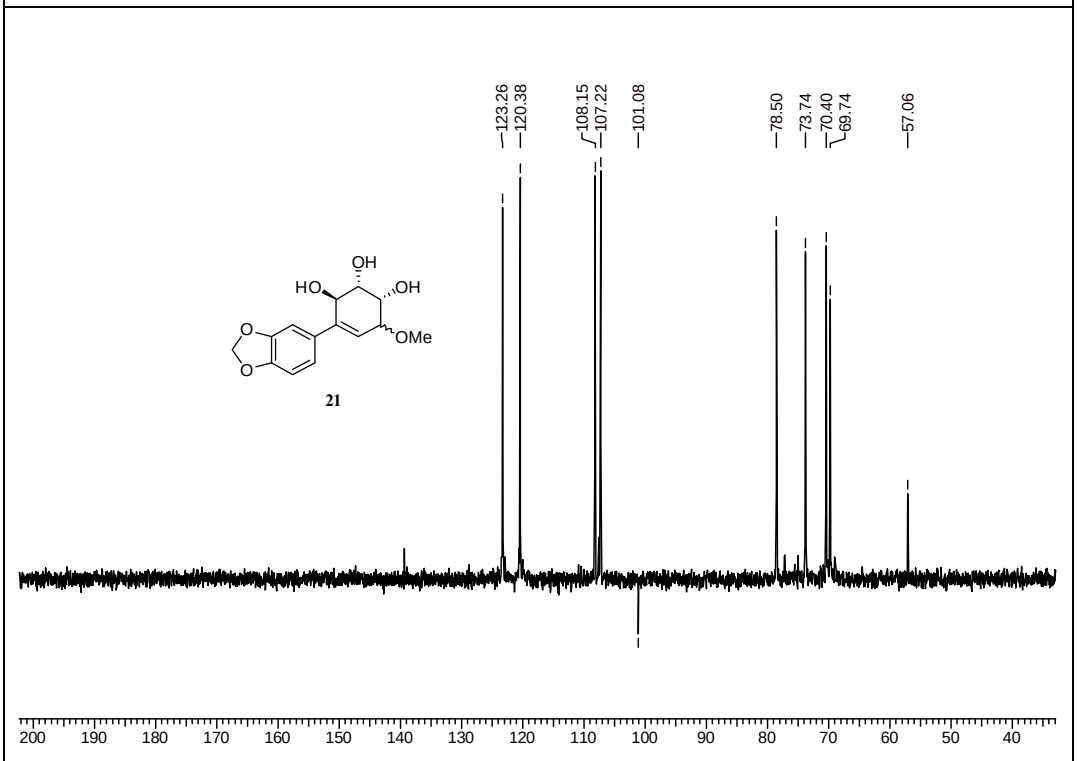
^{1}H NMR spectrum of compound **21** ($CDCl_3$, 400 MHz)



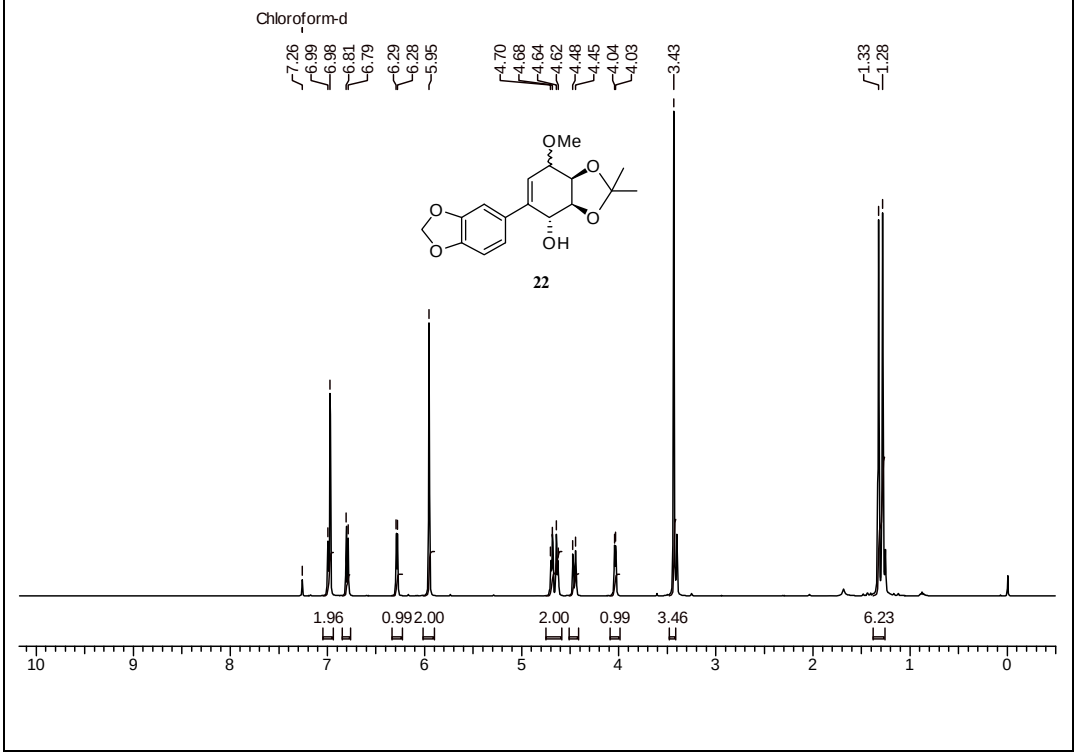
^{13}C NMR spectrum of compound **21** ($CDCl_3$, 100 MHz)



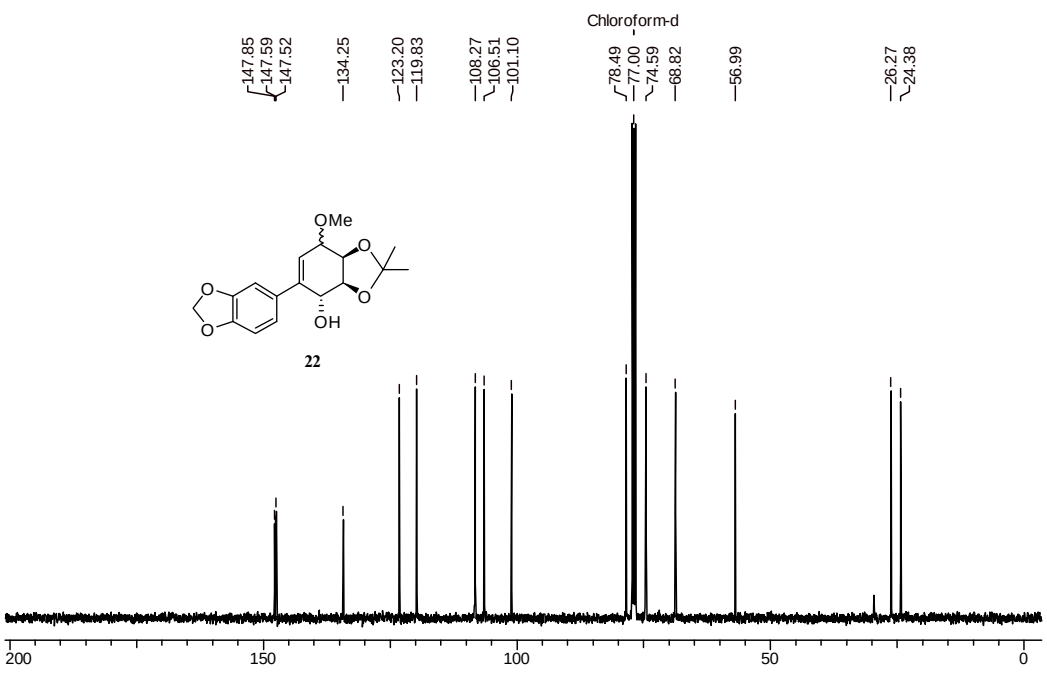
DEPT spectrum of compound **21** ($CDCl_3$, 100 MHz)



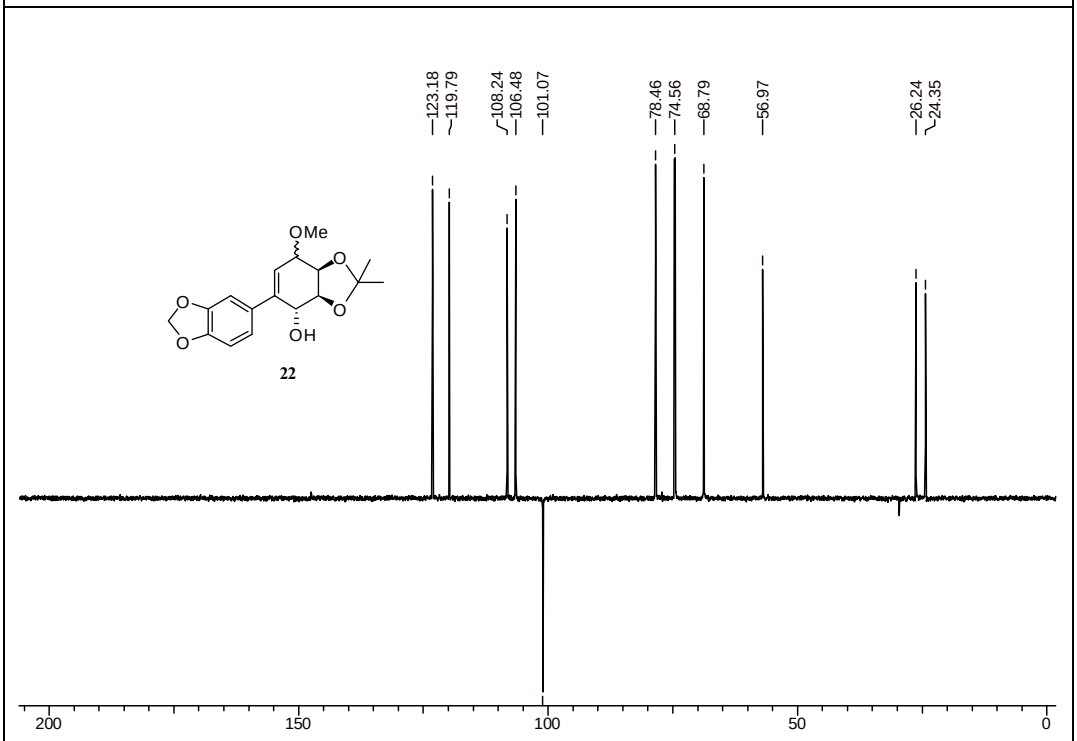
^{1}H NMR spectrum of compound **22** ($CDCl_3$, 400 MHz)



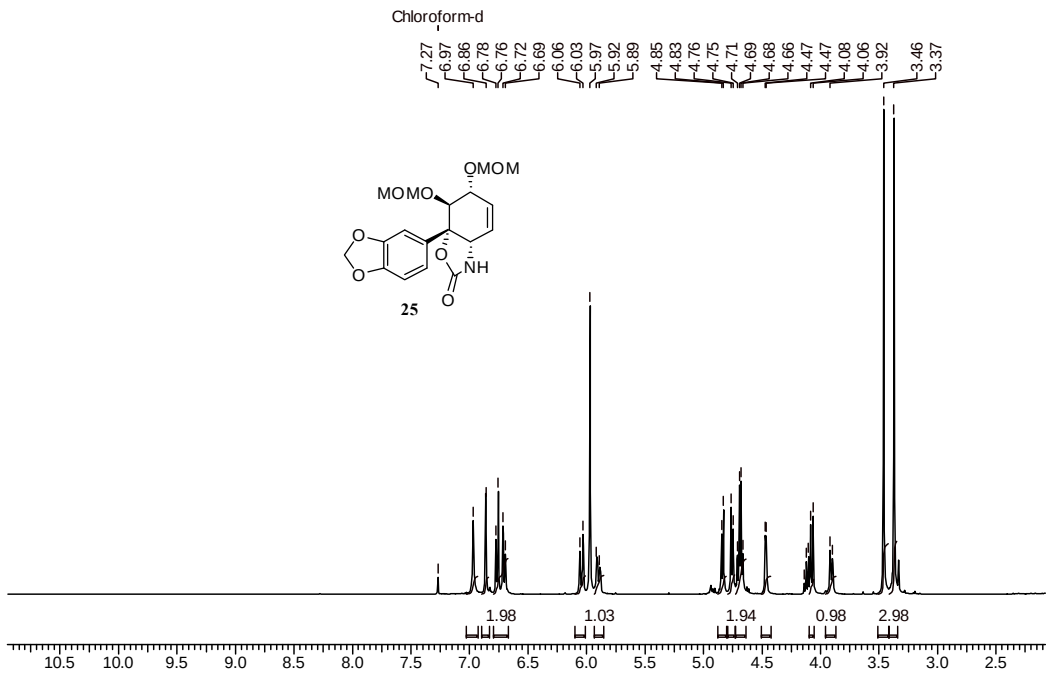
^{13}C NMR spectrum of compound **22** ($CDCl_3$, 100 MHz)



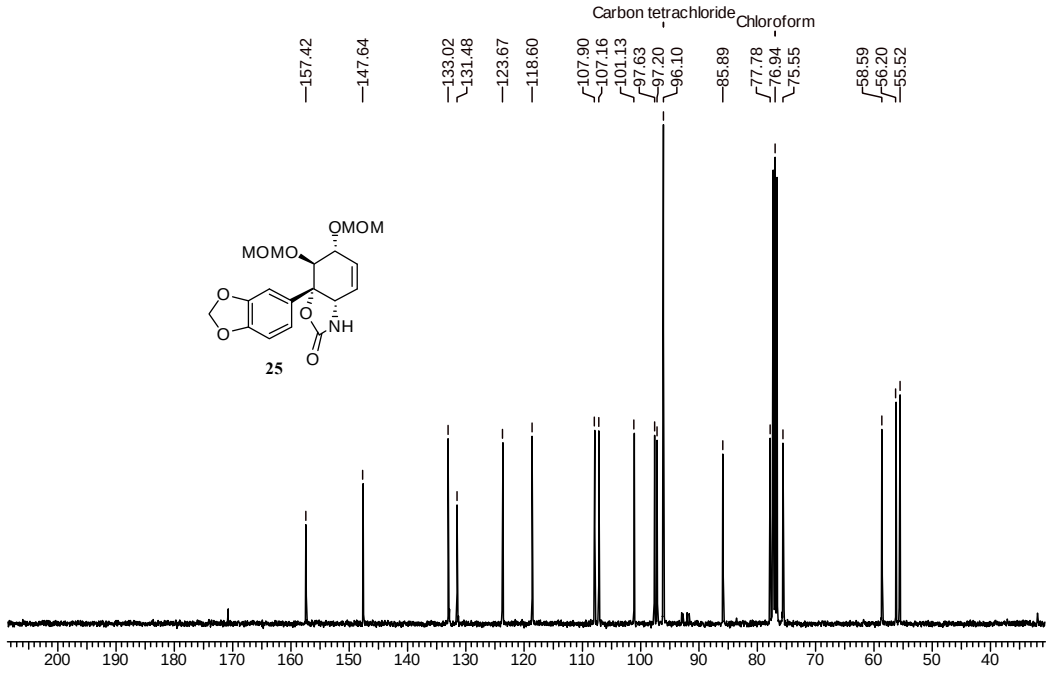
DEPT spectrum of compound **22** ($CDCl_3$, 100 MHz)



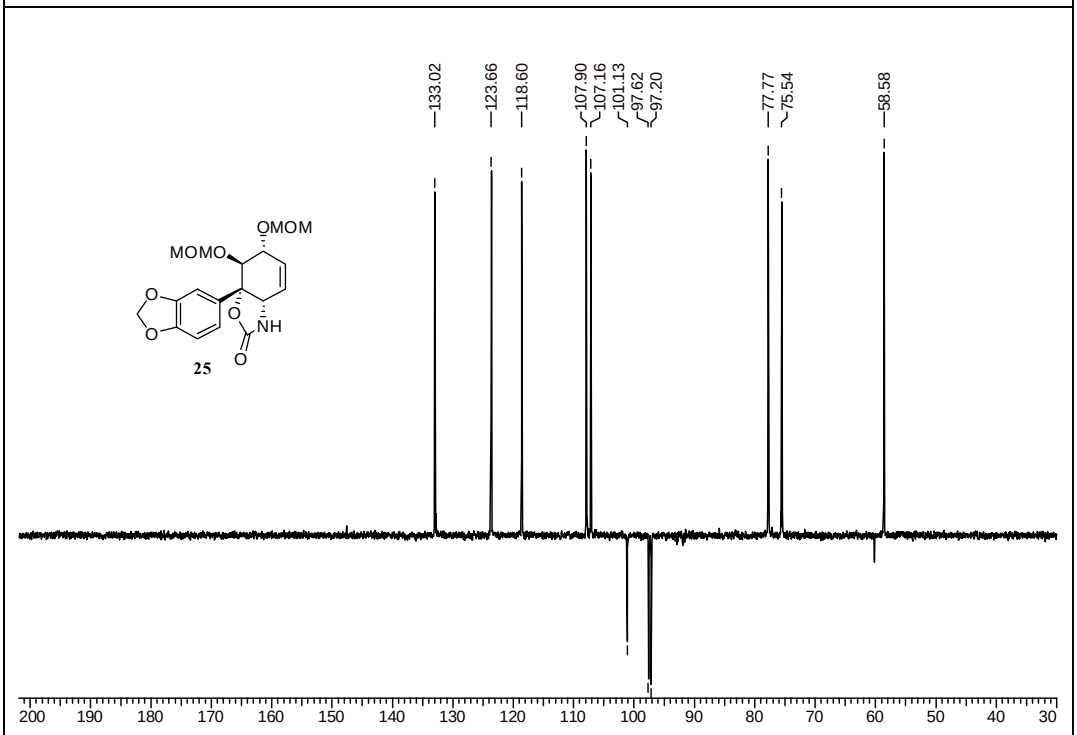
^{1}H NMR spectrum of compound **25** ($CDCl_3$ + CCl_4, 400 MHz)



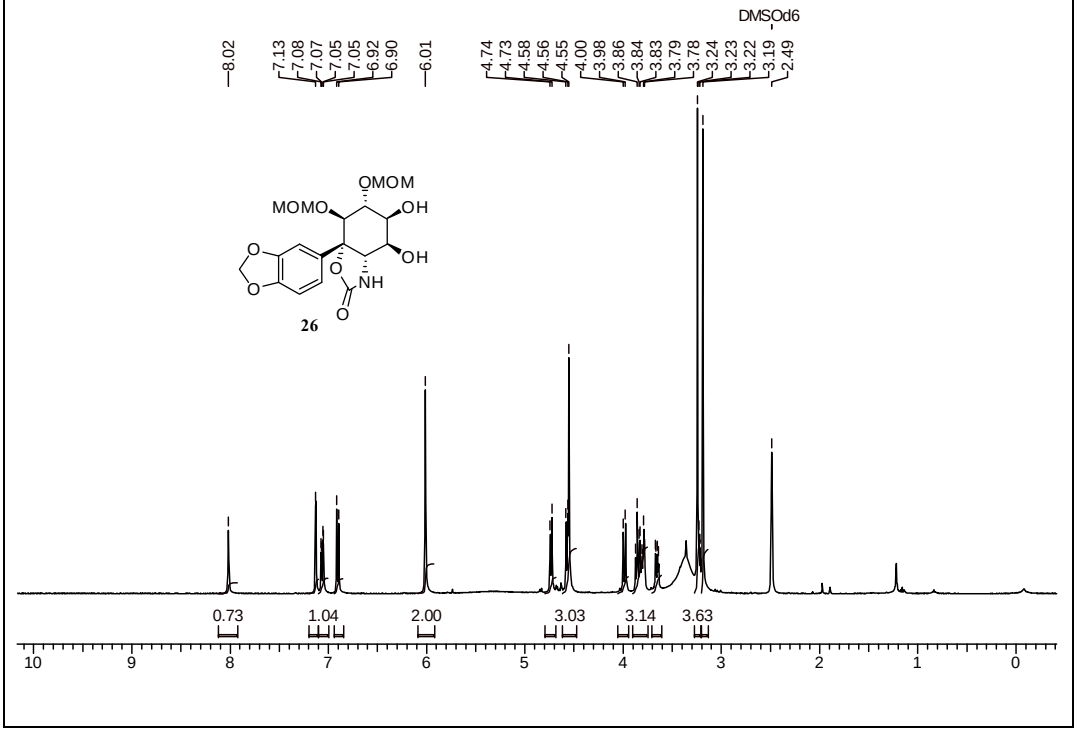
^{13}C NMR spectrum of compound **25** ($CDCl_3$ + CCl_4, 100 MHz)



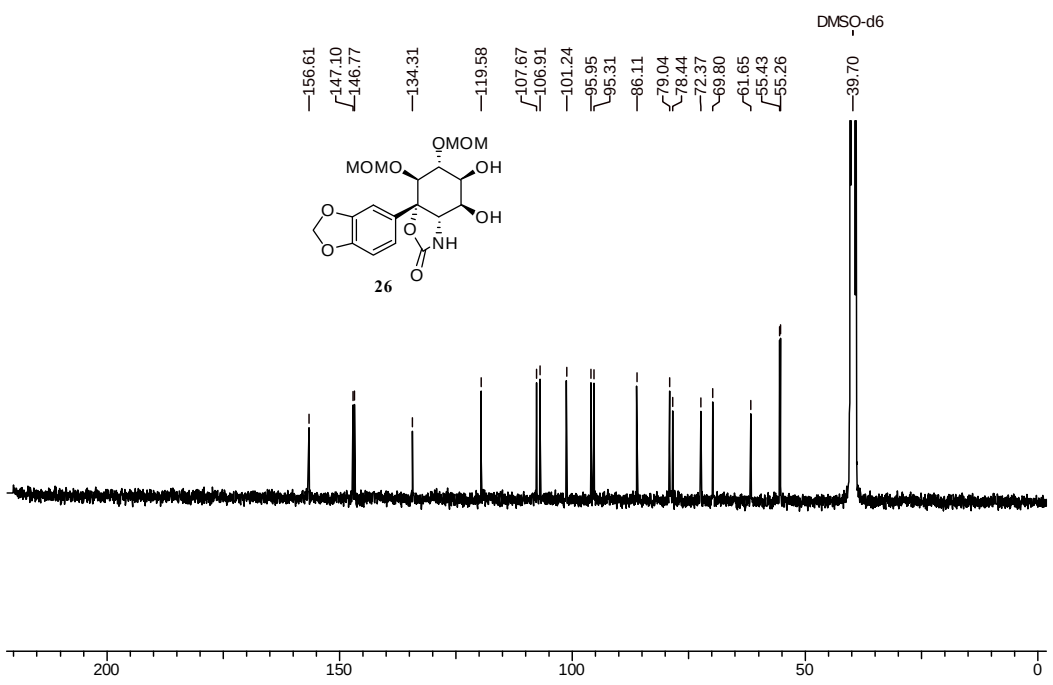
DEPT spectrum of compound **25** ($CDCl_3$ + CCl_4, 100 MHz)



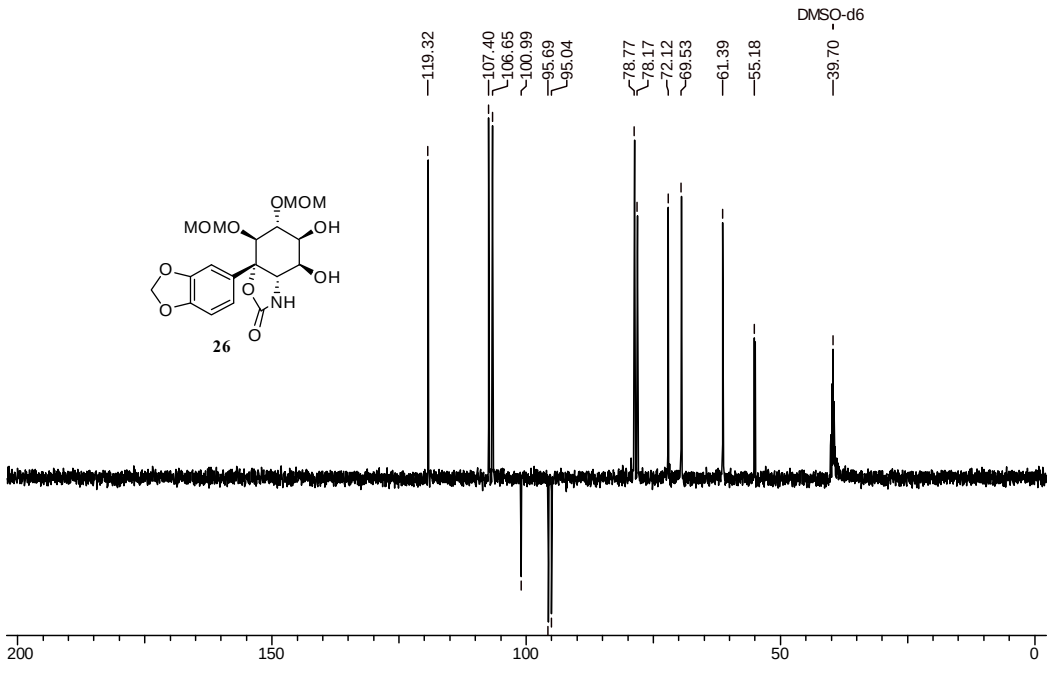
^{1}H NMR spectrum of compound **26** (DMSO-d_6, 400 MHz)



^{13}C NMR spectrum of compound **26** (DMSO-d_6, 100 MHz)



DEPT spectrum of compound **26** (DMSO-d_6, 100 MHz)



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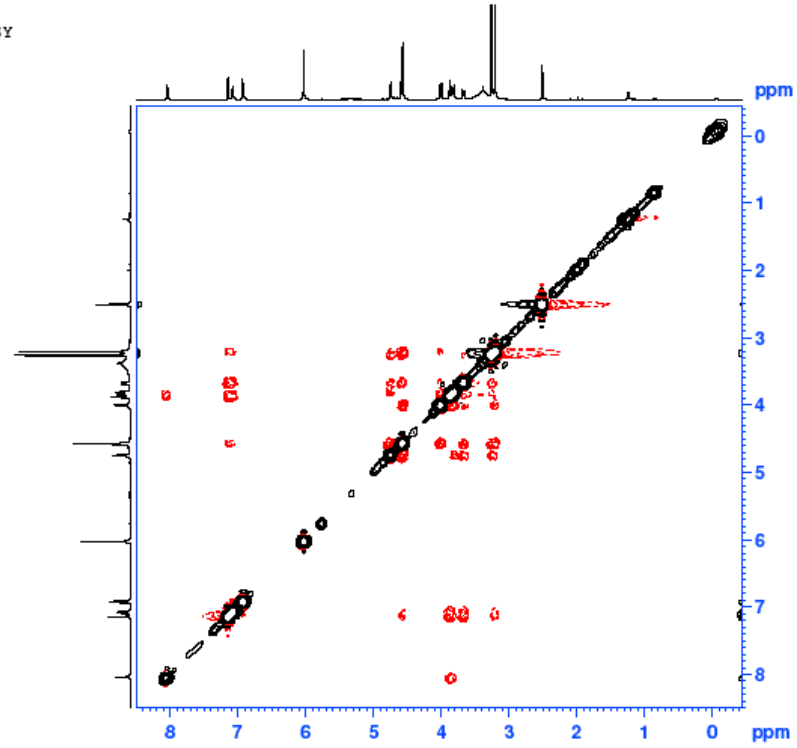
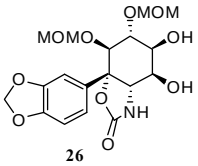
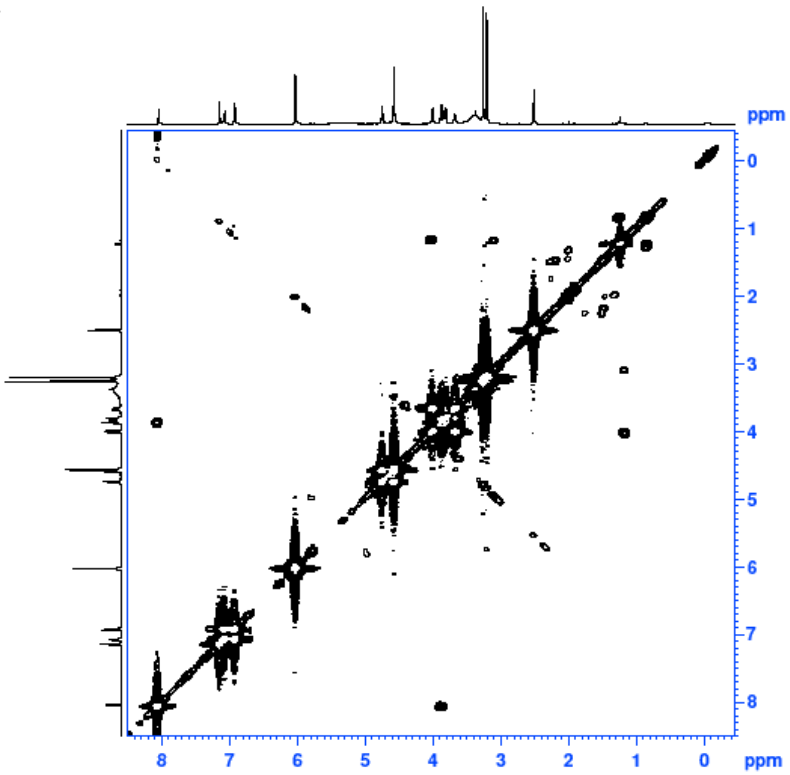
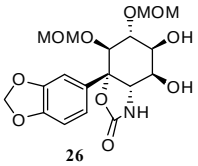




26

COSY





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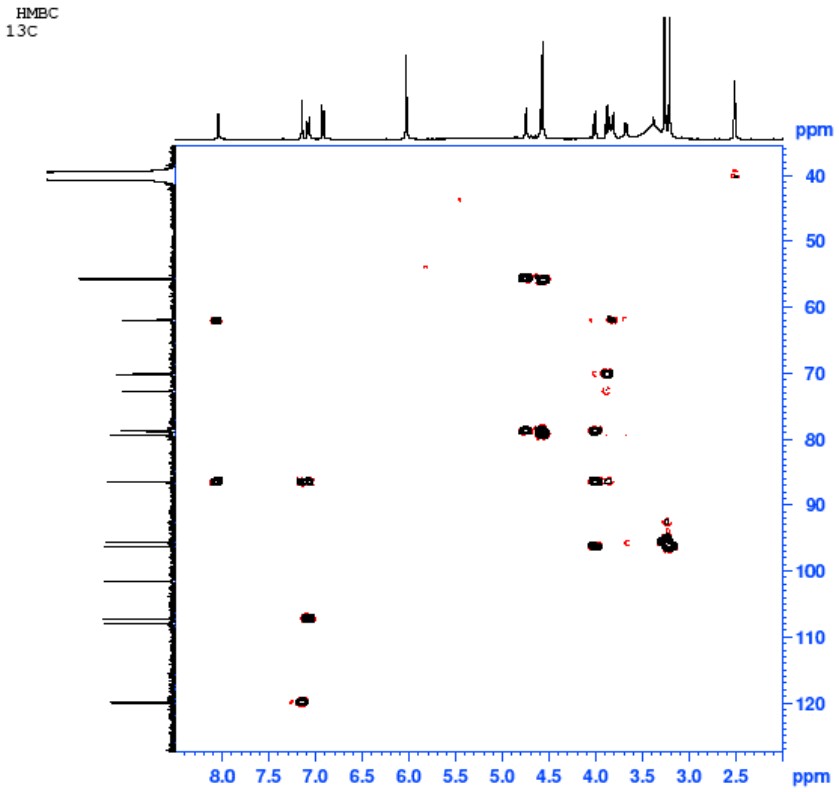
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80
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100
110
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6.5
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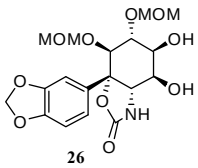
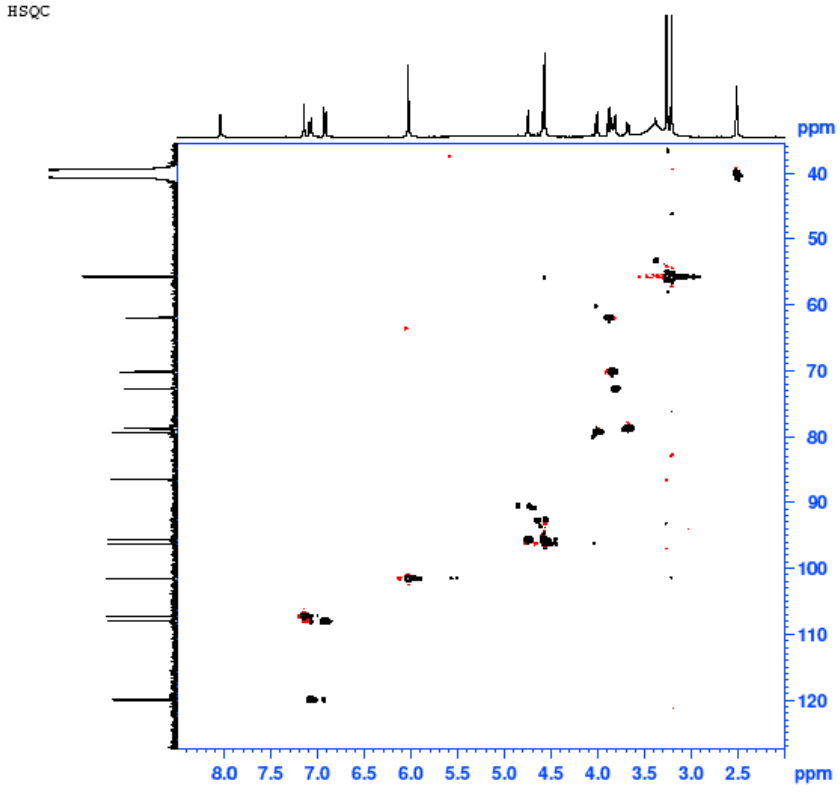
3.5
3.0
2.5
ppm


OMOM
MOMO
OH
OH
O
O
O
NH
O

26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100
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7.0
6.5
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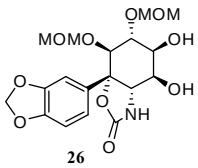
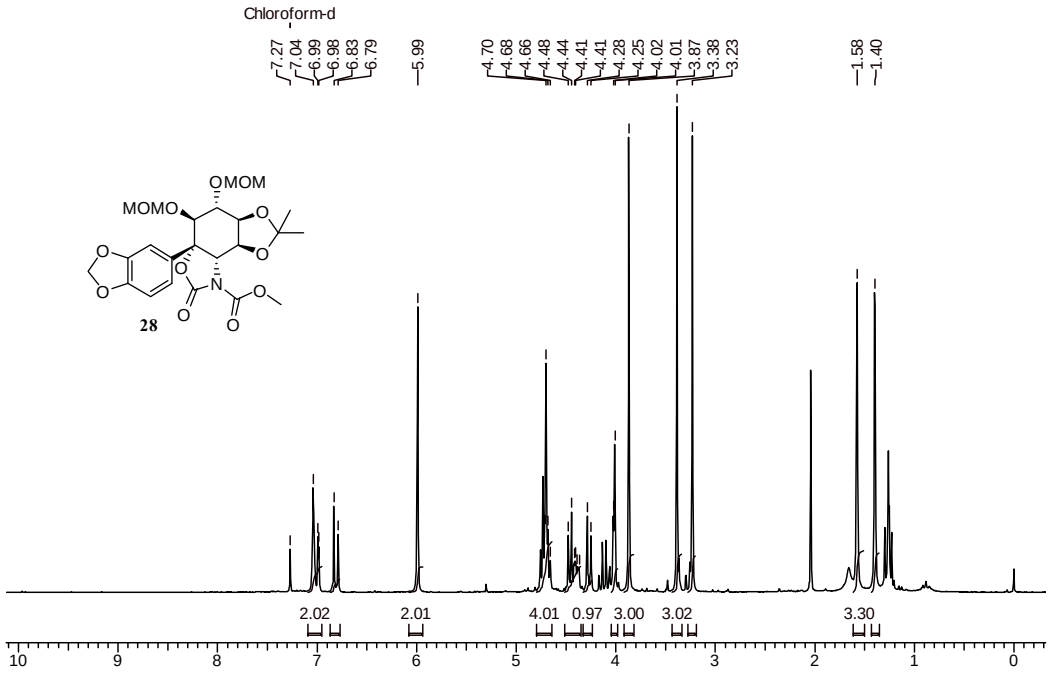
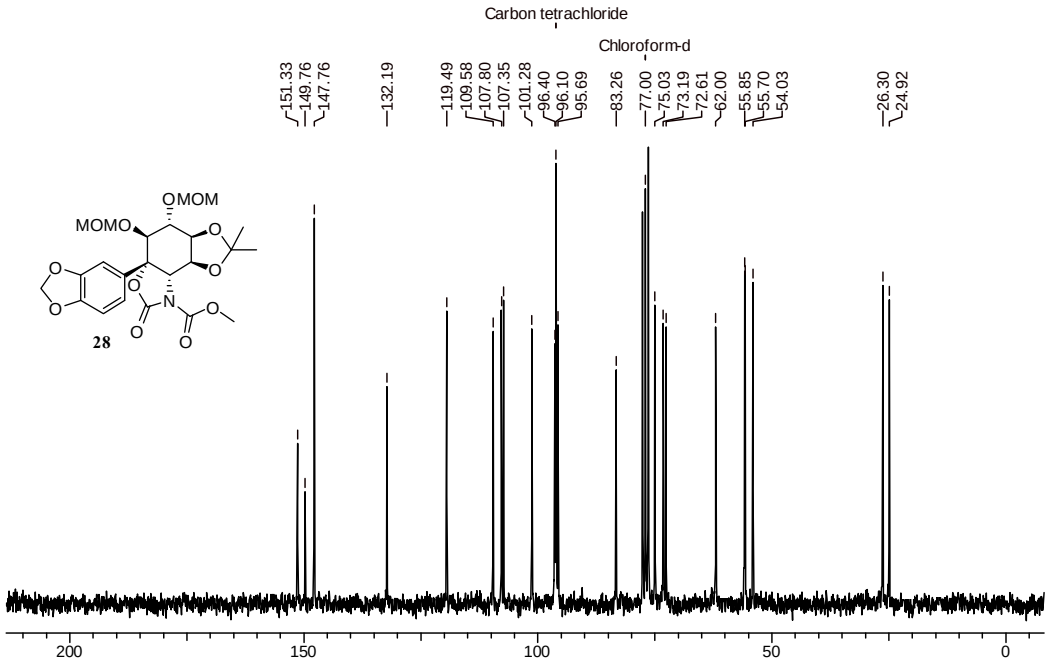

OMOM
MOMO
OH
OH
O
O
O
NH
O

26

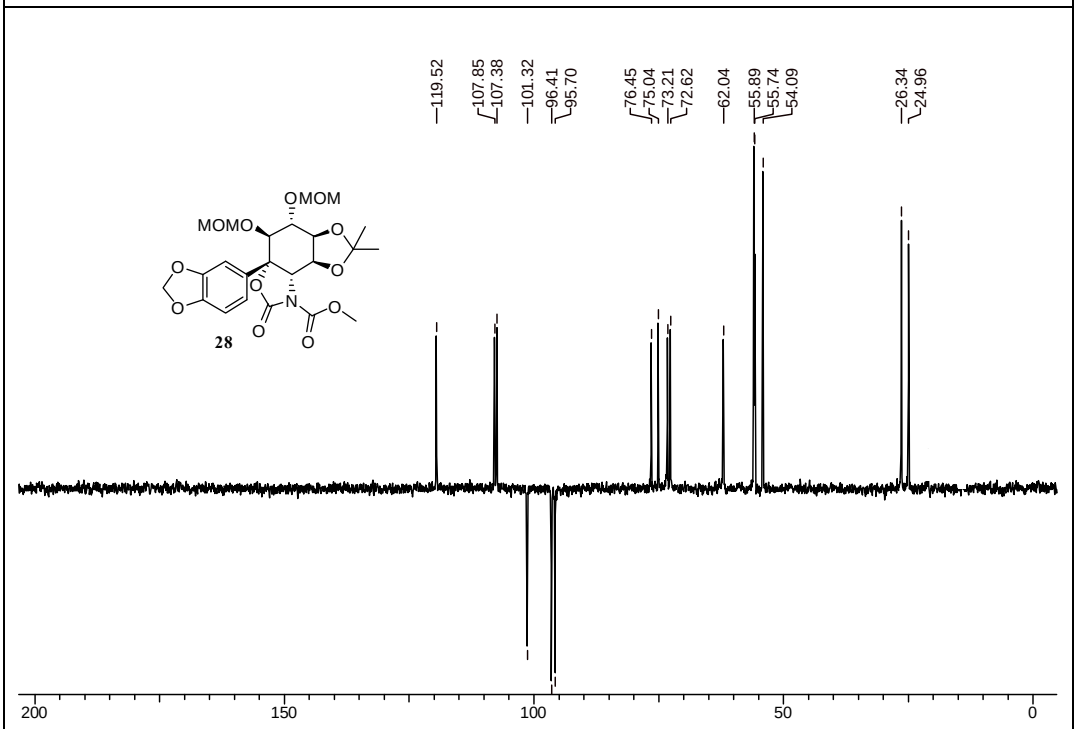
^{1}H NMR spectrum of compound **28** ($CDCl_3$ + CCl_4, 200 MHz)



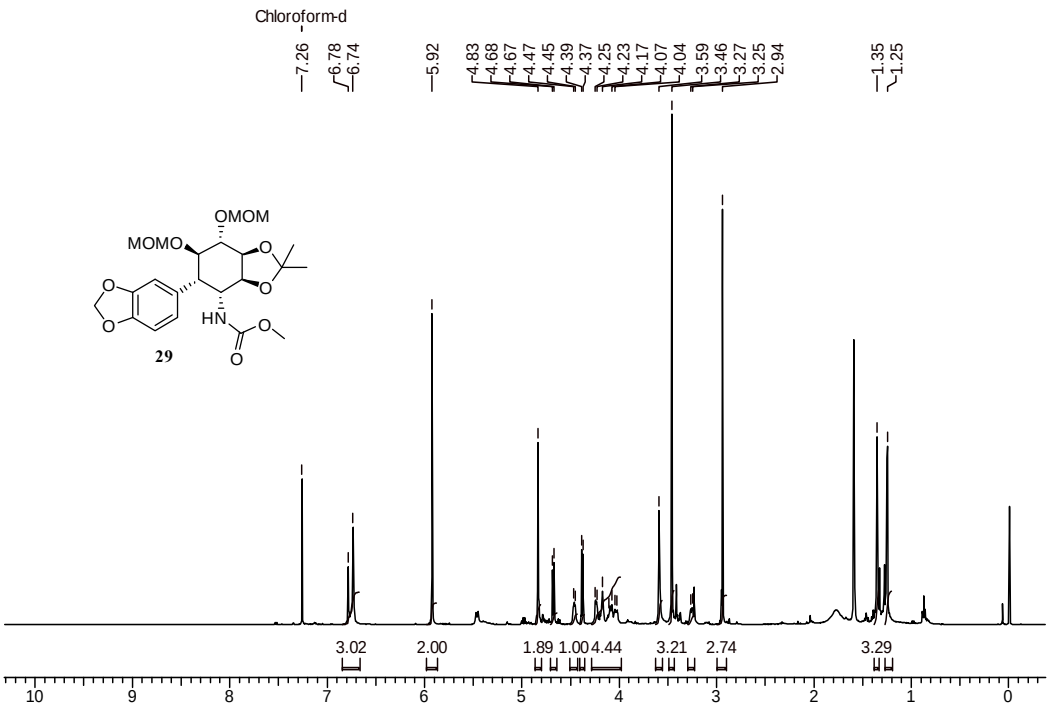
^{13}C NMR spectrum of compound **28** ($CDCl_3$ + CCl_4, 50 MHz)



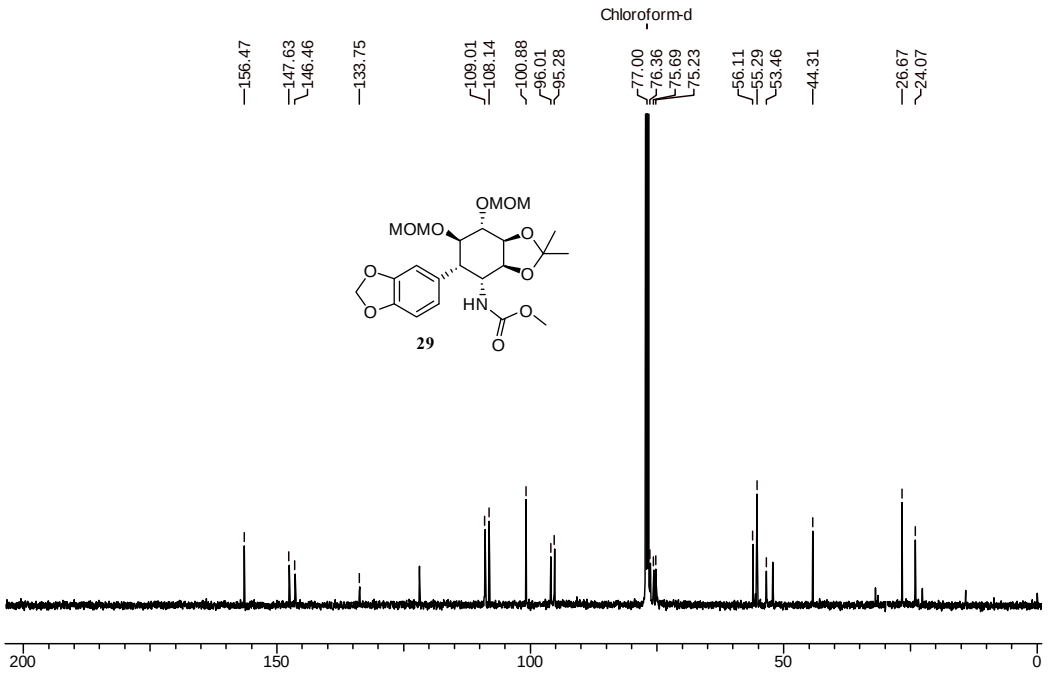
DEPT spectrum of compound **28** ($CDCl_3$ + CCl_4, 50 MHz)



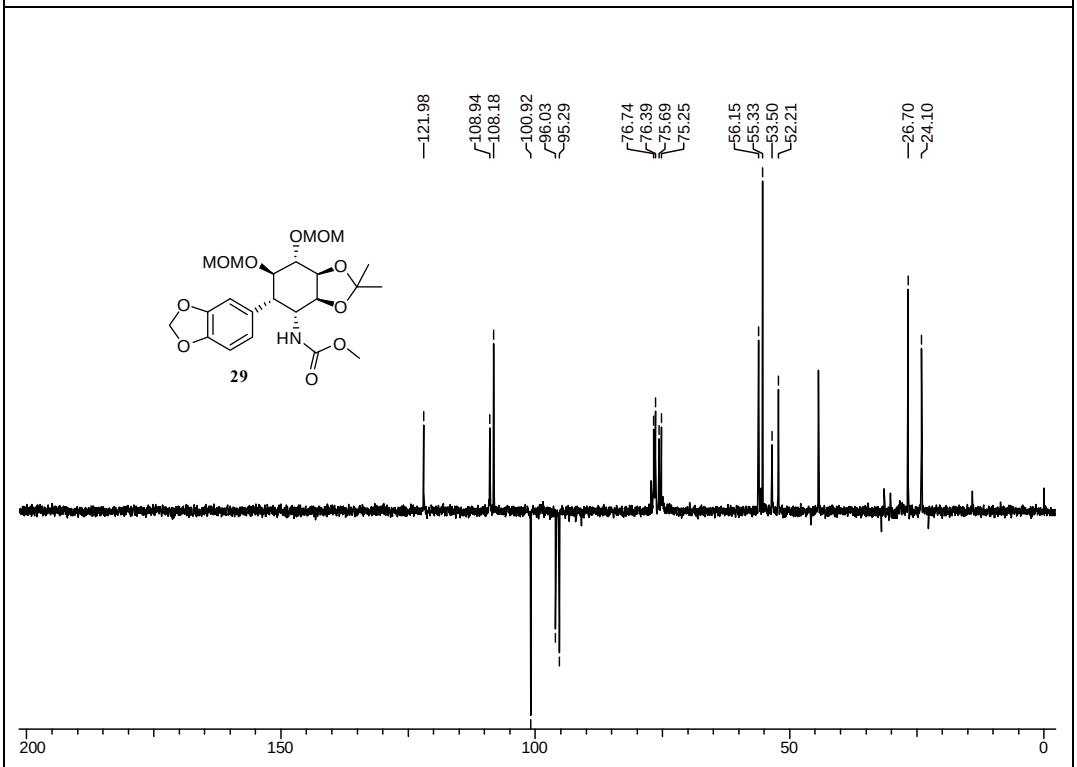
^{1}H NMR spectrum of compound **29** ($CDCl_3$, 500 MHz)



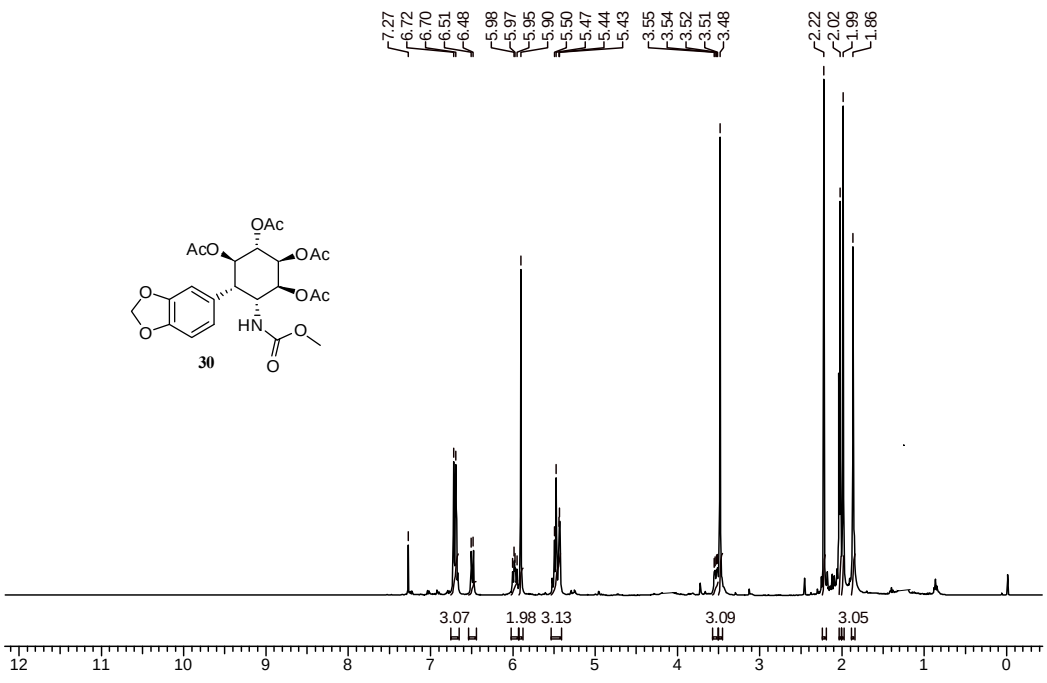
^{13}C NMR spectrum of compound **29** ($CDCl_3$, 125 MHz)



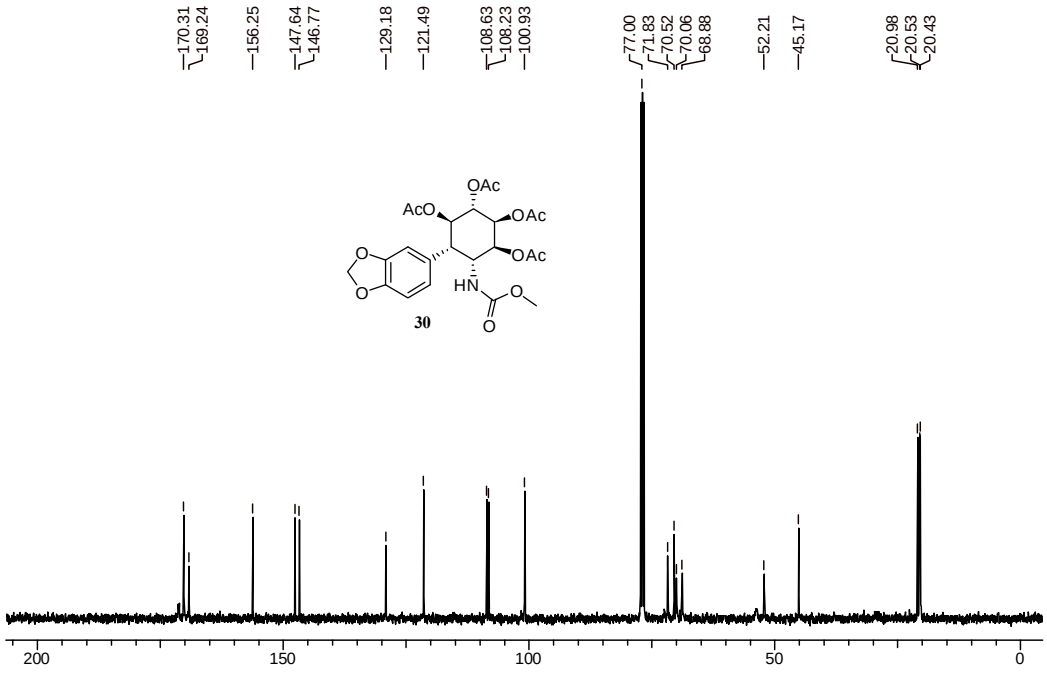
DEPT spectrum of compound **29** ($CDCl_3$, 125 MHz)



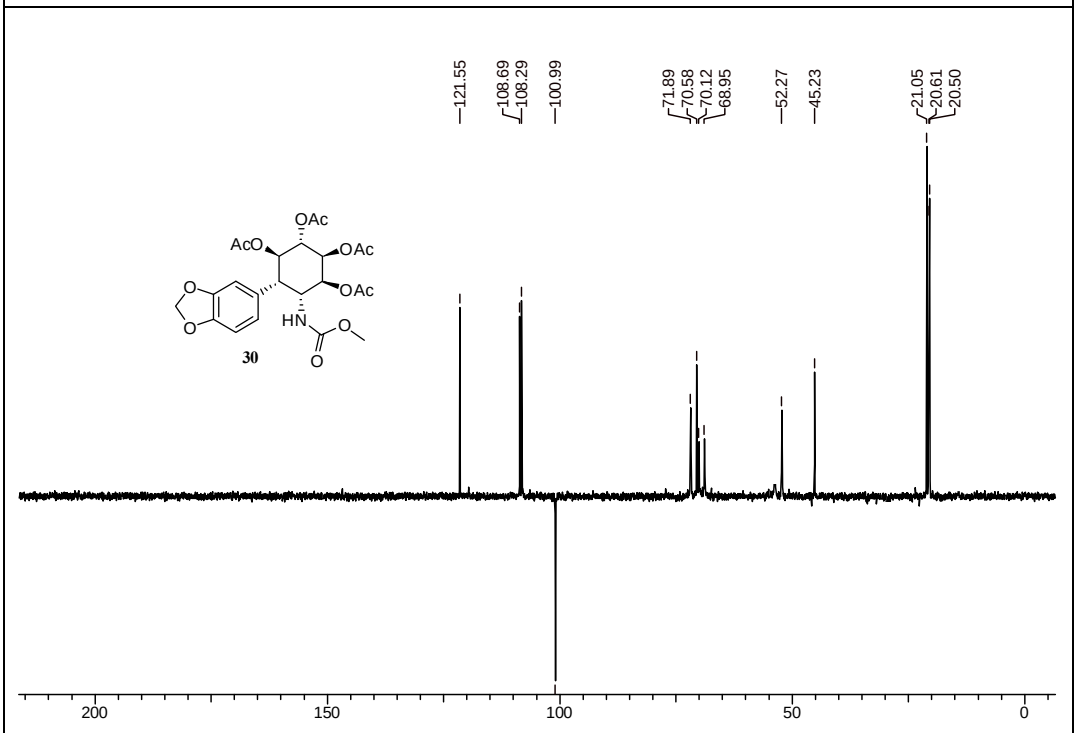
^{1}H NMR spectrum of compound **30** ($CDCl_3$, 400 MHz)



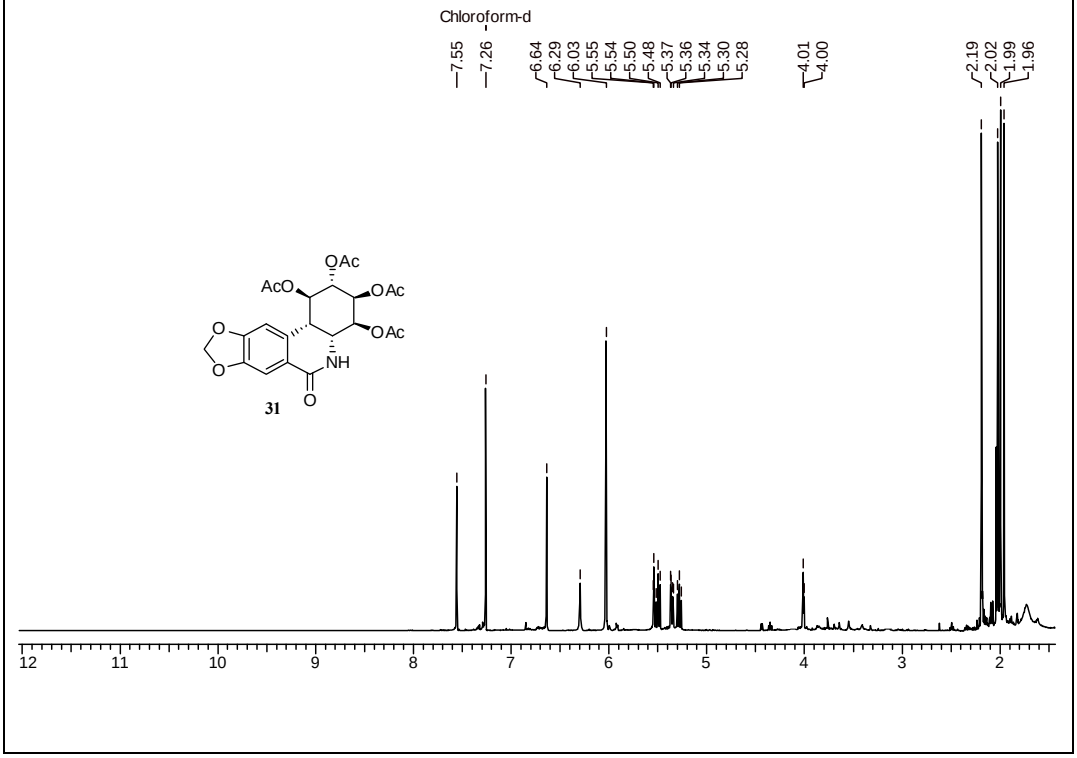
^{13}C NMR spectrum of compound **30** ($CDCl_3$, 100 MHz)



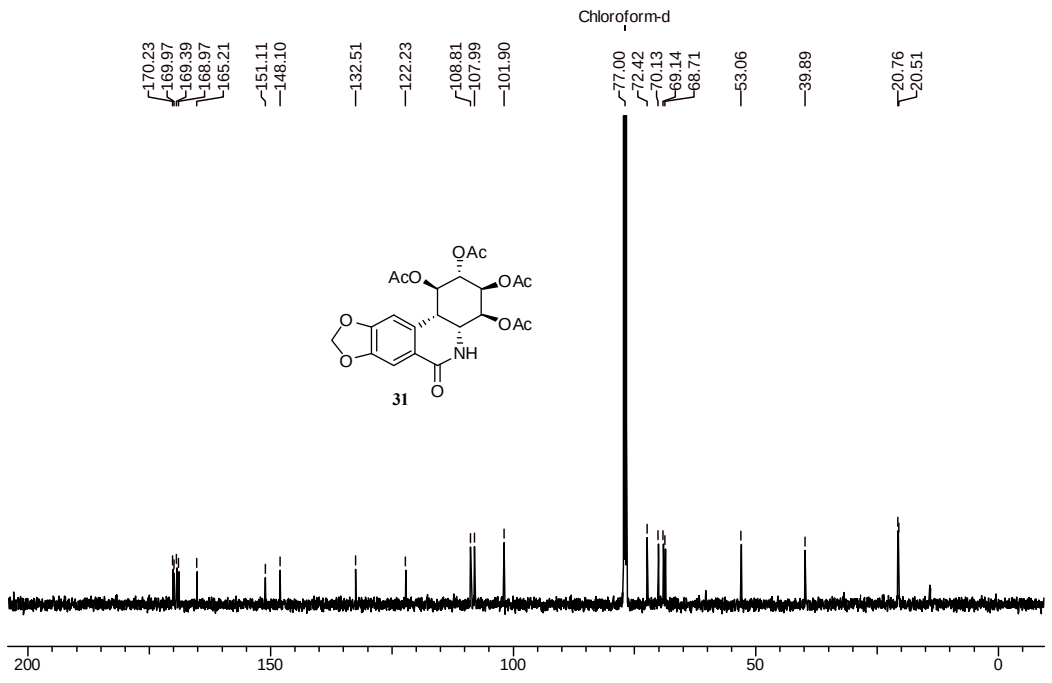
DEPT spectrum of compound **30** ($CDCl_3$, 100 MHz)



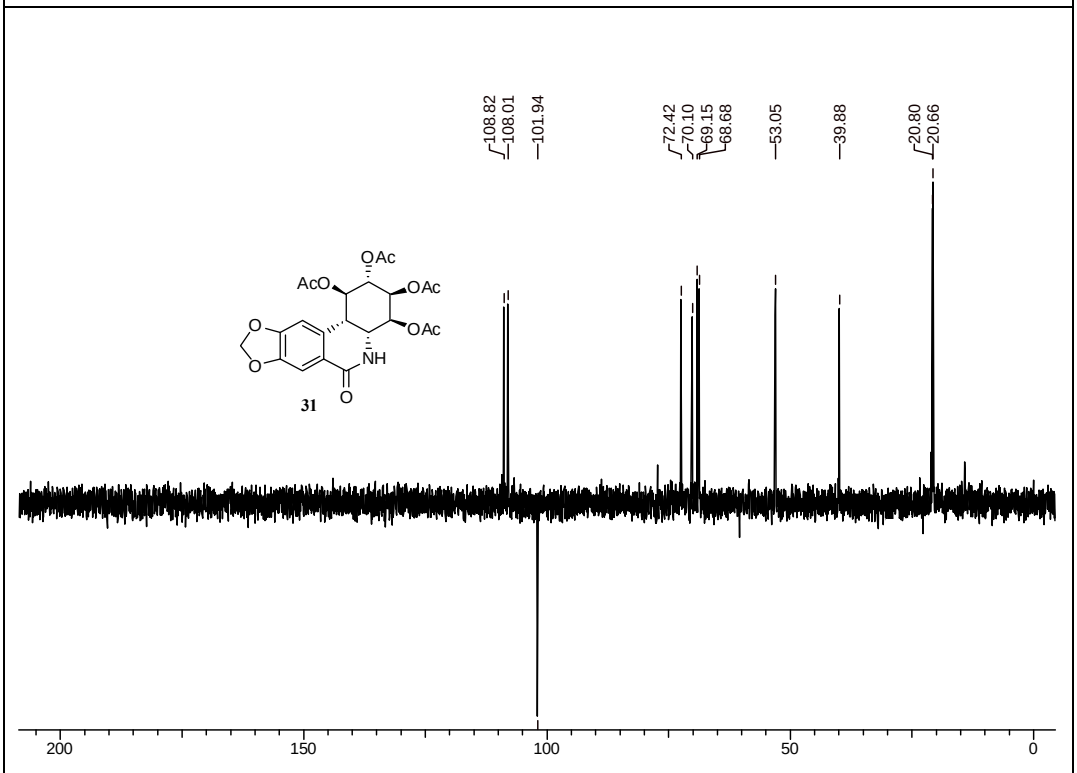
^{1}H NMR spectrum of compound **31** ($CDCl_3$, 500 MHz)



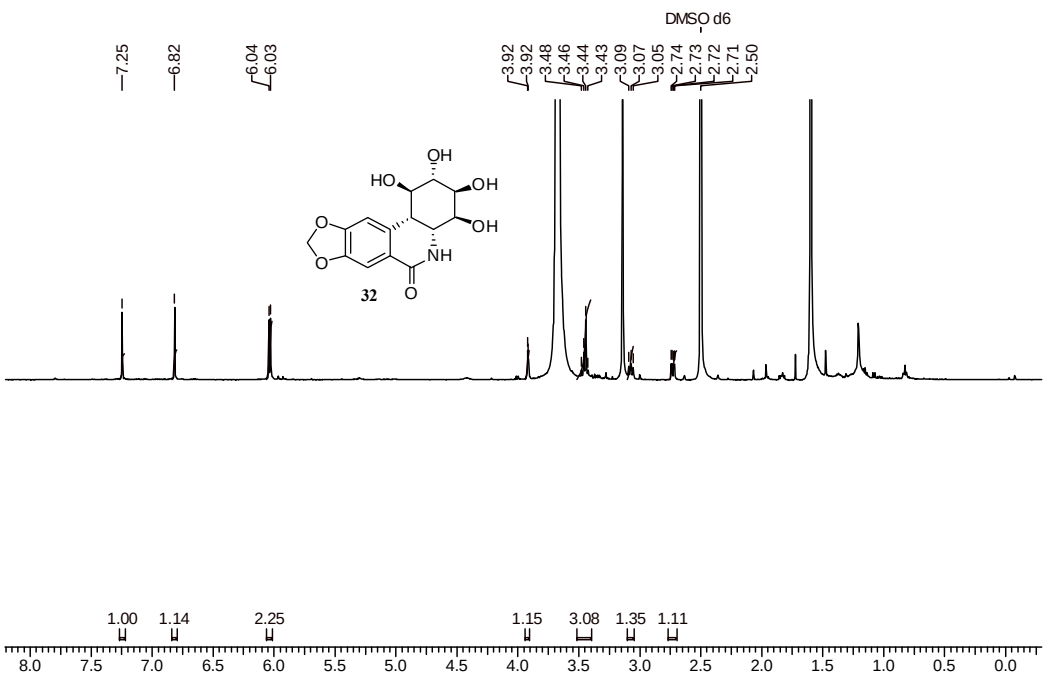
^{13}C NMR spectrum of compound **31** ($CDCl_3$, 125 MHz)



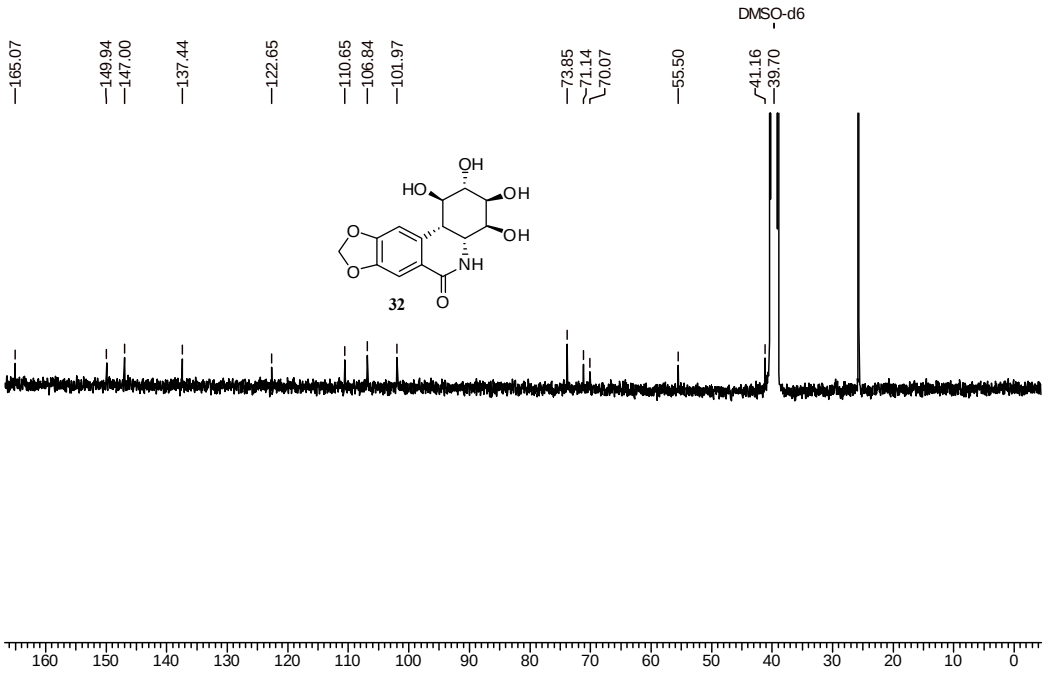
DEPT spectrum of compound **31** ($CDCl_3$, 125 MHz)



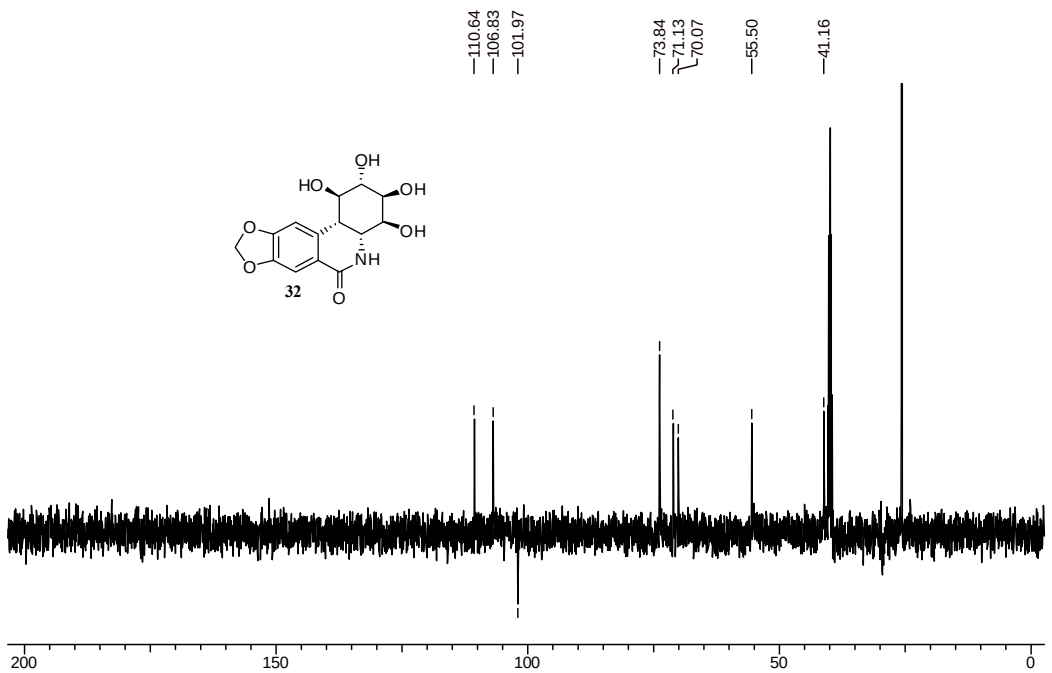
^{1}H NMR spectrum of compound **32** (DMSO-d_6, 500 MHz)



^{13}C NMR spectrum of compound **32** (DMSO-d_6, 125 MHz)



DEPT spectrum of compound **32** (DMSO-d_6, 125 MHz)



3.2.5. References

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4. Enantiomeric excess (*% ee*) was determined by Chiral HPLC analysis (Chiralcel OJ-H (250×4.6 mm), mobile phase: isopropanol: pet ether= 40:60, wave length= 254 nm, flow rate= 0.5 ml/min).
5. Enantiomeric excess (*% ee*) was determined by Chiral HPLC analysis (Kromasil 5-Amy Coat (250×4.6 mm), mobile phase: isopropanol: n-hexane = 5:95, wave length= 254 nm, flow rate= 1 ml/min).
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11. a) For '1-aryl-1-deoxyconduritols F' see Nadein, O. N.; Kornienko, A. *Org. Lett.* **2004**, *6*, 831. b) For review on conduritols see Balci, M.; Sütbeyaz, Y.; Secen, H. *Tetrahedron* **1990**, *46*, 3715.
12. Crystallographic data (excluding structure factors) for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 918587.
13. Previously Petit and co-workers (Pettit, G. R.; Melody, N.; Herald, D. L.; Knight, J. C.; Chapuis, J.-C. *J. Nat. Prod.* **2007**, *70*, 417) were also unable to get the correct stereochemistry at C10b centre by a radical deoxygenation reaction for the synthesis of pancratistatin.

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19. Crystallographic data (excluding structure factors) for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 918586.

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21. a) Hudlicky, T.; Rinner, U.; Gonzalez, D.; Akgun, H.; Schilling, S.; Siengalewicz, P.; Martinot, T. A.; Pettit, G. R. *J. Org. Chem.* **2002**, *67*, 8726; b) Rinner, U.; Siengalewicz, P.; Hudlicky, T. *Org. Lett.* **2001**, *4*, 115.

Chapter 3: Synthetic studies towards 7-deoxypancratistatin and retro-Reformatsky reaction

Section 3

A simple and straightforward retro-Reformatsky reaction

3.3.1. Introduction

Carbon-hydrogen (C-H) and carbon-carbon (C-C) bonds are the most important linkages of organic molecules. Synthetic organic chemistry community is interested in the construction of very complex chemical structure from relatively simple starting material by functional group interconversion and C-C bond forming sequence. The Reformatsky reaction[1] is one of the fundamental, practical and important organic reactions involving the formation of a C–C bond. The resulting product of this reaction is a *β*-hydroxy ester **3**, which can be converted into the essential building blocks of natural products or pharmaceutically important compounds.[2] Due to the inherent strength of the C-C bond,[3] the C-C bond cleavage poses a great challenge, while an efficient and rapid C-C bond cleavage is synthetically required by synthetic organic chemist to perform desired transformations. Accordingly, many research groups have been involved in developing new methodologies for C-C bond cleavage. There are several well documented methods for C-C bond cleavage, which generally are performed with the help of transition metal catalysts.[4]

As compared to well known and popular C-C bond forming Reformatsky reaction (Path I), the reverse C-C bond breaking retro-Reformatsky reaction (Path II) has been less attractive to organic chemists due to the unavailability of simple, efficient and direct method for such type of transformation (Figure 1). In literature there are a few

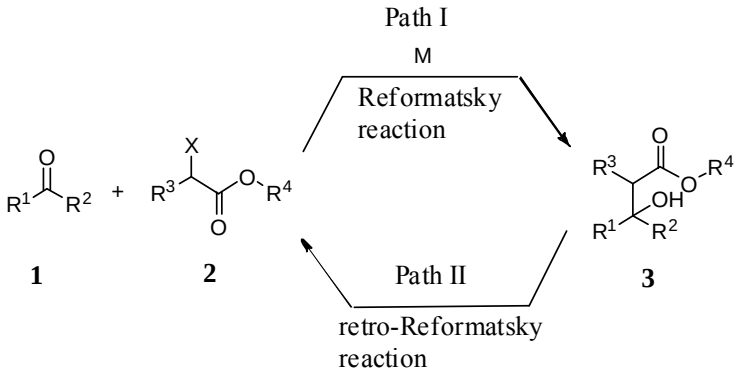


Figure 1. A Reformatsky and retro-Reformatsky reaction.

isolated reports on basic hydrolysis of β-hydroxy ester and / or lactone and/or acid which are shown to undergo very facile C-C bond cleavage, where it is claimed that such reactions as "retro-Reformatsky reaction"[5] but the details of reaction conditions

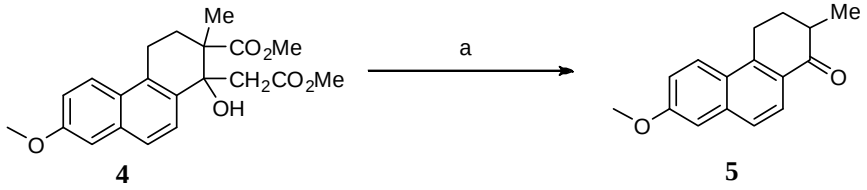
and yields are not clearly mentioned. Additionally no systematic study on the generality of these reactions is reported.

3.3.2. Retro-Reformatsky reaction: A review

A short descriptive presentation of the work reported by other groups is being presented to give a better comparative view of the different methods for retro-Reformatsky reaction of β-hydroxy esters. In literature, there are only few reports available on the retro-Reformatsky reaction of β-hydroxy esters.

Wilds's approach[5a-c] *(J. Am. Chem. Soc.* **1940,** *62,* 824; *J. Am. Chem. Soc.* **1940,** *62,* 2086; Organic Reactions; Wiley, **1942**, Denmark, S. E., Vol 1, P 14)

Wilds *et al.* observed that when they treated β-hydroxy ester **4** with hot concentrated KOH solution, the C-C bond gets cleaved and ketone **5** is formed in the reaction where they did not mention clearly about reaction conditions and yield of the reaction (Scheme 1).

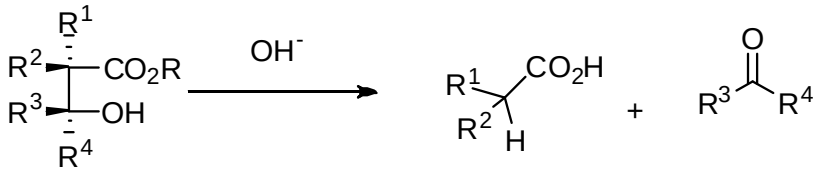


4 **5**

Scheme 1. Reagents and conditions: a) KOH

Adam's approach[5d-e] *(J. Am. Chem. Soc.***1972**, *94*, 2000; Comprehensive organic functional group transformations **2005**, Vol. 1, P 682.)

Adam *et al.* reported that during basic hydrolysis of monosubstituted and disubstituted β-hydroxy ester/acid **6,** it undergoes vary facile C-C bond cleavage. It is claimed



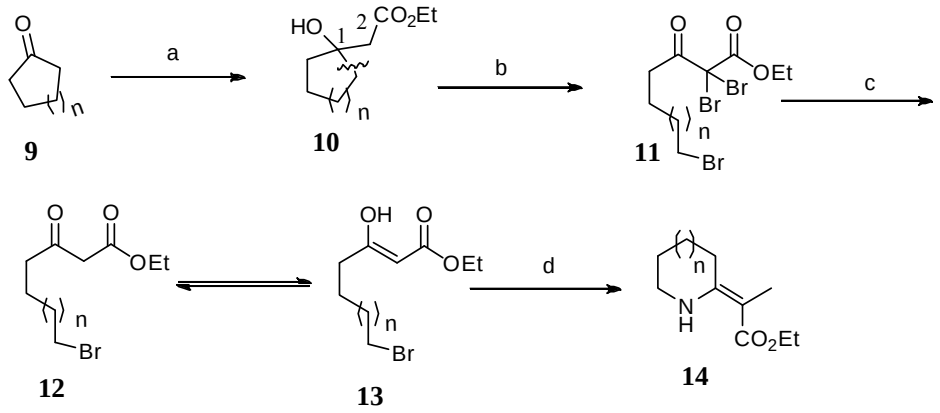
6 **7** **8**

Scheme 2

that such reaction is "retro-Reformatsky reaction, but they did not mention clearly about the yield of the reaction (Scheme 2).

Wang's approach[6] (*J. Org. Chem.* **2004**, *69*, 997)

Wang and co-workers[6] have developed for the formal ring enlargement of cyclic ketones **9**, which comprised of a retro-Reformatsky fragmentation reaction as the key step for a novel and practical synthesis of heterocyclic enamines **14** (Scheme 3). Under alkaline bromination conditions, the Reformatsky adducts **10** derived from five- to seven-membered cyclic ketones underwent efficiently a direct retro-Reformatsky fragmentation, followed by spontaneous α,α-dibromination, to produce α,α,*ω*- tribromo-*β*-ketoester compounds **11** in a one-pot reaction. The reduction of α,α,*ω*-tribromo-*β*-ketoesters **11** with Cu-Zn alloy afforded *ω*-bromo-*β*- ketoesters **12** in good to excellent yields. It is pertinent to mention that the C-C bond cleaved during this process is not the same which is formed during Reformatsky reaction.



Scheme 3. Reagents and conditions: a) $BrCH_2CO_2Et$, Zn, TMSCl, 51-97%; b) Br_2/K_2CO_3, $CHCl_3$, 0 °C; c) Cu/Zn, $MeOH.NH_4Cl$, 10-15 ^{0}C, 15 min; d) NaN_3/DMSO, 80 °C, H_2/Pd/C.

3.3.3. Results and discussion

In the present work, a powerful, one step C-C bond cleavage methodology for a broad range of acyclic β-aryl-β-hydroxy ester substrates utilizing NaH as a base is described (Figure 3). This methodology provides a highly robust C-C bond cleavage protocol for a diverse array of acyclic β-aryl-β-hydroxy esters.

Li and co-workers[7] reported direct retro-Barbier fragmentation reaction of cyclic tertiary alcohol under Br_2/K_2CO_3 reaction conditions to produce *ω*-bromoketone in

excellent yields. Wang and co-workers[6] reported a direct retro-Reformatsky fragmentation reaction of cyclic tertiary β-hydroxy ester **10** with Br_2/K_2CO_3 to give ω-bromo-β-ketoester **11** in good yields, where C1-C2 bond was formed in the Reformatsky reaction while C1-C3 bond gets cleaved during retro-Reformatsky fragmentation (Figure 2).

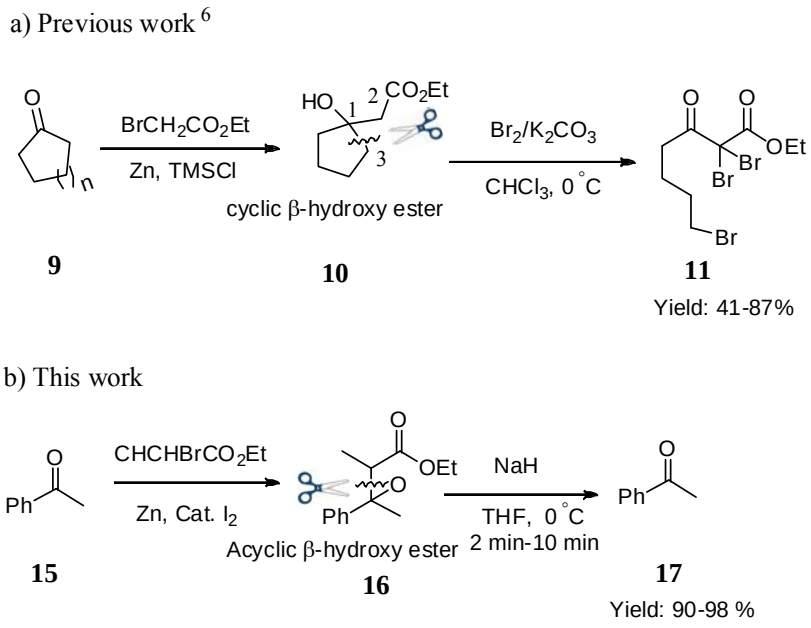
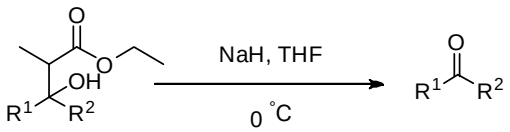


Figure 2. Comparison between previous work and present work.

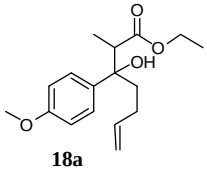
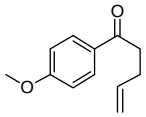
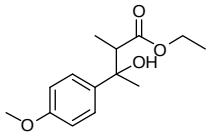
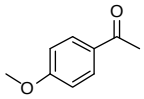
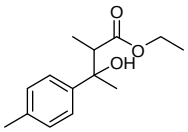
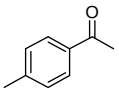
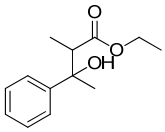
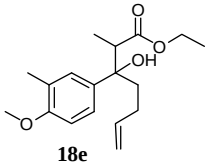
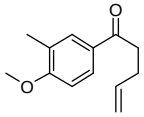
The initial investigation was carried out on the **18a** as a model substrate with 3 equiv of NaH at 0 °C in THF solvent. Delightfully, the desired retro-Reformatsky fragmentation product **19a**[8] was obtained in excellent yield (98%) by stirring for very short time (2 min) at 0 °C (Table 1, entry 1). Subsequently, ^{1}H NMR and ^{13}C NMR analysis of the crude reaction mixture showed it to be very pure product. The efficiency of the reaction was further confirmed by GC analysis of the reaction mixture. Encouraged by this excellent result, it was decided to optimize the reaction conditions. Accordingly, under the identical reaction conditions different mild bases like $NaHCO_3$ and K_2CO_3 were tested, but did not furnish the ketone. In order to optimize the reaction conditions the quantity of NaH was varied and it was found that the reaction worked exceptionally well with 3 equivalents of NaH. The best result were obtained with 3 eq. NaH as a base and THF as the solvent which was used as optimum reaction condition.

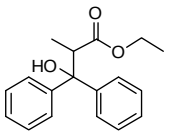
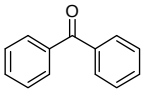
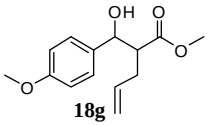
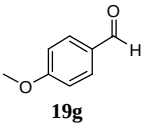
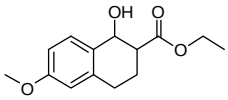
After establishing the optimum reaction conditions, the attention was turned to examine the scope of this reaction. The retro-Reformatsky fragmentation reactions were examined on various types of acyclic β-aryl-β-hydroxy esters and the results are summarized in Table 1.

Table 1. retro-Reformatsky fragmentation reaction



18 **19**

S.N.	Reactant[a]	Product	Reaction time[b]	Yield (%)[c]
1	 **18a**	 **19a**	2 min	98%
2	 **18b**	 **19b**	5 min	94%
3	 **18c**	 **19c**	2 min	98%
4	 **18d**	 **19d**	2 min	95%
5	 **18e**	 **19e**	2 min	95%

6	 **18f**	 **19f**	5 min	98%
7	 **18g**	 **19g**	10 min	90%
8	 **18h**	---	---	---

[a] esters were prepared by literature procedure[9] except **17g** and **17h**. [b] after addition of NaH. [c] isolated yield.

The influence of nature of aromatic ring (R^1 group) of the β-aryl-β-hydroxy esters on the retro-Reformatsky fragmentation reaction was examined under optimized reaction condition. Reformatsky adduct of acetophenone **18d**, *p*-methyl acetophenone **18e**, *p*-methoxy acetophenone **18b** and 2-methyl anisole **18e** had no adverse effect on the efficiency of C-C bond cleavage reactions, furnishing corresponding ketones in excellent yields (94-98%) in very short time (entry 2-5). The aliphatic part (R^2 group) of the β-aryl-β-hydroxy esters was also varied, to study the effect on the efficiency of the reaction. Accordingly, when the aliphatic part of the Reformatsky adduct was changed from methyl **18b** to homoalyllic **18a** to benzene **18f** (entry 1-2 and 6), C-C bond cleavage occoured smoothly and there was hardly any effect on the yield and reaction time (94-98%, 2-5 min).

Having established the usefulness of our method for different kinds of tertiary β-aryl-β-hydroxy esters, it was decided to establish the versality and generality of our method for the secondary β-aryl-β-hydroxy esters. It is worth noting that, when acyclic secondary β-aryl-β-hydroxy ester **18g** was subjected to the standard reaction condition, gratifyingly, we found that it also underwent very smooth C-C bond cleavage within 10 min in very good yield (90%) at 0 °C (entry 7). Thus this method is completely compatible with tertiary as well as secondary β-aryl-β-hydroxy esters. However, when cyclic secondary β-aryl-β-hydroxy ester **18h** was treated under optimized reaction condition it failed to cleave C-C bond (entry 8).

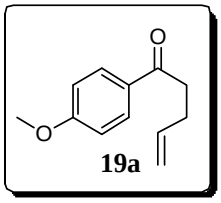
3.3.4. Conclusion

In conclusion, an efficient single step C-C bond cleavage reaction of tertiary as well as secondary Reformatsky adduct, β-aryl-β-hydroxy ester by using NaH as a base has been developed. Based on these finding, this methodology could be generalized for the temporary protection and deprotection strategy of carbonyl group, where deprotection can be carried out under basic condition because the C-C bond cleavage reaction involving a wide scope of β-aryl-β-hydroxy ester in excellent yields and in very short reaction times. No detailed study of the mechanism of the cleavage has been undertaken. Current work in this laboratory is aimed at exploring and expanding the full scope of this facile transformation and understanding the mechanism of this new C-C bond cleavage methodology. It was believed that the finding from the present study should provide on impetus to pave way for the further research into alternative, metal free C-C bond fission methodologies.

3.3.5. Experimental

General procedure for retro-Reformatsky reaction: To a cold (0 ºC), magnetically stirred solution of Reformatsky adduct (1 molar equiv) in anhydrous THF, was added 60% NaH (3 molar equiv) in one portion under nitrogen. The resulting mixture was stirred at that temperature until the completion of reaction. The reaction mixture was quenched with 10% aq. NH_4Cl solution and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The crude reaction mixture was purified by flash silica gel column chromatography (SiO_2) using pet ether/ethyl acetate as eluent to furnish the carbonyl compound.

1-(4-Methoxyphenyl)pent-4-en-1-one (19a)

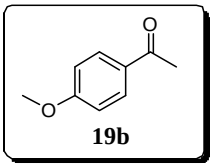


19a

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4) : δ 2.42-25.54 (m, 2H), 3.02 (t, J=7.3 Hz, 2H), 3.86 (s, 3H), 4.96-5.13 (m, 2H), 5.80-6.00 (m, 1H), 6.92 (d, J=9.0 Hz, 2H), 7.94 (d, J= 9.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) : δ 28.56, 37.48, 55.53, 113.79, 115.22, 130.14, 130.36, 137.57, 163.49, 198.08.

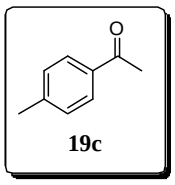
1-(4-Methoxyphenyl)ethanone (19b)


19b

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4) : δ 2.55 (s, 3H), 3.87 (s, 3H), 6.92 (d, *J*=10 Hz, 2H), 7.92 (d, *J*=10 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4) : 26.1, 55.2, 113.5, 130.2, 130.4, 163.3, 196.0.

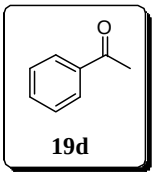
1-*p*-Tolylethanone (19c)


19c

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4) : δ 2.41 (s, 3H), 2.56 (s, 3H), 7.23 (d, *J*= 8 Hz, 2H), 7.84 (d, *J*=8 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4) : 21.1, 25.9, 128.0, 128.7, 134.3, 143.1, 196.7.

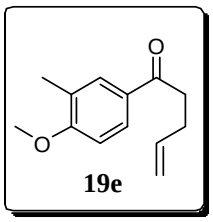
Acetophenone (19d)


19d

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4) : δ 2.61 (s, 3H), 7.42-7.57 (m, 3H), 7.93-7.98 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4) : 26.4, 128.2, 128.5, 132.9, 137.0, 197.6.

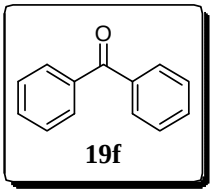
1-(4-Methoxy-3-methylphenyl)pent-4-en-1-one (19e)


19e

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 2.25 (s, 3H), 2.42-2.54 (m, 2H), 3.02 (t, *J*=7.1 Hz, 2H), 3.90 (s, 3H), 4.97-5.14 (m, 2H), 5.80-6.01 (m, 1H), 6.84 (d, *J*=8.9 Hz, 1H), 7.78 (d, *J*=2.5 Hz, 1H), 7.83 (dd, *J*=2.3, 8 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$ +CCl_4): δ 16.21, 28.37, 37.19, 55.32, 109.06, 115.04, 126.55, 128.04, 129.47, 130.52, 137.51, 161. 56, 197.77.

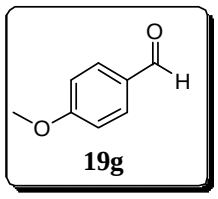
Benzophenone (19f)


19f

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.44-7.59 (m, 6H), 7.79-7.83 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$ +CCl_4): δ 128.19, 129.98, 132.28, 137.56, 196.24.

Anisaldehyde (19g)



19g

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 3.87 (s, 3H), 6.98 (d, J=8.7 Hz, 2H), 7.81 (d, J=8.7, 2H), 9.86 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$ +CCl_4): 55.37, 114.20, 129.96, 131.83, 164.47, 190.28.

3.3.6. References

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List of Publications

1. Subhash P. Chavan,* **Sumanta Garai** and Uttam R. Kalkote "A highly diastereoselective total synthesis of (±)-heritonin and (±)-heritol" *Tetrahedron* **2012**, *68*, 8509-8514.

2. Subhash P. Chavan,* **Sumanta Garai**, Achintya Kumar Dutta, and Sourav Pal "Friedel–Crafts Acylation Reactions Using Esters" *Eur. J. Org. Chem.* **2012**, *2012*, 6841–6845.

3. Subhash P Chavan*, **Sumanta Garai** and Kailash P Pawar "Asymmetric total synthesis of (−)-venlafaxine using an organocatalyst" *Tetrahedron Lett.* (dx.doi.org/10.1016/j.tetlet.2013.02.029).

4. Subhash P Chavan*, **Sumanta Garai** "A highly stereocontrolled asymmetric total synthesis of epimer of 7-deoxypancratistatin" (communicated to *Eur. J. Org. Chem.*).

5. Subhash P Chavan*, **Sumanta Garai** "A simple and straightforward retro-Reformatsky reaction" (manuscript to be communicated).

List of Patents

1. Subhash P Chavan*, **Sumanta Garai** and Kailash P Pawar "Asymmetric total synthesis of (−)-venlafaxine using organocatalyst" Indian Patent. Provisional filling no.- 2300DEL2012, date 26th July, 2012.

Erratum