SYNTHETIC STUDIES TOWARDS SESQUITERPENE BUTENOLIDES, (*S*)-ar-HIMACHALENE,DEVELOPMENT OF SYNTHETIC METHODOLOGY AND ITS APPLICATION IN SYNTHESIS OF (*R*)-VENLAFAXINE.

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By

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled ***"Synthetic Studies towards sesquiterpene butenolides, (S)-ar-himachalene, development of synthetic methodology and its application towards (R)-(-)-venlafaxine"*** *submitted by* ***Harshali Suresh Khatod*** *was carried out under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.*

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DECLARATION

I hereby declare that the thesis entitled ***"Synthetic Studies towards sesquiterpene butenolides, (S)-ar-himachalene, development of synthetic methodology and its application towards (R)-(-)-venlafaxine"*** submitted for Ph. D. degree to the University of Pune has been carried out at Division of Organic Chemistry, National Chemical Laboratory, Pune, under the supervision of Dr. Subhash P. Chavan and the work is original and has not been submitted in part or full by me for any degree or diploma to this or any other university.

May, 2016

Division of Organic Chemistry

National Chemical Laboratory,

Pune-411 008

Harshali Suresh Khatod

Dedicated to

……..My Family

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NCL, Pune *Harshali S. Khatod.*

1. All melting points and boiling 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 particular section only.
3. All solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80 ^{o}C.
4. Organic layers were dried over anhydrous sodium sulfate.
5. The reaction progress was monitored by the TLC analysis 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 (60-120 or 200-400 mesh) was used as the stationary phase or otherwise as stated.
7. IR spectra were recorded on a Perkin-Elmer Infrared Spectrophotometer Model 68B or on a Perkin-Elmer 1615 FT Infrared spectrophotometer.
8. ^{1}H NMR and ^{13}C NMR spectra were recorded on **Bruker AV-200** (50 MHz) or **Bruker AV-400** (100 MHz) or **Bruker DRX-500** (125 MHz). Figures in the parentheses refer to ^{13}C frequencies. Tetramethylsilane was used as the internal standard.
9. Optical rotations were recorded at ambient temperature on JASCO Dip-181 digital polarimeter using sodium vapor lamp.
10. Mass spectra were recorded at ionization energy 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-Tof micro with spray source (ESI^{+}) mode.
11. Starting materials were obtained from commercial sources or prepared using known procedures.
12. Microanalytical data were obtained using a Carlo-Erba CHNS-O EA 1108 Elemental analyzer, within the limits of accuracy (± 0.4%).

Ac	Acetyl
Ar	Aryl
NH_4Cl	Ammonium chloride
aq	Aqueous
Bu	Butyl
^{t}Bu	*tertiary*-Butyl
Bz	Benzoyl
Cat.	Catalytic
$CDCl_3$	Deuterated Chloroform
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethylazodicarboxylate
DEG	Diethyleneglycol
DEPT	Distortionless Enhancement by Polarization Transfer
DIBAL	Diisobutyl aluminium hydride
DMP	Dess−Martin periodinane
DMAP	4-Dimethyl amino pyridine
DMF	*N,N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
DMS	Dimethyl sulfide
DMSO-d_6	Deuterated dimethylsulphoxide
Et	Ethyl
EtOAc	Ethyl acetate
g	gram (s)
h	hour (s)
IPA	*iso*-Propyl alcohol
IR	Infra red
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry

HTIB	Hydroxy(tosyloxyiodo)benzene
Hz	Hertz
LAH	Lithium aluminium hydride
LDA	Lithium diisopropyl amide
mCPBA	*m*-Chloroperoxybenzoic acid
Me	Methyl
Mes	Mesitylene
MOM	Methoxymethyl
min	Minute (s)
mL	Mililitre (s)
MP	Melting point
Ms	Methanesulfonyl
NMO	*N*-Methylmorpholine *N*-oxide
NMP	*N*-Methylpyrrolidinone
ORTEP	Oak Ridge Thermal Ellipsoid Plot
pet. ether	Petroleum ether
Piv.	Trimethyl acetyl (pivaloyl)
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Pd/C	Palladized carbon
Ph	Phenyl
PPA	Polyphosphoric acid
TBAF	Tetrabutylammonium fluoride
PPh_3	Triphenyl phosphine
^{i}Pr	Isopropyl
PTC	Phase Transfer Catalyst
*p*TSA	*p*-Toluenesulfonic acid
Py	Pyridine
RCM	Ring Closing Metathesis
NaOMe	Sodium methoxide
$NaBH_4$	Sodium borohydride
NaH	Sodium hydride
Na_2SO_4	Sodium sulphate
Na_2SO_3	Sodium sulphite

rt	Room temperature
TBAB	Tetrabutyl ammonium bromide
TBAI	Tetrabutyl ammonium iodide
TEMPO	2,2,6,6−Tetramethylpiperidin−1−yl)oxyl
TBSOTf	*tert*-Butyldimethylsilyl triflate
tert	*tertiary*
TFA	Trifluoroacetic acid
TFAA	Trifluroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	*N*,*N*,*N'*,*N'*-Tetramethylethylenediamine
TMSCl	Trimethylsilyl chloride
Ts	Toluenesulfonyl
TPAP	Tetra-*n*-propylammoniumperruthenate

The thesis entitled, **"Synthetic Studies Towards sesquiterpene butenolides, (*S*)-ar-himachalene, development of synthetic methodology and its application towards (*R*)-(-)-venlafaxine"** is divided into three chapters.

Chapter 1 deals with the introduction and model study of hydroxy cadinane sesquiterpene butenolides, model study and total synthesis of 8-*epi*-heritianin/ 10-*epi*-vallapin and is divided into three sections.

Chapter 2 deals with the introduction and synthesis of optically active *ar*-himachalene and acetylation/ and aroylation of hydroxy compounds by means of 2-IBA and *p*-TSA and is divided into three sections.

Chapter 3 deals with the exploration of diastereoselectivity and enantioselectivity in unusual Grignard reaction and its application in synthesis of styryl lactones and (*R*)-venlafaxine and is divided into three sections.

Chapter 1: Synthetic studies towards hydroxy cadinane sesquiterpene butenolides.

Section 1: Introduction to cadinane class of sesquiterpene butenolides.

Miles and co-workers have isolated cadinane sesquiterpene lactones heritol (**1**), heritonin (**2**), vallapin (**3**), heritianin (**4**) and vallapianin (**5**) (**Figure 1**) from the sap of the mangrove plant *Heritiera littoralis* of Philippines and other tropical countries, which were shown to possess ichthyotoxicity in ppm quantities to *Tilapia nilotica* fingerlings and is used by native fishermen to kill fish.

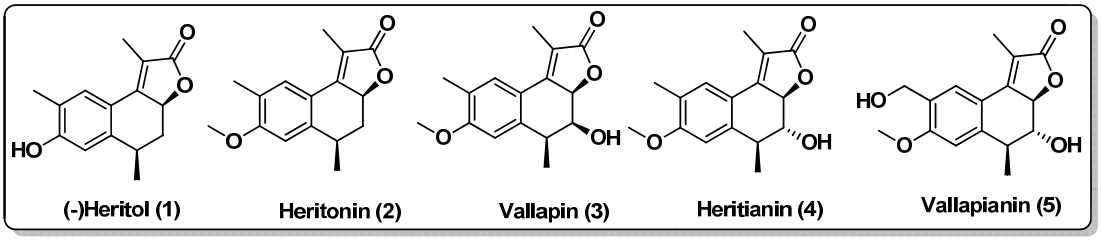
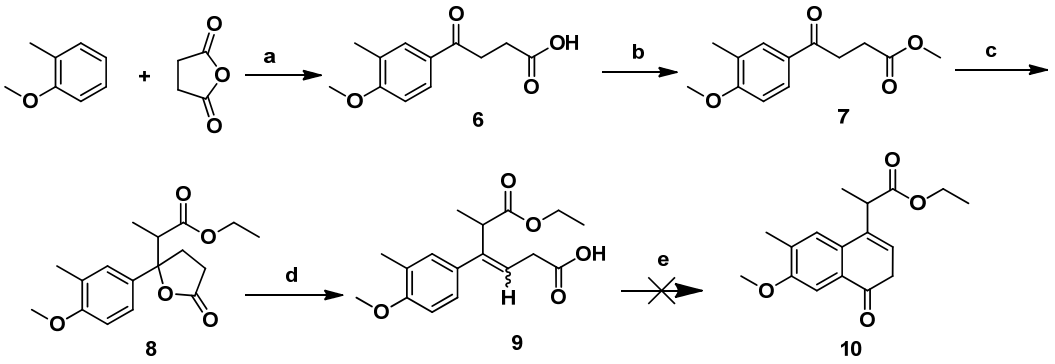


Figure 1 Cadinane sesquiterpenes

Section 2: Attempted synthesis of vallapin and model studies towards hydroxy cadinane butenolide framework.

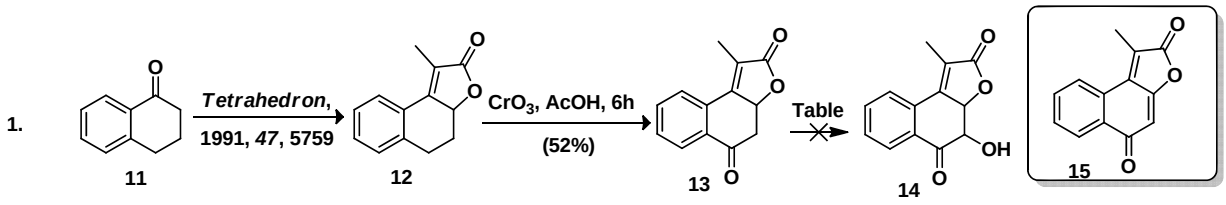
The synthesis was initiated from Friedal–Craft's acylation reaction between *o*–cresol methyl ether and succinic anhydride, furnished ketoacid **6** (**Scheme–1**). The ketoacid **6** was converted into it's methyl

ester **7** which was further treated with ethyl–2–bromopropionate and Zn under Reformatsky reaction, furnished lactone **8**, the lactone ring opening in **8** was observed, when it was treated with $AlCl_3$, furnished acid **9** in 89% yield. In order to cyclise the acid was treated with different reagents, unfortunately formation of cyclised product **10** was not observed.



Scheme–1 Attempted synthesis of vallapin; Reagents and conditions: *(a) $AlCl_3$, DCM, 0 °C– RT,78%; (b) MeOH, H_2SO_4, reflux, 3 h, 88%; (c) Ethyl–2–bromopropionate, Zn, I_2, ether, reflux, 2 h, 78%; (d) $AlCl_3$, DCM, RT, 89%.(e) TFA, TFAA/ and PPA/ and excess $AlCl_3$ (4 equiv.)/ and conc. H_2SO_4 (impregnated on silica).*

In order to perform model study (**Scheme–2**) compound **12** was treated with CrO_3 in presence of AcOH, to furnish compound **13**. Tetralone **13** was treated under various oxidation conditions. However, formation of eliminated product **15** was observed. The compound **13** was then subjected under hydrogenation conditions where formation of compound **16** was observed.

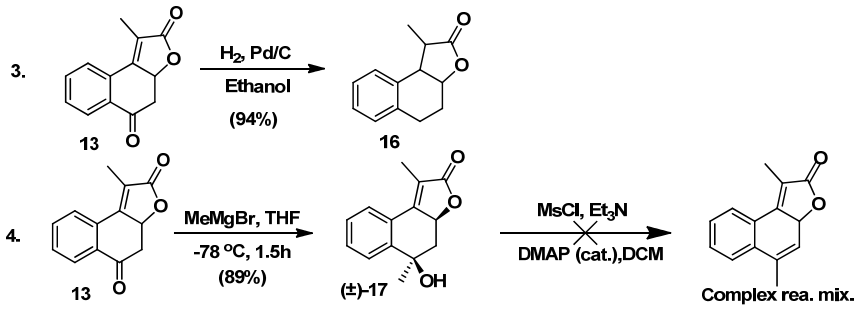


Scheme–2: Model study on cadinane framework

SN	Reagents and conditions	Process	Yield (%)
1	*m*–CPBA, $BF_3.OEt_2$, AcOH, H_2O, PhI (cat.), 20 h	Acetoxylation	**15** (38%)
2	Ac_2O, $BF_3.OEt_2$, H_2O_2, PhI (cat.), 30 °C, 7 h	Acetoxylation	**15** (49%)

3	*P*–TSA, PhI (cat.), *m*–CPBA, ACN, 50 ^{o}C, 5 h	Tosyloxylation	**15** (36%)
4	HTIB, ACN, RT, 2 h	Tosyloxylation	**15** (58%)
5	Oxone, TFAA, ACN: H_2O, PhI (cat.), 90 ^{o}C, 15 h	Hydroxylation	**15** (42%)

Further, compound **13** was trated with Grignard reagent at -78 ^{o}C afforded compound **17** which upon elimination furnished complex reaction mixture (**scheme-3).**

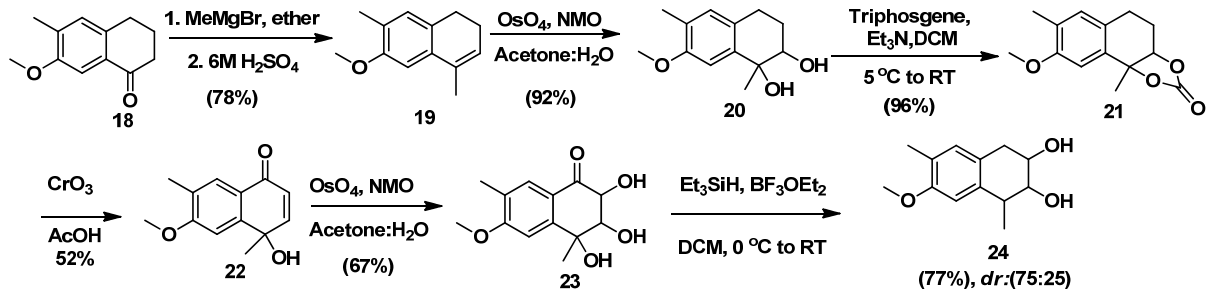


Scheme–3: Model study on cadinane framework

Model study on cadinane framework has been done, proved useful for developing further synthetic strategy.

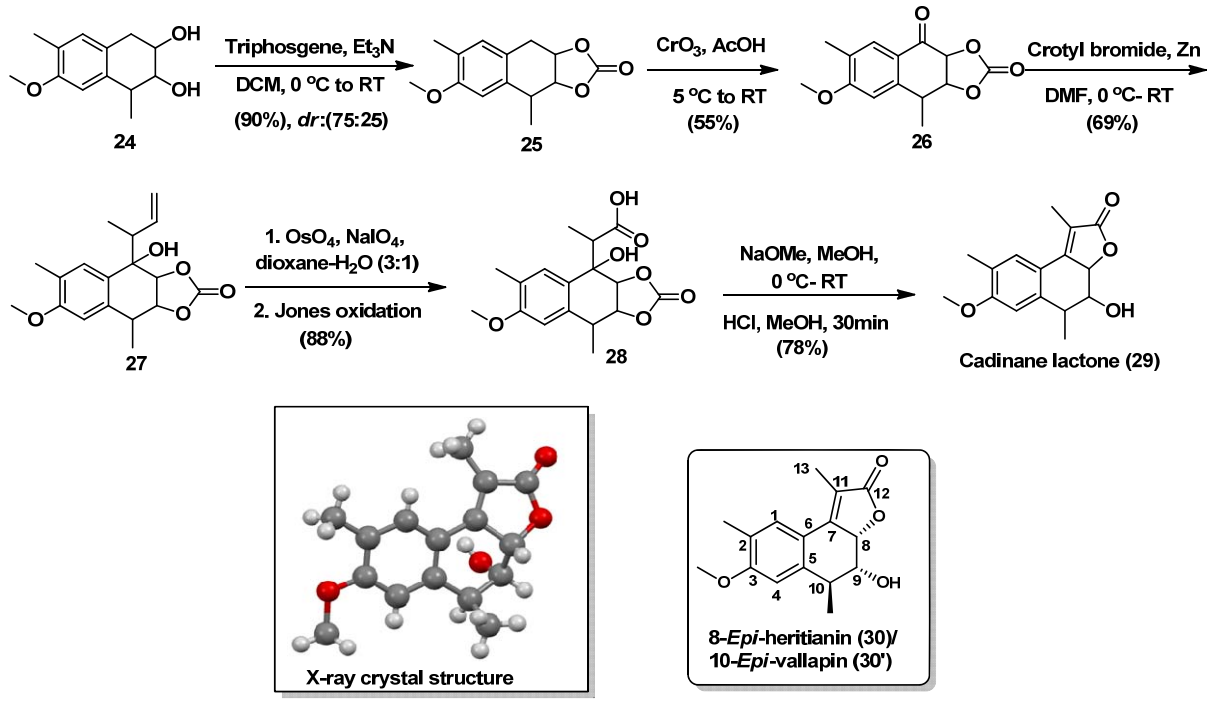
Section 3: Total synthesis of 8-*epi*-heritianin/ 10-*epi*-vallapin.

This section describes synthesis of cadinane lactone framework. The tetralone **18** after Girgnard reaction and acidic workup furnished compound **19** which underwent dihydroxylation to afford diol **20** which was protected as its carbonate. The carbonate **21** on treatment with CrO_3 in presence of AcOH furnished compound **22** in 58% yield (**Scheme-4**). The enone **22** upon dihydroxylation afforded triol **23** in 67% yield which was subjected for reductive removal of hydroxy group using Et_3SiH. The resulting diol **24** was then subjected for carbonate protection, furnished compound **25** followed by benzylic oxidation by using CrO_3 to give compound **26** which was treated under Barbier reaction conditions with crotyl bromide to furnish product **27**. Under OsO_4, $NaIO_4$ cleavage and Jones oxidation, formation of acid **28** was observed. The base



Scheme-4

mediated carbonate deprotection, butenolide formation under acidic conditions and elimination furnished cadinane lactone framework **29 (Scheme-5)**. The cadinane lactone thus synthesized, on X-ray characterisation proved to be 8-*epi*-heritianin (**30**)/ 10-*epi*-Vallapin (**30'**).



Scheme-5

Chapter 2: Synthetic studies towards (*S*)-*ar*-himachalene and acetylation/ and aroylation of hydroxy compounds by means of 2-IBA and *p*-TSA.

Section 1: Introduction to *ar*-himachalene.

Ar-himachalene was isolated in 1952 by Rao and Sukh Dev as a major sesquiterpene constituent of the essential oil from himalayan *Cedrus deodara Loud*. It was later also isolated in 2001 by Bartelt and

co-workers as a male pheromone component of the flea beetles *Aphthona flava* and *Phyllotreta cruciferae* (**Figure-2**).

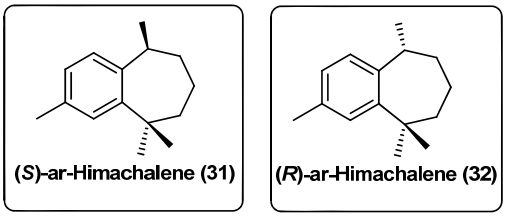
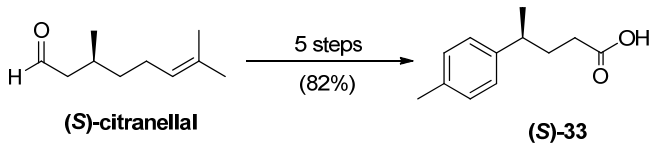


Figure 2: Structurally related sesquiterpines

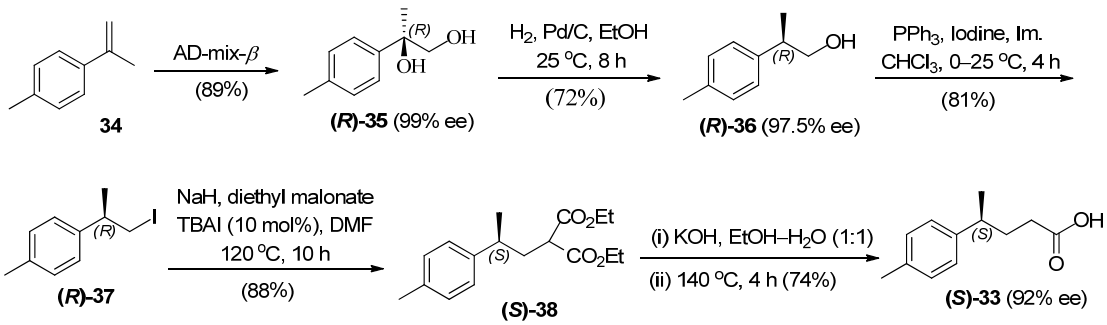
Section 2: Asymmetric total synthesis of *ar*-himachalene by chiral pool and chirality induction approach.

(*S*)-*ar*-Himachalene (**31**) can be accessed from (*S*)-4-(*p*-tolyl)-pentanoic acid (**33**) which was prepared by two routes, (i) from (*S*)-citronellal by one pot Michael addition, Robinson annulation and decarboxylation, followed by aromatization and Jones oxidation reaction (**Scheme-6**) and (ii) from the *p*-methyl *α*-methyl styrene (**34**), in which chirality at benzylic position can be introduced using the Sharpless asymmetric dihydroxylation as the key step.



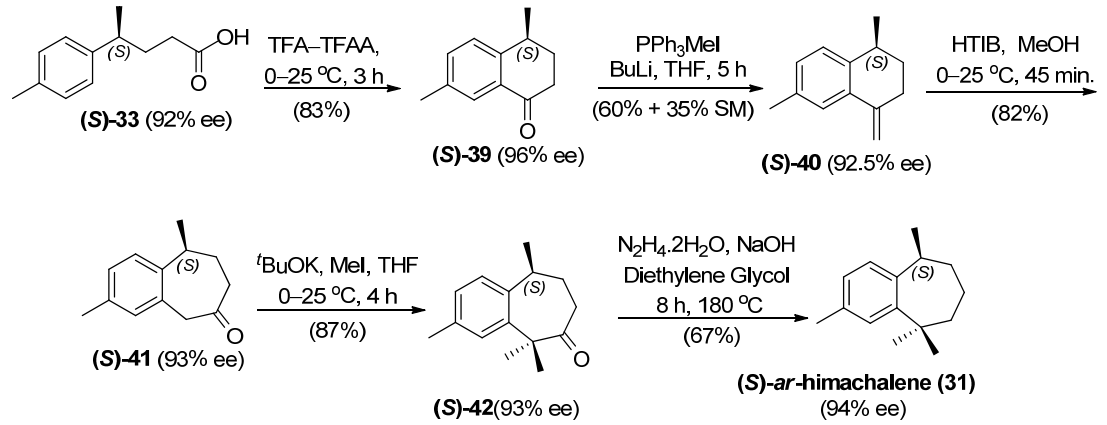
Scheme 6. Preparation of (*S*)-4-(*p*-tolyl)pentanoic acid (**33**) from (*S*)-citronellal

Sharpless asymmetric dihydroxylation of styrene derivative **34** was carried out in the presence of AD-mix-*β*, furnished diol **35** in 89% yield and 97% *ee*. This diol **35** was then converted to alcohol **36** by hydrogenolysis. The best result for inversion was obtained by using 10% Pd/C with 97% *ee* and 72% yield. Alcohol **36** was converted to its iodo derivative **37**, by using triphenylphosphine, imidazole and iodine in 81% yield, which was further converted into diester **38**. The diester was hydrolysed under basic conditions to diacid which was further heated to furnish the desired chiral acid **33** (**Scheme 7**).



Scheme 7. Synthesis of (*S*)-*ar*–himachalene

Compound **33** under TFAA/ TFA mediated cyclisation furnished tetralone **39**. One carbon Wittig olefination of (*S*)-**39** gave compound (*S*)-**40** with exocyclic methylene group. This compound upon treatment with Koser's reagent underwent facile ring expansion to furnish ketone (*S*)-**41**. Further, dimethylation of the keto compound **41** was done, furnished the dimethyl compound **42**, followed by Wolff–Kishner reduction to furnish the target molecule (*S*)-*ar*–himachalene (**32**) (**Scheme-8**). The opposite enantiomer (*R*)–*ar*–himachalene (**32**) was also synthesized with equivalent overall yields and 97% *ee* (by chiral GC).



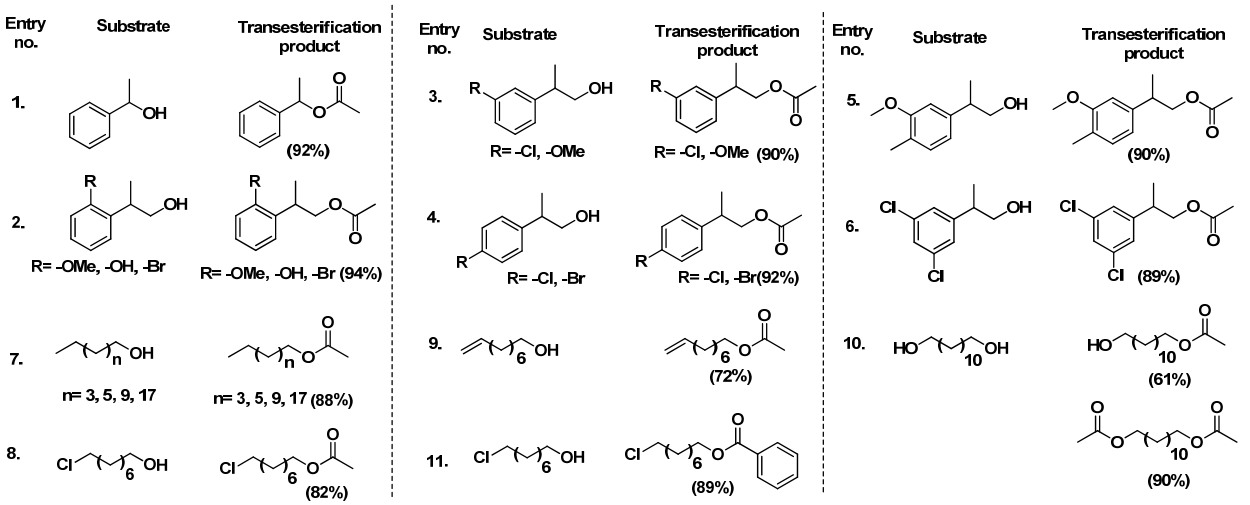
Scheme 8. Completion of synthesis of (*S*)-*ar*–himachalene

Section 3: Acid catalysed protocol for acetylation/ and aroylation of hydroxy compounds by means of 2-iodobenzoic acid (2-IBA) and *p*-TSA.

Esters are usually synthesizes from alcohols and carboxylic acids or acid chlorides and acid anhydrides or rarely from ester as the acylating agent. Many acidc or basic catalysts have been used for this purpose. A variety of Lewis acids such as $Sc(NTf_2)_3$, $TiCl(OTf)_3$, $La(Oi\text{-}Pr)_3$, $Sn(OTf)_2$, TMSCl and

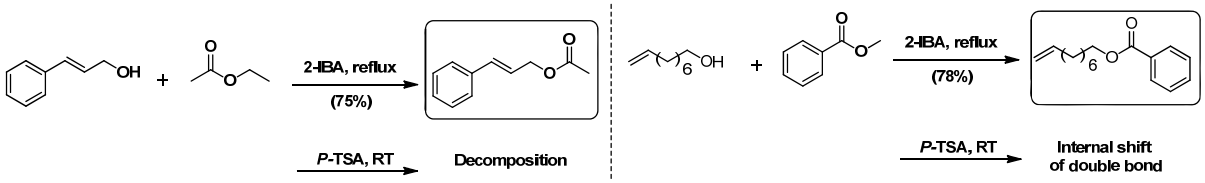
TMSOTf, have also been applied as catalysts and reagents to mediate the reaction between alcohols and acylating agent. This section describes transesterification/ acetylation/ and hydroxy group protection of alcohol by means of 2-IBA/ and *p*-TSA.

Table-2: Acetylation/ and benzoylation of benzylic, homobenzylic and aliphatic alcohols



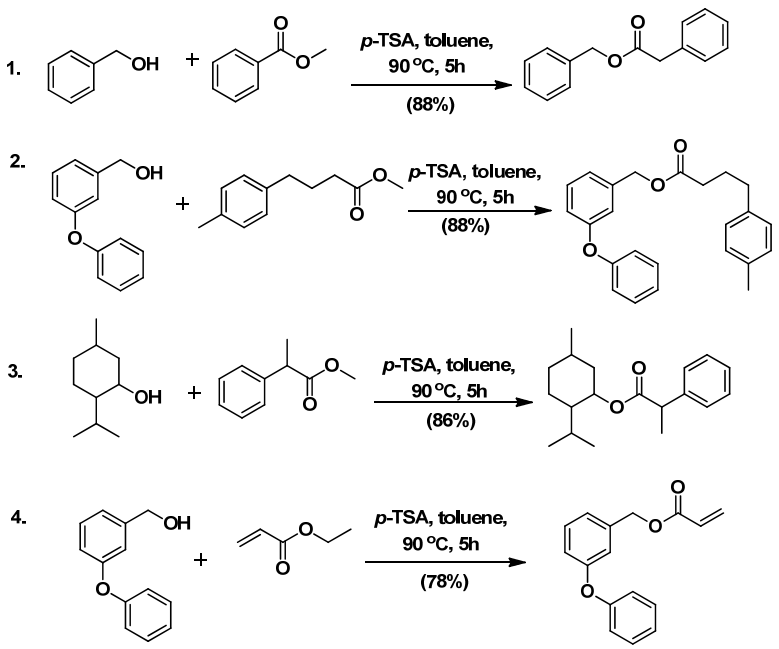
[c]reaction conditions: alcohol (1 eq.), ester (1.2 eq.), IBA (1.2 eq.)

It was found that use of *p*TSA is unreliable if substrate contains acid sensitive groups, in such case application of 2-IBA provides satisfactory results (**Scheme 9**).



Scheme 9.

Acetylation of alcohol with *p*TSA and 2-IBA in presence of EtOAc, a solvent as well as acetylating reagent at RT resulted in the corresponding acetates in good yields. Aroylation of sterically hindered alcohols also proceeded smoothly in presence of *p*-TSA (**Scheme-10**).

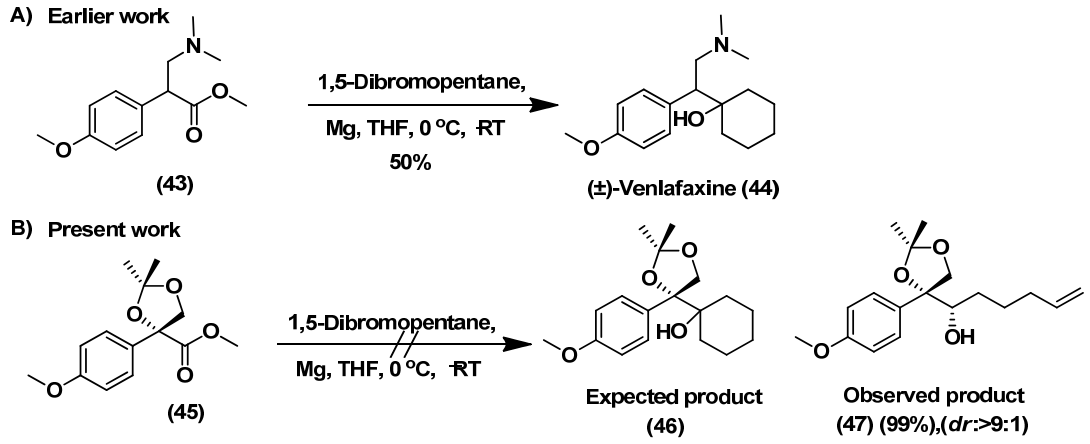


Scheme-10: Miscellaneous examples of acid catalysed transesterification/ aroylation of alcohols.

Chapter 3: Exploration of unusual Grignard reaction with application towards synthesis of 7-*epi*-(+)-goniodiol, 8-*epi*-*(-)*-goniodiol and (*R*)-venlafaxine.

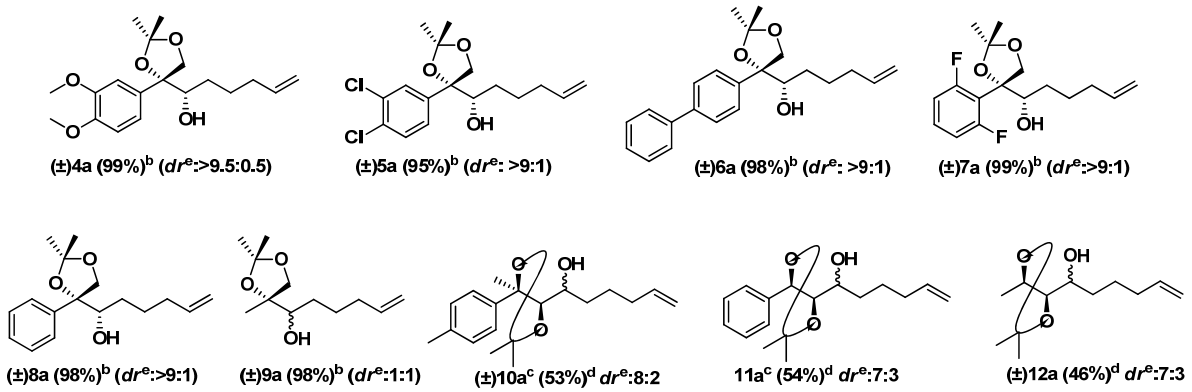
Section 1: Exploration of diastereoselectivity in unusual Grignard reaction.

Unusual diastereoselective Grignard reaction has been explored on a variety of carboxylic esters. In the present case steric bias due to presence of quaternary centre adjacent to acetonide ester at benzylic position is ascribed to the formation of an intramolecularly reduced product in almost quantitative yield. This steric hindrance is responsible for diastereoselectivity observed with a variety of aromatic as well as aliphatic esters. Unusual Grignard reaction product furnished long chain secondary alcohols possessing terminal olefin, which are synthetically important intermediates. The unusual Grignard reaction was observed during the following transformation (**Scheme-11**).



Scheme-11: Observation of unusual Grignard reaction

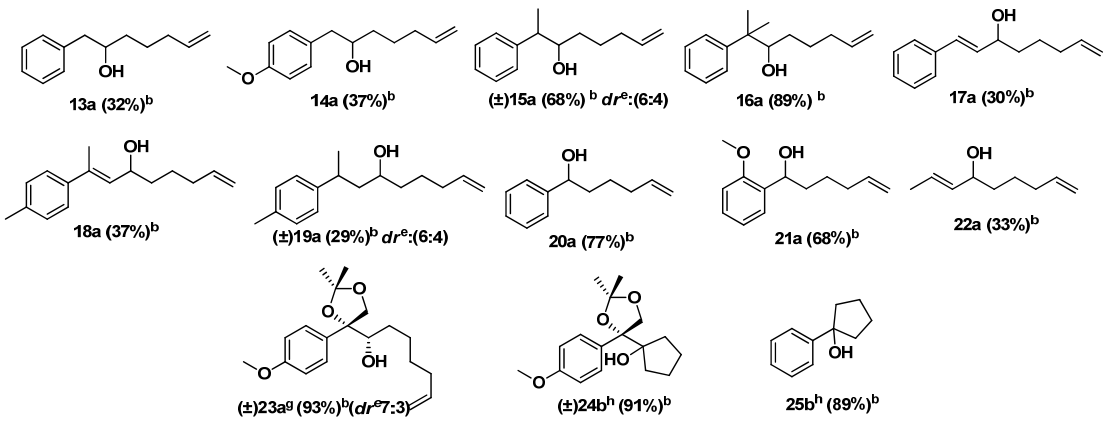
The reaction of *in situ* generated Grignard reagents was systematically studied on a diverse range of esters and the results obtained are depicted in (**Figure 4**).



a) Reaction conditions: 1,5−Dibromopentane, Mg, THF, 0 ^{o}C−RT, 5h, b) Yields calculated after column chromatographic purification, c) Unable to separate two alcohols by column chromatography so acetate protection of secondary alcohol followed by its purification from respective unreacted cycloalkanol and deprotection furnished pure products d) Yield and *dr* calculated over 2 steps, e) *dr*: diastereomeric ratio determined by ^{1}H-NMR analysis.

Figure 4. Unusual Grignard reaction of acetonide protected ester substrates

Furthermore, variety of esters were reacted under similar reaction conditions, they led to the formation of unusual products but in reduced yields due to decrease in the steric bulk. It is evident from the above study that absence of acetonide steric bias does affect the yield and diastereoselectivity (**Figure-5**). In order to study the scope and limitations of the above observation, the esters were subjected to the treatment with terminal di(bromomagnesio)alkanes, with varying chain lengths (examples- 23a, 24b, 25b, Figure-5).



a), b), and e) same as Figure-4, g)1,6−Dibromohexane, Mg, THF, RT, 5h; h) 1,4−Dibromobutane, Mg, THF, 0 ^{o}C−RT, 5h.

Figure-5: Exploration of unusual Grignard reaction

Section 2: Styryl lactones: A brief Review including diastereoselective synthesis of 7-*epi*-(+)-goniodiol and 8-*epi-(-)*-goniodiol.

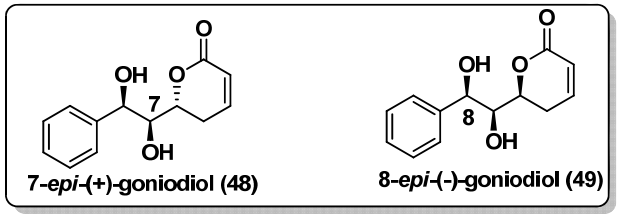
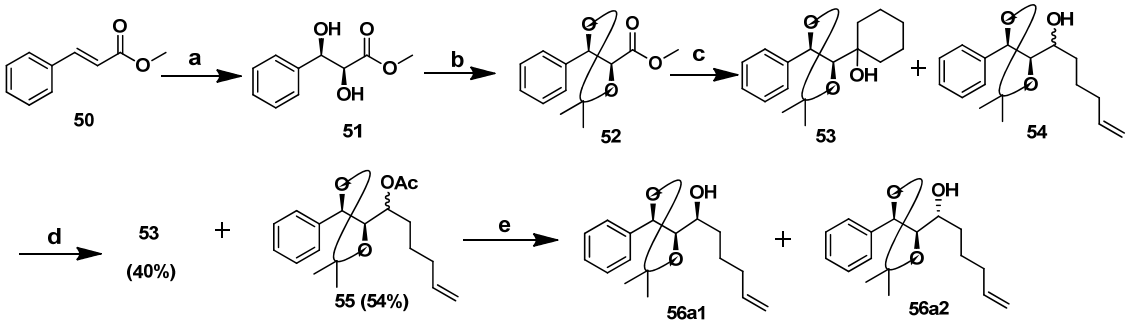


Figure 6: Styryl lactones

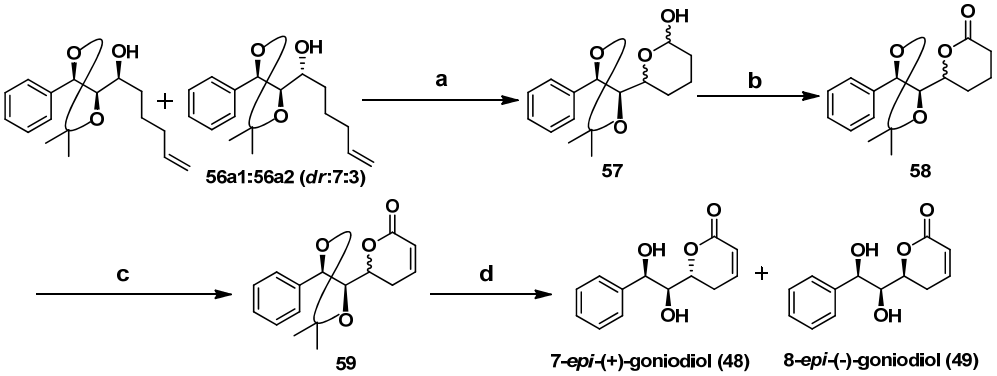
The plants of the Goniothalamus genus provide multi-functionalized molecules known as styryl lactones, isolated from the leaves and twigs of *Goniothalamus sesquipedalis.* These natural products have been shown to exhibit potent and selective cytotoxic activity (**Figure-6**).



Scheme 12−Application of unusual Grignard reaction in the synthesis of 7−*epi*−(+)−goniodiol (**48**) and 8−*epi*−(−)−goniodiol (**49**)

Reagents and conditions− *(a) $K_3Fe(CN)_6$, K_2CO_3, methane sulphonamide, OsO_4, $(DHQD)_2PHAL$, $^tBuOH:H_2O$, 0 ^oC, 24 h, 78%, >99% ee; (b) 2,2−Dimethoxypropane, P−TSA (cat.), DMF, RT, 6 h, 97%; (c) 1,5−Dibromopentane, Mg metal turnings, THF, 0 ^oC− RT, 5 h, 90%, (dr: 7:3), >98% ee; (d) Acetic anhydride, triethylamine, DMAP (cat.), DCM, 0 ^oC− RT, 2 h; (e) K_2CO_3, MeOH, 0 ^oC− RT, 2 h, 95%,.*

The dihydroxylation of cinnamate **50** was carried out using OsO_4 in presence of NMO, furnished corresponding diol **51**, which was protected as its acetonide **52**. This acetonide protected diol **52** was treated with Grignard reagent prepared from 1,5-dibromopentane at RT to furnish secondary alcohol **54** along with **53**. Separation of structural isomers **53** and **54** was carried out by acetate protection of alcohol and its deprotection (**Scheme-12**).



Scheme 13−Completion of diastereoselective synthesis of 7−*epi*−(+)−goniodiol (**48**) and 8−*epi*−(−)−goniodiol (**49**).

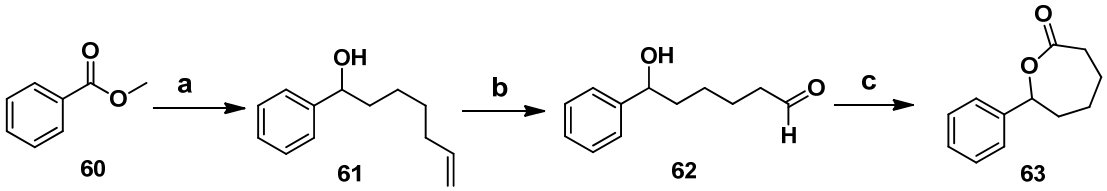
Reagents and conditions− *(a) OsO_4, NaIO4, dioxane:H_2O (9:1), 8 h, RT, 79%; (b) TPAP, NMO, DCM, RT, 15 min., 77%, (dr:8:2); (c) i) LDA, PhSeBr, THF, −78 ^oC. 1 h, ii) H_2O_2, pyridine, −78 ^oC− RT, 2 h, 68%, (dr:8:2); (d) (50%) Aq. AcOH, 80 ^oC, heat, 1h, 88%, (dr:8:2).*

Oxidative cleavage of compound **56** resulted in formation of lactol **57** which was oxidised using TPAP in the presence of NMO to furnish lactone **58**. The lactone **58** was alkylated using phenylselenyl bromide employing LDA as the base at -78 ^oC and subsequent oxidation– elimination gave compound **59** in good yields. Compound **59** after acetonide deprotection thus furnished 7−*epi*−(+)−goniodiol (**48**) and 8−*epi*−(−)−goniodiol (**49**) in *dr*-8:2 **(Scheme-13)**.

Synthesis of substituted caprolactones:

A regioselective route for preparation of substituted ε−caprolactone has been developed in reduced number of steps by utilising unusual Grignard reaction. Methyl benzoate (**60**) was subjected to unusual

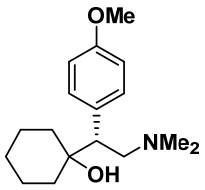
Grignard reaction using 1,6-dibromohexane at RT, furnished secondary alcohol **61** in 68% yield which upon OsO_4, $NaIO_4$ Cleavage gave aldehyde **62** in 79% yield. Compound **62** upon TEMPO catalyzed oxidative lactonization afforded substituted caprolactone (**63**) in 61% yield **(Scheme-14)**.



Scheme−14: Synthesis of substituted caprolactone (**74**)

Reagents and conditions: *(a) 1,6−Dibromohexane, Mg metal turnings, THF, RT, 5 h, 68%; (b) OsO_4, $NaIO_4$, dioxane:H_2O (9:1), 8 h, RT, 79%; (c) TEMPO (cat.), $PhI(OAc)_2$, DCM, RT, 6 h, 61%.*

Section-3: Synthetic studies towards (*R*)-venlafaxine by chirality induction approach

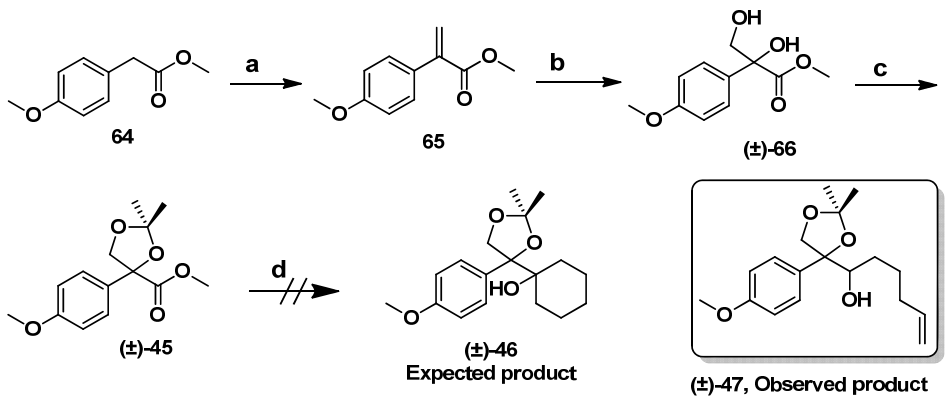


(*R*)-**Venlafaxine**

Figure 7. Structure of venlafaxine

Venlafaxine is a new generation antidepressant drug developed by Wyeth-Ayerst company in 1993. It inhibits reuptake of biogenic amine like serotonin and norepinephrine, hence called as serotonin norepinephrine reuptake inhibitor (SNRI). Although venlafaxine is sold as a racemate, (-)-venlafaxine (**Figure-7**) is a more potent inhibitor of norepinephrine synaptosomal uptake while (+)-venlafaxine is a more selective in serotonin uptake. It is licensed for the treatment of depression, panic disorder, social phobia, anxiety and vasomotor symptoms as it works by altering unbalanced chemicals in brain.

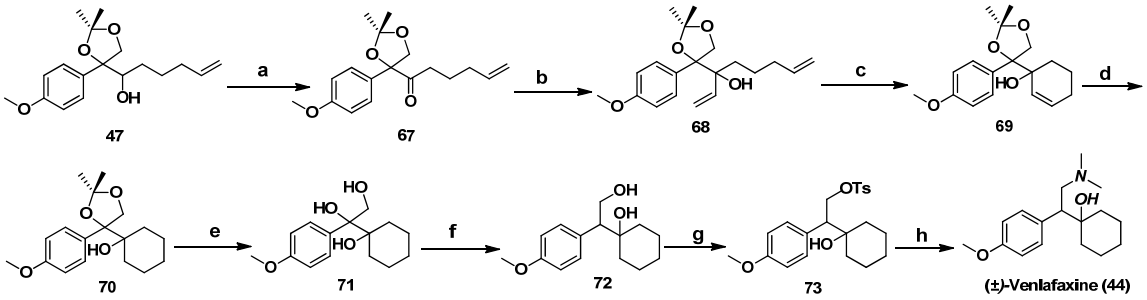
Thus, methylester of *p*-methoxy phenylacetic acid (**64**) on reaction with paraformaldehyde afforded compound **65** which was then subjected to OsO_4 catalysed dihydroxylation in presence of NMO, to furnish diol **66**. This diol was then protected as it's acetonide **45** and treated with Grignard reagent prepared from 1,5-dibromopentane instead of addition, it underwent elimination–reduction to afford the terminal olefin **47** (**Scheme-15**).



Scheme 15: Observation of unusual Grignard reaction

Reagents and conditions: *(a) Paraformaldehyde, K_2CO_3, TBAI (cat.), toluene, 80 ^oC, 5 h; (b) OsO_4, NMO, acetone:H_2O (3:1), RT, 5 h, 80%; (c) 2,2-DMP, P-TSA(cat.), DMF, RT, 6 h, 97%; (d)1,5-Dibromopentane, Mg metal turnings, THF, 0 ^oC-RT, 5 h, 99%.*

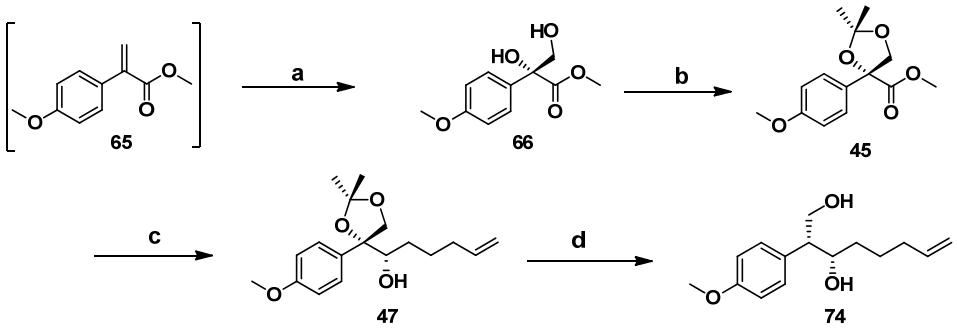
The IBX oxidation of **47** gave desired ketone **67** in 89% yield. Compound **67** on treatment with vinyl magnesium bromide furnished alcohol **68** in 85% yield which was subjected to RCM reaction in the presence of the Grubbs' first generation catalyst to furnish cyclohexene **69**, which was reduced under hydrogenation conditions to furnish reduced product **70** in 95% yield. Compound **70** when refluxed in the presence of catalytic *p*-TSA in THF as a solvent for 1 h gave acetonide deprotected triol **71**. Then, ionic hydrogenation employing triethylsilylhydride in presence of catalytic $BF_3.OEt_2$ was performed to furnish product **72.** The primary hydroxy group in compound **72** was then treated with tosyl chloride in the presence of Et_3N to give the corresponding tosyl alcohol **73**, which on displacement with aq. dimethyl amine at RT for 10 h afforded racemic venlafaxine **44** (**Scheme-16**). In order to prepare optically active, (*R*)-venlafaxine (**44'**) the retrosynthetic plan was revised.



Scheme 16: Completion of synthesis of (±)-venlafaxine

Reagents and conditions: *(a) IBX, ethyl acetate, reflux, 3 h, 89%; (b) vinyl magnesium bromide, THF, 0 ^{o}C-RT, 2 h, 85%; (c) Grubbs' first generation cat., DCM, RT, 2 h, 92%, (dr: 6:4); (d) H_2, Pd/C, EtOH, RT, 2 h, 95%; (e) THF:H_2O (1:1), P-TSA (cat.), reflux, 1 h, 90%; (f) Et_3SiH, Cat. $BF_3.OEt_2$, RT; (g) Tosyl chloride, triethyl amine, DMAP (cat.), DCM, RT, 88%; (h) aq.(10%) dimethyl amine, RT, 10 h, 70%.*

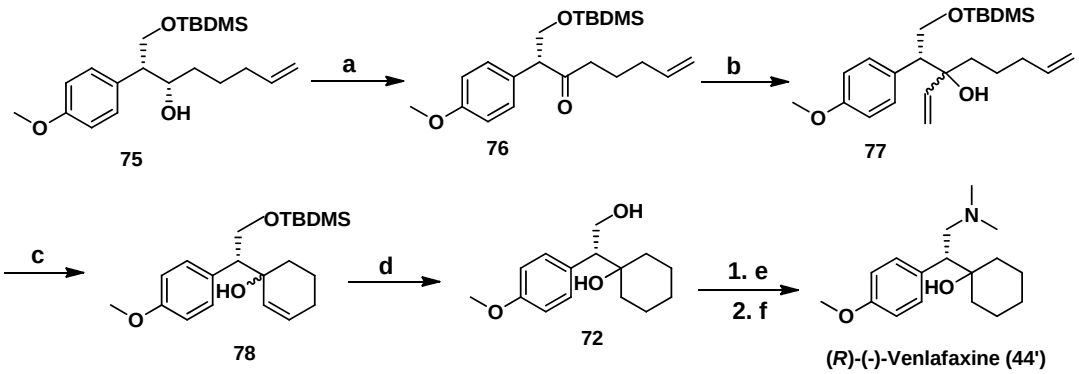
The exomethylene compound **65** was then subjected to Sharpless asymmetric dihydroxylation, by employing $(DHQD)_2PHAL$ as the chiral catalyst to furnish diol **66** in 85% yield and in 99% *ee* (**Scheme-17**). The diol **66** was protected as its acetonide **45** and then subjected to Grignard reaction to furnish alcohol **47** (>98% *ee*), proves that the Grignard reaction was highly diastereoselective.



Scheme 17- Synthesis of (*R*)-(-)-venlafaxine

Reagents and conditions: *(a) $K_3Fe(CN)_6$, K_2CO_3, methane sulphonamide, OsO_4, $(DHQD)_2PHAL$, $^{t}BuOH:H_2O$, 0 ^{o}C, 24 h, 78%, >99% ee; (b) 2,2-Dimethoxypropane, p-TSA (cat.), DMF, RT, 6 h, 97%; (c) 1,5-Dibromopentane, Mg, THF, 0 ^{o}C- RT, 5 h, 99%; (d) Et_3SiH, BF_3 $(OEt)_2$, DCM, - 40 ^{o}C, 3 h, 59%, ee >96%.*

The newly generated secondary hydroxyl, acts as a handle to influence its chirality to the adjacent benzylic centre. Thus. deoxygenation of **47** using Et_3SiH furnished product **74** in excellent enantioselectivity 96% *ee*. The primary alcohol in **74** was protected as its TBDMS ether to furnish compound **75**. Oxidation of secondary hydroxy in compound **75** with DMP was carried out to obtain ketone **76** in >92% *ee* which was subjected to Grignard reaction with vinyl magnesium bromide to furnish alcohol **77** in 85% yield. The compound **77** was treated with Grubbs' 1st generation catalyst to obtain cyclohexene **78** in 92% yield. Compound **78** was subjected under hydrogenation conditions to furnish diol **72**. Following the same sequence of reactions as in racemic synthesis, compound **72** was converted into (*R*)-(-)-venlafaxine (**44'**) in 97% *ee* after recrystallisation (**Scheme-18**).



Scheme 18- Completion of synthesis of (*R*)-(-)-venlafaxine (**44**')

Reagents and conditions: *(a) DMP, DCM, RT, 2 h, 72%; (b) vinyl magnesium bromide, THF, 0 ^{o}C-RT, 2 h, 88%; (c) Grubbs'first generation cat., DCM, RT, 2 h, 92%; (d) H_2, Pd/C, EtOH, RT, 2 h, 95%; (e) THF:H_2O (1:1), p-TSA (cat.), reflux, 1 h, 90%; (e) Tosyl chloride, triethyl amine, DMAP (cat.), DCM, RT, 88%; (f) aq.(10%) dimethyl amine, RT, 10 h, 70%.*

Contents

3.2.1. A brief review of styryl lactones:

Historically, plants were a folkloric source of medicinal agents. From the *pre*−medieval use to the present day development of therapeutics, natural products continue to play a major role in the development of a drug. In addition to the plant derived natural products, natural products from micro−organisms and marine sources provided key drugs for cancer chemotherapy (for *eg* daunomycin, doxorubicin and discodermolide). Natural products themselves serve as lead molecules, thus providing a platform which can be modified to afford the therapeutically valuable pharmaceutical analogues.[1] The impact of natural products on drug development is profound virtually in every major therapeutic area, evident from the fact that out of 90 new chemical entities (NCE) approved by FDA, 10% were natural products while another 68% were natural product derived. 74% of the anticancer agents approved between 1981 and 2002 were natural products, natural product derived, or natural product inspired, while many of the antifungal agents are based on natural products.[2] However, complexity of many of the natural products can hinder the process of their chemical modifications leading to different structures for therapeutic evaluations while continuous supply from biological sources can be problematic. The increasing efficiency of organic chemistry had reduced the barrier for the supply of these compounds to circumvent the limited natural supply. The rich structural diversity and complexity of the natural products prompted the synthetic chemist to produce them, as well as their analogues in laboratory often with their medicinal applications in view.

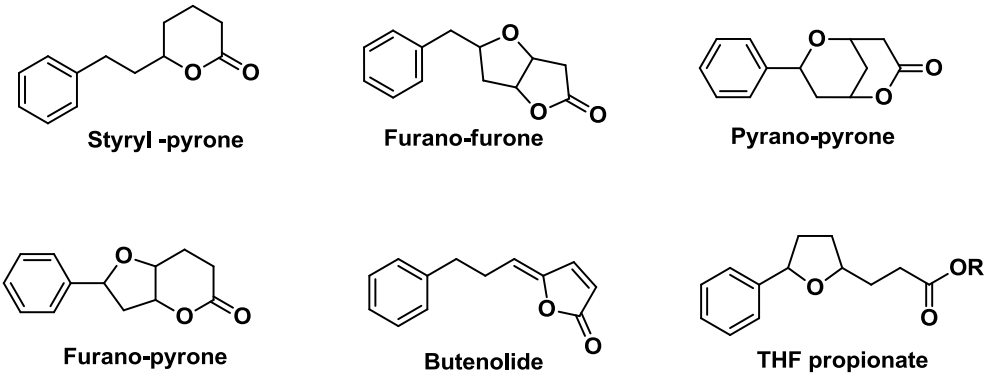


Figure 1: Structural features of styryllactone isolated from the genus Goniothalamus.

The present section deals with the aspect of the enantiospecific synthesis of bio−active styryllactones. Styryllactones are homogeneous and relatively reduced group of secondary metabolites from the *Goniothalamus sp*. comprising a basic skeleton of 13 carbon atoms (C_6 + C_3 + C_4 unit) that includes in their structure a styryl or a pseudo−styryl fragment linked to a

lactone moiety (either a furanone or a pyranone). These highly oxygenated lactones are also characterized by the presence of saturated or unsaturated mono or bicyclic core structures, with the presence of γ−lactone (α−furone) or δ−lactone (α−pyrone).[3] Classification of these styryllactones is based on the structural characteristics of the six different skeletons (**Figure.1***)*. Stryryllactones were shown to exhibit moderate to significant biological activity including antitumour, antifungal as well as antibiotic properties.[4] Because of their unique and intriguing structures and the activity associated much effort has been centered on the development of methodology for the synthesis of these compounds. More than fifty bioactive stryryllactones, with a large variety of basic structures, were isolated from several species of the genus *Goniothalamus* (*Annonaceae*). The structures and relative configurations of these compounds were determined either by X−ray crystallography or by extensive NMR spectral analysis and by mass spectroscopic techniques.[5] Some of the styryllactones, comprising the above structural units possessing promising anti−cancer activity are shown in Figure 2. The (+)−goniodiol (I) is a representative member of this family whereas other styryl lactones like (+)−6−*epi*−goniodiol (II), (+)−7−*epi*−goniodiol (III), (+)−8−*epi*−goniodiol (IV), leiocarpin−A (V) and (+)−9−deoxy−goniopypyrone (VI) are structural isomers. The structurally similar lactones, 8−*epi*−goniodiol (IV), 6−epi−goniodiol (II), and the recently isolated 7−*epi*−goniodiol (III), serve as precursors for the synthesis of other bio−active styryllactones such as 9−deoxygoniopypyrone (VI), and leiocarpin A (V) (**Figure- 2**).

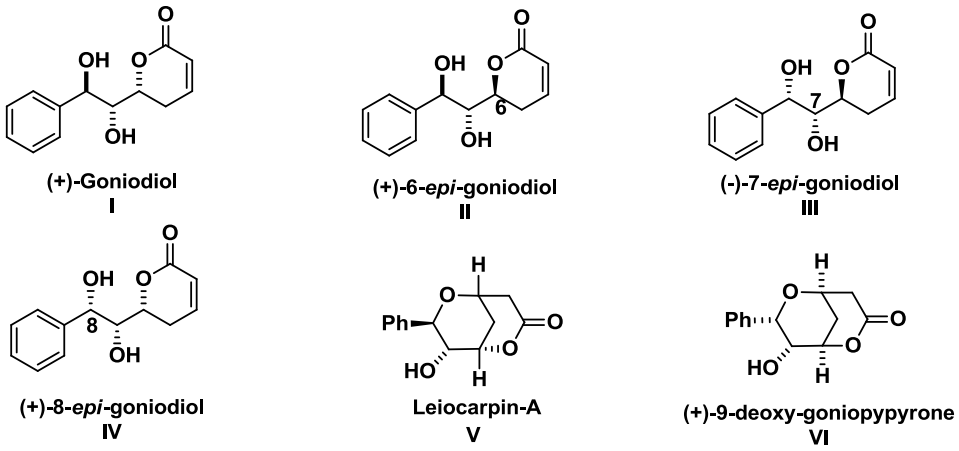
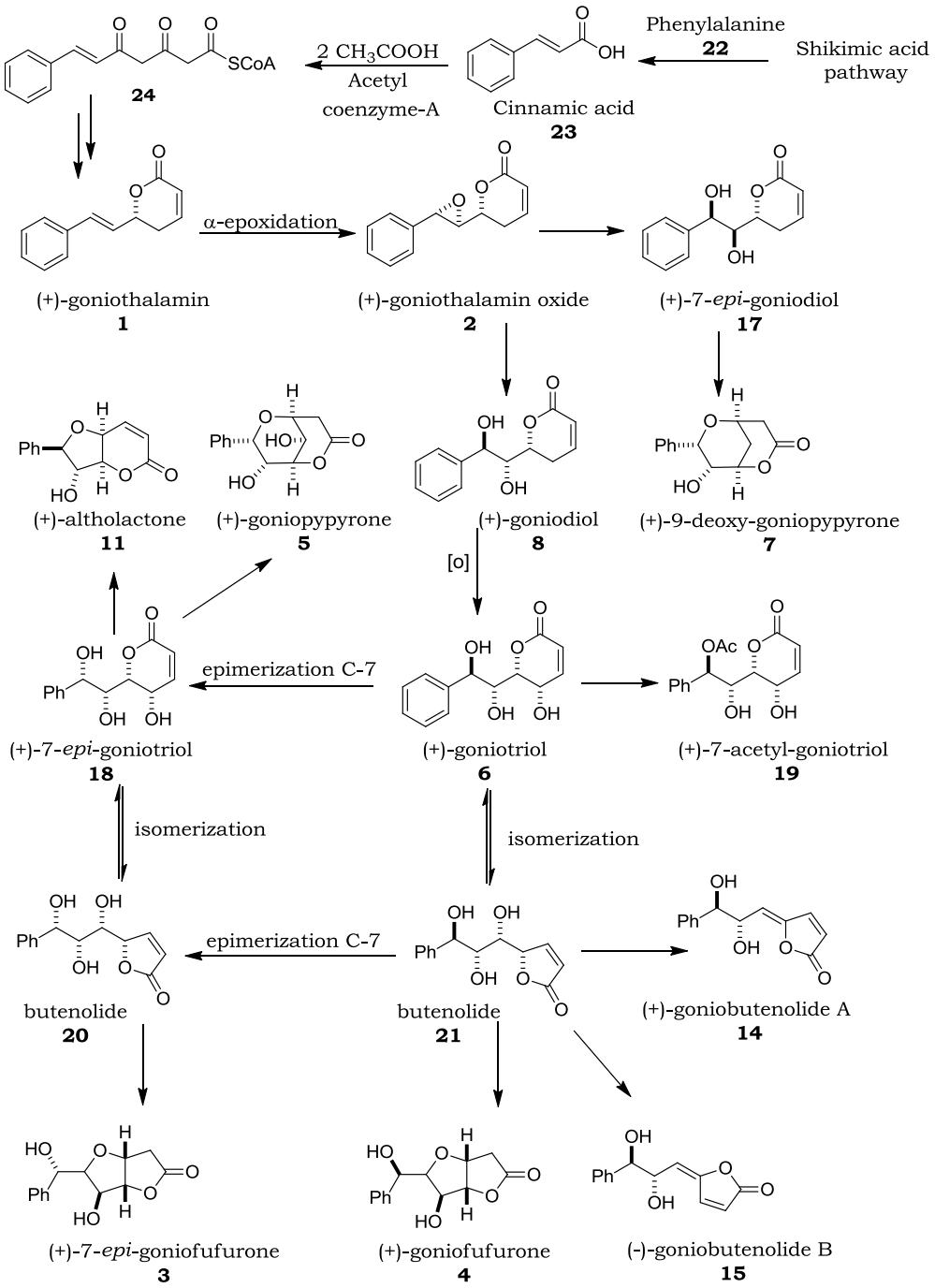


Figure 2: Styryl lactones

Mclaughlin *et.al* and Shing *et.al* [6] proposed that the biosynthesis of styryllactones occur *via* the shikimic acid pathway. It proceeds through the formation of cinnamic acid from

phenylalanine, followed by incorporation of two acetate−malonate units (**Scheme 1**). Coupling of these two units by lactonization would generate the simplest styryl−pyrone (+)−goniothalamin **1**, which undergoes various transformations such as epoxidation, isomerizations, epimerizations *etc*. to give the styryllactones.



Scheme 1: *Proposed biogenetic pathway for the formation of diverse styryllactones*

According to the hypothetical biogenesis proposed by Shing *et al.*[6c] 6 α−epoxidation of the double bond in goniothalamin **1** will lead to (+)−goniothalamin oxide **2**. *Trans* opening of the epoxide at the benzylic carbon in **2** will result in (+)−goniodiol **8**, while *cis* opening of the epoxide at the benzylic carbon in **2** will give (+)−7−*epi*−goniodiol **17**, which on an intramolecular Michael type ring closure would form **(**+)−9−deoxygoniopypyrone **7**. Allylic hydroxylation of **8** will lead to (+)−goniotriol **6**. A possible rearrangement of **6** to butenolide **21**, followed by an intramolecular Michael type ring closure might have been involved in the formation of **(**+)−goniofufurone **4**. Both (+)−goniobutenolide−A **14** and (+)−goniobutenolide−B **15** might have been generated by elimination of the hydroxy group at *C*−5 position in butenolide **21**. Epimerization at the benzylic carbon in **6** will result in (+)−7−*epi*−goniotriol **18** which upon an intramolecular Michael type ring closure will lead to (+)−goniopypyrone **5**. (+)−Altholactone **11**, might have been produced from (+)−7−*epi*−goniotriol **18** *via* an intramolecular ring closure with inversion at the benzylic carbon. Isomerization (+)−7−*epi*−goniotriol **18** to butenolide **20** followed by an intramolecular Michael addition might be the pathway for formation of (+)−7−*epi*−goniofufurone **3**.

3.2.2 Introduction

Styryl lactones are a group of secondary metabolites reported mainly within the genus *Goniothalamus* and include linear, epoxy and cyclic styryl lactone derivatives.[6] They acts as antiinflammatory, immunosupressor, trypanocidal and antifertility agents. In China, this class of styryl lactone compounds have been utilized traditionally as pesticide agents and because of strong cytotoxic activity exhibited by these styryl lactones [7] they have been one of the most sought after worldwide phytochemicals due to their promising role in oncopharmacology. [8]

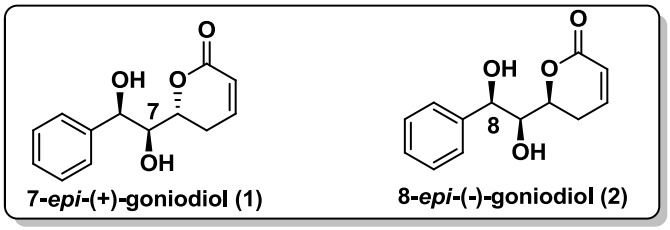


Figure 3: Styryl lactones

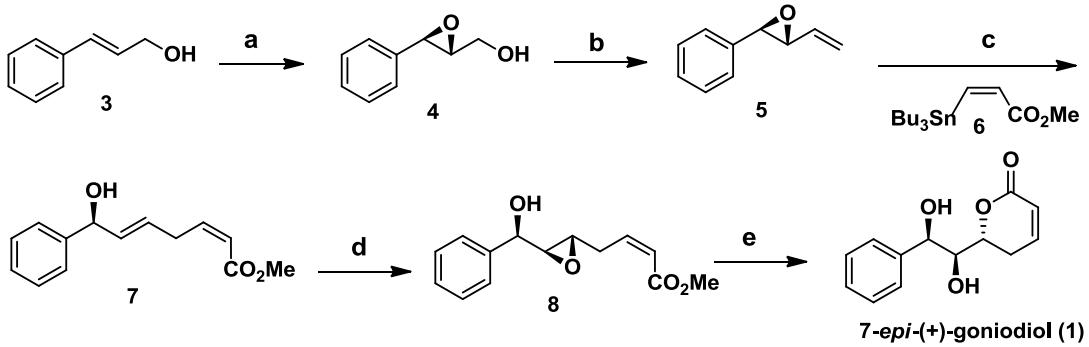
7−*epi*−(+)−goniodiol (**1**) (**Figure 3**) is one of the newly isolated styryl lactone by Mu and co−workers in 1999, from the ethanolic extracts of stem barks of *Goniothalamus leiocarpus* of family annonaceae, a tropical plant widely spread in the south of the Yunnan province in China,

having a 25 mM MIC value against *Listeria denitrificans*. [9] Along with that it is the only stereoisomer amongst the other stereoisomers of styryl lactones which showed highest activity against Gram positive bacteria. [10] It possesses selective activities in trypan blue dye exclusion method test and have strong inhibition against HL−60 (<1μg/mL). Significant anti−tumour and cytotoxic activities associated with styryllactones of *Goniothalamus* have promoted a detailed chemical investigation of the different styryllactones. Various synthetic approaches of styryl lactones have been reported in the literature, highlighting synthesis of goniodiol, [11] as it is the source of a variety of its natural analogues. [12−17]

3.2.3. Literature review on synthesis of 7−*epi*−(+)−goniodiol (1) and 8−*epi*−(−)−goniodiol (2)

1). Lin's approach. [12] (*Tetrahedron Letters*, **2004**, *45*, 8111–8113).

The asymmetric epoxidation with the Pd−catalyzed coupling of vinyl epoxide with vinyltributylstannane opens an access to styryllactones such as 7−*epi*−(+)−goniodiol (**1**).



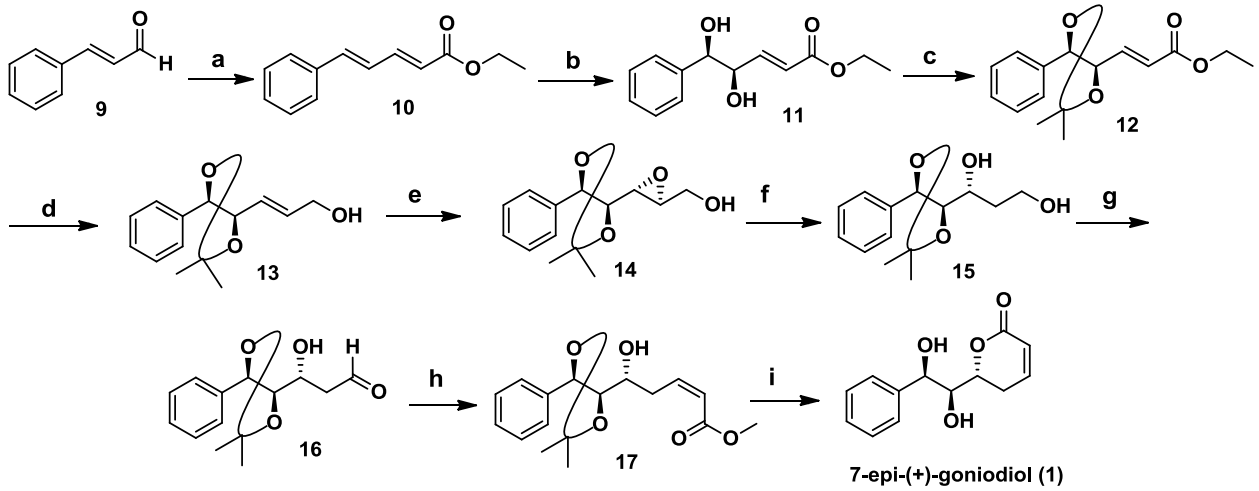
Scheme 2. Reagents and conditions: *(a) TBHP, Ti(OiPr)$_4$, L−DIPT, 40 sieves, CH_2Cl_2, −15 ^oC to 0 ^oC, 90%, 98% ee; (b) (1) $(COCl)_2$, DMSO, Et_3N, −78 ^oC–rt, 89%, (2) t−BuOK, Ph_3PCH_3 I, THF, 0 ^oC, 1h, 86%; (c)* **6**, *$PdCl_2(CH_3CN)_2$ (5% mol), DMF:H_2O (4:1), 83%, (E:Z= 95:5), >98% ee; (d) m−CPBA, $NaHCO_3$, CH_2Cl_2, −20 ^oC, 82%, (threo:erythro= 2.5:1); (e) 30% $HClO_4$ in MeOH, 0 ^oC, 74%.*

The Sharpless epoxidation of cinnamyl alcohol (**3**) led to formation of the epoxy alcohol **4** >98% *ee*. Swern oxidation of the epoxide **4**, followed by Wittig methylenation provided the vinyl epoxide **5** loss of optical purity. Further the vinyl epoxide was treated with vinyltributylstannane **6** furnished diene **7** in 83% yield and good stereoselectivity (*E:Z*= 95:5). The asymmetric epoxidation of alcohol **7** was conducted in presence of *m*−CPBA, which led to

the formation of threo epoxide **8** as the major product with the ratio (*threo: erythro*= 2.5:1), in 82% yield. The epoxide **8** was lactonized by treatment of 30% $HClO_4$ in methanol to give 7−*epi*−(+)−goniodiol (**1**).

2) J. S. Yadav's approach [13] (*Synthesis*, **2007**, *3*, 0385–0388).

In this approach, a novel and highly efficient methodology for the synthesis of a styryllactone, 7−*epi*−(+)−goniodiol (**1**), in nine steps has been described.



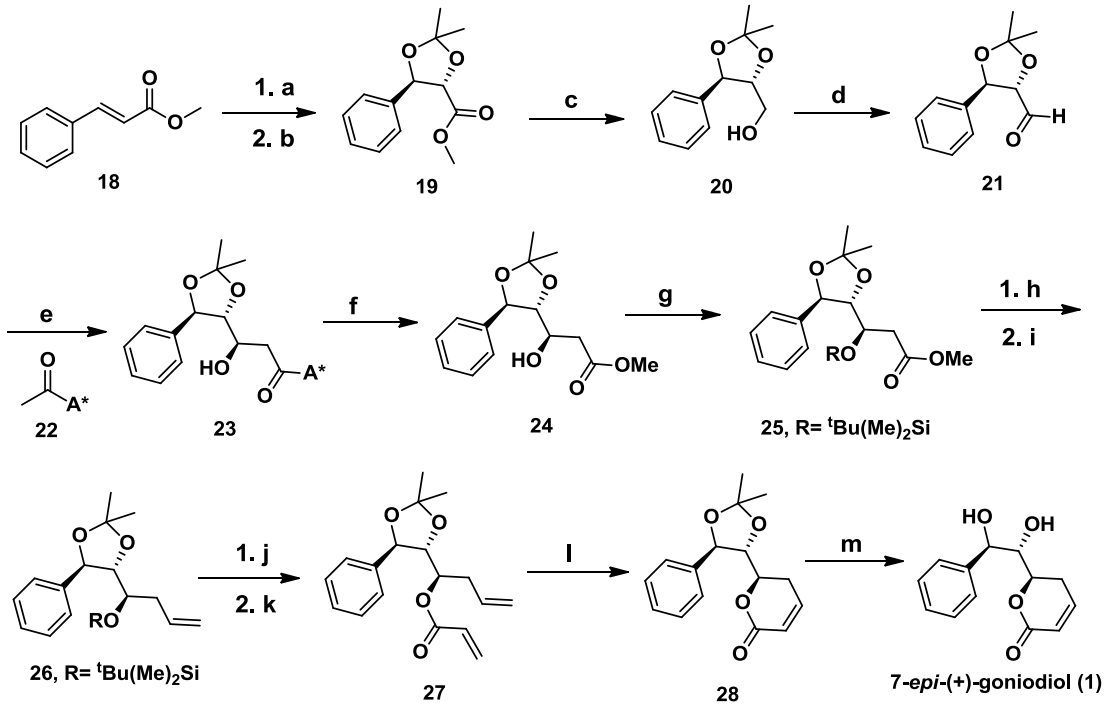
Scheme 3 *Reagents and conditions*: *(a) $Ph_3P=CHCO_2Et$, benzene, r.t., 4 h, 90%; (b) AD−mix−β, $MsNH_2$ (cat.), $^tBuOH–H_2O$ (1:1), 18 h, 78%; (c) $Me_2C(OMe)_2$, PPTS, acetone, 0 °C to r.t., 12 h, 95%; (d) DIBAL−H, CH_2Cl_2, 0 °C, 2 h, 84%; (e) (+)−L−DET, $Ti(O−i−Pr)_4$, t−BuOOH, MS 4A°, DCM, , 3 h, 87%; (f) Red−Al, THF, –15 °C then r.t., 3 h, 80%; (g) IBX, CH_2Cl_2, DMSO, 0 °C to r.t., 2 h, 60%; (h) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, NaH, THF, –78 °C, 84%; (i) benzene, pTSA, r.t., 6 h, 73%.*

The cinnamaldehyde (**9**) was subjected to the Wittig reaction to afford the unsaturated ester **10** in 90% yield. Regioselective monodihydroxylation of conjugated diene **10** produced exclusively enediol **11** in 78% yield. After protection of the 1,2−*syn*−diol as an acetonide, the resulting ester **12** was then reduced with DIBAL-H to afford allyl alcohol **13**. In the next step, the allylic alcohol **13** was subjected to Sharpless asymmetric epoxidation using (+)−diethyl L−tartrate to furnish the desired epoxy alcohol **14** in 87% yield. The epoxy alcohol **14** was regioselectively reduced with Red−Al to give the corresponding 1,3−diol **15**. The oxidation of primary hydroxy group in compound **15** using IBX in DCM and DMSO afforded the aldehyde **16** in 60% yield. The aldehyde **16** was subjected to the Horner–Wadsworth–Emmons reaction

using NaH and bis(2,2,2−trifluoroethyl) [(methoxycarbonyl) methyl]phosphonate in dry THF at –78 °C to afford the ester **17**, predominantly as the *Z*−isomer. The cyclization of the hydroxy ester was achieved in refluxing benzene using a catalytic amount of *p*-TSA to afford the 7−*epi*−(+)−goniodiol (**1**) in 73% yield.

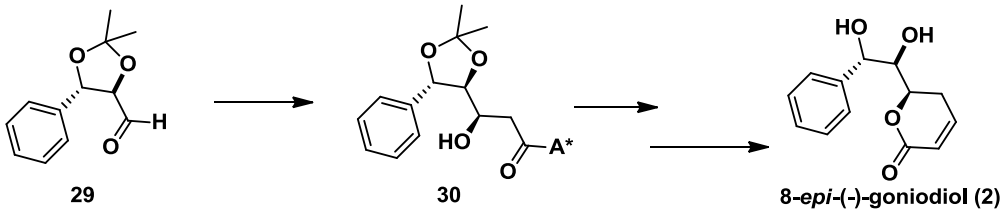
3) Kumaraswamy's approach [14] (*Helvetica Chimica Acta*, **2013**, *96*, 1366−1375)

The methyl cinnamate (**18**) was subjected to asymmetric hydroxylation with $(DHQD)_2PHAL$ and subsequent protection of the resulting diol with 2,2−DMP under acidic conditions leading to **19** in 80% yield with 99% *ee*. Further reduction in presence of LAH furnished alcohol **20** in 75% yield. The reduction followed by oxidation, furnished aldehyde **21** in 56% yield. With access to aldehyde **21**, exploration of the asymmetric aldol addition reaction, employing lithium enolate of 1−acetyloxazolidinone (A*) **22** resulted in the compound **23**.



Scheme−4: *Reagents and conditions a) $(DHQD)_2PHAL$, NMO, $^tBuOH/ H_2O$ (1:1), 0 ^oC, 12 h; b) 2,2−DMP, TsOH, 0 ^oC, DCM, 80%, 99% ee; c).LAH, THF, 0 ^oC, 12 h, 75%; d) $(COCl)_2$, DMSO, Et_3N, 75% e).A*= (4R)−4−Benzyl−2−oxo−1,3−oxazolidin−3−yl (**22**), LDA, THF, −78 ^oC, 4 h, 80%; f) BuLi, MeOH, 0 ^oC, THF; g) TBSCl, 1H−imidazole, DCM, 0 ^oC, 4 h; h) DIBAL−H, toluene, −78 ^oC, 2 h i) $(Ph)_3P+$ MeI. ^tBuOK, benzene, THF, 0 ^oC, 1 h, 90%; j) TBAF/THF, 0 ^oC, 3 h; k) Acryloyl chloride, Et_3N, DCM, 0 ^oC, 2 h, 69%; l) 10 mol % of 2nd gen. Grubbs' cat., DCM, reflux, 2 h, 69%; m) aq. AcOH (50%), 80 ^oC, 1 h, 70%.*

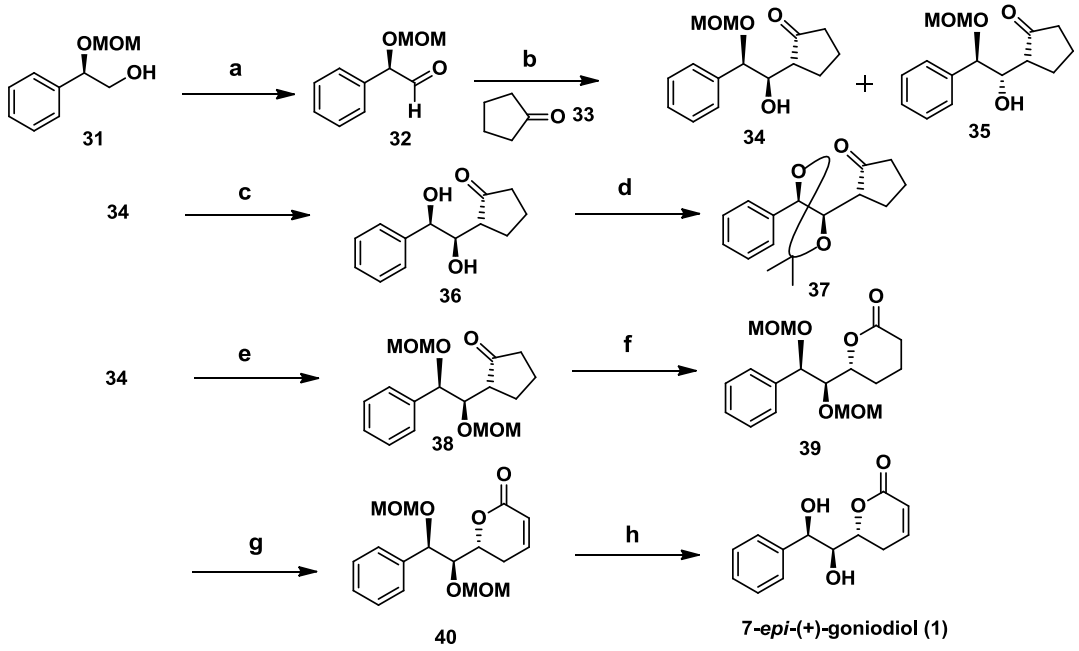
Methanolysis of enantiomerically pure **23** with MeOLi (BuLi+MeOH, 0 ^{o}C, THF) provided **24** in 82% yield, and subsequent protection of secondary alcohol in presence of ^{t}Bu(Me)$_2$−SiCl and 1H−imidazole at RT furnished compound **25**. The protection followed by DIBAL−H reduction of ester to aldehyde and subsequent olefination, resulting in the protected homoallylic alcohol **26** in 90% yield. Fluoride ion induced deprotection of the silyl ether and subsequent reaction of the resulting secondary alcohol with acryloyl chloride under basic conditions furnished **27** in 69% yield (**Scheme 4**). Finally, RCM reaction in presence of Grubbs' 2nd generation catalyst led to the compound **28**, which was heated in presence of aq. AcOH resulted in 7−*epi*−(+)−goniodiol (**1**) in 71% yield.



Scheme−5 Synthesis of 8−*epi*−(−)−goniodiol (**2**)

Under similar conditions, the reaction between aldehyde **29** and **22** resulted in **30** in 60% yield. Further, the amide was transformed to the methyl ester, followed by protection with TBDMSCl, for **19'** (70% over two steps). The similar sequence of consecutive reactions as followed in the synthesis of (**1**), was followed resulted in the 8−*epi*−(−)−goniodiol (**2**) in 71% yield (**Scheme−5**).

4) Bacchu veena's approach [15](*Synlett*, **2014,** *25*, 1283–1286)

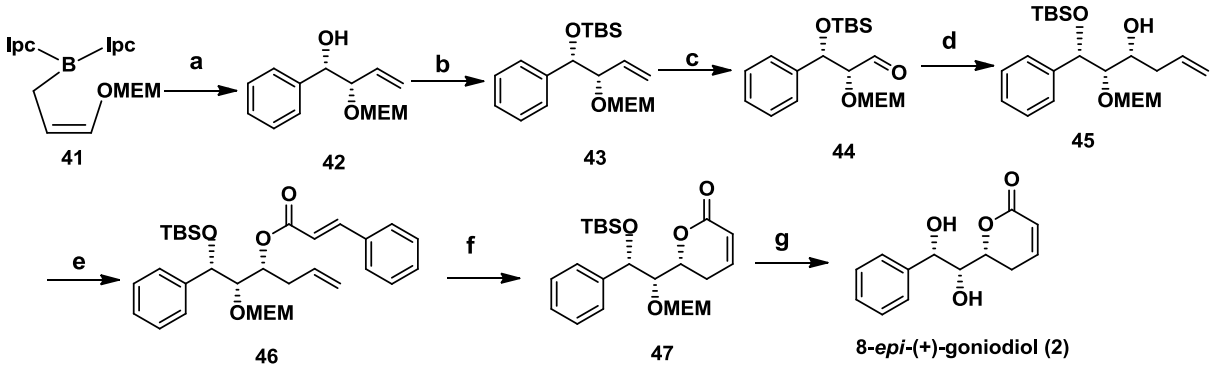


Scheme 6 *Reagents and conditions*: *(a) IBX, DMSO, EtOAc, reflux, 2 h; (b) L−proline, 12 h, r.t., 82%; (c) $FeCl_3·6H_2O$, CH_2Cl_2, r.t., 2 h; (d) 2,2−DMP, PPTS, CH_2Cl_2, r.t., 5 h, 78%; (e) MOMCl, DIPEA, 0 °C- r.t., 12 h, 85%; (f) mCPBA, $NaHCO_3$, CH_2Cl_2, 0 °C- r.t., 4 h, 88%; (g) i) PhSeBr, LiHMDS, THF, –78 °C; ii) 30% H_2O_2 (aq)–CH_2Cl_2 (2:1), 0 °C, 10 min, 72%; (h) $FeCl_3·6H_2O$, CH_2Cl_2, r.t., 2 h,78%.*

In this approach synthesis began with the oxidation of MOM protected known alcohol **31**, (**Scheme 6**) with IBX in EtOAc and DMSO at reflux for 2 h gave the corresponding aldehyde **32** which was subjected to L−proline catalyzed aldol reaction with cyclopentanone **33** at RT for 12 hours to afford a diastereomeric mixture of **34** and **35** in a ratio of 88:12, respectively. The major diastereomer **34** was subjected to deprotection with $FeCl_3·6H_2O$ in DCM at RT for 2 h to give the diol **36**, which, on subsequent treatment with 2,2−DMP and PPTS in DCM at RT, afforded the acetonide **37** in 78% yield (**Scheme 6**). When alcohol **34** was subjected to reaction with MOMCl and DIPEA, afforded MOM ether **38** in 85% yield. Baeyer–Villiger oxidation of ketone **38** with m-CPBA at RT furnished lactone **39** in 88% yield. Treatment of **39** with LiHMDS and phenylselenenyl bromide in THF at –78 °C followed by oxidative elimination by reaction with 30% H_2O_2 gave compound **40**. Deprotection of the MOM groups in **40** was achieved by reaction with $FeCl_3·6H_2O_8$ in DCM at RT to afford 7−*epi*−(+)−goniodiol (**1**).

5.) P. V. Ramachandran's approach [16] (*J. Org. Chem*. **2002**, *67*, 7547−7550)

The synthesis started with alkoxyallylboration of benzaldehyde with **41**, furnished excellent diastereo− and enantioselectivities and the product *R*−alkoxyhomoallylic alcohol **42** was obtained in 98% *ee*. The free hydroxy group in **42** was protected as its -OTBS ether **43**, and the oxidative cleavage

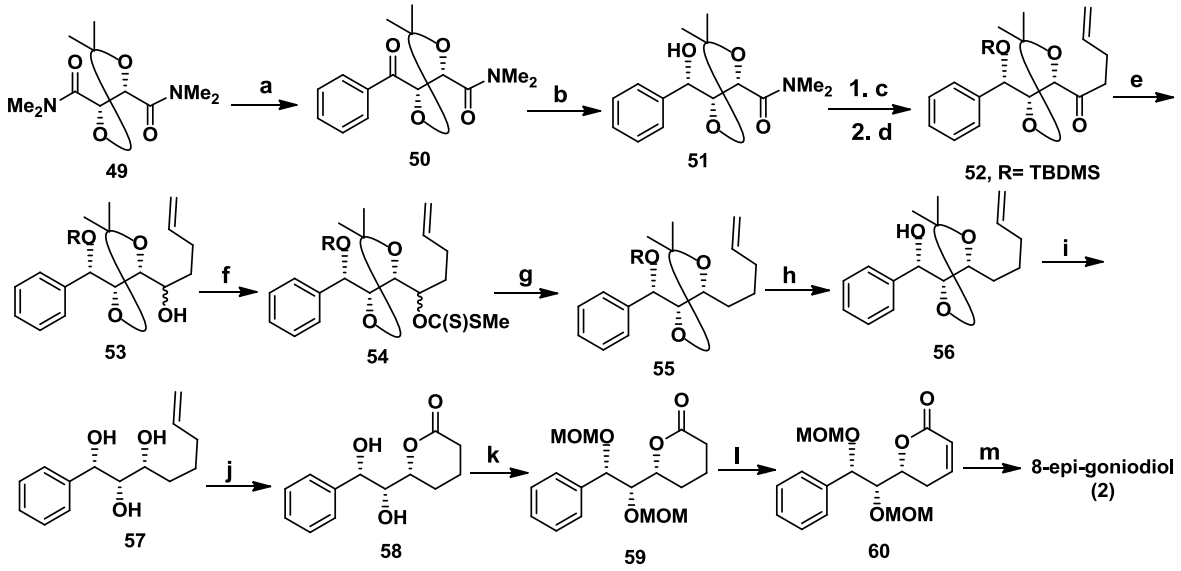


Scheme−7: *Reaction conditions: (a) (i) PhCHO, −100 °C; (ii) $NaOH/H_2O_2$, 25 °C, 71%. (b) TBSCl, imidazole, DMF, 0 °C, 89%. (c) (i) OsO_4, NMO, acetone:water, 0 °C, 6 h; (ii) $NaIO_4$,*

*acetone: water, 20 min, 50%. (d) (i) (+)−**48**, ether−pentane, −100 °C, 2h; (ii) NaOH, H_2O_2, rt, 6 h, 73%. (e) (E)−Cinnamoyl chloride, Py, DMAP, CH_2Cl_2, 0 °C, 15 h, 70%. (f) 10 mol % of 2nd generation Grubbs' cat., toluene, 120 °C, 3 h, 77%. (g) HCl: THF: H_2O (1:8:1), 68%.*

of the terminal olefin in **43**, under Lemiuex−Johnson reaction conditions furnished aldehyde **44**, followed by allylboration with **48**, provided the corresponding homoallylic alcohol **45** in 73% yield. The *de* was determined to be 92% by derivatizing the alcohol as its cinnamate ester **46**. Ring−closing metathesis of the cinnamate ester **46** with Grubbs' 2nd generation catalyst provided the *R*−pyrone **47** in 77% yield. Both TBS and MEM groups were deprotected in a single step with HCl in THF to afford 8−*epi*−(+)−goniodiol (**2**) (**Scheme−7**).

6). K. Prasad's approach [17] (*Tetrahedron Letters* **2007**, *48*, 4679–4682)



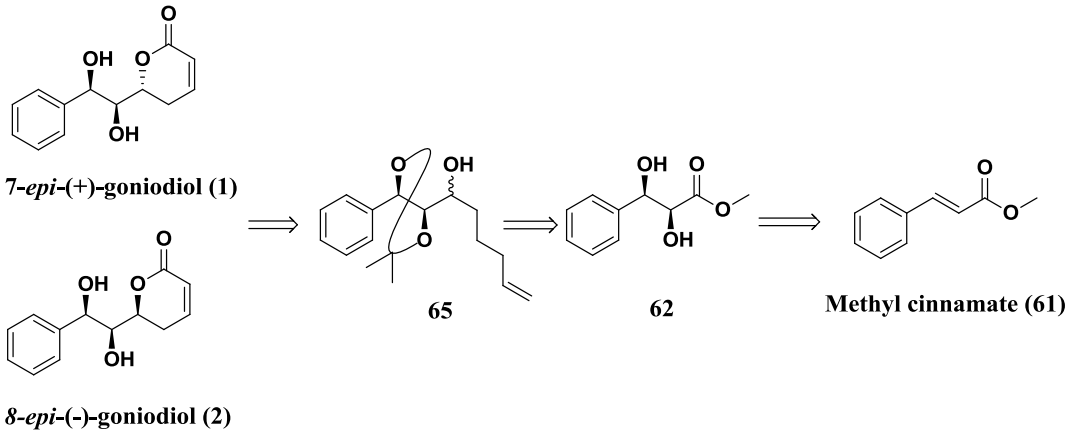
Scheme 8: *Reaction conditions: (a) PhMgBr (1.5 eq), THF, −10 °C, 0.5 h, 92%; (b) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, −78 °C, 2 h, 86%*; *(c) TBDMSCl, DMAP (cat), Imidazole, DMF, rt, 6 h, 98%. (d) 3−butenylmagnesiumbromide, THF, −10 °C, 0.5 h, 93%; (e) $NaBH_4$, MeOH, 0 °C, 0.5 h, 99% (dr 64:36); (f) NaH, CS_2, MeI, THF, reflux, 3 h,96%; (g) Bu_3SnH, AIBN (cat), benzene, reflux, 2 h, 94%; (h) TBAF, THF, 0 °C to rt, 1 h, 98%; (i) $FeCl_3.6H_2O$, CH_2Cl_2, rt, 2 h, 95%; (j) i) O_3/Me_2S, CH_2Cl_2:MeOH, −78 °C to 0 °C, 6 h;ii) Ag_2CO_3/Celite, toluene, reflux, 0.5 h, 78% for two steps; (k) MOMCl, iPr_2NEt, DMAP, CH_2Cl_2, reflux, 6 h, 83%; (l) i) LiHMDS, PhSeBr, THF,−78 °C, 1 h; ii) 30% H_2O_2, CH_2Cl_2, 0 °C , 0.5 h, 68% for two steps; (m) $FeCl_3.6H_2O$, CH_2Cl_2, rt, 5 h, 80%.*

The synthesis starts with the selective Grignard addition of PhMgBr on dimethylamide **49** furnished compound **50** in 92% yield. Luche reduction conditions furnished γ−hydroxybutyramide **51**. Protection of the free hydroxy group in **51** as the silyl ether followed by the addition of 3−butenylmagnesium bromide afforded ketone **52**. Reduction of ketone in compound **52** with $NaBH_4$ resulted in a diastereomeric mixture (*dr* 64:36) of compound **53**. Alcohol **53** was converted to the corresponding xanthate **54**, which on sreaction with Bu_3SnH furnished product **55** in 94% yield. Reaction of **55** with TBAF produced the free alcohol **56**. Deprotection of acetonide with $FeCl_3$. $6H_2O$ resulted in triol **57**. Ozonolysis of **57**, and oxidation of the resulting lactol gave lactone **58** in 76% yield. The free hydroxyl group in **58** was protected as the corresponding MOM ether resulted in the formation of compound **59**. Selenation and deselenation of lactone **59** resulted in *α, β*−unsaturated lactone **60**. Deprotection of the MOM ether in **60** with $FeCl_3.6H_2O$ afforded 8−*epi*−(+)−goniodiol (**2**) (**Scheme−8**).

3.2.4. Present Work- Diastereoselective total synthesis of 7−*epi*−(+)−goniodiol (1) and 8−*epi*−(−)−goniodiol (2).

3.2.4.1. Retrosynthetic analysis:

The biological activities and interesting structural features of styryllactones have attracted attention for their synthesis. As per the proposed retrosynthetic plan depicted in (**Scheme−9**), 7−*epi*−(+)−goniodiol (**1**) and 8−*epi*−(−)−goniodiol (**2**) could be accessed from secondary alcohol **65** by oxidative cleavage followed by lactonization and selenium mediated elimination reaction. Compound **65** could be prepared from diol **62** by acetonide protection and unusual Grignard

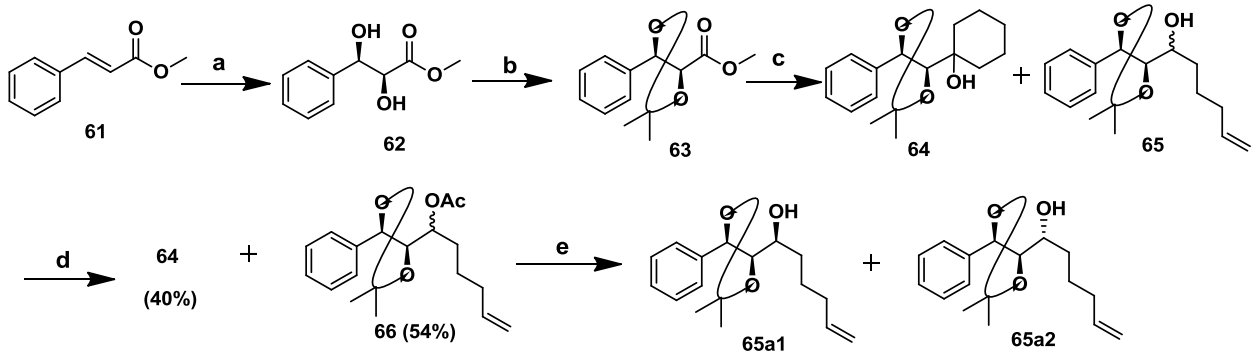


Scheme 9− Retrosynthetic analysis of 7−*epi*−(+)−goniodiol (**1**) and 8−*epi*−(−)−goniodiol (**2**)

reaction. The chiral diol **62** could be easily prepared under Sharpless dihydroxylation reaction conditions [18] from inexpensive and easily available starting material methyl cinnamate (**61**).

3.2.4.2. Results and discussion

According to the retrosynthetic analysis, the synthesis started with the Sharpless asymmetric dihydroxylation reaction[18] on methyl cinnamate (**61**) by using AD−mix−*β* to furnish corresponding chiral diol **62** in 78% yield and 99% *ee* as confirmed by chiral HPLC analysis. The diolester compound **62** was protected as its acetonide using 2,2−DMP and *p*−TSA to furnish known compound **63**, [19] which is a requisite for unusual Grignard reaction. The unusual Grignard reaction which has been explored in Chapter-3, section−I on various types of ester substrates proved to be important for synthesis of styryl lactone skeleton. Compound **63** was then subjected to Grignard reaction with the Grignard reagent prepared from 1,5−di(bromomagnesio) pentane, in THF as a solvent, to furnish a mixture of cycloalkanol **64** and a long chain secondary alcohol bearing a terminal olefin **65** in 90% overall yield. As the acetonide protection in starting ester compound **63** was present on a secondary carbon atom adjacent to reaction centre, the product distribution was seen between usual and unusual Grignard products. Such system, present in acetonide protected ester provide less steric hindrance hence quantitative yields of unusual Grignard product was not observed. Formation of the structural isomers **64** and **65** was confirmed from ^{1}H−NMR as well as ^{13}C NMR analysis. Isolation of these structural isomers through a column chromatography was found to be tedious (**Scheme−10**).

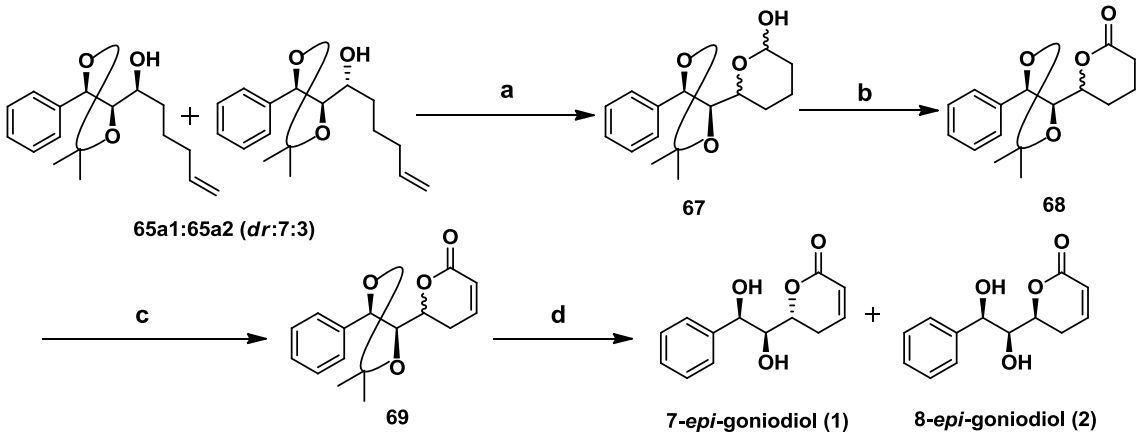


Scheme 10−Application of unusual Grignard reaction in the synthesis of (**1**) and (**2**)

Reagents and conditions− *(a) $K_3Fe(CN)_6$, K_2CO_3, methane sulphonamide, OsO_4, $(DHQD)_2PHAL$, $^{t}BuOH:H_2O$, 0 ^{o}C, 24 h, 78%, >99% ee; (b) 2,2−DMP, p-TSA (cat.), DMF, RT, 6 h, 97%; (c) 1,5−Dibromopentane, Mg metal, THF, 0 ^{o}C− RT, 5 h, 90%, (dr: 7:3), >98% ee;*

(d) Acetic anhydride, triethylamine, DMAP (cat.), DCM, 0 $^{o}C-$ RT, 2 h; (e) K_2CO_3, MeOH, 0 $^{o}C-$ RT, 2 h, 95%, (dr:7:3).

In order to obtain the expected long chain isomer **65** in pure form, the mixture of compounds was subjected for acetate protection of secondary alcohol. After completion of reaction, acetate **66** was readily separated from cycloalkanol **64**. The formation of **66** was confirmed by appearance of singlet at δ 2.10 (2.12H) and δ 1.84 (0.88H) corresponding to methyl of acetate and (*dr*= 7:3). The mixtre of compounds **64** and **66** could be separated easily through column chromatography.The pure acetate protected acetonide **66** was further subjected for K_2CO_3 mediated acetate deprotection gave long chain alcohol which was the unusual Grignard reaction product **65** in 99% *ee* with diastereomeric ratio (7:3), as confirmed with chiral HPLC analysis. It was decided to proceed towards synthesis of styryl lactones with inseparable diastereomeric mixture of **65a1:65a2** having *dr* (7:3).



Scheme 11−Completion of diastereoselective synthesis of (**1**) and (**2**)

Reagents and conditions− *(a) OsO_4, NaIO4, dioxane:H_2O (9:1), 8 h, RT, 79%; (b) TPAP, NMO, DCM, RT, 15 min., 77%, (dr:8:2); (c) i) LDA, PhSeBr, THF, −78 ^{o}C. 1 h, ii) H_2O_2, pyridine, −78 $^{o}C-$ RT, 2 h, 68%, (dr: 8:2); (d) (50%) Aq. AcOH, 80 ^{o}C, heat, 1h, 88%, (dr:8:2).*

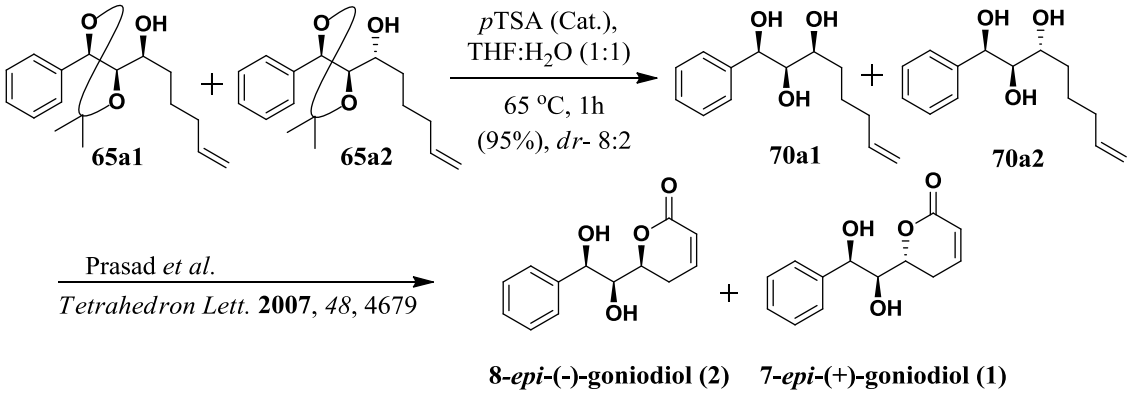
In the next step compound **65** was treated under Lemiuex−Johnson reaction conditions for oxidative cleavage of terminal double bond. Thus, oxidative cleavage of compound **65** in presence of OsO_4 and subsequent addition of $NaIO_4$ resulted in formation of lactol **67** in 79% yield and (*dr*: 6:4), which was further oxidised using oxidant TPAP in the presence of *NMO* as a co−oxidant to furnish lactone **68** in 77% yield.[19] The appearance of ν_{max}: 1740, cm^{-1} absorption frequency in IR spectrum confirmed formation of lactone **68**. Also disappearance of diastereomeric peaks for proton adjacent to lactol −OH group (*C<u>H</u>−OH*) in $^{1}H-$NMR spectrum

along with ^{13}C−NMR spactra (*C*H−*OH*) was found to be in line with the said transformation of lactol to lactone.[19]

The lactone **68** was alkylated using phenylselenyl bromide employing LDA as the base at −78 ^{o}C and subsequent oxidation–elimination in the presence of hydrogen peroxide, pyridine gave compound **69** in good yields. The formation of *α*, *β*−unsatureted compound **69** was confirmed with the mass spectra exhibits (*m/z*): 257 corresponds to $[M+Na]^{+}$. The ^{1}H−NMR and ^{13}C−NMR spectral analysis of penultimate compound **69** was found to be in good agreement with the reported literature data for synthesis of 7−*epi*−(+)−goniodiol (**1**) and 8−*epi*−(−)−goniodiol (**2**). The ^{1}H−NMR and ^{13}C−NMR spactral analysis suggests formation of diastereselective mixture of 7−*epi*−(+)−goniodiol (**1**) and 8−*epi*−(−)−goniodiol (**2**) in the ration (*dr*: 8:2). The formation of final product was achieved when compound **69** was heated with (1:1) AcOH–H_2O, at 80 ^{o}C for an hour furnished 7−*epi*−(+)−goniodiol (**1**) and 8−*epi*−(−)−goniodiol (**2**) (**Scheme−11**). The spectral details of **1** and **2** were in accordance with the reported data.[14, 17] One of the diastereomer was enriched during chromatographic purification, in the final step. Hence, diastereomeric ratio of final compound exhibits *dr:* 8:2 with respect to (**1**) and (**2**).

3.2.4.3. Formal synthesis of 8−*epi*−(−)−goniodiol and 7−*epi*−(+)−goniodiol

On the other hand, mixture of **65a1** and **65a2** (*dr*: 7:3), when subjected for acetonide deprotection produced respective triol compounds **70a1** and **70a2** (*dr*: 8:2) which are reported intermediates for total synthesis of goniodiol and 8−*epi*−(−)−goniodiol (**2**) by Prasad *et al.*[17] (**Scheme−12**). Thus, this also constitutes an alternative route for formal synthesis of styryl lactones 7−*epi*−(+)−goniodiol (**1**) and 8−*epi*−(−)−goniodiol (**2**).



Scheme 12: Formal synthesis of 8−*epi*−(−)−goniodiol (**2**) and 7−*epi*−(+)−goniodiol (**1**)

3.2.5. Synthesis of substituted caprolactone

Lactone is a common structural motif widely found in biologically active natural products and pharmaceuticals. Lactone rings occur widely as building blocks in nature.

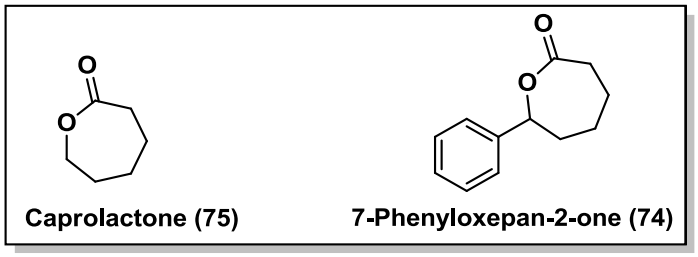
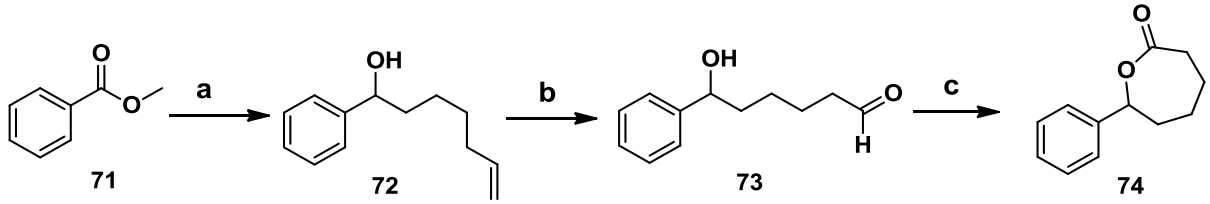


Figure 4− Structure of caprolactone (**75**) and substituted caprolactone (**74**)

Caprolactone (**75**) is a cyclic ester a member of the lactone family, with a seven−membered ring with the molecular formula $(CH_2)_5CO_2$. Caprolactone is prepared industrially by Baeyer-Villiger oxidation with peracetic acid. This is a colorless liquid miscible with most of the organic solvents. It is produced on a very large scale as a starting material to prepare caprolactam. It is also a useful monomer used in the manufacture of highly specialised polymers, used as suture material of plaster in surgery.

Baeyer–Villiger oxidation of cyclic ketones is one of the standard route to prepare lactones. Various types of oxidative reagents like Magnesium Monoperoxyphthalate, lanthanide based catalysts and hypervalent iodine reagents were reported in literature to promote cyclisation of aryl substituted carboxylic acids. [20] Enzymes like, lipase and Baeyer–Villiger monooxygenase mediated enzymatic oxidation of ketones were also used to prepare heptolide kind of framework.[21]



Scheme−13: Synthesis of substituted caprolactone (**74**)

Reagents and conditions: *(a) 1,6−Dibromohexane, Mg metal turnings, THF, RT, 5 h, 68%; (b) OsO_4, $NaIO_4$, dioxane:H_2O (9:1), 8 h, RT, 79%; (c) TEMPO (cat.), $PhI(OAc)_2$, DCM, RT, 6 h, 61%*

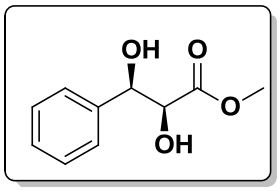
A regioselective route for preparation of substituted ε−caprolactone in reduced number of steps has been developed by utilising this unusual Grignard reaction followed by oxidative lactonization (**Scheme−13**). Accordingly, when methyl benzoate **71** was treated under Grignard reaction conditions in presence of 1,6−di(bromomagnesio)hexane and THF as a solvent at RT, it afforded seven carbon long chain alcohol **72** containing terminal double bond. The formation of **72** was confirmed by ^{1}H−NMR spectral analysis which contained a signal for doublet of a doublet of a triplet at δ 5.79 (J = 16.93, 10.11, 6.70 Hz), for one proton corresponds to terminal (C=C<u>H</u>). This long chain secondary alcohol **72** proved to be immensely important intermediate for the facile synthesis of seven membered lactones.[22] In the next step alcohol **72** was treated under Lemieux–Johnson oxidation reaction conditions [23] to furnish aldehyde **73** in 79% yield. Its formation was established with IR absorption frequency at ν_{max}: 2827, 1720, cm^{-1}. This aldehyde **73** was then subjected to TEMPO catalyzed oxidative lactonization in presence of (diacetoxyiodo)benzene to afford lactone **74** in 61% yield. [24] This procedure is free from use of expensive reagent, problem of regioselectivity and lower yields than other reported routes.

3.2.6. Conclusion

In summary, the new method for the synthesis of styryl lactones has been developed. As an application of unusual Grignard reaction diastereoselective synthesis of styryl lactones 7−epi−(+)−goniodiol (**1**) and 8−epi−(−)−goniodiol (**2**), has been accomplished in reduced number of steps than the ones reported in the literature. Synthesis of substituted 7−membered lactone was achieved, which is exemplified by preparation of lactone, 7−phenyloxepan−2−one (**74**).

3.2.7. Experimental

Preparation of (2*S*,3*R*)−methyl 2,3−dihydroxy−3−phenylpropanoate (62)

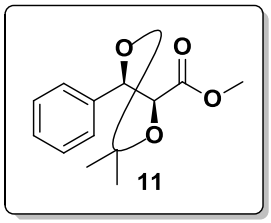


To a stirred solution of potassium ferricyanide (18.2 g, 3.0 mmol, 3.0 equiv.) and potassium carbonate (7.66 g, 3.0 mmol, 3.0 equiv.) in water (150 mL), methane sulphonamide (1.94 g, 1.1 mmol, 1.1 equiv.) was added followed by *tert*−butanol (150 mL) and vigorously stirred until the reaction suspension became clear. Then ligand $(DHQD)_2PHAL$ (0.045g, 4.0 mol%) followed by 1M solution of osmium tetroxide in *tert*−butanol (0.010 mL, 1.0 mol%) were added to it at 0

^{o}C and the resulting suspension was stirred until orange color was obtained. To this mixture, solution of methyl cinnamate (**61**, 3 g, 1.0 mmol, 1.0 equiv.) in *tert*−butanol (5 mL) was added in dropwise manner. The resultant heterogeneous reaction mixture was stirred at 0 ^{o}C for 24 h. The reaction mixture was quenched by addition of sodium sulfite (5 g) and the resulting suspension stirred at RT for 0.5 h. The reaction mixture was extracted with EtOAc (4 X 20 mL). The organic layer was washed with brine, then dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue. The obtained residue was purified by using 60–120 silica gel column chromatography (30% EtOAc–pet. ether) to furnish the diol (2*S*,3*R*)−methyl 2,3−dihydroxy−3−phenylpropanoate **62** as a colorless oil (5.65 g, 78%, 99% *ee*). **Molecular formula:** $C_{10}H_{12}O_4$; **Yield:** 78%; $[\alpha]^{25}_{D} = -10.4$ (*c* 1, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.37−7.25 (m, 5H), 4.96 (br s, 1H), 4.32 (br s, 1H), 3.76 (s, 3H), 3.36 (br s, 1H), 3.15 (br s, 1H); **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4):** δ 173.1, 139.9, 128.3, 127.9, 126.2, 74.8, 74.4, 52.7; **MS (ESI)** (*m/z*): 219 $[M+Na]^+$.

(4*S*,5*R*)−Methyl 2,2−dimethyl−5−phenyl−1,3−dioxolane−4−carboxylate (63)



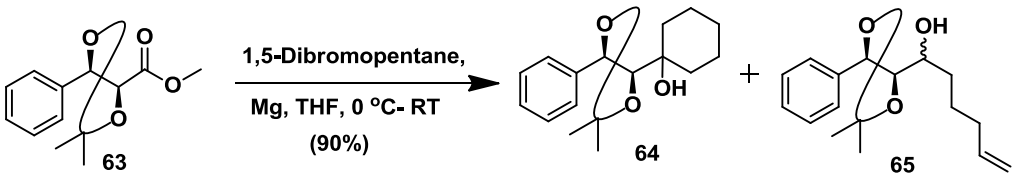
To a stirred solution of (2*S*,3*R*)−methyl 2,3−dihydroxy−3−phenylpropanoate (**62**) (0.800 g, 0.45 mmol, 1.0 equiv.) in dry DMF (4 mL) as a reaction solvent, was added 2,2−DMP (0.403 mL, 1 mmol, 1.1 equiv.) followed by *p*-TSA (0.067 g, 0.1 mmol, 0.1 equiv.). The reaction mixture was stirred at 25 ^{o}C and monitored by TLC. After completion (6 h), reaction mixture was diluted with EtOAc. The reaction mixture was washed with brine and extracted with EtOAc (3 X 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue obtained was then purified by column chromatography using 60–120 silica gel (5% EtOAc–pet. ether) to furnish the respective acetonide protected ester (4*S*,5*R*)−methyl-2,2−dimethyl−5−phenyl−1,3−dioxolane−4−carboxylate (**63**) as a colorless viscous oil; (0.934 g, 97%).

Molecular formula: $C_{13}H_{16}O_4$; **Yield:** 97%; $[\alpha]^{25}_{D} = +23$ (*c* 1, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.41−7.33 (m, 5H), 5.15 (d, *J* = 7.71 Hz, 1H), 4.33 (d, *J* = 7.58 Hz, 1H), 3.79 (s, 3H), 1.61 (s, 3H), 1.56 (s, 3H); **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4)**: δ

170.6, 137.7, 128.58, 128.51, 126.4, 111.5, 81.2, 80.6, 52.3, 26.9, 25.8; **MS (ESI)** (*m/z*): 259 $[M+Na]^+$.

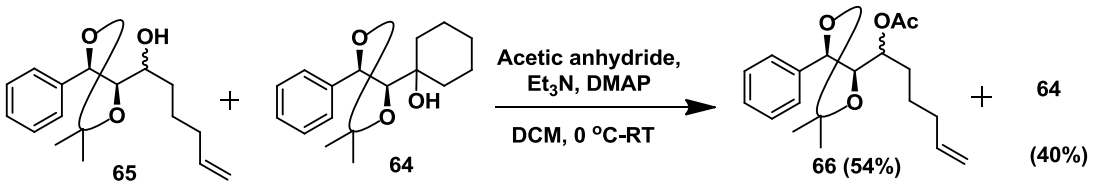
The unusual Grignard reaction



In a two neck round bottom flask (100 mL) containing Mg metal (4.78 mmol, 3 equiv.) in dry THF (3 mL), solution of 1,5−dibromopentane (2.37 mmol, 1.5 equiv.) in dry THF (2 mL) was added in a dropwise manner at 0− 5 ^oC. After addition, the reaction mixture was allowed to warm upto RT and stirred for 2 h. The reaction mixture becomes turbid indicating generation of a Grignard reagent.

To a pre−cooled (0−5 ^oC) solution of ester methyl−4−(4−methoxyphenyl)−2,2−dimethyl −1,3−dioxolane−4−carboxylate (**63**) (1.00 g, 1.60 mmol, 1.0 equiv.) in THF (2 mL) was added the above generated solution of Grignard reagent carefully in a dropwise manner. After addition, the reaction mixture was warmed upto RTwithin 0.5 h and then stirred for additional 2.5 h. The suspension was quenched slowly with the addition of saturated NH_4Cl solution at 0 ^oC, followed by extraction with EtOAc (3 X 15 mL). The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography using 200–400 silica gel and 12% EtOAc–pet. ether as a eluent, to furnish inseparable mixture of structural isomeric compounds **64** and **65** in 90% yield.

Preparation of 1−(2,2−dimethyl−5−phenyl−1,3−dioxolan−4−yl)hex−5−en−1−yl acetate (66)



To a stirred solution of a mixture of 1−(2,2−dimethyl−5−phenyl−1,3−dioxolan−4−yl)hex−5−en−1−ol (**65**) and 1−(2,2−dimethyl−5−phenyl−1,3−dioxolan−4−l)cyclohexanol (**64**) (0.5 g) in dry DCM (3 mL) was added acetic anhydride (0.280 g , 6.59 mmol) followed by Et_3N (0.160 g, 9.42 mmol), and DMAP (cat.). The resulting mixture was stirred at RT for 1 h. After completion of reaction, the reaction mixture was diluted with DCM (10 mL), washed with 10% HCl solution followed by water and brine. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue thus obtained was purified by 200–400 silica gel column chromatography using (5% EtOAc–pet. ether) as eluent to give pure 1−(2,2−dimethyl−5−phenyl−1,3− dioxolan−4−yl)hex−5−en−1−yl acetate (**66**) (0.310 g, 54%) and unreacted 1−(2,2−dimethyl−5−phenyl −1,3−dioxolan−4 −l)cyclohexanol (**64**) (0.230 g, 40%) was recovered.

Data for **1−(2,2−dimethyl−5−phenyl−1,3−dioxolan−4−yl)hex−5−en−1−yl acetate (66)**

Molecular formula: $C_{19}H_{28}O_4$; **Yield:** 54%.

^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): (*dr*: 7:**3**) δ 7.40−7.35 (m, 4H),7.33−7.30 (m, 1H), 5.70 (m, 1H), 5.18−5.14 (m, 0.25H), 5.06−5.03 (m, 0.75H), 4.97−4.91 (m, 2H),4.82 (d, J = 8.24 Hz, 0.25H), 4.69 (d, J = 8.55 Hz, 0.75H), 3.98 (dd, J = 8.24, 6.10 Hz, 0.25H), 3.86 (dd, J = 8.55, 2.75 Hz, 0.75H), 2.10 (s, 2.12H), 2.02−1.97 (m, 2H), 1.84 (s, 0.88H), 1.75−1.67 (m, 1H), 1.63−1.60 (m, 1H), 1.57 (s, 3H), 1.51 (s, 3H), 1.37−1.32 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 170.7, **170.4**, 138.1, **137.5**,128.6, **128.5**, 128.3, **127.5**, 126.7, 114.8, 109.4, 83.9, **83.2**, **80.8**, 78.9,**72.8**, 70.3, 33.3, 31.0, **30.5**, 27.1, 26.8, 26.7, 24.7, 24.2, **20.9**, 20.8.

MS (ESI) (*m/z*): 341 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 2850, 1740, 1620 cm^{-1}.

HRMS (ESI): Calculated for $C_{19}H_{26}O_4$ $[M+Na]^{+\cdot}$341.1935, found 341.1932.

Data for **1−(2,2−dimethyl−5−phenyl−1,3−dioxolan−4−l)cyclohexanol (64)**

Molecular formula: $C_{17}H_{24}O_3$; **Yield:** 40%.

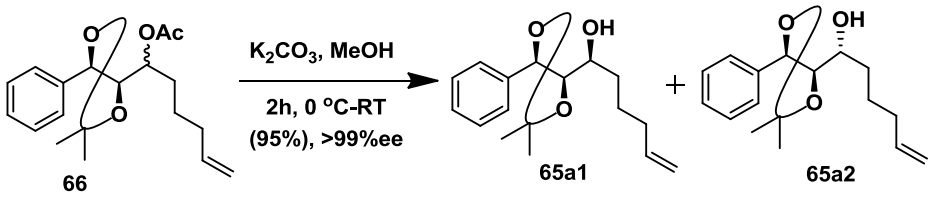
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.46−7.32 (m, 5H), 5.00 (d, *J* = 8.57 Hz, 1H), 3.93 (d, *J* = 8.57 Hz, 1H), 2.06 (br s, 1H), 1.70−1.58 (m, 2H), 1.56 (s, 3H), 1.50 (s, 3H), 1.55−1.40 (m, 6H), 1.36−1.27 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 138.6, 128.5, 128.3, 108.6, 87.8, 78.5, 70.3, 36.3, 32.7, 27.6, 27.0, 25.5, 21.4, 21.1.

MS (ESI) (*m/z*): 299 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3035, 2850, 1620 cm^{-1}.

HRMS (ESI): Calculated for $C_{17}H_{24}O_3$ $[M+Na]^+$ 299.1618, found 299.1620.

Preparation of 1−(2,2−dimethyl−5−phenyl−1,3−dioxolan−4−yl)hex−5−en−1−ol (65)



To a stirred solution of 1−(2,2−dimethyl−5−phenyl−1,3−dioxolan −4−yl)hex−5−en−1−yl acetate (**66**), (0.300 g, 0.068 mmol) in dry MeOH (0.5 mL) was added K_2CO_3 (0.040 g, 0.146 mmol) at RT and the resulting solution was stirred for 30 min. The reaction mixture was diluted with EtOAc (10 mL) and washed with 0.1M aq. NaOH (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined filtrates were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude residue. The purification was carried out by column chromatography using 200–400 silica gel (2% EtOAc–pet. ether) as a eluent to furnish 1−(2,2−dimethyl−5−phenyl−1,3−dioxolan −4−yl)hex−5−en−1−ol (**65**) as a colorless oil (0.247 g, 95%, *ee*: 98%).

Molecular formula: $C_{17}H_{24}O_3$; **Yield:** 95%.

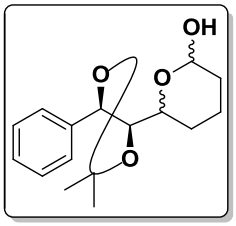
^{1}H NMR (200 MHz, $CDCl_3$): (*dr*: 7:**3**) δ 7.43−7.29 (m, 5H), 5.79−5.52 (m, 1H), 4.98−4.84 (m, 3 H), 3.94−3.50 (m, 2H), 2.11(br s, 1 H), 2.02−1.86 (m, 2H), 1.56 (s, 3H), 1.50 (s, 3H), 1.41−1.15 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 138.4, **138.2**, 137.6, **137.4**, 128.5, **128.4**, **128.35**, 128.30, **127.7**, 126.8, 114.6, 109.1, **108.8**, 85.6, **85.2**, 79.3, **78.5**, **70.3**, 68.6, 34.6, 33.4, **33.3**, **31.7**, **27.3**, 27.2, 27.0, **26.9**, **25.1**, 24.8.

MS (ESI) (*m/z*): 328 $[M+Na+MeOH]^+$; **IR ($CHCl_3$)** ν_{max}: 3435, 2989, 1620 cm^{-1}.

HRMS (ESI): Calculated for $C_{17}H_{24}O_3$ $[M+Na]^+$ 299.1618, found 299.1614.

Preparation of 6−(2,2−dimethyl−5−phenyl−1,3−dioxolan−4−yl)tetrahydro−2*H*−pyran−2−ol (67)



To a stirred solution of 1−(2,2−dimethyl−5−phenyl−1,3−dioxolan−4−yl)hex− 5−en−1−ol (**65**) (0.130 g, 0.32 mmol, 1.0 equiv.) in dioxane−water (3:1, 8 mL) at room temperature, was added 1M solution of OsO_4 (0.0032 mmol, 0.01 equiv.) carefully in a dropwise manner. The resulting reaction mixture was continuously stirred for half an hour followed by addition of $NaIO_4$ (0.162 g, 0.76 mmol, 2.4 equiv.) in one portion. The reaction mixture was then stirred vigorously for 20 h. After completion of reaction, the reaction was quenched with sat. aq. Na_2SO_3 (5 mL) and stirred vigorously for 30 min. The biphasic mixture was then extracted with EtOAc (3 X 10 mL) and the combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product obtained was subjected for column chromatography using 200−400 silica gel with 25−35% EtOAc–pet. ether as a eluent to furnish 6−(2,2−dimethyl−5−phenyl−1,3 −dioxolan−4−yl)tetrahydro−2*H*−pyran−2−ol (**67**) (0.098 g, 79% yield) as a colorless oil.

Molecular formula: $C_{16}H_{22}O_4$; **Yield:** 79%.

^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): (*dr*: 6:4) δ 7.44−7.23 (m, 5H), 5.29−5.17 (m, 0.58 H), 4.91 (d, *J* = 7.79 Hz, 0.50H), 4.84 (d, *J* = 8.24 Hz, 0.50H), 4.66 (d, *J* = 8.70 Hz, 0.42H), 4.09 (ddd, *J* = 11.45, 4.35, 2.52 Hz, 0.52H), 3.94 (dd, *J* = 8.24, 4.35 Hz, 0.40H), 3.85 (dd, *J* = 8.24, 4.58 Hz, 0.60H), 3.60 (ddd, *J* = 10.99, 5.04, 2.29 Hz, 0.48H), 1.93−1.80 (m, 1H), 1.73−1.58 (m, 3H), 1.53 (s, 3H), 1.49 (s, 3H), 1.39−1.27 (m, 2H).

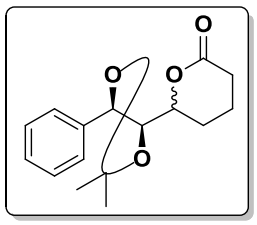
^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 138.4, 128.4, 128.1, 127.1, 127.0, 109.4, 96.6, 91.9, 85.0, 84.6, 80.4, 80.0, 76.3, 68.5, 32.8, 29.6, 27.3, 27.1, 26.3, 26.0, 21.5, 16.9.

MS (ESI) (*m/z*): 303 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3325, 2950, 2851, 1340, 1160, 650 cm^{-1}.

HRMS (ESI): Calculated for $C_{16}H_{24}O_4$ $[M+Na]^+$ 303.2064, found 303.2062.

Preparation of

6−(2,2−dimethyl−5−phenyl−1,3−dioxolan−4−yl)tetrahydro−2*H*−pyran−2−one (68)



To a stirred solution of 6−(2,2−dimethyl−5−phenyl−1,3−dioxolan−4−yl) tetrahydro−2*H*−pyran−2−ol (**67**) (0.088 g, 1.0 equiv.) in dry DCM (2 mL) was added solid TPAP (0.003 mg, 0.03 mmol, 5 mol%) in one portion followed by NMO (0.039 mg, 0.82 mmol, 1.5 equiv.) and 4 A^o molecular sieves (0.107 g, 0.5 g/mmol of lactol) at RT. After completion, reaction mixture was filtered through celite, washed with DCM (3 X 10 mL) and the combined filtrate were concentrated under reduced pressure to give the crude product which was further washed with aq. Na_2SO_3 (2 X 10 mL) and extracted with DCM to afford crude lactone. Purification of crude residue by column chromatography on 200−400 silica gel (30% EtOAc–pet. ether) furnished 6−(2,2−dimethyl−5−phenyl−1,3−dioxolan−4−yl)tetrahydro −2*H*−pyran−2−one (**68**, 0.076 g, 87%, *dr*: 8:**2**) as a colorless oil.

Molecular formula: $C_{16}H_{20}O_4$; **Yield:** 87%.

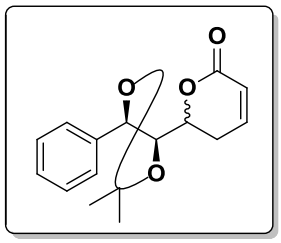
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): (*dr*: 8:**2**) δ 7.49−7.23 (m, 5H), 5.18 (d, *J* = 8.72 Hz, 0.22H), 4.97 (d, *J* = 7.71 Hz, 0.78H), 4.46−4.26 (m, 1H), 3.99 (dd, *J* = 7.71, 5.49 Hz, 0.78H), 3.71 (dd, *J* = 8.72, 1.45 Hz, 0.22H), 2.55 (br s, 1H), 2.68−2.29 (m, 2H), 2.06−1.64 (m, 4H), 1.54 (s, 3H), 1.50 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ **170.5**, 169.8, 138.1, **137.3**, **128.7**, 128.5, 128.3, 126.9, **126.8**, 110.0, **109.8**, **84.9**, 83.9, 80.3, 79.9, **77.9**, **75.3**, **30.0**, 29.7, **27.4**, 27.2, 27.0, **26.6**, **25.5**, 24.1, **18.5**, 18.2.

MS (ESI) (*m/z*): 301$[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}**:** 1740, 1620, 1440 cm^{-1}.

HRMS (ESI): Calculated for $C_{16}H_{22}O_4$ $[M+Na]^+$ 301.3435, found 301.3439.

Preparation of (69)



To a stirred solution of diisopropylamine (1.9 mL, 0.60 mmol, 4.0 equiv.), *n*−BuLi [(790 μL, 4.0 equiv.) 1.6 M], in dry THF (5 mL) at −78 ^{o}C, was added dropwise a solution of 6−(2,2−dimethyl−5−phenyl−1,3−dioxolan−4−yl)tetrahydro−2*H*−pyran −2−one (**68**) (0.067 mg, 0.15 mmol, 1.0 equiv.) in dry THF (3 mL) over 15 minutes. After 45 minutes of stirring at this temperature, a solution of phenylselenyl bromide (0.075 g, 0.32 mmol) dissolved in dry THF (2 mL) was added in the reaction mixture. The resulting solution was stirred at the same temperature and after the reaction was complete, monitored by TLC (1 h), reaction mixture was quenched with sat.NH_4Cl (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were combined, washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to afford the crude selenide, which was used in the next step without further purification.

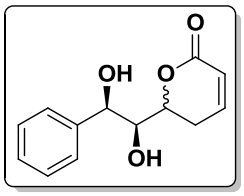
To a stirred solution of crude selenide obtained as a result of above reaction was dissolved in (6 mL) of anhydrous dichloromethane. To this solution pyridine (0.05 mL, 0.42 mmol) was added at −78 ^{o}C followed by careful addition of H_2O_2 (1.1 mL of 30% w/v in water) in dropwise manner. The resultant mixture was stirred at the same temperature until the reaction was complete (monitored by TLC, 1.5 h). Water (10 mL) was added to the reaction mixture and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude residue thus obtained was subjected for purification by flash column chromatography using 200–400 silica gel (25% EtOAc–pet. ether) as eluent to give *α*, *β*−unsaturated compound (**69**) (0.045 g, 68%) as a colorless oil.

Molecular formula: $C_{16}H_{18}O_4$; **Yield:** 68%.

^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): (*dr*: 8:**2**) *δ* 7.45−7.42 (m, 2H),7.38 (t, *J* = 7.32 Hz, 2H), 7.33−7.30 (m, 1H), 6.90−6.84 (m, 1H), 6.03−5.99 (m, 1H), 5.24 (d, *J* = 8.55 Hz, 0.20H), 4.98 (d, *J* = 7.93 Hz, 0.80H), 4.55 (dt, *J* = 10.68, 5.04 Hz, 0.80H), 4.42−4.39 (m, 0.20H), 4.11 (dd, *J* = 7.93, 5.04 Hz, 0.80H), 3.81 (dd, *J* = 8.55, 1.68 Hz, 0.20H), 2.70−2.65 (m, 0.20H), 2.58−2.45 (m, 1.60H), 2.27−2.21 (m, 0.20H), 1.58 (s, 0.69H), 1.57 (s, 2.31H), 1.55 (s, 0.69H), 1.52 (s, 2.31H);

^{13}C NMR (125 MHz, $CDCl_3$): δ **163.5**, 162.8, 144.8, **144.7**, 137.7, **137.0**, **128.7**, 128.6, 128.5, 126.9, **126.7**, 121.2, **121.1**, 110.2, **109.9**, **83.7**, 83.0, 80.4, **77.5**, 77.2, **73.4**, **27.2**, 27.1, 26.9, **26.6**, **26.5**, 25.4; **MS (ESI)** (*m/z*): 297 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}**:** 2950, 1729, 1448, 1312 cm^{-1}.

Preparation of 7−epi−(+)−goniodiol (1) and 8−epi−(−)−goniodiol (2)

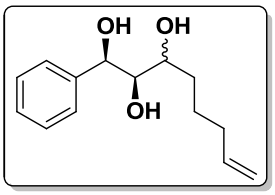


The stirred solution of enone (**69**) (0.03 g, 1.1 mmol) in AcOH: water (1:1, 3.0 mL) was heated at 80 ^oC for 1h. After completion of reaction, the reaction mixture was cooled to RT and quenched with the addition of cooled sat. $NaHCO_3$ (1 mL). The resulting solution was stirred vigorously for 15 min and extracted with EtOAc (3 X 10 mL), the organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude residue thus obtained was concentrated under reduced pressure followed by purification by means of column chromatography using 60−120 silica gel, (25−30% EtOAc–pet. ether) as a eluent to furnish a diastereomeric mixture of **1** and **2** (0.022 g, 88%).

Molecular formula: $C_{13}H_{14}O_4$; **Yield:** 88%.

^{1}H NMR (500 MHz, $CDCl_3$): (*dr*: 8:**2**) δ 7.42−7.31 (m, 5H), 6.92 (ddd, *J* = 8.85, 6.41, 2.14 Hz, 0.82H), 6.88 (ddd, *J* = 10.07, 6.41, 3.05 Hz, 0.18H), 6.00 (dd, *J* = 8.85, 2.14 Hz, 0.80H), 5.97 (dd, *J* = 10.07, 3.05 Hz, 0.20H), 4.96 (d, *J* = 7.33 Hz, 0.18H), 4.91 (d, *J* = 4.89 Hz, 0.82H), 4.44−4.40 (m, 0.82H), 4.24−4.20 (m, 0.18H), 3.95 (t, *J* = 4.89 Hz, 0.80H), 3.65 (d, *J* = 7.33 Hz, 0.20H), 2.96 (br s, 1H), 2.81 (br s, 1H), 2.65−2.58 (m, 1H), 2.52−2.47 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$+CCl_4)**: δ 163.8, **163.6**, **145.8**, 145.6, 140.0, 128.79, **128.71**, 128.3, **126.8**, 126.4, 120.9, **120.6**, **76.5**, 76.1, **74.0**, 71.9, **25.9**, 24.8; **MS (ESI)** (*m/z*): 257 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}**:** 3435, 2930, 1700, 1640 cm^{-1}.

Preparation of 1−phenyloct−7−ene−1,2,3−triol (70)



To a stirred solution of alcohol **65** (0.068 g, 1.1 mmol) in THF: water (1:1, 3.0 mL) was added (cat.) amount of *p*-TSA. The reaction mixture was heated at 65 ^oC for 1h. After completion of reaction, the mixture was cooled to RT and extracted using EtOAc (3 X 10 mL) followed by washing with aq. $NaHCO_3$ (3 X 5 mL). The organic extracts were combined and dried over

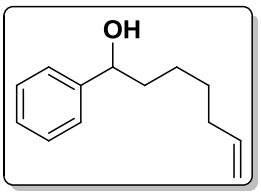
anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the pure product obtained (**70**) (0.051 g, 95% yield) as a white solid.

Molecular formula: $C_{14}H_{20}O_3$; **Yield:** 78%; **Mp**: 77−79°C.

^{1}H NMR (500 MHz, $CDCl_3$+CCl_4): (*dr*: 8:**2**) δ 7.41−7.30 (m, 5H), 5.85−5.72 (m, 1H), 5.04−4.92 (m, 2H), 4.81 (d, *J* = 5.49 Hz, 1H), 3.74−3.54 (m, 2H), 3.11 (br s, 1H), 1.62−1.34 (m, 4H), 2.87 (br s, 1H), 2.32 (br s, 1H), 2.12−2.07 (m, 0.20H), 2.04−2.01 (m, 1.80H); **^{13}C NMR (125 MHz, $CDCl_3$+CCl_4)**: δ 140.6, 138.4, 128.5, 128.1, **127.9**, 126.6, **126.2**, **114.8**, 114.7, 76.88, 76.80, 75.6, **73.5**, **73.2**, 71.4, 33.7, 33.4, **32.0**, **25.1**, 24.8.

MS (ESI) (*m/z*): 259 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3450, 2928, 1640, 1442 cm^{-1}.

Preparation of 1−phenylhept−6−en−1−ol (72)



In a two neck round bottom flask (100 mL) containing Mg metal (4.78 mmol, 3 equiv.) in dry THF (3 mL), solution of 1,6−dibromopentane (2.37 mmol, 1.5 equiv.) in dry THF (2 mL) was added dropwise at RT and stirred for 2 h. To a pre−cooled (0−5 ^oC) solution of methyl benzoate (**71**) (1.00 g, 1.60 mmol, 1.0 equiv.) in THF (2 mL) was added the above solution of Grignard reagent in a dropwise manner. After addition, the reaction mixture was warmed upto RT within 0.5 h and then stirred for additional 2.5 h. The suspension was quenched with addition of the sat. NH_4Cl solution (10 mL), followed by extraction with EtOAc (3 X 15 mL). The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was subjected for olumn chromatography using 200–400 silica gel (15% EtOAc–pet. ether) to furnish 1−phenylhept−6−en−1−ol (**72**, 0.617 g, 66%.) as a colorless oil.

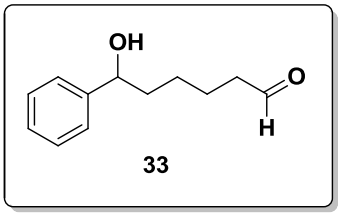
Molecular formula: $C_{13}H_{18}O$; **Yield:** 66%.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.33–7.27 (m, 5H), 5.79 (ddt, *J* = 16.93, 10.11, 6.70 Hz, 1H), 5.09−4.89 (m, 2H), 4.64 (t, *J* = 6.07 Hz, 1H), 2.09−2.01 (m, 2H), 1.92 (br s, 1H), 1.77−1.70 (m, 2H), 1.45−1.29 (m, 4H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 144.9, 138.7, 128.4, 127.5, 125.8, 114.5, 74.6, 38.9, 33.7, 28.8, 25.3.

MS (ESI) (*m/z*): 213 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3435, 1630, 1405 cm^{-1}.

HRMS (ESI): Calculated for $C_{13}H_{18}O$ $[M+Na]^+$ 213.2560, found 213.2562.

Preparation of 6−hydroxy−6−phenylhexanal (73):



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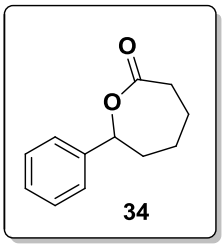
The above transformation was carried out as per the procedure for preparation of compound **67**. Column chromatography using 200–400 silica gel (12% EtOAc–pet. ether).

Molecular formula: $C_{12}H_{16}O_2$; **Yield:** 0.478 g, 79%.

^{1}H NMR (200 MHz, $CDCl_3$): δ 9.68 (t, J = 1.71 Hz, 1H), 7.37−7.12 (m, 5H), 4.60 (dd, J = 7.39, 5.75 Hz, 1H), 3.62 (s, 1H), 2.36 (td, J = 7.39, 1.71 Hz, 2H), 1.94 (br s, 1H), 1.77−1.53 (m, 4H), 1.52−1.36 (m, 2H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 201.9, 144.7, 128.4, 127.5, 125.8, 74.2, 67.0, 43.7, 38.7, 25.3, 21.9; **MS (ESI) (m/z):** 215$[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}**:** 2827, 1720, 1605 cm^{-1}.

Preparation of 7−phenyloxepan−2−one (74):



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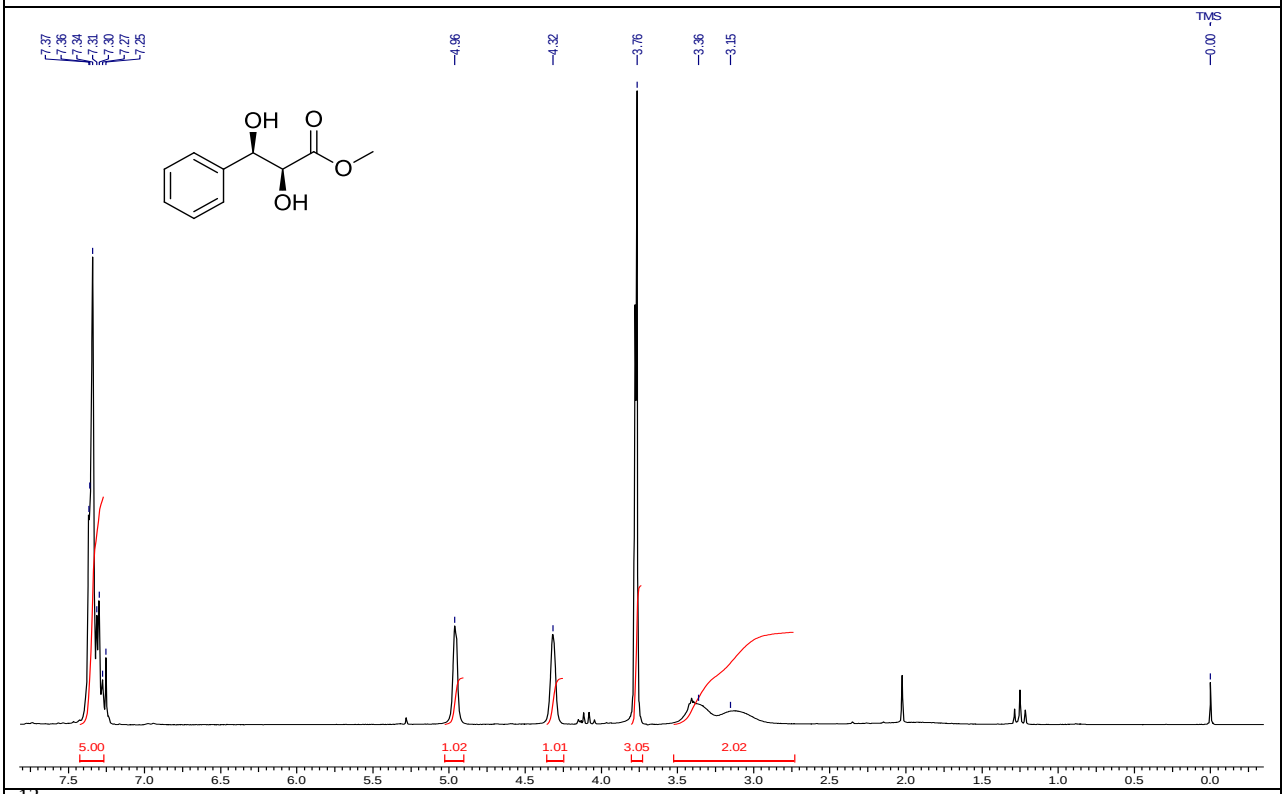
To a stirred solution of aldehyde **73** (0.400 g, 1.25 mmol) in anhydrous DCM (7 mL), was added (2,2,6,6−Tetramethylpiperidin−1−yl)oxyl (TEMPO) (0.42 g, 0.275 mmol) followed by addition of (diacetoxyiodo)benzene (0.88 g, 2.75 mmol). The resultant reaction mixture was stirred at RT for overnight. After completion, the reaction mixture was washed with sat. aq. $NaHCO_3/Na_2SO_3$ solution (1:1, v/v, 3 X 8 mL) followed by brine. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue thus obtained was purified by flash column chromatography with eluent (8% EtOAc–pet. ether) to furnish **74** (0.241 g, 61%), as a pure product.

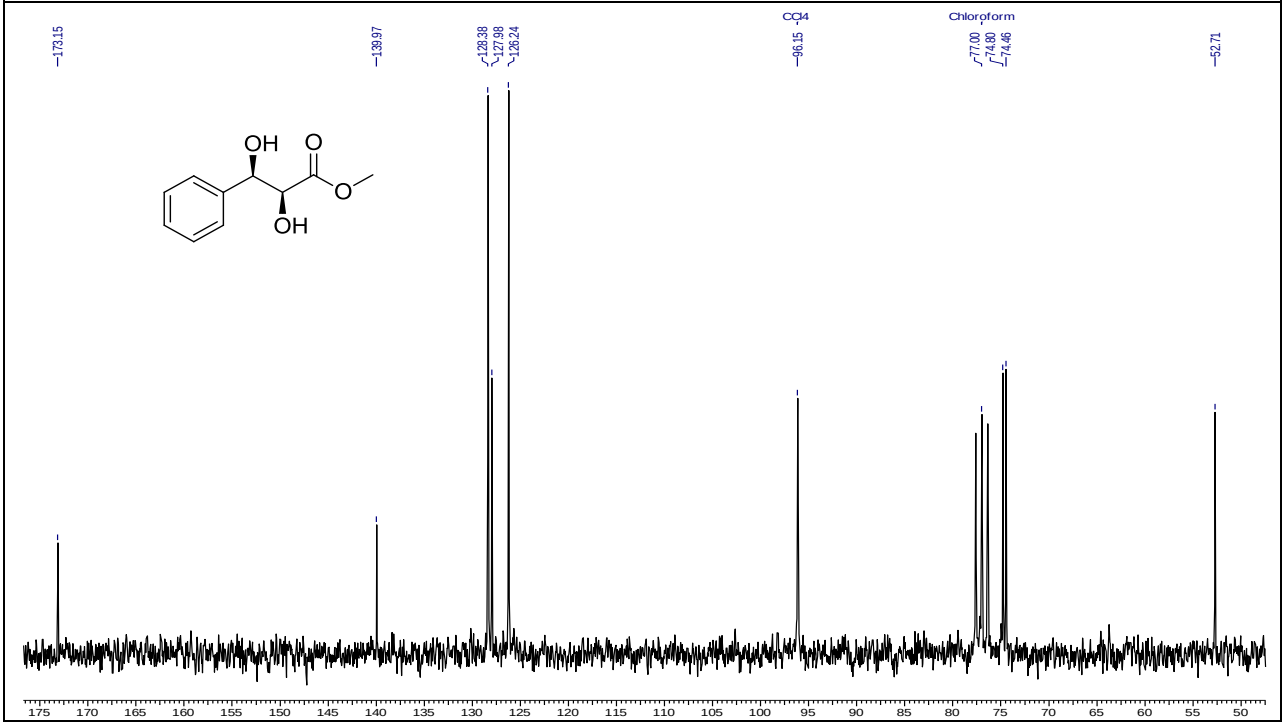
Molecular formula: $C_{12}H_{14}O_2$; **Yield:** 61%; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.39−7.37 (m, 5H), 5.29 (d, J = 9.29 Hz, 1H), 2.80−2.73 (m, 2H), 2.13−2.00 (m, 4H), 1.83−1.64 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$+CCl_4):** δ 174.8, 140.7, 128.4, 128.0, 125.7, 82.0, 37.3, 34.8, 28.5, 22.7; **MS (ESI) (m/z):** 213 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}**:** 2951, 1730 cm^{-1}; **HRMS (ESI):** Calculated for $C_{12}H_{14}O_2$ $[M+Na]^+$ 213.2542, found 213.2546.

3.2.7.1. Spectral data

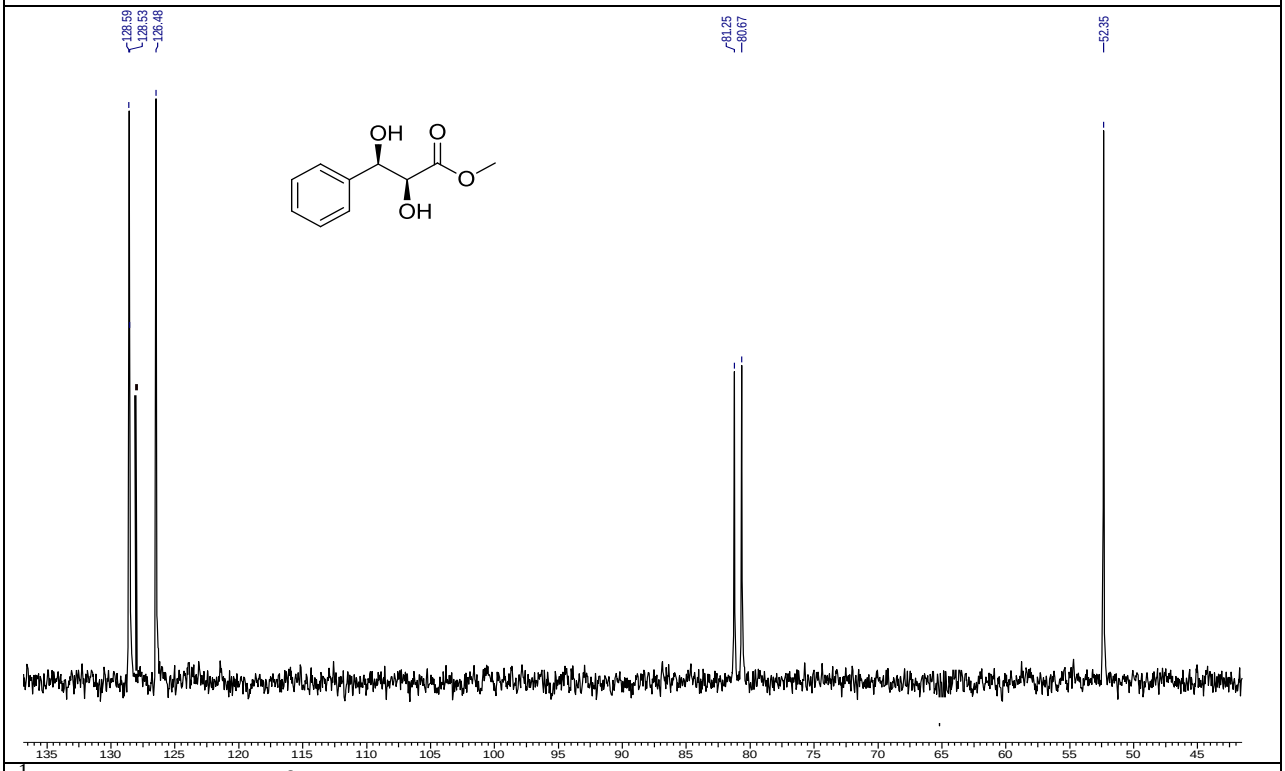
^{1}H NMR spectrum of compound **62** ($CDCl_3$+CCl_4, 200 MHz)



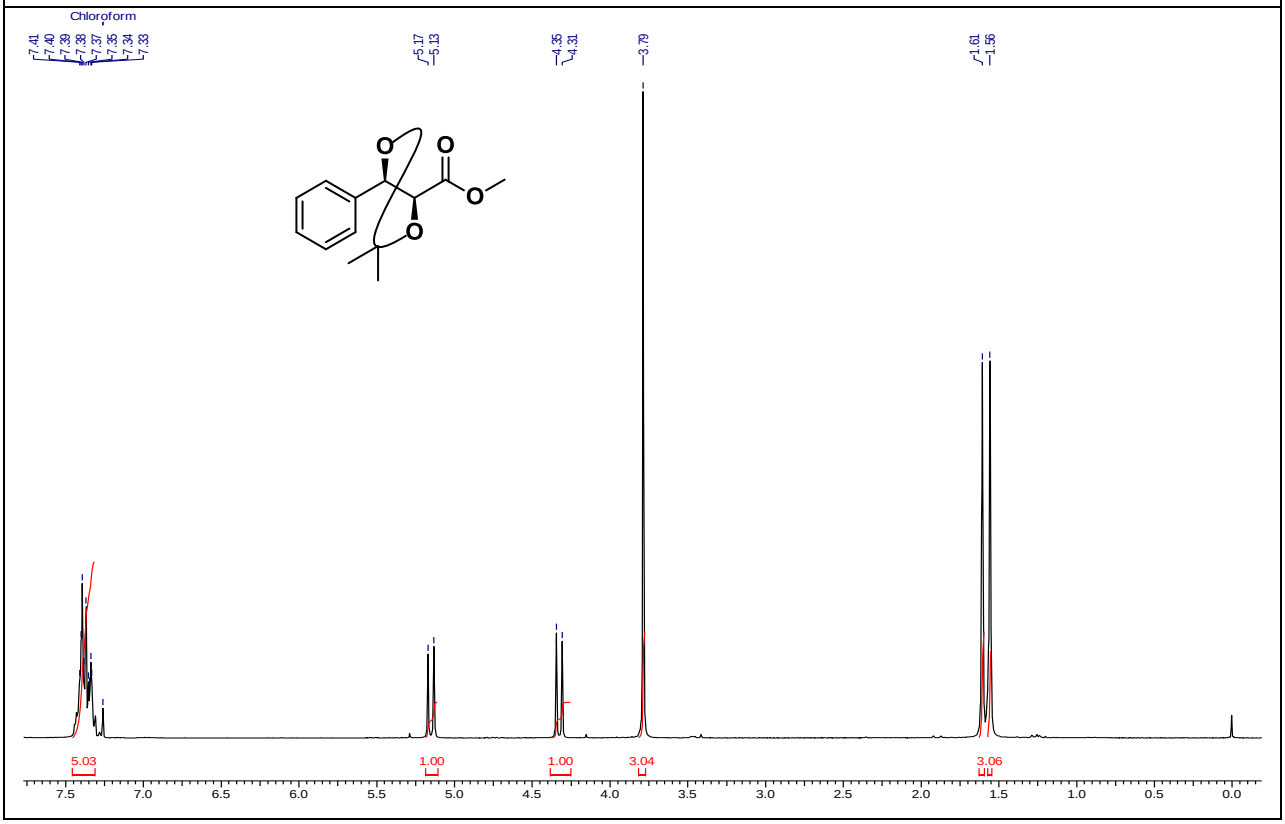
^{13}C NMR spectrum of compound **62** ($CDCl_3$+CCl_4, 50 MHz)



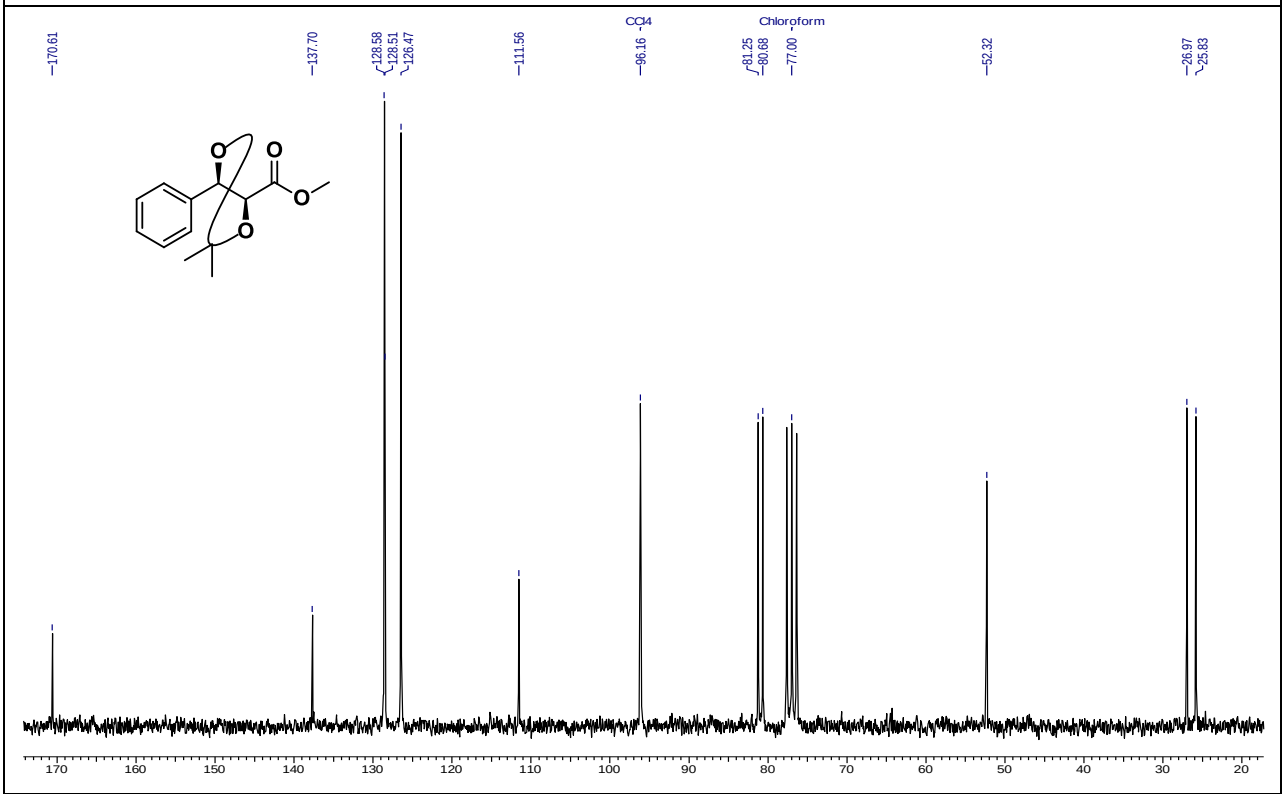
DEPT spectrum of compound **62** ($CDCl_3$+CCl_4, 50 MHz)



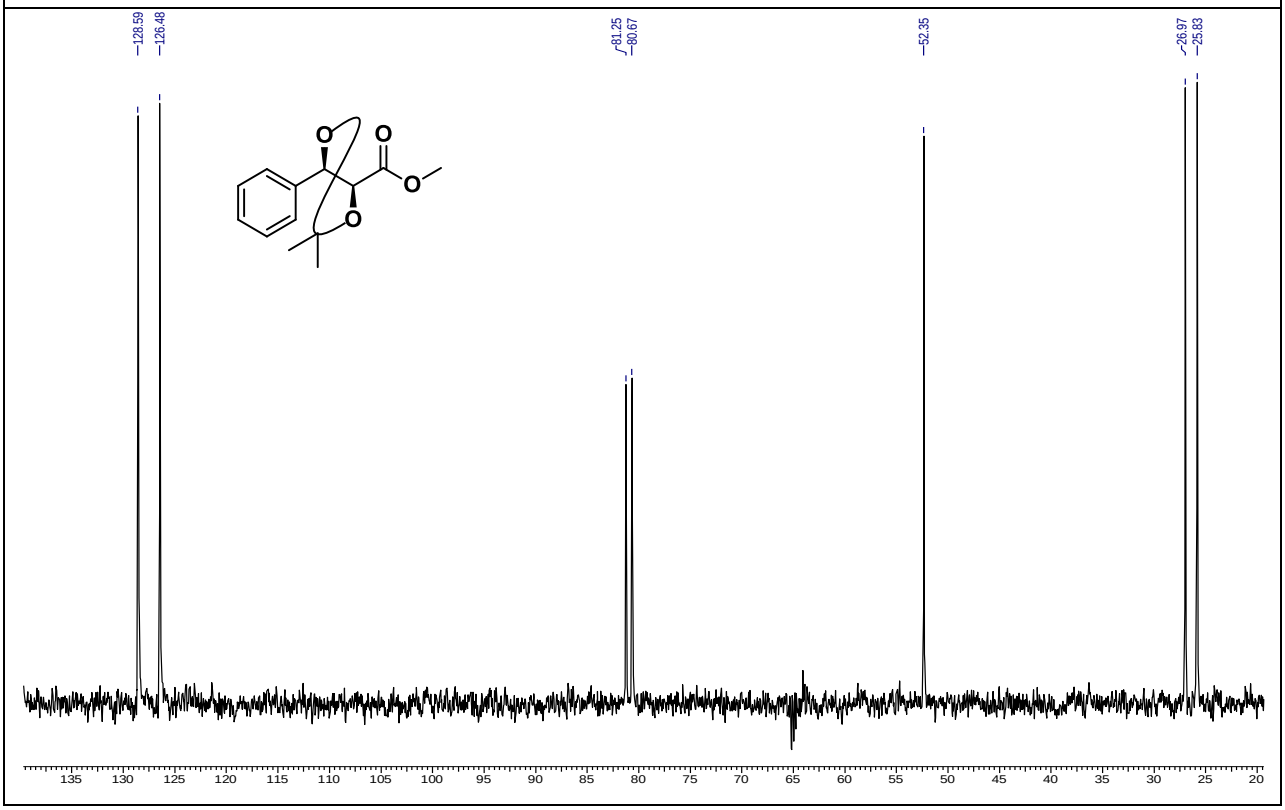
^{1}H NMR spectrum of compound **63** ($CDCl_3$+CCl_4, 200 MHz)



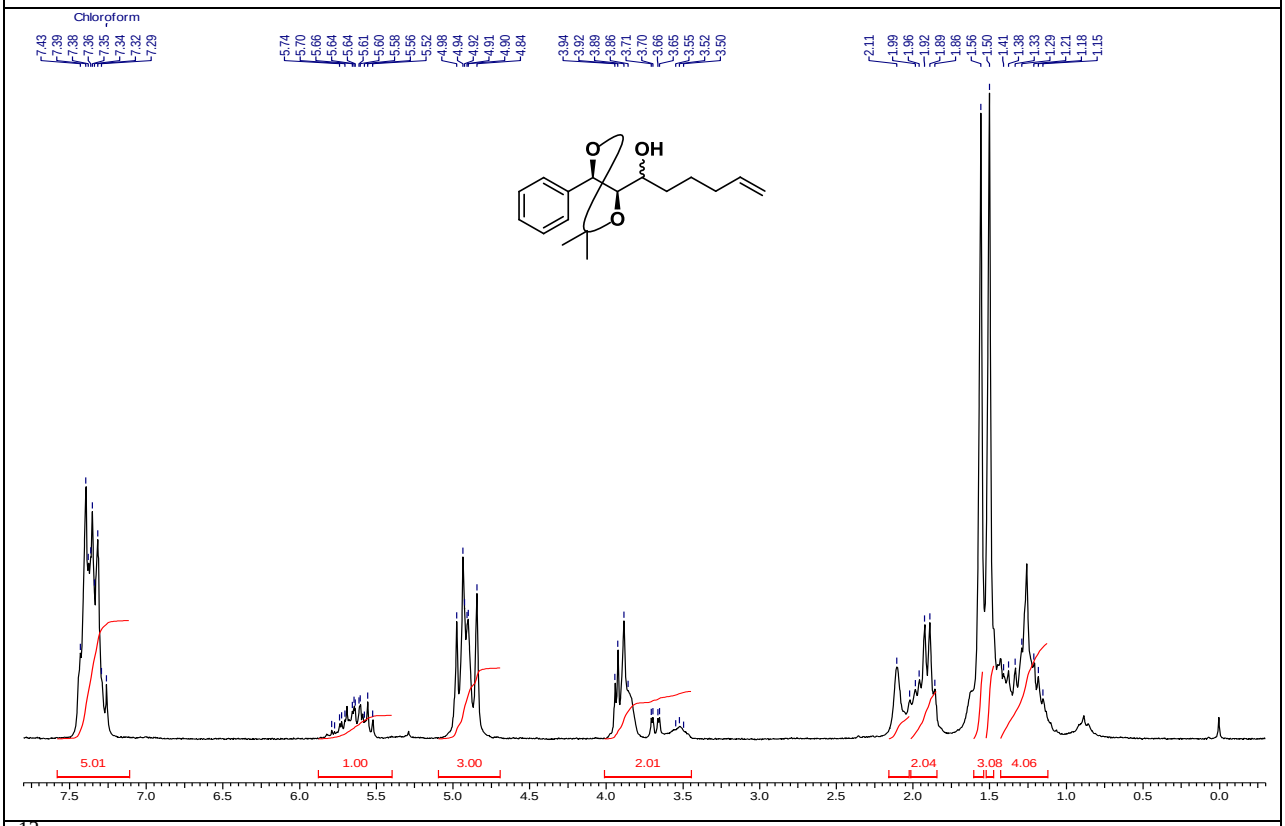
^{13}C NMR spectrum of compound **63** ($CDCl_3$+CCl_4, 50 MHz)



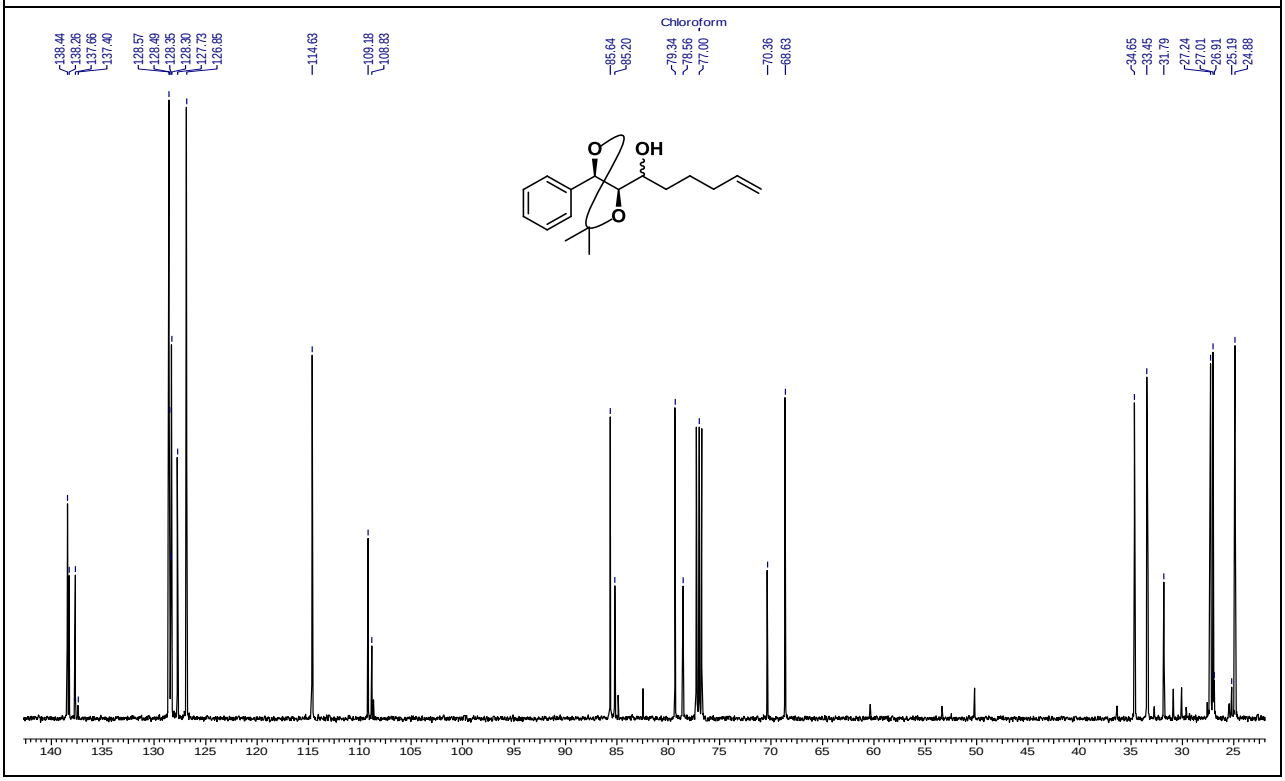
DEPT spectrum of compound **63** ($CDCl_3$+CCl_4, 50 MHz)



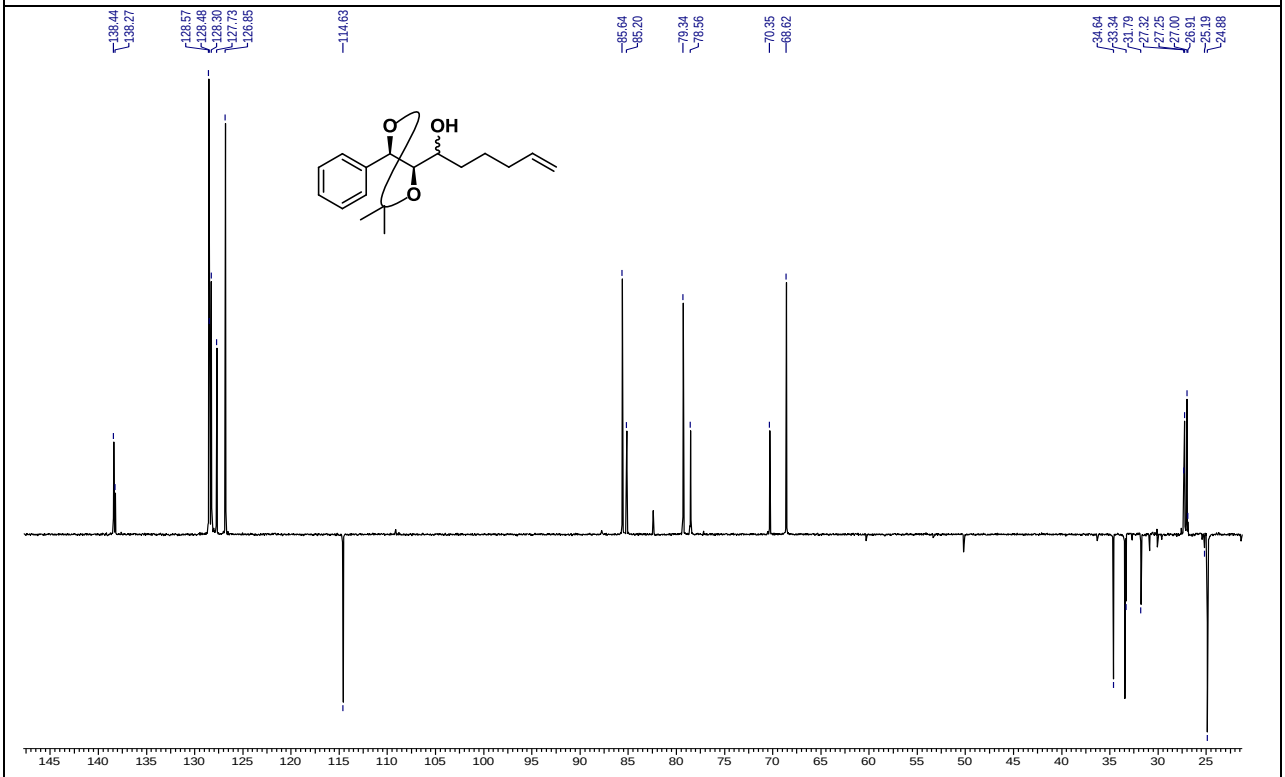
^{1}H NMR spectrum of compound **65** ($CDCl_3$+CCl_4, 200 MHz)



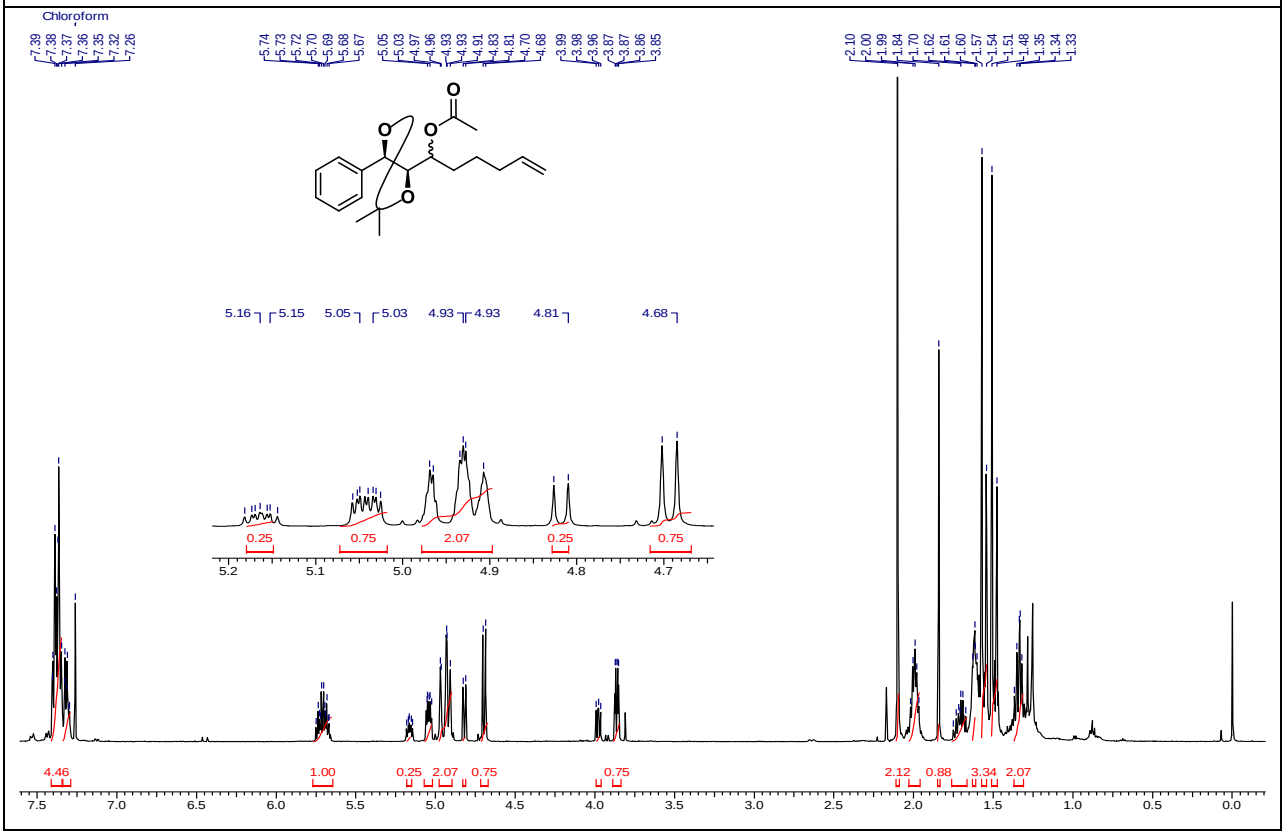
^{13}C NMR spectrum of compound **65** ($CDCl_3$+CCl_4, 50 MHz)



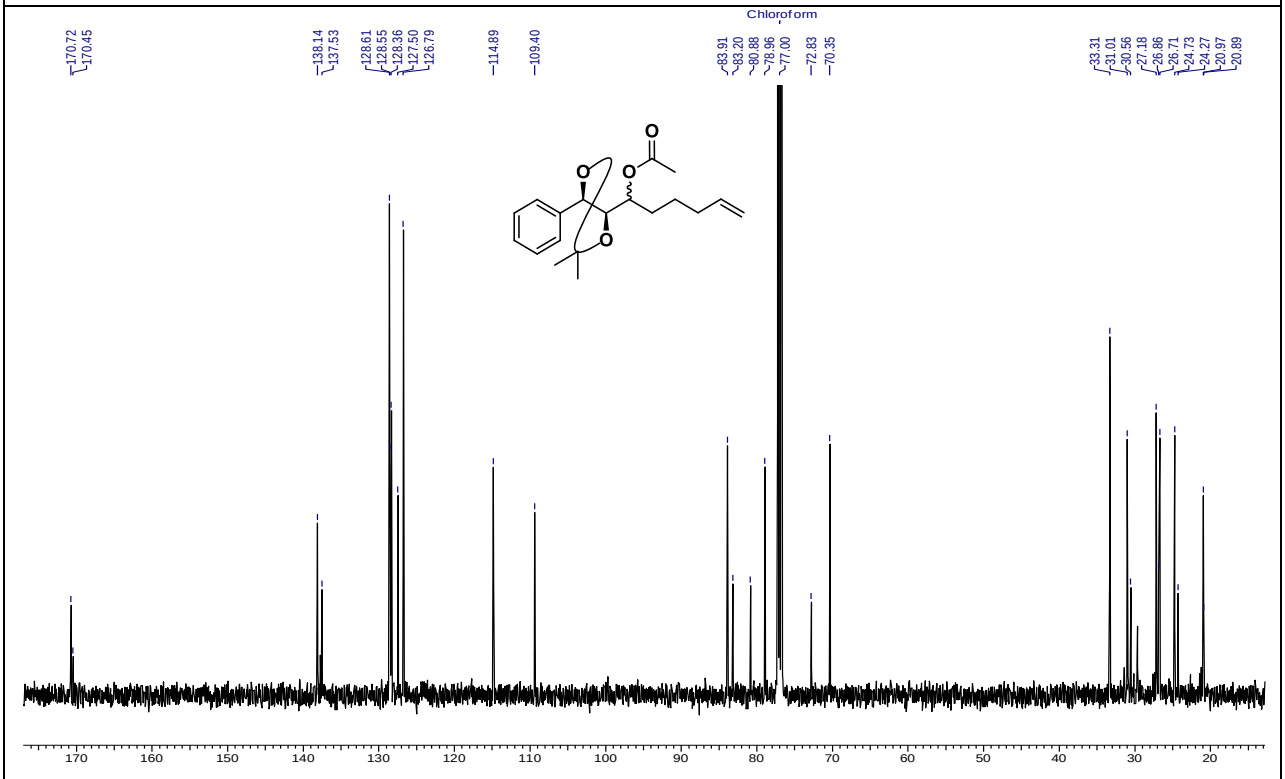
DEPT spectrum of compound **65** ($CDCl_3$+CCl_4, 50 MHz)



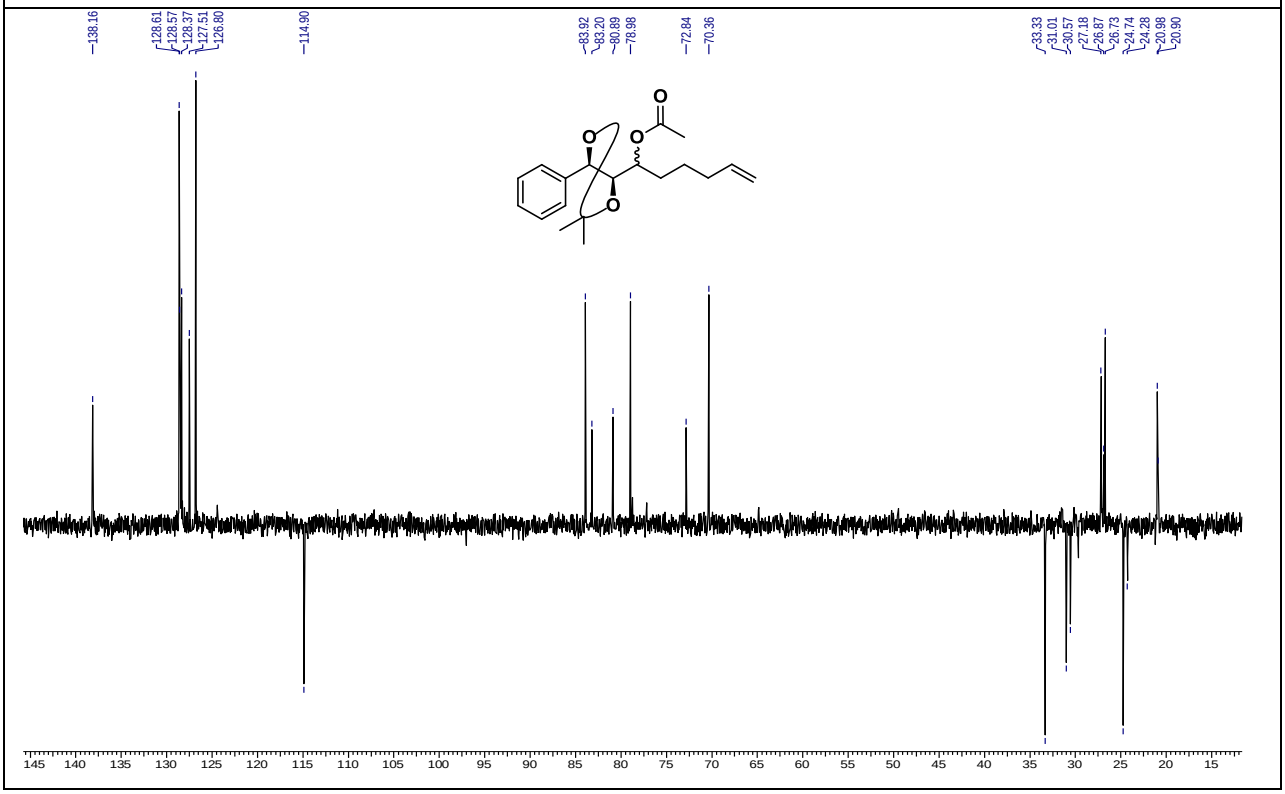
^{1}H NMR spectrum of compound **66** ($CDCl_3$+CCl_4, 500 MHz)



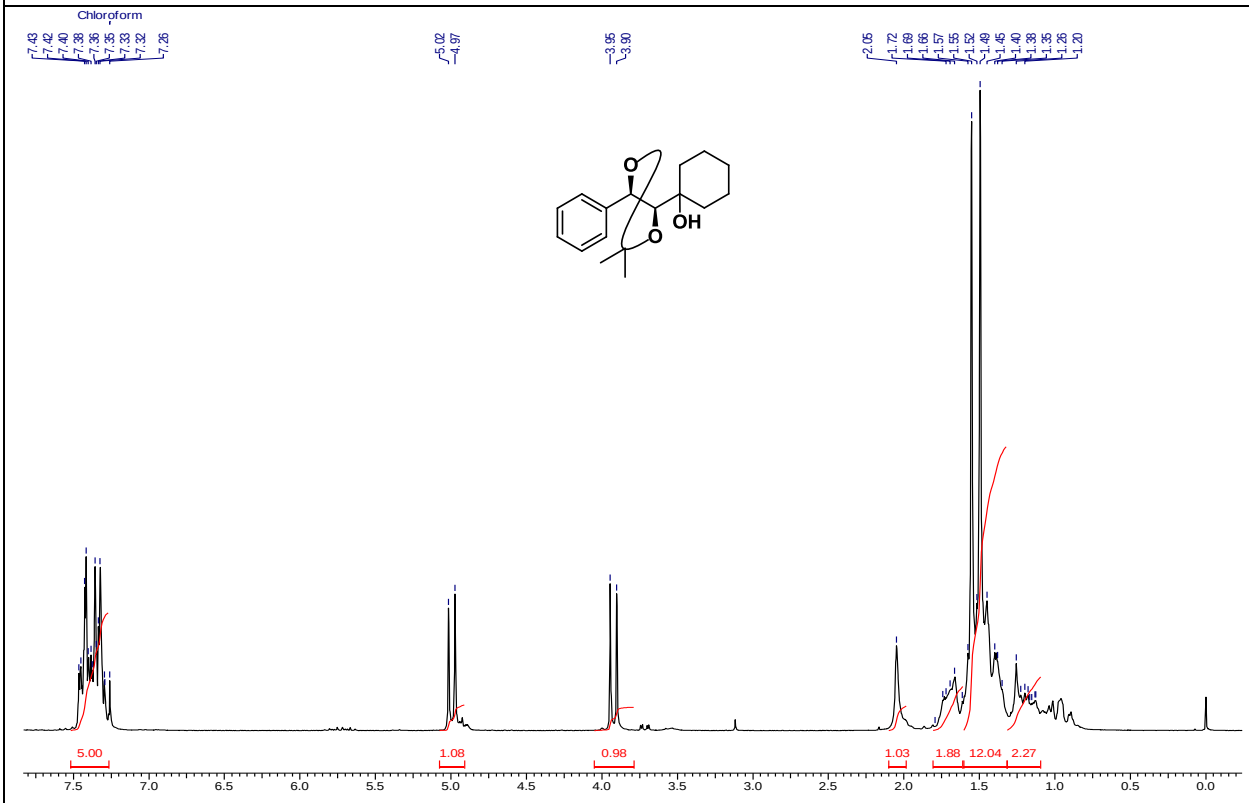
^{13}C NMR spectrum of compound **66** ($CDCl_3$+CCl_4, 125 MHz)



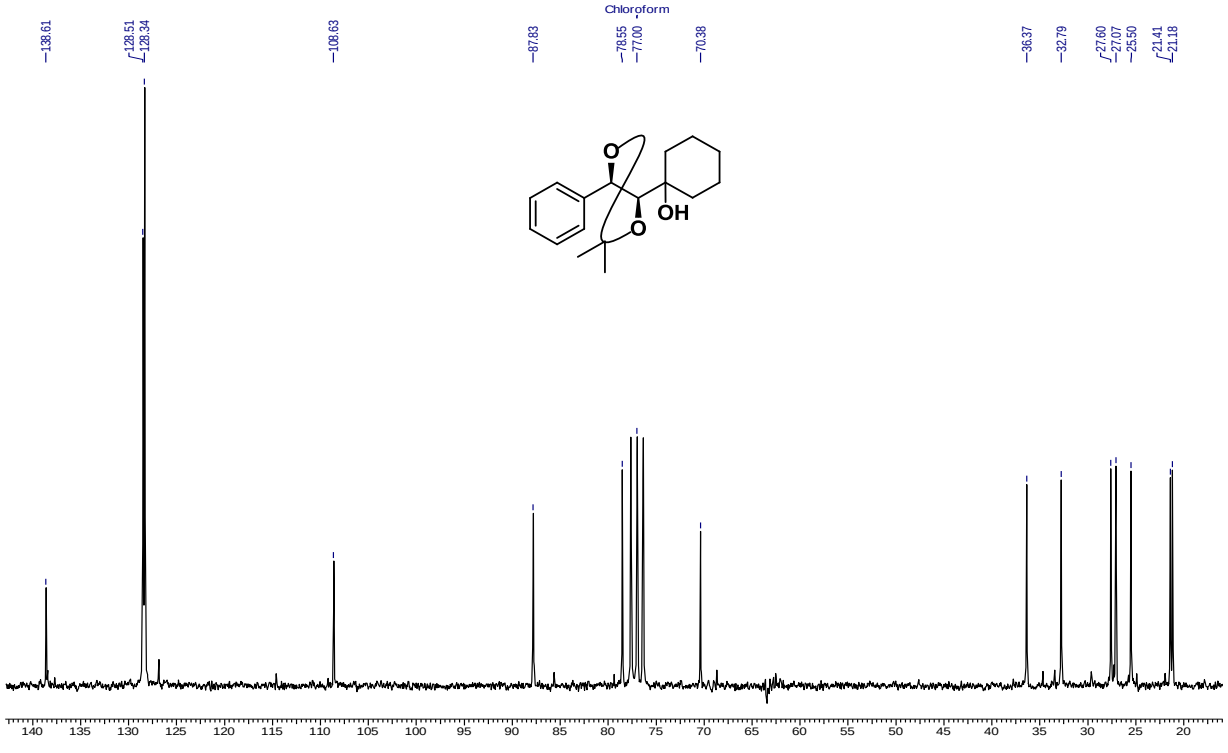
DEPT spectrum of compound **66** ($CDCl_3$+CCl_4, 125 MHz)



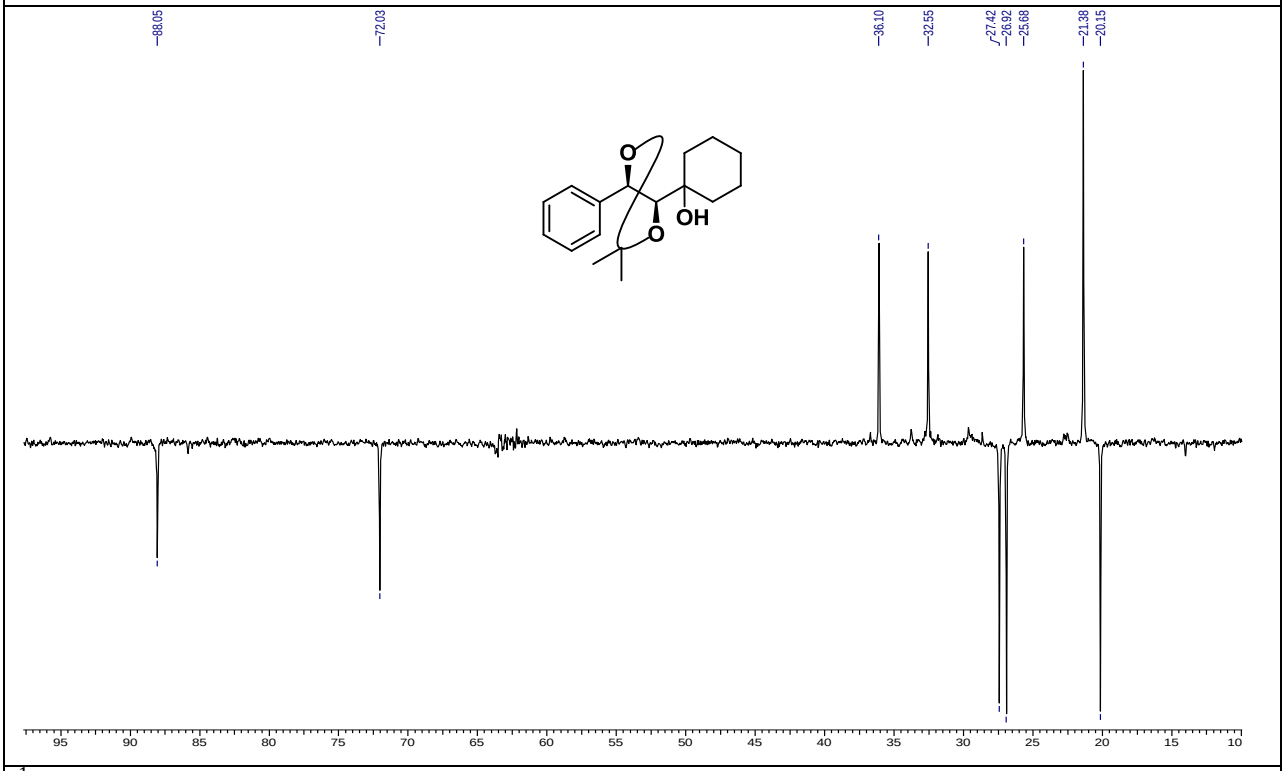
^{1}H NMR spectrum of compound **64** ($CDCl_3$+CCl_4, 200 MHz)



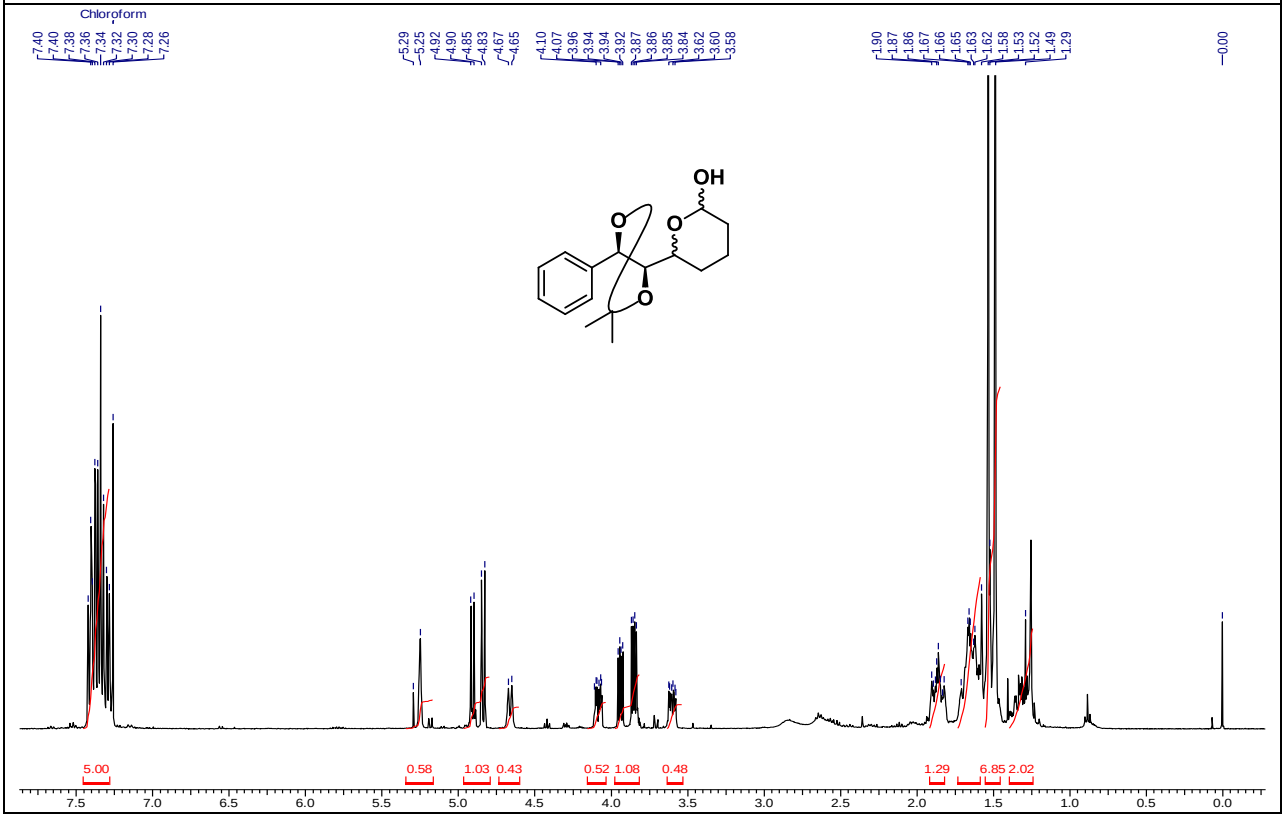
^{13}C NMR spectrum of compound **64** ($CDCl_3$+CCl_4, 50 MHz)



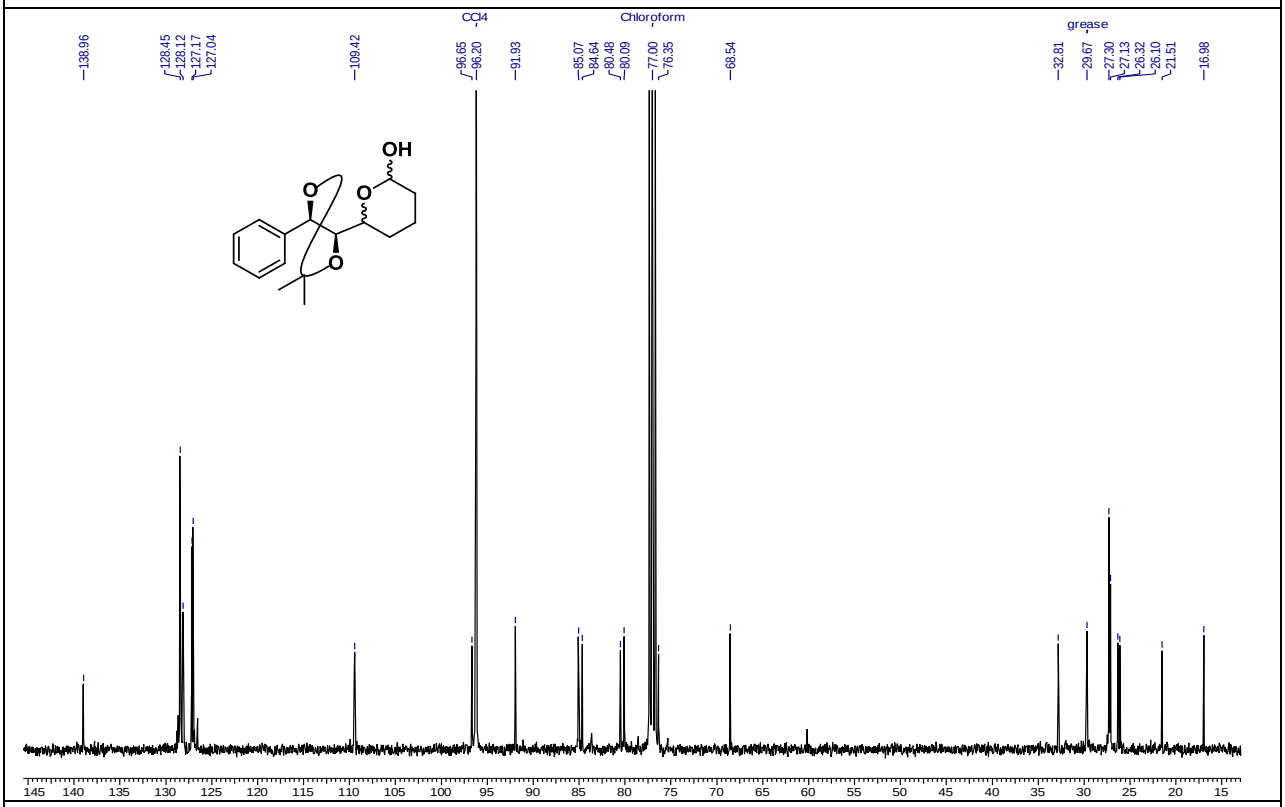
DEPT spectrum of compound **64** ($CDCl_3$+CCl_4, 50 MHz)



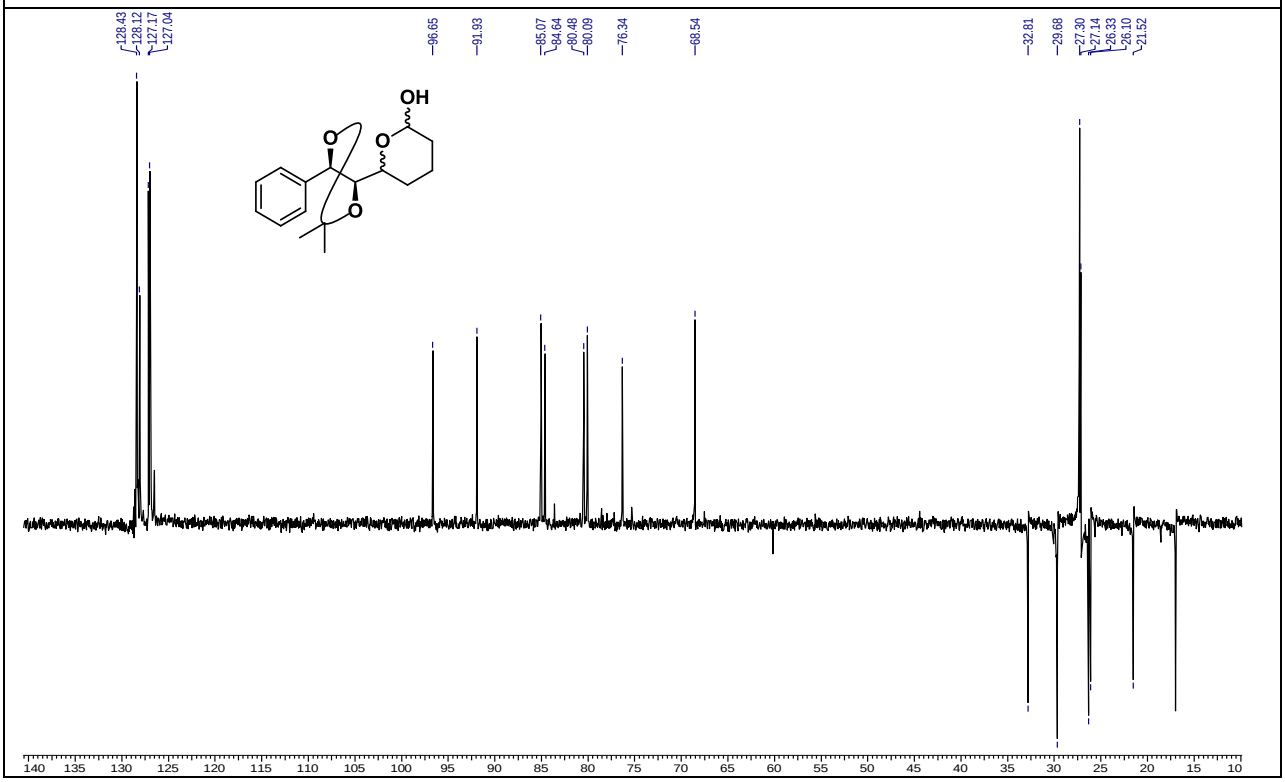
^{1}H NMR spectrum of compound **67** ($CDCl_3$+CCl_4, 400 MHz)



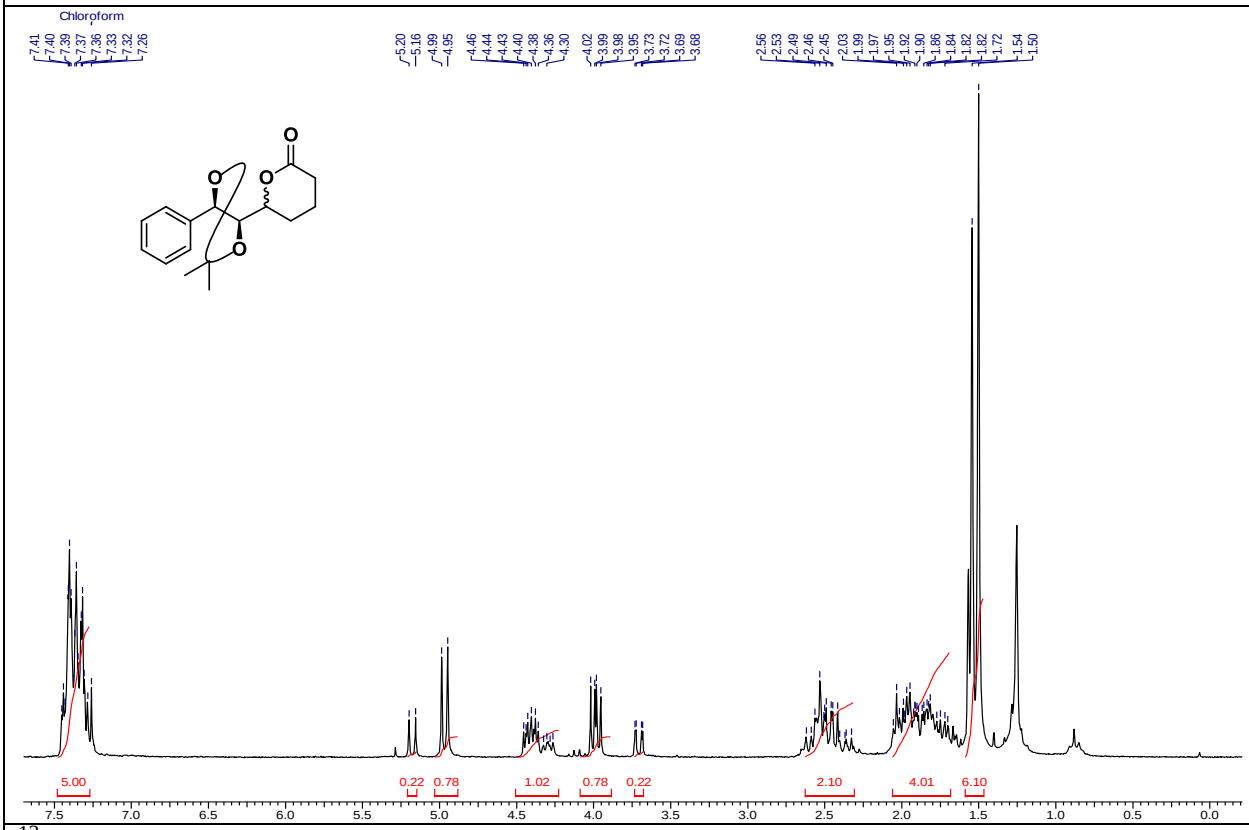
^{13}C NMR spectrum of compound **67** ($CDCl_3$+CCl_4, 100 MHz)



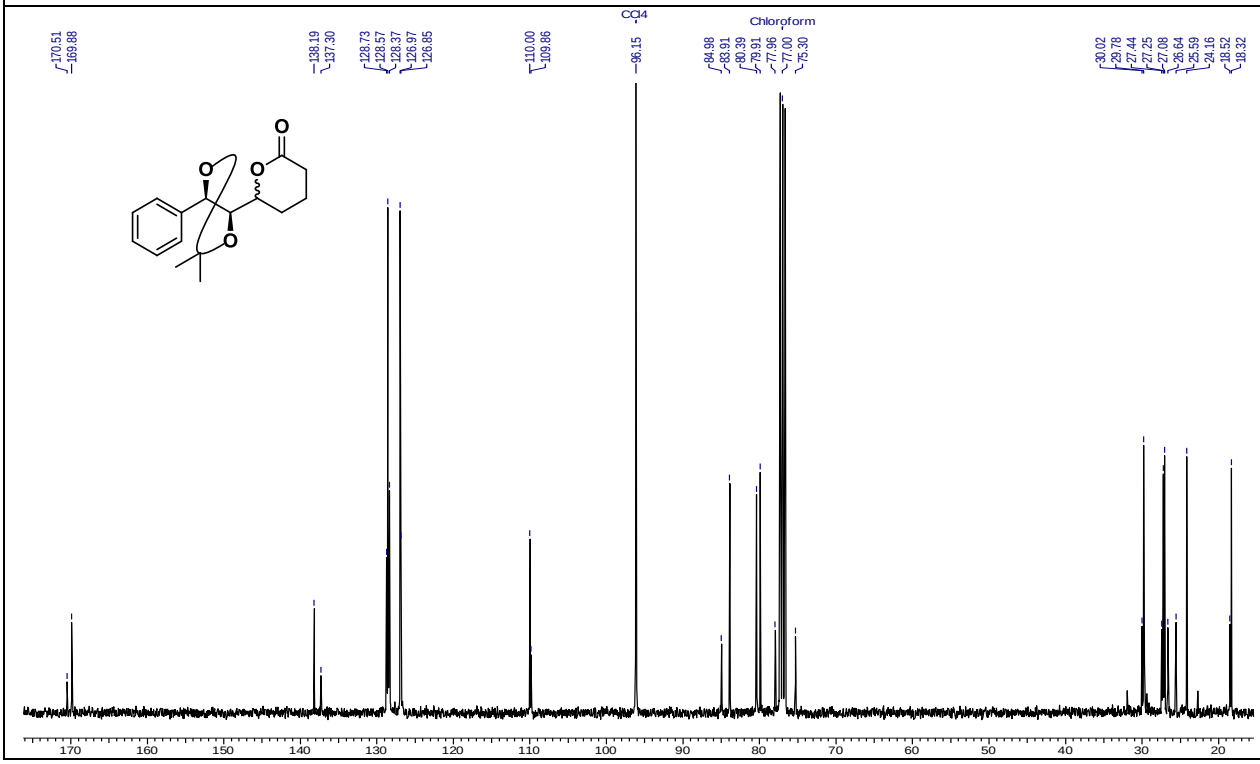
DEPT spectrum of compound **67** ($CDCl_3$+CCl_4, 100 MHz)



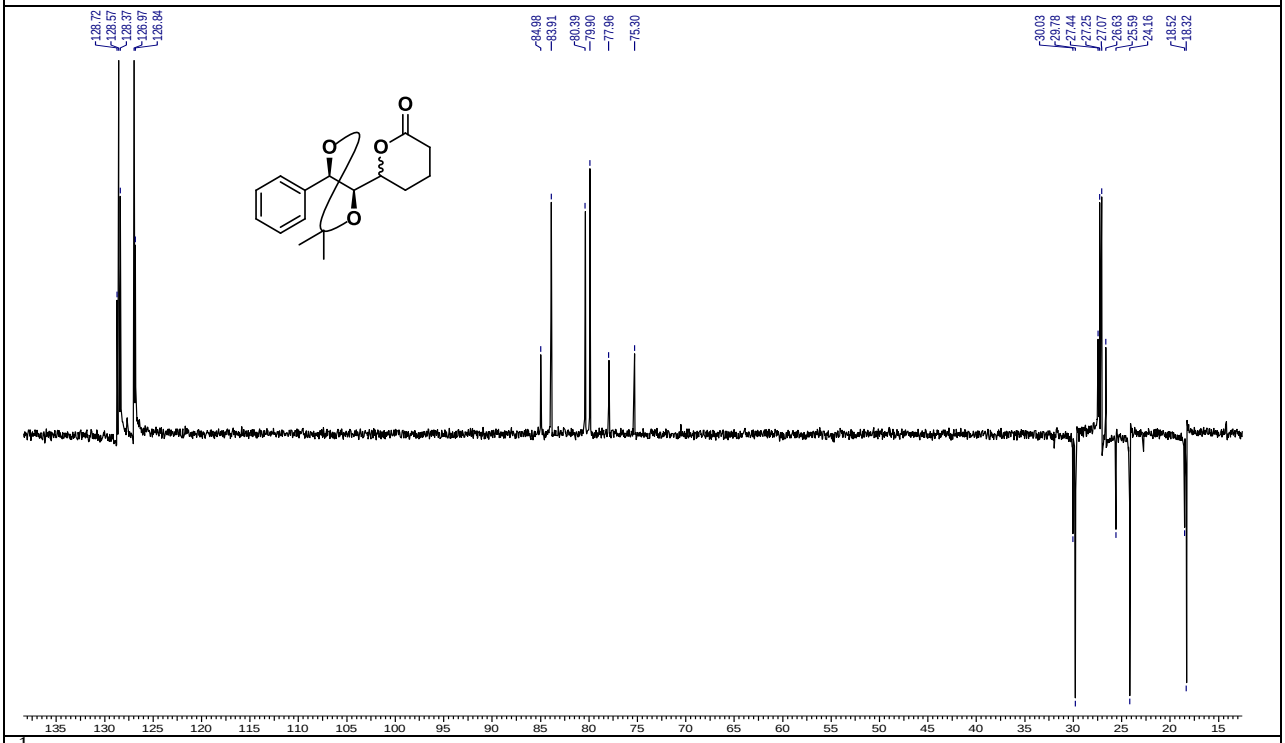
^{1}H NMR spectrum of compound **68** ($CDCl_3$+CCl_4, 200 MHz)



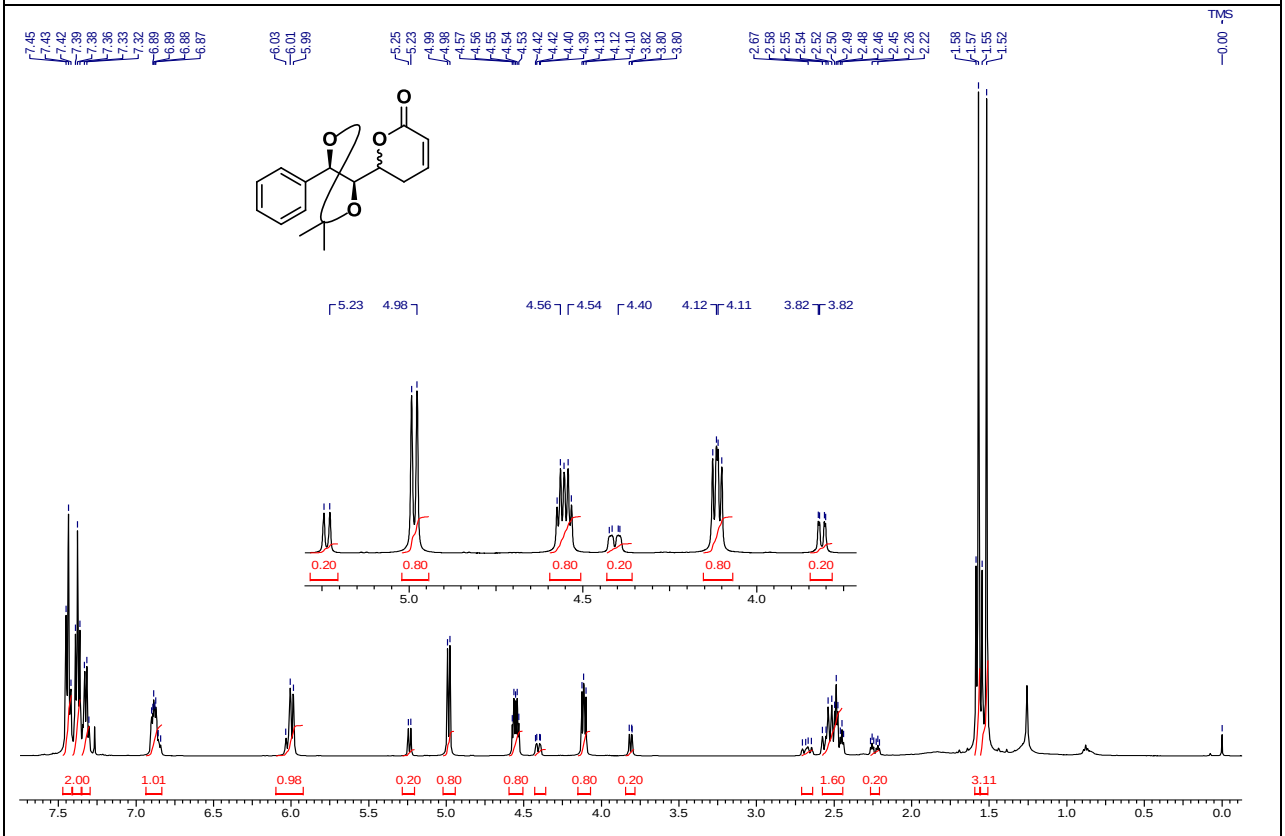
^{13}C NMR spectrum of compound **68**($CDCl_3$+CCl_4, 50 MHz)



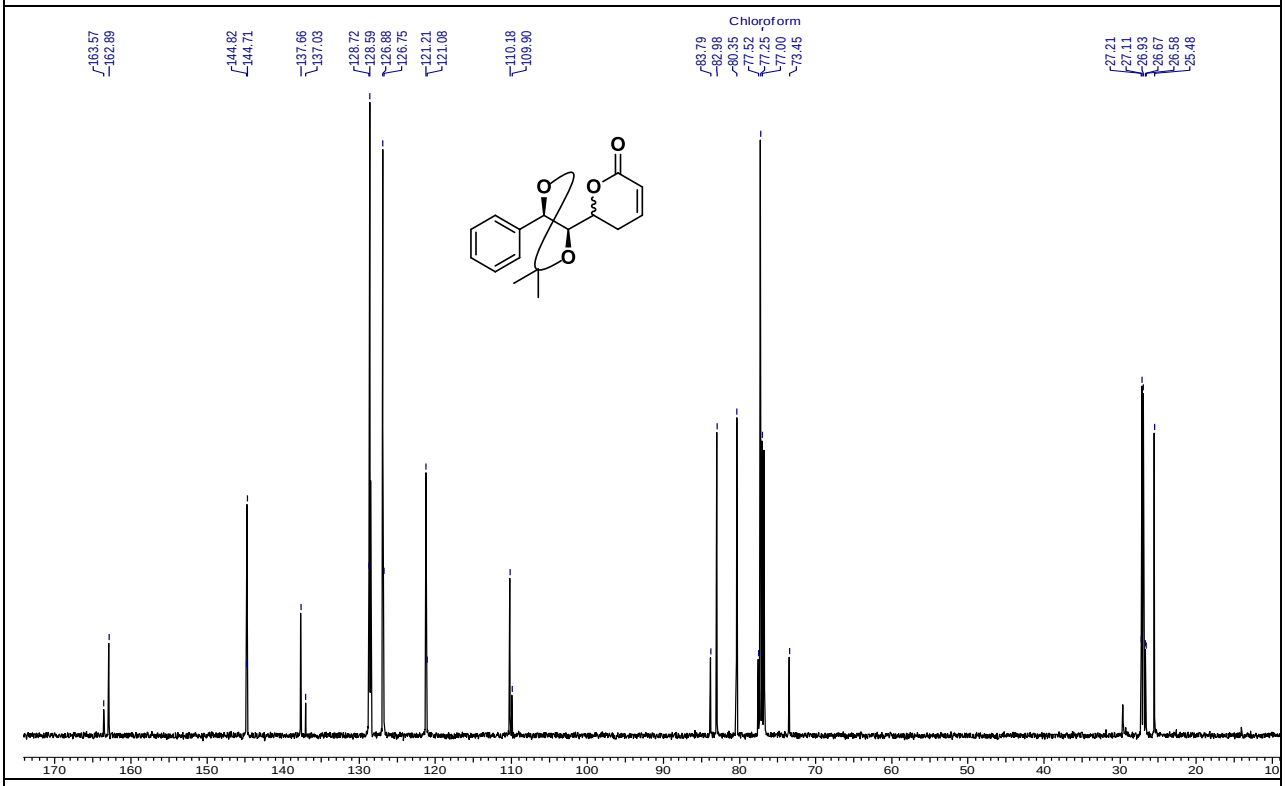
DEPT spectrum of compound **68** ($CDCl_3$+CCl_4,50 MHz)



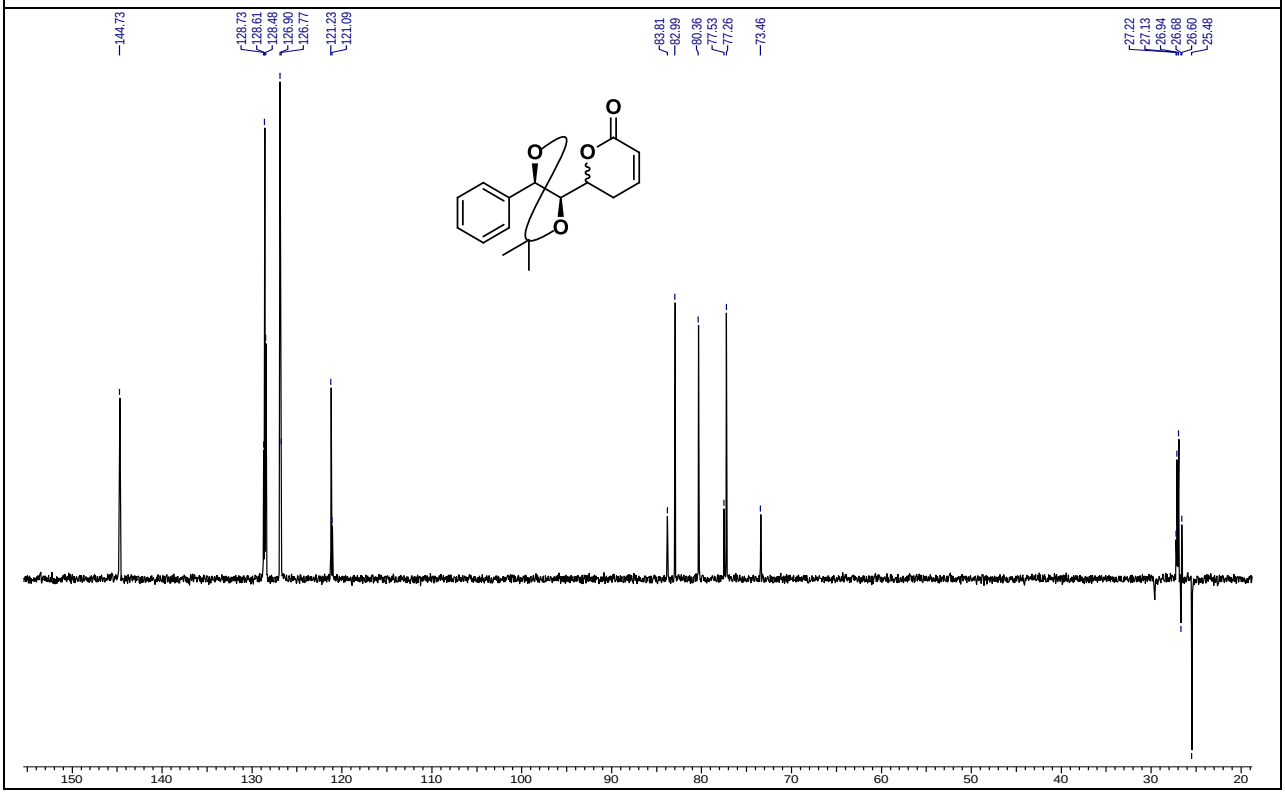
^{1}H NMR spectrum of compound **69** ($CDCl_3$+CCl_4, 500 MHz)



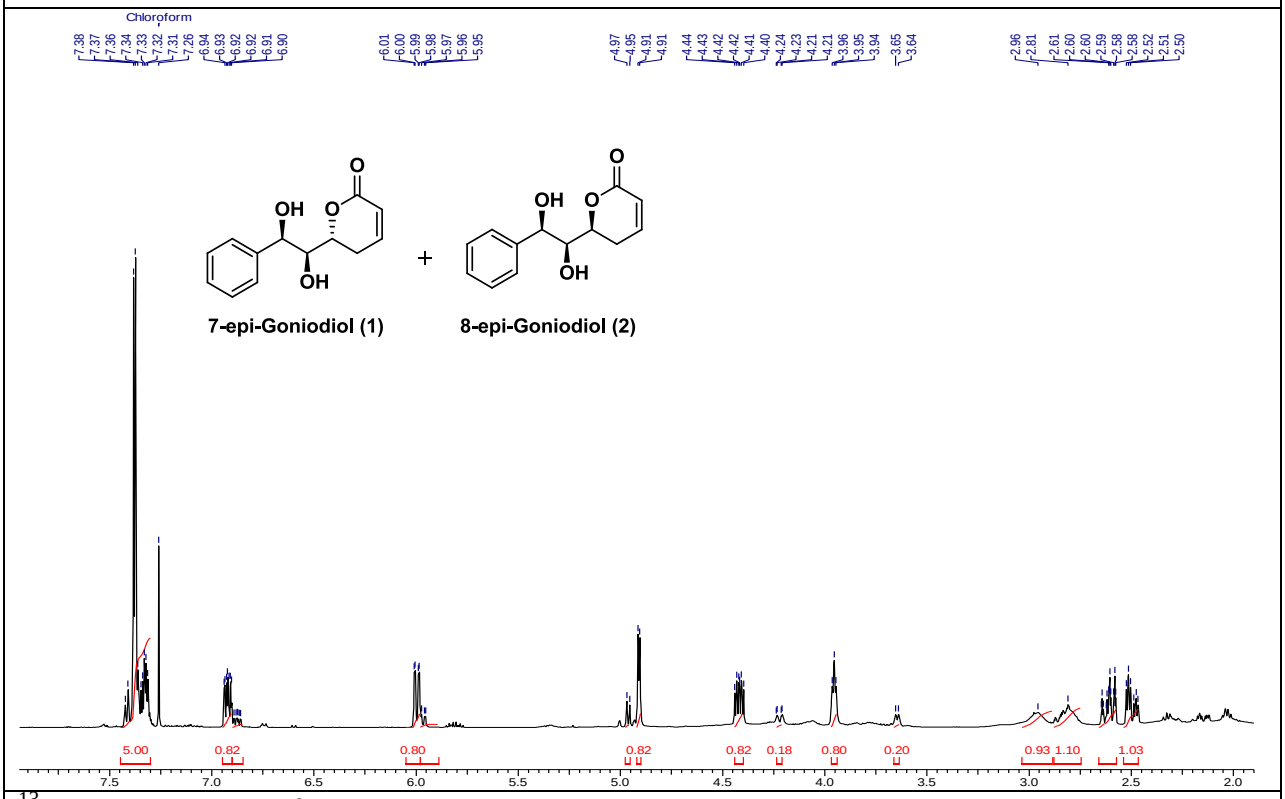
^{13}C NMR spectrum of compound **69** ($CDCl_3$+CCl_4, 125 MHz)



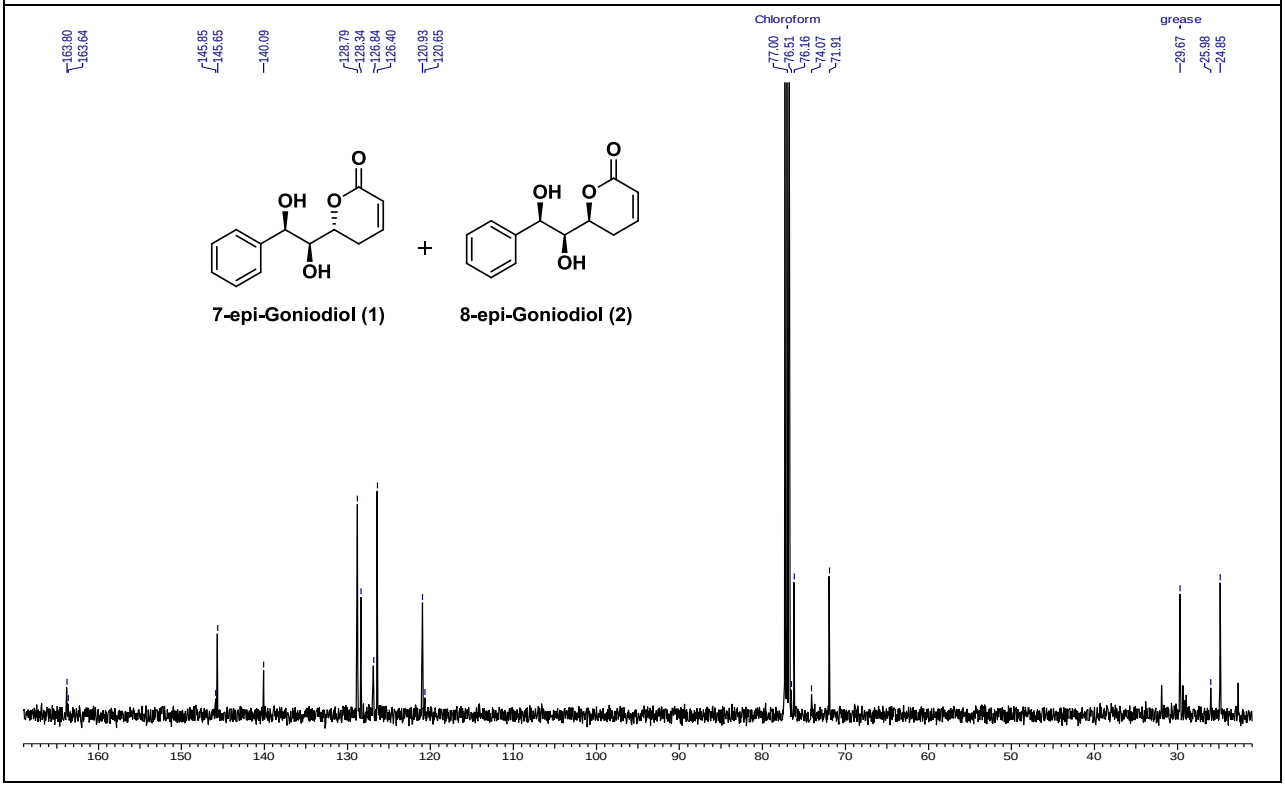
DEPT spectrum of compound **69** ($CDCl_3$+CCl_4, 125 MHz)



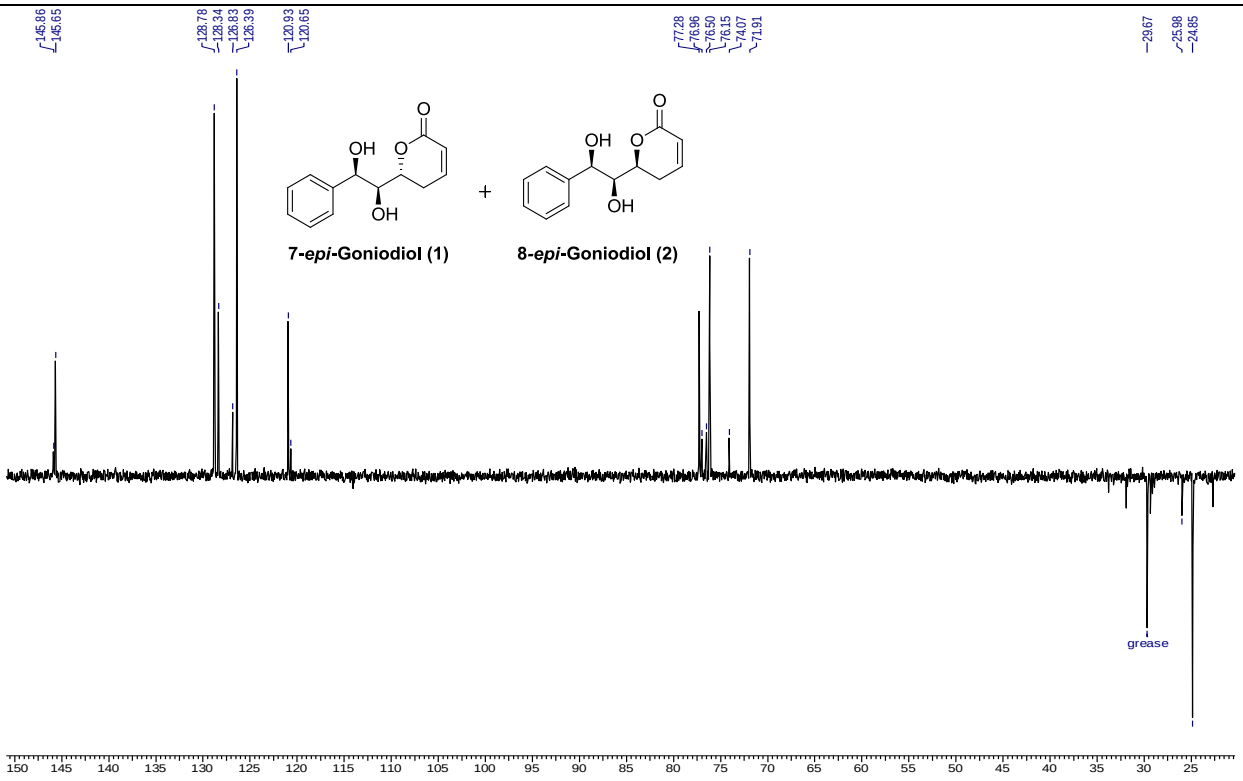
^{1}H NMR spectrum of compound **(1+2)** ($CDCl_3$+CCl_4, 500 MHz)



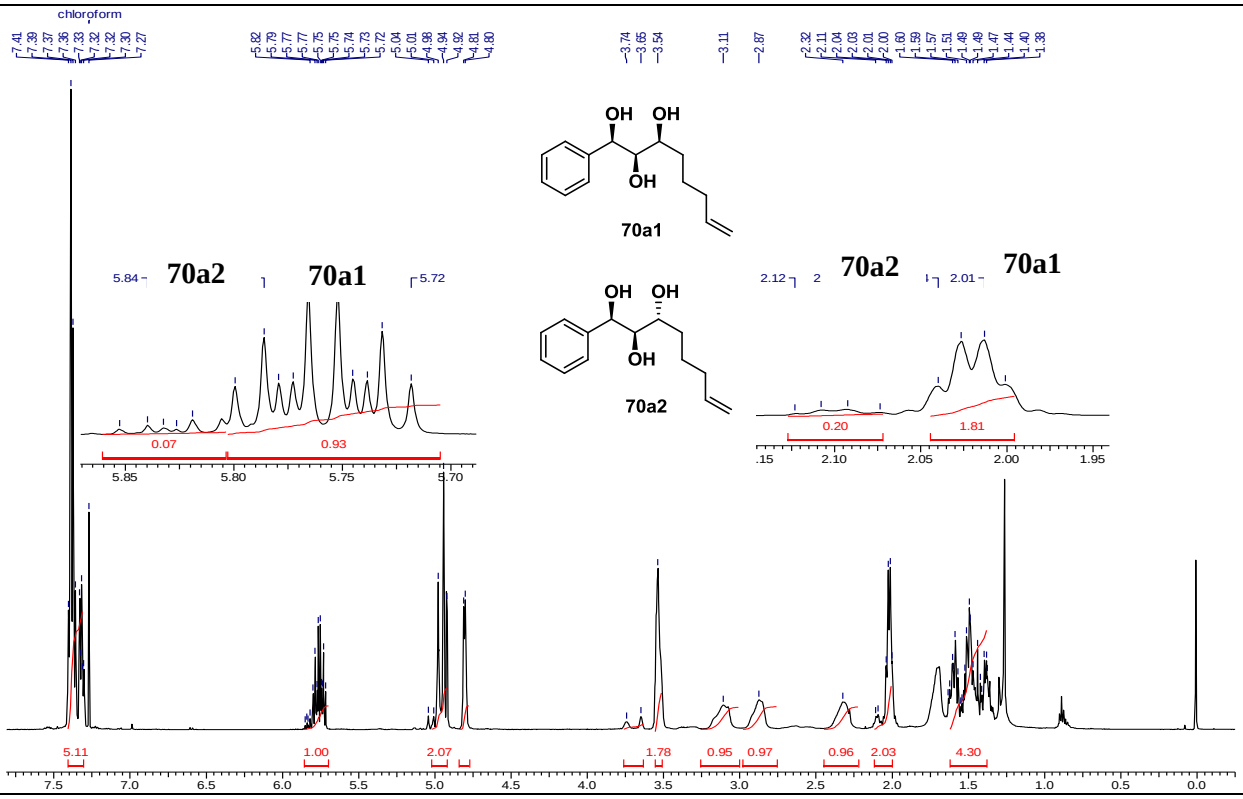
^{13}C NMR spectrum of compound **(1+2)** ($CDCl_3$+CCl_4, 125 MHz)



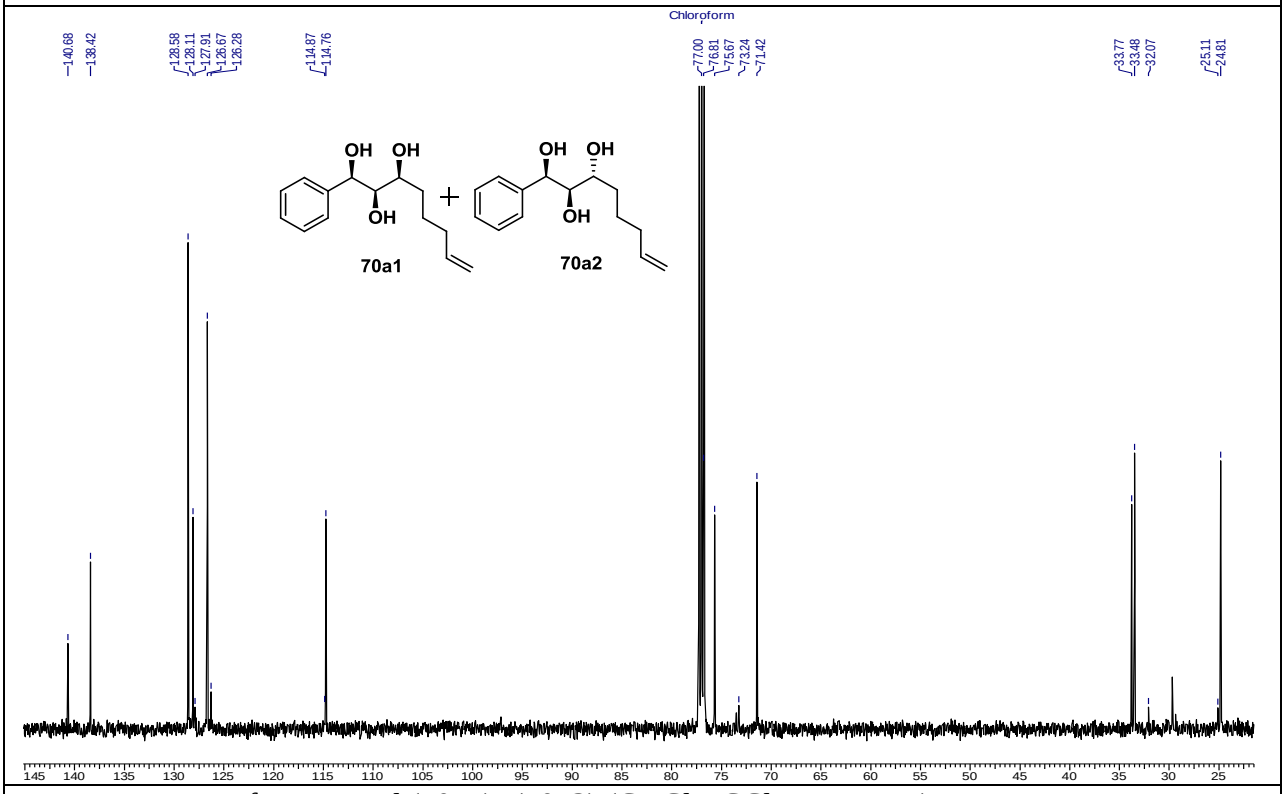
DEPT spectrum of compound **(1+2)** ($CDCl_3$+CCl_4, 125 MHz)



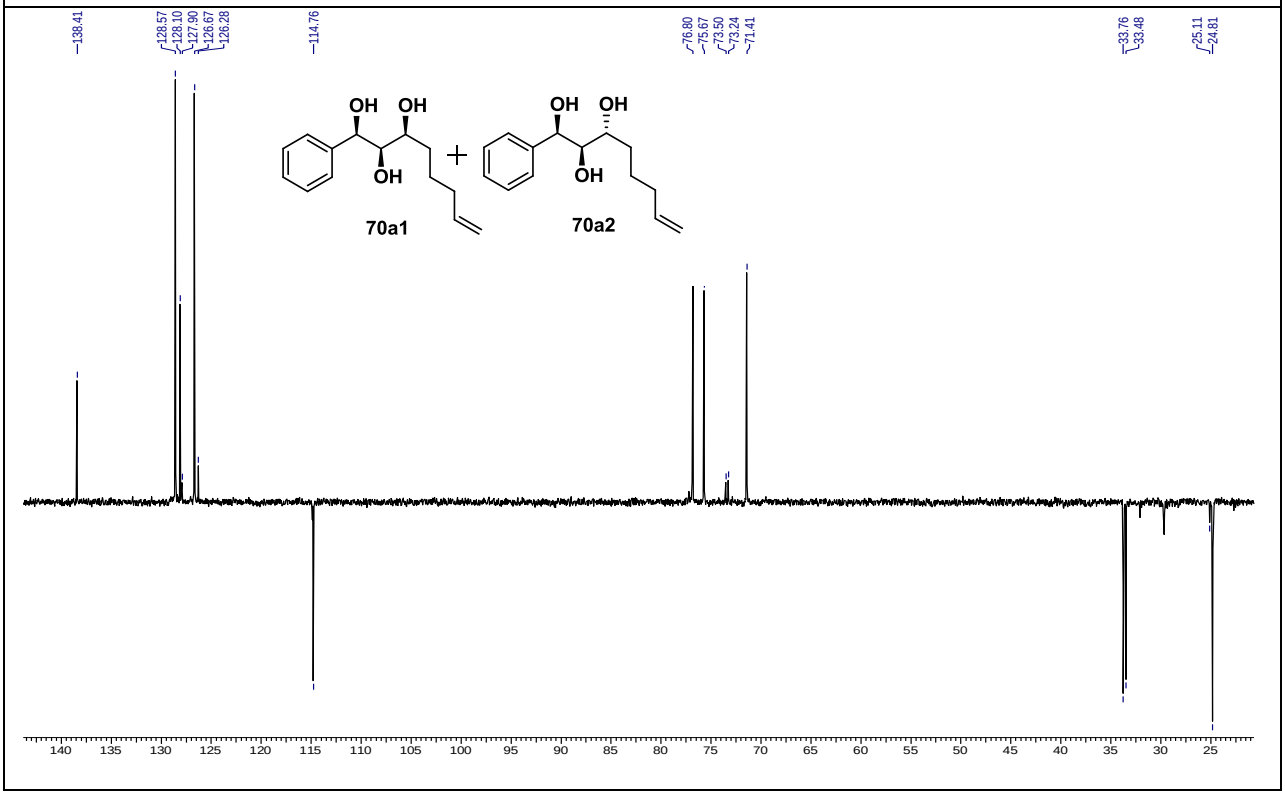
^{1}H NMR spectrum of compound **(70a1): (70a2)** ($CDCl_3$+CCl_4, 500 MHz)



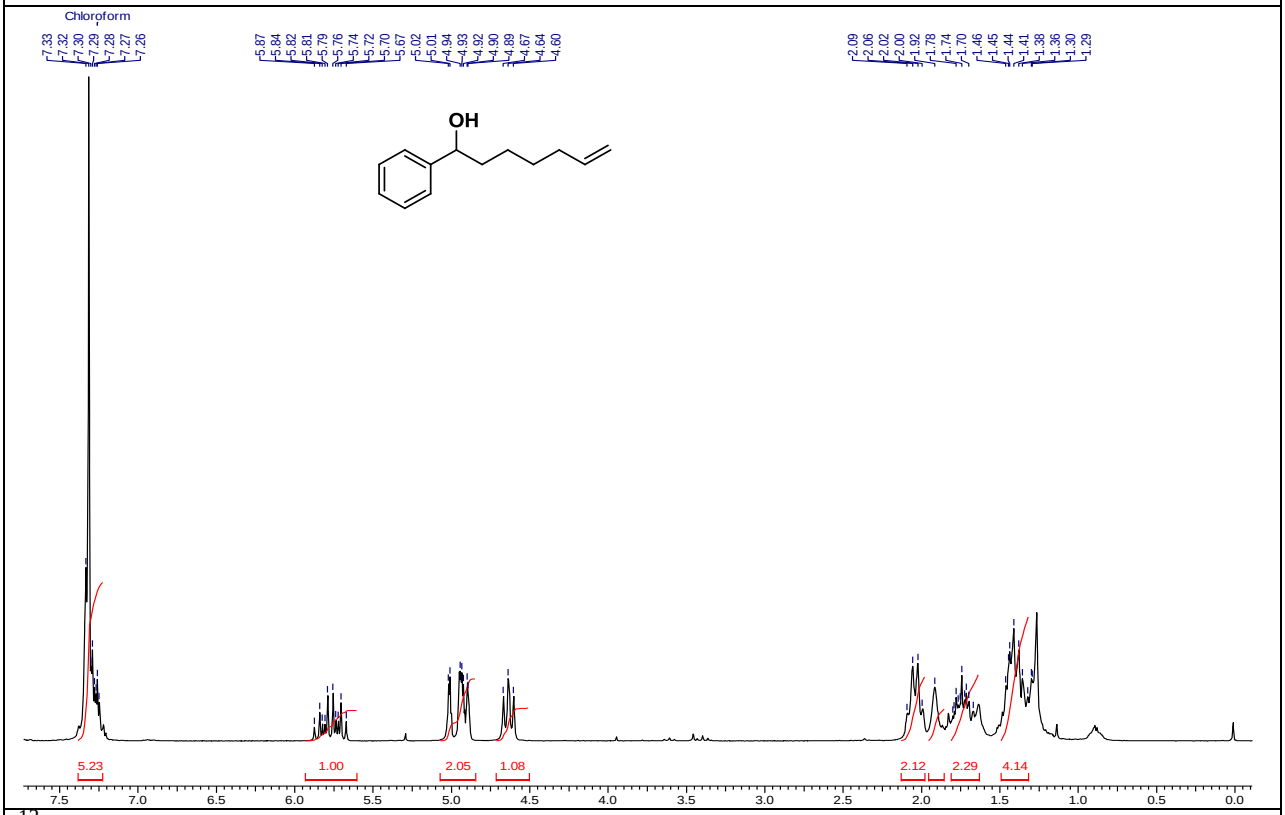
^{13}C NMR spectrum of compound **(70a1): (70a2)** ($CDCl_3$+CCl_4, 125 MHz)



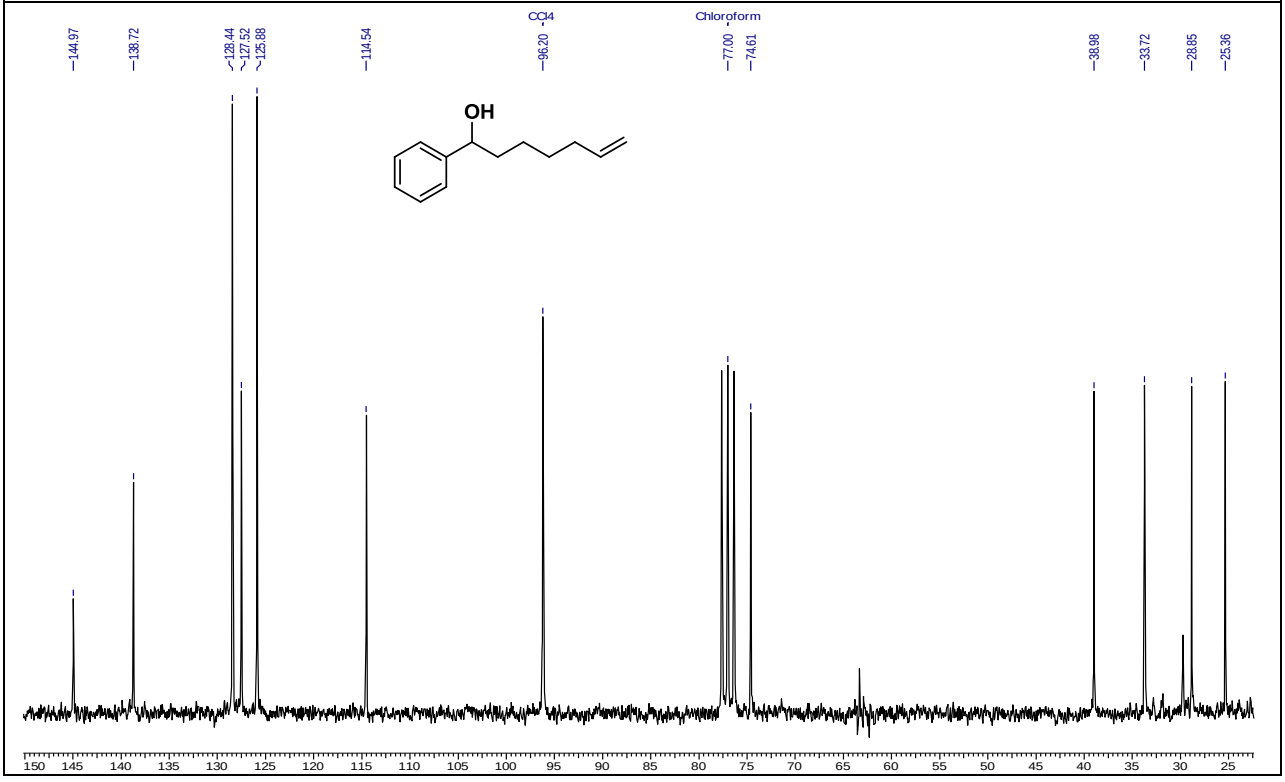
DEPT spectrum of compound **(70a1): (70a2)** ($CDCl_3$+CCl_4, 125 MHz)



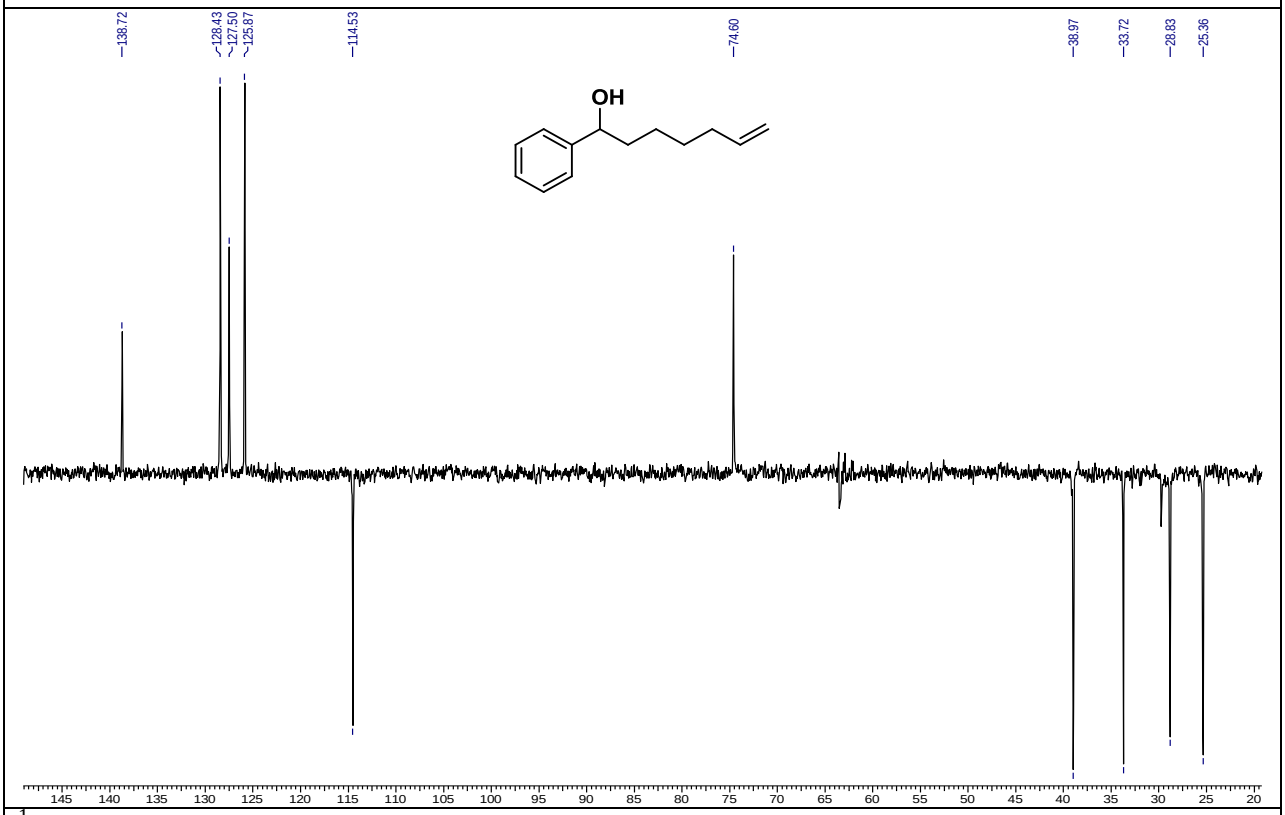
^{1}H NMR spectrum of compound **72** ($CDCl_3$+CCl_4, 200 MHz)



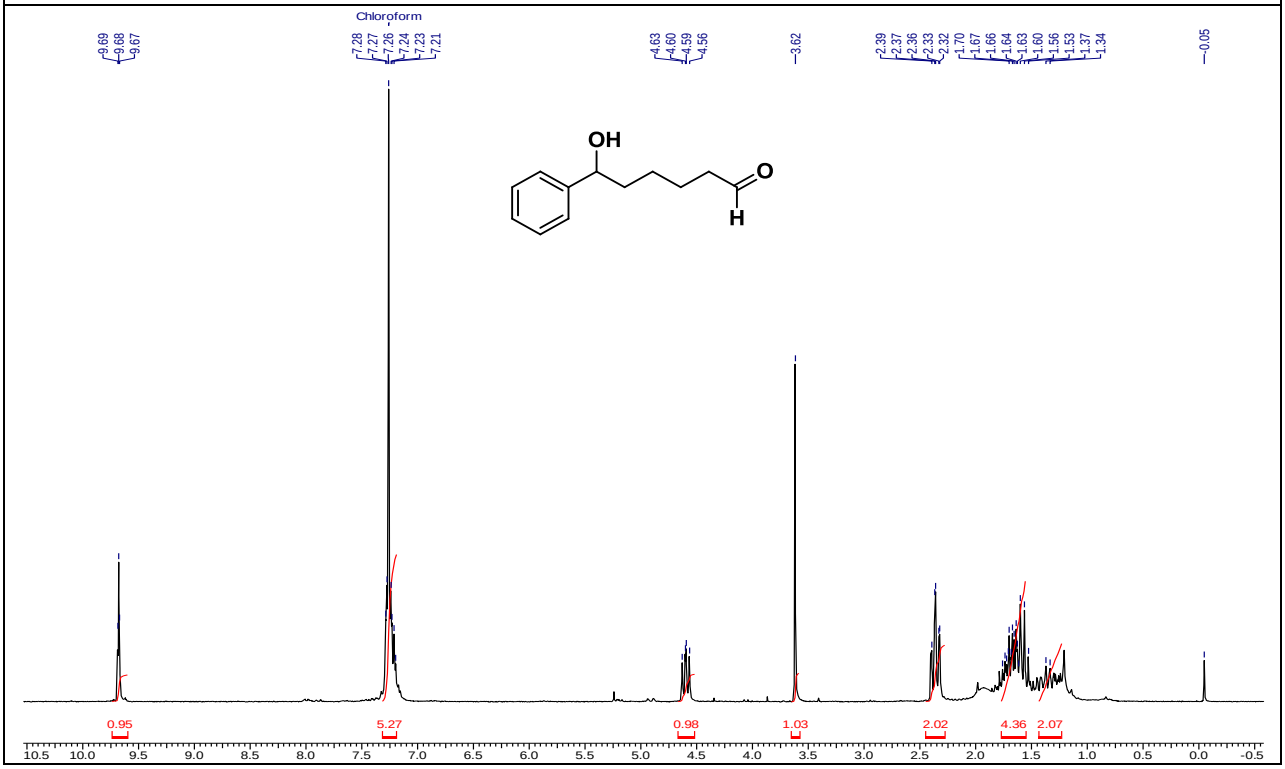
^{13}C NMR spectrum of compound **72** ($CDCl_3$+CCl_4, 50 MHz)



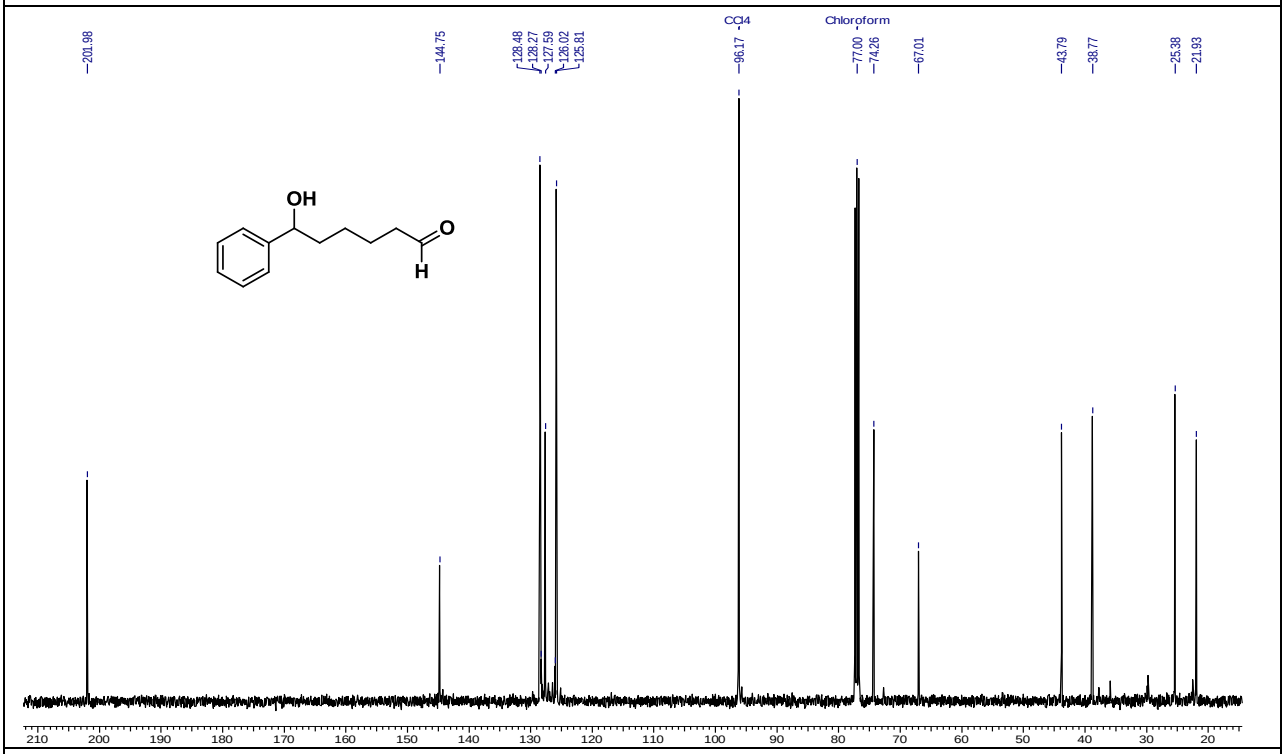
DEPT spectrum of compound **72** ($CDCl_3$+CCl_4, 50 MHz)



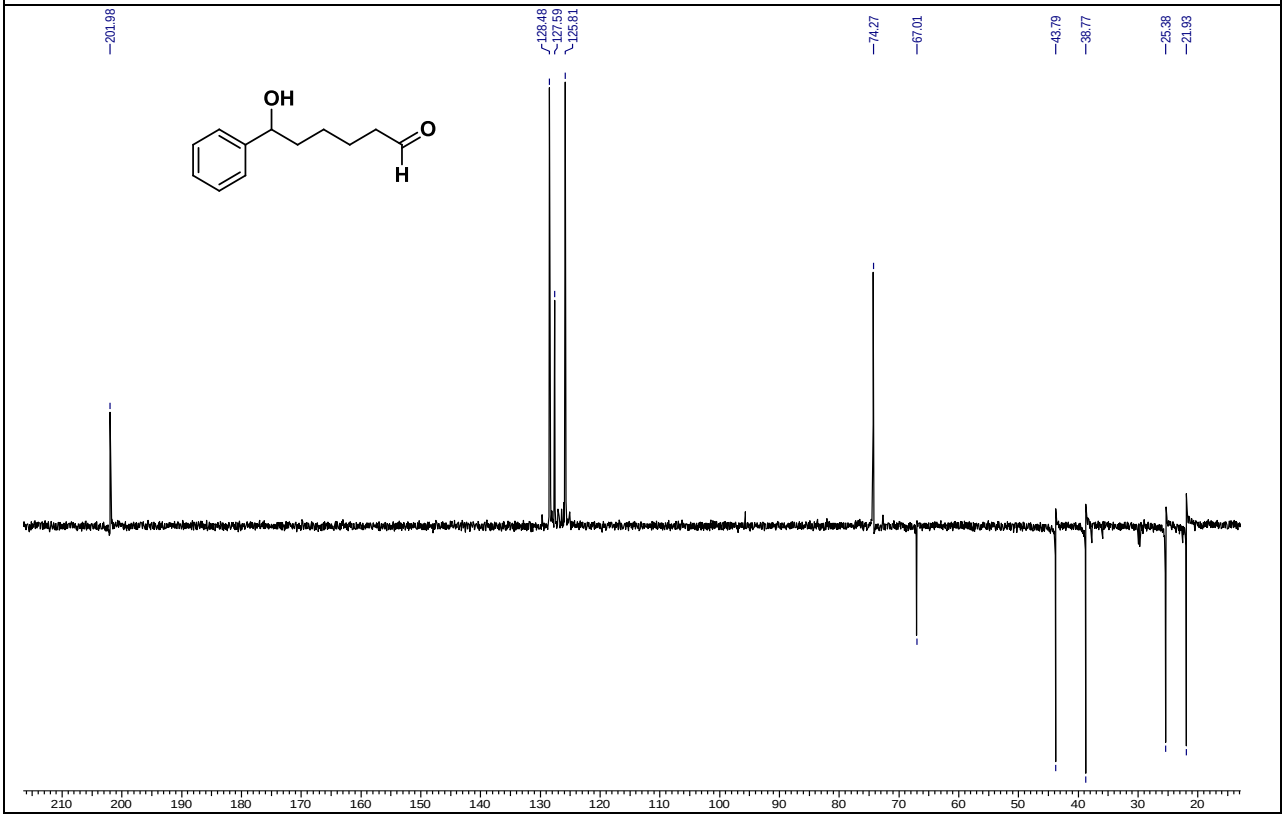
^{1}H NMR spectrum of compound **73** ($CDCl_3$+CCl_4, 200 MHz)



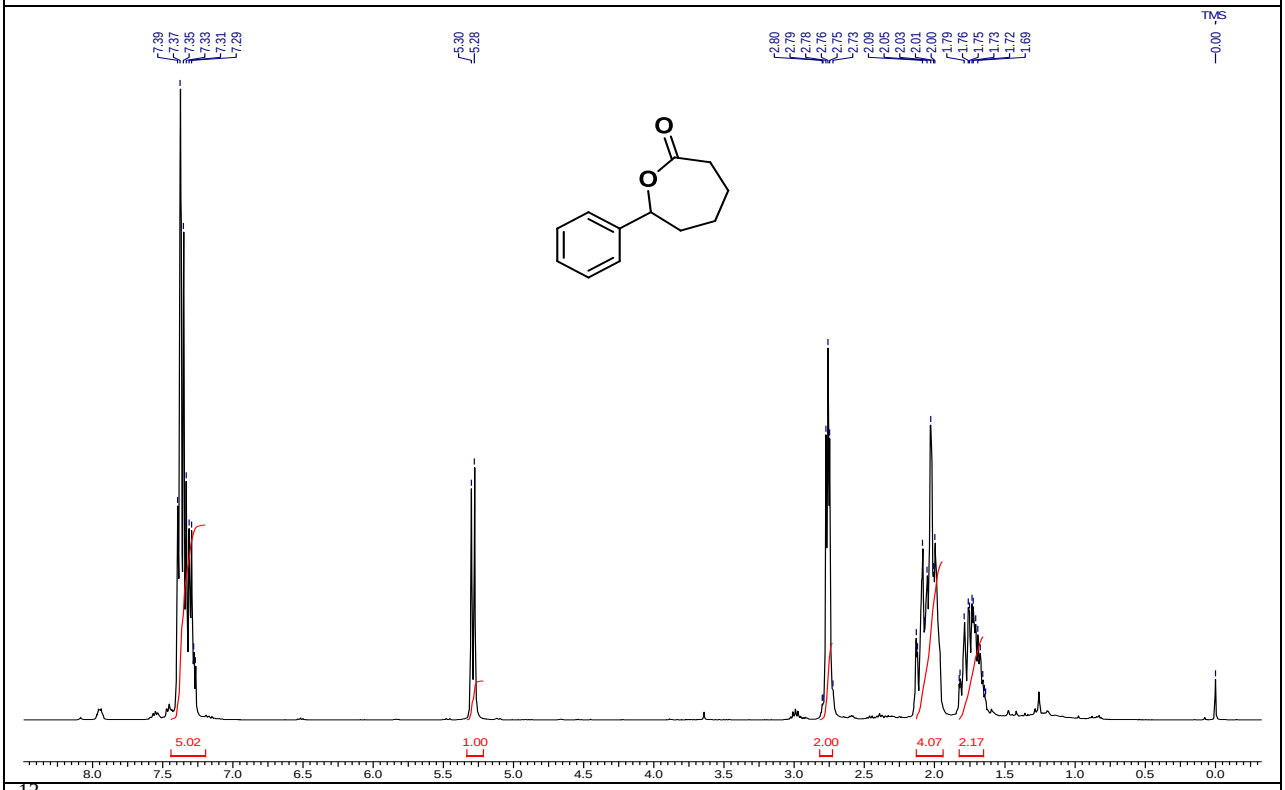
^{13}C NMR spectrum of compound **73** ($CDCl_3$+CCl_4, 50 MHz)



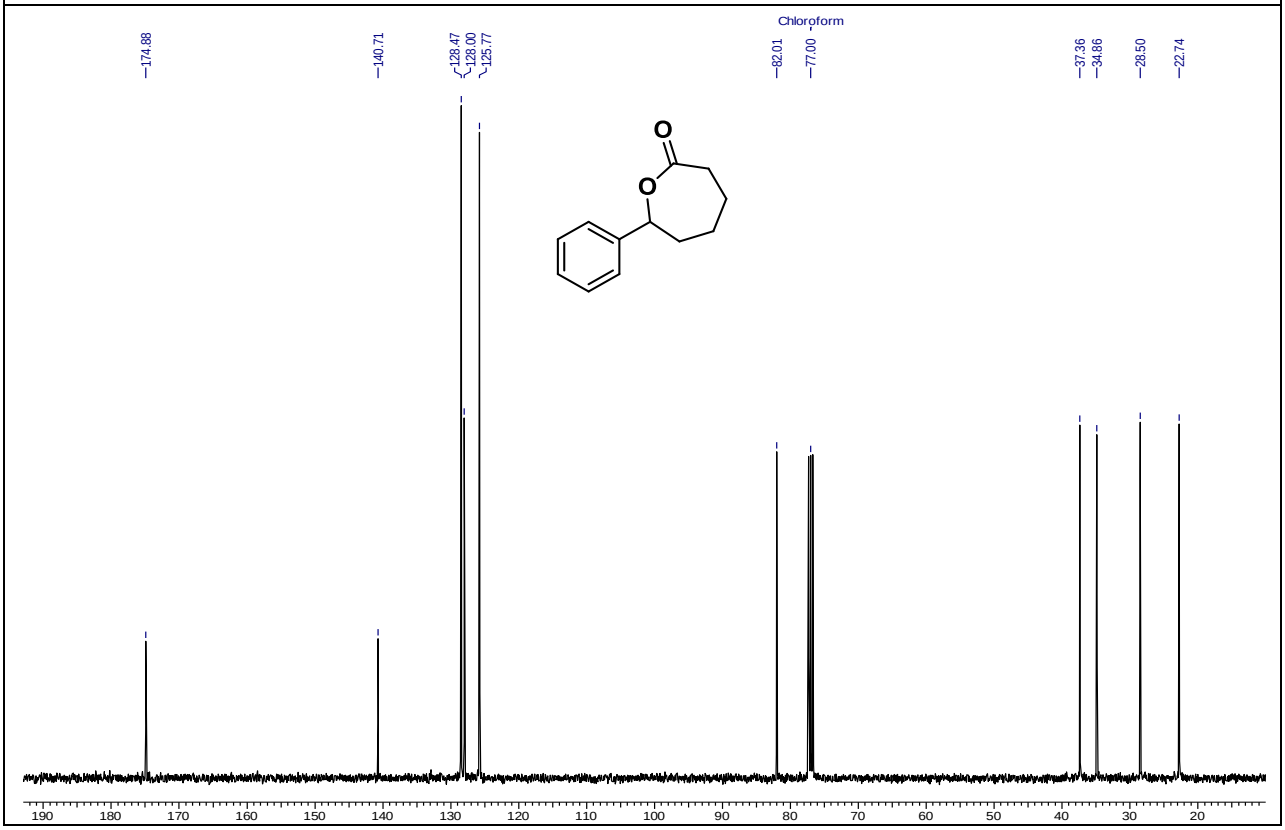
DEPT spectrum of compound **73** ($CDCl_3$+CCl_4, 50 MHz)



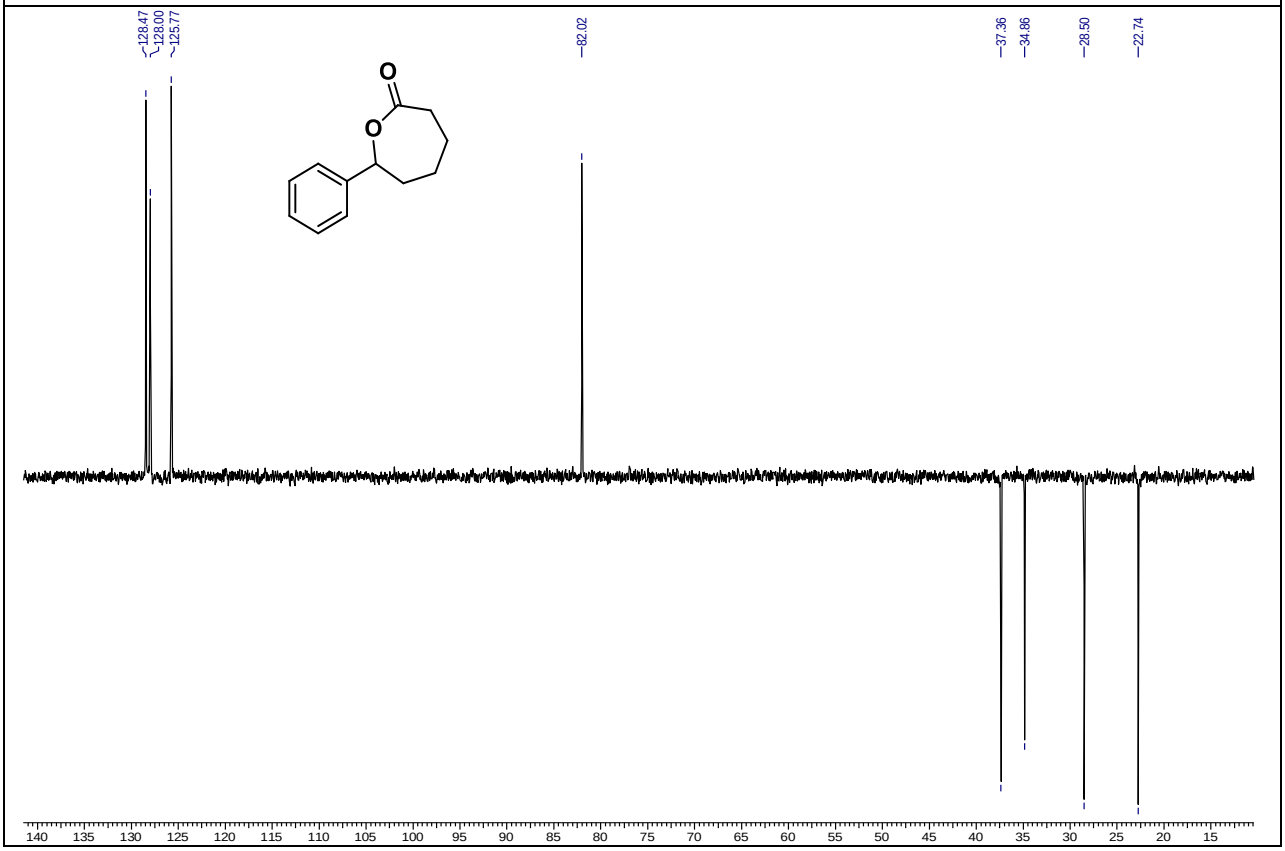
^{1}H NMR spectrum of compound **74** ($CDCl_3$+CCl_4, 400 MHz)



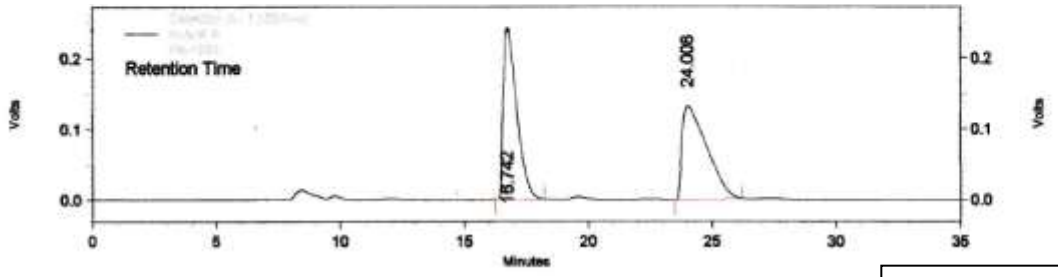
^{13}C NMR spectrum of compound **74** ($CDCl_3$+CCl_4, 100 MHz)

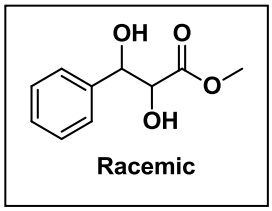


DEPT spectrum of compound **74** ($CDCl_3$+CCl_4, 100 MHz)



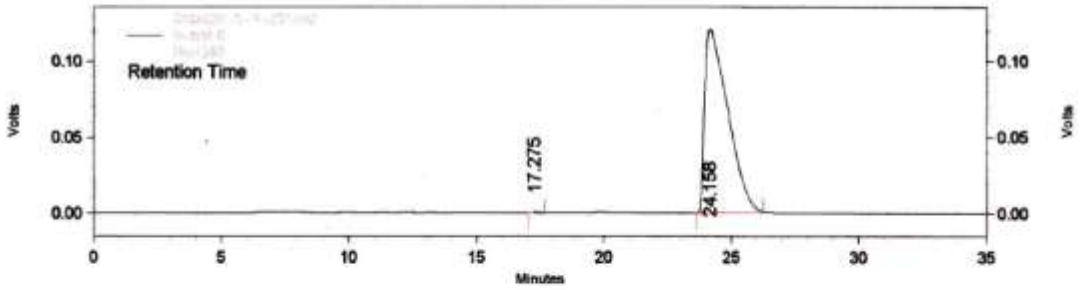
3.2.7.2. HPLC of compound 62

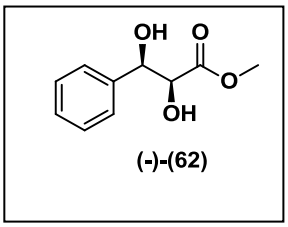




Detector A - 1 (254nm)

Retention Time	C Area	Area %
16.742	9082318	50.033
24.008	9070370	49.967
Totals	18152688	100.000



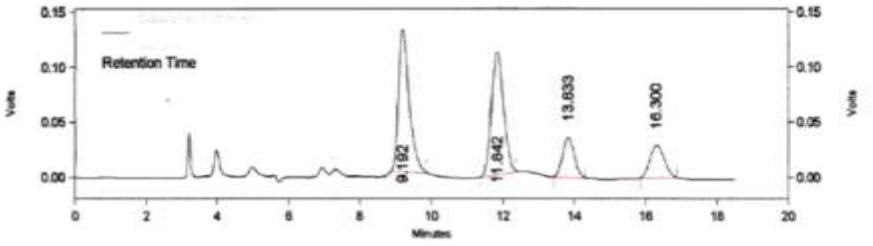


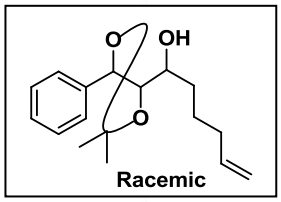
Detector A - 1 (254nm)

Retention Time	C Area	Area %
17.275	8428	0.110
24.158	7664366	99.890
Totals	7672794	100.000

Project Leader : Dr.S.P.Chavan
Column : Chiralcel OJ-H (250x4.6 mm)
Mobile Phase :IPA: Pet ether (30:70)
Wavelength :254nm
Flow Rate :0.5 ml/min(36kgf)
conc. : 1mg/1.0 mL
Inj vol- :20ul

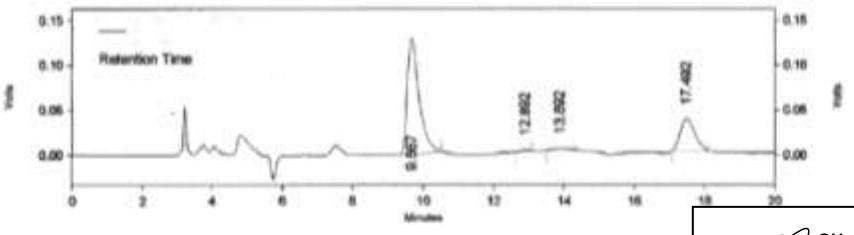
HPLC of racemic 65

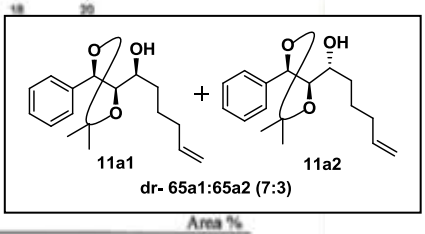




Detector A - 1 (220nm)

Retention Time	C Area	Area %
9.192	1334927	38.785
11.842	1296528	37.669
13.833	406330	11.806
16.300	404068	11.740
Totals	3441853	100.000





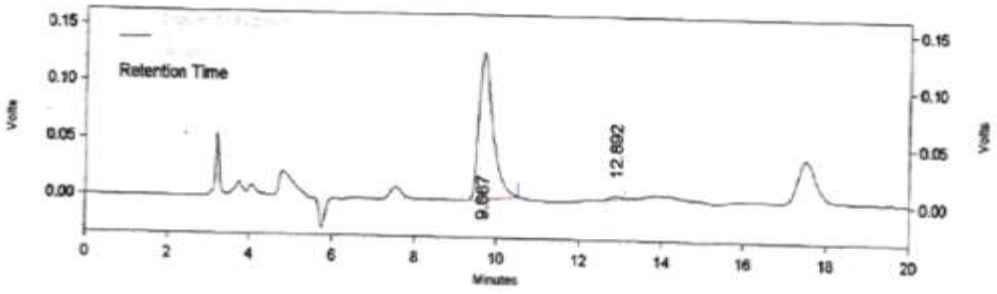
Detector A - 1 (220nm)

Retention Time	C Area	Area %
9.667	1502476	73.385
12.892	14334	0.700
13.892	27732	1.355
17.492	502854	24.561
Totals	2047396	100.000

Project Leader :Dr.S. P. Chavan
Column :Chirulpak AD-H (250 X4.6mm)
Mobile Phase :IPA: Pet Ether (01:99)
Flow Rate : 1.0ml/min (515PSI)
Wavelength : 220nm
Con. : 1mg /1.0ml
Inject vol. :5ul

HPLC of chiral 65

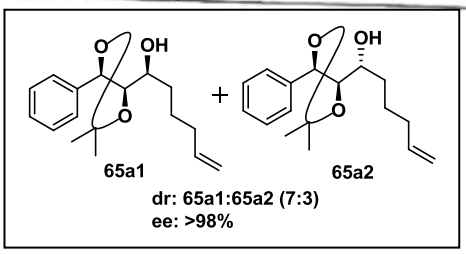
Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr. CHAVAN S. P\Hk-1559
User: System
Acquired: 12/15/15 4:35:35 PM
Printed: 12/15/15 5:25:38 PM
Sample Name G-C



Detector A - 1 (220nm)

Retention Time	C Area	Area %
9.667	1502476	99.055
12.892	14334	0.945
Totals	1516810	100.000

Project Leader :Dr.S. P. Chavan
Column :Chiralpak AD-H (250 X4.6mm)
Mobile Phase :IPA: Pet Ether (01:99)
Flow Rate : 1.0ml/min (515PSI)
Wavelength : 220nm
Con. : 1mg /1.0ml
Inject vol. :5ul



3.2.9. References:

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1.1.1. Introduction

In the literature, there are confusing reports about cadinane and cadinene. In order to remove any ambiguity few lines are devoted to its classification. This skeleton has been given the general name cadinene. The Wallach named this class of sesquiterpenes as cadinene. [1]

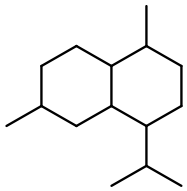


Figure-1: The basic cadinene skeleton

A sesquiterpene unit consisting of decalin system having two methyl substituents at the 1- and 6-positions, an isopropyl substituent at the 4-position and (1*S*,4*S*,4a*S*,6*S*,8a*S*)-configuration comprises the basic skeleton of cadinanes (**figure-1**). [2]

Cadinene is a discrete class of compounds with respect to stereochemistry emerged, which is now referred to as the cadinane class. The parent compound (+)-8-cadinene (**7**), which was isolated from the oil of a berry of a tropical shrub of the pepper family known as cubebs [3] is believed to arise from a hydride shift of carbocation as shown in (**figure-2**)

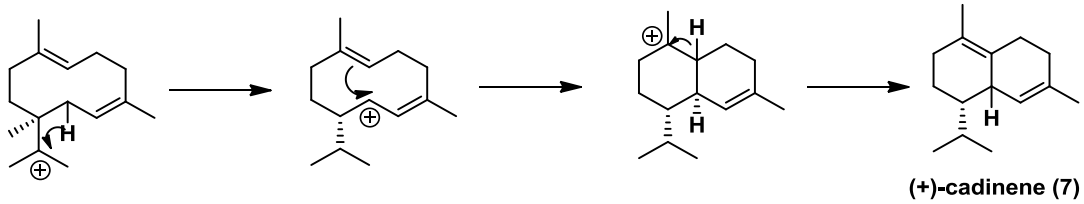


Figure-2: Biosynthesis of (+)-cadinene

A (+)-8 cadinane synthase cDNA has been recently identified and it has been demonstrated that it encodes for the enzyme that converts farnesyl pyrophosphate to (+)-8-cadinene. This is strong evidence that farnesyI pyrophosphate is the true precursor of (+)-8-cadinene.[4] Cadinenes have been further subdivided into four classes based on the nature of the ring fusion and the orientation of the isopropyl group at C-4 (**figure-3**). (i) Muurolanes: The basic skeleton of this group is (l*R*,6*R*,7*S*)-7-(2-propy1)-4,10-dimethylbicyclo[4.0.4]decane or its mirror image, (ii) Cadinanes: the basic skeleton of this group is (l*S*,6*R*,7*S*)-7-(2-propyl)-4,10-dimethylbicyclo

[4.0.4] decane or its mirror image, (iii) Bulgaranes: the basic skeleton of this group is (l*R*,6*S*,7*S*)-7-(2-propy1)-4,10-dimethylbicyclo[4.0.4]decane or its mirror image, and (iv) Amorphanes: the basic skeleton of this group is (1*S*,6*S*,7*S*)-7-(2-propyl)-4,l0-dimethylbicyclo[4.0.4] decane or its mirror image.[5,6]

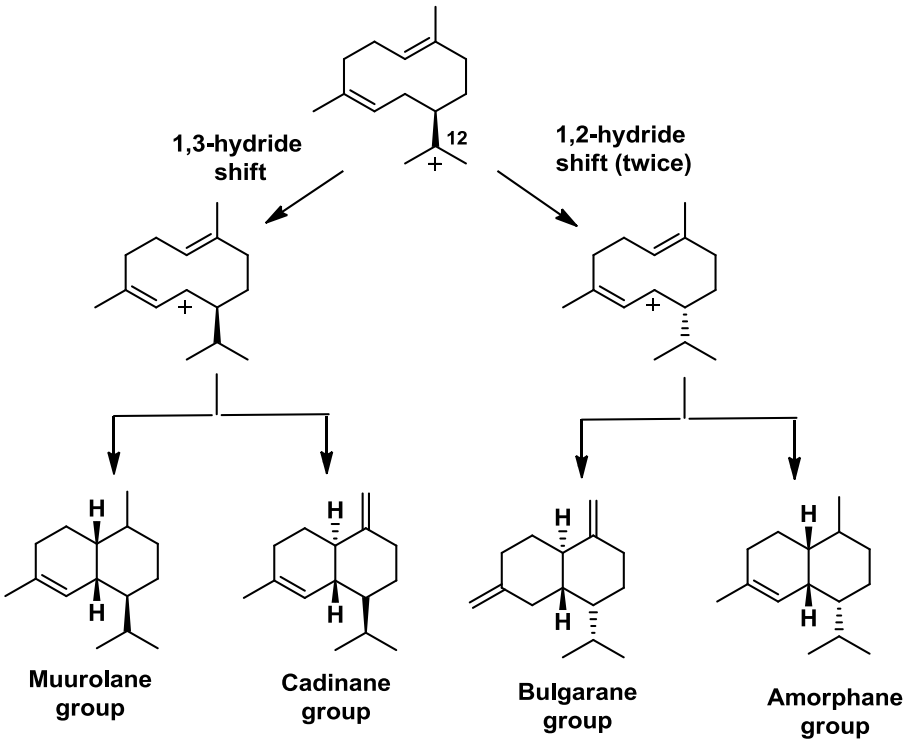


Figure-3: Classification of cadinenes

In addition to these four classes of cadinenes, aromatic compounds with a cadinene skeleton have also been found to be widely distributed in nature. The formation of these four classes of cadinenes has been rationalized by assuming a cyclization process involving a 1,3-hydride shift to the carbonium ion at C-12 of the germacrene (Scheme l), for muurolane and cadinane groups and for the formation of amorphane and bulgarane groups, by the double 1,2-hydride shift of the C-12 carbonium ion.[7] These sesquiterpenes possess a wide spectrum of biological activity through which they appear to play a role in plant defense mechanisms. Due to their bioactivity, some sesquiterpenes with the cadinane skeleton have been evaluated for antifungal or insecticidal activity. Cadinane-type sesquiterpenes constitute a fairly large family of more than two hundred compounds mainly isolated from the woody parts of plants, and they are often associated with decay resistance.

1.1.1.2. Introduction to cadinane sesquiterpene lactones

Miles and co-workers have isolated cadinane sesquiterpene lactones heritol (**1**),[8] heritonin (**2**),[9,10] vallapin (**4**),[11, 12] vallapianin (**5**)[11, 12] and heritianin (**6**)[12] (Figure 1) from the sap of the mangrove plant *Heritiera littoralis* (common name- sundari tree) of Philippines and other tropical countries, which were shown to possess ichthyotoxicity in ppm quantities to *Tilapia nilotica* fingerlings.

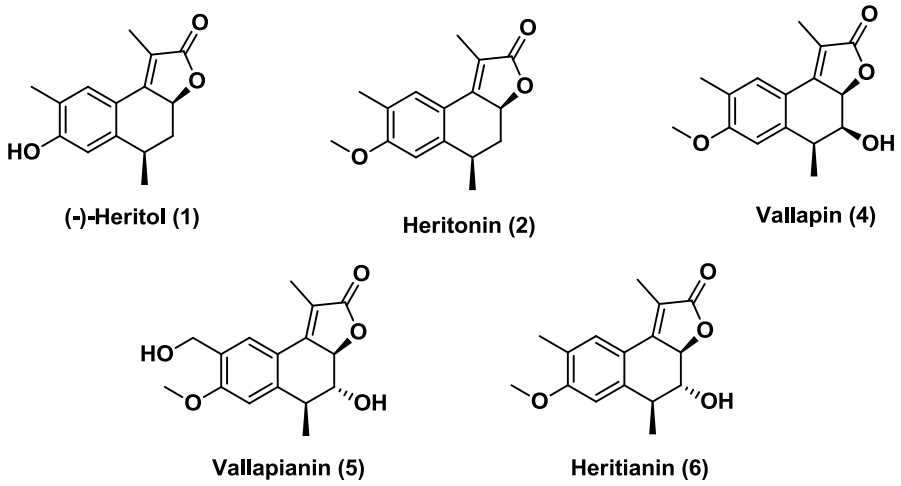


Figure-4 Cadinane sesquiterpene lactones isolated from mangrove plants

Ichthyotoxins are compounds which are either toxic to fish or are toxins produced by fish. They can cause fish deaths on a large scale. The hexane extract of this mangrove plant has shown toxicity to fish hence is used by native fishermen to kill fish. The sap of plant is used as a fish arrowhead and spearhead poison by natives of the Philippine islands. These compounds represent a novel class of sesquiterpenes and possess unusual oxygenation pattern not generally encountered in cadinane family (**figure-4**).

These compounds possess a unique butenolide ring and have been suggested to be potential biocompatible pesticides. A bioassay of vallapin showed activity against boll weevils, a type of pest of the cotton plant, at an inhibition level of 80% at a very lower dose of 0.6 mg when administered. Although total synthesis of heritonin and heritol, were reported in the literature, literature survey revealed that total synthesis of heritianin and vallapin is not reported till date.

1.1.2. Structure Elucidation

1.1.2.1. Heritol and heritonin:

Miles' *et al.* have isolated, established the structure and relative stereochemistry of heritol (**1**) [8, 9] (**figure-5**) from its spectral data and confirmed it by its single crystal X-ray diffraction analysis. Pure heritol was crystallized from methanol as a white needles (mp 271-272 ^{o}C, $[\alpha]^{25}_{D}$ = +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 peak 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.

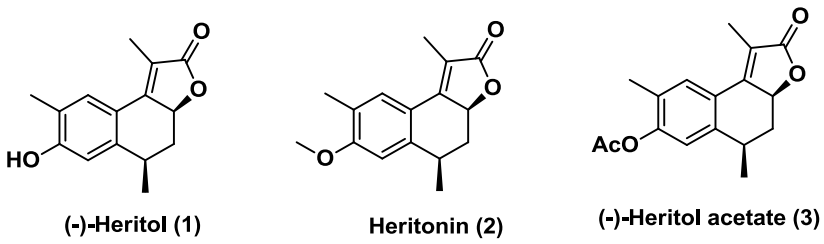


Figure-5: Heritol and heritonin

The presence of a hydroxyl group and an α, β-unsaturated γ-lactone moiety was indicated by the IR spectrum, that shows absorptions at 3450 cm^{-1} and 1750 cm^{-1}. This was further supported by the UV (recorded in cyclohexane) absorption at 228 nm (ε 11950), characteristic of butenolide moiety. The ^{1}H 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 non-equivalent 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 as 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 ^{1}H NMR spectrum also gave a clear 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.

The ^{13}C NMR spectrum was recorded for acetate **3** of heritol, due to solubility problem with this compound, which gave seventeen 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 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 single crystal X-ray diffraction 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**, which is nothing but the methyl ether of heritol.

1.1.2.2. Vallapin:

In 1991 Miles' *et al.* have conducted the chemoecological study of mangrove toxins in the Philippines islands and established the structure and relative stereochemistry of vallapin (figure-6) from its spectral data and confirmed it by its single crystal X-ray analysis. [11, 12] The pure vallapin was isolated from (**4**) the 100% $CHCl_3$ fraction. It was recrystallized from methanol to yield 90 mg of vallapin, as a white needles (MP = 269 ^oC, $[\alpha]^{25}_D$ −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 (recorded in cyclohexane) absorption at 228 nm (ε 11950), characteristic of

butenolide moiety. The ^{1}H NMR ($CDCl_3$, 200MHz) 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, ^{1}H NMR spectrum provided evidence of the three nonequivalent methyl groups, by revealing resonances at δ 1.45 (d, J = 10.0 Hz, 3H), 2.31 (s, 3H). Two of these resonances were as 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 ^{1}H 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**,** 1H), a proton at δ 4.42 (s**,** 1H), 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.

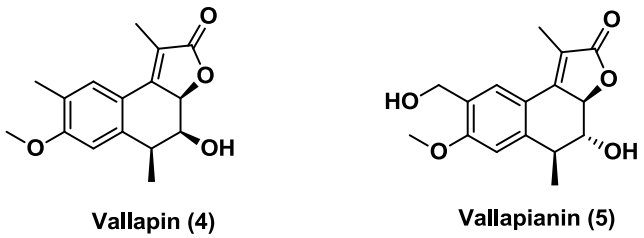


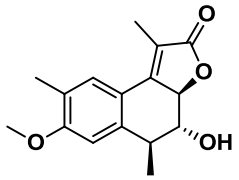
Figure-6: Vallapin and vallapianin

1.1.2.3. Vallapianin

Vallapianin (figure-6) was isolated from the 20% MeOH: $CHCl_3$ fraction. It was recrystallized from ether to yield 60 mg of vallapianin as a white powder. The melting point was recorded as 182 ^{o}C. A molecular formula of $C_{16}H_{18}O_5$ was determined by HRMS (ESI): calculated for $C_{16}H_{18}O_5$, 290.1150, found 290.1154. This formula indicated eight degrees of unsaturation. The mass spectrum exhibits base peak at ($[M]^+$ *m/z* = 290.115). The presence of aromaticity was indicated by the IR absorption bands at 1600 cm^{-1} and 1490 cm^{-1}. The IR absorption frequency peaks at 1750 cm^{-1} and 1640 cm^{-1} indicated the presence of an α,β-unsaturated γ-lactone. Presence of an absorption band at 3250-3350 cm^{-1} the IR spectrum also indicated the presence of a much larger band for a hydroxy group

The aromatic nature of vallapianin (**5**) was confirmed by the analysis of ^{1}H-NMR spectrum, which showed resonances at δ 7.58 (s) and δ 6.89 (s) that corresponds to two isolated

signals of an aromatic protons. Further analysis of ^{1}H-NMR spectrum showed resonances of doublet of a doublet for a proton on a carbon-bearing oxygen at δ 4.80 (dd, J = 1.8 Hz,) and a singlet for two methylene protons at δ 4.71 (s). The singlet that appeared at δ 3.91 (s) corresponds to three methoxy protons present in the molecule along with a multiplet corresponds to one benzylic proton at δ 3.01 (m). The evidence of two non-equivalent methyl groups were also provided by ^{1}H-NMR spectral analysis which showed resonance for a singlet at δ 2.15 (s, 3H) and a doublet at δ 1.55 (d, J = 7 Hz, 3H). A singlet at δ 2.15 indicated that this methyl group was attached to a quaternary carbon wheras the presence of a doublet at δ 1.55 indicated that this methyl group was attached to a methine carbon. Along with the above signals, resonance peaks for two hydroxyl groups at δ 1.23 and δ 1.60 were also present. The fragmentation pattern of mass spectrum indicates presence of peaks at *m/z*= 259, 141, 128, 115, 91, and 77 indicated that the fragmentations at *m/e*= 77 and *m/e*= 91 pointed to the presence of aromatic and benzylic functionalities respectively. These spectroscopic data led to assignment of the basic skeleton of vallapianin.



Heritianin (6)

Figure-7: Structure of heritianin

The ^{1}H-NMR spectrum analysis revealed that the structure of vallapianin was similar with that of the heritianin (**6**) (figure-7) except for the absence of a methyl group at δ 2.25 (s, 3H) and the addition of a methylene group at δ 4.71 (s, 2H). The methyl group at δ 2.25 was found to be absent in heritianin. Also the IR absorption spectrum was similar with heritianin except a much larger band was found to be present for a hydroxy group.

1.1.3. References:

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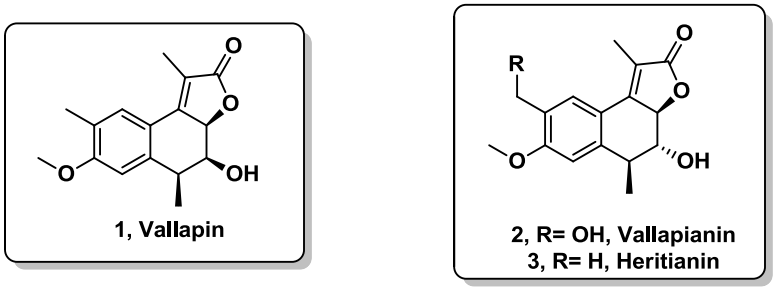
1.2.1. Literature review

The uncommon cadinane sesquiterpene butenolides vallapin (**1**), vallapianin (**2**) and heritianin (**3**) (**Figure–1)** were isolated as toxicants from mangrove plants, identified as novel compounds with ichthyotoxicity.



Figure–1: Cadinane sesquiterpene butenolides

This group is engaged in the synthesis of biologically active compounds and earlier this group has established a practical and efficient synthetic routes as well as methodologies for the synthesis of different biologically active terpenes.[1]

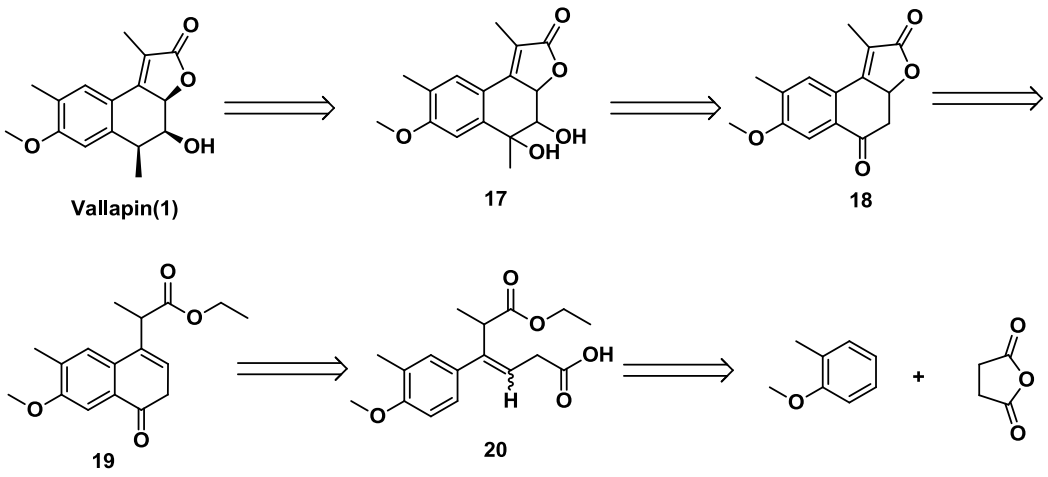
1.2.2. Present Work

Racemic as well as enantioselective total synthesis of heritol(**4**) and heritonin (**5**) were found to be well reported in the literature.[2] This group reported racemic[3] as well as first enantiospecific total synthesis of heritol (**4**) along with heritonin (**5**)[4]. In continuation of search for practical routes for such molecules, synthesis of vallapin (**1**) and heritianin (**3**) was undertaken. Although different methods for the synthesis of heritol were well reported in the literature, no reports were found in the context of total synthesis of vallapin, vallapianin and heritianin. Keeping in mind; (i) the biological activities (ii) absence of any previous synthetic reports and (iii) structural complexity associated with these natural products, plan for total synthesis was implemented.

1.2.3. Attempted synthesis of vallapin

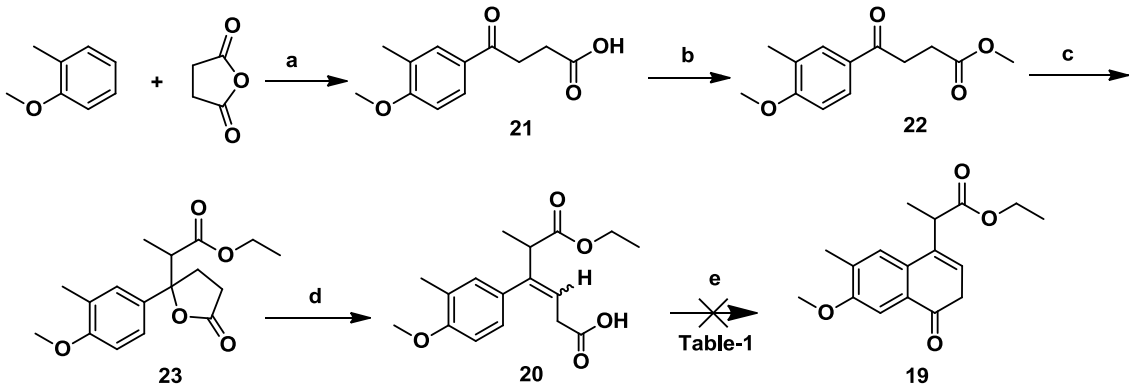
Thus, as shown in the retrosynthetic analysis (**Scheme–1**), vallapin (1) could be assembled from diol **17**, by removal of tertiary hydroxy group under hydrogenation rection

conditions. Compound **17** could be prepared from tetralone derivative **18**, by one carbon Grignard reaction, subsequent elimination followed by dihydroxylation. Compound **18** could be obtained from ester **19** by dihydroxylation and acid catalysed butenolide ring formation. Preparation of compound **19** could be achieved from ester **20** under acid catalysed cyclisation. Compound **20** could be prepared from Friedal–Craft's acylation reaction between *o*–cresol methyl ether and succinic anhydride, followed by Reformatsky reaction. The *o*–cresol methyl ether and succinic anhydride are easily available inexpensive starting materials.



Scheme–1: Retrosynthetic analysis for vallapin (**1**)

Accordingly, the synthesis was initiated from Friedal–Craft's acylation reaction between *o*–cresol methyl ether and succinic anhydride, which is a reported protocol for preparation of ketoacid **21** (**Scheme–2**).[2a] Under acid catalysed esterification reaction conditions the ketoacid **21** was converted into it's methyl ester [9] in 88% yield. Formation of compound **22** was evident from a characteriatic singlet of $-OCH_3$ at δ 3.80, in it's ^{1}H NMR spectrum. Ester **22** was further treated with ethyl–2–bromopropionate and activated Zn under Reformatsky reaction, furnished lactone **23** in 78% yield and (*dr*: ~6:4). Formation of lactone **23** was established by IR spectroscopy by absorption at (ν_{max}): 1773 cm^{-1} for lactone, ^{1}H NMR spectrum shows a multiplet over the range δ 3.02–2.88 for one proton, and ^{13}C NMR spectrum revealed the resonance at δ 175.8 for lactone carbonyl group. Formation of lactone **23** was finally confirmed with mass spectrum shows peak at (*m/z*): 285 [M+Na]$^+$.



Scheme–2 Attempted synthesis of vallapin

Reagents and conditions: *(a) $AlCl_3$, DCM, 0 ^oC– RT,78%; (b) MeOH, H_2SO_4, reflux, 3 h, 88%; (c) Ethyl–2–bromopropionate, Zn, I_2, ether, reflux, 2 h, 78%; (d) $AlCl_3$, DCM, RT, 89%.(e)* ***Table-1***

SN	Reagents	Conditions	Product and Yield (%)
1	TFA, TFAA	0 ^{o}C to RT	——
2	PPA, DCM	Reflux	——
3	excess $AlCl_3$(4 equiv.), DCM	RT/ Reflux	Starting Material
4	conc. H_2SO_4 (impregnated on silica), DCM	Reflux	Starting Material (22%)

In order to convert lactone **23** into tetralone derivative **19** several attempts were carried out. The lactone ring opening in compound **23** was observed when it was treated with $AlCl_3$, furnished acid **20** in 89% yield (*E/Z*: 90:10). This acid was subjected for TFA and TFAA as well as with polyphosphoric acid catalysed cyclisation, where formation of unidentified product was observed. Starting material was recovered when acid **20** was treated with excess of $AlCl_3$ at RT and or under refluxing temperature. When acid **20** was reacted with conc. H_2SO_4 impregnated on silica, decomposition along with 22% recovery of starting material was observed (**Table–1**).

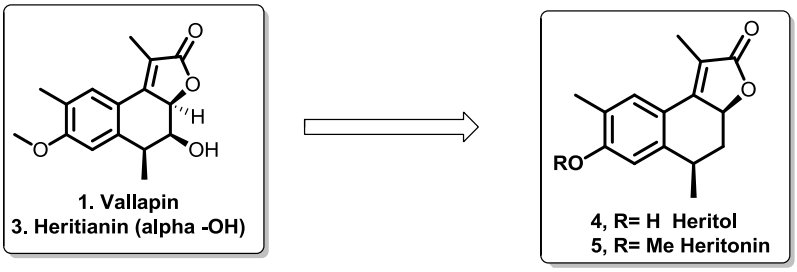
Not only under Upjohn dihydroxylation reaction but also under flash dihydroxylation reaction conditions formation of complex reaction mixture were observed (**Table–2**).

Table–2

SN	Reagents	Conditions	Product and Yield (%)
1	OsO_4, NMO, ACN:H_2O (9:1)	RT	Complex rea. mix.
2	$RuCl_3$, $NaIO_4$, H_2SO_4, EtOAc:ACN:H_2O (3:3:1)	0 ^oC to RT	Complex rea. mix.

1.2.4. Model study

After failure with all the attempts for preparation of compound **19** as per the discussed retrosynthetic analysis, there was a need for more advanced and revised synthetic approach. Therefore, in order to decide a good synthetic strategy towards synthesis of hydroxy cadinane butenolide sesquiterpenes, model study on cadinane framework has been carried out. Earlier, synthesis of heritol was reported from this group, it was planned to focus on introduction of secondary hydroxy group at alpha position to the butenolide ring junction present in the cadinane framework (**Figure–2**).

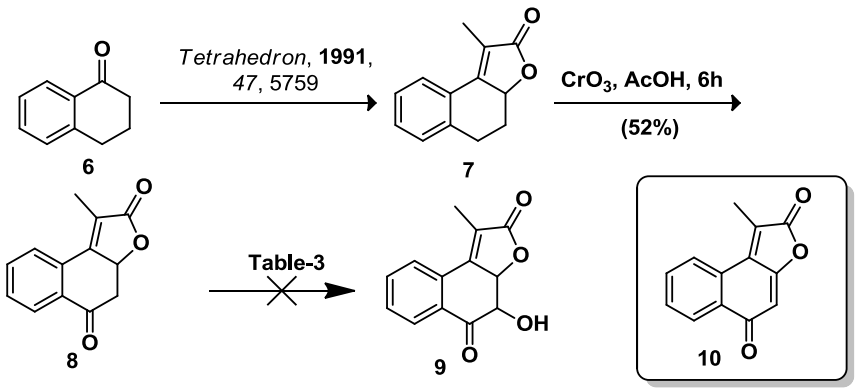


Figure–2: Preparation of hydroxy cadinane butenolide from heritol

Remarkable presence of the secondary hydroxyl group placed adjacent to benzylic methyl group and butenolide ring junction diffrentiates cadinane sesquiterpene heritol (**4**) and heritonin (**5**) mainly from novel hydroxy cadinane sesquiterpenes *viz*. vallapin (**1**), vallapianin (**2**) and heritianin (**3**). The literature survey revealed that there is a lack of any synthetic strategy for preparation of these molecules although their isolation was reported in 1991.[5]

In order to perform model study and to establish the further synthetic strategy, preparation of cadinane framework was undertaken (**Scheme–3**). Thus, cadinane framework was

prepared by converting commercially available tetralone (**6**) to butenolide **7** by reported protocol from this lab. [2a, 2b] The product formation was confirmed by it's IR and NMR spectral data with those of literature values and were found to be in good agreement with the proposed structure. It was envisioned that the free benzylic methylene could be oxidised to achieve α hydroxylation of the resulting ketone. Therefore, compound **7** was oxidized at benzylic position by treatment with CrO_3 in presence of AcOH, to furnish compound **8** in 52% yield. Formation of compound **8** was checked with IR absorption frequency for carbonyl group at 1710 cm^{-1}.



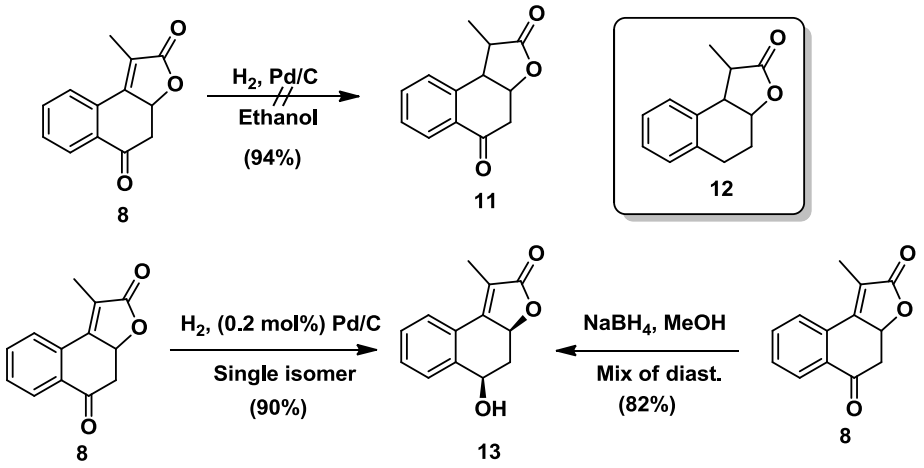
Scheme–3: Model study on cadinane framework

Table–3

SN	Reagents and conditions	Process	Product/ yield
1	*m*–CPBA, $BF_3.OEt_2$, acetic acid, H_2O, PhI (cat.), 20 h	Acetoxylation	**10** (38%)
2	Ac_2O, $BF_3.OEt_2$, H_2O_2, PhI (cat.), 30 ^oC, 7 h	Acetoxylation	**10** (49%)
3	*P*–TSA, PhI (cat.), *m*–CPBA, ACN, 50 ^oC, 5 h	Tosyloxylation	**10** (36%)
4	HTIB, ACN, RT, 2 h	Tosyloxylation	**10** (58%)
5	Oxone, TFAA, ACN: H_2O, PhI (cat.), 90 ^oC, 15 h	Hydroxylation	**10** (42%)

The next crucial reaction was the introduction of hydroxyl group alpha to benzylic carbonyl group for which alpha oxidation was envisioned as the key reaction. In that context compound **8** was treated under various oxidizing reagents under different conditions. As shown in table–2, under the process of alpha acetoxylation formation of nonpolar compound **10** was observed.[6] The ^{1}H–NMR spectrum of compound **10** showed downfield shift for one proton at δ 6.23 (s), characteristic for olefin proton. Formation of **10** was also supported by disappearance of

a multiplet from ^{1}H–NMR spectrum of starting compound **8** at δ 5.45–5.37 (m, 1H), characteristic for butenolide ring junction proton. This is indicative of formation of highly conjugated compound **10** by means of *in situ* elimination of –OAc with highly acidic proton present adjacent at butenolide ring junction. Formation of **10** was also confirmed by it's IR, ^{13}C–NMR and mass spectral data, and further ascertained by it's HRMS analysis. This data supports that this transformation is probably an outcome of *in situ* formation of acetate of compound **9** and it's subsequent elimination. In an another attempt compound **8** was subjected under oxytosylation reaction [7] conditions in order to generate a *o*-tosylate group was alpha to the carbonyl. In presence of *P*–TSA, *m*–CPBA (entry–3) formation of compound **10** found to be in 36% yield whereas in presence of HTIB (entry–4), compound **10** was obtained in 58% yield. Formation of compound **10** was also observed under alpha hydroxylation[8] conditions in presence of oxone (entry–5) in 42% yield (**Table–3**).



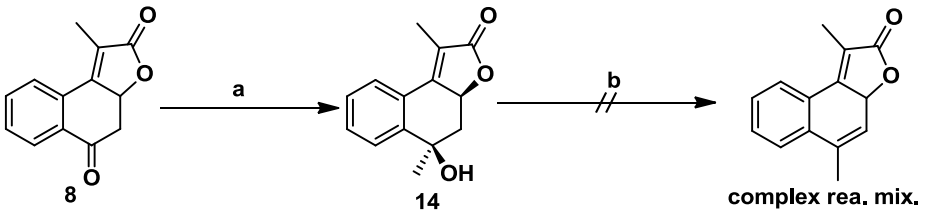
Scheme–4: Model study on cadinane framework

Reagents and conditions*:– (a) H_2, Pd/C (10 mol %.), ethanol, RT, 3 h, 94%; (b) H_2, Pd/C (0.3 mol %), ethanol, RT, 3 h, 66% + 27% SM; (c) $NaBH_4$, MeOH, 0 ^{o}C– RT, 82%.*

From the above observations under all three protocols, acetoxylation, *o*-tosyloxlation and hydroxylation, elimination was observed with formation of compound **10** as the only product. It was confirmed that isolation of compound **9** was at the most not possible, as soon as it gets generate, underwent elimination under the influence of acidity of proton present at butenolide ring junction. So, there was a need to change strategy, by lowering the acidity of proton that is

prone for elimination and in that regard to disturb the extensive conjugation responsible for generation of compound **10**. Instead of alpha hydroxylation and elimination, it was decided to reduce double bond present in the butenolide ring of compound **8**, followed by alpha hydroxylation reaction could furnish a stable hydroxy cadinane lactone framework (**Scheme–4**).

Accordingly compound **8** was then subjected under hydrogenation conditions in presence of H_2, Pd/C (10 mol%) to reduce double bond in butenolide ring. Instead of desired compound **11**, formation of lactone **12** was observed as a result of reduction of double bond along with benzylic carbonyl group. Further, compound **8** was reacted under controlled hydrogenation conditions, using 0.3 mol% of Pd/C and formation of single diastereomer of compound **13** was observed, [4] as a result of reduction of carbonyl to hydroxy. Although double bond present in compound **8** was found to remain intact. Presence of hydroxyl group stretching frequency in the IR spectrum at 3407 cm^{-1} and downfield shift of the proton, attached to the carbon bearing a secondary hydroxyl group along with a broad singlet at δ 3.24 (1H), in the ^{1}H NMR spectrum of the isolated product, suggested the formation of undesired compound **13**. Formation of compound **13** was also confirmed by reduction of compound **8** in presence of $NaBH_4$, furnished (1:1) mixture of diastereomers.

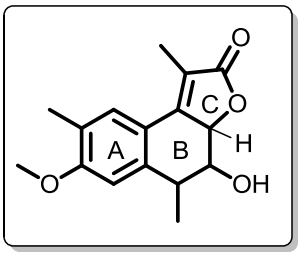


Scheme–5: Model study on cadinane framework

Reagents and conditions:–*(a) MeMgBr, THF, –78 ^{o}C, 1 h, 89%: (b) MsCl, Et_3N, DCM, 3 h.*

Under several attempts to synthesize hydroxy cadinane butenolide framework compound **8** was subjected for one carbon Grignard reaction at –78 ^{o}C and THF as a solvent (**Scheme–5**). Formation of compound **14** was observed with 89% yield. Compound **8** was characterised by it's IR and NMR spectral data. Absence of stretching band at 1710 cm^{-1} in the IR spectrum of the isolated product suggested absence of the carbonyl functionality. There were additional absorption bands at 3414 cm^{-1} in the IR spectrum, which suggested the presence of hydroxyl groups. This was further supported by shift of the (–$C\underline{H}_3$) in at δ 1.60 as a singlet, in it's ^{1}H NMR spectrum. In order to convert tertiary hydroxy group into a good leaving group compound **14** was

treated with mesyl chloride in presence of triethyl amine. This transformation produced number of products from which desired product could not be isolated.

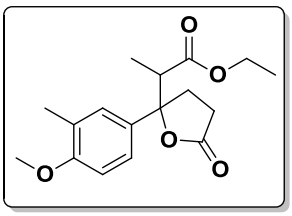


Figure–3: Cadinane framework

In conclusion, model study on cadinane framework has been done, proved useful for developing further synthetic strategy by considering structural features of hydroxy cadinane framework such as– (i) acidity of proton (prone for elimination), (ii) aromatisation (stability) and (iii) preference for construction of **B** ring/ and **C** ring first.

1.2.5. Experimental data

Preparation of ethyl 2–(2–(4–methoxy–3–methylphenyl)–5–oxotetrahydrofuran–2–yl)propanoate (23)



To a magnetically stirred solution of methyl 4–(4–methoxy–3–methylphenyl)–4–oxobutanoate (**22**) (0.600 g, 1 equiv.) in anhydrous diethyl ether (20 mL) was slowly added activated Zn (0.228 g, 3 equiv.) followed by catalytic amount of iodine and a solution of ethyl 2–bromopropionate (0.528 mL, 1.5 equiv.) in anhydrous diethyl ether (5 mL) over a period of 15 min. The resulting reaction mixture was refluxed (80 °C) for 3 h under an argon atmosphere. The reaction mixture was cooled to 0 ºC and quenched with 10% HCl (10 mL) and extracted with EtOAc (3 X 8 mL). The combined organic extracts were washed with brine (7 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product thus obtained was purified by 200–400 silica gel column chromatography using a 10% EtOAc: petroleum ether as a eluent to furnish pure ethyl 2–(2–(4–methoxy–3–methylphenyl)–5–oxotetrahydrofuran–2–yl)propanoate (**23**) (0.606 g, 78%) as an oily product .

Molecular formula: $C_{17}H_{22}O_5$; **Yield:** 78%; (*dr*: 6:**4**).

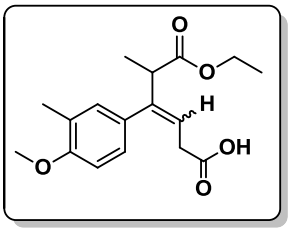
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.16–7.05 (m, 2H), 6.74 (d, J = 8.72 Hz, 1H), 4.11–4.00 (m, 2H), 3.80 (s, 3H), 3.02–2.88 (m, 1H), 2.88–2.37 (m, 4H), 2.18 (s, 3H), 1.25–1.05 (m, 6H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 175.8, **175.5**, 172.8, **172.5**, **157.4**, 157.2, 133.7, **131.6**, **128.2**, 127.2, 126.5, **126.3**, **124.3**, 123.5, 109.2, **109.0**, **89.0**, 88.1, **60.6**, 60.5, 55.1, 50.0, **49.5**, 31.2, **30.1**, 28.64, **28.60**, 16.4, **14.08**, 14.04, 12.8, **12.3**.

MS (ESI) (*m/z*): 307 $[M+1]^+$; **IR ($CHCl_3$)** ν_{max}: 3020, 1773, 1732, 1610, 1504, 1464, 1215 cm^{-1}.

HRMS (ESI): Calculated for $C_{17}H_{22}O_5$ $[M+Na]^+$329.1467, found 329.1463.

Preparation of (*E/Z*)–6–ethoxy–4–(4–methoxy–3–methylphenyl)–5–methyl–6–oxohex–3–enoic acid (20)



To a magnetically stirred solution of ethyl 2–(2–(4–methoxy–3–methylphenyl)–5–oxotetrahydrofuran–2–yl)propanoate (**23**, 0.800 g, 1 equiv.) in dry DCM (5 mL), was added anhydrous crystalline $AlCl_3$ (0.340 g, 1.1 equiv.) in one portion under nitrogen atmosphere. The resulting mixture was warmed to RT and the reaction mixture was stirred at RT until the consumption of starting material. 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 under reduced pressure. The crude product thus obtained was purified by 200–400 silica gel column chromatography using a 10% EtOAc: pet. ether, to furnish (*E/Z*)–ethoxy–4–(4–methoxy–3–methylphenyl)–5–methyl–6–oxohex–3–enoic acid (**20**, 0.739 g, 89%) as a oily product, contains mixture of (*Z*) isomer in (~8%).

Molecular formula: $C_{17}H_{22}O_5$; **Yield:** 89%.

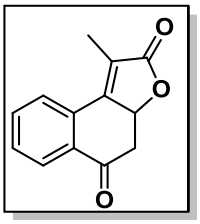
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.07–6.86 (m, 2H), 6.78–6.69 (m, 1H), 5.6–5.69 (m, 1H), 4.26–4.04 (m, 2H), 3.83 (s, 3H), 3.47–3.31 (m, 1H), 3.02–2.81 (m, 2H), 2.19 (s, 3H), 1.25 (s, 3H), 1.20 (t, J = 7.20 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 177.6, 174.0, 157.0, 143.8, 130.7, 130.3, 127.0, 126.4, 119.4, 109.5, 60.5, 55.1, 47.8, 34.4, 16.37, 16.36, 14.2.

MS (ESI) (*m/z*): 329 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3456, 3020, 2950, 1740, 1651,1507 cm^{-1}.

HRMS (ESI): Calculated for $C_{17}H_{22}O_5$ $[M+Na]^+$329.1467, found 329.1464.

Preparation of 1–methyl–3*a*,4–dihydronaphtho[2,1–*b*]furan–2,5–dione (8)



To a stirred solution of butenolide (**7**) (0.030 g, 1 equiv.) in AcOH (2 mL) at 5 ^{o}C, a solution of CrO_3 (0.045 g, 3 equiv.) in AcOH and water (0.9: 0.1 mL) was added slowly in portions over a period of 0.5 h. The resulting reaction mixture was stirred at the same temperature for 2 h and then at RT for additional 2 h. After completion of reaction, saturated $NaHCO_3$ solution was added, followed by dilution with EtOAc (10 mL). The resulting solution was extracted with EtOAc (3 X 10 mL). The combined organic extracts washed with brine (7 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product thus obtained was purified by 200–400 silica gel column chromatography using a 10% EtOAc–pet. ether as a eluent to furnish pure 1–methyl–3a,4–dihydronaphtho[2,1–*b*]furan–2,5–dione (**8**, 0.015 g, 52%) as a light brown solid.

Molecular formula: $C_{13}H_{10}O_3$; **Yield:** 52%; **MP:** 148-150 ^{o}C.

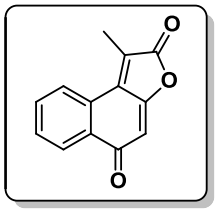
^{1}H NMR (500 MHz, $CDCl_3$+ DMSO–d_6+CCl_4): δ 7.44 (d, J = 7.93 Hz, 1H), 7.18–7.13 (m, 2H), 6.99–6.96 (m, 1H), 4.77–4.74 (m, 1H), 2.80 (dd, J = 15.87, 6.11 Hz, 1H), 2.03–1.97 (m, 1H), 1.54 (d, J = 1.23 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$+ DMSO–d_6+CCl_4): δ 191.7, 173.0, 152.0, 134.2, 131.9, 131.6, 130.3, 127.2, 127.0, 122.3, 76.0, 44.8, 4.34.

MS (ESI) (*m/z*): 237 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 2923, 2860, 1745, 1710, 1638, 1511 cm^{-1}.

HRMS (ESI): Calculated for $C_{13}H_{10}O_3$ $[M+Na]^+$ 237.0630, found 237.0632.

Preparation of 1–methylnaphtho[2,1–*b*]furan–2,5–dione (10)



I) Under alpha acetoxylation reaction condition: (1) To a stirred solution of compound (**8**) (0.110 g, 1 equiv.) in AcOH (2 mL) and water (0.027 g, 3 equiv.) was added *m*–CPBA (0.123 g, 1.4 equiv.) followed by BF_3OEt_2 (0.214 g, 3 equiv.) and iodobenzene (0.024 g, 0.3 equiv.) at RT. The resulting reaction mixture was stirred for 20 h. The reaction mixture was diluted with EtOAcfollowed by addition of saturated 10 % $NaHCO_3$ solution. The resulting solution was extracted with EtOAc (3 X 10 mL) and washed with brine. The combined filtrate

was evaporated under reduced pressure and the obtained residue was purified using 200–400 silica gel column chromatography (10% EtOAc–pet ether) to furnish 1–methylnaphtho[2,1–*b*]furan–2,5–dione (**10**, 0.041 g, 38% yield) as a brown solid.

(2) A solution of 30% H_2O_2 (0.063 g, 3.8 equiv.) and acetic anhydride (0.959 g, 19 equiv.) was stirred at 40 °C for 4 h and then cooled to 0 °C. To the above solution $BF_3{\cdot}OEt_2$ (0.210 g, 3 equiv.) at RT followed by (**8**) (0.100 g, 1 equiv.) and iodobenzene (0.020 g, 0.2 equiv.) were slowly added and stirred at 30 °C for 7 h. After completion of reaction, 10% aq Na_2CO_3 solution was added and extracted with EtOAc (3 X 10 mL). The combined filtrate was evaporated and the residue was purified under column chromatography to furnish (**10)** (0.041 g, 49% yield).

II) Under alpha *o*-tosyloxylation reaction condition: (1) To a solution of (**8**) (0.120 g, 1 mmol) in MeCN (5 mL) were added iodobenzene (0.020 g, 0.1 mmol), *p*–TSA (0.209 g, 1.1 mmol) and *m*–CPBA (0 292 g, 1.1 mmol). The mixture was stirred for 5 h at 50 °C under nitrogen atmosphere. The reaction mixture was poured into sat. $NaHCO_3$ and extracted with DCM (3 X 20 mL). The combined filtrate was evaporated and the obtained residue was purified under column chromatography to furnish product (**10**, 0.042 g, 36% yield).

(2) To a solution of (**8**) (0.500 g, 1 equiv.) in 30 mL of ACN was added hydroxy(tosyloxy)iodobenzene (HTIB) (1.09 g, 1.1 equiv.). After being stirred 2 h at RT, the reaction mixture was filtered, washed with H_2O (2 X 10 mL) and DCM (3 X 10 mL). The combined filtrate was evaporated under reduced pressure and the obtained residue was purified under column chromatography to furnish product (**10**, 0.287 g, 58% yield).

III) Under alpha hydroxylation reaction condition: A solution of Oxone® (6.56 g, 2.7 equiv.), TFAA (5.820 g, 7 equiv.) and H_2O (20 mL) was stirred at 40 °C for 7 h and then cooled to RT. To this solution compound (**8**) (0.800 g, 1 equiv.) and iodobenzene (0.161 g, 0.2 equiv.) in ACN (60 mL) were added at RT and stirred at 90 ^oC for 15 h. After completion of reaction, 10% aq Na_2CO_3 solution was added followed by extraction with DCM (3 X 15 mL). The combined filtrate was evaporated under reduced pressure and the obtained residue was purified under column chromatography to furnish product (**10**, 0.332 g, 42% yield).

Molecular formula: $C_{13}H_8O_3$; **MP:** Decomposition observed after 290 ^oC.

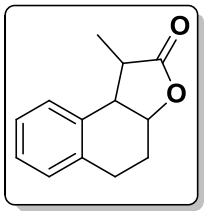
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 8.26 (d, *J* = 6.53 Hz, 1H), 7.91 (d, *J* = 6.53 Hz, 1H), 7.70–7.64 (m, 2H), 6.23 (s, 1H), 2.49 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 184.0, 168.6, 161.1, 138.7, 132.8, 131.3, 131.0, 128.5, 128.1, 127.4, 126.7, 105.7, 11.6.

MS (ESI) (*m/z*): 244 $[M+MeOH]^+$; **IR ($CHCl_3$)** ν_{max}: 3019, 1685, 1617, 1472, 1215 cm^{-1}.

HRMS (ESI): Calculated for $C_{13}H_8O_3$ $[M+Na]^+$ 235.2125, found 235.2122.

Preparation of 1–methyl–1,4,5,9*b*–tetrahydronaphtho[2,1–*b*]furan–2(3a*H*)–one (11)



To a stirred solution of 1–methyl–3*a*,4–dihydronaphtho[2,1–*b*]furan–2,5–dione (**8**) (0.110 g, 20 mmol) in ethanol (5 mL) was added Pd/C (10 mol%). The reaction mixture was stirred under hydrogen atmosphere at 25 ^{o}C and 1–2 psi for 3 h. After completion of the reaction, the catalyst was filtered off and the residue washed with hot ethanol (3 X 5 mL). The combined filtrate was evaporated under reduced pressure and the obtained residue was purified using 60–120 silica gel column chromatography (15% EtOAc–petroleum ether) to furnish (**11)** (0.109 g, 94% yield).

Molecular formula: $C_{13}H_{14}O_2$; **Yield:** 94%.

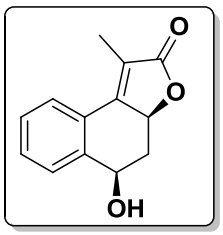
^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 7.20–7.11 (m, 3H), 7.05–7.03 (m, 1H), 5.04–5.00 (m, 1H), 3.89 (dd, *J* = 9.62, 6.87 Hz, 1H), 3.10–3.06 (m, 1H), 2.91–2.84 (m, 1H), 2.65–2.59 (m, 1H), 2.31–2.24 (m, 1H), 1.92–1.84 (m, 1H), 1.03 (d, *J* = 7.33 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 179.3, 137.5, 131.8, 130.6, 128.9, 126.7, 126.1, 77.3, 41.3, 39.3, 27.5, 24.2, 13.4.

MS (ESI) (*m/z*): 257 $[M+Na+MeOH]^+$; **IR ($CHCl_3$)** ν_{max}: 3019, 1792, 1654, 1590, cm^{-1}.

HRMS (ESI): Calculated for $C_{13}H_{14}O_2$ $[M+Na]^+$225.3167, found 225.3164.

Preparation of 5–hydroxy–1–methyl–4,5–dihydronaphtho[2,1–*b*]furan–2(3*aH*)–one (13)



To a stirred solution of 1–methyl–3*a*,4–dihydronaphtho[2,1–*b*]furan–2,5–dione (**8**) (0.110 g, 20 mmol) in EtOH (5 mL) was added Pd/C (0.3 mol%). The reaction mixture was stirred under hydrogen atmosphere at 25 ^{o}C and 1–2 psi for 3 h. After completion of reaction, the catalyst was filtered off and the residue washed with hot ethanol (3 X 5 mL). The combined filtrate was evaporated and the obtained residue was purified using 60–120 silica gel column chromatography (15% EtOAc–pet. ether) to furnish 5–hydroxy–1–methyl–4,5–dihydronaphtho[2,1–*b*]furan–2(3*aH*)–one (**13**, 0.077 g, 66% yield)as a light brown solid.

Molecular formula: $C_{13}H_{12}O_3$; **Yield**: 66%; **MP:** 145 ^oC.

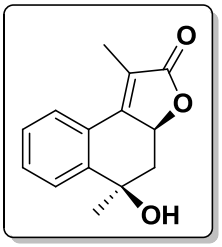
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.89 (d, *J* = 6.56 Hz, 1H), 7.66 (dd, *J*= 6.56, 0.63 Hz, 1H), 7.52–7.36 (m, 2H), 5.01–4.87 (m, 2H), 3.24 (brs, 1H), 2.98–2.87 (m, 1H), 2.13 (d, *J* = 1.52 Hz, 3H), 1.76–1.59 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$+ DMSO–d_6+CCl_4): δ 173.2, 154.6, 141.5 (2C), 129.2, 126.6, 126.4, 124.7, 117.4, 75.6, 64.7, 39.1, 8.65

MS (ESI) (*m/z*): 248 $[M+MeOH]^+$; **IR ($CHCl_3$)** ν_{max}: 3407, 3018, 2924, 1792, 1654, 1460 cm^{-1}.

HRMS (ESI): Calculated for $C_{17}H_{22}O_5$ $[M+Na]^+$ 239.1787, found 239.1784.

Preparation of 5–hydroxy–1,5–dimethyl–4,5–dihydronaphtho[2,1–*b*]furan–2(3*aH*)–one (14)



To a dry round bottom flask was added 1–methyl–3*a*,4–dihydronaphtho[2,1–*b*]furan–2,5–dione (**3**) (0.100 g, 1.4 mmol) in dry THF (2 mL). The resulting solution was cooled to –78 ºC and MeMgBr (1.4 M solution in THF, Aldrich make) (0.40 mL, 0.6 mmol) was added dropwise. The reaction was stirred at –78 ºC for 1 h, then allowed to warm upto RT and further stirred at the same temperature for 2 h. The reaction was quenched with sat. NH_4Cl solution and extracted with EtOAc (3 X 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product thus obtained was purified by flash column chromatography using eluent (20% EtOAc: pet. ether) to provide 5–hydroxy–1,5–dimethyl–4,5–dihydronaphtho[2,1–*b*]furan–2(3*aH*)–one (**14,** 0.101 mg).

Molecular formula: $C_{14}H_{14}O_3$; **Yield:** 89%; **MP:** 91 ^oC.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.76 (d, *J* = 7.95, 1.51 Hz, 1H), 7.60 (dd, *J* = 7.95, 1.51 Hz, 1H), 7.52–7.35 (m, 2H), 5.01–4.90 (m, 1H), 2.80 (dd, *J* = 12.38, 4.80 Hz, 1H), 2.12 (d, *J* = 1.77 Hz, 3H), 1.86 (t, *J* = 12.38 Hz, 1H), 1.60 (s, 3H).

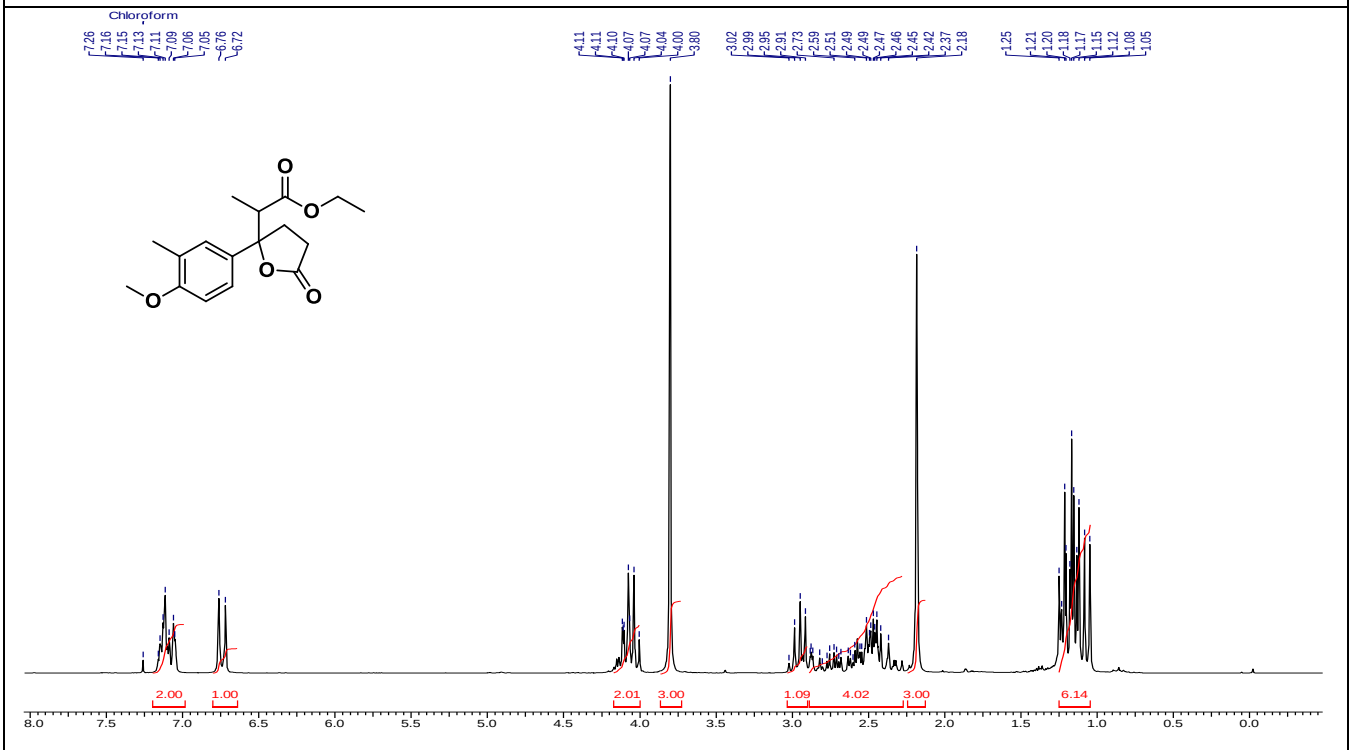
^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 174.5, 155.4, 145.2, 131.0, 128.0, 127.2, 127.0, 126.4, 119.7, 77.1, 71.3, 46.2, 31.9, 9.91.

MS (ESI) (*m/z*): 253 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3539, 2935, 2853, 1733, 1645, 1613 cm^{-1}.

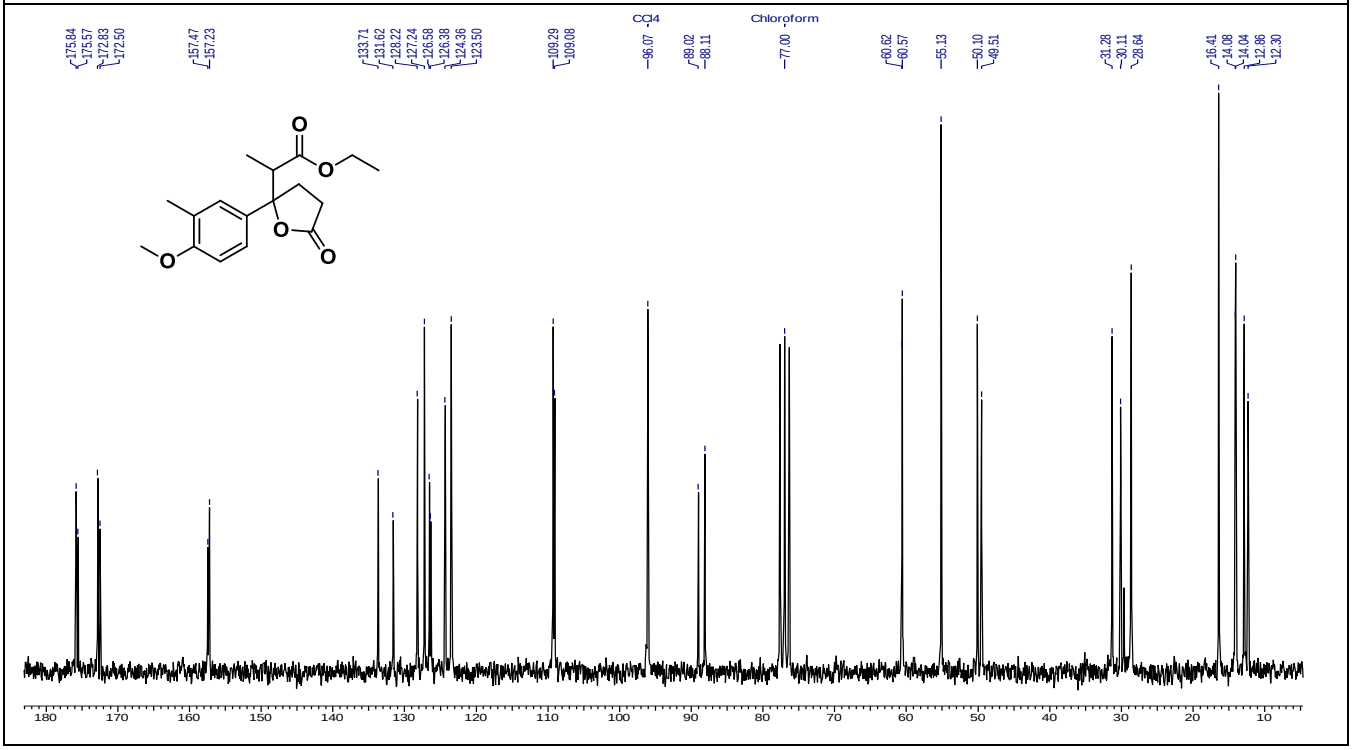
HRMS (ESI): Calculated for $C_{14}H_{14}O_3$ $[M+Na]^+$253.9460, found 253.9464.

1.2.5.1. Spectral data

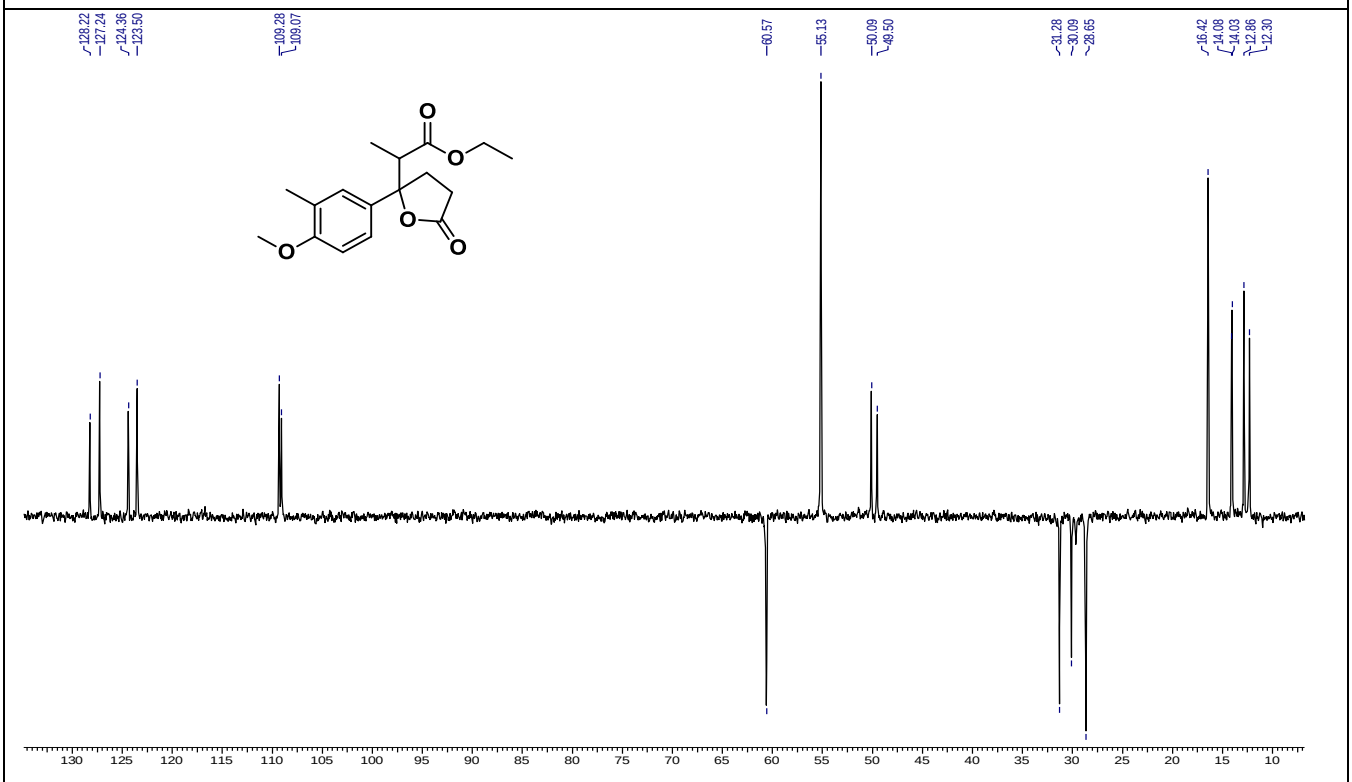
^{1}H NMR spectrum of compound **23** ($CDCl_3$+CCl_4, 200 MHz)



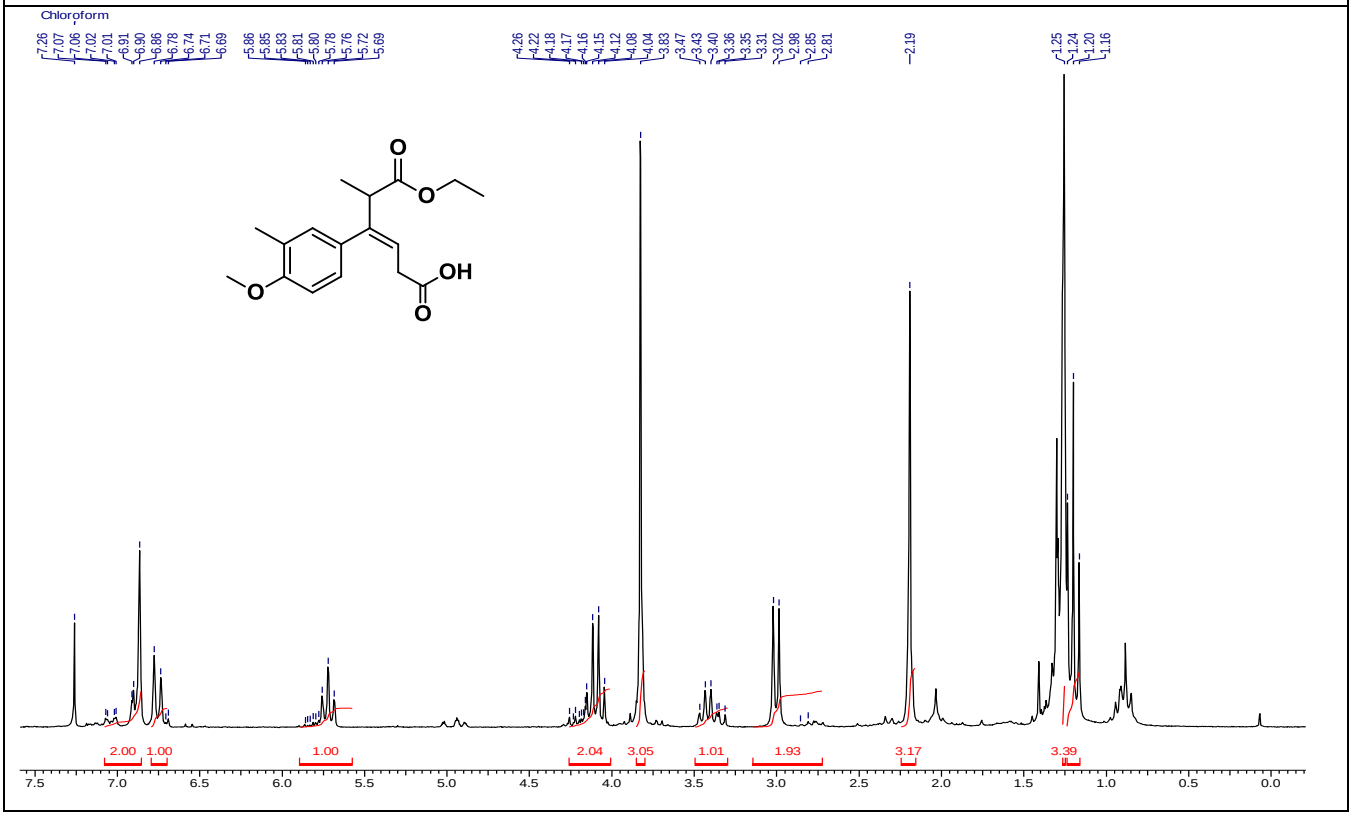
^{13}C NMR spectrum of compound **23** ($CDCl_3$+CCl_4, 50 MHz)



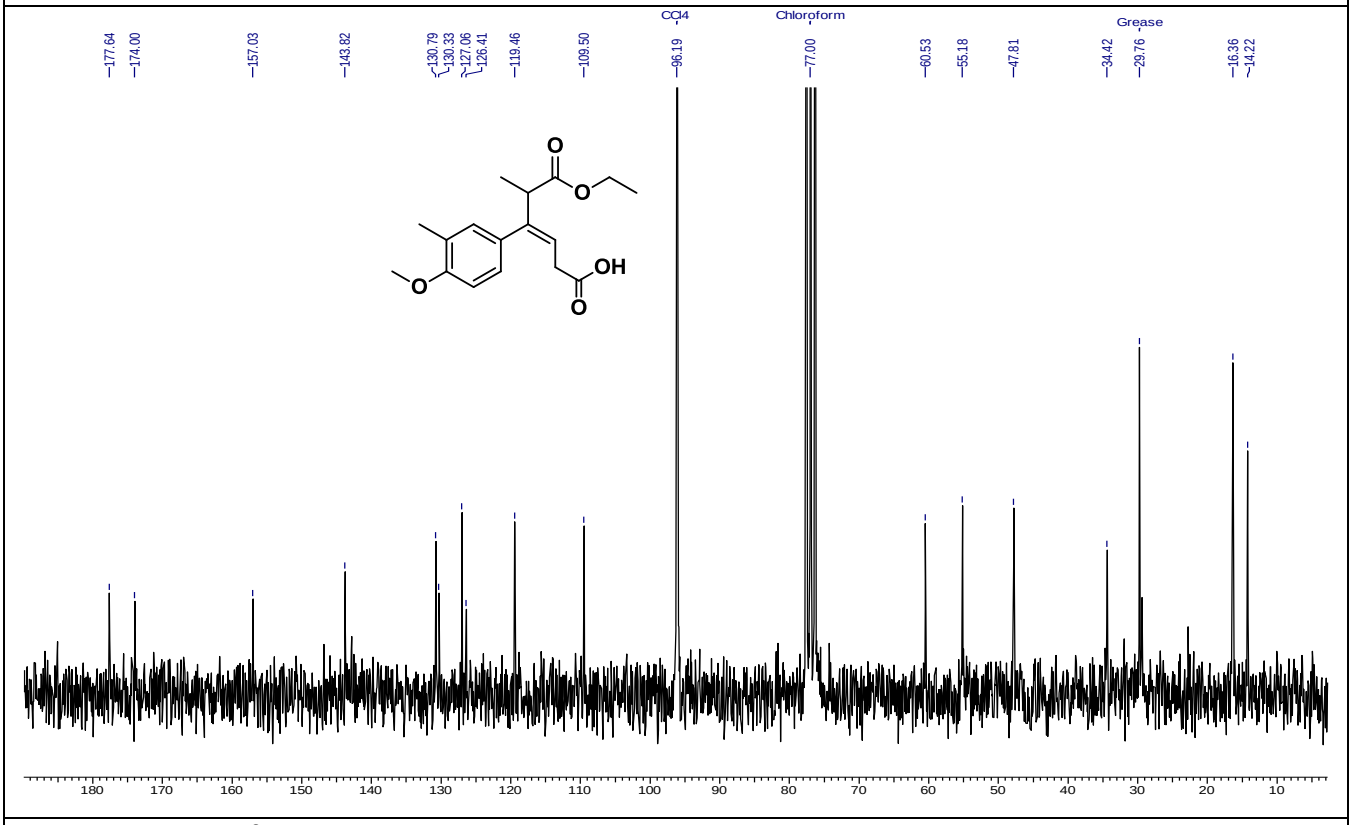
DEPT spectrum of compound **23** ($CDCl_3$+CCl_4, 50 MHz)



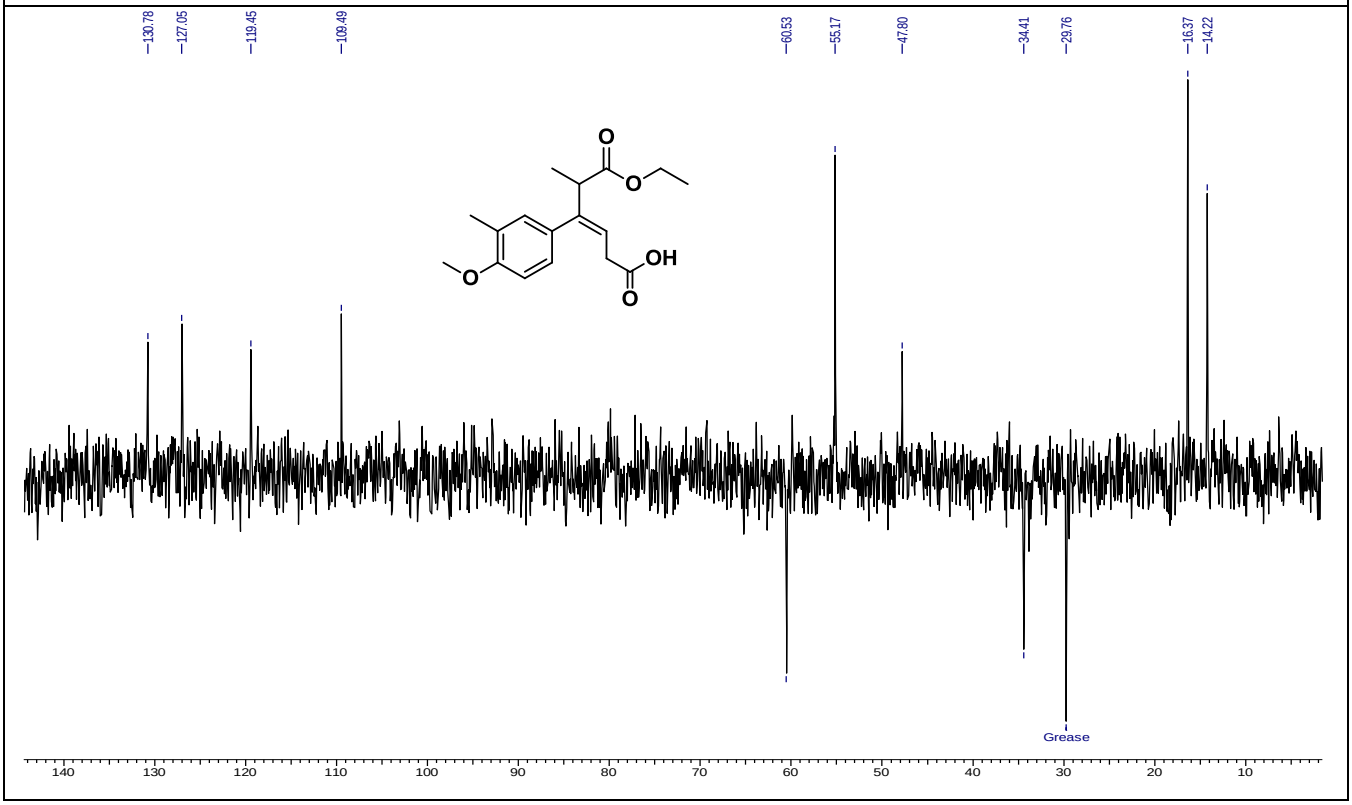
^{1}H NMR spectrum of compound **20** ($CDCl_3$+CCl_4, 200 MHz)



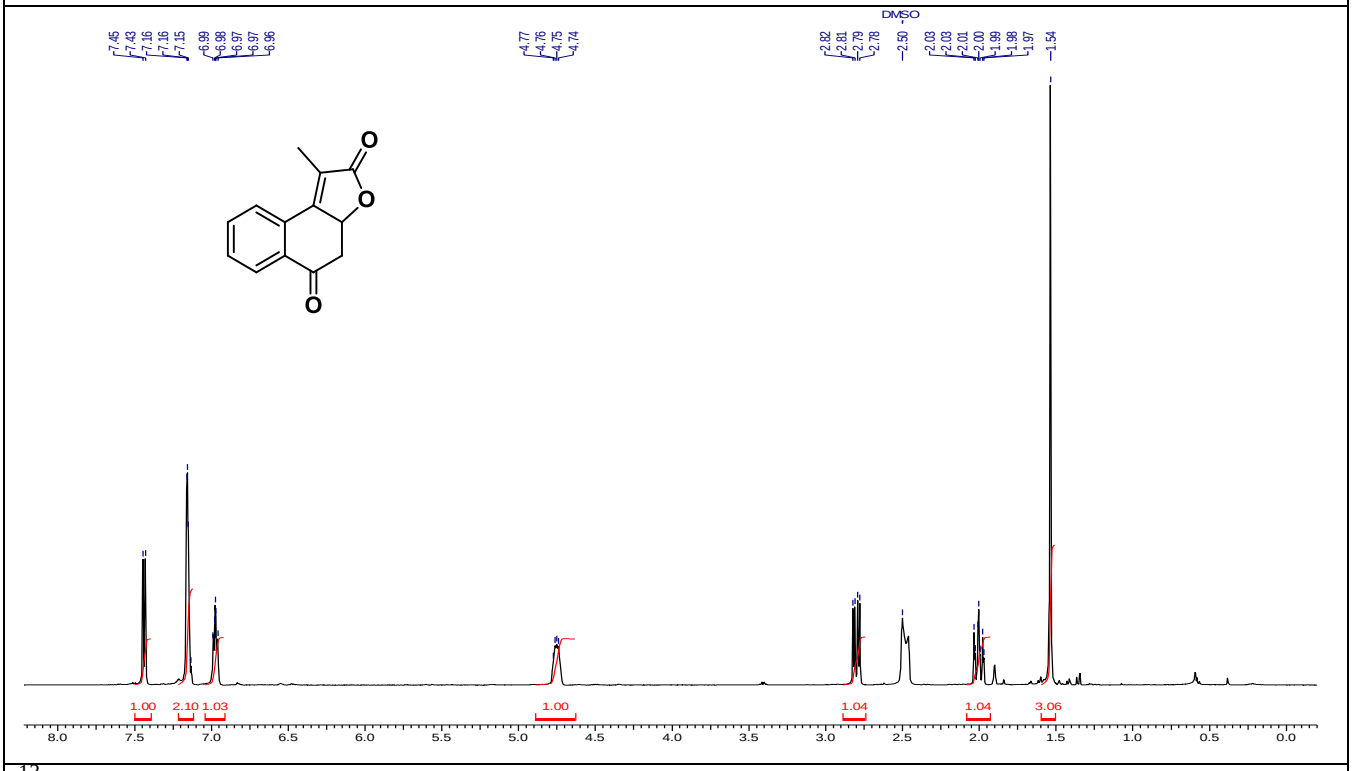
^{13}C NMR spectrum of compound **20** ($CDCl_3$+CCl_4, 50 MHz)



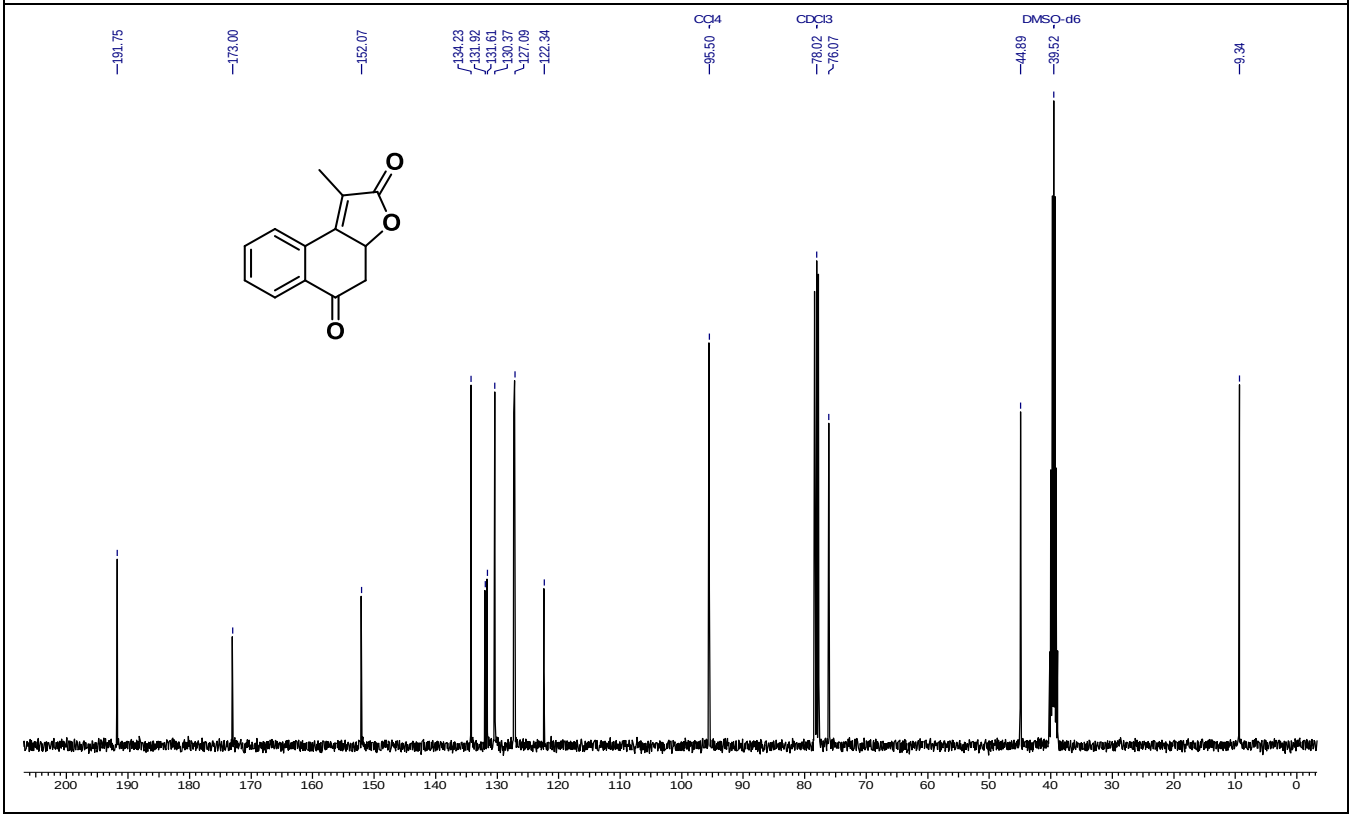
DEPT spectrum of compound **20** ($CDCl_3$+CCl_4, 50 MHz)



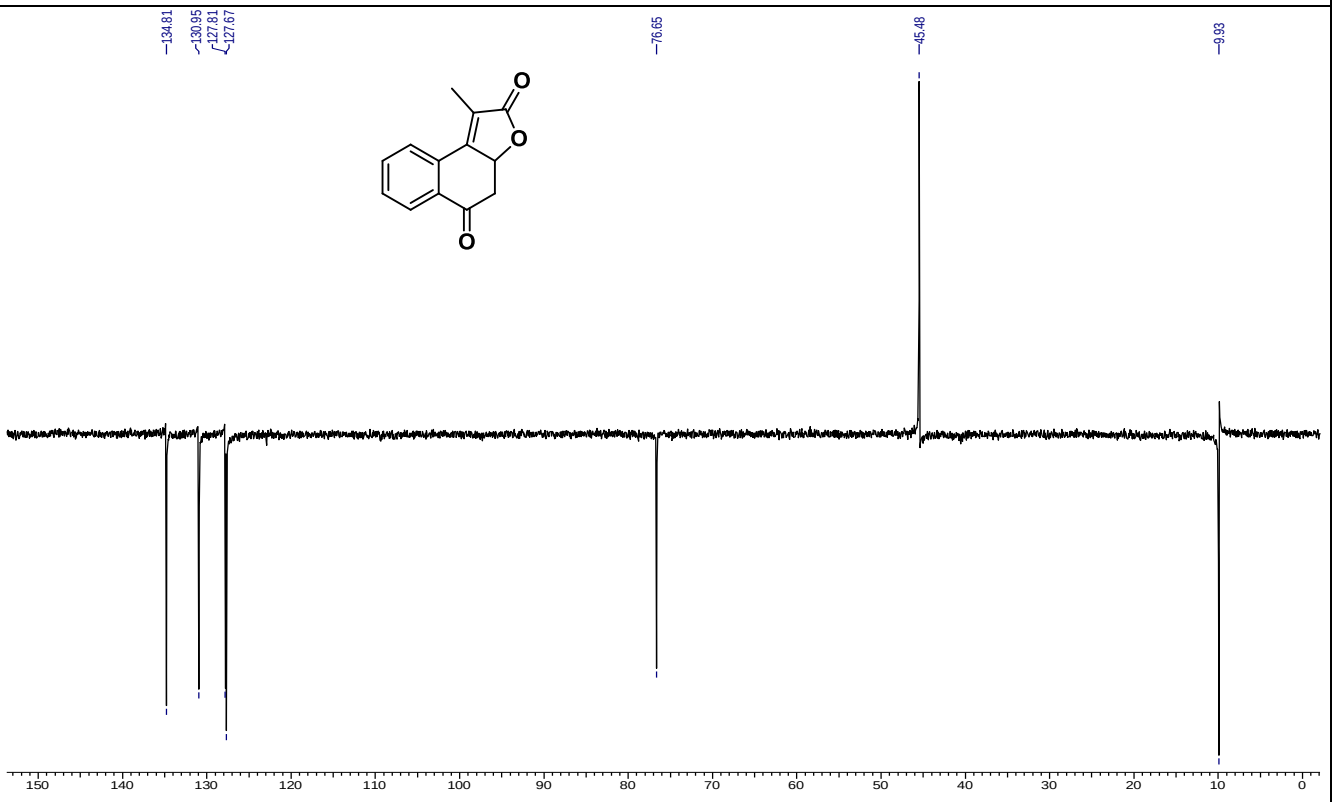
^{1}H NMR spectrum of compound **8** ($CDCl_3$+ DMSO–d_6+CCl_4, 500 MHz)



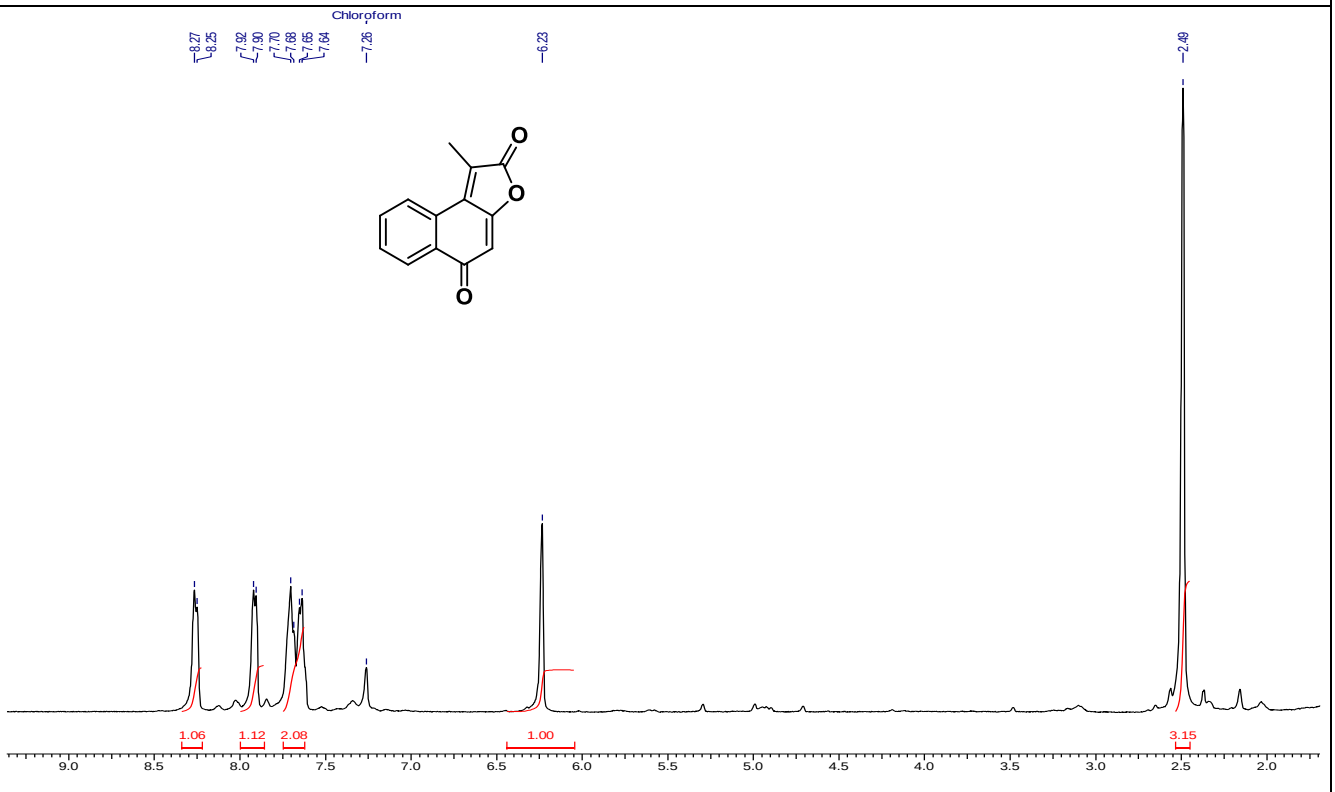
^{13}C NMR spectrum of compound **8** ($CDCl_3$+ DMSO–d_6+CCl_4, 125 MHz)



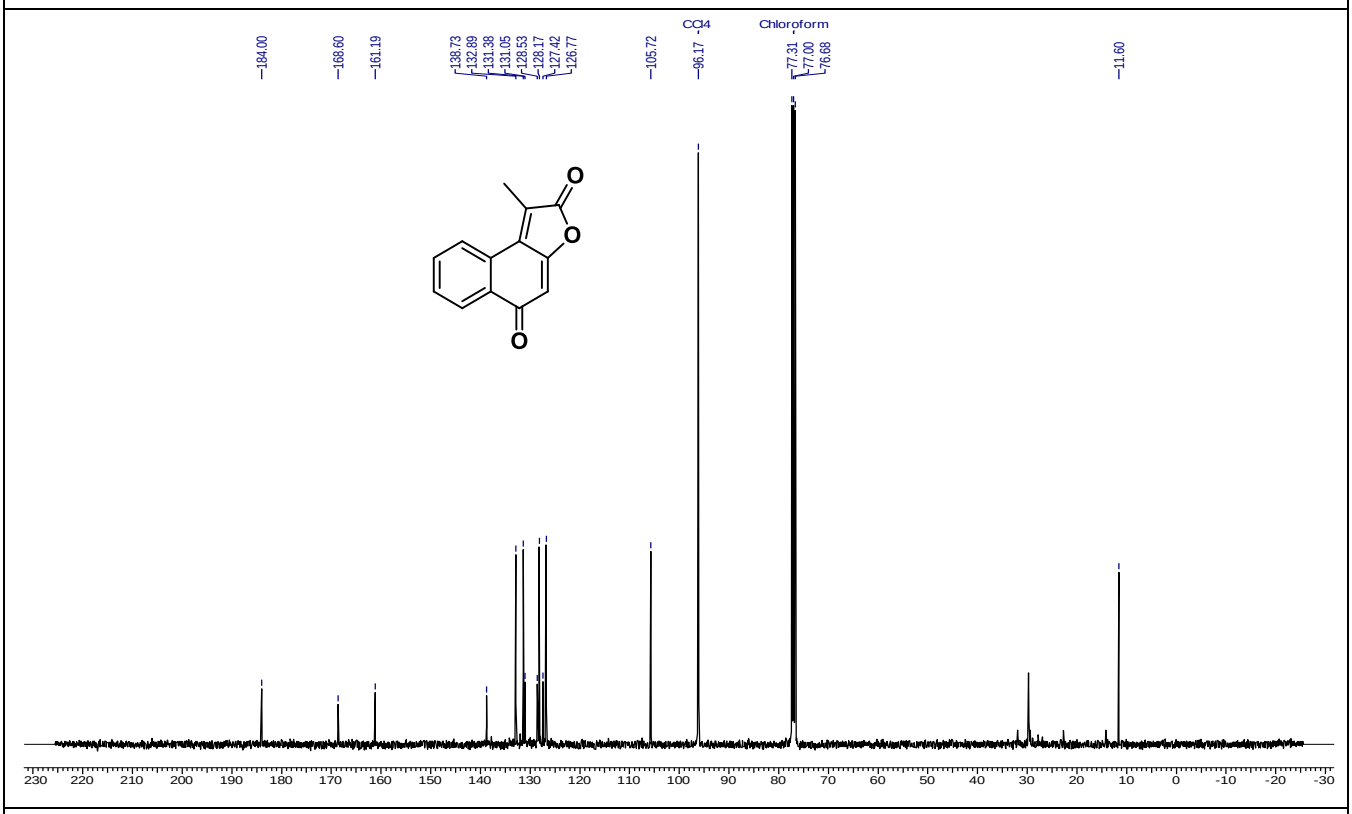
DEPT spectrum of compound **8** ($CDCl_3$+ DMSO–d_6+CCl_4, 125 MHz)



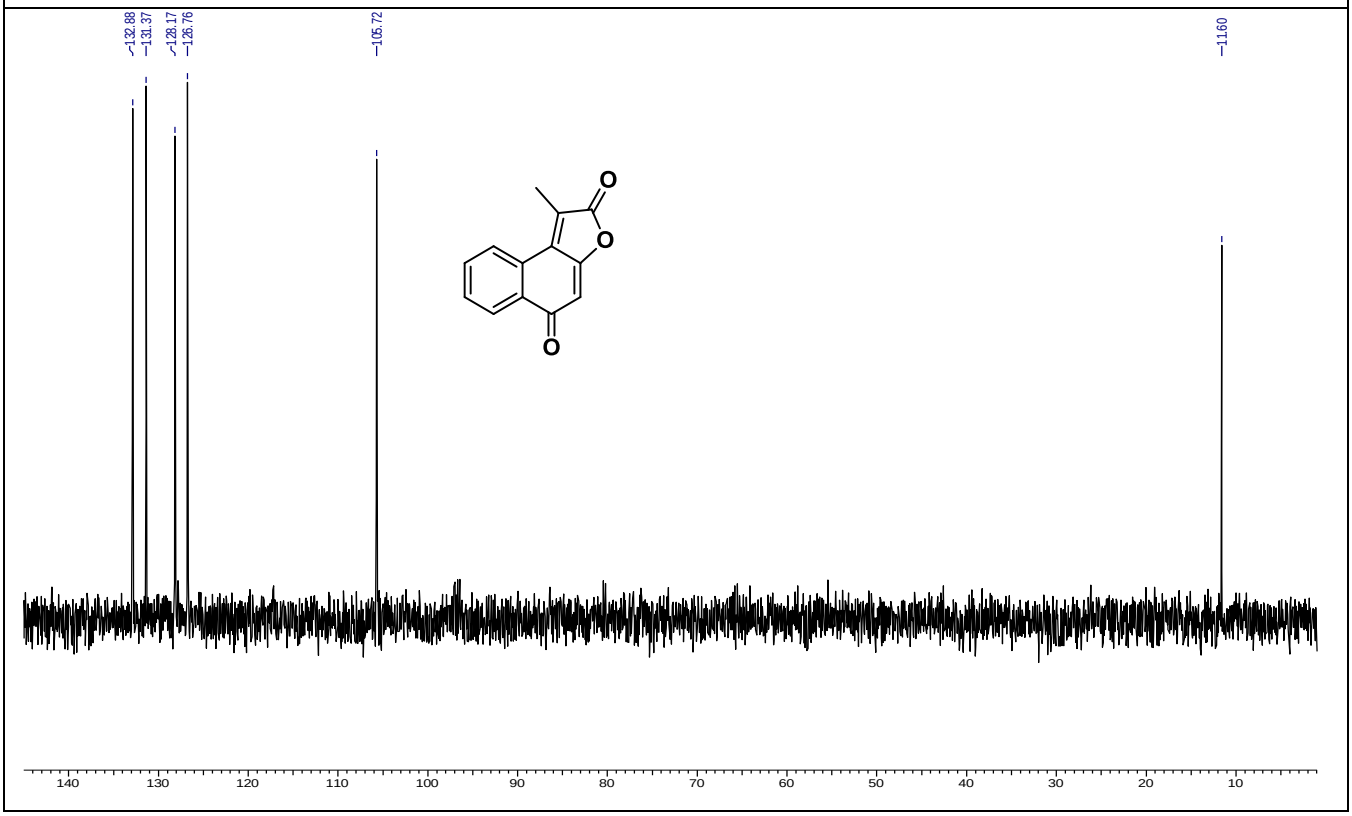
^{1}H NMR spectrum of compound **10** ($CDCl_3$+CCl_4, 200 MHz)



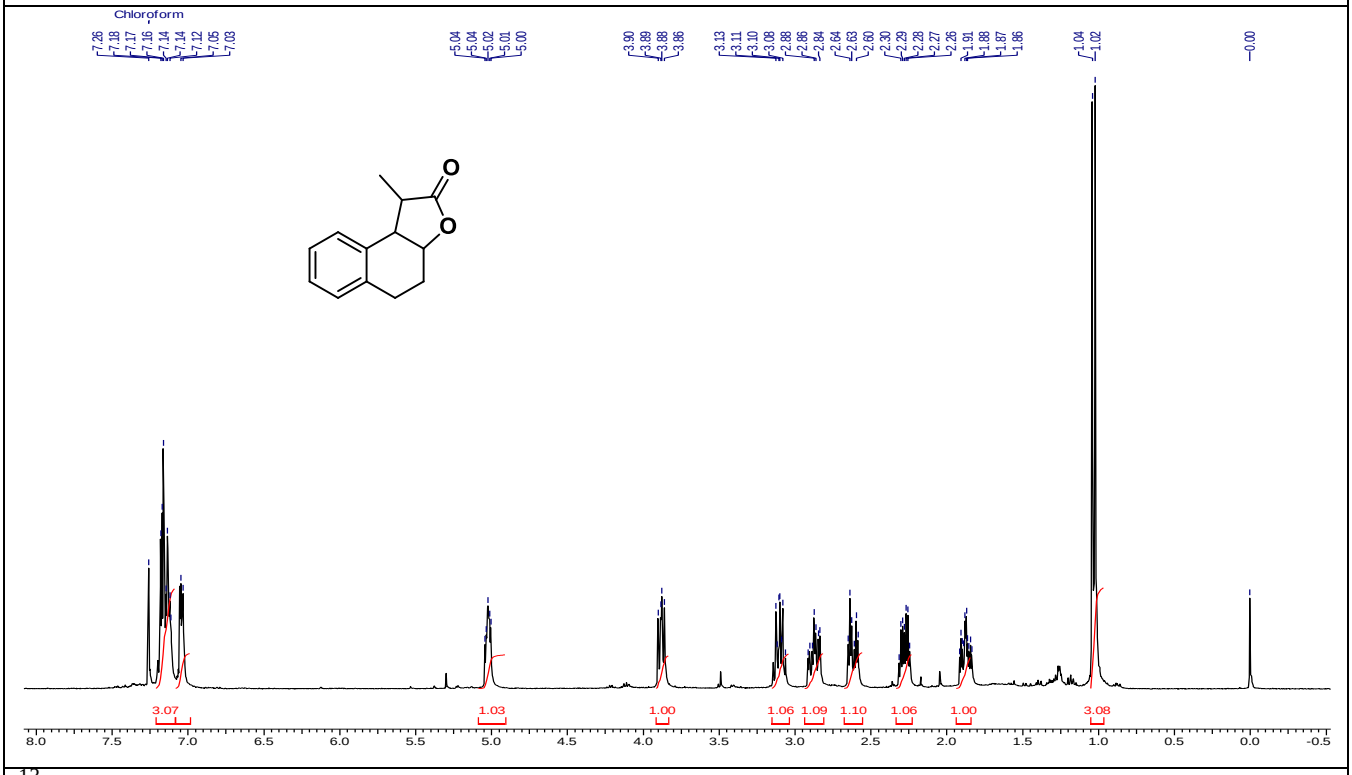
^{13}C NMR spectrum of compound **10** ($CDCl_3$+CCl_4, 50 MHz)



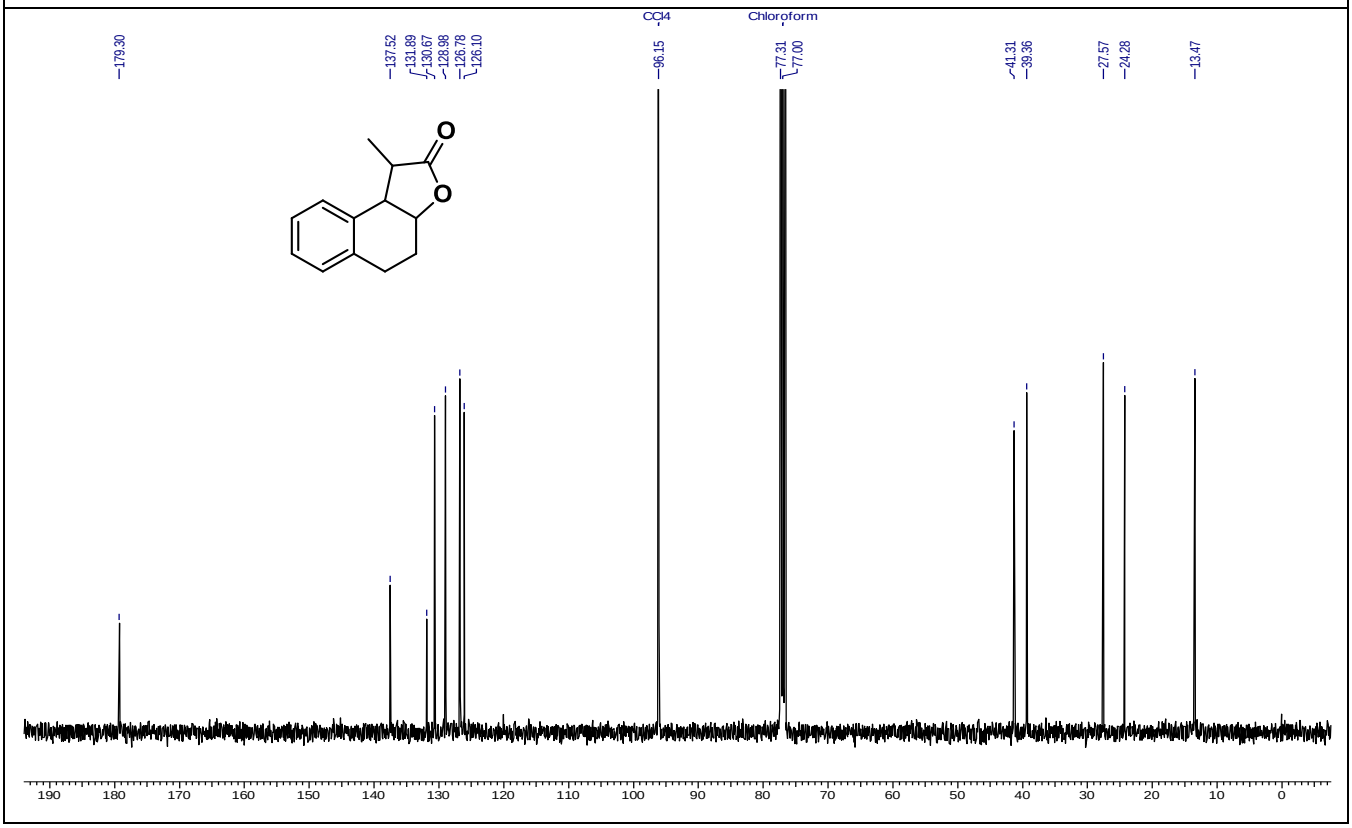
DEPT spectrum of compound **10** ($CDCl_3$+CCl_4, 50 MHz)



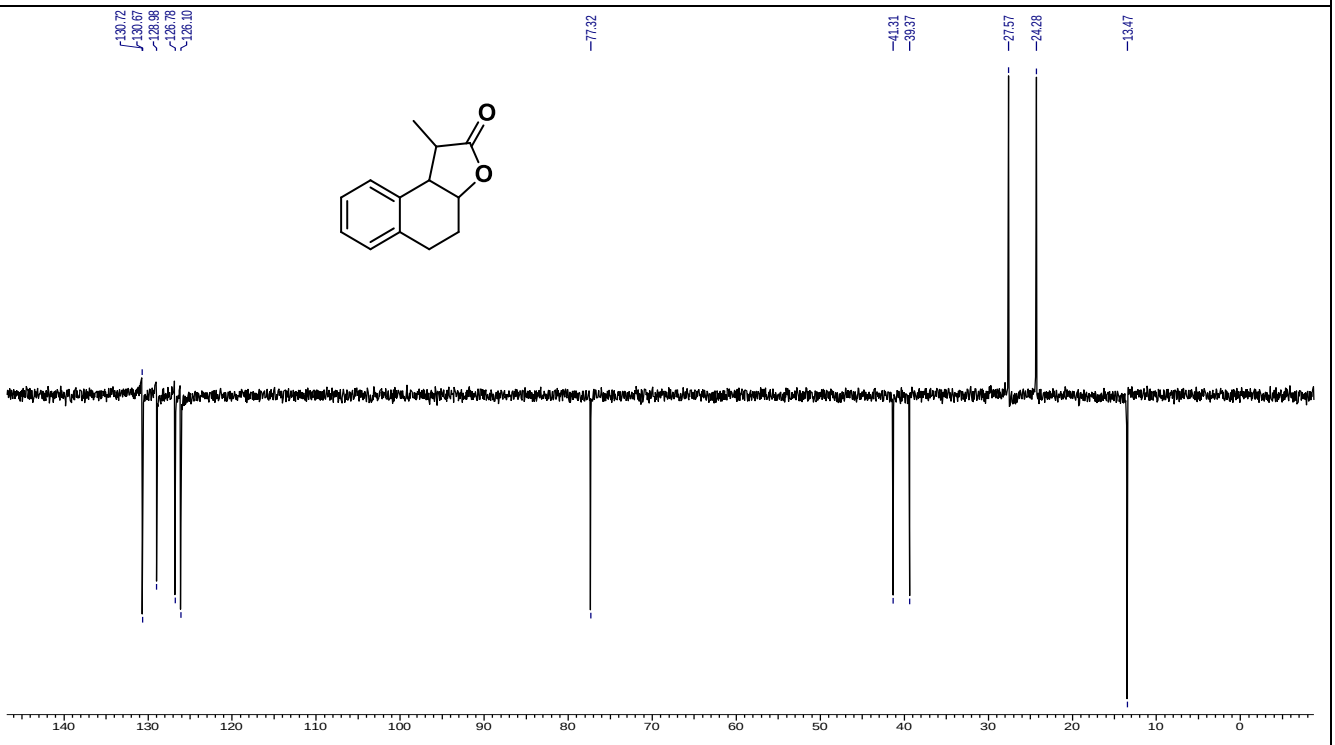
^{1}H NMR spectrum of compound **12** ($CDCl_3$, 400 MHz)



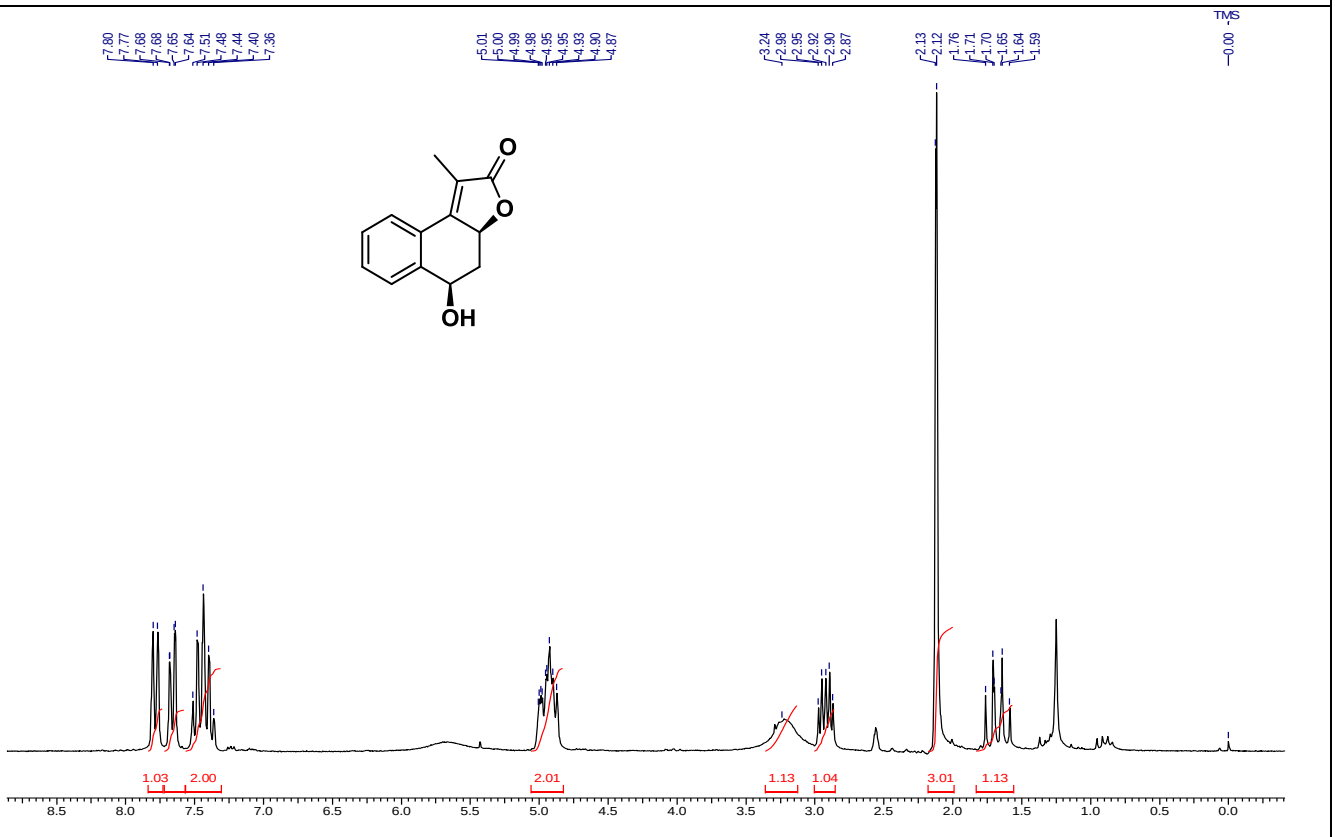
^{13}C NMR spectrum of compound **12** ($CDCl_3$+CCl_4, 100 MHz)



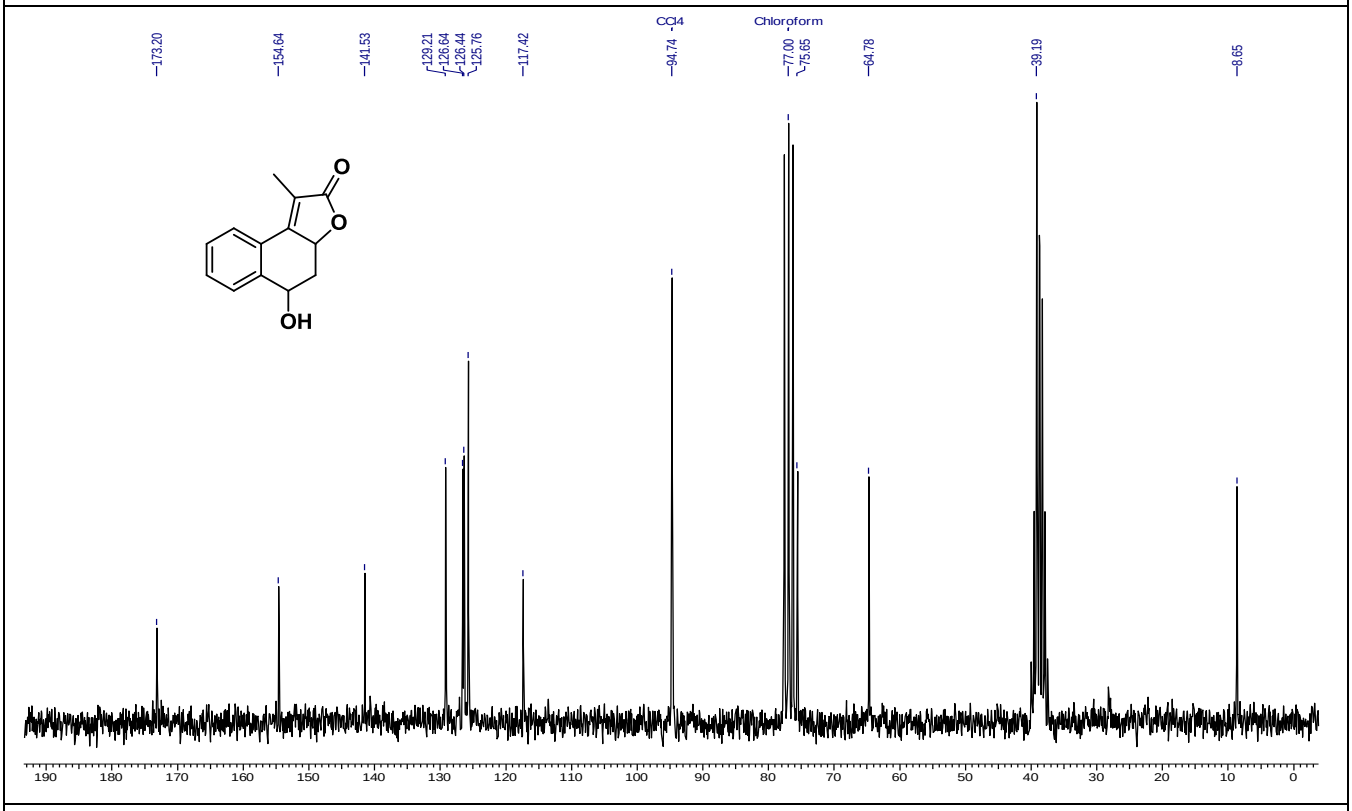
DEPT spectrum of compound **12** ($CDCl_3$+CCl_4, 100 MHz)



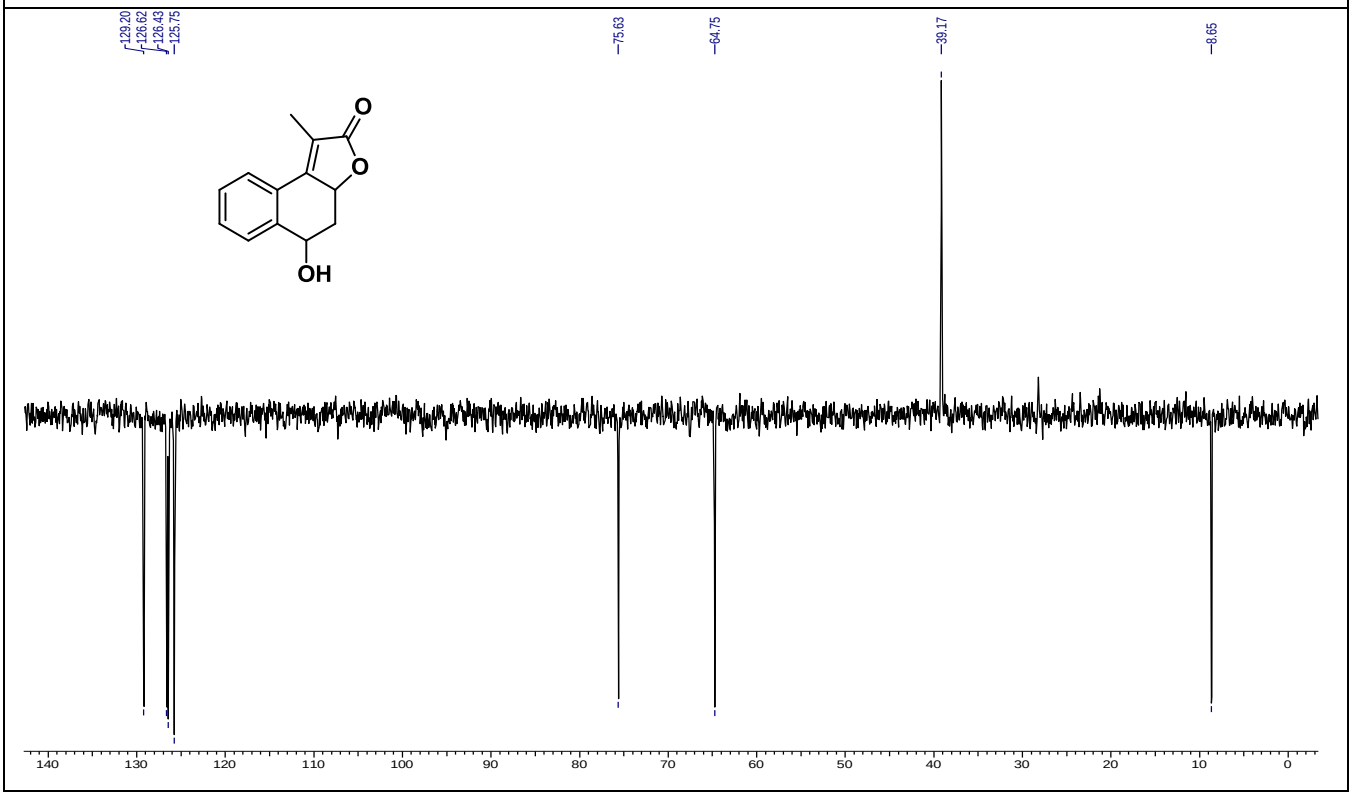
^{1}H NMR spectrum of compound **13** ($CDCl_3$+CCl_4, 200 MHz)



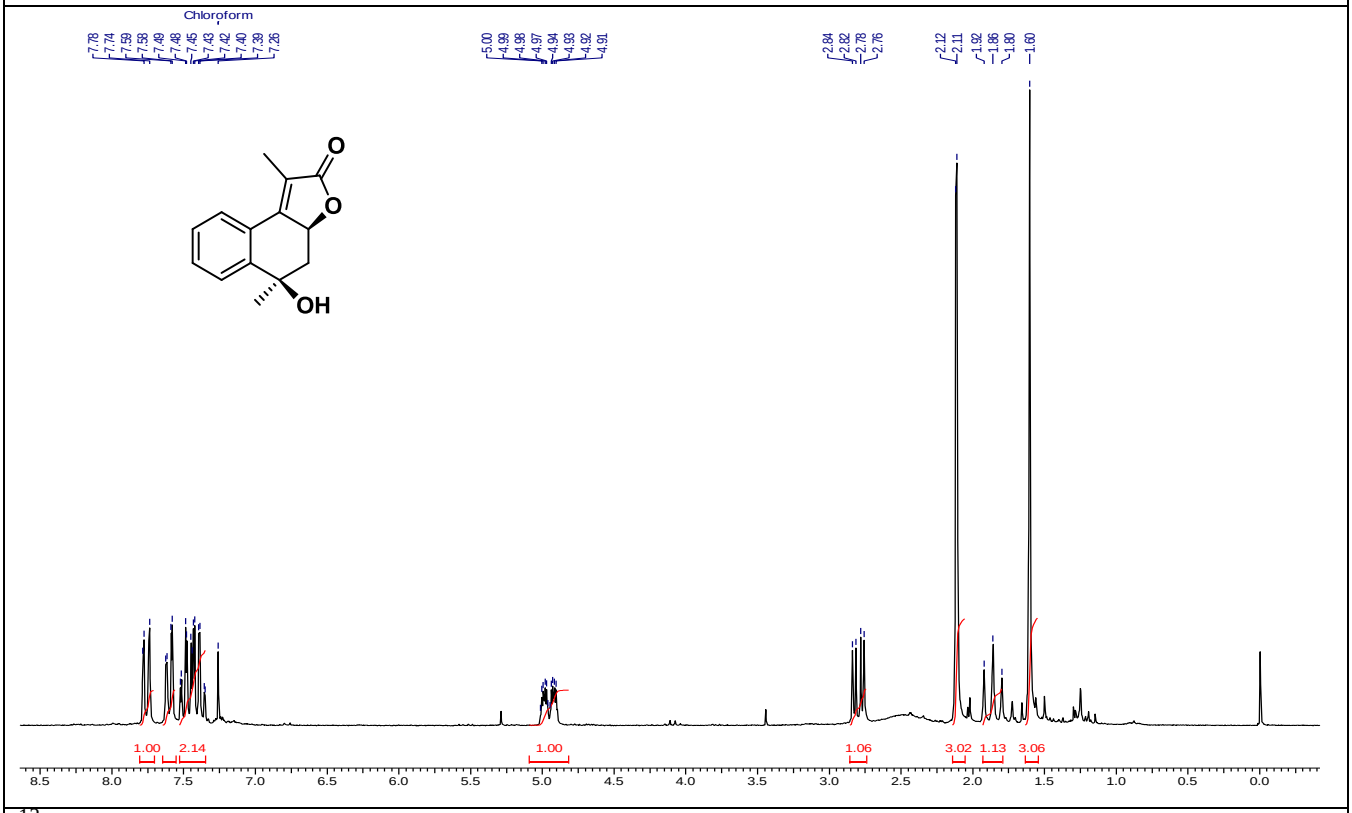
^{13}C NMR spectrum of compound **13** ($CDCl_3$+ DMSO–d_6+CCl_4 50 MHz)



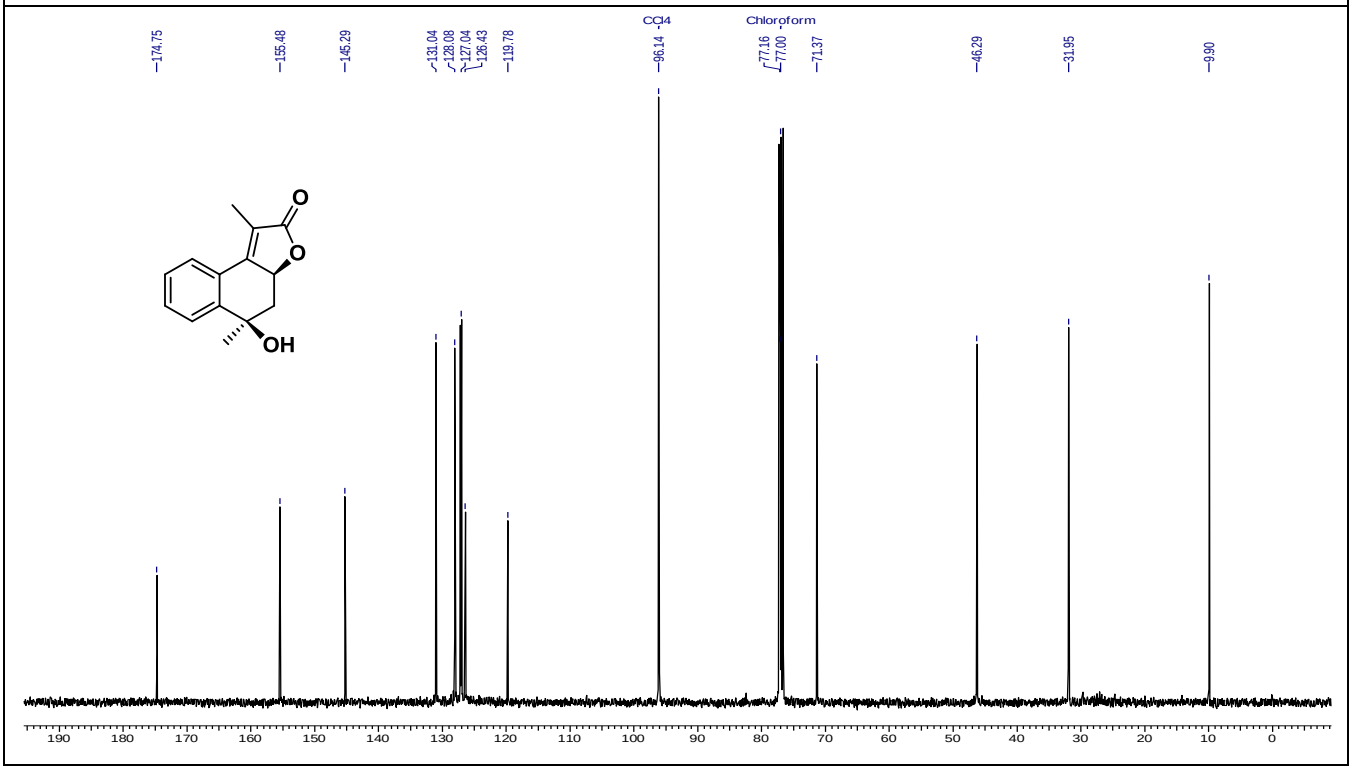
DEPT spectrum of compound **13** ($CDCl_3$+ DMSO–d_6+CCl_4, 50 MHz)



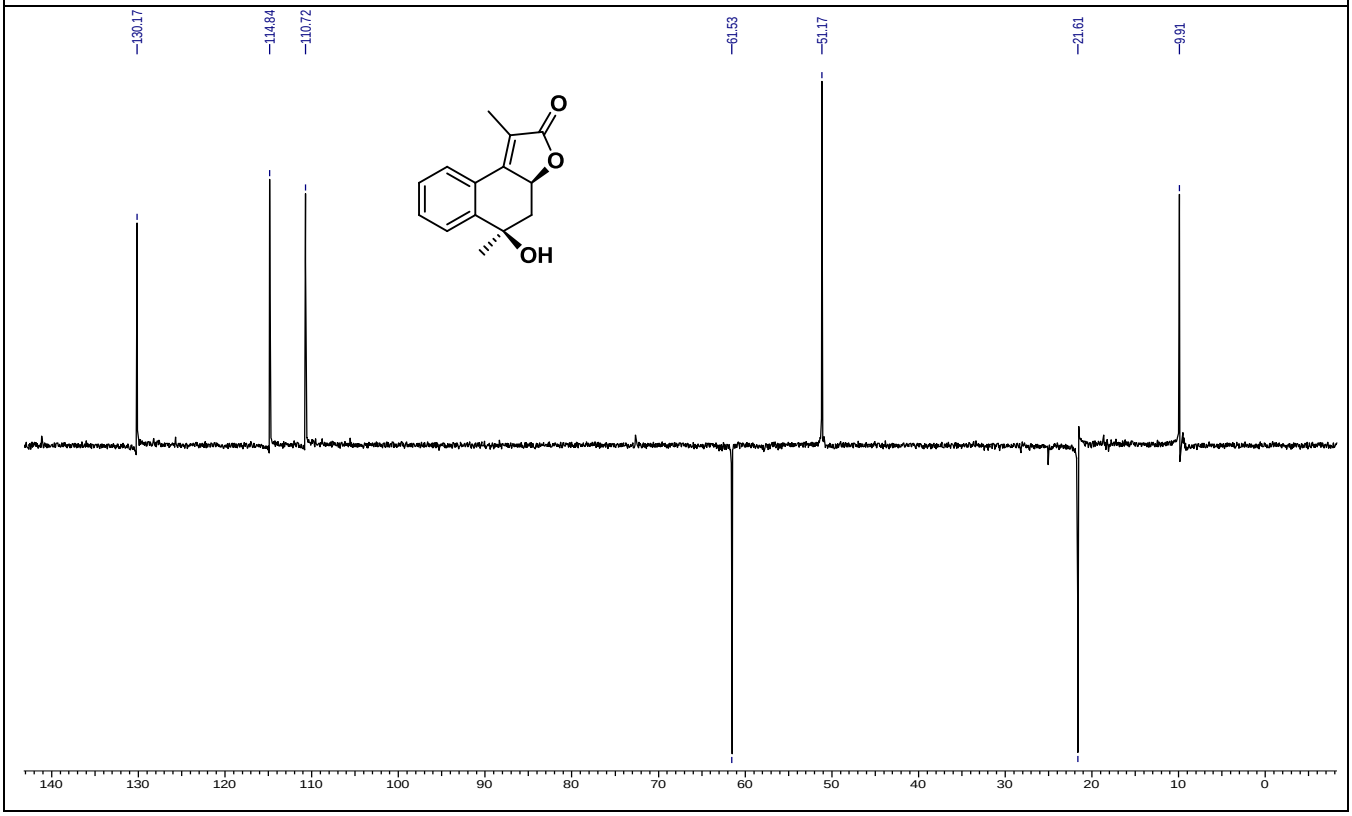
^{1}H NMR spectrum of compound **14** ($CDCl_3$+CCl_4, 200 MHz)



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



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



1.2.6. References:

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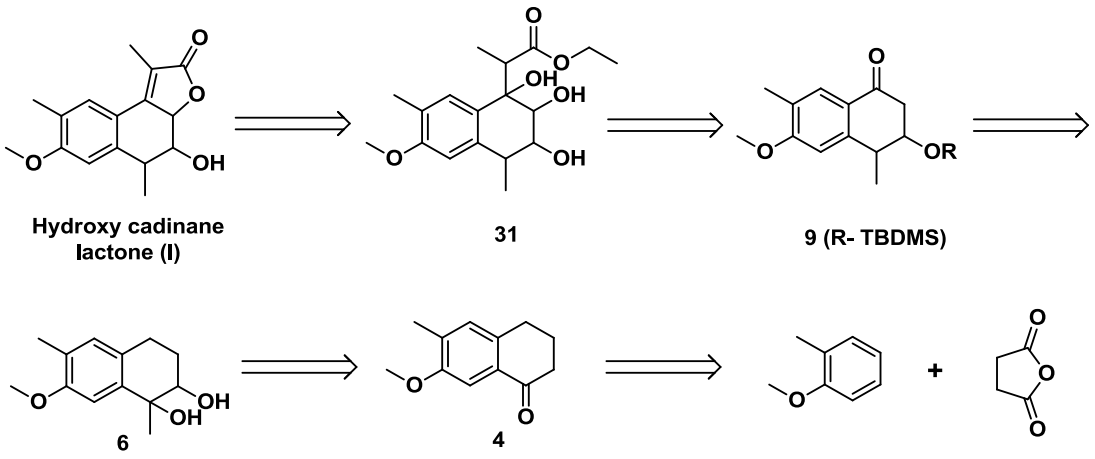
1.3.1. Present work

1.3.1.1. Objective

Although a few syntheses of aromatic cadinane lactones are known, the total synthesis of hydroxy cadinane lactones (**I**) *viz*– vallapin, vallapianin and heritianin is not reported in literature. They are sesquiterpene lactones which belong to cadinane class, contain unusual oxygenation pattern, an aromatic ring, *α*, *β*–unsaturated *γ*–lactone moiety and secondary hydroxy group present at alpha position to the butenolide ring junction.[1] Considering these extraordinary structural features the retrosynthetic analysis was planned (**Scheme–1**).

1.3.1.2. Retrosynthetic analysis:



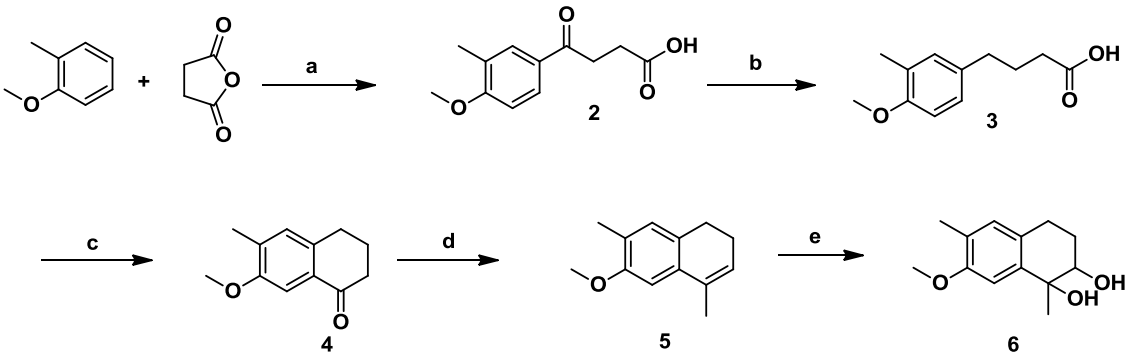
Scheme–1: Retrosynthetic analysis

The hydroxy cadinane lactone framework (**I**) can be synthesized from ester **31** by acid catalyzed butenolide ring formation, which could be obtained from compound **9** by Reformatsky reaction, subsequent elimination of the resulting tertiary hydroxy group, followed by osmium tetroxide mediated dihydroxylation reaction. The compound **9** could be obtained from the diol **6** by benzylic dehydroxylation reaction followed by hydrogenolysis of benzylic hydroxy group, further protection of the resulting secondary hydroxy group and CrO_3 mediated oxidation in presence of AcOH. The diol **6** could be prepared by one carbon Grignard reaction, elimination and subsequent dihydroxylation on tetralone **4**. The compound **4** could be synthesized from Friedal–Craft's acylation reaction between *o*–cresol methyl ether and succinic anhydride,

followed by Clemmenson's reduction of benzylic carbonyl group and trifluoroacetic acid/ trifluoroacetic anhydride mediated cyclisation. The *o*–cresol methyl ether and succinic anhydride are easily available inexpensive starting materials.

1.3.2. Synthesis of hydroxy cadinane lactone framework

The protocol for preparation of tetralone **4** was earlier reported by this group.[2] Accordingly *o*–cresol methyl ether and succinic anhydride were treated under Friedal–Craft's acylation reaction conditions in presence of $AlCl_3$, furnished the ketoacid **2** in 89% yield. The ketoacid **2** was further refluxed under Clemmenson's reduction conditions in presence of zinc amalgm, conc. HCl and toluene, for 24 h to produce acid **3** in 84% yield. The acid **3** was further cyclised in presence of trifluoroacetic acid and trifluoroacetic anhydride furnished the tetralone **4** in 84% yield and treated under conditions of one carbon Grignard reaction and subsequent acidic workup furnished compound **5** as per the literature reports (**Scheme–2**).[2c]

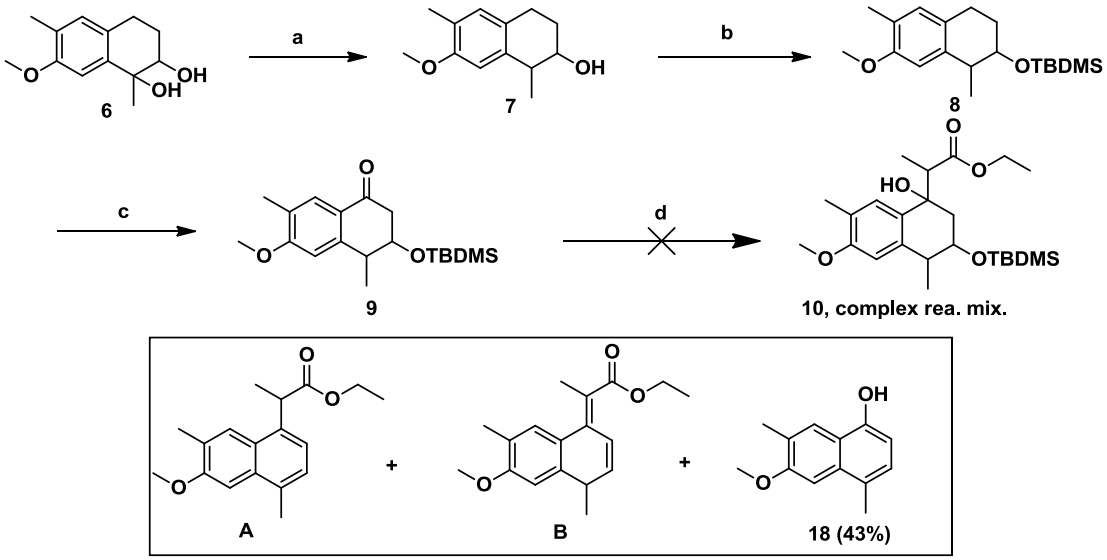


Scheme–2

Reagents and conditions:– *(a) $AlCl_3$, DCM, 0 ^oC– RT, 5 h, 89%; (b) Zn (Hg), conc. HCl, H_2O, toluene, reflux, 24 h, 84%; (c) TFA, TFAA, 0 ^oC– RT, 4 h, 84%; (d) i) Mg, MeI, diethyl ether, 0 ^oC– RT, 5 h, ii) 6M H_2SO_4, overnight, 78%; (e) OsO_4, NMO, acetone: water (3:1), RT, 6 h, 92%.*

Compound **5** was the reported intermediate for synthesis of heritol from this group.[2a] The double bond in **5** was dihydroxylated by means of OsO_4 mediated dihydroxylation reaction in presence of NMO acting as a co–oxidant to afford diol **6** in 92% yield. The formation of polar diol **6** from nonpolar compound **5** was easily detectable on TLC. Presence of absorption frequency at 3350 cm^{-1}, characteristic of secondary hydroxyl group in it's IR suggested the

formation of the proposed diol **6**. Presence of a downfield multiplet over the range at δ 3.81–3.78 for one proton (*CH–OH*) in ^{1}H NMR and resonance for the benzylic quaternary carbon attached to hydroxy group at δ 72.1 in ^{13}C NMR spectrum confirmed the formation of diol **6**.



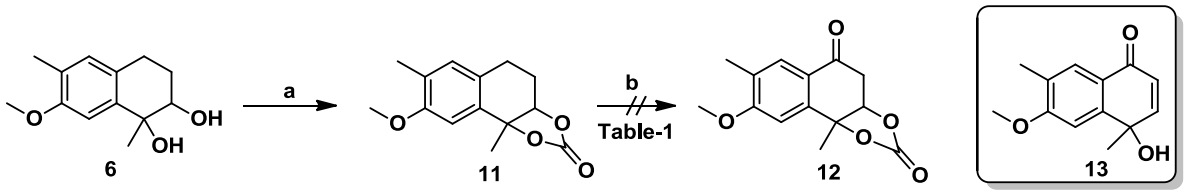
Scheme–3

Reagents and conditions: *(a) Et_3SiH, BF_3OEt_2, DCM, 0 ^{o}C– RT, 5 h, 82%; (b) t–Butydimethylsilyl chloride, imidazole, dichloromethane, DMAP (cat.), RT, 90%; (c)* CrO_3*, AcOH, 5 ^{o}C– RT, 3 h, 59%; (d) Ethyl 2–bromopropionate, Zn, I_2, diethyl ether, 40 ^{o}C, 5 h.*

The diol **6** was treated with Et_3SiH in presence of BF_3OEt_2 in order to remove benzylic hydroxyl group and to produce compound **7** in 82% yield (**Scheme–3**). The formation of compound **7** was confirmed with multiplet in ^{1}H–NMR spectrum at δ 2.06–1.86 corresponded to one proton (*Ar–CH–CH_3*) present at benzylic position. The compound **7** was formed as a diastereomeric mixture in the ratio 6:4 which is recognisable from ^{1}H–NMR and ^{13}C–NMR spectral analysis. The secondary hydroxyl group present in compound **7** was protected as it's TBDMS ether by treatment with TBDMS–Cl and imidazole, to furnish compound **8** in 90% yield. Appearance of two singlets in ^{1}H NMR spectrum at δ 0.95 and δ 0.12 for nine and six protons respectively for –OTBDMS protection confirmed the formation of compound **8**, which was subjected to benzylic oxidation in presence of CrO_3 and AcOH to deliver compound **9** in 59% yield (*dr*: 6:4). Presence of absorption at 1710 cm^{-1} in it's IR spectrum and a downfield

shift in aromatic region at δ (7.76) for one proton in ^{1}H NMR spectrum suggested the desired transformation.

For the purpose of butenolide formation compound **9** was refluxed under Reformatsky reaction, in presence of ethyl 2–bromopropionate and Zn metal dust. This transformation ended up in complex reaction mixture, as after generation of tertiary hydroxyl group system became prone for elimination and hence aromatization. Hence, instead of desired product **10**, number of side products formed in this reaction, constitute an inseparable complex reaction mixture of compounds **A**, **B** and **18** (**Scheme–3**) (A and B are tentatively assigned). Out of which only product **18** could be separated as a pure compound in 43% yield.[3]



Scheme–4

Reagents and conditions:– *(a) Triphosgene, Et_3N, DCM, 5 ^oC– RT, 2 h, 96%; (b) Table–1*

It was decided to utilize the diol **6** for further synthetic strategy and it was protected as carbonate derivativein the presence of triphosgene and triethyl amine at 5 ^{o}C to RT, yielded diol protected as it's carbonate **11** in 96% yield (**Scheme–4**).[4] The presence of IR absorption peak at ν_{max}: 1796 cm^{-1} suggested required conversion. The ^{1}H NMR spectrum revealed a downfield triplet of a proton attached to a secondary hydroxy group at δ 4.72 (J = 4.93 Hz). In ^{13}C NMR resonance of a singlet at δ 157.0 found to be in agreement with the said transformation.

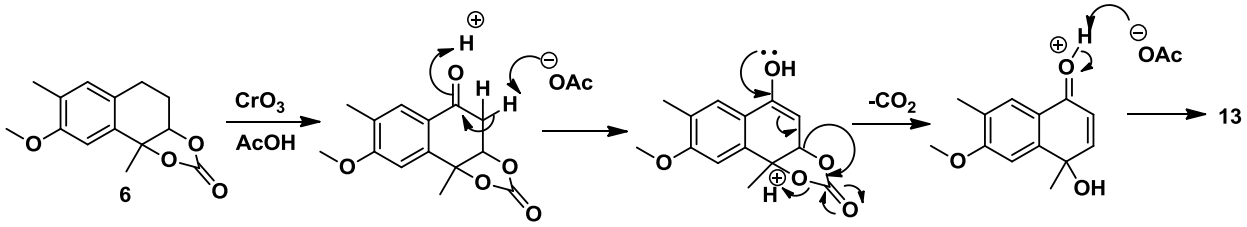
The next job was to introduce a carbonyl group at benzylic position, for that purpose carbonate **11** was then subjected under various oxidation reaction conditions at highly reactive benzylic methylene carbon. In the literature various oxidation processes were known for such transformation, were tried (**Table–1**).[5a–g] Starting material was recovered unreacted upon treatment of compound **11** with IBX, Oxone and MnO_2 (entry no.–1, 2 and 3). When compound **11** was treated with SeO_2 and DDQ, formation of complex reaction mixture was observed. In case of reaction of compound **11** with DDQ in presence of AcOH at RT aromatization along with number of other unidentified products as an inseparable mixture were formed and under

refluxing conditions decomposition was observed. Thus, carbonate **11** on treatment with CrO_3 in presence of AcOH at 5 ^oC to RT furnished the compound **12** in 52% isolated yield as a result of oxidation, elimination and deprotection.

Table–1

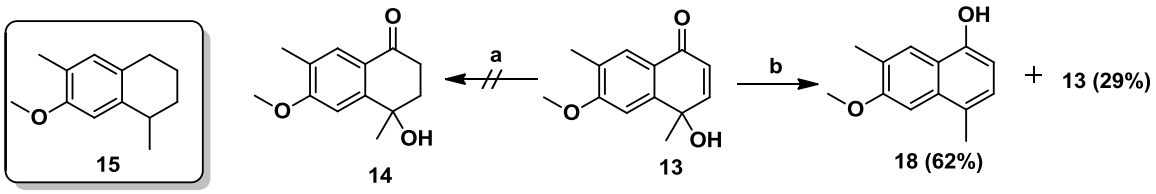
Sr. No.	Reagents for benzylic oxidation	Conditions	Product and Yield (%)
1	IBX, fluorobenzene:DMSO (2:1) IBX, EtOAc	85 ^oC, 12 h Reflux	SM SM
2	Oxone, KBr, nitromethane	50 ^oC, 24 h	SM
3	MnO_2, $KMnO_4$ DCM,	0 ^oC to RT, 24 h	SM
4	DDQ, dioxane	Reflux, 8 h	Complex reaction mixture
5	SeO_2, dioxane	Reflux, 12 h	Complex reaction mixture
6	DDQ, AcOH: H_2O DDQ, AcOH: H_2O	RT, 2 h Reflux, 0.5 h	Aromatisation Decomposition
7	CrO_3 (1.5 eq.), AcOH CrO_3 (3.5 eq.), AcOH CrO_3 (4.5 eq.), AcOH	5 ^oC to RT, 4 to 6h 5 ^oC to RT, 4 to 6h 5 ^oC to RT, 4 to 6h	**13** (12%) + **11** (45%) **13** (22%) + **11** (30%) **13** (52%)

The IR spectrum of the product **13** indicated the presence of the enone functionality by exhibiting absorptions at ν_{max}: 1710 cm^{-1} and 1624 cm^{-1}. It's ^1H NMR spectrum exhibited two doublets in the olefinic region at δ 6.92 (J = 10.23 Hz) and δ 6.18 (J = 10.23 Hz) which were assigned to the two conjugated olefinic protons (*O=C*<u>*H*</u>*=C*<u>*H*</u>*–*) with carbonyl group. The ^{13}C NMR spectrum showed two resonances at δ 152.4 and δ 128.6 for olefinic carbons (*–*<u>*C*</u>*H=*<u>*C*</u>*H–*) and also revealed five quaternary singlets at δ 162.0, 147.9, 127.2, 122.1 and 68.3, attributed to the five quaternary carbon atoms and one at δ 184.1, attributed to the carbonyl carbon. This suggested that the transformation went through– i) oxidation at benzylic carbon, ii) elimination



Scheme–5: Mechanism for formation of compound 13

of proton under acidic conditions and iii) decarboxylation. Hence, formation of compound **13** after subsequent three steps (**Scheme–5**) was observed. This was further confirmed by it's mass spectrum, which exhibited a peak of $[M+Na]^+$ at (*m/z*): 241.

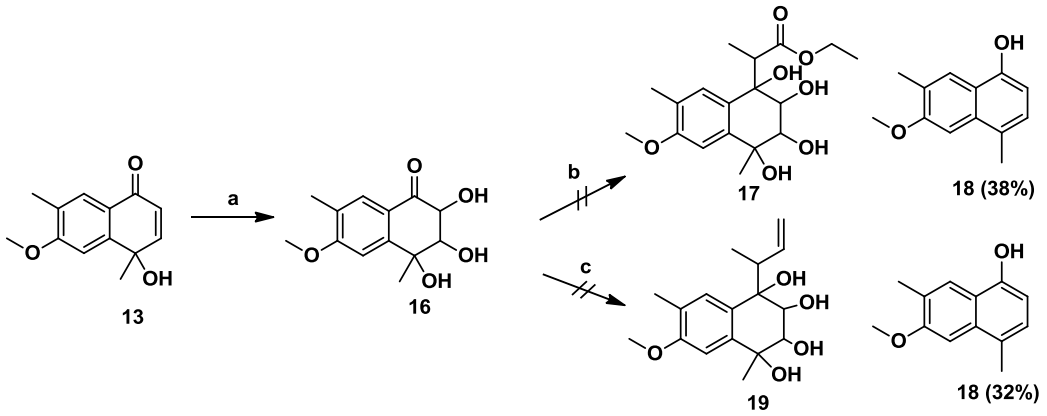


Scheme–6

Reagents and conditions: *(a) Pd/C (1.1 equiv.), H_2 (60 psi), EtOH, 25 ^oC, 4 h, 78%; (b) Pd/C (0.3 equiv.), H_2 (1–3 psi), EtOH, 25 ^oC, 3 h.*

Instead of desired compound **12**, formation of compound **13** was confirmed hence, next synthetic strategy was decided to reduce the double bond present in compound **13** (**Scheme–6**). Under hydroganation conditions using catalyst Pd/C (10 mol%), formation of product **15** was observed with comlplete reduction. When Pd/C (0.3 mol%) was used, the phenolic compound **18** was observed as a major product along with recovery of the starting material compound **13**.

An hydroxyl group absorption at 3396 cm^{-1} in it's IR spectrum and an aromatic singlet at δ 157.1 in it's ^{13}C NMR spectrum suggested the phenolic nature of the intermediate **18**. Further, ^1H NMR spectrum revealed resonances at δ 7.93 and δ 7.06 (s), integrated for one proton each, along with δ 7.04 (d, J = 7.71 Hz) and δ 6.54 (d, J = 7.71 Hz) for one proton each was assigned to the aromatic protons. Also, singlet at δ 3.97 (3H) was assigned to the methoxy group, two singlets at δ 2.56 and δ 2.40 were assigned for two methyl groups in it's ^1H NMR spectrum. The structure of phenol **18** was finally confirmed by it's mass spectrum, which exhibited a peak at 234 for $[M+MeOH]^+$.[6]



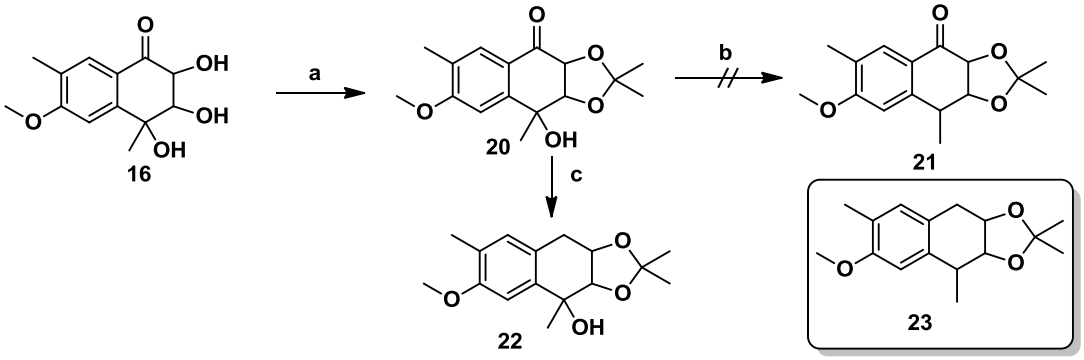
Scheme–7

Reagents and conditions: *(a) OsO_4, NMO, acetone:water (3:1), RT, 8 h, 67%; (b) Ethyl 2–bromopropionate, Zn, I_2, diethyl ether, 40 ^oC, 2 h; (c) Crotyl bromide, Zn, DMF, 0 ^oC– RT, 5 h.*

The compound **13** possess a benzylic carbonyl group with *α*, *β*– unsaturated double bond and a tertiary hydroxyl group present at benzylic position. So, instead of reduction of double bond, it's interconversion to other functional group was decided (**Scheme–7**). The double bond in compound **13** was dihydroxylated by means of Upjohn dihydroxylation reaction in order to assemble a butenolide ring and to generate a secondary hydroxyl group. Thus, compound **13** was subjected to OsO_4 mediated dihyroxylation reaction in presence of NMO, acting as a co–oxidant with acetone: water system (3:1) for 8 h at RT to furnish the highly polar compound **16** in 67% yield. Since the nature of compound **16** was extremely polar, it was purified by performing a simple filter column chromatography. The disappearance of olefinic peaks present in starting compound **13** in ^{1}H–NMR spectrum confirms formation of the compound **16**. The said transformation was also supported by ^{13}C–NMR and DEPT spectrum which exhibited the presence of two signals for two (*CH–OH*) at *δ* 79.7 and *δ* 74.1.

In order to construct the butenolide ring and to prepare compound **17**, the tetralone **16** was subjected to Reformatsky reaction, under reflux conditions in presence of ethyl 2–bromopropionate and active zinc metal (**Scheme–8**). In an another approach, compound **16** was also treated under Barbier reaction conditions in presence of crotyl bromide and zinc metal at RT. Formation of compound **18** was observed under both the reaction conditions instead of

desired products **17** and **19** respectively. The formation of phenolic compound **18** was attributed to the stability of the aromatic system.



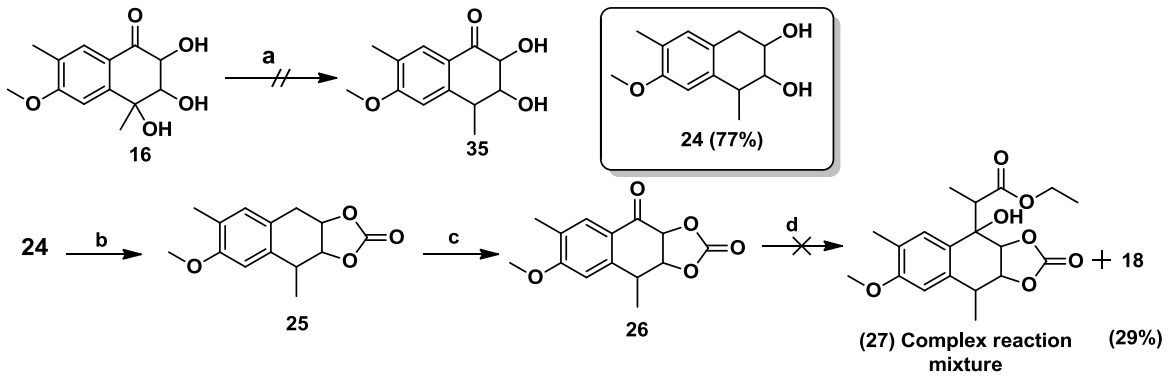
Scheme–8

Reagents and conditions: *(a) 2,2–Dimethoxypropane, p–TSA, DMF, 6 h, 82%; (b) Pd/C (1.1 equiv.), H_2(60 psi), EtOH, RT, 5 h, 62%; (c) Pd/C (0.3 equiv.), H_2 (1–3 psi), EtOH, RT, 3 h, 85%.*

With the purpose of protection of free secondary hydroxyl groups in compound **16**, it was treated with 2,2–dimethoxypropane in presence of *p*–TSA, yielded compound **20** in 82% yield. Removal of tertiary hydroxyl was planned by means of hydrogenolysis at 60 psi and stoichiometric amount of catalyst Pd/C was used, where compound **23** was obtained as a result of reduction of tertiary hydroxy along with the benzylic carbonyl group. When the reaction was carried out under controlled hydrogenolysis using (0.3 mol%) Pd/C and 1–3 psi pressure, it furnished compound **22** in 85% yield with selective reduction of the carbonyl group (**Scheme–8**).

The next task to be performed was the removal of tertiary hydroxy group present at benzylic position in compound **16** using alternative conditions. For this purpose compound **16** was subjected to ionic hydrogenation and was treated with Et_3SiH and BF_3OEt_2 at 0 ^oC to RT for 5 h to yield product in 77% and as a inseparable mixture of diastereomers (*dr*: 60:40). After complete spectral analysis it was proved, this transformation did not provide the desired tetralone product **35**. In this case also, diol **24** was formed as a result of both carbonyl reduction along with the removal of tertiary hydroxy group (**Scheme–9**).

With compound **24** in hand, it's benzylic oxidation was planned by treatment with CrO_3 in presence of AcOH and hence protection of diol was changed from acetonide to carbonate



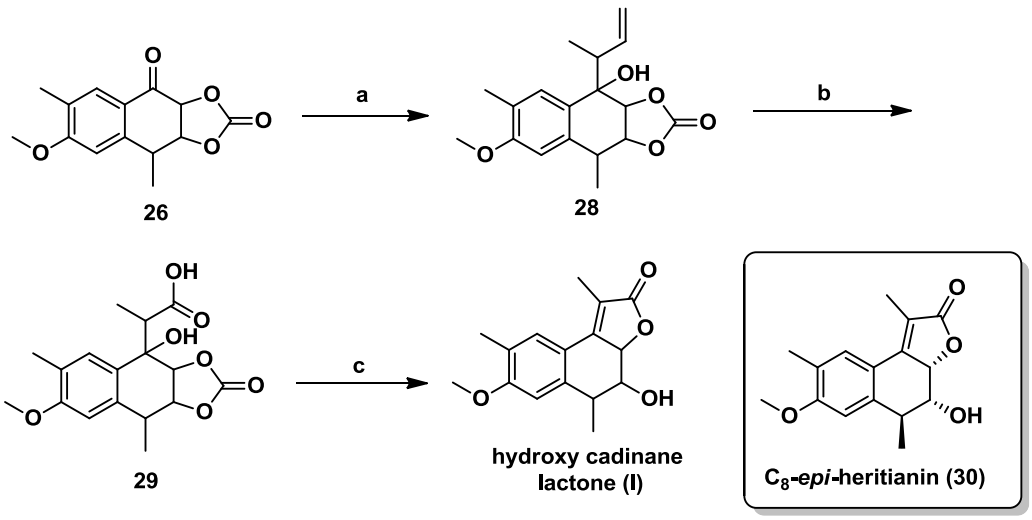
Scheme–9

Reagents and conditions: *(a) Triethylsilyl hydride, BF_3OEt_2, DCM, 0 ^oC–RT, 5 h, 77%; (b) Triphosgene, triethyl amine, DCM, 0 ^oC– RT,2 h, 90%, (dr: 80:20); (c)* CrO_3*, AcOH, 5 ^oC– RT, 3 h, 55%; (d) Ethyl 2–bromopropionate, Zn, I_2, diethyl ether, 40 ^oC, 2 h.*

group. The diol **24** was treated with triphosgene in the presence of triethylamine at 0 ^oC to RT for 5 h, furnished carbonate protected diol **25** in 90% yield as a separable diastereomeric mixture in the ratio (80:20). It's IR spectrum exhibited carbonate absorption at ν_{max}: 1802 cm^{-1} thereby confirming the assigned structure. The ^{13}C NMR revealed resonance at δ 154.2 which is typical for carbonate protection confirmed the formation of compound **25**. The major diastereomer of compound **25** was carried further for benzylic oxidation by means of CrO_3 and AcOH, furnished product **26** in 55% yield. Reformatsky reaction on compound **26** in presence of ethyl 2–bromopropionate and active zinc metal under refluxing temperature furnished complex reaction mixture,[7] that was inseparable on column chromatography along with isolation of phenol **18** in 29% yield (**Scheme–9**). This proved that such system is highly prone for aromatisation and needs milder reaction conditions for functionalisation at highly reactive benzylic position.

Butenolide ring construction from tetralone **26** would have readily completed the synthesis of hydroxy cadinane lactone. This was achieved by treatment of compound **26** under much milder Barbier reaction conditions compared to Reformatsky reaction (**Scheme–10**).[8] Thus in presence of crotyl bromide and zinc metal tetralone **26** was converted into desired alcohol **28** in 69% yield. The alcohol **28** was obtained as a mixture of diastereomers (80:20). Since the stereochemistry at newly generated chiral centers would be destroyed at the later stages of synthesis during the formation of butenolide moiety, it's stereochemistry was of no consequence.

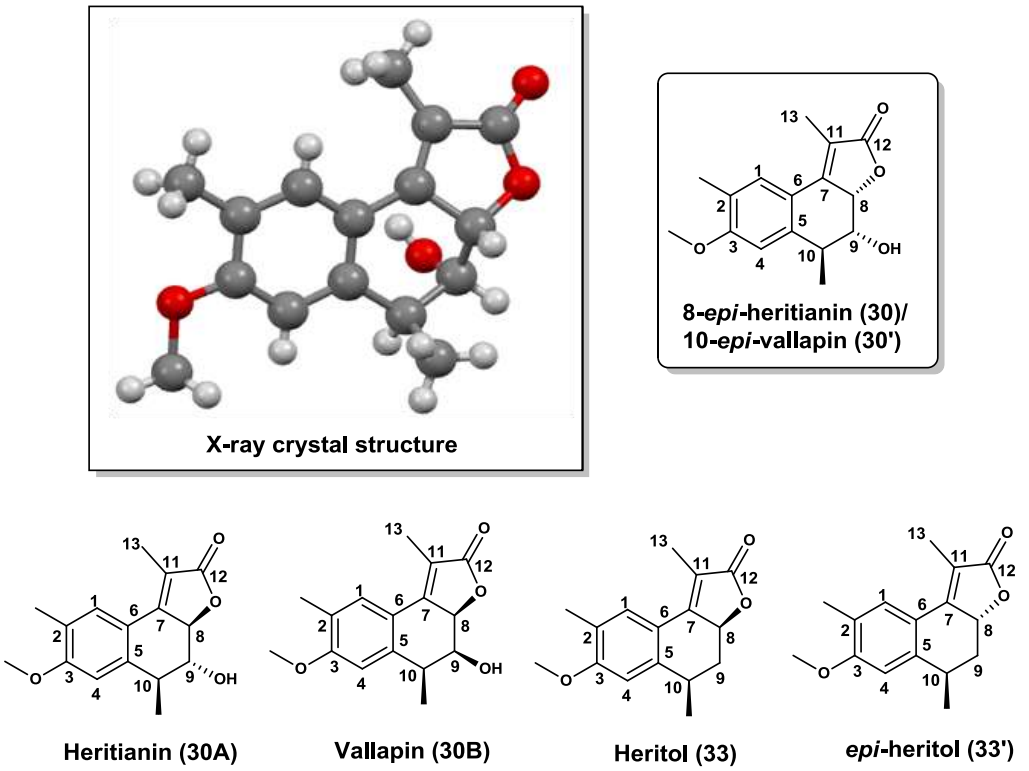
In order to record spectral data, attempt was made to isolate and identify the diastereomers. Both of these intermediate compounds were confirmed by IR, NMR and mass spectral data.



Scheme–10: Completion of synthesis

Reagents and conditions*: (a) Crotyl bromide, Zn, DMF, 0 ^{o}C– RT, 5 h, 69%, (dr: 80:20); (b) i) OsO_4, $NaIO_4$, dioxane–H_2O (3:1), 12 h, ii) Jones reagent, acetone, 1.5 h, 77%; (c) i) NaOMe, MeOH, 0 ^{o}C– RT, 5 h, ii) HCl (10%), 0.5 h, 78%.*

The next job was lactone formation and for oxidative double bond cleavage, Lemieux–Johnson's reagent was opted, which involed sodium periodate in combination with OsO_4 (cat.) in aqueous dioxane. The intermediate aldehyde obtained by this method was immediately treated with freshly prepared Jones reagent to yield acid **29** in 77% yield. Compound **29** was completely characterized by it's IR, NMR and mass spectral data. It's IR spectrum revealed a strong stretching band at 1708 cm^{-1}, characteristic of a carbonyl group of an acid derivative; and also a broad absorption band extended from 3300 cm^{-1} to 2700 cm^{-1}, which distinguishes the carboxylic acid derivatives from the rest of the carbonyl compounds. Further, absence of multiplet of an olefin proton at δ 5.09 in the ^{1}H NMR spectrum of the isolated product suggested said transformation. This was further confirmed by the analysis of it's ^{13}C NMR spectrum, which showed a quaternary carbon singlet at δ 179.9 for the carbonyl group. Mass spectrum finally ascertained the formation of acid **29**.



Figure–1: Single X–ray Crystal structure of compound **30** and comparison of synthetic compound (**I**) with the compounds reported in the literature.

The penultimate acid **29** was further processed in order to build the butenolide moiety. Accordingly the acid **29** was reacted with NaOMe in methanol at 0 ^{o}C. This base mediated carbonate deprotection [9] was carried out followed by construction of a butenolide ring under acidic conditions. Thus, addition of (10%) HCl solution to the reaction mixture furnished hydroxy cadinane lactone framework (**I**) (**Scheme–10**). After consumption of starting material in the reaction mixture, formation of the new spot was observed which was nonpolar than the starting acid. The final compound was recrystallised from hot methanol and pure compound thus obtained was characterised and compared with the spectral data of literature reports for heritianin (**30A**) and vallapin (**30B**)[1] as well as with heritol (**33**) and *epi*–heritol (**33'**) (**Figure–1**).[10]

The IR absorption at ν_{max} 1744 cm^{-1}, characteristic for butenolide moiety and absence of streching frequency for acidic functional group pointed towards butenolide formation. The ^{1}H NMR spectrum showed broad singlet at δ 5.12 (brs, 1H), a characteristic peak for proton attached to the butenolide oxygen. In ^{13}C NMR spectrum presence of a single peak at δ 78.3 for –CH of butenolide ring junction provided additional proof for butenolide formation. Also in the

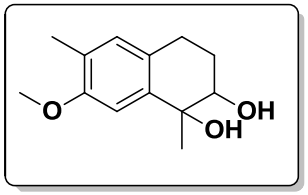
mass spectrum peak at (*m/z*): 297 attributed for $[M+Na]^+$ suggested formation of desired compound which was also confirmed by HRMS data. The hydroxy cadinane framework (**I**) was synthesized which was finally confirmed with single crystal X–ray analysis, proved to be **8–*epi*–heritianin (30)/ 10–*epi*–vallapin** (**30'**) (**Figure–1**).

1.3.3. Conclusion

For the first time hydroxy cadinane framework has been synthesized successfully. The present synthesis includes following key steps– oxidative decarbonylation, Barbier reaction and base mediated carbonate deprotection. Thus, first total synthesis of (±)–8–*epi*–heritianin (**30**)/ (±)–10–*epi*–vallapin (**30'**) has been achieved in fourteen steps with 2.3% overall yield, starting with easily available commercial starting materials.

1.3.4. Experimental data

Preparation of 7–methoxy–1,6–dimethyl–1,2,3,4–tetrahydronaphthalene–1,2–diol (6)



To a magnetically stirred solution of 6–methoxy–4,7–dimethyl–1,2–dihydronaphthalene (**5**) (0.430 g, 1 equiv.) in acetone: water (3:1) (8 mL), catalytic OsO_4 (0.1 M solution in toluene) was added in presence of NMO (0.542 g, 2 equiv.) and stirred for 6 h at RT. The reaction was quenched with saturated 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 X 10 mL). The combined organic layer was washed with brine (5 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue on a 60–120 silica gel column using (45%) ethyl acetate–pet. ether as eluent furnished **7**–methoxy–1,6–dimethyl–1,2,3,4–tetrahydronaphthalene–1,2–diol (**6**) (0.472 g, 92%) as a off white solid.

Molecular formula: $C_{13}H_{18}O_3$; **Yield:** 92%, **MP:** 109–110 ^oC.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.03 (s, 1H), 6.83 (s, 1H), 3.83 (s, 3H), 3.81–3.78 (m, 1H), 2.98–2.79 (m, 2H), 2.70–2.50 (m, 2H), 2.16 (s, 3H), 2.03–1.94 (m, 2H), 1.50 (s, 3H)

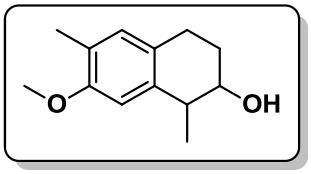
^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 156.5, 139.1, 130.4, 126.3, 126.1, 107.9, 73.6, 72.1, 55.3, 28.5, 26.9, 24.0, 15.9.

MS (ESI) (*m/z*): 245 $[M+Na]^+$, 277 $[M+Na+MeOH]^+$

IR ($CHCl_3$) ν_{max}: 3618, 3350, 2989, 1610, 1568, 1212 cm^{-1}.

HRMS (ESI): Calculated for $C_{13}H_{18}O_3$ $[M+Na]^+$ 245.1255, found 271.1256.

Preparation of 7–methoxy–1,6–dimethyl–1,2,3,4–tetrahydronaphthalen–2–ol (7)



To a stirred solution of 7–methoxy–1,6–dimethyl–1,2,3,4–tetrahydronaphthalene–1,2–diol (**6**) (0.040 g, 1 equiv.) at 0 ^oC Et_3SiH (0.041 g, 2 equiv.) and BF_3OEt_2 (0.012 g, 0.5 equiv.) were added. The resulting mixture was stirred at the same temperature for 3 h. The reaction mixture was quenched with saturated NH_4Cl solution at RT. The resulting solution was extracted with DCM (2 X 10 mL) and brine. The combined organic extracts dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product thus obtained was purified by 60–120 silica gel column chromatography using 25% ethyl acetate–pet. ether as a eluent to furnish 7–methoxy–1,6–dimethyl–1,2,3,4–tetrahydronaphthalen–2–ol (**7**) (0.030 g, 82%) as a white solid.

Molecular formula: $C_{13}H_{18}O_2$; **Yield**: 82%, **MP:** 50–52 ^oC.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): (*dr*: ~6:**4**) δ 6.86 (s, 1H), 6.70–6.61 (m, 1H), 4.13–4.04 (m, 0.60H), 3.84 (s, 3H), 3.81–3.76 (m, 0.40H), 3.06–2.67 (m, 3H), 2.20 (s, 3H), 2.10–1.78 (m, 2H), 1.36 (d, *J* = 7.08 Hz, 1.19H), 1.31 (d, *J* = 7.07 Hz, 1.81H).

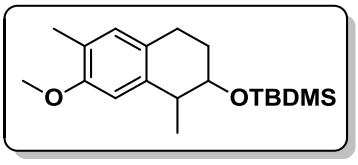
^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 156.1, 138.3, 130.6, 126.3, 124.6, 109.8, **108.2**, **72.6**, 70.3, 55.2, **40.4**, 38.6, **28.2**, 27.5, 26.2, **25.2**, **17.1**, 16.6, 15.8.

MS (ESI) (*m/z*): 229 $[M+Na]^+$.

IR ($CHCl_3$) ν_{max}: 3352, 2989, 1639, 1600, 1510, 1467, 1205 cm^{-1}.

HRMS (ESI): Calculated for $C_{13}H_{18}O_2$ $[M+Na]^+$ 229.1309, found 229.1307.

Preparation of *tert*–butyl((7–methoxy–1,6–dimethyl–1,2,3,4–tetrahydronaphthalen–2–yl)oxy)dimethylsilane (8)



To a magnetically stirred solution of 7–methoxy–1,6–dimethyl–1,2,3,4–tetrahydronaphthalen–2–ol (**7**) (0.050 g, 1

equiv.) in dry DCM (5 mL), imidazole (0.0329 g, 2 equiv.), *tert*–butyldimethylsilyl chloride (0.070 g, 1.8 equiv.) and 2,2–dimethylaminopyridine (cat.) were added in a sequence at 0 ^{o}C. The resulting reaction mixture was stirred at RT for 4 h. The reaction mixture was extracted with DCM (2 X 10 mL) and washed with water followed by brine. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product obtained was purified by 60–120 silica gel column chromatography using 10% ethyl acetate–petroleum ether as a eluent to furnish *tert*–butyl((7–methoxy–1,6–dimethyl–1,2,3,4–tetrahydronaphthalen–2–yl)oxy)dimethylsilane (**8**) (0.069 g, 90%) as an off white solid.

Molecular formula: $C_{19}H_{32}O_2Si$; **Yield:** 90%, **MP:** 122–123 ^{o}C.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): (*dr*: ~6:**4**) δ 6.83 (s, 1H), 6.70–6.56 (m, 1H), 4.13–4.04 (m, 0.65H), 3.83 (s, 3H), 3.79–3.69 (m, 0.35H), 2.95–2.69 (m, 2H), 2.18 (s, 3H), 2.06–1.86 (m, 1H), 1.81–1.70 (m, 1H), 1.33–1.23 (m, 3H), 0.95 (s, 9H), 0.12 (s, 6H).

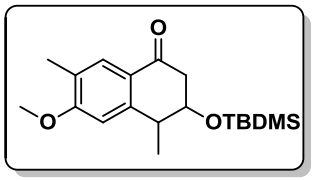
^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 155.9, 139.5, **138.3**, 130.6, **127.2**, 126.4, 124.3, **123.9**, 110.1, **109.6**, **73.6**, 70.8, 55.2, **41.5**, 39.7, **29.7**, **29.5**, 27.4, 27.2, 25.9, **25.7**, **20.4**, **18.2**, 17.2, 15.8, –3.49, –4.66.

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

IR ($CHCl_3$) ν_{max}: 3017, 2930, 1616, 1581, 1464, 1325, 1251, 1216, 1098 cm^{-1}.

HRMS (ESI): Calculated for $C_{19}H_{32}O_2Si$ $[M+Na]^+$ 343.2172, found 343.2175.

Preparation of 3–((*tert*–butyldimethylsilyl)oxy)–6–methoxy–4,7–dimethyl–3,4–dihydronaphthalen–1(2*H*)–one (9)



To a stirred solution of *tert*–butyl((7–methoxy–1,6–dimethyl–1,2,3,4–tetrahydronaphthalen–2–yl)oxy)dimethylsilane (**8**) (0.1 g, 1 equiv.) in AcOH (2 mL) at 5 ^{o}C, solution of CrO_3 (0.125 g, 4 equiv.) dissolved in AcOH (0.9 mL) and H_2O (0.1 mL) was added in a dropwise manner over a period of 0.5 h. The resulting mixture was stirred at the same temperature for 1 h and then additional 2 h at RT. The reaction was quenched at 5 ^{o}C with addition of cool sat. $NaHCO_3$ solution. The aq. layer was extracted with EtOAc (3 X 10 mL) and washed with brine. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product thus obtained was purified by 60–120 silica gel column chromatography using 30% ethyl acetate–petroleum ether as a eluent to

furnish 3–((*tert*–butyldimethylsilyl)oxy)–6–methoxy–4,7–dimethyl–3,4–dihydronaphthalen–1(2*H*)–one (**9**) (0.061 g, 59%) as a pale yellow viscous oil.

Molecular formula: $C_{19}H_{30}O_3Si$; **Yield:** 59%.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): (*dr*: ~6:**4**) δ 7.76 (s, 1H), 6.61 (m, 1H), 4.35–4.24 (m, 0.63H), 4.04–3.95 (m, 0.37H), 3.88 (s, 3H), 3.11–2.93 (m, 1H), 2.81–2.50 (m, 2H), 2.17 (s, 3H), 1.38–1.26 (m, 3H), 0.88 (s, 9H), 0.07 (s, 6H).

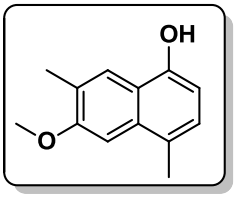
^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 195.6, **195.1**, 162.4, **146.2**, 129.4, **129.2**, 125.8, **125.4**, **124.7**, 124.3, 108.6, **108.1**, **72.9**, 69.3, 55.4, **45.1**, 43.3, **42.0**, 40.9, 25.8, **18.4**, 18.1, **15.8**, 15.7, **–4.9**, –4.7.

MS (ESI) (*m/z*): 357 $[M+Na]^+$.

IR ($CHCl_3$) ν_{max}: 2989, 1710, 1600, 1534, 1420, 1212 cm^{-1}.

HRMS (ESI): Calculated for $C_{19}H_{30}O_3Si$ $[M+Na]^+$ 357.1967, found 357.1964.

Preparation of 6–methoxy–4,7–dimethylnaphthalen–1–ol (18)



To a stirred suspension of 3–((*tert*–butyldimethylsilyl)oxy)–6–methoxy–4,7–dimethyl–3,4–dihydronaphthalen–1(2*H*)–one (**9**) (0.1 g, 0.21 mmol), activated Zn (0.027 g, 0.42 mmol) and a catalytic amount of iodine in anhydrous diethyl ether (10 mL), a solution of ethyl 2–bromopropionate (0.076 g, 0.42 mmol) in anhydrous diethyl ether (2 mL) was slowly added at 25 °C under argon atmosphere. The reaction mixture was further refluxed for 5 h, quenched with saturated NH_4Cl (5 mL) solution. The obtained residue was diluted with ethyl acetate (20 mL). The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4 and filtered. The organic layer concentrated under reduced pressure followed by 200–400 silica gel column chromatographic purification of the resulting residue using (10%) ethyl acetate–petroleum ether as an eluent to provide the pure product 6–methoxy–4,7–dimethylnaphthalen–1–ol (**18**, 0.020 g, 43% yield) as a dark yellow oil

Molecular formula: $C_{13}H_{14}O_2$; **Yield:** 43%.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.06 (s, 1H), 7.04 (d, J = 7.71 Hz, 1H), 6.54 (d, J = 7.71 Hz, 1H), 3.97 (s, 3H), 2.56 (s, 3H), 2.40 (s, 3H).

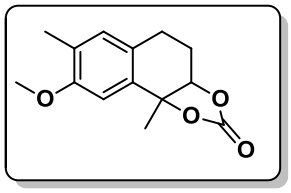
^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 157.1, 149.6, 133.7, 127.0, 125.8, 124.8, 123.3, 119.4, 106.1, 101.2, 55.1, 19.1, 17.0

MS (ESI) (*m/z*): 234 $[M+MeOH]^+$.

IR ($CHCl_3$) ν_{max}: 3584, 3396, 3020, 1740, 1599, 1422, 1215 cm^{-1}

HRMS (ESI): Calculated for $C_{13}H_{14}O_2$ $[M+Na]^+$ 234.4965, found 234.4962.

Preparation of 8–methoxy–7,9*b*–dimethyl–3*a*,4,5,9*b*–tetrahydronaphtho[1,2–*d*][1,3]dioxol–2–one (11)



To a cooled (0 ^oC) stirred solution of 7–methoxy–1,6–dimethyl–1,2,3,4–tetrahydronaphthalene–1,2–diol (**6**) (9.5 g, 1 equiv.) in dry DCM was added triethyl amine (36.8 mL, 6 equiv.). To this solution triphosgene (7.60 g, 0.6 equiv.) was added in portions at 0 ^oC and the resulting reaction mixture was stirred at RT for 3 h. The reaction was quenched by adding saturated NH_4Cl (20 mL), extracted with DCM (3 X 20 mL) and washed with brine. The organic extracts combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product obtained was purified by 60–120 silica gel using 20% ethyl acetate–petroleum ether as a eluent to furnish 8–methoxy–7,9*b*–dimethyl–3*a*,4,5,9*b*–tetrahydronaphtho[1,2–*d*][1,3]dioxol–2–one (**11**, 10.1 g, 96% yield) as a white solid.

Molecular formula: $C_{14}H_{16}O_4$; **Yield:** 96%, **MP**: 103 ^oC.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.91 (d, J = 2.02 Hz, 2H), 4.72 (t, J = 4.93 Hz, 1H), 3.84 (s, 3H), 2.92–2.78 (m, 1H), 2.64–2.50 (m, 2H), 2.19 (s, 3H), 2.17–2.04 (m, 2H), 1.81 (s, 3H).

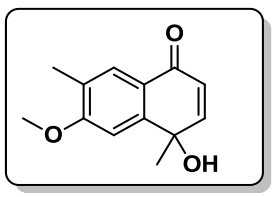
^{13}C NMR (50 MHz, $CDCl_3$): δ 157.0, 154.1, 132.2, 130.3, 128.1, 127.1, 108.2, 82.0, 81.8, 55.4, 27.3, 25.6, 23.0, 15.8.

MS (ESI) (*m/z*): 271 $[M+Na]^+$.

IR ($CHCl_3$) ν_{max}: 2926, 2857, 1796, 1611, 1501, 1364, 1160, 1034 cm^{-1}.

HRMS (ESI): Calculated for $C_{13}H_{14}O_3$ $[M+Na]^+$ 271.2559, found 271.2556.

Preparation of 4–hydroxy–6–methoxy–4,7–dimethylnaphthalen–1(4*H*)–one (13)



To a stirred solution of 8–methoxy–7,9*b*–dimethyl–3*a*,4,5,9*b*–tetrahydronaphtho[1,2–*d*][1,3]dioxol–2–one (**11**) (1.2 g, 1 equiv.) in AcOH (10 mL) at 5 ^oC, solution of CrO_3 (2.16 g, 4.5 equiv.) dissolved

in AcOH (8 mL) and H_2O (0.8 mL) was added slowly over a period of half an hour. The resulting reaction mixture was stirred at the same temperature for 1 h and then allowed to warm up to 25 ^oC and stirred for additional 2 h. The reaction was quenched at 5 ^oC with careful addition of cool saturated $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate (3 X 25 mL) and washed with brine. The organic extracts combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product obtained was purified by 60–120 silica gel column chromatography using 30% ethyl acetate–petroleum ether as a eluent to furnish 4–hydroxy–6–methoxy–4,7–dimethylnaphthalen–1(4*H*)–one (**13**) (0.548 g, 52% yield) as a off white solid.

Molecular formula: $C_{13}H_{14}O_3$; **Yield:** 52%, **MP**: 176–178 ^oC.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.08 (s, 1H), 6.92 (d, *J* = 10.23 Hz, 1H), 6.18 (d, *J* = 10.23 Hz, 1H), 3.93 (s, 3H), 2.20 (s, 3H), 1.60 (s, 3H).

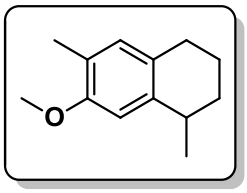
^{13}C NMR (50 MHz, $CDCl_3$): δ 184.1, 162.0, 152.4, 147.9, 128.6, 127.2, 127.0, 122.1, 106.4, 68.3, 55.6, 30.6, 15.8.

MS (ESI) (*m/z*): 241 $[M+Na]^+$.

IR ($CHCl_3$) ν_{max}: 3435, 2964, 1710, 1624, 1504, 1420, 1446, 1214 cm^{-1}.

HRMS (ESI): Calculated for $C_{13}H_{14}O_3$ $[M+Na]^+$ 241.0749, found 241.0746.

Preparation of 7–methoxy–1,6–dimethyl–1,2,3,4–tetrahydronaphthalene (15)



To a stirred solution of 4–hydroxy–6–methoxy–4,7–dimethylnaphthalen–1(4*H*)–one (**13**) (0.110 g, 20 mmol) in EtOH (5 mL) was added Pd/C (90 mg, 10 wt%). The reaction mixture was stirred under hydrogen atmosphere at 25 ^oC and 60 psi pressure for 6 h. After completion of the reaction, the catalyst was filtered off and the residue washed with hot EtOH (3 X 5 mL). The combined filtrate evaporated under reduced pressure and the residue was purified using 60–120 silica gel column chromatography (1% ethyl acetate–petroleum ether) furnished 7–methoxy–1,6–dimethyl–1,2,3,4–tetrahydronaphthalene (**15**, 0.074 g, 78%) as a colorless oil.

Molecular formula: $C_{13}H_{18}O$; **Yield:** 78%.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 6.84 (s, 1H), 6.66 (s, 1H), 3.84 (s, 3H), 2.99–2.83 (m, 1H), 2.69 (t, *J* = 6.95 Hz, 2H), 2.20 (s, 3H), 2.00–1.54 (m, 4H), 1.33 (d, *J* = 6.95 Hz, 3H).

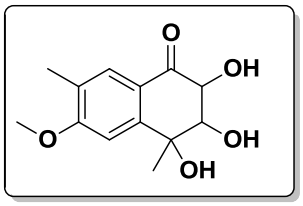
^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 155.8, 140.1, 131.1, 128.1, 123.9, 109.3, 55.2, 32.6, 31.6, 29.0, 23.1, 20.6, 15.8.

MS (ESI) (*m/z*): 213 $[M+Na]^+$.

IR ($CHCl_3$) ν_{max}: 3018, 2935, 1616, 1500, 1465, 1325, 1249, 1215 cm^{-1}.

HRMS (ESI): Calculated for $C_{13}H_{18}O$ $[M+Na]^+$ 213.9543, found 213.9546.

Preparation of 2,3,4–trihydroxy–6–methoxy–4,7–dimethyl–3,4–dihydronaphthalen–1(2*H*)–one (16)



To a magnetically stirred solution of 4–hydroxy–6–methoxy–4,7–dimethylnaphthalen–1(4*H*)–one (**13**) (0.2 g, 1 equiv.) in acetone: water (3:1) (8 mL), cat. OsO_4 (0.1 mL, 0.1 M solution in toluene) was added in presence of NMO (0.214 g, 2 equiv.) and stirred for 8 h at RT. The reaction was quenched with saturated Na_2SO_3 (5 mL) and stirred for 30 min. The solvent was evaporated and the residue was extracted with ethyl acetate (3 X 10 mL). The combined organic layer was washed with brine (5 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue on a 60–120 silica gel column using (90%)ethyl acetate–petroleum ether as eluent furnished the 2,3,4–trihydroxy–6–methoxy–4,7–dimethyl–3,4–dihydronaphthalen–1(2*H*)–one (**16**) (0.154 g, 67%) as an off white solid.

Molecular formula: $C_{13}H_{16}O_5$; **Yield:** 67%, **MP**: 182–184 ^oC.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4+DMSO–d_6): δ 7.24 (s, 1H), 6.77 (s, 1H), 4.08 (d, J = 2.40 Hz, 1H), 3.75 (d, J = 2.40 Hz, 1H), 3.53 (s, 3H), 1.80 (s, 3H), 1.06 (s, 3H).

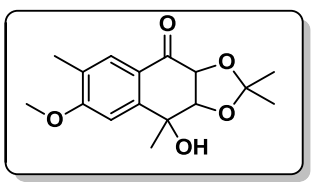
^{13}C NMR (50 MHz, $CDCl_3$+CCl_4+DMSO–d_6): δ 196.8, 162.5, 148.9, 127.5, 125.6, 121.4, 107.2, 79.7, 74.1, 71.5, 56.2, 27.8, 15.5.

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

IR ($CHCl_3$) ν_{max}: 3435, 3075, 2932, 1690, 1530, 1119 cm^{-1}

HRMS (ESI): Calculated for $C_{13}H_{16}O_5$ $[M+Na]^+$ 275.0998, found 275.0994.

Preparation of 9–hydroxy–7–methoxy–2,2,6,9–tetramethyl–9,9*a*–dihydronaphtho[2,3–*d*][1,3]dioxol–4(3*aH*)–one (20)



To a stirred solution of 2,3,4–trihydroxy–6–methoxy–4,7–dimethyl–3,4–dihydronaphthalen–1(2*H*)–one (**16**) (0.800 g, 0.45

mmol, 1.0 equiv) in anhydrous DMF (4 mL) as a reaction solvent, was added 2,2–DMP (0.388 mL, 1 mmol, 1.1 equiv) followed by *p*–TSA (0.058 g, 0.1 mmol, 0.1 equiv). The reaction mixture was stirred at 25 ^{o}C and monitored by TLC. After completion (6 h), reaction mixture was diluted with ethyl acetate. The reaction mixture was subsequently washed with brine and worked up with ethyl acetate (3 X 15 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a crude residue. The obtained residue was then purified by 60–120 silica gel column chromatography using (20% ethyl acetate–petroleum ether) to furnish the respective acetonide protected compound 9–hydroxy–7–methoxy–2,2,6,9–tetramethyl–9,9*a*–dihydronaphtho[2,3–*d*][1,3]dioxol –4(3*aH*)–one (**20**) (0.760 g, 82%) as a semisolid.

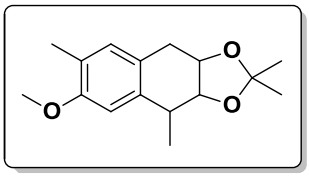
Molecular formula: $C_{16}H_{20}O_5$; **Yield:** 82%.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.72 (s, 1H), 6.91 (s, 1H), 4.57–4.50 (m, 2H), 3.93 (s, 4H), 2.23 (s, 3H), 1.74 (s, 3H), 1.41 (s, 3H), 0.86 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 194.6, 163.5, 146.3, 128.4, 127.9, 120.7, 110.2, 107.6, 83.5, 79.2, 72.0, 55.7, 27.4, 26.9, 24.8, 16.0.

MS (ESI) (*m/z*): 315 $[M+Na]^+$.
IR ($CHCl_3$) ν_{max}: 3584, 3396, 3020, 1710, 1639, 1522, 1105 cm^{-1}
HRMS (ESI): Calculated for $C_{16}H_{20}O_5$ $[M+Na]^+$ 315.1311, found 315.1312.

Preparation of 6–methoxy–2,2,4,7–tetramethyl–3*a*,4,9,9*a*–tetrahydronaphtho[2,3–*d*][1,3]dioxole (2)



To a stirred solution of 9–hydroxy–7–methoxy–2,2,6,9–tetramethyl–9,9*a*–dihydronaphtho[2,3–*d*][1,3]dioxol–4(3*aH*)–one (**20**) (0.110 g, 20 mmol) in EtOH (5 mL) was added Pd/C (10 mol%). The reaction mixture was stirred under hydrogen atmosphere at 25 ^{o}C and 1–2 psi pressure for 4 h. After completion, the reaction mixture was filtered off and the residue washed with hot EtOH (3 X 5 mL). The combined filtrate was evaporated under reduced pressure and the residue was purified using 60–120 silica gel column chromatography (10% ethyl acetate–petroleum ether) to furnish 6–methoxy–2,2,4,7–tetramethyl–3*a*,4,9,9*a*–tetrahydronaphtho[2,3–*d*][1,3]dioxole (**23**, 0.061 g, 62% yield) as a viscous oil.

Molecular formula: $C_{16}H_{22}O_3$; **Yield**: 62%.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 6.92 (s,1H), 6.68 (s. 1H), 4.71–4.64 (m, 0.15H), 4.50–4.32 (m, 0.85H), 3.91 (d, *J* = 7.45 Hz, 1H), 3.84 (s, 3H), 3.03 (dd, *J* = 15.41, 5.81 Hz, 0.85H), 2.86 (dd, *J* = 15.41, 2.40 Hz, 0.15 H) 2.78–2.59 (m,2H), 2.18 (s, 3H), 1.42 (d. *J* = 7.45 Hz, 3H), 1.41 (s, 3H), 1.35 (s, 3H).

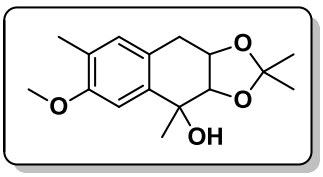
^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 156.8, 135.2, 130.4, 126.3, 124.3, 108.6, 107.8, 80.6, 74.3, 55.4, 38.2, 33.7, 27.1, 24.4, 15.8, 15.3.

MS (ESI) (*m/z*): 285 $[M+Na]^+$.

IR ($CHCl_3$) ν_{max}: 3020, 1610, 1599, 1422, 1215 cm^{-1}

HRMS (ESI): Calculated for $C_{16}H_{22}O_3$ $[M+Na]^+$ 285.1565, found 285.1569.

Preparation of 6–methoxy–2,2,4,7–tetramethyl–3*a*,4,9,9*a*–tetrahydronaphtho[2,3–*d*][1,3]dioxol–4–ol (22)



To a stirred solution of 9–hydroxy–7–methoxy–2,2,6,9–tetramethyl–9,9*a*–dihydronaphtho[2,3–*d*][1,3]dioxol–4(3*aH*)–one (**8**) (0.110 g, 20 mmol) in EtOH (5 mL) was added Pd/C (10 mol%). The reaction mixture was stirred under hydrogen atmosphere at 25 ^oC and 60 psi pressure for 3 h. After completion of the reaction, the catalyst was filtered off and the residue washed with hot EtOH (3 X 5 mL). The combined filtrate was evaporated under reduced pressure and the obtained residue was purified using 60–120 silica gel column chromatography (15% ethyl acetate–petroleum ether) to furnish 6–methoxy–2,2,4,7–tetramethyl–3*a*,4,9,9*a*–tetrahydronaphtho[2,3–*d*][1,3]dioxol–4–ol (**22**) as a solid.

Molecular formula: $C_{16}H_{22}O_4$; **Yield:** 85%, **MP:** 93–94 ^oC.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.83 (d, *J* = 5.43 Hz, 2H), 4.18 (d, *J* = 2.02 Hz, 1H), 4.05–3.96 (m, 1H), 3.82 (s, 3H), 3.03–2.79 (m, 2H), 2.16 (s, 3H), 1.61 (s, 3H), 1.43 (s, 3H), 0.96 (s, 3H).

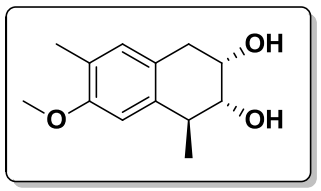
^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 156.9, 137.4, 130.3, 126.6, 123.6, 109.2, 108.0, 82.9, 81.6, 67.4, 55.3, 32.5, 27.7, 27.3, 27.2, 15.9.

MS (ESI) (*m/z*): 333 $[M+Na+MeOH]^+$.

IR ($CHCl_3$) ν_{max}: 3584, 3396, 1625, 1599, 1422, 1215 cm^{-1}

HRMS (ESI): Calculated for $C_{16}H_{22}O_4$ $[M+Na]^+$ 301.1518, found 301.1520.

Preparation of 7–methoxy–1,6–dimethyl–1,2,3,4–tetrahydronaphthalene–2,3–diol (24)



To a magnetically stirred solution of (**16**) (0.060 mg, 0.11 mmol) in dry DCM (5 mL) at 0 ºC was added $BF_3.OEt_2$ (0.14 mL, 0.55 mmol) and Et_3SiH (0.2 mL, 0.66 mmol) dropwise. The reaction was allowed to warm up to RT and stirred at RT for 5 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 a 60–120 silica gel column chromatography (30% ethyl acetate–pet. ether) furnished product 7–methoxy–1,6–dimethyl–1,2,3,4–tetrahydronaphthalene–2,3–diol (**24**, 0.040 g, 77% yield) as a white solid. Compound obtained as a mixture of diastereomers. The stereochemistry shown above is for major diastereomer, as per the X-ray crystal structure of final compound **30**.[11]

Molecular formula: $C_{13}H_{18}O_3$; **Yield:** 77%, **MP**: 134–135 ^oC.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): (*dr*: 6:**4**) δ 6.82 (s, 1H), 6.67 (s, 0.45H), 6.59 (s, 0.55H), 4.13–3.92 (m, 1.49 H), 3.80 (s, 3H), 3.76–3.73 (m, 0.51H), 3.05–2.74 (m, 3H), 2.36 (brs, 1H), 2.30 (brs, 1H), 2.15 (s, 3H), 1.46 (d, *J* = 7.20 Hz, 1.38H), 1.33 (d, *J* = 7.20 Hz, 1.83H).

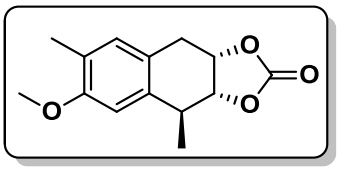
^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ **156.6**, 156.5, 136.4, **135.2**, 131.1, **130.9**, **125.1**, 124.9, 123.6, 109.5, **108.4**, 75.1, **74.0**, **70.0**, 67.5, 55.2, 39.5, **37.3**, 33.4, **32.9**, 20.9, **16.5**, 15.8.

MS (ESI) (*m/z*): 245 $[M+Na]^+$.

IR ($CHCl_3$) ν_{max}: 3379, 3019, 1606, 1501, 1437, 1215 cm^{-1}

HRMS (ESI): Calculated for $C_{13}H_{18}O_3$ $[M+Na]^+$ 245.1258, found 245.1256.

Preparation of 6–methoxy–4,7–dimethyl–3a,4,9,9*a*–tetrahydronaphtho[2,3–*d*][1,3]dioxol–2–one (25)



To a cooled (0 ^oC) magnetically stirred solution of 7–methoxy–1,6–dimethyl–1,2,3,4–tetrahydronaphthalene–2,3–diol (**24**)

(0.114 g, 1 equiv.) in dry DCM (5 mL), Et_3N (0.444 mL, 6 equiv.) followed by triphosgene (0.091 g, 0.6 equiv.) were added in portions at 0 ^oC and the resulting reaction mixture was stirred at RT for 2 h. The reaction was quenched by addition of saturated NH_4Cl (20 mL), extracted with dichloromethane (3 X 20 mL) and washed with brine. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product thus obtained was purified by 60–120 silica gel column chromatography using 20% ethyl acetate–pet. ether as a eluent to furnish 6–methoxy–4,7–dimethyl–3*a*,4,9,9*a*–tetrahydronaphtho[2,3–*d*][1,3]dioxol–2–one (**25**) (0.114 g, 90% yield) as a white solid.

Molecular formula: $C_{14}H_{16}O_4$

1st diastereomer (25); **Yield**: (0.101 g, 80%), **MP:** 150–151 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 6.94 (s, 1H), 6.66 (s, 1H), 4.94 (ddd, *J* = 11.91, 8.70, 5.95 Hz, 1H), 4.51 (dd, *J* = 8.70, 6.87 Hz, 1H), 3.84 (s, 3H), 3.14 (dd, *J* = 15.11, 6.87 Hz, 1H), 3.04 (quint, *J* = 6.87 Hz, 1H), 2.91 (dd, *J* = 15.11, 6.87 Hz, 1H), 2.18 (s, 3H), 1.43 (d, *J* = 6.87 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 157.6, 154.2, 135.3, 131.0, 125.9, 122.8, 108.3, 80.2, 74.8, 55.3, 37.4, 32.4, 32.0, 15.8, 15.4.

MS (ESI) (*m/z*): 271 $[M+Na]^+$.

IR ($CHCl_3$) ν_{max}: 2923, 1802, 1654, 1616, 1411 cm^{-1}.

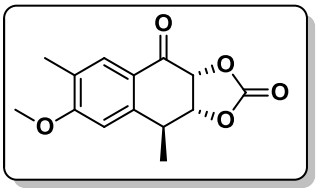
HRMS (ESI): Calculated for $C_{18}H_{22}O_5$ $[M+Na]^+$ 271.1749, found 341.1746.

2nd diastereomer (25'); **Yield**: (0.013 g, 20%), **MP:** 140–141 ^oC.

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 6.95 (s, 1H), 6.71 (s, 1H), 5.22–5.14 (m, 1H), 4.98 (dd, *J* = 8.72, 2.91 Hz, 1H), 3.84 (s, 3H), 3.06 (dd, *J* = 15.91, 2.91 Hz, 1H), 2.84–2.67 (m, 2H), 2.18 (s, 3H), 1.57 (d, *J* = 7.07 Hz, 3H)).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 157.5, 154.2, 134.0, 131.1, 125.5, 123.1, 107.8, 79.6, 75.4, 55.3, 34.8, 31.8, 15.8, 13.4.

Preparation of 7–methoxy–6,9–dimethyl–9,9*a*–dihydronaphtho[2,3–*d*][1,3]dioxole–2,4(3*aH*)–dione (26)



To a stirred solution of 6–methoxy–4,7–dimethyl–3*a*,4,9,9*a*–tetrahydronaphtho[2,3–*d*][1,3]dioxol–2–one (**25**) (0.065 g, 1

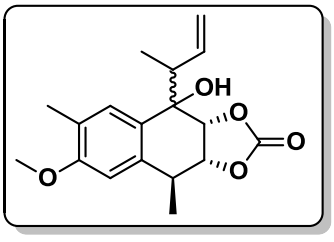
equiv.) in AcOH (2 mL) at 5 ^{o}C, solution of CrO_3 (0.104 g, 4 equiv.) dissolved in AcOH (0.9 mL) and H_2O (0.1 mL) was added in a dropwise manner over a period of half an hour. The resulting reaction mixture was stirred at the same temperature for 1 h and then allowed to warm up to 25 ^{o}C and stirred for additional 2 h. The reaction was quenched at 5 ^{o}C with careful addition of cool saturated $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate (3 X 10 mL) and washed with brine. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product obtained was purified by 60–120 silica gel column chromatography using 30% ethyl acetate–petroleum ether as a eluent to furnish 7–methoxy–6,9–dimethyl–9,9*a*–dihydronaphtho[2,3–*d*][1,3]dioxole–2,4(3*aH*)–dione (**26**) (0.037 g, 55%) as an off white solid.

Molecular formula: $C_{14}H_{14}O_5$

Yield: 55%, **MP:** 114–115 ^{o}C

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.75 (s, 1H), 6.67 (s, 1H), 5.10 (dd, *J* = 7.33, 4.30 Hz, 1H), 4.99 (d, *J* = 7.33 Hz, 1H), 3.94 (s, 3H), 3.48–3.35 (m, 1H), 2.22 (s, 3H), 1.35 (d, *J* = 7.32 Hz, 3H);
^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 185.8, 164.0, 153.1, 144.2, 130.8, 127.8, 122.7, 108.6, 79.0, 74.6, 55.7, 35.6, 20.9, 15.9.
MS (ESI) (*m/z*): 285 $[M+Na]^+$.
IR ($CHCl_3$) ν_{max}: 3488, 2980, 2686, 1770, 1682, 1449, 1393, 1093cm^{-1}.
HRMS (ESI): Calculated for $C_{14}H_{14}O_5$ $[M+Na]^+$ 285.0844, found 285.0848.

Preparation of 4–(but–3–en–2–yl)–4–hydroxy–7–methoxy–6,9–dimethyl–3*a*,4,9,9*a*–tetrahydronaphtho[2,3–*d*][1,3]dioxol–2–one (28)



To a stirred solution of 7–methoxy–6,9–dimethyl–9,9*a*–dihydronaphtho[2,3–*d*][1,3]dioxole–2,4(3*a*H)–dione (**26**) (0.3 g, 1 equiv.) in dry DMF (3 mL), Zn metal dust (0.223 g, 3 equiv.) was added in one portion at 0 ^{o}C. To this solution crotyl bromide (0.230 g, 1.5 equiv.) dissolved in DMF (0.5 mL) was added at the same temperature and the resulting reaction mixture was stirred at RT for 5 h. After completion of reaction, the mixture was diluted with addition of ethyl acetate (10 mL) and brine (5 mL) followed by extraction with ethyl acetate (3 X 15 mL). The organic extracts were combined,

dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product obtained was purified by 200–400 silica gel using 30– 40% ethyl acetate–petroleum ether as a eluent to furnish 4–(but–3–en–2–yl)–4–hydroxy–7–methoxy–6,9–dimethyl–3*a*,4,9,9*a*–tetrahydronaphtho[2,3–*d*][1,3]dioxol–2–one (**28**, 0.251g, 69%) as a solid compound.

Molecular formula: $C_{18}H_{22}O_5$

1st diastereomer (**28**), **Yield:** (0.200 g, 55%), **MP:** 140 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 7.36 (s, 1H), 6.69 (s, 1H), 6.09 (dt, *J* = 17.40, 10.37 Hz, 1H), 5.19 (d, *J* = 8.55 Hz, 1H), 5.15 (dd, *J* = 10.37, 1.83 Hz, 1H), 5.01 (dd, *J* = 8.55, 3.66 Hz, 1H), 3.85 (s, 3H), 3.10–3.06 (m, 1H), 2.43 (brs, 1H), 2.37–2.31 (m, 1H), 2.22 (s, 3H), 1.56 (d, *J* = 6.71 Hz, 3H), 0.90 (d, *J* = 6.71 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 157.7, 153.4, 140.2, 131.8, 129.1, 128.7, 125.4, 116.1, 107.7, 79.9, 78.6, 74.5, 55.3, 42.9, 33.1, 15.9, 15.1, 13.6.

MS (ESI) (*m/z*): 341 $[M+Na]^+$.

IR ($CHCl_3$) ν_{max}: 2989, 2859, 1809, 1641, 1460, 1189 cm^{-1}.

HRMS (ESI): Calculated for $C_{18}H_{22}O_5$ $[M+Na]^+$ 341.1254, found 341.1252.

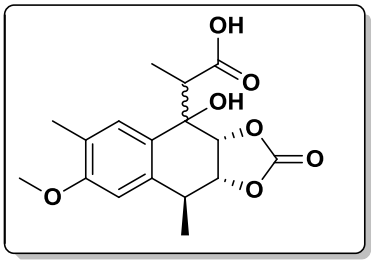
2nd diastereomer (**28'**), **Yield:** (0.051 g, 14%), **MP:** 182–184 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (s, 1H), 6.59 (s, 1H), 5.33–5.27 (m, 1H), 5.14–5.08 (m, 2H), 4.69 (d, *J* = 2.69 Hz, 1H), 3.98 (brs, 1H), 3.85 (s, 3H), 3.25–3.18 (m, 1H), 3.15–3.06 (m, 1H), 2.21 (s, 3H), 2.19 (brs, 1H), 1.31 (d, *J* = 6.84 Hz, 3H), 1.27 (d, *J* = 6.84 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 154.3, 137.0, 136.6, 129.0, 126.6, 123.5, 119.8, 117.9, 109.3, 84.5, 75.7, 70.3, 55.2, 45.2, 38.5, 18.1, 16.2, 11.5.

MS (ESI) (*m/z*): 341 $[M+Na]^+$.

Preparation of (±)–2–(4–hydroxy–7–methoxy–6,9–dimethyl–2–oxo–3*a*,4,9,9*a*–tetrahydronaphtho[2,3–*d*][1,3]dioxol–4–yl)propanoic acid (29)



To a stirred solution of 4–(but–3–en–2–yl)–4–hydroxy–7–methoxy–6,9–dimethyl–3*a*,4,9,9*a*–tetrahydronaphtho[2,3–*d*][1,3]dioxol–2–one **28** (0.1 g, 1 equiv.) in dioxane: water (3:1) (10 mL), catalytic OsO_4 (0.1 mL, 0.1 M solution in toluene) was

added and stirred for 30 min at 25 ^{0}C, followed by addition of $NaIO_4$ (0.138 g, 2.2 equiv) in one portion. The reaction mixture was then stir for 12 h. After consumption of starting material, freshly prepared Jones reagent (6 mL) was added in a dropwise fashion. The reaction mixture was stirred at RT for 1.5 h, excess of Jones reagent was quenched by using isopropanol (5 mL). Acetone was removed under reduced pressure, followed by dilution with water and extraction with EtOAc (3 X 10 mL). The combined organic layers were washed brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (60% ethyl acetate–pet.ether) to gave 2–(4–hydroxy–7–methoxy–6,9–dimethyl–2–oxo–3*a*,4,9,9*a*–tetrahydronaphtho[2,3–*d*][1,3]dioxol–4–yl)propanoic acid (**29**, 0.088 g, 88%) as an off white solid.

Molecular formula: $C_{17}H_{20}O_7$; **Yield:** 88%, **MP:** 252–255 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$+CCl_4+DMSO–d_6): δ 7.18 (s, 1H), 6.67 (s, 1H), 5.33 (d, *J* = 3.97 Hz, 1H), 4.11–4.85 (m, 1H), 3.83 (s, 3H), 3.28–3.24 (m, 1H), 2.94–2.90 (m, 1H), 2.56 (brs, 1H), 2.17 (s, 3H) 1.44 (d, *J* = 7.02 Hz, 3H), 1.38 (d, *J* = 7.02 Hz, 3H).

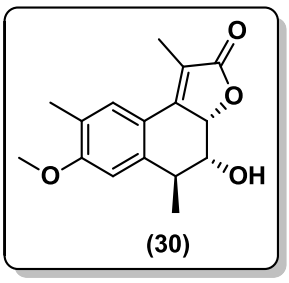
^{13}C NMR (100 MHz, $CDCl_3$+CCl_4+DMSO–d_6): δ 173.5, 157.7, 154.2, 137.3, 128.5, 125.1, 123.7, 107.1, 95.6, 82.5, 76.9, 69.0, 54.9, 49.0, 33.5, 15.6, 12.0.

MS (ESI) (*m/z*): 359 $[M+Na]^+$.

IR ($CHCl_3$) ν_{max}: 3625, 3350, 3019, 1780, 1709, 1654, 1613, 1456 cm^{-1}.

HRMS (ESI): Calculated for $C_{17}H_{20}O_7$ $[M+Na]^+$ 359.1204, found 359.1209.

Preparation of 4–hydroxy–7–methoxy–1,5,8–trimethyl–4,5–dihydronaphtho[2,1–*b*]furan–2(3*aH*)–one (30)/ (30')



(30)

To a stirred solution of (±)–2–(4–hydroxy–7–methoxy–6,9–dimethyl–2–oxo–3*a*,4,9,9*a*–tetrahydronaphtho[2,3–*d*][1,3]dioxol–4–yl)propanoic acid (**29**) (0.200 g, 1 equiv.) in methanol (5 mL), NaOMe (0.035 g, 1.1 equiv., 98% pure) was added at 0 ^{o}C. The resulting reaction mixture was vigorously stirred for 5 h at RT. After complete consumption of starting material, as monitored with TLC the reaction was acidified with the addition of solution of 10% HCl (0.5 mL) and stirred at 25 ^{o}C for additional 0.5 h. The MeOH in the reacion mixture was removed under reduced pressure. The

crude reaction mass was washed with water and extracted with ethyl acetate (3 X10 mL). The combined organic filtrates washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude product thus obtained was crystallized from hot methanol to provide crystalline 4–hydroxy–7–methoxy–1,5,8–trimethyl–4,5–dihydronaphtho[2,1–*b*]furan–2(3*aH*)–one (**30/ 30'**, 0.127 g, 78%) as a white solid.

Molecular formula: $C_{16}H_{18}O_4$; **Yield:** 78%, **MP:** 289–291 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 7.41 (s, 1H), 6.66 (s, 1H), 5.12 (s, 1H), 4.34 (s, 1H), 3.88 (s, 1H), 3.31–3.26 (m, 1H), 2.23 (s, 3H), 2.15 (s, 3H), 1.39 (d, J = 7.83 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 175.5, 159.9, 152.3, 140.4, 129.5, 125.9, 119.7, 118.8, 110.8, 78.3, 71.9, 55.3, 41.0, 21.7, 16.1, 10.1.

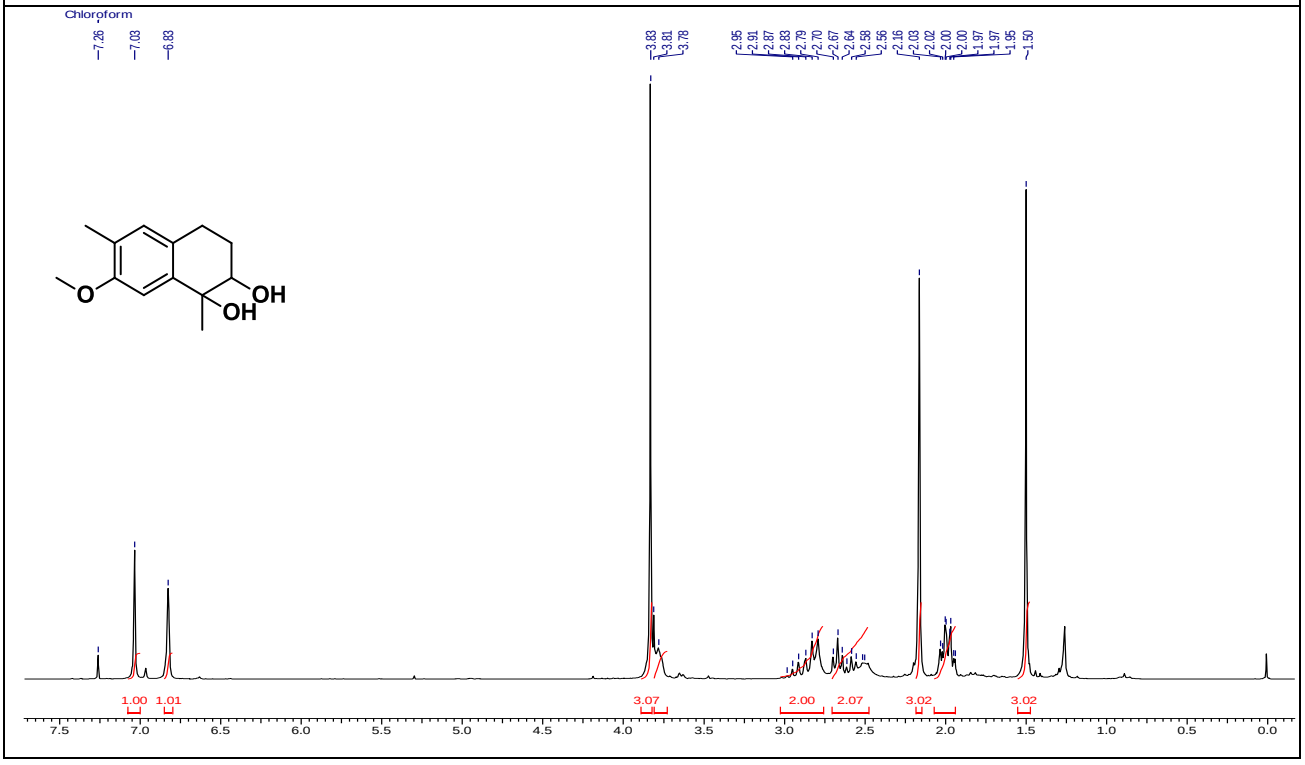
MS (ESI) (*m/z*): 297 $[M+Na]^+$.

IR ($CHCl_3$) ν_{max}: 3595, 3350, 3019, 2960, 1744, 1654, 1613 cm^{-1}.

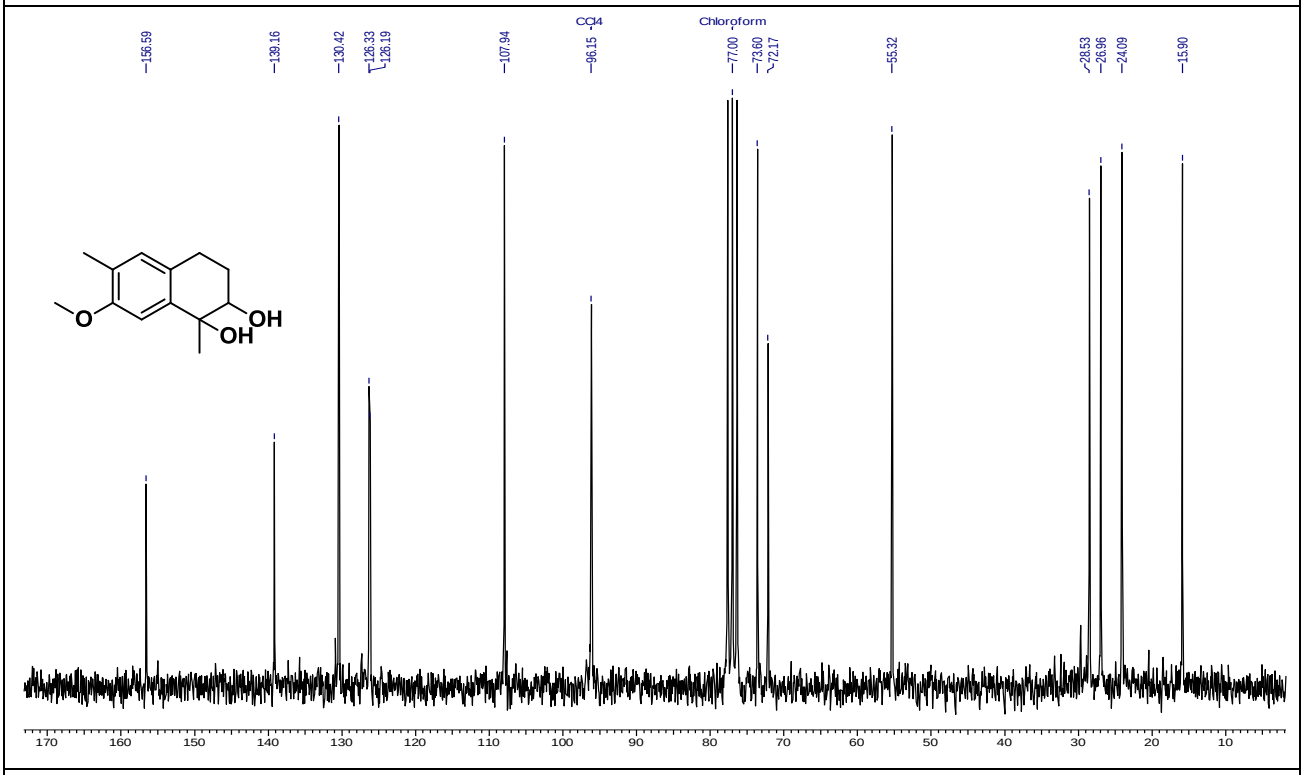
HRMS (ESI): Calculated for $C_{16}H_{18}O_4$ $[M+Na]^+$ 297.1254, found 297.1252.

1.3.4. 1. Spectra

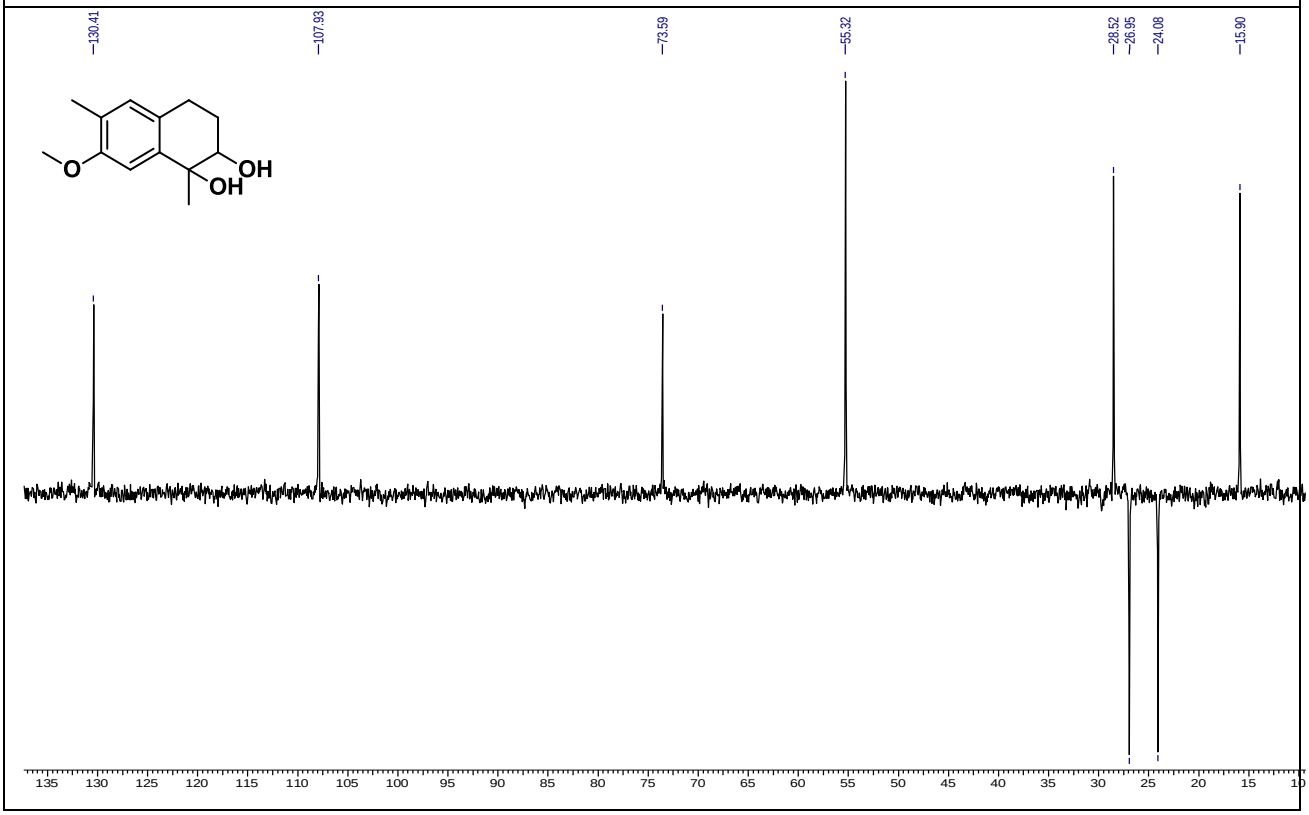
^{1}H NMR spectrum of compound **6** ($CDCl_3$+CCl_4, 200 MHz)



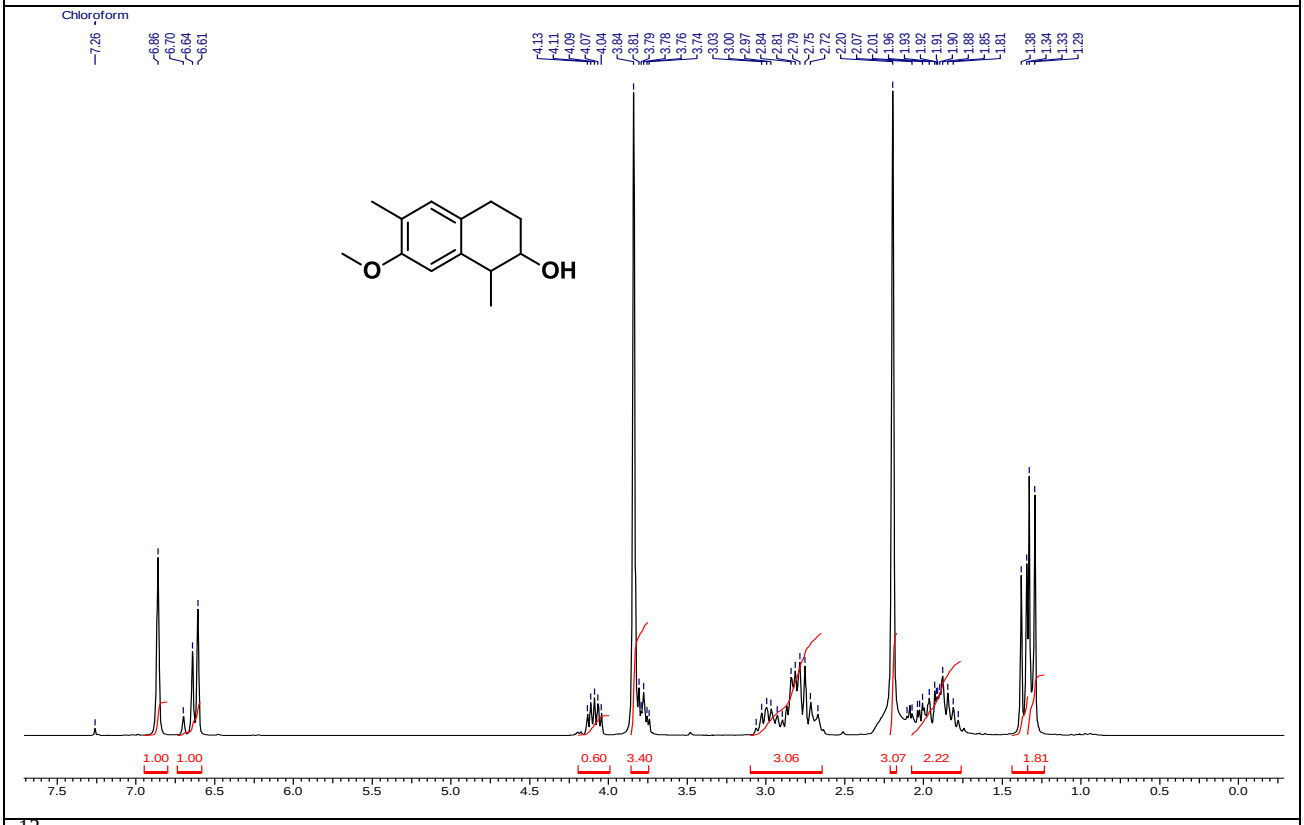
^{13}C NMR spectrum of compound **6** ($CDCl_3$+CCl_4, 50 MHz)



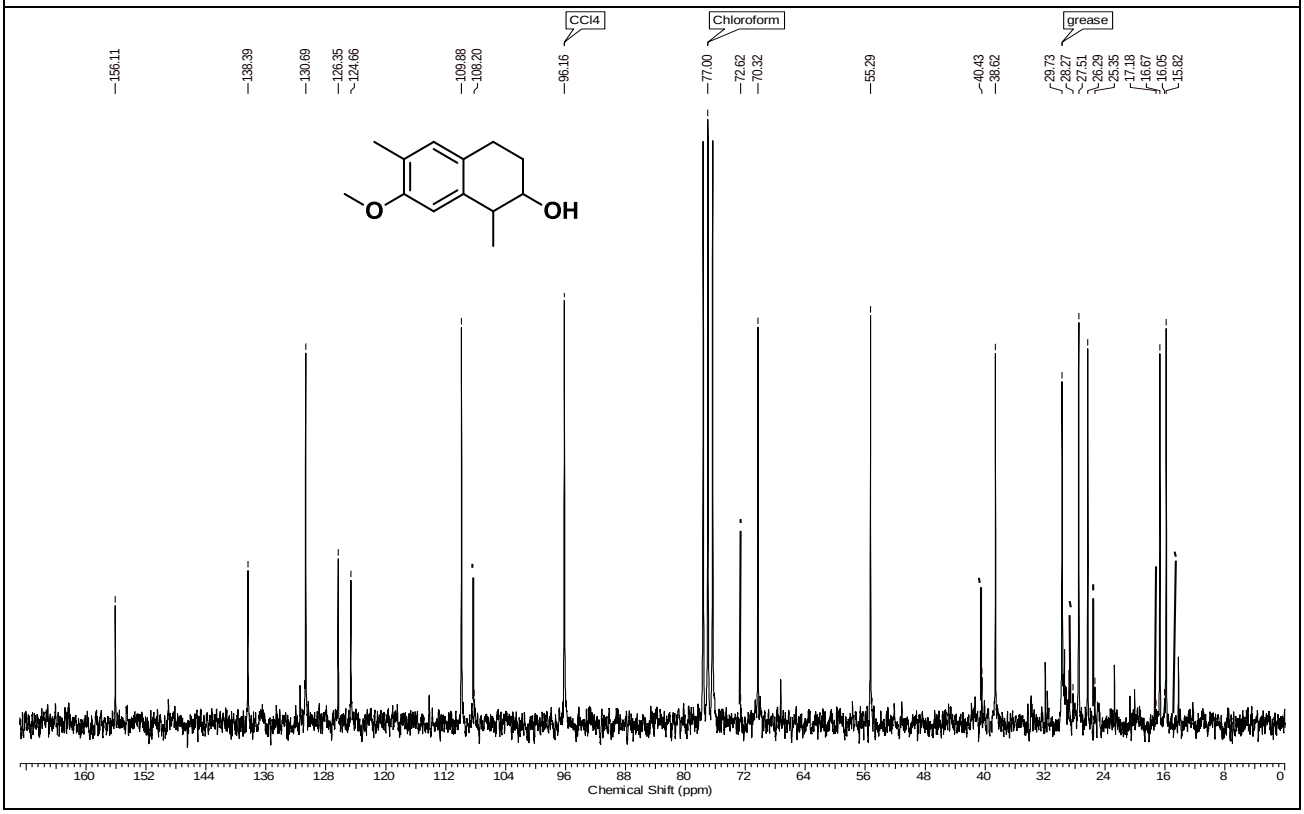
DEPT spectrum of compound **6** ($CDCl_3$+CCl_4, 50 MHz)



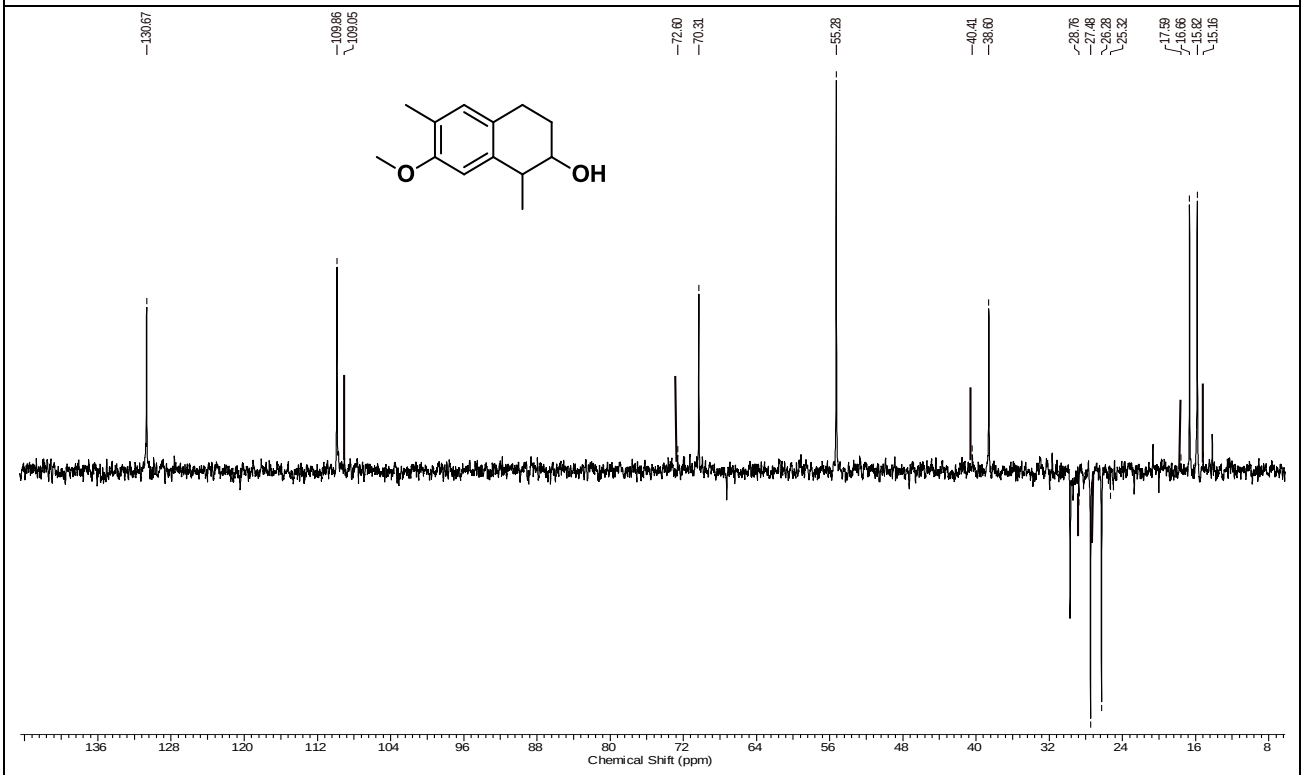
^{1}H NMR spectrum of compound **7** ($CDCl_3$+CCl_4, 200 MHz)



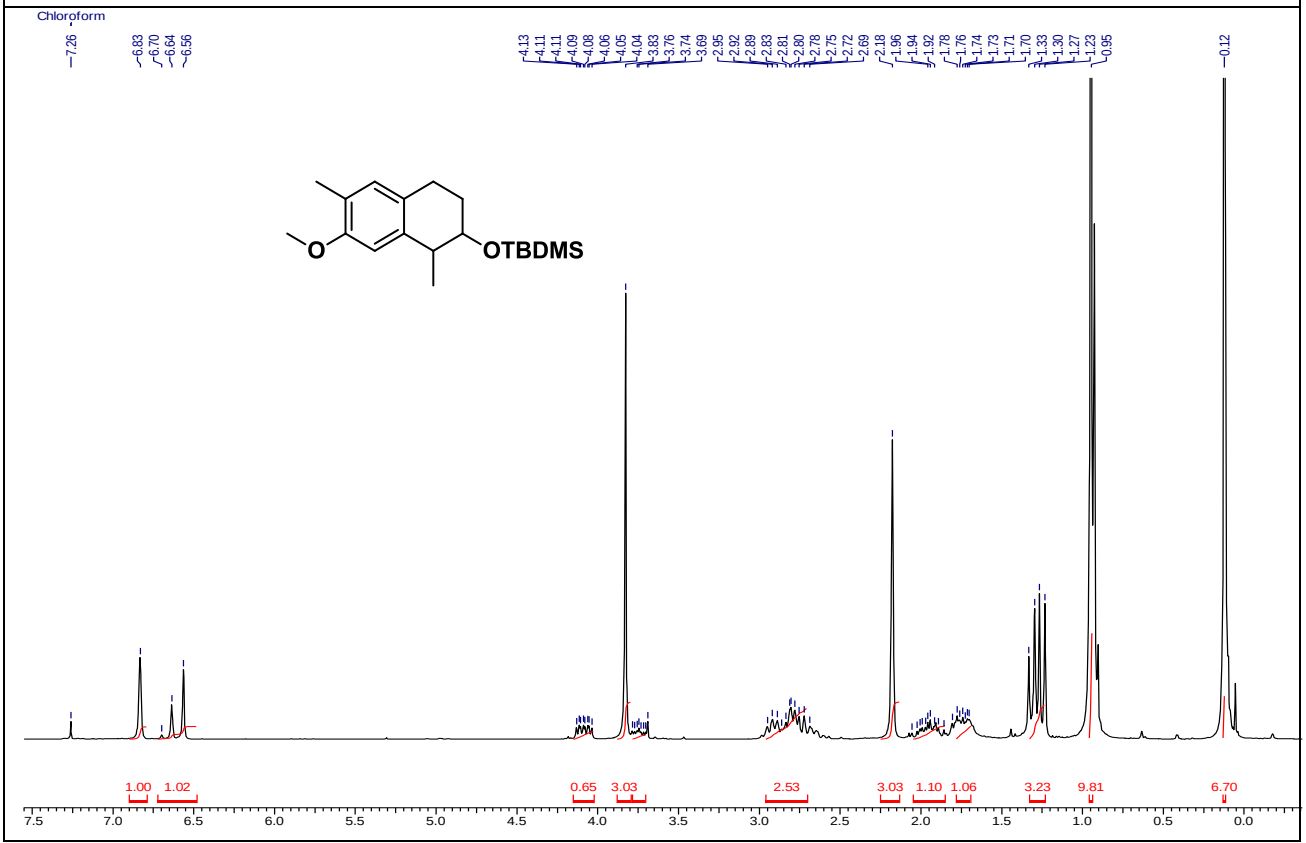
^{13}C NMR spectrum of compound **7** ($CDCl_3$+CCl_4, 50 MHz)



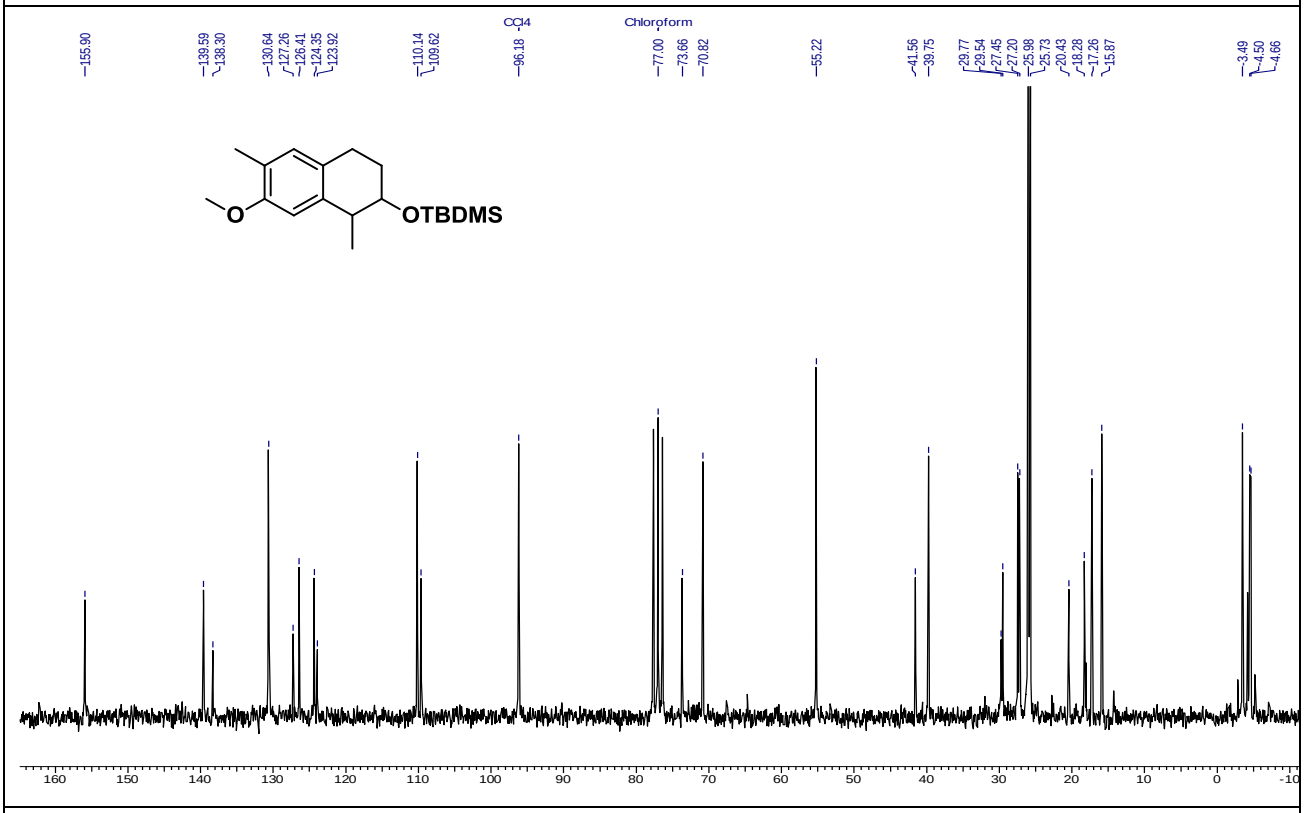
DEPT spectrum of compound **7** ($CDCl_3$+CCl_4, 50 MHz)



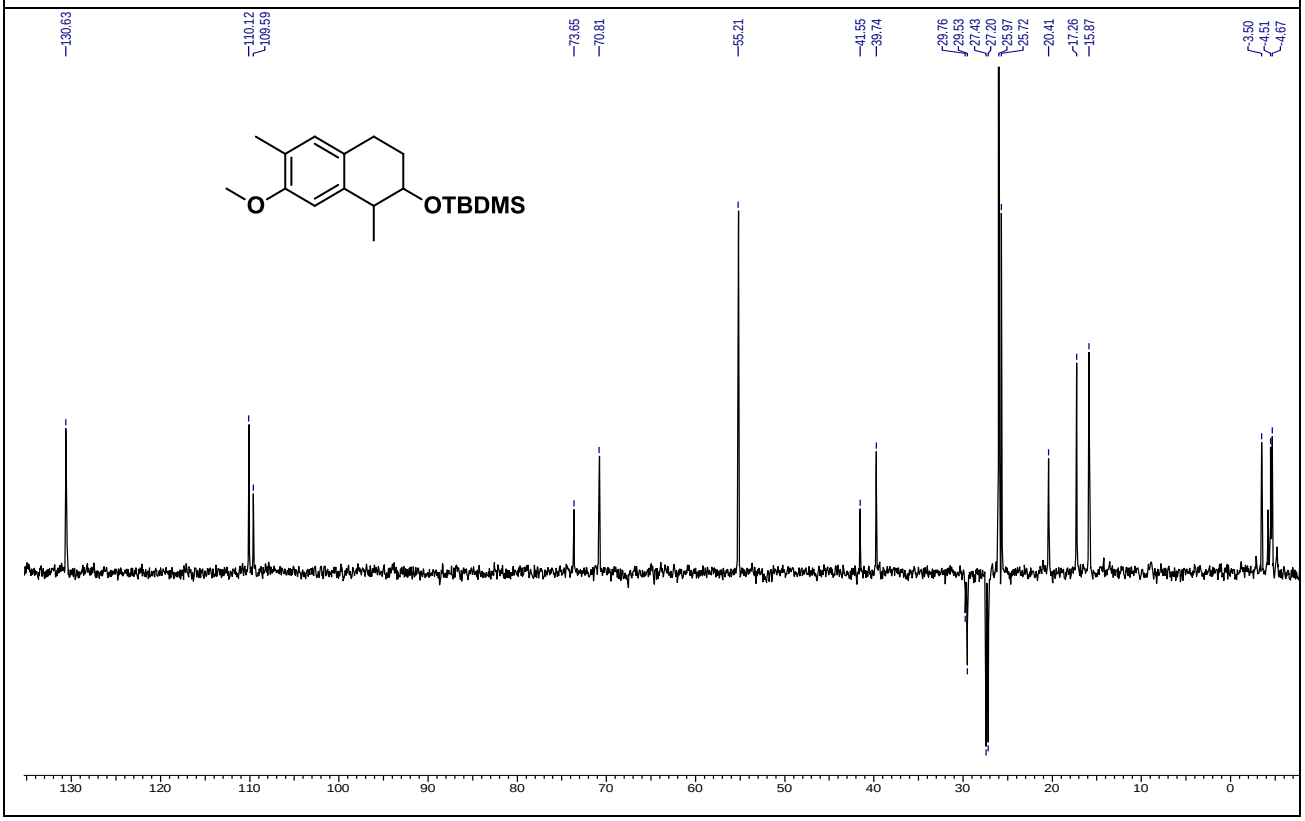
^{1}H NMR spectrum of compound **8** ($CDCl_3$+CCl_4, 200 MHz)



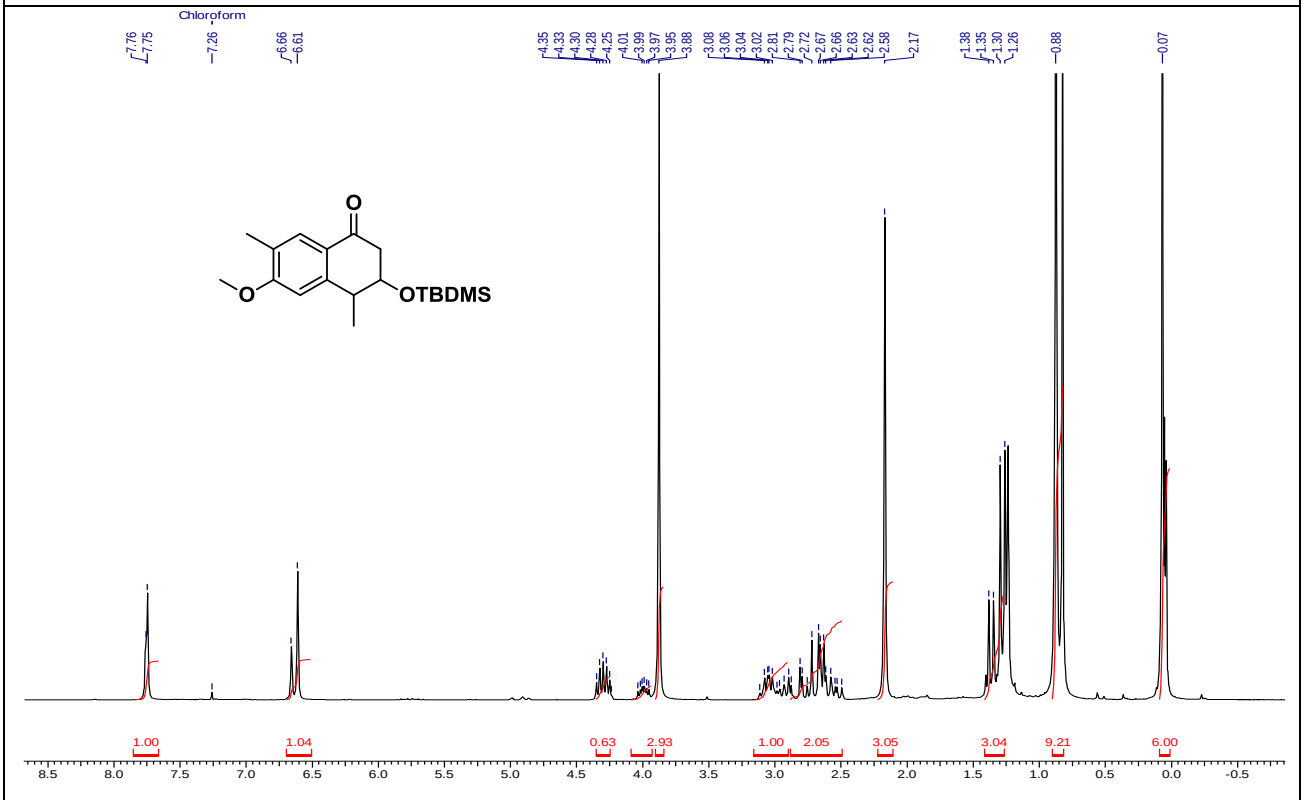
^{13}C NMR spectrum of compound **8** ($CDCl_3$+CCl_4, 50 MHz)



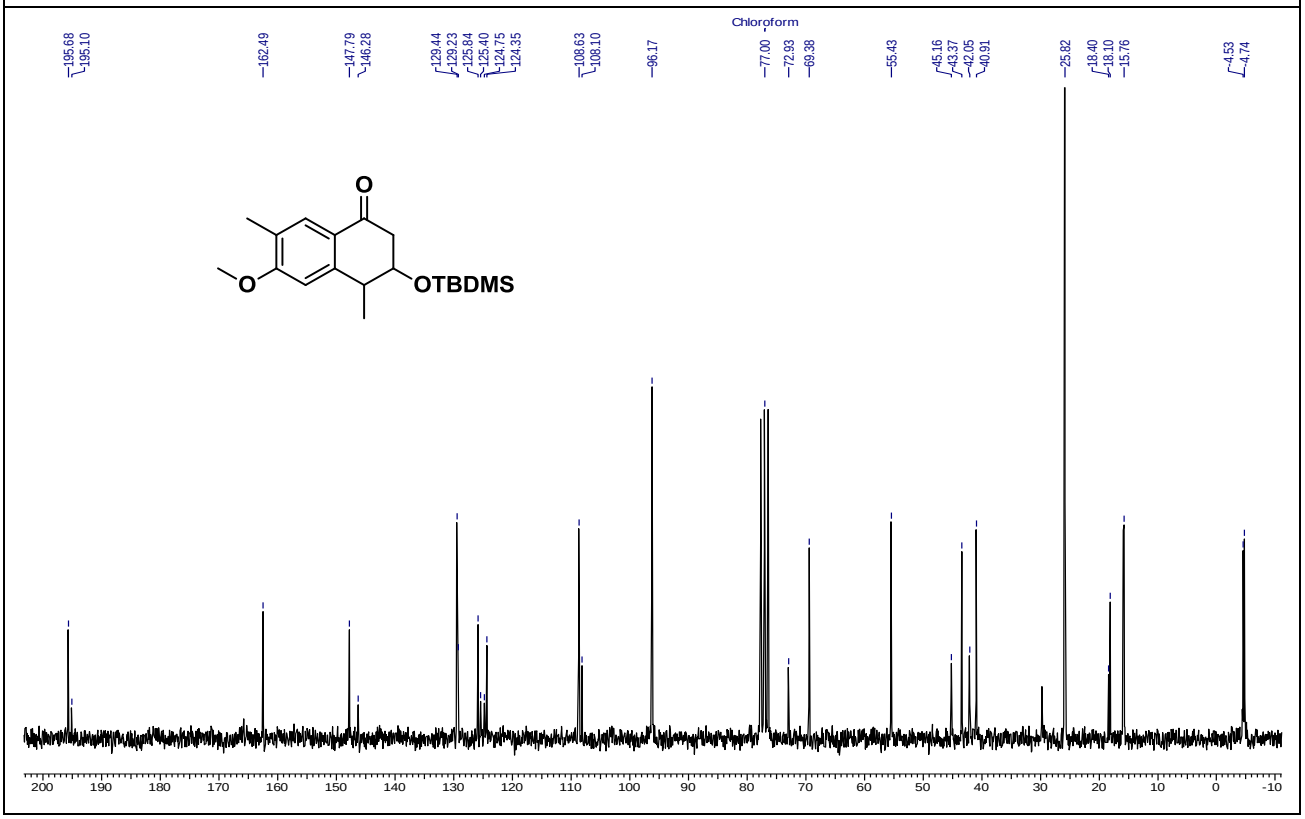
DEPT spectrum of compound **8** ($CDCl_3$+CCl_4, 50 MHz)



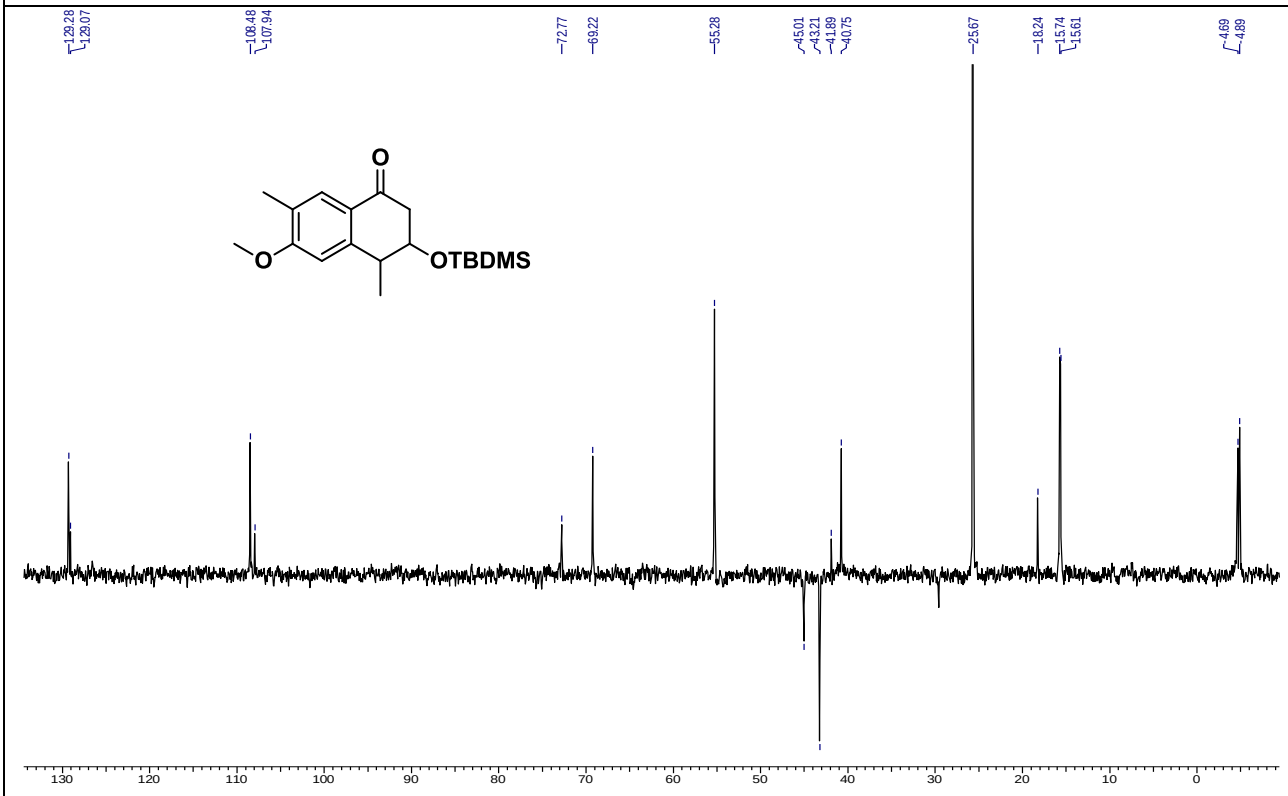
^{1}H NMR spectrum of compound **9** ($CDCl_3$+CCl_4, 200 MHz)



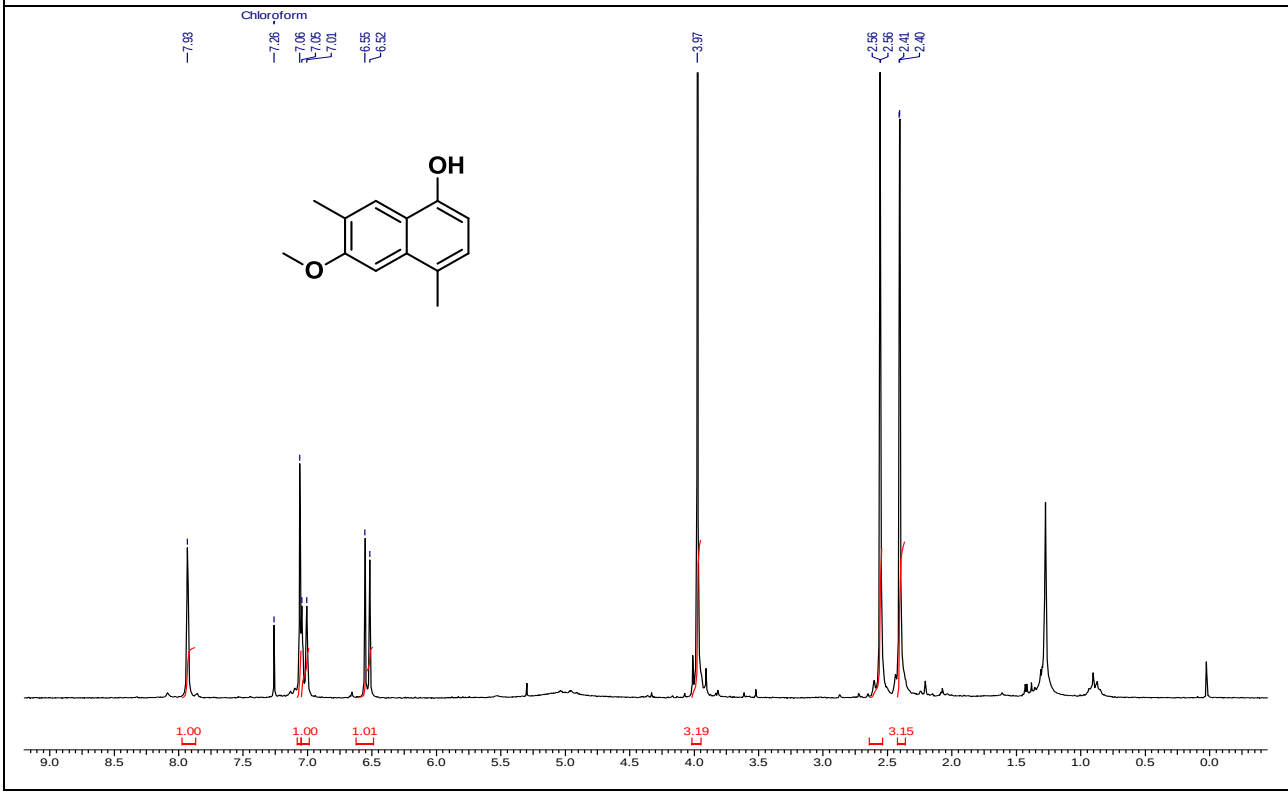
^{13}C NMR spectrum of compound **9** ($CDCl_3$+CCl_4, 50 MHz)



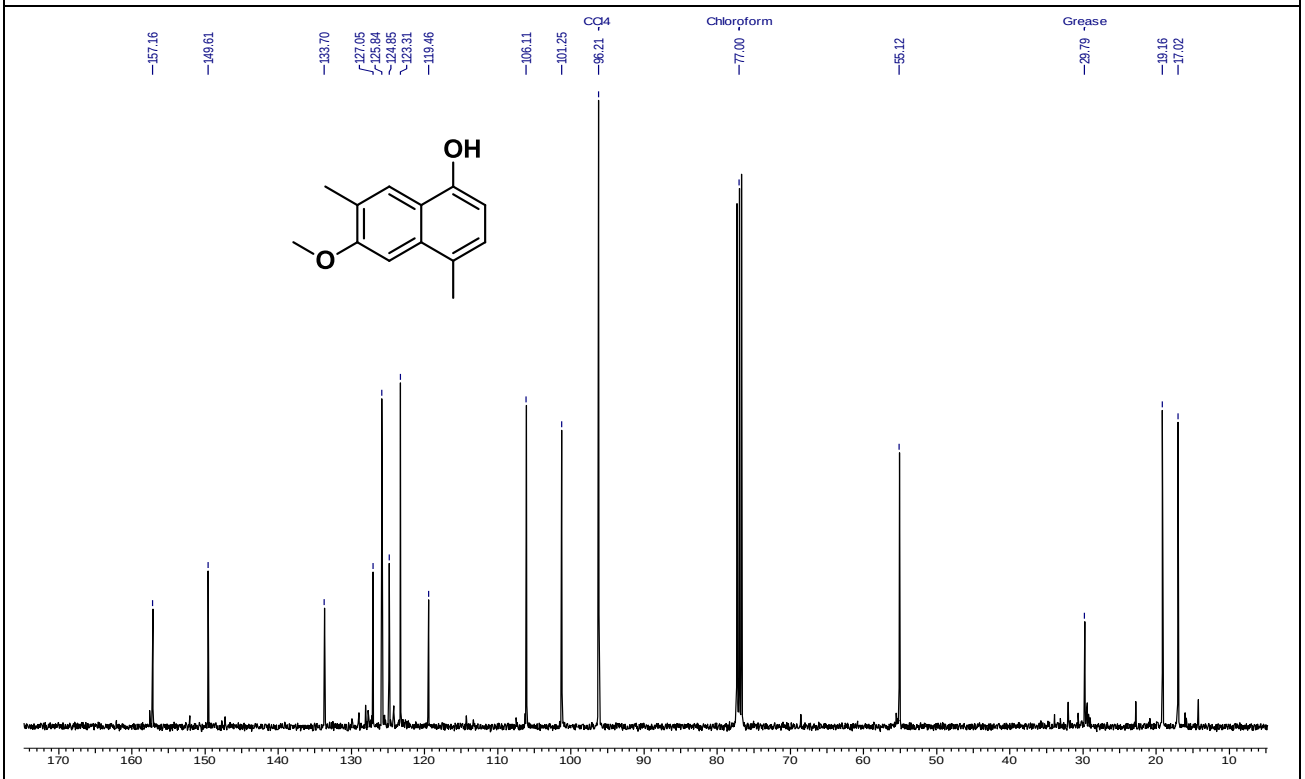
DEPT spectrum of compound **9** ($CDCl_3$+CCl_4, 50 MHz)



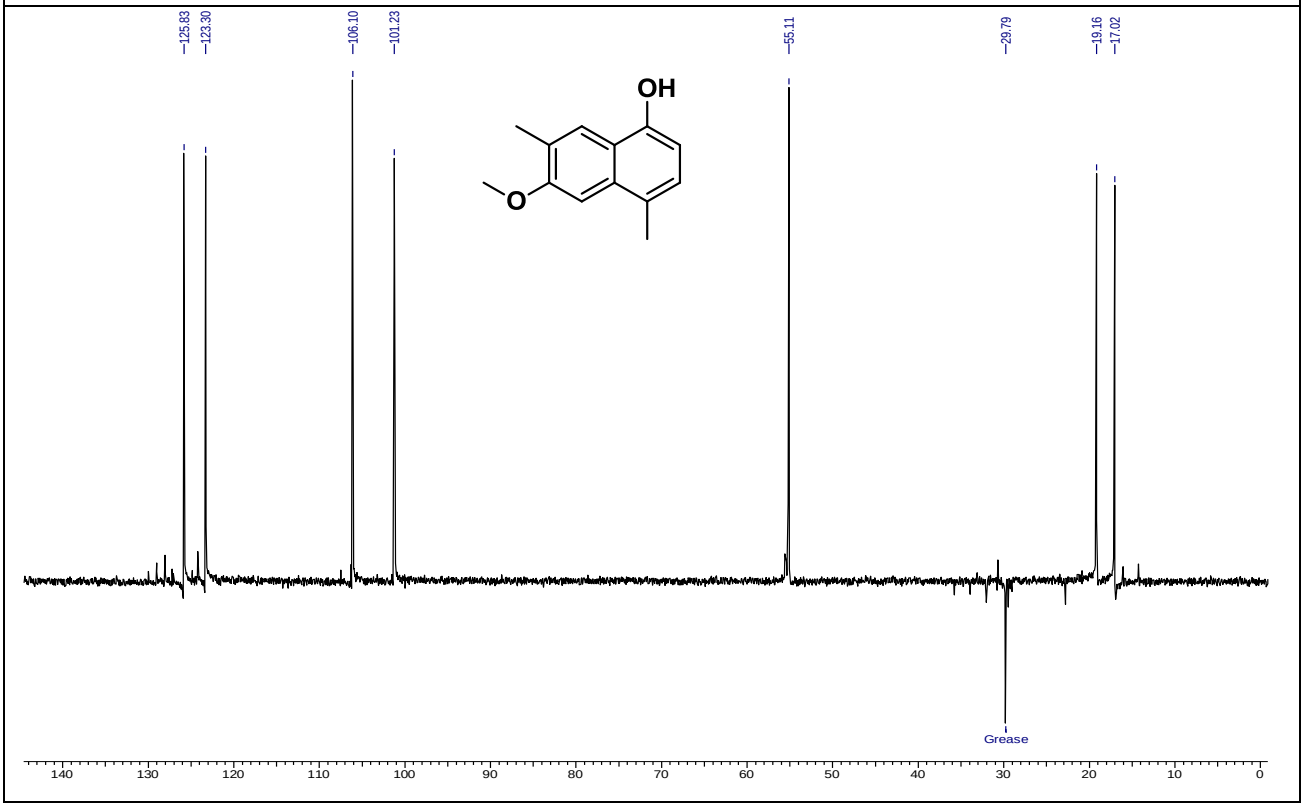
^{1}H NMR spectrum of compound **18** ($CDCl_3$+CCl_4, 200 MHz)



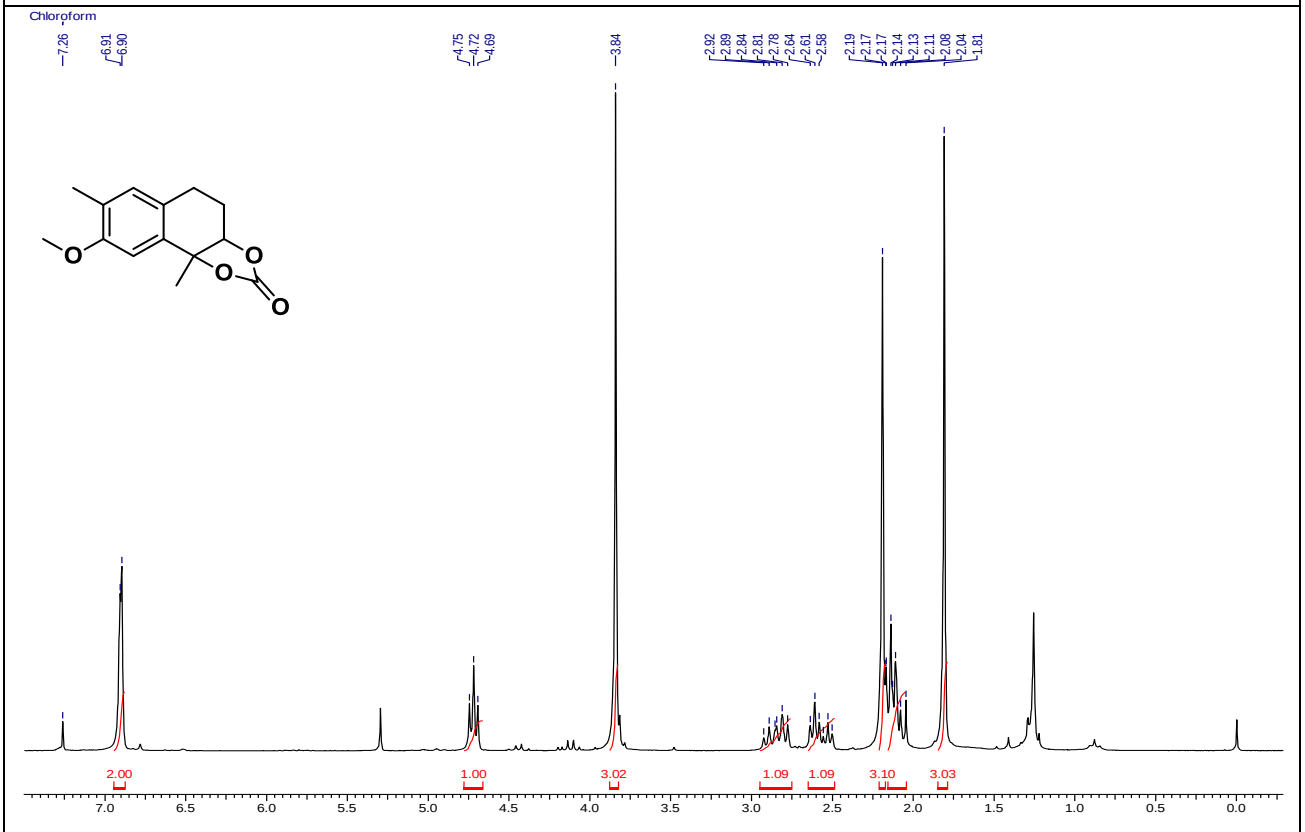
^{13}C NMR spectrum of compound **18** ($CDCl_3$+CCl_4, 50 MHz)



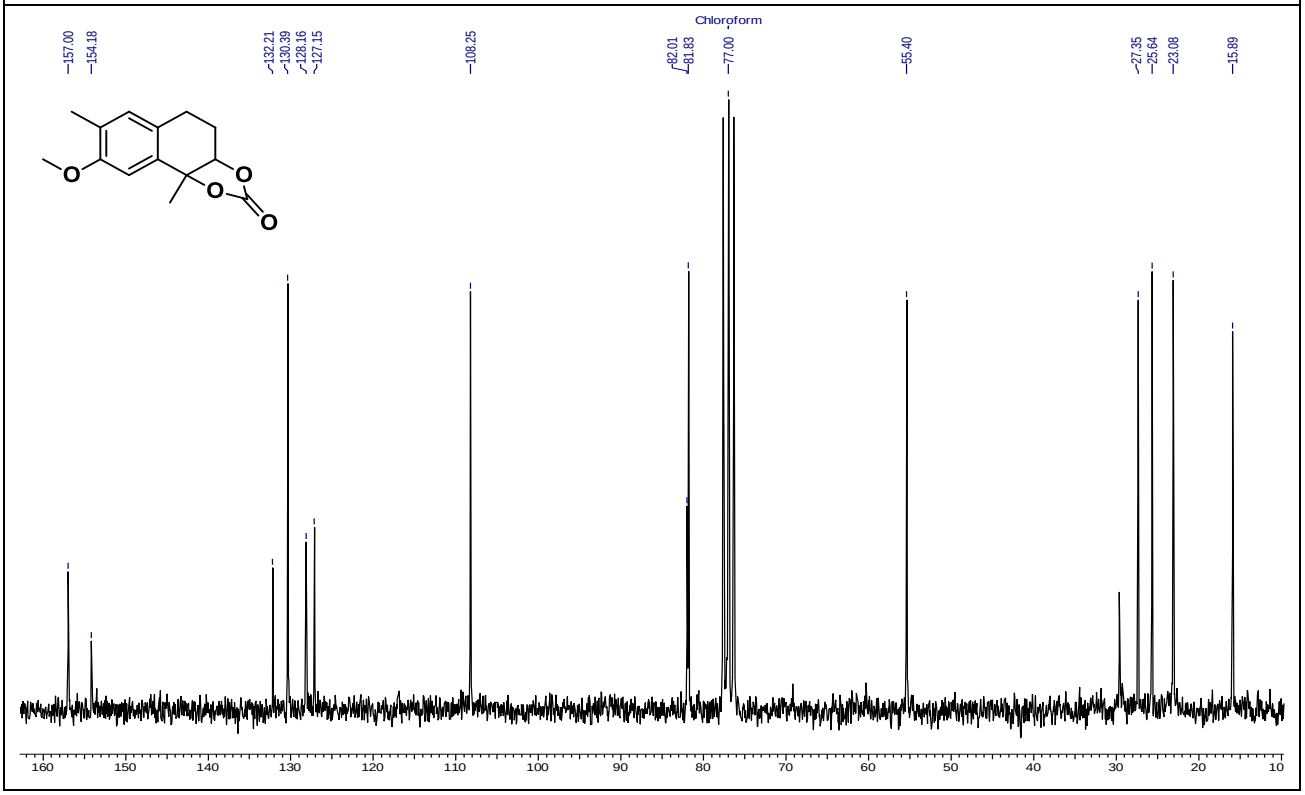
DEPT spectrum of compound **18** ($CDCl_3$+CCl_4, 50 MHz)



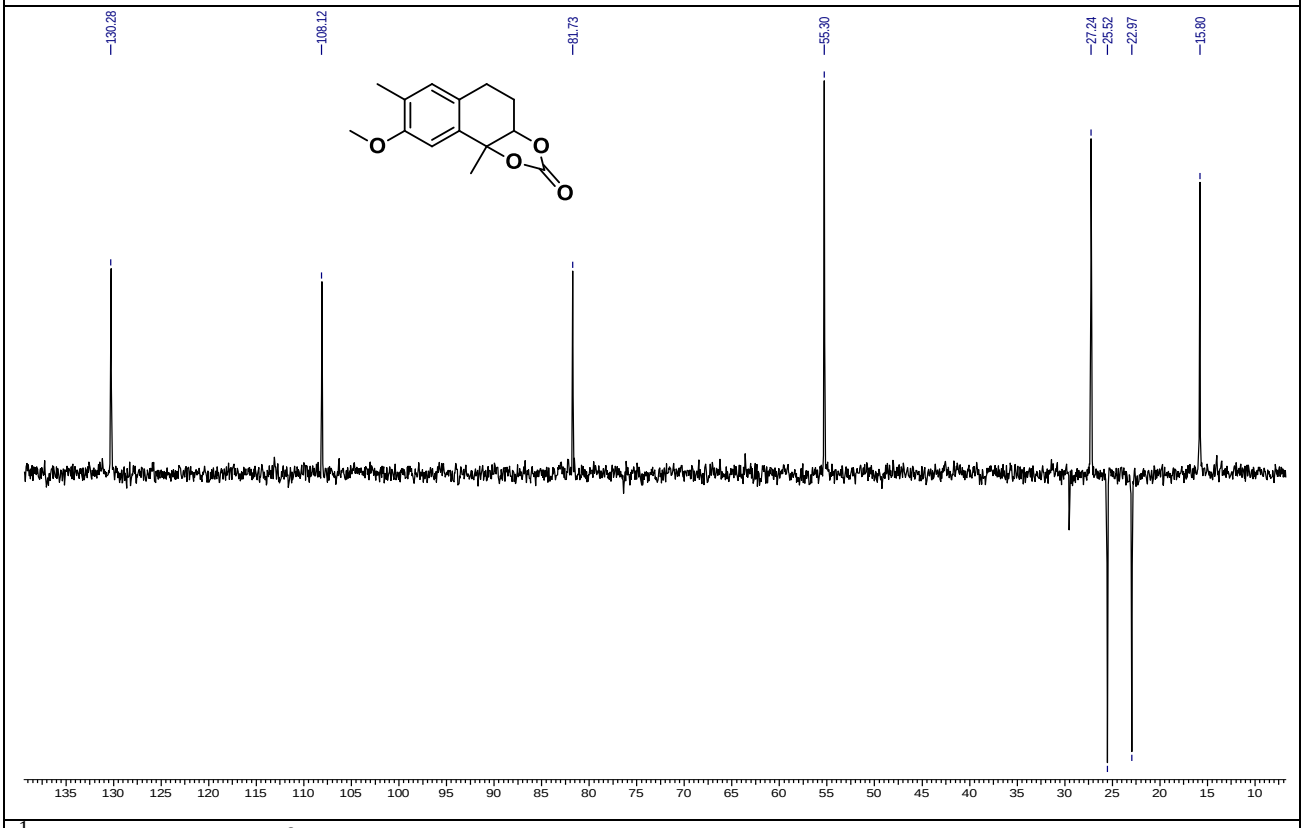
^{1}H NMR spectrum of compound **11** ($CDCl_3$, 200 MHz)



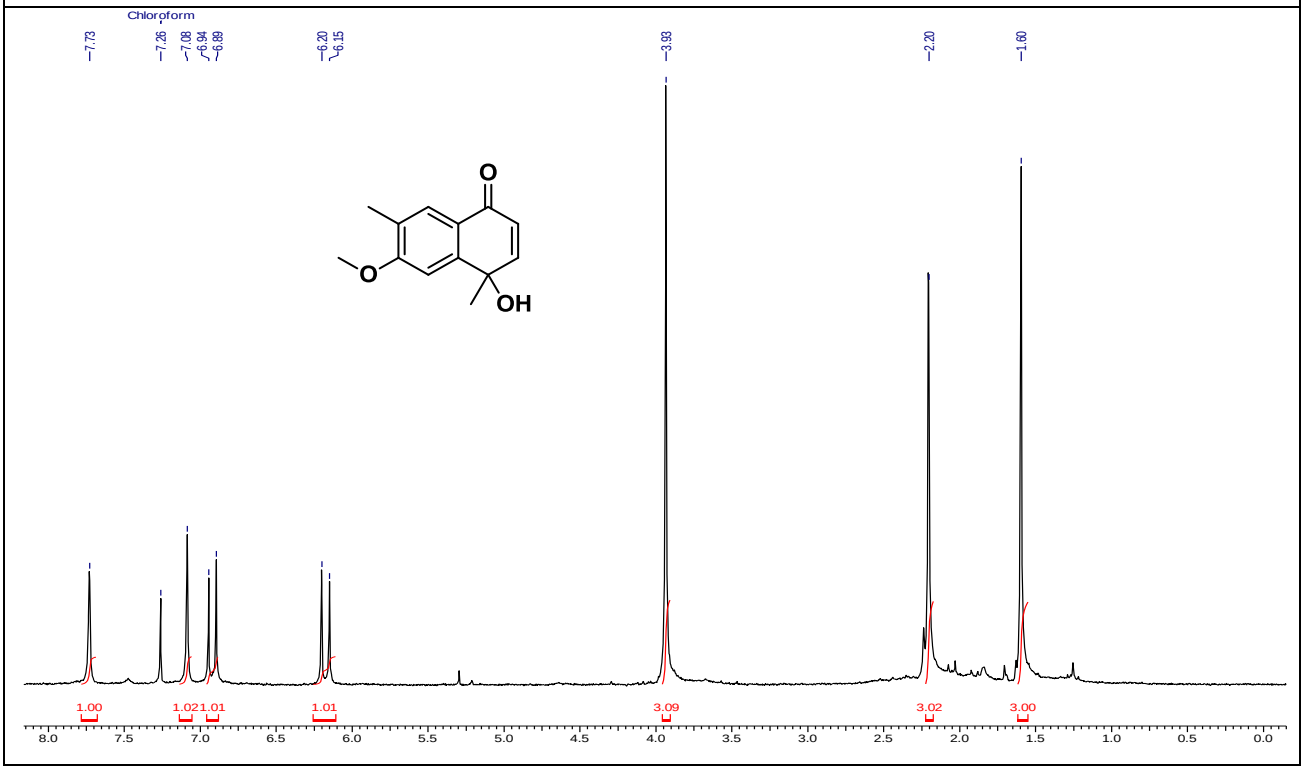
^{13}C NMR spectrum of compound **11** ($CDCl_3$, 50 MHz)



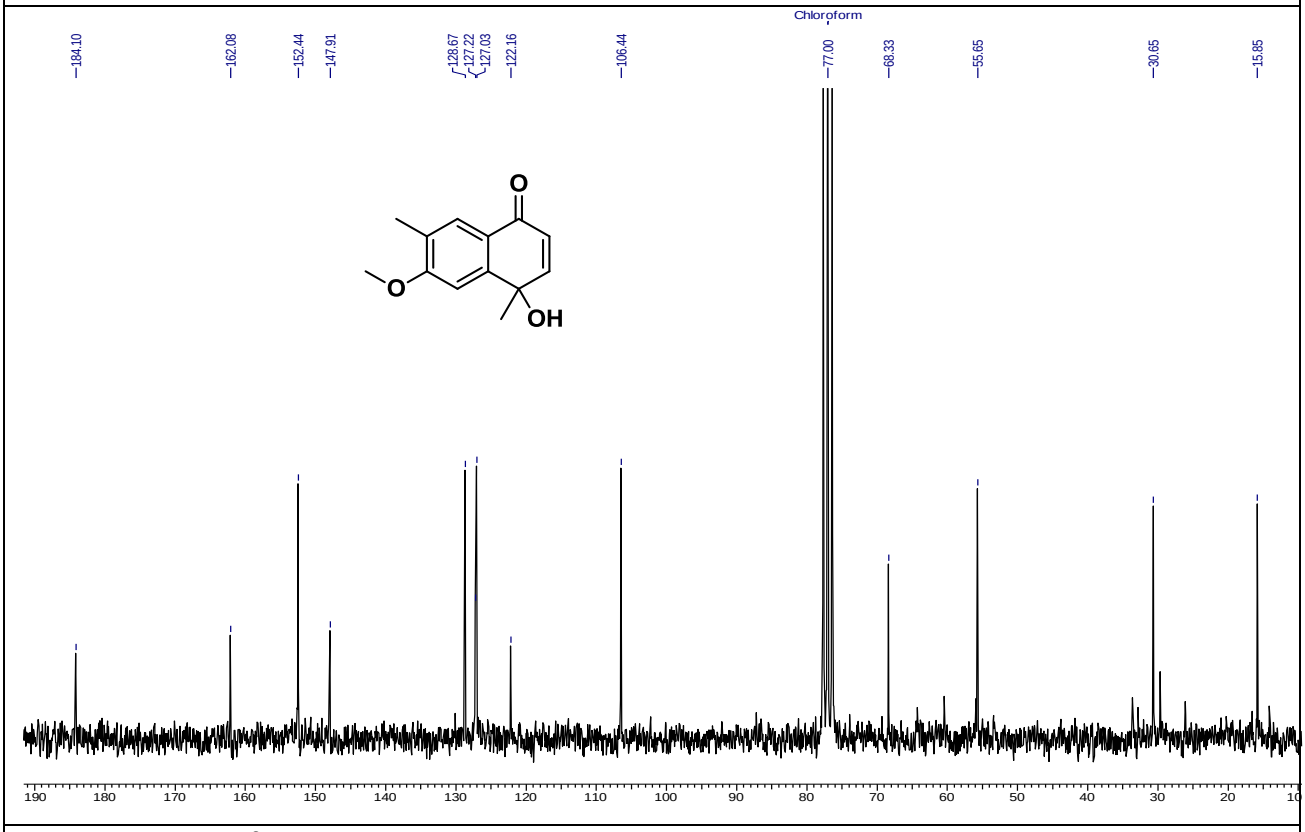
DEPT spectrum of compound **11** ($CDCl_3$, 50 MHz)



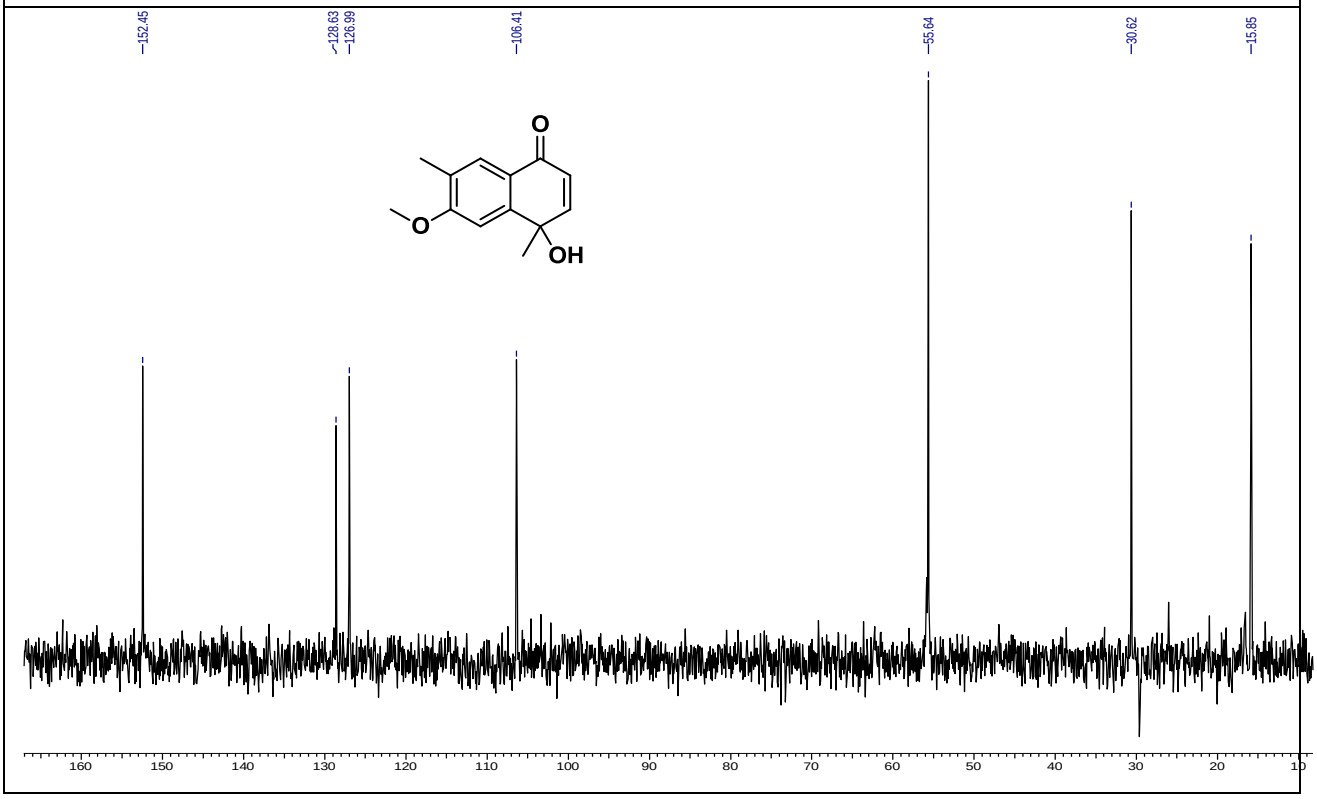
^1H NMR spectrum of compound **13** ($CDCl_3$, 200 MHz)



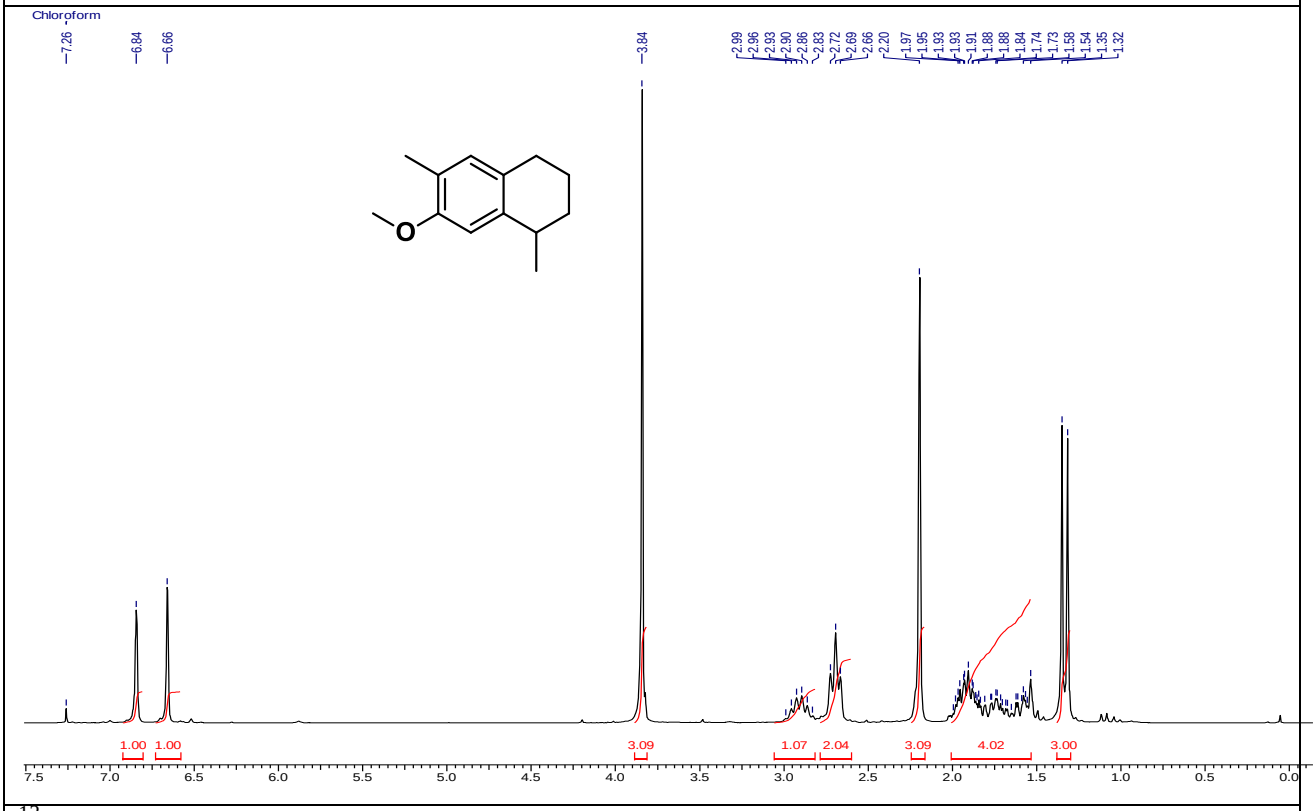
^{13}C NMR spectrum of compound **13** ($CDCl_3$, 50 MHz)



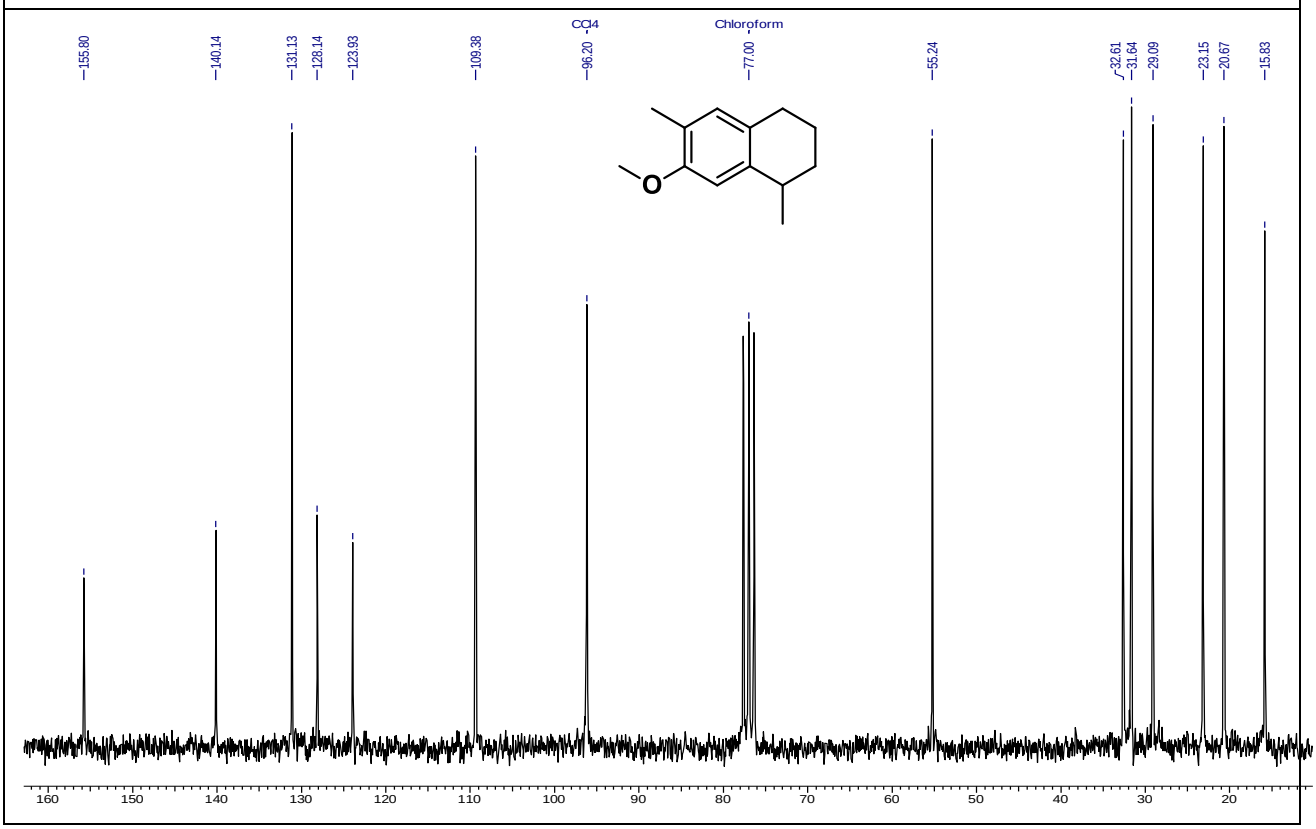
DEPT spectrum of compound **13** ($CDCl_3$, 50 MHz)



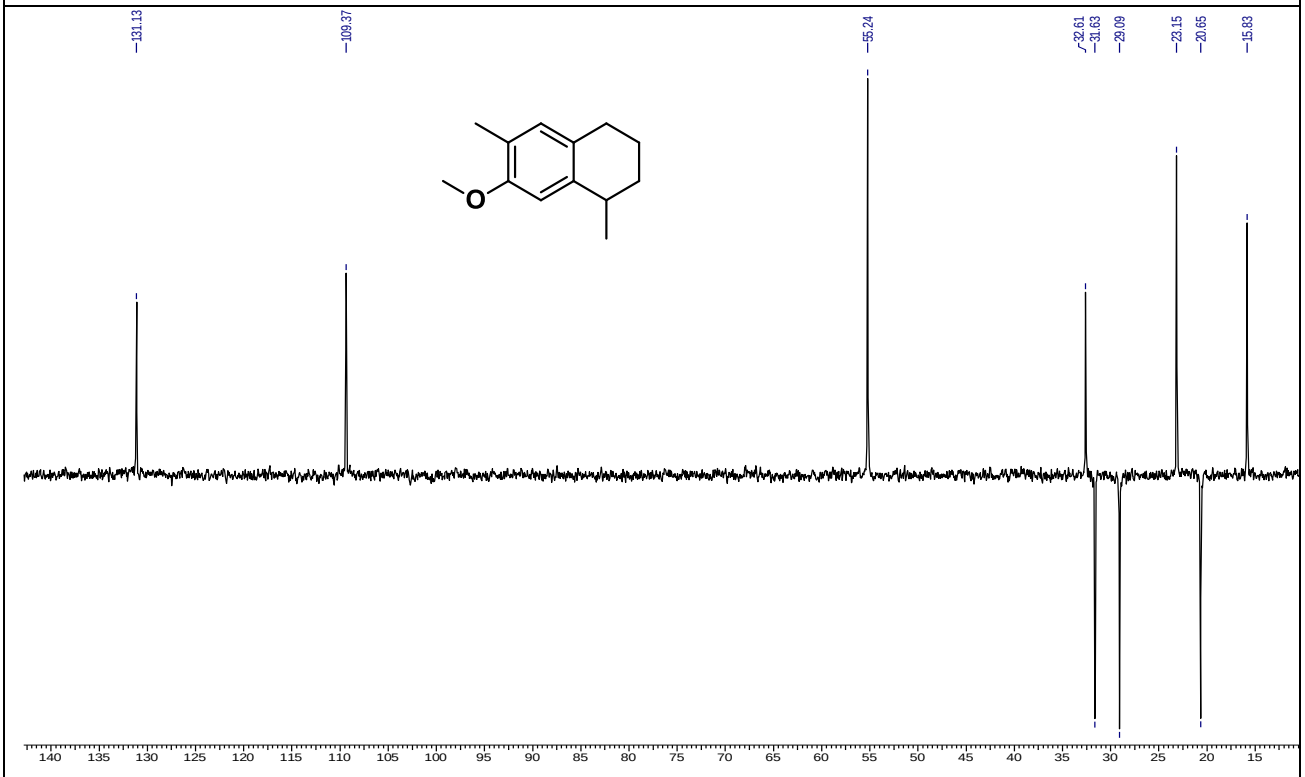
^{1}H NMR spectrum of compound **15** ($CDCl_3$+CCl_4, 200 MHz)



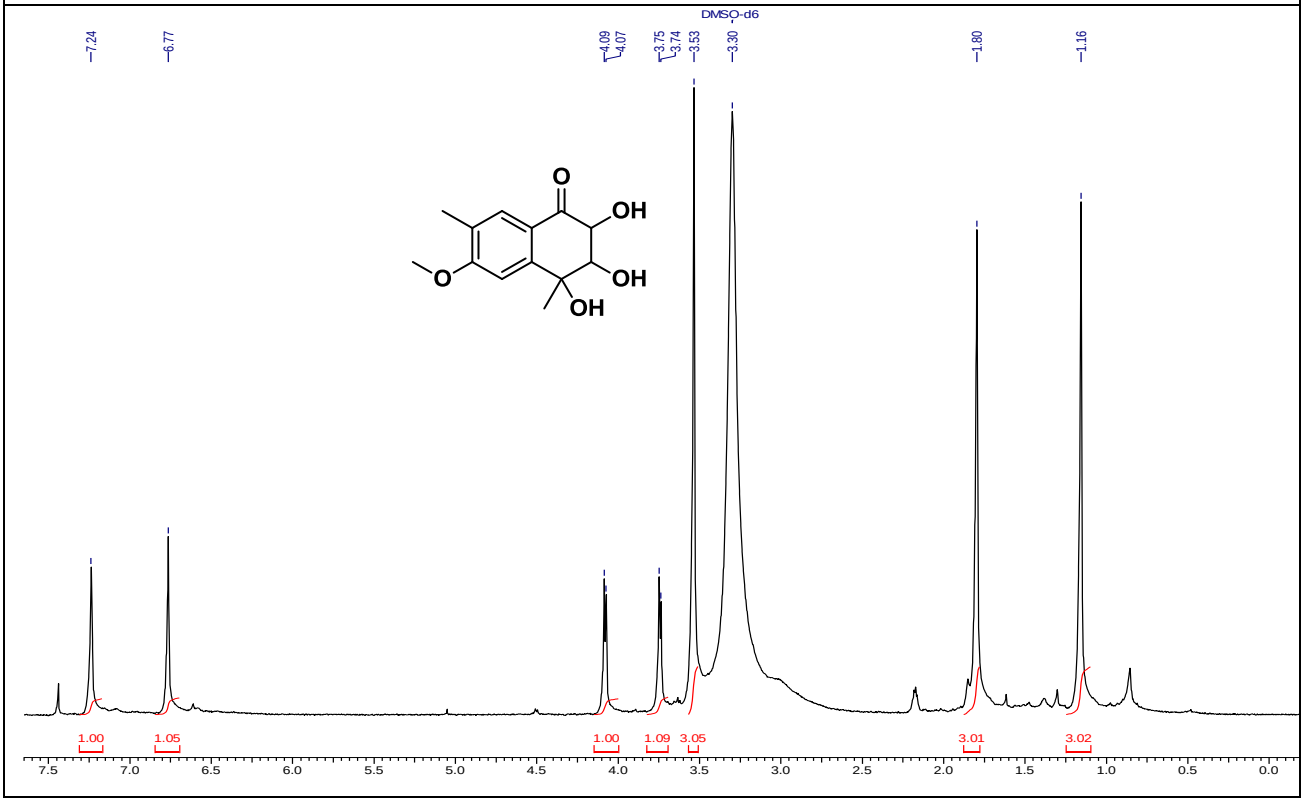
^{13}C NMR spectrum of compound **15** ($CDCl_3$+CCl_4, 50 MHz)



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



^{1}H NMR spectrum of compound **16** ($CDCl_3$+CCl_4+DMSO–d_6, 200 MHz)



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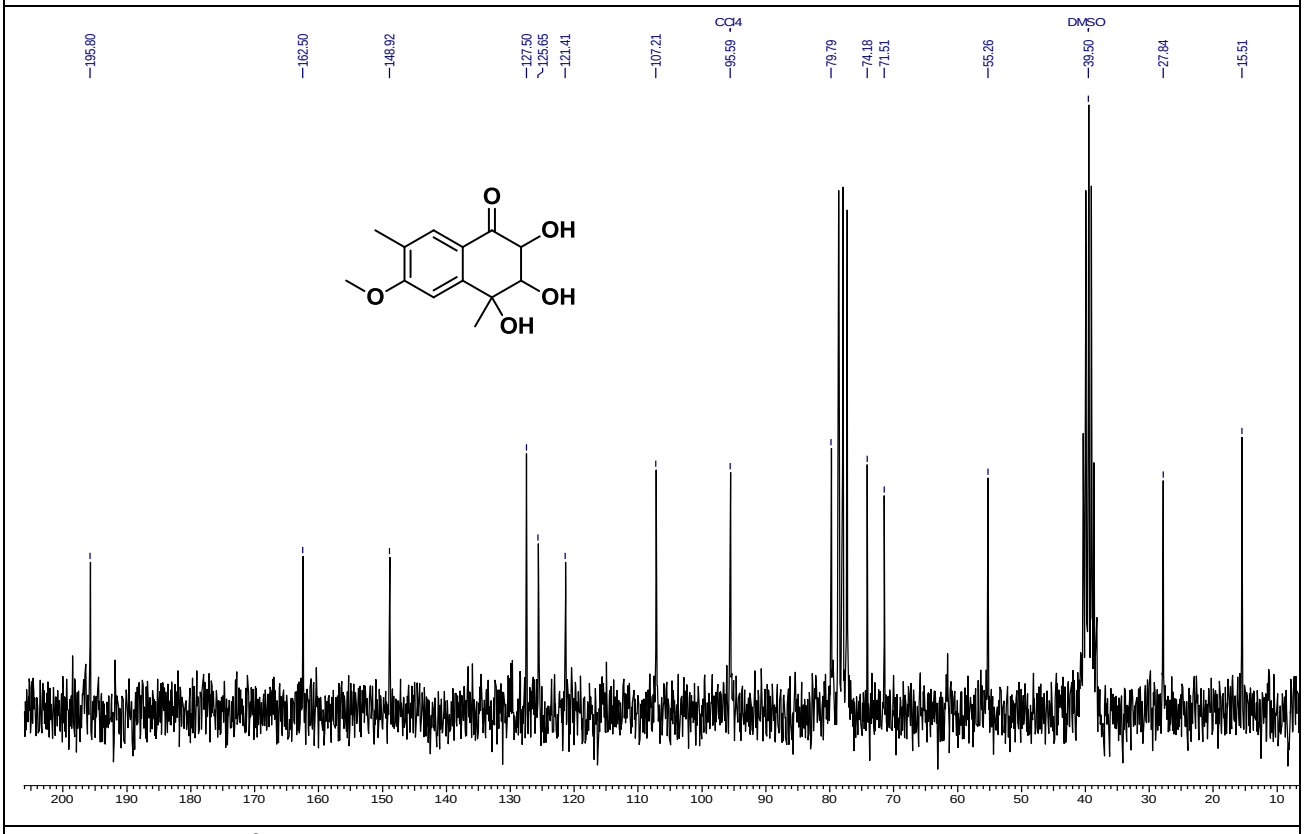
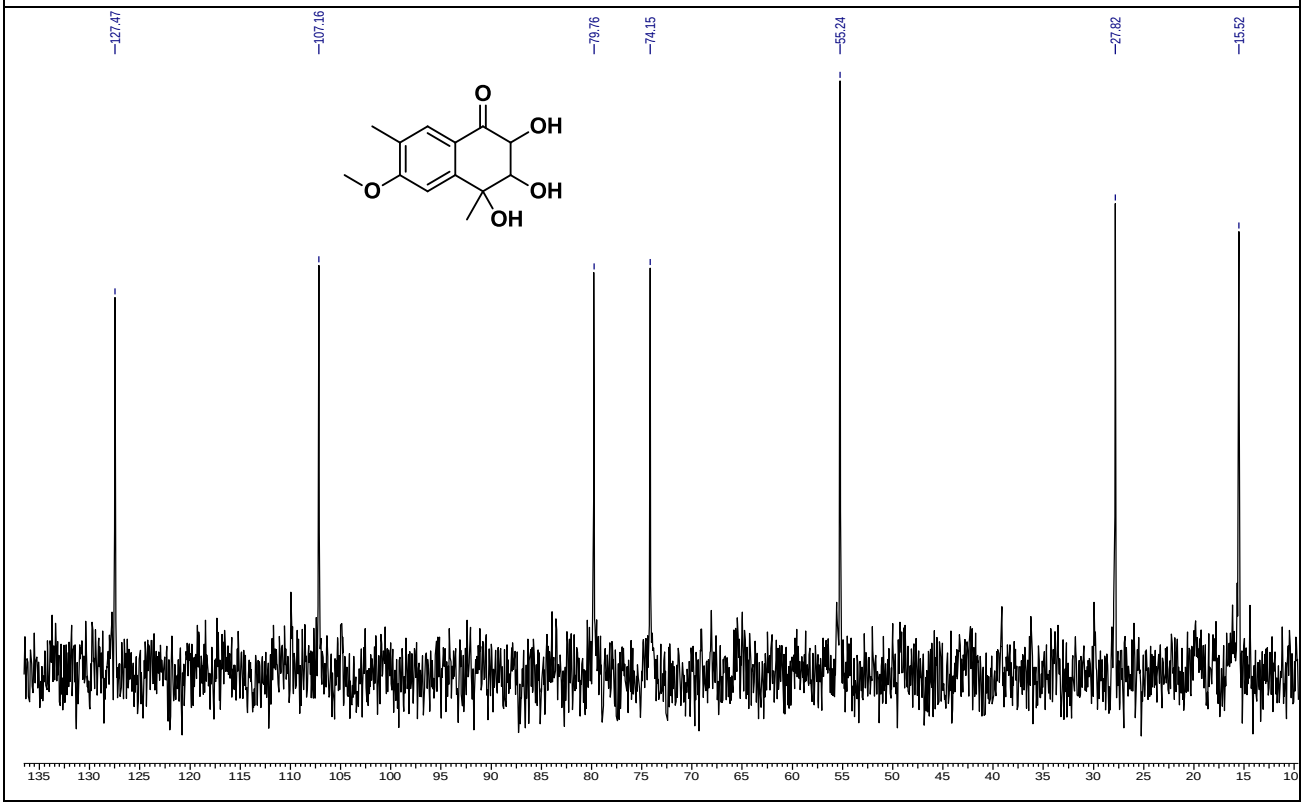
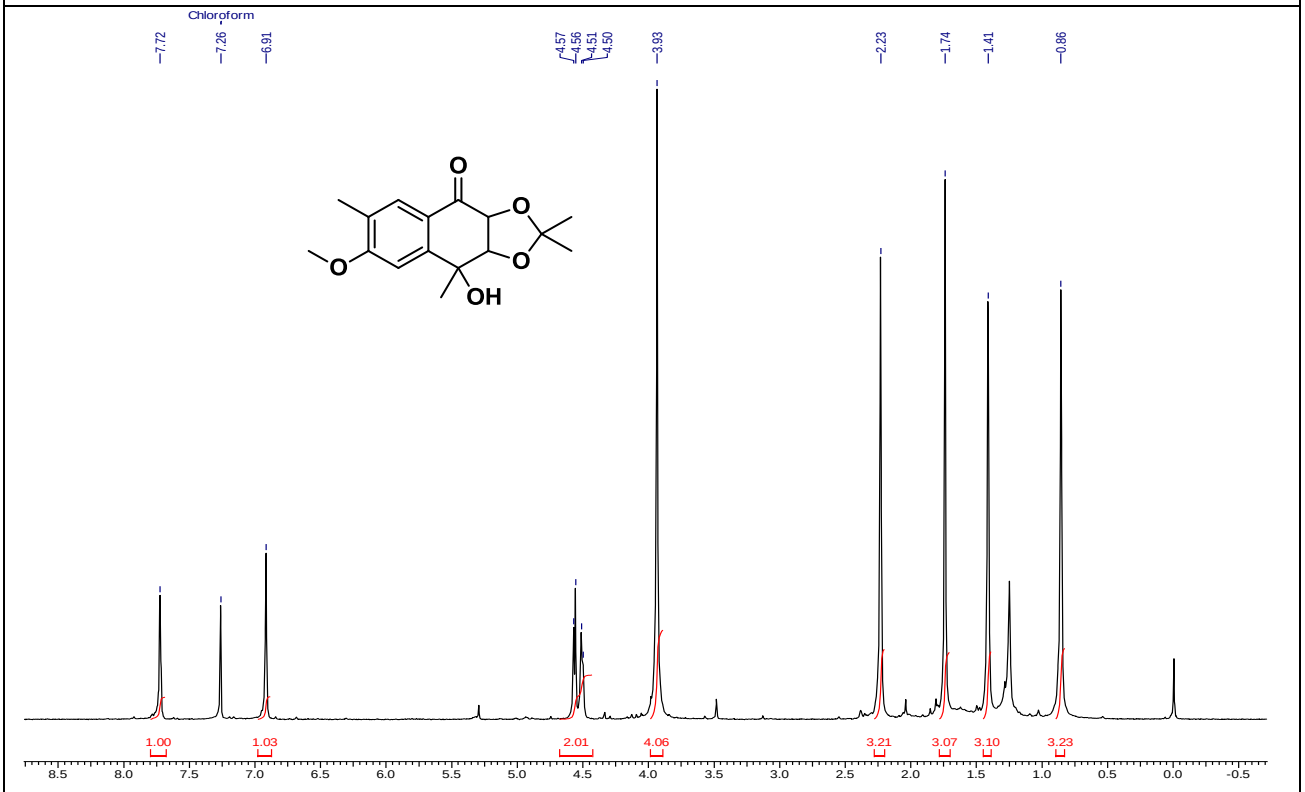


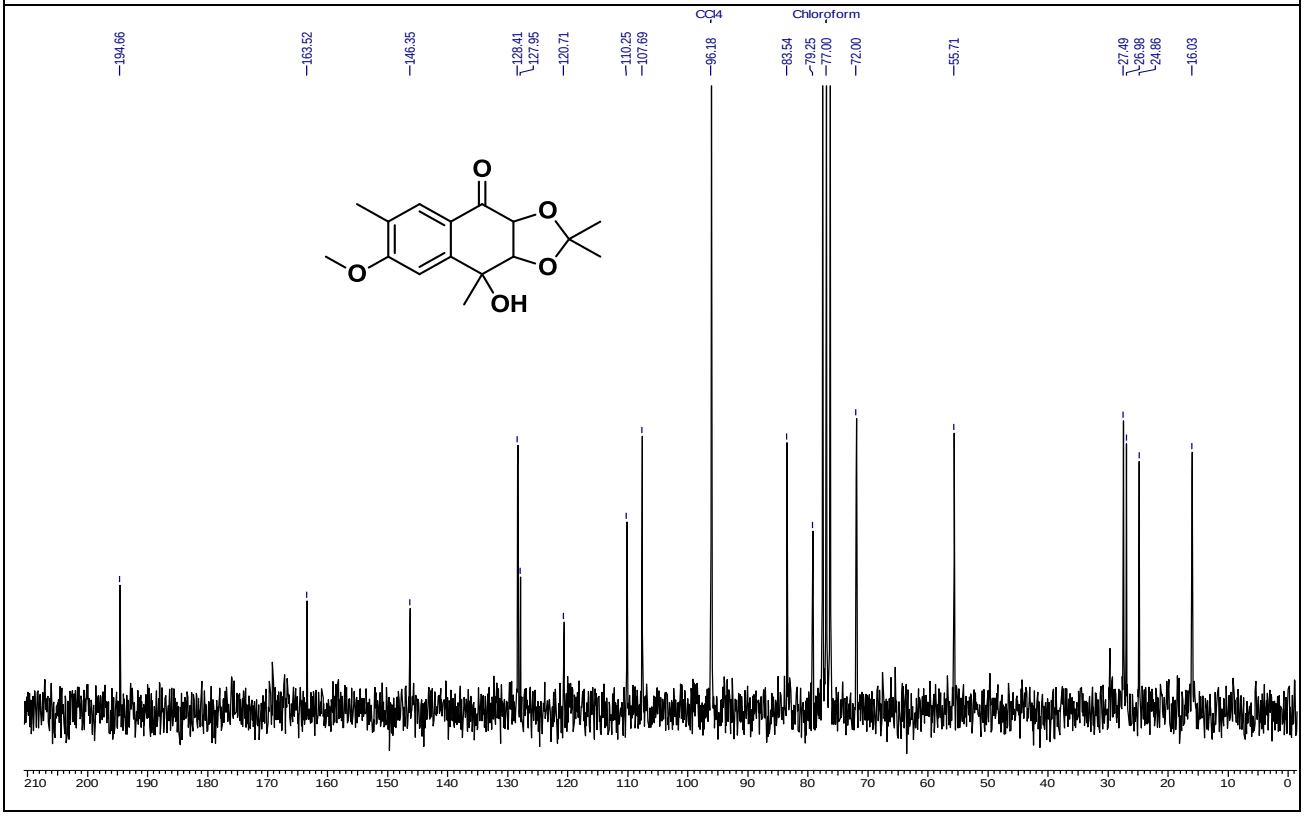
DEPT spectrum of compound **16** ($CDCl_3$+CCl_4+DMSO–d_6, 50 MHz)



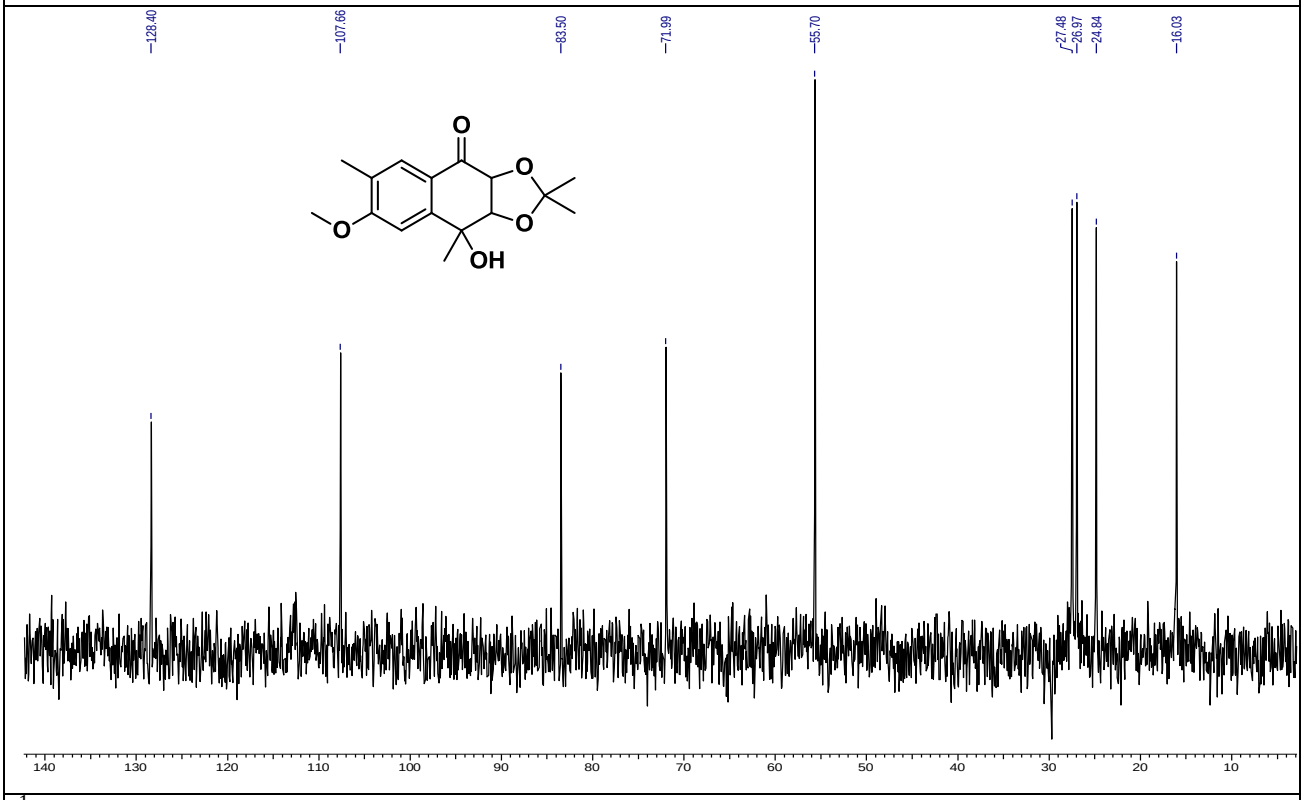
^{1}H NMR spectrum of compound **20** ($CDCl_3$+CCl_4, 200 MHz)



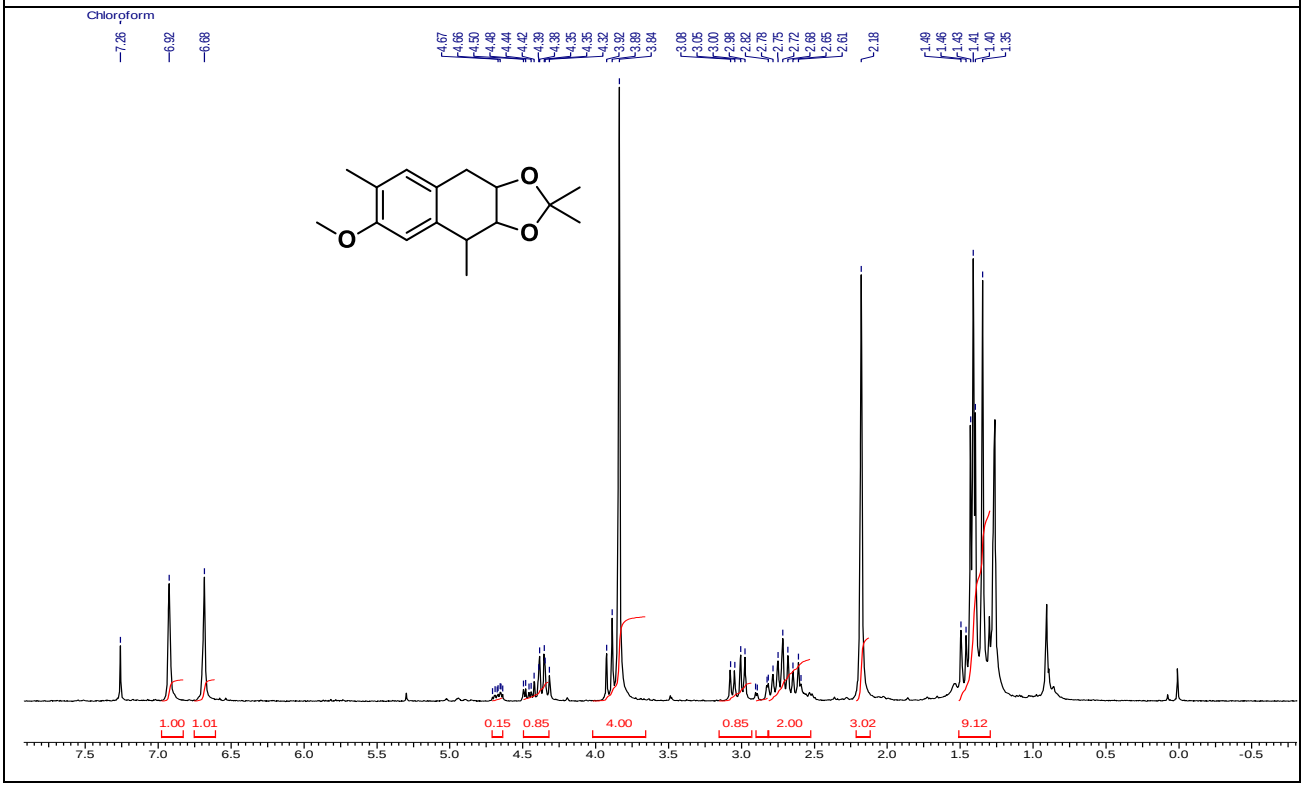
^{13}C NMR spectrum of compound **20** ($CDCl_3$+CCl_4, 50 MHz)



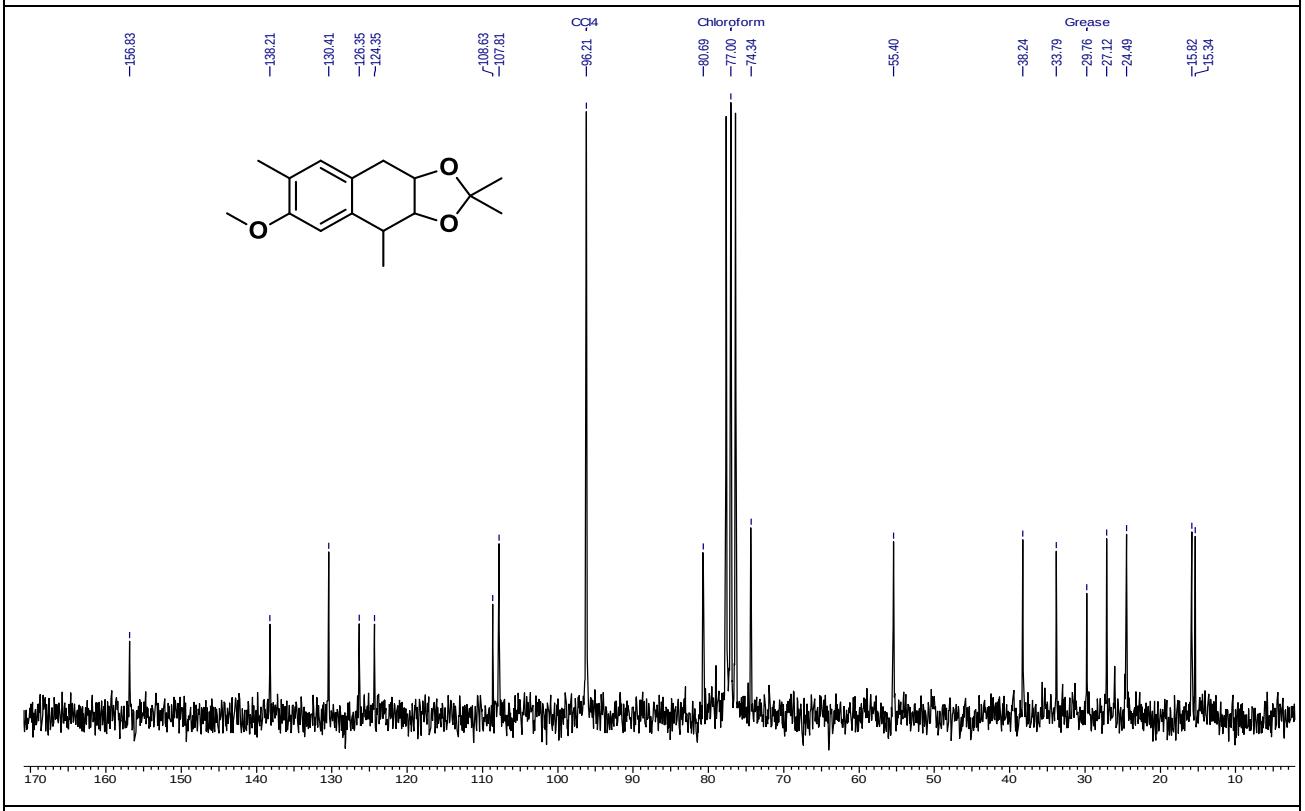
DEPT spectrum of compound **20** ($CDCl_3$+CCl_4, 50 MHz)



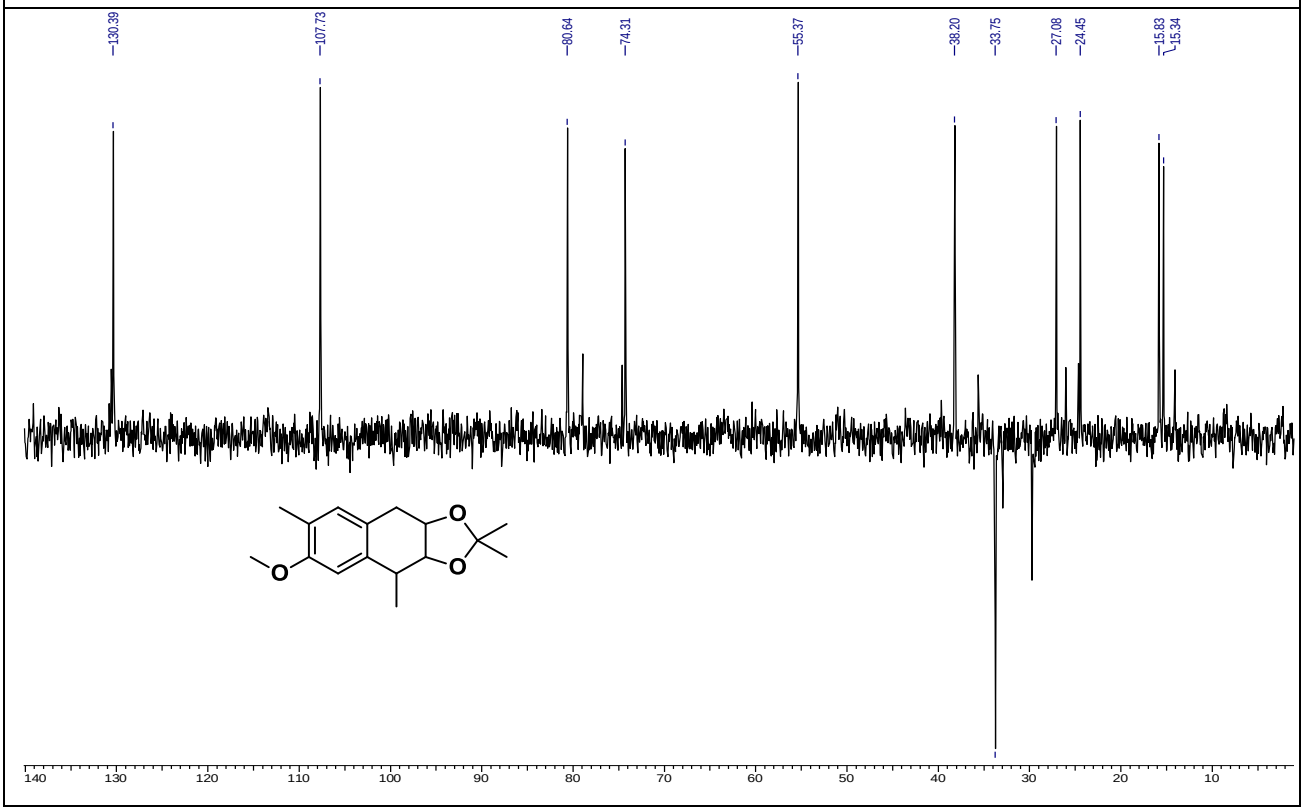
^{1}H NMR spectrum of compound **23** ($CDCl_3$+CCl_4, 200 MHz)



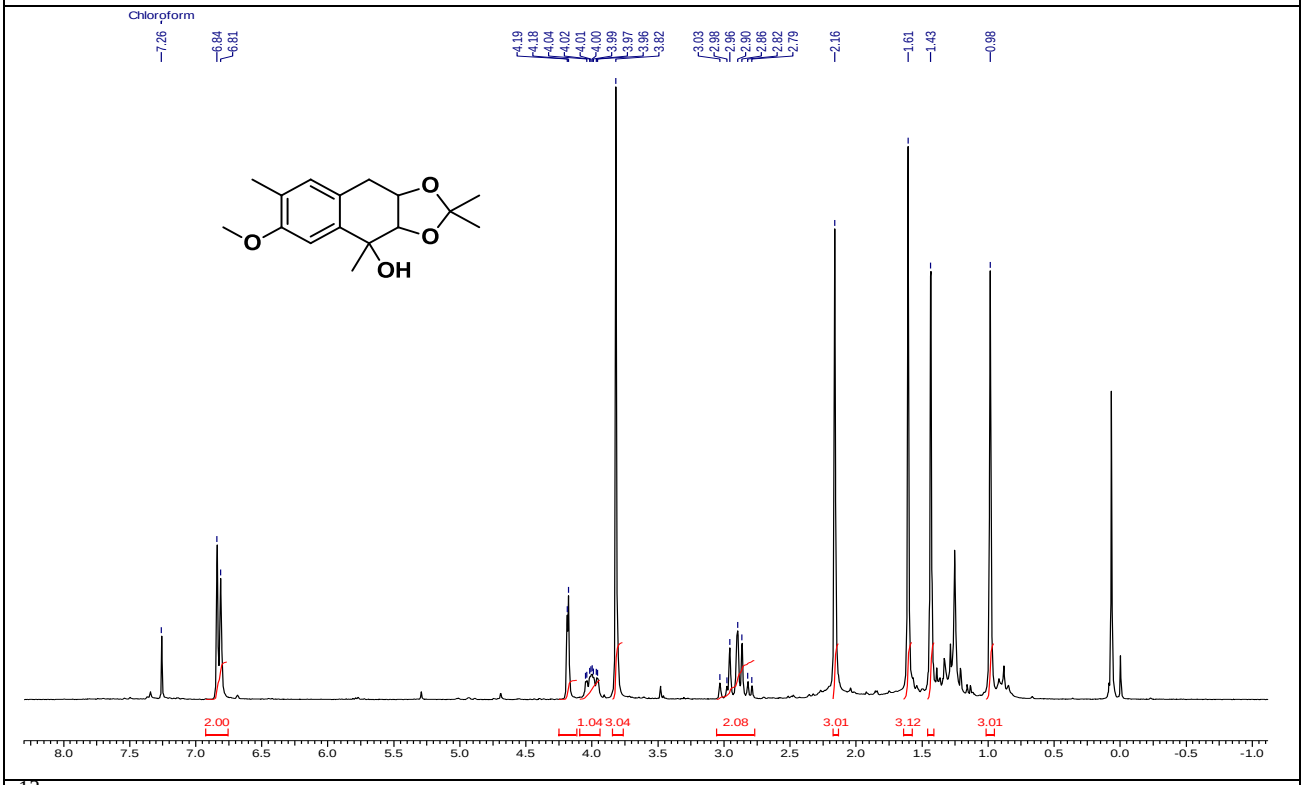
^{13}C NMR spectrum of compound **23** ($CDCl_3$+CCl_4, 50 MHz)



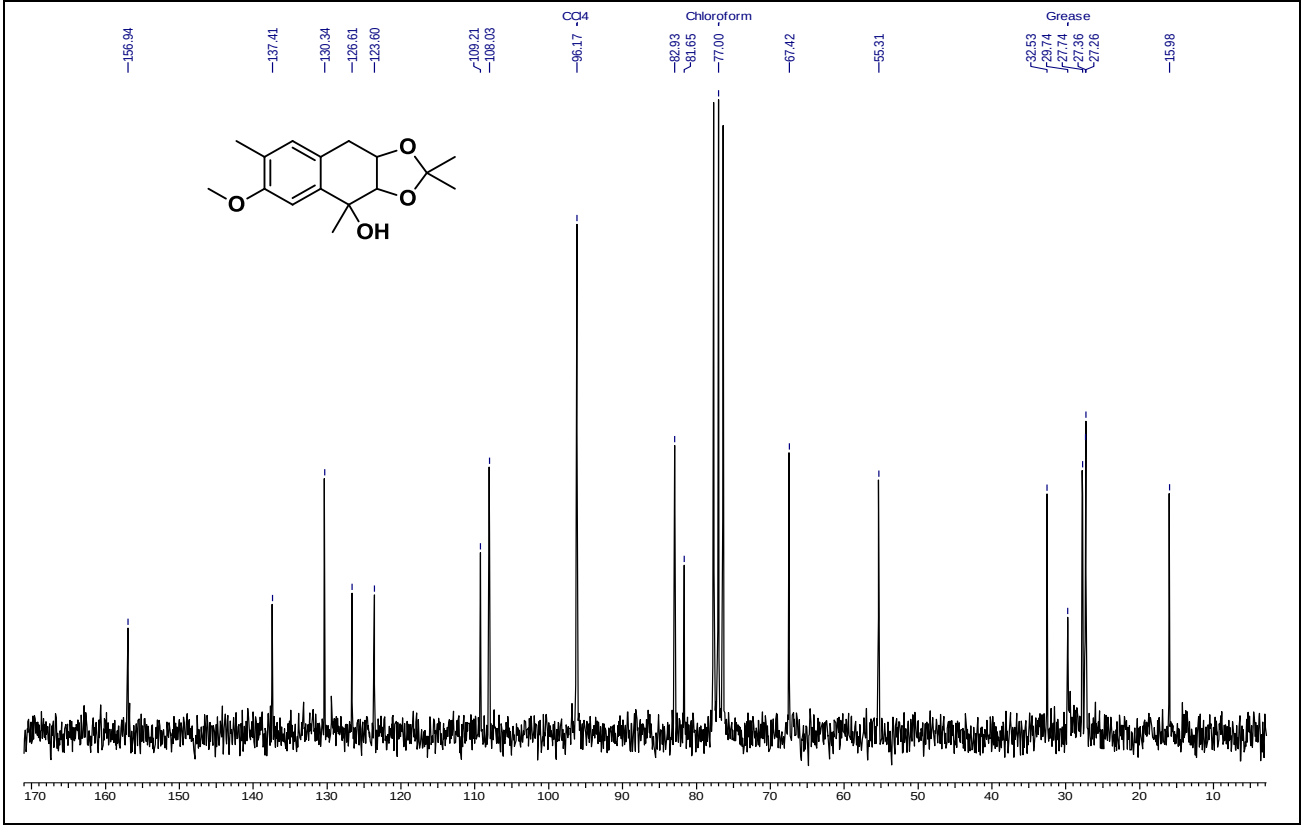
DEPT spectrum of compound **23** ($CDCl_3$+CCl_4, 50 MHz)



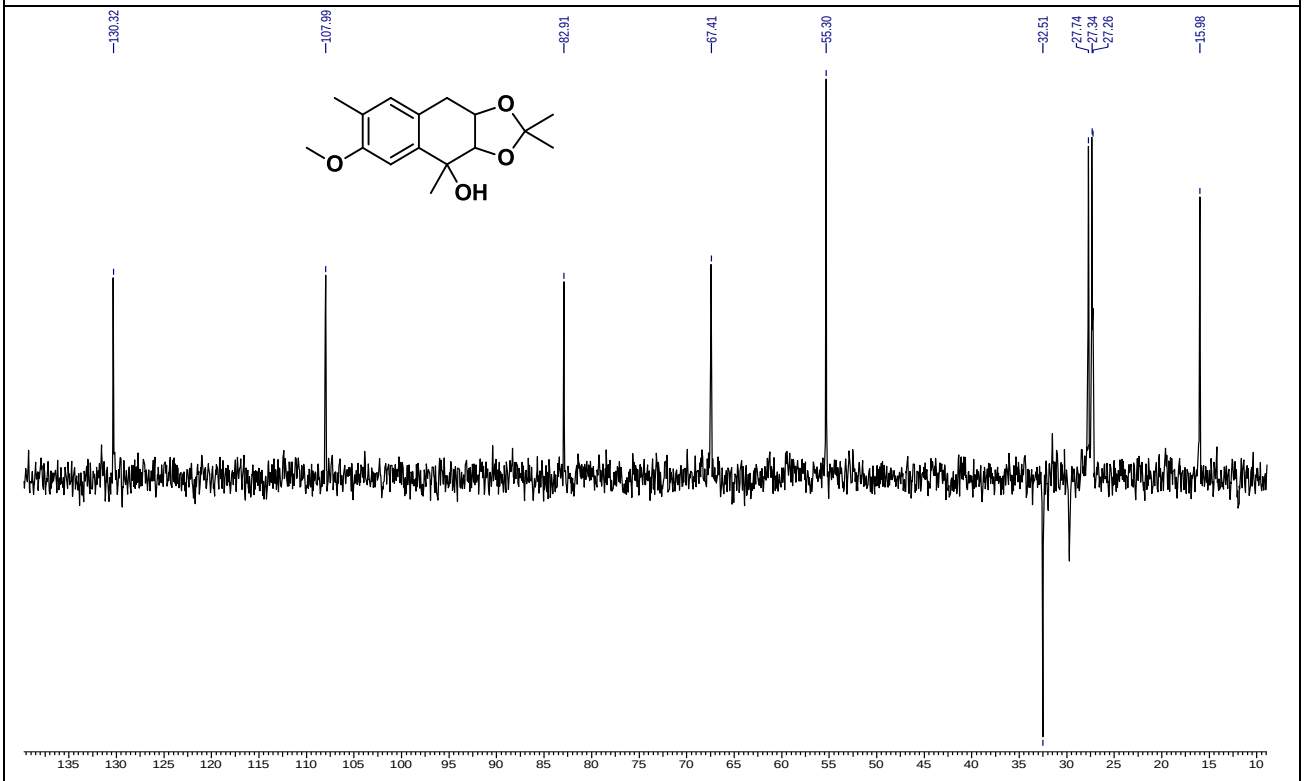
^{1}H NMR spectrum of compound **22** ($CDCl_3$+CCl_4, 200 MHz)



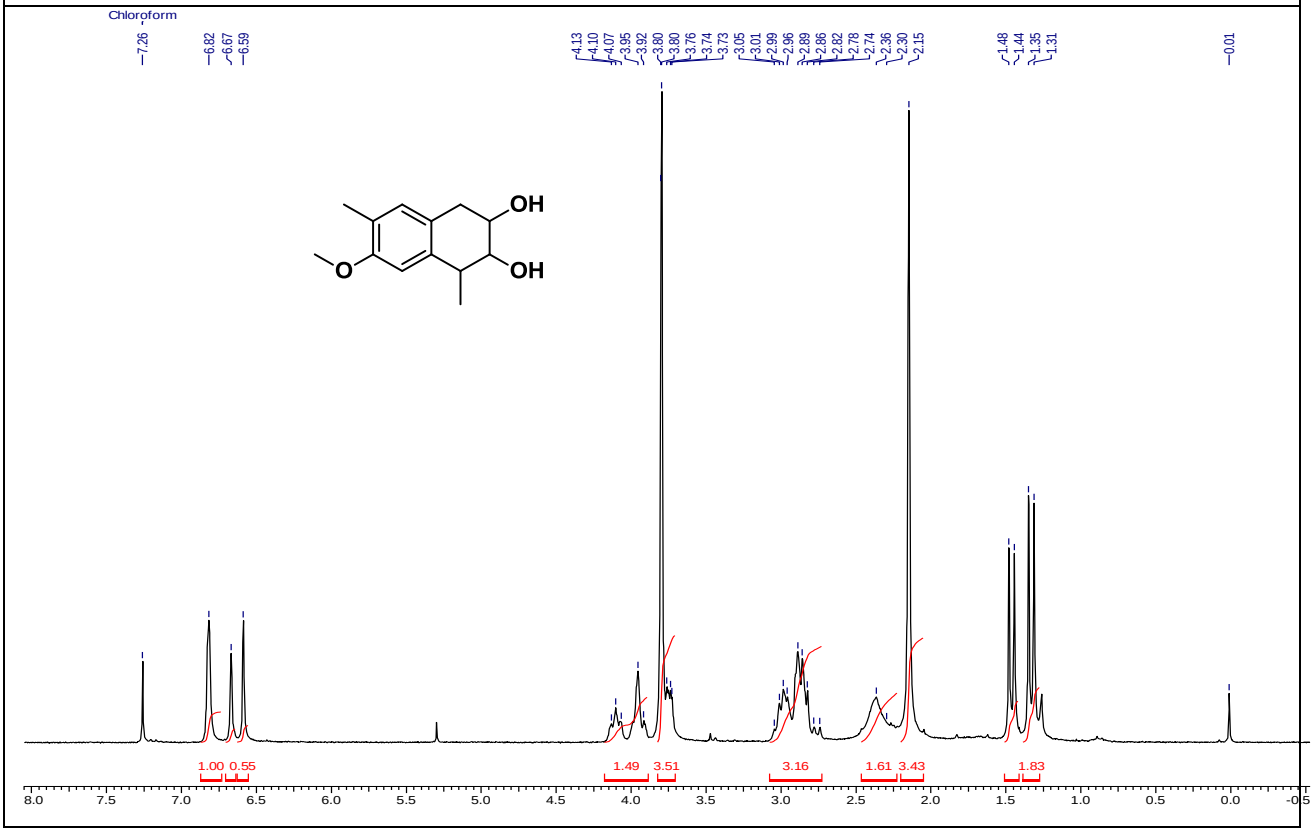
^{13}C NMR spectrum of compound **22**($CDCl_3$+CCl_4, 50 MHz)



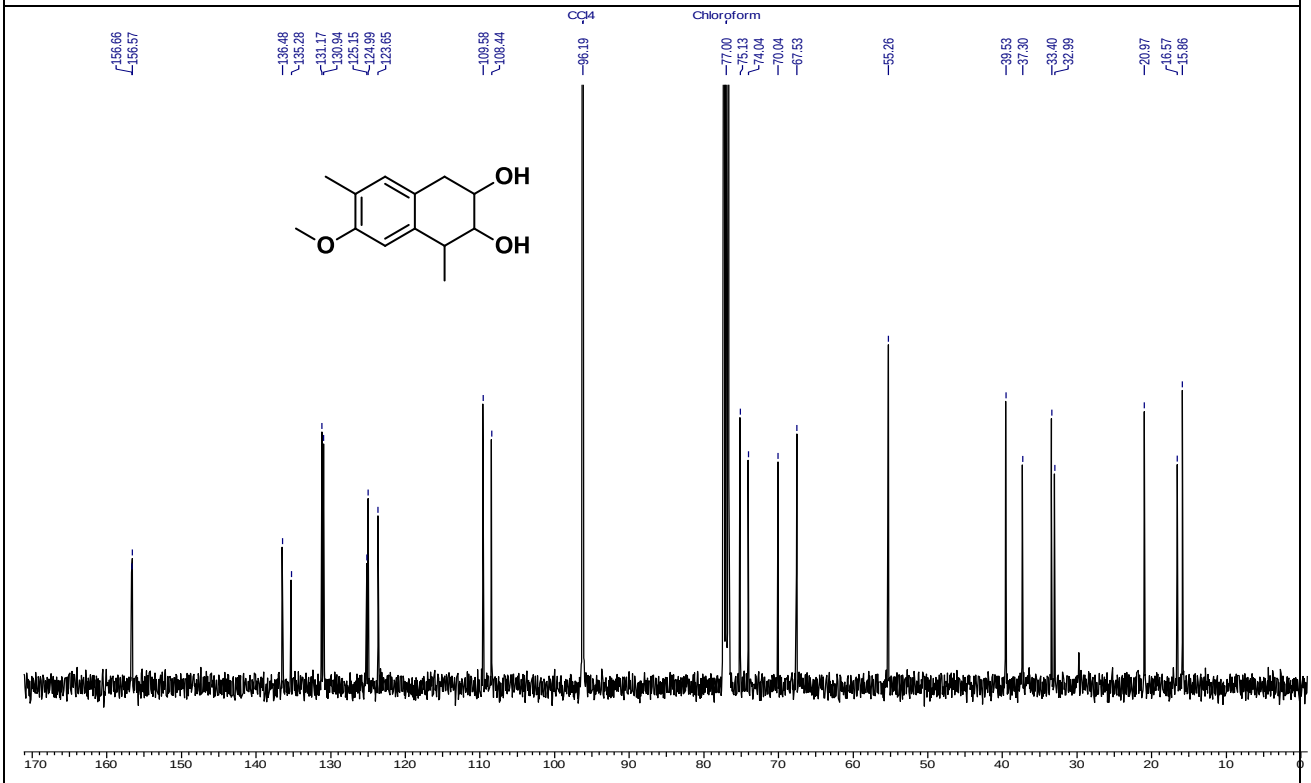
DEPT spectrum of compound **22** ($CDCl_3$+CCl_4, 50 MHz)



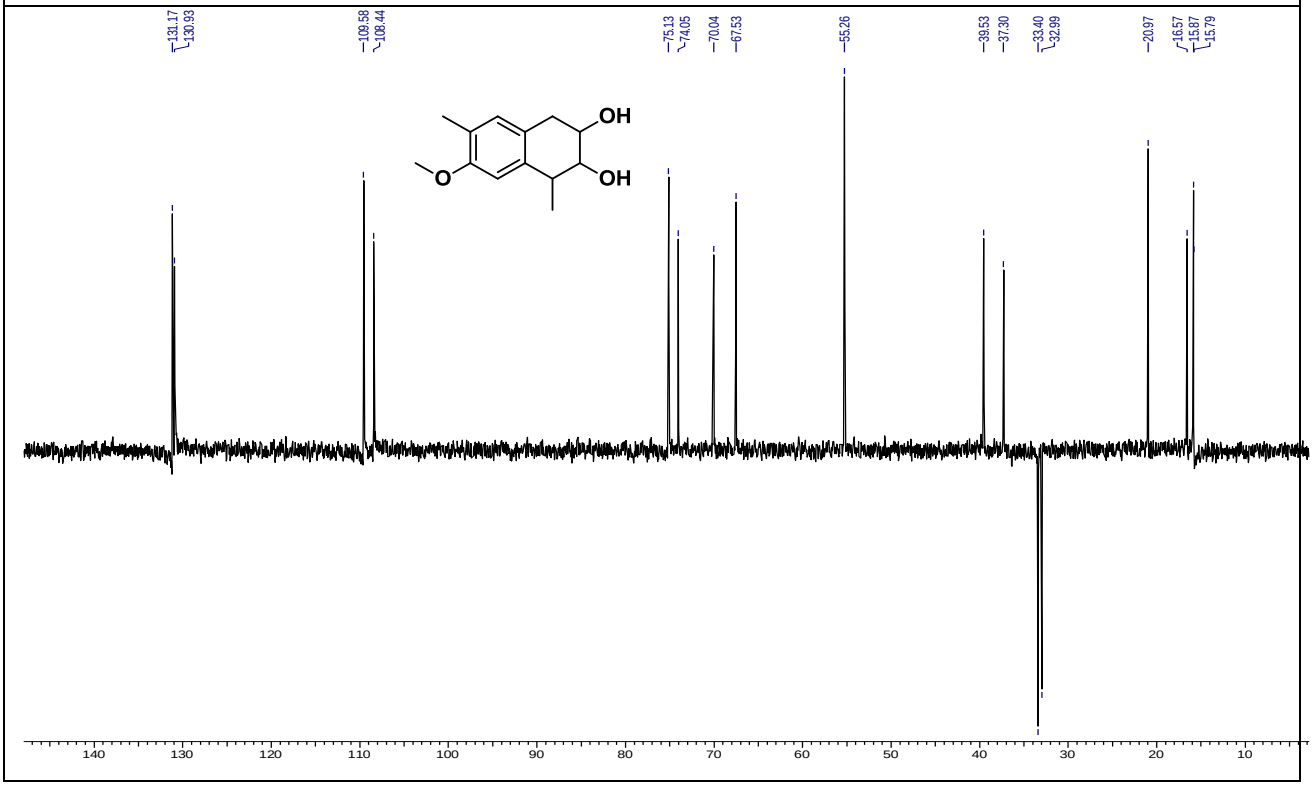
^{1}H NMR spectrum of compound **24** ($CDCl_3$+CCl_4, 200 MHz)



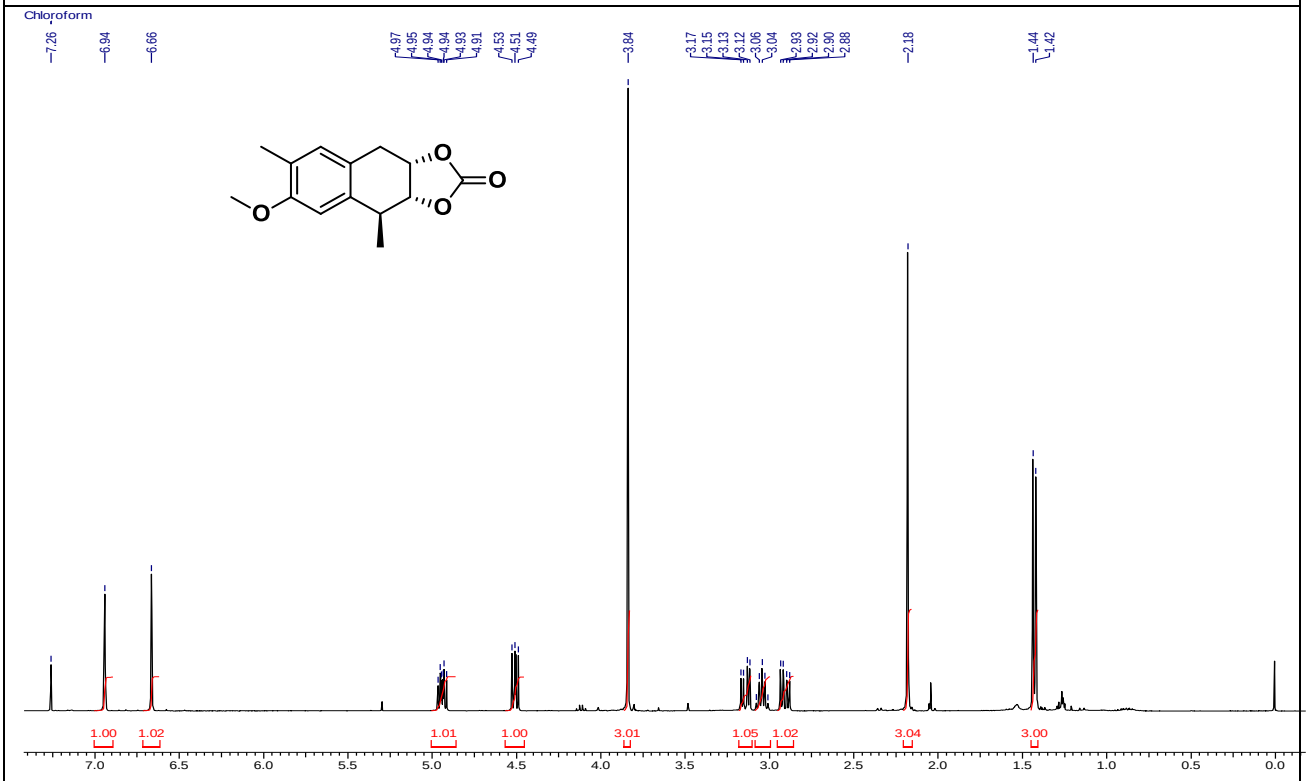
^{13}C NMR spectrum of compound **24** ($CDCl_3$+CCl_4, 100 MHz)



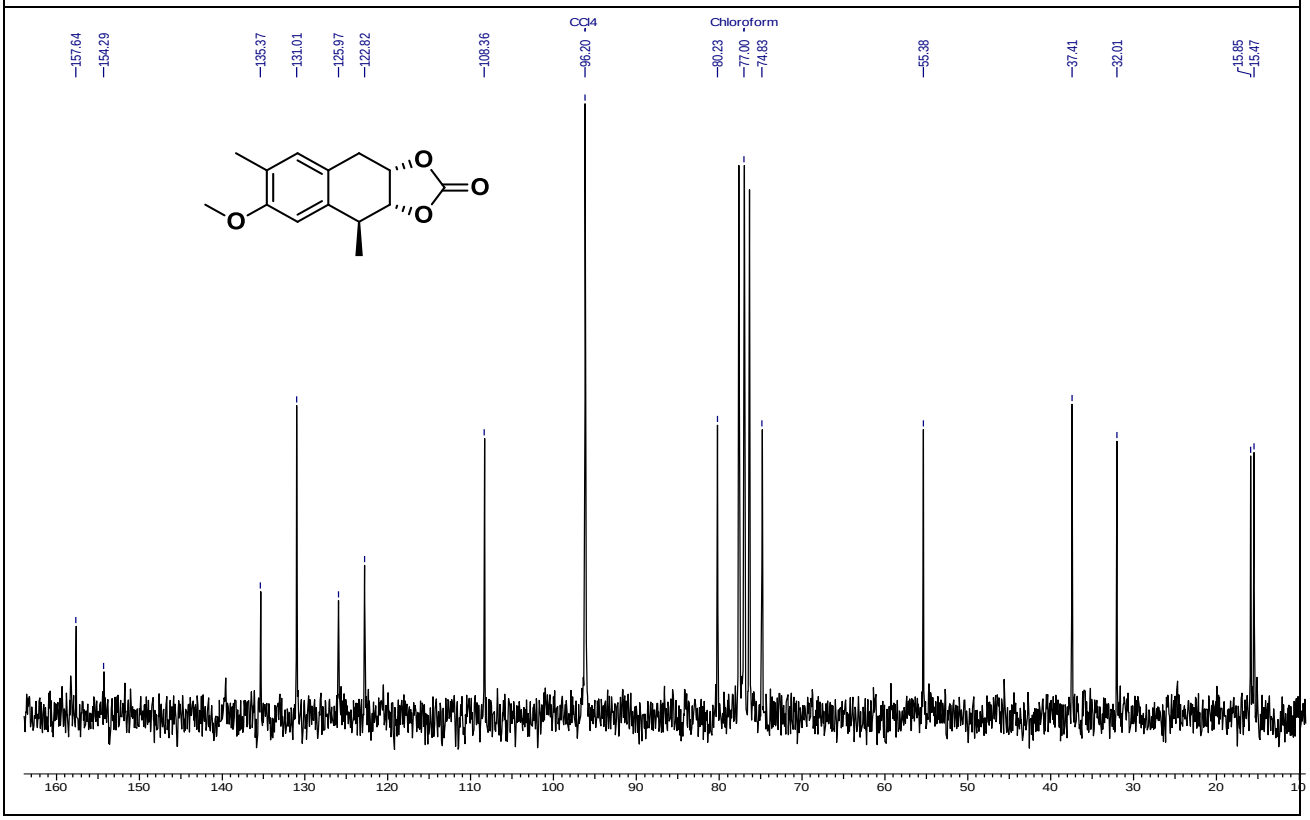
DEPT spectrum of compound **24** ($CDCl_3$+CCl_4, 100 MHz)



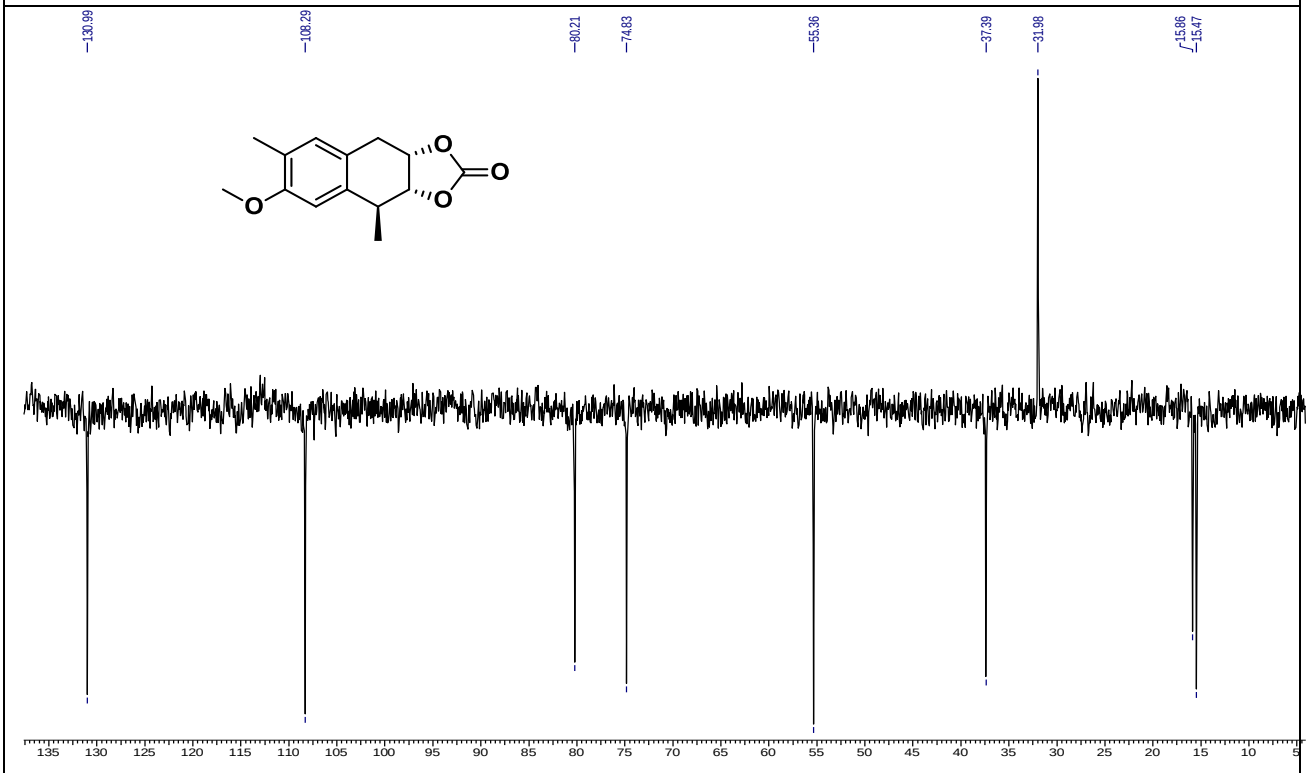
^{1}H NMR spectrum of compound **25** ($CDCl_3$+CCl_4, 200 MHz)



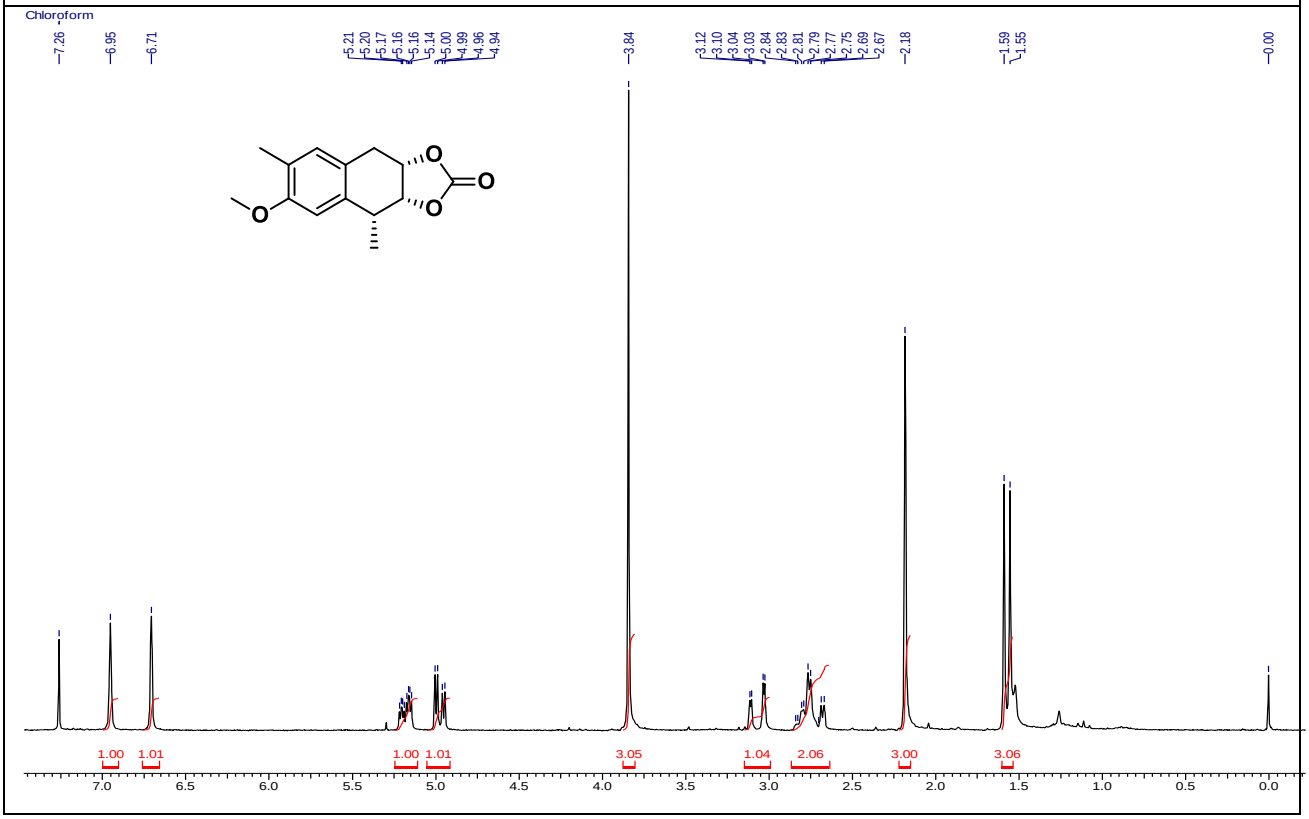
^{13}C NMR spectrum of compound **25** ($CDCl_3$+CCl_4, 50 MHz)



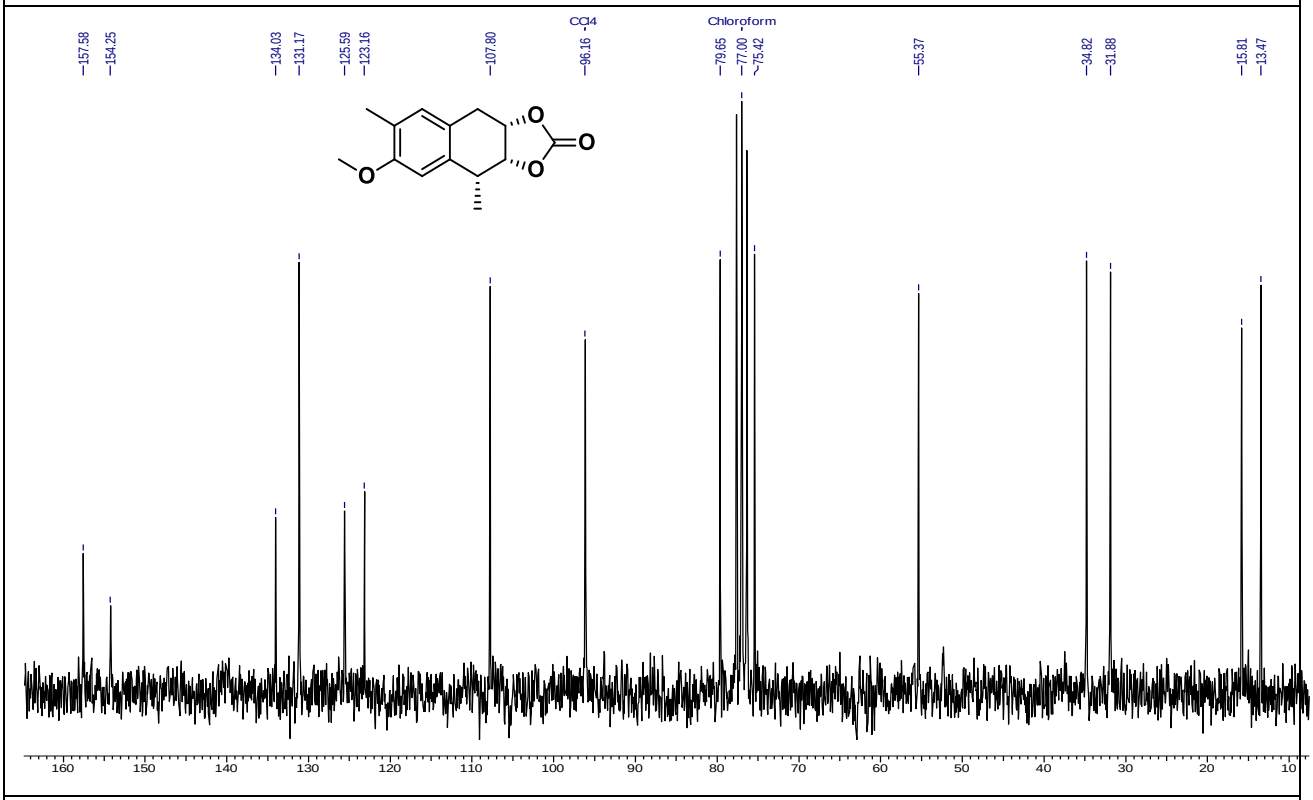
DEPT spectrum of compound **25** ($CDCl_3$+CCl_4, 50 MHz)



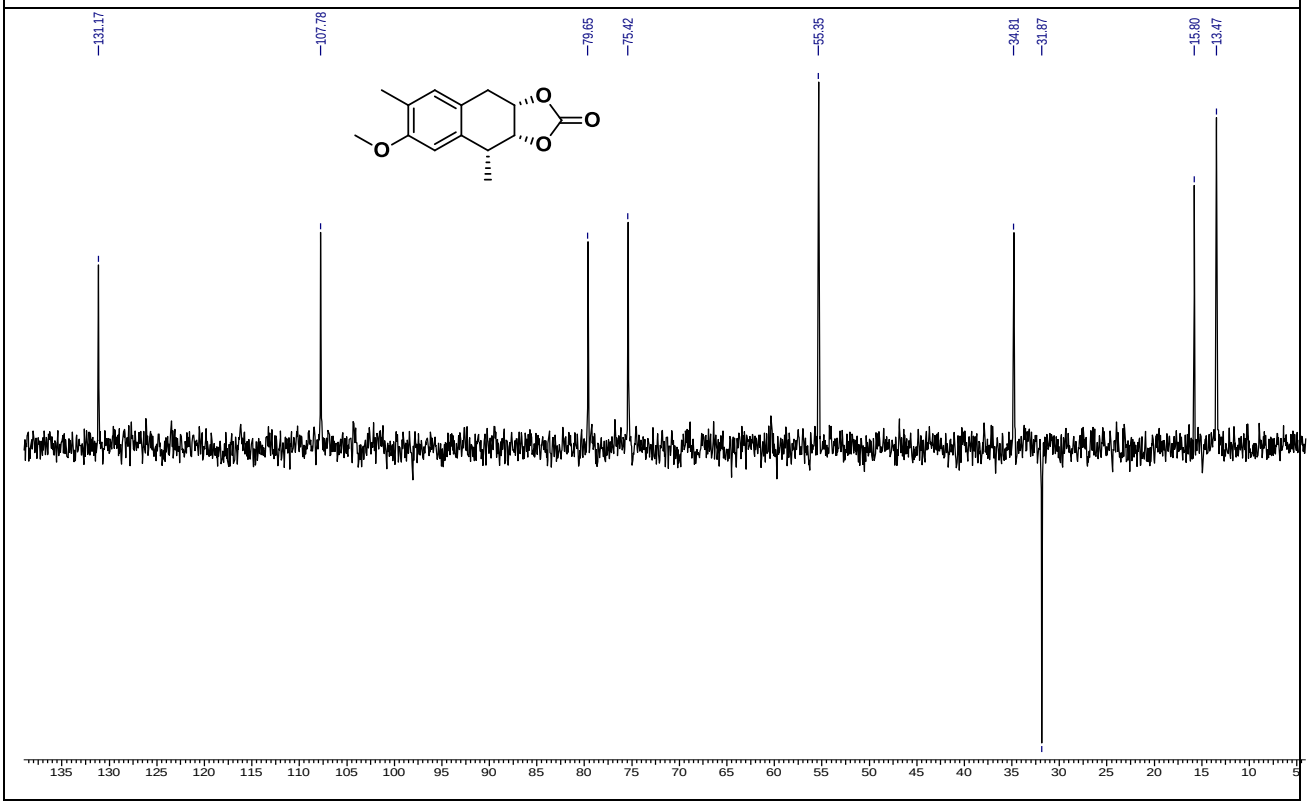
^{1}H NMR spectrum of compound **25'** ($CDCl_3$+CCl_4, 200 MHz)



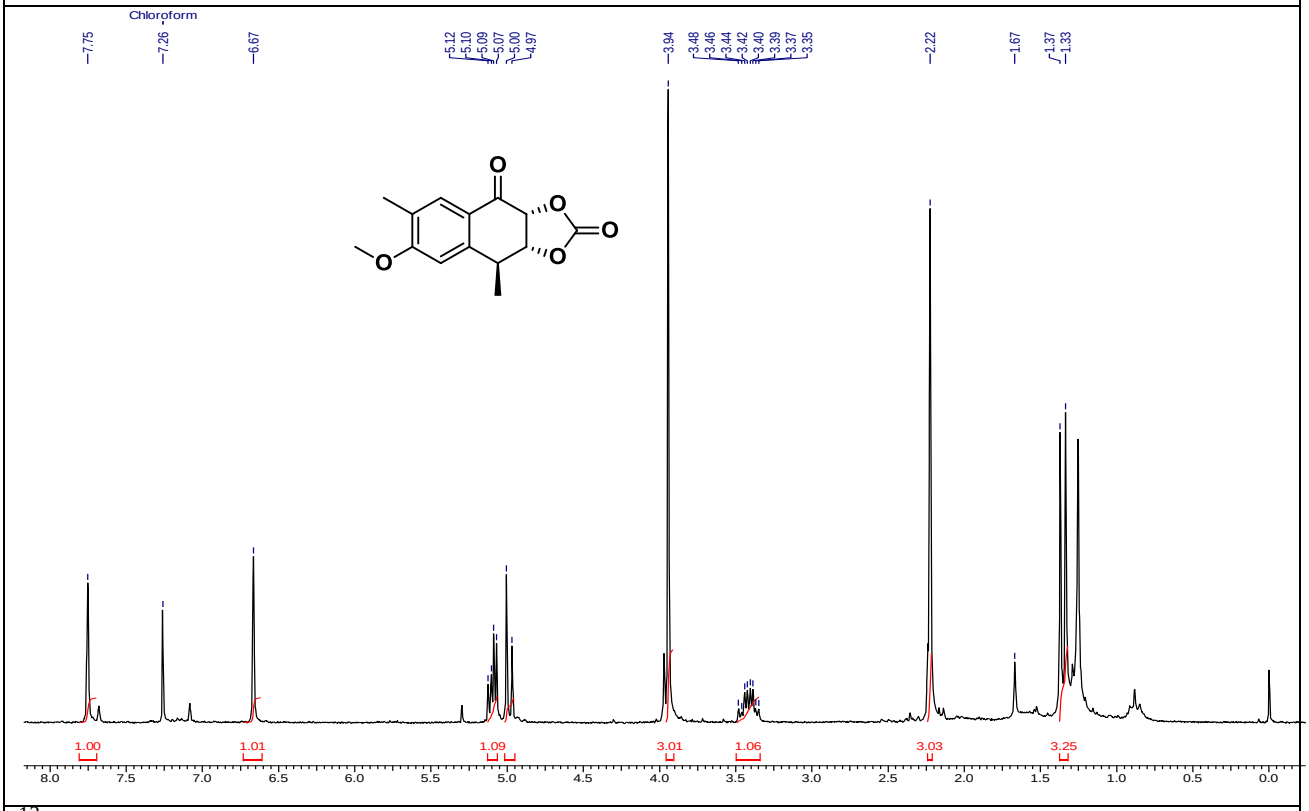
^{13}C NMR spectrum of compound **25'** ($CDCl_3$+CCl_4, 50 MHz)



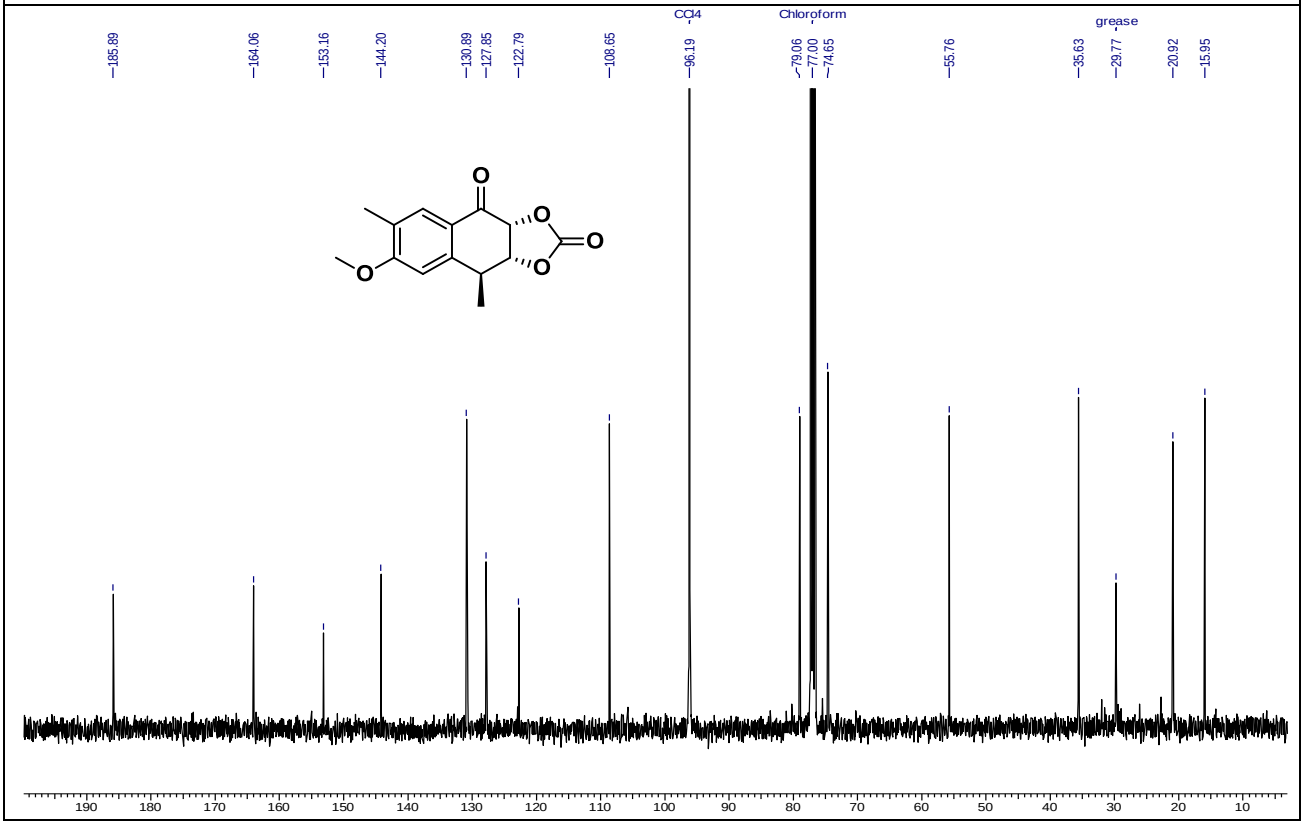
DEPT spectrum of compound **25'** ($CDCl_3$+CCl_4, 50 MHz)



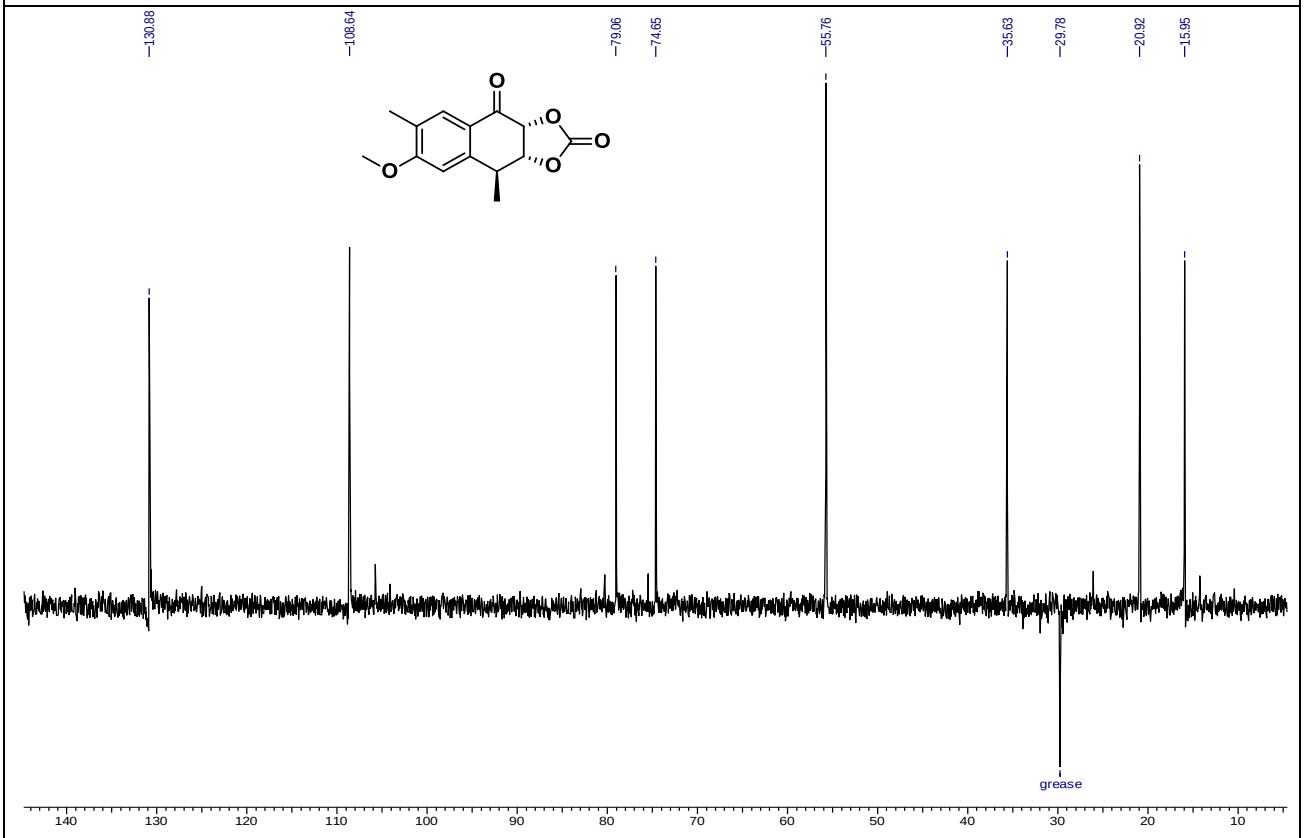
^{1}H NMR spectrum of compound **26** ($CDCl_3$+CCl_4, 200 MHz)



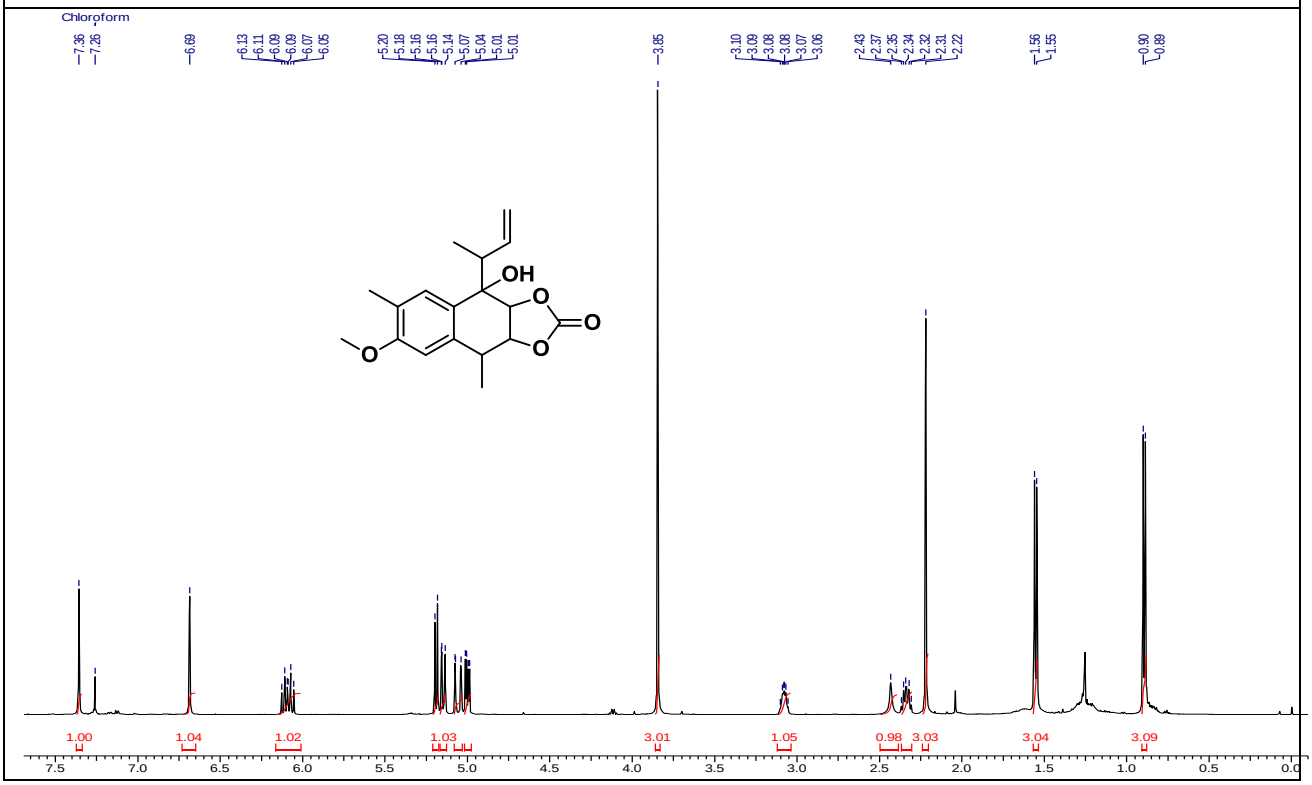
^{13}C NMR spectrum of compound **26** ($CDCl_3$+CCl_4, 50 MHz)



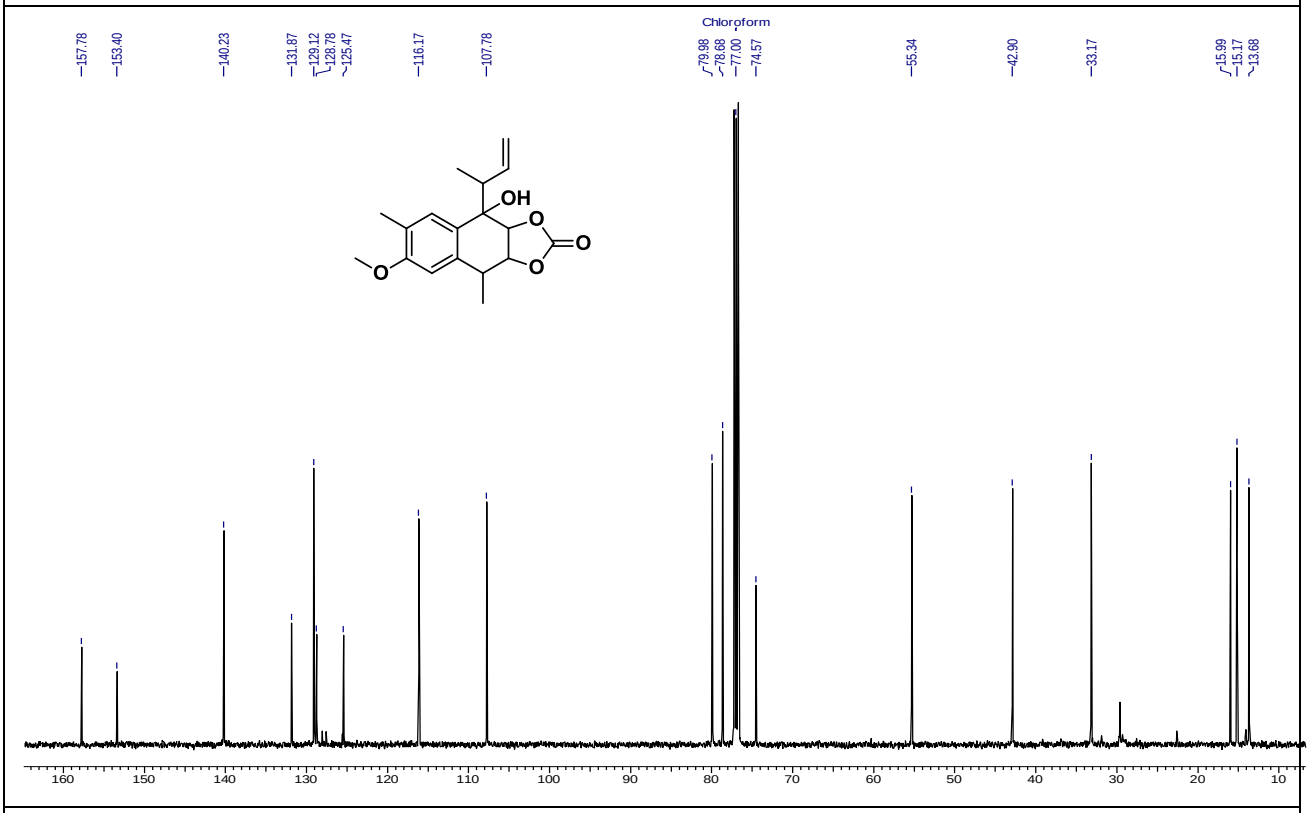
DEPT spectrum of compound **26** ($CDCl_3$+CCl_4, 50 MHz)



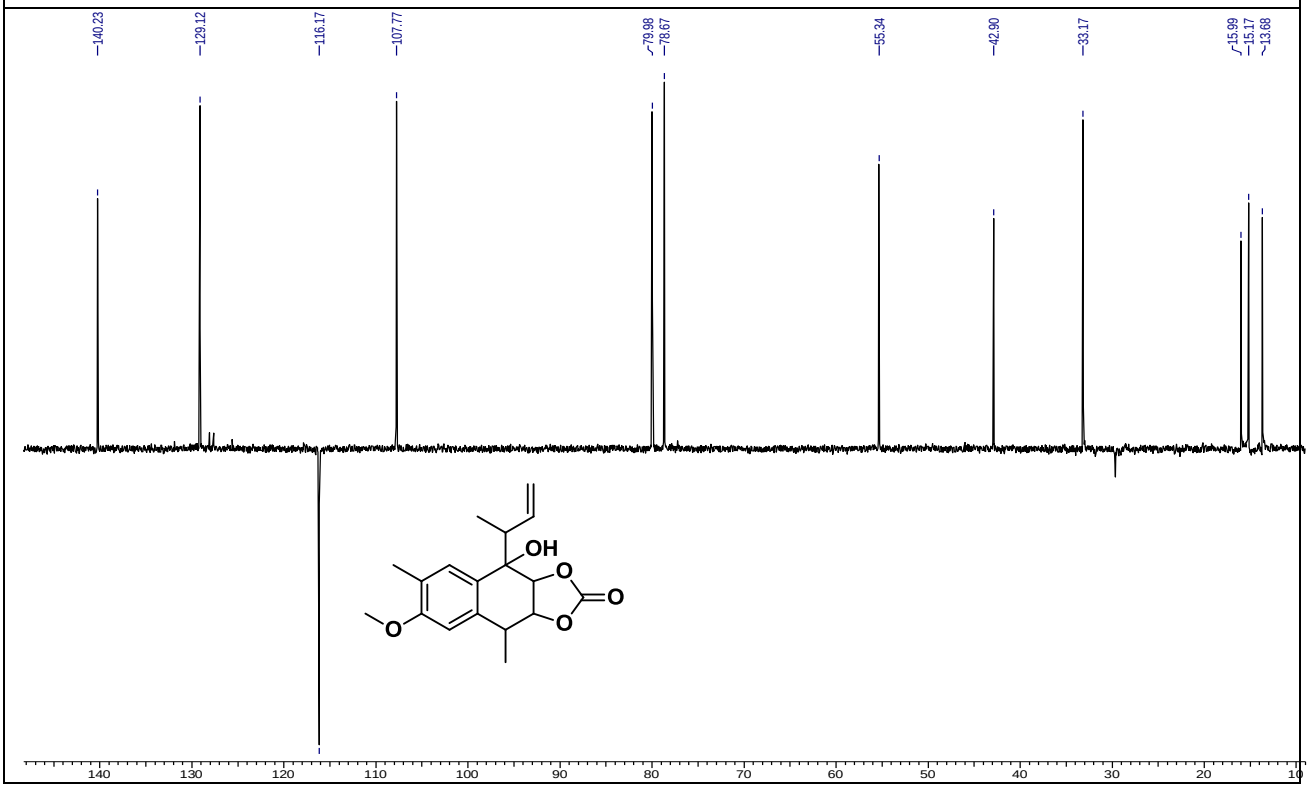
^{1}H NMR spectrum of compound **28** ($CDCl_3$+CCl_4, 200 MHz)



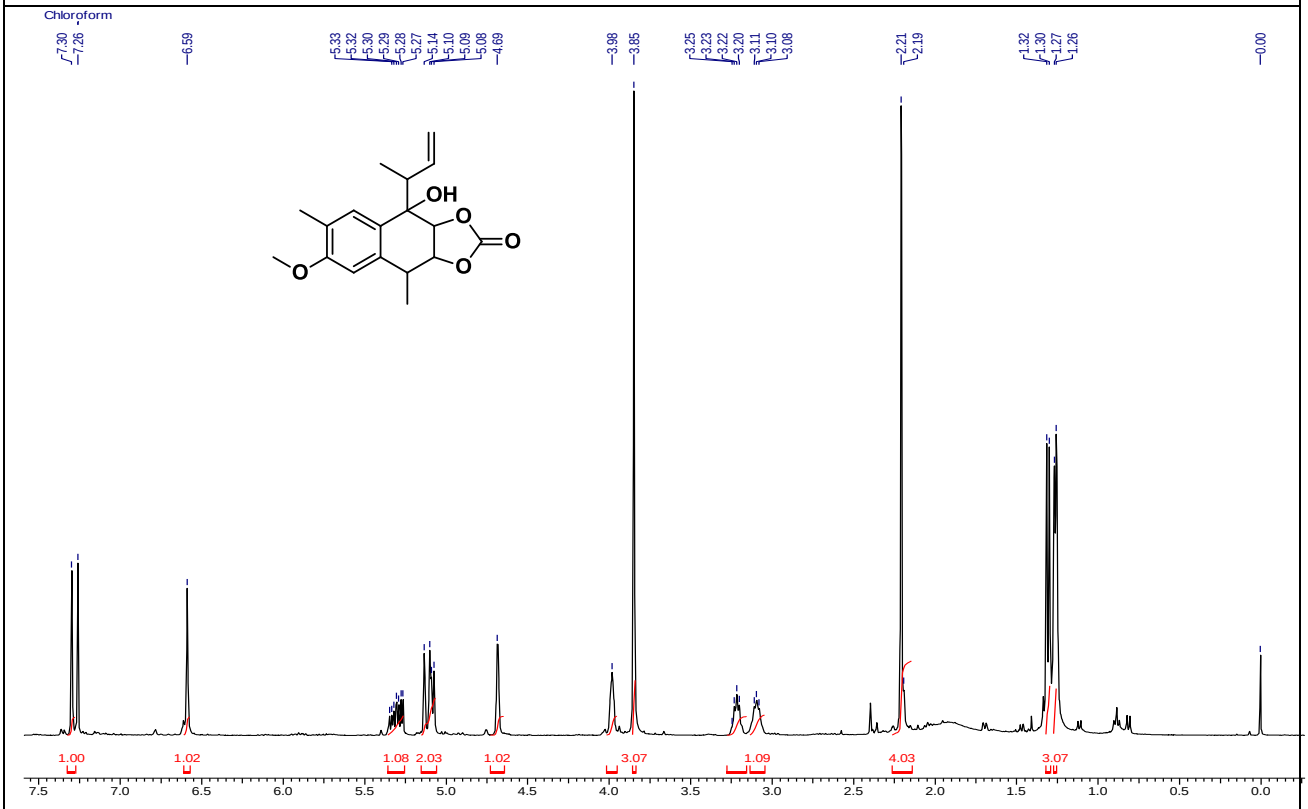
^{13}C NMR spectrum of compound **28** ($CDCl_3$+CCl_4, 50 MHz)



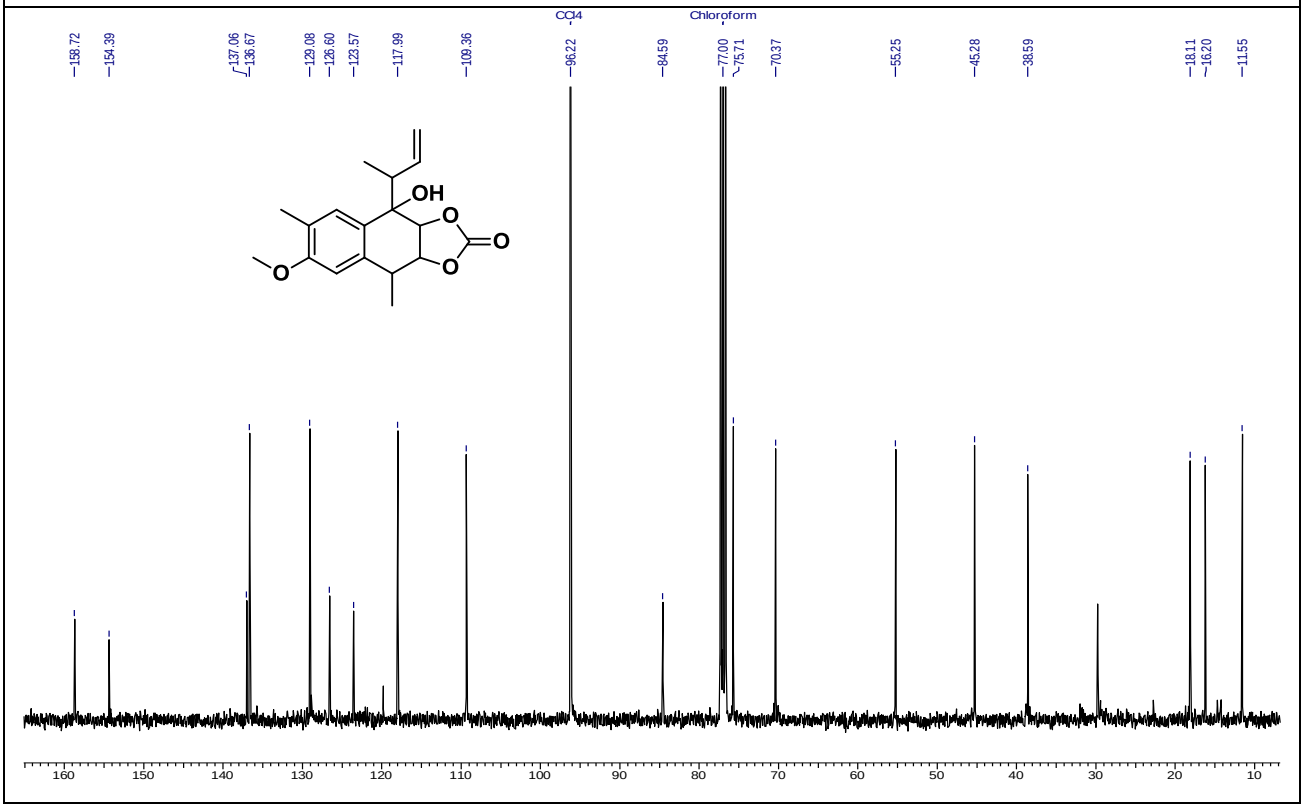
DEPT spectrum of compound **28** ($CDCl_3$+CCl_4, 50 MHz)



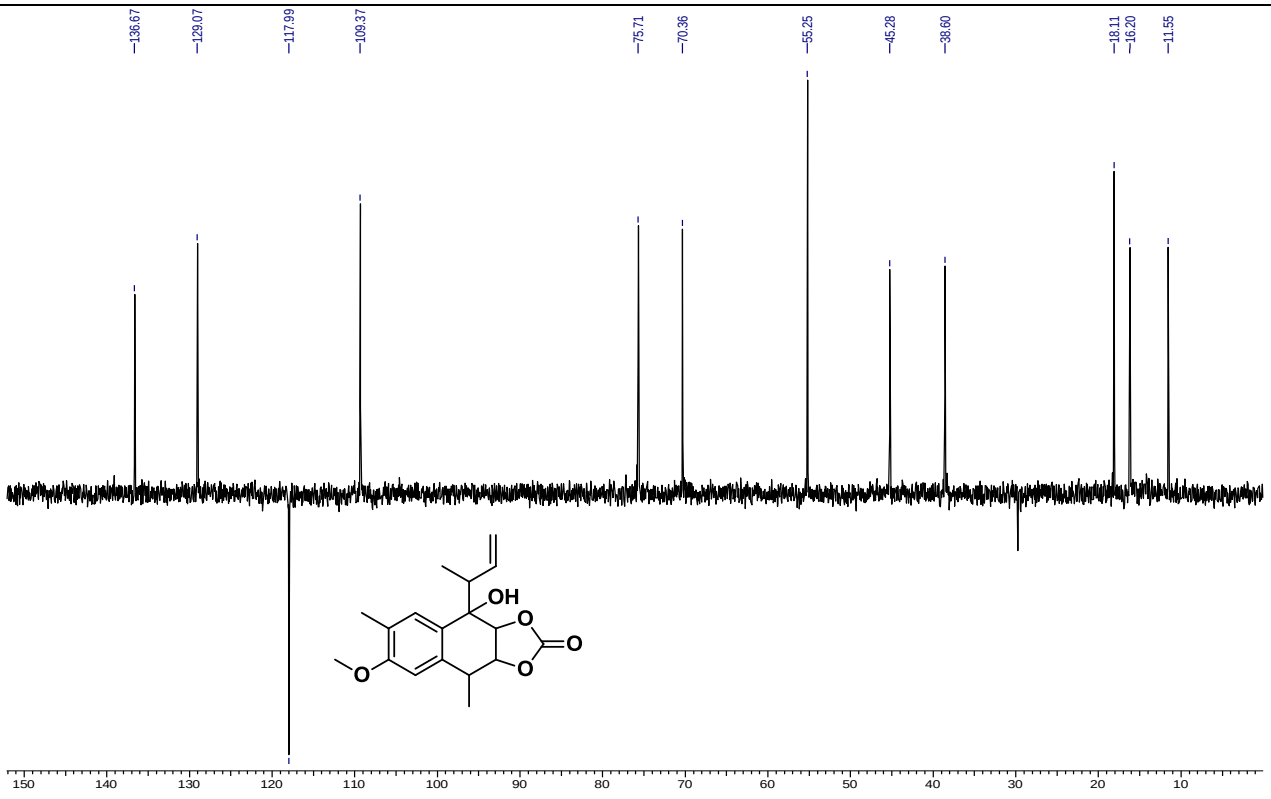
^{1}H NMR spectrum of compound **28'** ($CDCl_3$+CCl_4, 200 MHz)



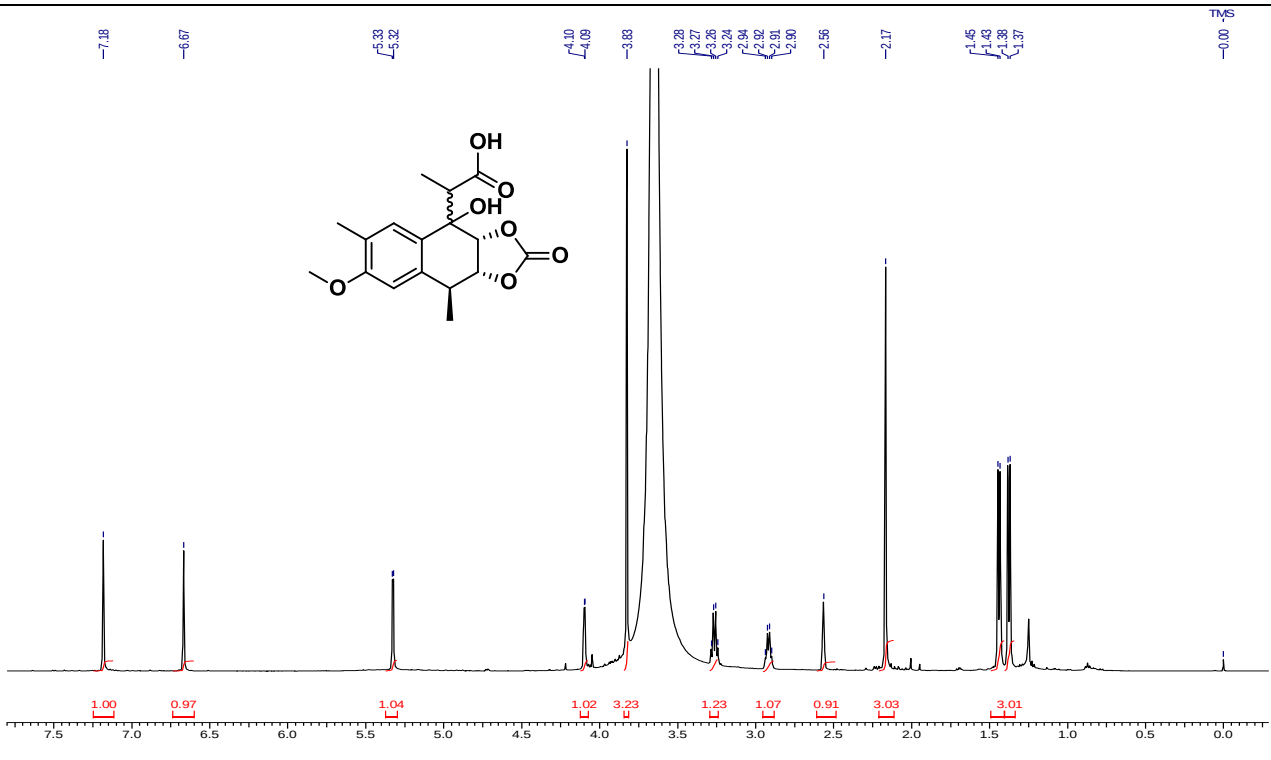
^{13}C NMR spectrum of compound **28'** ($CDCl_3$+CCl_4, 50 MHz)



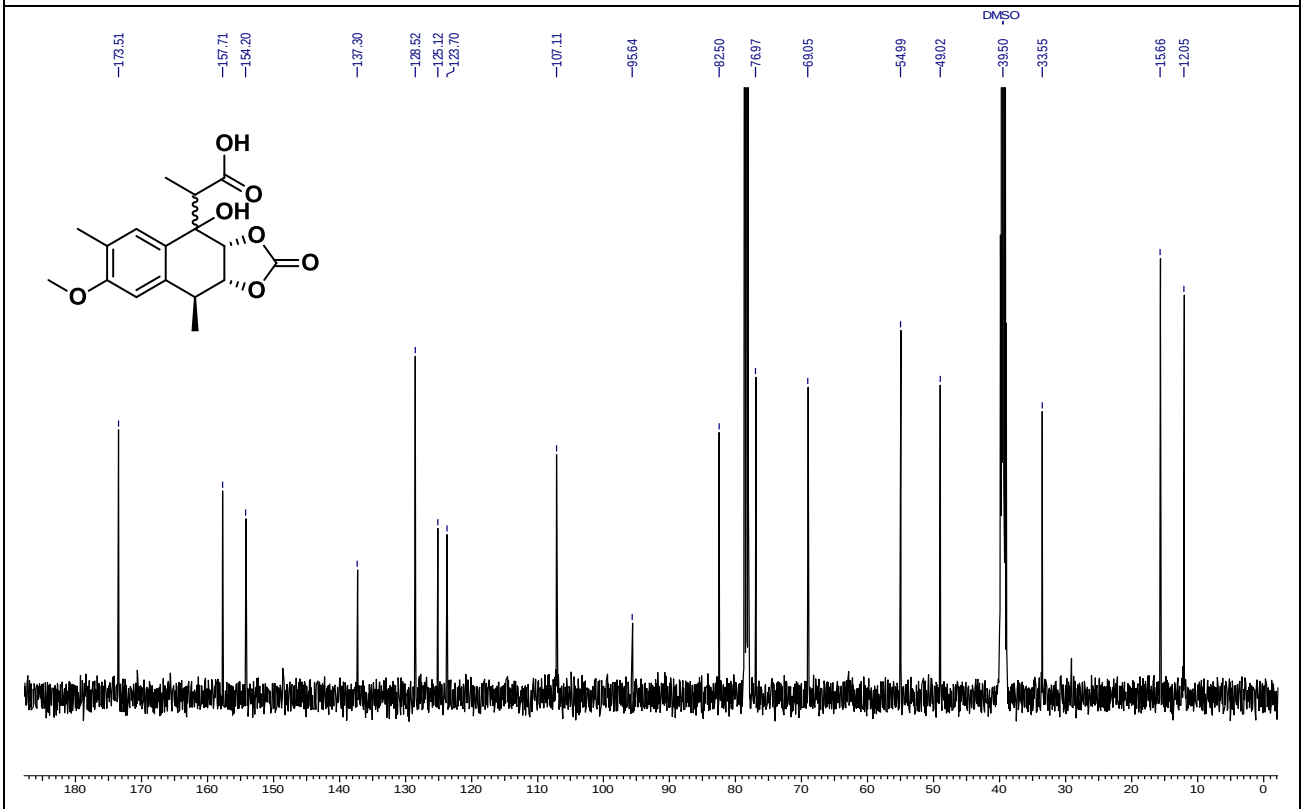
DEPT spectrum of compound **28'** ($CDCl_3$+CCl_4, 50 MHz)



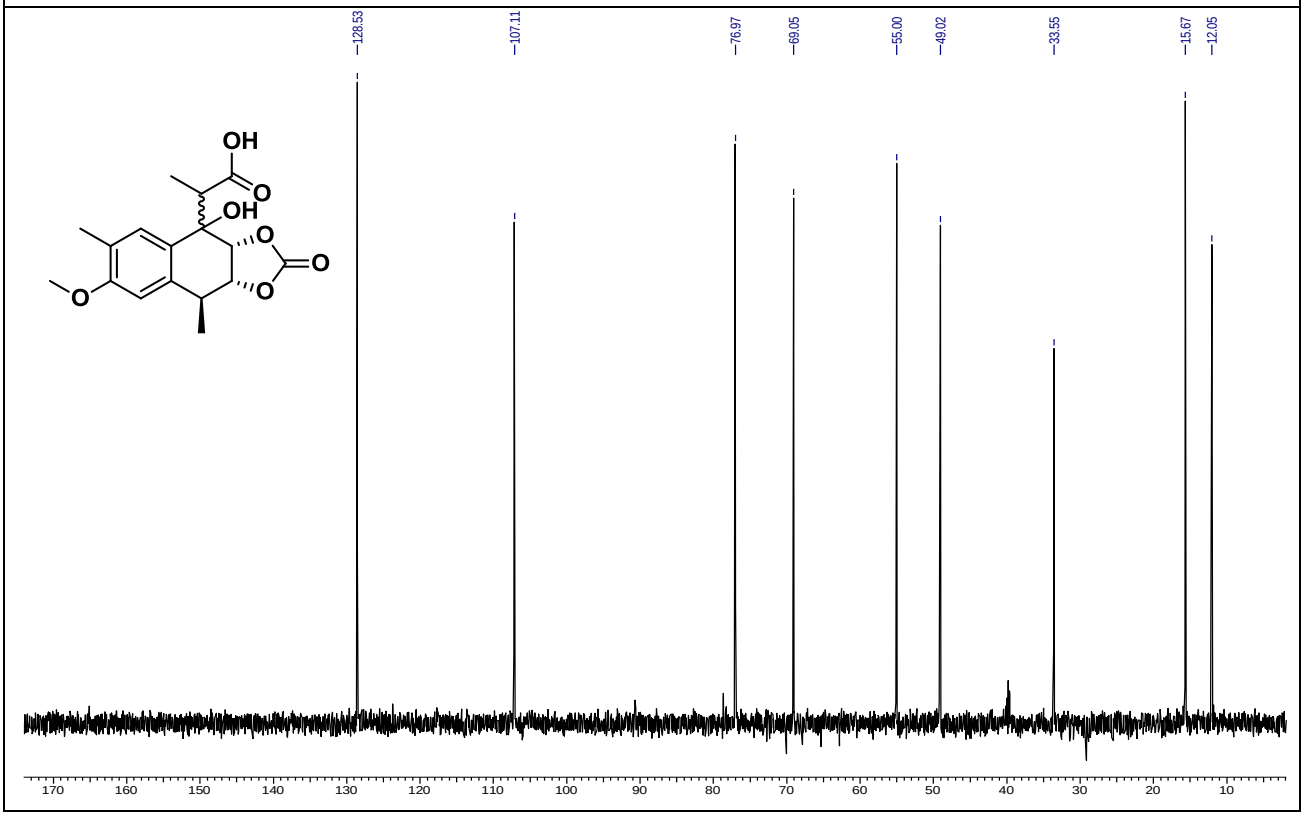
^{1}H NMR spectrum of compound **29** ($CDCl_3$+CCl_4+DMSO–d_6, 400 MHz)



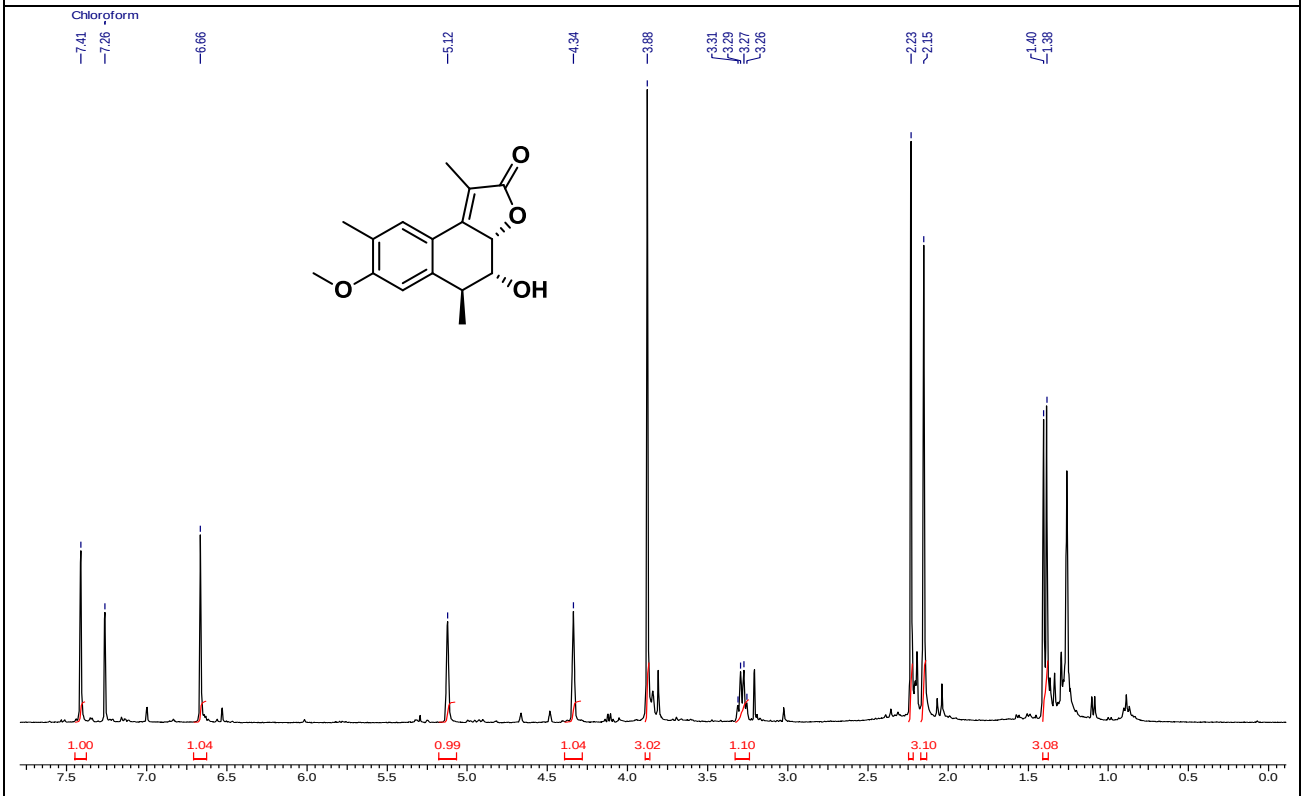
^{13}C NMR spectrum of compound **29** ($CDCl_3$+CCl_4+DMSO–d_6, 100 MHz)



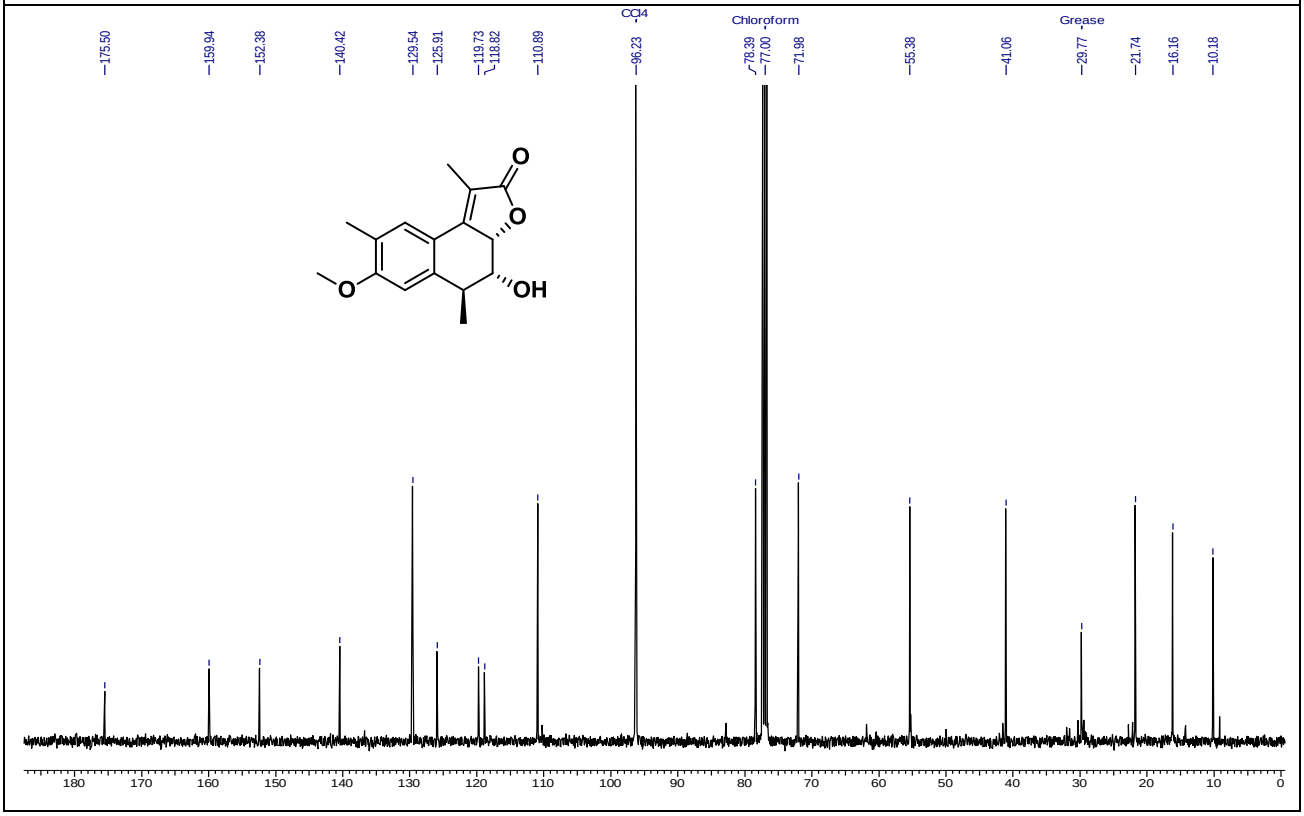
DEPT spectrum of compound **29** ($CDCl_3$+CCl_4+DMSO–d_6, 100 MHz)



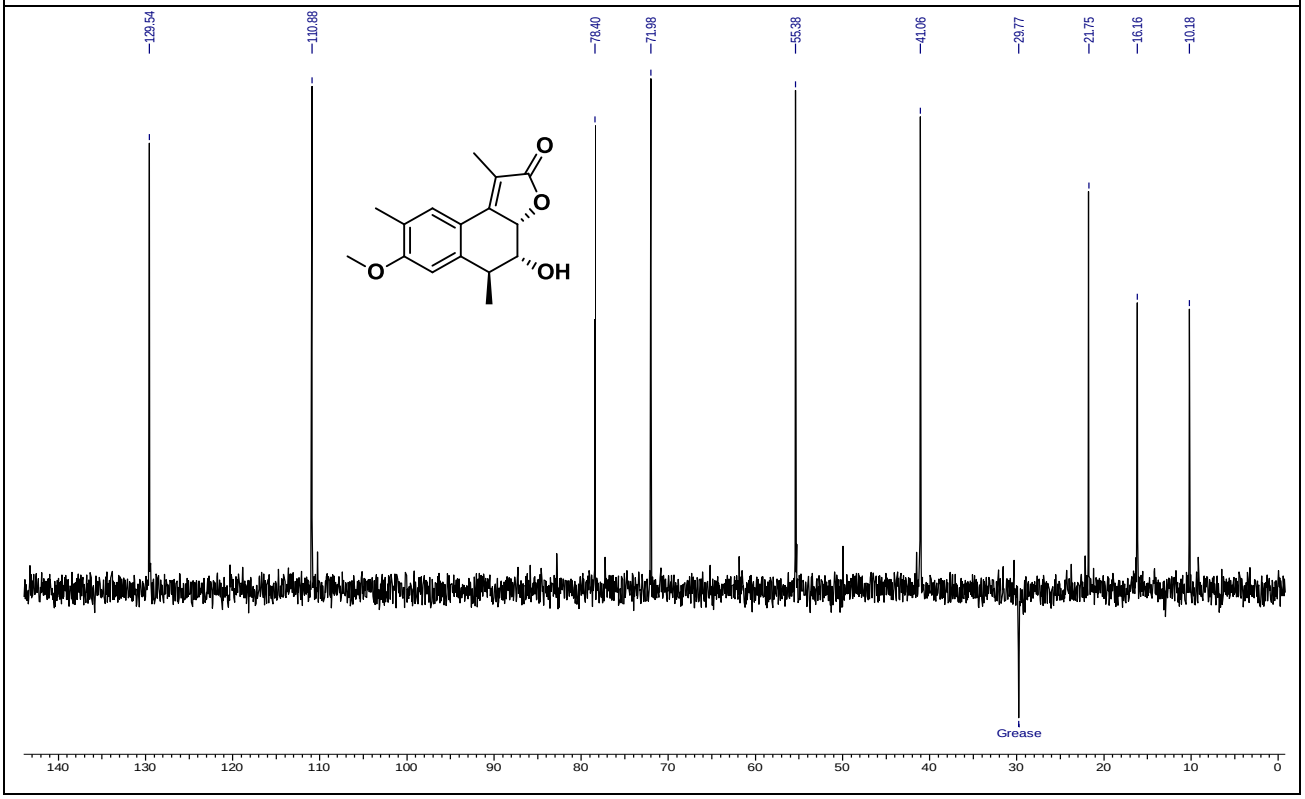
^{1}H NMR spectrum of compound **30** ($CDCl_3$+CCl_4, 400 MHz)



^{13}C NMR spectrum of compound **30** ($CDCl_3$+CCl_4, 100 MHz)



DEPT spectrum of compound **30** ($CDCl_3$+CCl_4, 100 MHz)



1.3.5. References

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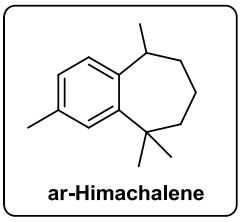
11. The stereochemistry of intermediate compounds shown was derived from the X-ray crystal structure obtained for final compound **30**.

2.1.1 Introduction

Sesquiterpenes are defined as the group of 15 carbon compounds derived by the assembly of three isoprenoid units (molecular formula= $C_{15}H_{24}$) and they are found mainly in higher plants but also in invertebrates. Sesquiterpenes along with monoterpenes, are an important constituents of essential oils in plants. They are the most diverse group of isoprenoids. Sesquiterpene structures are widely present in several acyclic, mono–, bi–, tri–, and tetracyclic systems. They are present in almost all essential oils, some of natural sesquiterpenoids are gossonerol, bisabolol, zingibarene, zingiberenol, bisacumol, turmerone, curcumene, curcuphenol, sesquiphellandrene etc. The chemistry of essential oils tells us that sesquiterpenes are the largest group of terpenes known naturally in the plant and animal kingdom! Cedarwood (98%), Sandalwood (95%), Ginger (70%) and Myrrh (60%) contain high amounts of sesquiterpenes.

Recently, several structurally interesting and biologically important terpenes and sesquiterpenes, have been isolated and synthesized in view of their promising biological activities. Approximately 5000 sesquiterpenes have been reported, most of them are appear to be derived from mevalonic acid. A large number of naturally occurring sesquiterpenes have been known in the literature possessing a broad range of applications in drugs, pharmaceuticals, rubber, paints, perfumery, agriculture *etc*. Many elegant methods are reported for the synthesis of these natural products.

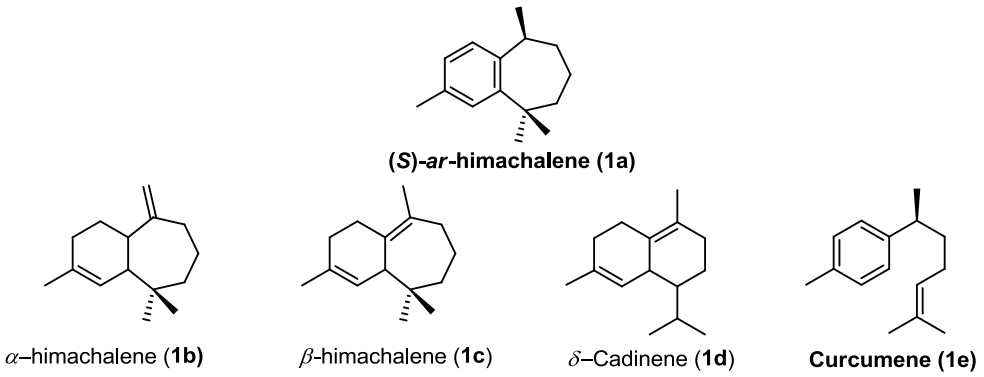


Figure–1: An aromatic himachalene (**1**)

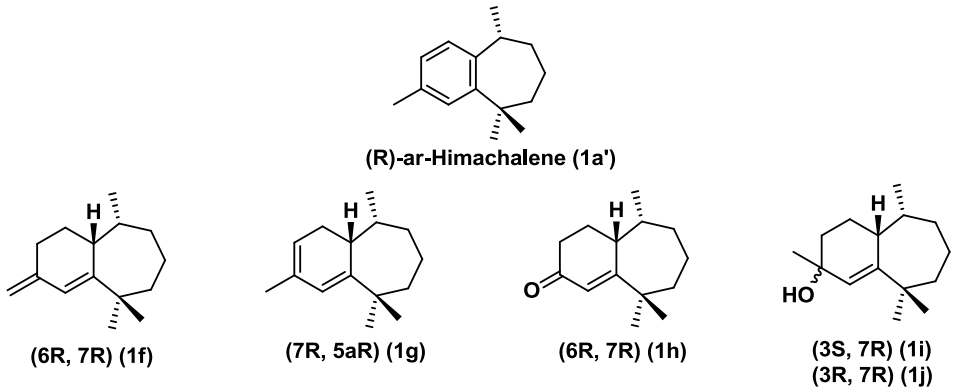
Himachalene (**1**) represents one of the structurally and biologically important class of the naturally occurring sesquiterpene hydrocarbons containing synthetically challenging benzo[7]annulene ring system (**Figure–1**).[1] They are found as essential oil components in several cedar woods which includes *Cedrus deodara* Loud, *Cedrus atlantica* and *Cedrus libani*[2] found in Himalayan and Morroccon forests. The potential of essential oil and different constituents of *C. deodara* accounted for the insecticidal and larvicidal action for their effective use in agricultural pest management as well as insect control [**Figure–2 (I)**].[3] Himachalene was also isolated as a male specific aggregation pheromonal component of the flea beetles, *Aphthona*

flava and *Phyllotreta cruciferae*.[4] These aggregation pheromones, which are typically produced by only one sex (males) and attracts both sex,[5] have become important scientific tools for monitoring and managing economic insects [**Figure–2 (II)**].

(I). Essential oil components from cedar wood



(II). Pheromonal components of flea beetles



Figure–2: Natural sesquiterpenes isolated along with *ar*–himachalene

Beetles were introduced into volatiles collectors, containing host plant material (chunks of mature cabbage head for *P. cruciferae* or spurge shoots with ends in water vials for *Aphthona* species). Collections of volatiles from beetles were routinely combined for GC monitoring. Samples from all groups were scrutinized by GC–MS, especially those for which GC comparisons indicated the presence of sex–specific peaks. Compounds from *A. flava.* by GC retention time and MS found to be identical to *ar*–himachalene, which was first described from Himalayan cedar (by Joseph and Dev, 1968). The proton NMR spectrum had the following shifts in (benzene–d_6): δ 1.31 (d, J = 6.5 Hz, 3H), 1.33 (s, 3H), 1.42 (s, 3H), 2.27 (s, 3H), 3.24 (m, 1H), 7.04 (dd, J = 7.9, 1.6 Hz, 1H), 7.21 (d, J = 7.9 Hz, 1H), and 7.31 (d, J = 1.6, 1H). Two geminal methyls, a secondary methyl adjacent to a benzene ring, an aromatic methyl, and three aromatic

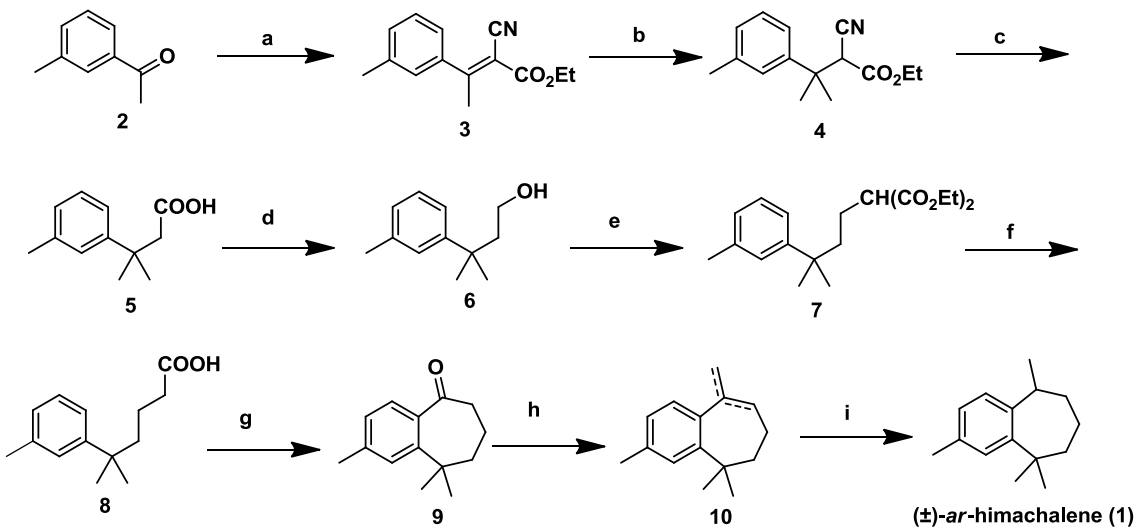
protons were indicated, supporting the *ar*–himachalene structure. The corresponding shifts in ($CDCl_3$) were 1.33, 1.33, 1.42, 2.31, 3.26, 6.98, 7.11, and 7.18, which were very similar to those reported by Pandy and Dev in (CCl_4). However, only the (*R*)–enantiomer of *ar*–himachalene exhibits the desired pheromonal activity[6] which intrinsically requires the compound to be used in enantiomerically pure form. Although, (*R*)–*ar*–himachalene can be used under field experiments to have a control on economically important insects, it constitutes only 0.5% of the total oil of *Aphthona flava*[4] thereby emphasizing the need for its synthesis.

2.1.2 Literature Review

In the recent time several himachalene type sesquiterpenes came in focus because of the revision of its absolute stereochemistry by Mori *et al*.[8] Several syntheses of the himachalenes based on Friedel Crafts acylation, Robinson annulations and also starting from citronellal as a chiral building block have been reported in the literature[9] along with other structurally important synthetic compounds.[10]

Sukh Dev's approach [2b] (*Tetrahedron* **1968**, *24*, 3829–3839)

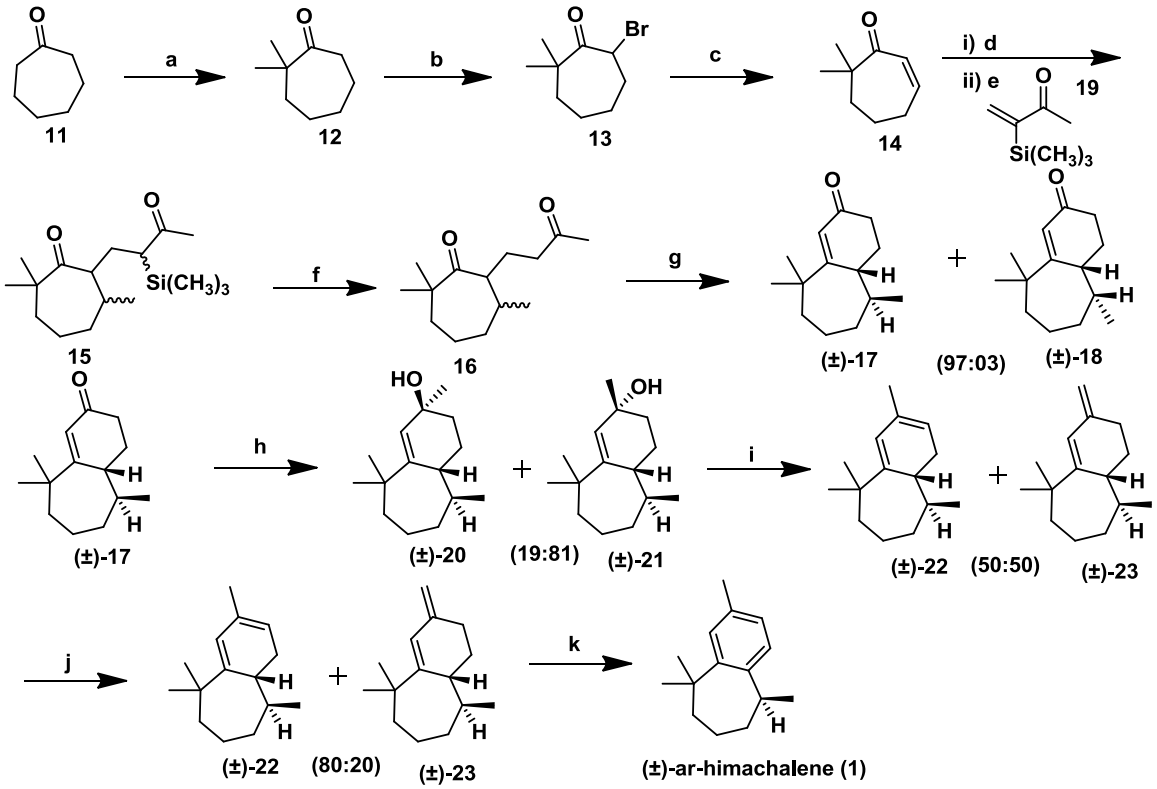
After isolation of *ar*–himachalene as an essential oil component from Himalayan plant species and description of its structural analogs, in 1968, the first total synthesis of (±)–*ar*–himachalene (**1**) was reported by Sukh Dev *et al*. *m*–Methyl acetophenone **2** on interaction with ethyl cyanoacetate in presence of AcOH furnished the required ester **3**. The 1,4– conjugate addition of MeMgI, carried out in presence of Cu_2Cl_2 to furnish compound **4**. The crude cyanoester **4** was directly hydrolysed and subsequently decarboxylated provided acid **5** which on LAH reduction under refluxing conditions furnished alcohol **6** in 84% yield. The alcohol **6** was converted into it's tosylate in presence of tosyl chloride. The chain extension by two carbon atoms was carried out by condensation of tosyl protected alcohol in presence of diethyl malonate and NaH as a base to finally give diester **7**. Compound **7** was hydrolyzed under acidic hydrolysis conditions and the corresponding crude diacid was decarboxylated under refluxing conditions to furnish the acid **8** in 85% yield. The acid **8** was acylated in presence of polyphosphoric acid to furnish seven membered cyclised ketone **9** in 82% yield. Reaction of MeLi on ketone **9** furnished mixture of compounds on elimination, the unsaturated hydrocarbon **10**, was then hydrogenated in presence of Adams' platinum oxide to give the *ar*–himachalene (**1**) in 9 steps.



Scheme 1. Reagents and conditions ***:*** *a) $CNCH_2CO_2Et$, benzene, AcOH, 16 h, 70%; b)MeMgI, Cu_2Cl_2, ether, reflux, 5 h, 80%; c) (i) MeOH–HCl, 24 h, (ii) MeOH–KOH, reflux 4 h, 32%; d) MeOH, H_2SO_4, reflux, 6 h, (ii) LAH. ether, reflux, 6 h, 84% (over two steps); (e) (i) TsCl, pyridine, ether, 0 ^oC, 3 h, (ii) $CH_2(COOMe)_2$,NaH, THF, reflux, 24 h, 61% (over two steps); f) HCl, AcOH, reflux, 24 h, 85%; g) PPA, pet ether, reflux, 5 h, 82%; h) MeLi,benzene, reflux, 12h, 46%; i) Adam's catalyst, H_2, AcOH, 56%*.

Bartelt's approach [7] (*Synthesis*. **2003**, *1*, 117–123)

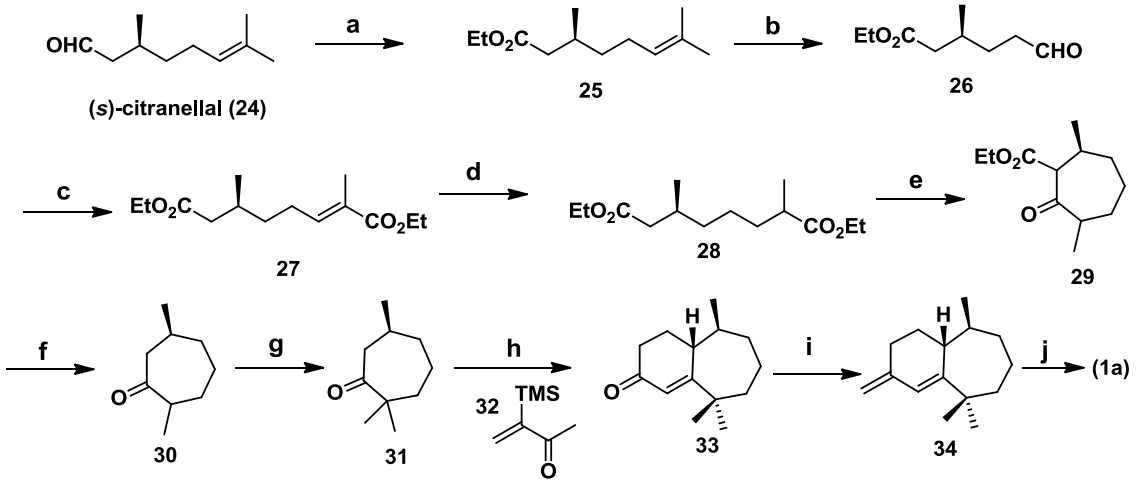
Total synthesis of (±)–*ar*–himachalene (**1**) was carried by Bartelt *et al*. after re–discovering it in 2001. Cycloheptanone (**11**) was dimethylated to **12** with MeI and *t*–BuOK, formation of product **12** was observed with 82% yield. This geminal dimethyl ketone **12** was brominated to **13** by means of liquid bromine at RT. The bromo ketone **13** was converted to corresponding enone **14** with LiBr–Li_2CO_3 in hot DMF. Conjugate methylation of **14**, followed by Michael addition of the resulting copper enolate to silyl ketone **19** at –78 °C gave silyl diketone **15** which is treated with ethanolic KOH to furnish **17** and **18**. Importantly, the ratio of the two possible synthetic diastereomers was (97:3) in favor of the desired one. Ketone **17** was converted to **20** and **21** by methylation with MeLi. Alcohols **20** and **21** were readily dehydrated to a nearly (50:50) mixture of **22** and **23** by treatment with an acidic ion exchange resin. The diastereomeric ratio could be shifted to about (80:20) in favor of **22** by equilibration in warm formic acid and MeOH. Finally, diastereomerically enriched **22** was aromatized to racemic (**1**) with chloranil in 95% yield.



Scheme 2. *Reagents and conditions: (a) MeI, t–BuOK, t–BuOH, r.t., 82%; (b) Br_2, Et_2O, r.t., 93%; (c) LiBr, Li_2CO_3, DMF, 130 °C, 92%; (d) Me_2CuLi, Et_2O,–78 °C; (e)* ***19****, Et_2O, –78 °C, 54% (over two steps); (f) KOH (3.5 N), EtOH, r.t.; (g) KOH (3.5 N), EtOH, reflux, 44%.(over two steps); (h) MeLi, Et_2O, –78 °C, quant; (i) Dowex 50W–X4, Et_2O, r.t., 64%; (j) HCOOH (15% in MeOH), 50 °C, quant.; (k) chloranil, benzene, 75 °C, 95%.*

Kenji Mori's approach [8c] (*Eur. J. Org. Chem.* **2004**, 1946–1952)

This group in order to prepare (*S*)–*ar*–himachalene (**1a**) used the (*S*)–citronellal (**24**) as a starting precursor which was oxidized to acid on treatment with potassium dichromate and subsequently esterified using ethyl iodide and K_2CO_3 as the base to give ethyl ester **25**. The cleavage of double bond was carried out by means of ozonolysis of **25** and the resulting ozonide was quenched with DMS to afford aldehyde **26** in 72% yield which was then converted to unsaturated ester **27** by Horner–Wadsworth–Emmons reaction in 96% yield. Hydrogenaton of **27** over Adams' catalyst gave saturated diester **28** in almost quantitative yield. Dieckmann condensation of **28** by treatment with t–BuOK and *m*–xylene as a solvent gave **29**. The ester moiety present alpha to ketone in compound **29** was hydrolyzed and resulting acid was



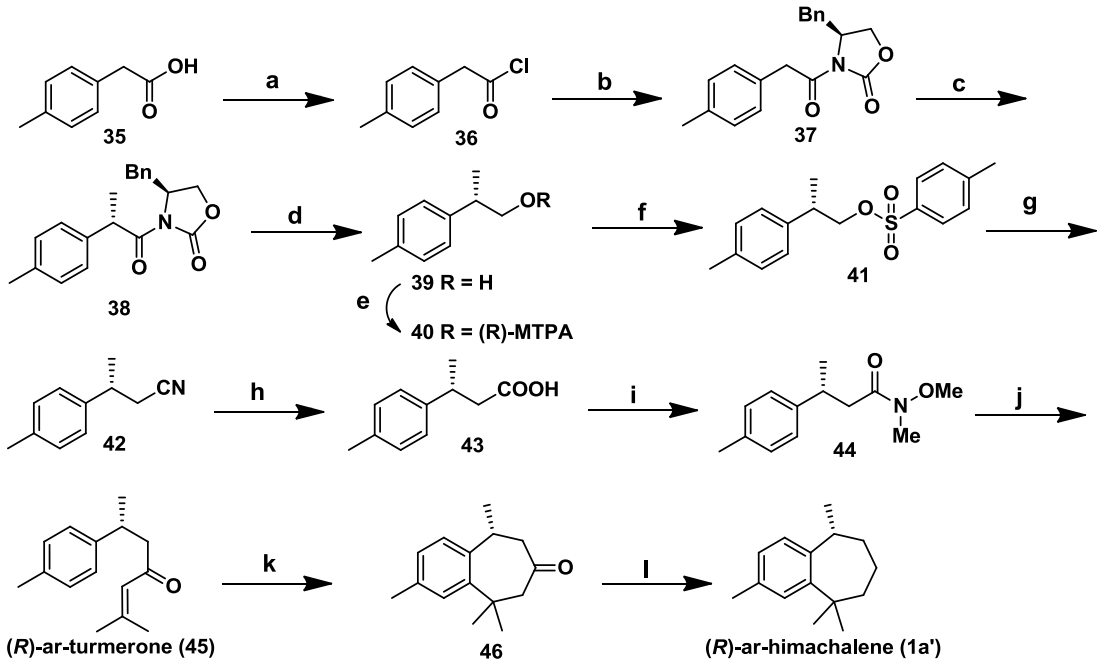
Scheme–3: Reagents and conditions ***:*** *(a) i) PDC, DMF, ii) EtI, K_2CO_3, DMF,74%; (b) i)O_3, MeOH, ii) Me_2S 72%; (c) $(EtO)_2P(O)CH(Me)CO_2Et$, NaH, THF, 96%; (d) H_2, PtO_2. EtOAc, quant.; (e) t–BuOK, m–xylene,79%; (f) aq. NaOH, MeOH, reflux 85%; (g) t–BuOK, MeI, t–BuOH 88%; (h) i) LDA, TMSCl, THF, ii) MeLi, **32**, iii) MeONa, MeOH, 44%; (i) Ph_3PMeBr, n–BuLi, THF, 69%; (j) chloranil, C_6H_6, 63%.*

decarboxylated to give **30** in 85% yield (**Scheme–3**). This dimethyl ketone **30** was further methylated to give **31** which was converted to crystalline ketone **33** by Stork modification of the Robinson annelation. The bicyclic enone **33** was converted to exomethylene compound **34** following one carbon Wittig reaction. Diene **34** was aromatized in presence of chloranil into (*S*)–*ar*–himachalene (**1a**).

Kenji Mori's approach [8a] (*Tetrahedron: Asymmetry* **2005**, *16*, 685–692)

In another approach (*R*)–*ar*–Himachalene (**1a'**) was synthesized by using Evans' asymmetric alkylation as the key step (**Scheme 4).** 4–Methylphenylacetic acid **35** was heated with $SOCl_2$ in benzene to give the corresponding acyl chloride **36**. Acylation of (*S*)–4–benzyl–2–oxazolidinone with **36** afforded crystalline **37**, which was methylated with MeI and NaHMDS in THF at –78 ^oC to furnish **38** with the (*dr*: 95:5). The major isomer was assigned as **38,** according to the established stereochemical outcome of the Evans' alkylation. Reduction of **38** with LAH gave oily alcohol (*S*)–**39** in 53% yield. The alcohol **39** was converted into Mosher ester on treatment with (*S*)–Mosher acid chloride and ^1H–NMR analysis of the corresponding (*R*)–(MTPA ester) **40** established formation of **39** in 89% *ee*. The Mosher ester **40** was treated with tosyl chloride to furnish tosylate **41**. NaCN and a small amount of NaI in DMSO converted **41** to

oily nitrile **42**, which was hydrolyzed with KOH in hot aq. ethylene glycol to give **43**. The next step was the conversion of acid **43** to Weinreb amide **44** by treatment with *N,O*–dimethylhydroxylamine hydrochloride and EDC. The resulting oily amide **44** was then treated with 2–methylpropenylmagnesium bromide to give oily **45** in 74% yield.



Scheme–4: Reagents and conditions ***:*** *(a) $SOCl_2$,C_6H_6, reflux, quant.; (b) (S)–4–benzyl–2–oxazolidinone, n–BuLi, THF, 78 ^oC– RT, 79%; (c) NaHMDS, MeI, THF, 78 ^oC– RT, 97%; (d) $LiAlH_4$, THF, 0 ^oC– RT, 69%; (e) (S)–MTPACl, C_5H_5N, DMAP; (f) TsCl, DMAP, C_5H_5N, 0 ^oC–5 ^oC, 2 h, 95%; (g) NaCN, NaI, DMSO, 110 ^oC, 30 min, 78%; (h) KOH, $HO(CH_2)_2OH$, H_2O, 100 ^oC, 3 h, 91%; (i) MeNHOMeHCl, EDC, DMAP, $(i–Pr)_2NEt$, CH_2Cl_2,0 ^oC, 4 d, 84%; (j) Me_2C=CHMgBr, THF, 20 ^oC– RT, 2 h, 88%.(k) $AlCl_3$, CS_2, –40 ^oC to –20 ^oC, 1 h, then reflux (46 ^oC), 4 h, 40%; (l) N_2H_4 H_2O, KOH, diethylene glycol, 200–210 ^oC, 3 h, 42%.*

Conversion of **45** to (*R*)–ar–himachalene (**1**) was carried out according to Pandey and Dev.[2] Thus, (*R*)–**45** in carbon disulfide was treated with $AlCl_3$ for 1 h at –40 ^oC to –20 ^oC. Later, the reaction mixture was allowed to warm upto RT and further refluxed at 46 ^oC for 1 h gave oily ketone (*R*)–**46**, in 40% yield. The initial low temperature was proved to be essential for the success of this cyclization step. Wolff–Kishner reduction of the ketone (*R*)–**46** afforded oily (*R*)–*ar*–himachalene (**1a'**) in 42% yield.

2.1.3 References:

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2.2.1. Present Work

2.2.1.1. Objective

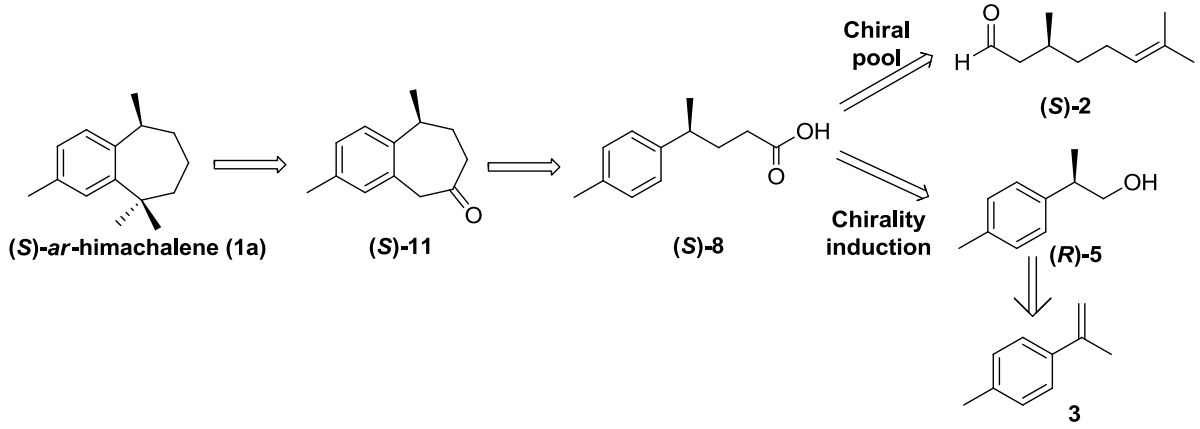
Literature survey revealed that (*S*)-*ar*–himachalene (**1a**) and (*R*)-*ar*–himachalene (**1a'**) (**Figure-1**) have attracted many organic chemists towards their total synthesis due to the potential interesting biological activity and unique structural features. In an approach described by Sukh Dev *et al*., they first prepared a cyano derivative from *m*–methyl acetophenone, which upon chain elongation followed by PPA mediated cyclization gave racemic *ar*–himachalene.[1a] Bartelt *et al*. synthesized *ar*–himachalene from cycloheptanone using Robinson annulation strategy.[1b] Mori *et al*. first time acheived enantioselective synthesis of *ar*–himachalene from commercially available chiral citronellal. They first constructed seven membered ring which was further converted to (*R*)–(+)–himachalene. While in an another approach they used Evans' chiral auxiliary to introduce a chiral methyl at benzylic position.[1c, d]

Figure–1: Enantiomers of *ar*–himachalene

The construction of seven–membered ring fused to an aromatic ring, introduction of chiral center at benzylic position and geminal dimethyl groups are the main tasks of its enantioselective total synthesis (figure–1). Many chemical transformations of *ar*–himachalene are also known to afford other structurally important synthetic compounds.[2] Therefore, these remarkable pheromonal activities as well as interesting structural features, was the inspiration to undertake its synthesis. The present work describes an enantioselective synthesis of both the isomers of an *ar*–himachalene starting from the enantiomerically pure citronellal and from the *p*–methyl *α*–methyl styrene as an application of chiral pool and chirality induction approach respectively. The key reactions involved in the synthesis includes the Sharpless asymmetric dihydroxylation for the induction of chirality at benzylic carbon bearing methyl group and the use of hypervalent iodine reagent or trimethylsilyldiazomethane ($TMSCHN_2$) for the six to seven member ring expansion.

2.2.1.2. Retrosynthetic analysis

As a part of ongoing program towards the synthesis of bioactive sesquiterpene natural products [3] it was envisioned that the enantiomerically pure citronellal (**2**) can be used as a chiral building block for the enantioselective synthesis of *ar*–himachalene. Based on the chemistry involving Sharpless asymmetric dihydroxylation and intramolecular ring expansion either by using hypervalent iodine reagent or by using TMS diazomethane, it was realized that *ar*–himachalene could be synthesized in enantiomerically pure form from the *p*–methyl *α*–methyl styrene (**3**). As per the proposed retrosynthetic plan (**Scheme 1**), (*S*)–*ar*–himachalene can be accessed from (*S*)–4–(*p*–tolyl)–pentanoic acid (**8**) by using trifluoroacetic acid and trifluoroacetic anhydride mediated cyclization



Scheme 1. Retrosynthetic analysis for (*S*)–*ar*–himachalene (**1a**)

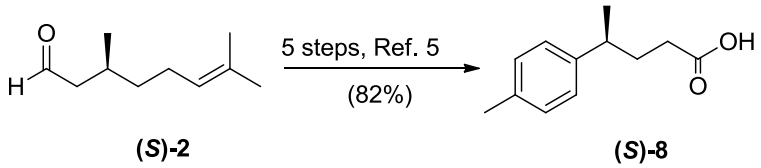
followed by subsequent ring expansion reaction. Further, acid (*S*)–**8** can be obtained by two routes, (i) from (*S*)–citronellal (**2)** by one pot Michael addition, Robinson annulation and decarboxylation, followed by aromatization and Jones oxidation reaction and (ii) from the *p*–methyl *α*–methyl styrene (**3**), in which chirality at benzylic position can be introduced using the Sharpless asymmetric dihydroxylation reaction as the key step.

2.2.2. Results and discussions

2.2.2.1. Synthesis of *ar*–himachalene by chiral pool approach

According to the retrosynthetic analysis, synthesis started with an ideal chiral building block *viz.*– (*S*)–citronellal (**2**)[4] to obtain an acid (*S*)–**8** using the procedure reported earlier from this group (**Scheme 2**).[5] The key intermediate, optically active 4–(*p*–tolyl)pentanoic acid (**8**) was obtained from

commercially readily available citronellal. (*S*)– Citronellal (**2**) was converted to enone **4** following a reported procedure.[6] Wittig methylenation[7] of **4** gave triene **5** in good yield (80%). The aromatization[8] of **5** was achieved by refluxing it in DMF in the presence of sulfur to furnish the aromatic compound **6** in 70% yield. One pot oxidative cleavage of the double bond [9] via the corresponding diol to optically pure acid **8** was achieved in 82% yield.

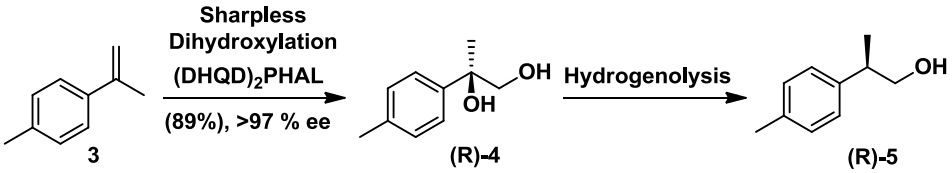


Scheme 2: Preparation of (*S*)–4–(*p*–tolyl)pentanoic acid (**8**) from (*S*)–citronellal

2.2.2.2. Preparation of (*S*)–4–(*p*–tolyl)pentanoic acid (8) by chirality induction approach :

Alternatively, acid (*S*)–**8** was also obtained from a styrene derivative **3**. According to the retrosynthetic analysis, the synthesis begins with a styrene derivative **15**, which was prepared from commercially available *p*–methyl acetophenone, by adding MeMgBr followed by eliminating tertiary hydroxyl using $KHSO_4$.[10] Sharpless asymmetric dihydroxylation of *p*–methyl *α*–methyl styrene (**3**) by the use of AD–mix–*β*, furnished diol (*R*)–**4** in 89% yield and 99% *ee* (by chiral HPLC) (**Scheme–3**).[11] The diol (*R*)–**4** was then subjected for hydrogenolysis to obtain a primary alcohol (*R*)–**5**. Various reagents were studied under different hydrogenation conditions for the removal of tertiary hydroxyl group and introduction of chirality at the benzylic position (**Table 1**).

As expected in most of the cases inversion of configuration was observed.[12] Whereas, the use of freshly activated Raney Ni in refluxing ethanol gave (*S*)–**5** that is retention of configuration in 78% yield with 86% *ee*. (by chiral HPLC) (entry 7). The use of Et_3SiH in presence of Lewis acid catalyst gave product with very poor *ee* (entry 1 and 2). Whereas, $Pd(OH)_2$ under room temperature as well as under reflux conditions gave moderate yields with good *ee* (entry 3 and 4).[13] $Pd(OH)_2$ in the presence of ammonium formate as a hydrogen source resulted in decomposition of starting material (entry 8). The best result for inversion was observed by using 10% Pd/C under hydrogen atmosphere of 60 psi to obtain product (*R*)–**5** with 72 % yield and 97.5% *ee* (by chiral HPLC) (entry 5).[14]



Scheme– 3: Synthesis of *ar*–himachalene by chirality induced approach.

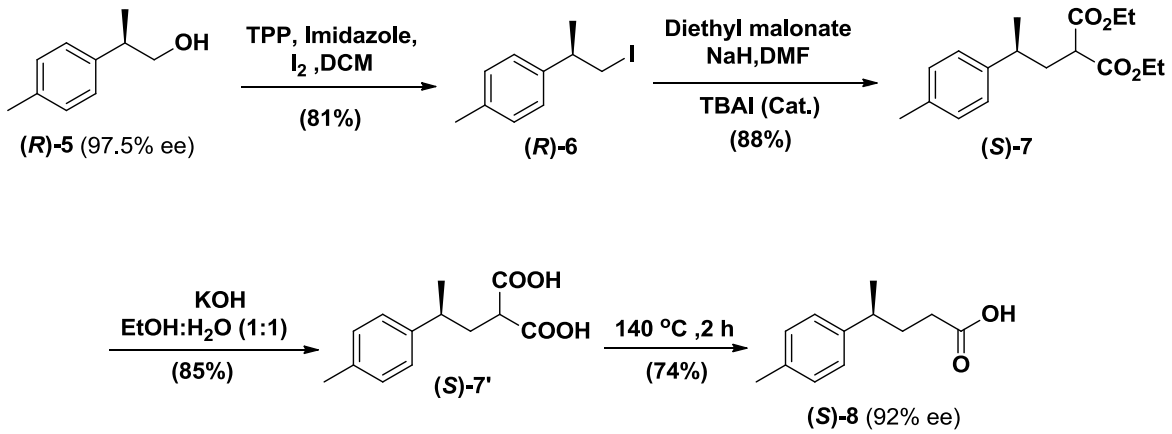
Table 1. Asymmetric hydrogenolysis of (*R*)–2–(*p*–tolyl)propane–1,2–diol (**4**) under different hydrogenation conditions

Entry	**Catalyst**	**Reaction conditions**	**(%) yield of [(R)–5]**	**$[\alpha]^{25}_{D}$ [a]**	**% *ee***
1	CF_3COOH	Et_3SiH, 25 ^oC, 3 h	79	*b*	–
2	$BF_3.OEt_2$	Et_3SiH, 25 ^oC, 3 h	62	*b*	–
3	$Pd(OH)_2$	H_2(60 psi), EtOH, 25 ^oC, 7 h	74	+16.8	93
4[c]	$Pd(OH)_2$	H_2, EtOH, reflux, 4 h	83	+13.9	84
5	Pd/C	H_2(60 psi), EtOH, 25 ^oC, 10 h	72	+17.4	97.5
6[c]	Pd/C	H_2, EtOH, reflux, 12 h	88	+16.2	92
7	Raney Ni	EtOH, reflux, 3 h	78	−15.1 [d]	86
8	NH_4CO_2H, $Pd(OH)_2$	THF−MeOH (1:1), reflux, 5 h	*e*	–	–

a Optical rotations measured (*c* 1 ,$CHCl_3$), *b* Racemic product formation, *c* Reaction was performed under balloon pressure under hydrogen atmosphere, *d* Product formed with retention of configuration (*S*– alcohol), *e* Decomposition of starting material was observed.

The alcohol (*R*)–**5** was then converted into its iodo derivative (*R*)–**6** by using triphenylphosphine, imidazole and iodine in 81% yield. The iodo compound (*R*)–**6** was further treated with diethyl malonate, sodium hydride and tetrabutyl ammonium iodide (TBAI) as a phase transfer catalyst to obtain diester (*S*)–**7** in 88% yield. The formation of diester compound was confirmed from IR absorption frequency exhibited at 1744 cm^{-1}. The diester (*S*)–**7** was then hydrolyzed under basic condition to its corresponding diacid (*S*)–**7'** in 85% yield. Neat thermal

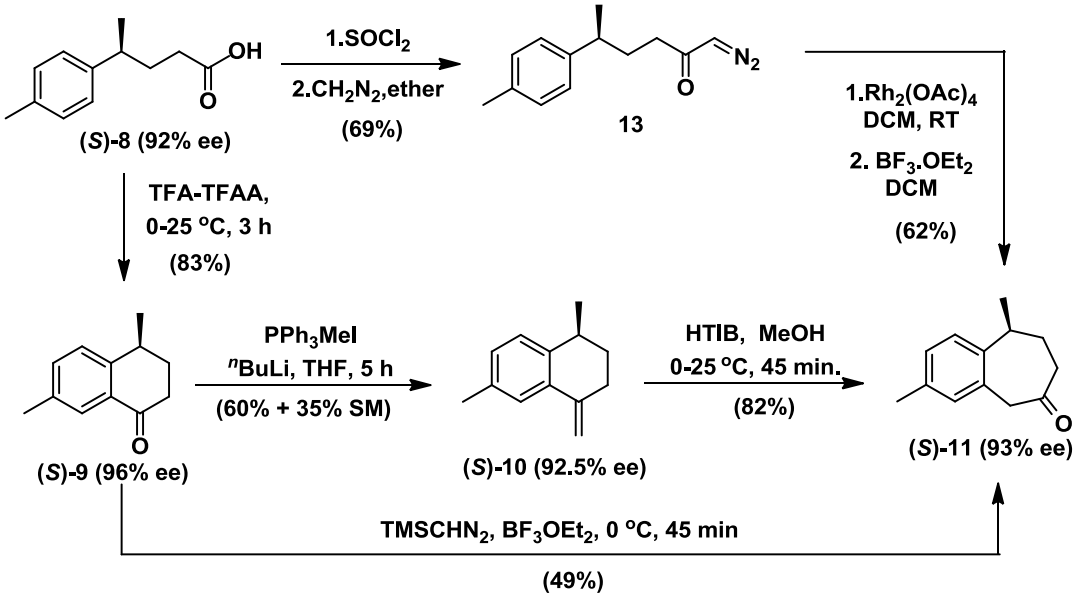
decarboxylation of (*S*)–**7'** furnished the desired chiral acid (*S*)–**8** in 83% yield with 96% *ee* (by chiral HPLC) (**Scheme 4**).



Scheme 4: Synthesis of (*S*)–4–(*p*–tolyl)pentanoic acid (**8**)

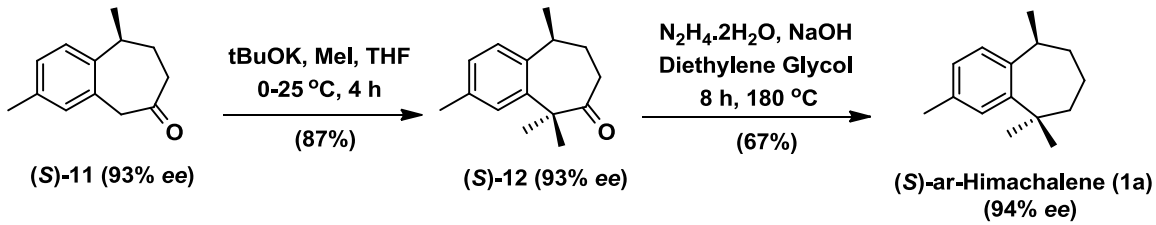
This acid **8** is the common intermediate that was prepared previously using chiral pool approach from (*S*)–citronellal (**2**). In the first approach, the acid **8** was converted into acid chloride, using thionyl chloride and further treatment of it with diazomethane gave diazo compound **13** in 69% yield. Further ring expansion was done using Buchner reaction conditions to furnish cyclic ketone **11** with 62% yield (**Scheme 5**).[20]

In an another approach, cyclization of acid (*S*)–**8** was achieved by trifluoroacetic anhydride [15] mediated intramolecular acylation reaction to obtain enantiomerically enriched tetralone**,** the (*S*)–trinorsesquiterpene (**9**) in 83% yield with 96% *ee* (by chiral HPLC). It is worth mentioning that the trinorsesquiterpene is a natural product which was isolated from the Japanese species *J. truncate* as a 1:1 mixture of both enantiomers.[16] Although, it is difficult to construct the seven membered ring fused to aromatic ring, few references are known in the literature to make this framework.[17, 18, 19] The Koser's reagent and $TMSCHN_2$ were chosen for the six to seven membered ring expansion. One carbon Wittig olefination of *p*–methyl–tetralone (*S*)–**9** gave compound (*S*)–**10** with exocyclic methylene group in 60% yield with 35% starting material was recovered. This compound **10** upon treatment with Koser's reagent i.e. [hydroxy(tosyloxy)iodo]benzene (HTIB) underwent facile ring expansion to furnish ketone (*S*)–**11** in 82% yield.[18] The ketone (*S*)–**11** was also obtained directly from *p*–methyl–tetralone (*S*)–**9** by insertion of methylene group using trimethylsilyl diazomethane in 49% yield.[19]



Scheme 5: Different approaches attempted for ring expansion

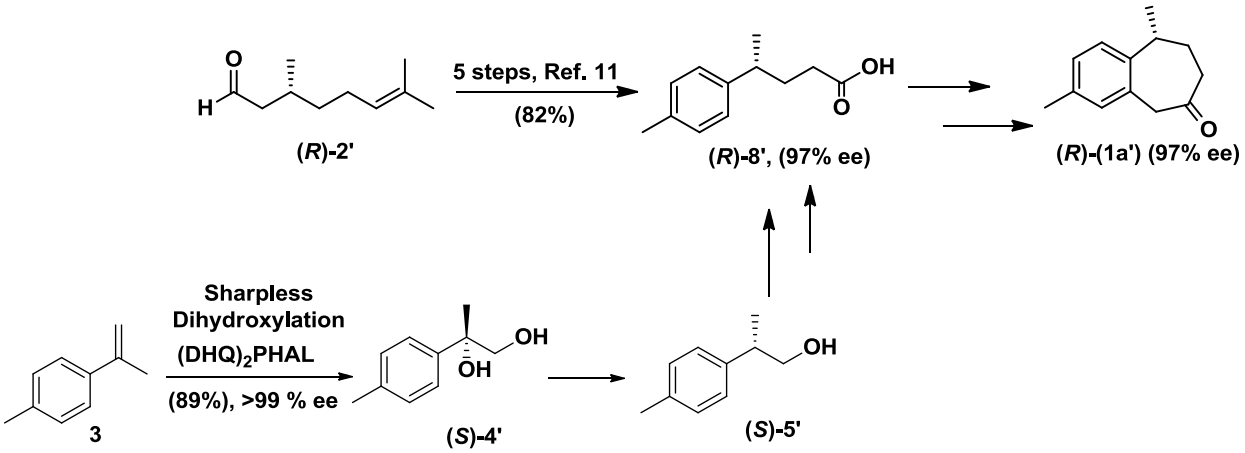
Further, dimethylation of compound (*S*)–**11** with excess of methyl iodide using potassium *tert*–butoxide as the base, furnished compound (*S*)–**12** in 87% yield which after Wolff−Kishner reduction of carbonyl group furnished the (*S*)–*ar*–himachalene (**1a**) in 67% yield (**Scheme 6**).[20] It was decided to check the enantiomeric purity of the final natural product (*S*)–**1a** by using chiral HPLC method but, all our attempts to resolve a sample of (±)–*ar*–himachalene on suitable chiral HPLC column were unsuccessful. Finally, chiral GC analysis was carried out and the enantiomeric excess was determined to be 94% for the final (*S*)–*ar*–himachalene (**1a**).[21]



Scheme 6. Completion of total synthesis of (*S*)–*ar*–himachalene **(1a)**

Mori *et al*. reported (*R*)–*ar*–himachalene was dextrorotatory in *n*–hexane and levorotatory in chloroform.[1d] On similar lines it was observed that (*S*)–*ar*–himachalene is dextrorotatory in chloroform while levorotatory in ^{n}hexane.

Thus, the enantioselective total synthesis of (*S*)–*ar*–himachalene starting from (*S*)–citronellal (**2**) and *p*–methyl *α*–methyl styrene (**3**) was accomplished in 10 and 11 steps respectively in 5% and 6% overall yields respectively. The opposite enantiomer (*R*)–*ar*–himachalene (**1a'**) was also synthesized by following the same reaction sequence starting from (*R*)–citronellal by chiral pool approach and also from *p*–methyl *α*–methyl styrene (**3**) followed by Sharpless asymmetric dihydroxylation, applying AD–mix–*α* for the induction of chirality with equivalent overall yields and 97% *ee* (by chiral GC) (**Scheme–7**).



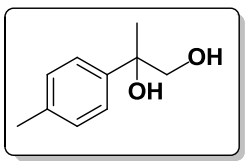
Scheme–7: Synthesis of (*R*)–ar–himachalene (**1a'**)

2.2.3. Conclusion

In summary, the enantioselective synthesis of both the isomers of an *ar*–himachalene has been accomplished. The synthetic sequence involved Sharpless asymmetric dihydroxylation reaction, hydrogenolysis, and the use of $TMSCHN_2$ or hypervalent iodine reagent for the ring expansion. It is believed that this protocol will be of general interest and also useful for designing of several complex bioactive natural and unnatural products.

2.2.4. Experimental

2–(*p*–Tolyl)propane–1,2–diol (4).



To a stirred solution of potassium ferricyanide (22.3 g, 3.0 mmol) and potassium carbonate (9.4 g, 3.0 mmol) in water (150 mL) was added methane sulphonamide (2.2 g, 1.1 mmol) followed by *tert*–butanol (150 mL) and allowed to stir until the

suspension became clear. Then ligand $(DHQD)_2PHAL$ (for *R* isomer) or $(DHQ)_2PHAL$ (for *S* isomer) (0.055 g, 4.0 mol%) followed by 1M solution of osmium tetraoxide in *tert*–butanol (0.010 mL, 1.0 mol%) were added to it at 0 ^oC and the resulting suspension was stirred until orange color was obtained. To this mixture was added *p*–methyl *α*–methyl styrene **(3)** (3.0 g, 1.0 mmol) in dropwise manner. The resultant heterogeneous suspension was stirred vigorously at 0 ^oC until the reaction was complete, monitored by TLC (24 h). Sodium sulfite (5 g) was added slowly to the reaction mixture and the resulting suspension stirred at room temperature for 1 h. The reaction mixture was transferred into a 100 mL separatory funnel and extracted with ethyl acetate (4 X 20 mL). The organic layer was washed with brine then dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue. The residue thus obtained was purified by using 60–120 silica gel column chromatography, (30% ethyl acetate–petroleum ether) to furnish the diol **4** as a colourless oil (3.36 g, 89%, 99% ee for *R* isomer, 97% ee for *S* isomer[22]).

Molecular formula: $C_{10}H_{14}O_2$; **Yield:** 89%.

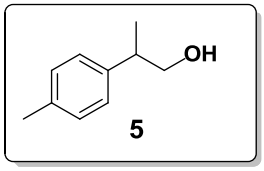
$[\alpha]^{25}_D$= –10.7; (*c* 1, $CHCl_3$ for *R* isomer); **$[\alpha]^{25}_D$**= +10.5 (*c* 1, $CHCl_3$ for *S* isomer).

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.29 (d, *J* = 8.54 Hz, 2H), 7.13 (d, *J* = 8.46 Hz, 2H), 3.71 (d, *J* = 11.12 Hz, 1H), 3.54 (d, *J* = 11.09 Hz, 1H), 2.80 (br s, 2H), 2.33 (s, 3H), 1.46 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 142.2, 136.5, 129.0 (2 carbons), 125.0 (2 carbons), 74.8, 70.8, 25.9, 21.0.

MS (ESI) (*m*/*z*): 189 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3448, 3049, 1216, 1040 cm^{-1}.

2–(4–Methylphenyl)propanol (5).



5

Method A: with Raney Ni: To a stirred solution of (*R*)–2–(*p*–tolyl)propane–1,2–diol **(4)** (0.850 g, 20 mmol) in EtOH (20 mL) was added freshly prepared Raney Ni (2 g, 80 mmol) at 25 ^oC and the reaction mixture was refluxed for 3 h. After completion of the reaction, it was allowed to cool to RT and the catalyst was filtered off through a bed of celite and the residue was washed with ethanol (3 X 5 mL). The combined filtrate was evaporated under reduced pressure and the residue was purified using 60–120 silica gel column chromatography (5% ethyl acetate–petroleum ether) to afford the alcohol (*S*)–**5** as a colorless oil (0.663 g, 78%, 86% *ee* , 93% for *S* isomer). [23]

Molecular formula: $C_{10}H_{14}O$, **Yield:** 78%.

[α]$^{25}_{D}$= −15.1 (*c* 1, $CHCl_3$, for *S* isomer).

Method B: with H_2, Pd/C: To a stirred solution of 2–(*p*–tolyl)propane–1,2–diol **(4)** (0.110 g, 20 mmol) in EtOH (5 mL) was added Pd/C (90 mg, 10 wt%). The reaction mixture was stirred under hydrogen atm. at 25 ^{o}C and 60 psi pressure for 6 h. After completion of the reaction, the catalyst was filtered off and the residue washed with hot EtOH (3 X 5 mL). The filtrate was evaporated under reduced pressure and the obtained residue was purified using 60–120 silica gel column chromatography (5% ethyl acetate–pet. ether) to furnish alcohol **5** as a colorless oil (0.075 g, 72%, 97.5% *ee* for *R* isomer[23]).

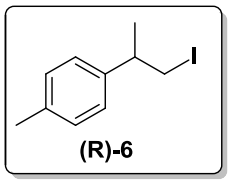
Yield: 72%; **[α]$^{25}_{D}$**= +17.4 (*c* 1, $CHCl_3$ for *R* isomer).

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.25–7.00 (m, 4H), 3.67 (d, *J* = 6.13 Hz, 2H), 2.92 (sextet, *J* = 8.10 Hz, 1H), 2.36 (s, 3H), 1.28 (d, *J* = 8.06 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 140.6, 136.0, 129.3 (2 carbons), 127.3 (2 carbons), 68.6, 42.0, 21.0, 17.7.

MS (ESI) (*m*/*z*):151 $[M+H]^+$; **IR ($CHCl_3$)** ν_{max}: 3320, 1606, 1515 cm^{-1}.

1–Iodo–2–(4–methylphenyl) propane (6).



To a stirred solution of alcohol **5** (3.9 g, 26 mmol) together with triphenyl phosphine (8.86 g, 33.8 mmol) and imidazole (2.30 g, 33.8 mmol) in methylene dichloride (40 mL), iodine (8.59 g, 33.8 mmol) was added in three equal portions at 10 ^{o}C and the solution was allowed to warm at 25 ^{o}C and stirred for 4 h. After completion of reaction, petroleum ether (40 mL) was added to the reaction mixture and it was filtered through celite and washed with petroleum ether–ethyl acetate (10:1 mL). The combined filtrate was evaporated under reduced pressure and the obtained residue was purified using 60–120 silica gel column chromatography (petroleum ether) to obtain the compound **6** as a thick oil (5.4 g, 82%).

Molecular formula: $C_{10}H_{13}I$; **Yield:** 82%.

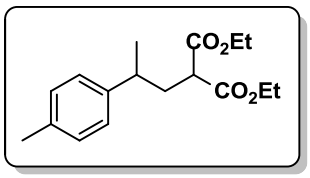
[α]$^{25}_{D}$ = +30.1 (*c* 1, $CHCl_3$ for *R* isomer); **[α]$^{25}_{D}$**= –29.7 (*c* 1, $CHCl_3$ for *S* isomer).

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.20–7.05 (m, 4H), 3.50–3.23 (m, 2H), 3.03 (sextet, *J* = 8.11 Hz, 1H), 2.36 (s, 3H), 1.43 (d, *J* = 8.09 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 141.3, 136.3, 129.3 (2 carbons), 126.6 (2 carbons), 42.1, 21.7, 21.2, 14.9.

MS (ESI) (*m*/*z*): 301 $[M+K]^+$; **IR ($CHCl_3$)** ν_{max}: 3012, 2925, 1514, 668 cm^{-1}.

Diethyl 2–(2–(*p*–tolyl)propyl)malonate (7).



To a stirred suspension of NaH (60% dispersion in mineral oil, 1.12 g, 28 mmol) in dry DMF (10 mL) at 0 ^oC was added diethyl malonate (4.25 mL, 28 mmol) in a dropwise manner. After half an hour, iodo compound **6** (5.2 g, 20 mmol) in dry DMF (5 mL) was added dropwise over a period of 10 min. followed by catalytic amount of tetrabutyl ammonium iodide (10 mol%) and the reaction mixture was heated at 120 ^oC for 10 h. The reaction mixture was then allowed to cool to room temperature and then diluted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue. The obtained residue was then purified by flash column chromatography using 60–120 silica gel (5% ethyl acetate–petroleum ether) to furnish the diester compound **7** as a viscous oil (5.19 g, 88%).

Molecular formula: $C_{17}H_{24}O_4$; **Yield:** 88%.

$[\alpha]^{25}_D$ = +22.4 (*c* 1, $CHCl_3$ for *S* isomer); **$[\alpha]^{25}_D$**= –22.2 (*c* 1, $CHCl_3$ for *R* isomer).

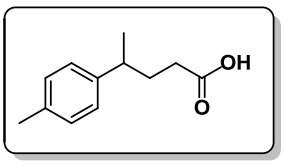
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.20–6.95 (m, 4H), 4.30–4.00 (m, 4H), 3.14 (dd, *J* = 10.14 and 6.06 Hz, 1H), 2.81–2.54 (m, 1H), 2.33 (s, 3H), 2.27–2.00 (m, 2H), 1.43–1.05 (m, 9H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 169.3, 142.3, 135.8, 129.2 (2 carbons), 127.0 (2 carbons), 61.2, 50.3, 37.4, 37.0, 29.7, 22.6, 21.0, 14.2.

MS (ESI) (*m*/*z*): 315 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3021, 1744, 1724 cm^{-1}.

HRMS (EI) calcd for $C_{17}H_{25}O_4$ $[M + H]^+$ 293.1752, found 293.1747.

4–(*p*–Tolyl)pentanoic acid (8).



To a solution of diester **7** (5 g 17.1 mmol) in water (20 mL) and ethanol (20 mL) was added solution of KOH (3.83 g, 68.4 mmol) in 10 mL of water and the reaction mixture was stirred for 2–3 h at room temperature till the emulsion became clear. The ethanol was removed under reduced pressure and the aqueous solution was neutralized with 10% HCl, extracted with diethyl ether (3 X 10 mL), dried

over anhydrous sodium sulphate, filtered and removal of solvent under reduced pressure afforded diacid. This crude product was used as such for further decarboxylation, and was heated at 140 ^{o}C for 4 h. The residue was dissolved in DCM (2.5 mL) and passed through silica gel flash column chromatography (10% ethyl acetate–pet ether) to furnish the acid **8** as viscous oil (2.52 g, 78%, 92% *ee* for *S* isomer, 97% *ee* for *R* isomer[24]).

Molecular formula: $C_{12}H_{16}O_2$; **Yield:** 78%.

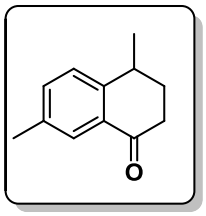
[α]$^{25}_{D}$ = +14.2 (*c* 1, $CHCl_3$ for *S* isomer); **[α]$^{25}_{D}$** = –14.5 (*c* 1, $CHCl_3$ for *R* isomer).

^{1}H NMR (200 MHz, $CDCl_3$): δ 10.4 (s, 1H), 7.30–6.95 (m, 4H), 2.86–2.59 (m, 1H), 2.36 (s, 3H), 2.26 (t, *J* = 8.02 Hz, 2H), 2.13–1.77 (m, 2H), 1.31 (d, *J* = 6.12 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 180.1, 143.0, 135.7, 129.2 (2 carbons), 126.8 (2 carbons), 38.8, 32.9, 32.3, 22.3, 21.0.

MS (ESI) (*m*/*z*): 263 $[M+K+MeOH]^+$; **IR ($CHCl_3$)** ν_{max}: 1707, 1217 cm^{-1}.

4,7–Dimethyl–3,4–dihydronaphthalen–1(2*H*)–one (Trinorsesquiterpene, 9).



Acid **8** (2.4 g, 12.5 mmol) was dissolved in minimum amount of freshly distilled trifluoroacetic acid (8 mL) in a 25 mL round bottom flask under nitrogen atmosphere. To this solution, freshly distilled trifluoroacetic anhydride (10.6 g, 15 mmol) was added dropwise at 0 ^{o}C under constant stirring. Then the reaction mixture was allowed to warm to room temperature and further stirred for 3 h. After completion of reaction, it was neutralized with saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (3 X 5 mL), dried over anhydrous sodium sulphate, filtered and solvent was evaporated under reduced pressure to obtain a residue. The obtained residue was purified by using 60–120 silica gel column chromatography, (5% ethyl acetate–petroleum ether) to furnish the trinorsesquiterpene (**9**) as viscous oil (1.75g, 83%, 96% *ee* for *S* isomer, 93% *ee* for *R* isomer[25]).

Molecular formula: $C_{12}H_{14}O$; **Yield:** 83%.

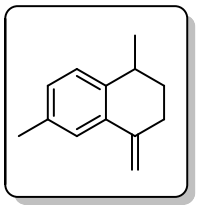
[α]$^{25}_{D}$ = –10.0 (*c* 1, $CHCl_3$ for *S* isomer); **[α]$^{25}_{D}$** = +9.4 (*c* 1, $CHCl_3$ for *R* isomer).

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.83 (s, 1H), 7.37–7.15 (m, 2H), 3.17–2.95 (m, 1H), 2.88–2.45 (m, 2H), 2.36 (s, 3H), 2.34–2.14 (m, 1H), 1.99–1.77 (m, 1H), 1.39 (d, *J* = 8.04 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 198.1, 145.9, 136.0, 134.5, 131.7, 127.5, 127.3, 36.4, 32.5, 30.8, 20.8 (2 carbons).

MS (ESI) (*m*/*z*): 197 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 1683, 1611 cm^{-1}.

1,6–Dimethyl–4–methylene–1,2,3,4–tetrahydronaphthalene (10).



To a mechanically stirred mixture of methyltriphenylphosphonium iodide (7.67 g, 19 mmol) in dry THF (50 mL) at 0 ^{o}C was slowly added 1.6 M THF solution of *n*–BuLi (11. 9 mL, 19 mmol) under argon atmsphere and the solution was stirred vigorously for 20 minutes. Then a solution of tetralone **9** (1.32 g, 7.60 mmol) in dry THF (20 mL) was added to the reaction mixture over a period of 5 minutes in a dropwise manner. The color of the mixture gradually changed from yellow to orange. After 5 h the reaction was quenched by addition of saturated solution of NH_4Cl and the resulting precipitate was filtered off through a bed of celite, washed thoroughly with diethyl ether (3 X 30 mL). The combined filtrate was washed with water, brine, dried over anhydrous sodium sulphate and filtered. Solvent was concentrated under vacuum to obtain a residue. The obtained residue was purified by using 60–120 silica gel column chromatography, eluted with petroleum ether furnished compound **10** as a colorless oil (0.78 g, 60%, 92.5% *ee* for *S* isomer, 93.4% *ee* for *R* isomer[26]).

Molecular formula: $C_{13}H_{16}$; **Yield:** 60%.

$[\alpha]^{25}_{D}$ = +3.2 (*c* 1, $CHCl_3$for *S* isomer); **$[\alpha]^{25}_{D}$** = – 3.6 (*c* 1, $CHCl_3$for *R* isomer).

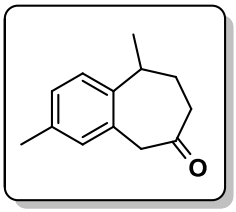
^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 7.47 (s, 1H), 7.15 (d, *J* = 8.15 Hz, 1H), 7.07 (d, *J* = 8.15 Hz, 1H), 5.48 (s, 1H), 4.96 (d, *J* = 2.06 Hz, 1H), 3.57–2.91 (m, 1H), 2.75–2.62 (m, 1H), 2.56–2.45 (m, 1H), 2.38

(s, 3H), 2.13–1.98 (m, 1H), 1.75–1.60 (m, 1H), 1.35 (d, *J* = 8.04 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 143.9, 139.2, 135.0, 134.1, 128.8, 128.0, 124.8, 107.6, 33.0, 31.8, 30.3, 22.4, 21.2.

MS (ESI) (*m*/*z*): 227 $[M+ Na+MeOH]^+$; **IR ($CHCl_3$)** ν_{max}: 1629, 1217 cm^{-1}.

3,9–Dimethyl–8,9–dihydro–5*H*–benzo[7]annulen–6(7*H*)–one (11).



Method A: Compound **9** (1.20 g, 33.6 mmol) was suspended in Et_2O (34 mL) and cooled to 0 ^oC under nitrogen atmosphere. To it $BF_3.OEt_2$ (4.70 mL, 37.1 mmol) was added followed by dropwise addition of $TMSCHN_2$ (18.5 mL, 37.0 mmol). The mixture was stirred at 0 ^oC for 45 min and saturated aq. $NaHCO_3$ (100 mL) was carefully added. The two layers were separated and the aqueous layer was extracted with diethyl ether (3 X 20 mL). The combined organic layer was washed with water and brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a yellow oil which was purified by using 60–120 silica gel column chromatography, (5% ethyl acetate–petroleum ether) to give compound **11** as a light yellow oil (0.635 g, 49%).

Yield: 49%.

Method B: To a stirred solution of **10 (**1.43 g, 11.0 mmol) in methanol (40 mL) was added crystalline HTIB (3.92 g, 10.0 mmol). The solid dissolved rapidly to give a colorless solution. The solution was stirred at room temperature for 30 minutes and the solvent was removed to obtain an oily mixture. This mixture was then partitioned between CH_2Cl_2 (50 mL) and H_2O (25 mL) and transferred to a separatory funnel. The organic layer was separated, washed with water and brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a bright yellow oil which was purified by using 60–120 silica gel column chromatography, (5% ethyl acetate–petroleum ether) to give tetralone **11** as a light yellow oil (0.720 g, 82%, 93% *ee* for *S* isomer, 93.3% *ee* for *R* isomer[27]).

Molecular formula: $C_{13}H_{16}O$; **Yield:** 82%.

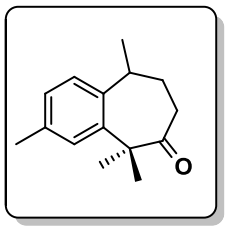
$[\alpha]^{25}_D$ = +69.2 (*c* 1, $CHCl_3$ for *S* isomer); **$[\alpha]^{25}_D$** = –69.4 (*c* 1, $CHCl_3$ for *R* isomer).

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.22–7.02 (m, 2H), 6.94 (s, 1H), 3.85 (d, *J* = 18.12 Hz, 1H), 3.48 (d, *J* = 18.12 Hz, 1H), 3.25–3.00 (m, 1H), 2.32 (s, 3H), 2.62–2.22 (m, 2H), 2.22–1.98 (m,1H), 1.74–1.46 (m, 1H), 1.40 (d, *J* = 8.17 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 210.2, 140.0, 136.1, 133.8, 130.4, 128.2, 125.1, 49.5, 41.3, 34.2, 34.1, 20.8, 19.5.

MS (ESI) (*m*/*z*): 197 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 1705, 1216 cm^{-1}.

3,5,5,9–Tetramethyl–8,9–dihydro–5*H*–benzo[7]annulen–6(7*H*)–one (12).



To a magnetically stirred solution of **11** (0.6 g, 3.2 mmol) and methyl iodide (2.7 g, 19.2 mmol) in anhydrous THF (5 mL) under nitrogen atmosphere, was added potassium *tert*–butoxide (1.07 g, 9.6 mmol) in a three equal portions over a period of 30 minutes. The reaction mixture was stirred at room temperature for 4 h and poured into ice–water slurry and extracted with diethyl ether (3 X 50 mL). The combined organic layer was washed with saturated sodium bicarbonate solution (2 X 10 mL) followed by brine (2 X 10 mL), dried over anhydrous sodium sulphate and filtered. The solvent was removed under reduced pressure. The obtained residue was purified by using 60–120 silica gel column chromatography, (5% ethyl acetate–petroleum ether) to furnish the ketone **12** as a colorless oil (0.602 g, 87%, 93% *ee* for *S* isomer, 93.3% *ee* for *R* isomer[28]).

Molecular formula: $C_{15}H_{20}O$; **Yield:** 87%.

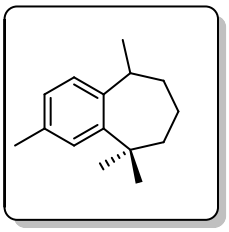
$[\alpha]^{25}_{D}$ = +32.1(*c* 1, $CHCl_3$ for *S* isomer); **$[\alpha]^{25}_{D}$** = –32.3 (*c* 1, $CHCl_3$ for *R* isomer).

^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.25–7.05 (m, 3H), 3.04–2.80 (m, 1H), 2.80–2.57 (m, 1H), 2.38 (s, 3H), 2.29–2.03 (m, 2H), 1.50 (s, 3H), 1.43–1.26 (m, 6H),

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 217.5, 143.9, 137.8, 136.0, 127.9, 126.0, 124.8, 52.6, 36.9, 35.9, 32.5, 26.5, 25.8, 21.3, 19.3.

MS (ESI) (*m*/*z*): 238 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 1702, 1216 cm^{-1}.

2,5,9,9–Tetramethyl–6,7,8,9–tetrahydro–5*H*–benzo[7]annulene (1).



A mixture of **12** (0.4 g, 1.85 mmol), anhydrous hydrazine hydrate (0.360 g, 360 µl, 7.4 mmol) and sodium hydroxide (0.296 g, 7.4 mmol) in a freshly distilled diethylene glycol (5 mL) was heated at 150 ^oC. After 1 h the excess hydrazine hydrate was removed and the bath temperature was allowed to rise to 180 ^oC. Refluxing was continued for an additional hour. The cooled reaction mixture was poured into ice and extracted with ether (3 X 50 mL). The combined organic layer was washed with saturated sodium bicarbonate solution (2 X 10 mL) followed by brine (2 X 10 mL) and dried over

anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude product obtained was purified by using 60–120 silica gel column chromatography, (petroleum ether only) to furnish *ar*–himachalene **1** (0.242 g, 64%, 94% *ee* for *S* isomer[20], 97% *ee* for *R* isomer[21]).

Molecular formula: $C_{15}H_{22}$; **Yield:** 64%.

$[\alpha]^{25}_D$ = +2.9 (*c* 1, $CHCl_3$ for *S* isomer); **$[\alpha]^{25}_D$** = –2.1 (*c* 1, $CHCl_3$ for *R* isomer).

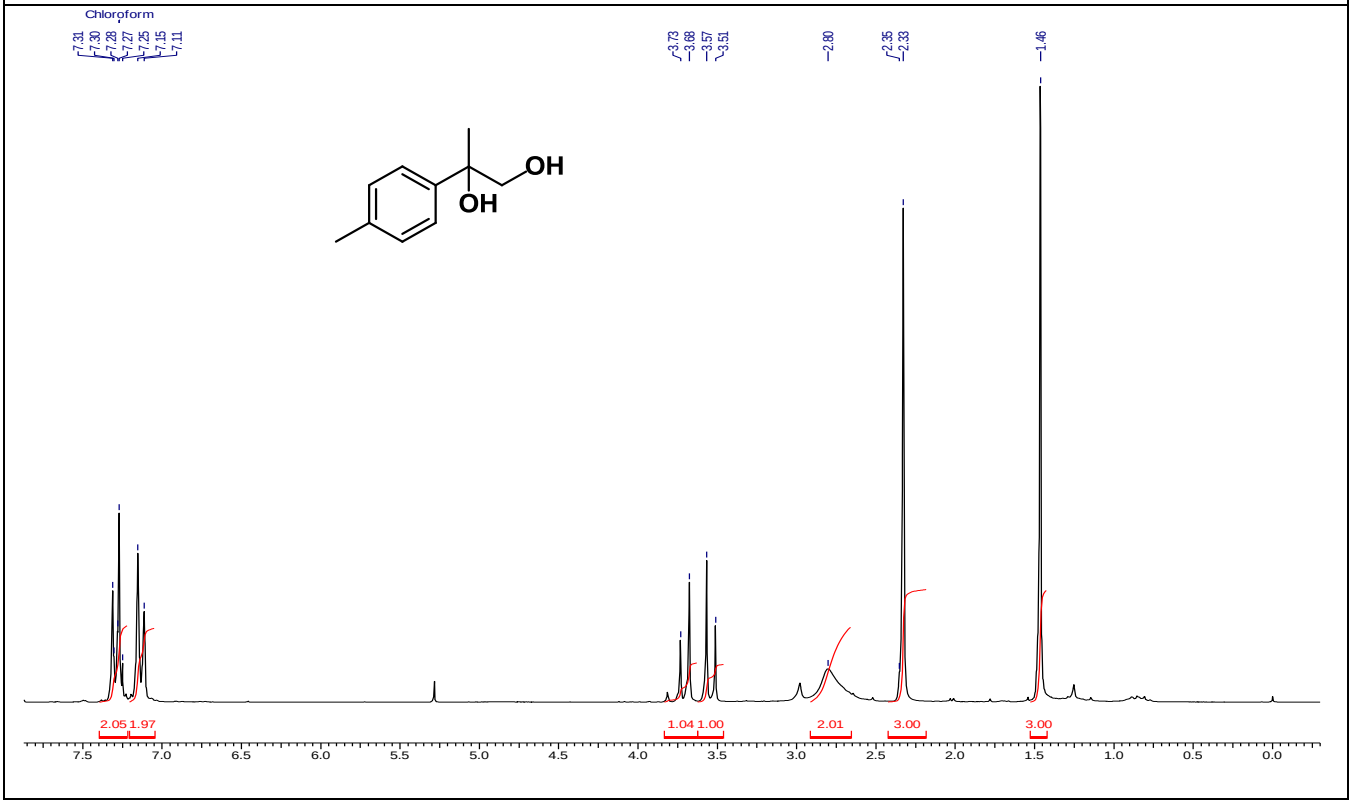
^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.24 (s, 1H), 7.17 (d, *J* = 8.08 Hz, 1H), 7.03 (d, *J* = 8.08 Hz, 1H), 3.44–3.22 (m, 1H), 2.38 (s, 3H), 1.95–1.55 (m, 4H), 1.50 (s, 3H), 1.46–1.36 (m, 6H).

^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 147.6, 141.1, 134.9, 127.5, 126.6, 125.4, 41.2, 36.6, 34.5, 34.1, 29.8, 24.1, 21.3, 21.1, 39.5.

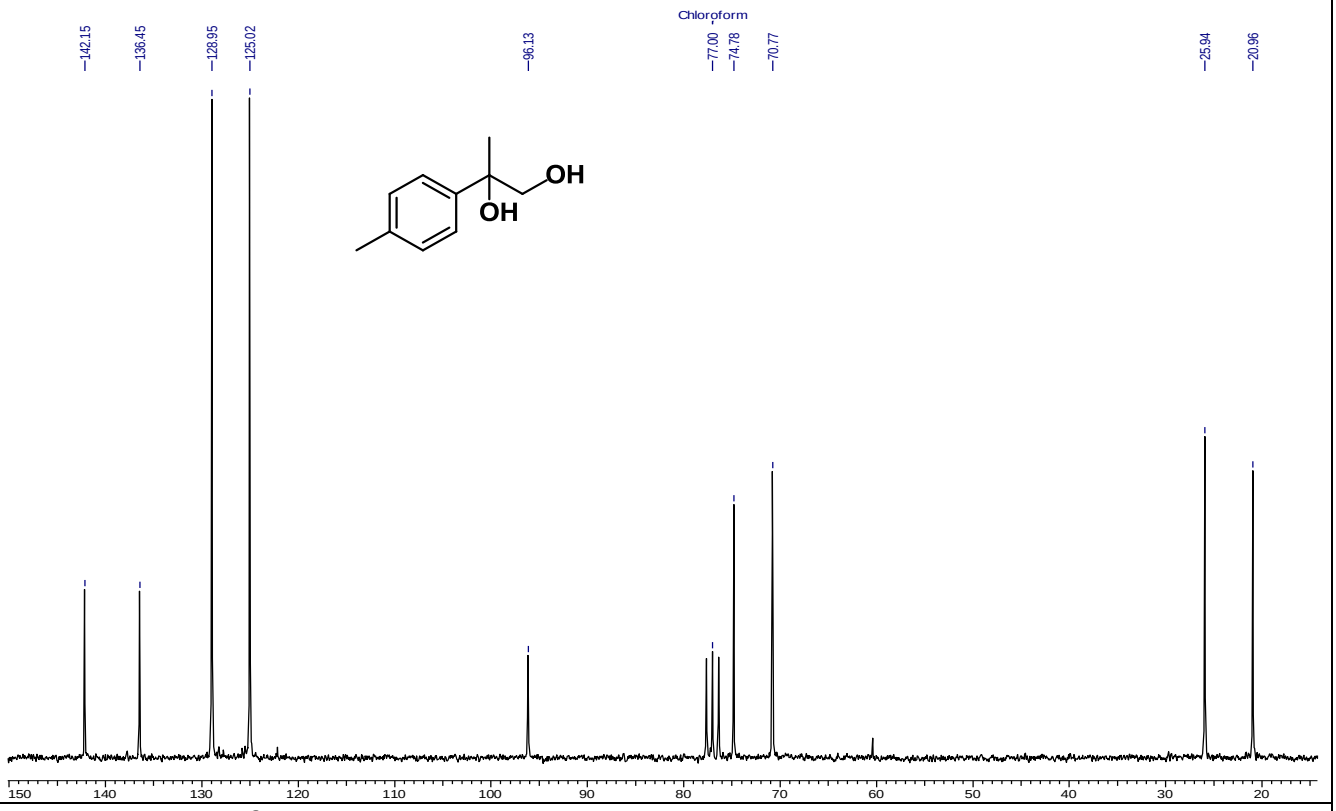
MS (ESI) (*m*/*z*): 203 $[M + H]^+$; **IR ($CHCl_3$)** ν_{max}: 3008, 2961, 1456, 1216 cm^{-1}.

2.2.4.1. NMR Spectra

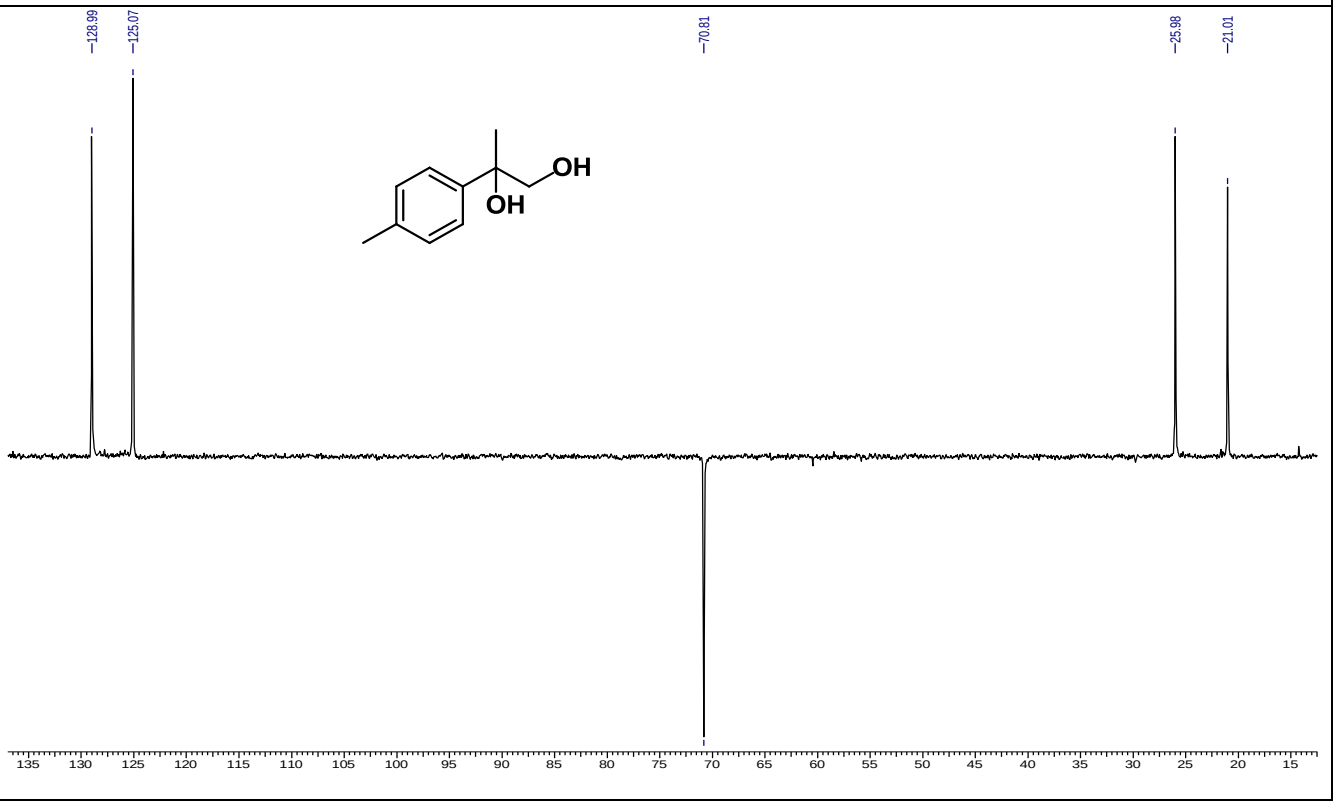
^{1}H NMR spectrum of compound 4 ($CDCl_3$+CCl_4, 200 MHz)



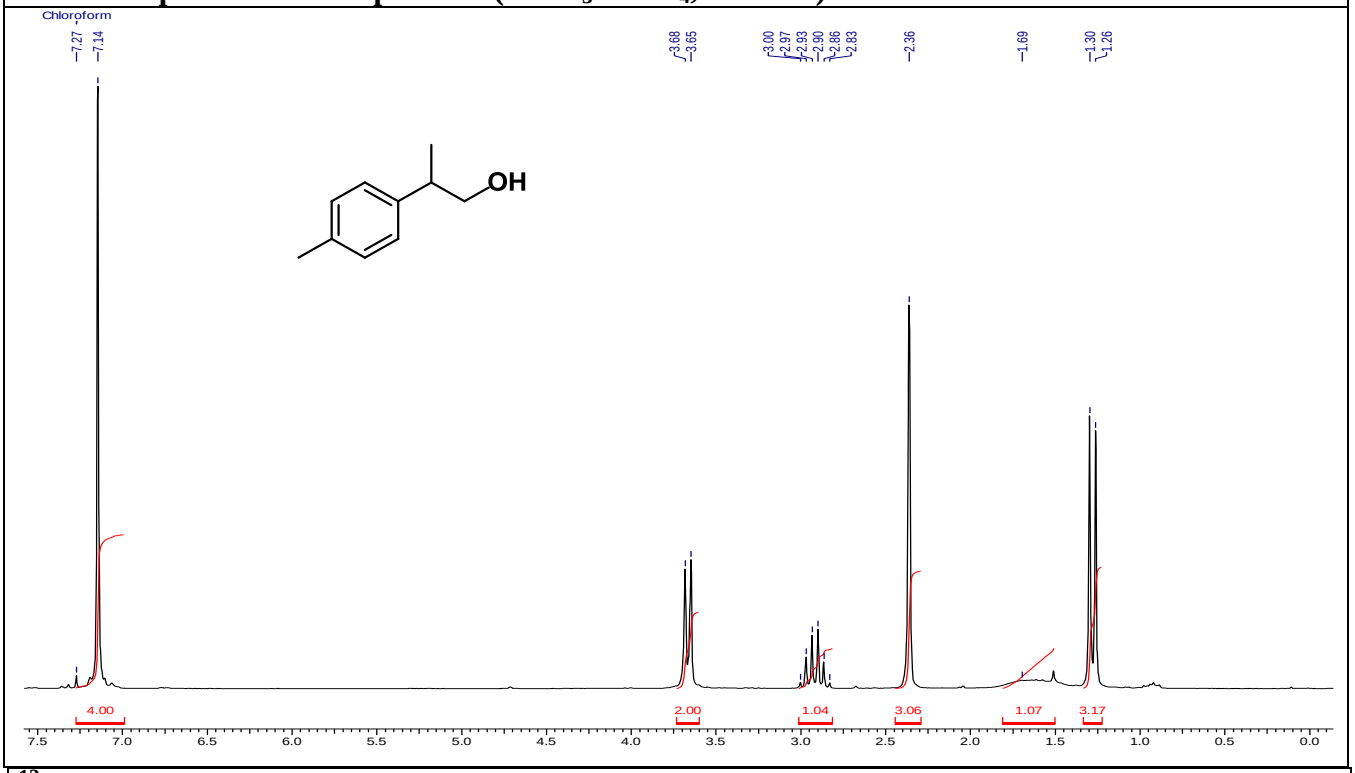
^{13}C NMR spectrum of compound 4 ($CDCl_3$ + CCl_4, 50 MHz)



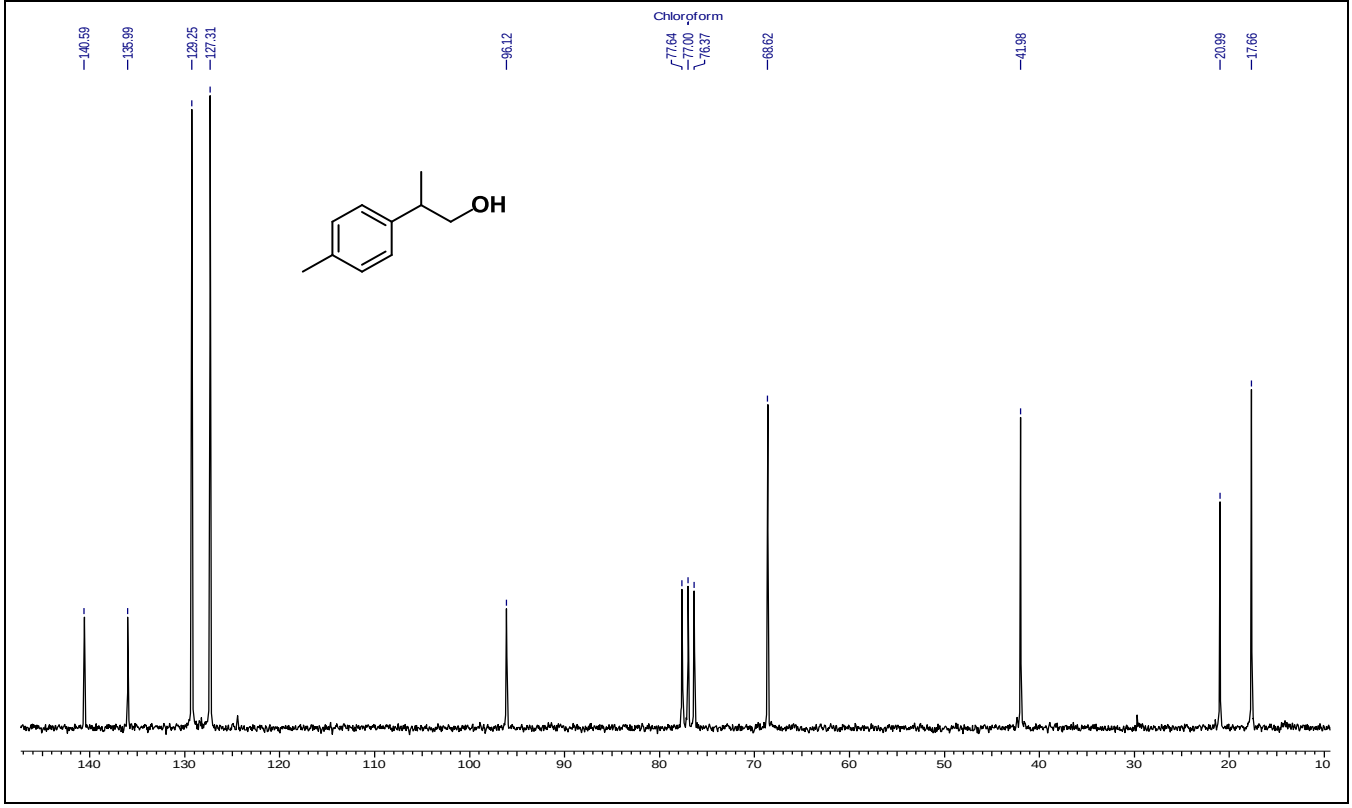
DEPT spectrum of compound 4 ($CDCl_3$+CCl_4, 200 MHz)



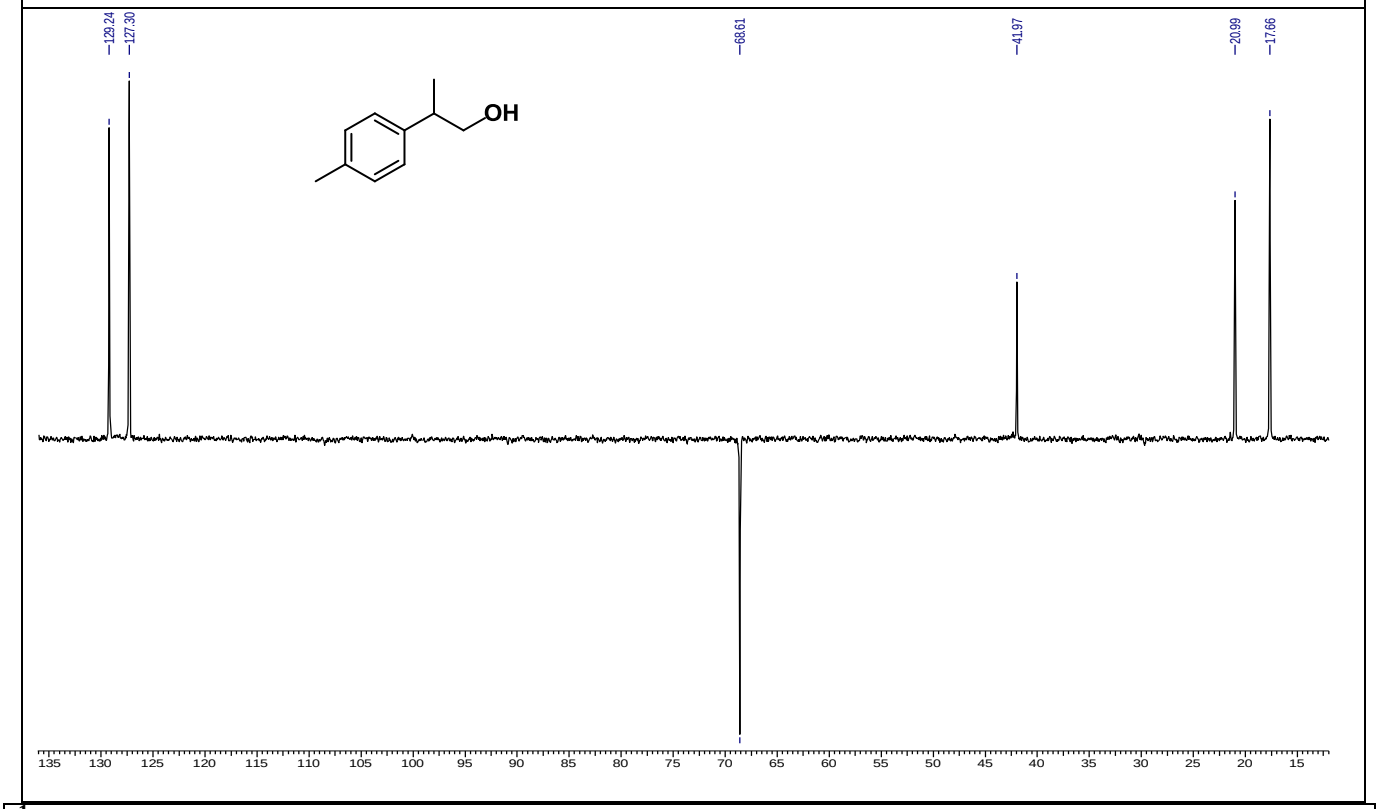
^{1}H NMR spectrum of compound 5 ($CDCl_3$ + CCl_4, 50 MHz)



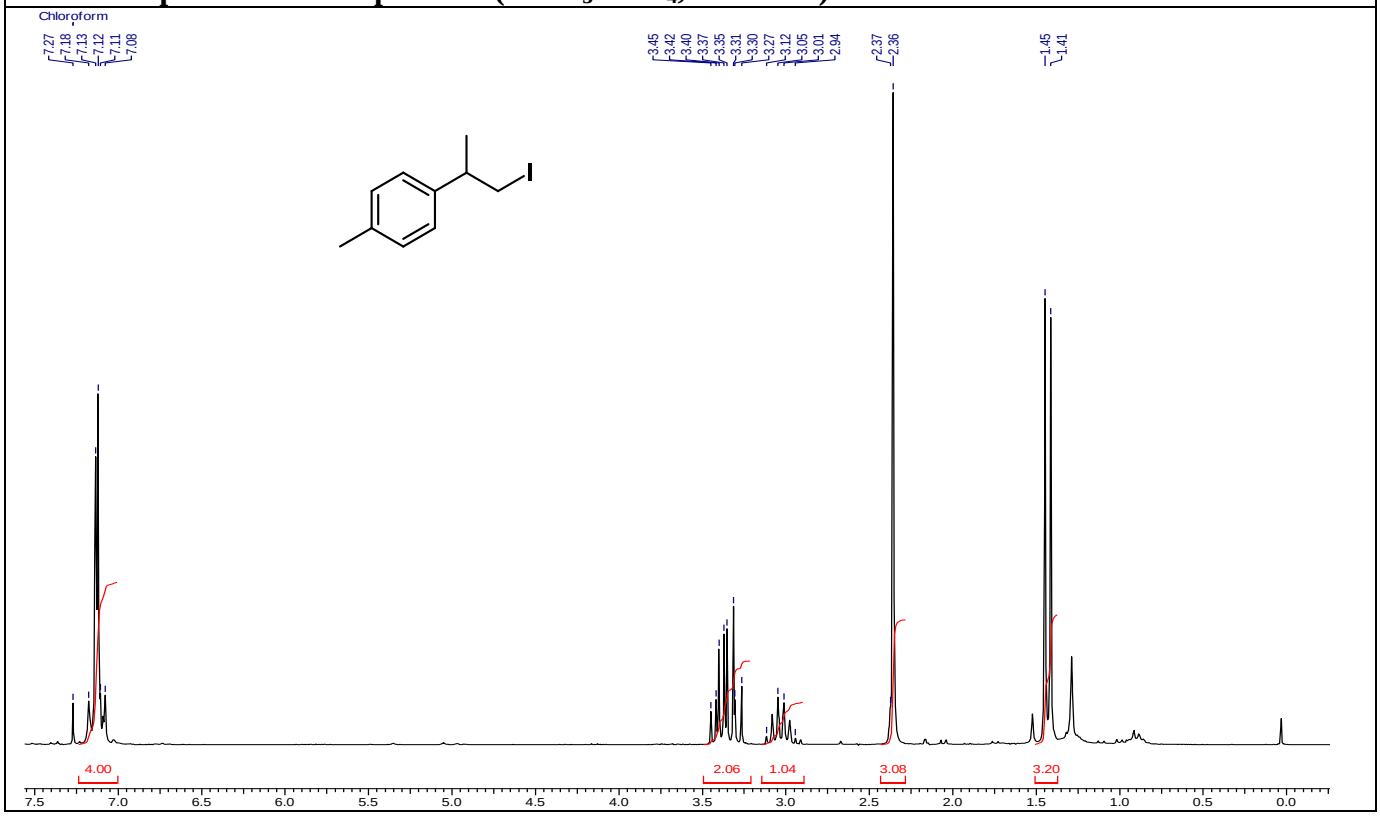
^{13}C NMR spectrum of compound 5 ($CDCl_3$ + CCl_4, 50 MHz)



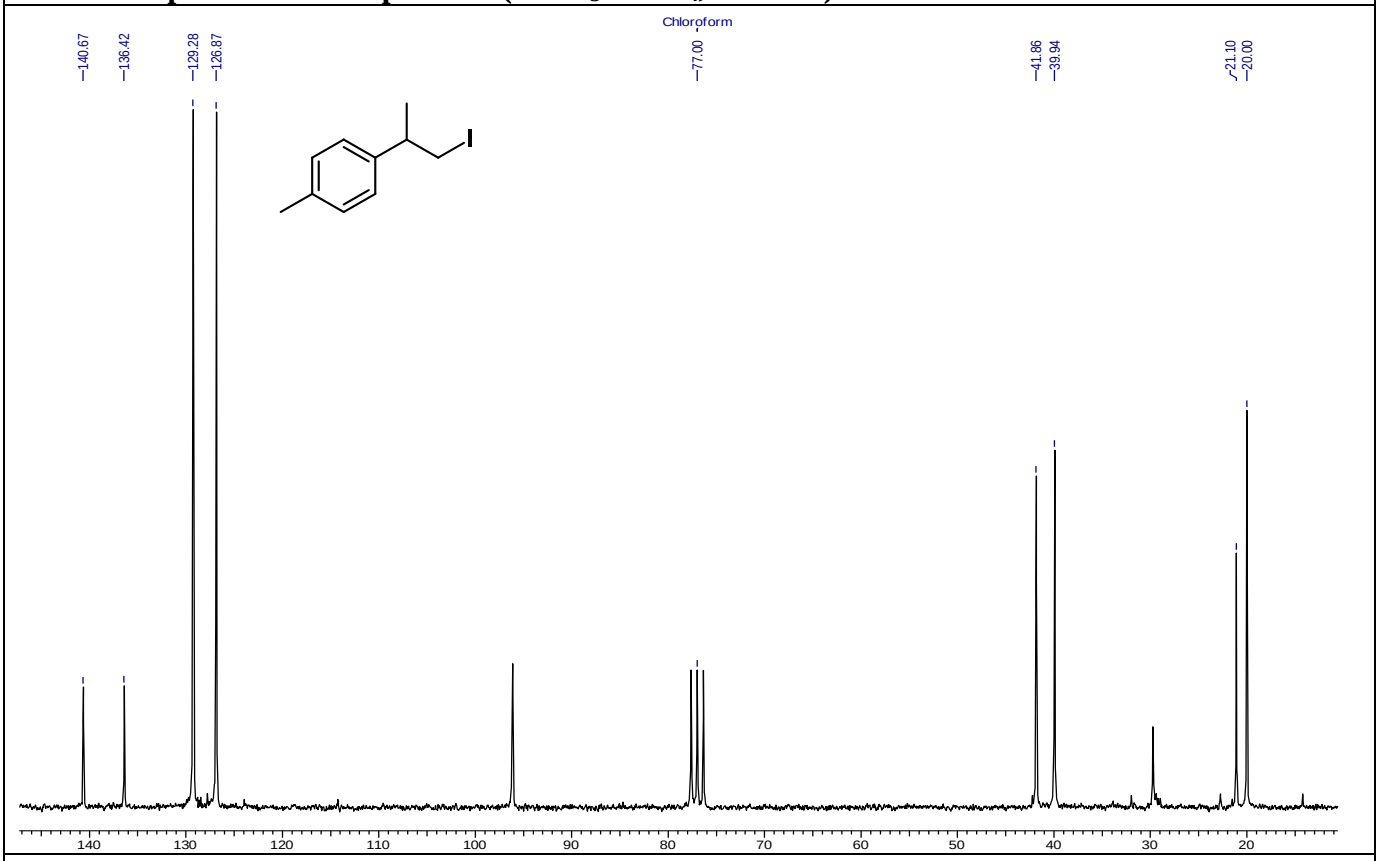
DEPT spectrum of compound 5 (CDCl3+CCl4, 200 MHz)



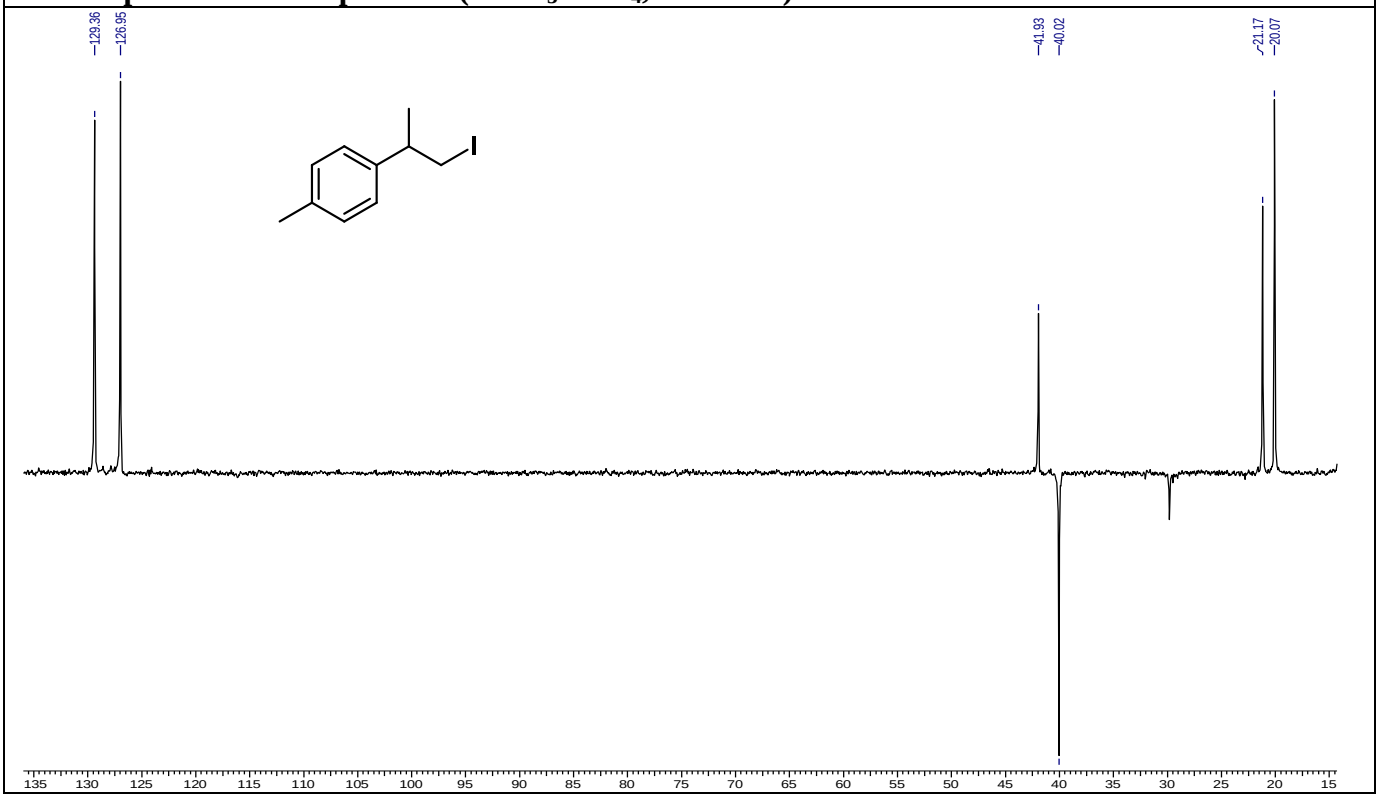
^{1}H NMR spectrum of compound 6 ($CDCl_3$+CCl_4, 200 MHz)



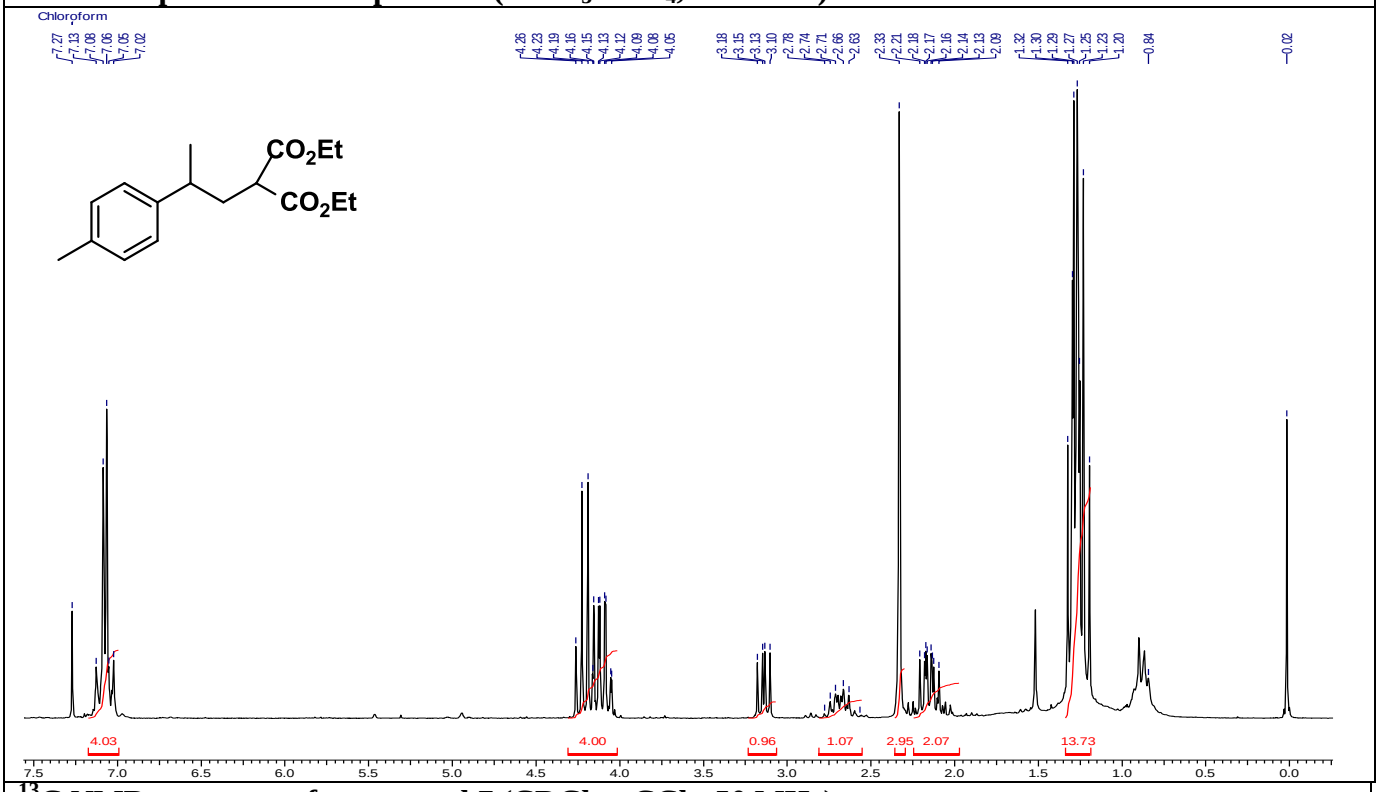
^{13}C NMR spectrum of compound 6 ($CDCl_3$ + CCl_4, 50 MHz)



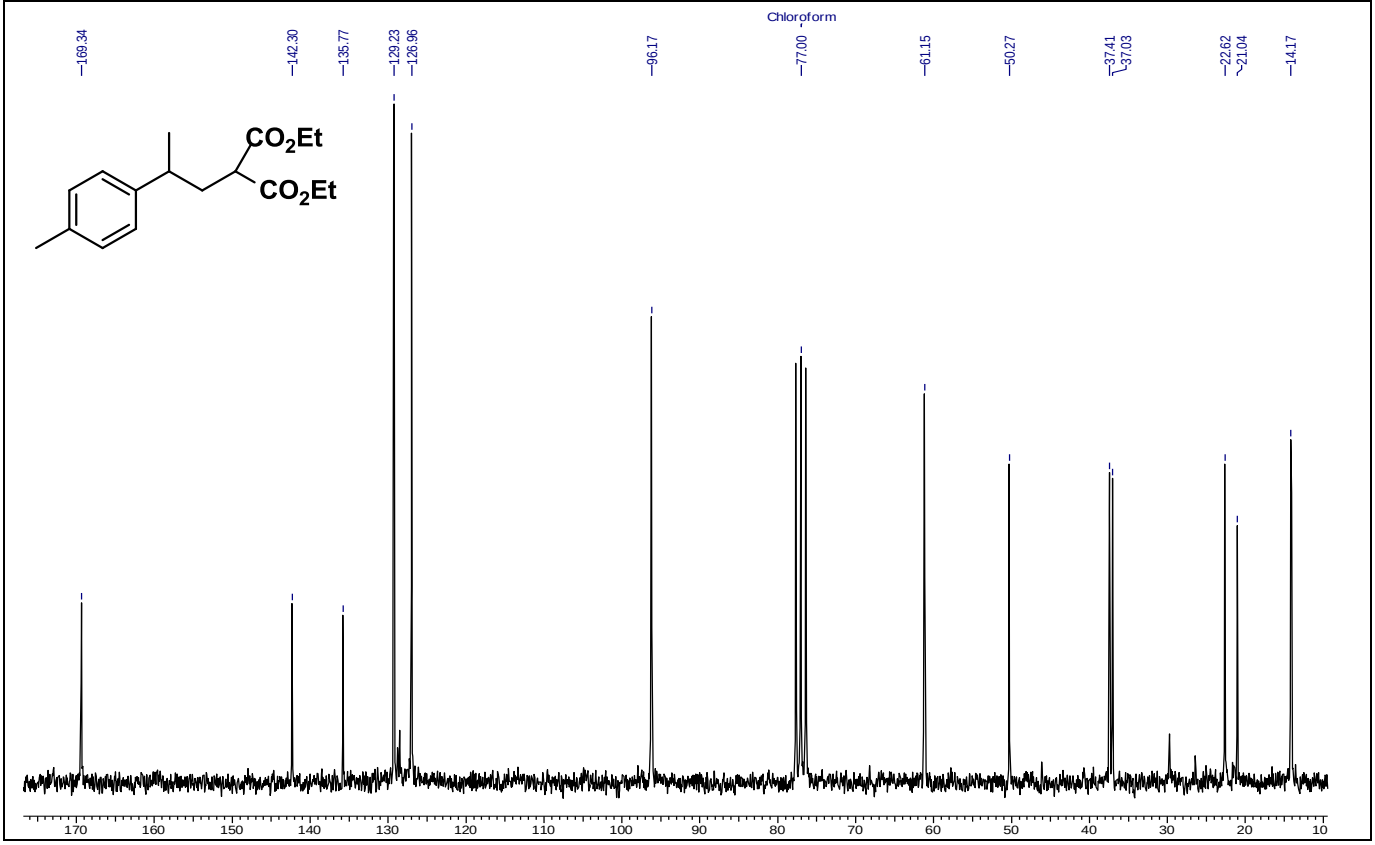
DEPT spectrum of compound 6 ($CDCl_3$+CCl_4, 200 MHz)



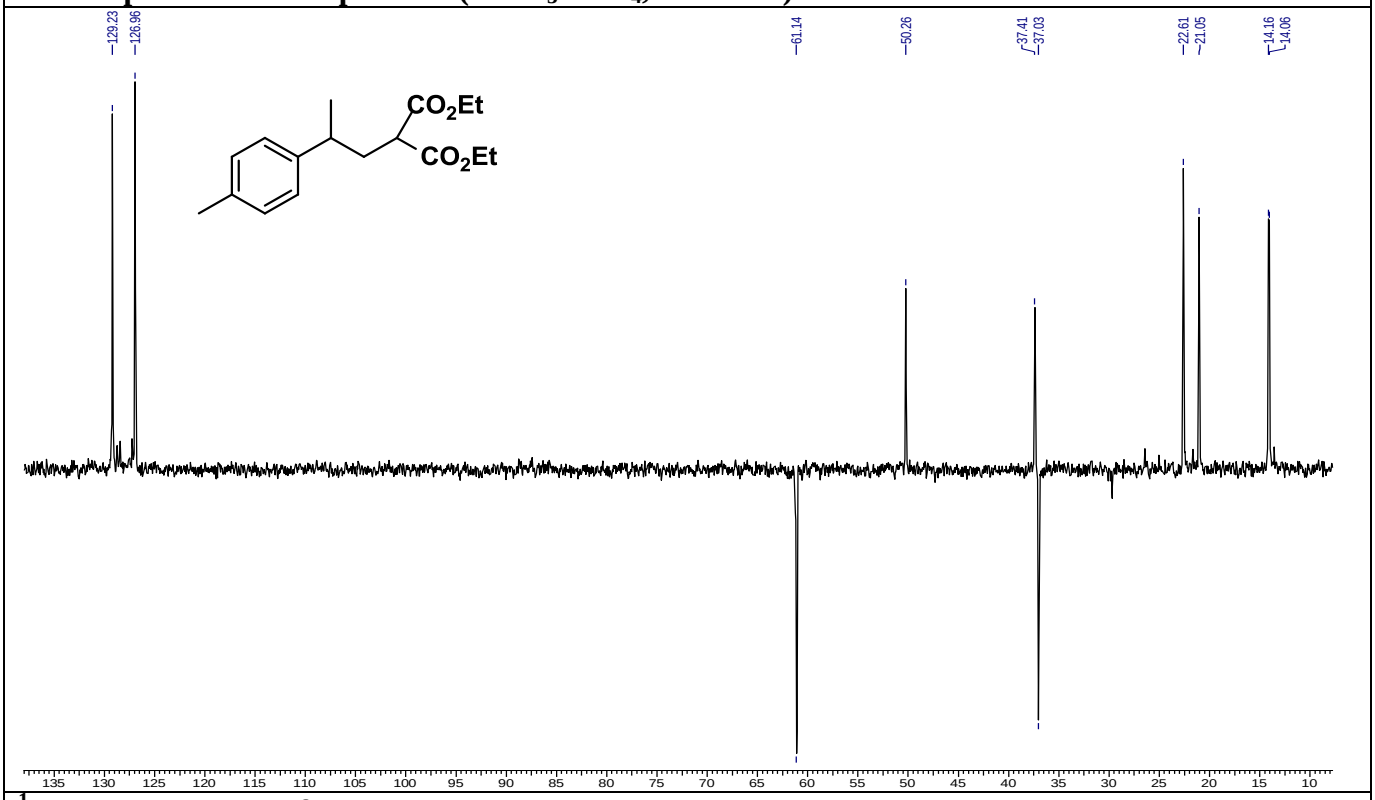
^{1}H NMR spectrum of compound 7 ($CDCl_3$+CCl_4, 200 MHz)



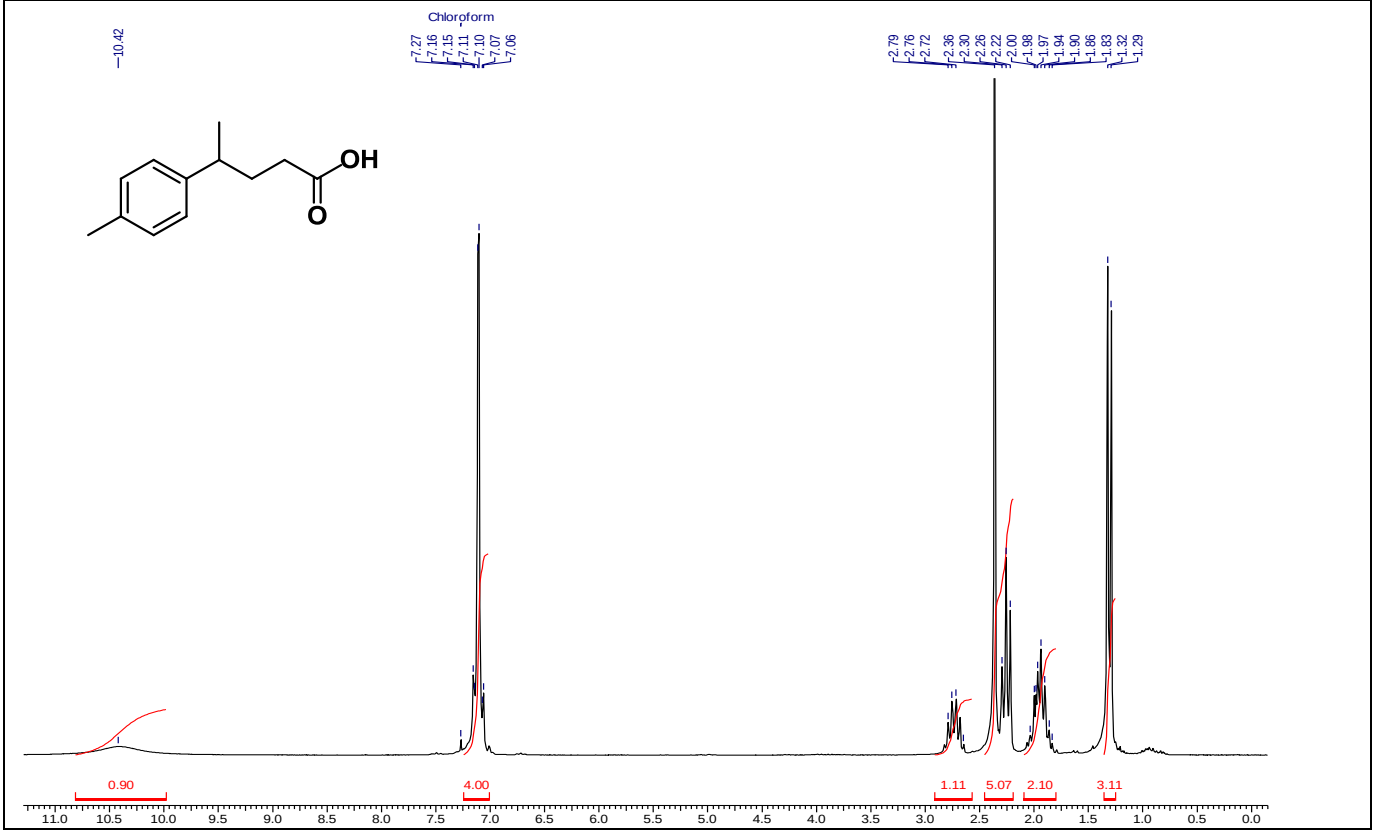
^{13}C NMR spectrum of compound 7 ($CDCl_3$ + CCl_4, 50 MHz)



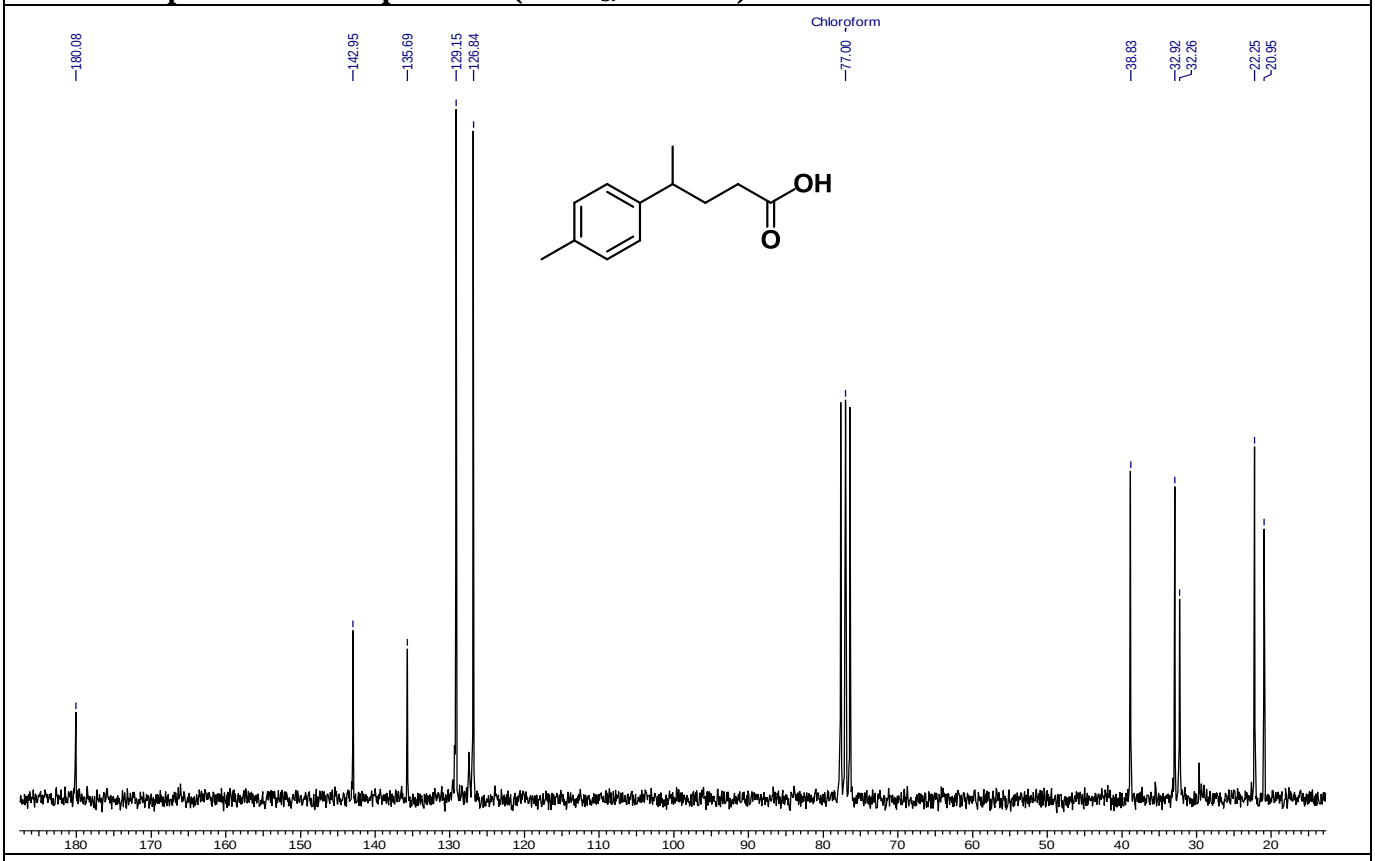
DEPT spectrum of compound 7 ($CDCl_3$+CCl_4, 200 MHz)



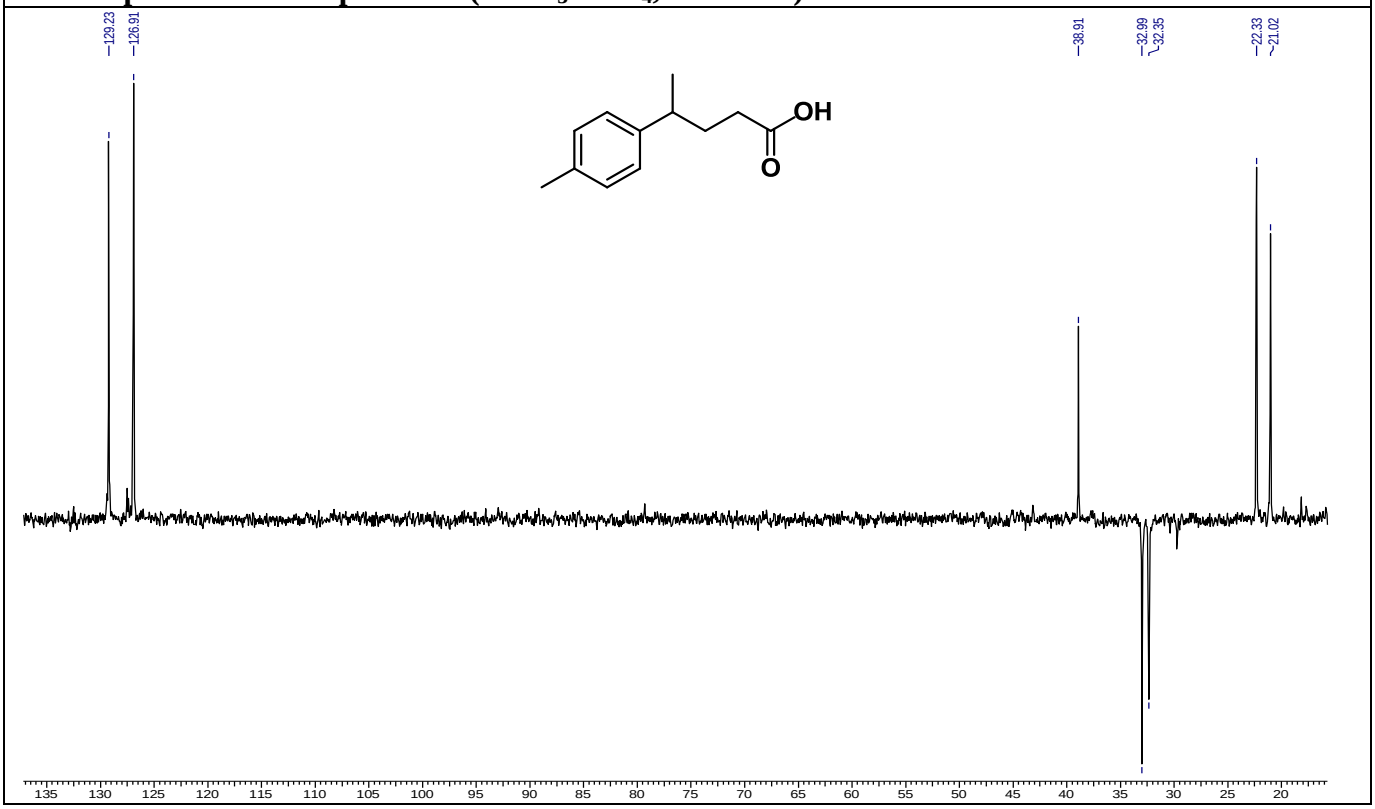
^{1}H NMR spectrum of compound 7' ($CDCl_3$+CCl_4, 200 MHz



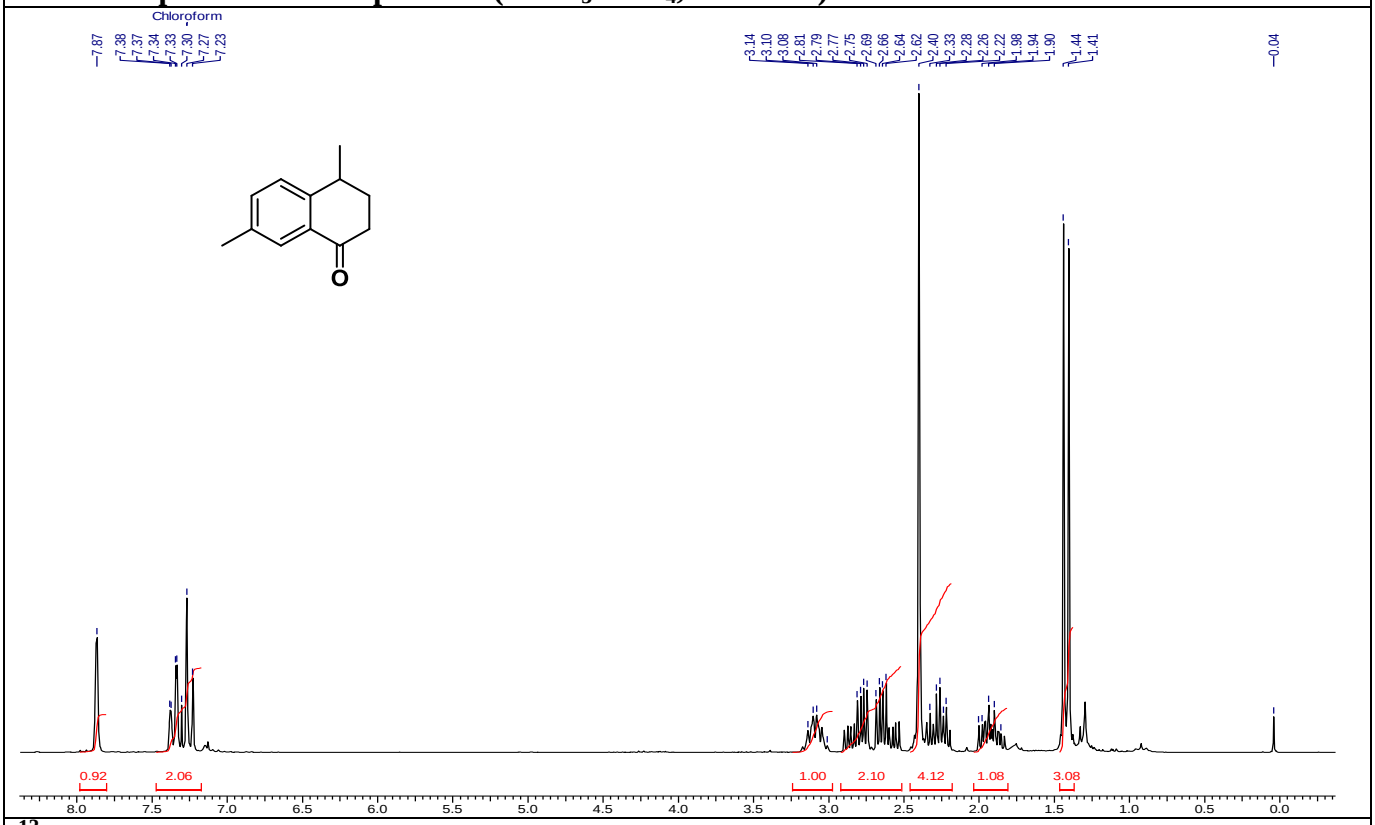
^{13}C NMR spectrum of compound 7' ($CDCl_3$, 50 MHz)



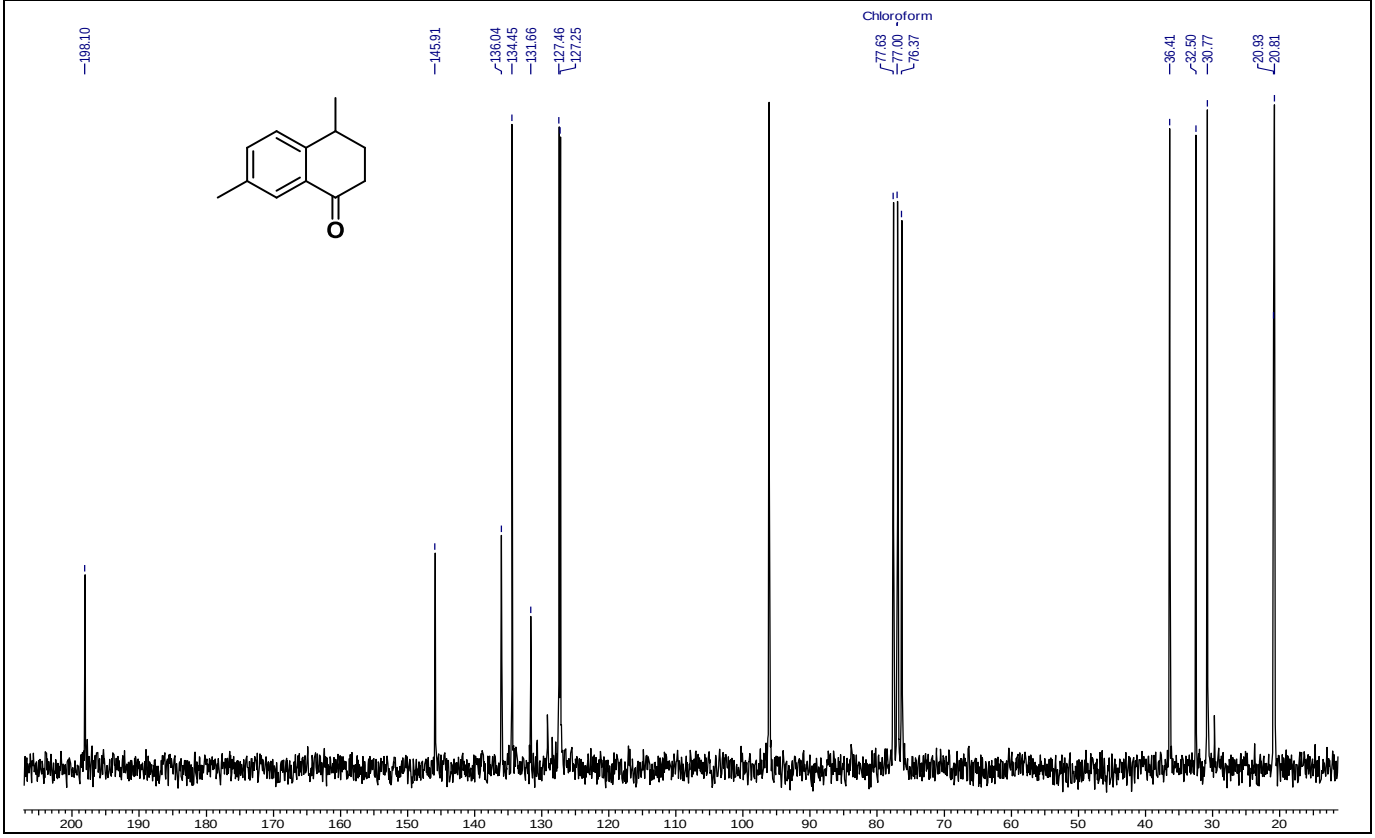
DEPT spectrum of compound 7' ($CDCl_3$+CCl_4, 200 MHz)



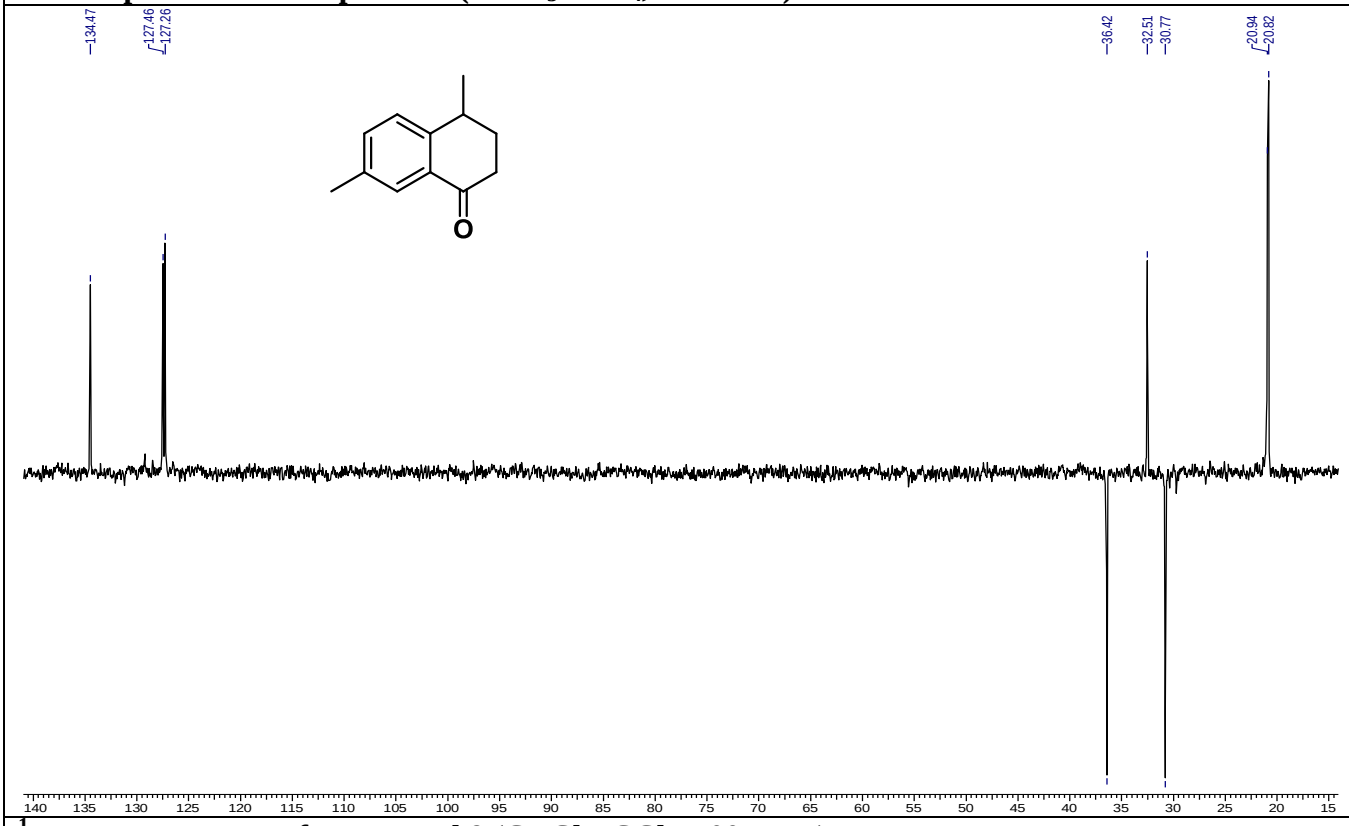
^{1}H NMR spectrum of compound 8 ($CDCl_3$+CCl_4, 200 MHz)



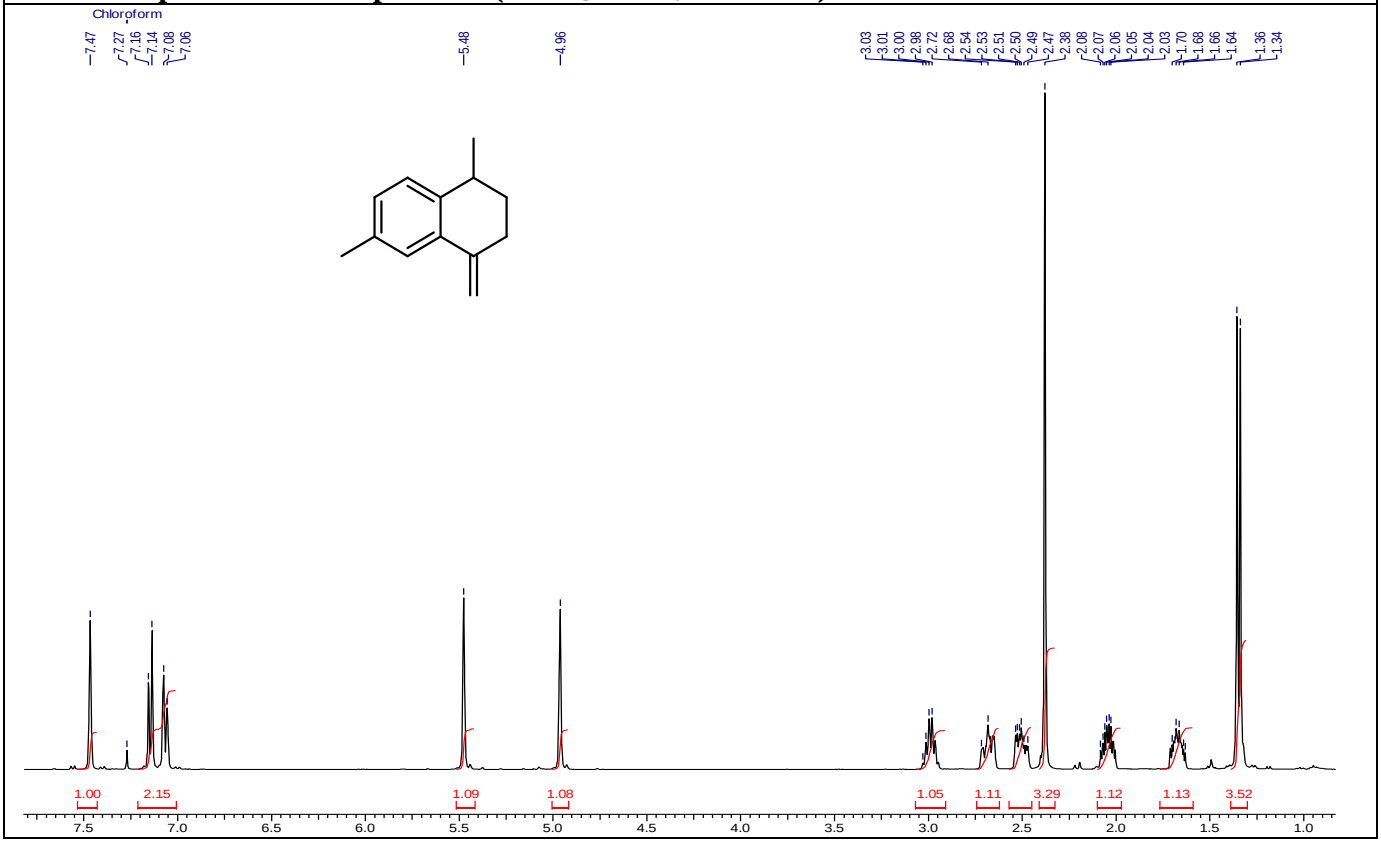
^{13}C NMR spectrum of compound 8 ($CDCl_3$ + CCl_4, 50 MHz



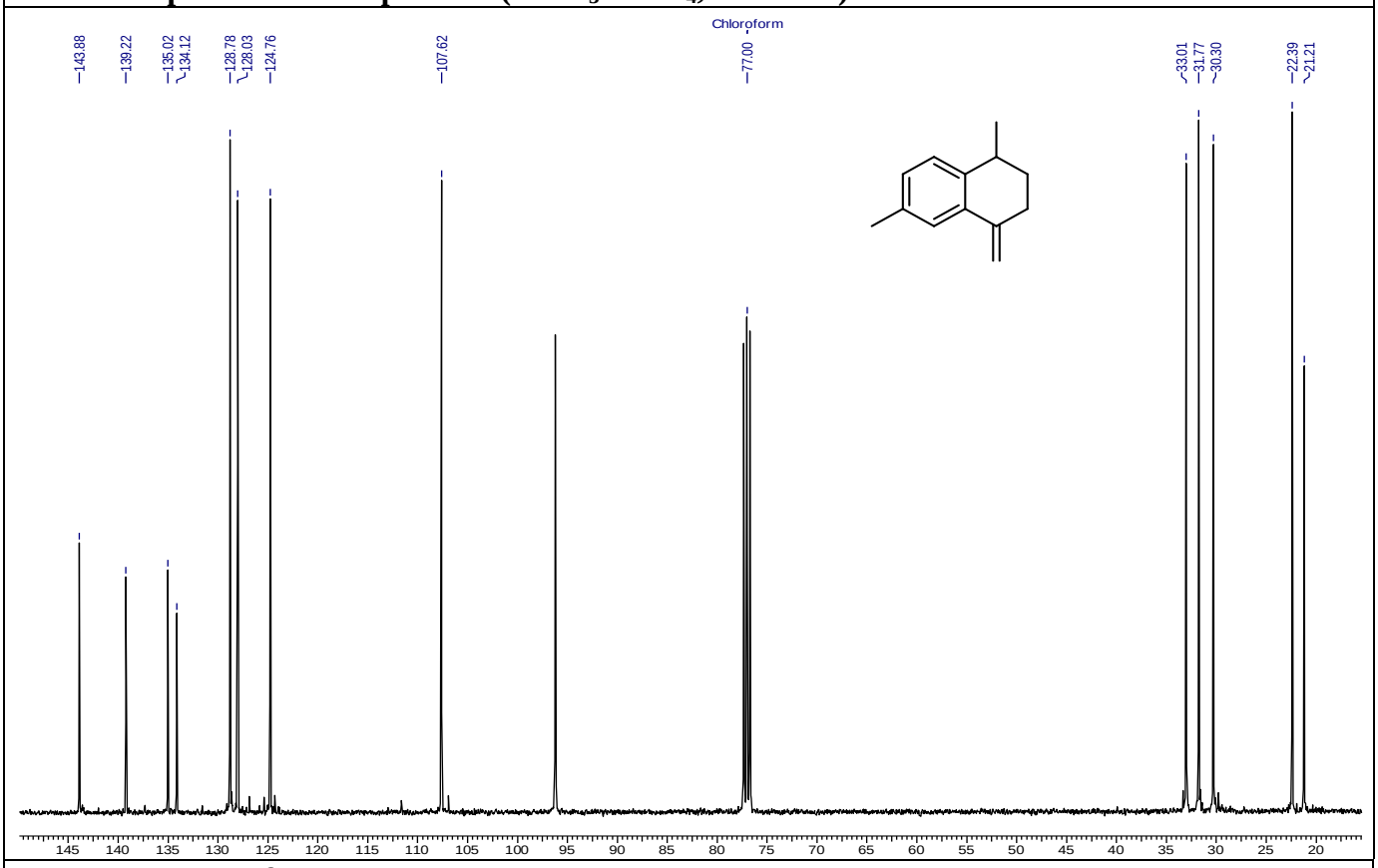
DEPT spectrum of compound 8 ($CDCl_3$+CCl_4, 200 MHz)



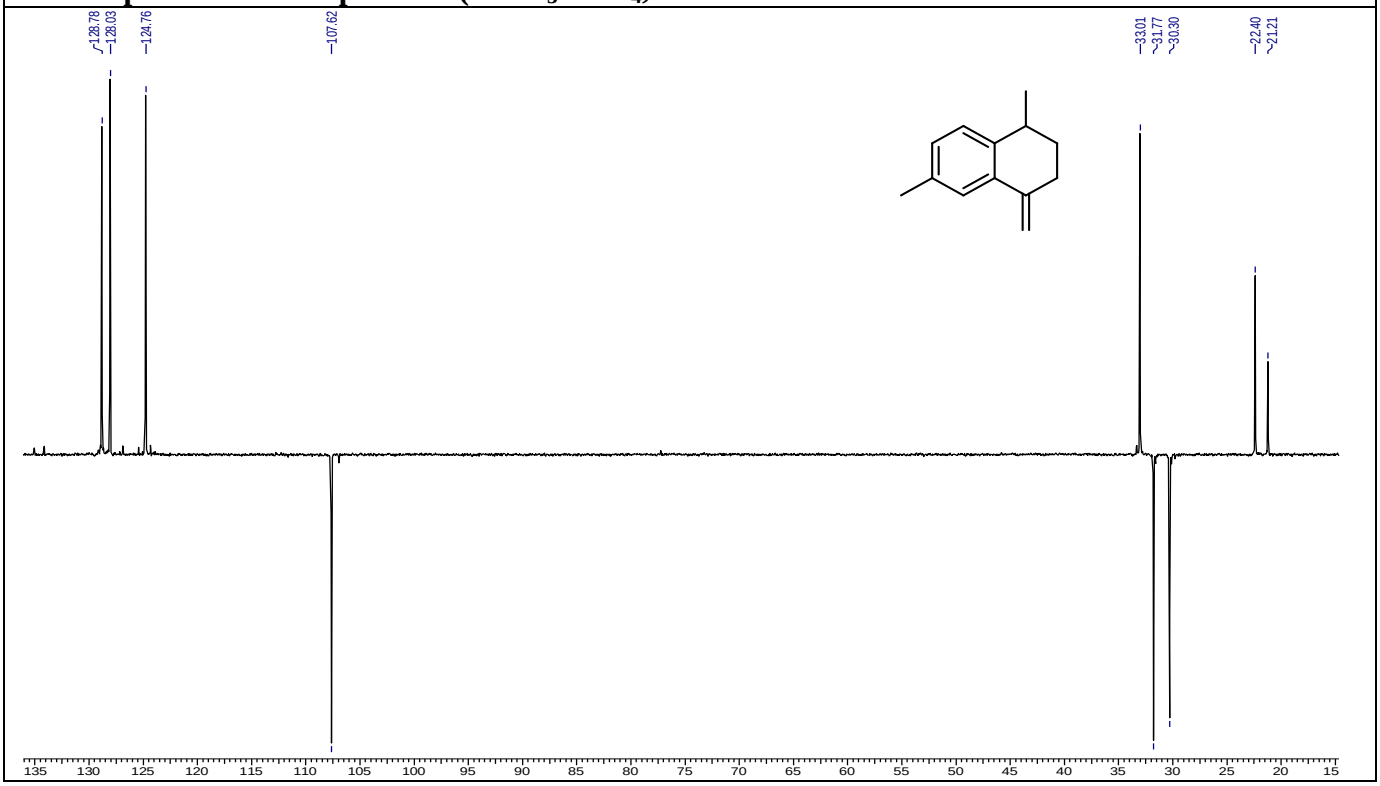
^{1}H NMR spectrum of compound 9 ($CDCl_3$+CCl_4, 400 MHz)



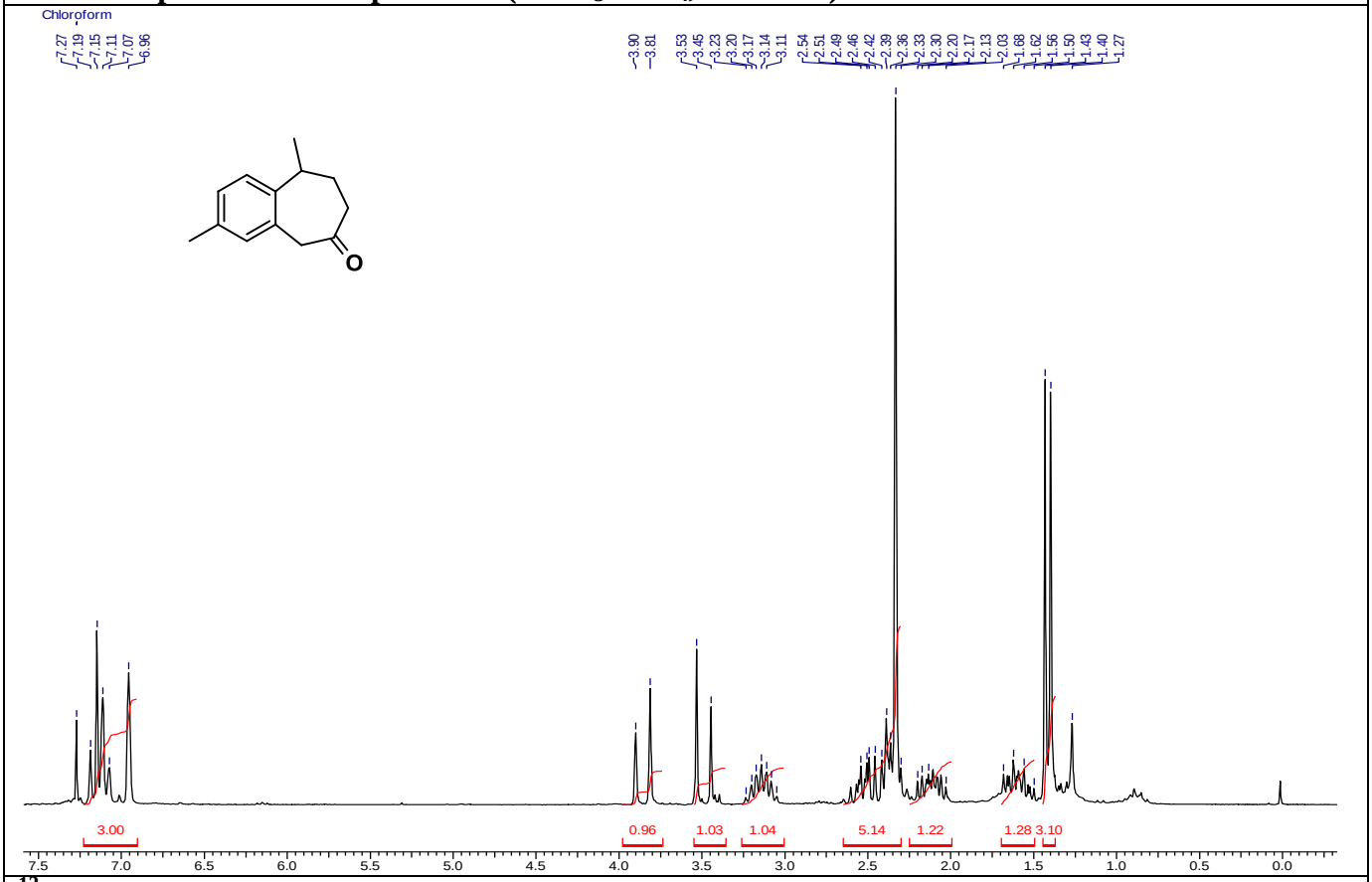
^{13}C NMR spectrum of compound 9 ($CDCl_3$ + CCl_4, 100 MHz)



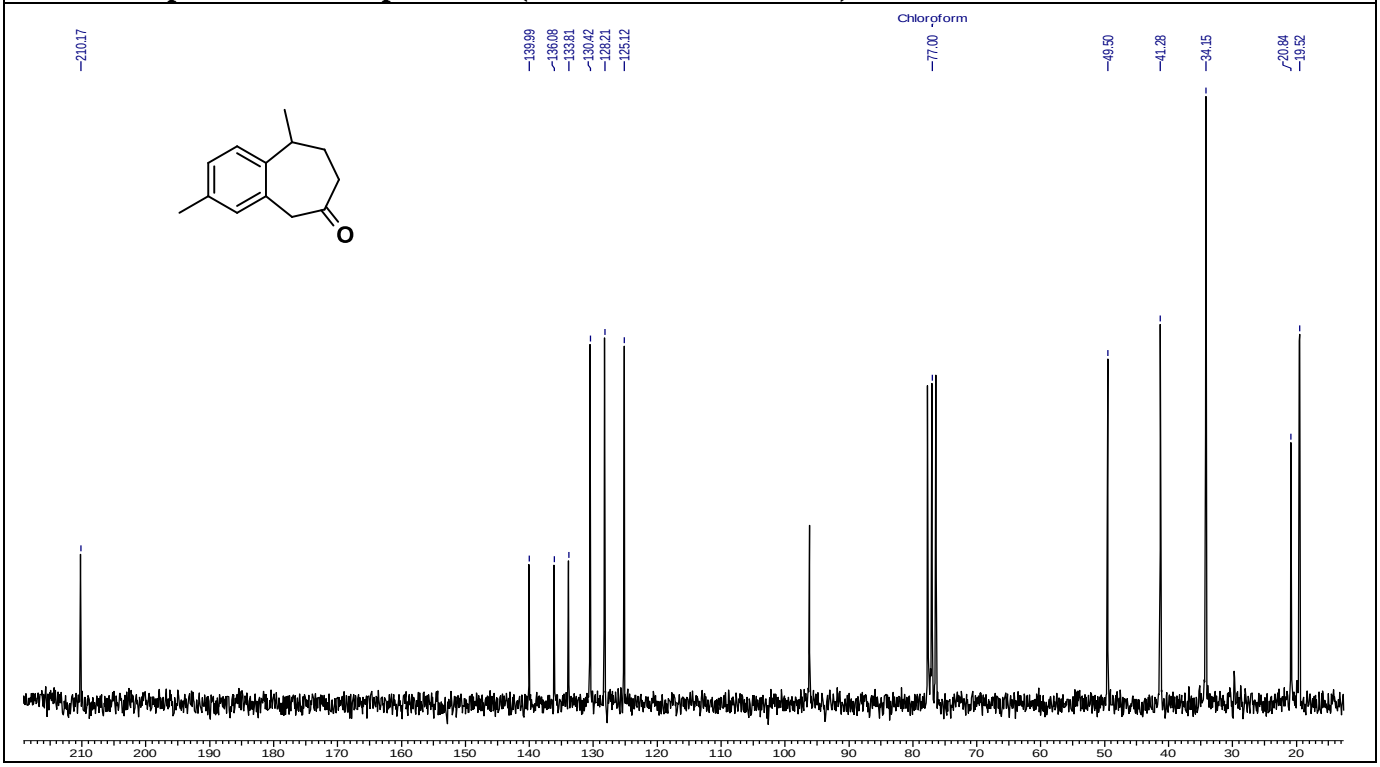
DEPT spectrum of compound 9 ($CDCl_3$+CCl_4, 200 MHz



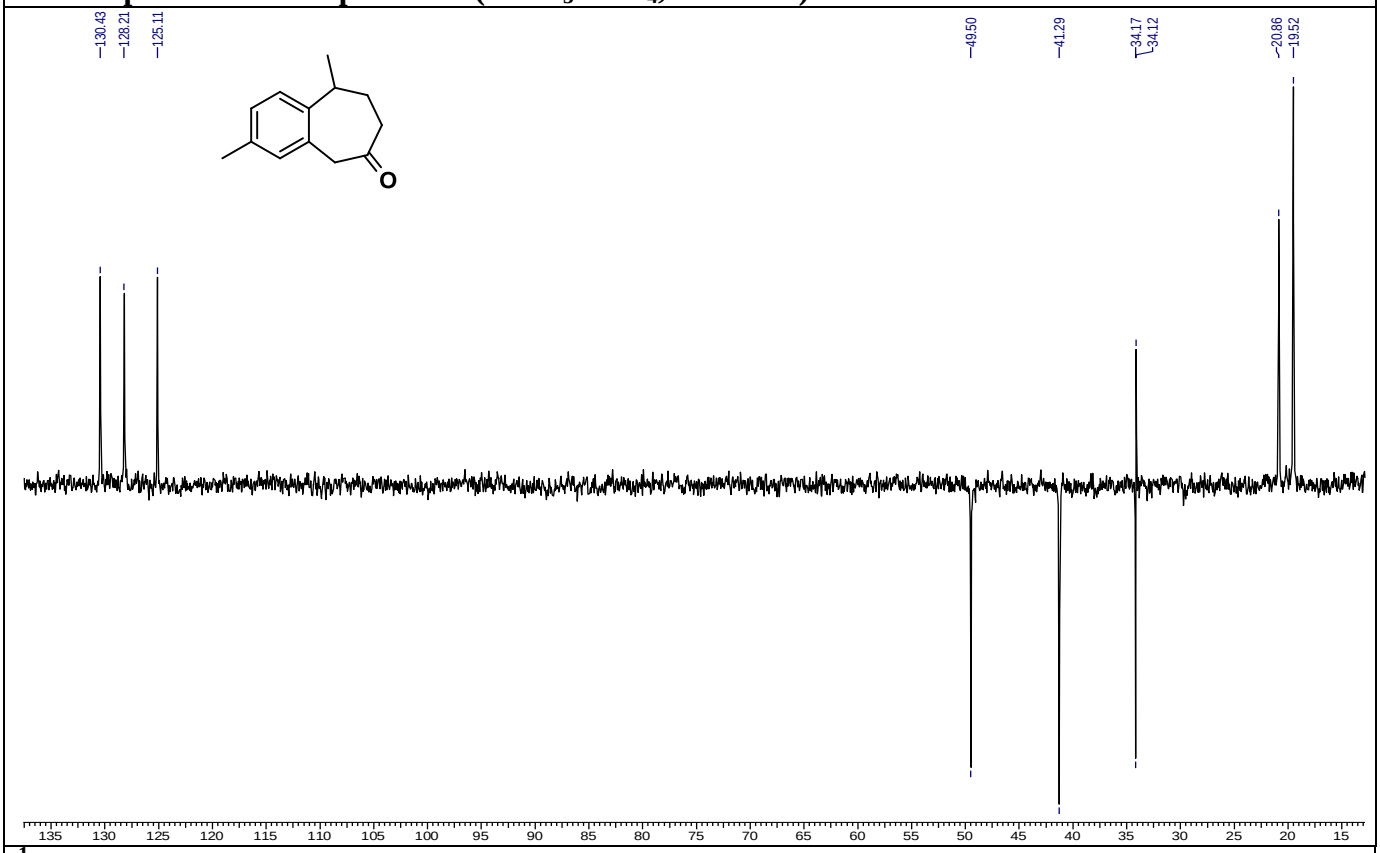
^{1}H NMR spectrum of compound 10 ($CDCl_3$+CCl_4, 200 MHz)



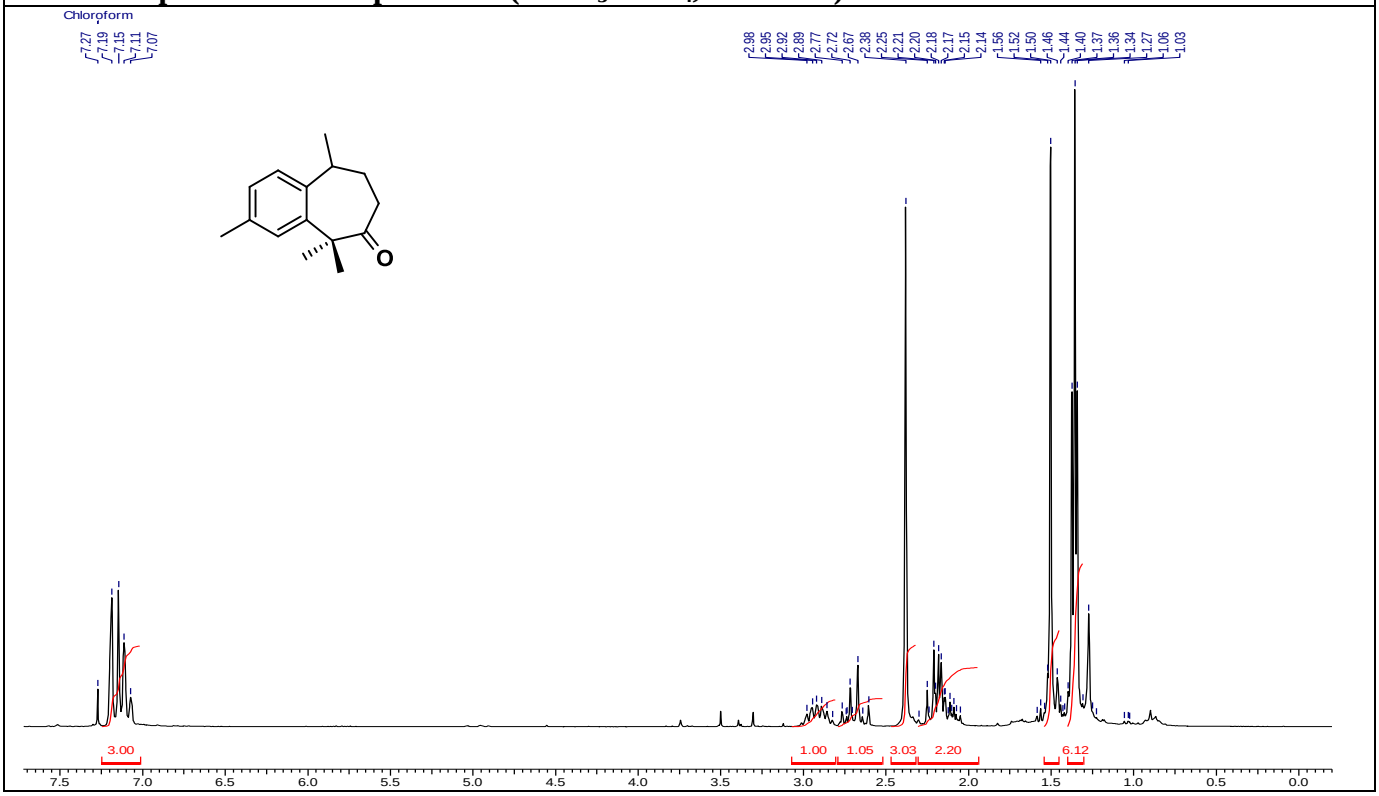
^{13}C NMR spectrum of compound 10 ($CDCl_3$ + CCl_4, 50 MHz)



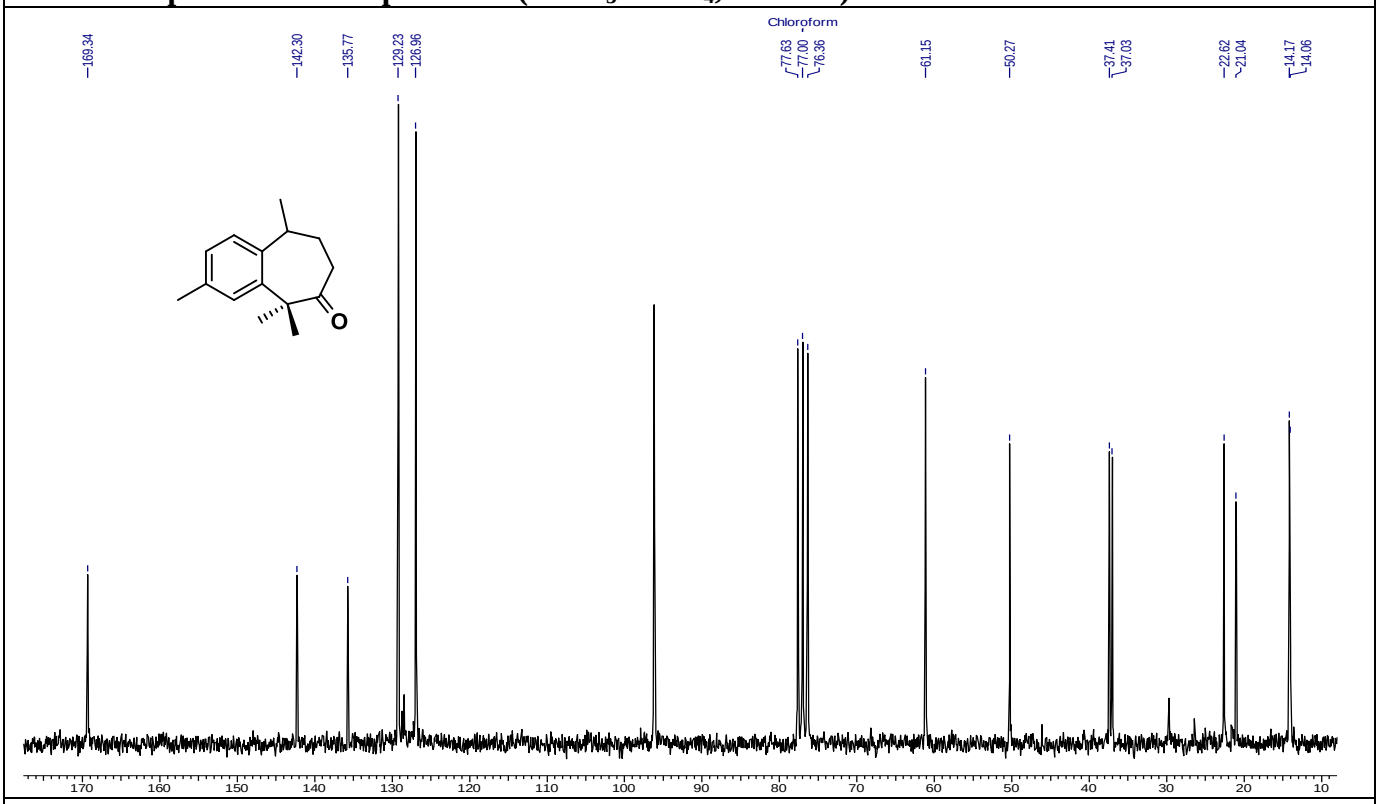
DEPT spectrum of compound 10 ($CDCl_3$+CCl_4, 200 MHz)



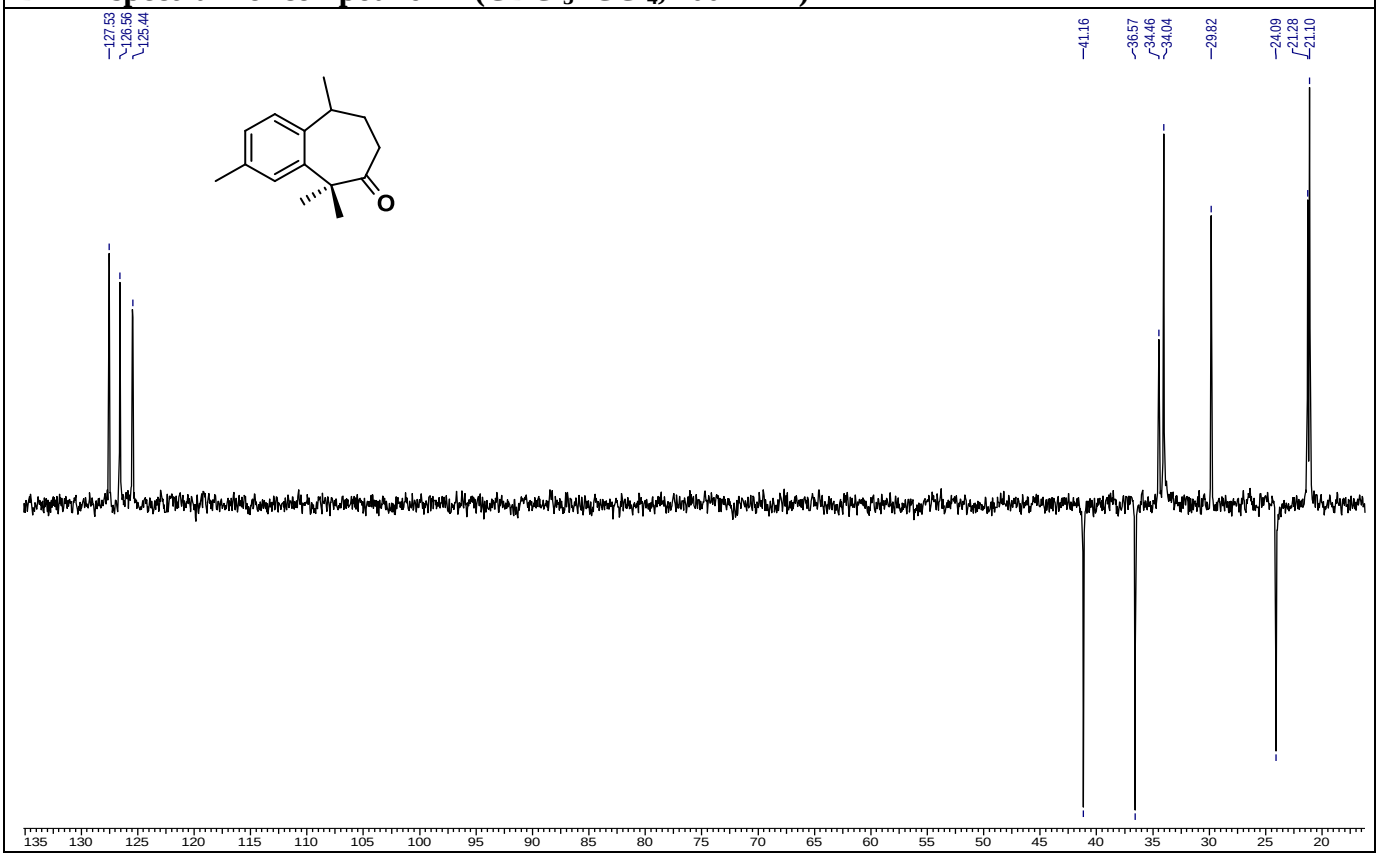
^{1}H NMR spectrum of compound 11 ($CDCl_3$+CCl_4, 200 MHz)



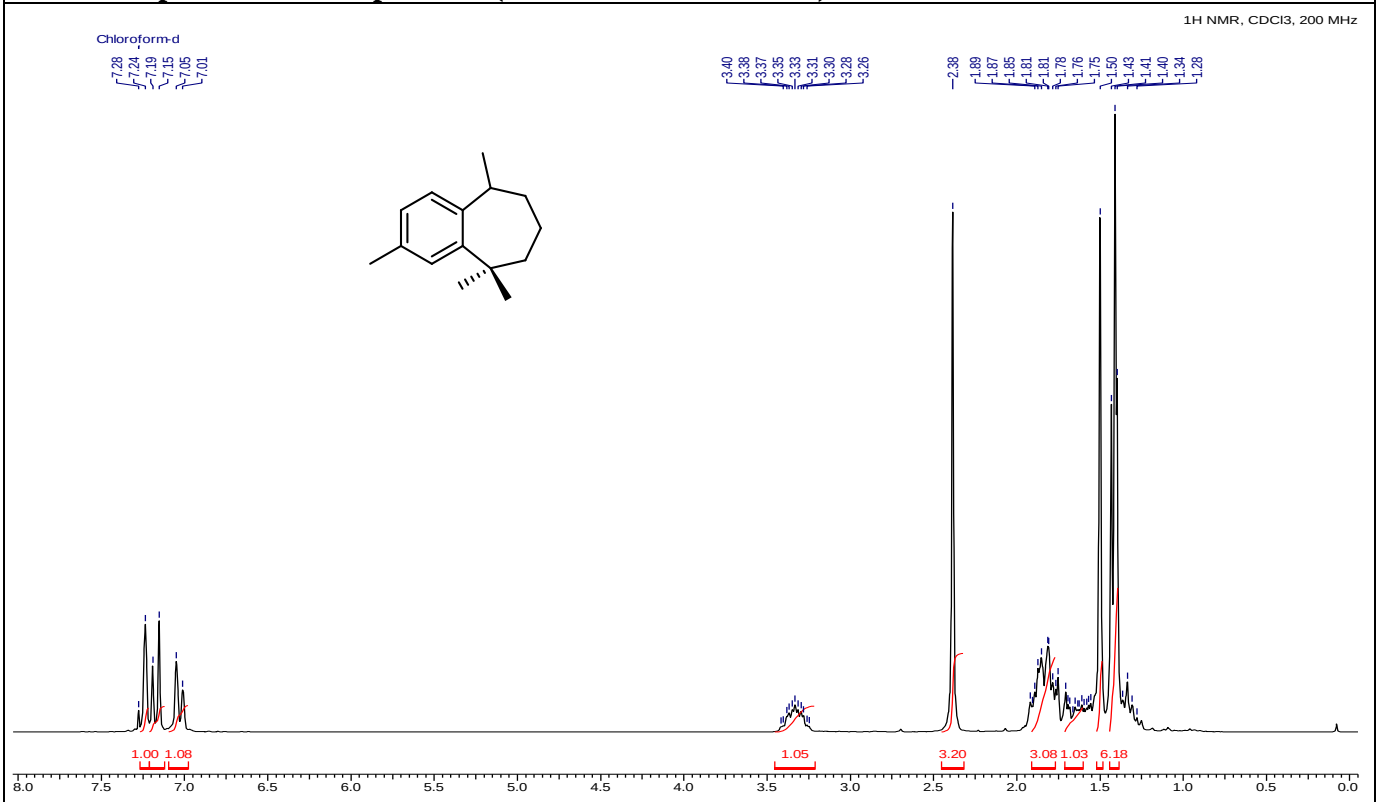
^{13}C NMR spectrum of compound 11 ($CDCl_3$ + CCl_4, 50 MHz)



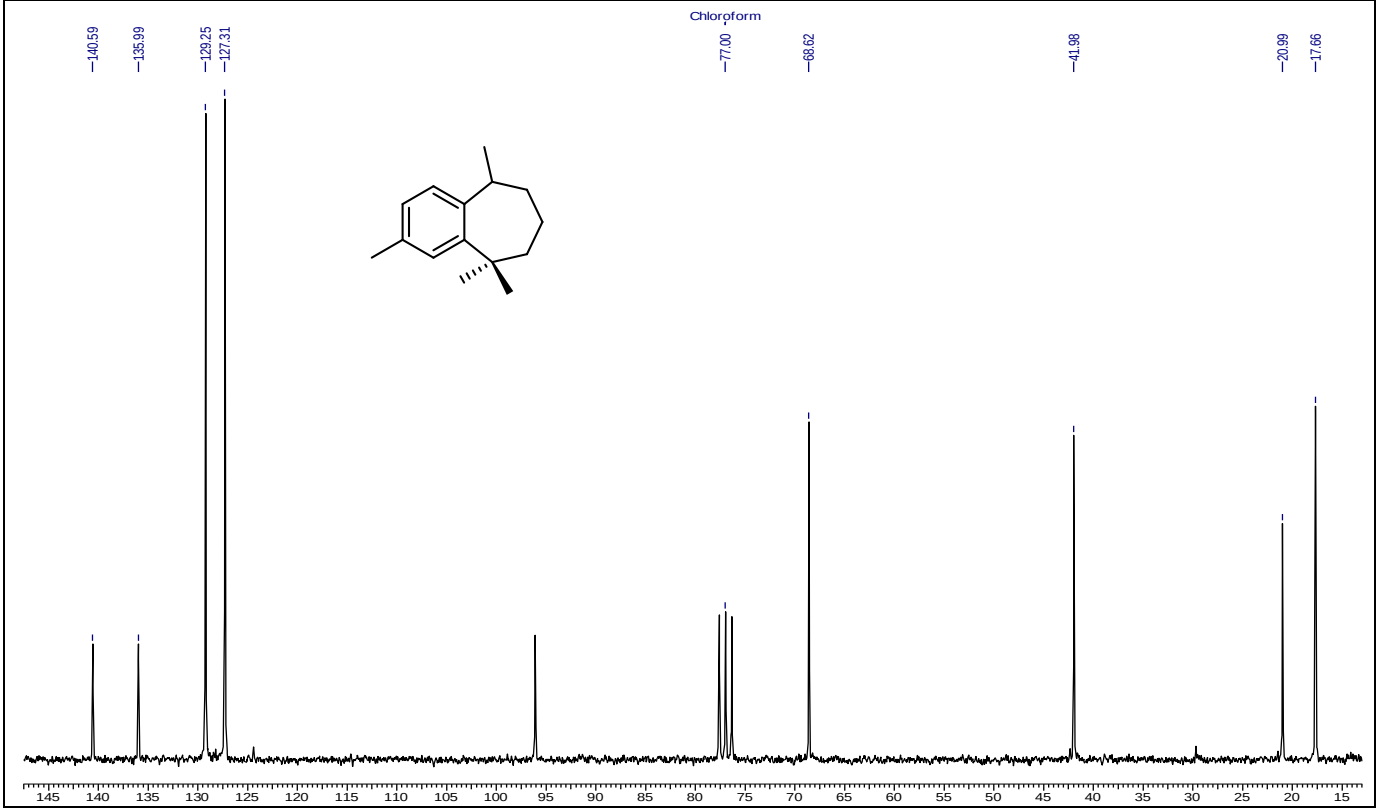
DEPT spectrum of compound 11 ($CDCl_3$+CCl_4, 200 MHz)



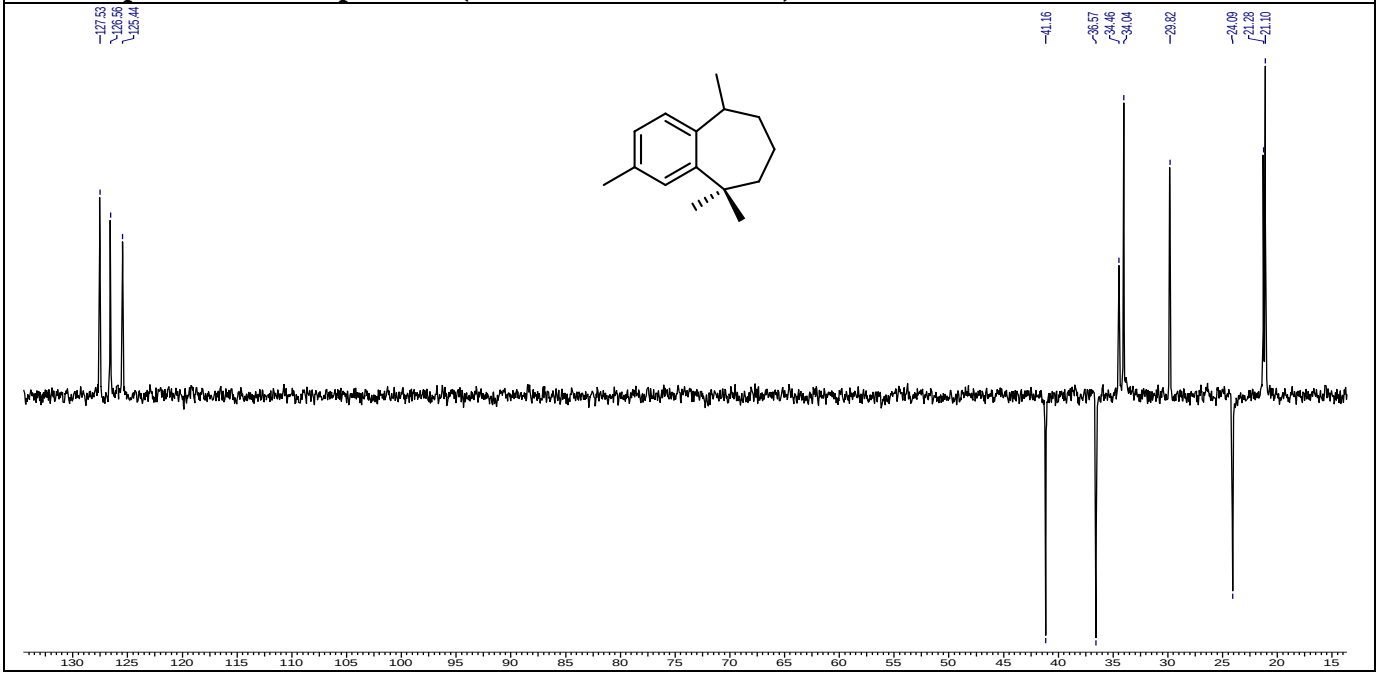
^{1}H NMR spectrum of compound 1 ($CDCl_3$+CCl_4, 200 MHz)



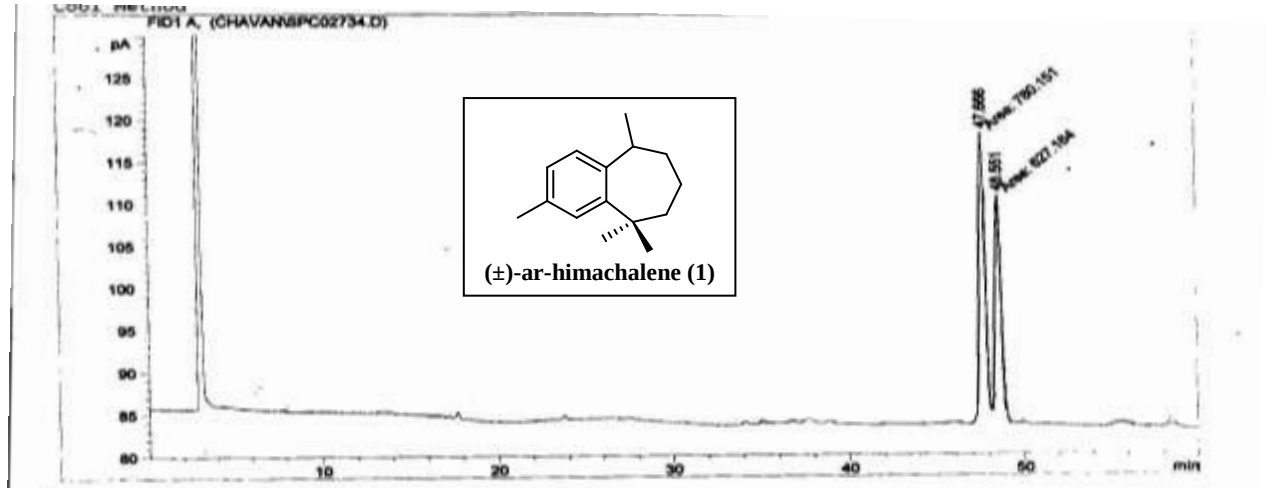
^{13}C NMR spectrum of compound 1 ($CDCl_3$ + CCl_4, 50 MHz)



DEPT spectrum of compound 1 ($CDCl_3$+CCl_4, 200 MHz)



2.2.4.2. Chiral GC data

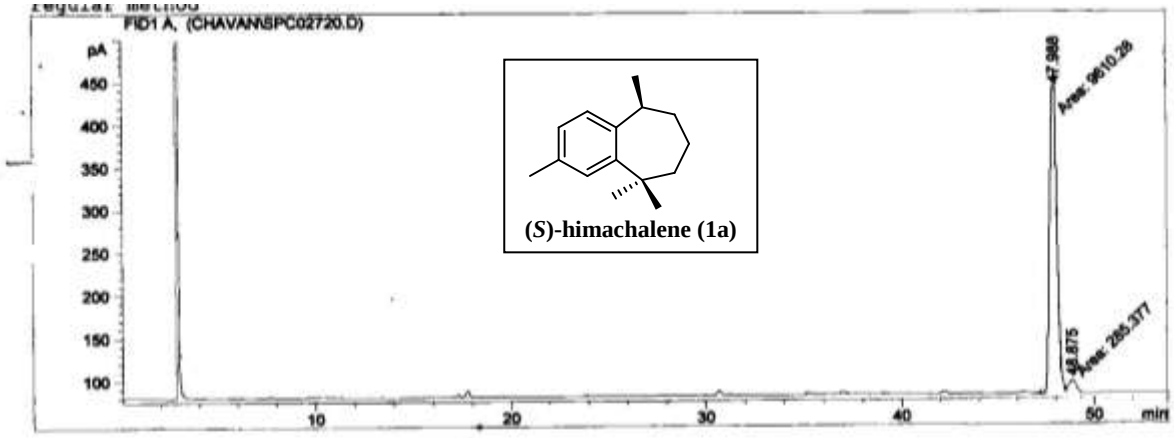


Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	47.666	MM	0.3855	780.15112	33.72841	55.43541
2	48.551	MM	0.4000	627.16449	26.13411	44.56459



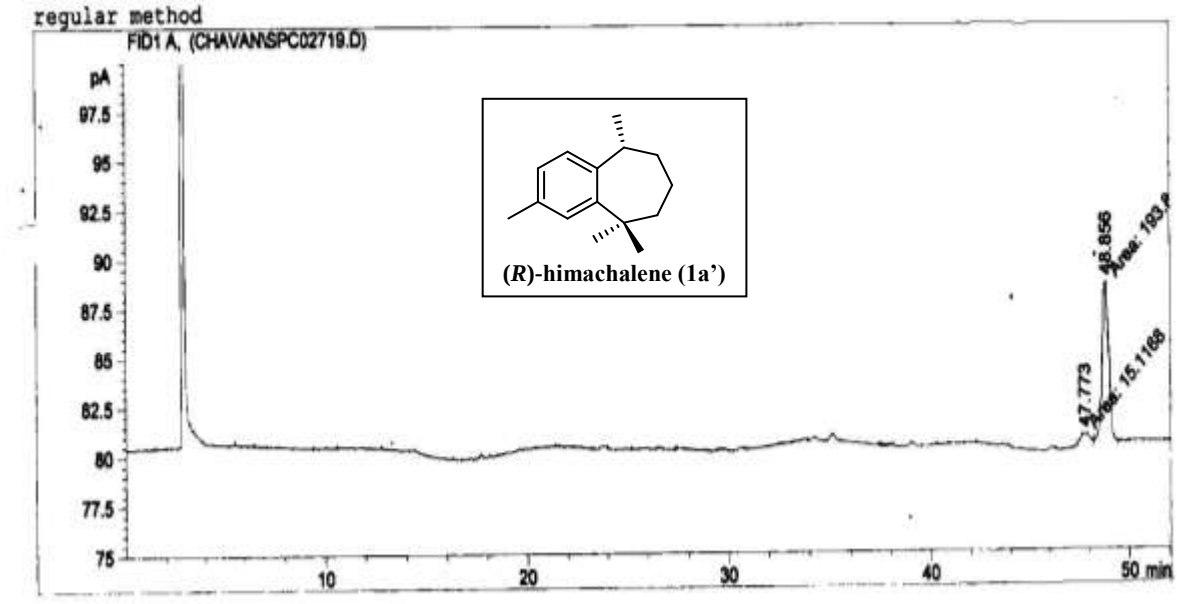
(*S*)-himachalene (1a)

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	47.988	MM	0.4235	9610.27637	378.22937	97.11614
2	48.875	MM	0.3821	285.37653	12.44661	2.88386



(*R*)-himachalene (1a')

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	47.773	MM	0.4818	15.11676	5.22962e-1	1.23540
2	48.856	MM	0.3973	193.81104	8.13099	98.76460

2.2.5. References

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(21) GC Analysis conditions: chiral GC column: Cyclodextrin–B at 120 ^{o}C, t_R :47.9 min = 97.1%, t_R : 48.8 min=2.8%.

(22) HPLC Analysis conditions: Chiral HPLC column: Chiralcel– OJ–H at λ_{max}: 254 nm, flow rate–0.5 mL/min, injecting volume–05 μL, mobile phase– IPA: pet. ether (40:60).

(23) HPLC Analysis conditions: Chiral HPLC column: Kromasil–5–Amycoat at λ_{max}: 220 nm, flow rate–0.5 mL/min, injecting volume–05 μL, mobile phase – IPA: ^{n}hexane (08:92).

(24) HPLC Analysis conditions: Chiral HPLC column; Kromasil–5–Cellucoat at λ_{max}: 254 nm, flow rate–0.5 mL/min, injecting volume–10 μL, mobile phase – IPA: ^{n}hexane: TFA (3.5:96.4:0.1).

(25) HPLC Analysis conditions: Chiral HPLC column: Chiralcel– OD–H at λ_{max}: 254 nm, flow rate–0.5 mL/min, injecting volume–05 µL, mobile phase: IPA– pet. ether (02:98).

(26) HPLC Analysis conditions: Chiral HPLC column: Kromasil–5–Cellucoat at λ_{max}: 254 nm, flow rate–0.5 mL/min, injecting volume–05 μL, mobile phase – IPA: pet. ether (0.1:99.9).

(27) HPLC Analysis conditions: Chiral HPLC column: Chiralcel– OJ–RH at λ_{max}: 230 nm, flow rate–0.5 mL/min, injecting volume–05 μL, mobile phase – acetonitrile: water (50:50).

(28) HPLC Analysis conditions: Chiral HPLC column: Chiralcel– OJ–H at λ_{max}: 220nm, flow rate–0.5 mL/min, injecting volume–20 μL, mobile phase – IPA: ^{n}hexane (5:95).

2.3.1. Introduction

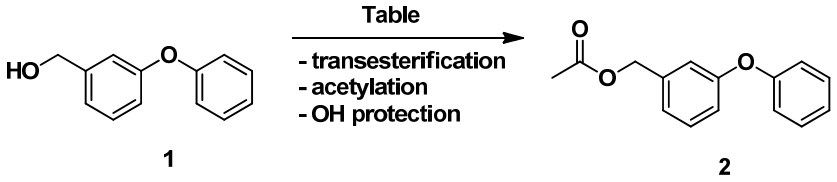
Acetylation or acylation of alcohol is one of the most frequently used fundamental process in organic chemistry [1,2] as it provides an efficient and inexpensive means for protecting hydroxyl groups in multi-step synthesis process. A direct esterification of alcohol with carboxylic acids, the Fischer esterification, is generally avoided because the equilibrium that is established between the reagent and the products requires the use of large excesses of either the alcohol or acid and elimination of water from the reaction mixture to drive the process towards completion by azeotropic removal of water. Alternatively, Fischer esterifications can be driven to completion but the use of strong mineral acids lead to highly acidic waste streams affecting hazardous problems in surrounding environment.

Esters are usually synthesized from alcohols and carboxylic acids or acid chlorides and acid anhydrides or an ester as the acylating agent. Many useful methods have been reported in the literature.[3-5] Some of the recently developed methods involve the use of organic[6-8], inorganic[9] and organometallic reagents.[10] Many acidic or basic catalysts have been used for this purpose. A variety of Lewis acids such as $Sc(NTf_2)_3$, $TiCl(OTf)_3$, $La(Oi\text{-}Pr)_3$, $Sn(OTf)_2$, TMSCl and TMSOTf, have also been used as catalysts and reagents to mediate the reaction between alcohols and acylating agent. A variety of procedures involving different catalysts have been developed for this transformation and this process is under constant study to make it more effective and selective. However, most of these methods suffer from one or more of the following disadvantages- longer reaction time, vigorous reaction conditions, the occurrence of side reactions and unavailability of the reagents, as well as poor yields of the desired product in many cases.

Since transesterification is an equilibrium driven reaction, it was decided to study the transesterification of alcohols with esters under acid catalysed reactions. Initial study involved the acid catalysed reaction of alcohols with commercially readily available solvent *viz*. ethyl acetate. The net result of this reaction was acylation of alcohols.

2.3.2. Present work:

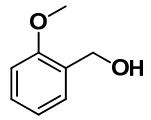
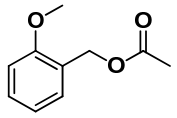
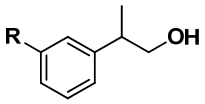
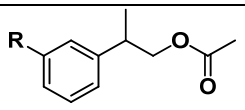
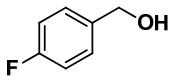
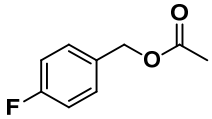
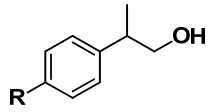
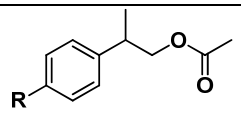
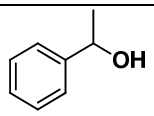
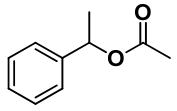
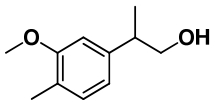
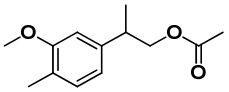
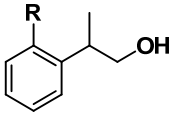
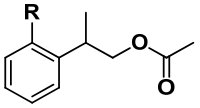
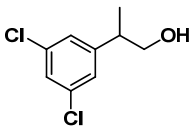
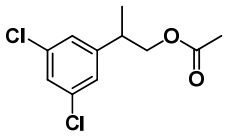
When alcohol **1** was refluxed with 2-IBA, in presence of excess ethyl acetate formation of ester **2** was observed in 82% yield (**Scheme-1**). Literature survey revealed that 2-IBA was not reported for such type of transformation where acetylation of alcohol was observed. The process could also be reffered to as transesterification and/ hydroxy protection.



Scheme-1

Variety of hydroxy compounds, reacted under standardized conditions in order to study scope of the present protocol. The acetylation of benzylic and homobenzylic alcohols (from **a** to **l**, table-1), exhibited formation of respective esters (**a'**to **l'**) in excellent yields.

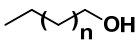
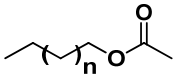
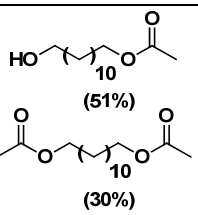
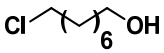
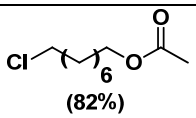
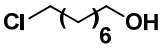
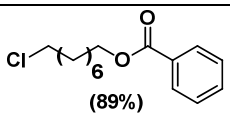
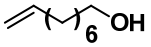
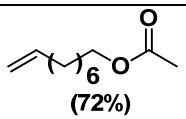
Table-1: Acetylation of benzylic and homobenzylic alcohols

SN	Substrate[I]	product	SN	Substrate[I]	product
1.	 **a**	 **a'**(75%)	5.	 R= -Cl (**g**), -OMe (**h**)	 R= -Cl (**g'**), -OMe (**h'**) (~94%)
2.	 **b**	 **b'**(86%)	6.	 R= -Cl (**i**), -Br (**j**)	 R= -Cl (**I'**), -Br (**j'**) (~92%)
3.	 **c**	 **c'**(92%)	7.	 **k**	 **k'** (90%)
4.	 R= -OMe (**d**), -OH (**e**) -Br (**f**)	 R= -OMe (**d'**), -OH (**e'**), -Br (**f'**) (~89-90%)	8.	 **l**	 **l'** (92%)
[1]reaction conditions: alcohol (1 eq.), IBA (1.2 eq.), ethyl acetate (3 mL), reflux, 5-8 h.					

The acetylation as well as benzoylation, of aliphatic alcohols (from **m** to **q**, table-2) was studied under above conditions, furnished esters (m'to q') in excellent yields respectively. In case of the diol **p** mixture

of acetylated products p' and p'' were observed. In case of benzoylation of 1-chlorooctanol, entry-5, table-3, formation of ester q'was observed in 89% yield. Thus, it was proved that this process render not only benzoylation of alcohol but also acetylation of hydroxy compounds.

Table-2: Acetylation and benzoylation of aliphatic alcohols

SN	substrate	product	SN	substrate	product
1.[II]	 n= 3, 5, 9, 17 **m**	 n= 3, 5, 9, 17 (88%) **m'**	4.[I]	 **p**	 (51%) (30%) **p', p''**
2.[II]	 **n**	 (82%) **n'**	5.[II]	 **q**	 (89%) **q'**
3.[II]	 **o**	 (72%) **o'**	[I] reaction conditions: alcohol (1 eq.), 2-IBA (1.2 eq.), ethyl acetate (3 mL), reflux, 5-8 h. [II] reaction conditions: alcohol (1 eq.), 2-IBA (1.2 eq.), methyl benzoate (1.5 eq.), reflux, 5-8 h.		

In order to study applicability of other benzoic acid derivatives and several other acidic reagents for the said transformation, conversion of alcohol **1** into ester **2** were tested, and the results obtained are summarized in table-3. The best results were obtained in case of 2-IBA and *p*TSA, under refluxing conditions and at room temperature respectively in the presence of ethyl acetate as the reaction solvent as well as acetylating reagent.

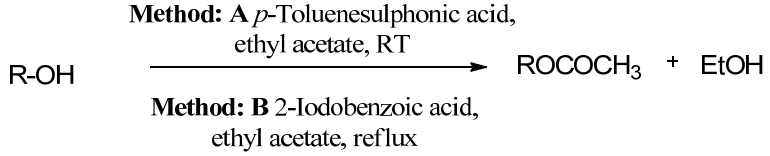
Table-3

SN	Reagent	pKa[III]	Equiv.	Reaction conditions	Yield (%)
1.	**2-Iodobenzoic acid**	**2.8**	**1.2** **1.2**	EtOAc, RT, 8h **EtOAc, reflux, 5h**	**---** **82**
2.	Benzoic acid	4.19	2	EtOAc, reflux, 8h	38

3.	2-Nitrobenzoic acid	2.19	2	EtOAc, reflux, 8h	NA
4.	4-Nitrobenzoic acid	3.41	2	EtOAc, reflux, 8h	60
5.	3-Chlorobenzoic acid	3.83	2	EtOAc, reflux, 8h	55
6.	Acetic acid	4.8	1.2	EtOAc, reflux, 8h	32
7.	Triflic acid	-5.9	0.5	DCM, EtOAc, RT, 8h DCM, EtOAc, reflux 8h	20 complex rea. mix.
8.	Trifluoroacetic acid	0.2	1.2	EtOAc, reflux, 8h	40
9.	[c]H_2SO_4 impregnated on silica	-9.0	Cat.	EtOAc, RT, 8h EtOAc, reflux, 5h	40 69
10.	***p*-Toluenesulphonic acid**	**-2.8**	**1.2** **0.2**	**EtOAc, RT, 8h** **EtOAc, reflux, 12h**	**84** **80**
11.	Amberlyst-15		w/w	EtOAc, reflux, 10h	68
12.	$AlCl_3$		1.2	EtOAc, RT, 8h	28
III: Values reported in the literature.					

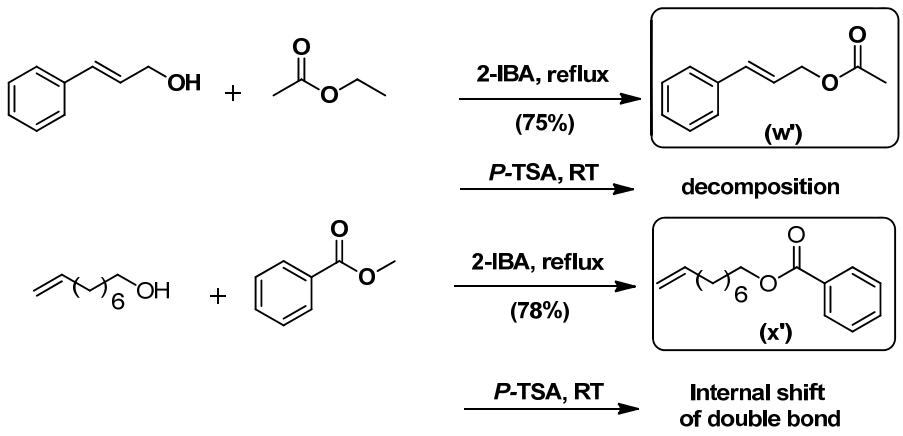
Till date esterification or transesterification or acylation of alcohols was reported in literature in the presence of *p*TSA, using acetic acid or anhydrides or sometimes acid chlorides which require longer reaction conditions, results into lower yields and tedious workups.

Thus, this study involves transesterification/ acetylation/ and hydroxy group protection of alcohol by means of two methods. *viz*. i) **Method-A**: treatment of alcohol with *p*-TSA in presence of ethyl acetate as a solvent as well as acylating reagent at room temperature the corresponding acetate was obtained in excellent yield and ii) **Method-B**: reaction of the alcohol with 2-iodobenzoic acid (IBA) under refluxing conditions in presence of ethyl acetate it furnished corresponding acetate in good yield **(Scheme-2)**.



Scheme-2

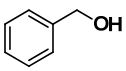
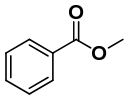
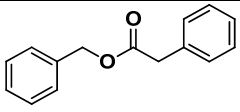
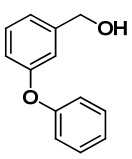
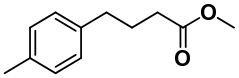
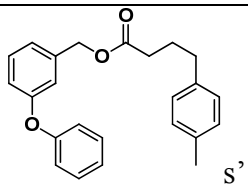
It was found that use of *p*TSA (*p*Ka = -2.8) is unreliable if substrate contains acid sensitive groups. In such cases utilisation of 2-IBA (*p*Ka = 2.8) provides satisfactory results. This was evident when an allylic alcohol like cinnamic alcohol, was treated with *p*TSA decomposition was observed in the reaction and to overcome this problem when the reaction was performed in the presence of 2-IBA, under reflux with ethyl acetate, desired cinnamyl acetate (**w'**) formation was observed in 78% yield. Likewise, 1-nonene-ol was treated with IBA in presence of methyl benzoate, at 80 ^{o}C, benzoate ester of starting alcohol (**x'**) was produced in 75% yield while reaction with *p*TSA furnished mixture of benzoate esters with the internal shift of double bond (**Scheme 3**).

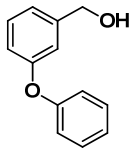
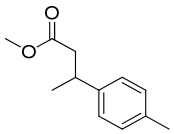
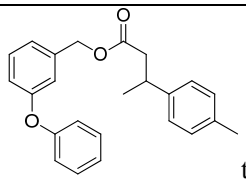
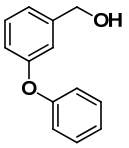
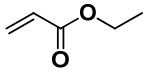
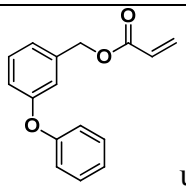
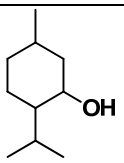
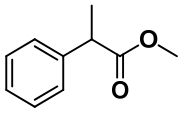
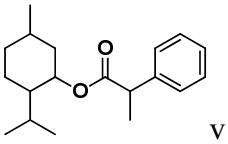


Scheme 3

Aroylation of sterically hindered alcohols proceeds in presence of *p*-TSA as well as 2-IBA in comparable yields (Table-5).

Table-5: Miscellaneous examples of acid catalysed transesterification/ aroylation of alcohols

SN	alcohol	ester	product	Yield (%)
1.			 r'	(88%) ^{I} (81%) ^{II}
2.			 s'	(88%) ^{I} (85%) ^{II}

3.			 t’	(80%)^{I} (80%)^{II}
4.			 u’	(78%)^{I} (72%)^{II}
5.			 v’	(86%)^{I} (81%)^{II}

Reaction conditions- I). Method-A: alcohol (1 equiv.), ester (1.2 equiv.), *p*TSA (1.2 equiv.), toluene (2 mL), 90 ^{o}C, 5 h; II). Method-B: alcohol (1 equiv.), ester (1.2 equiv.), 2-IBA (1.2 equiv.), toluene (2 mL), 100 ^{o}C, 5-8 h.

2.3.3. Conclusion:

Thus, 2-iodobenzoic acid (2-IBA) has been investigated for transesterification reaction. 2-IBA has been proved to be useful reagent for transesterification of compounds containing acid sensitive groups. When this transformation was carried out in presence of the *p*TSA, use of acetic acid or anhydrides or acid chlorides was avoided. Hence, present protocol provides operational simplicity and use of inexpensive reagents could be useful in the synthesis of various natural products.

2.3.4. Experimental:

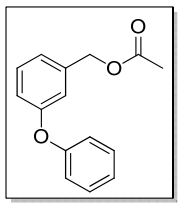
General procedures: Method-(A): To a stirred solution of alcohol (1 equiv.) in ethyl acetate (3 mL) was added *p*-toluenesulphonic acid (1.2 equiv.), the reaction mixture was allowed to be stirred for 6-8 h at room temperature. After completion of reaction, monitored by TLC, saturated $NaHCO_3$ solution was added to the reaction mixture to remove *p*-toluenesulphonic acid, organic layer was washed with water and extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to furnish crude product.

Method-(B): To a stirred solution of alcohol (1 equiv.) in ethyl acetate (3 mL) was added 2-iodobenzoic acid (1.2 equiv.), the reaction mixture was allowed to reflux for specified time. After completion of reaction as monitored by TLC, reaction mixture was coolup to room temperature and then saturated

solution of $NaHCO_3$ was added to remove unreacted 2-iodobenzoic acid, organic layer was washed with water and extracted with ethyl acetate, the combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure, furnished crude product.

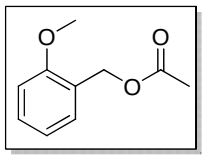
2.3.4.1. Spectral data

3-Phenoxybenzyl acetate (2)[18]



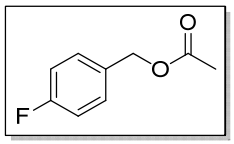
Molecular formula: $C_{15}H_{14}O_3$; **Eluent:** ethyl acetate: pet. ether:- 5%; Yield: 84%; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 7.37-7.22 (m, 3H), 7.13-6.90 (m, 6H), 5.06 (s, 2H), 2.09 (s, 3H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 170.5, 157.5, 156.9, 137.9, 129.7, 123.4, 122.6, 119.0, 118.3, 65.7, 20.9; **MS (ESI)** (*m/z*): 265 $[M+Na]^+$; **IR($CHCl_3$):** 1742cm^{-1}; **HRMS (ESI):** Calculated for 265.0835$[M+Na]^+$; found 265.0835.

2-methoxybenzyl acetate (a')[18]



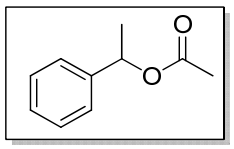
Molecular formula: $C_{10}H_{12}O_3$; **Eluent**: ethyl acetate: pet. ether:-5%; **Yield**: 75%; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 7.33 (dd, J = 8.47, 6.57 Hz, 1H), 7.28 (d, J = 7.45 Hz, 1H), 6.97 (dd, J = 7.45, 6.57 Hz, 1H), 6.90 (d, J = 8.47 Hz, 1H), 5.17 (s, 2H), 3.84 (s, 3H), 2.11 (s, 3H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 171.0, 157.5, 129.8, 129.7, 124.1, 120.4, 110.4, 61.7, 55.0, 21.0; **MS (ESI)** (*m/z*): 203 $[M+Na]^+$; **IR ($CHCl_3$):** 1740 cm^{-1}.

4-Fluorobenzyl acetate (b') [19]



Molecular formula: $C_9H_9FO_2$**; Eluent**: ethyl acetate: pet. ether:-5%; **Yield**: 86%; **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 7.30 (dd, J = 8.46, 5.43 Hz, 2H), 7.01 (dt, J = 8.72, 2.15 Hz, 2H), 5.02 (s, 2H), 2.04 (s, 3H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 170.5, 162.4 (d, J = 246.6 Hz), 131.6 (d, J = 2.93 Hz), 130.1 (d, J = 8.05 Hz), 115.3 (d, J = 21.5 Hz), 65.3, 20.7; **MS (ESI)** (*m/z*):199 $[M+MeOH]^+$; **IR($CHCl_3$):** 1736 cm^{-1}.

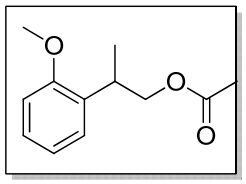
1-Phenylethyl acetate (c')[19]



Molecular formula: $C_{10}H_{12}O_2$; **eluent**: ethyl acetate: petroleum ether:-5%; **Yield**: 92%; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 7.29-7.20 (m, 5H). 5.80 (q, J = 6.70 Hz, 1H), 2.00 (s, 3H), 1.46 (d, J = 6.70 Hz, 3H); **^{13}C NMR (50 MHz,**

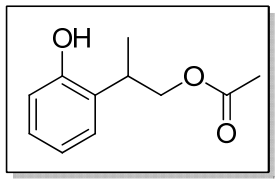
$CDCl_3$): δ 170.1, 141.6, 127.8, 126.0, 72.2, 22.2, 21.3; **MS (ESI)** (*m/z*): 187 $[M+Na]^+$; **IR ($CHCl_3$):** 1729cm^{-1}.

2-(2-Methoxyphenyl)propyl acetate (d')[13]



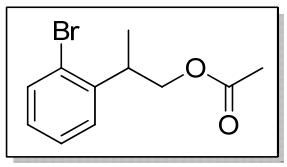
Molecular formula: $C_{12}H_{16}O_3$; **eluent**: ethyl acetate: petroleum ether:-5%; **Yield**: 94%; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 7.23 (dd, J = 8.46, 6.57 Hz, 1H), 7.19 (d, J = 7.45 Hz, 1H), 6.95 (dd, J = 7.45, 6.57 Hz, 1H), 6.87 (d, J = 8.46 Hz, 1H), 4.22-4.08 (m 1H), 3.81 (s, 3H), 3.60-3.43 (m, 1H), 2.00 (s, 3H), 1.27 (d, J = 6.9 Hz, 3H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 170.9, 157.0, 131.0, 127.4, 127.2, 120.5, 110.3, 68.3, 55.1, 31.9, 29.6, 20.8, 16.8; **MS (ESI)** (*m/z*): 231 $[M+Na]^+$; **IR ($CHCl_3$):** 1738, 1236 cm^{-1}.

2-(2-Hydroxyphenyl)propyl acetate (e')[13]



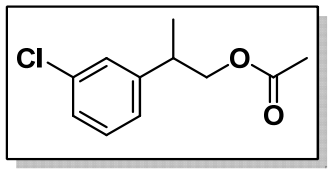
Molecular formula: $C_{11}H_{14}O_3$; **eluent**: ethyl acetate: pet. ether:-5%**; Yield**: 94%; **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.15-7.07 (m, 2H), 6.92-6.80 (m, 2H), 5.92 (brs, 1H), 4.30 (dd, J = 10.90, 5.32 Hz, 1H), 3.98 (dd, J = 10.90, 7.80 Hz, 1H), 3.45-3.33 (m, 1H), 2.08 (s, 3H), 1.36 (d, J = 7.80 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 171.8, 154.1, 128.1, 127.8, 127.2, 120.6, 116.0, 69.5, 32.5, 21.0, 16.4; **MS (ESI)** (*m/z*): 217 $[M+Na]^+$; **IR ($CHCl_3$):** 3395, 1716 cm^{-1}; **HRMS (ESI):** Calculated for $C_{11}H_{14}O_3$ $[M+Na]^+$217.0835, found 217.0835.

2-(2-Bromophenyl)propyl acetate (f')[12]



Molecular formula: $C_{11}H_{13}BrO_2$; **eluent**: ethyl acetate: petroleum ether:-5%; **Yield**: 94%; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 7.56 (d, J = 7.45 Hz, 1H), 7.35-7.21 (m, 2H), 7.14-7.03 (m, 1H), 4.19 (d, J = 6.94 Hz, 2H), 3.74-3.56 (m, 1H), 2.03 (s, 3H), 1.30 (d, J = 6.94 Hz, 3H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 170.7, 142.0, 133.0, 128.1, 127.6, 127.5, 124.9, 68.0, 37.4, 20.8, 17.4; **MS (ESI)** (*m/z*): 279 $[M+Na]^+$; **IR ($CHCl_3$):** 1739 cm^{-1}.

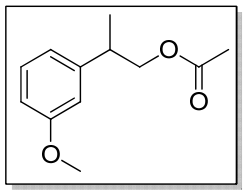
2-(3-chlorophenyl)propyl acetate (g'):



Molecular formula: $C_{11}H_{13}ClO_2$; **eluent**: ethyl acetate: pet. ether:-5%; **Yield**: 90%; **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 7.26-7.18 (m, 2H), 7.20 (s,

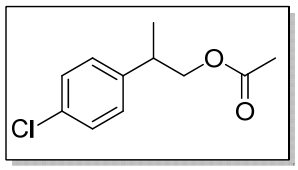
1H), 7.11-7.07 (m, 1H), 4.17 (dd, *J* = 10.99, 6.19 Hz, 1H), 4.09 (dd, *J* = 10.99, 6.19 Hz, 1H), 3.15-2.98 (m, 1H), 2.01 (s, 3H), 1.29 (d, *J* = 7.08 Hz, 3H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 170.6, 145.2, 134.4, 129.7, 127.5, 126.9, 125.4, 68.9, 38.7, 29.7, 20.8, 18.0; **IR ($CHCl_3$)**: 1739, 786 cm^{-1}; **MS (ESI)** (*m/z*):235 $[M+Na]^+$

2-(3-Methoxyphenyl)propyl acetate (h'):



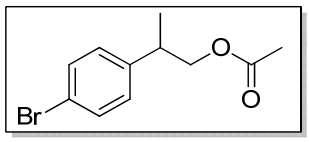
Molecular formula: $C_{12}H_{16}O_3$; **eluent**: ethyl acetate: pet. ether:-5%; **Yield**: 90%; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 7.22 (dd, *J* = 8.97, 7.83 Hz, 1H), 6.86-6.69 (m, 3H), 4.22-4.05 (m, 1H), 3.79 (s, 3H), 3.14-2.96 (m, 1H), 2.01 (s, 3H), 1.29 (d, *J* = 6.95 Hz, 3H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 170.7, 159.7, 144.7, 129.4, 119.5, 113.3, 111.7, 69.2, 55.0, 39.0, 20.8, 18.1; **MS (ESI)** (*m/z*): 231 $[M+Na]^+$; **IR ($CHCl_3$):** 1738, 1236 cm^{-1}; **HRMS (ESI):** Calculated for $C_{12}H_{16}O_3$ $[M+Na]^+$231.0992, found 231.0992.

2-(4-Chlorophenyl)propyl acetate (I')[11]



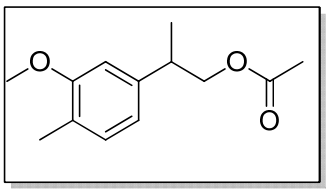
Molecular formula: $C_{11}H_{13}ClO_2$; **eluent**: ethyl acetate: pet. ether:-5%; **Yield**: 92%; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 7.29 (d, *J* = 8.72 Hz, 2H), 7.16 (d, *J* = 8.72 Hz, 2H), 4.17 (dd, *J* = 10.87, 6.19 Hz, 1H), 4.09 (dd, *J* = 10.87, 6.19 Hz, 1H), 3.16-2.99 (m, 1H), 2.01 (s, 3H), 1.28 (d, *J* = 7.07 Hz, 3H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 171.0, 141.6, 132.3, 128.6, 69.0, 38.3, 20.8, 17.9; **MS (ESI)** (*m/z*): 235 $[M+Na]^+$; **IR ($CHCl_3$)**: 1739 cm^{-1}.

2-(4-Bromophenyl)propyl acetate (j')[11]



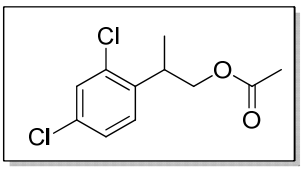
Molecular formula: $C_{11}H_{13}BrO_2$; **eluent**: ethyl acetate: pet. ether:-5%; **Yield**: 92%; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 7.43 (d, *J* = 8.46 Hz, 2H), 7.10 (d, *J* = 8.46 Hz,2H), 4.15 (dd, *J* = 10.86, 5.93 Hz, 1H), 4.11 (dd, *J* = 10.86, 5.93 Hz, 1H), 3.15-2.97 (m, 1H), 2.00 (s, 3H), 1.27 (d, *J* = 7.07 Hz, 3H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 170.9, 142.1, 131.5, 128.9, 120.3, 68.9, 38.3, 29.6, 20.8, 17.9; **MS (ESI)** (*m/z*): 280 $[M+Na]^+$; **IR ($CHCl_3$):** 1739 cm^{-1}.

2-(3-Methoxy-4-methylphenyl)propyl acetate(k')[12]



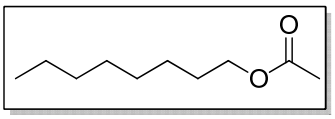
Molecular formula: $C_{13}H_{18}O_3$; **eluent**: ethyl acetate: pet. ether:-5%; **Yield**: 90%; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 7.05 (d, J = 7.57 Hz, 1H), 6.25 (d, J = 7.57 Hz, 1H), 6.66 (s, 1H), 4.20 (dd, J = 10.74, 6.95 Hz, 1H), 4.09 (dd, J = 10.86, 7.45 Hz, 1H), 3.83 (s, 3H), 3.14-2.96 (m, 1H), 2.18 (s, 3H), 2.03 (s, 3H), 1.29 (d, J = 7.07 Hz, 3H); **^{13}C NMR (50MHz, $CDCl_3$):** δ 170.8, 157.7, 142.0, 130.5, 124.9, 118.8, 109.0, 69.5, 55.1, 39.0, 20.9, 18.3, 15.9; **MS (ESI)** (*m/z*): 245 $[M+Na]^+$; **IR ($CHCl_3$):** 1739 cm^{-1}.

2-(2,4-Dichlorophenyl)propyl acetate (l')



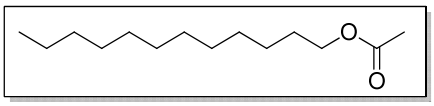
Molecular formula: $C_{11}H_{12}C_{l2}O_2$; **eluent**: ethyl acetate: pet. ether:-5%; **Yield**: 89%; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 7.38 (s, 1H), 7.21-7.18 (m, 2H), 4.20 (dd, J = 10.99, 4.93 Hz, 1H), 4.12 (dd, J =10.99, 4.93 Hz, 1H), 3.71-3.53 (m, 1H), 2.01 (s, 3H), 1.27 (d, J = 7.07 Hz, 3H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 170.5, 139.0, 134.7, 132.8, 129.4, 128.3, 127.3, 96.1, 67.6, 34.4, 20.8, 17.2; **MS (ESI)** (*m/z*): 270 $[M+Na]^+$; **IR ($CHCl_3$):** 1741 cm^{-1}.

Octyl acetate [18, 14]



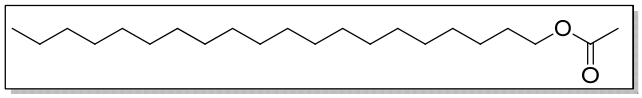
Molecular formula: $C_{10}H_{20}O_2$; **eluent**: ethyl acetate: petroleum ether:-5%; **Yield**: 88%; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 4.03 (t, J = 6.70 Hz, 2H), 1.69-1.57 (m, 2H), 1.28 (s, 10H), 0.87 (t, J = 6.31 Hz, 3H), 2.03 (s, 3H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 171.0, 64.5, 31.7, 29.6, 29.2, 28.6, 25.9, 22.6, 20.9, 14.0; **MS (ESI)** (*m/z*): 192 $[M+Na]^+$; **IR ($CHCl_3$):** 2925, 1743 cm^{-1}.

Dodecyl acetate[14]



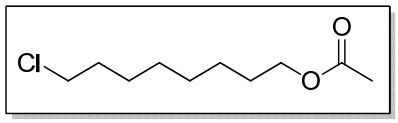
Molecular formula: $C_{14}H_{28}O_2$; **eluent**: ethyl acetate: petroleum ether:-5%; **Yield**: 88%; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 4.02 (t, J = 6.70 Hz, 2H), 2.01 (s, 3H), 1.68-1.55 (m, 2H), 1.24 (s, 18H), 0.86 (t, J = 6.82 Hz, 3H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 171.9, 64.5, 31.9, 29.56, 29.52, 29.3, 28.6, 25.9, 22.6, 20.9, 14.0; **MS (ESI)** (*m/z*): 283 $[M+Na+MeOH]^+$; **IR ($CHCl_3$):** 2928, 1743 cm^{-1}; **HRMS (ESI):** Calculated for $C_{14}H_{28}O_2$ $[M+Na]^+$ 251.1982, found 251.1982.

Icosyl acetate (m')[14]



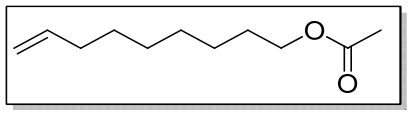
Molecular formula: $C_{22}H_{44}O_2$; **eluent**: ethyl acetate: petroleum ether:-5%; **Yield**: 88%; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 4.04 (t, J = 6.70 Hz, 2H), 2.04 (s, 3H), 1.70-1.55 (m, 2H), 1.25 (s, 36H), 0.88 (t, J = 6.70 Hz, 3H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 171.0, 64.6, 31.9, 29.7, 29.5, 29.3, 28.6, 25.9, 22.7, 20.9, 14.1; **MS (ESI)** (*m/z*): 341 $[M+1]^+$;**IR ($CHCl_3$):** 2926, 1734 cm^{-1}.

8-Chlorooctyl acetate (n')[15]



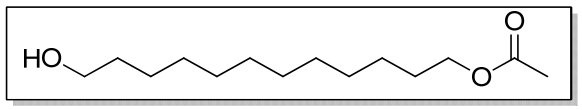
Molecular formula: $C_{10}H_{19}ClO_2$; **eluent**: ethyl acetate: pet. ether:-5%; **Yield**: 82%; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 4.04 (t, J = 6.57 Hz, 2H), 3.52(t, J = 6.57 Hz, 2H), 2.04 (s, 3H), 1.83-1.59 (m, 2H), 1.25 (m, 8H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 171.0, 64.4, 44.9, 32.5, 29.0, 28.7, 28.5, 26.7, 25.8, 20.9; **MS (ESI)** (*m/z*): 229 $[M+Na]^+$; **IR ($CHCl_3$):** 1742 cm^{-1}.

Non-8-en-1-yl acetate (o')[16]



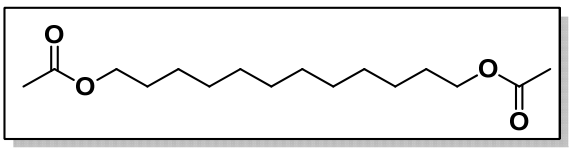
Molecular formula: $C_{11}H_{20}O_2$; **eluent**: ethyl acetate: petroleum ether:-5%; **Yield**: 72%; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 5.78 (ddt, J = 16.80, 10.10, 6.57 Hz, 1H), 5.01-4.87 (m, 2H), 4.02 (t, J = 6.70 Hz, 2H), 2.06-1.96 (m, 2H), 2.02 (s, 3H), 1.69-1.53 (m, 2H), 1.39-1.25 (m, 8H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 138.9, 114.1, 64.5, 33.7, 29.3, 29.1, 28.9, 28.8, 28.5, 25.8, 20.9; **MS (ESI)** (*m/z*): 237 $[M+Na+MeOH]^+$; **IR ($CHCl_3$):** 2930, 1740cm^{-1}.

12-Hydroxydodecyl acetate (p')[17]



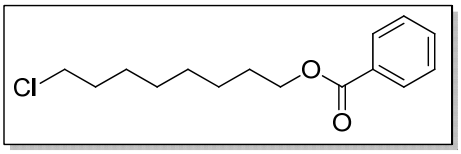
Molecular formula: $C_{16}H_{30}O_4$; **eluent**: ethyl acetate: pet. ether:-5%; **Yield**: 61%; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 4.04 (t, J = 6.82 Hz, 2H), 3.63 (t, J = 6.57 Hz, 2H), 2.04 (s, 3H), 1.64-1.58 (m, 4H), 1.27(s, 16H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 171.2, 64.6, 63.0, 32.7, 29.4, 29.2, 28.5, 25.8, 25.7, 20.9; **MS (ESI)** (*m/z*): 245 $[M+1]^+$, 267 $[M+Na]^+$; **IR ($CHCl_3$):** 2929, 1728 cm^{-1}; **HRMS (ESI):** Calculated for $C_{14}H_{28}O_3$ $[M+Na]^+$267.1931, found 267.1928.

Dodecane-1,12-diyl diacetate (p'')[17]



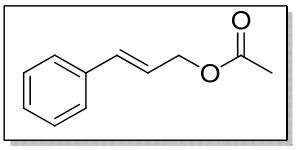
Molecular formula: $C_{16}H_{30}O_4$; **eluent**: ethyl acetate: pet. ether:-5%; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 3.98 (t, J = 6.70 Hz, 4H), 1.98 (s, 6H), 1.65-1.49 (m, 4H), 1.21 (s, 16H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 171.0, 64.4, 29.3, 29.0, 28.4, 25.7, 20.7; **MS (ESI)** (*m/z*): 287 $[M+1]^+$, 309 $[M+Na]^+$; **IR ($CHCl_3$):** 1736 cm^{-1}; **HRMS (ESI):** Calculated for $C_{16}H_{30}O_4$ $[M+Na]^+$309.2036,found 309.2033.

8-Chlorooctyl benzoate (q'):



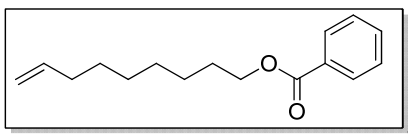
Molecular formula: $C_{15}H_{21}ClO_2$; **Eluent**: ethyl acetate: pet. ether:-2%; **Yield**: 89%; **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 8.07-8.02 (m, 2H), 7.56-7.30 (m, 3 H), 4.31 (t, J = 6.67 Hz, 2H), 3.53 (t, J = 6.67 Hz, 2H), 1.81-1.67 (m, 4H), 1.48-1.28 (m, 8H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 166.6, 132.7, 130.4, 129.4, 128.2, 64.9, 45.0, 32.5, 29.0, 28.7, 26.7, 25.8; **MS (ESI)** (*m/z*): 291 $[M+Na]^+$; **IR ($CHCl_3$):** 1717, 758 cm^{-1}; **HRMS (ESI):** Calculated for $C_{15}H_{21}ClO_2$ $[M+Na]^+$ 305.0915, found 305.0912.

(*E*)-3-Phenylprop-2-enyl acetate (w')[18]



Molecular formula: $C_{12}H_{14}O_2$; **Eluent**: ethyl acetate: pet. ether:-2% **Yield**: 75%; **^{1} H NMR (200 MHz, $CDCl_3$)**: δ 7.39–7.25 (m, 5H), 6.64 (d, J = 15.9 Hz, 1H), 6.33–6.22 (dt, J = 6.44, 6.34 Hz, 1H), 4.72 (dd, J = 6.32, 1.14 Hz, 2H), 2.07 (s, 3 H); **13C NMR (50 MHz, $CDCl_3$):** δ 170.6, 136.0, 134.0, 128.5, 127.9, 126.5, 123.0, 64.9, 20.8; **MS (ESI)** (*m/z*): 215 $[M+K]^+$; **IR($CHCl_3$):** 1739, 3030 cm^{-1}.

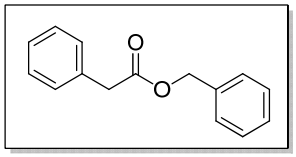
Non-8-en-1-yl benzoate (x')



Molecular formula: $C_{16}H_{22}O_2$; **Eluent**: ethyl acetate: pet. ether:-2%; **Yield:** 78%; **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 8.05 (d, J = 1.0 Hz, 2H), 7.55 (t, J = 7.6 Hz, 1H), 7.47-7.44 (m, 2H), 5.81 (ddt, J = 17.09,10.38, 6.71 Hz, 1 H), 5.01-4.94 (m, 2H), 4.31 (t, J = 6.7 Hz, 2H), 2.06-2.03(m, 2H), 1.77-1.73 (m, 2H), 1.40-1.35 (m, 4H), 1.32-1.30 (m, 4H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 166.7, 139.1, 134.2, 132.7,

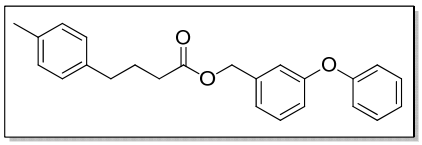
129.5, 128.3, 114.1, 65.1, 33.7, 29.3, 29.2, 28.8, 26.0; **MS (ESI)** (*m/z*):301 $[M+Na+MeOH]^+$; **IR($CHCl_3$):** 1739 cm^{-1}.

Benzyl 2-phenylacetate (r')[21]



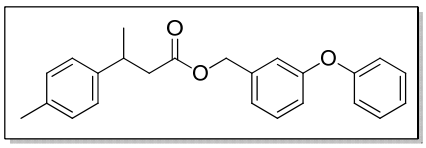
Molecular formula: $C_{15}H_{14}O_2$; **Eluent**: ethyl acetate: pet. ether:-5%; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 7.30 (s, 5H), 7.28 (m, 5H), 5.11 (s, 2H), 3.64(s, 2H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 171.2, 135.7, 133.7, 129.1, 128.4, 128.0, 126.9, 66.4, 41.1; **MS (ESI)** (*m/z*): 249 $[M+Na]^+$; **IR ($CHCl_3$):** 1737 cm^{-1}.

3-Phenoxybenzyl 4-(p- tolyl) butanoate (s')



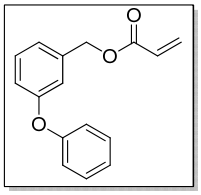
Molecular formula: $C_{24}H_{24}O_3$**; Eluent**: ethyl acetate: petroleum ether:-2%; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 7.36-7.32 (m, 3H), 7.10-7.01 (m, 10H), 5.09 (s, 2H), 2.59 (t, *J* = 7.20 Hz, 2H), 2.39 (t, *J* = 7.20 Hz, 2H), 2.33 (s, 3H), 1.70-1.65 (m, 2H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 173.2, 157.5, 156.8, 138.9, 138.0, 135.1, 129.8, 129.7, 128.9, 128.2, 123.4, 122.5, 119.0, 118.2, 118.1, 65.5, 35.0, 34.0, 24.5, 20.9; **MS (ESI)** (*m/z*): 397 $[M+MeOH]^+$; **IR ($CHCl_3$):** 1587, 1740 cm^{-1}; **HRMS (ESI):** Calculated for 383.1618 $[M+Na]^+$; found 383.1618.

3-Phenoxybenzyl 3-phenylbutanoate (t')



Molecular formula: $C_{24}H_{24}O_3$; **Eluent**: 2% ethyl acetate- pet. ether; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.53-7.43(m, 3H), 7.31-7.26 (m, 1H), 7.26 (s, 4H), 7.19-7.10 (m, 5H), 5.19 (s, 2H), 3.42 (dt, *J* = 14.18, 7.09 Hz, 1H), 2.79 (dq, *J* = 14.18, 7.34 Hz, 2H), 2.46 (s, 3H), 1.44 (d, *J* = 6.84 Hz, 3H); **^{13}C NMR (101 MHz,$CDCl_3$):** δ 172.1, 157.4, 156.9, 142.5, 137.9, 135.9, 129.9, 129.8, 129.2, 129.1,126.6, 123.4, 122.6, 119.0,118.3, 118.2, 118.0, 77.3, 77.2, 76.7, 65.6, 42.9, 42.8, 36.1, 22.0, 21.9, 21.0; **MS (ESI)** (*m/z*): 383 $[M+Na]^+$; **IR ($CHCl_3$):** 1587, 1740 cm^{-1}.

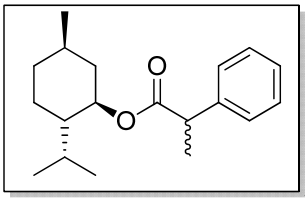
3-Phenoxybenzyl acrylate (u')



Molecular formula: $C_{16}H_{14}O_3$; **Eluent**: ethyl acetate: pet. ether: 2%; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 7.34-7.29 (m, 3H), 7.10-6.98 (m, 6H), 6.45 (dd, *J* = 17.31,

1.65 Hz, 1H), 6.17 (dd, *J* = 17.31, 10.23 Hz, 1H), 5.82 (dd, *J* = 10.23, 1.65 Hz, 1H), 5.12 (s, 2H); **^{13}C NMR (50 MHz, $CDCl_3$):** *δ* 165.7, 157.4, 156.7, 137.7, 131.1, 129.9, 129.7, 128.6, 128.0, 123.3, 122.5, 118.9, 118.2, 118.1, 65.6; **MS (ESI)** (*m/z*): 277 $[M+Na]^+$; **IR ($CHCl_3$):** 1726 cm^{-1}; **HRMS (ESI):** Calculated 277.0836 $[M+Na]^+$; found 277.0835.

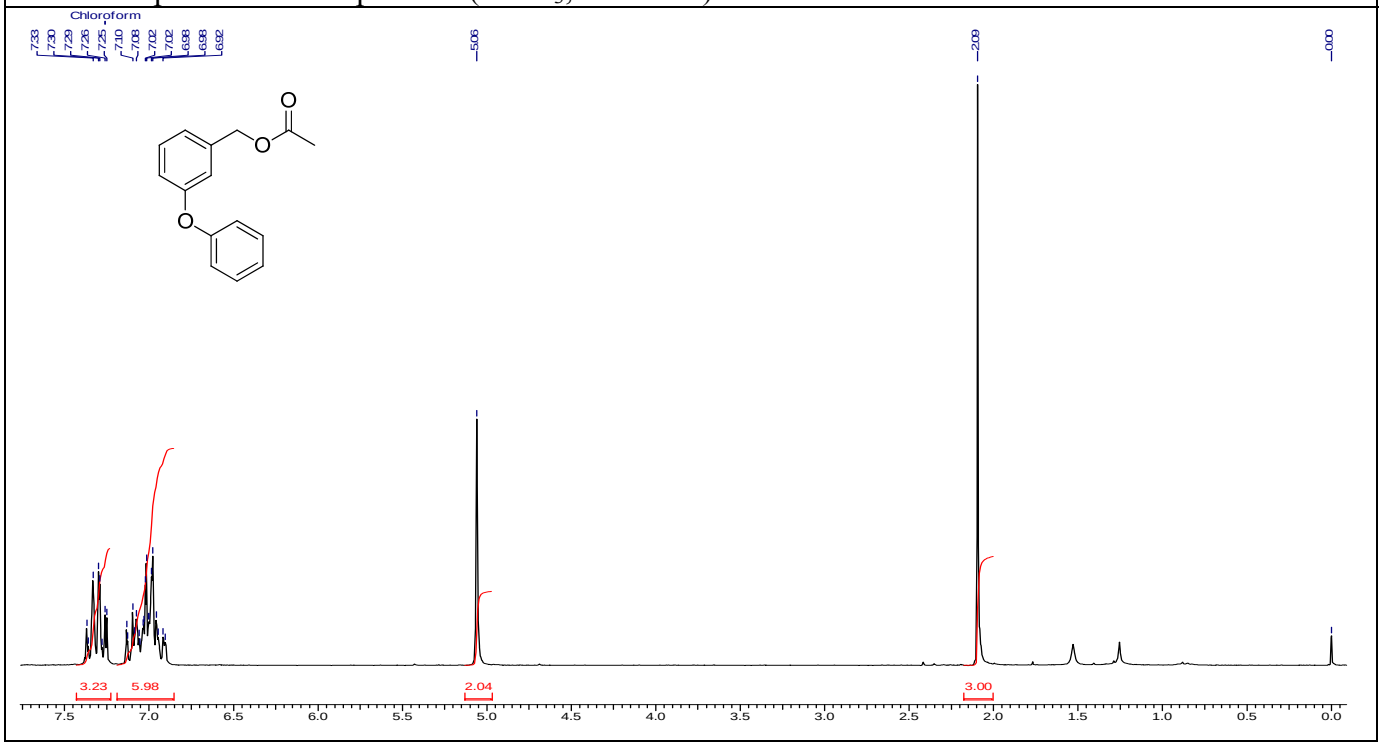
2-Isopropyl-5-methylcyclohexyl 2-phenylpropanoate (v') [22]



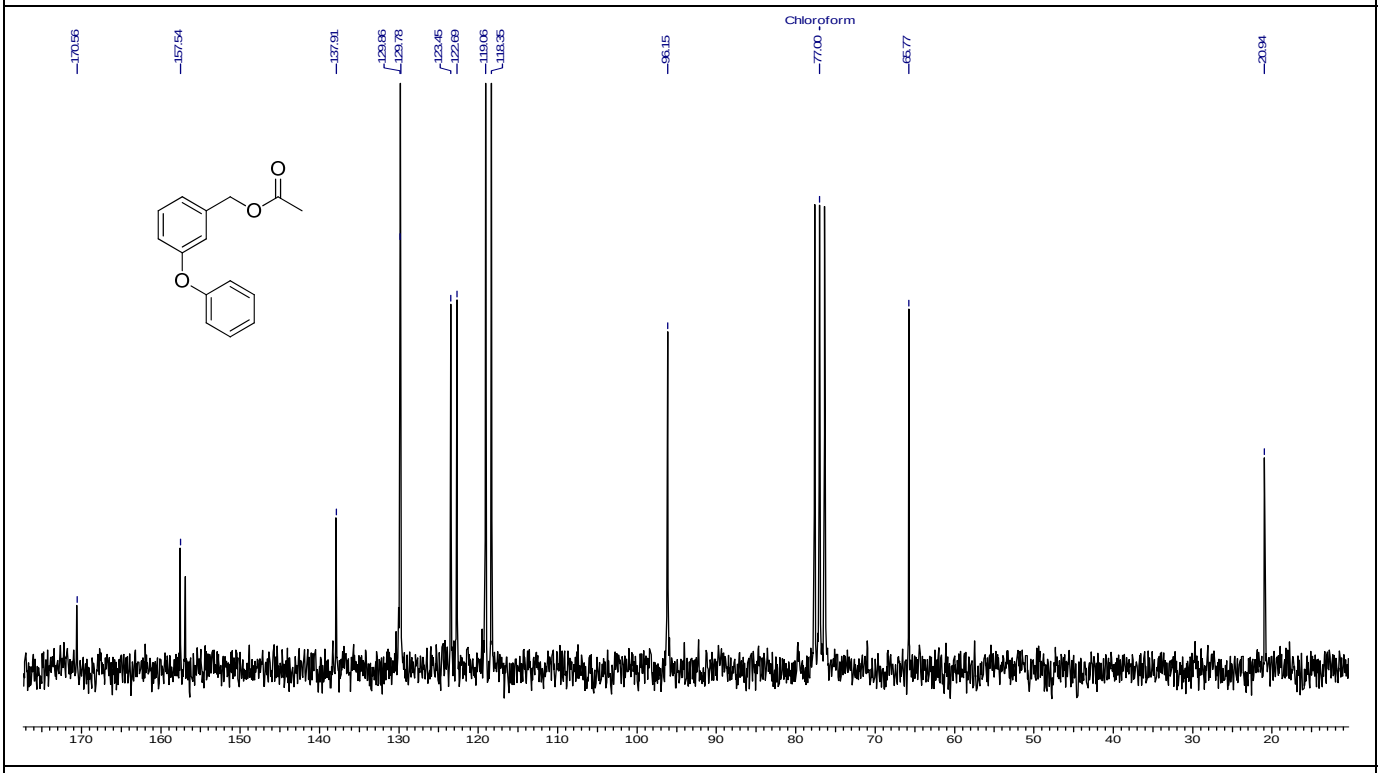
Molecular formula: $C_{19}H_{28}O_2$; **Eluent**: ethyl acetate: petroleum ether:- 5%; **^{1}H NMR (200 MHz, $CDCl_3$):** (*dr*: ~6:**4**)*δ* 7.27-7.21 (m, 5H), 4.70-4.51 (m, 1H), 3.73-3.59 (m, 1H), 2.01-1.66 (m, 2H), 1.64-1.53 (m, 4H), 1.40-1.18 (m, *J* 1H), 1.06-0.88 (m, 1H), 0.85 (t, *J* = 6.31 Hz, 3H), 0.66 (d, *J* = 6.82 Hz, 1.75H), 0.49 (d, *J* = 6.82 Hz, 1.25H); **^{13}C NMR (101 MHz, $CDCl_3$):** *δ* **174.1**.174.0, 140.8, **140.7**, **128.6**, 128.4, 127.4, 127.4, **127.1**, 126.9, 74.4, **74.3**, 47.0, **46.9**, 45.9, **45.7**, 45.3, 40.7, **40.3**, 34.2, 31.3, **31.3**, 26.1, **25.6**, 23.3, **23.1**, 22.0, **20.7**, **20.5**, 18.5, **18.4**, 18.2, **16.2**, 15.8; **MS (ESI)** (*m/z*): 311 $[M+Na]^+$; **IR ($CHCl_3$):** 1740 cm^{-1} **HRMS (ESI):** Calculated for $C_{19}H_{28}O_2$ $[M+Na]^+$311.1982, found 311.1982.

2.3.4.2. Spectra

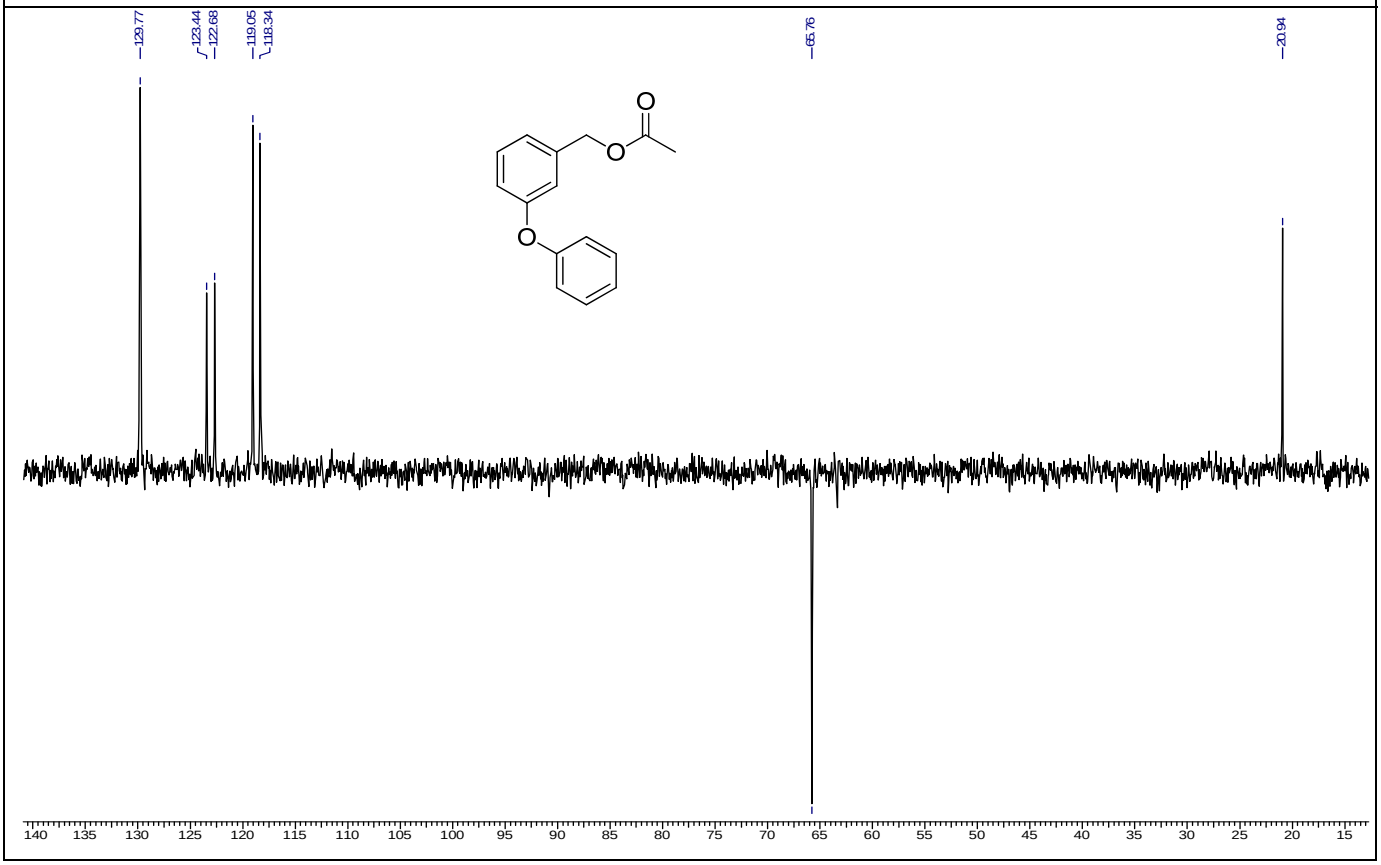
^{1}H NMR spectrum of compound **2** ($CDCl_3$, 200 MHz)



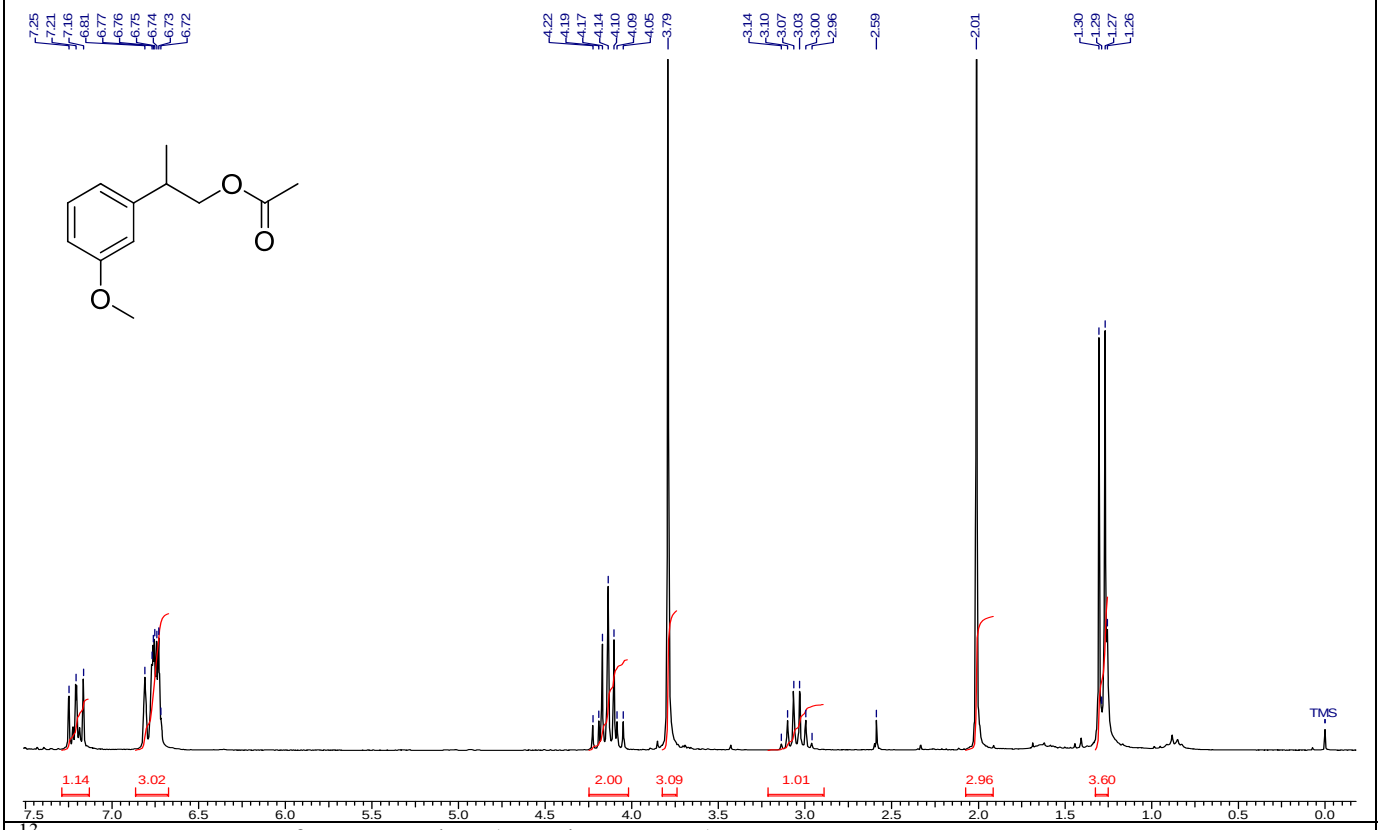
^{13}C NMR spectrum of compound **2** ($CDCl_3$, 50 MHz)



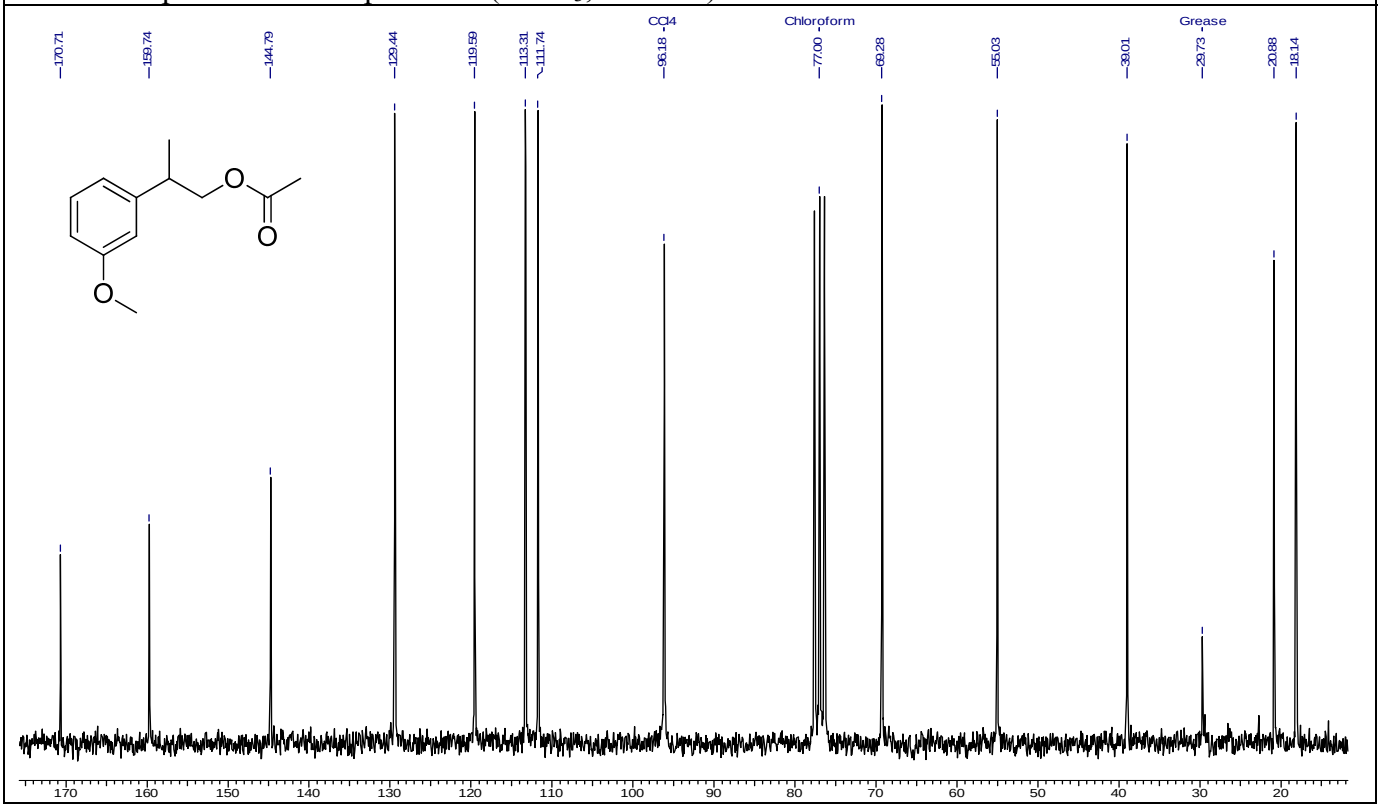
DEPT spectrum of compound **2** ($CDCl_3$, 50 MHz)



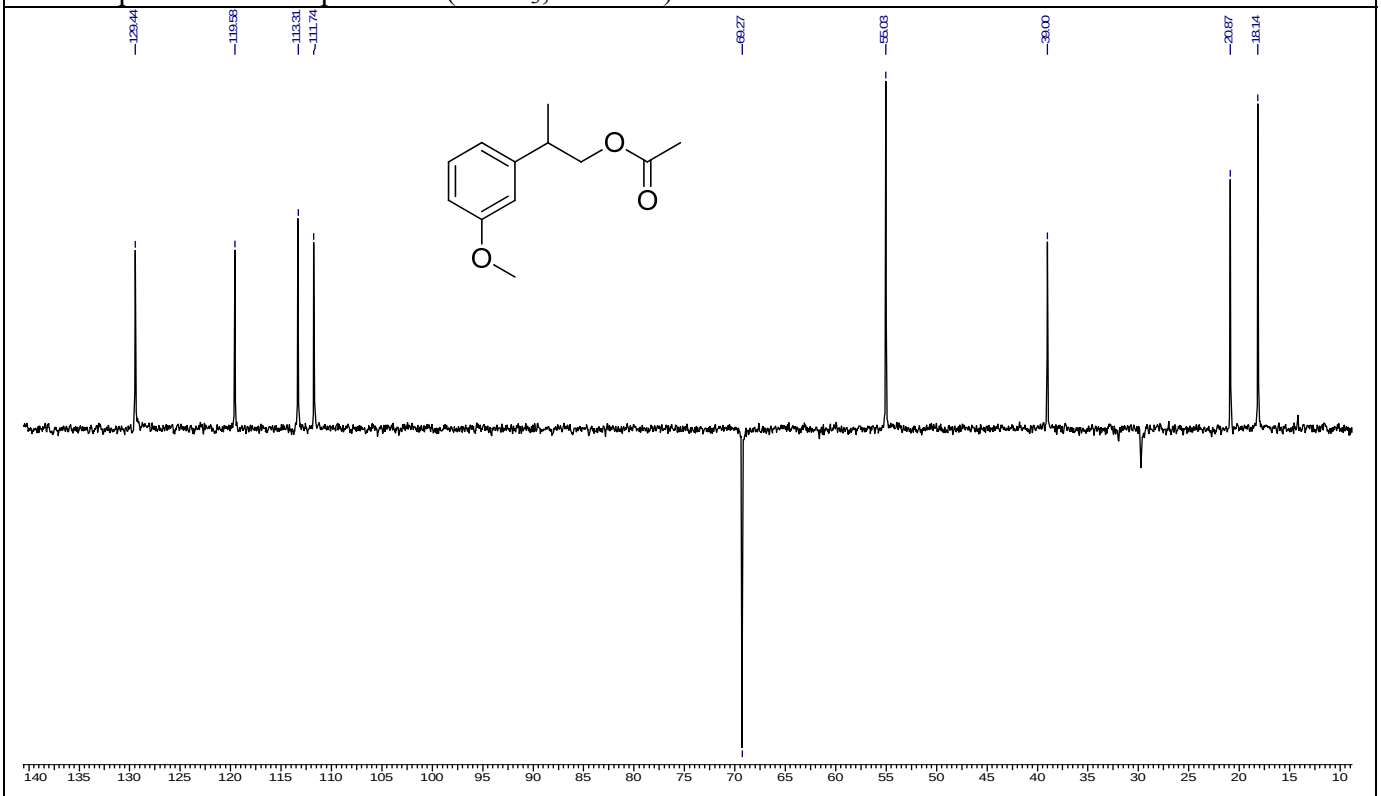
^{1}H NMR spectrum of compound **h'** ($CDCl_3$, 200 MHz)



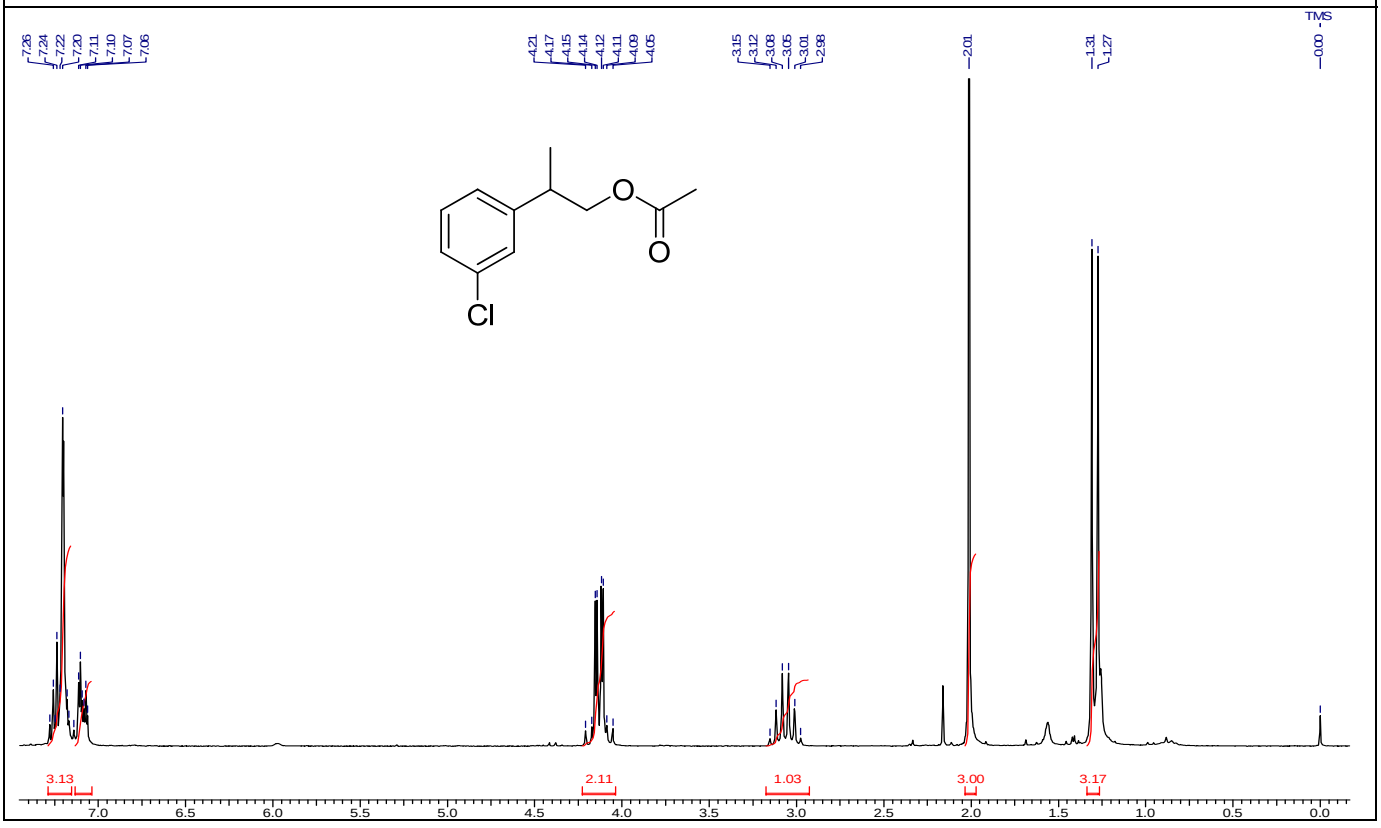
^{13}C NMR spectrum of compound **h'** ($CDCl_3$, 50 MHz)



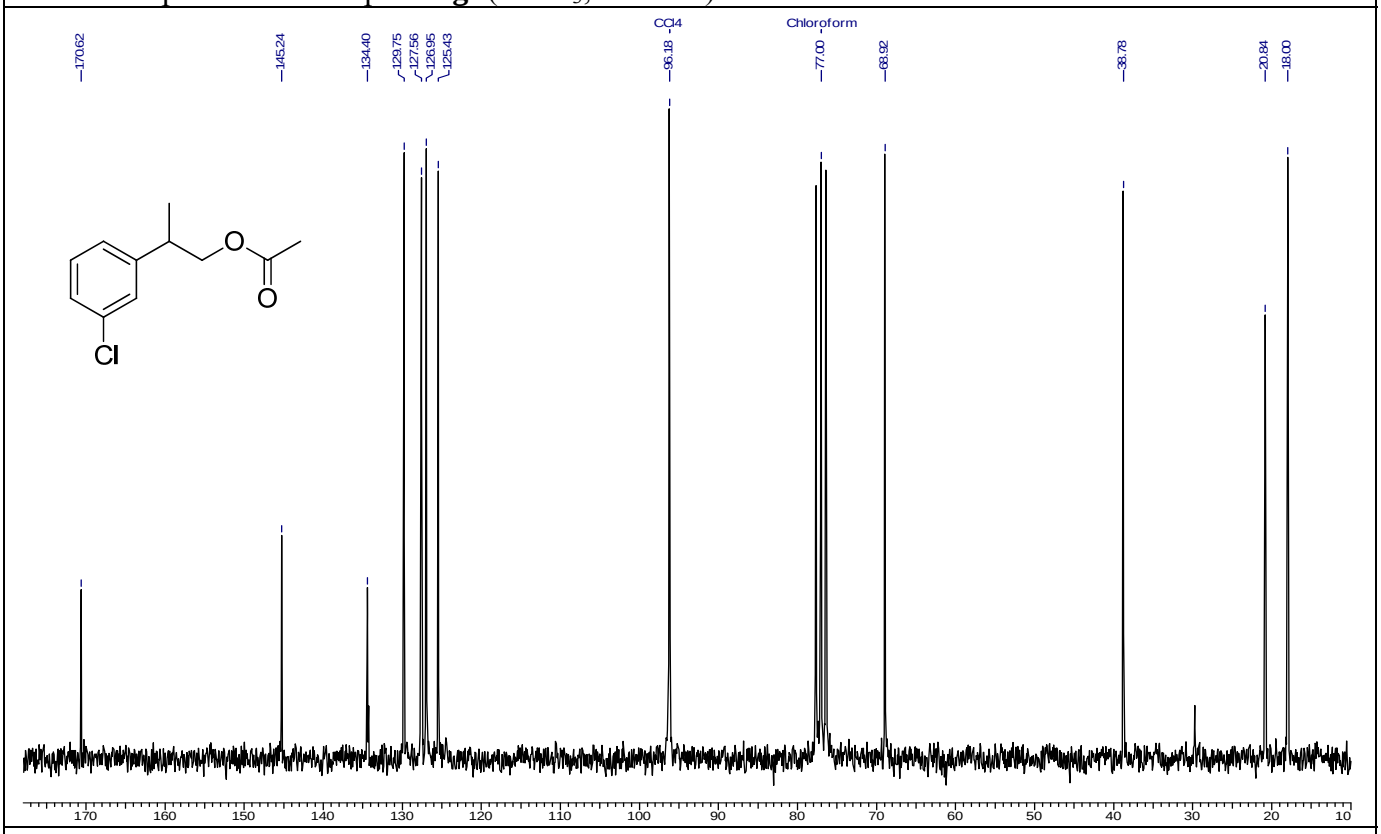
DEPT spectrum of compound **h'** ($CDCl_3$, 50 MHz)



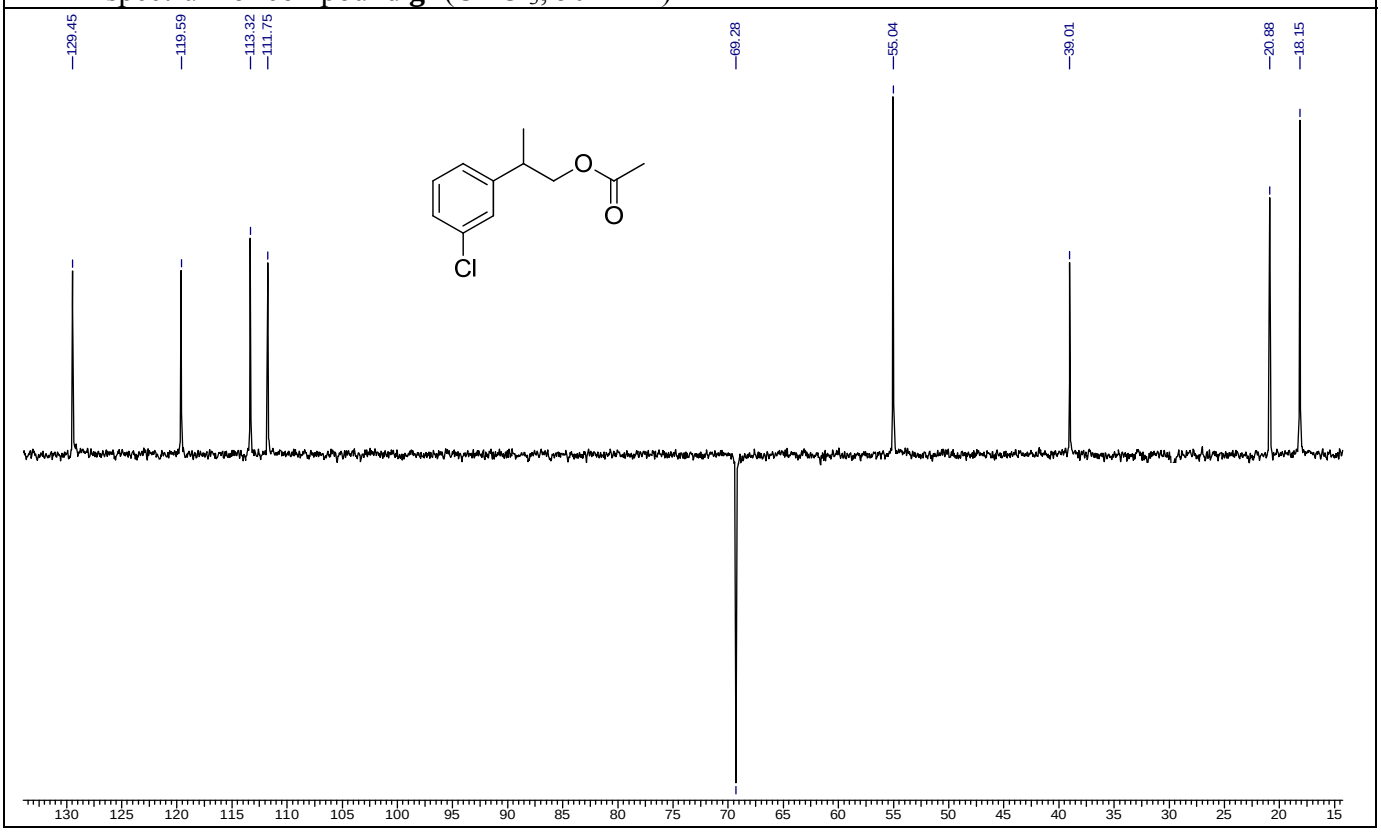
^1H NMR spectrum of compound **g'** ($CDCl_3$, 200 MHz)



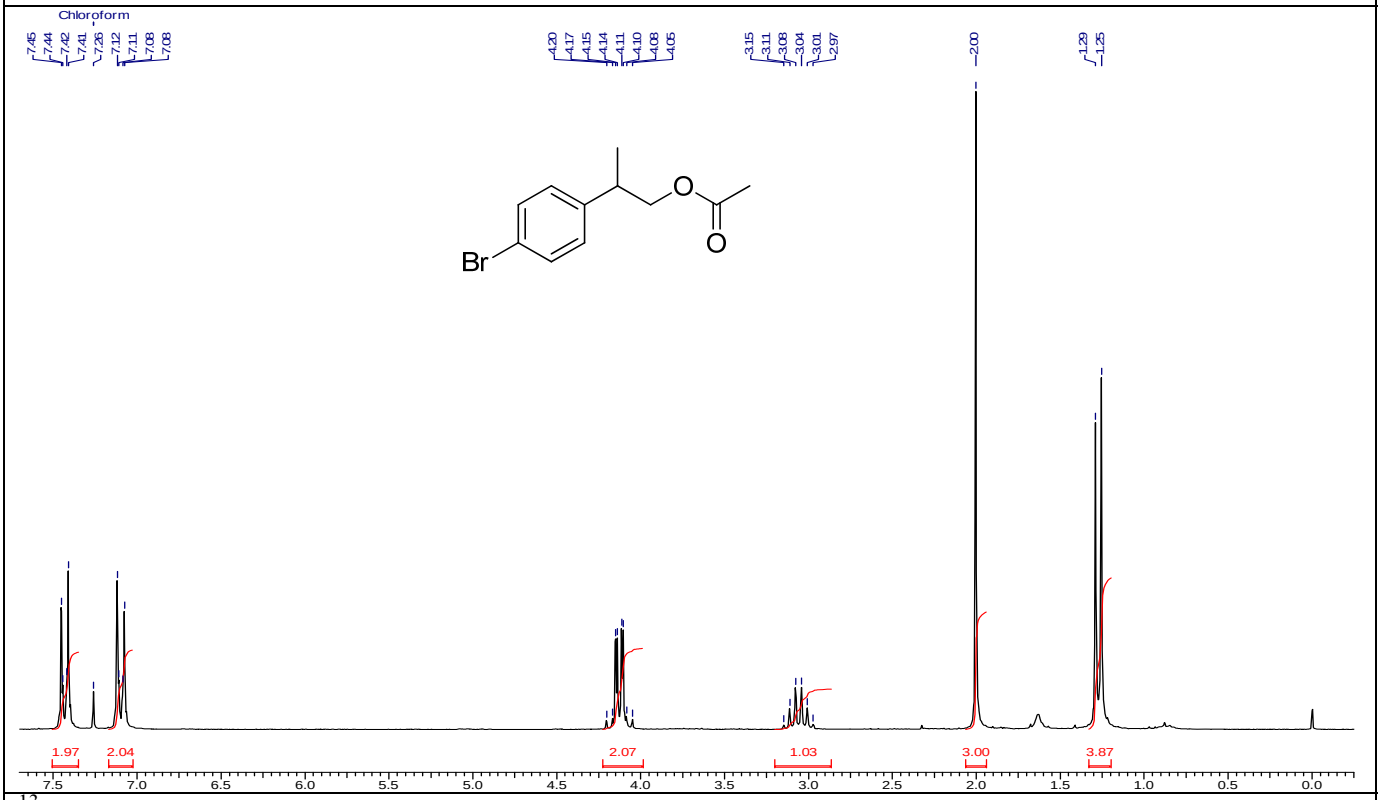
^{13}C NMR spectrum of compound **g'** ($CDCl_3$, 50 MHz)



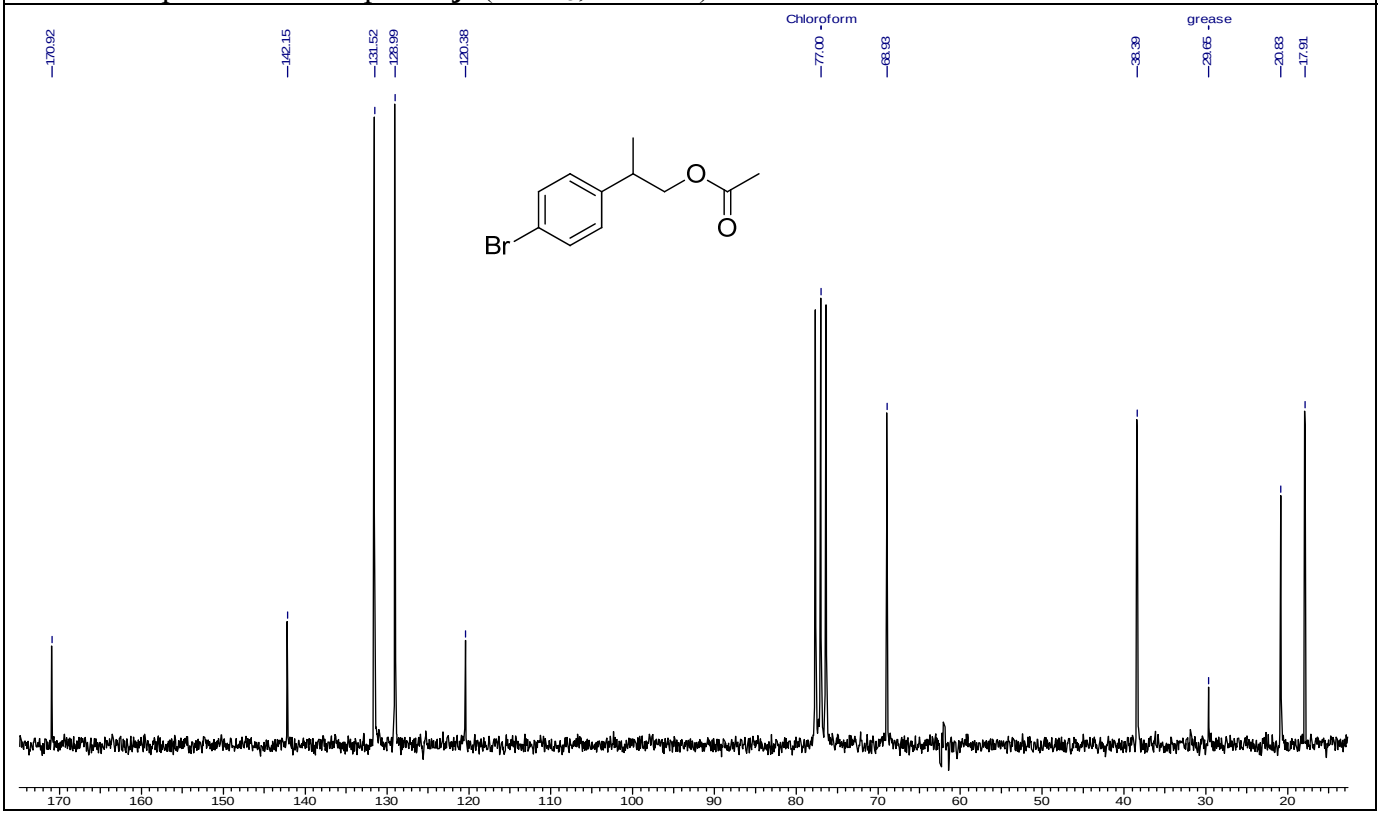
DEPT spectrum of compound **g'** ($CDCl_3$, 50 MHz)



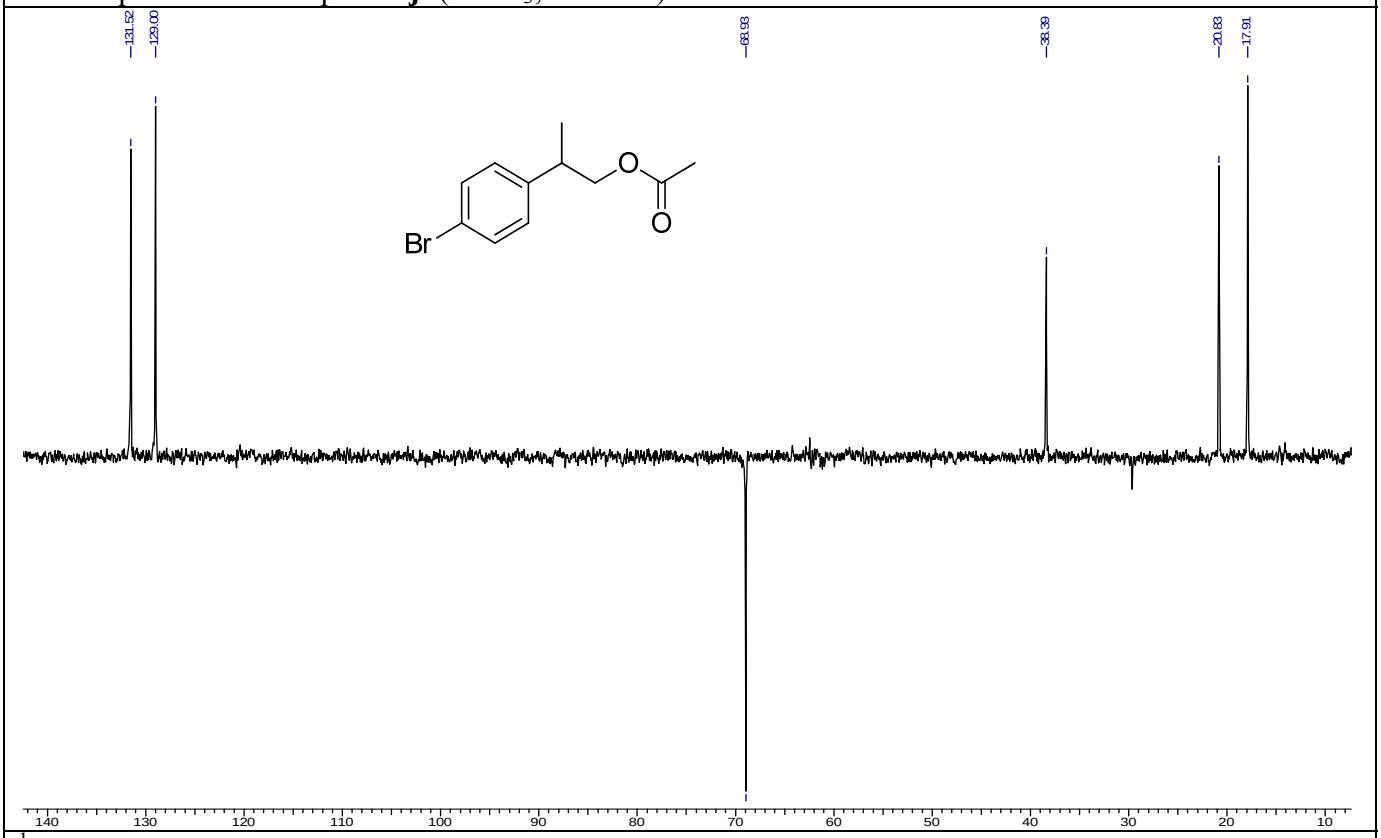
^{1}H NMR spectrum of compound **j'** ($CDCl_3$, 200 MHz)



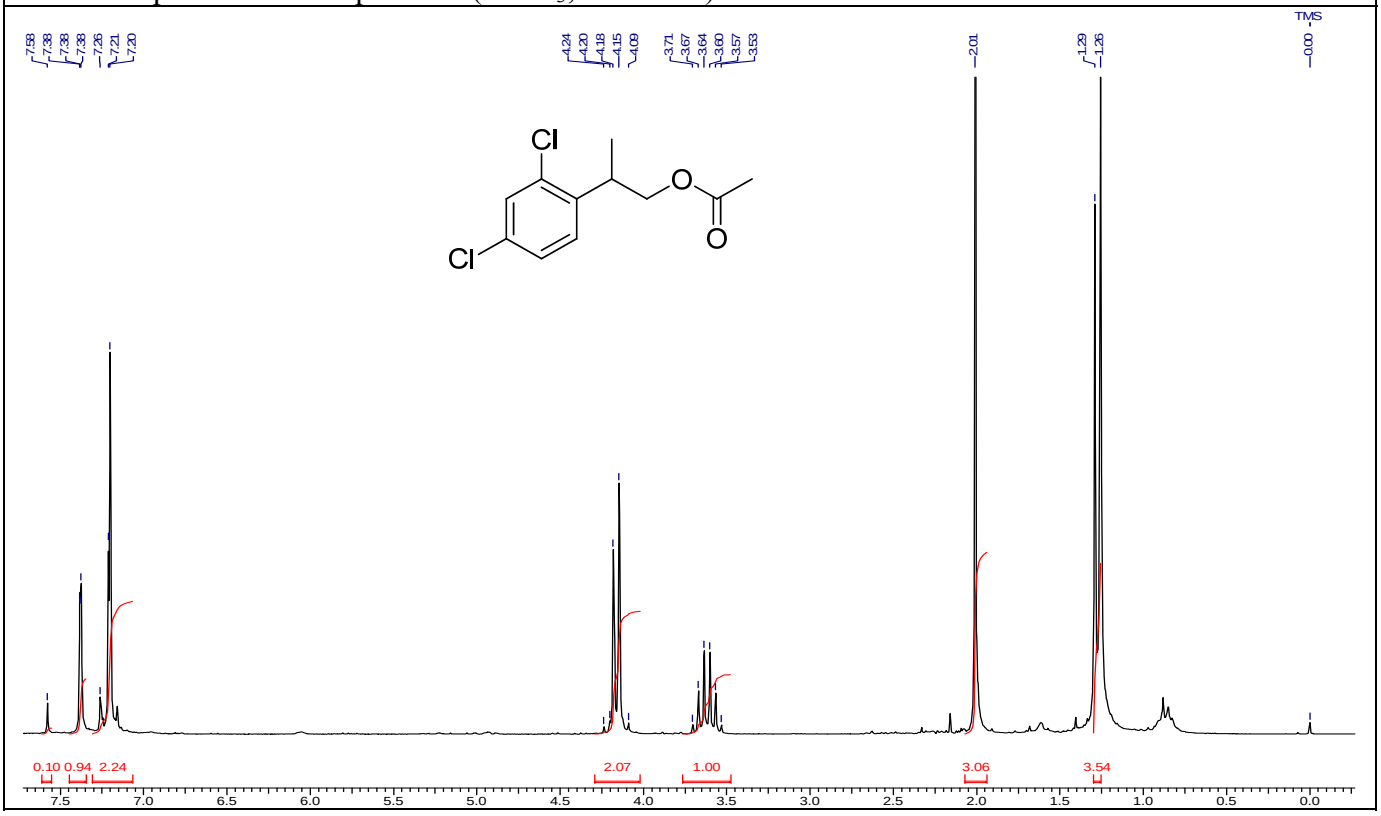
^{13}C NMR spectrum of compound **j'** ($CDCl_3$, 50 MHz)



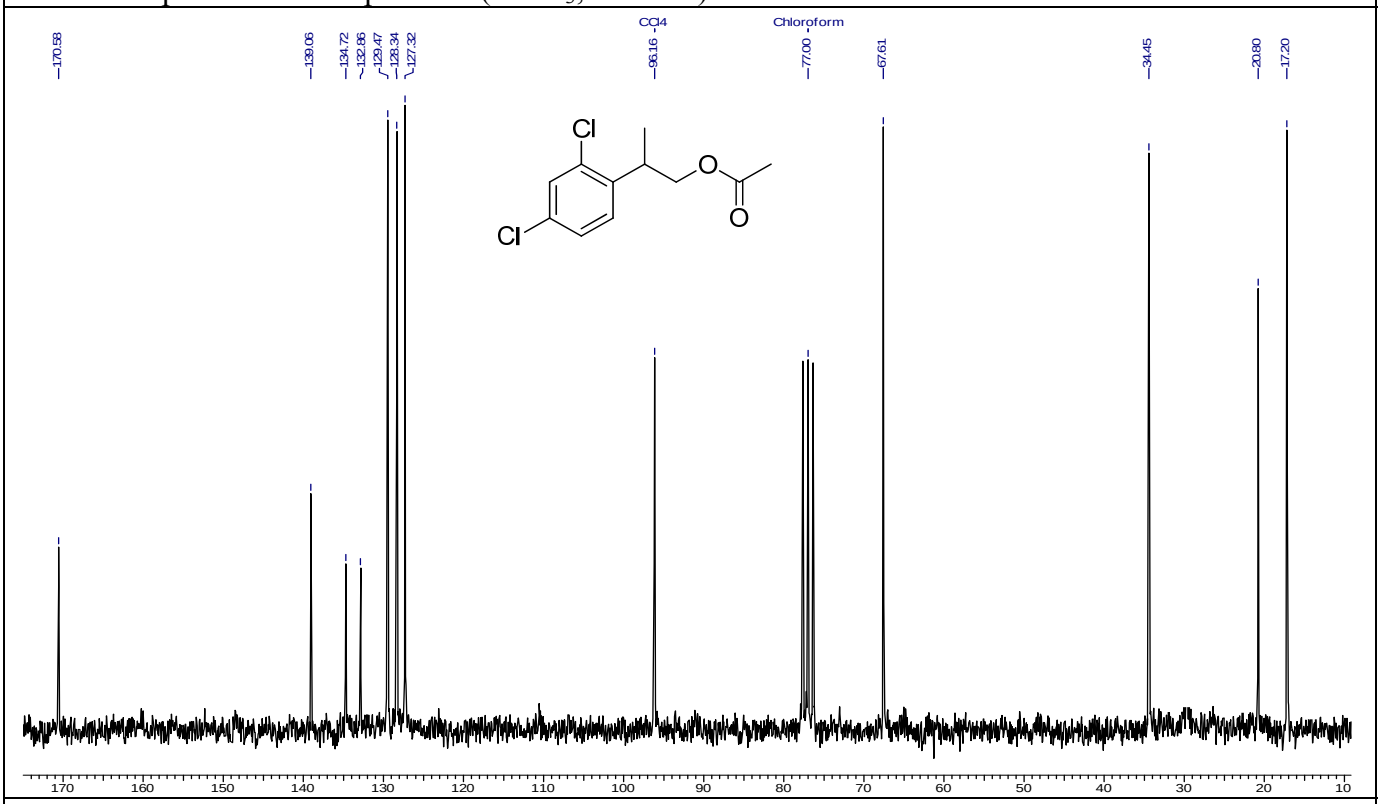
DEPT spectrum of compound **j'** ($CDCl_3$, 50 MHz)



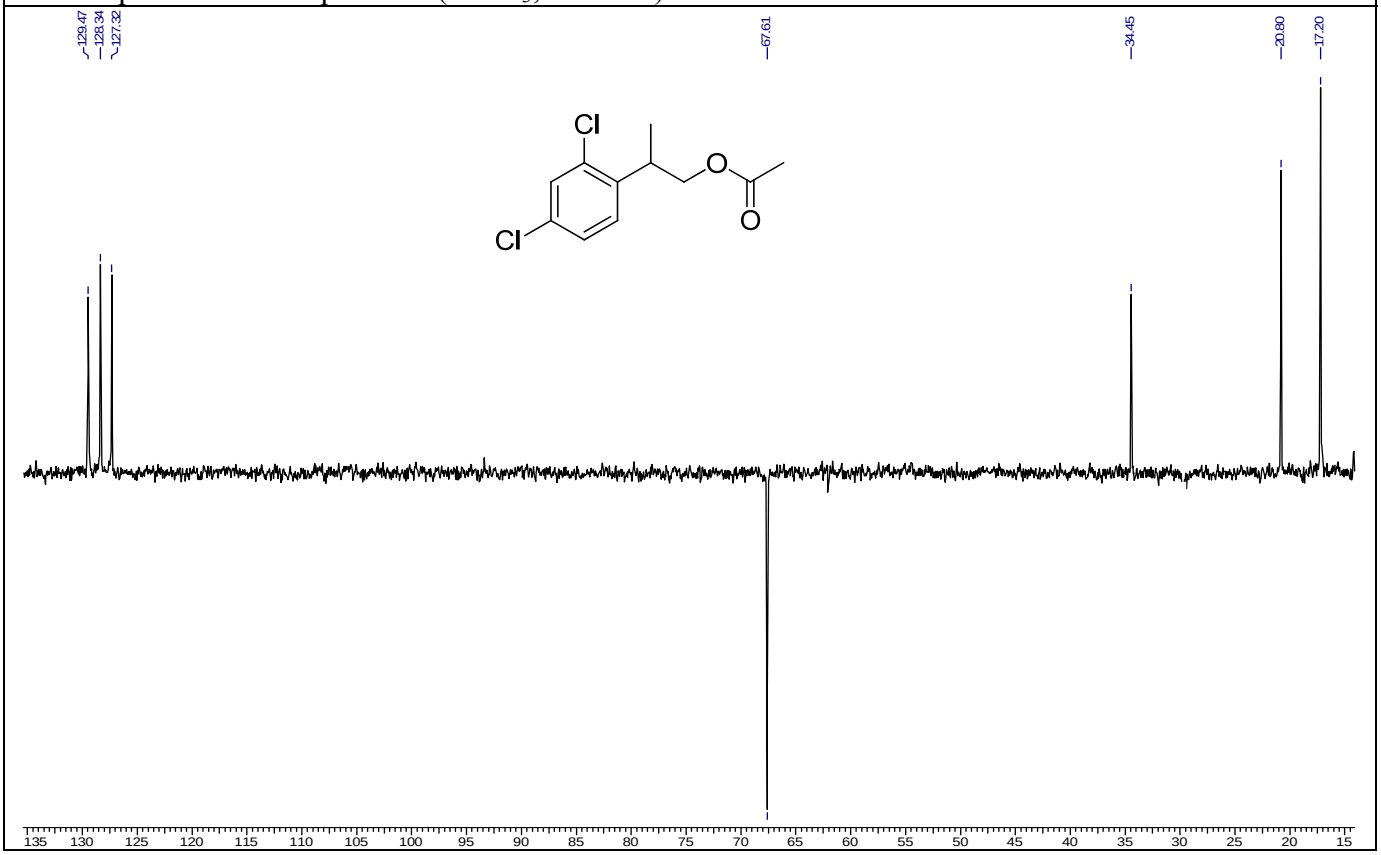
^{1}H NMR spectrum of compound **l'** ($CDCl_3$, 200 MHz)



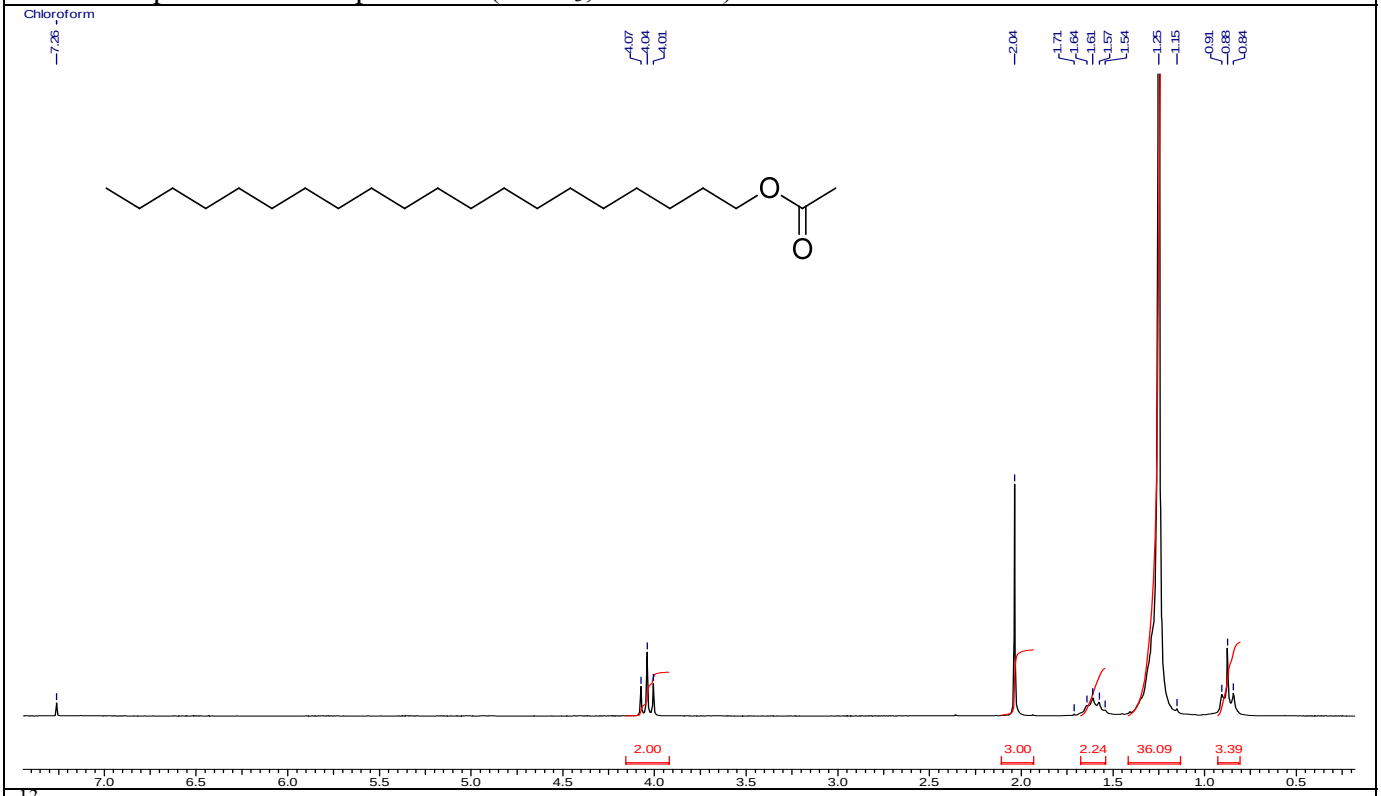
^{13}C NMR spectrum of compound **l'** ($CDCl_3$, 50 MHz)



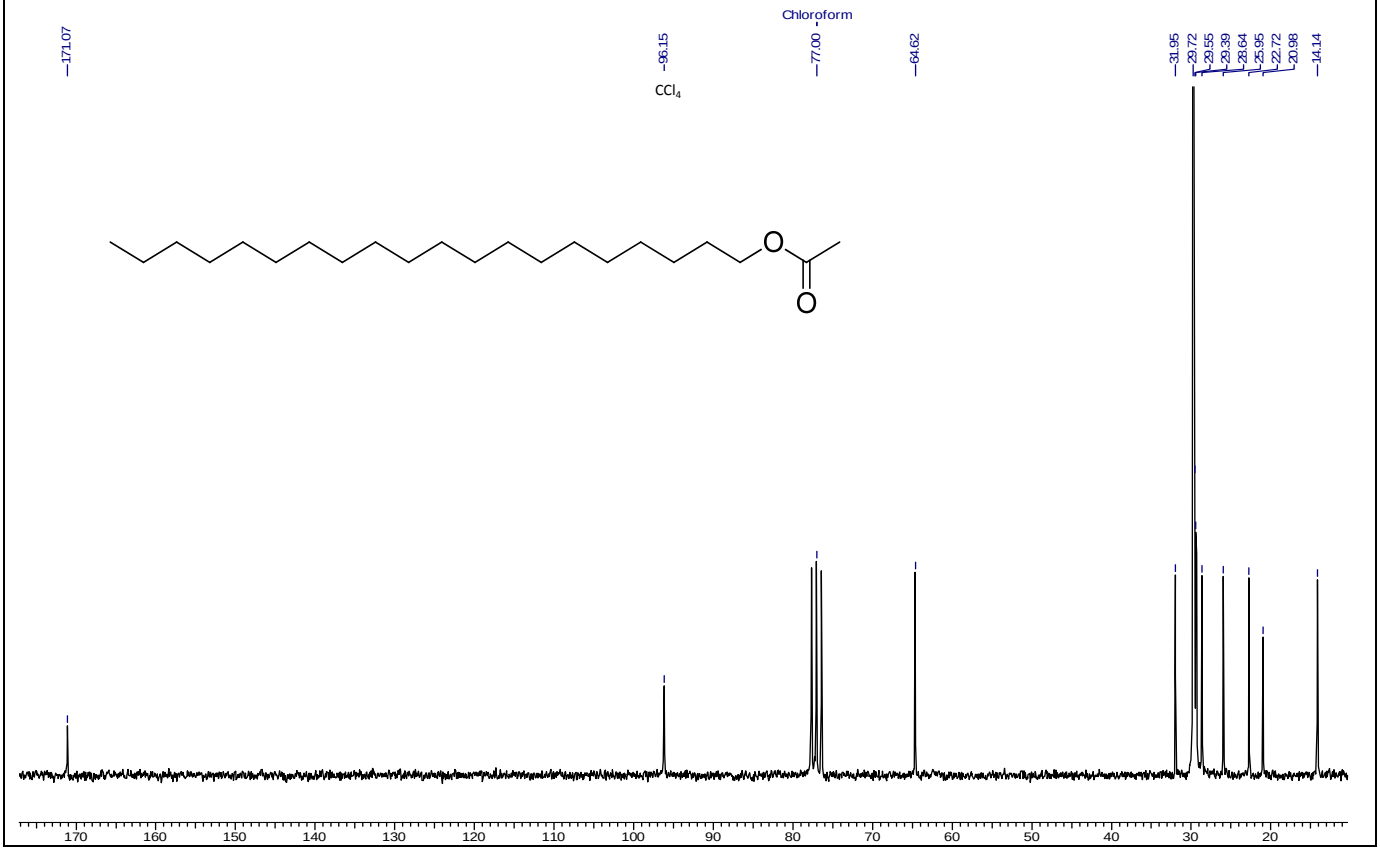
DEPT spectrum of compound **l'** ($CDCl_3$, 50 MHz)



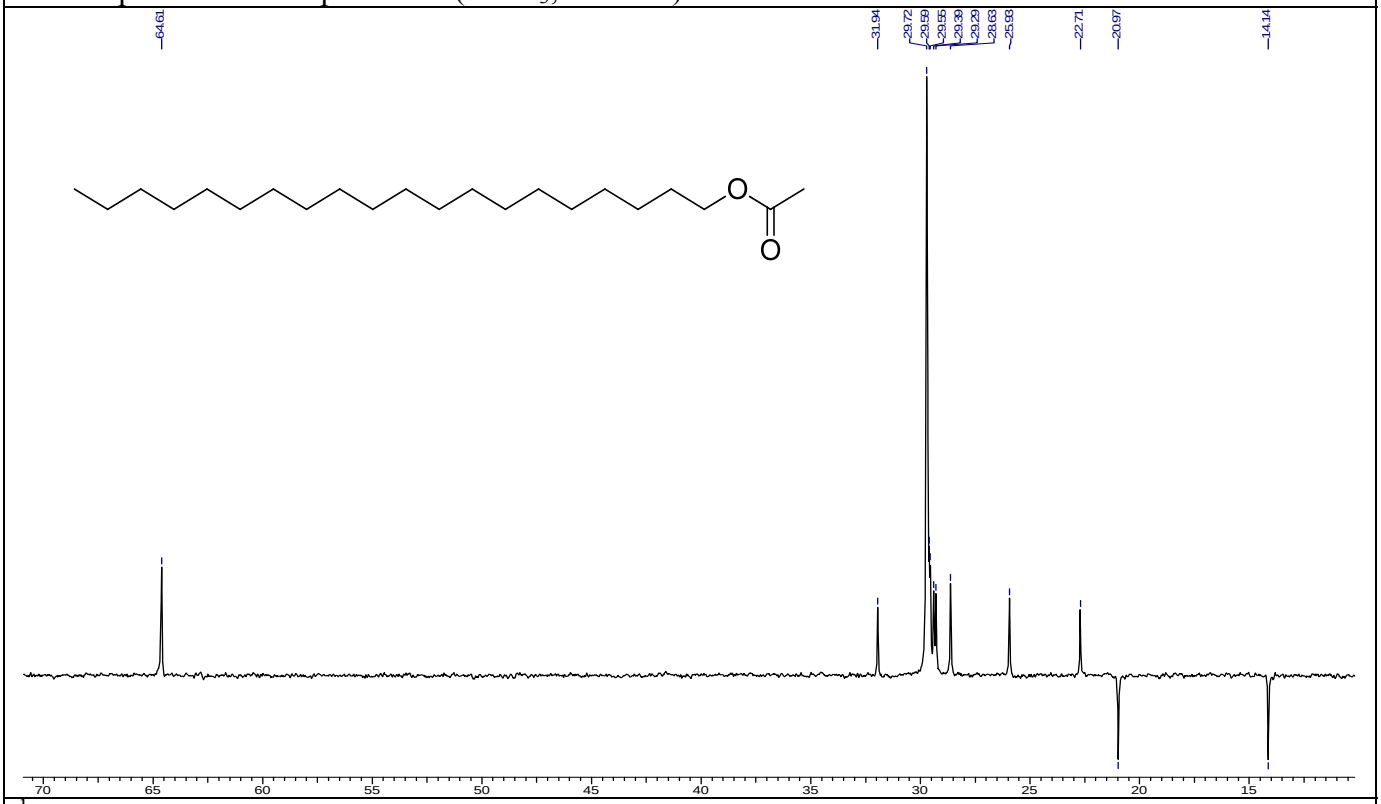
^{1}H NMR spectrum of compound **m'** ($CDCl_3$, 200 MHz)



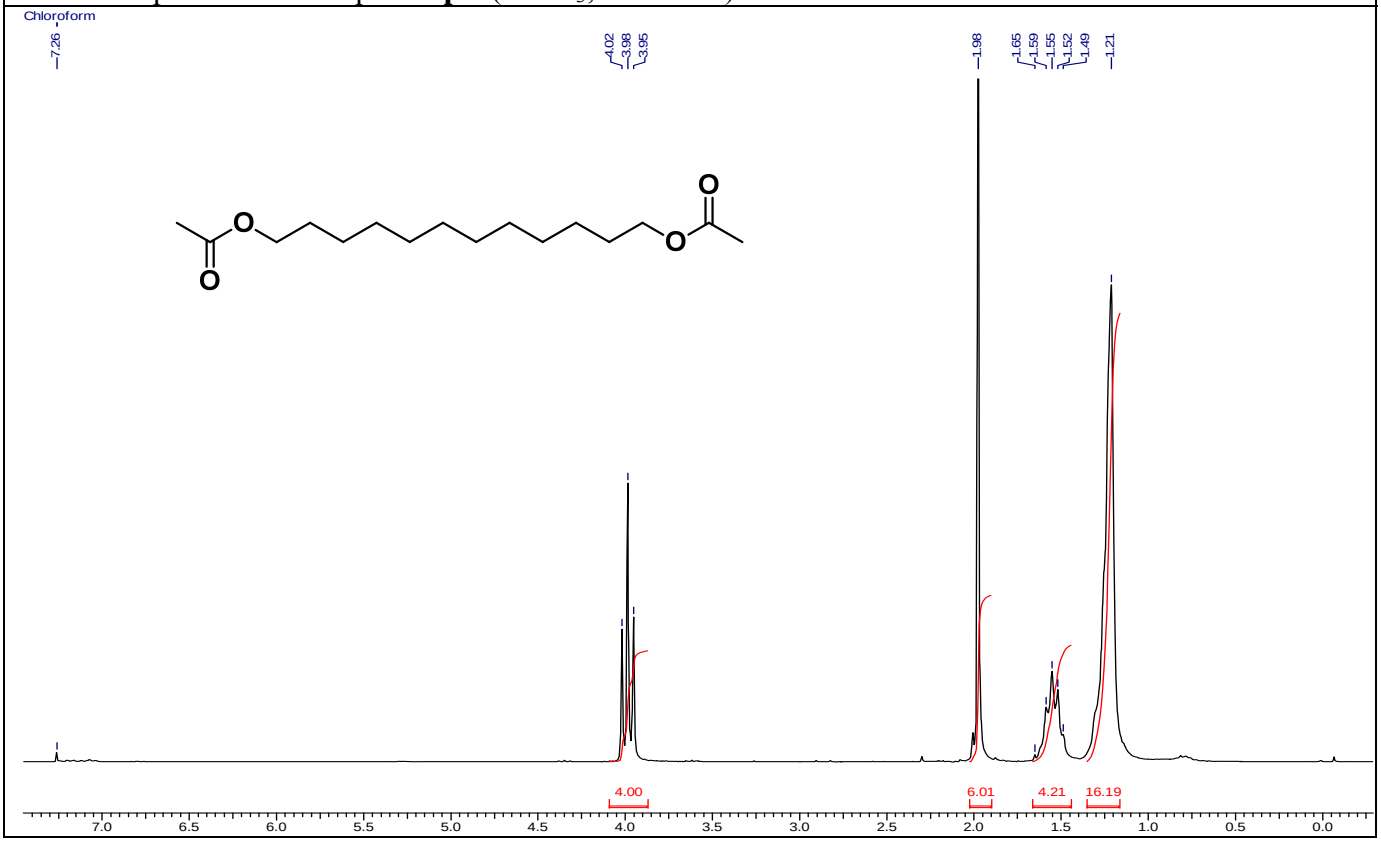
^{13}C NMR spectrum of compound m' ($CDCl_3$, 50 MHz)



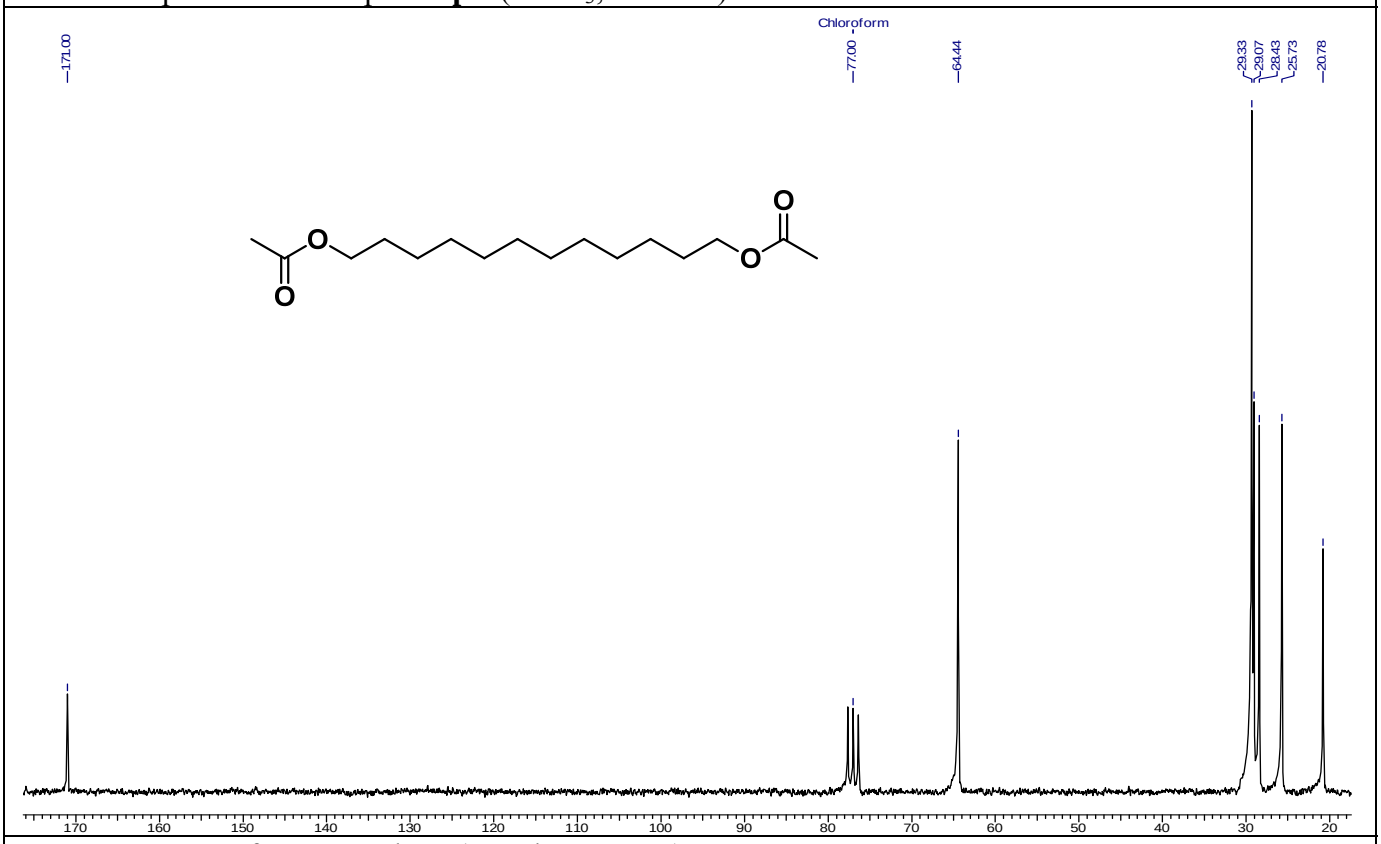
DEPT spectrum of compound **m'** ($CDCl_3$, 50 MHz)



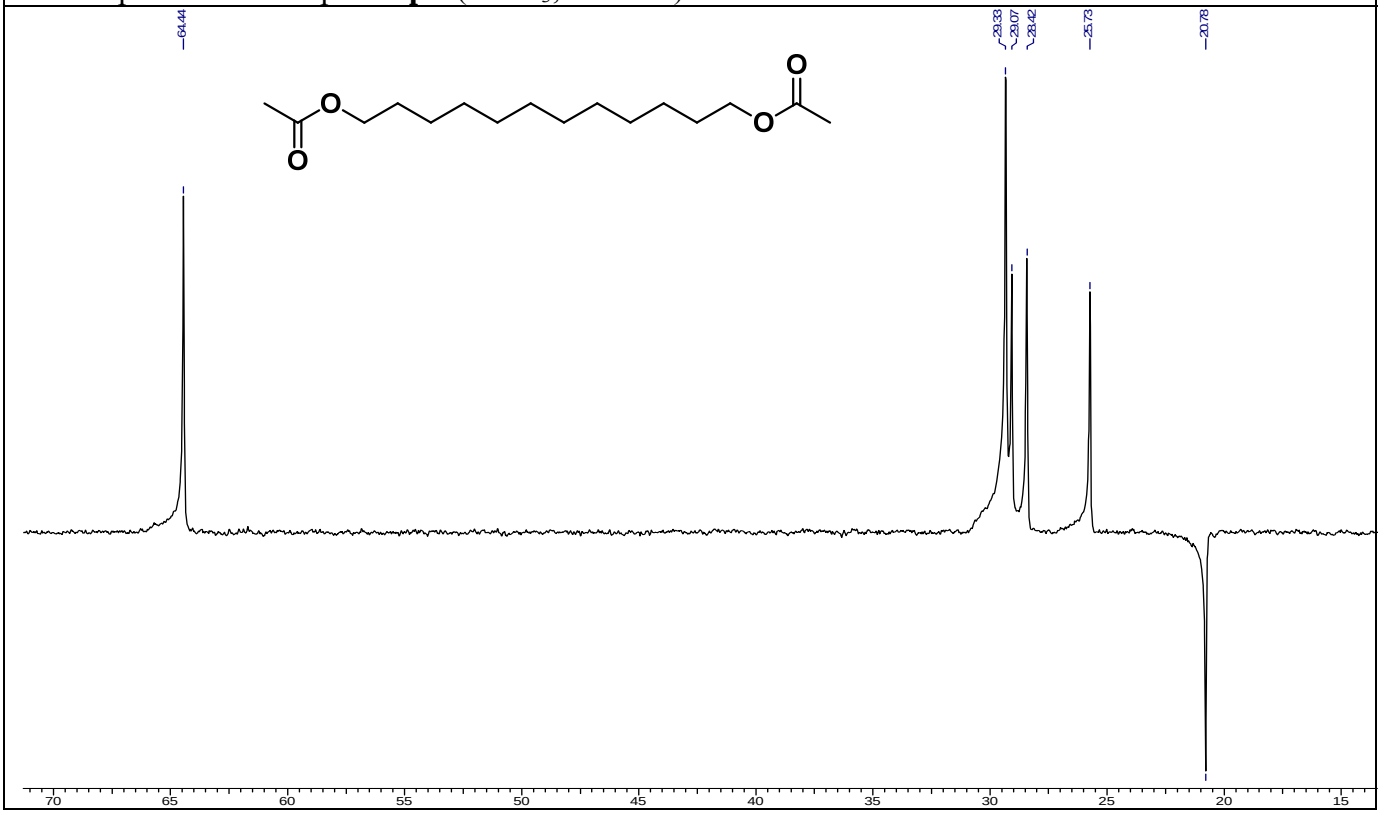
^{1}H NMR spectrum of compound **p''** ($CDCl_3$, 200 MHz)



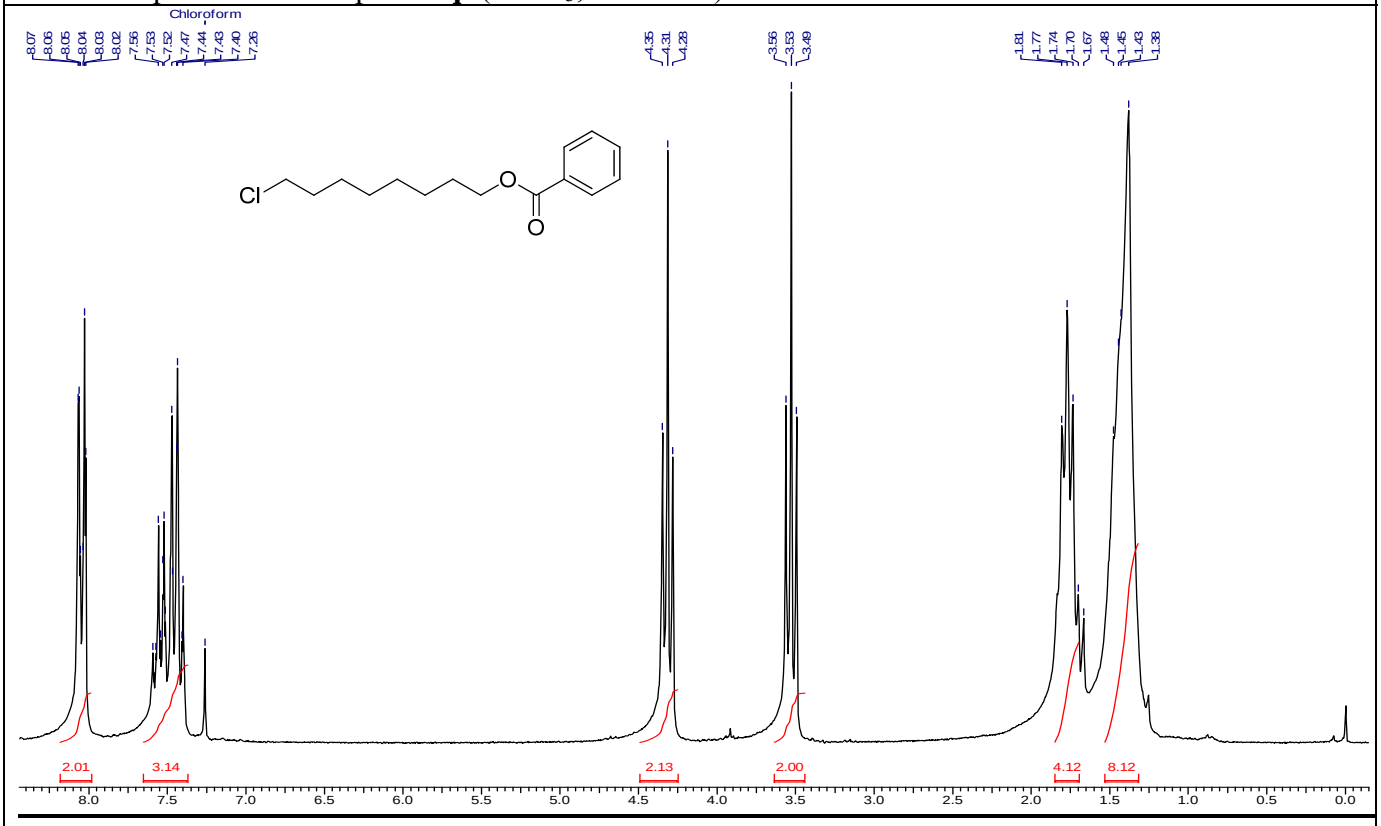
^{13}C NMR spectrum of compound **p''** ($CDCl_3$, 50 MHz)



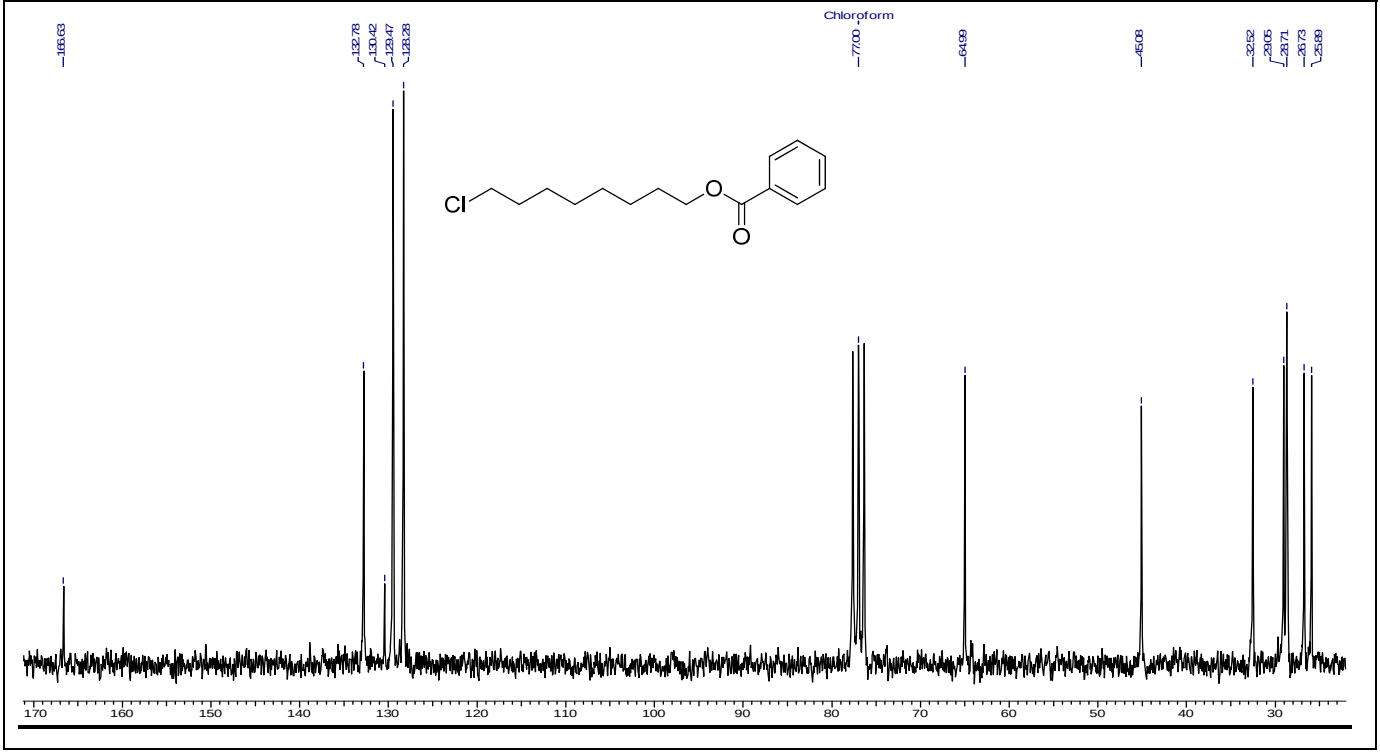
DEPT spectrum of compound **p''** ($CDCl_3$, 50 MHz)



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

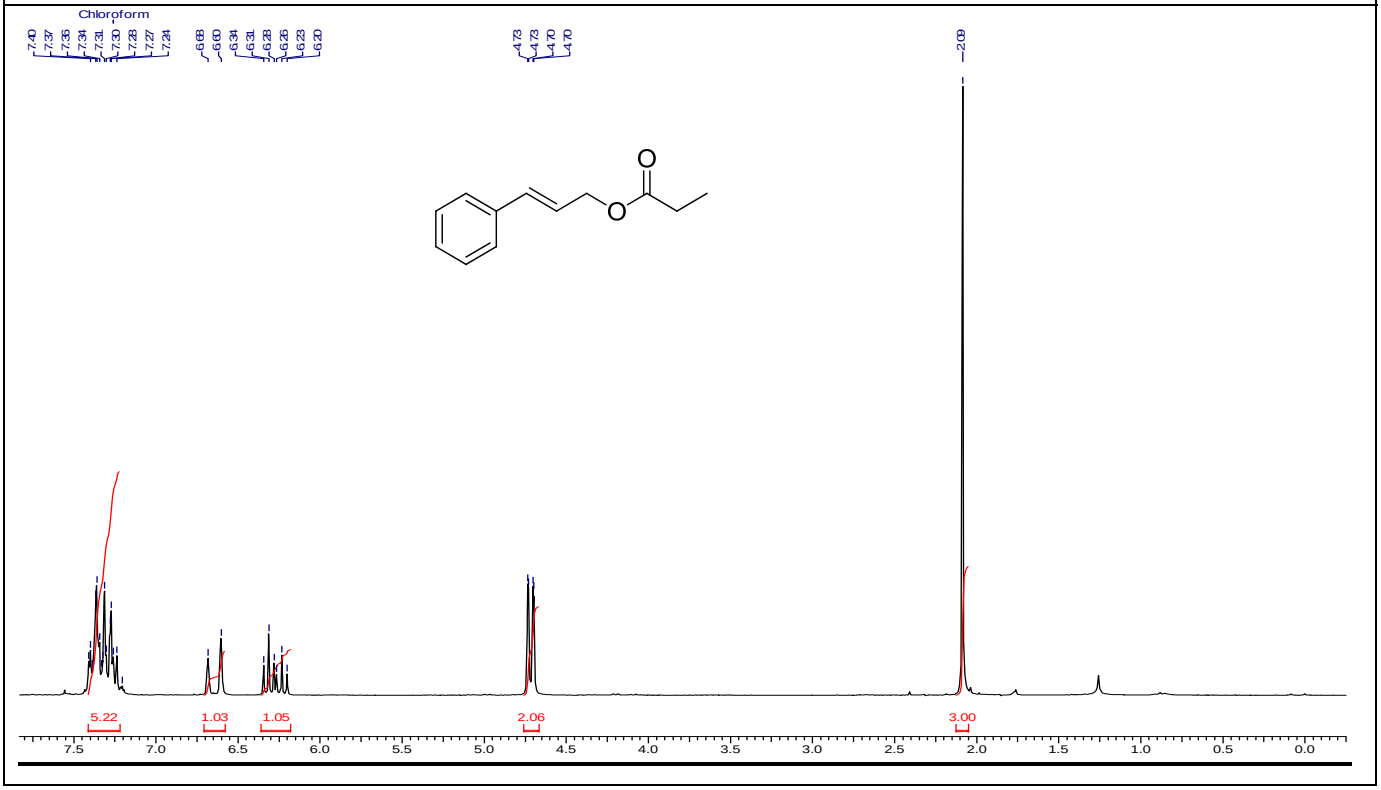


^{13}C NMR spectrum of compound **q'** ($CDCl_3$, 50 MHz)

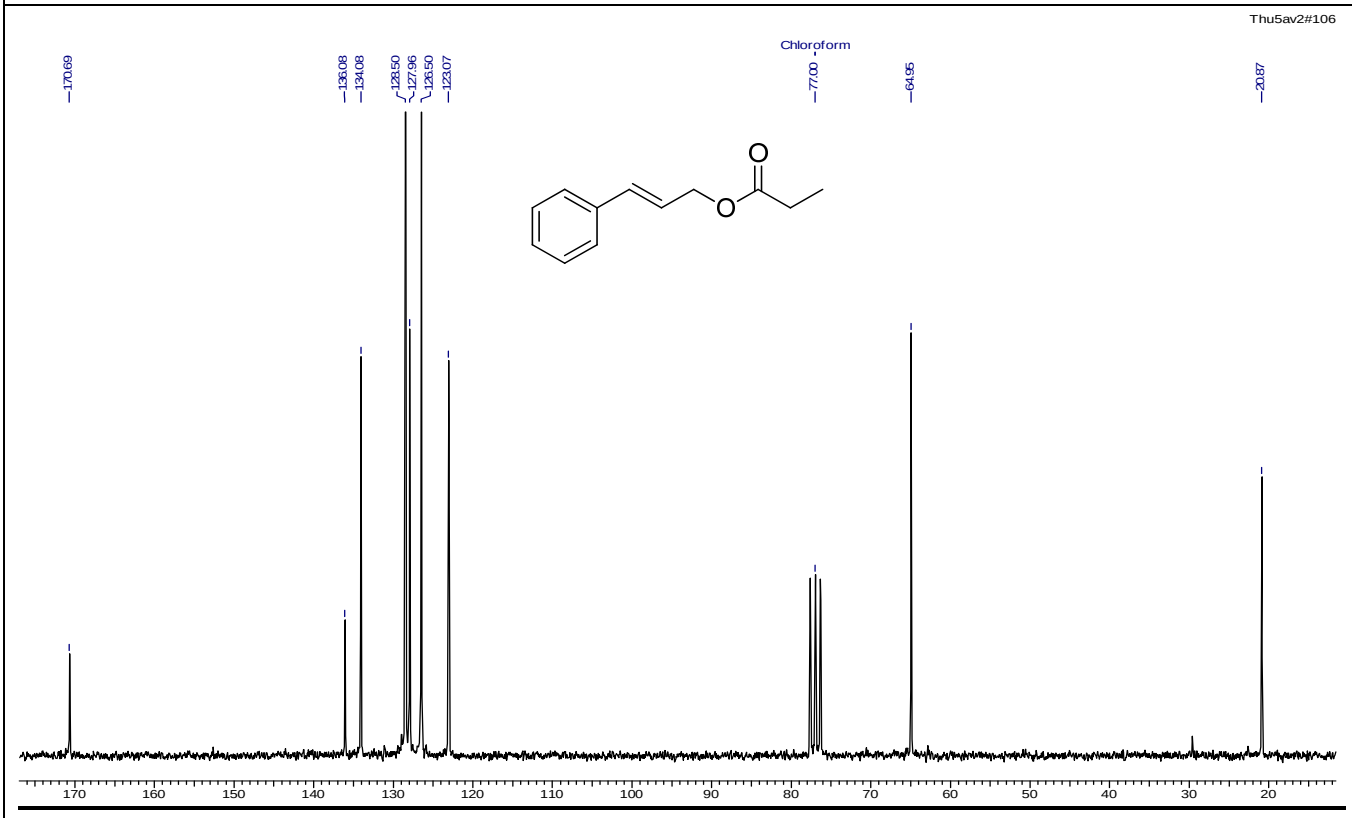


DEPT spectrum of compound **q'** ($CDCl_3$, 50 MHz)

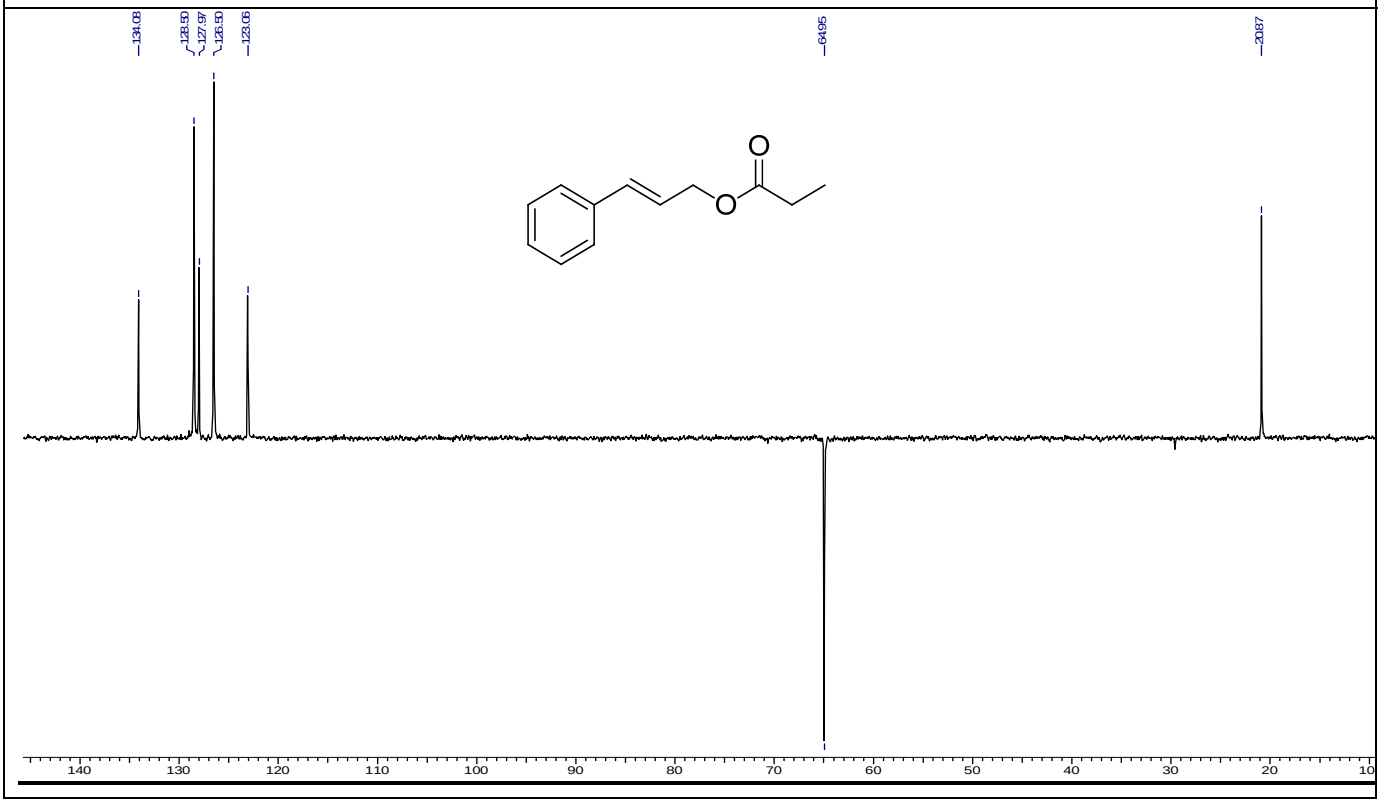
^{1}H NMR spectrum of compound **w'** ($CDCl_3$, 200 MHz)



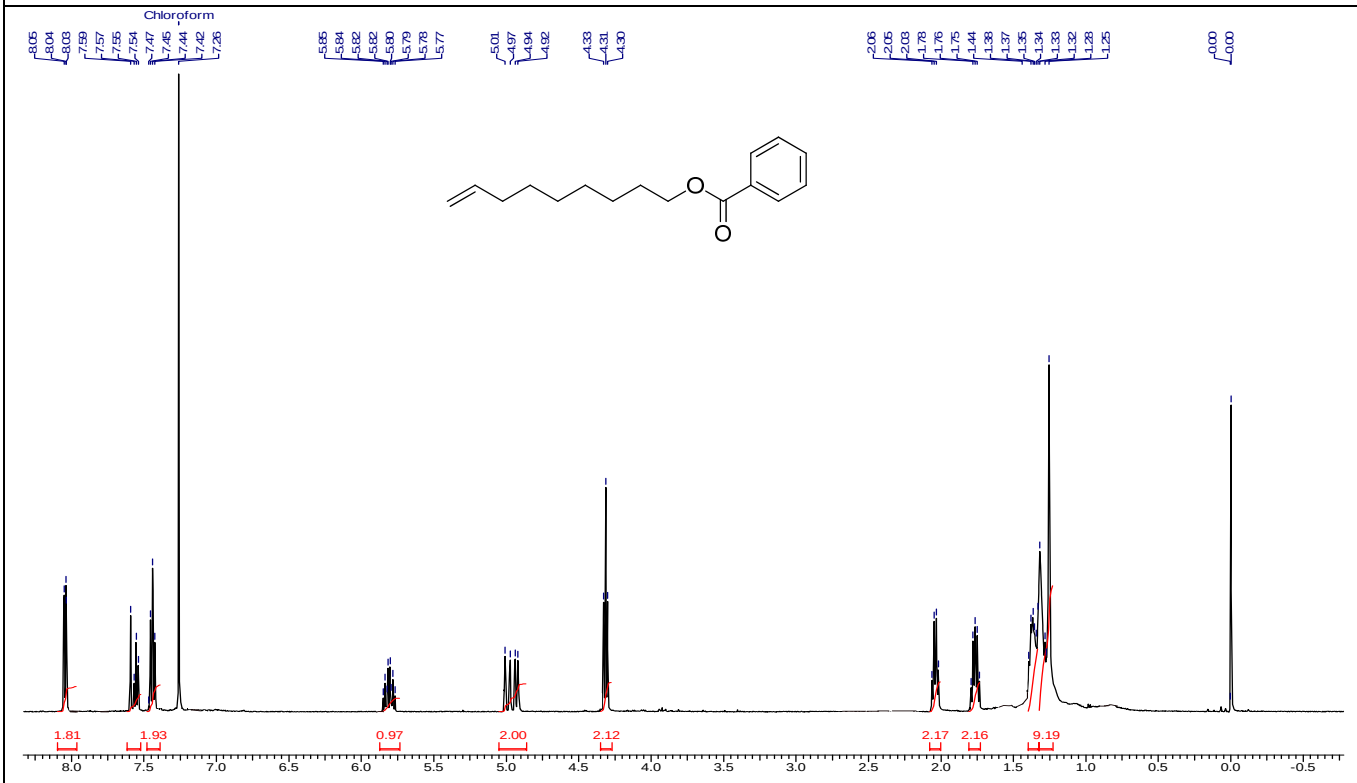
^{13}C NMR spectrum of compound **w'** ($CDCl_3$, 50 MHz)



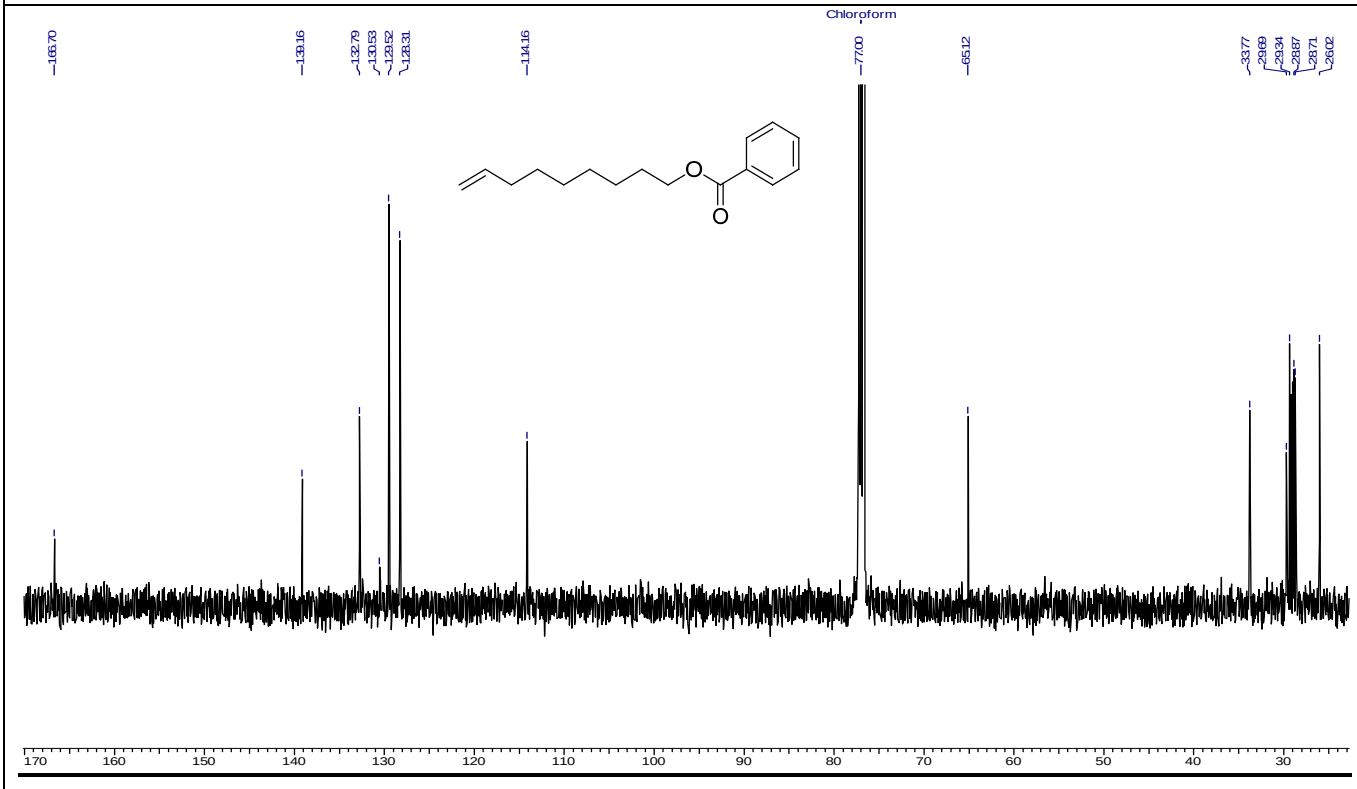
DEPT spectrum of compound **w'** ($CDCl_3$, 50 MHz)



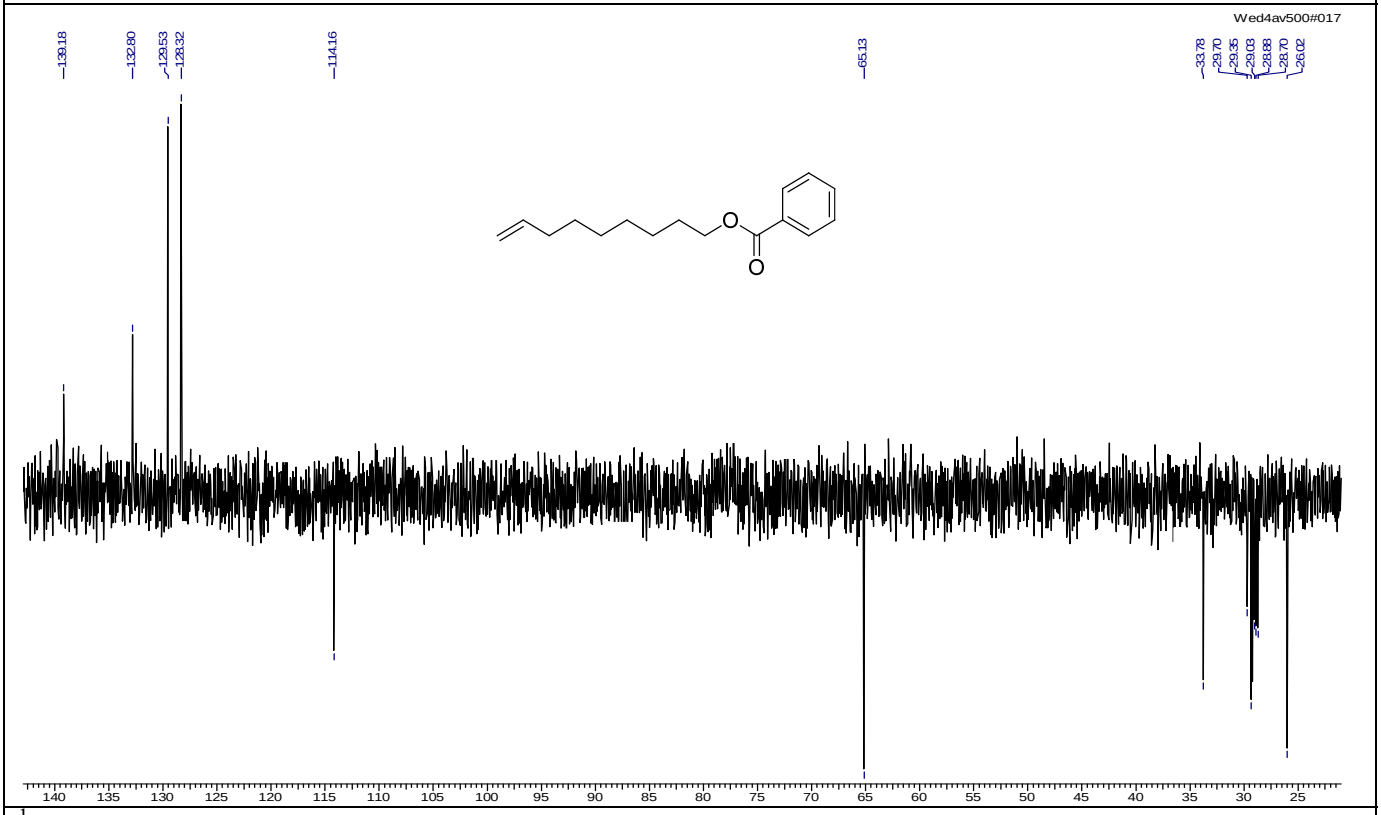
^{1}H NMR spectrum of compound **x'** ($CDCl_3$, 200 MHz)



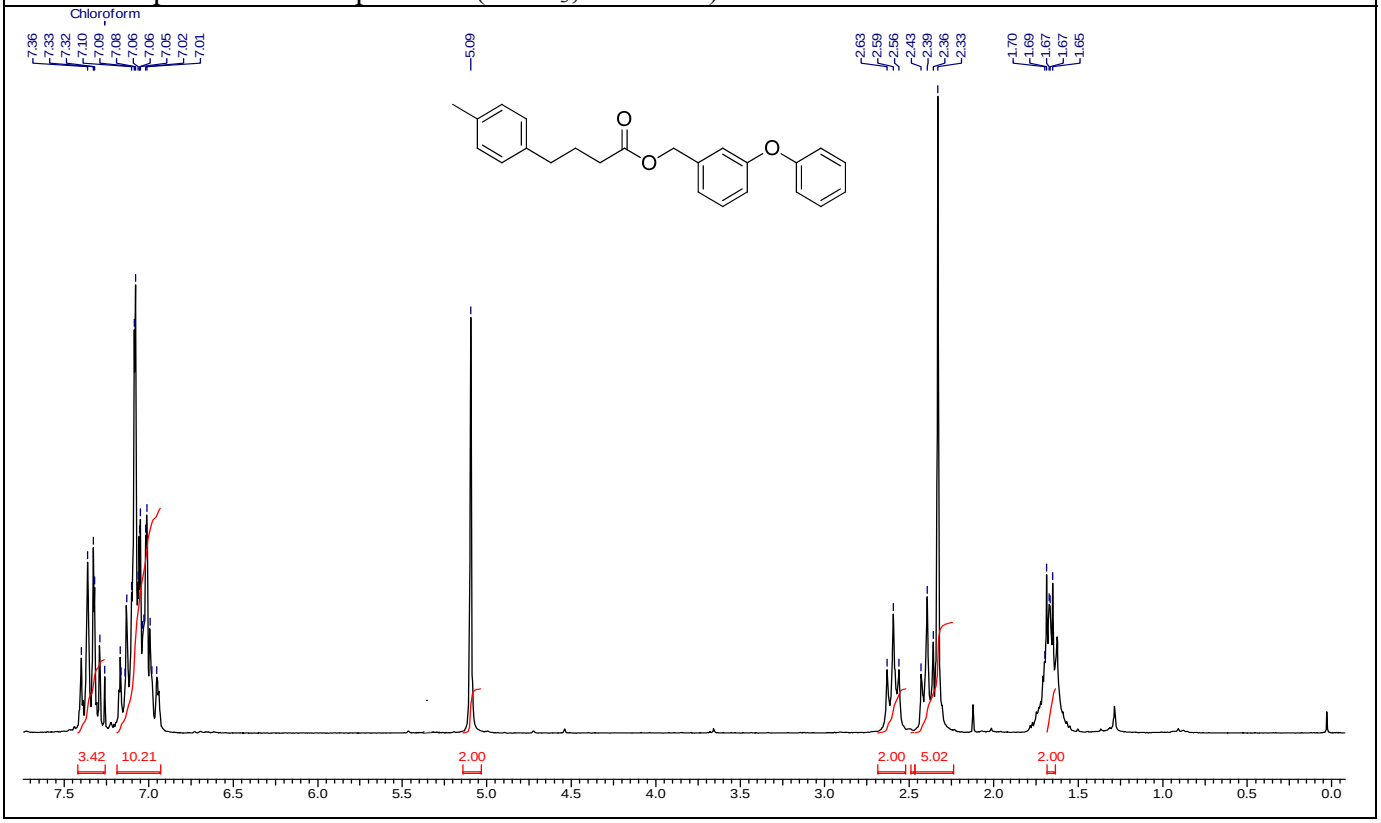
^{13}C NMR spectrum of compound **x'** ($CDCl_3$, 50 MHz)



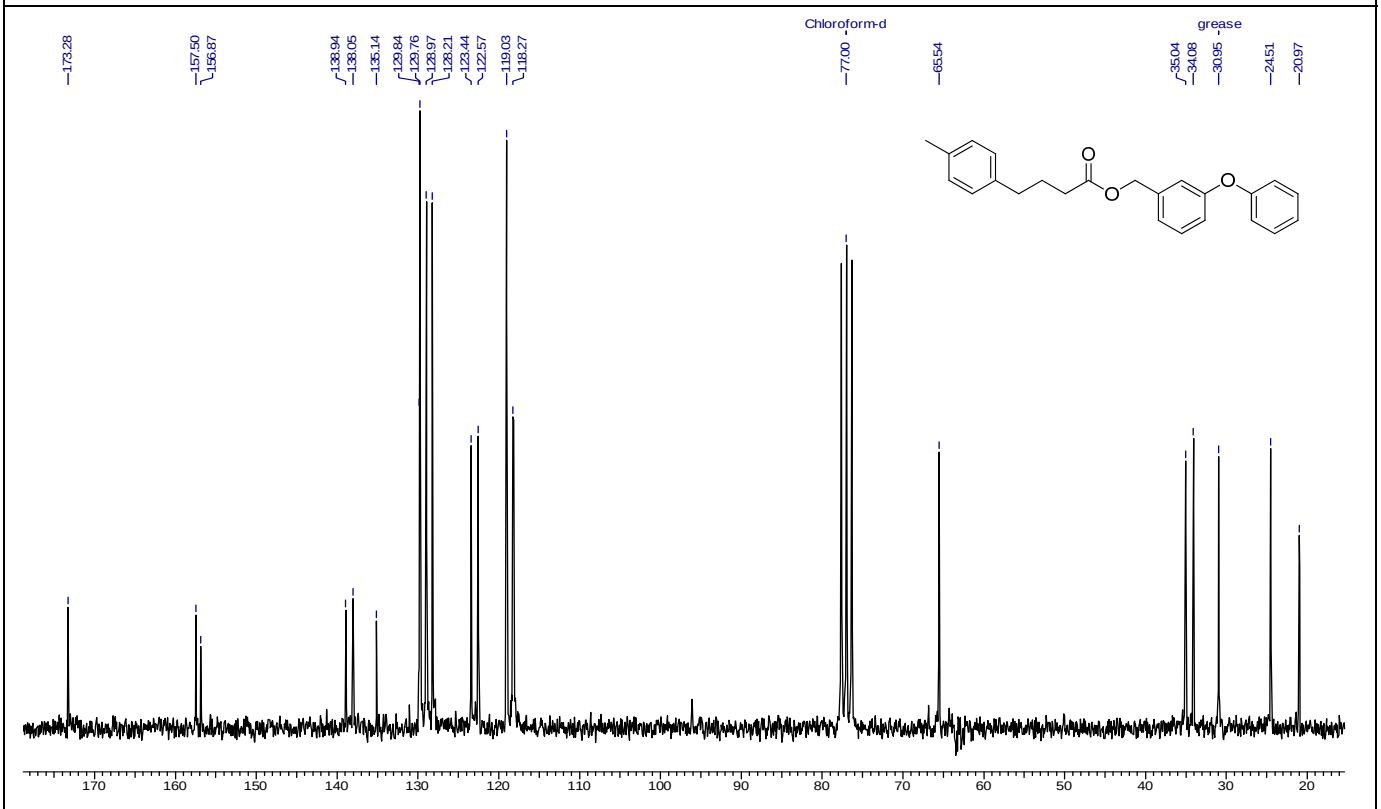
DEPT spectrum of compound **x'** ($CDCl_3$, 50 MHz)



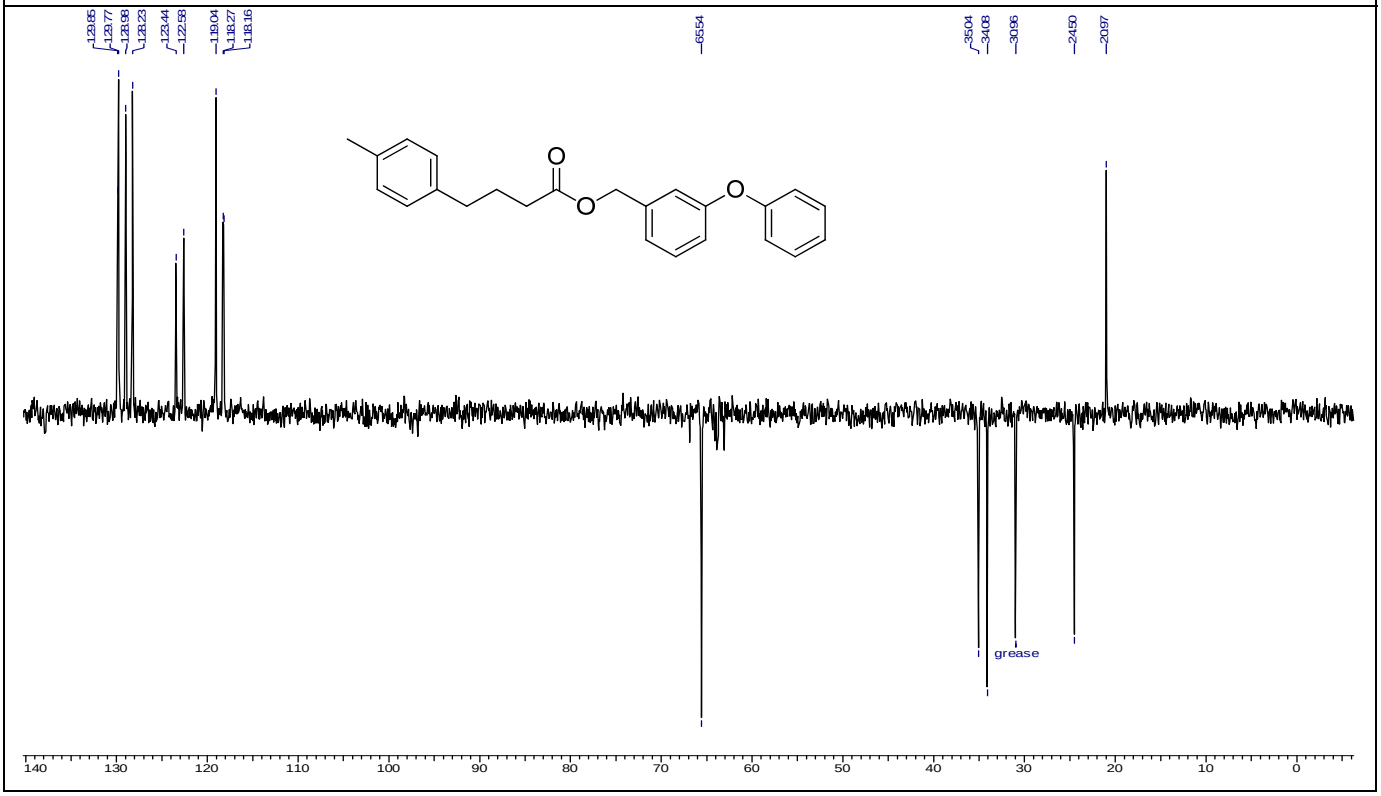
^{1}H NMR spectrum of compound **s'** ($CDCl_3$, 200 MHz)



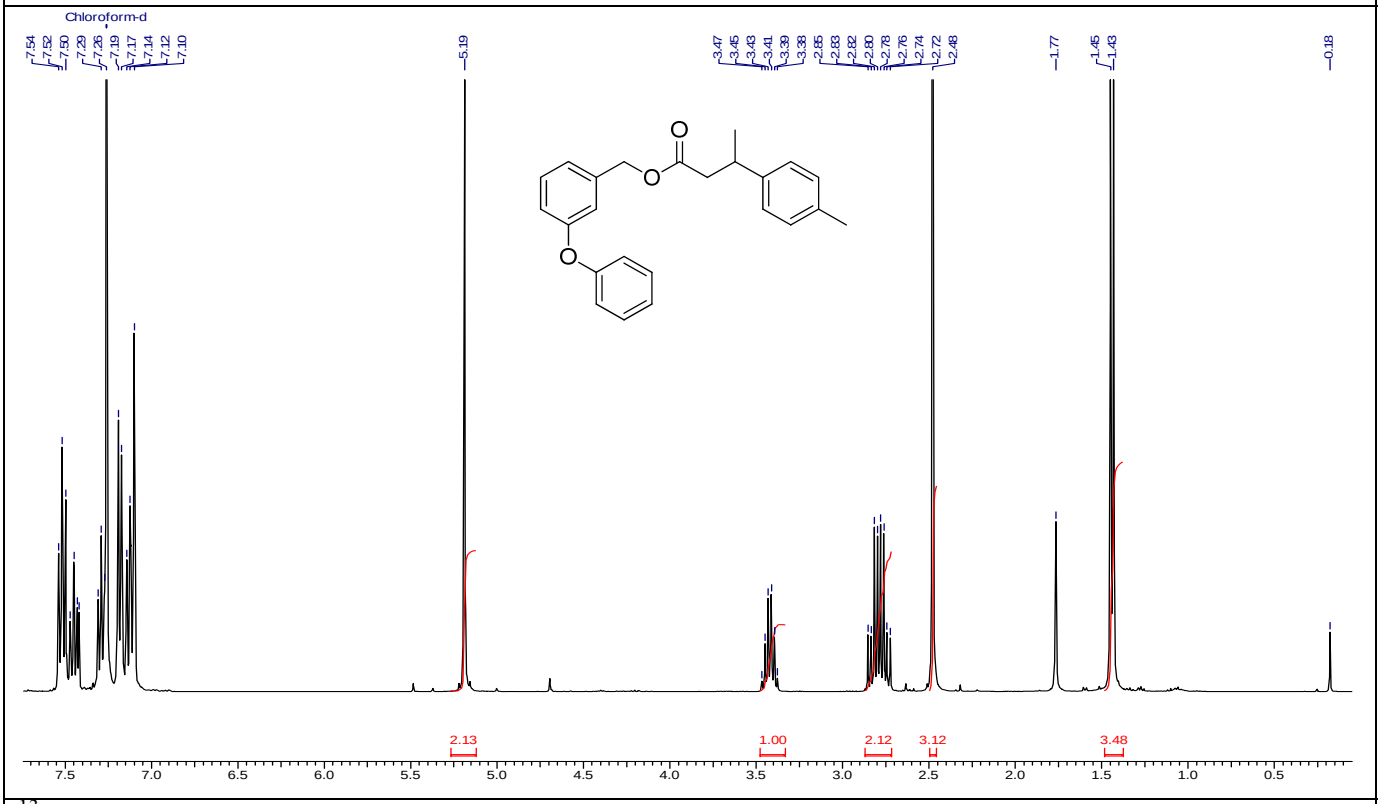
^{13}C NMR spectrum of compound **s'** ($CDCl_3$, 50 MHz)



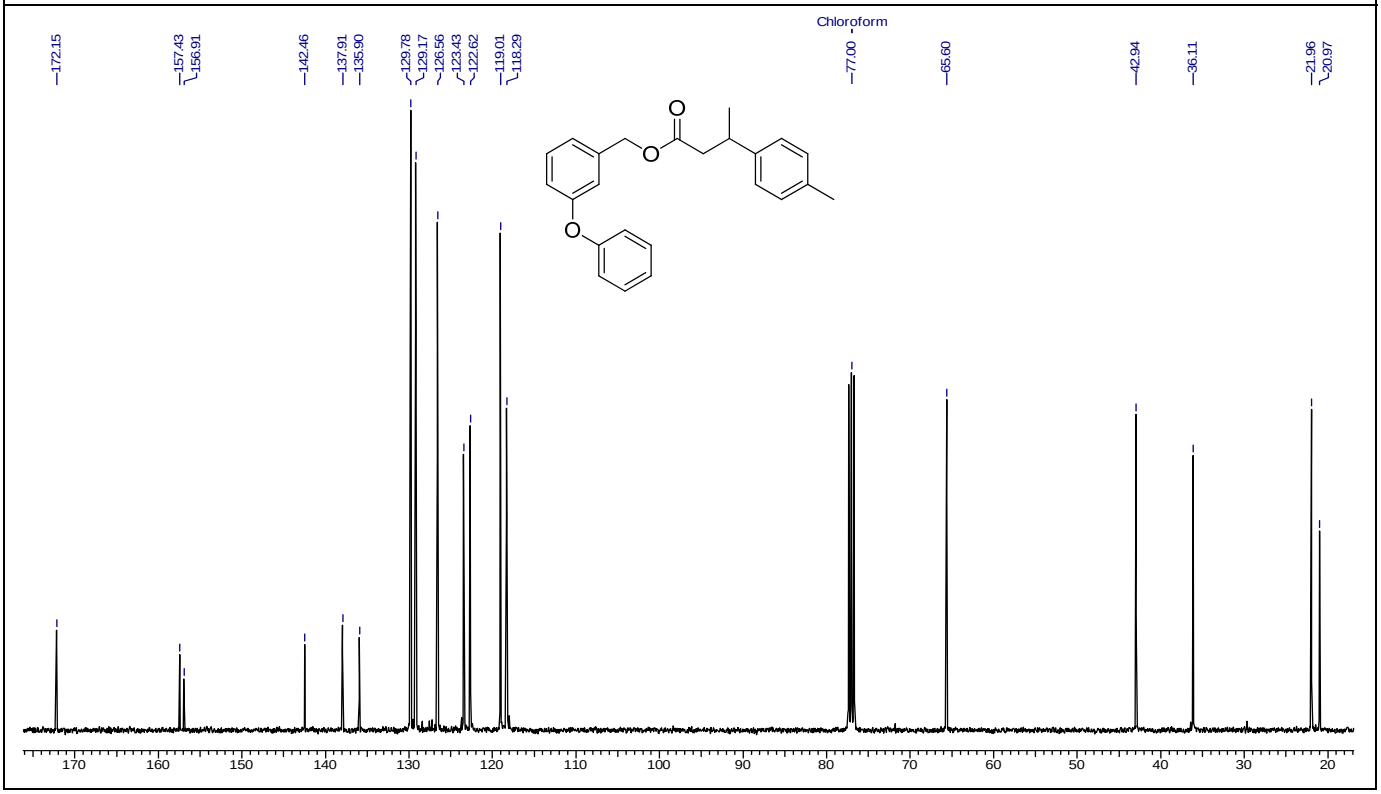
DEPT spectrum of compound **s'** ($CDCl_3$, 50 MHz)



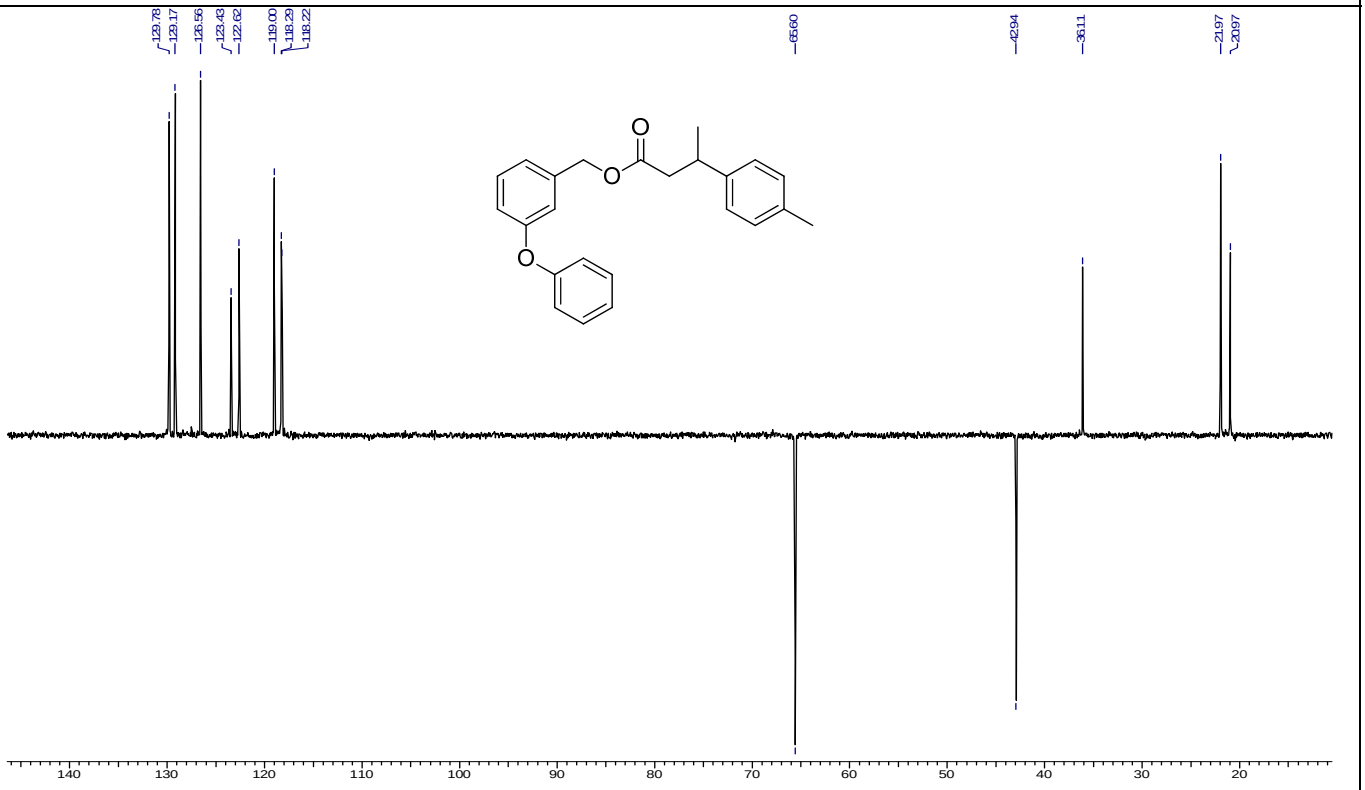
^{1}H NMR spectrum of compound **t'** ($CDCl_3$, 200 MHz)



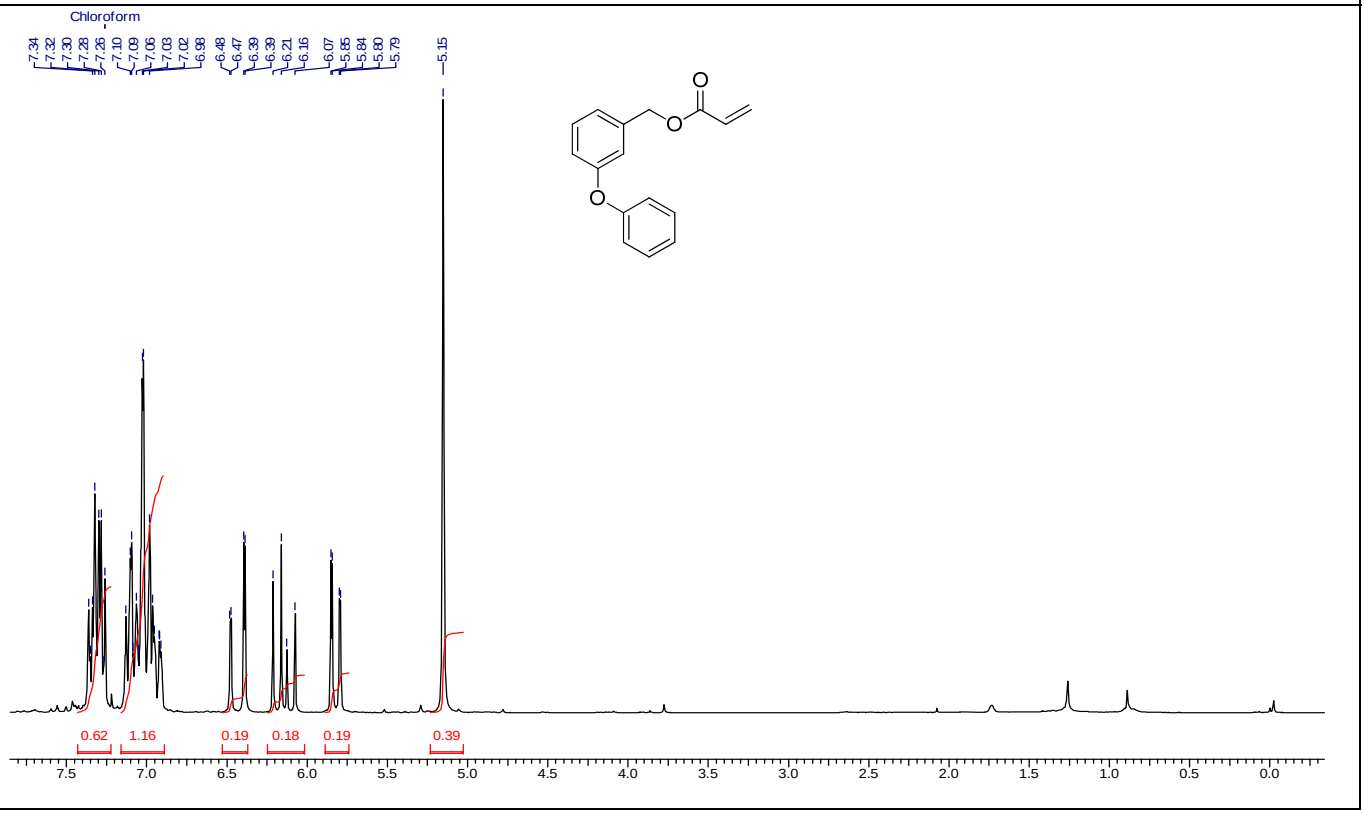
^{13}C NMR spectrum of compound **t'** ($CDCl_3$, 50 MHz)



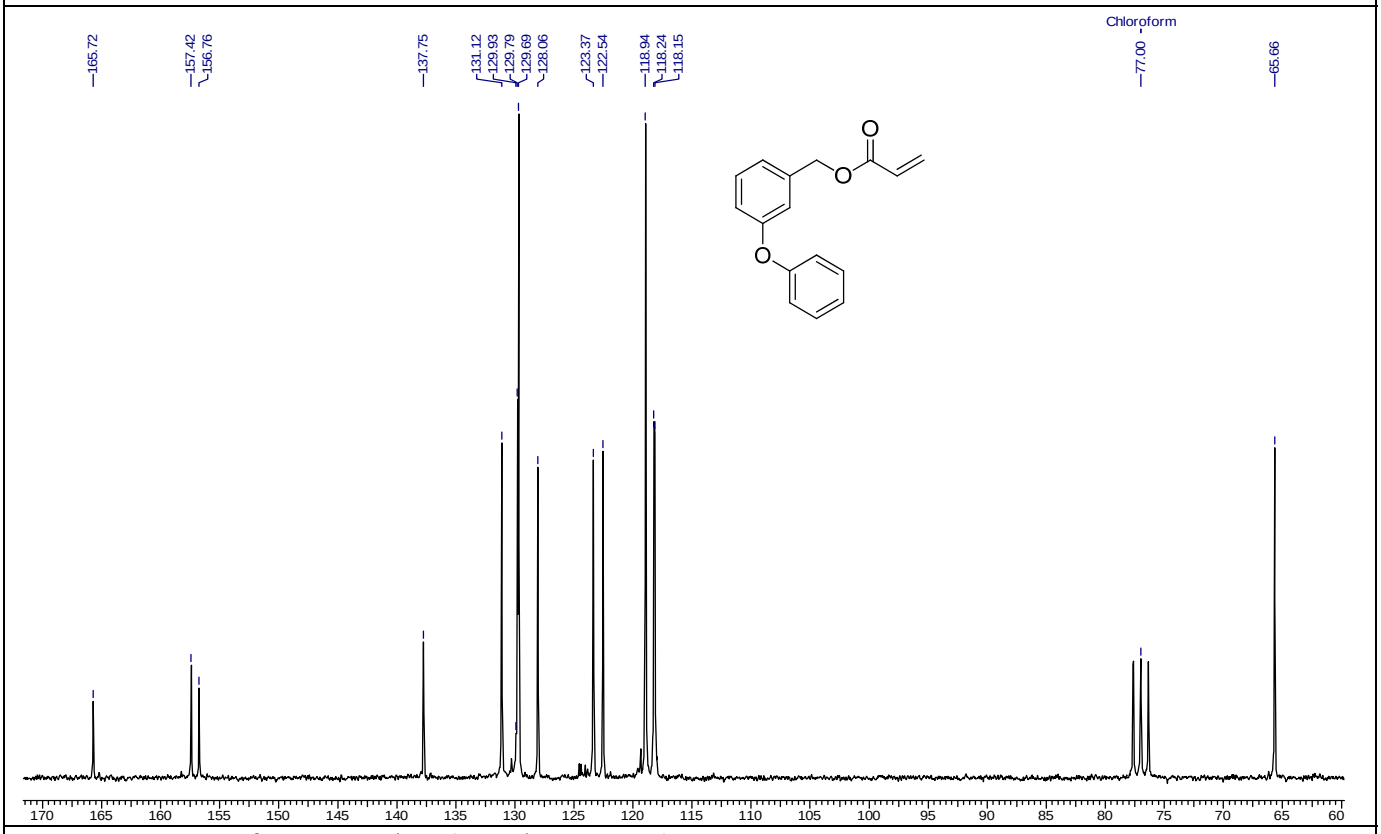
DEPT spectrum of compound **t'** ($CDCl_3$, 50 MHz)



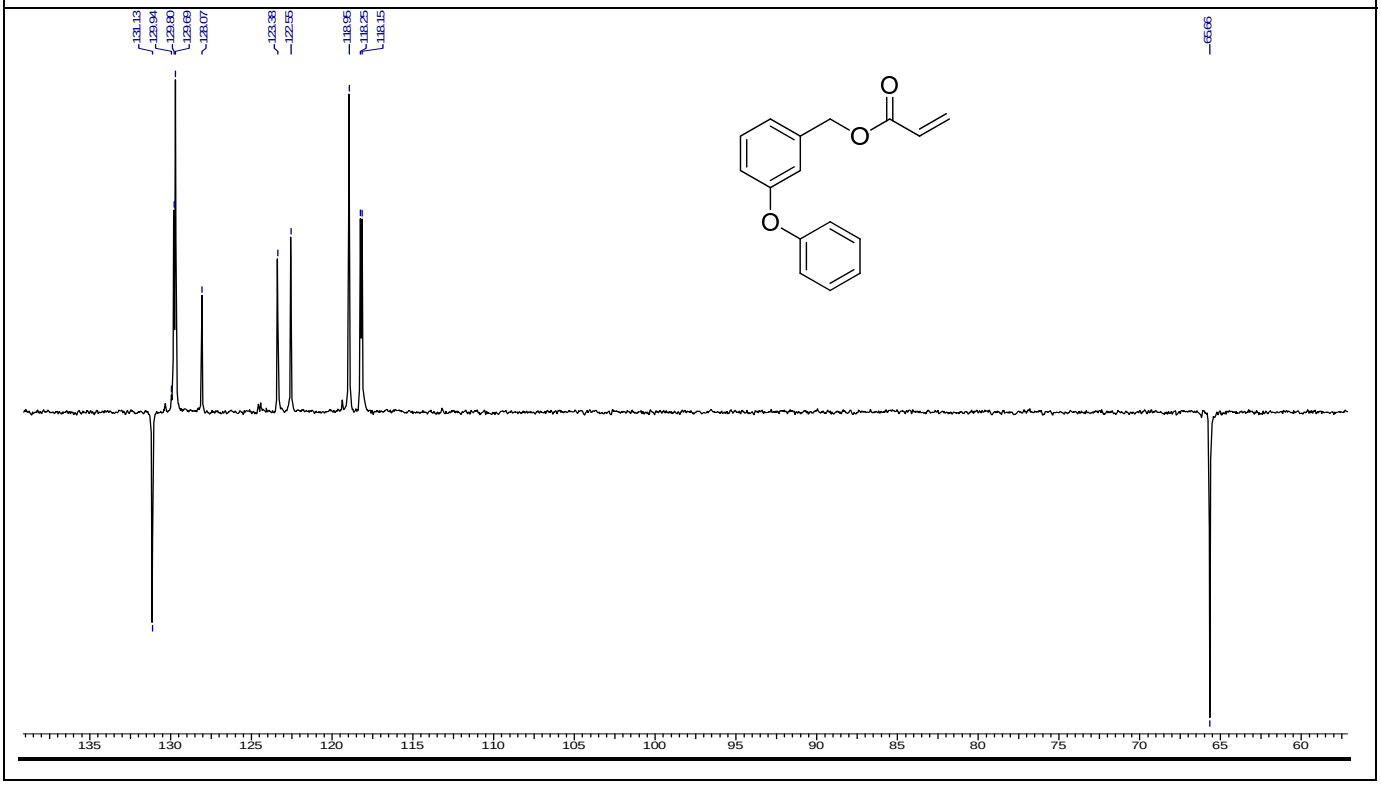
^{1}H NMR spectrum of compound **u'** ($CDCl_3$, 200 MHz)



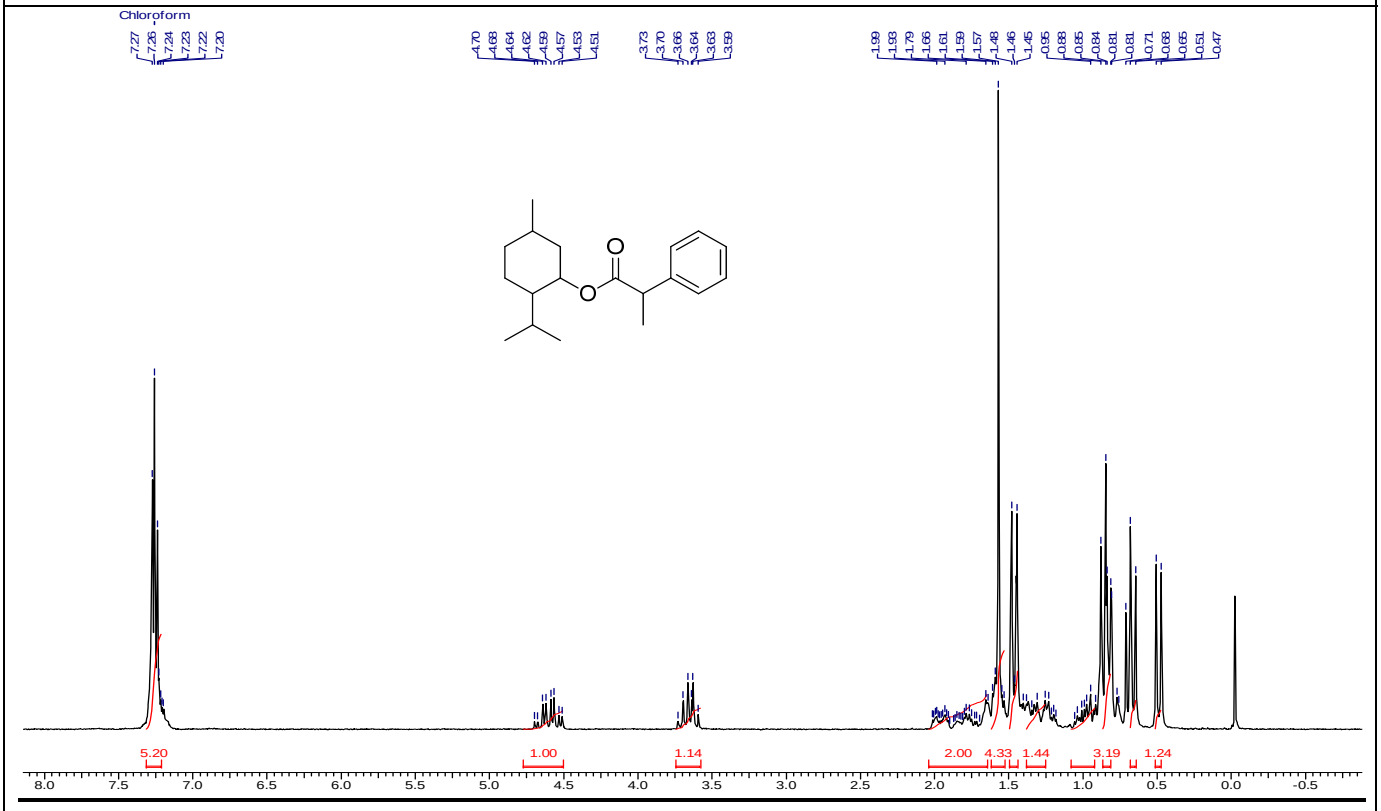
^{13}C NMR spectrum of compound **u'** ($CDCl_3$, 50 MHz)



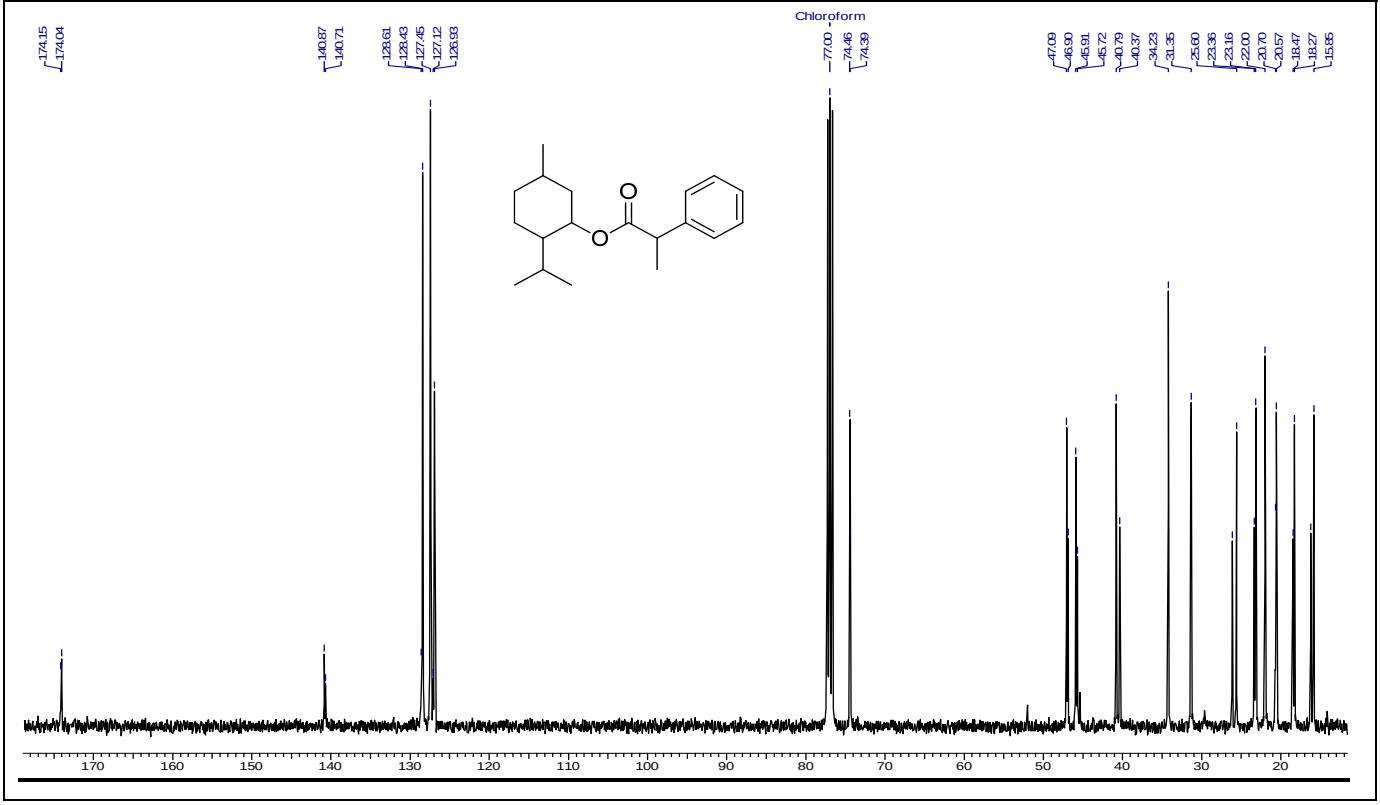
DEPT spectrum of compound **u'** ($CDCl_3$, 50 MHz)



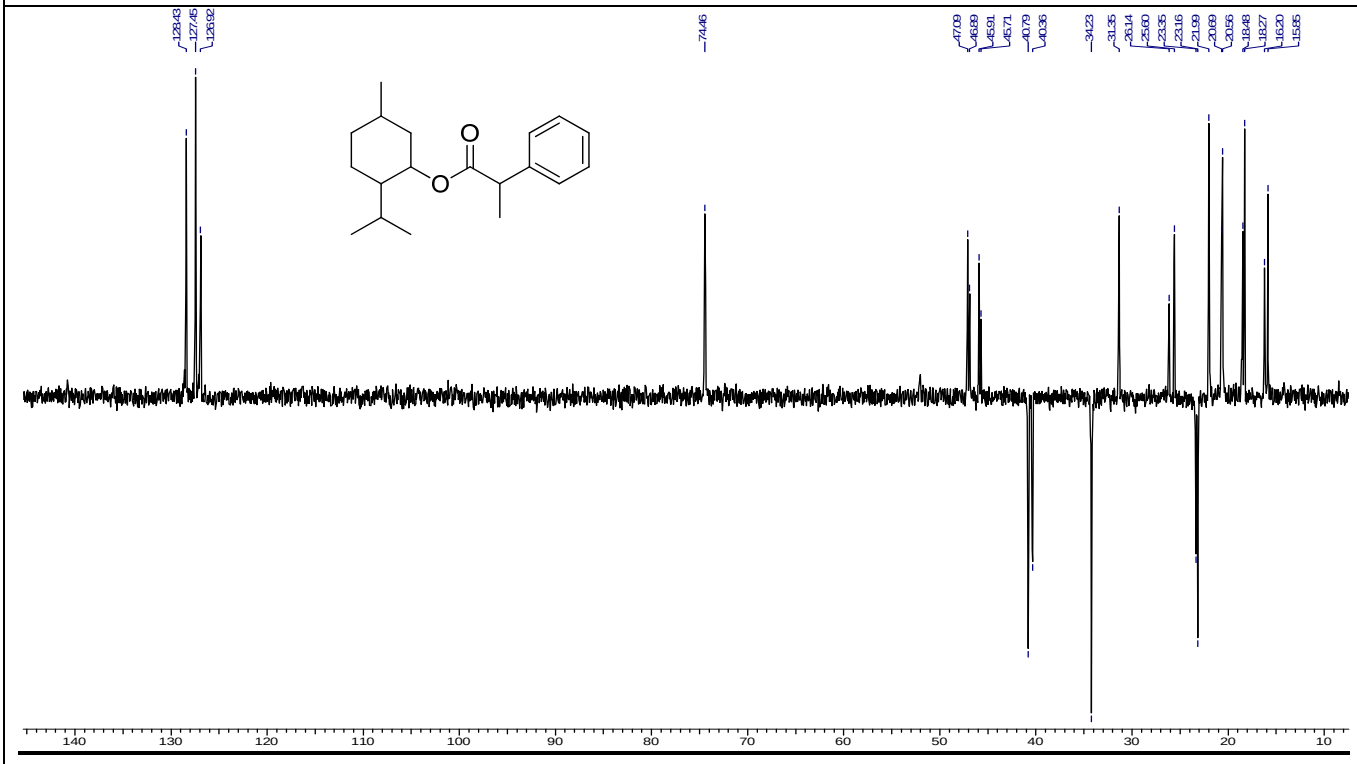
^{1}H NMR spectrum of compound **v'** ($CDCl_3$, 200 MHz)



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



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



2.3.5. References:

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3.1.1. Introduction:

The Grignard reaction is one of the most fundamental and convenient tool for the formation of carbon−carbon bonds hence is essential, widely performed reaction in organic synthesis. Till date Grignard reagents are extensively utilized organometallic species in total synthesis. Grignard reactions and reagents are named after the French chemist Victor Grignard, who was awarded the 1912 Nobel prize in chemistry for this work.[1]

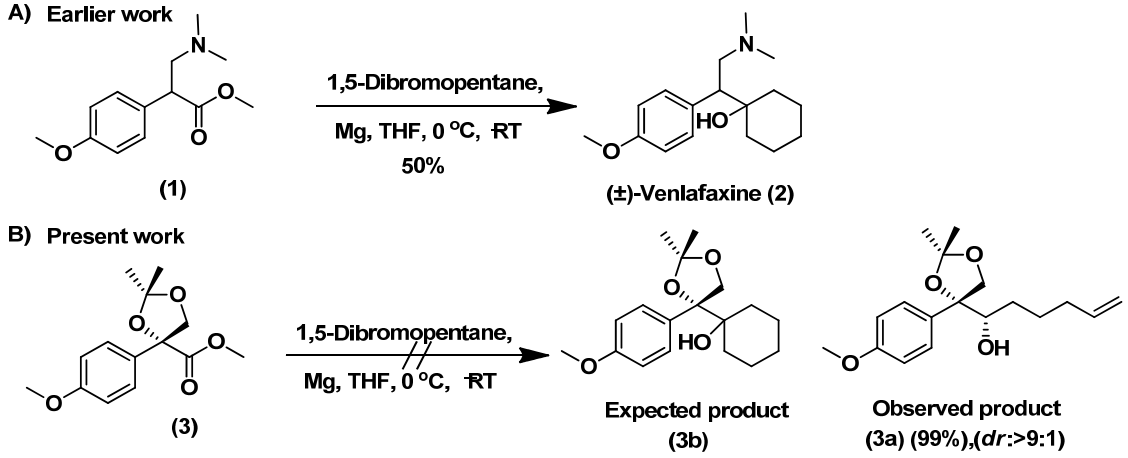
Grignard reagents are similar to ornanolithium reagents because both are strong nucleophiles that can form new carbon–carbon bonds. From its invention, a number of different kinds of transformations of original reaction are also reported in the literature.[2–7] Kohler *et al*.[2] reported about the reducing power of Grignard reagents which was earlier mistaken for enolization. Whitmore and co−workers[3a, 3b] reported abnormal Grignard reaction where they pointed out, this conversion most frequently depends upon addition of the reagent to the carbonyl group. On the other hand, speed of the addition reaction is greatly reduced due to steric conditions either around the carbonyl in the substrate or in the Grignard reagent, as a result slower side reactions of enolization, reduction and condensation may take place. Nenitzesku and co−workers[4] reported that the reaction between terminal di(bromomagnesio)alkanes and esters furnished cyclic alcohols and subsequent elimination in presence of acid resulted into cyclic olefins. Addition of di(halomagnesio)alkanes on various lactones as well as acid anhydrides furnished diol, spirolactone and Spiroether compounds, as observed by Canonne and co−workers. [5] Ferles [6] reported about the reaction of 1,4−di(bromomagnesio)butane on ethyl isonicotinate with a very low (<10%) yield for the annelation product. Canonne *et al*.[7] inspired from Ferles observation, had reported about steric effects in Grignard reactions with respect to alkyl halides like 1,5−dibromopentane and 1,4−dibromobutane which were used in the preparation of Grignard reagent. When these di(bromomagnesio)alkanes were treated with different aromatic and heteroaromatic carboxylic esters, produced secondary alcohol whose formation was postulated by an intramolecular reduction as the major product instead of the expected tertiary alcohol.

Various carboxylic esters have been studied by Canonne and co−workers in order to determine which factors affect the product distribution. For that purpose not only the addition products but also those of reduction and enolization were also investigated. Largely different product distributions were observed on the action of various carboxylic esters with

1,4−di(bromomagnesio)butane and its homologue 1,5−di(bromomagnesio)pentane. The much larger yields of reduction product with the latter are the evidence for the structural geometric requirements for the annelation step.

3.1.2. Results and discussion:

In accordance with one of the total synthesis project from this lab, a very practical synthesis of commercially important antidepressant drug (±)−venlafaxine (**2**) was reported.[8] Here, the aminoester **1** was treated with Grignard reagent derived from 1,5−dibromopentane to furnish product **2** in 50% yield (Scheme−1). So in order to increase overall yield and render the process more efficient an enantioselective approach for synthesis of the drug was planned, where Grignard reaction on acetonide protected ester **3** was carried out with the Grignard

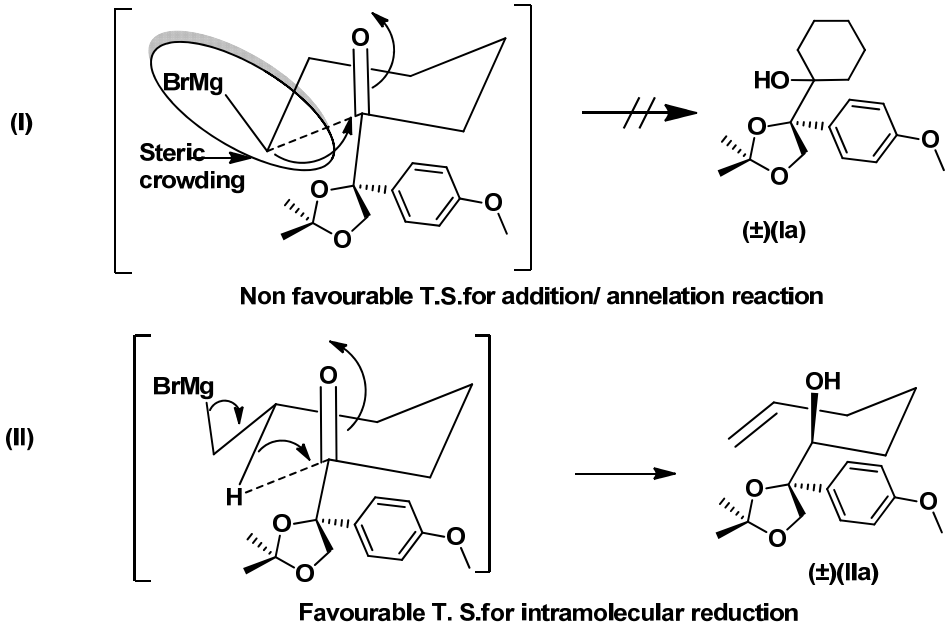


Scheme−1: Observation of unusual Grignard reaction

reagent prepared from 1,5−dibromopentane in presence of THF as a solvent with the hope to get alcohol **3b**. Surprisingly it did not furnish the desired addition product **3b**. After careful observation and characterization of the product formed it was found to contain a secondary alcohol having terminal double bond. It is clear that instead of expected nucleophilic addition, it underwent simultaneous elimination−reduction sequence of reactions (Scheme−1). Almost quantitative formation of compound **3a** over the annelation product **3b** was the reason to investigate the observed result in details.

This could be explained by considering two transition states as shown in (Figure-1). After the first nucleophilic addition of di(bromomagnesio)pentane on carbonyl carbon of the acetonide protected ester, there are two alternative possibilities: **I)** second intramolecular

nucleophilic addition reaction on ketone which is now comparatively more electrophilic than starting ester and **II)** instead of the expected addition reaction, intramolecular hydride transfer leading to elimination at terminal carbon–carbon bond, to give straight chain secondary alcohol containing terminal double bond as the only product and not the expected tertiary cyclohexanol. The steric hindrance of acetonide functionality at benzylic center positioned alpha to the ester resulted in hydride transfer preferentially from one



Figure−1: Transition state model for unusual Grignard reaction

face. This hydride shift could be either from alpha or beta face with respect to orientation of the acetonide steric bulk hence is responsible for diastereoselectivity observed in present reaction. It is believed that this transformation proceeds through six membered, stable and favourable transition state (**II**), which thus explains the outcome of the reaction. This rigid and sterically hindered system blocks second nucleophilic attack of Grignard reagent on more electrophilic intermediate ketone as compared to hydride transfer so the formation of the annelation product was not observed as shown in transition state model (**I**). To understand proposed hypothesis on even firmer ground, it was decided to undertake DFT calculations.

DFT calculations were done at the PBE/TZVP level of theory in order to understand the mechanism as well as the formation of the addition (**VIII**) and unusual (**VI**) products of the reaction. In the first step the nucleophilic addition of the Grignard reagent [9] on the carbonyl

carbon of acetonide protected ester I- the activation energy barrier *via* transition state II was found to be 17.3 kcal/mol (ΔG). The second step of the reaction is much more important,

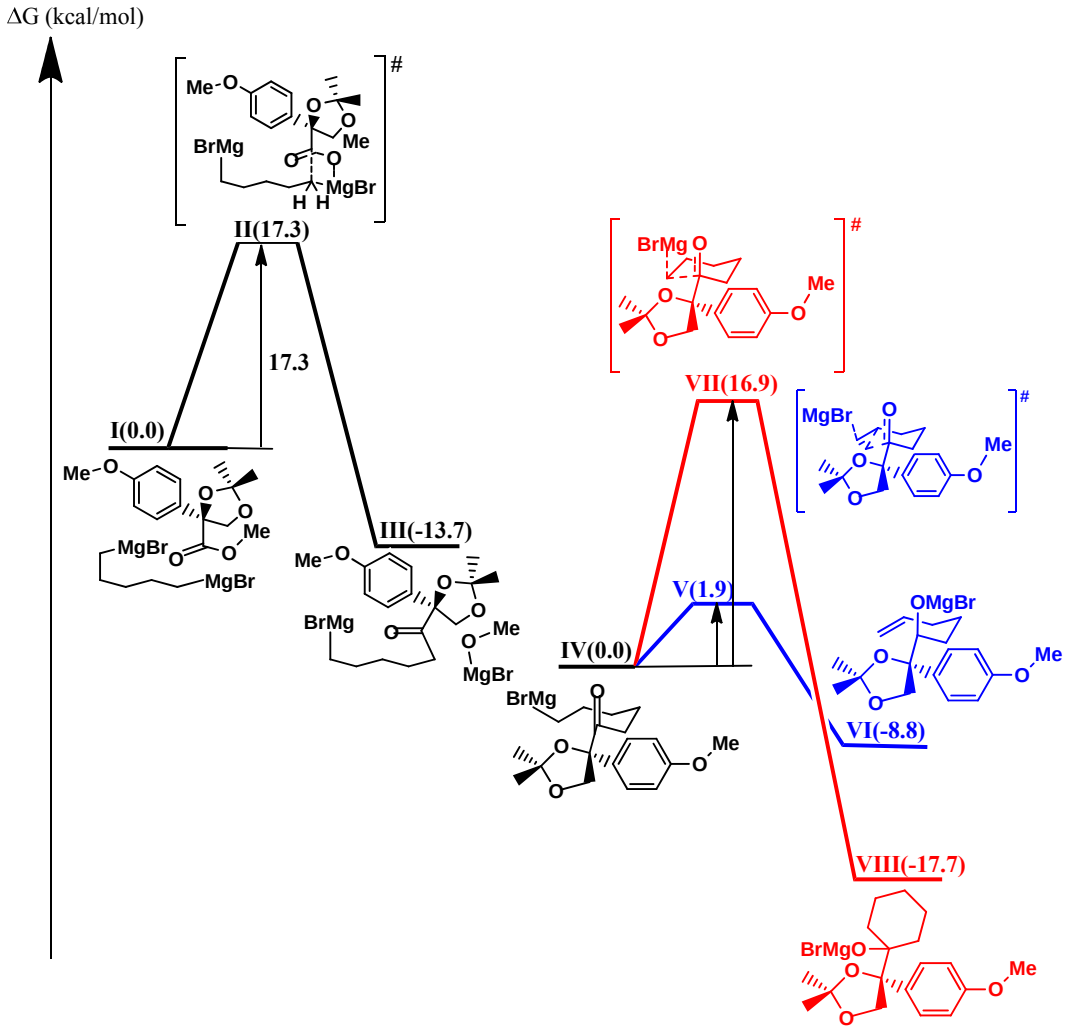
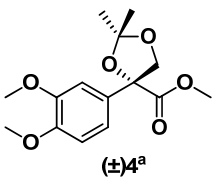
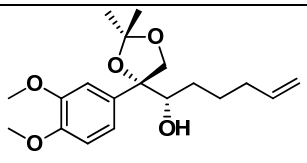
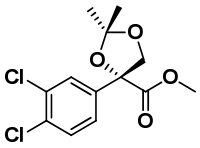
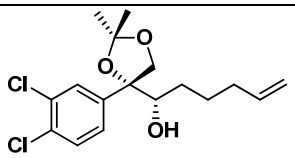
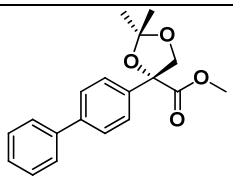
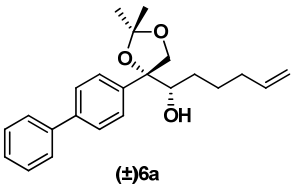
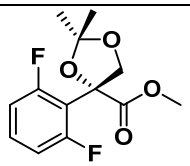
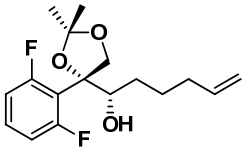
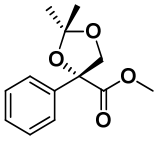
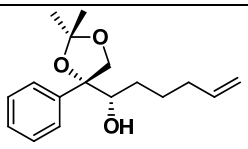
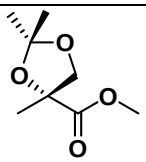
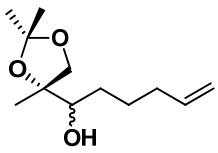


Figure-2.: DFT calculations comparing free energy profiles *via* two different transition states.

because there are two possibilities– (i) another nucleophilic addition of Grignard to the more electrophilic carbonyl carbon leading to the formation of the (**VIII**) or (ii) the hydride transfer to the carbonyl carbon of ketone to give the straight chain secondary alcohol containing terminal double bonds (**VI**). From our DFT study, two transition states **V** and **VII** were found corresponding to the two different pathways starting from the same reactant geometry **IV** (Figure-2). In case of the addition product (**VIII**), the energy barrier was found to be 16.9 kcal/mol whereas for the unusual product (**VI**) the energy barrier was reduced by almost 15.0 kcal/mol. Therefore, the second pathway where the energy barrier was found to be only 1.9 kcal/mol is kinetically much more favourable and leads to the formation of the undesired

straight chain secondary alcohol as the major product. This low barrier suggested that in this reaction, the eventual outcome of the reaction is governed by the kinetics of the reaction.

Table−1: Unusual Grignard reaction of acetonide protected ester substrates

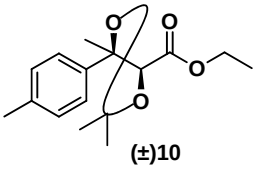
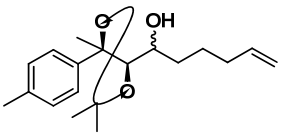
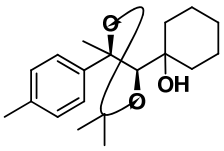
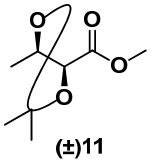
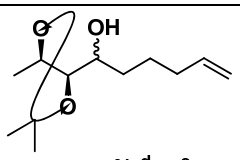
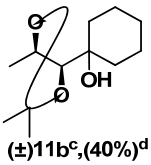
Entry no.	Substrate ester	Unusual product	Yield (%)[b] and *dr*[e]
1.	 (±)4[a]	 (±)4a	(99) (*dr*: >9.5:0.5)
2.	 (±)5[a]	 (±)5a	(95) (*dr*: >9:1)
3.	 (±)6[a]	 (±)6a	(98) (*dr*: >9:1)
4.	 (±)7[a]	 (±)7a	(99) (*dr*: >9:1)
5.	 (±)8[a]	 (±)8a	(98) (*dr*: >9:1)
6.	 (±)9[a]	 (±)9a	(98) (*dr*: 1:1)

a) Reaction conditions: 1,5−Dibromopentane, Mg, THF, 0 ^{o}C−RT, 5h, b) Product yields calculated after column chromatographic purification, e) *dr*: diastereomeric ratio determined by ^{1}H−NMR analysis, f) Relative stereochemistry was determined by extensive chemical transformations into known compound (*R*)-venlafaxin, described in Chapter-3, section-3.

The reaction of *in situ* generated Grignard reagents obtained from terminal dihalogenated alkyl compounds is systematically studied on a diverse range of aromatic and aliphatic carboxylic ester compounds and the results obtained are depicted in Table 1.

Initially the Grignard reactions of the reagent prepared from 1,5−dibromopentane, [di(bromomagnesio) pentane] were studied. The observation that the steric crowding present at alpha position of the ester functionality favours the formation of intramolecularly reduced product in almost quantitative yields (entries 1−6) is found to be consistent. The lowering of diastereoselectivity was observed in case of the acetonide protected aliphatic carboxylic ester **9**, prepared from methyl methacrylate (entry−6), where in under the similar reaction conditions the reduced product **9a** was formed in 98% yield and gives diastereomeric mixture (1:1). Thus, this observation proves that reaction gave excellent yields not only in case of sterically crowded aromatic carboxylic esters but also in case of aliphatic carboxylic esters.

Table−2: Unusual Grignard reaction of acetonide protected ester substrates

Entry no.	Substrate ester[a]	Unusual product Yield (%)[b] and *dr*[e]	Addition product Yield (%)[b] and *dr*[e]
1.	 (±)10	 (±)10a[c], (53%)[d], *dr*[e]:8:2	 (±)10b[c],(43%)[d]
2.	 (±)11	 (±)11a (46%)[d],*dr*[e]:7:3	 (±)11b[c],(40%)[d]

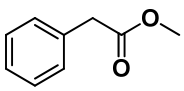
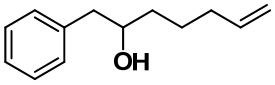
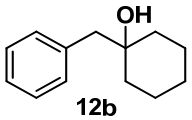
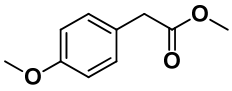
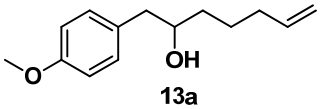
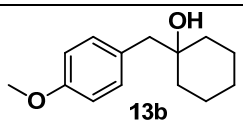
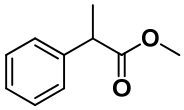
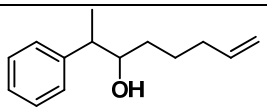
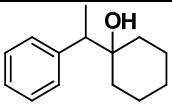
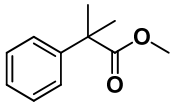
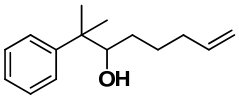
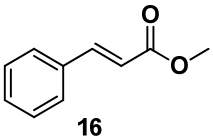
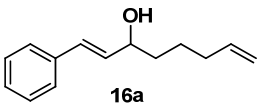
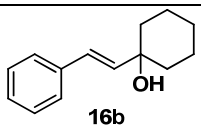
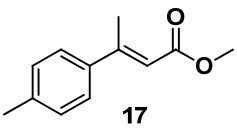
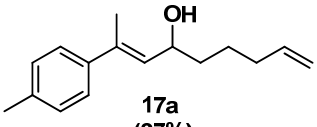
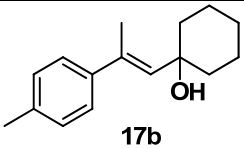
a) Reaction conditions: 1,5−Dibromopentane, Mg, THF, 0 ^{o}C−RT, 5h, b) Product yields calculated after column chromatographic purification, c) Unable to separate two alcohols by column chromatography so acetate protection of secondary alcohol its purification from respective cycloalkanol and subsequent deprotection was carried out thus pure products isolated in order to obtain data, d) Yield and *dr* calculated over two steps, e) *dr*: diastereomeric ratio determined by ^{1}H−NMR analysis.

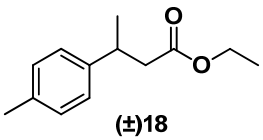
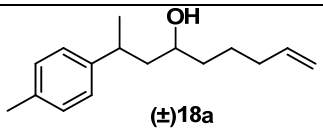
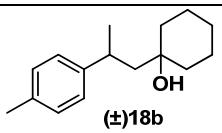
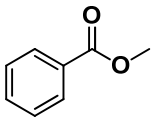
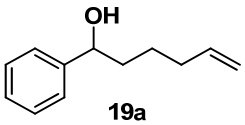
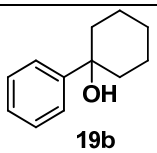
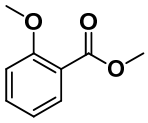
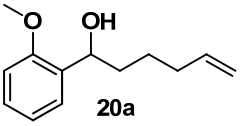
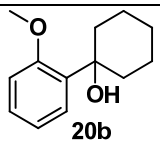
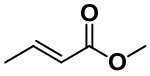
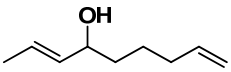
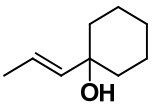
When acetonide protection is placed on secondary carbon alpha to the carboxylic carbon of esters **10** and **11** and not at the benzylic position as shown in (entries-1, 2: Table−2), it results in notable decrease in the yields of respective reduced products **10a** and **11a**. From the above

observations, position of acetonide functionality on tertiary carbon proved to be critical and essential, for higher diastereoselectivity.

In addition to above results, number of other carboxylic esters were examined under the similar Grignard reaction conditions. The decrease in steric bulk at benzylic position alpha to the starting ester substantially decreases yield of the reduced product as summarized in (Table−3). When methyl ester of phenyl acetic acid **12**, (entry−1), and its *para* methoxy derivative **13** (entry−2), were treated under the above mentioned conditions at RT, furnished alcohols **12a** and **13a** were obtained in 32% and 37% yields respectively.

Table−3: Exploration of unusual Grignard reaction

Entry no.	Substrate ester	Unusual Product Yield[b] (%) and *dr*[c]	Addition product Yield (%)
1.	 **12**	 **12a (32%)**	 **12b (62%)**
2.	 **13**	 **13a (37%)**	 **13b (60%)**
3.	 **(±)14**	 **(±)14a (68%) *dr*:(6:4)**	 **(±)14b (29%)**
4.	 **15**	 **15a (89%)**	----- **(0%)**
5.	 **16**	 **16a (30%)**	 **16b (67%)**
6.	 **17**	 **17a (37%)**	 **17b (58%)**

7.	 (±)18	 (±)18a (29%) *dr*:(6:4)	 (±)18b (62%)
8.	 19	 19a (77%)	 19b (22%)
9.	 20	 20a (68%)	 20b (30%)
10.	 21	 21a (33%)	 21b (63%)

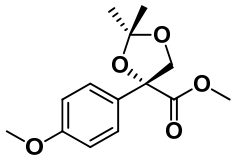
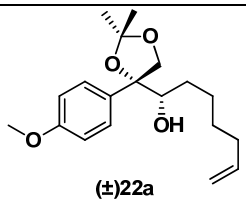
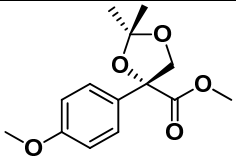
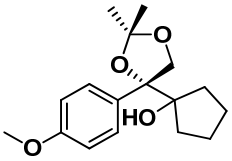
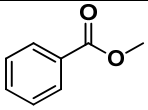
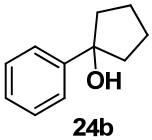
a) Reaction conditions: 1,5−Dibromopentane, Mg, THF, 0 ^{o}C−RT, 5h, b) Product yields calculated after column chromatographic purification, e) *dr*: diastereomeric ratio determined by ^{1}H−NMR analysis.

Introduction of one methyl group at benzylic position as shown in compound **14**, (entry−3), resulted significant enhancement in the yield of reduced product **14a**, upto 68% with 1:1 diastereoselectivity. Presence of two methyl groups at benzylic position of starting ester **15**, [21] (entry−4), resulted in the formation of product **15a** in 84% yield with the absence of addition product, cycloalkanol **15b**. Thus, formation of **15a** highlights presence of tertiary carbon alpha to the carboxylic ester which is found to be important and presence of acetonide oxygen imparts steric hindrance which leads to unusual product. Absence of acetonide steric bias does affect the yield and diastereoselectivity. Furthermore, when α, β−unsaturated esters as shown in entries **16** and **17**, were reacted under similar reaction conditions, they led to the formation of secondary alcohols **16a** and **17a** in reduced yields due to decrease in the steric bulk. Thus, formation of cyclohexanol ring products **16b** and **17b**, as a result of normal nucleophilic addition was found to be in good yields.

It is important to note that esters **18**, **19** and **20**, (entries 7, 8 and 9), when subjected to Grignard reaction, furnished products consistent with the reported results. When methyl crotonate **21**, (entry−10), produced 33% of secondary alcohol **21a** and cycloalkanol **21b** in 63% yield. In

order to extend the scope of the above observation, the esters were subjected to the treatment with terminal di(bromomagnesio)alkanes, with varying chain length. Similar results were obtained when acetonide protected ester **3**, (entry−1), was subjected to the unusual Grignard reaction with 1,6−di(bromomagnesio)hexane (Table−4), wherein the reduced product **22a** was formed in 93% yield.

Table−4: Exploration of unusual Grignard reaction

SN	Substrate ester	product	Yield (%)[b] and *dr*[e]
1.	 **(±)3[g]**	 **(±)22a**	(93) (*dr*: 7:3)
2.	 **(±)3[h]**	 **(±)23b**	(91)
3.	 **20[h]**	 **24b**	(89)

b) Product yields calculated after column chromatographic purification, g) Reaction conditions :1,6−Dibromohe-xane, Mg, THF, RT, 3.5h, h) Reaction conditions :1,4−Dibromobutane, Mg, THF, 0 ^{o}C− RT, 3h.

The reaction of 1,4−di(bromomagnesio)butane on ester **3**, (entry 2), always ended up with the formation of usual addition product **23b** in 91% yield. As expected methyl benzoate (**20**), (entry 3), when treated with 1,4−di(bromomagnesio)butane, gave stable cyclopentanol ring product **24b** in 89% yield.

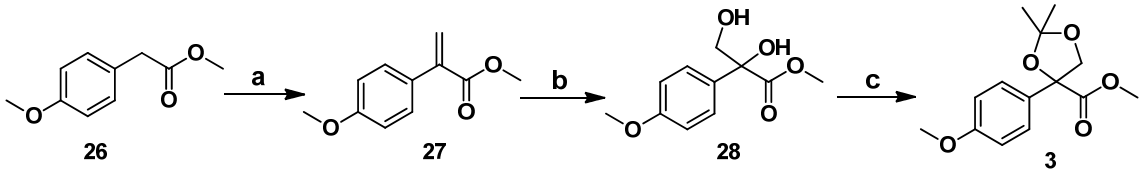
3.1.3. Conclusion

Unusual diastereoselective Grignard reaction has been explored where Grignard reagents are derived from 1,*n*−dihaloalkanes. Steric bias due to a presence of quaternary centre adjacent to the acetonide ester at benzylic position is ascribed to the formation of an intramolecularly reduced product in almost quantitative yield. This steric hindrance is responsible for diastereoselectivity observed with a variety of aromatic as well as aliphatic esters. Unusual

Grignard reaction product furnished long chain secondary alcohols possessing terminal olefin, which are synthetically important intermediates. Unusual diastereoselective Grignard reaction has been explored on diverse and synthetically important substrates. Presence of acetonide protection in starting ester, determines fate of product formation as well as diastereoselectivity of reduced product. Investigation of unusual Grignard reaction on wide range of aliphatic and aromatic substrates, demonstrates the potential scope of this protocol and its applicability.

3.1.4. Experimental:

General procedure for preparation of compounds (±)3, (±)4, (±)5, (±)6, (±)7, (±)8 and (±)9



Reagents and conditions*: (a) Paraformaldehyde, K_2CO_3, TBAI (cat.), toluene, 80 ^oC, 5 h, 72%; (b) OsO_4, NMO, acetone:H_2O (3:1), RT, 5 h, 80%; (c) 2,2−Dimethoxypropane, P−TSA (cat.), DMF, RT, 6 h, 97%.*

General procedure for preparation of exomethylene compound from ester[8]: To a stirred solution of ester (20.62 mmol, 1.0 equiv.), paraformaldehyde (35.0 mmol, 1.6 equiv.), K_2CO_3 (42.0 mmol, 2.0 equiv.) and TBAI (1.03 mmol, 0.04 equiv.) were added and reaction mixture was heated in anhydrous toluene (16 mL) at 80–85^{o}C for 5 h. After completion of the reaction, monitored by TLC, reaction mixture was allowed to cool to room temperature. Water (100 mL) was added to the reaction mixture and stirred vigorously for 10 min. The aqueous layer was extracted with DCM (3 X 20 mL), washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.The obtained residue was then purified by flash column chromatography using 60–120 silica gel to furnish the respective olefin compound as a colorless oil.

General procedure for preparation of diol from exomethylene compound: To a stirred solution of exocyclic methylene compound (0.32 mmol, 1.0 equiv.) in acetone−water (3:1, 8 mL) at room temperature was added *N*−methylmorpholine−*N*−oxide (NMO) (0.62 mmol, 1.9

equiv.) followed by 1M solution of osmium tetroxide (0.0032 mmol, 0.01 equiv.) carefully in a dropwise manner. The resulting reaction mixture was continuously stirred for 5 h. The reaction was then quenched by addition of sat. aq. Na_2SO_3 (5 mL) and the reaction mixture was stirred vigorously for 30 min. The biphasic reaction mixture was then extracted with ethyl acetate (3 X 10 mL) and the combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product obtained was subjected for column chromatography using 60–120 silica gel to furnish the respective diol.

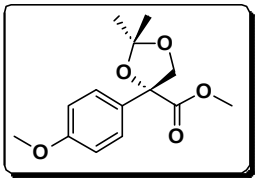
General procedure for preparation of acetonide from diol: To a stirred solution of diol (0.45 mmol, 1.0 equiv.) in anhydrous DMF (4 mL) as a reaction solvent was added 2,2− DMP (1 mmol, 2.2 equiv.) followed by *para*−toluenesulphonic acid (0.1 mmol). The reaction mixture was stirred at 25 ^oC until the reaction was complete, monitored by TLC (6 h), reaction mixture was diluted with ethyl acetate. The reaction mixture was subsequently washed with brine and worked up with ethyl acetate (3 X 15 mL). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a crude residue. The obtained residue was then purified by column chromatography using 60–120 silica gel to furnish the respective acetonide protected ester compound as a viscous oil.

General procedure for unusual Grignard reaction: In a two neck round bottom flask (100 mL) containing Mg metal turnings (4.75 mmol, 2.9 equiv.) in anhydrous THF (3 mL), solution of dibromoalkane (2.33 mmol, 1.4 equiv) in anhydrous THF (2 mL) was added cautiously in a dropwise manner at 0–5 ^oC. After addition, the reaction mixture was allowed to warm upto room temperature and vigorously stirred for 2 h.

To a pre−cooled (upto 0–5^oC) solution of ester (1.60 mmol, 1.0 equiv.) in THF (2 mL) was added the above generated solution of Grignard reagent carefully through syringe in a dropwise manner. After addition, the reaction mixture was warmed upto room temperature within 0.5 h and then stirred for additional 2.5 h. The suspension was quenched slowly with the addition of saturated NH_4Cl solution at 0 ^oC, followed by extraction with ethyl acetate (3 X 15 mL). The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography using 200–400 silica gel to furnish pure product.

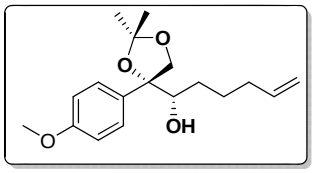
Spectral data

Methyl 4−(4−methoxyphenyl)−2,2−dimethyl−1,3−dioxolane−4−carboxylate(±3):



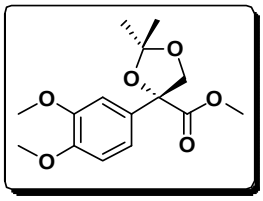
Column chromatography: 60–120 silica gel (8% EtOAc–pet. ether); **Molecular formula:** $C_{14}H_{18}O_5$; **Yield:** 0.847 g, 90%; **^{1}H NMR (200 MHz, $CDCl_3$+CCl_4)**: δ 7.50−7.45 (m, 2H), 7.39−7.26 (m, 2H), 4.88 (d, J = 8.59 Hz, 1H), 3.97 (d, J = 8.59 Hz, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 1.52 (s, 3H), 1.43 (s, 3H); **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4)**: δ 172.8, 159.5, 130.4, 126.2, 113.8, 111.5, 85.0, 73.3, 55.1, 52.7, 26.4, 25.9; **MS (ESI)** (*m/z*): 289 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 2989, 1740, 1600 cm^{-1}; **HRMS (ESI)**: Calculated for $C_{14}H_{18}O_5$ $[M+Na]^+$ 289.1154, found 289.1152.

1−(4−(4−Methoxyphenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)hex−5−en−1−ol (±3a)



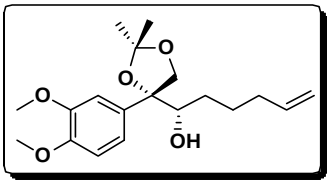
Column chromatography: 200–400 silica gel (12% EtOAc–pet. ether); **Molecular formula:** $C_{18}H_{26}O_4$; **Yield:** (0.910 g, 99%); **^{1}H NMR (200 MHz, $CDCl_3$+CCl_4)**: δ 7.30 (d, J = 8.85 Hz, 2H), 6.85 (d, J = 8.85 Hz, 2H), 5.72 (ddt, J = 17.01, 10.25, 6.58 Hz, 1H), 4.98−4.87 (m, 2H), 4.39 (d, J = 8.59 Hz, 1H), 4.22 (d, J = 8.59 Hz, 1H), 3.81 (s, 3H), 3.63 (dd, J = 8.53, 1.45 Hz, 1H), 2.09 (br s, 1H), 2.03−1.92 (m, 2H), 1.67−1.61 (m, 1H), 1.50 (s, 3H), 1.44−1.21 (m, 2H), 1.21 (s, 3H), 1.11−1.01 (m, 1H); **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4)**: δ 158.7, 138.4, 133.7, 127.4, 114.5, 113.2, 109.6, 86.7, 75.5, 70.0, 55.0, 33.4, 30.4, 26.8, 26.0, 25.5; **MS (ESI)** (*m/z*): 329 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3445, 2829, 1606, 1461 cm^{-1};**HRMS (ESI)**: Calculated for $C_{18}H_{26}O_4$ $[M+Na]^+$ 329.1718, found 329.1723.

Methyl 4−(3,4−dimethoxyphenyl)−2,2−dimethyl−1,3−dioxolane−4−carboxylate (±4):



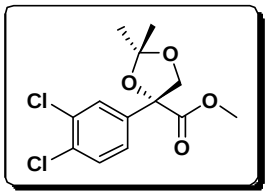
Column chromatography: 60–120 silica gel (8% EtOAc–pet. ether); **Molecular formula:** $C_{15}H_{20}O_6$, **Yield:** (0.832 g, 90%); **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 6.61 (d, J = 2.27 Hz, 2H), 6.36 (t, J = 2.27 Hz, 1H), 4.83 (d, J = 8.72 Hz, 1H), 3.93 (d, J = 8.72 Hz, 1H), 3.74 (s, 6H), 3.71 (s, 3H), 1.50 (s, 3H), 1.42 (s, 3H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 172.2, 160.7, 140.5, 111.5, 102.8, 99.9, 85.1, 73.0, 55.1, 52.7, 26.2, 25.4; **MS (ESI)** (*m/z*): 319 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 2989, 1735, 1620 cm^{-1}; **HRMS (ESI)**: Calculated for $C_{15}H_{20}O_6$ $[M+Na]^+$ 319.1262, found 329.1260.

1−(4−(3,4−Dimethoxyphenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)hex−5−en−1−ol (±4a):



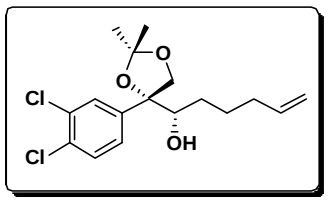
Column chromatography: 200–400 silica gel (12% EtOAc–pet. ether); **Molecular formula:** $C_{19}H_{28}O_5$; **Yield:** (0.898 g, 98%); **^{1}H NMR (200 MHz, $CDCl_3$+CCl_4)**: δ 6.53 (d, J = 2.15 Hz, 2H), 6.37 (d, J = 2.15 Hz, 1H), 5.75 (ddt, J = 16.80, 10.23, 6.57 Hz, 1H), 5.03−4.83 (m, 2H), 4.36 (d, J = 8.59 Hz, 1H), 4.17 (d, J = 8.59 Hz, 1H), 3.78 (s, 6H), 3.62 (dd, J = 9.28, 5.24 Hz, 1H), 1.98 (br s, 1H), 2.03−1.96 (m, 2H), 1.74−1.57 (m, 2H), 1.49 (s, 3H), 1.43−1.30 (m, 2H), 1.24 (s, 3H); **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4)**: δ 160.4, 144.4, 138.5, 114.4, 109.9, 104.5, 98.9, 87.0, 75.7, 70.3, 55.2, 33.4, 30.5, 26.7, 25.8, 25.5; **MS (ESI)** (*m/z*): 359 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3494, 2936, 1600, 1158 cm^{-1}; **HRMS (ESI)**: Calculated for $C_{19}H_{28}O_5$ $[M+Na]^+$ 359.1829, found 359.1829.

Methyl 4−(3,4−dichlorophenyl)−2,2−dimethyl−1,3−dioxolane−4−carboxylate (±5):



Column chromatography: 60–120 silica gel (8% EtOAc–pet. ether); **Molecular formula:** $C_{13}H_{14}Cl_2O_4$; **Yield:** (0.829 g, 90%); **^{1}H NMR (200 MHz, $CDCl_3$+CCl_4)**: δ 7.55 (d, J = 1.89 Hz, 1H), 7.38−7.28 (m, 2H), 4.77 (d, J = 8.84 Hz, 1H), 3.89 (d, J = 8.84 Hz, 1H), 3.69 (s, 3H), 1.47 (s, 3H), 1.38 (s, 3H); **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4)**: δ 171.9, 138.7, 132.8, 132.5, 130.4, 127.3, 124.5, 112.2, 84.2, 73.2, 53.1, 26.1, 25.7; **MS (ESI)** (*m/z*): 328 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3065, 1739, 756 cm^{-1}; **HRMS (ESI)**: Calculated for $C_{13}H_{14}Cl_2O_4$ $[M+Na]^+$ 328.1534, found 328.1539.

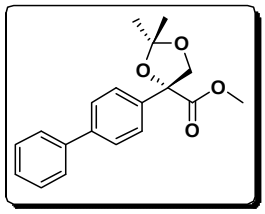
1−(4−(3,4−Dichlorophenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)hex−5−en−1−ol (±5a):



Column chromatography: 200–400 silica gel (12 EtOAc–pet. ether); **Molecular formula:** $C_{17}H_{22}Cl_2O_3$; **Yield:** (0.752 g, 95%); **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 7.52 (d, J = 1.96 Hz, 1H), 7.42 (d, J = 8.31 Hz, 1H), 7.26−7.23 (m, 1H), 5.74 (ddt, J = 16.87, 10.21, 6.69 Hz, 1H), 4.98−4.90 (m, 2H), 4.42 (d, J = 8.80 Hz, 1H), 4.15 (d, J = 8.80 Hz, 1H), 3.64 (dd, J = 10.39, 5.01 Hz, 1H), 1.96 (br s, 1H), 2.07−1.94 (m, 2H), 1.59−1.54 (m, 1H), 1.50 (s, 3H), 1.42−1.30 (m, 2H), 1.24 (s, 3H), 1.03−0.95 (m, 1H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 142.2,

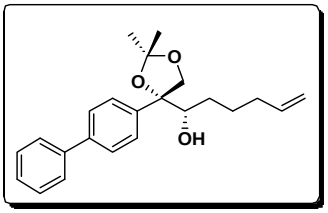
138.3, 132.2, 131.5, 129.9, 128.5, 125.8, 114.7, 110.3, 86.1, 75.5, 70.4, 33.3, 30.5, 26.7, 25.9, 25.3; **MS (ESI)** (*m/z*): 367 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3446, 2928, 1466, 759 cm^{-1}; **HRMS (ESI)**: Calculated for $C_{17}H_{22}Cl_2O_3$ $[M+Na]^+$ 367.0838, found 367.0835.

Methyl 4−([1,1'−biphenyl]−4−yl)−2,2−dimethyl−1,3−dioxolane−4−carboxylate (±6):



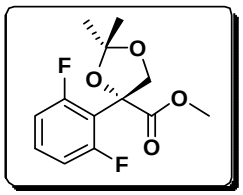
Column chromatography: 60–120 silica gel (10% EtOAc–pet. ether); **Molecular formula:** $C_{19}H_{20}O_4$; **Yield:** (0.825 g, 90%); **^{1}H NMR (200 MHz, $CDCl_3$+CCl_4):** δ 7.57 (s, 5H), 7.47−7.34 (m, 4H), 4.93 (d, J = 8.59 Hz, 1H), 4.04 (d, J = 8.59 Hz, 1H), 3.77 (s, 3H), 1.57 (s, 3H), 1.48 (s, 3H); **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4)**: δ 160.4, 144.4, 138.5, 114.4, 109.9, 104.5, 98.9, 87.0, 75.7, 70.3, 55.2, 33.4, 30.5, 26.7, 25.8, 25.5; **MS (ESI)** (*m/z*): 335 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3070, 1740, 1483 cm^{-1}; **HRMS (ESI)**: Calculated for $C_{19}H_{20}O_4$ $[M+Na]^+$ 367.3597, found 367.3595.

1−(4−([1,1'−Biphenyl]−4−yl)−2,2−dimethyl−1,3−dioxolan−4−yl)hex−5−en−1−ol (±6a):



Column chromatography: 200–400 silica gel (12% EtOAc–pet. ether); **Molecular formula:** $C_{23}H_{28}O_3$; **Yield:** (0.939 g, 98%); **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 7.61−7.57 (m, 4H), 7.46−7.41 (m, 4H), 7.37−7.32 (m, 1H), 5.74 (ddt, J = 16.87, 10.21, 6.69 Hz, 1H), 4.90−4.96 (m, 2H), 4.45 (d, J = 8.80 Hz, 1H), 4.29 (d, J = 8.80 Hz, 1H), 3.70 (dd, J = 10.51, 4.89 Hz, 1H), 2.01 (br s, 1H), 2.07−1.93 (m, 2H), 1.62−1.55 (m, 2H), 1.53 (s, 3H), 1.43−1.33 (m, 1H), 1.25 (s, 3H), 1.11−1.02 (m, 1H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 140.7, 140.6, 140.2, 138.5, 128.7, 127.3, 127.0, 126.78, 126.71, 114.5, 109.9, 87.0, 75.7, 70.0, 33.4, 30.4, 26.8, 26.1, 25.5; **MS (ESI)** (*m/z*): 375 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3457, 3070, 2930, 1641 cm^{-1}; **HRMS (ESI)**: Calculated for $C_{23}H_{28}O_3$ $[M+Na]^+$ 375.1921, found 375.1923.

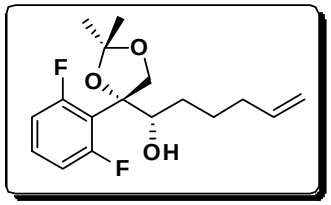
Methyl 4−(2,6−difluorophenyl)−2,2−dimethyl−1,3−dioxolane−4−carboxylate (±7):



Column chromatography: 60–120 silica gel (10% EtOAc–pet. ether); **Molecular formula:** $C_{13}H_{14}F_2O_4$; **Yield:** (0.862 g, 92%); **^{1}H NMR (200 MHz, CDCl)**: δ 7.36−7.14 (m, 1H), 6.95−6.86 (m, 2H), 4.82 (dt, J = 9.47,

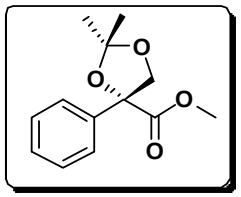
2.02 Hz, 1H), 4.44 (dt, *J* = 9.47, 2.02 Hz, 1H), 3.76 (s, 3H), 1.61 (s, 3H), 1.40 (s, 3H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 171.2, 163.1 (d, J_{C-F} = 251.7 Hz, 1C), 158.1 (d, J_{C-F} = 252.1 Hz, 1C), 130.1 (t, *J* = 11.13 Hz, 1C), 115.5 (d, *J* = 16.10 Hz, 1C), 112.4 (d, *J* = 2.56 Hz, 1C), 111.9 (d, *J* = 2.56 Hz, 1C), 111.7, 81.8, 72.2 (t, *J* = 7.32 Hz, 1C), 53.0, 26.3, 25.3; **MS (ESI)** (*m/z*): 295[M+Na]$^+$; **IR ($CHCl_3$)** ν_{max}: 1740, 1625, 1462, 1065 cm^{-1}; **HRMS (ESI)**: Calculated for $C_{13}H_{14}F_2O_4$ [M+Na]$^+$ 295.0860, found 295.0862.

1−(4−(2,6−Difluorophenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)hex−5−en−1−ol (±7a):



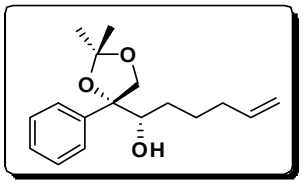
Column chromatography: 200–400 silica gel (15% EtOAc–pet. ether); **Molecular formula:** $C_{17}H_{22}F_2O_3$; **Yield:** (0.908 g, 99%); **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 7.30−7.11 (m, 1H), 6.87 (dd, *J* = 9.79, 8.40 Hz, 2H), 5.76 (ddt, *J* =17.04, 10.25, 6.63 Hz, 1H), 5.01−4.83 (m, 2H), 4.44 (dt, *J* = 9.72, 2.15 Hz, 1H), 4.35 (dt, *J* = 9.72, 1.14 Hz, 1H), 3.75 (dd, *J* = 8.97, 5.05 Hz, 1H), 2.05 (br s, 1H), 1.89−2.17 (m, 2H), 1.71−1.58 (m, 2H), 1.54 (s, 3H), 1.46−1.29 (m, 2H), 1.25 (s, 3H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 163.1 (d, J_{C-F} = 248.4 Hz, 1C), 158.1 (d, J_{C-F} = 249.5 Hz, 1C), 138.5, 129.2 (t, *J* = 11.16 Hz, 1C), 118.8 (d, *J* = 20.50 Hz, 1C), 114.6, 112.5 (d, *J* = 2.56 Hz, 1C), 111.9 (d, *J* = 2.56 Hz, 1C), 109.6, 86.0 (d, *J* = 4.03 Hz, 1C), 75.3, 70.2 (t, *J* = 8.05 Hz, 1C), 33.4, 30.0, 26.3, 25.4, 24.4; **MS (ESI)** (*m/z*): 335 [M+Na]$^+$; **IR ($CHCl_3$)** ν_{max}: 3454, 2989, 1625, 1065 cm^{-1}; **HRMS (ESI)**: Calculated for $C_{17}H_{22}F_2O_3$ [M+Na]$^+$ 335.1427, found 335.1429.

Methyl 2,2−dimethyl−4−phenyl−1,3−dioxolane−4−carboxylate (±8)[1b]:



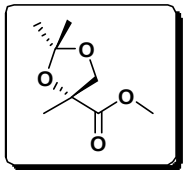
Column chromatography: 60–120 silica gel (10% EtOAc–pet. ether); **Molecular formula:** $C_{13}H_{16}O_4$; **Yield:** (0.535 g, 89%); **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 7.50−7.42 (m, 2H), 7.40−7.32 (m, 3H), 4.88 (d, *J* = 8.72 Hz, 1H), 3.97 (d, *J* = 8.72 Hz, 1H), 3.74 (s, 3H), 1.54 (s, 3H), 1.45 (s, 3H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 172.7, 138.3, 128.4, 128.2, 124.9, 111.7, 85.3, 73.3, 52.8, 26.4, 25.8; **MS (ESI)** (*m/z*): 236 [M+Na]$^+$; **IR ($CHCl_3$)** ν_{max}: 3075, 1736, 1625 cm^{-1}; **HRMS (ESI):** Calculated for $C_{13}H_{16}O_4$ [M+Na]$^+$ 236.2637, found 236.2635.

1−(2,2−Dimethyl−4−phenyl−1,3−dioxolan−4−yl)hex−5−en−1−ol (±8a):



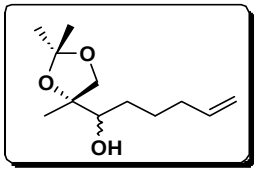
Column chromatography: 60–120 silica gel (15% EtOAc–pet. ether); **Molecular formula:** $C_{17}H_{24}O_3$; **Yield:** (0.458 g, 98%); **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 7.30−7.12 (m, 5H), 5.62 (ddt, J = 17.01, 10.25, 6.58 Hz, 1H), 4.88−4.76 (m, 2H), 4.31 (d, J = 8.59 Hz, 1H), 4.12 (d, J = 8.59 Hz, 1H), 3.54 (dd, J = 10.29, 3.35 Hz, 1H), 1.89 (br s, 1H), 1.95−1.82 (m, 2H), 1.41 (s, 3H), 1.54−1.38 (m, 2H), 1.35−1.20 (m, 2H), 1.11 (s, 3H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 141.7, 138.5, 128.0, 127.9, 127.3, 126.2, 125.5, 114.4, 109.8, 87.0, 75.6, 70.0, 33.4, 30.4, 26.8, 25.9, 25.4; **MS (ESI)** (*m/z*): 299 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}**:** 3494, 2989, 1462 cm^{-1}; **HRMS (ESI)**: Calculated for $C_{17}H_{24}O_3$ $[M+Na]^+$ 299.1618, found 299.1613.

Methyl−2,2,4−trimethyl−1,3−dioxolane−4−carboxylate (±9)[10] :



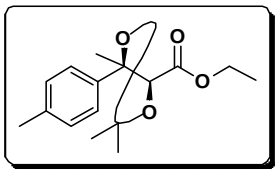
Column chromatography: 60–120 silica gel (8% EtOAc–pet. ether); **Molecular formula:** $C_8H_{14}O_4$; **Yield:** (0.603 g, 93%); **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 4.38 (d, J = 8.72 Hz, 1H), 3.79 (d, J = 8.72 Hz, 1H), 3.78 (s, 3H), 1.44 (s, 3H), 1.36 (d, J = 2.53 Hz, 6H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 173.9, 110.9, 81.0, 72.7, 52.2, 26.3, 25.7, 22.8; **MS (ESI)** (*m/z*): 197 $[M+Na]^+$.

1−(2,2,4−Trimethyl−1,3−dioxolan−4−yl)hex−5−en−1−ol (±9a)



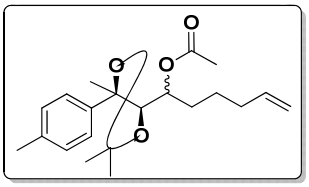
Column chromatography: 200–400 silica gel (8% EtOAc–pet. ether); **Molecular formula:** $C_{12}H_{22}O_3$, **Yield:** (0.482 g, 98%); **^{1}H NMR (200 MHz, $CDCl_3$)**: first diastereomer δ 5.80 (ddt, J = 16.89, 10.26, 6.63 Hz, 1H), 5.08−4.87 (m, 2H), 4.02 (d, J = 8.34 Hz, 1H), 3.65 (d, J = 8.34 Hz, 1H), 3.53 (d, J = 10.36 Hz, 1H), 2.28 (br s, 1H), 1.43 (s, 3 H), 1.36 (s, 3H), 2.15−1.97 (m, 2H), 1.78−1.48 (m, 2H), 1.44−1.13 (multiplet of 5H including singlet at 1.24 for 3H,); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 138.5, 114.7, 109.2, 83.8, 74.3, 70.0, 33.5, 30.5, 27.4, 26.5, 25.8, 21.7; **MS (ESI)** (*m/z*): 237 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3478, 1620 cm^{-1}; **HRMS (ESI)**: Calculated for $C_{12}H_{22}O_3$ $[M+Na]^+$ 237.1461,found 237.1460.

Ethyl−2,2,5−trimethyl−5−(*p*−tolyl)−1,3−dioxolane−4−carboxylate(±10)



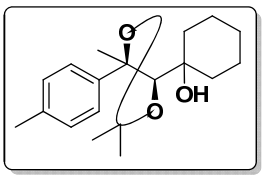
Column chromatography: 60–120 silica gel (8% EtOAc–pet. ether); **Molecular formula:** $C_{16}H_{22}O_4$, **Yield:** (0.743 g, 79%); **^{1}H NMR (500 MHz, $CDCl_3$)**: (*dr*: 9.5:0.5) δ 7.86 (d, J = 8.55 Hz, 0.09H), 7.46 (d, J = 8.24 Hz, 1.91H), 7.30 (d, J = 8.55 Hz, 0.09H), 7.17 (d, J = 8.24 Hz, 1.91H), 4.70 (s, 1H), 4.36−4.28 (m, 2H), 2.35 (s, 3H), 1.67 (s, 3H), 1.50 (s, 3H), 1.38 (s, 3H), 1.34 (t, J = 7.02 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)** of major isomer: δ 169, 142.1, 136.9, 128.8, 125.1, 110.1, 84.3, 83.1, 61.3, 28.0, 26.3, 25.6, 20.9; 14.1; **MS (ESI)** (*m/z*): 301 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 1735, 1615, 1455 cm^{-1}; **HRMS (ESI)**: Calculated for $C_{16}H_{22}O_4$ $[M+Na]^+$ 301. 3435, found 301. 3439.

1−(2,2,5−Trimethyl−5−(*p*−tolyl)−1,3−dioxolan−4−yl)hex−5−en−1−yl acetate (±10'a)



Column chromatography: 200–400 silica gel (5% EtOAc–pet. ether); **Molecular formula:** $C_{21}H_{30}O_4$; **Yield:** 53%; **^{1}H NMR (400 MHz, $CDCl_3$)**: (*dr*: 8:2) δ 7.40 (d, J = 7.78 Hz, 0.18H), 7.35 (d, J = 8.70 Hz, 1.82H), 7.16 (d, J = 8.70 Hz, 1.67 H), 7.11 (d, J = 7.78 Hz, 0.33H), 5.64 (ddt, J = 16.89, 10.48, 6.70, 1H), 5.28−5.22 (m, 1H), 4.94−4.86 (m, 2H), 3.90 (d, J = 4.58 Hz, 0.80H), 3.80 (d, J = 8.70 Hz, 0.20H), 2.34 (s, 3H), 2.12 (s, 3H), 1.96−1.84 (m, 2H), 1.58 (s, 3H), 1.50 (s, 3H), 1.49 (s, 3H), 1.31−1.28 (m, 2H), 1.22−1.15 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** of major isomer: δ 170.7, 140.6, 138.1, 137.1, 129.1, 125.4, 114.8, 107.6, 84.4, 83.0, 70.1, 33.2, 31.7, 28.5, 26.5, 24.2, 21.9, 21.3, 20.9; **MS (ESI)** (*m/z*): 369 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 1735, 1615, 1455 cm^{-1}; **HRMS (ESI)**: Calculated for $C_{21}H_{30}O_4$ $[M+Na]^+$ 369.4605, found 369. 4608.

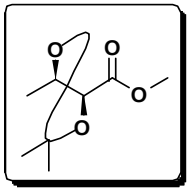
1−(2,2,5−Trimethyl−5−(p−tolyl)−1,3−dioxolan−4−yl)cyclohexanol (±10b)



Column chromatography: 200–400 silica gel (8% EtOAc–pet. ether); **Molecular formula:** $C_{19}H_{28}O_3$; **Yield:** 43%; **^{1}H NMR (400 MHz, $CDCl_3$)**: 7.40 (d, J = 8.70 Hz, 2H), 7.14 (d, J = 8.70 Hz, 2H), 3.79 (s, 1H), 2.33 (s, 3H), 2.01 (brs, 1H), 1.82−1.61 (m, 2H), 1.73 (s, 3H), 1.57 (s, 3H), 1.56 (s, 3H), 1.52−1.34 (m, 6H), 1.11−1.03 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 140.7, 136.8, 128.7, 126.7, 106.2, 88.7, 83.4, 71.1, 38.0, 32.5, 28.6, 26.9, 25.4, 21.9, 21.4, 21.1,

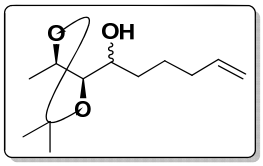
20.9; **MS (ESI)** (*m/z*): 327 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3435, 1615, 1515 cm^{-1}; **HRMS (ESI)**: Calculated for $C_{19}H_{28}O_3$ $[M+Na]^+$ 327. 1934, found 327. 1931.

Methyl−2,2,5−trimethyl−1,3−dioxolane−4−carboxylate (±11)[12]



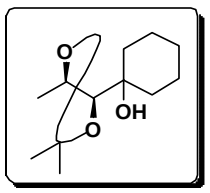
Column chromatography: 60–120 silica gel (10% EtOAc–pet. ether); **Molecular formula:** $C_8H_{14}O_4$; **Yield:** (0.459 g, 70%); **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 4.22−4.09 (m, 1H), 4.02 (d, J = 7.96 Hz, 1H), 3.74 (s, 3H), 1.42−1.38 (m, 9H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 170.7, 110.4, 80.2, 74.9, 52.1, 26.9, 25.5, 18.3; **MS (ESI)** (*m/z*):197 $[M+Na]^+$.

1−((4*R*,5*R*)−2,2,5−Trimethyl−1,3−dioxolan−4−yl)hex−5−en−1−ol (±11a)



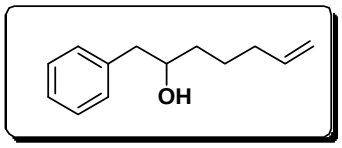
Column chromatography: 200–400 silica gel (12% EtOAc–pet. ether); **Molecular formula:** $C_{12}H_{22}O_3$; **Yield:** (0.225 g, 46%); **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 5.82 (ddt, J = 16.80, 10.10, 6.57 Hz, 1H), 5.07−4.95 (m, 2H), 4.12−3.99 (m, 1H), 3.48−3.43 (m, 2H), 2.19−2.06 (m, 3H), 1.64−1.48 (m, 4H), 1.43 (s, 3H), 1.40 (s, 3H), 1.30 (d, J = 6.06 Hz, 3H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 138.5, 114.7, 108.4, 85.2, 73.2, 69.9, 34.2, 33.5, 27.4, 26.9, 24.9, 18.0; **MS (ESI)** (*m/z*): 269 $[M+Na+MeOH]^+$; **IR ($CHCl_3$)** ν_{max}: 3435, 1620cm^{-1}; **HRMS (ESI)**: Calculated for $C_{12}H_{22}O_3$ $[M+Na]^+$ 237.3013, found 237.3016.

1−(2,2,5−Trimethyl−1,3−dioxolan−4−yl)cyclohexanol(±11b)



Column chromatography: 200–400 silica gel (10% EtOAc–pet. ether); **Molecular formula:** $C_{12}H_{22}O_3$; **Yield:** (0.196 g, 40%); **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 4.14 (dq, J = 8.08, 6.03 Hz, 1H), 3.44 (d, J = 8.08 Hz, 1H), 1.75−1.48 (m, 8H), 1.40 (s, 3H), 1.39 (s, 3H), 1.32 (d, J = 6.06 Hz, 3H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 107.7, 88.0, 72.0, 69.9, 36.0, 32.5, 27.4, 26.9, 25.6, 21.3, 20.1; **MS (ESI)** (*m/z*): 237 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3435, 2850 cm^{-1}; **HRMS (ESI)**: Calculated for $C_{12}H_{22}O_3$ $[M+Na]^+$237.3013, found 237.3013.

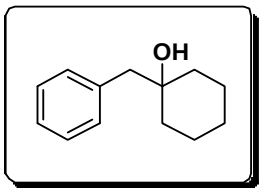
1−Phenylhept−6−en−2−ol (12a) [13]



Column chromatography: 200–400 silica gel (12% EtOAc–pet. ether); **Molecular formula:** $C_{13}H_{18}O$; **Yield:** (0.162 g, 32%); **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 7.39−7.22 (m, 5H), 5.85 (ddt, J =

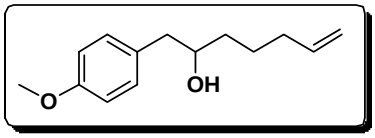
16.80, 10.11, 6.57 Hz, 1H), 5.09−4.94 (m, 2H), 3.91−3.79 (m, 1H), 2.88 (dd, *J* = 13.52, 4.30 Hz, 1H), 2.77−2.61 (m, 1H), 2.16−2.06 (m, 2H), 1.70−1.62 (m, 2H); **^{13}C NMR (50 MHz, $CDCl_3$)**: *δ* 138.6, 138.5, 129.4, 128.5, 126.4, 114.6, 72.5, 44.0, 36.2, 33.6, 25.0; **MS (ESI)** (*m/z*): 213 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3445, 2928 cm^{-1}.

1−Benzylcyclohexanol (12b) [13]



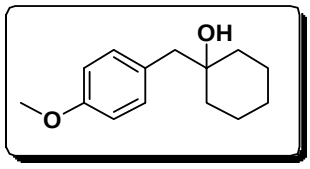
Column chromatography: 200–400 silica gel (10% EtOAc–pet. ether); **Molecular formula:** $C_{13}H_{18}O$; **Yield:** (0.314 g, 62%); **^{1}H NMR (200 MHz, $CDCl_3$)**: *δ* 7.39−7.23 (m, 5H), 2.78 (s, 2H), 1.82 (br s, 1H), 1.66−1.26 (m, 10H); **^{13}C NMR (50 MHz, $CDCl_3$)**: *δ* 137.1, 127.9, 126.2, 71.0, 48.6, 37.1, 25.6, 21.9; **MS (ESI)** (*m/z*): 191 $[M+1]^+$.

1−(4−Methoxyphenyl)hept−6−en−2−ol (13a):



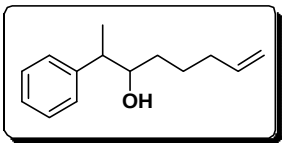
Column chromatography: 200–400 silica gel (12% EtOAc–pet. ether); **Molecular formula:** $C_{14}H_{20}O_2$; **Yield:** (0.180 g, 37%); **^{1}H NMR (200 MHz, $CDCl_3$)**: *δ* 7.11 (d, *J* = 8.59 Hz, 2H), 6.84 (d, *J* =8.59 Hz, 2H), 5.81 (ddt, *J* = 16.93, 10.11, 6.57 Hz, 1H), 3.79 (s, 3H), 3.76 (br s, 1H), 3.81−3.70 (m, 1H), 2.77 (dd, *J* = 13.77, 4.29 Hz, 1H), 2.67−2.51 (m, 1H), 2.11−2.03 (m, 2H), 1.54−1.47 (m, 4H), 5.05−4.92 (m, 2H); **^{13}C NMR (50 MHz, $CDCl_3$)**: *δ* 158.2, 138.6, 130.4, 130.3, 114.5, 113.9, 72.5, 55.2, 43.1, 36.1, 33.6, 25.0; **MS (ESI)** (*m/z*): 243 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3454, 1590, 1420 cm^{-1}; **HRMS (ESI)**: Calculated for $C_{14}H_{20}O_2$ $[M+Na]^+$ 243.2274, found 243.2272.

1−(4−Methoxybenzyl)cyclohexanol (13b)



Column chromatography: 200–400 silica gel (10% EtOAc–pet. ether); **Molecular formula:** $C_{14}H_{20}O_2$; **Yield**: (0.293 g, 60%); **^{1}H NMR (200 MHz, $CDCl_3$+CCl_4)**: *δ* 7.11 (d, *J* = 8.59 Hz, 2H), 6.82 (d, *J* = 8.59 Hz, 2H), 3.79 (s, 3H), 2.67 (s, 2H), 1.64−1.22 (m, 10H); **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4)**: *δ* 158.3, 131.5, 129.0, 113.6, 71.0, 55.1, 47.8, 37.3, 25.8, 22.1; **MS (ESI)** (*m/z*): 243 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3435, 2985, 1620 cm^{-1}; **HRMS (ESI)**: Calculated for $C_{14}H_{20}O_2$ $[M+Na]^+$ 243.2274, found 243.2270.

2−Phenyloct−7−en−3−ol (±14a)[14]**:**

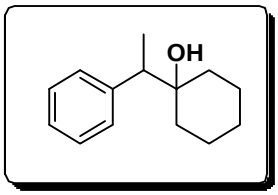


Column chromatography: 200–400 silica gel (10−12% EtOAc–pet. ether); **Molecular formula:** $C_{14}H_{20}O$; **Yield:** (0.422 g, 68%); (*dr*: 6:4)

1st diastereomer, **Yield:** (0.279 g, 45%); **^{1}H NMR (200 MHz, $CDCl_3$+CCl_4)**: δ 7.37−7.22 (m, 5H). 5.82 (ddt, *J* = 16.82, 10.26, 6.63 Hz, 1H), 5.07−4.93 (m, 2H), 3.67 (t, *J* = 7.58 Hz, 1H), 2.82−2.68 (m, 1H), 2.10−2.03 (m, 2H), 1.67−1.55 (m, 2H), 1.49−1.39 (m, 2H), 1.28 (d, *J* = 7.58 Hz, 3H); **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4)**: δ 143.4, 138.7, 128.5, 128.1, 126.6, 114.5, 75.8, 46.1, 33.8, 33.7, 24.9, 17.9; **MS (ESI)** (*m/z*): 227 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3433, 2930, 1602, 1494 cm^{-1}; **HRMS (ESI)**: Calculated for $C_{14}H_{20}O$ $[M+Na]^+$ 227.1406,found 227.1404.

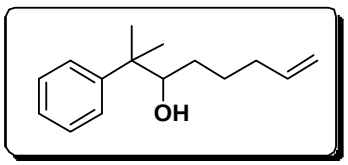
2nd diastereomer, **Yield:** (0.142 g, 23%); **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 7.40−7.23 (m, 5H), 5.81 (ddt, *J* = 16.99, 10.23, 6.66 Hz, 1H), 5.07−4.93 (m, 2H), 3.75−3.66 (m, 1H), 2.88−2.75 (m, 1H), 2.11−2.01 (m, 2H), 1.64−1.42 (m, 4H), 1.37 (d, *J* = 7.07 Hz, 3H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 144.5, 138.6, 128.4, 128.1, 127.7, 126.3, 114.4, 76.0, 45.5, 34.0, 33.5, 25.3, 15.3.

1−(1−Phenylethyl)cyclohexanol (14b) [14]



Column chromatography: 200–400 silica gel (8% EtOAc–pet. ether); **Molecular formula:** $C_{14}H_{20}O$; **Yield:** (0.180 g, 29%); **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 7.35−7.18 (m, 5H), 2.76 (q, *J* = 7.20 Hz, 1H), 1.71−1.45 (m, 6H), 1.33 (d, *J* = 7.20 Hz, 3H), 1.49−1.32 (m, 2H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 144.5, 138.6, 128.4, 128.1, 127.7, 126.3, 114.4, 76.0, 45.5, 34.0, 33.5, 25.3, 15.3; **MS (ESI)** (*m/z*): 227 $[M+Na]^+$.

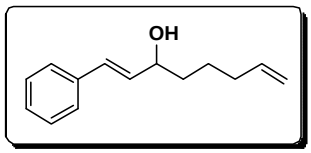
2−Methyl−2−phenyloct−7−en−3−ol (15a):



Column chromatography: 200–400 silica gel (12% EtOAc–pet. ether); **Molecular formula:** $C_{15}H_{22}O$; **Yield:** (0.514 g, 89%); **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 7.41−7.22 (m, 5H), 5.78 (ddt, *J* = 16.80, 10.11, 6.57 Hz, 1H), 5.02−4.89 (m, 2H), 3.61 (d, *J* = 9.85 Hz, 1H), 2.12−1.97 (m, 2H), 1.69−1.38 (m, 4H), 1.34 (s, 3H), 1.32 (s, 3H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 147.1, 138.7, 128.2, 126.4, 126.0, 114.4, 79.4, 42.6, 33.6, 30.8, 26.2, 24.2, 23.4; **MS**

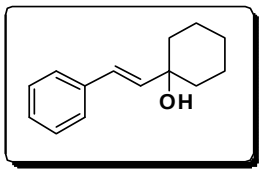
(ESI) (*m/z*): 219 $[M+1]^+$; **IR ($CHCl_3$)** ν_{max}: 3422, 2930, 1452 cm^{-1}; **HRMS (ESI)**: Calculated for $C_{15}H_{22}O$ $[M+Na]^+$241.1563, found 241.1560.

(*E*)−1−Phenylocta−1,7−dien−3−ol (16a) [15]**:**



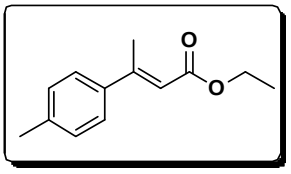
Column chromatography: 200–400 silica gel (12% EtOAc–pet. ether); **Molecular formula:** $C_{14}H_{18}O$; **Yield:** (0.149 g, 30%); **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 7.41−7.23 (m, 5H), 6.58 (d, J = 15.91 Hz, 1H), 6.22 (dd, J = 15.91, 6.82 Hz, 1H), 5.82 (ddt, J = 16.80, 9.98, 6.82 Hz, 1H), 5.06−4.93 (m, 2H), 4.34−4.25 (m, 1H), 2.16−2.03 (m, 2H), 1.69−1.63 (m, 2H), 1.53−1.45 (m, 2H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 138.5, 136.6, 132.4, 130.3, 128.5, 127.6, 126.4, 114.7, 72.9, 36.7, 33.6, 24.7; **MS (ESI)** (*m/z*): 225 $[M+Na]^+$.

(*E*)−1−Styrylcyclohexanol (16b) [15]



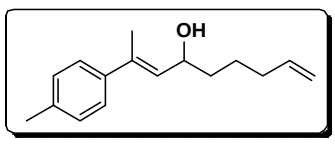
Column chromatography: 200–400 silica gel (10% EtOAc–pet. ether); **Molecular formula:** $C_{14}H_{18}O$; **Yield:** (0.333 g, 67%); **^{1}H NMR (200 MHz, $CDCl_3$+CCl_4)**: δ 7.36−7.17 (m, 5H), 6.59 (d, J = 16.16 Hz, 1H), 6.27 (d, J = 16.16 Hz, 1H), 1.62−1.45 (m, 10H); **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4)**: δ 137.4, 137.1, 128.5, 127.3, 127.0, 126.4, 71.6, 38.0, 25.5, 22.1; **MS (ESI)** (*m/z*): 225 $[M+Na]^+$.

(*E*)−Methyl 3−(*p*−tolyl)but−2−enoate (17) [16]



Column chromatography: 60–120 silica gel (10% EtOAc–pet. ether); **Molecular formula:** $C_{13}H_{16}O_2$; **Yield:** (0.659 g, 82%); **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 7.39 (d, J = 8.33 Hz, 2H), 7.16 (d, J = 8.33 Hz, 2H), 6.13 (d, J = 1.14 Hz, 1H), 4.20 (q, J = 7.14 Hz, 2H), 2.56 (d, J = 1.14 Hz, 3H), 2.35 (s, 3H), 1.31 (t, J = 7.14 Hz, 3H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 166.9, 155.3, 139.1, 139.0, 129.1, 126.1, 116.1, 59.6, 21.0, 17.7, 14.2; **MS (ESI)** (*m/z*): 231 $[M+1]^+$.

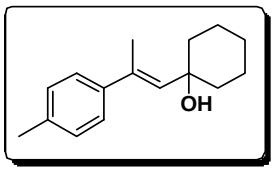
(*E*)−2−(*p*−Tolyl)nona−2,8−dien−4−ol (17a):



Column chromatography: 200–400 silica gel (8% EtOAc–pet. ether); **Molecular formula:** $C_{16}H_{22}O$; **Yield:** (0.146 g, 37%); **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 7.29 (d, J = 8.07 Hz, 1.69H), 7.21 (d, J = 10.27 Hz, 0.32H), 7.12 (d, J = 8.07 Hz, 1.86H), 7.06 (d, J = 10.27 Hz, 0.24H), 5.81 (ddt, J =

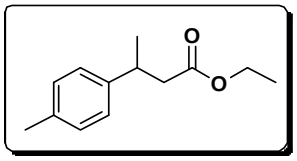
16.87, 10.03, 6.60 Hz, 1H), 5.73 (d, *J* = 8.56 Hz, 1H), 5.03−4.94 (m, 2H), 4.55−4.50 (m, 1H), 2.33 (s, 3H), 2.07 (s, 3H), 2.13−2.02 (m, 1H), 1.70 (br s, 1H), 1.67−1.55 (m, 1H), 1.53−1.44 (m, 4H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 139.9, 138.5, 136.9, 136.7, 129.9, 128.8, 125.5, 114.5, 68.8, 37.0, 33.6, 24.6, 20.9, 16.2; **MS (ESI)** (*m/z*): 253[M+Na]$^+$; **IR ($CHCl_3$)** ν_{max}: 3422 cm^{-1}; **HRMS (ESI):** Calculated for $C_{16}H_{22}O$ [M+Na]$^+$ 253.3453,found 253.3451.

(*E*)−1−(2−(*p*−Tolyl)prop−1−en−1−yl)cyclohexanol (17b) [16]



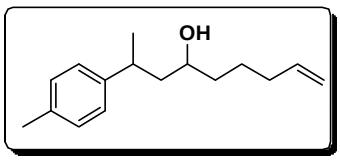
Column chromatography: 200–400 silica gel (8% EtOAc–pet. ether); **Molecular formula:** $C_{16}H_{22}O$, **Yield:** (0.235 g, 58%); **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 7.29 (d, *J* = 8.34 Hz, 2H), 7.12 (d, *J* = 8.34 Hz, 2H), 5.80 (d, *J* = 1.26 Hz, 1H), 2.34 (s, 3H), 2.29 (d, *J* = 1.26 Hz, 3H), 1.79−1.46 (m, 10H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 141.9, 138.0, 136.5, 133.5, 128.8, 125.7, 72.1, 39.3, 25.4, 22.6, 20.9, 17.1; **MS (ESI)** (*m/z*): 253[M+Na]$^+$.

Ethyl 3−(*p*−tolyl)butanoate (18)[17]



Column chromatography: 60–120 silica gel (10% EtOAc–pet. ether); **Molecular formula:** $C_{13}H_{18}O_2$; **Yield:** (0.494 g, 98%); **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 7.18−6.96 (m, 4H), 4.06 (q, *J* = 7.20 Hz, 2H), 3.39−3.09 (m, 1H), 2.67−2.40 (m, 2H), 2.29 (s, 3H), 1.27 (d, *J* = 6.95 Hz, 3H), 1.17 (t, *J* = 6.95 Hz, 3H);**^{13}C NMR (50 MHz, $CDCl_3$)**: δ 172.2, 142.5, 135.5, 128.9, 126.4, 59.9, 42.8, 35.9, 21.6, 20.7, 13.9; **MS (ESI)** (*m/z*): 229 [M+Na]$^+$.

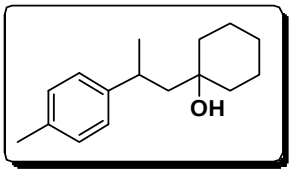
2−(*p*−Tolyl)non−8−en−4−ol (±18a):



Column chromatography: 200–400 silica gel (12% EtOAc–pet. ether); **Molecular formula:** $C_{16}H_{24}O$; **Yield:** (0.106 g, 29%); **^{1}H NMR (200 MHz, $CDCl_3$)**: (*dr*: 6:**4**) δ 7.11−7.10 (m, 4H), 5.78 (ddt, *J* = 16.79, 10.07, 6.72 Hz, 1H), 5.02−4.91 (m, 2H), 3.65−3.61 (m, 0.74H), 3.34−3.30 (m, 0.26H), 3.01−2.92 (m, 0.37H), 2.90−2.83 (m, 0.63H), 2.32 (s, 3H), 2.35−2.31 (m, 1H), 2.06 (br s, 1H), 2.02−1.98 (m, 1H), 1.74−1.64 (m, 2H), 1.56−1.48 (m, 2H), 1.43−1.37 (m, 2H), 1.25 (d, *J* = 6.95 Hz, 3H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 144.3, **144.6**, 138.7, **138.6**, 135.6, **135.4**, 129.2, **129.1**, **126.9**, 126.7, 114.56, **114.53**, 70.1, **69.5**, 46.2, **45.7**, **37.4**, 37.0, 36.4, **35.9**, 33.6,

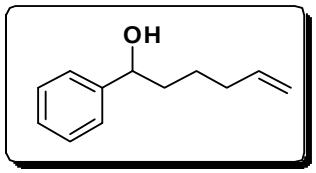
32.7, **25.7**, 24.7, 22.1, **20.9**; **MS (ESI)** (*m/z*): 255 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3445, 2928 cm^{-1}; **HRMS (ESI):** Calculated for $C_{16}H_{24}O$ $[M+Na]^+$ 255.1719, found 255.1715.

1−(2−(*p*−Tolyl)propyl)cyclohexanol (18b)



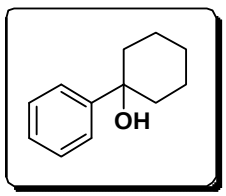
Column chromatography: 200–400 silica gel (10% EtOAc–pet. ether); **Molecular formula:** $C_{16}H_{24}O$; **Yield**: (0.226 g, 62%); **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 7.18−7.08 (m, 4H), 3.03−2.90 (m, 1H), 2.31 (s, 3H), 1.93 (dd, J = 14.53, 8.85 Hz, 1H), 1.74 (dd, J = 14.53, 4.80 Hz, 1H), 1.59−1.37 (m, 8H), 1.25 (d, J = 6.95 Hz, 3H); **^{13}C NMR (50 MHz, $CDCl_3$)**: δ 145.1, 135.4, 129.3, 126.9, 71.9, 50.8, 38.1, 37.8, 34.7, 25.7, 25.2, 22.1, 22.0, 20.9; **MS (ESI)** (*m/z*): 255 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3445, 2928, 1610 cm^{-1}; **HRMS (ESI)**: Calculated for $C_{16}H_{24}O$ $[M+Na]^+$ 255.1719, found 255.1715.

1−Phenylhex−5−en−1−ol (19a) [18]



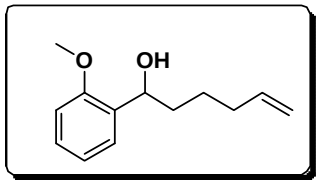
Column chromatography: 200–400 silica gel (12% EtOAc–pet. ether); **Molecular formula:** $C_{12}H_{16}O$; **Yield**: (0.398 g, 77%); **^{1}H NMR (200 MHz, $CDCl_3$+CCl_4)**: δ 7.32−7.20 (m, 5H), 5.72 (ddt, J = 17.01, 10.22, 6.66 Hz, 1H), 4.98−4.86 (m, 2H), 4.59 (dd, J = 7.14, 5.87 Hz, 1H), 2.07−1.92 (m, 2H), 1.95 (br s, 1H), 1.85−1.57 (m, 2H), 1.52−1.21 (m, 2H); **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4)**: δ 144.8, 138.4, 128.4, 127.5, 125.8, 114.8, 74.4, 38.5, 33.6, 25.0; **MS (ESI)** (*m/z*): 199 $[M+Na]^+$.

1−Phenylcyclohexanol (19b) [18]



Column chromatography: 200–400 silica gel (10% EtOAc–pet. ether); **Molecular formula:** $C_{12}H_{16}O$; **Yield**: (0.113 g, 22%); **^{1}H NMR (200 MHz, $CDCl_3$+CCl_4)**: δ 7.48−7.41 (m, 2H), 7.35−7.19 (m, 3H), 1.82−1.55 (m, 10H); **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4)**: δ 149.4, 128.1, 126.6, 124.5, 73.0, 38.8, 25.6, 22.2; **MS (ESI)** (*m/z*): 199 $[M+Na]^+$.

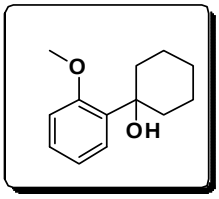
1−(2−Methoxyphenyl)hex−5−en−1−ol (20a):



Column chromatography: 200–400 silica gel (12% EtOAc–pet. ether); **Molecular formula:** $C_{13}H_{18}O_2$; **Yield:** (0.337 g, 68%); **^{1}H**

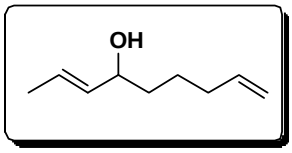
NMR (200 MHz, $CDCl_3$+CCl_4): δ 7.29−7.16 (m, 2H), 6.96−6.81 (m, 2H), 5.79 (ddt, *J* = 16.81, 10.11, 6.57 Hz, 1H), 5.02−4.81 (m, 3H), 3.83 (s, 3H), 2.60 (br s, 1H), 2.12−1.80 (m, 2H), 1.78−1.70 (m, 2H), 1.57−1.33 (m, 2H); **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4)**: δ 156.3, 138.7, 132.7, 128.0, 126.8, 120.7, 114.5, 110.3, 70.3, 55.1, 36.7, 33.6, 25.2; **MS (ESI)** (*m/z*): 229 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}**:** 3454cm^{-1}; **HRMS (ESI):** Calculated for $C_{13}H_{18}O_2$ $[M+Na]^+$ 229.1197, found 229.1199.

1−(2−Methoxyphenyl)cyclohexanol (20b) [18]**:**



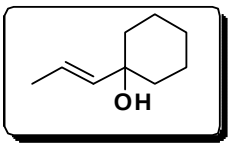
Column chromatography: 200–400 silica gel (10% EtOAc–pet. ether); **Molecular formula:** $C_{13}H_{18}O_2$; **Yield:** (0.148 g, 30%); **^{1}H NMR (200 MHz, $CDCl_3$+CCl_4)**: δ 7.31−7.14 (m, 2 H), 6.95−6.86 (m, 2 H), 3.88 (s, 3 H), 2.03−1.53 (m, 10 H); **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4):** δ 157.2, 136.5, 127.8, 125.7, 121.1, 111.3, 72.9, 55.2, 36.7, 26.0, 21.9; **MS (ESI)** (*m/z*): 229 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3454cm^{-1}; **HRMS (ESI):** Calculated for $C_{13}H_{18}O_2$ $[M+Na]^+$ 229.1197, found 229.1196.

(*E*)−Nona−2,8−dien−4−ol (21a) [19]



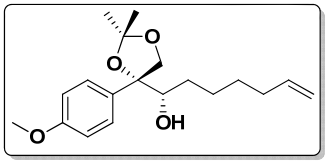
Column chromatography: 200–400 silica gel (10% EtOAc–pet. ether); **Molecular formula:** $C_9H_{16}O$; **Yield:** (0.151 g, 33%); **^{1}H NMR (200 MHz, $CDCl_3$+CCl_4)**: (*E:Z*= 7:**3**) δ 5.88−5.40 (m, 3H), 5.04−4.09 (m, 2H), 4.06−3.97 (m, 1H), 2.11−2.01 (m, 2H), 1.70 (d, *J* = 5.43 Hz, 3H), 1.54−1.45 (m, 4H) **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4):** δ **139.1**, 138.6, 134.4, 126.6, **126.3**, 114.7, 72.9, **38.1**, 36.7, **25.6**, 24.8, **22.7**, 22.5, **17.9**, 17.7; **MS (ESI)** (*m/z*): 163 $[M+Na]^+$.

(*E*)−1−(Prop−1−en−1−yl)cyclohexanol (21b) [19]



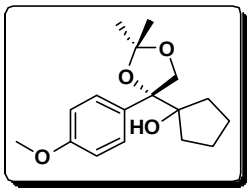
Column chromatography: 200–400 silica gel (10% EtOAc–pet. ether); **Molecular formula:** $C_9H_{16}O$; **Yield:** (0.288 g, 60%); **^{1}H NMR (200 MHz, $CDCl_3$+CCl_4)**: δ 5.76−5.51 (m, 2H), 1.69 (d, *J* = 5.05 Hz, 3H), 1.64−1.43 (m, 10H); **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4):** δ 139.1, 122.5, 71.1, 38.0, 25.6, 22.2, 17.8; **MS (ESI)** (*m/z*): 163 $[M+Na]^+$.

1−(4−(4−Methoxyphenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)hept−6−en−1−ol (±22a):



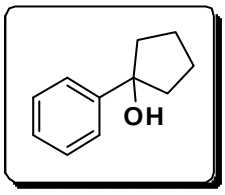
Column chromatography: 200–400 silica gel (12% EtOAc–pet. ether); **Molecular formula:** $C_{19}H_{28}O_4$; **Yield:** (0.615 g, 93%); **^{1}H NMR (200 MHz, $CDCl_3$+CCl_4):** (*dr*: 7:**3**) δ 7.28 (d, *J* = 9.10 Hz, 2H), 6.85 (d, *J* = 9.10 Hz, 2H), 5.84−5.67 (m, 1H), 4.98−4.85 (m, 2H), 4.45 (d, *J* = 8.21 Hz, 0.25H), 4.37 (d, *J* = 8.59 Hz, 0.75H), 4.20 (d, *J* = 8.59 Hz, 0.75H), 4.10 (d, *J* = 8.21 Hz, 0.25H), 3.78 (s, 3H), 3.66−3.56 (m, 1H), 2.00 (br s, 1H), 2.03−1.82 (m, 2H), 1.62−1.55 (m, 2H), 1.49 (s, 3H), 1.42−1.26 (m, 4H), 1.19 (s, 3H); **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4):** δ 158.9, **158.7**, **138.8**, 138.7, **134.9**, 133.7, 127.5, **126.7**, 114.48, **114.41**, **113.5**, 113.4, **110.1**, 109.7, **87.2**, 86.9, **76.4**, 75.8, **72.7**, 69.8, 55.1, 33.7, **32.8**, **31.7**, 30.8, 28.7, 27.0, 26.2, 25.8, **25.7**; **MS (ESI)** (*m/z*): 343 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3435 cm^{-1}; **HRMS (ESI):** Calculated for $C_{19}H_{28}O_4$ $[M+Na]^+$ 343.1880, found 343.1882.

1−(4−(4−Methoxyphenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)cyclopentan−1−ol (±23b):



Column chromatography: 200–400 silica gel (15% EtOAc–pet. ether); **Molecular formula:** $C_{17}H_{24}O_4$, **Yield:** (0.519 g, 91%); **^{1}H NMR (200 MHz, $CDCl_3$+CCl_4):** δ 7.32 (d, *J* = 8.85 Hz, 1H), 6.82 (d, *J* = 8.85 Hz, 1H), 4.46 (d, *J* = 8.46 Hz, 1H), 4.22 (d, *J* = 8.46 Hz, 1H), 3.79 (s, 3H), 1.79−1.66 (m, 5H), 1.50 (s, 3H), 1.56−1.42 (m, 3H), 1.16 (s, 3H); **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4):** δ 158.7, 135.4, 128.0, 112.9, 109.9, 87.5, 85.3, 72.1, 55.1, 35.7, 35.0, 26.5, 25.7, 24.0, 23.6; **MS (ESI)** (*m/z*): 315 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3435, 1620, 1405 cm^{-1}; **HRMS (ESI):** Calculated for $C_{17}H_{24}O_4$ $[M+Na]^+$ 315.1675, found 315.1678.

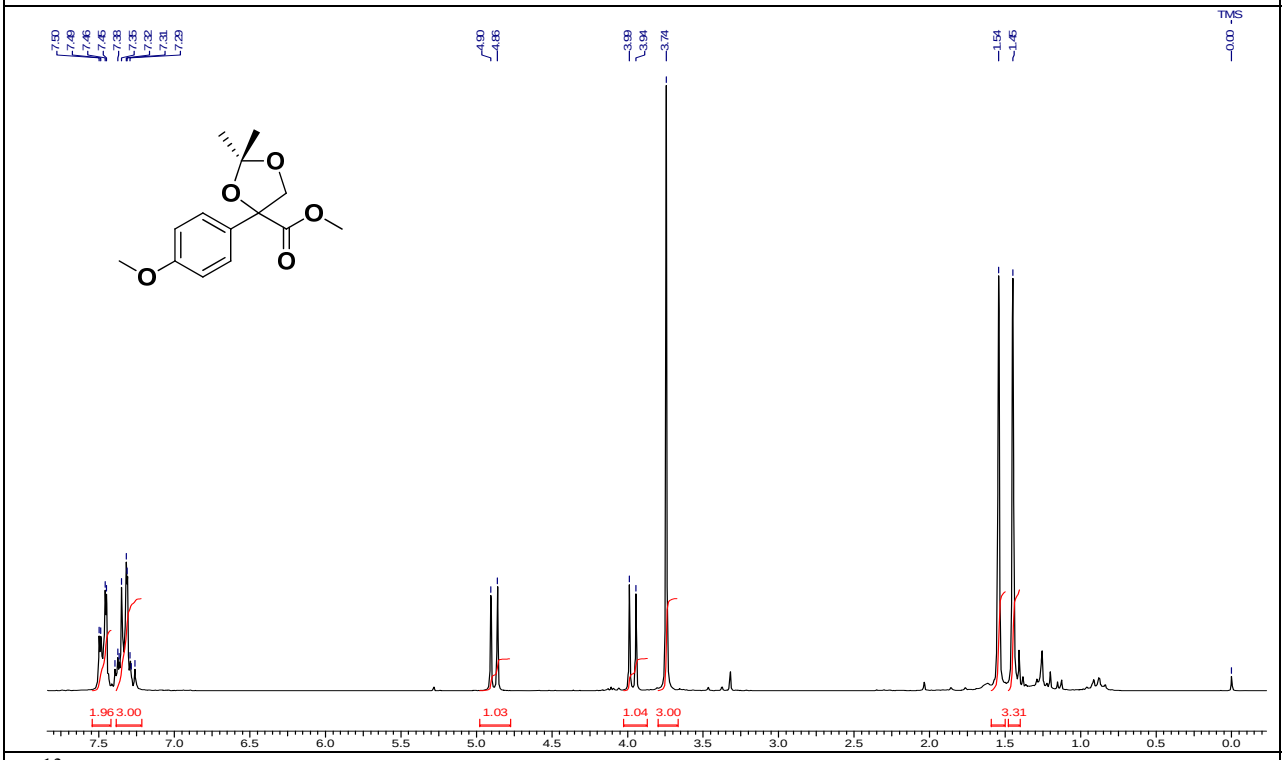
1−Phenylcyclopentanol (24b) [20]



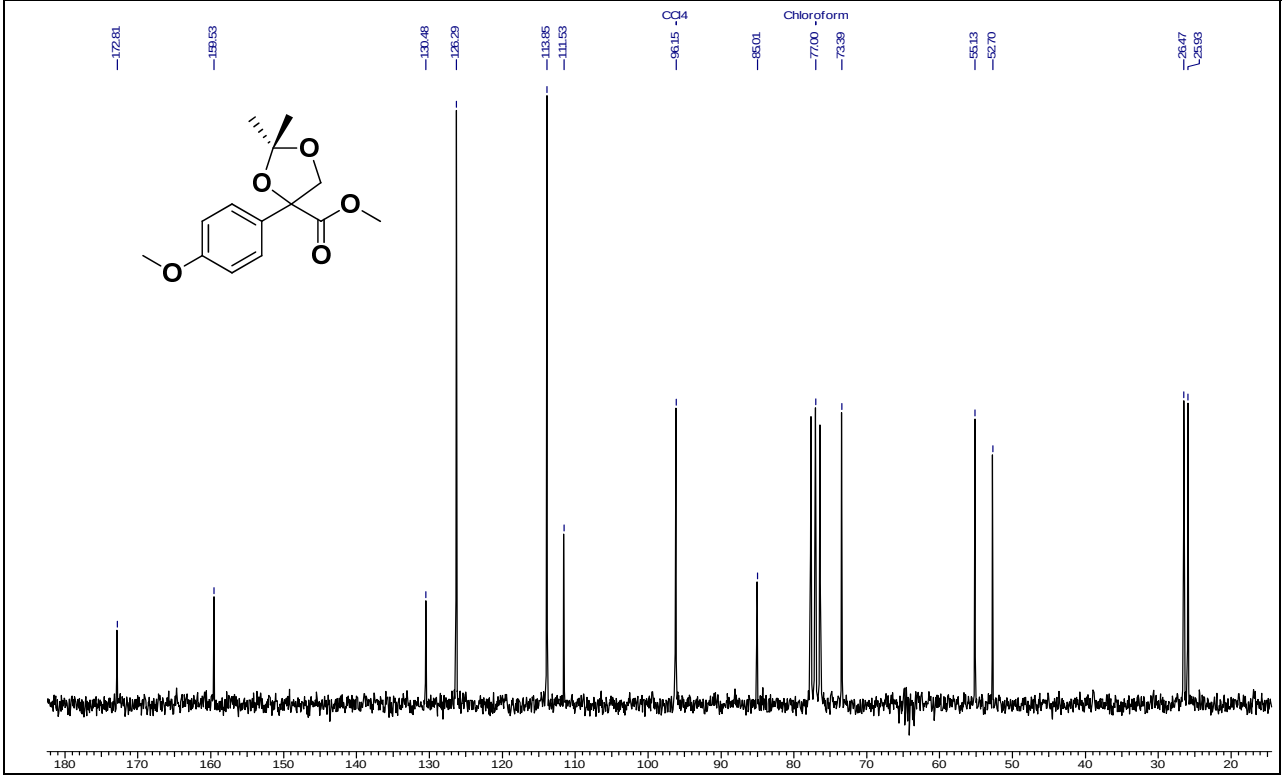
Column chromatography: 200–400 silica gel (12% EtOAc–pet. ether); **Molecular formula:** $C_{11}H_{14}O$, **Yield:** (0.529 g, 89%); **^{1}H NMR (200 MHz, $CDCl_3$+CCl_4)**: δ 7.44−7.37 (m, 2H), 7.30−7.11 (m, 3H), 1.94−1.74 (m, 8H); **^{13}C NMR (50 MHz, $CDCl_3$+CCl_4):** δ 147.0, 128.1, 126.7, 125.0, 83.4, 41.8, 23.8; **MS (ESI)** (*m/z*): 185 $[M+Na]^+$.

3.1.4.1. ^{1}H and ^{13}C NMR Spectra

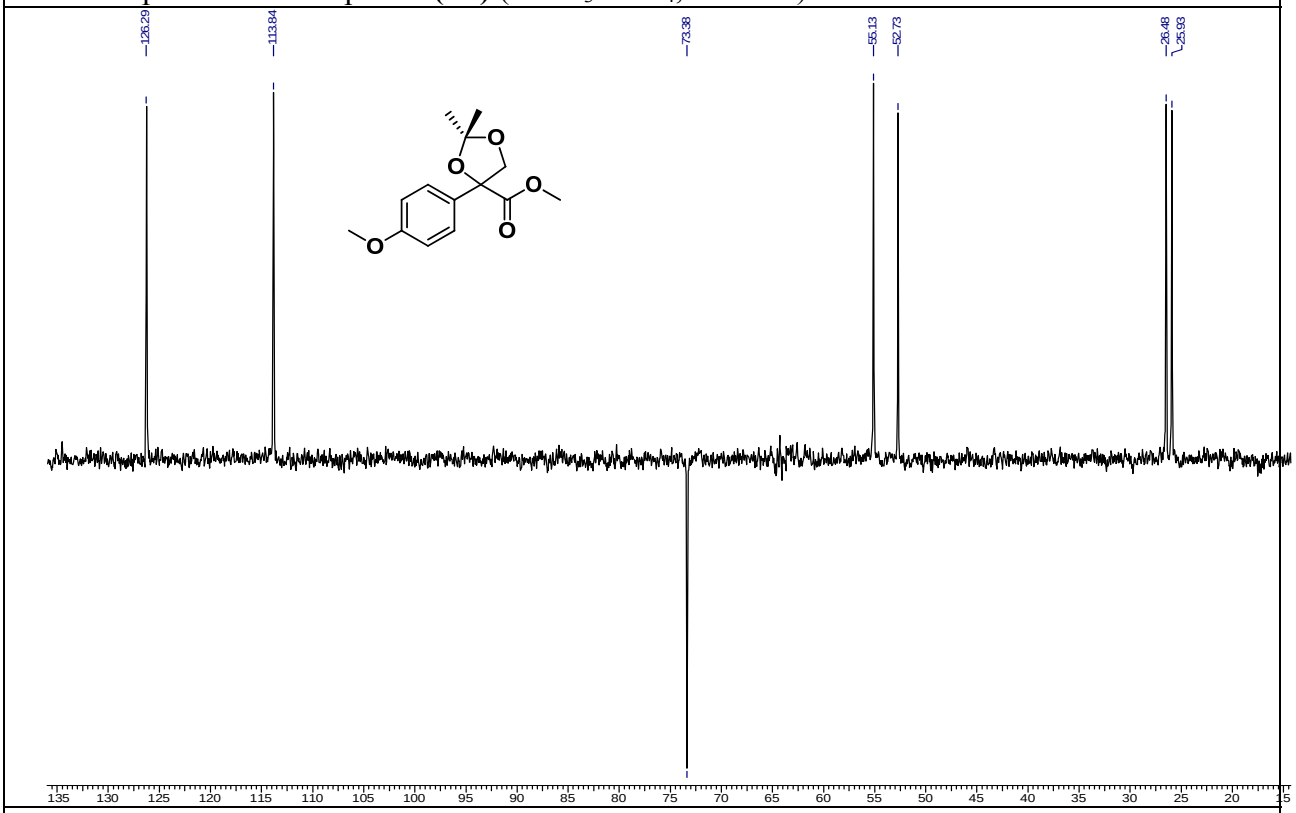
^{1}H NMR spectrum of compound **(±3)** ($CDCl_3$+CCl_4, 200 MHz)



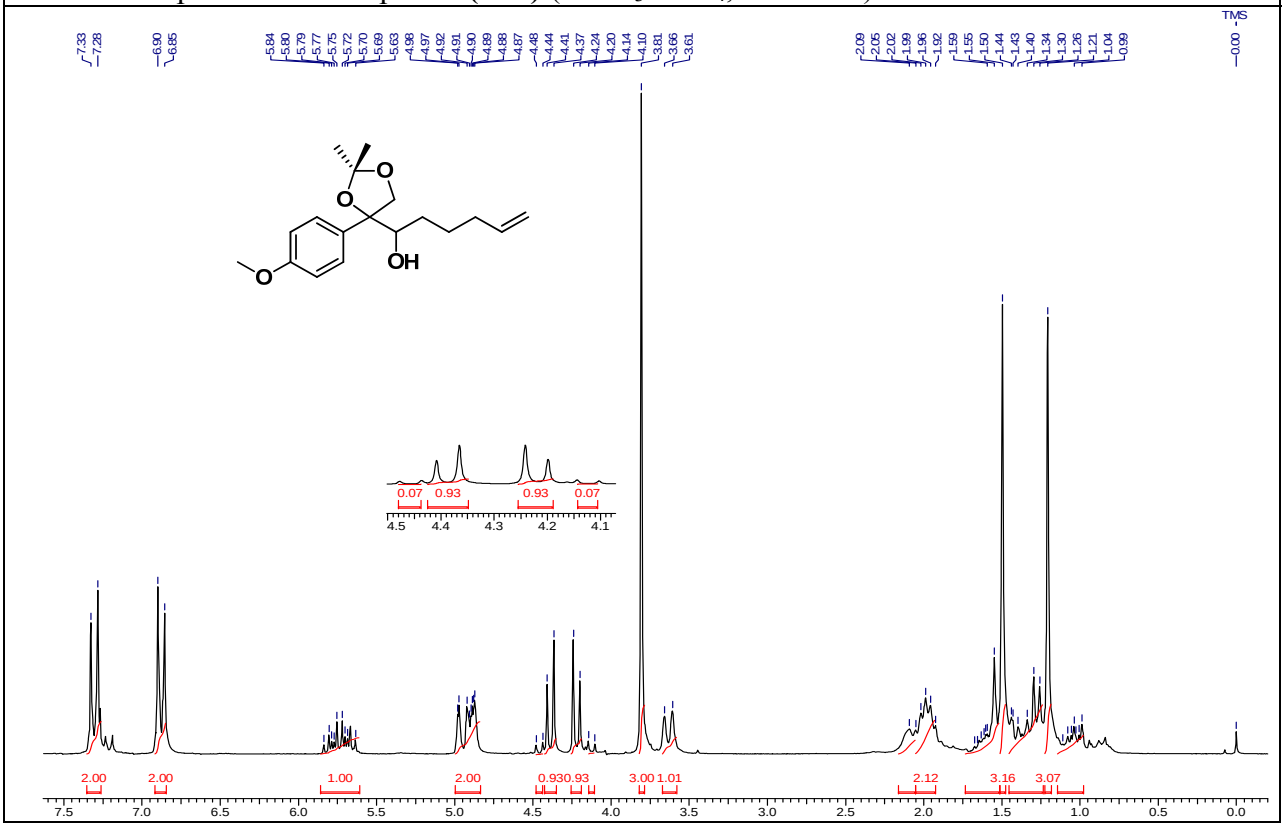
^{13}C NMR spectrum of compound **(±3)** ($CDCl_3$+CCl_4, 50 MHz)



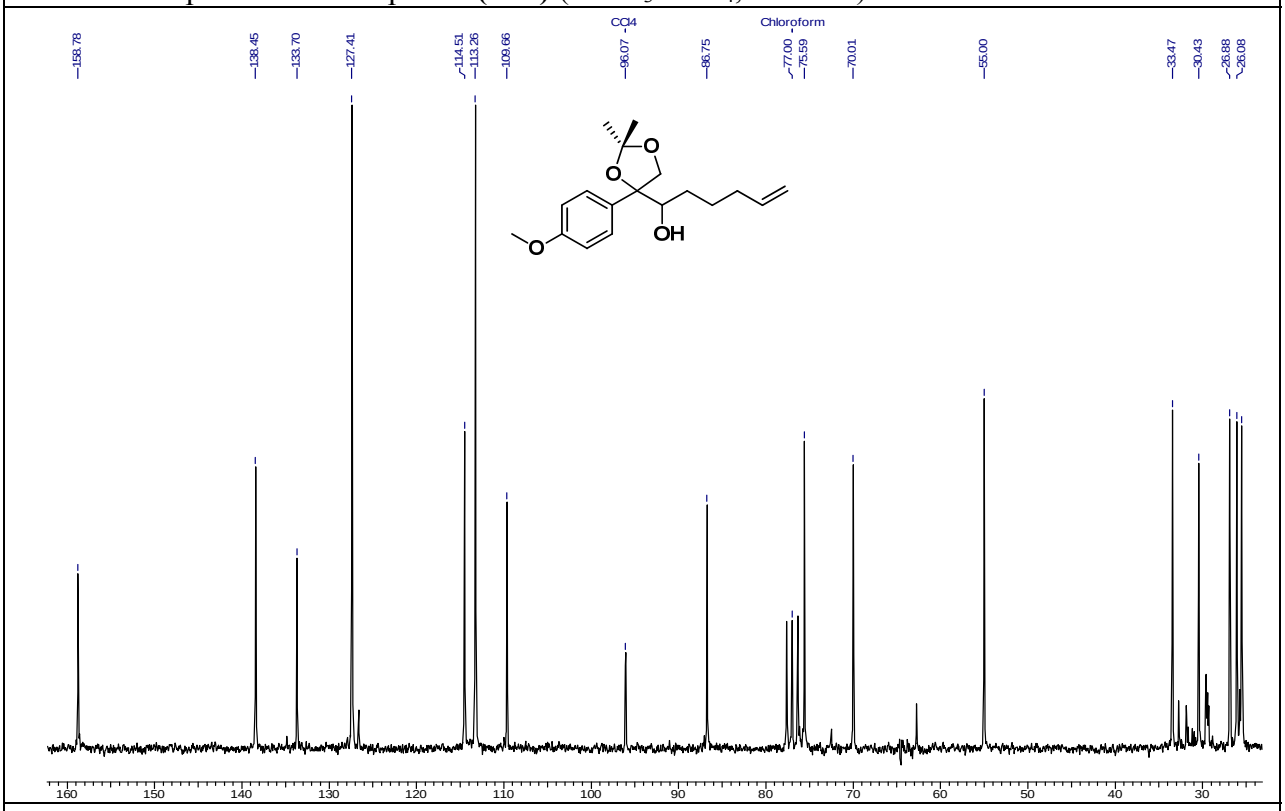
DEPT spectrum of compound **(±3)** ($CDCl_3$+CCl_4, 50 MHz)



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

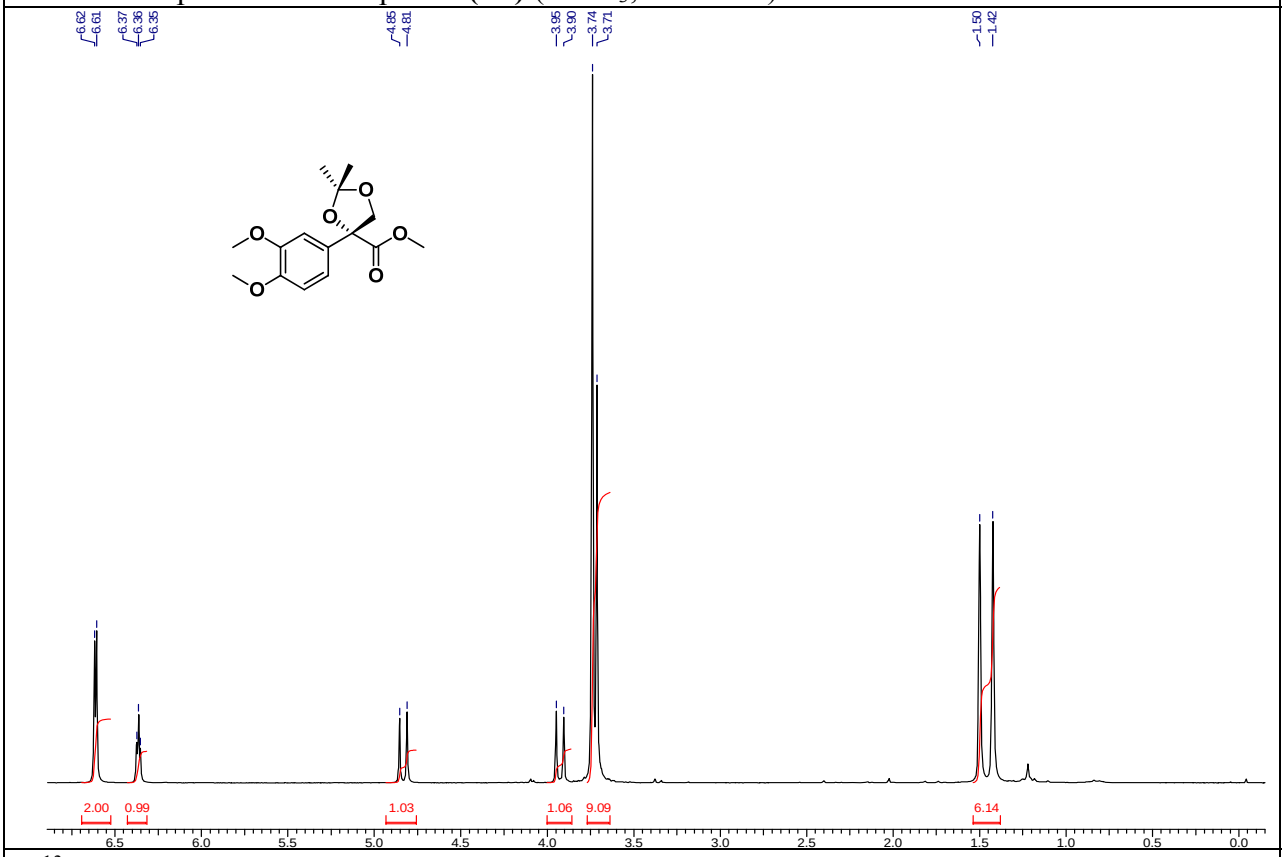


^{13}C NMR spectrum of compound **(±3a)** ($CDCl_3$+CCl_4, 50 MHz)

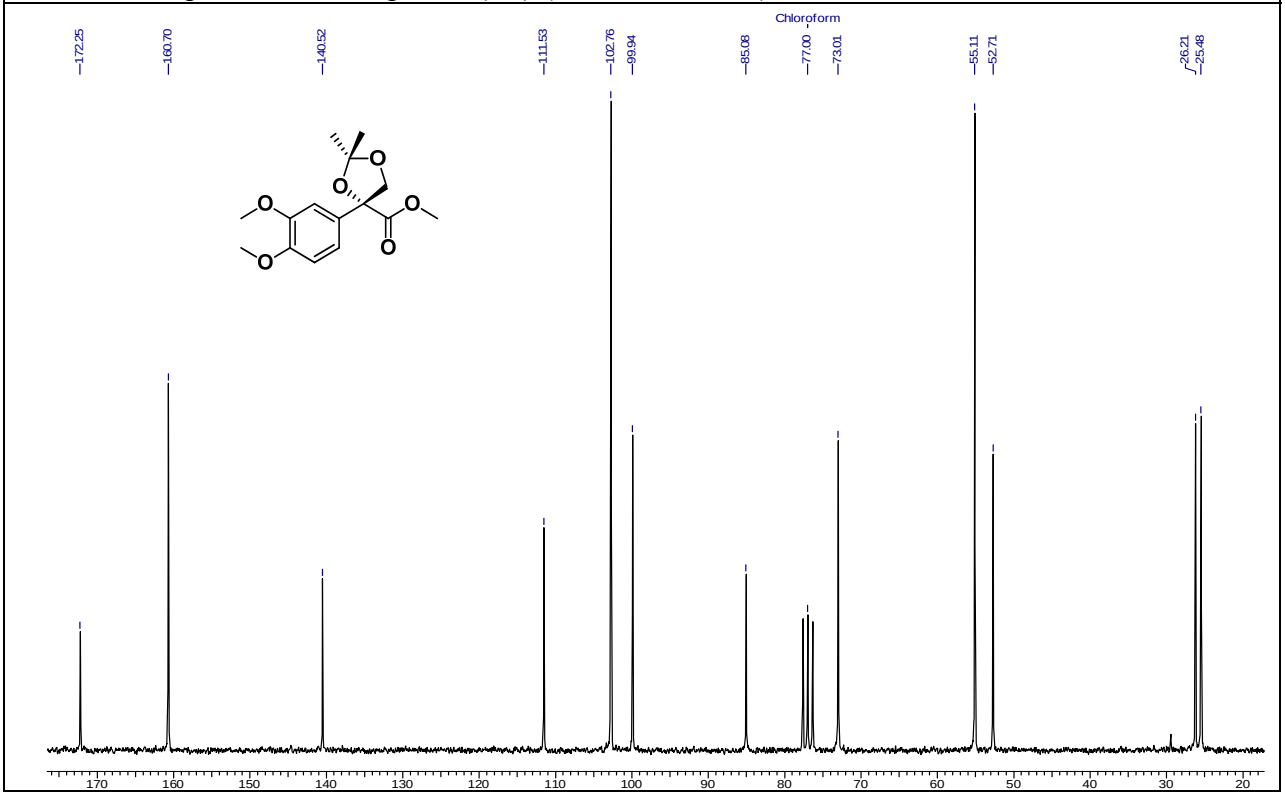


DEPT specrum of compound **(±3a)** ($CDCl_3$+CCl_4, 50 MHz)

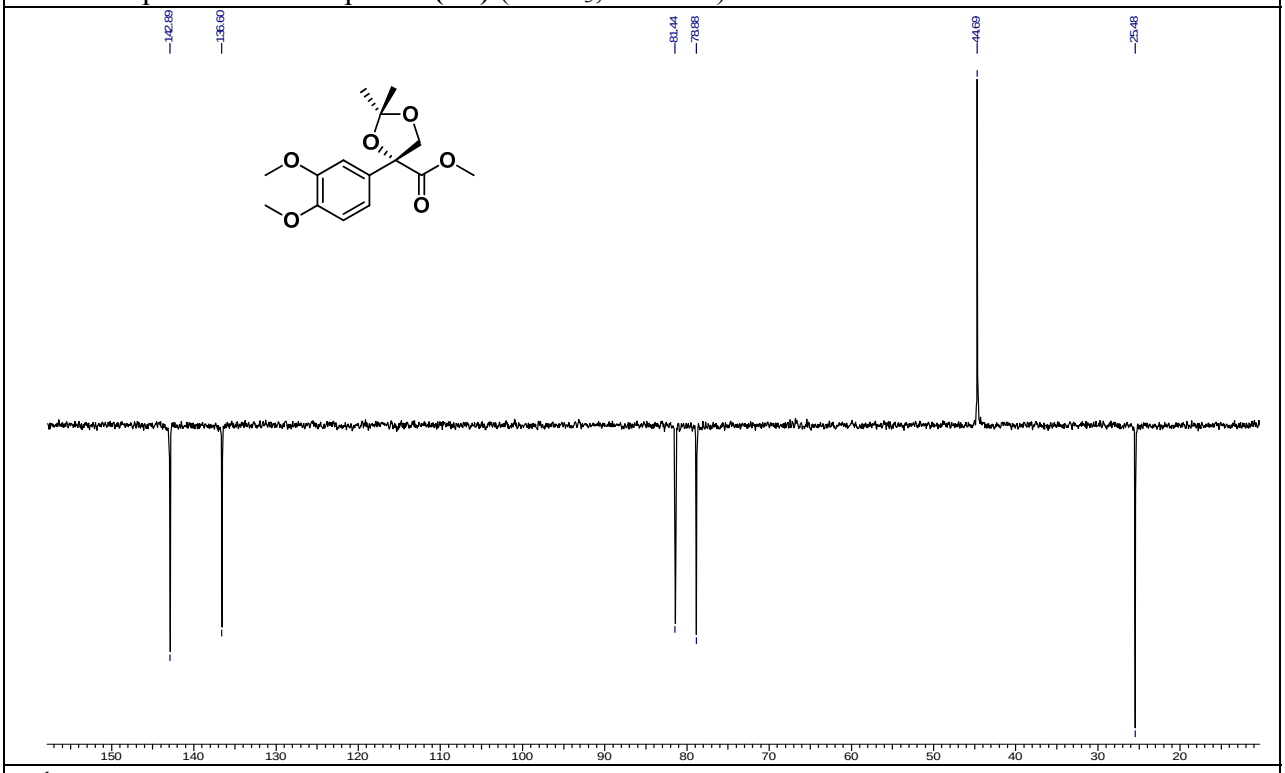
^{1}H NMR spectrum of compound **(±4)** ($CDCl_3$, 200 MHz)



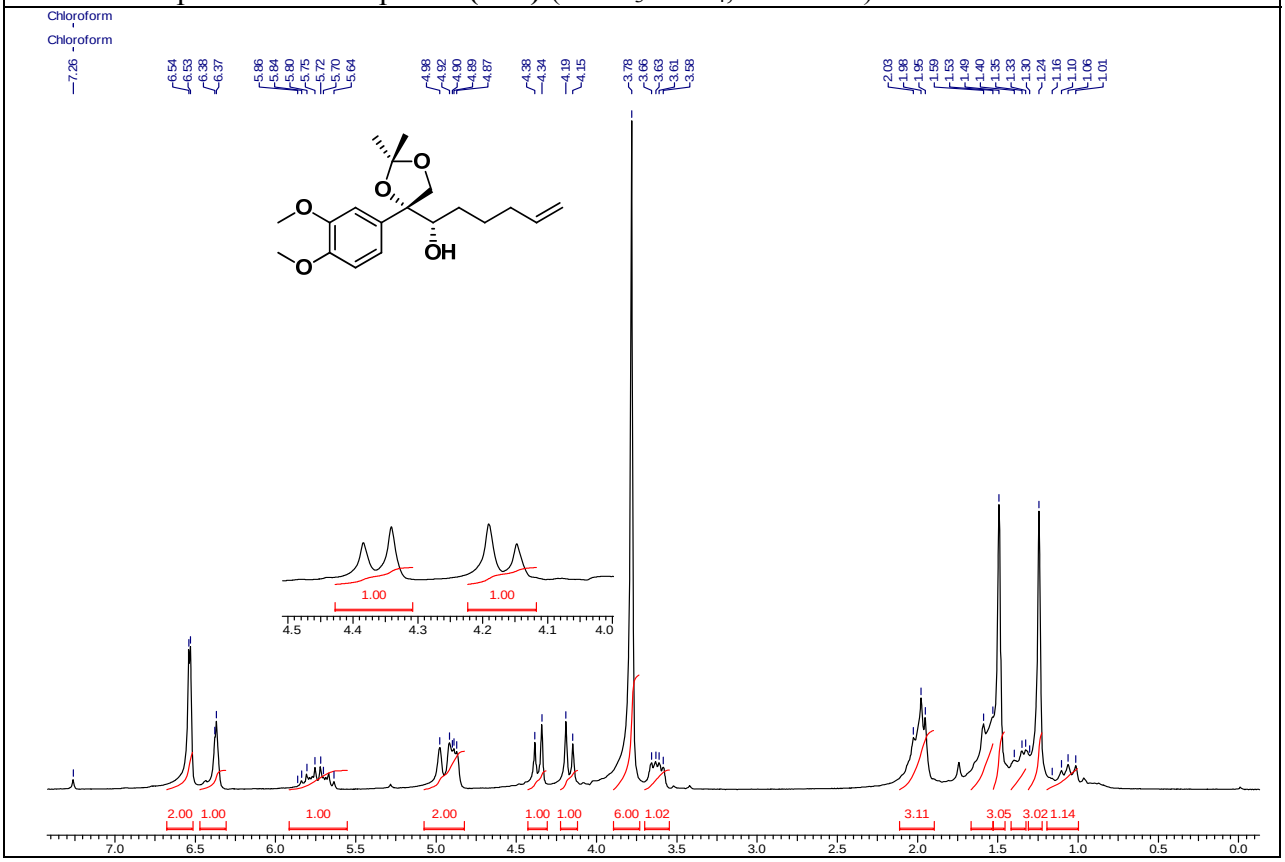
^{13}C NMR spectrum of compound **(±4)** ($CDCl_3$, 50 MHz)



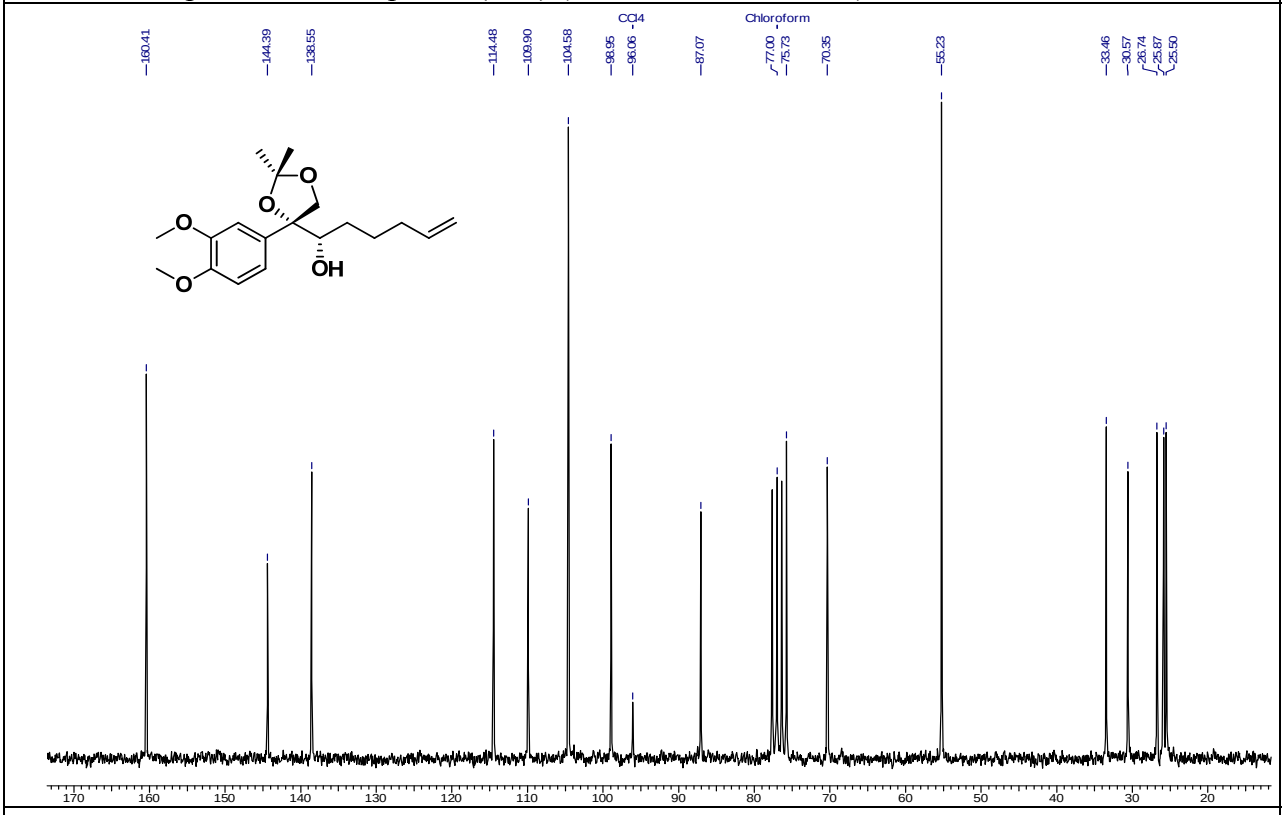
DEPT spectrum of compound **(±4)** ($CDCl_3$, 50 MHz)



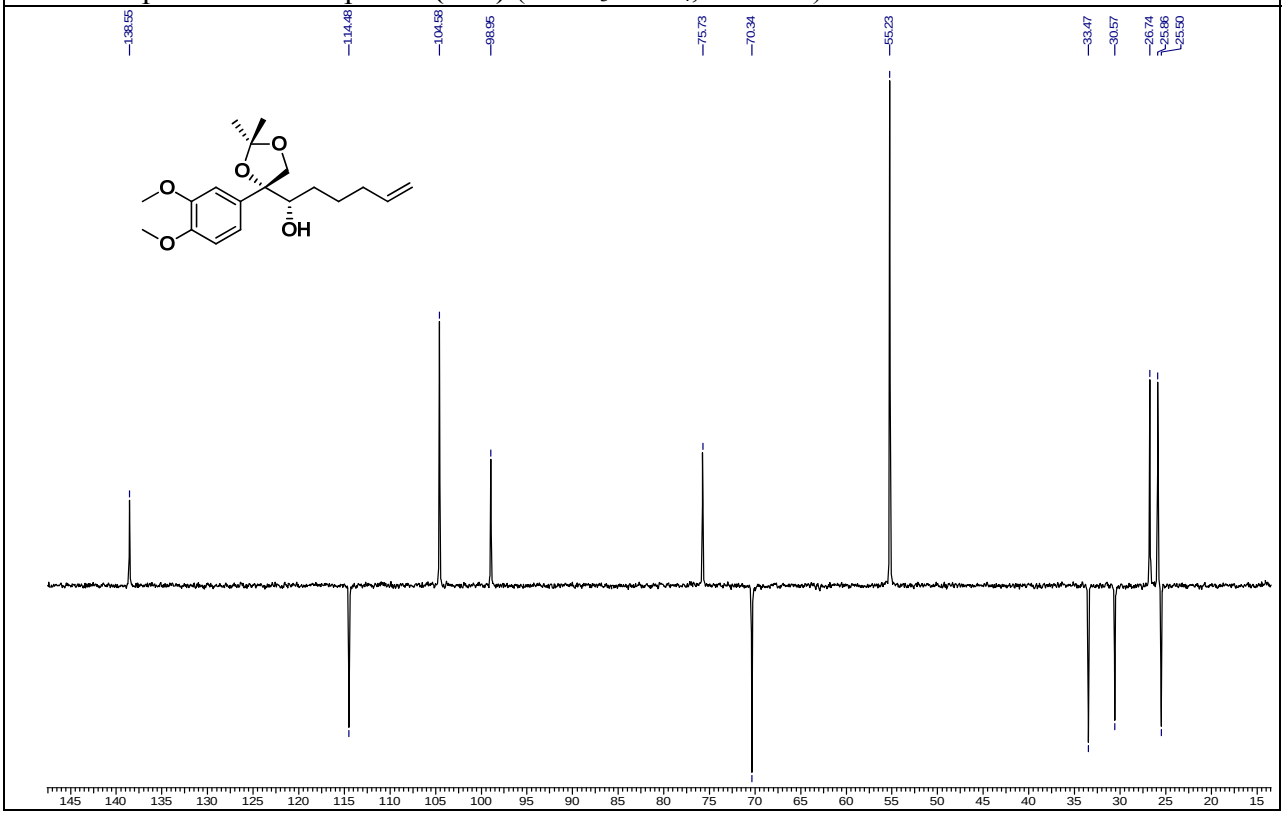
^{1}H NMR spectrum of compound **(±4a)** ($CDCl_3$+CCl_4, 200 MHz)



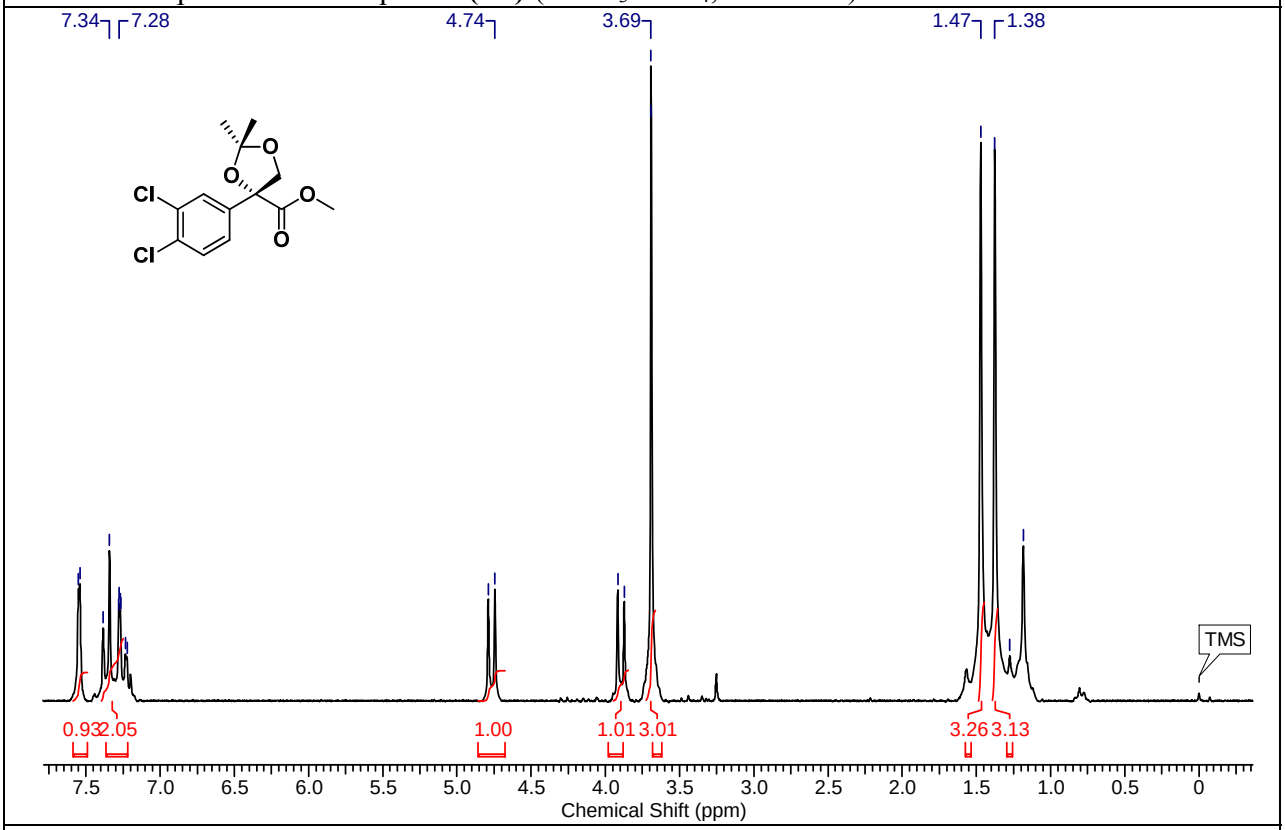
^{13}C NMR spectrum of compound **(±4a)** ($CDCl_3$+CCl_4, 50 MHz)



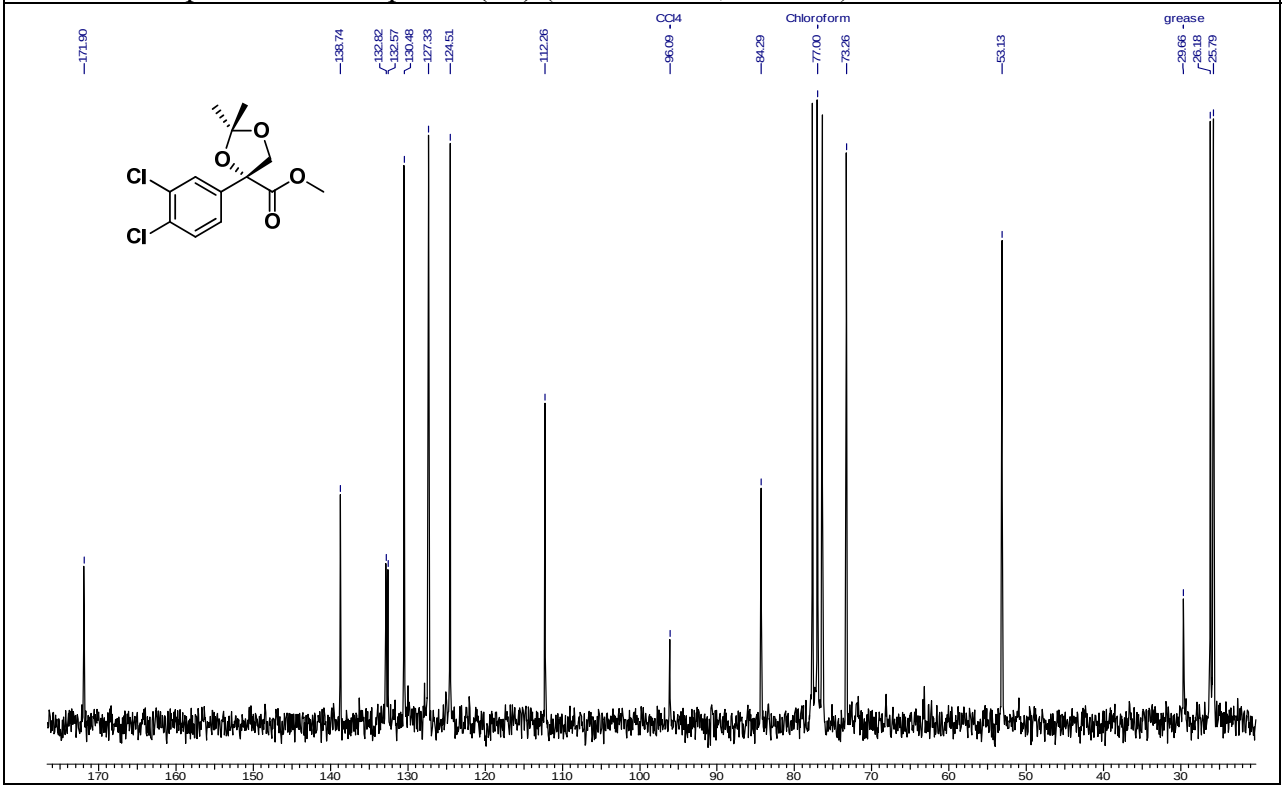
DEPT spectrum of compound **(±4a)** ($CDCl_3$+CCl_4, 50 MHz)



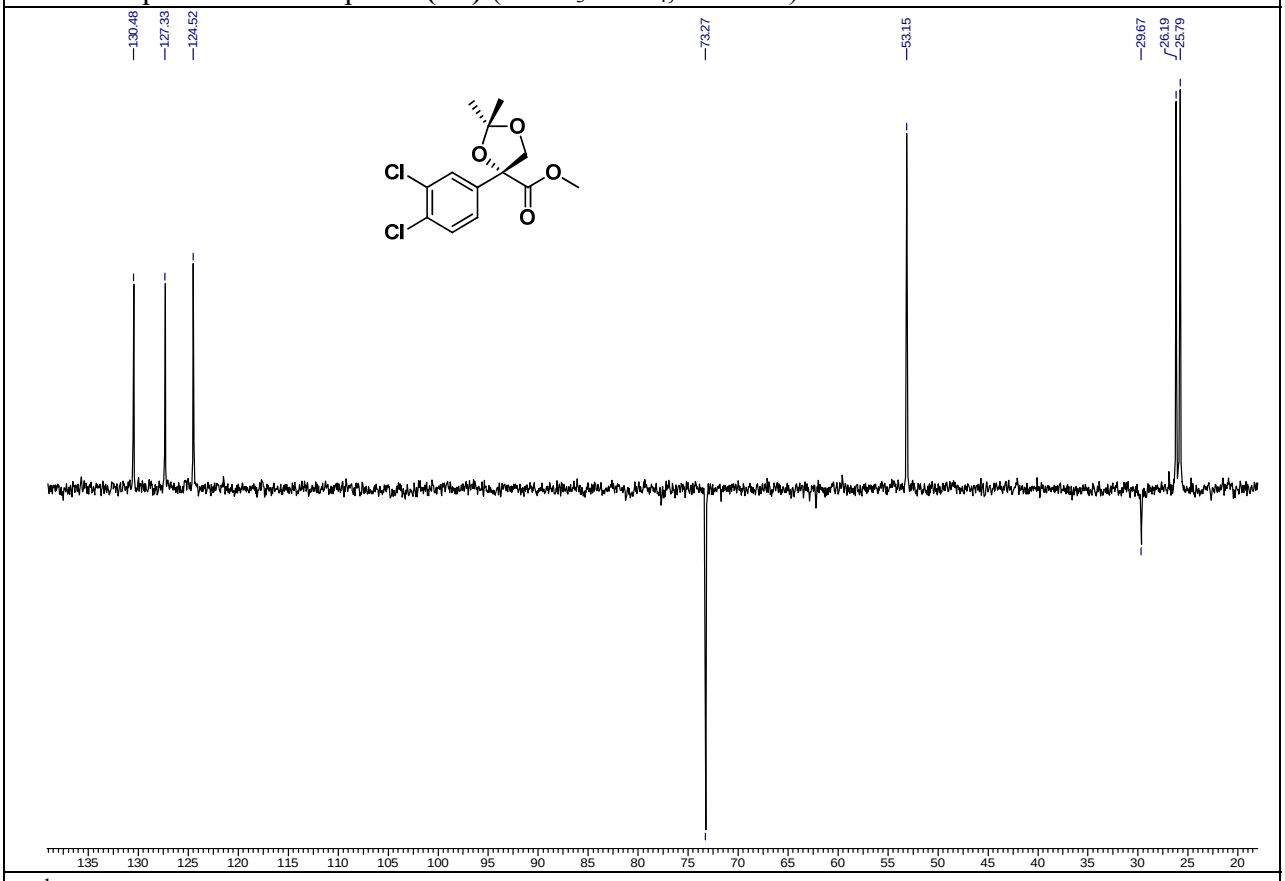
^{1}H NMR spectrum of compound **(±5)** ($CDCl_3$+CCl_4, 200 MHz)



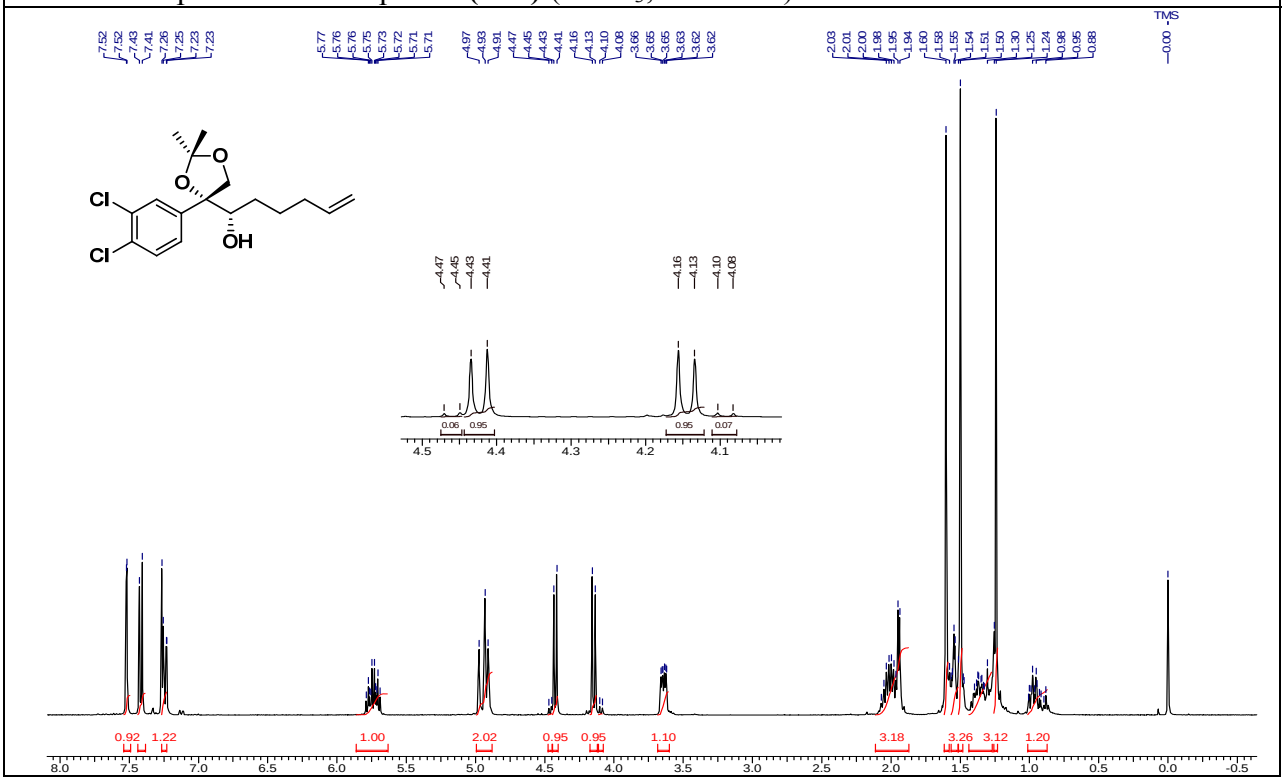
^{13}C NMR spectrum of compound **(±5)** ($CDCl_3$+CCl_4, 50 MHz)



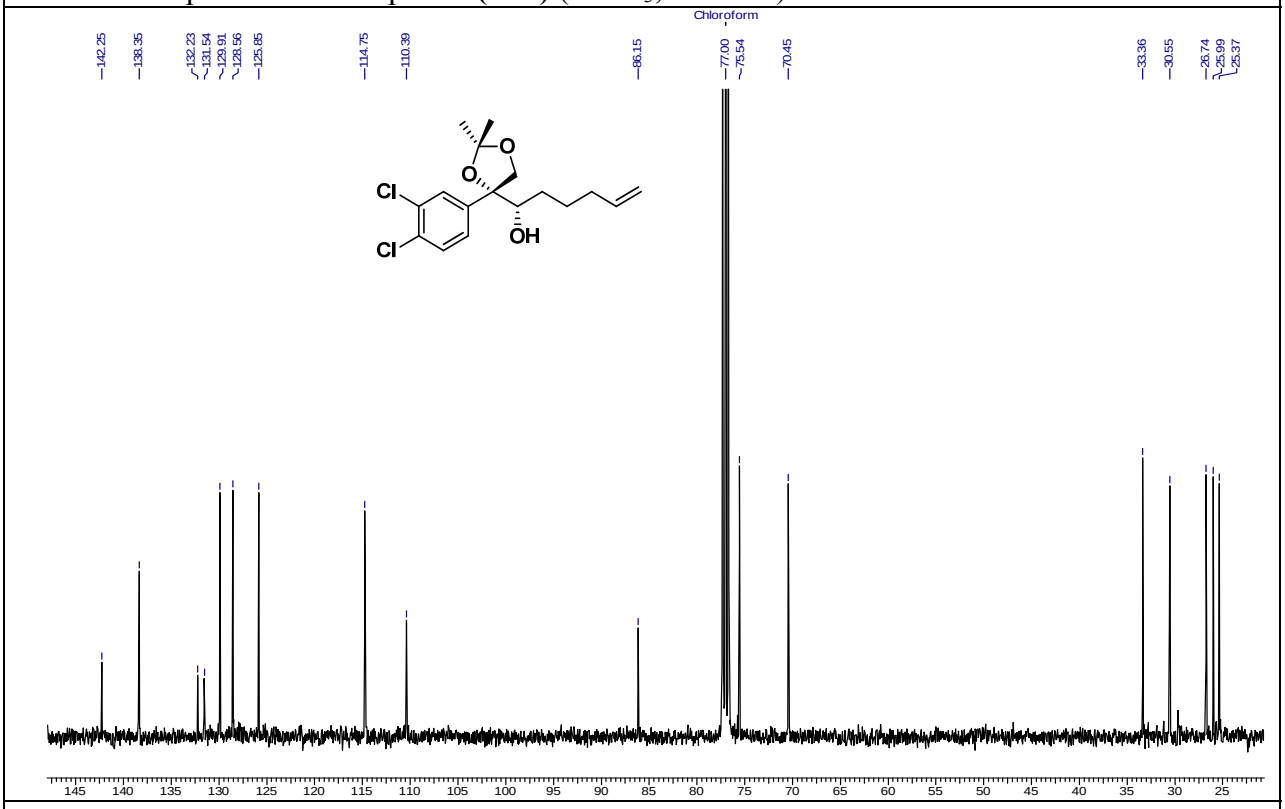
DEPT spectrum of compound**(±5)** ($CDCl_3$+CCl_4, 50 MHz)



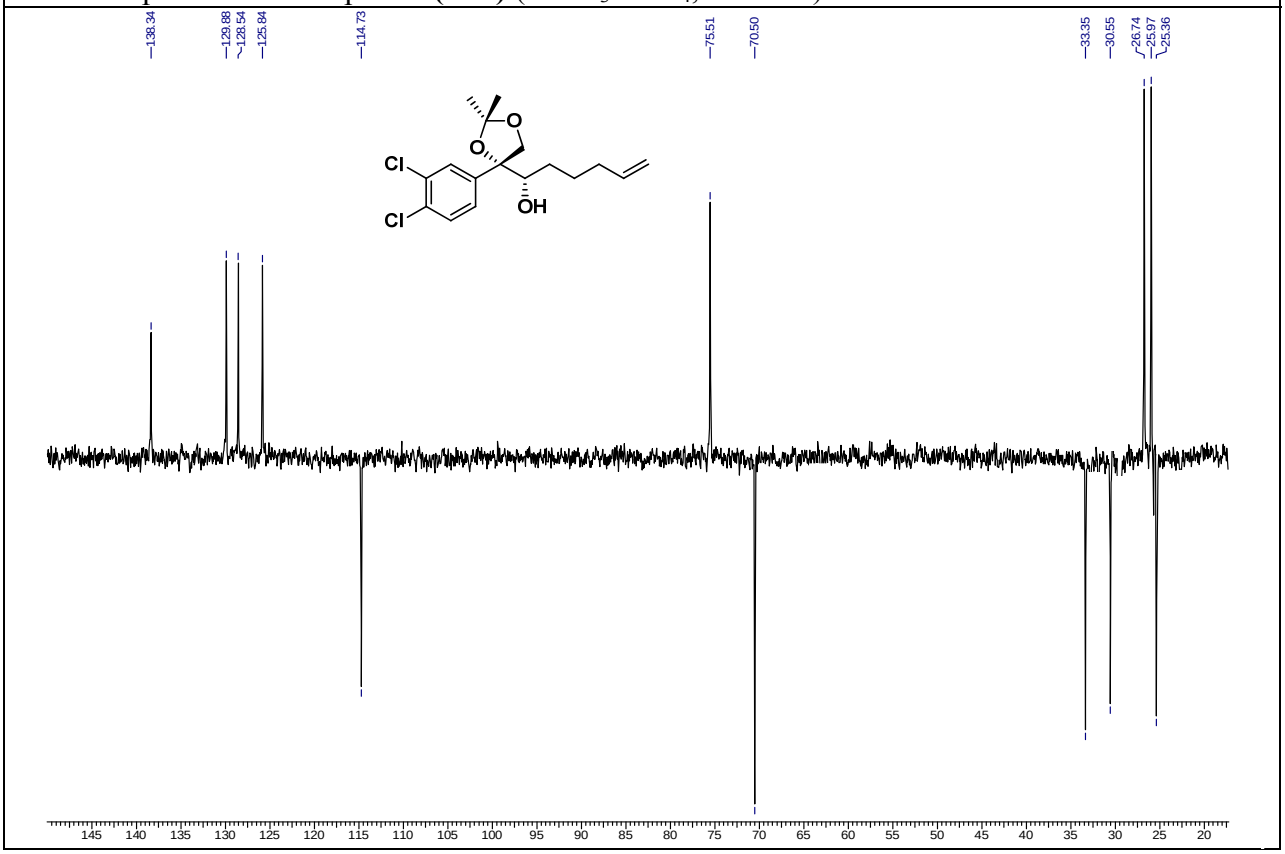
^{1}H NMR spectrum of compound **(±5a)** ($CDCl_3$, 200 MHz)



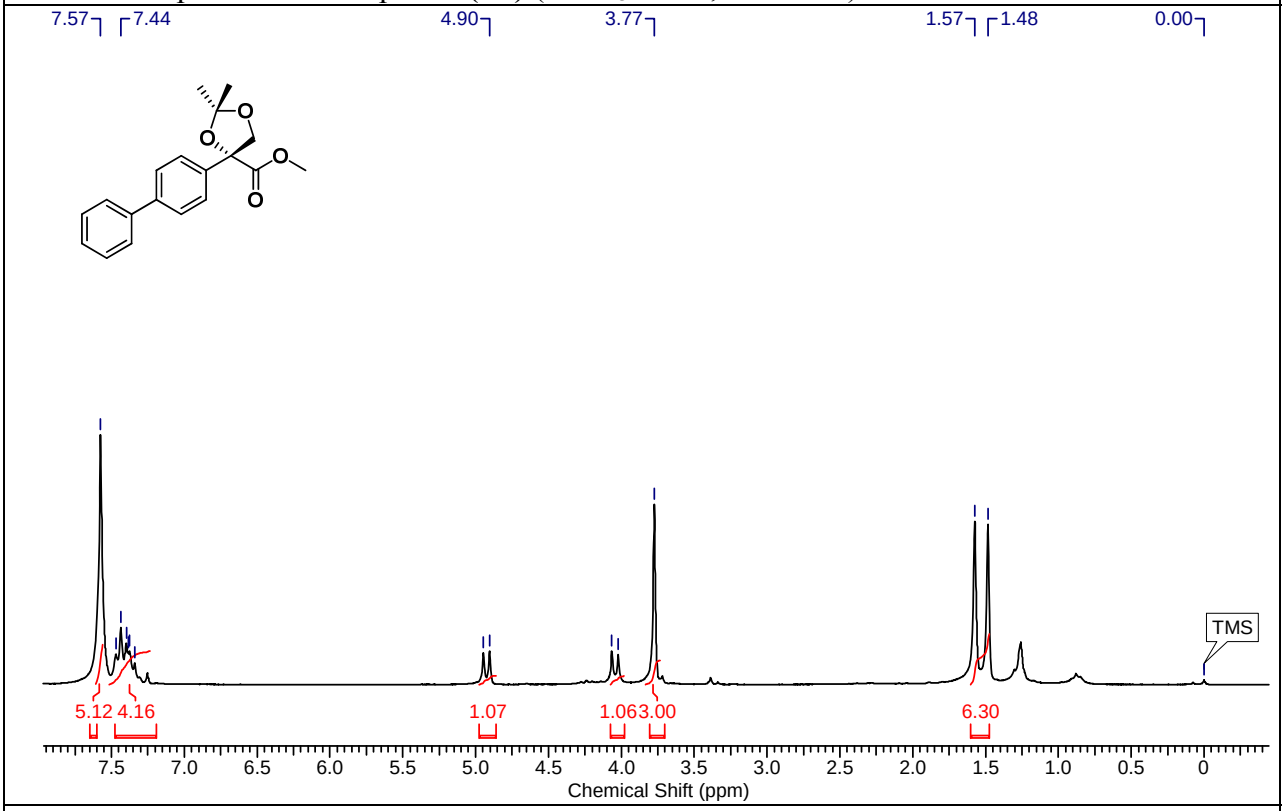
^{13}C NMR spectrum of compound **(±5a)** ($CDCl_3$, 50 MHz)



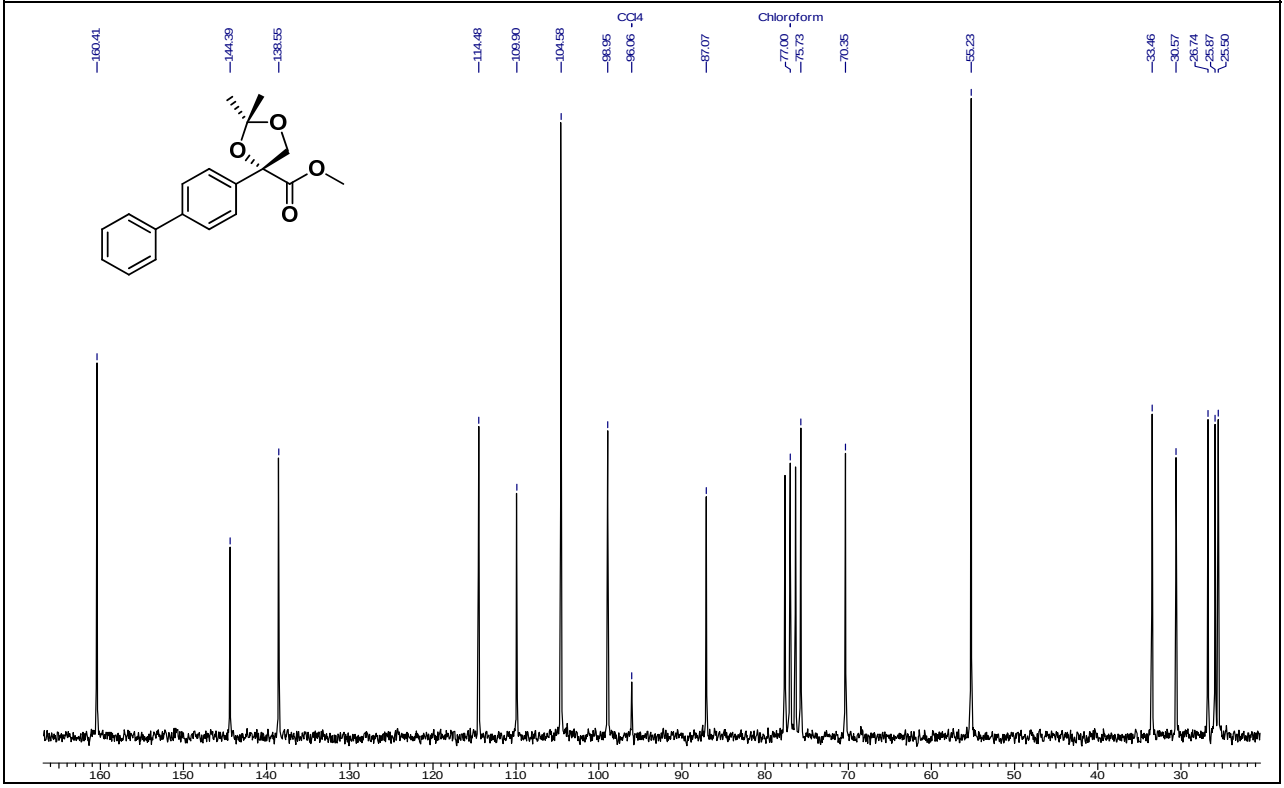
DEPT spectrum of compound **(±5a)** ($CDCl_3$+CCl_4, 50 MHz)



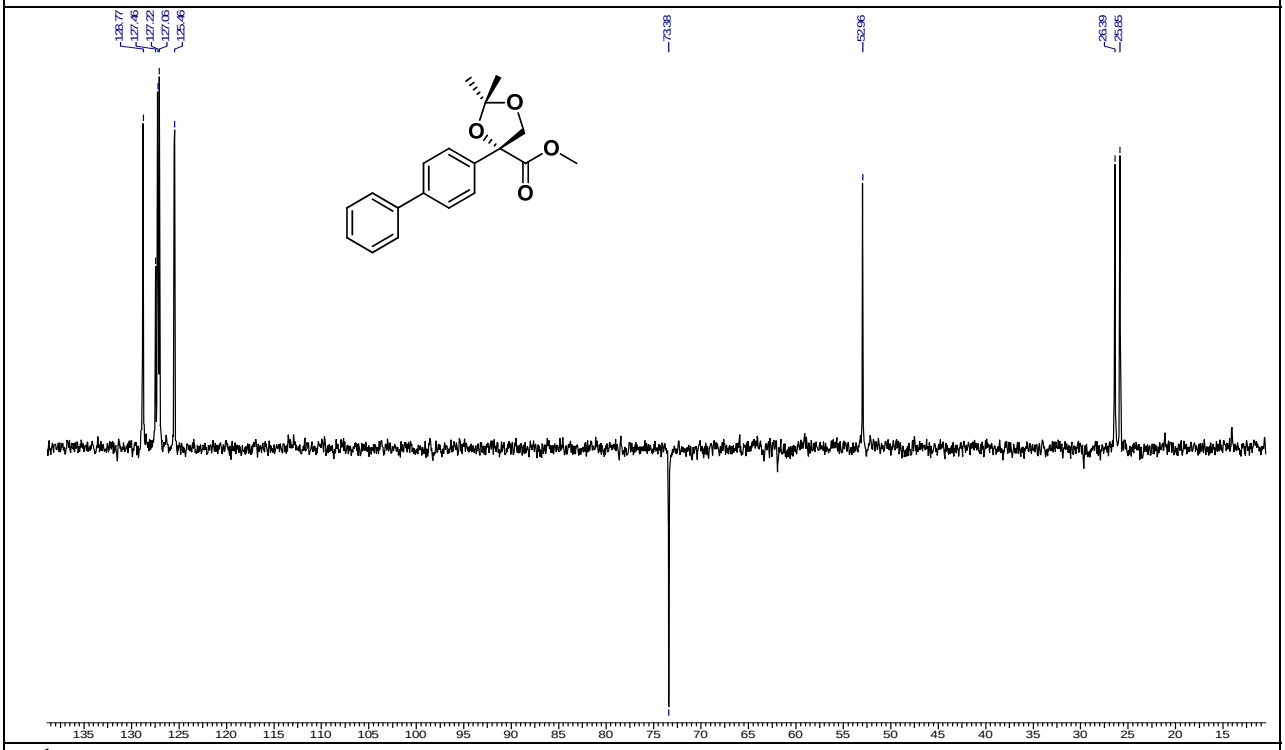
^{1}H NMR spectrum of compound **(±6)** ($CDCl_3$+CCl_4, 200 MHz)



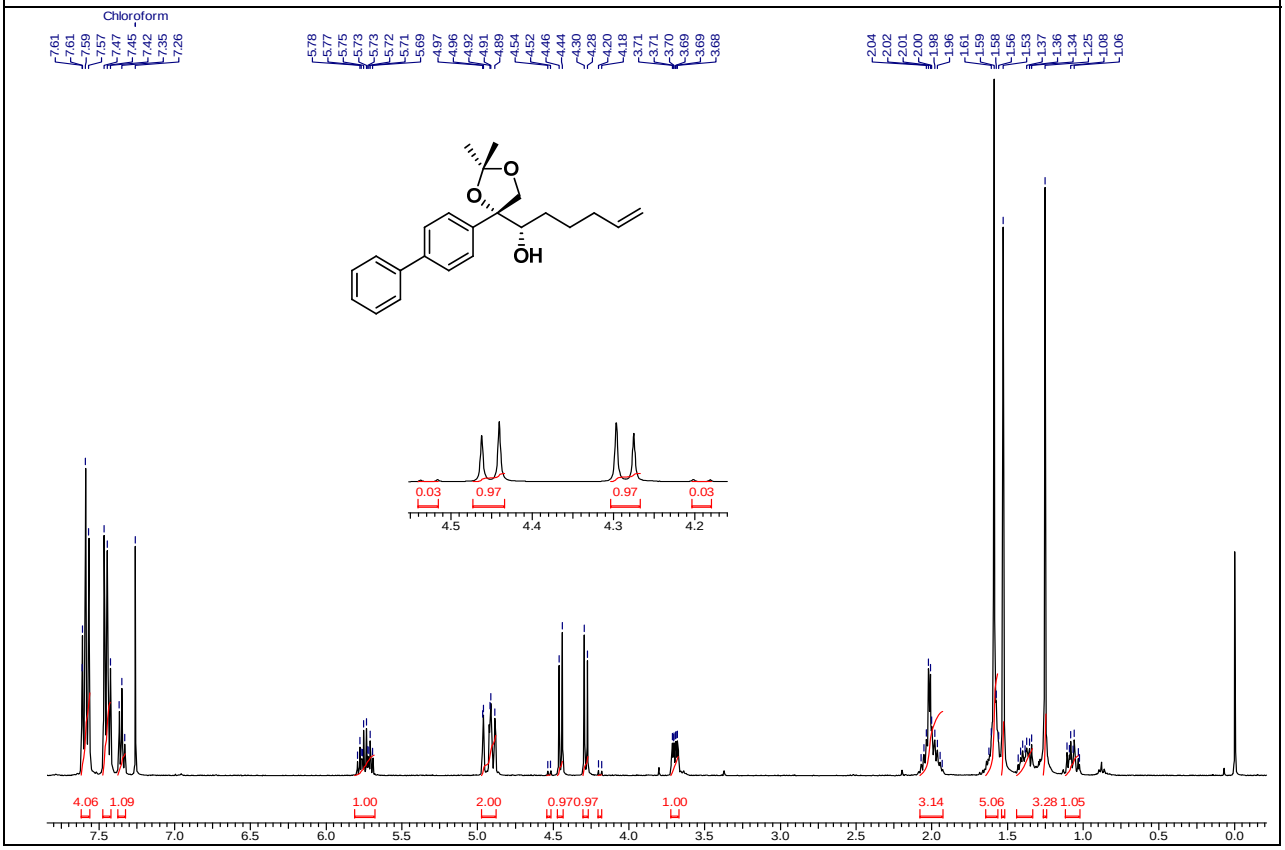
^{13}C NMR spectrum of compound **(±6)** ($CDCl_3$+CCl_4, 50 MHz)



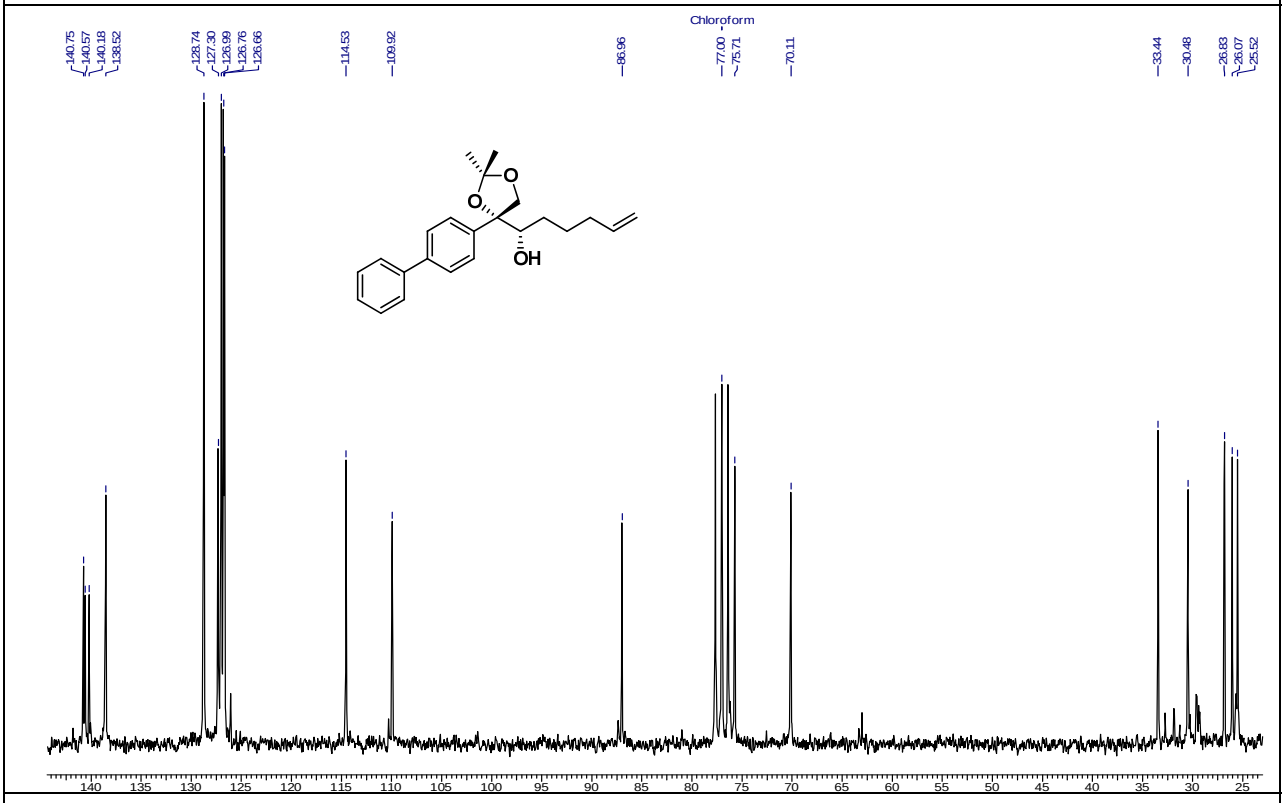
DEPT spectrum of compound **(±6)** ($CDCl_3$+CCl_4, 50 MHz)



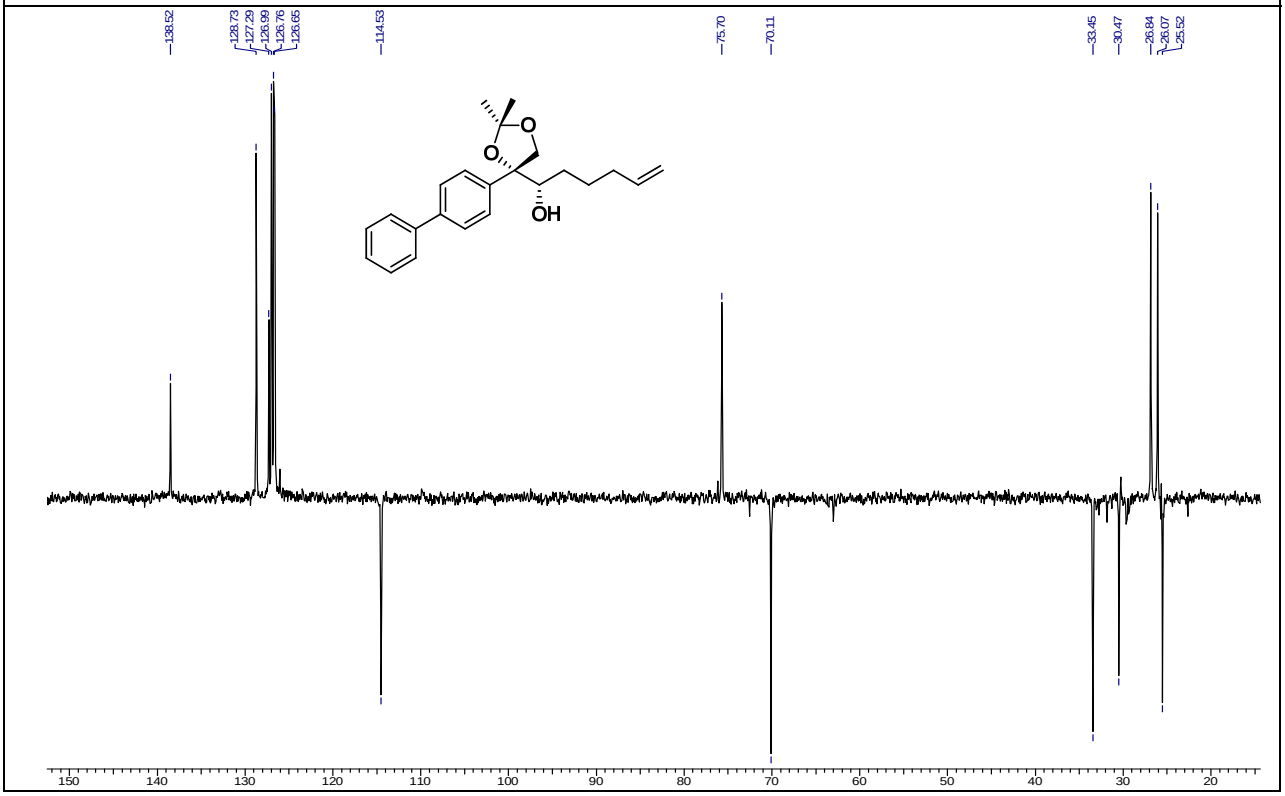
^{1}H NMR spectrum of compound **(±6a)** ($CDCl_3$, 200 MHz)



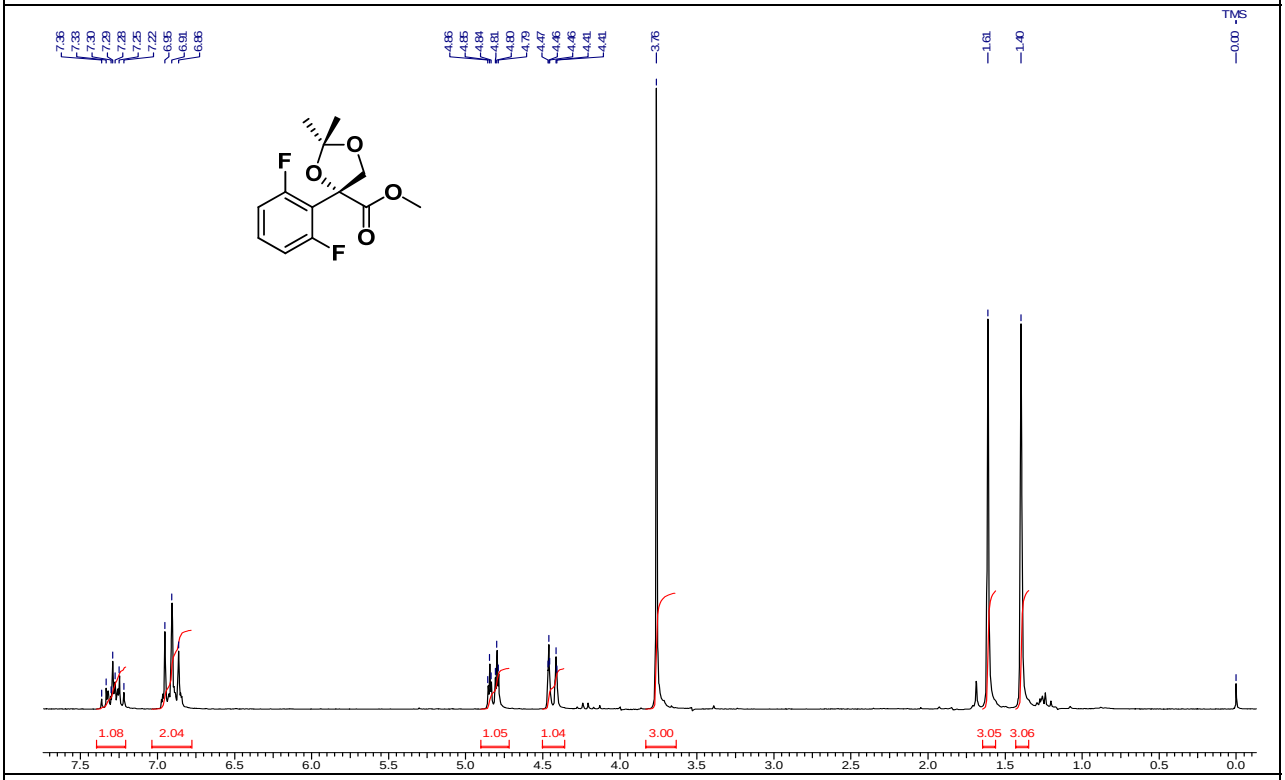
^{13}C NMR spectrum of compound **(±6a)** ($CDCl_3$, 50 MHz)



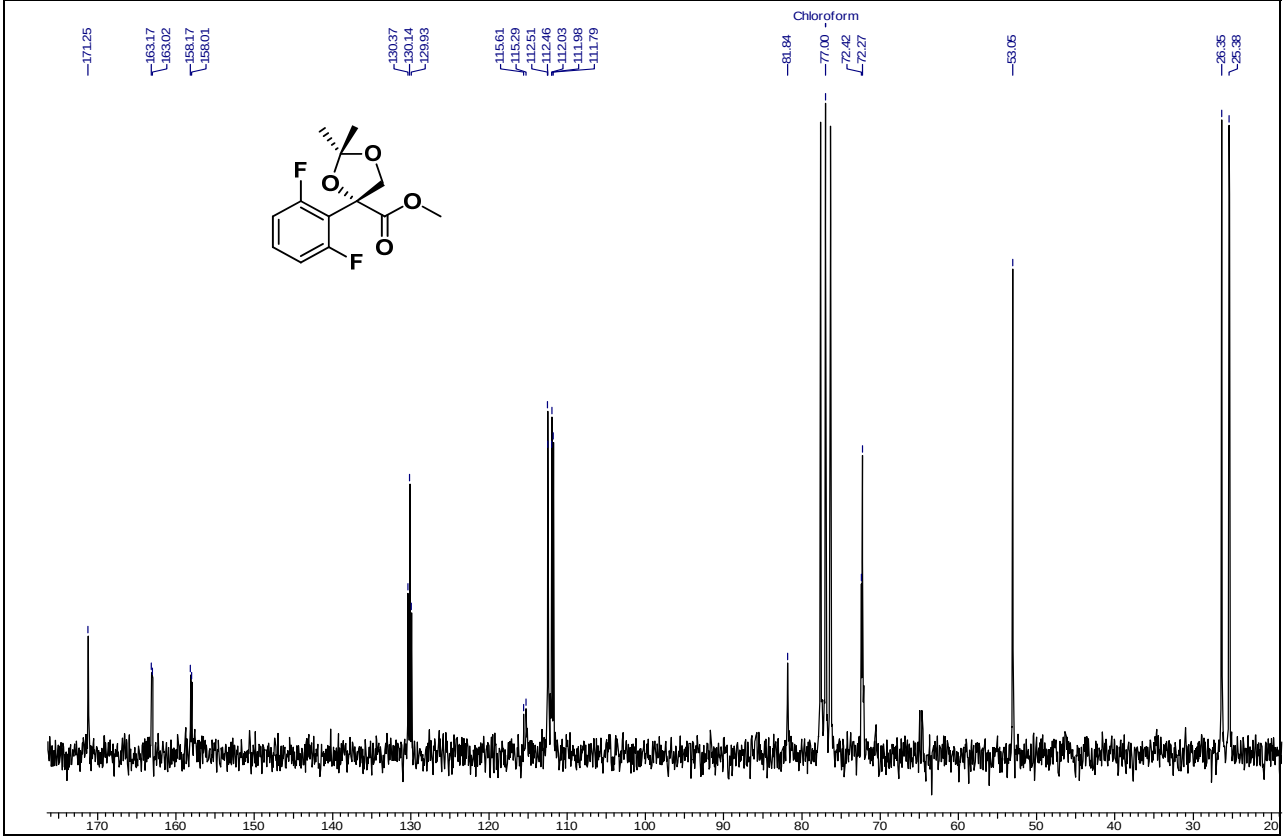
DEPT spectrum of compound **(±6a)** ($CDCl_3$, 50 MHz)



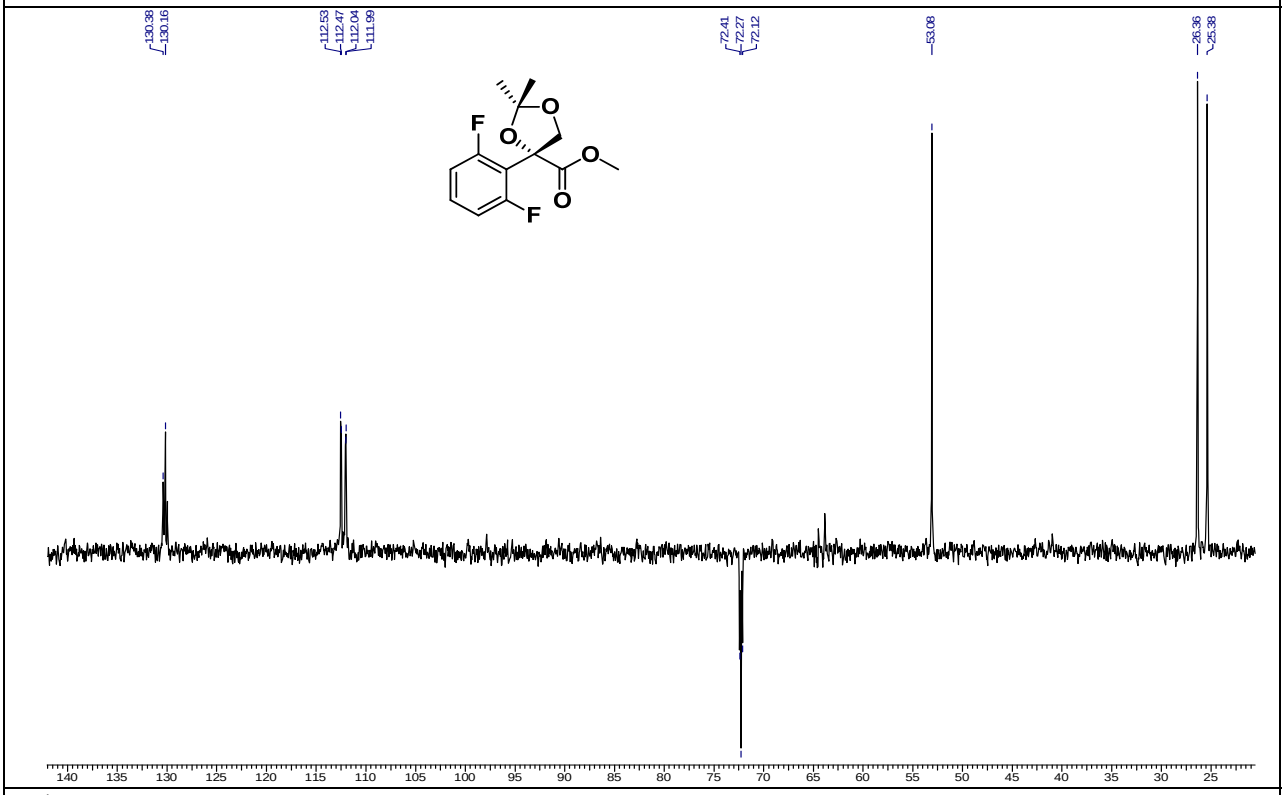
^{1}H NMR spectrum of compound **(±7)** ($CDCl_3$, 200 MHz)



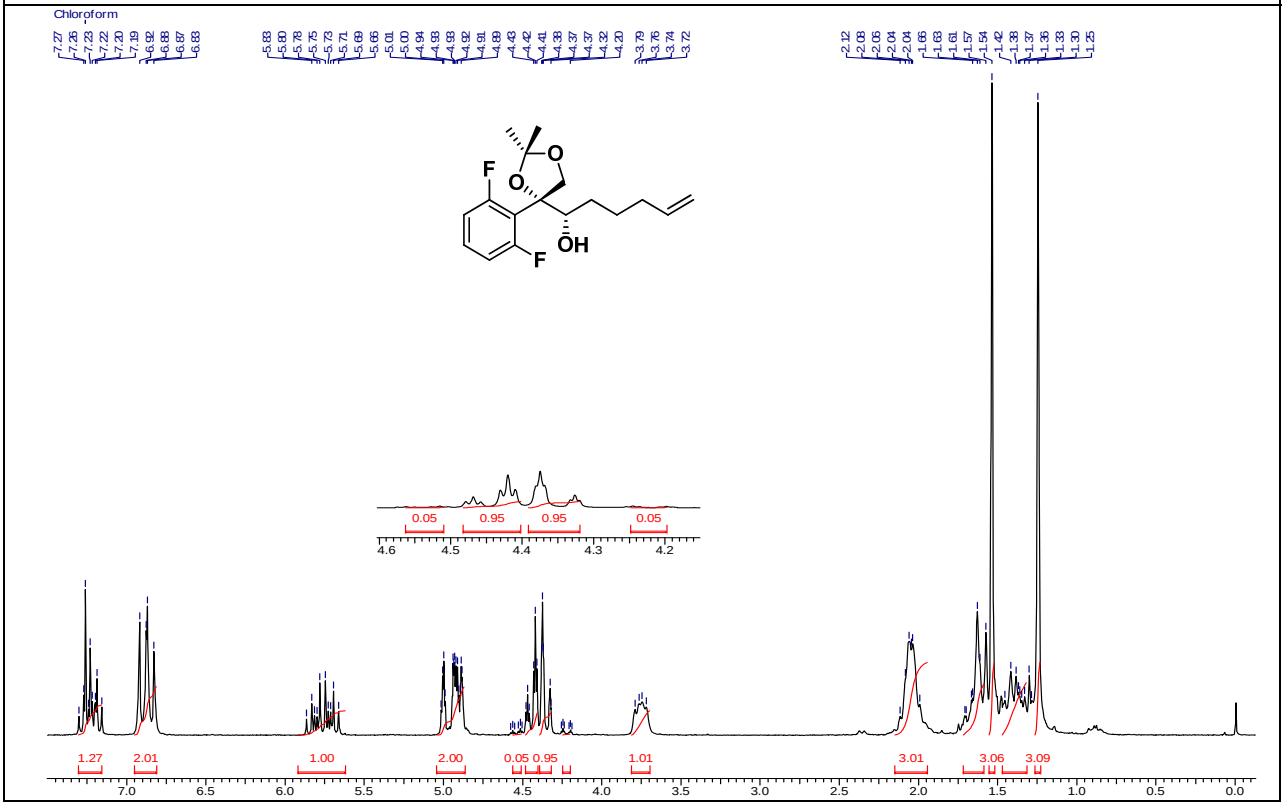
^{13}C NMR spectrum of compound **(±7)** ($CDCl_3$, 50 MHz)



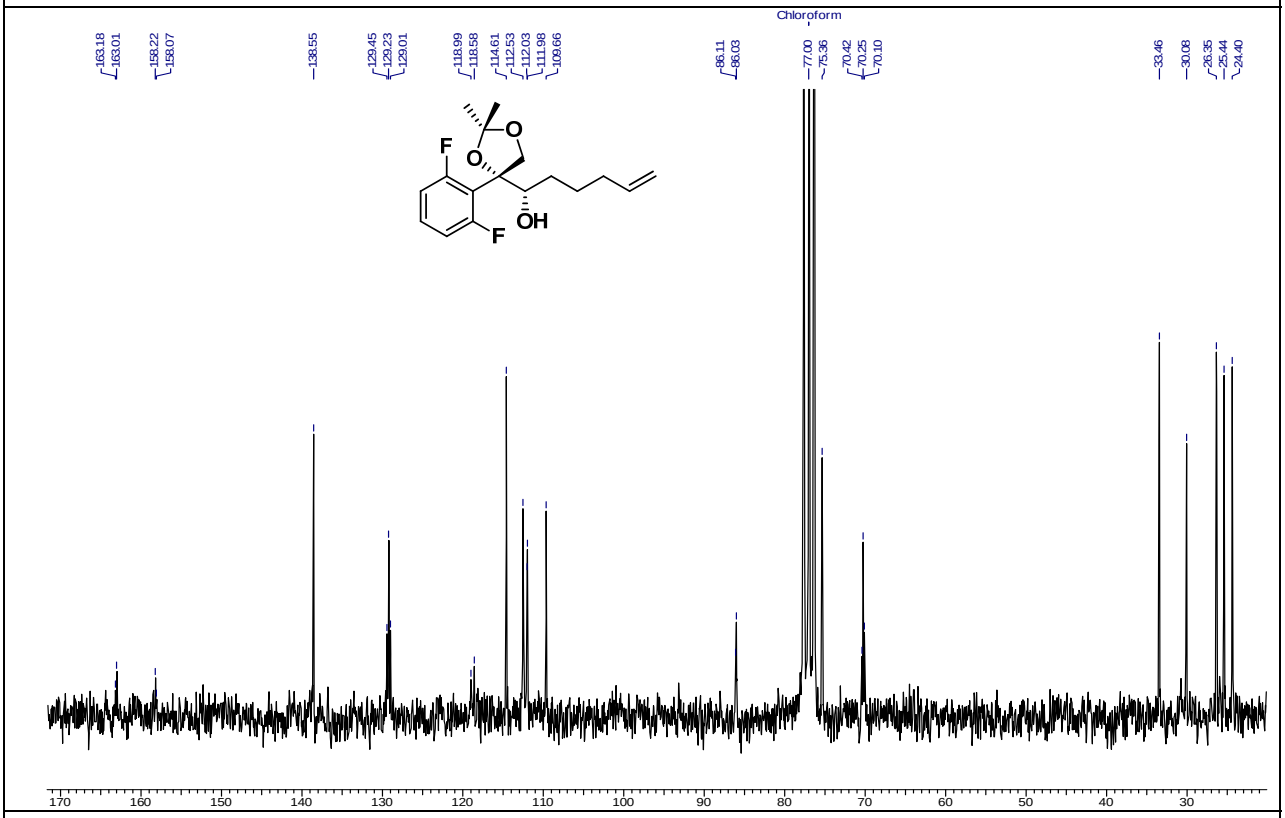
DEPT spectrum of compound **(±7)** ($CDCl_3$, 50 MHz)



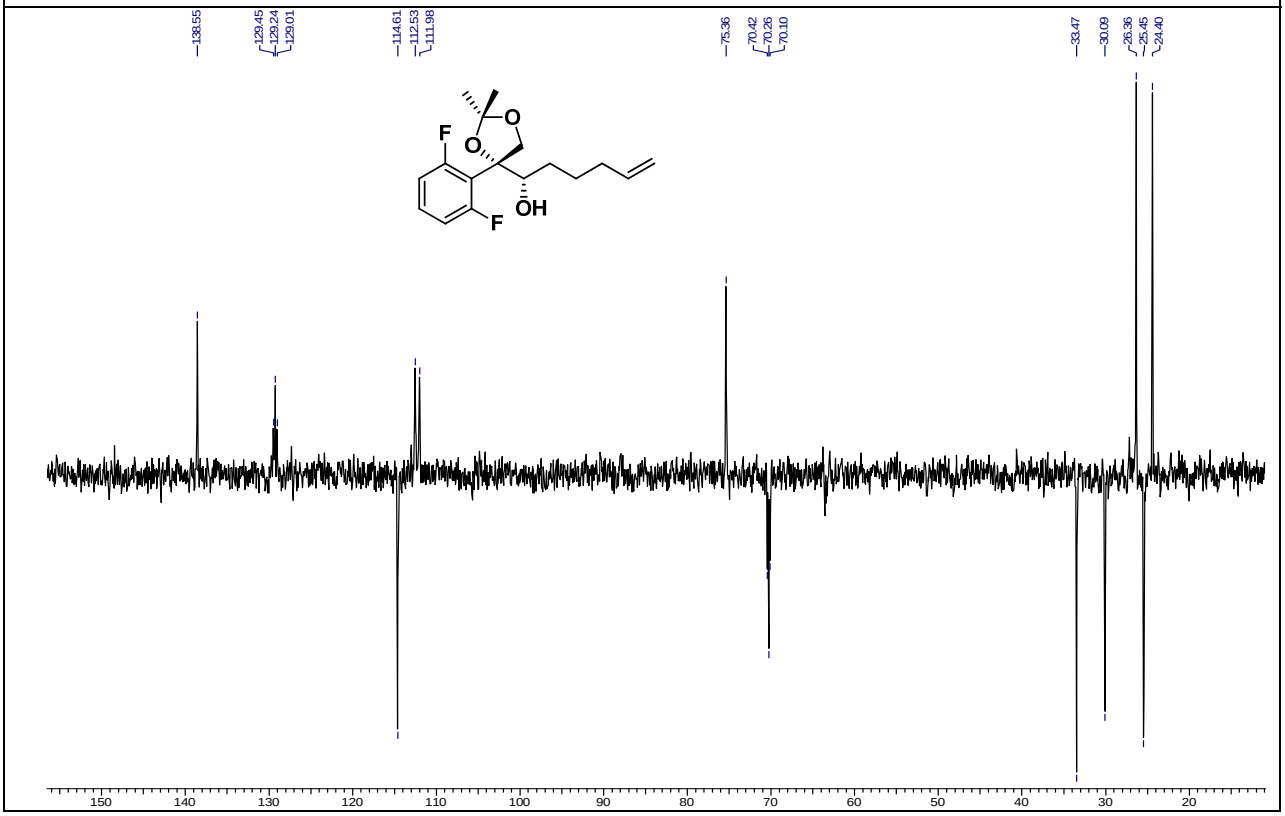
^{1}H NMR spectrum of compound **(±7a)** ($CDCl_3$, 200 MHz)



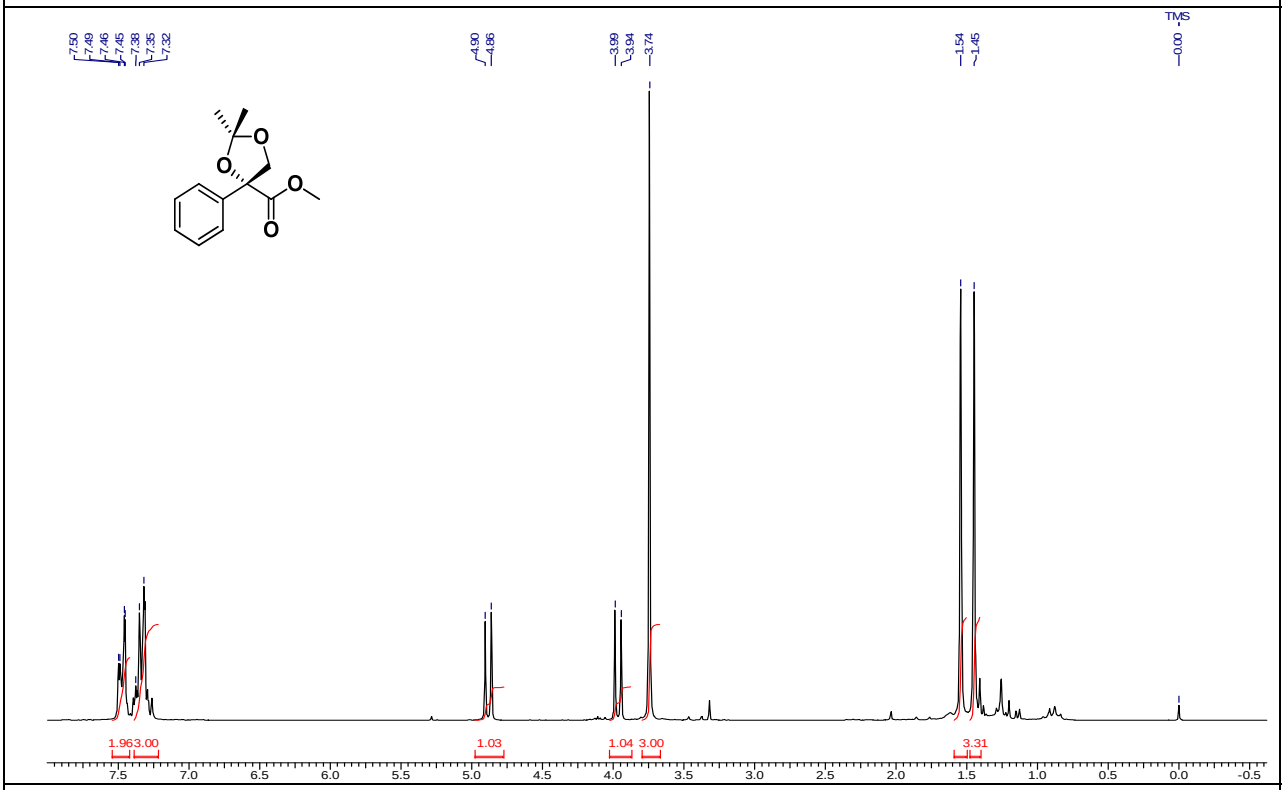
^{13}C NMR spectrum of compound **(±7a)** ($CDCl_3$, 50 MHz)



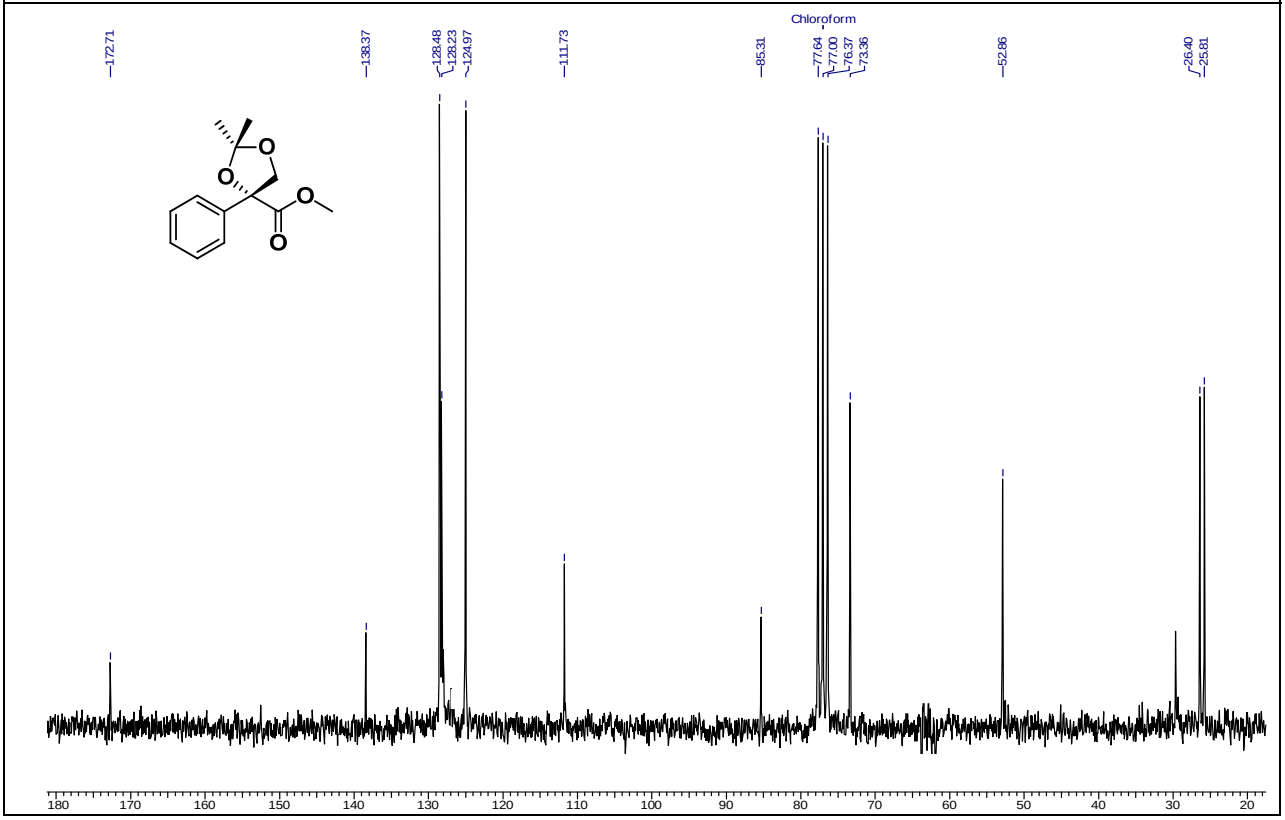
DEPT spectrum of compound **(±7a)** ($CDCl_3$, 50 MHz)



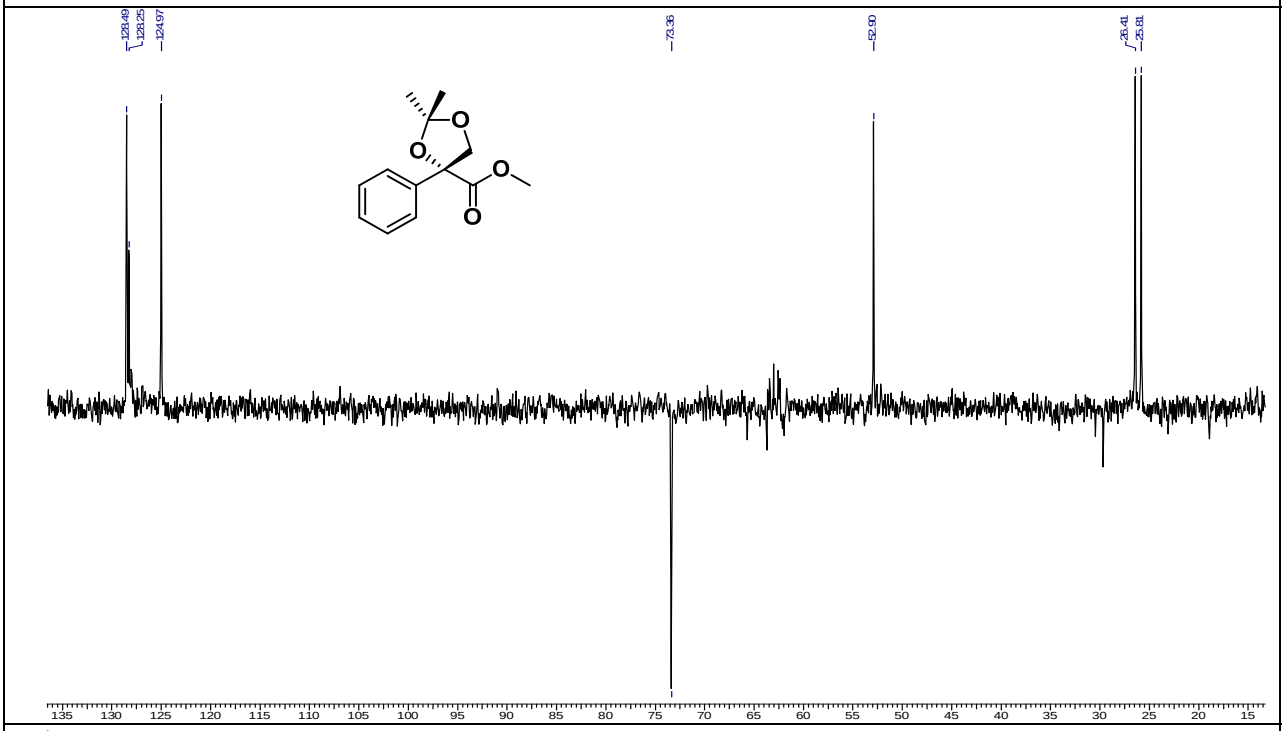
^{1}H NMR spectrum of compound **(±8)** ($CDCl_3$, 200 MHz)



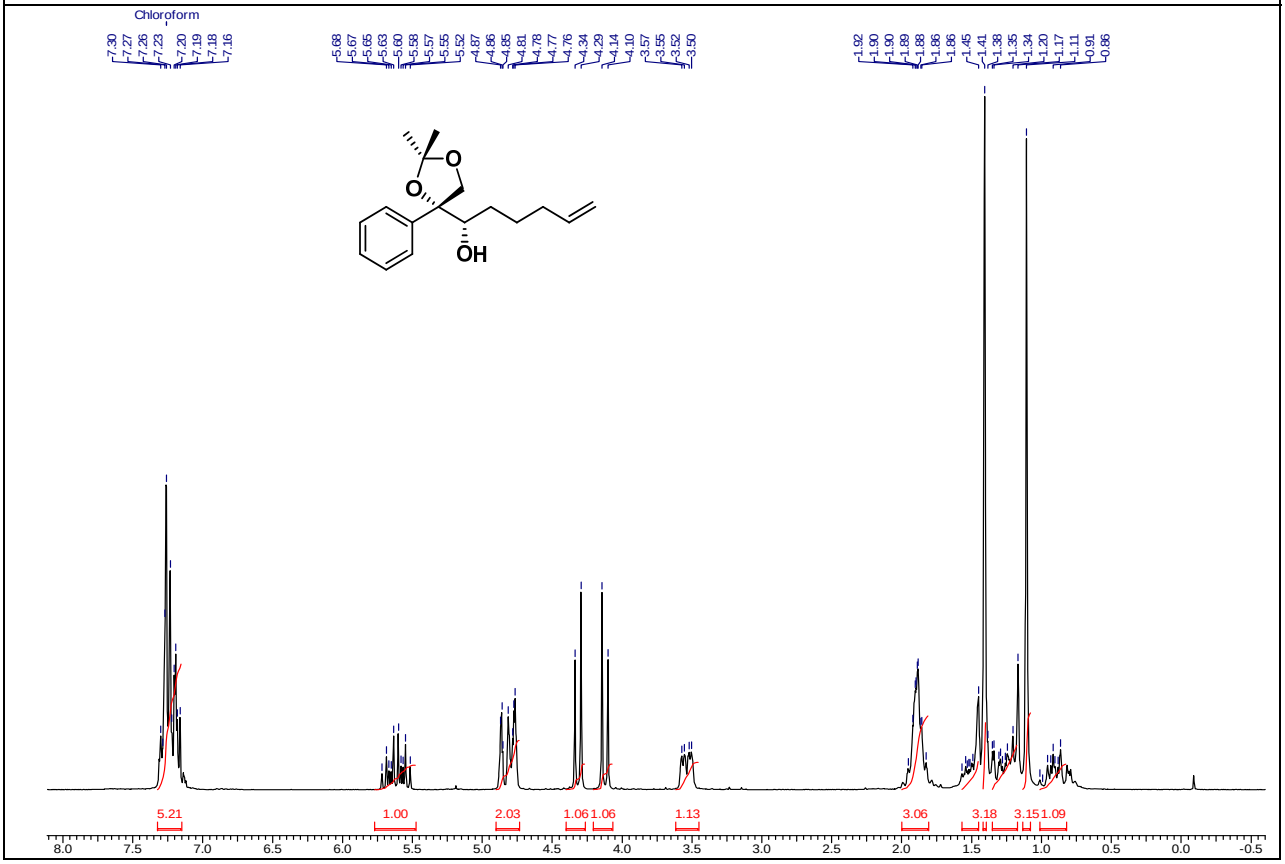
^{13}C NMR spectrum of compound **(±8)** ($CDCl_3$, 50 MHz)



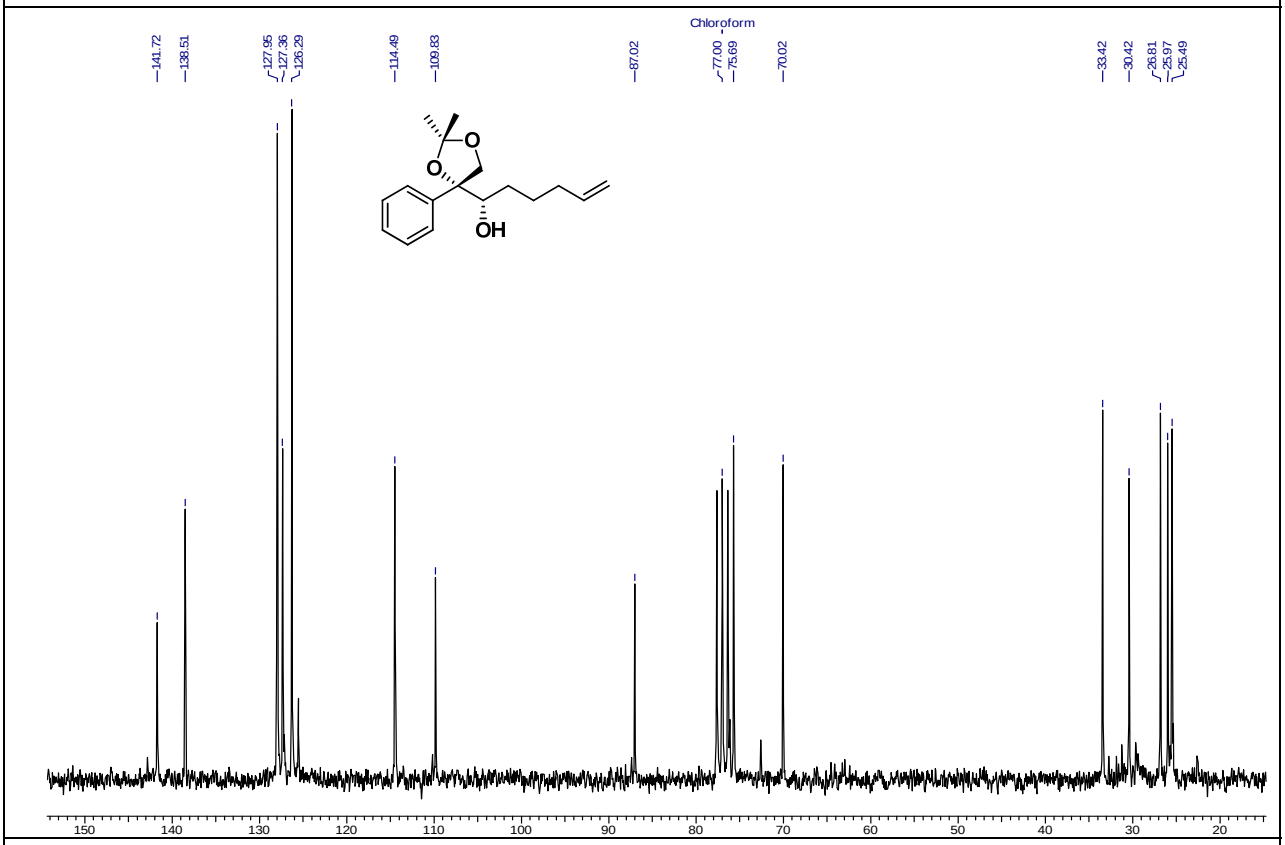
DEPT spectrum of compound **(±8)** ($CDCl_3$, 50 MHz)



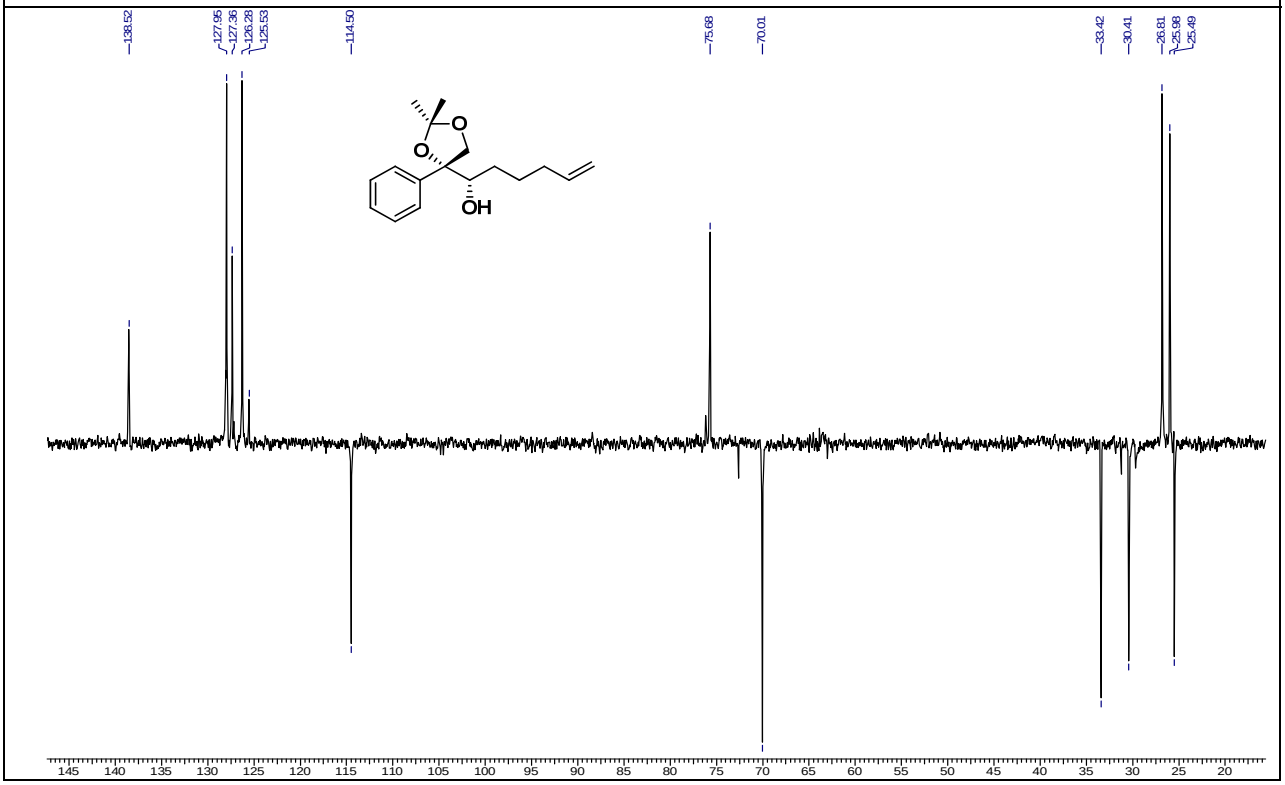
^{1}H NMR spectrum of compound **(±8a)** ($CDCl_3$, 200 MHz)



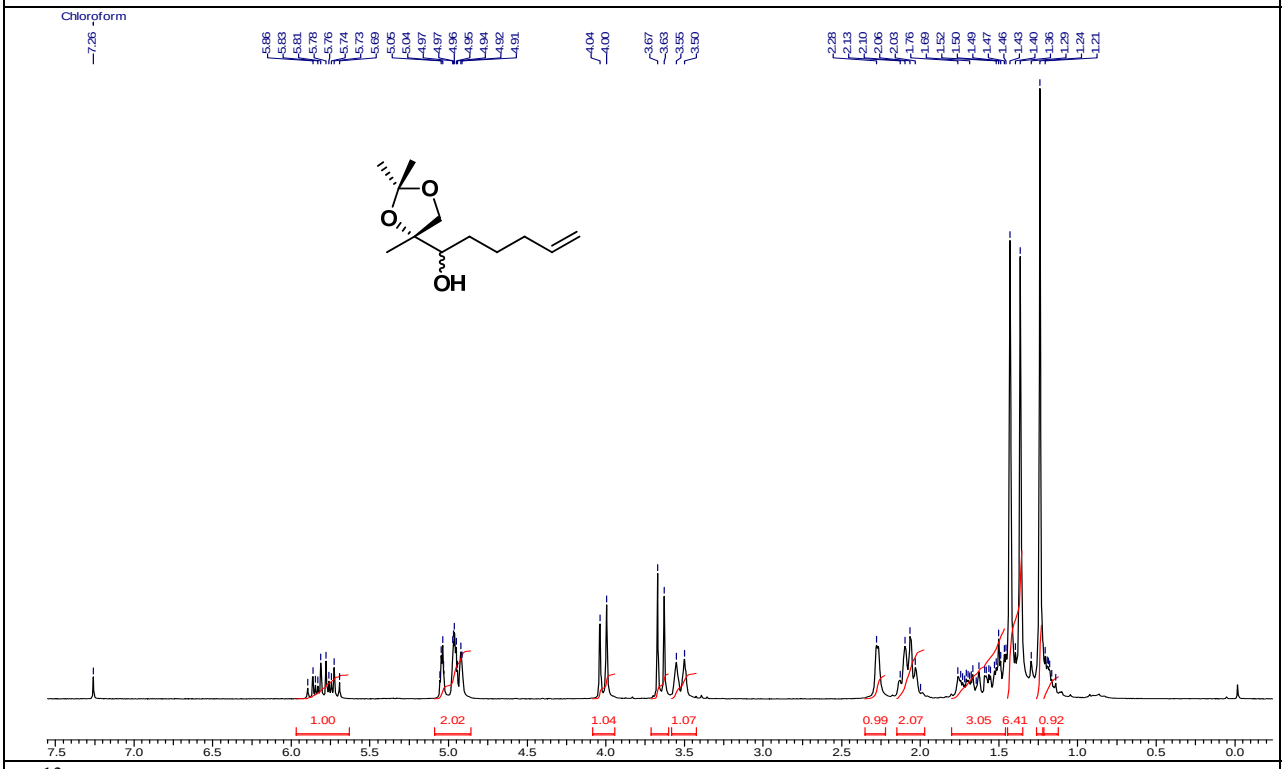
^{13}C NMR spectrum of compound **(±8a)** ($CDCl_3$, 50 MHz)



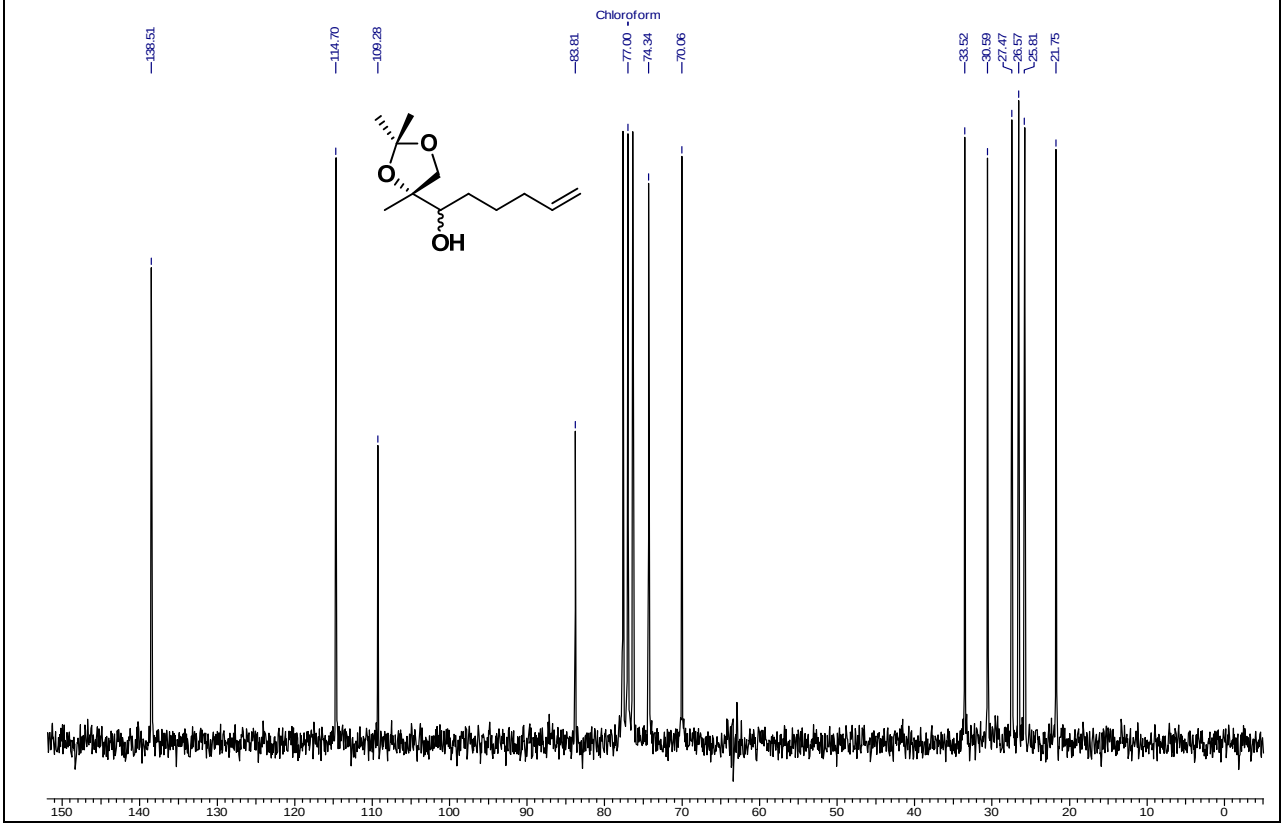
DEPT spectrum of compound **(±8a)** ($CDCl_3$, 50 MHz)



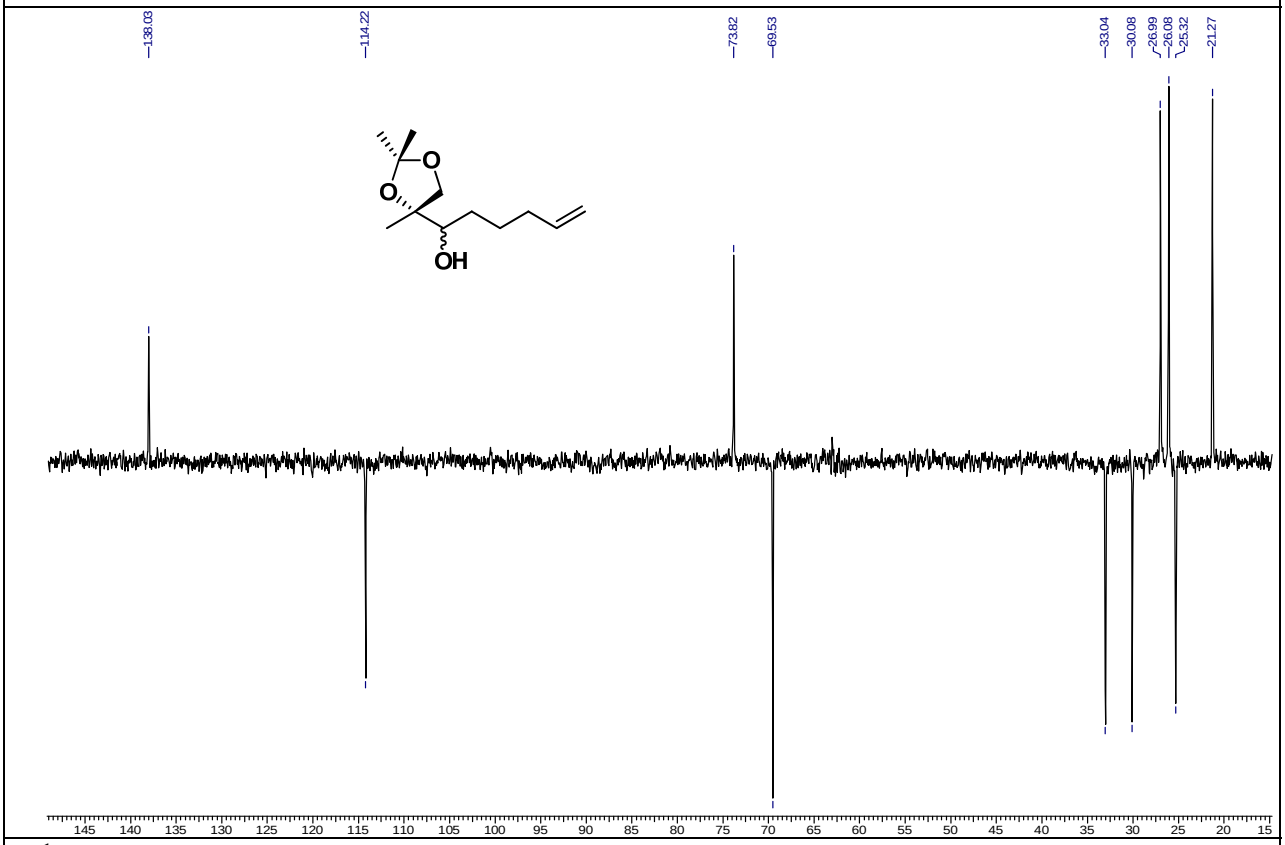
^{1}H NMR spectrum of compound **(±9a)** ($CDCl_3$, 200 MHz)



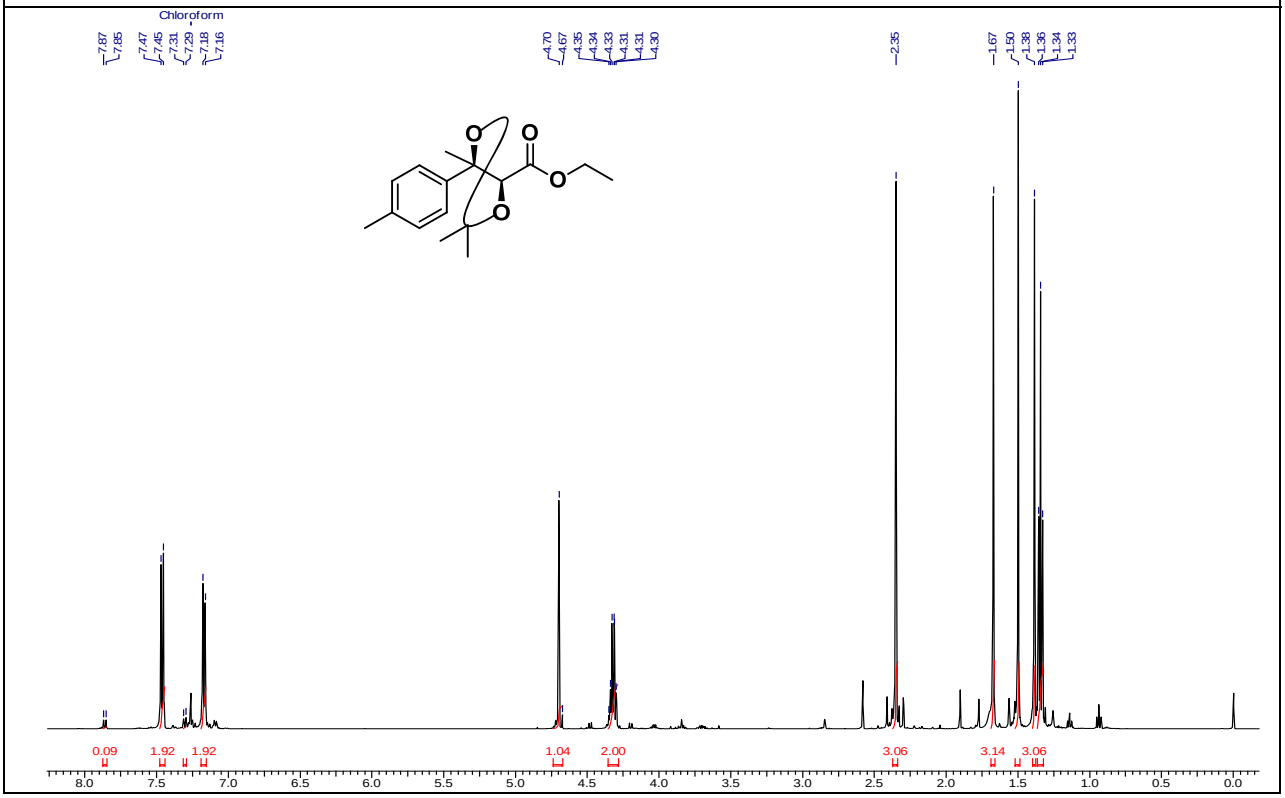
^{13}C NMR spectrum of compound **(±9a)** ($CDCl_3$, 50 MHz)



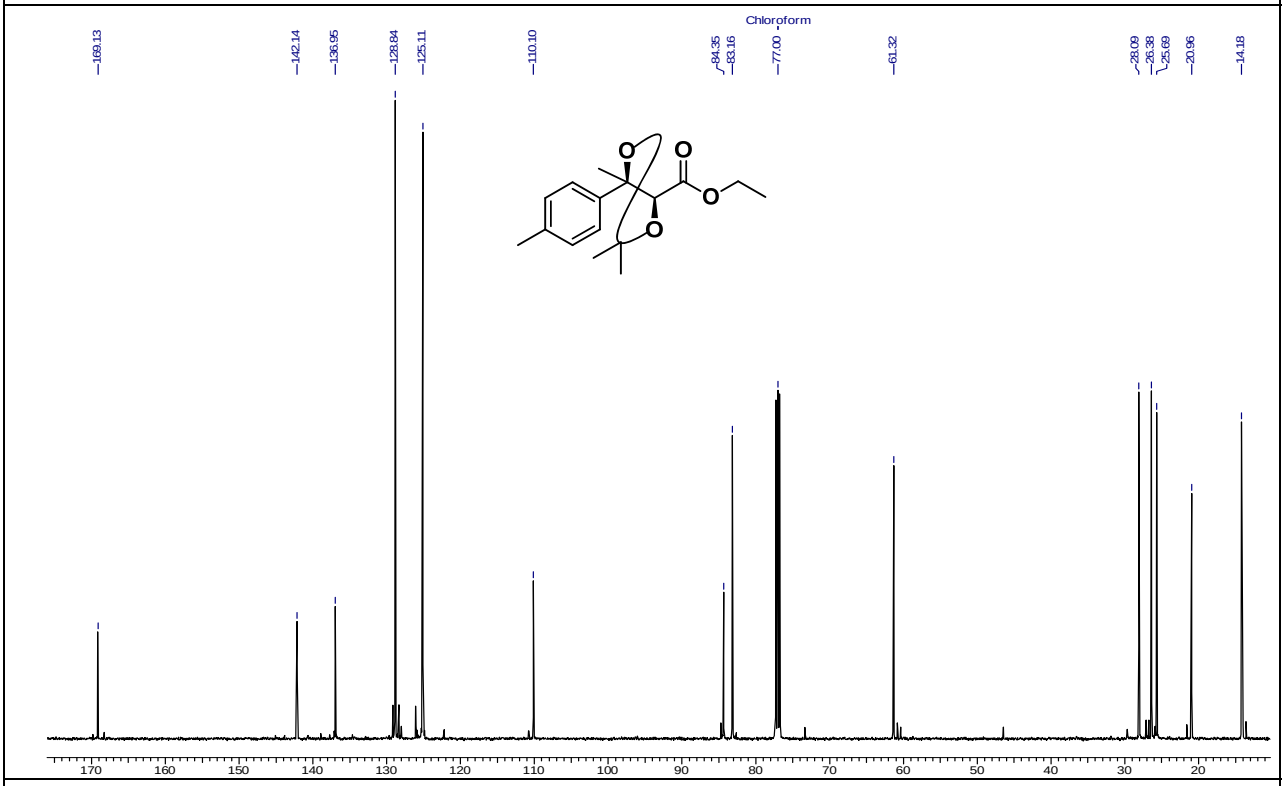
DEPT spectrum of compound **(±9a)** ($CDCl_3$, 50 MHz)



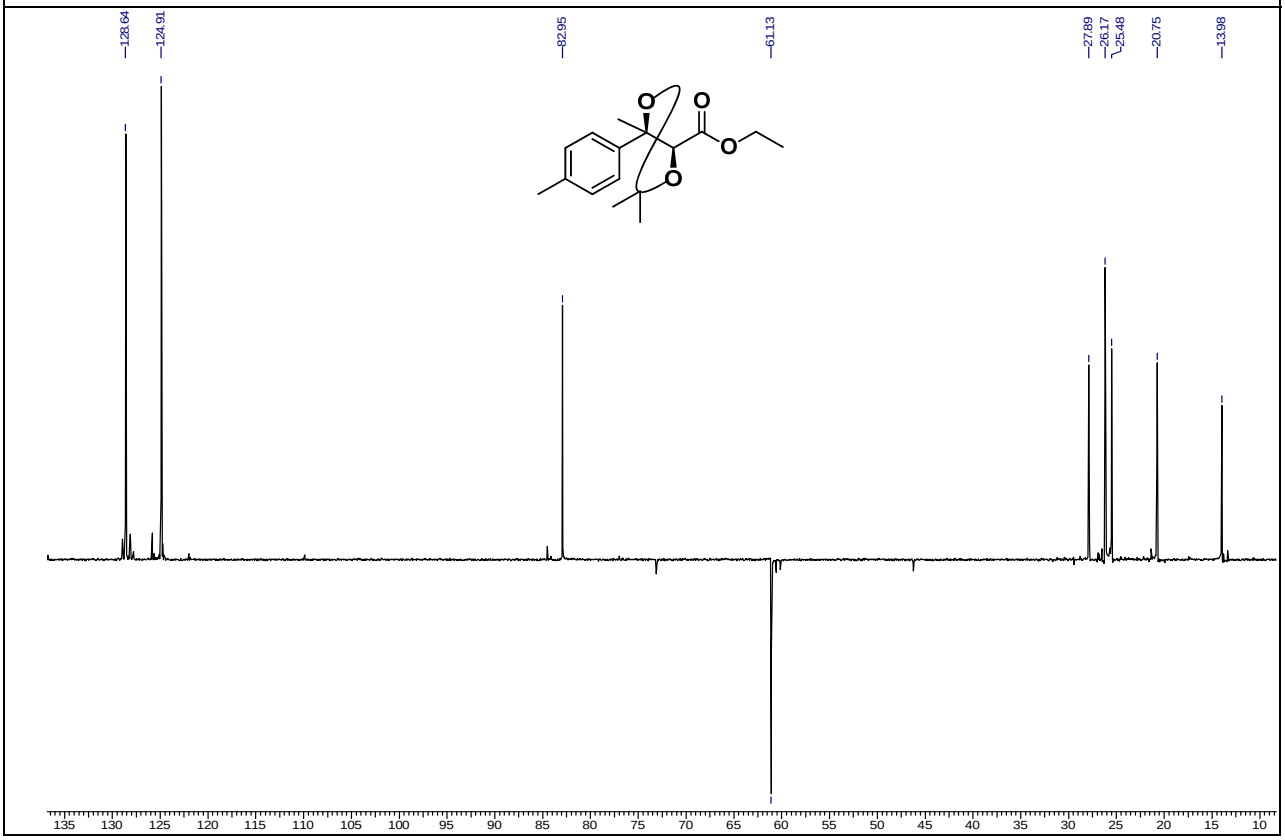
^{1}H NMR spectrum of compound **(±10)** ($CDCl_3$, 500 MHz)



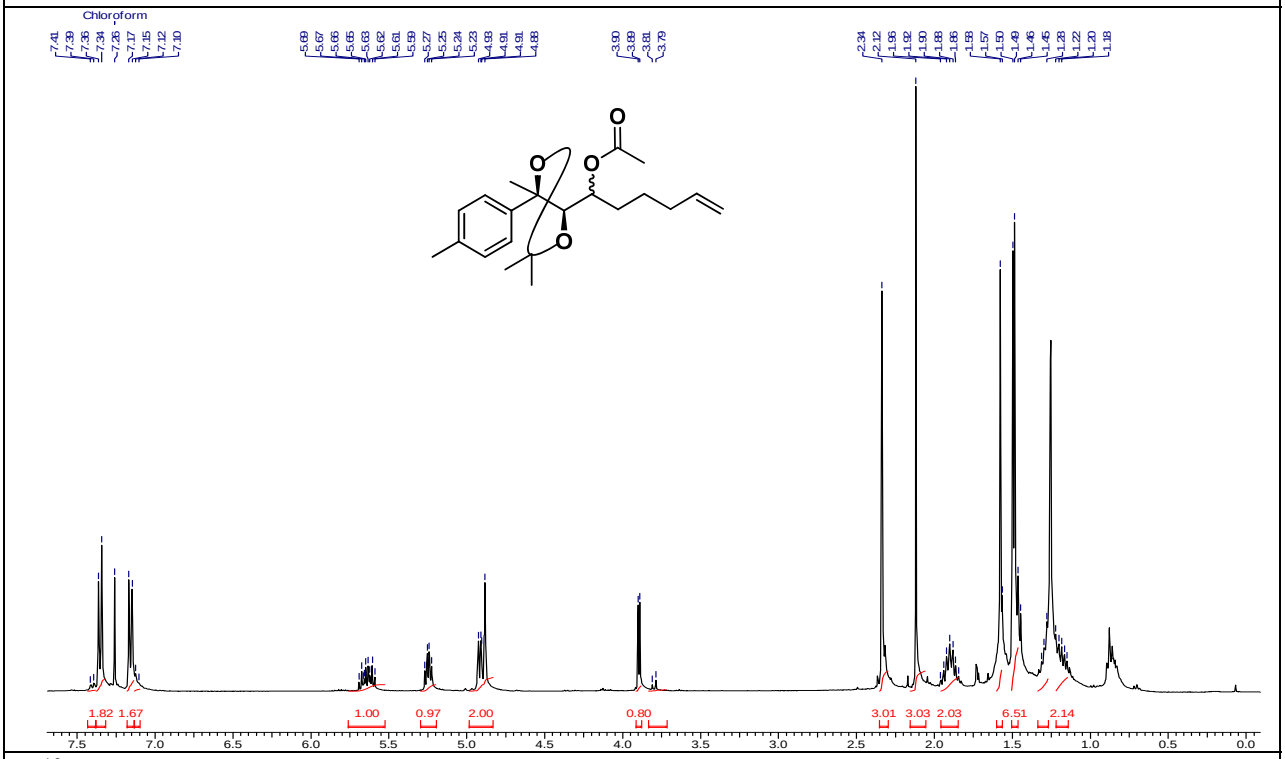
^{13}C NMR spectrum of compound **(±10)** ($CDCl_3$, 125 MHz)



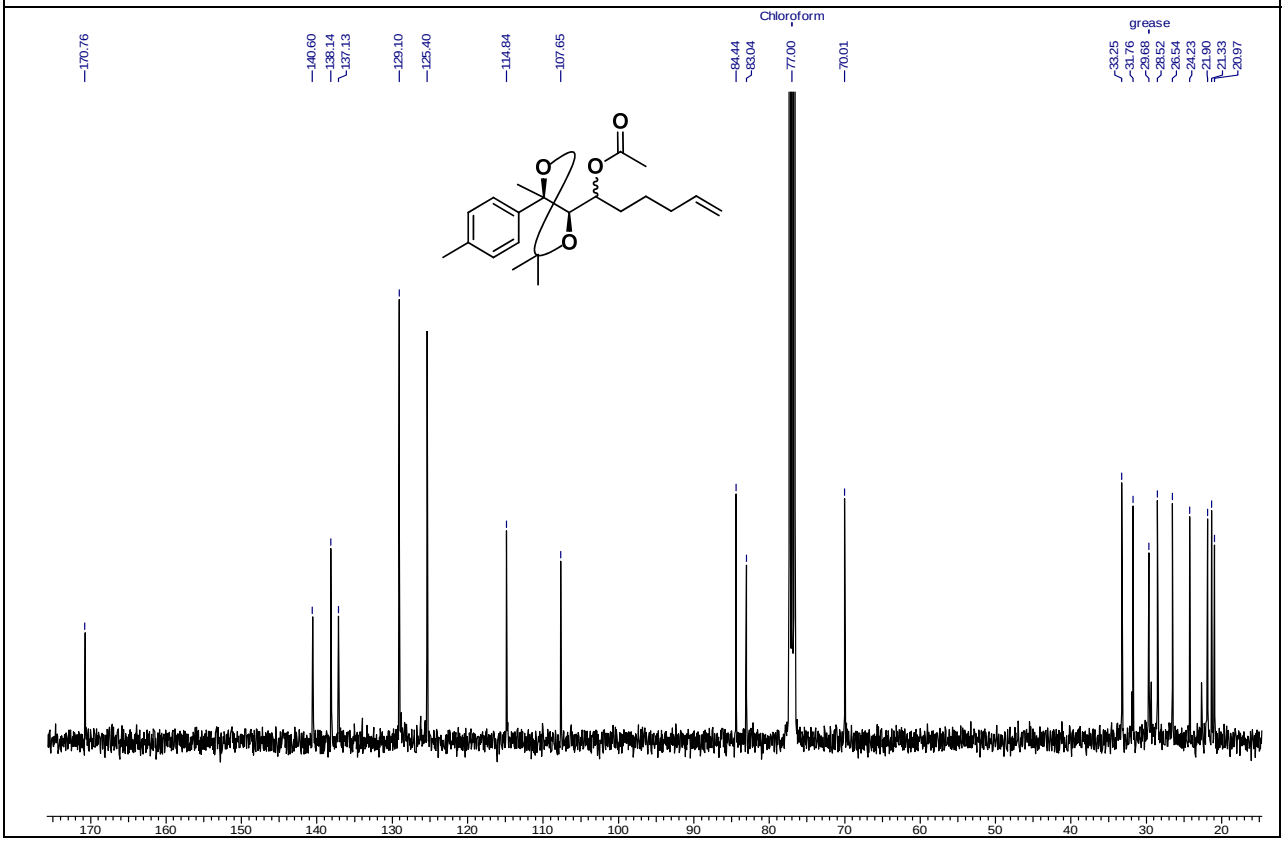
DEPT spectrum of compound **(±10)** ($CDCl_3$, 125 MHz)



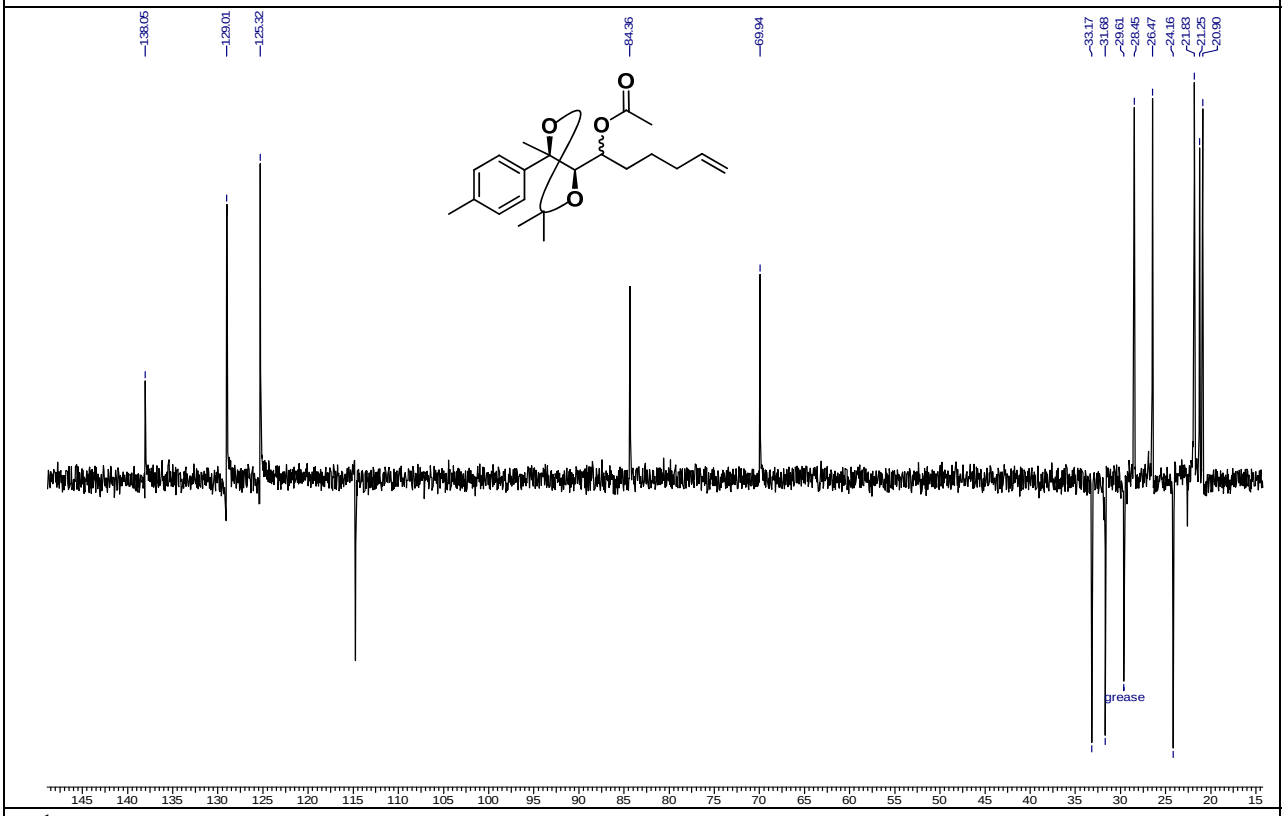
^{1}H NMR spectrum of compound **(±10'a)** ($CDCl_3$, 400 MHz)



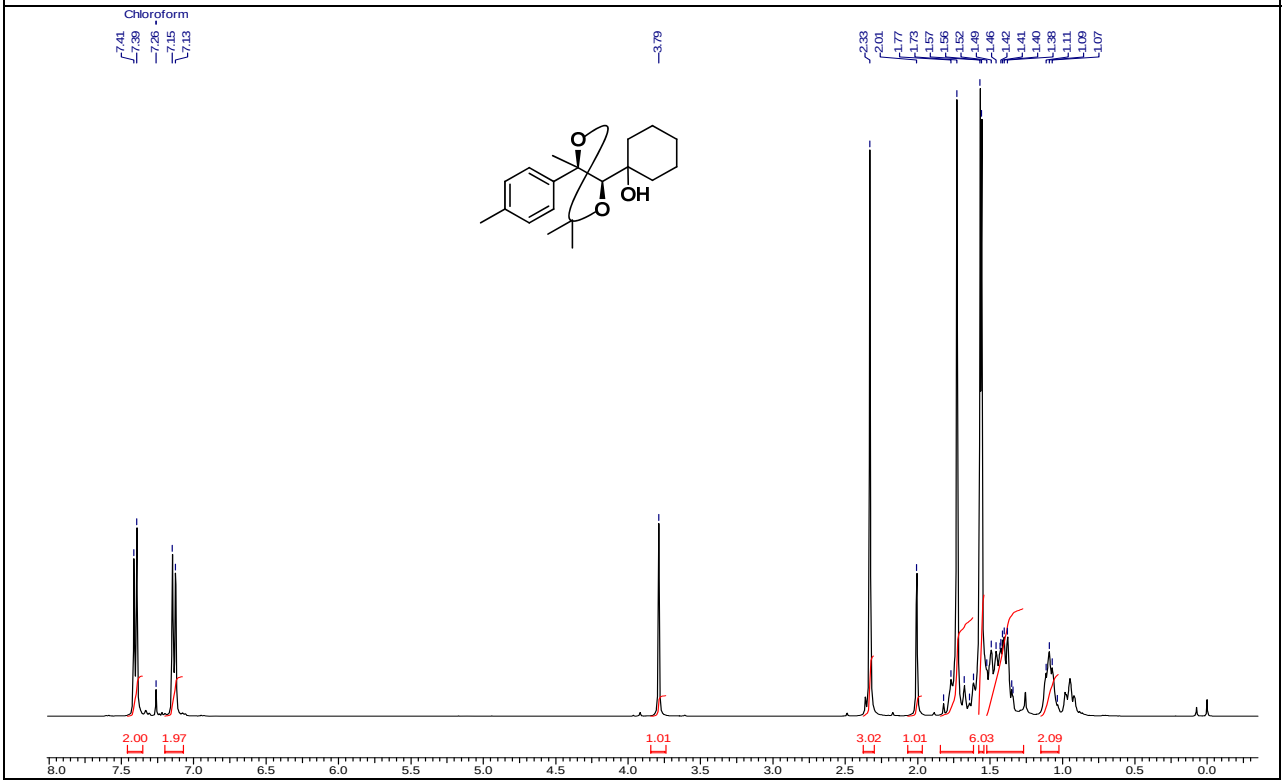
^{13}C NMR spectrum of compound **(±10'a)** ($CDCl_3$, 100 MHz)



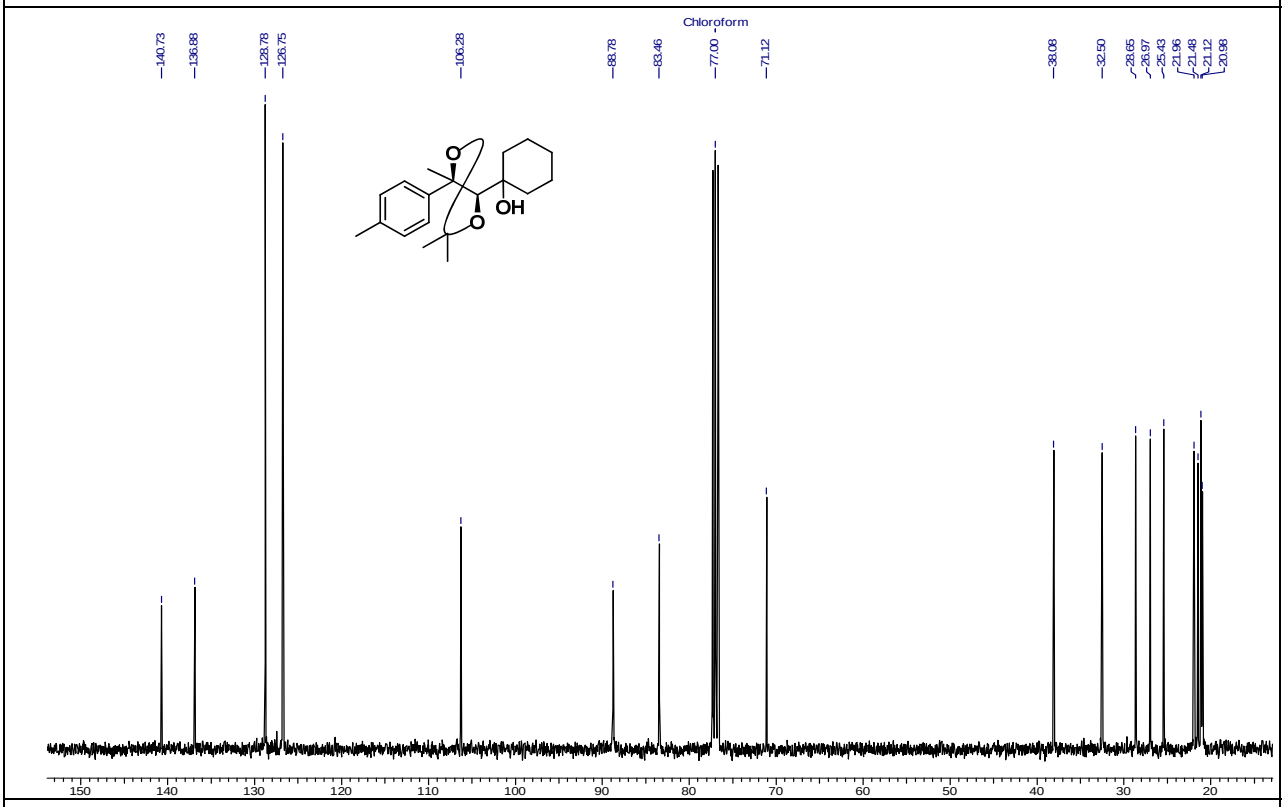
DEPT spectrum of compound **(±10'a)** ($CDCl_3$, 100 MHz)



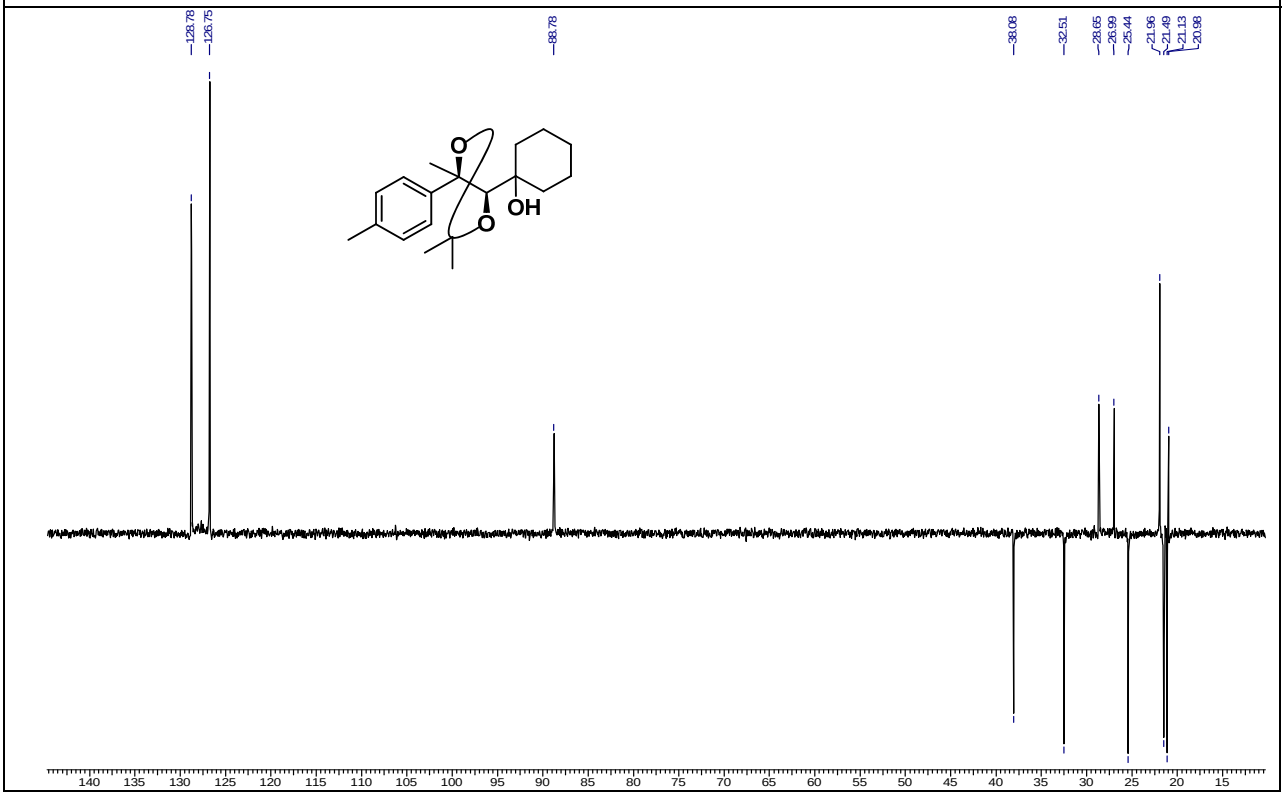
^{1}H NMR spectrum of compound **(±10b)** ($CDCl_3$, 400 MHz)



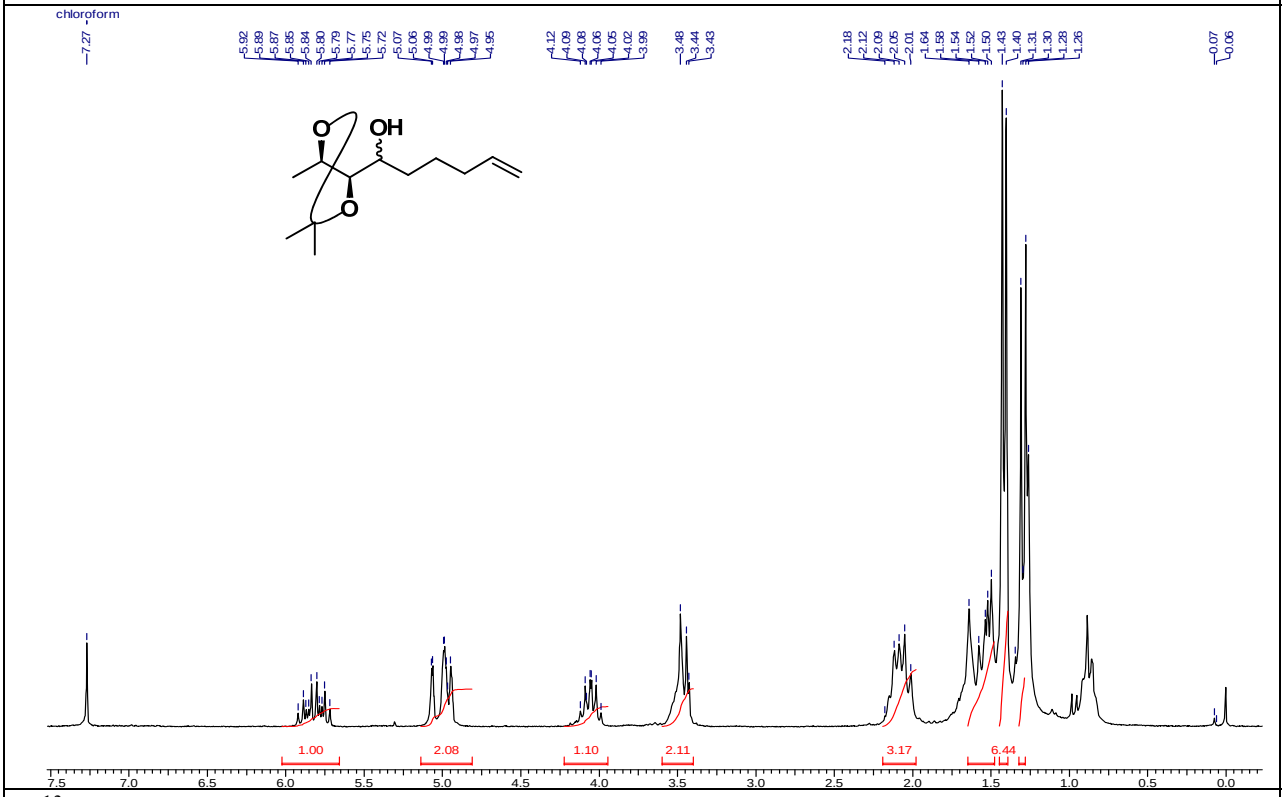
^{13}C NMR spectrum of compound **(±10b)** ($CDCl_3$, 100 MHz)



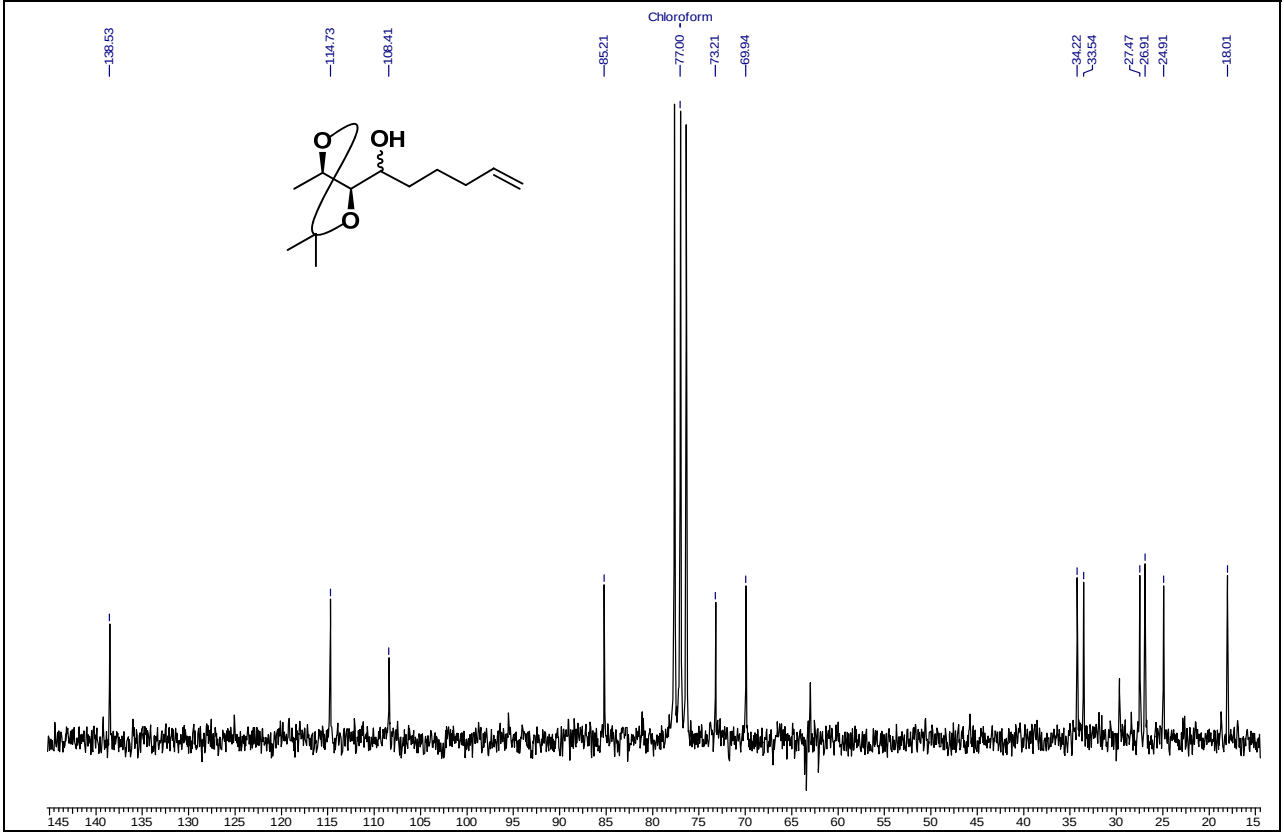
DEPT spectrum of compound **(±10b)** ($CDCl_3$, 100 MHz)



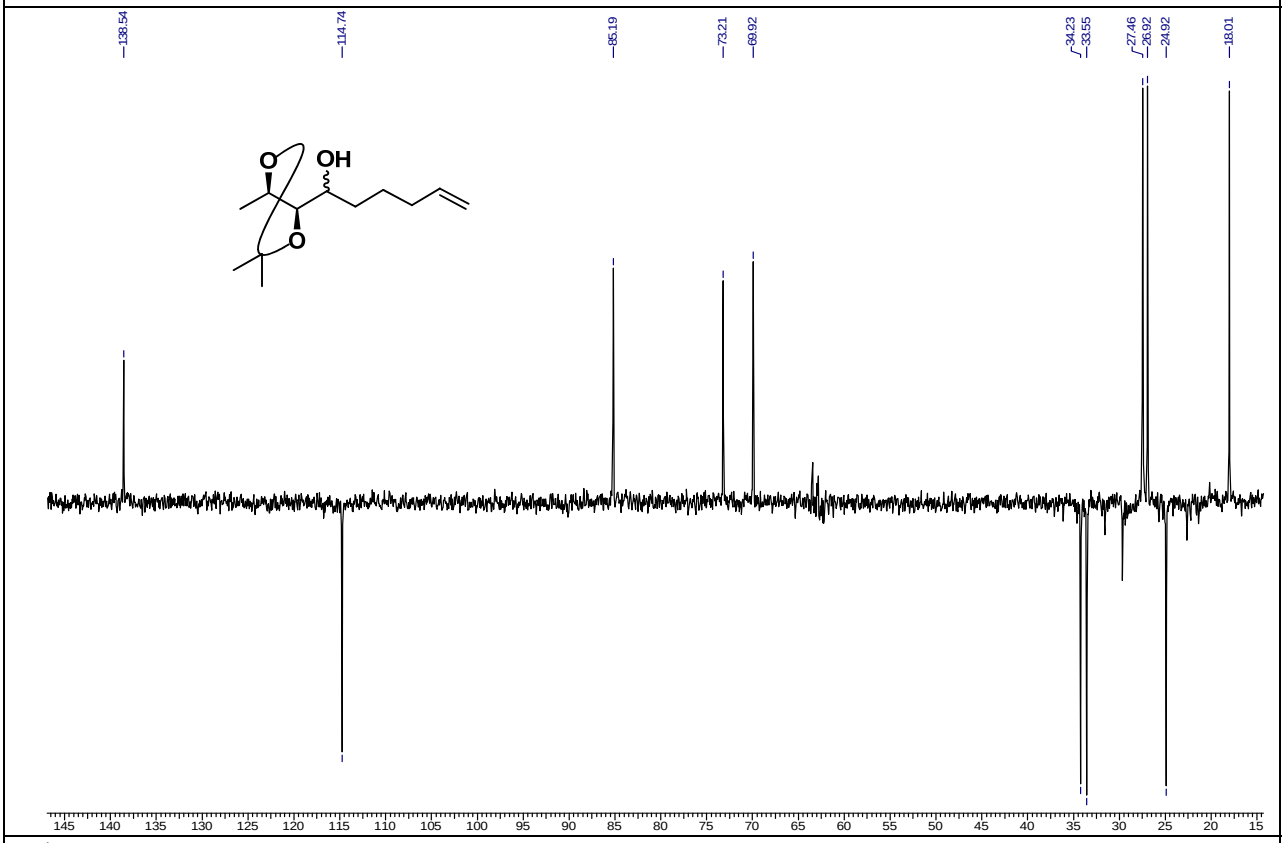
^{1}H NMR spectrum of compound **(±11a)** ($CDCl_3$, 200 MHz)



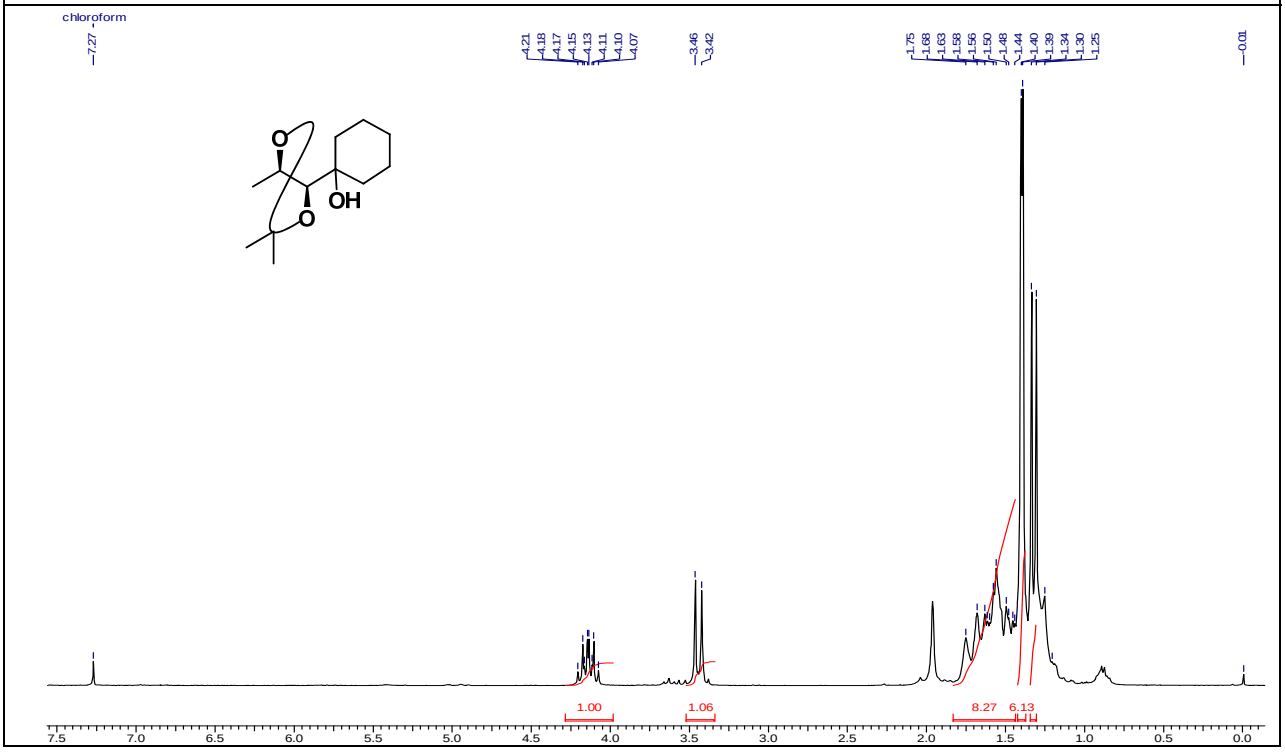
^{13}C NMR spectrum of compound **(±11a)** ($CDCl_3$, 50 MHz)



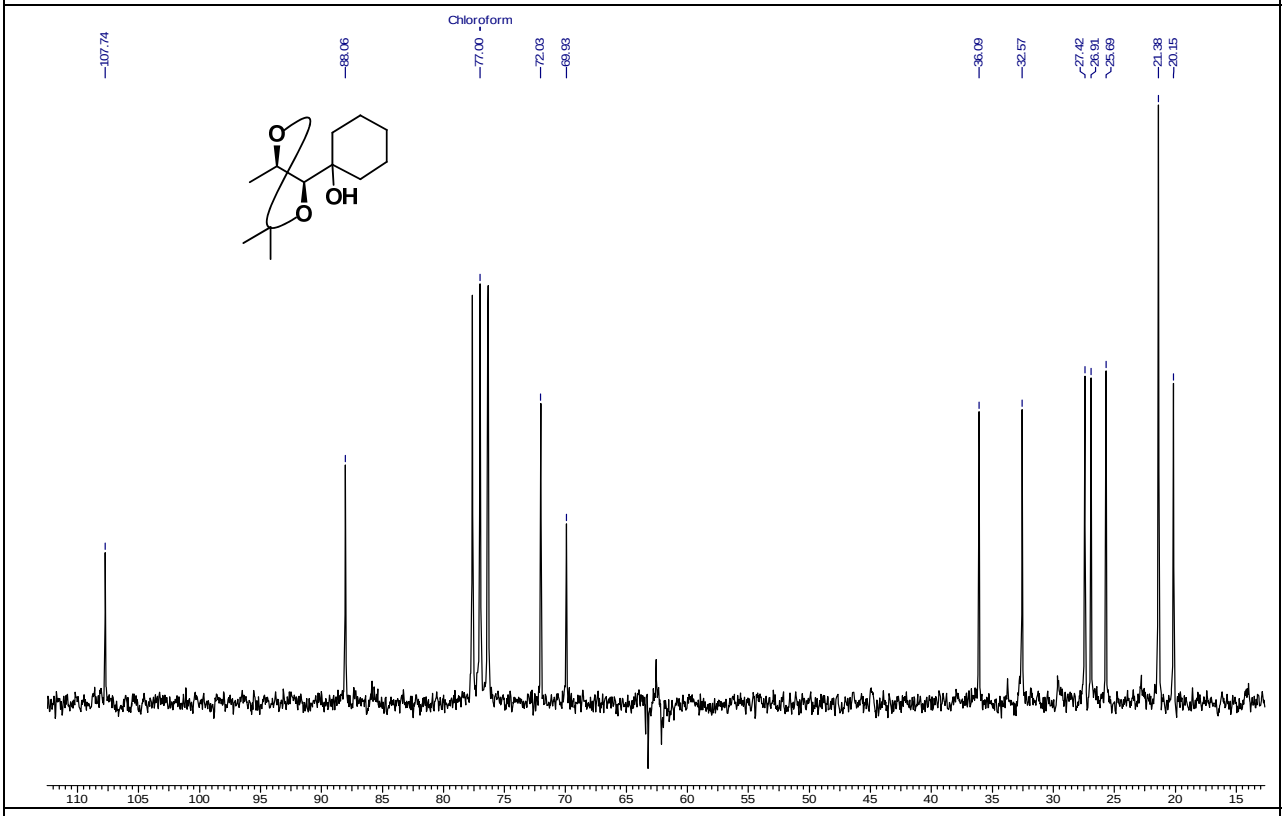
DEPT spectrum of compound **(±11a)** ($CDCl_3$, 50 MHz)



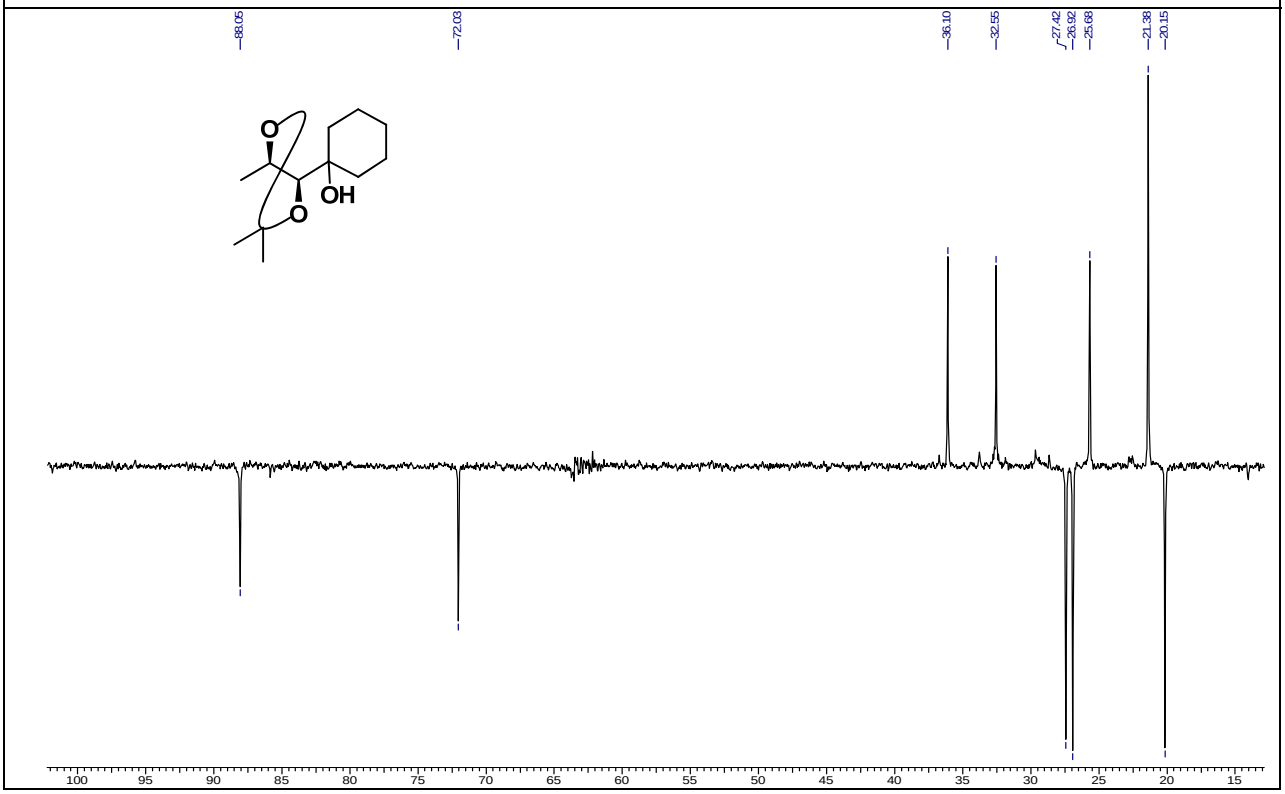
^{1}H NMR spectrum of compound **(±11b)** ($CDCl_3$, 200 MHz)



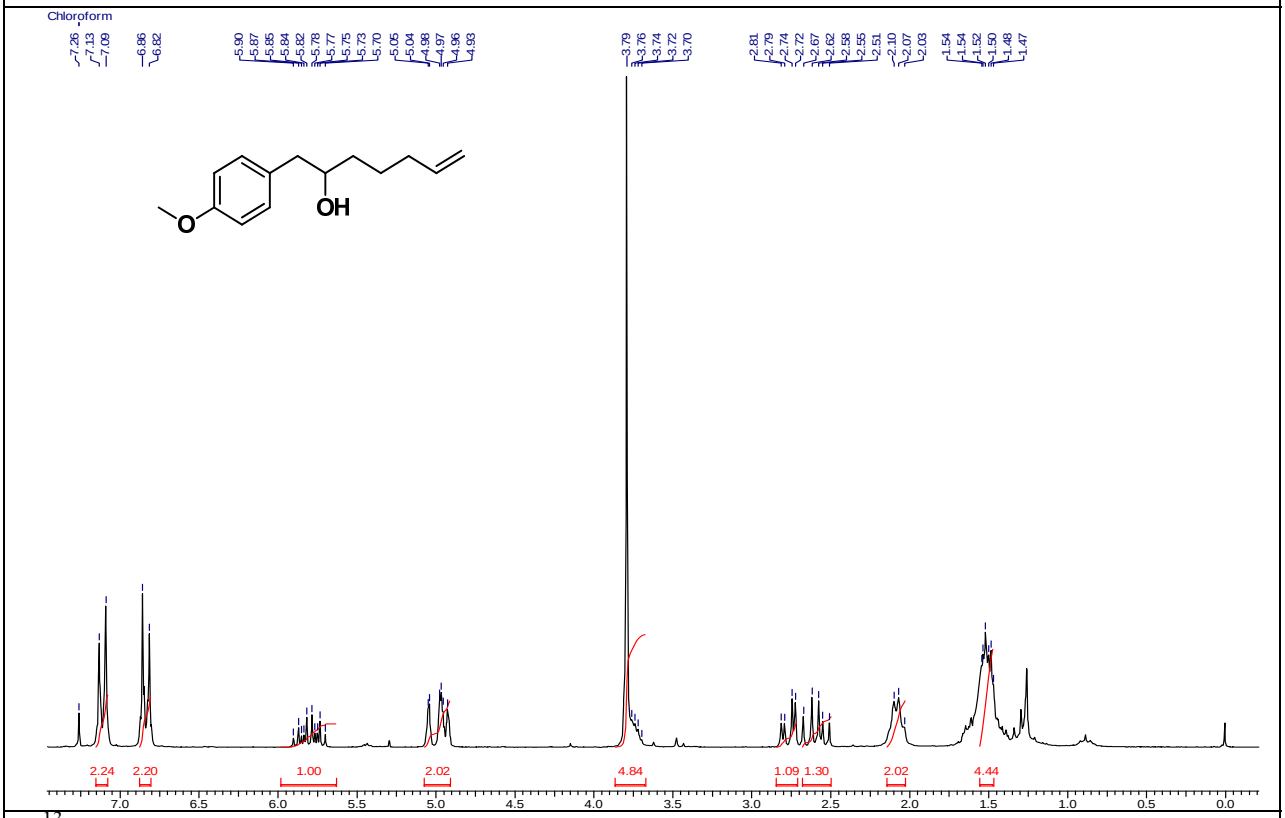
^{13}C NMR spectrum of compound **(±11b)** ($CDCl_3$, 50 MHz)



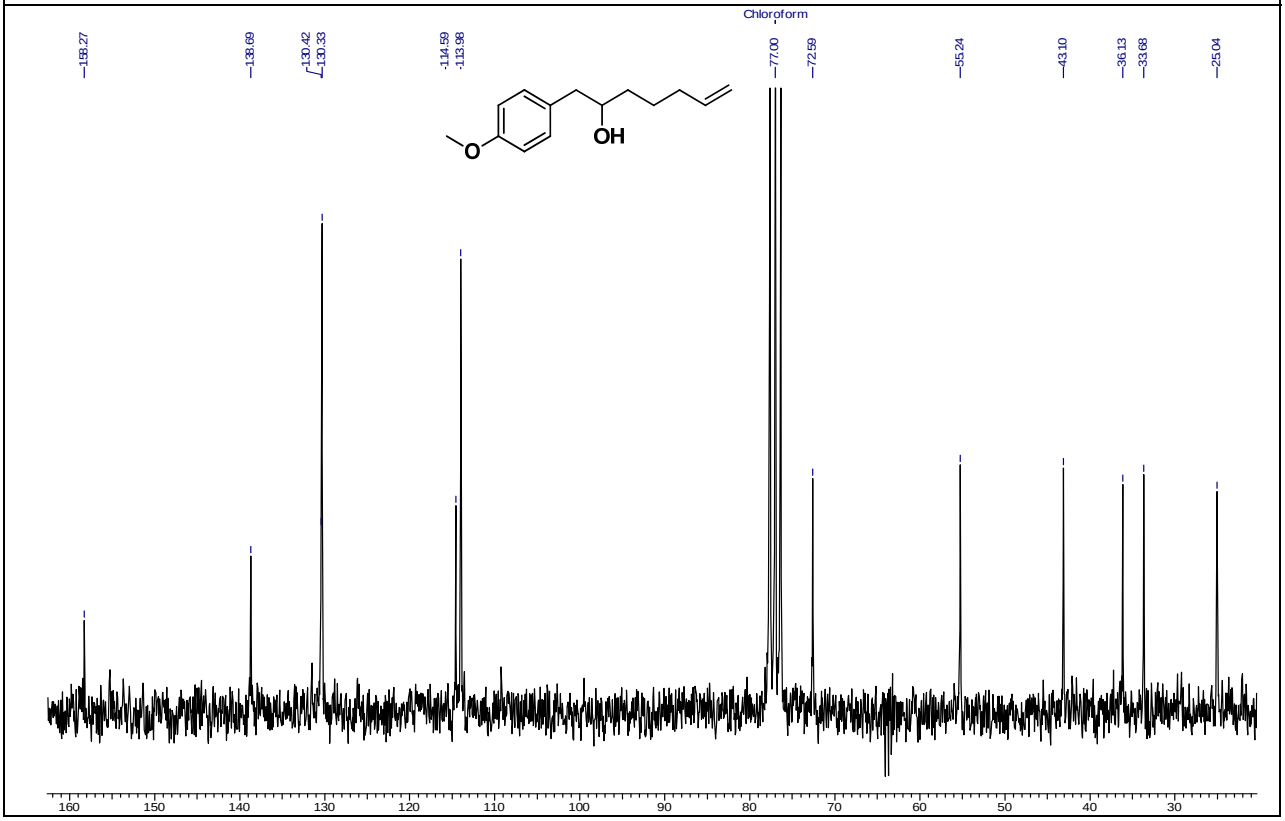
DEPT spectrum of compound **(±11b)** ($CDCl_3$, 50 MHz)



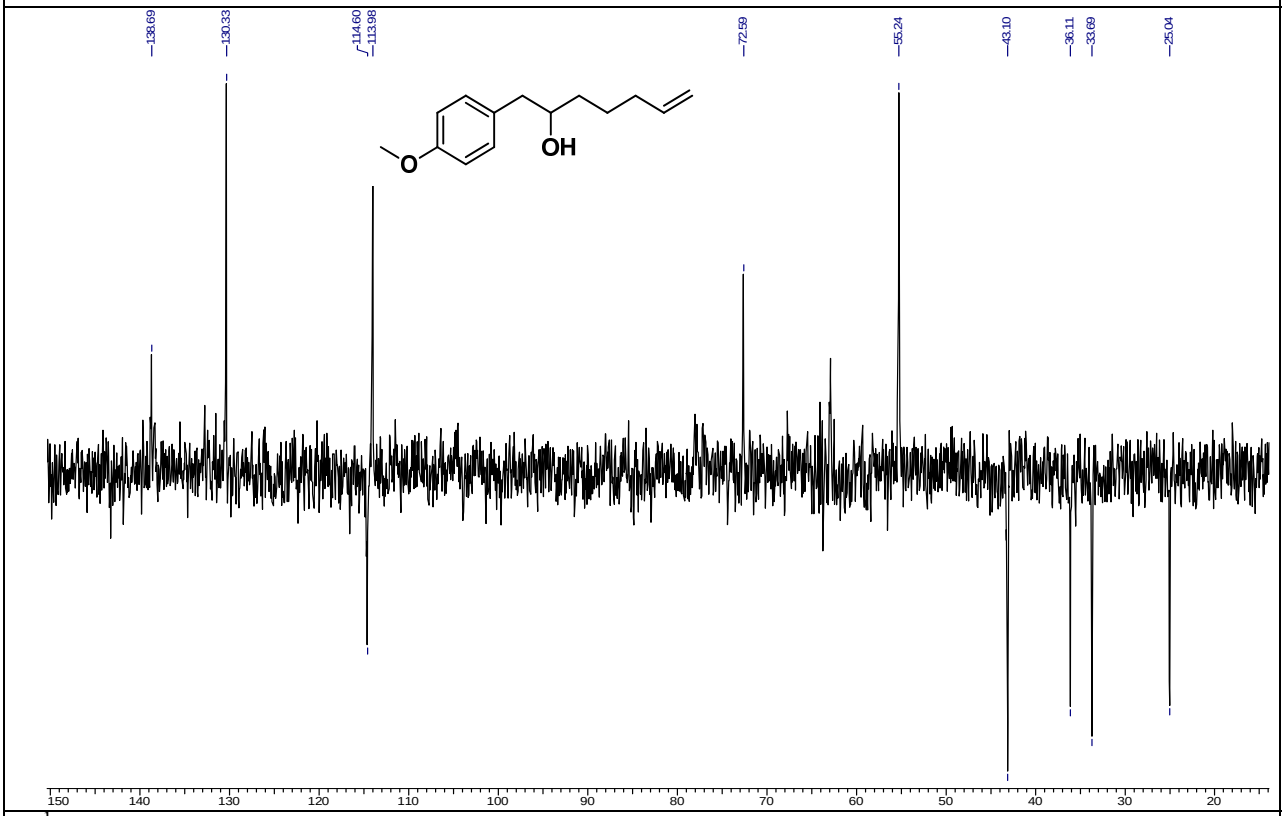
^{1}H NMR spectrum of compound **(13a)** ($CDCl_3$, 200 MHz) **(14a)**



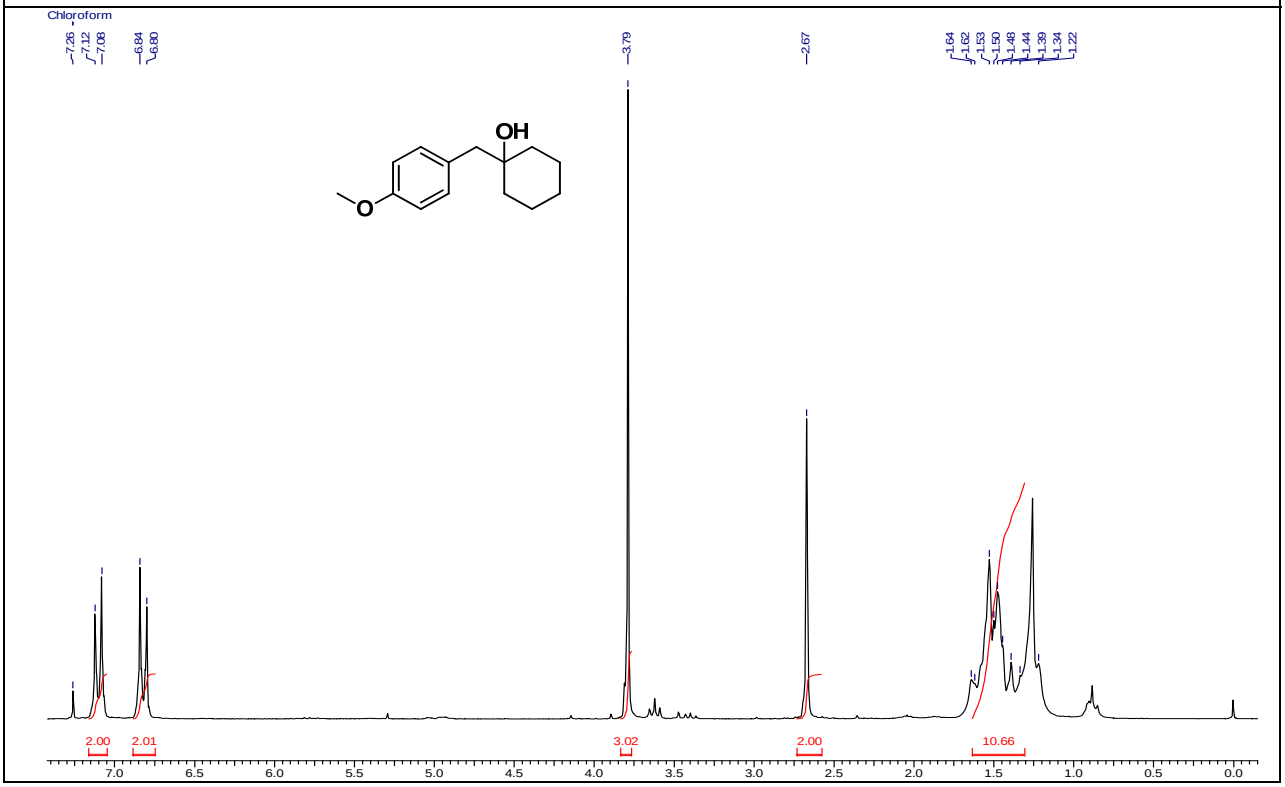
^{13}C NMR spectrum of compound **(13a)** ($CDCl_3$, 50 MHz)



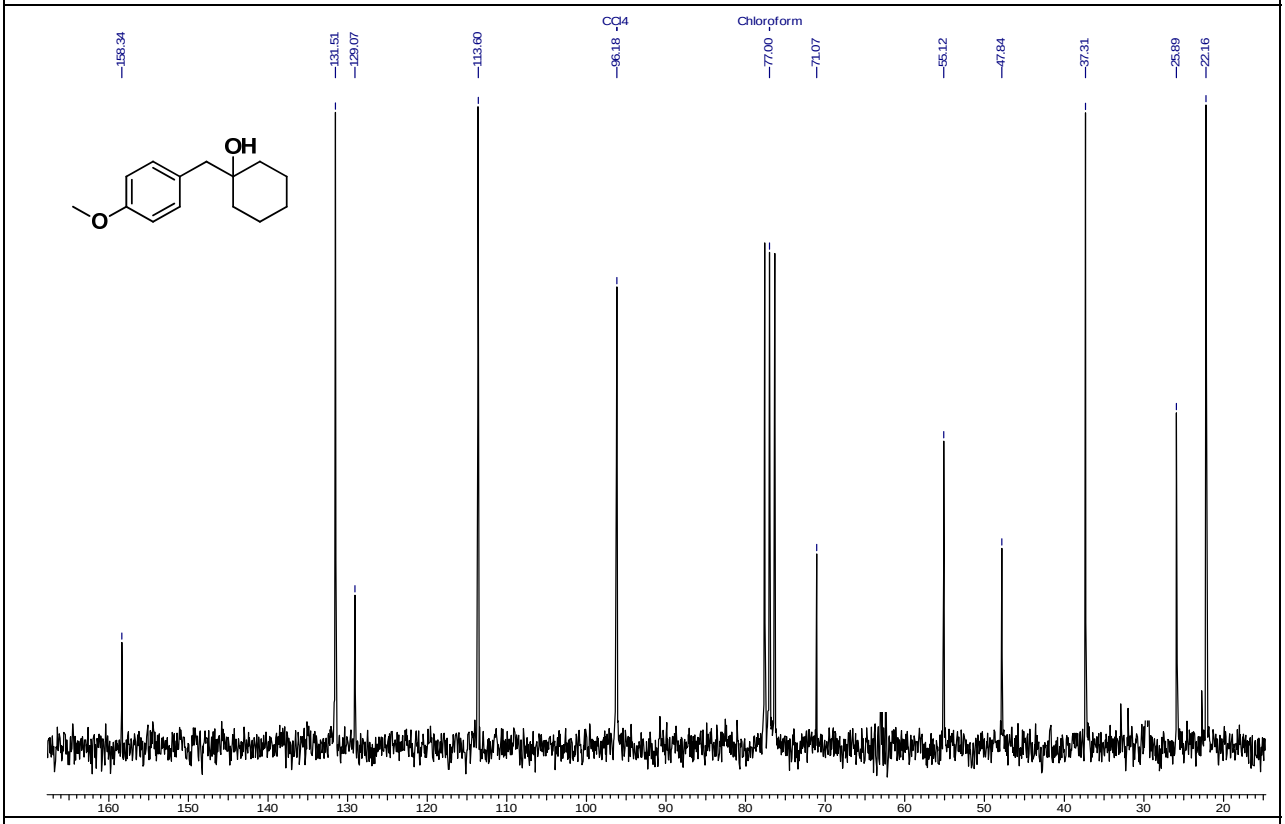
DEPT spectrum of compound **(13a)** ($CDCl_3$, 50 MHz)



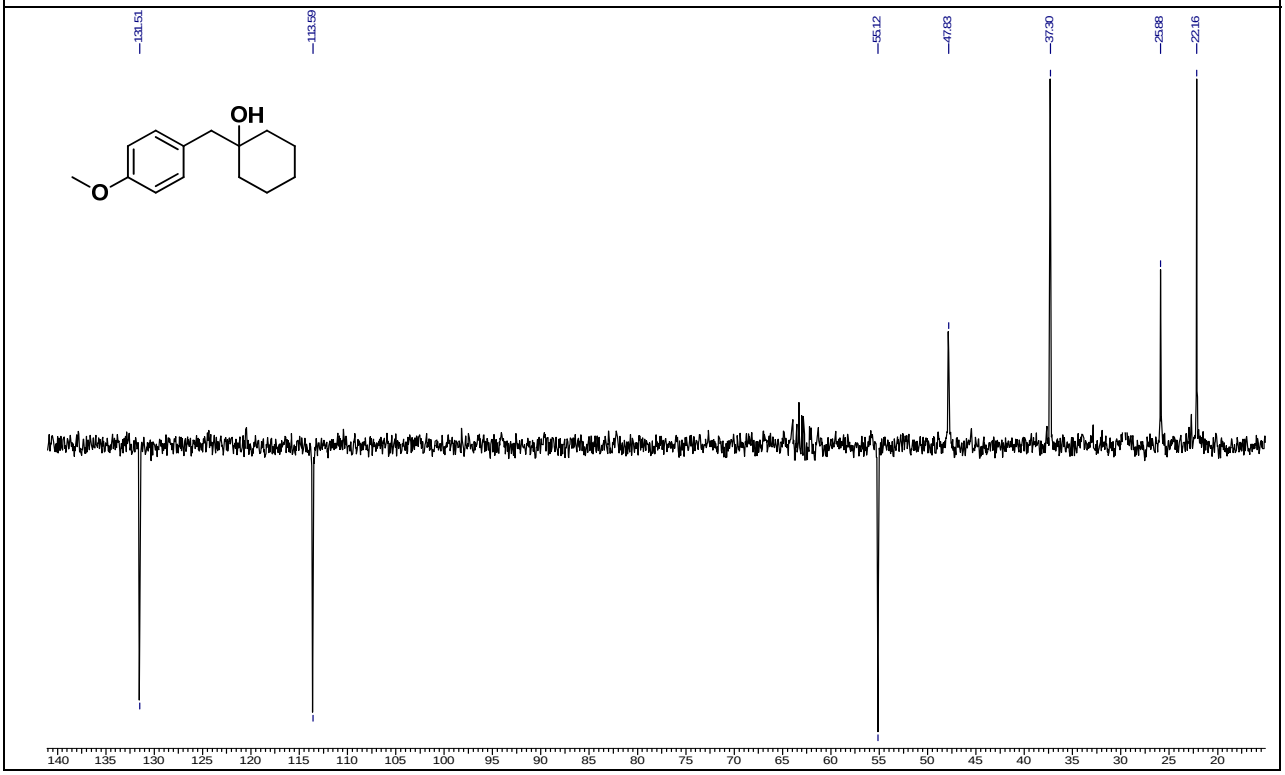
^{1}H NMR spectrum of compound **(13b)** ($CDCl_3$+CCl_4, 200 MHz)



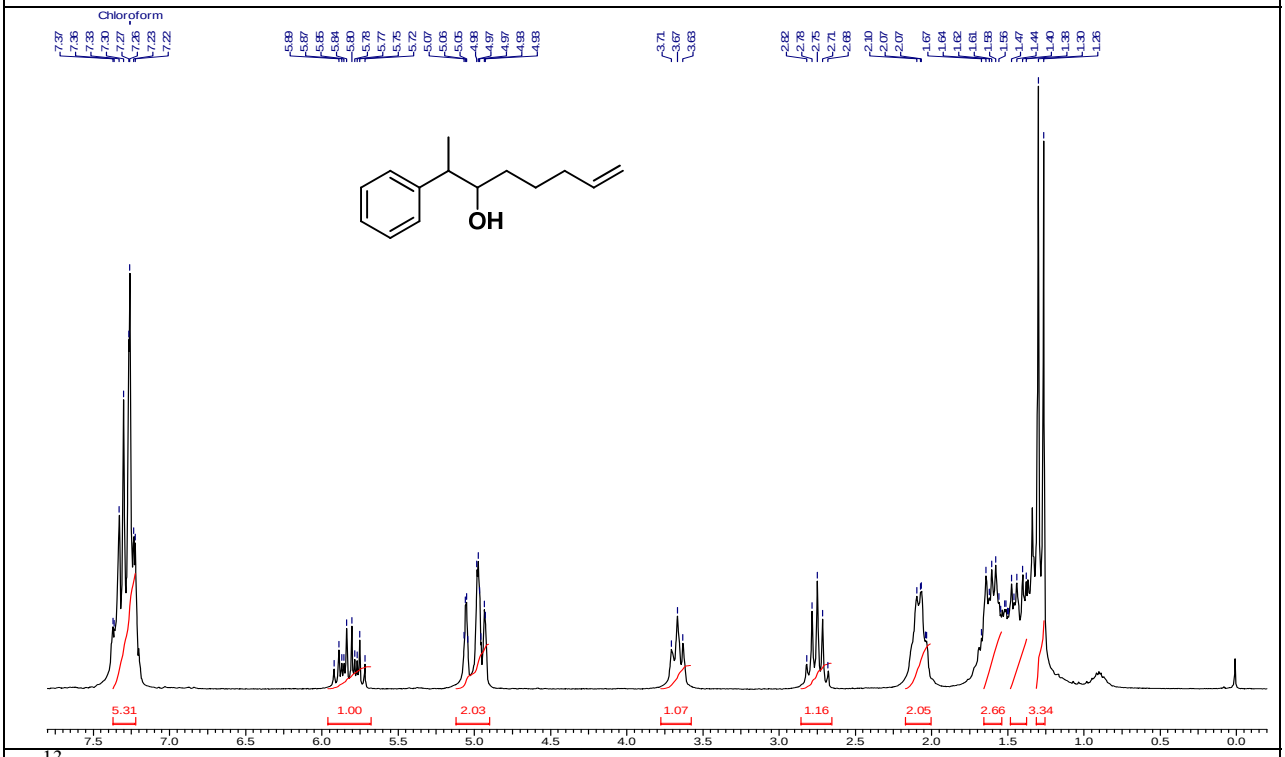
^{13}C NMR spectrum of compound **(13b)** ($CDCl_3$+CCl_4, 50 MHz)



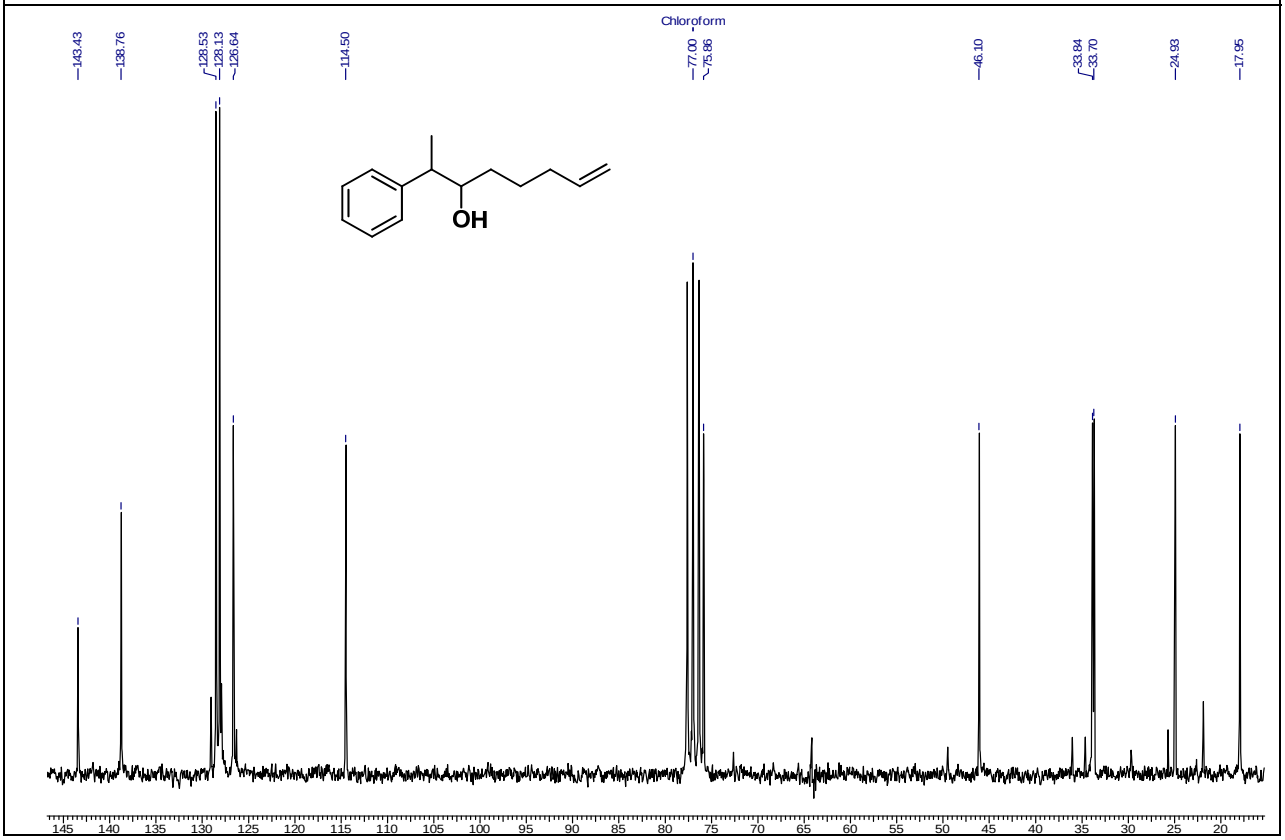
DEPT spectrum of compound **(13b)** ($CDCl_3$+CCl_4, 50 MHz)



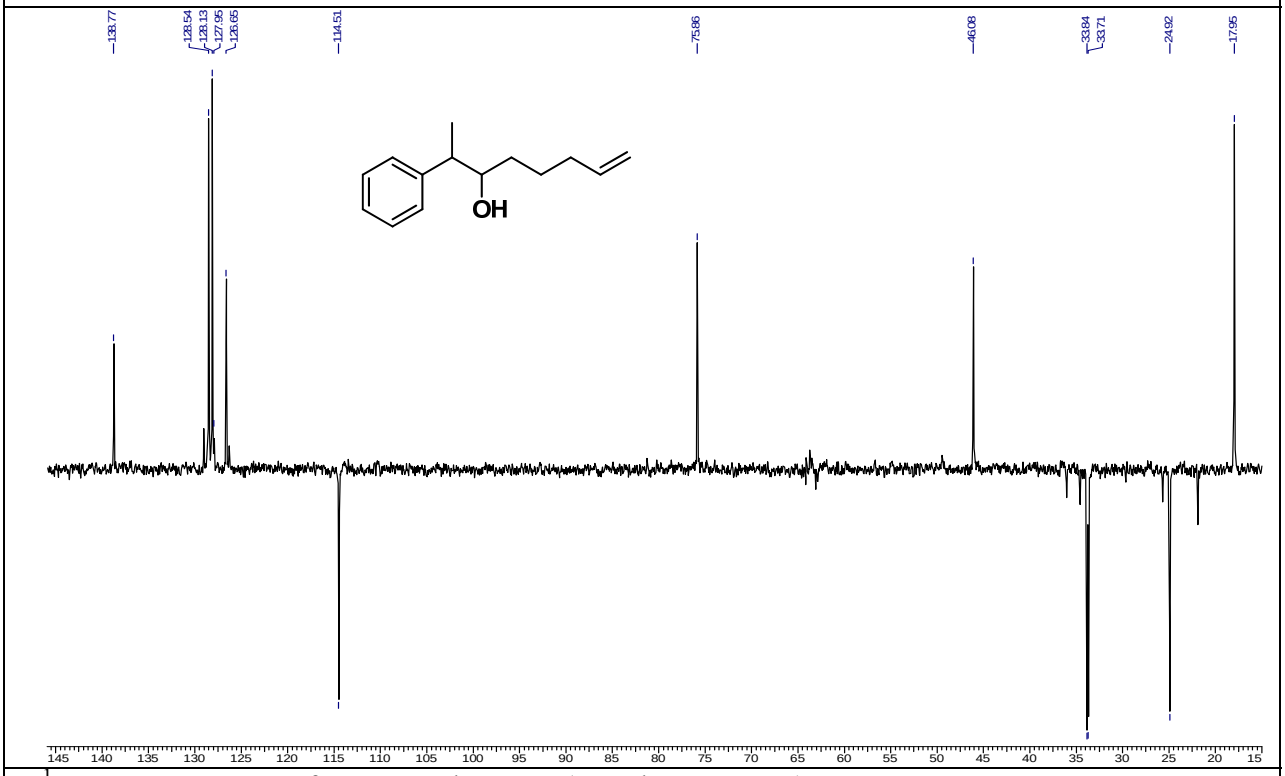
^{1}H NMR spectrum of compound **(±14a)** ($CDCl_3$, 200 MHz) **first diastereomer**



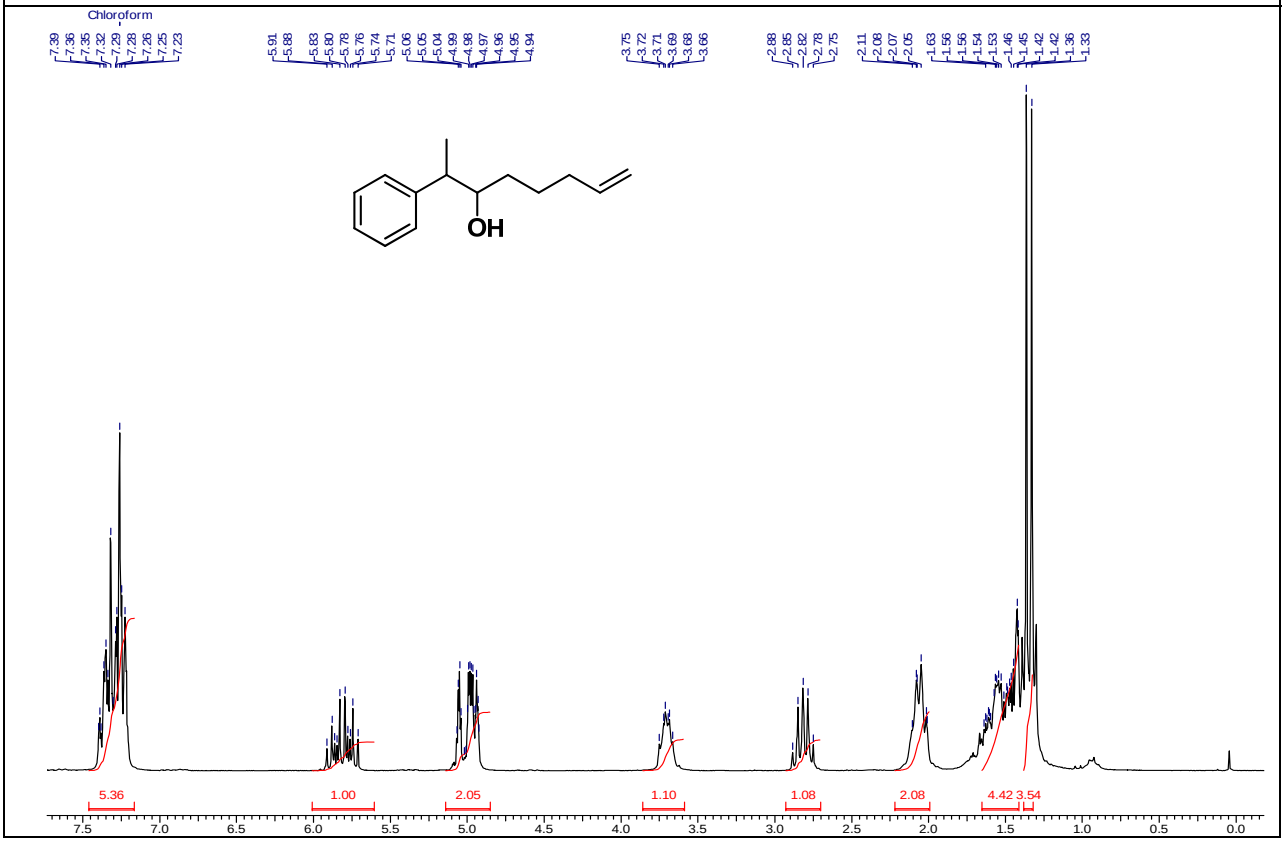
^{13}C NMR spectrum of compound **(±14a)** ($CDCl_3$, 50 MHz) **first diastereomer**



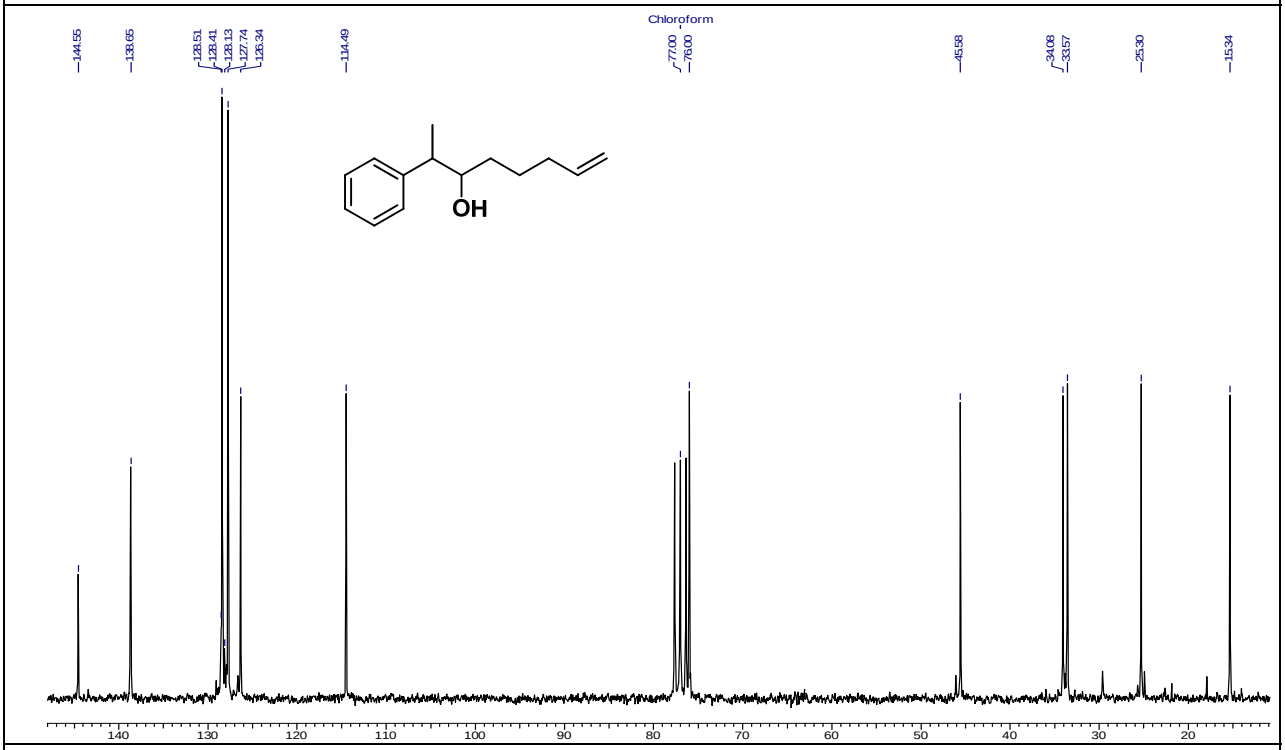
DEPT spectrum of compound **(±14a)** ($CDCl_3$, 50 MHz)



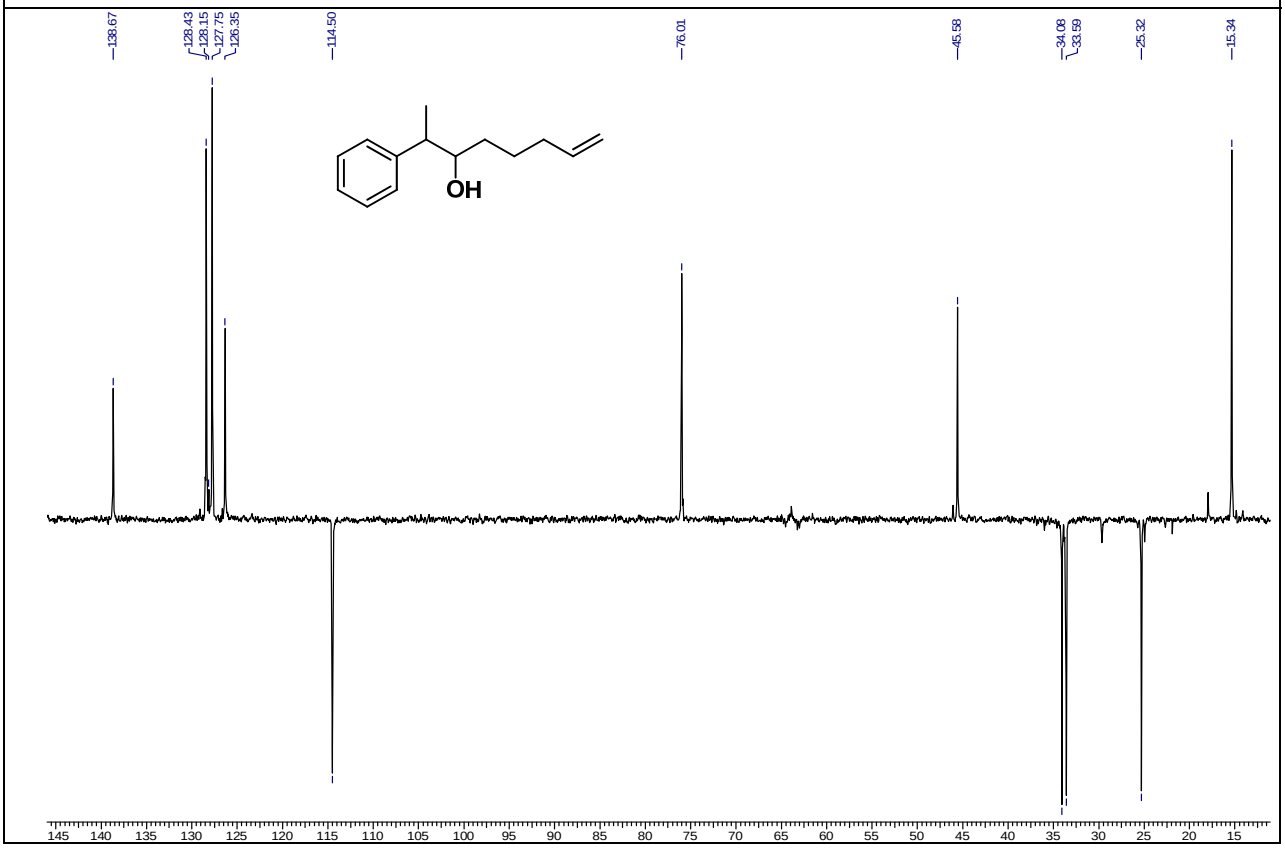
^{1}H NMR spectrum of compound **(±14a)** ($CDCl_3$, 200 MHz) **second diastereomer**



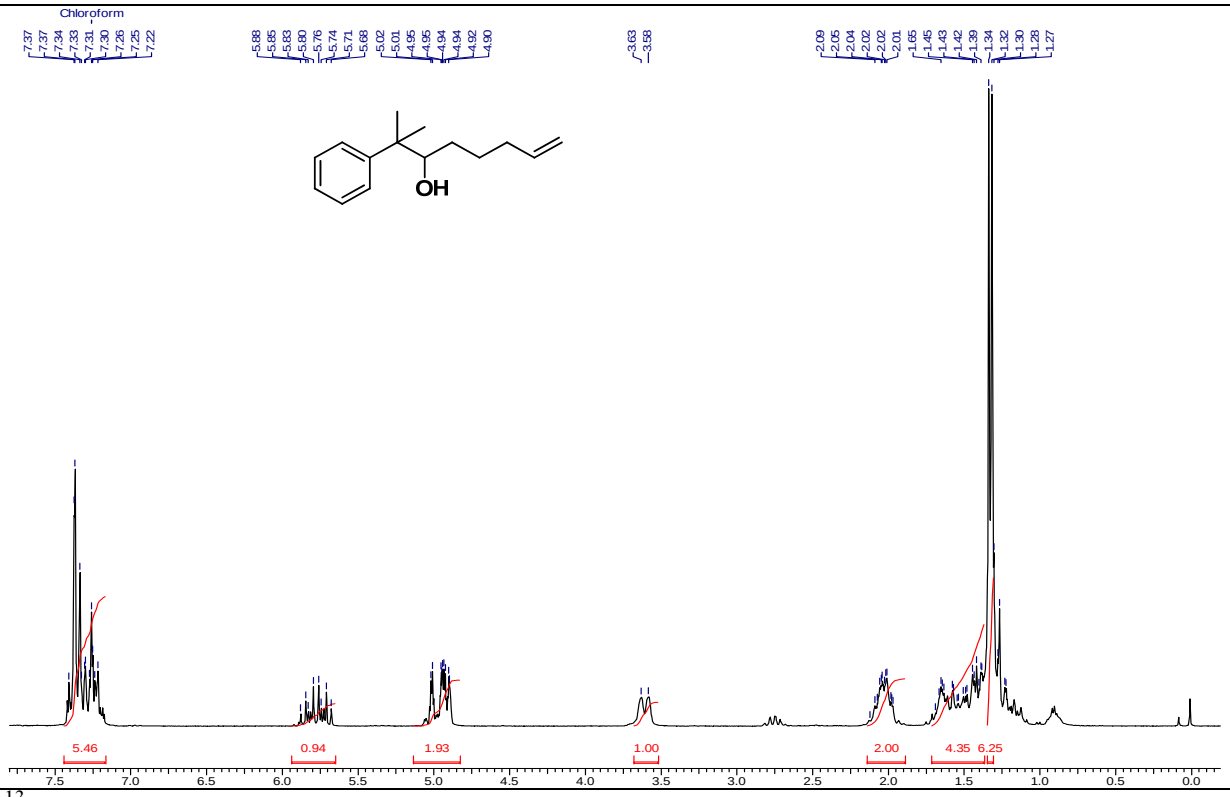
^{13}C NMR spectrum of compound **(±14a)** ($CDCl_3$, 50 MHz) **second diastereomer**



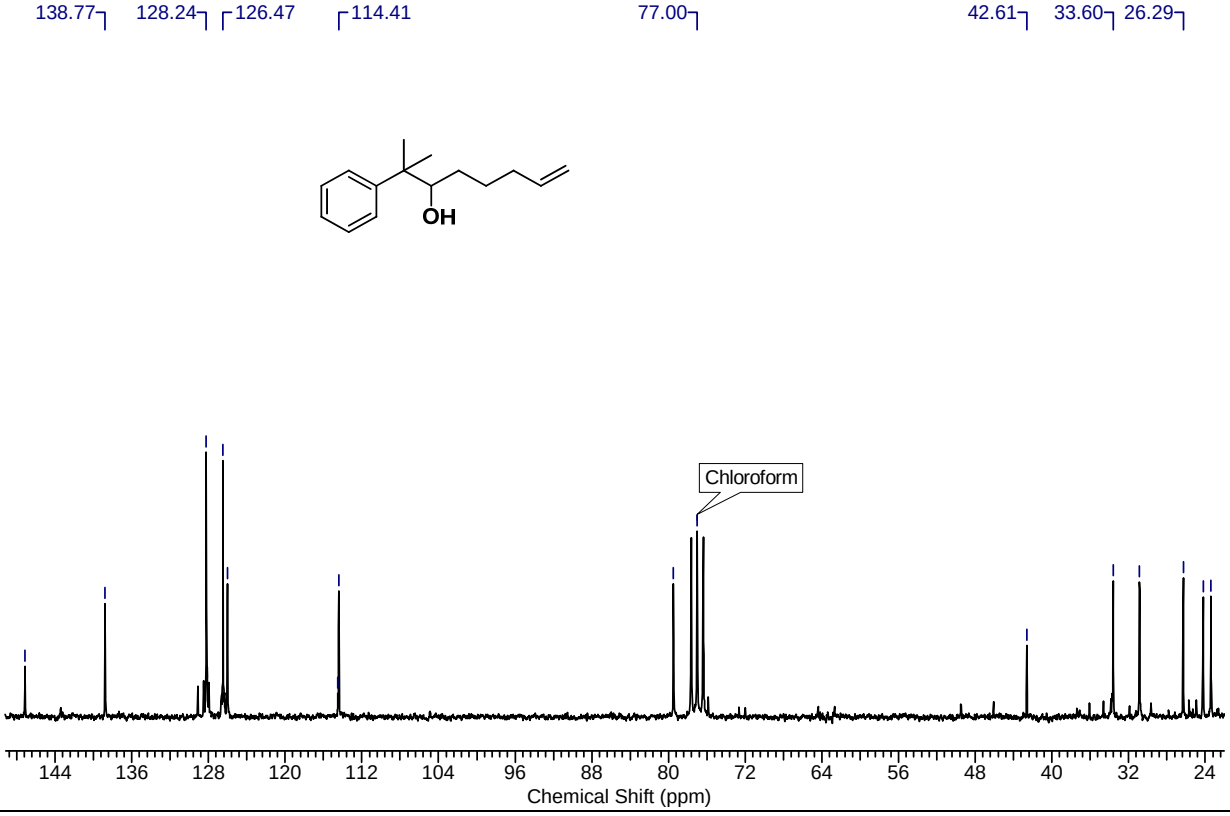
DEPT spectrum of compound **(±14a)** ($CDCl_3$, 50 MHz) **second diastereomer**



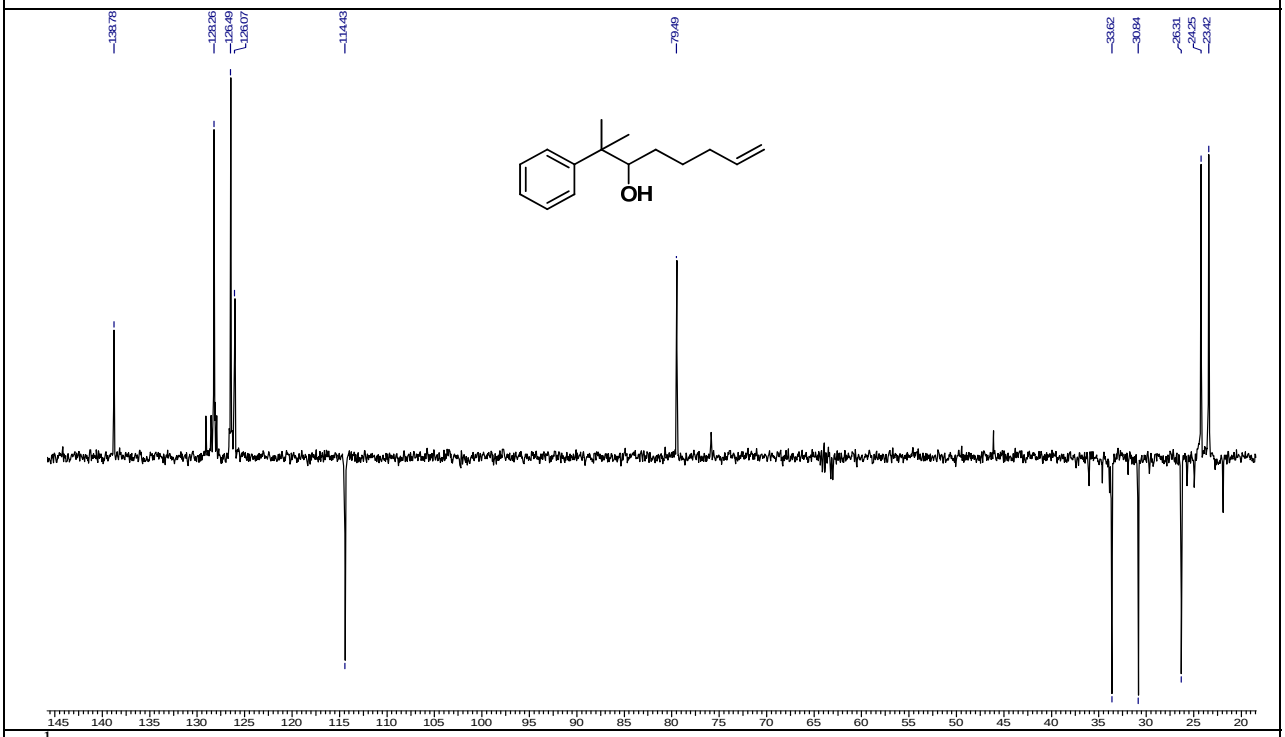
^{1}H NMR spectrum of compound **(15a)** ($CDCl_3$, 200 MHz)



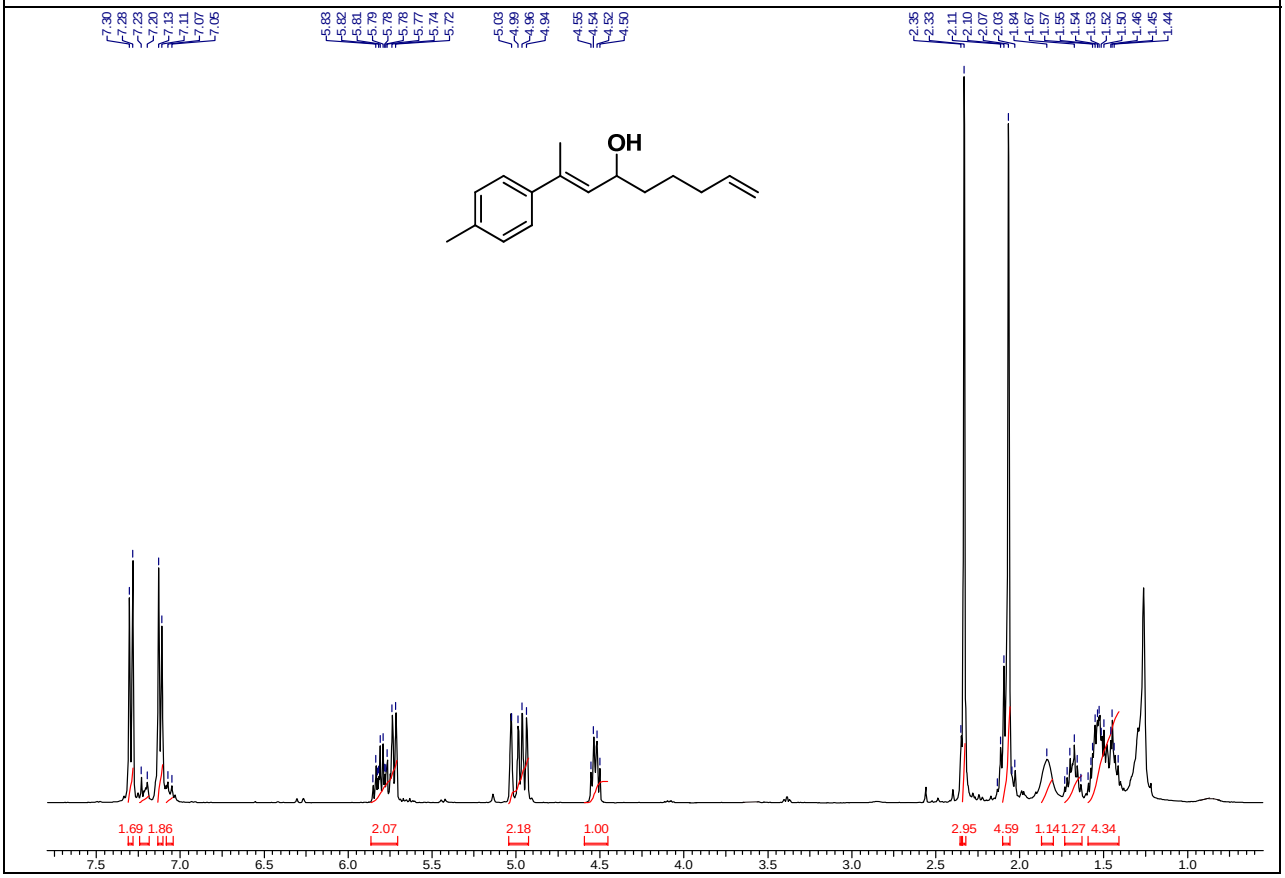
^{13}C NMR spectrum of compound **(15a)** ($CDCl_3$, 50 MHz) **(16a)**



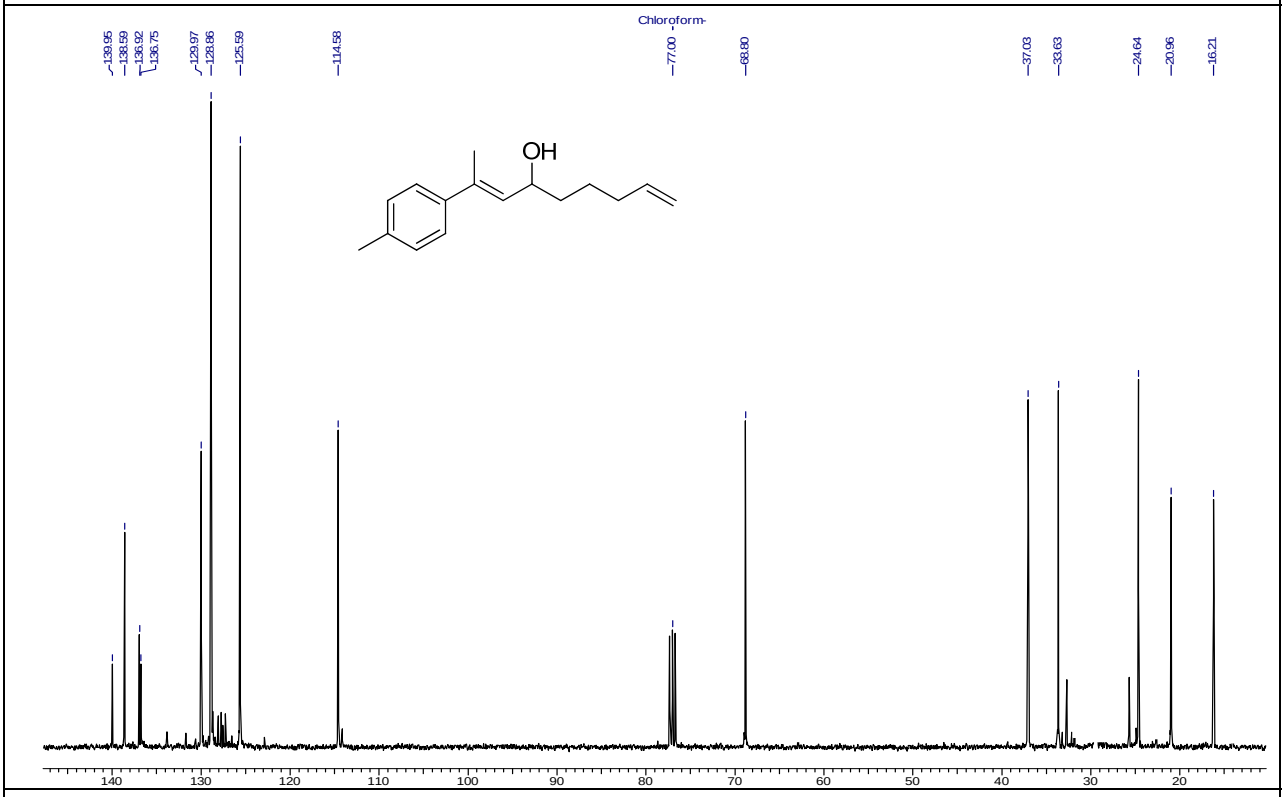
DEPT spectrum of compound **(15a)** ($CDCl_3$, 50 MHz)



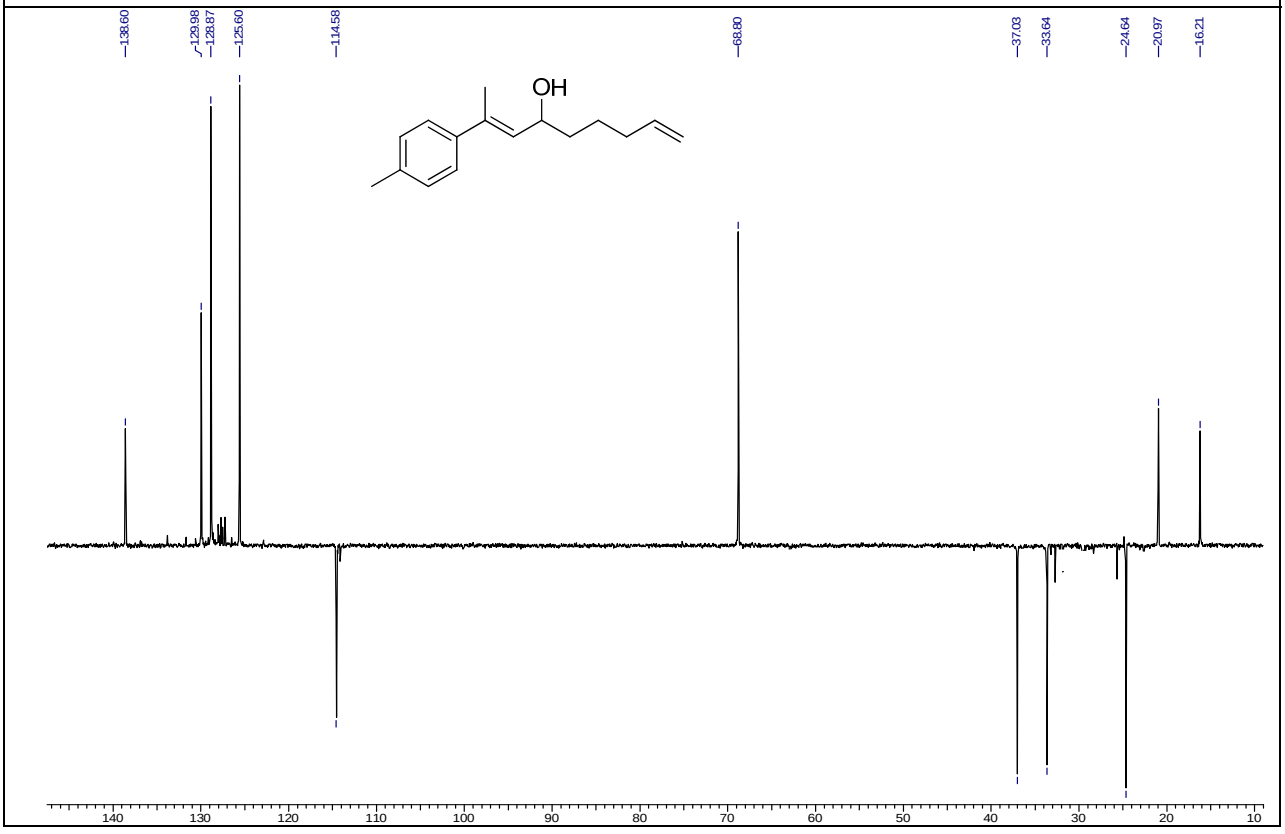
^{1}H NMR spectrum of compound **(17a)** ($CDCl_3$, 200 MHz)



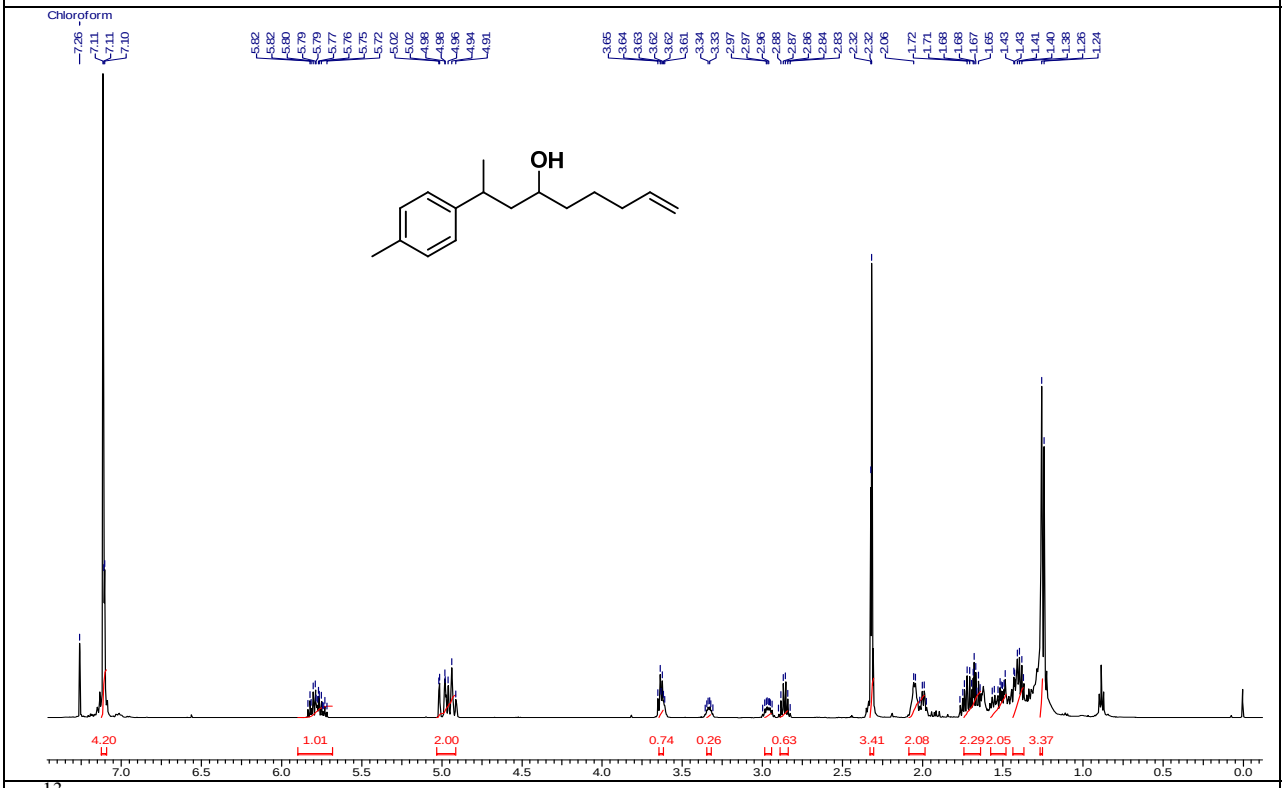
^{13}C NMR spectrum of compound **(17a)** ($CDCl_3$, 50 MHz)



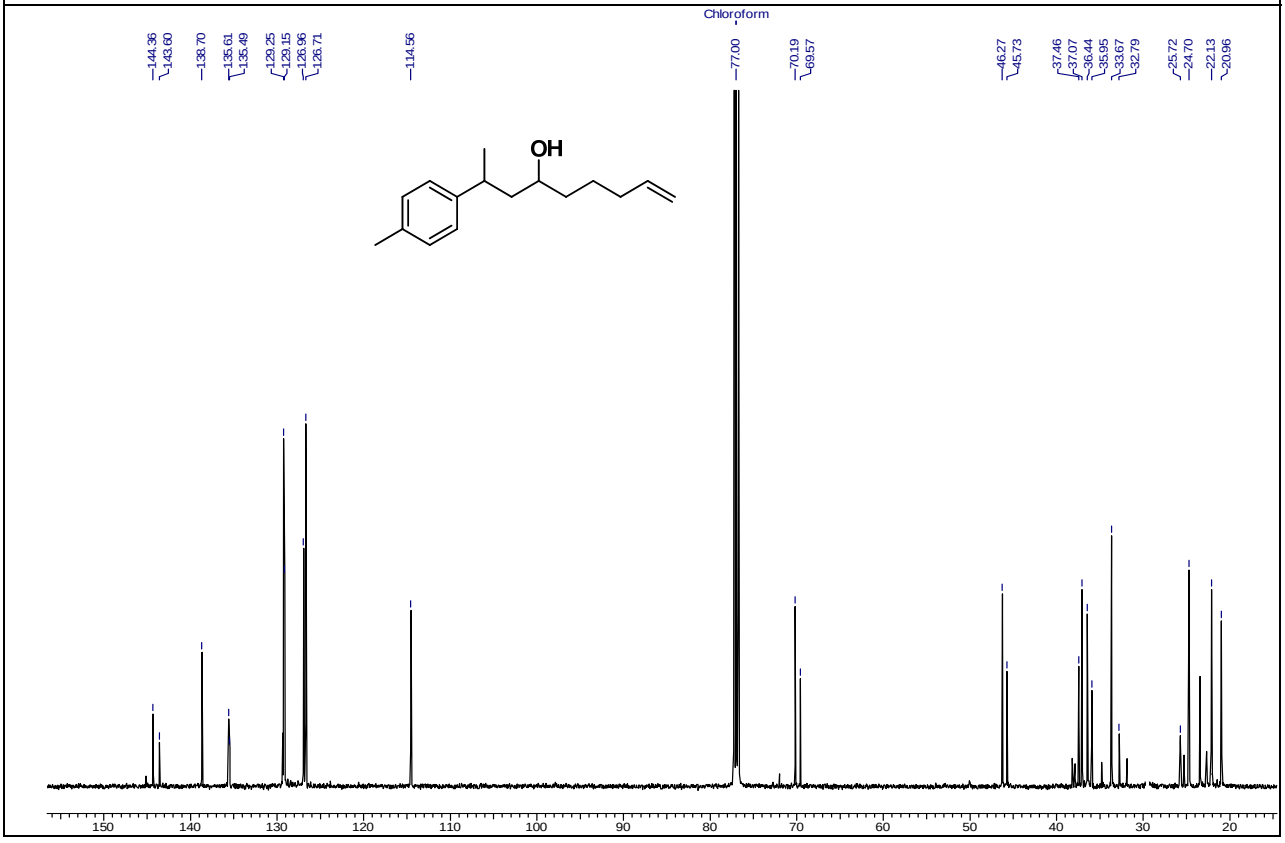
DEPT spectrum of compound **(17a)** ($CDCl_3$, 50 MHz)



^{1}H NMR spectrum of compound **(±18a)** ($CDCl_3$, 200 MHz)

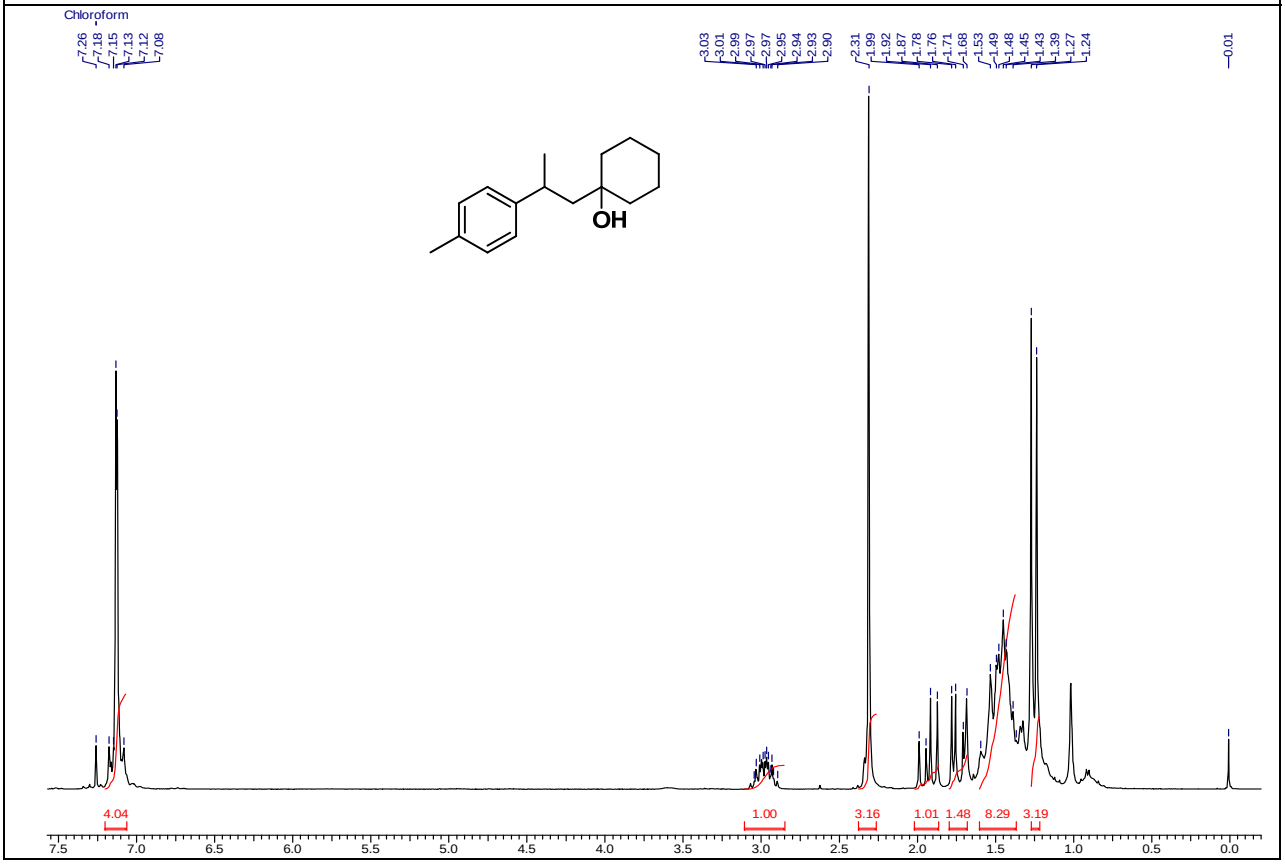


^{13}C NMR spectrum of compound **(±18a)** ($CDCl_3$, 50 MHz)

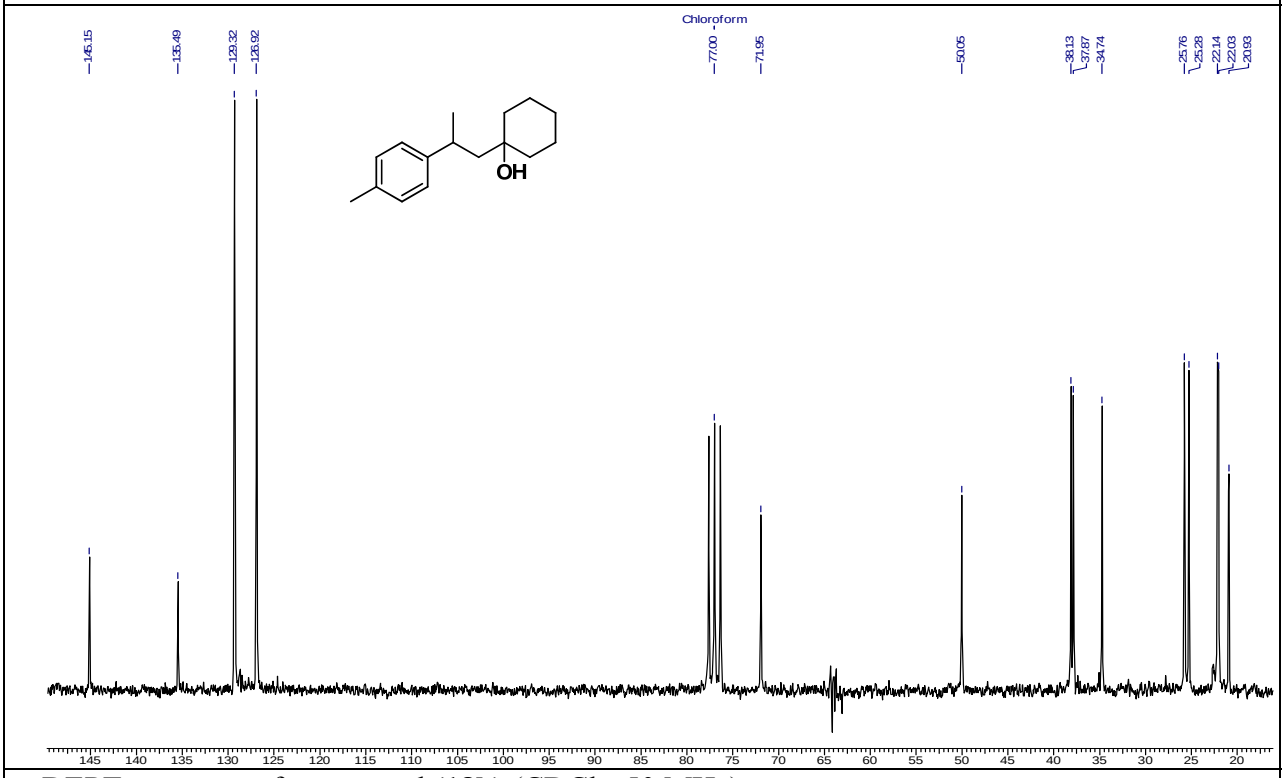


DEPT spectrum of compound **(±18a)** ($CDCl_3$, 50 MHz)

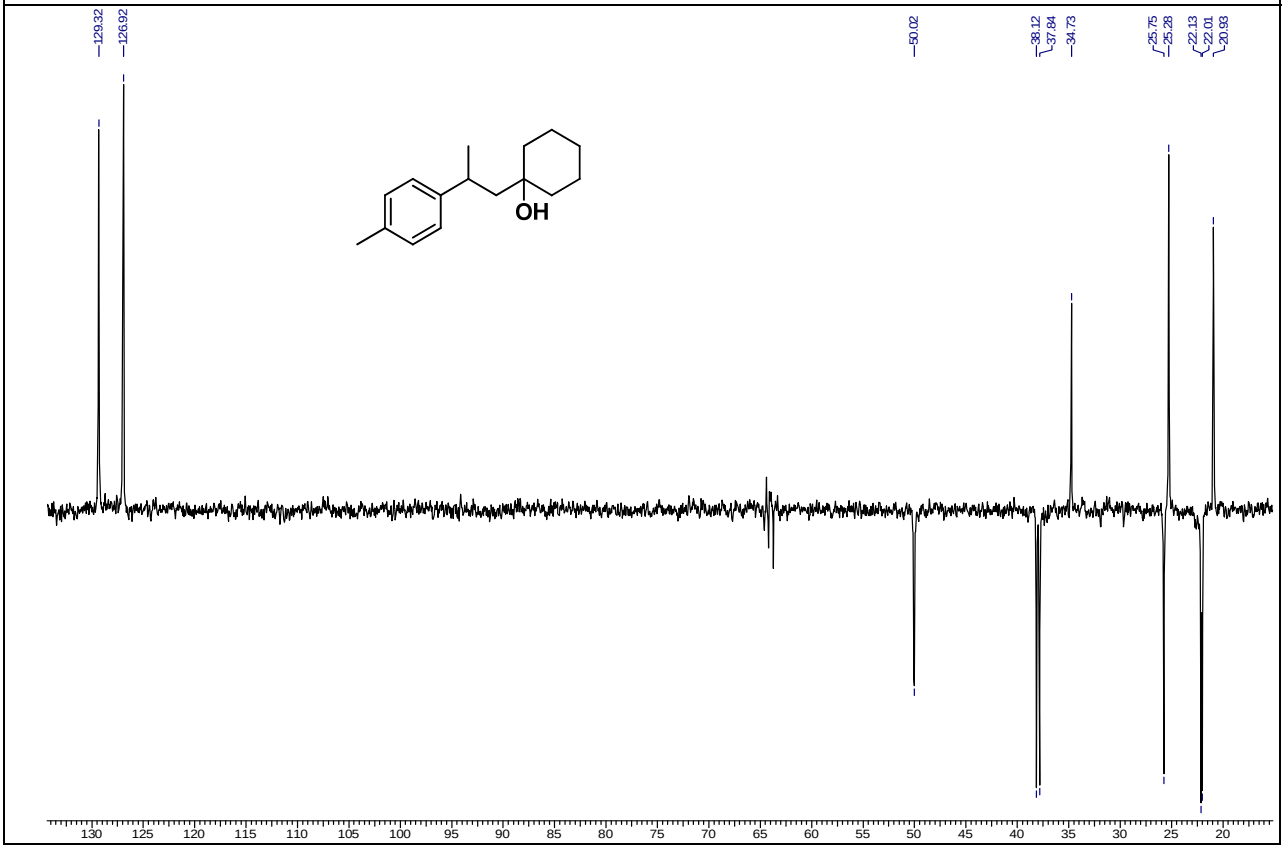
^{1}H NMR spectrum of compound **(18b)** ($CDCl_3$, 200 MHz)



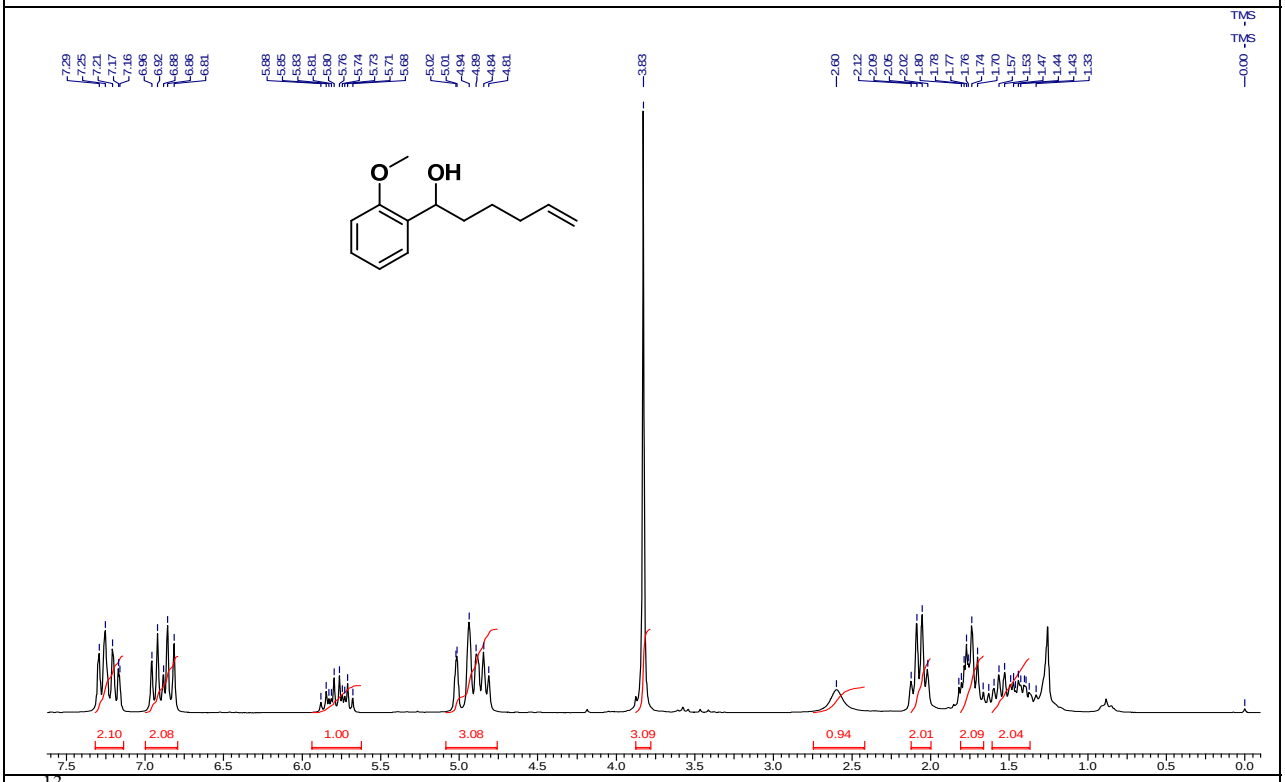
^{13}C NMR spectrum of compound **(18b)** ($CDCl_3$, 50 MHz)



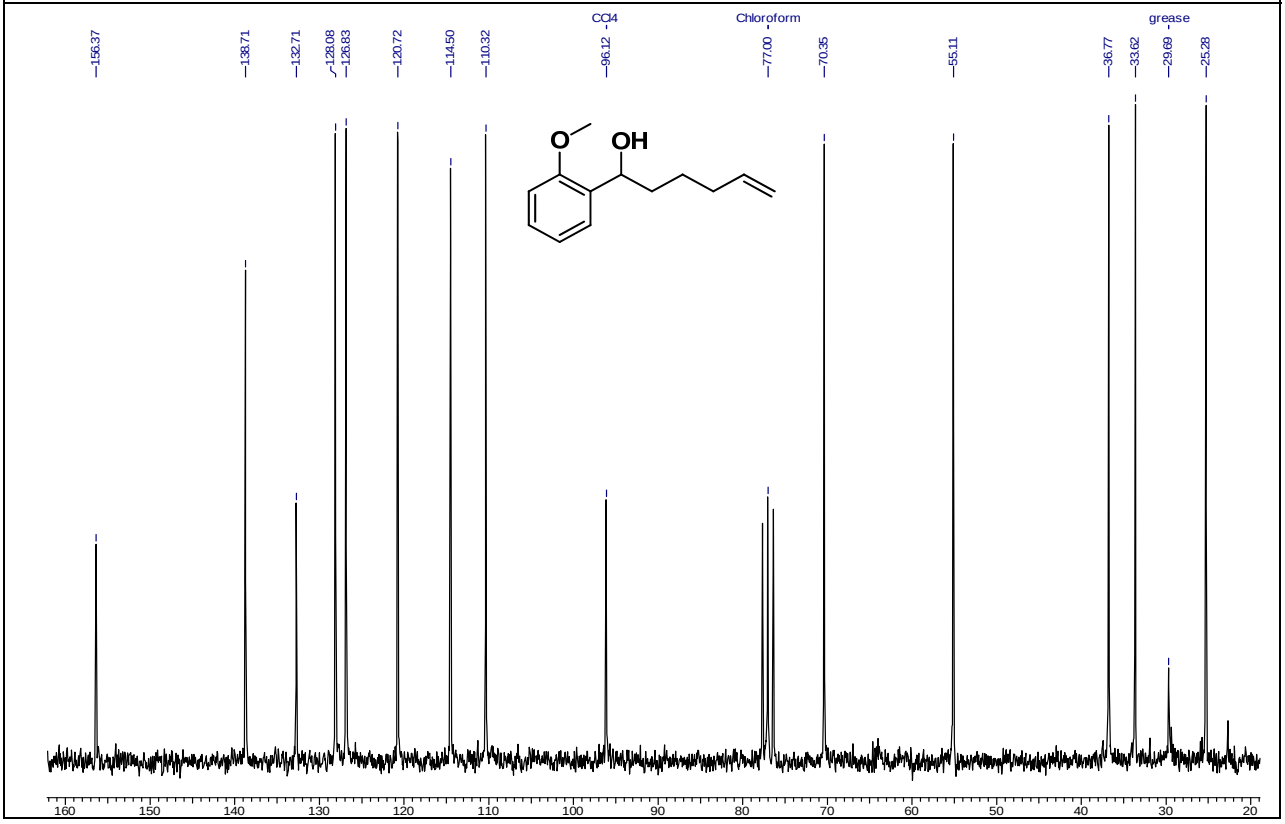
DEPT spectrum of compound **(18b)** ($CDCl_3$, 50 MHz)



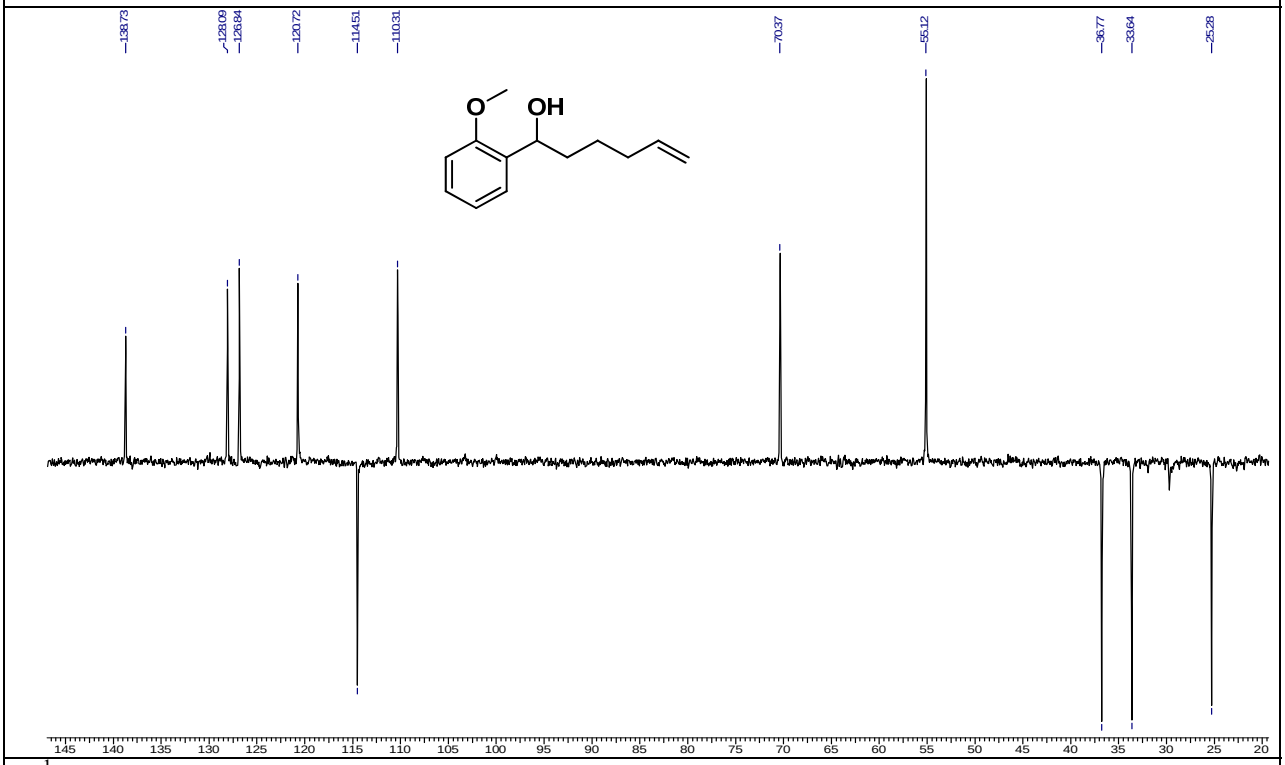
^{1}H NMR spectrum of compound **(20a)** ($CDCl_3$+CCl_4, 200 MHz)



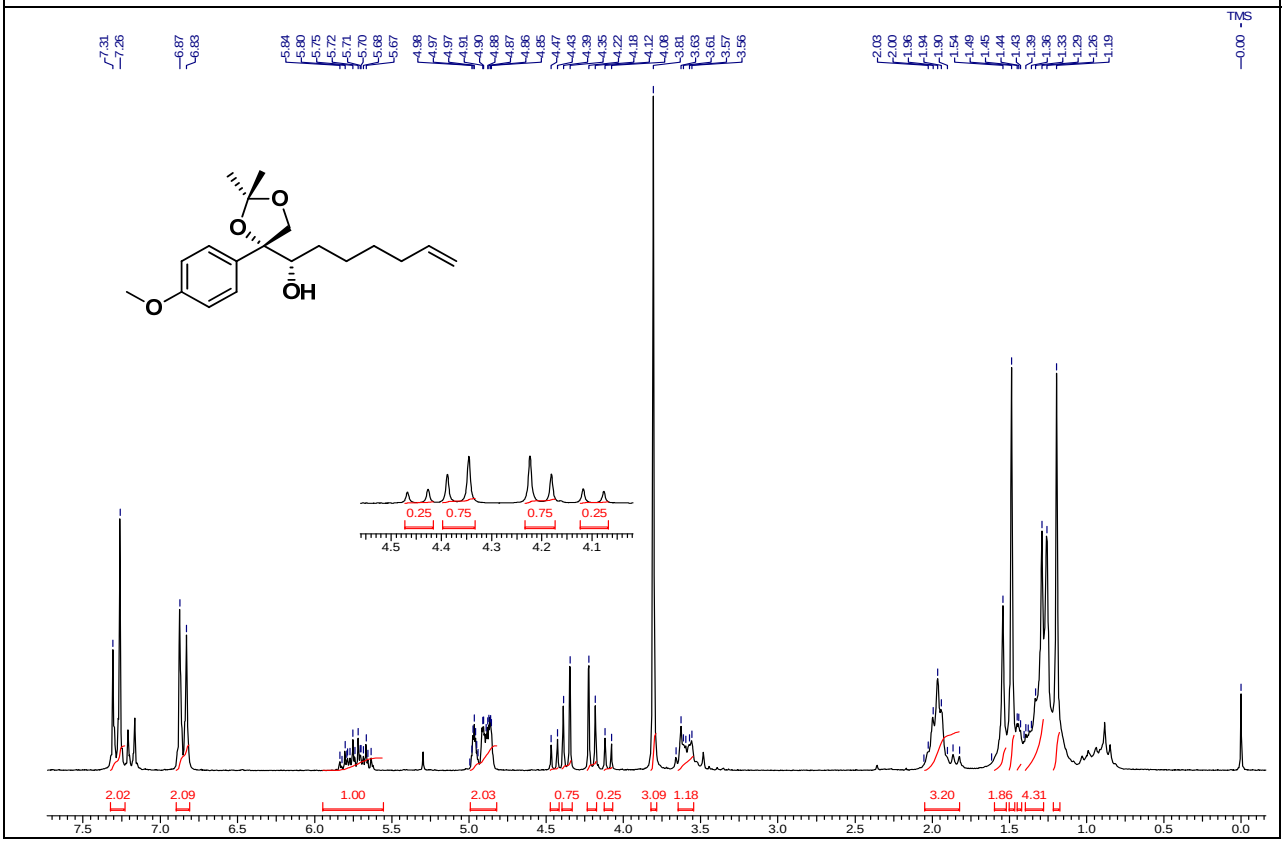
^{13}C NMR spectrum of compound **(20a)** ($CDCl_3$+CCl_4, 50 MHz)



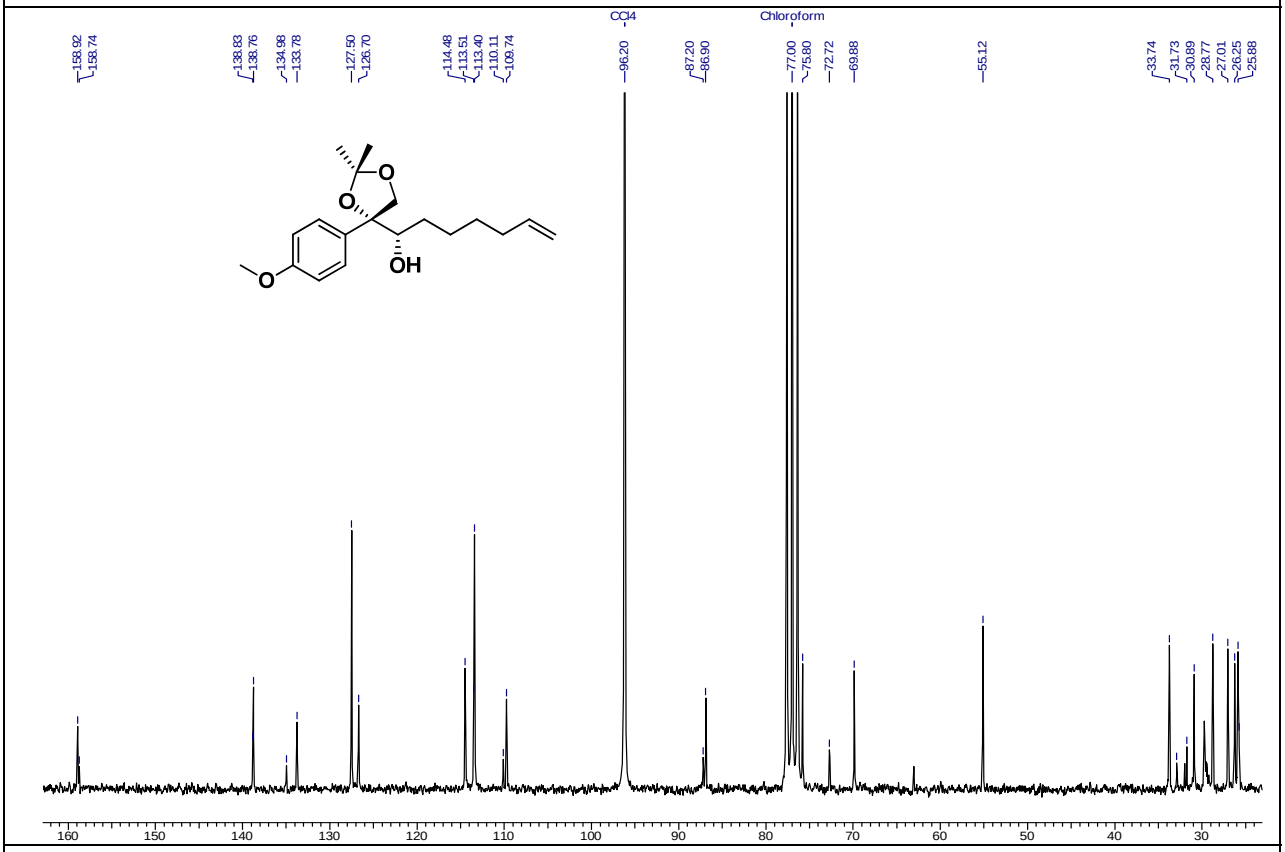
DEPT spectrum of compound **(20a)** ($CDCl_3$+CCl_4, 50 MHz)



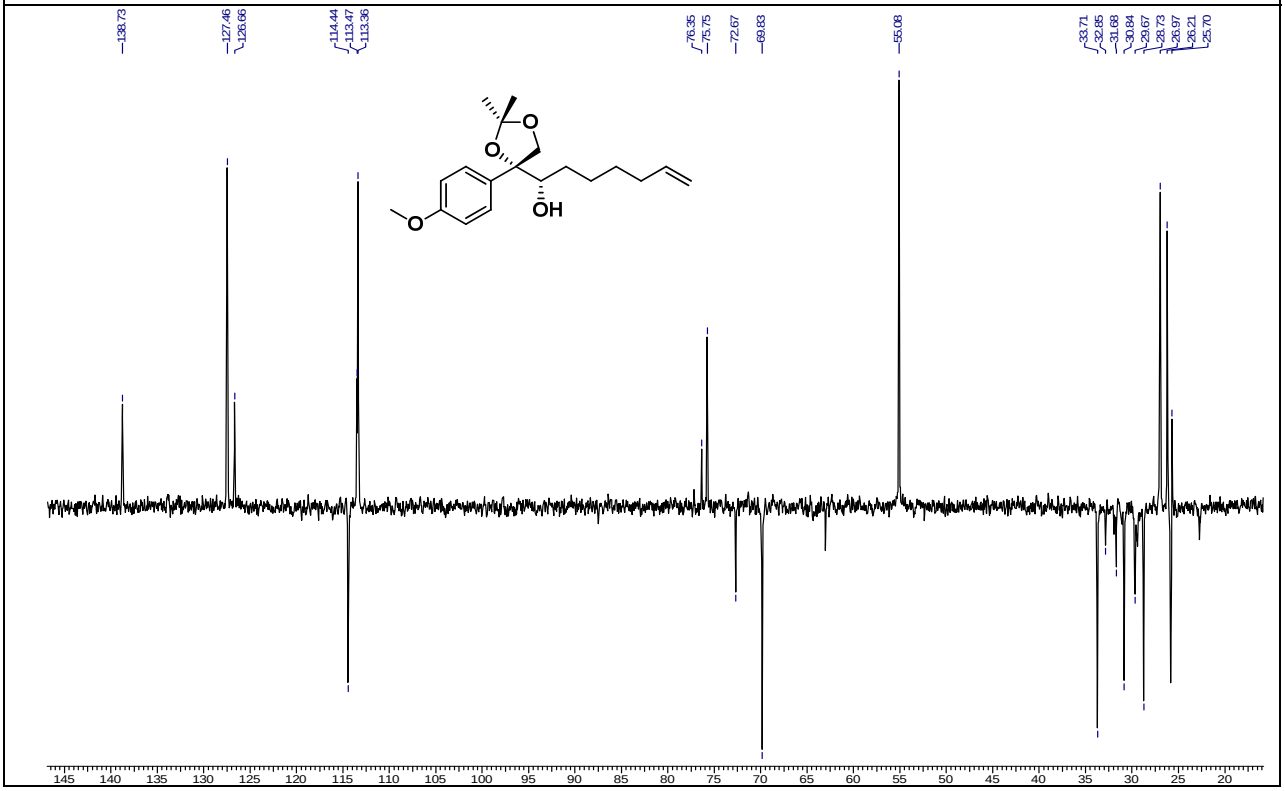
^{1}H NMR spectrum of compound **(±22a)** ($CDCl_3$+CCl_4, 200 MHz)



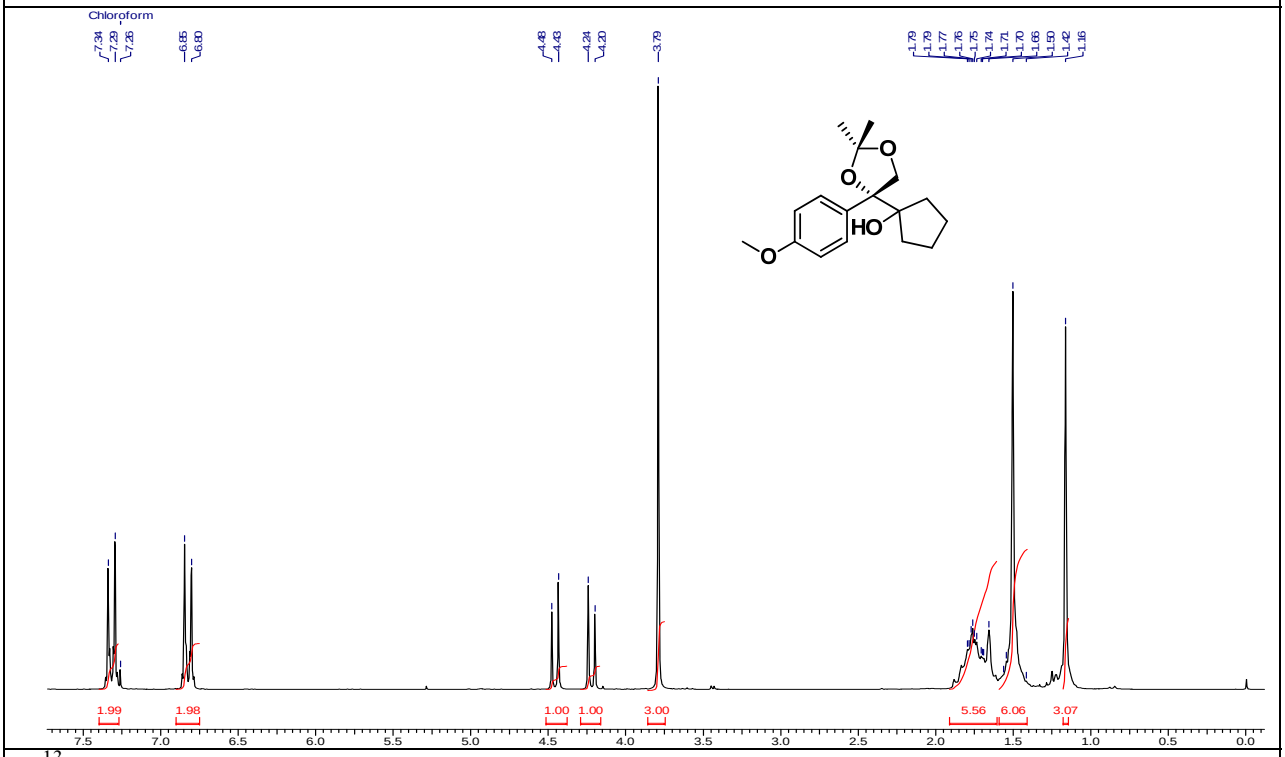
^{13}C NMR spectrum of compound **(±22a)** ($CDCl_3$+CCl_4, 50 MHz)



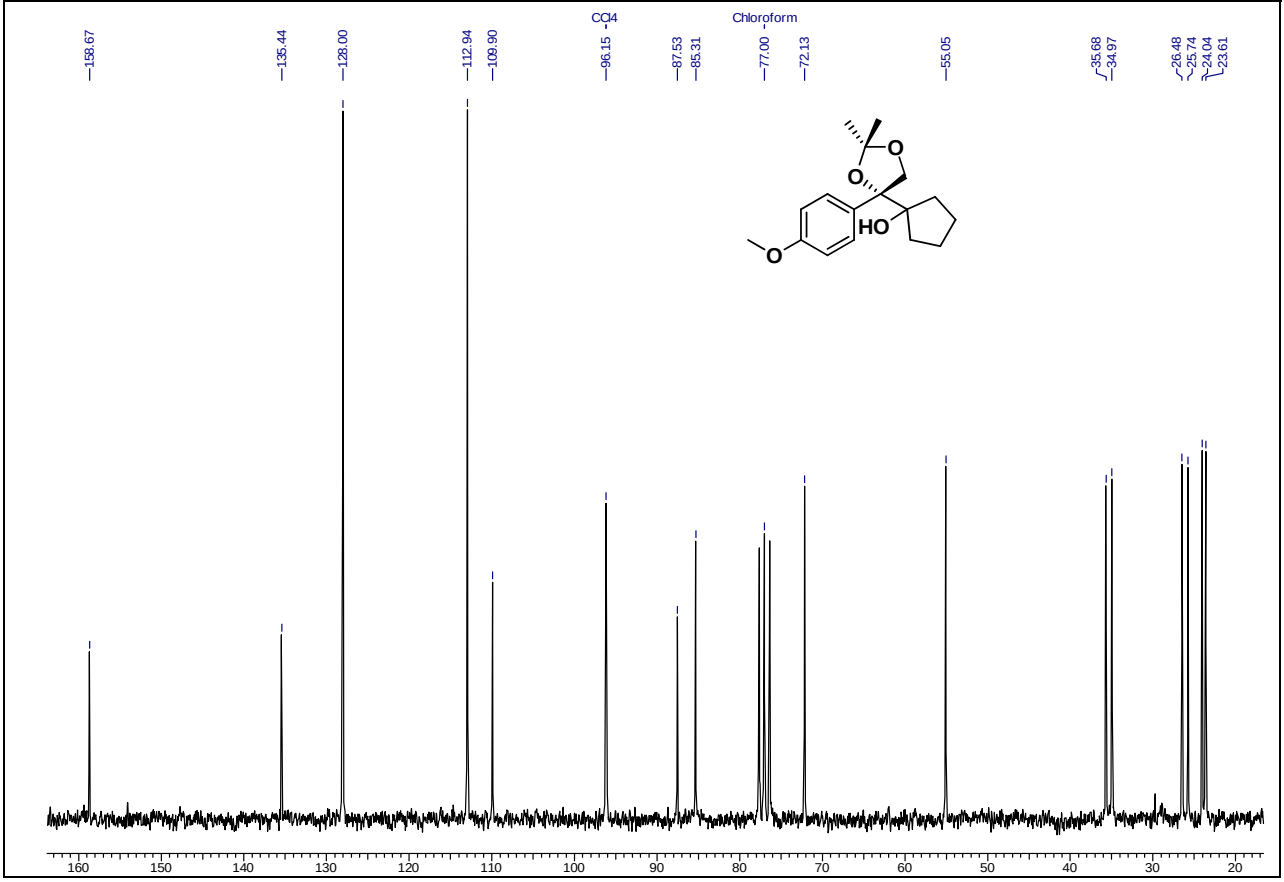
DEPT spectrum of compound **(±22a)** ($CDCl_3$+CCl_4, 50 MHz)



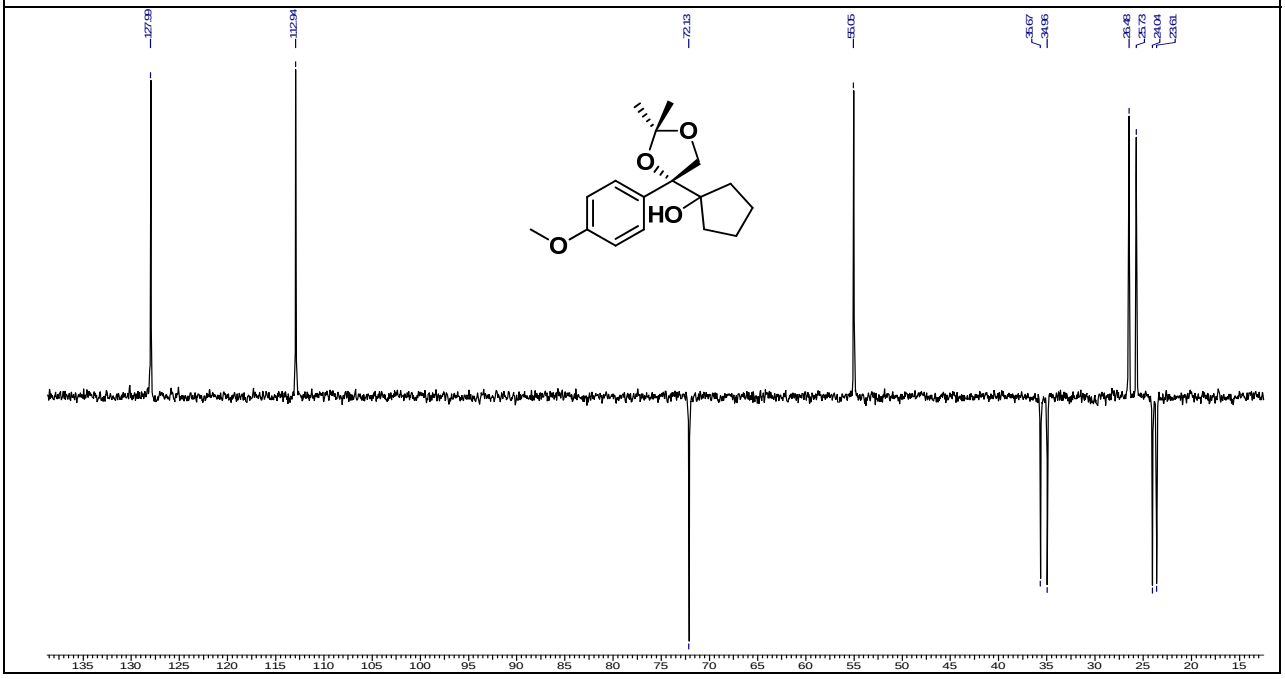
^{1}H NMR spectrum of compound **(23a)** ($CDCl_3$+CCl_4, 200 MHz)



^{13}C NMR spectrum of compound **(23a)** ($CDCl_3$+CCl_4, 50 MHz)



DEPT spectrum of compound **(23a)** ($CDCl_3$+CCl_4, 50 MHz)



3.1.5. References:

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3.3.1. Introduction

WHO reported that for all ages and both the sexes depression is expected to be the second most common health problem in the world by the year 2020.[1] Venlafaxine is a modern age "in practice" antidepressant drug. It is licensed for the treatment of depression, panic disorder, social phobia, anxiety and vasomotor symptoms as it works by altering unbalanced chemicals in brain. It is marketed in the racemic form under trade names Effexor/ Effexor-XR for the extended-release dosing property. It shows minimum protein binding property as compared to other antidepressants hence is activity specific and demonstrates significantly minimum risk of side effects.[2] It inhibits reuptake of biogenic amines like serotonin and norepinephrine, hence called as serotonin norepinephrine reuptake inhibitor. Under placebo-controlled clinical trials, the efficacy of venlafaxine was shown to be significantly superior to placebo on the Hamilton depression rating scale and clinical global impression. Venlafaxine is among the best sold antidepressants in the world during the period ranging from 2008 to 2010.[4] Wyeth's second generation drug is a metabolite of venlafaxine, named as Pristiq® (*O*-desmethylvenlafaxine succinate) and was approved in 2008 for the treatment of major depressive disorders which is also in phase II developmental clinical trials for the treatment of fibromyalgia (**Figure 1**).[5]

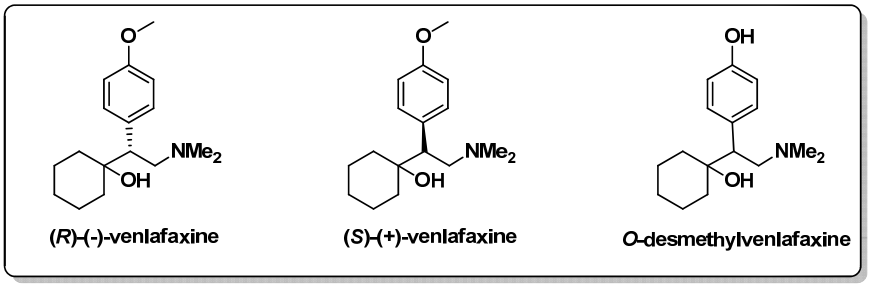


Figure 1. Structure of venlafaxine and *O*-desmethylvenlafaxine

However both enantiomers have a role in the antidepressant activity with the (*S*)-(+)-enantiomer inhibiting serotonin reuptake and the (*R*)-(-)-enantiomer inhibiting nor-epinephrine reuptake.[3] It is different from other antidepressants in that it has no or little activity on a variety of neuroreceptors[3] (eg. α or β-adrenergic receptors, muscarinic receptors, cholinergic receptors, histaminic receptors etc.). 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 dopamie reuptake at high dosage. The absence of other significant sites of pharmacological

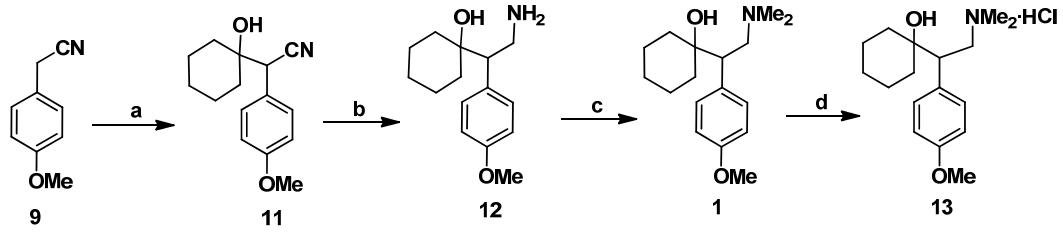
action gives it a wide therapeutic window. Co-administration of two drugs, which inhibit individually either serotonin or norepinephrine uptake, has been shown to shorten the treatment time. The efficacy of venlafaxine as a treatment for major depressive disorder has been established under five placebo-controlled, short-term trials.[4,5]

3.3.2. Literature review on synthesis of venlafaxine

From past few years this lab is one of the active group in synthesis of venlafaxine[5] although over period of time many total syntheses of this drug featuring racemic as well as chiral syntheses were reported in the literature.[9-18]

a) Racemic synthesis of venlafaxine

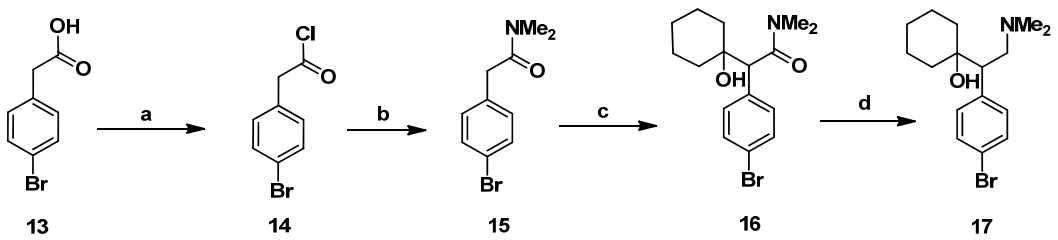
Yardley's Approach[9](*J. Med. Chem.***1986**, *33*, 2899; US Patent No. 4, 535, 186, **1985**)



Scheme 1. *Reagents and conditions: a) LDA, THF, –78 °C, 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, 12 h; d) HCl (20% in iPrOH) 80%.*

p-Methoxyphenylacetonitrile (**9**) was condensed with cyclohexanone **10** using LDA at –78 °C to furnish cyanoalcohol **11**. Under hydrogenation reaction condition with Rh/Al_2O_3 in NH_3/EtOH compound **11** was converted into aminoalcohol **12** in 57% yield. For *N,N*-dimethylation of the primary amine, compound **12** was treated with formaldehyde, formic acid and refluxed overnight, to afford venlafaxine **1**. Hydrochloride salt of venlafaxine, **13** was prepared using 20% HCl in IPA (**Scheme 1**).

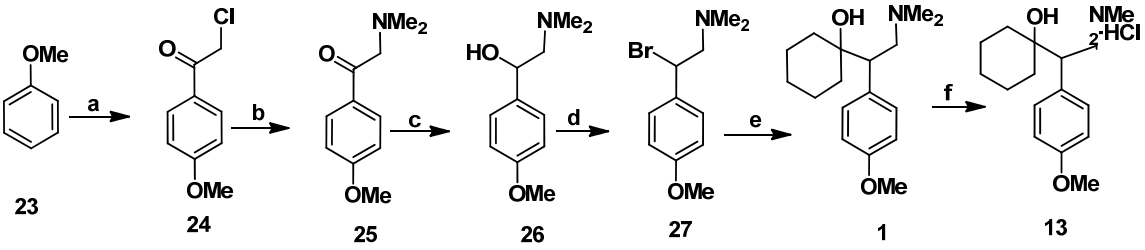
In a modified route (**Scheme 2**), acid chloride **14** was prepared from corresponding *p*-bromophenylacetic acid **13**. Acid chloride **14** treated with Me_2NH to give corresponding acetamide **15**. Condensation of cyclohexanone **10** withacetamide **15** with at –78 °C using LDA furnished amidoalcohol **16**, which was further reduced using LAH to yield venlafaxine analog **17**. Small libraries of several analogues of venlafaxine were also prepared by these methods.



Scheme 2. *Reagents and conditions: a) $(COCl)_2$, DMF, DCM, r t, 4 h; b) Me_2NH, DCM, r t, 12 h, 97% ; c) LDA, THF, –78 ^oC, cyclohexanone* ***10****, 50 min, 44%; d) $LiAlH_4$, conc. H_2SO_4, THF, 0 ^oC, 1 h, 40%.*

Jinpei's aproach[10](*J. China Pharm. Univ*. **1999**, *30*, 249)

Anisole **23** was refluxed with chloroacetyl chloride under Friedel-Craft's acylation reaction condition in the presence of $AlCl_3$ to yield chloroketone **24**. Compound **24** which upon



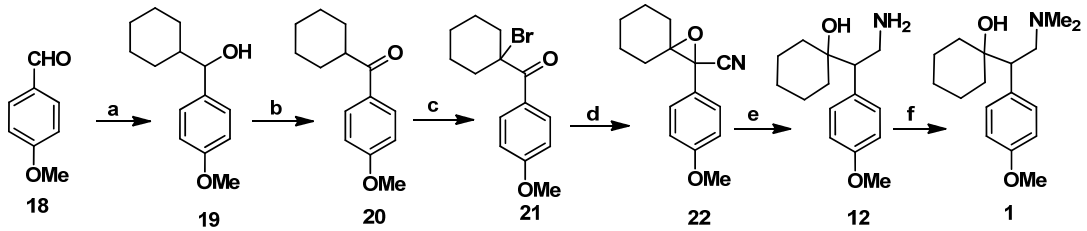
Scheme 3. *Reagents and conditions: a) $ClCO_2CH_2Cl$, $AlCl_3$, PhH, reflux, 4 h, 70%; b) 33% aq. Me_2NH, EtOH, r t, 15 h; c) KBH_4, EtOH, r t, 8 h, 64%; d) PBr_3, $CHCl_3$, 0 ^oC then reflux, 15 h, 53%; e) Mg, THF, reflux, then 0 ^oC, cyclohexanone* ***34*** *then reflux, 1 h; f) conc. HCl, 47%.*

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 under refluxing conditions. 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 3**).

Rathod's approach[11] (EP 1249447, **2001**)

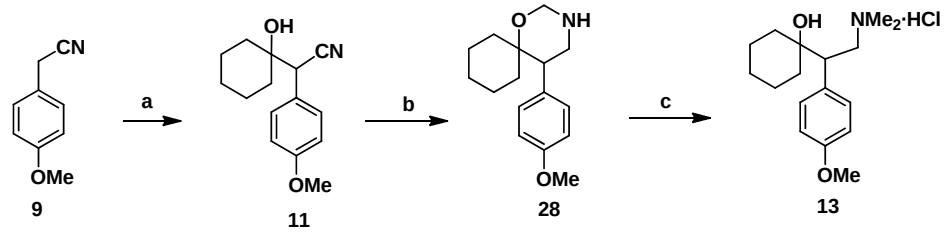
Rathod*et al.* patented a protocol for the synthesis of venlafaxine **1** involving Grignard reaction of cyclohexyl magnesium bromide with *p*-anisaldehyde **18** to yield **19**. This alcohol was subjected to reaction with CrO_3 to give corresponding ketone **20**, which was again treated with PTAB to

give α-bromoketone **21**. *α*-Bromoketone **21**in turn was treated with NaCN to yield spiroepoxide **22**. Opening of the epoxide ring of **22**and concomittant reduction of cyanide was performed with Raney nickel to afford aminoalcohol **12**, which was converted into venlafaxine **1** by the known procedure (**Scheme 4**).



Scheme 4. *Reagents and conditions: a) CyclohexylMgBr, THF, 10 ^{o}C- 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%.*

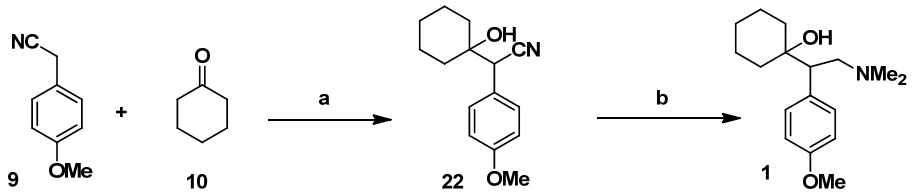
Rangappa's appraoch[12] (*Bioorg. Med. Chem. Lett.***2004**, *14*, 3279-3281)



Scheme 5. *a) cyclohexanone **34**, NaOH, Bu_4NBr, H_2O-MeOH, r t, 15 h, 96%; b) Raney Ni, H_2, NH_3-MeOH, 35-40 ^{o}C, formalin, RT, 3 h, 83%; c) HCO_2H, HCHO, reflux, 25-30 h, HCl in iPrOH, 85%.*

Condensation of **9** with cyclohexanone **10** was prepared using NaOH in MeOH-H_2O (1:1) medium. Cyanoalcohol **11** with Raney nickel followed byreaction with formalin gave oxazine **28**, which was further subjected to Eschweiler-Clarke reaction conditions to obtain venlafaxine **1**. Treatment of **1** with ^{i}PrOH/HCl gave **13** (**Scheme 5**).

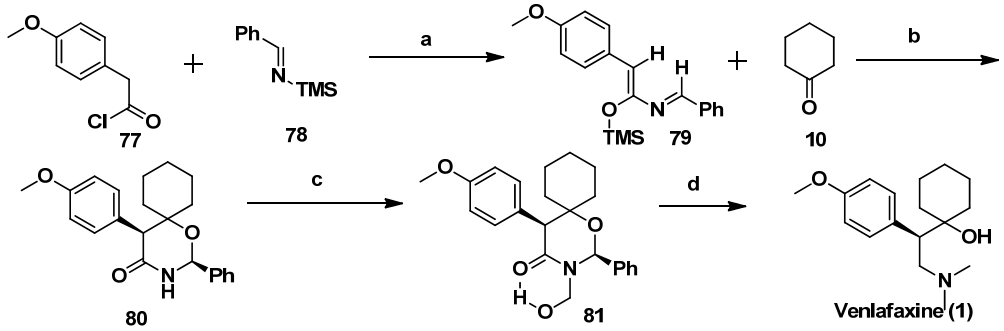
Chavan's approach[13] (US 6,504,044B2, **2003,** *Tet. Lett.***2004**, *45*, 7291, *Syn. Commun.* **2007**, *37*, 2007) This group reported a green, novel and mild method for condensation of phenylacetonitrile **9** with cyclohexanone **10** to give cycloalkanol **22**. By using this protocol this group reported the practical synthesis of venlafaxine **1** (**Scheme 6**).



Scheme 6. *Reagents and conditions: a)10% aqueous NaOH, TBAHSO$_4$, 0-15 °C, 30 min1 h, quantitative yield; (b) H$_2$, 280 psi, formalin, MeOH, 100 °C, 30% (60% starting).*

Mu's approach (*Synthesis*, **2008**, *11*, 1753-1756) [14].

Synthesis of venlafaxine from azadiene via a Hetero-Diels-Alder approach executes new microwave assisted transketalization and hydroxymethylation reactions (**Scheme-7**).



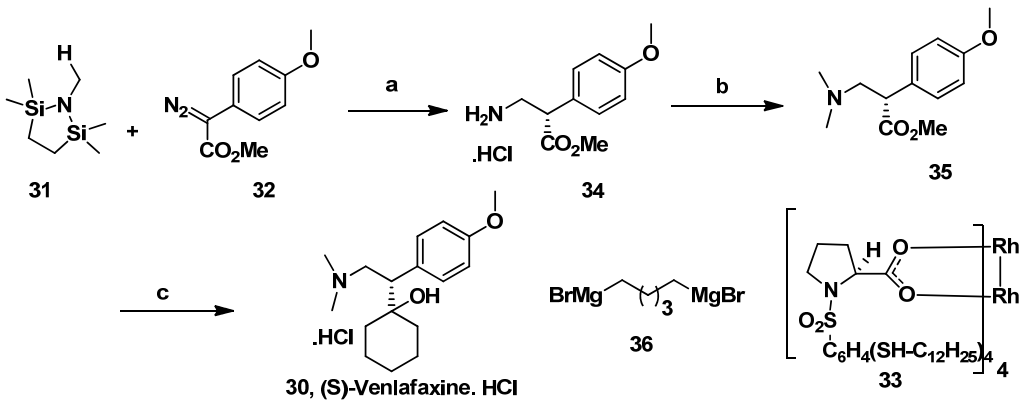
Scheme-7 *Reagents and conditions: a) i) TMSCl, DCM, ii) Et$_3$N, quant.yield; b) BF$_3$OEt$_2$, DCM, -78 oC, 8 h, 62%; c) HCHO, HCOOH, MW, 1 min, 58%; d) LAH, THF, 66%.*

Azadiene **79**was prepared from (4-methoxyphenyl)acetyl chloride (**77**) and the trimethylsilylbenzaldimine (**78**). Azadiene was treated with $BF_3OEt_2$and dienophile cyclohexanone (**10**) under [4+2]-hetero-Diels-Alder reaction at -78 ^oC for 8 h to furnish perhydroxazin-4-one**80**. It was treated with mixture of formic acid and formaldehyde under microwave irradiation furnished transketalized derivative**81**. Reduction of compound **81**with LAH provided racemic **1** in 66% yield.

b) Asymmetric synthesis

Davies's approach[15] **(***Chem. Comm.***2006**, 3110–3112)

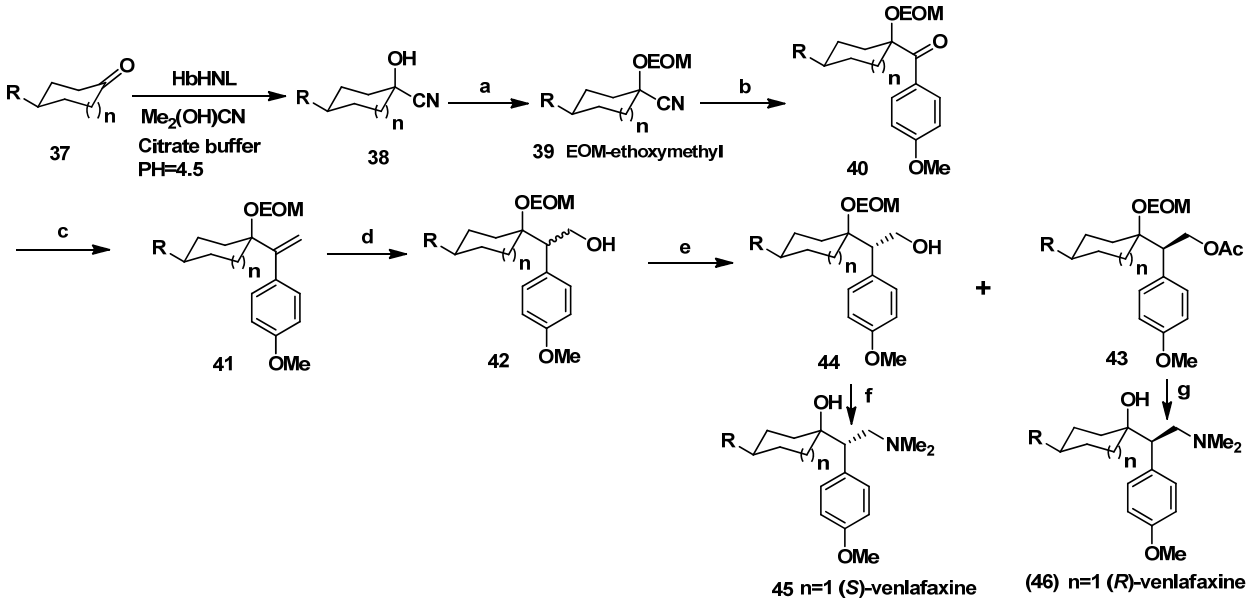
Davies *et al.* developed a method for synthesis chiral *β*-Amino esters **34** from the rhodium (II) prolinate **33** catalyzed intermolecular C–H insertion between methyl aryl diazoacetates **32** anda



Scheme 8. *:a) i)* ***33****, -40 °C; ii) HCl/ether; b) HCHO/NaBH(OAc)$_3$, DCM ; c) i)* ***36****; ii) HCl/ether.*

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 *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 8**).

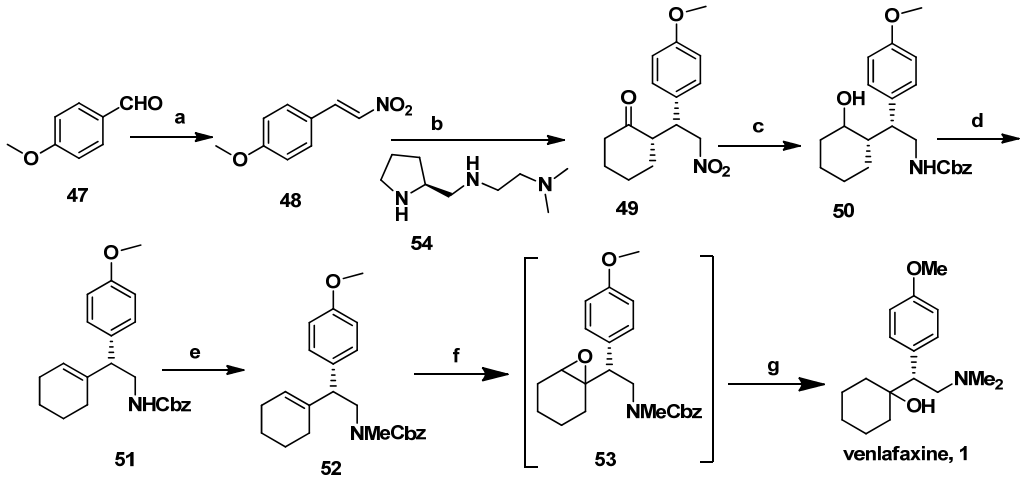
Nanda's approach[16] (*Tetrahedron. Lett.***2012**, *53*, 1990–1992)



Scheme 9. *Reagents and conditions: (a) EOM-Cl, DIPEA, 90%; (b) p-MeOC$_6$H$_4$MgBr, 85%; (c) Ph$_3$P$^+$MeI, KO^{t}Bu, 82%; (d) BH$_3$.SMe$_2$, KOH, H$_2$O$_2$, 84%; (e) CH$_2$=CHOAc, Lipase PS-D, MS 4 Å, 48%; (f) (i) p-TSCl, Et$_3$N, DMAP, 88%; (ii) Me$_2$NH, 80 °C, 48 h; (iii) pTSA, MeOH, 65% (over two steps); (g) (i) K$_2$CO$_3$, MeOH; then same reaction sequences as in(f).*

Nanda *et al.* synthesized both the enantiomers of venlafaxine (**1**) and its analogues by using chemoenzymatic kinetic resolution as the key step. Cyclohexanone **37** is converted to its corresponding cyanohydrin **38** by reaction with acetonecyanohydrin and HbHNL as the enzyme. The free hydroxyl group in compound **38** was protected as it's EOM derivative to afford cyanohydrin **39**. Addition of Grignard reagent of 4-bromoanisole on compound **39** followed by acidic work-up gave **40**. After one carbon homologolation, ketone **40** was converted to olefine **41**. Hydroboration of compound **41** with $BH_3.SMe_2$ afforded the racemic compound **42** which was subjected to lipase catalyzed enzymatic kinetic resolution with vinyl acetate to give optically pure compound **43** and **44** respectively. Compound **43** was converted to its corresponding tosylate derivative followed by treatment with dimethyl amine and deprotection of EOM protecting group in presence of PTSA, afforded **45**[(*S*)-venlafaxine]. Compound **43** was treated with K_2CO_3–MeOH, and by following the similar reaction sequences as described above (*R*)-venlafaxine **46** was obtained (**Scheme 9**).

Chavan's approach[17](*Tetrahedron Lett.***2013**, *54*, 2137)

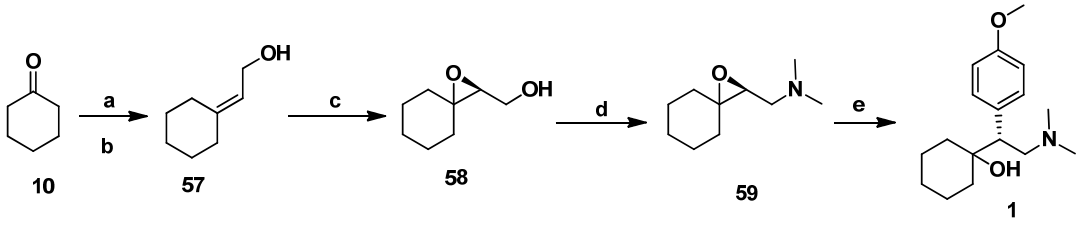


Scheme 10. *Reagents and conditions: a) CH_3NO_2, AcOH, NH_4OAc, sonication, 4 h; b) Cyclohexanone,***54** *DMF, pTSA, 48 h, rt, 99% ee, 80%; c) i) $NaBH_4$, THF: H_2O (9:1); ii) $NiCl_2$, $6H_2O$, $NaBH_4$, MeOH, CbzCl, Et_3N, 60%; d) i) MsCl, Et_3N, DCM, rt then reflux; ii) DBU, CH_3CN, reflux, 90%; e) NaH, MeI, 12 h, rt, 90%; f) m-CPBA, $NaHCO_3$, 30 min, rt, 75%; g) $LiAlH_4$, THF, reflux, 80%.*Anisaldehyde **47** was converted to nitrostyrene **48** under Henri reaction condition (**Scheme 10**). Nitrostyrene **48** was subjected to asymmetric Michael addition of cyclohexanone by using proline derived catalyst **54** to afford nitro keto compound **49**. It was then reduced to *N*-Cbz protected amino alcohol **50** using $NaBH_4$, $NiCl_2$:$6H_2O$ and *in situ* Cbz

protection. The hydroxy group was elminated to afford olefin **51**. Free amine in the olefin**51** was methylated with methyl iodide to furnish **52** and epoxidation of olefine in **52** was carried out by using *m*-CPBA. This epoxide **53** was regioselectively opened with $LiAlH_4$ to afford (-)-venlafaxine **1**.

Chavan's approach[18] (*RSC adv*. **2014**, *4,* 14468)

Cyclohexanone (**10**) was treated with two carbon ylide in toluene under reflux to furnish the unsaturated ester. Subsequently selective ester reduction with Red-Al furnished allyl alcohol **57** which was subjected for asymmetric Sharpless epoxidation furnished **58** in 83% yield. The primary hydroxyl group ofcompound **58** was converted into it's mesyl derivative and displaced with dimethyl amine to get



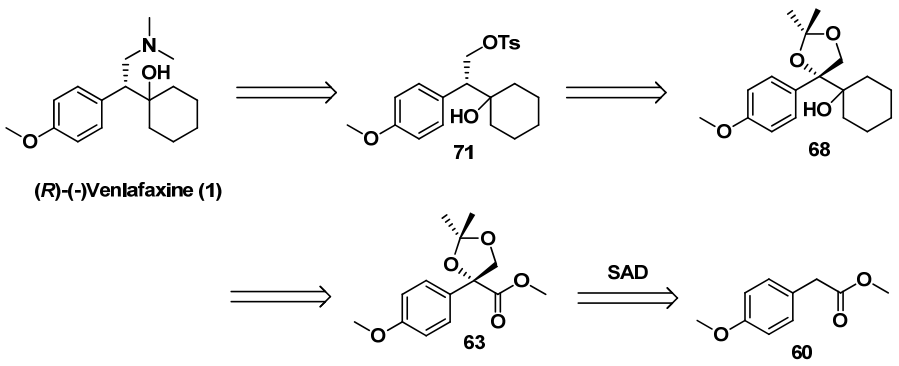
Scheme 11. *Reagents and conditions: a) $Ph_3PCHCOOEt$, toluene, reflux, 24 h, 98%; b) Red-Al, 30 min, toluene, 97%; c) (+)DET,$Ti(OiPr)_4$, MS 4Å, t-BuOOH, DCM, 6 h, -50 ^oC, 83%; d) i) MsCl, Et_3N, DCM, 15 min; ii) Dimethylamine (40% aq. sol.), 10 h, 95%; e) p-Methoxyphenylmagnesium bromide, CuI, THF, -40 ^oC, 8 h, 71%.*

compound **59**. The epoxy amine **59** was subjected for epoxide ring opening, with *p*-methoxyphenylmagnesium bromide and CuI to produce **1** (**Scheme-11**).

3.3.3. Present Work

Retrosynthetic analysis:

In continuation of the ongoing research towards the enantioselective synthesis of venlafaxine, chirality induction was planned by means of Sharpless asymmetric dihydroxylation. As per reterosynthetic analysis (Scheme 12), (*R*)-venlafaxine (**1**) can be accessed from compound **71** by displacing the tosyl group with dimethyl amine. The tosylate **71** can be easily prepared from compound **68** by hydrogenolysis at benzylic centre. The tricyclic compound **68** can be synthesized from acetonide protected ester **63** by means of Grignard reaction with 1,5-(



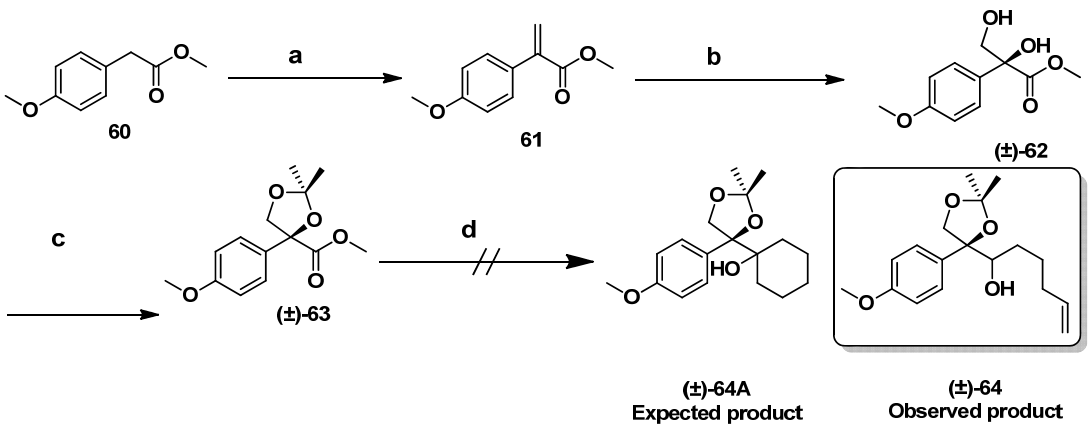
Scheme 12- Chirality induced approach towards total synthesis of (*R*)-(-)-venlafaxine (1)

dibromomagnesio)pentane. The optically active ester **63** in turn can be obtained by exomethylenation followed by Sharpless asymmetric dihydroxylation of olefin easily obtained from methylester of *p*-methoxyphenylacetic acid (**60**). Before undertaking the asymmetric synthesis and to optimize the proposed sequence of reactions, first racemic synthesis of venlafaxine was executed (**Scheme-13**).

3.3.3.1. Total synthesis of (±)-venlafaxine

As per the retrosynthetic analysis methylester of *p*-methoxyphenylacetic acid (**60**), on reaction with paraformaldehyde in presence of K_2CO_3 as base and TBAI as a phase transfer catalyst afforded nonpolar olefin**61** which was then subjected to OsO_4 catalysed dihydroxylation in presence of NMO, to furnish diol **62** in 89% yield over two steps. This diol was then protected as it's acetonide **63**.Its formation was confirmed from two singlets at δ1.52 (3H), 1.43 (3H) in ^{1}H-NMR spectum, were assigned to acetonide (-*C*$\underline{H_3}$)'s. The acetonide protected ester **63**was treated with the Grignard reagent prepared from 1,5-dibromopentane. Surprisingly it did not furnish the desired addition product **64A**. Appearance of a doublet of doublet of a triplet at δ 5.72 (J = 17.01, 10.25, 6.58 Hz) integrating for one proton characteristic of =*C*$\underline{H}$ proton present at terminal double bond along with doublet of a doublet at δ 3.63 (J = 8.53, 1.45 Hz) for one proton *HO-C*$\underline{H}$ next to a secondary hydroxy group in the ^{1}H-NMR spectum, signifies formation of a long chain compound rather than a cyclic product. After careful observation of the mechanism it was found that instead of addition, it underwent elimination–reduction to afford the terminal olefin**64** (**Scheme-13**).

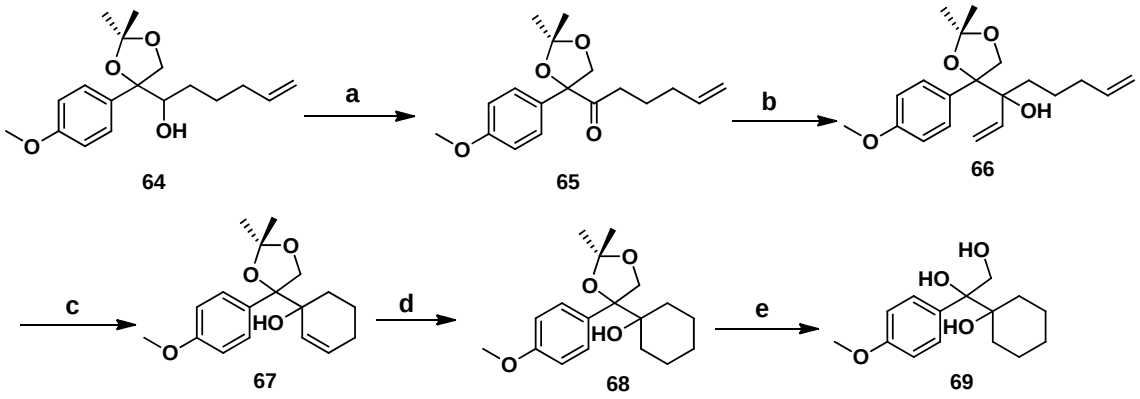
With this secondary alcohol **64** in hand, it was decided to proceed towards synthesis of the target



Scheme 13: Observation of unusual Grignard reaction

Reagents and conditions: *(a) paraformaldehyde, K_2CO_3, TBAI (cat.), toluene, 80 ^oC, 5 h;(b) OsO_4, NMO, acetone:H_2O (3:1), RT, 5 h, 80%; (c) 2,2-DMP, P-TSA(cat.), DMF, RT, 6 h, 97%; (d)1,5-Dibromopentane, Mg metal, THF, 0 ^oC-RT, 5 h, 99%.*

molecule (**Scheme-14**). Accordingly IBX oxidation of **64** gave desired ketone **65** in 89% yield which was confirmed from appearance of peak at δ 209.8 in ^{13}C NMR spectrum along with IR absorption at 1710 cm^{-1} and mass peak at 327 $[M+Na]^+$ Compound **65** on treatment with vinyl magnesium bromide furnished alcohol **66** in 85% yield and *dr* (7:3). This diastereomeric mixture could not be completely separatedby column chromatography so it was subjected for ring closing metathesis in presence of the Grubbs' first generation catalyst to furnish **67**. The ^1H NMR spectrum showed a downfeild shift of multiplet corresponding to two olefin protons of the endocyclic double bond. The formation of **67** was observed in *dr* (6:4) and this has also obtained



Scheme 14: Synthesis of (±)-venlafaxine

Reagents and conditions: *(a) IBX, ethyl acetate, reflux, 3 h, 89%; (b) vinyl magnesium bromide, THF, 0 ^{o}C-RT, 2 h, 85%; (c) Grubbs'first generation cat., DCM, RT, 2 h, 92%, (dr: 6:4); (d) H_2, Pd/C, EtOH, RT, 2 h, 95%; (e) THF:H_2O (1:1), P-TSA (cat.), reflux, 1 h, 90%.*

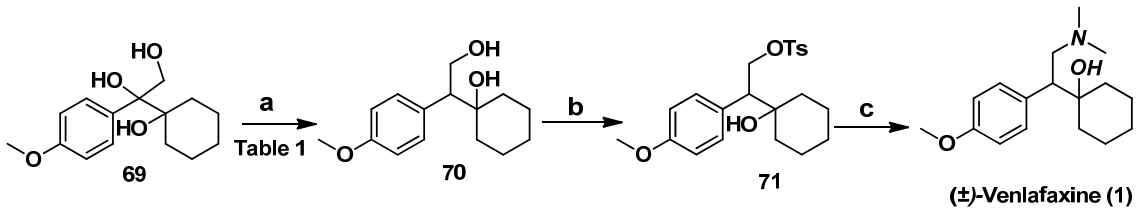
as an inseparable diastereomeric mixture. The compound **67** was reduced under hydrogenation conditions to furnish reduced product **68** in 95% yield. Compound **68** when refluxed in the presence of catalytic *p*TSA in THF as the solvent for 1 h, gave acetonide deprotected, highly polar triol **69** in 90% yield. Disappearance of two -$C\underline{H_3}$ peaks in ^{1}H NMR spectrum was indicative of the said transformation. Encouraged by the previous results obtained in case of enantioselective hydrogenolysis at benzyliccentre[19] in the synthesis of optically active *ar*-himachalene, this triol **69** was subjected for hydrogenation reaction. Different hydrogenating reagents were tried under various conditions for conversion of compound **69** into compound **70** (Table-1).It was found that by using Raney Ni, Pd/C, Pearlman's catalyst *etc*. the starting material was recovered unchanged.

Table-1: Hydrogenolysis of compound **69**

Entry	Reagent	Hydrogenation Condition	Time(h)	(%) Yield
1	Raney Ni	EtOH, reflux	3	SM
2	Pd/C	H_2, EtOH	10	SM
3	Pd/C	H_2, EtOH, reflux	12	SM
4	$Pd(OH)_2$	H_2, EtOH	6-8	SM
5	$Pd(OH)_2$	H_2, EtOH, reflux	4	SM
7	Cat. $BF_3.OEt_2$	Et_3SiH, RT	3	62

It was hypothised that most probably steric crowding around the benzylic hydroxy must be the probable reason for the failure of reaction.Then, ionic hydrogenation employing triethylsilyl hydride in presence of catalytic $BF_3.OEt_2$ was performed to furnish product **70**. Formation of diol**70** was confirmed by^{1}H NMR shift of triplet at δ 2.80 (J = 6.44 Hz), corresponding to thebenzylic proton. ^{13}C NMR spectrum along with DEPT also confirmed presence of methylenecarbon at δ 56.2. Since ionic conditions leads to the formation of carbocation as per the wellstudied mechanism, the expected product was predicted to be racemic. Although

reterosynthesis was planned for the chiral venlafaxine, as per the nature of above results obtained, the racemic synthesis was concluded (**Scheme-15**).



Scheme 15: Completion ofsynthesis of (±)-venlafaxine

Reagents and conditions: *(a)Table-1; (b) Tosyl chloride, triethyl amine, DMAP (cat.), DCM, RT, 88%; (c) aq.(10%) dimethyl amine, RT, 10 h, 70%.*

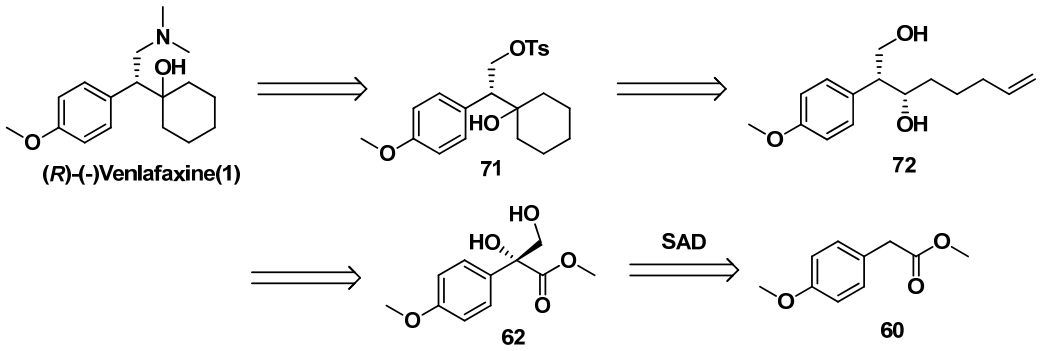
The racemic synthesis of venlafaxine was completed according to the following modified scheme. The primary hydroxy group in compound **70** was then reacted with tosyl chloride in the presence of Et_3N to give the corresponding tosyl alcohol **71**. The two extra doublets in aromatic region for two protons each at δ 7.57 (J = 8.24 Hz) and 7.25 (J = 7.93 Hz) in ^{1}H NMR spectrum along with the mass spectrum of compound **71** showed a peak at (*m/z*) 427 corresponding to $[M+Na]^+$ signifies formation of **71**. The tosyl group in compound **71** was displaced with dimethyl amine on tratment with 10% aq. dimethyl amine at RT for 10 h afforded racemic venlafaxine **1** (**Scheme-15**). The final compound was characterised with ^{1}H NMR, ^{13}C NMR spectrum along with DEPT and mass spectra. All data obtained were in good agreement with the data reported in literature.

3.3.3.2.Synthesis of (*R*)-(-)-venlafaxine

Revised retrosynthetic analysis:

The chiral approach which was planned earlier for synthesis of (*R*)-venlafaxine as mentioned in the above section eventually turned out to be a racemic synthesis. With certain important encouraging results in hand there was a need for revision of retrosynthetic planning. Disappointment in achieving asymmetric hydrogenolysis at benzylic carbon for the synthesis of (*R*)-venlafaxine along with the motivating observation of unusual Grignard reaction, the retrosynthetic analysis was revised (**Scheme 16**). As the steric crowding around benzylic

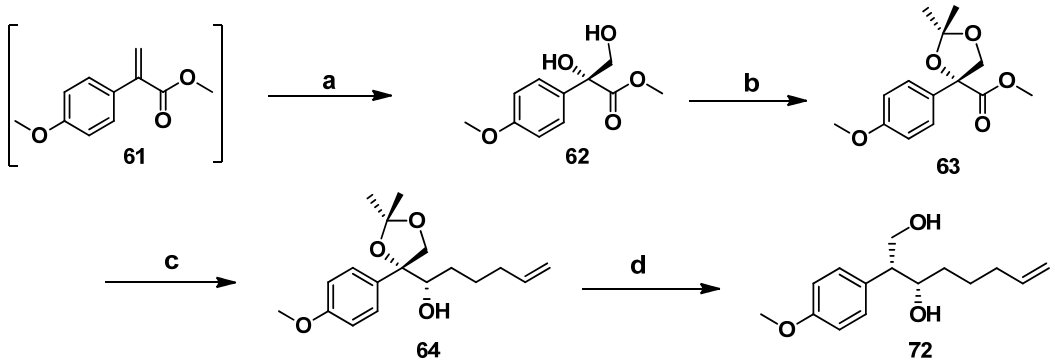
hydroxy was the suspected reason for the failure of enantioselective hydrogenolysis reaction, it was planned to remove benzylic hydroxy functionality at an earlier stage itself.



Scheme 16- Revised retrosynthetic approach for synthesis of (*R*)-(-)-venlafaxine

(*R*)-venlafaxine (**1**) can be accessed from compound **71** by displacing the tosyl group with dimethyl amine. The tosylate **71** can be easily prepared from compound **72** by oxidation of a secondary hydroxy group followed by vinyl magnesium Grignard reaction and subsequent Grubbs'ring closing metathesis. Accordingly, diol **72** could be obtained by Grignard reaction of 1,5-dibromopentane with ester **62** followed by hydrogenolysis at benzylic carbon. The chiral ester **62** could be obtained by Sharpless asymmetric dihydroxylationof olefin easily obtained from methylester of *p*-methoxyphenylacetic acid (**60**).

Synthesis of (*R*)-(-)-venlafaxine

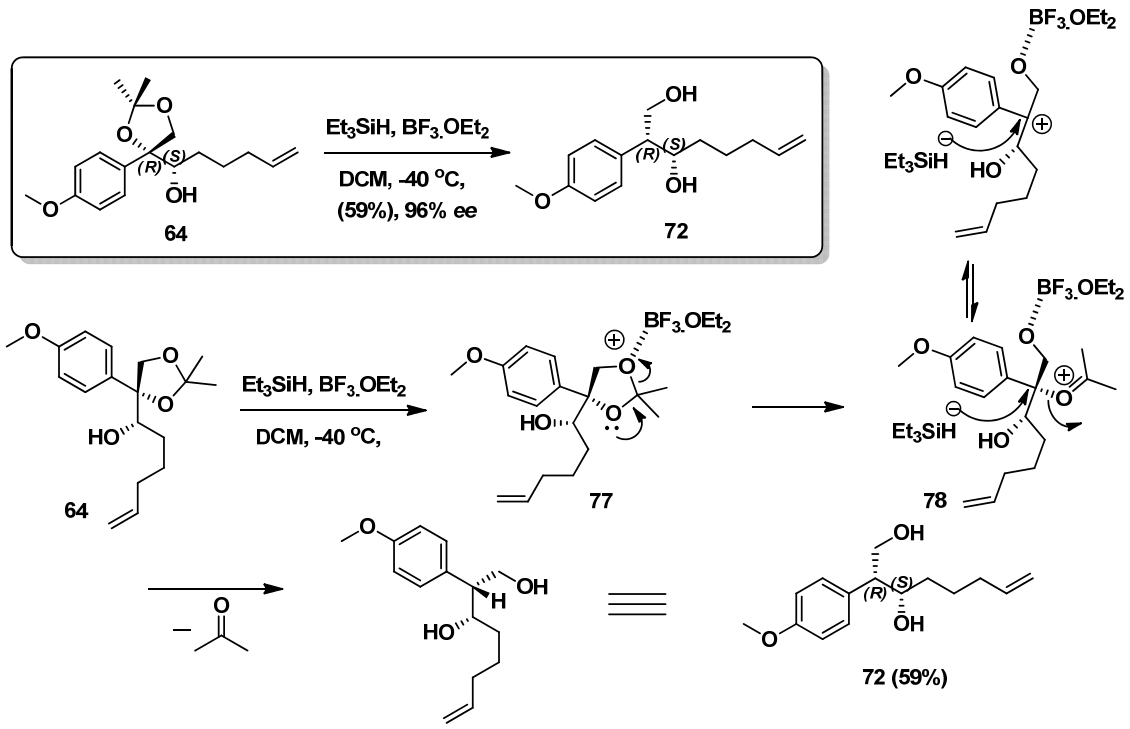


Scheme 17- Synthesis of (*R*)-(-)-venlafaxine

Reagents and conditions: *(a)$K_3Fe(CN)_6$, K_2CO_3, methane sulphonamide, OsO_4, $(DHQD)_2PHAL$, ^{t}-BuOH:H_2O, 0 ^oC, 24 h, 78%, >99% ee; (b) 2,2-Dimethoxypropane, P-TSA (cat.), DMF, RT, 6 h, 97%; (c) 1,5-Dibromopentane, Mg metal turnings, THF, 0 ^oC- RT, 5 h, 99%, de >93%, ee >98%, (d) Triethylsilyl hydride, BF_3 $(OEt)_2$, DCM, - 40 ^oC, 3 h, 59%, ee >96%.*

The exomethylene compound **61**prepared as previously mentioned in the racemic synthesis was then subjected to Sharpless asymmetric dihydroxylation, by employing $(DHQD)_2PHAL$ as the chiral catalyst to furnish diol **62** in 85% yield and enantioselectivity in 99%*ee* as confirmed with HPLC analysis (**Scheme-17**). The diol **62** was protected as its acetonide to furnish optically active compound **63**and then subjected for Grignard reaction with 1,5 (dibromomagnesio)pentane to furnish optically active olefinic alcohol **64**. The compound **64** was obtained in excellent yield and diastereoselectivity with >93% *de* as discerned from ^{1}H-NMR spectrum and reverse phase HPLC analysis.

The fact that compound **64**was obtained in >98%*ee* when checked by chiral HPLC analysis, proves that the Grignard reaction was highly diastereoselective as well as enantioselective.Taking advantage of newly generated optically active secondary hydroxyl centre, acting as a handle to transfer its chirality to the adjacent benzylic centre, deoxygenation was carried out. The unusual Grignard product **64**was then subjected to removal of benzylic hydroxy using triethylsilyl hydride and catalytic $BF_3.OEt_2$-40 ^oC.

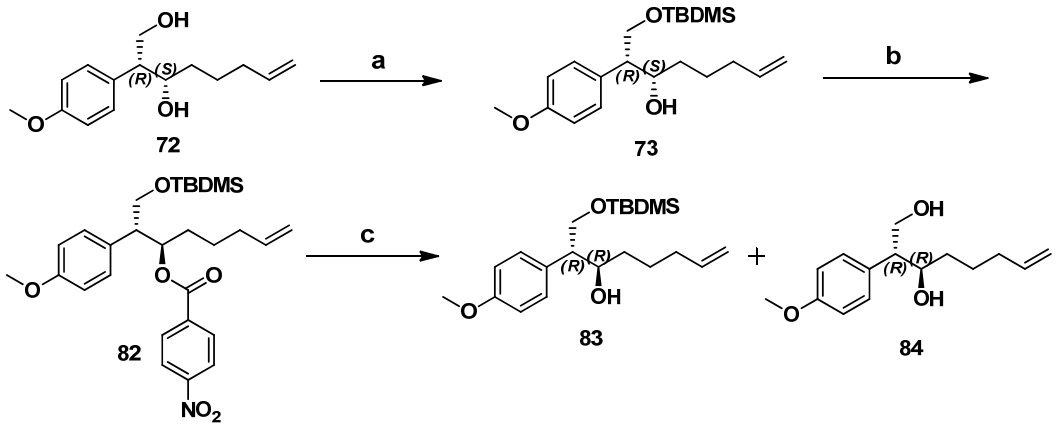


Scheme 18-Mechanism for transformation of compound **64** into compound **72**

Although it involved formation of benzylic carbocation, deoxygenated product **72** was obtained in 59% yield. Presence of two absorption frequencies at 3625 cm^{-1} and 3350 cm^{-1},

characteristic of primary and secondary hydroxyl groups in it's IR spectrum suggested the formation of the proposed diol.Disappearance of two -$C\underline{H}_3$ peaks in ^{1}H NMR spectrum along with signal integrating for one proton as a doublet of a doublet of a triplet at δ2.84 (J = 11.11, 6.83, 4,55 Hz) was observed, in line with the said transformation. Analysis of ^{13}C NMR and DEPTspectrum, resonance atδ 52.2 suggested presence of benzylic tertiary carbon (*Ar*-$\underline{C}H$). The formation of polar diol **72** was finally confirmed with mass peak at 273 corresponds to $[M+Na]^+$. When analysed for the optical purity compound **72**(**Scheme-17**)was obtained in excellent diastereoselectivity exhibiting 96% *ee*as per HPLC analysis.

Thus, it proved to be a novel diastereoselective method for creation of chiral centre at a highly reactive benzylic position, under ionic conditions. After number of subsequent transformations into final molecule venlafaxine when checked for its optical activity and the absolute configuration at benzylic chiral centre was found to be '*R*'. Thus mechanism of transformation of compound **64** into compound **72** was predicted as shown in (**Scheme-18**). The product diol **72** formed with complete inversion of configuration as orientation of -CH_2OH present at benzylic carbon found to be inversed. The mechanism involved complex formation of acetonide oxygen with Lewis acid BF_3OEt_2 at -40 ^oC, attack of hydride from beta face leads to the formation compound **72**. The primary alcohol in **72** was selectively protected as it's TBDMS ether to furnish compound**73**. The *cis* relative configuration in compound **73** was determined by inverting the free secondary hydroxy chiral centre by treatment under Mitsonobu reaction

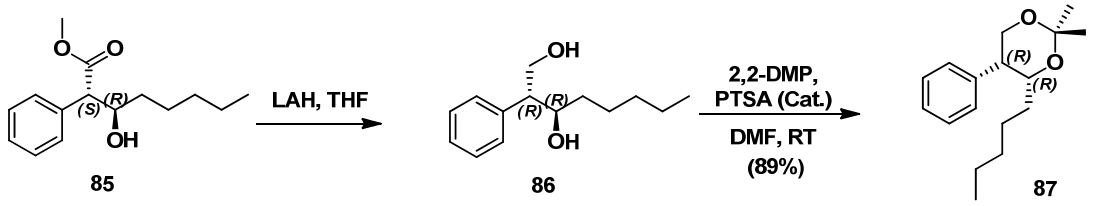


Scheme 19-Determination of relative configuration

Reagents and conditions:- *(a) TBDMS-Cl, imidazole, DMAP, DCM, 88%: (b) Diethyl azodicarboxylate, PPh_3, 4-nitrobenzoic acid, DCM, 0 ^oC-RT, 6 h, 88% (c) 5% aq. NaOH, 60 ^oC, 8 h, 58% for (**83**) and 41% (for **84**)*

conditions (**Scheme-19**).[20] The absolute stereochemistry at benzylic position was established based on the relative stereochemistry with respect to the secondary alcohol. After comparative ^{1}H NMR spectra analysis of compound **72** and compound **84** which are diastereomers of each other relative stereochemistry in **72** was found to be *cis* and *trans* in inverted Mitsonobu product **84**. The characteristic peaks in **72**, for benzylic -*C<u>H</u>* found at δ 2.84 (ddd, J = 11.11, 6.83, 4.55 Hz, 1H), aromatic protons present at *meta* position to methoxy group appeared at δ 7.18 (d, J = 8.55 Hz, 2H) and of that in **84** at δ 2.78 (ddd, J = 13.12, 8.24, 4.88 Hz, 1H) aromatic protons present at *meta* position to methoxy group found at δ 7.08 (d, J = 8.55 Hz, 2H).

The relative configuration was confirmed not only by conversion into inverted Mitsonobu product but also by preparation of known compounds and its comparison with the reported literature data for similar compounds (**Scheme-20**).[21]The *cis* relative configuration in compound **72** was also determined and finally confirmed by conversion of **72** and **84**into their acetonides **88** and **89** respectively (**Scheme-21**). The decoupling experiment on *trans* acetonide **89** at



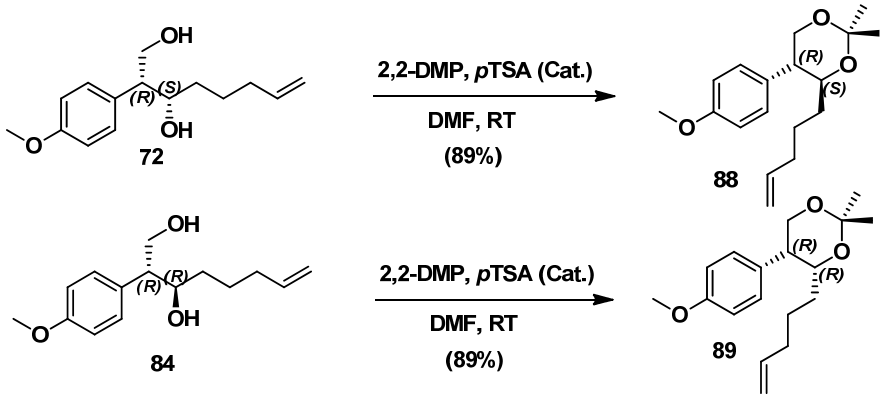
85 86 87

Scheme 20-Determination of relative configuration

J-coupling constant values at benzylic -*C<u>H</u>*(In Hz)

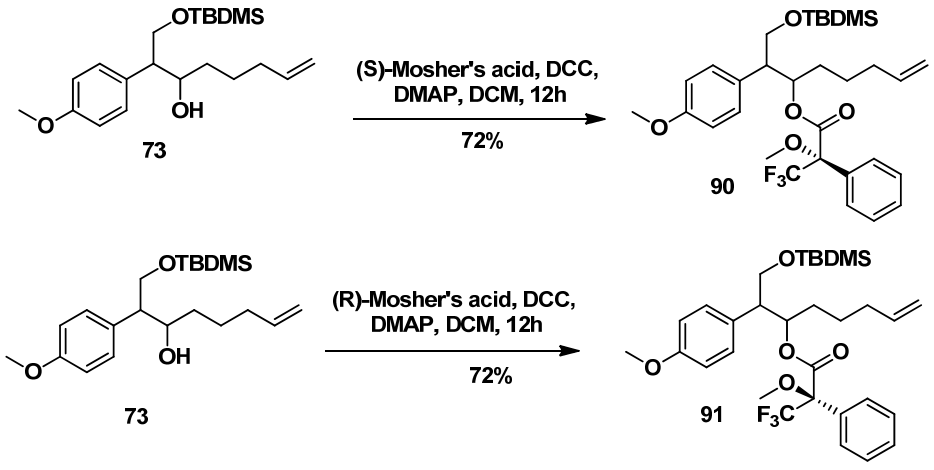
	Diol	Its acetonide
Known compound (**86**)	13.2, **8.4**, 4.5 Hz	(**87**) 16.3, **10.4**, 5.4 Hz
After Mitsonobu (**84**)	13.1, **8.2**, 4.8 Hz	(**89**) 16.4, **10.8**, 5.5 Hz
Before Mitsonobu (**72**)	11.1, **6.8**, 4.5 Hz	(**88**) 11.2, **6.8**, 4.6 Hz

benzylic proton proved that original **88** was perfectly in *cis* relative stereochemistry. All above experimental proofs supports determination of structure of compound **72** prepared from compound **64** is valid. Once relative stereochemistry was established as *cis*, the absolute stereochemistry of the secondary alcohol present adjacent to benzylic carbon (*Ar-CH-CH-OH)* was established with the help of well known, standard method for determination of absolute configuration by Mosher (**Scheme-22**).[22]



Scheme 21-Determination of relative configuration by acetonide formation

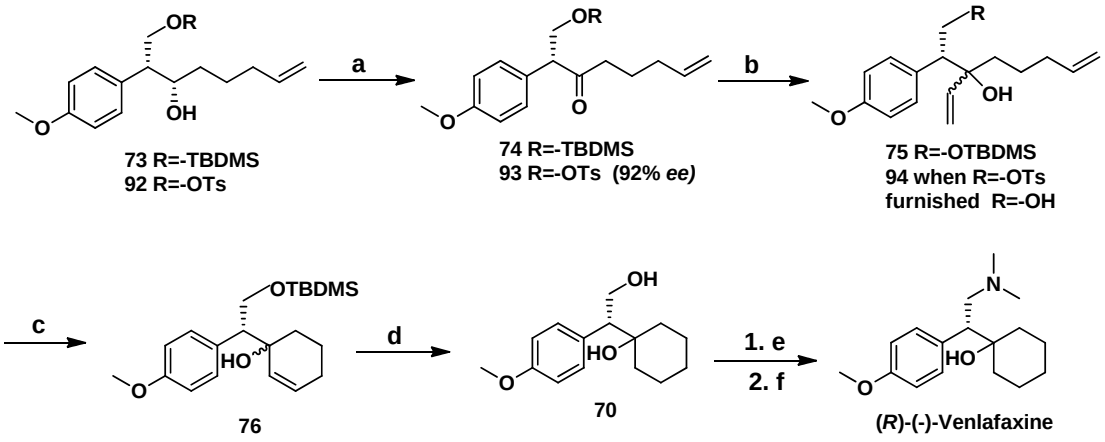
In order to prepare Mosher ester derivatives, optically active secondary alcohol **73** was condensed with (*S*) and (*R*) Mosher acids in presence of DCC to furnish compounds **90** and **91** respectively. These Mosher esters **90** and **91** were purified and analysed as per the model proposed by Mosher for determination of absolute stereochemistry. After careful ^{1}H-NMR



Scheme-22 Determination of absolute configuration

analysis of both the enantiomers of Mosher's esters prepared from compound **73**, the stereochemistry at the carbon bearing secondary hydroxyl group was assigned to be '***R***'.

Having established the relative and absolute stereochemistry, oxidation of secondary hydroxy in compound **73** with Dess-Martin periodinane was carried out to obtain ketone **74** in >92% *ee*. The IR absorption at 1715 cm^{-1} confirmed presence of ketone functional group in compound **74**. This protected ketone **74** was subjected for Grignard reaction with vinyl magnesium bromide to furnish alcohol **75** in 85% yield.However, it was possible to separate out two spots by flash column chromatography, which were further characterized to be a mixture of diastereomers by it's ^{1}H and ^{13}C NMR spectral data, but as there is need to destroy the newly generated chiral centers in the next step of the synthesis, no attempt was made to separate or characterize the diastereomers and their ratios as well.The compound **75** was treated under ring closing metathesis conditions in presence of Grubbs' first generation catalyst to obtain



Scheme 23- Completion of synthesis of (*R*)-(-)-venlafaxine

Reagents and conditions: *(a) DMP, DCM, RT, 2 h, 72%; (b) vinyl magnesium bromide, THF, 0 ^{o}C-RT, 2 h, 88%; (c) Grubbs'first generation cat., DCM, RT, 2 h, 92%; (d) H_2, Pd/C, EtOH, RT, 2 h, 95%; (e) THF:H_2O (1:1), p-TSA (cat.), reflux, 1 h, 90%; (e)Tosyl chloride, triethyl amine, DMAP (cat.), DCM, RT, 88%; (f) aq.(10%) dimethyl amine, RT, 10 h, 70%.*

cyclohexene **76** in 92% yield. Compound **76** was subjected under hydrogenation conditions for 8 h interestingly led to the double bond reduction along with TBDMS deprotection to furnish diol **70**.[23]Literature survey revealed of similar reports of deprotection under hydrogenation

conditions. Following the same sequence of reactions as in racemic synthesis, compound **70** was converted into (*R*)-(-)-venlafaxine in 97% *ee*(**Scheme-23**),[24] after recrystallisation. The venlafaxine thus obtained matched well with the reported spectroscopic data in the literature. By employing $(DHQ)_2PHAL$ as the chiral catalyst in Sharpless asymmetric dihydroxylation reaction the '*S*' enantiomer can also be prepared following the above reaction sequence.

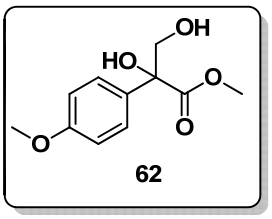
3.3.4 Conclusion

In summary, racemic synthesis of venlafaxine was carried out starting with easily available commercial starting materials. The enantioselective synthesis of(*R*)-(-)-venlafaxine was accomplished with exploration of diastereoselective and enantioselective unusual Grignard reaction. The synthetic sequence involvedSharpless asymmetric dihydroxylation reaction for chirality induction and unusual diastereoselective Grignard reaction for the installation of secondary alcohol which can be utilized as a chirality transferring handle. The relative as well as absolute configurations of newly generated chiral centres were determined employing Mitsonobu reaction and preparation of Mosher ester derivatives respectively. A convenient protocol for enantioselective transfer of chirality at benzylic site was shown as an application of unusual Grignard reaction for the first time.

3.3.5. Experimental data

Synthesis of (±)−venlafaxine

Methyl−2,3−dihydroxy−2−(4−methoxyphenyl)propanoate (62)



62

To a stirred solution of methyl ester of *p*−methoxyphenylacetic acid (**60**, 16.0 g, 1.0 equiv.), paraformaldehyde (6.35 g, 1.6 equiv.), K_2CO_3 (23.1 g, 2.0 equiv.) and TBAI (1.21 g, 0.04 equiv.) were added and reaction mixture was heated in drytoluene (30 mL) at 80– 85 ^oC for 5 h. After completion, reaction mixture was allowed to cool to RT. Water (100 mL) was added to the reaction mixture and stirred vigorously for 10 min. The aqueous layer was extracted with DCM (3 X 30 mL), washed systematically with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude residue

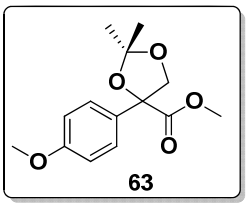
of exomethylene compound, methyl 2−(4−methoxyphenyl)acrylate (**61**, 14.5 g) was subjected for further dihydroxylation reaction.

To a stirred solution of crude methyl 2−(4−methoxyphenyl)acrylate (**61**, 14.0 g, 1.0 equiv.) in acetone−water (3:1, 30 mL) at RT was added NMO (17.0 g, 1.9 equiv.) followed by 1M solution of osmium tetroxide (0.370 mL, 0.02 equiv.) in a dropwise manner. The resulting reaction mixture was continuously stirred for 8 h. The reaction was then quenched with sat. aq. Na_2SO_3 (30 mL) and stirred vigorously for 30 min. The biphasic reaction mixture was then extracted with ethyl acetate (3 X 30 mL) and the combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filteredand concentrated under reduced pressure. The crude product obtained was subjected for column chromatography using 200−400 silica gel with eluent (40% ethyl acetate–petroleum ether) to furnish the methyl−2,3−dihydroxy−2−(4−methoxyphenyl)propanoate(**62**, 14.5 g, 89 % over two steps).

Molecular formula:$C_{11}H_{14}O_5$; **Yield:** 89%

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45 (d, J = 8.97 Hz, 2H), 6.85 (d, J = 8.97 Hz, 2H), 4.27−4.09 (m, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.72−3.64 (m, 1H), 3.00 (br s, 1H); **^{13}C NMR (50 MHz, $CDCl_3$):**δ 174.3, 159.5, 130.1, 126.6, 113.8, 79.3, 68.2, 55.2, 53.4; **MS (ESI)** (*m/z*): 249 $[M+Na]^+$; **IR ($CHCl_3$):** 3482, 2975, 2865, 1735, 1458, 1069 cm^{-1}; **HRMS (ESI):** Calculated for $C_{11}H_{14}O_5$ $[M+Na]^+$249.0841 found 249.0844.

Methyl−4−(4−methoxyphenyl)−2,2−dimethyl−1,3−dioxolane−4−carboxylate (63)

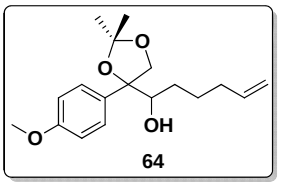


63

To a stirred solution of methyl−2,3−dihydroxy−2−(4−methoxyphenyl)propanoate (**62**) (4.00 g, 1.0 equiv.) in anhydrous DMF (8 mL) as thesolvent was added 2,2−DMP (4.76 g, 2.2 equiv.) followed by *p-TSA* (0.330 g, 0.1 equiv.). The reaction mixture was stirred at 25 ^oC until the reaction was complete, monitored by TLC (6 h). The reaction mixture was diluted with ethyl acetate. The reaction mixture was subsequently washed with brine and worked up with ethyl acetate (3 X 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a crude residue. The obtained residue was then purified by column chromatography using 60–120 silica gel (5% EtOAc: pet. ether) to furnish the acetonide protected ester:

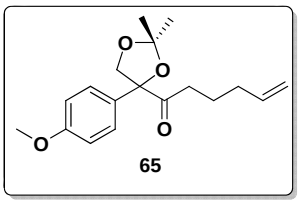
methyl−4−(4−methoxyphenyl)−2,2−dimethyl−1,3−dioxolane−4−carboxylate (**63**, 4.56 g, 90%) as a colorless viscous oil. **Data of 63 tabulated in experimental section Chapter-3, section-1**

1−4−(4−Methoxyphenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)hex−5−en−1−ol (64)



Compound **64** was prepared as per the experimental procedure and data for the same is provided in Chapter-3, section-1.

1−(4−(4−Methoxyphenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)hex−5−en−1−one (65)

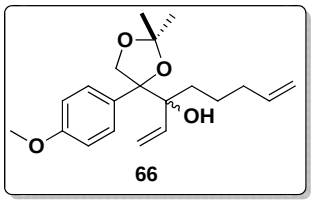


The alcohol 1−4−(4−methoxyphenyl)−2,2−dimethyl−1,3−dioxolan −4−yl)hex−5−en−1−ol (**64**) (1.50 g, 1.00 mmol) was dissolved in ethyl acetate (8 mL), and IBX (3.75 g, 2.50 mmol) was added in one portion. The resulting suspension was immersed in an oil bath set to 80 °C and stirred vigorously. After 3 h the reaction was cooled to RTand filtered,the filter cake was washed with (3 X 3 mL) of ethyl acetate, and the combined filtrates were concentrated to furnish ketone as ancolorless oily compound 1−(4−(4−methoxyphenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)hex−5−en−1−one (**65**, 1.32 g, 89%).

Molecular formula: $C_{18}H_{24}O_4$; **Yield:** 89%

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.29 (d, J = 8.85 Hz, 2H), 6.84 (d, J = 8.85 Hz, 2H), 5.75−5.55 (m, 1H), 4.90−4.81 (m, 3H), 3.82 (s, 1H), 3.78 (s, 3H), 2.76−2.60 (m, 1H), 2.48−2.32 (m, 1H), 1.96−1.84 (m, 2H), 1.62−1.51 (m, 2H),1.48 (s, 3H), 1.42 (s, 3H); **^{13}C NMR (50 MHz, $CDCl_3$):**δ 209.8, 159.4, 137.9, 130.7, 126.0, 115.1, 114.0, 111.0, 89.8, 71.9, 55.1, 35.7, 32.9, 26.7, 25.8, 22.5; **MS (ESI)** (*m/z*): 327 $[M+Na]^+$; **IR ($CHCl_3$)**ν_{max}: 2948, 1710, 1660, 1558, 1492 cm^{-1}; **HRMS (ESI):** Calculated for $C_{18}H_{24}O_4$ $[M+Na]^+$ 327.3231 found 327.3228.

3−4−(4−Methoxyphenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)octa−1,7−dien−3−ol (66)



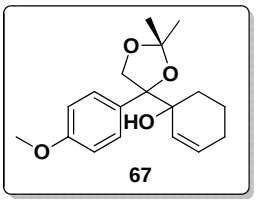
A solution of ketone 1−(4−(4−methoxyphenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)hex−5−en−1−one (**65**), (3.00 g, 20 mmol) in THF (15 mL) was added dropwise to a solution of vinylmagnesium bromide

(12.0 mL of a 1.7 M solution in THF, 22 mmol) in THF (20 mL) at 0 °C. After 30 min, the reaction was quenched with aq. NH_4Cl (10 mL). The organic phase extracted with diethyl ether and combined extracts washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography using 200–400 silica gel (8% EtOAc:pet. ether), to furnish pure 3−4−(4−methoxyphenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)octa−1,7−dien−3−ol (**66**, 2.77 g, 85%).

Molecular formula: $C_{20}H_{28}O_4$; **Yield:** 85%

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.28 (d, J = 8.85 Hz, 2H), 6.81 (d, J = 8.85 Hz, 2H), 5.76−5.62 (m, 2H), 5.29−5.15 (m, 2H), 4.94−4.83 (m, 2H), 4.45 (d, J = 8.34 Hz, 1H), 4.15 (d, J = 8.34 Hz, 1H), 3.78 (s, 3H), 1.96−1.85 (m, 2H), 1.59−1.50 (m, 1H), 1.47 (s, 3H), 1.41−1.19 (m, 3H), 1.15 (s, 3H); **^{13}C NMR (50 MHz, $CDCl_3$):**δ 158.8, 139.3, 138.6, 134.3, 128.5, 114.6 and 114.5(in DEPT 114.69 and 114.61 for two =CH), 112.8, 110.0, 88.7, 77.9, 71.7, 55.0, 34.4, 34.0, 26.4, 26.0, 22.4; **MS (ESI)** (*m/z*): 355 $[M+Na]^+$; **IR ($CHCl_3$)**ν_{max}: 3435, 2968, 1610, 1525, 1393, 1272 cm^{-1}; **HRMS (ESI):** Calculated for $C_{20}H_{28}O_4$ $[M+Na]^+$ 355.4828 found 355.4825.

1−4−(4−Methoxyphenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)cyclohex−2−en−1−ol (67)



67

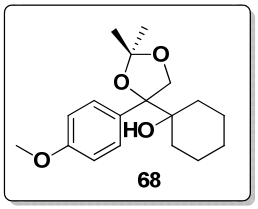
In a round−bottom flask, Grubbs' 1st generation catalyst (0.720 g, 0.2 equiv.) was dissolved in dry DCM (8 mL). To this mixture 3−4−(4−methoxyphenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)octa−1,7−dien−3−ol(**66**) (2.00 g, 1 equiv.) was added and stirred for 2 h. After completion, reaction mixture was filtered and washed with DCM (3 X 3 mL). The solvent extracts were combined and evaporated under reduced pressure. The crude residue was purified by column chromatograpy using (3:1) EtOAc:pet. ether as a eluent yielding 1−4−(4−methoxyphenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)cyclohex−2−en−1−ol (**67**) (1.68 g, 92%) as a colorless oil.

Molecular formula: $C_{18}H_{24}O_4$; **Yield:**92%

^{1}H NMR (200 MHz, $CDCl_3$):(*dr*:6:**4**) δ 7.30 (d, J = 8.72 Hz, 2H), 6.80 (d, J = 8.72 Hz, 2H), 6.01−5.63 (m, 2H), 4.61 (d, J = 8.59 Hz, 0.63H), **4.47** (d, J = 8.59 Hz, 0.37H), 4.24−4.05 (m, 1H), 3.78 (s, 3H), 2.15−1.80 (m, 3H), 1.72−1.56 (m, 2H), 1.53 and 1.48 (s, 3H), 1.42−1.28 (m,

1H), 1.23 and 1.16 (s, 3H) **^{13}C NMR (50 MHz, $CDCl_3$):δ158.6**, 158.5, 134.7, **134.4**, 133.7, 131.3, 128.9, 128.27, **128.21**, 121.5, 112.6, 110.0, **88.9**, 88.3, **72.3**, 72.1, **71.6**, 70.9, 54.9, **31.8**, 31.1, 26.3, **26.0**, 25.6, **25.0**, 24.9, 18.2, **18.1**; **MS (ESI)** (*m/z*): 327 $[M+Na]^+$; **IR($CHCl_3$)**ν_{max}: 3466, 2931, 1668, 1393 cm^{-1}; **HRMS (ESI):** Calculated for $C_{18}H_{24}O_4$ $[M+Na]^+$327.6936 found 327.6935.

1−(4−(4−Methoxyphenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)cyclohexan−1−ol (68)



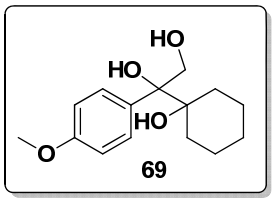
68

To a stirred solution of 1−4−(4−methoxyphenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)cyclohex−2−en−1−ol (**67**, 1.5 g) in anhydrous ethanol (5 mL) was added catalytic amount (10 mol %) of Pd/C in a single portion and the resulting reaction mixture was vigorously stirred at RT for 2 h under hydrogen atmosphere (1−2 PSi). After completion of the reaction the mixture was filtered and washed carefully with ethanol. The ethanol extracts were combined and evaporated under reduced pressure. The crude product thus obtained was subjected for column chromatography using 60−120 silica gel and ethyl acetate: petroleum ether (15%) as an eluent furnished pure reduced product 1−(4−(4−methoxyphenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)cyclohexan−1−ol (**68**, 1.43 g, 95%).

Molecular formula: $C_{18}H_{26}O_4$; **Yield:** 95%

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.30 (d, J = 8.85 Hz, 2H), 6.83 (d, J = 8.85 Hz, 2H), 4.53 (d, J = 8.47 Hz, 1H), 4.20 (d, J = 8.47 Hz, 1H), 3.81 (s, 3H), 1.83 (brs, 1H), 1.62−1.55 (m, 4H), 1.50 (s, 3H), 1.38−1.24 (m, 4H), 1.30 (s, 3H), 1.12−0.91 (m, 2H); **^{13}C NMR (50 MHz, $CDCl_3$):**δ 158.6, 134.6, 128.3, 112.7, 109.7, 89.7, 73.8, 70.8, 55.1, 32.1, 31.6, 26.4, 26.1, 25.5, 21.5, 21.3; **MS (ESI)** (*m/z*): 329 $[M+Na]^+$; **IR($CHCl_3$)**ν_{max}: 3475, 2930, 1608, 1293 cm^{-1}; **HRMS (ESI):** Calculated for $C_{18}H_{26}O_4$ $[M+Na]^+$ 329.4020 found 329.4022.

1−(1−Hydroxycyclohexyl)−1−(4−methoxyphenyl)ethane−1,2−diol (69)



69

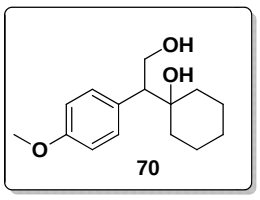
To a stirred solution of alcohol 1−(4−(4−methoxyphenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)cyclohexan−1−ol (**68**) (1.0 g, 1.1 mmol) in THF:water (1:1, 12 mL) was added cat. *p*-TSA. The resulting reaction

mixture was heated at 65 ^{o}C for 1 h. After completion of reaction, the reaction mixture was cooled to RT. The reaction mixture was extracted using EtOAc (3 X 20 mL) followed by subsequent washing with aq. $NaHCO_3$ (3 X 25 mL). The organic extracts were combined and dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure to obtain 1−(1−hydroxycyclohexyl)−1−(4−methoxyphenyl)ethane−1,2−diol (**69**, 0.869 g, 90%).

Molecular formula: $C_{15}H_{22}O_4$; **Yield:** 90%

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.37 (d, J = 8.84 Hz, 2H), 6.85 (d, J = 8.84 Hz, 2H), 4.16−3.96 (m, 2H), 4.24 (d, J = 11.50 Hz, 1H), 3.89 (d, J = 11.50 Hz, 1H), 3.80 (s, 3H), 1.89−1.65 (m, 4H), 1.89−1.65 (m, 4H), 1.59−1.38 (m, 6H); **^{13}C NMR (50 MHz, $CDCl_3$):**δ 158.7, 132.8, 128.0, 113.2, 79.7, 76.3, 66.3, 55.1, 31.6, 31.4, 25.5, 21.6, 21.0; **MS (ESI)** (*m/z*): 289 $[M+Na]^+$; **IR ($CHCl_3$)**ν_{max}: 3435, 3075, 2932, 1620, 1560, 1219 cm^{-1}; **HRMS (ESI):** Calculated for $C_{15}H_{22}O_4$ $[M+1]^+$ 267.5621 found 267.5618.

1−(2−Hydroxy−1−(4−methoxyphenyl)ethyl)cyclohexanol (70)



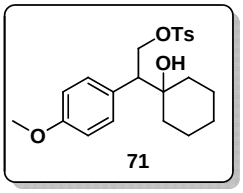
70

To a stirred solution of 1−(1−hydroxycyclohexyl)−1−(4−methoxyphenyl)ethane−1,2−diol (**69**) (0.8 g, 1 equiv.) in 6 mL DCM at 0 ºC was added Et_3SiH (0.693 mL, 2 equiv.) followed by dropwise addition of $BF_3.OEt_2$ (0.20 mL, 0.5 equiv.). The reaction was allowed to warm up to RT over 30 min and stirred for 3 h. After completion of reaction as monitored by TLC, reaction mixture was quenched by careful addition of aq. $NaHCO_3$ (5 mL) and extracted with DCM (3 X 15mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. Purification of the residue on a 60−120 silica gel column chromatography (40% EtOAc:pet. ether) furnished 1−(2−hydroxy−1−(4−methoxyphenyl)ethyl)cyclohexanol (**70**, 0.46 g, 62%).

Molecular formula: $C_{15}H_{22}O_3$; **Yield:** 62%

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.19 (d, J = 8.72 Hz, 2H), 6.84 (d, J = 8.72 Hz, 2H), 4.16−3.96 (m, 2H), 3.79(s, 3H), 2.80 (t, J = 6.44 Hz, 1H), 2.25 (brs, 2H), 1.74−1.25 (m, 10H); **^{13}C NMR (50 MHz, $CDCl_3$):**δ 158.6, 131.3, 130.5, 113.8, 74.0, 63.3, 56.2, 55.1, 36.7, 34.7, 25.6, 21.7, 21.6; **MS (ESI)** (*m/z*): 305 $[M+Na+MeOH]^+$; **IR ($CHCl_3$)**ν_{max}: 3461, 3002, 2936, 2589, 1612 cm^{-1}; **HRMS (ESI):** Calculated for $C_{15}H_{22}O_3$ $[M+Na]^+$ 273.3329 found 273.3332.

2−(1−Hydroxycyclohexyl)−2−(4−methoxyphenyl)ethyl 4−methylbenzenesulfonate (71)

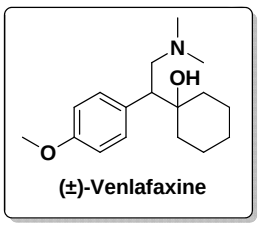


A round−bottomed flask was charged with 1−(2−hydroxy−1−(4−methoxyphenyl)ethyl)cyclohexanol (**70**) (0.250 g, 1.00 equiv.) and dry DCM (10 mL). The resulting solution was cooled to 0 °C before adding 4−dimethylaminopyridine (0.087 g, 0.6 equiv.), *p*−toluenesulfonyl chloride (0.339 g, 1.5 equiv.) in portions and triethylamine (0.16 mL, 1.00 equiv.) in dropwise manner. The resulting solution was stirred until TLC showed complete consumption of starting material (4 h). The resulting suspension was diluted with diethyl ether (20 mL), stirred for a further 30 minutes and the precipitate removed by filtration. The solution was then washed with 10% aqueous $NaHCO_3$ (2 x 10 mL) and brine (20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by 200−400 silica gel column chromatography by using eluent (8% EtOAc:pet. ether) to furnish 2−(1−hydroxycyclohexyl)−2−(4−methoxyphenyl)ethyl −4−methylbenzenesulfonate (**71**, 0.355 g, 88%) as a pale yellow solid.

Molecular formula: $C_{22}H_{28}O_5S$; **Yield:** 88%; **MP:** 108 ^oC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, J = 8.24 Hz, 2H), 7.25 (d, J = 8.24 Hz, 2H), 6.97 (d, J = 8.55 Hz, 2H), 6.74 (d, J = 8.55 Hz, 2H), 4.61 (dd, J = 9.76, 4.88 Hz, 1H), 4.30 (t, J = 9.76 Hz, 1H), 3.78 (s, 3H), 2.91 (dd, J = 8.85, 5.19 Hz, 1H), 2.44 (s, 3H), 1.68−1.64 (m, 2H), 1.67 (brs, 1H), 1.54−1.50 (m, 3H), 1.42−1.37 (m, 3H), 1.22−1.16 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 158.6, 144.2, 133.1, 130.2, 129.6, 127.9, 113.6, 72.6, 70.6, 55.0, 53.7, 36.2, 36.1, 25.4, 21.8, 21.6; **MS (ESI)** (*m/z*): 427 $[M+Na]^+$; **IR ($CHCl_3$)** ν_{max}: 3056, 2952, 1611, 1312, 1132, 725 cm^{-1}; **HRMS (ESI):** Calculated for $C_{22}H_{28}O_5S$ $[M+Na]^+$ 427.1690 found 427.1692.

1−(2−(Dimethylamino)−1−(4−methoxyphenyl)ethyl)cyclohexan−1−ol (1)



To a stirred solution of 2−(1−hydroxycyclohexyl)−2−(4−methoxyphenyl)ethyl 4−methylbenzenesulfonate (**71**) (0.220 g, 1.0 equiv) was added 40% aq. solution of *N, N*− dimethyl amine (3 mL). The resultant reaction mixture was vigorously stirred at RT for 10 h. After completion the reaction mixture was concentrated under reduced pressure at 60 ^oC to furnish crude residue. The crude residue was subjected for further purification by

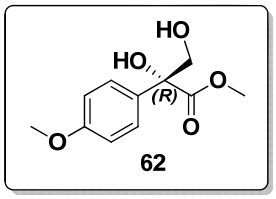
60−120 silica gel column chromatography (100% ethyl acetate) to furnish (**1,** 0.105 g, 70%) and after recrystalization in ethyl acetate (64%) as a pale yellow solid.

Molecular formula: $C_{17}H_{27}NO_2$; **Yield:**70%, after recrystalization (64%); **MP:**286^oC

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.03 (d, J = 8.84 Hz, 2H), 6.79 (d, J = 8.84 Hz, 2H), 3.78 (s, 3H), 3.32 (t, J = 12.30 Hz, 1H), 2.95 (dd, J = 12.30, 3.29 Hz, 1H), 2.35 (s, 3H), 2.31−2.28 (m, 1H), 1.78−1.26 (m, 8H), 1.03−0.88 (m, 2H); **^{13}C NMR (50 MHz, $CDCl_3$):**δ 158.3, 132.6, 130.3, 130.1, 113.4, 74.1, 61.2, 55.1, 51.7, 45.4, 38.0, 31.2, 26.0, 21.6, 21.3; **MS (ESI)** (*m/z*): 278 $[M+1]^+$; **IR($CHCl_3$)**ν_{max}: 3164, 2982, 2938, 2860, 2782, 1610 cm^{-1}; **HRMS (ESI):**Calculated for $C_{17}H_{28}NO_2[M+1]^+$.278.2120 found 278.2118

Enantioselective synthesis of (*R*)−(−)−venlafaxine

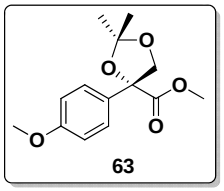
Methyl (*R*)−2,3−dihydroxy−2−(4−methoxyphenyl)propanoate (62)



62

To a stirred solution of potassium ferricyanide (22.3 g, 3.0 mmol) and K_2CO_3 (9.4 g, 3.0 mmol) in water (150 mL) was added methane sulphonamide (2.2 g, 1.1 mmol) followed by ^tBuOH(150 mL) and allowed to stir until the suspension became clear. Then ligand $(DHQD)_2PHAL$ (0.055 g, 4.0 mol%) followed by 1M solution of OsO_4 in *tert*−butanol (0.010 mL, 1.0 mol%) were added to it at 0 ^oC and the resulting suspension was stirred until orange color was obtained. To this mixture was added compound (**61**) (3.0 g, 1.0 mmol) in a dropwise manner. The resultant heterogeneous suspension was stirred vigorously at 0 ^oC until the reaction was complete, monitored by TLC (24 h). Na_2SO_3 (5 g) was added slowly to the reaction mixture and the resulting suspension stirred at RT for 1 h. The reaction mixture was transferred into a 100 mL separatory funnel and extracted with ethyl acetate (4 X 20 mL). The organic layer was washed with brine then dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish a residue. The obtained residue was purified by using 60–120 silica gel column chromatography, (30% EtOAc:pet. ether) to furnish the diol **6** (3.36 g, 89%, 99% *ee*). **Yield:**89%; **$[\alpha]^{25}_D$**= +27 (*c* 1, $CHCl_3$).

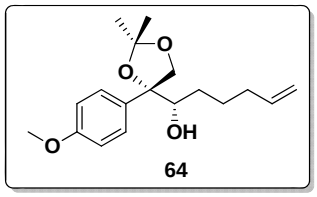
Methyl (*R*)−4−(4−methoxyphenyl)−2,2−dimethyl−1,3−dioxolane−4−carboxylate (63)



Compound **63** was prepared as per the previously mentioned experimental procedure

[α]$^{25}_{D}$= –42 (*c* 1, $CHCl_3$).

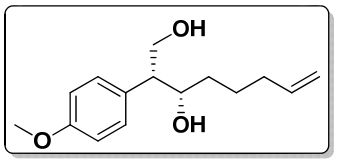
(*S*)−1−((*R*)−4−(4−Methoxyphenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)hex−5−en−1−ol (64)



Compound **64** was prepared as per the previously mentioned experimental procedure.

[α]$^{25}_{D}$= +26 (*c* 1, $CHCl_3$).

(2*R*,3*S*)−2−(4−Methoxyphenyl)oct−7−ene−1,3−diol (72)

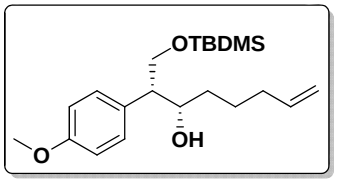


To a magnetically stirred solution of hydroxyl compound (*S*)−1−((*R*)−4−(4−methoxyphenyl)−2,2−dimethyl−1,3−dioxolan−4−yl)hex− 5−en−1−ol (**64**) (1.5 g, 1 equiv.) in dryDCM (3 mL) at −40 ºC was added Et_3SiH (1.38 mL, 2 equiv.) followed by dropwise addition of $BF_3.OEt_2$ (0.39 mL, 0.5 equiv.). The reaction was stirred over 3 h at the same temperature. After completion,the reaction mixture was quenched by addition of aq. NH_4Cl (0.5 mL) and allowed to warm up to RT, further extracted with DCM (3 X 15mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filteredand the solvent was evaporated under reduced pressure. Purification of the residue on a 200−400 silica gel column chromatography (20% EtOAc:pet. ether) furnished diol (2*R*,3*S*)−2−(4−methoxyphenyl)oct−7−ene−1,3−diol (**72**, 0.385 g, 59%) as a white solid.

Molecular formula: $C_{15}H_{22}O_3$; **Yield:** 59%; **MP:** 64 ^{o}C; **[α]$^{25}_{D}$:** + 30 (*c* 1, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): *δ* 7.22 (d, *J* = 8.71 Hz, 2H), 6.89 (d, *J* = 8.71 Hz, 2H), 5.78 (ddt, *J* = 16.93, 11.11, 6.83 Hz, 1H), 5.03−4.88 (m, 2H), 4.08−3.84 (m, 3H), 3.80 (s, 3H), 2.84 (ddd, *J* = 11.11, 6.83, 4,55 Hz, 1H), 2.08−1.99 (m, 2H), 1.83 (brs, 2H), 1.59−1.32 (m, 4H); **^{13}C NMR (50 MHz, $CDCl_3$):***δ* 158.7, 138.5, 130.3, 130.2, 114.7, 114.0, 72.3, 64.6, 55.1, 52.2, 34.4, 33.6, 25.2; **MS (ESI)** (*m/z*): 273 $[M+Na]^+$; **IR($CHCl_3$)**ν_{max}: 3625, 3350, 2925, 2860, 1616, 1435, 1069 cm^{-1}; **HRMS (ESI):** Calculated for $C_{15}H_{22}O_3$ $[M+Na]^+$ 273.0659 found 273.0655.

(2*R*,3*S*)−1−((*Tert*−butyldimethylsilyl)oxy)−2−(4−methoxyphenyl)oct−7−en−3−ol (73)

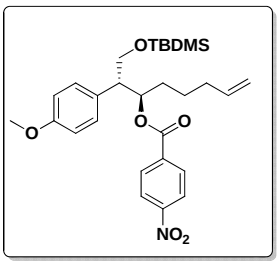


To a stirred solution of (2*R*,3*S*)−2−(4−methoxyphenyl)oct−7−ene−1,3−diol (**72**) (1.20 g, 1.0 equiv.) in dry DCM (10 mL)was added TBDMSCl (0.705 g, 1.0 equiv.) followed by imidazole (0.480 g, 1.5 equiv.) and DMAP (0.058 g, 0.1 equiv.). The reaction mixture was stirred at RT for 3h and diluted with DCM (10 mL), washed with aq. NH_4Cl (10 mL), and extracted with DCM (3 X 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by 200−400 silica gel column chromatography using eluent 10% ethyl acetate:pet ether to furnish (2*R*,3*S*)−1−(*tert*−butyldimethylsilyl)oxy)−2−(4−methoxyphenyl)oct−7−en−3−ol (**73**, 1.53 g) **Molecular formula:** $C_{21}H_{36}O_3Si$; **Yield:** 88%; **$[\alpha]^{25}_D$:** –28 (*c* 1, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.18 (d, *J* = 8.55 Hz, 2H), 6.82 (d, *J* = 8.55 Hz, 2H), 5.77 (ddt, *J* = 17.09, 10.38, 6.72 Hz, 1H), 4.98−4.90 (m, 2H), 4.03−3.98 (m, 2H), 3.87 (dd, *J* = 10.38, 4.88 Hz, 1H), 3.79 (s, 3H), 2.76−2.73 (m, 1H), 2.06−2.01 (m, 2H), 1.62−1.55 (m, 2H), 1.45−1.39 (m, 2H), 0.89 (s, 9H), 0.02 (s, 6H); **^{13}C NMR (50 MHz, $CDCl_3$):**δ 158.3, 138.7, 131.3, 130.2, 114.4, 113.5, 72.7, 65.6, 55.1, 51.4, 34.0, 33.6, 25.8, 25.3, 18.1, −5.6; **MS (ESI)** (*m/z*):387 $[M+Na]^+$; **IR($CHCl_3$)**ν_{max}: 3438, 2936, 2861, 1614, 1461, 1269 cm^{-1}; **HRMS (ESI):** Calculated for $C_{21}H_{36}O_3Si$ $[M+Na]^+$ 387.2326, found 387.2324.

Determination of relative configuration of compound 73 using Mitsonobu reaction protocol

(2*R*,3*R*)−1−((*t*butyldimethylsilyl)oxy)−2−(4−methoxyphenyl)oct−7−en−3−yl 4−nitrobenzoate (82)



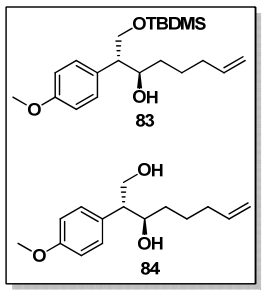
To a stirred solution of (2*R*,3*S*)−1−((*tert*−butyldimethylsilyl)oxy)−2−(4−methoxyphenyl)oct−7−en− 3−ol (**73**) (0.050 g, 1 equiv.), in dryTHF(8 mL) were added triphenyl phosphine (0.141 g, 3.8 equiv.), 4−nitrobenzoic acid (0.094 g, 4 equiv.) and diethyl azodicarboxylate (0.109 g, 4.4 equiv.) at 0 ^oC. The resulting reaction mixture was stirred for 6 h at RT. The reaction mixture was diluted with addition of ethyl acetate, aq. $NaHCO_3$ and worked up with ethyl acetate (3 X 10 mL). The combined organic

layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was loaded to 200−400 silica gel column chromatography to furnish (2*R*,3*R*)−1−((*tert*−butyldimethylsilyl)oxy)−2−(4−methoxyphenyl)oct−7−en−3−yl-4−nitrobenzoate (**82**, 0.038 g, 55%) as a yellow oil..

Molecular formula: $C_{25}H_{29}NO_7$; **Yield:** 55%.

^{1}H NMR (200 MHz, $CDCl_3$): δ 8.31 (d, J = 9.09 Hz, 2H), 8.22 (d, J = 9.09 Hz, 2H), 7.16 (d, J = 8.72 Hz, 2H), 6.84 (d, J = 8.72 Hz, 2H), 5.77−5.57 (m, 2H), 4.95−4.84 (m, 2H), 3.86−3.83 (m, 2H), 3.81 (s, 3H), 3.13−3.03 (m, 1H), 2.04−1.88 (m, 2H), 1.62−1.34 (m, 4H); **^{13}C NMR (50 MHz, $CDCl_3$):**δ 164.1, 158.5, 150.4, 138.1, 135.9, 131.8, 130.6, 129.7, 123.5, 114.7, 113.7, 76.0, 64.3, 55.1, 50.8, 33.3, 31.4, 25.7, 24.2, 18.1, −5.7; **MS (ESI)** (*m/z*): 514 $[M+1]^+$; **IR($CHCl_3$)**ν_{max}: 3021, 2950, 1735, 1554, 1255 cm^{-1}; **HRMS (ESI):** Calculated for $C_{28}H_{39}NO_6Si$ $[M+1]^+$514.2547 found 514.2550.

(2*R*,3*R*)−1−((*Tert*−butyldimethylsilyl)oxy)−2−(4−methoxyphenyl)oct−7−en−3−ol (83) and (2*R*,3*R*)-2-(4-methoxyphenyl)oct-7-ene-1,3-diol (84)



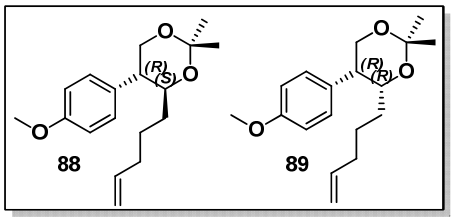
The 5% aq. NaOH (5 mL) was added to (2*R*,3*R*)−1−((*tert*−butyldimethylsilyl)oxy)−2−(4−methoxyphenyl)oct−7−en−3−yl-4−nitrobenzoate (**82**, 0.035 g, 1 equiv.) and the resulting reaction mixture was stirred at 60 ^oC for 5 h. The reaction mixture was allowed to cool to RT and concentrated under reduced pressure. The residue was diluted with addition of ethyl acetate (10 mL), 10% aq. HCl (2 X 4 mL) and worked up with ethyl acetate. The combined organic layers were concentrated under reduced pressure and the crude product was purified by 60−120 silica gel column chromatography using 10−20% ethyl acetate−petroleum ether to furnish mixture of nonpolar monoprotected diol (2*R*,3*R*)−1−(*tert*−butyldimethylsilyl)oxy)−2−(4−methoxyphenyl)oct−7−en−3−ol (**83**, 0.014 g, 58%) and silyl ether deprotected diol (2*R*,3*R*)−2−(4−methoxyphenyl)oct−7−ene−1,3−diol (**84**, 0.007 g, 41%).

Spectroscopic data for compound **83**; **Yield**: 58%; **^{1}H NMR (200 MHz, $CDCl_3$)**: δ 7.04 (d, J = 8.86 Hz, 2H), 6.83 (d, J = 8.86 Hz, 2H), 5.72 (ddt, J = 17.09, 10.38, 6.72 Hz, 1H), 4.94−4.85 (m,

2H), 4.34 (s, 1H), 4.05−4.01 (m, 1H), 3.96 (t, *J* = 9.46 Hz,1H), 3.87 (dd, *J* = 10.38, 4.27 Hz, 1H), 3.87 (dd, *J* = 9.46, 4.27 Hz, 1H), 3.79 (s, 3H), 2.73 (ddd, *J* = 13.13, 9.16, 3.97 Hz, 1H), 1.99−1.88 (m, 1H), 1.59−1.53 (m, 1H), 1.41−1.36 (m, 1H), 1.24−1.21 (m, 2H), 0.91 (s, 9H), 0.07 (d, *J* = 2.14 Hz, 6H); **^{13}C NMR (50 MHz, $CDCl_3$):***δ* 158.3, 138.7, 131.3, 130.2, 114.4, 113.5, 72.7, 65.6, 55.1, 51.4, 34.0, 33.6, 25.8, 25.3, 18.1, −5.6; **MS (ESI)** (*m/z*): 387 $[M+Na]^+$.

Spectroscopic data for compound **84**; **Yield**: 41%; **^{1}H NMR (200 MHz, $CDCl_3$)**: *δ* 7.08 (d, *J* = 8.55 Hz, 2H), 6.85 (d, *J* = 8.55 Hz, 2H), 5.72 (ddt, *J* = 17.09, 10.38, 6.72 Hz, 1H), 4.95−4.88 (m, 2H), 4.05−3.97 (m, 2H), 3.90−3.86 (m, 1H), 3.79 (s, 3H), 2.78 (ddd, *J* = 13.12, 8.24, 4,88 Hz, 1H), 2.45 (brs, 2H), 2.02−1.90 (m, 2H), 1.56−1.51 (m, 1H), 1.41−1.30 (m, 3H); **^{13}C NMR (50 MHz, $CDCl_3$):***δ* 158.5, 138.5, 132.0, 129.1, 114.6, 114.1, 76.2, 67.1, 55.2, 52.7, 35.1, 33.4, 24.4.

(4*R*,5*S*)−5−(4−Methoxyphenyl)−2,2−dimethyl−4−(pent−4−en−1−yl)−1,3−dioxane (88) and (4*R*,5*R*)−5−(4−Methoxyphenyl)−2,2−dimethyl−4−(pent−4−en−1−yl)−1,3−dioxane (89)



To a stirred solution of diol (0.45 mmol, 1.0 equiv.) in dry DMF (4 mL) was added 2,2−DMP (1 mmol, 2.2 equiv.) followed by *p*TSA(0.1 mmol).The reaction mixture was stirred at 25 ^oC for 4 h. After completion, reaction mixture was worked up with ethyl acetate (3 X 15 mL) and subsequently washed with brine. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue obtainedwas then purified by column chromatography using 60–120 silica gel (5% EtOAc:pet ether) to furnish the respective acetonides as a viscous oil.

Molecular formula:$C_{18}H_{26}O_3$; **Yield:**89%.

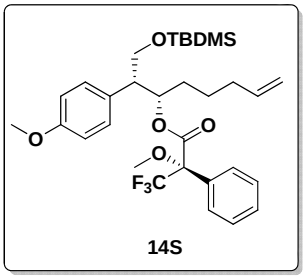
Before Mitsonobu reaction: data for compound (**88**); **^{1}H NMR (500 MHz, $CDCl_3$)**: (*dr*: 9:**1**) *δ* 7.40 (d, *J* = 8.53 Hz, 2H), 7.08 (d, *J* = 8.53 Hz, 0.30H), 6.82 (d, *J* = 8.78 Hz, 2H), 5.71 (ddt, *J* = 17.06, 10.29, 6.77 Hz, 1H), 4.95−4.86 (m, 2H), 4.31 (dd, *J* = 11.55, 3.77 Hz, 1H), 4.13 (ddd, *J* = 10.29, 6.77, 3.26 Hz, 1H), 3.97−3.87 (m, 1H), 3.80 (s, 3H), **2.68 (ddd, *J* = 16.17, 10,68, 5.19 Hz, 0.10H)**, 2.46−2.40 (m, 0.90H), 1.97−1.92 (m, 2H), 1.53 (s, 3H), 1.52 (s, 3H), 1.42−1.31 (m, 1H), 1.34−1.30 (m, 1H), 1.20−1.14 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):***δ***158.6**, 158.3, **138.7**, 138.6, **132.7**, **131.1**, 130.5, 129.0, 114.5, **114.4**, **114.1**, 113.4, 96.8, **96.2**, **73.3**, 71.2, 65.7, **55.1**,

55.0, **46.5**, 43.1, **33.6**, 33.5, 33.0, **32.9**, **29.4**, 24.7, **24.4**, **19.4,** 19.1; **MS (ESI)** (*m/z*):313 $[M+Na]^+$; **IR($CHCl_3$)**ν_{max}: 1610, 1556, 1412, 1226 cm^{-1}; **HRMS (ESI):** Calculated for $C_{18}H_{26}O_3$ $[M+Na]^+$313.2103 found 313.2108.

After Mitsonobu reaction: data for compound (**89)**; **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.10 (d, J = 8.55 Hz, 2H), 6.86 (d, J = 8.55 Hz, 2H), 5.72 (ddt, J = 16.79, 10.07, 6.41 Hz, 1H), 4.94−4.86 (m, 2H), 3.97 (ddd, J = 10.07, 6.41, 3.36 Hz, 1H), 3.91 (t, J = 11.29 Hz, 1H), 3.82−3.77 (m, 1H), 3.79 (s, 3H), 2.70 (ddd, J = 16.79, 10.68, 5.19 Hz, 1H), 2.33−2.29 (m, 1H), 2.06−1.98 (m, 1H), 1.96−1.90 (m, 1H), 1.57 (s, 3H), 1.54−1.48 (m, 1H), 1.45 (s, 3H), 1.34−1.30 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):**δ 158.5, 138.8, 131.0, 129.0, 114.2, 114.1, 98.3, 73.2, 65.8, 55.2, 46.5, 33.5, 32.8, 24.3, 19.3.

Determination of absolute configuration by Mosher's method

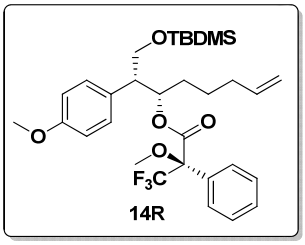
(*S*)−(2*R*,3*S*)−1−((*Tert*−butyldimethylsilyl)oxy)−2−(4−methoxyphenyl)oct−7−en−3−yl 3,3,3−trifluoro−2−methoxy−2−phenylpropanoate (**90**)



To a solution of (*S*)−(2*R*,3*S*)−1−((*tert*−butyldimethylsilyl)oxy)−2−(4−methoxyphenyl)oct−7−en−3−yl−3,3,3−trifluoro−2−methoxy−2−phenylpropanoate (**73**)(0.040 g, 3.1 equiv.) in dry DCM (5 mL) was added DCC (0.054 g, 3.1 equiv.) followed by DMAP (0.040 g, 3.1 equiv.) and ***S*−MTPA** (0.080 g, 3.1 equiv.) at 0 °C. The resulting reaction mixture was stirred at RT for 12 h. After completion of reaction it was concentrated under reduced pressure and the residue obtained was purified by flash column chromatography using 8% EtOAc:pet ether to furnish (**90**, 0.049 g 72%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38−7.30 (m, 5H), 7.10 (d, J = 8.80 Hz, 2H), 6.78 (d, J = 8.80 Hz, 2H), 5.75−5.65 (m, 2H), 4.98−4.92 (m, 2H), 3.78 (s, 3H), 3.72−3.69 (m, 2H), 3.32 (s, 3H), 2.96−2.91 (m, 1H), 2.05−1.96 (m, 2H), 1.62−1.56 (m, 2H), 1.40−1.28 (m, 2H), 0.87 (s, 9H), 0.04 (s, 6H); **^{13}C NMR (125 MHz, $CDCl_3$):**δ 166.0, 158.5, 138.1, 132.3, 130.8, 130.1, 129.3, 128.2, 127.4, 114.8, 113.6, 77.2, 76.5, 64.2, 55.1, 55.0, 49.9, 33.3, 31.2, 21.6, 25.7, 23.9, 18.1, −5.55, −5.62; **MS (ESI)** (*m/z*): 581 $[M+1]^+$; **IR($CHCl_3$)**ν_{max}: 2952, 1752, 1672, 1643, 1172 cm^{-1}; **HRMS (ESI):** Calculated for $C_{31}H_{43}F_3O_5Si$ $[M+1]^+$ 581.2374 found 581.2378.

(*R*)−(2*R*,3*S*)−1−((*Tert*−butyldimethylsilyl)oxy)−2−(4−methoxyphenyl)oct−7−en−3−yl 3,3,3−trifluoro−2−methoxy−2−phenylpropanoate (91)



The compound (**91**) was prepared using ***R*−MTPA** instead of ***S*−MTPA** and by following the experimental precedure given for praparation of compound (**90**); **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.48−7.44 (m, 2H), 7.39−7.32 (m, 3H), 7.03 (d, J = 8.85 Hz, 2H), 6.75 (d, J = 8.85 Hz, 2H), 5.74 (ddt, J = 16.78, 10.07, 6.71 Hz, 1H), 5.62−5.59 (m, 1H), 5.00−4.92 (m, 2H), 3.77 (s, 3H), 3.60−3.54 (m, 2H), 3.43 (s, 3H), 2.91−2.87 (m, 1H), 2.05−2.01 (m, 2H), 1.66−1.58 (m, 2H), 1.46−1.40 (m, 2H), 0.86 (s, 9H), −0.06 (s, 3H), −0.07 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):**δ 165.9, 158.5, 138.0, 132.5, 130.2, 129.3, 128.2, 127.5, 127.2, 114.9, 113.5, 77.2, 76.4, 63.9, 55.3, 55.1, 50.1, 33.2, 31.4, 25.7, 24.5, 18.0, −5.55, −5.60.

Analysis of Mosher's derivatives: Table 1. Absolute configuration predicted by the Mosher's method using ^{1}H NMRspectroscopy analysis of compound**90** and **91**

	Chemical shift in ppm (^{1}H)		
Protons (ppm)	(*S*)−MTPA[a]	(*R*)−MTPA[a]	$\Delta\delta_{SR} = \delta_S - \delta_R$(ppm)
H−2	1.56	1.58	0.02 (−)
H−3	1.28	1.40	0.12 (−)
H−4	1.96	2.01	0.05 (−)
H−7	2.91	2.87	0.04 (+)
H−8	3.69	3.54	0.15 (+)
H−9	7.10	7.03	0.07 (+)
H−10	6.78	6.75	0.03 (+)
H−11	3.78	3.77	0.02 (+)

[a]The Mosher's ester derivatives were purified by a small column chromatography on silica gel.

In order to determine the absolute configuration of the hydroxy group in **73**, the Mosher's (^{1}H-NMR) method was used. Therefore, the 2−methoxy− 2−phenyl−2−(trifluoromethyl)−acetic acid [(*S*) and (*R*) MTPA] derivatives of compounds **73** werepreprared, chromatographed and analyzed by ^{1}H-NMR. **Table 1**, which depicts the $\Delta\delta_{SR}$ values obtained for the MTPA esters of compound **73**, shows that the protons with NMR signalswith $\Delta\delta > 0$ are located below the plane

(on the right side) of the MTPA plane and those with $\Delta\delta > 0$ are located above the MTPA plane (its left side) as shown in (**Figure−3**).

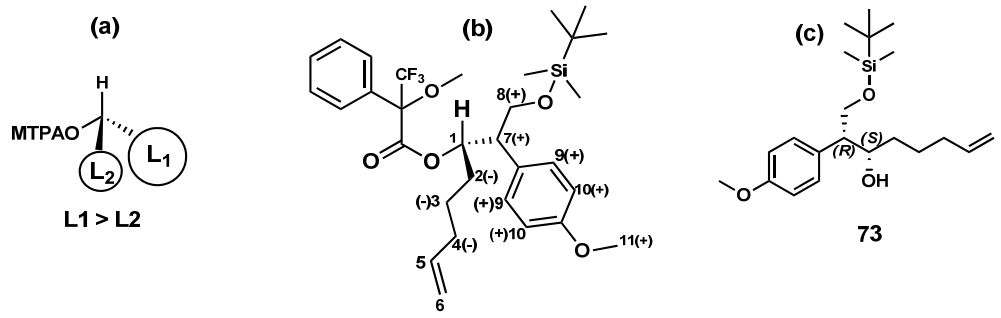


Figure 3 (a) Configurational correlation model for the (*R*)−MTPA and the (*S*)−MTPA esters by Mosher, (b) MTPA ester analysed compound **73** and (c) absolute configuration derived at chiral centres.

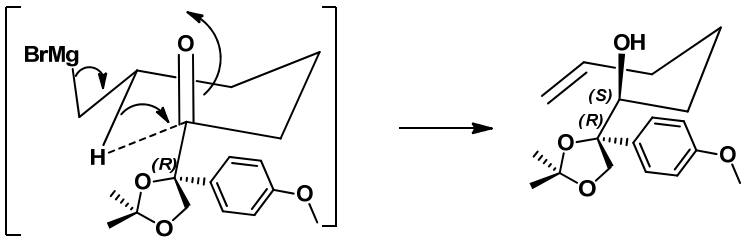
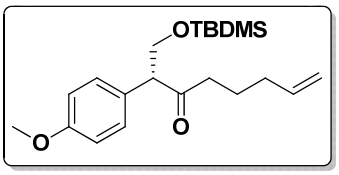


Figure: 4 Mechanism of unusual Grignard reaction

It can be noted that these $\Delta\delta$ values are proportional to the distance between the protons and the MTPA moiety. This result indicates that the addition reaction of Grignard reagent to acetonide **63** affords the '*S*' hydroxy configuration with high diastereoselectivity as well as enantioselectivity in compond**64**, consistent with the open−chain model. Additionally, these results are in agreement with the already studied nucleophilic addition of dialkyl Grignard reagent to acetonide protected ester functionality, where the reaction exhibits high diastereoselectivity (**Figure−4**).

(*R*)−1−((*Tert*−butyldimethylsilyl)oxy)−2−(4−methoxyphenyl)oct−7−en−3−one (74)



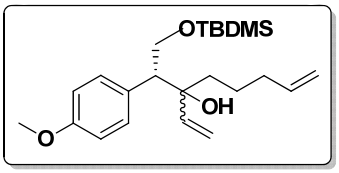
The compound (2*R*,3*S*)−1−((*tert*−butyldimethylsilyl)oxy)−2−(4−methoxyphenyl)oct−7−en−3−ol(**73**) (0.8 g, 1.0 equiv.) in dry DCM (35 mL) was added DMP (1.12 g, 1.5 equiv.) in one portion at 0 °C. The reaction mixture was stirredat RT for 2 h. The reaction was quenched by addition of saturated aq. solution of $Na_2S_2O_3$ and $NaHCO_3$ (1:1, 20 mL) to destroy any unreacted Dess−Martin reagent. The

reaction mixture was worked up with DCM (3 X 20 mL) and washed with brine. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to furnish ketone (*R*)−1−((*tert*−butyldimethylsilyl)oxy)−2−(4−methoxyphenyl)oct−7−en−3−one (**74**, 0.572 g, 72%) almost pure product which was isolated as a colorless oil.

Molecular formula: $C_{21}H_{34}O_3Si$; **Yield:** 72%; **$[\alpha]^{25}_D$:** –32 (*c* 1, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.15 (d, *J* = 8.71 Hz, 2H), 6.85 (d, *J* = 8.71 Hz, 2H), 5.80−5.60 (m, 1H), 4.19 (dd, *J* = 9.35, 8.84 Hz, 1H), 3.88 (dd, *J* = 8.84, 5.24 Hz, 1H), 3.78 (s, 3H), 3.65 (dd,*J* = 9.35, 5.44 Hz, 1H), 2.47−2.29 (m, 2H), 2.03−1.91 (m, 2H), 1.69−1.58 (m, 2H), 0.84 (s, 9H), −0.02 (d, *J* = 3.16 Hz, 6H); **^{13}C NMR (50 MHz, $CDCl_3$):**δ 209.7, 158.9, 137.9, 129.4, 128.0, 115.0, 114.0, 65.0, 59.9, 55.2, 42.3, 32.9, 25.8, 22.5, 18.2, −5.58; **MS (ESI)** (*m/z*): 385 $[M+Na]^+$; **IR($CHCl_3$)**ν_{max}: 2967, 1715, 1611, 1510 cm^{-1}; **HRMS (ESI):** Calculated for $C_{21}H_{34}O_3Si$ $[M+Na]^+$ 385.2168 found 385.2165.

3−((*R*)−2−((*Tert*−butyldimethylsilyl)oxy)−1−(4−methoxyphenyl)ethyl)octa−1,7−dien−3−ol (75)



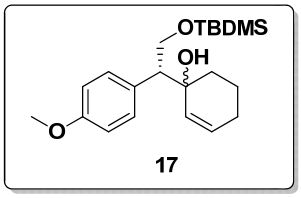
A solution of ketone (**74**), (2.50 g, 20 mmol) in dry THF (5 mL) was added to a solution of vinylmagnesium bromide (10.0 mL of a 1.7 M solution in THF, 22 mmol) at 0 °C. After 30 min, the reaction was quenched with a sat. NH_4Cl (10 mL). Aq. HCl was then added until the Mg salts were dissolved, and the phases were separated. The organic phase was then extracted with diethyl ether, combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography using 200–400 silica gel (8% EtOAc:pet ether), to furnish 1−((*R*)−2−((*tert*−butyldimethylsilyl)oxy)−1−(4−methoxyphenyl)ethyl)cyclohex−2−enol (**75**, 2.38 g, 88%) as a colorless oil.

Molecular formula: $C_{23}H_{38}O_3Si$; **Yield:**88%

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.71 Hz, 2H), 6.83 (d, *J* = 8.71 Hz, 2H), 5.87−5.61 (m, 2H), 5.41 (dd, *J* = 17.05, 2.02 Hz, 1H), 5.21 (dd, *J* = 10.49, 2.02 Hz, 1H), 4.97−4.32 (m, 2H), 4.15 (dd, *J* = 9.98, 4.17 Hz, 1H), 4.08 (brs, 1H), 3.88 (dd, *J* = 9.98, 4.17 Hz, 1H), 3.80 (s,

3H), 2.63 (t, *J* = 4.04 Hz, 1H), 1.96−1.85 (m, 2H), 1.43−1.37 (m, 2H), 1.34−1.28 (m, 2H), 0.89 (s, 9H), −0.03 (s, 6H); **^{13}C NMR (50 MHz, $CDCl_3$):**δ 158.4, 143.6, 138.8, 132.1, 130.9, 114.3, 113.7, 113.3, 78.4, 66.3, 55.0, 53.4, 38.1, 34.1, 25.8, 22.6, 18.1, −5.7; **MS (ESI)** (*m/z*): 413 $[M+Na]^+$; **IR($CHCl_3$)**ν_{max}: 3449, 2941, 1611, 1252, 1090 cm^{-1}; **HRMS (ESI):** Calculated for $C_{23}H_{38}O_3Si$ $[M+Na]^+$ 413.2482 found 413.2480.

1−((*R*)−2−((*Tert*−butyldimethylsilyl)oxy)−1−(4−methoxyphenyl)ethyl)cyclohex−2−enol (76)



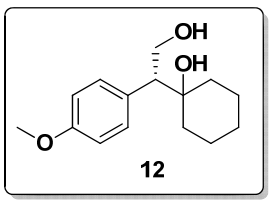
17

In a round−bottom flask, Grubbs 1st generation catalyst (0.690 g, 0.2 equiv.) was dissolved in anhydrous DCM (8 mL). To this mixture 1−((*R*)−2−((*tert*−butyldimethylsilyl)oxy)−1−(4−methoxyphenyl)ethyl)cyclohex−2−enol (**75**) (2.31 g, 1 equiv.) was added and stirred for 2 h. The reaction mixture was filtered and washed with DCM (3 X 3 mL). The solvent extracts were combined and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatograpy using (3:1) EtOAc:pet. ether yielding 1−((*R*)−2−((*tert*−butyldimethylsilyl)oxy)−1−(4−methoxyphenyl)ethyl)cyclohex−2−enol (**76**) (1.62 g, 92%) as a colorless oil.

Molecular formula: $C_{21}H_{34}O_3Si$; **Yield:**92%; **$[\alpha]^{25}_D$:** +15 (*c* 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.80 Hz, 2H), 6.82 (d, *J* = 8.80 Hz, 2H), 5.85 (d, *J* = 10.27 Hz, 1H), 5.74−5.69 (m, 1H), 4.17−4.09 (m, 2H), 3.78 (s, 3H), 2.90 (t, *J* = 5.38 Hz, 1H), 2.02−1.97 (m, 1H), 1.88−1.80 (m, 1H), 1.77−1.69 (m, 1H), 1.66−1.57 (m, 1H), 0.91 (s, 9H), 0.05 (s, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):**δ 158.2, 132.5, 132.4, 130.4, 128.8, 113.2, 72.5, 65.4, 55.1, 53.8, 33.0, 25.7, 25.0, 18.7, 18.0, −5.7; **MS (ESI)** (*m/z*): 385 $[M+Na]^+$; **IR($CHCl_3$)**ν_{max}: 3460, 2931, 2868, 1675, 1350, 1096 cm^{-1}; **HRMS (ESI):** Calculated for $C_{21}H_{34}O_3Si$ $[M+Na]^+$ 385.5432 found 385.5437.

(*R*)−1−(2−Hydroxy−1−(4−methoxyphenyl)ethyl)cyclohexanol (70)



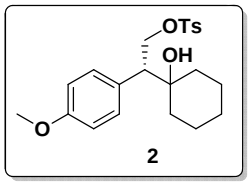
12

To a stirred solution of 1−((*R*)−2−((*tert*−butyldimethylsilyl)oxy)−1−(4−methoxyphenyl)ethyl)cyclohex−2−enol (**76**) (0.5 g) in EtOH (5 mL) was added catalytic amount (10 mol %) of Pd/C in a single portion and the resulting mixture was

stirred at RT for 8 h under hydrogen atmosphere (1−2 psi). After complete utilization of starting material the reaction mixture was filtered through a short pad of celite and washed carefully with ethanol. The ethanol extracts were combined and evaporated under reduced pressure. The crude product thus obtained was subjected for simple column chromatography using 60−120 silica gel and EtOAc:pet ether (15%) as an eluent furnished pure reduced product (*R*)−1−(2−hydroxy−1−(4−methoxyphenyl)ethyl)cyclohexanol (**70**, 0.328 g, 95%).

Yield:95%; **$[\alpha]^{25}_{D}$:**+12.4 (*c* 1, $CHCl_3$)

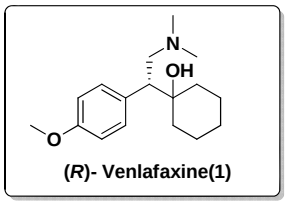
(*R*)−2−(1−Hydroxycyclohexyl)−2−(4−methoxyphenyl)ethyl 4−methylbenzenesulfonate (2)



Compound **2** was prepared as per the previously mentioned experimental procedure.

$[\alpha]^{25}_{D}$: −18.8 (*c* 1, $CHCl_3$)

(*R*)−1−(2−(Dimethylamino)−1−(4−methoxyphenyl)ethyl)cyclohexan−1−ol (1)

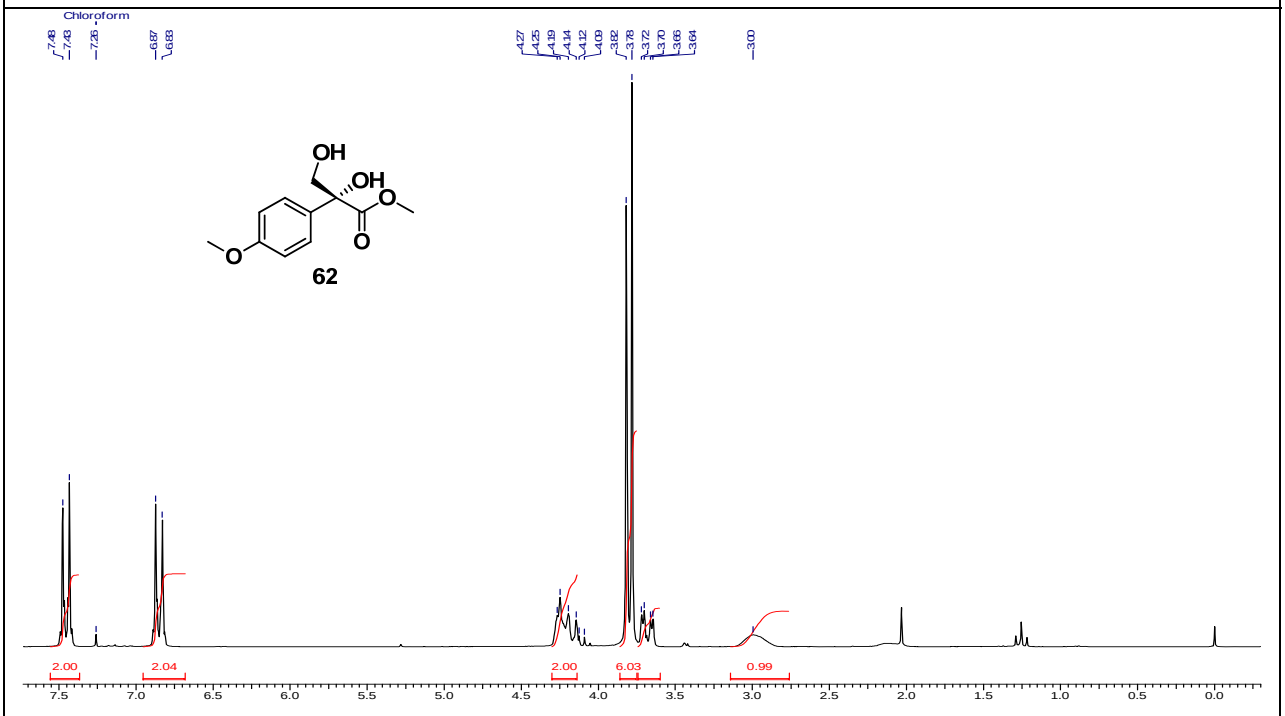


Compound **1** was prepared as per the previously mentioned experimental procedure.

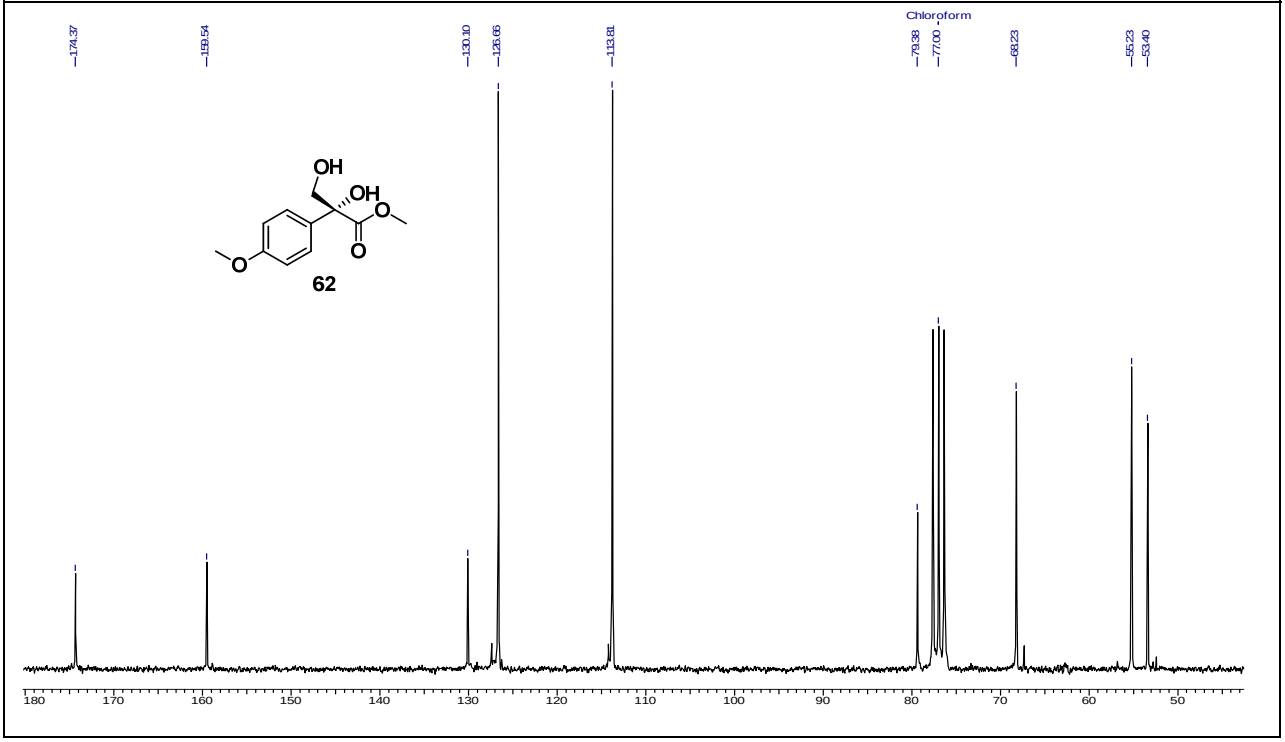
$[\alpha]^{25}_{D}$: −23.5 (*c* 1, EtOH).

3.3.5.1.. Spectral data

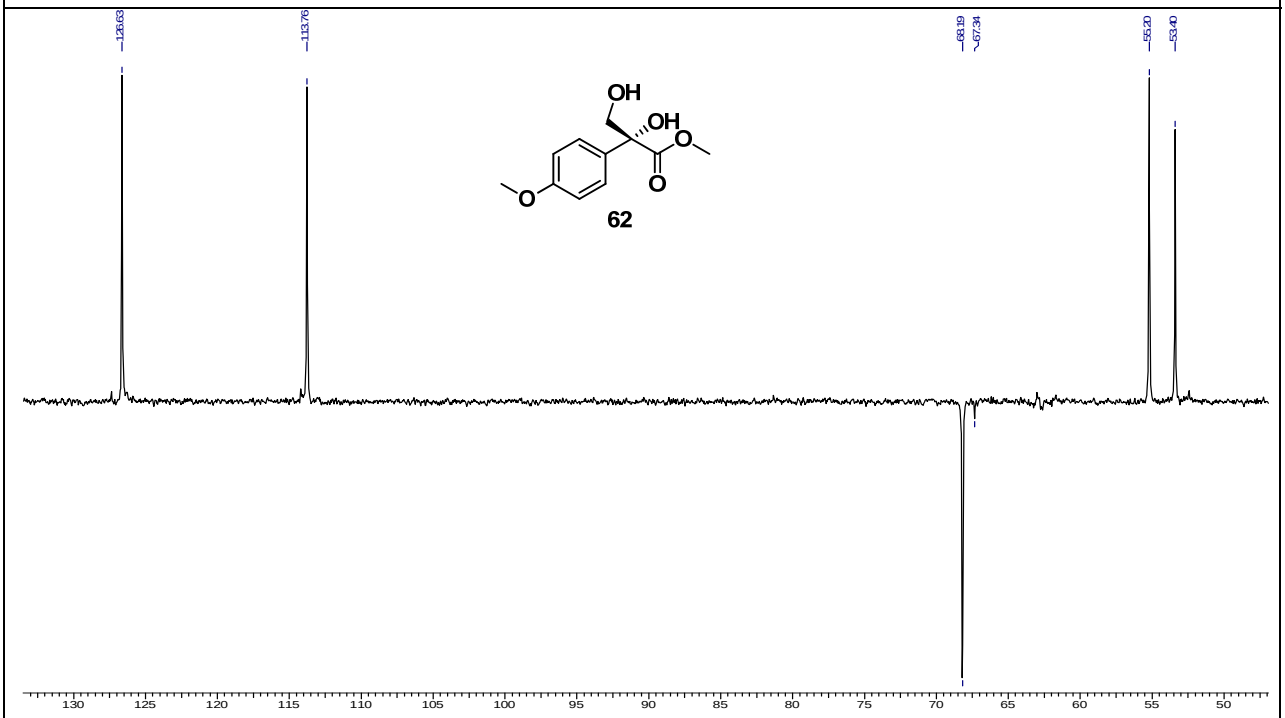
^{1}H NMR spectrum ofcompound **62** ($CDCl_3$, 200 MHz)



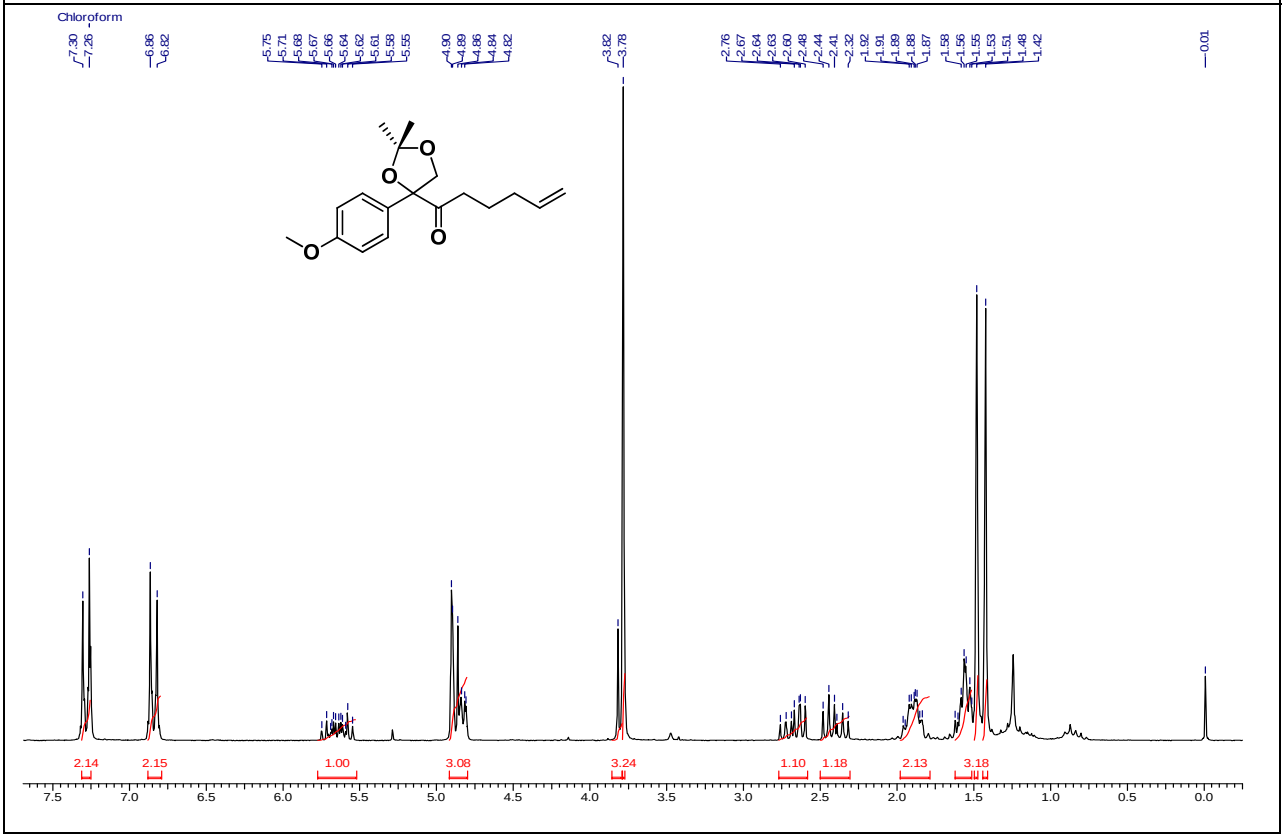
^{13}C NMR spectrum ofcompound **62** ($CDCl_3$, 50 MHz)



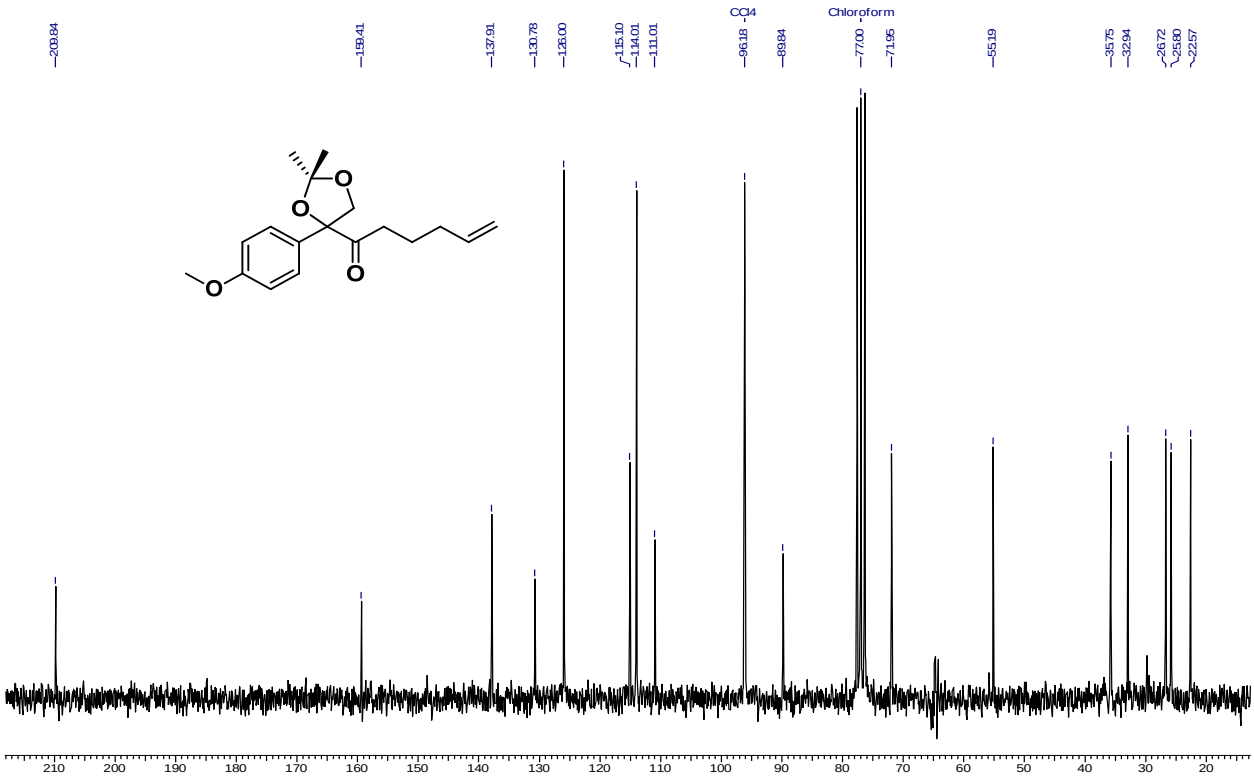
DEPT spectrum of compound **62** ($CDCl_3$, 50 MHz)



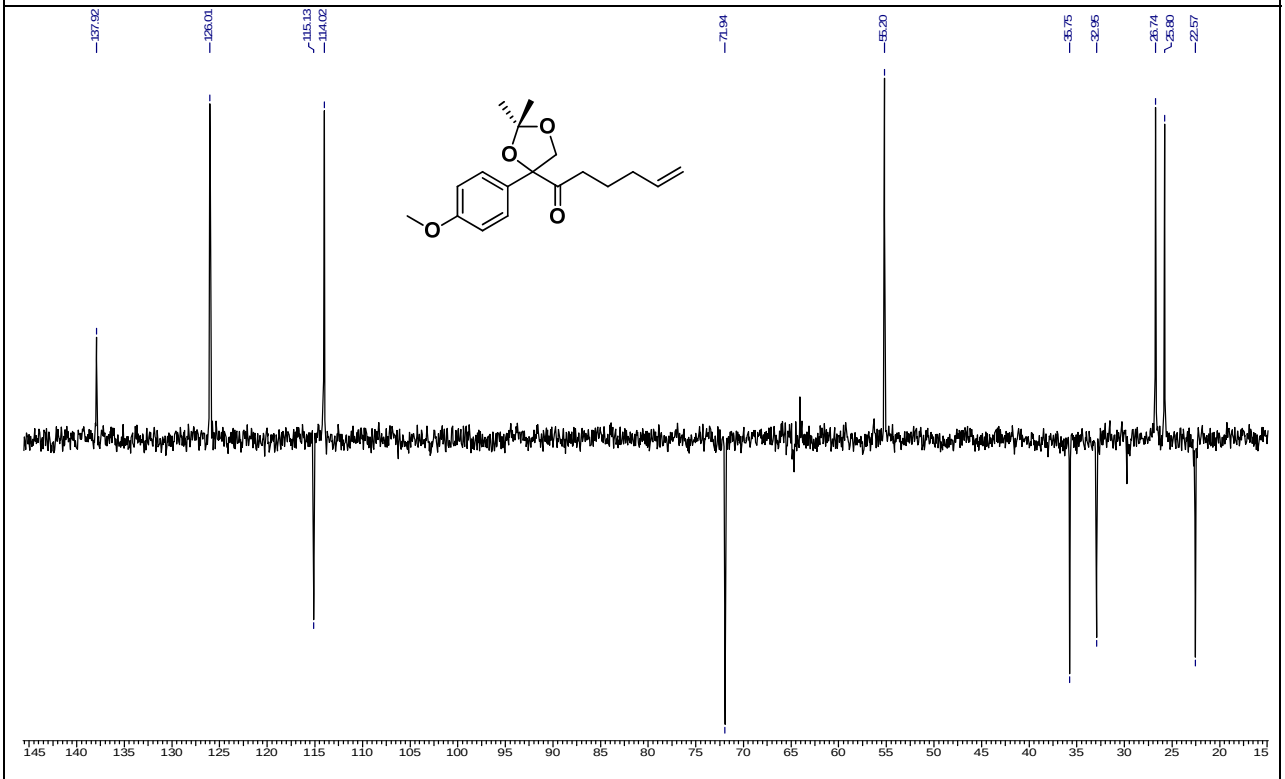
^{1}H NMR spectrum ofcompound **65** ($CDCl_3$+CCl_4, 200 MHz)



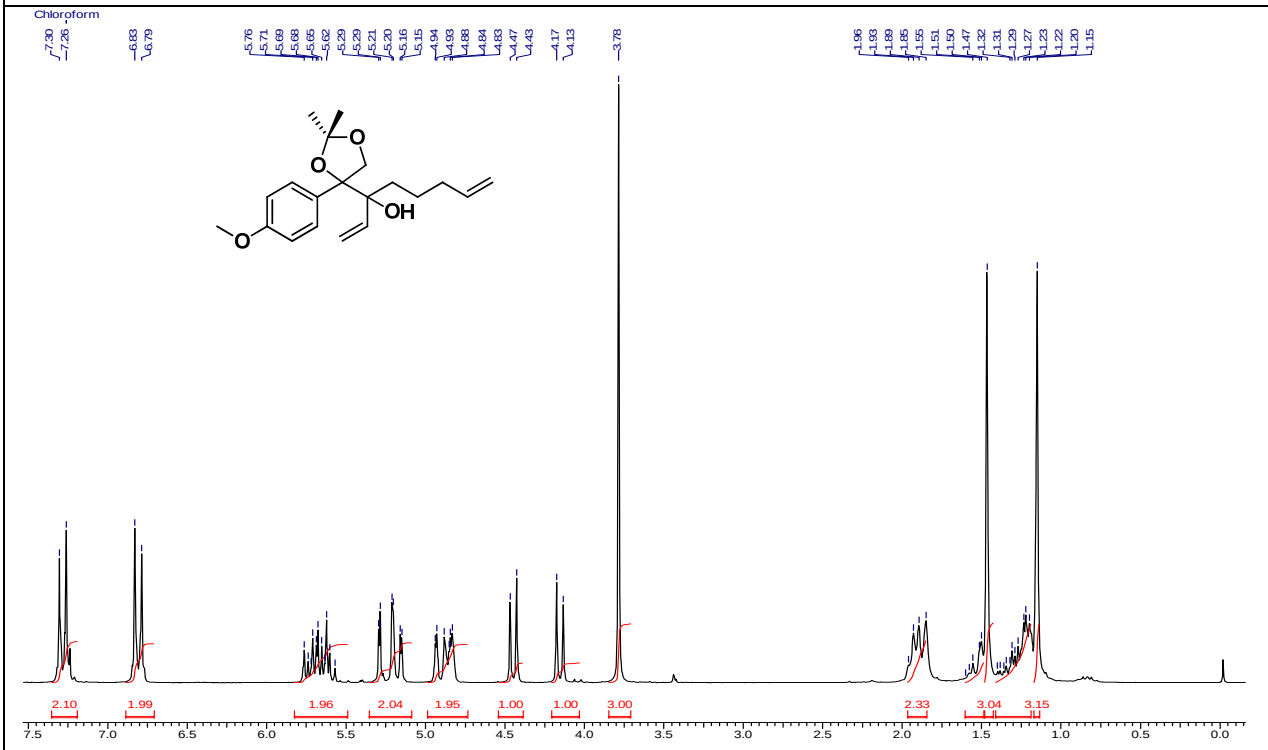
^{13}C NMR spectrum ofcompound **65** ($CDCl_3$+CCl_4, 50 MHz)



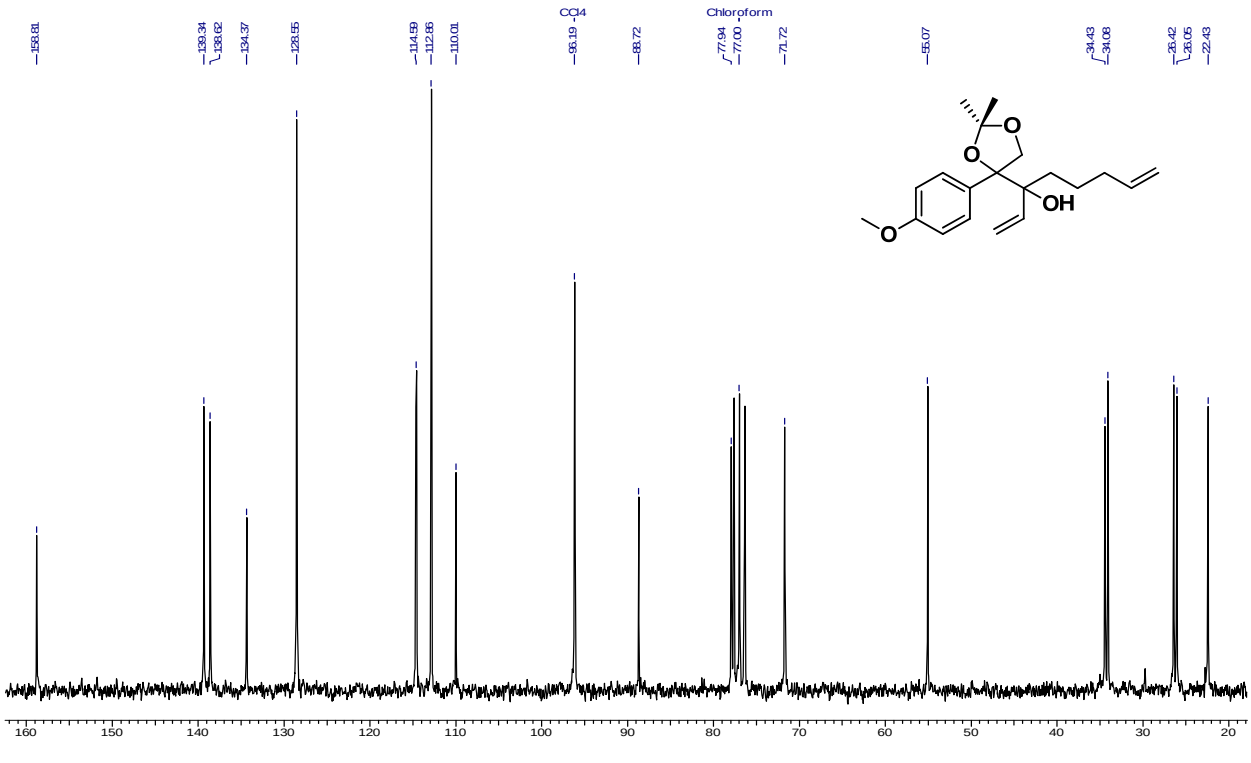
DEPT spectrum of compound **65** ($CDCl_3$+CCl_4, 50 MHz)



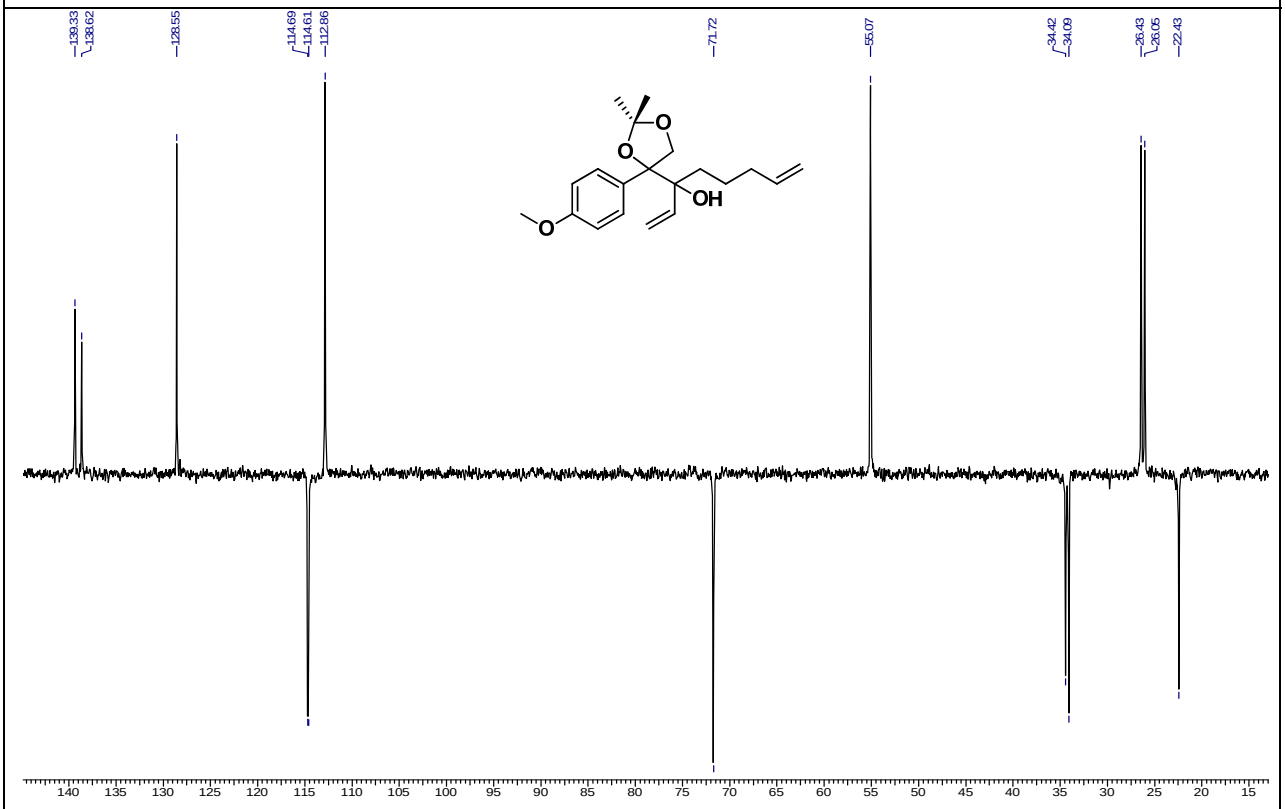
^{1}H NMR spectrum ofcompound **66** ($CDCl_3$+CCl_4, 200 MHz)



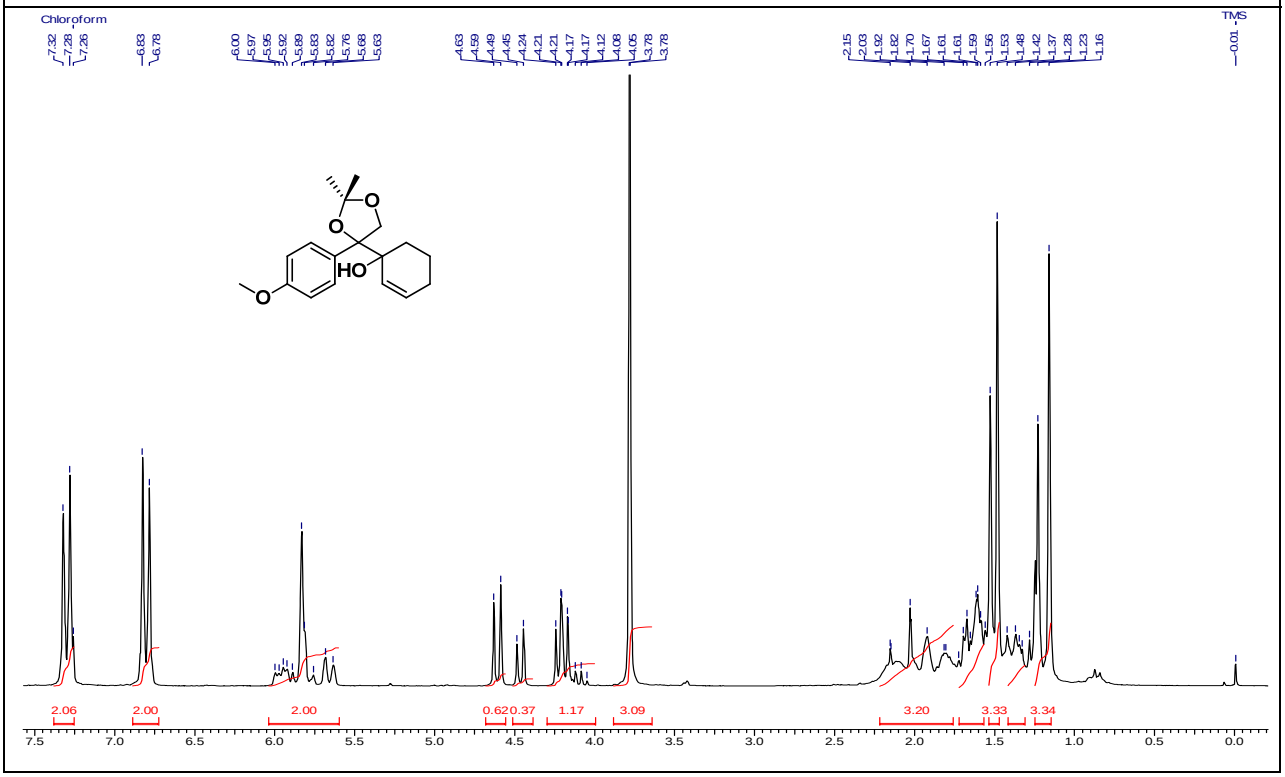
^{13}C NMR spectrum ofcompound **66** ($CDCl_3$+CCl_4, 50 MHz)



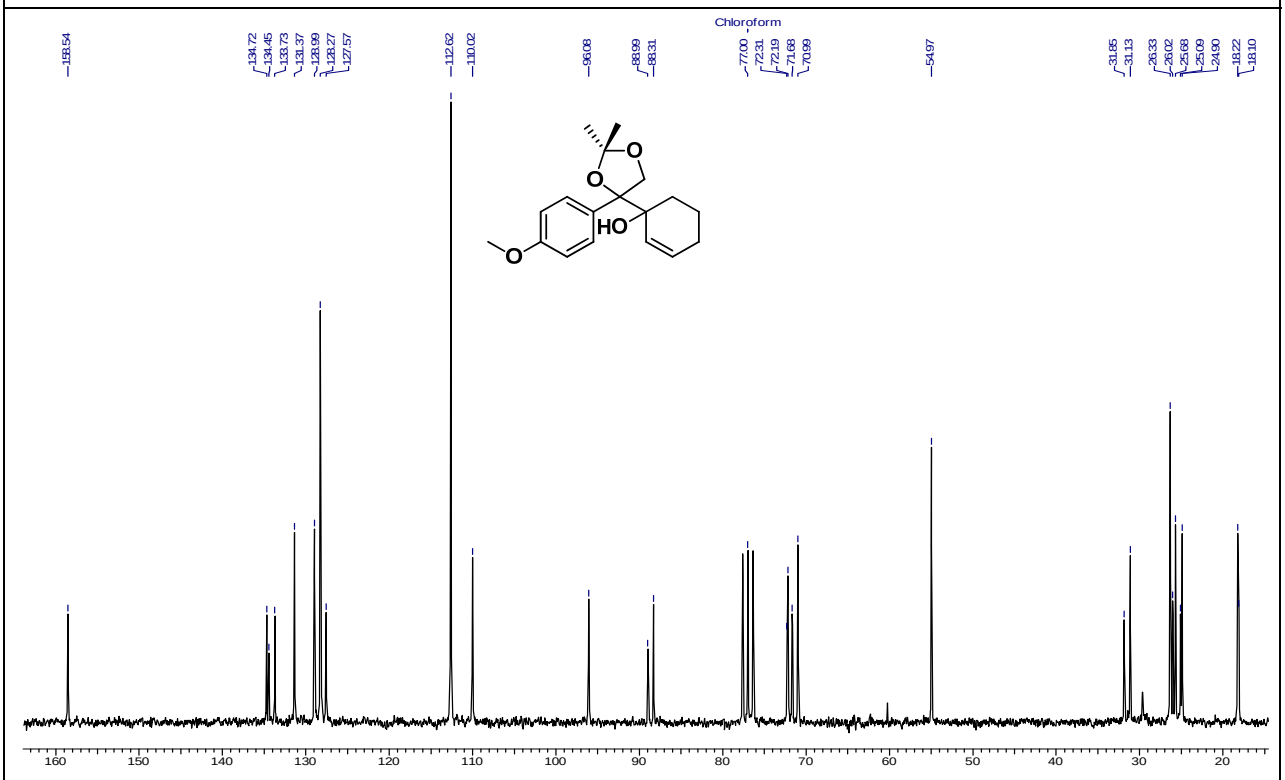
DEPT spectrum of compound **66** ($CDCl_3$+CCl_4, 50 MHz)



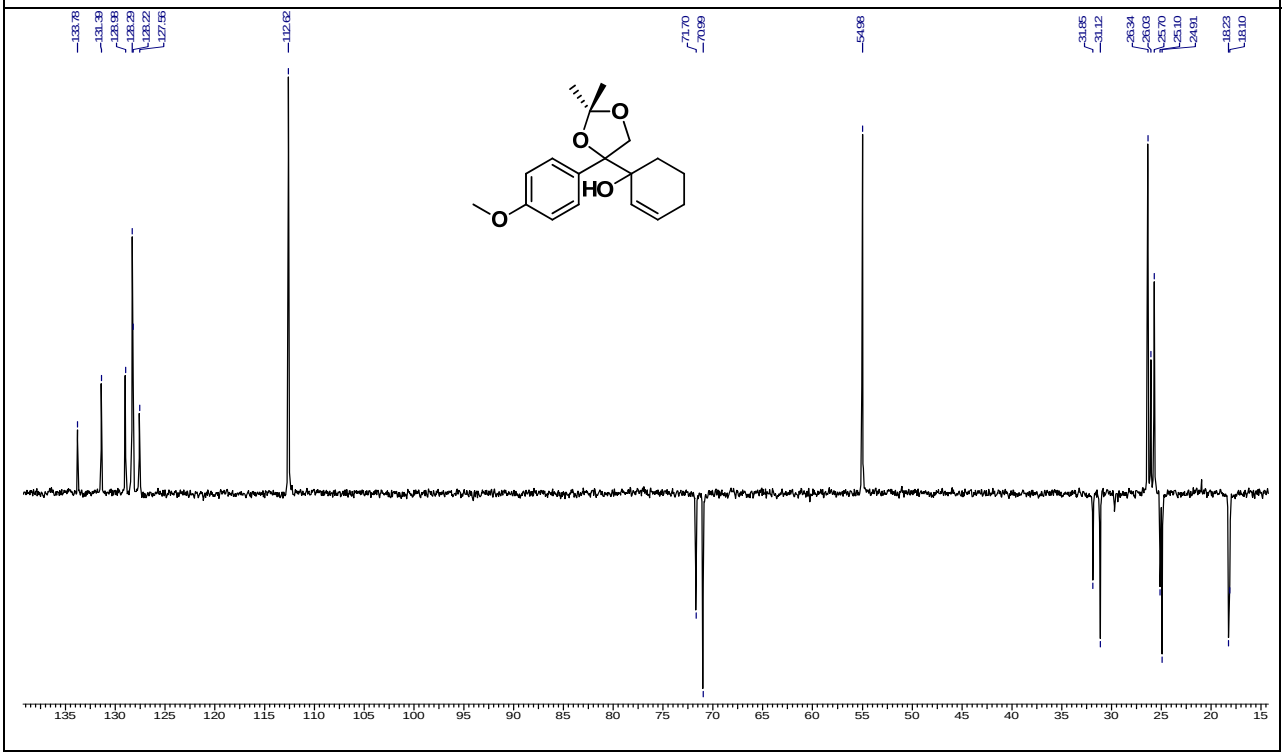
^{1}H NMR spectrum ofcompound **67** ($CDCl_3$+CCl_4, 200 MHz)



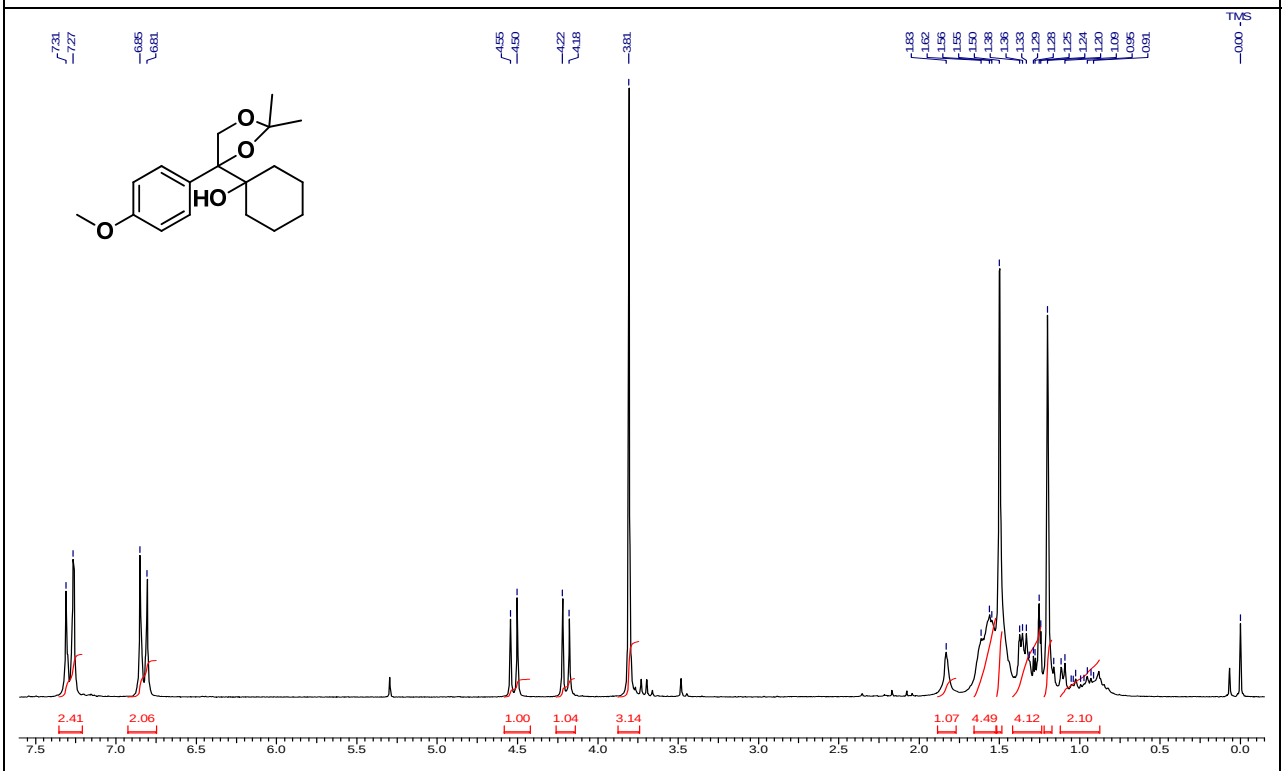
^{13}C NMR spectrum ofcompound **67** ($CDCl_3$+CCl_4, 50 MHz)



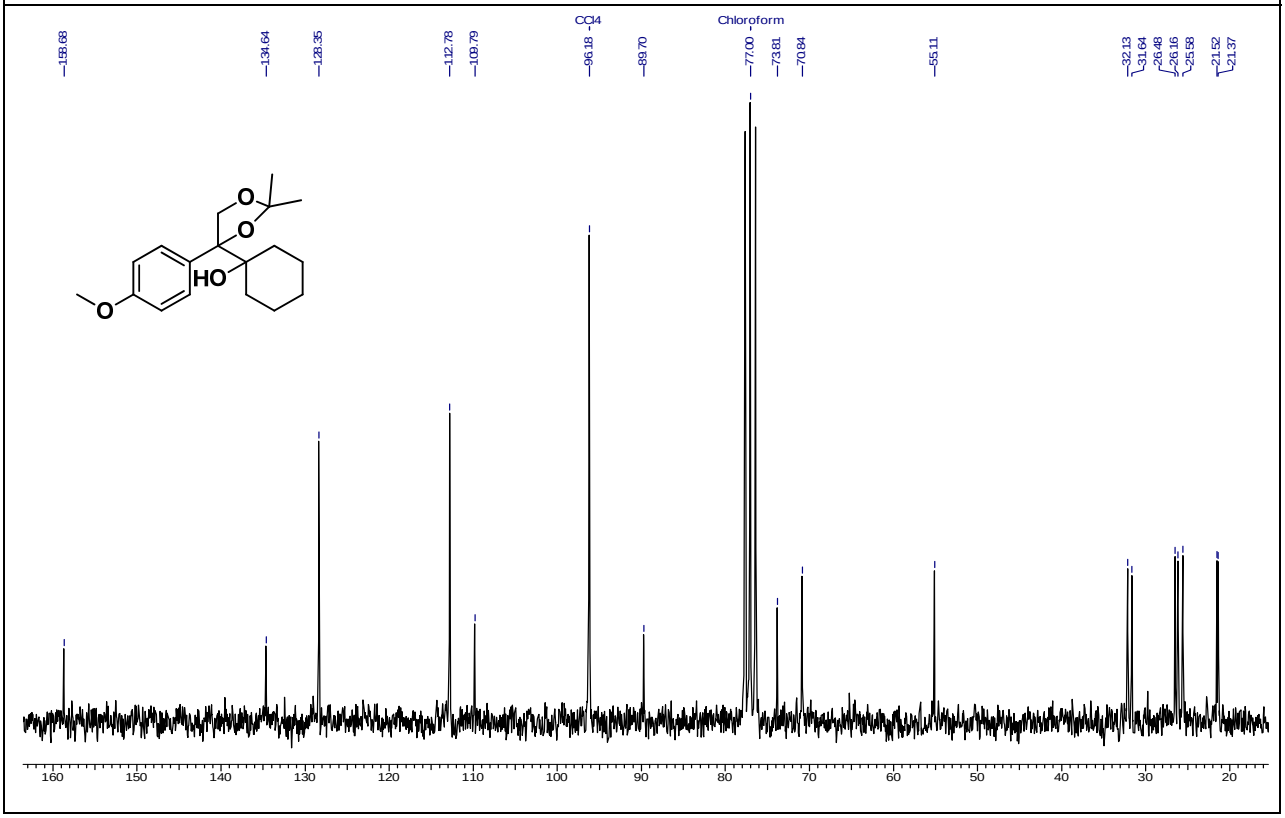
DEPT spectrum of compound **67** ($CDCl_3$+CCl_4, 50 MHz)



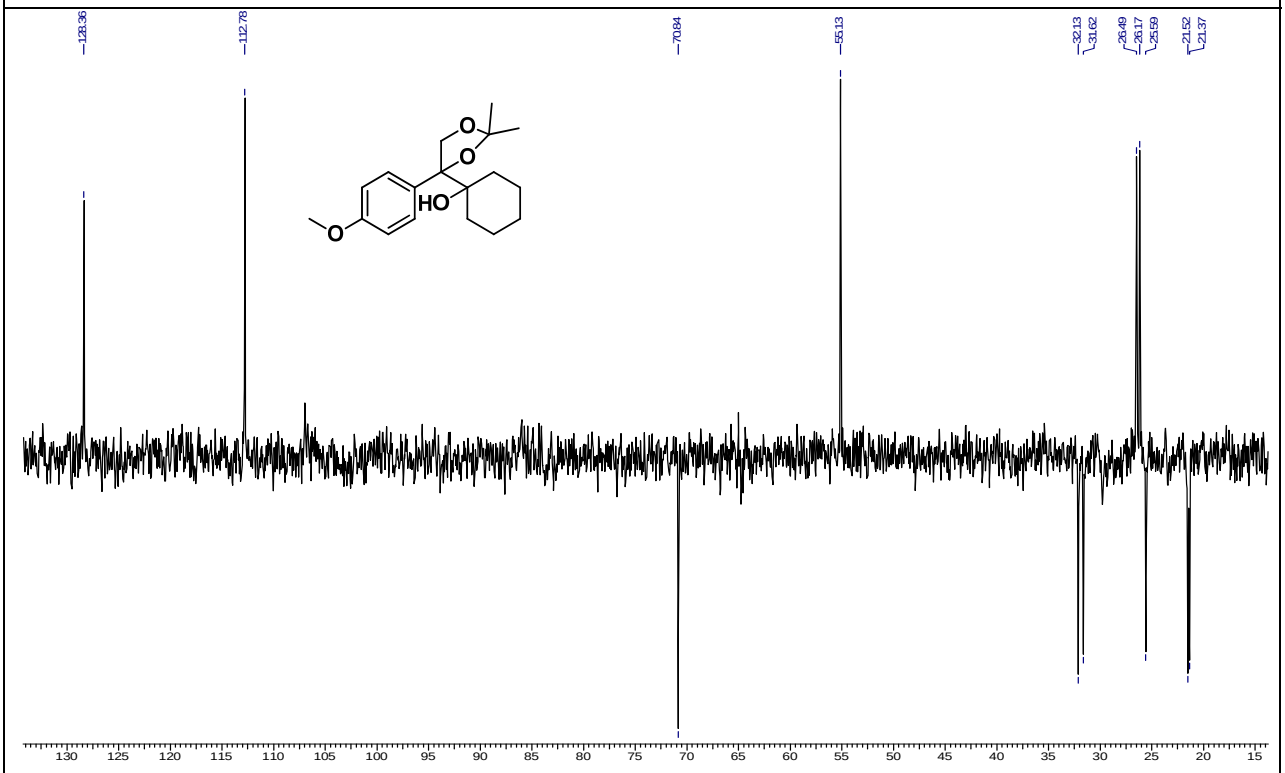
^{1}H NMR spectrum ofcompound **68** ($CDCl_3$+CCl_4, 200 MHz)



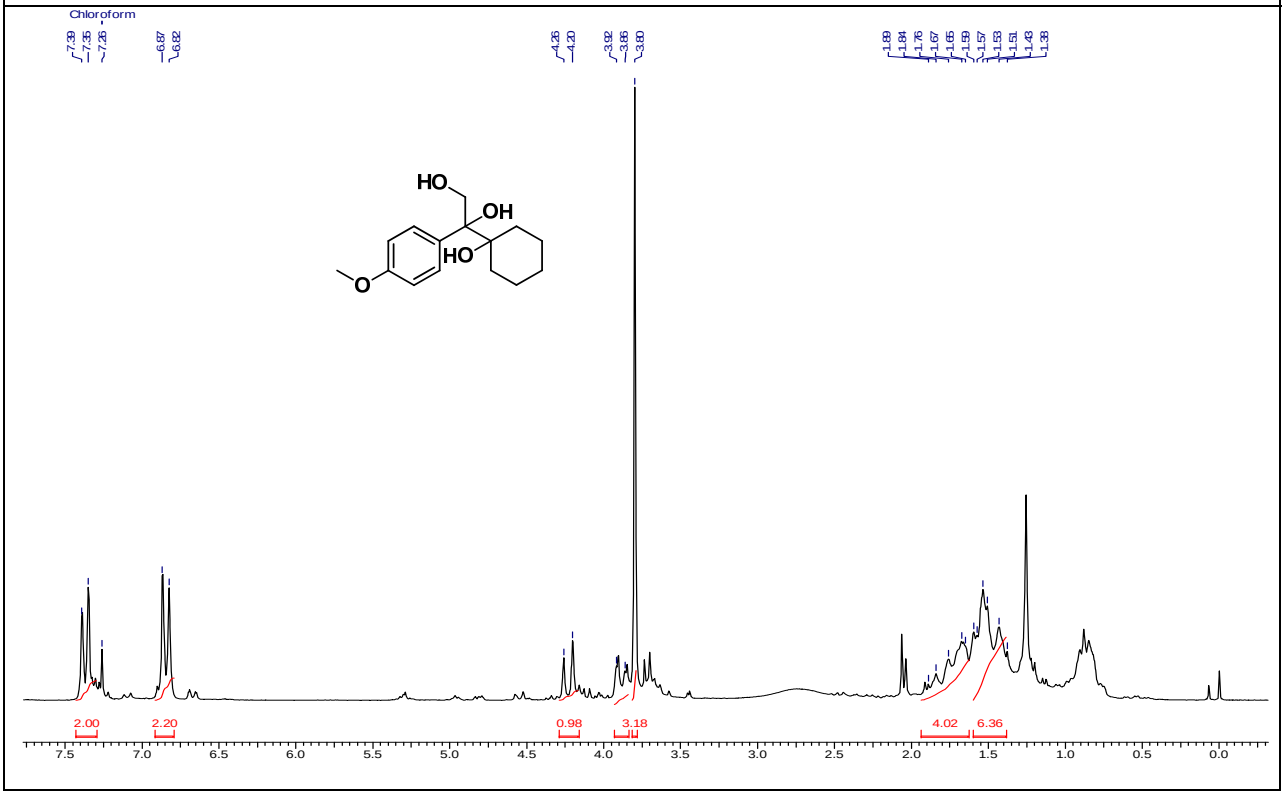
^{13}C NMR spectrum of compound 68 ($CDCl_3$+CCl_4, 50 MHz)



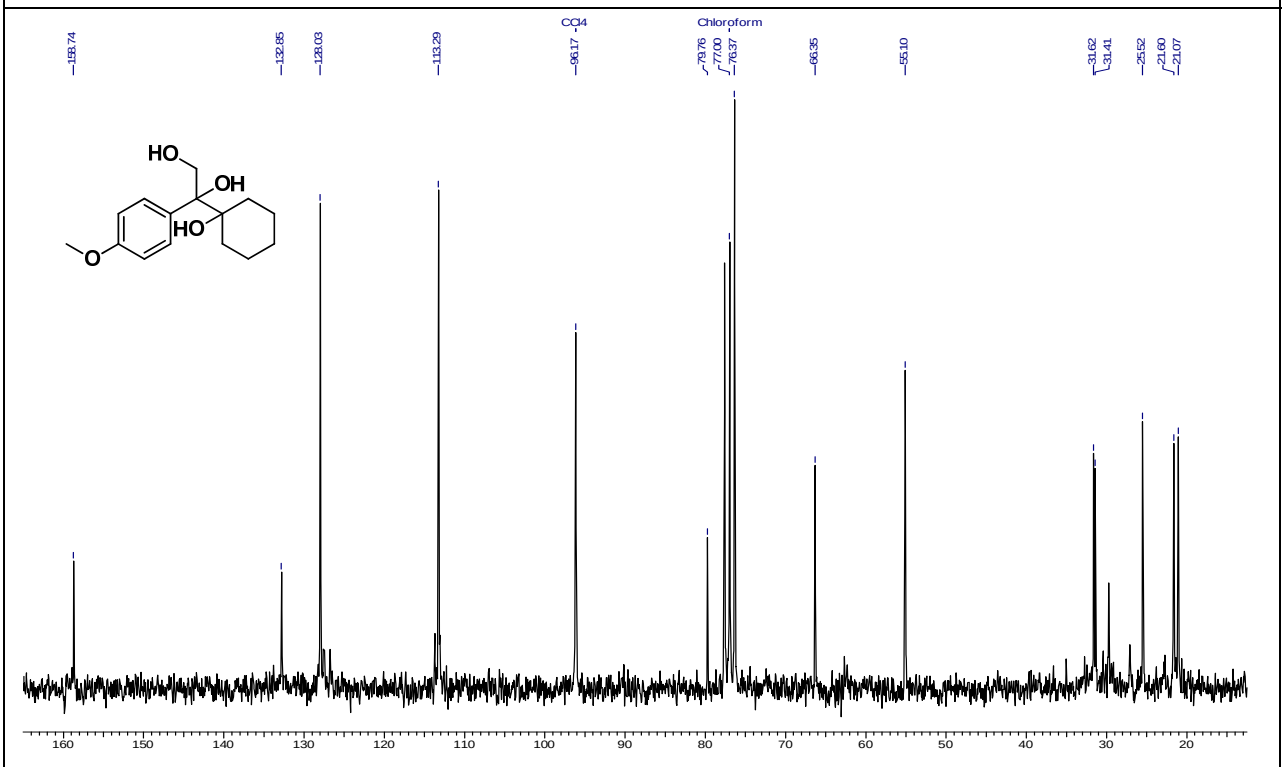
DEPT spectrum of compound **68** ($CDCl_3$+CCl_4, 50 MHz)



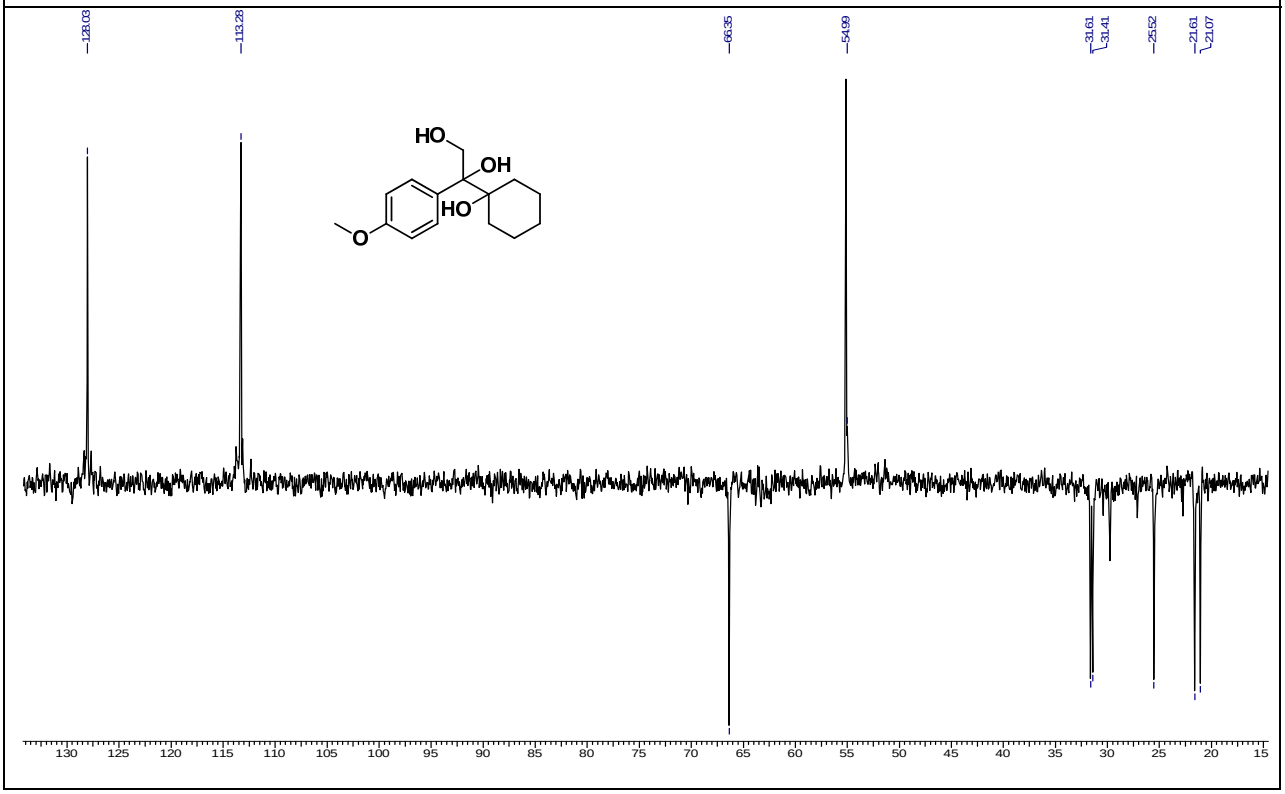
^{1}H NMR spectrum of compound **69** ($CDCl_3$+CCl_4, 200 MHz)



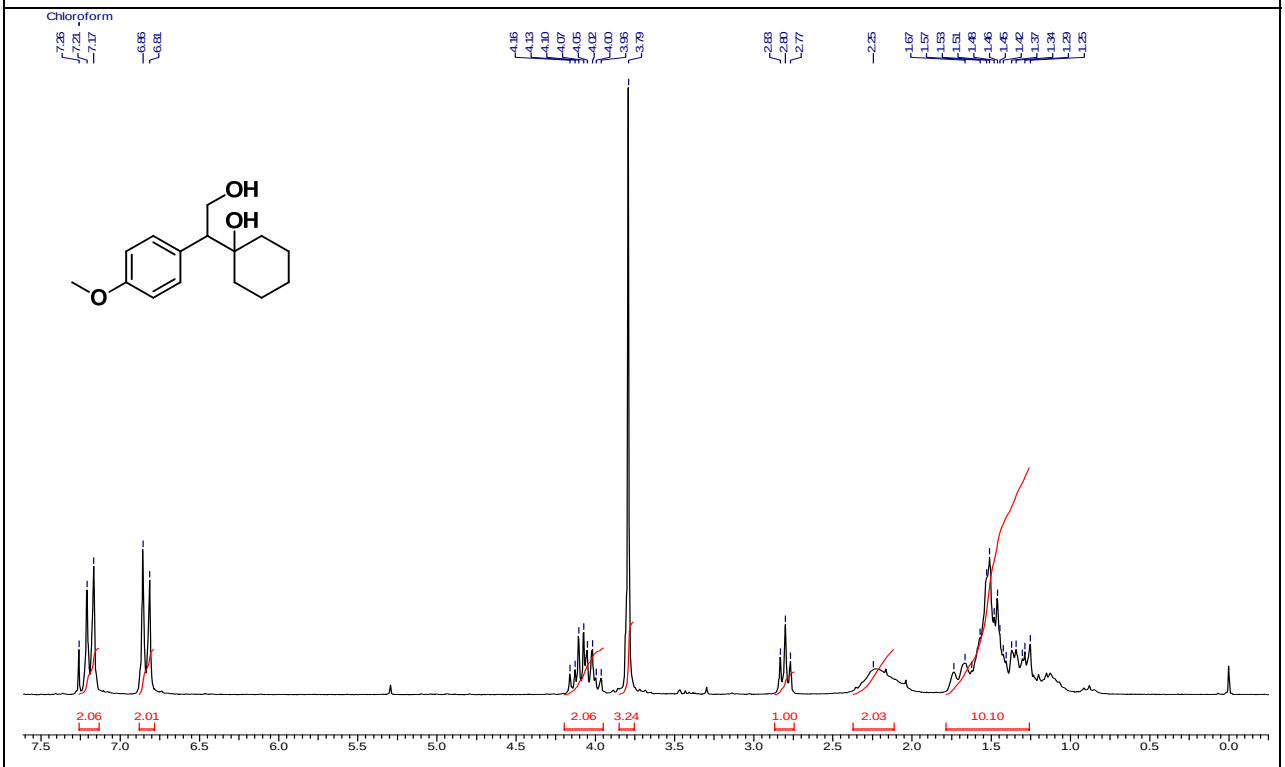
^{13}C NMR spectrum of compound **69** ($CDCl_3$+CCl_4, 50 MHz)



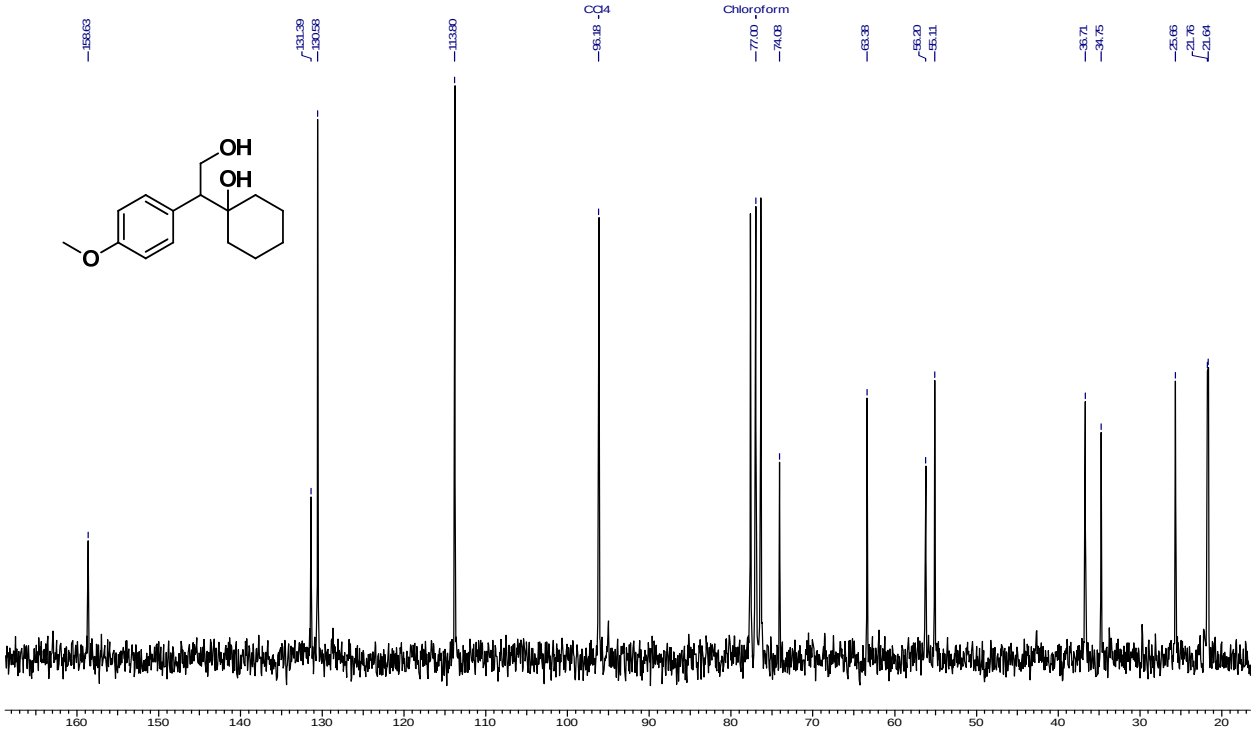
DEPT spectrum of compound **69** ($CDCl_3$+CCl_4, 50 MHz)



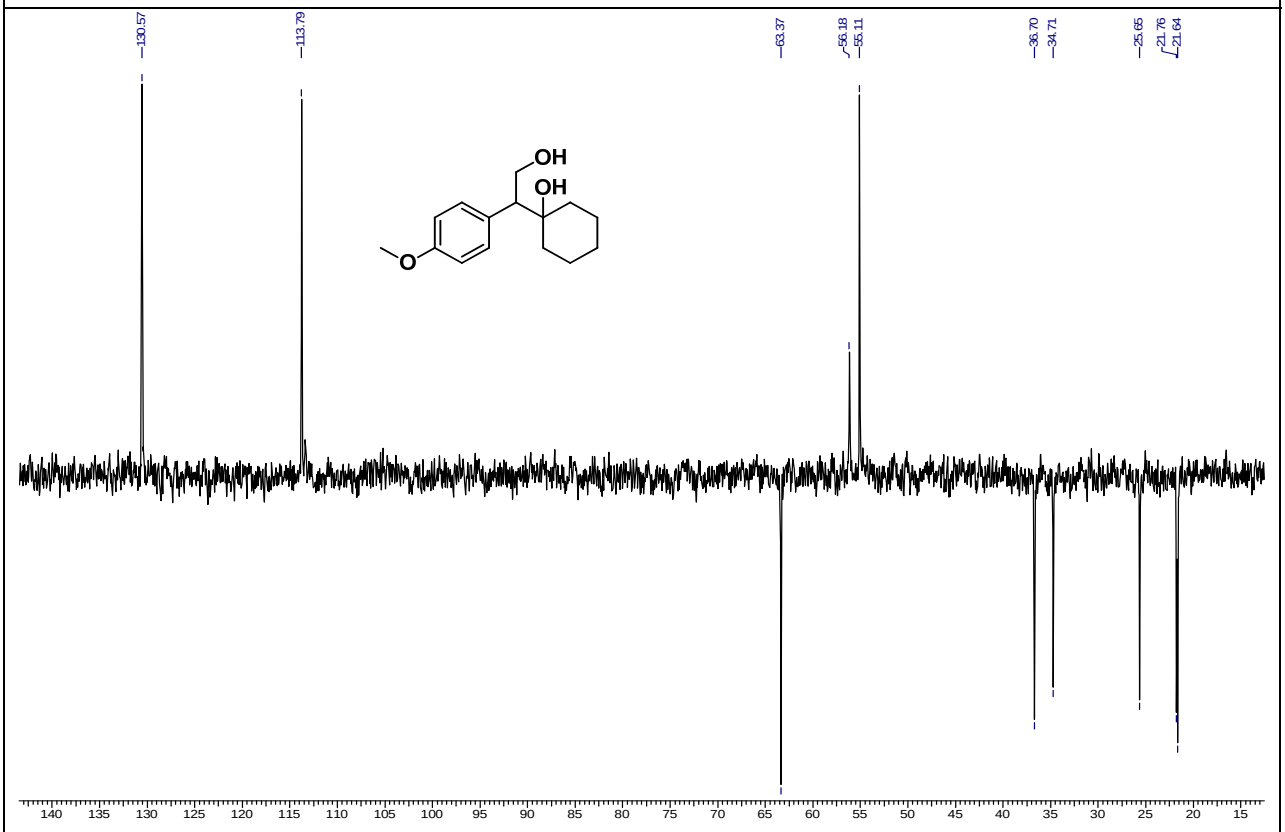
^{1}H NMR spectrum of compound **70** ($CDCl_3$+CCl_4, 200 MHz)



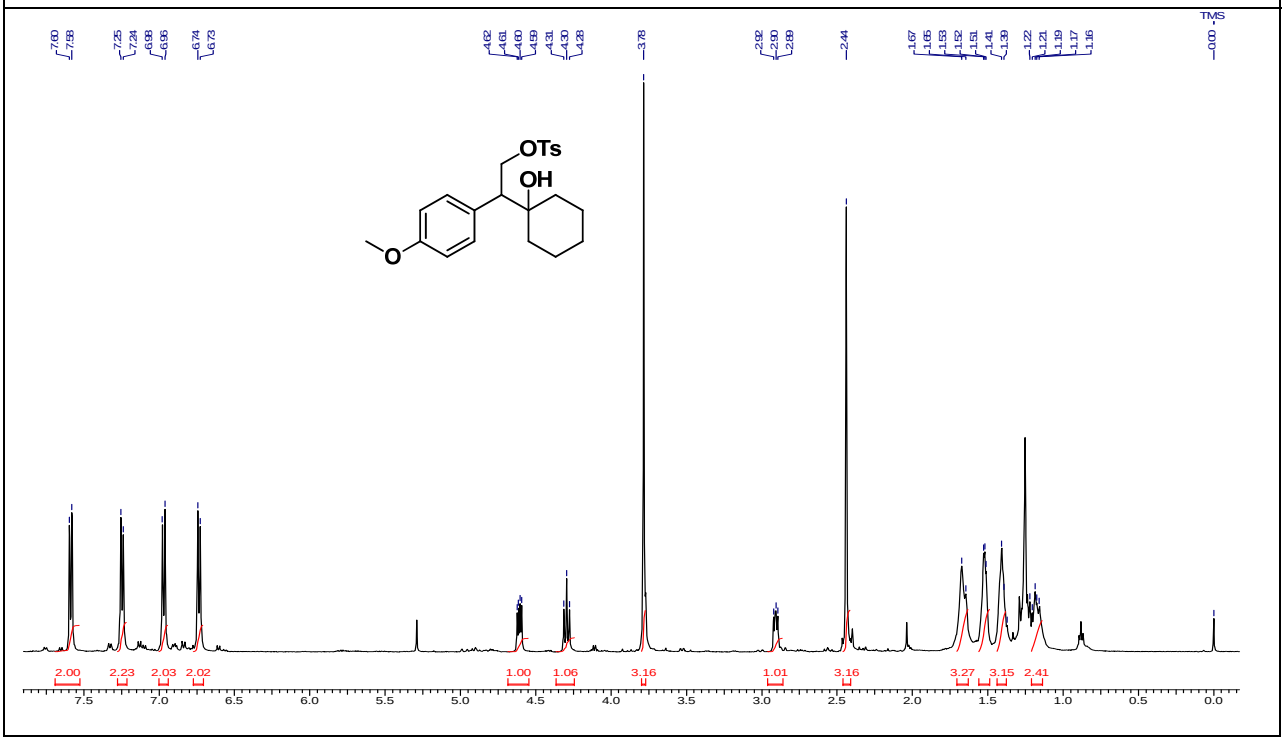
^{13}C NMR spectrum ofcompound **70** ($CDCl_3$+CCl_4, 50 MHz)



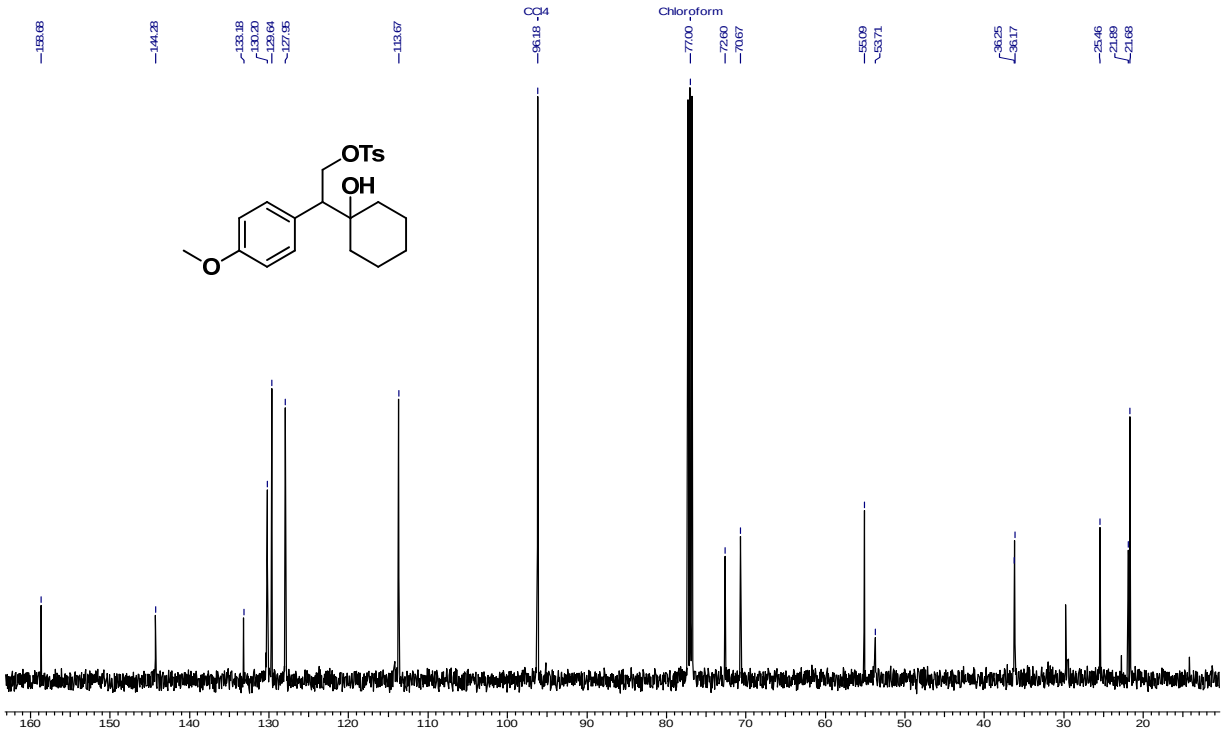
DEPT spectrum of compound **70** ($CDCl_3$+CCl_4, 50 MHz)



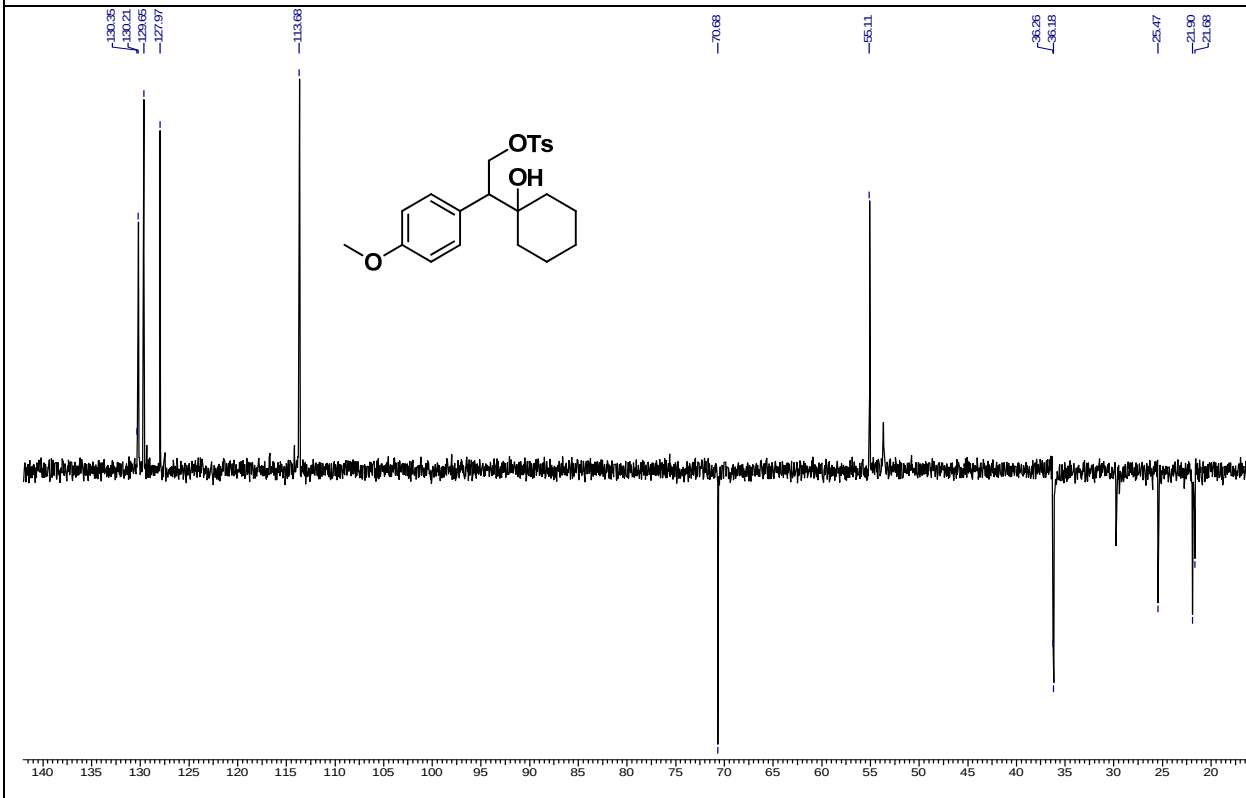
^{1}H NMR spectrum ofcompound **71** ($CDCl_3$+CCl_4, 500 MHz)



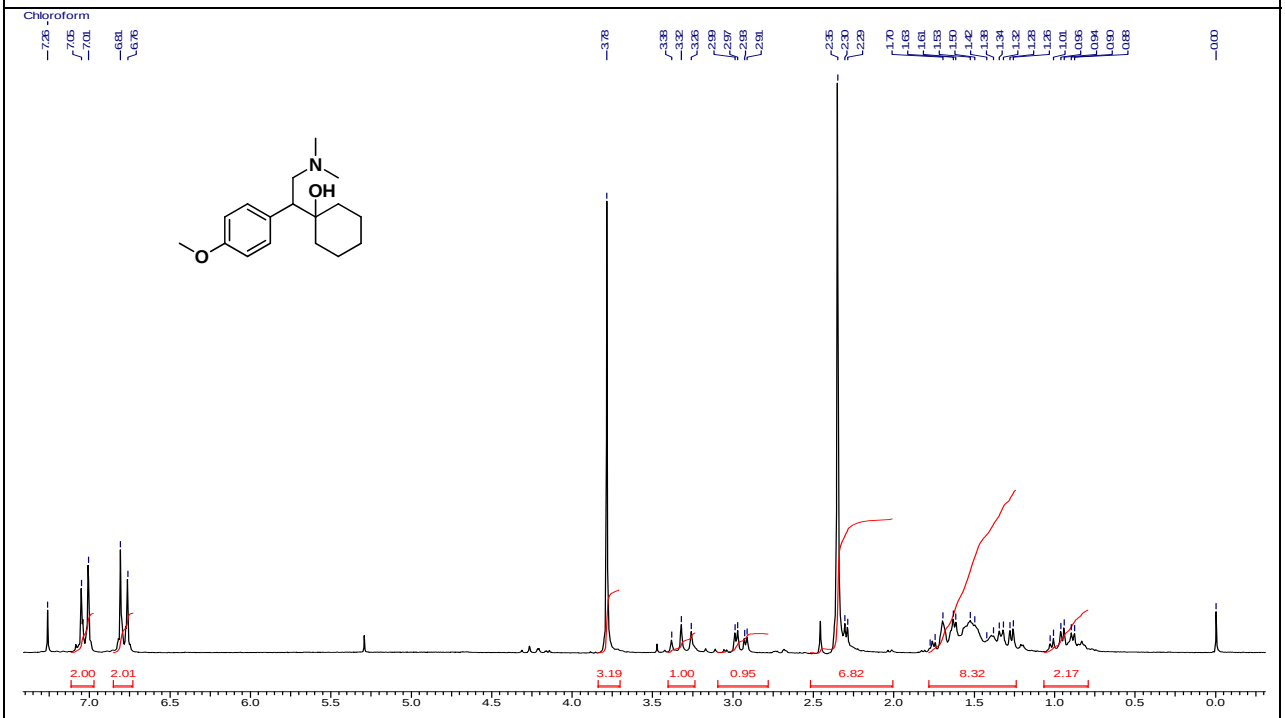
^{13}C NMR spectrum ofcompound **71** ($CDCl_3$+CCl_4, 125 MHz)



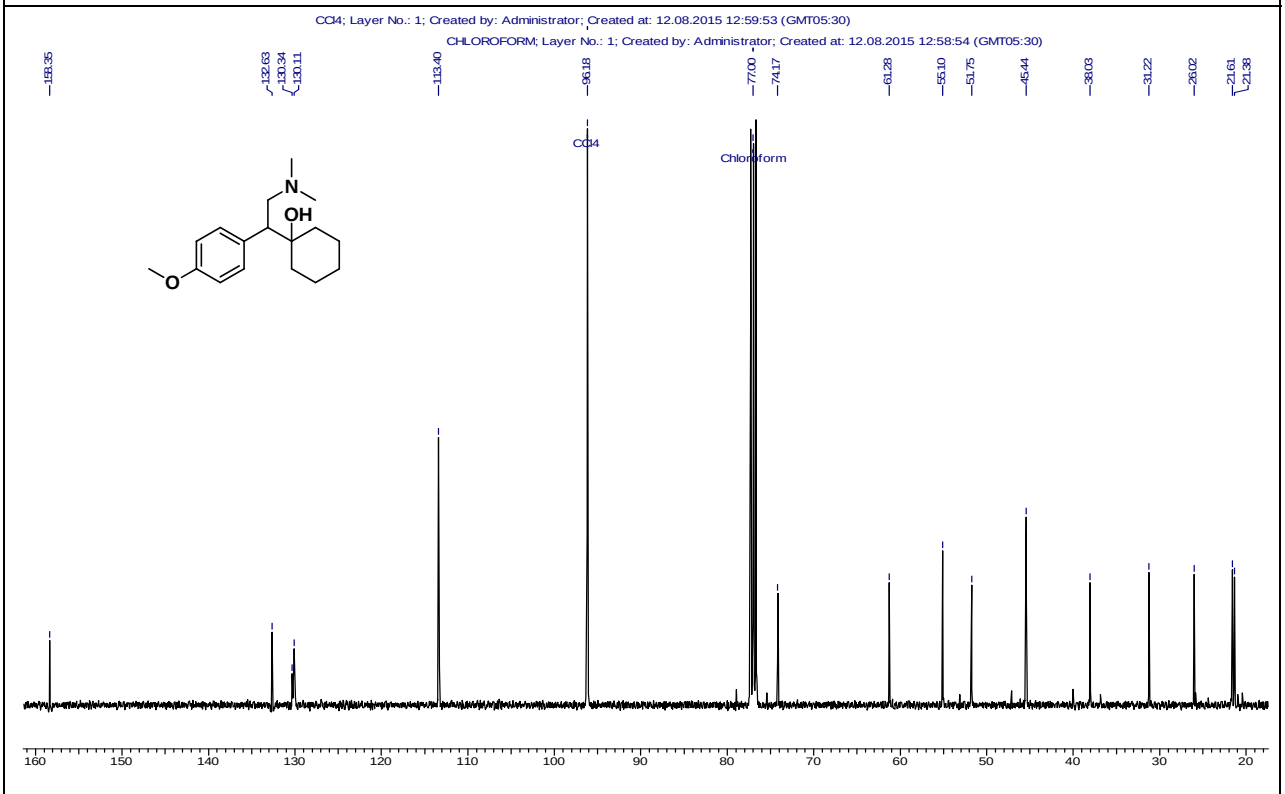
DEPT spectrum of compound **71** ($CDCl_3$+CCl_4, 125 MHz)



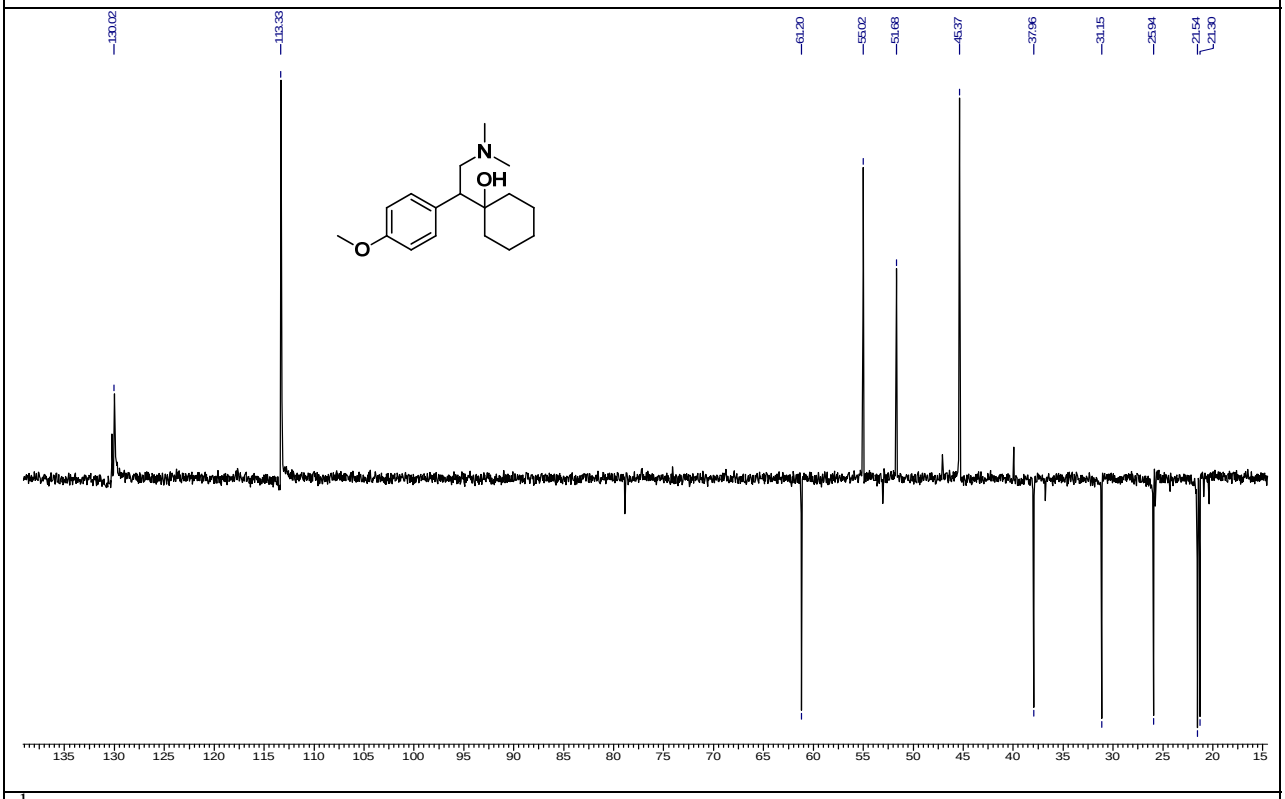
^{1}H NMR spectrum ofcompound **1** ($CDCl_3$+CCl_4, 200 MHz)



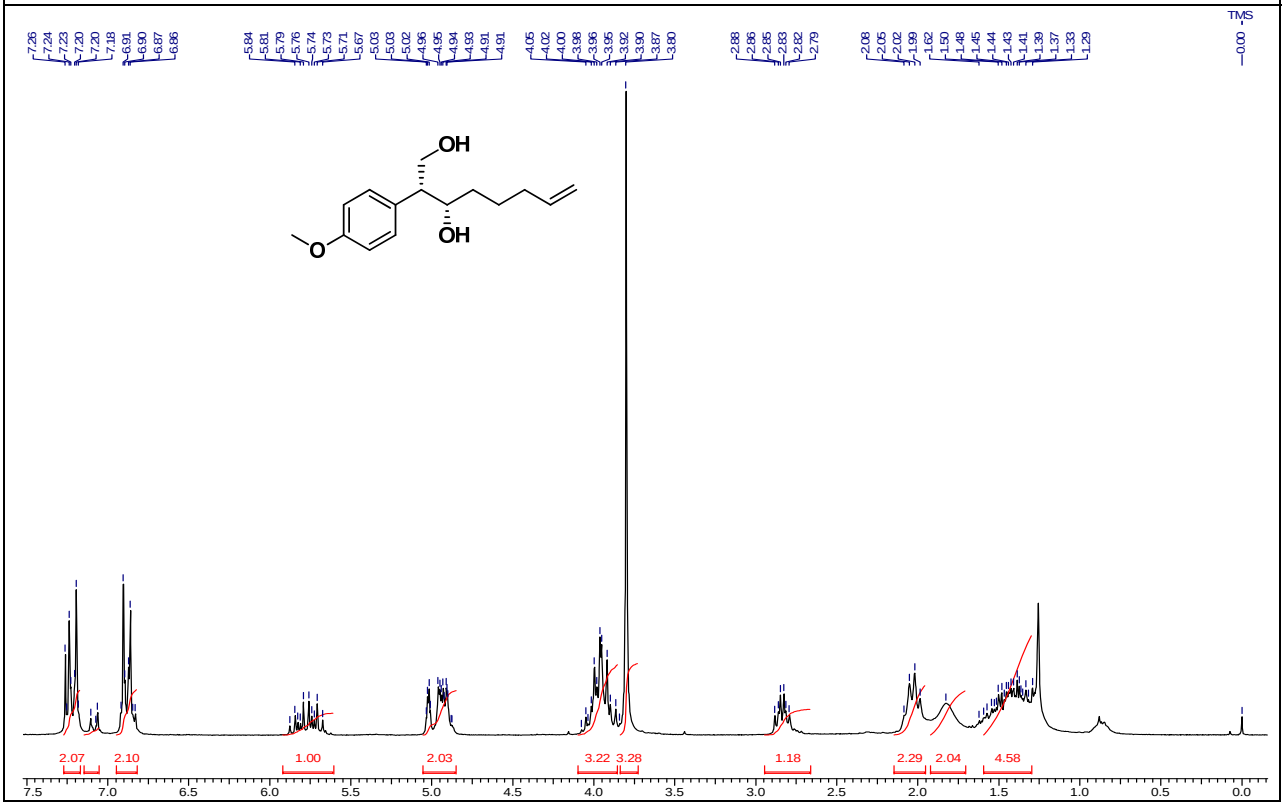
^{13}C NMR spectrum of compound **1** ($CDCl_3$+CCl_4, 50 MHz)



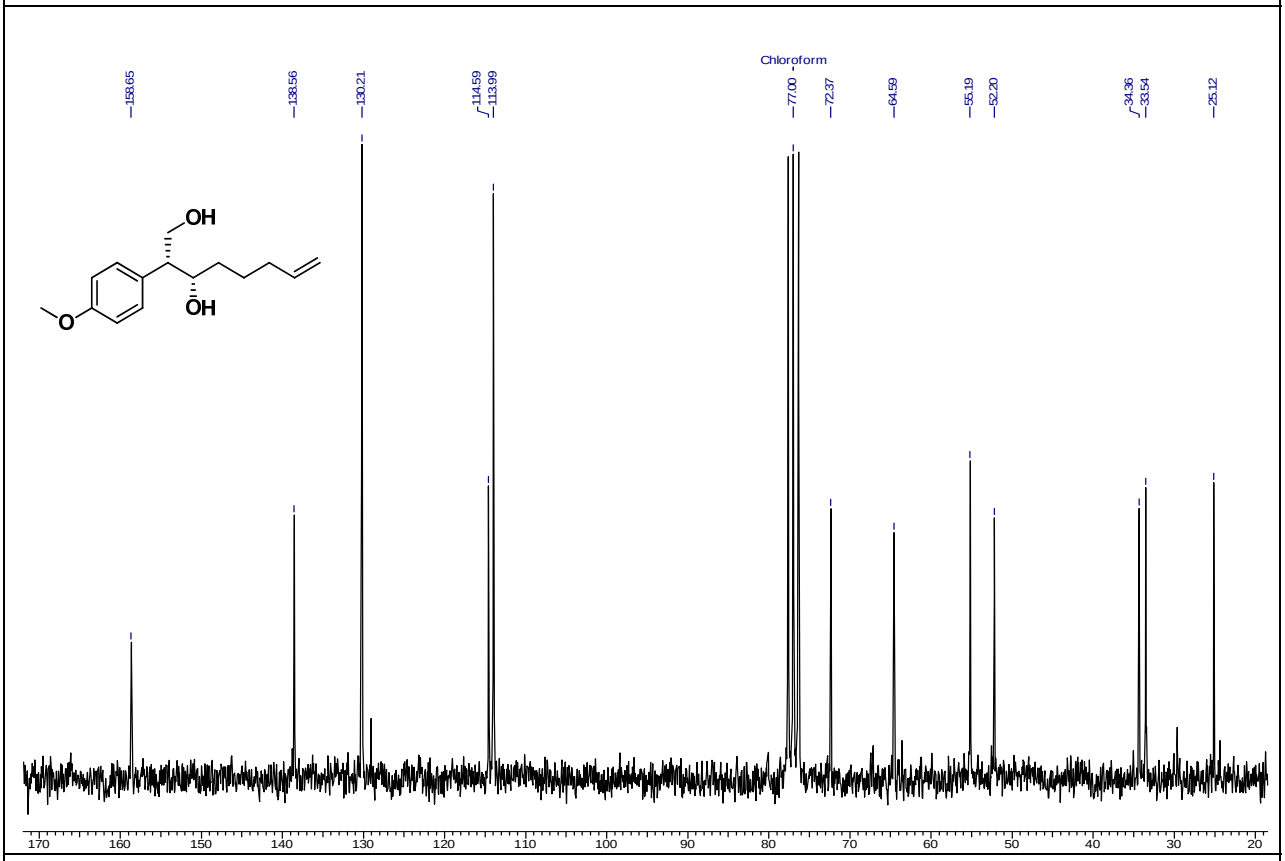
DEPT spectrum of compound **1** ($CDCl_3$+CCl_4, 50 MHz)



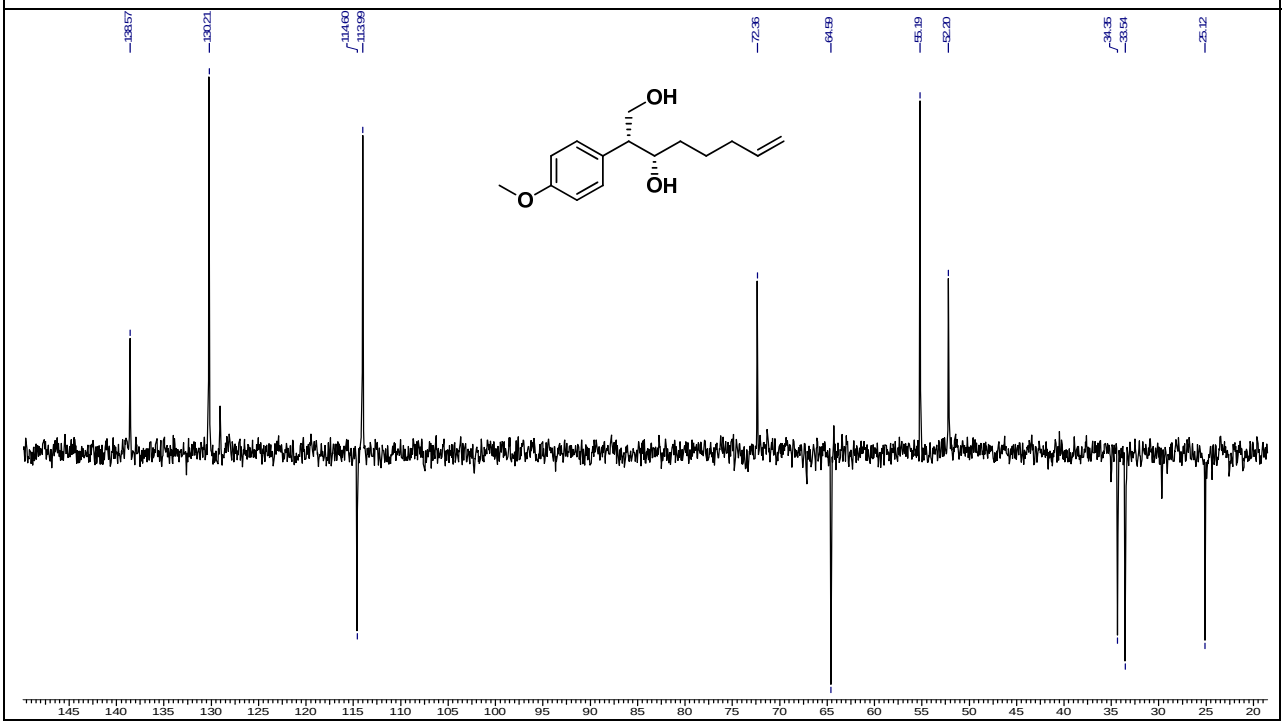
^{1}H NMR spectrum of compound **72** ($CDCl_3$, 200 MHz)



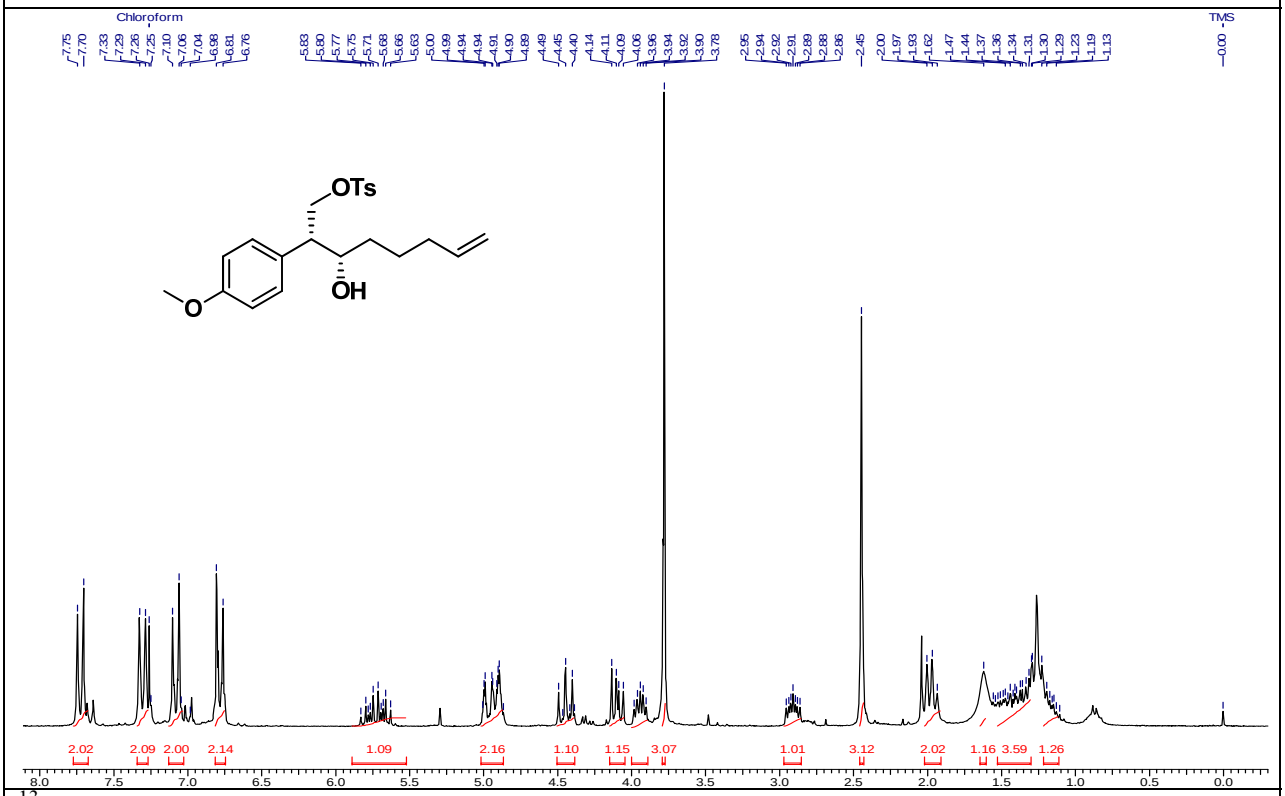
^{13}C NMR spectrum ofcompound **72** ($CDCl_3$, 50 MHz)



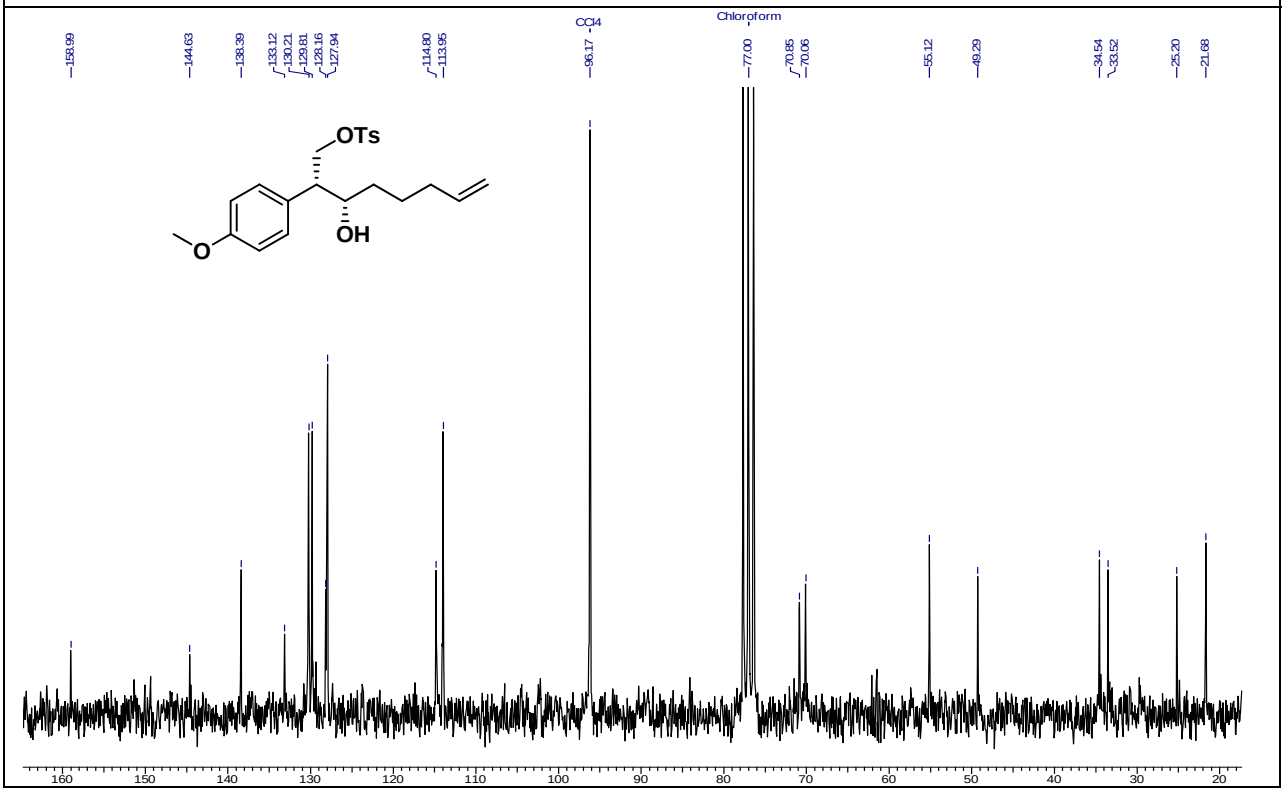
DEPT spectrum of compound **72** ($CDCl_3$, 50 MHz)



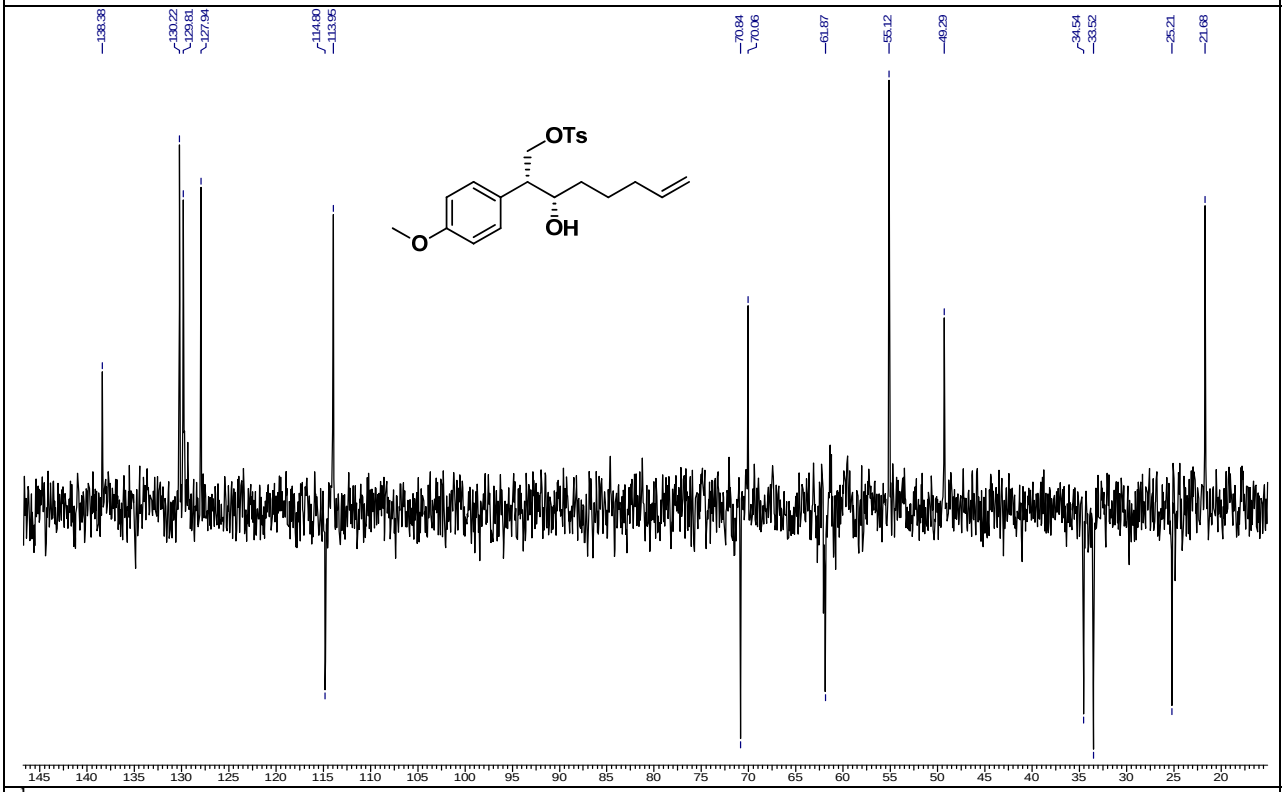
^{1}H NMR spectrum ofcompound **92** ($CDCl_3$+CCl_4, 200 MHz)



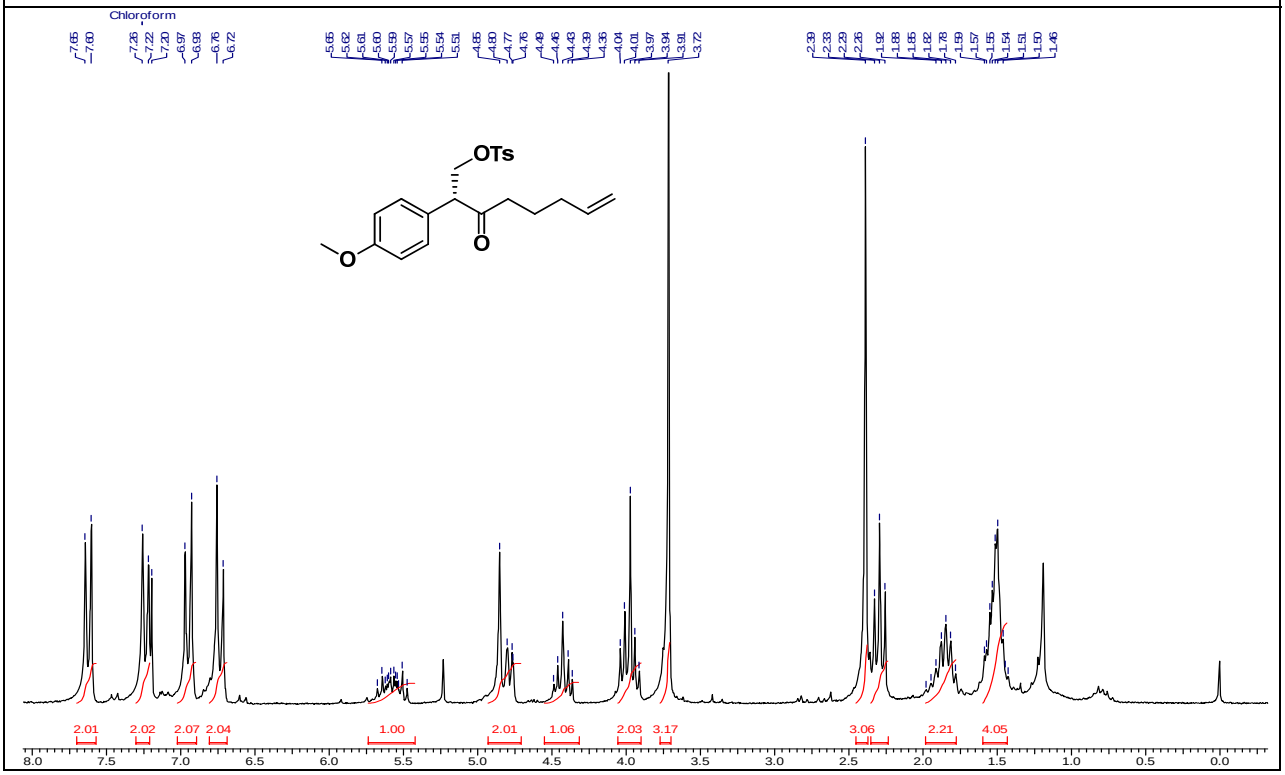
^{13}C NMR spectrum ofcompound **92** ($CDCl_3$+CCl_4, 50 MHz)



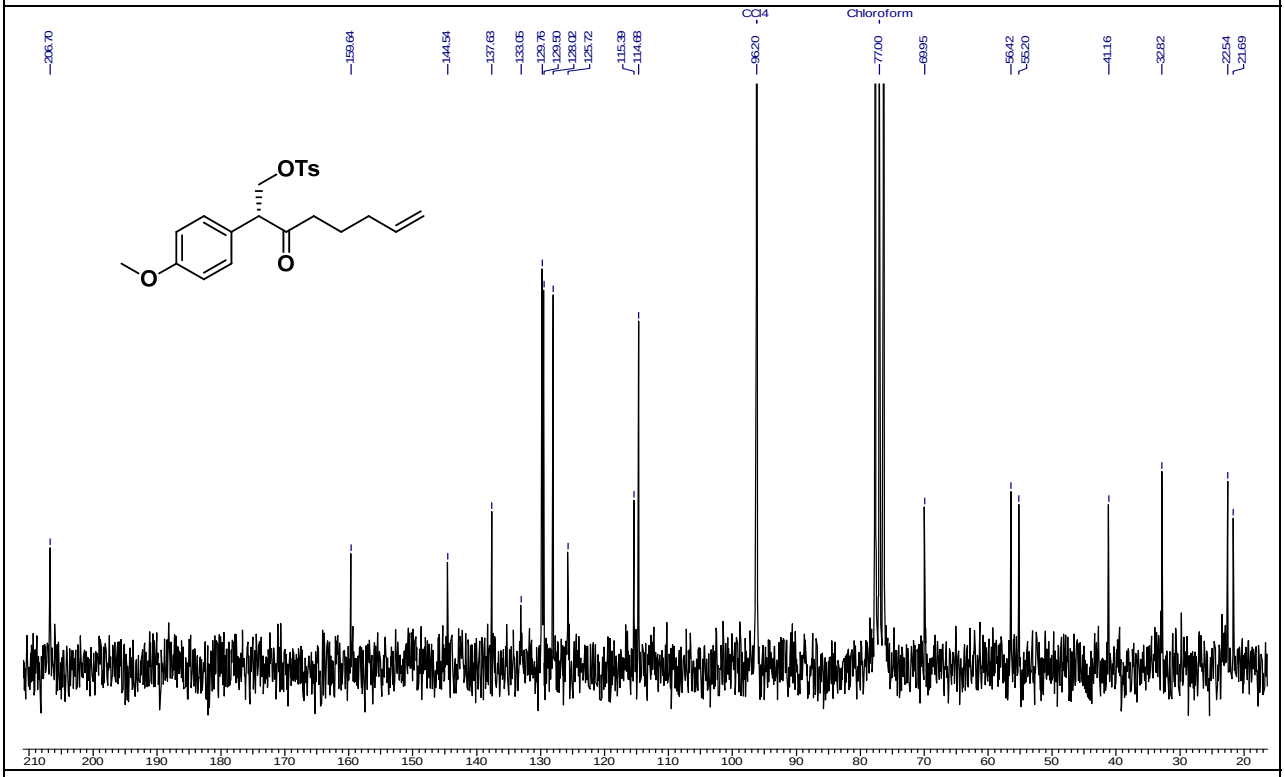
DEPT spectrum of compound **92** ($CDCl_3$+CCl_4, 50 MHz)



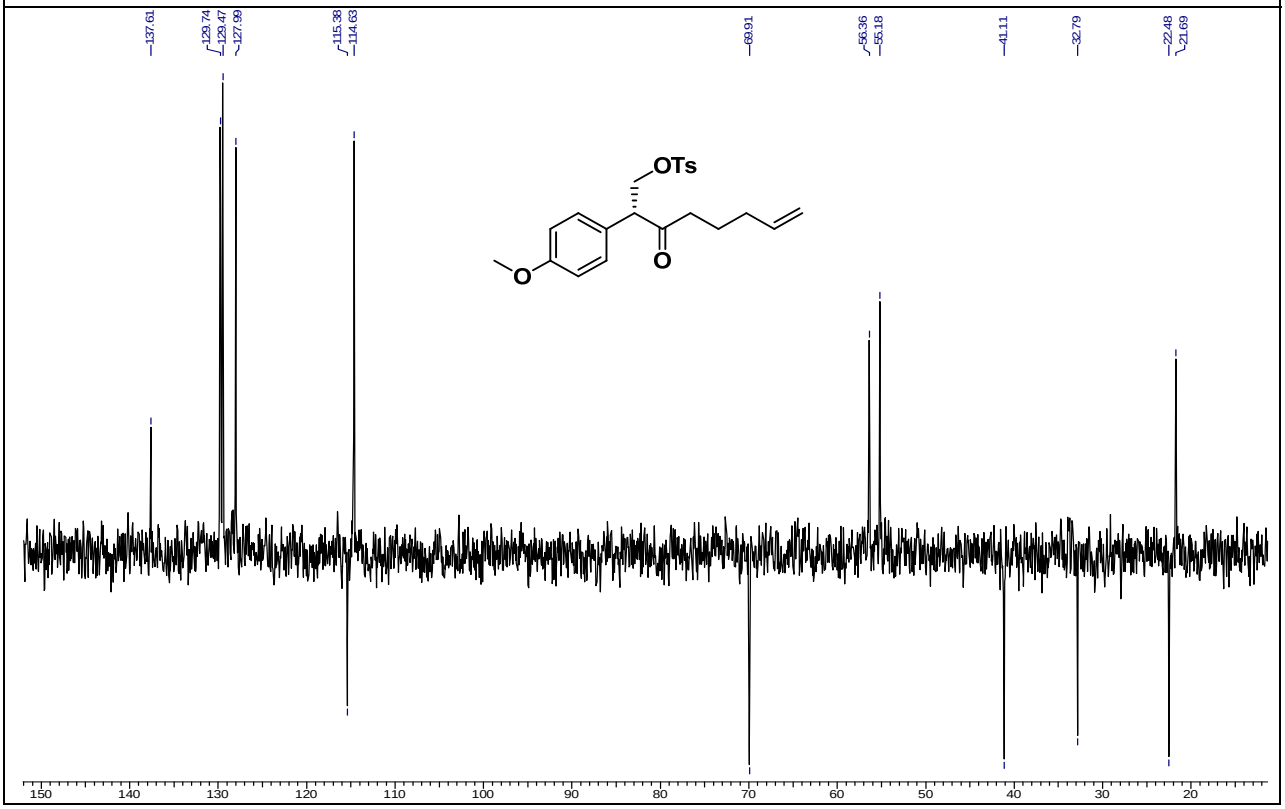
^{1}H NMR spectrum ofcompound **93** ($CDCl_3$+CCl_4, 200 MHz)



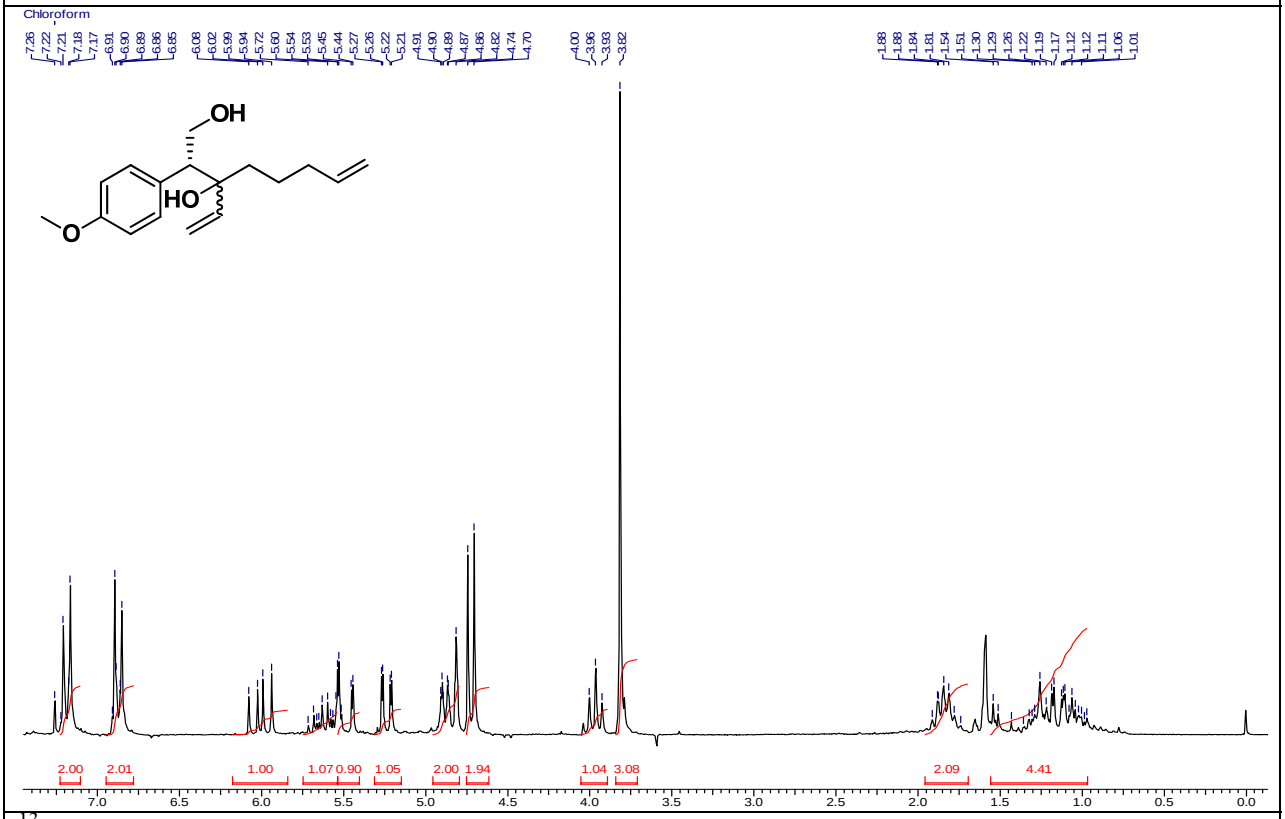
^{13}C NMR spectrum ofcompound **93** ($CDCl_3$+CCl_4, 50 MHz)



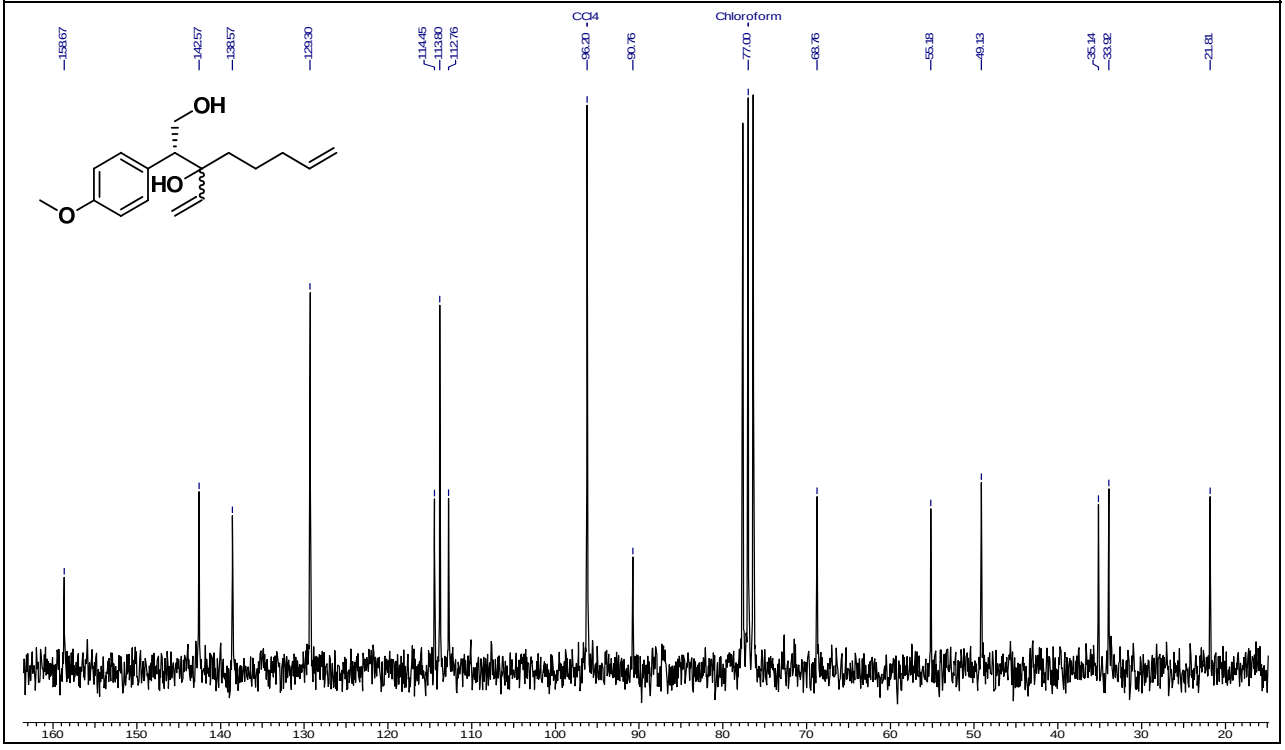
DEPT spectrum of compound **93** ($CDCl_3$+CCl_4, 50 MHz)



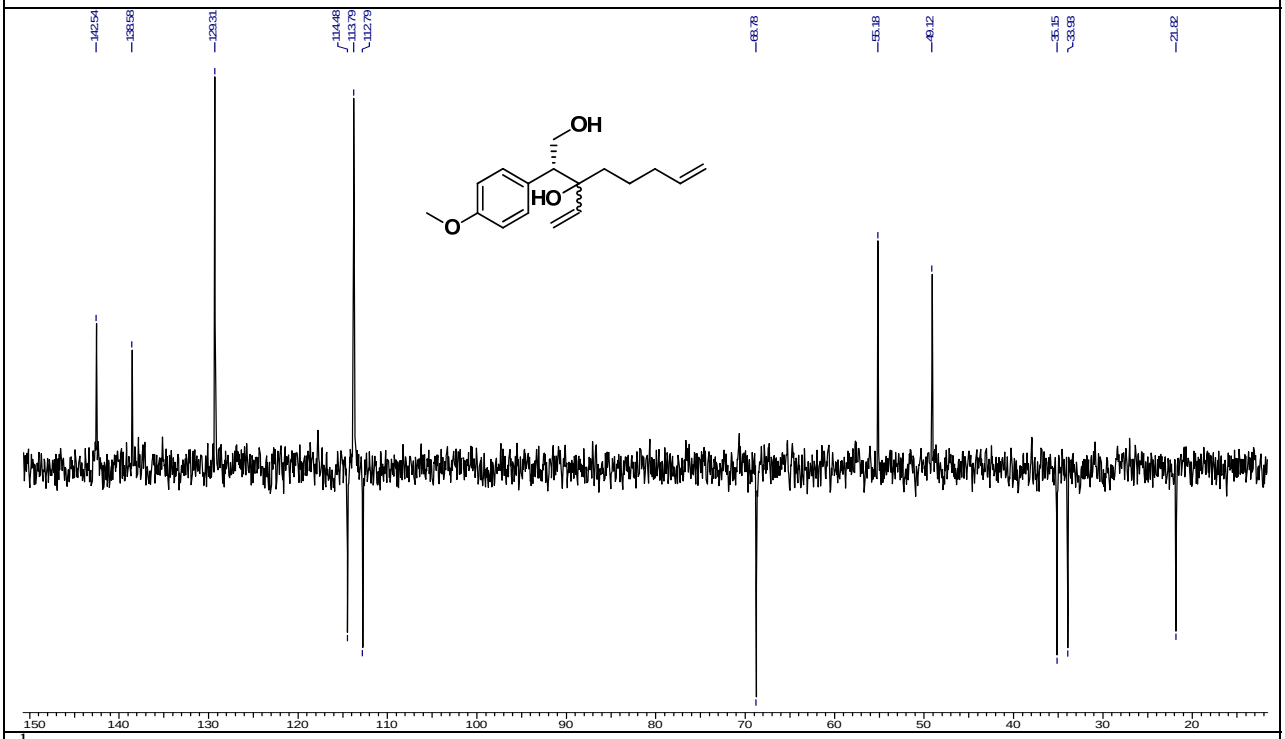
^{1}H NMR spectrum ofcompound 9**4** ($CDCl_3$+CCl_4, 200 MHz)



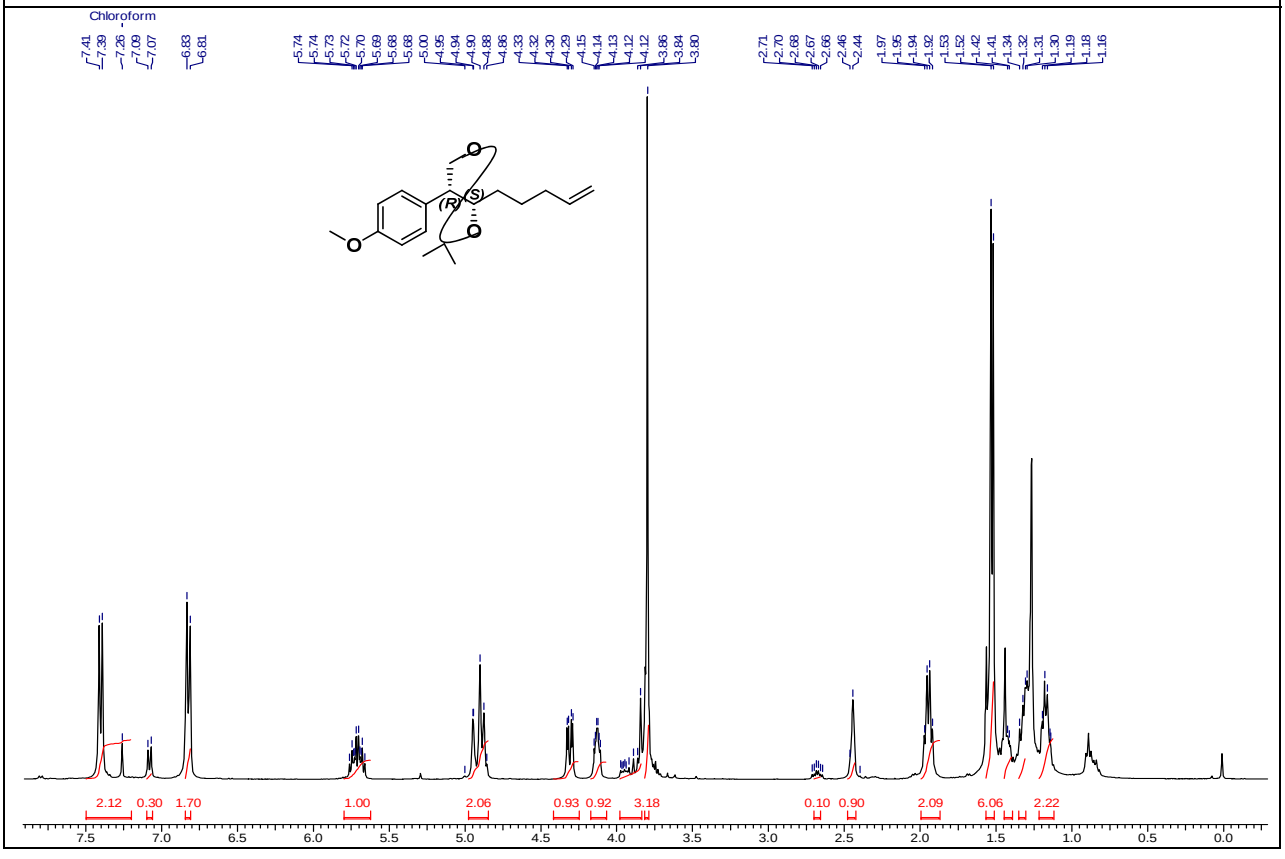
^{13}C NMR spectrum ofcompound **94** ($CDCl_3$+CCl_4, 50 MHz)



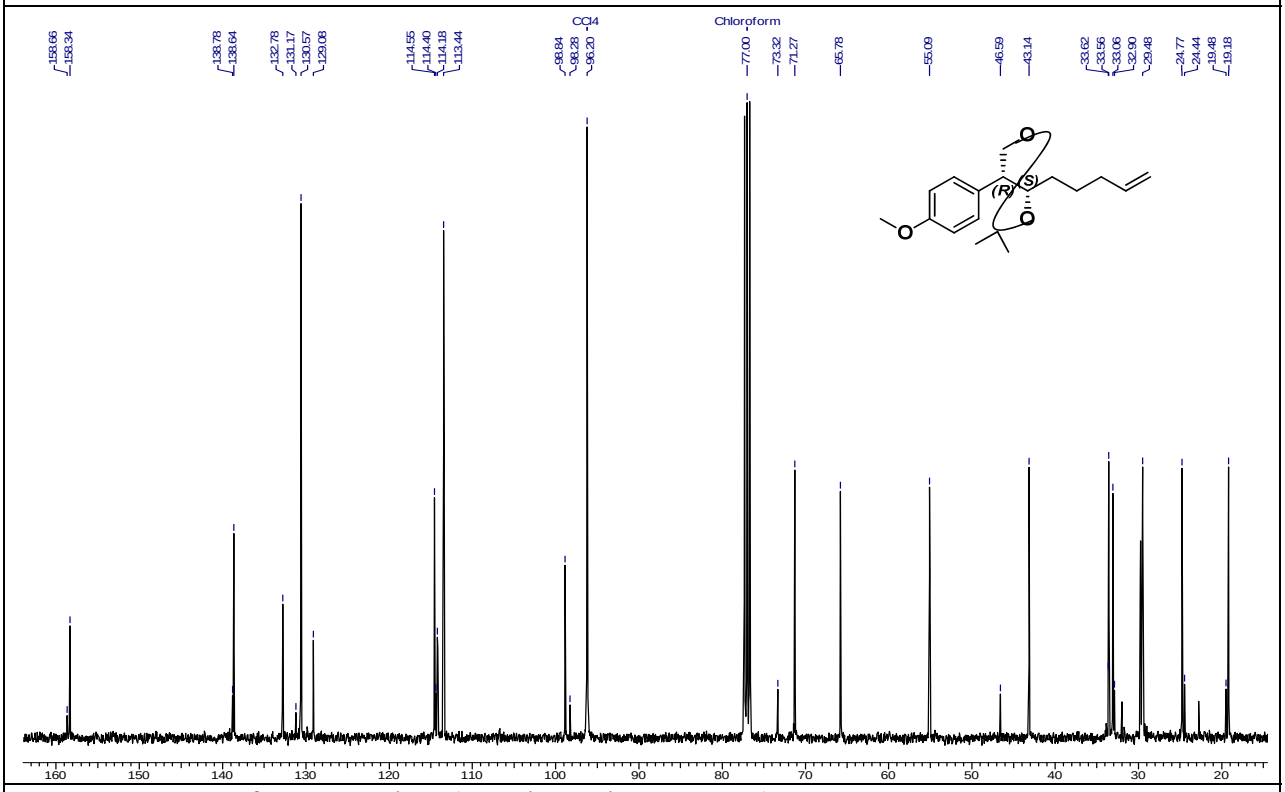
DEPT spectrum of compound **94** ($CDCl_3$+CCl_4, 50 MHz)



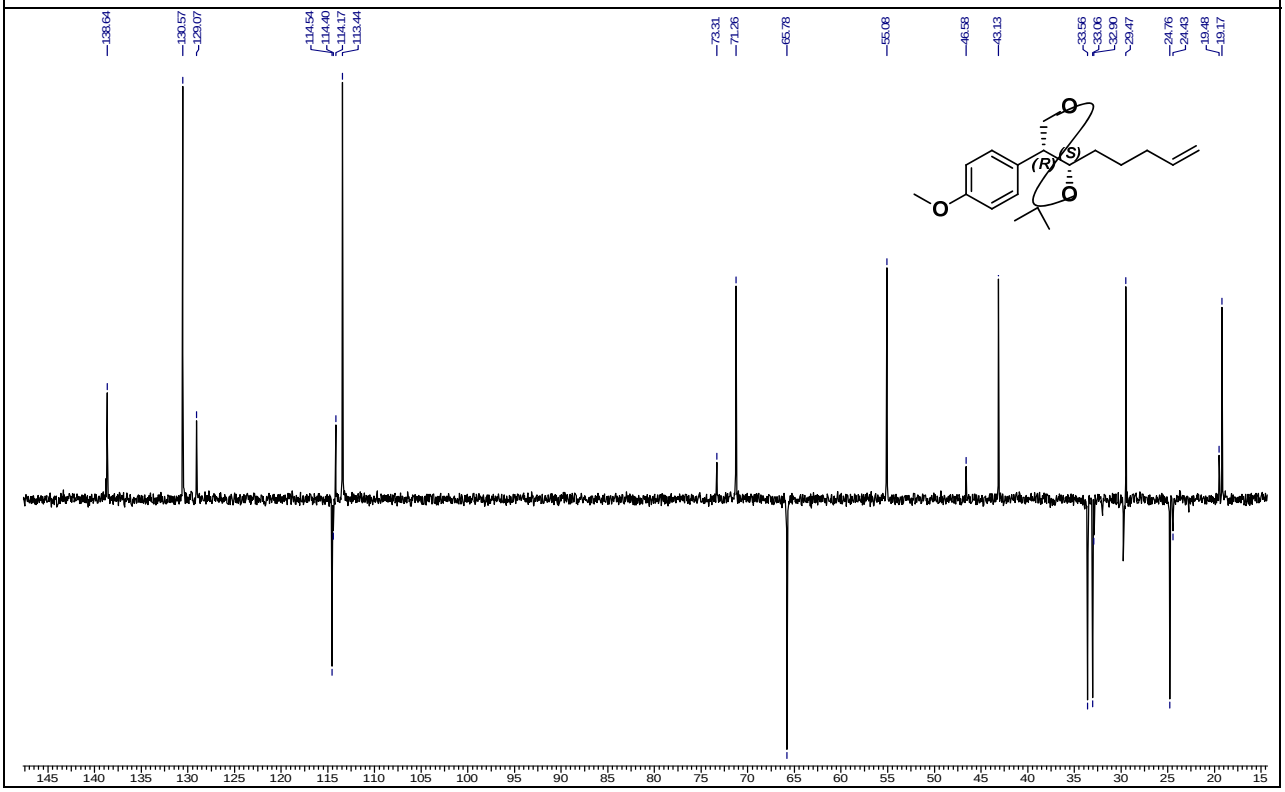
^{1}H NMR spectrum ofcompound **88** ($CDCl_3$+CCl_4, 500 MHz)



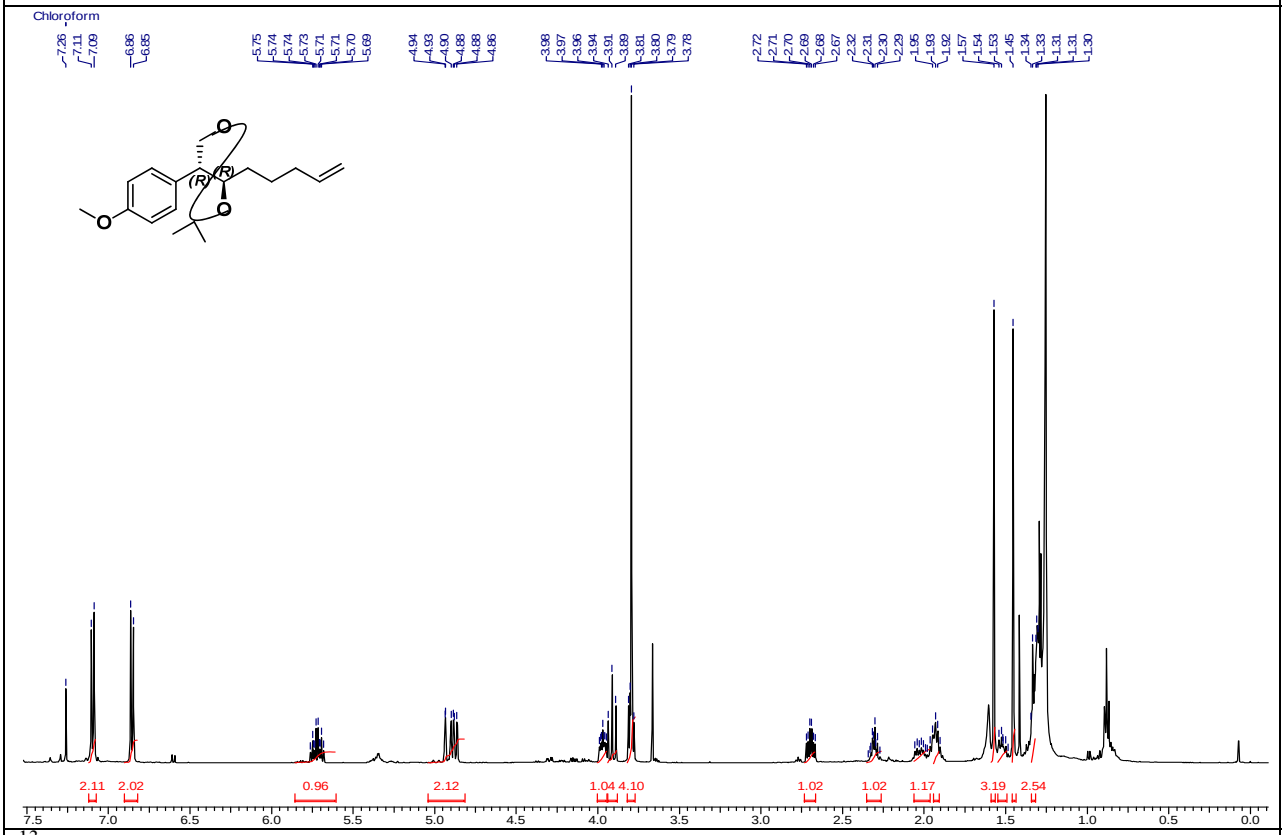
^{13}C NMR spectrum ofcompound **88** ($CDCl_3$+CCl_4, 125 MHz)



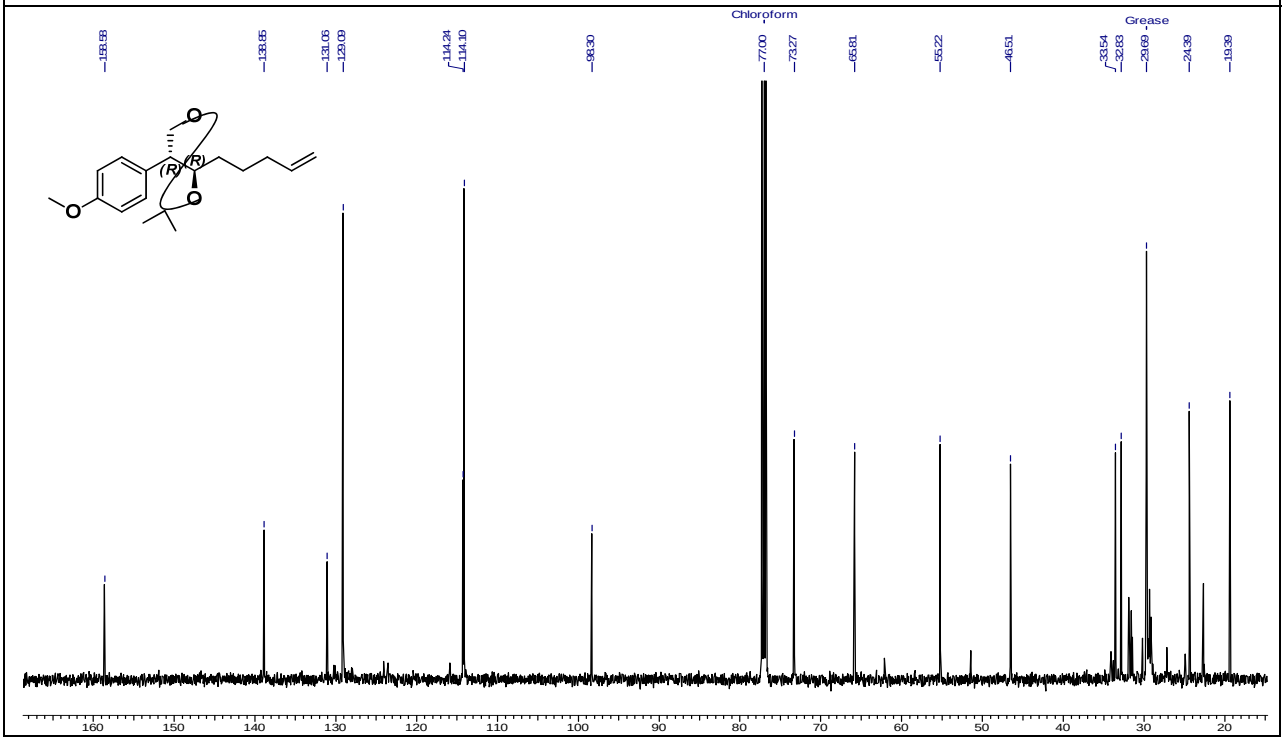
DEPT spectrum of compound **88** ($CDCl_3$+CCl_4, 125 MHz)



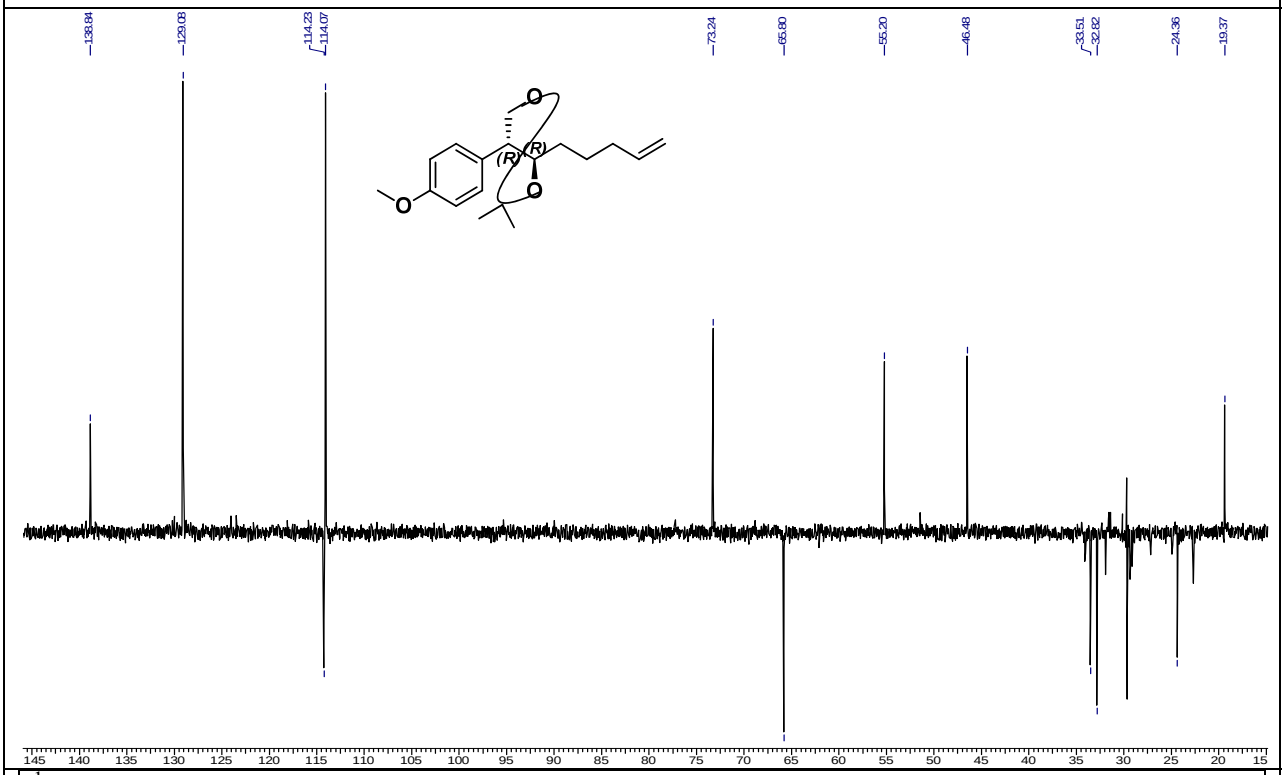
^{1}H NMR spectrum ofcompound **89** ($CDCl_3$, 500 MHz)



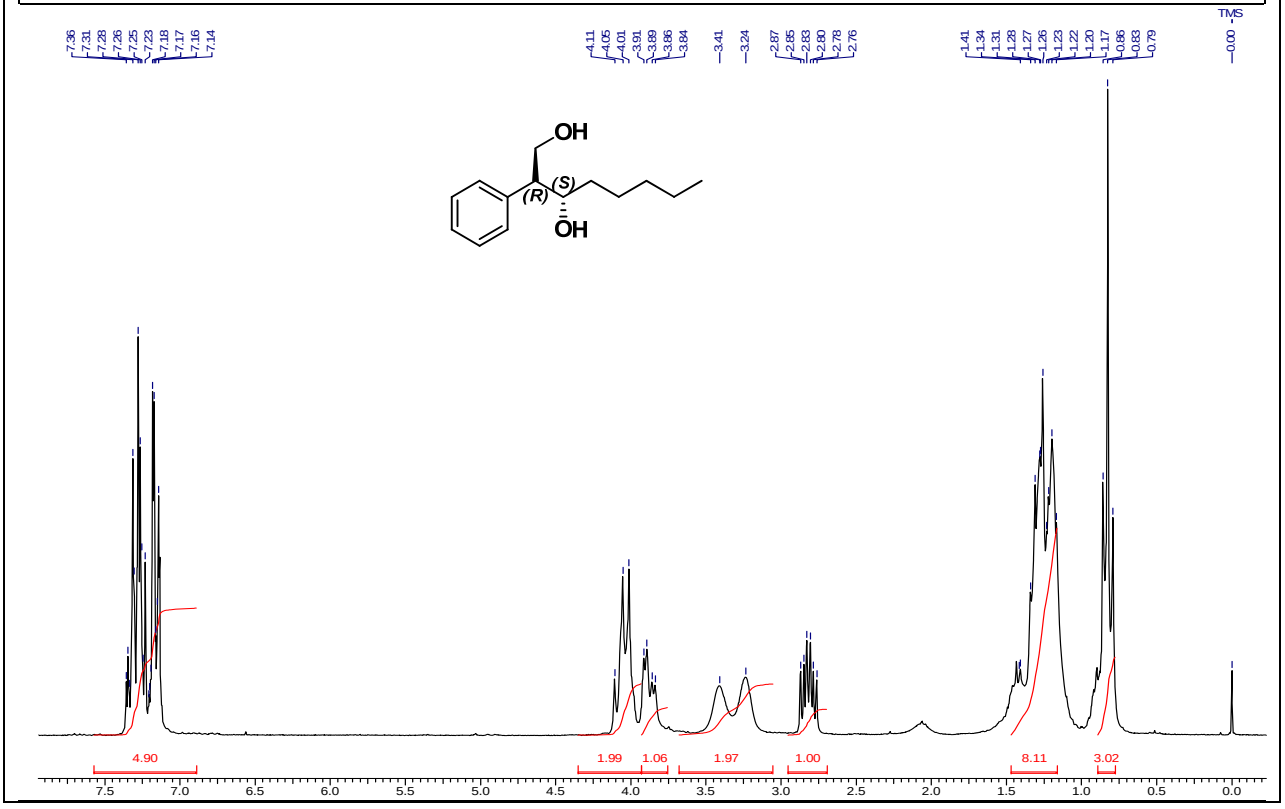
^{13}C NMR spectrum ofcompound **89** ($CDCl_3$, 125 MHz)



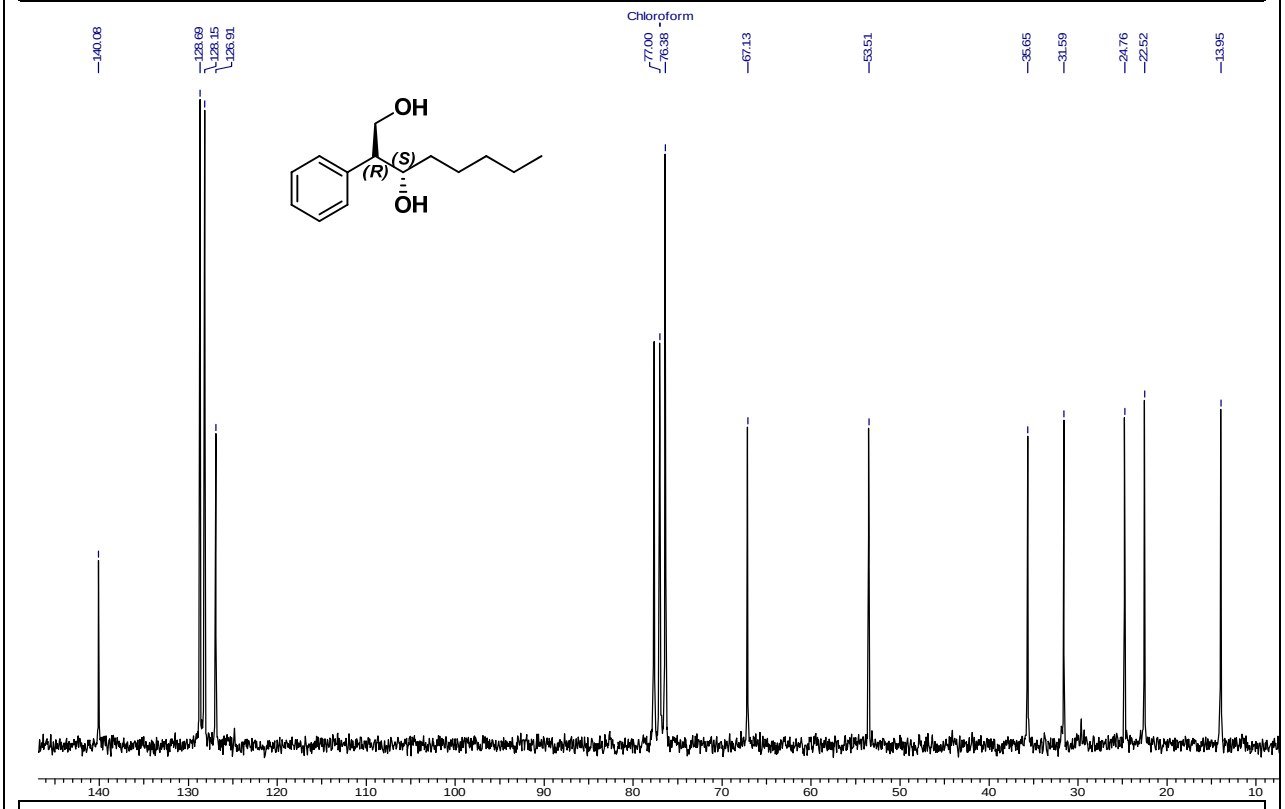
DEPT specrum of compound **89** ($CDCl_3$, 125 MHz)



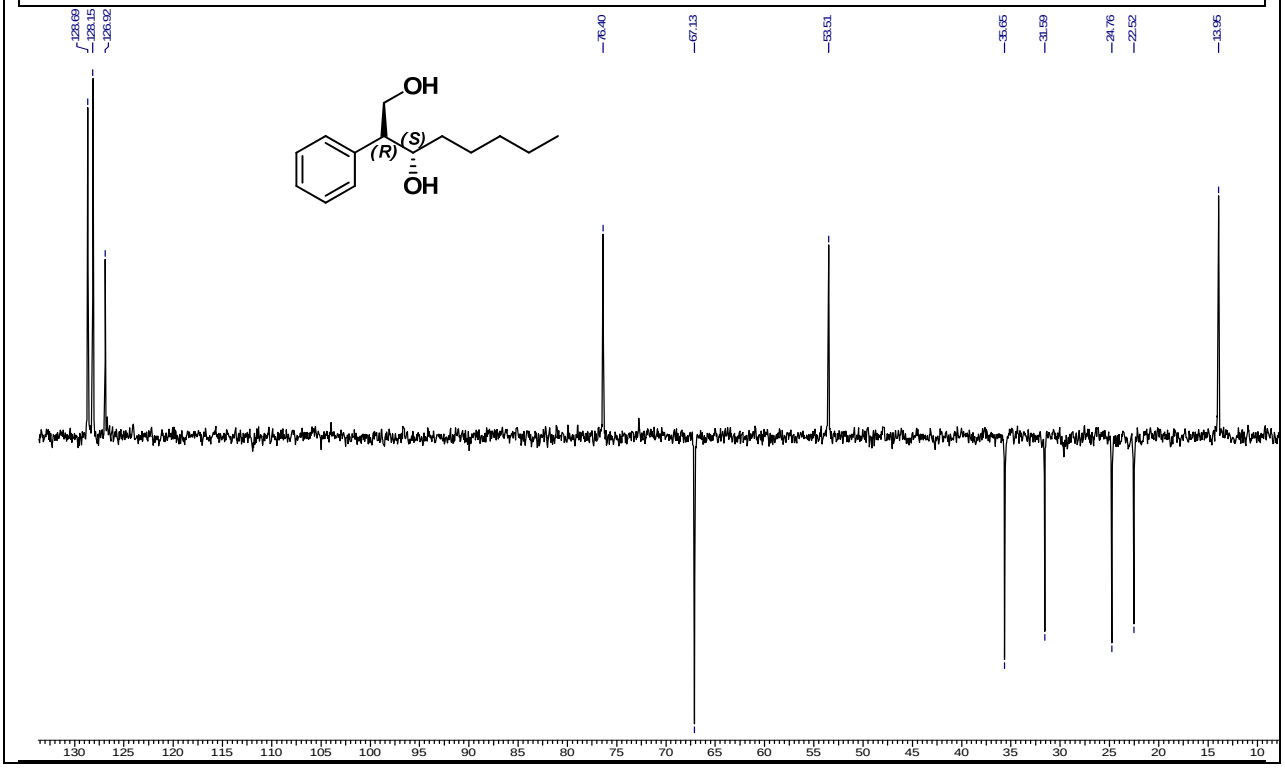
^1H NMR spectrum ofcompound **86** ($CDCl_3$, 200 MHz)



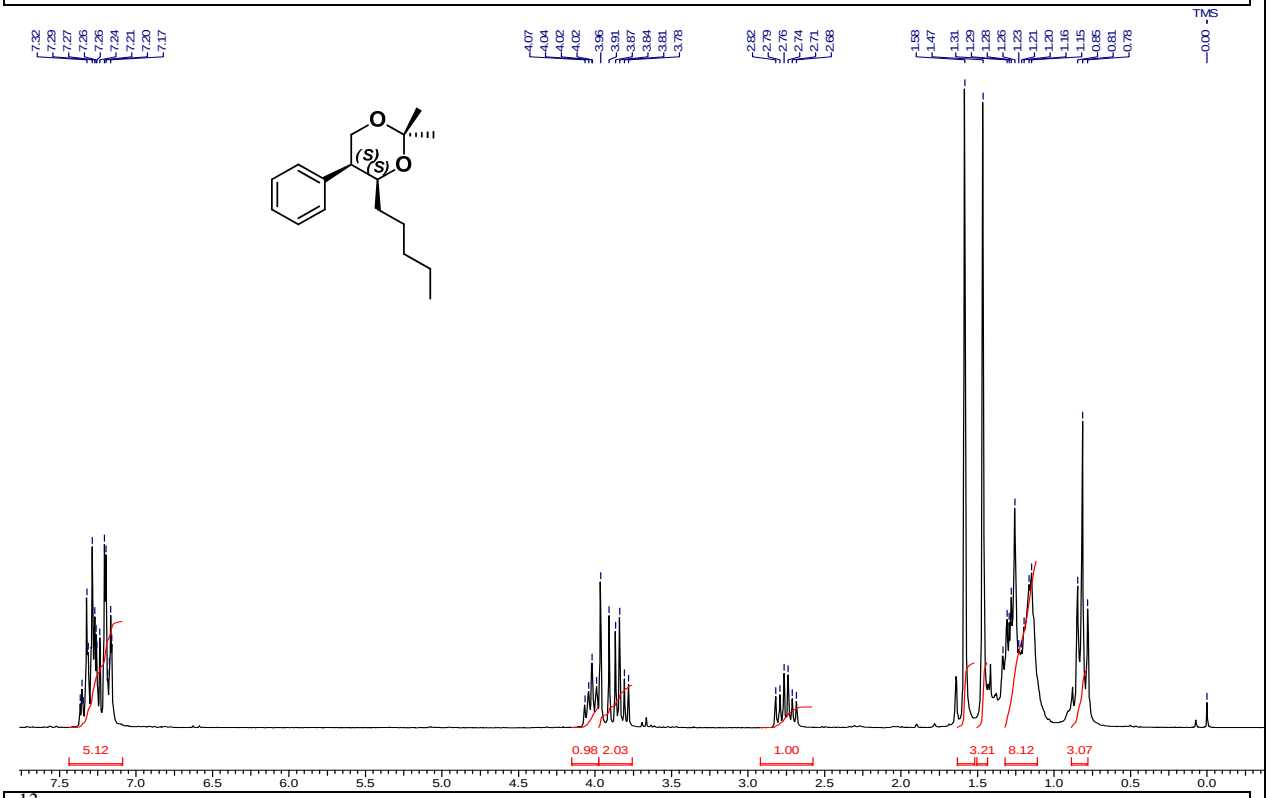
^{13}CNMR spectrum ofcompound **86** ($CDCl_3$, 50 MHz)



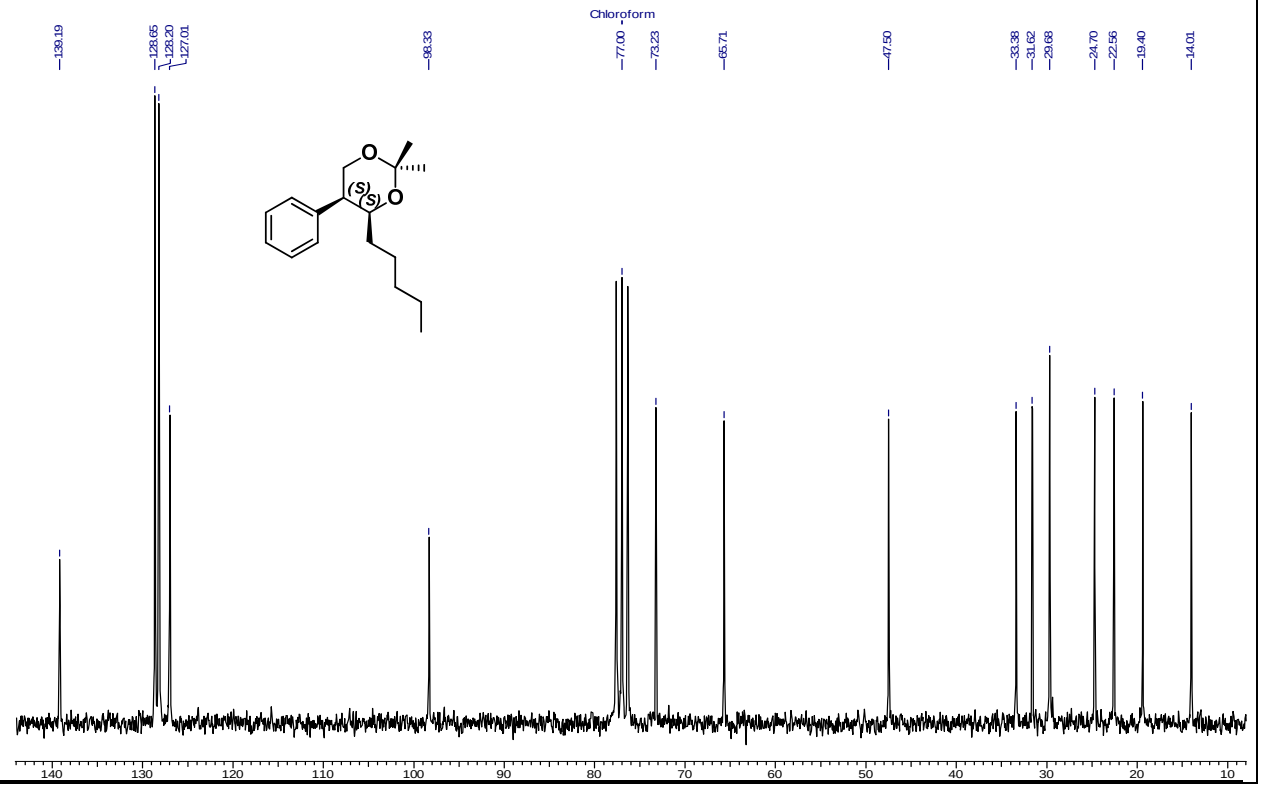
DEPT spectrum of compound **86** ($CDCl_3$, 50 MHz)



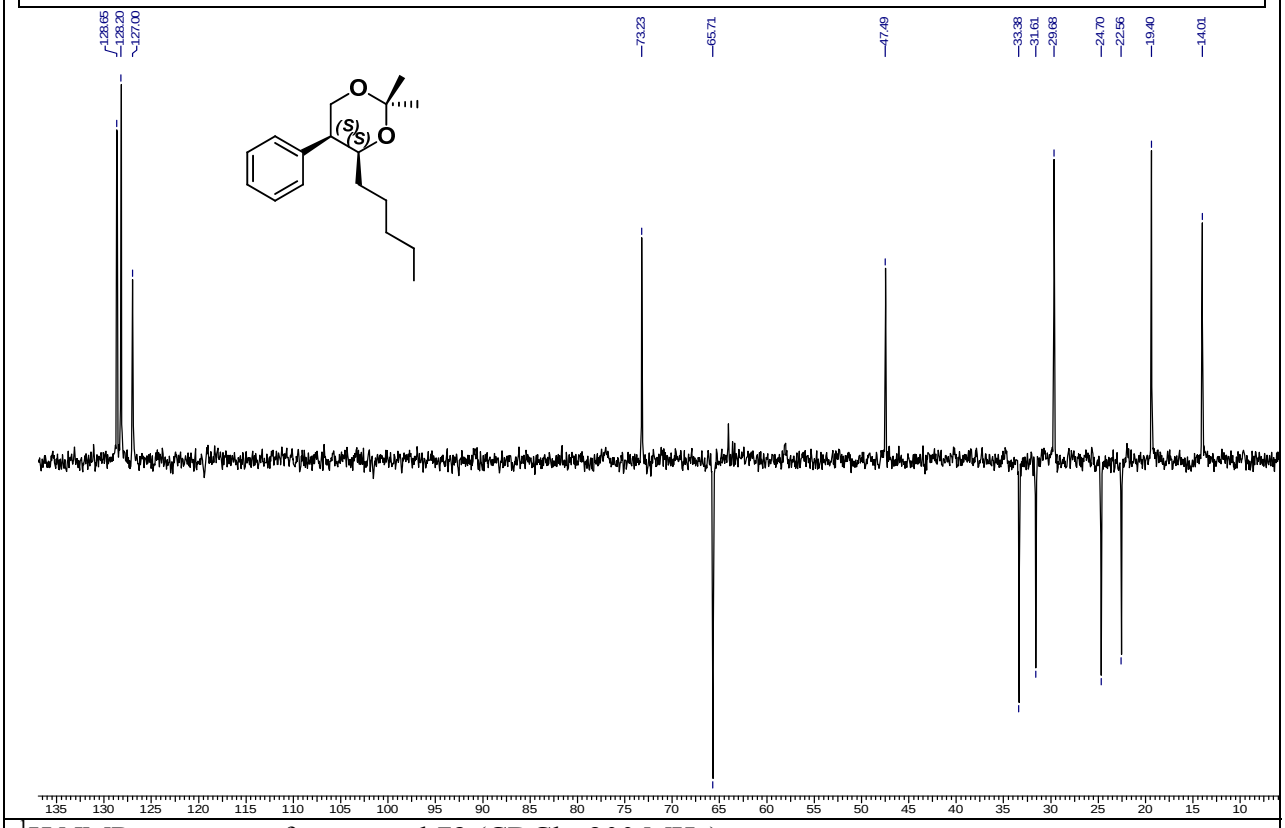
^{1}H NMR spectrum ofcompound **87** ($CDCl_3$, 200 MHz)



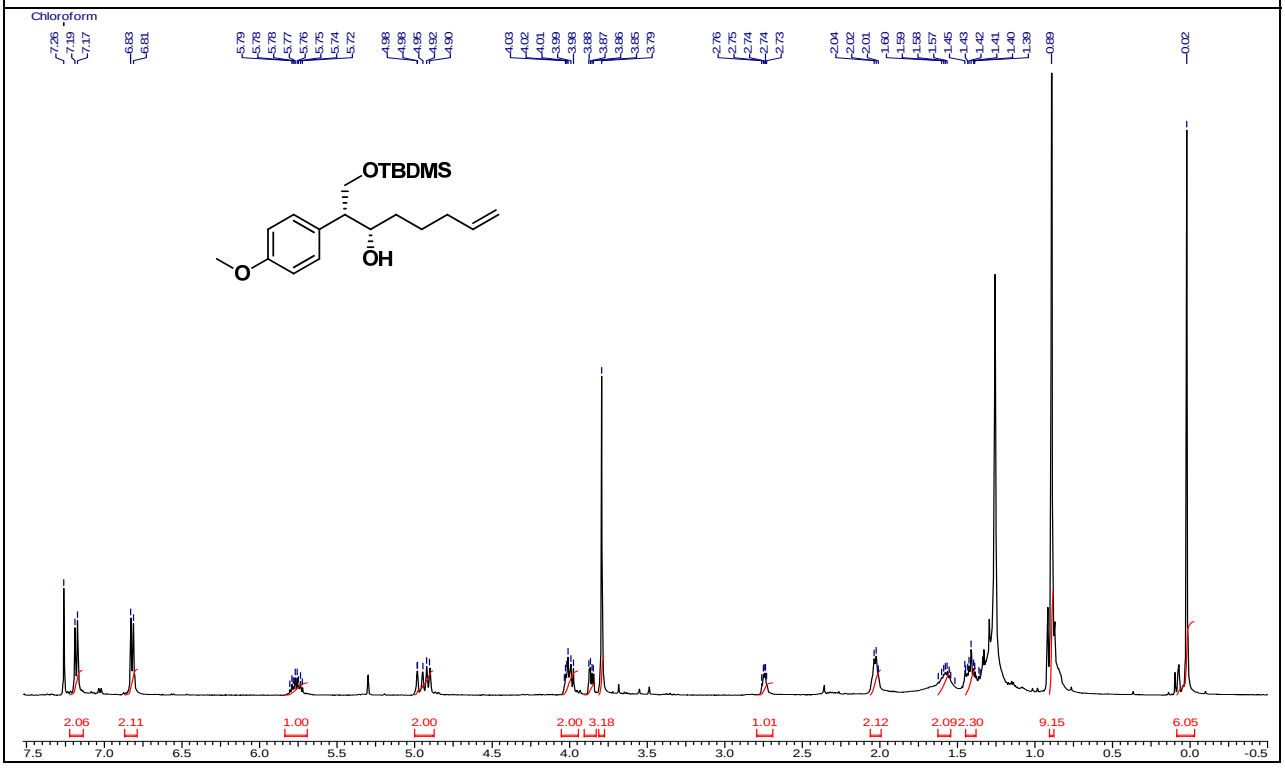
^{13}CNMR spectrum ofcompound **87** ($CDCl_3$, 50 MHz)



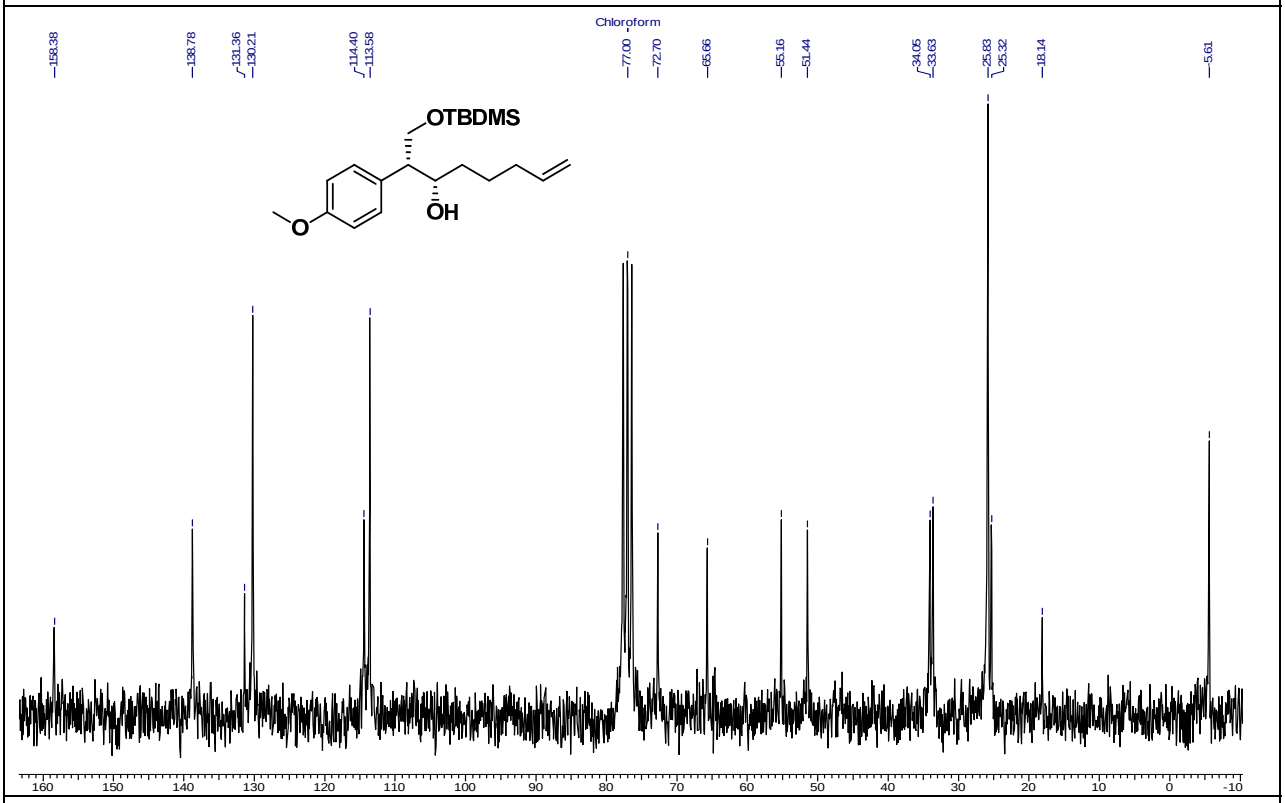
DEPT spectrum of compound **87** ($CDCl_3$, 50 MHz)



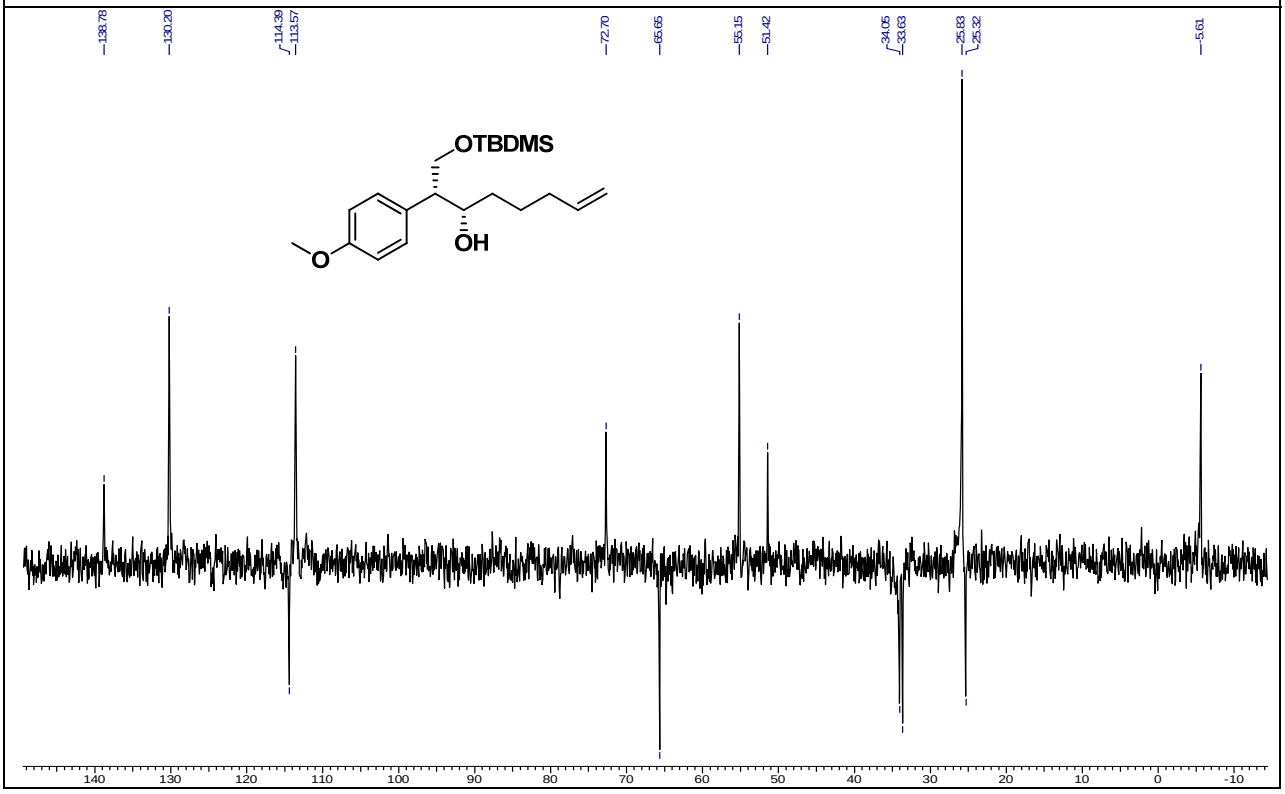
^{1}H NMR spectrum ofcompound **73** ($CDCl_3$, 200 MHz)



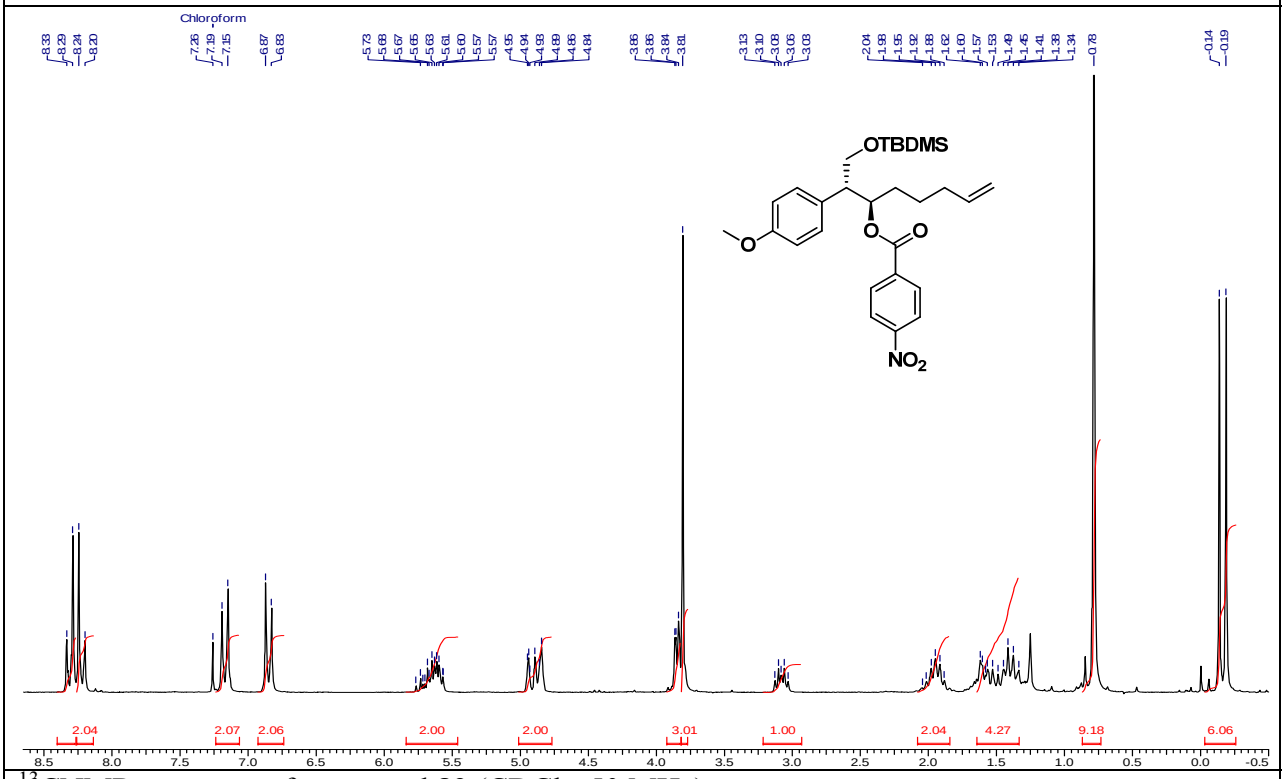
^{13}CNMR spectrum ofcompound **73** ($CDCl_3$, 50 MHz)



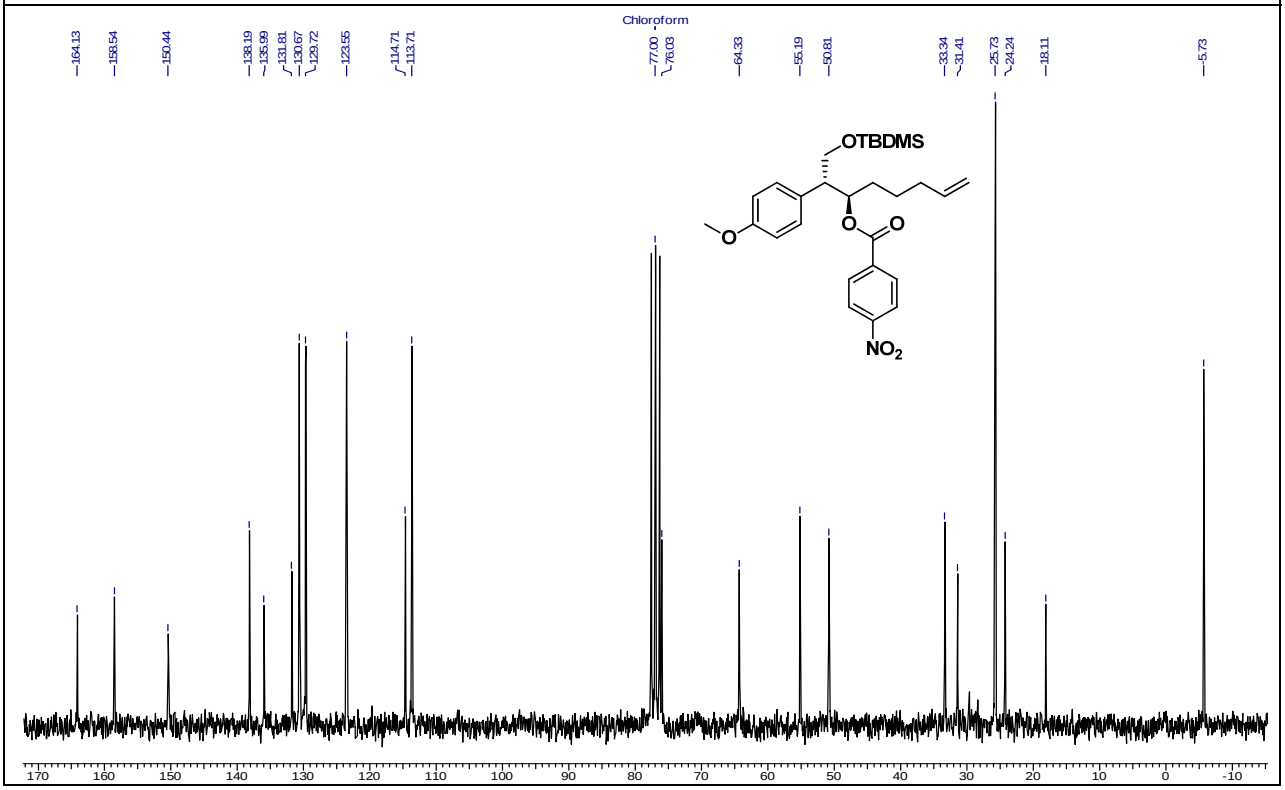
DEPT specrum of compound **73** ($CDCl_3$, 50 MHz)



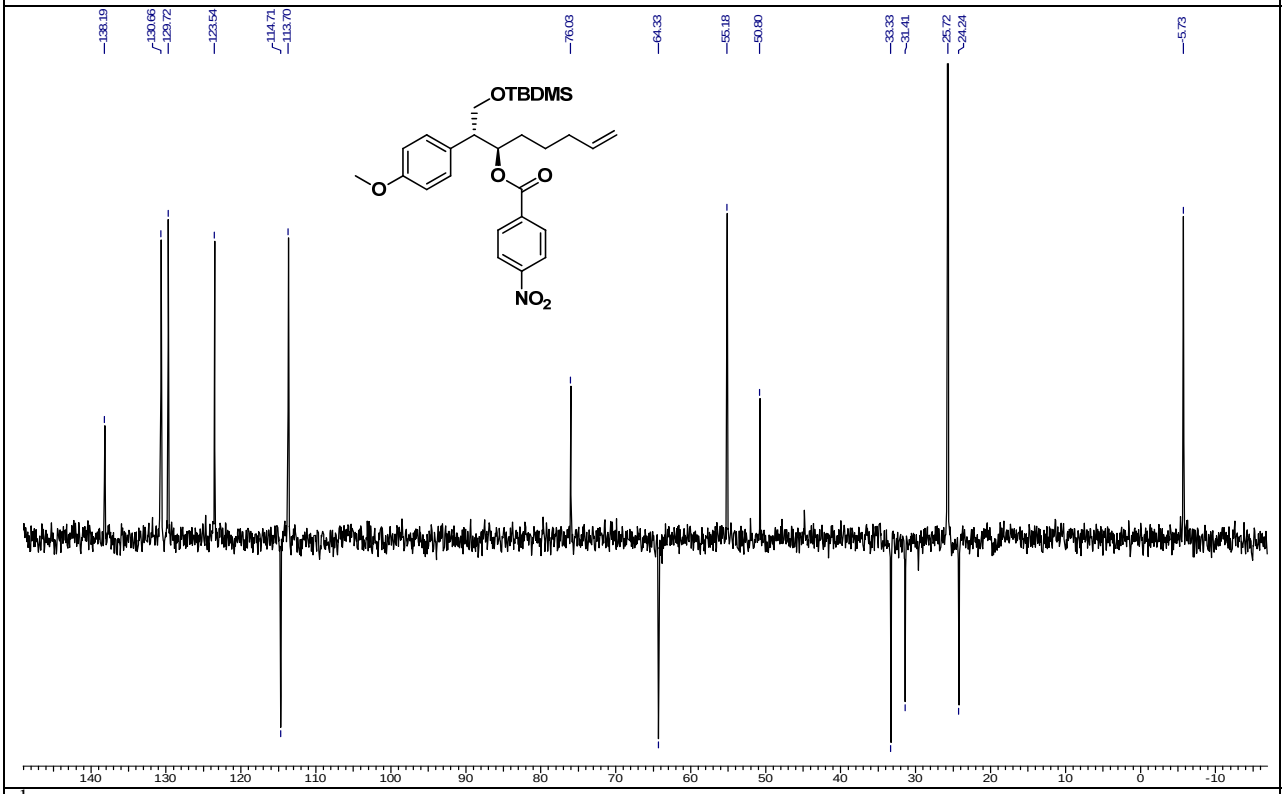
^{1}H NMR spectrum ofcompound **82** ($CDCl_3$, 200 MHz)



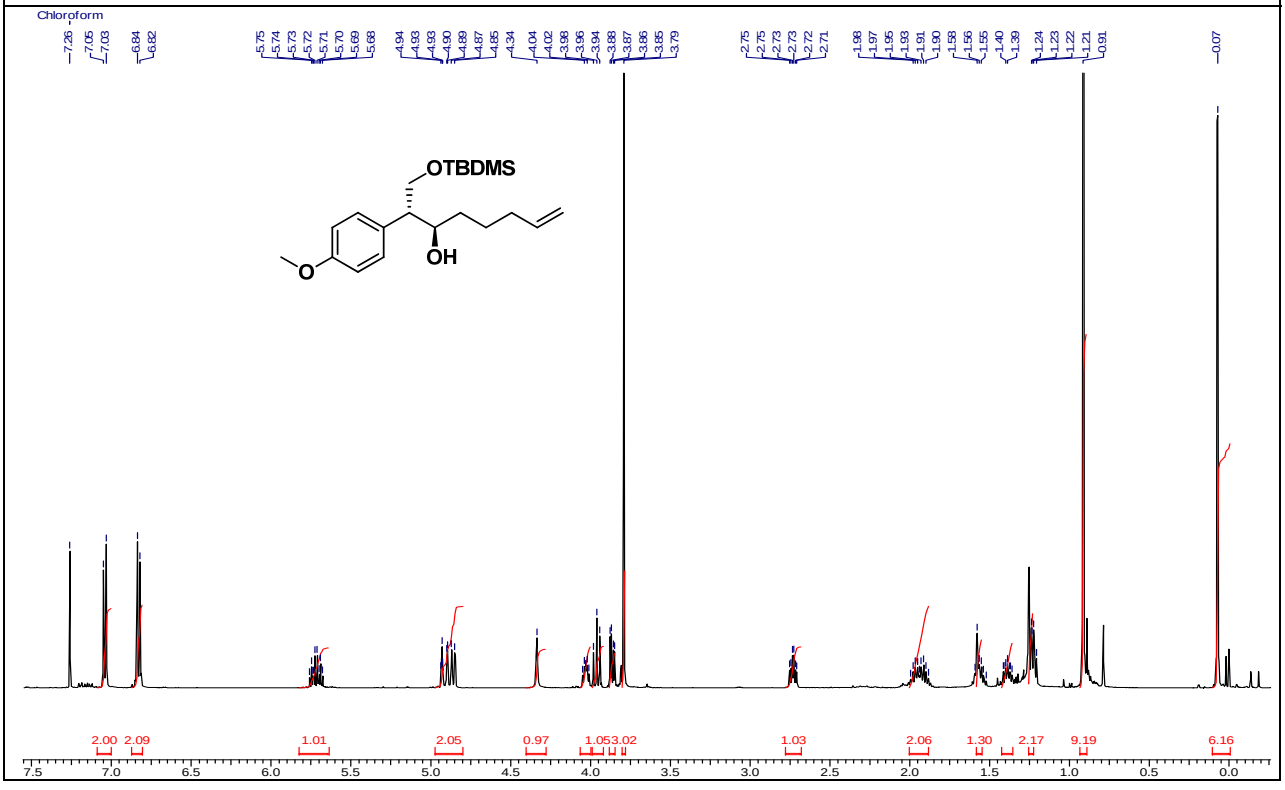
^{13}CNMR spectrum ofcompound **82** ($CDCl_3$, 50 MHz)



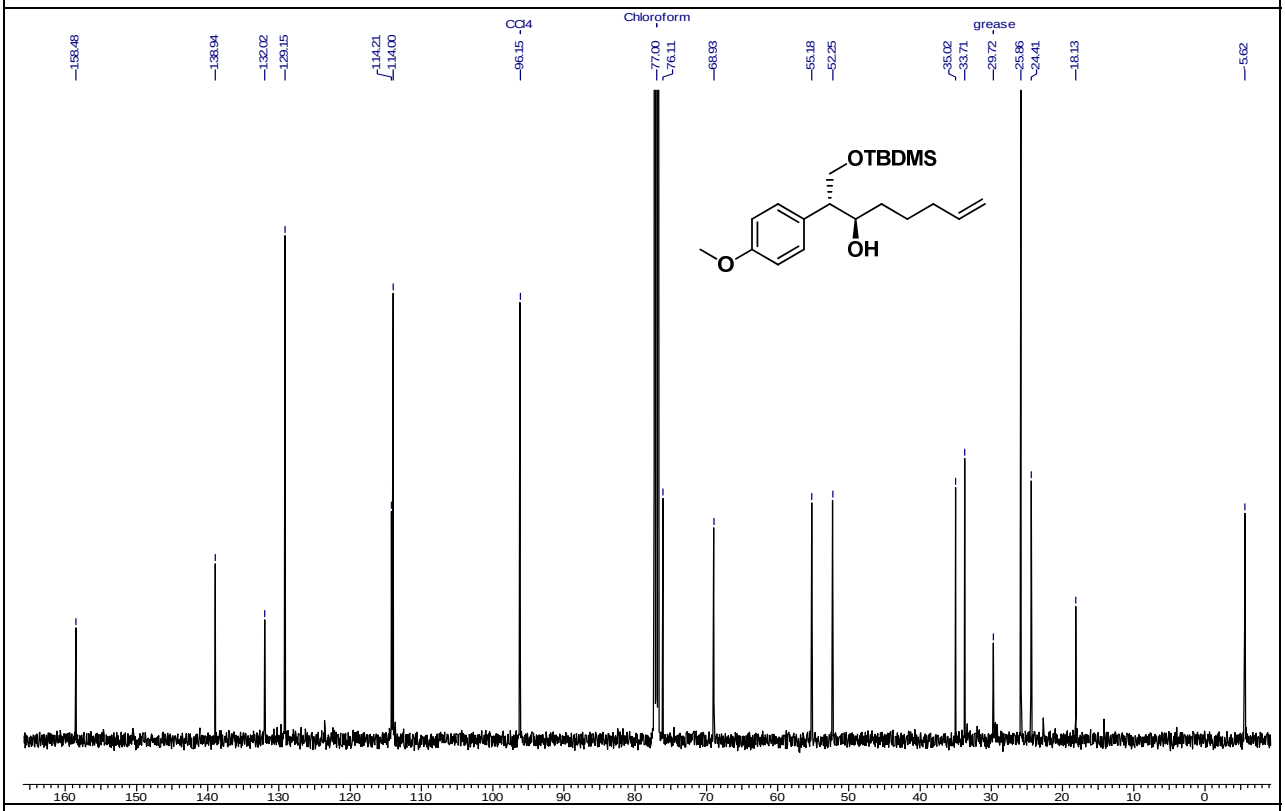
DEPT spectrum of compound **82** ($CDCl_3$, 50 MHz)



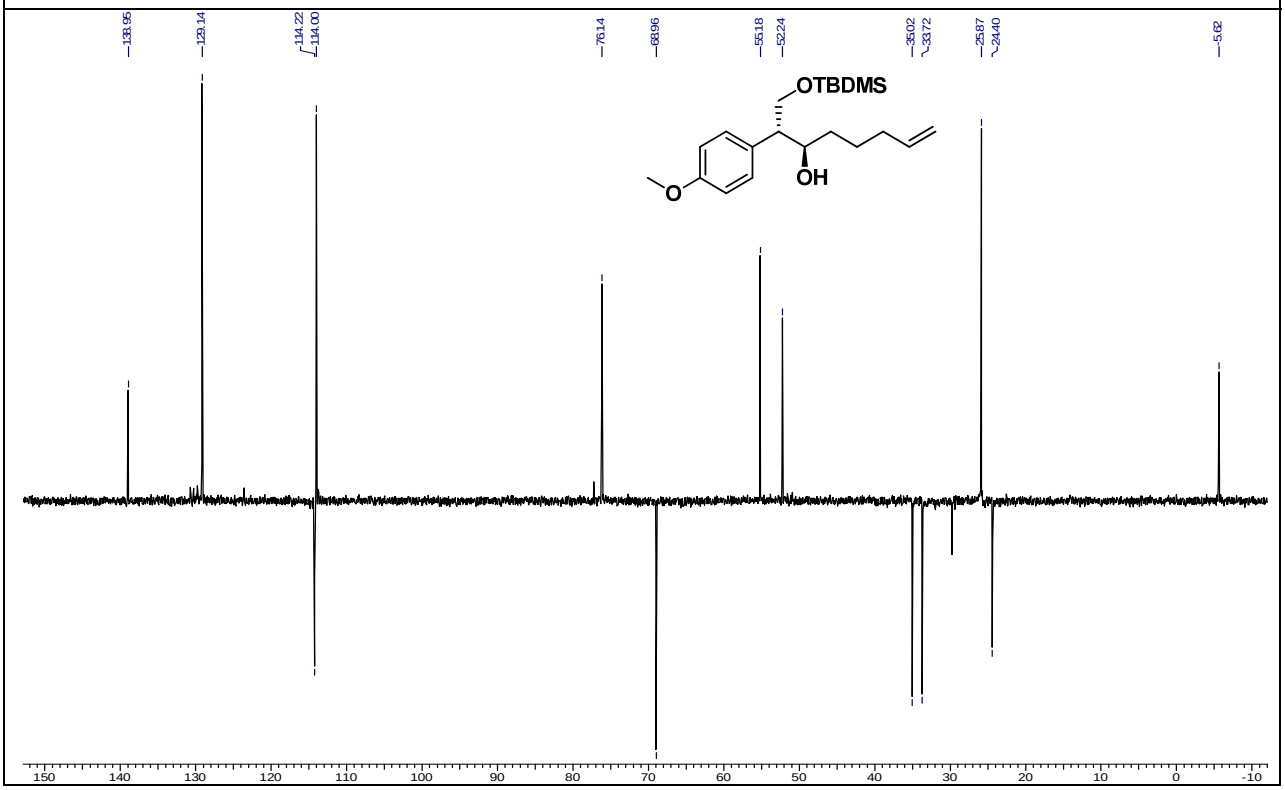
^{1}H NMR spectrum ofcompound **83** ($CDCl_3$+CCl_4, 200 MHz)



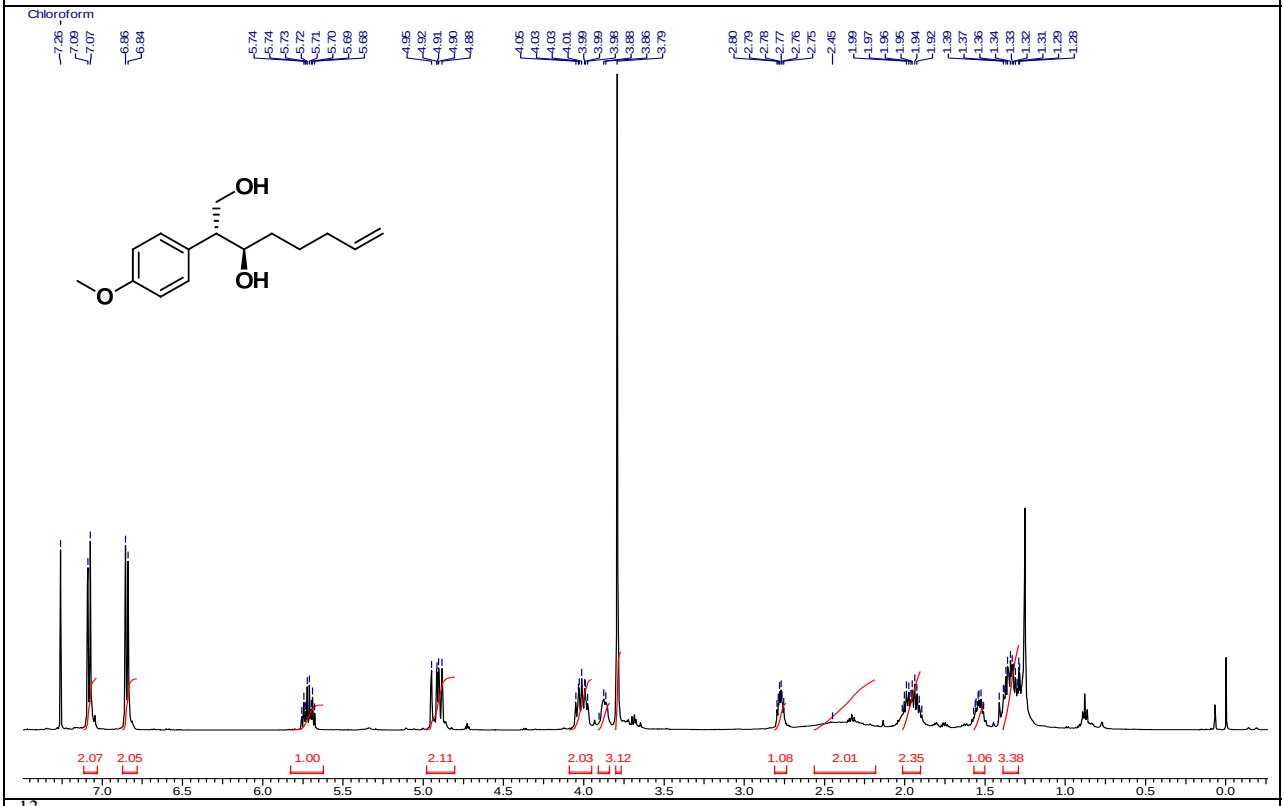
^{13}CNMR spectrum ofcompound **83** ($CDCl_3$+CCl_4, 50 MHz)



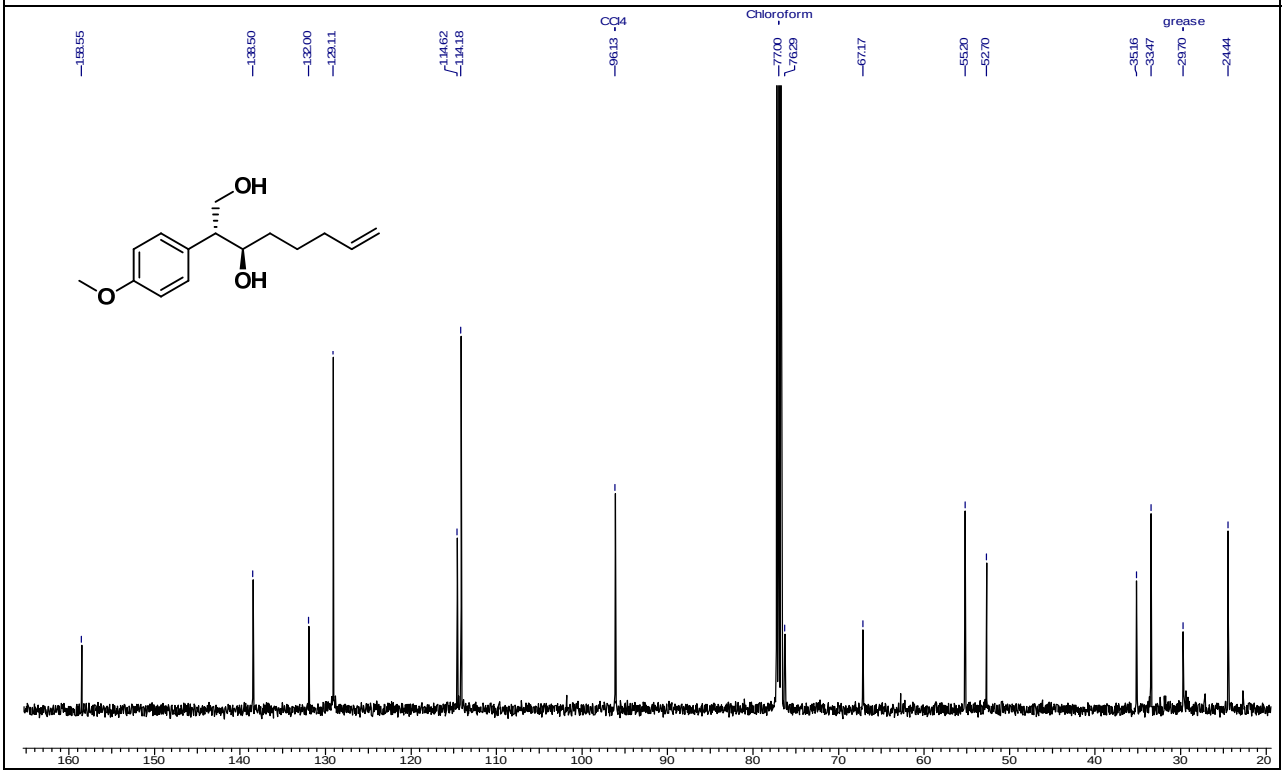
DEPT spectrum of compound **83** ($CDCl_3$+CCl_4, 50 MHz)



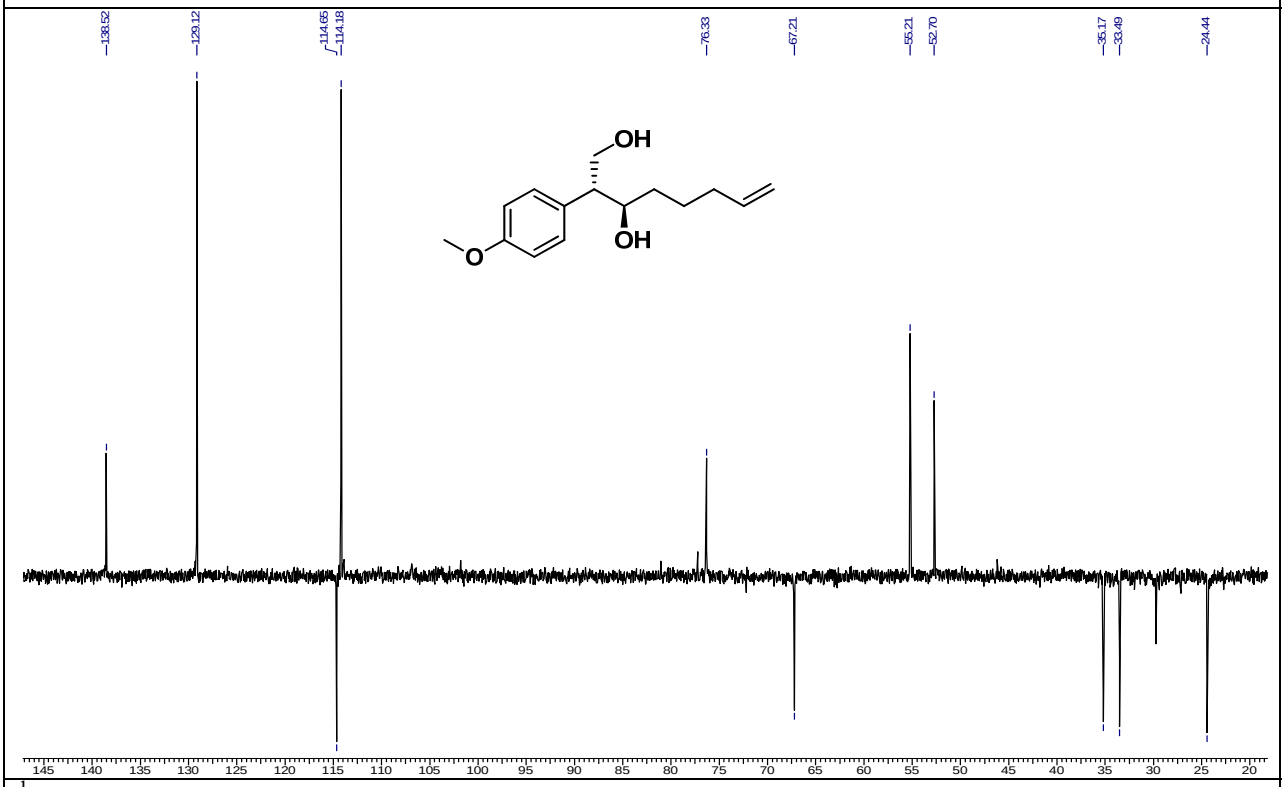
^{1}H NMR spectrum ofcompound **84** ($CDCl_3$+CCl_4, 200 MHz)



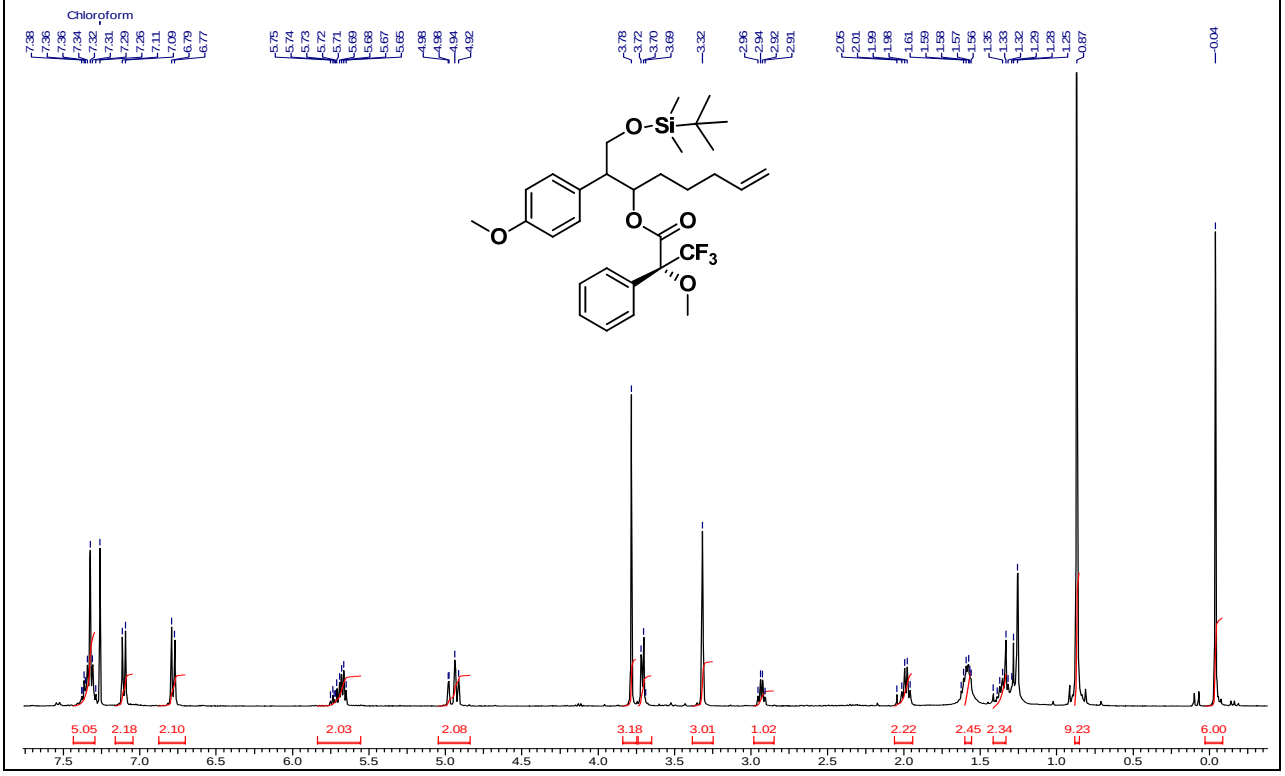
^{13}CNMR spectrum ofcompound **84** ($CDCl_3$+CCl_4, 50 MHz)



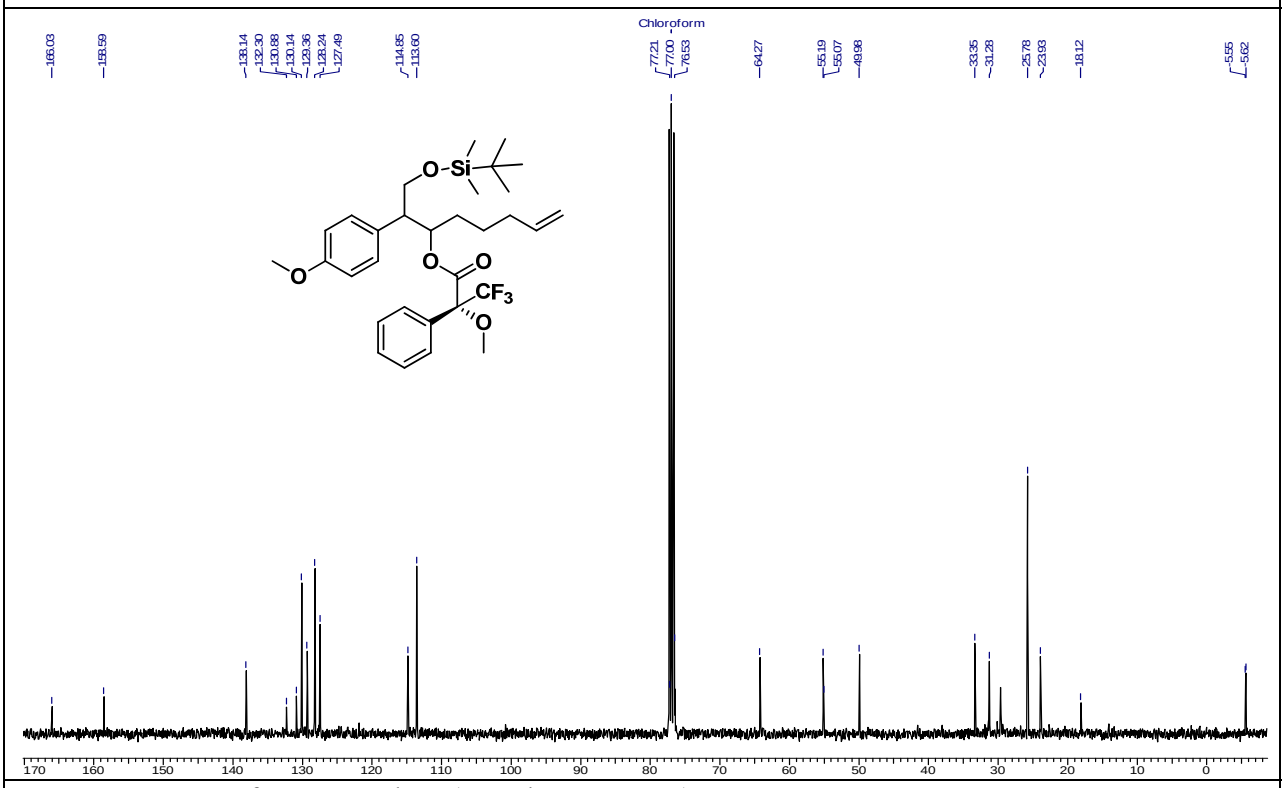
DEPT spectrum of compound **84** ($CDCl_3$+CCl_4, 50 MHz)



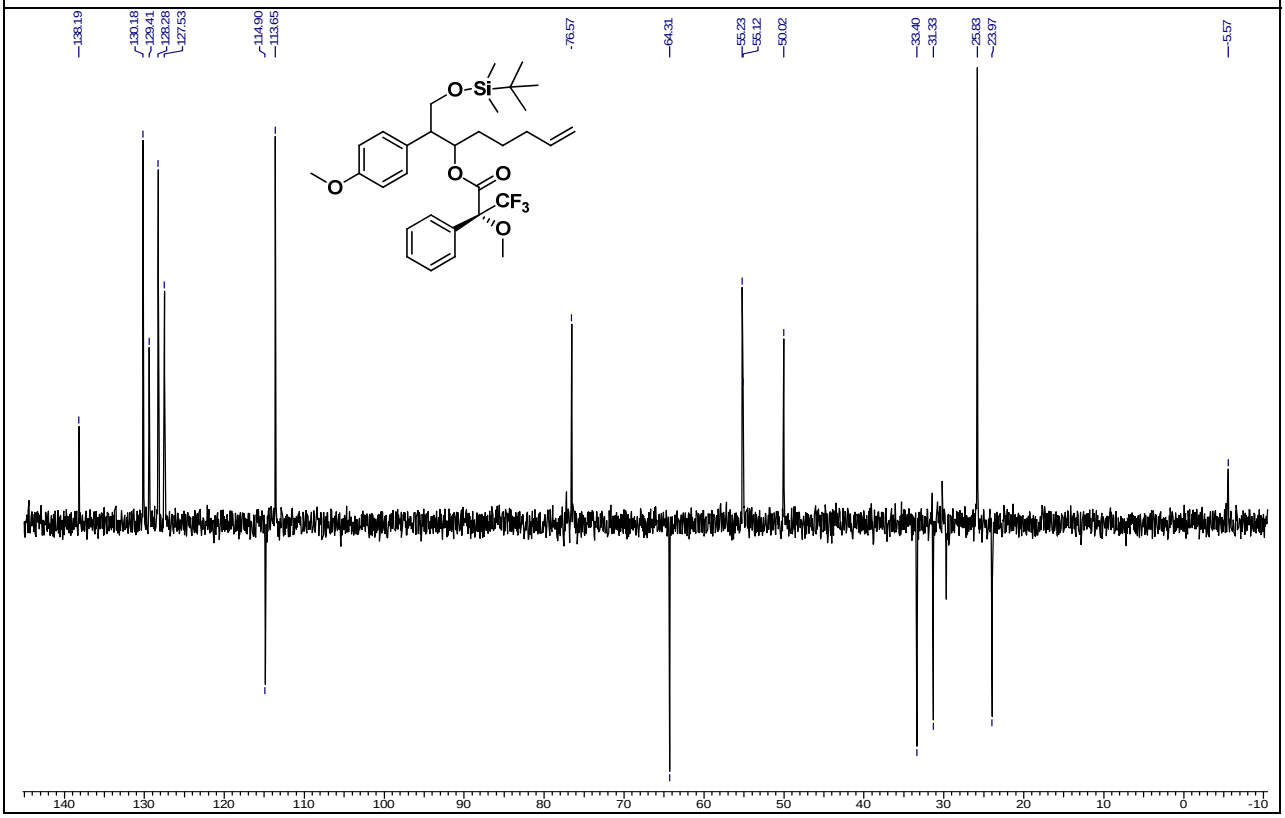
^{1}H NMR spectrum ofcompound **88** ($CDCl_3$, 500 MHz)



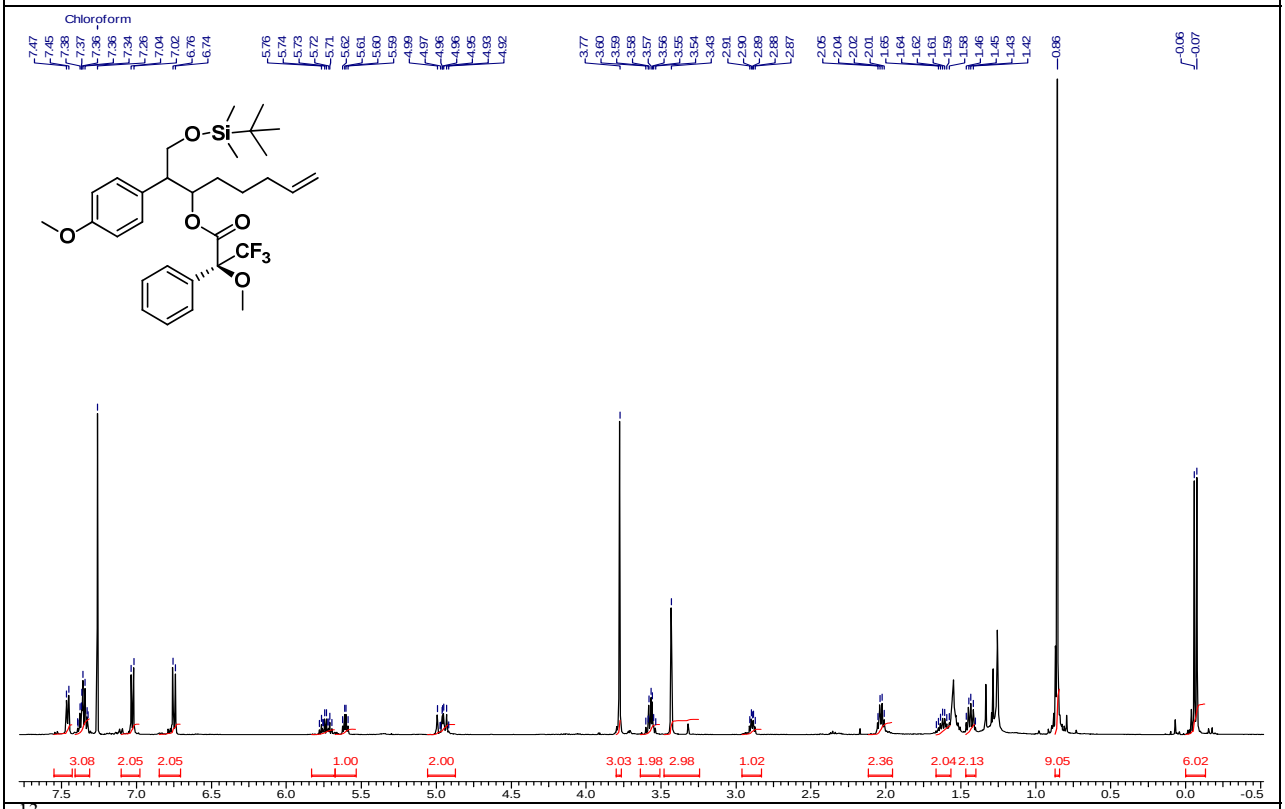
^{13}CNMR spectrum ofcompound **88** ($CDCl_3$, 125 MHz)



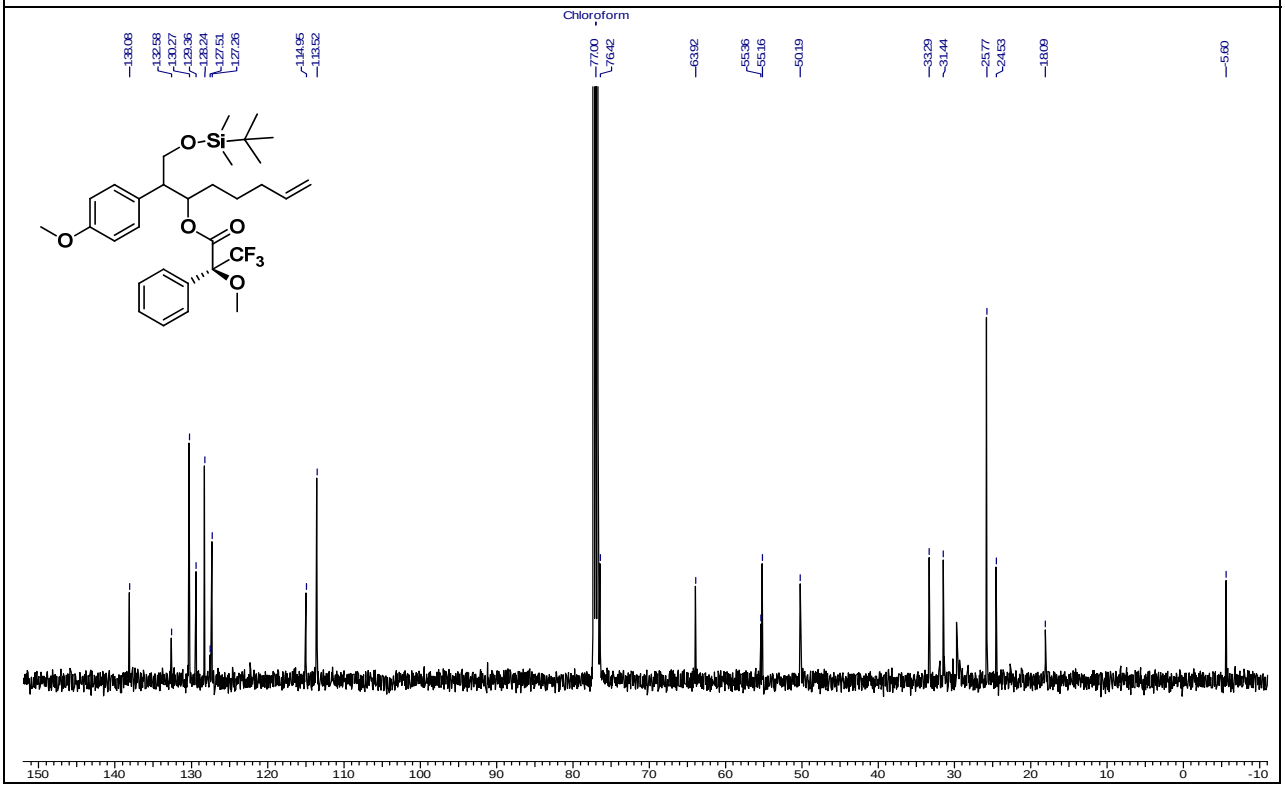
DEPT spectrum of compound **88** ($CDCl_3$, 125 MHz)



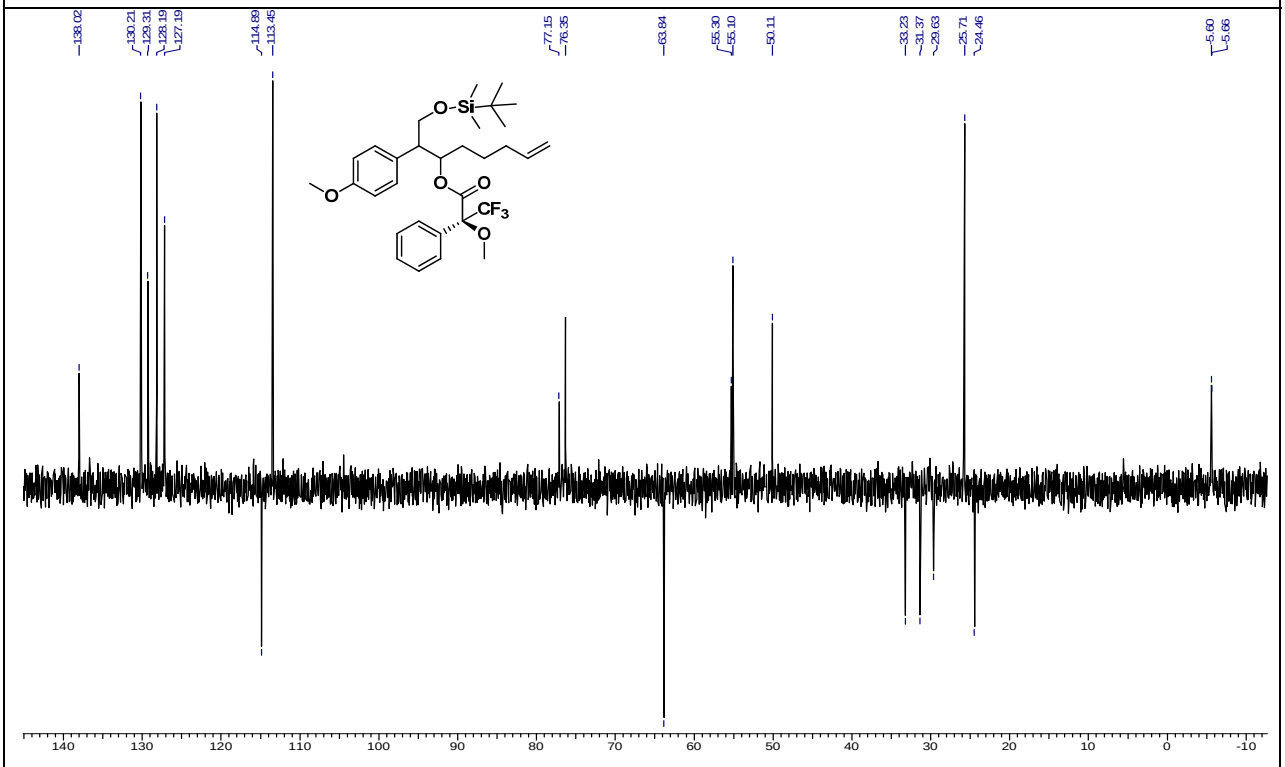
^{1}H NMR spectrum ofcompound **89** ($CDCl_3$, 500 MHz)



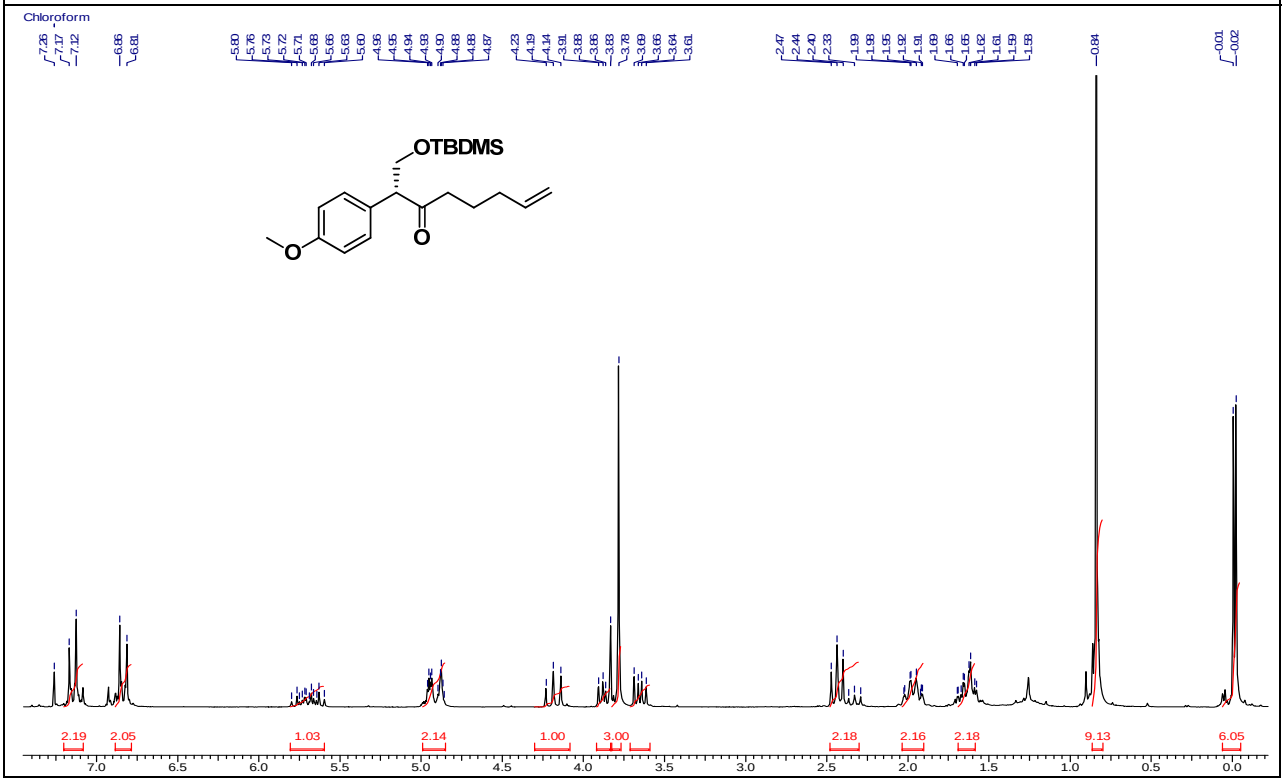
^{13}CNMR spectrum ofcompound **89** ($CDCl_3$, 125 MHz)



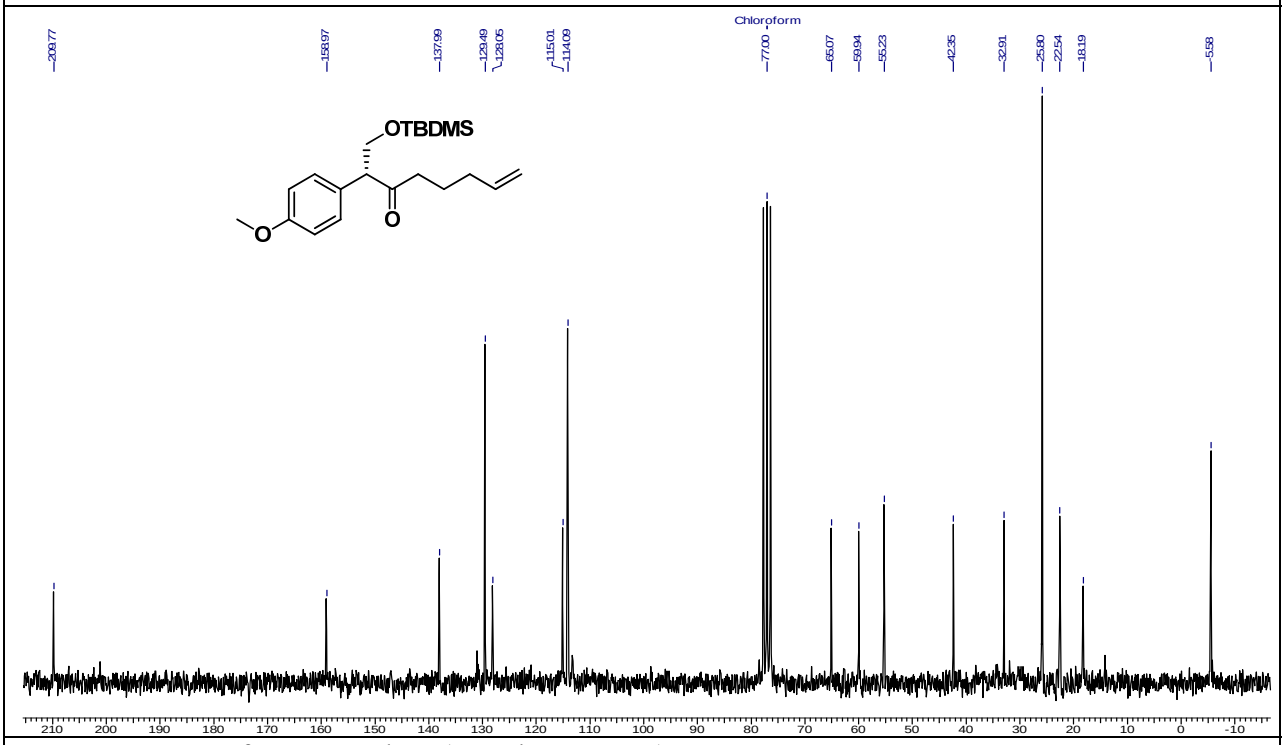
DEPT spectrum of compound **89** ($CDCl_3$, 125 MHz)



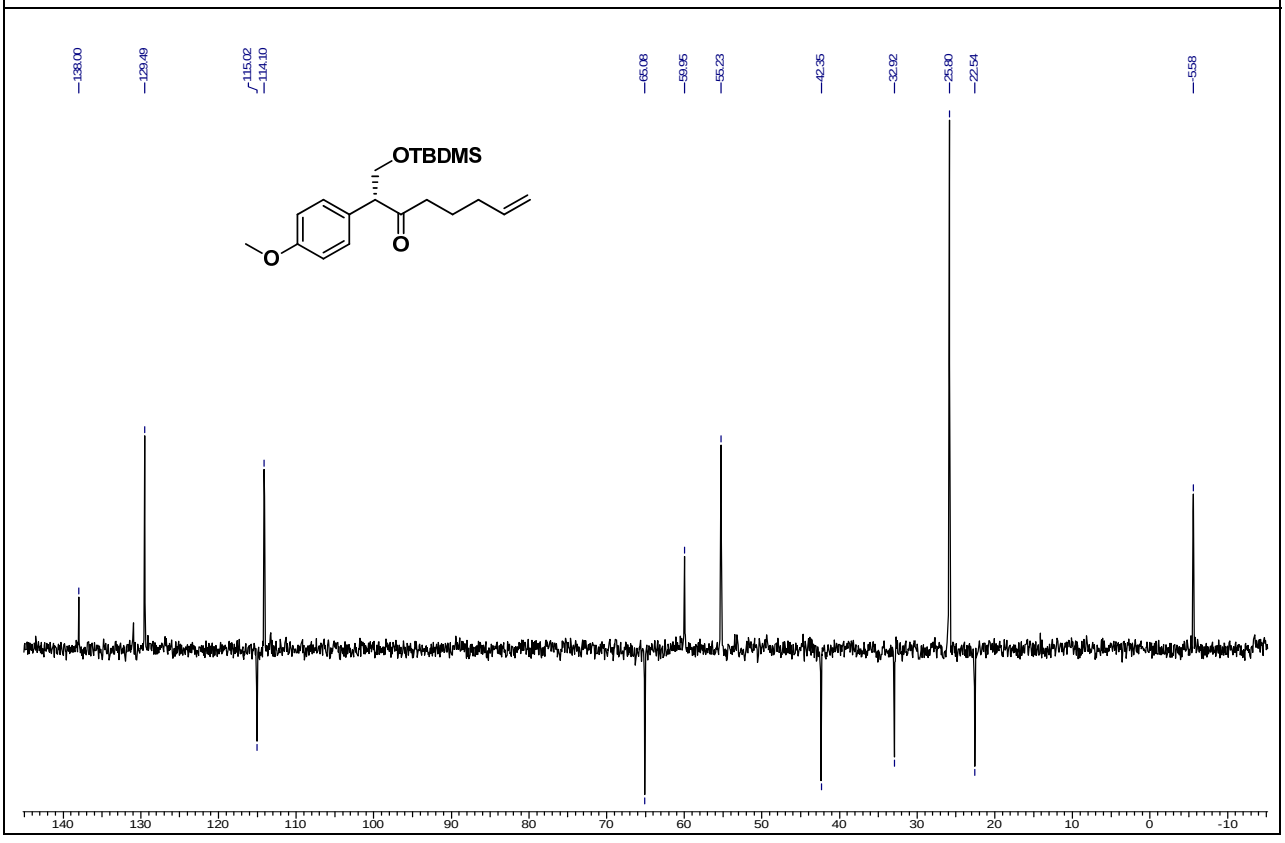
^{1}H NMR spectrum ofcompound **74** ($CDCl_3$, 200 MHz)



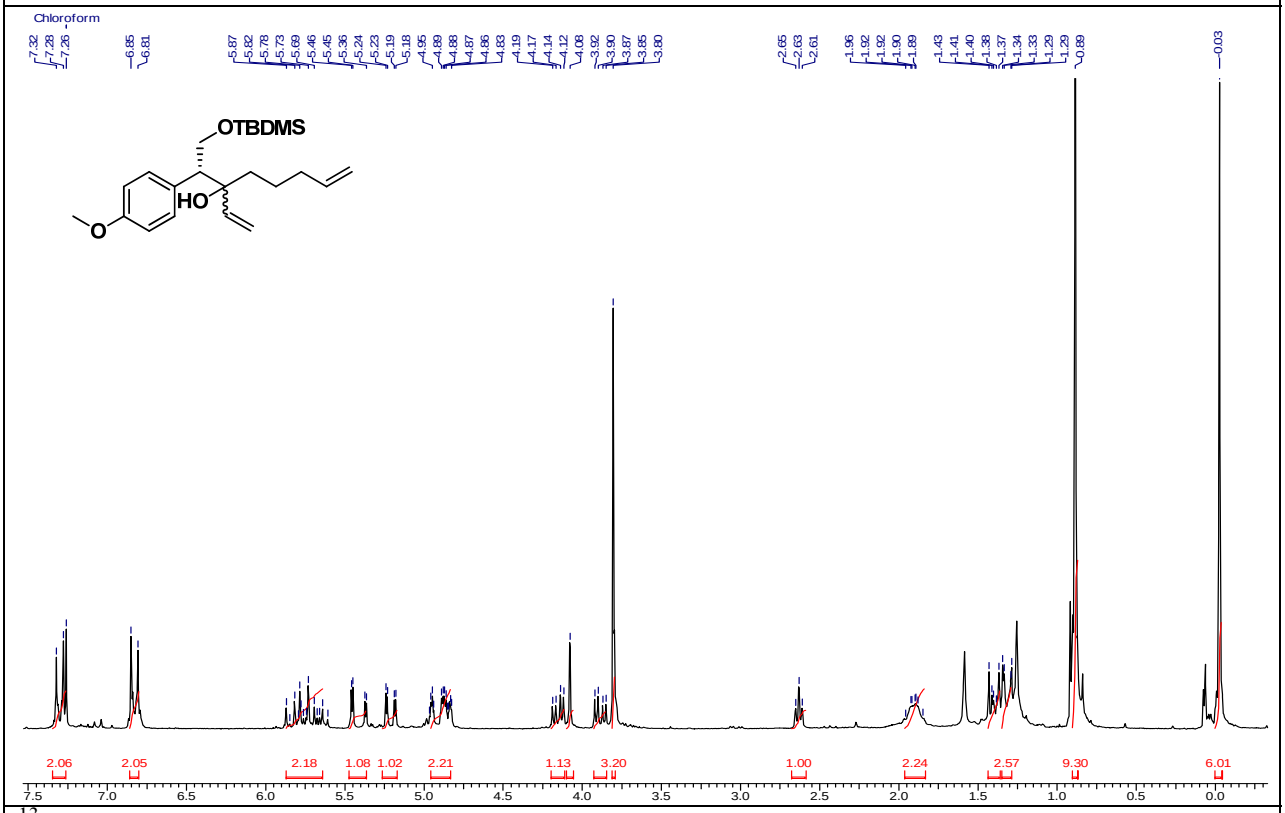
^{13}CNMR spectrum ofcompound **74** ($CDCl_3$, 50 MHz)



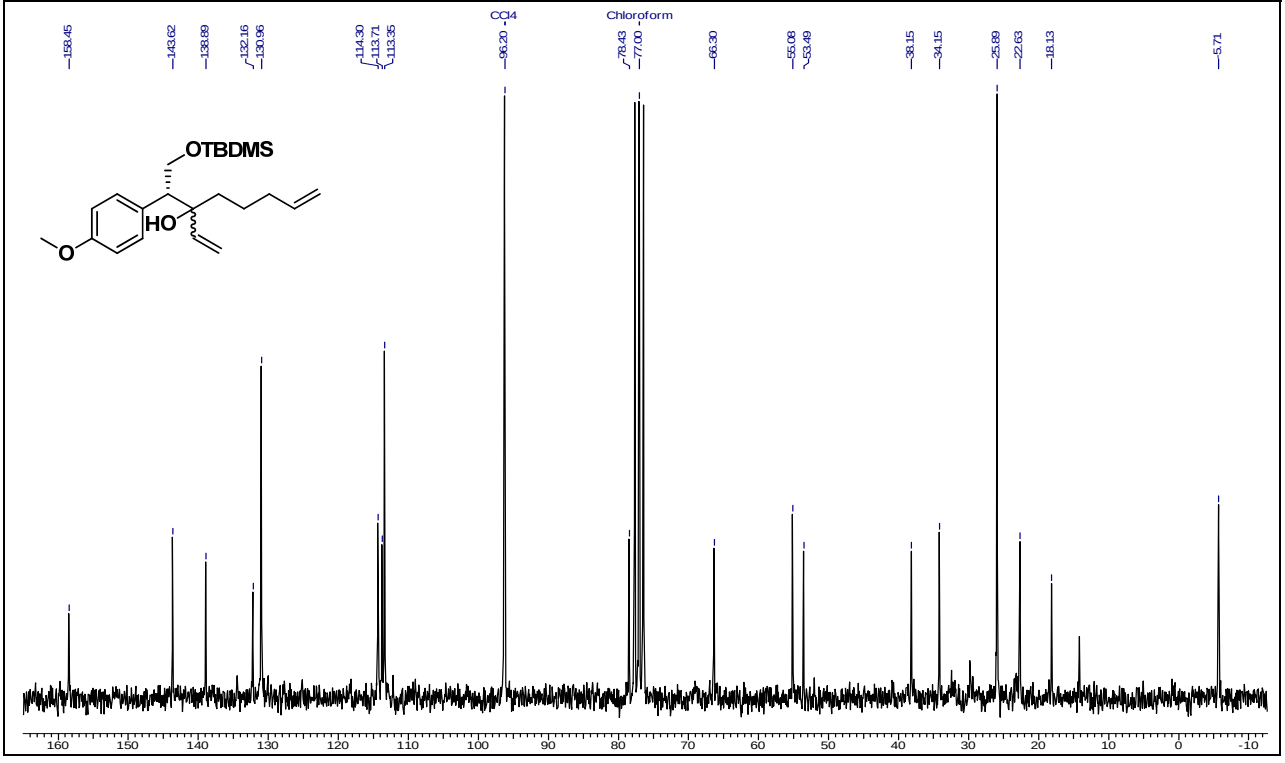
DEPT specrum of compound **74** ($CDCl_3$, 50 MHz)



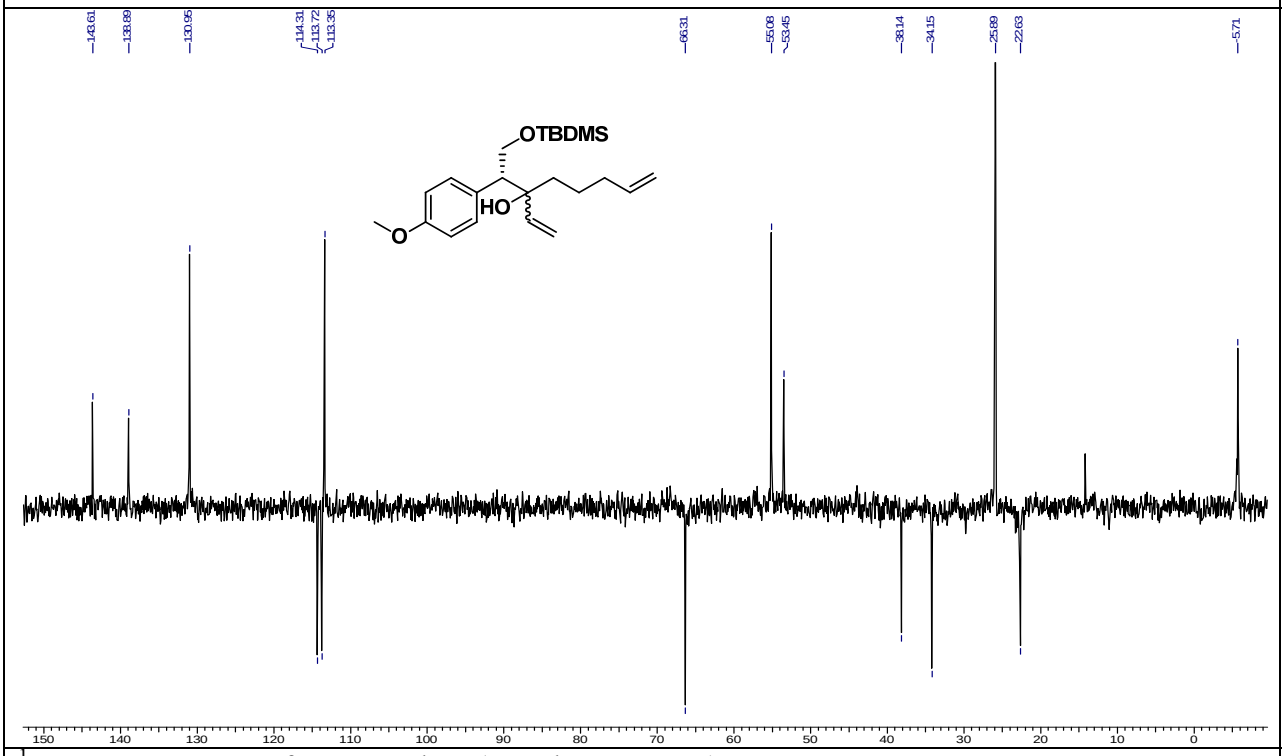
^{1}H NMR spectrum ofcompound **75** ($CDCl_3$+CCl_4, 200 MHz)



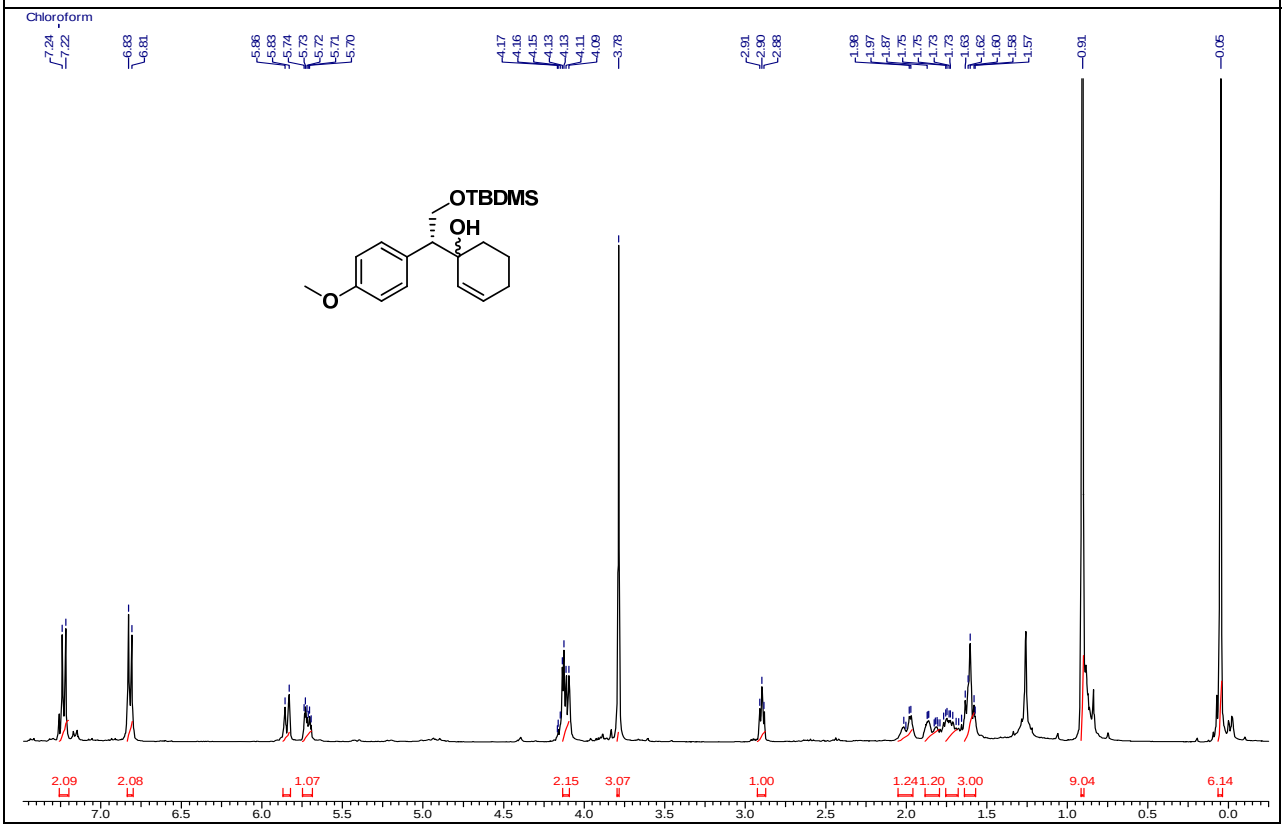
^{13}CNMR spectrum ofcompound **75** ($CDCl_3$+CCl_4, 50 MHz)



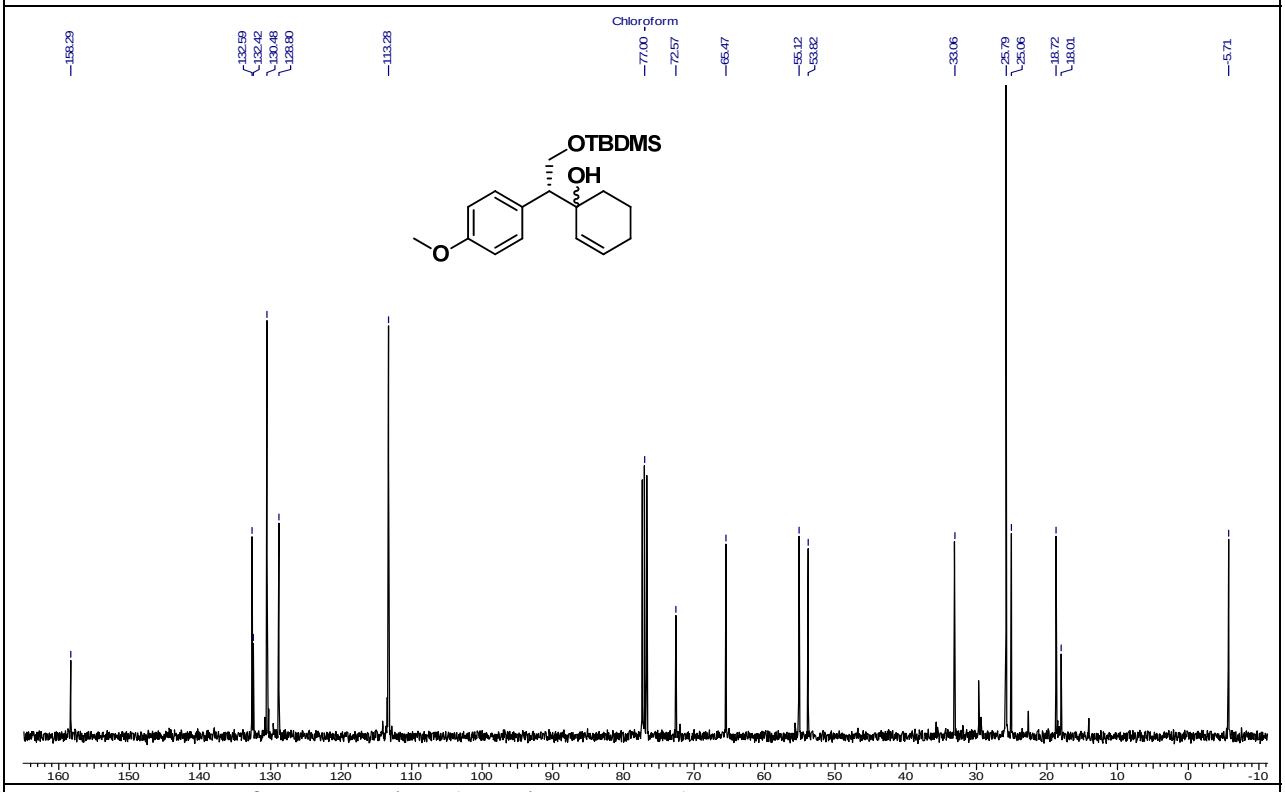
DEPT spectrum of compound **75** ($CDCl_3$+CCl_4, 50 MHz)



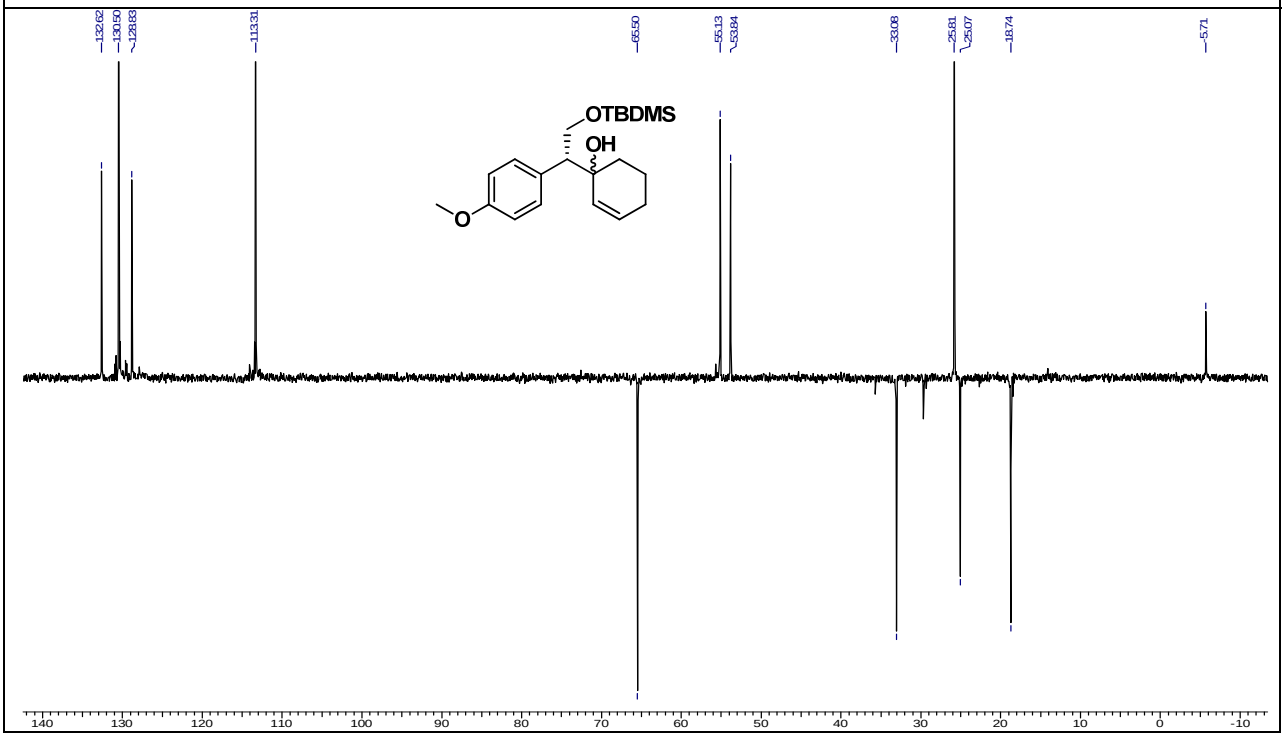
^{1}H NMR spectrum ofcompound **76** ($CDCl_3$, 400 MHz)



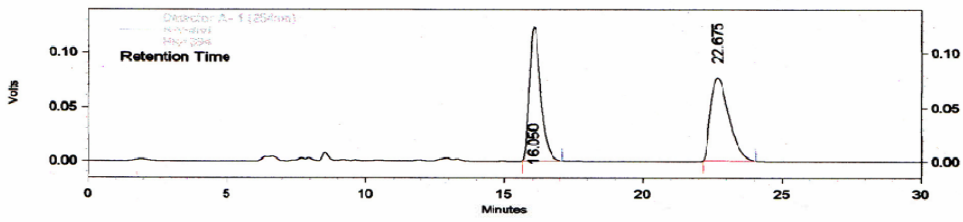
^{13}CNMR spectrum ofcompound **76** ($CDCl_3$, 100 MHz)

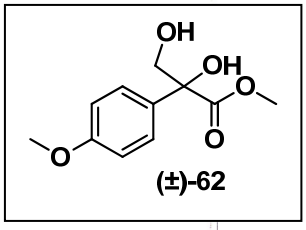


DEPT spectrum of compound **76** ($CDCl_3$, 100 MHz)



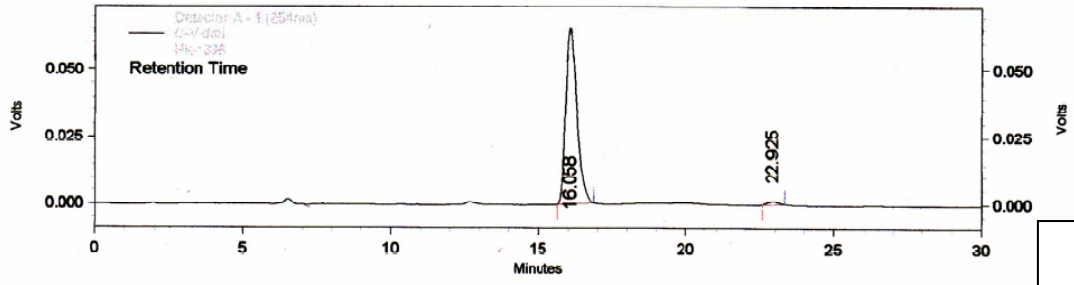
3.3.5.2. HPLC data

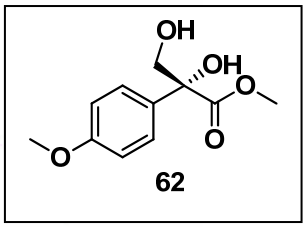




Detector A - 1 (254nm)

Retention Time	C Area	Area %
16.050	3617659	50.214
22.675	3586874	49.786
Totals	7204533	100.000





Detector A - 1 (254nm)

Retention Time	C Area	Area %
16.058	1671585	98.285
22.925	29172	1.715
Totals	1700757	100.000

Project Leader : Dr.S.P.Chavan
Column :Chiralcel OJ-H (250x4.6 mm)
Mobile Phase :IPA:PE (50:50)
Wavelength :254nm
Flow Rate :0.5ml/min (560psi)
Sample Con. :1 mg/1.0ml
Inj vol- :10 ul

D-7000 HSM: NCLOC Series: 6227 Report: modified System: Sys 1

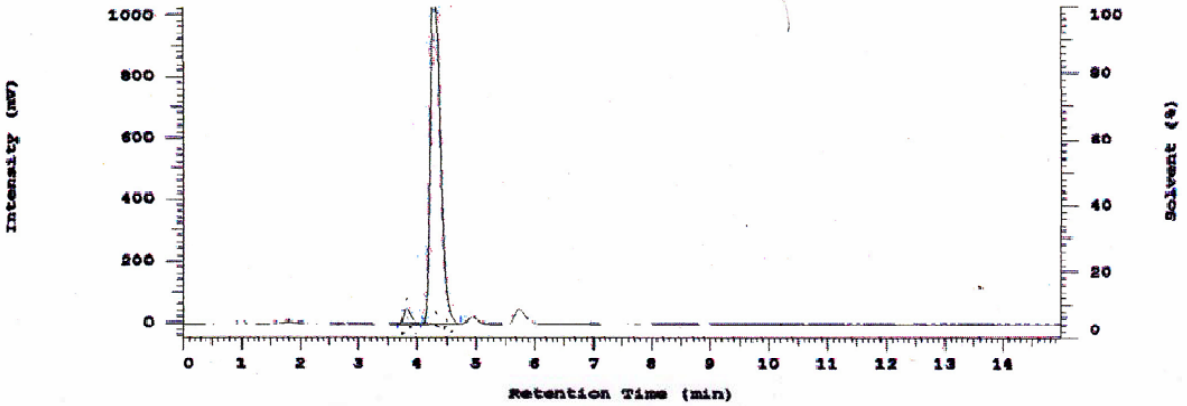
NATIONAL CHEMICAL LABORATORY

ORGANIC CHEMISTRY TECHNOLOGY

Analyzed: 06/17/13 11:45 AM Reported: 06/17/13 12:05 PM
Data Path: f:\win32app\hsm\NCLOC\DATA\6227\
Processing Method: Lichrosphere RP-18 (250-4) Acquisition Method: Lichrosphere RP-18 (250-4)

System(acquisition): Sys 1 Series:6227
Sample Name: V - 5GC Vial Number: 3
Injection from vial: 1 of 1 Vial Type: UNK
Volume: 10.0 ul

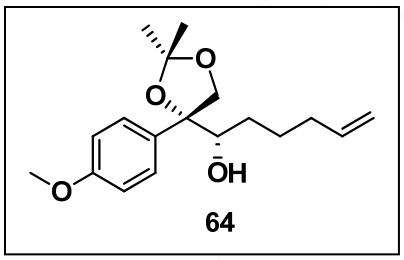
Chrom Type: HPLC Channel : 1



Peak Quantitation: AREA Calculation Method: AREA%

No.	RT	Height	Area	Area %
1	3.81	47963	452336	3.695
2	4.30	1090416	11790382	96.305
		1138379	12242718	100.000

Peak rejection level: 0



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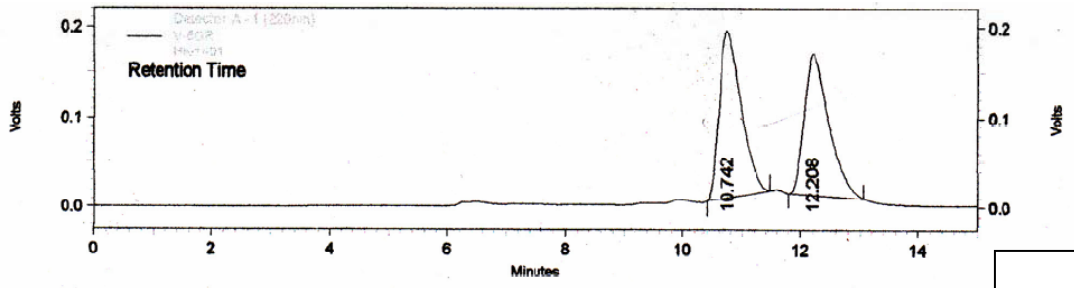
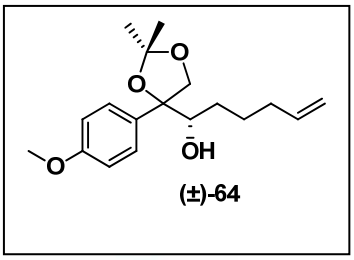
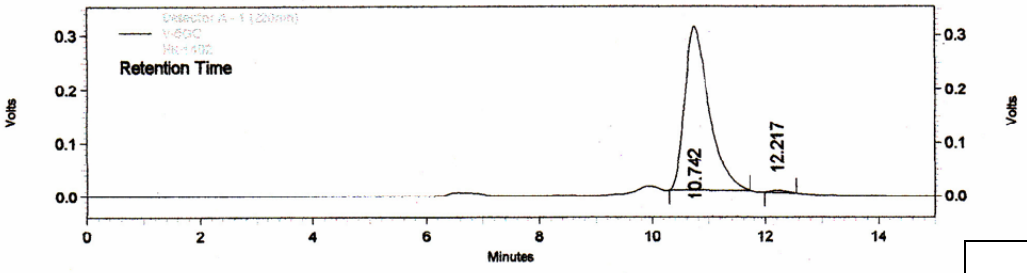
Group Leader : Dr.S. P. Chavan
Column :Kromasil RP-18(250 x 4.6 mm)
M.P. :ACN:H2O (75:25)
Flow Rate : 1.0 ml/min (1195psi)
Sample conc: 1. mg/1.0ml
Inj vol: : 5 ul
WAVELENGTH : 220 nm

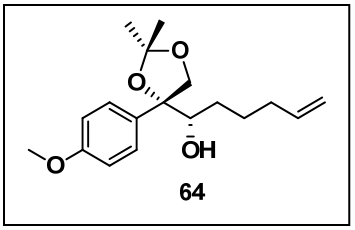




Detector A - 1 (220nm)

Retention Time	C Area	Area %
10.742	4769751	51.187
12.208	4548516	48.813
Totals	9318267	100.000

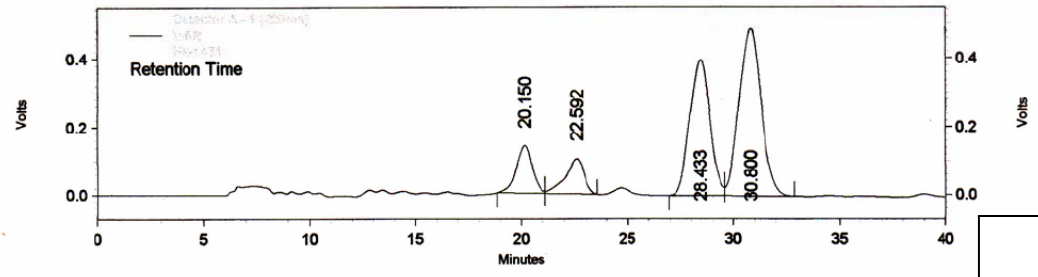


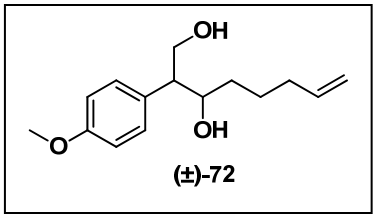


Detector A - 1 (220nm)

Retention Time	C Area	Area %
10.742	9111683	99.195
12.217	73949	0.805
Totals	9185632	100.000

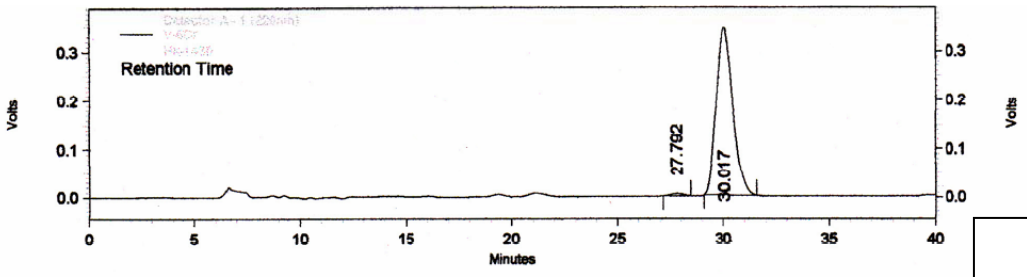
Project Leader	:Dr.S P CHAVAN
Column	:Chiracel OD-H (250 x4.6mm)
Mobile Phase	:IPA:*n-Hexane* (08:92)
Wavelength	: 220 nm
Flow Rate	:0.5 ml/min
conc.	:1 mg/ 1.0 ml
Inj vol-	:2 ul.

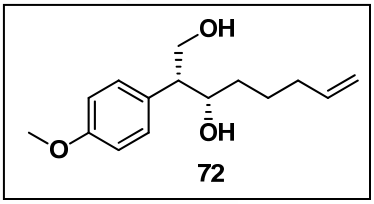




Detector A - 1 (220nm)

Retention Time	C Area	Area %
20.150	7353043	9.755
22.592	6363889	8.443
28.433	26219174	34.785
30.800	35437910	47.016
Totals	75374016	100.000

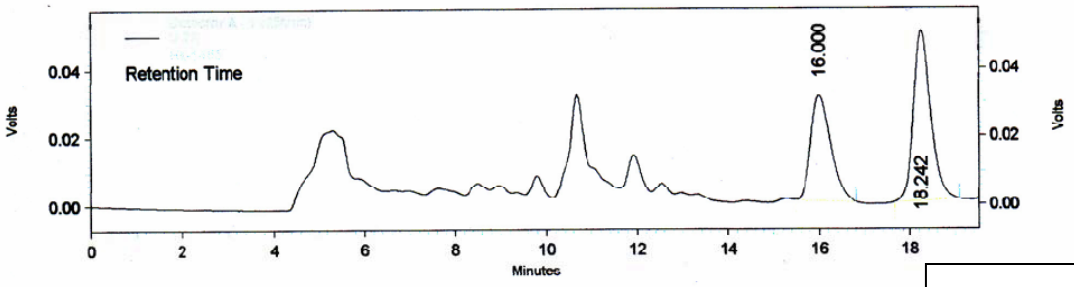


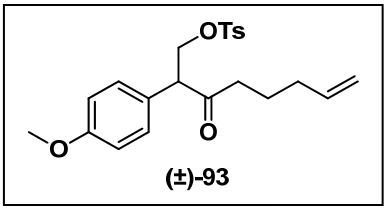


Detector A - 1 (220nm)

Retention Time	C Area	Area %
27.792	210436	1.078
30.017	19305078	98.922
Totals	19515514	100.000

Project Leader : Dr.
Column :Chiracel OJ-H (250 x4.6mm)
Mobile Phase :ETOH:PET ETHER (08:92)
Wavelength : 220 nm
Flow Rate :0.5 ml/min
Conc. :1 mg/ 1.0 ml
Inj vol- :5ul.





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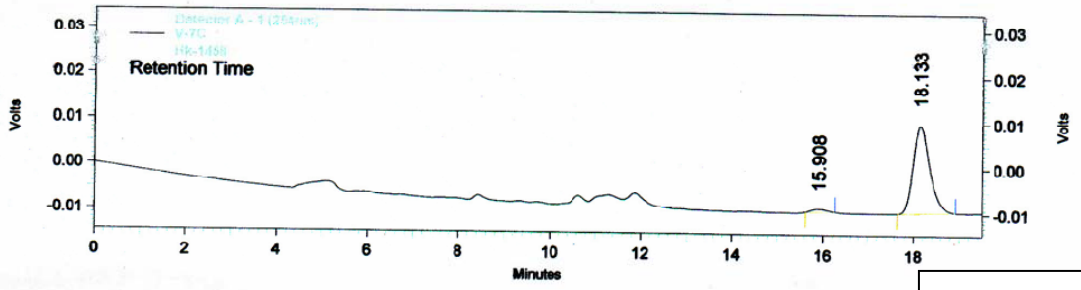
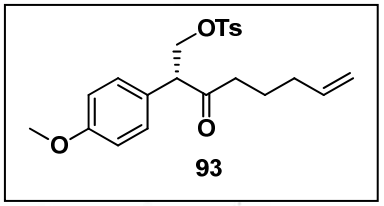
Detector A - 1 (254nm) Retention Time	C Area	Area %
16.000	466250	41.882
18.242	646985	58.118
Totals	1113235	100.000

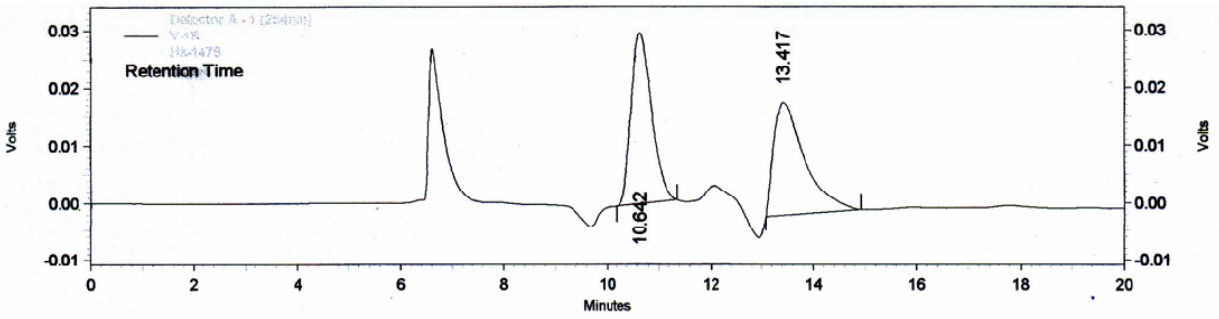




93

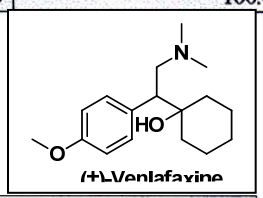
Detector A - 1 (254nm) Retention Time	C Area	Area %
15.908	14489	2.857
18.133	492650	97.143
Totals	507139	100.000

Project Leader : Dr.S.P.Chavan
Column : Chiralcel OJ-H (250 X 4.6cm)
Mobile Phase : IPA:Pet Ether (30:70)
Flow Rate : 0.7ml/min 450psi
Wavelength : 254nm
Con. : 1mg /1ml
Inject vol. :5ul

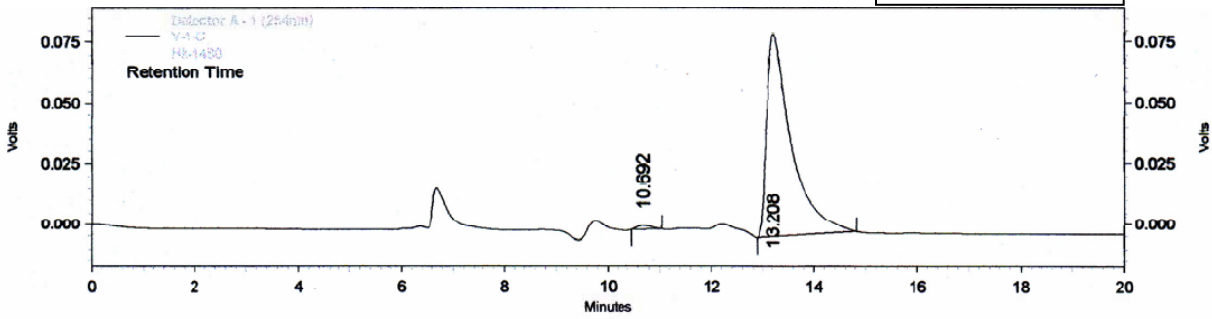


Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	10.642	797527	49.711
2	13.417	806811	50.289
Totals		1604338	100.000



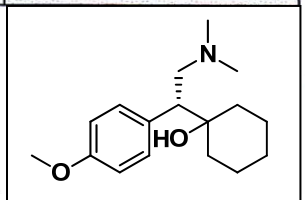
(+)-Venlafaxine



Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	10.692	29065	1.015
2	13.208	2835190	98.985
Totals		2864255	100.000

Project Leader :Dr.S P Chavan
Column :Kromasil AmyCoat (250mm x 4.6mm)
Mobile Phase :ethanol:Pet Ethar:DEA (05:95:0.1)
Wavelength : 254 nm
Flow Rate : 0.5mL/min
Inj vol- : 05 uL



(*R*)-(-)-Venlafaxine

3.3.6. References

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24. HPLC conditions: column-Kromasil AmyCoat (250mm X 4.6mm), mobile phase-Ethanol: Petroleum ether: Diethyl amine (05:94.9:0.1), Wavelength- 254 nm, flow rate-0.5 mL/min, Injecting volume-05 µL.