SYNTHETIC APPROACHES TOWARDS ARTEMISININ, OTHER TERPENOIDS, (*8E*,*10Z*)-PENTADECADIEN-1-OL ACETATE, CIPROFLOXACIN & NORFLOXACIN AND PYRIDINES

A thesis submitted to
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in
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By

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September 2001

DEDICATED

TO

MY PARENTS

&

TEACHERS

CERTIFICATE

Certified that the work incorporated in the thesis entitled **"Synthetic Approaches Towards Artemisinin, Other Terpenoids, (*8E*,*10Z*)-pentadecadien-1-ol acetate, Ciprofloxacin & Norfloxacin and Pyridines"** submitted by ***Mr. Rajendra Kanhaiyalal Kharul*** was carried out by the candidate under my supervision. Such material as has been obtained from other sources and has been duly acknowledged in the thesis.

September 2001 Dr. Subhash P. Chavan

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I am very thankful to CSIR, New Delhi for fellowship.

Rajendra K. Kharul

Abbreviations

Ac	Acetyl
Ar	Aryl
BMS	Borane dimethyl sulfide complex
B.P.	Boiling point
CAN	Ceric ammonium nitrate
DBU	1,8—Diazabicyclo-[5,4,0]-undec-7-ene
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DEG	Diethylene glycol
DIBAL-H	Diisobutylaluminium hydride
DME	Dimethoxy ethane
DMF	*N*,*N*-dimethyl formamide
DMSO	Dimethyl sulfoxide
EtOAc	Ethyl acetate
G	Gram
H	Hour
IR	Infrared
LDA	Lithium diisopropylamide
m-CPBA	*m*-chloroperbenzoic acid
mg	Milligram
Me	Methyl
Me_2SO_4	Dimethylsulfate
M.P.	Melting point
M^+	Molecular ion
MS	Mass spectrum
NaH	Sodium hydride
NBS	N-Bromosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
TEG	Triethylene glycol
pTSA	*p*-Toluene sulfonic acid
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSCl	Trimethylsilyl chloride
WHO	World Health Organization

General Remarks

1. All melting points and boiling points are uncorrected and the temperature is expressed in degree scale.
2. The compound numbers, scheme numbers and reference numbers given in each section refers 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°C.
4. Organic layers were dried over anhydrous sodium sulfate (Na_2SO_4).
5. TLC analyses were carried out on glass plates using silica gel: GF-254 and the plates were analyzed by keeping in the iodine chamber.
6. In cases where chromatographic purification was done, SiO_2 was used as a stationary phase.
7. The IR spectra were recorded on Perkin-Elmer infrared spectrophotometer model 683B or 1605 FTIR and IR absorbance is expressed in cm^{-1}
8. The ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AC 200, MSL 300 and DRX 500. ^1H NMR and ^{13}C NMR spectra are reported in parts per million from internal standard (tetramethylsilane) on δ scale.
9. Optical rotations were recorded at ambient temperature on JASCO Dip – 181 digital polarimeter using sodium vapor lamp.
10. Mass spectra were recorded at an ionization energy 70eV on Finnigan MAT-1020, automated GC/MS instrument and mass values are expressed as m/e.
11. GLC were carried out on Hewlett Packard 5890

ABSTRACT

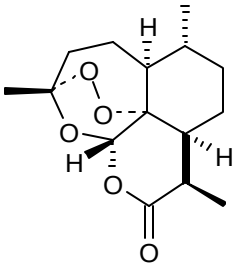
Thesis entitled **"Synthetic Approaches Towards Artemisinin, Other terpenoids, (8*E*, 10*Z*)-pentadecadien-1-ol Acetate, Ciprofloxacin & Norfloxacin And Pyridines"** is divided into two chapters.

CHAPTER 1: This chapter is divided into four sections.

Section I

Synthetic Approaches Towards Artemisinin

Artemisinin is highly oxygenated sesquiterpene. It was discovered to be an essential active principal component of an ancient Chinese herbal extract used as remedy for common cold, chills and fever. Among different species, artemisinin occurs mainly in *Artemisia annua*. However, the artemisinin content obtained directly from the plant sources is only 0.01-0.17%. Special horticulture methods and plant tissue culture techniques are employed to enhance artemisinin contents. However, the success is not very high.



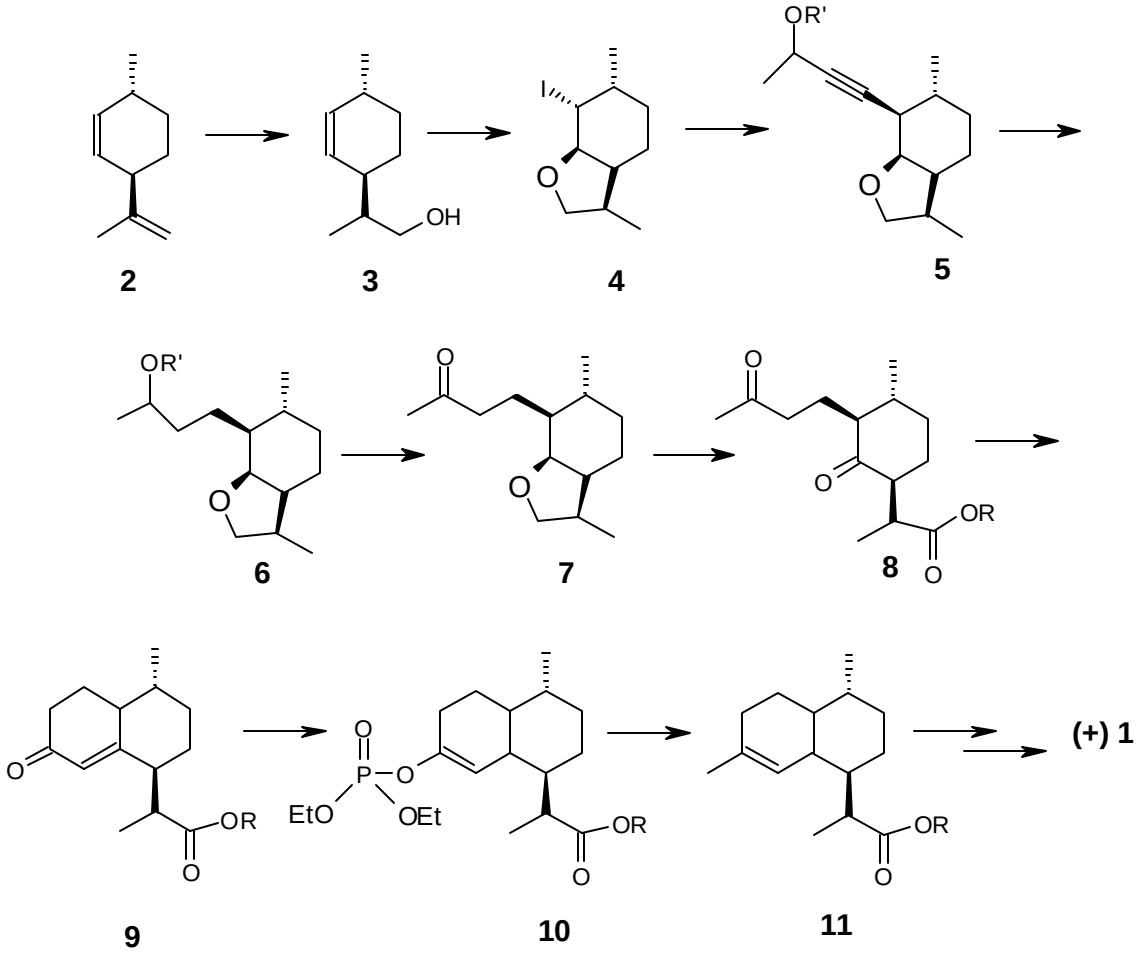
1

Recently artemisinin and its derivatives have been developed and have attracted attention as potent antimalarials, particularly active against *Plasmodium falciparum* that causes lethal cerebral malaria.[1]

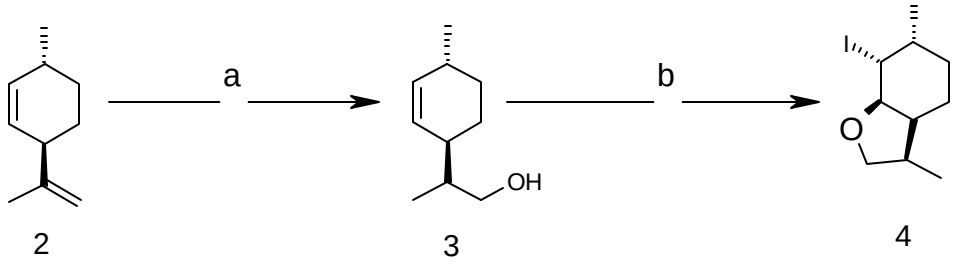
The comparative non-abundance[2,3] of the species and the low content of the artemisinin thus necessitates good synthetic strategy for its production and also its analogues. Though number of synthetic strategies are known, efforts are directed towards finding simpler, convenient and more practical method for it's synthesis.

From isolimonene involving iodoetherification approach, the scheme proposed is outlined below (**Scheme 1**).

Scheme 1



Scheme 2



Reagents and conditions:

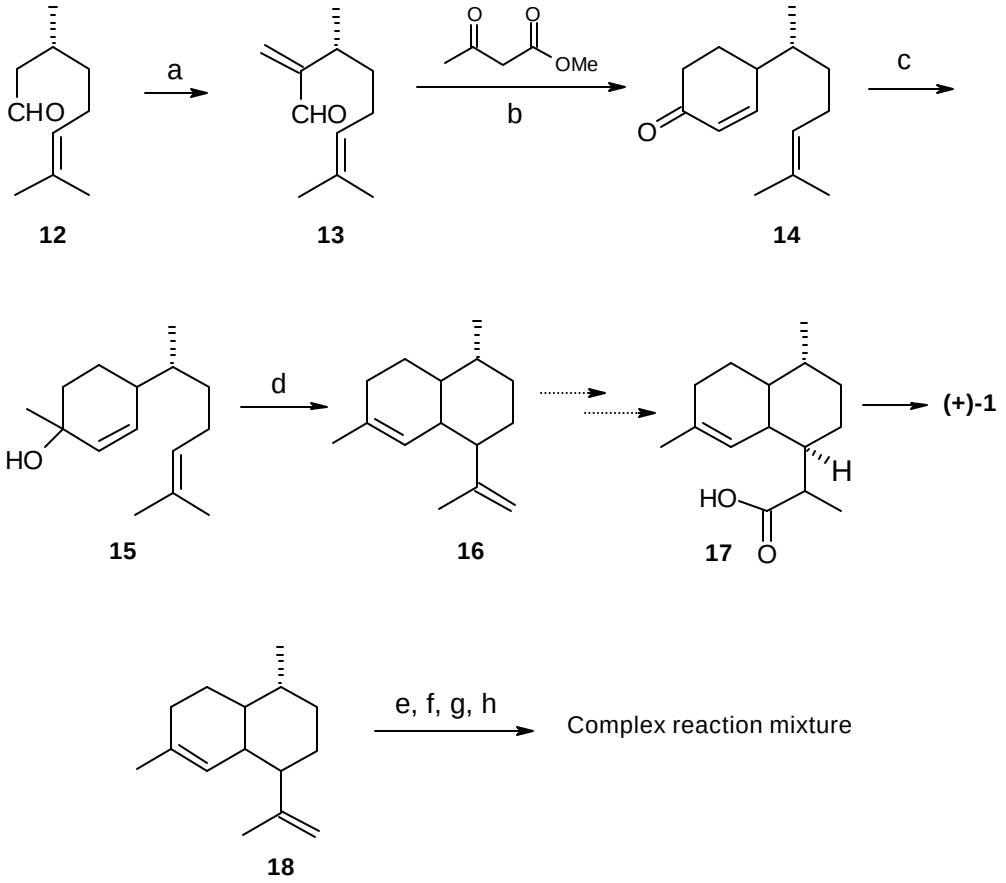
a) i. 9-BBN/THF, 0^0C-rt, ii. H_2O_2/HO^-, 76%. b) I_2/saturated $NaHCO_3$, Et_2O, 0^0C-rt, 24 h, 60%.

Thus according to the proposed scheme, isolimonene **2** was hydroborated regioseletively using 9-BBN and oxidized with alkaline H_2O_2 to furnish alcohol **3** which was then converted into iodoether **4** (**Scheme 2**).

This iodoether was subjected to carbon homologation reaction under various reaction conditions and reagents, but none of them furnished the desired product.

Due to unexpected failure during carbon homologation reaction, we switched on to another scheme. From the point of practical synthesis of artemisinin **1**, an alternate approach (**Scheme 3**) was attempted. According to the proposed plan, the key reaction involves an intramolecular ene reaction of the carbinol **15** to **16** and regioselective conversion of isopropenyl unit to propionate.

Scheme 3



Reagents and Conditions:

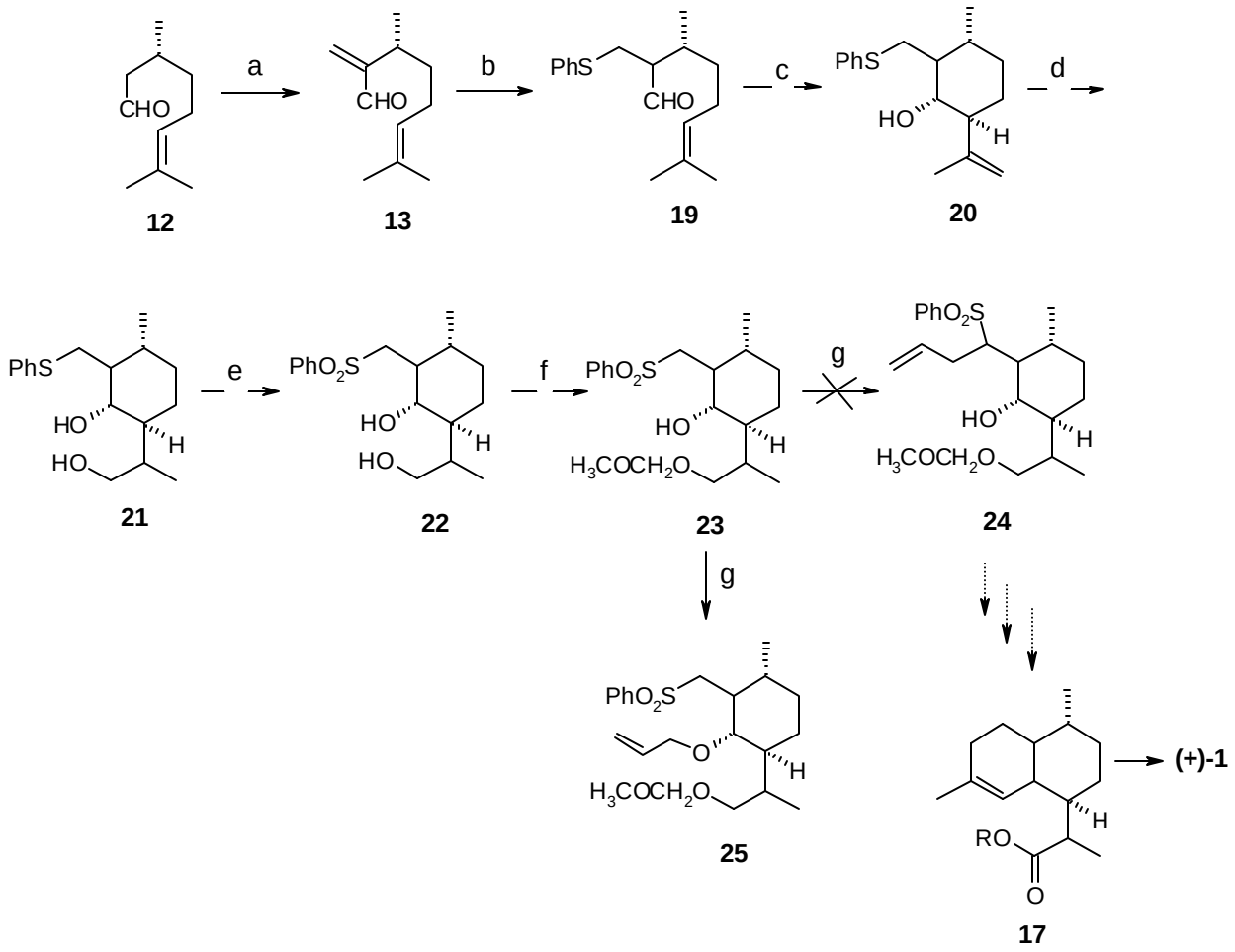
a) HCHO (35%), piperidine acetate, reflux, 2h, 86%. b) Dry MeOH, Cat. MeONa, rt-60^{0}C-reflux, 47%. c) MeMgI, Et_2O, 0^{0}C-rt. d) 50% $HClO_4$, 78%.e) $RuCl_3.3H_2O$, rt, 45 sec.,

f) $OsO_4/NaIO_4$, aq. THF, rt-reflux. g) Br_2/CH_3COOH, 0^{0}C. h) Aq. NBS, rt.

Intramolecular ene reaction of carbinol **15** was achieved with 50% $HClO_4$ in 78% yield to furnish diene **16**. The structure of diene **16** was assigned and confirmed by IR, ^{1}H-NMR and mass spectral analysis. The next task was the regioselective conversion of isopropenyl unit of **16** into propionate. In order to convert isopropenyl unit into propionate, it was thought to functionalize exomethylene double bond regioselectively. For this purpose, various attempts have been made

such as a) flash dihydroxylation with $RuCl_3.3H_2O$, b) Oxidative cleavage with $OsO_4/NaIO_4$, c) formation of dibromide using bromine in acetic acid, d) formation of bromohydrin using aqueous *N*-bromosuccinimide. Unfortunately, none of the reactions tried met with the success and the complex reaction mixture resulted. Hence we were forced to attempt another approach as described in (**Scheme 4**).

Scheme 4



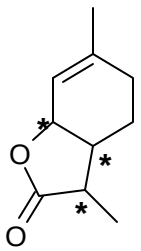
Reagents and Conditions:

a) HCHO (35%), piperidine acetate, reflux. b) PhSH, Et_3N, C_6H_6, rt. c) $ZnCl_2$, C_6H_6, 0^0C.

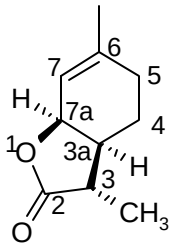
d) i. BMS/THF, ii) H_2O_2/HO^-. e) Oxone. f) H_3COCH_2Cl, NaH, THF. g) Allyl bromide, *n*-BuLi, THF, 0^0C-rt.

Section II: Efficient and Simple Synthesis of (-)-Wine Lactone.

(-)-Wine lactone, **(-)-26a** is a bicyclic terpenoid found in white wine, Gewurztraminer and Scheurebe as an important flavor component. Recently, wine lactone was also found in orange juice and black pepper.[6] In 1975, Southwell identified a group of bicyclic terpenoid lactones in the urine of koala animals after feeding of the leaves of *Eucalyptus punctata.* One of these lactones was assigned the constitution **26** [3a,4,5,7a-tetrahydro-3,6-dimethylbenzofuran-2(3H)-one].



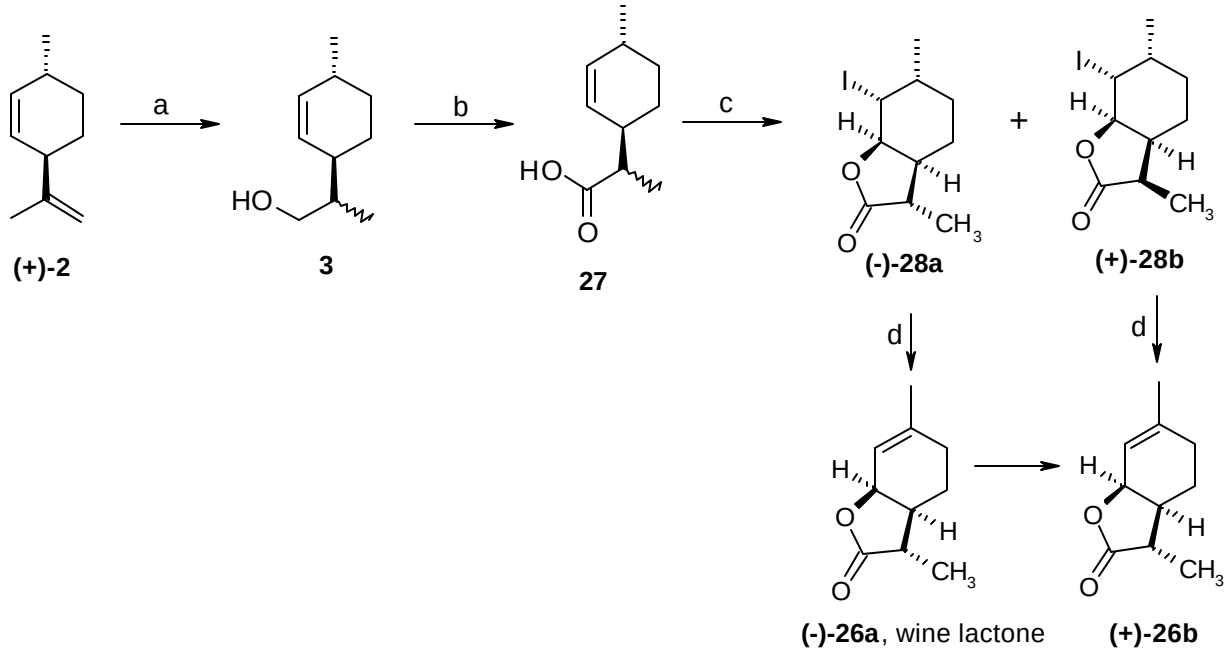
26



(-)-26a, Wine lactone
(-)-(3S, 3aS, 7aR)

Efficient and simple synthesis of (-)-wine lactone has been achieved in 26% overall yield in very short sequence starting with (+)-isolimonene involving iodolactonisation as the key step (**scheme 5**). Thus alcohol **3** was oxidized to acid **27** followed by iodolactonization mediated by $NaI/FeCl_3$ to furnish mixture of iodolactones **(-)-28a** and **(+)-28b** in the ratio 60:40. Both the iodolactones were separated by column chromatography. Iodolactone **(-)-28a** was dehydrohalogenated with DBU to furnish (-)-wine lactone **(-)-26a**. Iodolactone **(+)-28b** on dehydrohalogenation with DBU furnished *epi*-wine lactone **(+)-26b**.

Scheme 5



(+)-2 **3** **27** **(-)-28a** **(+)-28b**

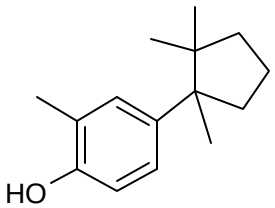
(-)-26a, wine lactone **(+)-26b**

Reagents and conditions:

a) i. 9-BBN/THF, 0^0C-rt. 15 h ii. NaOH/H_2O_2, 0^0C-rt., 1h, 76% b) Jone's reagent, 0^0C- rt., 2h, 78% c) NaI/$FeCl_3$, CH_3CN, reflux, 2.5 h, 59% d) DBU/THF, rt., 5h, 71-76%.

Section III: Synthetic Approaches Towards (±)-β-Herbertenol

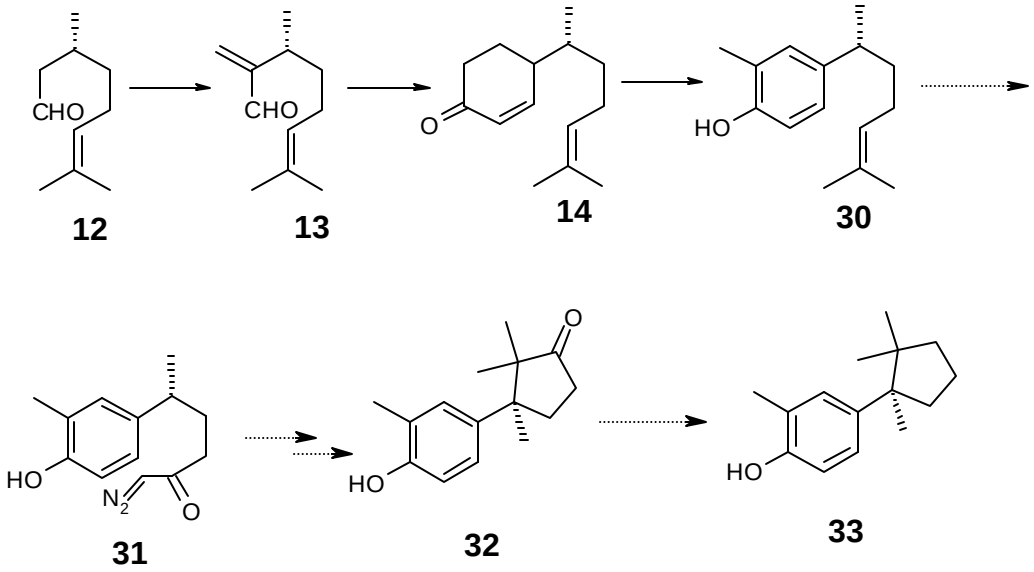
β-Herbertenol **29** along with other sesquiterpenes α-herbertenol, herbertene, herbertenolide occurs in *Herberta Adunca*.[8] Up till now only one synthetic approach is known towards β-herbertenol.[9]



29

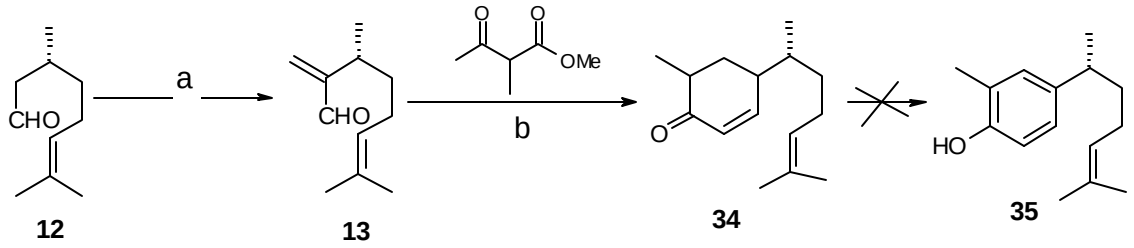
The abundancy of (*R*)-citronellal as the natural product from Indian plant prompted us to devise a strategy for the synthesis of β- herbertenol which is outlined below (**scheme 6**).

Scheme 6



According to the synthetic plan, citronellal **12** was converted into enone **14** by known procedure. Various efforts to alkylate enone at the α-carbon to carbonyl failed. Hence first methylation of methylacetoacetate was carried out by literature method. Then enone **34** was prepared (**scheme 7**).

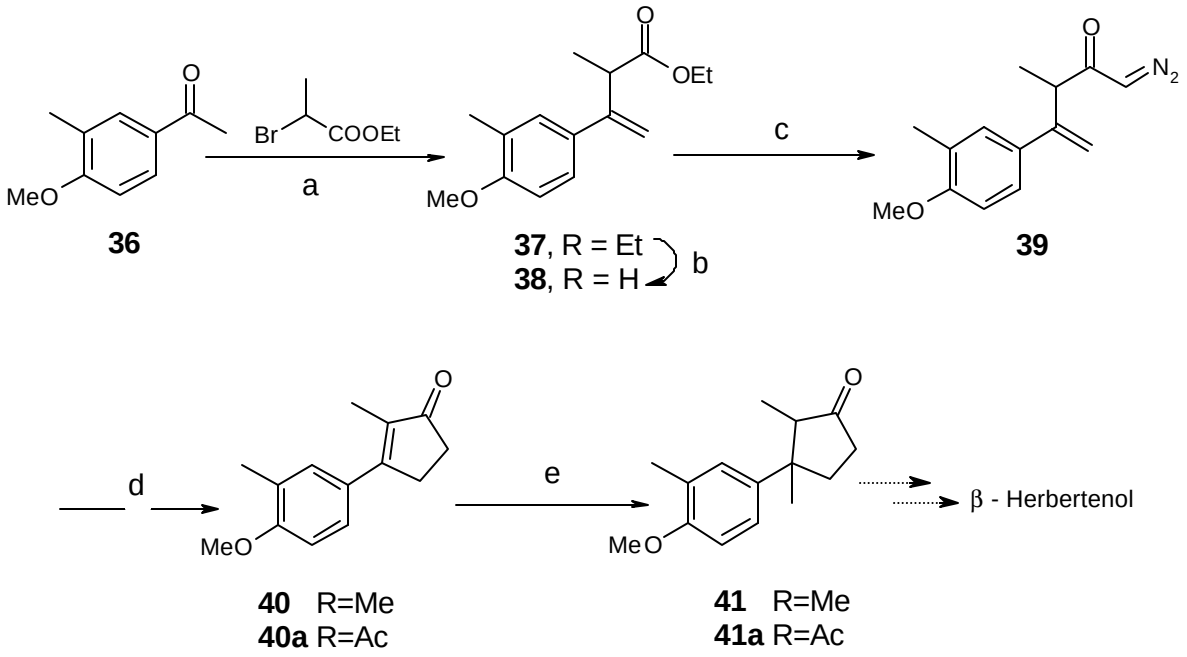
Scheme 7



Various efforts to aromatize enone **34** failed, hence the scheme was abandoned.

In an another approach, 4-Methoxy-3-methylacetophenone **36** was subjected to Reformatsky reaction followed by acidic workup to furnish ester **37.** Ester was hydrolyzed to acid with KOH/MeOH in water. Preparation of diazoketone **39** *via* acid chloride proceeded smoothly which was then cyclized by BF_3- Et_2O to furnish enone **40**. 1,4 – addition with $AlMe_3$ gave the product **41** (**scheme 8**).

Scheme 8



Reagents and conditions:

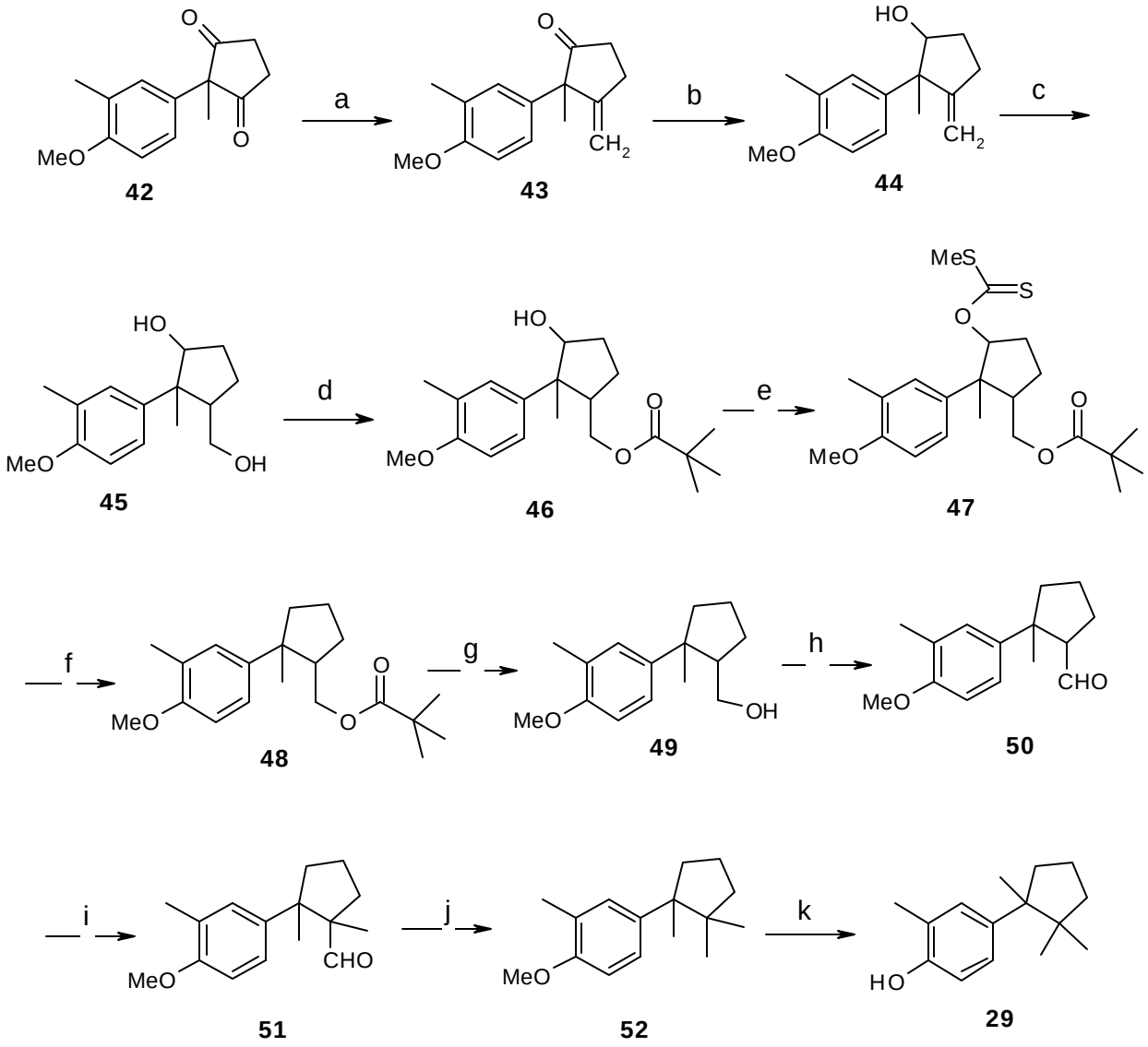
a) i. Zn, Et_2O, reflux, 5h, ii. 50% HCl, rt, 20h. b) KOH/MeOH. c) i. $SOCl_2$, C_6H_6, DMF (cat), 0^0C-rt, 2h ii. CH_2N_2, Et_2O, 0^0C-rt. d) $BF_3.Et_2O$, DCM., e) $AlMe_3$, $Ni(acac)_2$, THF, rt, 6h.

Due to irreproducible results obtained during 1,4-addition of $AlMe_3$ to the enone **40**, we switched on to another scheme (**Scheme 9**).

According to the proposed plan, cyclopentadione **42** was converted to its exomethylene derivative **43** by Wittig reaction followed by reduction with $NaBH_4$ furnished alcohol **44**. The alcohol was hydroborated followed by alkaline hydrolysis furnished diol **45**. Diol **45** was protected regioselectively as pivaloate ester to yield **46**, which was converted to its xanthate derivative **47**. Deoxygenation of the xanthate derivative with *tri-n*-butyltin hydride followed by cleavage of pivaloate ester with $LiAlH_4$ furnished primary alcohol **49**.

Primary alcohol **49** was oxidized with PCC to yield aldehyde **50** which was alkylated with methyl iodide to furnish aldehyde **51**. Wolff-Kishner reduction of aldehyde furnished methyl ether **52** which on demethylation furnished (±)-β-herbertenol **29**.

Scheme 9



Reagents and Conditions:

a) $PPh_3{}^+MeI^-$, K^+*tert*. BuO^- C_6H_6, reflux-rt, 72%. b) $NaBH_4$, EtOH, rt, 30 min, 98%. c) i. BMS, THF, 0^0C, 2h then at rt 24h, ii. H_2O_2,HO^-, 0^0C-rt, 1h.71%. d) $(CH_3)_3CCOCl$, Et_3N, CH_2Cl_2, 0^0C-rt, 84%. e) NaH (1.5 equiv.) THF:CS_2, 4:1, rt, 3h, then MeI (3 equiv.) rt 16h, 86% f) TBTH (5 equiv.), AIBN, toluene, reflux, 1.5 h, 83%. g) $LiAlH_4$, THF, rt 92%. h) PCC, CH_2Cl_2, 0^0C-rt, 1h, 86%. i) NaH, DME, 0^0C, 30 min, MeI, 0^0C, 3h, then at rt 16h, 65% j) $H_2NNH_2.H_2O$, NaOH, TEG, 195^0C, 7h, 52%. k) BBr_3, CH_2Cl_2, -78^0C-rt, 1h 81%.

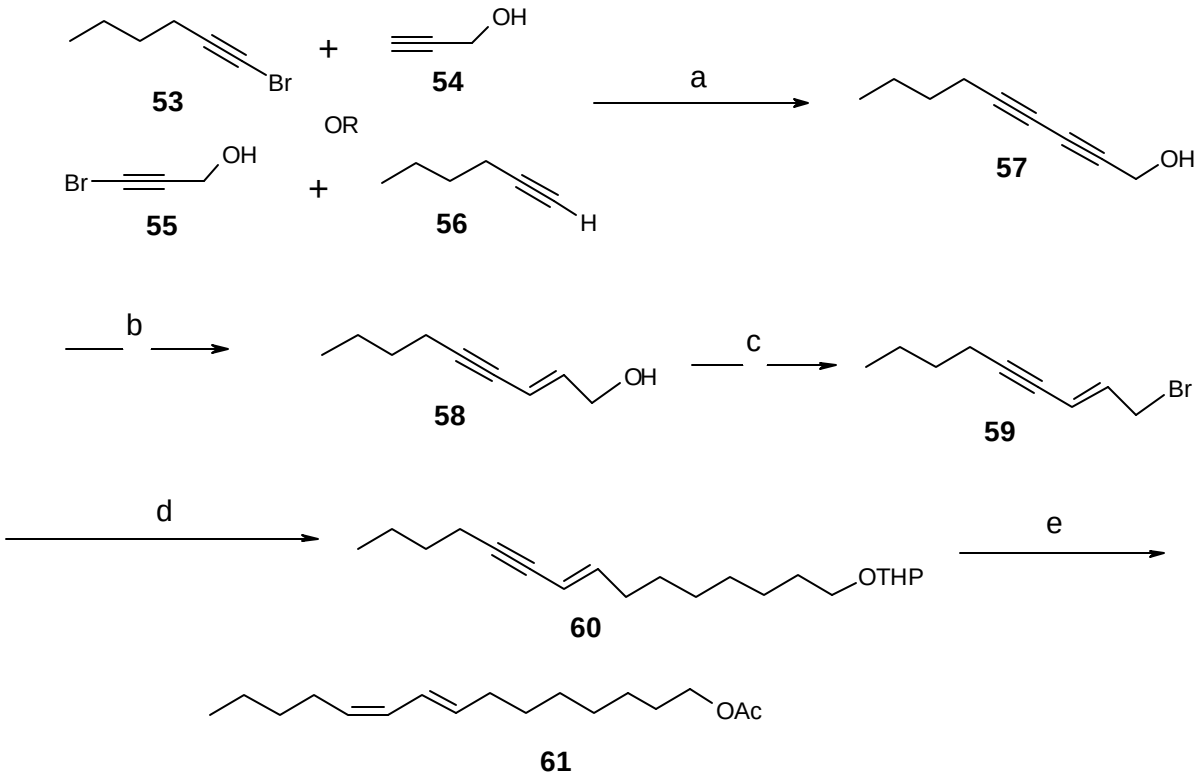
Section IV

Synthetic Approach Towards (*8E,10Z*)- Pentadecadien-1-ol Acetate

A composition of (*8E,10Z*)-pentadecadien-1-ol acetate and (*E*)-9- pentadecen-1-ol acetate is a highly effective attractant for male cranberry fruit worm (*Acrobasis vaccinni*).[10] (*8E,10Z*) is a major essential component of pheromonal activity observed for cranberry fruitworm. The novel composition provides a sensitive tool for detection of this pest. By attracting male cranberry fruitworm moths to field traps, the composition provides a means for detecting, surveying, monitoring and controlling the cranberry fruitworm.[11]

In this section, a concise synthesis of pheromone (*8E,10Z*)- Pentadecadien-1-ol acetate involving Cadiot-Chodkiewich coupling as the key step and the selective elaboration of one triple bond to *Z* and the other to *E* and it's further conversion to the target molecule is described (**Scheme 10**).

Scheme 10



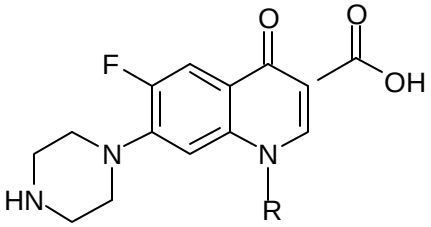
Reagents and Conditions:

a) $EtNH_2$, CuCl, $NH_2OH.HCl$, rt, MeOH, 2h b) $LiAlH_4$, THF, rt, 79% c) PPh_3Br_2, CH_2Cl_2, 0^0C-rt, 10 min, 84% d) $MgBr\text{-}CH_2\text{-}(CH_2)_4\text{-}CH_2\text{-}OTHP$ **21**, CuBr, THF, -78^0C-rt, 40%. e) i. P_2-Ni, EtOH, rt, 20 min, 79%, **23** ii. AcCl/AcOH, rt, 12h, 88%.

CHAPTER 2 Chapter 2 is further divided into two sections.

Section I:

Condensation of chlorofluroquinolone carboxylic acid with piperazine.



62a: R = cyclopropyl
62b: R = ethyl

Quinolone antibiotics *viz*. Ciprofloxacin **62a** and Norfloxacin **62b** are widely used antibiotics in bulk quantities.

Ciprofloxacin is widely used as third generation quinolone antibiotics as it is superior to chloramphenicol, amino glycosides, cephalosporin and it is commonly used for curing enteric fever, septicaemia, bronchopneumonia, oesteromylitis and non-genococeal urethritis.

Ciprofloxacin is commonly prepared by the condensation of 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,2-dihydroquinoline-3-carboxylic acid with piperazine in the presence of pyridine or triethyl amine as the solvent. Alternatively, this is also prepared by making borate or fluoroborate complex of quinoline carboxylic acid in DMSO or DMF or dimethyl acetamide as the solvent to give piperazino-quinolone carboxylic acid borate or fluoroborate complex that is hydrolyzed to yield ciprofloxacin.

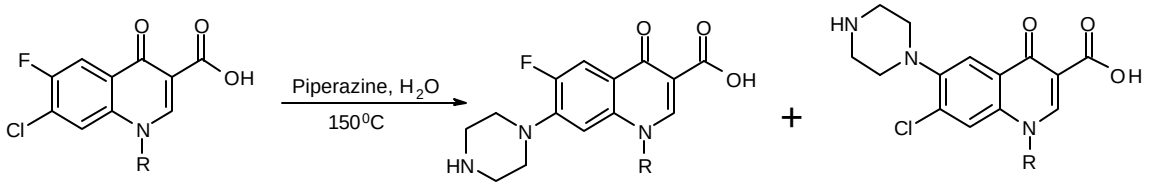
With the current global awareness in developing eco-friendly technologies and secondly the use of water as a non-hazardous reaction medium, water is emerging as solvent for organic synthesis. Keeping this in mind, we have studied reactivity and impurity profile for the condensation of piperazine with chloro-fluoro quinolone carboxylic acid in aqueous medium.

We have studied the effect of various parameters such as temperature, reaction time and concentration at varying degrees. Under the optimized conditions, it was found that piperazine

reacts at both the positions C_6 (replacement of fluorine) and at C_7 (replacement of chlorine). The major product (65%) was obtained by substitution at C_7 yielding ciprofloxacin.

In order to check generality of the above study for other quinolone antibiotics **63b** was treated with piperazine under the similar conditions to yield Norfloxacin **62b** (**scheme 11).**

Scheme 11



63a, R = cyclopropyl
63b, R = ethyl

62a, R = cyclopropyl
62b, R = ethyl

64a, R = cyclopropyl
64b, R = ethyl

Thus the efficacy of water as the solvent was established in the condensation reaction and hence avoiding the costly/hazardous solvents generally utilized in these reactions.

Section II:

Oxidation of 1,4-dihydropyridines to Pyridines.

Amlodipine besylate, Nifedipine and related dihydropyridines are important as calcium channel blockers and these compounds are rapidly emerging as one of the most important classes of the drugs for the treatment of cardiovascular diseases including hypertension. In the human body, it has been observed that these compounds undergo oxidation to form pyridines. These oxidized compounds lack pharmacological activity of the parent compounds.

These metabolites are important as reference standards and hence development of convenient method for their oxidation is important, particularly for the synthesis of radiolabled compounds to study their biological degradation.

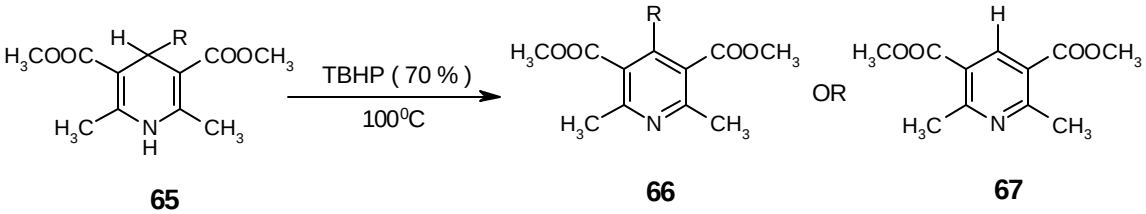
A variety of oxidizing agents *viz*. NO, N_2O_3, HNO_2, HNO_3, pyridinium chlorochromate, ceric ammonium nitrate, ferric nitrate, cupric nitrate on solid support have been reported for the conversion of dihydropyridines to pyridines.

Part A

Because of current interest in oxidation processes using *tert*- butylhydroperoxide in our laboratory and development of ecofriendly benign technologies with special emphasis on performing the reactions in aqueous medium,[13] we planned to study the oxidation of 1,4-

dihydropyridines to corresponding pyridines using aqueous TBHP. We have successfully established an efficient methodology towards the oxidation of 1,4-dihydropyridines using aqueous TBHP in good to excellent yields. (**scheme 12**).

Scheme 12

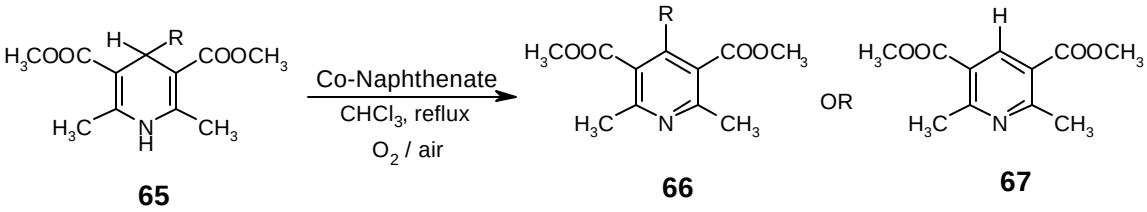


65 **66** **67**

Part B

In continuation of our interest to study aromatization of 1,4-dihydropyridines to pyridines in our laboratory, we have studied the auto oxidation of these compounds catalyzed by Cobalt-naphthenate using molecular oxygen. We have successfully established a convenient and efficient catalytic oxidation protocol for the conversion of 1,4-dihydropyridines to pyridines (Scheme 12). Details of these two protocols will be presented in this section.

Scheme 13



65 **66** **67**

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CHAPTER 1

SECTION I

Synthetic Studies Towards Artemisinin

1.1.1 Introduction

Globally malaria is once again threatening mankind.[1] Indeed the word malaria comes from the Italian mal' aria or 'bad air' and the ancient Chinese term *Zhangqi* means much the same. Malaria is one of the most widespread parasitic diseases caused by protozoan parasites of the class of *Plasmodium*, which enter red blood corpuscles when in the human blood stream.[2] It is estimated that there are still 6.5 million people who are chronically affected and there are 3 million new cases are reported and of which 2 million are killed ever year.[3,4] Studies by a number of workers showed that humans are affected by four species of *Plasmodium*, three of which produce the mild forms of malaria by destroying red blood cells in peripheral capillaries and thus causing anaemia. The bouts of fever correspond to the reproductive cycle of the parasite. However, the most dangerous is the fourth species, *Plasmodium falciparum*. In this case the infected red blood cells become sticky and form clumps in the capillaries of the deep organs of the body and cause microcirculatory arrest. If this happens in the brain delirium, coma, convulsions, and death may cause. Cerebral malaria is by far the most serious form of the infection.

As early as 16th century, natural products gained wide acceptance in treatment of malaria, when the therapeutic action of the bark of cinchona tree was observed by indigenous people from South America. Cinchona bark must be one of the most successful of all herbal remedies and illustrates the value of folk medicine. The active principle quinine isolated in 1820 was mainly used for malaria until other synthetic antimalarials were developed. During 1920, a synthetic quinoline derivative pamaquin was found to be more effective than quinine in killing malaria parasites lodged in the liver. Also mepacrine was developed as a synthetic alternative to quinine.

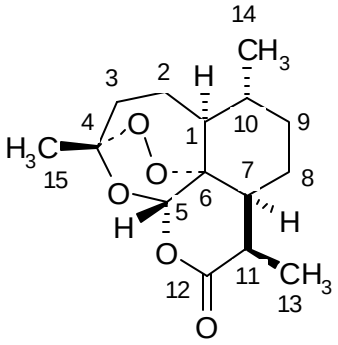
Further more research led to the production of chloroquine which has fewer side effects. Primaquin is another quinoline derivative with antimalarial properties particularly effective against *Plasmodium viva.* A biquanidine compound proquanil also has powerful antimalarial properties but it is more generally used as prophylactic pyrimidine derivative, pyrimethamine by itself is used for suppression only. Most of the drugs for the treatment of malaria are derivatives of quinoline and acridine. Unfortunately no vaccine to prevent malaria is available and using quinoline derivatives (eg. Chloroquine) to cure malaria is becoming much less effective particularly against *Plasmodium falciparum* due to parasites' rapidly increasing resistance to such standard drugs [5].

In 1967, the government of the Peoples Republic of China embarked on a systematic examination of indigenous plants used in traditional remedies as a source of drugs. One such plant,

a pervasive weed with a long history of use (more than 1500 years) is known as Qinghao (*Artemisia annua L*.). Its earlier mention date back to 200 years in the "Recipes for 52 kinds of Diseases" found in the Mawangdui Han dynasty tomb dating from 168 B.C.[6] In that work the herb was recommended for the use in heamorrhoids. This plant was mentioned further in the *Zhou Hou Bei Ji Fang* (Handbook of Prescriptions for Emergency Treatment) written in 340 A.D. In the 15th century, Li Shizhen[7] in his *Ben Cao Gang Mu* (Compendium of malaria medica) wrote that chills and fever of malaria can be treated with qinghao. A decoction of *Artemisia annua* and Carapaxtrionycis was suggested in the *Wenbing Tiaobian* in 1798 as a treatment of malaria.[8]

The crystalline active principle component qinghaosu (Artemisinin) **1** was then isolated in 1972.[9] Extraction of dried leaves of *Artemisia annua* with petroleum ether at low temperature and chromatography on silica gel with subsequent recrystallization gave fine crystals with m.p. 156-157^{o}C and $[\alpha]_D$=+66.3^{o} (C=1.64 $CHCl_3$).[10] Most of the active principle is found in the leaves and flowering topes of the plant, the highest yield being obtained just before flowering. Studies on artemisinin production requirements conducted in China, India, Europe and USA indicate that yields vary between 0.01 and 0.17% weight per weight (w/w), depending on plant variety, cultivation conditions, and harvest season and locality. In India, artemisinin is reported to have been isolated to the extent of 0.17 (w/w) from *Artemisia annua* occurring around Lucknow.[11] Surprisingly, in 1986, Liersch *et al* established the presence of artemisinin in *A. apiaceae* (0.08%).[12]

Artemisa annua was found to have other terpenes and related compounds like 1,8-cineole, borneol acetate, 1-β-pinene, cuminal β-caryophyllene, coumarin, stigmasterol, camphene, cadinene, arteannuin-B, camphor, β-fernesene, arteannuin A, hydroarteannuin, scopolin, scopoletin, artemisia ketone, artemisinic acid and benzylisovalerate.[8,13]



(+)-1

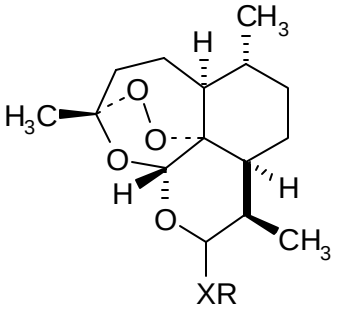
High resolution mass spectrum[14] (m/z 282.1745 M^+) combined with elemental analysis led Chinese workers to assign an empirical formula of $C_{15}H_{22}O_5$ which showed no absorption in the UV range while in IR region there were absorption peaks at 1745 cm^{-1} (lactone) and at 722, 831, 881, 1115 cm^{-1} (peroxide). ^1H and ^{13}C-NMR spectral analysis led to the assignment of three methyl groups, an acetal function and several other carbon atoms. The structure of artemisinin together with its absolute configuration was finally resolved by X-ray diffraction studies.[15] Absolute configuration of the lactone ring has been reached by a comparison of its ORD spectrum with a structurally related known sesquiterpene arteannuin-B **7**. The most unusual feature of the chemical structure is the 1,2,4-trioxane ring which may also be viewed as a bridging peroxide group. Artemisinin is the only known 1,2,4-trioxane occurring in nature, although compounds with peroxide bridges are common, particularly in marine organisms. This unusual compound has a peroxide grouping but lacks nitrogen containing heterocyclic ring system, which is found in most antimalarial compounds.

1.1.2 Biological Activity

In extensive clinical trials in China,[16] artemisinin **1** showed promising results in the treatment of otherwise drug resistant malarial parasites, notably *Plasmodium falciparum*. This unusual compound has peroxide grouping but lacks a nitrogen containing heterocyclic system which is found in most antimalarial compounds. It is almost certain that this crucial structural part in artemisinin which gives its antimalaraial activity is the peroxide bridge since the reduced peroxide deoxyartemisinin is completely inactive. Other parts of the molecule may be modified without loss of antimalarial activity. Removal of one or two of the methyl groups at 13 and 14, leaves a molecule which is still active against *Plasmodium falciparum*.[17] The lactol **2a** obtained by reduction of artemisinin is a better antimalarial agent than artemisinin **1** itself, indicating clearly that carbonyl function is not essential for the activity.[18]

Although the peroxide bridge may be crucial structural part in artemisinin, the rest of the molecule has a profound effect on the *in vitro* and *in vivo* antimalarial activity of artemisinin and related compounds. The ether derivative **2b** is a better antimalarial agent than artemisinin itself.[19] Esters **2c** are generally as effective as artemisinin but the corresponding acid **2d** are much less so, carbonates **2e** are least effective of this group of compounds. Sodium artelinate **2f** only slightly less

effective than artemisinin *in vivo*. A number of highly effective antimalarial agents have been obtained by replacing the carbonyl group of artemisinin by amino group **2g**.[20]



2

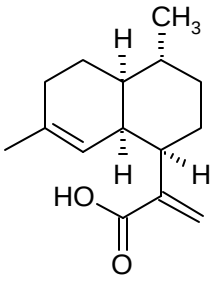
2a: XR= OH
b: XR= Oalkyl
c: XR= $OCOR^1$
d: XR= $OCOOR^1$
e: XR= $OCOCH_2CH_2COOH$
f: XR= $OCH_2C_6H_4COONa$
g: XR= NHR

1.1.3 Mode of Action

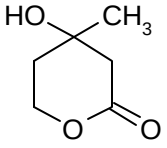
After infection of a person by the bite of an infected female *Anopheles*, *Plasmodium* parasites, first accumulate in hepatocytes then invade the erythrocytes for the next stage of their maturation. After a few days, the infected red blood cells burst open and the merozoites are released causing the periodic fever of malaria. These released merozoites infect new erythrocytes and the intraerythrocyte cycle starts again. Within erythrocytes, the parasite degrades the hemoglobin of the host and digest 30% or more of the protein moiety using it as a source of amino acids for synthesis of its own proteins. The resulting free and potentially toxic heme residues are then polymerized as a microcrystalline redox inactive iron (III) heme pigment known as hemozoin, which is insoluble in biological conditions and accumulates in food vacuole.[21, 22] Only a small amount of heme is degraded by the parasite to be used as an iron source for its own metalloenzymes. The studies showed that the major modes of reactivity of artemisinin is its reductive activation leading to the homolytic cleavage of its peroxide bond. The resulting alkoxy radicals are rearranged in non-sterically hindered C-centered radicals acting as powerful alkylating agents. The alkylation reactions involve the generation of drug radicals in the vicinity of heme in a solvent-cage controlled reaction instead of as freely diffusible radicals. Thus artemisinin **1** or its derivatives or other synthetic antimalarial compounds with endoperoxide should be able to alkylate either heme itself or parasitic proteins. This alkylation process occurs at a pharmacologically relevant concentrations of the drug, and would inhibit the proteases responsible for the hemoglobin digestion within infected erythrocytes, thus starving the parasite of essential amino acids.[23] The alkylation and inactivation of proteins involved in the heme polymerization namely the histidine-rich protein would poison the parasite with redox active heme molecules. High heme

concentrations are supposed to be responsible for oxidative stress within the cell inducing a disruption of membranes and they have also been shown to inhibit a parasitic hemoglobinase.[24] Alkylation of heme by a drug derived radical may also be responsible for parasitic death through accumulation of non polymerizable redox active heme adducts which could also behave as inhibitors for heme polymerization enzymes.

1.1.4 Biosynthesis



3a



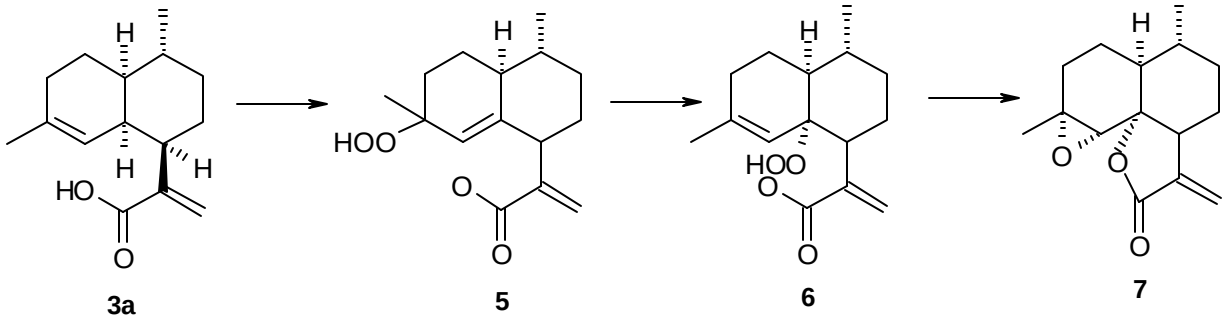
4

Artemisinin appears to be unique to *Artemisia annua* and is at a maximum concentration in the upper leaves at the beginning of budding. Labeling experiments have identified two intermediates *enroute* to artemisinin **1**: artemisinic acid **3** and mevalonic acid lactone **4.**[25]

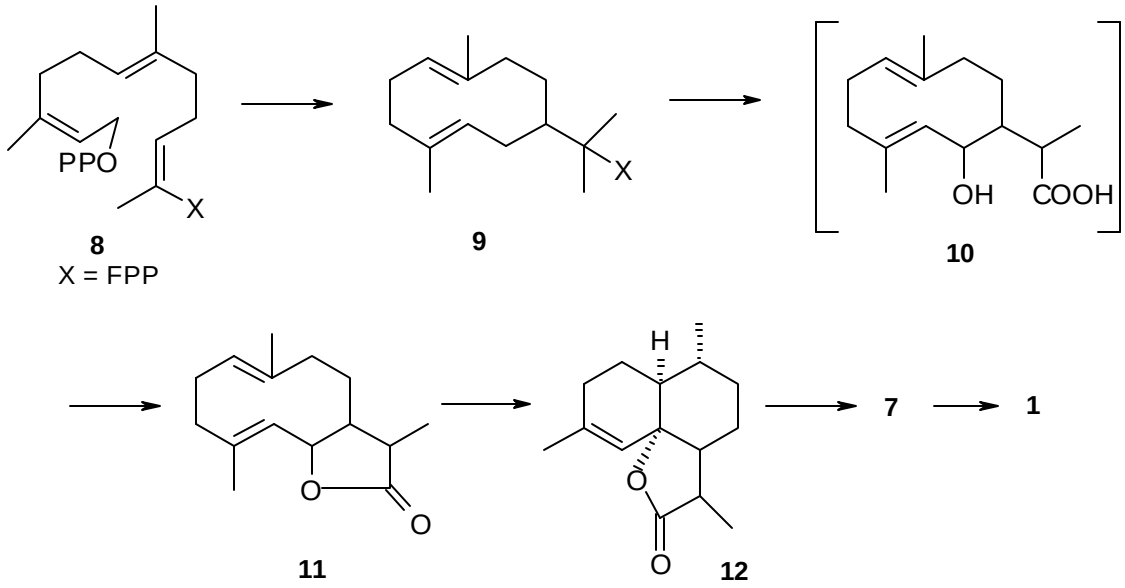
El-Feraly *et al*[26] reported that **(Scheme 1)**, artemisinic acid **3** gets converted to hydroperoxide **5** which rearranges to **6** and epoxidation, deoxygenation followed by lactonization of which yields arteanuin-B **7**. From this it was inferred that artemisinic acid **3** could serve as biogenetic precursor for artemisinin.

In 1987, Akhila *et al*[27] reported **(Scheme 2)** arteannuin-B **7** to be a late precursor in the biosynthetic pathway of artemisinin **1**. Their suggested pathway is that cis-isomer of farnesyl pyrophosphate **8** may cyclize to **9** which then enters the pathway **9** to **10** to dihydro-costunolide **11**, cadinanolide **12**, arteannuin-B **7** and finally to artemisinin **1**. In 1988, Yu *et al*[28] reported incorporation of [15-34] isomer of artemisinic acid **3** into biosynthesis of artemisinin **1** and arteannuin-B **7** in qinghao plant homogenate system and inferred that artemisinic acid **3** to be a key intermediate in the biosynthesis of artemisinin and arteannuin-B **7**.

Scheme 1:

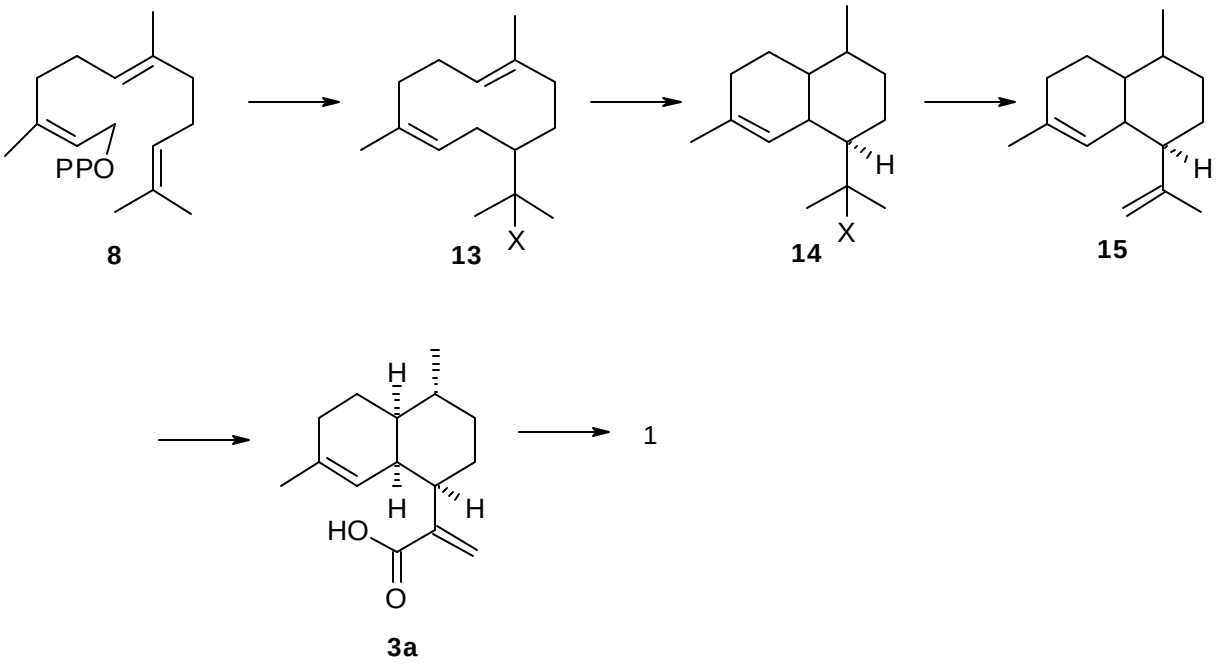


Scheme 2:



In 1990, Akhila *et al*[29] reported complete biosynthesis of artemisinic acid **3** in *Artemisia annua* which has been found to play vital role in the biosynthetic pathway of artemisinin **1**. According to suggested biosynthetic pathway, the *cis*-isomer of farnesyl pyrophosphate **8** (**Scheme 3**) cyclizes to **13** which forms cadinane skeleton **14** from which artemisinic acid **3a** is formed *via* intermediate **15**.

Scheme 3:

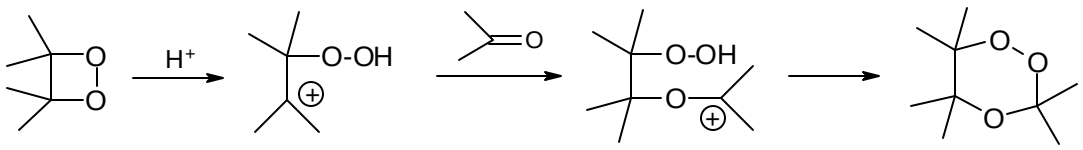


1.1.5 Synthesis of (+)-Artemisinin: A Literature survey

The low natural abundance (0.01-0.95% dry weight) of artemisinin together with its complex chemical structure have prompted the development of several successful synthetic strategies. Synthesis have been reported from monoterpenes such as (-)-isopulegol, R(+)-citronellal, (+)-pulegone, (-)-β-pinene, (+)-3-carene. Arteannuic acid, an inactive congener and biochemical precursor of artemisinin has also been used to synthesize artemisinin.

Two types of strategies have been used for the total synthesis of artemisinin **1**. In the first, total synthesis of artemisinic acid **3** has been carried out stereospecifically, which was then elaborated to artemisinin **1** using the photoxygenation methodology used by Roth and Acton[35] or Jung *et al*[39] or Haynes.[41] In the second, the pioneering work of Avery *et al*[33] describes the total synthesis of artemisinin **1** making used of ozonolysis of vinyl silanes as the key step. During photooxygenation as the key step, in most cases the 1,2,4-trioxane ring has been formed by the addition of the singlet oxygen to olefin in the presence of photosensitizer followed by protonation and reaction with a carboxyl compound (**Scheme 4**). This approach to the synthesis of trioxane has been fully explored by Jefford and his co-workers.[29]

Scheme 4:

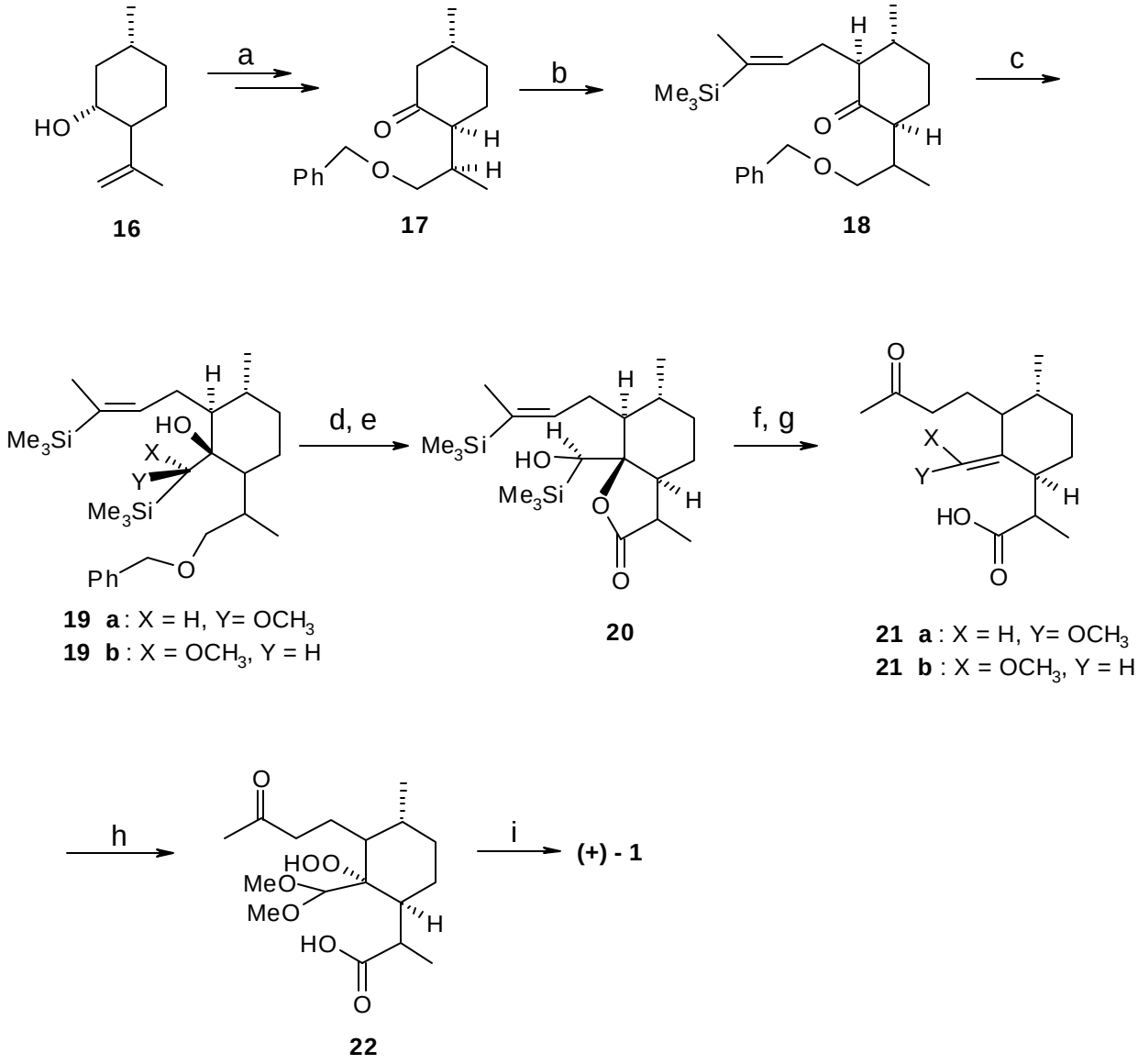


Schmid's Approach[31] (Scheme 5, 1983)

Schmid *et al*[31] reported the first total synthesis of (+)-artemisinin starting with (-)-isopulegol **16** in 1983. (-)-Isopulegol **16** was converted into methoxymethyl ether followed by its hydroboration with B_2H_6 at 0°C in THF to give after oxidative workup with alkaline H_2O_2 the 8-(*R*) alcohol (80%) along with its 8-(*S*)-epimer (10%). The primary hydroxy group was protected as benzyl ether and then MOM-ether was cleaved and resulting secondary alcohol was oxidized with PCC to furnish (benzyloxy) methane **17**. The overall yield for the conversion of (-)-isopulegol into **17** was 58%. Kinetic deprotonation of **17** and treatment of the resulting enolate with *E*-(3-iodo-1-methyl-1-propenyl)trimethylsilane provided a 6:1 mixture of epimeric alkylation products from which major isomer **18** was isolated in 62% yield.

The key intermediate enol ether **21** was directly prepared from the reaction of ketone **18** with 1 equivalent of lithium methoxy(trimethylsilyl)methylide, two diastereomeric alcohols, **19a** and **19b** were obtained in a 1:1 ratio and almost in quantitative yield. By use of a 10 fold excess of the silyl reagent the ratio of **19a** to **19b** was shifted to 8:1 and **19a** was isolated in 89% yield. The compound **19a** was debenzylated with Li-liq.NH_3 and the resulting alcohol was oxidized to the lactone **20** with PCC in 75% yield. When lactone **20** was treated with m-CPBA followed by fluoride ion, smooth desilylation occurred with simultaneous generation of enol ether and carboxylic acid function **21**. The final key step involved the irradiation of the methalonic solution of **21** in the presence of singlet oxygen with methylene blue as sensitizer at –78°C to give hydroperoxide intermediate **22**. On treatment of the crude mixture of **22** with formic acid crystalline artemisinin (+)-1 was obtained in 30% yield. This synthesis is noteworthy not only because of this is the first synthesis of artemisinin but it provided a key sub target *viz* the enol ether **21** which can become the basis of synthetic design for other workers.

Scheme 5: Schmid's approach, *JACS*, **1983**, 105, 624



16 **17** **18**

19 a : X = H, Y= OCH_3
19 b : X = OCH_3, Y = H

20

21 a : X = H, Y= OCH_3
21 b : X = OCH_3, Y = H

22

Reagents and Conditions:

a) i. $ClCH_2OCH_3$, $PhN(CH_3)_2$, CH_2Cl_2 rt. ii. B_2H_6, THF, 0^0C, H_2O_2/HO^-. iii. $PhCH_2Br$, KH, 4:1 THF:DMF, 0^0C. iv. CH_3OH, HCl, 40^0C, 5h. v. PCC, CH_2Cl_2, rt. b) LDA, THF, TMS (Me) C=CH-CH_2I c) TMS(Li)C(OCH_3)H, THF, -78^oC. d) Liq. NH_3, Li. e) PCC. f) m-CPBA, THF, TFA. g) N-Bu_4NF, THF. h) O_2, MB, MeOH, hν, -78^oC. i) HCOOH, CH_2Cl_2.

Zhou's Approach [32]: (Scheme 6, 1986)

Zhou *et al*[32] reported second synthesis of artemisinin **1** in 1986 using a similar approach starting from *R*-(+)-citronellal **23**. Citronellal **23** was converted to benzyloxymethanone **17** in four steps in 51% overall yield from *R*-(+) citronellal **23**.

Kinetic deprotonation of **17** with LDA and the reaction of resulting enolate with silylated vinylketone gave the 1,3-diketone **25** alongwith simultaneous cleavage of trimethylsilyl group. The 1,3-diketone **25** was then cyclized with $Ba(OH)_2$ and on dehydration with 2-5% oxalic acid gave the enone **26**. This enone **26** was converted to saturated ketone **27** by reduction with sodium borohydride in pyridine followed by oxidation with Jones reagent. Ketone **26** on treatment with Grignard reagent CH_3MgI and subsequent dehydration with p-TsOH furnished the mix of **28** and its A^3-isomer in 1:1 ratio which was separated by flash chromatography. The ketone **28** was then debenzylated with sodium in liquid ammonia to furnish alcohol, which was oxidized with Jones reagent to the acid. Acid was esterified with diazomethane to afford **29** in 72% overall yield in three steps. Ozonolysis followed by reductive work-up with Me_2S of **29** furnished the ketoaldehyde **30** which was regioselectively protected at the ketonic carbonyl with 1,3-propanedithiol, aldehyde was converted to its acetal by treatment with trimethylorthoformate. The thioketal was then deprotected using mercuric chloride in aqueous acetonitrile to give intermediate enol ether **21**. Photooxidation of the methanolic solution of **21** in the presence of oxygen and Rose Bengal at -78 °C followed by acid treatment furnished atemisinin **1** in 28% yield. The synthesis involves a long sequence (22 steps) to obtain the artemisinin starting from citronellal. The design of synthesis is mainly the application of general methodologies available for ring formation, usual functional group transformations, selective protection and deprotection.

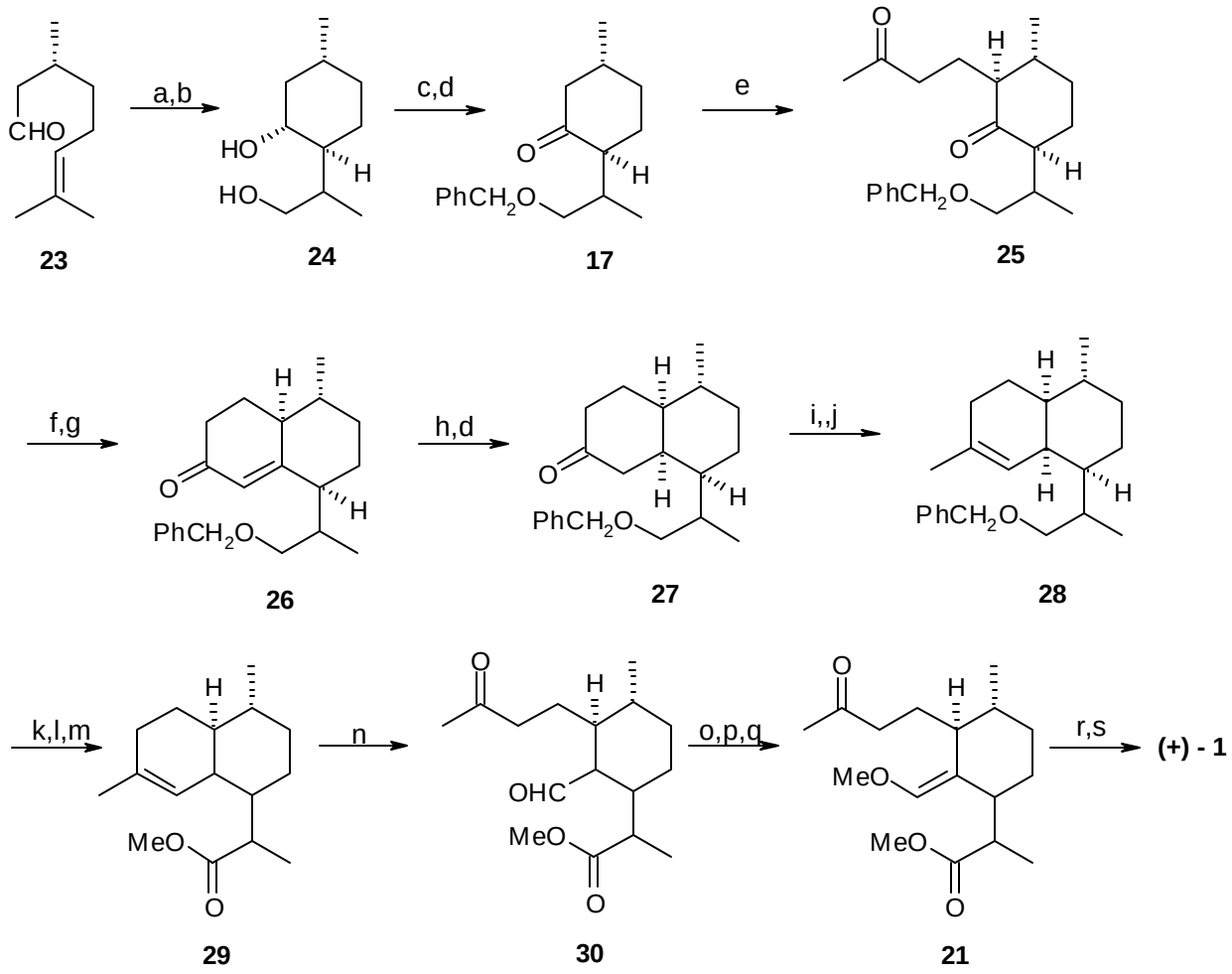
Avery's Approach[33] **(Scheme 7, 1992)**

Chiral sulfoxide **32** was used as starting material and transformed into optically active ketone **34** alongwith unwanted isomer as a minor product through two steps. Chiral sulfoxide **32** was obtained from (R)-(+)-pulegone **31** (**Scheme 7**).

(R)-(+)-pulegone was epoxidized with alkaline H_2O_2. Thiophenoxide opening of epoxide with concomitant retro-aldol expulsion of acetone yielded regiosiomerically pure phenyl thio ketone, which was oxidized with peracid to sulfoxide **32**. Reaction of keone **34** with tosylhydrazine followed by treatment with 4-equivalents of n-BuLi and trapping of the resultant vinyl anion with DMF yielded α,β-unsaturated aldehyde **36**.

1,2-addition of tris (trimethylsilyl)aluminium etherate to aldehyde **36** and subsequent quenching with acetic anhydride yielded a single silyl acetate **37**. Upon treatment of **37** with lithiumdiethylamide (LDEA) an Ireland-Claisen rearrangement took place, forming

Scheme 6: Zhou's approach, *Tetrahedron* **1986**, 42, 819.



Reagents and Conditions:

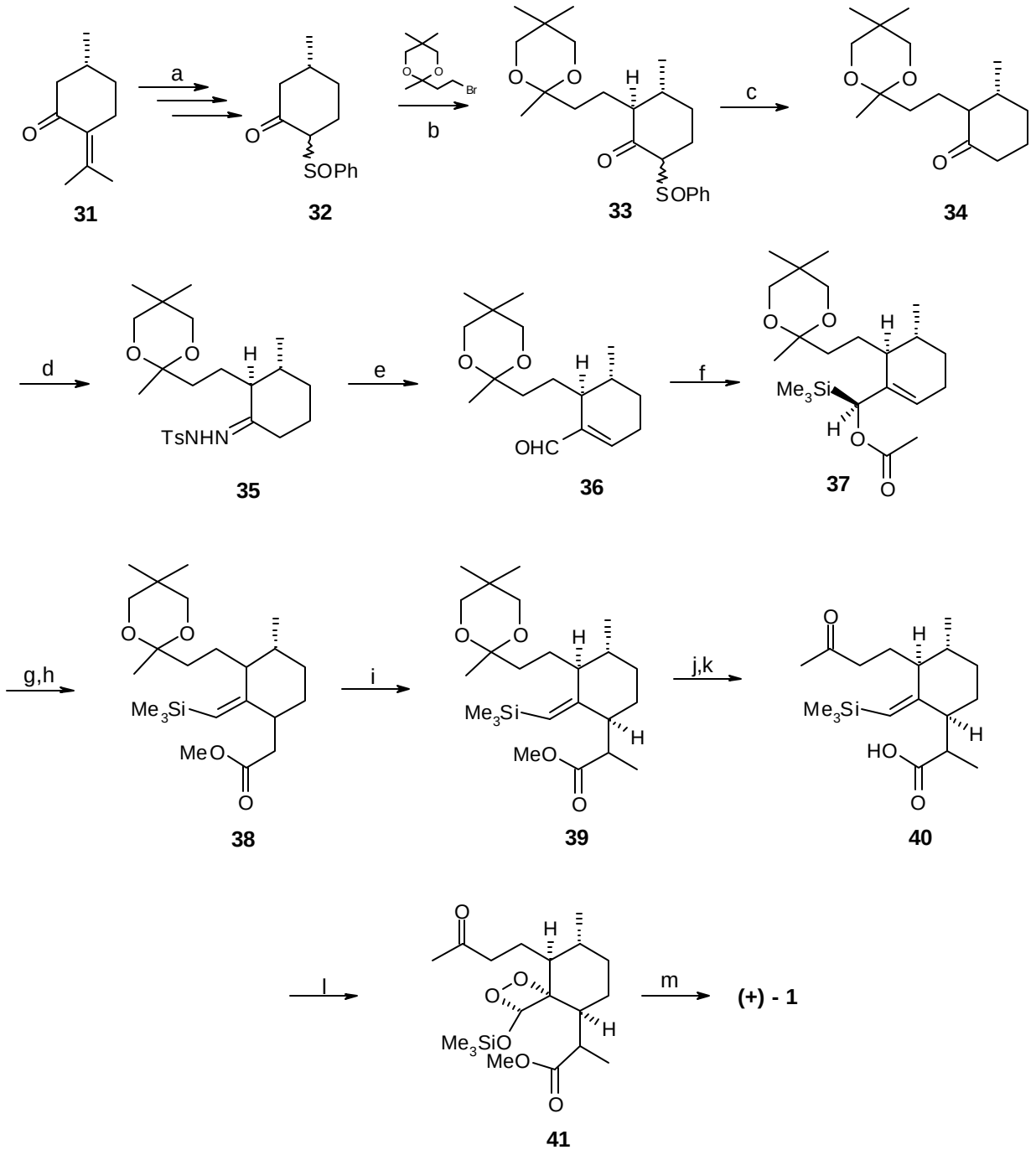
a) $ZnBr_2$. b) B_2H_6, H_2O_2, HO^-. c) $PhCH_2Cl$, NaH. d) Jone's reagent.

e) LDA, $CH_2=C(Me_3Si)COCH_3$. f) $Ba(OH)_2.8H_2O$. g) $(COOH)_2$. h) $NaBH_4$-Py. i) CH_3MgI.

j) p-TsOH. k) Na-liq.NH_3. l) Jone's reagent. m) CH_2N_2. n) O_3, Me_2S. o) $HS(CH_2)_3SH$, $BF_3.Et_2O$, CH_2Cl_2. p) $CH(OMe)_3$, p-TsOH. q) $HgCl_2$-$CaCO_3$, aq. CH_3CN. r) O_2, MeOH, Rose Bengal, hν, -78^{0}C. s) 70% $HClO_4$.

regioselectively the vinyl silane moiety and connecting stereoselectively the acetic acid function to give desired product **38**. Methylation of **38** with 2 equivalents of LDA leads to a single, diastereoisomerically pure homologues ester **39**. Ester **39** was hydrolyzed with KOH/MeOH to yield acid **40**. The acid **40** was converted in a one pot procedure involving sequential treatment

Scheme 7: Avery's approach, *JACS*, **1992**, 114, 574



Reagents and Conditions:

a). i. Alkaline H_2O_2, THF. ii. NaSPh, THF. iii. m-CPBA, CH_2Cl_2, -78^{0}C. b). LDA, HMPA, -78^{0}C. c) Al(Hg) amalgam, wet THF.d) $TsNHNH_2$, pyridine, THF.e) n-BuLi, TMEDA, DMF. f) $(Me_3Si)_3Al.OEt_2$, -78^{0}C, Ac_2O, DMAP, -78^{0}C to 23^{0}C. g) LDEA, -78^{0}C-23^{0}C.

h) K_2CO_3, Me_2SO_4. i) LDA, MeI. j) KOH/MeOH. k) Aq. $H_2Cr_2O_4$. l) O_3, MeOH.
m) CF_3COOH.
with ozone followed by wet acidic silica gel to effect a complete process of dioxetane formation **39**, ketal deprotection and cyclization to the natural product artemisinin **1** in 33-39% yield.

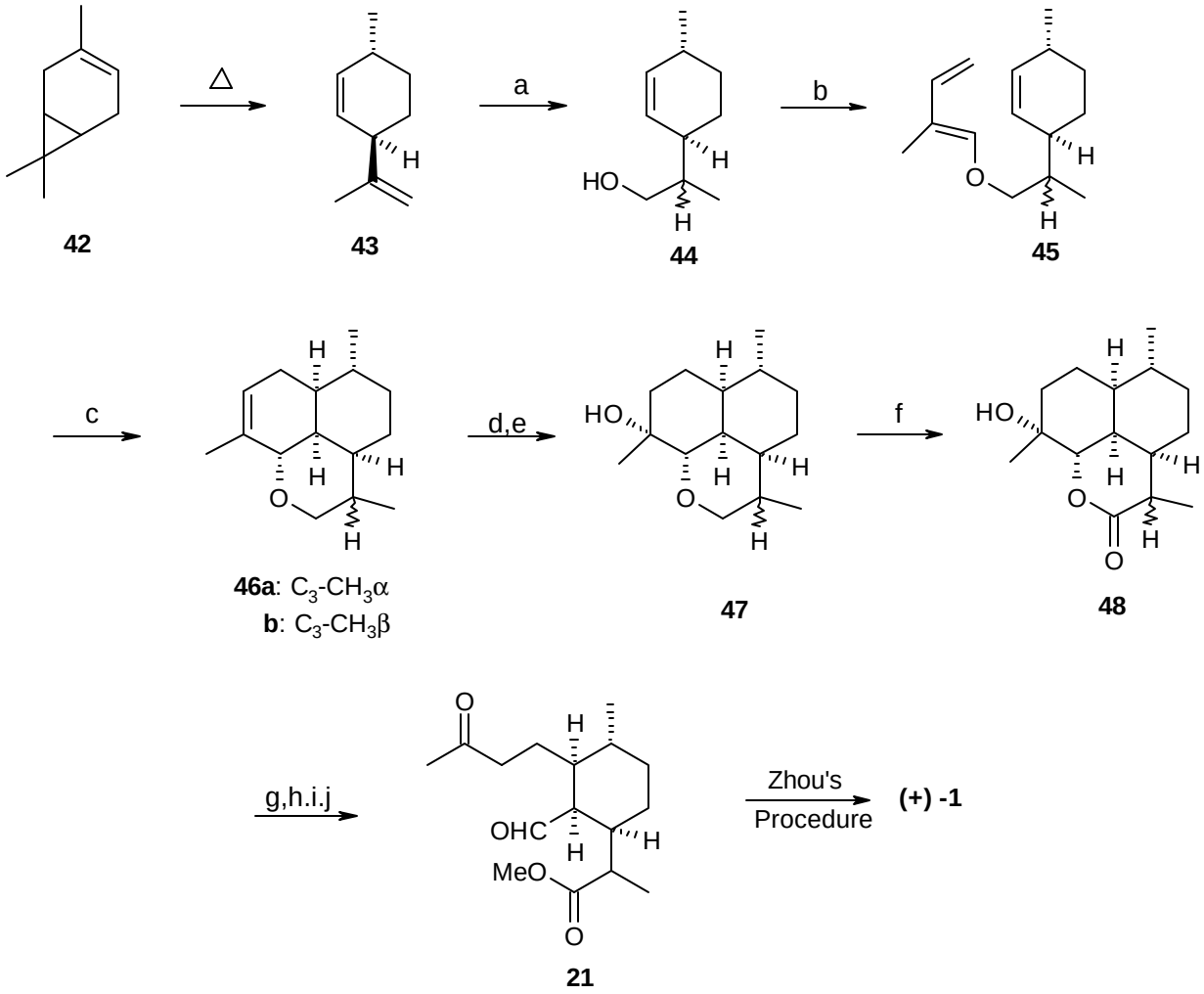
This synthesis is more elegant and more promising from practical point of view, although lacking to some extent in terms of stereospecificity.

Ravindranathan's Approach[34] **(Scheme 8, 1990)**

Ravindranthan *et al*[34] reported stereoselective synthesis of artemisinin **(+)-1** from (+)-isolimonene **43** (**Scheme 8**) which in turn can be easily obtained from (+)-car-3-ene a cheap abundantly available monoterpene. Isolimonene **43** was hydroborated regioselectively with 9-BBN followed by oxidative work-up with alkaline H_2O_2 to yield epimeric mixture of alcohols **44**. Alcohol **44** was converted to enolether **45** by transesterification with 1-ethoxy-2-methyl-1,3-butadiene. The triene **45** underwent an intramolecular Diels-Alder reaction to furnish an epimeric mixture of ethers **46a** and **46b** in 25-30% yield. The mixture of **46** was then epoxidised with m-CPBA, reduced with $LiAlH_4$ followed by oxidation with $RuCl_3.3H_2O$-$NaIO_4$ to furnish the epimeric mixture (7:3) of lactone **48**. Epimeric lactones **48a** and **48b** were separated and characterized by ^{1}H-NMR and X-ray analysis. Pure **48a** could be equilibrated with NaOMe/MeOH to obtain equilibrium mixture of **48a** and **48b** in a ratio 6:4 and thus both the epimers can be converted to artemisinin *via* **21**.

Since the conversion of **21** to artemisinin **1** can be preformed by the procedure reported by Zhou *et al*[32], this constituted a formal total synthesis of artemisinin **1**.

Scheme 8: Ravindranathan's approach, *Tet. Lett*. **1990**, 31, 755.



42 **43** **44** **45**

46a: C_3-$CH_3\alpha$
b: C_3-$CH_3\beta$

47 **48**

21

Reagents and Conditions

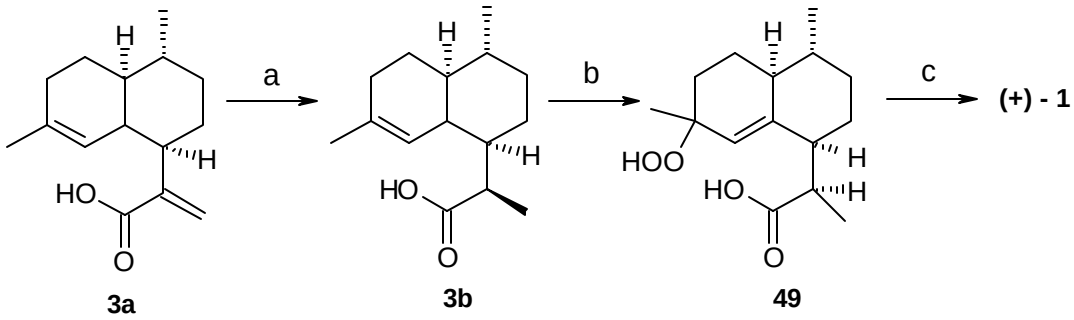
a) 9-BBN (1 equiv), H_2O_2, NaOH (3N).b) 1-Ethoxy-2-methyl-1,3-butadiene, $Hg(OAc)_2$, NaOAc.c) Toluene, 210^0C, sealed tube, 72h.d) m-CPBA, CH_2Cl_2, 0^0C. e) $LiAlH_4$, Et_2O. f) $RuCl_3.3H_2O$, $NaIO_4$, H_2O:CCl_4:CH_3CN. g) $NaOCH_3$, MeOH. h) NaOH (1eq.) i) $NaIO_4$. j) CH_2N_2, Et_2O.

Roth & Acton's Approach[35]: (Scheme 9, 1991)

Roth & Acton[35] reported a facile partial synthesis of artemisinin **1** from artemisinic acid **3a** in two steps. Thus, artemisinic acid **3a** on treatment with $NaBH_4$ and $NiCl_2.6H_2O$ in MeOH furnished dihydroartemisinic acid **3b**. Photooxidation of dihydroartemisinic acid **3b** at -78°C in

dichloromethane with methylene blue as sensitizer followed by change of solvent to pet. ether and stirring the reaction at room temperature for 4 days yielded artemisinin **1** in 30% yield.

Scheme 9: Roth's approach, *J. Chem. Edu*, **1991**, 68, 612



3a **3b** **49**

Reagents and Conditions:

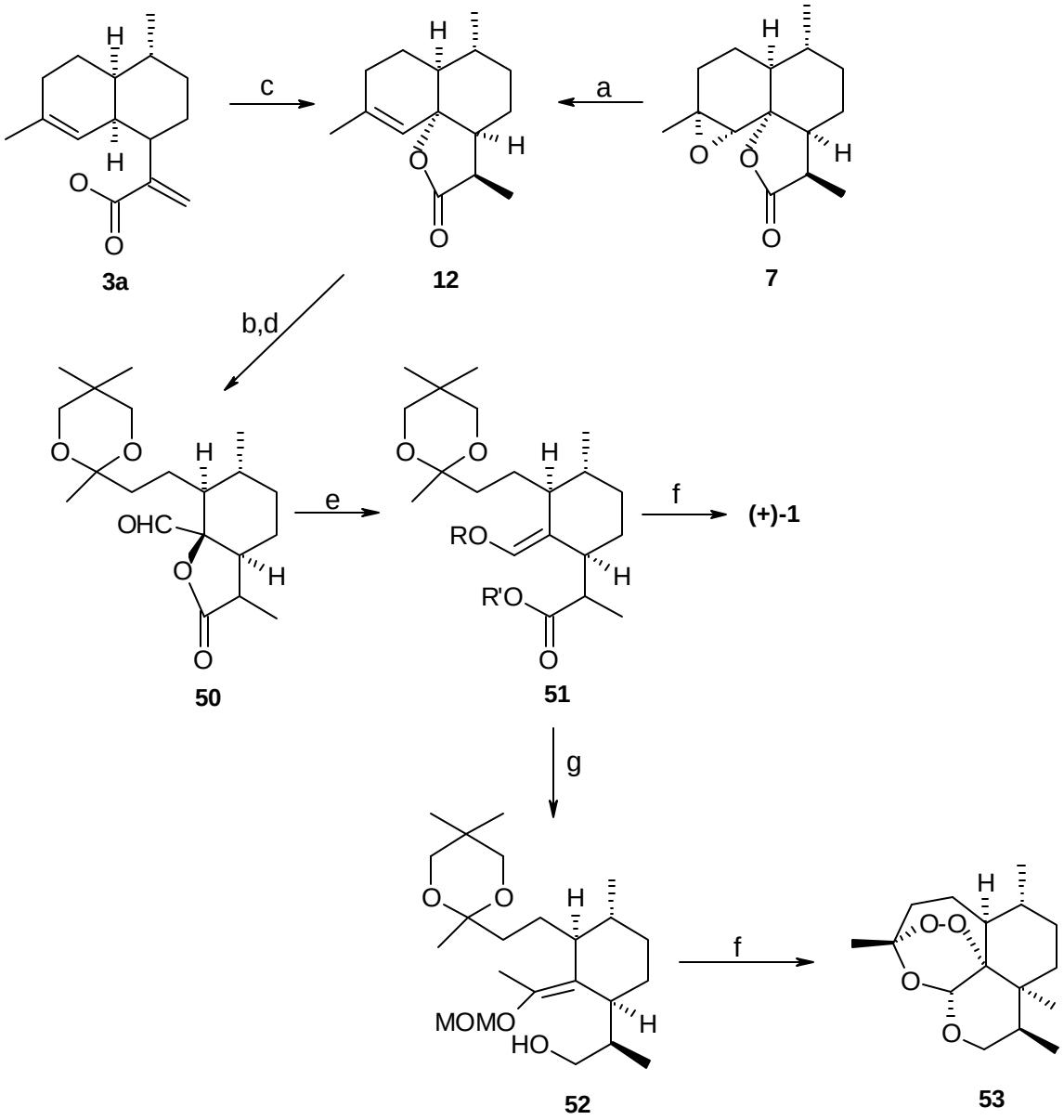
a) $NaBH_4$, $NiCl_2.6H_2O$. b) hν, O_2, MB. c) Air, TFA, Pet. Ether.

Lansbury's Approach[36]: (Scheme 10, 1992)

Lansbury *et al*[36] reported an efficient partial synthesis of artemisinin **1** and deoxoartimisinin **51**. Thus artemisinic acid **3a** and arteannuin-B **7** were used as starting material and separately converted into **12**. Ozonolysis of **12** and selective protection of the resulting ketone carbonyl afforded **50**. Reductive cleavage of **50** with sodium napthalenide followed by *in situ* reaction with alkylating agents (CH_3I and CH_3CH_2COCl) produced enol ether-ester **51a** and **51b**. $^1O_2$ reaction of **51a** and **51b** with Rose Bengal as sensitizer resulted in 30-35% isolated yield, of artemisinin **1**.

Reduction of **51a** and **51b** with $LiAlH_4$ produced alcohol **53**. $^1O_2$ reaction of alcohol **52** furnished deoxoartemisinin **53** which has been known to possess *in vitro* and *in vivo* antimalarial activity superior to that of artemisinin **1**.

Scheme 10: Lansbury's approach *Tetrahedron Lett*., **1992**, 33, 1029.



Reagents and Conditions:

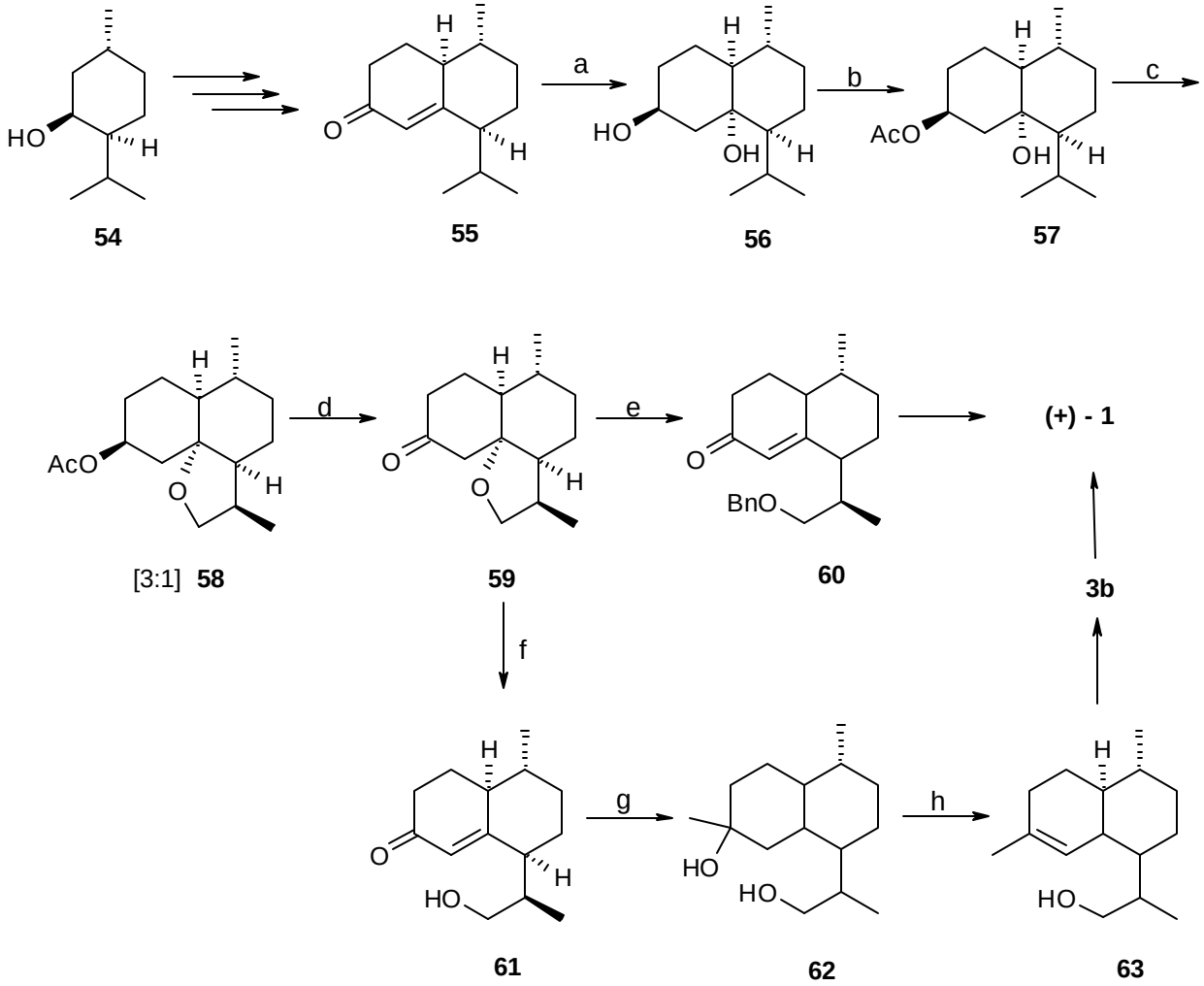
a) n-BuLi, Tungsten hexachloride, THF. b) O_3/O_2. c) CrO_3, 3,5-dimethyl pyrazole, CH_2Cl_2.

d) 1,2-bis(trimethylsilyl)oxyethane, TMSOTf, CH_2Cl_2. e) Sodium naphthalenide, THF,then MeI, CH_3OCH_2Cl. f) O2, Rose Bengal, CSA. g) $LiAlH_4$.

Ravindranathan's Approach[37]:(Scheme 11, 1994)

In 1994, Ravindranathan *et al*[37] reported second stereoselective synthesis of (+)-artemisinin starting from menthol (**Scheme 11**). Menthol **54** was converted to the ketone **55** in four steps. Epoxidation of **55** with alkaline H_2O_2 furnished mainly the α-epoxide, which on reductive opening with $LiAlH_4$ furnished β-secondary alcohol **56**. Regioselective acylation of secondary alcohol **56** with Ac_2O and pyrindine gave **57**. For the C-2 functionalization of C-H of primary methyl from isopropyl group in **57**, a lead tetraacetate and iodine combination along with photolysis was used.

Scheme 11[37]: Ravindranathan's approach, TL, **1994**, 35, 5489



Reagents and Conditions:

a). i. 30% H_2O_2, NaOH, MeOH, -10^0C. ii. $LiAlH_4$ Ether, reflux. b) Ac_2O, py, rt. c) LTA, I_2, C_6H_{12}, hν (500W, Tungsten Lamp), reflux, then Zn-dust, AcOH. d). i. KOH, EtOH, H_2O, rt. ii. PCC. e) NaH, DMF, -10^0C, 45 min, then $PhCH_2Br$ in DHF, -10^0C. f) Acidic alumina. g). i. H_2 (20psi), 10% Pd/C, MeOH, rt. ii. $MeMgI/I_2$/ether. h). i. Ac_2O, py, r.t. ii. $POCl_3$, py, rt. iii. KOH, EtOH, rt.

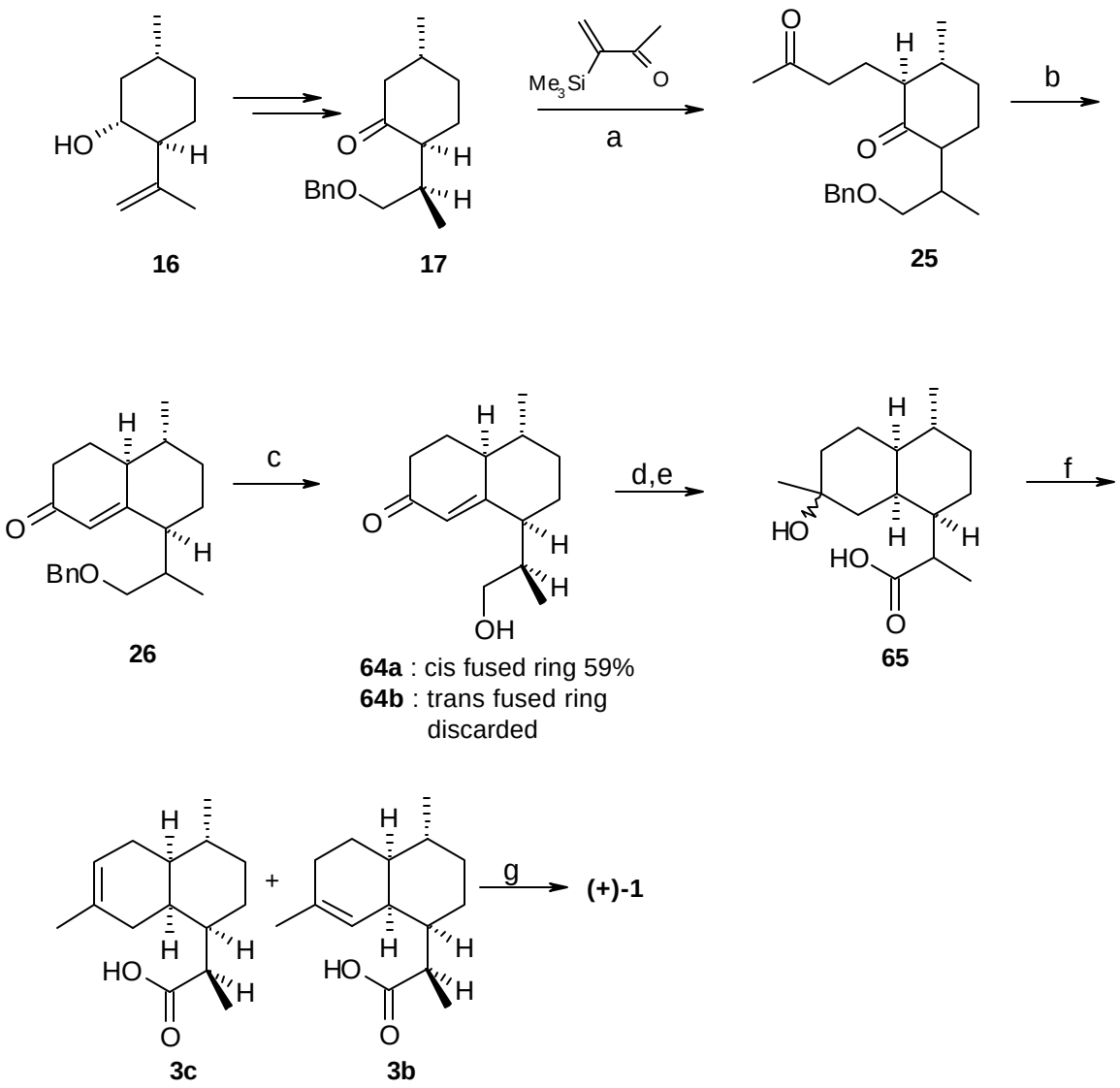
Saponification followed by PCC oxidation gave **59**. The reaction of **59** with sodium hydride in DMF at −10°C followed by addition of benzylbromide gave kinetic benzylation product **60**. Synthesis of (+)-artemisinin from **60** is reported by Zhou *et al*.

Alternately, treatment of **59** with acidic alumina furnished **61** in 68% yield. Catalytic reduction of **61** with 10% Pd/C at 20 psi as room temperature was stereoselective and only the *cis*-junctured non-steroidal ketoalcohol was obtained. Treatment of ketoalcohol with 2.5 equivalents of MeMgI gave quantitative yield of Grignard product **62**. Subsequently, the primary alcoholic group of **62** was acylated which on treatment with $POCl_3$ and pryidine gave 50:50 mixture of regioisomers. The separation of the desired isomer was possible after saponification to furnish **63**. The conversion of artemisiol **63** to (+)-artemisinin 1 is reported.[38,39]

Constantino's Approach[40] (**Scheme 12, 1996)**

Constantino *et al*[40] reported the total synthesis of (+)-artemisinin **1** starting from (-)-isopulegol **16** (**Scheme 12**), a cheap and abundantly available monoterpene. Thus isopulegol **16** was converted to the benzyloxymenthone **17** in three steps. A three step Robinson annulation starting with menthone **17** furnished enone **26** in 37% yield. The simultaneous reduction of double bond and hydrogenolysis of the benzyl group were affected by hydrogenating **26** with 5% Pd/C furnishing two isomers **64a** and **64b**. The major isomer, *cis*-fused ring system **64a** was separated by column chromatography in 59% yield. Compound **64a** on oxidation with PDC furnished ketoacid. The carbonyl group of the ketoacid furnished a mixture of epimeric tertiary alcohols **65a** and **65b** on treatment with methyllithium. The treatment of the mix of isomeric **65** with p-TSA in benzene gave dihydroartemisinic acid **3b** in 43% yield alongwith its regioisomer **3c**. Finally, dihydroartemisinic acid **3b** was converted into artemisinin **1** by using Roth & Acton procedure.[35]

Scheme 12: Constantino *et al*, *Synth. Commun.*, **1996**, 26, 321.



Reagents and Conditions:

a) LDA. b) i. $Ba(OH)_2$ ii. Oxalic acid c) H_2, Pd/C. d) PDC e) 2MeLi f) p-TSA g) i. O_2/hν ii. TFA, air.

1.1.6 Present work:

The present section primarily concerns with synthetic studies towards (+)-artemisinin **1**, a naturally occurring endoperoxide sesquiterpene. Artemisinin was isolated from *Artemisia annua* in 1972.[9] Among different species, artemisinin occurs mainly in *Artemisia annua* and it is also

isolated from *Artemisia apoaceae* (0.08%).[12] Low natural contents of artemisinin and even special horticulture methods or plant tissue culture methods have been employed to enhance artemisinin contents, but the success is not very high. The comparative non-abundance of the species and low contents of artemisinin would probably require a good synthetic strategy for its production and also analogues which may finally be found useful in therapy.

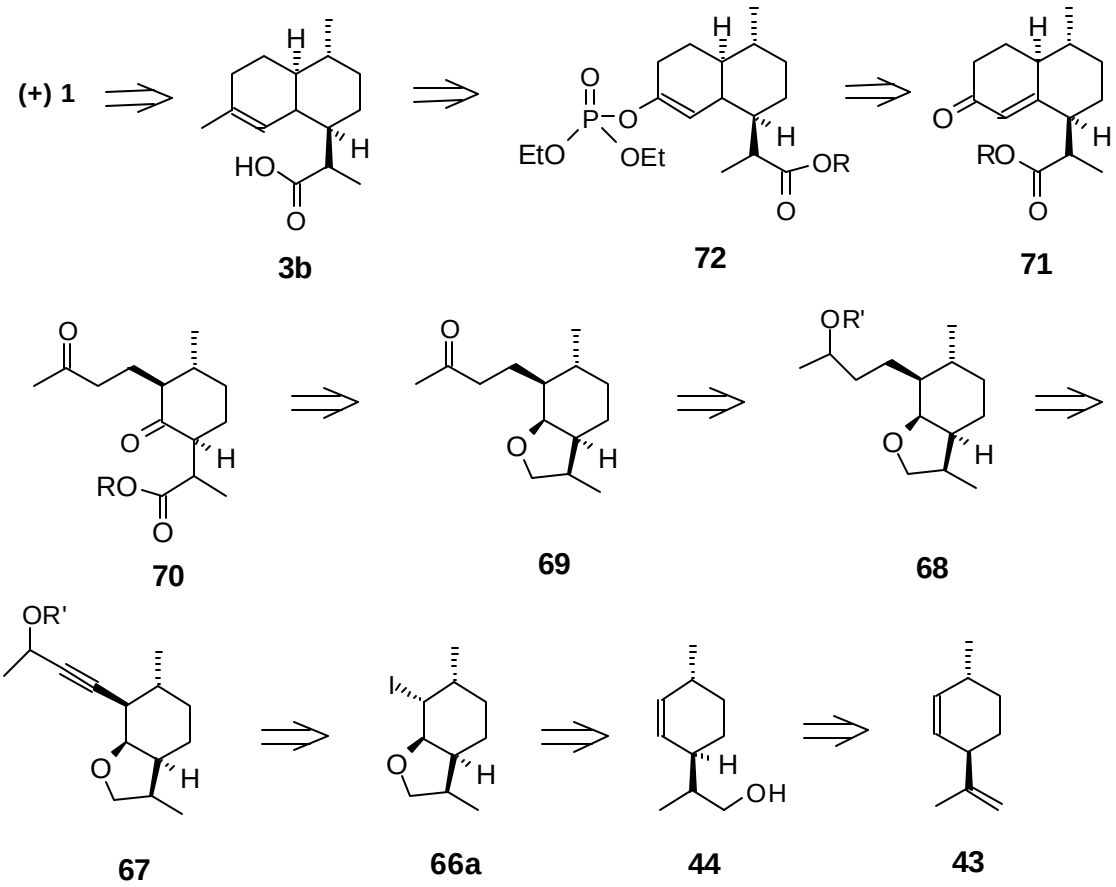
The unusual structure and antimalarial activity of artemisinin prompted organic chemists to develop synthetic routes towards it.[31-41] The present work describes synthetic studies towards artemisinin **1**.

1.1.7 Results and Discussions:

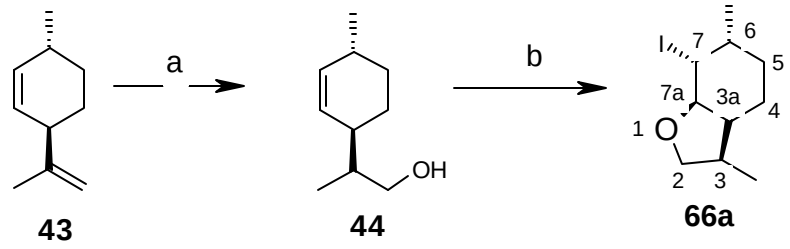
Retrosynthetic analysis for artemisinin was outlined below (**Scheme 13**). The retrosynthetic analysis revealed that, Artemisinin **1** could be obtained from the key intermediate artemisinic acid **3b**. In turn, artemisinic acid **3b** could be obtained from the enone **71** which could be prepared from iodoether **66a** by various synthetic transformations. Iodoether **66a** could be obtained from (+)-isolimonene **43** which is available abundantly and naturally occurring, thus making it an ideal candidate to start with the studies.

Isolimonene **43** was regioselectively hydroborated at the terminal double bond.[42] Thus regioselective hydroboration of isolimonene **43** with 9-BBN followed by oxidative alkaline hydrolysis with H_2O_2 furnished isolimonene alcohol **44** in 76% yield (**Scheme 14**). The stereochemistry at the newly formed chiral center could not be controlled since the addition of borane takes place from both sides of the plane containing the olefin resulting in the formation of both the epimers. IR spectrum of the alcohol **44** showed broad absorption peak at 3350-3500 cm^{-1} indicating the presence of hydroxy group. ^{1}H-NMR of the alcohol **44** displayed two closely placed doublets for epimeric methyl group (CH_3CH-CH_2-OH) and a doublet for ring methyl group (-CHCH_3) giving rise to multiplet in the region δ 0.8-1.0. A multiplet (5H) at δ 1.2-2.0 for methylene groups and a methine proton. Multiplet (2H) at δ 2.35-2.50 for allylic protons, multiplet (2H) at δ 3.4-3.8 (-CH_2OH), a multiplet (2H) at δ 5.5 for olefinic protons were the other peaks in the ^{1}H-NMR spectrum of the compound **44**. Mass spectrum of alcohol showed M^+ peak at 154.

Scheme 13:



Scheme 14:



Reagents and Conditions:

a) i. 9-BBN, THF, 0^0C-rt ii. H_2O_2, NaOH (3N), 0^0C-rt, 76%. b) I_2, $NaHCO_3$, Et_2O, 0^0C-rt 2, 54%.

Alcohol **44** thus obtained was subjected to iodoetherification[43] with I_2 and saturated $NaHCO_3$ at 0^0C in diethyl ether to furnish iodoether **66a** in 60% yield. IR spectrum of the compound **66a** showed disappearance of the broad absorption peak at 3350-3500 cm^{-1}. ^{1}H-NMR of the compound **66a** displayed a multiplet at δ 0.8-1.0 for epimeric methyl group (*CH*$_3$-CH-CH$_2$-)

and ring methyl group (-CH*CH*$_3$). A multiplet (3H) at δ 1.16-1.40. a multiplet (0.3 H) at δ 1.49-1.55 whose counterpart proton appeared as multiplet (0.7 H) at δ 2.4-2.5, a multiplet (1H) at δ 1.65-1.80, a multiplet (2H) at δ 1.95-2.20, a dd (1H) at δ 3.55, a triplet (0.3 H) at δ 4.00 and its counterpart proton at δ 4.20 (t, 0.7 H, J=8 Hz), a multiplet (1H) at δ 4.40-4.45 and a multiplet at δ 4.55-4.65 were the other remaining distinguishing peaks in the ^{1}H-NMR spectrum of the compound **66a**. The multiplet (0.3 H) at δ 1.5-1.55 and its counterpart proton (m, 0.7 H) at δ 2.40-2.50 indicated C-3 epimeric methyl group. It was further confirmed from ^{13}C-NMR analysis of the compound **66a**. ^{13}C-NMR displayed 20 signals for 10 carbons in the molecule indicative of diastereomeric mixture. Mass spectrum of the compound **66a** showed M^+ peak at 280 (6) with base peak at 153. Thus the structure of the iodoether **66a** was assigned and confirmed by IR, ^{1}H & ^{13}C-NMR, mass spectral analysis.

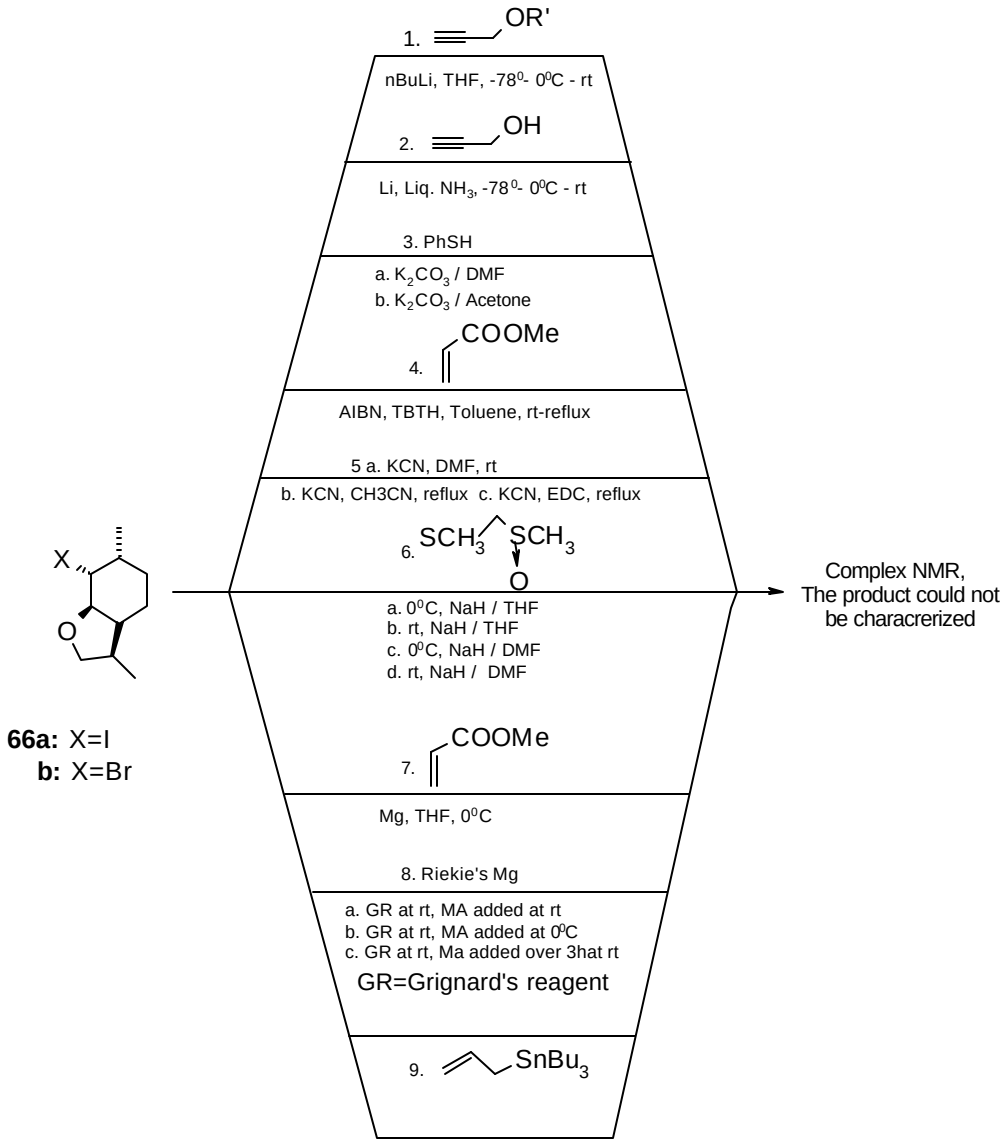
The next task was to homologate C-7 carbon either by nucleophilic displacement of iodo group or by homolytic cleavage of C-I bond using free radical reactions. For the purpose, anion generated from propargyl alcohol or its protected derivative using either *n*-BuLi or Li/liq. NH_3 as the base, was treated with iodoether **66a**. Unfortunately, it was not possible to assign and confirm the desired product from the complex ^{1}H-NMR spectrum. In an another attempt, nucleophilic displacement of iodo was tried with the thiophenol[44] using K_2CO_3 as the base either in dimethyl formamide or acetone as a solvent without success. When iodoether **66a** was subjected to the nucleophilic displacement with KCN[45] in dimethyl formamide or acetonitrile or ethylene dichloride at room temperature or reflux temperature, ^{1}H-NMR spectrum was too complex from which the formation of the desired product could not be ascertained. Another attempt to homologate C-7 carbon atom was the Grignard reaction of iodoether. Thus, the Grignard reagent was prepared at room temperature by using Rieke's magnesium[46] and the reagent was treated with methyl acrylate at 0^0C or at room temperature. The desired product could not be obtained. In an another attempt, anion generated from methyl methylthiomethyl sulfoxide[47] either at 0^0C or at room temperature using NaH as the base and was treated with iodoether **66a** in a hope to effect C-C bond formation without success.

In an attempt to effect C-C bond formation with methyl acrylate when homolytic cleavage of C-I bond was tried by reacting, *tri*-n-butyltin hydride[48] in refluxing toluene in the presence of AIBN as an initiator, the reaction mixture showed complex pattern on TLC. In an another attempt, when iodoether **66a** was treated with allyl *tri*-n-butyltin,[49] ^{1}H-NMR was too complex and did not reveal the formation of desired product. All the reactions for carbon homologation were tried with

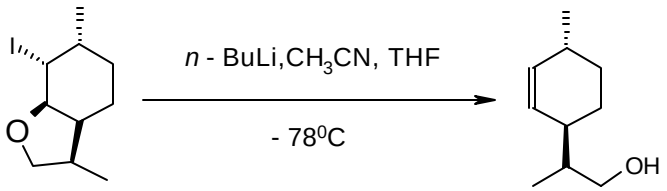
bromoether **66b** also without success. All these negative results obtained during carbon homologation are summarized in the scheme (**Scheme 15**).

In an another attempt for carbon homologation, when iodoether **66a** was treated with anion generated from acetonitrile[50] using *n*-BuLi as the base, alcohol **44** was obtained which was confirmed by NMR spectral analysis (**Scheme 16**).

Scheme 15:



Scheme 16:



66a **44**

The failure of carbon homologation at C-7 of iodoether **66a** or bromoether **66b** might be attributed to the steric reasons.

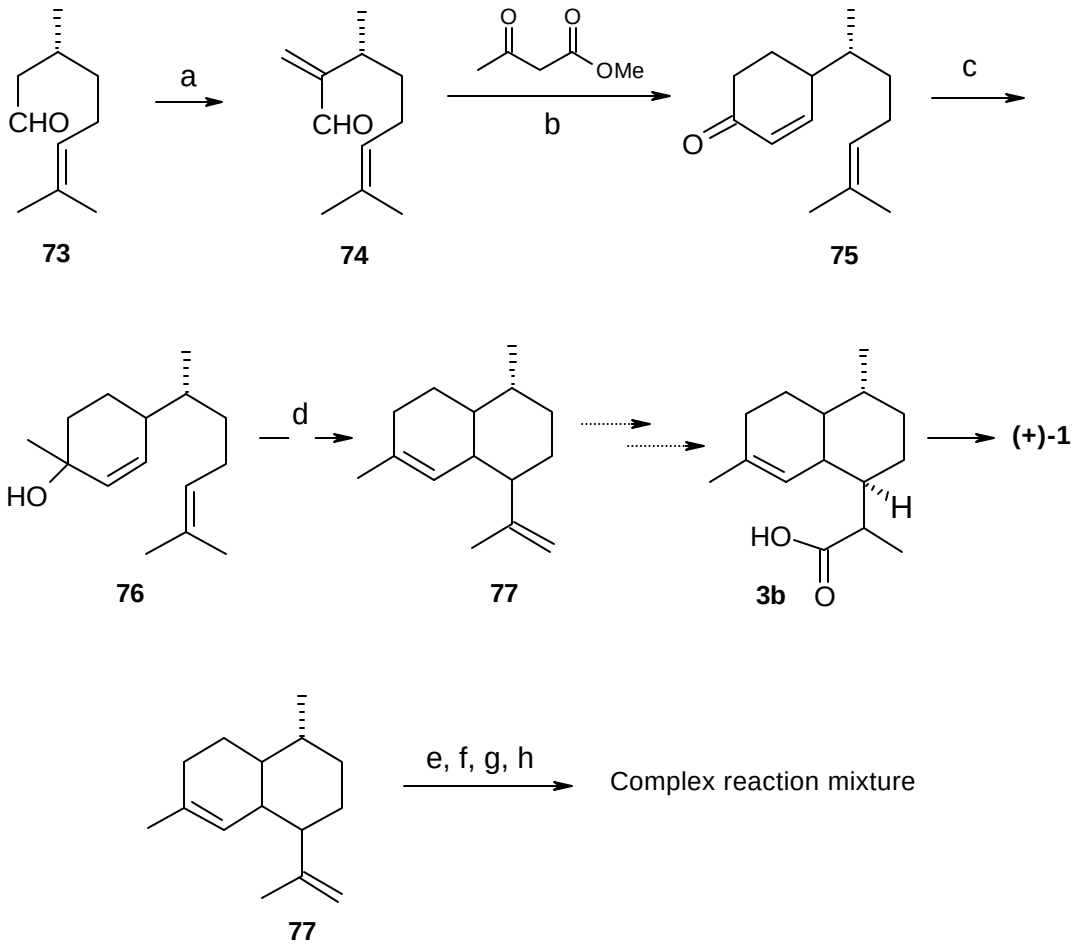
Due to unexpected failure during carbon homologation reaction, we switched on to another scheme (**Scheme 17**). From the point of practical synthesis of artemisinin **1**, an alternate approach (**Scheme 17**) was attempted. This route was earlier attempted in our group,[51] however key reactions and reagents remained to be settled for meaningful conclusion. In order to address those issues, this scheme was reinvestigated. According to the proposed plan, the key reaction involves an intramolecular ene reaction of the carbinol **76** to **77** and regioselective conversion of isopropenyl unit to propionate. During attempting the scheme, stereochemistry problem was expected but the aim was to synthesize diastereomeric mixture of containing predominantly dihydroartemisinic acid **3b** and its separation to develop a short and practical synthesis of (+)-artemisinin.

Thus *R*-(+)-citronellal **73** was converted to enone **75** *via* exomethylene derivative **74**.[52] Grignard reaction[53] of enone **75** with methylmagnesium iodide furnished carbinol **76** which was characterized by IR, NMR and mass spectral analysis. IR spectrum of **76** showed broad absorption peak at 3450 cm^{-1} for hydroxy group and 1670 cm^{-1} for C=C stretching, disappearance of carbonyl stretch at 1680 cm^{-1}. ^{1}H-NMR spectrum of **76** displayed signals at δ 5.6 (br, 2H) for *CH=CH* and disappearance of signals at δ 6.3 (dd, 1H) and at δ 6.9 (dd, 1H) of *CH=CH*-C. Mass spectrum showed M^+ at 222.

Intramolecular ene reaction[54] of carbinol **76** was achieved with 50% $HClO_4$ in 78% yield to furnish diene **77**. IR spectrum of diene **77** showed disappearance of absorption at 3450 cm-1 for hydroxy group. ^{1}H-NMR spectrum of **77** displayed signals at δ 4.7 (d, 2H) for exomethylene protons, and at δ 5.4 (1H) of olefinic proton and disappearance of signal at δ 5.6 (bs, 2H) for –*CH=CH* and signal at δ 5.1 (t, 1H) for –*CH*=C- olefinic proton. Mass spectrum showed M^+ at 204 (100). Thus the structure of diene **77** was assigned and confirmed by IR, ^{1}H-NMR and mass

spectral analysis. The next task was the regioselective conversion of isopropenyl unit of **77** into propionate.

Scheme 17:



Reagents and Conditions:

a) HCHO (35%), piperidine acetate, reflux, 2h, 86%. b) Dry MeOH, Cat. MeONa, rt-60^{0}C-reflux, 47%. c) MeMgI, Et_2O, 0^{0}C-rt. d) 50% $HClO_4$, 78%.e) $RuCl_3.3H_2O$, rt, 45 sec.,
f) $OsO_4/NaIO_4$, aq. THF, rt-reflux. g) Br_2/CH_3COOH, 0^{0}C. h) Aq. NBS, rt.

In order to convert isopropenyl unit into propionate, it was thought to functionalize exomethylene double bond regioselectively. For this purpose, various attempts have been made such as a) flash dihydroxylation with $RuCl_3.3H_2O$,[55] b) Oxidative cleavage with $OsO_4/NaIO_4$,[56] c) formation of dibromide using bromine in acetic acid, d) formation of bromohydrin using aqueous N-bromosucciniamide.[57] Unfortunately, none of the reactions tried met with the success and the

complex reaction mixture resulted. Hence we were forced to explore another approach as described in (**Scheme 18**). Earlier in our group, part of the scheme was attempted without much success. Here the emphasis was to have a handle for further elaboration to A ring of the artemisinic acid. Sulpher was thought to be the right candidate as it can function both, as nucleophile as well as electrophile and can stabilize the anion α to it in higher oxidation state.

The key reaction involves stereoselective intramolecular ene reaction of **78** to **79**. Thus according to the proposed plan, (+)-citronellal **73** was converted to its exomethylene derivative **74** by the literature method.[51] Michael addition of thiophenol to exomethylene compound **74** in the presence of catalytic amount of triethyl amine furnished Michael adduct **78** in excellent yield. IR spectrum of the compound **78** displayed absorption at 1705 cm^{-1} and 1600 cm^{-1} indicating the presence of aldehyde and olefin. ^{1}H-NMR spectrum of the compound **78** displayed disappearance of the signals at δ 6.1 (s, 1H) and at δ 6.2 (s, 1H) for exomethylene protons and appearance of the signal at δ 7.1-7.5 (m, 5H) for aromatic protons. Mass spectrum of the compound **78** showed M^+ peak at 276 (4). Thus the structure of the compound **78** was assigned and confirmed by IR, ^{1}H-NMR and mass spectral analysis.

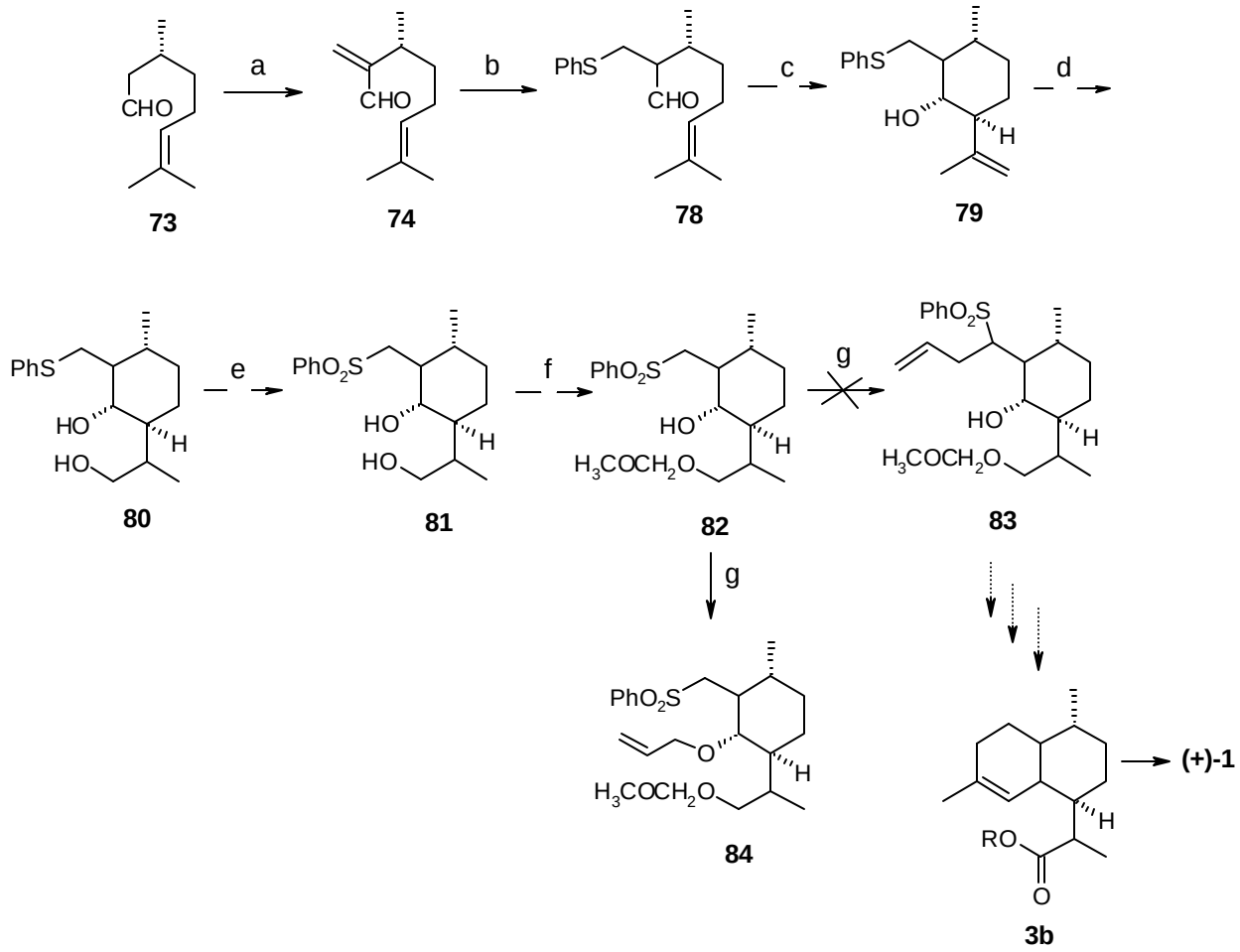
Intramolecular ene reaction was achieved by $ZnCl_2$ in benzene at 10^0C to furnish the adduct **79** in 75% yield. IR spectrum of the compound **79** showed broad absorption peak at 3450 cm^{-1} indicating the presence of hydroxy group and at 1600 cm^{-1} for C=C stretching. ^{1}H-NMR spectrum of the compound displayed signals at δ 4.9 (d, 2H) and 3.5 (m, 1H) for exomethylene protons and -*CH*-OH. Mass spectrum of the compound **79** showed M^+ peak at 276 (2) confirming the structure **79**.

Compound **79** thus obtained was subjected to the hydroboration with borane dimethylsulfide complex followed by oxidative alkaline hydrolysis with H_2O_2 to furnish diol **80** in 80% yield. IR spectrum of the compound **80** showed broad absorption at 3450 cm^{-1} indicating
The presence of hydroxy groups. ^{1}H-NMR of the compound **80** displayed disappearance of the signals at δ 4.9 (d, 2H) for exomethylene protons and the appearance of the signal at δ 3.55 (m, 4H) for $–CH_2OH$ and $–CH_2SPh$. Mass spectrum of **80** showed (M^+-18) at 276 as parent peak.

The diol **80** thus obtained was oxidized by oxone.®[58] to furnish sulfone in 89% yield. IR spectrum of the compound **81** showed absorption at 3450 cm^{-1}. ^{1}H-NMR spectrum of **81** showed multiplet (2H) at δ 7.86-7.97, a multiplet (3H) at δ 7.56-7.72 for aromatic protons, a multiplet (2H) at δ 3.56-3.69 for $–CH_2OH$ and a multiplet (2H) at δ 3.41-3.53 for $–CH_2SO_2Ph$..

Primary hydroxy group of sulfone was regioselectively protected as MOM ether in THF to furnish **82**. IR spectrum of **82** showed broad peak at 3450 cm^{-1} for hydroxy group. ^{1}H-NMR spectrum displayed appearance of the signals at δ 4.59 (s, 2H) for (–OCH_2O-) and signal at δ 3.56 (s, 3H) for (–OCH_3).

Scheme 18:



Reagents and Conditions:

a) HCHO (35%), piperidine acetate, reflux. b) PhSH, Et_3N, C_6H_6, rt. c) $ZnCl_2$, C_6H_6, 0^0C.

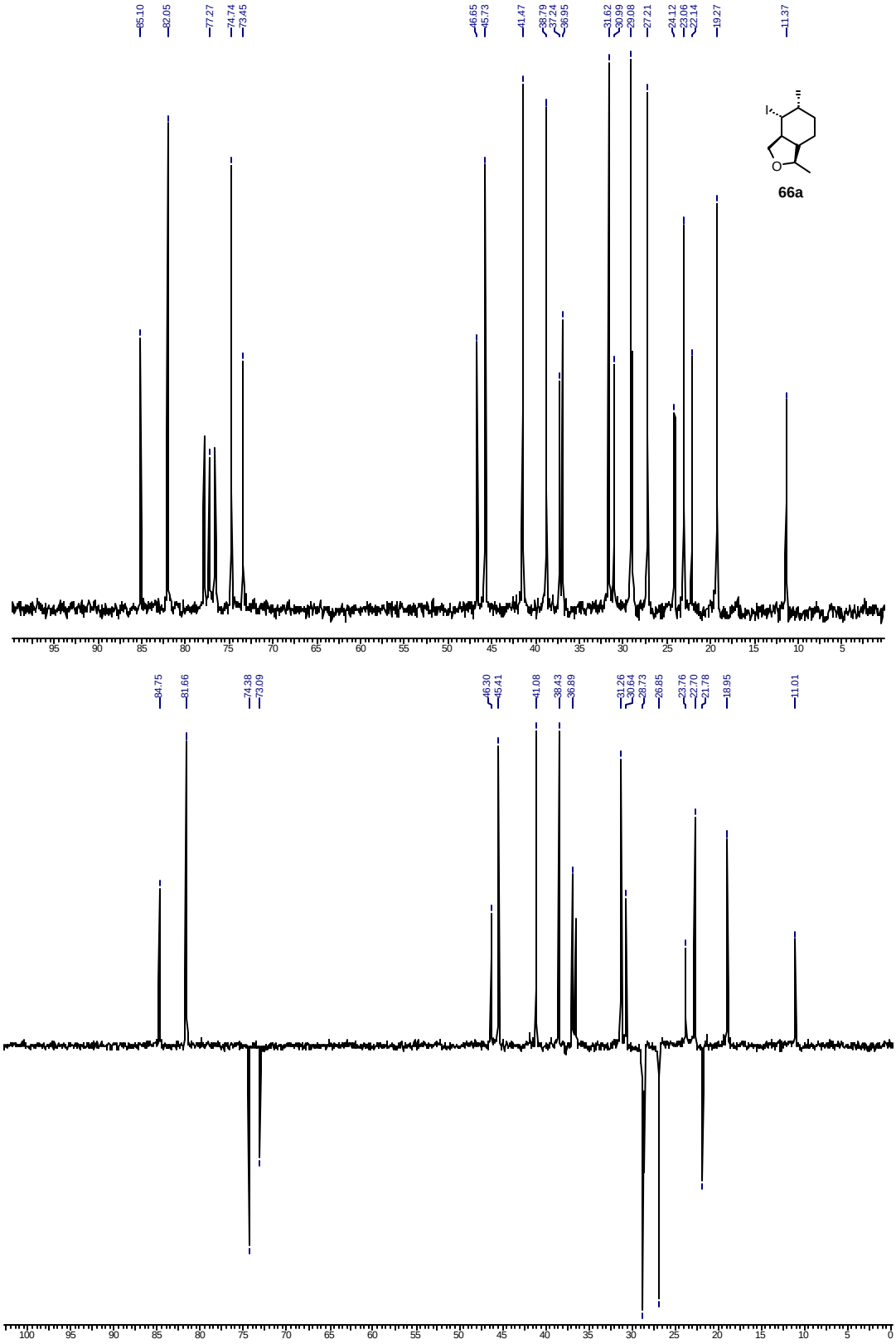
d) i. BMS/THF, ii) H_2O_2/HO^- e) Oxone f) H_3COCH_2Cl, NaH, THF. g) Allyl bromide, n-BuLi, THF, 0^0C-rt.

Alkylation of the compound **82** was performed with allyl bromide using excess of *n*-BuLi as a base in the hope to get allyl group incorporated at α-carbon to the -SO_2Ph. ^{1}H & ^{13}C-NMR

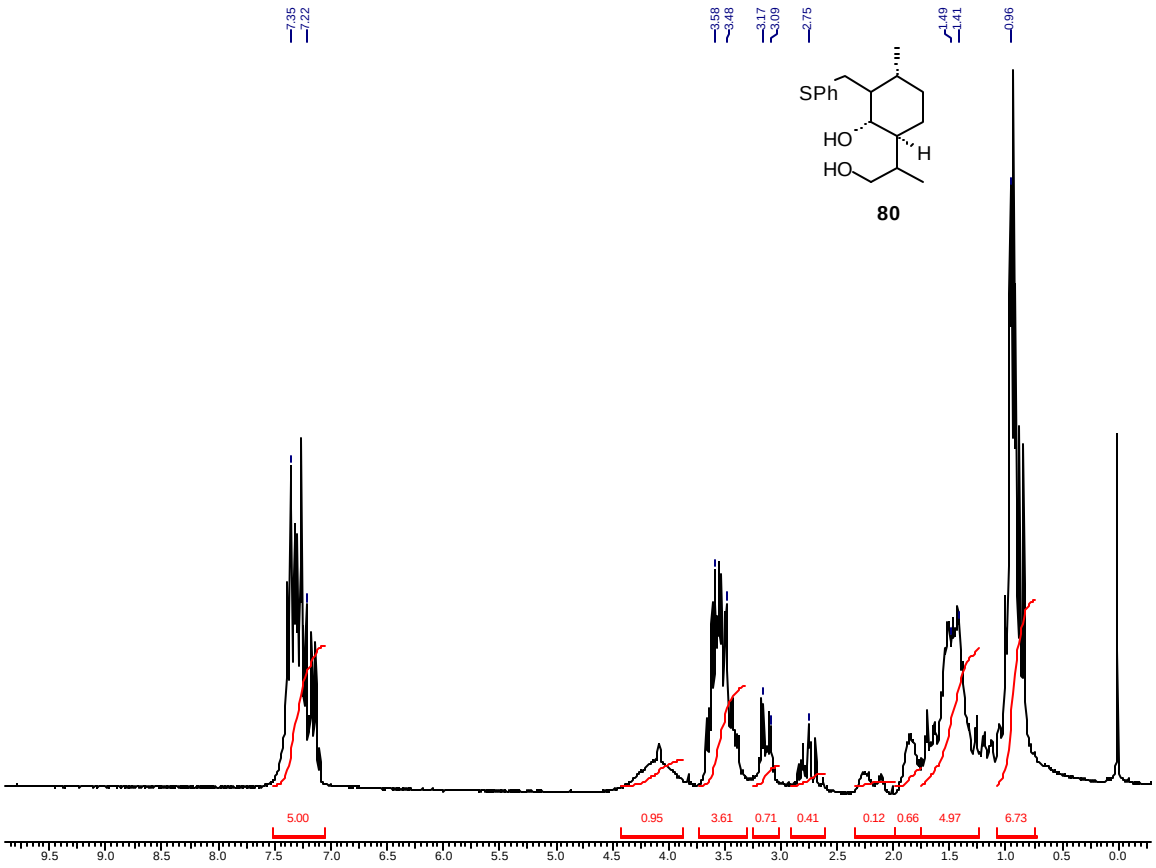
analysis of the product thus obtained revealed that instead of getting incorporated at α-caron to SO_2Ph, the secondary hydroxy group was protected as allyl ether. IR spectrum of the compound **84** showed the absence of hydroxy group. ^{1}H-NMR spectrum showed multiplet (1H) at δ 5.82-5.98 (-*CH*=CH_2), dd (2H) at δ 5.27 (-CH=*CH_2*). ^{13}C-NMR showed 20 peaks for 22 carbons in the molecule. Among those signals, triplet at δ 115.95 (-CH=*CH_2*), a doublet at δ 133.23 (-*CH*=CH_2), a triplet at δ 69.64 (-$OCH_2CH=CH_2$) were the distinguishing peaks in the ^{13}C-NMR of the compound **84**. Thus the structure of the compound **84** was assigned and confirmed by IR, ^{1}H & ^{13}C-NMR analysis.

1.1.8 Conclusions

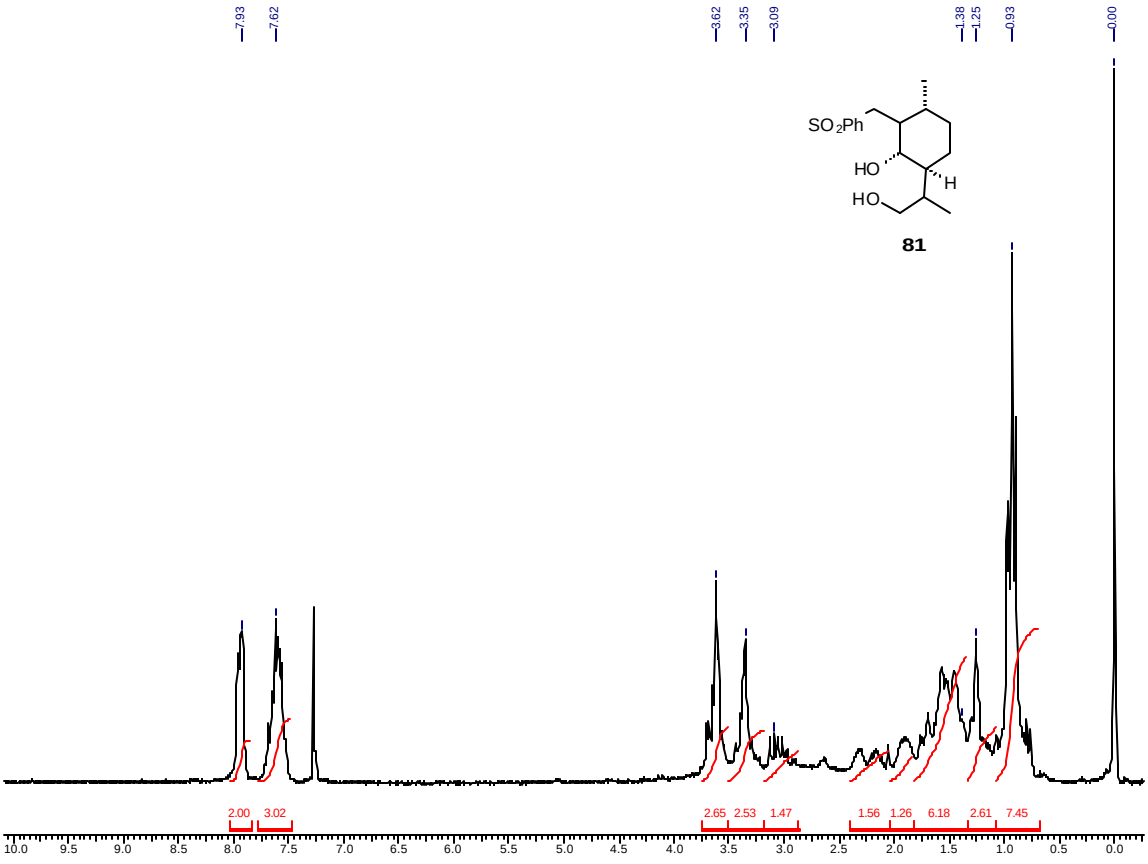
1. Due to paucity of time this scheme could not be taken to artemisinic acid. However, with proper choice of reagents and reaction conditions this could be taken to artemisinic acid.
2. Although, the few schemes attempted towards the artemisinic acid could not be completed due to time constraints and difficulties encountered, these routes have a potential of becoming reality with proper modifications.



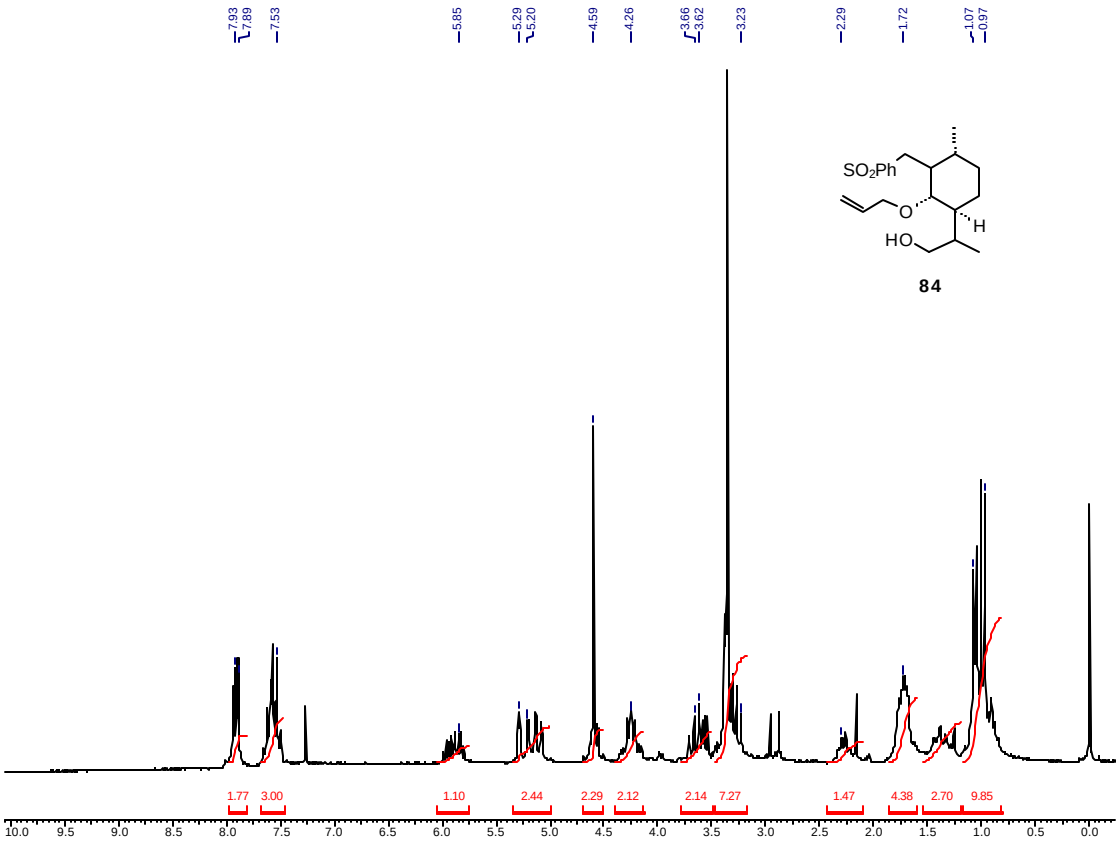
^{13}C-NMR & DEPT ($CDCl_3$, 50 MHz) of Compound 66a



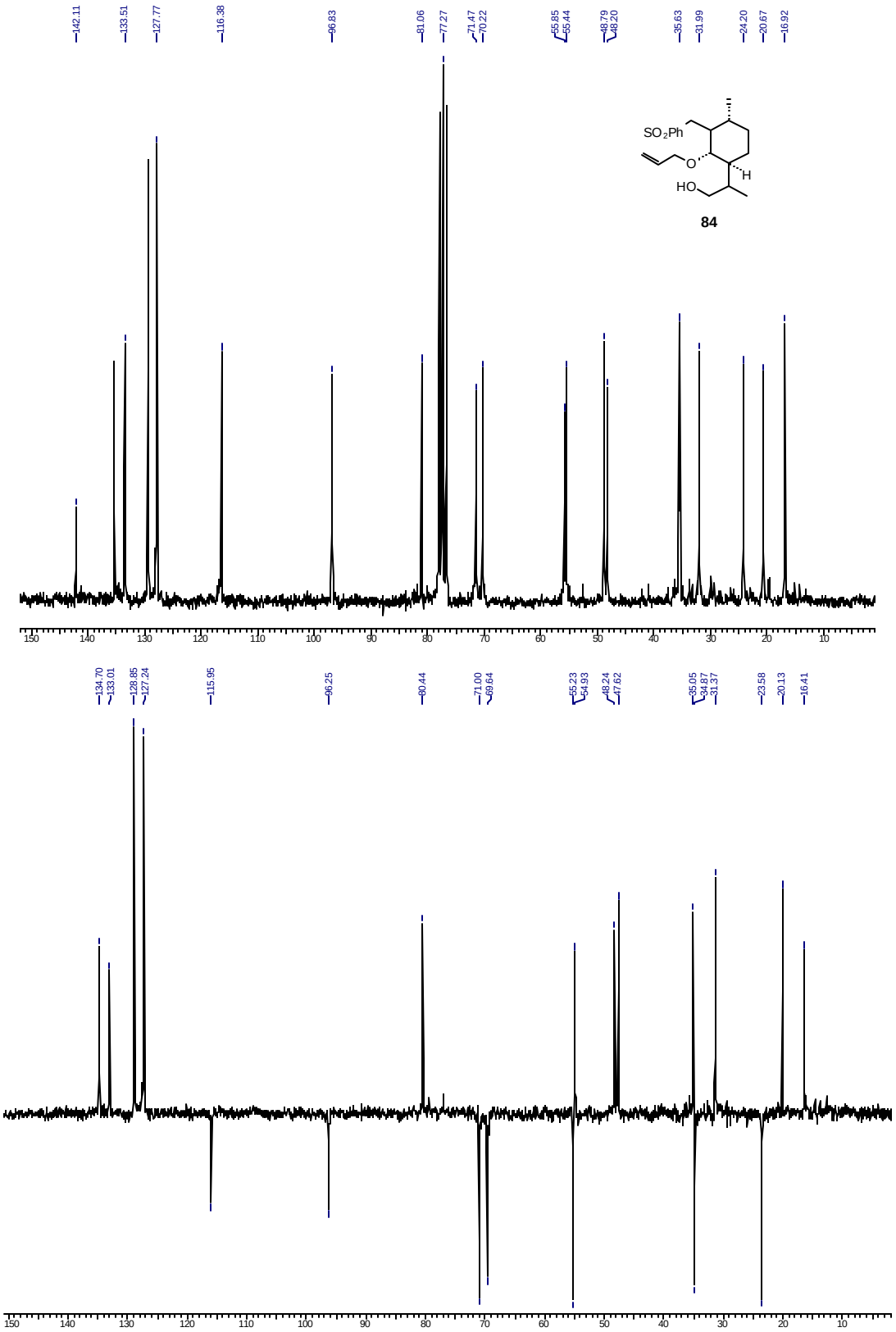
^{1}H-NMR spectrum ($CDCl_3$, 200 MHz) of Compound 80



^{1}H-NMR spectrum ($CDCl_3$, 200 MHz) of Compound 81



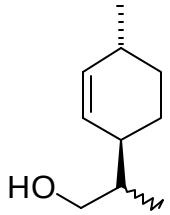
^{1}H-NMR spectrum ($CDCl_3$, 200 MHz) of Compound 84



^{13}C-NMR and DEPT ($CDCl_3$, 50 MHz) of Compound 84

1.1.8 Experimental:

1. 2-[(*1R, 4R*)-Methyl-cyclohex-2-enyl]-propan-1-ol,[42] 44

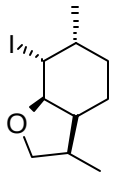


44

A solution of (+)-isolimonene **43** (6.138 g, 0.045 mol) in tetrahydrofuran (35 mL) was introduced into a three necked 250 mL round bottomed flask under argon atmosphere. The 9-borabicyclo[3.3.1]nonane (9-BBN, 0.5 M solution in THF, 110 mL, 6.71 g, 0.055 mol) was added slowly at 0^0C over a period of 1h with stirring. The reaction mixture was stirred at 0^0C for 2h, brought to room temperature and stirred for 5 hr. Then 3N NaOH (25 mL) was added in a single portion at 0^0C and H_2O_2 (50%, 14.4 mL) was added dropwise at such a rate that the temperature of the reaction should not rise above 10^0C. The reaction was stirred at room temperature for 2h. The aqueous phase was saturated with NH_4Cl and extracted with diethyl ether. The combined organic extracts were washed with water (30 mL), brine (30 mL) was dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator at reduced pressure to furnish crude alcohol **44**. The alcohol was purified by column chromatography (silica gel 60-120 mesh, eluent ethyl acetate:pet. ether 5:95).

Yield:	5.283 g (76%).
Molecular formula:	$C_{10}H_{18}O$.
IR ν_{max} cm^{-1} ($CHCl_3$):	3500-3350 (broad absorption), 3015, 2940, 1281.
^{1}H-NMR ($CDCl_3$, 200 MHz): δ:	0.8-1 (m, 6H), 1.2-2.00 (m, 5H), 2.35-2.51 (m, 2H), 3.45-3.87 (m, 2H), 5.5 (d, 2H).
Mass (m/z):	154 (M+, 23), 121 (20), 107 (37), 94 (100), 79 (42), 67 (27).

2. Iodoether 66a



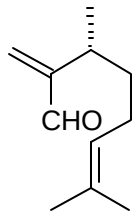
66a

To an ice cold solution of alcohol **44** (5.0 g, 32.5 mmol) in diethyl ether (45 mL) was added saturated $NaHCO_3$ solution (18 mL) followed by portion wise addition of iodine (9 g, 35.75 mmol) over 30 min. The reaction mixture was allowed to warm up to room temperature, and then stirred for 24 h. The reaction mixture was diluted with ethyl acetate (50 mL). The organic layer was washed with sodium thiosulphate (30 mL), water (2×30 mL), brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford iodoether **66a**. The product was purified by column chromatography (SiO_2) (eluent: Ethyl acetate:pet. ether 2:98) to furnish iodoether 66a as colourless oil.

Yield:	5.23 g (60%).
Molecular formula:	$C_{10}H_{17}IO$.
IR ν_{max} cm-1:	2930, 1415, 1270, 1000.
^{1}**H-NMR** (CDCl3, 200 MHz) δ:	0.90-1.05 (m, 6H), 1.17-1.36 (m, 3H), 1.39-1.56 (m, 0.3 H), 1.59-1.72 (m, 1H), 1.89-2.11 (m, 2H), 2.29-2.46 (m, 0.7H), 3.48 (dd, 0.7H), 3.51 (dd, 0.3H), 4.00 (t, 0.3 H J=8 Hz), 4.19 (t, 0.7H, J=8 Hz), 4.42 (m, 1H), 4.59 (m, 1H)
^{13}**C-NMR** (CDCl3, 50 MHz) δ:	11.01(q), 18.95 (q), 21.78 (t), 22.70 (q), 23.14 (q), 26.78 (t), 28.69 (t), 28.78 (t), 30.94 (d), 31.26 (d), 36.23 (d), 36.47 (d), 38.43 (d), 41.08 (d), 45.41 (d), 46.07 (d), 73.08 (t), 74.38 (t), 81.66 (d), 84.75 (d).
Mass (m/z):	280 (M^+, 4), 153 (100), 135 (78), 107 (37), 95 (67).

Bromoether **66b** was also prepared by using bromine instead of iodine and using the same procedure in 60% yield.

3. **a** -Methylene-3,7-dimethyl-6-octenal [74][51]



74

This compound was prepared from citronellal **73** according to literature procedure[51]

Yield: 86%

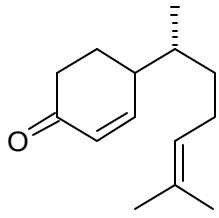
Molecular Formula: $C_{11}H_{18}O$

IR (Neat): 1730, 1600, 1400, 1100, 1040 cm^{-1}

^{1}H-NMR (CDCl3, 200 MHz): δ: 1.1 (d, 3H, J = 6.5 Hz); 1.3-1.5 (m, 2H); 1.55 (s, 3H); 1.6 (s, 3H); 1.8-2.0 (q, 2H); 2.7 (quintet, 1H); 5.1 (t, 1H); 6.0 (s, 1H) 6.2 (s, 1H); 9.5 (s, 1H).

Mass (m/z): 166 (M^+, 8%); 151 (8); 133 (6); 123 (12); 109 (76); 105 (8); 95(37); 93(20); 91(10); 83 (37); 81(42); 79(16); 77(11); 69 (86); 67(76); 65? (11); 63 (2); 59 (6); 55 (100); 53 (32); 51 (10).

4. Enone [75]



75

To a stirred solution of methylacetoacetate (2g, 17.39 mmol) in dry methanol (15 mL) was added MeONa (catalytic) and the mixture was stirred at room temperature for 30 min. Exomethylene compound **74** (2.87g, 17.39 mmol) in dry methanol (10 mL) was added dropwise. The reaction mixture was stirred at room temperature for 2h, at 60^0C (oil bath temperature) for next 2h, and then refluxed for 2h. Methanol was removed on rotary evaporator at reduced pressure

and the residue was extracted with ethyl acetate (40 mL). The organic layer was washed with water (20 mL), brine (20 mL) and dried over anhydrous sodium sulphate, filtered, and concentrated at reduced pressure to furnish enone **75**. Enone **75** was purified by column chromatography on silica gel (eluent ethyl acetate:pet. ether 5:95).

Yield: 1.67 g, 47%.

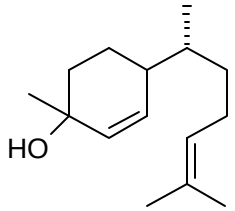
Molecular formula: $C_{14}H_{22}O$.

IR (Neat) cm^{-1}: 1690, 1600, 1466, 1385, 1250, 1143, 961 cm^{-1}.

^{1}H -NMR ($CDCl_3$, 90 MHz): δ 0.9 (d, 3H, J= 6 Hz); 1.2-1.5 (m, 4H); 1.6 (s, 3H); 1.7 (s, 3H); 1.6-1.7 (m, 2H); 2.00 (m, 2H); 2.5 (m, 2H); 5.00 (t, 1H); 5.9 (dd, 1H, J = J2 = 1.5 Hz); 6.9 (m, 1H).

Mass (m/z): 206 (M^+, 20%); 191 (6); 179 (7); 162 (8); 149 (8); 136 (10); 123(58); 109 (20); 94 (25); 79 (25); 69 (100); 55 (53).

5. Carbinol [76]



76

Grignard reagent was prepared from Mg turnings (174 mg, 7.25 mmol) and methyl iodide (1.026 g, 7.25 mmol) in anhydrous ether (10 ml). To this Grignard reagent, enone **75** (1 g, 4.854 mmol) was added dropwise in anhydrous ether under ice cold conditions and stirred at the same temperature for 3 hours. An excess of Grignard reagent was destroyed by addition of aqueous ammonium chloride solution (1mL) at 0°C and the reaction mixture was extracted with ether (3x10ml). The ether extract was washed with brine, water, dried over anhydrous sodium sulfate filtered and concentrated under vacuum to furnish the residue which was purified by column chromatography (SiO_2) to afford carbinol **76** as a colorless oil.

Yield: 0.8 g, 75%.

Molecular formula: $C_{15}H_{26}O$.

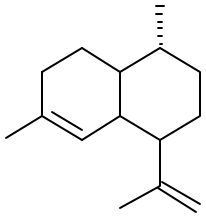
IR (Neat): cm^{-1} 3450, 1670, 1450, 1390, 1110, 980, 910.

^{1}H -NMR ($CDCl_3$, 200 MHz): δ: 0.8 (d, 3H, J=5.0 Hz), 1.00-1.20 (m, 3H), 1.3 (s, 3H),

1.35-1.50 (m, 2H), 1.6 (s, 3H), 1.7 (s, 3H), 1.8-2.2 (m, 6H), 5.1 (t, 1H), 5.5 (m, 2H).

Mass (m/z): 222 (M+, 10), 204 (100), 81 (8), 70 (50), 55 (10).

6. [7-(*S*)-Isopropene 10-(*R*)]-4-dimethyl bicyclo [4:4:0]-dec-4-ene [77]



77

To a stirred solution of carbinol **76** (50mg, 0.22mmol) in aqueous THF (3ml), was added $HClO_4$ solution (catalytic) at room temperature and reaction mixture was stirred at same temperature for 5 hours. The THF was removed under reduced pressure and diluted with water (30ml). It was extracted with ethyl acetate (3x10ml), washed with brine, water and concentrated in vacuum to give residue which was purified by column chromatography (SiO_2) to furnish diene **77** as a colorless oil.

Yield: 35 mg, 78%.

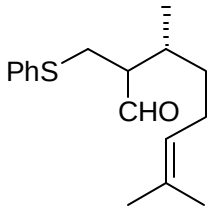
Molecular Formula: $C_{15}H_{24}$.

IR (Neat): 1440, 1380, 1200, 1030 cm^{-1}.

^{1}H -NMR ($CDCl_3$, 200 MHz): δ: 0.9 (d, 3H, J = 5.00 Hz); 1.1-1.5 (m, 6H); 1.6 (s, 3H); 1.7 (s, 3H); 1.8-2.1 (m, 5H); 2.3 (m,1H); 4.7 (d, 2H, J = 3.0 Hz); 5.4 (s, 1H).

Mass (m/z): 204 (M+, 100), 189 (22), 161 (33), 147 (15), 133 (30), 119 (76), 115 (10), 105 (9), 77 (4), 55 (2).

7. Michael adduct [78]

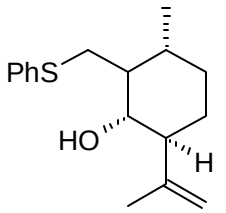


78

To a stirred solution of exomethylene compound **74** (10.75 g, 64.75 mmol) and thiophenol (7.123 g, 64.75 mmol) in dry benzene ((50 ml), triethylamine (catalytic) was added and the reaction mixture was stirred at ambient temperature for 12 hours. The reaction mixture was then poured into aqueous potassium hydroxide solution (3N) and was extracted with diethyl ether. The ether extract was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to a residue which was chromatographed over SiO_2 to afford the Michael adduct **78** as a colorless liquid.

Yield:	15 g, 84%.
Molecular Formula:	$C_{17}H_{24}OS$.
IR (Neat):	1705, 1640, 1600, 1460, 1390, 1260 cm^{-1}.
^{1}H -NMR ($CDCl_3$, 200 MHz): δ	1.00 (d, 3H, J=5.4 Hz); 1.3-1.5 (m, 4H); 1.6 (s. 3H); 1.7 (s, 3H); 2.00 (m, 2H); 3.00 (m, 1H); 3.3 (m, 1H); 5.1 (t, 1H, J = 3.5 Hz); 7.1-7.5 (m, 5H); 9.7 (d, 1H, J = 1.5 Hz).
^{13}C -NMR ($CDCl_3$, 50 MHz): δ	203.81 (s); 202.90 (s); 202.60 (s); 135.74 (s); 135.64(s); 131.60 (d); 129.75 (d); 129.64 (d); 129.09 (d); 128.83 (d); 126.26 (d); 125.81 (d); 123.60 (d); 55.54 (d); 85.34 (d); 33.94 (t); 33.16(t); 32.32 (t); 30.44 (t); 30.00 (t); 29.10 (t); 25.51 (t); 22.91 (t); 22.15 (q); 17.51 (q); 16.25 (q); 15.94 (q).
Mass (m/z):	276 (M^+, 4%); 258 (2); 207 (1); 177 (1); 165 (2); 148 (6); 135 (100); 123 (40); 110 (94); 95 (31); 81 (34); 77 (20); 69 (75); 55 (38).

8. Ene product [79]



79

To an ice cooled, stirred solution of Michael adduct **78** (15g, 54.34 mmol) in anhydrous benzene (60 ml), powdered $ZnCl_2$ (76.4 g, 56.17 mmol) was added carefully (in portions), while the reaction temperature was kept at 5-10°C. The precipitate of $ZnCl_2$ was filtered off and water was added to the reaction mixture. The reaction mixture was extracted with ethyl acetate (3 x 50 ml), combined ethyl acetate extracts were washed with water and then brine and concentrated to furnish a residue. The residue on purification by column chromatography (SiO_2) afforded ene product **79** as colorless viscous liquid.

Yield: 13.645 g, 91%.

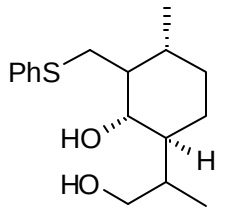
Molecular Formula: $C_{17}H_{24}OS$.

IR (Neat): 3450, 1600, 1480, 1440, 1380, 1090, 1040cm^{-1}

^{1}H -NMR ($CDCl_3$, 200 MHz): δ 1.00 (d, 3H, J = 5 Hz); 1.2 – 1.6 (m, 4H); 1.7 (s, 3H); 1.9-2,2 (m, 2H); 2.25-2.5 (m, 1H); 2.75 (m, 1H); 3.2 (m, 1H); 3.5 (m, 1H); 4.9 (d, 2H); 7.00-7.5 (m, 5H).

Mass (m/z): 276 (M^+, 2%); 166 (2); 149 (8); 135 (56); 123 (50); 110 (100); 93 (31); 81 (26); 77 (20); 69 (30); 61 (4); 55 (35).

9. Diol 80



80

To a stirred solution of borane dimethyl sulfide complex (1.1 g, 14.47 mmol) in ether at 0°C was added the ene adduct **79** (2g, 7.2 mmol) dropwise and the reaction mixture was stirred for 24 hours. To this solution was added 30% NaOH (1,8 ml) dropwise under ice cooling followed by

30 % H_2O_2 (1.5 ml) dropwise. After stirring the above reaction mixture for 1.5 hours, it was extracted with dichloromethane, dried and the solvent was removed under vacuum to afford viscous oil, which was chromatographed over SiO_2 (20% ethyl acetate : pet ether) to furnish the diol **80**.

Yield: 1.7g, 80%.

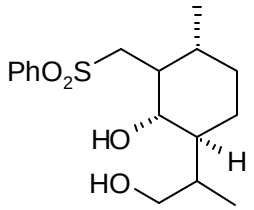
Molecular formula: $C_{17}H_{26}O_2S$.

IR (Neat): cm^{-1} 3450, 1600, 1500, 1400, 1350, 1330, 1300, 1260, 1100.

^{1}H -NMR ($CDCl_3$, 200 MHz): δ 0.9 (d, 6H, J=5 Hz), 1.15-2.00 (m, 6H), 2.00-2.2 (m, 2H), 2.4 (m, 1H), 2.8 (m, 1H), 3.3 (m, 1H), 3.5 (m, 1H), 3.8 (m, 2H), 7.4 (m, 5H).

Mass (m/z): 294 (M^+), 252 (1), 235 (1), 217 (1), 207 (1), 194 (8), 179 (16), 165 (4), 149 (8), 135 (18), 123(37), 109 (46), 95 (60), 91 (30), 87 (27), 81 (79), 77 (42), 67 (66), 61 (38), 55 (100).

10. Sulfone [81]



81

Diol **80** (0.604 g, 2.06 mmol) was dissolved in methanol (5 mL) and cooled to 0^0C. To this solution was added a solution of oxone® (3.80 g, 6.18 mmol) in water (5 mL). The resulting cloudy slurry was stirred for 4h at room temperature. Methanol was removed at reduced pressure, and the residue thus obtained was diluted with ethyl acetate (40 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure to furnish crude sulfone **81**. This was purified by column chromatography (SiO_2) (eluent:Ethyl acetate:pet. ether 40:60).

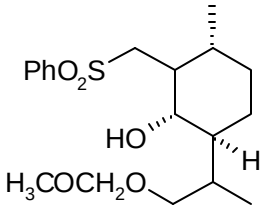
Yield: 0.616 g (92%).

Molecular formula: $C_{17}H_{26}O_4S$.

IR ν_{max} ($CHCl_3$) cm-1: 3455 (broad), 2985, 2930, 2305, 1710, 1445, 1422, 1264, **1145.**

^{1}H-NMR (CDCl3, 200 MHz) δ: 0.88-.097 (m, 6H), 1.22-1.28 (m, 2H), 1.33-1.1.98 (m, 6H), 2.07-1.28 (m, 1H), 2.18-2.24 (m, 1H), 3.02 (m, 1H), 3.26-3.38 (m, 2H), 3.59-3.66 (m, 2H), 7.62 (m, 3H), 7.93 (m, 2H).

11. MOM-ether [82]



82

MOM ether **82** was prepared by regioselective protection of hydroxy group of sulfone. Thus, NaH (60% dispersion in oil, 54 mg, 1.32 mmol) was successively washed with dry *n*-hexane. To this suspension, sulfone **81** (216 mg, 0.66 mmol) in anhydrous THF (2 mL) was added dropwise at 0^0C.After ceasing of the gas evolution, methoxy methylchloride (84 mg, 1.32 mmol) in anhydrous THF (1mL) was added dropwise at 0^0C. The reaction mixture was stirred at 0^0C for 1h and then brought to room temperature. The reaction was monitored by TLC. After completion of the reaction, saturated ammonium chloride solution (2 mL) was added and the reaction mixture was diluted with ethyl acetate (25 mL). The organic layer was then washed with water (10 mL), brine (10 mL) dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to furnish crude product. The product was purified by column chromatography (SiO_2) (eluent: ethyl acetate:pet ether 20:80)

Yield: 192 mg, 78%.

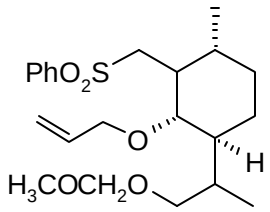
Molecular formula: $C_{19}H_{30}O_5S$.

IR ν_{max} cm^{-1}: 3455, 2984, 2471, 2297, 2086, 1886, 1735, 1446, 1370, 1240, 1100, 1045.

^{1}H-NMR ($CDCl_3$, 200 MHz): δ: 0.97 (d, 3H, J=7.09 Hz), 1.02 (d, 3H, J=5.89 Hz) 1.39-1.42 (m, 2H), 1.46-1.52 (m, 2H), 1.55-1.69 (m, 3H), 2.41-2.56 (bs, 1H), 2.68-3.16 (m, 2H), 3.33 (, 3H),

3.34-3.43 (m, 2H), 3.51-3.62 (m, 2H), 4.62 (s, 2H),
7.48-7.68 (m, 3H), 7.91 (dd, 2H, J=1.76 Hz, J=6.89 Hz)

12. Sulfone [84]



84

A mixture of MOM-ether **82** (0.196 mg, 0.531 mmol) and *n*-BuLi (85 mg, 1.32 mmol) in anhydrous THF (5 mL) was stirred at 0^0C for 30 min. Allyl bromide (160 mg, 1.32 mmol) in anhydrous THF (1 mL) was added dropwise and the reaction mixture was stirred at 0^0C for 1h then it was brought to room temperature and stirred for 4h. After completion of the reaction, saturated ammonium chloride (1 mL) was added. Then the reaction mixture was extracted with ethyl acetate (20 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to furnish sulfone **84**. It was purified by column chromatography (SiO_2) (eluent: Ethyl acetate:pet. ether 5:95).

Yield: 143 mg, 66%

Molecular formula: $C_{22}H_{33}O_5S$

^{1}H-NMR ($CDCl_3$, 200 MHz):δ: 0.97 (d, 3H, J= 7.09 Hz), 1.02 (d, 3H J=5.89 Hz), 1.26-1.48 (m, 2H), 1.64-1.77 (m, 4H) 2.26-2.39 (m, 1H) 3.24-3.44 (m, 3H), 3.35 (s, 3H), 3.56-3.74 (m, 2H), 4.22-4.42 (m, 2H), 4.59 (s, 2H), 5.26 (dd, 2H), 5.89-5.97 (m, 1H) 7.51-7.64 (m, 3H), 7.93 (dd,2H, J=1.76 Hz, J=6.89 Hz)

^{13}C-NMR ($CDCl_3$, 50 MHz): δ: 16.65(q), 20.40 (q), 23.93 (t), 31.72 (d), 35.96 (d), 47.93 (d), 48.53 (d), 55.17 (q), 55.57 (t), 69.94 (t), 71.19 (t), 80.79 (d), 96.55 (t), 116.11 (t), 127.50 (d), 129.08 (d), 133.23 (d), 153.03 (d), 141.83 (s).

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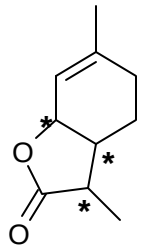
SECTION-II

Efficient and Simple Synthesis of (-)-Wine lactone

1.2.1 Introduction

(-)-Wine lactone, **(-)-1a** is a bicyclic terpenoid found in white wine, Gewurztraminer and Scheurebe as an important flavor component.[1] Recently, wine lactone was also found in orange juice and black pepper.[2] In 1975, Southwell identified a group of bicyclic terpenoid lactones[3] in the urine of koala animals after feeding of the leaf of *Eucalyptus punctata.* One of these lactones was assigned the constitution **1** [3a,4,5,7a-tetrahydro-3,6-dimethylbenzofuran-2(3H)-one].



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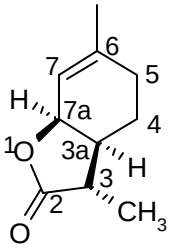


(-)-1a, Wine lactone
(-)-(3S, 3aS, 7aR)

Guth[4] identified one of the eight stereoisomers with constitution **1** in white wine types Gewurztraminer & Scheurebe as an important flavor component in 1997. Later Guth synthesized all the eight stereoisomers and compared their threshold values which differed considerably.[4] The compound with the highest odor activity is the lactone **(-)-1a**, which was found to be identical to the natural product and was named "wine lactone". The odor of the wine lactone **(-)-1a** is described as woody and coconut-like with an odor threshold as low as 0.02 pg/L of the air; the odor activity of the enantiomer, **(+)- 1a** displaying a threshold value of > 1 μg/L of the air, is lower by a factor of > 10^8.

1.2.2: Synthesis of Wine lactone: A Literature Survey

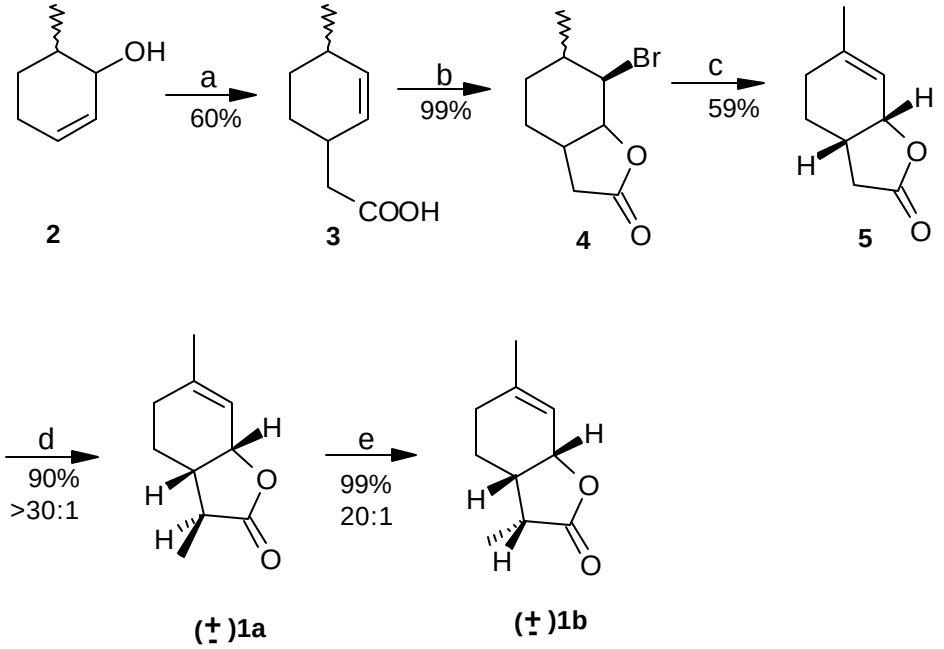
In order to judge an adequate background and to appreciate the problem involved in the synthesis, a brief survey of the reported racemic and chiral syntheses of the wine lactone is presented.

Bartlett's Approach[5] (Scheme 1, 1981)

Prior to the discovery of the wine lactone, a diastereoselective route was developed in 1981 by Bartlett *et al*[5] who prepared racemic **1a** and its *endo* C-3-epimer **1b** by utilizing the potential of

Claisen rearrangement of 2-cyclohexenol derivative **(scheme 1)**. Orthoacetate Claisen rearrangement of a 3:1 mixture of *trans*- and *cis*-6-methyl-2-cyclohexenols **2** led to *trans*/*cis* mixture of methylcyclohexenylacetic acids **3** in 60% yield after ester hydrolysis. Bromolactonization of this material and DBU induced dehydrohalogenation convert both the isomers to the unsaturated lactone **5**. Alkylation of the lithium enolate of the lactone **5** with methyl iodide provided the *exo*-methyl isomer **1a** stereospecifically. The epimeric lactone **1b** was obtained on kinetically controlled protonation of the enolate of **1a**.

Scheme 1[5]**:** Bartlett *et al*, *J. Org. Chem.*, **1981**, 46, 3896.



Reagents & conditions:

a) $Me(OEt)_3$, *o*-NO_2-PhOH, 150^0C, HO^-, MeOH, 60%

b) NBS/$CHCl_3$, 99% c) DBU/Xylene, reflux, 59% d) LDA/THF, -78^0C, CH_3I, 90%, >30:1

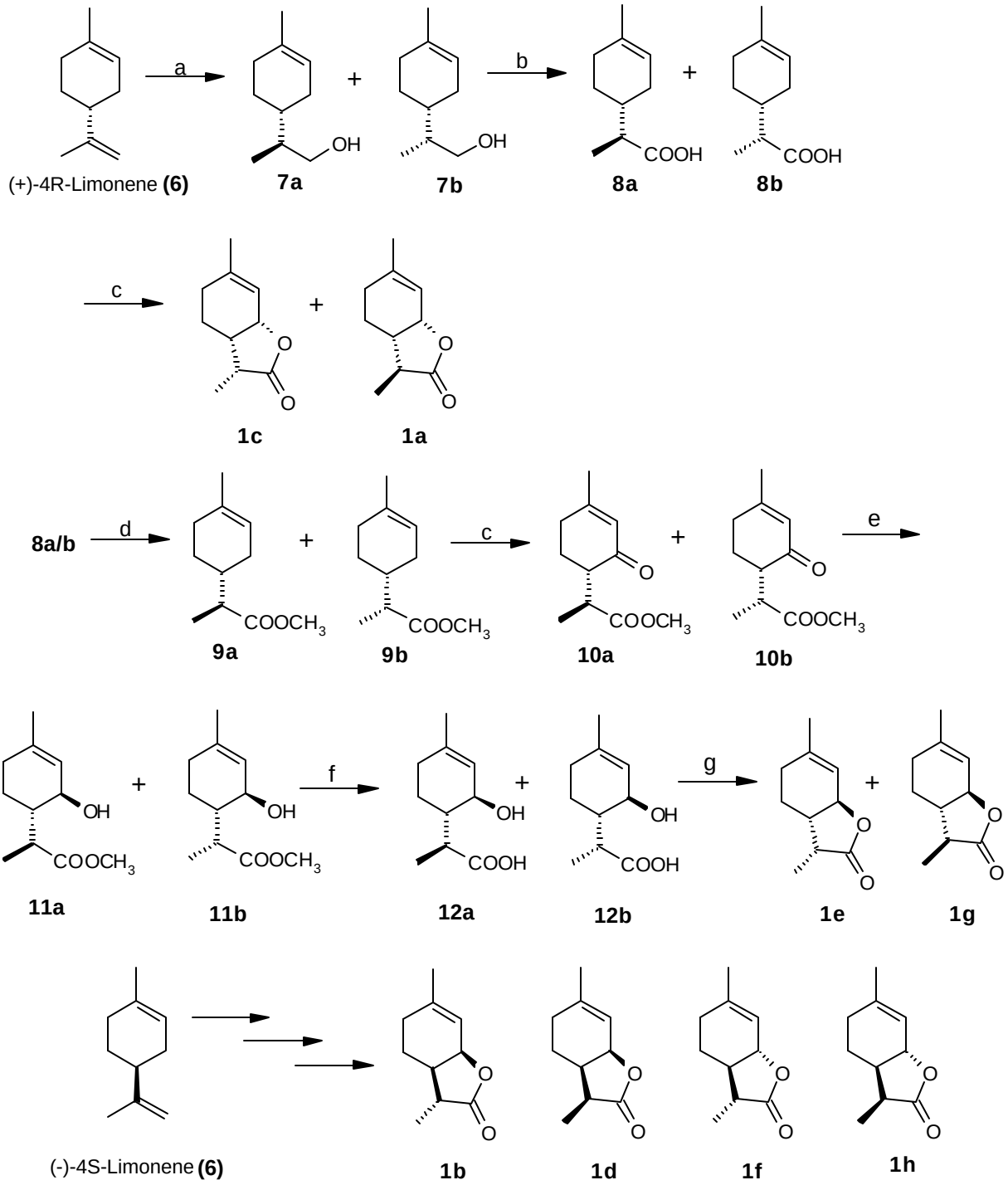
e) LDA/THF, -78^0C, AcOH, 99%, 20:1

Guth's Approach[5] **(Scheme 2, 1996)**

Starting from (+)- and (-)-limonene,[5] Guth prepared the eight stereoisomers with constitution **1** as a mixture of diastereomers and separated them by preparative HPLC. Thus according to Guth's approach **(scheme 2)**, (+)-limonene **6** was hydroborated regioselectively with

9-BBN followed by oxidation to yield diastereomeric mixture of alcohols **7a** & **7b** which was oxidized to the corresponding acids **8a** & **8b**. Cyclization of the acids **8a** & **8b** with PDC/*tert*-BuOOH in benzene gave *cis*-lactones **1a** & **1c**. Analogously, lactones **1b** & **1d** were obtained in moderate yield 30% as 1:1 mixture starting from (-)-limonene. *Trans*-lactones **1e** &

Scheme 2[4]: Guth, H., *Helv. Chim. Acta.*, **1996**, 79, 1559.



Reagents & conditions:

a) 9-BBN/THF b) PDC/DMF c) PDC/C_6H_6/*tert*-BuOOH

d) MeOH/H_2SO_4 e) $NaBH_4$, $CaCl_2$, *iso*-PrOH f) NaOH/MeOH/H_2O g) DCC/C_6H_6

1g were obtained from diastereoisomeric acids **8a** & **8b** by converting to methyl esters **9a** & **9b**. Allylic oxidation and hydride reduction furnished allylic alcohols **11a** & **11b** which were then

saponified into *trans*-hydroxy acids **17a** & **17b,** on cyclization yielded **1e** & **1g**. Analogously, **1f** & **1h** were obtained from (-)-limonene.

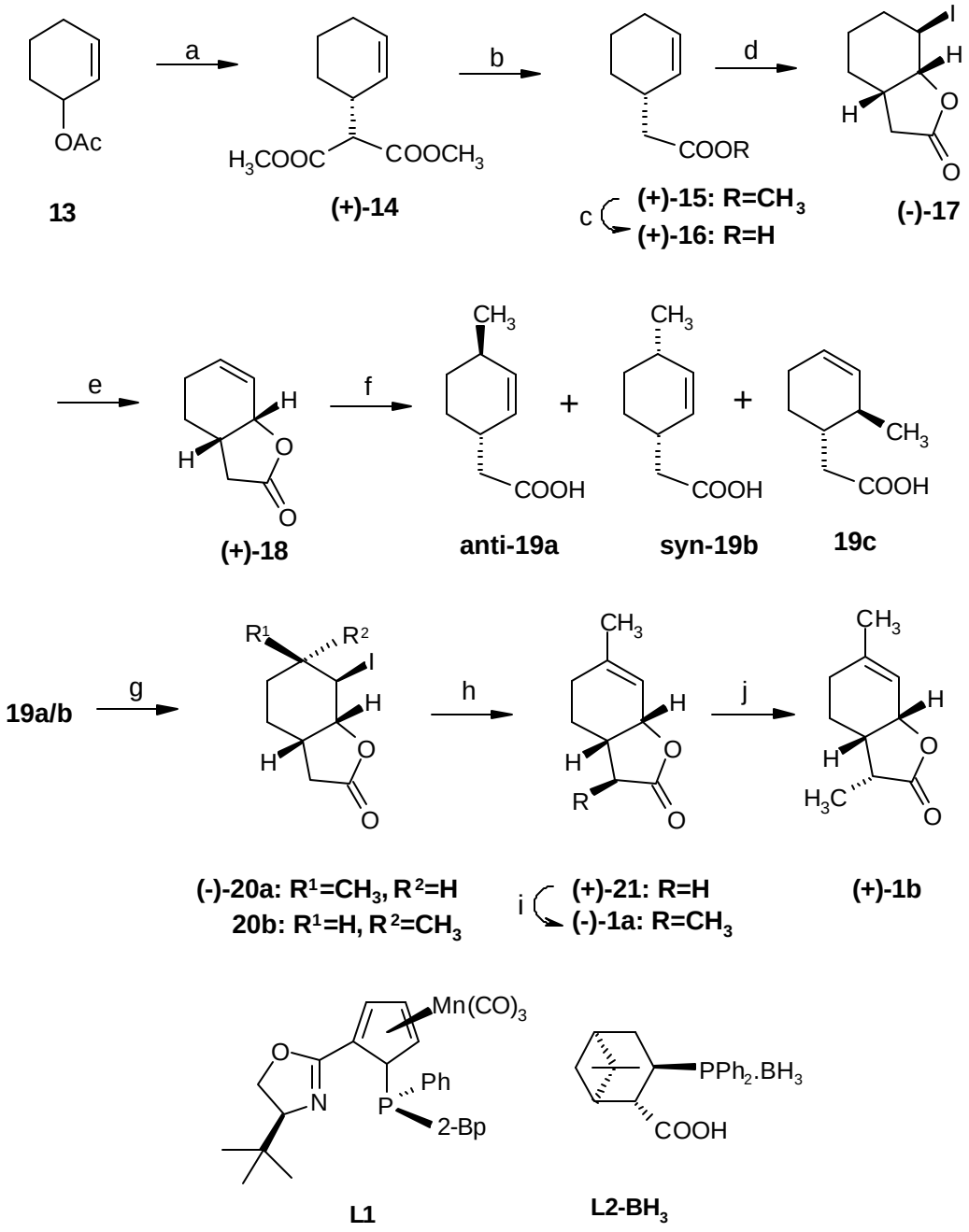
Eventhough, this route is short and provides all the eight stereoisomers of wine lactone, it is not diastereoselective/enantioselective and involves tedious separation techniques such as HPLC.

Bergner's Approach[6] (Scheme 3, 2000):

Bergner *et al*[6] reported the first chiral synthesis of enantiomerically pure (-)-wine lactone, **(-)-1a** and its C-3-epimer **(+)-1b**. Enantioselectivity was provided by asymmetric palladium catalyzed allylic substitution of 2-cyclohexen-1-yl acetate **13** with dimethylmalonate,[7] while diastereoselectivity was provided by iodolactonization of **16** and enolate alkylation of **17**. Asymmetric allylic substitution on **13** was followed by Krapcho decarbomethoxylation[8] of **(+)-14** to **15** on saponification and iodolactonization of the corresponding acid **16** furnished **(-)-17**. Dehydrohalogenation of **17** with DBU yielded the unsaturated lactone **(+)-18**. Reaction of **(+)-18** with a reagent prepared from methyllithium and CuBr in diethyl ether at -20^0C gave a mixture of regioisomers **19a/19b:19c** = 55:45. Iodolactonization of **19a/19b** gave a 92:8 mixture of diastereomers **(-)-20a** and **20b**. Major diastereomer **(-)-20a** was obtained in pure form by recrystallization. Dehydrohalogenation with DBU gave lactone **(+)-21**. Finally alkylation of **(+)-21** with methyl iodide furnished **(-)-1a**. The epimeric lactone **(+)-1b** was prepared from **(-)-1a** by deprotonation and subsequent reprotonation.

Although this route is the first enantio- and in all steps the diastereoselective, it is too lengthy and involves use the of expensive Pd-complexes for the allylic substitution.

Scheme 3[6]: Bergner *et al*, *Eur. J. Org. Chem*., **2000**, 419.



Reagents & conditions:-

Procedure 1: 0.1 mol% of $[C_3H_5PdCl]_2$, 0.12 mol% of **L1**, THF, $NaCH(COOCH_3)_2$, 5^0C, 88%, 82% *ee* Procedure 2: 3.0 mol% of $[C_3H_5PdCl]_2$, 9 mol% of **L2**, THF, $LiCH(COOCH_3)_2$, room temp., 91%, 95% *ee* b) NaCl, H_2O, DMSO, 160^0C, 74% c) NaOH, 120^0C, 95% d) KI, I_2, $NaHCO_3$, H_2O, 82%, > 99.9% ee e) DBU, THF, reflux, 82-91% f) i. MeLi/CuI, Et_2O ii. MeMgCl/CuBr, Me_2S, THF/Me_2S, -20^0C-0^0C g) KI, I_2, $NaHCO_3$, H_2O, THF, room temp., 95%, dr=92:8 after

recrystallization 60%, dr = 99:1 h) DBU/THF reflux, 92% i) LDA, MeI, THF, -78^{0}C, 79-90%. j) LDA, THF then $H_2C(COOt\text{-}Bu)_2$, -78^{0}C, 61-74%

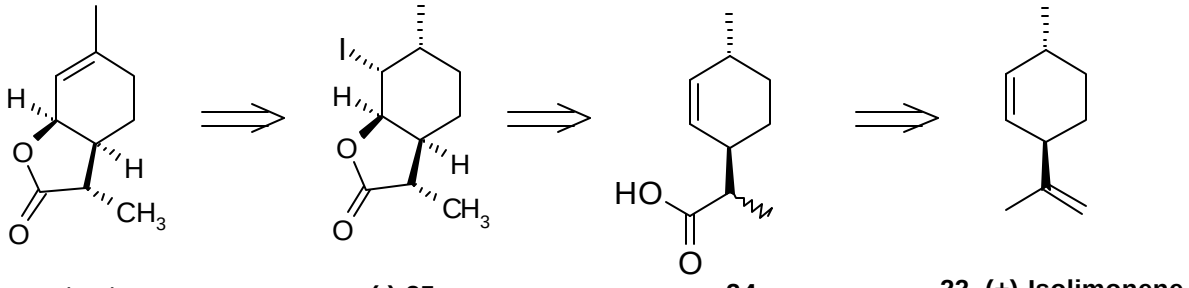
1.2.3 Present work

The present section primarily concerns with the diastereoselective synthesis of (-)-wine lactone **(-)-1a**, a bicyclic terpenoid, an important flavor component found in white wine,[1] orange juice and black pepper.[2] The literature survey (1.1) indicates that wine lactone has been synthesized in both racemic[4] and optically pure form.[5,6] Prior to the discovery of wine lactone, Bartlett *et al*[4] synthesized various bicyclic terpenoids including racemic wine lactone and its *endo*-C-3-epimer using Claisen rearrangement. Guth[5] synthesized all the eight stereoisomers and separated them by chromatography in order to compare their threshold values. The earlier syntheses are non-stereoselective and lead to formation of other stereoisomers also whereas the recent synthesis by Helmchen *et al*[6] involves use of expensive Pd-complexes for asymmetric allylic substitution involving large number of steps (12 steps). Due to our interest in terpenic antimalarial compound *viz*. artemisinin which involved isolomonene as the starting material, it was thought worthwhile to attempt the synthesis of wine-lactone. Additionally, isolimonene has the requisite number of carbon atoms as that of wine lactone with the isopropenyl group strategically placed in the desired stereochemical disposition. It was thought worthwhile to attempt the synthesis of wine lactone through selective functionalization of the double bond. The present work describes the diastereoselective and short (4 steps) synthesis of (-)-wine lactone involving a novel iodolactonization protocol, starting with (+)-isolimonene, which is abundantly available in nature, thus making it an ideal candidate.

1.2.4 Results and Discussions:

The retrosynthetic plan for (-)-wine lactone is outlined in the **scheme 4**.

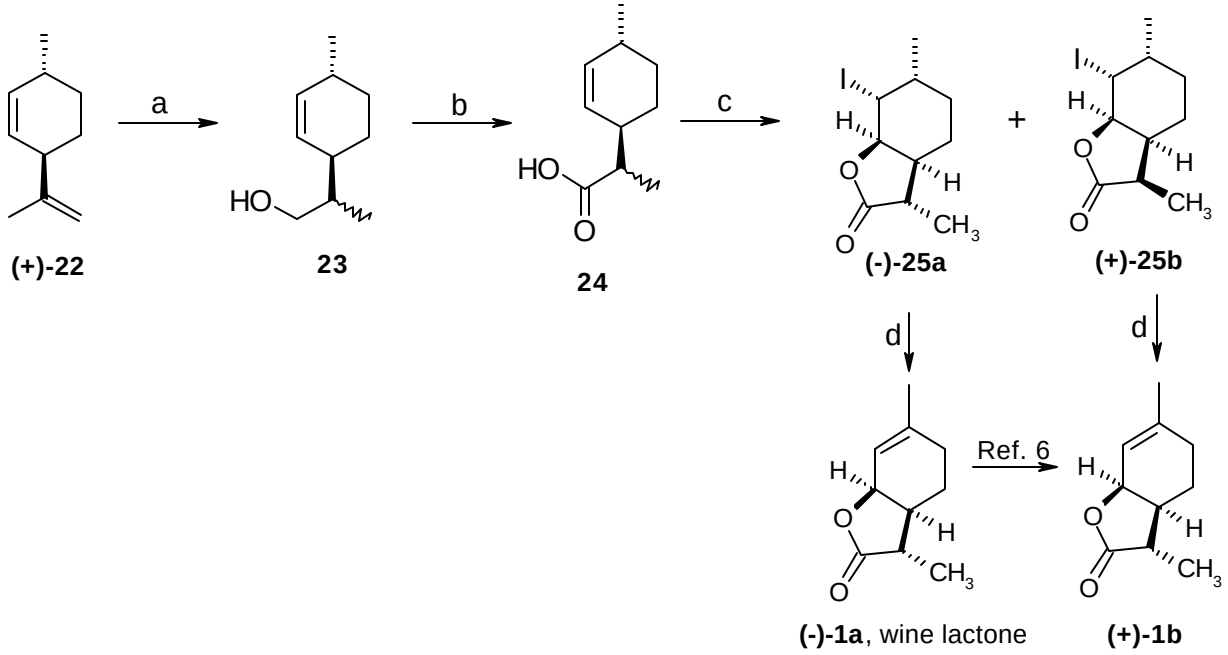
Scheme 4



(-)-1a, Wine lactone **(-)-25a** **24** **22, (+)-Isolimonene**

As briefed in **scheme 4**, the key intermediate, iodolactone **(-)-25a** could be obtained by the iodolactonization of the corresponding γ,δ-unsaturated acid **24**. In order to obtain γ,δ-unsaturated acid **24**, the ideal starting material was obviously (+)-isolimonene **22**, which is a natural product and available readily. To accomplish epimeric iodolactones **(-)-25a** & **(+)-25b**, (+)-isolimonene **22** was hydroborated regioselectively. Thus (+)-isolimonene was selectively hydroborated at the terminal double bond with 9-borabicyclo[3.3.1]-nonane (9-BBN)[9] and subsequent oxidative hydrolysis with alkaline H_2O_2 to furnish alcohol **23** in 76% yield.

Scheme 5:



(+)-22 **23** **24** **(-)-25a** **(+)-25b**

(-)-1a, wine lactone **(+)-1b**

Reagents and conditions:

a) i. 9-BBN/THF, 0^0C-room temp. 15 h ii. $NaOH/H_2O_2$, 0^0C-room temp., 1h, 76% b) Jone's reagent, 0^0C- room temp., 2h, 78% c) $NaI/FeCl_3$, CH_3CN, reflux, 2.5 h, 59% d) DBU/THF, room temp., 5h, 71-76%.

The alcohol **23** thus obtained was oxidized with Jone's reagent[10] at 0^0C to furnish γ,δ-unsaturated acid **24** in 78% yield. IR spectrum of the compound **24** showed broad absorption band at 3000 cm^{-1} for carboxylic group and a strong acid carbonyl at 1700 cm^{-1}. ^{1}H-NMR spectrum showed a doublet at δ 0.95 (J=6.83 Hz) for the methyl group in the cyclohexene ring, two doublets at δ 1.15 (J=6.84 Hz) for the methyl α-to carboxylic group, and a multiplet at δ 5.42-5.58 (2H) for olefinic protons.

Acid **24** thus obtained was subjected to the iodolactonization[11] using I_2 and saturated $NaHCO_3$ at 0^0C to furnish a mixture of iodolactones **25a** & **25b** in 52% yield. Recently, we have developed $FeCl_3$/NaI mediated iodolactonization and iodoetherification protocol.[12] The unique ability of $FeCl_3$ to act both, as a Lewis acid and as oxidant was exploited. $FeCl_3$ oxidizes KI to I_2 and in turn, further activates I_2 to undergo facile iodolactonization reaction. By using this protocol, $FeCl_3$/NaI mediated iodolactonization of the acid **24** in refluxing CH_3CN yielded a mixture of iodolactones **25a** & **25b** in 59% yield. This may be contrasted with the conventional protocol of iodolactonization which involves the use of I_2 and $NaHCO_3$ at 0^0C. Under these conditions 52% yield of the same iodolactone was observed. The mixture of iodolactones were separated by careful column chromatography (silica gel 60-120 mesh, eluent: ethyl acetate:pet ether 0.75:99.25). The probable structures of both the iodolactones were assigned by IR, ^{1}H & ^{13}C-NMR and mass spectral analysis. IR spectrum of the compound **25a** showed absorption at 1780 cm^{-1} for lactone carbonyl and the absence of broad absorption peak at 3300 cm^{-1} for hydroxyl group. ^{1}H-NMR spectrum of iodolactone **25a** showed doublet at δ 1.01 (3H) for
-CHC*H*$_3$ with J=6.34 Hz while the same methyl protons appeared at δ 0.94 (3H, -CHC*H*$_3$) with J= 5.37 Hz for its epimeric iodolactones **25b**. Another doublet appeared at δ 1.29 (3H) with J= 7.33 Hz for –COCHC*H*$_3$ for **25a**. The same methyl protons of the iodolactone **25b** appeared at the same δ value *i.e.* at δ 1.29 as doublet with J=6.98 Hz. Even methylene (-CH_2) and methine
(-C*H*) protons differ for both the iodolactones **25a** & **25b,** which is evident and presented in the experimental section. Multiplet at δ 1.39-1.47 (4H) for methylene group, multiplet at δ 1.81-1.93 for methine group (-COC*H*CH_3), multiplet at δ 2.35-2.51 for methylene group, a triplet at δ 4.66 with J=3.76 Hz for methine proton (-C*H*I), a dd at δ 4.93 with J= 3.92 Hz for methine proton (-C*H*O-) were the other distinguishing peaks in the ^{1}H NMR spectrum of the iodolactone **25a**. Similarly, multiplet at δ 1.21-1.43 (4H) for methylene group, a multiplet at δ 1.64-1.75 for methine protons, multiplet at δ 2.74-2.83 (2H) for methylene protons and another multiplet at δ 4.72-4.77

(2H) for methylene protons were the other distinguishing peaks in the ^{1}H-NMR spectrum of the epimeric iodolactone **25b**. ^{13}C-NMR spectrum of iodolactones **25a** & **25b** differ considerably. ^{13}C-NMR of the iodolactone **25a** revealed a quartet at δ 14.02 for –CH*C*H$_3$, the same methyl group appeared as quartet at δ 8.93 for iodolactone **25b**. Another quartet appeared at δ 22.26 for (-COCH*C*H$_3$) for **25a**, the same methyl group appeared as quartet at δ 23.71 for epimer *i.e*. **25b**. Triplet at δ 26.27 (-*C*H$_2$), triplet at δ 28.06 (-*C*H$_2$), doublet at δ 31.81 for methine carbon (-*C*HCH$_3$), doublet at δ 38.81 (-*C*H), doublet at δ 41.55 (-*C*HI), doublet at δ 43.39 (-CO*C*HCH3), doublet at δ 81.73 (-*C*HO-) and a singlet at 179.07 for lactone carbonyl were the other distinguishing peaks in the ^{13}C-NMR of the iodolactone **25a**. A triplet at δ 23.28 (-*C*H$_2$), triplet at δ 27.85 (-*C*H$_2$), a doublet at δ 30.66 (-*C*HCH$_3$), doublet at δ 35.66 (-*C*H), doublet at δ 42.25 (-*C*HI), doublet at δ 42.59 (-CO*C*HCH3), a doublet at δ 82.23 (-*C*HO-) and a singlet at δ 179.07 for lactone carbonyl were the other distinguishing peaks in ^{13}C-NMR of the compound **25b**. The stereochemistry of the lactone methyl could be ascertained at this juncture by comparison of the ^{13}C values of the methyl α to lactone with wine lactone and *epi*-wine lactone. Thus the iodolactone whose ^{13}C NMR of CH$_3$ α to lactone which appeared at δ 13.44 matched well with ^{13}C of wine lactone which appeared at δ 13.62, was assigned the structure as
(-)-25a. Similarly, the other isomeric iodolactone whose ^{13}C-NMR of CH$_3$ α to lactone which appeared at δ 8.93 compared well with the ^{13}C-NMR shift of *epi*-wine lactone which appeared at δ 9.13 was assigned structure as **(+)-25b**. Further confirmation of the stereochemistry was established after conversion of the iodolactone to wine lactone and its epimer as described below.

The structures of both the iodolactones **25a** and **25b** were confirmed by subjecting the respective iodolactones to dehydrohalogenation with DBU at room temperature in tetrahydrofuran. Thus iodolactone **25a** on dehydrohalogenation with DBU furnished the natural wine lactone **(-)-1a**. The physical and spectral properties of **(-)-1a** thus obtained were found to be identical in all respects with the data reported in the literature.[6] Since iodolactone **25a** furnished **(-)-1a**, the structure of the iodolactone was confirmed to be **(-)-25a.** On the similar line, when the iodolactone **25b** was dehydrohalogenated with DBU, it furnished G-3-epimer of **(-)-1a** *i.e*. **(+)-1b**. The spectral data and the physical properties of **(+)-1b** thus obtained were identical in all respects with the values reported in the literature.[6] Since the iodolactone **25b** furnished **(+)-1b** on dehydrohalogenation, the structure of the iodolactone was confirmed as **(+)-25b**. Additionally, mass spectrum showed M^{+} at 294 for (+)-**25b**.

Enantiomeric purity of both the iodolactones **(-)-25a** & **(+)-25b** and wine lactone **(-)-1a** & its C-3-epimer **(+)-1b** were determined by chiral GC analysis on Chrompack β-CD (25m × 0.25 mm) at 180^0C. Iodolactone **(-)-25a** showed *ee* of 98.99% with retention time $\mathbf{t_R}$= 29.152 min while its epimer **(+)-25b** showed *ee* of 99.06% with retention time $\mathbf{t_R}$= 31.022 min. Thus both the iodolactones **(-)-25a** & **(+)-25b** were well separated on GC. The optical rotation observed was $[\alpha]_D^{20}$ = -37.26 (c=3, $CHCl_3$) for iodolactone **(-)-25a** and $[\alpha]_D^{20}$ = +21.63 (c=3, $CHCl_3$) for epimeric iodolactone **(+)-25b**.

Dehydrohalogenation of iodolactone **(-)-25a** with DBU in tetrahydrofuran at room temperature furnished the natural wine lactone **(-)-1a** in 75% yield. The synthetic wine lactone thus obtained was found to be in > 99% *ee*. ^{1}H-NMR spectrum of **(-)-1a** showed doublet at δ 1.25 (3H) with J=7.39 Hz for methyl group (-CH*CH*$_3$). Doublet at δ 1.01 (3H) for methyl group in ^{1}H-NMR spectrum of **(-)-25a** collapsed to a singlet at δ 1.73 (3H) (-CH=C*CH3*) indicating downfield shift after dehydrohalogenation. Triplet at δ 4.66 (1H, -*CH*I) observed in ^{1}H-NMR spectrum of **(-)-25a** disappeared and appearance of multiplet at δ 5.51 (1H) confirmed the presence of olefinic proton. ^{13}C-NMR spectrum of the compound **(-)-1a** displayed 10 signals corresponding to 10 carbons in the molecule. Among these signals, doublet at δ 118.49 (H_3CC=*C*H) and a singlet at δ 140.84 (H_3C*C*=CH) were characteristics of the olefinic carbons. Mass spectrum showed M^+ peak at 166 (32). The optical rotation observed was $[\alpha]_D^{20}$=-13.48 (c=3, $CHCl_3$), literature[6] $[\alpha]_D^{20}$ = -13.1 (c=3, $CHCl_3$).

On the similar line, epimeric iodolactone **(+)-25b** was also dehydrohalogenated with DBU in tetrahydrofuran at room temperature to furnish unnatural isomer of the wine lactone *i.e.* **(+)-1b** in 71% yield.

^{1}H-NMR spectrum of the compound **(+)-1b** showed multiplet at δ 1.12-1.16 (1H), a doublet at δ 1.19 (3H) for methyl group (-CH*CH*$_3$) with J= 7.35 Hz, multiplet at δ 1.66-1.70 (1H), a singlet at δ 1.79 for methyl group attached to the olefinic carbon (-CH=C*CH*$_3$), a multiplet at δ 1.95-2.03 (2H) for methylene group, a multiplet at δ 2.23-2.31 (1H) for methine proton (-*CH*$CHCH_3$), a dq at δ 2.89 (1H) with J=7.52 Hz & J=7.33 Hz for methine proton
(-*CH*CH_3), a multiplet at δ 5.65-5.68 (1H) confirmed the presence of olefin. ^{13}C-NMR of the compound **(+)-1b** displayed 10 signals corresponding to 10 carbons in the molecule. Among these signals, doublet at δ 116.80 (H_3CC=*CH*-) and a singlet at δ 143.93 (CH_3*C*=CH-) were the characteristics peaks for olefinic carbons. The optical rotation observed $[\alpha]_D^{20}$ = +112.15 (c=3,

$CHCl_3$), literature[6] $[\alpha]_D^{20}$ = +112 (c=3, $CHCl_3$). Enantiomeric purity was determined by chiral GC to be 99.86% (retention time $\mathbf{t_R}$=13.271 min). Mass spectrum showed M^+ peak at 166(22).

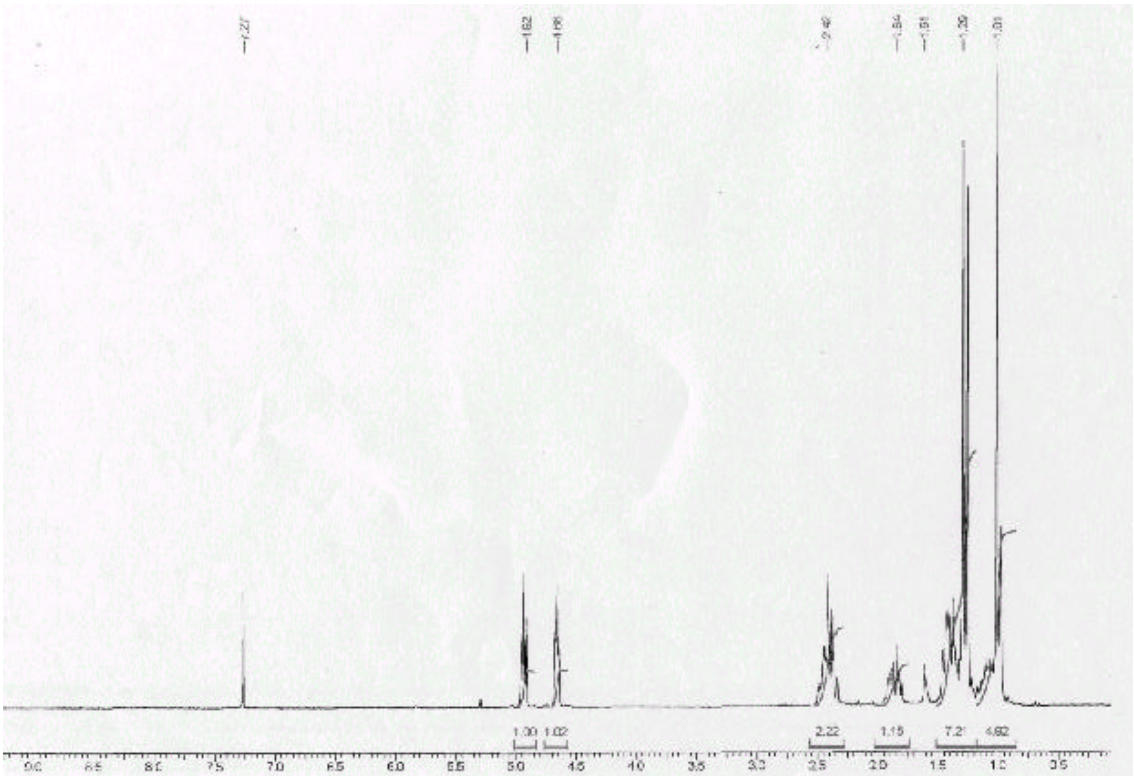
1.2.5 Conclusions

1. A diastereoselective route, simple synthesis of natural wine lactone **(-)-1a** and its C-3-epimer in 26% overall yield has been achieved.

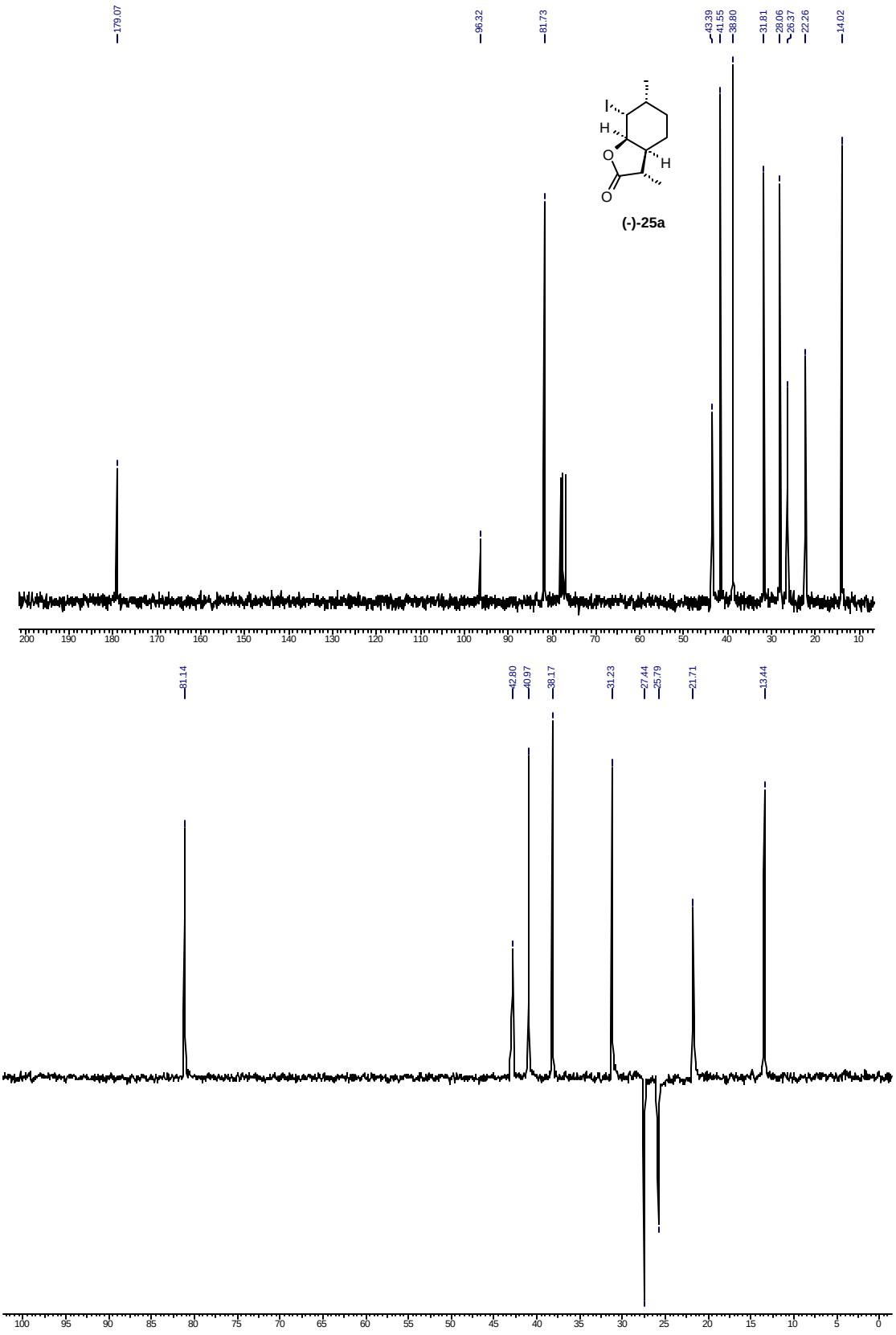
2. $FeCl_3$/NaI mediated iodolactonization, a novel protocol developed by us has been utilized as the key step to accomplish epimeric iodolactones **(-)-25a** & **(+)-25b**.

3. The starting material (+)-isolimonene is a natural product and available readily.

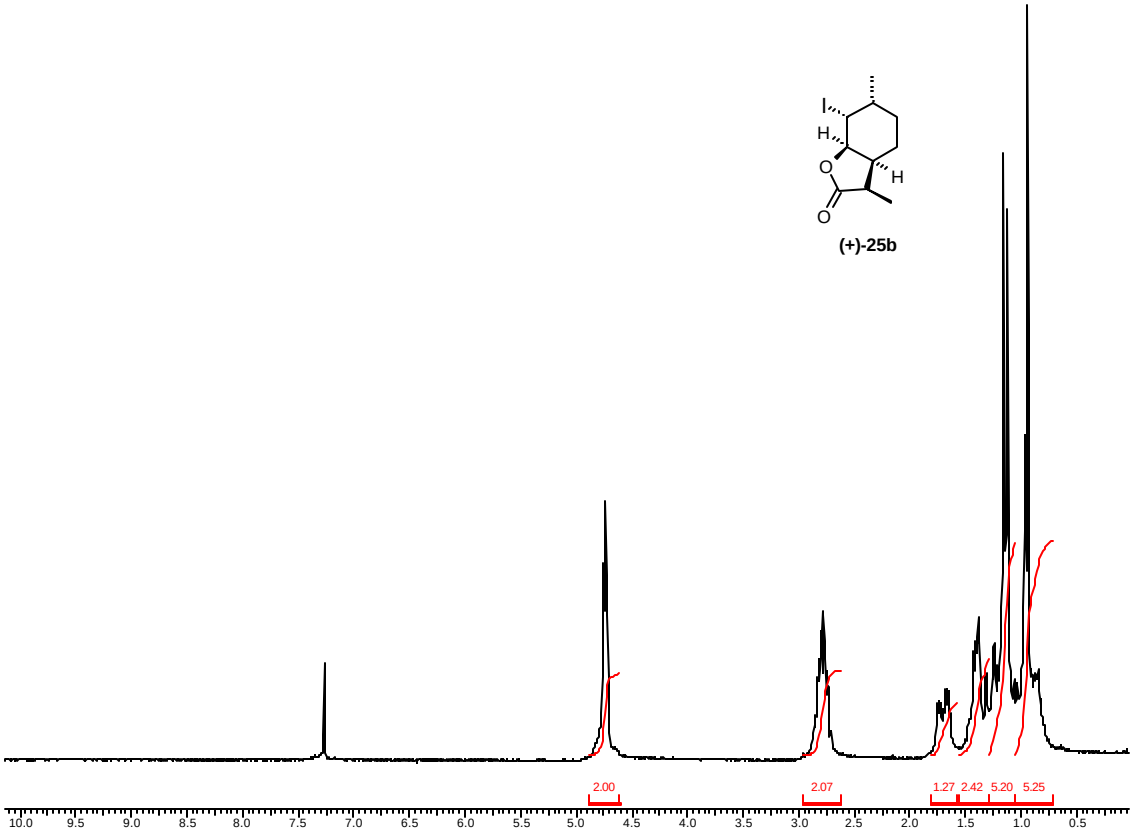
4. The reagents used and the reaction conditions employed are easy and thereby making the sequence efficient and attractive.



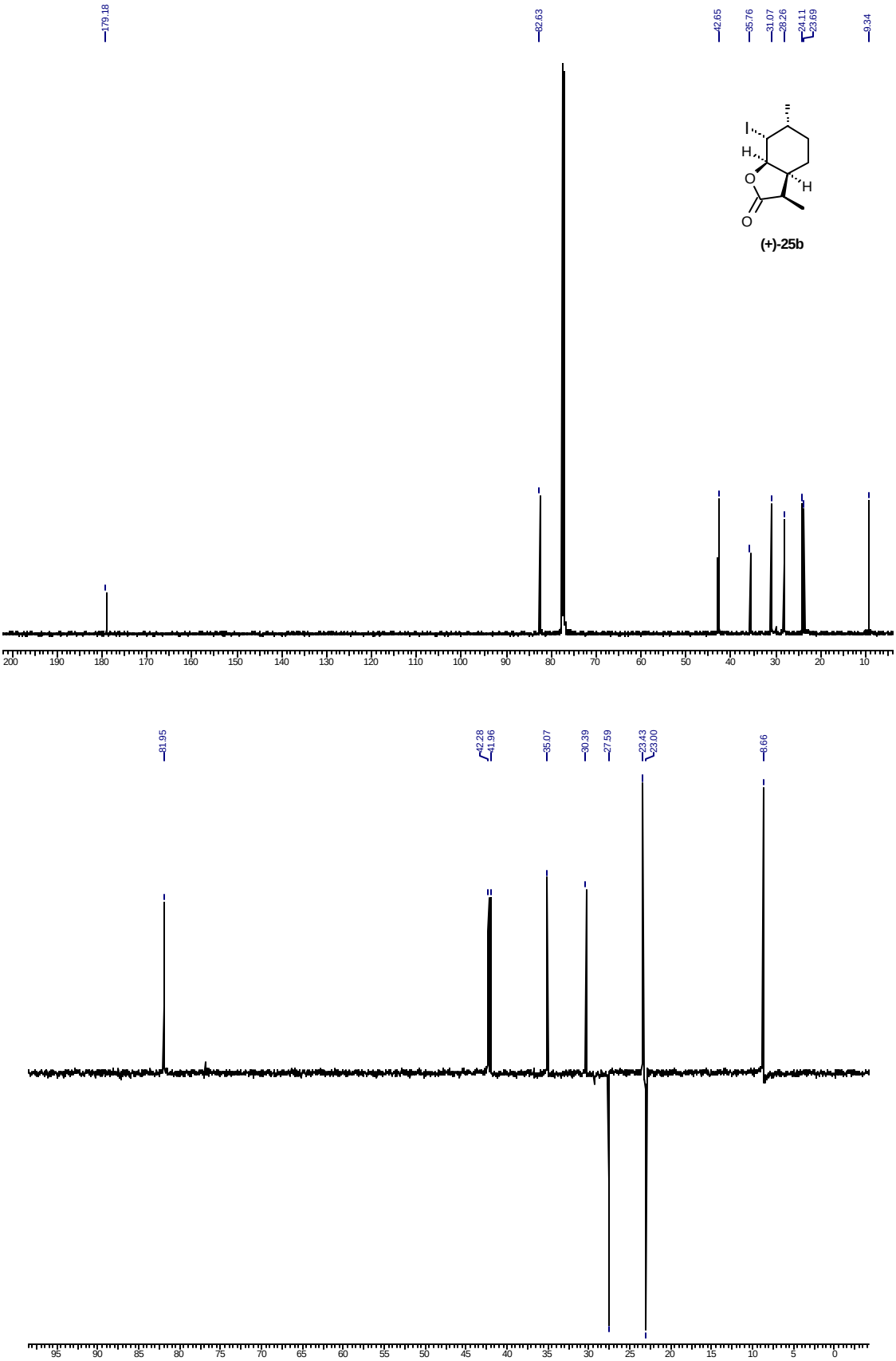
***[1]H-NMR spectrum of Compound (-)-25a* (CDCl$_3$, 200 MHz)**



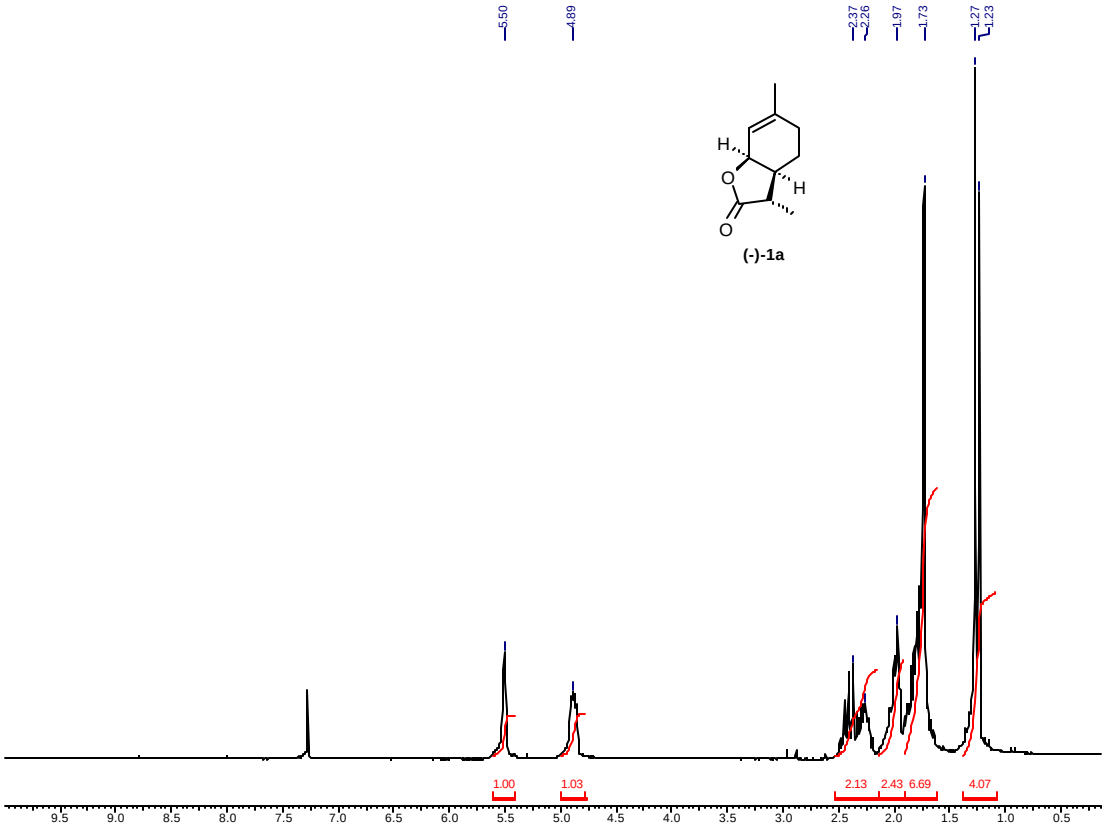
^{13}C-NMR & DEPT of compound (-)-25a ($CDCl_3$+CCl_4, 50 MHz)



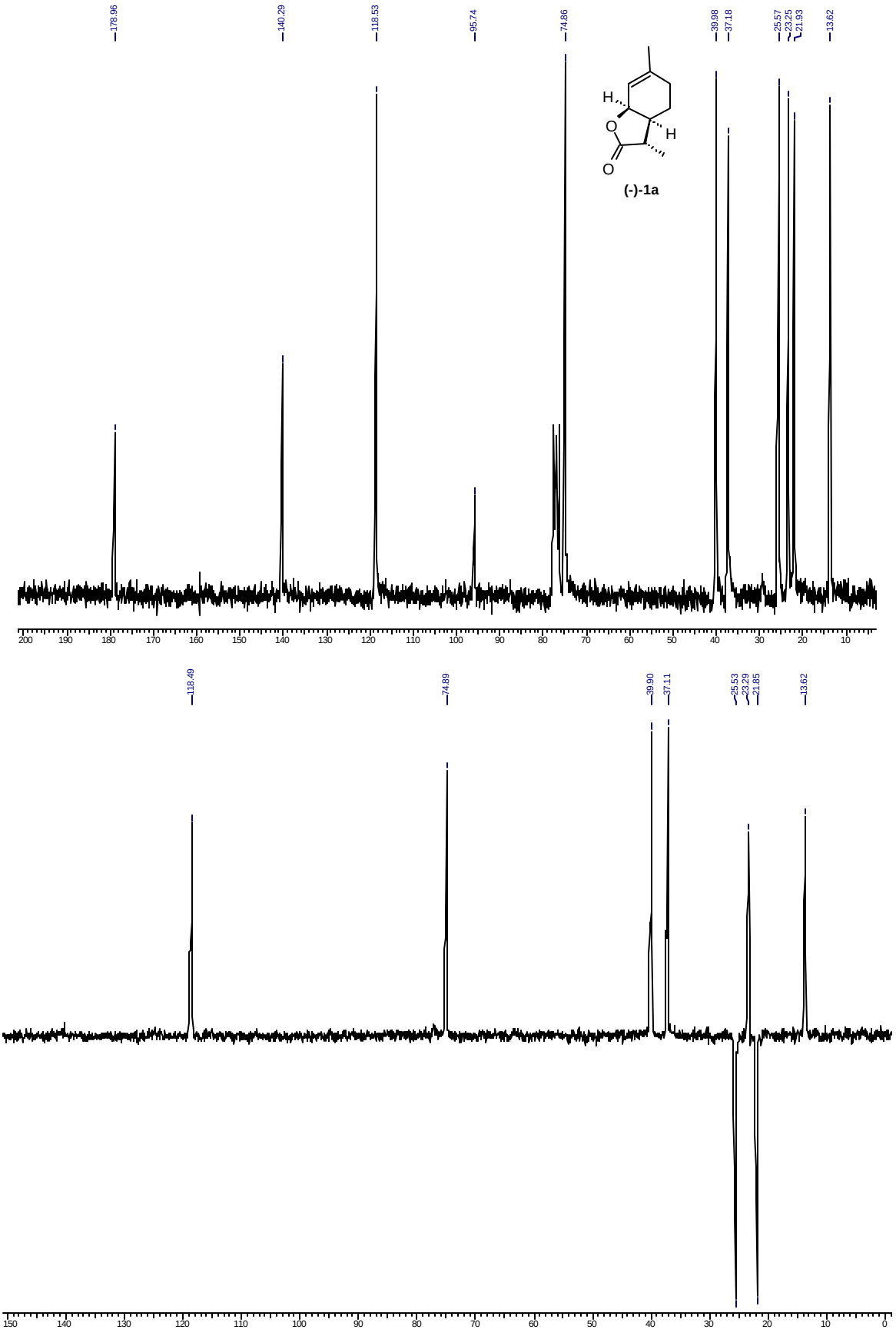
^{1}H-NMR spectrum of Compound (+)-25b ($CDCl_3$, 200 MHz)



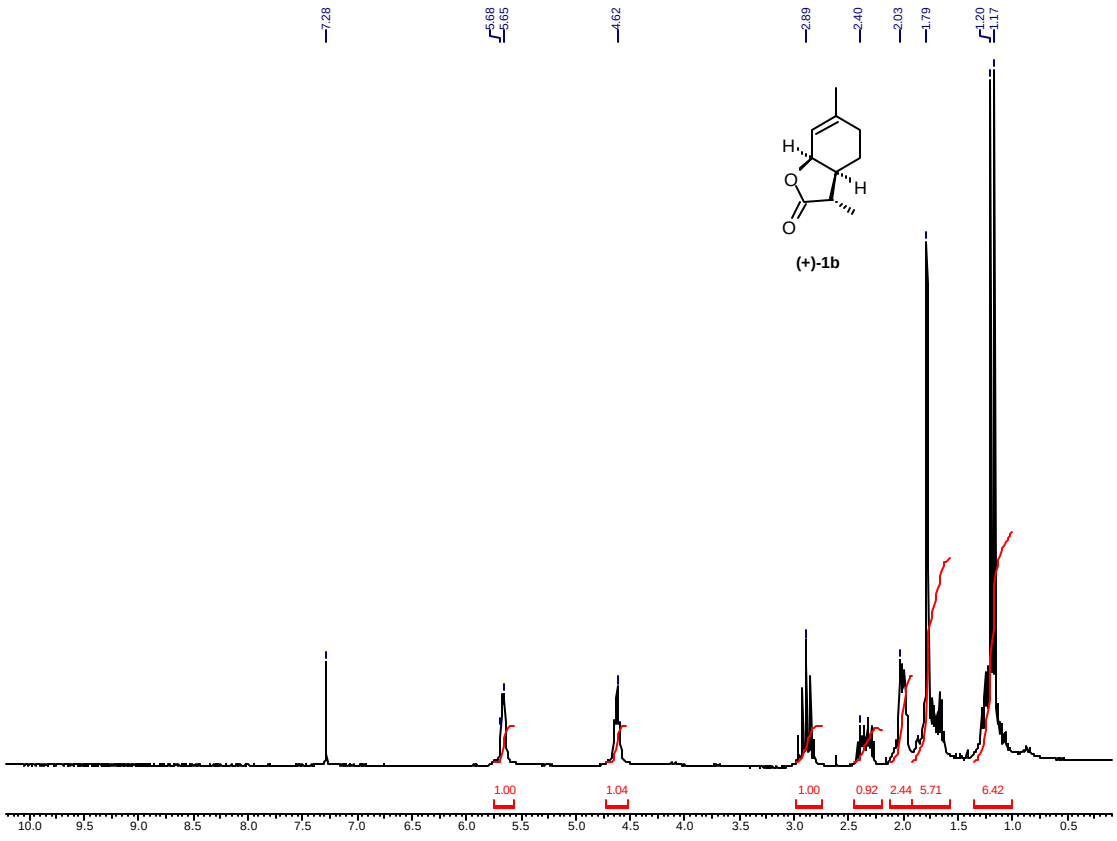
^{13}C-NMR & DEPT of compound (+)-25b:



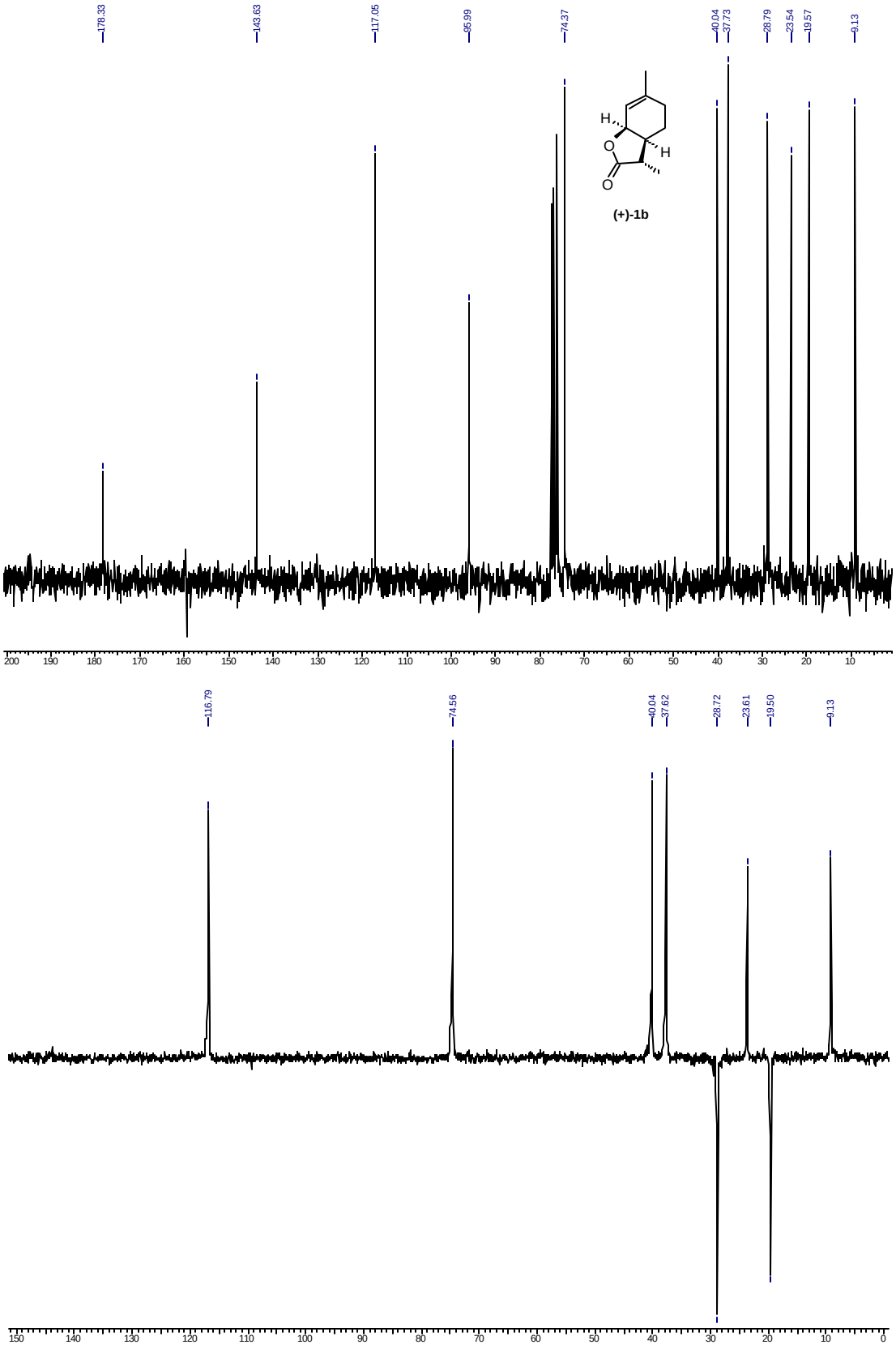
^{1}H-NMR spectrum of compound (-)-1a, Wine lactone ($CDCl_3$, 200 MHz)



^{13}C-NMR & DEPT of compound (-)-1a, Wine lactone ($CDCl_3$+CCl_4, 50 MHz)



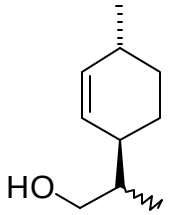
^{1}H-NMR spectrum of compound (+)-1b ($CDCl_3$, 200 MHz)



^{13}C-NMR & DEPT of compound (+)-1b ($CDCl_3$+CCl_4, 50 MHz)

1.2.6 Experimental

1. 2-[(*1R, 4R*)-Methyl-cyclohex-2-enyl]-propan-1-ol[9], [23]

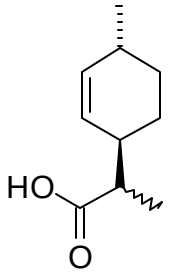


23

This compound was prepared as described in section I.

Yield:	5.283 g (76%).
Molecular Formula:	$C_{10}H_{18}O$
IR ν_{max} cm^{-1} ($CHCl_3$):	3500-3350 (broad absorption), 3015, 2940, 1281.
^{1}H-NMR ($CDCl_3$, 200 MHz): δ:	0.8-1 (m, 6H), 1.2-2.00 (m, 5H), 2.35-2.51 (m, 2H), 3.45-3.87 (m, 2H), 5.5 (d, 2H).
Mass (m/z):	154 (M+, 23), 121 (20), 107 (37), 94 (100), 79 (42), 67 (27).

2. 2-[(*1R, 4R*)-Methyl-cyclohex-2-enyl]-propionic acid[10], [24]



24

The alcohol **23** (2.4 g, 15.6mmol) was dissolved in acetone (25 mL) and cooled to 0^0C. Jones' reagent was added dropwise till the dark orange brown colour persisted. The reaction mixture was brought to room temperature and stirred for 2 h. Diethyl ether (45mL) was added to precipitate out the chromous salts. The reaction mixture was filtered through short bed of celite and

the residue was washed with diethyl ether (2 × 20mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure to furnish crude acid. The acid was purified by column chromatography (silica gel 60-120 mesh, eluent:ethyl acetate:pet. ether 12:88).

Yield: 2.07 g (78%).

Molecular Formula: $C_{10}H_{15}O_2$.

IR ν_{max} cm^{-1} ($CHCl_3$): 3000-2500, 1690, 1280.

^{1}H-NMR ($CDCl_3$, 200 MHz): δ: 0.95 (d, 3H, J=6.93 Hz), 1.15 (dd, 3H, J=6.84 Hz), 1.25-1.5 (m, 2H), 1.7-1.95 (m, 2H), 2.1-2.25 (m, 1H), 2.3-2.55 (m, 2H), 5.45 (d, 1H, J=10 Hz), 5.59 (d, 1H, J=10 Hz).

Mass (m/z): 167 (M^+-1, 9), 94 (100), 79 (32).

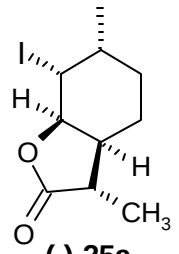
3. Iodolactones[12] (-)25a & (+)-25b

To a solution of isolimonene acid **24** (1.5 g, 8.93 mmol) in acetonitrile (12 mL) was added anhydrous $FeCl_3$ (2.901 g, 17.86 mmol) & NaI (2.68 g, 17.86 mmol), in CH_3CN (35 mL). The solution was refluxed for 2.5 h. The reaction mixture was then cooled to room temperature, quenched with water (8 mL) and extracted successively with dichloromethane (4 × 30 mL). The organic layer was washed with saturated $Na_2S_2O_3$ (25 mL), water (25 mL), and finally with brine (25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure to furnish crude epimeric mixture of iodolactones **(-)-25a** & **(+)-25b**. Both the iodolactones were separated by careful column chromatography (60-120 mesh, eluent: ethyl acetate:pet ether 0.75:99.25).

Iodolactones **(-)-25a** & **(+)-25b** were also obtained as mixture by conventional method using saturated $NaHCO_3/I_2$ in diethyl ether at 0^0C in 52% yield.[11]

Yield: 1.55 g (59%).

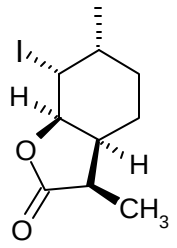
[(*3S, 3aS, 6R, 7R, 7aR*)-(*3a*, 4, 5, 6, 7, *7a*)-Hexahydro-3,6-dimethylbenzofuran-2(3H)-one, Iodolactone [(-)-25a]



(-)-25a

MP.:	75-76^{0}C
Ee:	98.99% t_R [(-)-8a]: 29.152 min
[a]$_D^{20}$:	-37.26, (c = 3, $CHCl_3$)
IR ν_{max} ($CHCl_3$) cm^{-1}:	2965, 2873, 1780, 1455, 1385.
^{1}H NMR (200 MHz, $CDCl_3$):δ:	1.01 (d, 3H, J=6.34 Hz, -CHC*H*$_3$), 1.29 (d, 3H, J = 7.33 Hz,-COCHC*H*$_3$), 1.39-1.47 (m, 4H, -C*H*$_2$), 1.81-1.93 (m, 1H, -COC*H*CH_3), 2.35-2.51 (m, 2H, -C*H*$_2$), 4.66 (t, 1H, J = 3.76 Hz, -C*H*I), 4.92 (dd, 1H, J = 3.92 Hz, -C*H*O).
^{13}C NMR (50 MHz, $CDCl_3$): δ:	14.02 (q, -CH*C*H_3), 22.26 (q, -COCH*C*H_3), 26.37 (t, -*C*H_2), 28.06 (t, -*C*H_2), 31.81 (d, -*C*HCH3), 38.81 (d, -*C*H), 41.55 (d, -*C*HI), 43.39 (d, -CO*C*HCH_3), 81.73 (d, *C*HO), 179.07 (s, *C*O).
Mass (m/z):	294 (M^+, 8), 167 (76), 149 (18), 121 (48), 93 (100), 81 (32), 67 (11).
$C_{10}H_{15}IO_2$ (294.13)	Calcd: C 40.83 H 5.14 I 43.14 Found: C 40.90 H 5.20 I 42.71

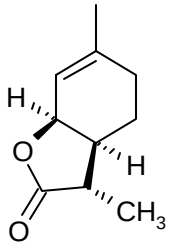
[(*3R, 3aS, 6R, 7R, 7aR*)-(*3a*, 4, 5, 6, 7, *7a*)-Hexahydro-3,6-dimethylbenzofuran-2(3H)-one, Iodolactone [(+)-25b]



(+)-25b

MP.:	72-73^{0}C.
Ee:	99.06% $\mathbf{t_R}$ [(+)-8b]: 31.022 min.
[a]$_D^{20}$:	+21.63, (c = 3, $CHCl_3$).
IR ν_{max} ($CHCl_3$) cm^{-1}:	2965, 2934, 2875, 1781, 1455, 1385, 1328.
^{1}H NMR (200 MHz, $CDCl_3$):δ:	0.94 (d, 3H, J=5.37 Hz, -CHC*H*$_3$), 1.29 (d, 3H, J = 6.98 Hz, -COCHC*H*$_3$), 1.21-1.43 (m, 4H, -C*H*$_2$), 1.64-1.75 (m, 1H), 2.74-2.83 (m, 2H), 4.72-4.77 (m, 2H).
^{13}C NMR (50 MHz, $CDCl_3$): δ:	8.93 (q, -CH*C*H$_3$), 23.28 (t, *C*H$_2$), 23.70 (q, -COCH*C*H$_3$), 27.85 (t, -*C*H$_2$), 30.66 (d, -*C*HCH3), 35.66 (d, -*C*H), 42.25 (d, -*C*HI), 42.59 (d, -CO*C*HCH$_3$), 82.23 (d, *C*HO), 179.07 (s, *C*O).
Mass (m/z):	294 (M^+, 7), 167 (94), 149 (18), 121 (54), 93 (100), 77 (12), 67 (8).
$C_{10}H_{15}IO_2$ (294.13)	Calcd: C 40.83 H 5.14 I 43.14 Found: C 40.95 H 5.02 I 42.83

4. (-)-(*3S,3aS,7aR*)-*3a*,4,5,*7a*-Tetrahydro-3,6-dimethylbenzofuran-2(3H)-one: Wine lactone [(-)-1a]



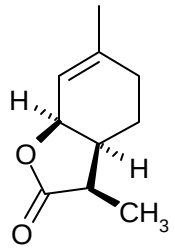
(-)-1a, wine lactone

A solution of **(-)-25a** (0.250 g, 0.85mmol) & DBU (0.166 g, 1.09mmol) in dry tetrahydrofuran (10mL) was stirred at room temperature for 5h. 6N HCl (15mL) was added and the

mixture was extracted with diethyl ether (4×20mL). The combined organic layer was washed with water (5mL), brine (5mL) and dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator at reduced pressure to furnish crude wine lactone **(-)-1a**. The lactone was purified by column chromatography (eluent: ethyl acetate:pet.ether 1:99). The lactone was further purified by crystallization from ethyl acetate/hexane.

Yield:	0.107 g, (76%).
MP. (Lit):	49-50^{0}C (48-50^{0}C)[6].
Ee:	99.58% $\mathbf{t_R}$ [(-)-1a]: 10.939 min.
[a]$_D^{20}$(Lit):	-13.48, (c = 3, $CHCl_3$), [-13.1, (c = 3, $CHCl_3$).
IR ν_{max} ($CHCl_3$) cm^{-1}:	3020, 2981, 2935, 1761, 1216.
^{1}H NMR (200 MHz, $CDCl_3$):δ:	1.25 (d, 3H, J = 7.39 Hz, CH*C*H_3), 1.73 (s, 3H, HC=C*C*H_3), 1.77-2.02 (m, 4H, *C*H_2), 2.19-2.32 (m, 1H, -*C*H-CH-CH_3), 2.34-2.45 (m, 1H, -*C*HCH_3), 4.85-4.90 (m, 1H, C*H*O), 5.51 (m, 1H, C=*C*H).
^{13}C NMR (50 MHz, $CDCl_3$): δ:	13.62 (q, CH*C*H_3), 21.85 (t, *C*H_2), 23.29 (q, C=*C*H_3), 25.53 (t, *C*H_2), 37.11 (d, *C*HCH_3), 39.90 (d, *C*HCHCH_3), 74.89 (d, *C*HO), 118.49 (d, =*C*H), 140.84 (s, CH_3*C*=), 179.51 (s, *C*=O).
Mass (m/z):	166 (M$^+$, 22), 151 (37), 138 (12), 123 (14), 107 (40), 93 (100), 79 (87), 67 (52), 55 (88).
$C_{10}H_{14}O_2$ (166.22)	Calcd: C 72.26 H 8.49 Found: C 72.37 H 8.46

5. (+)-(*3R,3aS,7aR*)-*3a*,4,5,*7a*-Tetrahydro-3,6-dimethylbenzofuran-2(3H)-one: [(+)-1b]



(+)-1b

A solution of **(-)-25b** (0.250 g, 0.85mmol) & DBU (0.166 g, 1.09mmol) in dry tetrahydrofuran (10mL) was stirred at room temperature for 5h. 6N HCl (15mL) was added and the

mixture was extracted with diethyl ether (4×20mL). The combined organic layer was washed with water (5mL), brine (5mL) and dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator at reduced pressure to furnish crude wine lactone **(-)-1b**. The lactone was purified by column chromatography (eluent: ethyl acetate:pet. ether 1:99). The lactone was further purified by crystallization from ethyl acetate/hexane.

Yield:	0.1 g, (71%).
MP. (Lit):	58-60^{0}C (57-59^{0}C)[6].
Ee:	99.86% $\mathbf{t_R}$ [(+)-1b]: 13.271 min.
[a]$_D^{20}$(Lit):	+112.15, (c = 3, $CHCl_3$), [+112, (c = 3, $CHCl_3$).
IR ν_{max} ($CHCl_3$) cm^{-1}:	3020, 2981, 2935, 1761, 1216.
^{1}H NMR (200 MHz, $CDCl_3$):δ:	1.12-1.16 (m, 1H, C*H*$_2$), 1.19 (d, 3H, J = 7.35 Hz, CHC*H*$_3$), 1.66-1.70 (m, 1H, *CH*$_2$), 1.79 (s, 3H, CH=CC*H*$_3$), 1.95-2.03 (m, 2H, *CH*$_2$), 2.23-2.31 (m, 1H, C*H*CHCH3), 2.89 (dq, 1H, J = 7.52 Hz, J = 7.33 Hz, CH-CH_3), 4.60-4.64 (m, 1H, C*H*O), 5.65-5.68 (m, 1H, *H*C=C).
^{13}C NMR (50 MHz, $CDCl_3$): δ:	9.13 (q, CH*C*H$_3$), 19.51 (t, *C*H$_2$), 23.62 (q, C=*C*H$_3$), 28.73 (t, *C*H$_2$), 37.62 (d, *C*HCHCH$_3$), 40.05 (d, *C*HCH$_3$), 74.56 (d, *C*HO), 116.80 (s, =*C*H), 143.92 (s, H$_3$C*C*=), 178.33 (s, *C*=O).
Mass (m/z):	166 (M$^+$, 32), 151 (57), 138 (12), 123 (19), 93 (100), 79 (65), 55 (39).
$C_{10}H_{14}O_2$ (166.22)	Calcd: C 72.26 H 8.49. Found: C 72.40 H 8.52

1.2.7 References

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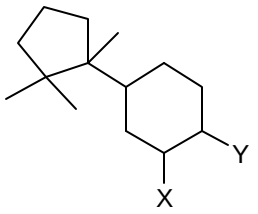
SECTION III

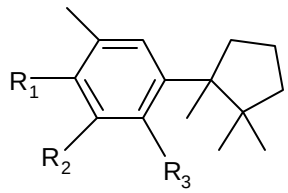
Synthetic Studies Towards (±)-b-Herbertenol

1.3.1 Introduction

The unique plant group, '*Liverworts*' contain several oil bodies characteristic of the species. Indeed, in general, a significant biochemical characteristic of the *liverworts* (*Hepaticae*) is that, they produce sesquiterpenoid metabolites which are enantiomers of those compounds produced by the higher plants. Particularly, *Herbertus* species is a rich source of *Herbertene* (*iso-cuparene*) type **1** as well as *cuparene* type **2** sesquiterpenoids.[1]



X = CH_3, Y = H: Herbertene skeleton **(1)**
X = H, Y = CH_3: Cuparene skeleton **(2)**



$R_1 = R_2 = H$; $R_3 = OH$: (±)-α-Herbertenol **(3)**
$R_1 = H$, $R_2 = R_3 = OH$: (±)-Herbertenediol **(4)**
R1 = OH, R2 = R3 = H : (±)-β-Herbertenol **(5)**
$R_1 = R_2 = R_3 = H$; (±)-Herbertene **(6)**

Numerous *herbertene* type sesquiterpenoids, an expanding group of natural products possessing a 3-methyl-1-(1,2,2-trimethylcyclopentyl) cyclohexane skeleton **1** have been isolated from *Herbertous* species and other *liverworts*.[1,2] Some of these compounds, particularly, those with an oxygenated aromatic six membered ring [*e.g.* (–)-α-Herbertenol, (–)-β-Herbertenol, (–)-Herbertenediol] show a wide spectrum of biological properties which include potent antifungal,[1a,b] neurutrophic,[3] and anti-lipid peroxidation[4] activities. Some complicated dimeric phenols, belonging to this class also have been found to be biologically active compounds.

1.3.2 Synthesis of (±)-β-Herbertenol: A Literature Review

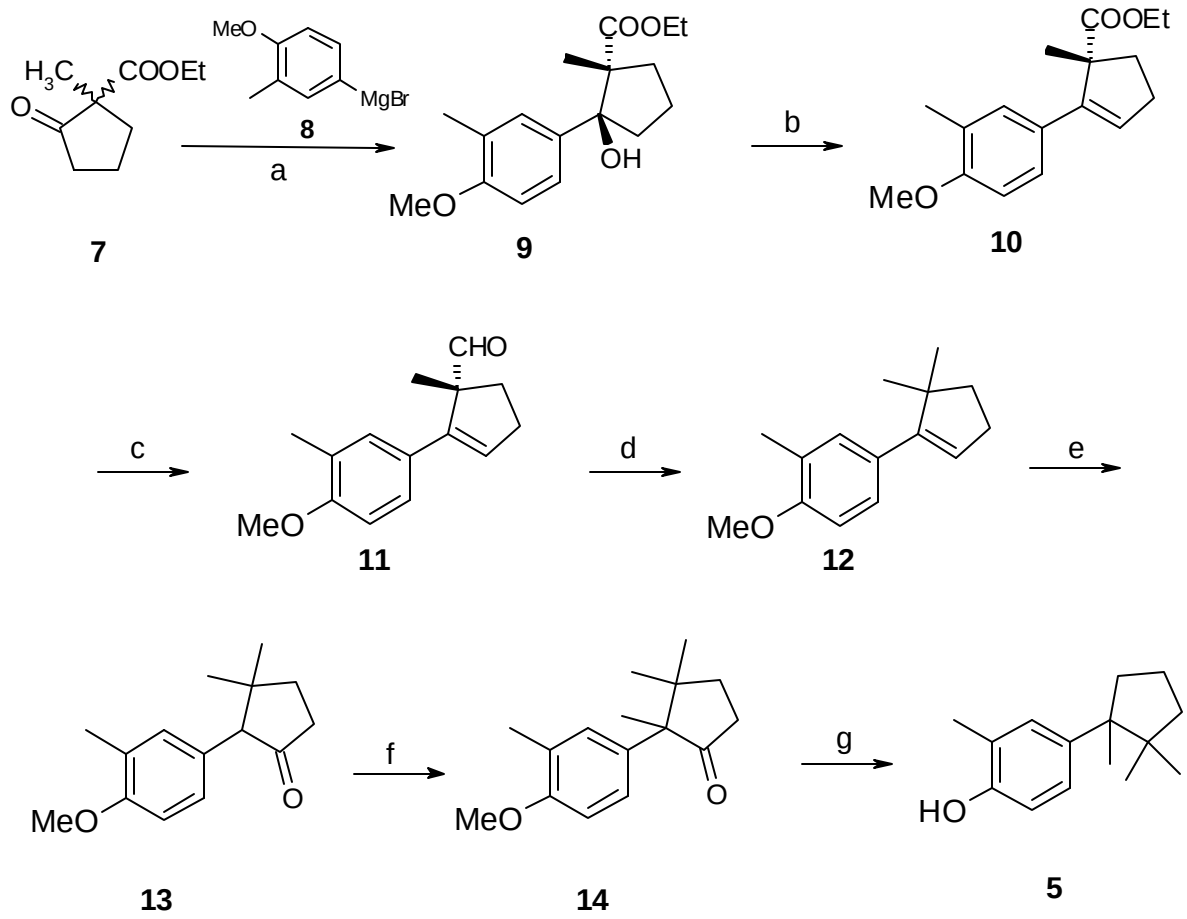
The total synthesis of Herbertene-type as well as cuparene-type sesquiterpenoids have attracted the attention of several synthetic organic chemist due to the difficulty associated with the construction of the vicinal quaternary carbons in the cyclopentane ring.[5] Literature survey clearly indicates that, eventhough a several synthetic strategies are reported towards (±)-Herbertene **6**,[5b]

(±)-α-Herbertenol **3**,[5a,e,6] (±)-Herbertenediol **4**[5d] and their asymmetric syntheses also, only one synthetic strategy is reported towards (±)-β-Herbertenol **5**.[6]

Eicher's Approach:[6] (**Scheme 1**, **1996**)

(±)-β-Herbertenol **5** was synthesized **(Scheme 1)** starting with distereoselective coupling of cyclopentanone derivative **7** with the Grignard reagent **8**[7] derived from 4-bromo-2-methylanisole to furnish *tert*. alcohol **9**.

Scheme 1: Eicher *et al Synthesis* **1996**, 863



Reagents and Conditions:

a) THF, -40^{0}C-rt, 77%, 100% ds. b) $KHSO_4$, 140^{0}C, 1h, 99%. c) i. $LiAlH_4$, THF ii. PCC, CH_2Cl_2, 48%, d) $N_2H_4.H_2O$, NaOH, DEG, 195^{0}C, 7h, 50%. e) i. $NaBH_4$, BF_3-Et_2O, ii. NaOH, H_2O_2, iii.

PCC, NaOAc, 43%. f) NaH, CH_3I, DMF, -50^{0}C-rt, 67%. g) $N_2H_4.H_2O$, NaOH, DEG, 220^{0}C, 3 days, 45%.

The *tert*.alcohol **9** was transformed to the cyclopentene derivative **10**. The cyclopentene derivative **10** was reduced with $LiAlH_4$ followed by oxidation with pyridiniumchlorochromate to furnish aldehyde **11**. Aldehyde **11** was reduced to saturated methyl group with hydrazine hydrate to furnish dimethylcyclopentene **12**. Hydroboration/oxidation followed by oxidation with pyridiniumchlorochromate in acetate buffer introduced the carbonyl auxiliary function in **13**. Cyclopentanone **13** was alkylated regioselectively at the benzylic angular carbon with methyl iodide to yield **14**. During Wolff-Kishner reduction of **14** with hydrazine hydrate /NaOH, additional cleavage of methylether protective group occurred giving rise to (±)-β-Herbertenol **5** in 3% overall yield in 9-steps sequence.

1.3.3 Present work

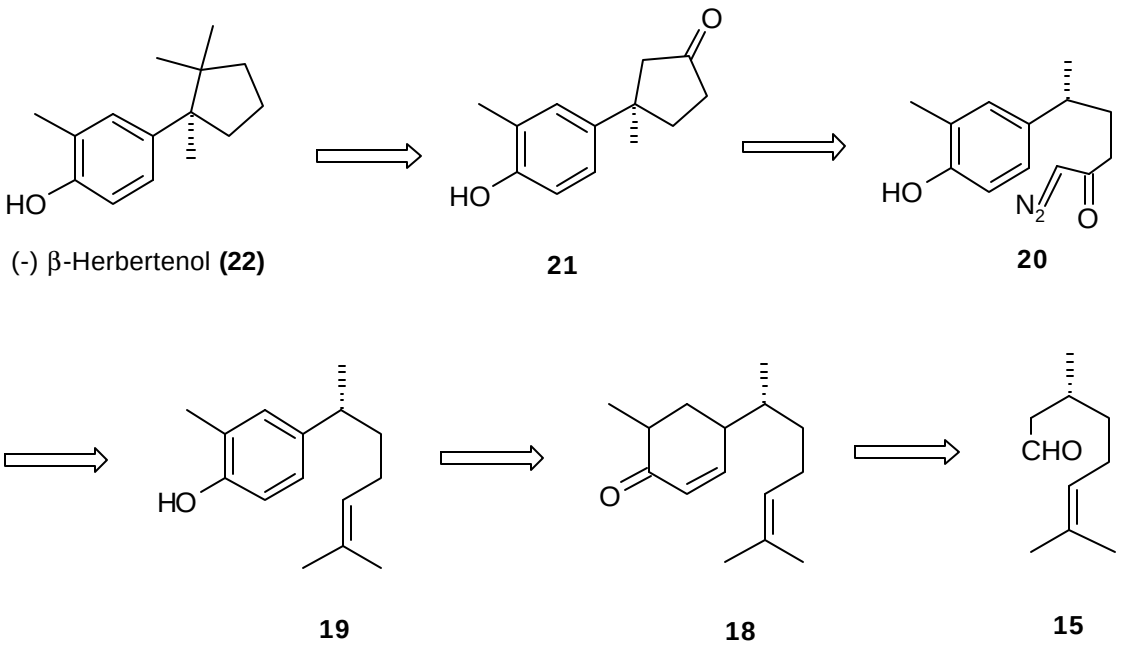
In continuation of our interest towards the total synthesis of cuparene-type sesquiterpenoid, viz. (±)-α-cuparenone,[8] we planned synthetic strategy towards (±)-β-Herbertenol **5**. The present section primarily concerns with synthetic studies towards (±)-β-Herbertenol **5**; which is reported to have antifungal activity, isolated from *Herberta adunca*.[1a] There is only one report on the synthesis of (±)-β-Herbertenol **5** till date. As described earlier, Eicher *et al*[6] reported the synthesis of (±)-β-Herbertenol **5** in 9 steps in 3% overall yield. Hence, the need for the development of short, efficient and simple strategy was felt necessary. Eicher *et al* constructed carbon skeleton of β-Herbertenol by intermolecular diastereoselective Grignard reaction of reagent **8** with cyclopentene derivative **7**. Our emphasis was on the concept that, the aryl part of cyclopentane ring of β-Herbertenol would arise from the same molecule. The ideal starting material for this concept would be R (+)-Citronellal. Additionally, citronellal will provide access to the quaternary carbon center at the benzylic position in the cyclopentane ring of the target molecule through an insertion reaction. Present work describes our synthetic studies towards (±)-β-Herbertenol **5**.

1.3.4 Results and Discussions

The retrosynthetic analysis reveals **(scheme 2)** that, (±)-β-Herbertenol **5** could be obtained from the cyclopentanone **21** which in turn could be obtained from the diazoketone **20** by dirhodium (II) catalyzed C-H insertion reaction.[9] The diazoketone **20** could be obtained from citronellal **15**.

The abundancy of R-(+)-citronellal as the natural product from the Indian plant prompted us to design a strategy for the synthesis of β-Herbertenol **5**.

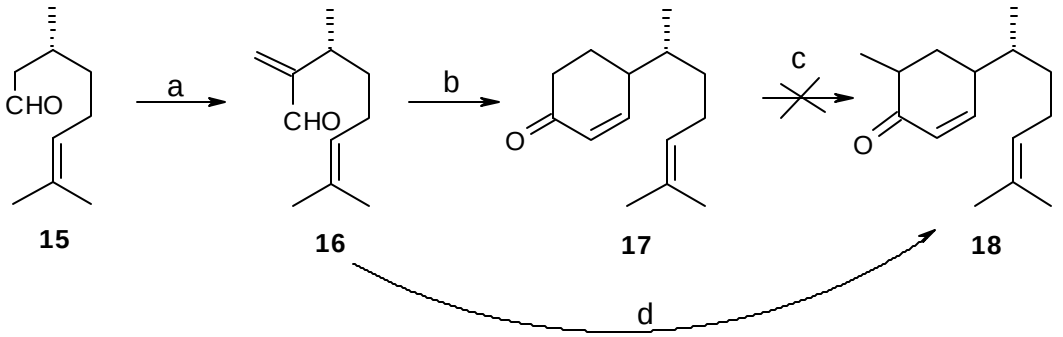
Scheme 2:



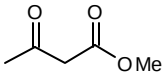
(-) β-Herbertenol **(22)** **21** **20**

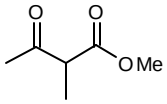
19 **18** **15**

Scheme 3:



a. Formalin (35% w/v), piperidine acetate, 90^{0}C, 86%

b.  NaOMe (catalytic), dry MeOH, rt to 60^{0}C, 5h, 47% c. MeI, base

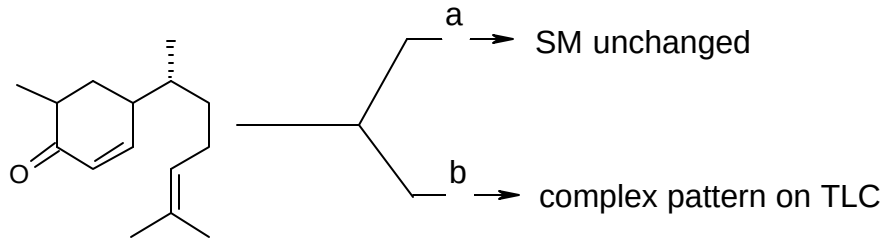
d.  NaOMe (catalytic), dry MeOH, rt to 60^{0}C, 5h, 51%

According to the synthetic plan, **(scheme 3)** *R*-(+)-citronellal **15** was converted to its exomethylene derivative, α-methylene-3,7-dimethyl-6-octanal **16** by the literature method[10] in high yield. The conversion of *R*-(+)-citronellal **15** to enone **17** can be referred to as "Umpolungs-Michael addition". This can be explained as; the potential side chain of the exomethylene compound **16** becomes a Michael acceptor. The requisite Michael donor, methylacetoacetaete was then added to the exomethylene compound **16** in dry methanol in the presence of catalytic amount of sodium methoxide at 60^{0}C for 5h. Under these conditions, addition, ring closure, and decarboxylation simultaneously take place yielding enone **17** in 47% yield **(scheme 3)**. The spectral data and physical properties of exomethylene compound **16** and enone **17** were identical with the ones reported in literature.[10] In order to introduce methyl group in aryl part of β-herbertenol, alkylation of enone **17** was proposed. Various efforts to alkylate enone **17** at the α-carbon to the carbonyl carbon with methyl iodide and various bases failed. ^{1}H-NMR and mass spectral analysis showed polymethylation was the problem. To circumvent this problem, first alkylation of methylacetoacetate was carried out using the general protocol with methyl iodide and potassium carbonate to yield α-methyl methylacetoacetate. Again exomethylene compound **16** was subjected to "Umpolunges-Michael Addition" using α-methyl methylacetoacetate as Michael donor under the identical conditions as for enone **17** to furnish enone **18** in 51% yield. The structure of enone **18** was fully assigned and confirmed by IR, NMR, mass spectral analysis. IR

spectrum of enone **18** showed absorption at 1690 cm^{-1} characteristic of α,β-unsaturated carbonyl group. ^{1}H-NMR analysis showed the presence of doublet at δ 1.12 for methyl group at α-position to the carbonyl carbon. Mass spectral analysis revealed a peak M^+ at 220 which confirmed the structure of enone **18**. The next assignment was the aromatization of the enone **18**. This seemingly simple task could not be completed under the conditions tried. Thus various efforts to aromatize enone **18** were failed. Attempted reaction with trimethyl orthoformate/methanol[11a] in benzene at its reflux temperature, led to recovery of the enone **18** with no trace of either enol ether or acetal formation, while aromatization with acetic acid/acetic anhydride and concentrated sulfuric acid at 90^0C showed a complex pattern on TLC. In an another attempt for aromatization was attempted with sulphur in dimethylformamide[11b] at its reflux temperature or with DDQ[11c] in benzene at 80^0C, however, enone **18** did not aromatize and the starting material **18** was recovered back **(scheme 4)**.

Due to unexpected failure observed during the aromatization of enone **18** to phenol **19**, this scheme was terminated and another approach was looked into. In connection with our interest towards total synthesis of (±)-α-cuparenone,[8] we planned the strategy on the similar grounds towards synthesis of (±)-β-Herbertenol **5**.

Scheme 4:



18

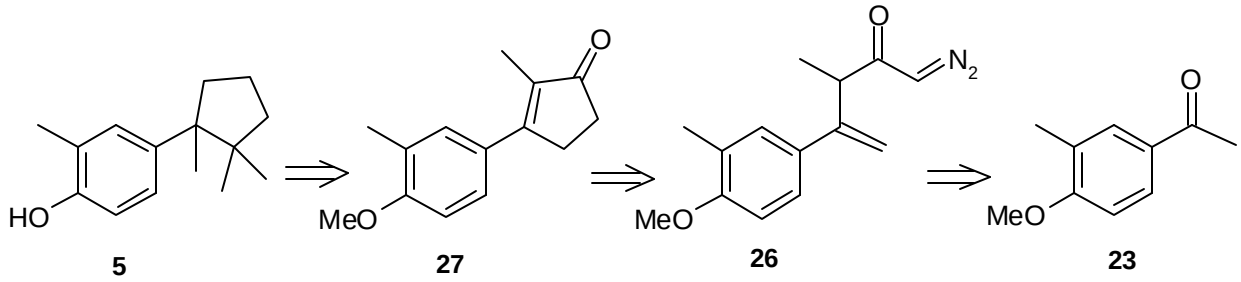
Reagents and Conditions:

a. i) $CH(OCH_3)_3$, MeOH, C_6H_6, reflux ii) S/DMF, 140^0C,

iii) DDQ/C_6H_6, 80^0 b) $CH_3COOH/(CH_3CO)_2O$, Conc. H_2SO_4, 90^0C.

The retrosynthetic analysis **(scheme 5)** reveals that, BF_3. Et_2O catalyzed cyclization of β-γ unsaturated α-diazoketone **26** to furnish cyclopentene **27** would serve as ideal substrate and this reaction would be utilized as the key step of the sequence.

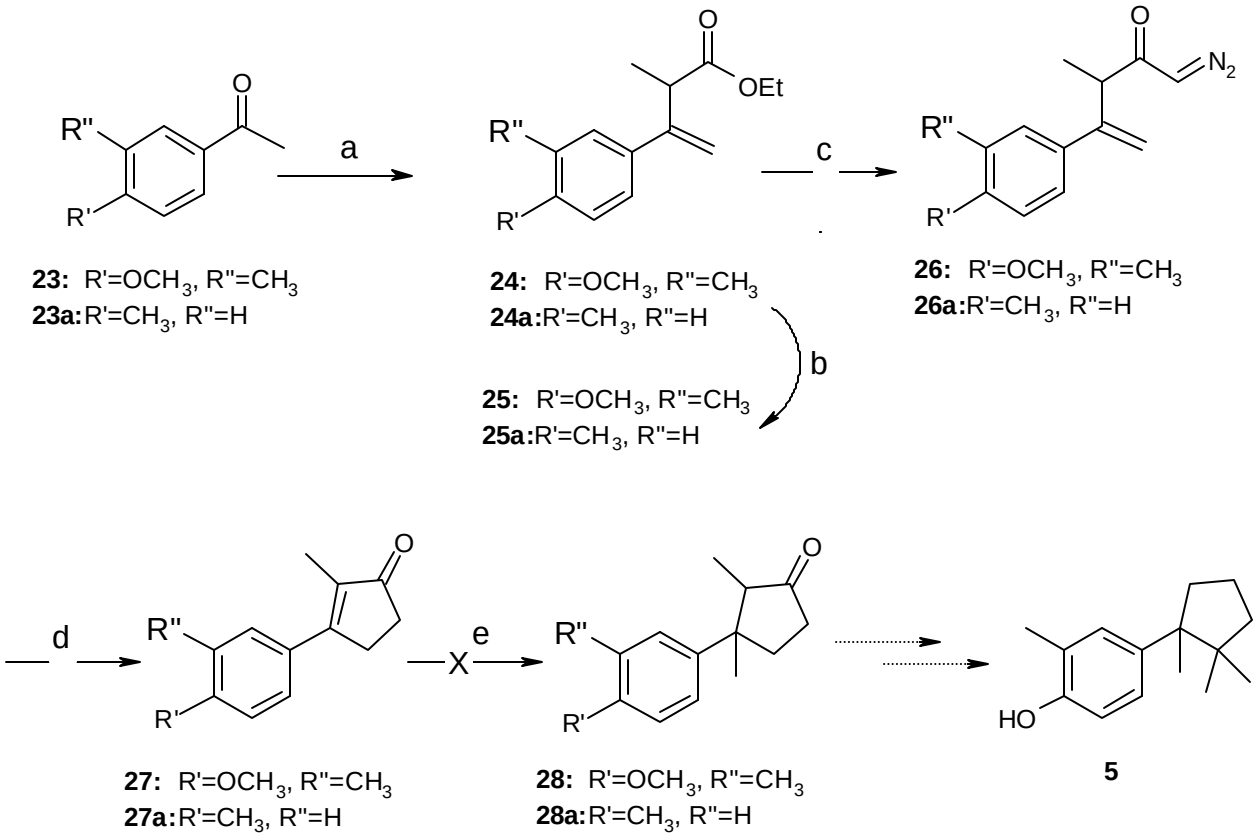
Scheme 5:



5 **27** **26** **23**

Thus according to the synthetic plan (scheme 6), 4-methoxy-3-methylacetophenone 23 was subjected to Reformatsky reaction[12] with α-bromopropionate in dry diethyl ether followed by acidic work up to furnish β-γ unsaturated ester 24 in 66% yield. The ester was well characterized by IR, NMR and mass spectral analysis. The IR spectrum of 24 showed absorption at 1730 cm^{-1} for ester carbonyl group indicating it to be as an isolated β-γ unsaturated ester as against α-β unsaturated ester, which would absorb at a lower frequency. The ^{1}H NMR analysis revealed two singlets at δ 5.32 and 5.13 for Ar-C=CH_2 and a doublet at δ 1.39 for H_3C-CH-COOEt clearly establishing the assigned structure 24. M^+ at 248 and ^{13}C-NMR analysis confirmed the structure of β-γ unsaturated ester 24. The α-β unsaturated ester though apparently more stable is not formed. Although, the exact reason for this is not very clear, this may possibly be ascribed to the "peri" interaction of the aliphatic methyl group with "ortho" aromatic protons.

Scheme 6:



23: R'=OCH_3, R''=CH_3
23a: R'=CH_3, R''=H

24: R'=OCH_3, R''=CH_3
24a: R'=CH_3, R''=H

25: R'=OCH_3, R''=CH_3
25a: R'=CH_3, R''=H

26: R'=OCH_3, R''=CH_3
26a: R'=CH_3, R''=H

27: R'=OCH_3, R''=CH_3
27a: R'=CH_3, R''=H

28: R'=OCH_3, R''=CH_3
28a: R'=CH_3, R''=H

5

Reagents and Conditions:

a) i. $BrCHCH_3COOEt$, Zn, diethyl ether, reflux, 5h ii. 50% HCl, 10h, rt, 66% b) KOH/EtOH, 2h, rt, 93%. c) i. $SOCl_2$, Benzene, Cat. DMF, 0^0C-rt 2h ii. CH_2N_2, diethyl ether, 0^0C, rt, 86%, d) $BF_3.Et_2O$, DCM, 0^0C, 45%, e) $AlMe_3$, $Ni(acac)_2$, 0^0C-rt, 6h,

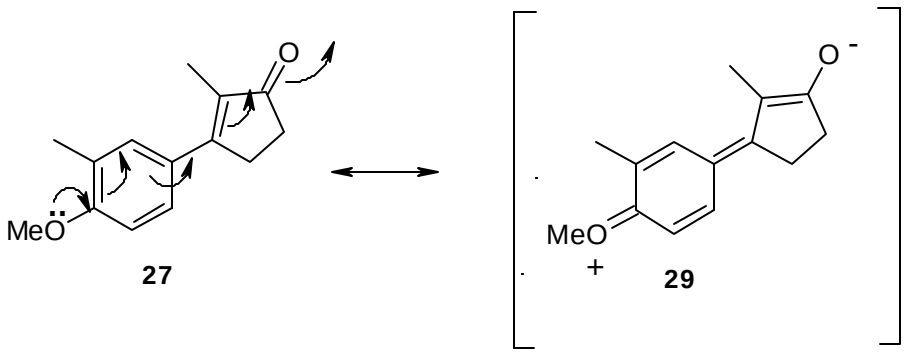
Hydrolysis of the ester 24 using ethanolic potassium hydroxide at reflux temperature afforded acid β,γ-unsaturated 25 in 92% yield. IR spectrum of the compound 25 showed broad absorption peak at 3100 cm^{-1} responsible for carboxylic group. The ^{1}H-NMR spectrum revealed two singlets at δ 5.27 and 5.45 for Ar-C=CH_2 and disappearance of triplet at δ 1.19 and quartet at δ 4.10 for –COOC$H_2$$CH_3$. Doublet at δ 1.39 for CH_3-CH-COOH confirmed that ester 24 was hydrolyzed without isomerization of the double bond. M^+ at 220 and ^{13}C-NMR analysis confirmed the structure of β-γ unsaturated acid 25.

The α-diazoketone 26 was prepared using Scott's procedure.[13] Thus, β-γ unsaturated acid 25 was converted to its acid chloride in the presence of catalytic amounts of dry

dimethylformamide in dry benzene followed by quenching the acid chloride with CH_2N_2 in diethyl ether at 0^0C to furnish diazoketone 26. The structure of diazoketone 26 was confirmed by IR and ^{1}H-NMR analysis. IR spectrum of compound 26 showed characteristic absorption peak at 2100 cm^{-1} (C–N≡N) and 1640 cm^{-1} for (C–N_2) absorption and 1730 cm^{-1} for carbonyl, 1600 cm^{-1} for olefin. The ^{1}H-NMR showed singlet at δ 5.16 (–C*H*=N_2) and two singlets at δ 5.32 and 5.45 for two olefinic protons (Ar-C=CH_2).

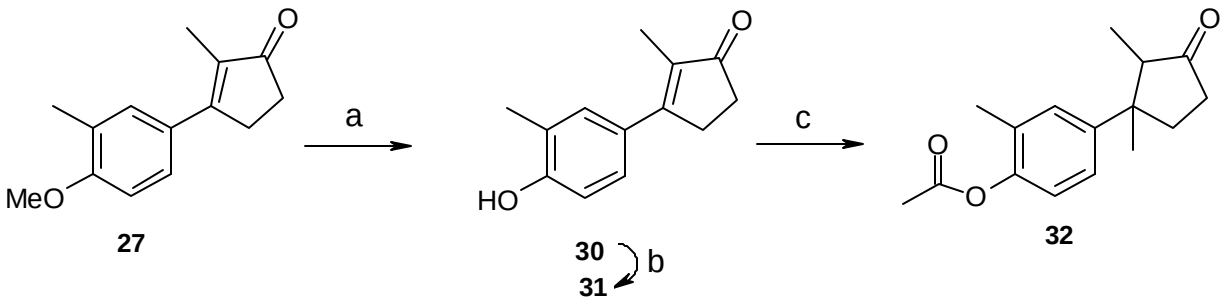
The cyclization of α-diazoketone 26 with 1 equiv. of BF_3-Et_2O[14] in CH_2Cl_2 at 0^0C afforded enone 27 in 40% yield. The structure of the enone 27 was confirmed by IR, NMR and mass spectral analysis. The IR spectrum displayed a characteristic carbonyl frequency at 1700 cm^{-1} for conjugated enone with disappearance of absorption at 2100 cm^{-1}. ^{1}H-NMR spectrum showed disappearance of the peaks at δ 5.16, 5.32, 5.45 and exhibited the following peaks in the spectrum at δ 1.96 (s, 3H, H_3C-CH=CH), 2.23 (s, 3H, Ar-CH_3), 2,47 (m,2H), 2.81 (m, 2H), 3.81 (s, 3H, Ar-CH_3), 6.83 (d, 1H) 7.33 (m, 2H). The ^{13}C-NMR spectrum of 27 revealed 13 signals for 14 carbons. Downfield shift of carbonyl carbon from δ 182.2 to 209.72 was indicative of a ketone carbonyl. Singlets at δ 166.27 and 159.23 indicated *tetra*-substituted olefinic carbons. Triplets at δ 28.95 and 33.84 indicated two methylene groups. M^+ at 216 with base peak at 115 confirmed the structure of enone 27. Thus enone 27 was fully characterized by IR, ^{1}H & ^{13}C NMR, mass spectral analysis.

Thus the key intermediate 27 was ready for the next task. What remained to be done was the introduction of two methyl groups at 1 & 2 position with respect to carbonyl carbon. The seemingly simple nucleophilic 1,4-conjugate addition of methyl across the double bond with trimethylaluminium catalyzed by $Ni(acac)_2$[15] was the total surprise to us. Unfortunately, 1,4-conjugate addition with trimethylaluminium did not furnish the desired cyclopentanone derivative 28. The reason for failure may be attributed to the delocalization of the lone-pair of oxygen as shown in the structure 29 and thereby reducing the partial positive character at the β-position which is unfavorable for 1,4-conjugate addition.



In order to curb oxygen lone-pair participation, we synthesized acetate 32 (scheme7)**.**

Scheme 7:



Reagents and Conditions:

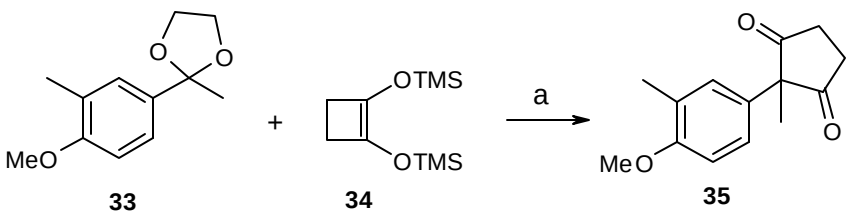
a) i. BBr_3/DCM, -78^{0}C, 89% b). AcCl, Et_3N, DCM, 0^{0}C-rt, 83% c) $AlMe_3$, $Ni(acac)_2$, 0^{0}C-rt, 6h, 66%.

Demethylation[16] of enone **27** with BBr_3 at –78^{0}C in dry dichloromethane furnished the corresponding phenol derivative **30** in 89% yield. The IR spectrum of the phenol showed the broad absorption peak at 3150-3300 cm^{-1}. The ^{1}H NMR spectrum displayed the disappearance of singlet at δ 3.82 (Ar-OC*H*$_3$). M^+ at 202 in mass spectral analysis with base peak 187 conformed the structure of phenol derivative.

Acetylation of phenol with acetyl chloride and triethyl amine in dichloromethane in the presence of catalytic DMAP at 0^{0}C yielded acetate **31** in 83% yield. The structure of acetate **31** was fully confirmed by IR, NMR, and mass spectral analysis. IR spectrum of the acetate **31** showed absorption at 1730 cm^{-1} for the ester carbonyl group. ^{1}H-NMR showed the appearance of

singlet at δ 2.35 (OCOCH_3). ^{13}C-NMR of the compound **31** showed 14 signals for 15 carbons in the molecule due to 2 overlapping signals. Mass spectrum of the compound **31** displayed M^+ peak at 244, confirming the assigned structure of the acetate **31**. Since the oxygen lone pair participation was curbed, acetate **31** was subjected to Michael addition with trimethylaluminium catalyzed by $Ni(acac)_2$.[18] Michael addition product **32** was obtained in 66% yield thereby confirming the our hypothesis. ^{1}H-NMR of compound **32** displayed singlet at δ 1.20 for newly introduced methyl group, doublet at δ 1.06 for methyl group (-CH-CH_3). Unfortunately, we were unable to reproduce this Michael addition. One probable reason for the failure might be the quality of the trimethylaluminium. Hence to check the quality of the reagent *viz*. Me_3Al, Michael addition of the same reagent material on substrate **27a**, precursor for α-cuparenone[8] was carried out successfully. Failure despite of several attempts to reproduce conjugate addition on sustrate **31** to furnish **32**, this scheme although very close to the target molecule, had to be abandoned.

Failure of this scheme led to another scheme when the central idea was to construct cyclopenta-1,3-dione system **35** where the tertiary methyl group would be introduced at an early stage in the synthesis and then to elaborate it to β-herbertenol. Cyclopenta-1,3-dione **35**[19] was prepared in 68% yield by condensing dioxolane **33**[20] with 1,2-disilyloxycyclobutene **34**[21] at -78^0C. The structure of the cyclopenta-1,3-dione **35** was assigned and confirmed by IR, ^{1}H & ^{13}C-NMR, mass spectral analysis. IR spectrum of diketone **35** showed absorption at 1764 cm^{-1} & 1724 cm^{-1} for two carbonyl groups. ^{1}H-NMR of the compound **35** displayed singlet at δ 1.39 for quaternary methyl group in cyclopentane ring, a singlet at δ 2.18 (3H) for methyl group attached to aromatic ring, a multiplet between δ 2.62-3.12 (4H) for two methylene groups, a singlet at δ 3.81 (3H) for methoxy group. Aromatic protons were observed at δ 6.77 (d, 1H, J=8 Hz) & at δ 6.96-7.01 (m, 2H). ^{13}C-NMR of the compound **35** displayed 11 signals for 14 carbons in the molecule due to overlapping signals. Among these signals, both the methylene groups were observed at δ 32.34. Singlet at δ 154.83 represented both the carbonyl groups. Mass spectrum displayed M^+ peak at 232 (88) with the base peak 148.

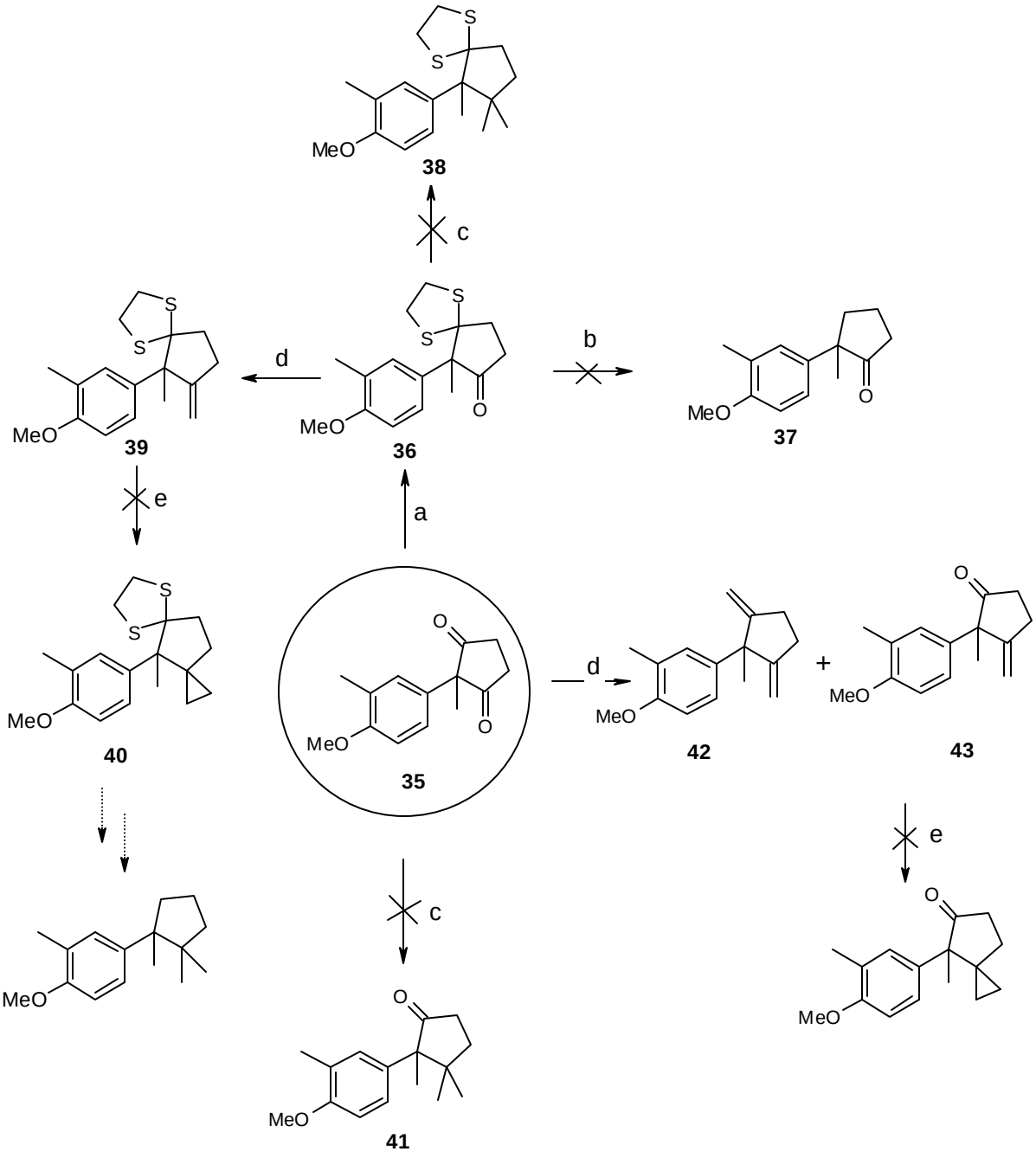


Reagents and Conditions:

a) $BF_3.Et_2O$, CH_2Cl_2, -78^{0}C, 8h, then at rt, 10h 68%.

The cyclopenta-1,3-dione could be further converted to β-Herbertenol by several ways. For that purpose various efforts have been made **(scheme 8)**. First, one of the carbonyl groups was protected regioselectively with 1,2-ethanedithiol[22] to yield dithioacetal **36** in 82% yield. The structure of dithioacetal derivative **36** was assigned and confirmed by IR, ^{1}H & ^{13}C-NMR, mass spectral analysis.

Scheme 8:



Reagents and Conditions:

a. 1,2-$HSCH_2CH_2SH$, $BF_3.OEt_2$, 12h, rt, 82%. b. Desulfurization, Ra-Ni, various reaction conditions. c. $AlMe_3$, TMSOTf. d. $PPh_3{}^+MeI^-$, K^+*tert*. BuO^- C_6H_6, reflux-rt, 72%.

e. Cyclopropanation, various reaction conditions.

By protecting one of the carbonyl group regioselectively, we can exploit the other carbonyl group towards β-herbertenol. Hence desulfurization[23] of dithioketal derivative **36** with Raney-nickel[23a,b], $LiAlH_4/CuCl_2/ZnCl_2$[23c], $NiCl_2/NaBH_4$[23d] under various reaction conditions were tried without success in order to get cyclopentanone derivative **37**.

Another attempt involved introduction of geminal dimethyl groups on dithioacetal **36** with $AlMe_3$/TMSOTf[24] to obtain **38**, where the starting material was recovered.

Since desulfurization of thioacetal derivative **36** failed, we turned our attention towards another carbonyl group. The idea was to subject thioketal derivative **36** for Clemmensen reduction in order to reduce carbonyl group to methylene group followed by regeneration of the carbonyl group by deprotecting dithioketal derivative **36**. When Clemmensen reduction of dithioketal derivative **36** was carried out, we obtained a complex reaction mixture from which the desired product could not be identified.

Since the Clemensen reduction of the dithioketal derivative 36 failed, another obvious option remained was Wittig reaction of dithioketal derivative 36, followed by Simmon-Smith cyclopropanation. Thus Wittig reaction of 36 with ylide ($CH_2=PPh_3$) yielded exomethylene derivative 39 in 72% yield. IR spectrum of the compound 39 showed disappearance of the absorption signal at 1724 cm^{-1} for the carbonyl group. ^{1}H-NMR of compound 39 showed appearance of two singlets at δ 5.17 & 4.92 for olefinic protons. ^{13}C-NMR of the compound 39 displayed 17 signals for 17 carbons of the molecule. Among those signals, triplet at δ 108.56 ($C=CH_2$), singlet at δ 156.64 ($C=CH_2$) confirmed the presence of olefin. Additionally disappearance of the singlet at δ 216.56 (C=O) was also observed. Mass spectrum of the compound 39 showed M^+ peak at 306 as a base peak. Thus the structure of the exomethylene compound 39 was assigned and confirmed by IR, ^{1}H & ^{13}C-NMR and mass spectral analysis. The next task was to convert exomethylene group in to cyclopropyl group by Simmon-Smith cyclopropanation[25]. Thus cyclopropanation of exomethylene derivative 39 with standard reagents *viz*. Et_2Zn/CH_2I_2, $AlMe_3/CH_2I_2$,[25f-g] $Cu(I)Cl/CH_2I_2/Zn$[25h-j] was tried without success. In all these attempts, starting material 39 was cleanly recovered back.

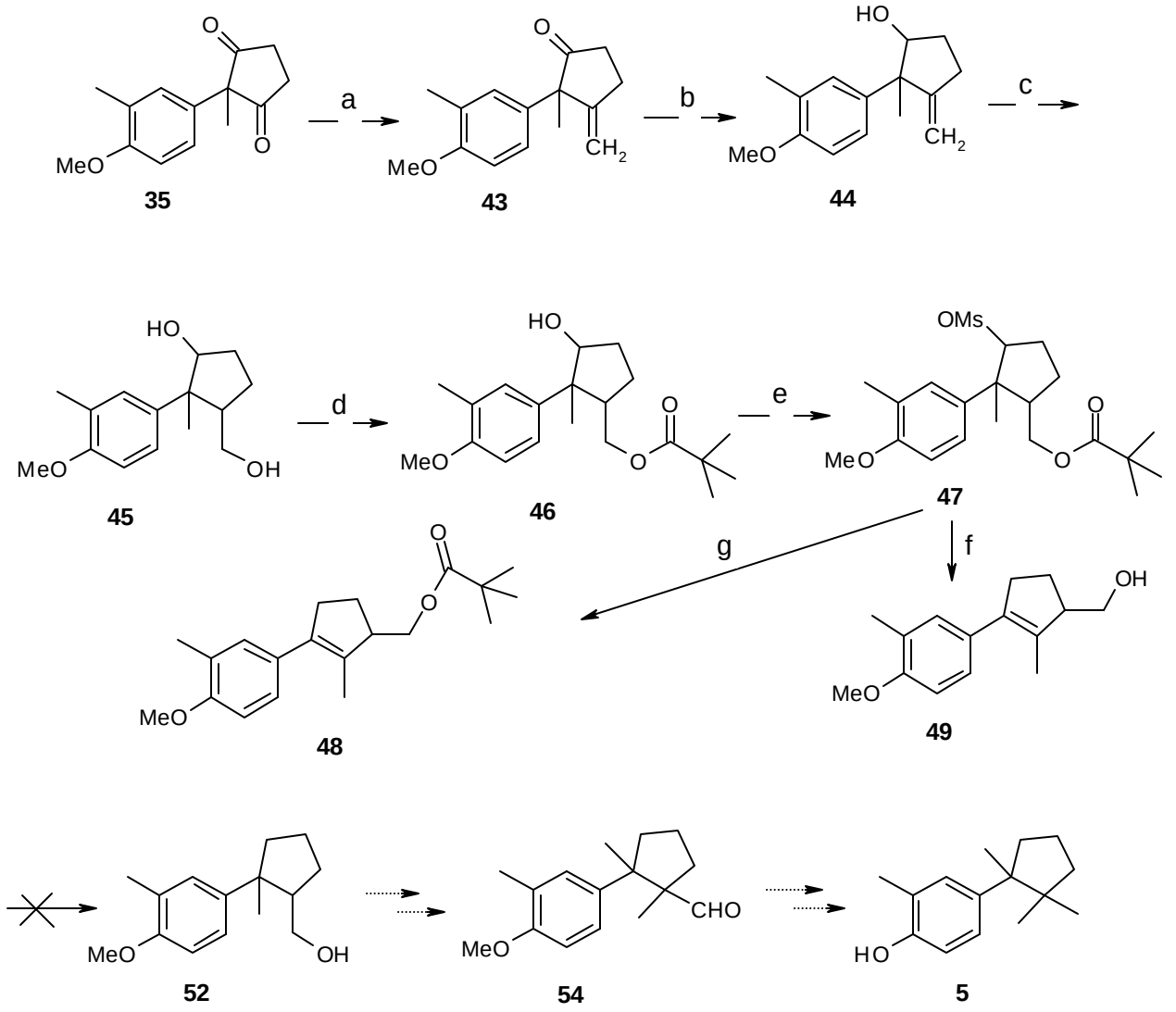
Due to all the failures during the functionalization of one of the carbonyl groups, we subjected cyclopentadione **35** to Wittig reaction expecting mono-olefination. Under optimized reaction conditions, cyclopentadione **35** was added at room temperature to the *in situ* generated ylide (1 equiv.prepared from Wittig salt $PPh_3^+MeI^-$ & K^+*tert*.BuO^- in refluxing benzene for 1h) stirred for 15 minutes, followed by addition of Wittig salt (1 eqiuv.) and the base (1 equiv.) and refluxing it for 15 minutes followed by further addition of Wittig salt (0.25 equiv) and the base (0.25 equiv.) and further refluxing the reaction mixture for 15 minutes to ensure the completion of the reaction. Thus the exomethylene derivative **43** was obtained in 73% yield as a major product along with minor amounts (3%) of di-exomethylene compound **42**. If the Wittig salt (in all 2.25 equiv.) and the base (in all 2.25 equiv.) were mixed in a single portion and the ylide was generated once, cyclopentadione **35** furnished di-exomethylene compound **42** as the major product. IR spectrum of the compound **43** showed absorption at 1740 cm^{-1} for C=O. ^{1}H-NMR spectrum of the compound **42** displayed two singlets at δ 5.33 and 5.12 indicating the presence of olefinic protons. ^{13}C-NMR displayed 14 signals for 15 carbons in the molecule. Among those signals, triplet at δ 109.48 for exomethylene carbon (-C=C*H*$_2$) and a singlet at δ 153.18 for quaternary olefinic carbon, a singlet at δ 215.85 for carbonyl carbon confirmed the assigned structure of exomethylene compound **43**. Mass spectrum showed M^+ peak at 230 (48) with base peak at 187.

Exomethylene compound **43** was reduced with $NaBH_4$ in ethanol at room temperature to furnish secondary alcohol **44**. IR spectrum of the alcohol **44** displayed broad absorption at 3450 cm^{-1} indicating the presence of hydroxy group and disappearance of peak at 1740 cm^{-1} for C=O. ^{1}H-NMR of the compound **44** displayed multiplet for 1H at δ 1.54-1.62, a multiplet at δ 1.85-2.12 for 1H, a multiplet (2H) at δ 2.42-2.73 for methylene group. A multiplet (1H) was merged with the signal for methoxy group at δ 3.84 for methine proton (-C*H*OH). Mass spectrum of the compound **44** displayed M^+ peak at 232 (88) with base peak at 173 confirming the assigned structure of **44**.

The secondary alcohol **44** was subjected to hydroboration[27] with BMS complex followed by oxidative work up with alkaline H_2O_2 to furnish compound **45**. IR spectrum showed absorption at 3455 cm^{-1} for hydroxy group. ^{1}H-NMR spectrum of the compound **45** displayed the absence of olefinic protons at δ 5.13 & 5.33. A multiplet at δ 1.76-2.37 presented five protons *i. e.* two methylene groups and a methine proton (-C*H*CH_2OH). A dd (1H) at δ 3.53 represented one of the protons from two prochiral protons of the methylene group (-C*H*$_2$OH), a doublet (1H) at δ 3.79 and a multiplet δ 4.24 (1H) were the other remaining distinguishing peaks in the ^{1}H-NMR spectrum of

the compound **45**. ^{13}C-NMR of the compound **45** displayed 15 signals for 15 carbons in the molecule. Disapperance of the triplet at δ 109.57 and a singlet at δ 153.18 in the ^{13}C-NMR for the olefinic carbons were the indicative of the formation of compound **45**. A doublet at δ 79.23 (-*C*HOH) and a triplet at δ 62.94 (-*C*H_2OH) were the other distinguishing peaks. Mass spectrum of the compound **45** showed M^+ peak at 250 (10). Thus the structure of the compound **45** was assigned and confirmed by IR, ^{1}H & ^{13}C-NMR and mass spectral analysis.

Scheme 9:



Reagents and Conditions:

a) $PPh_3^+MeI^-$, K^+*tert*. BuO^- C_6H_6, reflux-rt, 72%. b) $NaBH_4$, EtOH, rt, 30 min, 98%. c) i. BMS, THF, 0^0C, 2h then at rt 24h, ii. H_2O_2,HO^-, 0^0C-rt, 1h.71%. d) $(CH_3)_3CCOCl$, Et_3N, DCM, 0^0C-rt, 84%. e) MsCl,Et_3N, dry DCM, 0^0C-rt, 78%. f) $LiAlH_4$, THF, rt g) Silica gel.

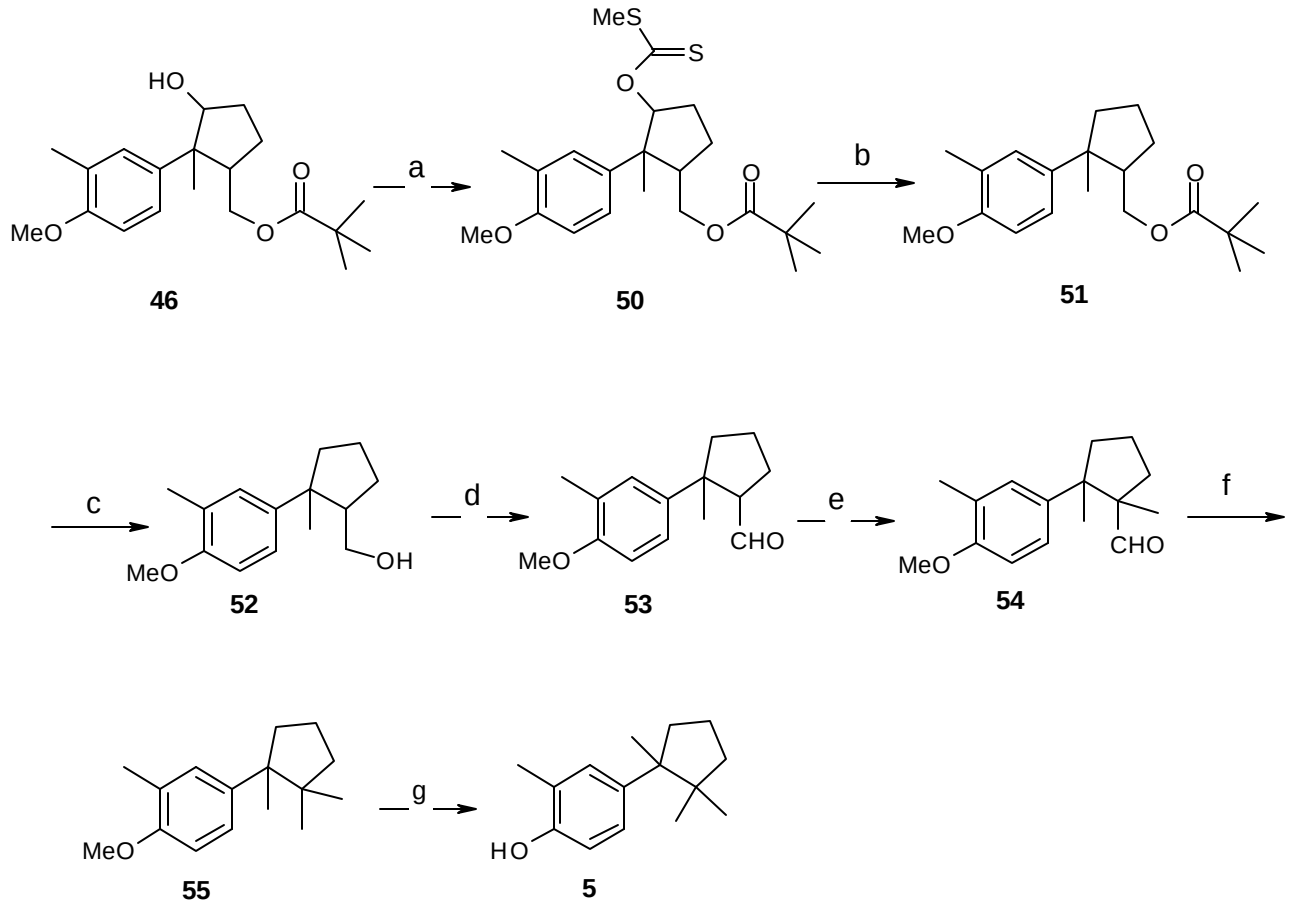
Diol **45** thus obtained was protected regioselectively as pivaloate ester[28] to furnish **46** in 84% yield. The structure of the compound **46** was assigned and confirmed by the aid of IR, ^{1}H & ^{13}C-NMR and mass spectral analysis. IR spectrum of the compound **46** displayed absorption peaks at 3450 cm^{-1} & 1717 cm^{-1} indicating presence of hydroxy and carbonyl groups respectively. ^{1}H-NMR spectrum of the compound **46** showed a singlet (9H) at δ 1.16 for $-C(CH_3)_3$, singlet (3H) at δ 1.33 for methyl group, a multiplet (4H) at δ 1.79-2.14 for two methylene groups, a singlet (3H) at δ 2.22 for aromatic methyl group, a multiplet (1H) at δ 2.34-2.39 for methine proton. ^{13}C-NMR of the compound **46** displayed 17 signals for 20 carbons in the molecule. Among those signals, a quartet at δ 28.28 for methyl groups (-CMe_3) and a singled at δ 179.23 for carbonyl group were the characteristics peaks. Mass spectrum of the compound **46** displayed M^+ peak at 334 (9) with the base peak at 149.

The next task was deoxygenation of the pivaloate **46**. For deoxygenation, it was decided to convert secondary hydroxy group of the pivaloate ester **46** to its mesylate followed by the reduction with $LiAlH_4$. Under these conditions, cleavage of pivaloate ester to primary alcohol was also expected. Thus pivaloate **46** was treated with methane sulfonyl chloride at 0^0C to yield mesylate **47**. ^{1}H-NMR of the compound **47** showed a singlet at δ 2.88 (3H) for methyl group (H_3C-SO_2-). This mesylate **47** was found to be very labile. During column chromatography on silica gel (60-120), mesylate **47** was converted to faster moving product. This faster moving product was identified as the rearranged product **48**. Formation of **48** may be attributed to the neighboring group participation of aryl group. During neighboring group participation, either methyl group or the aryl group can migrate, but it is well known that migratory aptitude of the aryl group is more than methyl group. On the basis of IR, ^{1}H & ^{13}C-NMR and mass spectral analysis the most probable structure of the rearranged product would be **48**.

Due to the rearranged product obtained during the column chromatography, mesylate **47** without purification was put further for reductive deoxygenation with $LiAlH_4$ in THF at room temperature. However, it was found that, mesylate group was too labile and induced the rearrangement without the desired reduction. Under these conditions, only the reductive cleavage of pivaloate ester took place furnishing **49**. ^{1}H-NMR of **49** displayed the disappearance of the

singlet (9H) at δ 1.17. Downfield shift from δ 1.33 to 1.78 was observed for methyl group attached to cyclopentene ring. ^{13}C-NMR of the compound **49** showed disappearance of the quartet (3×*C*H$_3$) at δ 26.78 responsible for methyl groups indicating the cleavage of pivaloate ester. From IR, ^{1}H & ^{13}C-NMR, mass spectral analysis, the structure of the compound **49** was confirmed.

Scheme 10:



Reagents and Conditions:

a) NaH (1.5 equiv.) THF:CS_2, 4:1, rt, 3h, then MeI (3 equiv.) rt 16h, 86% b) TBTH (5 equiv.), AIBN, toluene, reflux, 1.5 h, 83%. c) $LiAlH_4$, THF, rt 92%. d) PCC, CH_2Cl_2, 0^0C-rt, 1h, 86%.

e) NaH, DME, 0^0C, 30 min, MeI, 0^0C, 3h, then at rt 16h, 65% f) $H_2NNH_2.H_2O$, NaOH, TEG, 195^0C, 7h, 52%. g) BBr_3, CH_2Cl_2, -78^0C-rt, 1h 81%.

Due to the problems encountered during the deoxygenation of the mesylate **47**, it was decided to convert pivaloate ester **46** to its xanthate derivative followed by the deoxygenation with *tri*-n-butyltinhydride. Thus pivaloate **46** was converted into its xanthate derivative[29] by treating it

with NaH/CS_2 followed by the addition of methyl iodide. IR spectrum of the compound **50** showed disappearance of absorption peak at 3450 cm^{-1} for hydroxy group. ^{1}H-NMR of the compound **50** displayed a singlet at δ 2.35 (3H, -SC*H*$_3$). A multiplet at δ 3.84-3.95 (1H), a multiplet at δ 4.26-4.32 (1H), multiplet at δ 6.01-6.14 (1H) were the other distinguishing peaks in the ^{1}H-NMR of the compound **50**. ^{13}C-NMR of the compound **50** displayed 22 signals for 22 carbons in the molecule. Among those signals, a quartet at δ 19.13 (-S*C*H$_3$), doublet at δ 91.83 (-*C*H-O-C=S-), singlet at δ 179.06 (-*C*=S) were the distinguishing peaks in ^{13}C-NMR. A downfield shift for methine carbon (-*C*H-O-C=S) was observed as compared to the corresponding methine carbon (-*C*HOH, δ 80.31) in its precursor, pivaloate **46**. Mass spectrum of the compound **50** showed M^+ peak at 424 with base peak 215. Thus the structure of the compound **50** was assigned and confirmed by IR, ^{1}H & ^{13}C-NMR and mass spectral analysis.

The xanthate derivative **50**, thus obtained was subjected to deoxygenation[29a,30] with *tri*-n-butyltinhydride in refluxing toluene with AIBN as an initiator to furnish the compound **51**. ^{1}H-NMR of compound **51** showed disappearance of the singlet at δ 2.35 (-SC*H*$_3$) and displayed a multiplet at δ 3.72-3.80 (1H) and a dd at δ 3.48.

Compound **51** thus obtained was cleaved with $LiAlH_4$ in anhydrous THF at room temperature to furnish compound **52**. The structure of the compound **52** was confirmed by IR, NMR and mass spectral analysis. IR spectrum of the compound **52** showed broad absorption at 3450 cm^{-1} for hydroxy group. ^{1}H-NMR of the compound **52** showed disappearance of the singlet (9H) at δ 1.17 indicating cleavage of the pivaloate group. Multiplet at δ 3.08-3.12 (1H), a multiplet at δ 3.32-3.37 (1H) were the other distinguishing peaks in the NMR spectrum of the compound **52**. ^{13}C-NMR spectrum of compound **52** displayed 15 signals for 15 carbons in the molecule. Disappearance of quartet (C*Me*$_3$) at δ 29.61and singlet at δ 178.17 for ester carbonyl were indicative of the cleavage of pivaloate ester.

Primary alcohol **52** thus obtained was oxidized with PCC in dichloromethane to furnish compound **53**. IR spectrum of the compound **53** showed the disappearance of the absorption peak at 3450 cm^{-1} (broad) for hydroxyl group and the presence of absorption peak at 1703 cm^{-1} for aldehyde carbonyl. ^{1}H-NMR of the compound **53** revealed a doublet at δ 9.18 (J=4 Hz) indicating the presence of aldehyde. ^{13}C-NMR spectrum of **53** displayed 15 signals for 15 carbons in the molecule. ^{13}C-NMR spectrum revealed disappearance of triplet (-*C*H$_2$OH) at δ 64.23 and

appearance of doublet (-*CHO*) at δ 203.72. Mass spectrum of the compound **53** showed M^+ peak at 232 (12) with base peak at 175.

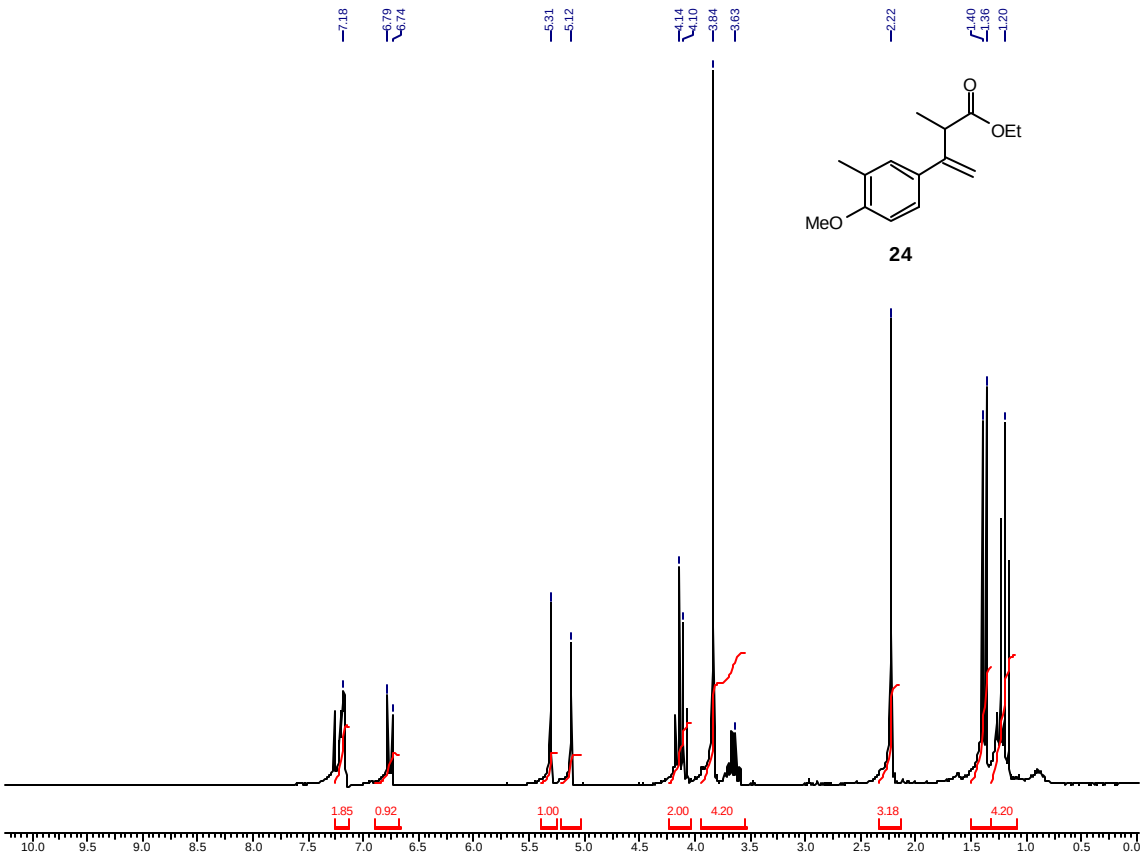
Aldehyde **53** thus obtained was alkylated with CH_3I/NaH to furnish **54**. ^{1}H-NMR spectrum of **54** revealed the presence of singlet at δ 1.25 (1.5 H) and at δ 1.31 (1.5 H). Singlet at δ 9.04 (-*CHO*) was the other distinguishing peak in ^{1}H-NMR spectrum of **54**.

Aldehyde functionality of the aldehyde **54** was reduced to methyl by Wolff-Kishner reduction in 52% yield. IR spectrum of the compound **55** showed the absence of absorption peak at 1703 cm^{-1}. ^{1}H-NMR spectrum of the compound **55** displayed disappearance of the singlet at δ 9.03. Singlet (3H) at δ 0.56, singlet (3H) at δ 1.06, singlet (3H) at δ 1.25 were the other distinguishing peaks in the ^{1}H-NMR of the compound **55**. ^{13}C-NMR of **55** displayed 15 signals due to overlapping signals for 16 carbons in the molecule. Among these signals, quartet at δ 24.46 and another quartet at δ 24.68 were the other distinguishing peaks in the spectrum.

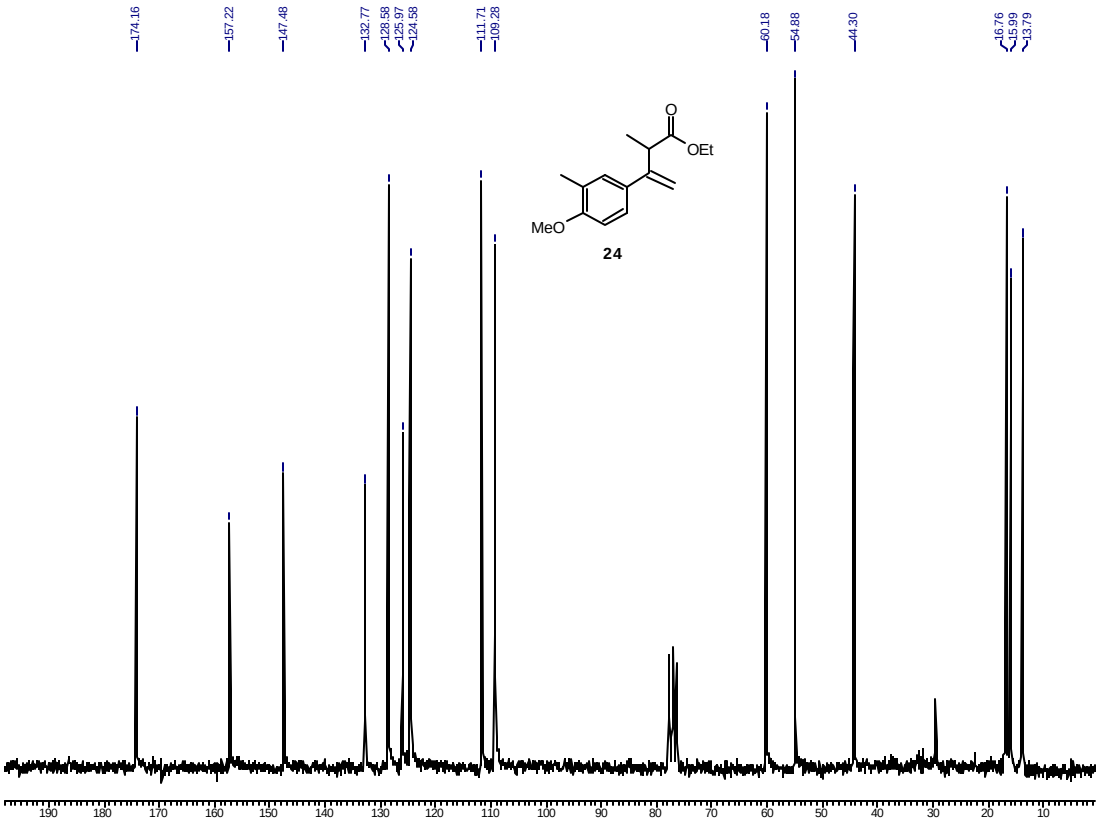
Compound **55** was demethylated with BBr_3 in dichloromethane at -78^0C to furnish (±)-β-herbertenol **5**. ^{1}H-NMR spectrum of (±)-β-herbertenol **5** displayed disappearance of singlet at δ 3.84 (-OCH_3) and appearance of broad singlet at δ 4.75 (Ar-*OH*) thereby confirming the demethylation of **55**. ^{13}C-NMR of 5 displayed 15 signals for 15 carbons in the molecule. Disappearance of quartet at δ 55.26 (-OCH_3) was indicative of demethylation. Upfield shift for aromatic carbons was also observed. Thus (±)-β-herbertenol **5** has physical and spectral properties identical with the ones reported in the literature.[1a,6]

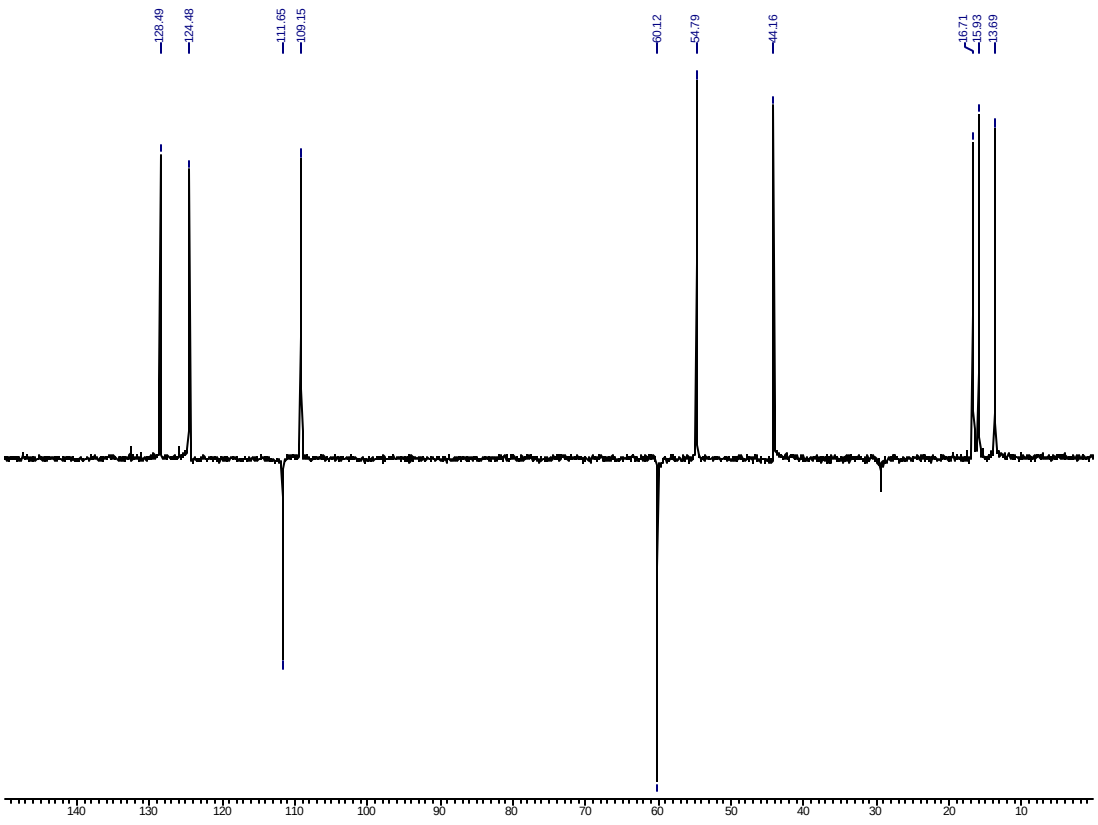
1.3.5 Conclusions

1. A convenient and practical total synthesis of (±)-β-herbertenol has been achieved in 6.5% overall yield.
2. The formation of cyclopentadione **35** onto the aromatic moiety, which is better than the reported synthesis, is the key feature of this protocol.
3. This methodology by virtue of involvement of prochiral intermediate *i.e.* cyclopentadione **35** has a potential to synthesize chiral compounds of this family by desymmetrization chemical and/or enzymatic protocols.

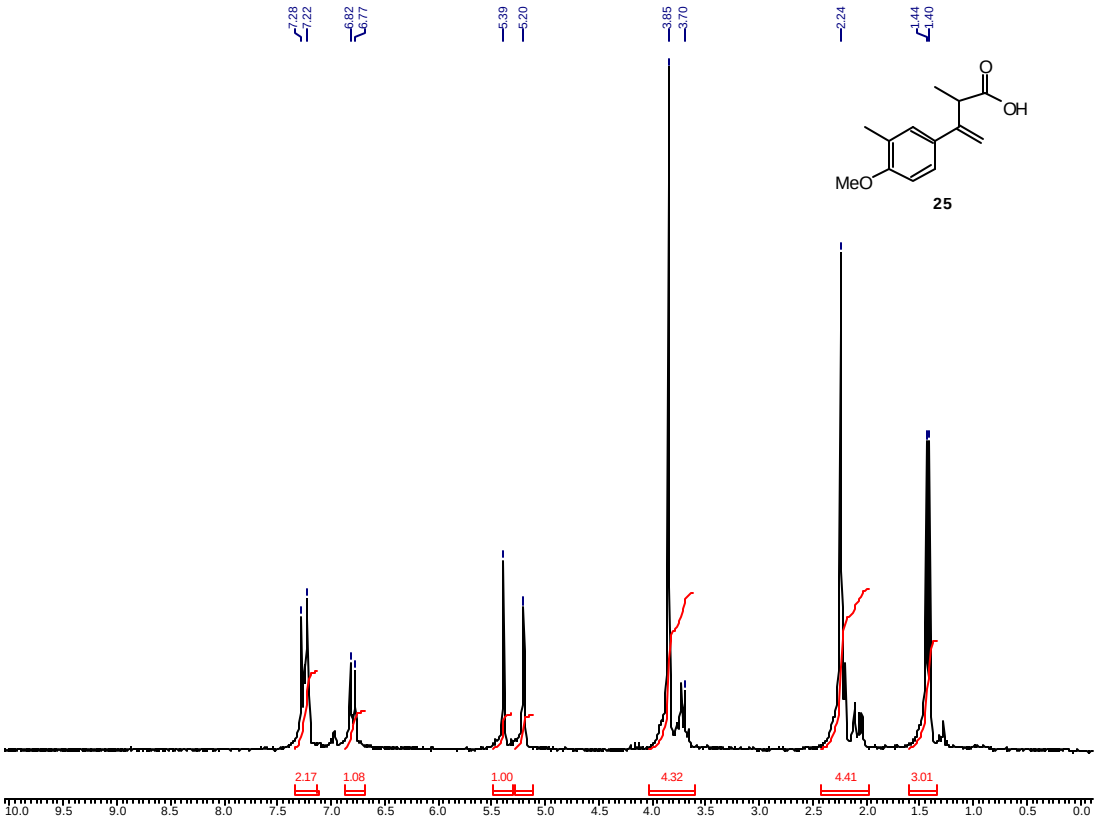

7.18
6.79
6.74
5.31
5.12
4.14
4.10
3.84
3.63
2.22
1.40
1.36
1.20
O
OEt
MeO
24
1.85
0.92
1.00
2.00
4.20
3.18
4.20
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

^{1}H-NMR spectrum ($CDCl_3$, 200 MHz) of Compound 24

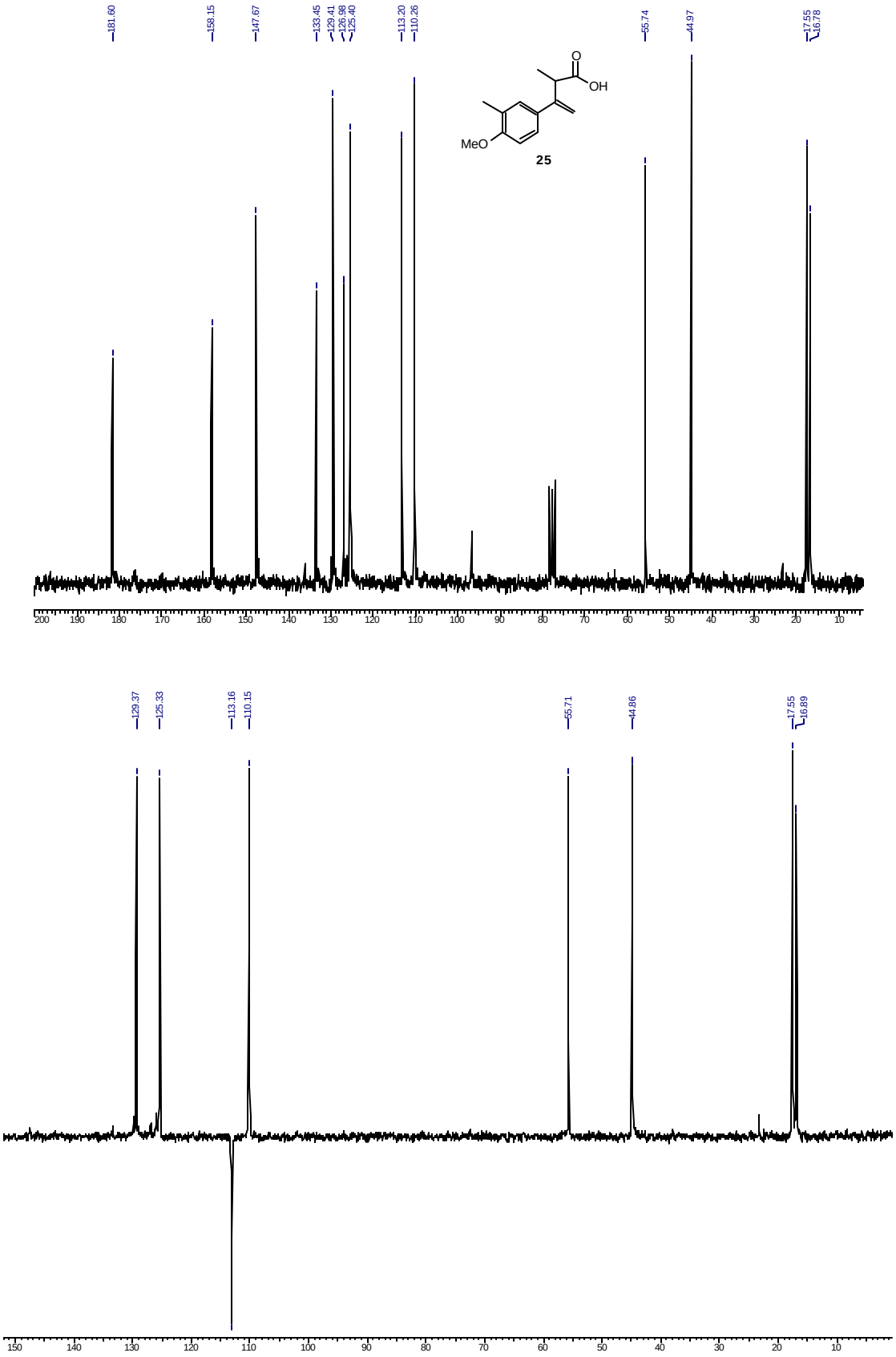




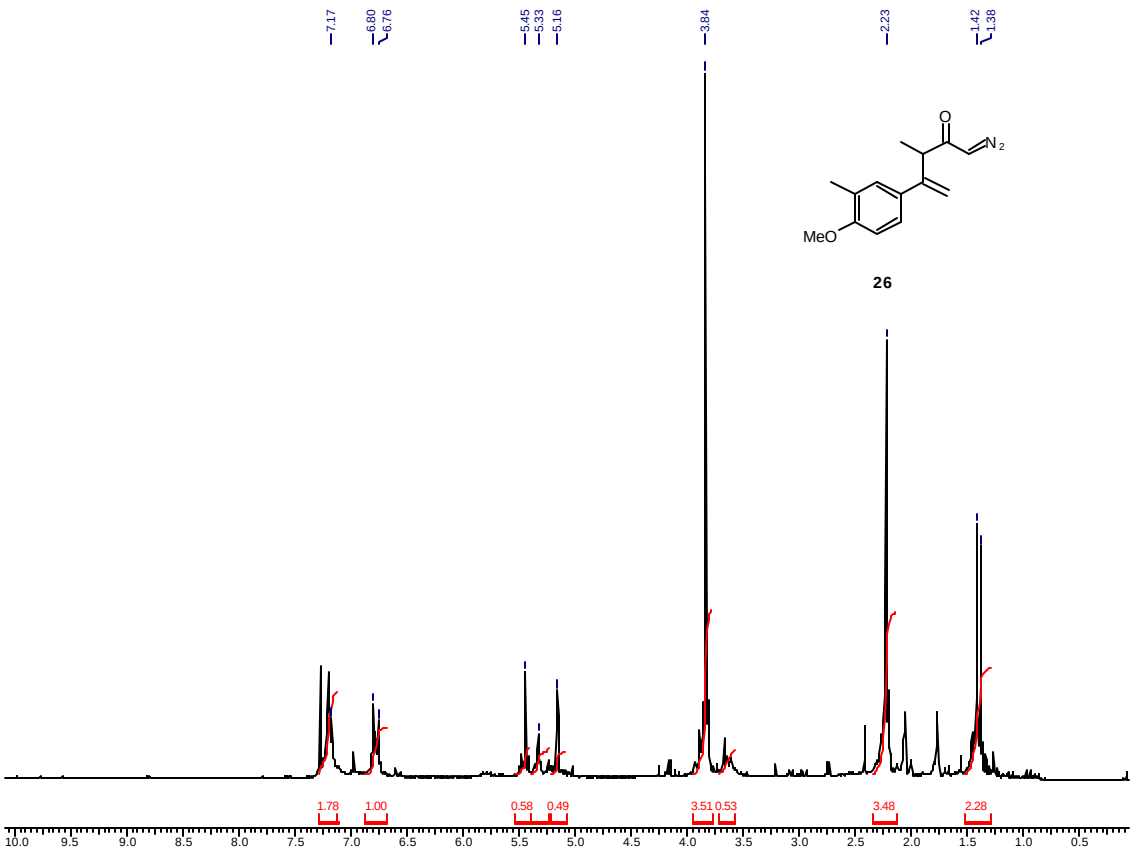
^{13}C-NMR and DEPT ($CDCl_3$, 50 MHz) of Compound 24:



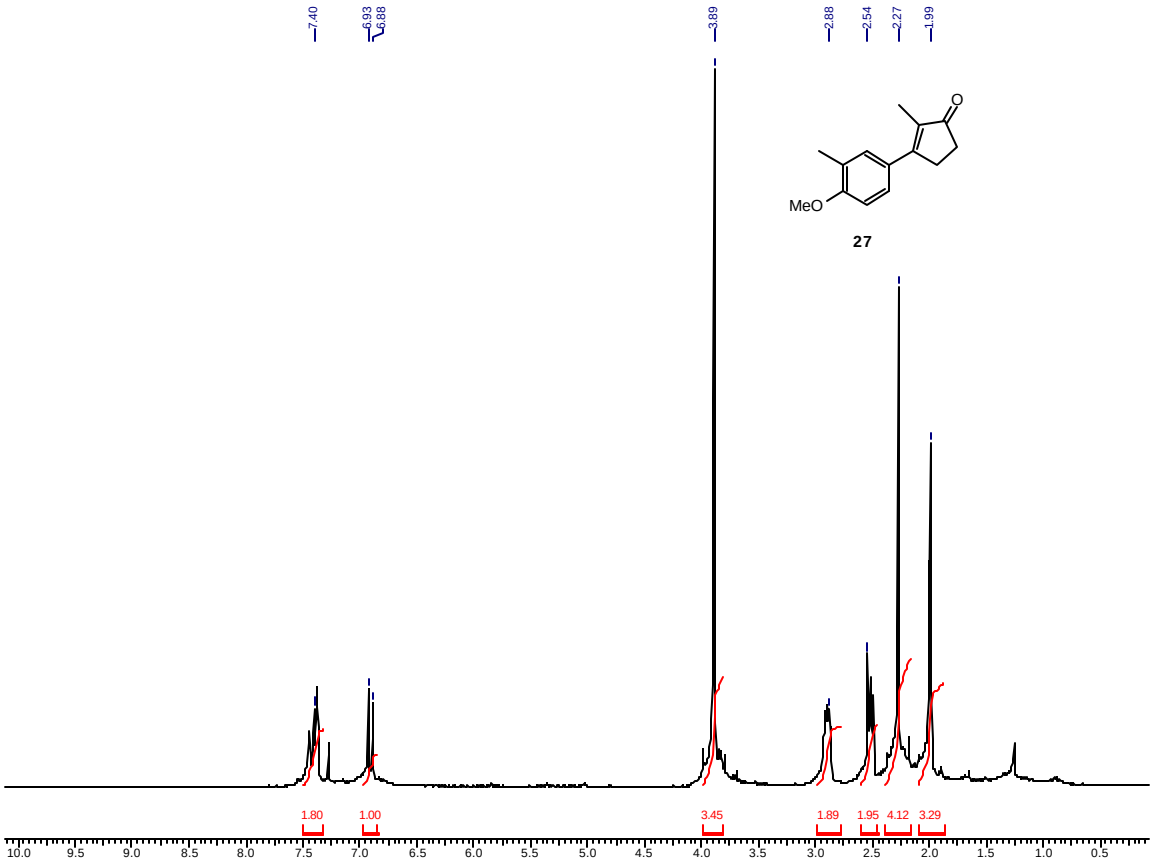
^{1}H-NMR spectrum ($CDCl_3$, 200 MHz)of Compound 25



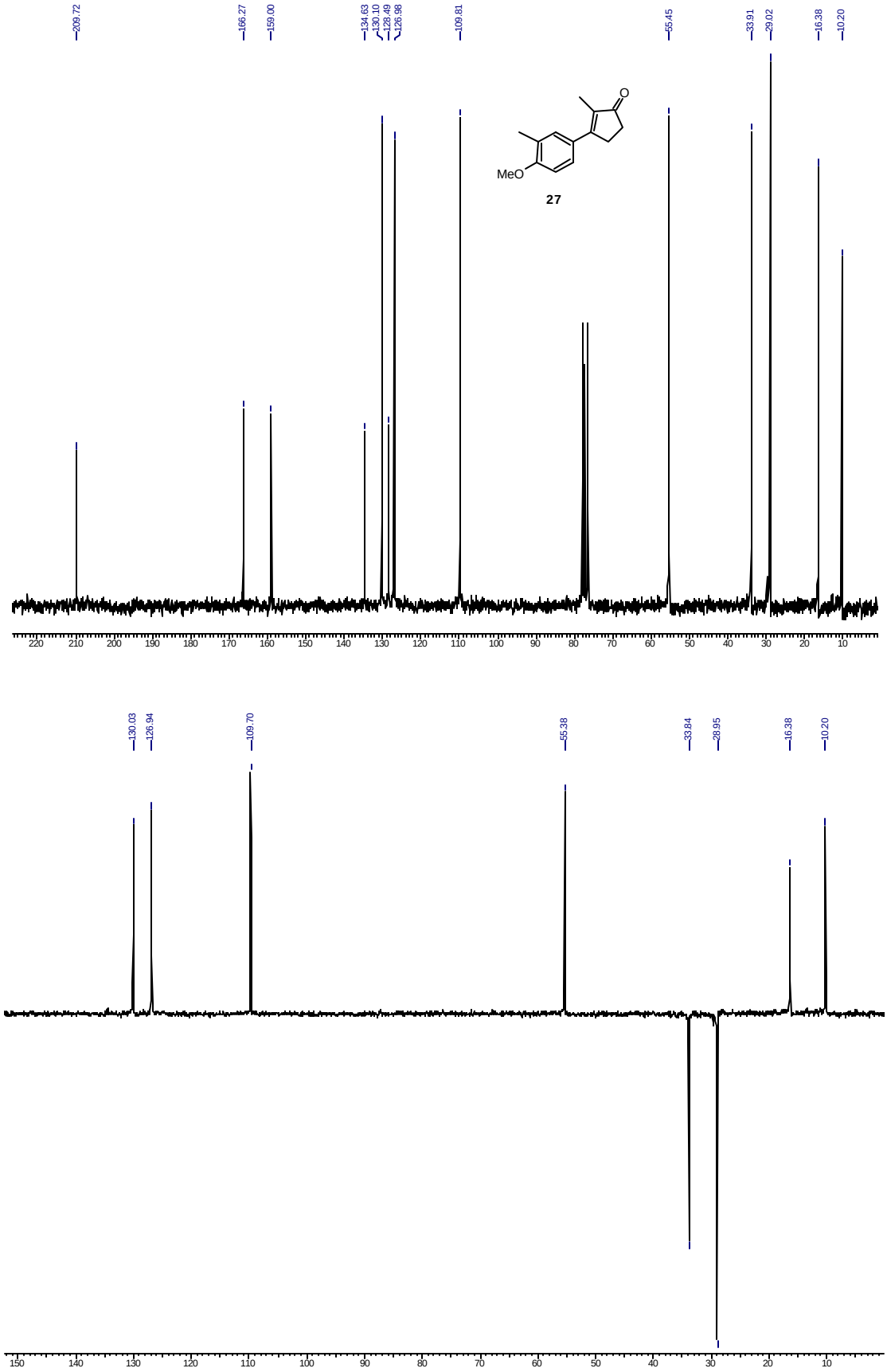
^{13}C-NMR and DEPT ($CDCl_3$, 50 MHz) of Compound 25



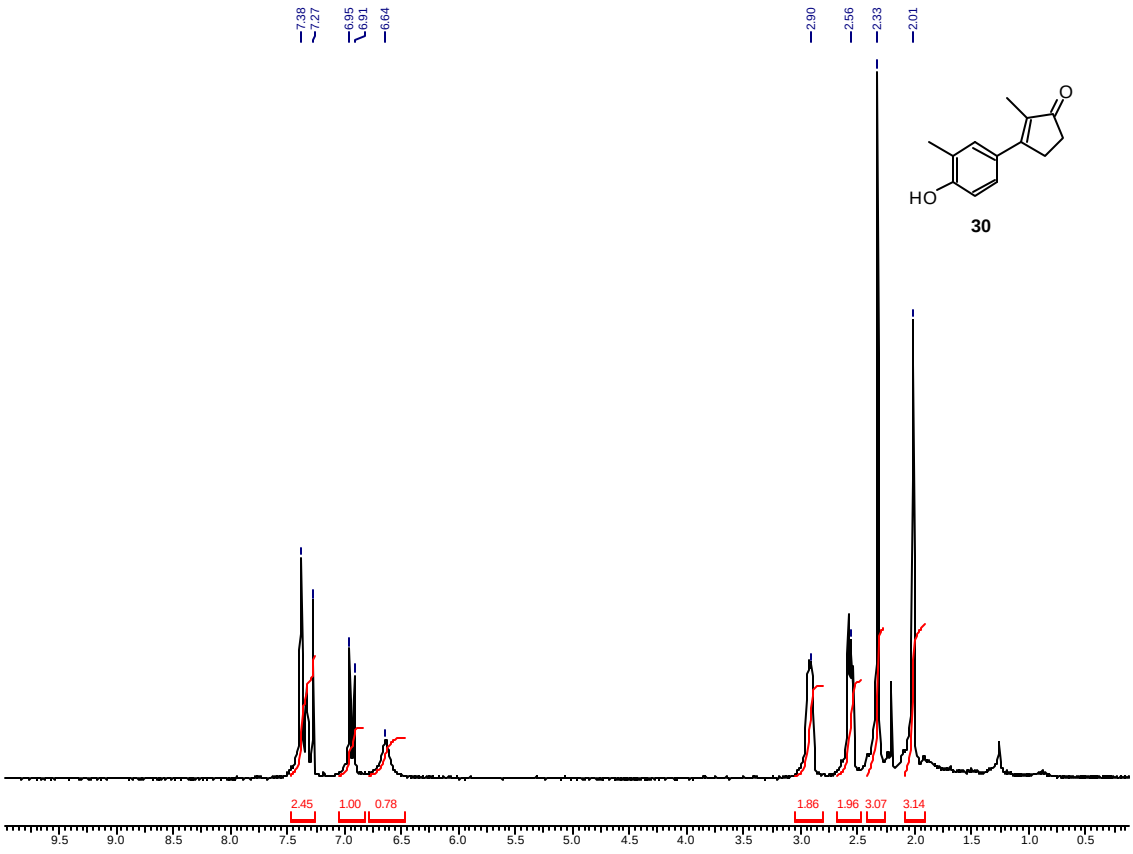
^{1}H-NMR spectrum ($CDCl_3$, 200 MHz) of Compound 26



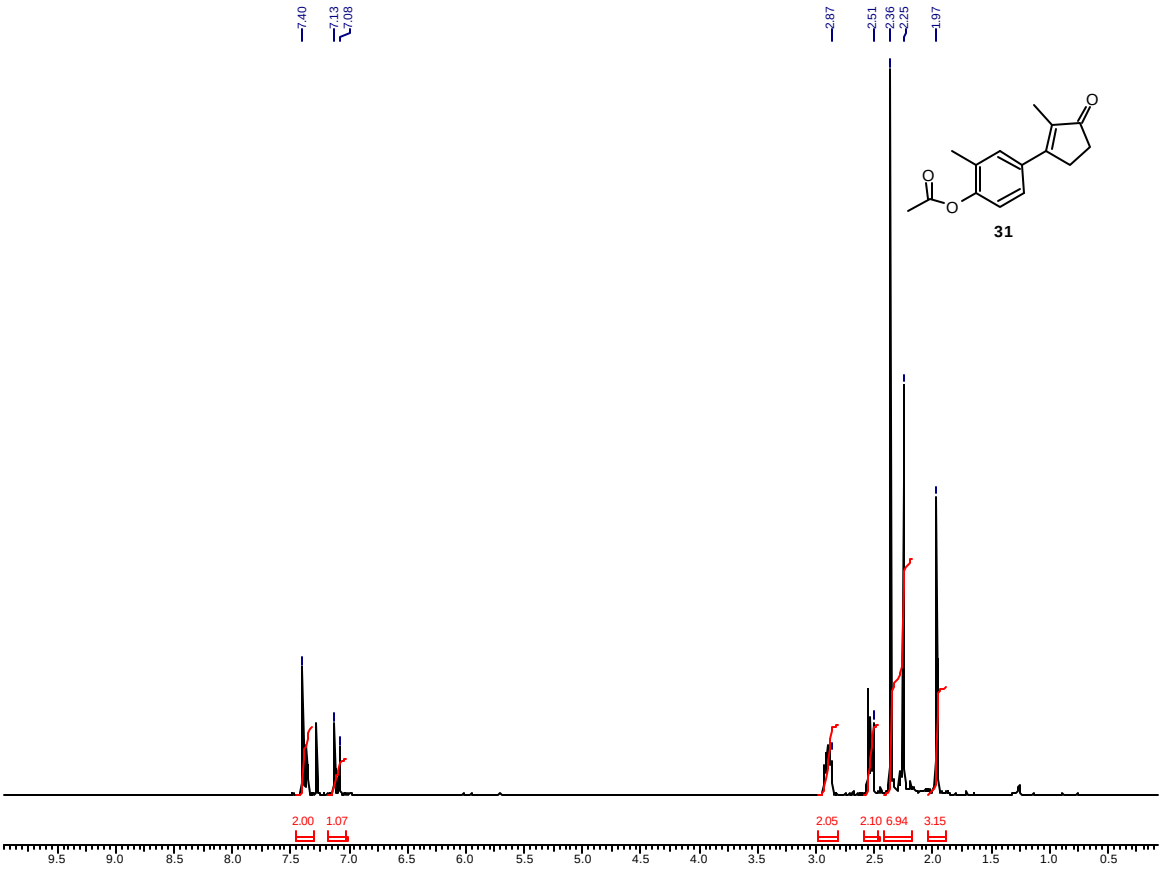
^{1}H-NMR spectrum (CDCl$_3$, 200 MHz) of 27



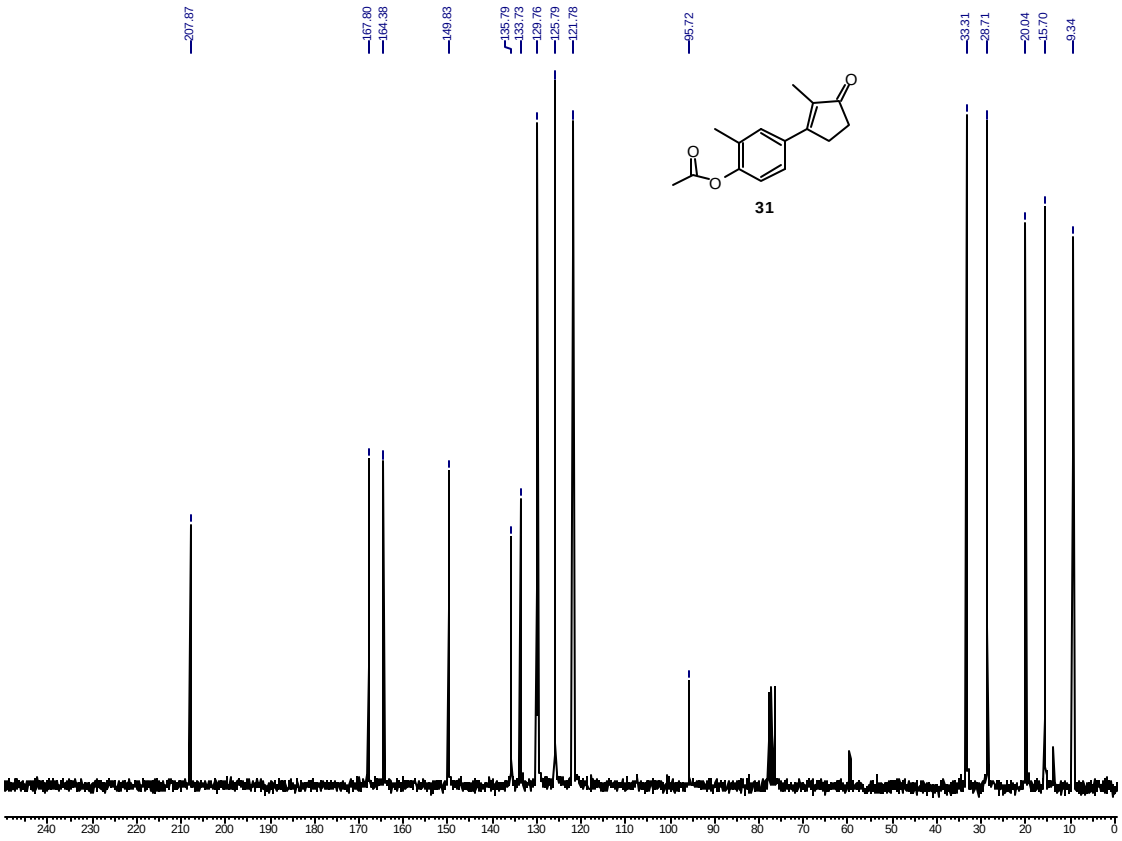
^{13}C-NMR and DEPT ($CDCl_3$, 50 MHz) of compound 27



^{1}H-NMR spectrum (CDCl$_3$, 200 MHz) of Compound 30



^{1}H-NMR spectrum ($CDCl_3$, 200 MHz) of Compound 31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149.83
135.79
133.73
129.76
125.79
121.78
95.72
33.31
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15.70
9.34
O
O
O
31
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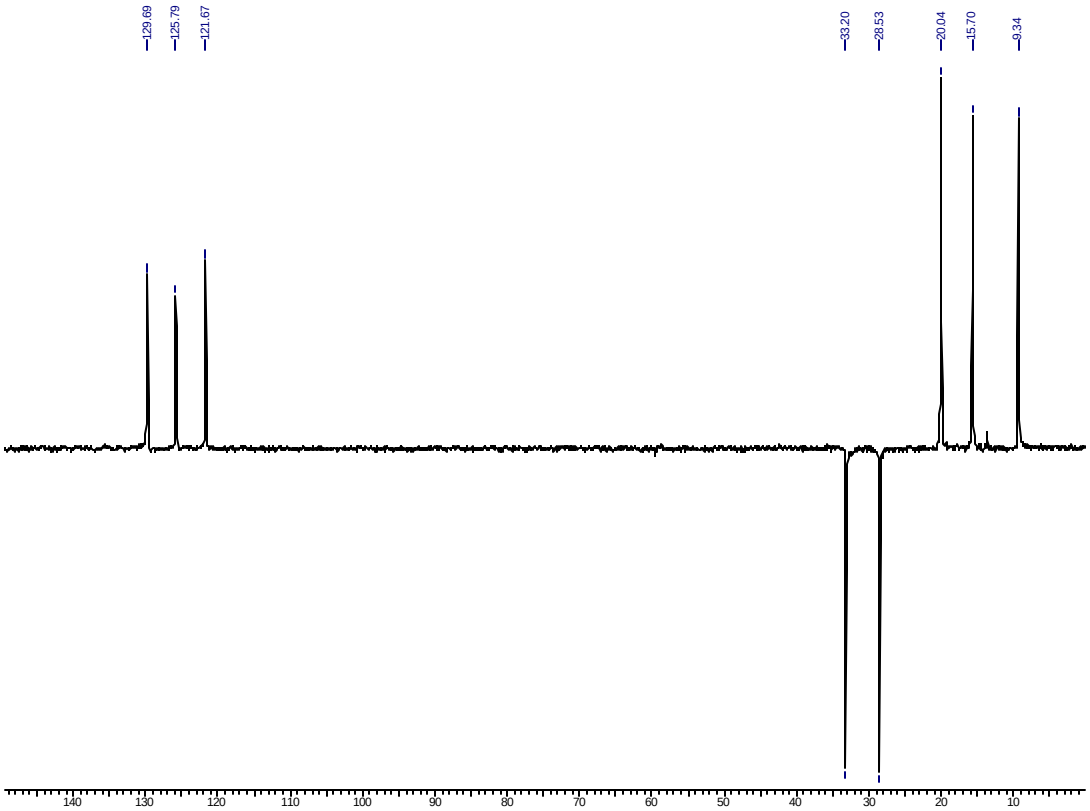
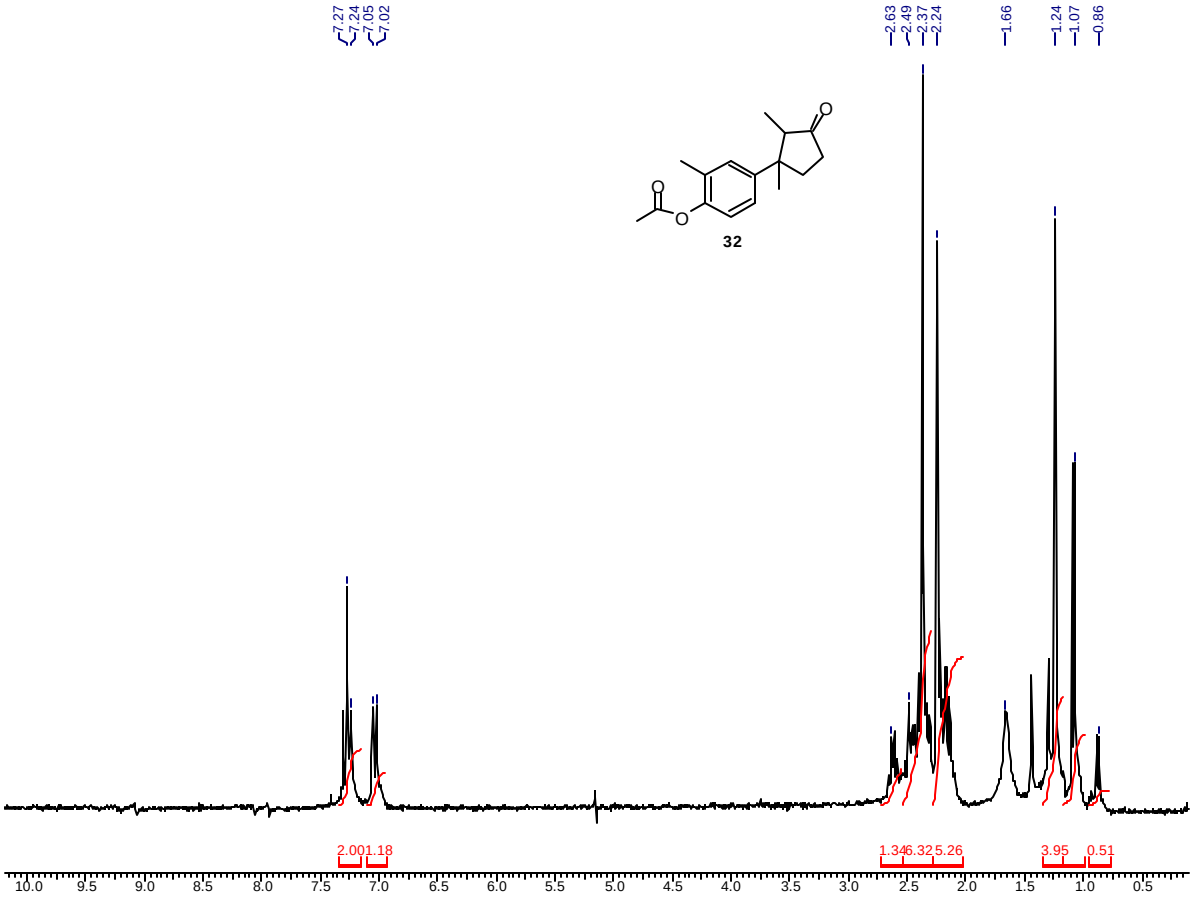
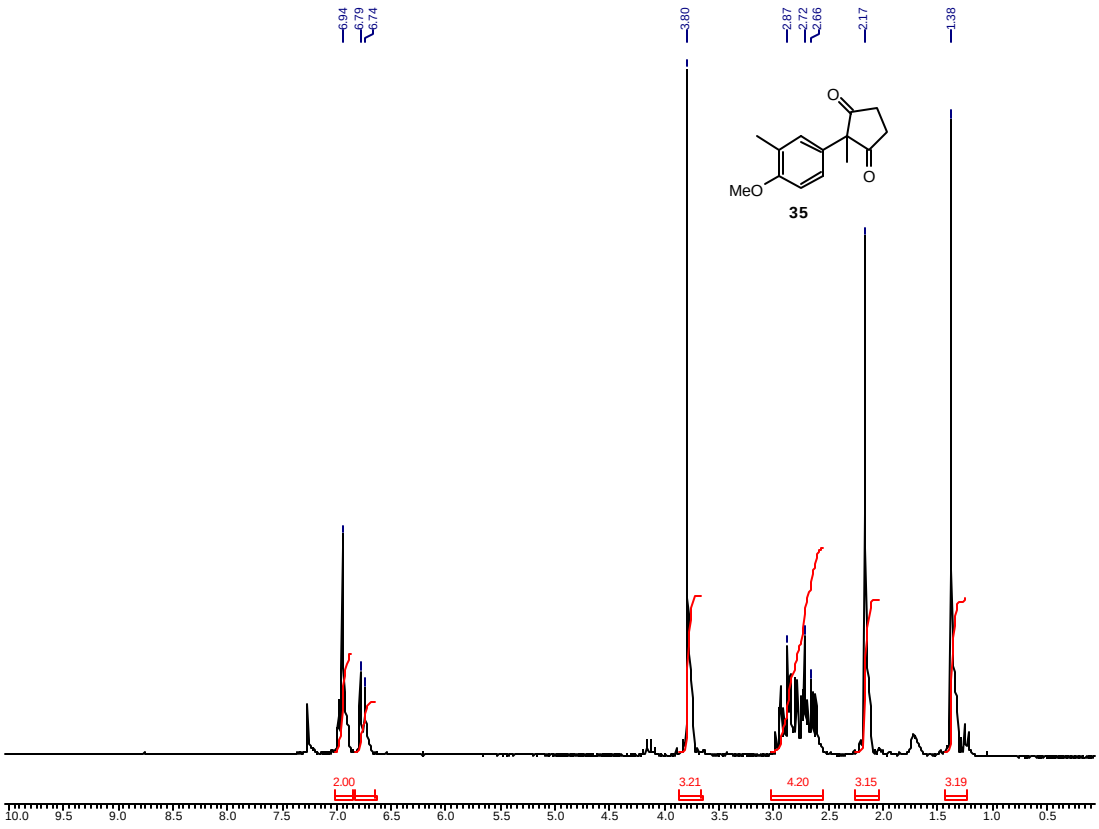


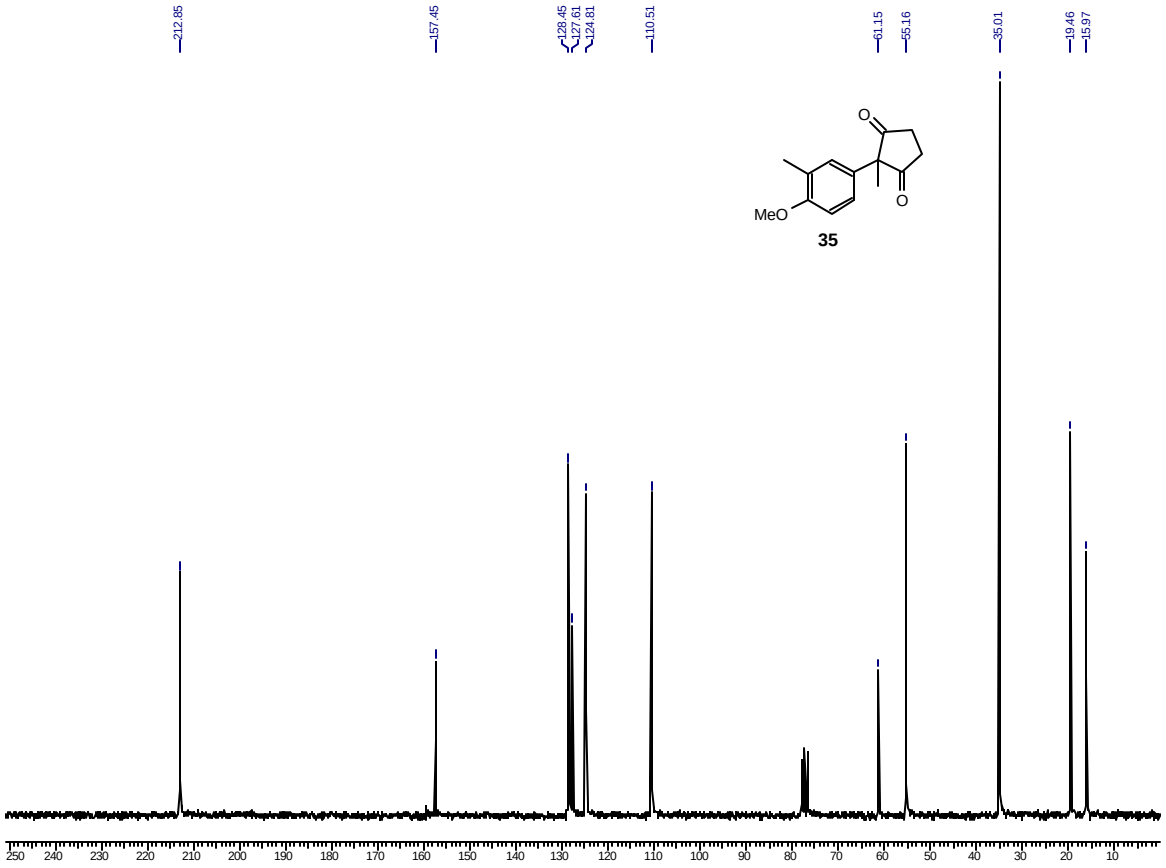
^{13}C-NMR and DEPT ($CDCl_3$+CCl_4, 50 MHz) of Compound 31

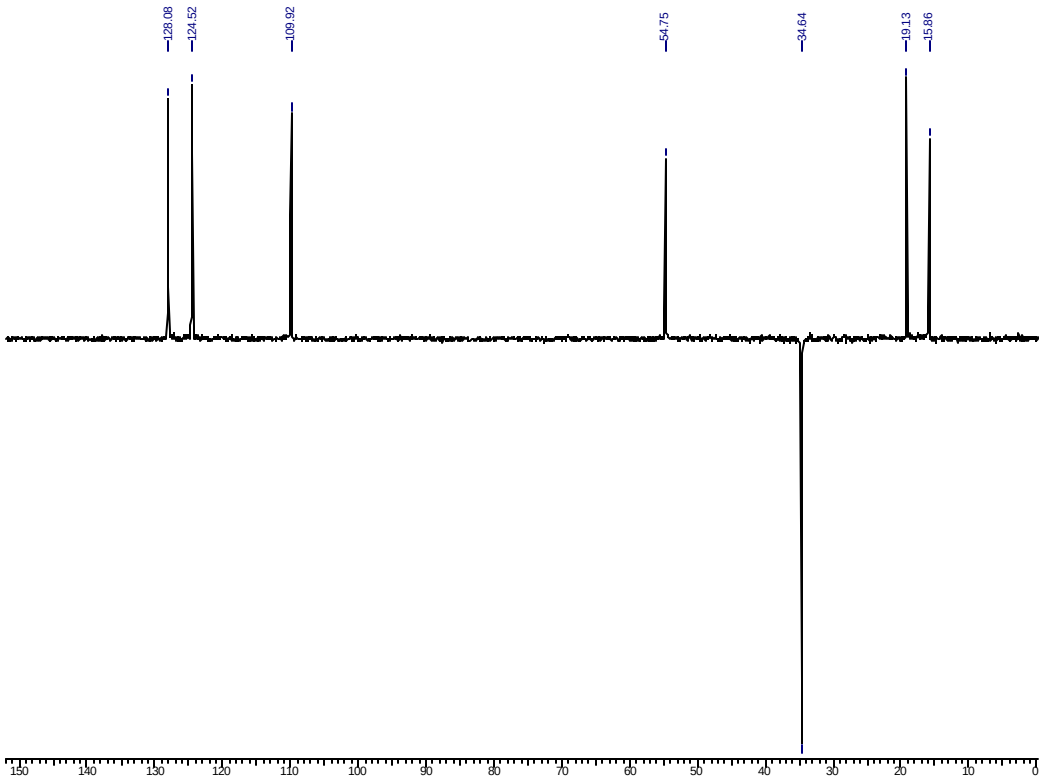


^{1}H-NMR spectrum ($CDCl_3$, 200 MHz) of Compound 32

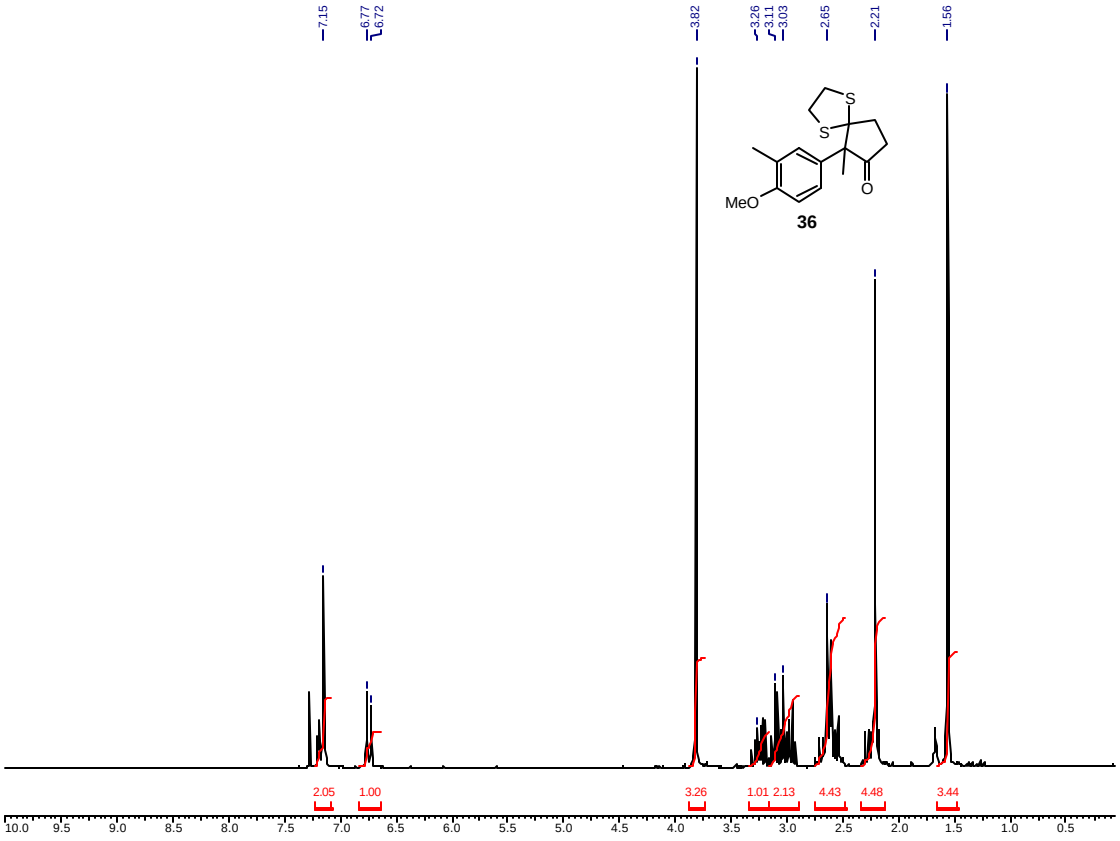


^{1}H-NMR spectrum (CDCl$_3$, 200 MHz) of Compound 35

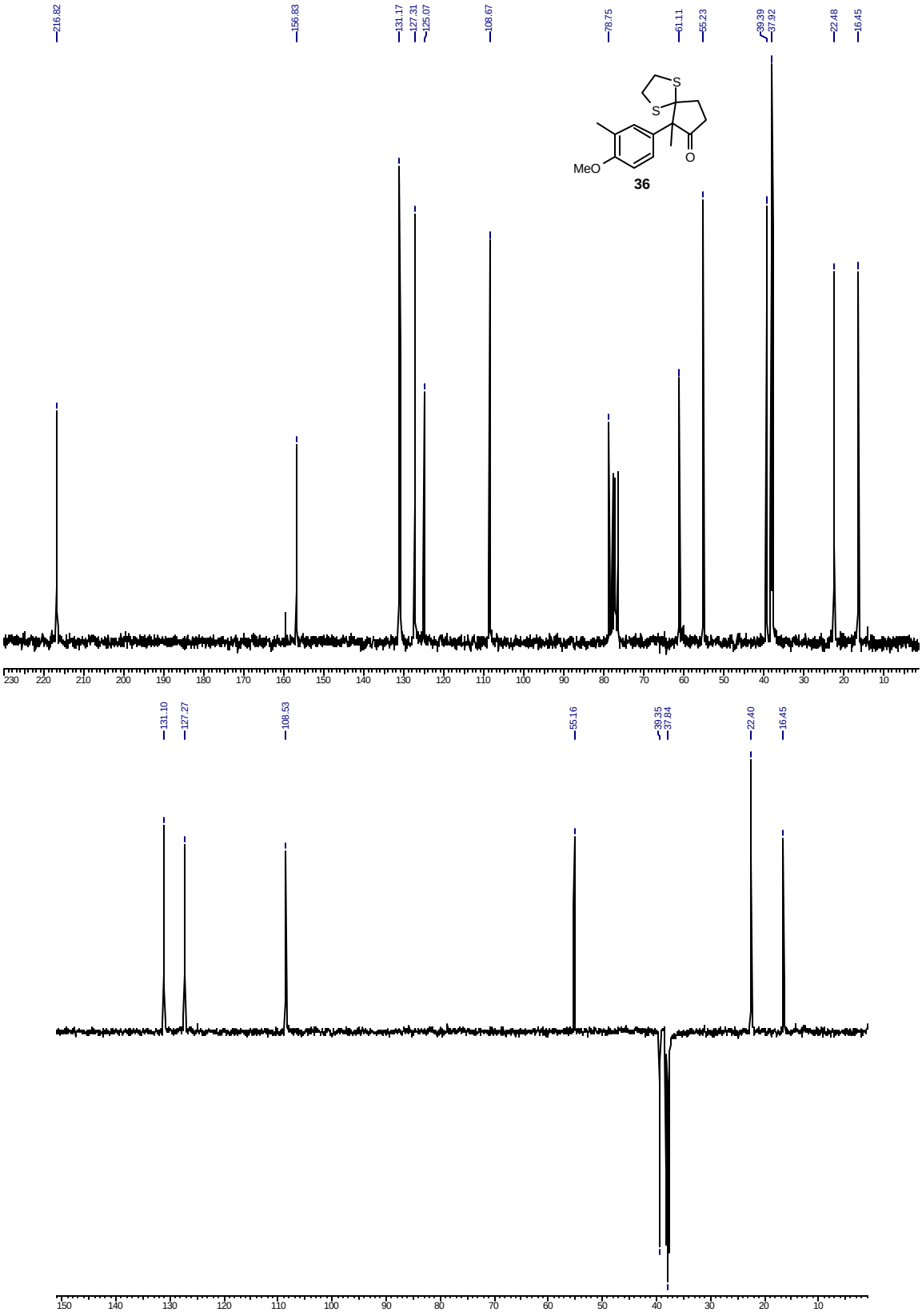

212.85
157.45
128.45
127.61
124.81
110.51
61.15
55.16
35.01
19.46
15.97
O
O
MeO
35
250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10


128.08
124.52
109.92
54.75
34.64
19.13
15.86
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

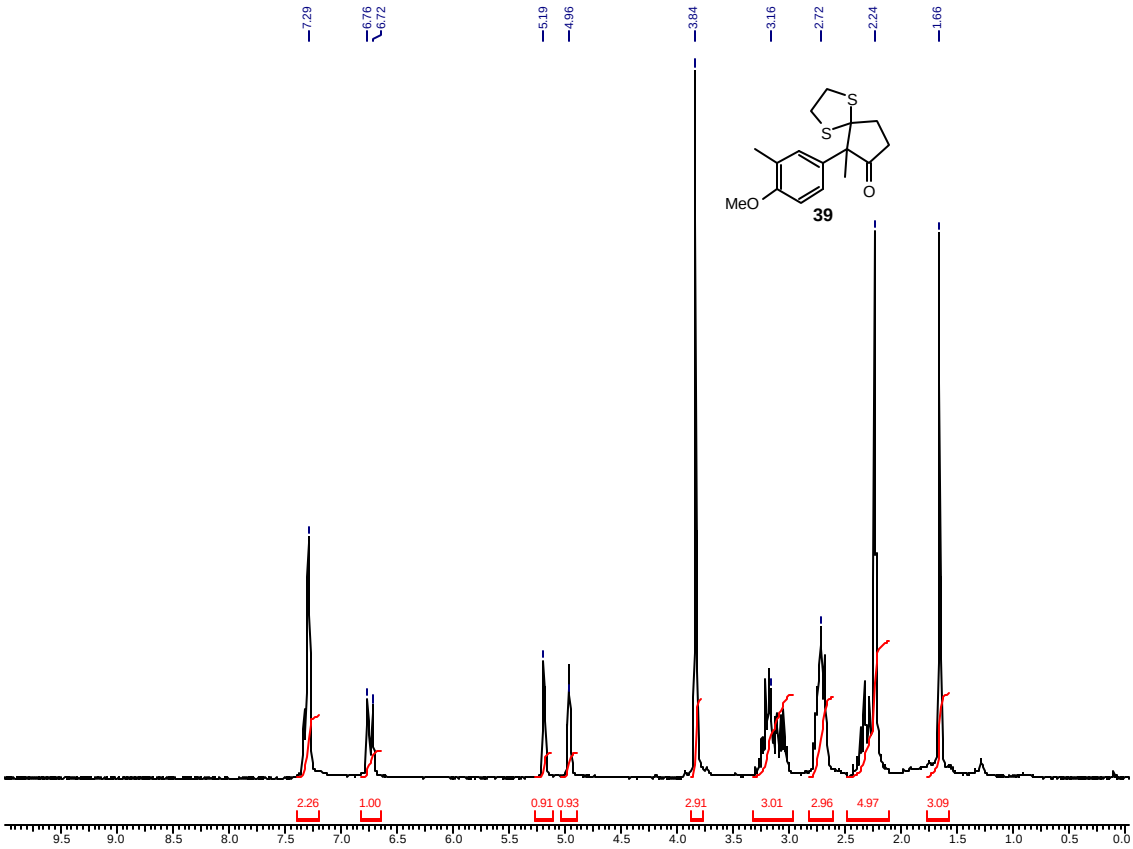
^{13}C-NMR and DEPT of ($CDCl_3$, 50 MHz) Compound 35



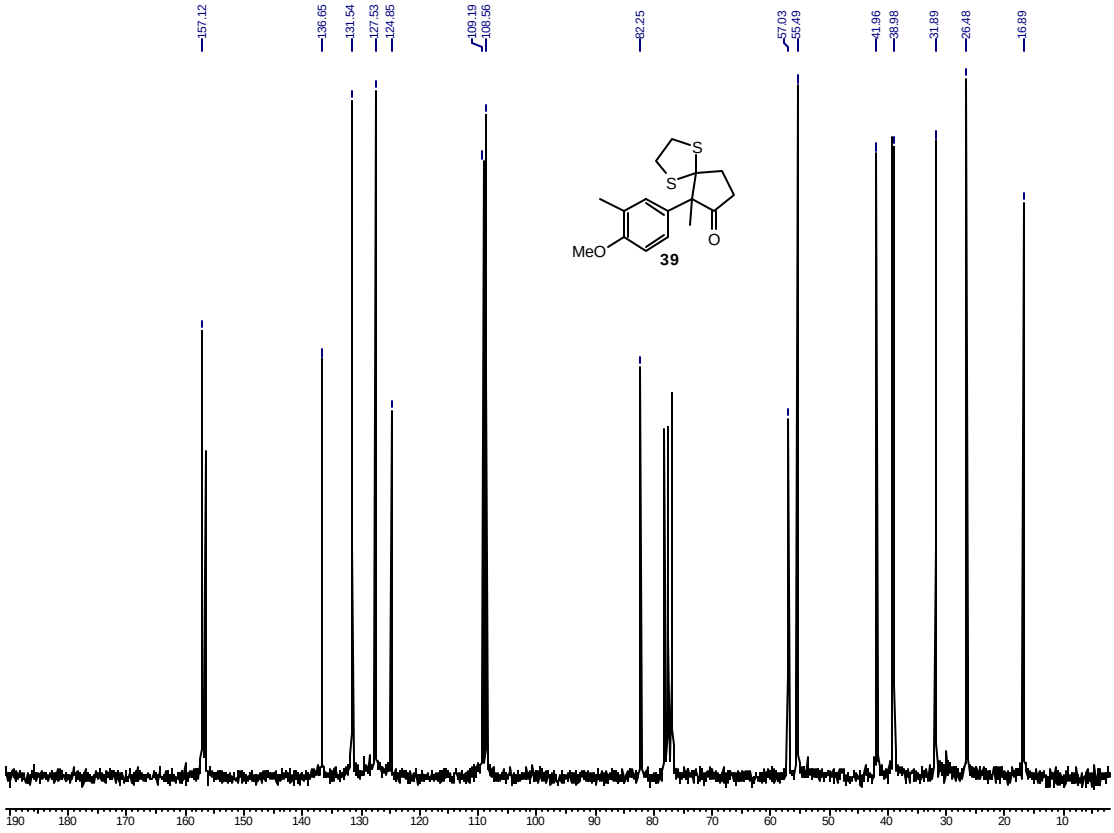
^{1}H-NMR spectrum ($CDCl_3$, 200 MHz) of Compound 36

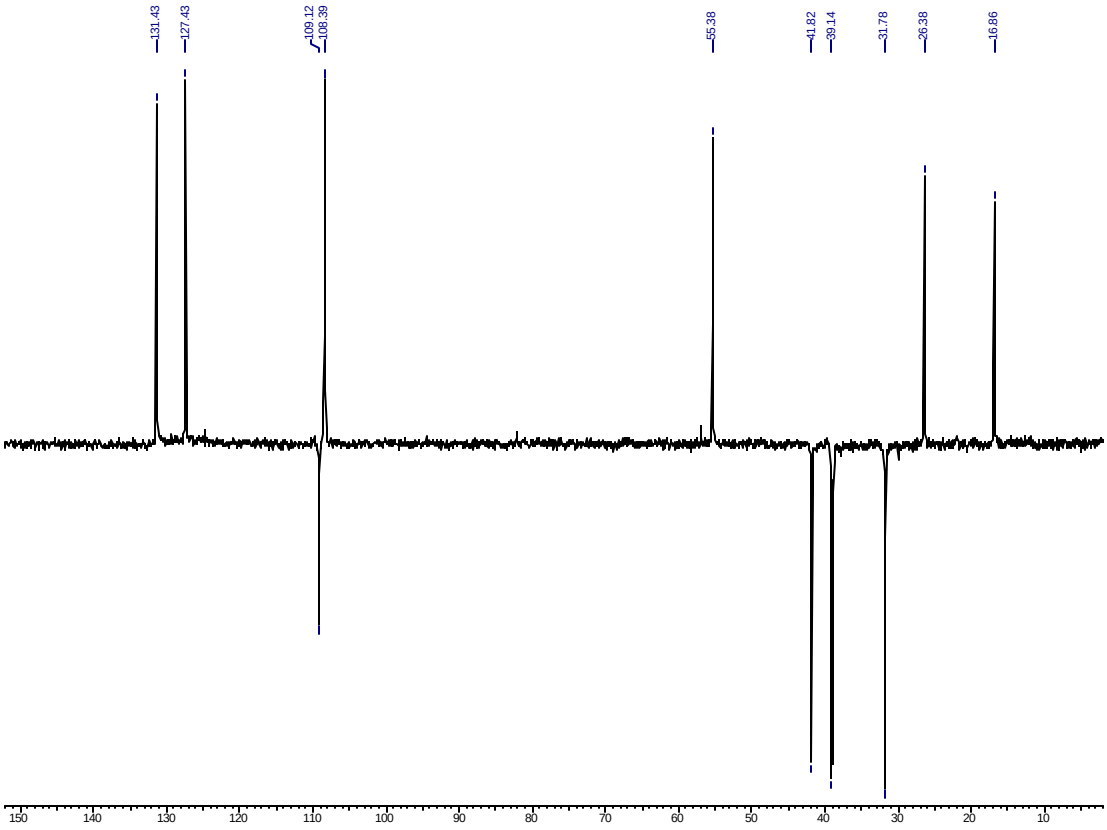


^{13}C-NMR and DEPT ($CDCl_3$, 50 MHz) of Compound 36

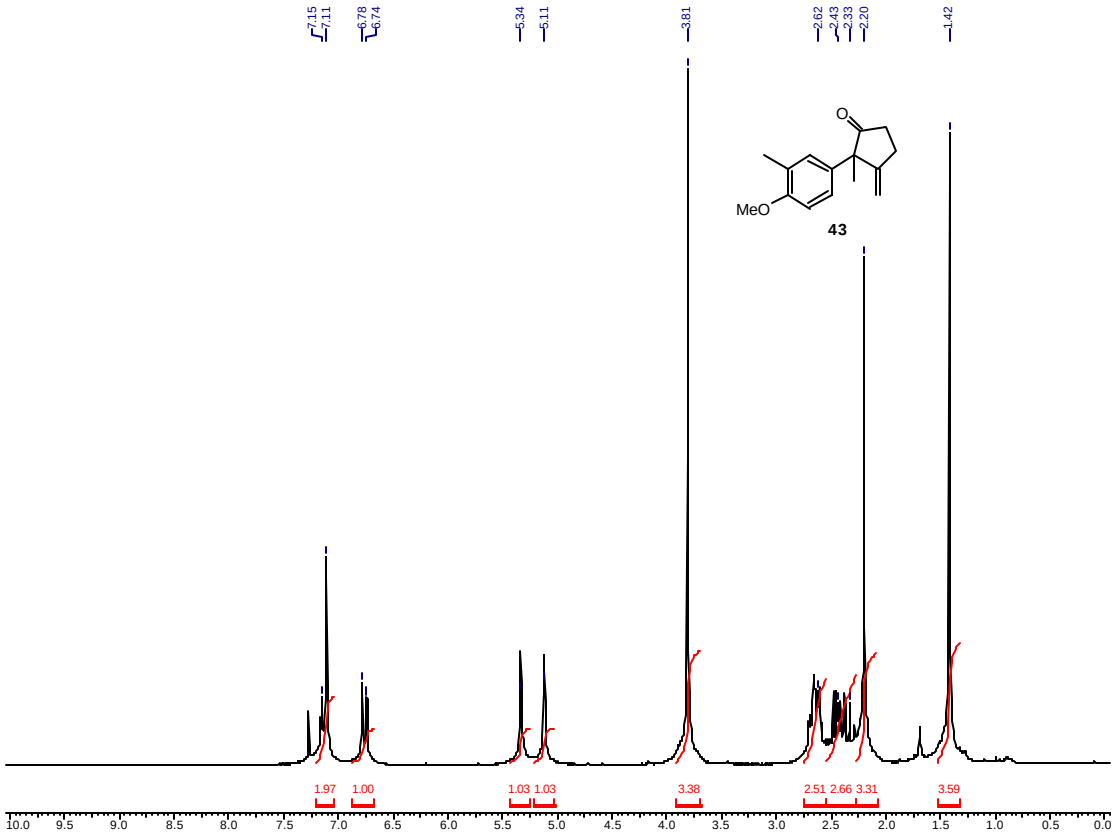


^{1}H-NMR spectrum ($CDCl_3$, 200 MHz) of Compound 39

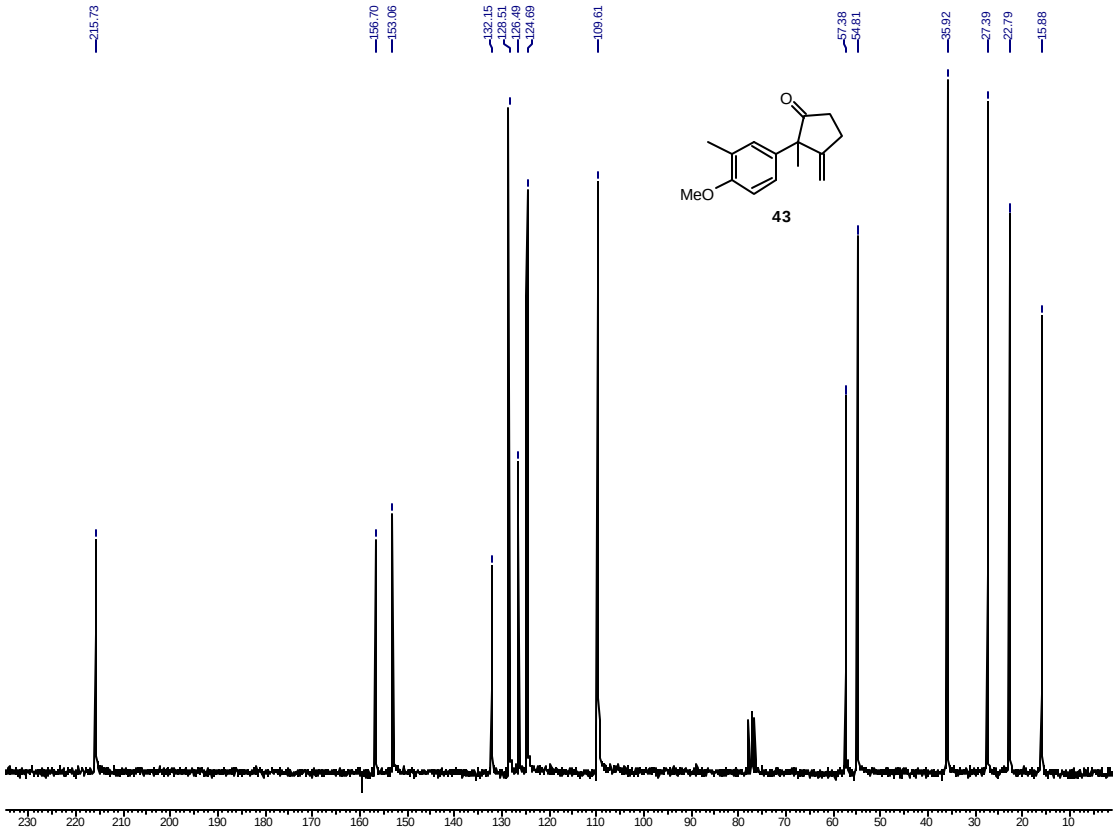

157.12
136.65
131.54
127.53
124.85
109.19
108.56
82.25
57.03
55.49
41.96
38.98
31.89
26.48
16.89
S
S
MeO
O
39
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

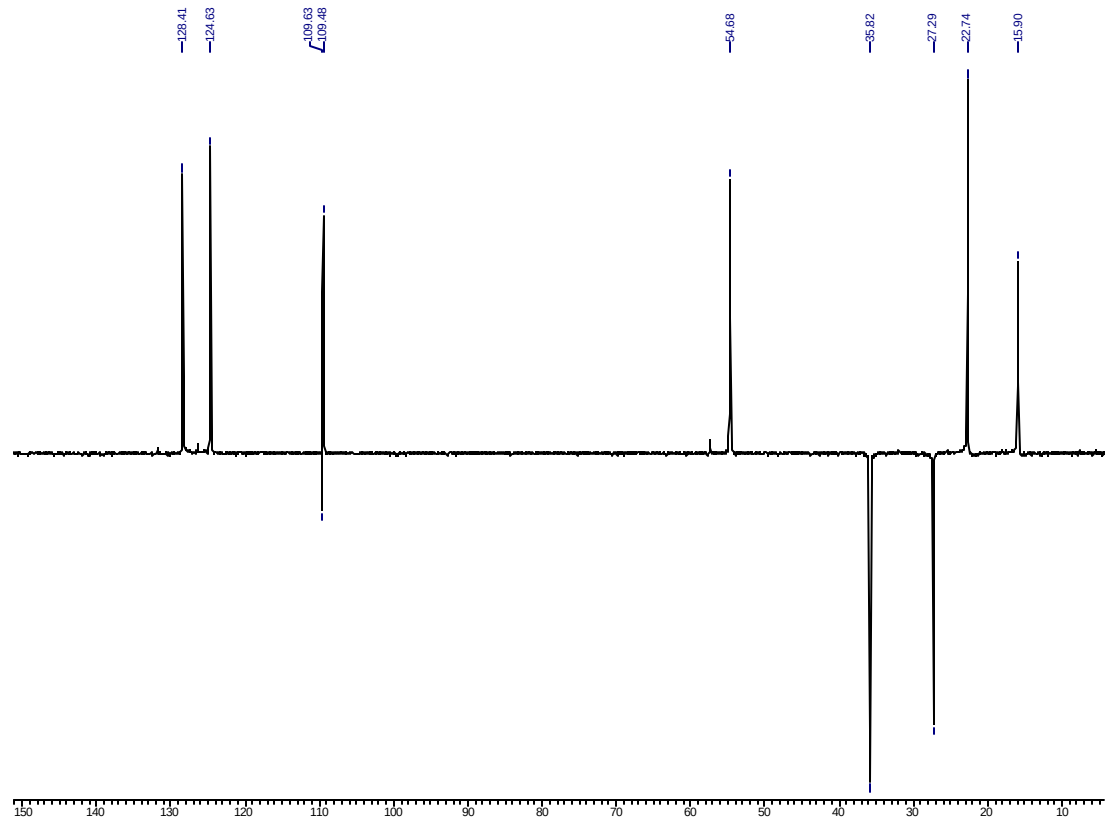


^{13}C-NMR and DEPT ($CDCl_3$, 50 MHz) of Compound 39

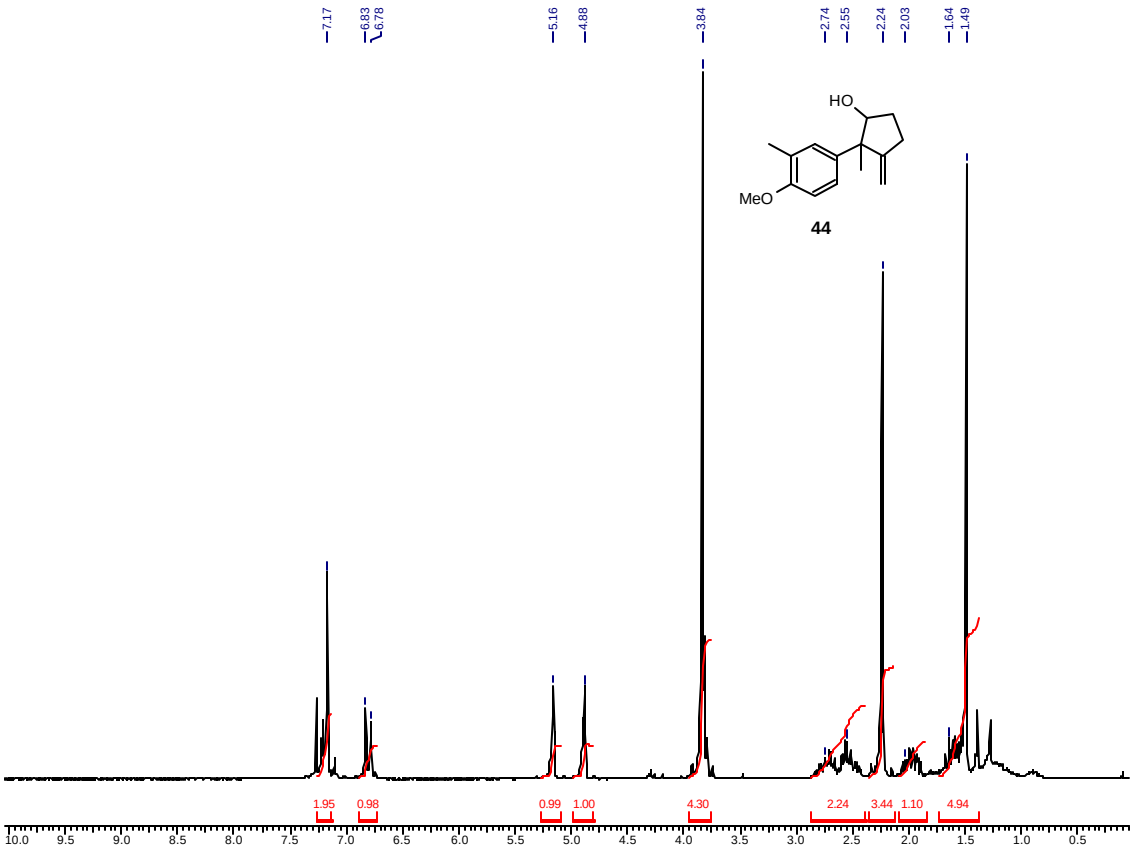


^{1}H-NMR spectrum ($CDCl_3$, 200 MHz) of Compound 43

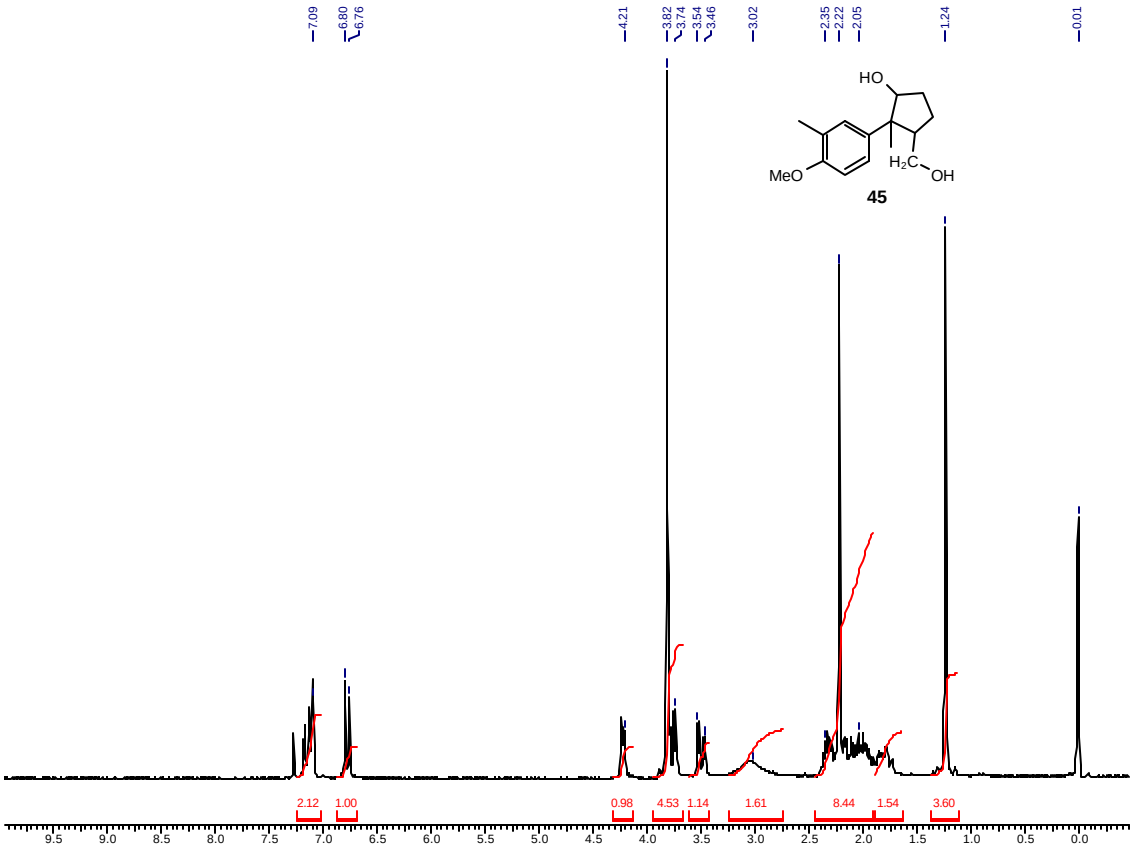




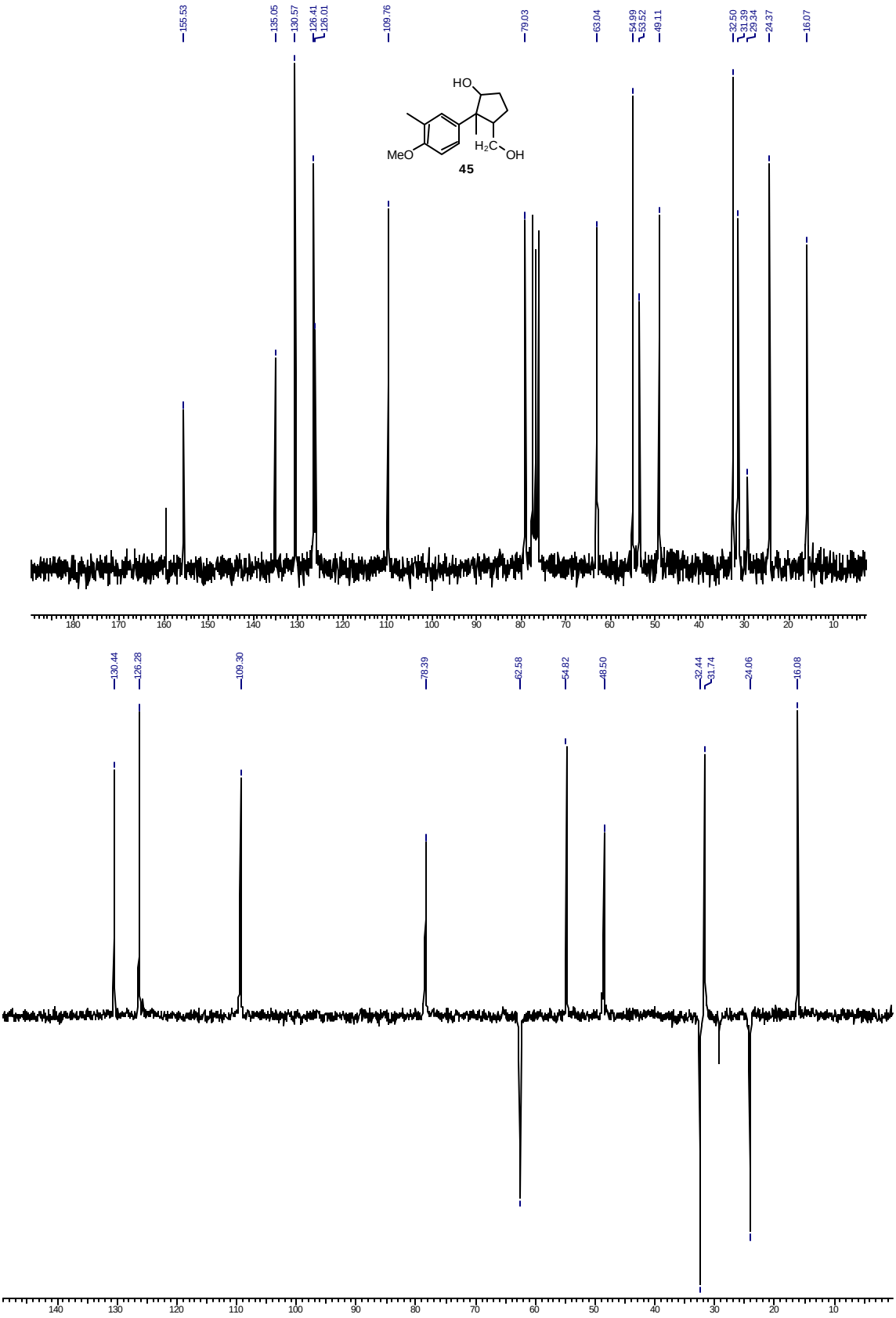
^{13}C-NMR and DEPT ($CDCl_3$, 50 MHz) of Compound 43



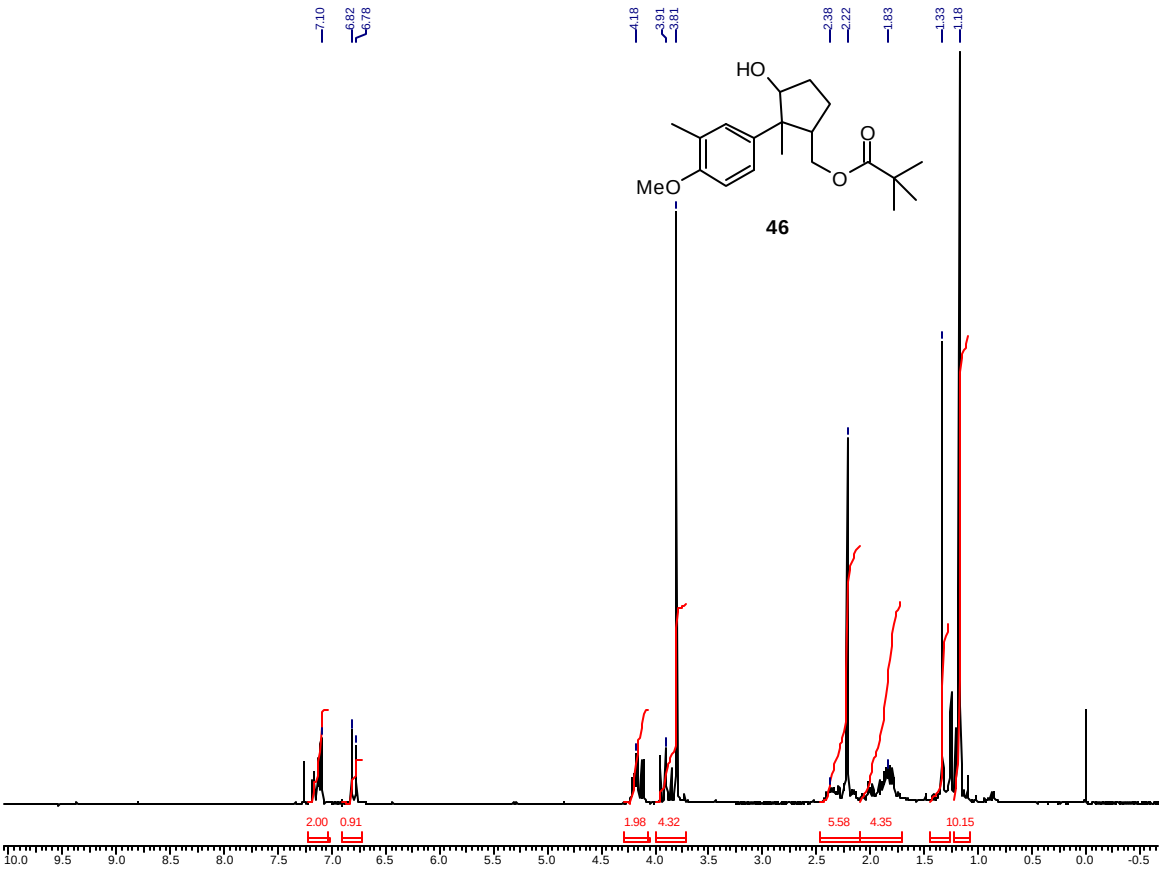
^{1}H-NMR spectrum ($CDCl_3$, 200 MHz) of Compound 44



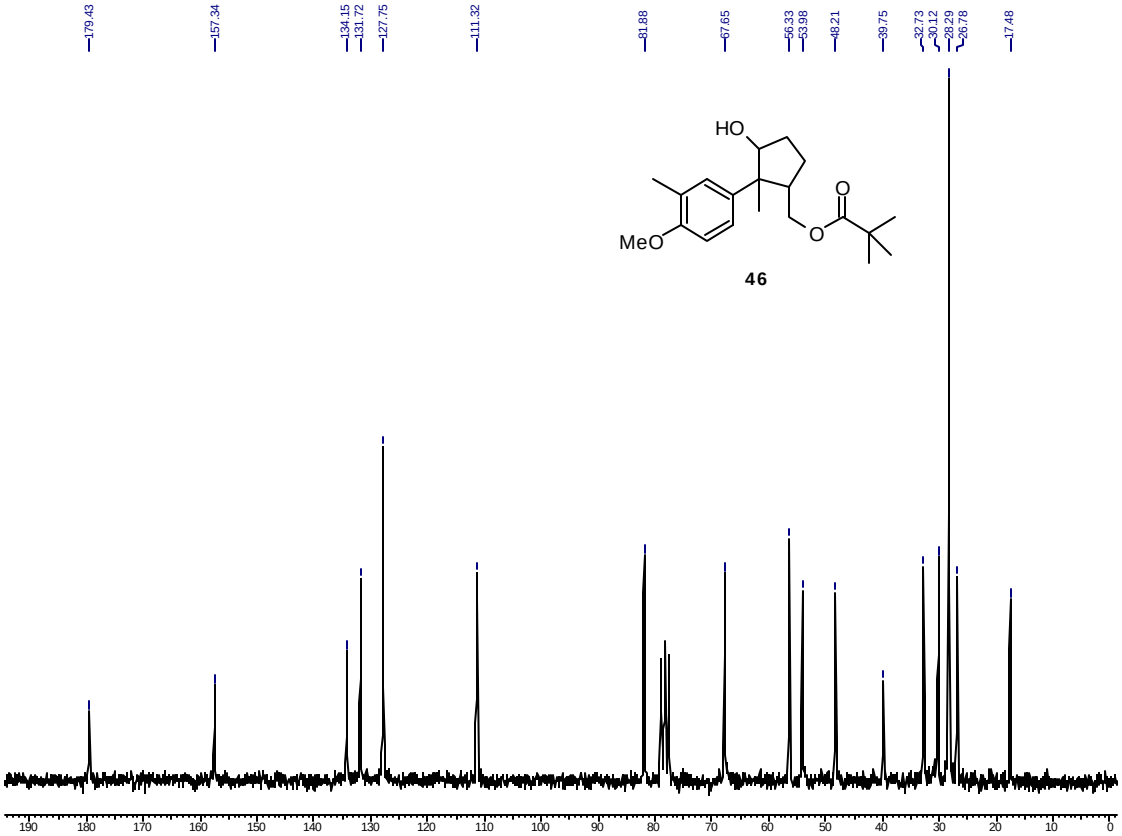
[1]H-NMR spectrum (CDCl3, 200 MHz) of Compound 45

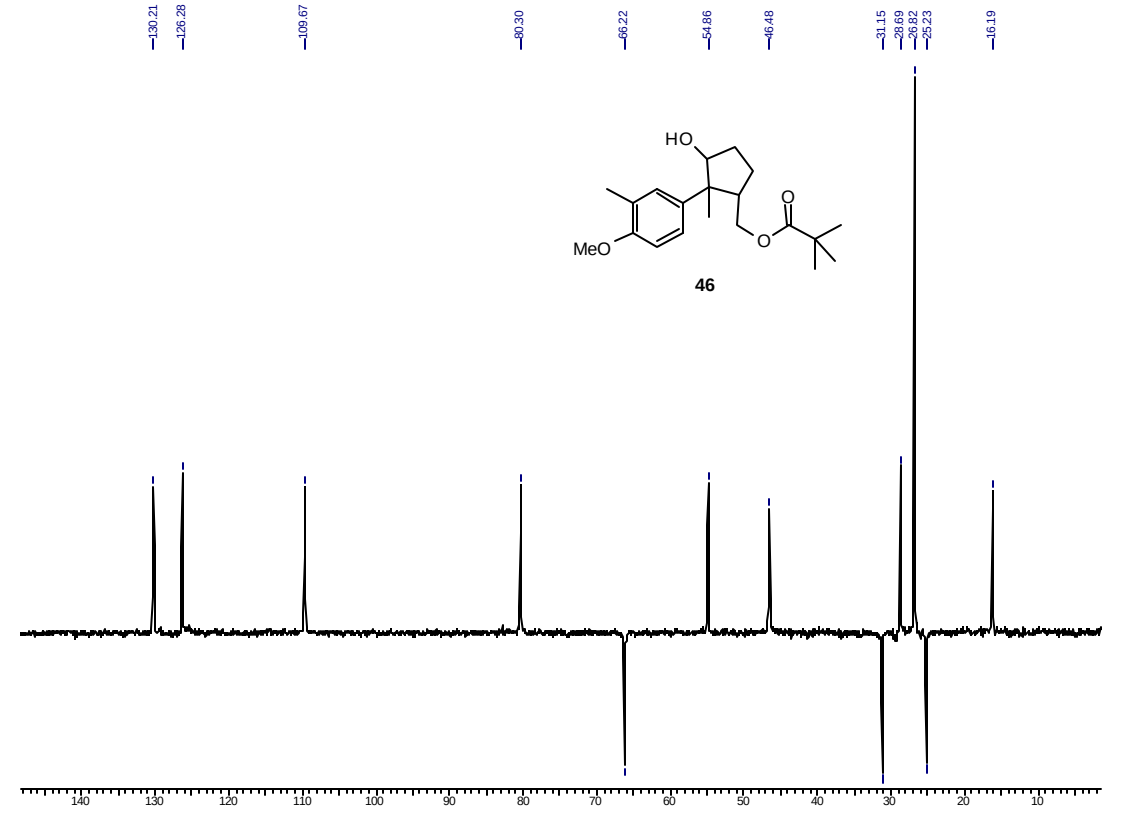


^{13}C-NMR and DEPT ($CDCl_3$, 50 MHz) of Compound 45

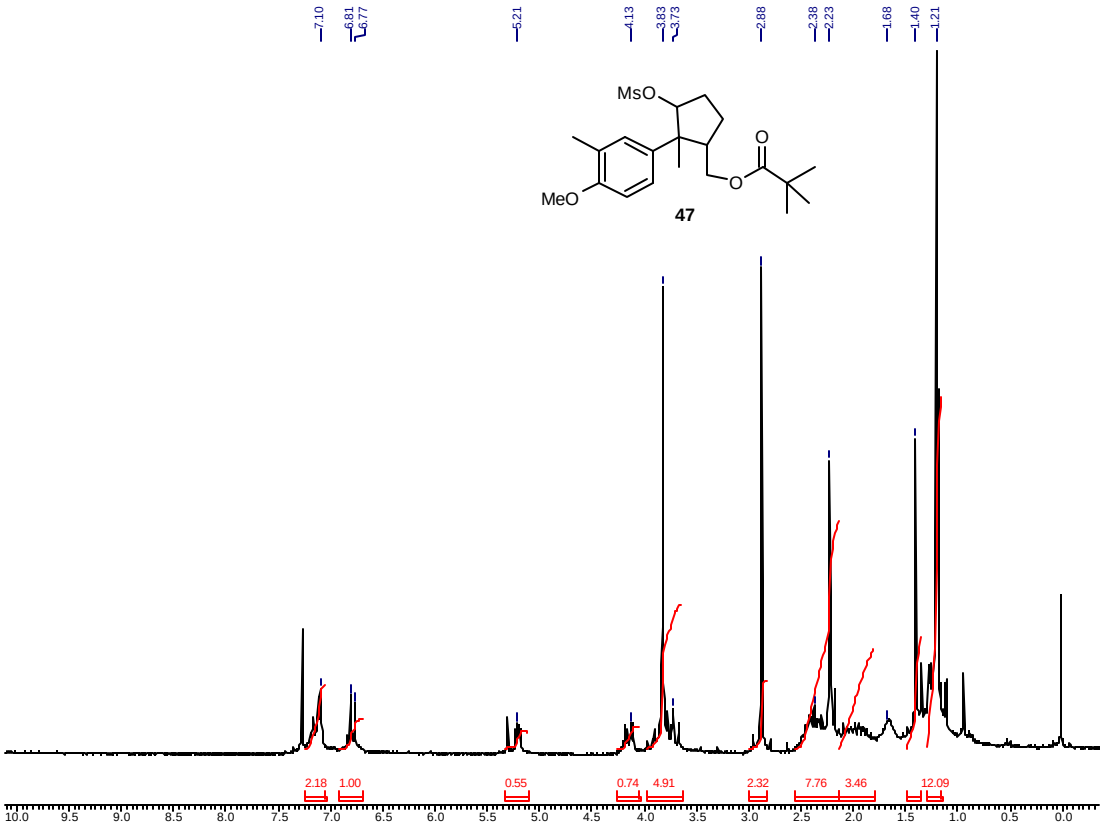


^{1}H-NMR spectrum (CDCl$_3$, 200 MHz) of Compound 46

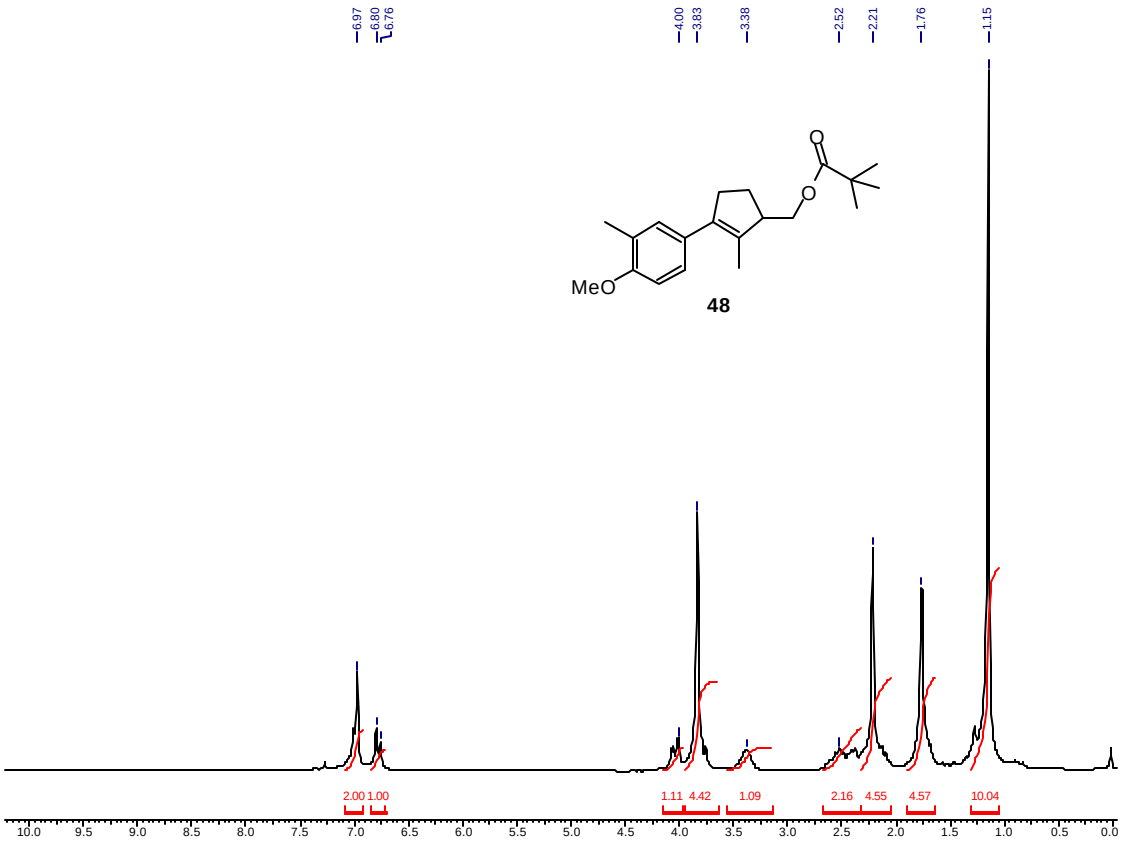

179.43
157.34
134.15
131.72
127.75
111.32
81.88
67.65
56.33
53.98
48.21
39.75
32.73
30.12
28.29
26.78
17.48
HO
MeO
O
O
46


130.21
126.28
109.67
80.30
66.22
54.86
46.48
31.15
28.69
26.82
25.23
16.19
HO
MeO
O
O
46

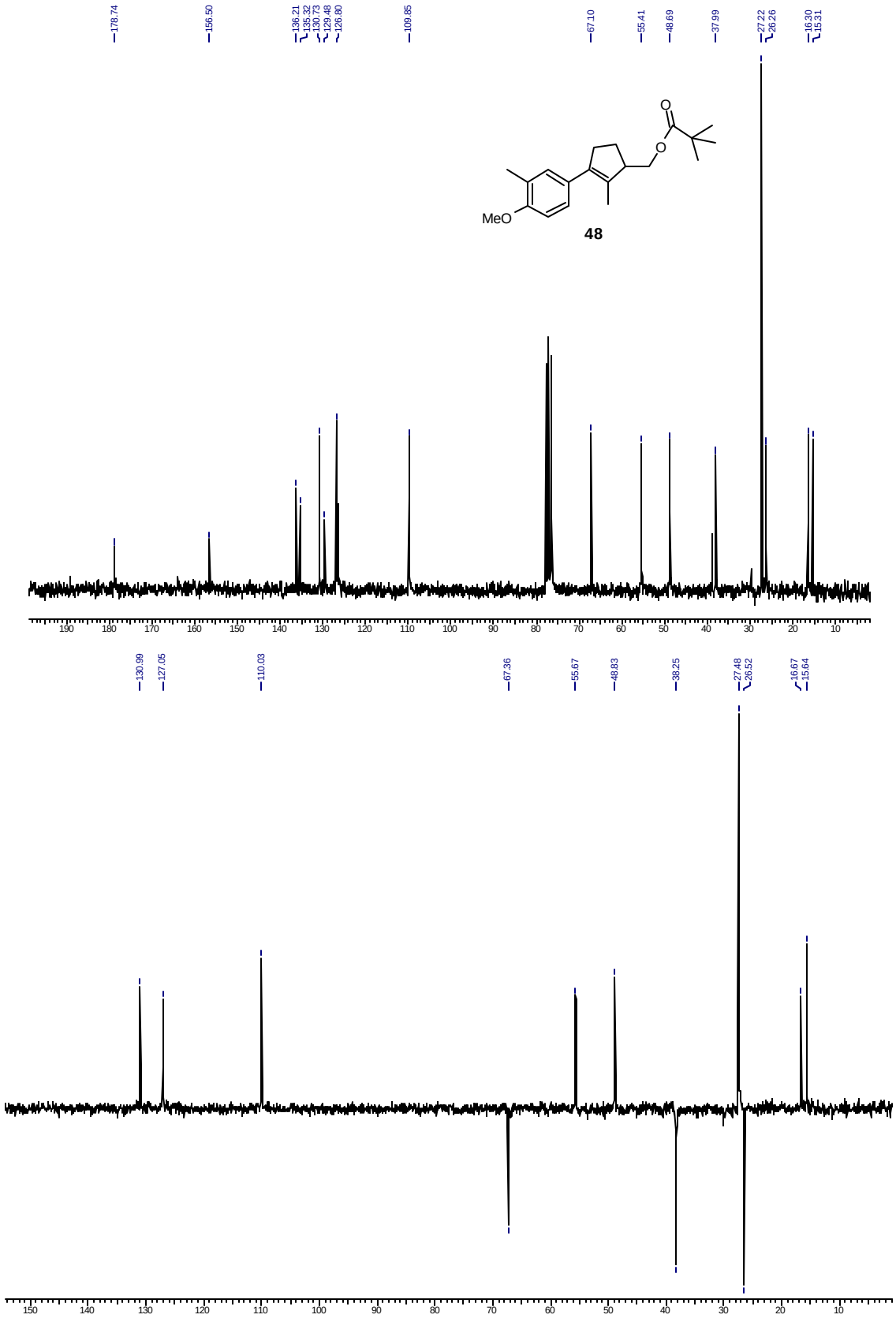
^{13}C-NMR and DEPT ($CDCl_3$, 50 MHz) of Compound 46



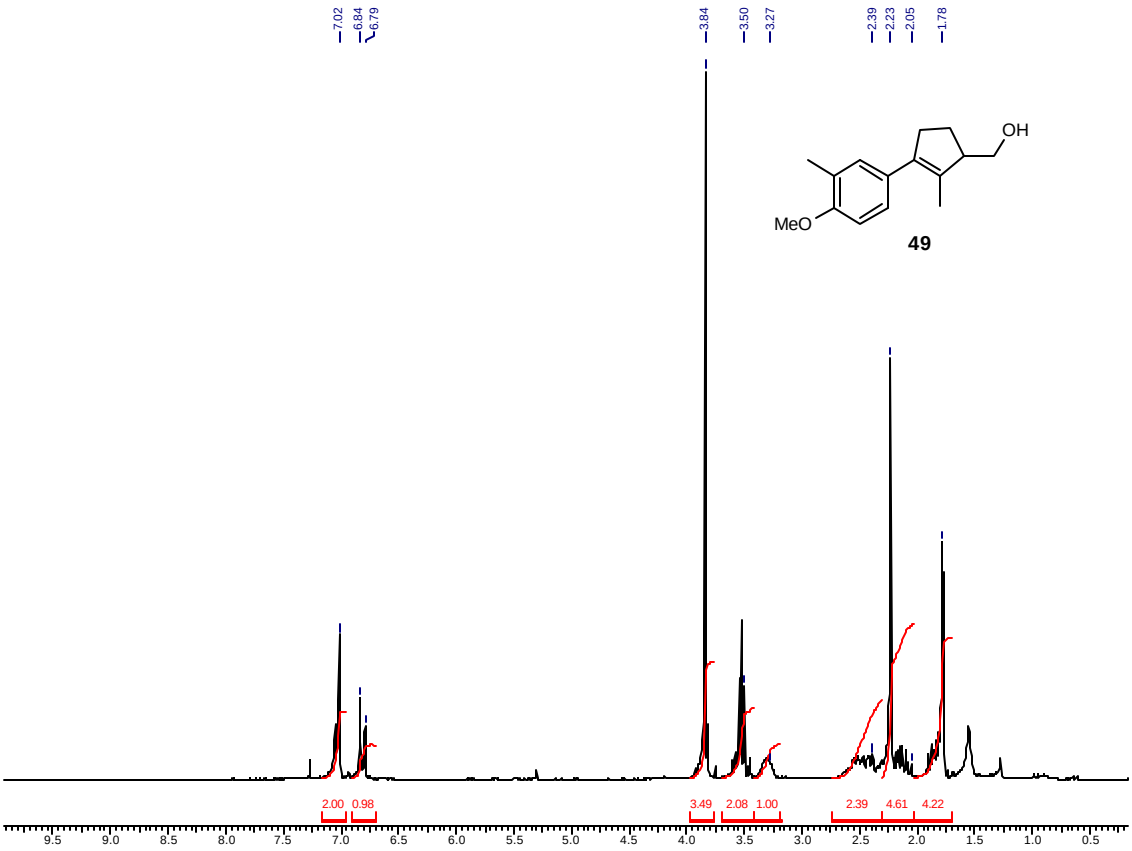
^{1}H-NMR spectrum ($CDCl_3$, 200 MHz) of Compound 47



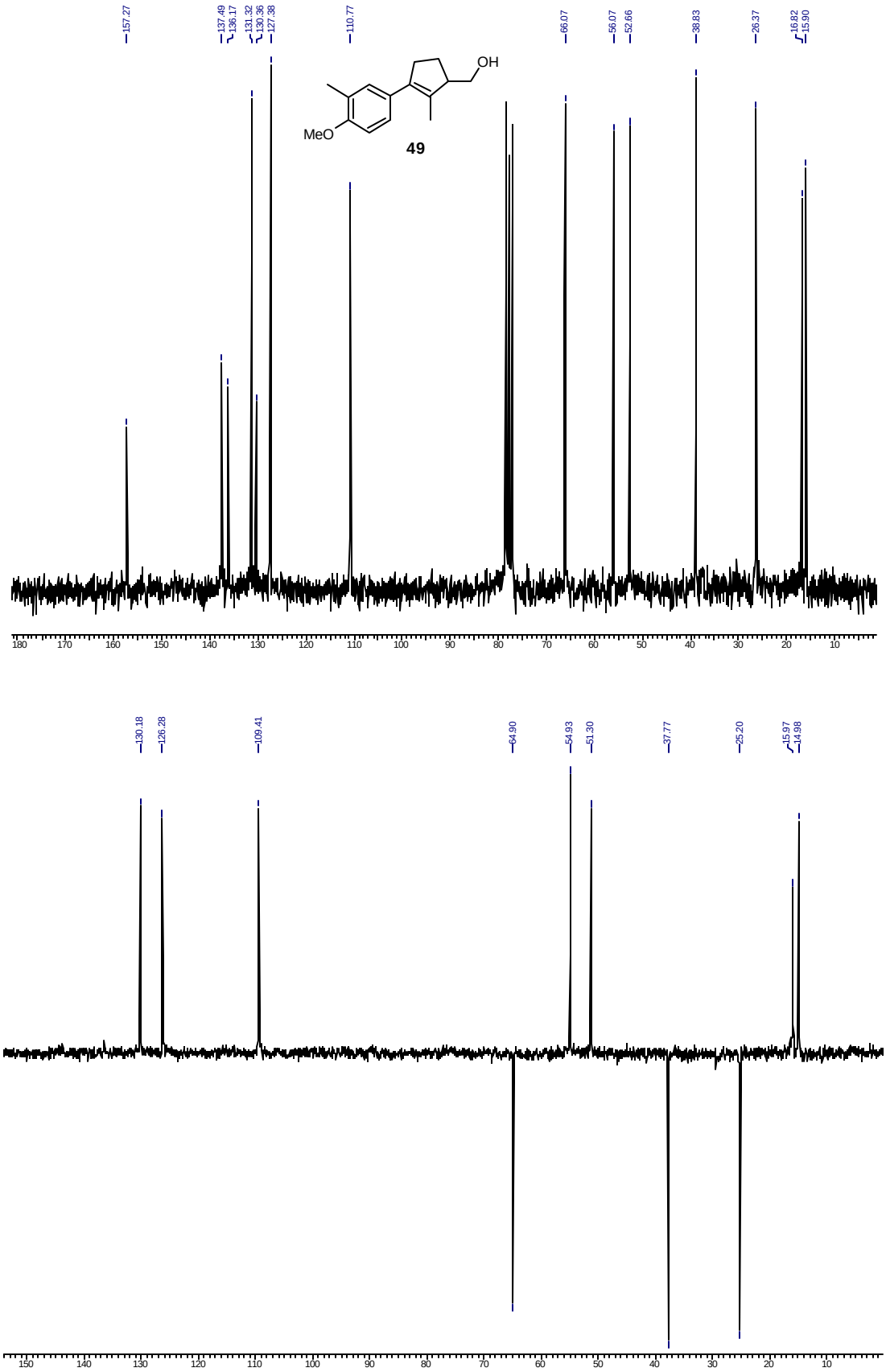
^{1}H-NMR spectrum ($CDCl_3$, 200 MHz) of Compound 48



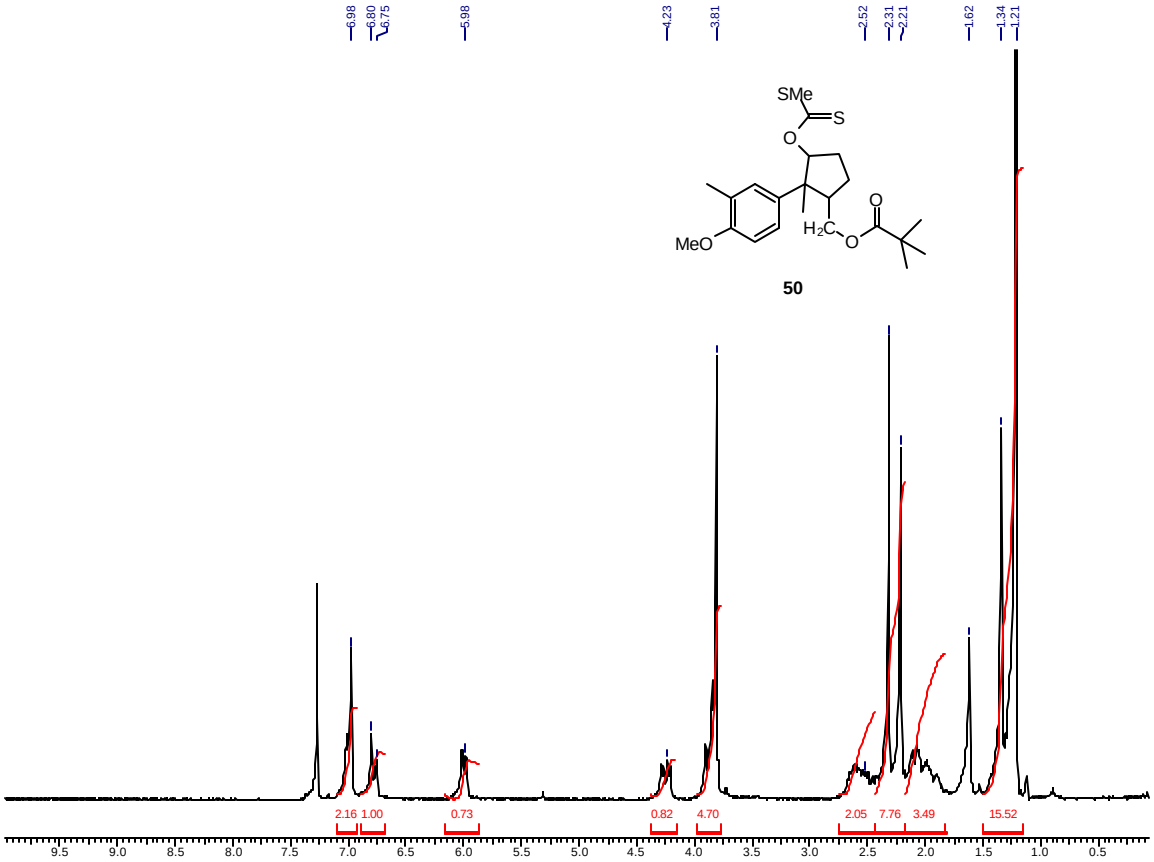
^{13}C-NMR and DEPT ($CDCl_3$, 50 MHz) of Compound 48



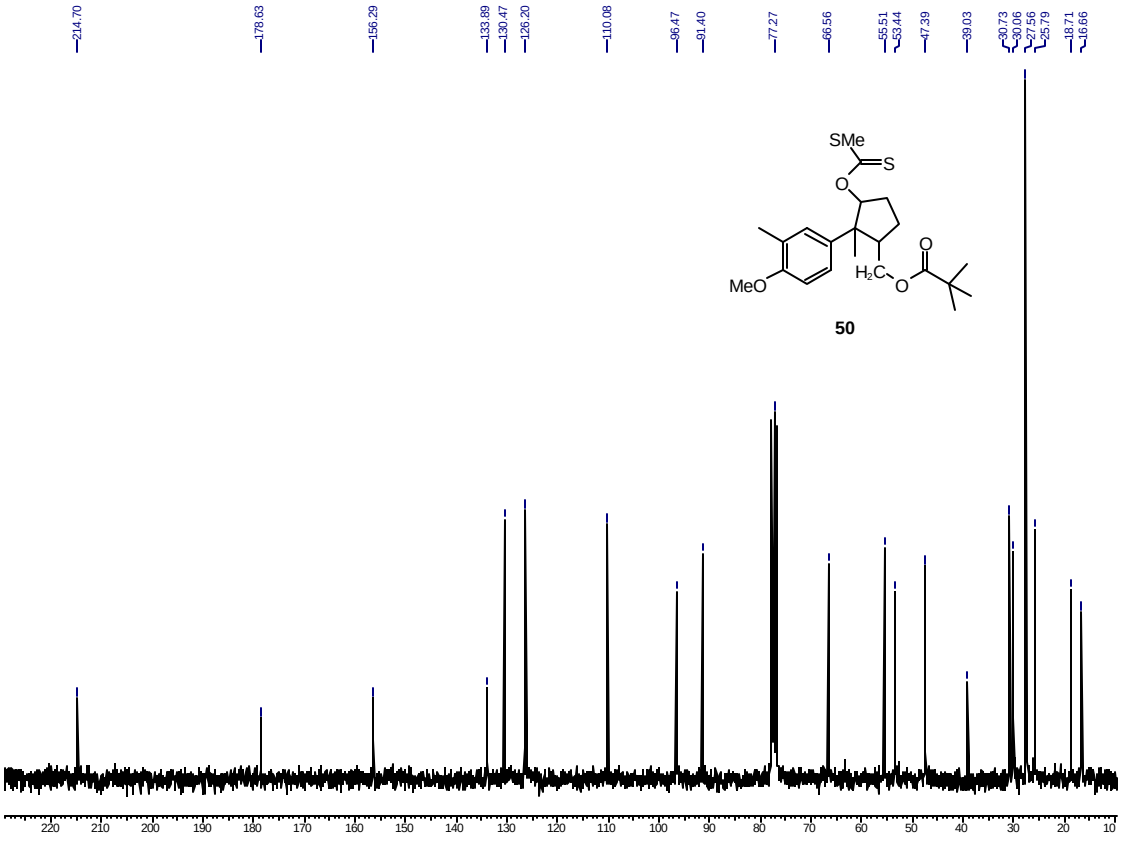
^{1}H-NMR spectrum ($CDCl_3$, 200 MHz) of Compound 49

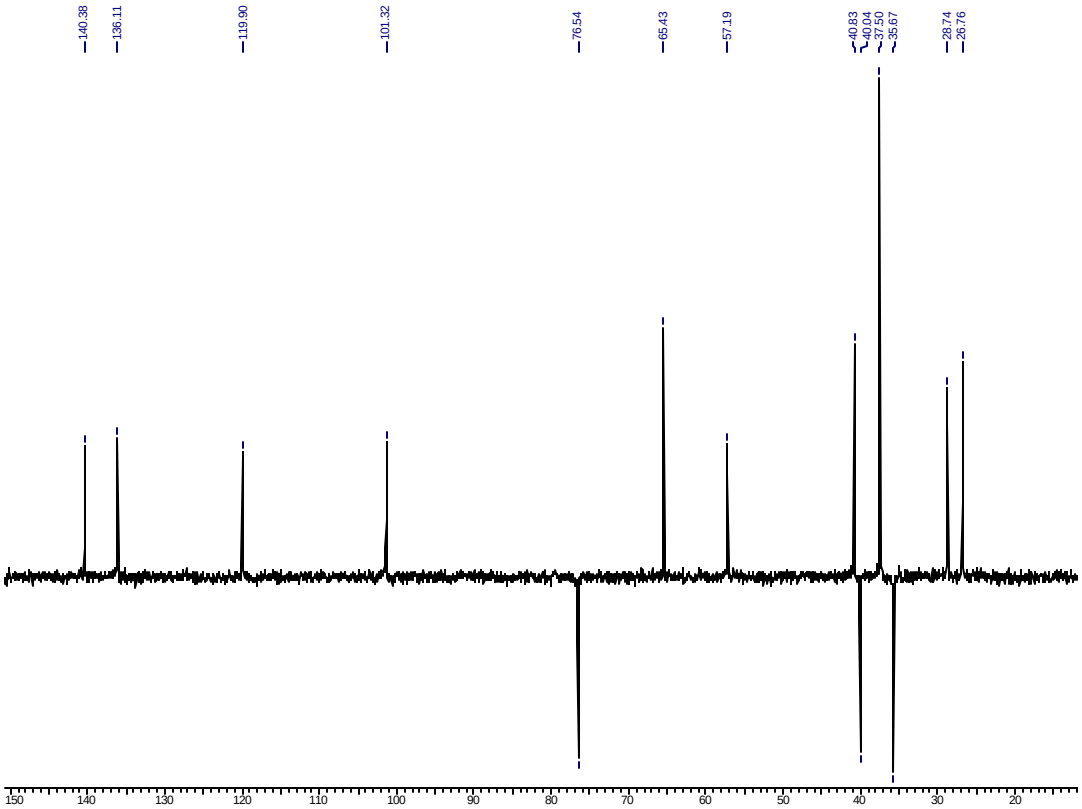


^{13}C-NMR and DEPT ($CDCl_3$, 50 MHz) of Compound 49

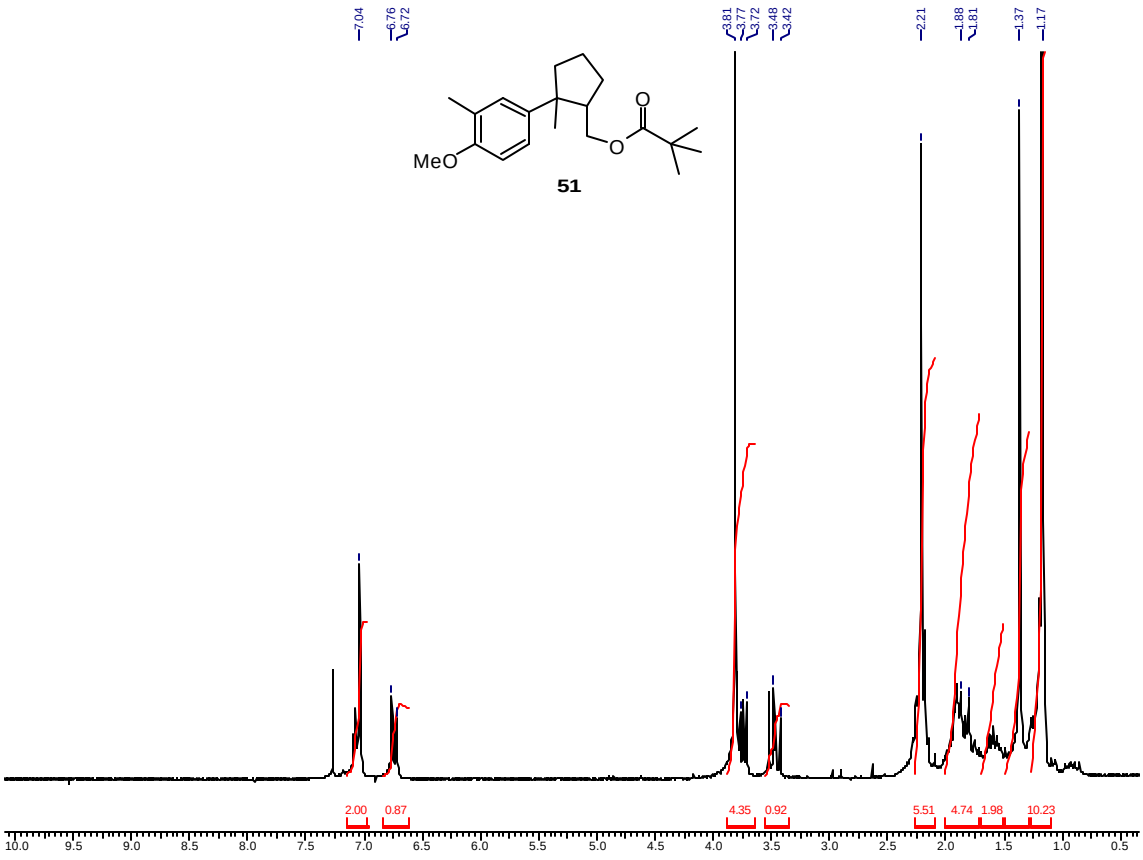


^{1}H-NMR spectrum ($CDCl_3$, 200 MHz) of Compound 50

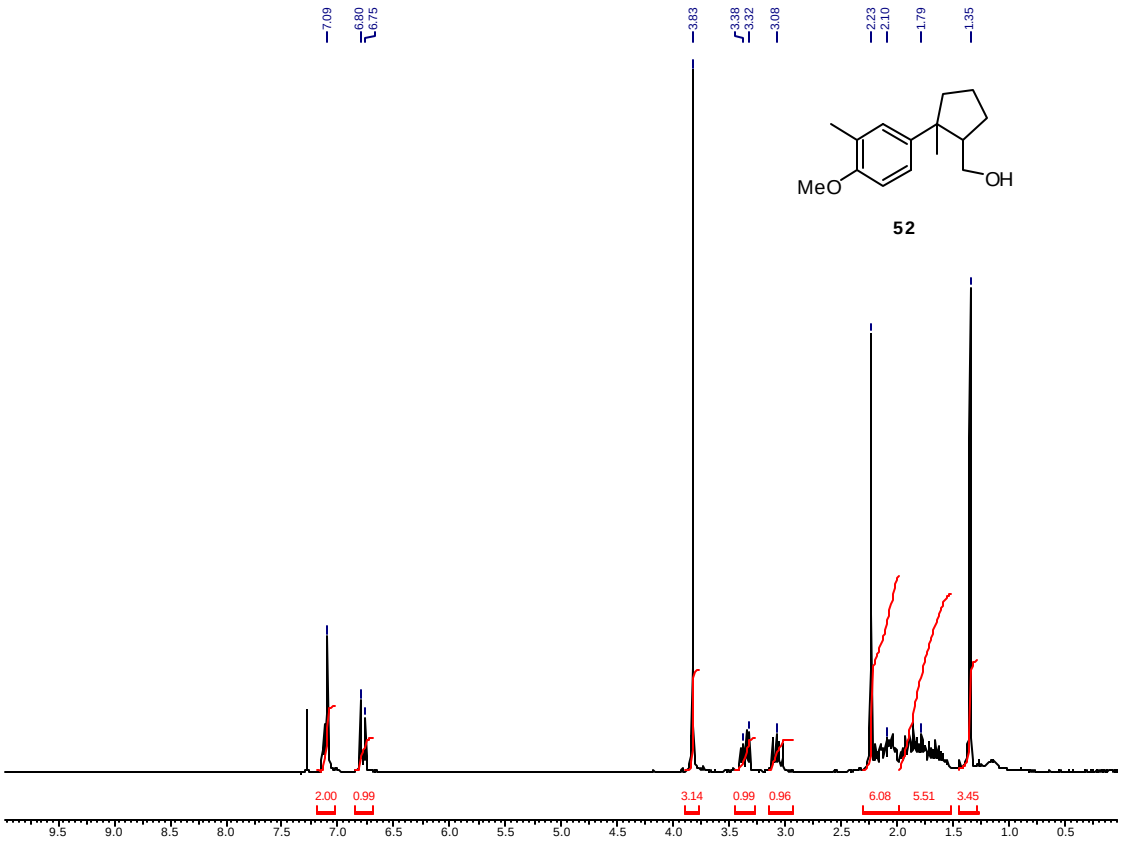




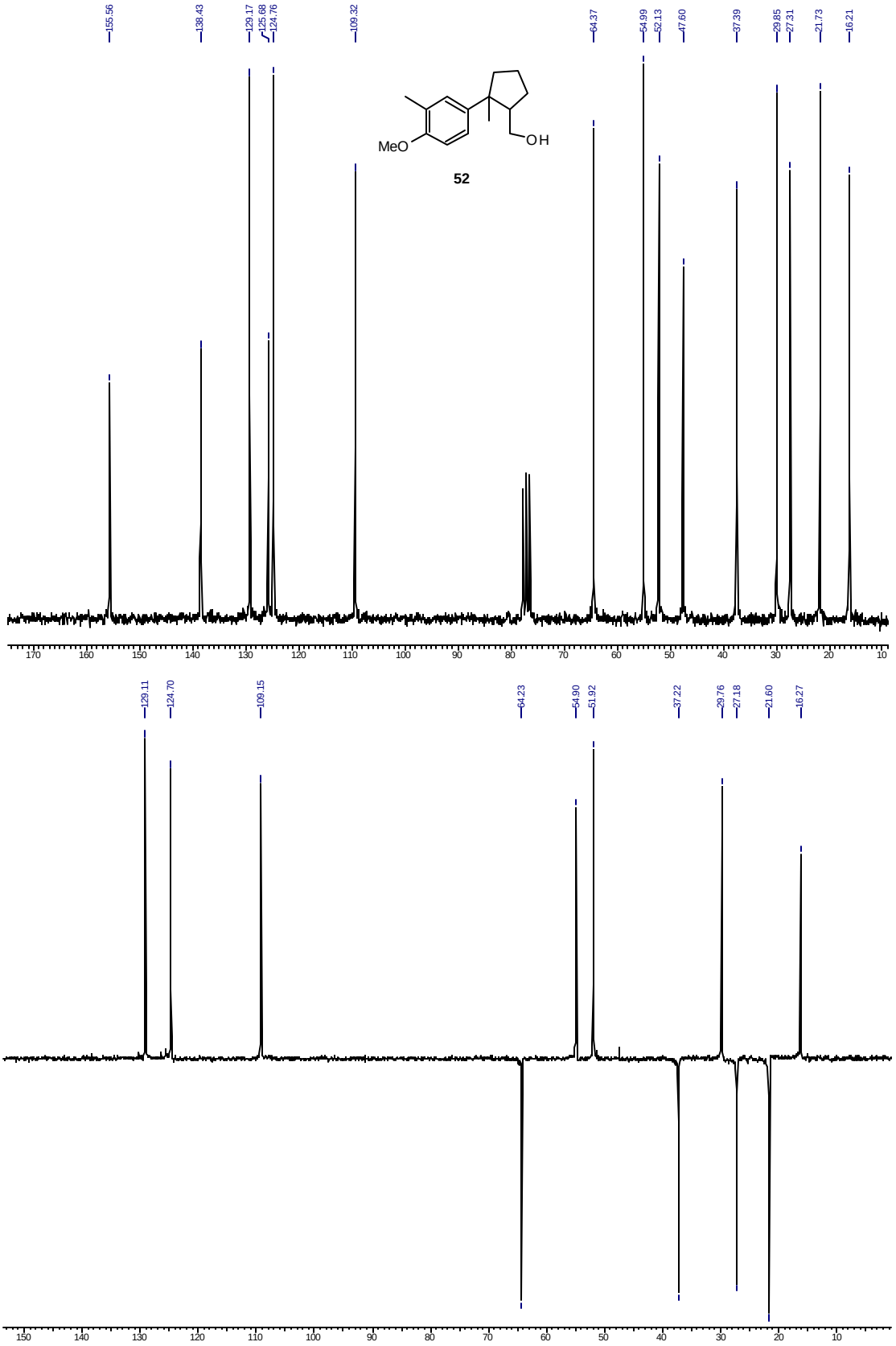
^{13}C-NMR and DEPT ($CDCl_3$, 50 MHz) of Compound 50



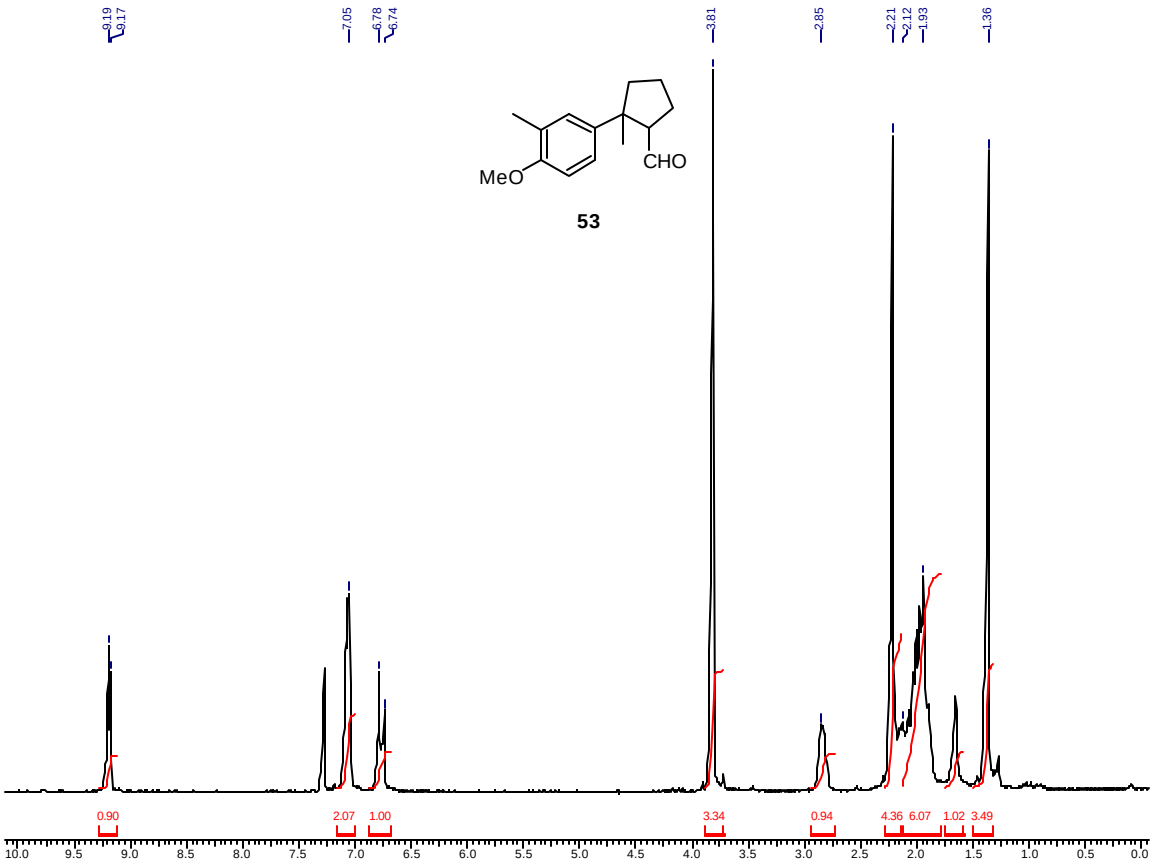
^{1}H-NMR spectrum ($CDCl_3$, 200 MHz) of Compound 51



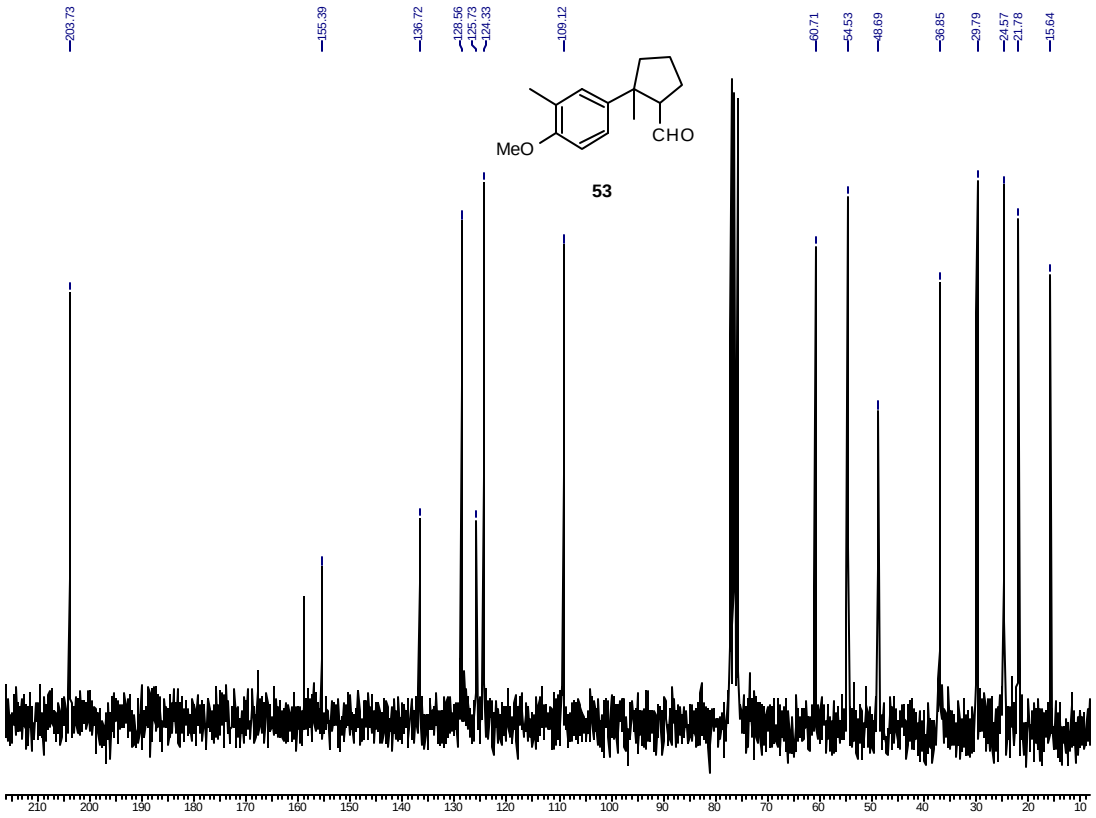
^{1}H-NMR spectrum ($CDCl_3$, 200 MHz) of Compound 52

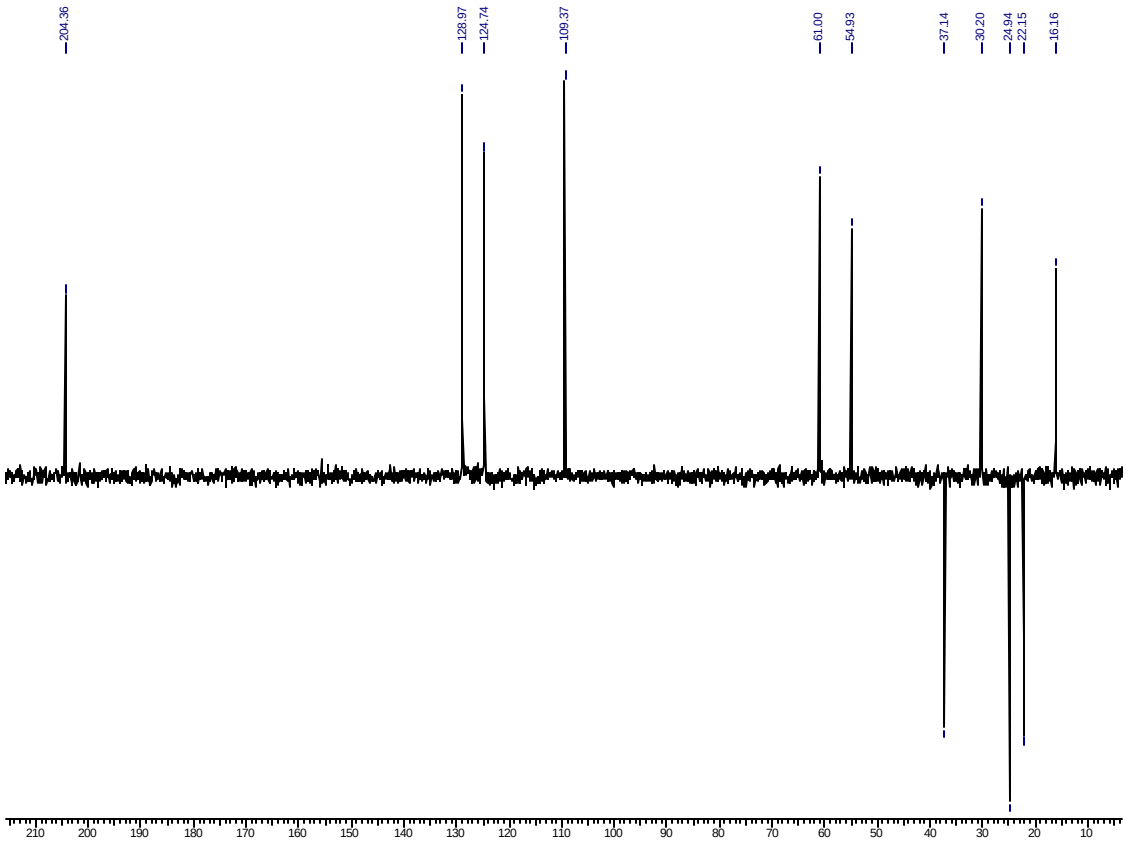


^{13}C-NMR and DEPT ($CDCl_3$, 50 MHz) of Compound 52

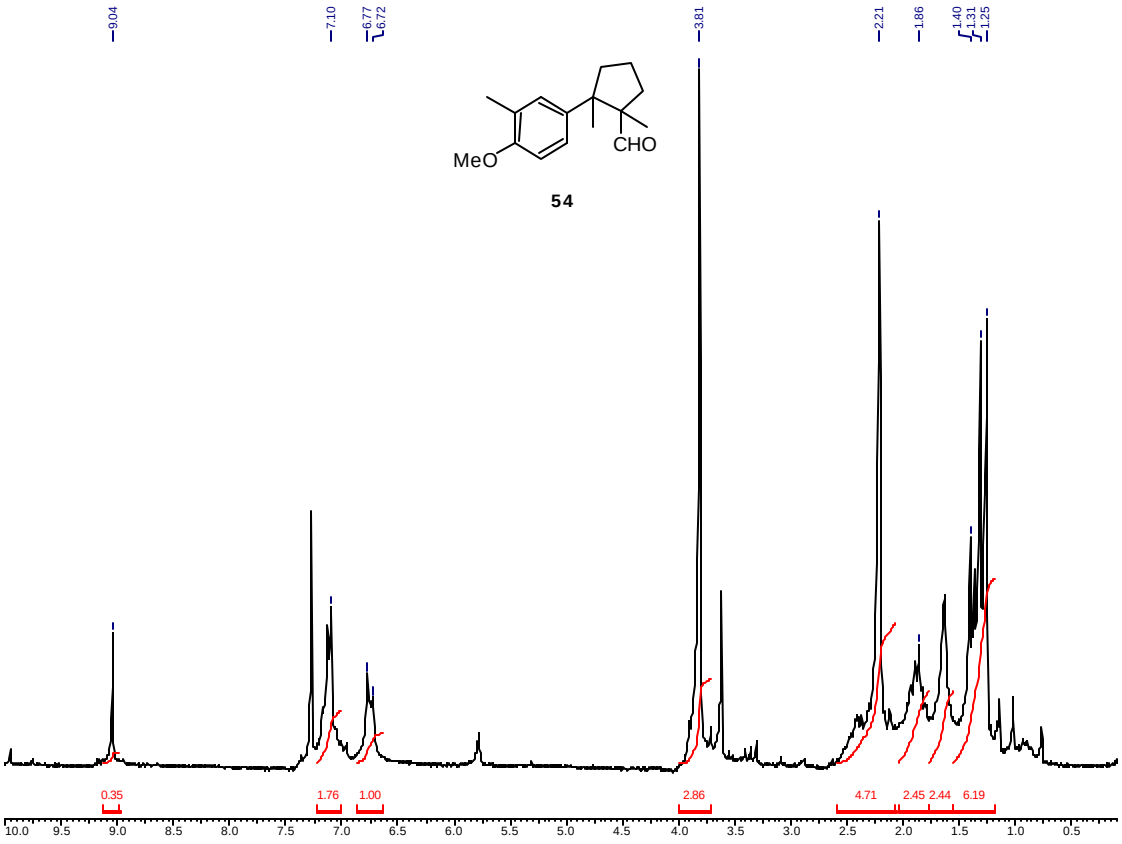


^{1}H-NMR spectrum ($CDCl_3$, 200 MHz) of Compound 53

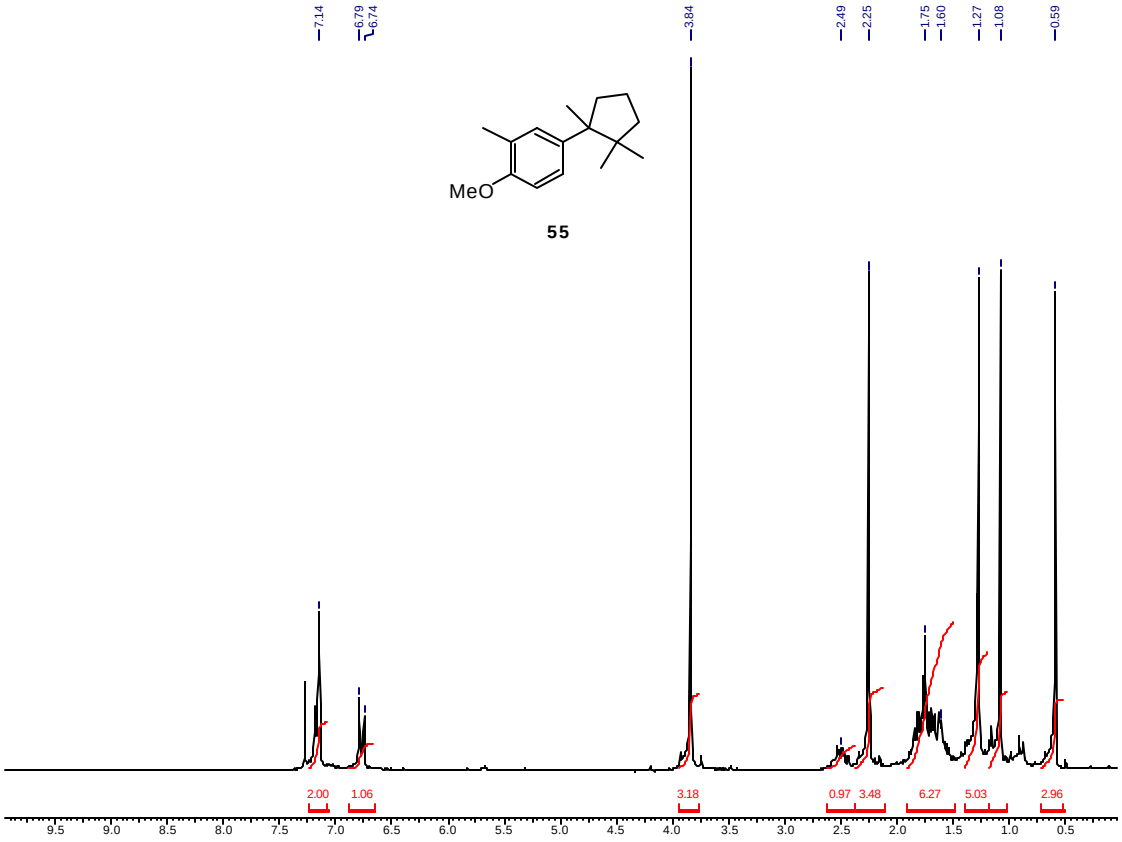

203.73
155.39
136.72
128.56
125.73
124.33
109.12
60.71
54.53
48.69
36.85
29.79
24.57
21.78
15.64
MeO
CHO
53
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10



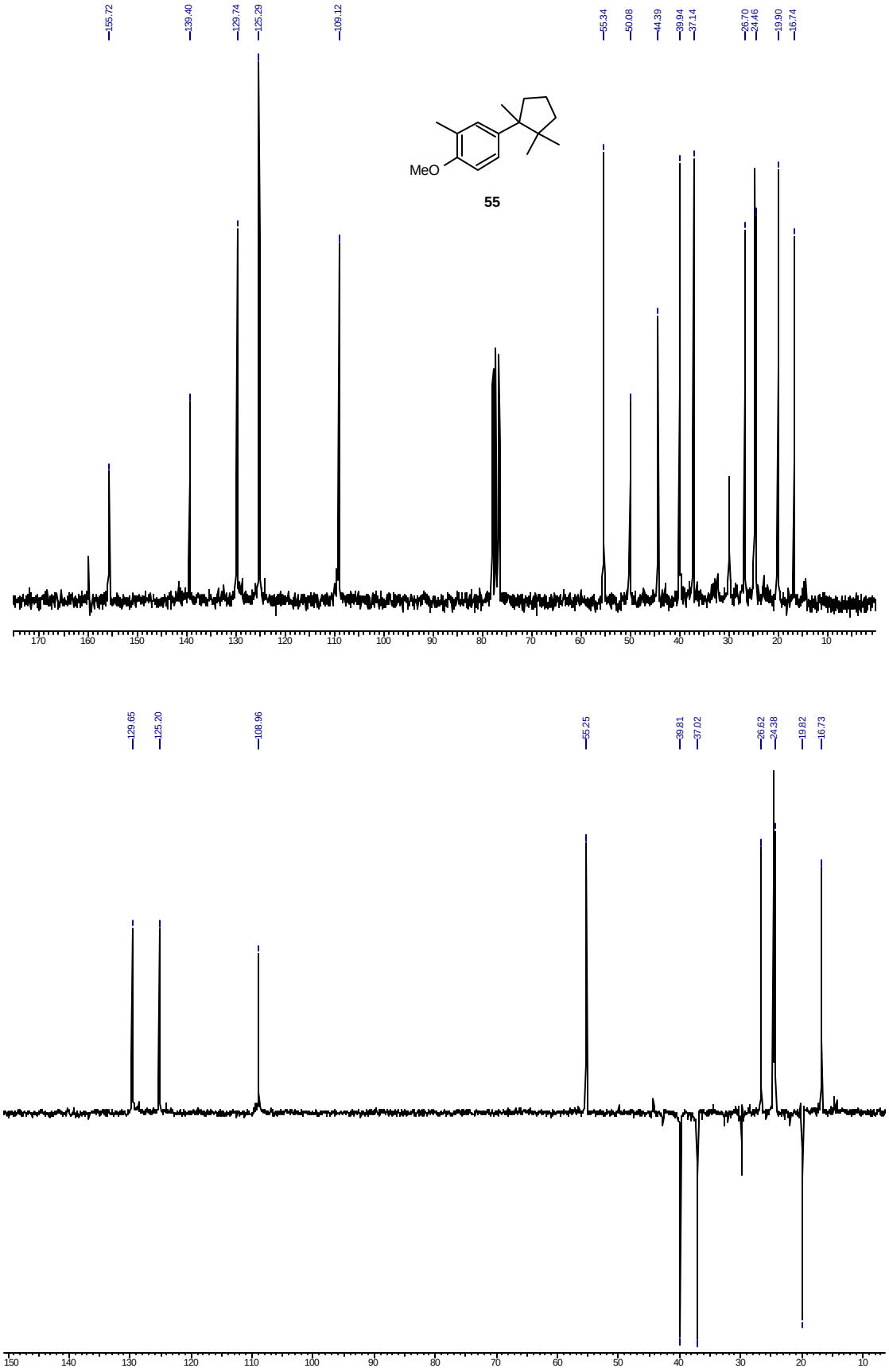
^{13}C-NMR and DEPT ($CDCl_3$, 50 MHz) of Compound 53



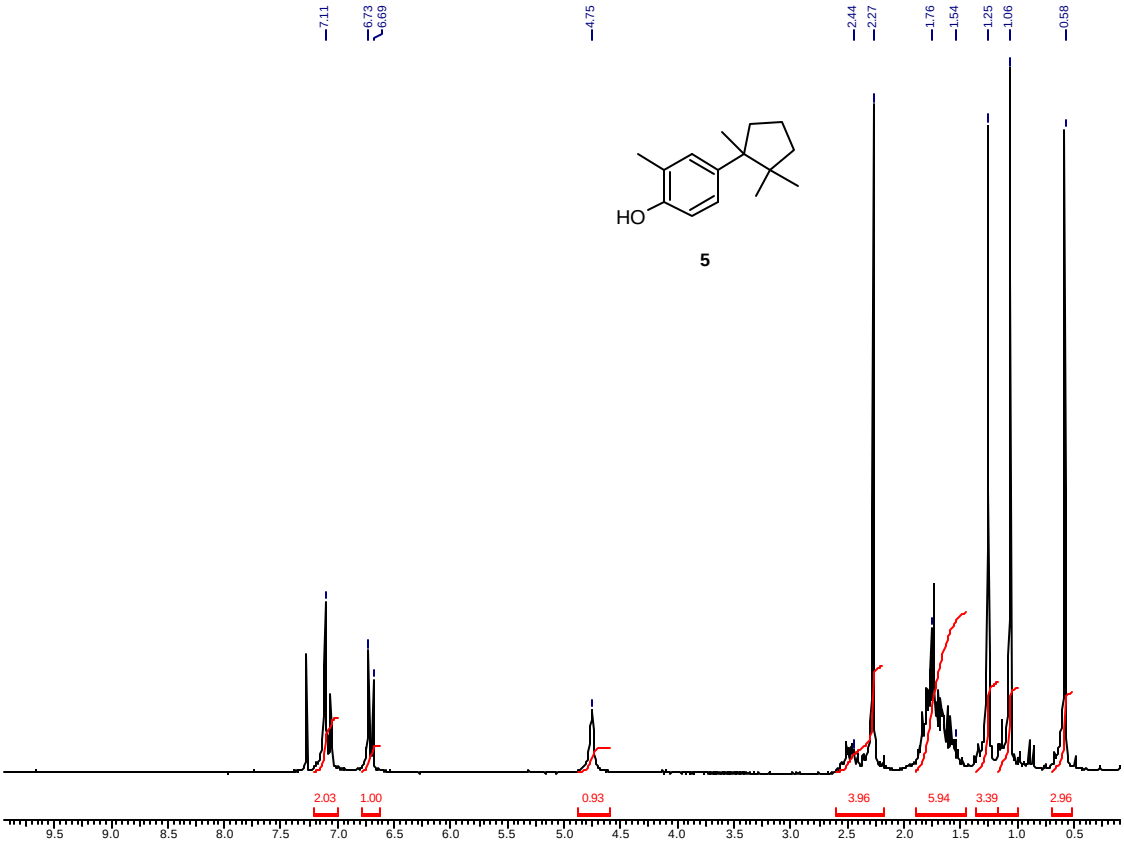
^{1}H-NMR Spectrum (CDCl$_3$, 200 MHz) of Compound 54



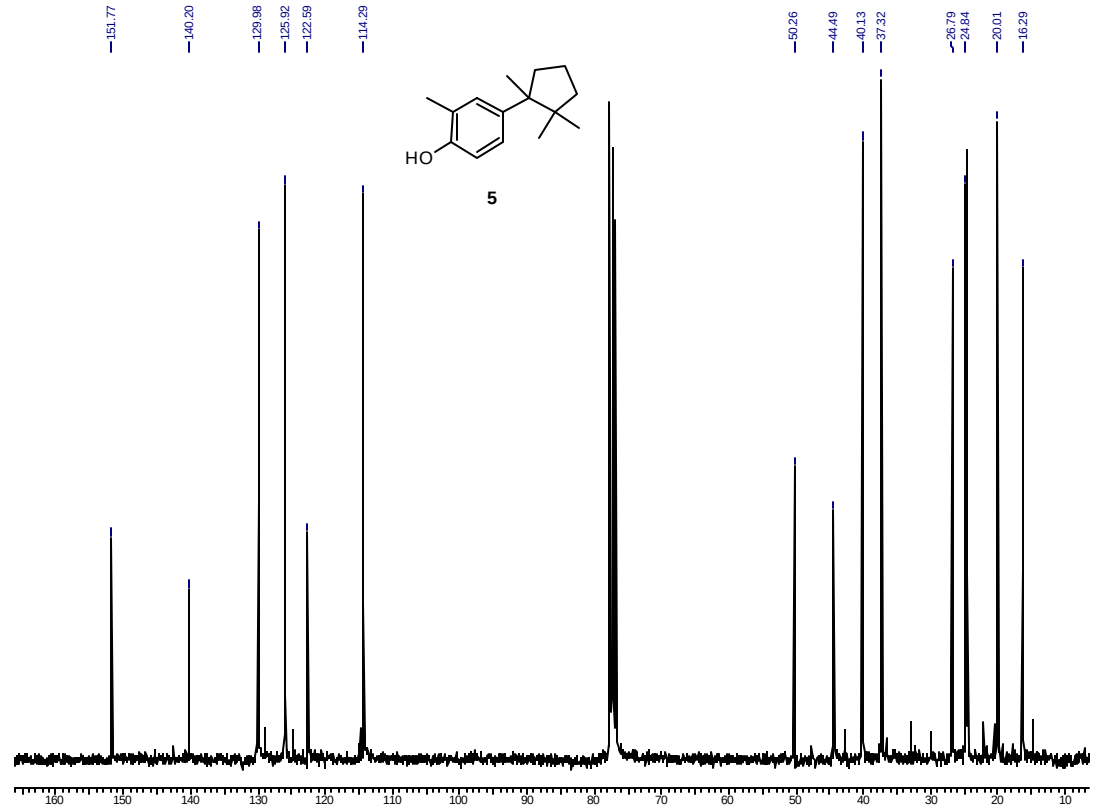
^{1}H-NMR Spectrum ($CDCl_3$, 200 MHz) of Compound 55

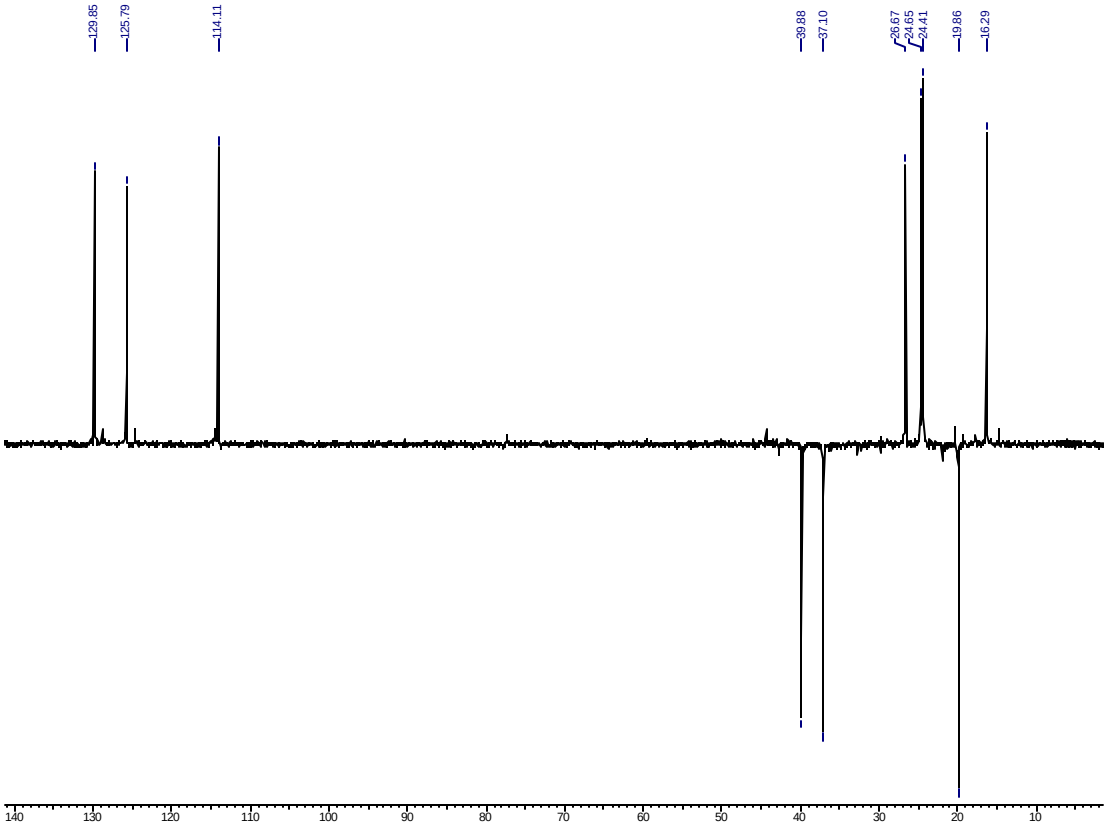


^{13}C-NMR and DEPT ($CDCl_3$, 50 MHz) of Compound 55



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

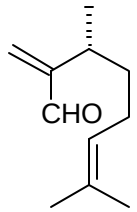

151.77
140.20
129.98
125.92
122.59
114.29
50.26
44.49
40.13
37.32
26.79
24.84
20.01
16.29
HO
5


129.85
125.79
114.11
39.88
37.10
26.67
24.65
24.41
19.86
16.29

^{13}C-NMR and DEPT ($CDCl_3$, 75 MHz) of Compound 5

1.3.6 Experimental

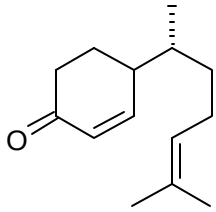
1. α-Methylene-3,7-dimethyl-6-octenal [16]



16

This compound was prepared by literature method[10] as described in the section 1.

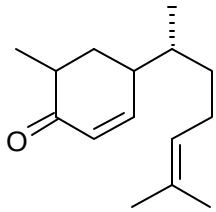
2. 4-(1,5-Dimethyl-hex-4-enyl)-cyclohex-2-enone [17]



17

This compound was prepared as described in the section 1

3. 4-[1,5-Dimethyl-hex-4-enyl)-cyclohex-2-enone [18]



18

To a stirred solution of α-methyl methylacetoacetate (2g, 15.38 mmol) in dry methanol (15 mL) was added MeONa (catalytic) and the mixture was stirred at room temperature for 30 min. and exomethylene compound **16** (2.55g, 15.38 mmol) in dry methanol (10 mL) was added dropwise. The reaction mixture was stirred at room temperature for 2h, at 60^0C (oil bath temperature) for next 2h, and then refluxed for 2h. Methanol was removed on rotary evaporator at reduced pressure and the residue was extracted with ethyl acetate (40 mL). The organic layer was washed with water (20 mL), brine (20 mL) and dried over anhydrous sodium sulphate, filtered, and concentrated at reduced pressure to furnish enone **18**. Enone **18** was purified by column chromatography on silica gel (eluent: ethyl acetate:pet. ether 5:95).

Yield: 1.73 g (51%).

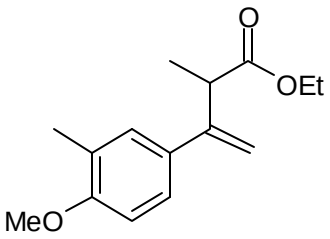
Molecular Formula: $C_{15}H_{24}O$.

IR ($CHCl_3$) ν_{max} cm^{-1}: 2950, 1670, 1605, 1507 1450, 1346, 1250, 1145, 984.

^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 0.85-.98 (m, 6H), 1.12-1.19 (m, 2H), 1.21-1.54 (m, 4H), 1.59 (s, 3H), 1.67-1.81 (m, 1H), 1.72 (s, 3H), 1.96-2.10 (m, 2H), 5.12 (t, 1H), 5.56 (m, 2H).

Mass (m/z): 220 (M+, 28), 135 (52), 121 (26), 108 (36), 95 (29), 79 (18), 69 (100), 55 (54).

4. 2-Methyl-3-(4'-methoxy-3'-methylphenyl)but-3-enoic acid, ethyl ester [24]



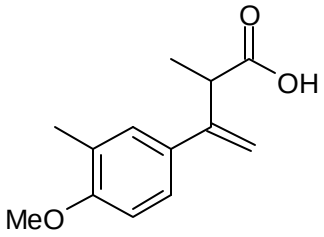
24

The ester **24** was prepared by using general Reformatsky reaction. To a mixture of 4-methoxy-3-methylacetophenone (25g, 0.153 mol) and α-bromopropionate (30.35g, 0.167 mol) in dry diethyl ether (200mL) was added zinc powder (15.3g, 0.23mol) and iodine crystals to catalyze the reaction. Gentle reflux was maintained by external heating. The reaction was monitored by TLC. After the completion of reaction (5h), 50% HCl was added and the reaction mixture stirred at

room temperature for 20h. The reaction mixture was extracted with diethyl ether (3x100mL). Ether extract was washed with water (3x100mL) and brine (2x100mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated in vacuum to furnish a viscous oil. Column chromatography on silical gel (60-120 mesh) [eluent: ethyl acetate:petroleum ether 5:95] afforded ester **24**.

Yield:	26.8g (71%).
Molecular Formula:	$C_{15}H_{20}O_3$.
IR ($CHCl_3$) ν_{max} cm^{-1}:	2980, 1730, 1410, 1360, 1320, 1180.
^{1}H NMR ($CDCl_3$, 200MHz) δ:	1.19 (t, 3H, J=6.98 Hz), 1.38 (d, 3H, J=8Hz), 2.22 (s, 3H), 3.66 (q, 1H, J=7.14 Hz), 3.83, (s,3H), 4.10 (q, 2H, J=7.34 Hz), 5.13 (s, 1H), 5.32 (s, 1H), 6.75, (d, 1H, J=9.16 Hz), 7.15 (m, 2H).
^{13}C NMR: ($CDCl_3$,50MHz) δ:	13.79 (q), 15.99 (q), 16.76 (q), 44.30 (d), 54.88 (q), 60.18 (t), 109.28 (d), 111.7 (t), 124.58 (d), 125.97 (s), 128.28 (d), 132.77 (s), 147.48 (s), 157.22 (s), 174.16 (s).
Mass (m/z) :	248 (M^+, 100), 233 (28), 205 (32), 176 (79), 159 (32), 147 (72), 135 (63), 115 (27), 91(29), 77 (18).

5. 2-Methyl-3-(4'-methoxy-3'-methylphenyl)but-3-enoic acid [25]



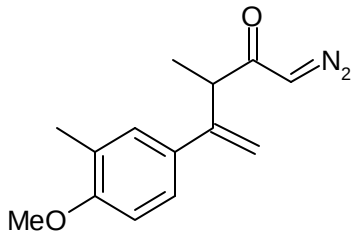
25

Acid **25** was obtained by alkaline hydrolysis of ester **24** in ethanol. Thus ester **24** [23.6g, 0.095mol] was added to the solution of KOH [5.33g, 0.095mol] in water-ethanol (1:1, 300mL) and stirred at room temperature for 2h. The reaction was monitored by TLC. After completion of the reaction, ethanol was removed on rotary evaporator under reduced pressure. The aqueous layer was then neutralized with 50%HCl (30mL) and extracted with saturated $NaHCO_3$ solution (3x100mL).

The aqueous layer was neutralized with 50% HCl (30mL) and extracted with ethyl acetate (3x100mL). The combined organic layer was washed with water (50 mL), brine (50 mL) dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure to afford *title acid* **25** as colourless solid.

Yield:	19.26g (92%).
Molecular Formula:	$C_{13}H_{16}O_3$.
Mp:	75-76^{0}C.
IR ($CHCl_3$) ν_{max} cm^{-1}:	3100 (broad), 2900, 1720, 1640, 1520, 1460, 1420.
^{1}H NMR ($CDCl_3$, 200MHz)δ:	1.42 (d, 3H, J=6.96 Hz), 2.24 (s, 3H), 3.78 (q, 1H, J=7.18 Hz), 3.85 (s, 3H), 5.20 (s, 1H), 5.39 (s, 1H), 6.78 (d, 1H, J=8.96 Hz), 7.22 (m,2H).
^{13}C NMR ($CDCl_3$, 50MHz) δ:	16.89 (q), 17.5 (q), 44.86 (d), 55.71 (q), 110.15 (d), 113.16 (t), 125.4(d), 126.98 (s), 129.41 (d), 133.5 (s), 147.67 (s), 158.15(s), 180.6(s).
Mass (m/z):	220 (M^+, 82), 205 (26), 192 (18), 174 (4), 159 (23), 147 (100), 139 (22), 115 (31), 91(39), 77 (22).
Elemental analysis:	Calculated C= 70.90%, H=7.27%.
	Found C=70.90%, H=7.12%.

6. 2-Methyl-3-(4'-methoxy-3'-methylphenyl)but-3-ene-1-diazonium [26]



26

Thionyl chloride (3.1g, 0.026mol) was added at 0^{o}C to stirred solution of acid **25** (4.66g, 0.021mol) in dry benzene (25mL) followed by a catalytic amount of DMF (1 drop). The reaction mixture was stirred at room temperature for 2h. After removal of excess of thionyl chloride and benzene (~ 25mL) the acid chloride was taken up in dry ether (40mL) and was slowly added at -

78^{o}C to a solution of triethylamine (2.12g, 0.021mol) and ethereal solution of diazomethane prepared from nitrosomethyl urea (5.24g, 0.050mol), KOH (20mL, 50%) in ether (100mL) and stirred at room temperature for 2h. Removal of ether at reduced pressure afforded unsaturated ketone **26**.

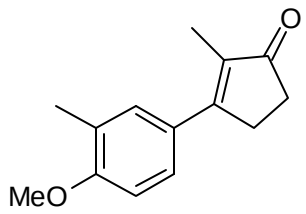
Yield: 2.86g (55%).

Molecular Formula: $C_{14}H_{16}N_2O_2$.

IR ($CHCl_3$) ν_{max} cm^{-1}: 2900, 2100, 1730, 1640, 1500, 1440, 1350, 1140, 800.

^{1}H NMR ($CDCl_3$, 200MHz) δ: 1.38 (d, 3H, J=6.87 Hz), 2.23 (s,3H), 3.78 (q, 1H, J=7.39), 3.84 (s, 3H), 5.16 (s,1H), 5.33 (s,1H), 5.45 (s,1H), 6.80 (d, 1H, J=9.96 Hz), 7.20 (m, 2H).

7. 3-(4-Methoxy-3-methylphenyl)-2-methyl cyclopent-2-enone. [27]



27

A solution of β-γ-unsaturated diazoketone **26** (2.86g, 11.7mmol) in dry dichloromethane (20mL) under argon atmosphere was cooled to 0^0C. To this solution, $BF_3.Et_2O$ (1.5mL, 11.7mmol) was added slowly and spontaneous evolution of nitrogen was observed. The reaction mixture was stirred at 0^0C for 1h, brought to room temperature. The reaction was monitored by TLC. After completion of the reaction, it was extracted with dichloromethane (3x25mL). The combined organic extracts were washed with water (2x20mL), brine (20mL) and dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish the crude *title compound* **27**. Column chromatography (silica gel 60-120 mesh, eluent: ethyl acetate:petroleum ether 10:90) of the residue furnished the pure product as colourless oil.

Yield: 0.92g (40%).

Molecular Formula: $C_{14}H_{16}O_2$.

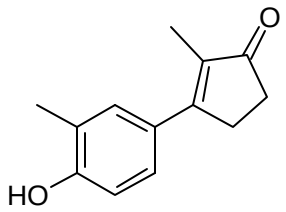
IR ($CHCl_3$) ν_{max} cm^{-1}: 2900, 1700, 1620, 1520, 1450, 800.

^{1}H NMR ($CDCl_3$, 200MHz)δ: 1.95 (s,3H), 2.23 (s,3H), 2.47 (m, 2H), 2.81 (m,2H), 3.84 (s,3H), 6.83 (d, 1H, J=9.92 Hz), 7.35 (m, 2H).

^{13}C NMR ($CDCl_3$, 50MHz):δ 10.20 (q), 16.38 (q), 29.02 (t), 33.91 (t), 55.45 (q), 109.81 (d), 126.98 (d), 128.49 (s), 130.10 (d), 134.63 (s), 159.4 (s), 166.27 (s), 209.72 (s).

Mass (m/z): 216 (M+, 76), 201 (87), 185 (62), 173 (29), 159 (24), 145 (35), 128 (51), 115 (100), 91 (68), 77 (36).

8. 3-(4-Hydroxy-3-methylphenyl)-2-methyl cyclopent-2-enone [30]



30

The phenol **30** was obtained by demethylation of the corresponding methyl ether **27**. Thus the solution of methyl ether **27** (0.477g, 2.2mmol) in dry dichloromethane (15mL) was cooled to -78^{o}C and then BBr_3 (1.44M solution in dichloromethane, 2.762g, 7.7mL, 11.04mmol) was added dropwise. The reaction mixture was stirred at -78^{o}C for 2h. The reaction was monitored by TLC. After completion of the reaction, the reaction was quenched with saturated $NaHCO_3$ (5mL), extracted with dichloromethane (2x20mL). The combined organic extracts were washed with water (5mL), brine (5mL) and dried over anhydrous sodium sulphate, filtered and concentrated at reduced pressure on rotary evaporator to furnish crude phenol **30** as yellow solid. The phenol derivative was purified by column chromatography on silica gel (60-120 mesh, eluent: ethylacetate:petroleum ether 20:80).

Yield: 0.397g (89%).

Molecular formula: $C_{13}H_{14}O_2$.

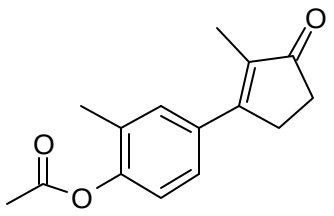
Melting point: 188^{0}C

IR ($CHCl_3$) ν_{max} cm^{-1}: 3440 (broad), 3020, 1660, 1650, 1215, 1095, 770, 670.

^{1}H NMR ($CDCl_3$, 200MHz) δ: 1.98 (s, 3H), 2.24 (s, 3H), 2.55 (m, 2H), 2.90 (m, 2H), 7.07 (d, 1H, J=9.82 Hz), 7.39 (m, 2H).

Mass (m/z): 202 (M^+, 89), 187 (100), 159 (52), 145 (54), 131 (56), 115 (71), 91 (31), 77 (16).

9. Acetic acid 2-methyl-4-(2-methyl-3-oxo-cyclopent-1-enyl) phenyl ester [31]



31

The acetate **31** was obtained by acetylation of phenol **30**. Thus to an ice-cold solution of phenol **30** (0.404g, 2mmol), triethylamine (0.506g, 0.7mL, 5mmol), dimethylaminopyridine (catalytic) in dichloromethane (10mL) was added acetyl chloride (0.236g, 0.2mL) dropwise. The reaction mixture was stirred at 0^oC for 30 minutes and brought to room temperature. The reaction was monitored by TLC. After completion, the reaction mixture was diluted with ethyl acetate (25mL), washed with water (2x10mL) and brine (10mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish crude acetate **31**. The acetate **31** was purified by column chromatography on silica gel (60-120 mesh, eluent: ethyl acetate:Petroleum ether 5:95).

Yield: 0.405g (83%).

Molecular Formula: $C_{15}H_{16}O_3$.

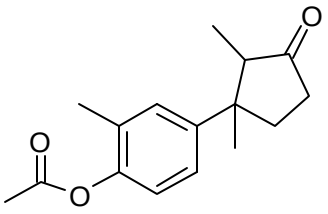
IR (CHCl3) ν_{max} cm^{-1} 2930, 1747, 1500, 1371, 1215, 1120, 763, 668.

^{1}H NMR ($CDCl_3$, 200MHz) δ: 1.97 (s, 3H), 2.25 (s, 3H), 2.36 (s, 3H), 2.56 (m, 2H), 2.88 (m, 2H), 7.13 (d, 1H, J=9.44 Hz), 7.40 (m, 2H).

^{13}C NMR ($CDCl_3$, 50MHz) δ: 9.22 (q), 15.58 (q), 19.92 (q), 28.59 (t), 33.18 (t), 121.66 (d), 125.67 (d), 129.64 (d), 133.61 (s), 135.67 (s), 149.71 (s), 164.26 (s), 167.68 (s), 207.75 (s).

Mass (m/z): 244 (M^+, 26), 202 (100), 187 (82), 159 (16), 145 (8), 126 (9), 115 (11), 77(5).

10. Acetic acid 4-(1,2-dimethyl-3-oxo-cyclopentyl)-2-methyl phenyl ester [32]

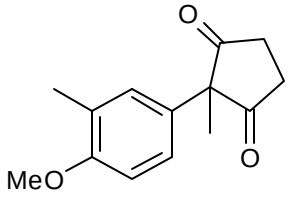


32

Trimethylaluminium (2M solution in toluene, 0.109mL, 16mg, 0.218mmol) was added to a magnetically stirred solution of $Ni(acac)_2$ (3.0mg, 0.012mmol) and enone **31** (45mg, 0.2mmol) in anhydrous THF (1mL) at 0^0C. The green coloured reaction mixture turned black. After stirring at 0^0C for 2h. and then at room temperature for 4h. the reaction mixture was diluted with hexane (8mL) and quenched by careful addition of saturated NH_4Cl solution (1mL). Stirring was continued further at room temperature for 2h. and the resulting solid was filtered through a short bed of celite. The residue was washed with THF (3x5mL). Evaporation of the solvent at reduced pressure and column chromatography on silica gel (60-120 mesh, eluent: ethyl acetate:petroleum ether 10:90) afforded the ketone **32**

Yield:	34mg (66%).
Molecular formula:	$C_{16}H_{20}O_3$.
IR ($CHCl_3$) ν_{max} cm^{-1}:	2900, 1750, 1520, 1370, 1220, 1120, 763, 668.
^{1}H NMR ($CDCl_3$, 200MHz) δ:	0.85(d, 0.6H, J=7.54 Hz), 1.02(d, 2.4H, J=7.54 Hz), 1.20 (s, 2.4H), 1.22(s, 0.6H), 2.08-2.14(m, 2H), 2.20(s, 3H), 2.33(s, 3H), 2.41-2.44(m, 2H), 2.56-2.65(m, 1H), 6.98 (d, 1H, J=8.78 Hz), 7.22(m, 2H)
Mass (m/z):	260 (M^+, 22), 218 (68), 203 (42), 161 (100), 148 (49), 135 (41), 121 (13), 91 (24), 77 (16).

11. 2-(4-Methoxy-3-methylphenyl)-2-methyl cyclopentane-1,3-dione [35]



35

In an inert and moisture free atmosphere, $BF_3.Et_2O$ (55.56g, 49mL, 0.39mol) was added dropwise to the solution of 1,3-dioxolane **33** (8.13g, 0.039mol) and trimethylsilyloxycyclobutene **34** (27g, 0.12mol) in dry dichloromethane (85mL) at -78^0C. The reaction mixture was stirred at -78^0C for 8h, then slowly brought to room temperature over 1h and stirred overnight. The raction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (100mL) and quenched by addition of saturated $NaHCO_3$ (80mL) in portions. The organic layer was washed with water (2x50mL), brine (50mL), dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure to furnish cyclopentadione **35**. The product was purified by crystallization from hexane:ethyl acetate 90:10.

Yield: 6.16g (68%).

Molecular Formula: $C_{14}H_{16}O_2$.

Melting point: 71-72^{0}C.

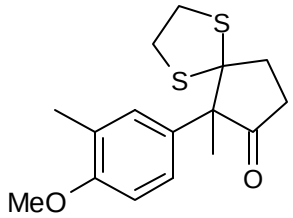
IR ($CHCl_3$) ν_{max} cm^{-1}: 2975, 1765, 1725, 1505, 1440, 1301, 1254, 1217, 1145, 1030, 815, 757, 668.

^{1}H NMR ($CDCl_3$, 200MHz) δ: 1.39 (s, 3H), 2.18 (s, 3H), 2.61-2.98 (m, 4H), 3.81 (s, 3H), 6.82 (d, 1H, J=8.46 Hz), 6.98 (m, 2H).

^{13}C NMR ($CDCl_3$, 50MHz) δ: 15.07 (q), 19.46 (q), 35.01 (t, 2x-CH_2), 110.51 (d), 124.81 **(d), 127.82 (s), 157.45 (s), 212.85 (s).**

Mass (m/z): 232 (M^+, 82), 189 (8), 176 (34), 162 (36), 148 (100), 133 (62), 115 (22), 103 (24), 91 (20), 77 (48), 55 (16).

12. 6-(4-Methoxy-3-methylphenyl)-6-methyl-1,4-dithiaspiro-[4.4]-nonan-7-one [36]



36

The dithioacetal derivative **36** was prepared by regioselective protection of one of the carbonyl groups with ethanedithiol. Thus cyclopentadione **35** (4.0g, 17.25mmol) was dissolved in dry DCM (50mL) and 1,2-ethanedithiol (1.2g, 1.06mL, 12.92mmol) was added dropwise followed

by $BF_3.Et_2O$ (0.5mL). The reaction mixture was stirred overnight at room temperature. The reaction was monitored by TLC. After completion of the reaction, dichloromethane (75mL) was added, followed by 5% NaOH (35mL). The organic layer was separated, washed with water (2x50mL), brine (50mL), dried over anhydrous sodium sulphate, filtered and concentrated under vacuum to furnish crude dithioketal derivative **36**. The dithioketal derivative was purified by column chromatography on silica gel (60-120 mesh, eluent: ethyl acetate:petroleum ether 12:88).

Yield: 4.36g (82%).

Molecular Formula: $C_{16}H_{20}O_2S_2$.

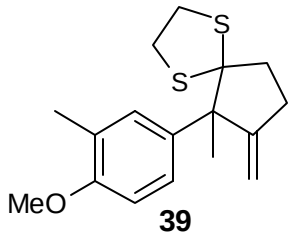
IR ($CHCl_3$) ν_{max} cm^{-1} : 3015, 2920, 1740, 1505, 1460, 1135, 760, 667.

^{1}H NMR ($CDCl_3$, 200MHz) δ: 1.56 (s, 3H), 2.21 (s, 3H), 2.19-2.27 (m, 1H), 2.46-2.78 (m, 4H), 2.92-3.25 (m, 2H), 3.27-3.31 (m, 1H), 3.82 (s, 3H), 6.75 (d, 1H, J=8.36 Hz), 7.15 (m, 2H).

^{13}C NMR ($CDCl_3$, 50MHz) δ: 16.19 (q), 22.15 (q), 37.44 (t, 2x-CH_2), 37.49 (t), 39.09 (t), 54.97 (q), 60.85 (s), 78.49 (s), 108.42 (d), 124.96 (s), 127.05 (d), 130.91 (d), 156.02 (s), 216.56 (s).

Mass (m/z): 308 (M^+, 68), 149 (100), 131 (48), 119 (9), 91 (10), 71 (7).

3. 6-(4-Methoxy-3-methylphenyl)-6-methyl-7-methylene-1,4-dithiaspiro-[4.4]-nonane [39]



39

The olefin **39** was obtained by Wittig reaction of corresponding dithioacetal **36**. Thus the ylide was generated by refluxing Wittig salt $PPh_3^{\oplus}CH_3I^{\theta}$ (0.506g, 1.25mmol) with the base *tert*-$BuO^{\theta}K^{\oplus}$ (0.153g, 1.25mmol) for 1h in dry benzene (10mL) and cooled to the room temperature. Dithioketal derivative **36** (0.308g, 1mmol.) in dry benzene (5mL) was added dropwise over 10 minutes and stirred at room temperature for 30 minutes. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (20mL), saturated

NH_4Cl (15mL) was added and stirred at room temperature for 30 minutes. The organic layer was washed with water (2x10mL), saturated NH_4Cl (10mL) and dried over anhydrous sodium sulphate, filtered, concentrated under reduced pressure to furnish crude exomethylene compound **39**. Column chromatography on silica gel (60-120, eluent: ethyl acetate : petroleum ether 2:98) furnished the pure exomethylene compound **39** as colourless solid.

Yield 0.220g (72%).

Molecular formula: $C_{17}H_{22}OS_2$.

Melting point: 74^0C.

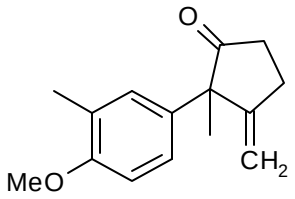
IR ($CHCl_3$) ν_{max} cm^{-1} : 3025, 2920, 1607, 1502, 1230, 1170, 770, 668.

^{1}H NMR ($CDCl_3$, 200MHz) δ: 1.66 (s, 3H), 2.24 (s, 3H), 2.25-2.46 (m, 2H), 2.68-2.82 (m, 3H), 3.11-3.25 (m, 3H), 3.84 (s, 3H), 4.96 (s, 1H), 5.18 (s, 1H), 6.74 (d, 1H, J=9.08 Hz), 7.29 (m, 2H).

^{13}C NMR ($CDCl_3$, 50MHz) δ: 16.89 (q), 26.48 (q), 31.89 (t), 38.98 (t), 39.20 (t), 41.96 (t), 55.49 (q), 57.03 (s), 82.25 (s), 108.56 (d), 109.19 (t), 124.85 (s), 127.53 (d), 131.54 (d), 136.65 (s), 154.64 (s), 157.12 (s).

Mass (m/z): 306 (M^+, 100), 278 (4), 231 (6), 213 (39), 187 (40), 173 (72), 157 (28), 128 (16), 115 (22), 91 (24).

14. 2-[4-Methoxy-3-methylphenyl)-2-methyl-3-methylene cyclopentenone [43]



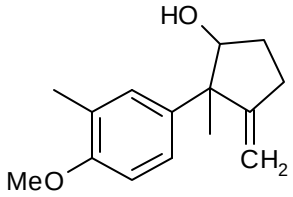
43

The exomethylene compound **43** was obtained by the Wittig reaction of corresponding cyclopentadione **35**. Thus the ylide was generated from Wittig salt $PPh_3^{\oplus}CH_3I^{\theta}$ (6.97g, 17.24mmol) and $tBuO^{\theta}K^{\oplus}$ (1.93g, 17.24mmol) in refluxing benzene (35mL) for 1h. It was cooled to room temperature and cyclopentadione **35** (4g, 17.24mmol) in dry benzene (15mL) was added dropwise over 10minutes.The reaction mixture was stirred at room temperature for 15 minutes. Again Wittig salt $PPh_3^{\oplus}CH_3I^{\theta}$ (6.97g, 17.24mmol) and *tert*-$BuO^{\theta}K^{\oplus}$ (1.93g, 17.24mmol) were

added and refluxed for 30 minutes. The reaction was monitored by TLC. To ensure the completion of the reaction, Wittig salt $PPh_3^{\oplus}CH_3I^{\theta}$ (1.75g, 4.32mmol) and *tert*-$BuO^{\theta}K^{\oplus}$ (0.485g, 4.32mmol) were added and refluxing was continued for 10 minutes further. The reaction mixture was allowed to cool to room temperature diluted with ethyl acetate (75mL), saturated NH_4Cl solution (50mL) was added and stirred at room temperature for 30 minutes. The organic layer thus separated was washed with water (2x100mL), saturated NH_4Cl (100mL), dried over anhydrous sodim sulphate, filtered and concentrated under vacuum to furnish crude exomethylene compound **43**. Column chromatography on silica gel (60-120mesh, eluent: ethyl acetate:petroleum ether 3:97) furnished pure exomethylene compound **43** in 73% yield as colourless thick syrup.

Yield:	2.89g (73%).
Molecular formula:	$C_{15}H_{18}O_2$.
Melting point:	62-63^{0}C.
IR ($CHCl_3$) ν_{max} cm^{-1}:	2960, 2930, 1741, 1660, 1605, 1503, 1465, 1440, 1300, 1280, 1120, 895, 754.
^{1}H NMR ($CDCl_3$, 200MHz) δ:	1.42 (s, 3H) 2.20 (s, 3H), 2.25-2.48 (m, 2H), 2.59-2.67 (m, 2H), 3.81 (s, 3H), 5.12 (s, 1H), 5.33 (s, 1H), 6.76 (d, 1H, J=7.92 Hz), 7.11 (m, 2H).
^{13}C NMR ($CDCl_3$, 50MHz) δ:	16.00 (q), 22.91 (q), 27.5 (t), 34.03 (t), 54.71 (q), 60.71 (s), 109.73 (d), 109.81 (t), 124.63 (d), 126.73 (s), 128.41 (d), 132.72 (s), 153.18 (s), 156.82 (s), 212.85 (s).
Mass (m/z):	230 (M^+, 48), 187 (100), 173 (16), 159 (17), 144 (8), 128 (13), 115 (16), 105 (58), 91 (14), 77 (41).

15. 2-[4-Methoxy-3-methylphenyl)-2-methyl-3-methylene cyclopentanol [44]

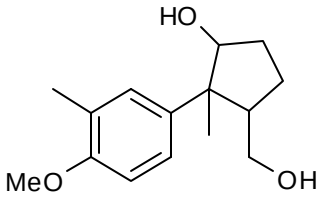


44

To the solution of ketoolefin **43** (2.028g, 8.82mmol) in ethanol (25mL), $NaBH_4$ (0.502g, 13.22 mmol) was added portionwise over 10 minutes at room temperature. Then the reaction mixture was stirred at room temperature for 30 minutes further. The reaction was monitored by TLC. After completion of the reaction, ethanol was removed at reduced pressure. The crude residue thus obtained was extracted with ethyl acetate. The organic layer was washed with water (20mL), brine (20mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish compound **44** as white solid. The compound **44** was purified by crystallization from ethyl acetate:petroleum ether (5:95).

Yield:	2g, (98%).
Molecular formula:	$C_{15}H_{20}O_2$.
Melting point:	128^0C.
IR ($CHCl_3$) ν_{max} cm^{-1}:	3450(broad), 2960, 1650, 1630, 1500, 1410, 1385, 1220, 1140, 1035, 768.
^{1}H NMR ($CDCl_3$, 200MHz): δ	1.49 (s, 3H), 1.52-1.68 (m, 1H), 1.89-2.09 (m, 1H), 2.24 (s, 3H), 2.41-2.88 (m, 2H), 3.84 (s, 3H), 3.81-3.85 (m, 1H), 4.88 (s, 1H), 5.16 (s, 1H), 6.80 (d, 1H, J=7.98 Hz), 7.17 (m, 2H).
Mass (m/z):	232 (M^+, 88), 214 (16), 199 (24), 189 (52), 173 (100), 157 **(23), 149 (35), 115 (92), 91 (23), 77 (17).**

16. 3-Hydroxymethyl-2-(4-methoxy-3-methylphenyl)-2-methylcyclopentanol [45]



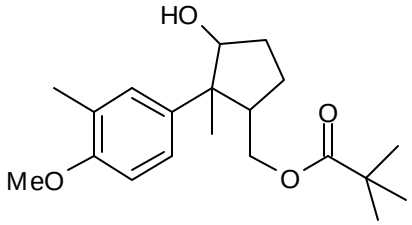
45

The diol **45** was obtained by hydroboration of cyclopentanol **44** with boranedimethylsulphide complex followed by oxidative alkaline hydrolysis with H_2O_2. Thus to the solution of cyclopentanol **44** (2 g, 8.62 mmol) in dry THF (30mL) at 0^0C, BMS complex (2M solution in THF, 1.638g, 10.6mL, 21.55mmol) was added dropwise. The reaction mixture was brought to room temperature and stirred overnight. The reaction mixture was then cooled to 0^0C,

30% NaOH (8mL) was added in a single lot followed by H_2O_2 (30%, 8mL) dropwise. The reaction mixture was stirred at room temperature for 30 minutes and then diluted with ethyl acetate. The organic layer thus separated was washed with water (2x30mL), brine (30mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish crude diol **45**. Column chromatography of the diol on silica gel (60-120 mesh, eluent: ethyl acetate :petroleum ether 25:75) furnished pure diol **45** as crystalline white solid.

Yield:	1.53 g (71%).
Molecular formula:	$C_{15}H_{22}O_3$.
Melting Point:	149-151^{0}C.
IR ($CHCl_3$) ν_{max} cm^{-1}:	3450(broad), 3020, 1250, 1210, 761, 669.
^{1}H NMR ($CDCl_3$, 200MHz): δ	1.24 (s, 3H), 1.77-1.89 (m, 1H), 1.91-2.24 (m, 3H), 2.22 (s, 3H), 2.26-2.37 (m, 1H), 3.52 (dd, 1H, J= 3,9 Hz, 10.7 Hz,), 3.80 (dd, 1H, J=3.9, 11.2 Hz), 3.82 (s, 3H), 4.42 (m, 1H), 6.78 (d, 1H, J=8.98 Hz), 7.11 (m, 2H)
^{13}C NMR ($CDCl_3$, 50MHz): δ	16.07 (q), 24.37 (t), 31.39 (q), 32.50 (t), 49.11 (d), 53.52 (s), 54.9 (q), 63.04 (t), 79.03 (d), 109.76 (d), 126.01 (s), 126.21 (d), 130.57 (d), 135.05 (s), 155.53 (s).
Mass (m/z):	250 (M^+, 11), 232 (5), 217 (5), 189 (10), 175 (12), 149 (100), 135 (8), 115 (9), 91 (15), 77 (6).

17. Pivaloate ester of diol, [46]



46

To an ice-cold solution of the diol **45** (1.53g, 6.12mmol.), Et_3N (1.55g, 2.12mL, 15.3mmol.) and DMAP (catalytic) in dry DCM (45mL) was added pivaloyl chloride (0.886g, 0.9mL, 7.35mmol) dropwise. The reaction mixture was stirred at 0^{0}C. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (25mL) and washed with water (2x20mL), brine (20mL). The organic layer was dried over

anhydrous sodium sulphate, filtered and concentrated under reduced pressure to yield crude pivoloate ester **46**. Column chromatography on silica gel (60-120 mesh, eluent: ethyl acetate: petroleum ether 12:88) yielded pure pivaloate ester **46** as colourless oil.

Yield: 1.67g. (84%).

Molecular formula: $C_{20}H_{30}O_4$.

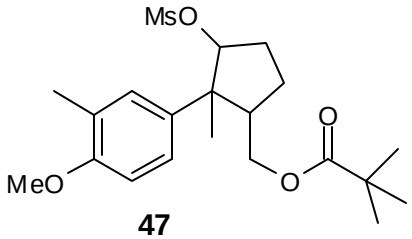
IR ($CHCl_3$) ν_{max} cm^{-1}: 3020, 2970, 1717, 1506,1480, 1290, 1254, 1160, 765, 668.

^{1}H NMR ($CDCl_3$, 200MHz) δ: 1.18 (s, 9H), 1.33 (s, 3H), 1.77-2.11 (m, 3H), 2.15-2.42 (m, 2H), 2.22 (s, 3H), 3.81 (s, 3H), 3.84 (dd, 1H, J=9.3 Hz, 11.3 Hz), 4.15 (m, 2H), 6.80 (d, 1H, J=8.78 Hz), 7.11 (m, 2H).

^{13}C NMR ($CDCl_3$, 50MHz) δ: 16.19 (q), 25.49 (t), 27.00 (q, 3x-CH3), 28.83 (q), 31.44 (t), 38.47 (s), 46.92 (d), 52.69 (s), 55.04 (q), 66.36 (t), 80.59 (d), 110.03 (d), 126.46 (d), 130.43 (d), 132.86 (s), 156.05 (s), 178.15 (s).

Mass (m/z): 334 (M^+, 8), 232 (10), 217 (7), 199 (4), 189 (14), 175 (21), 162 (9), 149 (100), 135 (9), 115 (7), 91 (10), 77 (6).

18. Mesylate [47]



47

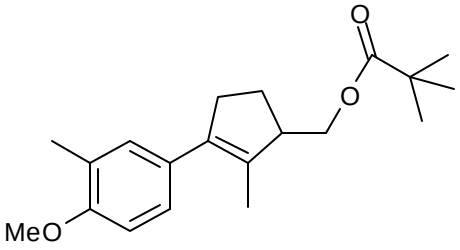
To an ice-cold solution of pivaloate ester **46**, (96mg, 0.276mmol), triethylamine (140mg, 1.38mmol) in dry dichloromethane (4mL), mesyl chloride (80mg, 0.69mmol) in dry dichloromethane (1mL) was added dropwise. Stirred at 0^0C for 2h. and then at room temperature for 2h. The reaction was monitored by TLC. After completion, the reaction mixture was diluted with dichloromethane (10mL). The organic layer was washed with water (2x5mL), brine (5mL) and dried over anhydrous sodium sulphate, filtered and concentrated in vacuum to furnish mesylate **47**. Mesylate **47** could not be purified by column chromatography as it underwent rearrangement to furnish **48**.

Yield: 0.105g. 92% (crude).

Molecular Formula: $C_{21}H_{32}O_5S$.

^{1}H NMR ($CDCl_3$, 200MHz) δ: 1.21 (s, 9H), 1.40 (s, 3H), 1.76-2.22 (m, 3H), 2.23 (s, 3H), 2.24-2.49 (m, 3H), 2.88 (s, 3H), 3.70-3.81 (m, 1H), 3.83 (s, 3H), 4.11-4.15 (m, 0.5H), 5.15-5.21 (m, 0.5H), 6.79 (d, 1H, J=8Hz), 7.11 (m,2H).

19. Compound [48]



48

This compound was obtained from mesylate **47** during its column chromatography.

Yield: 76 mg.

Molecular Formula: $C_{20}H_{28}O_2$

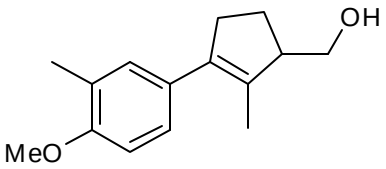
IR ($CHCl_3$) ν_{max} cm^{-1}: 2968, 1720, 1600, 1503, 1480, 1285, 1250, 1215, 1165, 1035, 760, 668.

^{1}H NMR ($CDCl_3$, 200MHz) δ: 1.15 (s, 9H), 1.72-1.75 (m, 1H), 1.76 (s, 3H), 2.16-2.20 (m, 1H), 2.21 (s, 3H), 2.25-2.59 (m, 2H), 3.79-3.82 (m, 1H), 3.84 (s, 3H) 3.87-3.92 (m, 1H), 6.78 (d, 1H, J=8Hz), 6.97 (m, 2H).

^{13}C NMR ($CDCl_3$, 50MHz) δ: 15.31 (q), 16.30 (q), 26.26 (t), 27.22 (q, 3x-CH3), 37.99 (t), 38.83 (s), 48.69 (d), 55.41 (q), 67.10 (t), 109.85 (d), 126.28(s), 126.80(d), 129.48(s), 130.73(d), 135.32(s), 136.21(s), 156.50 (s), 178.74(s).

Mass (m/z): 316 (M+, 4), 214 (58), 199 (28), 183 (24), 173 (12), 149 (15), 115 (15), 91 (21), 77 (19), 57 (100).

20. [3-(4-Methoxy-3-methylphenyl)-2-methyl-cyclopent-2-enylmethyl ester [49]



49

This compound was obtained when mesylate **47** was treated with $LiAlH_4$ in THF at room temperature. Mesylate **47** (96 mg, 0.24 mmol) was treated with $LiAlH_4$ (18 mg, 0.48 mmol) in THF at room temperature. The reaction was monitored by TLC. TLC showed faster moving spot. Reaction mixture was diluted with diethyl ether (10 mL) and filtered through a short bed of celite. The filtrate was concentrated at reduced pressure. Column chromatography (SiO_2) (eluent:ethyl acetate:pet ether) furnished the compound **49**.

Yield: 62 mg.

Molecular Formula: $C_{15}H_{20}O_2$

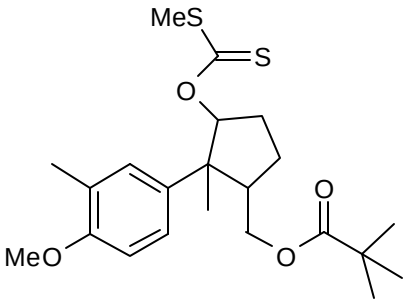
IR ($CHCl_3$) ν_{max} cm^{-1}: 3440 (broad), 2930, 2840, 1605, 1503, 1226, 1245, 1170, 815, 770, 668.

^{1}H NMR ($CDCl_3$, 200MHz) δ: 1.55 (s, 3H), 1.56-1.92 (m, 1H), 2.12-2.19 (m, 2H), 2.23 (s, 3H), 2.27-2.57 (m, 2H), 3.48-3.62 (m, 2H), 3.84 (s, 3H), 6.80 (d, 1H, J=8Hz), 7.02 (m, 2H).

^{13}C NMR ($CDCl_3$, 50MHz) δ: 15.41 (q), 16.33 (q), 25.89 (t), 38.35 (t), 52.71 (d), 55.59 (q), 65.58 (t), 110.28 (d), 126.71 (s), 126.90 (d), 129.87 (s), 130.83 (d), 135.68 (s), 137.01 (s), 156.78 (s).

Mass (m/z): 232 (M^+,44), 201 (100), 186 (22), 173 (18), 158 (9), 141 (11), 135 (8), 128 (15), 115 (26), 91 (16), 77 (15).

21. Xanthate derivative [50]

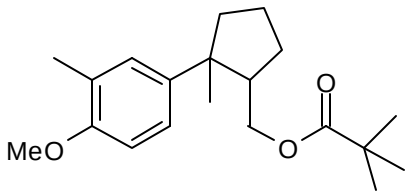


50

This xanthate derivative was prepared by using general literature method. NaH (60% dispersion in oil, 0.3g., 7.5mmol) was successively washed with dry hexane under an inert atmosphere. To this, pivaloate ester **46** (1.67g, 5mmol) in dry THF (16 mL) was added dropwise. The reaction mixture was stirred at room temperature for 3h, then carbon disulphide (4mL) was added dropwise. The reaction mixture was stirred further for 3h, methyl iodide (2.13g, 15mmol) in dry THF (4mL) was added. The reaction mixture was stirred for an additional 16h at room temperature. The reaction was monitored by TLC. After the completion of the reaction, THF was removed under reduced pressure. The residue was extracted with ethyl acetate (2x30mL). The organic layer was washed with water (2x15mL), brine(15mL), dried over anhydrous sodium sulphate, filtered, concentrated in vacuum to furnish crude xanthate derivative **50**. Column chromatography on silica gel (60-120 mesh, eluent: ethyl acetate:petroleum ether 3:97) furnished xanthate **50** as colourless oil.

Yield:	1.817g (86%)
Molecular formula:	$C_{22}H_{32}O_4S_2$.
IR ($CHCl_3$) ν_{max} cm^{-1}:	3020, 1716, 1505, 1215, 1160, 770, 670.
^{1}H NMR ($CDCl_3$, 200MHz) δ:	1.21 (s, 9H), 1.34 (s, 3H), 1.84-2.18 (m, 3H), 2.21 (s, 3H), 2.31 (s, 3H), 2.48-2.66 (m, 2H), 3.81 (s, 3H), 3.82-3.96 (m, 1H), 4.24-4.28 (m, 1H), 5.98-6.02 (m, 1H), 6.76 (d, 1H, J=8Hz), 6.98 (m, 2H).
^{13}C NMR ($CDCl_3$, 50MHz) δ:	17.09 (q), 19.13 (q), 20.21 (t), 27.98 (q, 3xCH3), 30.49 (t), 31.16 (q), 39.46 (s), 47.82 (d), 53.86 (s), 55.94 (q), 66.99 (t), 91.83 (d), 110.51 (d), 120.62 (d), 126.72 (s), 130.90 (d), 134.31 (s), 156.72 (s), 179.06 (s), 215.13 (s).
Mass (m/z):	424 (6), 316 (4), 231 (4), 215 (100), 199 (18), 187 (15), 173 (17), 135 (28), 91 (26), 77 (7)

22. Pivaloate ester [51]

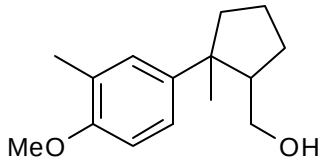


51

This pivaloate ester was obtained by deoxygenation of xanthate derivative **51**. Thus a mixture of xanthate derivative **51 (**1.812g, 4.27mmol), tri-n-butyltinhydride (6.22g, 5.66mL,21.37 mmol) and AIBN (catalytic) in dry toluene was refluxed for 3h. The reaction mixture was cooled to room temperature and the reaction mixture was diluted with ethyl acetate (50mL). The excess of *tri*-n-butyltinhydride was destroyed by aqueous KF (10% solution, 20mL). The organic layer was successively washed with aqueous KF (10%, 3x20mL), water (2x20mL), brine (20mL), dried over anhydrous sodium sulphate, filtered and concentrated in vacuum to furnish crude pivaloate ester. Column chromatography on silica gel (60-120mesh, eluent: ethyl actetate:petroleum ether 1:99) furnished the pure pivaloate ester **51**.

Yield:	1.11g (83%).
Molecular formula:	$C_{20}H_{30}O_3$.
IR ($CHCl_3$) ν_{max} cm^{-1}:	3020, 1713, 1605, 1508, 1215, 1160, 770, 670.
^{1}H NMR ($CDCl_3$, 200MHz) δ:	1.17 (s, 9H), 1.37 (s, 3H), 1.44-2.08 (m, 4H), 2.12-2.20 (m, 3H), 2.21 (s, 3H), 3.48 (dd, 1H, J_1=8.56 Hz, J_2=2.46), 3.72 (dd, 1H, J1=J2=5.54 Hz), 3.81 (s, 3H), 6.74 (d, 1H, J=8Hz), 7.05 (m, 2H).
^{13}C NMR ($CDCl_3$, 50MHz) δ:	16.14 (q), 21.65 (t), 26.91 (q, 3xCH_3), 27.1 (t), 29.70 (q), 37.64 (d), 37.76 (s), 47.75 (s), 48.63 (d), 54.96 (q), 66.20 (t), 109.32 (d), 124.80 (d), 125.57 (s), 129.10 (d), 137.73 (s), 155.60 (s), 178.17 (s).

23. [2-(4-Methoxy-3-methylphenyl)-2-methylcyclopentyl] methanol [52]

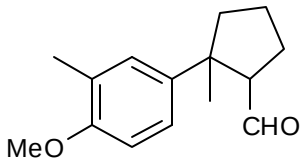


52

$LiAlH_4$ (0.266g, 7mmol) was added to THF solution (25mL) of pivaloate ester **51** (1.11g, 3.5mmol) and stirred at room temperature. The reaction was slightly exothermic and was monitored by TLC. After the completion of reaction, THF was removed under reduced pressure and the residue was extracted with diethyl ether (3x25mL). The organic layer was washed with dilute HCl (5%, 20mL), water (3x25mL), brine (30mL) dried over anhydrous sodium sulphate, filtered and concentrated under vacuum to yield crude alchohol **52**. The column chromatography on silica gel (60-120 mesh, eluent ethyl acetate:petroleum ether 12:88) furnished the pure product as colourless oil.

Yield:	0.726g. (92%).
Molecular formula	$C_{15}H_{22}O_2$.
IR ($CHCl_3$) ν_{max} cm^{-1}:	3450 (broad), 3020, 2910, 1205, 1160, 770, 668.
^{1}H NMR ($CDCl_3$, 200MHz) δ:	1.34 (s, 3H), 1.61-1.72 (m, 2H), 1.74-1.99 (m, 3H), 2.02-2.18 (m, 2H), 2.22 (s, 3H), 3.02-3.15 (m, 1H), 3.26-3.39 (m, 1H), 3.82 (s, 3H), 6.76 (d, 1H, J=8Hz), 7.07 (m, 2H).
^{13}C NMR ($CDCl_3$, 50MHz):	16.21 (q), 21.73 (t), 27.18 (t), 29.85 (q), 37.39 (t), 47.71 (s), 51.92 (d), 54.99 (q), 64.37 (t), 109.32 (d), 124.70 (d), 125.68 (s), 129.11 (d), 139.43 (s), 155.56 (s).

24. 2-(4-Methoxy-3-methylphenyl)-2-methylcyclopentane-1-carbaldehyde [53]

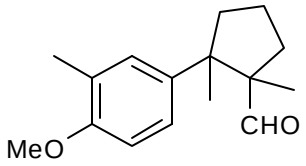


53

To an ice-cold solution of primary alcohol **52** (0.421g, 1.78mmol) in dry dichloromethane (20mL), pyridinium chlorochromate (0.578g, 2.67mmol) was added in a single portion. As the reaction proceeds, the orange coloured reaction mixture turned black. The reaction was monitored by TLC. After completion of the reaction, diethyl ether (30mL) was added in order to precipitate out chromous salts, filtered through a short bed of celite. The filtrate was successively washed with water (3x20mL), brine (2x20mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under vacuum to yield aldehyde **53**.

Yield:	0.359g (86%).
Molecular Formula:	$C_{15}H_{20}O_2$.
IR ($CHCl_3$) ν_{max} cm^{-1}:	2960, 1703, 1611, 1505, 1250, 771, 670.
^{1}H-NMR ($CDCl_3$, 200 MHz) δ:	1.36 (s, 3H), 1.90-2.15 (m, 6H), 2.21 (s, 3H), 2.80-2.85 (m, 1H), 3.81 (s, 3H) 6.76 (d, 1H, J=8 Hz), 7.05 (m, 2H), 9.17 (d, 1H, J=4 Hz).
^{13}C-NMR ($CDCl_3$, 50 MHz) δ:	15.64 (q), 21.78 (t), 24.57 (t), 29.79 (q), 36.85 (t), 48.69 (s), 54.53 (q), 60.71 (d), 109.12 (d), 124.33 (d), 125.73 (s), 128.56 (d), 136.72 (s), 155.39 (s), 203.73 (d).
Mass (m/z):	232 (M+, 12), 189 (14), 175 (100), 162 (78), 147 (32), 137 (17), 115 (21), 105 (15), 91 (48), 77 (34).

25. 1-Methyl-2-(4-methoxy-3-methylphenyl)-2-methylcyclopentane-1-carbaldehyde [54]



54

NaH (60% dispersion in oil, 0.275g, 6.90mmol.) was successively washed with dry n-haxane (2x5mL). To this, aldehyde **53** (0.320g, 1.38mmol) in dry DME (10mL) was added dropwise at -10^0C. Hydrogen evolution was induced by warming up the reaction mixture to 0^0C, stirred at 0^0C for 30 minutes. Methyl iodide (0.980g, 6.9mmol) in dry DME (4mL) was added dropwise. The reaction mixture was stirred at 0^0C for 3h and then at room temperature for 16h.

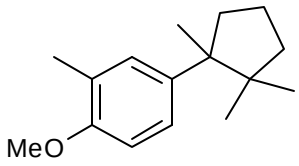
Then the reaction mixture was poured into water (5mL) and extracted with diethyl ether (3x20mL). The combined organic layers were washed with brine and then dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish aldehyde **54**. The column chromatography on silica gel (60-120 mesh, eluent ethyl acetate:petroleum ether 1:99) furnished the pure aldehyde.

Yield: 0.220g (65%).

Molecular formula: $C_{16}H_{22}O_2$.

^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.25 (s, 1.5H), 1.31 (s,1.5H), 1.34 (s, 1.5H), 1.40 (s, 1.5H), 1.56-1.63 (m, 2H), 1.77-1.94 (m, 2H), 2.11-2.41 (m, 2H), 2.21 (s, 3H), 3.81 (s, 3H), 6.76 (d, 1H, J=7.86 Hz), 7.10 (m, 2H), 9.04 (s, 1H)

26. 1,1-Dimethyl-2-methyl-2-(4-methoxy-3-methylphenyl)-2-methylcyclopentane [55]



55

A mixture of **54** (0.2g, 0.81mmol), hydrazine hydrate (0.285 g, 0.35 mL, 5.69mmol), NaOH (0.287g, 7.15 mmol) and triethylene glycol (5 mL) was heated at 195^{o}C (oil bath temperature) for 7h. After cooling to room temperature, water (5mL) was added and the mixture extracted with diethyl ether (4x20mL). The combined organic extracts were washed with brine (20mL), dried over anhydrous sodium sulphate, filtered and concentrated to furnish compound **55**. Column chromatography on silica gel (60-120 mesh, eluent:ethyl acetate:petroleum ether 1:99) furnished the pure product **55**.

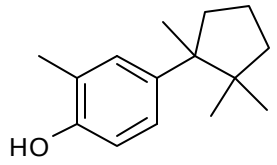
Yield: 98 mg (52%).

MF: $C_{16}H_{24}O$.

^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 0.59 (s, 3H), 1.08 (s, 3H), 1.27 (s, 3H), 1.53-1.86 (m, 5H), 2.25 (s, 3H), 2.43-2.60 (m, 1H), 3.84 (s, 3H) 6.76 (d, 1H, J=7.89 Hz), 7.14 (m, 2H)

^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 16.74 (q), 19.90 (t), 24.46 (q), 24.68 (q), 26.70 (q), 37.14 (t), 39.94 (t), 44.39 (s), 50.08 (s), 55.34 (q), 109.12 (d), 125.29 (d), 129.75 (d), 139.40 (s), 155.73 (s).

27. (±)-β-Herbertenol [5]



5

BBr_3 (1M solution in CH_2Cl_2, 0.251g, ~1mL, 1mmol) was added dropwise to methyl ether 55 (45mg, 0.19 mmol) in dry CH_2Cl_2 (5mL) at -78^0C. The reaction mixture was brought to room temperature and stirred for 30 min. The reaction was monitored by TLC. After completion, the reaction mixture was diluted with CH_2Cl_2 (10mL) and excess of BBr_3 was quenched with saturated $NaHCO_3$ (1mL). The organic layer was washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure to furnish crude (±)-β-Herbertenol. It was purified by column chromatography (SiO_2) (eluent:ethyl acetate:pet. ether 5:95)

Yield: 34mg (81%)

MF: $C_{15}H_{22}O$

MP: 85-86^{0}C (84^0C)[6]

IR (CHCl3) ν_{max} cm-1: 3450 (broad), 3020, 2960, 1610, 1215, 1106, 766, 670.

^{1}H-NMR **($CDCl_3$, 200 MHz) δ:** **0.58 (s, 3H), 1.06 (s, 3H), 1.25 (s, 3H), 1.48-1.52 (m, 1H), 1.56-1.73 (m, 2H), 1.73-1.84 (m, 2H), 2.27 (s, 3H), 2.39-2.53 (m, 1H), 4.75 (bs, 1H), 6.72 (d, 1H, J=7.86 Hz), 7.05 (m, 2H).**

^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 16.29 (q), 20.02 (t), 24.57 (q), 24.84 (q), 26.79 (q), 37.32 (t), 40.13 (t), 44.49 (s), 50.26 (s), 114.29 (d), 122.59 (s), **125.92 (d), 129.98 (d), 140.20 (s), 151.77 (s).**

Mass (m/z): 218 (M+, 24), 161 (52), 148 (100), 135 (48), 121 (23), **91 (21), 77 (22), 55 (27).**

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CHAPTER 2

SECTION I

Condensation of Chloro-fluoro-quinolinecarboxylic acid with piperazine.

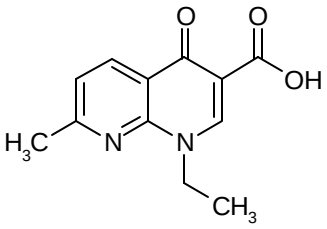
2.1.1 Introduction

The synthetic efforts in the past few years have uncovered a number of highly potent broad-spectrum antibacterial agents, several of which have been introduced into clinical use. Almost all of the recent clinically useful quinolones bear fluorine atom at the C_6 –position of the quinolone, naphthpyridine or benzoaxazine ring system. Because of the presence of the fluorine atom in the molecule, these antibacterial agents are described as fluoroquinolones. The appearance of the third generation of antibacterial fluoroquinolones (based on Nalidixic acid) in early 1980's gave a new impulse and direction for the intense international competition to synthesize more effective agents with broader spectrum activity[1]. Since then, as a result of these efforts, near to a dozen representatives of this class have been synthesized and introduced into human and veterinary therapy for a broad variety of clinical indications. Pharmaceutical research on the fluoroquinolones has made considerable progress in expanding their initial indication of treating urinary tract infection to include systemic infections other than urinary tract infections (UTI).

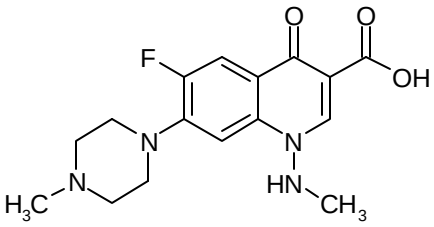
2.1.2 Structure-activity Relationships

The structure-activity relationships of fluoroquinolones have been the subject of extensive review. The antibacterial activity of fluoroquinolones however, is the result of combination of bacterial cell penetration and DNA gyrase inhibitory activity. During various structure activity studies[2], the ethyl group at the position-1 of Nalidixic acid **1** has been replaced by methylamino and cyclopropyl group to give Amifloxacin **2** and Ciprofloxacin **3a**, one of the most clinically successful agents.

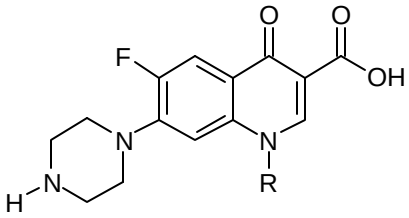
The antibacterial activity of quinolones depends not only on the bicyclic heteroaromatic system combining the 1,4-dihydro-4-pyridine-3-carboxylic acid and an aromatic ring, but also on the nature of the peripheral substituent and their spatial relationship. These substituents exert their influence on the antibacterial activity by providing additional affinity for the bacterial enzyme, enhancing the cell penetration or altering the pharmacokinetics.



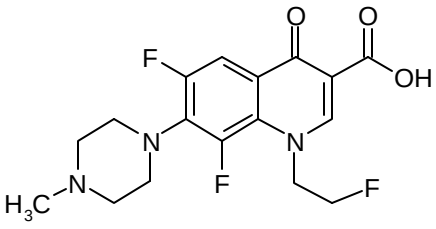
Nalidixic acid **1**



Amifloxacin **2**



3a: R = cyclopropyl; (Ciprofloxacin)
3b: R = ethyl; (Norfloxacin)



Fleroxacin **4**

The most important structural features necessary for meaningful antibacterial activity of new quinolones include a carboxylic acid group attached to the 3-position of the quinoline nucleus and a small alkyl or aryl group at the 1-position. In addition to these, the joint presence of two types of substituents; a fluorine atom attached to the 6-position and nitrogen heterocycle attached to 7-position is also important for the biological activity. This nitrogen heterocycle is often a piperazine or pyrrolidine derivative. It is these two substitutions jointly, which in majority of cases, determine the amplitude of the bactericidal spectrum and the efficacy of the bactericidal activity. These two substituents do not serve any purpose individually[3]. In general, the upper portion of the molecule which includes the C-3 carboxy and C-4 keto moieties, is required for hydrogen bonding interactions with DNA bases in the single stranded regions of duplex DNA created by the action of the enzyme and therefore it is essential. The lower portion of the molecule *i.e.* N-1 and C-8 should be relatively small and lipophilic to enhance the self association.

The fluorine atom at the 6-position provides a significant enhancement in the antibacterial activity for many quinolones presumably by increasing cellular penetration and the inhibitory activity against the enzyme. In case of norfloxacin **3b**, a fluorine at the 6-position provides a compound which is 16-fold more potent against *E.coli* than non-fluorinated derivative[4]. Substituents other than fluorine at the 6-position have provided some enhancement in activity over the 6-H compound, but this has been less than provided by fluorine[5]. In some cases, the effect of the 6-fluorine is much smaller, depending on the group at the 7-position.

The modification of the C-7 position of the quinolone molecule has been extensively investigated. Studies show that substituent changes at the C-7 have a great impact on potency, spectrum, solubility and pharmacokinetics. Norfloxacin **3b** having C-7 piperazinyl group as well as a C-6 fluorine atom has antibacterial potency far superior than the earlier classical quinolones. Antibacterial spectrum includes both Gram-positive and Gram-negative bacteria. Generally speaking, quinolone with small or linear C-7 substituents such as H, Cl, CH_3, $NHCH_2CH_2NH_2$, $NHCH_3$ and $NHNH_2$ possess moderate to weak antibacterial activity. Substituted or unsubstituted 5- or 6- membered heterocycles such as pyrrolidinyl, pyrrolyl, thiomorphonyl, morpholinyl and piperazinyl at the C-7 position produced quinolones with good antibacterial activities. Although, piperazine is a favorable substituent, nonbasic biosteric replacement for the piperazinyl groups yield quinolones with excellent, anti-Gram-positive activity with a slight decrease in anti-Gram-negative activity[6].

An ethyl group at the 1-position was found to be optimum in earlier quinolones compared with a methyl or propyl group at this position and thus based on these steric considerations, it is retained in many subsequent quinolone structures. Other group at the 1-position includes the 2-fluoroethyl substituent in fleroxacin **4** and an aminomethyl group in amifloxacin **2**; these groups all have similar steric requirements. Along with norfloxacin **3b**, these agents offer good Gram-negative activity, particularly active against *E. coli.*

Steric factors, however, are not the only important considerations for groups at the 1-position. Ciprofloxacin **3a** with a cyclopropyl group at the 1-position, when compared with its ethyl analogue, norfloxacin **3b**, offers increased antibacterial potency by 4-8 times against many organisms and approximately 30-fold against *E.coli.* Additionally, ciprofloxacin **3a** has improved *in vitro* potency over norfloxacin **3b**[7]. The increase in activity afforded by the cyclopropyl substituent over that of the ethyl group cannot be explained simply on the steric grounds and it was suggested that, through space, electronic interactions may be important[8]. The 2,4-difluorophenyl group in tosufloxacin and temafloxacin provides these agents with excellent antibacterial activity comparable with that found for ciprofloxacin **3a** and also gives these agents *in vivo* activity superior to that offered by ciprofloxacin **3a**. Quinolones with *tert*. butyl group at the 1-position also compare favorably with the ciprofloxacin[9].

The broad spectrum, potent activity of the new quinolones coupled with their availability as oral and intravenous dosage forms, has made them extremely useful for treating simple, serious and chronic infections. They have been used successfully to treat infections ranging from simple urinary tract infections to endocarditis and osteomylitis.

2.1.3 Synthesis of ciprofloxacin and norfloxacin:A literature survey

Ciprofloxacin, norfloxacin and related fluoroquinolone derivatives are third generation quinolone antibiotics and wide range of research has been carried out including their syntheses and structure-activity relationships.

Ciprofloxacin **3a** is conventionally prepared by the condensation of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid **11** with piperazine in the presence of pyridine[10] or triethylamine[11] as the solvents. Ciprofloxacin is also prepared by making borate or fluoroborate complex of quinoline carboxylic acid and then condensation with piperazine in dimethyl sulfoxide, dimethyl formamide or dimethyl acetamide as the solvent to yield piperazine-quinolone carboxylic acid borate or fluoroborate derivative which on hydrolysis yielded ciprofloxacin[12].

Petersen's approach[13]: (Scheme 1, 1986)

Petersen *et al* synthesized ciprofloxacin by condensing 2,4-dichloro-5-fluorobenzoyl chloride **5** with diethyl malonate **6** and magnesium ethoxide as a base in anhydrous ether to yield diethyl-2,4-dichloro-5-fluorobenzoyl malonate **7**. Partial hydrolysis of the diester followed by decarboxylation with p-TSA furnished ethyl-2,4-dichloro-5-fluorobenzoylacetate **8**. This acetate was treated with ethyl orthoformate followed by nucleophilic replacement of ethoxy group with cyclopropyl amine and cyclization provided 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid **11**. Condensation of this acid with piperazine in DMSO at 135-140^{0}C furnished ciprofloxacin (**scheme 1**).

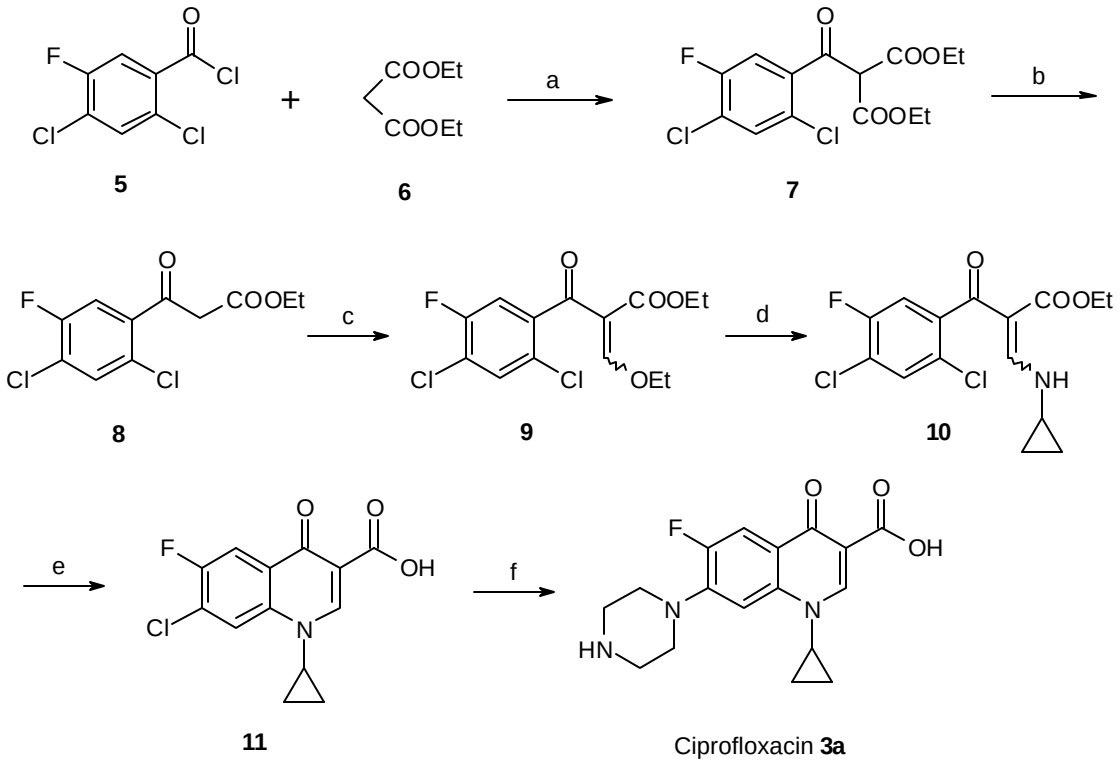
Grohe's approach [14] : (Scheme 2, 1987)

Grohe *et al* synthesized ciprofloxacin by condensation of 2,4-dichloro-5-fluorobenzoyl chloride **5** with methyl-3-cyclopropylamino acrylate **12** to give the methyl-3-cyclopropylamino-2-(2,4-dichloro-5-fluorobenzoyl)acrylate **13**. Cyclization with potassium *tert*-butoxide yielded methyl-1-cyclopropyl-7-chloro-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylate, which upon hydrolysis furnished 1-cyclopropyl-6-fluoro-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid **11**. Condensation of this acid with piperazine yielded ciprofloxacin (**scheme 2**).

Ramage's approach [15]: (Scheme 3, 1998)

In the recent years, solid phase organic synthesis has attracted the chemists worldwide paving its way through combinatorial chemistry. Combinatorial chemistry has recently emerged as a powerful tool for drug discovery.

Scheme1: Petersen's approach, *US patent,* **1986**, 4,563,488



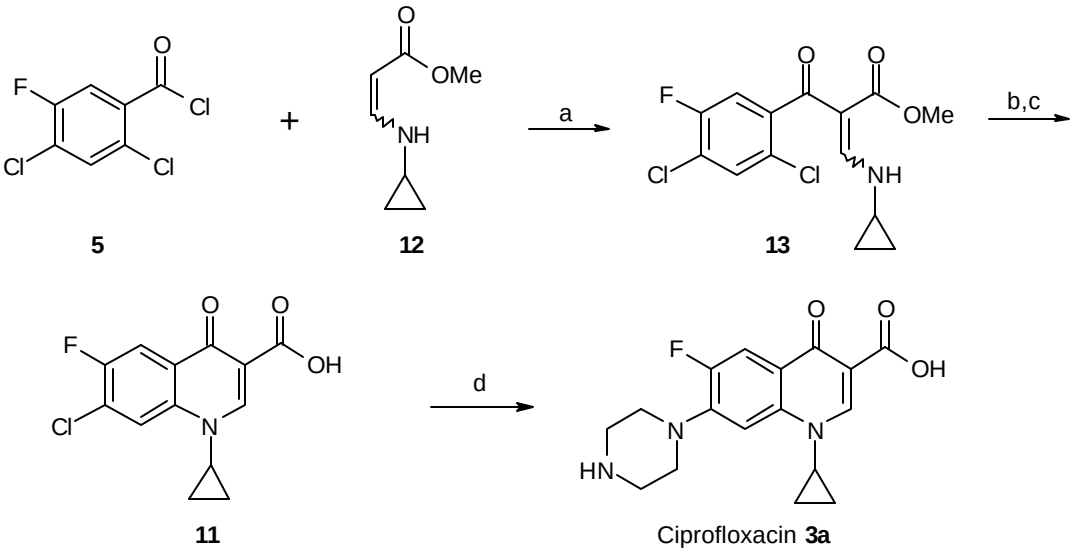
Ciprofloxacin **3a**

Reagents and conditions:

a) $Mg(OEt)_2$, dry Et_2O, 2h b) *p*-TSA/H_2O, 100^0C, 3h c) $(EtO)_3CH$, Ac_2O, 150^0C, 2h

d) Cyclopropyl amine, EtOH, 0^0C e) i. NaH/dioxane, 0^0C-rt, 30 min ii. KOH/H_2O, reflux, 1.5h, f) piperazine, DMSO, 135-140^{0}C, 2h.

Scheme 2: Grohe's approach, *Liebigs Ann. Chem.*, **1987**, 1, 29



5 **12** **13**

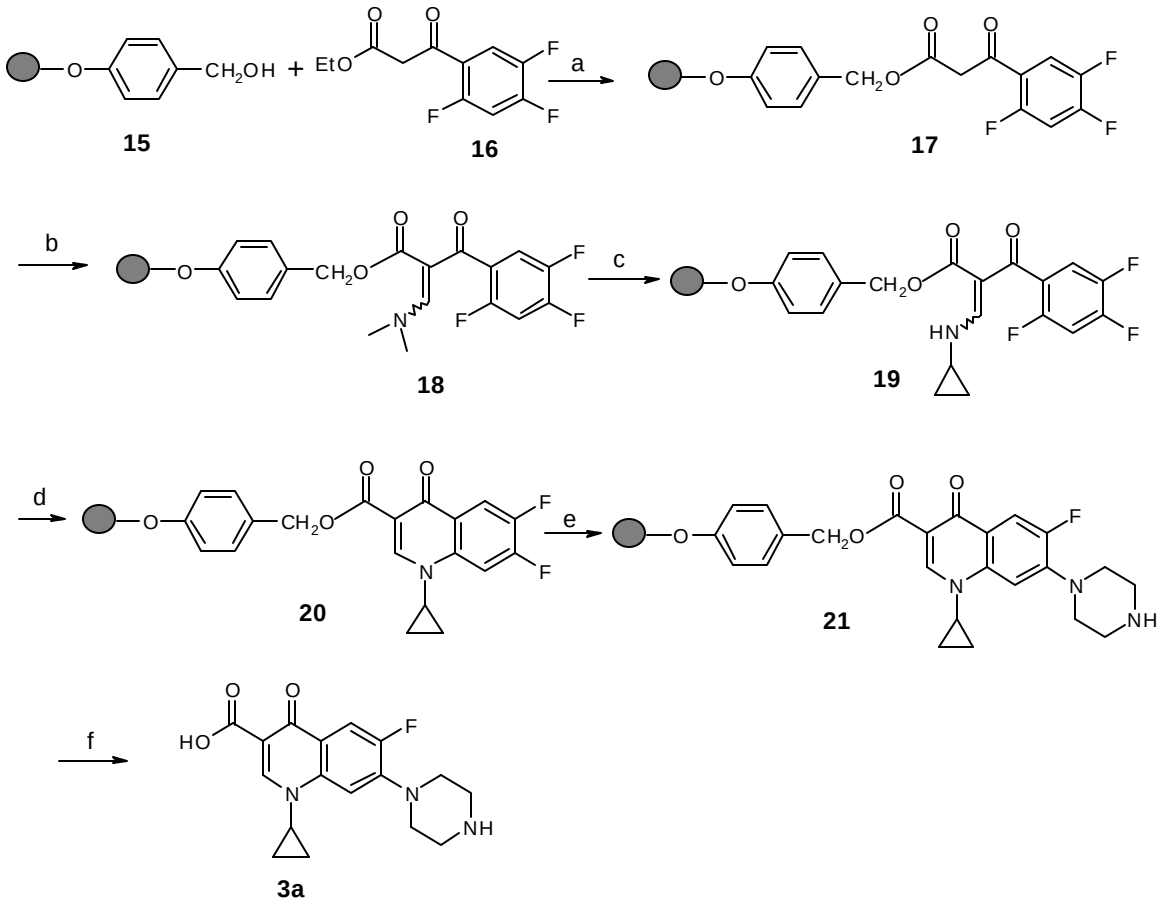
11 Ciprofloxacin **3a**

Reagents and conditions:

a) TEA b) K^{+}*tert*-BuO^{-} c) NaOH d) Piperazine.

Ramage *et al* reported the solid phase organic synthesis of ciprofloxacin using tetrabenzo [a,c,g,i] fluorene as an anchor group. Cleavage of quinolone from the Tbf-anchor group with 90% aqueous TFA in dichloromethane furnished the desired product ciprofloxacin **(scheme 3).**

Scheme 3: Ramage's approach, *Tetrahedron Lett.*, **1998**, 39, 8721



Reagents and conditions:

a) DMAP (cat), toluene, reflux, 40h b) $(CH_3)_2NCH(OCH_3)_2$ (6 equiv), THF, rt, 24h.

c) Cyclopropyl amine (12 equiv.) THF, rt, 20h d) Tetramethylguanidine, THF, reflux, 20h.

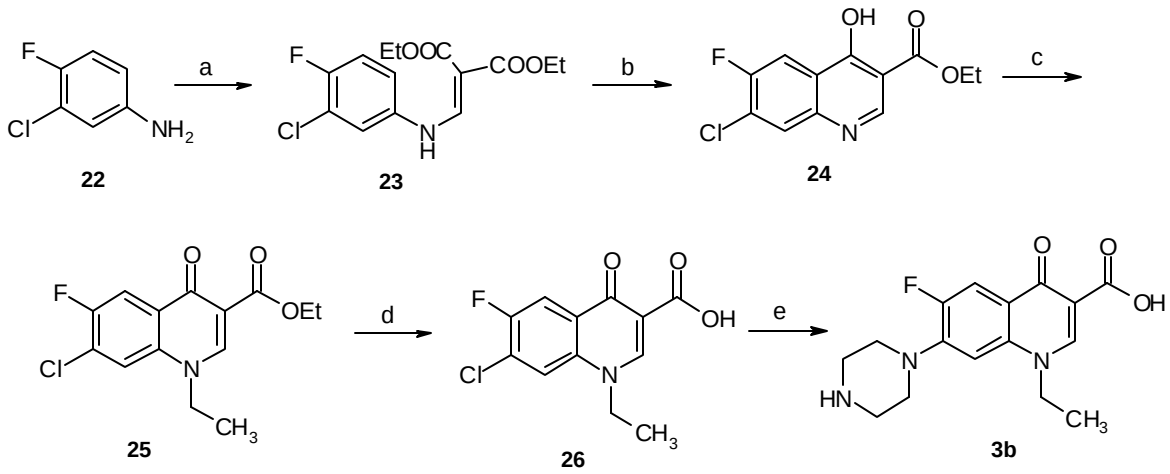
e) Piperazine, pyridine, reflux, 6h. f) 90% aq. TFA, CH_2Cl_2.

Koga's approach for norfloxacin [5]: (Scheme 4, 1980)

The synthesis of norfloxacin reported by Koga *et al* involves the Gould-Jacobs cyclization route by condensation of 3-chloro-4-fluoroaniline with diethylethoxymethylenemalonate followed by thermal cyclisation to give ethyl-4-hydroxy-6-fluoro-7-chloroquinoline-3-carboxylate. Alkylation of this 4-hydroxyquinoline with ethyliodide

and subsequent hydrolysis and displacement of the 7-chloro group with piperazine yielded norfloxacin.

Scheme 4: Koga's approach, *J. Med. Chem.*, **1980**, 23, 1358



Reagents and conditions:

a) Diethyl ethoxymethylenemalonate, 120-130^{0}C, 2h b) Ph_2O, heat, 1h c) DMF/K_2CO_3, EtI, 80-90^{0}C d) 2N NaOH, reflux, 2h. e) piperazine, 130-140^{0}C, 5h.

2.1.4 Present work

This section concerns with the study of reactivity and impurity profile in the condensation of piperazine with chloro-fluoroquinoline carboxylic acid in aqueous medium to yield ciprofloxacin **3a** and norfloxacin **3b**.

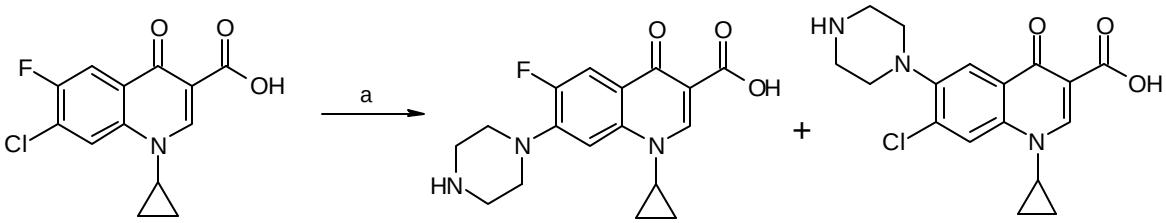
With the current global awareness in developing environmentally friendly technologies and our attention in this direction prompted us to design environmentally benign technology. Hence it was decided to carry out the reaction in non-hazardous solvent. Performing the reaction in water as the reaction medium is the ultimate aim of the organic chemist. This section describes our efforts in this direction.

The literature methods used excess of piperazine (5 equi. of piperazine per equi. of chloro-fluoroquinoline carboxylic acid) and the solvents like DMSO, DMF or DMAC. Piperazine being water soluble, excess piperazine is not recoverable.

In order to study the reactivity of piperazine with chloro-fluoroquinoline carboxylic acid and to avoid the excess of piperazine, solvents which are normally employed (DMF, DMSO, DMAC) in the known processes, the condensation of piperazine with 7-chloro-1-cyclopropyl-6-fluoroquinoline carboxylic acid was studied by varying different parameters such as temperature, time and concentration.

2.1.5 Results and Discussions:

Scheme 5:



11 **3a** **26**

Reagents and conditions:

a) Piperazine, TBAB, H_2O, 150^0C, 50 psi

In order to optimize the quantity of piperazine and to search an alternate solvent for the condensation reaction between piperazine and chloro-fluoroquinoline carboxylic acid, we carried out several experiments.

During the first run, we followed the literature procedure by reducing the quantity of piperazine from 5 to 3.9 equivalents per equivalent of the acid. Thus piperazine (0.106 mol) and the chloro-fluoroquinoline carboxylic acid (0.027 mol) was refluxed in pyridine for 6 h. After work up and purification, ciprofloxacin was obtained in 69% yield. In order to improve the condensation yields, avoid the use of excess of piperazine and the solvent like pyridine, we decided to study the reaction in water by varying reaction time, temperature and concentrations.

During this study, the purity of the product was monitored by HPLC. HPLC was performed by using column Novapak C-18 SS cartridge, mobile phase: acetonitrile : triethylamine phosphate buffer (13:87), UV-278 nm. The insolubility of the starting acid, 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid in mobile phase

made it impossible to check its presence by HPLC in the reaction mixture. Hence the presence of the starting material in the reaction mixture was checked by TLC (Eluent: Dichloromethane:Methanol:Ammonium hydroxide:Acetonitrile 4:4:2:1).

To start with the study, the mixture of piperazine (3.44 g, 0.04 mol) and chloro-fluoroquinoline carboxylic acid (5.36 g, 0.02 mol) in water (30 mL) was heated at 130 ^{0}C for 5h, but the presence of starting material was observed by TLC. Due to the incomplete reaction, we performed an other experiment by taking piperazine (2.5 equiv.) and heating the reaction mixture at 130 ^{0}C. But again the presence of the starting material was observed on TLC. The reason for the incompletion of the reaction might be due to escape of the piperazine along with water at 130 ^{0}C. Therefore we decided to carry out the reaction in autoclave. In order to improve the condensation yield, we thought of using phase transfer catalyst, tetraethyl ammonium bromide. Thus, in a typical experiment, the mixture of piperazine (0.12 mol), chlorofluoro acid (0.06 mol) and tetrabutyl ammonium bromide (2 g) in water (50 mL) was heated in autoclave at 150 ^{0}C autogenous pressure of 50 psi for 5h. The reaction mixture was filtered and the solid obtained was purified by trituration with 10% acetic acid to furnish ciprofloxacin in 65% yield. It was found that piperazine reacts at both positions, at C_6 (replacement of fluorine) and at C_7 (replacement of chlorine). The impurity was present in the filtrate. The filtrate was concentrated and the impurity was purified by preparative HPLC. The impurity was obtained in 8-10% yield. The impurity was found to be 7-chloro-1,4-dihydro-4-oxo-6-(1-piperazinyl)-quinoline carboxylic acid **26,** which was characterized by ^{1}H, ^{13}C and mass spectral analysis.

As the condensation in water gave side product and slightly low yield of the required product, neat condensation of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydroquinoline carboxylic acid (0.03 mol) with piperazine (0.15 mol) in the presence of tetrabutyl ammonium bromide was carried out at 140-145 ^{0}C for 90 min. After the work up and purification, the ciprofloxacin was obtained in 73% yield.

In order to check the generality of the study for other quinolone antibiotics, 7-chloro-6-fluoro-1,4-dihydro-1-ethylquinoline carboxylic acid was treated with piperazine under identical conditions to furnish norfloxacin **3b** in 50% yield. 7-Chloro-1-ethyl-1,4-dihydro-4-oxo-6-(1-piperazinyl)-quinoline-3-carboxylic acid was also obtained as impurity in 12-14% due to replacement of C-6 fluorine[5].

2.1.6 Conclusions

Thus, we have demonstrated that water can be conveniently used as a solvent of choice for the reaction, which is an ultimate aim of organic chemist for condensation reaction without compromising the yield.

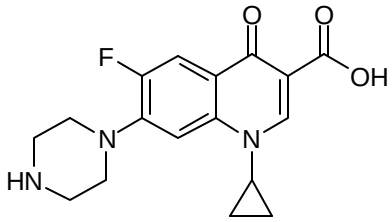
^{1}H-NMR Spectrum (CD_3COOD, 200 MHz) of Compound 3a (Ciprofloxacin)

^{1}H-NMR Spectrum (CD_3COOD, 200 MHz) of Compound 26

^{1}H-NMR Spectrum (CD_3COOD, 200 MHz) of Compound 3b (Norfloxacin)

2.1.7 Experimental

1. 1-Cyclopopyl-6-fluoro-1,4-dihydro-4-oxo-7- (1-piperazinyl)-quinoline-3-carboxylic acid: Ciprofloxacin [3a]



Ciprofloxacin **3a**

Experiment 1

A mixture of 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **11** (16.89g, 0.06mol) and piperazine (15.06g, 0.175mol) in pyridine (50mL) was refluxed for 6h. The completion of the reaction was checked by TLC. Pyridine was removed under vacuum and the residue was treated with water (50mL). The solid thus obtained was filtered and washed with water (2×25mL) to give 6.6 g of product. On drying in vacuum oven at 120 ^{0}C. The purity of the product was determined by HPLC.

Yield: 69%.

HPLC purity: 94%.

M. P.: 254-256^{0}C (**Lit. MP:** 255-257^{0}C, decomposes).

Experiment 2

A mixture of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid **11** (16.89g, 0.06mol), piperazine (10.32g, 0.12mol), phase transfer catalyst: tetrabutylammonium bromide (1.2g) in water (50mL) was heated to 150 ^{0}C at autogeneous pressure, 50 psi in Parr autoclave. The reaction was monitored by TLC. After completion (5h), the reaction mixture was cooled to room temperature, filtered, solid residue was washed with water (2×25mL). The crude product was dried in vacuum oven at 120^{0}C for 3h. The crude product was purified by trituration with 10% acetic acid.

Yield: 65%.

HPLC purity: 94%.

Experiment 3

A mixture of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid **11** (16.89g, 0.06mol), piperazine (25.80g, 0.30mol), and phase transfer catalyst: tetrabutylammonium bromide (1.2g) was heated at 150^0C in Parr autoclave at 50 psi. The reaction was monitored by TLC. After completion of the reaction (5h), water (50mL) was added at 100^0C to it, stirred for 10 min. at 100^0C and then cooled to room temperature, filtered, washed with water (2×25mL) to furnish the crude product. The crude product was purified by trituration with 10% acetic acid.

Yield: 68%.

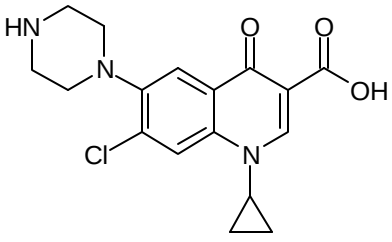
HPLC purity: 94%.

^{1}H NMR (200 MHz, CD_3COOD) δ: 1.24 (m, 2H), 1.50 (m, 2H), 3.65 (s,4H), 3.75 (s, 5H), 7.65 (d, J= 7 Hz, 1H, H-8), 7.92 (d, J= 13 Hz, 1H, H-5), 8.75 (s, 1H).

^{13}C NMR (50 MHz, CD_3COOD) δ: 8.3 (t), 36.77 (d), 44.3 (t), 47.27 (t), 107.3 (d), 112.2 (d), 120.1 (s), 120.3 (s), 140.0 (s), 145.4 (s), 145.6 (s), 149 (d), 169.2 (s), 177.3 (s).

Mass (m/z): 331 (M^+, 31%), 287 (82%), 245 (100%).

2. 1-Cyclopropyl-7-chloro-6-(1-piperazinyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid [26]



26

This compound was obtained during the condensation reaction due to replacement of C-6 fluorine by piperazine as an impurity in 8-13%. It was detected in filtrate of each experiment. It

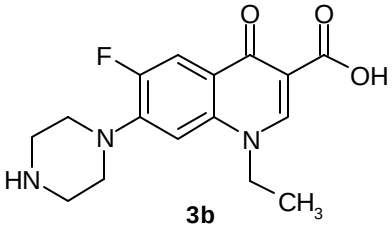
was isolated by concentrating the filtrate and then recrystallization from water. The structure of the impurity was assigned and confirmed by ^{1}H, ^{13}C, mass spectral analysis.

^{1}H NMR: (200 MHz, CD_3COOD) δ: 1.25 (m, 2H), 1.48 (m, 2H), 3.45 (s, 4H), 3.55 (s, 4H), 3.82 (m, 1H), 8.08 (s, 1H), 8.40 (s, 1H), 8.93 (s, 1H).

^{13}C NMR: (50 MHz, CD_3COOD) δ: 8.3 (t), 36.8 (d), 44.88 (t), 48.95 (t), 108.2 (s), 117.2 (d), 121.3 (d), 125.8 (s), 137.8 (s), 139.5 (s), 147.7 (s), 149.5 (d), 169.5 (s), 178.4 (s).

Mass (m/z): 347 (M^+, 7%), 69 (25%), 56 (100%).

3. 1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-quinoline-3-carboxylic acid, Norfloxacin [3b]



3b

A mixture of 7-chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (15.77 g, 0.06 mol), piperazine (10.32 g, 0.12 mol), tetrabutylammonium bromide (1g) in water (50mL) was heated in an autoclave at 150^0C for 5h at 50 psi. The reaction mixture was cooled to room temperature, filtered. The solid residue was washed with water (2×25mL). The product was dried in vacuum oven. The crude product was purified by trituration with 10% acetic acid.

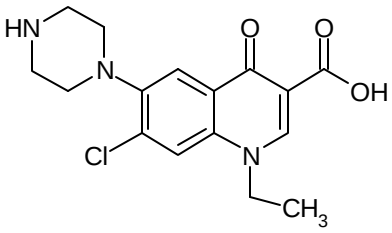
Yield: 50%.

HPLC purity: 94%.

MP: 226 ^{0}C, (Lit. 227-228 ^{0}C).

^{1}H NMR (200 MHz, $CDCL_3$ + CD_3COOD 2:1): δ: 1.78 (t, J = 7 Hz, 3H), 3.76 (m, 2H), 4.12 (m, 2H), 4.88 (q, J = 7 Hz, 2H), 7.50 (d, 1H, J=8 Hz), 8.35 (d, 1H, J=10 Hz), 9.32 (s, 1H).

4. 7-Chloro-1-ethyl-1,4-dihydro-4-oxo-6-(1-piparazinyl)-quinoline-3-carboxylic acid [27].



27

This compound was obtained during condensation of piperazine with 7-chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid as impurity in 12-14% yield. It was isolated by concentrating filtrate and then crystallization from water. The spectral properties of the compound are identical with reported in the literature.

^{1}H NMR: (CF_3COOD, 200 MHz): δ 1.8 (t, 3H, J= 7 Hz), 3.6-3.9 (m, 8H), 4.87 (q, 2H, J =7Hz), 8.29 (s 1H), 8.40 (s, 1H), 9.40 (s, 1H).

2.1.8: References

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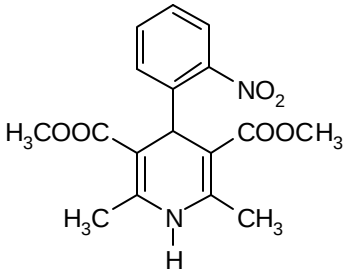
SECTION II

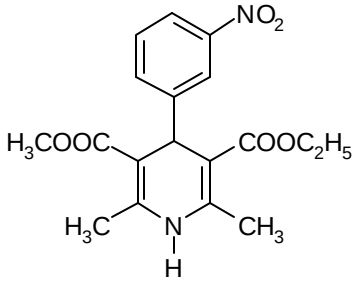
Oxidation of 1,4-Dihydropyridines To Pyridines

2.2.1 Introduction

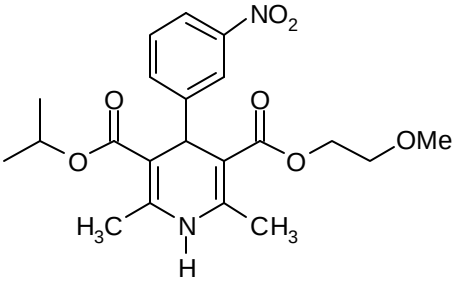
The aryldihydropyridines, first prepared by Hantzsch[1] almost more than 100 years ago. Substantial research activities have been devoted recently to the chemistry & biology of the Hantzsch dihydropyridine derivatives (*e. g.* Hantzsch esters) because of their wide applications in hot areas such as synthesis of substituted pyridines[5], serving as effective redox catalysts under mild conditions, modeling the NAD(P)H coenzyme to study its oxidation mechanism in living system[3] and emerging as highly effective calcium channel antagonist with suitable pharmacological profiles. Hantzsch 1,4-dihydropyridine nucleus is common to numerous bioactive compounds, which include various vasodilator[2a], antihypertensive[2b], bronchodilator[2c], antiatherosclerotic, hepatoprotective, antitumor, antimutagenic, geroprotective and antidiabetic agents. DHPs have found commercial utility as calcium channel blockers, as exemplified by therapeutic agents such as Nifedipine **1**[2d], Nitrendipine **2**[2e], Nimodipine **3**[2f] & Amlodipine **4**.



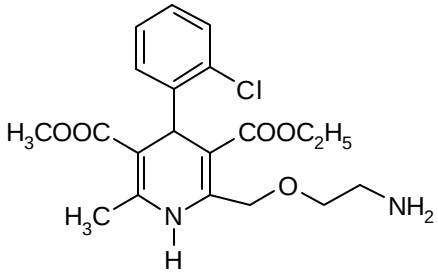
Nifedipine **1**



Nitrendipine **2**



Nimodipine **3**



Amlodipine **4**

In the human body, 1,4-dihydropyridine based drugs are oxidatively converted to the corresponding pyridine derivatives by the action of cytochrome P-450 or other related enzymes in the liver[3a]. These oxidized compounds are largely devoid of the pharmacological activity of

the parent compounds. These metabolites are important as reference standards and hence development of convenient method for their oxidation is important particularly for the synthesis of radiolabled compounds to study their biodegradation. Additionally, dihydropyridines are often produced in synthetic sequence, which have to be oxidized to pyridines; and provide the easiest method to obtain pyridine derivatives.

2.2.2 Literature review

Calcium Antagonist

"Calcium antagonist" are inhibitors of electromechanical coupling which cause a dose – dependent reduction of transmembranal Ca^{2+} influx into the cells of contractile system such that the Ca^{2+}- dependent myofibril-ATPase converts less phosphate bound energy into mechanical work. Accordingly, the oxygen demand of the beating heart and contractile tonus of the coronary and the peripheral resistance vessels are reduced. This mechanism of action results in three different fundamental effects,

a.the direct damping of myocardial workload metabolism

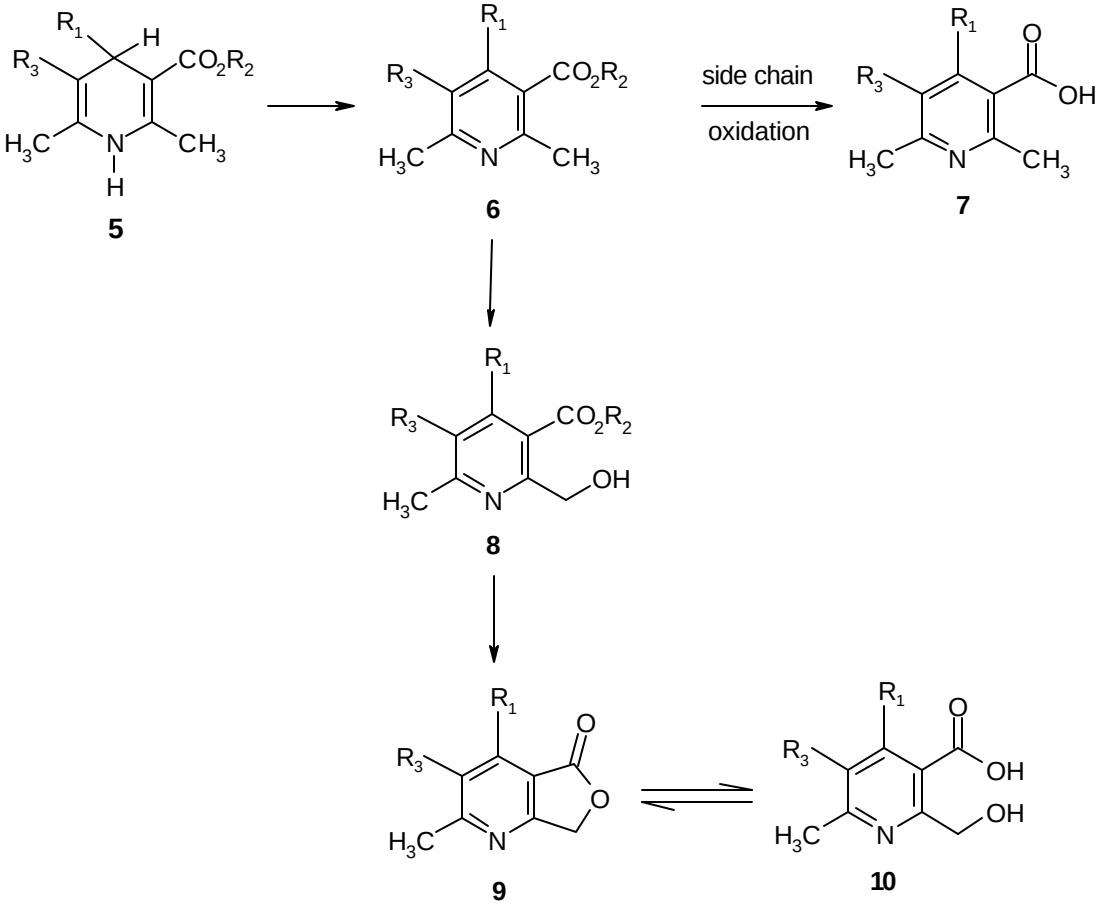
b. an increase in blood supply to the coronary vessels,

c. a reduction in arterial flow resistance.

The vasodilating effect of calcium antagonist find clinical application especially in the treatment of oxygen deficiency of the heart such as angina pectoris [4a,b].

Scheme 1 represents generalized scheme for metabolism of 1,4-dihydropyridine drugs. According to this scheme, P-450 enzymes have been shown to catalyze pyridine formation, methyl hydroxylation (often accompanied by lactone formation involving anchimeric assistance) and various modes of side chain oxidation, including the oxidative cleavage of R_2.

Scheme 1: Generalized scheme for metabolism of 1,4- DHP drugs



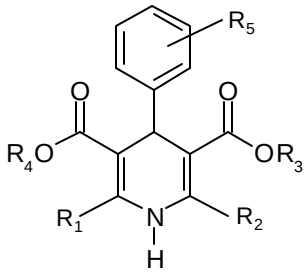
2.2.3 Structure-activity relationships

An optimum in biological activity, (vasodilation, reduction in blood pressure) of 1,4-DHPs is to be expected when the following structural parameters are met;

1. 1,4-DHP unsubstituted at nitrogen.

2. Lower alkyl groups are optimal substituent (R_1 & R_2) in 2, 6 position. Replacement of one alkyl group by amino is tolerated.

3. Carboxylate groups are superior to the other acceptor substituents such as CN, COR, SO_2R, $CONR_2$, NO_2 etc. both in the position 3 & 5. The alcohol component of the ester group can be saturated, unsaturated, straight or branched chain. 1,4-DHPs with non-identical ester



11

groups ($R_3 \neq R_4$) are in many cases superior to the corresponding derivative with identical substitution.

4. A phenyl substituent is superlative in the 4-position, eventhough its replacement by other monocyclic or polycyclic arenes or heteroarenes is possible within limits. Monosubstitution of phenyl ring (R_5) by acceptor substituents such as NO_2, CN, CF_3 etc. in ortho or meta position has positive influence, para-substitution on the other hand causes a marked reduction or even loss of activity.

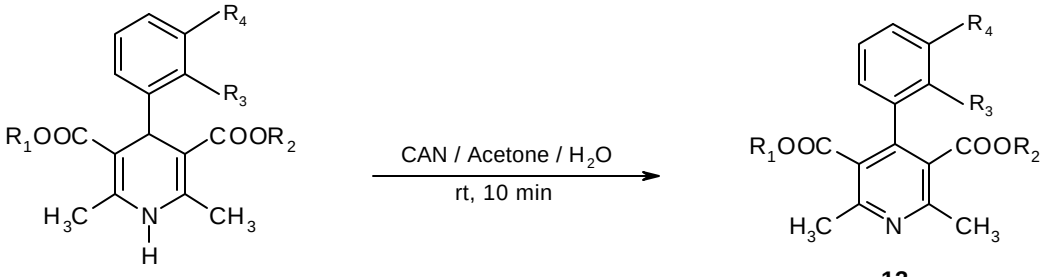
Since 1,4-DHPs constitute an important class of bioactive molecules and also provide the easiest way to pyridine derivatives, newer and improved methods to effect the oxidation of 1,4-DHP systems continued to be investigated.

2.2.4 Literature survey for aromatization of 1,4-DHPs

A vast amount of literature[5] is known on conversion of 1,4-dihydropyridines to the corresponding pyridines. This section is restricted to only few of the recent methods described in the literature.

Pfister *et al*[5a] reported the aromatization of 1,4-DHPs using aqueous solution of ceric ammonium nitrate (CAN, 2 equiv) and acetonitrile as the solvent at room temperature **(scheme 2)**.

Scheme 2[5a]: Pfister *et al.*,*Synthesis*, **1990**, 689.

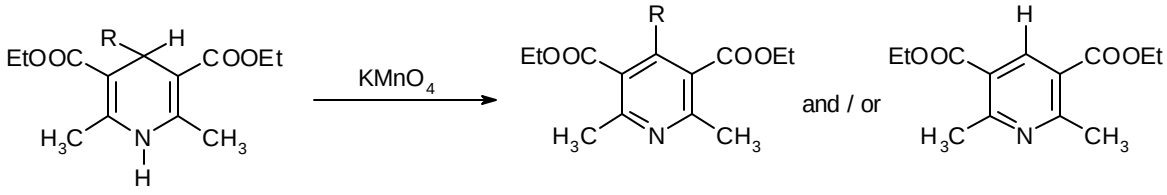


12 **13**

This reaction is general and fast but used expensive reagent like CAN. Secondly, CAN slowly attacks solvents.

Eynede *et al*[5b] reported oxidation of 1,4-DHPs using potassium permanganate either supported on montmorillonite KSF or by using 15-crown-5 as the catalyst to yield **15** and/or **16 (scheme 3)**.

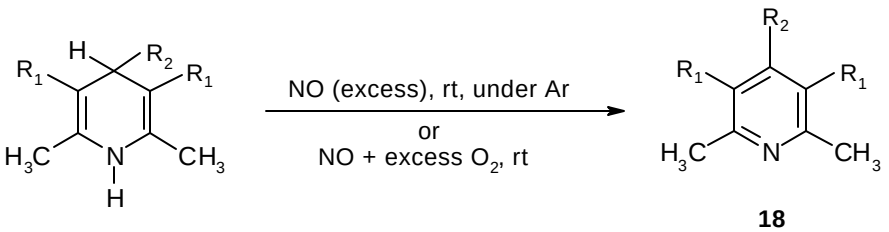
Scheme 3[5b]: Eynede *et al.*, *Tetrahedron*, **1994**, 50, 2479.



14 **15** **16**

Ohasawa *et al*[5c] described oxidation of 1,4-DHPs either in absence or presence of oxygen. Under anaerobic conditions, excess of nitric oxide is required and under aerobic conditions, excess of molecular oxygen is required which oxidizes nitric oxide to NO_2, which eventually oxidizes 1,4-DHPs **(scheme 4)**. The reaction system is although quite simple and easy to perform since the oxidant used is supplied as gas, the ease of availability of gaseous NO makes it less attractive. This reaction lacks generality since NO was used in excess.

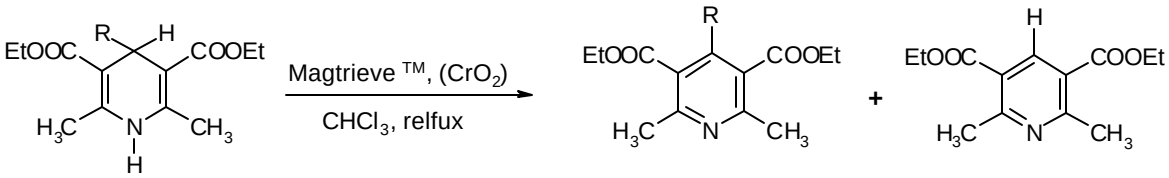
Scheme 4[5c]: Ohasawa *et al, Tetrahedron Lett*., **1995**, 36, 2269.



17 **18**

Recently, Ko *et al*[5d] described oxidation of 1,4-DHPs using magnetically retrievable and safe oxidant Magtrieve in chloroform under reflux **(scheme 5)**.

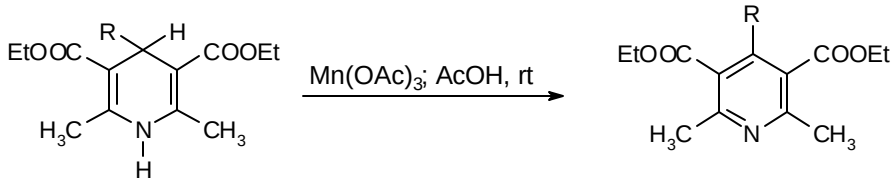
Scheme 5[5d]: Ko *et al., Tetrahedron Lett.,* **1998**, 40, 3207.



19 **20** **21**

Varma *et al*[5e] reported manganese triacetate mediated oxidation of 1,4-DHPs by employing acetic acid as the solvent at room temprature **(scheme 6)**.

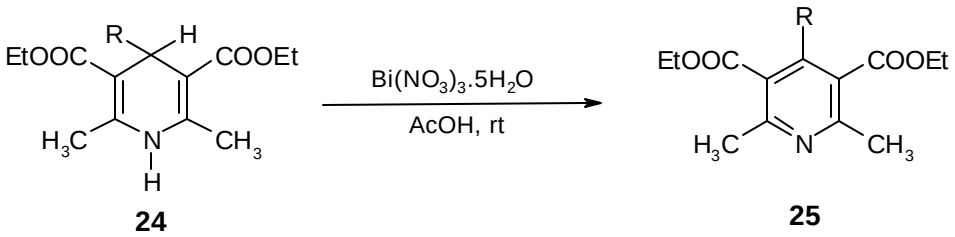
Scheme 6[5e]: Varma *et al., Tetrahedron Lett.*, **1999**, 40, 21.



22 **23**

Mashraqui *et al*[5f] reported the oxidation using easily available $Bi(NO_3)_3.5H_2O$ using acetic acid as the solvent. The reaction is very simple and the reagent used is easily available and economically cheap but the major drawback of the reaction is the ring nitration **(scheme 7).**

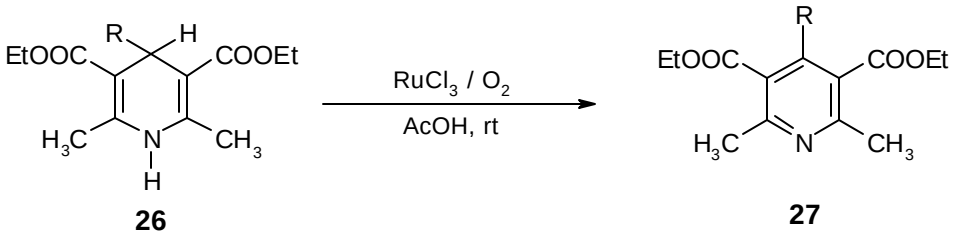
Scheme 7[5f]: Mashraqui *et al Synthesis,* **1998**, 713.



24 **25**

Mashraqui *et al*[5g] reported recently the oxidation of 1,4-DHPs using $RuCl_3$ and molecular oxygen at room temperature using acetic acid as the solvent of choice. But the reaction involved use of costly reagent $RuCl_3$ **(scheme 8)**. Yields are poor to quantitative depending on the substrate DHP.

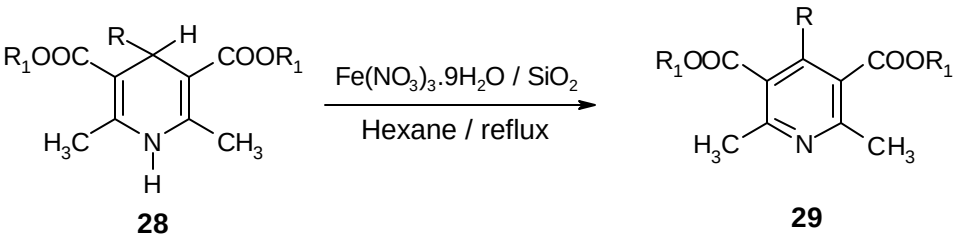
Scheme 8[5g]: Mashraqui *et al, Tetrahedron Lett*. **1998**, 39, 4895.



26 **27**

Khadilkar *et al*[5h] utilized ferric nitrate supported on silica gel for the aromatization of 1,4-DHPs in refluxing hexane **(scheme 9)**.

Scheme 9[5h]: Khadilkar *et al., Synth. Commun.* **1998**, 28,207.



28 **29**

2.2.5 Present Work

From the literature review,[5] it is evident that the oxidation of 1,4-dihydropyridines to the corresponding pyridine derivatives is well documented. However, many of the reported oxidation procedures either suffer from strong oxidants (HNO_3,[3a] CrO_3,[5k] $KMnO_4$,[5b]), require severe conditions (S[5p] and Pd/C dehydrogenations[5q]), need excess of oxidants (CAN,[5a] PCC[5l]) or cumbersome workup procedure.[5f,g]

In view of the above limitations, we decided to develop a practical, mild and general approach for this oxidative transformation. The present section deals with the development of simple, practical and mild strategies for the aromatization of 1,4-dihydropyridines to the corresponding pyridine derivatives. This section was further divided into two parts: **part A** describes the protocol using 70% aqueous *tert*-butylhydroperoxide, **part B** describes the protocol using molecular oxygen & Co-naphthenate as the catalyst.

Part A *Aromatization of 1,4-DHPs with tert-Butyl hydroperoxide*

tert- Butyl hydroperoxide is well known oxidizing agent to effect various oxidative transformations. It is used for oxidation of various substrates to give epoxides, ketones, aldehydes, carboxylic acid esters, nitro or azoxy compounds. It is widely used in combination with different metal catalysts for the epoxidation of alkenes[6]. In the presence of $Ti(O\text{-}iPr)_4$ and (+) or (–)- dialkyl tartarate, allylic alcohols undergo enantioselective Sharpless epoxidation[7].

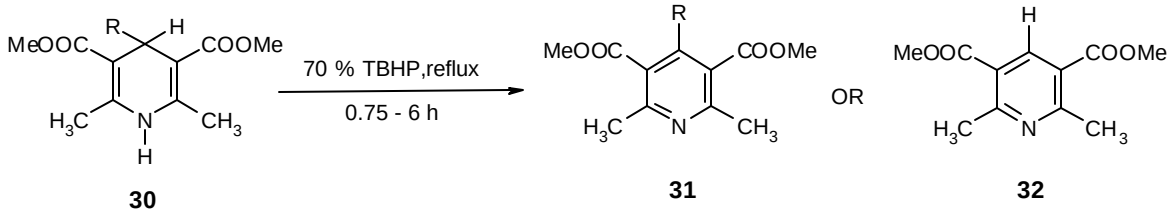
Because of our current interest in oxidation processes using aqueous *tert*-butyl hydroperoxide in our laboratory and development of environmentally benign technologies with a special emphasis on performing the reactions in aqueous medium[8], we planned to study the conversion of 1,4-dihydropyridines to the corresponding pyridine derivatives employing 70% aqueous *tert*-butyl hydroperoxide.

2.2.6.1 Results and Discussions

A variety of 1,4-DHPs were treated with 70% TBHP at 100^0C under reflux to give the corresponding pyridine derivatives in good to excellent yields. In a typical experiment as shown in **scheme 10**, a mixture of 1,4-dihydro-2,6-dimethyl-4-phenyl-3,5-pyridinedicarboxylic acid, dimethyl ester (**30e**, 0.420 g, 1.4 mmol) and 70% TBHP (1mL, 7.7 mmol) was refluxed at 100^0C

for 3h. The product formed was extracted with ethyl acetate. The crude product was purified either by column chromatography or crystallization.

Scheme 10:



30 **31** **32**

The product thus formed was characterized by IR, ^{1}H &^{13}C NMR and mass spectroscopy. In ^{1}H NMR, the disappearance of the singlet at δ = 5.0 – 5.3 (DHP CH-4) was diagnostic of the oxidation.

In order to prove the generality of the above protocol, a variety of DHPs were subjected to aromatization with 70% TBHP. The results have been summarized in the table 1.

Table 1:

Entry	R	1,4-DHP	Product	Time (hr)	Yield %	MP (Lit. MP) ^{0}C
1	-H	30a	32	0.75	88	100 (101)
2	- CH_2CH_3	30b	32	0.75	87	100 (101)
3	- $CH_2CH_2CH_3$	30c	32	0.75	85	100 (101)
4	- $CH(CH_3)_2$	30d	32	0.75	86	100 (101)
5	C_6H_5-	30e	31a	3.00	77	137 (135-6)
6	4'- OCH_3-C_6H_4-	30f	31b	2.00	77	115
7	4'-Cl-C_6H_4-	30g	31c	3.50	75	137-139
8	2'-Cl-C_6H_4-	30h	31d	3.00	75	70
9	4'-NO_2-C_6H_4-	30i	31e	6.00	75	148
10	2'-NO_2-C_6H_4-	30j	31f	5.00	73	104-5 (106)

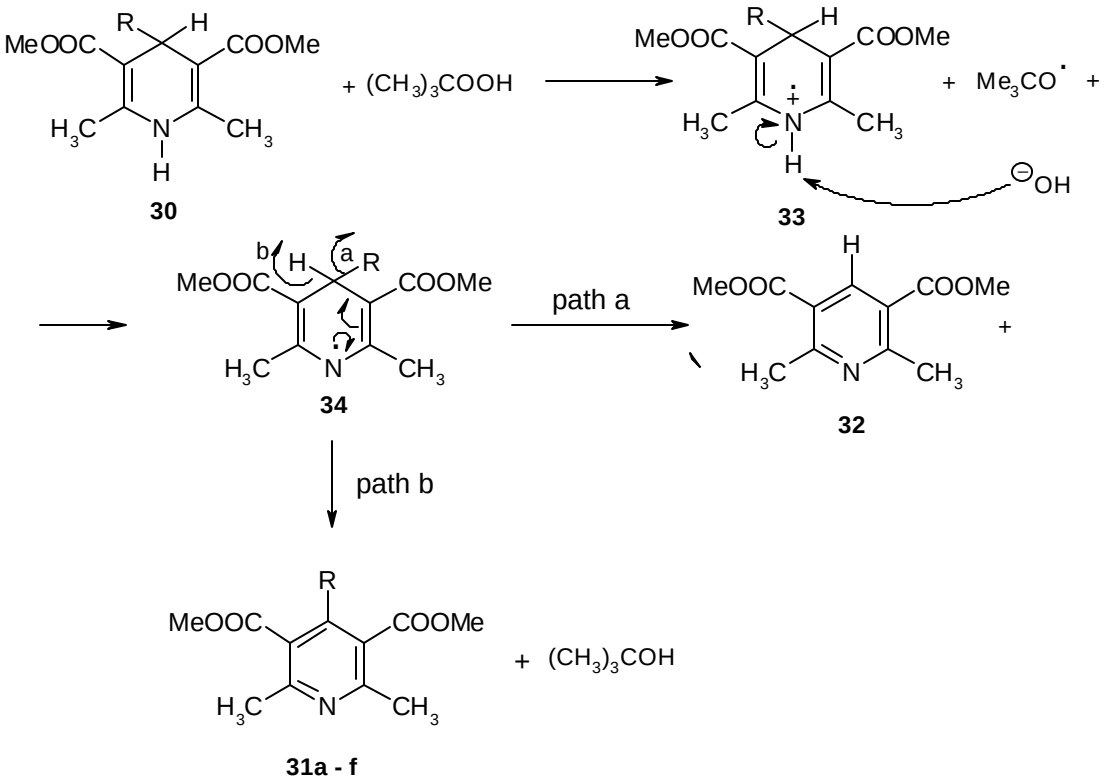
2.2.7.1 Conclusions

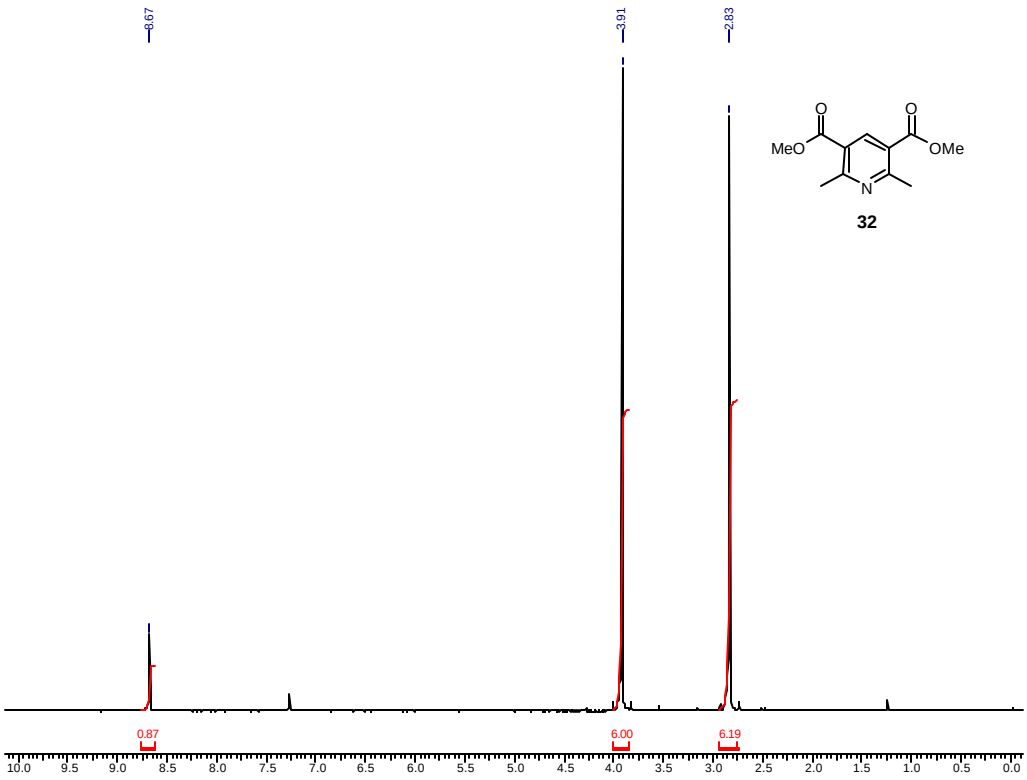
1. Aqueous *tert*- butylhydroperoxide has been used effectively to aromatize 1,4-dihydropyridines.
2. A variety of 1,4-DHPs have been aromatized in good to excellent yield.
3. A very simple, mild and convenient protocol for the aromatization of 1,4-DHPs has been developed.
4. A general protocol for obtaining differently substituted pyridine derivatives has been established.
5. The reaction has been carried out in aqueous medium. Thus developed environmentally benign technology leading towards "Green Chemistry".
6. Aqueous *tert*-butyl hydroperoxide is cheap and readily available.

2.2.8.1 Proposed Mechanism

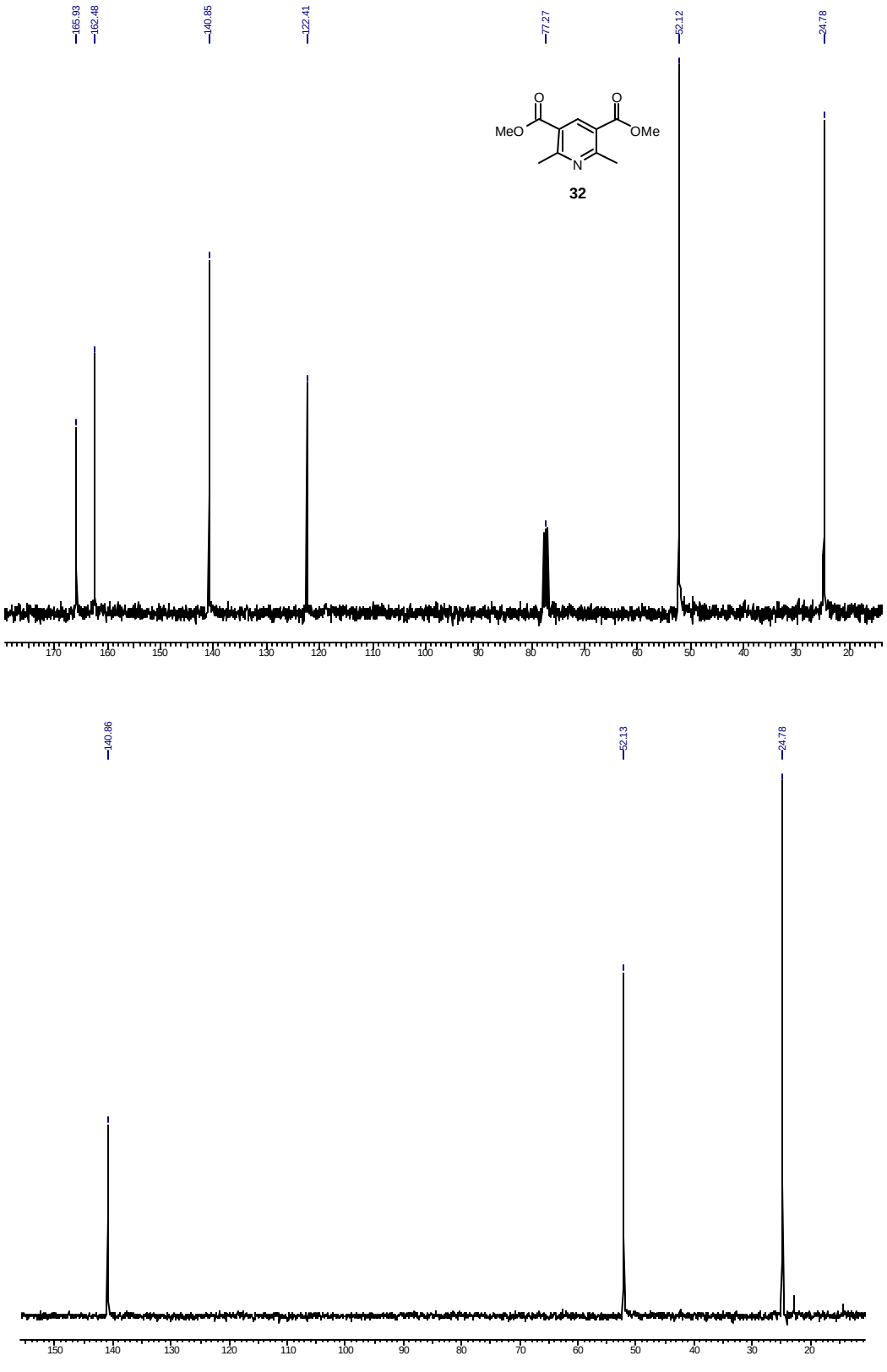
From the chemists' point of view, it is evident from the **scheme 10** that the key steps of this biologically related transformation must involve sequential cleavage of the N-H and C-H bonds of the central DHP nucleus. From this point of view, we propose probable mechanism for aromatization of DHPs. During aromatization of various DHPs, we propose that *tert*-butyl hydroperoxide undergoes homolytic cleavage to produce *tert*-butyloxy radical and hydroxy radical. One electron transfer from 1,4-DHP nucleus gives rise to radical cation in DHP nucleus leading to formation of **33** and hydroxyl anion. This hydroxyl anion picks up the proton from radical cation generating radical in DHP nucleus **34** and in turn lead to formation of water molecule. DHP radical **34** undergoes aromatization in two different paths as shown in the **scheme 11**. Path a leads to dealkylated product **32** and path b gives rise to product **31**.

Scheme 11:

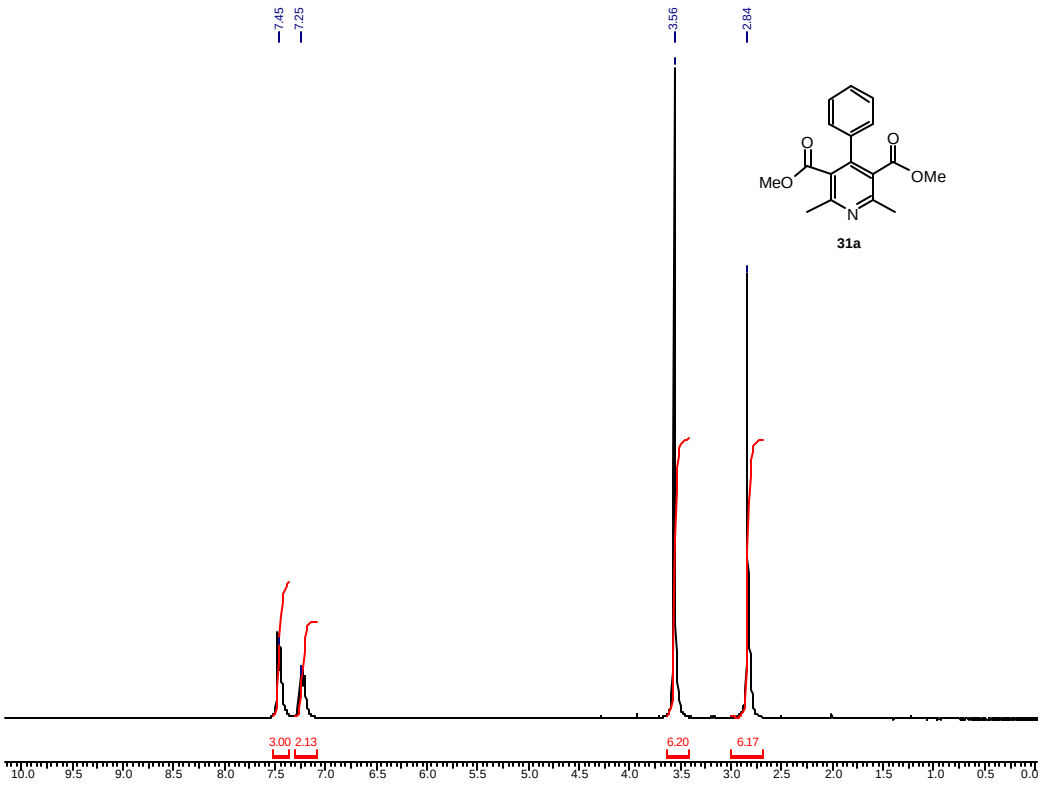

MeOOC
R
H
COOMe
H3C
N
CH3
H
+ (CH3)3COOH
+ Me3CO· +
OH
30
33
b
a
path a
34
32
path b
31a - f
+ (CH3)3COH



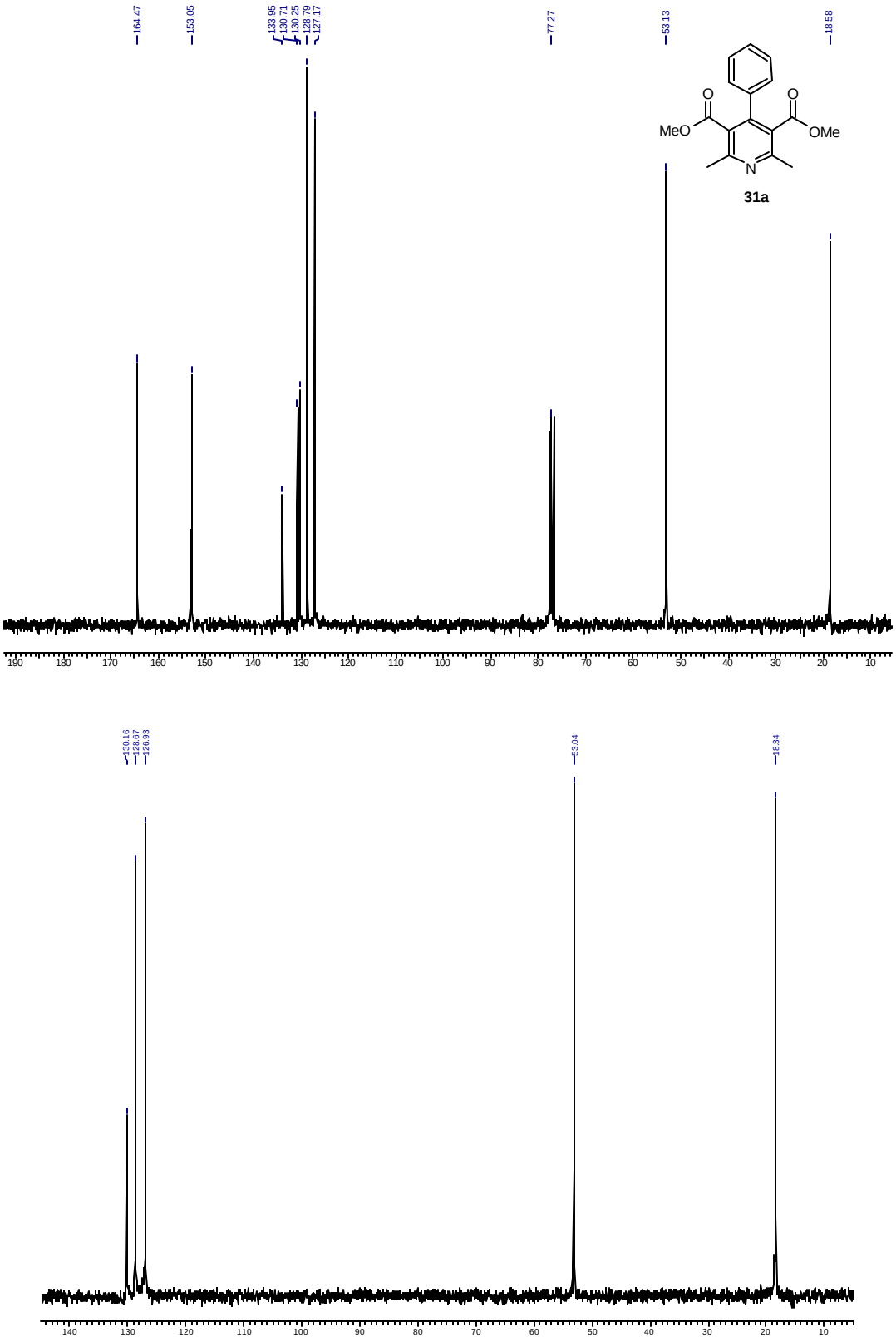
^{1}H-NMR Spectrum ($CDCl_3$, 200 MHz) of Compound 32



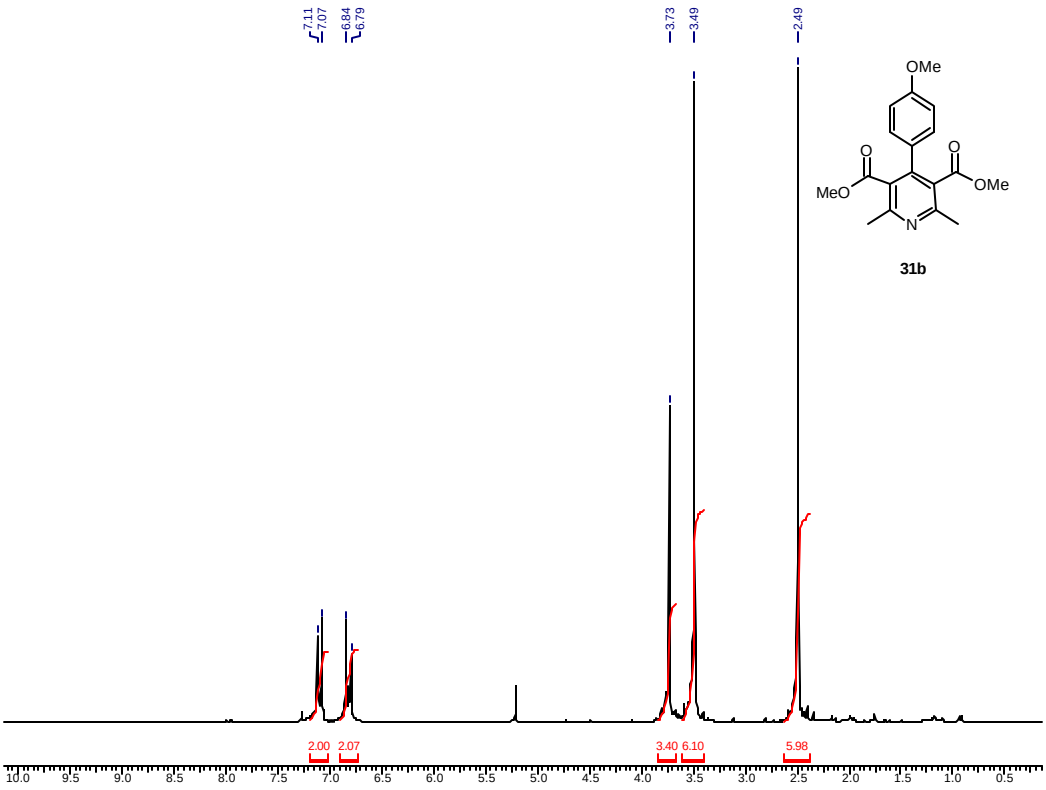
^{13}C-NMR and DEPT ($CDCl_3$, 50 MHz) of Compound 32



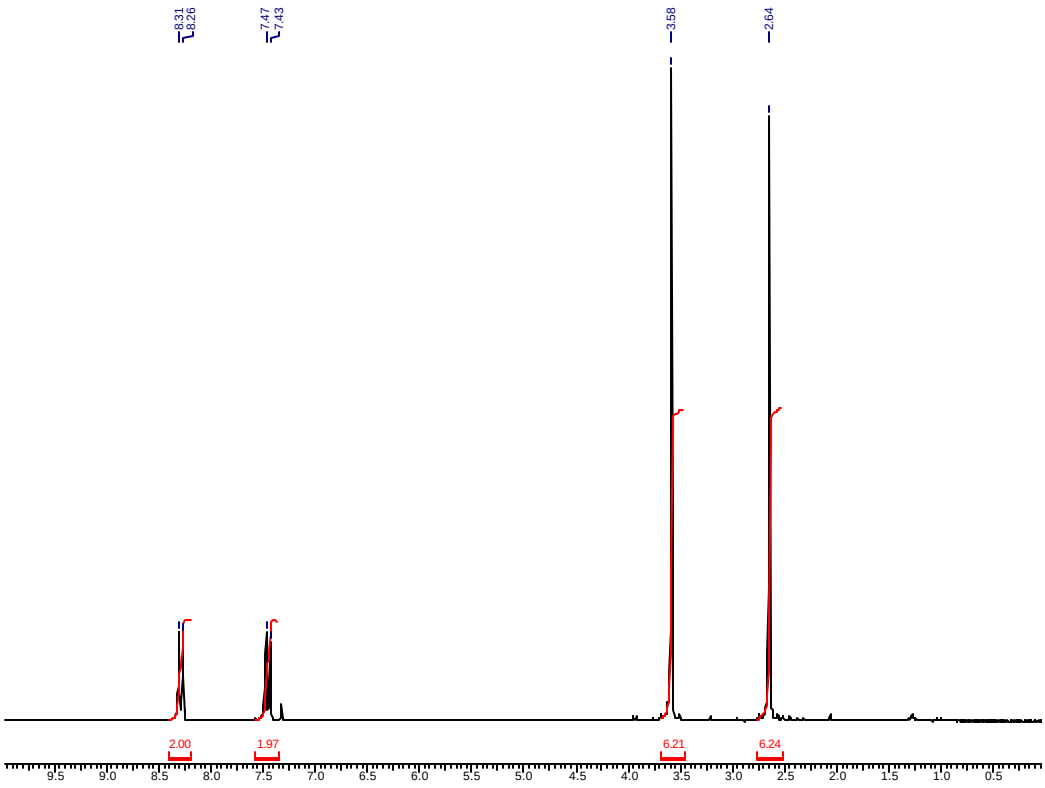
^{1}H-NMR Spectrum ($CDCl_3$, 200 MHz) of Compound 31a



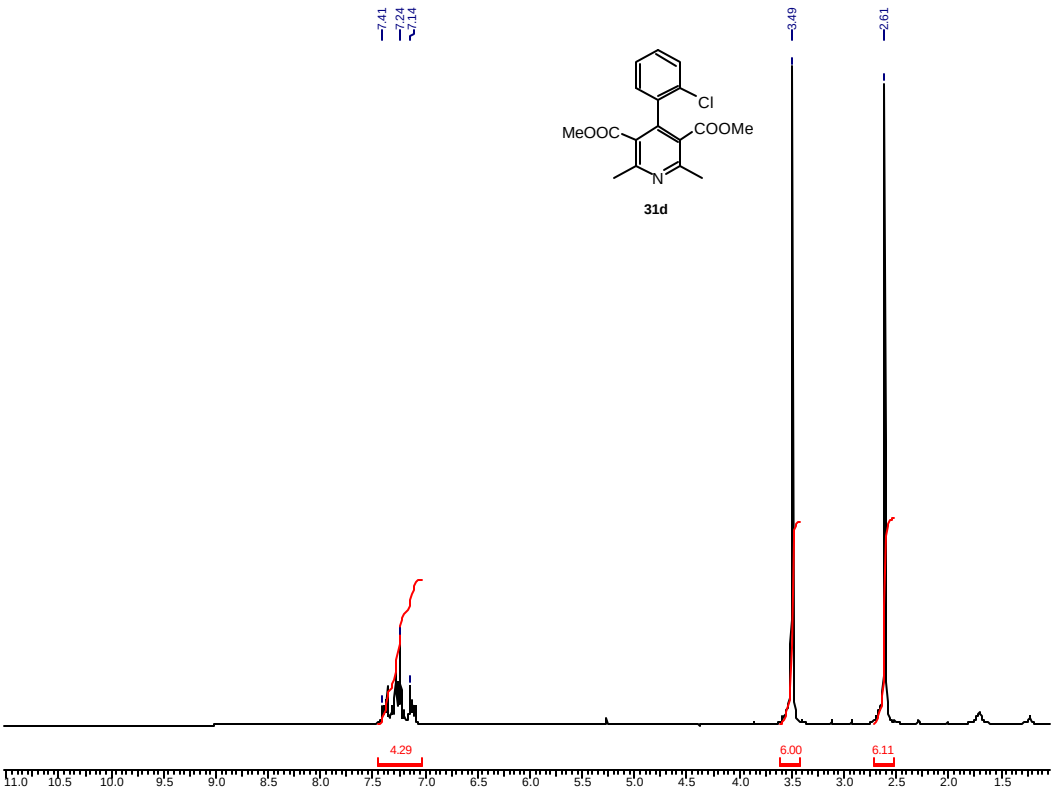
^{13}C-NMR and DEPT ($CDCl_3$, 50 MHz) of Compound 31a



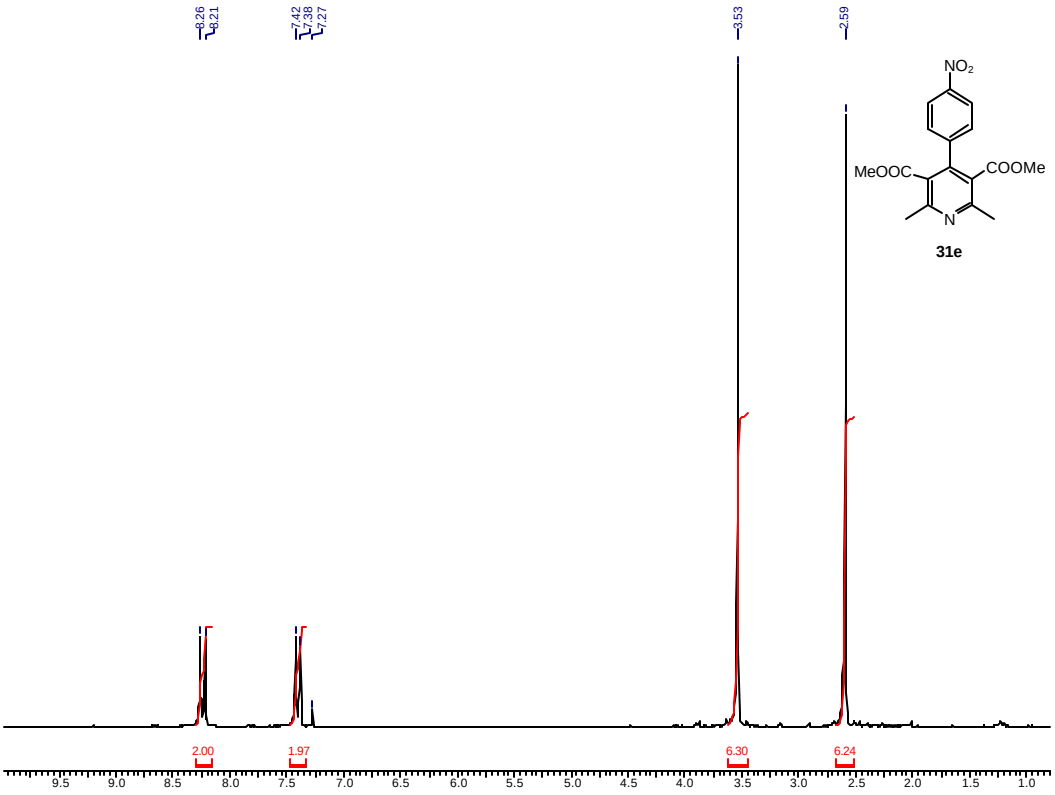
^{1}H-NMR Spectrum ($CDCl_3$, 200 MHz) of Compound 31b



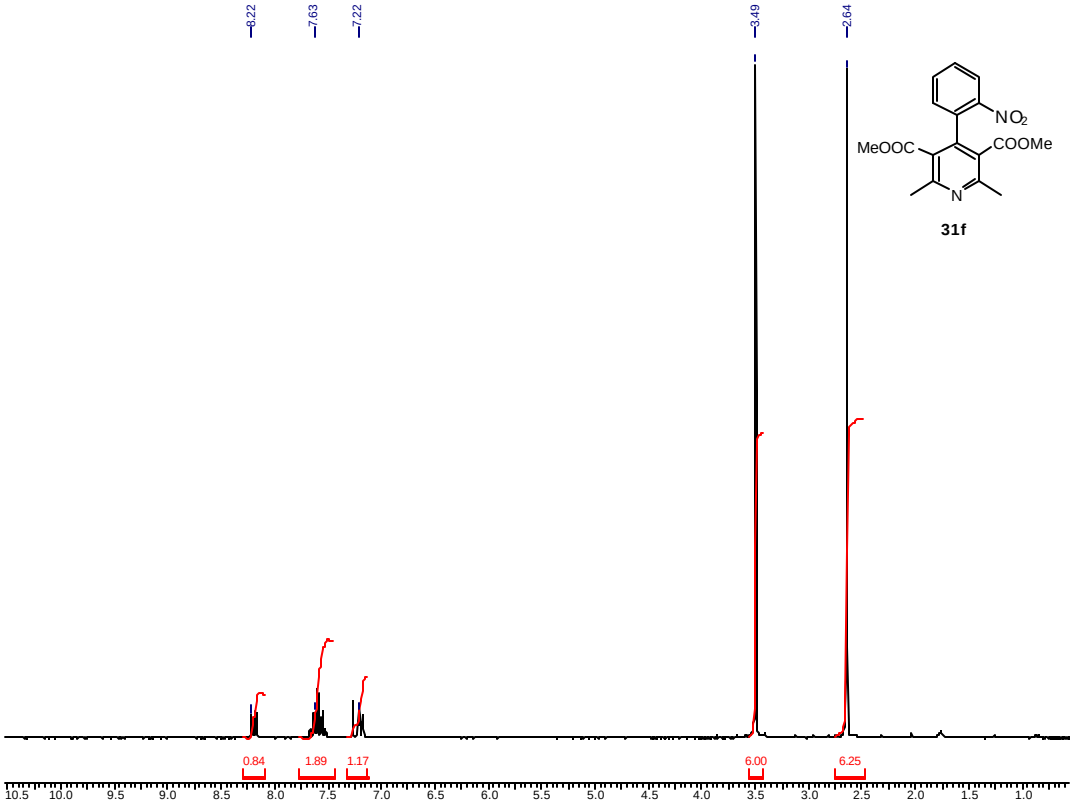
^{1}H-NMR Spectrum ($CDCl_3$, 200 MHz) of Compound 31c



^{1}H-NMR Spectrum ($CDCl_3$, 200 MHz) of Compound 31d



^{1}H-NMR Spectrum ($CDCl_3$, 200 MHz) of Compound 31e



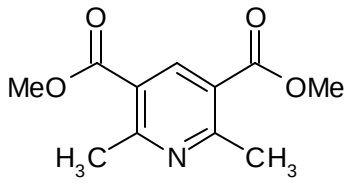
^{1}H-NMR Spectrum ($CDCl_3$, 200 MHz) of Compound 31f

2.2.9.1: Experimental

General Procedure

A mixture of 4-substituted 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester (1.4mmol) and 70 % *tert*-butylhydroperoxide (7.7mmol) was refluxed. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and then diluted with ethyl acetate (10mL). The organic layer was washed with saturated ammonium chloride (3×4mL) solution. The organic layer dried on anhydrous sodium sulphate and concentrated in vacuum. The product was purified by column chromatography (eluent: 20:80 ethyl acetate:pet ether), to furnish the oxidized pyridines.

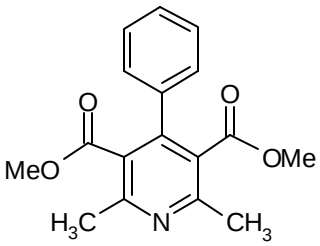
1. 2,6-Dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester [32]



32

Mol. Formula:	$C_{11}H_{13}NO_4$.
Yield:	88%.
MP (Lit MP):	100^0C (101^0C).
IR ($CHCl_3$) cm^{-1} :	3040, 1725, 1410, 1390, 1220, 1110, 750.
^{1}H NMR (200 MHz, $CDCl_3$) δ:	2.83 (s, 6H); 3.91 (s, 6H); 8.67 (s, 1H).
^{13}C NMR (50 MHz, $CDCl_3$) δ:	24.08 (q); 51.42 (q); 121.71 (s); 140.14 (d); 161.78 (s); 165.23 (s).
Mass (m/z):	223 (M^+, 61), 192 (78), 164 (28), 149 (13), 120 (14), 104 (17), 91 (21), 57 (100).

2. 2,6-Dimethyl-4-phenyl-3,5-pyridinedicarboxylic acid, dimethyl ester [31a]



31a

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

Yield: 77%.

MP (Lit MP): 136-138^{0}C (135-136^{0}C).

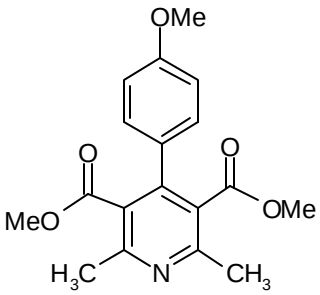
IR ($CHCl_3$) cm^{-1}: 3040, 1740, 1640, 1600, 1410, 1250, 1200, 760.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.84 (s, 6H); 3.56 (s, 6H); 7.22 (m, 2H); 7.47 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 18.31 (q); 52.86 (q); 126.96 (d); 128.62 (d); 129.98 (d); 130.44 (s); 133.67 (s); 152.78 (s); 153.09 (s); 164.19 (s).

Mass (m/z): 299 (M^+, 92), 284 (7), 268 (52), 236 (100), 224 (15), 208 (22), 180 (23), 153 (23), 139 (39), 115 (21), 91 (18),

3. 2,6-Dimethyl-4-(4-methoxyphenyl)-3,5-pyridinedicarboxylic acid, dimethyl ester [31b]



31b

Mol. Formula: $C_{18}H_{19}NO_5$.

Yield: 77%.

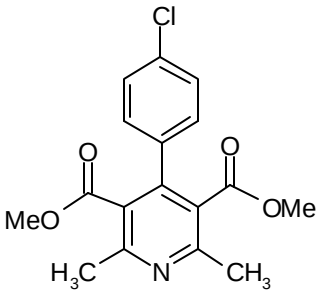
MP: 115^{0}C.

IR ($CHCl_3$) cm^{-1}: 3040, 1730, 1370, 1220, 760.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.55 (s, 6H); 3.55 (s, 6H); 3.81 (s,3H); 6.90 (d, 2H, J=10

	Hz); 7.17 (d, 2H, J = 8 Hz).
^{13}C NMR (50 MHz, $CDCl_3$) δ	22.40 (q), 51.77 (q), 54.68 (q), 96.91 (s), 113.27 (d), 127.26 (s), 129.23 (s), 130.13 (d), 146.18 (s), 155.98 (s), 161.12 (s).
Mass (m/z):	329 (M^+, 100), 298 (18), 267 (74), 266 (76), 254 (12), 238 (14), 212 (11), 195 (9), 168 (11), 149 (21), 135 (23), 99 (26), 77 (22), 57 (24).

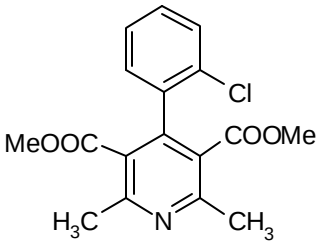
4. 2,6-Dimethyl-4-(4-chlorophenyl)-3,5-pyridinedicarboxylic acid dimethyl ester [31c]



31c

Mol. Formula:	$C_{17}H_{16}ClNO_4$.
Yield:	75%.
MP:	137-139^{0}C.
IR ($CHCl_3$) cm^{-1}:	3040, 1730, 1370, 1220, 760.
^{1}H NMR (200 MHz, $CDCl_3$) δ:	2.59 (s, 6H); 3.56 (s, 6H); 6.90 (d, 2H, J = 10 Hz); 7.17 (d, 2H, J = 8 Hz).
^{13}C NMR (50 MHz, $CDCl_3$) δ:	22.79 (q), 51.92 (q), 122.99 (d), 126.09 (s), 128.52 (d), 142.82 (s), 143.92 (s), 147.02 (s), 154.92 (s), 167.87 (s)
Mass (m/z):	299 [$(M\text{-}Cl)^+$+1, 33], 298 (M^+- Cl 100), 282 (3), 252 (7), 251(7), 224 (7), 223 (7), 180 (5), 152 (6), 127 (7), 77 (7).

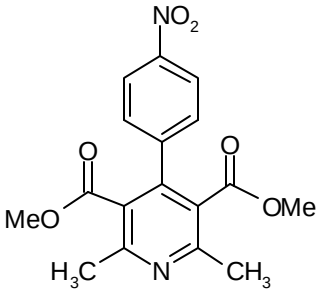
5. 2,6-Dimethyl-4-(2-chlorophenyl)-3,5-pyridinedicarboxylic acid, dimethyl ester [31d]



31d

Mol. Formula:	$C_{17}H_{16}ClNO_4$.
Yield:	75%.
MP (Lit. MP)	69-70^{0}C (69-71^{0}C).
IR ($CHCl_3$) cm^{-1} :	3040, 1725, 1560, 1380, 1220, 1110, 1050, 760.
^{1}H NMR (200 MHz, $CDCl_3$) δ:	2.55 (s, 6H); 3.43 (s, 6H); 7.08 (m, 1H); 7.18 (m, 2H); 7.32 (m, 1H).
^{13}C NMR (50 MHz, $CDCl_3$) δ:	23.69 (q), 52.26 (q), 126.48 (d), 126.77 (s), 129.38 (d), 130.1 (d), 130.34 (d), 133.02 (s), 135.92 (s), 145.00 (s), 156.83 (s), 167.71 (s).
Mass (m/z) :	299, [(M-Cl)$^+$+1, 33], 298 (M$^+$- Cl 100), 266 (3), 224 (2), 196 (3), 152 (4), 139 (5), 59 (7).

6. 2,6-Dimethyl-4-(4-nitrophenyl)-3,5-pyridinedicarboxylic acid, dimethyl ester [31e]

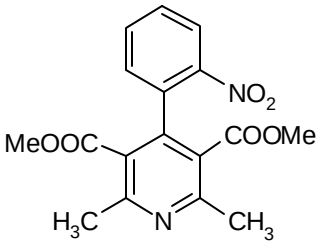


31e

Mol. Formula:	$C_{17}H_{16}N_2O_6$.
Yield:	75 %.
MP.	148^{0}C.

IR ($CHCl_3$) cm^{-1}:	3040, 1730, 1380, 1200, 750.
^{1}H NMR (200 MHz, $CDCl_3$) δ:	2.59 (s, 6H); 3.53 (s, 6H); 7.42 (d, 2H, J = 8 Hz); 8.26 (d, 2H, J = 10 Hz).
13C NMR (50 MHz, $CDCl_3$) δ:	22.77 (q), 52.10 (q), 123.01 (d), 125.82 (s), 128.74 (d), 143.01 (s), 144.06 (s), 148.00 (s), 155.62 (s), 168.23 (s).
Mass(m/z):	344 (M^+, 79), 313 (100), 297 (32), 280 (32), 267 (18), 236 (20), 209 (21), 181 (19), 140 (31), 77 (30), 59 (88).

7. 2,6-Dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylic acid, dimethyl ester [31f]



31f

Mol. Formula:	$C_{17}H_{16}N_2O_6$.
Yield:	73%.
MP (Lit. MP):	105^0C (106^0C).
IR ($CHCl_3$) cm^{-1}:	3040, 1705, 1530, 1290, 1150, 1110, 750.
^{1}H NMR (200 MHz, $CDCl_3$) δ:	2.64 (s, 6H); 3.50 (s, 6H); 7.21 (d, 1H, J=8Hz); 7.60 (m, 2H); 8.17 (d, 1H, J =10Hz).
^{13}C NMR (50 MHz, $CDCl_3$) δ:	22.24 (q), 50.86 (q), 125.08 (d), 125.37 (s), 127.98 (s), 128.61 (d), 128.94 (d), 132.00 (s), 134.96 (s), 145.98 (s), 155.82 (s), 166.92 (s).
Mass (m/z):	344 (M^+, 68), 313 (100), 297 (28), 280 (28), 267 (18), 236 (20), 209 (16), 181 (14), 139 (36), 77 (22), 59 (36).

Part B: Autooxidation of 1,4-DHPs to Pyridines.

Metal catalysis for the oxidation of various organic substrates is of synthetic as well as of biological interest[9]. Currently, there is an ongoing interest in developing catalytic oxidation methods using metals in their higher oxidation states [*e. g.* Co(III), Mn (III), Ce (IV), Ru (III)] along with a suitable co-oxidant to reoxidise the reduced metal species[9a,10].

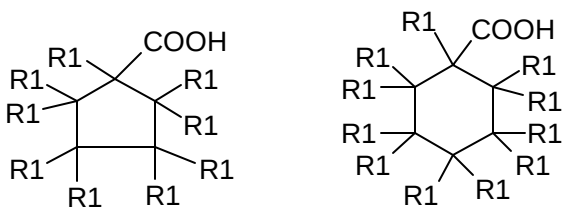
Activation of oxygen catalyzed by metals to effect a variety of organic transformations is a subject of topical interest[11]. Molecular oxygen when activated under appropriate conditions is one of the most versatile reactive species known to organic chemists for oxidations. Under appropriate conditions, it combines chemically with organic compounds.

The term "autooxidation" is applied to those reactions taking place in contact with oxygen or air under very mild conditions or at moderately elevated temperatures, ranging from ambient to 200^0C. Radical forming oxidation-reduction reactions are often triggered/accelerated by the addition of small amounts of soluble salts of certain transition metals, mostly first row transition elements. It is evident that the effective transition metals are those with fairly stable adjacent valence states i. e. those capable of undergoing one electron oxidation-reduction reactions fairly easily.

A wide range of organic compounds, particularly having one hydrogen atom bonded to a sp^3 hybridized carbon atom will undergo autooxidation easily catalyzed by transition metal salts. Compounds having allylic or benzylic hydrogens are especially prone to autooxidation.

2.2.6.2 Results and Discussions:

Keeping metal catalysis in mind, we decided to study autooxidation of 1,4-dihydropyridines using Co-naphthenate as catalyst. Co-naphthenate is a cobalt salt of naphthenic acids. The naphthenic acids are obtained as byproducts in petroleum refining and are cyclopentane and cyclohexane derivatives **35** & **36**.



35 **36**

R1 = H or alkyl

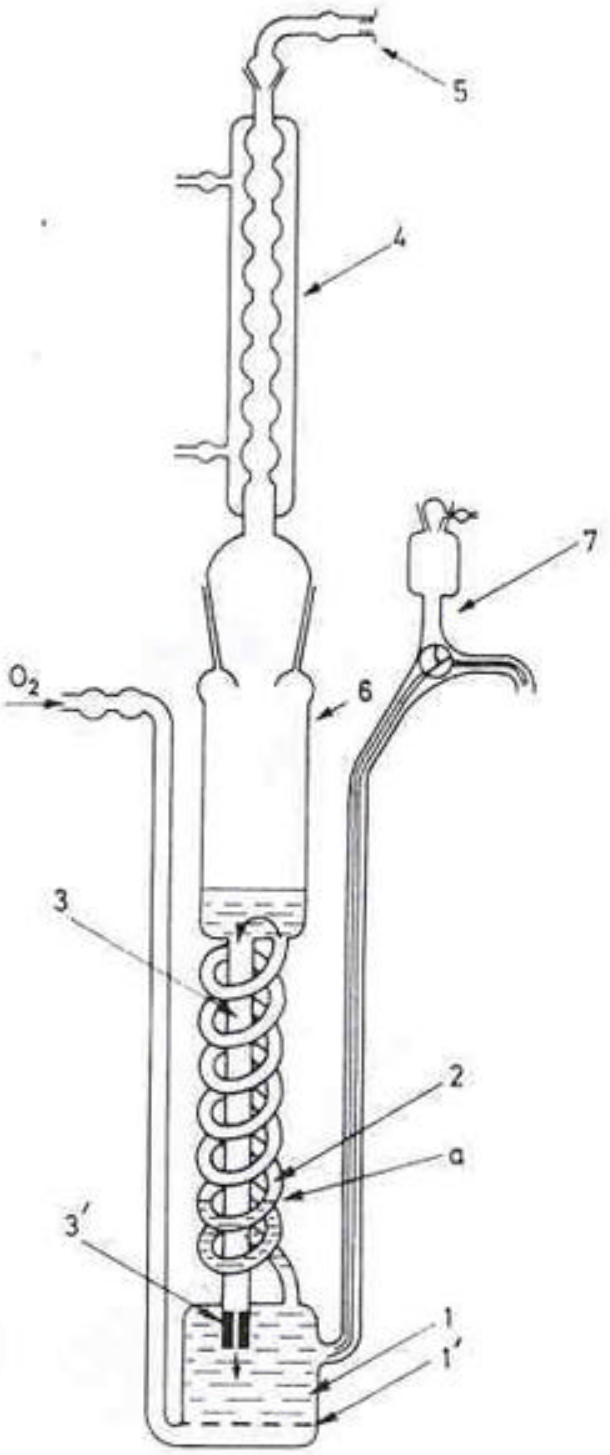


Fig. 1. *Hydroperoxidation apparatus*

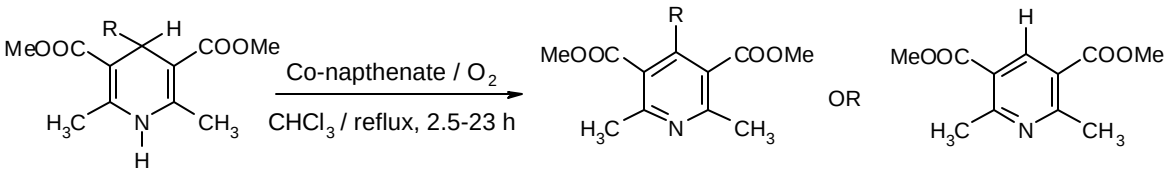
Figure I. Vodnar apparatus for autooxidation

The apparatus (fig. 1) comprises a tank containing the liquid to be hydroperoxidised (1), fitted with a perforated glass plate (1'), a spiral tube (2) in which the reaction takes place, and a recirculatory tube (3) with a capillary tube at the lower end (3'). A reflux cooler (4) fitted with a tube of calcium chloride (5) is situated above an upper vessel (6), and a sampling device (7) is provided. The apparatus may be constructed from glass or metal.

A variety of 1,4-dihydropyridines were subjected to autooxidation catalyzed by Co-naphthenate in chloroform at its reflux temperature to yield corresponding pyridine derivatives.

In a typical experiment, as shown in **scheme 12**, molecular oxygen was bubbled through a mixture of 2,6-dimethyl-1,4-dihydro-4-phenyl-3,5-pyridinedicarboxylic acid, dimethyl ester (**30e,** 0.6 g, 2.0 mmol) and Co-naphthenate [9% Co (II), 0.6 mL] in chloroform at its reflux temperature using Vodnar apparatus[12]. The reaction was monitored by TLC. After completion of the reaction, the chloroform was removed under vacuum and the product was purified by column chromatography or crystallization. The presence of the metal catalyst is essential for the success of the reaction. This was confirmed by performing the autooxidation of **(30e)** without the catalyst. It was found to be too sluggish (137 h) from practical point of view.

Scheme 12:



30 **31** **32**

The product thus obtained was characterized by IR, ^{1}H & ^{13}C NMR, mass spectroscopy. In ^{1}H NMR, the disappearance of the singlet at δ = 5.0-5.3 (DHP CH-4) was diagnostic for the oxidation.

In order to prove the generality of the above protocol, a variety of 1,4-DHPs were autooxidised under the identical reaction conditions as for the model 1,4-DHP **30e**. The results have been summarized in table 2.

2.2.7.2 Conclusions

1. Co (II)- catalyst has been used effectively to autooxidize 1,4-dihydropyridines.
2. A variety of DHPs have been oxidized in good to excellent yield.
3. 4-Alkyl substituted DHP (entries **30b-d**) suffered dealkylation to furnish pyridines.
4. A general protocol for obtaining differently substituted pyridine derivatives.
5. A very simple, efficient protocol has been devised.
6. Co-naphthenate, though used as catalyst cheap and available readily.

Table 2:

Entry	R	1,4-DHP	Product	Time (hr)	Yield %	MP (Lit. MP) ^0C
1	-H	30a	32	2.50	89	100 (101)
2	- CH_2CH_3	30b	32	2.50	84	100 (101)
3	- $CH_2CH_2CH_3$	30c	32	2.50	90	100 (101)
4	- $CH(CH_3)_2$	30d	32	2.50	91	100 (101)
5	C_6H_5-	30e	31a	8.00	92	141
6	4'- OCH_3-C_6H_4-	30f	31b	8.00	67	115
7	4'-Cl-C_6H_4-	30g	31c	8.00	73	137-139
8	2'-Cl-C_6H_4-	30h	31d	9.00	68	70
9	4'-NO_2-C_6H_4-	30i	31e	17.00	91	148
10	2'-NO_2-C_6H_4-	30j	31f	23.00	88	104-5 (106)

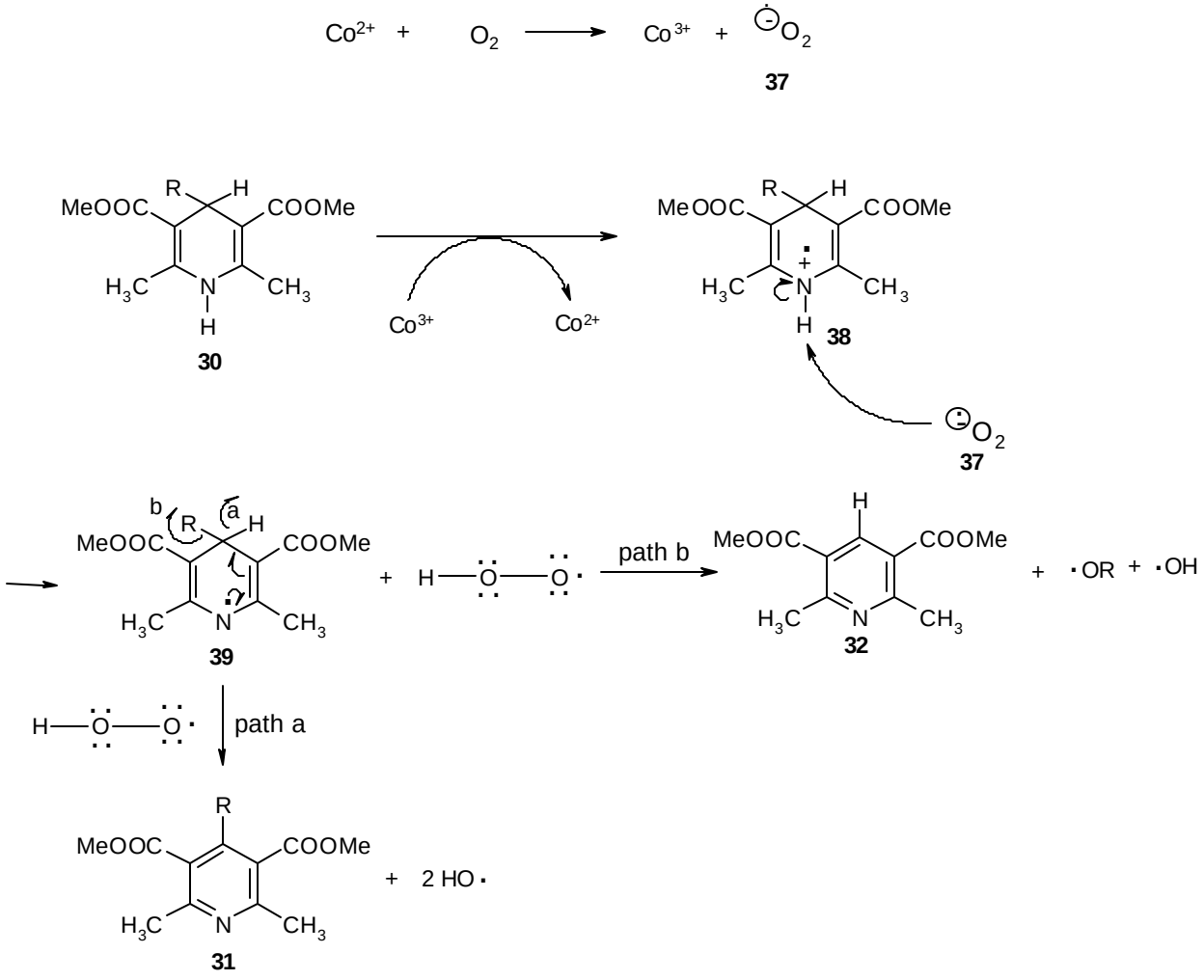
It was observed that, during aromatization reaction of 1,4-dihydropyridines (entries 5-10) bearing aryl substitution at 4-position furnished corresponding pyridine derivatives **(31a-f)**, however, alkyl substitution at 4-position (entries 1-4) gave dealkylated pyridine derivative **(32)**. This dealkylation is in agreement with the literature[5b,d].

2.2.8.2 Proposed Mechanism

The reactions with Co (II) complexes in the presence of molecular oxygen are believed to involve the formation of Co (III) species[11]. During autooxidation of 1,4-DHPs, it is proposed

that Co (II) gets oxidized to Co (III) which acts as an effective catalyst for the next steps in autooxidation. During oxidation of Co (II) to Co (III), oxygen radical anion **37** is formed. One electron transfer from 1,4-DHP nucleus reduces Co^{3+} to Co^{2+} and give rise to radical cation **38** in DHP nucleus. Radical anion **37** can abstract proton from radical cation **38** leading to formation of radical **39**. The radical **39** gets aromatized in two possible ways; path a and path b. Path a leads to the product **31** and two hydroxy radicals. Path b leads to dealkylated product **32** and alkoxy & hydroxy radicals. The radicals generated in the reaction course might undergo propagation or termination reactions.

Scheme 13



2.2.9.2 Experimental

General Procedure:-

All autooxidation reactions were carried out in Vodnar apparatus[11]. Molecular oxygen was bubbled through the mixture of 4-substituted 1,4-dihydropyridine derivative (2.0mmol), and Co-naphthenate (9% Co (II), 0.6mL) in chloroform at its reflux temperature. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to rt, diluted with chloroform. The organic layer was washed with brine (2×4mL) and then dried over sodium sulphate, filtered and concentrated in vacuum. The product was purified by column chromatography (eluent: 20:80 EtOAc:pet ether) or crystallization.

The pyridines **31a-f, 32** obtained were identical to the ones obtained by *tert*-butylhydroperoxide oxidation protocol (section **2.2.4.5**, page **24-29**) in all physical as well as spectral properties.

2.2. 10 References

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