Studies Towards Synthesis of β-Herbertenol And Other Biologically Active Molecules

A Thesis

Submitted to the

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in

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by

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November 2006

CERTIFICATE

Certified that the work incorporated in the thesis entitled ***"Studies Towards Synthesis of β-Herbertenol And Other Biologically Active Molecules"*** *submitted by* ***Mahesh Thakkar*** *was carried out under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.*

November, 2006

National Chemical Laboratory

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Subhash P. Chavan

Research Supervisor

DECLARATION

I hereby declare that the thesis entitled **"Studies Towards Synthesis of β-Herbertenol And Other Biologically Active Molecules"** submitted for Ph. D. degree to the University of Pune has been carried out at Organic Chemistry: Technology Division, National Chemical Laboratory, Pune, under the supervision of Dr. Subhash P. Chavan and the work is original and has not been submitted in part or full by me for any degree or diploma to this or any other university.

November, 2006

Organic Chemistry: Technology

National Chemical Laboratory,

Pune-411 008

Mahesh Thakkar

Dedicated To My Parents

Contents

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Finally I thank CSIR, New Delhi, for financial support.

NCL, Pune *Mahesh Thakkar*

General Remarks

1. All melting points and boiling points are uncorrected and the temperatures are in the centigrade scale.
2. The compound numbers, scheme numbers and reference numbers given in each section 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 ^{o}C.
4. Organic layers were dried over anhydrous sodium sulfate.
5. The reaction progress was monitored by the TLC analysis using thin layer plates pre-coated with silica gel 60 F254 (Merck) and visualized by fluorescence quenching or iodine or by charring after treatment with *p*-anisaldehyde.
6. In cases where chromatographic purification was done, silica gel (60-120 or 230-400 mesh) was used as the stationary phase or otherwise as stated.
7. IR spectra were recorded on a Perkin-Elmer Infrared Spectrophotometer Model 68B or on a Perkin-Elmer 1615 FT Infrared spectrophotometer.
8. ^{1}H NMR and ^{13}C NMR spectra were recorded on **Bruker AV-200** (50 MHz) or **Bruker AV-400** (100 MHz) or **Bruker DRX-500** (125 MHz). Figures in the parentheses refer to ^{13}C frequencies. Tetramethylsilane was used as the internal standard.
9. Optical rotations were recorded at ambient temperature on JASCO Dip-181 digital polarimeter using sodium vapor lamp.
10. Mass spectra were recorded at ionization energy 70 eV on Finnigan MAT-1020, automated GC/MS instrument and on API Q STARPULSAR using electron spray ionization [(ESI), solvent medium: a mixture of water, acetonitrile and ammonium acetate] technique and mass values are expressed as m/z. HRMS were recorded on a micromass Q-T of micro with spray source (ESI^{+}) mode.
11. Starting materials were obtained from commercial sources or prepared using known procedures.
12. Microanalytical data were obtained using a Carlo-Erba CHNS-O EA 1108 Elemental analyzer, within the limits of accuracy (± 0.4%).

Abbreviations

Ac	Acetyl
acac	acetylacetonate
AIBN	2,2-Azobis(isobutyronitrile)
Ar	Aryl
aq	Aqueous
BMS	Boran-dimethyl sulfide
Bn	Benzyl
Bu	Butyl
^{t}Bu	*tertiary*-Butyl
Bz	Benzoyl
CAN	Ceric ammonium nitrate
$CDCl_3$	Deuterated Chloroform
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N'*-Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethylazodicarboxylate
DEG	Diethyleneglycol
DEPT	Distortionless Enhancement by Polarization Transfer
DIBAL	Diisobutyl aluminium hydride
DIPT	Diisopropyltartrate
DMAP	4-Dimethyl amino pyridine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
dppf	(Bis-diphenylphosphino)ferrocenyl
Et	Ethyl
EtOAc	Ethyl acetate
g	gram/s
h	hour/s

HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
LAH	Lithium aluminium hydride
LDA	Lithium diisopropyl amide
mCPBA	m-Chloroperoxybenzoic acid
Me	Methyl
Mes	Mesitylene
min	minute/s
mL	mililitre/s
MOM	Methoxymethyl
mp	Melting point
Ms	Methanesulfonyl
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
NMP	*N*-Methylpyrrolidinone
ORTEP	Oak Ridge Thermal Ellipsoid Plot
pet. ether	Petroleum ether
Piv.	Trimethyl acetyl (pivaloyl)
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Pd/C	Palladized carbon
Ph	Phenyl
PPA	Polyphosphoricacid
PPh_3	Triphenyl phosphine
^{i}Pr	Isopropyl
PTC	Phase Transfer Catalyst
*p*TSA	*p*-Toluenesulfonic acid
Py	Pyridine
RCM	Ring Closing Metathesis

rt	room temperature
TBHP	*tertiary*-Butylhydrogenperoxide
TBTH	tri-*n*-Butyltin hydride
TEG	Triethyleneglycol
tert	*tertiary*
TFA	Trifluoroacetic acid
TFAA	Trifluroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	*N*,*N*,*N'*,*N'*-Tetramethylethylenediamine
TMSCl	Trimethylsilyl chloride
Ts	Toluenesulfonyl
TPAP	Tetra-*n*-propylammoniumperruthenate

Abstract

The thesis entitled **"Studies Towards Synthesis of β-Herbertenol And Other Biologically Active Molecules"** is divided into three chapters.

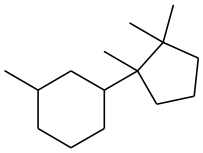
Chapter-1 : deals with the enantiospecific synthesis of β-herbertenol, and is further divided into two sections.

Chapter-2 : reports enantiospecific syntheses of (-)-parvifoline, (+)-isoparvifolinone and (-)-curcuquinone; and is divided into three sections.

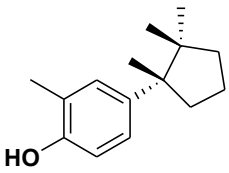
Chapter-3 : describes an enantiospecific synthesis of heritol.

Chapter-1 : Enantiospecific Synthesis of β-Herbertenol

Section-1 : Herbertenol : ***A Brief Review***



Herbertane skeleton, 1



(-)-2

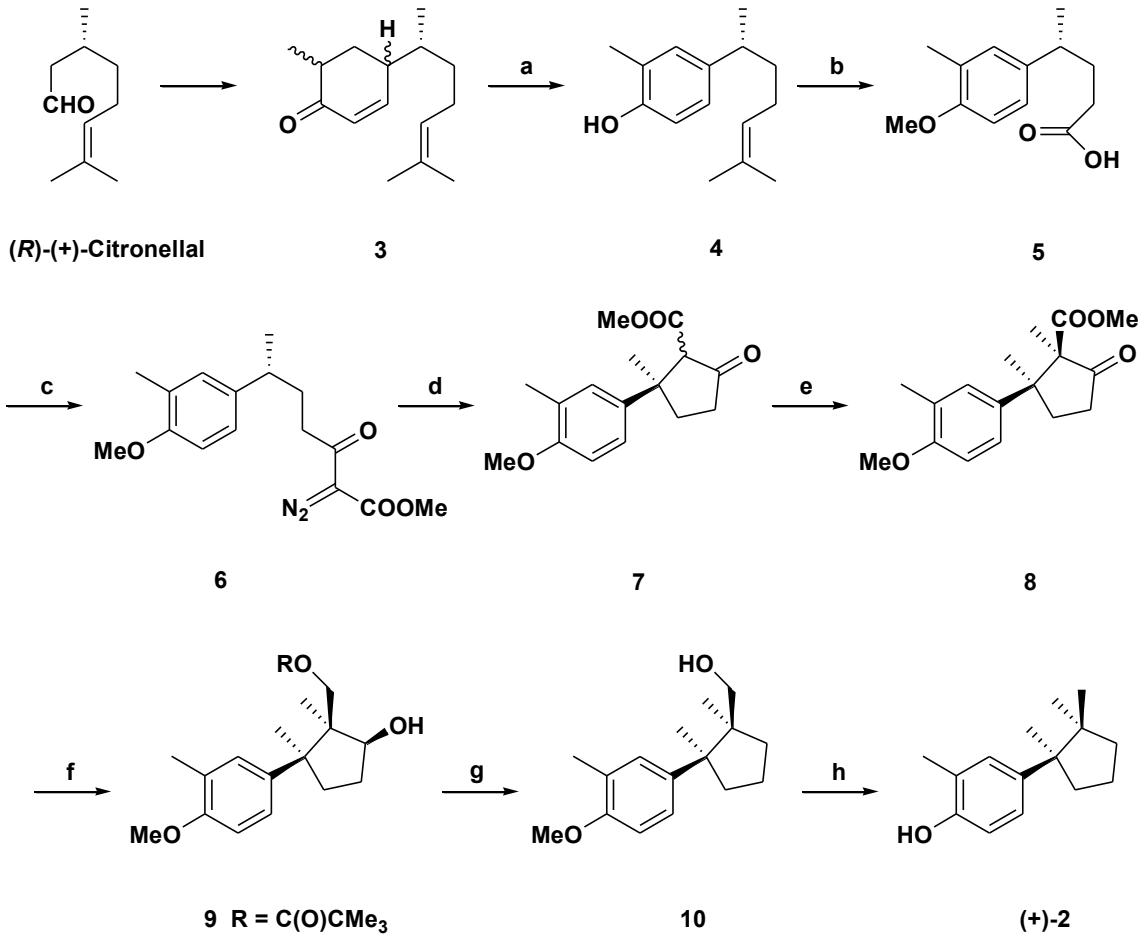
Section-1 begins with a brief introduction to the natural product, (-)-β-herbertenol **2** and other herbertene type sesquiterpenes. An account of the various synthetic routes of a few of the phenolic herbertanes, which possess 3-methyl-1-(1,2,2-trimethylcyclopentyl) cyclohexane skeleton, is presented briefly.

Section-2 : Enantiospecific Synthesis of (+)-β-Herbertenol

Difficulties associated with the construction of the vicinal quaternary carbons in the cyclopentane ring makes herbertanes and cuparanes challenging synthetic targets. Although, there have been synthetic strategies reported towards *rac*-β-herbertenol, not a single asymmetric synthesis has been attempted so far. Our interest in these skeletons has led to the synthesis of cuparenone and (±)-β-herbertenol. In continuation of our efforts towards the synthesis of herbertanes and cuparanes, enantiospecific synthesis of (+)-β-herbertenol was undertaken, where (*R*)-(+)-citronellal has been utilized as a source of

chirality and Taber's protocol of stereospecific C-H insertion by diazodecomposition of α-diazo-β-ketoester for the construction of cyclopentanones has been employed as the key step, which is presented in this section.

Scheme-1



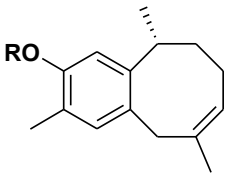
Reagents and conditions *: a) (i) LDA, THF, -78 °C, 1.5 h, TMSCl, -78 °C to rt, 5 h; (ii) NBS, THF, 0 °C, 0.5 h; (iii) Li_2CO_3, LiBr, DMF, 130-140 °C, 4 h, 75% from* ***3****; b) (i) K_2CO_3, Me_2SO_4, acetone, reflux, 12 h, 90%; (ii) OsO_4 (cat), Jones' reagent, acetone, rt, 5 h, 80%; c) (i) $SOCl_2$, CH_2Cl_2, reflux, 2 h; (ii) Meldrum's acid, pyridine, CH_2Cl_2, 0 °C to rt, 2 h; (iii) MeOH, reflux, 4 h, 78%; (iv) Et_3N, MsN_3, CH_2Cl_2, -5 °C to rt, overnight; d) $Rh_2(OAc)_4$ (cat), CH_2Cl_2, rt, 35% for 2 steps; e) K_2CO_3, MeI, acetone, rt, 24 h, 85%; f) (i) LAH, THF, 0 °C to rt, 5 h, 80%; (ii) pivaloyl chloride, Et_3N, CH_2Cl_2, -10 °C to rt, 4 h, 65%; g) (i) NaH, CS_2, THF, 0 °C, 2 h, then MeI, rt, 5 h, 95%; (ii) TBTH, AIBN (cat), toluene, reflux, 3 h, 80%; (iii) LAH, THF, rt, 2 h, quantitative; h) (i) PDC, CH_2Cl_2, 0 °C, 3 h; (ii) N_2H_4-H_2O, diethyleneglycol, 150 °C, 4 h, 190 °C, 3 h, 73% for 2 steps; (iii) BBr_3 in CH_2Cl_2, -78 °C to rt, overnight, 93%.*

Accordingly, (*R*)-(+)-citronellal was converted to the enone **3** using literature procedure, which on α-halogenation using Hassner's protocol, followed by dehydrohalogenation using lithium bromide and lithium carbonate in hot DMF provided the required phenol **4** in 75% overall yield (from **3**). This phenol **4** was transformed to the key α-diazo-β-ketoester intermediate **6** *via* an acid derivative **5**. The crucial C-H insertion reaction was then performed over **6** by using Taber's protocol of diazodecomposition, according to which **6** was treated with catalytic amount $Rh_2(OAc)_4$ to furnish cyclic β-ketoester **7** as a mixture of diastereomers. Having secured the key cyclopentanone in place, the remaining problem was to convert **7** to the geminal dialkylated cyclopentane skeleton. Accordingly, ester **7** was methylated using K_2CO_3, MeI in dry acetone, which gave a single diastereomer **8** in which methyl group and the aryl group on the adjacent quaternary carbons were *anti* to each other. The remaining carbonyl group deoxygenation was achieved using common functional group transformations, followed by methyl ether deprotection using BBr_3 to provide the required (+)-β-herbertenol **2** in good yields (Scheme-1).

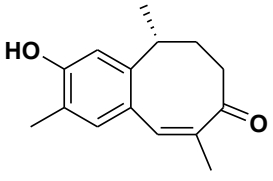
Thus, (+)-β-herbertenol has successfully been synthesized enantiospecifically, using naturally occurring (*R*)-(+)-citronellal as the source of chirality. The same idea can be applicable to the synthesis of naturally occurring (-)-β-herbertenol and other biologically active herbertanes also.

<u>Chapter-2</u> : Syntheses of (-)-Parvifoline, (+)-Isoparvifolinone and (-)-Curcuquinone

<u>Section-1</u> : Synthesis of Parvifoline & Curcuquinone : ***A Brief Review***



11 R = H
12 R = $Me_2CHCH_2C(O)$



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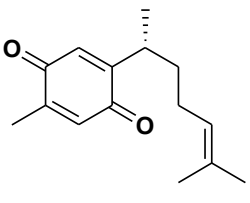


14

The title compound (-)-parvifoline **11**, along with isoparvifolinone **13** and parvifoline isovalerate **12** are sesquiterpenes, isolated from the genera *Coreopsis* and

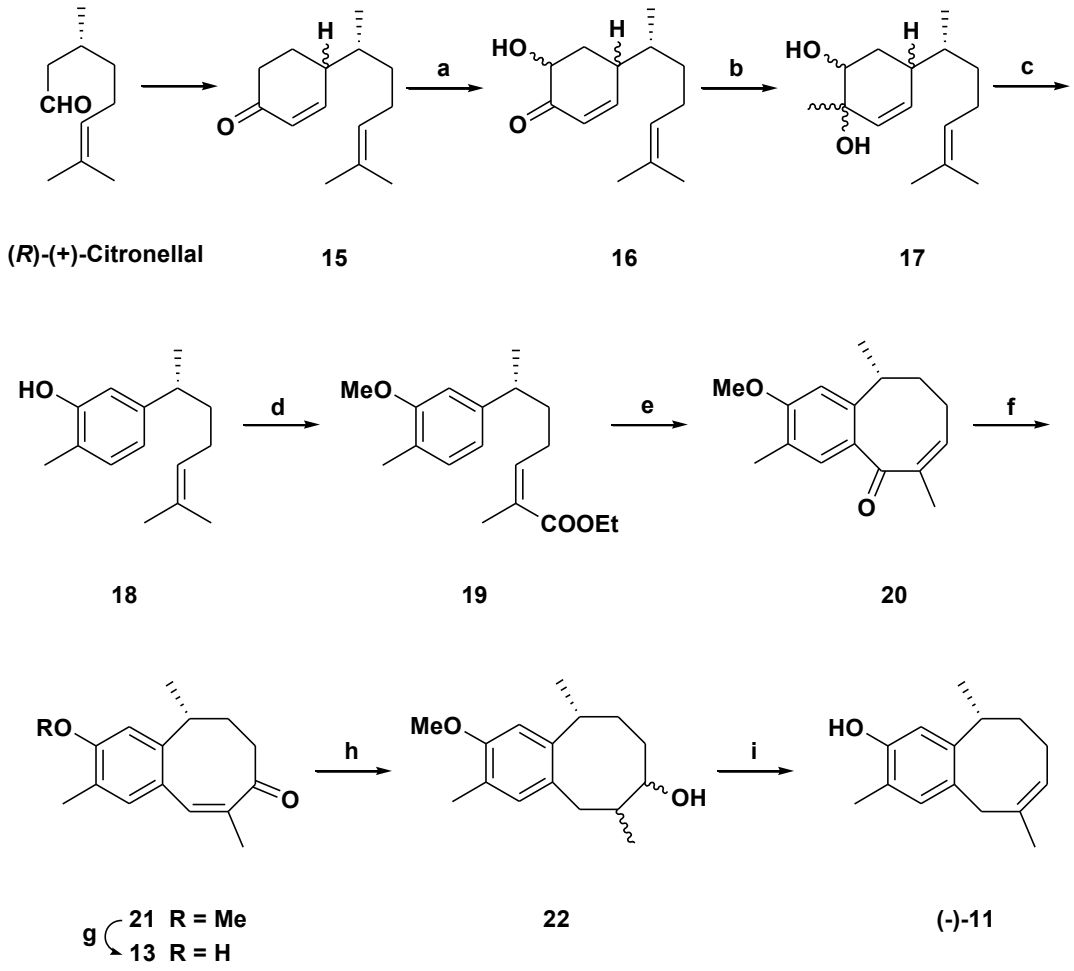
Perezia, and are the only examples of naturally occurring compounds with a trimethylbenzocyclooctane structural unit. The absolute configuration of (-)-parvifoline **11** was established by it's chemical transformation to (-)-curcuquinone **14**, a natural product of the known absolute configuration. Section-1 presents a brief introduction of the title sesquiterpenes, and various synthetic routes proposed for their synthesis.

<u>Section-2</u> : Enantiospecific Synthesis of (-)-Parvifoline & (+)-Isoparvifolinone : Friedel-Craft's Acylation Approach For Benzocyclooctane Ring Formation

The construction of an eight membered ring with a deconjugated double bond is the main structural feature that challenges the synthesis of (-)-parvifoline **11**. Moreover, introduction of the chirality at the nonfunctionalised benzylic position is difficult as well. Encouraged by the results achieved in the enantiospecific synthesis of (+)-β-herbertenol (chapter-1), an enantiospecific synthesis of (-)-parvifoline **11** and (+)-isoparvifolinone **13**, using Friedel-Craft's acylation as the key step was designed, which has been described in this section.

Accordingly, (*R*)-(+)-citronellal (98% ee) was converted to the enone **15** (1: 1 diastereomeric mixture) as reported in the literature, which was then converted to the α-hydroxyenone **16** using Rubottom's protocol in 70% overall yield from **15**. Methyl group introduction by 1,2-addition of the Grignard reagent MeMgI over hydroxyenone **16**, provided diol **17** as a mixture of diastereomers in 95% yield. The secondary hydroxyl group oxidation of the diol **17** under Swern oxidation conditions followed by mesylation of the crude product, resulted in tertiary hydroxyl group elimination with concomitant aromatization, which ended up in the mixture of phenol **18** and it's mesyl ester. The crude product was further hydrolyzed using KOH in refluxing methanol to give phenol **18** in 47% overall yield from diol **17**. Methyl ether protection of the phenol **18**, followed by dihydroxylation of the olefin functionality and periodate cleavage of the resulting diol gave corresponding aldehyde, over which two carbon olefination using Ando's protocol furnished the required *Z*-α, β-unsaturated ester **19** as the sole product in high yields. Ester **19** was then hydrolyzed to the corresponding acid under alkaline hydrolysis conditions, which was further converted to the corresponding acid chloride and immediately subjected to Friedel-Craft's acylation conditions, *i. e.* treatment with anhydrous aluminium chloride, to furnish cyclic enone **20** in 40% overall yield from **19** (Scheme-2).

Scheme-2



Reagents and conditions *: a) (i) LDA, THF, -78 °C, 1.5 h, then TMSCl, -78 °C to rt, 5 h; (ii) mCPBA, CH_2Cl_2, 0 °C to rt, 10 h; (iii) dilute HCl, CH_2Cl_2, 12 h, 70% overall; b) MeMgI, diethyl ether, 0 °C, then* ***16,*** *0 °C to rt, 12 h, 95%; c) (i) oxalyl chloride, CH_2Cl_2, -78 °C, DMSO, 15 min, then* ***17****, 30 min, Et_3N, -78 °C to rt, 5 h; (ii) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C to rt, 3 h, then reflux, 5 h; (iii) KOH, MeOH, reflux, 7 h, 47% overall; d) (i) Me_2SO_4, K_2CO_3, acetone, reflux, 12 h, 86%; (ii) OsO_4 (cat), NMO (50% in water), acetone, rt, 24 h; (iii) $NaIO_4$ supported over silica gel, CH_2Cl_2, rt, 3 h; (iv) $(o\text{-}CH_3C_6H_4O)_2P(O)CH(CH_3)COOEt$, NaH, THF, -78 °C, 3 h, 85% overall; e) (i) KOH, MeOH, reflux, 3 h; (ii) oxalyl chloride, CH_2Cl_2, 0 °C, 3 h; (iii) $AlCl_3$ (anhydrous), CH_2Cl_2, -20 °C to rt, 10 h, 40% overall; f) (i) $CeCl_3\text{-}7H_2O$, $NaBH_4$, MeOH, 0 °C, 30 min; (ii) PCC over silica gel, CH_2Cl_2, 2 h, 60% overall; g) BBr_3, CH_2Cl_2, rt, 1 h, 60%; h) (i) H_2, Pd/C (10%), MeOH, 24 h, followed by $NaBH_4$, 30 min, 55%; i) (i) pyridine, p-toluenesulfonylchloride, -4 °C, 3 days, then 100 °C, 10 h; (ii) EtSLi, DMF, 105 °C, 24 h, 58.5% overall.*

The keto functionality of the enone **20** was then reduced under Luche reduction conditions, followed by 1,3-carbonyl transposition using pyridinium chlorochromate over silica gel to afford isoparvifolinone methyl ether **21** in 60% overall yield. (+)-Isoparvifolinone **13** was then obtained by BBr_3 promoted methyl ether deprotection of **21** in 60% yield. Further, intermediate **21** on hydrogenation followed by borohydride reduction and tosylation of the resulting secondary alcohol **22**, provided the required parvifoline methyl ether derivative, which on deprotection by lithium thioethoxide in hot DMF gave (-)-parvifoline **11** in good yields.

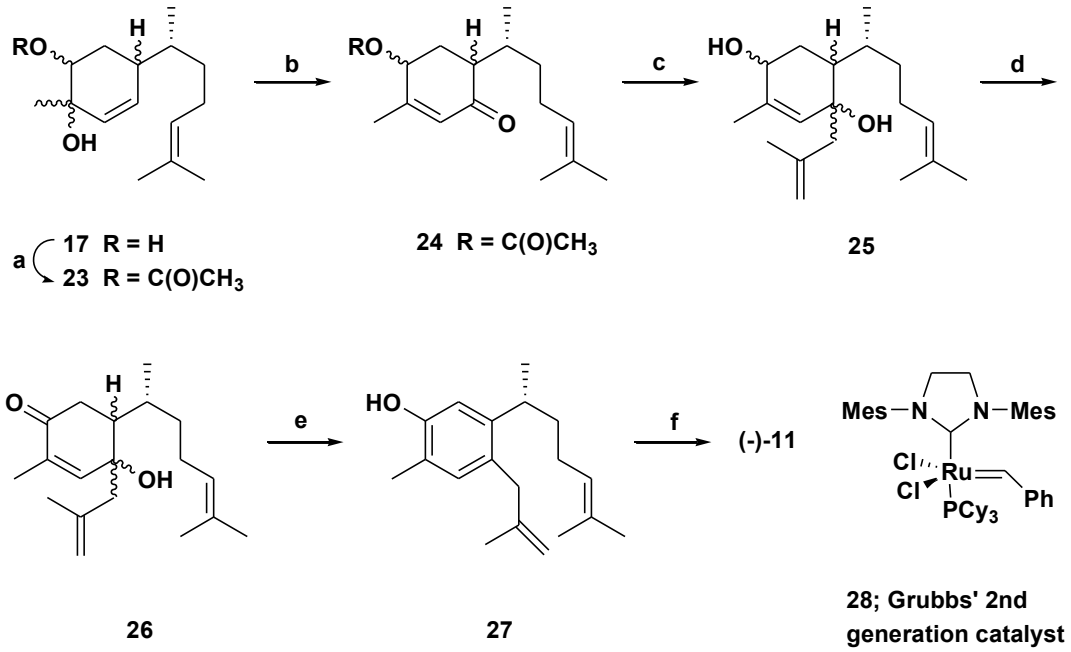
Thus, (-)-parvifoline and (+)-isoparvifolinone have been synthesized enantiospecifically, using Friedel-Craft's acylation as the key step.

<u>Section-3</u> : Enantiospecific Synthesis of (-)-Curcuquinone & (-)-Parvifoline : Ring Closing Metathesis Approach

Encouraged by the results achieved in the enantiospecific synthesis of **(-)-11**, ring closing metathesis reaction was envisaged as the key reaction for benzocyclooctene skeleton formation, in order to decrease the number of steps and to improve the overall yields. The present section describes enantiospecific synthesis of **(-)-11** using ring closing metathesis as the key step, and also enantiospecific synthesis of (-)-curcuquinone **14** utilizing (*R*)-(+)-citronellal as the chiron (Scheme-3 and 4).

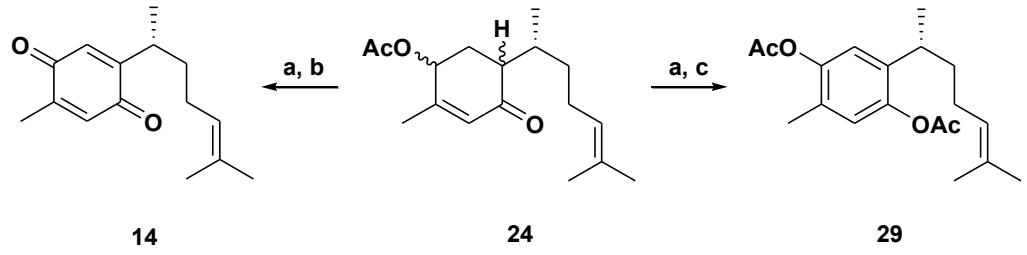
Accordingly, the synthesis commenced from diol **17**, which was synthesized as described in section-2. The secondary hydroxyl group of the diol **17** was protected as it's acetate **23**, followed by 1,3-ketone transposition using pyridinium chlorochromate to furnish the required conjugated ketone **24**. This enone **24** on 1,2-addition with methallyl magnesium chloride under Barbier conditions gave diol **25**, which on Dess-Martin periodinane oxidation followed by mesylation of the resulting hydroxy enone **26**, provided the required diolefin precursor **27** along with it's mesyl ester. Hydrolysis of the crude product under alkaline conditions provided the requisite intermediate **27** in high yields. Finally, the crucial eight membered ring formation was achieved by ring-closing metathesis of **27** employing second-generation Grubbs' catalyst **28**, to furnish (-)-parvifoline **11** in 90% isolated yield (Scheme-3).

Scheme-3



Reagents and conditions *: a) pyridine, acetyl chloride, 0 °C to rt, 12 h, 85%; b) PCC, CH_2Cl_2, 0 °C to rt, 7 h, 80%; c) Mg, THF, methallyl chloride, 0 °C, 24 h, 90%; d) DMP, CH_2Cl_2, 0 °C to rt, 4 h, 85%; e) (i) Et_3N, methanesulfonyl chloride, CH_2Cl_2, 0 °C to rt, 3 h, then reflux, 5 h; (ii) KOH, MeOH, reflux, 12 h, 79% for two steps; f) Grubbs' catalyst (second generation)* ***28****, toluene, 80 °C, 5 h, 90%.*

Scheme-4

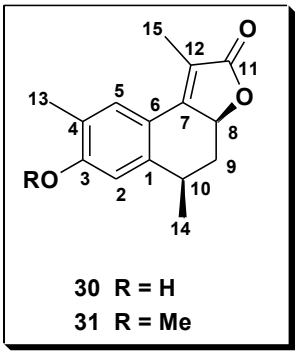


Reagents and conditions *: a) (i) K_2CO_3, MeOH, rt, 30 min; (ii) DMP, CH_2Cl_2, rt, 2 h,; b) (i) CH_2Cl_2, Et_3N, rt, 3 h; (ii) CAN, CH_2Cl_2-H_2O, 0 °C, 1 h, 60% overall; c) Et_3N, rt, 1 h, acetyl chloride, 0 °C to rt, overnight, 52% overall.*

The synthesis of (-)-curcuquinone **14** was easily accomplished from enone intermediate **24**. It was hydrolyzed using K_2CO_3 in methanol followed by Dess-Martin periodinane oxidation and treatment with triethylamine, to give the corresponding hydroquinone derivative, which without purification was subjected to oxidation using CAN as the oxidizing agent to provide (-)-curcuquinone **14** in 60% overall yield (Scheme-4).

Thus, (-)-parvifoline has been synthesized enantiospecifically, utilizing (*R*)-(+)-citronellal as the chiron and employing ring closing metathesis as the key step in 10% overall yield. (-)-Curcuquinone has also been synthesized.

<u>Chapter-3</u> : Synthesis of Heritol Using (*R*)-(+)-Citronellal



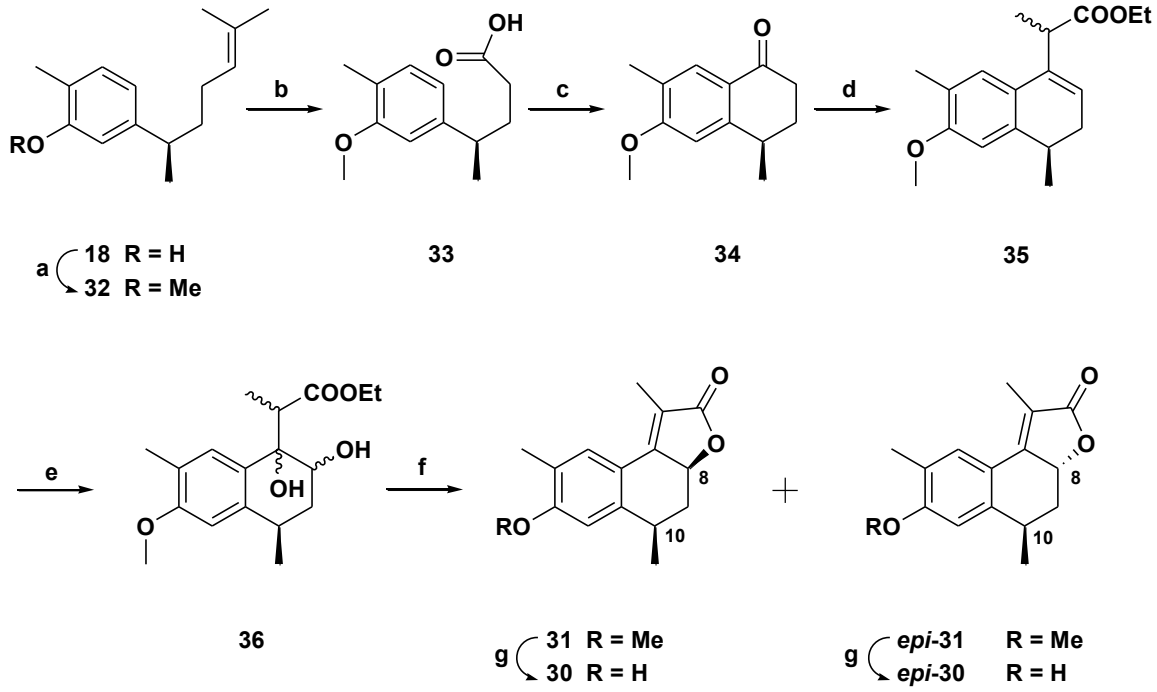
30 R = H
31 R = Me

Miles' *et al* have isolated an active toxin, called heritol **30**, a naturally occurring sesquiterpene, from the sap of the mangrove plant *Heritiera littoralis*, which was shown to possess itchthytoxicity in ppm quantities to *Tilapia nilotica* fingerlings. It has a novel structure of the cadinane sesquiterpene class with an unusual oxygenation pattern. The relative stereochemistry in heritol **30** was established by a single crystal X-ray analysis, but it's absolute configuration was just proposed to be ***R*** at $\mathbf{C_{10}}$ by it's analogy with other cadinanes. This chapter describes it's reported syntheses, and our approach towards enantiopure heritol **30** and heritonin **31**, utilizing (*R*)-(+)-citronellal as the chiron.

Thus, the synthesis initiated from phenol intermediate **18**, which was protected as it's methyl ether **32**. It was then subjected to Weinreb's condition to give an acid derivative **33** in 82% yield, which on treatment with trifluoroacetic anhydride underwent smooth cyclisation to furnish the key tetralone intermediate **34** in 80% isolated yield. This tetralone **34** was further converted to heritonin **31** by using Chavan's protocol, according to which it was subjected to 1,2-addition using ethyl-2-bromopropionate under Reformatsky reaction conditions, followed by acidic work-up to provide β, γ-unsaturated ester **35**, which on dihydroxylation furnished diol **36**. This diol on treatment with *p*TSA under refluxing benzene provided heritonin **31** and it's C-8 epimer (*epi*-**31**) in high yields, which were separated by repeated crystallization, and then deprotected to furnish the optically pure

heritol **30** and it's C-8 epimer (*epi*-**30**), respectively. Specific rotation of this synthetically obtained heritol was compared with that of naturally isolated one, and based on this observation absolute configuration of naturally isolated (+)-heritol was proposed to be (*S*, *R*) at C-10, C-8.

Scheme-5



Reagents and conditions *: a) Me_2SO_4, K_2CO_3, acetone, reflux, 12 h, 86%; b) OsO_4 (cat), Jones' reagent, acetone, rt, 7 h, 82%; c) triflouroacetic anhydride, triflouroacetic acid, 0 ^oC, 3 h, 80%; d) Zn, ethyl-2-bromopropionate, I_2, ether, reflux, 3 h, then H^+, 80%; e) OsO_4 (cat), NMO, CH_3CN: H_2O, 24 h, 95%; f) pTSA, benzene, reflux, 1 h, 90% overall; g) $AlCl_3$, EtSH, CH_2Cl_2, rt, 12 h, 80%.*

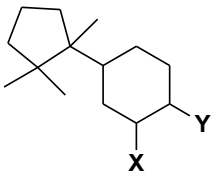
Thus, enantiopure heritol has been synthesized enantiospecifically from naturally occurring (*R*)-(+)-citronellal, and absolute configuration of the naturally isolated (+)-heritol has been proposed.

Chapter-1 : Enantiospecific Synthesis of β-Herbertenol

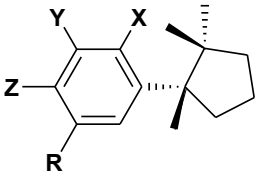
Section-1 : Herbertenol : A Brief Review

1.1.1 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 sesquiterpenoids metabolites, which are enantiomers of those compounds produced by the higher plants. Particularly, herbertous species is a rich source of *Herbertene* (*iso-cuparene*) type **1** as well as cuparene type **2** sesquiterpenoids.[1-3]

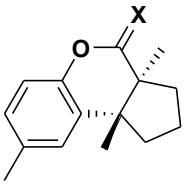


1 X = Me, Y = H; Herbertene skeleton
2 X = H, Y = Me; Cuparene skeleton

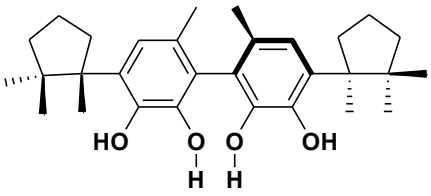


3a R = Me; X = Y = Z = H
3b R = Me; X = OH; Y = Z = H
3c R = Me; X = Y = H; Z = OH
3d R = Me; X = Y = OH; Z = H
3e R = CHO; X = OH; Y = Z = H
3f R = CHO; X = Y = OH; Z = H
3g R = COOMe; X = Y = OH; Z = H

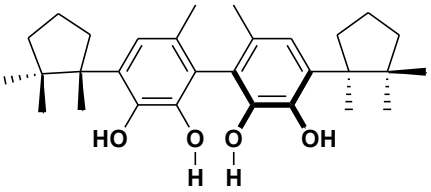
Isolation of the first members of the herbertane group; herbertene **3a**, α-herbertenol **3b**, β-herbertenol **3c**, herbertenediol **3d**, herbertenal **3e** and herbertenolide **4a** from *Herberta adunca* was reported earlier by Matsuo[1b] and co-workers. Subsequently, Rycroft *et al* reported the isolation of the aldehyde **3f** and the ester **3g** from *Herbertus aduncus*.[1c] The phenolic herbertanes, e. g., **3b-d** have been shown to possess interesting biological properties[1-3] such as growth inhibiting activity, antifungal, antilipid peroxidation and neurotropic activities. The dimeric herbertanes, mastigophorenes A and B (**5a** and **5b**), isolated[2] along with their isomers, mastigophorenes C and D, and herbertenols from the liverwort *Mastigophora diclados*, were shown to stimulate nerve growth. Recently, Asakawa[1d] and co-workers reported the isolation of seven new members of the herbertane group; herbertenelactol **4b**; 1,13-herbertenediol **6**; 1,14-herbertenediol **7**; 1,15-herbertenediol **8**; herbertenones A **(9a)** and B **(9b)**, and 12-methoxy herbertenediol **10** along with dimeric herbertanes (mastigophorenes A-C), from the Japanese liverworts *Herberta sakuraii*.



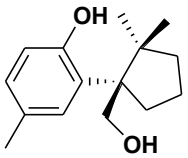
4a X = O
4b X = H, OH



5a



5b



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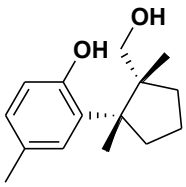

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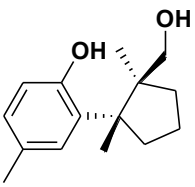

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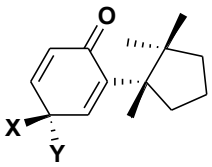
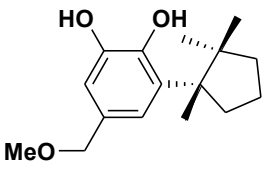


9a X = OH, Y = Me
9b X = Me, Y = OH



10

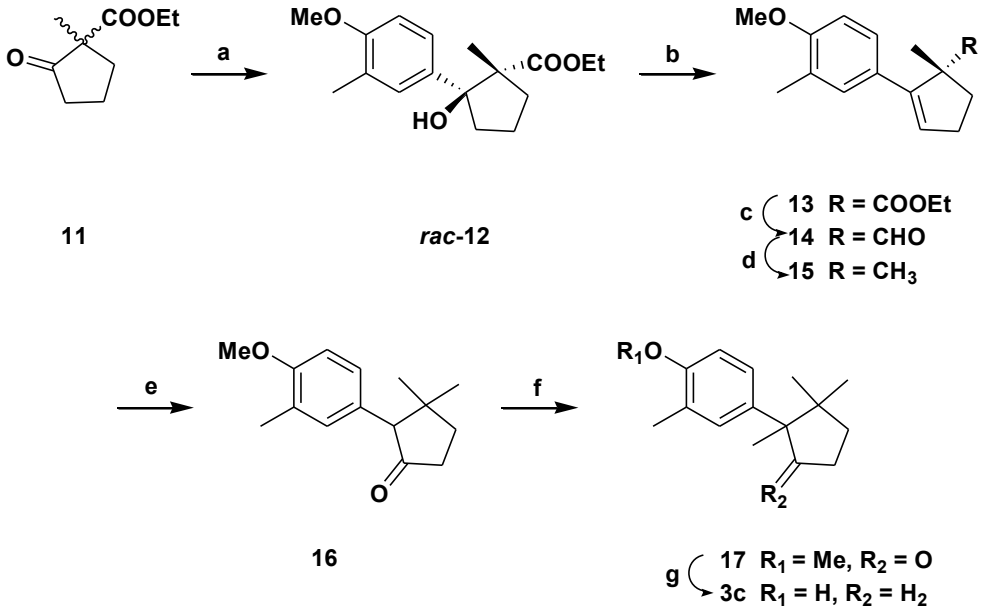
1.1.2 Total Synthesis of Herbertanes : *A Review*

The total synthesis of herbertanes as well as cuparene type sesquiterpenoids have attracted the attention of several synthetic organic chemists due to the difficulties associated with the construction of the vicinal quaternary carbons in the cyclopentane ring. However, despite their interesting biological properties, the phenolic herbertanes have received very little attention until recently. After 1999 only, several synthetic routes have been reported, which have been briefly reviewed here.

Eicher's Approach : (Scheme-1 and 2, 1996)[4]

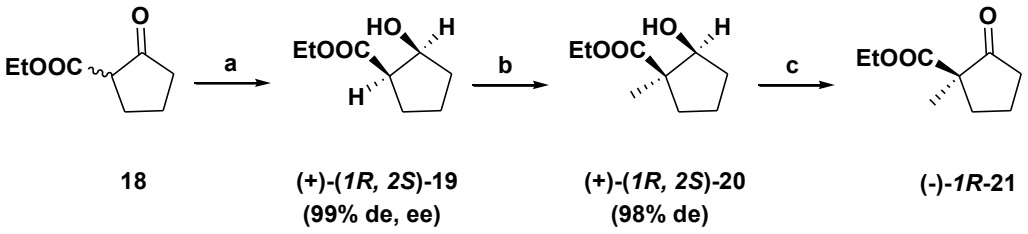
In this article, total synthesis of *rac*-α-herbertenol **3b**, *rac*-β-herbertenol **3c** and asymmetric synthesis of *ent*-herbertenolide, *i. e.* ***ent*-4a** using enzymatic resolution as the key step has been reported.

Scheme-1 : (Eicher *et al*, *Synthesis* **1996**, 863-870)



Reagents and conditions *: a) 4-methoxy-3-methylphenyl magnesium bromide, THF, -40 °C to rt, 77%; b) $KHSO_4$, 140 °C, 1 h, 99%; c) (i) LAH, THF; (ii) PCC, CH_2Cl_2, 48%; d) N_2H_4-H_2O, NaOH, DEG, 195 °C, 7 h, 50%; e) (i) $NaBH_4$, BF_3-OEt_2; (ii) NaOH, H_2O_2; (iii) PCC, NaOAc, 43%; f) NaH, MeI, DME, -50 °C to rt, 67%; g) N_2H_4-H_2O, NaOH, DEG, 220 °C, 3 d, 45%.*

Scheme-2



Reagents and conditions *: a) baker's yeast, H_2O, glucose, 65%; b) LDA, THF, MeI, HMPA, 84%; c) $Na_2Cr_2O_7$, H_2SO_4, Et_2O, 69%.*

The synthesis of *rac*-**3c** (Scheme-1) started from cyclopentanone derivative **11**, which on Grignard addition followed by dehydration provided intermediate **13**. It was further transformed to the dimethyl cyclopentene intermediate **15** in a few steps, which on hydroboration-oxidation and PCC oxidation in acetate buffer gave cyclopentanone **16** in

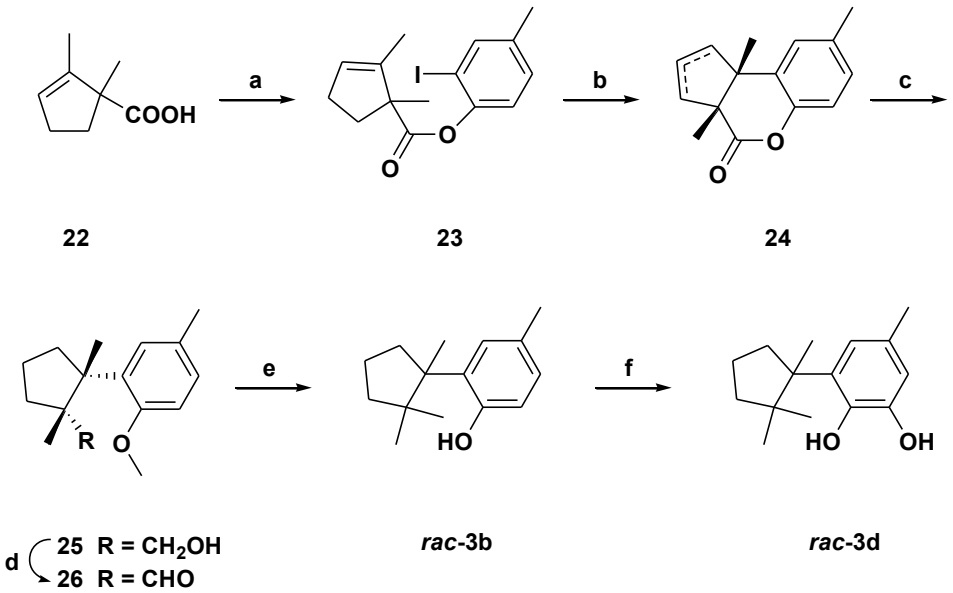
moderate yields. Further, intermediate **16** on methylation followed by Wolff-Kishner reduction provided the required *rac*-**3c**. Using similar strategy, *rac*-herbertenolide **4a** and *rac*-α-herbertenol **3b** have also been synthesized.

For the asymmetric synthesis of herbertenolide ***ent*-4a**, chiral β-keto ester **(-)-*1R*-21** was used, which was obtained by baker's yeast reduction of *rac*-**18**, followed by diastereoselective methylation of the resultant chiral ester **19** and oxidation of the secondary hydroxyl group (Scheme-2).

Fukuyama's Approach : (Scheme-3, 1996)[5]

This communication reported the first total synthesis of *rac*-herbertenediol **3d**, which was proposed to be biosynthetic precursor of mastigophorenes **5(a, b)**. Here, they utilized intramolecular Heck reaction for the construction of quaternary carbon at the benzylic position of *rac*-α-herbertenol **3b**, which was further transformed to *rac*-**3d**.

Scheme-3 : (Fukuyama *et al*, *Tetrahedron Lett.* **1996**, *37*, 1261-1264)



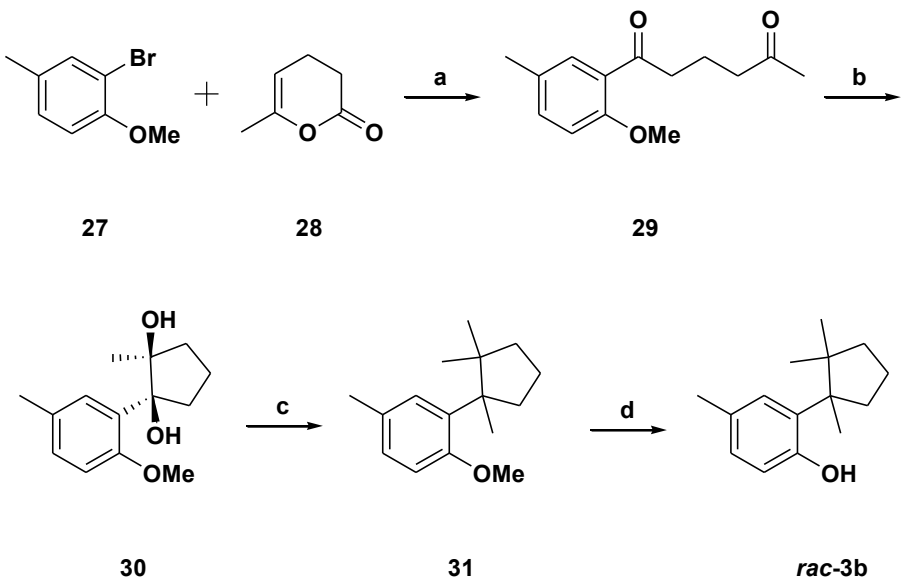
Reagents and conditions *: a) (i) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF; (ii) 2-iodo-4-methylphenol, DMAP, benzene, 63%; b) $Pd(OAc)_2$, $(o\text{-}Tol)_3P$, n-Bu_3N, DMF, 97%; c) (i) H_2, Pd/C, EtOH; (ii) LAH, THF, 93%; (iii) MeI, K_2CO_3, acetone; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 89%; e) (i) N_2H_4, NaOH, DEG; (ii) BBr_3, CH_2Cl_2, 81%; f) (i) MOMCl, i-Pr_2EtN, CH_2Cl_2; (ii) s-BuLi, TMEDA, MoOPH, THF; (iii) HBr, MeOH, 88%.*

Thus, cyclopentene carboxylic acid *rac*-**22** was treated with 2-iodo-4-cresol under Yamaguchi conditions to give an ester **23** in 63% yield, which on intramolecular Heck reaction provided lactone **24** in 97% yield as a mixture of double bond isomers. After hydrogenation of the double bond and a few functional group transformations, *rac*-α-herbertenol **3b** was obtained in high yields, which on hydroxylation by Vedejs'[6] method and MOM ether deprotection afforded *rac*-herbertenediol **3d** in 88% overall yield from **3b**.

Harrowven's Approach : (Scheme-4, 1998)[7, 8]

Synthesis of *rac*-α-herbertenol **3b** reported by Harrowven *et al* featured the use of dihydropyranone as a 1,5-diketone synthon.

Scheme-4 : (Harrowven *et al*, *Tetrahedron Lett.* **1998**, *39*, 9573-9574)



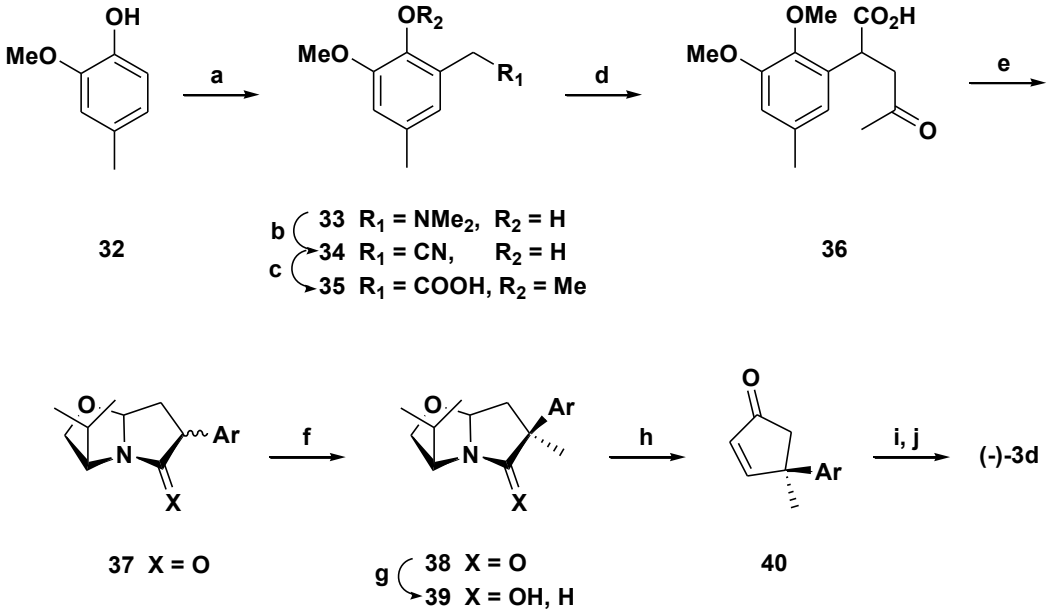
***Reagents and conditions** : a) n-BuLi, THF, -78 °C, 1h, then **28**, -78 °C, 15 min, TMSCl, rt, 77%; b) $TiCl_4$, Mg, THF, -40 °C, 1h, 61%; c) Me_2TiCl_2, CH_2Cl_2, 0 °C, 24 h, 40%; d) BBr_3, CH_2Cl_2, -78 °C, 1 h, rt, 16 h, 99%.*

Accordingly, organolithium reagent derived from **27** was treated with dihydropyranone **28**, which on quenching with chorotrimethylsilane provided 1,5-diketone **29** in 77% yield. Intramolecular Pinacol coupling reaction of diketone **29** induced by a low valent titanium resulted in diol **30**, which was then converted to *rac*-**3b** through exposure to dimethyltitanium dichloride, followed by methyl ether deprotection of the resulting intermediate **31**.

Meyer's Approach : (Scheme-5, 1999)[9]

In this particular approach, a non-*racemic* bicyclic latam **37** has been utilized to construct a chiral cyclopentane containing vicinal quaternary carbon centers in optically pure form of (-)-herbertenediol **3d**, which was further elaborated for asymmetric synthesis of (-)-mastigophorenes A **5a** and B **5b**.

Scheme-5 : (Meyer *et al*, *J. Am. Chem. Soc.* **1999**, *121*, 2762-2769)



Reagents and conditions *: a) HCHO, Me_2NH, 100%; b) (i) MeI; (ii) KCN, 90%; c) (i) Me_2SO_4, PTC, 100%; (ii) NaOH, MeOH, H_2O, 97%; d) (i) 2 equivalents LDA, rac-propyleneoxide; (ii) Swern oxidation, 80%; e) (S)-valinol, benzene, 83%; f) LDA, MeI, THF, -100 ^oC, 85% (33: 1); g) Red-Al; h) (i) KH_2PO_4, H_2O, EtOH; (ii) KOH, EtOH, 84%; i) NaH, MeI, DMF, 60%; j) (i) $(ArPS_2)_2$, toluene; (ii) Raney Ni, H_2, EtOH, 58%; (iii) BBr_3, 91%.*

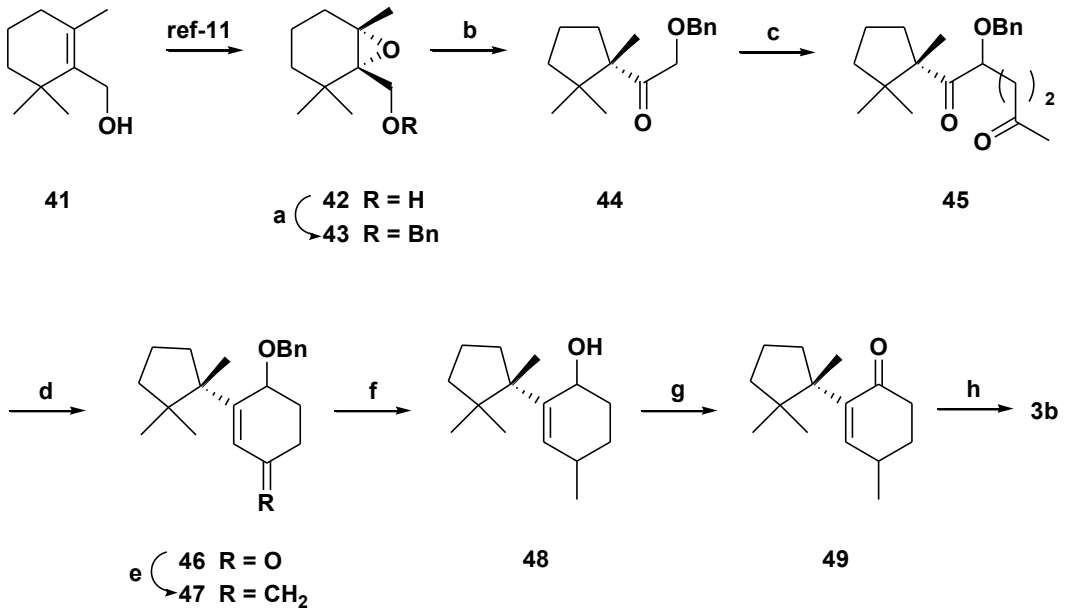
Thus, phenol **32** was subjected to Mannich conditions to afford benzylamine **33**, which was further quaternised and displaced by KCN to provide substituted phenyl acetonitrile **34** in high yields. Protection of phenol and alkaline hydrolysis of cyanide functionality gave phenylacetic acid **35** in almost quantitative yield. It's dianion was then quenched with propylene oxide to give γ-hydroxy acid, which was directly oxidized to afford the requisite ketoacid *rac*-**36** in 80% overall yield. It's condensation with (*S*)-valinol gave bicyclic lactam **37** as a 3: 2 mixture of *epimers*, which on *C*-methylation using LDA as the base furnished a 33: 1 mixture of *endo*: *exo* diastereomers **38**, which on reduction

with Red-Al followed by hydrolysis and base induced cyclisation of the resulting keto-aldehyde afforded chiral cyclopentenone **40** in 84% yield. This was further transformed to the required **(-)-3d** efficiently.

Abad's Approach : (Scheme-6, 1999)[10]

This article described enantioselective synthesis of (-)-α-herbertenol **3b** and (-)-herbertene **3a** by adopting the chemistry developed previously by the same authors for the enantioselective synthesis of several cuparanes,[11] where Katsuki-Sharpless asymmetric epoxidation was utilized for introduction of chirality.

Scheme-6 : (Abad *et al*, *J. Org. Chem.* **1999**, *64*, 1741-1744)



Reagents and conditions *: a) NaH, BnBr, 88%; b) $SnCl_4$, 85%; c) (i) NaHMDS; (ii) α-trimethylsilyl vinyl ketone; (iii) KOH, 80%; d) KOH, 120 ^oC, 78 %; e) $Ph_3P=CH_2$, 83%; f) (i) Pd/C, H_2, EtOAc; (ii) Pd, $CaCO_3$, $Pd(OH)_2$/C, H_2, EtOH; g) TPAP, NMO, 84% from **47**; h) S, 200 ^oC, 65%.*

Accordingly, enantiopure (*1S*, *2S*)-epoxy alcohol **42** was prepared in 89% yield (98% ee) from readily available β-cyclogeraniol **41** by Katsuki-Sharpless asymmetric epoxidation. The hydroxy group of it was protected as it's benzyl ether **43**, followed by Pinacol rearrangement using tin (IV) chloride in CH_2Cl_2 at low temperature to afford α-benzyloxy ketone **44** without loss of optical purity in 85% yield. The sodium enolate of **44**

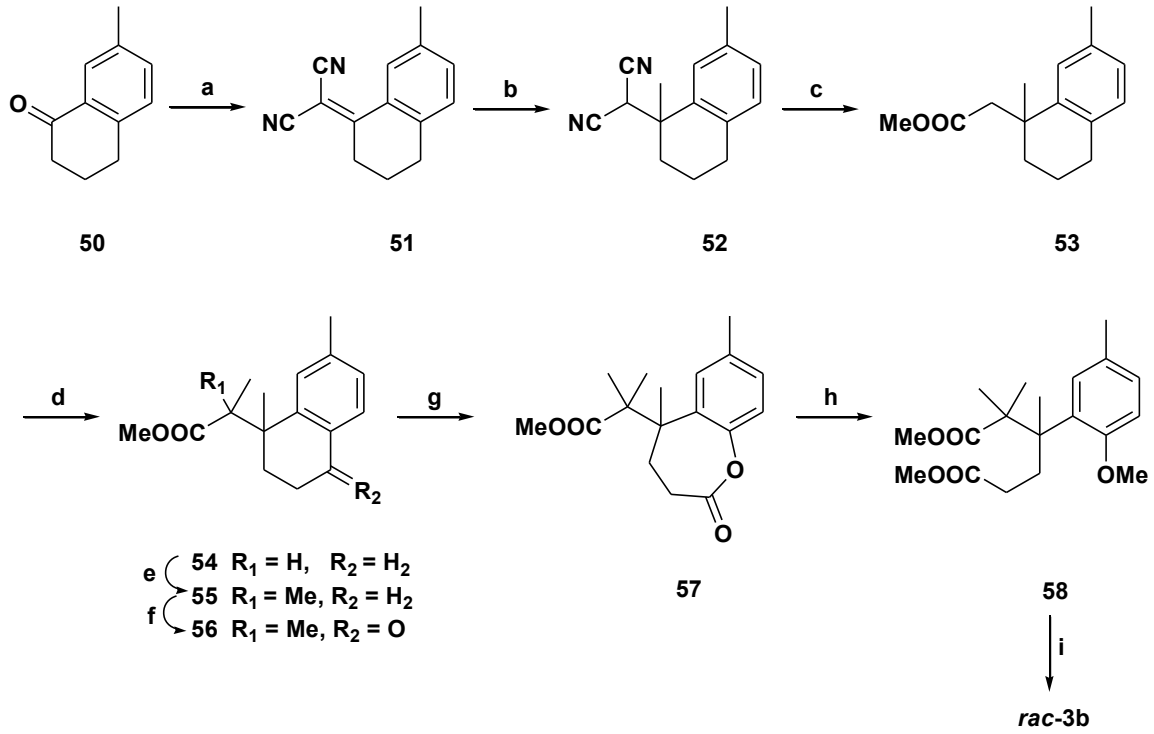
was then reacted with α-trimethylsilyl vinyl ketone followed by treatment with KOH in MeOH, which afforded benzyloxy ketone **45** in 80% isolated yield. It was further treated with KOH in a sealed tube at 120 ^{o}C for 6 h to furnish enone **46** in 78% yield, which on chemoselective hydrogenation followed by TPAP oxidation and finally aromatization using sulfur resulted in the requisite (-)-α-herbertenol **3b** in good yields.

Later in 2000, the same authors have reported enantioselective synthesis of (-)-α-formylherbertenol **3e** using similar synthetic strategy.[12]

Mukherjee's Appoach : (Scheme-7, 1999)[13]

The present communication dealt with the synthesis of *rac*-**3b** and other related herbertanes using α, α-dimethylation of the ester **53** as the key step.

Scheme-7 : (Mukherjee *et al*, *Tetrahedron Lett.* **1999**, *40*, 4733-4734)



Reagents and conditions *: a) $CH_2(CN)_2$, NH_4OAc, AcOH, benzene, reflux, quantitative; b) MeMgI, CuI, THF, 25 ^{o}C, then reflux, 89%; c) (i) KOH, $HOCH_2CH_2OH$, H_2O, reflux, H^+, 190 ^{o}C; (ii) CH_2N_2, 82%; d) LDA, THF, -20 ^{o}C, MeI, HMPA, -78 ^{o}C, 95%; e) LDA, HMPA, THF, 0 ^{o}C, MeI, 92%; f) CrO_3, AcOH, 10-25 ^{o}C, 75%; g) mCPBA, CH_2Cl_2, CF_3COOH, 0 to 25 ^{o}C, 84%; h) (i) aq. NaOH, MeOH, reflux, Me_2SO_4, H^+; (ii) CH_2N_2, 85%; i) (i) t-BuOK, benzene, reflux, H^+, DMSO, NaCl, 150 ^{o}C, 75%; (ii) N_2H_4, N_2H_4-2HCl, DEG, 130 ^{o}C, KOH, 210 ^{o}C, 75%; (iii) BBr_3, 72%.*

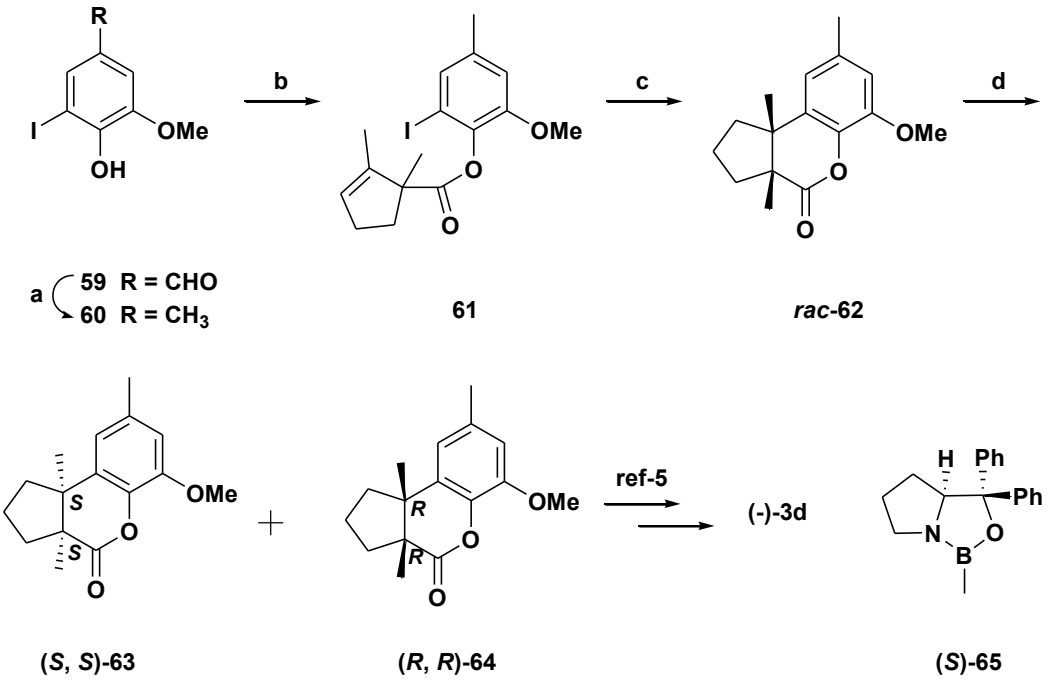
Accordingly, tetralone **50** was condensed with malononitrile to provide unsaturated nitrile **51** in quantitative yield. Conjugate addition of MeMgI on **51** followed by hydrolysis, decarboxylation and esterification afforded ester **53** in 73% overall yield. The ester **53** was alkylated with MeI at -78 ^{o}C using LDA (1 equivalent) as the base to provide ester **54** as a diastereomeric mixture, which was further alkylated with MeI in presence of LDA (1.7 equivalents) and HMPA (2 equivalents) at 0 ^{o}C to afford ester **55** in 87% yield. After a few functional group transformations, the resultant diester **58** was subjected to Dieckmann cyclisation followed by decarboxylation of the resultant crude β-keto ester, which on Huang-Minlon reduction and demethylation furnished *rac*-**3b**.

Later in 2000, the same authors have reported syntheses of *rac*-herbertene **3a**, *rac*-β-herbertenol **3c** and *rac*-herbertenediol **3d** using similar synthetic strategy.[14]

Bringmann's Approach : (Scheme-8, 2000)[15]

An enantioselective synthesis of (-)-herbertenediol **3d** has been described here, which is quite similar to Fukuyama's strategy[5] for the synthesis of *rac*-**3d**.

Scheme-8 : (Bringmann *et al*, *J. Am. Chem. Soc.* **2000**, *122*, 9127-9133)



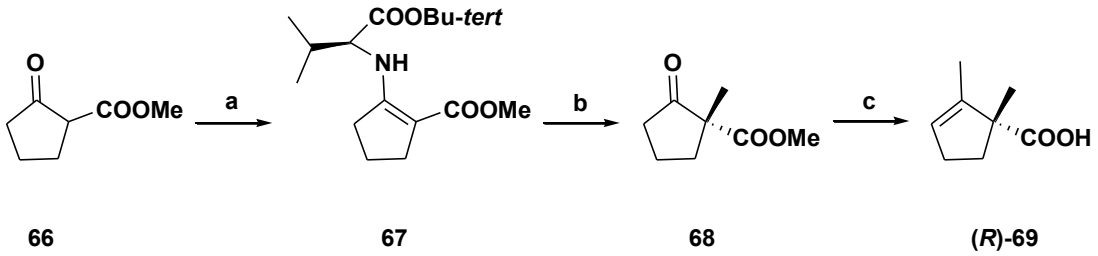
Reagents and conditions *: a) (i) $NaBH_4$; (ii) $(CBrCl_2)_2$, PPh_3; (iii) LAH, 82%; b)* ***22****, DCC, DMAP, 79%; c) (i) $Pd(OAc)_2$; (ii) H_2, Pd/C, 72%; d) BH_3-THF,* ***(S)-65****, -78 ^{o}C, 46%.*

However, this synthesis differs in two respects : First, dioxygenated aromatic building block **59** has been used as a starting material, which was transformed to *racemic* lactone **62** using diastereoselective intramolecular Heck coupling of ester **61** as one of the key steps. And second, authors have developed a route to enantiomerically pure material, which was achieved by kinetic resolution of the lactone **62** by subjecting it to CBS reduction. Under these conditions, reduction was found to proceed with perfect enantiomer-differentiating selectivity, which afforded unreacted enantiomer **(*R*, *R*)-64** in 99.9% ee after 51.5% conversion of the starting lactone **62**. This was further utilized for the synthesis of **(-)-3d** as reported earlier.[5]

Fukuyama's Approach : (Scheme-9, 2001)[16, 17]

This article entitled "Total syntheses of neuroprotective mastigophorenes A and B" reported enantioselective synthesis of (-)-herbertenediol **3d** by applying intramolecular Heck reaction as the key step as described earlier, except starting from (*R*)-carboxylic acid **69**, which was prepared by using Koga's protocol[18] as shown below.

Scheme-9 : (Fukuyama *et al*, *Tetrahedron* **2001**, *57*, 7127-7135)



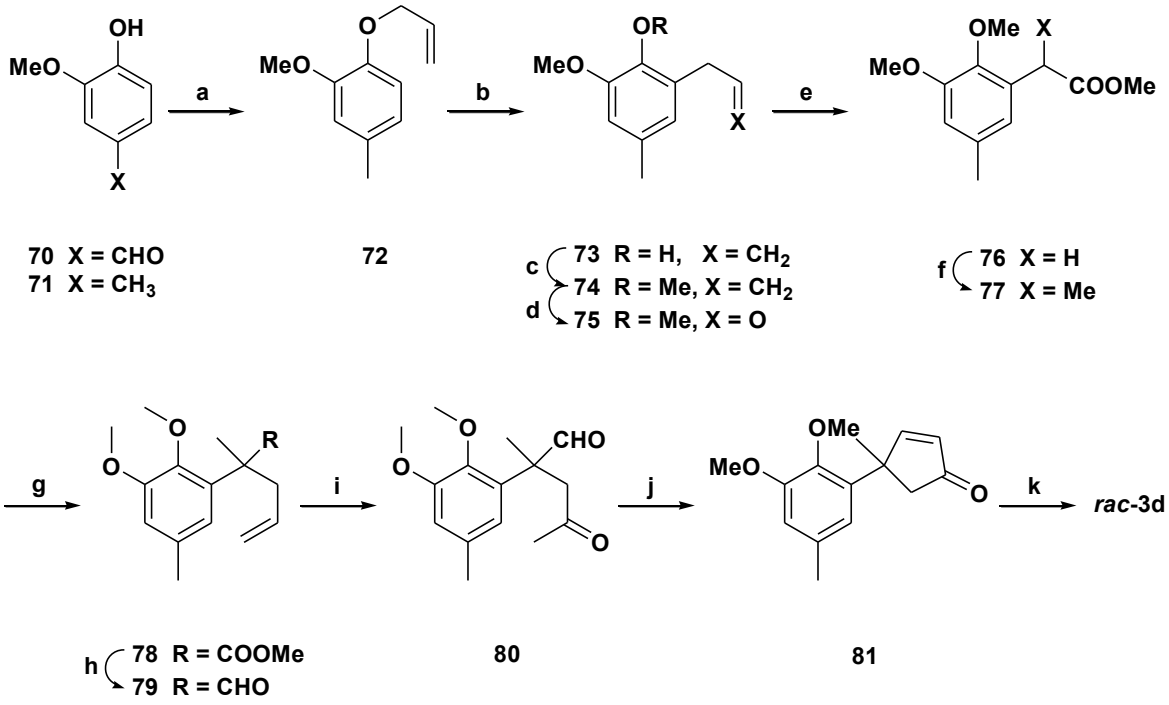
Reagents and conditions *: a) (S)-valine tert-butylester, BF_3-OEt_2, benzene, 99%; b) LDA, HMPA, MeI, -78 °C, then -25 °C, toluene, 40% (98% ee); c) (i) MeMgI, Et_2O; (ii) P_2O_5, benzene; (iii) KOH, MeOH, H_2O, 33% for 3 steps.*

Accordingly, lithiated chiral enamine **67**, prepared from methyl-2-oxo-cyclopentane carboxylic acid **66** and (*S*)-valine *tert*-butyl ester, was alkylated with MeI in toluene containing HMPA to give **(*R*)-68**, which was transformed to **(*R*)-69** following a few steps. (-)-Herbertenediol **3d**, thus synthesized from **(*R*)-69**, was further utilized for the synthesis of (-)-mastigophorenes A and B.

Srikrishna's Approach : (Scheme-10, 2001)[19, 20]

Claisen rearrangement based formal synthesis of *rac*-herbertenediol **3d** reported by Srikrishna *et al* started from vanillin **70**, which was subjected to Clemmensen reduction followed by *O*-allylation to furnish allyl ether **72**.

Scheme-10 : (Srikrishna *et al*, *Tetrahedron Lett.* **2001**, *42*, 5781-5782)



Reagents and conditions *: a) K_2CO_3, acetone, allylbromide, reflux, 92%; b) sealed tube, 180 ^oC, 67%; c) NaOH, Me_2SO_4, 87%; d) O_3, O_2, CH_2Cl_2, MeOH, -70 ^oC, Me_2S, rt; e) Jones' reagent, acetone, 0 ^oC to rt, MeOH, H_2SO_4, 94%; f) LDA, THF, MeI, -70 ^oC to rt, 88%; g) LDA, THF, HMPA, allylbromide, -70 ^oC to rt, 74%; h) (i) LAH, Et_2O; (ii) PCC, CH_2Cl_2, rt, 87%; i) $PdCl_2$, CuCl, DMF, H_2O, O_2, rt, 77%; j) KOH, MeOH, THF, rt, 92%; k) (i) NaH, THF, DMF, MeI, rt, 76%; (ii) Pd/C, H_2, EtOH, rt, 1 atm., 95%; (iii) ref-9.*

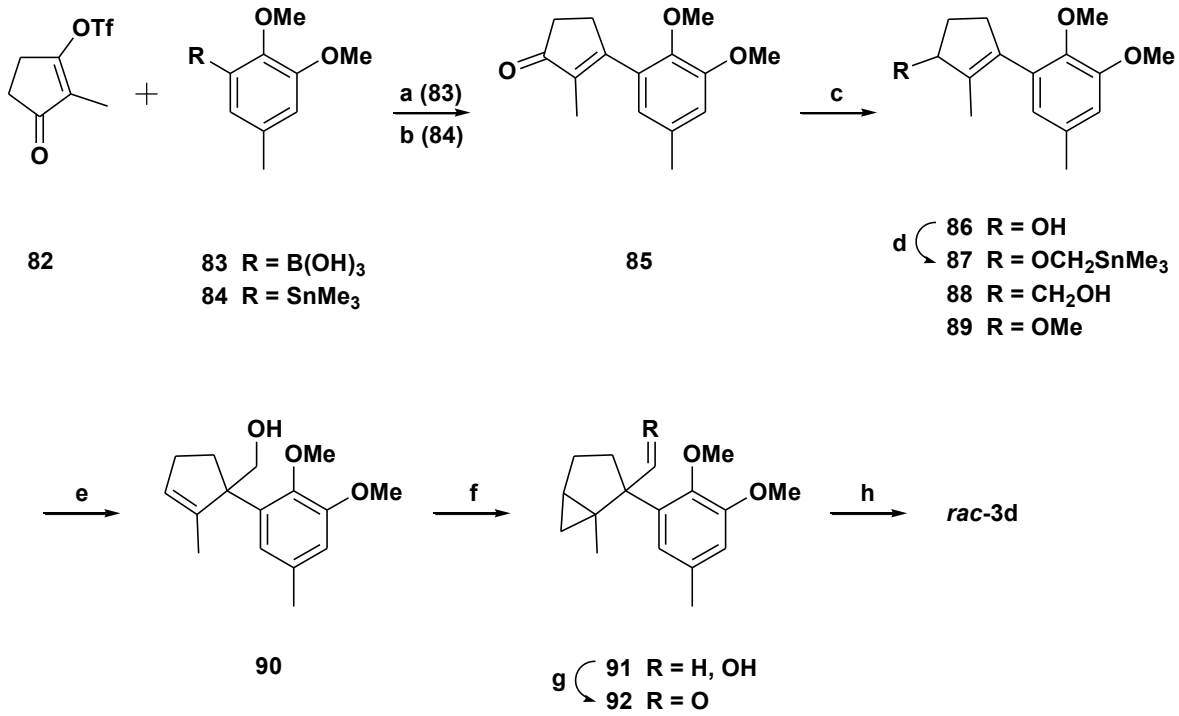
Thermal activation of **72** at 180 ^oC afforded *ortho* Claisen product **73** in 67% yield, which was transformed to ester **76** in a few steps. Alkylation of the ester **76** with MeI using LDA as the base generated the ester **77**, which on further allylation with allyl bromide using LDA, HMPA furnished the key intermediate **78**. A two step conversion of the ester to an aldehyde and Wacker oxidation of the terminal olefin, followed by intramolecular

aldol condensation of the resultant keto-aldehyde **80**, resulted in the cyclopentenone **81** in 61% overall yield. It was further utilized for the synthesis of the title compound.

Abad's Approach : (Scheme-11, 2001)[21]

An approach for the construction of the bicyclic herbertane system based on a Suzuki cross coupling reaction[22] and a [2,3]-sigmatropic Still-Wittig rearrangement[23] has been described here, which culminated in the synthesis of *rac*-herbertenediol **3d**.

Scheme-11 : (Abad *et al*, *Tetrahedron* **2001**, *59*, 9727-9735)



***Reagents and conditions** : a) $Pd(PPh_3)_4$, aq. Na_2CO_3, dioxane, reflux, 98%; b) $Pd_2(dba)_3$, NMP, rt, 60%; c) DIBAL, CH_2Cl_2, -78 ^oC, 98%; d) KH, THF, 0 ^oC, Me_3SnCH_2I, rt, 95%; e) n-BuLi, hexane, -78 ^oC to -10 ^oC, 55%; f) Et_2Zn, CH_2I_2, CH_2Cl_2, rt, 76%; g) Swern oxidation, 85%; h) (i) N_2H_4, DEG, NaOH, 160 ^oC, 75%; (ii) H_2, PtO_2, AcOH, NaOAc, 80%; (iii) BBr_3, 82%.*

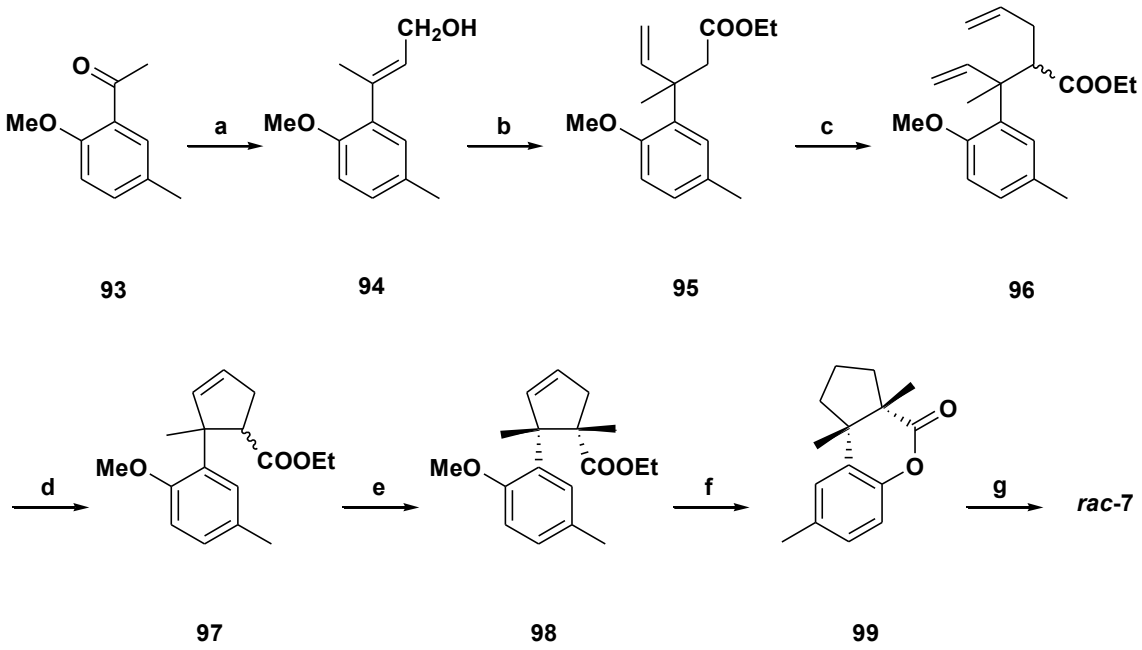
Thus, Suzuki cross coupling of the aryl boronic acid **83** with the enoltriflate **82** afforded the enone **85** in very high yield, which on DIBAL reduction at -78 ^oC gave allyl alcohol **86** in 98% yield. For the construction of the quaternary benzylic carbon, the alcohol **86** was transformed to the allylstannyl methyl ether **87**, which on treatment with n-BuLi at -78 ^oC generated the α-lithio ether, that underwent a smooth [2,3]-sigmatropic

rearrangement upon warming to -10 ^{o}C to deliver the homoallylic alcohol **90** in 55% overall yield, together with 3: 2 mixture of allylic alcohol **88** and a small amount of methyl ether **89**. Intermediate **90** on cyclopropanation followed by Swern oxidation of the primary hydroxyl group afforded **92**, which on Huang-Minlon reduction, reductive opening of the cyclopropane ring and demethylation furnished *rac*-herbertenediol **3d**.

Srikrishna's Approach : (Scheme-12, 2002)[24]

The second communication by Srikrishna *et al* described total synthesis of *rac*-1,14-herbertenediol **7** and *epi*-herbertenolide, *i. e.* 11-*epi*-**4a** using ring closing metathesis as the key step.

Scheme-12 : (Srikrishna *et al*, *Tetrahedron Lett.* **2002**, *43*, 151-154)



Reagents and conditions *: a) (i) NaH, $(EtO)_2P(O)CH_2COOEt$, THF, rt, 16 h; (ii) LAH, Et_2O, -70 ^{o}C to rt, 2 h, 87%; b) $MeC(OEt)_3$, EtCOOH, 180 ^{o}C, 76%; c) LDA, THF, -70 ^{o}C to rt, allylbromide, 4 h, 86%; d) Grubbs' catalyst, CH_2Cl_2, rt, 4 h, 95%; e) LDA, THF, HMPA, 0 ^{o}C to rt, MeI, 77%; f) (i) Pd/C, H_2, EtOH, rt, 93%; (ii) BBr_3, CH_2Cl_2, 0 ^{o}C to rt, 85%; g) LAH, Et_2O, -70 ^{o}C to rt, 92%.*

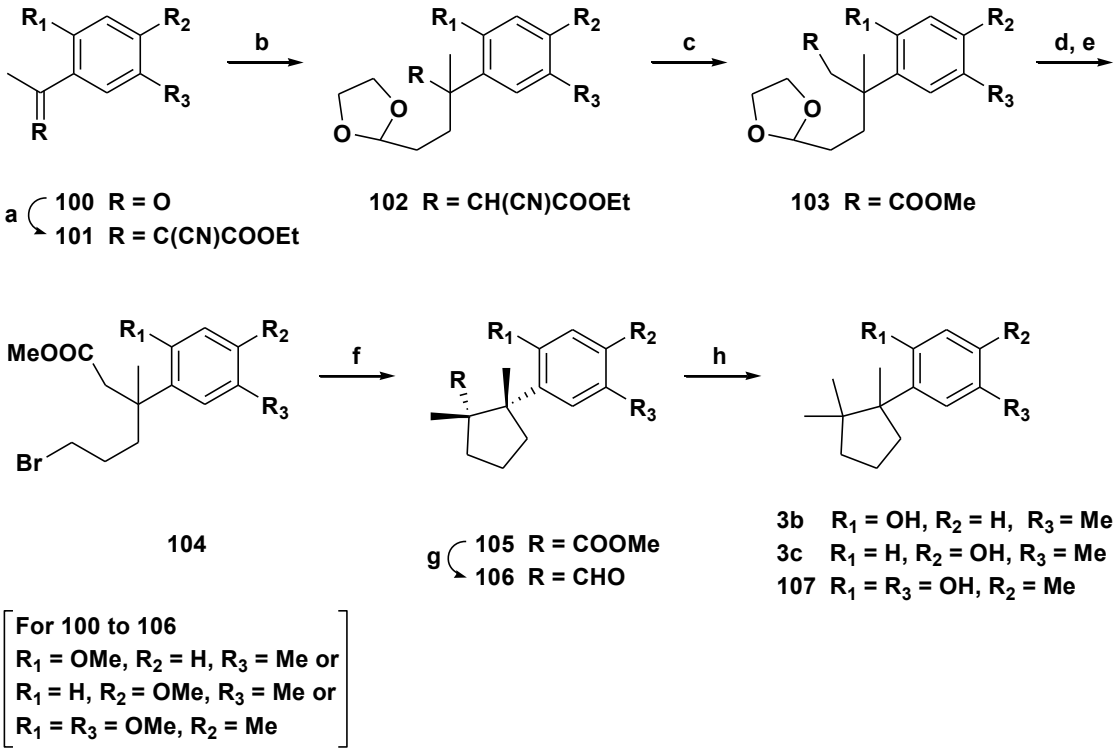
The synthesis of *rac*-**7** started from acetophenone **93**, which on Horner-Wadsworth-Emmons olefination followed by regioselective reduction of the ester functionality with LAH provided key intermediate **94**. The orthoester Claisen rearrangement of this allylic

alcohol **94** using triethylorthoacetate and propionic acid in a sealed tube at 180 ^{o}C furnished the ester **95**, which on *C*-allylation followed by ring closing metathesis of the resulting diene ester **96** provided **97**. It was further transformed to the title compound as depicted in the scheme-12.

Mukherjee's Approach : (Scheme-13, 2003)[25]

Stereoselective synthesis of *rac*-α-herbertenol **3b**, *rac*-β-herbertenol **3c** and *rac*-1,4-cuparenediol **107** have been described involving intramolecular cyclisation of 3-aryl-3-methyl-6-bromohexanoates **104** and *in situ* methylation of the resulting cyclopentane carboxylate as the key steps. The reaction sequence has been depicted in the following scheme.

Scheme-13 : (Mukherjee *et al*, *Tetrahedron Lett.* **2003**, *44*, 737-740)

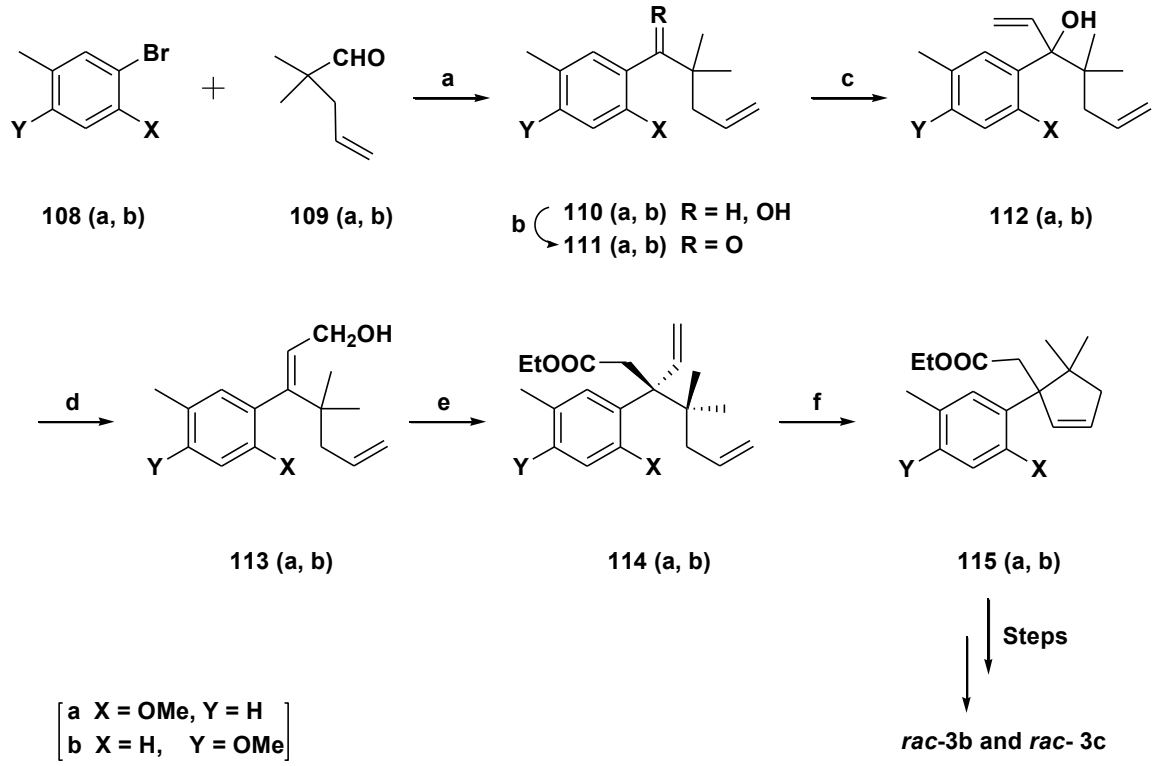


Reagents and conditions *: a) $CH_2(CN)COOEt$, NH_4Ac, AcOH, benzene, reflux, 75%; b) (-OCH_2CH_2O-)$CHCH_2CH_2MgBr$, CuBr-Me_2S, THF, Et_2O, 0 to 20 ^{o}C, 58%; c) (i) KOH, ethylene glycol, H_2O, reflux, AcOH, 0 ^{o}C; (ii) CH_2N_2, 0 ^{o}C, 75%; d) (i) AcOH-H_2O, 25 to 60 ^{o}C; (ii) $NaBH_4$, MeOH, 0 to 25 ^{o}C, 82%; e) PBr_3, benzene, 0 to 70 ^{o}C, 85%; f) (i) LDA, THF, HMPA, -70 ^{o}C; (ii) LDA, HMPA, THF, 0 ^{o}C, MeI, 85%; g) (i) LAH, THF, reflux, 85%; (ii) PCC, NaOAc, CH_2Cl_2, 25 ^{o}C, 85%; h) (i) N_2H_4, N_2H_4-2HCl, DEG, 125 ^{o}C, KOH, 210 ^{o}C; (ii) BBr_3, 70%.*

Srikrishna'a Approach : (Scheme-14, 2003)[26]

This particular approach resembles the previous one by Srikrishna *et al* in involvement of Claisen rearrangement and RCM as the key reactions.

Scheme-14 : (Srikrishna *et al*, *Tetrahedron Lett.* **2003**, *44*, 1027-1030)



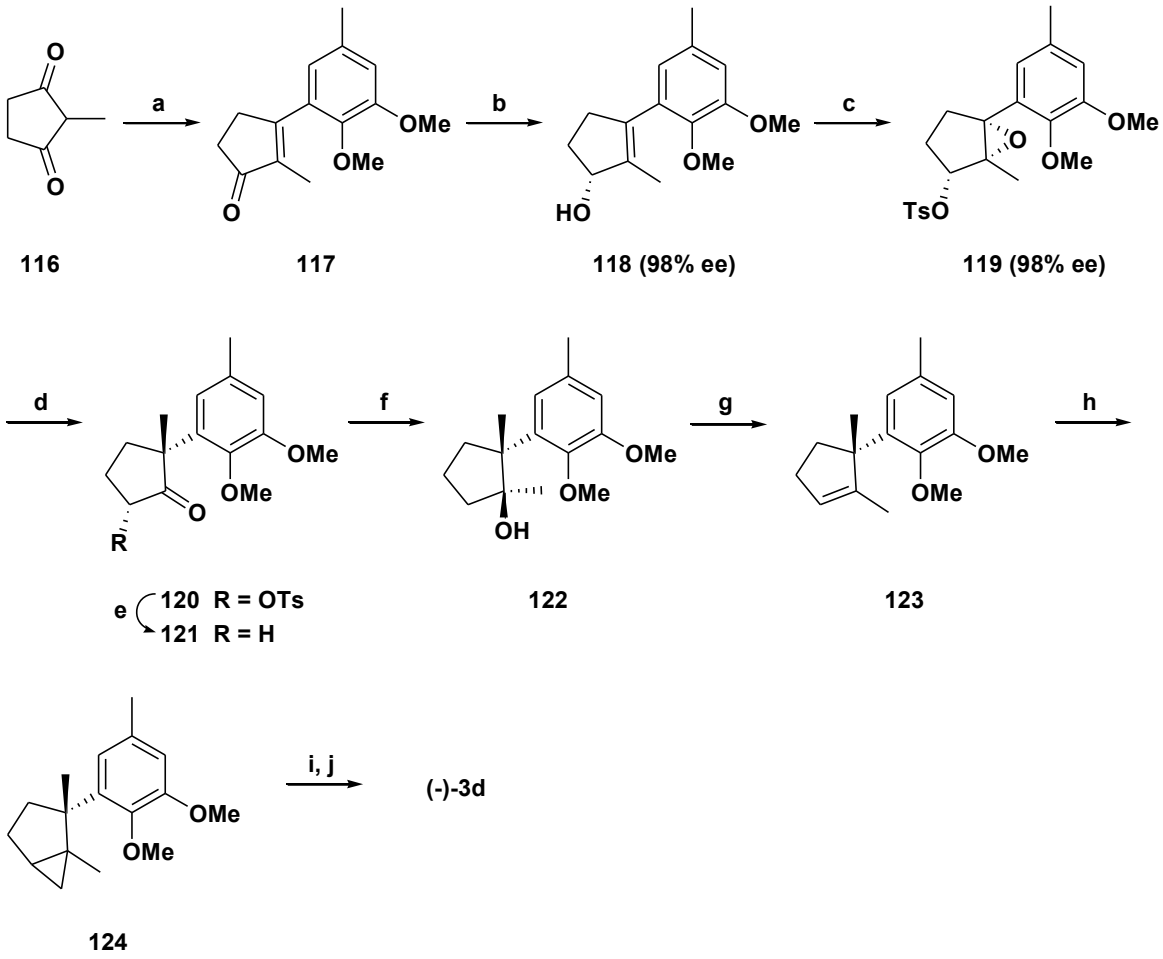
***Reagents and conditions** : a) Li, THF,))), 45 min, 72 and 79%; b) PCC, silica gel, CH_2Cl_2, 91 and 89%; c) vinyl magnesium bromide, THF, 78 and 80%; d) (i) PCC, silica gel, CH_2Cl_2, 84 and 76%; (ii) $NaBH_4$, MeOH, 0-5 ^oC, 89 and 81%; e) $MeC(OEt)_3$, EtCOOH, sealed tube, 180 ^oC, 30 and 45%; f) $PhCH=RuCl_2(PCy_3)_2$, CH_2Cl_2, rt, 88 and 94%.*

Scheme-14 represents the reaction sequence using which *rac*-α-herbertenol **3b** and *rac*-β-herbertenol **3c** have been synthesized.

Kita's Approach : (Scheme-15, 2003)[27]

This communication described asymmetric synthesis of (-)-herbertenediol **3d** using rearrangement of the optically active 3-aryl-2-methyl-2,3-epoxytosylate **119** (98% ee), which was synthesized from pentanedione **116** using CBS reduction and stereoselective epoxidation as the key steps.

Scheme-15 : (Kita *et al*, *Tetrahedron Lett.* **2003**, *44*, 411-413)



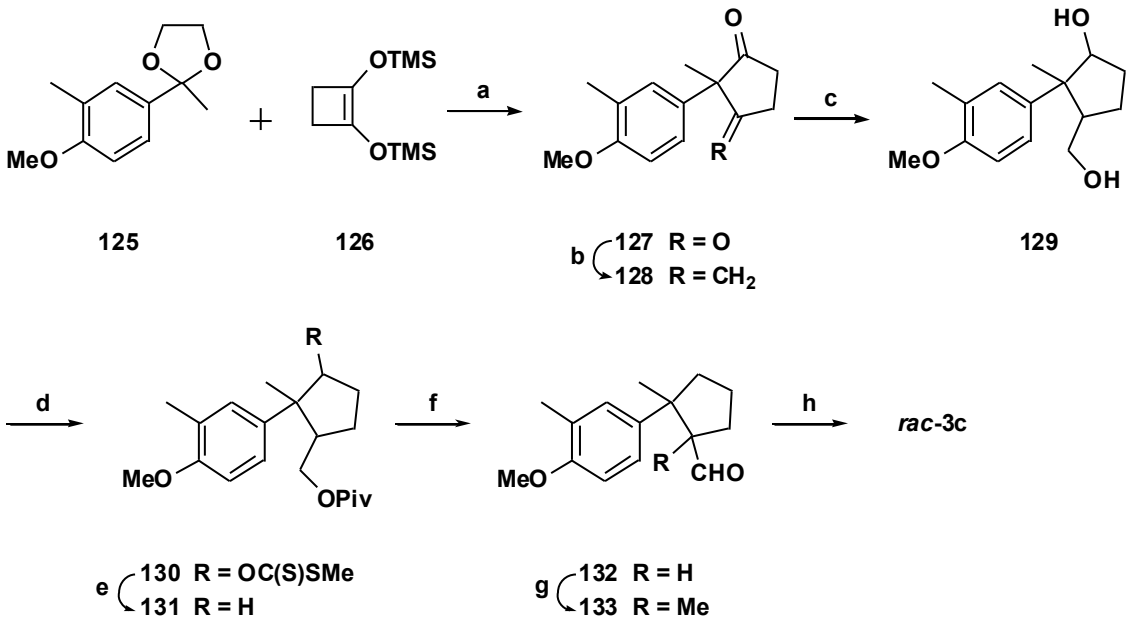
Reagents and conditions *: a) (i) TsOH, i-BuOH; (ii) 2,3-dimethoxy-5-methyl bromobenzene, n-BuLi, $CeCl_3$; b) BH_3-Me_2S, **65**, 100%; c) (i) $VO(acac)_2$, TBHP, 99%; (ii) TsCl, pyridine, 100%; d) $EtAlCl_2$, CH_2Cl_2, 99%; e) Zn, AcOH, 91%; f) MeLi, $CeCl_3$, THF, 92%; g) $EtN^+SO_2N^-COOMe$, THF, reflux, 82%; h) Et_2Zn, CH_2I_2, CH_2Cl_2, 76%; i) PtO_2, H_2, NaOAc, AcOH, 93 %; j) BBr_3, 93%.*

Thus, epoxide **119** (98% ee) on treatment with $EtAlCl_2$ afforded rearranged product **120** in high yield and without loss of optical purity. Reductive removal of the tosyloxy group followed by 1,2-addition of $MeCeCl_2$ gave alcohol **122**, which on dehydration using Burgess reagent followed by cyclopropanation of the resulting cyclopentene **123** under Simmons-Smith conditions, provided **124**. The reductive opening of the cyclopropane ring of **124** followed by demethylation furnished **(-)-3d** (98% ee). Similar strategy has also been employed for the enantioselective synthesis of (-)-α-herbertenol **3b**.[28]

Chavan's Approach : (Scheme-16, 2003)[29]

This article described synthesis of *rac*-β-herbertenol **3c** using 1,3-cyclopentadione annelation strategy[30] for the introduction of quaternary benzylic methyl group.

Scheme-16 : (Chavan *et al*, *Tetrahedron* **2003**, *59*, 2737-2741)



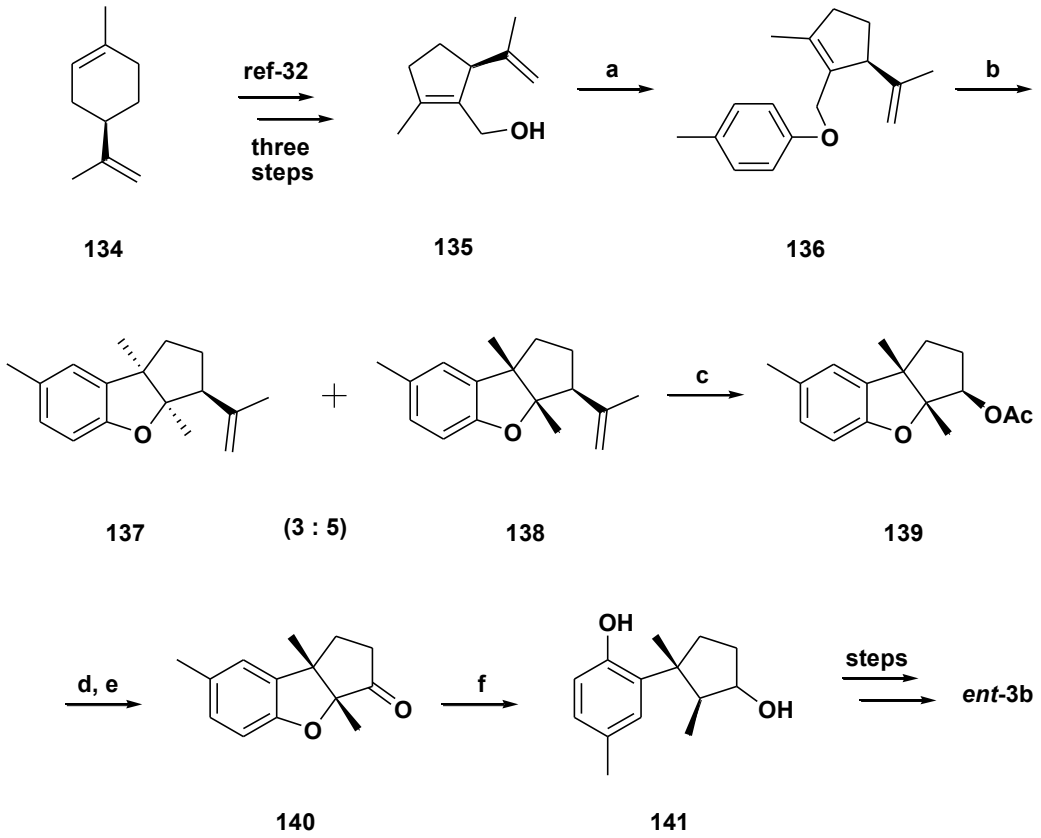
Reagents and conditions *: a) BF_3-OEt_2, -78 ^oC, 68%; b) Ph_3P^+ MeI^-, KOBu-tert, benzene, reflux, 72%; c) (i) $NaBH_4$, EtOH, 98%; (ii) BMS, THF, 0 ^oC to rt, then H_2O_2, OH^-, 0 ^oC to rt, 71%; d) (i) Me_3CCOCl, Et_3N, CH_2Cl_2, 0 ^oC to rt, 84%; (ii) NaH, CS_2, THF, rt, MeI, 86%; e) TBTH, AIBN, toluene, reflux, 83%; f) (i) LAH, THF, rt, 92%; (ii) PCC, CH_2Cl_2, 0 ^oC to rt, 86%; g) NaH, DME, 0 ^oC, MeI, rt, 65%; h) (i) N_2H_4-H_2O, NaOH, TEG, 195 ^oC, 52%; (ii) BBr_3, 81%.*

Thus, cyclopenta-1,3-dione **127** was prepared by annelation of 1,3-dioxolane **125** and 1,2-disilyloxycyclobutene **126**, which was further elaborated to the title compound using common functional group transformations in 4.5% overall yield (Scheme-16).

Srikrishna's Approach : (Scheme-17, 2004)[31]

The present approach dealt with the stereoselective synthesis of (+)-α-herbertenol, *i. e.* ***ent*-3b** using Claisen rearrangement of the aryl allyl ether **136** as the key step. This aryl allyl ether **136** was prepared from allylalcohol **135**, which in turn was synthesized in three steps from (*R*)-limonene **134**.[32]

Scheme-17 : (Srikrishna *et al*, *Tetrahedron* **2004**, *60*, 2125-2130)



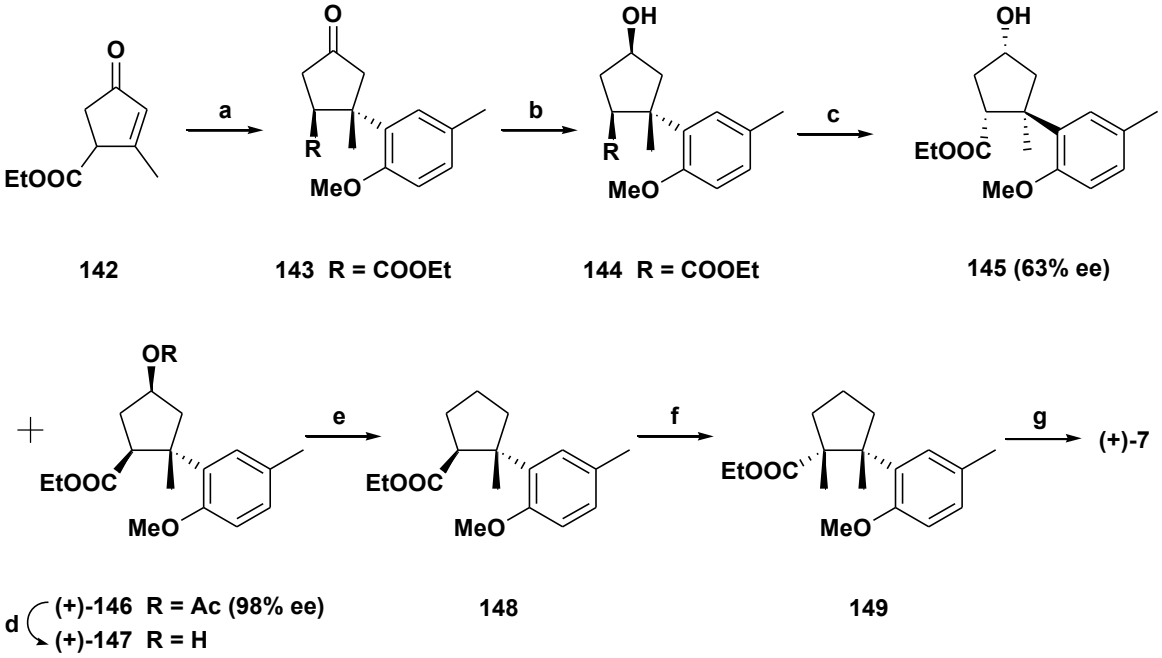
Reagents and conditions *: a) p-cresol, PPh_3, DIAD, THF, rt, 85%; b) $PhNMe_2$, sealed tube, 180 ^oC, 65%; c) O_3/O_2, CH_2Cl_2-MeOH, -70 ^oC, Ac_2O, Et_3N, DMAP, benzene, reflux, 75%; d) K_2CO_3, MeOH, rt, 83%; e) PCC, NaOAc, CH_2Cl_2, rt, 88%; f) Li, liquid NH_3, 83%.*

Thus, thermal activation of the ether **136** in *N*,*N*-dimethylaniline in a sealed tube at 180 ^oC afforded 3: 5 mixture of the cyclised product **137** and **138** in 65% overall yield, which were separated by silica gel and silver nitrate impregnated silica gel column chromatography. After creating the requisite new chiral quaternary carbon atoms, the original chiral center was disposed off *via* degradation of the isopropenyl group employing a Criegee rearrangement[33] to afford **139** in 75% yield. Hydrolysis of the acetate functionality of **139** and PCC oxidation of the resulting alcohol afforded ketone **140**, which on reductive cleavage using Li in liquid NH_3 furnished the diol intermediate **141**. It was further elaborated to (+)-α-herbertenol *ent*-**3b** in a few steps.

Acherar's Approach : (Scheme-18, 2004)[34]

An enantioselective synthesis of (+)-1,14-herbertenediol **7**, employing a lipase promoted kinetic resolution[35] of (±)-**144** as the key step, has been described in this particular approach.

Scheme-18 : (Acherar *et al*, *Eur. J. Org. Chem.* **2004**, 5092-5099)



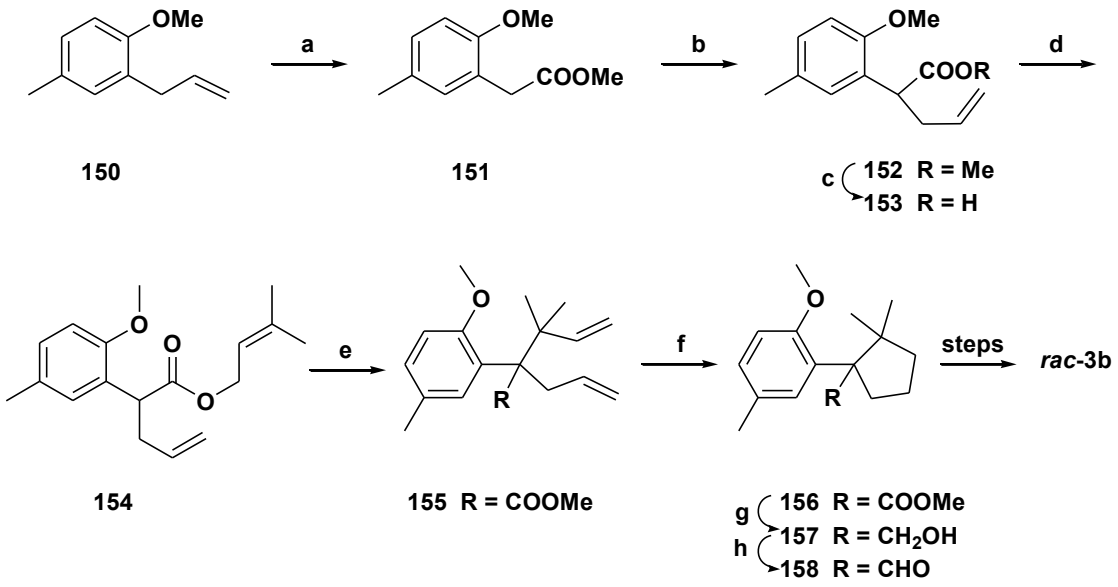
Reagents and conditions *: a) (i) 2-bromo-4-methylanisole, Mg, Et_2O; (ii) $ZnCl_2$, THF, 0 ^oC; (iii) $Ni(acac)_2$, THF, 0 ^oC, 96%; b) $NaBH_4$, $CeCl_3$-$7H_2O$, EtOH, -78 ^oC, quantitative; c) lipase AK, vinylacetate, rt, 2 d, 53%* ***(145)*** *and 45%* ***(146)****; d) Na_2CO_3, MeOH, rt, 97%; e) (i) NaH, CS_2, MeI, THF; (ii) TBTH, AIBN, toluene, reflux, 98%; f) LDA, HMPA, MeI, THF, -90 ^oC to rt, 65%; g) (i) BBr_3; (ii) LAH, Et_2O, 0 ^oC, 96%.*

The alcohol **144** was prepared by $Ni(acac)_2$-catalyzed 1,4-addition of the organozinc reagent, prepared from 2-methoxy-5-methylphenylmagnesium bromide followed by Luche reduction of the resulting intermediate **143**, in 96% overall yield. The acetate **(+)-146** obtained after resolution, was hydrolyzed under alkaline conditions and the resultant secondary hydroxyl group of **147** was deoxygenated under Barton-McCombie's conditions, followed by stereoselective methylation of the resulting intermediate **148** using LDA as the base to provide the single diastereomer **149**, which was further transformed to **(+)-7** by deprotection of methyl ether and reduction of the ester functionality in high yields. Intermediate **149** was also utilized for the synthesis of (-)-α-herbertenol **3b**.

Srikrishna'a Approach : (Scheme-19, 2005)[36]

This communication reported a combination of Ireland ester Claisen rearrangement and RCM as the key steps for the formal synthesis of *rac*-herbertene-1,13-diol **6**[37] and *rac*-α-herbertenol **3b**.

Scheme-19 : (Srikrishna *et al*, *Synlett* **2005**, *7*, 1173-1175)



Reagents and conditions *: a) O_3/O_2, MeOH-CH_2Cl_2, $NaHCO_3$, -70 ^oC, Ac_2O, Et_3N, benzene, DMAP, reflux, 70%; b) LDA, THF, allylbromide, -70 ^oC to rt, 85%; c) NaOH, MeOH-H_2O, reflux, 95%; d) DCC, DMAP, Me_2C=$CHCH_2OH$, CH_2Cl_2, rt, 92%; e) (i) LDA, THF, TMSCl, Et_3N, -70 ^oC to rt, reflux; (ii) dilute HCl; (iii) CH_2N_2, 77%; f) (i) $Cl_2Ru(PCy_3)_2$=$CHPh$, CH_2Cl_2, 98%; (ii) Pd/C, H_2, EtOH, 1 atm, 100%; g) LAH, Et_2O, 97%; h) PCC, silica gel, CH_2Cl_2, rt, 90%.*

The synthetic sequence started from anisole **150**, which on ozonolysis followed by Criegee rearrangement and *C*-allylation of the resulting ester **151**, afforded **152** in high yields. Further, dimethylallyl ester **154**, prepared by DCC coupling reaction of the acid **153** and the corresponding allyl alcohol, on Ireland ester Claisen rearrangement followed by hydrolysis and esterification using diazomethane gave ester **155** in 77% yield. This diene ester **155** on ring closing metathesis using Grubbs' first generation catalyst followed by hydrogenation afforded **156**, which was further transformed to the known aldehyde **158** in good yields and further converted to *rac*-**3b** efficiently.

1.1.3 References

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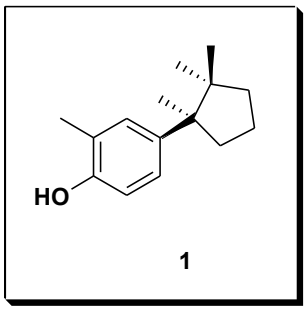
Chapter-1, Section-2 : Enantiospecific Synthesis of (+)-β-Herbertenol

1.2.1 Introduction

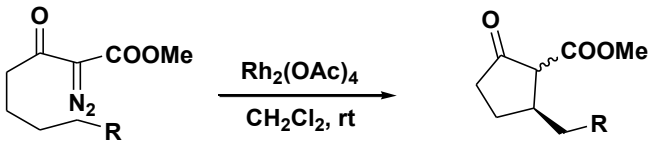
Keeping in mind; (i) the biological activities associated with the phenolic herbertanes and (ii) abundancy of (*R*)-(+)-citronellal in both plants and of synthetic origin, prompted it's utilization for the first enantiospecific synthesis of laevigatin;[1] which encouraged the design of enantiospecific synthesis of β-herbertenol **1**,[2] that could be applicable to other herbertanes also. Here, the primary focus was just to introduce chirality at the nonfunctionalised benzylic position using (*R*)-(+)-citronellal as the source of chirality for herbertane skeleton formation, *i. e.* synthesis of cyclopentane ring with vicinal quaternary carbons. Thus, this section describes the first enantiospecific synthesis of β-herbertenol, where Taber's protocol of diazodecomposition of C-H insertion was used as the key step.



1

In 1982, Taber[3] reported a simple method for the preparation of 2-carbalkoxy cyclopentanones by intramolecular C-H insertion under Rh-catalyzed diazodecomposition of α-diazo-β-ketoesters **2**. The functionalized cyclopentanones produced by this cyclisation were proved to be versatile intermediates for elaboration of complex natural products.[4]

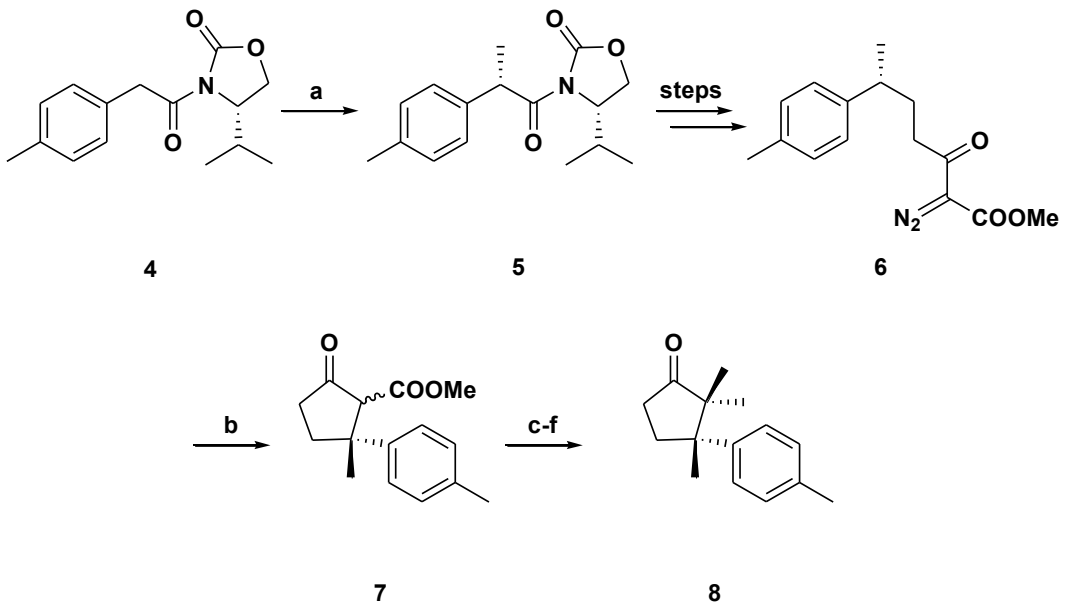
Scheme-1



2 **3**

However, initial studies described in this publication didn't give any evidence of the proposed stereospecificity of C-H insertion process, but it was lateron proved by the same authors in 1985 by successfully applying it to the enantioselective synthesis of (+)-α-cuparenone **8**,[5] where corresponding α-diazo-β-ketoester **6** was synthesized by diastereoselective alkylation of oxazolidene **4** followed by a few functional group transformations.

Scheme-2 : (Taber *et al*, *J. Am. Chem. Soc.* **1985**, *107*, 196-199)



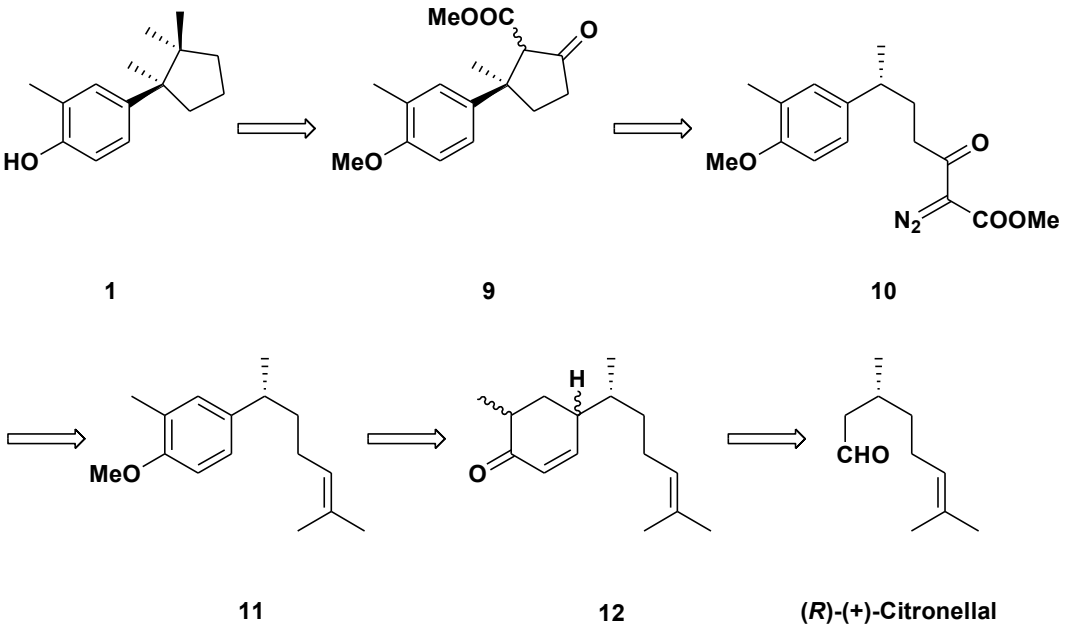
Reagents and conditions *: a) LDA, THF, MeI, 49%; b) $Rh_2(OAc)_4$, CH_2Cl_2, 52%; c) ethylene glycol, p-TsOH; d) DIBAL; e) HCl, H_2O, CH_2Cl_2, silica gel; f) L-Selectride, MeI, 26%.*

Intermediate **6** was further subjected to diazodecomposition by using $Rh_2(OAc)_4$ as the catalyst to furnish cyclic β-ketoester **7**, which on reductive alkylation resulted in (+)-α-cuparenone **8** (96% ee).

1.2.2 Present work : *Results and discussion*

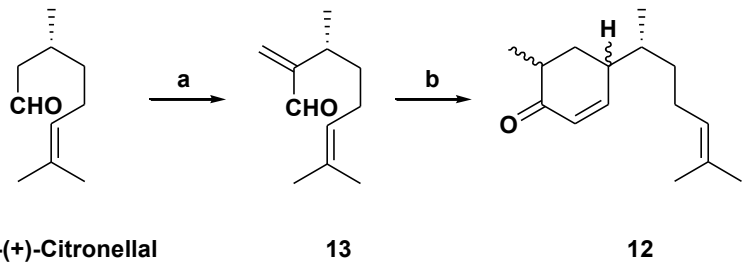
Thus, as shown in the retrosynthetic analysis (Scheme-3), β-herbertenol **1** could be synthesized from cyclic β-ketoester **9**, which in turn could be obtained from acyclic α-diazo-β-ketoester **10** by using Taber's protocol of stereospecific C-H insertion by diazodecomposition. The corresponding β-ketoester could be synthesized from the anisole **11**, which in turn could be synthesized enantiospecifically from (*R*)-(+)-citronellal *via* enone **12**.

Scheme-3



Accordingly, the synthesis initiated from enone **12**, which was prepared from (*R*)-(+)-citronellal as reported in the literature.[6]

Scheme-4



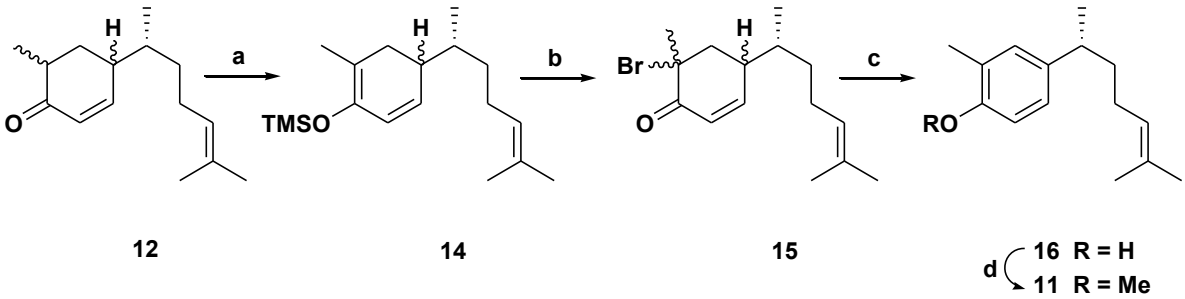
Reagents and conditions *: a) piperidine acetate, formalin, 110 °C, 4 h; b) methyl-2-methyl-3-oxobutanoate, NaOMe (cat), MeOH, rt, 2 h, reflux, 5 h, 36%.*

The product formation was confirmed by comparison of it's IR and NMR spectral data with those of literature values[6] and were found to be in good agreement with the proposed structure **12**. Also, enone **12** was found to be a mixture of diastereomers as suggested by it's NMR spectral data, but as these newly generated chiral centers would be destroyed in the subsequent steps of the synthesis, no attempt was made to separate or characterize them.

The next crucial reaction was the aromatization of enone **12**, for which dehydrohalogenation of the corresponding bromoenone **15** was envisioned as the key reaction. However, presence of an additional olefin functionality in the system forced us to opt for a method, which would provide selectivity and regiospecificity as well, in bromination of enone **12**. This was achieved by adopting Hassner's protocol,[7] where silyl enol ethers, derived from the corresponding aldehydes or ketones, were treated with 1 equivalent of NBS to afford the corresponding α-bromo carbonyl compounds. This methodology is applicable to a wide range of carbonyl compounds; particularly noteworthy is the bromination in the presence of an olefin or ester functionality. Also, as one can regiospecifically synthesize enol ethers,[8] this method would provide the required regiospecificity.

Accordingly, silyl enol ether **14** was prepared from enone **12** following the method developed by House *et al*,[8] that is by treatment of **12** with LDA as the base to generate the enolate, which was quenched by chlorotrimethylsilane (silylating agent). Sily enol ether **14** on treatment with *N*-bromosuccinimide in THF at 0 ^{o}C afforded the bromoenone **15** (mixture of diastereomers) as the sole product in 40% isolated yield after column purification (Scheme-5). The poor yield might be attributed to the unstability of the bromoenone **15**, which was characterized by it's NMR spectral data and was confirmed by it's mass spectrum, which exhibited a peak at 301 $(M+2)^{+}$.

Scheme-5



12 **14** **15**

Reagents and conditions *: a) LDA, THF, -78 ^{o}C, 1.5 h, TMSCl, -78 ^{o}C to rt, 5 h; b) NBS, THF, 0 ^{o}C, 30 min; c) Li_2CO_3, LiBr, DMF, 130-140 ^{o}C, 4 h, 75% overall; d) Me_2SO_4, K_2CO_3, acetone, reflux, 12 h, 90%.*

However, unstability associated with **15** necessitated to go for dehydrohalogenation without it's column purification, which was achieved by heating it with lithium carbonate

and lithium bromide in dry DMF at 130 ^{o}C and as anticipated, it furnished the requisite phenol derivative **16** in improved overall yield (75%) from **12** (Scheme-5).

IR spectrum of the product **16** indicated the presence of a phenolic hydroxyl group by revealing an absorption at 3416 cm^{-1}, further evident from a resonance at δ 151.7 (s) in it's ^{13}C NMR spectrum. Also, presence of three olefin protons in the olefin region of it's ^{1}H NMR spectrum; apart from one at δ 5.07 (t, J = 6.8 Hz), which corresponds to the side chain olefin proton; suggested the formation of **16**. Further, three proton singlet at δ 2.23, assigned to the methyl group attached to the aromatic ring, supported this. Other significant signals in it's ^{1}H NMR spectrum were : three proton doublet at δ 1.19 (J = 6.8 Hz), assigned to the only secondary methyl group and two singlets at δ 1.52 and 1.67, each integrating for three protons, assigned to the two vinylic methyl groups. It's mass spectrum revealed a peak of (M^{+}) at 218, thus confirming the phenol derivative **16**, which was finally ascertained by it's elemental analysis.

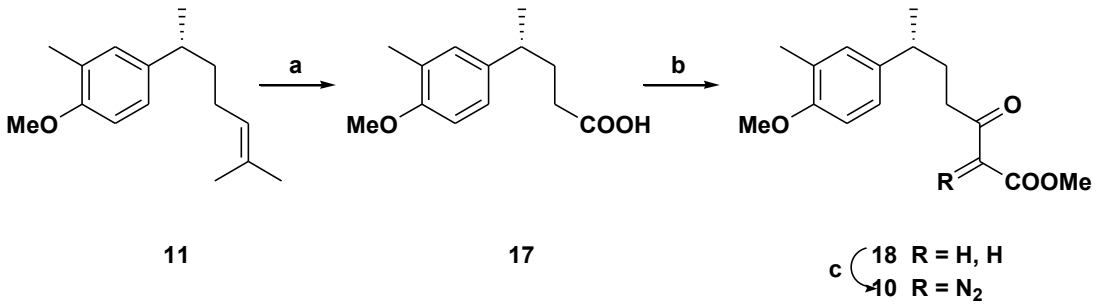
Phenol **16** was then protected as it's methyl ether **11** in 90% yield, using dimethyl sulfate and potassium carbonate in refluxing acetone (Scheme-5). Absence of absorption at 3416 cm^{-1} in it's IR spectrum and presence of a three proton singlet at δ 3.82 in it's ^{1}H NMR spectrum, characteristic of a methoxy group, suggested the formation of methyl ether derivative **11**, which was further evident from an additional methyl resonance at δ 55.1 in it's ^{13}C NMR spectrum. Mass spectrum finally confirmed **11** by exhibiting a peak of (M-1)$^{+}$ at 231.

Having successfully synthesized the requisite aromatic unit **11**, the key intermediate α-dizo-β-ketoester **10** could be obtained *via* an acid intermediate **17**, for which side chain double bond of **11** should be oxidatively chopped off. For this purpose, Weinrebs' protocol[9] was adopted, which uses combination of catalytic amount of osmium tetroxide and stoichiometric amount of Jones' reagent in acetone. It is believed that the process involves initial formation of an osmate ester, and osmium is then reoxidized by the chromate, which also cleaves the 1,2-diol. Under these conditions, olefin **11** afforded acid **17** in 80% isolated yield (Scheme-6).

Presence of a strong stretching band at 1709 cm^{-1}, characteristic of a carboxylic acid carbonyl group in the IR spectrum of the product indicated the required transformation, which was further evident from the absence of two singlets, characteristic of isopropylidene methyl groups and a triplet of olefin proton in it's ^{1}H NMR spectrum. A carbonyl resonance at δ 180.3 (s) in it's ^{13}C NMR spectrum further supported this.

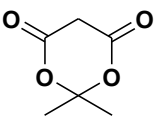
Intermediate **17** was finally confirmed by it's mass spectrum, which revealed a peak of $(M-1)^+$ at 221 and was ascertained by it's elemental analysis also.

Scheme-6



Reagents and conditions *: a) OsO_4 (cat), Jones' reagent, acetone, rt, 5 h, 80%; b) (i) $SOCl_2$, CH_2Cl_2, reflux, 2 h; (ii) Meldrum's acid* ***19****, pyridine, CH_2Cl_2, 0 ^oC to rt, 2 h; (iii) MeOH, reflux, 4 h, 78%; c) Et_3N, MsN_3, CH_2Cl_2, -5 ^oC to rt, overnight.*

To synthesize β-keto ester **18** from acid **17**, Meldrum's acid, *i. e.* 2,2-dimethyl-1,3-dioxane-4,6-dione **19**[10] was utilized. It could be easily acylated because of it's great acidity (*pKa* 13.7) to generate acyl Meldrum's acid, which on methanolysis afford corresponding β-ketoester. Thus, acid chloride, prepared from acid **17** using thionyl chloride, on treatment with Meldrum's acid **19** in dry CH_2Cl_2 in presence of pyridine as the base, followed by methanolysis of the crude acyl Meldrum intermediate, afforded β-ketoester **18** as the sole product in 78% overall yield.



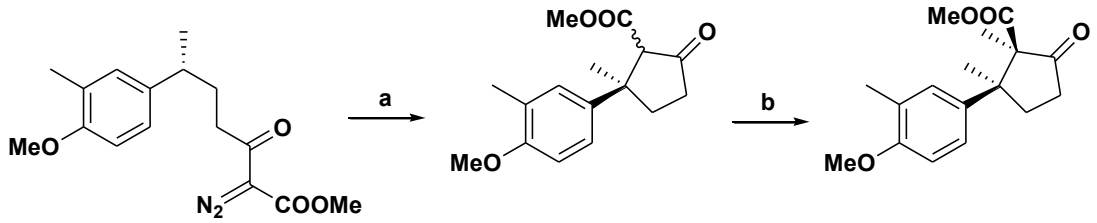
19 Meldrum's acid

Presence of two carbonyl stretching frequencies in the IR spectrum of the isolated product at 1747 cm^{-1}, characteristic of an ester carbonyl and 1718 cm^{-1}, characteristic of a keto carbonyl, indicated the formation of 1,3-diketone product, which was further supported by an additional three proton singlet at δ 3.69 and a two proton singlet at δ 3.33 in it's ^1H NMR spectrum, assigned to $-COOC\underline{H}_3$ and $-C(O)C\underline{H}_2COOMe$, respectively. This was further confirmed by two carbonyl resonances at δ 202.2 and 167.2, and an additional methylene resonance at δ 48.7 in it's ^{13}C NMR spectrum. Finally, formation of intermediate **18** was confirmed by it's mass spectrum, which exhibited a peak at 279 $(M+1)^+$ and by it's elemental analysis also, found to be in good agreement with the calculated values.

After successfully synthesizing the key β-keto ester intermediate **18**, the next job was to prepare α-dizo-β-ketoester **10** and to check the feasibility of Taber's protocol for the formation of cyclopentanone with quaternary benzylic center.

Intermediate **10** was prepared by adopting Regitz's protocol of diazo transfer,[11] according to which, β-ketoester **18** was treated with mesyl azide in dry CH_2Cl_2 in presence of triethylamine as the base, which provided the required diazo product **10** (Scheme-6). The formation of **10** was confirmed by it's IR spectrum (revealed a characteristic absorption at 2136 cm^{-1}), and was immediately subjected to diazodecomposition by treating it with catalytic amount of $Rh_2(OAc)_4$ in dry CH_2Cl_2 at room temperature, to afford cyclic β-ketoester **9** by C-H insertion at benzylic tertiary carbon atom, as a mixture of diastereomers in 35% overall yield from **18** (Scheme-7).

Scheme-7



10 **9** **20**

Reagents and conditions *: a) $Rh_2(OAc)_4$ (cat), CH_2Cl_2, rt, 30 min, 35% overall from **18**; b) K_2CO_3, MeI, acetone, rt, 24 h, 85%.*

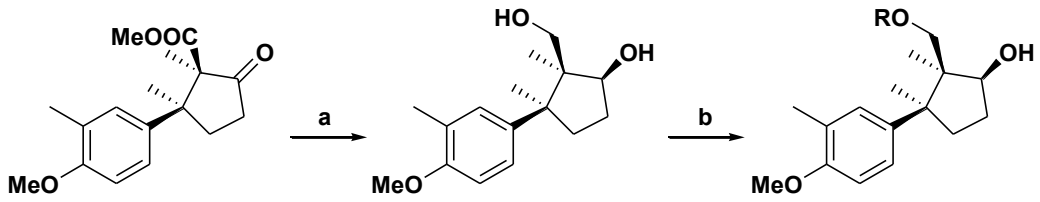
Intermediate **9** was characterized by it's IR, NMR spectral analysis and finally confirmed by it's HRMS, which exhibited a peak of M^+ at 276.1363 (expected; 276.1361). Also, as reported,[5] product should have retained the configuration at the reacting chiral center, which was decided to confirm by the sign of specific rotation of the final product, *i. e.* β-herbertenol, after completion of the synthesis and not at this stage.

The unstable cyclic β-ketoester **9** was further subjected to methylation using MeI in dry acetone using potassium carbonate as the base, which afforded single diastereomer **20** in 85% yield as the sole product with 100% diastereoselection, in which methyl and aryl groups on the adjacent quaternary carbons were *anti* to each other. The relative stereochemistry was proposed from it's ^1H NMR spectrum, in which the ester methyl singlet appeared at δ 3.30 ppm because of the shielding of methoxy carbonyl group by the

vicinal *cis* aryl group. Further, quaternary singlets at δ 49.2 and 64.4 supported the formation of this intermediate **20**. Other characteristic signals in it's ^{1}H NMR spectrum were : two singlets at δ 1.26 and 1.37, each integrating for three protons, due to two adjacent *cis*-methyl groups; and a three proton singlet at δ 2.19, assigned to Ar-C<u>H</u>$_3$. It's mass spectrum revealed a peak of $(M+1)^+$ at 291, thus confirmed the product formation, which was further ascertained by it's elemental analysis as well.

Having secured the requisite cyclopentanone **20**, deoxygenation of the two carbonyl functionalities followed by methyl ether deprotection should complete the synthesis of the target molecule, and this was achieved *via* diol intermediate **21**, which was synthesized by lithium aluminium hydride reduction of the ketoester **20** in dry THF at room temperature, in 80% isolated yield (Scheme-8).

<u>Scheme-8</u>

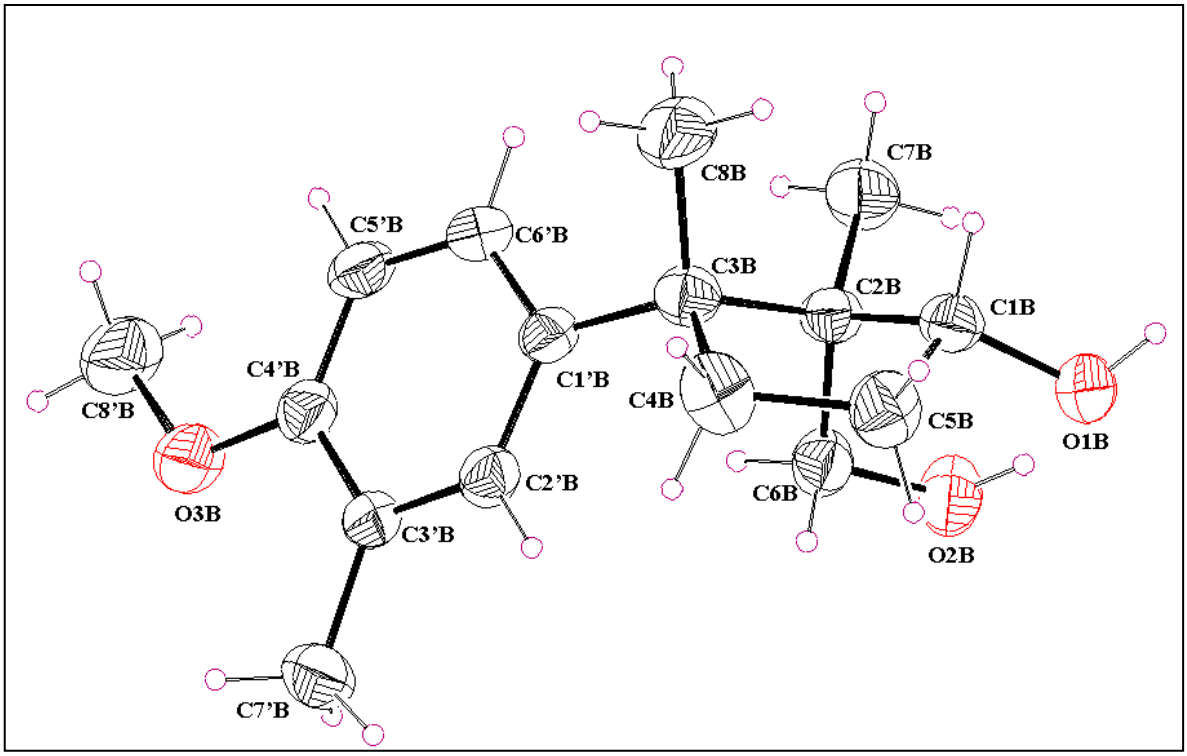


20 **21** **22 R = C(O)CMe$_3$**

<u>Reagents and conditions</u> : *a) LAH, THF, 0 ^{o}C to rt, 5 h, 80%; b) pivaloyl chloride, Et$_3$N, CH$_2$Cl$_2$, -10 ^{o}C to rt, 4 h, 65%.*

Intermediate **21** was a white crystalline solid having mp 133-134 ^{o}C. Presence of two absorption frequencies at 3625 cm^{-1} and 3350 cm^{-1}, characteristic of primary and secondary hydroxyl groups; and absence of a carbonyl absorption in it's IR spectrum suggested the formation of the proposed diol **21**. This was further evident from it's ^{13}C NMR spectrum, which revealed a methine resonance at δ 82.9, assigned to <u>C</u>H-OH and a methylene triplet at δ 67.6, assigned to <u>C</u>H$_2$-OH. Other characteristic signals in it's ^{1}H NMR spectrum were : two doublets at δ 3.56 and 3.76, each integrating for one proton with same coupling constant value (J = 11.2 Hz), were assigned to C<u>H$_2$</u>OH; and a doublet of doublet of one proton at δ 4.21 (J = 8.8, 6.4 Hz) was assigned to C<u>H</u>-OH. Finally, diol **21** was confirmed by it's mass spectrum, which exhibited a peak of $(M+1)^+$ at 265 and by it's elemental analysis also.

Figure-1 : ORTEP view of *rac*-21



The relative stereochemistry in diol **21** was proposed on the basis of a single crystal X-ray analysis of the corresponding *racemic* product. The ORTEP view of *rac*-**21** is reproduced in the figure-1, which further confirmed the relative stereochemistry at adjacent quaternary centers, *i. e.* at C2B and C3B as proposed earlier for intermediate **20**.

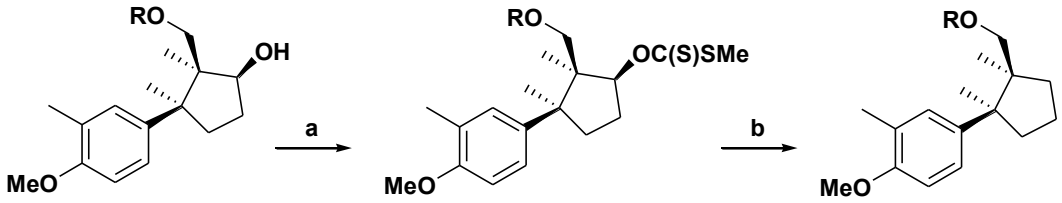
Keeping in mind the efficiency of Barton-McCombie's protocol[12] for deoxygenation of secondary alcohols, a stepwise deoxygenation was planned, *i. e.* first deoxygenation of secondary hydroxyl group and this warranted selective protection of the primary hydroxyl group, for which bulky pivaloyl ester derivative was opted. Thus, diol **21** on treatment with pivaloyl chloride in dry CH_2Cl_2 in presence of Et_3N as the base at 0 ^oC provided the required monopivaloyl ester **22** in 65% isolated yield (Scheme-8).

Formation of the monoester derivative **22** was evident from the only carbonyl stretching frequency at 1718 cm^{-1} in it's IR spectrum, which further revealed only one hydroxyl absorption at 3407 cm^{-1}. Also, downfield shift of two doublets of -C$\underline{H}_2$OR at δ 3.73 and 3.76 (J = 11.5 Hz) in it's ^1H NMR spectrum was suggestive of an ester formation at the primary hydroxyl group, while a doublet of doublet associated with –C$\underline{H}$OH was not shifted downfield, which indicated the selectivity in ester formation. A singlet at δ 1.17,

which integrated for nine protons, assigned to the three methyl groups of the pivaloyl ester, supported the presence of monoester. This was further confirmed by it's ^{13}C NMR spectrum, which revealed only one carbonyl resonance at δ 178.3. Finally, mass spectrum confirmed the formation of **22** by exhibiting a peak at 349 $(M+1)^+$, which was also ascertained by elemental analysis.

As Barton-McCombie's deoxygenation protocol involves treatment of the corresponding xanthate esters with tri-*n*-butyltin hydride, it was required to synthesize xanthate derivative **23**, which was achieved in 95% yield by treating alkoxide ion, generated from alcohol **22** using NaH as the base, with carbon disulfide followed by MeI in dry THF (Scheme-9).

Scheme-9



22 R = $C(O)CMe_3$ **23** R = $C(O)CMe_3$ **24** R = $C(O)CMe_3$

Reagents and conditions *: a) NaH, CS_2, THF, 0 ^oC, 2 h, MeI, rt, 5 h, 95%; b) TBTH, AIBN (cat), toluene, reflux, 3 h, 80%.*

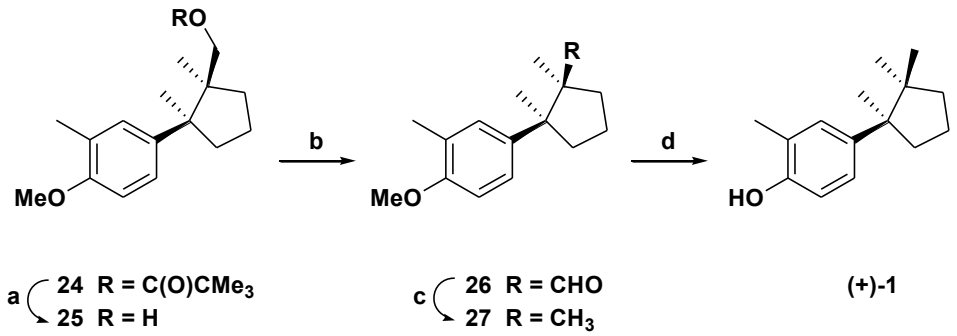
Absence of hydroxyl group stretching frequency in the IR spectrum and downfield shift of the proton, attached to the carbon bearing secondary hydroxyl group, from δ 4.08 to 5.75 (dd, J = 8.8, 4.8 Hz) in the ^1H NMR spectrum of the isolated product, suggested the formation of requisite *S*-methyldithiocarbonate **23**, which was further confirmed by the presence of a resonance at δ 214.8, attributed to the thiocarbonyl group, in it's ^{13}C NMR spectrum. Intermediate **23** was, finally confirmed by it's mass spectrum, which exhibited a peak of $(M+2)^+$ at 440 and ascertained by it's elemental analysis also.

Xanthate derivative **23** was then subjected to Barton's conditions, according to which it was treated with TBTH in refluxing toluene in the presence of catalytic amount of AIBN (radical initiator) to afford the requisite deoxygenated ester **24** in 80% isolated yield (Scheme-9).

Absence of one proton resonance at δ 5.75 (dd) and presence of five proton multiplet ranged over δ 1.48-1.84 in it's ^{1}H NMR spectrum indicated the required transformation, which was further supported by absence of a thiocarbonyl resonance at δ 214.8 and presence of an additional methylene triplet at δ 20.1 in it's ^{13}C NMR spectrum. Formation of intermediate **24** was finally established by it's mass spectral data and elemental analysis.

The remaining task to be performed was deoxygenation of primary hydroxyl group, which could be achieved by Wolff-Kishner reduction of the corresponding aldehyde and for this purpose, pivaloyl protecting group was first removed using LAH in quantitative yield to result in alcohol **25** (Scheme-10). Intermediate **25** was easily characterized by the presence of an absorption at 3378 cm^{-1} in it's IR spectrum, characteristic of an hydroxyl functionality. It was further characterized by it's NMR spectral analysis and finally confirmed by it's mass spectrum and elemental analysis also. The ^{1}H NMR spectrum of **25** revealed following characteristic resonances : two singlets at δ 1.12 and 1.29, each integrated for three protons, assigned to the vicinal methyl groups; a singlet at δ 2.23 (3H), assigned to the methyl group attached to the aromatic ring; two doublets at δ 3.03 and 3.11 (J = 11.1 Hz), integrated for one proton each, owed to -C$\underline{H}_2$OH; a singlet at δ 3.81 (3H) was assigned to Ar-OC$\underline{H}_3$; a doublet at δ 6.74 (J = 8.4 Hz, 1H) and a multiplet ranged over δ 7.15-7.20 (2H), were due to protons associated with the aromatic ring.

Scheme-10



Reagents and conditions *: a) LAH, THF, rt, 2 h, quantitative; b) PDC, CH_2Cl_2, 0 °C, 3 h; c) N_2H_4-H_2O, diethyleneglycol, NaOH, 150 °C, 4 h, 190 °C, 3 h, 73% from* ***25****; d) BBr_3, CH_2Cl_2, -78 °C to rt, overnight, 93%.*

Oxidation of alcohol **25** using pyridinium dichromate, provided the aldehyde intermediate **26**, which was characterized by it's ^{1}H NMR spectrum only (revealed a singlet at δ 9.0, characteristic of an aldehyde proton), and was immediately subjected to deoxygenation, owing to it's unstability, using Huang-Minlon modification[13] of Wolf-Kishner reduction protocol. Accordingly, it was treated with hydrazine hydrate in diethylene glycol in presence of potassium hydroxide at 190 ^{o}C, which resulted in formation of β-herbertenol methyl ether **27** in 73% overall yield from **25** (Scheme-10).

An additional methyl singlet at δ 0.64 in it's ^{1}H NMR spectrum and a methyl resonance at δ 24.4 in it's ^{13}C NMR spectrum were indicative of formation of **27**, which was further characterized by comparison of it's IR and NMR spectral data with those of reported one[14] and were found to be in good agreement.

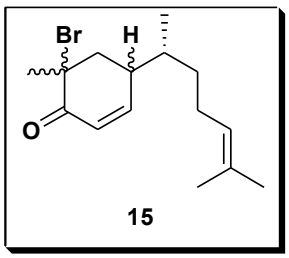
Finally, to complete the synthesis of β-herbertenol **1**, methyl ether of **27** was deprotected using boron tribromide in dry CH_2Cl_2, in 93% yield (Scheme-10). Formation of a phenol derivative was evident from the presence of an hydroxyl absorption at 3450 cm^{-1} in it's IR spectrum and disappearance of a three proton singlet at δ 3.87 from the ^{1}H NMR spectrum. The physical and chemical properties of **1**, thus obtained, were in good agreement with the literature values,[2] except sign of it's specific rotation, which was due to the opposite configuration. It showed specific rotation $[\propto]^{25}_D$ +61.26 (*c* 0.7, $CHCl_3$) {lit.[2] $[\propto]^{25}_D$ –47.0 (*c* 0.7, $CHCl_3$)}, which also suggested the optical purity of the product.

1.2.3 Conclusions

Thus, (+)-β-herbertenol **1** has successfully been synthesized enantiospecifically using naturally occurring monoterpene (*R*)-(+)-citronellal as the source of chirality, using Taber's protocol of diazodecomposition as the key step. Similar strategy can be applicable to the synthesis of it's natural isomer, *i. e.* (-)-β-herbertenol and other biologically active phenolic herbertanes also.

1.2.4 Experimental

6-Bromo-6-methyl-4-((*R*)-6-methylhept-5-en-2- yl)cyclohex-2-enone (15)



15

A 1 lit round bottom flask equipped with a magnetic stir bar and a condenser was charged with diisopropylamine (18.01 g, 178 mmol) and dry THF (250 mL) under N_2 atmosphere, and cooled to -78 ^oC. n-BuLi (102 mL, 164 mmol) (1.6 M solution in hexane) was added dropwise and stirred for 10 min, followed by dropwise addition of enone **12** (30 g, 136 mmol) in dry THF (50 mL). The reaction mixture was stirred for 1.5 h at -78 ^oC and then quenched using chlorotrimethylsilane (16.30 g, 150 mmol). It was allowed to come to 0 ^oC within 5 h and quenched with saturated $NaHCO_3$ solution (200 mL), extracted with pet. ether (250 mL x 3) and the combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 38 g of crude silyl enol ether **14**, which was confirmed by it's ^1H NMR spectrum.

To an ice-cold solution of crude silyl enol ether **14** (38 g) in dry THF (300 mL) was added *N*-bromosuccinimide (26.70 g, 150 mmol) portionwise, stirred for 30 min at 0 ^oC and quenched with saturated $NaHCO_3$ solution (300 mL). It was then extracted with pet. ether (300 mL x 2), and the combined organic layers were washed with brine (500 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 37 g of crude ∝-bromo enone **15** (mixture of diastereomers), which was directly used for the dehydrohalogenation.

Molecular Formula : $C_{15}H_{23}BrO$

IR (neat) ν_{max} (cm^{-1}) : 2964, 1688, 1504, 1446.

^1H NMR ($CDCl_3$, 200 MHz) : δ 0.76-0.86 (m, 3H); 1.08-1.34 (m, 2H); 1.52 (s, 3H); 1.59 (s, 3H); 1.71-1.78 (m, 2H); 1.77 (s, 3H); 1.85-2.01 (m, 2H); 2.10-2.47 (m, 1H); 2.54-2.76 (m, 1H); 4.98 (t, *J* = 6.8 Hz, 1H); 5.88-5.95 (m, 1H); 6.65-6.74 (m, 1H).

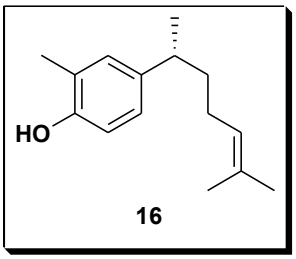
MS-ESI m/z : 301 $(M+2)^+$

Analysis

Expected : C, 60.21%; H, 7.75%

Found : C, 60.47%; H, 7.53%

(*R*)-2-Methyl-4-(6-methylhept-5-en-2-yl)phenol (16)



16

To a solution of crude ∝-bromo enone **15** in dry DMF (300 mL) under N_2 atmosphere, was added lithium carbonate (30.23 g, 409 mmol) and lithium bromide (23.69 g, 273 mmol) and was stirred at 130-140 ^oC for 4 h. The reaction mixture was allowed to come to room temperature and DMF was removed under reduced pressure. The residue was diluted with water (300 mL) and extracted with CH_2Cl_2 (300 mL x 3). The combined organic layers were washed with water (600 mL x 2) and brine (600 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 96 : 4) to provide phenol **16** (22.2 g) as a colourless oil.

Molecular Formula : $C_{15}H_{22}O$

Yield : 75% overall from **12**.

Specific Rotation : $[\propto]^{25}_D$ -39.09 (*c* 0.92, $CHCl_3$)

IR (neat) ν_{max} (cm^{-1}) : 3416, 2961, 1611, 1509, 1453, 1260.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.19 (d, *J* = 6.8 Hz, 3H); 1.52 (s, 3H); 1.48-1.60 (m, 2H); 1.67 (s, 3H); 1.80-1.91 (m, 2H); 2.23 (s, 3H); 2.50-2.67 (m, 1H); 5.07 (t, *J* = 6.8 Hz, 1H); 6.66 (d, *J* = 7.8 Hz, 1H); 6.84-6.90 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 15.9 (CH_3); 17.6 (CH_3); 22.6 (two CH_3); 25.7 (CH); 26.2 (CH_2); 38.6 (CH_2); 114.9 (CH); 123.5 (CH); 124.8 (CH); 125.3 (C); 129.6 (CH); 131.1 (C); 139.9 (C); 151.7 (C).

MS-ESI m/z : 218 (M^+)

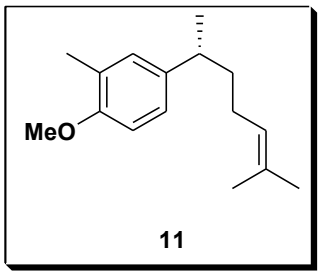
Analysis

Expected : C, 82.52%; H, 10.16%

Found : C, 82.31%; H, 10.19%

(*R*)-1-Methoxy-2-methyl-4-(6-methylhept-5-en-2-yl)benzene (11)

To a stirred solution of phenol **16** (21 g, 96 mmol) in dry acetone (200 mL) was added anhydrous K_2CO_3 (33.28 g, 241 mmol) and dimethyl sulfate (30.38 g, 241 mmol) under N_2 atmosphere. The reaction mixture was refluxed for 12 h, acetone was removed



11

under reduced pressure and the reaction mixture was diluted with water (200 mL). It was stirred overnight and then extracted with CH_2Cl_2 (200 mL x 3). The combined organic layers were washed with water (500 mL), brine (500 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 99 : 1) to provide the methyl ether **11** (20.2 g) as a colourless oil.

Molecular Formula : $C_{16}H_{24}O$

Yield : 90%

Specific Rotation : $[\propto]^{25}_{D}$ -44.18 (*c* 1.3, $CHCl_3$)

IR (neat) ν_{max} (cm^{-1}) : 2957, 1609, 1505, 1463, 1376, 1251, 1135.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.22 (d, *J* = 6.8 Hz, 3H); 1.46-1.60 (m, 2H); 1.55 (s, 3H); 1.69 (s, 3H); 1.78-1.94 (m, 2H); 2.23 (s, 3H); 2.53-2.71 (m, 1H); 3.82 (s, 3H); 5.10 (t, *J* = 6.8 Hz, 1H); 6.74 (d, *J* = 8.8 Hz, 1H); 6.94- 6.98 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.4 (CH_3); 17.7 (CH_3); 22.7 (two CH_3); 25.8 (CH); 26.2 (CH_2); 38.7 (CH_2); 55.1 (CH_3); 109.6 (CH); 124.8 (CH); 124.9 (CH); 126.2 (C); 129.3 (CH); 131.1 (C); 139.2 (C); 155.9 (C).

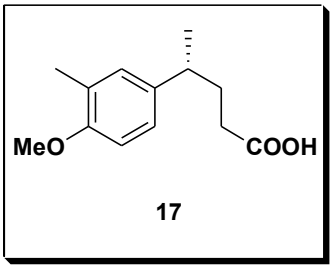
MS-ESI m/z : 231 $(M-1)^+$

Analysis

Expected : C, 82.70%; H, 10.41%

Found : C, 82.58%; H, 10.80%

(*R*)-4-(4-Methoxy-3-methylphenyl)pentanoicacid (17)



17

A 500 ml round bottom flask equipped with a magnetic stir bar and 100 mL addition funnel was charged with olefin **11** (16.34 g, 70.40 mmol) and acetone (200 mL). The reaction mixture was cooled to 0 ^oC and catalytic amount of OsO_4 (2 mL of 1% solution in toluene) was added to it, stirred for 15 min, followed by dropwise addition of Jones' reagent (94 mL). The reaction mixture was stirred at room temperature for additional 5 h before excess of Jones' reagent was quenched by using isopropanol (15 mL). Acetone was removed under reduced

pressure, followed by dilution with water and extraction with CH_2Cl_2 (150 mL x 3). The combined organic layers were washed with water (300 mL) and brine (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 9 : 1) to give acid **17** (12.5 g) as a colourless oil.

Molecular Formula : $C_{13}H_{18}O_3$

Yield : 80%

Specific Rotation : $[\alpha]^{25}_D$ -19.47 (*c* 0.8, $CHCl_3$)

IR (neat) ν_{max} (cm^{-1}) : 2957, 1709, 1610, 1507, 1456.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.27 (d, *J* = 6.9 Hz, 3H); 1.83-1.97 (m, 2H); 2.23 (s, 3H); 2.24-2.26 (m, 2H); 2.63-2.70 (m, 1H); 3.82 (s, 3H); 6.75 (d, *J* = 8.2 Hz, 1H); 6.95-6.97 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.4 (CH_3); 22.5 (CH_3); 32.4 (CH_2); 33.1 (CH_2); 38.5 (CH); 55.2 (CH_3); 109.8 (CH); 125.0 (CH); 126.5 (C); 129.2 (CH); 137.6 (C); 156.2 (C); 180.3 (C).

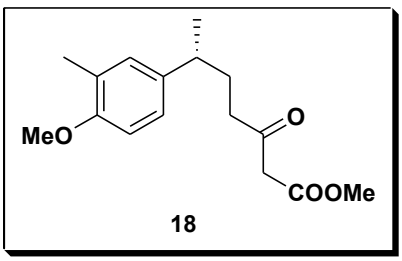
MS-ESI m/z : 221 $(M-1)^+$

Analysis

Expected : C, 70.24%; H, 8.16%

Found : C, 70.44%; H, 8.53%

(*R*)-Methyl-6-(4-methoxy-3-methylphenyl)-3-oxoheptanoate (18)



18

To a solution of acid **17** (14 g, 63 mmol) in dry CH_2Cl_2 (150 mL) was added thionyl chloride (9.0 g, 75.60 mmol) and catalytic amount of DMF (0.5 mL), under N_2 atmosphere. The reaction mixture was refluxed for 2 h and then CH_2Cl_2 was removed at atmospheric pressure. To remove the traces of thionyl chloride, dry benzene (25 mL) was added to the residue and distilled off under reduced pressure. The residue was used as such for the next step.

A 500 ml round-bottom flask equipped with a magnetic stir bar was charged with Meldrum's acid **19** (9.54 g, 66.30 mmol) and dry CH_2Cl_2 (150 mL), under N_2 atmosphere. The reaction mixture was cooled to -5 ^oC and pyridine (12.46 g, 158 mmol) was added to

it. After stirring for 30 min at 0 ^{o}C, acid chloride in dry CH_2Cl_2 (20 mL) was added dropwise. The reaction mixture was stirred at 0 ^{o}C for 1 h and at room temperature for an additional hour, followed by dilution with CH_2Cl_2. The reaction mixture was poured to 2N HCl solution (175 mL) containing crushed ice and aqueous layer was extracted using CH_2Cl_2 (150 mL x 2). The combined organic layers were washed with 2N HCl solution (200 mL), water (200 mL) and finally with brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude acyl Meldrum derivative, which was taken in dry methanol (300 mL) and refluxed for 4-5 h. Methanol was removed under reduced pressure and the residue was chromatographed using flash silica gel (pet. ether : EtOAc, 92 : 8) to give β-ketoester **18** (13.67 g) as a yellow oil.

Molecular Formula : $C_{16}H_{22}O_4$

Yield : 78%

Specific Rotation : $[\alpha]^{25}_{D}$ -19.91 (*c* 1.95, $CHCl_3$)

IR (neat) ν_{max} (cm^{-1}) : 2955, 1747, 1718, 1505, 1453.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.21 (d, *J* = 7.0 Hz, 3H); 1.70-1.95 (m, 2H); 2.18 (s, 3H); 2.32-2.41 (m, 2H); 2.50-2.64 (m, 1H); 3.33 (s, 2H); 3.69 (s, 3H); 3.79 (s, 3H); 6.71 (d, *J* = 9.0 Hz, 1H); 6.89-6.94 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.1 (CH_3); 22.5 (CH_3); 31.5 (CH_2); 38.1 (CH); 41.0 (CH_2); 48.7 (CH_2); 51.9 (CH_3); 54.9 (CH_3); 109.6 (CH); 124.8 (CH); 126.2 (C); 129.0 (CH); 137.5 (C); 156.0 (C); 167.2 (C); 202.2 (C).

MS-ESI m/z : 279 $(M+1)^+$

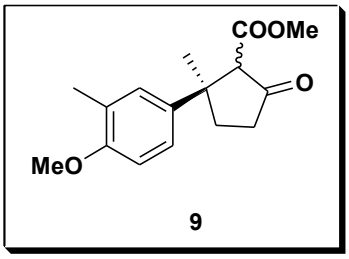
Analysis

Expected : C, 69.04%; H, 7.97%

Found : C, 69.04%; H, 8.16%

(*R*)-Methyl-2-(4-methoxy-3-methylphenyl)-2-methyl-5-oxocyclopentanecarboxylate (9)

A 500 mL round-bottom flask equipped with a magnetic stir bar was charged with ketoester **18** (9 g, 32.37 mmol) in dry CH_2Cl_2 (175 mL) and triethylamine (8.19 g, 80.9 mmol). The reaction mixture was cooled to -5 ^{o}C and mesyl azide (4.7 g, 38.8 mmol) in CH_2Cl_2 (25 mL) was added dropwise. The reaction mixture was stirred overnight at room



9

temperature, cooled to 0 ^{o}C and quenched with 5M NaOH solution (100 mL) and extracted using CH_2Cl_2 (100 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product, α-diazo-β-ketoester **10** was purified by filtering it through a short pad of silica gel (pet. ether : EtOAc, 9 : 1) and confirmed by it's IR spectrum.

IR (neat) ν_{max} (cm^{-1}) : 2956, 2136, 1724, 1656, 1616, 1506.

The oil was transferred to a flame dried 1 lit round-bottom flask equipped with a magnetic stir bar and maintained under N_2 atmosphere. CH_2Cl_2 (500 mL) (dried by filtering through anhydrous K_2CO_3) was added, followed by Rhodium (II) acetate dimer (0.15 g, 2% by weight). The reaction mixture was stirred at room temperature until evolution of nitrogen ceased (30 min). The solvent was removed in *vacuo* and the residue was chromatographed using flash silica gel (pet. ether : EtOAc, 93 : 7) to give ester **9** (3.13 g) as a colourless oil.

Molecular Formula **:** $C_{16}H_{20}O_4$

Yield **:** 35% from **18**

IR (neat) ν_{max} (cm^{-1}) **:** 2954, 1758, 1728, 1652, 1612, 1508.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.33, 1.45, 1.61 (s s s, total 3H); 1.92-2.65 (m, 4H); 2.19-2.22 (m, 3H); 3.40 (s, 1H); 3.62, 3.75, 3.80 (s s s, 3H total); 3.79 (s, 3H); 6.69-6.80 (m, 1H); 6.92-7.15 (m, 2H).

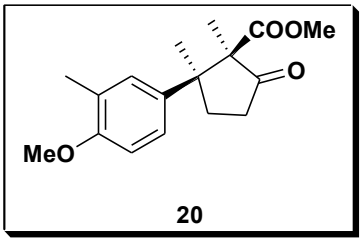
HRMS **:** M^+

Expected **:** 276.1361

Found **:** 276.1363

(*1R,2S*)-Methyl-2-(4-methoxy-3-methylphenyl)-1,2-dimethyl-5-oxocyclopentanecarboxylate (20)

To a solution of β-keto ester **9** (1.5 g, 5.44 mmol) in dry acetone (20 mL) was added anhydrous K_2CO_3 (0.751 gm, 5.44 mmol) and iodomethane (0.41 mL, 6.52 mmol), under N_2 atmosphere at 20 ^{o}C and stirred at room temperature for 24 h. The reaction mixture was filtered through a short pad of celite, solvent was evaporated under reduced



20

pressure and the residue was then chromatographed using flash silica gel (pet. ether : EtOAc, 94 : 6) to furnish **20** (1.34 g) as a colourless oil.

Molecular Formula : $C_{17}H_{22}O_4$

Yield : 85%

Specific Rotation : $[\propto]^{25}_{D}$ +126.3 (*c* 0.6, $CHCl_3$)

IR (neat) ν_{max} (cm^{-1}) : 2952, 1745, 1713, 1511.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.26 (s, 3H); 1.37 (s, 3H); 1.89-2.04 (m, 1H); 2.19 (s, 3H); 2.40-2.57 (m, 1H); 2.64-2.79 (m, 1H); 2.93-3.09 (m, 1H); 3.30 (s, 3H); 3.80 (s, 3H); 6.72 (d, *J* = 7.8 Hz, 1H); 6.99-7.15 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 14.7 (CH_3); 16.3 (CH_3); 25.4 (CH_3); 31.2 (CH_2); 35.4 (CH_2); 49.2 (C); 51.4 (CH_3); 54.9 (CH_3); 64.4 (C); 109.2 (CH); 123.9 (CH); 125.8 (C); 128.0 (CH); 135.6 (C); 156.3 (C); 170.8 (C); 215.3 (C).

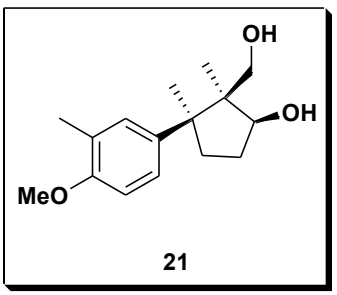
MS-ESI m/z : 291 $(M+1)^+$

Analysis

Expected : C, 70.32%; H, 7.64%

Found : C, 70.10%; H, 7.34%

(*1S,2S,3S*)-2-(Hydroxylmethyl)-3-(4-methoxy-3-methylphenyl)-2,3-dimethyl cyclopentanol (21)



21

A 50 mL two neck round-bottom flask equipped with a magnetic stir bar was charged with LAH (0.328 g, 8.60 mmol) and dry THF (10 mL), under N_2 atmosphere. The reaction mixture was cooled to 0 ^oC and ketoester **20** (1 g, 3.45 mmol) was added to it using dry THF (10 mL). The reaction mixture was stirred for additional 5 h at room temperature, cooled to 0 ^oC and excess of LAH was quenched by dilute HCl solution. THF was evaporated under reduced pressure and the aqueous layer was extracted with CH_2Cl_2 (25 mL x 3). The combined organic layers were washed with water (50 mL x 2), brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was

chromatographed using flash silica gel (pet. ether : EtOAc, 8 : 2) to give diol **21** (0.725 g) as a white solid.

Molecular Formula : $C_{16}H_{24}O_3$

Yield : 80%

Mp : 133-134 ^oC

Specific Rotation : $[\propto]^{25}_D$ +58.71 (*c* 1.1, $CHCl_3$)

IR ($CHCl_3$) ν_{max} (cm^{-1}) : 3625, 3350, 3017, 2966, 1506.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.19 (s, 3H); 1.21 (s, 3H); 1.42-1.87 (m, 2H); 2.20 (s, 3H); 2.26-2.36 (m, 1H); 2.63-2.89 (m, 2H); 3.56 (d, *J* = 11.2 Hz, 1H); 3.76 (d, *J* = 11.2 Hz, 1H); 3.80 (s, 3H); 4.21 (dd, *J* = 8.8, 6.4 Hz, 1H); 6.71 (d, *J* = 9.3 Hz, 1H); 6.94-7.15 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.9 (CH_3); 17.4 (CH_3); 27.0 (CH_3); 30.9 (CH_2); 34.2 (CH_2); 49.0 (C); 50.2 (C); 55.4 (CH_3); 67.6 (CH_2); 82.9 (CH); 109.6 (CH); 125.0 (CH); 126.1 (C); 129.3 (CH); 137.4 (C); 156.2 (C).

MS-ESI m/z : 265 $(M+1)^+$

Analysis

Expected : C, 72.69%; H, 9.15%

Found : C, 72.36%; H, 9.01%

Diffraction analysis of *rac*-21 ($C_{16}H_{24}O_3$, MZ 264.35). Single crystal of compound **21** obtained from S. P. Chavan *et al.* / Tetrahedron 61 (2005) 3873–3879, ethyl acetate–petroleum ether mixture. X-ray intensity data were collected on a Bruker SMART APEX CCD diffractometer with graphite-monochromatized (Mo KaZ 0.71073 A°) radiation at room temperature. All the data were corrected for Lorentzian, polarization and absorption effects using Bruker's SAINT and SADABS programs. SHELX-97 (G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Gottingen, Germany, 1997) was used for structure solution and full matrix least squares refinement on F2. Hydrogen atoms were included in the refinement as per the riding model.

Table 1 : Crystal data and structure refinement for *rac*-**21**.

Identification code	**21**
Empirical formula	$C_{16}H_{24}O_3$
Formula weight	264.35
Temperature	293 (2) K

Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P1
Unit cell dimensions	a = 7.606 (5) Å; α = 103.240 (12)º
	b = 9.793 (6) Å; β = 107.106 (11)º
	c = 10.946 (7) Å; γ = 96.723 (15)º
Volume	743.5 (8) $Å^3$
Z, Calculated density	2, 1.181 Mg/m^3
Absorption coefficient	0.080 mm^{-1}
F (000)	288
Crystal size	0.40 x 0.19 x 0.12 mm
Theta range for data collection	2.90 to 25.00º
Limiting indices	-9<=h<=9, -11<=k<=11, -12<=l<=12
Reflections collected / unique	7089/5082 [R(int) = 0.0290]
Completeness to theta = 25.00	99.6%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9905 and 0.9688
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5082 / 3 / 355
Goodness-of-fit on F^2	1.014
Final R indices [I>2sigma(I)]	R_1 = 0.0577, wR_2 = 0.1323
R indices (all data)	R_1 = 0.0964, wR_2 = 0.1498
Absolute structure parameter	0.7(14)
Largest diff. peak and hole	0.160 and -0.155 $e.Å^{-3}$

Table 2 : Bond lengths [Å] and angles [º] for *rac*-**21** (two molecules in an asymmetric unit)

O(1A)-C(1A)	1.430 (4)	C(7A)-C(2A)-C(1A)	111.5 (3)
O(2A)-C(6A)	1.420 (4)	C(6A)-C(2A)-C(1A)	110.0 (3)
O(3A)-C(4'A)	1.362 (4)	C(7A)-C(2A)-C(3A)	115.8 (3)
O(3A)-C(8'A)	1.419 (5)	C(6A)-C(2A)-C(3A)	108.7 (2)
C(1A)-C(5A)	1.512 (6)	C(1A)-C(2A)-C(3A)	101.6 (3)
C(1A)-C(2A)	1.535 (5)	C(4A)-C(3A)-C(1'A)	114.3 (3)
C(2A)-C(7A)	1.512 (5)	C(4A)-C(3A)-C(8A)	107.9 (4)
C(2A)-C(6A)	1.533 (5)	C(1'A)-C(3A)-C(8A)	108.3 (3)
C(2A)-C(3A)	1.570 (5)	C(4A)-C(3A)-C(2A)	102.9 (3)
C(3A)-C(4A)	1.534 (6)	C(1'A)-C(3A)-C(2A)	112.0 (3)
C(3A)-C(1'A)	1.539 (5)	C(8A)-C(3A)-C(2A)	111.3 (3)
C(3A)-C(8A)	1.556 (6)	C(5A)-C(4A)-C(3A)	106.9 (3)
C(4A)-C(5A)	1.517 (6)	C(1A)-C(5A)-C(4A)	106.9 (3)

O(1B)-C(1B)	1.433 (4)	O(2A)-C(6A)-C(2A)	113.8 (3)
O(2B)-C(6B)	1.423 (4)	C(4'B)-O(3B)-C(8'B)	117.7 (3)
O(3B)-C(4'B)	1.371 (4)	C(2'A)-C(1'A)-C(6'A)	115.7 (3)
O(3B)-C(8'B)	1.407 (5)	C(2'A)-C(1'A)-C(3A)	123.3 (3)
C(1'A)-C(2'A)	1.376 (5)	C(6'A)-C(1'A)-C(3A)	120.9 (3)
C(1'A)-C(6'A)	1.398 (5)	C(1'A)-C(2'A)-C(3'A)	124.9 (3)
C(2'A)-C(3'A)	1.378 (5)	C(2'A)-C(3'A)-C(4'A)	117.3 (3)
C(3'A)-C(4'A)	1.401 (5)	C(2'A)-C(3'A)-C(7'A)	122.1 (4)
C(3'A)-C(7'A)	1.485 (6)	C(4'A)-C(3'A)-C(7'A)	120.5 (3)
C(4'A)-C(5'A)	1.361 (5)	C(5'A)-C(4'A)-O(3A)	125.6 (3)
C(5'A)-C(6'A)	1.372 (5)	C(5'A)-C(4'A)-C(3'A)	119.2 (3)
C(1B)-C(5B)	1.503 (5)	O(3A)-C(4'A)-C(3'A)	115.1 (3)
C(1B)-C(2B)	1.536 (5)	C(4'A)-C(5'A)-C(6'A)	122.0 (3)
C(2B)-C(7B)	1.517 (5)	C(5'A)-C(6'A)-C(1'A)	120.9 (3)
C(2B)-C(6B)	1.531 (5)	O(1B)-C(1B)-C(5B)	111.8 (3)
C(2B)-C(3B)	1.565 (5)	O(1B)-C(1B)-C(2B)	113.0 (3)
C(3B)-C(1'B)	1.528 (5)	C(5B)-C(1B)-C(2B)	105.5 (3)
C(3B)-C(4B)	1.539 (5)	C(7B)-C(2B)-C(6B)	108.6 (3)
C(3B)-C(8B)	1.567 (6)	C(7B)-C(2B)-C(1B)	111.6 (3)
C(4B)-C(5B)	1.532 (6)	C(6B)-C(2B)-C(1B)	110.1 (3)
C(1'B)-C(6'B)	1.373 (5)	C(7B)-C(2B)-C(3B)	115.5 (3)
C(1'B)-C(2'B)	1.394 (5)	C(6B)-C(2B)-C(3B)	108.6 (3)
C(2'B)-C(3'B)	1.385 (5)	C(1B)-C(2B)-C(3B)	102.3 (3)
C(3'B)-C(4'B)	1.399 (5)	C(1'B)-C(3B)-C(4B)	115.0 (3)
C(3'B)-C(7'B)	1.502 (5)	C(1'B)-C(3B)-C(2B)	112.3 (3)
C(4'B)-C(5'B)	1.372 (5)	C(4B)-C(3B)-C(2B)	103.0 (3)
C(5'B)-C(6'B)	1.376 (5)	C(1'B)-C(3B)-C(8B)	109.5 (3)
C(4'A)-O(3A)-C(8'A)	117.0 (3)	C(4B)-C(3B)-C(8B)	107.0 (3)
O(1A)-C(1A)-C(5A)	111.9 (3)	C(2B)-C(3B)-C(8B)	109.7 (3)
O(1A)-C(1A)-C(2A)	113.0 (3)	C(5B)-C(4B)-C(3B)	107.2 (3)
C(5A)-C(1A)-C(2A)	105.8 (3)	C(1B)-C(5B)-C(4B)	106.5 (3)
C(7A)-C(2A)-C(6A)	109.0 (3)	O(2B)-C(6B)-C(2B)	113.7 (3)
C(6'B)-C(1'B)-C(2'B)	115.4 (3)	C(4'B)-C(3'B)-C(7'B)	120.8 (3)
C(6'B)-C(1'B)-C(3B)	121.6 (3)	O(3B)-C(4'B)-C(5'B)	125.4 (3)
C(2'B)-C(1'B)-C(3B)	122.8 (3)	O(3B)-C(4'B)-C(3'B)	114.9 (3)
C(3'B)-C(2'B)-C(1'B)	124.5 (3)	C(5'B)-C(4'B)-C(3'B)	119.8 (3)
C(2'B)-C(3'B)-C(4'B)	117.1 (3)	C(4'B)-C(5'B)-C(6'B)	120.6 (3)
C(2'B)-C(3'B)-C(7'B)	122.1 (3)	C(1'B)-C(6'B)-C(5'B)	122.5 (3)

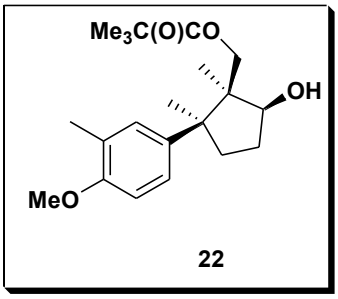
Table 3 : Torsion angles [°] for *rac*-**21**.

O(1A)-C(1A)-C(2A)-C(7A)	76.6 (4)	C(2A)-C(3A)-C(4A)-C(5A)	-27.0 (4)
C(5A)-C(1A)-C(2A)-C(7A)	-160.7 (3)	O(1A)-C(1A)-C(5A)-C(4A)	144.1 (4)
O(1A)-C(1A)-C(2A)-C(6A)	-44.5 (4)	C(2A)-C(1A)-C(5A)-C(4A)	20.7 (4)
C(5A)-C(1A)-C(2A)-C(6A)	78.2 (4)	C(3A)-C(4A)-C(5A)-C(1A)	4.5 (5)
O(1A)-C(1A)-C(2A)-C(3A)	-159.5 (3)	C(7A)-C(2A)-C(6A)-O(2A)	-55.9 (4)
C(5A)-C(1A)-C(2A)-C(3A)	-36.8 (3)	C(1A)-C(2A)-C(6A)-O(2A)	66.7 (4)
C(7A)-C(2A)-C(3A)-C(4A)	159.7 (3)	C(3A)-C(2A)-C(6A)-O(2A)	177.1 (3)
C(6A)-C(2A)-C(3A)-C(4A)	-77.3 (3)	C(4A)-C(3A)-C(1'A)-C(2'A)	25.2 (5)

C(1A)-C(2A)-C(3A)-C(4A)	38.7 (3)	C(8A)-C(3A)-C(1'A)-C(2'A)	145.5 (4)
C(7A)-C(2A)-C(3A)-C(1'A)	-77.0 (4)	C(2A)-C(3A)-C(1'A)-C(2'A)	-91.4 (4)
C(6A)-C(2A)-C(3A)-C(1'A)	46.0 (4)	C(4A)-C(3A)-C(1'A)-C(6'A)	-158.7 (4)
C(1A)-C(2A)-C(3A)-C(1'A)	162.0 (3)	C(8A)-C(3A)-C(1'A)-C(6'A)	-38.5 (5)
C(7A)-C(2A)-C(3A)-C(8A)	44.4 (4)	C(2A)-C(3A)-C(1'A)-C(6'A)	84.7 (4)
C(6A)-C(2A)-C(3A)-C(8A)	167.4 (3)	C(6'A)-C(1'A)-C(2'A)-C(3'A)	-1.8 (5)
C(1A)-C(2A)-C(3A)-C(8A)	-76.6 (4)	C(3A)-C(1'A)-C(2'A)-C(3'A)	174.4 (3)
C(1'A)-C(3A)-C(4A)-C(5A)	-148.8 (3)	C(1'A)-C(2'A)-C(3'A)-C(4'A)	1.6 (5)
C(8A)-C(3A)-C(4A)-C(5A)	90.7 (5)	C(1'A)-C(2'A)-C(3'A)-C(7'A)	-178.3 (4)
C(8'A)-O(3A)-C(4'A)-C(5'A)	-0.7 (6)	C(8B)-C(3B)-C(4B)-C(5B)	-92.5 (4)
C(8'A)-O(3A)-C(4'A)-C(3'A)	178.3 (4)	O(1B)-C(1B)-C(5B)-C(4B)	-147.3 (3)
C(2'A)-C(3'A)-C(4'A)-C(5'A)	-0.8 (5)	C(2B)-C(1B)-C(5B)-C(4B)	-24.1 (4)
C(7'A)-C(3'A)-C(4'A)-C(5'A)	179.2 (4)	C(3B)-C(4B)-C(5B)-C(1B)	0.1 (5)
C(2'A)-C(3'A)-C(4'A)-O(3A)	-179.9 (3)	C(7B)-C(2B)-C(6B)-O(2B)	56.1 (4)
C(7'A)-C(3'A)-C(4'A)-O(3A)	0.1 (5)	C(1B)-C(2B)-C(6B)-O(2B)	-66.3 (4)
O(3A)-C(4'A)-C(5'A)-C(6'A)	179.2 (3)	C(3B)-C(2B)-C(6B)-O(2B)	-177.6 (3)
C(3'A)-C(4'A)-C(5'A)-C(6'A)	0.2 (5)	C(4B)-C(3B)-C(1'B)-C(6'B)	157.2 (4)
C(4'A)-C(5'A)-C(6'A)-C(1'A)	-0.3 (6)	C(2B)-C(3B)-C(1'B)-C(6'B)	-85.5 (4)
C(2'A)-C(1'A)-C(6'A)-C(5'A)	1.1 (5)	C(8B)-C(3B)-C(1'B)-C(6'B)	36.6 (5)
C(3A)-C(1'A)-C(6'A)-C(5'A)	-175.2 (3)	C(4B)-C(3B)-C(1'B)-C(2'B)	-27.3 (5)
O(1B)-C(1B)-C(2B)-C(7B)	-75.4 (4)	C(2B)-C(3B)-C(1'B)-C(2'B)	90.0 (4)
C(5B)-C(1B)-C(2B)-C(7B)	162.2 (3)	C(8B)-C(3B)-C(1'B)-C(2'B)	-147.8 (4)
O(1B)-C(1B)-C(2B)-C(6B)	45.2 (4)	C(6'B)-C(1'B)-C(2'B)-C(3'B)	2.0 (5)
C(5B)-C(1B)-C(2B)-C(6B)	-77.2 (4)	C(3B)-C(1'B)-C(2'B)-C(3'B)	-173.8 (3)
O(1B)-C(1B)-C(2B)-C(3B)	160.6 (3)	C(1'B)-C(2'B)-C(3'B)-C(4'B)	-1.5 (5)
C(5B)-C(1B)-C(2B)-C(3B)	38.2 (4)	C(1'B)-C(2'B)-C(3'B)-C(7'B)	176.1 (4)
C(7B)-C(2B)-C(3B)-C(1'B)	77.2 (4)	C(8'B)-O(3B)-C(4'B)-C(5'B)	2.9 (6)
C(6B)-C(2B)-C(3B)-C(1'B)	-45.0 (4)	C(8'B)-O(3B)-C(4'B)-C(3'B)	-178.1 (4)
C(1B)-C(2B)-C(3B)-C(1'B)	-161.4 (3)	C(2'B)-C(3'B)-C(4'B)-O(3B)	-178.6 (3)
C(7B)-C(2B)-C(3B)-C(4B)	-158.5 (3)	C(7'B)-C(3'B)-C(4'B)-O(3B)	3.7 (5)
C(6B)-C(2B)-C(3B)-C(4B)	79.3 (3)	C(2'B)-C(3'B)-C(4'B)-C(5'B)	0.5 (5)
C(1B)-C(2B)-C(3B)-C(4B)	-37.1 (3)	C(7'B)-C(3'B)-C(4'B)-C(5'B)	-177.2 (4)
C(7B)-C(2B)-C(3B)-C(8B)	-44.8 (4)	O(3B)-C(4'B)-C(5'B)-C(6'B)	178.9 (4)
C(6B)-C(2B)-C(3B)-C(8B)	-167.0 (3)	C(3'B)-C(4'B)-C(5'B)-C(6'B)	-0.1 (5)
C(1B)-C(2B)-C(3B)-C(8B)	76.6 (4)	C(2'B)-C(1'B)-C(6'B)-C(5'B)	-1.5 (5)
C(1'B)-C(3B)-C(4B)-C(5B)	145.6 (3)	C(3B)-C(1'B)-C(6'B)-C(5'B)	174.4 (3)
C(2B)-C(3B)-C(4B)-C(5B)	23.1 (4)	C(4'B)-C(5'B)-C(6'B)-C(1'B)	0.6 (6)

((*1S,2S,5S*)-5-Hydroxy-2-(4-methoxy-3-methylphenyl)-1,2-dimethylcyclopentyl)methylpivalate (22)

To a solution of diol **21** (0.59 g, 2.24 mmol) in dry CH_2Cl_2 (20 mL) maintained under N_2 atmosphere, was added triethylamine (0.27 g, 2.68 mmol), and it was cooled to -10 ^oC. Pivaloyl chloride (0.28 g, 2.35 mmol) in dry CH_2Cl_2 (5 mL) was added and it was stirred at 0 ^oC for 4 h, diluted with water (50 mL). The aqueous layer was extracted using



22

CH_2Cl_2 (25 mL x 3), the combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 9 : 1) to provide pivaloyl ester **22** (0.51 g) as a colourless oil.

Molecular Formula : $C_{21}H_{32}O_4$

Yield : 65%

Specific Rotation : $[\alpha]^{25}_D$ +23.54 (*c* 0.9, $CHCl_3$)

IR (neat) ν_{max} (cm^{-1}) : 3407, 3018, 2972, 1718, 1608, 1504.

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 1.09 (s, 3H); 1.17 (s, 9H); 1.31 (s, 3H); 1.64-1.78 (m, 2H); 2.18 (s, 3H); 2.33-2.41 (m, 1H); 2.66-2.72 (m, 1H); 3.73 (d, *J* = 11.5 Hz, 1H); 3.76 (d, *J* = 11.5 Hz, 1H); 3.80 (s, 3H); 4.08 (dd, *J* = 8.7, 4.8 Hz, 1H); 6.72 (d, *J* = 8.4 Hz, 1H); 7.11-7.15 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz) : δ 16.7 (CH_3); 18.2 (CH_3); 26.7 (CH_3); 27.3 (CH_3); 31.4 (CH_2); 35.3 (CH_2); 38.8 (C); 49.0 (C); 50.9 (C); 55.1 (CH_3); 67.7 (CH_2); 81.3 (CH); 109.3 (CH); 125.0 (CH); 125.8 (C); 129.4 (CH); 137.3 (C); 156.1 (C); 178.3 (C).

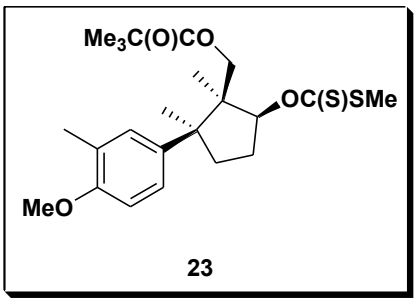
MS-ESI m/z : 349 $(M+1)^+$

Analysis

Expected : C, 72.38%; H, 9.26%

Found : C, 72.74%; H, 8.96%

((*1S,2S,5S*)-2-(4-Methoxy-3-methylphenyl)-1,2-dimethyl-5-(methylthiocarbonothioloxy)cyclopentyl)methylpivalate (23)



23

A 50 mL two-neck round-bottom flask was charged with NaH (60%) (0.12 g, 3.0 mmol) and dry THF (7 mL). Alcohol **22** (0.7 g, 2.0 mmol) in dry THF (7 mL) was added at 0 ^oC, under N_2 atmosphere and stirred for 30 min. Then, carbon disulphide (0.23 g, 3.0 mmol) was added at 0 ^oC and stirred for 2 h at room temperature, followed by addition of iodomethane (0.85 g, 6.0 mmol) at 0 ^oC. It was stirred for

additional 5 h at room temperature, diluted with ice water (30 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with water (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 98 : 2) to give xanthate **23** (0.83 g) as a colourless oil.

Molecular Formula : $C_{23}H_{34}O_4S_2$

Yield : 95%

Specific Rotation : $[\alpha]^{25}_D$ +11.35 (*c* 1.6, $CHCl_3$)

IR (neat) ν_{max} (cm^{-1}) : 2971, 1725, 1608, 1508, 1479.

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 1.16 (s, 3H); 1.16 (s, 9H); 1.39 (s, 3H); 1.74-1.82 (m, 1H); 1.90-1.96 (m, 1H); 2.19 (s, 3H); 2.30 (s, 3H); 2.55-2.63 (m, 1H); 2.75-2.82 (m, 1H); 3.59 (d, *J* = 11.1 Hz, 1H); 3.80 (s, 3H); 3.86 (d, *J* = 11.1 Hz, 1H); 5.75 (dd, *J* = 8.8, 4.8 Hz, 1H); 6.70 (d, *J* = 8.3 Hz, 1H); 7.08-7.11 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz) : δ 16.7 (CH_3); 18.4 (CH_3); 18.7 (CH_3); 26.4 (CH_3); 27.3 (CH_3); 29.4 (CH_2); 36.2 (CH_2); 38.7 (C); 49.6 (C); 51.1 (C); 55.2 (CH_3); 67.2 (CH_2); 91.9 (CH); 109.3 (CH); 125.4 (CH); 125.7 (C); 129.7 (CH); 136.4 (C); 156.2 (C); 177.9 (C); 214.8 (C).

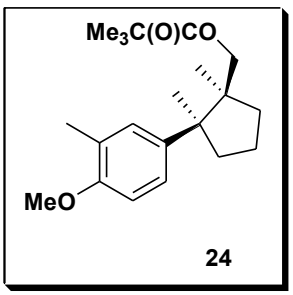
MS-ESI m/z : 440 $(M+2)^+$

Analysis

Expected : C, 62.98%; H, 7.81%

Found : C, 63.32%; H, 7.53%

((*1S,2S*)-2-(4-Methoxy-3-methylphenyl)-1,2-dimethylcyclopentyl)methylpivalate (24)



24

To a stirred solution of xanthate **23** (0.53 g, 1.21 mmol) in dry toluene (20 mL) was added TBTH (0.39 g, 1.33 mmol) and AIBN (0.020 g, catalytic), under N_2 atmosphere. The reaction mixture was refluxed for 3 h, toluene was removed under reduced pressure and the residue was chromatographed using flash silica gel (pet. ether : EtOAc, 98 : 2) to give **24** (0.32 g) as a colourless oil.

Molecular Formula : $C_{21}H_{32}O_3$

Yield **:** 80%

Specific Rotation **:** $[\propto]^{25}_{D}$ +16.7 (*c* 1.05, $CHCl_3$)

IR (neat) ν_{max} (cm^{-1}) **:** 2966, 1728, 1608, 1508, 1464.

^{1}H NMR ($CDCl_3$, 500 MHz) **:** δ 1.11 (s, 3H); 1.17 (s, 9H); 1.34 (s, 3H); 1.48-1.55 (m, 1H); 1.73-1.86 (m, 4H); 2.19 (s, 3H); 2.45-2.51 (m, 1H); 3.29 (d, *J* = 11.1 Hz, 1H); 3.63 (d, *J* = 11.1 Hz, 1H); 3.79 (s, 3H); 6.72 (d, *J* = 9.5 Hz, 1H); 7.10-7.12 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz) **:** δ 16.3 (CH_3); 19.3 (CH_3); 20.1 (CH_2); 24.8 (CH_3); 26.9 (CH_3); 34.4 (CH_2); 37.6 (CH_2); 38.6 (C); 47.4 (C); 49.3 (C); 55.0 (CH_3); 70.4 (CH_2); 108.9 (CH); 124.8 (CH); 125.3 (C); 129.1 (CH); 137.3 (C); 155.6 (C); 178.3 (C).

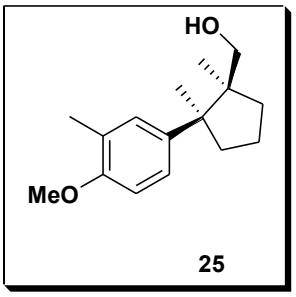
MS-ESI m/z **:** 231 (M- $OC(O)CMe_3$)$^+$

Analysis

Expected **:** C, 75.86%; H, 9.70%

Found **:** C, 75.46%; H, 9.76%

((*1S,2S*)-2-(4-Methoxy-3-methylphenyl)-1,2-dimethylcyclopentyl)methanol (25)



To a stirred solution of ester **24** (0.3 g, 0.9 mmol) in dry THF (10 mL) under N_2 atmosphere, was added LAH (0.69 g, 1.80 mmol) portionwise at room temperature and the reaction mixture was stirred for 2 h. Excess of LAH was quenched with dilute HCl solution at 0 ^oC, THF was evaporated under reduced pressure and the aqueous layer was extracted using CH_2Cl_2 (30 mL x 3). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 9 : 1) to give alcohol **25** (0.22 g) as a colourless oil.

Molecular Formula **:** $C_{16}H_{24}O_2$

Yield **:** quantitative

Specific Rotation **:** $[\propto]^{25}_{D}$ +42.08 (*c* 0.75, $CHCl_3$)

IR (neat) ν_{max} (cm^{-1}) **:** 3378, 2954, 1608, 1506.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.12 (s, 3H); 1.29 (s, 3H); 1.48-1.59 (m, 1H); 1.67-1.86 (m, 4H); 2.23 (s, 3H); 2.41-2.55 (m, 1H); 3.03 (d, *J* = 11.1 Hz, 1H); 3.11 (d, *J* = 11.1 Hz, 1H); 3.81 (s, 3H); 6.74 (d, *J* = 8.4 Hz, 1H); 7.15-7.18 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.6 (CH_3); 19.4 (CH_3); 20.2 (CH_2); 25.2 (CH_3); 35.0 (CH_2); 37.5 (CH_2); 49.0 (C); 49.1 (C); 55.1 (CH_3); 69.4 (CH_2); 109.3 (CH); 124.8 (CH); 125.8 (C); 129.1 (CH); 137.8 (C); 155.9 (C).

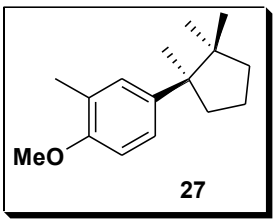
MS-ESI m/z **:** 230 $(M-H_2O)^+$

Analysis

Expected **:** C, 77.38%; H, 9.74%

Found **:** C, 77.19%; H, 9.58%

(*R*)-1-Methoxy-2-methyl-4-(1,2,2-trimethylcyclopentyl)benzene (27)[14]



To a stirred solution of alcohol **25** (0.1 g, 0.4 mmol) in dry CH_2Cl_2 (10 mL) was added pyridinium dichromate (0.228 g, 0.6 mmol) portionwise at 0 ^oC and allowed to stir at room temperature for 3 h. The reaction mixture was then diluted with diethyl ether (25 mL) and filtered through a short pad of celite, which was washed with diethyl ether (25 mL x 2). The combined organic layers were then washed with water (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue (0.11 g) was directly used for the next step, as aldehyde **26** was unstable. To a stirred solution of crude aldehyde **26** in diethylene glycol (4 mL) was added hydrazine monohydrate (0.024 g, 0.48 mmol) and sodium hydroxide (0.355 g, 8.875 mmol). The reaction mixture was stirred at 150 ^oC for 4 h and at 190 ^oC for additional 3 h. The reaction mixture was diluted with water (25 mL) and extracted using diethyl ether (15 mL x 2). The combined organic layers were then washed with water (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 99 : 1) to give **27** (68 mg) as a colourless oil.

Molecular Formula **:** $C_{16}H_{24}O$

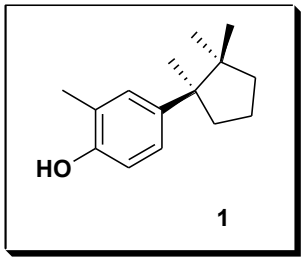
Yield **:** 73% overall.

Specific Rotation **:** $[\propto]^{25}_D$ +56 (*c* 1.25, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.64 (s, 3H); 1.13 (s, 3H); 1.32 (s, 3H); 1.55-1.94 (m, 5H); 2.29 (s, 3H); 2.48-2.61 (m, 1H); 3.87 (s, 3H); 6.77 (d, *J* = 7.9 Hz, 1H); 7.17-7.26 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.7 (CH_3); 19.8 (CH_2); 24.4 (CH_3); 24.6 (CH_3); 26.6 (CH_3); 37.0 (CH_2); 39.8 (CH_2); 44.3 (C); 49.9 (C); 55.1 (CH_3); 108.8 (CH); 125.1 (one CH and one C); 129.5 (CH); 139.1 (C); 155.5 (C).

(+)-β-Herbertenol (1)[2]



BBr_3 (1M solution in CH_2Cl_2, 0.251 g, ~1 mL, 1 mmol) was added dropwise to methyl ether **27** (45 mg, 0.19 mmol) in dry CH_2Cl_2 (5 mL) at -78 ^oC, under N_2 atmosphere. It was allowed to come to room temperature within 12 h, followed by dilution with CH_2Cl_2 (10 mL), excess of BBr_3 was neutralized with saturated $NaHCO_3$ (1 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 95 : 5) to give pure (+)-β-herbertenol **1** (0.039 g) as a white solid.

Molecular Formula **:** $C_{15}H_{22}O$

Yield **:** 93%

Mp **:** 79-80 ^oC [lit.[2] 80-81 ^oC crystallized from hexane]

Specific Rotation **:** $[\alpha]^{25}_D$ +61.26 (*c* 0.7, $CHCl_3$) {lit.[2] $[\alpha]^{25}_D$ –47.0 (*c* 0.7, $CHCl_3$)}

IR ($CHCl_3$) ν_{max} (cm^{-1}) **:** 3450 (broad), 3020, 2960, 1610, 1215, 1106.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.55 (s, 3H); 1.04 (s, 3H); 1.23 (s, 3H); 1.46-1.85 (m, 5H); 2.24 (s, 3H); 2.35-2.55 (m, 1H); 6.66 (d, *J* = 7.9 Hz, 1H); 7.01-7.06 (m, 2H).

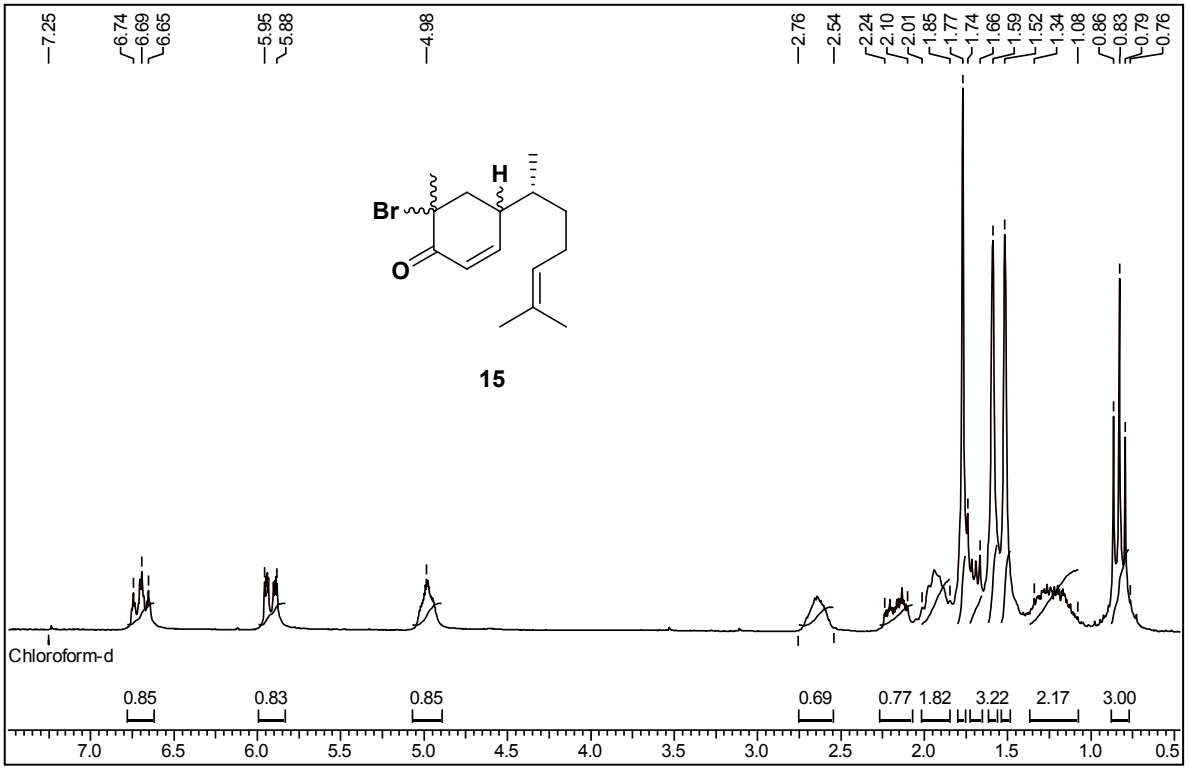
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.2 (CH_3); 19.7 (CH_2); 24.3 (CH_3); 24.6 (CH_3); 26.6 (CH_3); 37.0 (CH_2); 39.8 (CH_2); 44.2 (C); 49.9 (C); 114.0 (CH); 122.3 (C); 125.6 (CH); 129.7 (CH); 139.8 (C); 151.5 (C).

HRMS **:** M^+

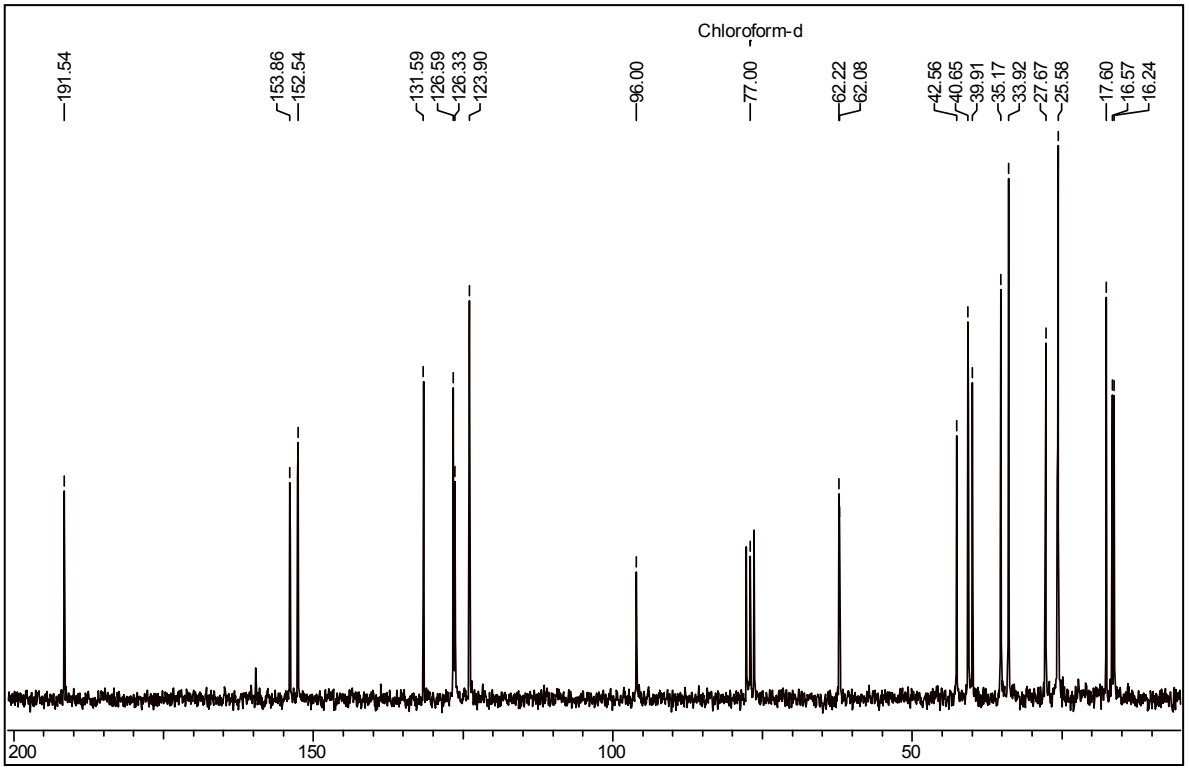
Expected **:** 218.1671

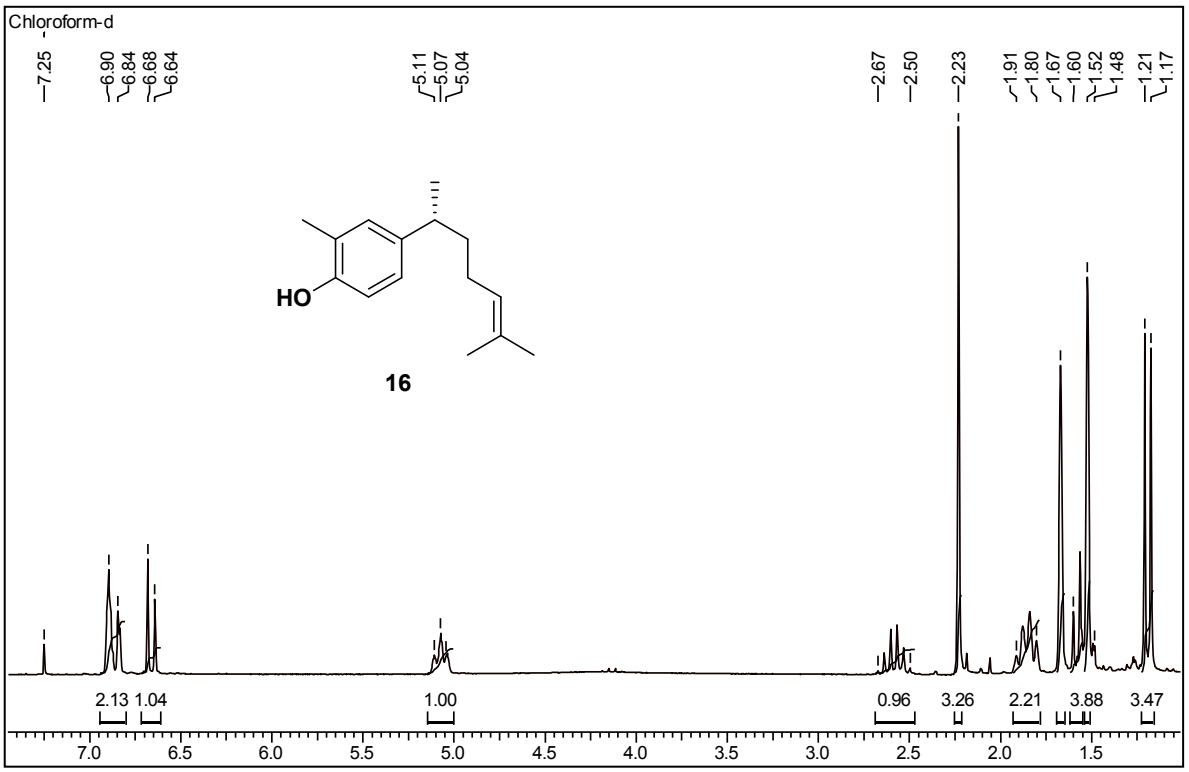
Found **:** 218.1669

1.2.5 Spectra

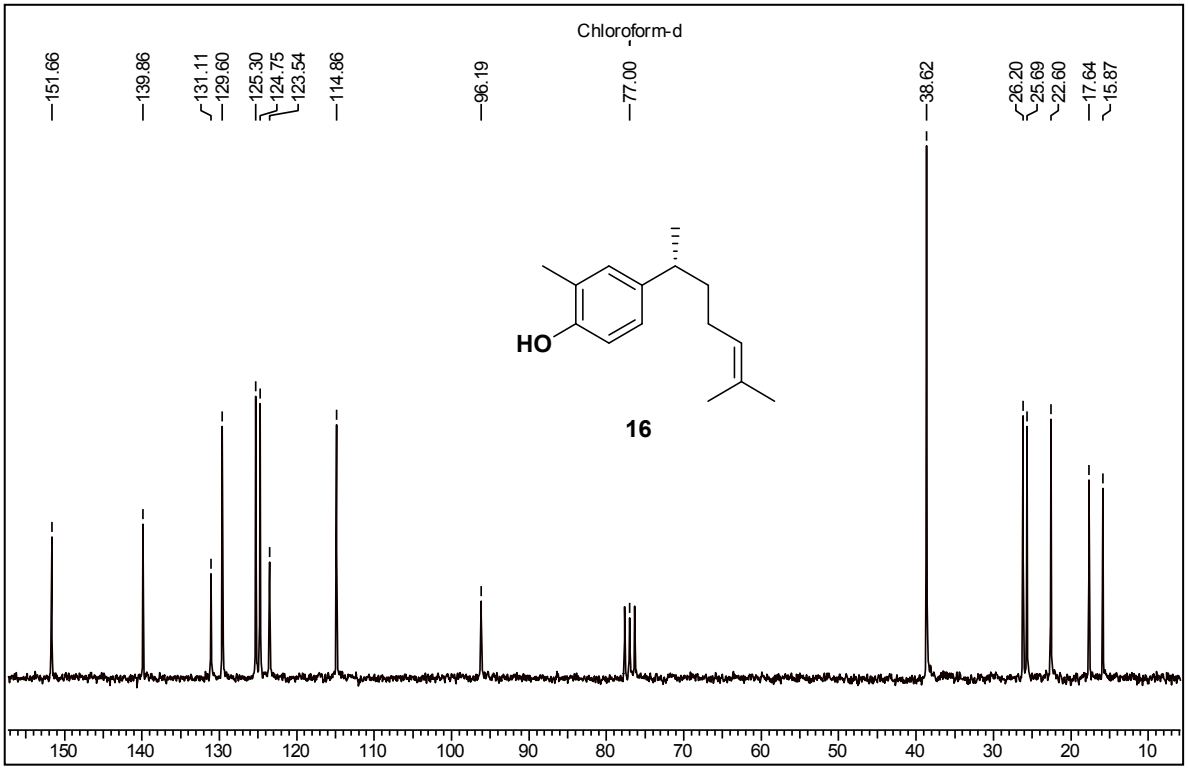


^{1}H (200 MHz) & ^{13}C (50 MHz) NMR SPECTRA ($CDCl_3$ + CCl_4)

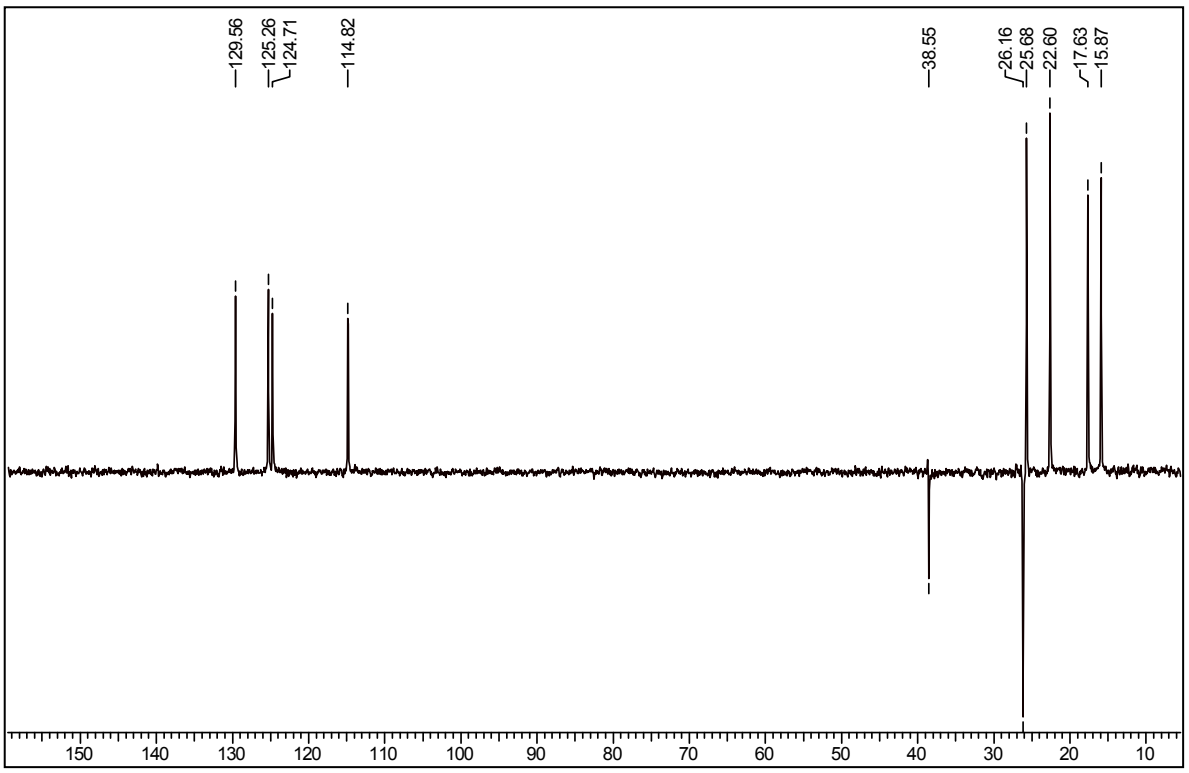


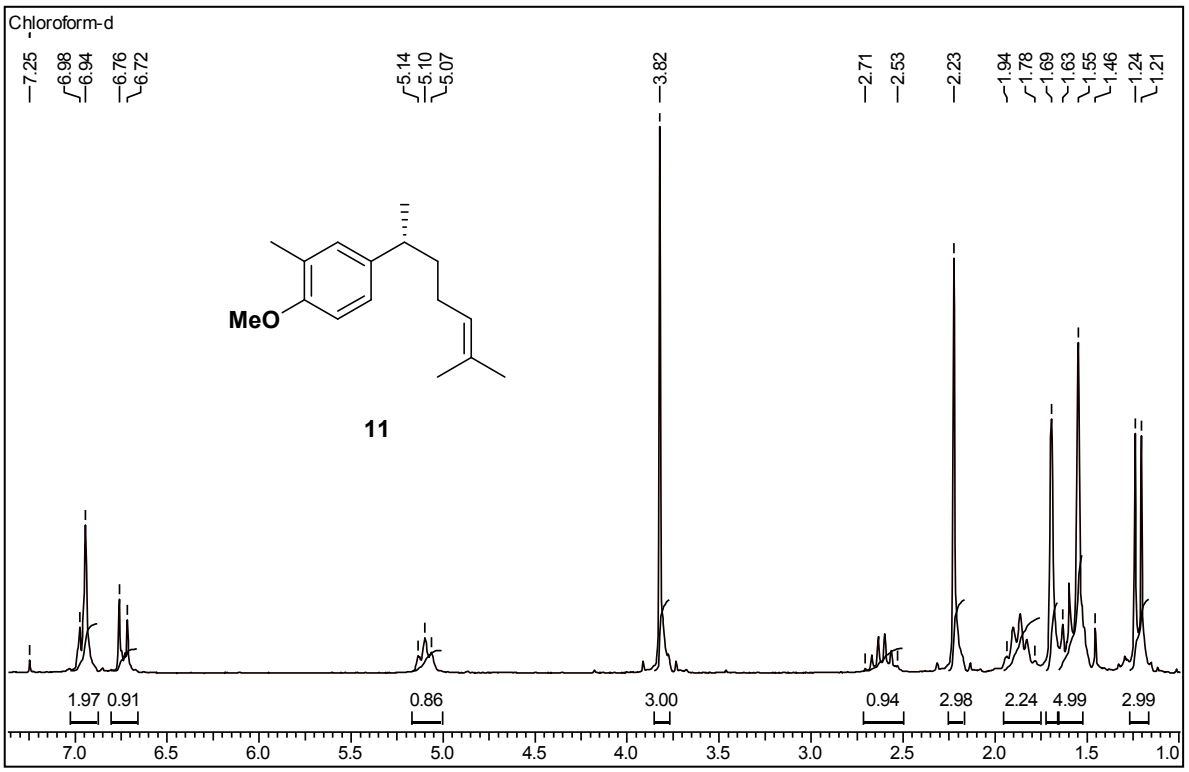


^{1}H NMR SPECTRUM ($CDCl_3$ + CCl_4, 200 MHz)

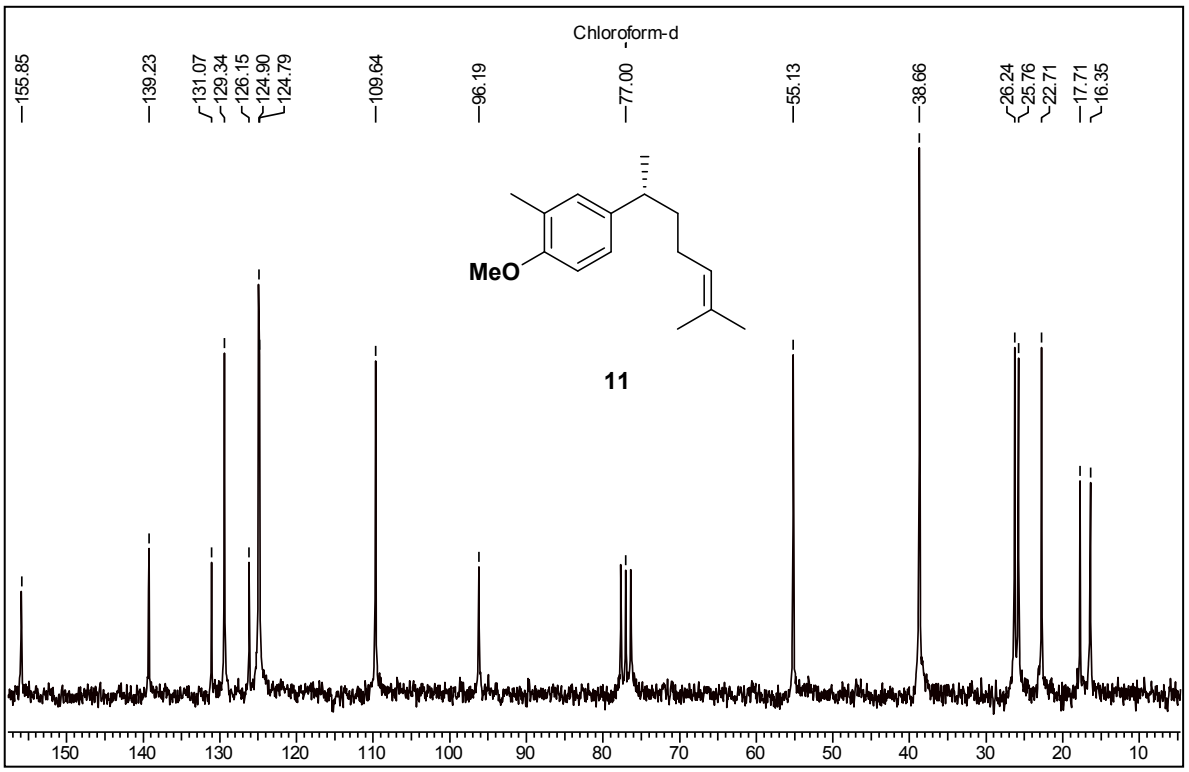


^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 50 MHz)

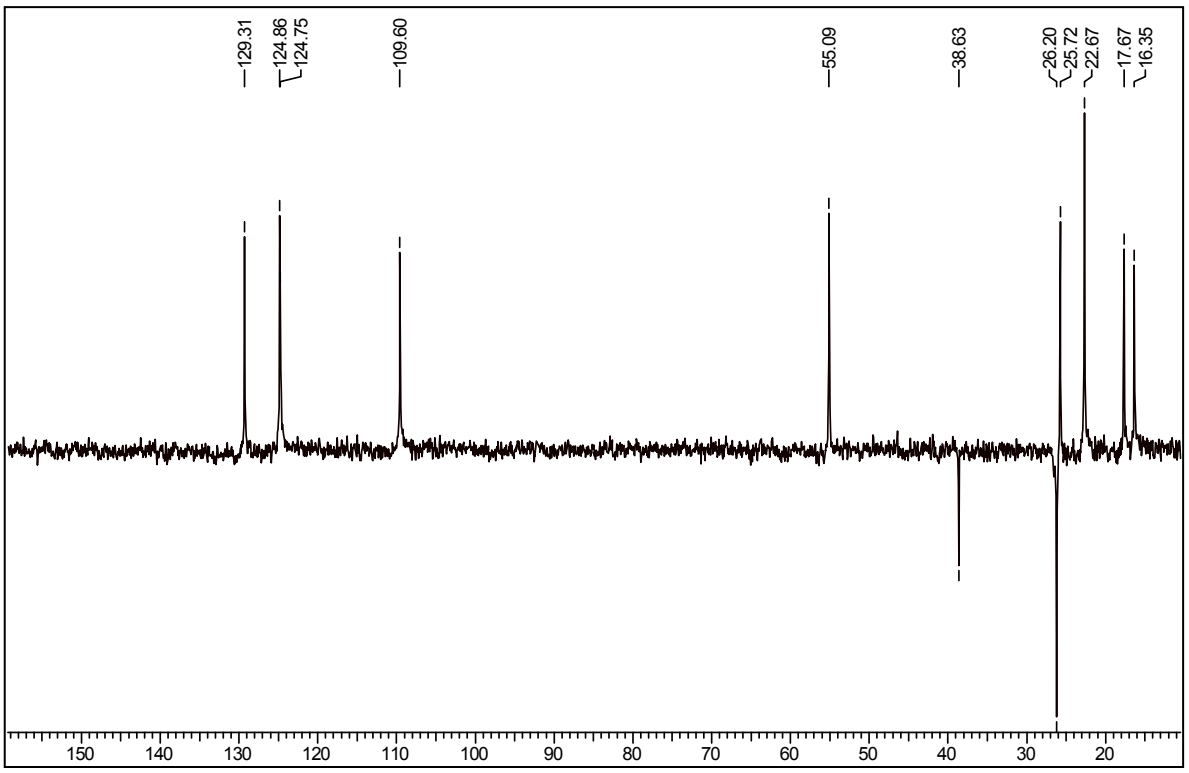


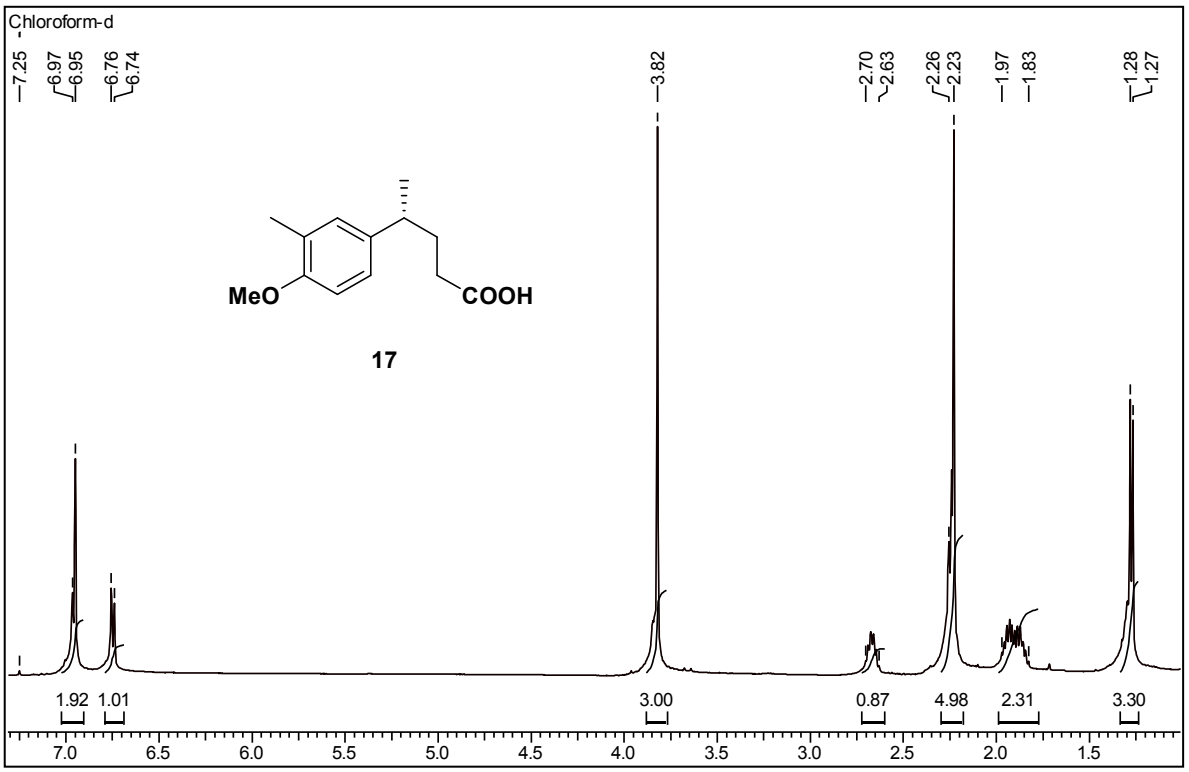


^{1}H NMR SPECTRUM ($CDCl_3$ + CCl_4, 200 MHz)

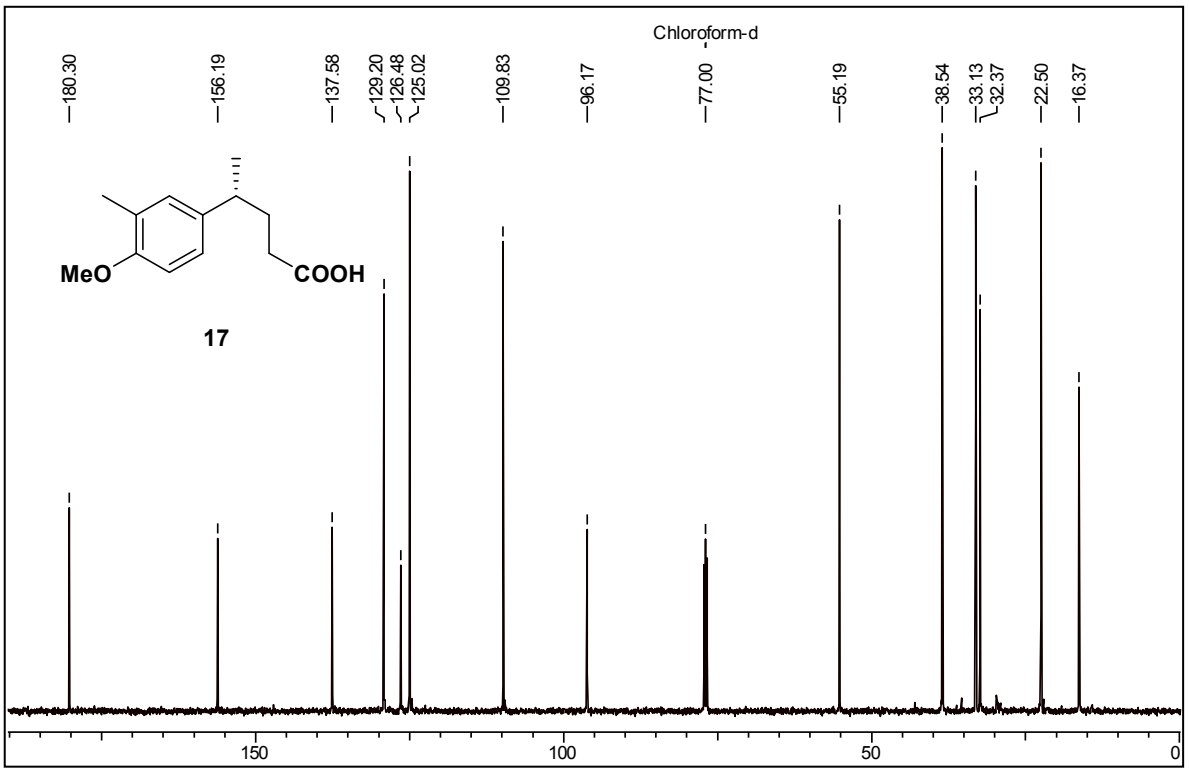


^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 50 MHz)



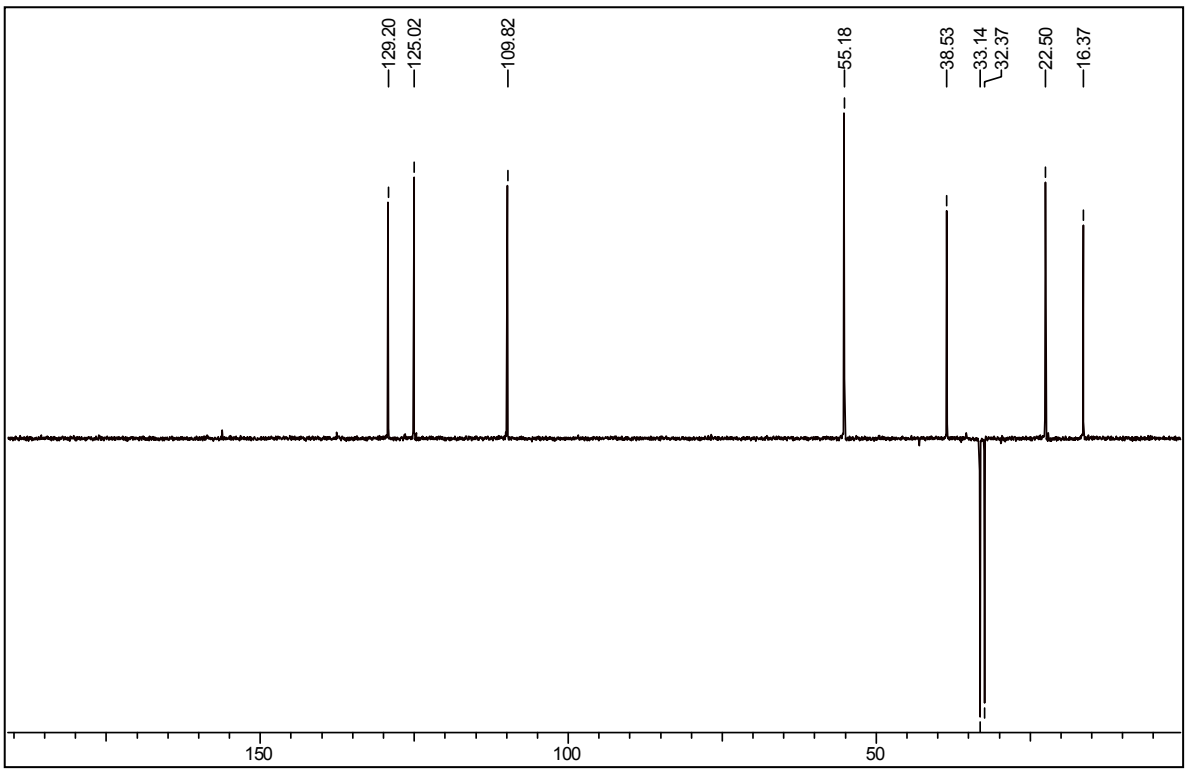


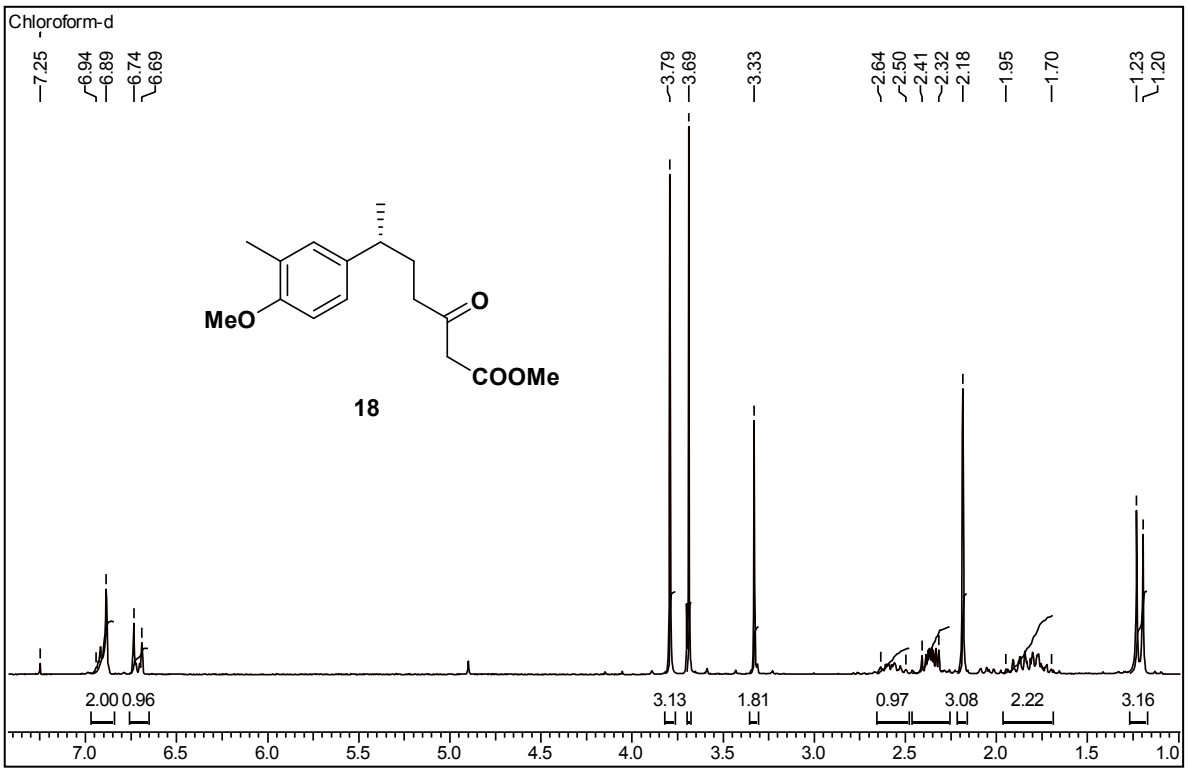
^{1}H NMR SPECTRUM ($CDCl_3$ + CCl_4, 200 MHz)



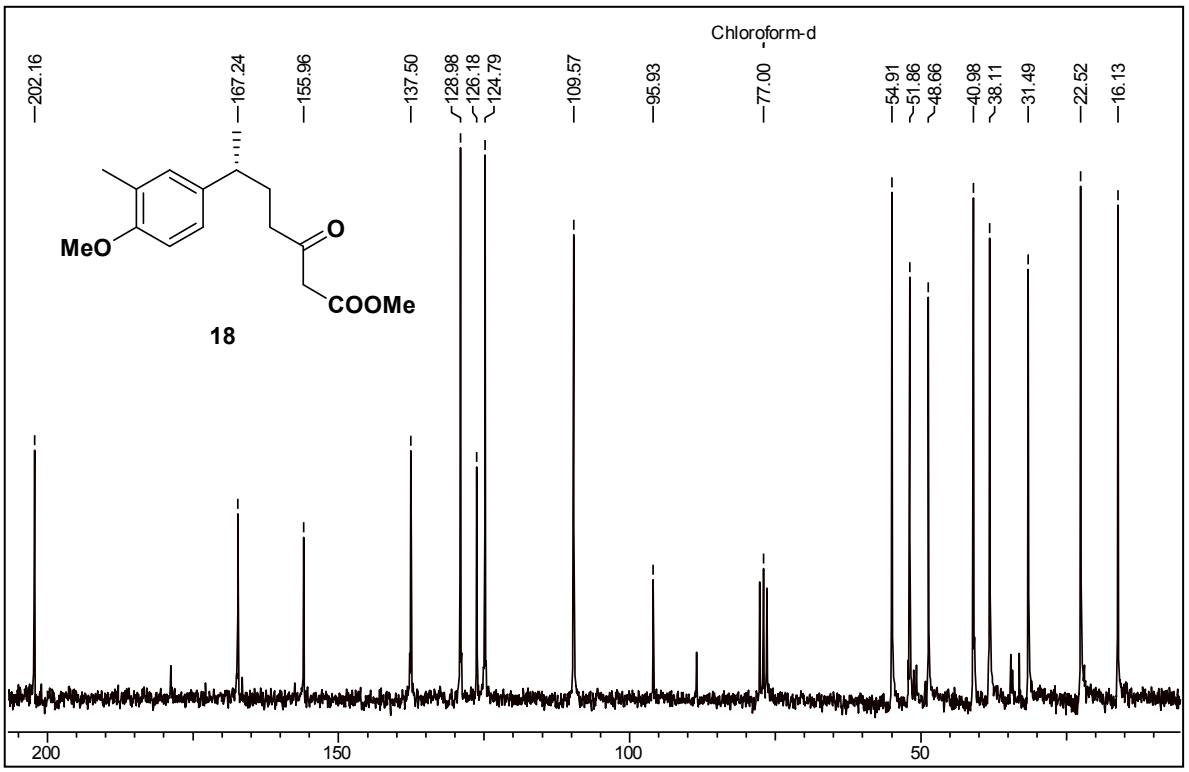
17

^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 50 MHz)

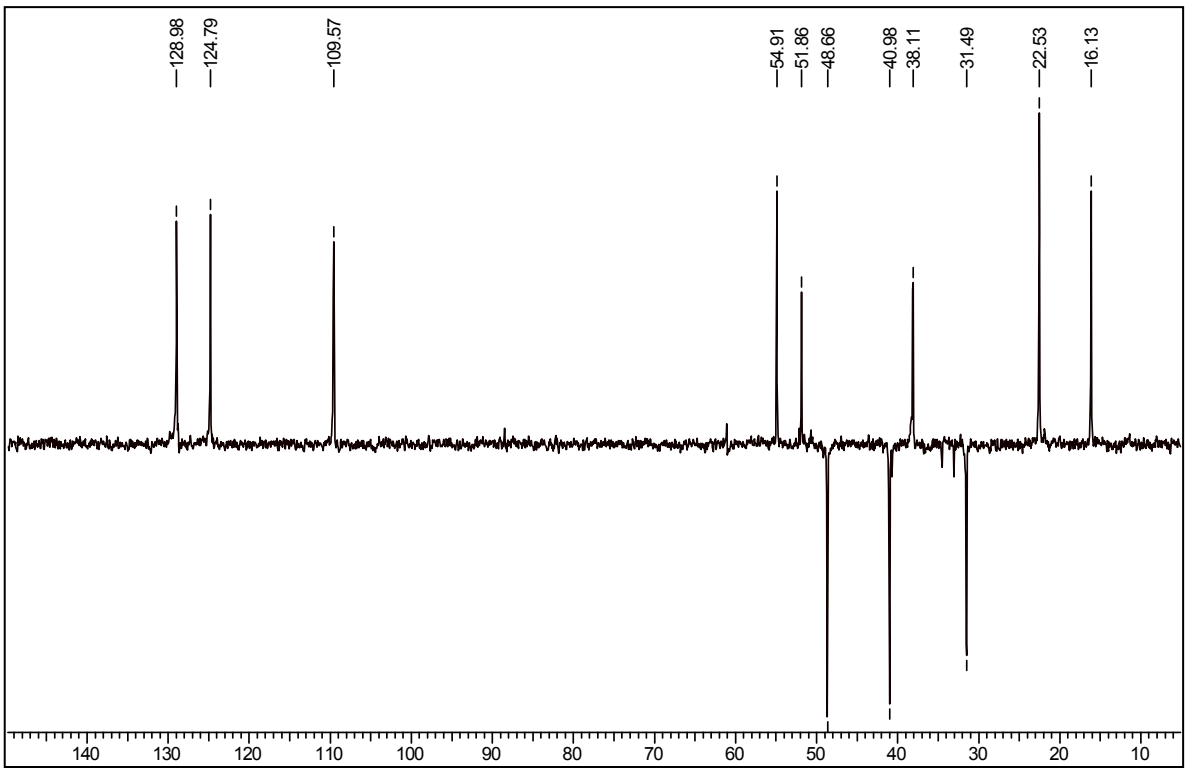


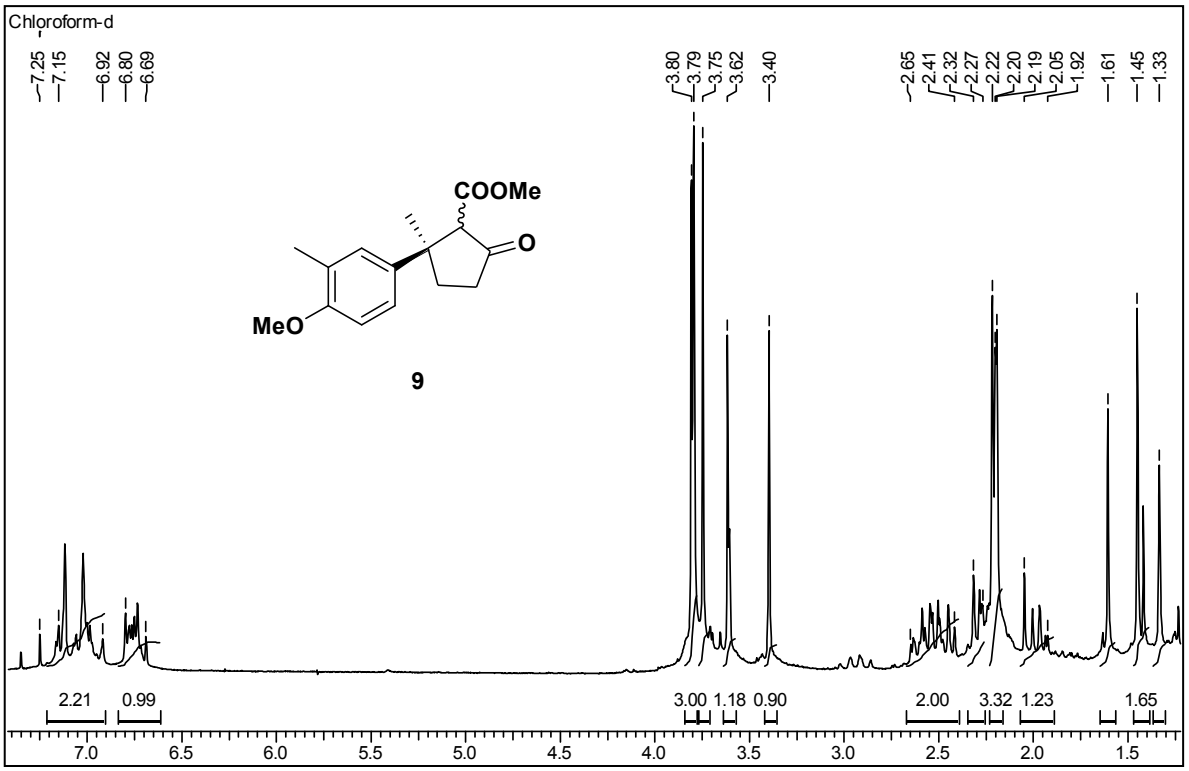


^{1}H NMR SPECTRUM ($CDCl_3$ + CCl_4, 200 MHz)

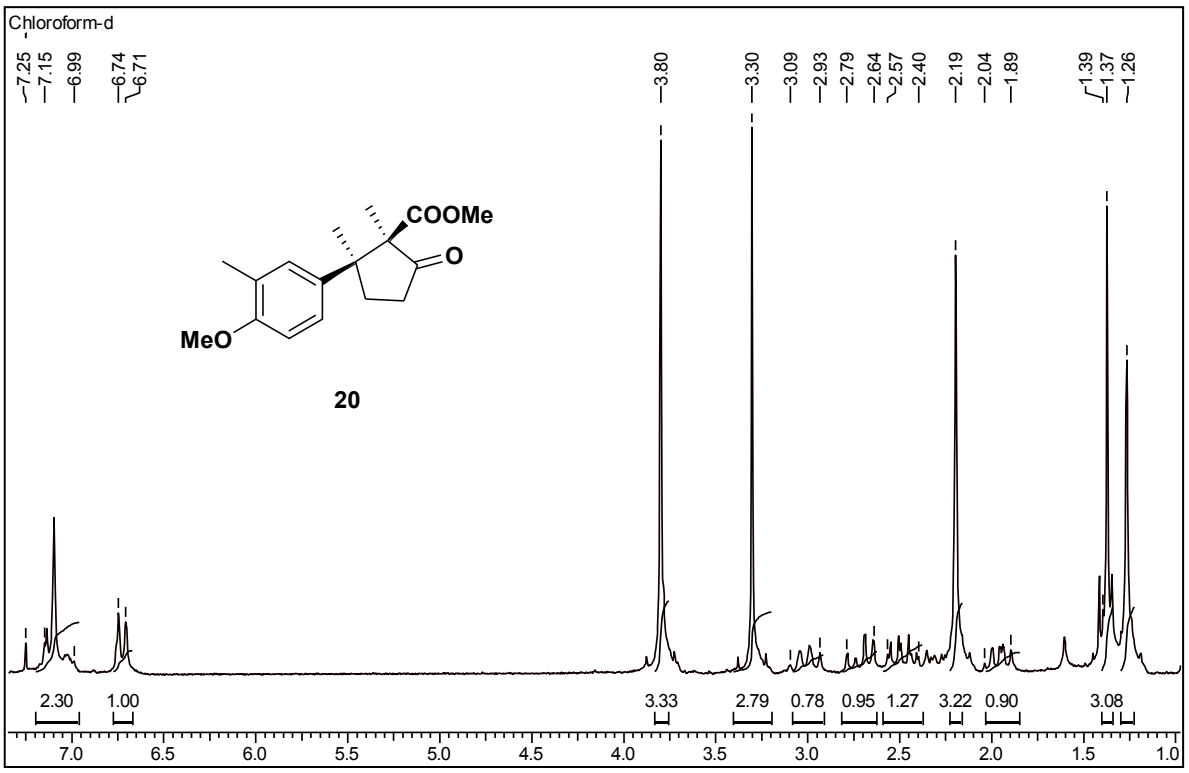


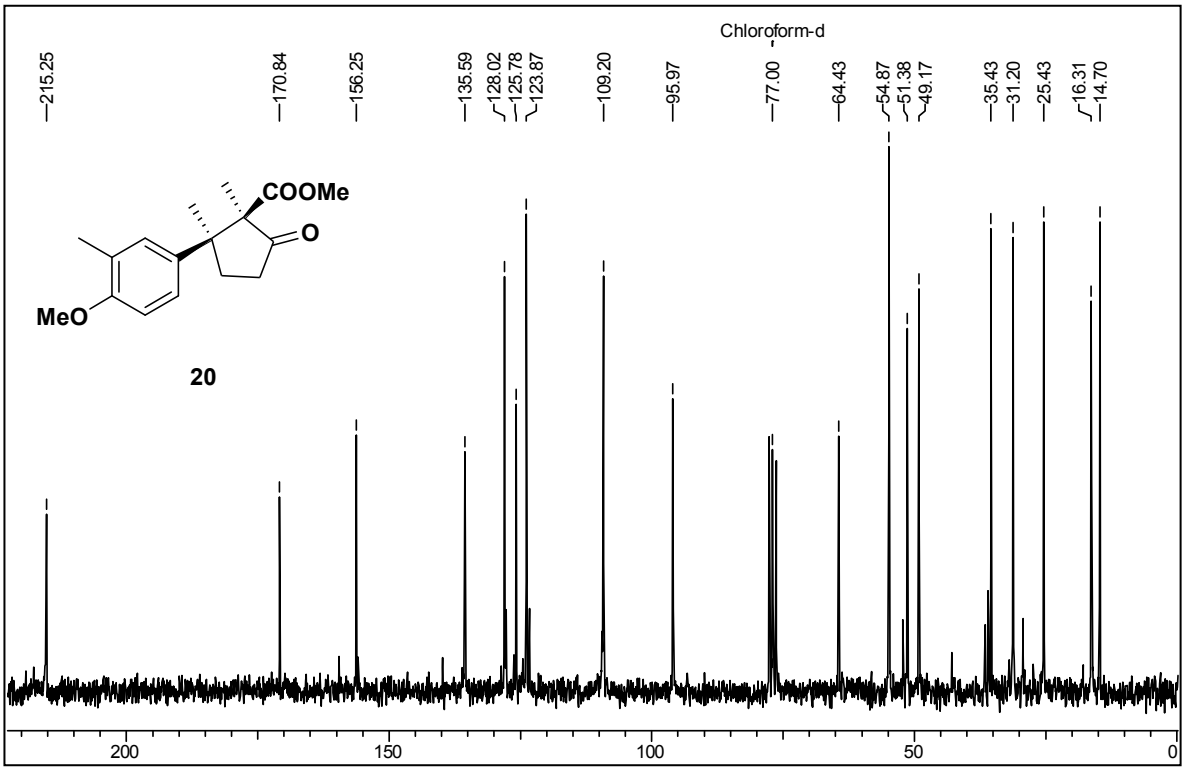
^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 50 MHz)





^{1}H NMR SPECTRA ($CDCl_3$ + CCl_4, 200 MHz)





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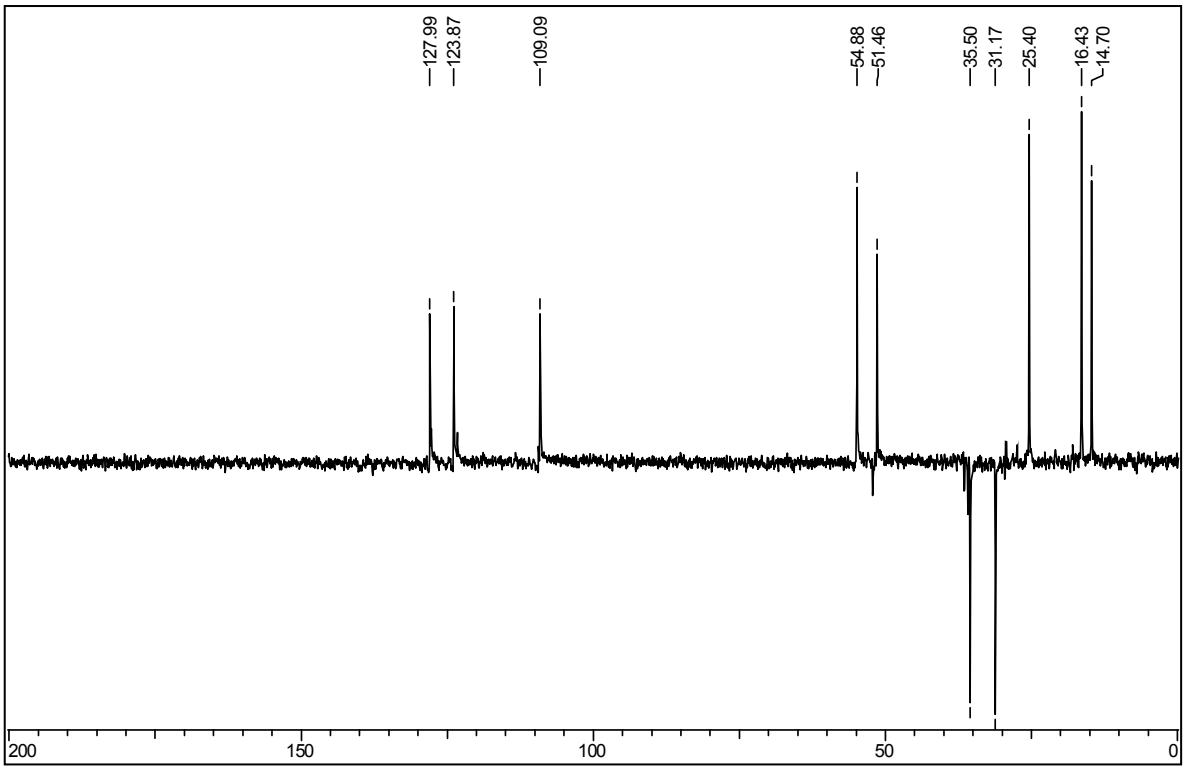
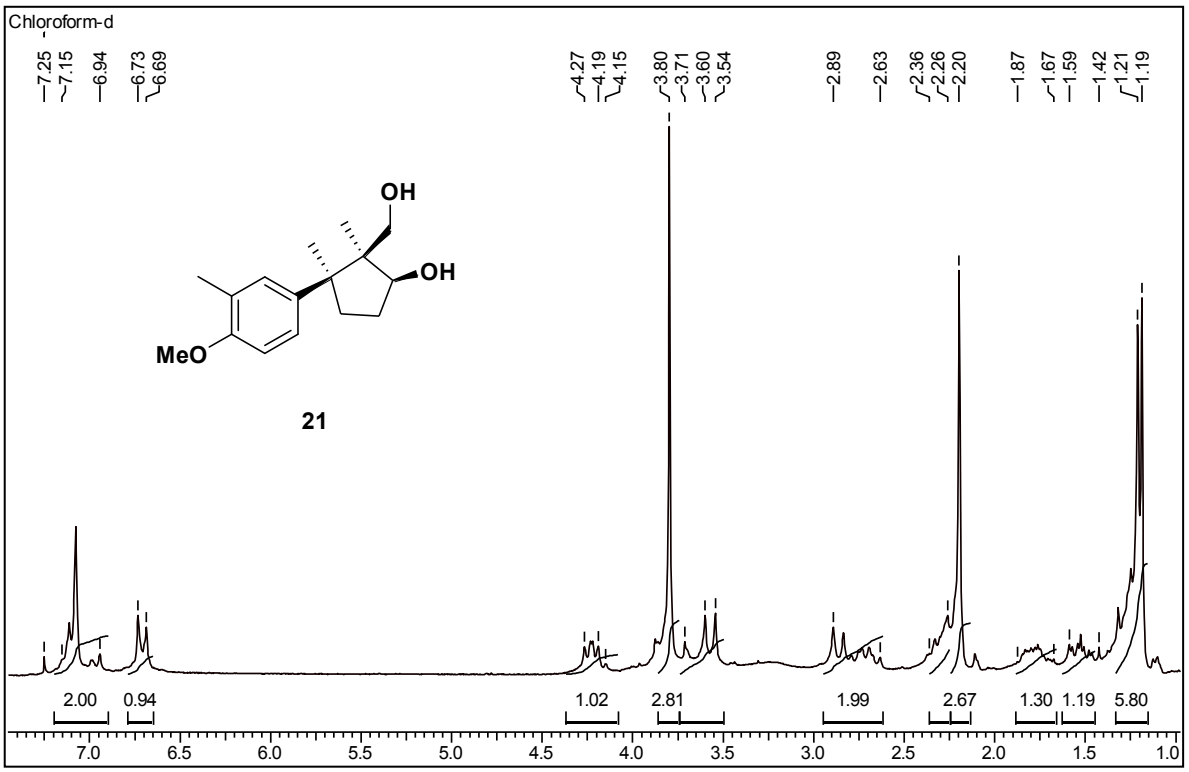
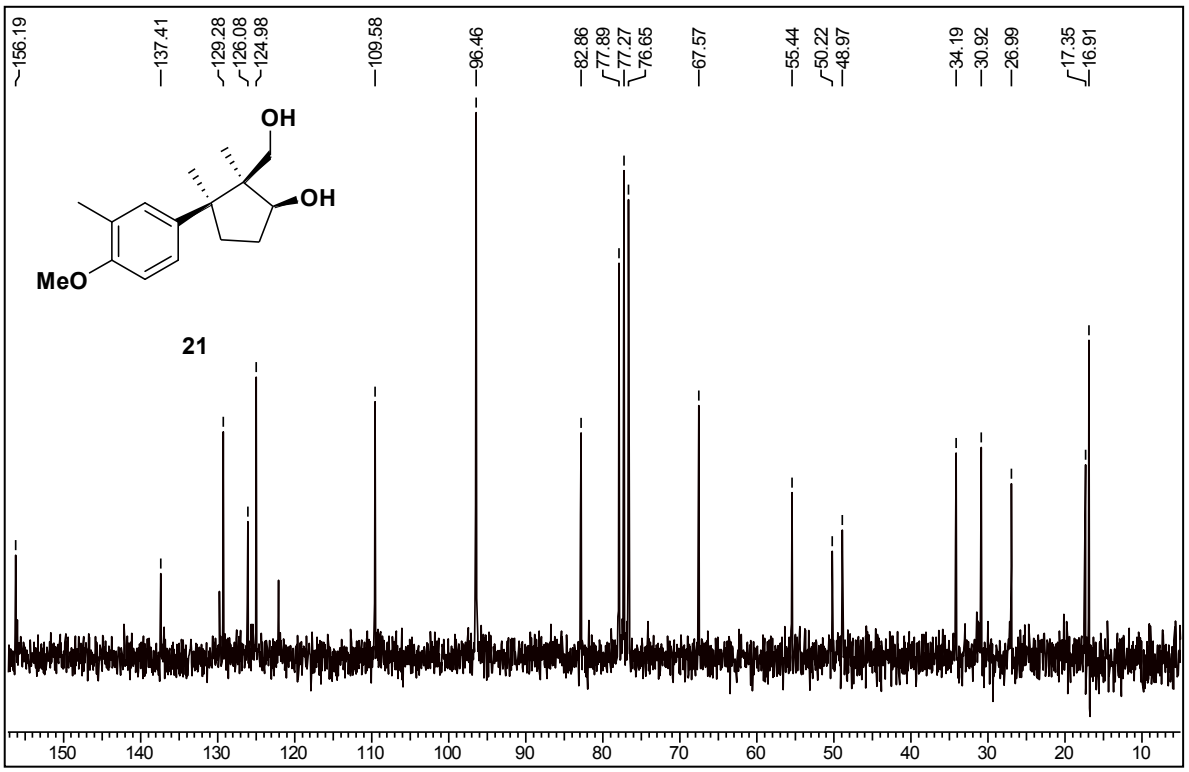
^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 50 MHz)

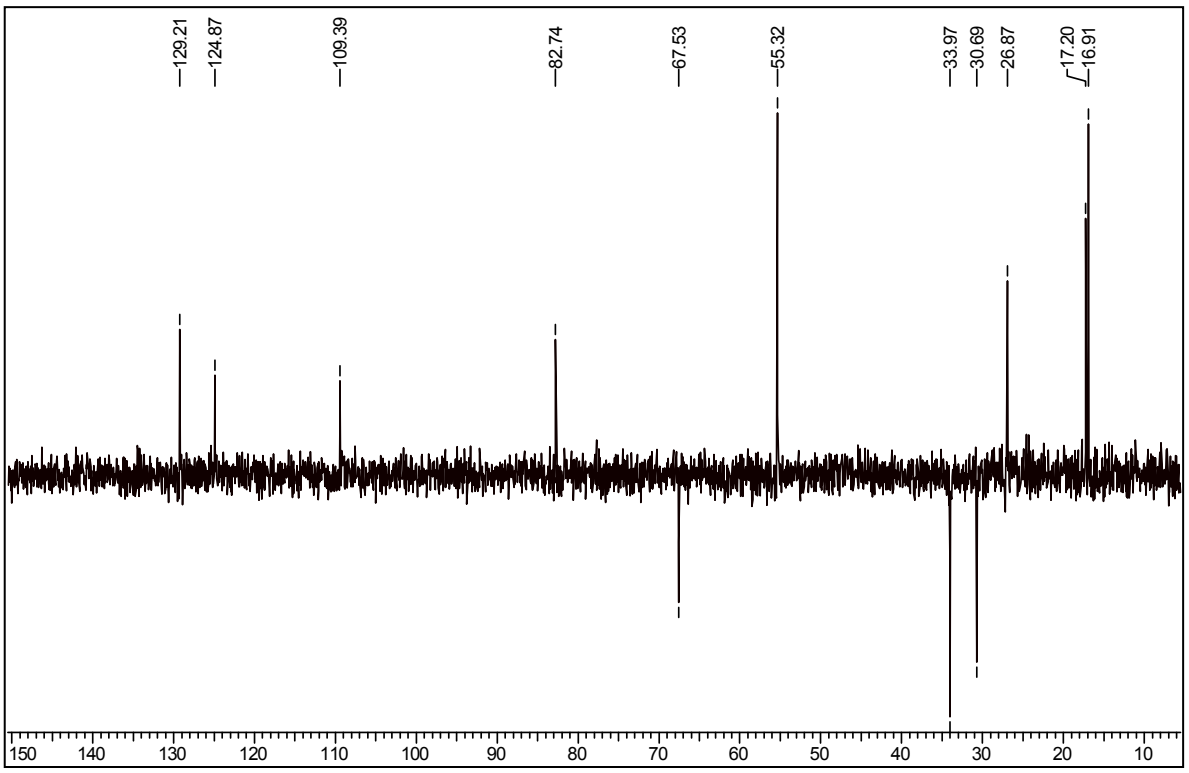


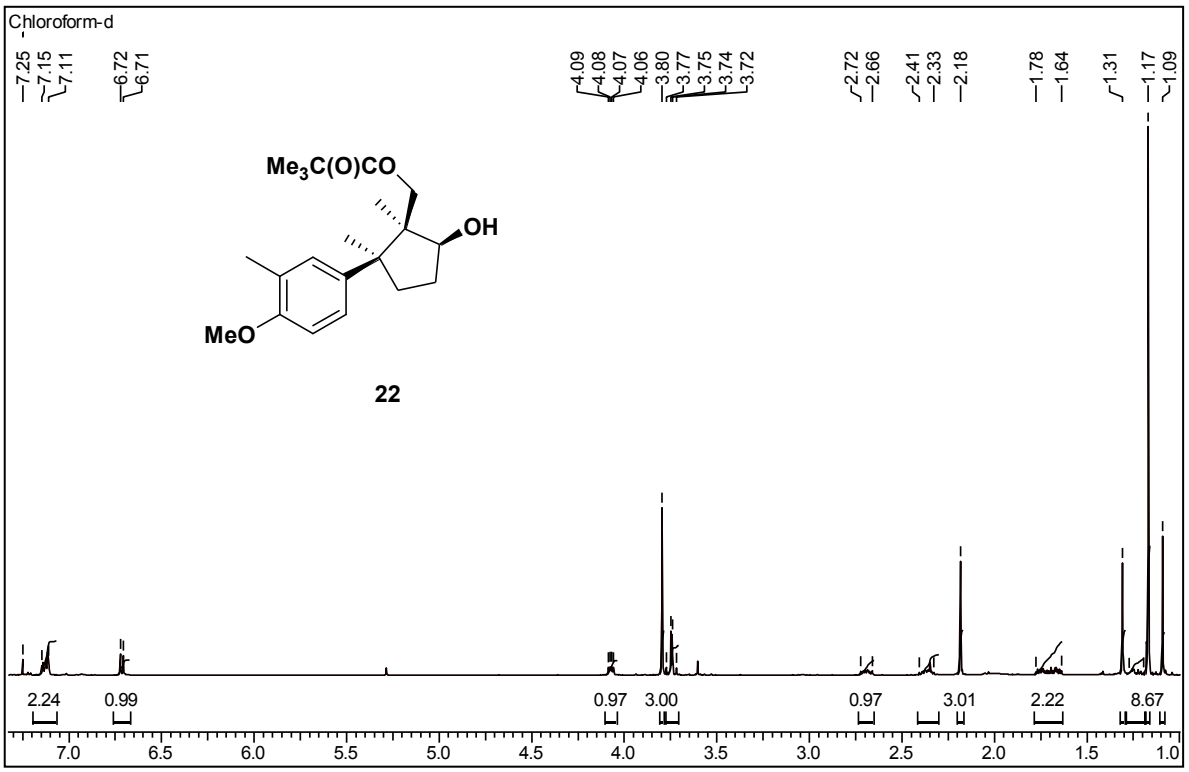


^{1}H NMR SPECTRUM ($CDCl_3$ + CCl_4, 200 MHz)

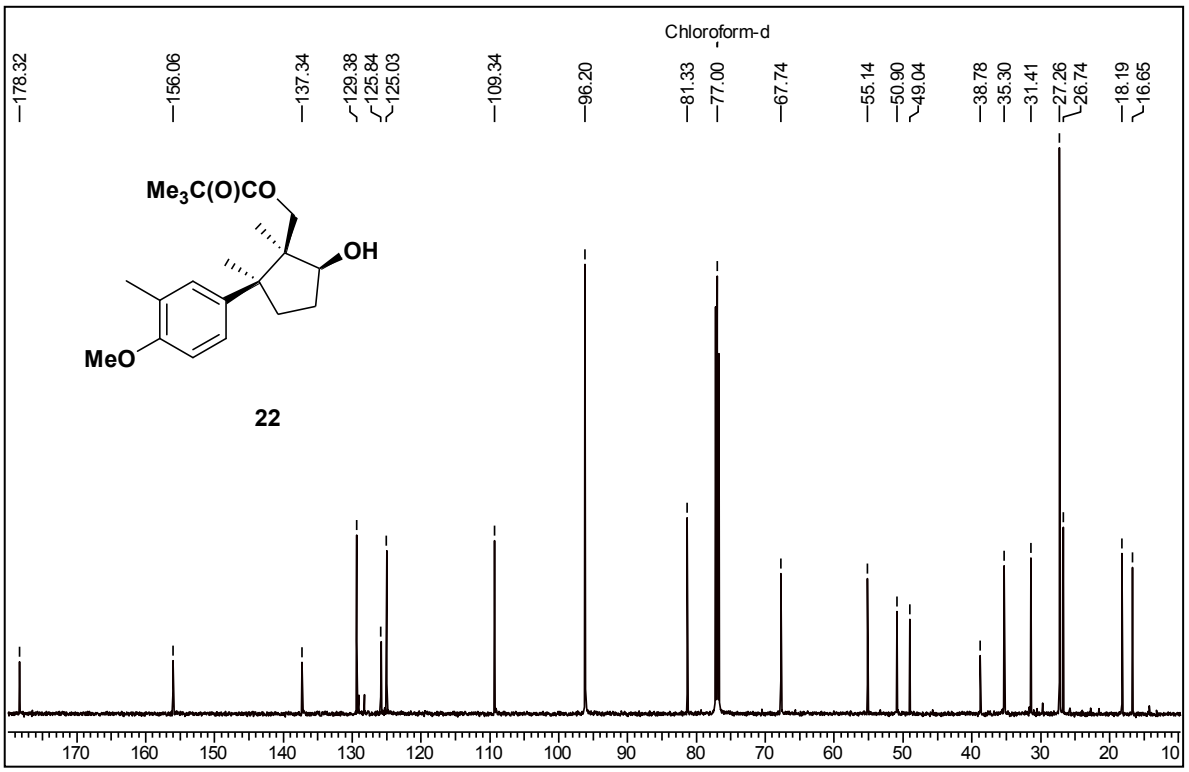


^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 50 MHz)

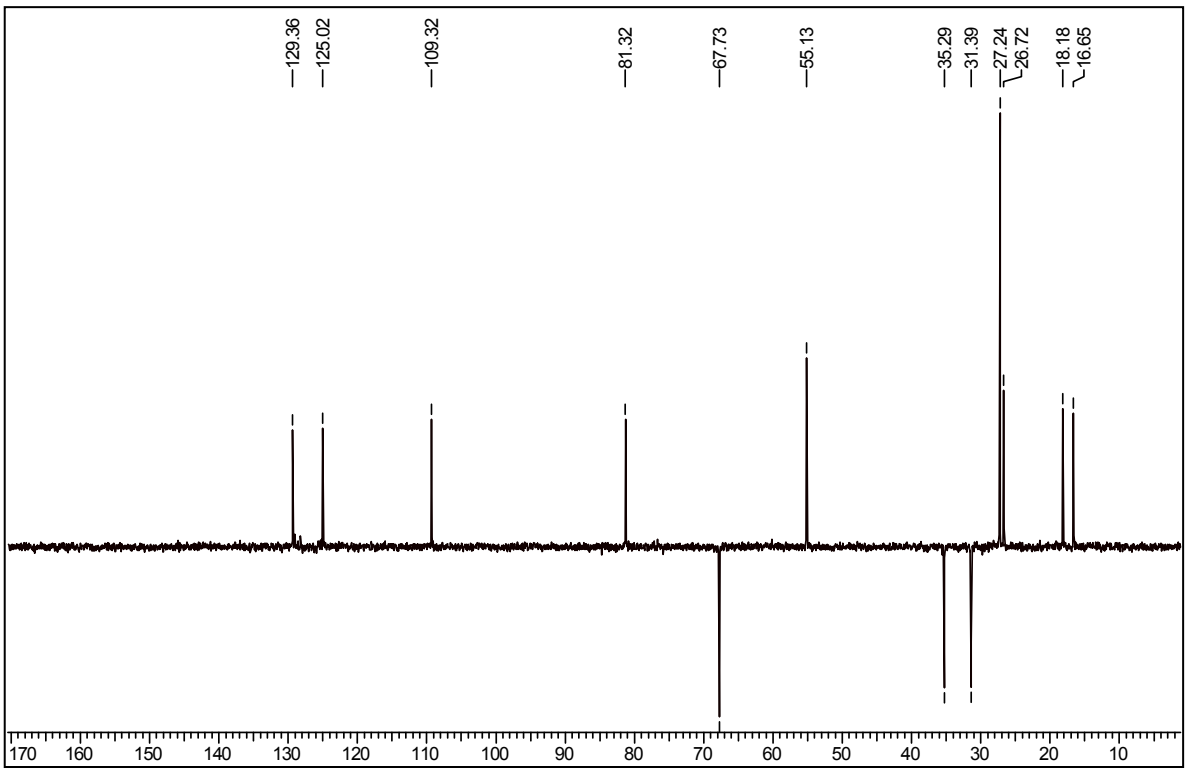


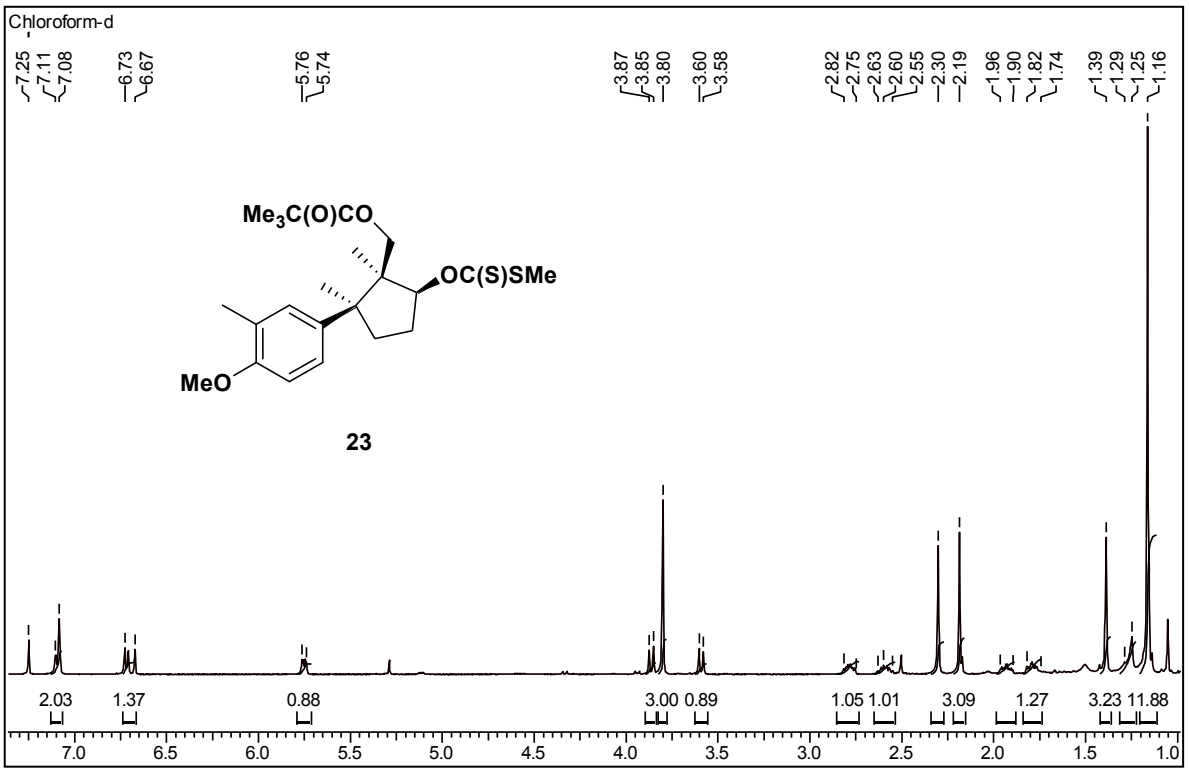


^{1}H NMR SPECTRUM ($CDCl_3$ + CCl_4, 500 MHz)

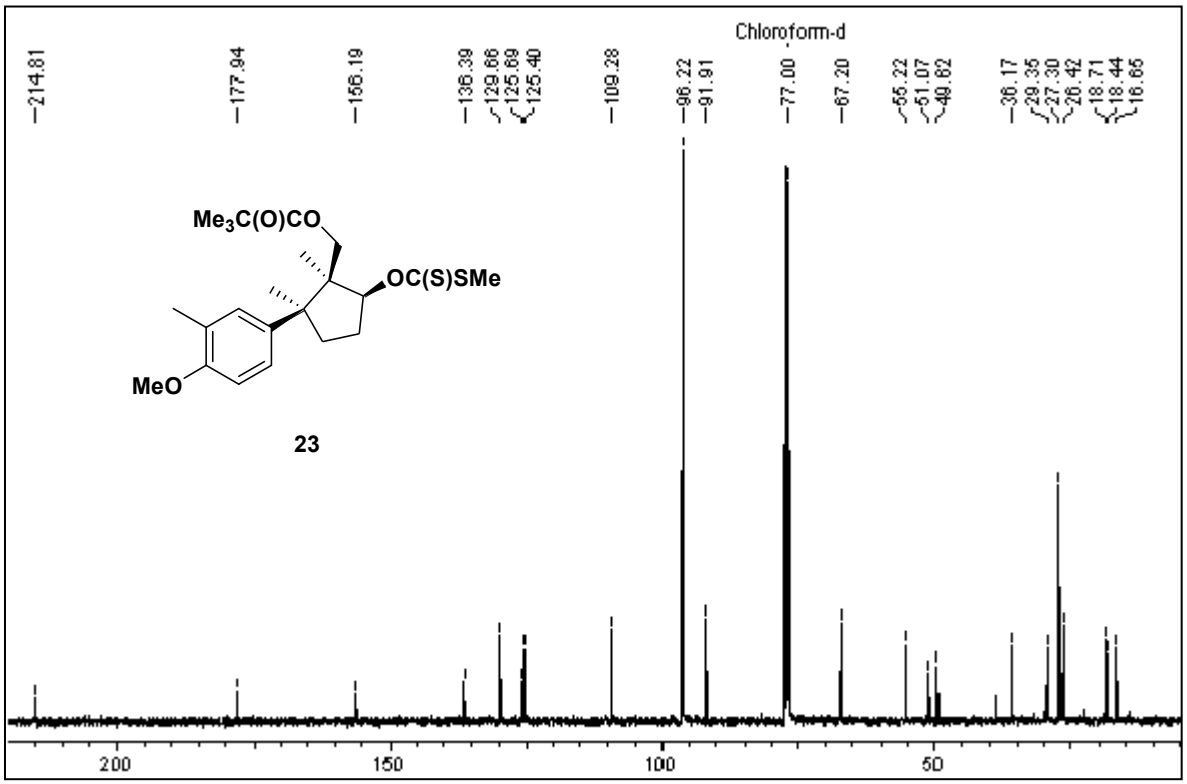


^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 125 MHz)



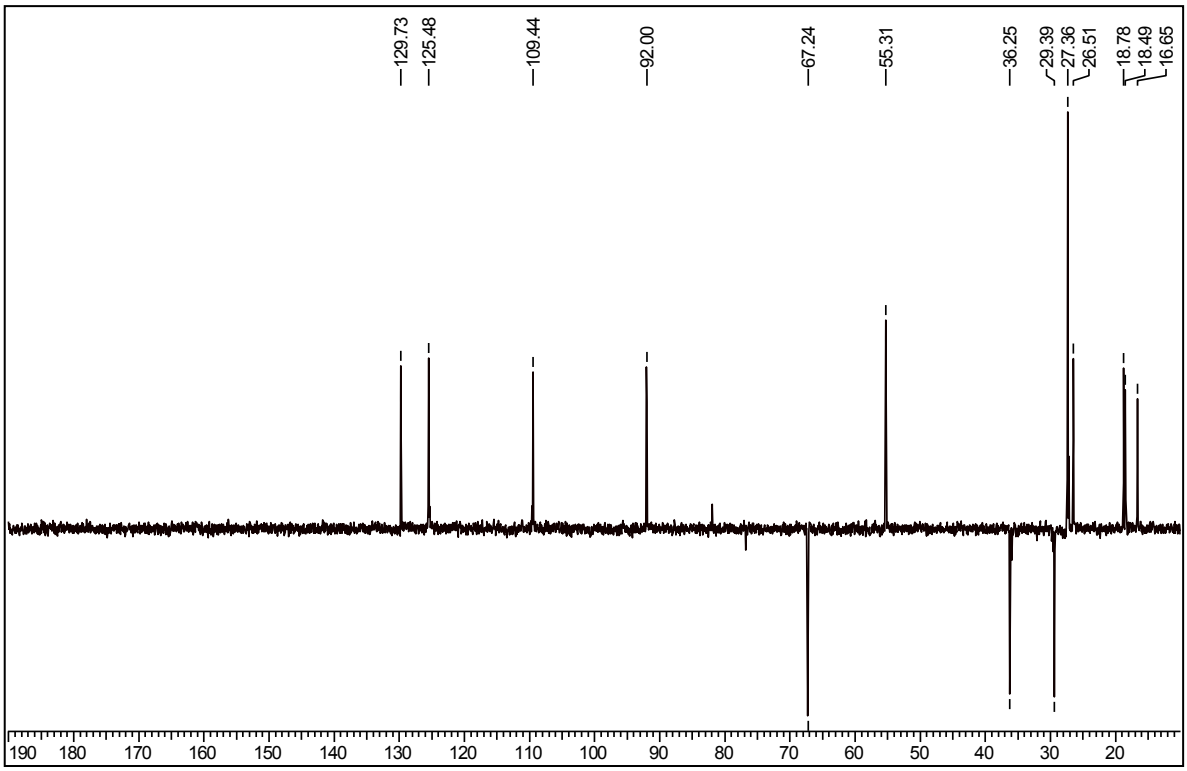


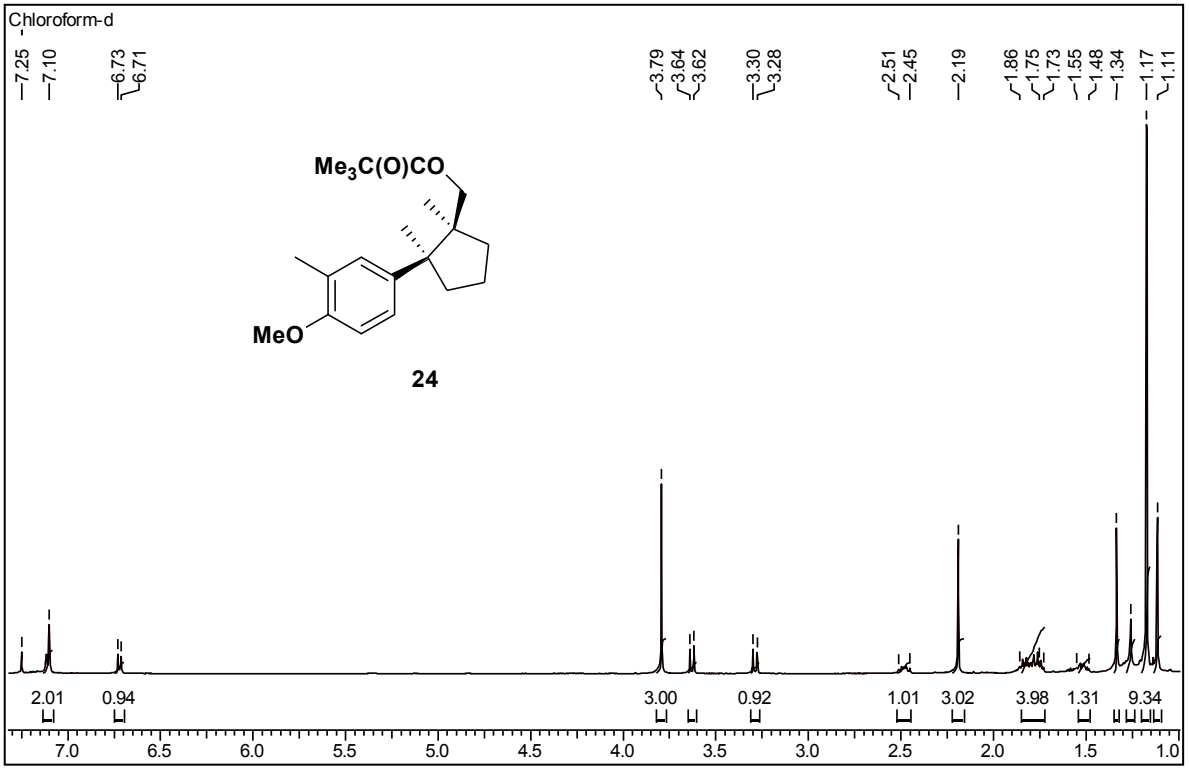
^{1}H NMR SPECTRUM ($CDCl_3$ + CCl_4, 500 MHz)



23

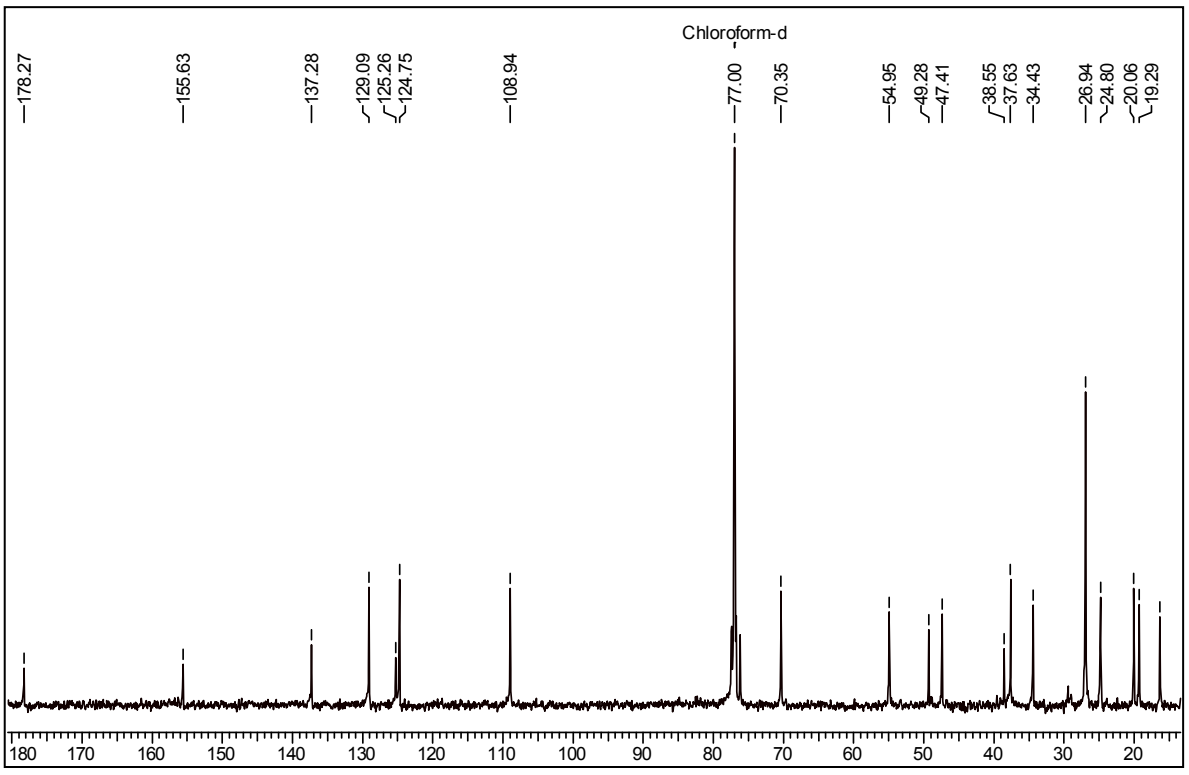
^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 125 MHz)

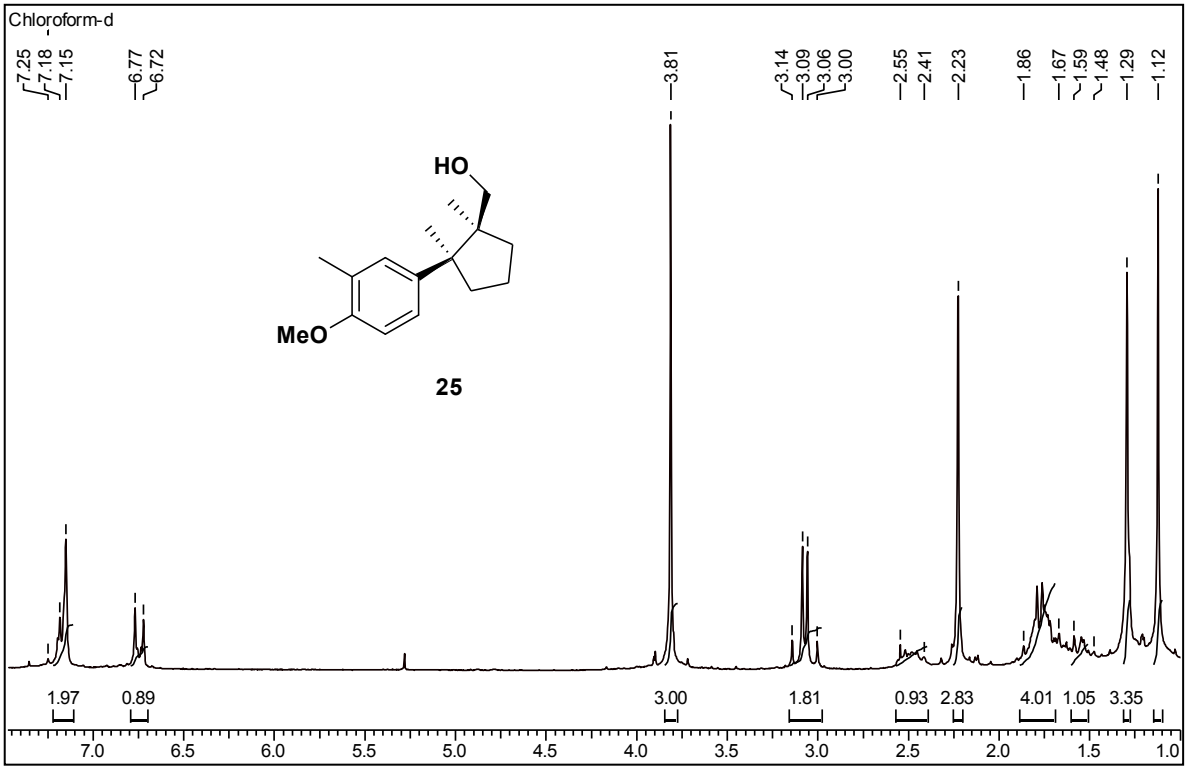




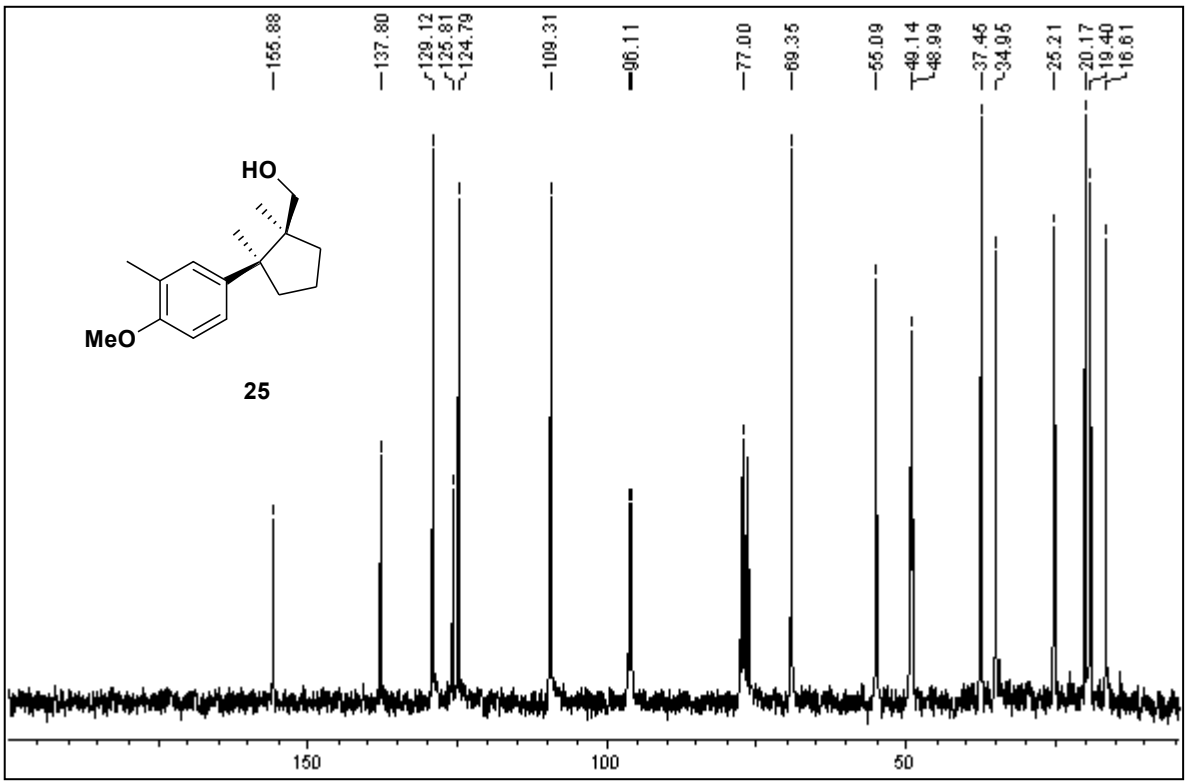
24

^{1}H (500 MHz) & ^{13}C (125 MHz) NMR SPECTRA ($CDCl_3$)

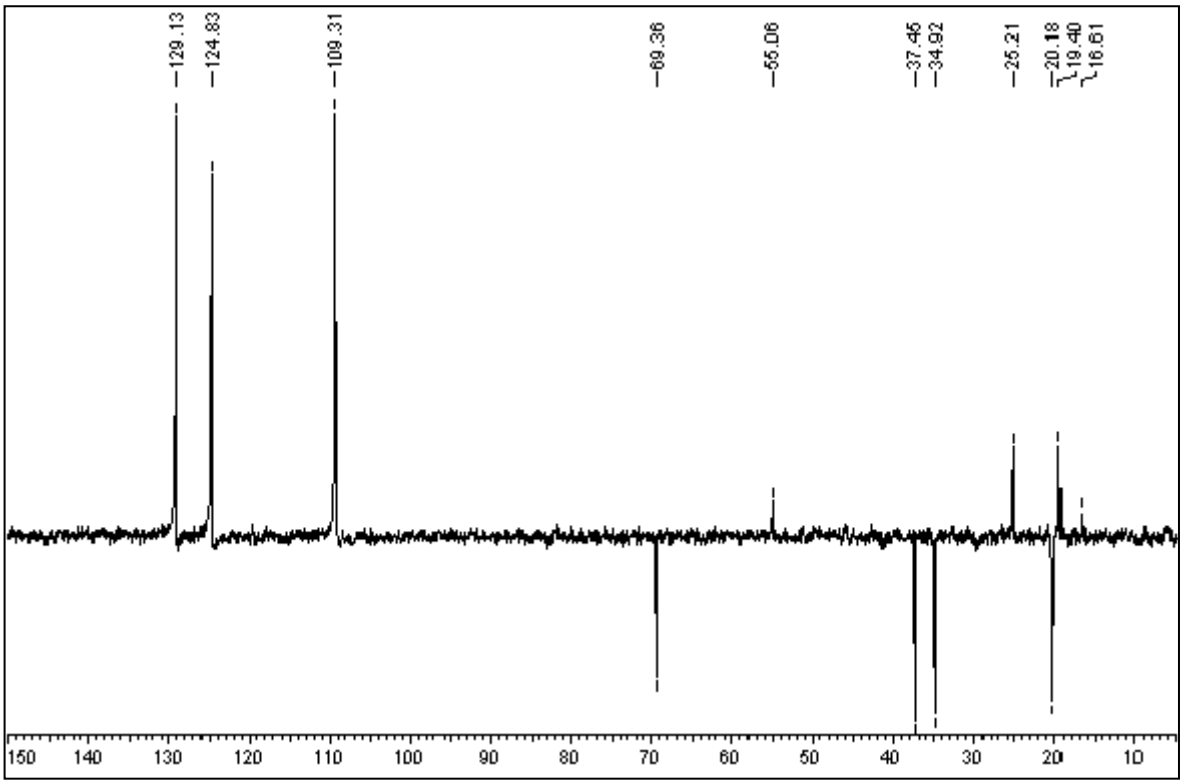


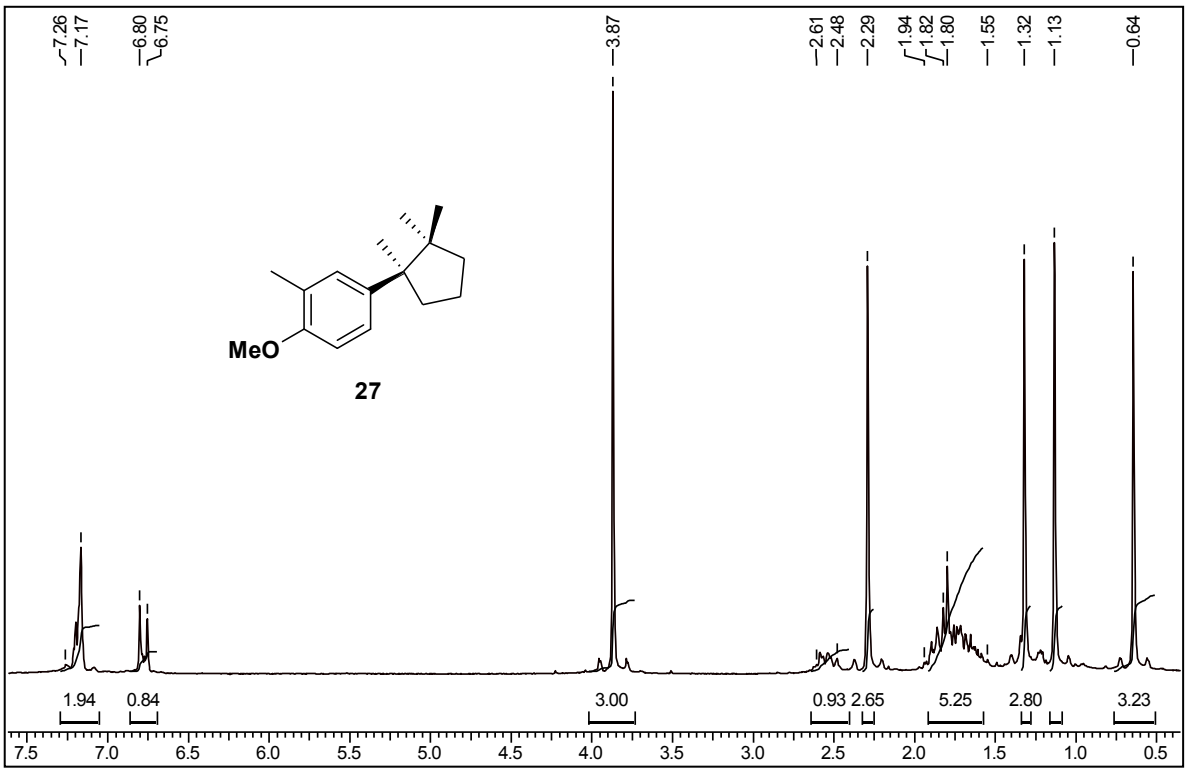


^{1}H NMR SPECTRUM ($CDCl_3$ + CCl_4, 200 MHz)



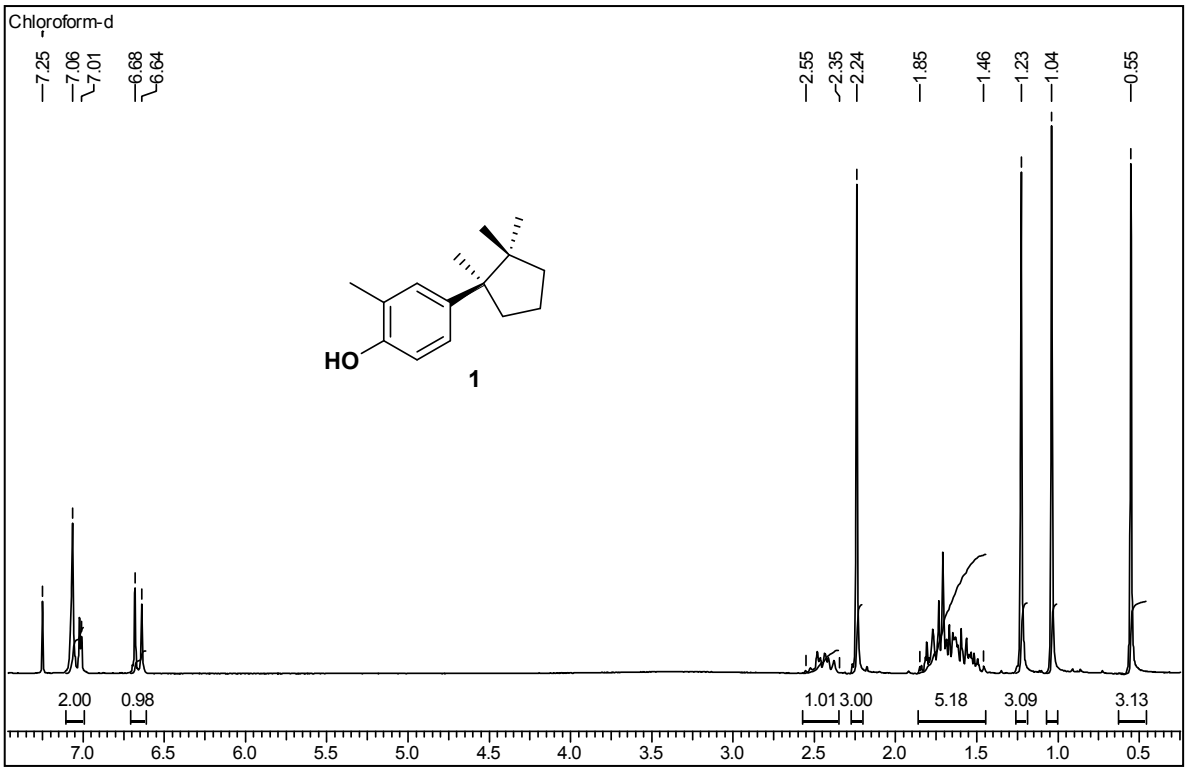
^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 50 MHz)



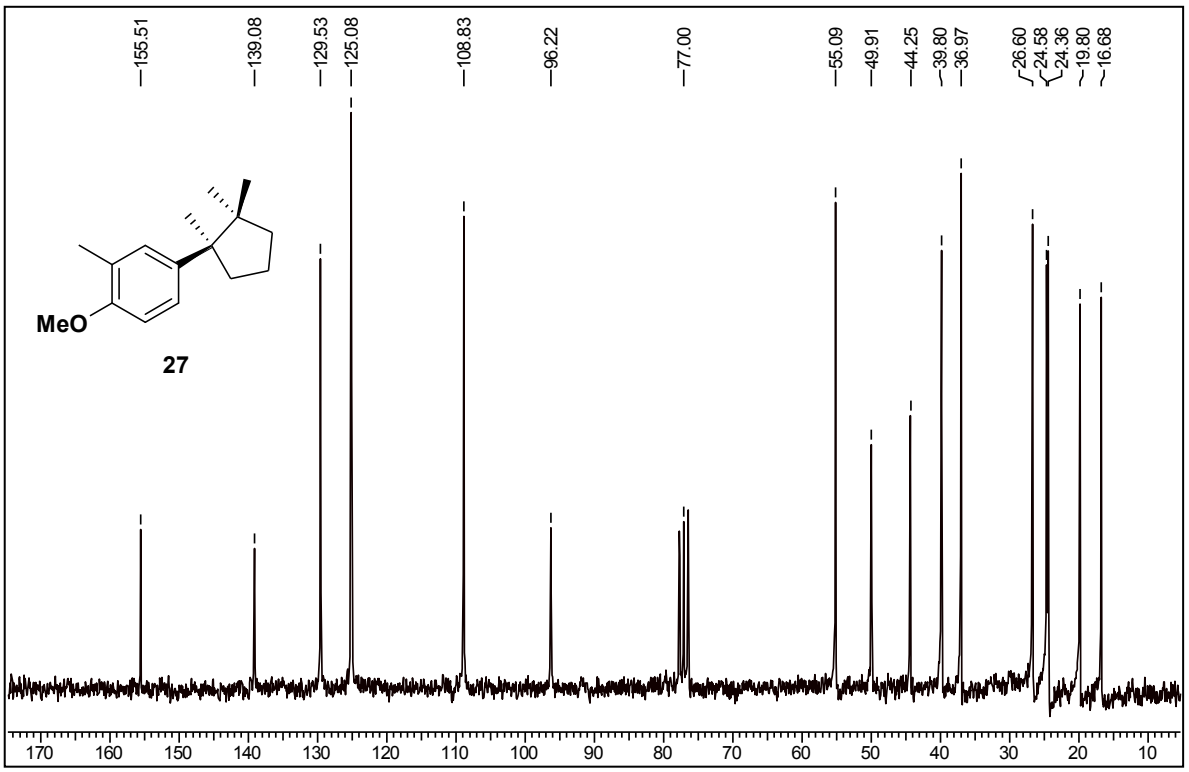


27

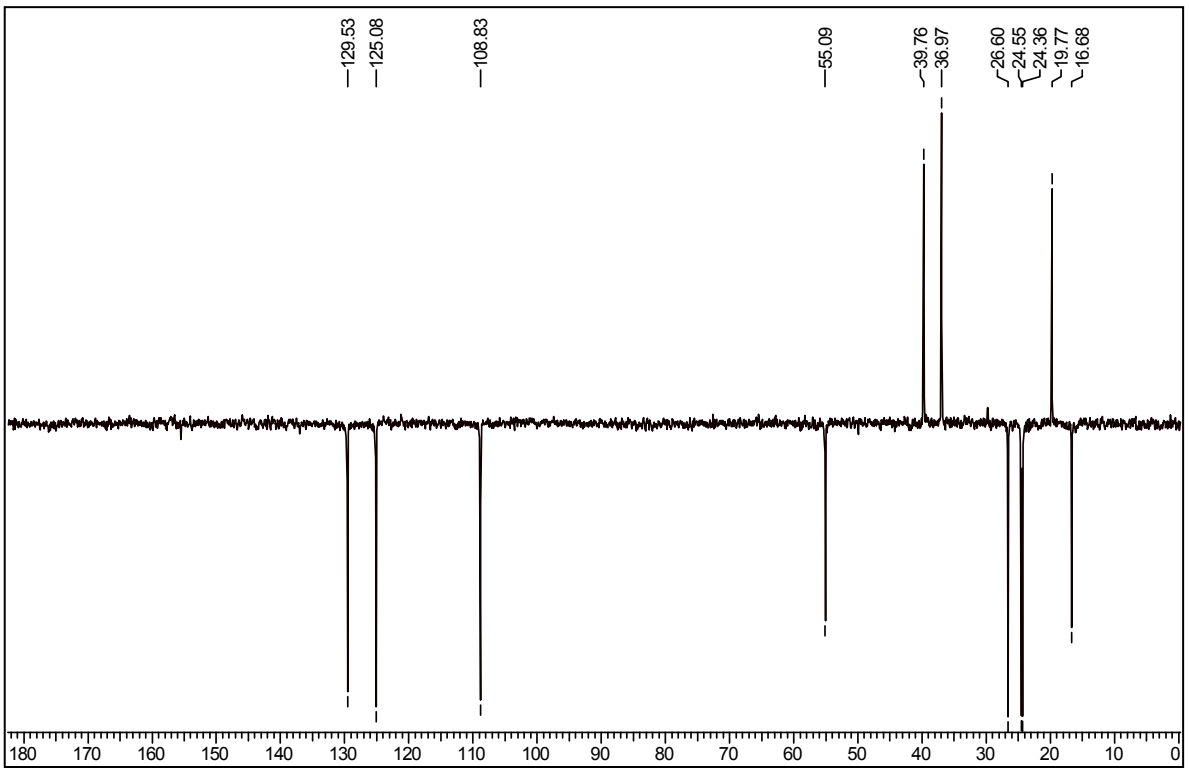
^{1}H NMR SPECTRA ($CDCl_3$ + CCl_4, 200 MHz)

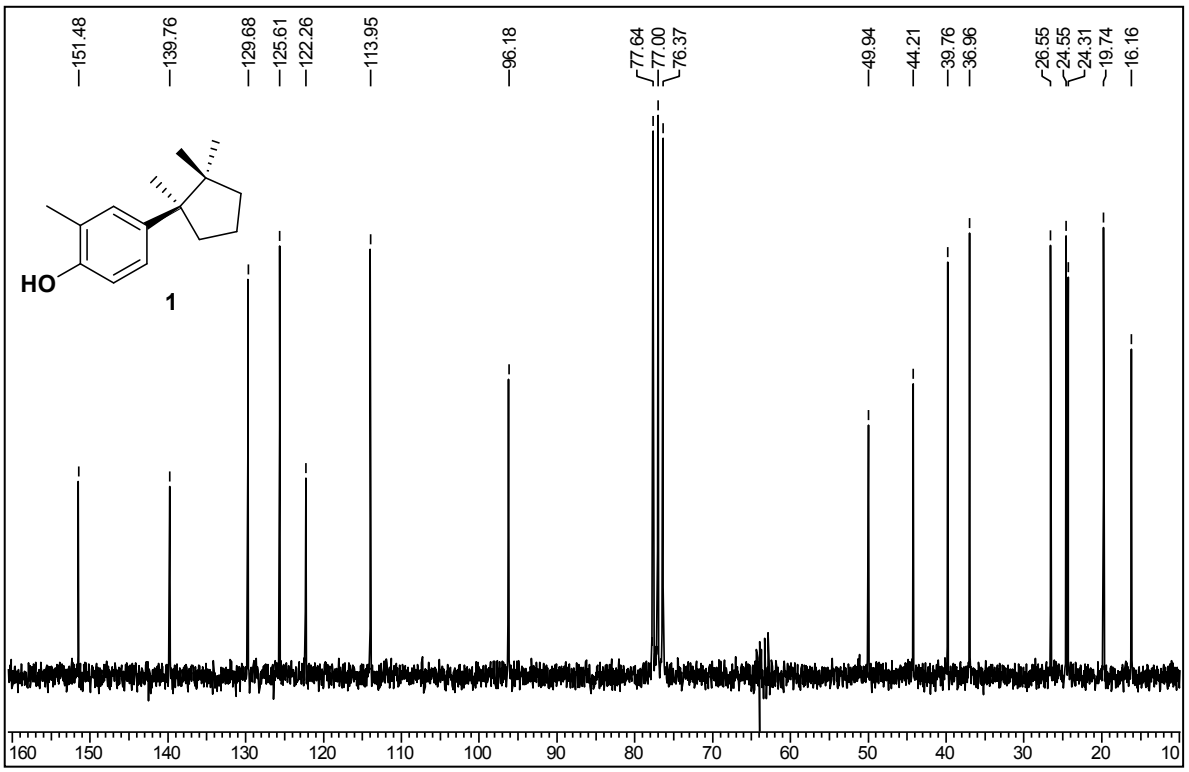


1

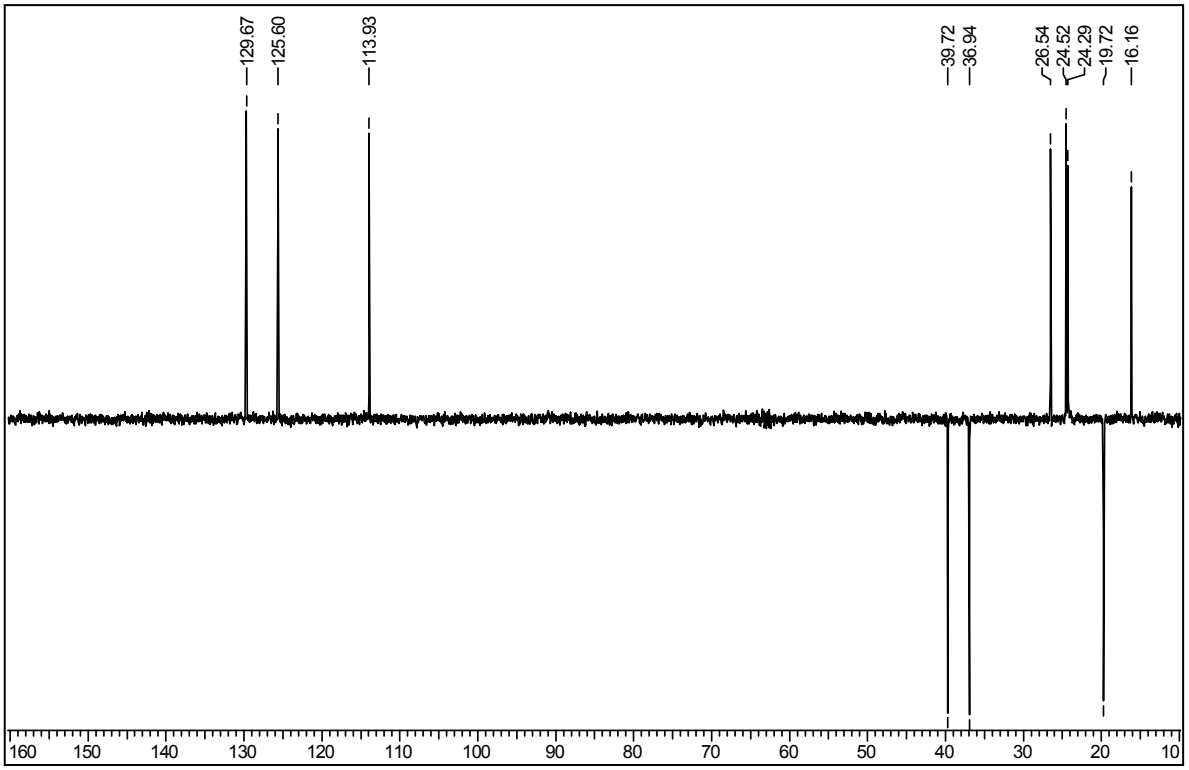


^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 50 MHz)





^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 50 MHz)



1.2.6 References

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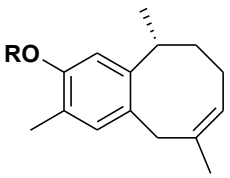
Chapter-2 : Syntheses of (-)-Parvifoline, (+)-Isoparvifolinone and (-)-Curcuquinone

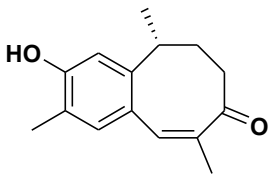
Section-1 : Synthesis of Parvifoline & Curcuquinone : A Brief Review

2.1.1 Introduction

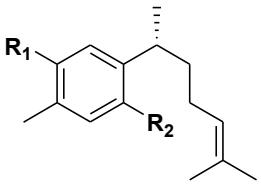
(-)-Parvifoline **1** is a bicyclic phenolic sesquiterpene, isolated from the genera *Coreopsis*[1] and *Perezia*[2] along with (+)-isoparvifolinone **2** and parvifoline isovalerate **1a**. These are the only natural substances, which contain trimethyl benzocyclooctene skeleton. Structure of parvifoline **1** was deduced from it's spectral data and a few chemical transformations, but no conclusive evidence about it's absolute configuration was described. However, it was later proved to be ***R*** by it's chemical transformation[3] into another sesquiterpene of known absolute configuration, called (-)-curcuquinone **4**.



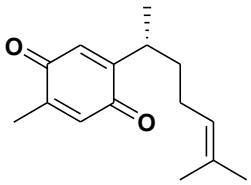
1 R = H
1a R = $Me_2CHCH_2C(O)$



2



3a R_1 = H; R_2 = OH
3b R_1 = OH; R_2 = OH



4

(-)-Curcuquinone **4** is the simplest monocyclic sesquiterpene benzoquinone, which was isolated from the *Pseudoterogorgia rigida*[4] together with two aromatic bisabolene sesquiterpenoids, named (-)-curcuphenol **3a** and (-)-curcuhydroquinone **3b**. All these compounds show antibacterial activity, but more importantly they have proven to be versatile chiral building blocks for the synthesis of related important natural products, such as heliannuols,[5] which represents a group of allelochemical phenolic sesquiterpenes.

2.1.2 Structure determination

(-)-Parvifoline **1** is a crystalline compound having mp 89-90 ^{o}C and specific rotation $[\alpha]^{25}_{D}$ –173 (*c* 1.73, $CHCl_3$). It was analyzed for $C_{15}H_{20}O$; and presence of oxygen as a phenolic group was proved from the IR spectra of the natural product and of the derived crystalline acetate, which showed absorptions at 3610 cm^{-1} and 1765 cm^{-1} respectively. However, it gave a negative $FeCl_3$ test, but from it's ^{1}H and ^{13}C NMR spectra, it was confirmed to be a phenol derivative. The singlet at δ 152.5 ppm in it's ^{13}C NMR spectrum was indicative of the phenolic nature of the natural product. Also, the aromatic ring was evident from the three more singlets at δ 143.9, 130.7, 120.4; and two doublets at δ 111.3 and 131.8 in it's ^{13}C NMR spectrum. It's ^{1}H NMR spectrum also supported the presence of aromatic ring with two aromatic *para* distributed protons by revealing two singlets at δ 6.91 and 6.62. In ^{13}C NMR spectrum, signals at δ 123.3 (d) and 137.5 (s) indicated the presence of a trisubstituted double bond, which was further supported by the resonance in ^{1}H NMR spectrum at δ 1.74 (br s) for three protons, corresponds to an allylic methyl group and δ 5.36 (t, *J* = 7.0 Hz) for one proton attached to the trisubstituted olefin. The remaining sp^3 signals were due to a secondary methyl group at benzylic position, a quartet at δ 19.2 and a doublet at δ 33.1 in the ^{13}C NMR spectrum. The secondary methyl group was further evident from a three proton doublet at δ 1.30 (*J* = 7.0 Hz), which was coupled to one proton methine multiplet at δ 3.18, in it's ^{1}H NMR spectrum. From all these spectral data, structure **1** was proposed for (-)-parvifoline.

(+)-Isoparvifolinone **2** is a solid compound (mp 157-158 ^{o}C) having molecular formula $C_{15}H_{18}O_2$. The nature of the two oxygen atoms was defined after inspection of it's IR spectrum, which revealed absorptions at 3600 cm^{-1} and 3350 cm^{-1}, attributed to an hydroxyl group. Also, it showed bands at 1660 cm^{-1} and 1590 cm^{-1}, corresponding to a conjugated carbonyl group, which was further confirmed from the UV absorption at 3.37 nm (ε 9200). The phenolic nature and substitution pattern in the aromatic ring were deduced after inspection of the ^{1}H and ^{13}C NMR spectral data. Apart from signals due to aromatic ring, other sp^2 ^{13}C signals were ascribed to a carbonyl group at δ 205.4, which is in conjugation with a trisubstituted double bond, responsible for a singlet at δ 135.6 and a doublet at δ 140.2. One of the substituents of the double bond was a methyl group, responsible for a three proton doublet at δ 2.02 (*J* = 1.7 Hz), coupled to a vinyl proton that appeared as a quartet with further unresolved long range couplings at δ 7.11 (*J* = 1.7 Hz). It's chemical shift being indicative of it's β-relation to the carbonyl group. All these data

and also bearing in mind those of parvifoline **1**, structure **2** was proposed for (+)-isoparvifolinone. Definitive evidence was obtained by it's partial synthesis from (-)-parvifoline **1**.

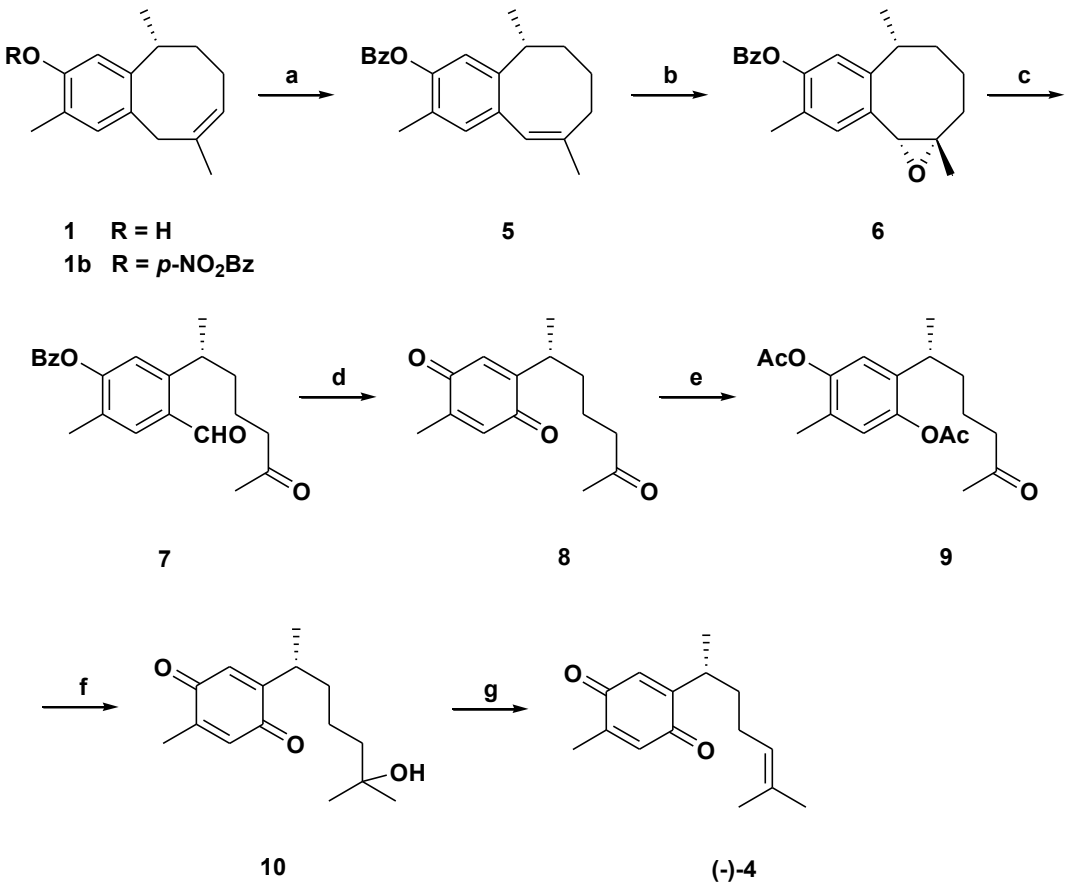
(-)-Curcuquinone **4** was isolated as a viscous yellow oil, which showed quinoid absorption at 1650 cm^{-1} in it's IR spectrum and λ_{max} 253 nm (ε 10,200) in it's UV spectrum. High resolution mass spectrometry indicated the parent ion composition of $C_{15}H_{20}O_2$. From comparison of it's NMR spectral data with those of curcuphenol **3a**, structure **4** was proposed for (-)-curcuquinone. Here are significant and characteristic resonances present in it's ^1H NMR spectrum : the only secondary methyl group at δ 1.11 (d, *J* = 7.0 Hz, 3H); two olefin protons at δ 6.42 (s, 1H) and 6.52 (q, *J* = 1.6 Hz, 1H); one proton of isopropylidene group at δ 5.01 (dd, *J* = 7.0, 7.0 Hz); two methyl groups of isopropylidene functionality at δ 1.50 (s) and 1.66 (s); remaining allylic methyl group (attached to the ring) at δ 1.98, further coupled to the adjacent olefin proton (*J* = 1.6 Hz).

2.1.3 Conformation and absolute configuration determination of Parvifoline : (Scheme-1, 1988)

As mentioned earlier, absolute configuration of (-)-parvifoline **1** was determined by it's conversion to (-)-curcuquinone **4**, a sesquiterpene with established absolute configuration. This particular work was done by Joseph-Nathan *et al*[3] after a decade of the isolation of (-)-parvifoline. Scheme-1 represents the reaction sequence using which (-)-parvifoline was transformed to curcuquinone.

Accordingly, (-)-**1** was protected as it's benzoate ester and subjected to acidic conditions to isomerise the double bond. It was achieved using HOAc/$ZnCl_2$ to yield isoparvifoline benzoate **5**, which was epoxidized using mCPBA followed by periodic acid cleavage to provide keto-aldehyde **7**. It was then hydrolyzed under alkaline condition, followed by oxidative decarbonylation using hydrogen peroxide to give quinone **8**. It was then converted to the hydroquinone diester **9**, which on 1,2-addition over side chain carbonyl group using MeMgI and oxidation of the resulting hydroquinone, provided **10**. Dehydration of tertiary hydroxyl group of **10** using silica gel/*p*TSA yielded curcuquinone **4**, identical to the natural product in all respect.

Scheme-1 : (Joseph-Nathan *et al*, *J. Nat. Prod.* **1988**, *51(4)*, 675-689)



Reagents and conditions *: a) (i) benzoyl chloride, pyridine; (ii) HOAc, $ZnCl_2$, 94%; b) mCPBA, 65%; c) HIO_4, 62%; d) (i) KOH, MeOH, 89%; (ii) H_2O_2, H_2SO_4, MeOH, 48%; e) Zn, Ac_2O, NaOAc, 78%; f) (i) MeMgI; (ii) aq. $FeCl_3$, MeOH, 68%; g) TsOH, silica gel, 48%.*

Curcuquinone **4** obtained from (-)-parvifoline **1** showed $[\alpha]^{25}_{D}$ –1.58, a value very close to that of reported for the natural product,[4] that is $[\alpha]^{25}_{D}$ –1.3. Now, as absolute configuration of (-)-curcuquinone is ***R***, it follows that (-)-parvifoline **1** also has the same absolute configuration, that is ***R***.

The conformations in solution were also deduced for derivatives **1b**, **5** and **6** using their ^{1}H and ^{13}C NMR spectral data, two dimensional $^{1}H/^{13}C$ heteronuclear chemical shift correlation diagrams and by H-C-C-H dihedral angles determinations. The X-ray diffraction analysis of compounds **1b**, **5** and **6** were also recorded and results regarding conformation in solid state then compared with those in solution, which showed that in each case the conformations were essentially same. From all these data, conformation of

the eight membered ring in **1** was proposed to be distorted twist boat, which also justifies the high specific rotation values of (-)-parvifoline **1** and (+)-isoparvifolinone **2** (probably due to the presence of inherently dissymmetric chromophores).

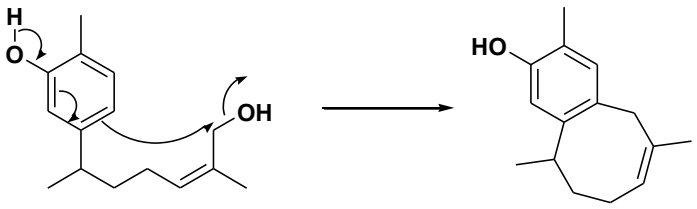
2.1.4 Total Synthesis of Parvifoline : *A Brief Review*

The main structural features that challenge the synthesis of parvifoline and isoparvifolinone are; (i) formation of benzocyclooctene framework and (ii) presence of a double bond next to conjugation, in case of parvifoline. There have been total four approaches reported todate for the synthesis of *rac*-parvifoline **1**, three of them used Grob fragmentation strategy, while the other one dealt with Dieckmann type intramolecular cyclisation of an ester sulfone. Apart from these approaches; in 1987, Bohlmann *et al* attempted synthesis of parvifoline following biomimetic pathway, but instead ended up in the synthesis of 2-hydroxycalamenene **17**. Further, in the year 1989, synthesis of isoparvifoline **30** was reported by Rao *et al*. These two attempts constitute the initial efforts towards synthesis of the title compounds.

Bohlmann's Attempt : (Scheme-2 and 3, 1987)[6]

This was the first attempt towards the synthesis of *rac*-parvifoline **1**, however, it was a failure, but the authors were successful in synthesizing three other sesquiterpenes named; xanthorrhizol **14**, hydroxy calamenene **17** and hydroxy cadalene **21**.

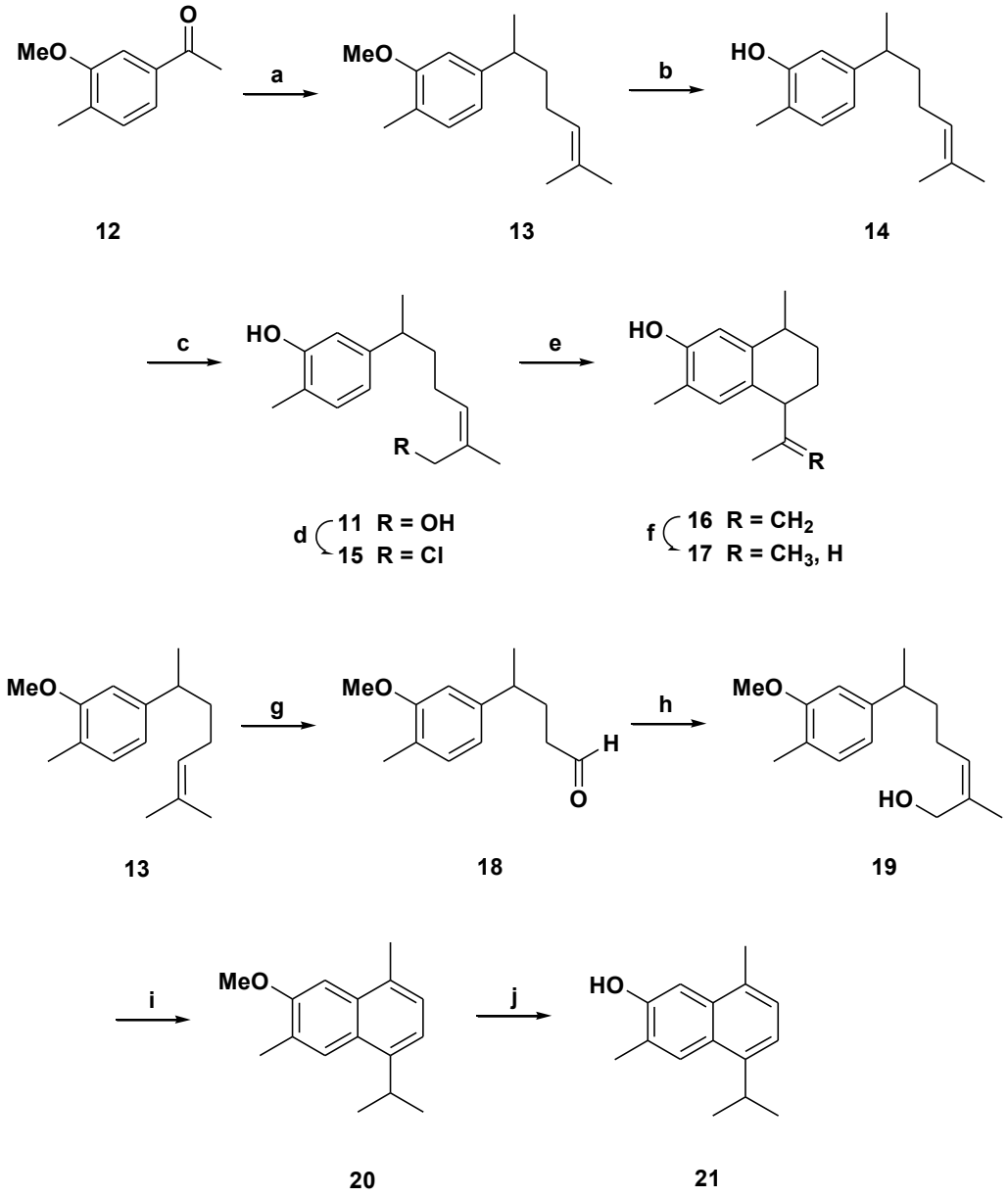
Scheme-2



11 **1**

The idea behind the synthesis was to check the feasibility of the proposed biomimetic pathway (Scheme-2) for the chemical synthesis of parvifoline from an unnatural 13-hydroxy xanthorrhizol **11**.

Scheme-3 : (Bohlmann *et al*, *Tetrahedron Lett.* **1987**, *28*, 2575-2578)



Reagents and conditions *: a) (i) $Me_2C{=}CHCH_2CH_2MgBr$, NH_4Cl; (ii) Et_3SiH, BF_3-OEt_2, 70% overall; b) MeMgI, xylene, 85%; c) (i) $ClCH(Me)OEt$, $EtN(CHMe_2)_2$; (ii) O_3, Me_2S, -70 ^oC; (iii) $Ph_3P{=}CHMe$, -78 ^oC; (iv) BuLi; (v) CH_2O; d) NCS, Me_2S, 0 ^oC; e) $KOBu^t$, tert-BuOH; f) H_2/Pd, 75%; g) O_3, Me_2S, -70 ^oC, 70%; h) (i) $Ph_3P{=}CHMe$, -78 ^oC; (ii) BuLi; (iii) CH_2O, 44% overall; i) (i) NCS, Me_2S, 0 ^oC; (ii) $ZnCl_2$, CH_2Cl_2, 24 h; j) BBr_3, -78 ^oC, 56% overall.*

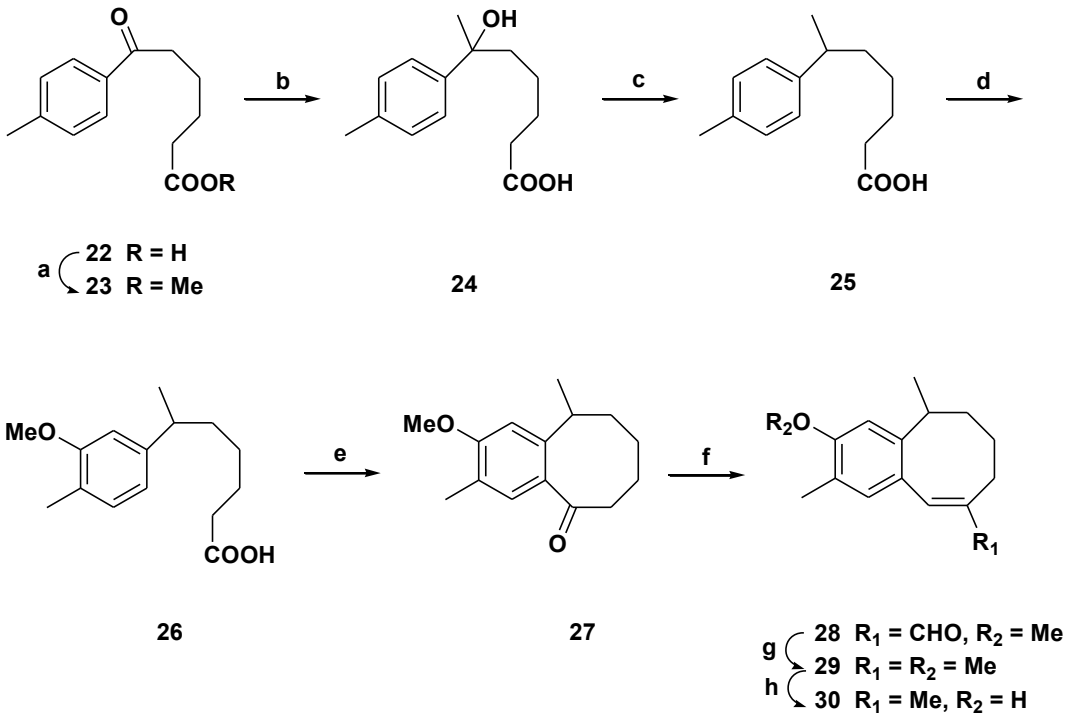
Accordingly, the key intermediate **15** was prepared from acetophenone **12** as depicted in the scheme-3, *via* xanthorrhizol **14** and allyl alcohol **11**, which was subjected to the base treatment to afford 2-hydroxy calamenene **17** and not the required *rac*-**1**. Also,

anisole derivative **19** on chlorination followed by treatment of the resulting halide with zinc chloride in CH_2Cl_2, provided 2-methoxy cadalene **20**.

Rao's Attempt : (Scheme-4, 1989)[7]

In this particular attempt, authors have used cyclodehydration of acid **26** as the key step for benzocyclooctanone ring formation. However, they could not synthesize parvifoline and instead ended up in it's double bond isomer, *i. e.* isoparvifoline **30**.

Scheme-4 : (Rao *et al*, *Indian J. Chem.* **1989**, *28B*, 219-222)



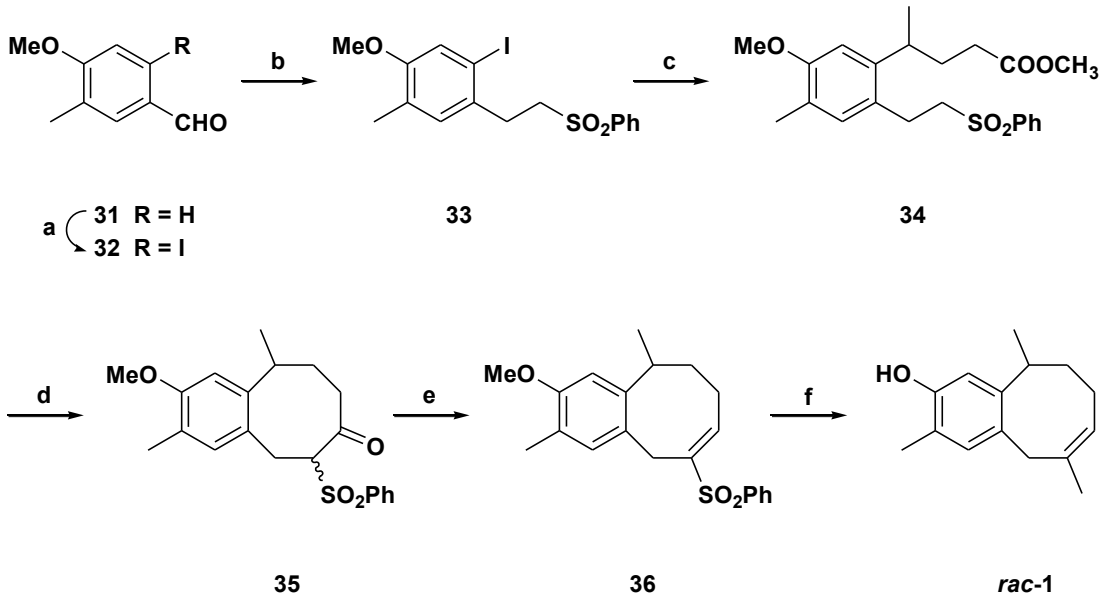
Reagents and conditions : *a) MeOH, H^+; b) (i) MeMgI; (ii) NaOH, EtOH, reflux, 90%; c) Li, NH_3, 85%; d) (i) HNO_3, H_2SO_4, 0 ^oC; (ii) $NaNO_2$, H_2SO_4, MeOH, -10 ^oC; (iii) Me_2SO_4, NaOH, 62% overall; e) PPA, 64%; f) (i) $NaBH_4$, MeOH; (ii) DMF, $POCl_3$, 90 ^oC, NaOAc, 73%; g) N_2H_4-H_2O, DEG, KOH, reflux, 2 h, 65%; h) BBr_3, 74%.*

Accordingly, acid **26** was prepared from keto acid **22**, which on treatment with polyphosphoric acid underwent intramolecular cyclodehydration to furnish **27**. It was further reduced using sodium borohydride, and was converted to the conjugated aldehyde **28** using Vilsmeier reaction, followed by deoxygenation of aldehyde to methyl group and deprotection of methyl ether **29** to provide isoparvifoline **30** (Scheme-4).

Grimm's Approach : (Scheme-5, 1994)[8]

The synthesis reported by Grimm *et al* differs from the rest of the syntheses in benzocyclooctane framework formation, which was achieved by intramolecular ketosulfone cyclisation[9] of **34**.

Scheme-5 : (Grimm *et al*, *Tetrahedron Lett.* **1994**, *35*, 5369-5372)



Reagents and conditions *: a) (i) MeN(Li)CH_2CH_2NHMe; (ii) n-BuLi; (iii) I_2, 53% overall; b) (i) $LiCH_2SO_2Ph$; (ii) Et_3SiH, TFA, 80% overall; c) (i) trans-3-penten-1-ol, $Pd(OAc)_2$; (ii) H_2CrO_4; (iii) CH_2N_2, 44% overall; d) LiHMDS, 80%; e) (i) $NaBH_4$, MeOH; (ii) CH_3SO_2Cl, Et_3N; (iii) LiHMDS, 75% overall; f) MeMgCl, $Ni(acac)_2$, 75%; (ii) EtSNa, DMF, 150 ^oC, 95%.*

Accordingly, the key intermediate sulfone ester **34** was synthesized from commercially available 3-methyl-4-anisaldehyde **31** (Scheme-5). Aldehyde **31** on α-amino alkoxide directed lithiation followed by reaction with iodine provided the iodo aldehyde **32** in 53% isolated yield, which on treatment with the anion of methyl phenyl sulfone followed by reduction of the crude product with triethylsilane and trifluoroacetic acid, afforded iodosulfone **33** in 80% overall yield. Ester side chain introduction was achieved by using Larock's palladium catalyzed coupling protocol, which gave **34** after chromic acid oxidation of the resulting alcohol followed by esterification, in 44% overall yield. The crucial ring closure over **34** was performed using LiHMDS to give ketosulfone **35** in 80% yield as a mixture of diastereomers (9: 1); followed by keto reduction, mesylation and it's

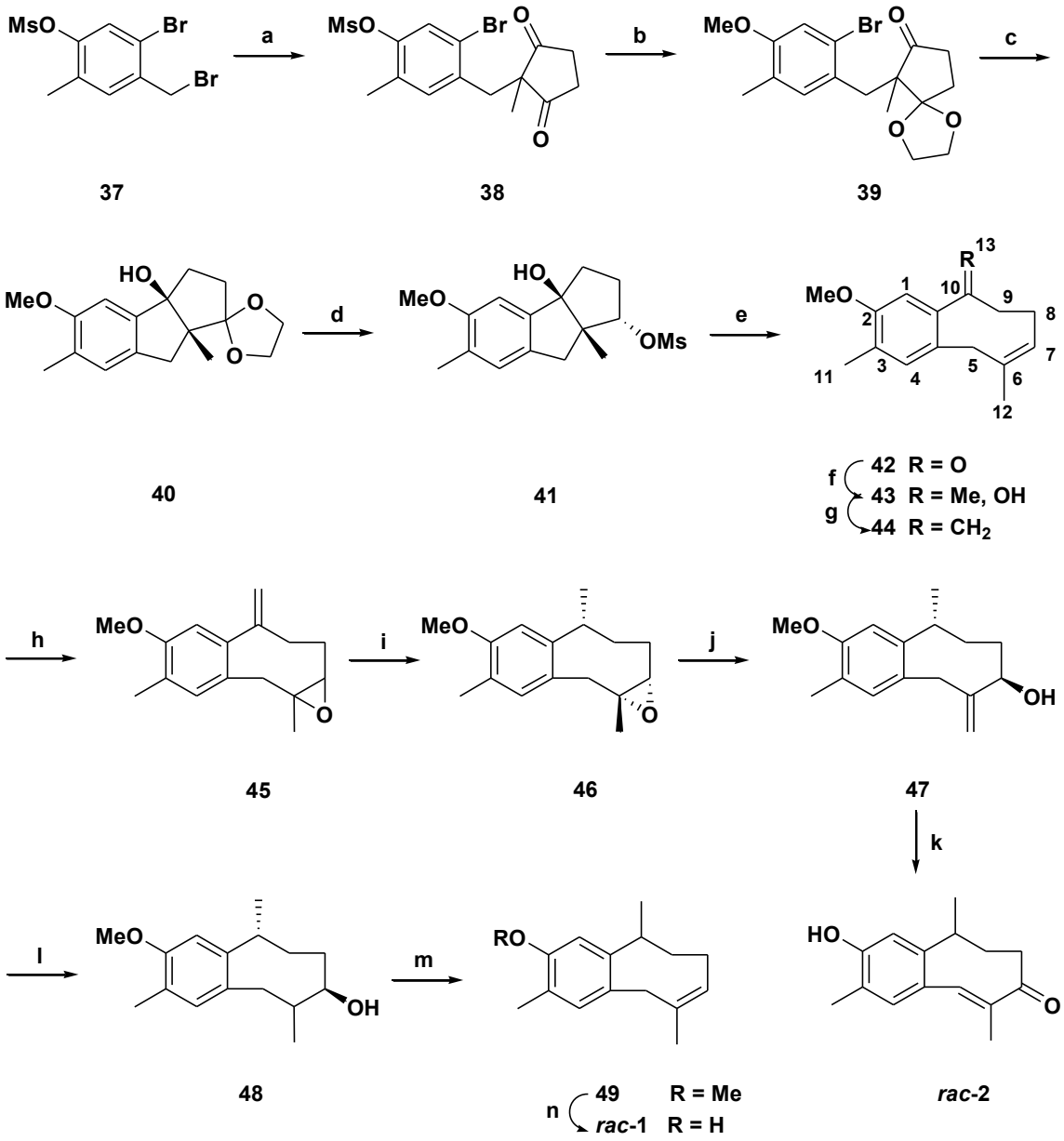
immediate elimination to give vinyl sulfone **36** in 75% overall yield. Methyl group was introduced using MgMgCl in the presence of $Ni(acac)_2$ in 75% yield, followed by demethylation using sodium thioethoxide to give *rac*-parvifoline **1** in about 6% overall yield.

Joseph-Nathan's Approach : (Scheme-6, 1995)[10]

The synthesis of *rac*-parvifoline reported by Joseph-Nathan *et al* (1994, 1995) was the first one to use Grob fragmentation reaction[11] for cyclooctene ring formation. They used dibromo compound **37** as a starting material for the synthesis, which on treatment with 2-methyl-1,3-cyclopentanedione in presence of potassium carbonate as the base and butanol-water mixture as a solvent gave *C*-alkylated product **38** as the major one, together with *O*-alkylated product. One of the keto group of intermediate **38** was protected as a cyclic acetal, followed by mesyl group deprotection using potassium hydroxide in methanol to give corresponding phenol, which was further protected as it's methyl ether **39** and was treated with lithium in THF to afford tricyclic intermediate **40** in 43% yield from **39**. Cyclic acetal of **40** was then deprotected under acidic condition followed by reduction of the keto group using sodium borohydride to give alcohol, which on mesylation gave the key intermediate **41** as the sole product. It possessed the required relative stereochemistry at C_7 and C_{10} to stereospecifically produce the *Z*-isomer in a Grob fragmentation reaction. Indeed, when **41** was treated with sodium methoxide in methanol, benzocyclooctenone **42** was obtained in 80% yield.

Intermediate **42** was then treated with MeLi followed by deoxygenation of resulting benzylic hydroxyl group using triethylsilane and borontrifluoride, which instead resulted in double bond reduction product. Therefore, it was thought to protect the C_6-C_7 double bond as an epoxide. But, before epoxidation, alcohol **43** was treated with mesyl chloride in pyridine to have it's mesylate, but instead eliminated product, *i. e.* diene **44** was obtained in 80% yield. It was selectively epoxidized using mCPBA in 77% yield, followed by hydrogenation of the exocyclic double bond to give isomer **46**. It was then treated with *p*TSA in benzene to provide intermediate **47** in 70% yield, which was converted to *rac*-isoparvifolinone by CrO_3 oxidation followed by demethylation using BBr_3 in 43% overall yield. Further, **47** was hydrogenated to give alcohol **48**, which was subjected to tosylation. Under this condition, it underwent elimination to give parvifoline methyl ether **49** in 83% yield, which was deprotected using lithium thioethoxide to give *rac*-**1** in 98% yield.

Scheme-6 : (Joseph-Nathan *et al*, *Tetrahedron* **1995**, *51*, 9285-9300)

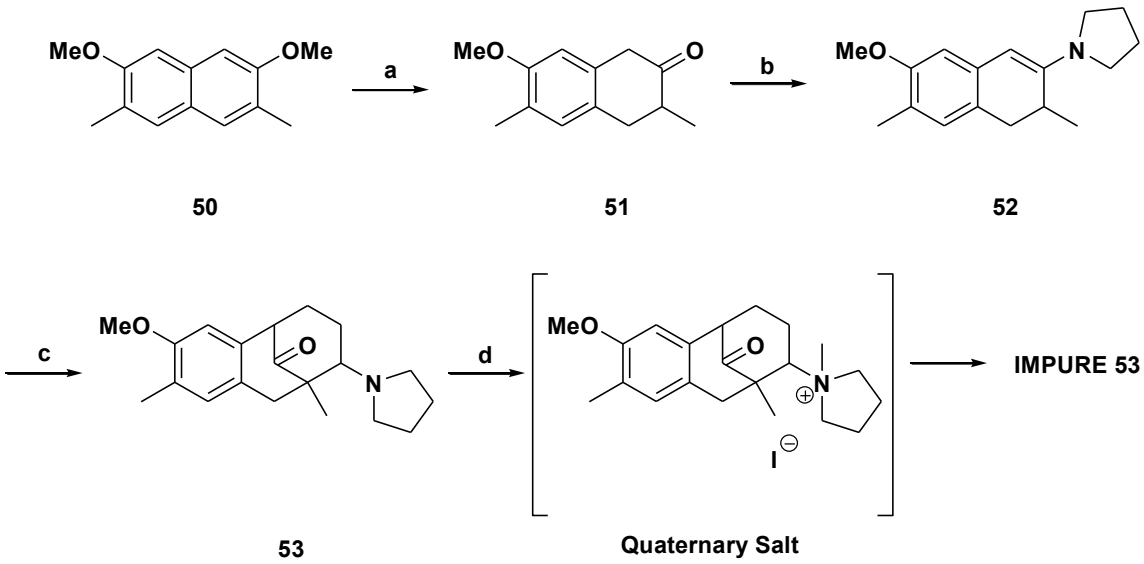


Reagents and conditions *: a) 2-methyl-1,3-cyclopentanedione, K_2CO_3, t-BuOH: H_2O (1.2: 1), reflux, 3 h, 50%; b) (i) ethylene glycol, pTSA, benzene, reflux, 95%; (ii) KOH, MeOH, reflux, 74%; (iii) dimethyl sulfate, acetone, reflux, 94%; c) Li, THF, 20 ^oC, 1 h, 43%; d) (i) H_2SO_4, MeOH, 20 ^oC, 30 min, 94%; (ii) $NaBH_4$, MeOH, 20 ^oC, 98%; (iii) mesyl chloride, pyridine, -4 ^oC, 68%; e) MeONa, MeOH, reflux, 2 h, 80%; f) MeLi, THF, -78 to -70 ^oC, 3 h, 75%; g) mesyl chloride, pyridine, -4 ^oC, overnight, 80%; h) mCPBA, CH_2Cl_2, 40 min, 70%; i) Pd/C/H_2, EtOH, rt, 95%; j) pTSA, benzene, rt, 1 h, 70%; k) (i) CrO_3, pyridine, rt, 80%; (ii) BBr_3, CH_2Cl_2, 54%; l) Pd/C/H_2, EtOH, rt, 1 h, 97%; m) p-TsCl, pyridine, -4 ^oC, 36 h, 83%; n) EtSLi, DMF, 85 ^oC, 24 h, 98%.*

Maldonado's Approach : (Scheme-7 and 8, 1998)[12]

This particular synthesis was also based on Grob fragmentation strategy, but the key intermediate was prepared by Stork-Landesman two carbon ring expansion[13] of β-tetralone **51**. They used readily available symmetrical naphthalene **50** as their starting material, which itself contains 80% of the carbon atoms of the target skeleton.

Scheme-7 : (Maldonado *et al*, *J. Org. Chem.* **1998**, *63*, 2918-2921)

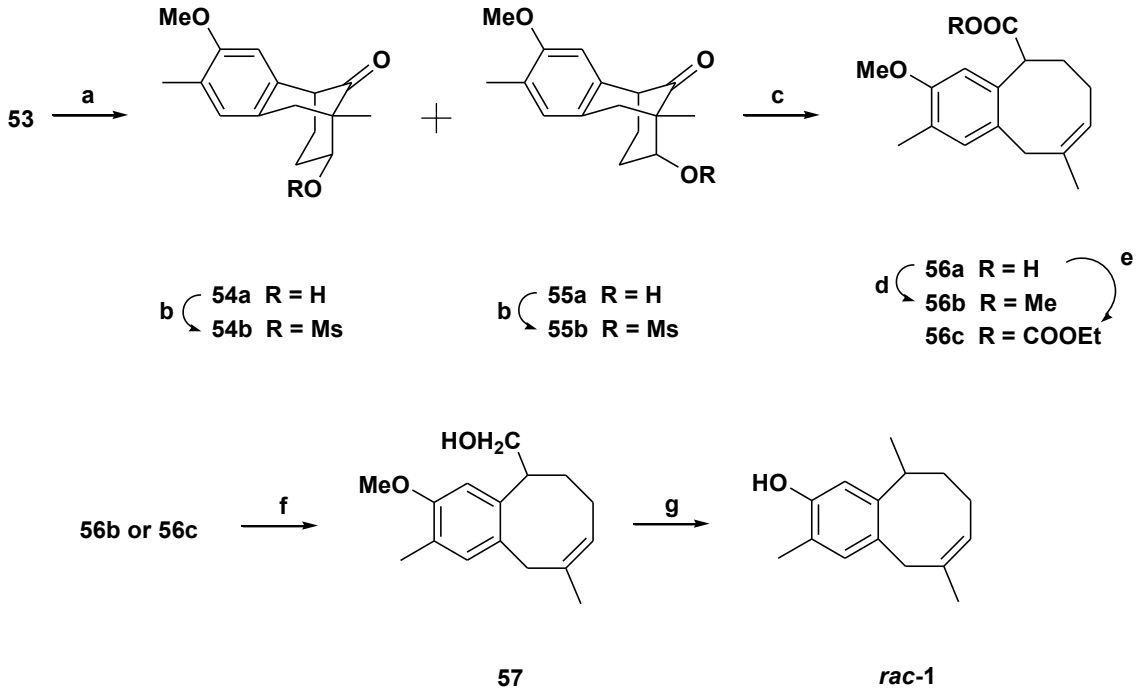


Reagents and conditions *: a) (i) Na, EtOH; (ii) H_3O^+, 95% overall; b) pyrrolidine, benzene; c) acrolein, dioxane; d) (i) MeI, $CHCl_3$; (ii) NaOH.*

Accordingly, β-tetralone **51** was obtained from naphthalene **50** by Na/EtOH reduction followed by acid catalyzed hydrolysis of the intermediate enol ether, in 95% yield. The Stork-Landesman ring expansion sequence was then performed over tetralone **51**. Thus, **51** was treated with pyrrolidine to give enamine **52**, followed by it's reaction with acrolein to furnish bridged amino ketone **53**. It was then quaternised using iodomethane and then treated with 15% aqueous NaOH solution to carry out Grob fragmentation. But instead of the required cyclooctene intermediate **56a**, it ended up in impure **53**, which was resulted by *N*-demethylation of the intermediate quaternary salt (Scheme-7).

This problem was then solved by mild acid treatment of **53** to give a mixture of ketols, which were separated by column chromatography and characterized by spectroscopy (and in the case of **55a** by a single crystal X-ray analysis) as the equitorial and axial isomers (**54a** and **55a**) in 3: 2 ratio and in 57% overall yield (Scheme-8).

Scheme-8



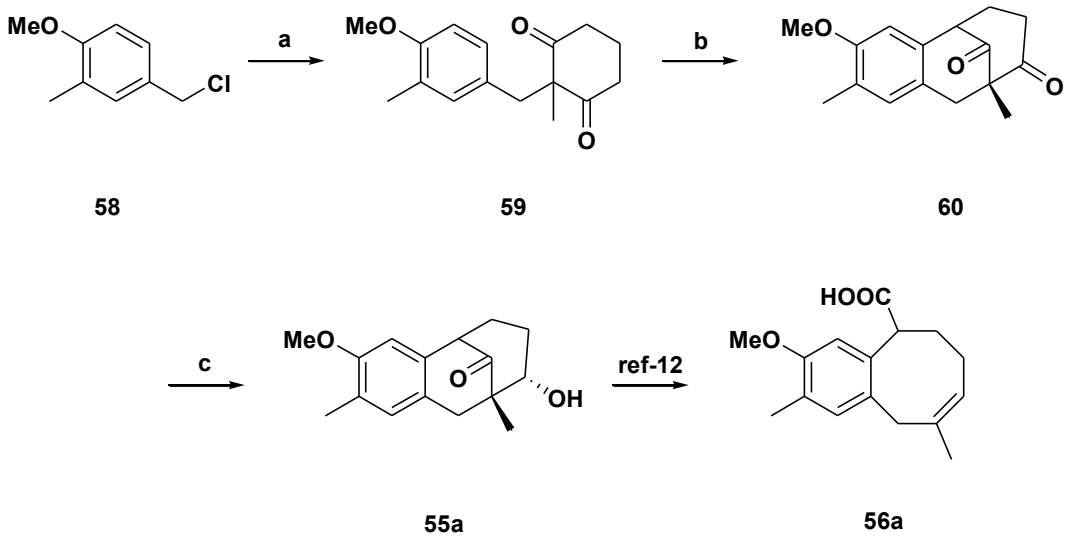
Reagents and conditions *: a) H_3O^+, 57% overall; b) $MeSO_2Cl$, Et_3N; c) NaOH, reflux, 2.5 h, 82%; d) CH_2N_2; e) ClCOOEt, THF, Et_3N; f) $NaBH_4$, 78-87%; g) (i) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (ii) $LiBHEt_3$, THF, rt, 10 h, 55%; (iii) EtSLi, DMF, 105 ^oC, 48 h, 97%.*

Grob fragmentation was performed over mesyl ester **54b** and **55b** by refluxing them with 15% aqueous NaOH solution to give benzocyclooctene carboxylic acid **56a** in 82% and 41% yield respectively. Finally, acid **56a** was reduced and deoxygenated followed by deprotection of methyl ether to give the final product in fairly good overall yields. It was also claimed that, however synthesis involves 12 chemical steps, it could be executed in only five synthetic operations.

Venkateswaran's Approach : (Scheme-9, 1999)[14]

In this formal synthesis, Mn(III)-catalyzed oxidative arylation[15] of ketone **59** was used as the key step, according to which ketone **59** was treated with $Mn(OAc)_3$ and $Cu(OAc)_2$-H_2O in acetic acid to provide the bridged bicyclo [3.3.1] nonadione **60** in 60% yield.

Scheme-9 : (Venkateswaran *et al*, *Tetrahedron Lett.* **1999**, *40*, 7431-7433)



Reagents and conditions *: a) 2-methyl-1,3-cyclohexanedione, NaOH, H_2O, NaI, 60 ^oC, 65%; b) $Mn(OAc)_3$, $Cu(OAc)_2$, HOAc, 80 ^oC, 60%; c) $Li(t\text{-}BuO)_3AlH$, THF, reflux, 65%.*

The least hindered carbonyl group of **60** was then regio and stereoselectively reduced using lithium hydrido tri-*tert*-butoxyaluminate to produce the equitorial ketol **55a** in 65% yield. This has previously been used for the synthesis of *rac*-**1** by Maldonado *et al*[12] using Grob fragmentation strategy.

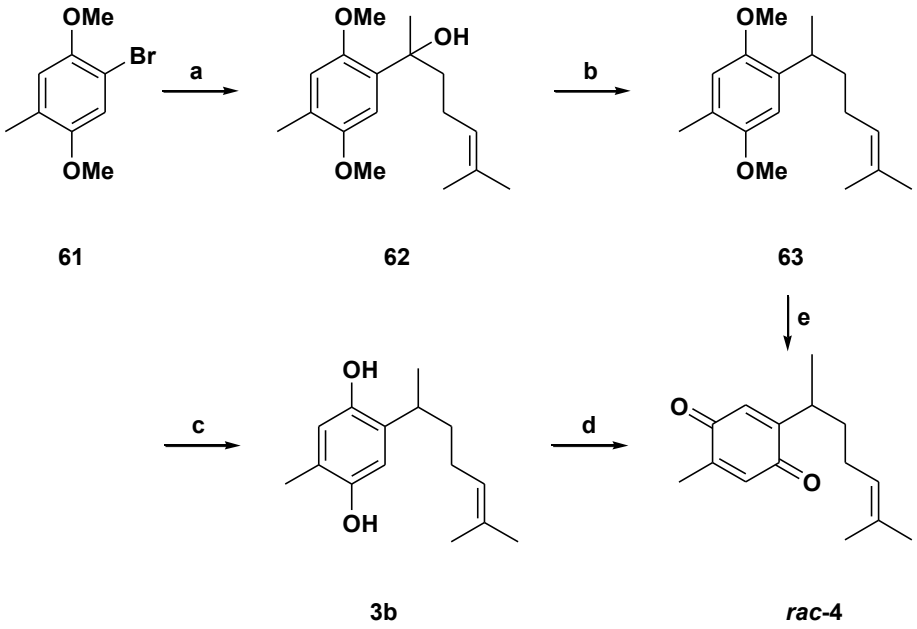
2.1.5 Total Synthesis of Curcuquinone : *A Brief review*

The main structural feature that challenges the synthesis of (-)-curcuquinone **4** is the introduction of chirality at the nonfunctionalised allylic position, which reflects in the number of synthesis of enantiopure **4**. There are four reports on the synthesis of optically pure curcuquinone, while the other three reported the synthesis of *rac*-**4**.

Joseph-Nathan's Approach : (Scheme-10, 1981)[16]

This was the first synthesis of *rac*-**4** and the corresponding hydroquinone **3b**. Here, the key reaction was Grignard addition of arylmagnesium bromide, generated from **61**, with commercially available 6-methyl-5-hepten-2-one, which gave benzyl alcohol **62**. This intermediate was further converted to the target molecules following a few functional group transformations (Scheme-10).

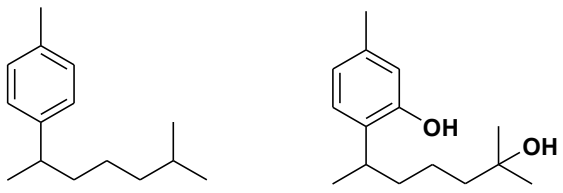
Scheme-10 : (Joseph-Nathan *et al*, *J. Org. Chem.* **1981**, *46*, 4666-4667)



Reagents and conditions *: a) Mg, 6-methyl-5-hepten-2-one, THF, reflux, 88%; b) (i) amberlyst-15 (cat), benzene, rt; (ii) Na, NH_3, -78 ^oC, 85% overall; c) BBr_3, CH_2Cl_2, 90%; d) air oxidation; e) Ag_2O, dioxane, HNO_3, rt, 70%.*

Ono's Approach : (Scheme-11, 1994)[17]

The idea behind this synthesis of *rac*-**4** was to develop a route, which could be applicable to the synthesis of enantiopure curcuquinone **4** and that's why the key intermediate **68** in this strategy, had a hydroxyl methyl group at benzylic position of the bisabolene congener, which could be resolved.

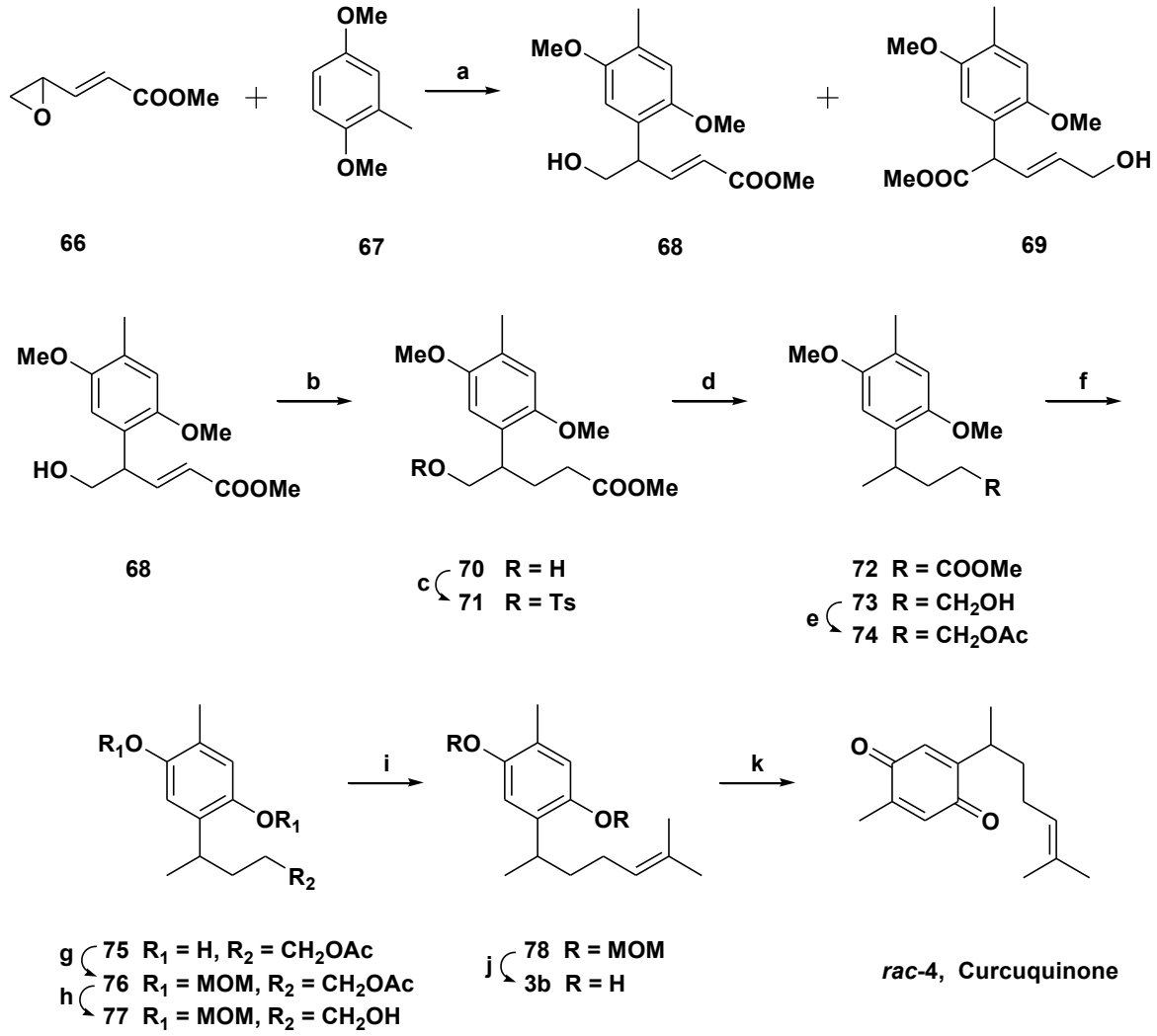


64, aromatic bisabolene skeleton **65, Curcudiol**

The reaction of α, β-epoxyesters and nucleophiles such as alcohols or phenols in the presence of Lewis acid are reported to give α, β-disubstituted esters,[18] and this was used in

this particular approach for the synthesis of key intermediate **68**. Accordingly, reaction of *rac*-**66** and **67** gave *rac*-**68** in 68% yield, together with 11% of *rac*-**69**. Intermediate **68** was further explored for the synthesis of *rac*-**4** as shown in the scheme-11.

Scheme-11 : (Ono *et al*, *Heterocycles* **1994**, *37*, 181-185)



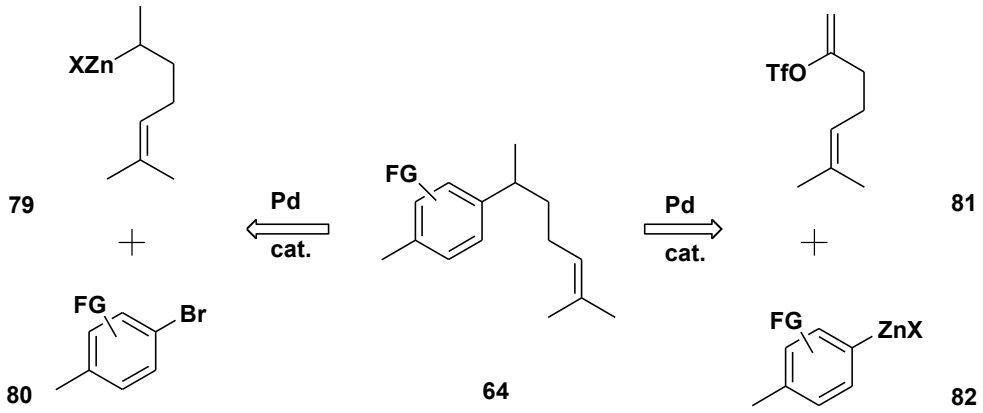
Reagents and conditions *: a) BF_3-OEt_2, -78 ^oC, 68% (**68**) and 11% (**69**); b) H_2, Pd/C; c) TsCl, pyridine, 86% overall; d) $NaBH_4$, DMSO; e) Ac_2O, pyridine, 96%; f) $AlCl_3$, EtSH; g) MOMCl, NaH, 18-crown-6, CH_3CN, 71% overall; h) 2N NaOH, MeOH, 88%; i) (i) PCC, CH_2Cl_2; (ii) $Ph_3P^+CHMe_2$ I^-, NaH, DMSO, 26% overall; j) 2N HCl, i-PrOH, 61%; k) $Ce(NH_4)_2(NO_3)_6$, H_2O, THF, 23%.*

Later on, similar strategy was used for the synthesis of *rac*-curcudiol **65**, *rac*-curcuphenol **3a** and *rac*-curcuhydroquinone **3b**.[19]

Vyvyan's Approach : (Scheme-12 and 13, 2004)[20]

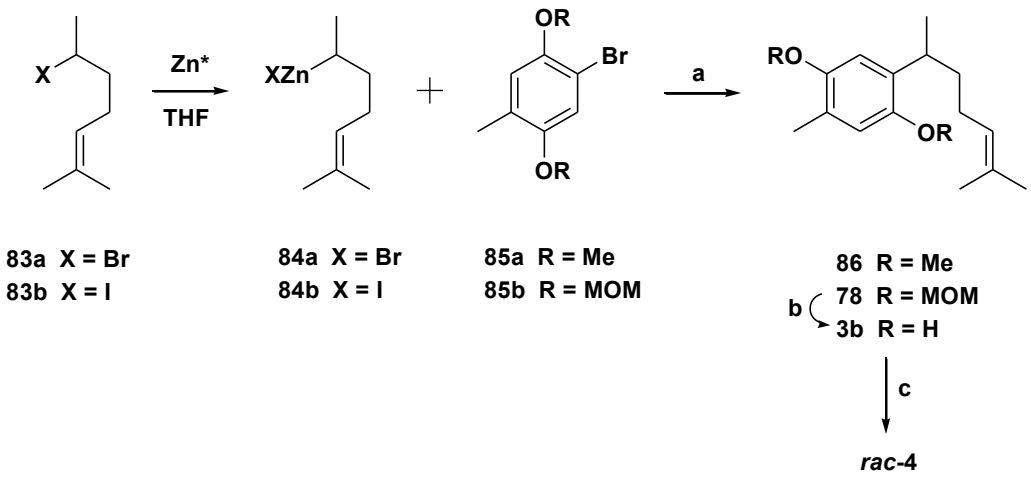
In this article, aromatic bisabolene skeleton **64** was prepared by Pd-catalyzed coupling of organozinc reagents with different aromatic rings.[21] Alkenyl triflates were also coupled to the arylzinc reagents[22] to prepare a few other aromatic bisabolenes.

Scheme-12 : (Vyvyan *et al*, *J. Org. Chem.* **2004**, *69*, 2461-2468)



Accordingly, organozinc reagents **84**, prepared by reaction of the corresponding halides **83** with Rieke zinc in tetrahydrofuran, were treated with aryl bromides **85** using Pd(dppf)Cl_2 as a catalyst to produce intermediates **86** and **78** in good yields (Scheme-13).

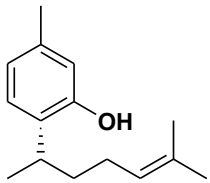
Scheme-13



Reagents and conditions *: a) Pd(dppf)Cl_2 (cat), THF, reflux, 71-81%; b) dilute HCl, 89 %; c) CAN, MeCN: H_2O, 83% from* ***86*** *and 98% from* ***3b****.*

However, as methyl ether **86** couldn't be deprotected to synthesize *rac*-**3b**, intermediate **78** was further elaborated to *rac*-**3b** and *rac*-**4** as shown in the scheme-13.

Ono's Approach : (Scheme-14, 1995)[23]



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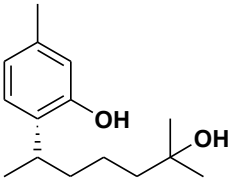

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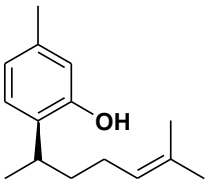
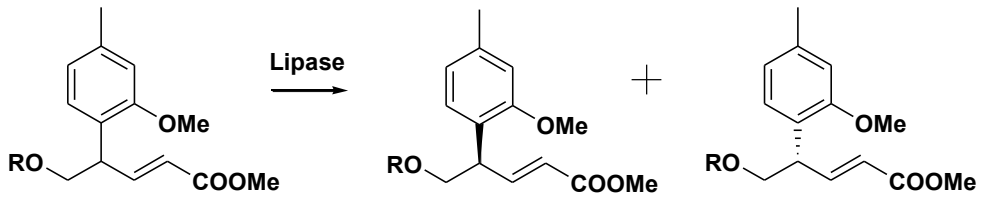


3a

First enantioselective synthesis of (*S*)-curcuphenol **87**, (*S*)-curcudiol **88** and (*R*)-curcuphenol **3a** have been described, where enzymatic resolution of *rac*-**89** using immobilized lipase in organic solvent had been used for the introduction of chirality at benzylic position and for this purpose, several commercially available lipases had been screened.

<u>Scheme-14</u> : (Ono *et al*, *Tetrahedron: Asymmetry* **1995**, *6*, 1829-1832)



***rac*-89 R = Ac**
(*S*)-90 R = H

(*R*)-89 R = Ac
(*R*)-90 R = H

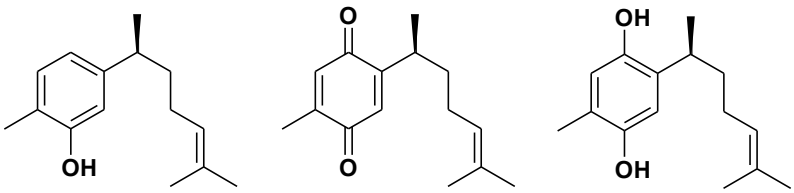
(*S*)-90 R = H
(*S*)-89 R = Ac

No	Substrate (g)	Lipase	Products % (% ee)	
1	*Rac*-89 (0.2)	MY-30 (Candida cylindracea)	(*R*)-89; 69 (36)	(*S*)-90; 27 (80)
2	*Rac*-89 (0.25)	Immobilized Lipase (MY-30)	(*R*)-89; 77 (24)	(*S*)-90; 22 (85)
3	*Rac*-89 (0.2)	OF-360 (Candida cylindracea)	(*R*)-89; 38 (83)	(*S*)-90; 60 (51)
4	*Rac*-89 (0.2)	Immobilized Lipase (OF-360)	(*R*)-89; 40 (90)	(*S*)-90; 52 (58)
5*	(*S*)-90	OF-360	(*S*)-89; 74 (90)	(*R*)-90; 16 (30)

* Optically active (*S*)-90 (80% ee) was employed.

Intermediate **(*S*)-89**, thus obtained, was further elaborated for the synthesis of the title compounds as described in the earlier synthesis of same (*racemic*) compounds.[17]

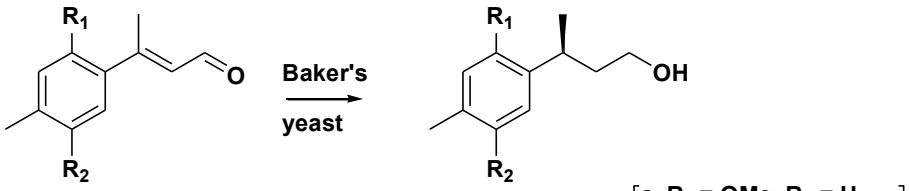
Serra's Approach : (Scheme-15 and 16, 2000)[24]



91 **92** **93**

This particular publication reported the enantioselective synthesis of (*S*)-(+)-curcuphenol **87**, (*S*)-(+)-xanthorhhizol **91**, (*S*)-(-)-curcuquinone **92** and (*S*)-(+)-curcuhydroquinone **93** using baker's yeast reduction of conjugated aldehyde **94** to enantiopure alcohols **95**, which were useful chiral building blocks.

Scheme-15 : (Serra *et al*, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3758-3764)

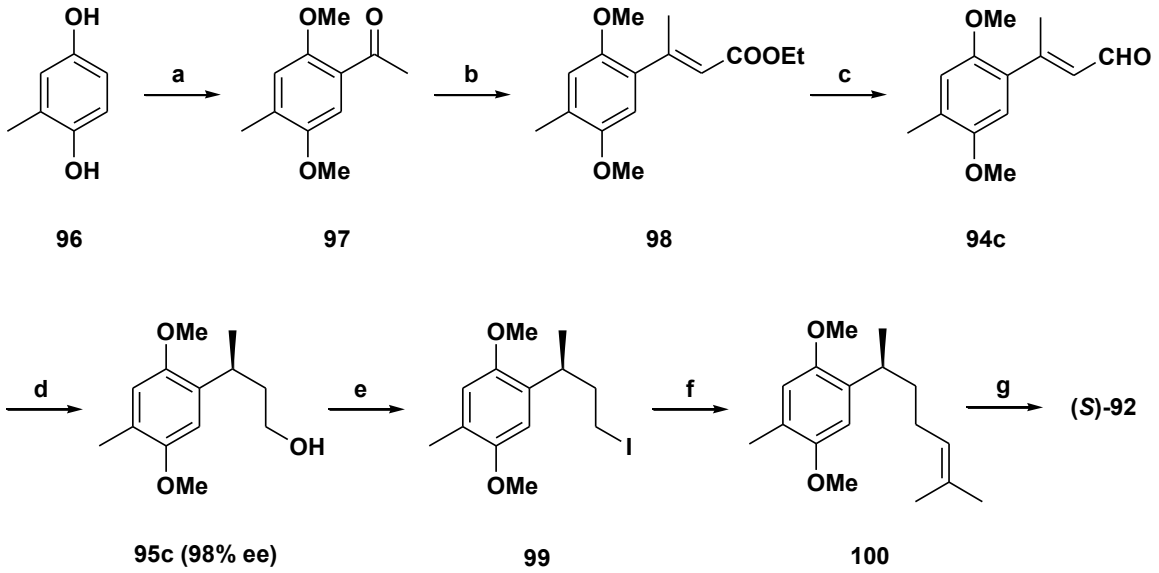


94 **95**

For the synthesis of (*S*)-(-)-curcuquinone **92**, the key intermediate **94c** was prepared from 2-methylhydroquinone **96** by (i) *O*-methylation using dimethyl sulfate, (ii) acylation using $SnCl_4$ as the Lewis acid, (iii) two carbon olefination of the resulting acetophenone using Wittig-Horner's protocol and (iv) reduction followed by Swern oxidation.

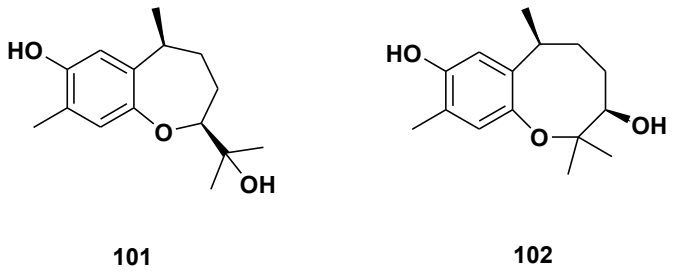
Intermediate **94c** on baker's yeast reduction provided alcohol **95c** with 98% ee. The hydroxyl functionality of **95c** was then transformed to iodide **99**, which was further coupled with isobutenyl magnesiumbromide using copper(I) iodide to afford bisabolene framework **100**. This on ceric ammonium nitrate oxidation furnished (*S*)-(-)-curcuquinone **92**. Using similar reaction sequence, other title compounds were also synthesized.

Scheme-16 : (Serra *et al*, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3758-3764)



Reagents and conditions *: a) (i) Me_2SO_4, K_2CO_3, acetone; (ii) AcCl, CH_2Cl_2, $SnCl_4$, 78%; b) $(EtO)_2POCH_2COOEt$, NaH, 14%; c) (i) DIBAL, THF; (ii) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, 70%; d) baker's yeast, 6 d, 56%; e) (i) TsCl, pyridine, CH_2Cl_2; (ii) NaI, acetone, reflux, 89%; f) Me_2C=CHMgBr, CuI (cat), THF, 89%; g) CAN, aq. MeCN, 87%.*

Shishido's Approach : (Scheme-17, 2000)[5]



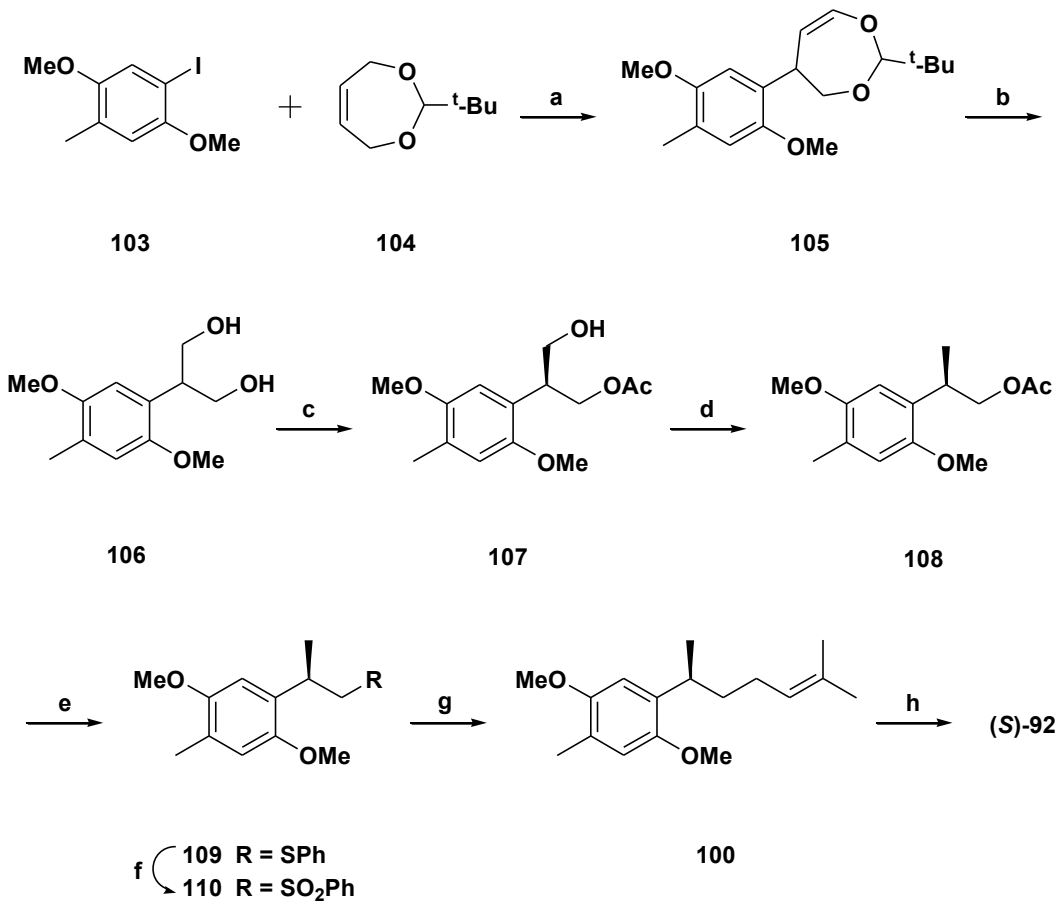
101 **102**

First enantioselective synthesis of heliannuol D **101** and A **102** *via* (S)-curcuquinone **92** using enzymatic transesterification of diol **106** as the key reaction, has been described here.

Thus, the key prochiral diol **106** was prepared by Heck reaction between **103** and **104**, followed by ozonolytic cleavage and reductive workup using $NaBH_4$, which on *Candida antactica* lipase (CAL)-catalyzed transesterification[25] in diethyl ether using vinyl acetate as an acetyl donor at room temperature produced the optically active monoacetate

107 in 87% yield. (S)-Curcuquinone **92** was synthesized from **107** *via* sulfone **110** following a few steps, which was further utilized for the syntheses of titled heliannuols.

Scheme-17 : (Shishido *et al*, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1807-1808)

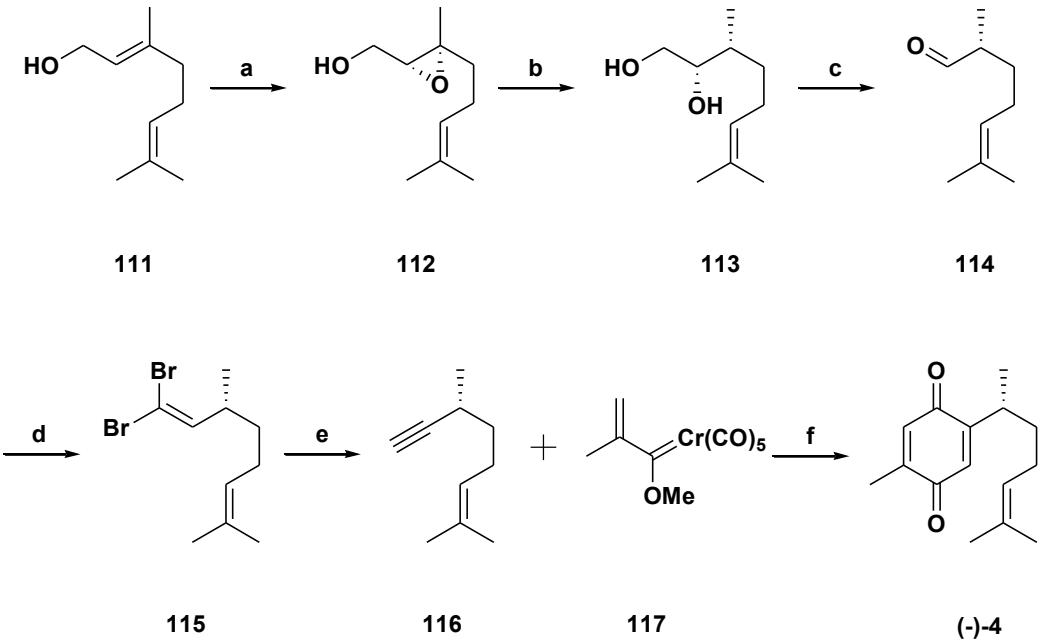


Reagents and conditions *: a) $Pd(OAc)_2$, Ph_3P, i-Pr_2NEt, DMF, 80 ^oC, 90%; b) O_3, MeOH, $NaBH_4$, 93%; c) CAL, Et_2O, rt, 87% (99% ee); d) (i) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 95%; (ii) $NaBH_4$, DMSO, 60 ^oC; e) (i) $LiAlH_4$, THF, rt, 99%; (ii) PhSSPh, n-Bu_3P, pyridine, rt, 99%; f) mCPBA, $KHCO_3$, CH_2Cl_2, rt, 97%; g) (i) n-BuLi, HMPA, THF, $Me_2C{=}CHCH_2Br$, -78 ^oC, 98%; (ii) Na-Hg (5%), $NaHPO_4$, MeOH, sonication, rt, 84%; h) $(NH_4)_2Ce(NO_3)_6$, MeCN, MeOH, H_2O, rt, 96%.*

Heinz Dotz' Approach : (Scheme-18, 2005)[26]

In this latest synthesis of (-)-curcuquinone **4**, Sharpless asymmetric epoxidation was used to introduce chirality and chromium mediated [3+2+1] benzannulation for overall skeletal formation.

Scheme-18 : (Heinz Dotz *et al*, *J. Org. Chem.* **2005**, *70*, 3745-3748)



Reagents and conditions : *a) (D)-(-)-DIPT, $Ti(O\text{-}i\text{-}Pr)_4$, TBHP, CH_2Cl_2, MS 4 Å, -20 ^oC, 1 h, 87%; b) $NaBH_3CN$, $BF_3\text{-}OEt_2$, THF, rt, 86%; c) $NaIO_4$, Bu_4NIO_4, H_2O, CH_2Cl_2, 0 ^oC, 95%; d) CBr_4, PPh_3, Zn, CH_2Cl_2, rt, 60%; e) n-BuLi, THF, -78 ^oC to rt, 99%; f) CH_2Cl_2, 55 ^oC, 2.5 h, CAN, H_2O, 0 ^oC, 30 min, 80%.*

Thus, this convergent synthesis was commenced from commercially available geraniol **111**, which on asymmetric epoxidation provided epoxide **112** in 95% ee. This epoxide on Lewis-acid mediated reductive ring opening followed by oxidative glycol cleavage using sodium periodate provided aldehyde **114**, which was transformed to terminal acetylene **116** using Corey-Fuch's protocol in 60% yield. Finally, synthesis of **(-)-4** was accomplished in 80% yield in a benzannulation[27] reaction of chromium carbene complex **117** with chiral terminal acetylene **116**. The reaction occurred with complete regioselectivity, which on direct oxidative work-up provided (-)-curcuquinone **4**.

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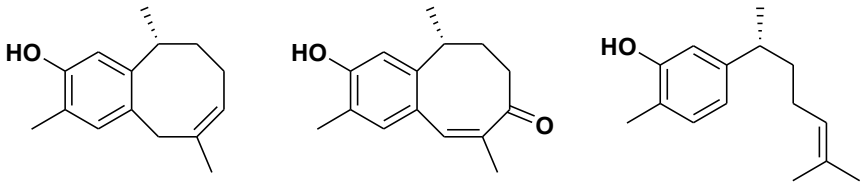
Chapter-2, Section-2 : Enantiospecific Synthesis of (-)-Parvifoline & (+)-Isoparvifolinone

: Friedel-Craft's Acylation Approach For Benzocyclooctane Ring Formation

2.2.1 Introduction

The main structural features that challenge the synthesis of (-)-parvifoline[1] are; a) benzocyclooctene framework formation with an acid sensitive deconjugated double bond, and b) presence of a chiral center at the non-functionalized benzylic position.



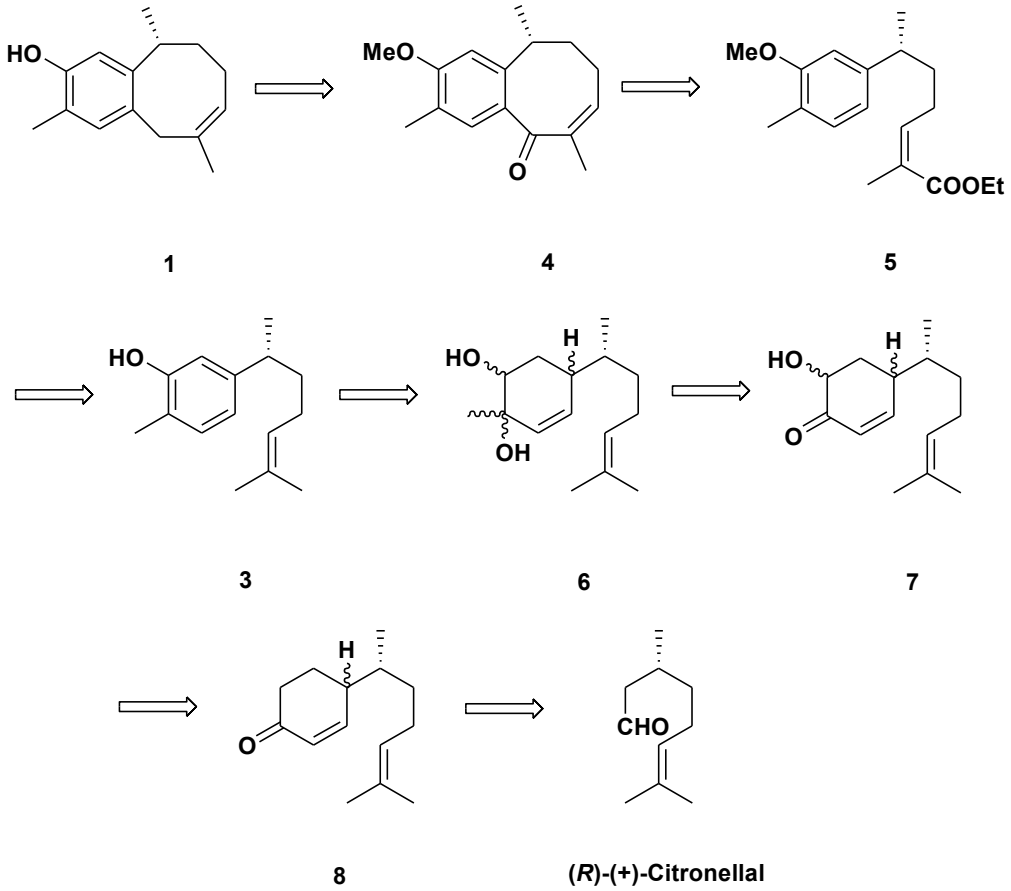
1 **2** **3**

As mentioned earlier, there have been four total syntheses of *rac*-parvifoline reported, but not a single asymmetric synthesis has been attempted. Further, the interest in employing the renewable resources of the nature for the synthesis of natural products has led to identification of (*R*)-(+)-citronellal as the key synthon, which is abundantly available both from plants and of synthetic origin, and using which synthesis of laevigatin[2] and β-herbertenol[3] have been accomplished. This particular section describes the enantiospecific synthesis of (-)-parvifoline **1** and (+)-isoparvifolinone **2** (*via* xanthorrhizol **3**) using intramolecular Friedel-Craft's acylation as the key step.

2.2.2 Present work : *Results and discussion*

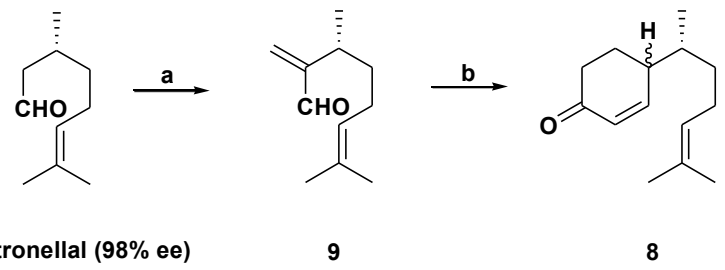
Encouraged by the results achieved in the enantiospecific synthesis of (+)-β-herbertenol,[3] it was envisioned that (*R*)-(+)-citronellal could very well serve as the source of chirality for the enantiospecific synthesis of (-)-parvifoline **1** *via* phenol intermediate **3**, which is also a naturally isolated one from the rhizomes of *Curcuma xanthorrhiza* Roxb, named xanthorrhizol.[4] Diol **6** would be the ideal precursor for the synthesis of **3**. Further, phenol **3** could be utilized for the synthesis of (+)-isoparvifolinone **2** and (-)-parvifoline **1**, *via* cyclooctenone intermediate **4**, which in turn could be synthesized from *Z*-α, β-unsaturated ester **5**. As depicted in the retrosynthetic analysis, diol **6** could be obtained enantiospecifically from (*R*)-(+)-citronellal *via* α-hydroxy enone **7** (Scheme-1).

Scheme-1



Thus, to start with, (*R*)-(+)-citronellal (98% ee) was converted to the enone intermediate **8** using literature method.[5]

Scheme-2

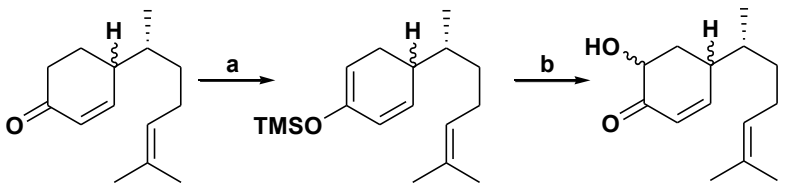


Reagents and conditions **:** *a) formalin (35%), piperidine acetate, 110 ^{o}C, 4 h; b) NaOMe (cat), methylacetoacetate, MeOH, reflux, 5 h, 45% overall.*

Accordingly, it was first treated with formalin solution (35%) in the presence of piperidine acetate as the base to give exomethylene derivative **9**, which on treatment with methylacetoacetate in the presence of catalytic amount of sodium methoxide, underwent Michael addition, aldol condensation and decarboxylation in one pot to deliver the required enone **8** as a 1: 1 mixture of diastereomers in 45% overall yield (Scheme-2). It was characterized by comparison of it's IR and NMR spectral data with those of the reported one.[5]

Next, to have the phenolic hydroxyl group in **3** at appropriate position, it was required to functionalize the α-position of enone **8** regiospecifically, which also has an additional olefin functionality in it's side chain. For this purpose, Rubottom's protocol[6] of α-hydroxylation was resorted to, which involves formation of the enol ether of the corresponding carbonyl compound, that could be achieved regiospecifically as described by House *et al*,[7] followed by peracid oxidation. Mechanistically this involves epoxide formation of an enol ether double bond by mCPBA, which rearranges to relieve the ring strain with migration of the silyl group to give the corresponding silylated α-hydroxy ketone. Accordingly, enone **8** was silylated using lithium diisopropylamine as the base and chlorotrimethylsilane as the silylating agent in dry THF at -78 ^{o}C.

Scheme-3



8 **10** **7**

Reagents and conditions : *a) (i) LDA, THF, -78 ^{o}C, 1.5 h, TMSCl, -78 ^{o}C to rt, 5 h; b) (i) mCPBA, CH_2Cl_2, 0 ^{o}C to rt, 10 h; (ii) dilute HCl, CH_2Cl_2, rt, 12 h, 70% overall.*

Under these conditions, enone **8** gave kinetically favored enol ether **10**, which was further oxidized using mCPBA (85%) in CH_2Cl_2 at 0 ^{o}C to provide trimethylsilyl ether of α-hydroxyenone **7**. It was hydrolyzed without it's purification using dilute HCl to furnish α-hydroxyenone **7** as a mixture of diastereomers in 70% overall yield (Scheme-3). As it

was planned to aromatize the cyclic system to the corresponding aromatic unit, the newly generated chiral centers of **8** (and **7** also) were of no consequence, and thus no attempt was made to separate or characterize them. Formation of **7** was confirmed by it's IR, NMR and mass spectral data, and further ascertained by it's elemental analysis.

Absorption at 3435 cm^{-1} in it's IR spectrum, and one proton doublet of a doublet at δ 4.32 (J = 12.9, 5.8 Hz) in it's ^{1}H NMR spectrum indicated the presence of a secondary hydroxyl group, which was further evident from a methine resonance at δ 69.5 in it's ^{13}C NMR spectrum. It's ^{1}H NMR spectrum revealed one proton triplet at δ 5.07 (J = 7.0 Hz), assigned to the side chain olefin proton; which also exhibited two singlets at δ 1.59 and 1.67, each integrated for three protons, assigned to the two methyl groups associated with the isopropylidene functionality. Presence of enone functionality was evident from a resonance at δ 200.1 in it's ^{13}C NMR spectrum, characteristic of the conjugated ketone carbonyl group. Finally, α-hydroxy enone **7** was confirmed by it's mass spectrum, which revealed a peak of $(M+1)^{+}$ at 223, and by it's elemental analysis also, which was in good agreement with the calculated values.

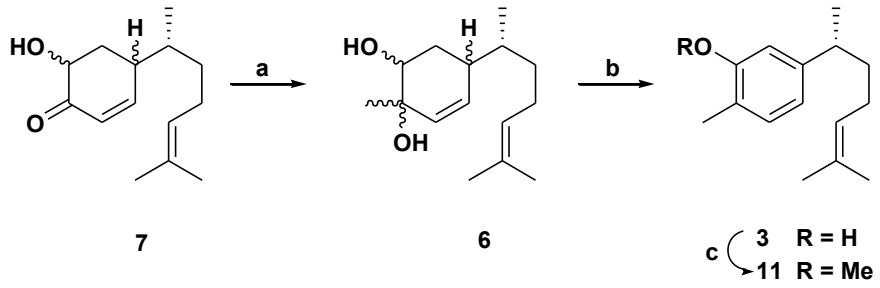
Keeping in mind the substitution pattern in phenol **3**, the next job was to introduce a methyl group over enone carbonyl group, which was achieved by 1,2-addition using methyl magnesium iodide to provide the diol **6** as a mixture of diastereomers in 95% yield. However, it was possible to separate out two spots by flash column chromatography, which were further characterized to be a mixture of diastereomers by it's ^{1}H and ^{13}C NMR spectral data, but as we were about to destroy the newly generated chiral centers in the next step of the synthesis, no attempt was made to separate or characterize the diastereomers and their ratios as well (Scheme-4).

Additional methyl group singlet at δ 1.22 (3H) and upfield shift of the olefin protons involved in the cyclohexene ring at δ 5.45-5.61 (m) in it's ^{1}H NMR spectrum were indicative of the required transformation, which was further evident from a quaternary carbon resonance at δ 71.2 apart from a methine doublet at δ 73.3, characteristic of carbons attached to an hydroxyl group, in it's ^{13}C NMR spectrum. Diol **6** was finally ascertained by it's mass spectrum, which exhibited a peak at 261 $(M+Na)^{+}$ and by it's elemental analysis also.

Diol **6** would be the ideal substrate for the synthesis of phenol **3**, as it contains a secondary hydroxyl group, which on oxidation might undergo elimination of tertiary hydroxyl group with concomitant aromatization. This was achieved under Swern oxidation

conditions, as other oxidizing agents (DMP, PDC) resulted in lower yield of the crude unstable oxidized product, which was difficult to purify.

Scheme-4



Reagents and conditions *: a) MeMgI, diethyl ether, 0 °C to rt, 12 h, 95%; b) (i) oxalyl chloride, DMSO, CH_2Cl_2, -78 °C, then diol* ***6****, 30 min, Et_3N, -78 °C to rt, 5 h; (ii) methanesulfonylchloride, Et_3N, CH_2Cl_2, 0 °C to rt, 3 h, reflux, 5 h; (iii) KOH, methanol, reflux, 7 h, 47% overall; c) K_2CO_3 dimethyl sulfate, acetone, reflux, 12 h, 86%.*

Accordingly, diol **6** was subjected to Swern oxidation[8] and as anticipated, it resulted in a mixture of the required phenol derivative **3** together with unstable α-hydroxy ketone intermediate (as indicated by TLC), which could not be isolated and furnished only impure phenol **3** after column purification, in very poor yields (25%). At this stage, tertiary hydroxyl group elimination of crude α-hydroxy ketone would have increased the overall yield of phenol **3** and to confirm this, crude product obtained after Swern oxidation was subjected to mesylation, which provided phenol **3** along with it's unseparable mesyl ester. Therefore, the crude product was further hydrolyzed using potassium hydroxide as the base under refluxing methanol to furnish the required phenol intermediate, *i. e.* xanthorrhizol[4] **3** in 47% isolated yield for three steps (Scheme-4).

An hydroxyl group absorption at 3411 cm^{-1} in it's IR spectrum and an aromatic singlet at δ 153.7 in it's ^{13}C NMR spectrum suggested the phenolic nature of the intermediate **3**. Further, ^1H NMR spectrum revealed resonances at δ 6.56-6.65 (m), integrated for two protons and δ 6.98 (d, J = 7.7 Hz) for one proton; were assigned to the aromatic protons. Also, a triplet (with further unresolved couplings) at δ 5.05 (J = 7.1 Hz, 1H) and two singlets at δ 1.55 (3H) and 1.66 (3H) in it's ^1H NMR spectrum, were assigned to the isopropylidene functionality (-CH=CMe_2), present in the side chain. Phenol **3** was

finally confirmed by it's mass spectrum, which exhibited a peak of M^+ at 218, and by it's elemental analysis also.

Further, phenol **3** was protected as it's methyl ether **11** in 86% yield, using dimethyl sulfate and potassium carbonate in refluxing acetone (Scheme-4). Absence of hydroxyl absorption at 3411 cm^{-1} in it's IR spectrum and presence of a three proton singlet at δ 3.83 in it's ^1H NMR spectrum suggested the success of required transformation, which was further evident from a methyl quartet at δ 55.1, characteristic of a methoxy group, in it's ^{13}C NMR spectrum. It was further ascertained by it's mass spectrum, which revealed a peak at 255 $(M+Na)^+$ and by it's elemental analysis as well.

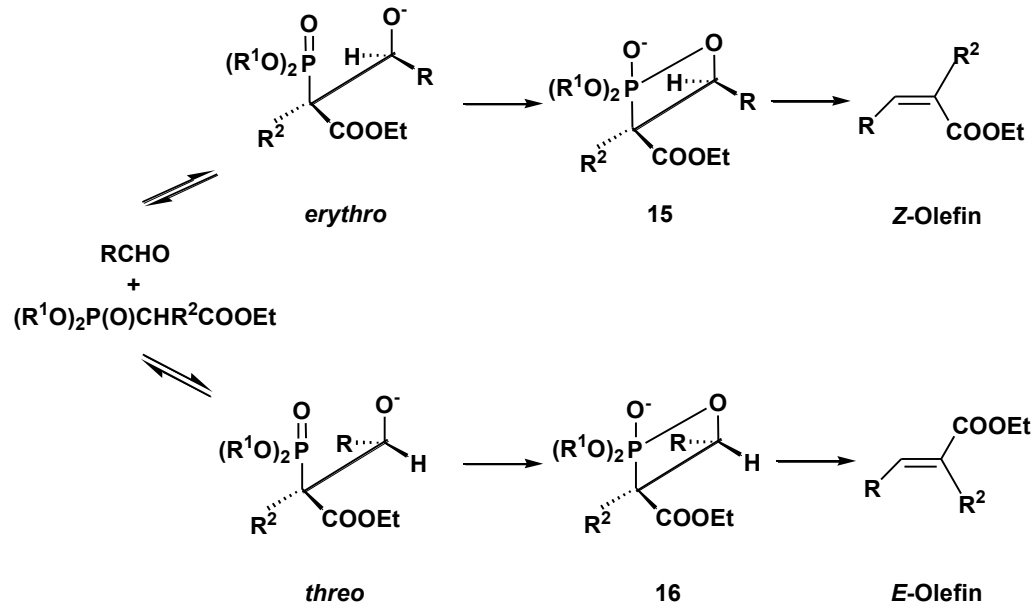
Having secured the aromatic unit **11**, the next major task was to check the feasibility of Friedel-Craft's acylation for benzocyclooctenone formation and for this purpose, it was required to have a *cis*-conjugated ester **5**. To synthesize ester **5**, double bond of the anisole derivative **11** had to be chopped off oxidatively to have an aldehyde, over which two carbon Wittig olefination would have served the purpose. To get the selectivity for *Z*-double bond isomer, Ando's modification[9] of Horner-Emmon's olefination was preferred, which uses diarylphosphono esters **12-14** in the presence of an inexpensive base, such as Triton B or NaH in THF for the synthesis of trisubstituted conjugated ester with high *Z*-selectivity, and thus use of excess of expensive and hygroscopic 18-Crown-6 required in Still's method of *cis*-olefination[10] was avoided.

$(PhO)_2P(O)CH(CH_3)COOEt$ ***(12)****, $(o\text{-}MePhO)_2P(O)CH(CH_3)COOEt$* ***(13)*** *or*

$(o\text{-}iPr\text{-}PhO)_2P(O)CH(CH_3)COOEt$ ***(14)***

The reaction is believed to proceed as shown in scheme-5, that is, the phosphoryl-stabilized carbanion attacks the carbonyl in a stepwise manner to give *erythro* and *threo* adducts, which then decompose *via* four centered transient species **15** and **16**, to the corresponding olefin products. The stereochemistry is determined by a combination of the stereoselectivity in the C-C bond forming step and reversibility of the intermediate adducts. Thus, conditions that favor more of the *erythro* adduct, lead to more of the *Z*-isomer. In the case of α-methyl esters, it is advised to use phosphonates with bulky substituents in the aryl ring and to carry out reaction at lower temperature for greater *Z*-selectivity.

Scheme-5

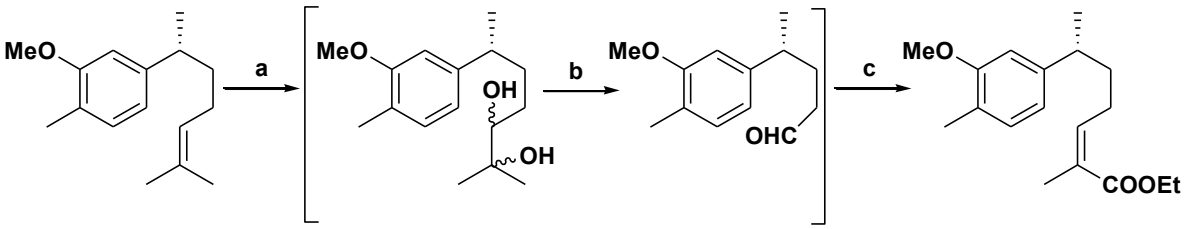


And for oxidative double bond cleavage, Lemieux-Johnson's reagent[11] was opted, which uses sodium periodate in combination with osmium tetroxide (catalytic) in aqueous dioxane. Aldehyde **18** obtained by this method was immediately subjected to two carbon olefination as described by Ando *et al*, which resulted in the requisite trisubstituted conjugated ester **5**, with exclusive selectivity for *cis*-isomer, but only in 50% isolated yield (Scheme-6).

Conjugated ester **5** was characterized completely by it's IR, NMR, mass spectral data and further ascertained by it's elemental analysis. IR spectrum of the isolated product showed absorptions at 1705 cm^{-1} and 1644 cm^{-1}; characteristic of the α, β-unsaturated esters. This was further supported by it's ^1H NMR spectrum, which revealed a resonance for one olefin proton at δ 5.87 (td, J = 7.6, 1.4 Hz). The downfield shift of this olefin proton indicated it's conjugation with an electron withdrawing substituent. Further, three proton triplet at δ 1.23 (J = 7.1 Hz) and two proton quartet at δ 4.14 (J = 7.1 Hz) were indicative of the presence of an ethyl ester functionality, which was further evident by a carbonyl resonance at δ 168.1 (s) and an additional methylene doublet at δ 60.0, in it's ^{13}C NMR spectrum. Absence of the singlets due to two methyl groups associated with the isopropylidene functionality of **11**, at δ 1.54 and 1.68 in the ^1H NMR spectrum of the isolated product, which instead revealed a three proton doublet at δ 1.86 (J = 1.3 Hz), assigned to CH=C(C<u>H</u>$_3$)COOEt, supported the proposed intermediate. The doublet was due

to allylic coupling with the adjacent olefin proton (at δ 5.87), which showed a triplet of doublet (*J* value of doublet in both the cases was quite close). Finally, unsaturated ester **5** was confirmed by it's mass spectrum, which exhibited a peak of $(M+1)^+$ at 291 and $(M-OEt)^+$ at 245, and by it's elemental analysis also.

Scheme-6



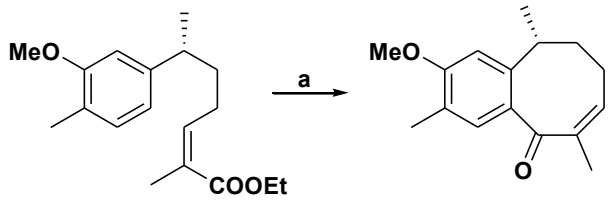
11 **17** **18** **5**

Reagents and conditions *: a) OsO_4 (cat), NMO (50% in water), acetone, rt, 24 h; b) $NaIO_4$ supported over silica gel, CH_2Cl_2, rt, 3 h; c) NaH (60%), **13**, THF, -78 ^oC, 3 h, 85% overall.*

The lower overall yield of the conjugated ester **5** might be attributed to the unstability of the aldehyde intermediate **18**, which was synthesized by Lemieux-Johnson's reagent in 24 hours, and to improve the yields, it was decided to go *via* more stable diol intermediate **17**. It was prepared by treating the olefin **11** with NMO (50%) in the presence of catalytic amount of osmium tetroxide in acetone at room temperature for 24 hours, which without purification was subjected to glycol cleavage using sodium periodate supported over silica gel in CH_2Cl_2 at room temperature. Under these conditions, reaction took just 3 hours for completion and as anticipated, the resultant aldehyde afforded ester **5** in improved overall yields, that is 85% under previously described reaction conditions.

After successful introduction of the ester functionality, the stage was set to check the crucial ring closure. Keeping in mind the reactivity of methacrylic acid derivatives towards polymerization, the corresponding acid derivative, obtained after hydrolysis of intermediate **5** using KOH as the base in refluxing methanol, was treated with oxalyl chloride at 0 ^oC for 3 hours, and the resultant acid chloride was immediately subjected to Friedel-Craft's acylation.[12] Thus, it was treated with anhydrous aluminium chloride in dry CH_2Cl_2 at -20 ^oC and stirred at room temperature for 10 hours to provide the required benzocyclooctenone intermediate **4** in 40% overall yield (Scheme-7).

Scheme-7



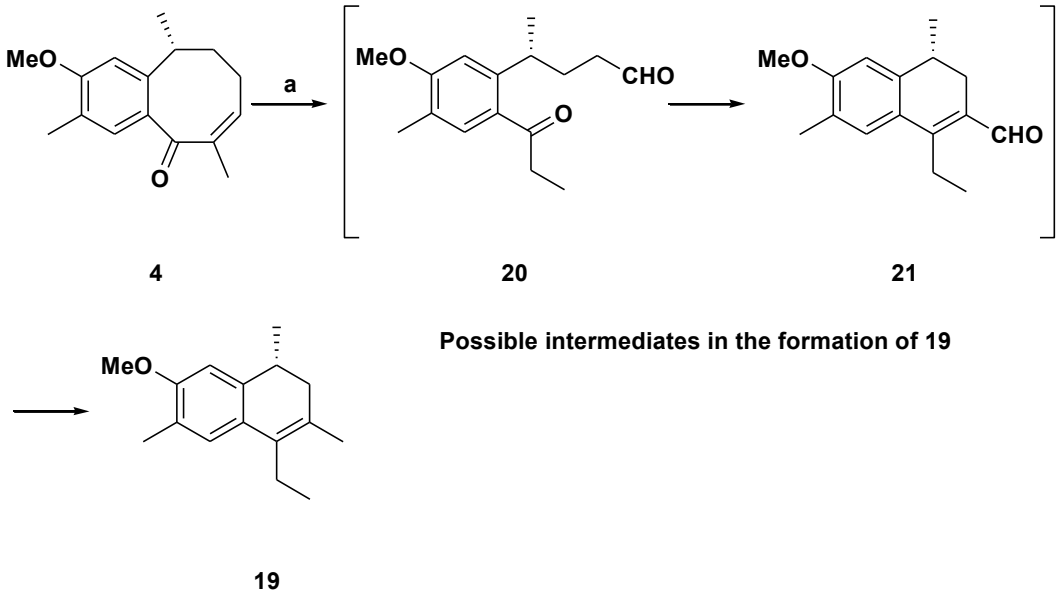
5 **4**

Reagents and conditions *: a) (i) KOH, MeOH, reflux, 3 h; (ii) oxalyl chloride, CH_2Cl_2, 0 ^oC, 3 h; (iii) anhydrous $AlCl_3$, CH_2Cl_2, -20 ^oC to rt, 10 h, 40% overall.*

IR spectrum of the isolated product indicated the presence of an enone functionality by exhibiting absorptions at 1710 cm^{-1} and 1624 cm^{-1}. Cyclisation of the side chain over aromatic ring was indicated by presence of only two aromatic resonances at δ 6.64 (s) and 7.41 (d, J = 0.8 Hz), characteristic of tetra substituted aromatic ring with *para* distributed protons. This was further supported by it's ^{13}C NMR spectrum, which revealed four quaternary signals at δ 124.5, 141.3, 143.0 and 160.6. Moreover, downfield shift of one olefin proton at δ 6.44 (td, J = 9.0, 1.4 Hz) in it's ^1H NMR spectrum was indicative of the formation of an eight membered ring with double bond still in conjugation with the carbonyl group, which in turn, was in conjugation with the aromatic ring. It was finally confirmed by it's mass spectrum, which exhibited a peak of $(M+1)^+$ at 245 and by it's elemental analysis also, which was found to be in good agreement with the calculated values.

Pleased with the benzocyclooctenone framework formation, the remaining task was deoxygenation of the enone carbonyl group, which should be performed under conditions that doesn't lead to the migration of the double bond in conjugation with the aromatic ring. Therefore, use of acidic conditions and thus Clemmenson reduction methodology was not of proper choice. Therefore, it was thought to try out Huang-Minlon modification[13] of Wolff-Kishner reduction for the required purpose. Accordingly, enone **4** was treated with hydrazine hydrate in the presence of KOH in diethylene glycol at 210 ^oC for 12 h, which instead of deoxygenated product (*i. e.* parvifoline methyl ether), resulted in **19**, formation of which was proposed on the basis of it's NMR spectral data (Scheme-8).

Scheme-8



Reagents and conditions **:** *a) hydrazine monohydrate, hydrazine dihydrochloride, KOH, 150 ^{o}C, 3 h, 210 ^{o}C, 12 h, 50%.*

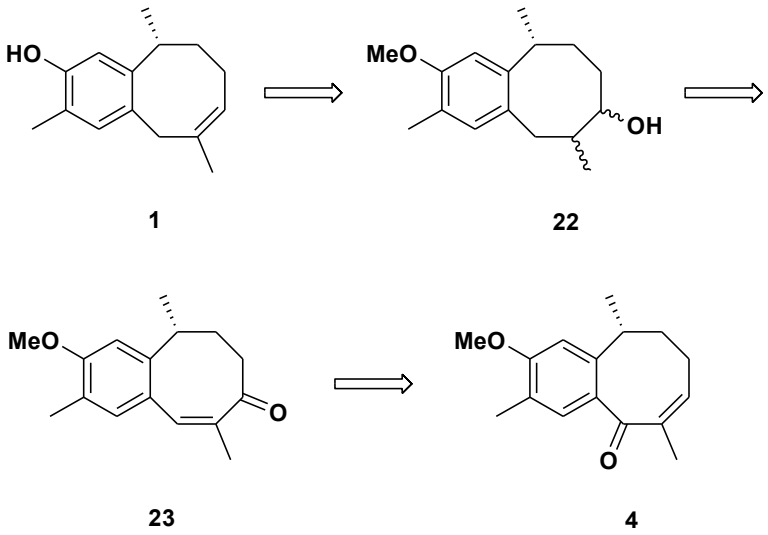
The ^{1}H NMR spectrum of the isolated product revealed a three proton triplet at δ 1.08 (J = 7.6 Hz) and a two proton quartet at δ 2.51 (J = 7.6 Hz), which suggested the presence of an ethyl group attached to an olefin carbon atom. Also, apart from a three proton singlet at δ 2.20 (characteristic of Ar-C$\underline{H}_3$), it's ^{1}H NMR spectrum exhibited a three proton singlet at δ 1.88, which indicated the presence of an allylic methyl group. Formation of **19** was also supported by it's ^{13}C NMR spectrum, which showed total 16 carbon resonances. There were eight carbon resonances in the olefin region of the spectrum, out of which only two were methine resonances (at δ 108.4 and 125.4), while the rest of the six resonances indicated quaternary carbon atoms. This indicated tetrasubstitution pattern of the olefin functionality, present in the cyclohexene ring. Further, ^{13}C NMR spectrum didn't exhibited any carbonyl resonance. Mass spectrum further supported the formation of **19** by exhibiting $(M+1)^{+}$ at 231 and also $(M-CH_2CH_3)^{+}$ at 201. From all these spectral data, structure **19** was proposed for the isolated product.

The plausible pathway of the formation of **19** has been proposed in the scheme-8, that is *via*, (i) retro aldol reaction to provide **20**; (ii) intramolecular aldol condensation of **20** to form highly facile six membered ring unit of conjugated aldehyde **21** and (iii)

deoxygenation of aldehyde to the methyl group, to provide **19**. However, unstability of the intermediate and also due to time constraint, **19** was not completely characterized.

Failure of Wolff-Kishner deoxygenation protocol for the required transformation necessitated to proceed *via* an alcohol intermediate **22** (Scheme-9), which has previously been reported by Joseph-Nathan *et al*[14] for the synthesis of *rac*-parvifoline **1**. However, in this case, it was planned to synthesize *via* isoparvifolinone methyl ether **23**, and thus to utilize the cyclic enone **4** for the enantiospecific synthesis of (+)-isoparvifolinone **2** as well.

Scheme-9

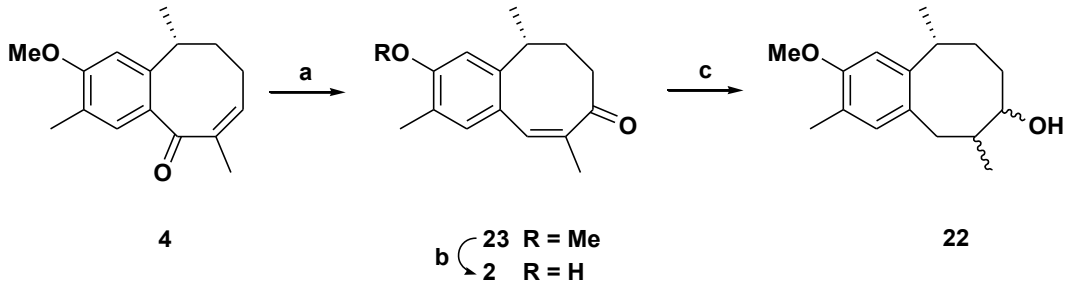


Thus, synthesis of isoparvifolinone methyl ether **23** was undertaken, for which enone **4** was selectively reduced under Luche reduction[15] conditions to provide the corresponding unstable benzyl alcohol, which on pyridinium chlorochromate[16] oxidation, underwent 1,3-ketone transposition to give **23** in 60% overall yield (Scheme-10).

It was characterized by it's IR and NMR spectral data comparison with those of reported one[14] and was found to be in good agreement. The characteristic features in it's NMR spectra were; a singlet at δ 6.76 (1H), attributed to the cyclooctenone olefin proton; three proton doublet due to allylic methyl group at δ 2.01 (d, J = 1.4 Hz) in it's ^{1}H NMR spectrum, and a carbonyl resonance at δ 204.0 (s) in it's ^{13}C NMR spectrum.

Intermediate **23** was finally subjected to methyl ether deprotection using BBr_3 in 60% yield, to complete the first enantiospecific synthesis of (+)-isoparvifolinone **2** (Scheme-10).

Scheme-10



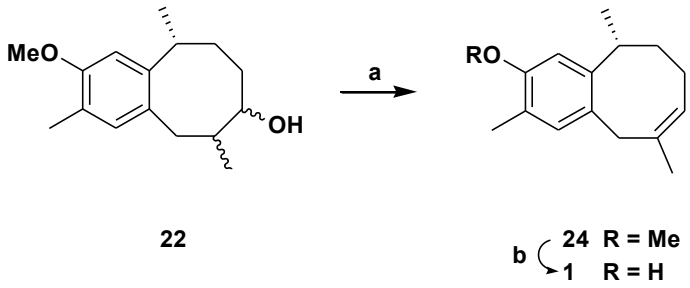
Reagents and conditions *: a) (i) $CeCl_3$-$7H_2O$, $NaBH_4$, MeOH, 0 °C, 30 min; (ii) PCC over silica gel, CH_2Cl_2, 2 h, 60% overall; b) BBr_3, CH_2Cl_2, rt, 1 h, 60%; c) H_2/10% Pd/C, MeOH, 24 h, then $NaBH_4$, 30 min, 55%.*

This chemically synthesized isoparvifolinone **2** was in complete agreement with the naturally isolated one[1b] mp 157-158 °C and specific rotation : $[\alpha]^{25}_D$ +850 (*c* 1, $CHCl_3$). {lit.[1b] mp 157-158 °C; specific rotation : $[\alpha]^{25}_D$ +854 (*c* 1, $CHCl_3$)}. The sign and value of the specific rotation suggested the configuration and optical purity of the product obtained.

Intermediate **23** was, further, hydrogenated using 10% Pd/C (catalytic) in methanol followed by sodium borohydride reduction in the same pot, which afforded the previously reported alcohol **22**[14] in 55% overall yield (Scheme-10). Intermediate **22** was confirmed by it's IR and NMR spectral data comparison with those of reported,[14] and was found to be in good agreement. It's IR spectrum showed absorption at 3616 cm^{-1} and 3454 cm^{-1}, attributed to an hydroxyl group. Absence of enone functionality was evident from it's ^{13}C NMR spectrum, which in addition revealed a methine doublet at δ 75.4, indicated the presence of a secondary hydroxyl group. However, it's ^1H and ^{13}C NMR spectra suggested high diastereomeric purity of the product obtained, but as these two centers were to be destroyed in the next step of the synthesis, no attempt was made to characterize the isomer.

Finally, to complete the synthesis of (-)-parvifoline **1**, secondary hydroxyl group elimination was attempted under the conditions, described by Nathan *et al.*[14] Accordingly, **22** was treated with *p*-toluenesulfonylchloride in pyridine at -4 °C for 3 days. Surprisingly, it ended up in the corresponding tosylate only, which was then heated at 100 °C in pyridine to furnish the required (-)-parvifoline methyl ether **24** in 65% yield (Scheme-11).

Scheme-11



Reagents and conditions *: a) p-toluenesulfonylchloride, pyridine, -4 °C, 3 days, then 100 °C, 10 h, 65%; b) EtSLi, DMF, 105 °C, 24 h, 90%.*

Formation of **24** was confirmed by it's IR and NMR spectral data comparison with those of the literature values[14] and was found to be in good agreement. It showed specific rotation $[\alpha]^{25}_{D}$ -200 (*c* 1, $CHCl_3$).

Methyl ether of **24** was finally deprotected using (highly nucleophilic and relatively nonbasic) lithium thioethoxide in DMF at 105 °C to complete the synthesis, which indeed delivered the final product, that is, (-)-parvifoline **1** in 90% yield.

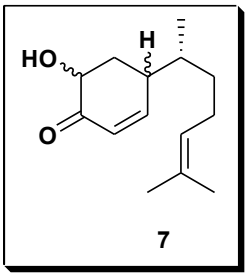
It was characterized by it's IR and NMR spectral data comparison with those of reported one.[1a] It's IR spectrum showed absorption at 3602 cm^{-1}, attributed to the phenolic hydroxyl group. It's ^1H NMR spectrum revealed characteristic doublets at δ 3.01 and 3.51 with same coupling constant (*J* = 18.3 Hz), assigned to Ar-C$\underline{H}_2$-C(Me)=CH; and a triplet at 5.34 (*J* = 7.0 Hz), assigned to the only olefin proton present in the cyclooctene ring. Specific rotation of the product was $[\alpha]^{25}_{D}$ -168 (*c* 1.73, $CHCl_3$) {lit.[1a] $[\alpha]^{25}_{D}$ -173 (*c* 1.73, $CHCl_3$)}, which also suggested the optical purity of the product and confirmed it's absolute configuration as well.

2.2.3 Conclusions

(-)-Parvifoline has been synthesized enantiospecifically, starting from naturally occurring (*R*)-(+)-citronellal as the source of chirality, using intramolecular Friedel-Craft's acylation as the key step. (+)-Isoparvifolinone has also been synthesized on similar lines.

2.2.4 Experimental

6-Hydroxy-4-((*R*)-6-methylhept-5-en-2-yl)cyclohex-2-enone (7)



7

A 100 mL round bottom flask equipped with a magnetic stir bar and a condenser was charged with diisopropylamine (3.83 g, 37.90 mmol) and dry THF (50 mL) under N_2 atmosphere, and cooled to -78 ^oC. To this mixture, n-BuLi (1.6 M solution in hexane) (22.4 mL, 36.4 mmol) was added dropwise and stirred for 10 min, followed by dropwise addition of the conjugated ketone **8** (6 g, 29.1 mmol) in dry THF (10 mL). The reaction mixture was stirred for 1.5 h at -78 ^oC and then quenched with chlorotrimethylsilane (3.48 g, 32 mmol). It was allowed to come to 0 ^oC within 5 h and quenched with saturated $NaHCO_3$ solution (200 mL). The mixture was extracted with pet. ether (50 mL x 3), and the combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 8 g of crude silyl enol ether, which was confirmed by it's ^1H NMR spectrum and used as such for the next step.

The crude silyl enol ether was taken in a 250 mL single neck round bottom flask, to which CH_2Cl_2 (100 mL) was added, followed by addition of 5% $NaHCO_3$ solution (100 mL). The reaction mixture was cooled to 0 ^oC and mCPBA (5.25 g, 30.5 mmol) was added to it portionwise. It was stirred at room temperature for 10 h and then diluted using saturated $NaHCO_3$ solution (100 mL), followed by extraction with CH_2Cl_2 (100 mL x 3). The combined organic layers were washed with saturated Na_2SO_3 solution (150 mL), saturated $NaHCO_3$ solution (150 mL), brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. It was then taken in CH_2Cl_2 (75 mL) in a 250 mL round bottom flask, cooled to 0 ^oC and to this was added 1.5 M HCl solution (75 mL). It was stirred at room temperature for 12 h, extracted using CH_2Cl_2 (75 mL x 2), the combined organic layers were washed with water (75 mL), brine (75 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 96 : 4) to give hydroxy enone **7** (4.5 g) as a colourless oil (mixture of diastereomers).

Molecular Formula : $C_{14}H_{22}O_2$

Yield **:** 70%

IR (neat) ν_{max} (cm^{-1}) **:** 3435, 2923, 1736, 1686.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.03 (d, *J* = 6.7 Hz, 3H); 1.18-1.55 (m, 2H); 1.59 (s, 3H); 1.67 (s, 3H); 1.74-2.09 (m, 4H); 2.31-2.50 (m, 2H); 3.46 (bs, 1H); 4.32 (dd, *J* = 12.9, 5.8 Hz, 1H); 5.07 (t, *J* = 7.0 Hz, 1H); 6.06 (d, *J* = 10.1 Hz, 1H); 6.97 (dd, *J* = 10.2, 4.9 Hz, 1H).

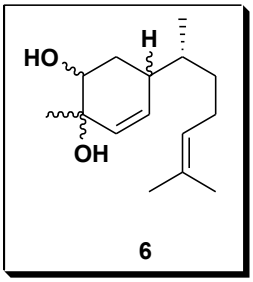
MS-ESI m/z **:** 223 $(M+1)^+$

Analysis

Expected **:** C, 75.63%; H, 9.97%

Found **:** C, 75.80%; H, 10.26%

2-Methyl-5-((*R*)-6-methylhept-5-en-2-yl)cyclohex-3-ene-1,2-diol (6)



6

A flame dried 250 mL round bottom flask equipped with a magnetic stir bar and a condenser was charged with Mg turnings (2.73 g, 112.2 mmol) and diethyl ether (100 mL), under N_2 atmosphere. MeI (15.9 g, 112.2 mmol) was added to it at 0 ^oC and stirred at room temperature for 2 h. To this Grignard reagent, enone **7** (8.3 g, 37.4 mmol) was added using diethyl ether (20 mL) at 0 ^oC and stirred at room temperature for 12 h. It was quenched using saturated NH_4Cl solution (100 mL) at 0 ^oC and extracted using ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 9 : 1) to give diol **6** (8.5 g) as a colourless oil. (two spots separated, each was found to be a mixture of diastereomers)

Molecular Formula **:** $C_{15}H_{26}O_2$

IR (neat) ν_{max} (cm^{-1}) **:** 3400, 2928, 1652.

Yield **:** 95%

Faster moving spot : ^{1}H NMR ($CDCl_3$, 200 MHz) : δ two doublets at 0.79 & 0.83 (*J* = 6.8 Hz, total 3H); 1.22 (s, 3H); 1.10-1.50 (m, 4H); 1.56 (s, 3H); 1.64 (s, 3H); 1.73-1.94 (m, 3H); 2.28-2.37 (m, 1H); 2.89 (bs, 2H); 3.72-3.74 (m, 1H); 5.05 (t, *J* = 7.1 Hz, 1H); 5.45-5.61 (m, 2H).

Slower moving spot : ^{1}H NMR ($CDCl_3$, 200 MHz) : δ two doublets at 0.84 & 0.87 (*J* = 6.8 Hz, total 3H); 1.24 (s, 3H); 1.03-1.50 (m, 4H); 1.56 (s, 3H); 1.65 (s, 3H); 1.68-2.02 (m, 3H); 2.16-2.29 (m, 1H); 2.54 (bs, 2H); 3.71-3.77 (m, 1H); 5.05 (t, *J* = 7.1 Hz, 1H), 5.56-5.58 (m, 2H).

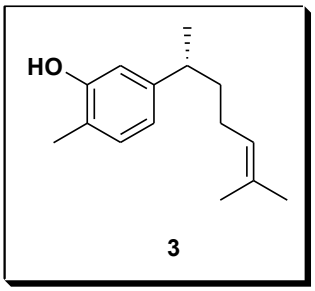
MS-ESI m/z **:** 261 $(M+Na)^+$

Analysis

Expected **:** C, 75.58%; H, 10.99%

Found **:** C, 75.57%; H, 11.06%

(*R*)-2-Methyl-5-(6-methylhept-5-en-2-yl)phenol (3)



3

A 1 lit round bottom flask equipped with a magnetic stir bar and a condenser was charged with CH_2Cl_2 (170 mL) followed by oxalyl chloride (26.4 g, 208 mmol), under N_2 atmosphere, and cooled to -78 ^oC. Dimethyl sulfoxide (32.5 g, 416 mmol) was added to it dropwise, during which internal temperature was maintained below -60 ^oC. After complete addition, the reaction mixture was stirred for 15 min and then diol **6** (15 g, 63 mmol) was added using CH_2Cl_2 (50 mL) dropwise, and stirred for 30 min. Finally, the reaction mixture was quenched using triethylamine (89.3 g, 882 mmol) at -78 ^oC and was brought to room temperature within 5 h. Water (200 mL) was added to it, followed by extraction with CH_2Cl_2 (100 mL x 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was carried forward without it's column purification.

The crude α-hydroxy ketone was taken in a 1 lit two neck round bottom flask and CH_2Cl_2 (150 mL) was added to it. The reaction mixture was cooled to 0 ^oC and triethylamine (38.3 g, 378 mmol) was added, followed by dropwise addition of methanesulfonylchloride (21.6 g, 189 mmol). The reaction mixture was stirred at room temperature for 3 h and then refluxed for additional 5 h. Finally, it was quenched with saturated $NaHCO_3$ solution (150 mL), and extracted using CH_2Cl_2 (100 mL x 3). The combined organic layers were washed using brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product, which contains phenol **3** as well as it's mesyl ester, was taken in methanol (150 mL), and KOH pellets

(10.61 g, 18.9 mmol) was added. It was refluxed for 7 h. Methanol was removed under reduced pressure and the reaction mixture was diluted using water (150 mL), and extracted with CH_2Cl_2 (100 mL x 3). The combined organic layers were washed using brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue obtained was chromatographed using flash silica gel (pet. ether : EtOAc, 96 : 4) to provide phenol **3** (6.5 g) as a colourless oil.

Molecular Formula : $C_{15}H_{22}O$

Yield : 47% overall.

IR ($CHCl_3$) ν_{max} (cm^{-1}) : 3411, 1621, 1589.

Specific Rotation : $[\propto]^{25}_D$ -37.91 (*c* 1.5, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.19 (d, *J* = 7.0 Hz, 3H); 1.52-1.66 (m, 2H); 1.55 (s, 3H); 1.66 (s, 3H); 1.80-1.91 (m, 2H); 2.20 (s, 3H); 2.53-2.64 (m, 1H); 5.05 (triplet with further unresolved couplings, *J* = 7.1 Hz, 1H); 6.56-6.65 (m, 2H); 6.98 (d, *J* = 7.7 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 15.5 (CH_3); 17.8 (CH_3); 22.5 (CH_3); 25.8 (CH_3); 26.2 (CH_2); 38.5 (CH_2); 39.1 (CH); 113.6 (CH); 119.4 (CH); 120.9 (C); 124.8 (CH); 130.8 (CH); 131.2 (C); 147.0 (C); 153.7 (C).

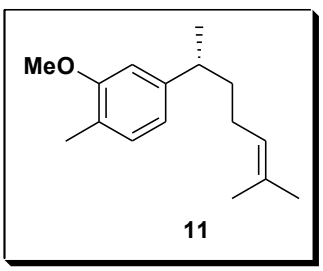
MS-ESI m/z : 218 $(M)^+$

Analysis

Expected : C, 82.52%; H, 10.16%

Found : C, 82.29%; H, 10.35%

(*R*)-2-Methoxy-1-methyl-4-(6-methylhept-5-en-2-yl)benzene (11)



11

To a stirred solution of phenol **3** (6 g, 27.5 mmol) in dry acetone (60 mL) was added anhydrous K_2CO_3 (9.5 g, 68.8 mmol) and dimethyl sulfate (8.7 g, 68.8 mmol), under N_2 atmosphere. The reaction mixture was refluxed for 12 h and then acetone was removed under reduced pressure, followed by dilution with water (200 mL). The reaction mixture was stirred overnight and then extracted with CH_2Cl_2 (200 mL x 3). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under

reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 99 : 1) to provide the methyl ether **11** (5.5 g) as a colourless oil.

Molecular Formula : $C_{16}H_{24}O$

Yield : 86%

Specific Rotation : $[\alpha]^{25}_{D}$ -40.97 (*c* 1.9, $CHCl_3$)

IR (neat) ν_{max} (cm^{-1}) : 1613, 1583.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.24 (d, *J* = 7.0 Hz, 3H); 1.54-1.68 (m, 2H); 1.54 (s, 3H); 1.68 (s, 3H); 1.83-1.94 (m, 2H); 2.18 (s, 3H); 2.56-2.73 (m, 1H); 3.83 (s, 3H); 5.09 (triplet with further unresolved couplings, *J* = 7.1 Hz, 1H); 6.61- 6.68 (m, 2H); 7.01 (d, *J* = 7.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 16.0 (CH_3); 17.9 (CH_3); 22.8 (CH_3); 25.9 (CH_3); 26.3 (CH_2); 38.6 (CH_2); 39.7 (CH); 55.1 (CH_3); 108.8 (CH); 118.7 (CH); 123.9 (C); 124.8 (CH); 130.5 (CH); 131.1 (C); 146.5 (C); 157.7 (C).

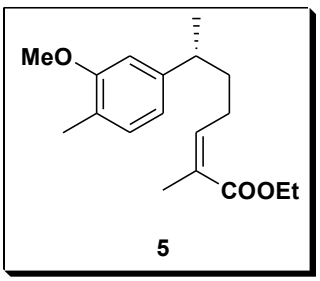
MS-ESI m/z : 255, $(M+Na)^+$; 271, $(M+K)^+$

Analysis

Expected : C, 82.71%; H, 10.41%

Found : C, 82.77%; H, 10.43%

(*R, Z*)-Ethyl-6-(3-methoxy-4-methylphenyl)-2-methylhept-2-enoate (5)



5

A 50 mL round bottom flask was charged with olefin **11** (3 g, 12.9 mmol) and acetone (25 mL). It was cooled to 0 ^oC and OsO_4 (0.1M solution in toluene) (1 mL) was added to it, followed by 50% NMO (in water) (4.6 mL, 19.4 mmol). The reaction mixture was stirred at room temperature for 24 h and then diluted with water (50 mL), followed by extraction with CH_2Cl_2 (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude diol was diluted using CH_2Cl_2 (150 mL), and added $NaIO_4$ supported over silica gel (10%) (61 g, 28.5 mmol). It was stirred for 3 h and filtered through a short pad of celite, washed with CH_2Cl_2 (50 mL x 4). The combined organic layers were evaporated under reduced pressure and the crude aldehyde, thus, obtained was subjected to two carbon olefination.

NaH (60%) (0.62 g, 15.5 mmol) was taken in a 100 mL two neck round bottom flask and THF (20 mL) was added to it under, N_2 atmosphere. The reaction mixture was cooled to 0 ^oC and phosphonate **13** (7 g, 19.4 mmol) was added to it using THF (10 mL). The reaction mixture was stirred at room temperature for 15 min and then cooled to -78 ^oC. To this was added crude aldehyde using THF (10 mL) at -78 ^oC, stirred for 3 h more at the same temperature and quenched using saturated NH_4Cl solution (100 mL). The solution was extracted using ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using (pet. ether : EtOAc, 95 : 5) to provide *cis*-olefin **5** (3.2 g) as a colourless oil.

Molecular Formula **:** $C_{18}H_{26}O_3$

Yield **:** 85% overall

Specific Rotation **:** $[\alpha]^{25}_D$ -37.23 (*c* 2.0, $CHCl_3$)

IR ($CHCl_3$) ν_{max} (cm^{-1}) **:** 3020, 2960, 1705, 1644, 1612, 1581.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.23 (t, *J* = 7.1 Hz, 3H); 1.25 (d, *J* = 6.7 Hz, 3H); 1.60-1.73 (m, 2H); 1.86 (d, *J* = 1.3 Hz, 3H); 2.17 (s, 3H); 2.28-2.50 (m, 2H); 2.57-2.71 (m, 1H); 3.82 (s, 3H); 4.14 (q, *J* = 7.1 Hz, 2H); 5.87 (triplet of doublet, *J* = 7.6, 1.4 Hz, 1H); 6.64-6.70 (m, 2H); 7.03 (d, *J* = 7.5 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 14.1 (CH_3); 15.8 (CH_3); 20.6 (CH_3); 22.2 (CH_3); 27.9 (CH_2); 38.0 (CH_2); 39.7 (CH); 55.2 (CH_3); 60.0 (CH_2); 108.9 (CH); 118.6 (CH); 123.9 (C); 127.2 (C); 130.4 (CH); 142.5 (CH); 146.2 (C); 157.6 (C); 168.1 (C).

MS-ESI m/z **:** 291 $(M+1)^+$, 245 $(M-OCH_2CH_3)^+$

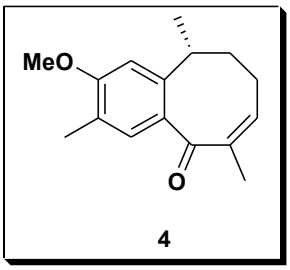
Analysis

Expected **:** C, 74.45%; H, 9.02%

Found **:** C, 74.36%; H, 8.81%

(*R, Z*)-2-Methoxy-3,6,10-trimethyl-9,10-dihydorbenzo[8]annulen-5(8H)-one (4)

The *Z*-ester **5** (2.5 g, 8.62 mmol) was taken in a 50 mL round bottom flask and methanol (25 mL) was added to it, followed by addition of 5M KOH solution (3.5 mL). The reaction mixture was refluxed for 3 h and acidified using 5% HCl solution (75 mL). It was, then, extracted using CH_2Cl_2 (50 mL x 3); the combined organic layers were washed



4

with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude acid was taken in a 100 mL round bottom flask and to this was added CH_2Cl_2 (25 mL), under N_2 atmosphere. It was, then, cooled to 0 ^oC and oxalyl chloride (2.2 g, 17.2 mmol) was added to it, dropwise. The reaction mixture was stirred at the same temperature for 3 h and then CH_2Cl_2 was evaporated under reduced pressure, at room temperature. The crude acid chloride was taken in CH_2Cl_2 (50 mL) and cooled to -20 ^oC, followed by addition of anhydrous $AlCl_3$ (1.26 g, 9.5 mmol), under N_2 atmosphere. It was allowed to come to room temperature within 10 h, followed by quenching using 10% HCl solution (50 mL). It was then extracted using CH_2Cl_2 (30 mL x 3). The combined organic layers were washed with water (60 mL), brine (60 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatogrphed using flash silica gel (pet. ether : EtOAc, 98 : 2) to provide cyclic enone **4** (0.85 g) as a white solid.

Mp **:** 65 ^oC

Molecular Formula **:** $C_{16}H_{20}O_2$

Yield **:** 40% overall.

Specific Rotation **:** $[\alpha]^{25}_D$ -220.13 (*c* 1.7, $CHCl_3$)

IR ($CHCl_3$) ν_{max} (cm^{-1}) **:** 3009, 2959, 1710, 1624, 1600.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.35 (d, *J* = 6.9 Hz, 3H); 1.58-2.02 (m, 4H); 2.02 (s, 3H); 2.19 (s, 3H); 3.08-3.27 (m, 1H); 3.86 (s, 3H); 6.44 (triplet of doublet, *J* = 9.0, 1.4 Hz, 1H); 6.64 (s, 1H); 7.41 (d, *J* = 0.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 15.6 (CH_3); 18.2 (CH_3); 21.2 (CH_3); 25.5 (CH_2); 31.7 (CH); 39.3 (CH_2); 55.3 (CH_3); 104.7 (CH); 124.5 (C); 132.2 (CH); 135.0 (C); 138.9 (CH); 141.3 (C); 143.0 (C); 160.6 (C); 195.4 (C).

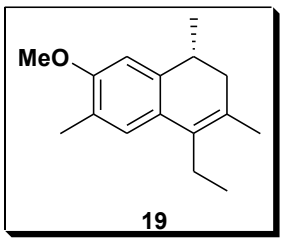
MS-ESI m/z **:** 245 $(M+1)^+$

Analysis

Expected **:** C, 78.65%; H, 8.25%

Found **:** C, 78.79%; H, 8.56%

(*R*)-4-Ethyl-7-methoxy-1,3,6-trimethyl-1,2-dihydronaphthalene (19)



19

Enone **4** (0.1 g, 0.41 mmol) was taken in diethylene glycol (5 mL) in a 25 mL single neck round bottom flask, equipped with a magnetic stir bar and a reflux condenser. Hydrazine monohydrate (0.1 g, 2 mmol), hydrazine dihydrochloride (0.2 g, 2 mmol) and KOH (85%) (0.6 g, 9.1 mmol) was added to it at room temperature and the reaction mixture was heated at 150 ^{o}C for 3 h, and then at 210 ^{o}C for additional 12 h. The reaction mixture was cooled to room temperature and diluted using water (25 mL), and extracted with ethyl acetate (25 mL x 3). The combined organic layers were washed using water (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (per. ether : EtOAc, 99 : 1) to give **19** (47 mg) as a pale yellow oil.

Molecular Formula **:** $C_{16}H_{22}O$

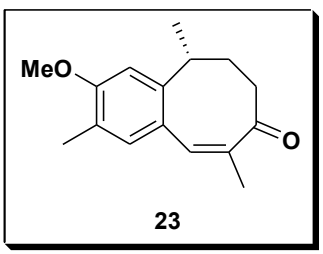
Yield **:** 50%

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.08 (t, *J* = 7.6 Hz, 3H); 1.18 (d, *J* = 7.0 Hz, 3H); 1.88 (s, 3H); 2.20 (s, 3H); 2.33-2.58 (m, 2H); 2.51 (q, *J* = 7.6 Hz, 2H); 2.73-2.83 (m, 1H); 3.83 (s, 3H); 6.63 (s, 1H); 7.03 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 13.8 (CH_3); 16.2 (CH_3); 20.1 (CH_3); 20.3 (CH_3); 21.0 (CH_2); 32.8 (CH); 38.6 (CH_2); 55.3 (CH_3); 108.4 (CH); 123.5 (C); 125.4 (CH); 126.7 (C); 127.4 (C); 130.3 (C); 139.7 (C); 155.8 (C).

MS-ESI m/z **:** 231 $(M+1)^+$; 201 $(M-CH_2CH_3)^+$; 253 $(M+Na)^+$

Isoparvifolinone methyl ether (23)[14]



23

Enone **4** (0.4 g, 1.64 mmol) was taken in a 25 mL round bottom flask and methanol (5 mL) was added to it, followed by $CeCl_3$-$7H_2O$ (1.22 g, 3.28 mmol). It was cooled to 0 ^{o}C, $NaBH_4$ (62 mg, 1.64 mmol) was added to it portionwise and stirred for 30 min, the reaction mixture was diluted using saturated NH_4Cl solution (30 mL) and extracted using ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and

concentrated under reduced pressure. The crude alcohol was taken in a 50 mL round bottom flask together with CH_2Cl_2 (20 mL), under N_2 atmosphere. Pyridinium chlorochromate over silica gel (1: 1) (2 g, 4.92 mmol) was added to it, followed by 2 h stirring. Finally, it was filtered over celite and was washed using CH_2Cl_2 (100 mL). The combined organic layers were concentrated under reduced pressure and the residue was chromatographed using flash silica gel (pet. ether : EtOAc, 97 : 3) to provide **23** (0.24 g) as a pale yellow oil.

Molecular Formula : $C_{16}H_{20}O_2$

Yield : 60%

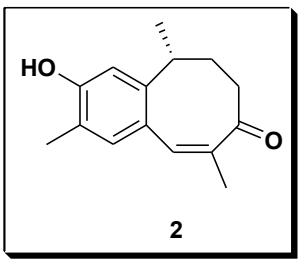
Specific Rotation : $[\alpha]^{25}_D$ +597.2 (*c* 1.1, $CHCl_3$)

IR ($CHCl_3$) ν_{max} (cm^{-1}) : 1648, 1610.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.30 (d, *J* = 6.7 Hz, 3H); 1.49-1.65 (m, 1H); 2.01 (d, *J* = 1.4 Hz, 3H); 2.20 (s, 3H); 2.11-2.27 (m, 2H); 2.41-2.58 (m, 1H); 2.91-3.07 (m, 1H); 3.87 (s, 3H); 6.76 (s, 1H); 7.02 (s, 1H); 7.08 (bs, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 15.6 (CH_3); 19.5 (CH_3); 20.5 (CH_3); 33.8 (CH); 39.0 (CH_2); 42.0 (CH_2); 55.2 (CH_3); 106.0 (CH); 124.3 (C); 128.9 (C); 132.7 (CH); 136.4 (C); 139.1 (CH); 143.6 (C); 158.4 (C); 204.0 (C).

Isoparvifolinone (2)[1b]



2

A solution of *O*-methylisoparvifolinone **23** (90 mg, 0.37 mmol) was treated with BBr_3 (2 mL, 1.0 M in CH_2Cl_2) in CH_2Cl_2 (5 mL), stirred at room temperature for 1 h and quenched with saturated $NaHCO_3$ solution (30 mL). It was extracted using CH_2Cl_2 (20 mL x 3), the combined organic layers were washed using brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 95 : 5) to give isoparvifolinone **2** (51 mg) as a white solid.

Mp : 157-158 ^oC {lit.[1b] mp 157-158 ^oC}

Molecular Formula : $C_{15}H_{18}O_2$

Yield : 60%

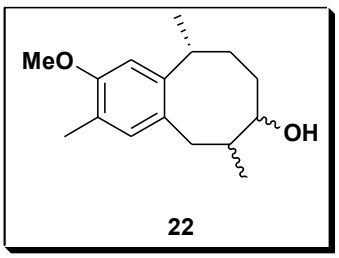
Specific Rotation **:** $[\alpha]^{25}_{D}$ +850 (*c* 1, $CHCl_3$) {lit.[1b] $[\alpha]^{25}_{D}$ +854, (*c* 1, $CHCl_3$)}

IR ($CHCl_3$) ν_{max} (cm^{-1}) **:** 3596, 3364, 3020, 2969, 1638, 1581.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.24 (d, *J* = 6.8 Hz, 3H); 1.45-1.61 (m, 1H); 2.02 (d, *J* = 1.2 Hz, 3H); 2.10-2.25 (m, 2H); 2.25 (s, 3H); 2.45-2.59 (m, 1H); 2.88-2.99 (m, 1H); 6.08 (bs, 1H); 6.79 (s, 1H); 7.03 (s, 1H); 7.10 (bs, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 15.3 (CH_3); 19.5 (CH_3); 20.6 (CH_3); 33.4 (CH); 39.1 (CH_2); 42.0 (CH_2); 111.4 (CH); 121.7 (C); 129.2 (C); 133.4 (CH); 136.3 (C); 139.7 (CH); 144.1 (C); 155.1 (C); 204.8 (C).

(*10R*)-2-methoxy-3,6,10-trimethyl-5,6,7,8,9,10-hexahydrobenzo[8]annulen-7-ol (22)[14]



22

Enone **23** (0.3 g, 1.23 mmol) was taken in a 25 mL round bottom flask and methanol (3 mL) was added to it, followed by addition of 10% Pd/C (30 mg). The reaction mixture was stirred under hydrogen atmosphere for 24 h and then $NaBH_4$ (47 mg, 1.23 mmol) was added to it at 0 ^oC and stirred for 30 min. It was finally quenched using dilute HCl solution (5%, 30 mL) and extracted with CH_2Cl_2 (30 mL x 2). The combined organic layers were washed using brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 95 : 5) to provide alcohol **22** (0.166 g) as a colourless oil.

Molecular Formula **:** $C_{16}H_{24}O_2$

Yield **:** 55%

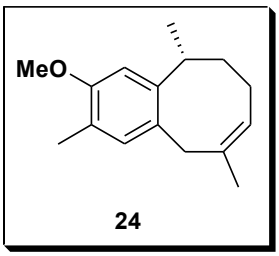
Specific Rotation **:** $[\alpha]^{25}_{D}$ -58.94 (*c* 1.1, $CHCl_3$)

IR ($CHCl_3$) ν_{max} (cm^{-1}) **:** 3616, 3454, 2958, 1614, 1578.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.96 (d, *J* = 6.9 Hz, 3H); 1.32 (d, *J* = 6.8 Hz, 3H); 1.25-1.53 (m, 3H); 1.70-2.04 (m, 3H); 2.17 (s, 3H); 2.31 (dd, *J* = 14.2, 3.5 Hz, 1H); 3.04-3.31 (m, 3H); 3.81 (s, 3H); 6.66 (s, 1H); 6.82 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 15.7 (CH_3); 17.4 (CH_3); 21.8 (CH_3); 32.4 (CH_2); 33.2 (CH_2); 34.7 (CH); 37.2 (CH_2); 41.6 (CH); 55.3 (CH_3); 75.4 (CH); 106.7 (CH); 122.7 (C); 128.5 (C); 133.3 (CH); 143.2 (C); 156.6 (C).

_O_-Methylparvifoline (24)[14]



24

A cold solution of **22** (0.1 g, 0.40 mmol) in pyridine (2 mL) was treated with *p*-TsCl (0.23 g, 1.22 mmol). The reaction mixture was stirred at -4 ^{o}C for 3 days and then heated at 100 ^{o}C for 10 h. It was diluted with EtOAc (50 mL) washed with dilute HCl solution (10%, 50 mL), saturated $NaHCO_3$ solution (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 99.5 : 0.5) to provide *O*-methylparvifoline **24** (60 mg) as a colourless oil.

Molecular Formula **:** $C_{16}H_{22}O$

Yield **:** 65%

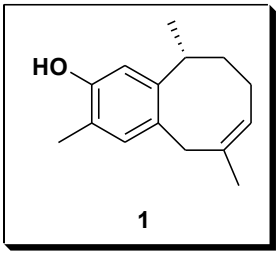
Specific Rotation **:** $[\alpha]^{25}_{D}$ -200 (*c* 1 , $CHCl_3$)

IR ($CHCl_3$) ν_{max} (cm^{-1}) **:** 1614, 1577, 1500.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.10-1.16 (m, 1H); 1.35 (d, *J* = 7.0 Hz, 3H); 1.55-1.75 (m, 2H); 1.75 (s, 3H); 1.75-1.82 (m, 1H); 2.15 (s, 3H); 3.02 (d, *J* = 18.3 Hz, 1H); 3.15-3.22 (m, 1H); 3.52 (d, *J* = 18.3 Hz, 1H); 3.81 (s, 3H); 5.34 (t, *J* = 7.5 Hz, 1H); 6.61 (s, 1H), 6.88 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 15.7 (CH_3); 19.5 (CH_3); 23.8 (CH_2); 26.5 (CH_3); 33.4 (CH); 40.1 (CH_2); 41.8 (CH_2); 55.3 (CH_3); 106.2 (CH); 123.2 (C); 123.5 (CH); 130.1 (C); 131.9 (CH); 137.7 (C); 143.3 (C); 157.1(C).

(-)-Parvifoline (1)[1a]



1

Ethanethiol (1 mL) was treated with n-BuLi (5 mL, 1.6 M in hexane) at -78 ^{o}C. The white solid (EtSLi) (0.103 g, 1.52 mmol) was added to a solution of **24** (70 mg, 0.30 mmol) in dry DMF (3 mL), under N_2 atmosphere. The reaction mixture was stirred at 105 ^{o}C for 24 h, cooled to room temperature and diluted with EtOAc (25 mL). The organic layer was washed with water (25 mL x 2), brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 9 : 1) and then purified by

preparative TLC (pet. ether : EtOAc, 95 : 5) to furnish parvifoline **1** (59 mg) as a white solid.

Mp **:** 85 ^{o}C {lit.[1a] 89-90 ^{o}C, crystallized from hexane : acetone}

Molecular Formula **:** $C_{15}H_{20}O$

Yield **:** 90%

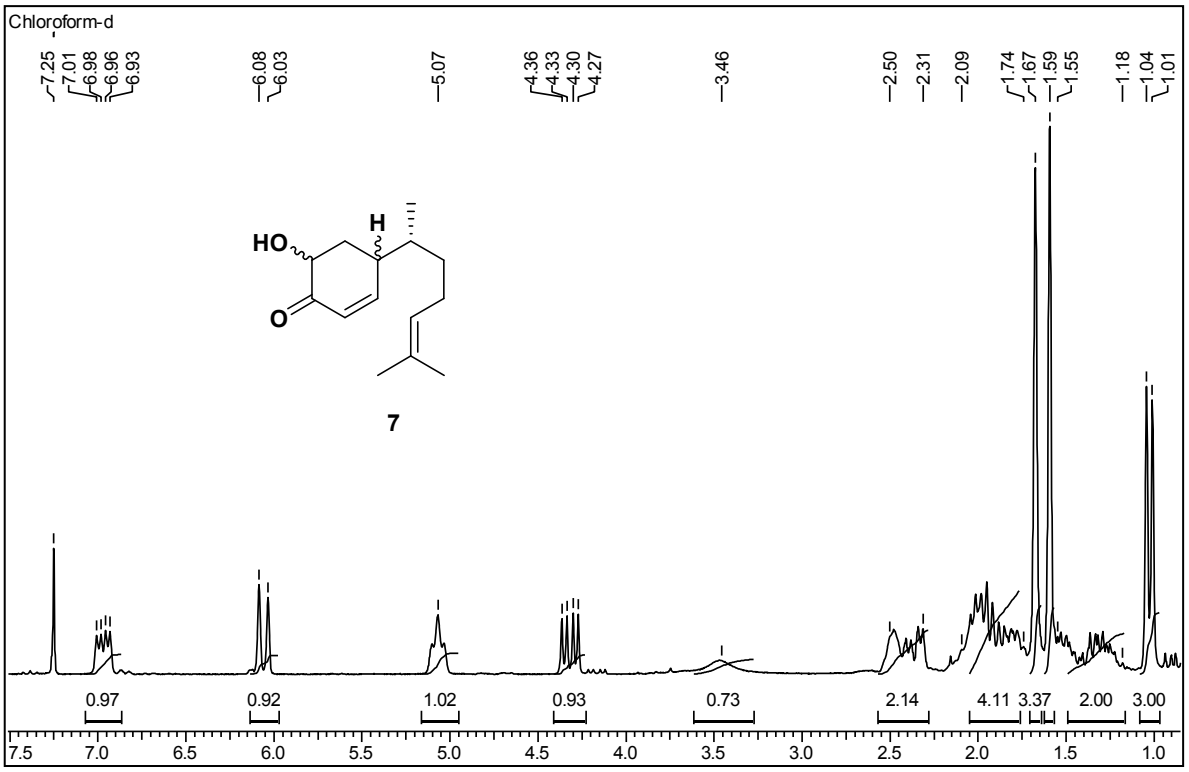
Specific Rotation **:** $[\alpha]^{25}_{D}$ -168 (*c* 1.73, $CHCl_3$) {lit.[1a] $[\alpha]^{25}_{D}$ –173, *c* 1.73, $CHCl_3$}

IR ($CHCl_3$) ν_{max} (cm^{-1}) **:** 3602, 3369, 1619.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.04-1.13 (m, 1H); 1.31 (d, *J* = 7.0 Hz, 3H); 1.74 (s, 3H); 1.46-1.84 (m, 3H); 2.18 (s, 3H); 3.01 (d, *J* = 18.3 Hz, 1H); 3.04-3.20 (m, 1H); 3.51 (d, *J* = 18.3 Hz, 1H); 4.53 (bs, 1H); 5.34 (t, *J* = 7.0 Hz, 1H); 6.56 (s, 1H); 6.86 (s, 1H).

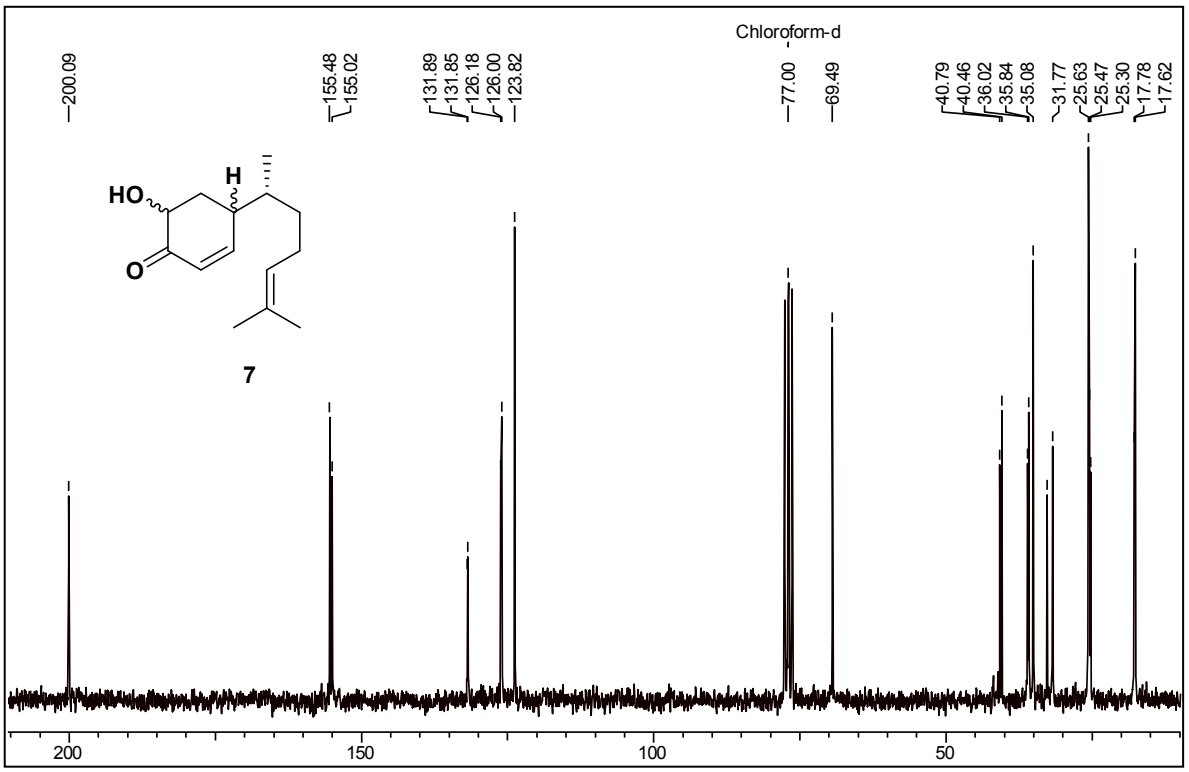
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 15.3 (CH_3); 19.4 (CH_3); 23.8 (CH_2); 26.4 (CH_3); 33.1 (CH); 40.1 (CH_2); 41.7 (CH_2); 111.2 (CH); 120.1 (C); 123.5 (CH); 130.7 (C); 131.9 (CH); 137.7 (C); 144.1 (C); 153.0 (C).

2.2.5 Spectra

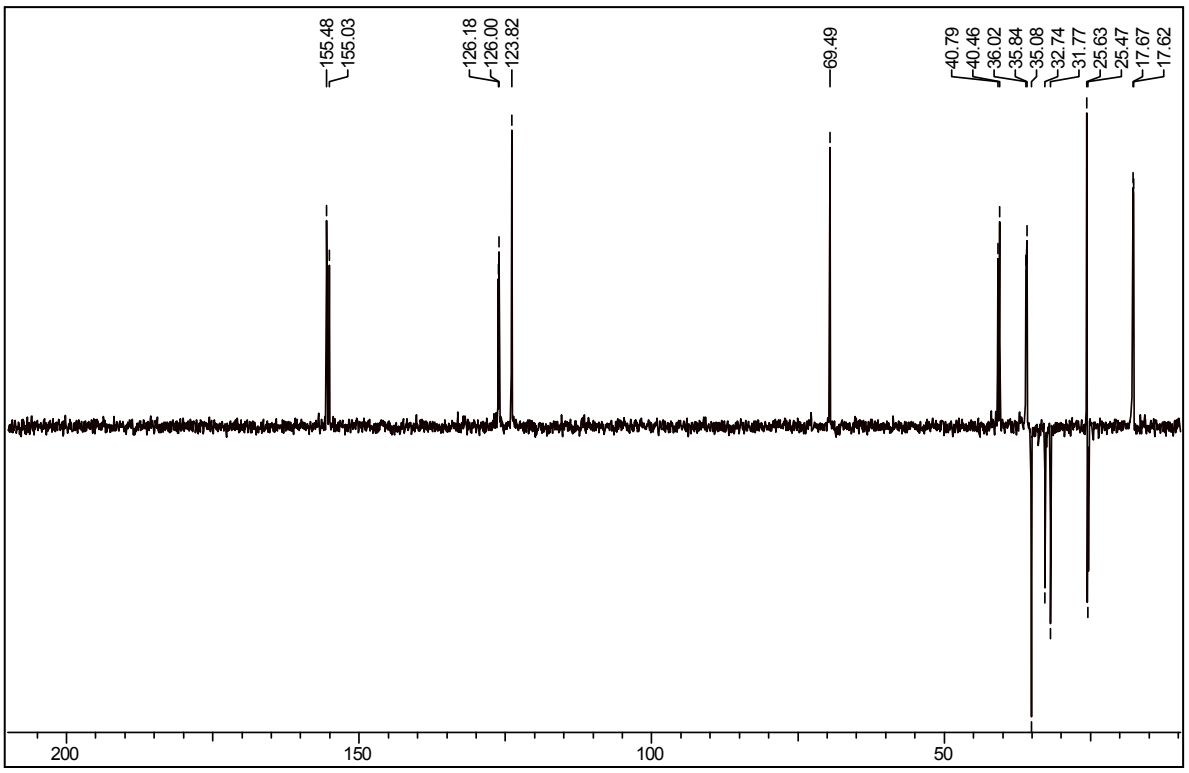


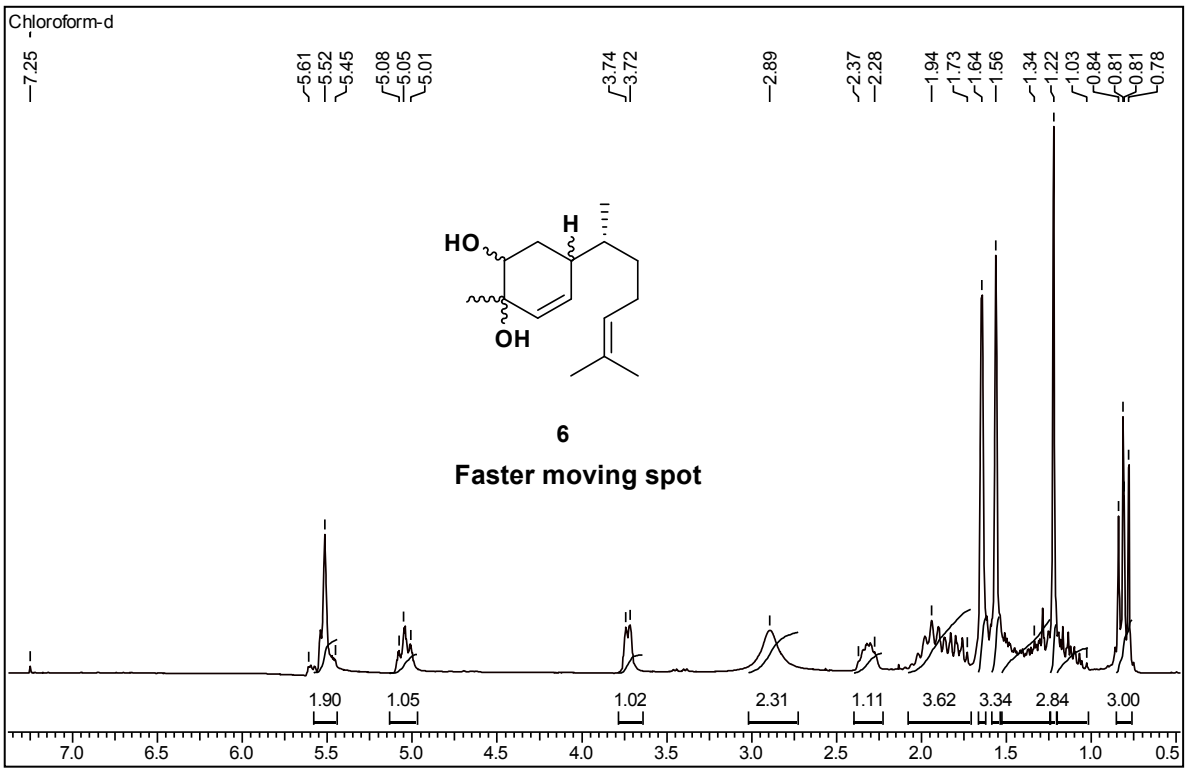
7

^{1}H NMR SPECTRUM ($CDCl_3$, 200 MHz)

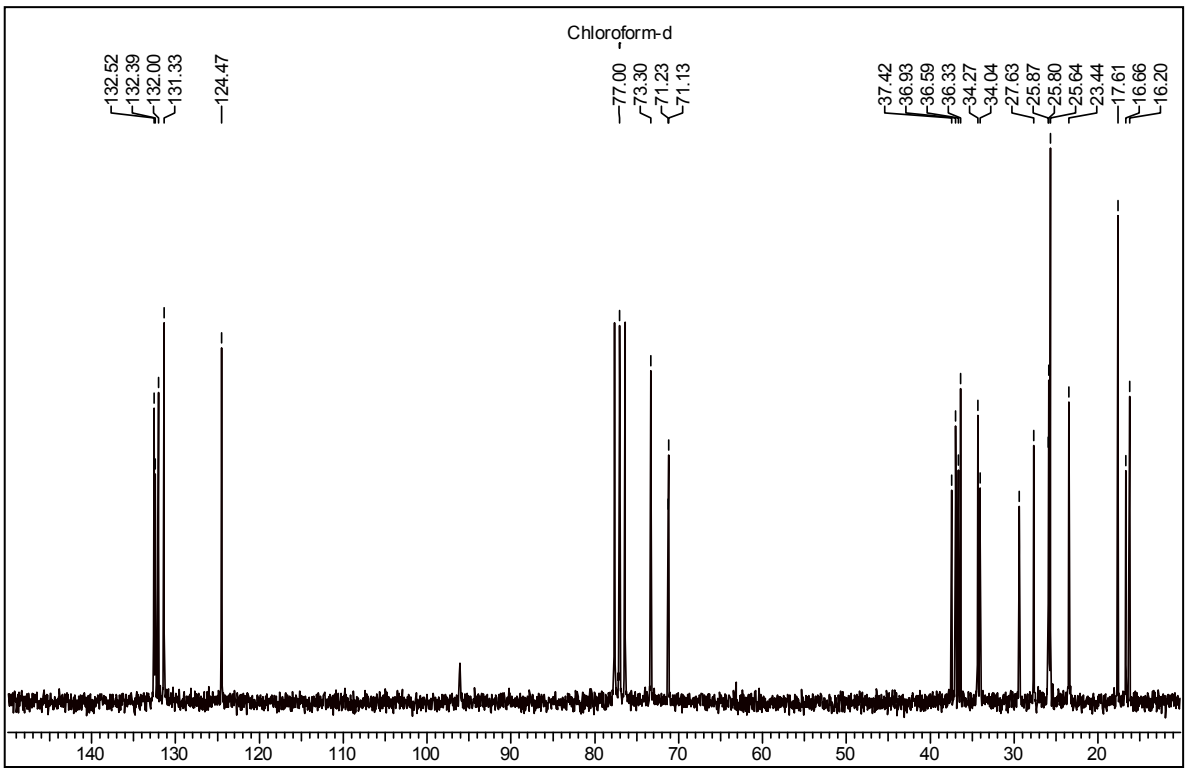


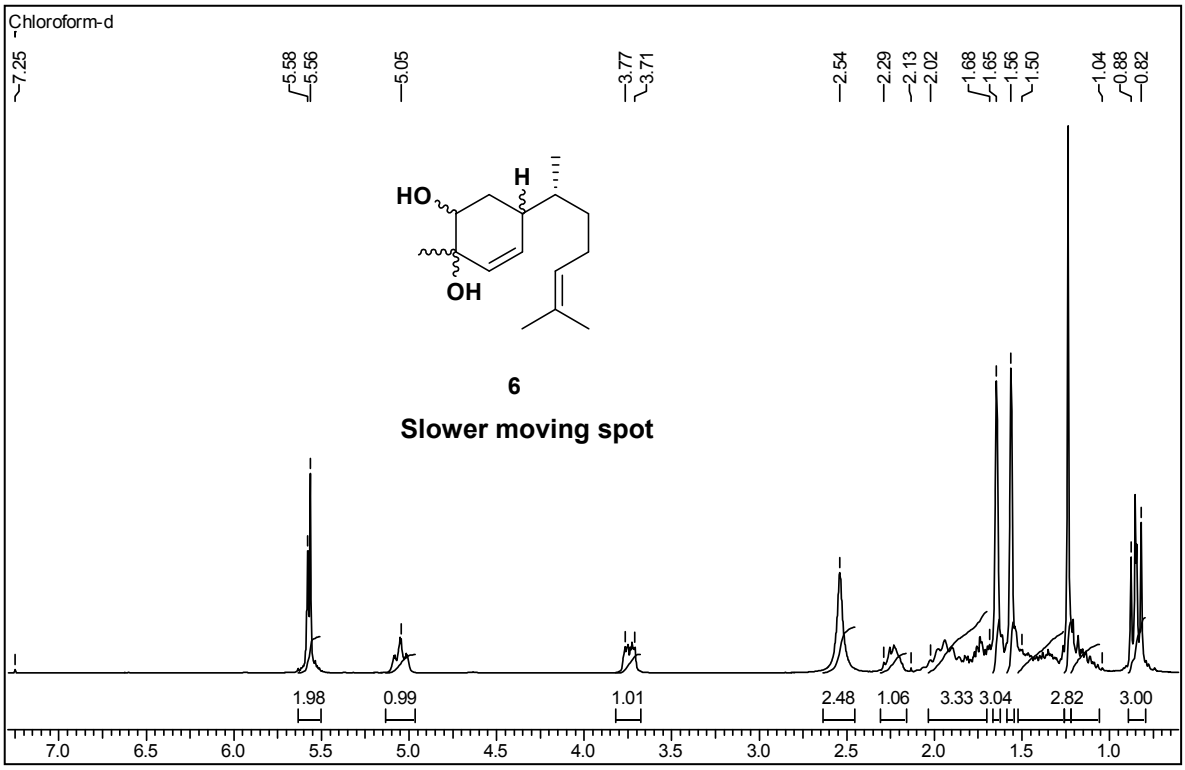
^{13}C & DEPT NMR SPECTRA ($CDCl_3$, 50 MHz)





^{1}H (200 MHz) & ^{13}C (50 MHz) NMR SPECTRA ($CDCl_3$)

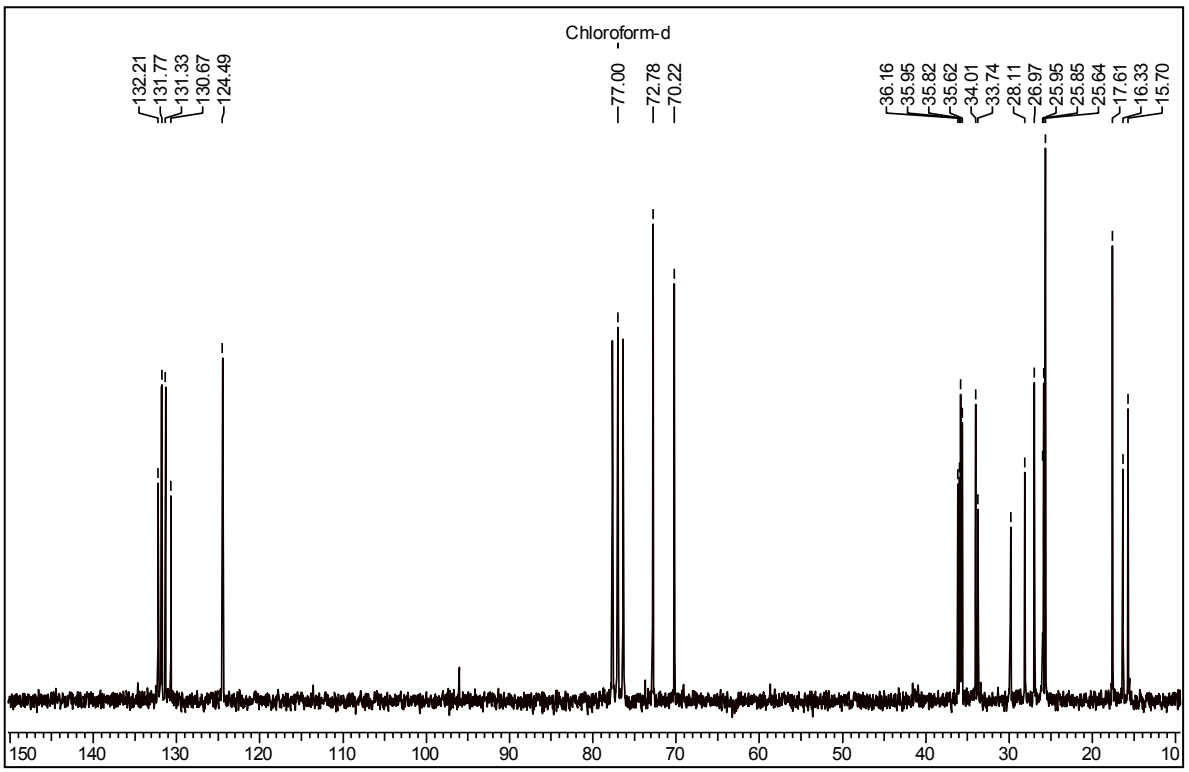


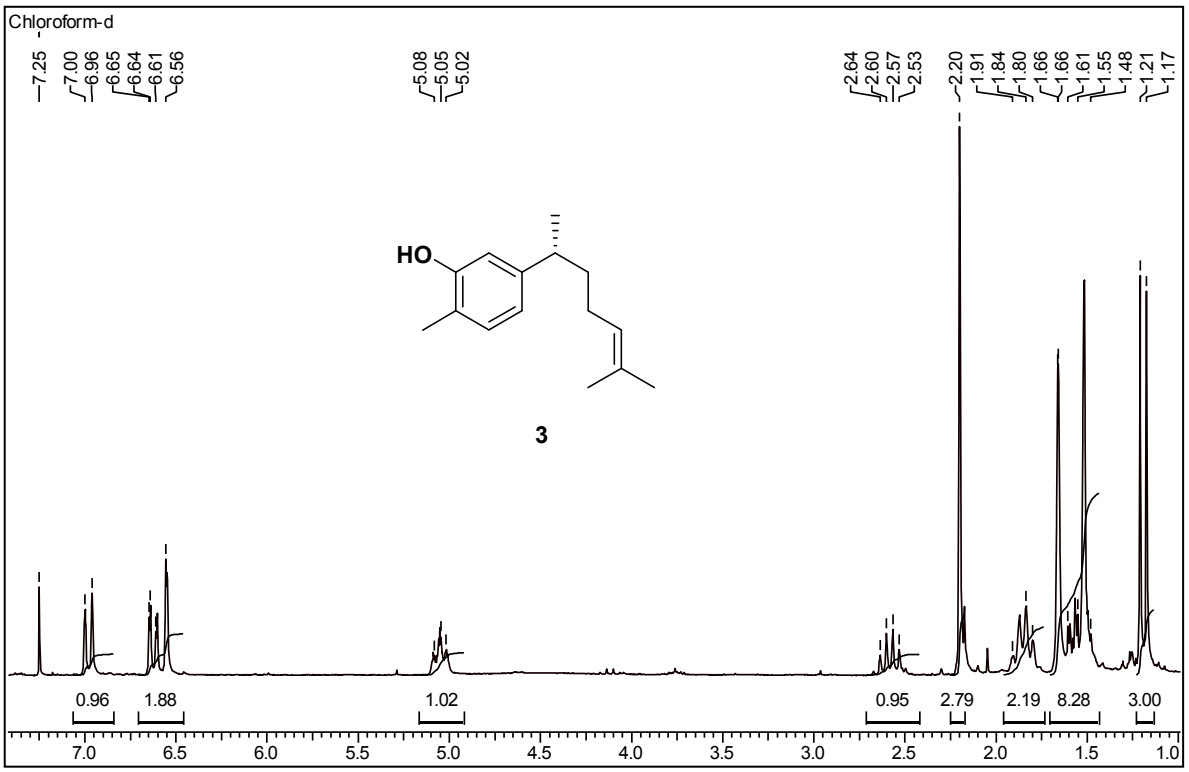


6

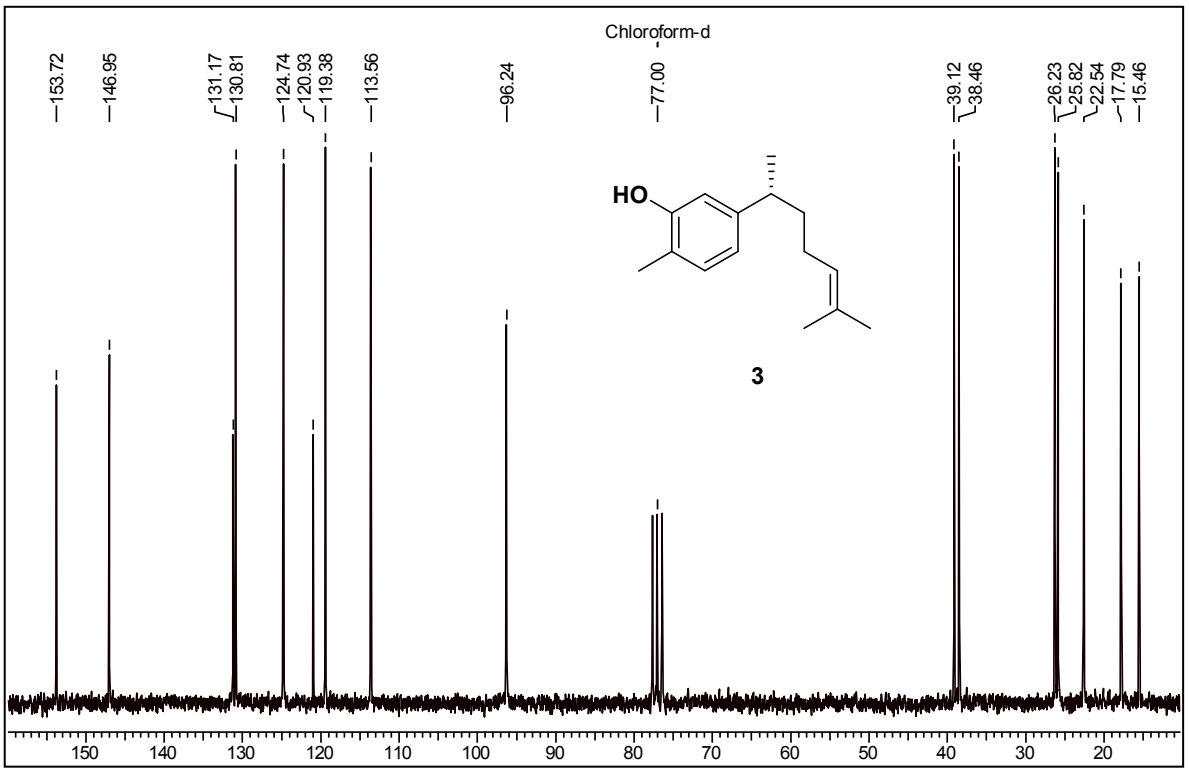
Slower moving spot

^{1}H (200 MHz) & ^{13}C (50 MHz) NMR SPECTRA ($CDCl_3$)

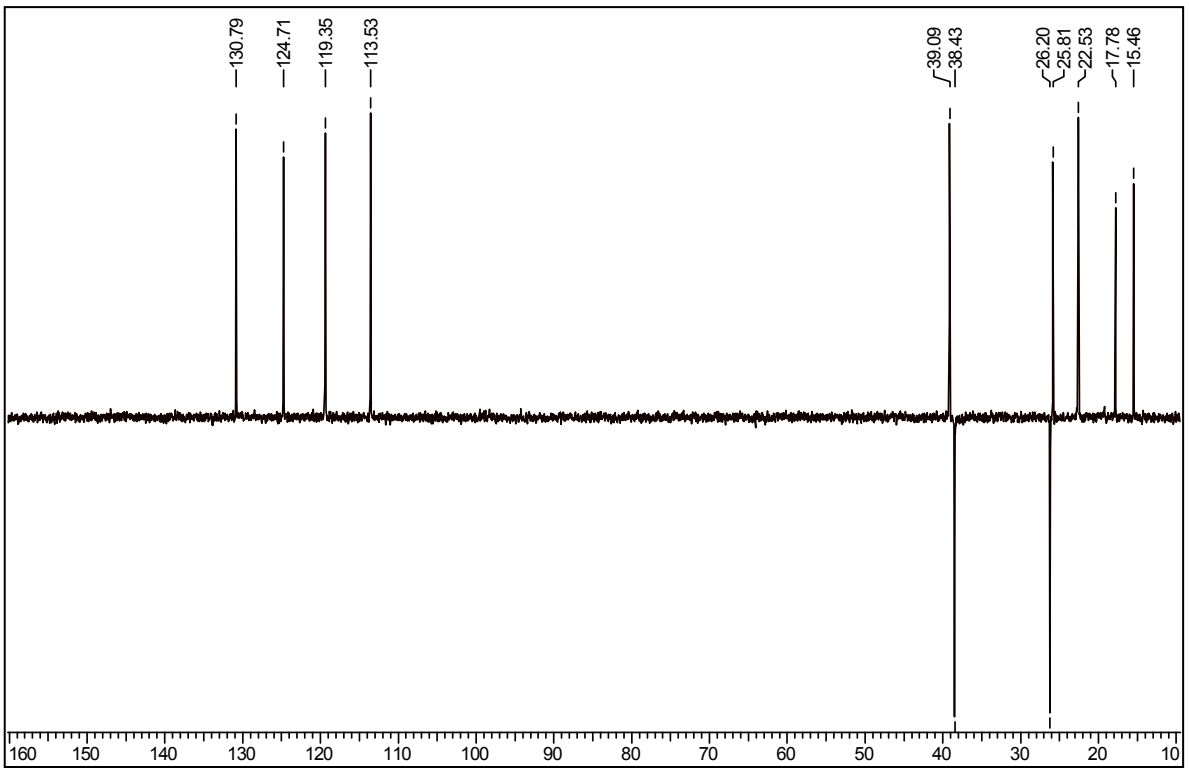


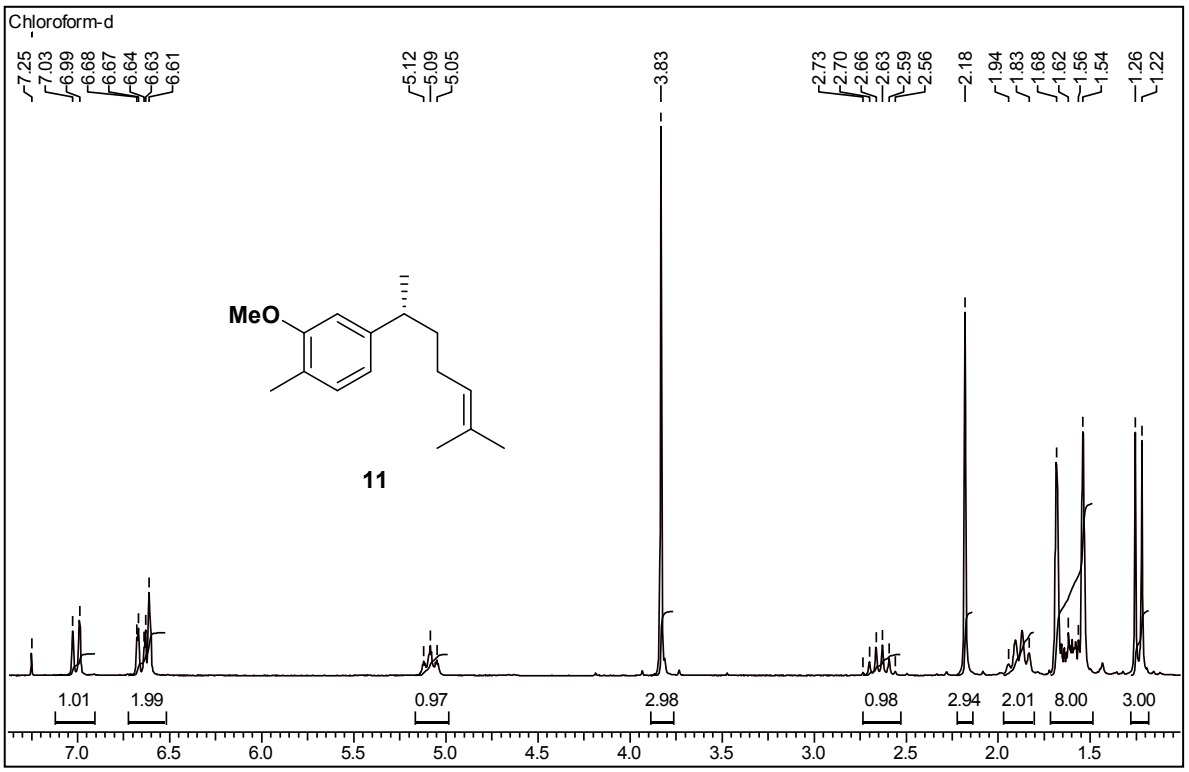


^{1}H NMR SPECTRUM ($CDCl_3$ + CCl_4, 200 MHz)

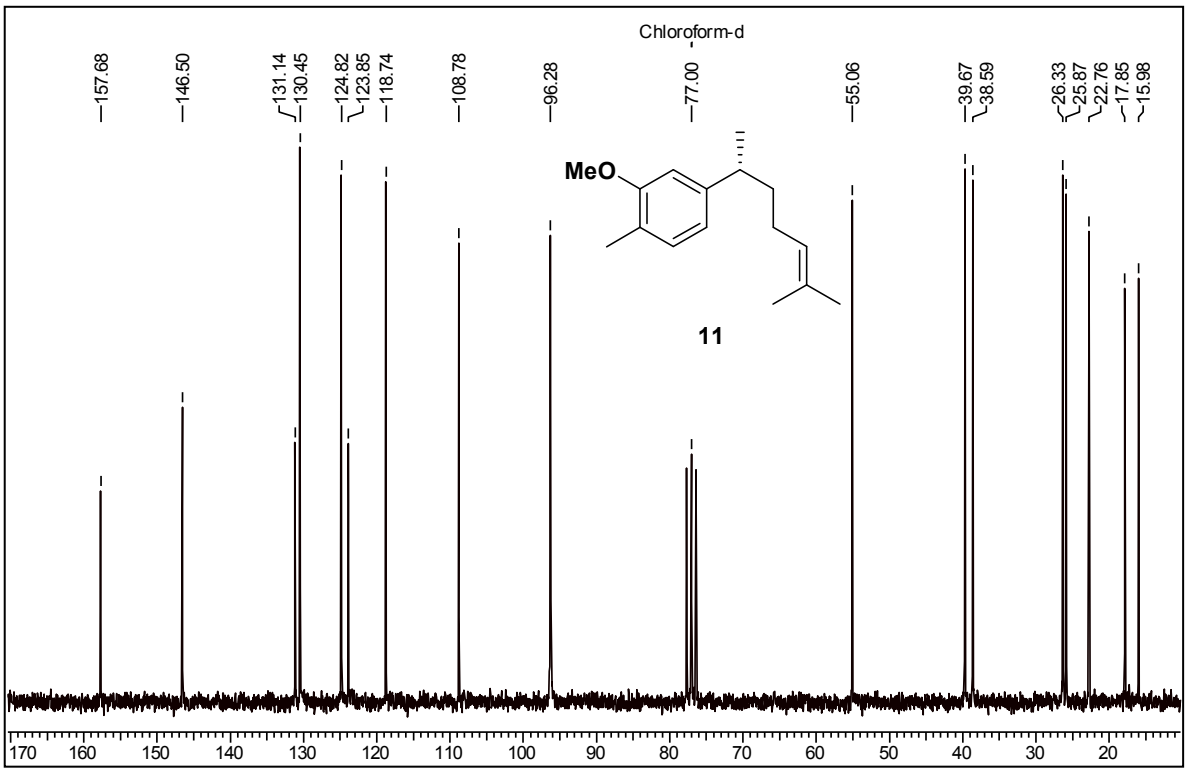


^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 50 MHz)

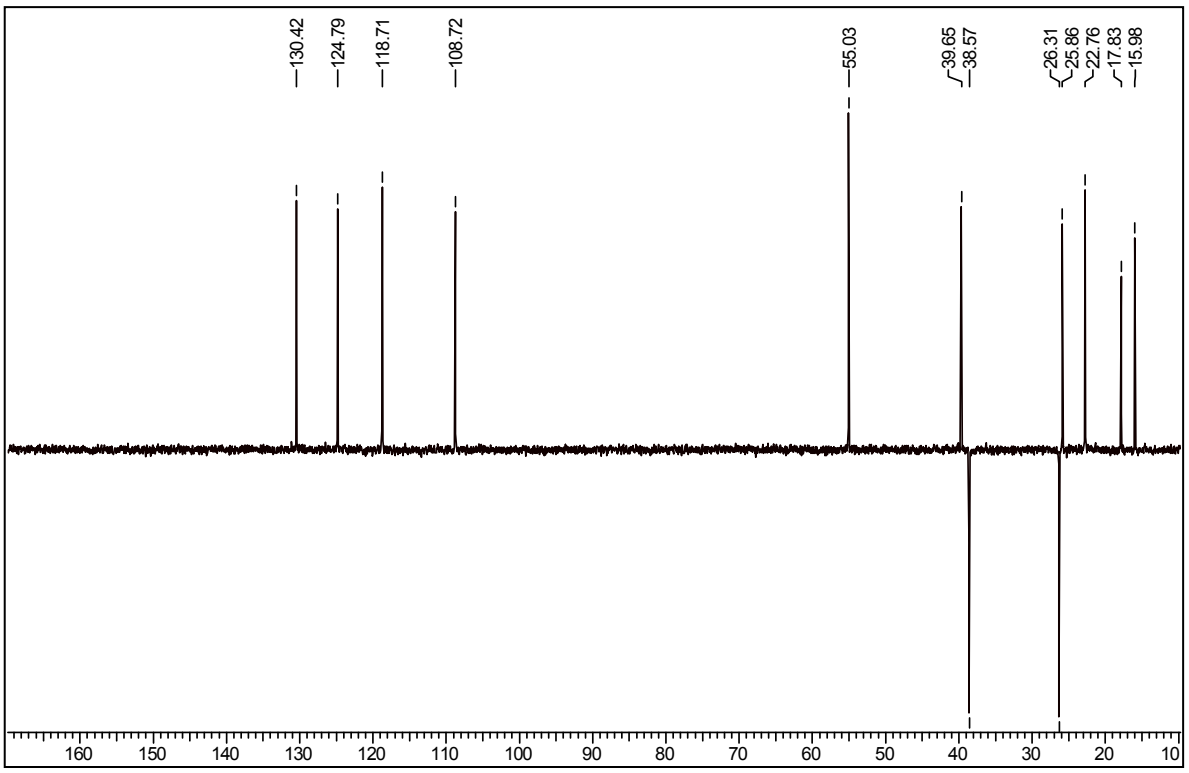


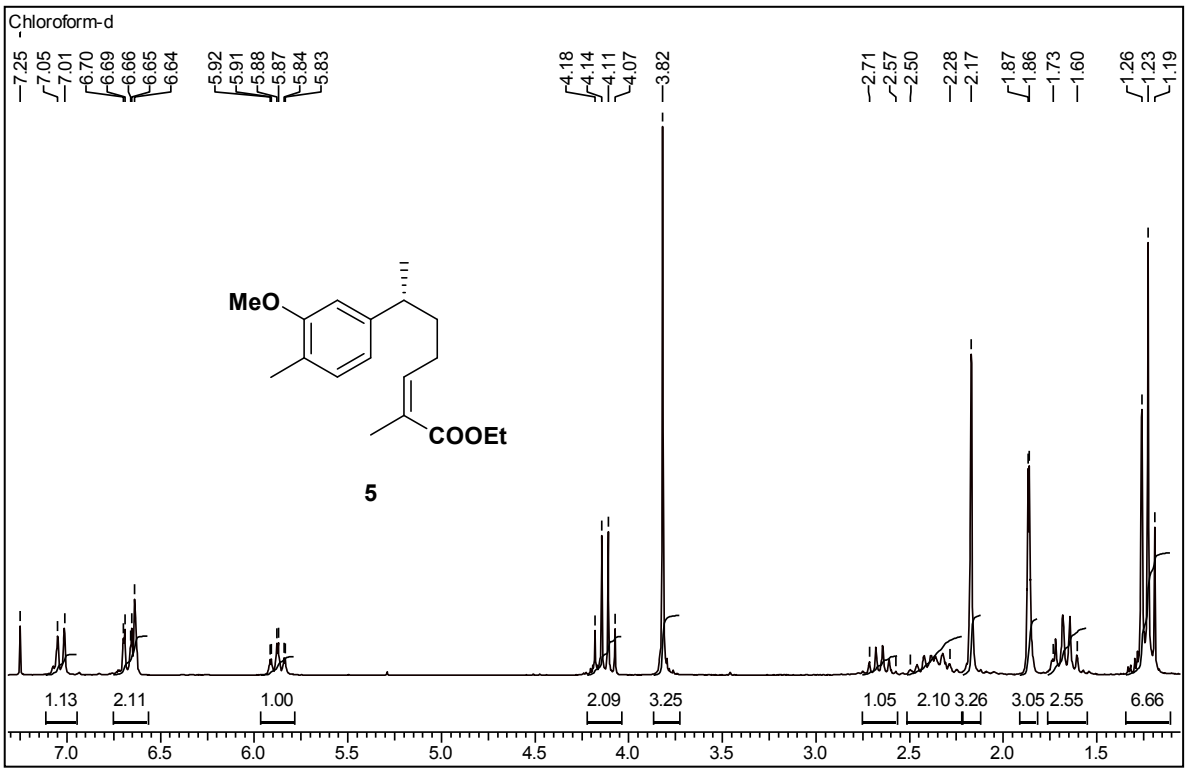


^{1}H NMR SPECTRUM ($CDCl_3$ + CCl_4, 200 MHz)

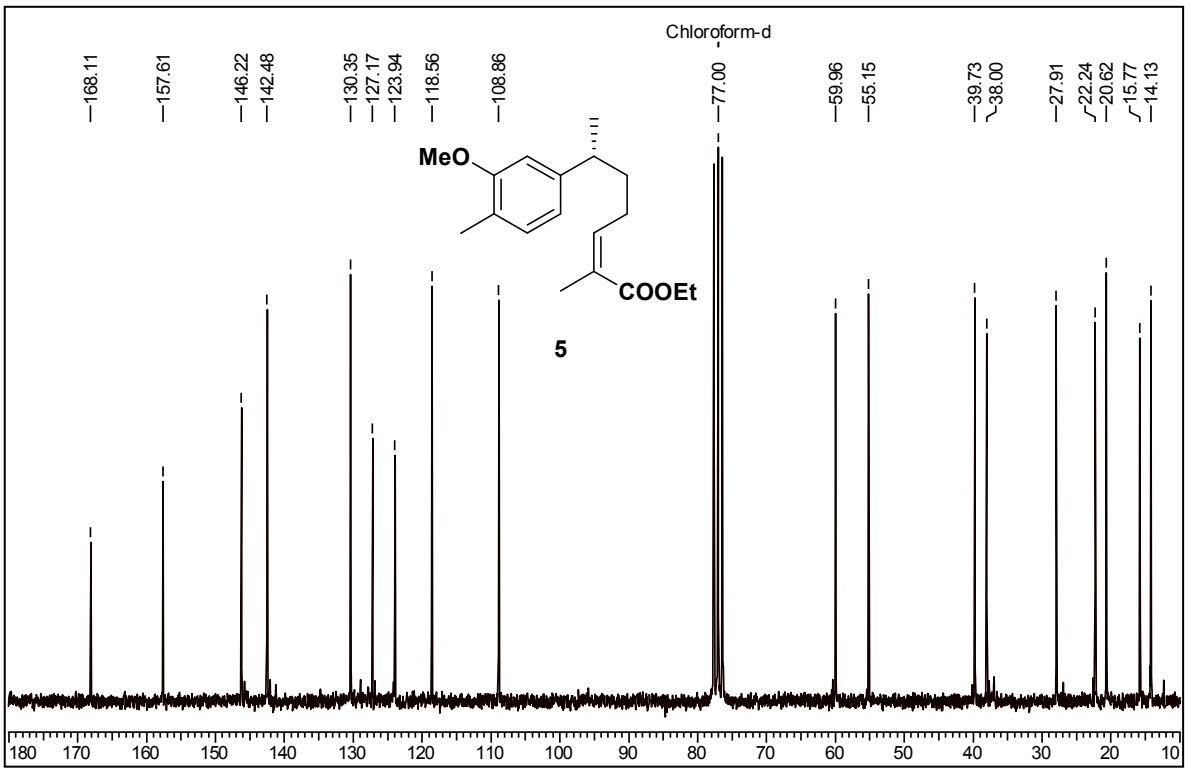


^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 50 MHz)

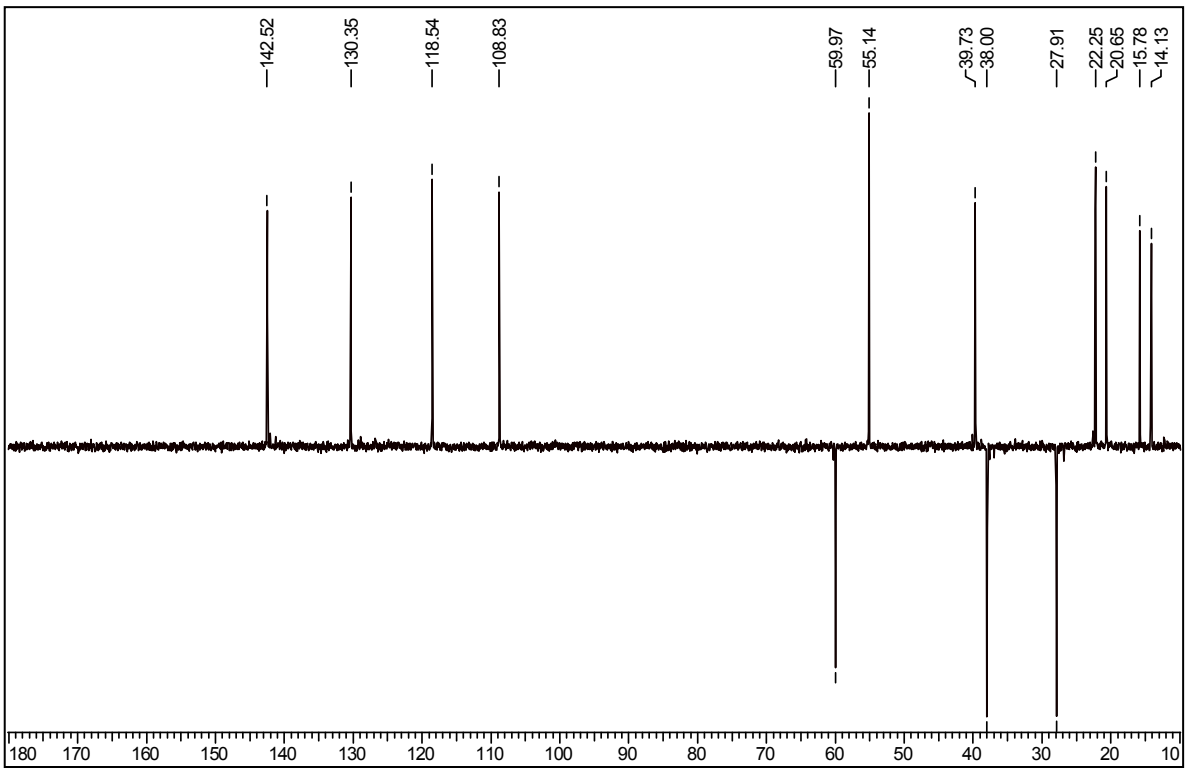


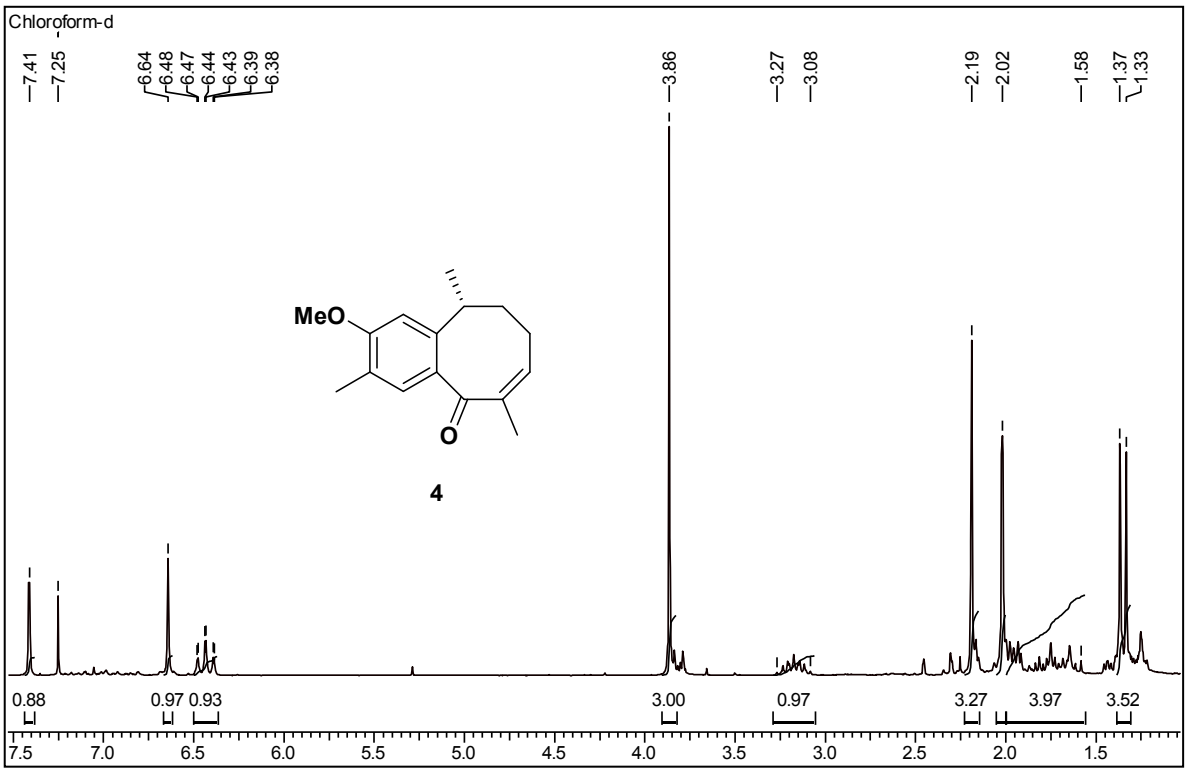


^{1}H NMR SPECTRUM ($CDCl_3$, 200 MHz)

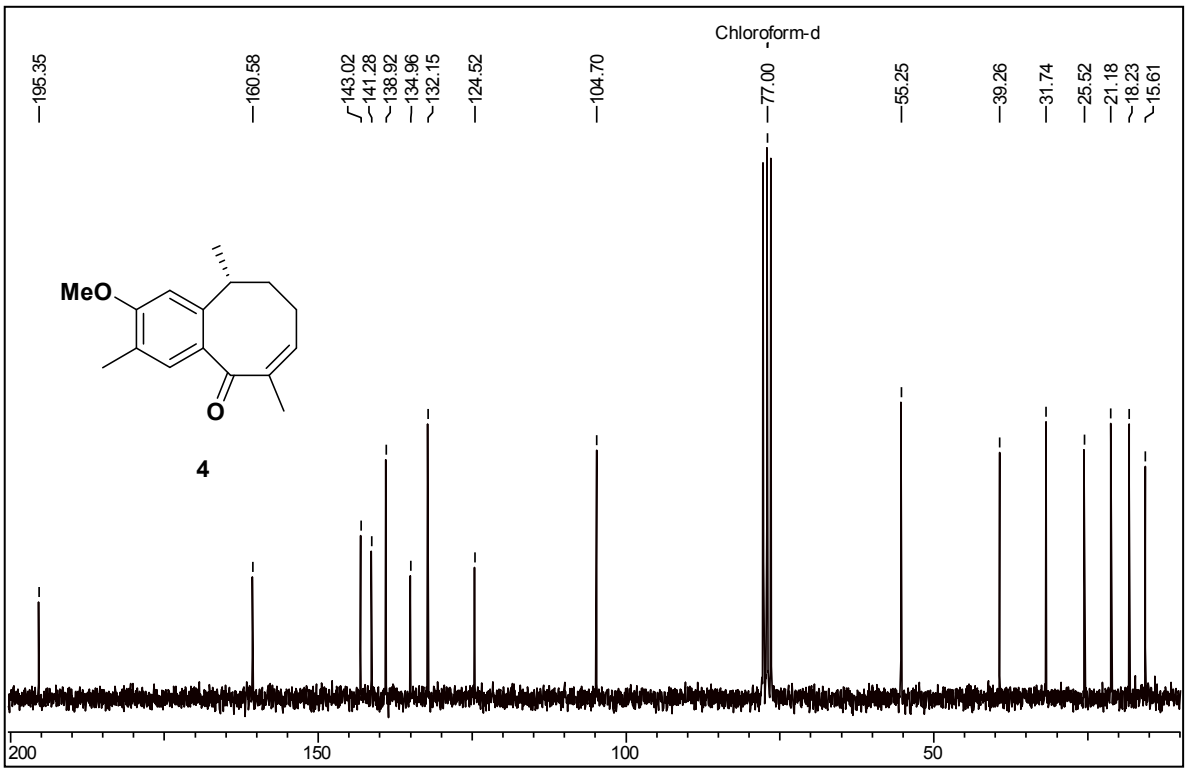


^{13}C & DEPT NMR SPECTRA ($CDCl_3$, 50 MHz)

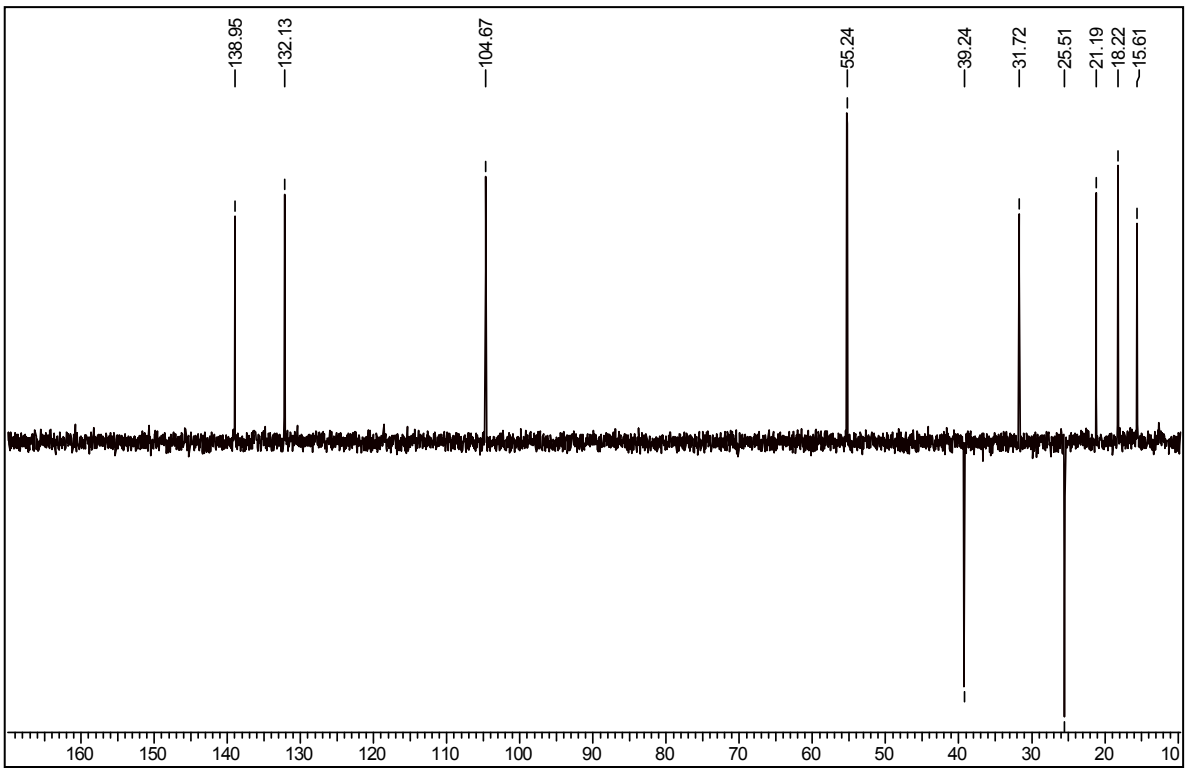


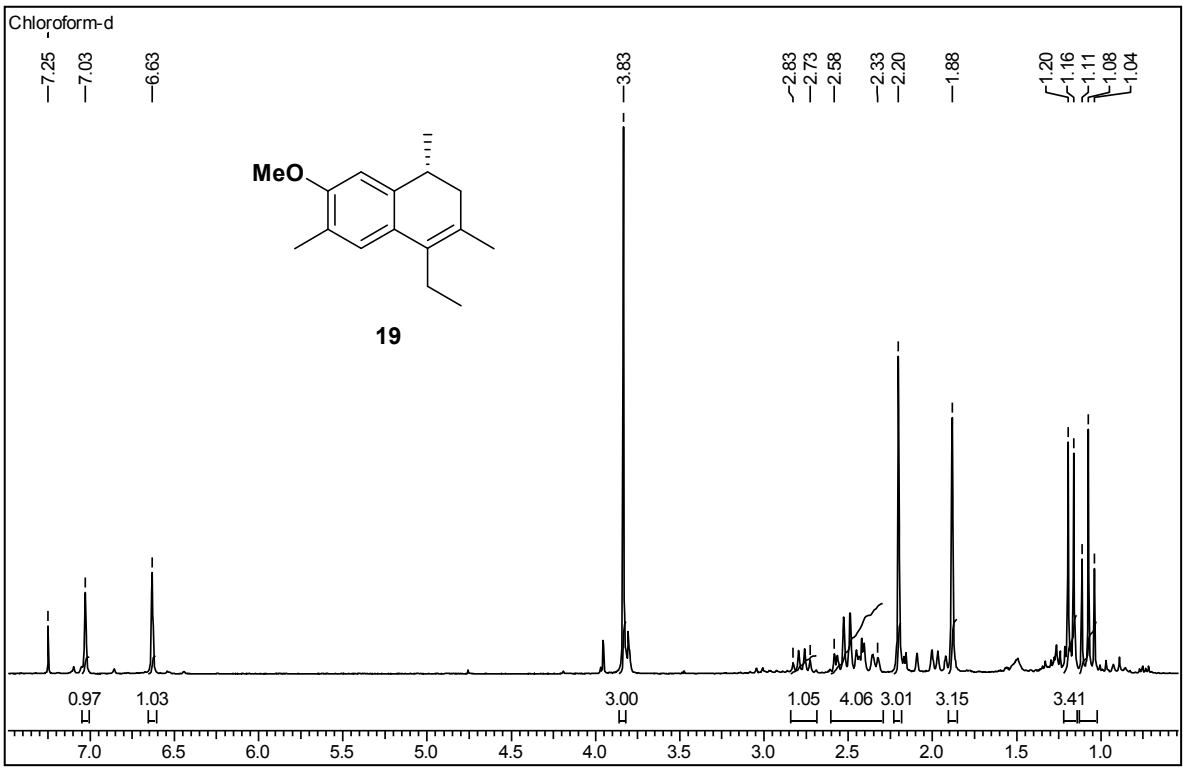


^{1}H NMR SPECTRUM ($CDCl_3$, 200 MHz)

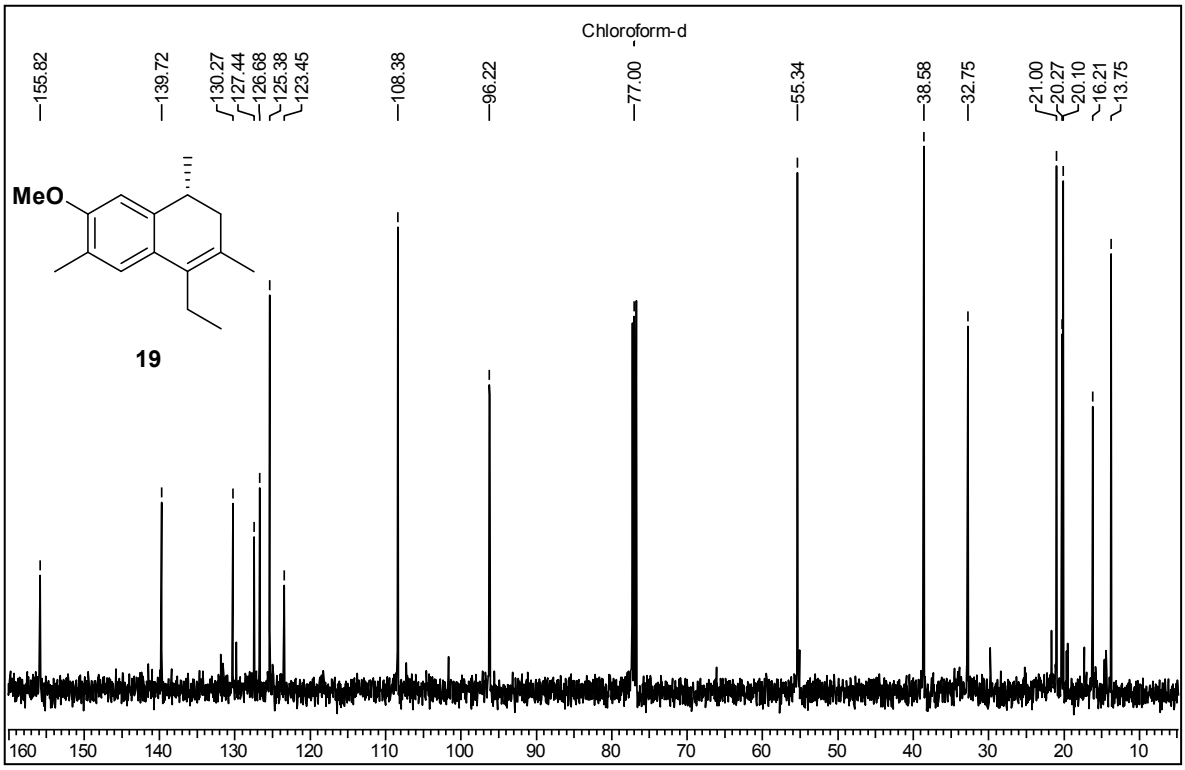


^{13}C & DEPT NMR SPECTRA ($CDCl_3$, 50 MHz)

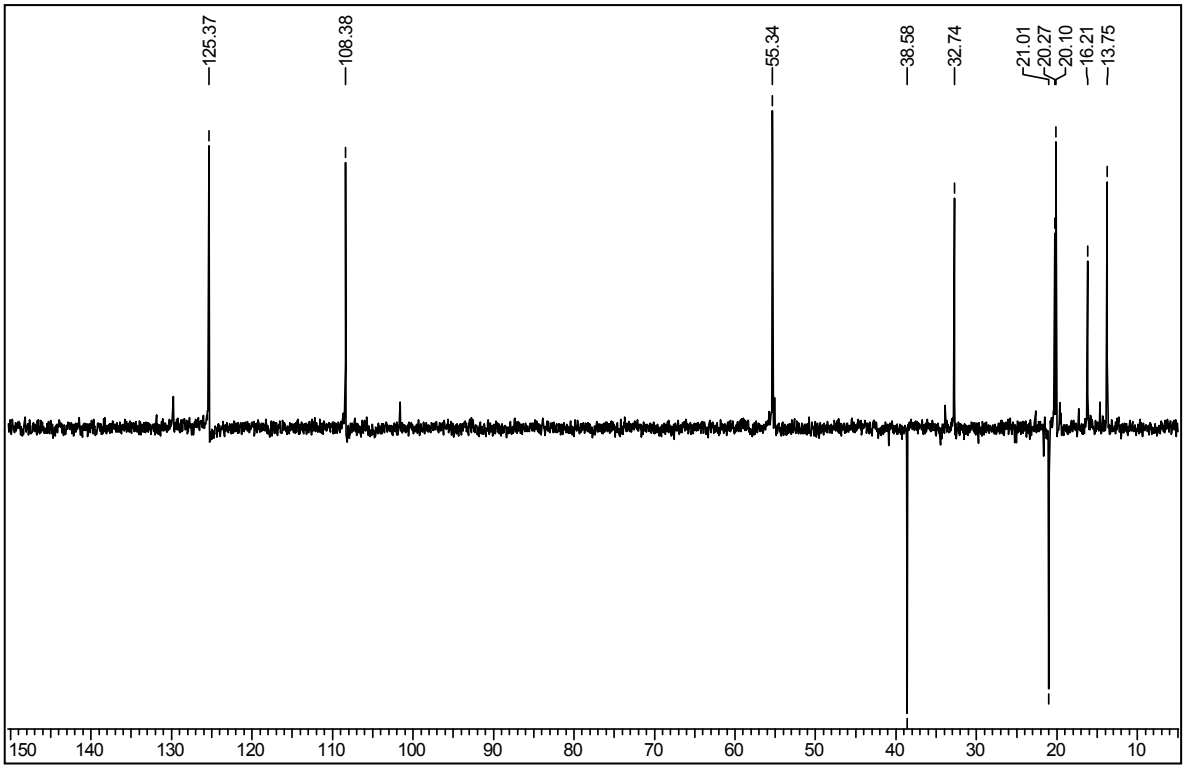


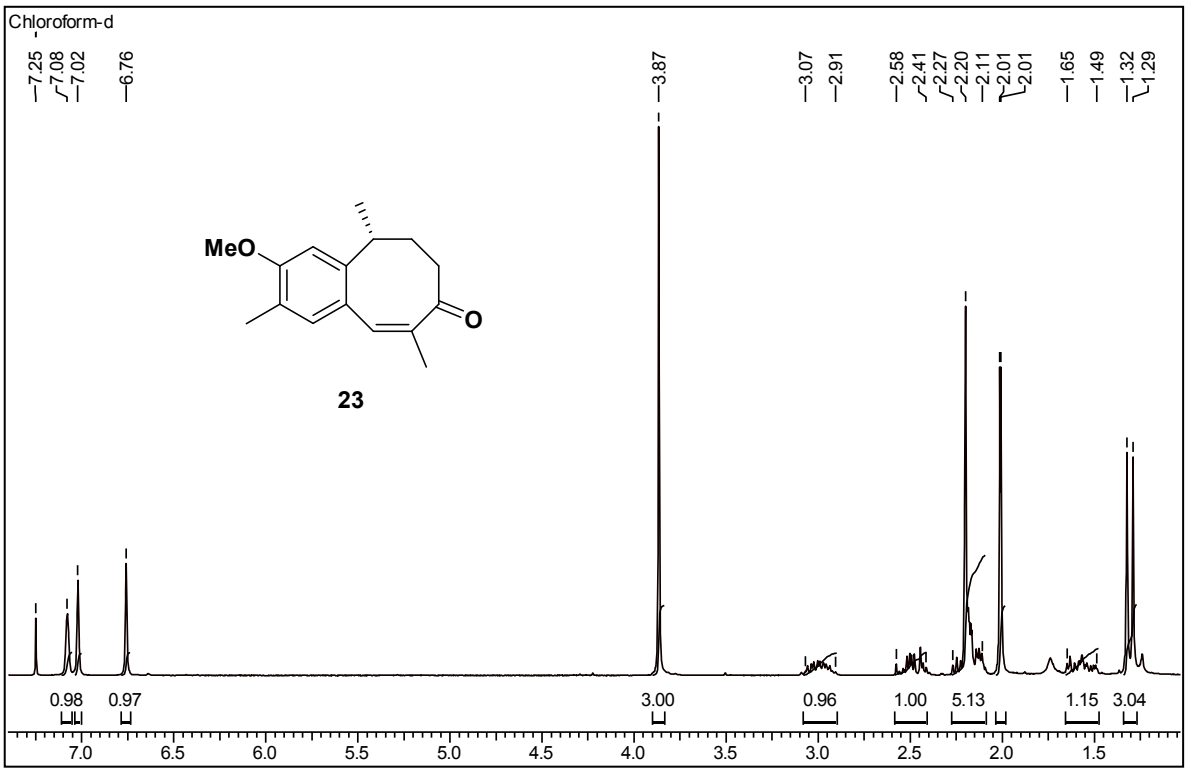


^{1}H NMR SPECTRUM ($CDCl_3$ + CCl_4, 200 MHz)

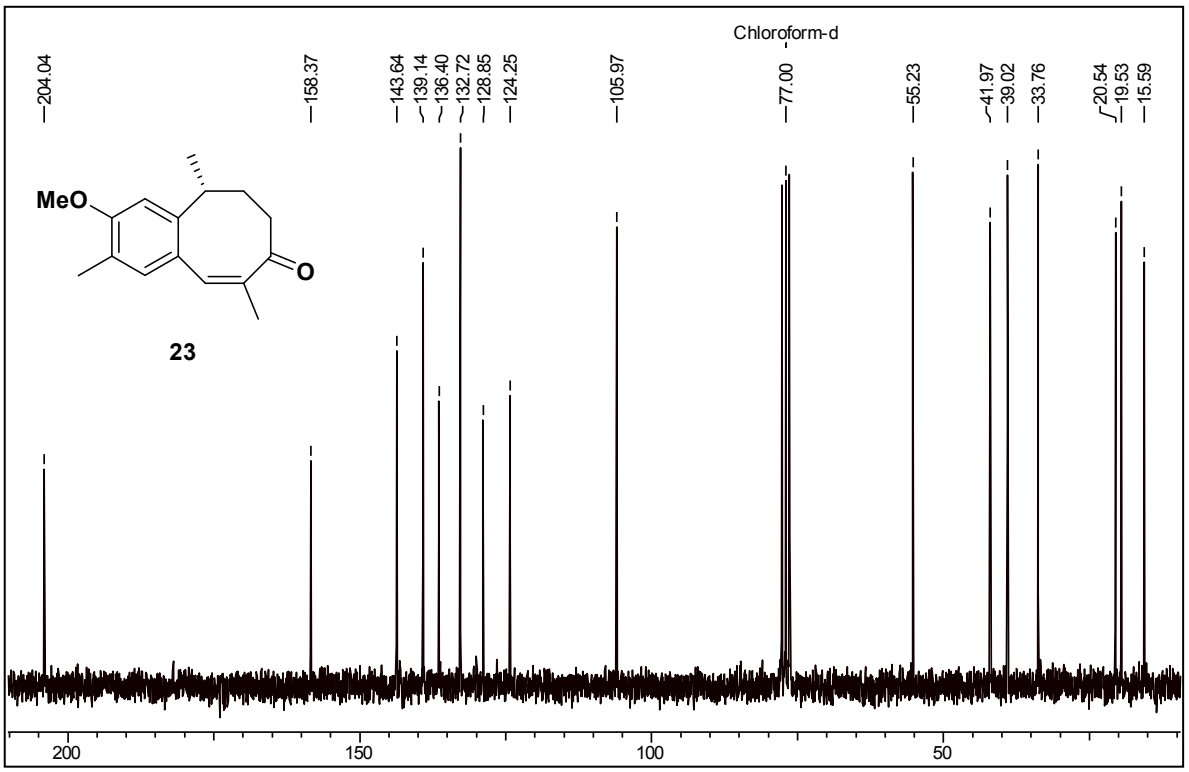


^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 50 MHz)

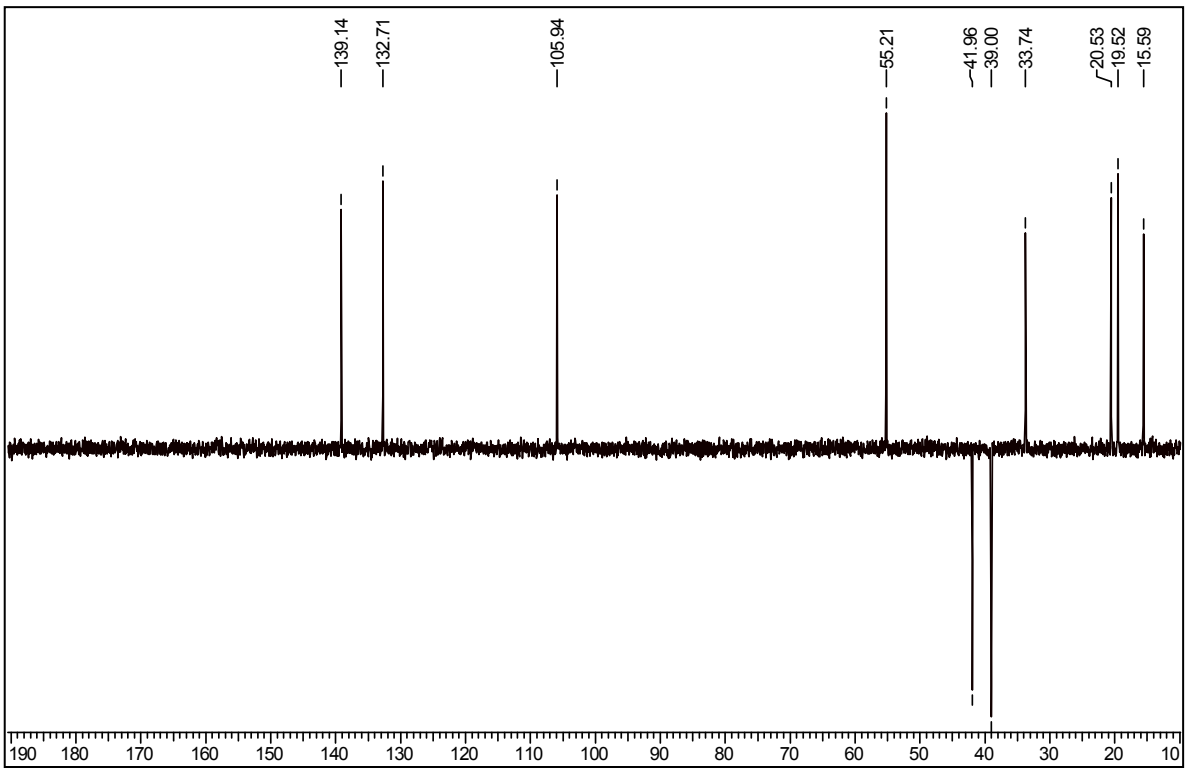


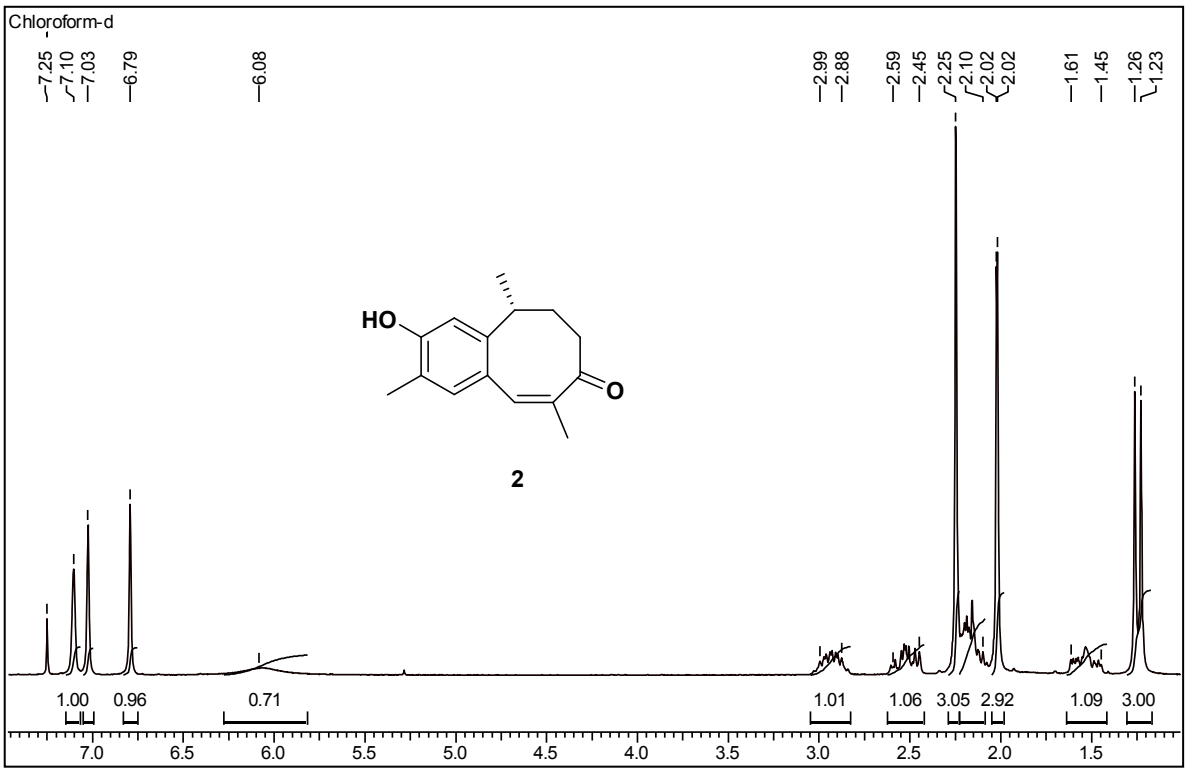


^{1}H NMR SPECTRUM ($CDCl_3$, 200 MHz)

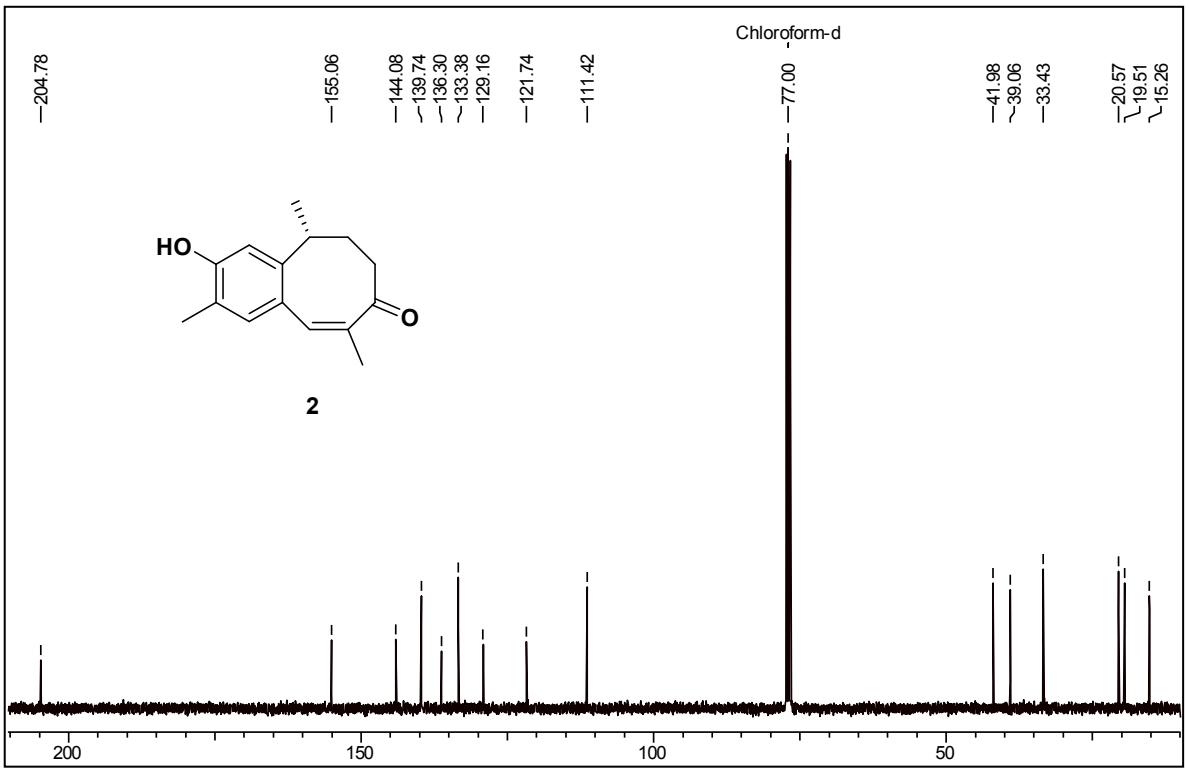


^{13}C & DEPT NMR SPECTRA ($CDCl_3$, 50 MHz)



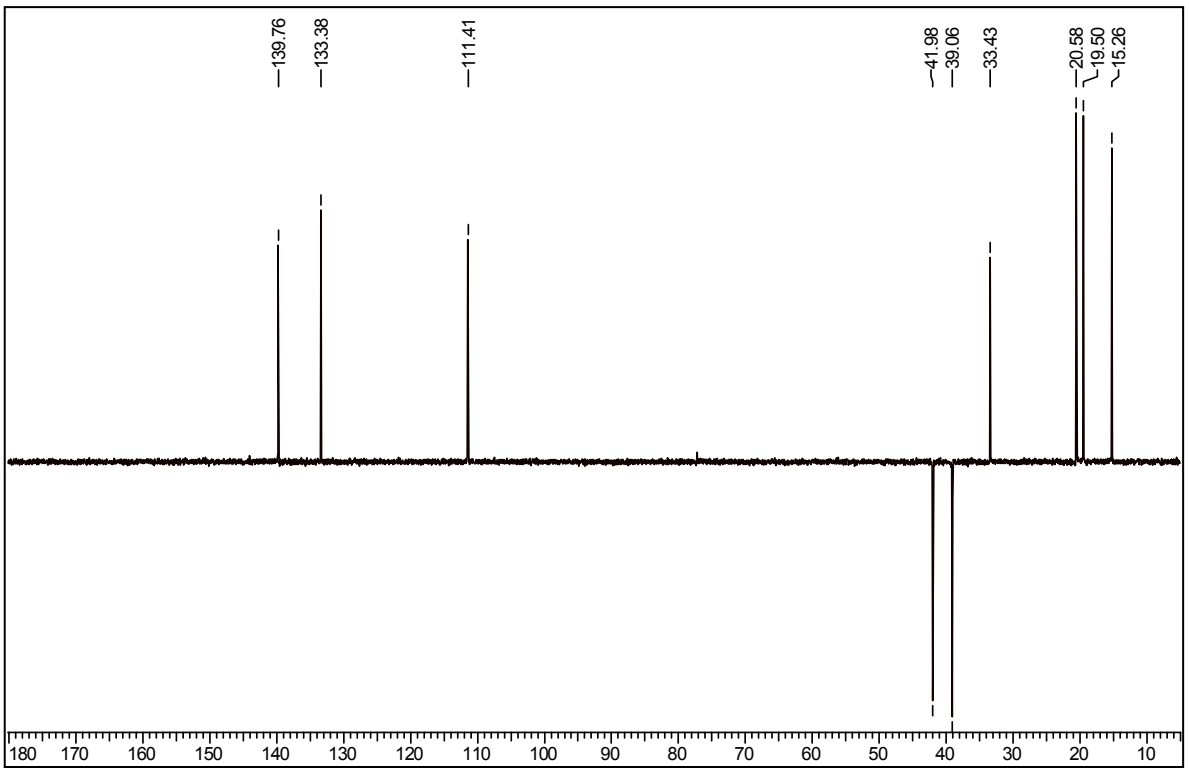


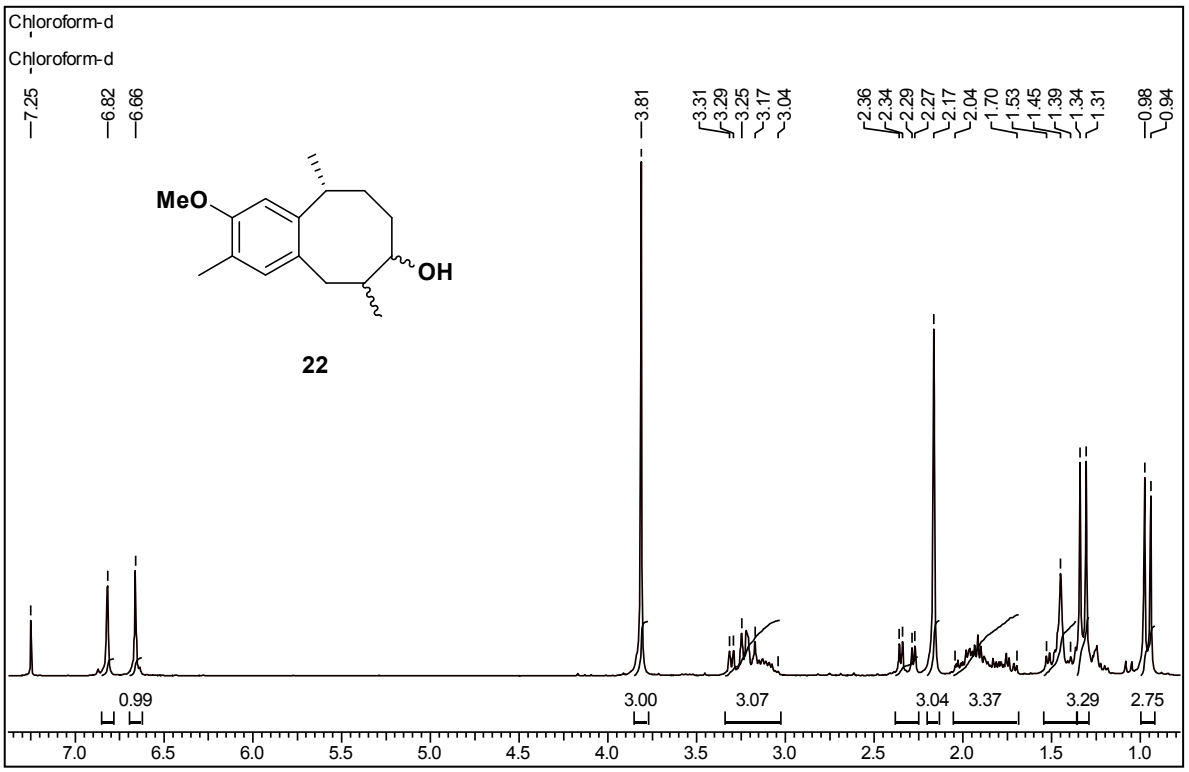
^{1}H NMR SPECTRUM ($CDCl_3$, 200 MHz)



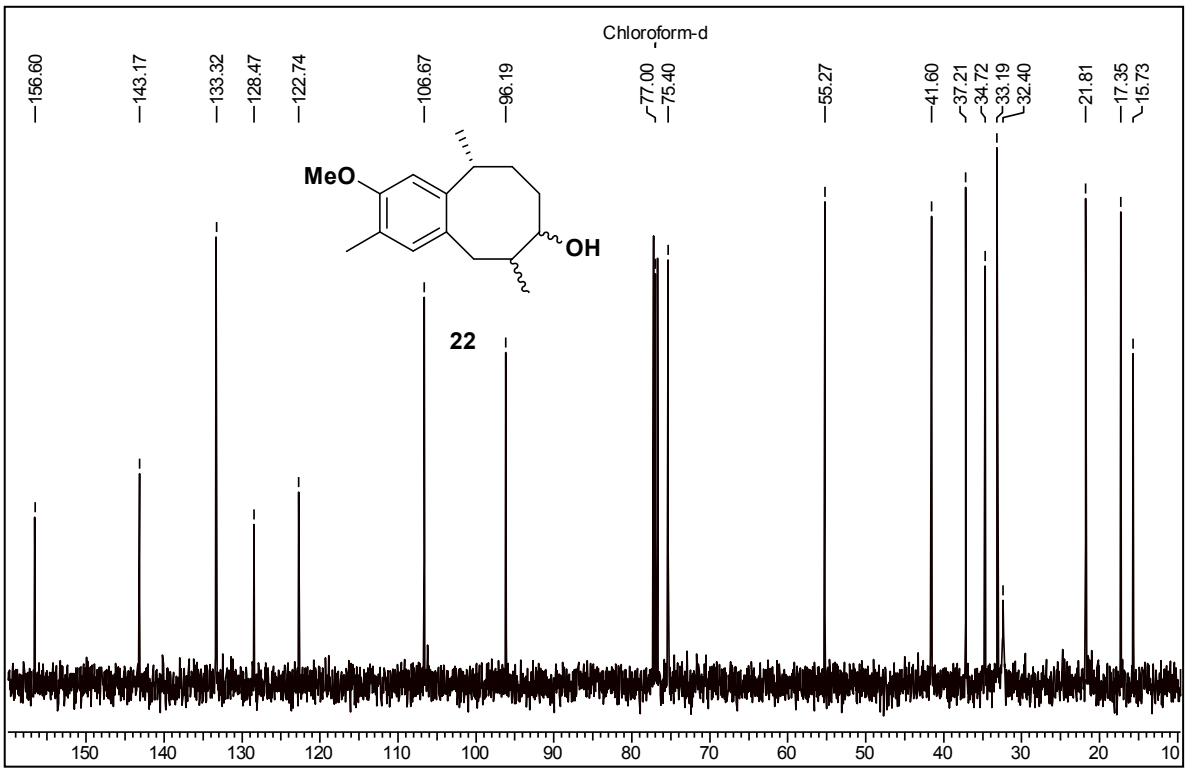
2

^{13}C & DEPT NMR SPECTRA ($CDCl_3$, 100 MHz)

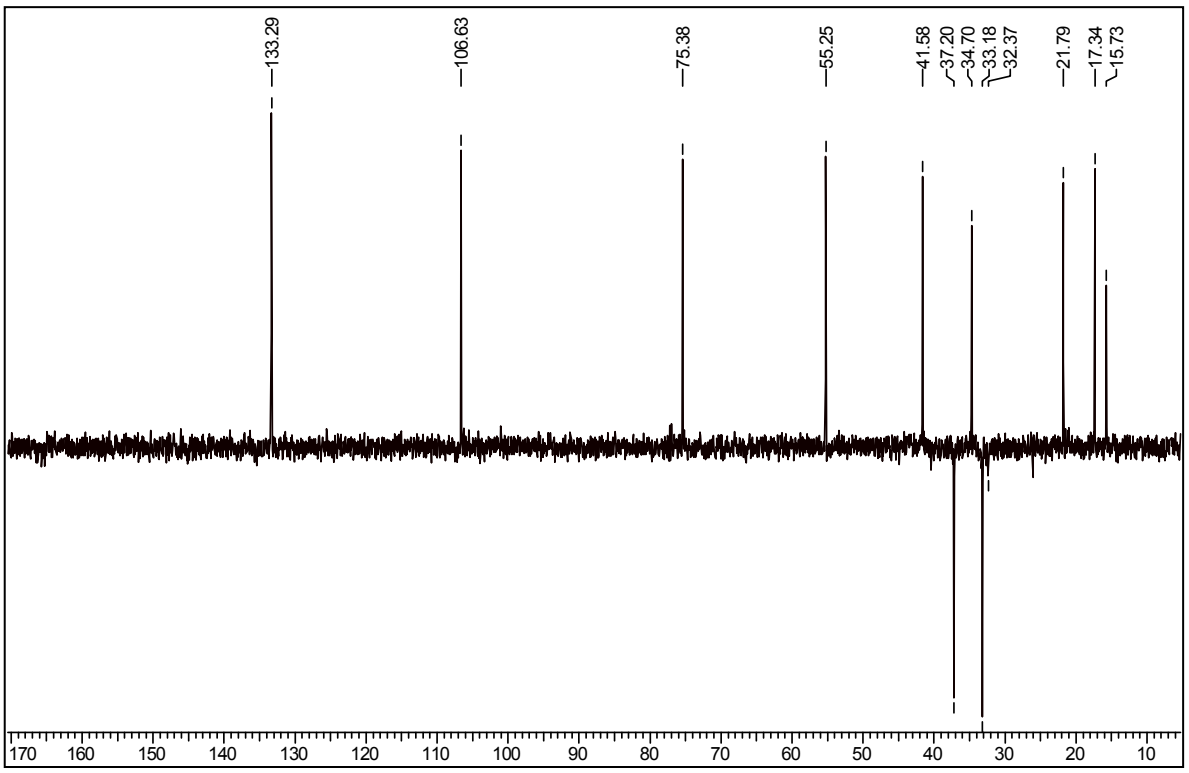


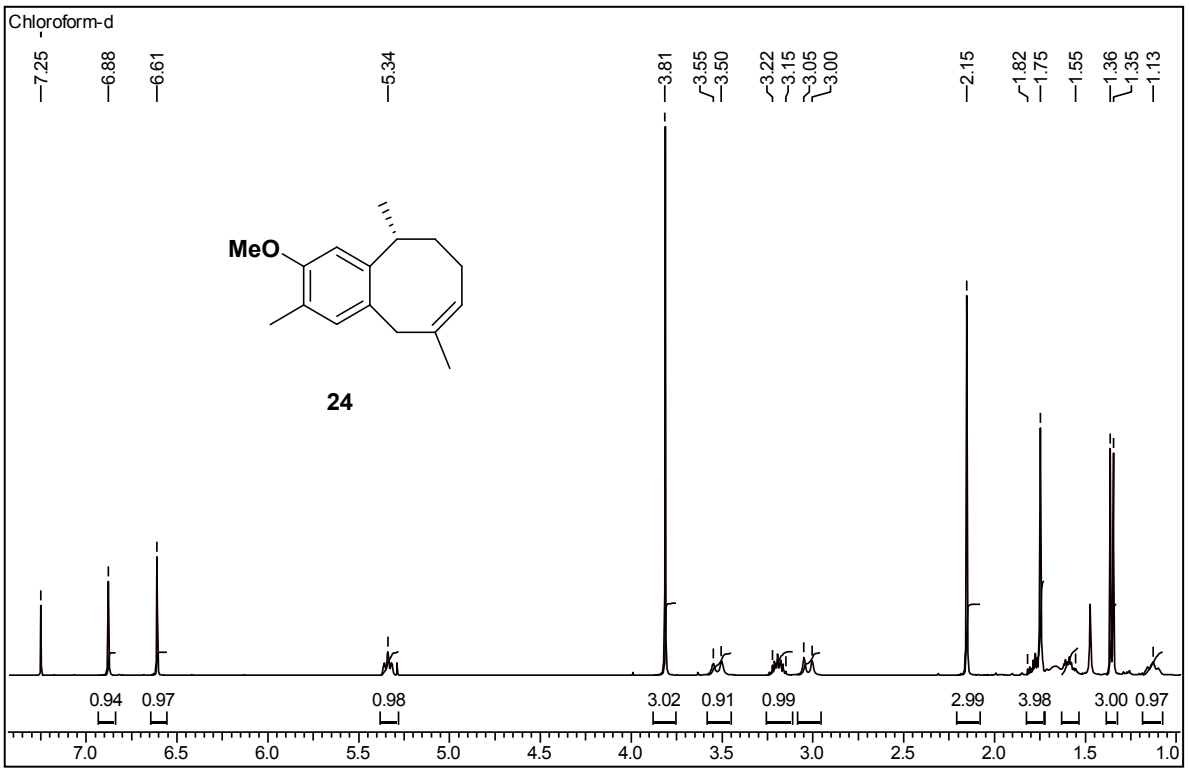


^{1}H NMR SPECTRUM ($CDCl_3$ + CCl_4, 200 MHz)

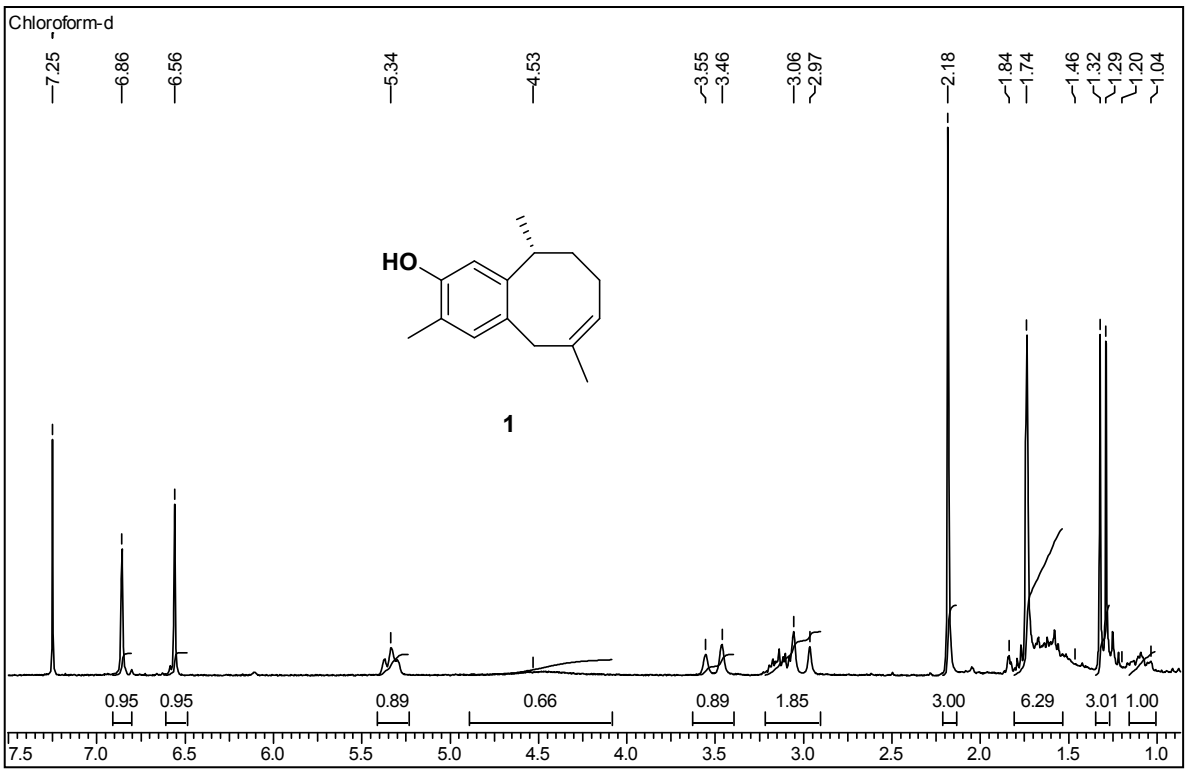


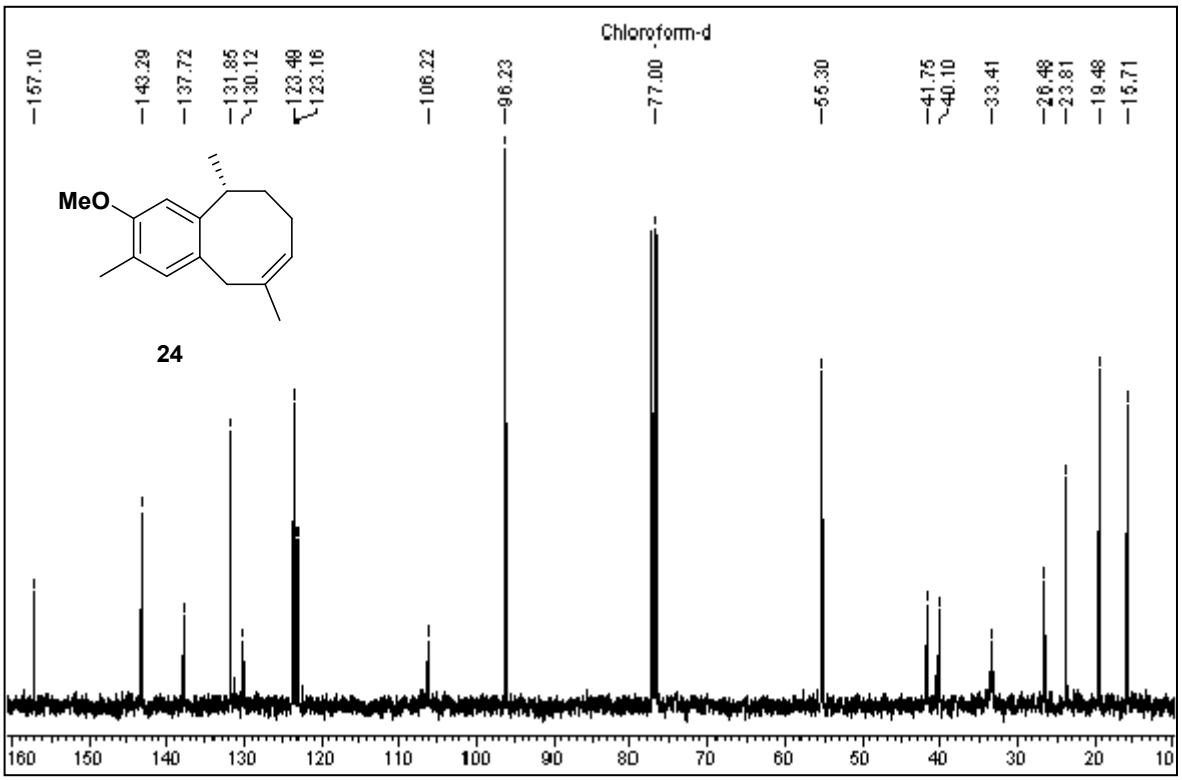
^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 50 MHz)



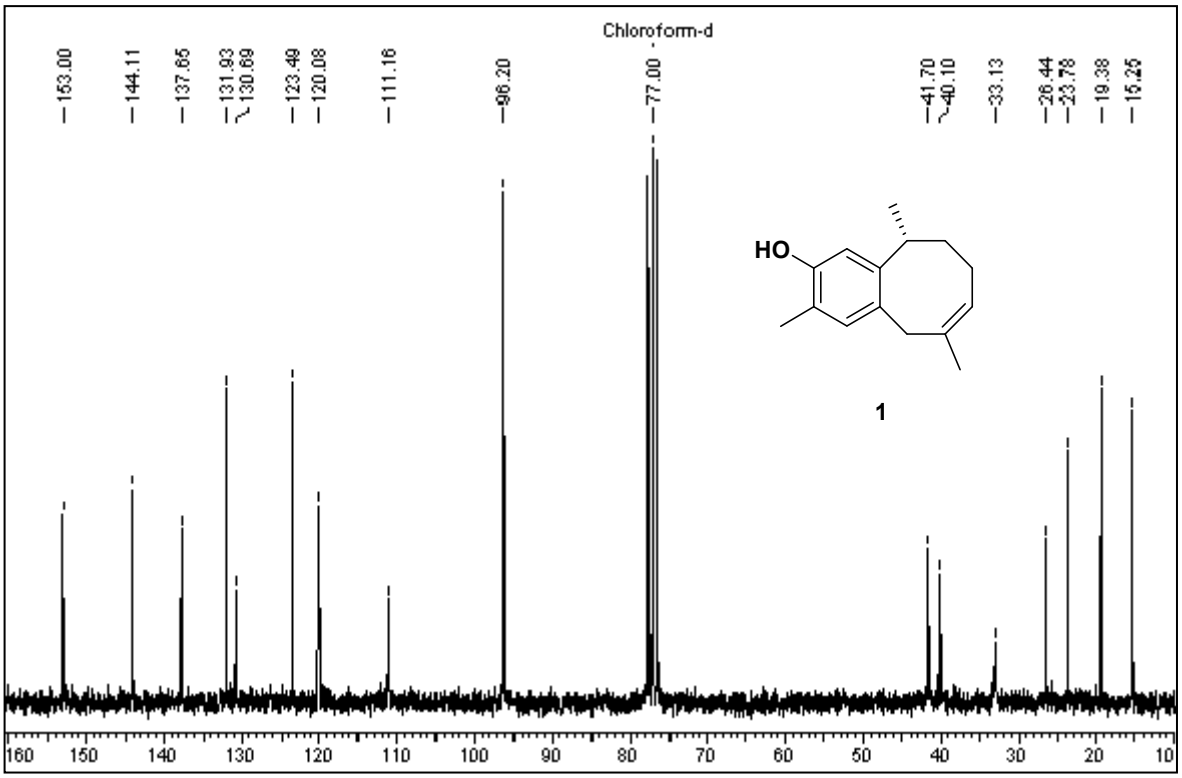


^{1}H NMR SPECTRA ($CDCl_3$ + CCl_4, 200 MHz)





^{13}C NMR SPECTRA ($CDCl_3$ + CCl_4, 50 MHz)



2.2.6 References

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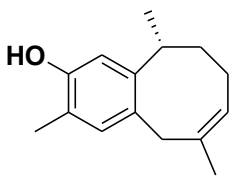
Chapter-2, Section-3 : Enantiospecific Synthesis of (-)-Curcuquinone & (-)-Parvifoline

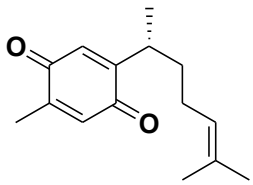
Ring Closing Metathesis Approach

2.3.1 Introduction

After successfully synthesizing (-)-parvifoline **1**[1] enantiospecifically from (*R*)-(+)-citronellal using intramolecular Friedel-Craft's acylation as the key step as described in section-1, attention towards even shorter and high yielding route led to explore about the feasibility of formation of benzocyclocyclooctene framework under Grubb's ring closing metathesis conditions and simultaneous installation of the acid sensitive deconjugated double bond of parvifoline at the appropriate location. Further, structural similarities between the intermediates obtained from (*R*)-(+)-citronellal (chapter-2, section-2) and (-)-curcuquinone **2** (the simplest monocyclic sesquiterpene benzoquinone, which was isolated from the *Pseudoterogorgia rigid*[2]) encouraged to utilize the same starting material for the enantiospecific synthesis of **2**, which has also been shown to possess antibacterial activity and more importantly, proven to be a versatile chiral building blocks for the synthesis of related important natural products, such as heliannuols.[3] The present section deals with the ring closing metathesis approach towards synthesis of (-)-parvifoline **1** and enantiospecific synthesis of (-)-curcuquinone **2**.



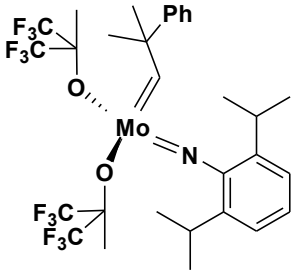
1



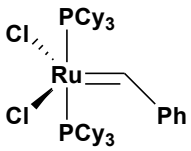
2

Olefin metathesis reactions are gaining increasing importance due to introduction of new and efficient catalysts during last decade[4] and have been successfully used for the preparation of both carbocyclic as well as heterocyclic ring systems. More importantly, medium and large rings[5] have been constructed efficiently and thus it has become a reliable tool for natural product synthesis.

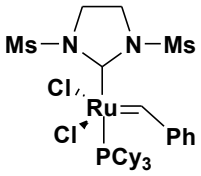
Olefin metathesis is a disproportionation process involving bond formation, bond breakage and reorganization. It was first reported by Anderson and Merckling in 1955, where Ti (IV) metal catalysts were used for polymerization of norbornene.[6]



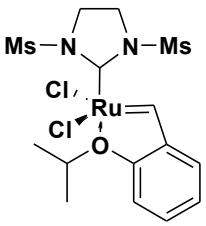
Schrock's catalyst, 3



Grubbs' 1st generation catalyst, 4

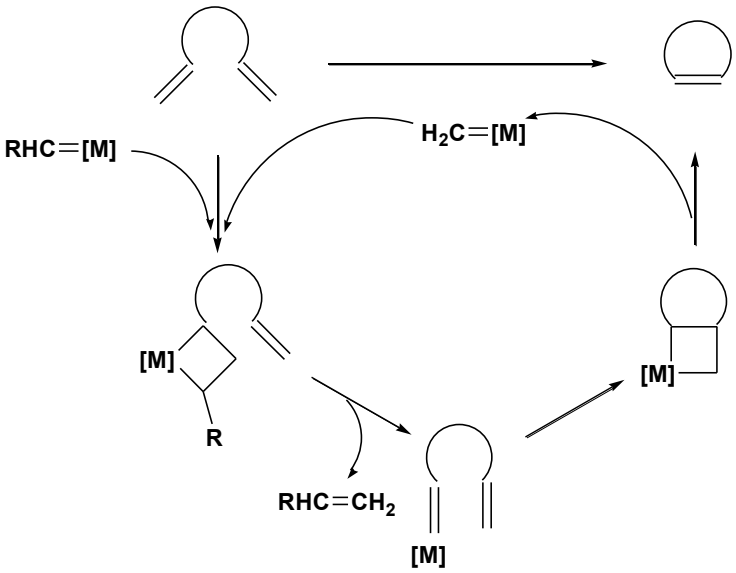


Grubbs' 2nd generation catalyst, 5



Hoveyda-Grubbs' catalyst, 6

Scheme-1



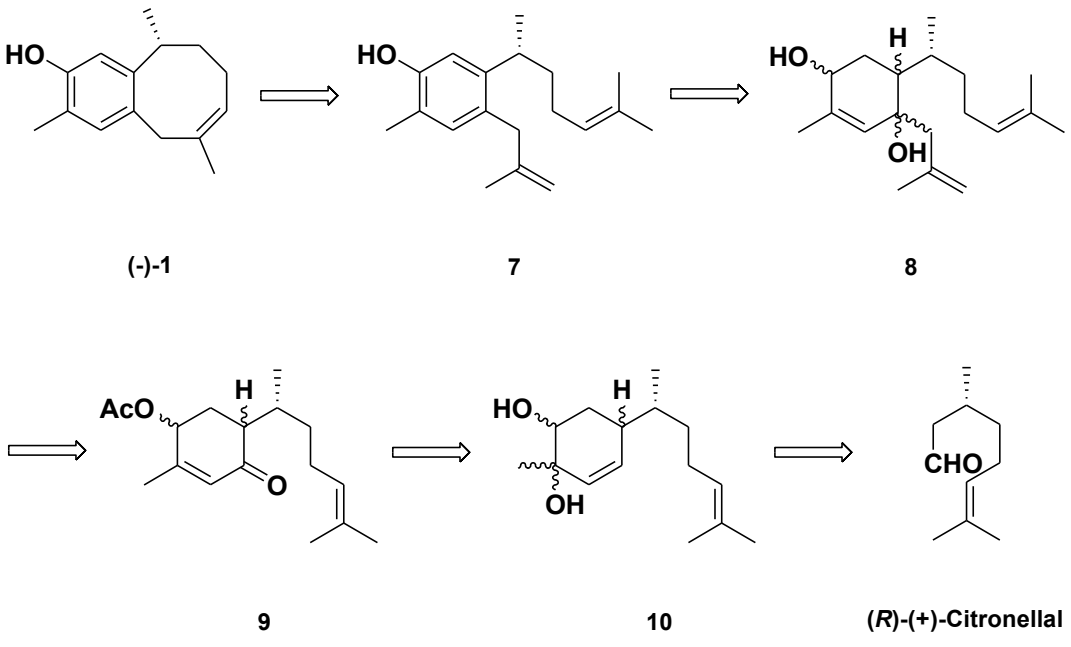
Later on, after introduction of Mo and Ru based catalysts by Schrock[7] and Grubbs,[8] which are air stable and are tolerant to diverse functional groups, olefin metathesis has become popular in organic synthesis as well.

Scheme-1 depicts the postulated mechanism for ring closing metathesis reaction, which involves an iterative process of [2+2] cycloaddition and cycloreversion between the olefins, metal alkylidene and metallocyclobutene species.

2.3.2 Present work : *Results and discussion*

As depicted in the retrosynthetic analysis (Scheme-2), ring closing metathesis could be performed over diolefin intermediate **7** to achieve the benzocyclooctene ring, and thus parvifoline **1**. Secondary hydroxyl group oxidation of diol **8** would have resulted in the required phenol derivative **7**, which in turn could be synthesized by Grignard addition over enone **9**. Enone **9** could be synthesized from tertiary allylic alchol **10** in a few steps, which has already been synthesized enantiospecifically utilizing (*R*)-(+)-citronellal as the source of chirality, as discussed in chapter-2, section-2.

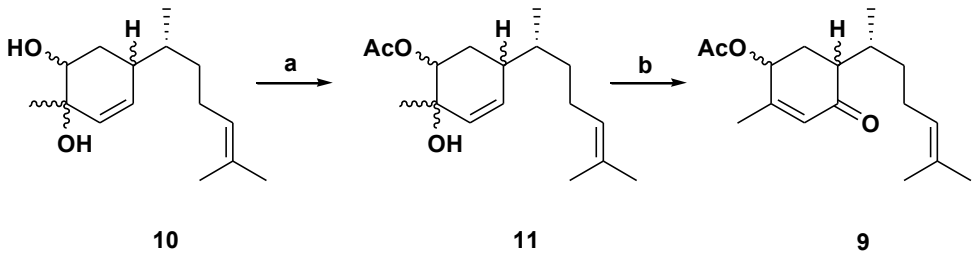
Scheme-2



Accordingly, the synthesis commenced from diol intermediate **10**, which was treated with acetyl chloride in pyridine at room temperature, to protect it's secondary hydroxyl group selectively, which indeed resulted in the requisite product **11** in 85% isolated yield (Scheme-3).

Presence of a strong stretching band at 1729 cm^{-1}, characteristic of an ester carbonyl group, in it's IR spectrum was indicative of the success of the attempted reaction. Further ^{1}H NMR spectrum exhibited a one proton multiplet ranged over δ 4.88-4.91, assigned to C<u>H</u>OC(O)CH_3, which appeared at δ 3.72-3.74 (m, 1H) in the diol intermediate **10**. The downfield shift of this particular proton suggested the formation of acetate **11**, which was also confirmed by a quaternary carbon resonance at δ 170.5 in it's ^{13}C NMR spectrum, indicating the presence of an ester carbonyl group. Finally acetate **11** was ascertained by it's mass spectrum and elemental analysis also.

<u>Scheme-3</u>



10 **11** **9**

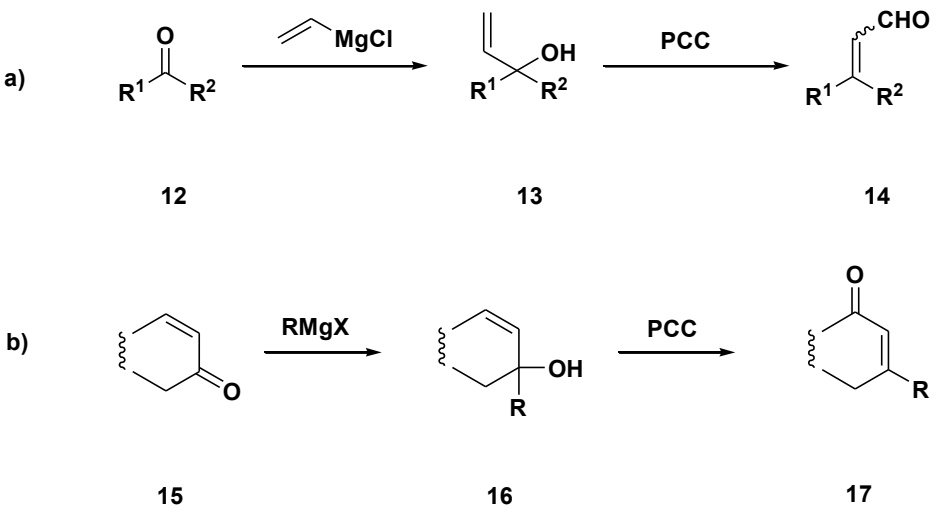
<u>Reagents and conditions</u> : *a) pyridine, acetyl chloride, 0 °C to rt, 12 h, 85%; b) PCC, CH_2Cl_2, rt, 7 h, 80%.*

As discussed in the retrosynthetic analysis, the next crucial reaction to be performed was carbonyl transposition to have an enone **9**, which would be useful in the second olefin side chain introduction at the required position. 1,3-carbonyl transposition by pyridinium chlorochromate protocol would have served this purpose.

Pyridinium chlorochromate is reported to be effective in 1,3-carbonyl transposition of tertiary allylic alhohols **13**, which was first reported by Babler *et al*,[9] where two carbon homologation of various ketones **12** have been achieved by addition of vinyl Grignard over keto functionality, followed by treatment of the resulting tertiary allylic alcohols **13** with PCC (Scheme-4a).

However, use of PCC for 1,3-carbonyl transposition was generalized by Dauben *et al* in 1977,[10] where various conjugated cyclic ketones **15** were also converted to the transposed 3-alkyl-α, β-unsaturated ketones **17** *via* tertiary allylic alcohols **16** in excellent yields (Scheme-4b).

Scheme-4



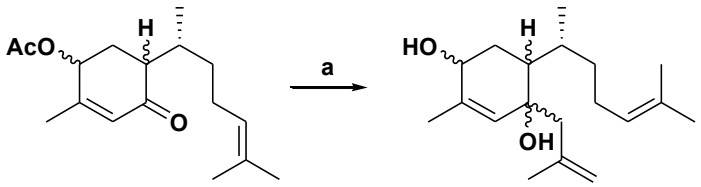
Working on similar lines, allyl alcohol **11** was treated with PCC in CH_2Cl_2 at room temperature for 7 hours to afford the requisite enone **9** (as a mixture of diastereomers) in 80% yield (Scheme-3).

The IR spectrum of the single isolated product **9** didn't show any absorption at 3444 cm^{-1}, indicated the absence of tertiary hydroxyl group, which also revealed absorptions at 1739 cm^{-1} and 1675 cm^{-1}, characteristic of an ester carbonyl (-OAc) and a conjugated carbonyl group, respectively. It's ^1H NMR spectrum showed only one proton multiplet ranged over δ 5.83-5.87, which was assigned to the only olefin proton in the cyclohexene ring. The downfield shift of this signal indicated allylic rearrangement of the double bond and presence of an enone functionality. Also, signal due to a proton attached to the carbon atom bearing acetate group further shifted downfield at δ 5.41-5.47 (m, 1H) supported this fact. Presence of one proton triplet at δ 5.03 (J = 7.1 Hz), characteristic of the side chain olefin proton, indicated no cyclisation of the side chain over cyclohexene ring. A carbonyl resonance at δ 199.5 in it's ^{13}C NMR spectrum further supported the presence of a conjugated carbonyl group. Enone **9** was finally confirmed by it's mass spectrum, which exhibited a peak of $(M+1)^+$ at 279 and by it's elemental analysis also, which was in good agreement with the calculated values.

To install a second olefin side chain for the metathesis reaction, it was required to introduce methallyl group over enone **9** at the carbon bearing carbonyl group. Accordingly, enone **9** was treated with methallyl magnesium chloride, generated separately in THF, but resulted in the recovery of starting material. So it was thought of doing the same reaction in

diethyl ether, which also met with the failure. This might be attributed to the reactivity of methallyl Grignard reagents towards self coupling. Finally, reaction was carried out under Barbier conditions, according to which it was treated with methallyl chloride and magnesium in THF at 0 ^{o}C for 24 h to provide the required diol **8** (as a mixture of diastereomers) in 90% yield (Scheme-5).

Scheme-5



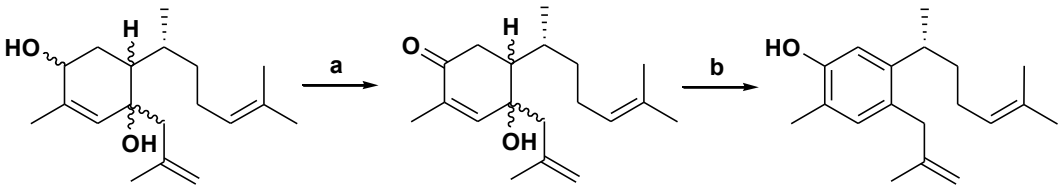
9 **8**

Reagents and conditions *: a) Mg, methallyl chloride, THF, 0 ^{o}C, 24 h, 90%.*

Intermediate **8** was characterized by it's IR and NMR spectral data. Absence of stretching band at 1675 cm^{-1} in the IR spectrum of the isolated product suggested absence of the carbonyl functionality. This was further supported by upfield shift of the only olefin proton in the cyclohexene ring ranged over δ 5.44-5.48 as a multiplet, in it's ^{1}H NMR spectrum. Further, IR spectrum of the product **8** didn't show any absorption of an ester carbonyl group at 1739 cm^{-1}, suggested deprotection of the *O*-acetate functionality. There were additional absorption bands at 3414 cm^{-1} in the IR spectrum, which suggested the presence of hydroxyl groups. Both of these facts were confirmed by it's ^{13}C NMR spectrum, which didn't show any characteristic carbonyl resonances of an ester or a conjugated enone at δ 170.2 and 199.5, respectively. Further, upfield shift of the signal for proton attached to the carbon bearing secondary hydroxyl group at δ 3.93-3.96 (m, 1H) supported acetate group deprotection. Presence of additional methylene protons at δ 4.73-4.75 (m, 1H) and 4.87-4.89 (m, 1H) in it's ^{1}H NMR spectrum, suggested the introduction of methallyl group, which was confirmed by the presence of olefin resonances at δ 110.4, 112.7 and 115.2 in it's ^{13}C NMR spectrum. Diol **8** was finally ascertained by it's mass spectrum and it's elemental analysis as well.

At this stage, intermediate **8** also could have been subjected for ring closing metathesis, but to minimize the number of steps after metathesis reaction, it was thought to aromatize the intermediate **8** to the required phenol derivative **7** first and then to go for metathesis, which also minimizes the risk of deconjugated double bond migration into conjugation of the resultant aromatic ring.

Scheme-6



8 **18** **7**

Reagents and conditions *: a) DMP, CH_2Cl_2, 0 ^oC to rt 4 h, 85%; b) (i) Et_3N, methanesulfonyl chloride, CH_2Cl_2, 0 ^oC to rt, 3 h, then reflux, 5 h; (ii) KOH, MeOH, reflux, 12 h, 79% for two steps.*

To carry out aromatization of **8** to **7**, secondary hydroxyl group of **8** should be oxidized first, so that the resulting enone **18** would help in the elimination of tertiary hydroxyl group and thus would result in aromatization, which also places the phenolic hydroxyl group in the required position. Accordingly, diol **8** was oxidized using Dess-Martin Periodinane[11] reagent in CH_2Cl_2 at room temperature to give the corresponding enone **18** in 85% yield (Scheme-6). Enone **18** was characterized by it's IR, mass and NMR spectral data.

It's IR spectrum exhibited absorption at 1667 cm^{-1}, indicative of an enone carbonyl group, which was further confirmed by a resonance at δ 200.3 in it's ^{13}C NMR spectrum. Downfield shift of the signal attributed to the cyclohexene olefin proton from δ 5.44-5.48 (m) to δ 6.44-6.47 (m) in it's ^1H NMR spectrum, also suggested conjugation of the double bond with the carbonyl group. Enone **18** was finally confirmed by it's mass spectrum, which revealed a peak at 291 $(M+1)^+$, and also by it's elemental analysis, which was in good agreement with the calculated values.

However, separation of diastereomers of intermediate **9** was attempted by preparative HPLC using chiral analytical OD column, which resulted in a failure. Also as the newly generated centers (in **11**, **9**, **8** and **18**) would be destroyed at the later stages in the synthetic sequence, no attempt was made, further, to separate or characterize them.

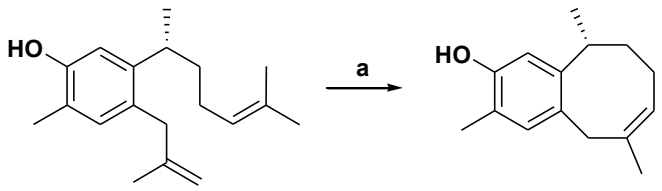
Enone **18** was then subjected to mesylation conditions, that is, treatment with 3 equivalents of methanesulfonylchloride in presence of 6 equivalents of triethylamine as the base in refluxing CH_2Cl_2, which as anticipated resulted in tertiary hydroxyl group elimination with concomitant aromatization to afford phenol **7** along with unseparable corresponding mesyl ester. The crude product was immediately hydrolyzed by using potassium hydroxide as the base in refluxing methanol to afford the required phenol derivative **7** in 79% overall yield starting from **18** (Scheme-6).

Presence of an hydroxyl group absorption at 3393 cm^{-1} in it's IR spectrum suggested the formation of a phenol derivative, which was further supported by a characteristic phenolic quaternary carbon resonance in it's ^{13}C NMR spectrum at δ 152.5 (s). It's ^{1}H NMR spectrum revealed two singlets at δ 6.60 and 6.81, each integrated for one proton, assigned to the *para* distributed aromatic protons. Also, one proton triplet at δ 5.06 (J = 7.0 Hz) was attributed to the isopropylidene olefin proton, while two singlets at δ 4.48 (1H) and 4.76 (1H) were assigned to methallyl protons ($CH_2C(Me)=C\underline{H}_2$), which was also confirmed by a methylene resonance at δ 111.4 in it's ^{13}C NMR spectrum. The presence of methallyl side chain was further evident from a doublet at δ 3.20 (J = 4.7 Hz, 2H) in it's ^{1}H NMR spectrum, assigned to Ar-$C\underline{H}_2C(CH_3)=CH_2$, which was supported by a methylene resonance at δ 40.5 in it's ^{13}C NMR spectrum. Other characteristic signals in it's ^{1}H NMR spectrum were : two singlets at δ 1.53 and 1.67, each integrating for three protons, were due to two methyl groups associated with isopropylidene side chain; a three proton doublet at δ 1.12 (J = 6.8 Hz) was assigned to the only secondary methyl group present; a three proton singlet at δ 1.71 was attributed to methallyl methyl group and a three proton singlet at δ 2.18 was characteristic of a methyl group attached to the aromatic ring. Finally, phenol **7** was confirmed by it's mass spectrum, which exhibited a peak of $(M+1)^+$ at 273, and also by it's elemental analysis, found to be in good agreement with the calculated values.

The stage was then set for the crucial ring closing metathesis reaction over diolefin precursor **7** to complete the synthesis of parvifoline **1**. Initially, Grubbs' first generation catalyst **4** was tried to achieve the required transformation, but without any success.

However the switchover to Grubbs' second generation catalyst **5** delightfully worked in hot toluene to provide the target molecule **(-)-1** in 90% isolated yield (Scheme-7).

Scheme-7



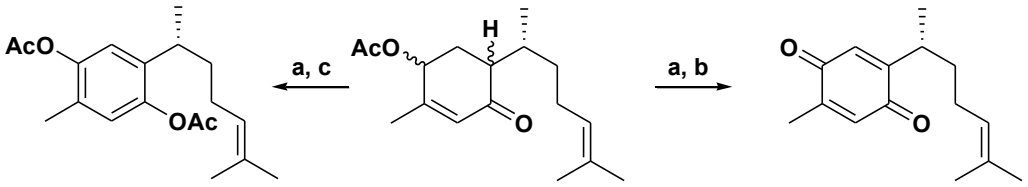
7 **1**

Reagents and conditions *: a) Grubbs' second generation catalyst* ***5****, toluene, 80 °C, 5 h, 90%.*

Formation of **1** was confirmed by it's IR and NMR spectral data comparison with those of the literature values.[1] The solid compound obtained after preparative TLC had mp 85 °C {lit.[1] 89-90 °C, crystallized from hexane: acetone} and specific rotation $[\alpha]^{25}_{D}$ -168 (*c* 1.73, $CHCl_3$) {lit.[1] $[\alpha]^{25}_{D}$ –173 (*c* 1.73, $CHCl_3$)}. It's specific rotation suggested the optical purity of the final product, and ascertained it's configuration also.

After successfully synthesizing (-)-parvifoline **1**, enantiospecific synthesis of (-)-curcuquinone **2** was undertaken, for which intermediate **9** was envisioned as the key intermediate. Enone **9** was hydrolyzed using K_2CO_3 in methanol to the corresponding hydroxyenone, which was then subjected to Dess-Martin periodinane oxidation conditions, followed by base (triethylamine) treatment in CH_2Cl_2 at room temperature. The crude product (believed to be corresponding hydroquinone) was immediately oxidized using ceric ammonium nitrate to provide the target molecule, that is, **(-)-2** in 60% overall yield (Scheme-8). The physical and chemical properties of this synthetically obtained product were in good agreement with those of naturally isolated one.[2]

Scheme-8



19 **9** **2**

Reagents and conditions **:** *a) (i) K_2CO_3, MeOH, rt, 30 min; (ii) DMP, CH_2Cl_2, rt, 2 h; (iii) Et_3N, CH_2Cl_2, rt, 3 h; b) CAN, CH_2Cl_2-H_2O, 0 ^oC, 1 h, 60%; c) acetyl chloride, Et_3N, CH_2Cl_2, 0 ^oC to rt, overnight, 52% overall.*

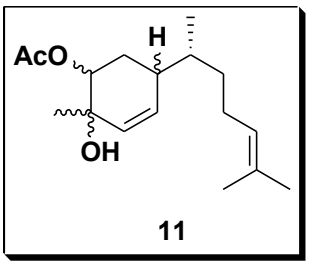
Further, to prove the intermediacy of the corresponding hydroquinone, the crude product obtained after DMP oxidation was treated with triethylamine and acetyl chloride to afford the diacetate derivative **19** in 52% isolated yield. It was completely characterized by it's IR, NMR and mass spectral analysis and ascertained by it's elemental analysis also.

2.3.3 Conclusions

Thus, (-)-parvifoline has been synthesized enantiospecifically from (*R*)-(+)-citronellal as the source of chirality, using ring closing metathesis as the key step in 10% overall yield. (-)-Curcuquinone has also been successfully synthesized from (*R*)-(+)-citronellal.

2.3.4 Experimental

2-Hydroxy-2-methyl-5-((*R*)-6-methylhept-5-en-2-yl)cyclohex-3-enylacetate (11)



11

Diol **10** (3.4 g, 14.3 mmol) was taken in a 100 mL two neck round bottom flask, equipped with a magnetic stir bar, and pyridine (50 mL) was added to it, under N_2 atmosphere. The reaction mixture was cooled to 0 ^oC and acetyl chloride (2.25 g, 28.6 mmol) was added to it. The reaction mixture was stirred at room temperature for 12 h. Pyridine was evaporated under reduced pressure and the reaction mixture was diluted using ethyl acetate (100 mL), washed using saturated $NaHCO_3$ solution (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 94 : 6) to give acetate **11** (3.4 g) as a colourless oil (mixture of diastereomers).

Molecular Formula : $C_{17}H_{28}O_3$

Yield : 85%

IR (neat) ν_{max} (cm^{-1}) : 3444, 1729.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.77-0.84 (m, 3H); 1.11-1.21 (m, 1H); 1.18 and 1.24 (two s, total 3H); 1.34-1.54 (m, 2H); 1.54 (s, 3H); 1.62 (s, 3H); 1.74-1.84 (m, 1H); 1.90-2.04 (m, 2H); 2.01 and 2.04 (two s, total 3H); 2.11-2.36 (m, 2H); 4.88-4.91 (m, 1H); 5.02 (t, *J* = 7.1 Hz, 1H); 5.52-5.67 (m, 2H).

MS-ESI m/z : 303 $(M+Na)^+$

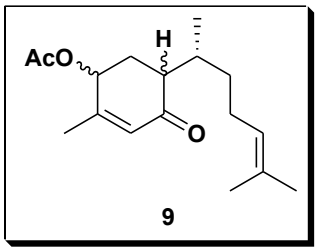
Analysis

Expected : C, 72.82%; H, 10.06%

Found : C, 72.90%; H, 10.24%

2-Methyl-5-((*R*)-6-methylhept-5-en-2-yl)-4-oxocyclohex-2-enylacetate (9)

The alcohol **11** (3.6 g, 12.86 mmol) was taken in a 100 mL two neck round bottom flask equipped with a magnetic stir bar, and CH_2Cl_2 (50 mL) was added to it. The reaction mixture was cooled to 0 ^oC and pyridinium chlorochromate (5.54 g, 25.7 mmol) was added to it. The reaction mixture was stirred at room temperature for 7 h and diluted using diethyl



9

ether (50 mL). The precipitated salt was then filtered through a short pad of celite, washed using diethylether (25 mL x 3), the solvent was evaporated on a rotary evaporator and the residue was chromatographed using flash silica gel (pet. ether : EtOAc, 97 : 3) to give enone **9** (2.86 g) as a colourless oil (mixture of diastereomers).

Molecular Formula : $C_{17}H_{26}O_3$

Yield : 80%

IR (neat) ν_{max} (cm^{-1}) : 2926, 1739, 1675.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ two doublets at 0.76 and 0.86 (J = 7.0 Hz, total 3H); 0.88-1.38 (m, 3H); 1.54 (s, 3H); 1.62 (s, 3H); 1.87-1.89 (m, 3H); 1.93-2.06 (m, 3H); 2.06 (s, 3H); 2.10-2.49 (m, 2H); 5.03 (t, J = 7.1 Hz, 1H); 5.41-5.47 (m, 1H); 5.83-5.87 (m, 1H).

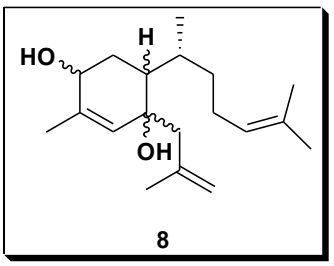
MS-ESI m/z : 279 $(M+1)^+$ and 301 $(M+Na)^+$

Analysis

Expected : C, 73.35%; H, 9.41%

Found : C, 73.66%; H, 9.37%

3-Methyl-1-(2-methylallyl)-6-((*R*)-6-methylhept-5-en-2-yl)cyclohex-2-ene-1,4-diol (8)



8

A 100 mL two neck round bottom flask, equipped with a magnetic stir bar was charged with Mg turnings (0.875 g, 35.97 mmol) and THF (30 mL), under N_2 atmosphere. The reaction mixture was cooled to 0 ^oC and enone **9** (2 g, 7.19 mmol) was added to it using THF (10 mL), followed by addition of methallyl chloride (3.26 g, 35.97 mmol). The reaction mixture was stirred at 0 ^oC for 24 h and quenched using saturated solution of NH_4Cl (100 mL). The extraction was carried out using EtOAc (50 mL x 3), the combined organic layers were washed using brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 9 : 1) to give diol **8** (1.9 g) as a colourless oil (mixture of diastereomers).

Molecular Formula : $C_{19}H_{32}O_2$

Yield : 90%

IR (neat) ν_{max} (cm^{-1}) : 3414, 2920, 1641.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ two doublets at 0.92 and 0.95 (d, *J* = 6.8 Hz, total 3H); 1.21-1.42 (m, 3H); 1.59 (s, 3H); 1.67 (s, 3H); 1.65-1.72 (m, 3H); 1.72-1.74 (m, 2H); 1.79 (two s, total 3H); 1.89-2.03 (m, 3H); 2.25-2.43 (m, 2H); 3.93-3.96 (m, 1H); 4.73-4.75 (m, 1H); 4.87-4.89 (m, 1H); 5.09 (t, *J* = 7.0 Hz, 1H); 5.44-5.48 (m, 1H).

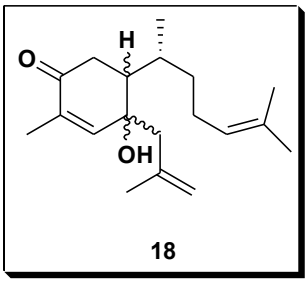
MS-ESI m/z : 315 $(M+Na)^+$

Analysis

Expected : C, 78.03%; H, 11.03%

Found : C, 77.70%; H, 11.18%

4-Hydroxy-2-methyl-4-(2-methylallyl)-5-((*R*)-6-methylhept-5-en-2-yl)cyclohex-2-enone (18)



18

A 50 mL two neck round bottom flask, equipped with a magnetic stir bar was charged with diol **8** (0.7 g, 2.4 mmol) and CH_2Cl_2 (20 mL), under N_2 atmosphere. To this was added Dess-Martin Periodinane reagent (1.02 g, 2.4 mmol). The reaction mixture was stirred at room temperature for 4 h and quenched using saturated $NaHCO_3$ solution (50 mL). Extraction was carried out using CH_2Cl_2 (25 mL x 3), the combined organic layers were washed using brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 94 : 6) to give enone **18** as a colourless oil. (0.59 g) (mixture of diastereomers).

Molecular Formula : $C_{19}H_{30}O_2$

Yield : 85%

IR (neat) ν_{max} (cm^{-1}) : 3444, 2922, 1667.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ two doublets at 0.90 and 0.93 (d, *J* = 6.7 Hz, total 3H); 1.19-1.41 (m, 2H); 1.57 (s, 3H); 1.66 (s, 3H); 1.75-1.80 (m, 5H); 1.84-2.11 (m, 5H); 2.27-2.64 (m, 4H); 4.77-4.78 (m, 1H); 4.94-4.95 (m, 1H); 5.01-5.11 (m, 1H); 6.44-6.47 (m, 1H).

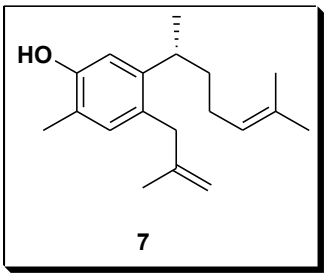
MS-ESI m/z : 291 $(M+1)^+$

Analysis

Expected **:** C, 78.57%; H, 10.41%

Found **:** C, 78.33%; H 10.77%

(*R*)-2-Methyl-4-(2-methylallyl)-5-(6-methylhept-5-en-2-yl)phenol (7)



7

Enone **18** (0.5 g, 1.724 mmol) was taken in a 50 mL two neck round bottom flask, equipped with a magnetic stir bar. To this was added CH_2Cl_2 (10 mL) and cooled to 0 ^oC, followed by dropwise addition of triethylamine (0.872 g, 8.62 mmol) and mesyl chloride (0.79 g, 6.90 mmol), under N_2 atmosphere. The reaction mixture was stirred at room temperature for 3 h and at reflux temperature for additional 5 h, quenched by addition of saturated $NaHCO_3$ solution (50 mL) and extracted using CH_2Cl_2 (25 mL x 3). The combined organic layers were washed using water (75 mL), brine (75 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

The crude product was taken in MeOH (20 mL) and to this was added KOH (0.2 g, 3.56 mmol), and refluxed for 12 h. Methanol was evaporated under reduced pressure and the reaction mixture was diluted with water (50 mL). The aqueous layer was extracted using CH_2Cl_2 (25 mL x 3), the combined organic layers were washed using brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 98 : 2) to give phenol **7** as a colourless oil (0.37 g).

Molecular Formula **:** $C_{19}H_{28}O$

Yield **:** 79%

Specific Rotation **:** $[\alpha]^{25}_D$ -33.1 (*c* 1.6, $CHCl_3$)

IR (neat) ν_{max} (cm^{-1}) **:** 3393, 2926, 1650, 1503.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.12 (d, *J* = 6.8 Hz, 3H); 1.46-1.58 (m, 2H); 1.53 (s, 3H); 1.67 (s, 3H); 1.71 (s, 3H); 1.82-1.98 (m, 2H); 2.18 (s, 3H); 2.74-2.91 (m, 1H); 3.20 (d, *J* = 4.7 Hz, 2H); 4.48 (s, 1H); 4.76 (s, 1H); 5.06 (t, *J* = 7.0 Hz, 1H); 6.60 (s, 1H); 6.81 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 15.3 (CH_3); 17.7 (CH_3); 22.1 (CH_3); 22.7 (CH_3); 25.7 (CH_3); 26.2 (CH_2); 33.4 (CH); 38.4 (CH_2); 40.5 (CH_2); 111.4 (CH_2); 112.3 (CH); 120.5 (C); 124.8 (CH); 128.9 (C); 131.3 (C); 132.8 (CH); 145.5 (C); 145.6 (C); 152.5 (C).

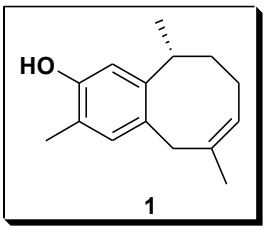
MS-ESI m/z **:** 273 $(M+1)^+$

Analysis

Expected **:** C, 83.77%; H, 10.36%

Found **:** C, 83.84%; H, 10.33%

(-)-Parvifoline (1)[1]



Phenol **7** (0.25 g, 0.92 mmol) was taken in a 50 ml two neck round bottom flask, equipped with a magnetic stir bar and a condenser. Toluene (25 mL) was added to it, followed by Grubbs' catalyst (second generation) **5** (78 mg, 0.092 mmol), under N_2 atmosphere, and stirred at 80 ^oC for 5 h. After completion of the reaction, toluene was removed under reduced pressure and the residue was chromatographed using flash silica gel (pet. ether : EtOAc, 99 : 1), which further purified by preparative TLC (silica gel, pet. ether : EtOAc, 95 : 5) to furnish parvifoline **1** (0.18 g) as a white solid.

Mp **:** 85 ^oC {lit.[1] 89-90 ^oC, crystallized from hexane : acetone}

Molecular Formula **:** $C_{15}H_{20}O$

Yield **:** 90%

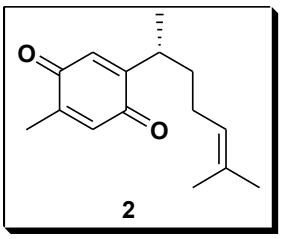
Specific Rotation **:** $[\alpha]^{25}_D$ -168 (*c* 1.73, $CHCl_3$) {lit.[1] $[\alpha]^{25}_D$ –173 (*c* 1.73, $CHCl_3$)}

IR ($CHCl_3$) ν_{max} (cm^{-1}) **:** 3602, 3369, 1619.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.04-1.13 (m, 1H); 1.31 (d, *J* = 7.0 Hz, 3H); 1.74 (s, 3H); 1.46-1.84 (m, 3H); 2.18 (s, 3H); 3.01 (d, *J* = 18.3 Hz, 1H); 3.04-3.20 (m, 1H); 3.51 (d, *J* = 18.3 Hz, 1H); 4.53 (bs, 1H); 5.34 (t, *J* = 7.0 Hz, 1H); 6.56 (s, 1H); 6.86 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 15.3 (CH_3); 19.4 (CH_3); 23.8 (CH_2); 26.5 (CH_3); 33.1 (CH); 40.1 (CH_2); 41.7 (CH_2); 111.2 (CH); 120.1 (C); 123.5 (CH);130.7 (C); 131.9 (CH); 137.7 (C); 144.1 (C); 153.0 (C).

(-)-Curcuquinone (2)[2]



2

Enone **9** (0.5 g, 1.80 mmol) was taken in a 50 mL round bottom flask along with methanol (5 mL). To this was added anhydrous K_2CO_3 (0.372 g, 2.70 mmol) and stirred for 30 min. Methanol was evaporated under reduced pressure; the residue was diluted with water (30 mL) and extracted using CH_2Cl_2 (30 mL x 3). The combined organic layers were washed using brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

The crude hydroxy enone was taken in CH_2Cl_2 (5 mL) in a 50 mL round bottom flask, under N_2 atmosphere. To this was added Dess-Martin periodinane (0.762 g, 1.80 mmol) and stirred at room temperature for 2 h. It was then quenched using saturated Na_2SO_3 (15 mL), followed by saturated $NaHCO_3$ solution (15 mL) and extracted using CH_2Cl_2 (30 mL x 3). The combined organic layers were washed using brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

The crude product was taken in a 50 mL round bottom flask. CH_2Cl_2 (5 mL) was added to it, followed by triethylamine (1.10 g, 11.00 mmol) and stirred for 3 h at room temperature. CH_2Cl_2 and triethylamine was then evaporated under reduced pressure and crude hydroquinone was added to the solution of ceric ammonium nitrate (6.90 g, 12.6 mmol) in water (30 mL) using CH_2Cl_2 (5 mL) at 0 ^oC. It was then stirred at the same temperature for 1 h and diluted using CH_2Cl_2 (25 mL). The organic layer was washed using saturated $NaHCO_3$ solution (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 9 : 1) to give a yellow oil **2** (0.25 g).

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

Yield : 60% overall

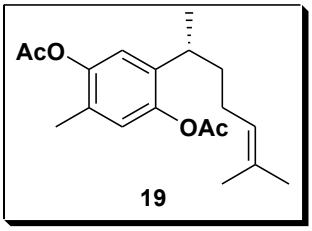
Specific Rotation : $[\alpha]^{25}_D$ -1.3 (*c* 9.1, $CHCl_3$) {lit.[2] $[\alpha]^{25}_D$ -1.3, *c* 9.1, ($CHCl_3$)}

IR (neat) ν(cm^{-1}) : 3272, 1657, 1610, 1452.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.08 (d, *J* = 7.0 Hz, 3H); 1.30-1.54 (m, 5H); 1.63 (d, *J* = 1.0 Hz, 3H); 1.88-1.95 (m, 2H); 2.01 (d, *J* = 1.5 Hz, 3H); 2.80-2.97 (m, 1H); 5.02 (t, *J* = 7.0 Hz, 1H); 6.48 (d, *J* = 0.9 Hz, 1H); 6.56 (d, *J* = 1.7 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 15.3 (CH_3); 17.6 (CH_3); 19.5 (CH_3); 25.6 (CH_3); 25.7 (CH_2); 31.2 (CH); 35.7 (CH_2); 123.8 (CH); 131.0 (CH); 132.0 (C); 133.8 (CH); 145.0 (C); 154.1 (C); 187.3 (C); 188.5 (C).

(*R*)-2-Methyl-5-(6-methylhept-5-en-2-yl)-1,4-phenylene diacetate (19)



19

Enone **9** (0.5 g, 1.80 mmol) was taken in a 50 mL round bottom flask along with methanol (5 mL). To this was added anhydrous K_2CO_3 (0.372 g, 2.70 mmol) and stirred for 30 min. Methanol was evaporated under reduced pressure; the residue was diluted with water (30 mL) and extracted using CH_2Cl_2 (30 mL x 3). The combined organic layers were washed using brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

The crude hydroxy enone was taken in CH_2Cl_2 (5 mL), in a 50 mL round bottom flask, under N_2 atmosphere. To this was added Dess-Martin periodinane (0.762 g, 1.8 mmol) and the reaction mixture was stirred at room temperature for 2 h. It was then quenched using saturated Na_2SO_3 solution (15 mL), followed by saturated $NaHCO_3$ solution (15 mL) and extracted using CH_2Cl_2 (30 mL x 3). The combined organic layers were washed using brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was taken in a 50 mL round bottom flask. CH_2Cl_2 (5 mL) was added to it, followed by triethylamine (1.1 g, 11mmol) and stirred for 3 h at room temperature, followed by recooling to 0 ^oC and dropwise addition of acetyl chloride (0.42 g, 5.40 mmol). The reaction mixture was stirred at room temperature overnight and diluted using saturated $NaHCO_3$ solution (30 mL). It was then extracted using CH_2Cl_2 (30 mL x 3), the combined organic layers were then washed using brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 95 : 5) to give **19** (0.3 g) as a yellow oil.

Molecular Formula **:** $C_{19}H_{26}O_4$

Yield **:** 52% overall

Specific Rotation **:** $[\alpha]^{25}_D$ -26.22 (*c* = 1.6, $CHCl_3$)

IR ($CHCl_3$) ν(cm^{-1}) **:** 3022, 1759, 1501, 1452.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.15 (d, *J* = 6.8 Hz, 3H); 1.45-1.59 (m, 2H); 1.52 (s, 3H); 1.66 (s, 3H); 1.84-1.95 (m, 2H); 2.11 (s, 3H); 2.28 (s, 3H); 2.29 (s, 3H); 2.69-2.87 (m, 1H); 5.05 (t, *J* = 7.0 Hz, 1H); 6.86 (s, 1H); 6.88 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 15.8 (CH_3); 17.5 (CH_3); 20.70 (CH_3); 20.77 (CH_3); 20.81 (CH_3); 25.6 (CH_3); 25.8 (CH_2); 31.9 (CH); 37.3 (CH_2); 120.3 (CH); 124.1 (CH); 124.4 (CH); 128.4 (C); 131.6 (C); 137.9 (C); 145.6 (C); 147.1 (C); 169.0 (C); 169.5 (C).

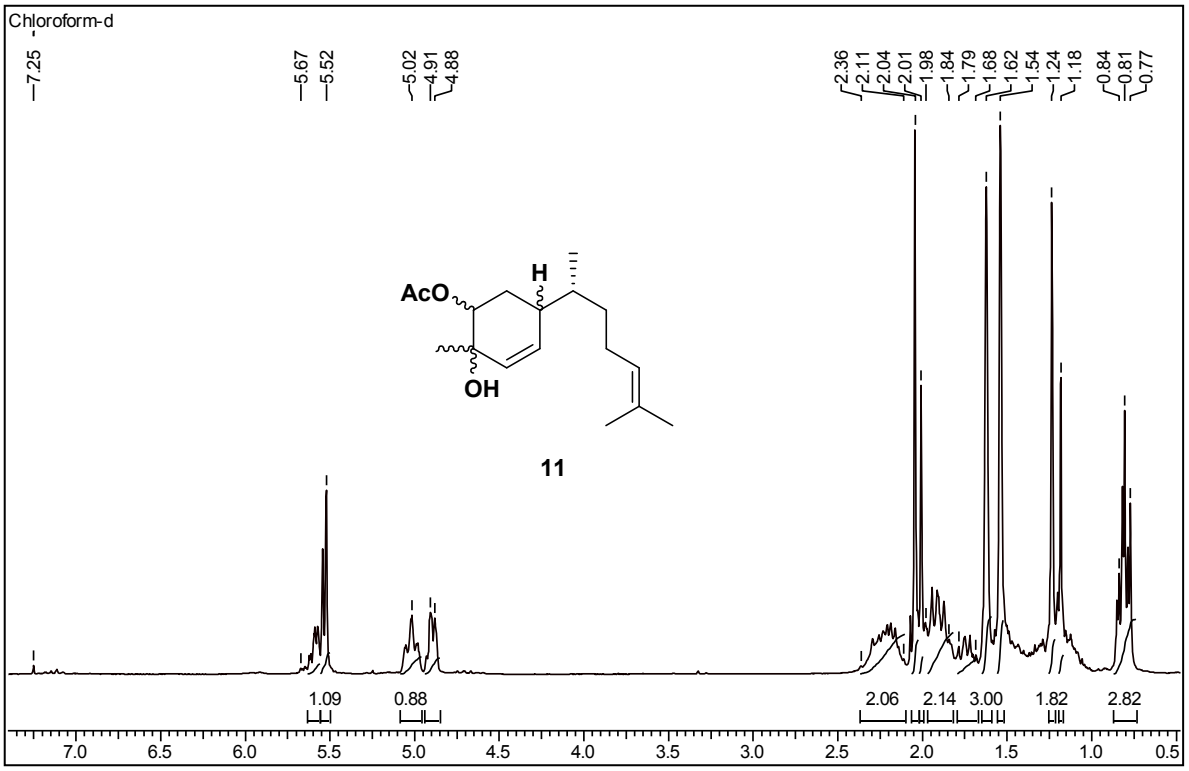
MS-ESI m/z **:** 319 $(M+1)^+$; 341 $(M + Na)^+$

Analysis

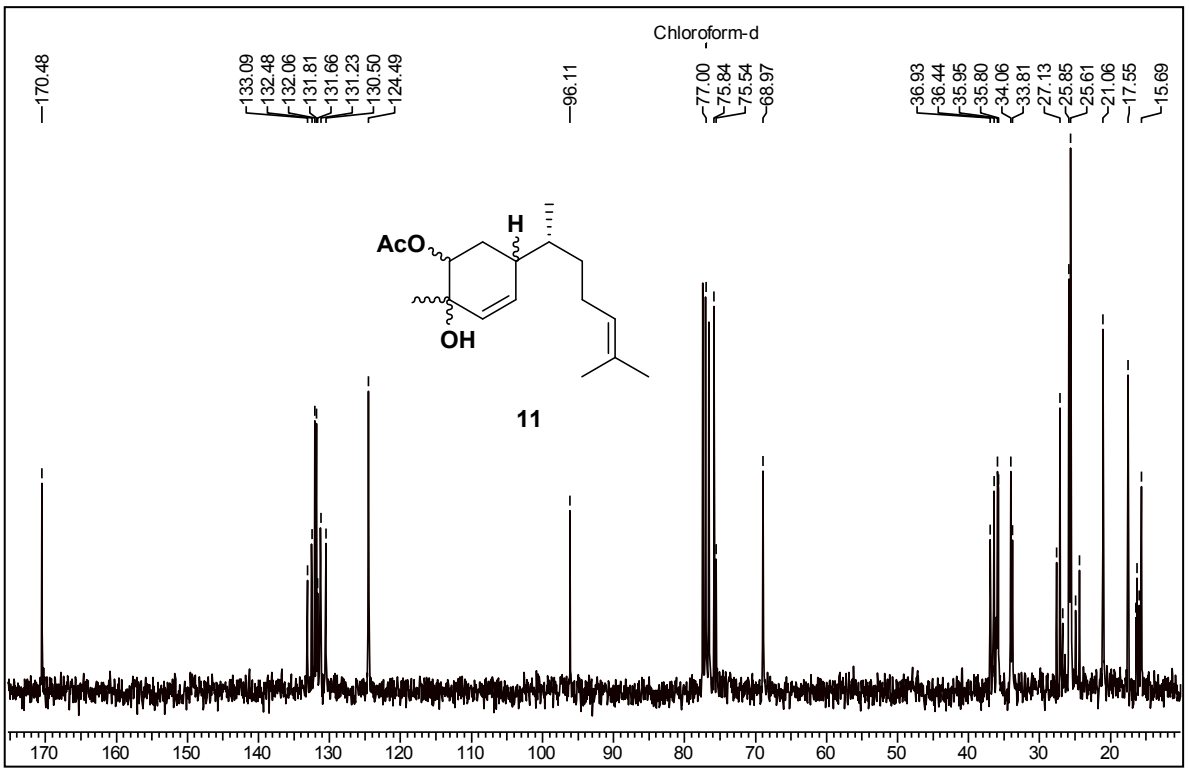
Expected **:** C, 71.67%; H, 8.23%

Found **:** C, 71.54%; H, 8.42%

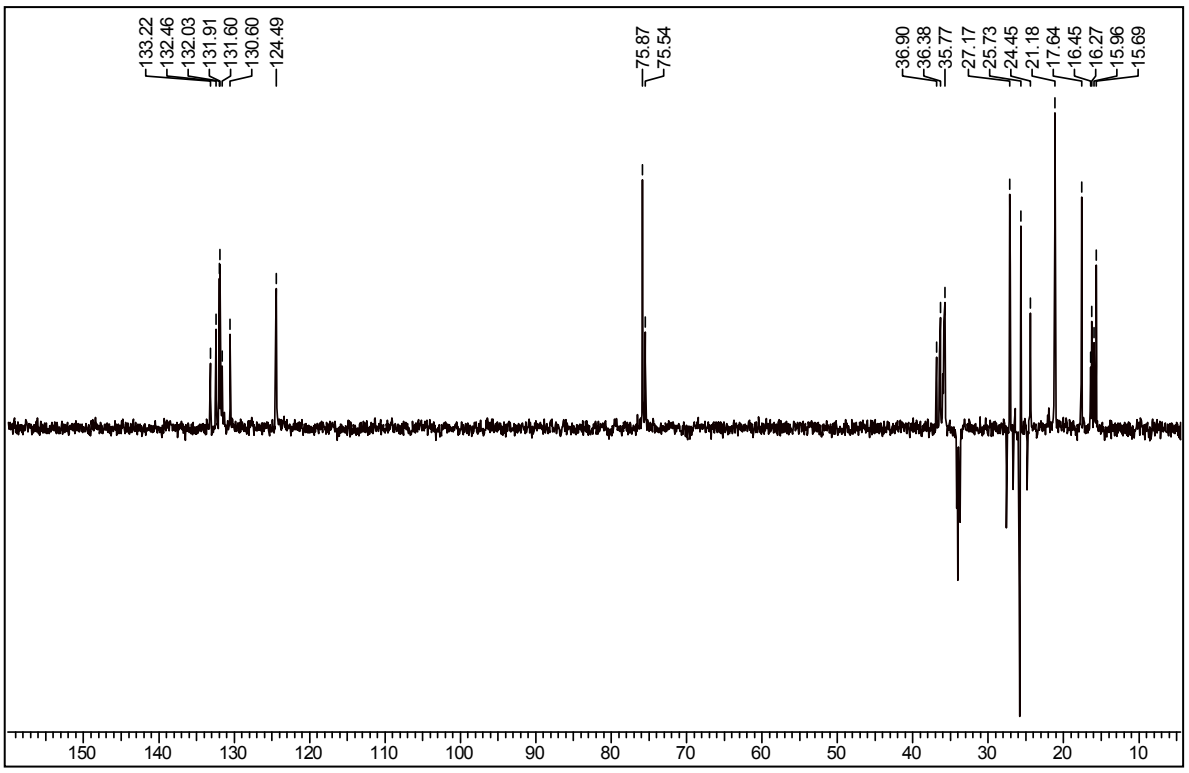
2.3.5 Spectra

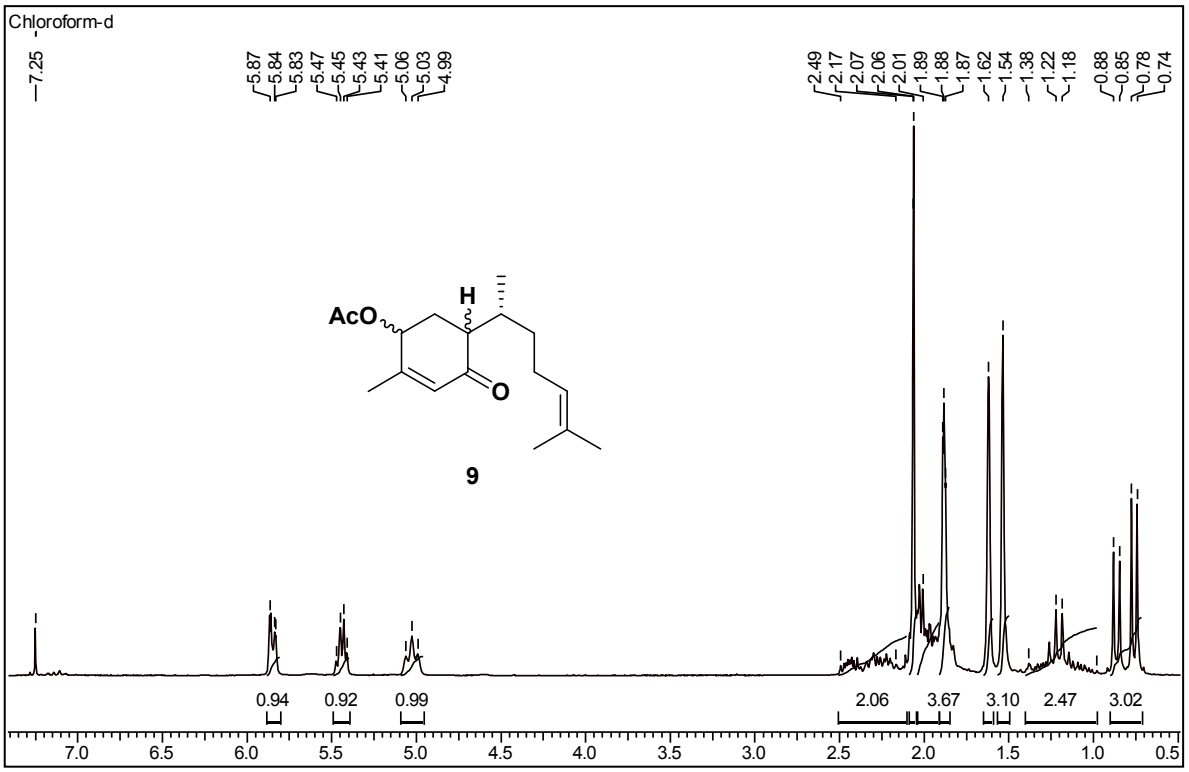


^{1}H NMR SPECTRUM ($CDCl_3$ + CCl_4, 200 MHz)

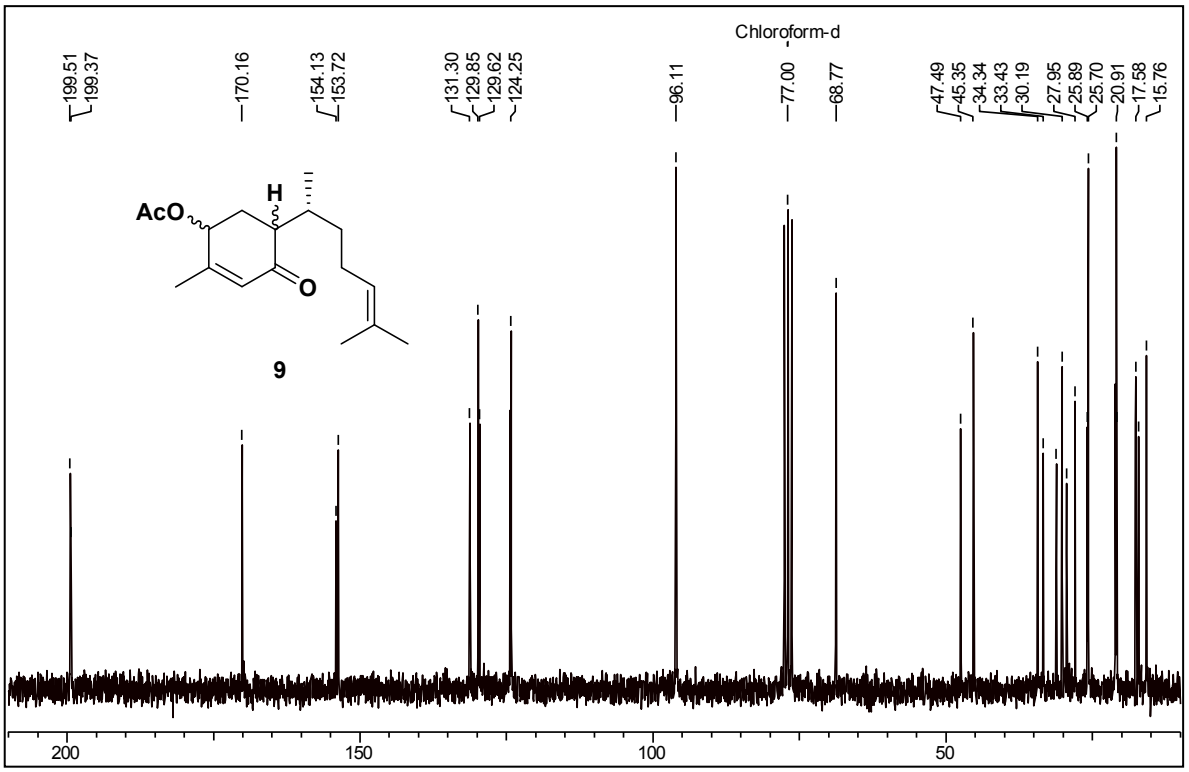


^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 50 MHz)

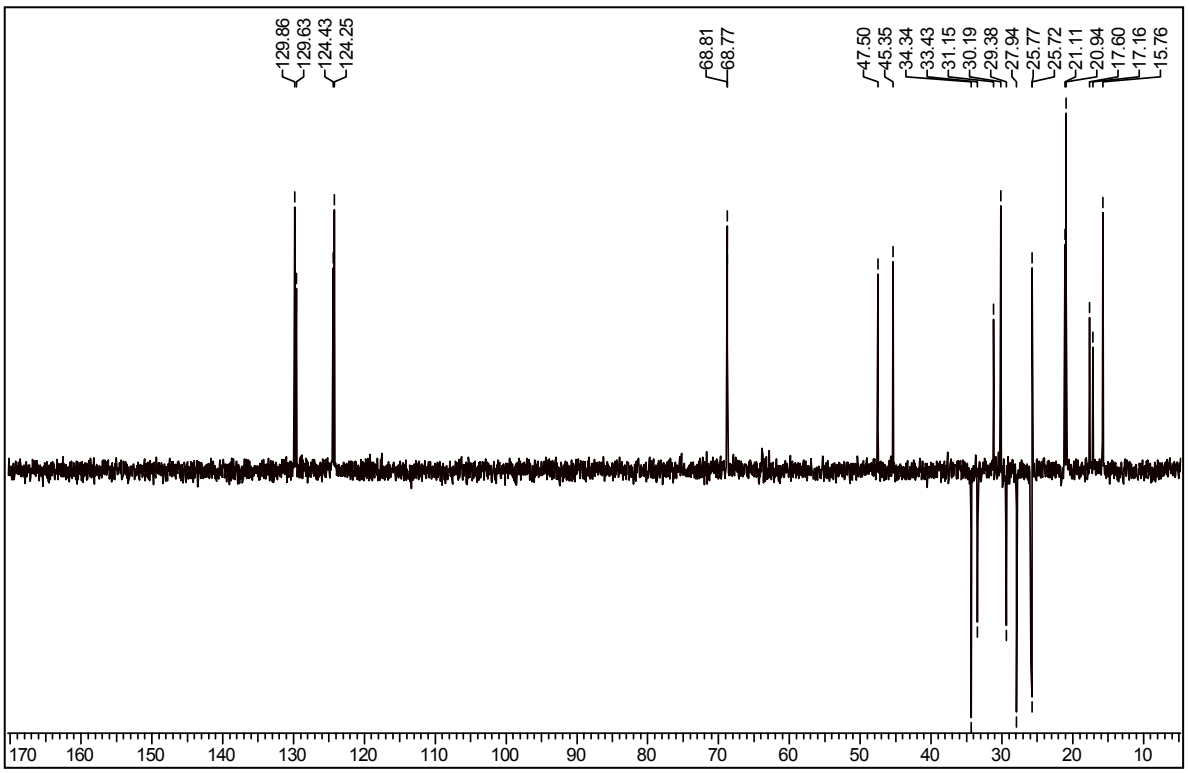


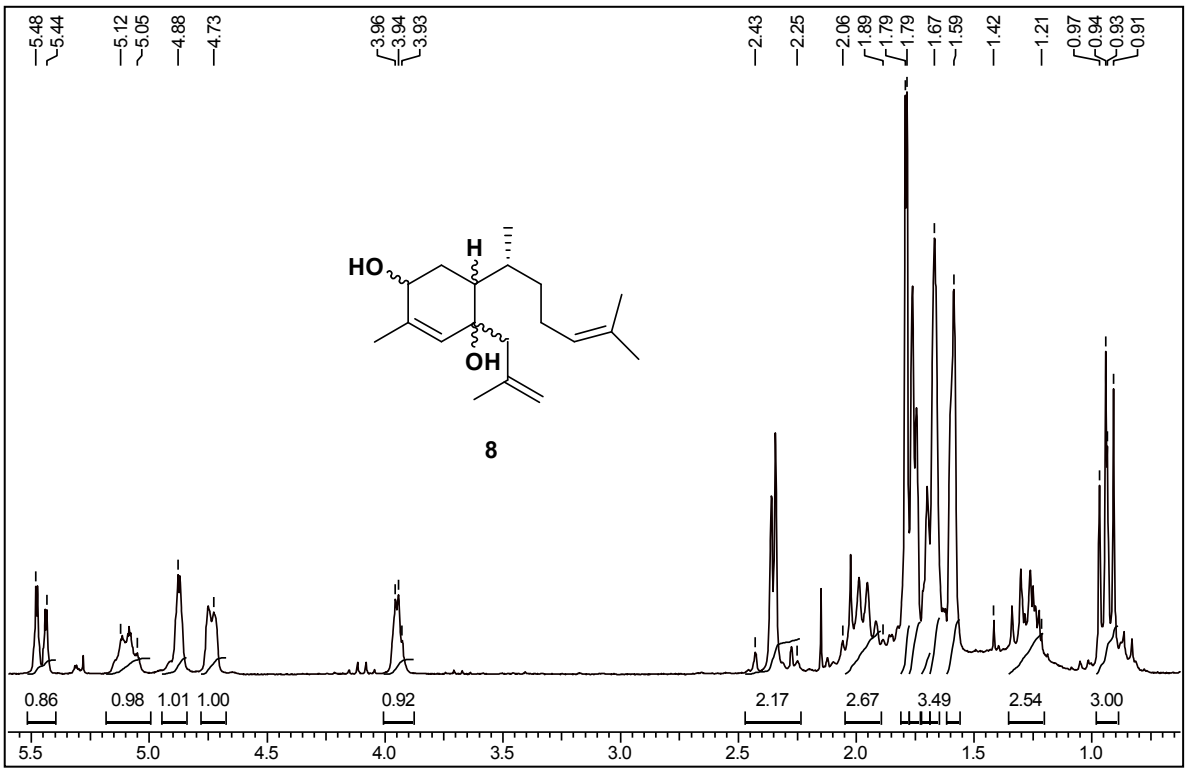


^{1}H NMR SPECTRUM ($CDCl_3$ + CCl_4, 200 MHz)

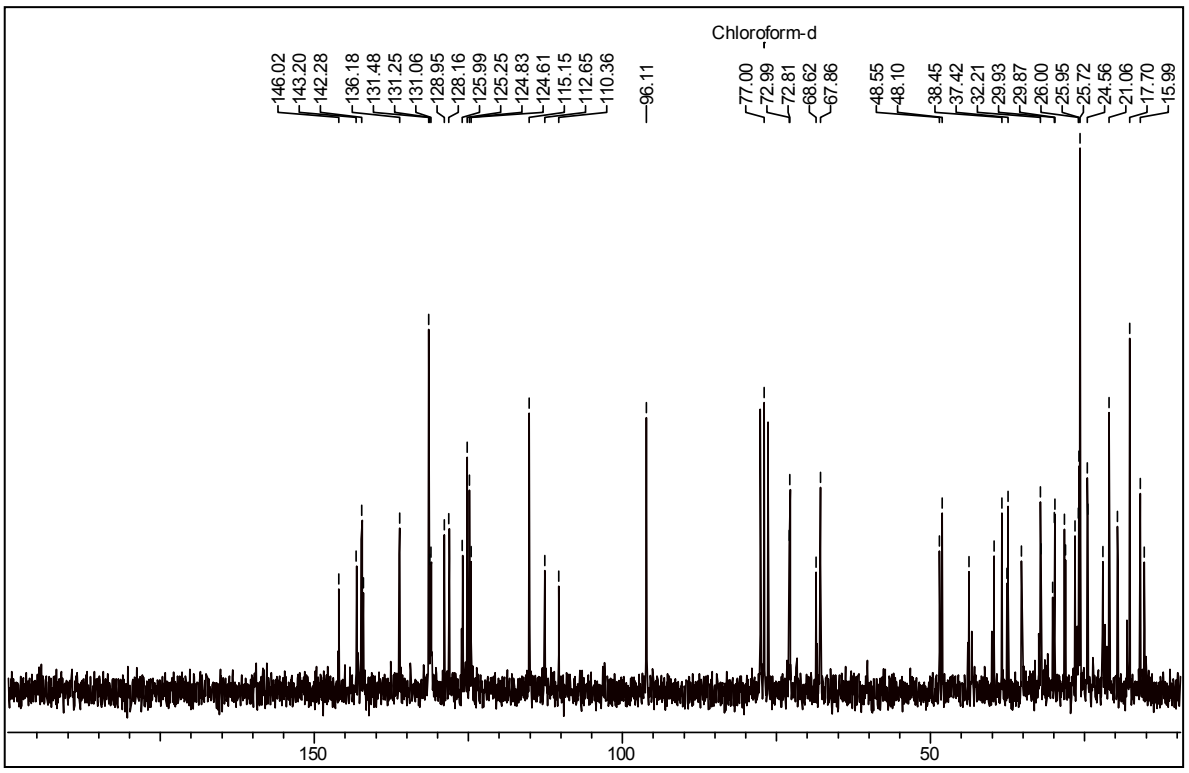


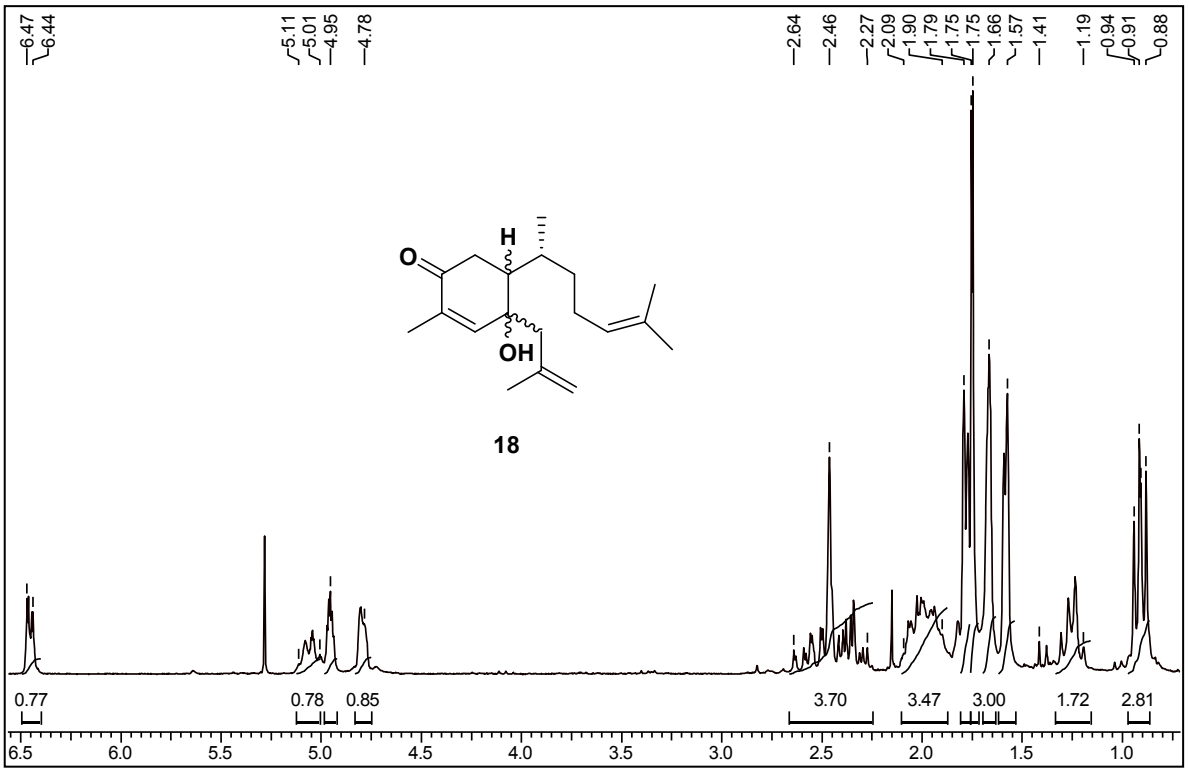
^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 50 MHz)





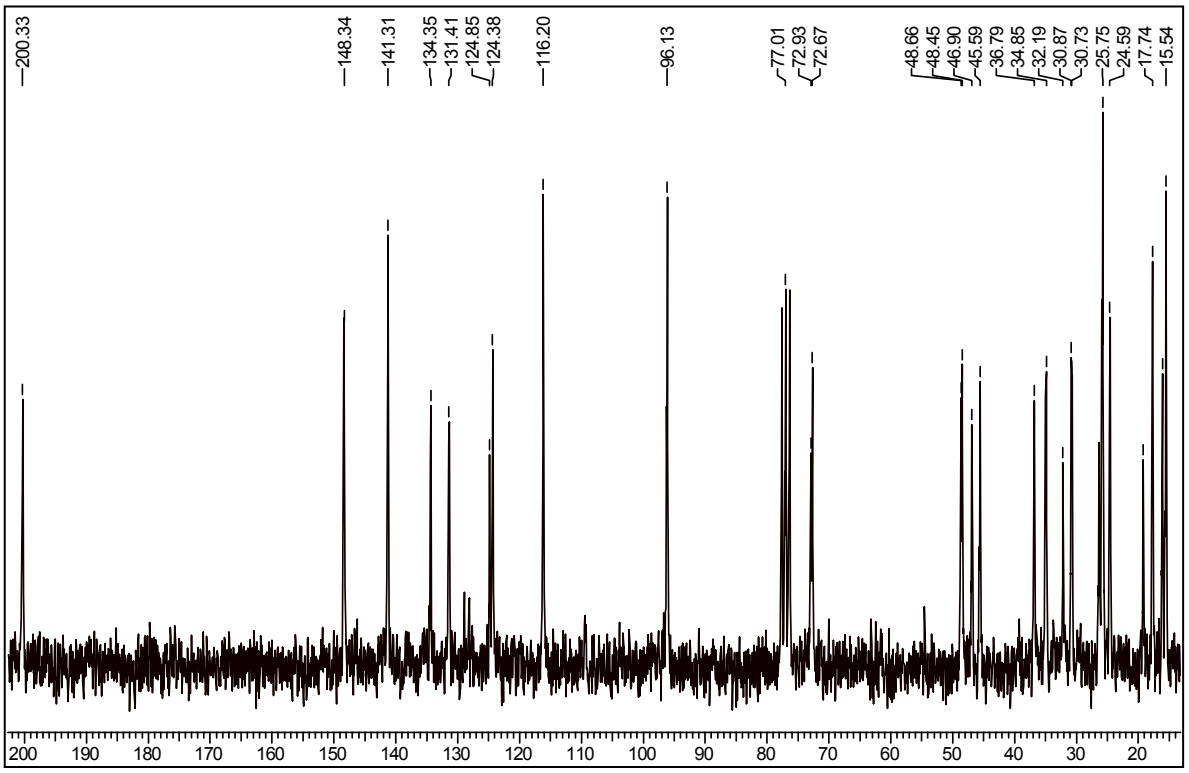
^{1}H (200 MHz) & ^{13}C (50 MHz) NMR SPECTRA ($CDCl_3$ + CCl_4)

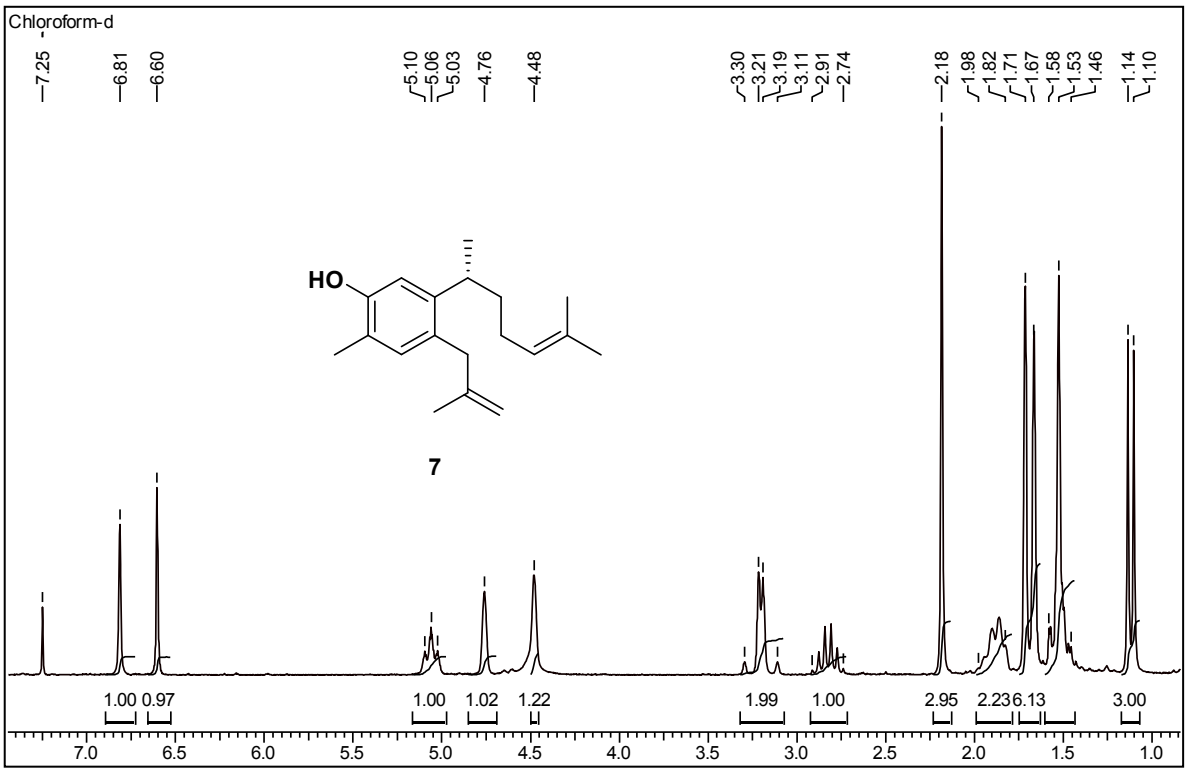




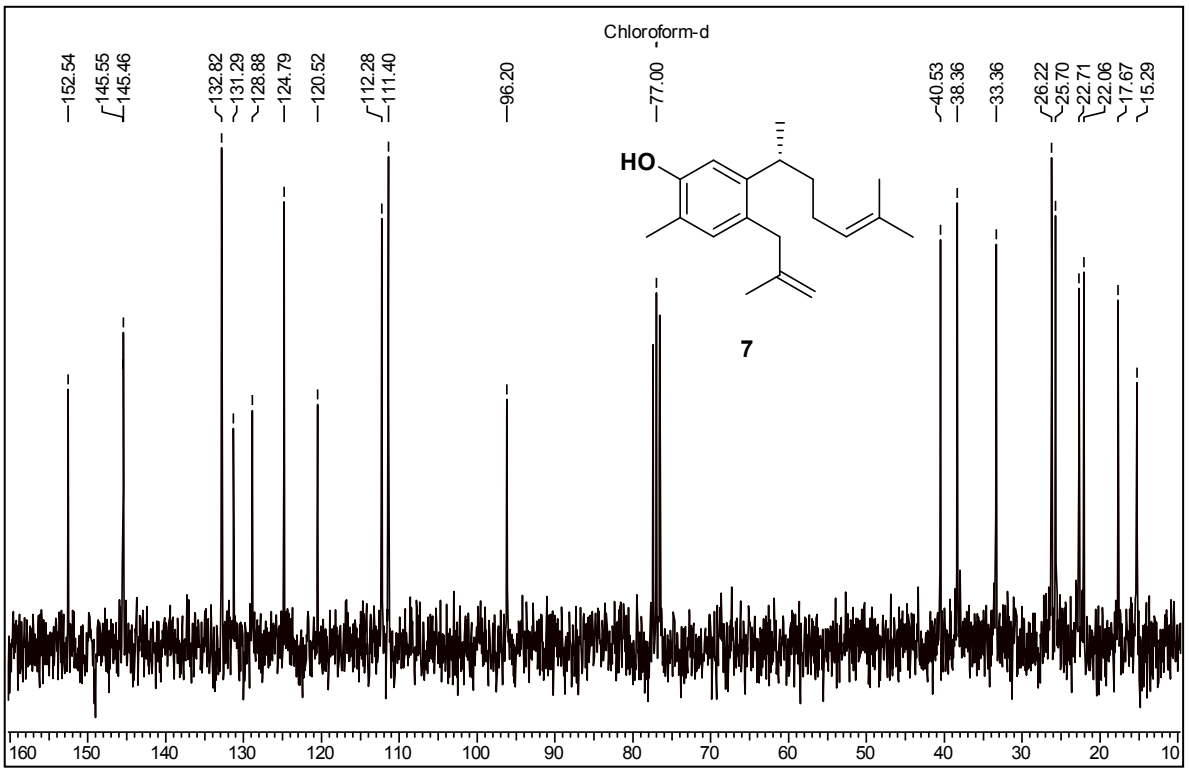
18

^{1}H (200 MHz) & ^{13}C (50 MHz) NMR SPECTRA ($CDCl_3$ + CCl_4)

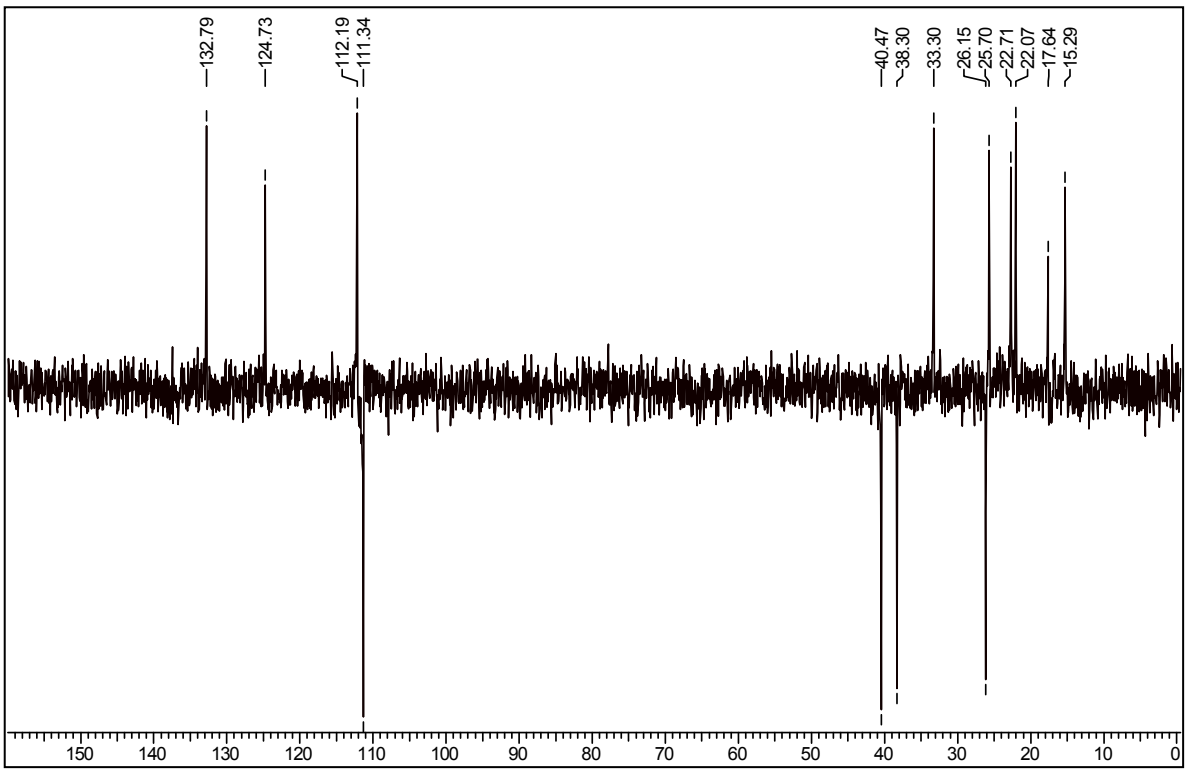


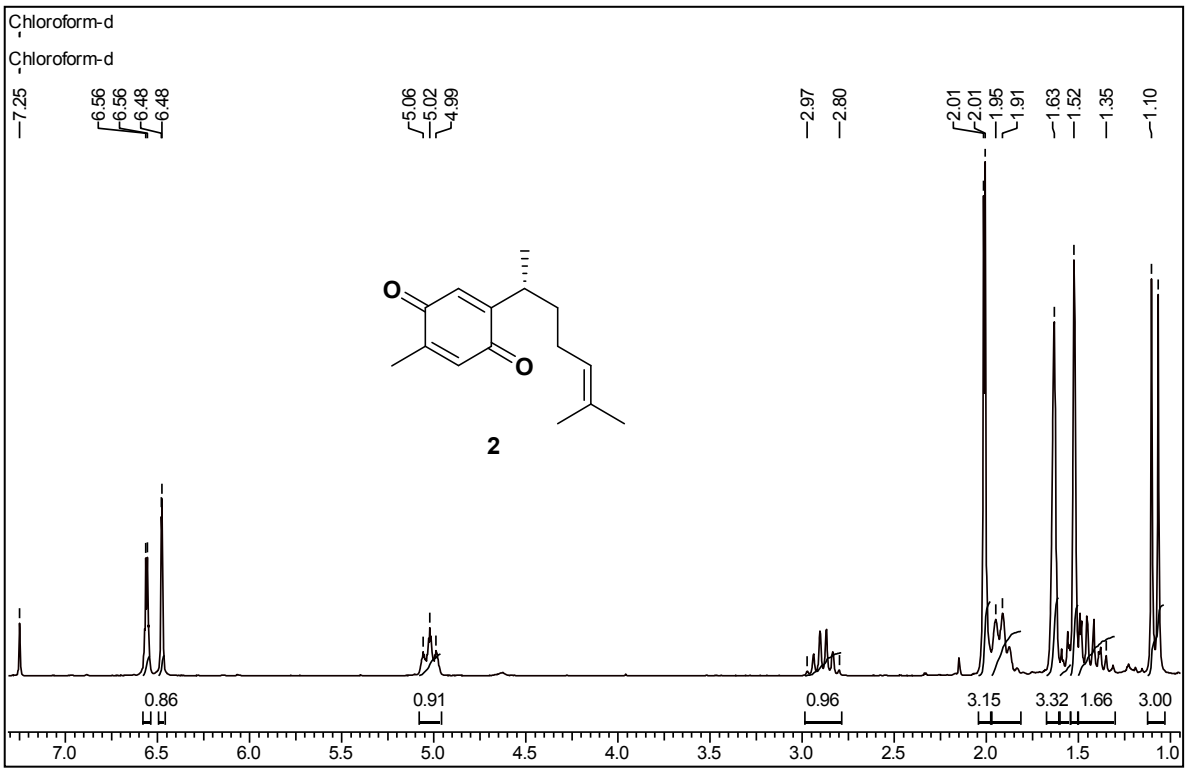


^{1}H NMR SPECTRUM ($CDCl_3$ + CCl_4, 200 MHz)

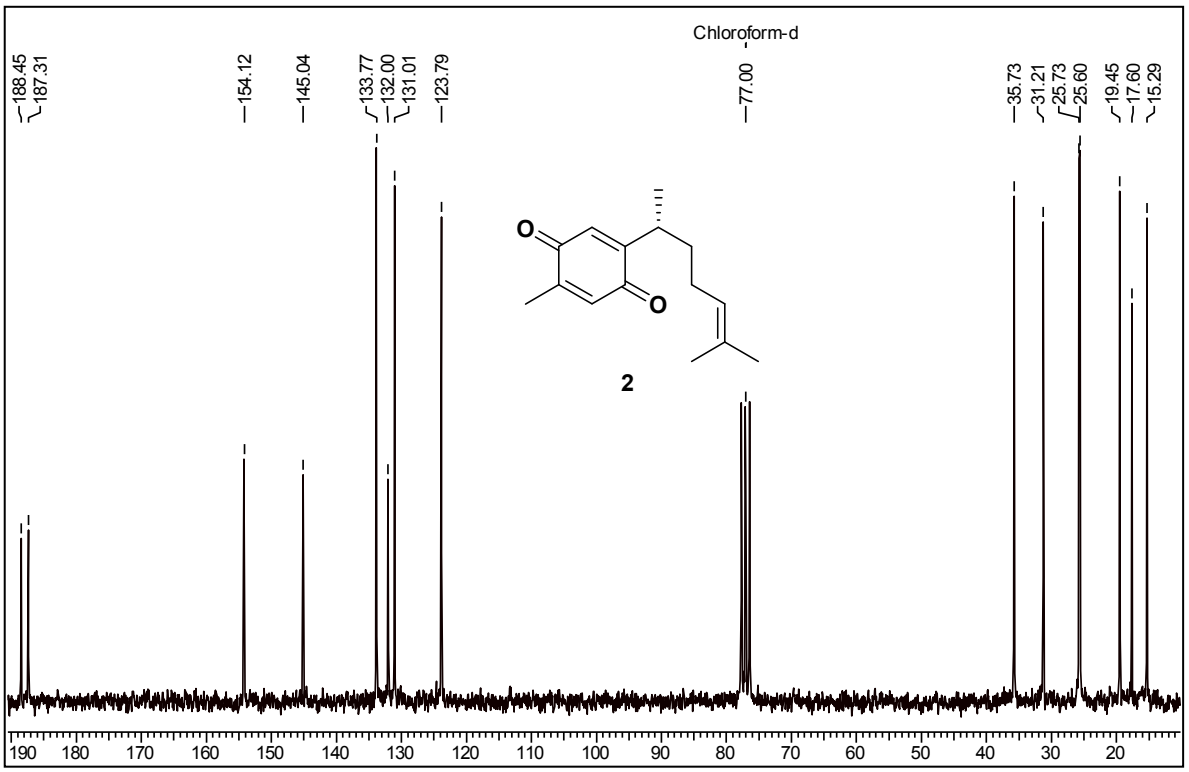


^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 50 MHz)

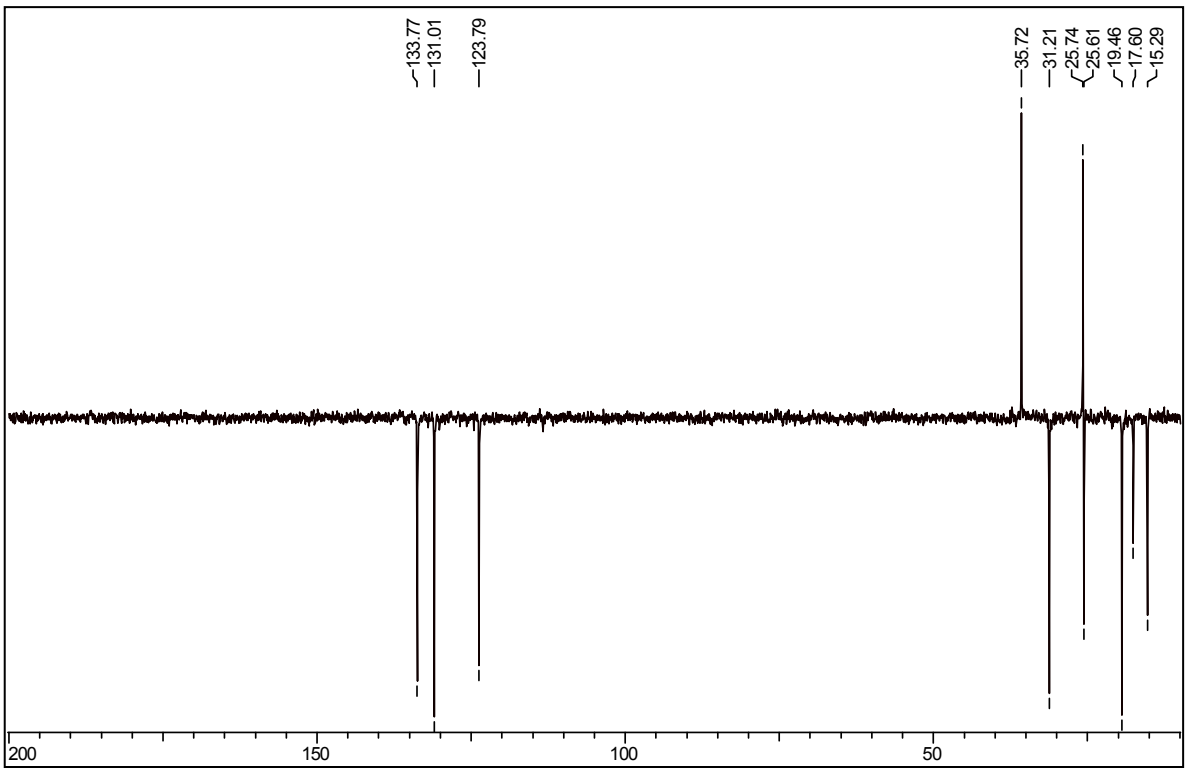


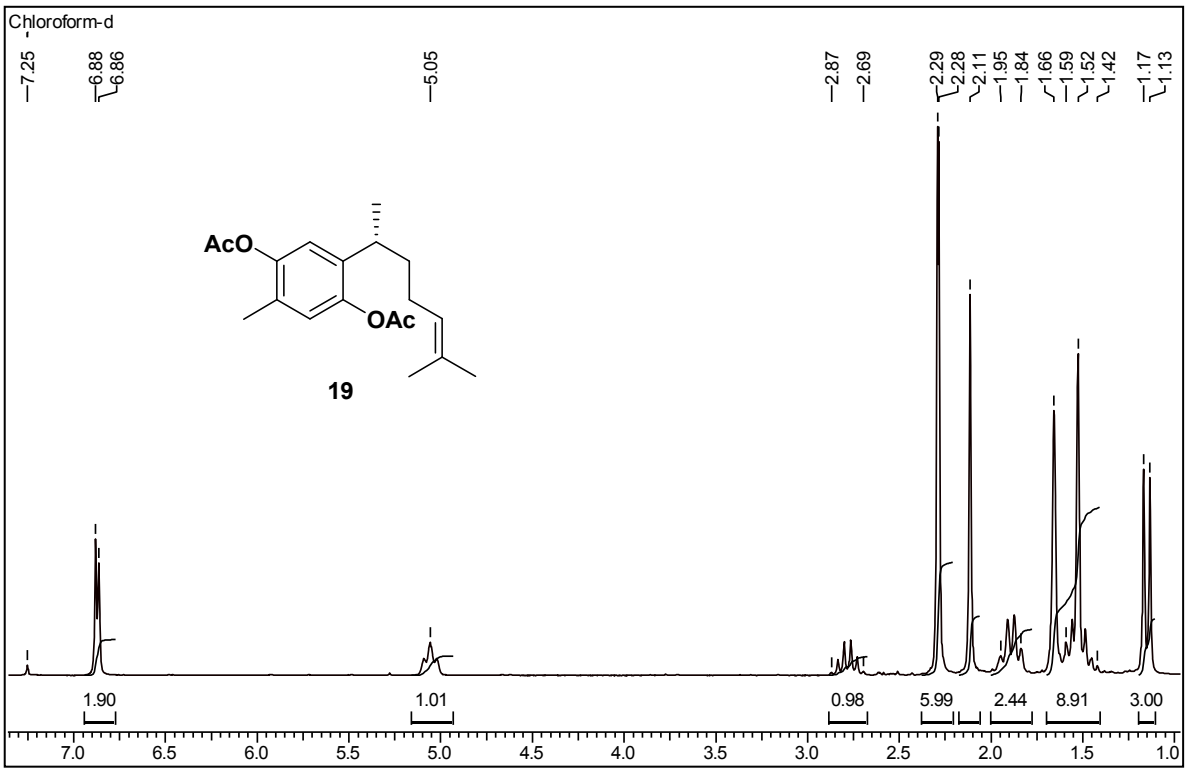


^{1}H NMR SPECTRUM ($CDCl_3$, 200 MHz)

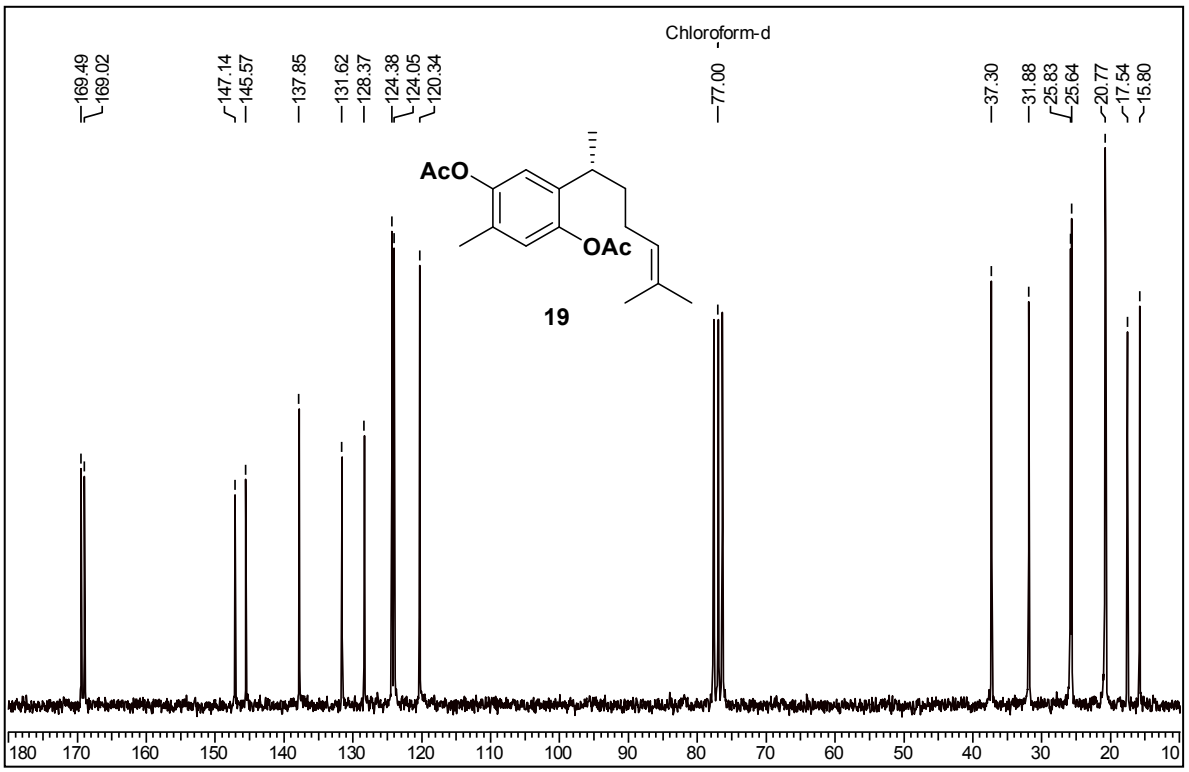


^{13}C & DEPT NMR SPECTRA ($CDCl_3$, 50 MHz)

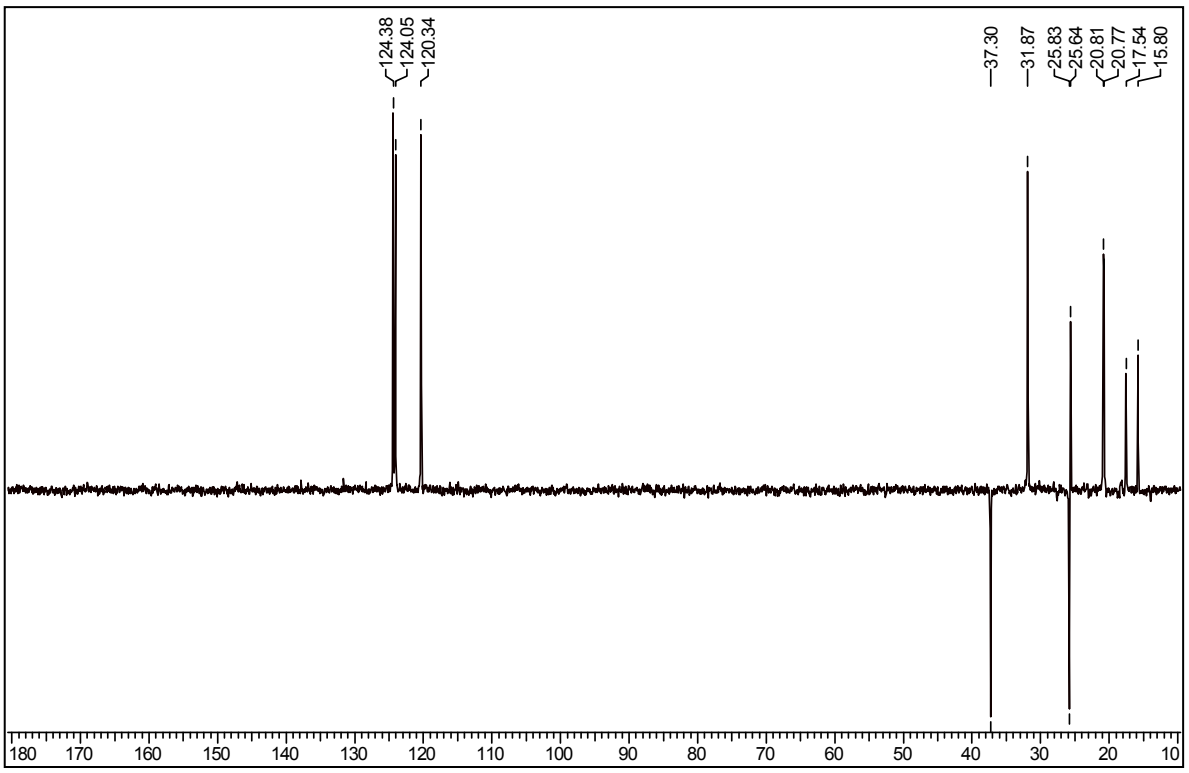




^{1}H NMR SPECTRUM ($CDCl_3$, 200 MHz)



^{13}C & DEPT NMR SPECTRA ($CDCl_3$, 50 MHz)



2.3.6 References

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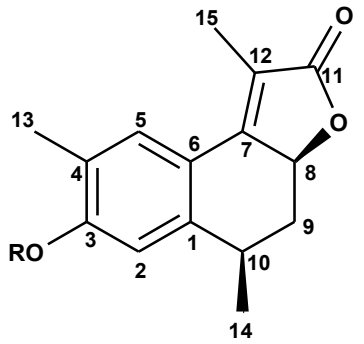
Chapter-3 : Synthesis of Heritol Using (R)-(+)-Citronellal

3.1 Introduction

In 1987, Miles'[1] *et al* have isolated an active toxin called heritol; a naturally occurring sesquiterpene from the sap of the mangrove plant *Heritiera littoralis*, which was shown to possess itchthytoxicity in ppm quantities to *Tilapia nilotica* fingerlings. Further in 1989, same authors have reported the isolation of a new natural pesticide, called heritonin (methyl ether derivative of heritol) from the same mangrove plant *Heritiera littoralis*,[2] which also possesses similar kind of toxicity. Both of these compounds have a novel structure of cadinane sesquiterpene class containing α, β-unsaturated γ-lactone moiety with an unusual oxygenation pattern.



1, R = H, (+)-Heritol

1a, R = Ac

2, R = Me, Heritonin

3.2 Structure determination

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

The IR spectrum revealed absorptions at 3450 cm^{-1} and 1750 cm^{-1}, indicating the presence of an hydroxyl group and an α, β-unsaturated γ-lactone moiety. This was further supported by the UV (cyclohexane) absorption at 228 nm (ε 11950), characteristic of butenolide moiety. The ^{1}H NMR spectrum gave resonances at δ 6.85 (s, 1H) and 7.42 (s, 1H), for two isolated protons on an aromatic ring, which was further supported by UV spectrum that gave absorptions at 217, 285 and 305 nm. Moreover, ^{1}H NMR spectrum

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

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

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

3.3 Synthesis of Heritol : *A Review*

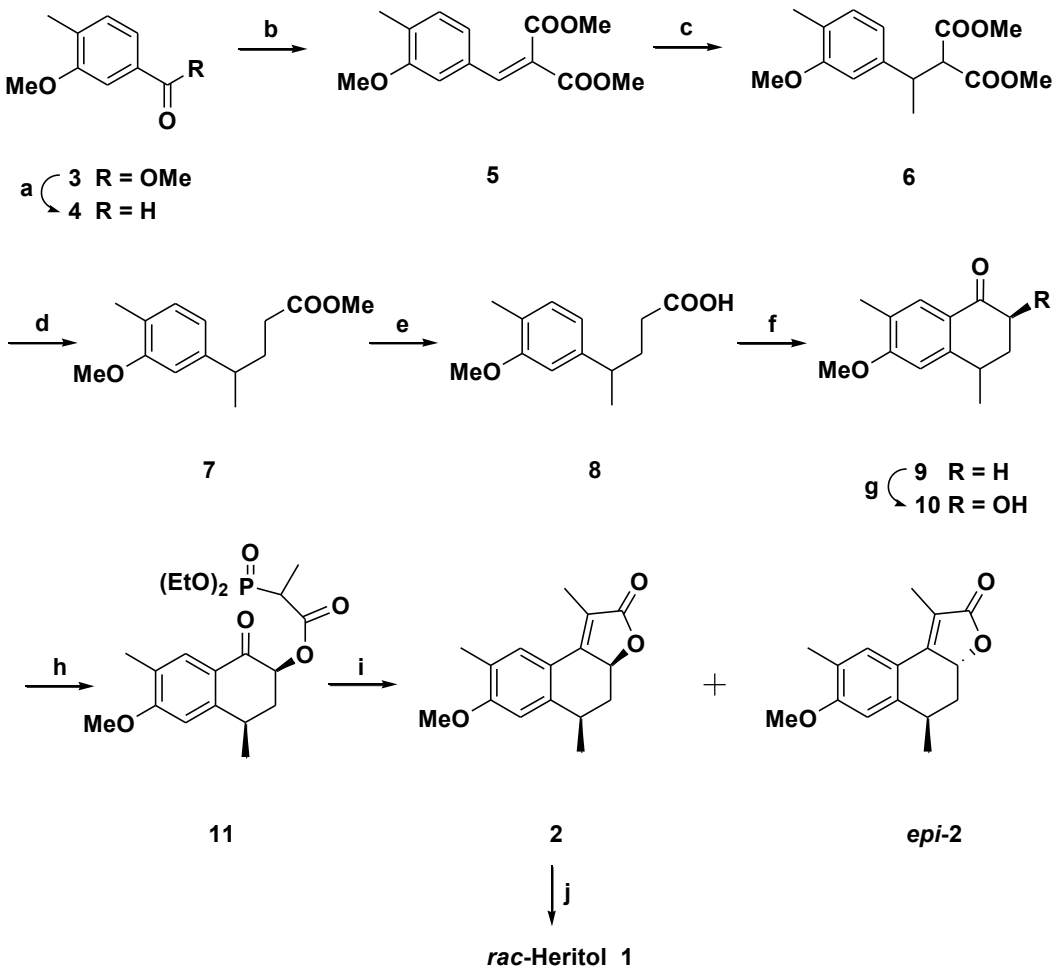
There have been only three reports on the synthesis of *rac*-heritol **1** and heritonin **2**. The first synthesis, reported by Irie *et al*,[3] employed intramolecular Wittig-Horner reaction as the key step for the construction of butenolide moiety. The other synthesis was from this group by Chavan *et al*,[4] where dihydroxylation over β, γ-unsaturated ester and elimination-lactonisation under basic conditions, were used as the key steps. Apart from these two syntheses, three methodologies have been developed by Chavan *et al* for the butenolide ring construction, using which synthesis of heritonin has been achieved. One of the methodology used *p*-toluenesulfonic acid for cyclisation of β, γ-dihydroxy ester to the butenolide; which was lateron modified by the same authors, where instead of *p*TSA,

amberlyst-15 was used for similar cyclisations. The third methodology used ceric ammonium nitrate for one step oxidative cyclisation of β, γ-unsaturated acid to the butenolide rings. The latest synthesis of *rac*-heritonin **2** was reported by Silveira *et al* in 2004, where Lewis acid catalyzed reaction of various aryl acetic acid with allylsilanes to provide 4-alkyl-2-tetralone, which was further elaborated for the synthesis of heritonin **2** and it's C-8 epimer, was described.

Irie's Approach (Scheme-1, 1990)[3]

The first synthesis of (±)-heritol **1** was reported by Irie *et al* utilizing tetralone **9**.

Scheme-1 : (Irie *et al*, *Chem. Pharm. Bull.* **1990**, *38 (7)*, 1852-1856)



Reagents and conditions *: a) (i) LAH; (ii) MnO_2; b) $CH_2(COOMe)_2$; c) Me_2CuLi, ether; d) (i) KOH, H^+, 150-170 ^oC; (ii) CH_2N_2; e) KOH; f) $(COCl)_2$, $AlCl_3$, 35% overall from **3**; g) $PhI(OAc)_2$, 67%; h) $CH_3CH[C(O)Cl]P(O)(OEt)_2$; i) NaH, benzene, 1.5%; j) BCl_3.*

The key step in the synthesis involves the construction of the butenolide moiety by intramolecular Wittig reaction (Wadsworth-Emmons modification), utilizing tetralone intermediate **9**, which was prepared by the following series of reactions from methyl 3-methoxy-4-methylbenzoate **3**. Thus, reduction of **3** with LAH followed by MnO_2 oxidation of the resulting alcohol gave aldehyde **4**. Condensation of **4** with diethyl malonate furnished the benzal malonate **5**. Methyl group was introduced by 1,4-addition using lithium dimethylcuprate on **5** to provide diester **6**, which was transformed to the ester **7** by alkaline hydrolysis of the diester **6** and concomitant decarboxylation at 150-170 ^oC, followed by Arnt-Eistert one carbon homologation of the corresponding acid. It was hydrolyzed to the corresponding acid **8**, which on treatment with oxalyl chloride followed by Friedel-Craft's acylation using aluminium chloride in CH_2Cl_2 furnished the tetralone **9**.

The overall yield of **9** from the methyl benzoate **3** was reported to be 35%. Oxidation of **9** with iodoso benzene diacetate gave the stereoisomeric α-hydroxy ketone **10** in 67% yield. Esterification of the hydroxy ketone **10** with α-(diethylphosphono) propionylchloride gave the phosphonate **11** in good yield. Intramolecular Emmons-Wadsworth reaction of the above phosphonate **11** with several bases in different solvents was sluggish and afforded inseparable mixture, consisting of **2** and it's C-8 epimer (10: 1 ratio respectively) in 1.5% overall yield. Demethylation of the heritol methyl ether **2** with boron trichloride afforded heritol **1** as a *racemic* mixture. The synthetic *rac*-heritol had mp 245-246 ^oC, lower than that of optically active (+)-heritol **1**. Heritol synthesized by above sequence of reactions was identical in all other respects with the natural product.

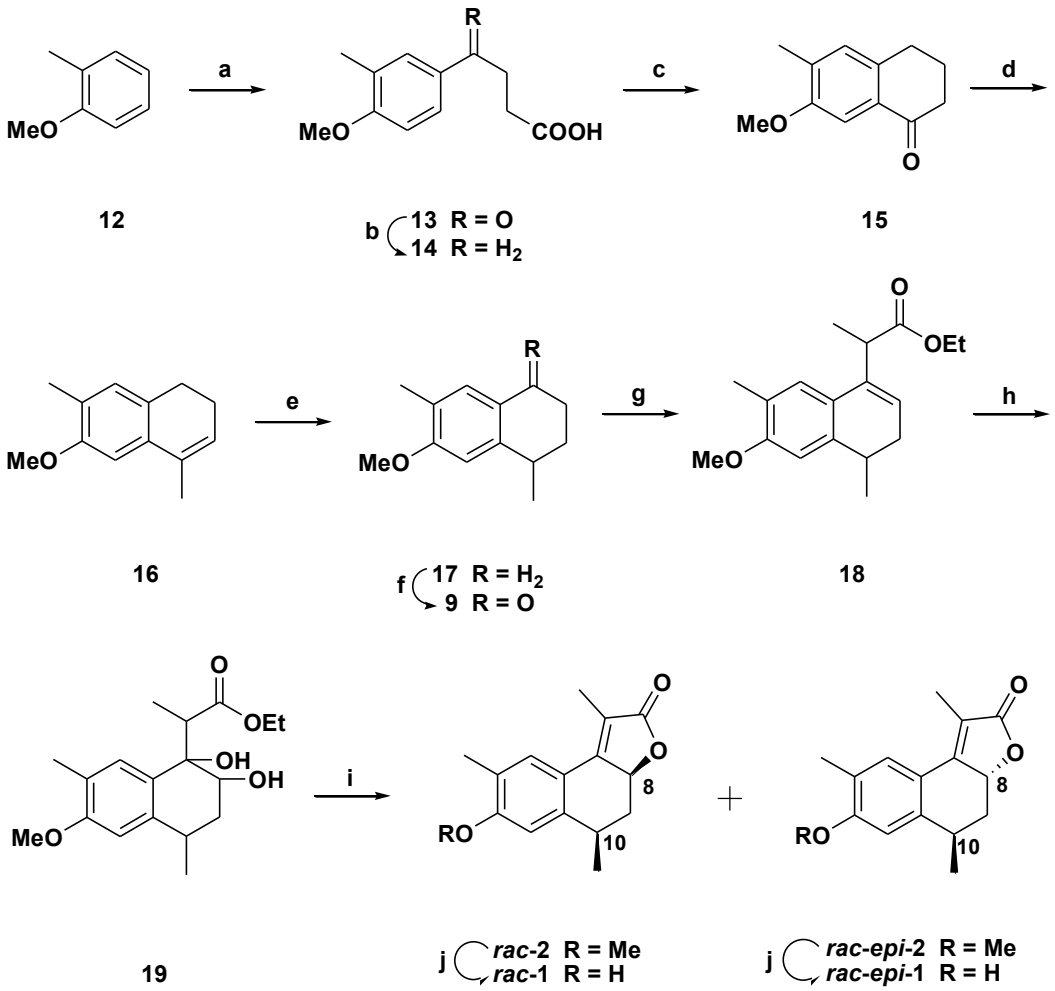
Chavan' s Approach (Scheme-2, 1991)[4]

The second synthesis of *rac*-heritol, reported by this group (Chavan *et al*) in 1991, used the same tetralone intermediate **9** (previously reported by Irie *et al*[3]) by a different route for butenolide ring construction, but in high yields compared to the previous one.

Accordingly, tetralone **9** was obtained starting from *o*-cresol methyl ether **12** by standard sequence of high yielding reactions. First of all, Friedel-Craft's acylation using succinic anhydride provided the keto acid **13** in 85% yield, which under Clemmenson's reduction condition underwent keto deoxygenation to give butyric acid derivative **14**. Intermediate **14** on trifluoroacetic anhydride treatment underwent cyclisation to furnish tetralone **15** in 80% yield. 1,4-Ketone transposition and introduction of methyl group was

achieved as shown in the scheme-2 using standard functional group transformations to provide required tetralone **9** in 40% overall yield starting form *o*-cresol methyl ether **12**.

Scheme-2 : (Chavan *et al*, *Tetrahedron* **1991** *47*, 5759-5768)



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

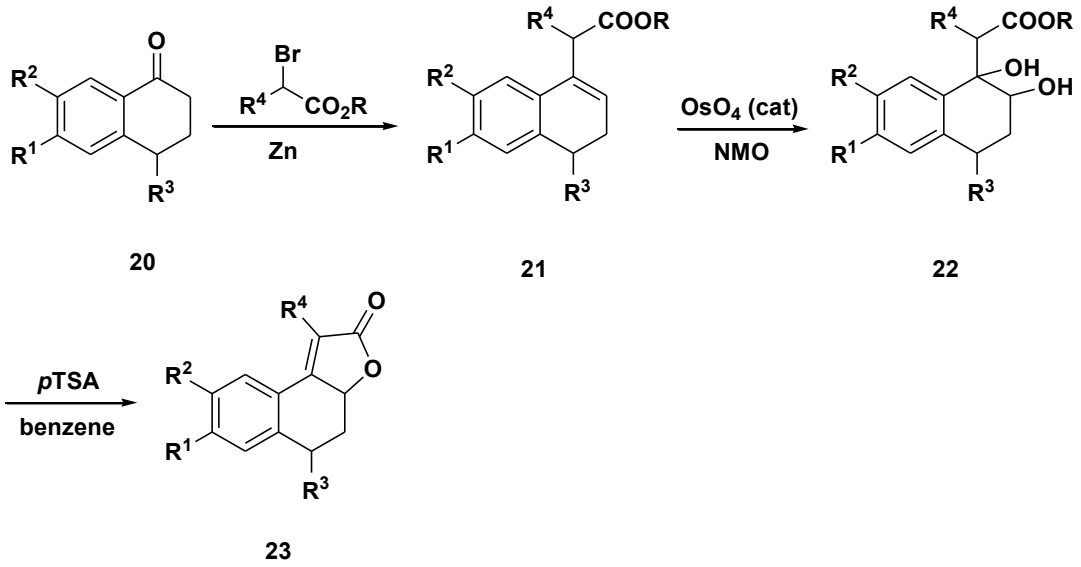
This tetralone **9** on Reformatsky reaction with ethyl-2-bromopropionate, followed by acidic work-up gave β, γ-unsaturated ester **18** as a mixture of diastereomers; which on dihydroxylation using osmium tetroxide gave the key diol intermediate **19**. Diol **19** on mesylation in refluxing benzene provided 3: 2 diastereomeric mixture of heritonin **2** and

it's C-8 epimer, which were separated by crystallization and deprotected using aluminium chloride-ethanethiol to give *rac*-**1** and it's C-8 *epimer* as the sole product, respectively.

Other butenolide ring construction protocols used for the synthesis of Heritol[5-7]

The first methodology reported by Chavan *et al*[5] used *p*-toluenesulfonic acid for one pot dehydration as well as lactonisation purpose. Accordingly; β, γ-unsaturated ester **21** prepared from tetralone **20** by Reformatsky reaction, was dihydroxylated to give diol **22**, which was then treated with *p*-toluenesulfonic acid in refluxing benzene to give required butenolide moiety **23** in high yields (Scheme-3). Using this methodology, heritonin and it's C-8 epimer has been synthesized in 90% overall yield. Instead of *p*TSA, amberlyst-15 has also been explored for the green synthesis of heritonin **2**, heritol **1** and it's analogs.[6]

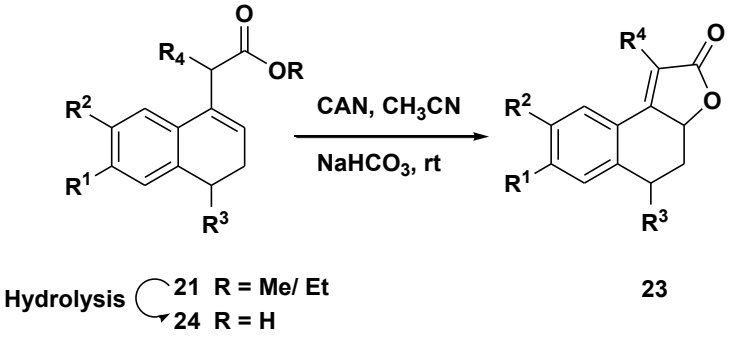
Scheme-3 : (Chavan *et al*, *Tetrahedron Lett.* **1992**, *33*, 4605-4608)



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

The second method reported by Chavan *et al*,[7] utilized ceric ammonium nitrate for oxidative cyclisation of the β, γ-unsaturated acid **24** to the required butenolides. Accordingly, acid **24**, prepared by alkaline hydrolysis of the β, γ-unsaturated ester **21**, on treatment with CAN in acetonitrile provided butenolides **23** in good to excellent yields (Scheme-4). Using this procedure, heritonin **2** was prepared from the corresponding acid in 36% yield.

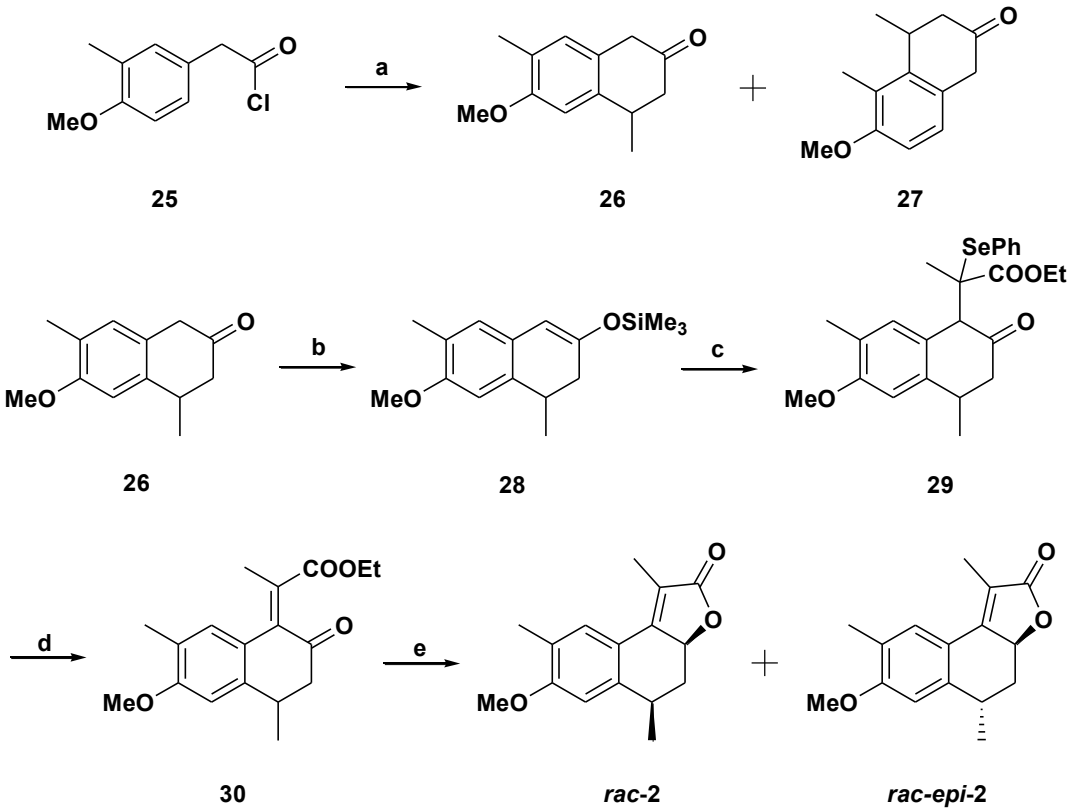
Scheme-4 : (Chavan *et al*, *J. Chem. Soc., Chem. Comm.* **1994**, 1101-1102)



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

Silveira's Approach (Scheme-5, 2004)[8]

Scheme-5 : (Silveira *et al*, *Tetrahedron Lett.* **2004**, *45*, 4077-4080)



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

This particular approach differs from the rest in butenolide ring construction. They have mainly used two key steps, (i) $AlCl_3$-mediated Friedel-Craft's reaction of aromatic acyl chlorides with allyltrimethylsilanes for the formation of β-tetralones[9] and (ii) Lewis acid-mediated alkylation of the silylenolethers with α-halo-α-phenylselenoesters.[10]

Accordingly, aryl acid chloride **25** was treated with allyltrimethylsilane in the presence of anhydrous aluminium chloride to give β-tetralone **26**, along with isomeric **27** in 41% overall yield. They were separated by repeated crystallization to give **26** in 25% isolated yield.

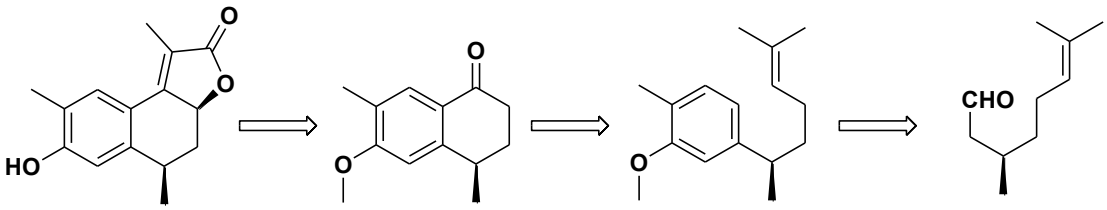
Further, for butenolide ring construction, enol ether **28**, prepared from β-tetralone **26**, was treated with α-chloro-α-phenylseleno-ethylpropionate in the presence of $ZnBr_2$ to furnish γ-ketoester **29**, which on mCPBA oxidation at -78 ^oC provided α, β-unsaturated ester **30** in 41% yield, together with 16% of it's isomeric *trans*-ester. Finally, ester **30** was cyclised upon reduction with $NaBH_4$ followed by acid hydrolysis to give *rac*-heritonin **2** and it's C-8 epimer as a 3: 2 diastereomeric mixture in 75% overall yield (Scheme-5).

3.4 Present work : *Results and discussion*

The present chapter primarily concerns with the asymmetric synthesis of heritol, a novel sesquiterpene lactone and thus confirmation of it's absolute configuration by the first enantiospecific synthesis using (*R*)-(+)-citronellal as the source of chirality.

The reasons behind undertaking it's synthesis were: (i) it was suggested that heritol is a potential biocompatible pesticide; (ii) difficulties associated with the introduction of chirality at the nonfunctionalised benzylic position; (iii) absolute configuration of heritol was not confirmed and (iv) interest in employing the renewable resources of the nature for the synthesis of natural products, therefore it was thought to synthesize enantiopure heritol, and for that purpose (*R*)-(+)-citronellal was found as the key synthon, which has already been utilized for the enantiospecific synthesis of laevigatin,[11] (+)-herbertenol,[12] (-)-parvifoline, (+)-isoparvifolinone and (-)-curcuquinone (Chapter-2). The present work describes the first synthesis of enantiopure heritol starting from (*R*)-(+)-citronellal, utilizing the methodology developed in these laboratories,[5] where *p*TSA has been used as the catalyst for butenolide ring construction from the corresponding β, γ-unsaturated ester.

Scheme-6

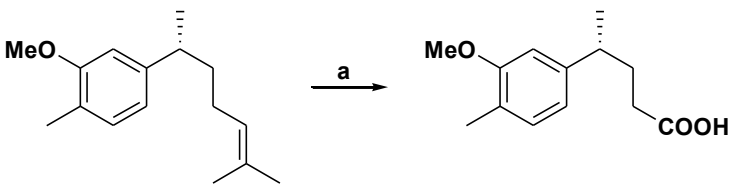


1 **31** **32** **(*R*)-(+)-Citronellal**

As delineated in the retrosynthetic analysis (Scheme-6)**,** anisole derivative **32** was envisioned as the starting material (which has previously been prepared as described in the chapter-2, section-2 for the synthesis of (-)-parvifoline), for the preparation of the key tetralone intermediate **31**. The remaining butenolide ring construction could be achieved by protocol reported earlier by this group for the synthesis of *rac*-heritol.[4]

Thus, the synthesis initiated from anisole **32**, which was prepared enantiospecifically from (*R*)-(+)-citronellal (98% ee) as the chiron. Then, the next target was to synthesize tetralone intermediate **31**. To get tetralone **31**, it was thought to utilize the same acid intermediate, as reported by Irie *et al*,[3] which might undergo cyclisation on either Friedel-Craft's acylation conditions or just by treatment with triflouroacetic anhydride. To have an acid intermediate **33**, double bond of the anisole derivative **32** must be oxidatively chopped off and for this purpose Weinreb's protocol[13] was adopted, according to which anisole derivative **32** was treated with Jones' reagent in the presence of osmium tetroxide (catalytic) in acetone at room temperature for 7 hours to furnish the required acid intermediate **33** in 82% isolated yield (Scheme-7).

Scheme-7



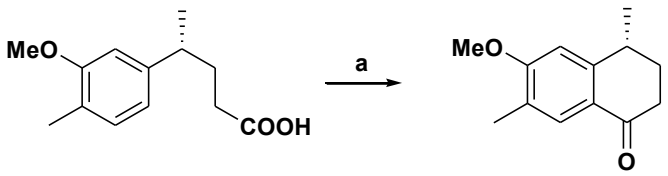
32 **33**

Reagents and conditions *: a) OsO_4 (cat), Jones' reagent, acetone, rt, 7 h, 82%.*

It was completely characterized by it's IR, NMR and mass spectral data. It's IR spectrum revealed a strong stretching band at 1708 cm^{-1}, characteristic of a carbonyl group of an acid derivative; and also a broad absorption band extended from 3300 cm^{-1} to 2700 cm^{-1}, which distinguishes the carboxylic acid derivatives from the rest of the carbonyl compounds. Further, absence of multiplet of an olefin proton at δ 5.09, and two singlets at δ 1.54 and 1.68, characteristic of the isopropylidene structural unit of **32**, in the ^{1}H NMR spectrum of the isolated product; which also revealed a broad singlet at δ 8.87, characteristic of a carboxylic acid functionality, clearly suggested the formation of intermediate **33**. This was further confirmed by it's ^{13}C NMR spectrum, which showed a quaternary carbon singlet at δ 179.9 for the carbonyl group. Elemental analysis and mass spectrum finally ascertained the formation of acid **33**.

After successfully synthesizing acid **33**, the next job was to cyclise it to the key tetralone intermediate **31**, for which **33** was treated with triflouroacetic anhydride[14] in triflouroacetic acid at 0 ^{o}C for 3 hours. Under this condition, tetralone **31** was obtained as the sole product in 80% isolated yield as a white solid (mp 110 ^{o}C) (Scheme-8).

Scheme-8



33 **31**

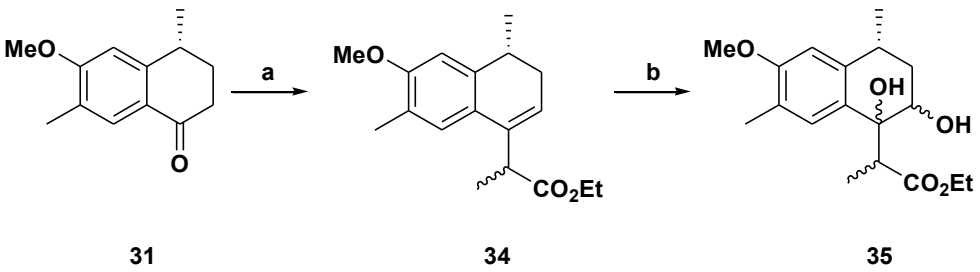
Reagents and conditions **:** *a) triflouroacetic anhydride, triflouroacetic acid, 0 ^{o}C, 3 h, 80%.*

The IR spectrum of **31** revealed absorption at 1670 cm^{-1}, characteristic of a conjugated carbonyl group. It's ^{1}H NMR spectrum exhibited a singlet in the aromatic region at δ 6.63 and a doublet δ 7.79 (J = 0.8 Hz), assigned to the two *para* distributed aromatic protons. Also, ^{13}C NMR spectrum revealed four quaternary singlets at δ 124.9, 125.4, 149.2 and 162.1; attributed to the four aromatic quaternary carbon atoms; and one at δ 196.8, attributed to the carbonyl carbon. This suggested the cyclisation of the acid side chain over aromatic ring. Also, resonance at δ 7.79 in the ^{1}H NMR spectrum indicated *para*

directed cyclisation due to electron releasing methoxy group. Tetralone **31** was further confirmed by it's mass spectrum, which exhibited a peak of $(M+1)^+$ at 205, and it was finally ascertained by it's elemental analysis, which was in good agreement with the calculated values.

Butenolide ring construction over tetralone **31** would have completed the synthesis of heritonin, which was achieved by utilizing the protocol developed in this group earlier.[4] Accordingly, tetralone **31** was converted to the β, γ-unsaturated ester **34** by Reformatsky reaction using ethyl-2-bromopropionate, which was further dihydroxylated using osmium tetroxide in the presence of *N*-methylmorpholine-*N*-oxide to provide the diol **35** in high yields (Scheme-9).

Scheme-9



31 **34** **35**

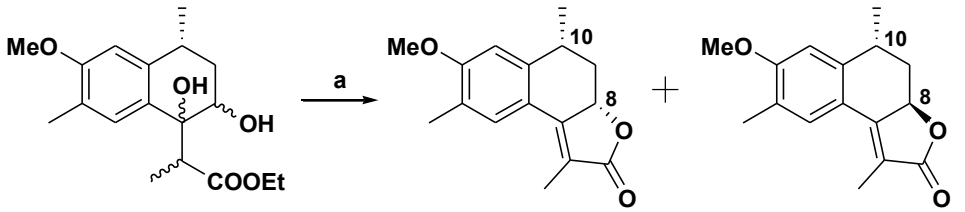
Reagents and conditions *: a) Zn, ethyl-2-bromopropionate, iodine, ether, reflux, 3 h, H^+, 80%; b) OsO_4 (cat), NMO, CH_3CN-H_2O, rt, 24 h, 95%.*

Both the intermediates **34** and **35** were mixture of diastereomers and as the stereochemistry at these newly generated chiral centers would be destroyed at the later stages during formation of butenolide moiety, it's stereochemistry was of no consequence and hence no attempt was made to identify the diastereomers as well as their ratios. Both of these intermediates were confirmed by their IR, NMR and mass spectral data comparison with those of previously reported.[4]

The next task to be performed was elimination of the tertiary hydroxyl group and lactonisation to furnish butenolide ring, which was achieved using a methodology developed by this group,[5] where such diols were treated with *p*-toluenesulfonic acid under

refluxing benzene for the butenolide ring construction. Following the same method, diol **35** gave a mixture of heritonin **2** and it's C-8 epimer in 3: 2 ratio, in overall 90% yield (Scheme-10).

Scheme-10



35 **2** ***epi*-2**

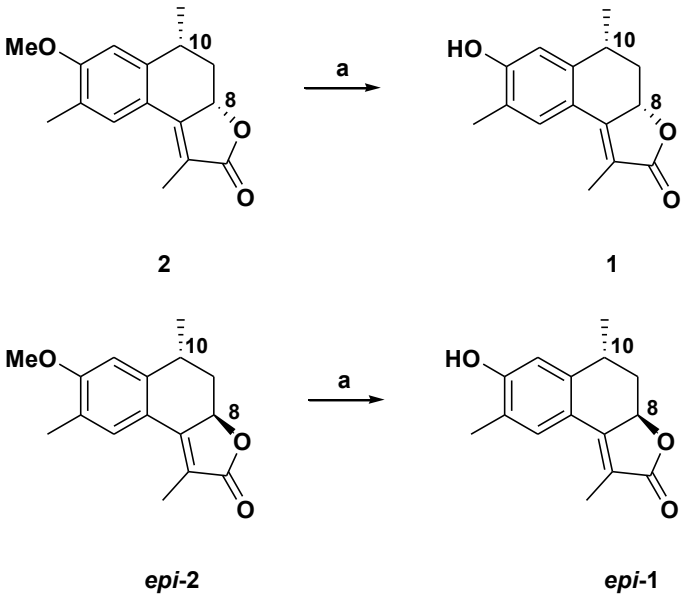
Reagents and conditions *: a) pTSA, benzene, reflux, 1 h, 90% overall.*

This could be seen in the ^{1}H NMR spectrum of the product obtained after column purification, which exhibited resonances at δ 4.88 (ddq, *J* = 12.9, 4.8, 1.6 Hz) and δ 5.08 (ddq, *J* = 13.1, 4.6, 1.6 Hz) in 3: 2 ratio, which corresponds to the proton on the carbon bearing oxygen atom of the lactone ring, characteristic of heritonin **2** and *epi*-heritonin (*epi*-**2**), respectively.[4] Both the isomers were separated by repeated crystallization. Pure heritonin **2** was first to be crystallized out from hot pet. ether as a white needles (mp 115-116 ^{o}C) {lit.[2] 115-116 ^{o}C}, while *epi*-heritonin was crystallized from the remaining fraction using hot 10% ethyl acetate in pet. ether, as a white crystals (mp 172-173 ^{o}C). Both the isomers were characterized by their IR and NMR spectral data comparison with those of literature values.[2, 4]

The IR spectrum of **2** revealed absorption at 1738 cm^{-1} and 1654 cm^{-1}, characteristic of the butenolide ring structure. The ^{1}H NMR spectrum of **2** exhibited the following salient features : a signal at δ 1.43 (d, *J* = 6.7 Hz, 3H) was attributed to the only secondary methyl group, while the peak at δ 2.11 (d, *J* = 1.6 Hz, 3H) was assigned to the methyl group attached to the butenolide ring.

Finally, heritol **1** was obtained by demethylation of **2** using anhydrous aluminium chloride in the presence of ethanethiol[15] in 80% yield, without any epimerisation at C-8 (Scheme-11).

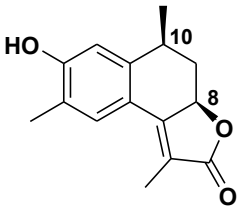
Scheme-11



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

Formation of heritol was established by it's IR and ^{1}H NMR spectral data comparison with those of literature values[1] and was found to be in good agreement. Presence of an absorption frequency at 3595 cm^{-1}, characteristic of a phenolic hydroxyl group in the IR spectrum, and absence of a three proton singlet at δ 3.87 in it's ^{1}H NMR spectrum, were indicative of the attempted deprotection. Further, it's ^{1}H NMR spectrum showed only one signal, corresponds to the proton at C-8, at δ 4.88 (ddq, J = 12.8, 4.8, 1.6 Hz), which indicated no epimerisation under the reaction conditions.

However, heritol thus synthesized from (*R*)-(+)-citronellal had specific rotation -240.5 (*c* 0.18, $CHCl_3$), while literature reports +261.3 (concentration and solvent in which specific rotation has been taken, is not reported). Assuming chloroform as the solvent, the opposite sign of rotation indicated that the naturally isolated (+)-heritol should have (*S*, *R*) configuration at C-10, C-8.



Proposed absolute configuration of naturally isolated (+)-heritol

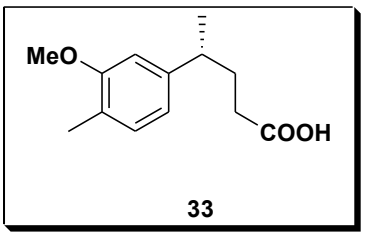
Under identical reaction conditions, pure *epi*-heritol (*epi*-**1**) (C-8 epimer of **1**) was obtained in 80% yield, (Scheme-11) which was characterized by it's IR and ^{1}H NMR spectral data comparison with those of reported one. It showed specific rotation +321.8 (*c* 0.17, $CHCl_3$).

3.5 Conclusions

Enantiopure (-)-heritol has been synthesized enantiospecifically from naturally occurring monoterpene (*R*)-(+)-citronellal. Absolute configuration of natural heritol has been proposed to be (*S*, *R*) at C-10, C-8 by comparison of it's specific rotation with that of synthetically obtained one.

3.6 Experimental

(*R*)-4-(3-Methoxy-4-methylphenyl)pentanoic acid (33)



33

A 500 mL round bottom flask, equipped with a magnetic stir bar and 50 mL addition funnel, was charged with olefin **32** {prepared from (*R*)-(+)-citronellal as described in chapter-2, section-2} (2 g, 8.62 mmol) and acetone (20 mL). The reaction mixture was cooled to 0 ^{o}C and OsO_4 (cat) was added to it, which was stirred for 15 min, followed by dropwise addition of Jones' reagent (12 mL). The reaction mixture was stirred at room temperature for 7 h before excess of Jones' reagent was quenched by addition of isopropanol (5 mL). Acetone was removed under reduced pressure, followed by dilution with water (50 mL) and extraction with CH_2Cl_2 (50 mL x 3). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 9 : 1) to give acid **33** (1.57 g) as a colourless oil.

Molecular Formula : $C_{13}H_{18}O_3$

Yield : 82%

Specific Rotation : $[\propto]^{25}_{D}$ -26.11 (*c* 1.2, $CHCl_3$)

IR (neat) ν_{max} (cm^{-1}) : 2961 (br), 1708, 1612.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.27 (d, *J* = 7.0 Hz, 3H); 1.82-1.96 (m, 2H); 2.17 (s, 3H); 2.17-2.27 (m, 2H); 2.60-2.78 (m, 1H); 3.82 (s, 3H); 6.62-6.69 (m, 2H); 7.03 (d, *J* = 7.5 Hz, 1H); 8.87 (bs, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 15.9 (CH_3); 22.4 (CH_3); 32.3 (CH_2); 33.0 (CH_2); 39.4 (CH); 55.2 (CH_3); 108.8 (CH); 118.6 (CH); 124.4 (C); 130.6 (CH); 144.9 (C); 157.8 (C); 179.9 (C).

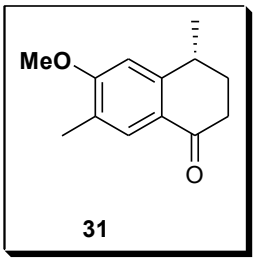
MS-ESI m/z : 221 $(M-1)^+$

Analysis

Expected : C, 70.24%; H, 8.16%

Found : C, 70.44%; H, 8.33%

(*R*)-6-Methoxy-4,7-dimethyl-3,4-dihydronaphthalen-1(2H)-one (31)



31

Acid **33** (1.4 g, 6.31 mmol) was taken in a 25 mL round bottom flask and to this was added trifluoroacetic acid (0.7 mL), followed by slow addition of triflouroacetic anhydride (1.6 g, 7.6 mmol) at 0 ^{o}C, under N_2 atmosphere. The reaction mixture was stirred at the same temperature for 3 h and was neutralized using saturated $NaHCO_3$ solution (50 mL), followed by extraction using CH_2Cl_2 (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 95 : 5) to provide tetralone **31** (1.03 g) as a white solid.

Mp **:** 110 ^{o}C

Molecular Formula **:** $C_{13}H_{16}O_2$

Yield **:** 80%

Specific Rotation **:** $[\propto]^{25}_{D}$ +26.87 (*c* 0.9, $CHCl_3$)

IR ($CHCl_3$) ν_{max} (cm^{-1}) **:** 1670, 1607, 1570.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.38 (d, *J* = 7.0 Hz, 3H); 1.79-1.95 (m, 1H); 2.18 (s, 3H); 2.21-2.30 (m, 1H); 2.43-2.79 (m, 2H); 2.94-3.07 (m, 1H); 3.88 (s, 3H); 6.63 (s, 1H); 7.79 (d, *J* = 0.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 15.8 (CH_3); 20.8 (CH_3); 30.8 (CH_2); 33.1 (CH); 35.8 (CH_2); 55.3 (CH_3); 107.4 (CH); 124.9 (C); 125.4 (C); 129.7 (CH); 149.2 (C); 162.1 (C); 196.8 (C).

MS-ESI m/z **:** 205 $(M+1)^+$

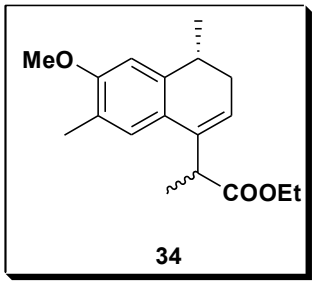
Analysis

Expected **:** C, 76.44%; H, 7.90%

Found **:** C, 76.11%; H, 8.18%

(*R*)-Ethyl-2-(6-methoxy-4,7-dimethyl-3,4-dihydronapthalen-1-yl)propanoate (34)[4]

To a stirred solution of tetralone **31** (0.5 g, 2.45 mmol), ethyl-2-bromopropionate (0.8 g, 4.42 mmol) and activated Zn (0.3 g, 4.9 mmol) in dry ether (20 mL), under an atmosphere of nitrogen; iodine crystals (1.2 g, 4.41 mmol) were added at such a rate so as



34

to effect the ether to reflux gently. After 3 h, the reaction mixture was quenched with 50% HCl-crushed ice solution. Extraction was carried out using ether (25 mL x 2), the combined organic layers were washed with saturated Na_2SO_3 solution (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 97 : 3) to furnish **34** (0.56 g) as a viscous yellow oil.

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

Yield : 80%

IR ($CHCl_3$) ν_{max} (cm^{-1}) : 2979, 1731, 1613, 1505.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.14-1.24 (m, 6H); 1.39 and 1.41 (two doublets, *J* = 7.0 Hz, total 3H); 1.97-2.14 (m, 1H); 2.17 (s, 3H); 2.36-2.50 (m, 1H); 2.72-2.86 (m, 1H); 3.64-3.79 (m, 1H); 3.83 (s, 3H); 4.04-4.21 (m, 2H); 5.75 (t, *J* = 4.7 Hz, 1H); 6.64 and 6.65 (two singlets, total 1H); 7.04 and 7.06 (two singlets, total 1H).

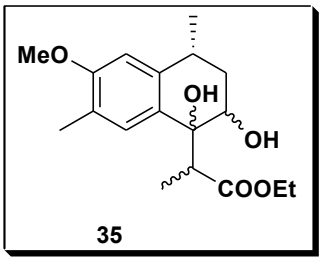
MS-ESI m/z : 289 $(M+1)^+$

Analysis

Expected : C, 74.97%; H, 8.39%

Found : C, 75.34%; H, 8.36%

(*R*)-Ethyl-2-(1,2-dihydroxy-6-methoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)propanoate (35) [4]



35

A 20 mL test tube was charged with β, γ-unsaturated ester **34** (0.5 g, 1.74 mmol), NMO (0.305 g, 2.6 mmol) and acetonitrile-water (9: 1, 0.5 mL). Catalytic amount of OsO_4 (0.8 mL, 0.09 mmol) (0.1 M solution in toluene) was syringed to it and stirred for 24 h at room temperature. The reaction mixture was diluted with ethyl acetate (30 mL), washed by saturated Na_2SO_3 solution (25 mL), brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using flash silica gel (pet. ether : EtOAc, 9 : 1) to provide diol **35** (0.53 g) as a viscous oil.

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

Yield : 95%

IR ($CHCl_3$) ν_{max} (cm^{-1}) : 3471, 2960, 2937, 1770, 1710, 1616, 1577.

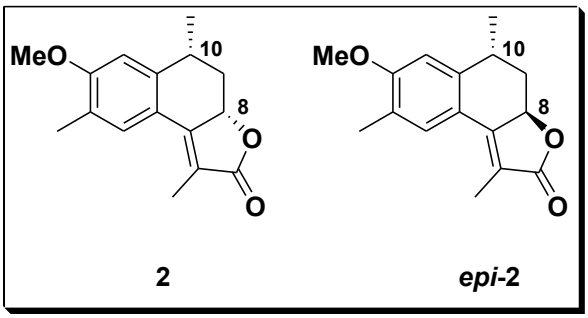
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.10-1.42 (m, 9H); 1.60-1.77 (m, 1H); 2.16 and 2.18 (two s, total 3H); 2.61-3.20 (m, 3H); 3.80 (s, 3H); 3.84-3.98 (m, 1H); 4.09-4.22 (m, 2H); 6.51-6.65 (m, 1H); 7.20-7.32 (m, 1H).

Analysis

Expected : C, 67.06%; H, 8.13%

Found : C, 67.40%; H, 8.28%

Heritonin (2) and it's C-8 epimer (*epi*-2)[2, 4, 5]



Diol **35** (0.4 g, 1.24 mmol) was taken in a 100 mL round bottom flask, to which benzene (20 mL) was added followed by catalytic amount of *p*TSA. The reaction mixture was refluxed for 1 h, concentrated under reduced pressure and the residue was chromatographed using flash silica gel (pet. ether : EtOAc, 9 : 1) to provide a mixture of **2** and ***epi*-2** in 3 : 2 ratio (0.29 g, overall 90%).

Recrystallization of the solid thus obtained in boiling pet. ether furnished heritonin **2** as a white needle shaped crystals.

Mp : 115-116 °C {lit.[2] 115-116 °C}

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

Specific Rotation : $[\propto]^{25}_D$ -312.97 (*c* 1.3, $CHCl_3$)

IR ($CHCl_3$) ν_{max} (cm^{-1}) : 3019, 1738, 1654, 1613.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.43 (d, *J* = 6.7 Hz, 3H); 1.36-1.64 (m, 1H); 2.11 (d, *J* = 1.6 Hz, 3H); 2.23 (s, 3H); 2.56-2.67 (m, 1H); 3.02-3.21 (m, 1H); 3.87 (s, 3H); 4.90 (ddq, *J* = 12.9, 4.8, 1.6 Hz, 1H); 6.84 (s, 1H); 7.40 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 9.8 (CH_3); 15.9 (CH_3); 21.7 (CH_3); 31.9 (CH); 38.6 (CH_2); 55.3 (CH_3); 78.1 (CH); 108.3 (CH); 115.8 (C); 120.6 (C); 125.6 (C); 129.5 (CH); 142.2 (C); 156.7 (C); 159.5 (C); 175.5 (C).

Concentration of the mother liquor followed by crystallization using hot 10% ethyl acetate in pet. ether provided (C-8) *epi*-heritonin (*epi*-**2**) as a white crystalline solid.

Mp **:** 172-173 ^{o}C

Molecular Formula **:** $C_{16}H_{18}O_3$

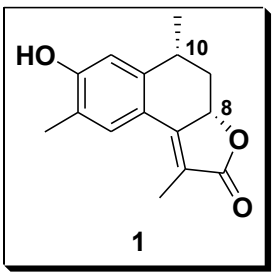
Specific Rotation **:** $[\propto]^{25}_{D}$ +397.03 (*c* 1.1, $CHCl_3$)

IR ($CHCl_3$) ν_{max} (cm^{-1}) **:** 2962, 1744, 1651, 1612.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.41 (d, *J* = 7.5 Hz, 3H); 1.79-1.95 (m, 1H); 2.10 (d, *J* = 1.6 Hz, 3H); 2.22 (s, 3H); 2.38 (ddd, *J* = 12.0, 4.8, 1.5 Hz, 1H); 3.21-3.35 (m, 1H); 3.86 (s, 3H); 5.07 (ddq, *J* = 13.1, 4.6, 1.6 Hz, 1H); 6.64 (s, 1H); 7.37 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 10.0 (CH_3); 16.1 (CH_3); 24.0 (CH_3); 33.3 (CH); 36.5 (CH_2); 55.3 (CH_3); 75.4 (CH); 110.1 (CH); 116.7 (C); 120.2 (C); 125.8 (C); 129.7 (CH); 142.7 (C); 156.1 (C); 159.5 (C); 175.2 (C).

Heritol (1)[1]



Ethanethiol (1 mL) was added to a stirred solution of heritol methyl ether **2** (20 mg, 0.078 mmol) in dichloromethane (1 mL), followed by addition of anhydrous aluminium chloride (0.050 g, 0.375 mmol), under N_2 atmosphere, at room temperature and stirred for 12 h. Water was added to the reaction mixture and the separated solid was extracted using dichloromethane (20 mL x 3). The combined organic layers were washed with water (30 mL x 2), brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a white solid, which was crystallized from hot methanol to provide white crystalline heritol **1** (15 mg).

Mp **:** 270-271 ^{o}C {lit.[1] mp 271-272 ^{o}C}

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

Yield **:** 80%

Specific Rotation **:** $[\propto]^{25}_{D}$ –240.5 (*c* 0.18, $CHCl_3$) {lit.[1] $[\propto]^{25}_{D}$ +261.3}

IR ($CHCl_3$) ν_{max} (cm^{-1}) **:** 3595, 2960, 1739, 1654, 1616.

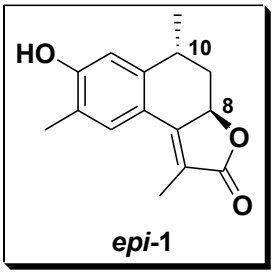
^{1}H NMR ($CDCl_3$, 400 MHz) : δ 1.40 (d, *J* = 6.8 Hz, 3H); 1.43-1.46 (m, 1H); 2.12 (d, *J* = 1.5 Hz, 3H); 2.28 (s, 3H); 2.57-2.63 (m, 1H); 3.01-3.13 (m, 1H); 4.88 (ddq, *J* = 12.8, 4.8, 1.8 Hz, 1H); 5.16 (bs, 1H); 6.82 (s, 1H); 7.40 (s, 1H).

Analysis

Expected : C, 73.75%; H, 6.60%

Found : C, 73.51%; H, 6.38%

***epi*-Heritol (*epi*-1)**[4]



It was prepared from ***epi*-2** by using the same procedure as described above.

Mp : 275 °C

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

Yield : 80%

Specific Rotation : $[\propto]^{25}_D$ +321.8 (*c* 0.17, $CHCl_3$)

IR ($CHCl_3$) ν_{max} (cm^{-1}) : 3593, 3020, 1739, 1655, 1617.

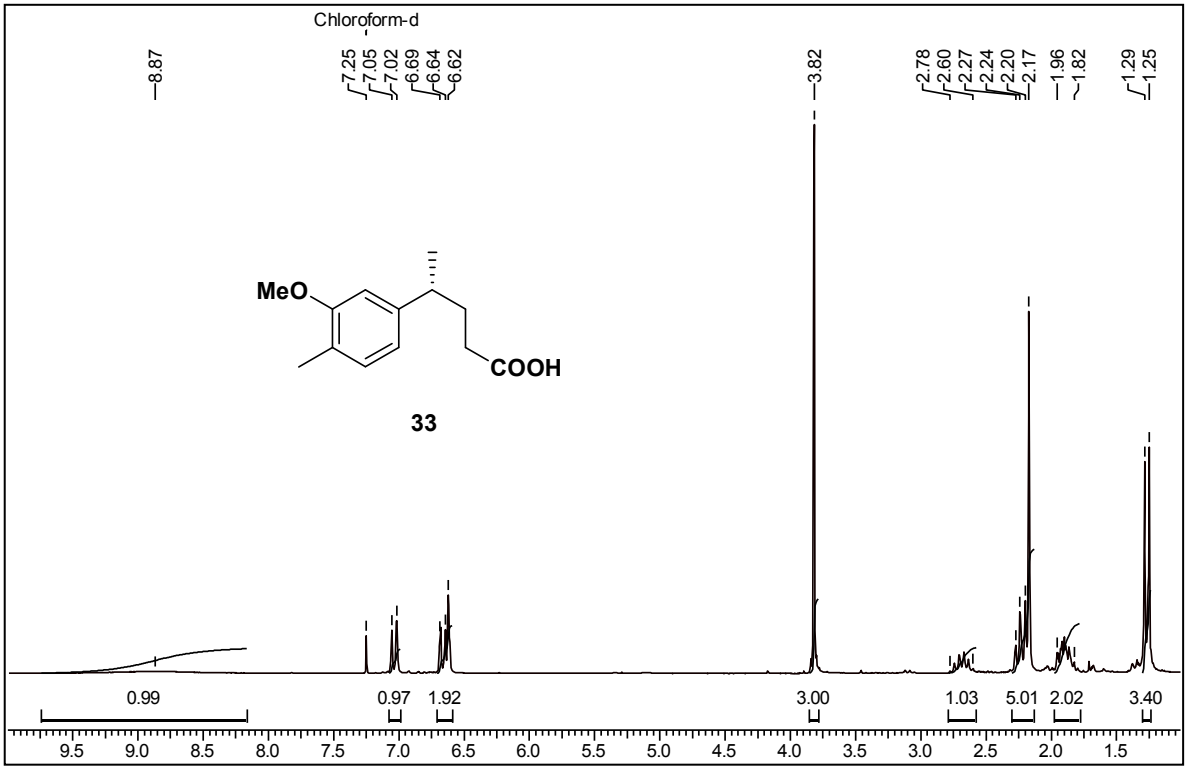
^{1}H NMR ($CDCl_3$, 400 MHz) : δ 1.39 (d, *J* = 7.3 Hz, 3H); 1.83-1.90 (m, 1H); 2.11 (d, *J* = 1.5 Hz, 3H); 2.27 (s, 3H); 2.35-2.40 (m, 1H); 3.20-3.27 (m, 1H); 5.08 (ddq, *J* = 13.1, 4.5, 1.5 Hz, 1H); 5.33 (bs, 1H); 6.66 (s, 1H); 7.38 (s, 1H).

Analysis

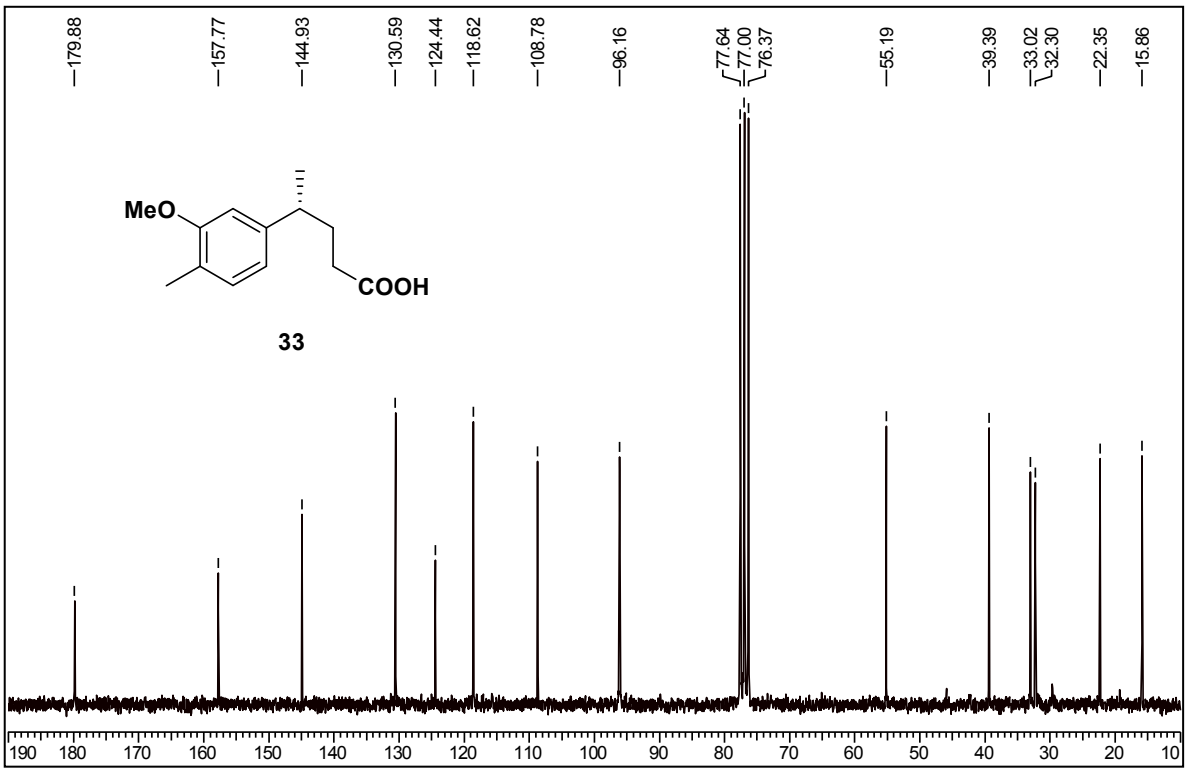
Expected : C, 73.75%; H, 6.60%

Found : C, 73.51%; H, 6.38%

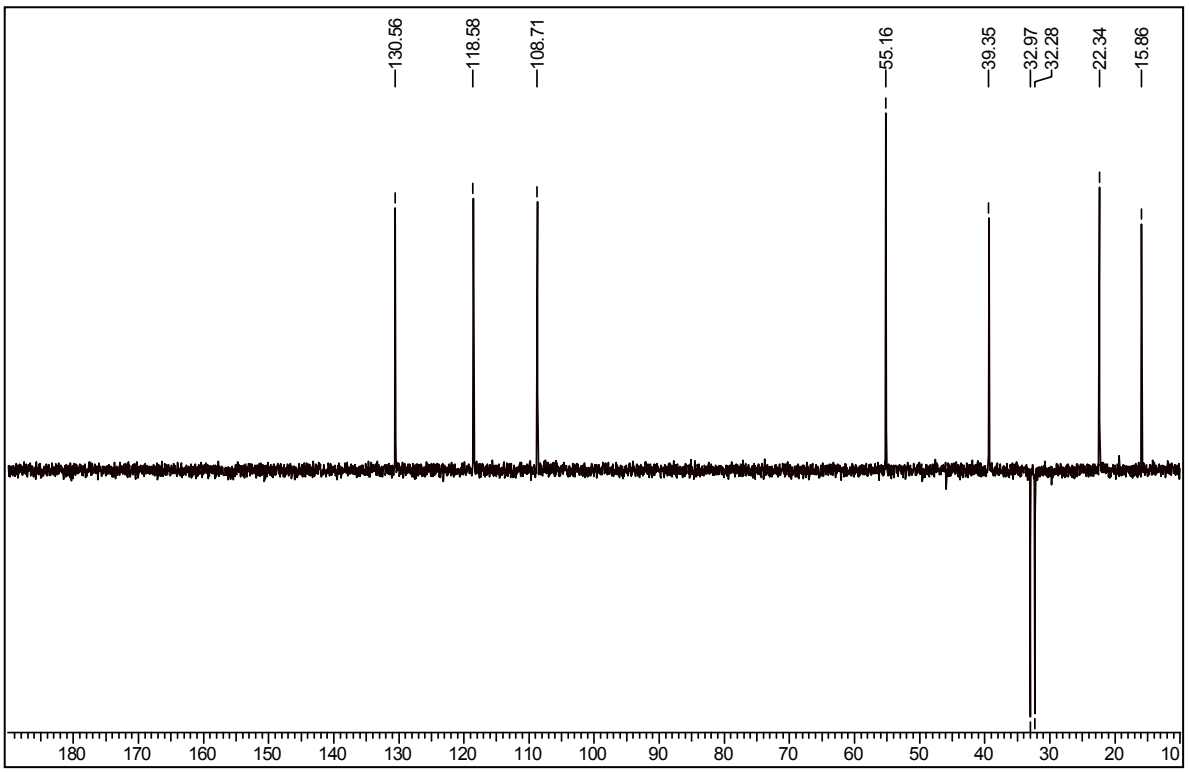
3.7 Spectra

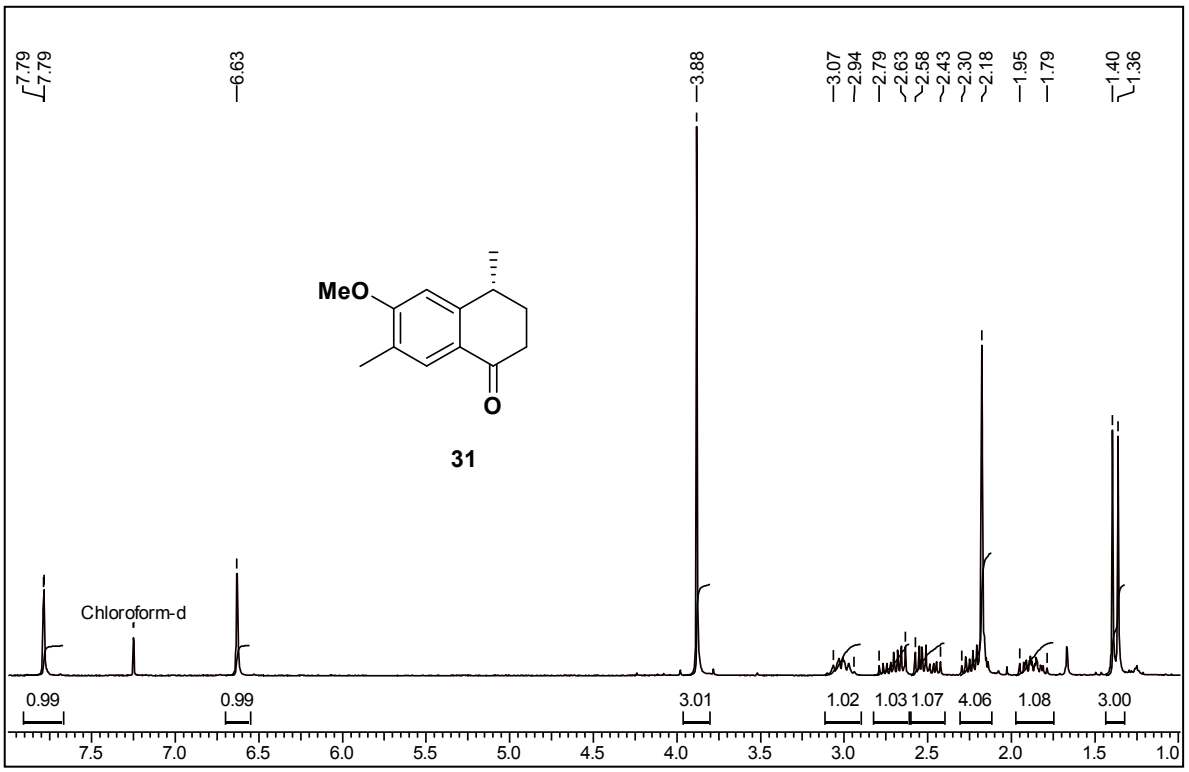


^{1}H NMR SPECTRUM ($CDCl_3$ + CCl_4, 200 MHz)

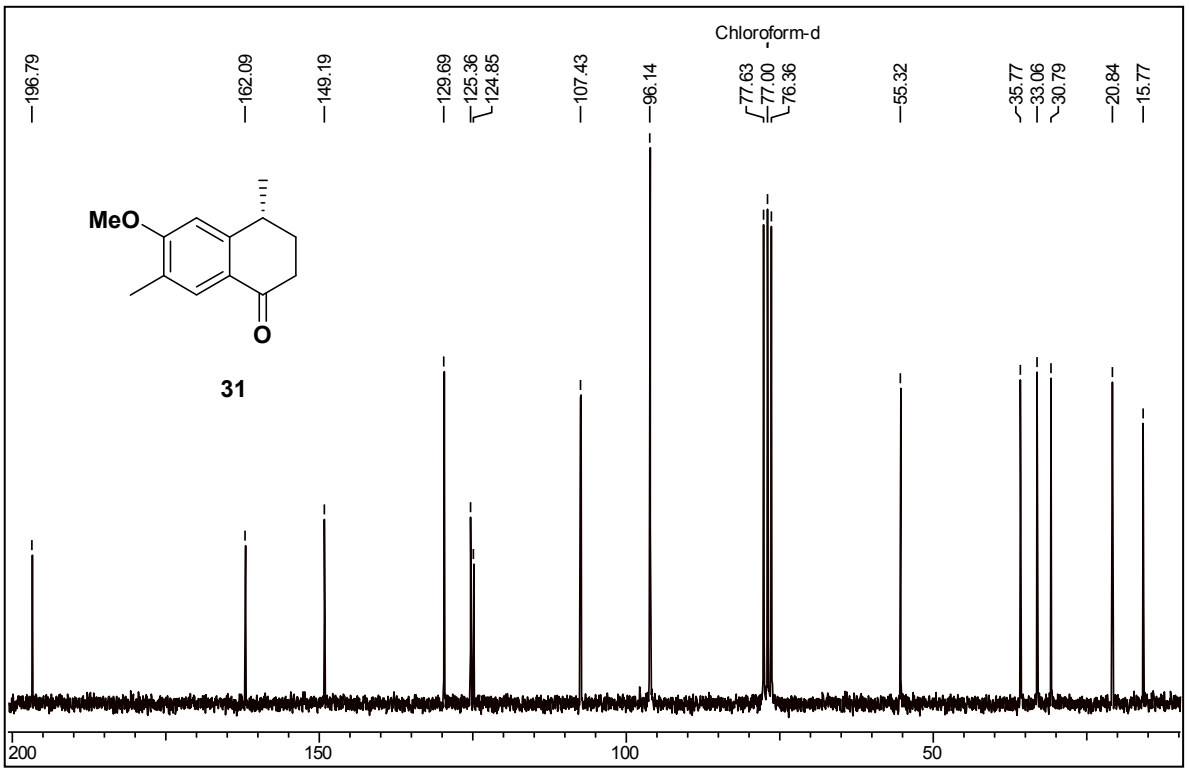


^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 50 MHz)

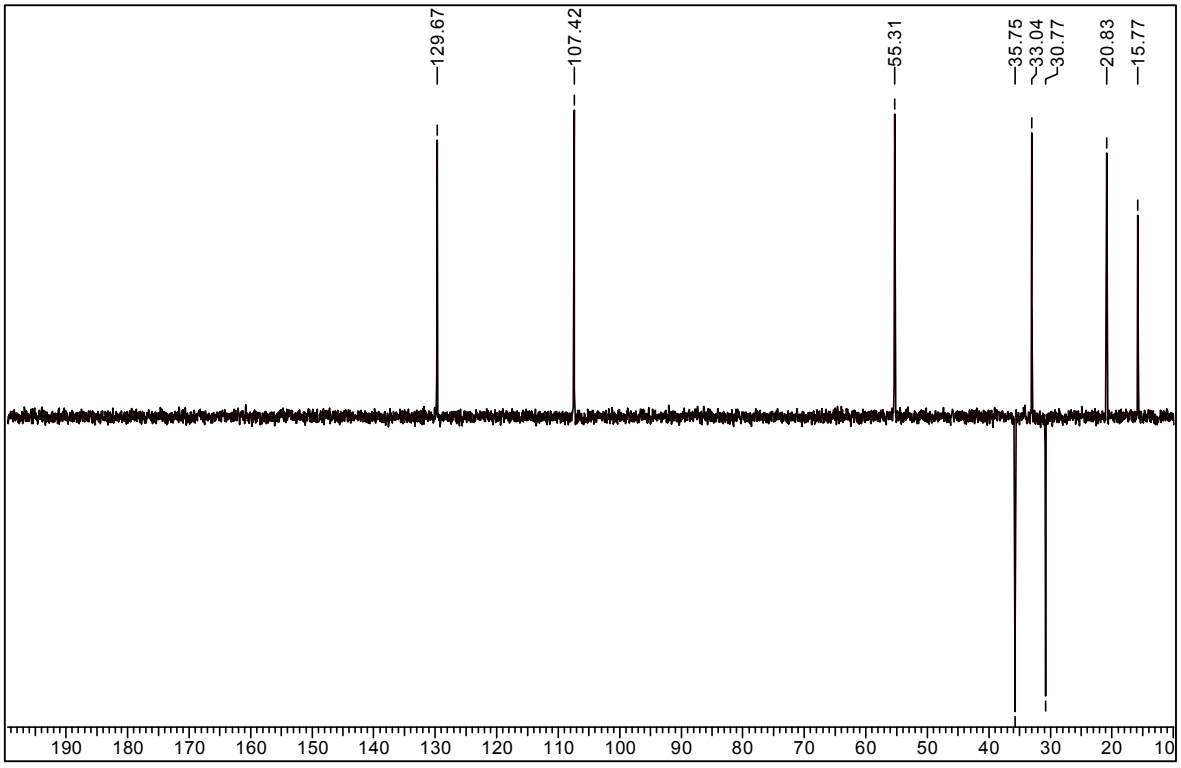


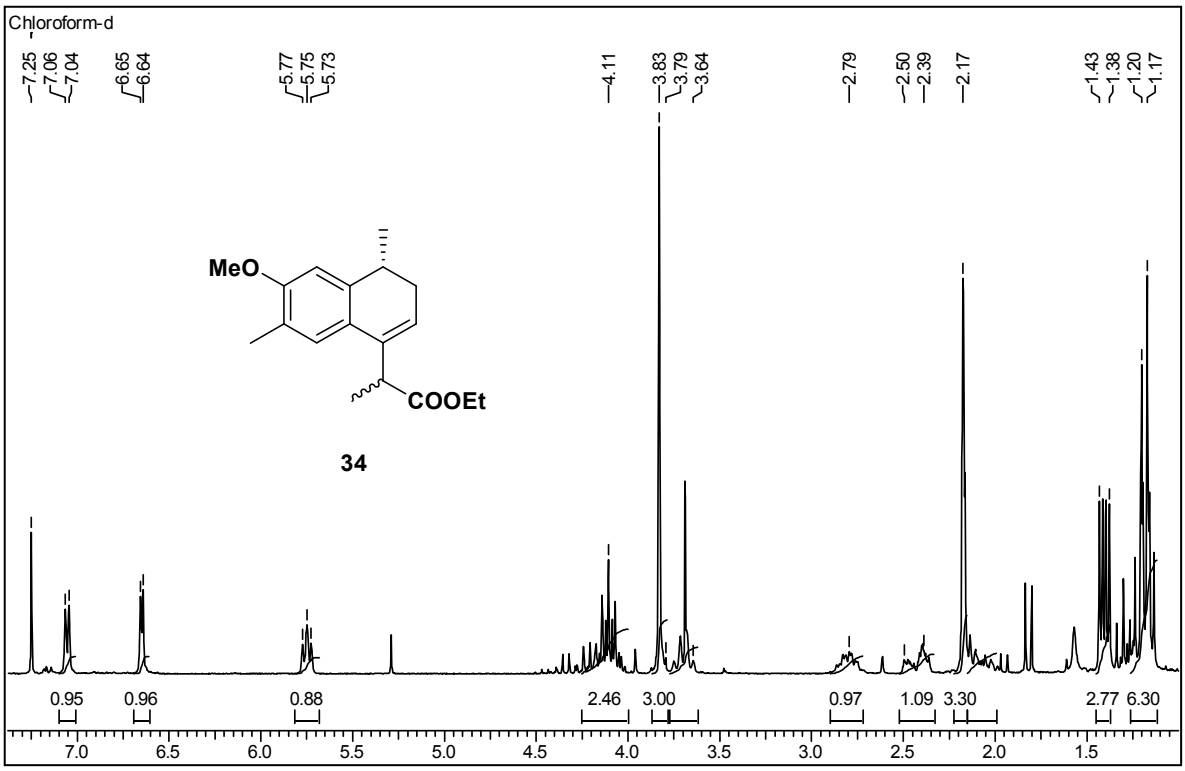


^{1}H NMR SPECTRUM ($CDCl_3$ + CCl_4, 200 MHz)

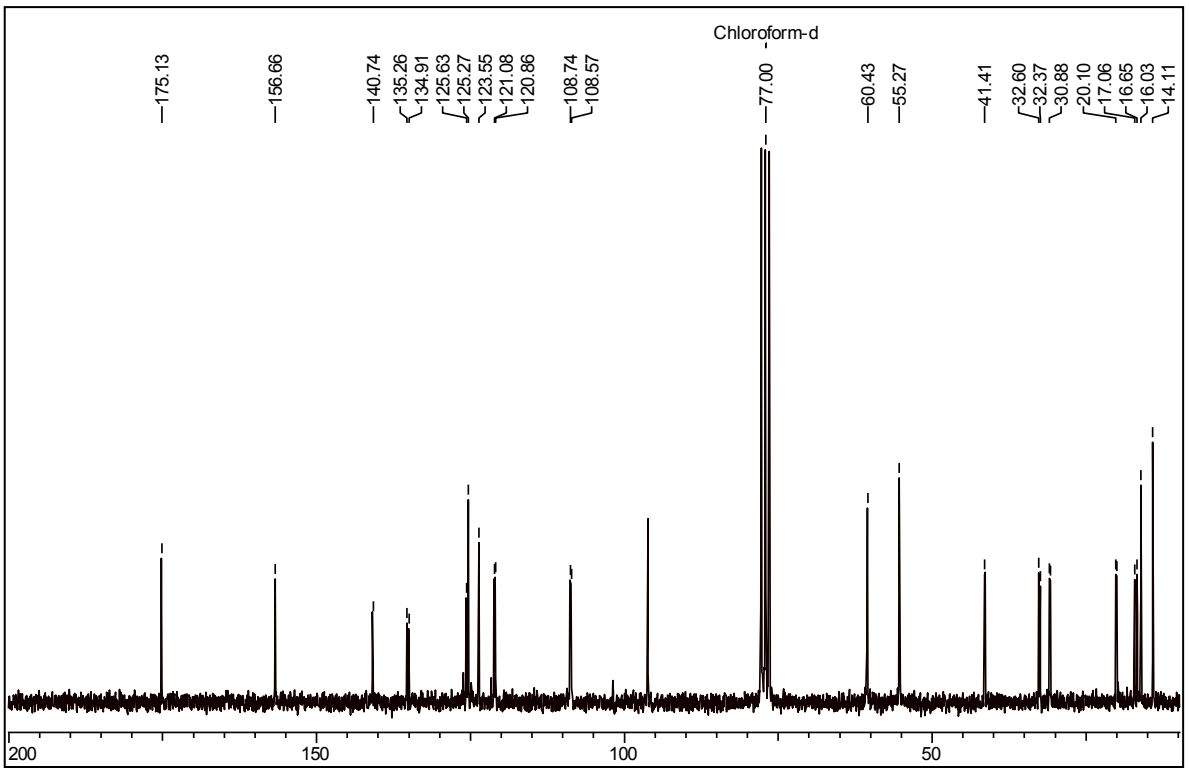


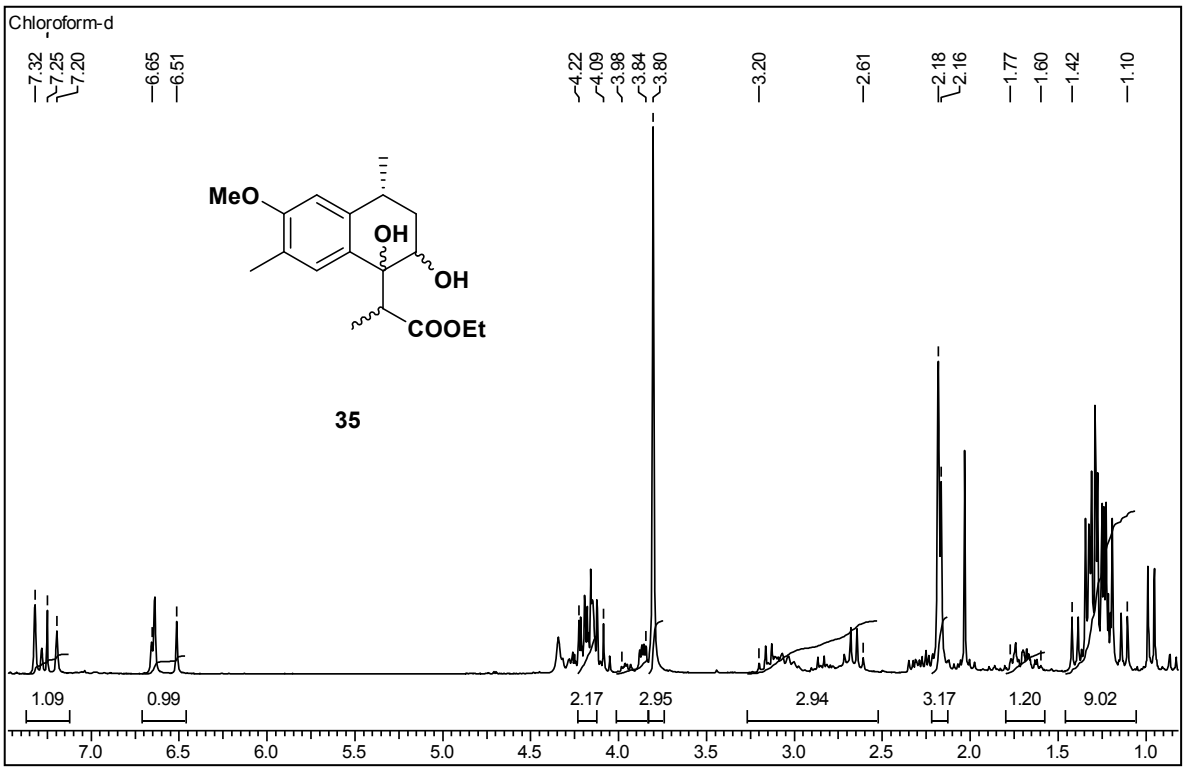
^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 50 MHz)



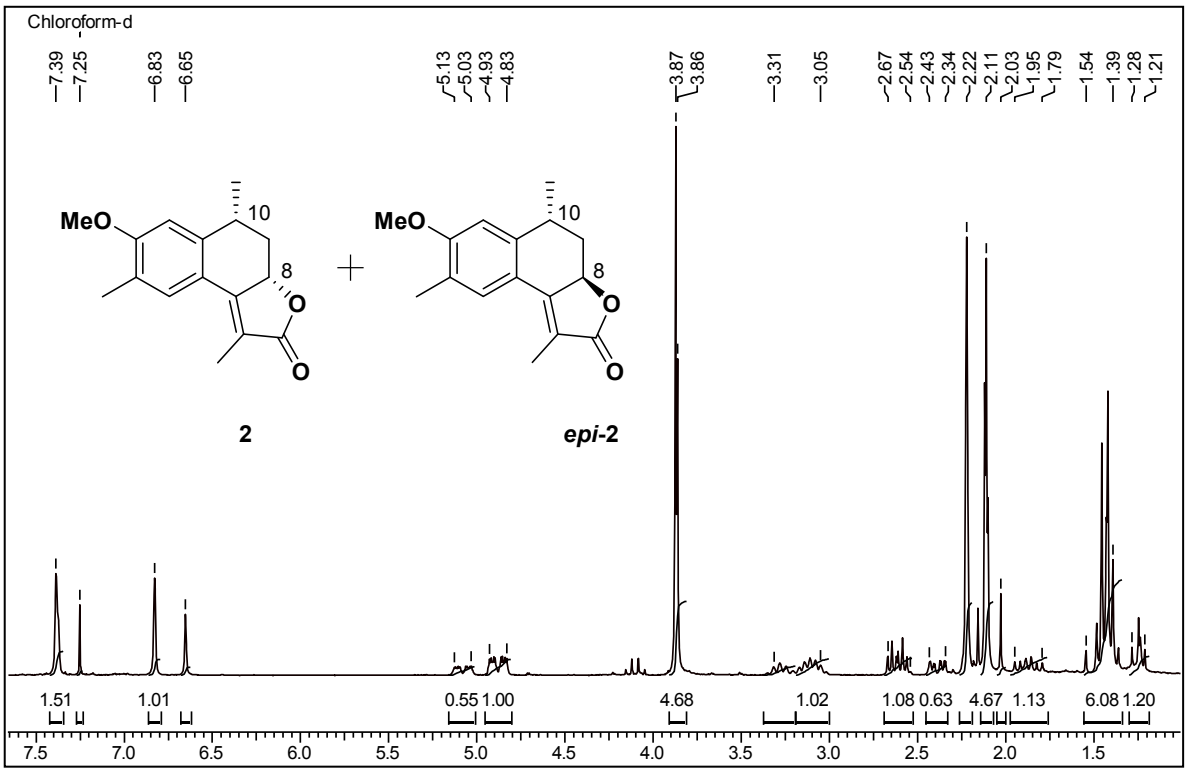


^{1}H (200 MHz) & ^{13}C NMR (50 MHz) SPECTRA ($CDCl_3$ + CCl_4)

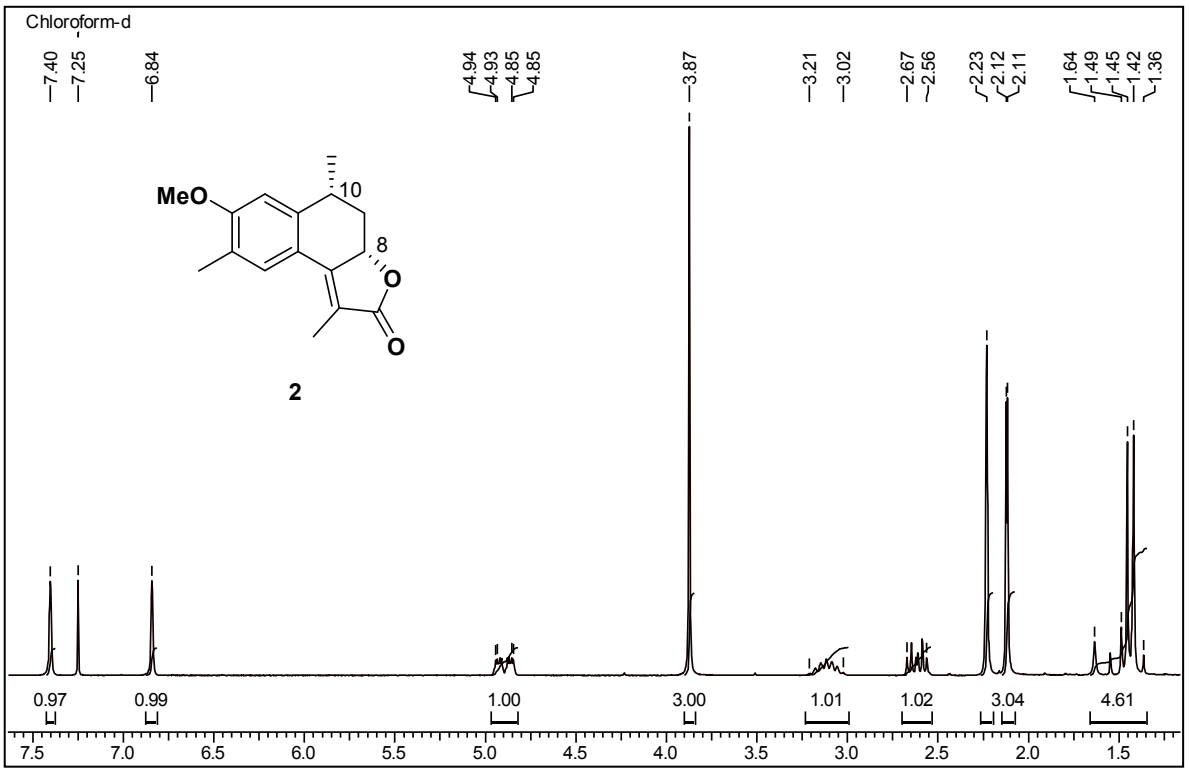




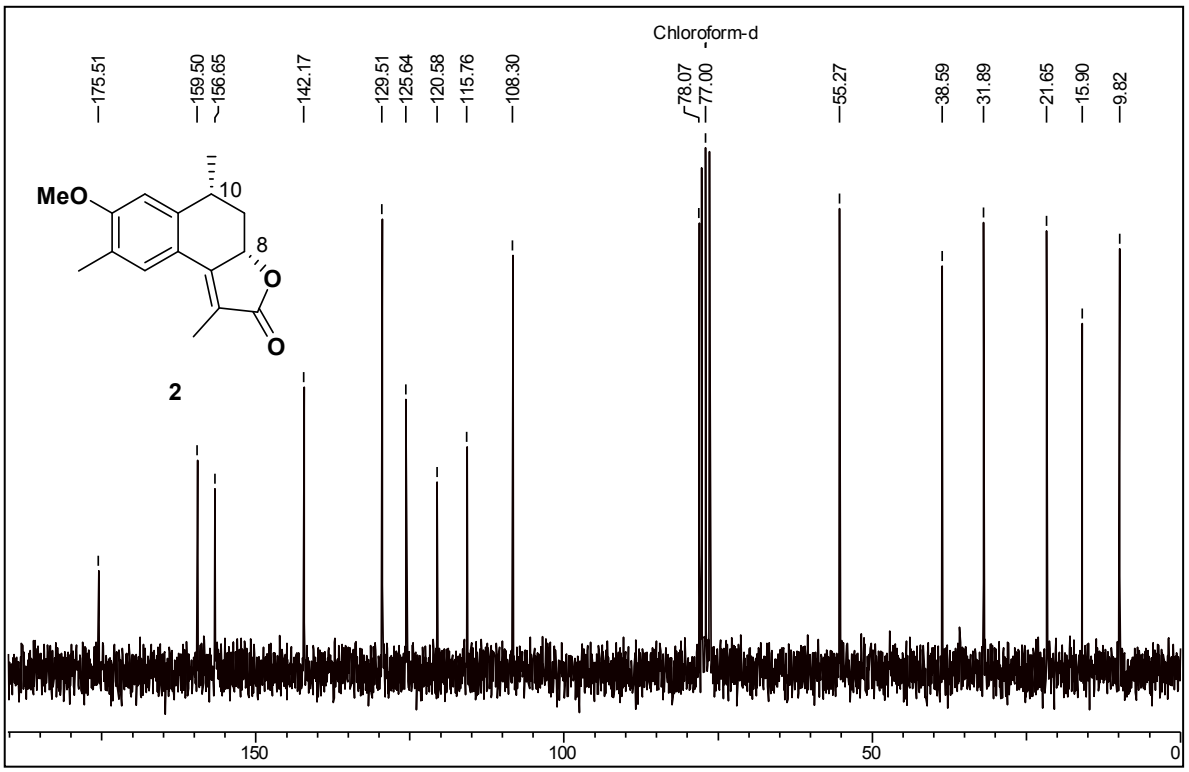
^{1}H NMR SPECTRUM ($CDCl_3$ + CCl_4, 200 MHz)



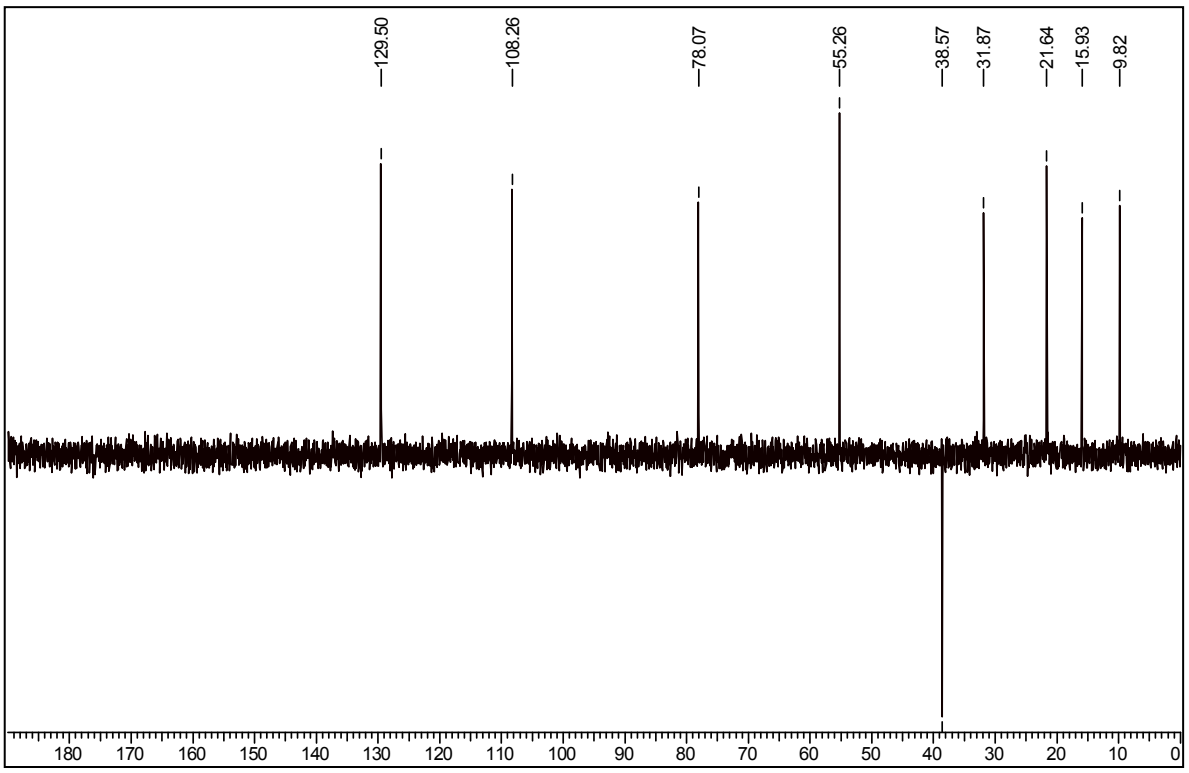
^{1}H NMR SPECTRUM ($CDCl_3$ + CCl_4, 200 MHz)

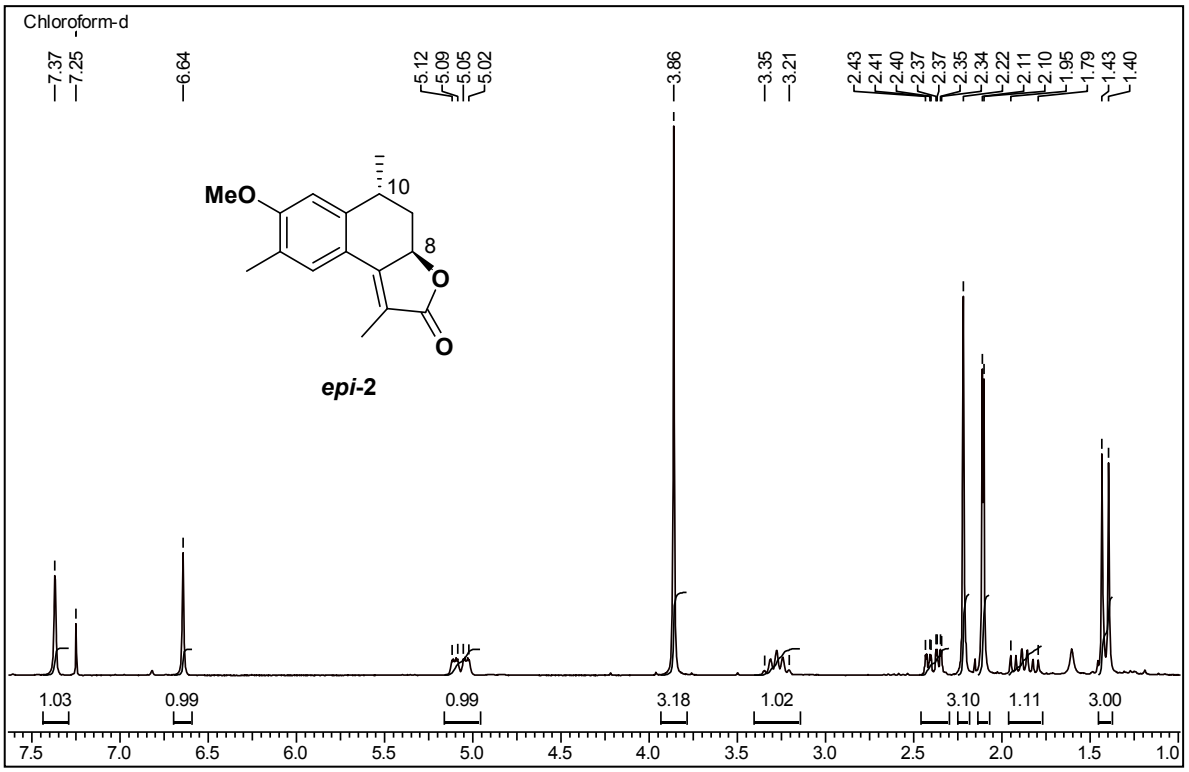


^{1}H NMR SPECTRUM ($CDCl_3$, 200 MHz)



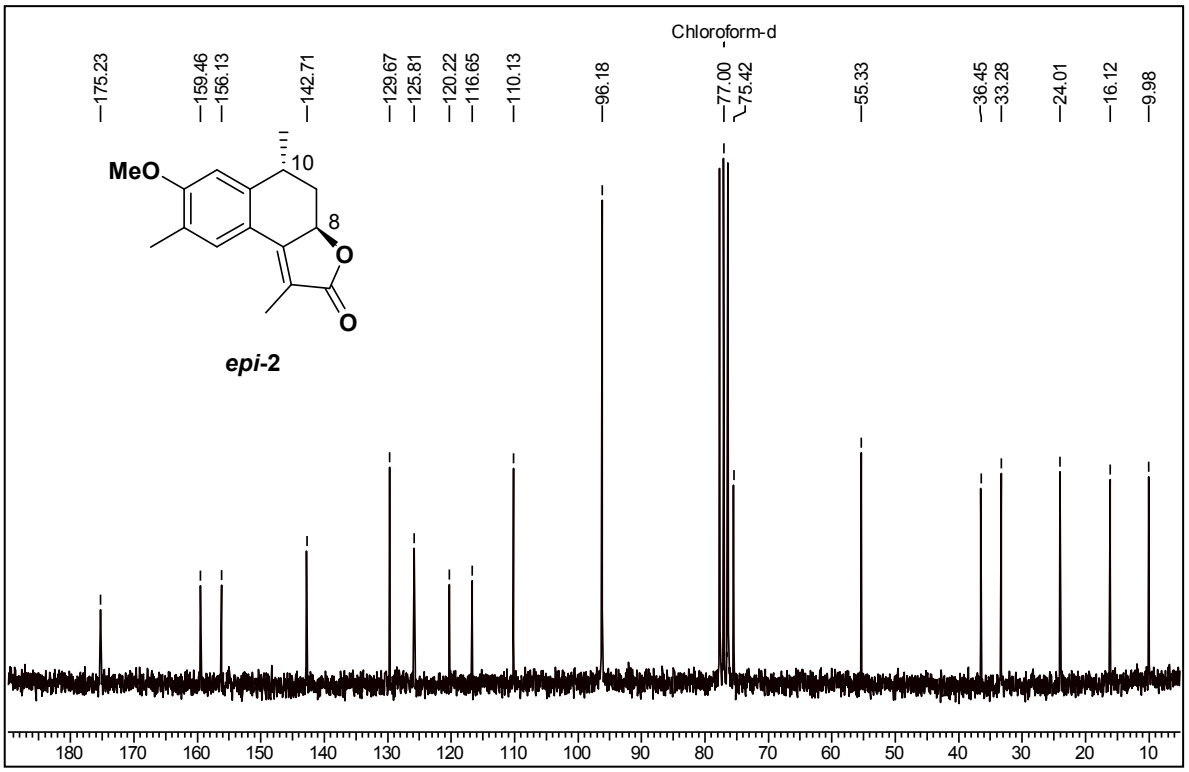
^{13}C & DEPT NMR SPECTRA ($CDCl_3$, 50 MHz)





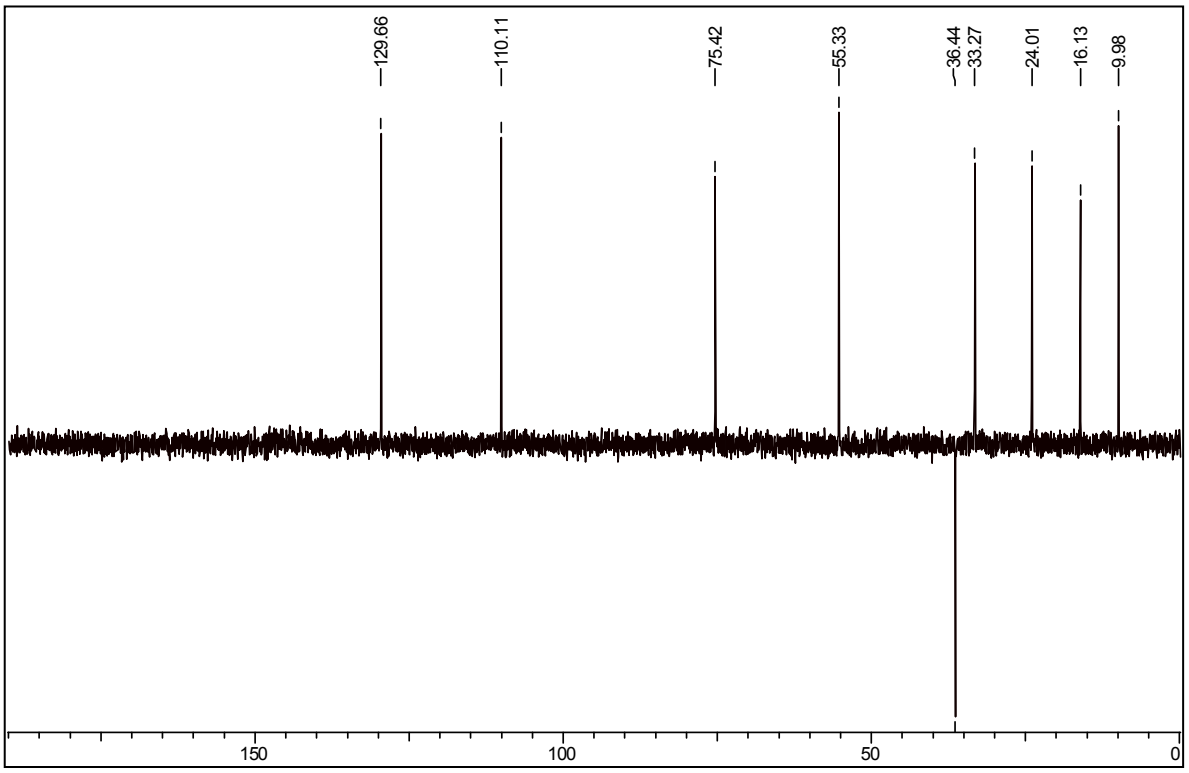
***epi*-2**

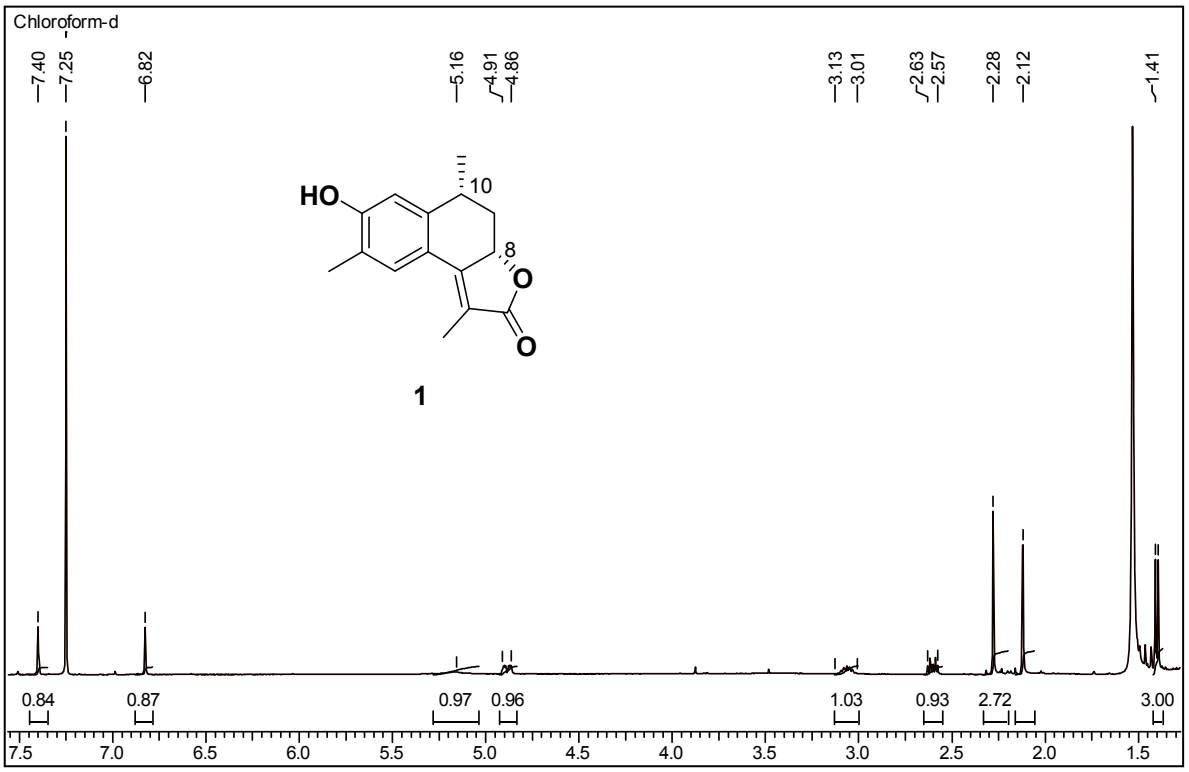
^{1}H NMR SPECTRUM ($CDCl_3$ + CCl_4, 200 MHz)



***epi*-2**

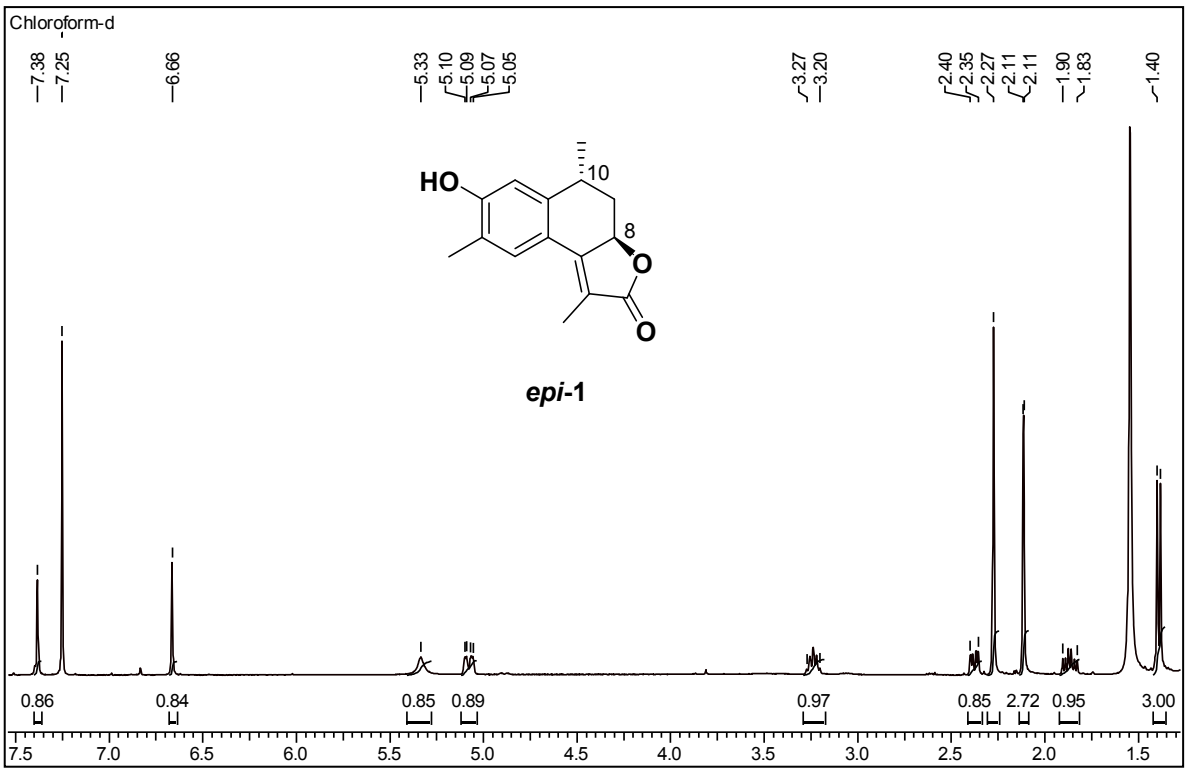
^{13}C & DEPT NMR SPECTRA ($CDCl_3$ + CCl_4, 50 MHz)





1

^{1}H NMR SPECTRA ($CDCl_3$ + CCl_4, 400 MHz)



***epi*-1**

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List of Publications :

1. "First enantiospecific synthesis of (+)-β-herbertenol" Subhash P. Chavan, Mahesh Thakkar, Rajendra K. Kharul, Ashok B. Pathak, Gaurav V. Bhosekar and Mohan M. Bhadbhade *Tetrahedron* **2005**, *61*, 3873-3879.
2. "First Enantiospecific Synthesis of (-)-Parvifoline and (-)-Curcuquinone" Subhash P. Chavan, Mahesh Thakkar, Ganesh F. Jogdand and Uttam R. Kalkote *J. Org. Chem.* **2006**, *71*, 8986-8988.
3. "First Enantiospecific Synthesis of Heritol: Absolute Configuration Determination" Subhash P. Chavan, Mahesh Thakkar and Uttam R. Kalkote; accepted for publication in *Tetrahedron Lett.* **2007**.
4. "Enantiospecific synthesis of (+)-Isoparvifolinone and (-)-Parvifoline" Subhash P. Chavan, Mahesh Thakkar and Uttam R. Kalkote; accepted for publication in *Tetrahedron Lett.* **2007**.