SYNTHETIC STUDIES TOWARDS TAXOL AND DEVELOPMENT OF SYNTHETICALLY USEFUL METHODOLOGY

A THESIS

SUBMITTED TO THE

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IN

CHEMISTRY

BY

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Synthetic Studies towards Taxol and Development of Synthetically Useful Methodology"** submitted by Mr. Sambhaji P. Chavan was carried out by him under my supervision at National Chemical Laboratory, Pune. Material that has been obtained from other sources is duly acknowledged in this thesis

Date:

Subhash P. Chavan

Research Supervisor

DECLARATION

I hereby declare that the thesis entitled **"Synthetic Studies towards Taxol and Development of Synthetically Useful Methodology"** submitted for Ph. D. degree to the University of Pune has been carried out at National Chemical Laboratory, under the supervision of Dr Subhash P. Chavan. This work is original and has not been submitted in part or full by me for any degree or diploma to this or any other university.

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Dedicated

To

My

Parents

Contents

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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. Solvents for anhydrous reaction were prepared according to the procedures reported in Perrin's book.
5. TLC analysis was carried out using thin layer plates pre-coated with silica gel 60 F254 (Merck) and visualized by fluorescence quenching or Iodine or by charring after treatment with *p*-anisaldehyde.
6. In cases where chromatographic purification was done, silica gel (60-120 mesh) was used as the stationary phase or otherwise as stated.
7. Microwave reactions were performed on a continuous mode of irradiations (ν = 2450 MHz) with irradiation power of either 300 or 600W using a Microwave Assisted Reactor System-5 [MARS-5 (CEM Corpn., USA)].
8. IR spectra were recorded on Perkin-Elmer Infrared Spectrophotometer Model 68B or on Perkin-Elmer 1615 FT Infrared spectrophotometer.
9. ^{1}H NMR and ^{13}C NMR were recorded on **Bruker AC-200** (50 MHz) or **Bruker MSL-300** (75 MHz) or **Bruker AV-400** (100 MHz) or **Bruker DRX-500** (125 MHz). Figures in parentheses refer to ^{13}C frequencies. Tetramethyl silane was used as the internal standard.
10. GCMS were recorded on Shimadzu's GCMS-QP5050-A.
11. Mass spectra were recorded at an ionization energy 70eV 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.
12. Starting materials were obtained from commercial sources or prepared using known procedures.
13. Microanalytical data were obtained using a Carlo-Erba CHNS-O EA 1108 Elemental analyzer within the limits of accuracy (± 0.4%)

Abbreviations

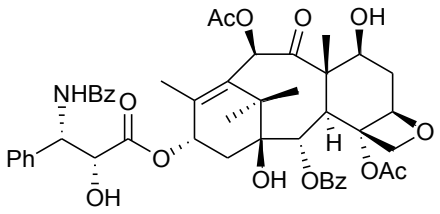
Ac	Acetyl
Acac	acetoacetate
AIDS	Acquired Immuno deficiency syndrome
Ar	Aromatic
Aq	Aqueous
AIBN	2,2-Azobis(isobutyronitrile)
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
nBu	normal butyl
sBu	secondary butyl
tBu	tertiary butyl
BMDA	MgBr(NiPr2)
BMCIA	MgBr(NRR') R = iPr, R' = cyclohexyl
BOC	*tert*-Butoxycarbonyl
Bz	Benzoyl
CSA	10-camphorsulfonic acid
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5,4,0]undec-7-ene
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless Enhancement by Polarization Transfer
DHP	Dihydropyran
DIBAL-H	Diisobutyl aluminium hydride
DMAP	N,N-Dimethyl amino pyridine
DME	Dimethoxy ethane
DMF	N,N-Dimethyl formamide
DMS	Dimethyl sulphate
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid

EDC	Ethylene dichloride
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
g	gram
GCMS	Gas Chromatograph Mass Spectrometer
HMPA	Hexamethylphosphoramide
HMDS	Hexamethyldisilazane
Im	Imidazole
IR	Infra red
ISC	Inter system crossing
LA	Lewis acid
LAH	Lithium Aluminium Hydride
LDA	Lithium diisopropyl amide
mCPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
MDR	multi drug resistance
mL	mililitre
Ms	Methane sulfonyl
MS	Mass spectroscopy
mmol	milimole
MOM	methoxy methyl
MEMCl	(2-methoxyethoxy)methyl chloride
mp	melting point
MW	Microwave
NCS	N-Chlorosuccinamide
NGF	Nerve growth factor
NIH	National Institute of Health
NMO	*N*-Methyl morpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PDC	Pyridinium dichromate
PCC	Pyridinium chlorochromate

Ph	Phenyl
PTSA	*para*-Toluene sulfonic acid
PPTS	Pyridinium p-toluene sulfonate
^{i}Pr	Isopropyl
Py	Pyridine
RADAR	Radio detecting and ranging
TBAF	Tetrabutyl ammonium fluoride
TEA	Triethyl amine
TES	Tri ethyl silyl
TFA	Trifluoroacetic acid
TFAA	Trifluroacetic anhydride
TLC	Thin Layer Chromatography
THF	Tetrahydrofuran
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBDPSCl	*tert*-Butyldiphenylsilyl chloride
Ts	Tosyl
TBHP	*tert*-butyl hydrogen peroxide
TBTH	tri-n-butyltin hydride
TMSOTf	Trimethylsilyl triflate
TBSOTf	*tert*-Butyldimethylsilyl triflate
TIPSOTf	Trimethylisopropylsilyl triflate
TMEDA	*N,N,N,N*-Tetramethylethylenediamine
TPAP	Tertrapropylammonium perruthenate
TMANO	Trimethylamine *N*-oxide
TMS	Tetra methyl silane

Abstract

The thesis entitled "**Synthetic Studies towards Taxol and Development of Synthetically Useful Methodology**" is divided into two chapters



Taxol **1**

The unique tricyclic skeleton of Taxol **1**, a diterpene isolated from pacific yew tree (*Taxus brevifolia)* has attracted considerable interest from synthetic organic chemists, owing to its promising activity against intractable ovarian, breast and lung cancer. The scarcity of Taxol and ecological impact of harvesting it, have also prompted intense interest towards the synthesis of less functionalised taxoids which still manifest useful or improved clinical activity.

Chapter-I: Synthesis of ABC skeletons of Taxol

Section-I: General Introduction of Taxol

Section-I begins with a brief introduction to the natural product Taxol and its current status as an anticancer agent. An account of the various synthetic routes of ABC skeletons of Taxol with special emphasis on construction of eight membered ring in order to put the theme in right perspective is presented.

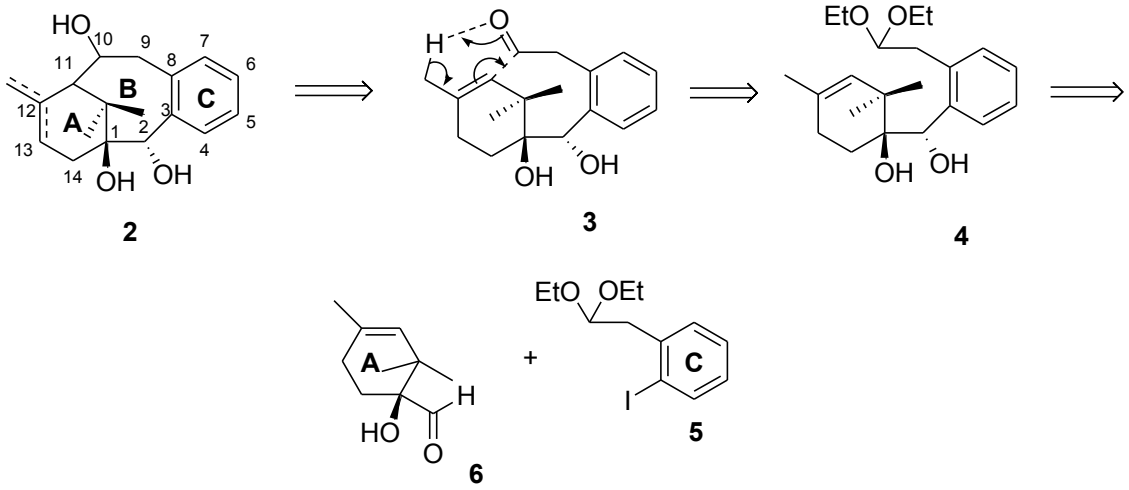
Section-II: Attempted synthesis of ABC skeleton of C-Aromatic taxane

Although taxol's unique mode of action and potential as an anti-cancer agent underlie much of the intense interest in this celebrated diterpene, synthetic chemist were most impressed with taxol's structure. The taxol molecule **1** is distinguished by a 6-8-6 tricyclic carbon framework, by a characteristic ester side chain, bridgehead double bond and by dense pattern of oxygenated functionality. Inspection of **1** reveals that of the fourteen carbon atoms defining the boundary of the molecule, nine are asymmetric and seven of this bear some form of oxygenation. The main challenge in taxol synthesis has been construction of the highly functionalized central eight membered ring and

installation of quaternary carbon center with desired stereochemistry. It is well known that the direct construction of eight membered ring is difficult due to unfavorable entropy, bond angle deformations, and destabilizing transannular interactions.

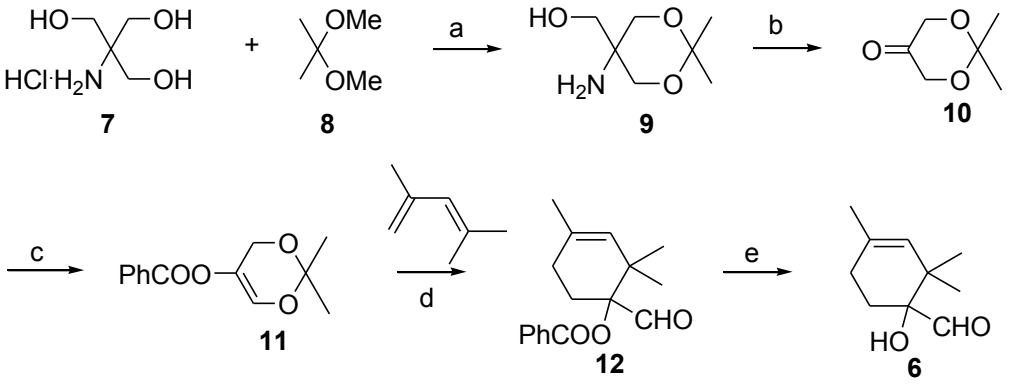
Owing to its complexity & challenge in synthesis it was decided to synthesize this molecule. Before directly jumping to total synthesis, it was planned to do model study, to construct ABC ring skeleton of taxol, taking C-ring as aromatic.

Scheme-1



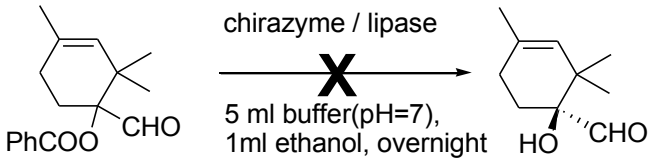
Retrosynthetic analysis (scheme-1) revealed that bond C10 and C11 can be connected using carbonyl-ene cyclization reaction. Thus, the potential precursor can be made by Barbier-type coupling of A-ring unit and C-ring unit.

Scheme-2



a. pTSA, DMF, 12h, 20 ^{o}C, 65% b. KH_2PO_4, $NaIO_4$, H_2O, 0 ^{o}C, 5h, 75% c. DMAP, Et_3N, PhCOCl, 0 ^{o}C, 83% d. CH_2Cl_2, 1% Hydroquinone, sealed- tube, 110 ^{o}C, 12h, 55% e. 20% LiOH, MeOH, R.T., 3h, 85%

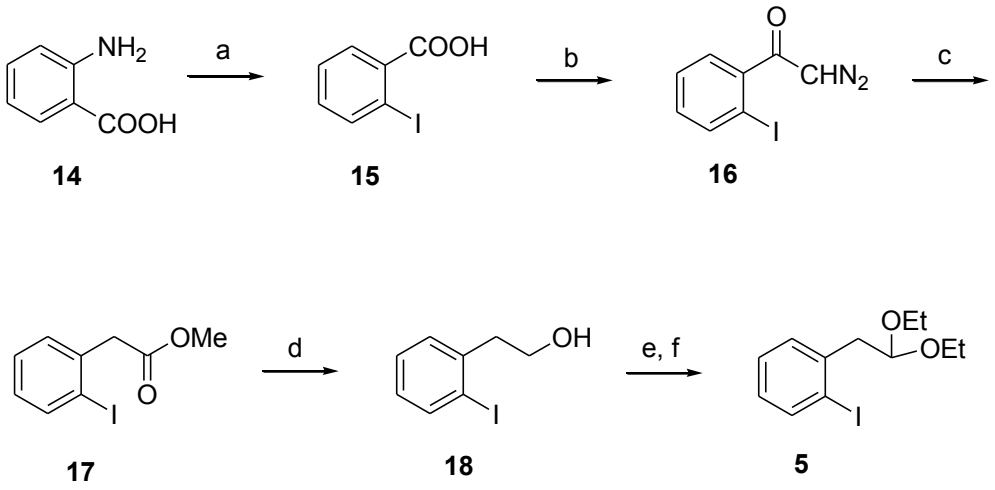
Scheme-3



12 **13**
optically pure

The acetonide protection of tris-buffer **7** was carried out with 2,2-dimethoxy propane in DMF catalysed by *para*-toluenesulfonic acid, resulted in compound **9** in 65% yield (Scheme-2). Thus, β-amino alcohol group in **9** was cleaved by aq. sodium periodate to get **10** in 75% yield. The *O*-benzoylation was carried out by benzoyl chloride in the presence of catalytic amount DMAP and triethyl amine, resulted in compound **11**. The next step i.e. Diels-Alder reaction of the dienophile (α-benzoyloxy acrolein) from **11** was generated *in-situ* and reacted with diene i.e. 2,4-dimethyl-1,3-pentadiene in a sealed tube at 110 ^{o}C for 12h resulted in adduct **12** in 55% yield**.** The benzoate ester was hydrolyzed by aqueous lithium hydroxide in methanol to form α-hydroxy A-ring unit **6** in 85% yield. Enzymatic hydrolysis was attempted to obtain optically pure A-ring unit (Scheme-3).

Scheme-4



14 **15** **16**

17 **18** **5**

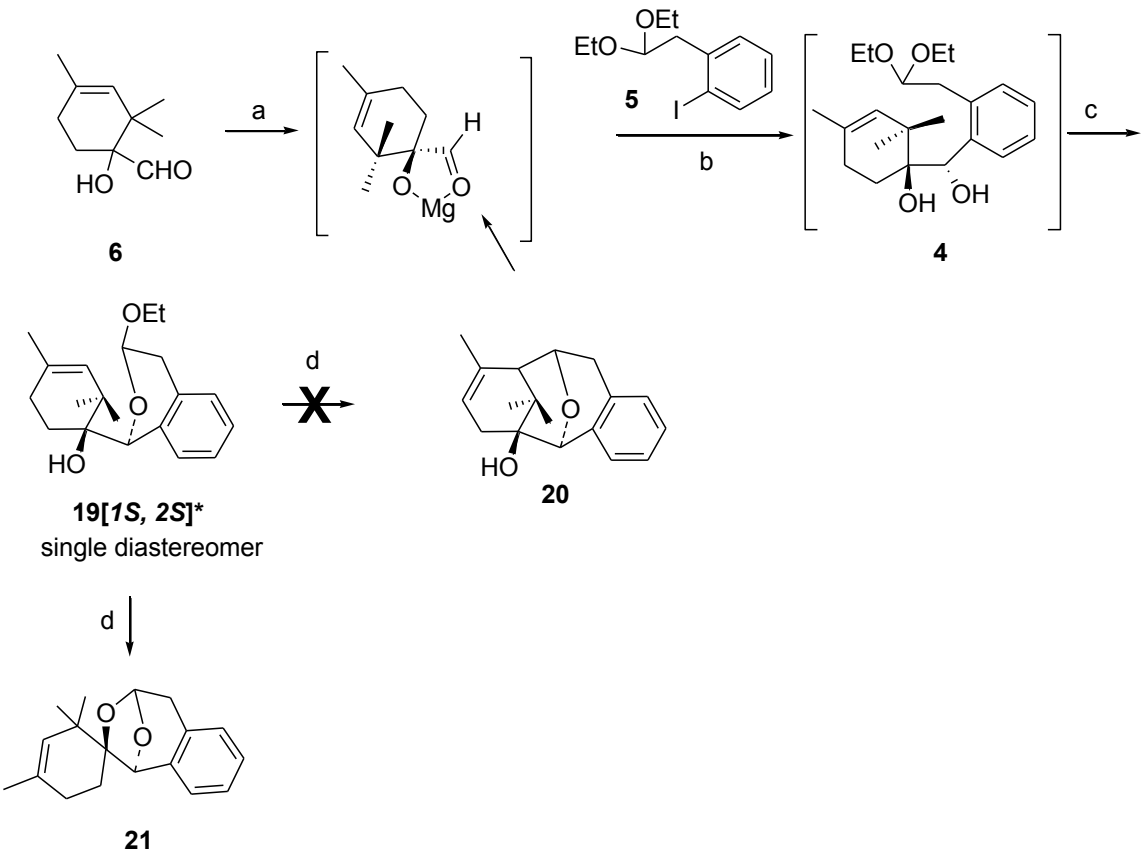
a. HNO_2, KI, 0 ^{o}C, 3h, 70% b. i. $SOCl_2$, benzene, reflux, 2h ii. CH_2N_2, Et_3N, benzene, -20 ^{o}C, 60% c. AgOBz, Et_3N, MeOH, 3h, 75% d. i. 5N NaOH, MeOH, 3h, 97% ii. B_2H_6, THF, 0 ^{o}C, 95% e. Dess-Martin Periodinane, 20 min., DCM, R.T., 92% f. $CH(OCH_2CH_3)_3$, pTSA, EtOH, reflux, 3h, 96%

The C-ring unit was prepared in six steps 26% overall yield from commercially readily available cheap material i.e. anthranilic acid, which was *in-situ* diazotised and treated with KI to get *o*-iodobenzoic acid **15**. Arndt-Eistert one carbon homologation

protocol was used to get **17** from **15** in two steps as delineated in Scheme-4. The methyl ester was reduced with diborane to form alcohol and subsequently oxidized with Dess-Martin periodinane to form aldehyde then and lastly protected with triethyl orthoformate to get C-ring unit **5**.

Further, Mg(II) ion complex was formed by adding *tert*-butyl magnesium chloride to compound **6** (Scheme-5). To this complex aryl lithium reagent, prepared from **5** on reductive metallation with nBuLi was added at –78 ^{o}C to obtain **4**, which was unstable and underwent trans acetalization to form compound **19**, as a single diastereomer. The compound **19** was subjected to Lewis acids ($BF_3.OEt_2$, $Ti[Cl_2(^{i}PrO)_2]$, $TiCl_4$, & $SnCl_4$) at various temperatures (–60 ^{o}C, 0 ^{o}C & R.T.) in dichloromethane to furnish unexpected spiro compound **21** instead of desired ene cyclized product **20**. The compound **21** was thoroughly characterized by ^{1}H NMR, ^{13}C NMR, MS and X-ray crystal structure. The X-ray structure of **21** revealed the relative configuration of C1 hydroxy and C2 hydroxy groups to be trans, which is same in naturally occurring taxol.

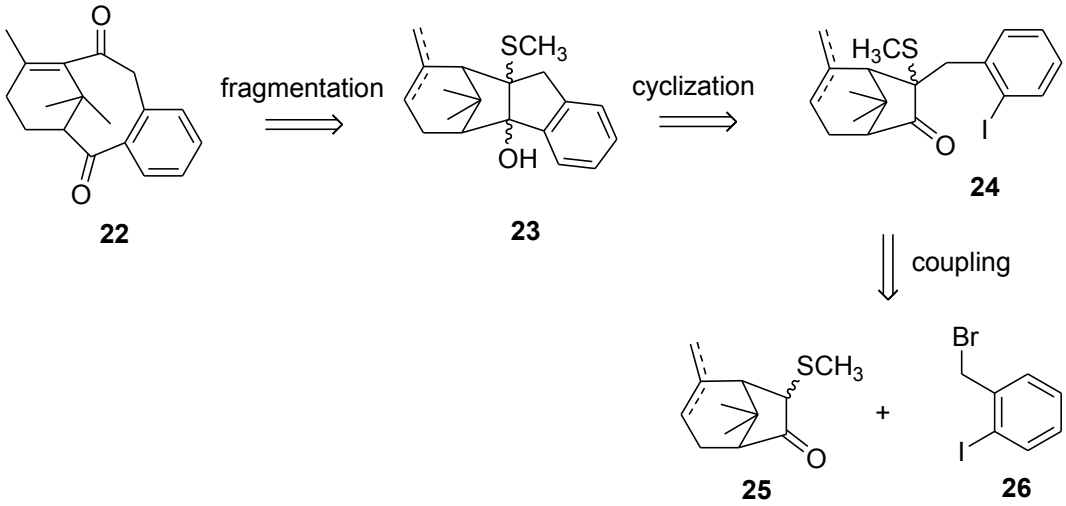
Scheme-5



a. ^{t}BuMgCl, diethyl ether, -78 ^{o}C, 1h b. ***5****, nBuLi, -78 ^{o}C, THF, 2h, 70% c. silica gel d. $SnCl_4$, CH_2Cl_2, -60 ^{o}C, 3h, 85%*

Section-III: Synthesis of C-Aromatic ABC-ring skeleton taxane system

Scheme-6

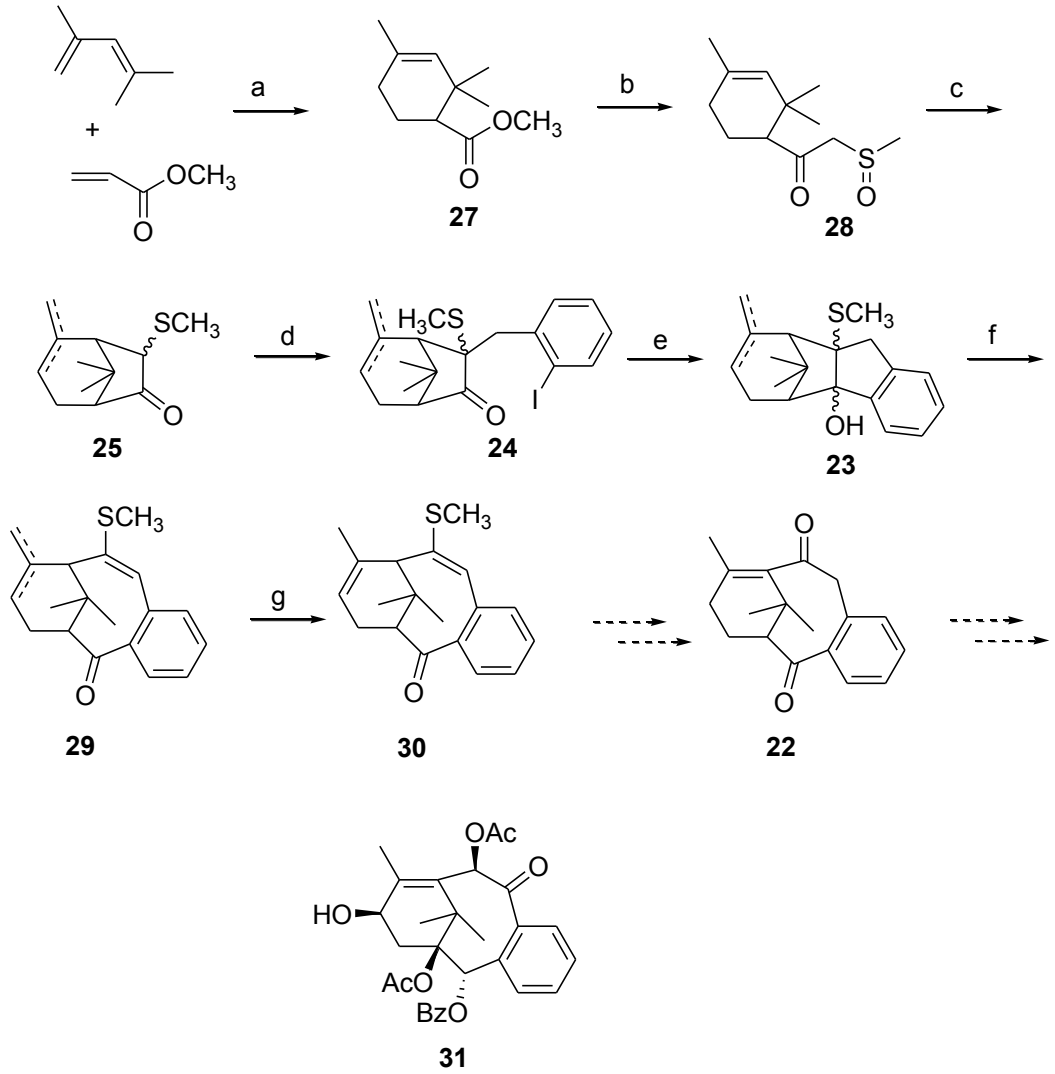


After failing to get desired oxonium-ene cyclization reaction in previous section, to form central eight membered B-ring, a totally new convergent route as shown in scheme-6 was adopted. Here the premise was that the eight-membered ring can be made by fragmentation reaction to get ABC taxane skeleton, hoping that, this strategy will overcome unfavorable entropy, bond angle deformations, and destabilizing transannular interactions associated with the direct construction of eight membered ring. Thus, retrosynthesis revealed two synthons **25** and **26**, which were prepared accordingly.

As delineated in scheme-7, **27** was prepared by Diels-Alder reaction. Thus, 2,4-dimethyl-1,3-pentadiene and methyl acrylate were heated in sealed-tube at 140 ^{o}C for 36h in dichlomethane to furnish adduct **27** in 75% yield. The methyl ester **27** was condensed with sodium dimsyl to furnish β-keto sulfoxide **28** in 70% yield**.** The Pummerer reaction condition was performed to form bicyclic ring **25**. Thus, after several reaction conditions 50% yield was obtained by using trifluoro acetic anhydride in refluxing dichlomethane for 3h. The compound **25** was obtained as a mixture of four isomers, which was confirmed by GCMS. The bicyclic compound **25** was further alkylated with 2-iodo-benzyl bromide **26** to form coupled product **24** in 70% yield. Intramolecular cyclization reaction was carried by metal halogen exchange method by adding n-butyl lithium at –78 ^{o}C to compound **24** to obtain tetracyclic compound **23** in 80% yield. Finally the key fragmentation reaction was carried out by lead tetraacetate at 0 ^{o}C to furnish the desired ABC skeleton **29** in 75 % yield of isomers as a 1:1 mixture which was confirmed by GCMS. The compound **29** was refluxed in ethanol over catalytic amount of Rhodium trichloride for 24h furnished thermodynamically more

stable endo cyclic double bond. The compound **30** was thoroughly characterized by IR, ^{1}H NMR, ^{13}C NMR, GCMS, Elemental Analysis and X-ray crystal structure.

Scheme-7



a. Sealed-tube, DCM, 140 ^{o}C, 36h, 75% b. Sodium dimsyl, THF, 0 ^{o}C to r.t., 70% c. $(CF_3CO)_2O$, DCM, 50 ^{o}C, 3h, 50% d. NaH, THF, 0 ^{o}C, 1h, ***26*** *in THF, 70% e. nBuLi, THF, –78 ^{o}C, 3h, 80% f. $Pb(OAc)_4$, toluene:AcOH (4:1), 0 ^{o}C, 6h, 75% g. $RhCl_3.3H_2O$, ethanol, 80 ^{o}C, 24h, 80%*

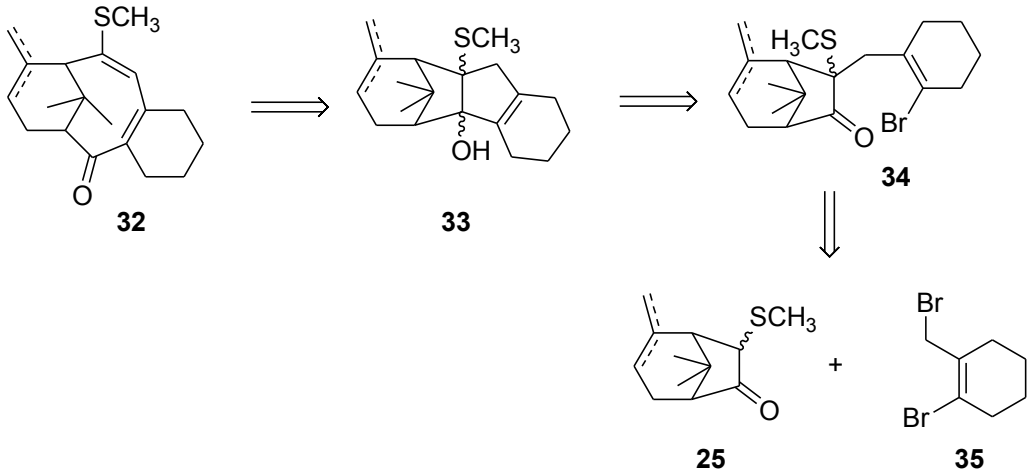
In order to install proper oxygenated functionality and bridgehead double bond to a AB-ring part of skeleton **30** which could lead to complete functionalised C-aromatic taxol **31,** various reactions conditions were attempted without any success. These attempts will be discussed. However, with the proper choice of reagents and conditions it should be possible to convert **30** to the properly functionalised ABC skeleton of taxol.

In conclusion, a synthesis of ABC ring skeleton of taxane system taking aromatic C-ring moiety has been accomplished. The salient feature of this protocol is the versatile role played by sulfur atom in formation of carbon-carbon bonds and the key fragmentation step.

Section-IV: Synthesis of C-alicyclic ABC-ring skeleton taxane system

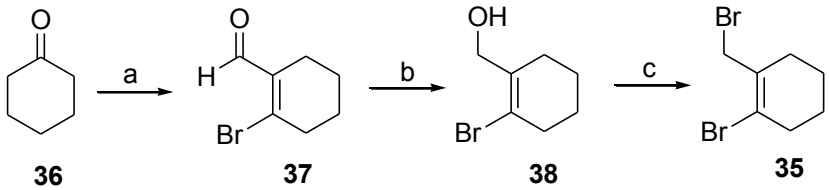
After successful completion of C-aromatic ABC skeleton system it was planned to adopt the same strategy of fragmentation reaction taking C-ring as alicycle as depicted below (scheme-8).

Scheme-8



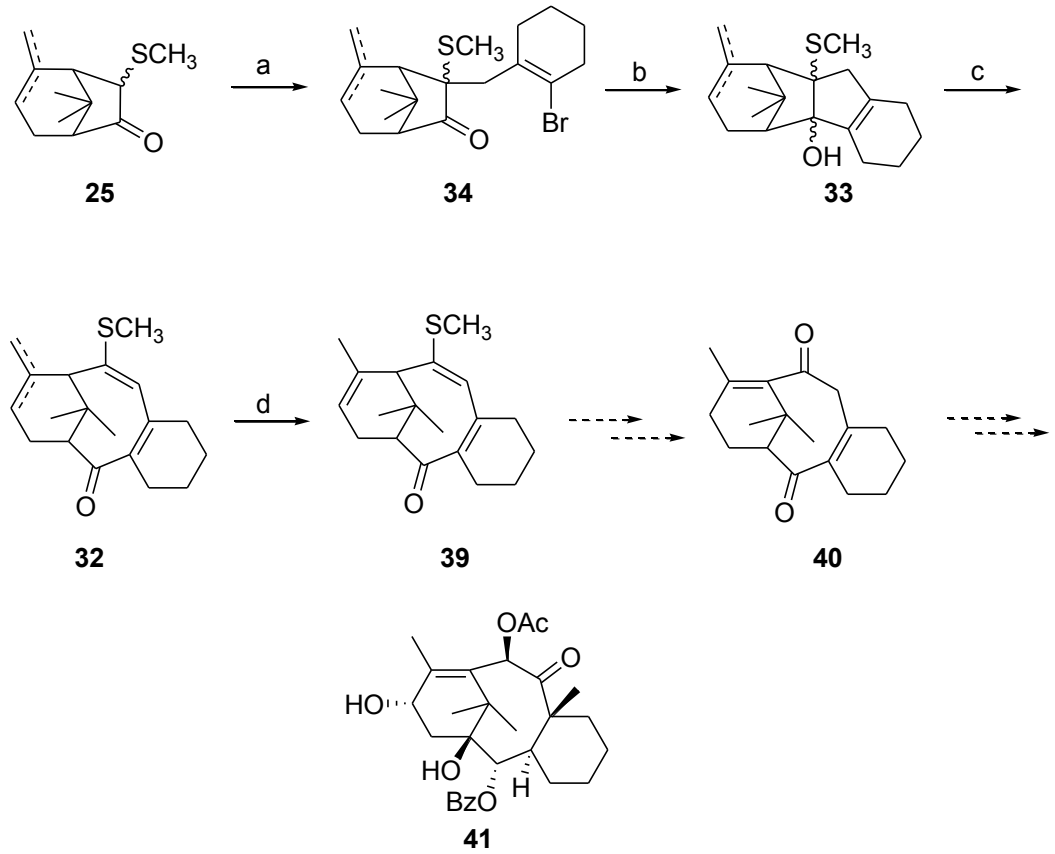
The retrosynthetic analysis revealed compound **35** as a C-ring synthon, which was prepared from cyclohexanone in three steps, 54% overall yield as delineated in scheme-9.

Scheme-9



a. DMF, PBr_3, $CHCl_3$, 0 ^oC, 75% b. $NaBH_4$, MeOH, 0 ^oC, 8h, 90% c. PBr_3, DCM, 0 ^oC, 80%

Scheme-10



a. NaH, THF, 0 ^{o}C, 1h, ***35*** *in THF, o.n., 70% b. sBuLi, THF, –100 ^{o}C, 3h, 60% c. Pb(OAc)$_4$, toluene:AcOH (4:1), 0 ^{o}C, 6h, 75% d. RhCl$_3$.3H$_2$O, ethanol, 80 ^{o}C, 24h, 80%*

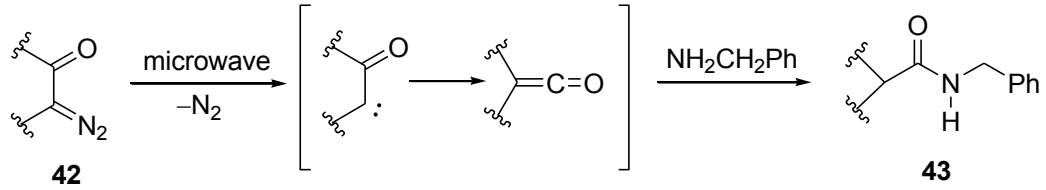
Thus, bicyclic α-ketosulfide **25** was subjected to reaction with sodium hydride and subsequently quenched with **35** to form **34** in 70% yield (scheme-10). The alkylated product **34** was subjected to intramolecular reductive metallation coupling by using sec-butyl lithium at –100 ^{o}C to furnish tetracyclic system **33** in 60% yield. All the four expected isomers were visualized by GCMS. Then, the key fragmentation step went smoothly in the presence of lead tetraacetate at 0 ^{o}C for 3h to obtain desired eight membered ring compound **32** in 75% yield. The product was thoroughly characterized by IR, ^{1}H NMR, ^{13}C NMR, GCMS and elemental analysis. In a similar way, the product **32** was isomerised by rhodium trichloride to yield more thermodynamically stable product **39**. Here too, various conditions to hydrolyze the enol ether to form the keto compound and which could further lead to a complete functionalised AB ring of skeleton obtained, were tried without success and would be presented. However, with the proper choice of reagents and conditions it should be possible to convert **39** to the properly functionalised ABC skeleton of taxol.

In conclusion it may be stated that the work outlined herein offers a concise, unique and convenient route for the synthesis of ABC skeletons (C-aromatic and C-alicyclic) of taxol utilizing β-hydroxy sulfide fragmentation reaction as a key step.

Chapter-II: Microwave Specific Wolff-rearrangement of α-diazoketones and its Relevance to the Non-thermal and Thermal Effect

The chapter begins with brief introduction to microwaves; its theory, instrumentation and current status. Few literature reports of microwave assisted organic synthesis will be discussed with special emphasis on much debated microwave specific thermal and non-thermal effect.

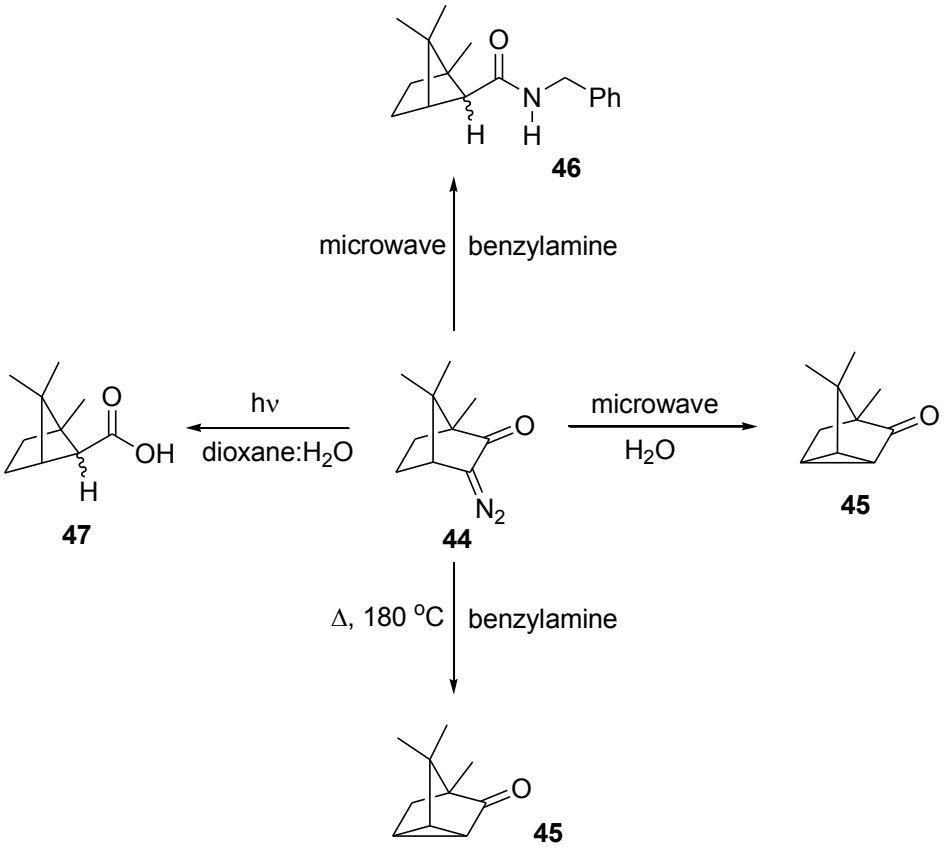
Scheme-11



42 **43**

α-Diazoketones possess high electric dipole moments, as a consequence of the dipolar nature of the diazocarbonyl functional group. The vectorial analysis, theoretical calculations (PM3 and *ab initio*), and literature reports based on experimental and theoretical calculations reveal a higher dipole moment for the *Z*-configuration of the diazo functional group. Microwave irradiation of various α-diazoketone *i.e.* aliphatic, aromatic and alicyclic promotes Wolff rearrangement specifically *via* the *Z*-configuration in excellent yields (Scheme-11). The dielectric properties of the solvent govern the course of the microwave rearrangement. 3-Diazocamphor **44** on microwave irradiation in benzylamine exhibits nonthermal effects to furnish exclusively the Wolff rearrangement product **46**, equivalent to its photochemical behavior (Scheme-12). In the presence of an aqueous medium, through solvent heating predominates, leading to the formation of a tricyclic ketone **45** as the principal product, arising from an intramolecular C-H insertion. This behavior is similar to its known thermal and transition metal catalyzed reactivity pattern.

Scheme-12


O
N
Ph
H
H
46
microwave
benzylamine
O
OH
H
47
hν
dioxane:H2O
O
N2
44
microwave
H2O
O
45
Δ, 180 °C
benzylamine
O
45

Chapter-I

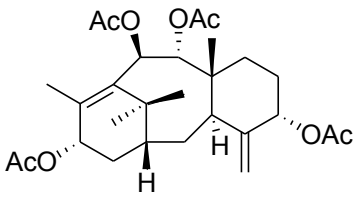
Synthesis of ABC skeletons of Taxol

Section-I

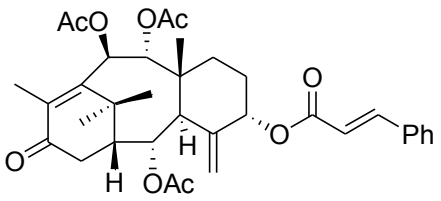
General Introduction of Taxol

1.1.1 Introduction:

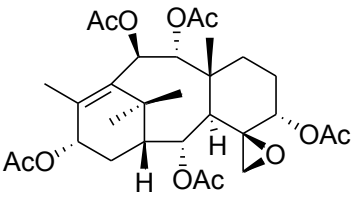
Taxanes are one of the most biologically interesting families of cyclooctanoid diterpenoids. These uniquely bridged tricyclic ring skeletons [$9.3.1.0^{3,8}$] are found in several species of yew trees. So far more than 400 taxane-type diterpenoids have been isolated from various *Taxus* plant.[1] Some of the most common taxanes are taxusin **1** taxinine **2,** baccatin I **3**, and taxol **4**.



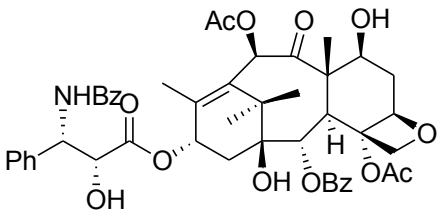
Taxusin **1**



Taxinine **2**



Baccatin I **3**



Taxol **4**

Figure-1

Taxol **4**, the most celebrity member of this class, is used today clinically as a single dose or in combination with cisplatin for the first line treatment for ovarian, breast, lung, head and neck, prostate, and cervical cancers, and AIDS-related Kaposi's sarcoma.[2] Taxol, along with Taxotere (anologue with a (*tert*-butoxy)carbonyl (Boc) group instead of the benzoyl (Bz) group in Taxol **4** side chain) is the largest selling anti-cancer drug of all time, with sale of $ 2 billion in 2003.[3] Besides oncological properties, some low-oxygenated taxanes are powerful inhibitors of P-glycoprotein mediated transport and act as MDR reversing agents.[4] For example, taxoids related to taxuyunnanine C 14 have NGF-like activity and have been claimed to be useful for the treatment of Alzheimer's disease.[5] Naturally occurring taxane diterpenes, such as taxezopidine G, have been reported to show inhibitory activities comparable to that of verapamil.[6] Other oncological potential applications of low-oxygenated taxoids possessing neither a fused oxetane ring nor a C-13 (*N*-acyl) phenylisoserin and C-2 *O*-benzoyl moieties, which had been regarded as very important for binding of taxoids to tubulin, are psoriasis, malaria,

arthritis, multiple sclerosis, polycystic kidney disease, and more likely to come.[7] Discovery of the bioactivity now known to be due to taxol was made in 1962, when Arthur Barclay, a botanist working for the US Department of Agriculture under contract to the US National Cancer Institute (NCI), made a collection of the stem and bark of *Taxus brevifolia NUTT* in Washington State. These plant samples, along with many others, were duly extracted and tested for bioactivity, and in 1964 the extract from *T. brevifolia* was found to be cytotoxic to KB cells. The extract was assigned to Dr Monroe Wall, Dr Mansukh Wani and co-workers at Research Triangle Institute, and taxol was isolated in 1967.[8] The structure was elucidated by a combination of X-ray studies of two degradation products and ^{1}H NMR analysis of the intact molecule, and was published in 1971.[9] Initial reaction to taxol as a potential anticancer drug was less than enthusiastic. Although it was clearly an active compound, with activity both in cell culture and also *in vivo* against various leukemia's and the Walker 256 carcinosarcoma, its activity was only modest in these assays. To add to its problems, it was highly insoluble in water, and would thus clearly present formidable formulation problems, and it was isolated in only very modest yield from the bark of a relatively uncommon and slow-growing tree. Not a good outlook for a potential drug candidate! Fortunately testing was carried out in some new *in vivo* bioassays that were introduced by NCI in the early 1970's, and it proved to be strongly active in a B16 mouse melanoma model.[10] On the basis of this activity, and with enthusiastic support from Dr Matthew Suffness at NCI and Dr Monroe Wall, taxol was selected as a development candidate in 1977. Development of taxol as a drug was a challenging task because of the problems with solubility and supply noted earlier, and also because of its relatively low potency. The solubility problem was successfully overcome with a formulation in ethanol and Cremophor, and this turned out to be important in both negative and positive ways. On the negative side, the high levels of Cremophor required led to hypersensitivity reactions and almost led to the withdrawal of taxol from clinical trials. On the positive side, there is some evidence that Cremophor has a pharmaceutical effect over and above its surfactant properties, and may act to reverse multidrug resistance. Interest in taxol as a drug candidate was increased significantly when Susan Horwitz reported in 1979 that it had what was then a completely new mechanism of action, taxol promotes polymerization of the cellular protein tubulin causing it to assemble into stable microtubles.[11] It is believed that this mechanism is responsible for taxol's action as an antitumor drug and **4** has, thus, become a valuable

biochemical tool for studying mitosis. This discovery proved to be important in maintaining interest in the development of taxol at a time when its initial clinical results were discouraging.

Taxol has drawn significant attention of organic chemists, medicinal chemists, biologist and pharmacologist due to its significant biological activity, molecular architecture, limited supplies, unique mechanism of action towards the cancer tumor cell and poor water solubility to formulate. Enormous effort has also been directed toward the total synthesis of taxol and now six groups led by Holton,[12] Nicolaou,[13] Danishefsky,[14] Wender,[15] Mukaiyama[16] and Kuwajima[17] have successfully accomplished this monumental task. Till today, synthesis of taxanes remains problematic because of the difficulties encountered during cyclooctane annulation owing to the high degree of strain and transannular interactions. As an alternative source of taxol, the total synthesis of taxol in the laboratory remains impractical as it is largely of an academic interest. However, in the last two-decade, synthetic efforts have contributed greatly to the development of several new synthetic methodologies.

1.1.2 Mechanism of action in cell biology:

For a cell to divide, the microtubule skeleton that gives it shape must first disassemble, then reform into spindle across which duplicate sets of DNA material line up, and finally disassemble once more and reform into skeletal systems for the two new cells. The extreme flexibility of the tubulin protein enables microtubules to shift through theses various formations. Taxol is mitotic stabilizer, when it binds to tubulin, the protein loses its flexibility and the microtubules can no longer disassemble. A schematic representation of taxol's effect on the tubulin polymerization process is shown in Figure-2.[18]

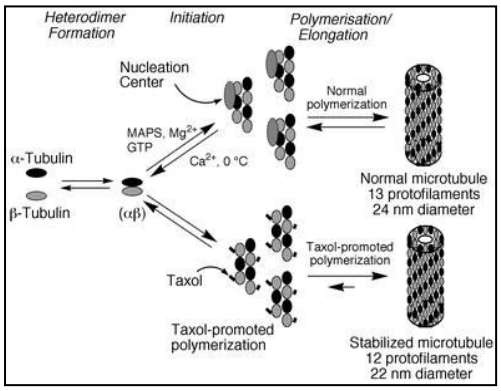


Figure-2: Schematic representation of normal microtubule assembly (upper) and taxol-promoted microtubule assembly (lower). (Picture courtesy Kingston, D. G. I. *Chem. Commun.* **2001**, 867.)

Several compounds, including the clinically used drugs vinblastine (Velban™) and vincristine (Oncovin ™), were known to operate as spindle poisons by *preventing* the assembly of tubulin into microtubules, but Taxol was the first compound in which the activity was linked to *promotion* of microtubule assembly.

The binding of taxol to tubulin polymers and the associated interruption of the cell cycle was thought for a long time to be its only significant mechanism of action, but in recent years it has been increasingly clear that taxol can bring about apoptotic cell death by a second mechanism which is independent of mitotic arrest.[19,20] The protein Bcl-2 has been identified as a second taxol-binding protein[21] which undergoes dose-dependent hyperphosphorylation in the presence of taxol.[22] The situation is complex, however, since it has also been shown that Bcl-2 phosphorylation in the presence of taxol is linked to the latter's tubulin-assembly activity, and it has thus been proposed that taxol- promoted assembly of microtubules leads to Raf-1 activation and Bcl-2 phosphorylation, and thence to apoptosis.[23] The binding of taxol to tubulin is thus clearly

biologically significant, and has been studied extensively by several methods. A detailed understanding of this binding has become much more achievable in recent years thanks to the work of Downing and his collaborators, who have reported the structure of tubulin at a resolution of 3.7 Å using electron crystallography on crystalline sheets formed in the presence of zinc.[24,25]

For many years taxol was the only compound known to promote the assembly of tubulin into microtubules, but over the past few years several other natural products have been discovered with the same or similar activity. The most important compounds of this class are the epothilones A and B,[26,27] discodermolide,[28] and eleutherobin,[29] but other compounds with this activity have also been discovered. These include rhazinilam,[30] which inhibits the disassembly of microtubules but has a different mechanism of action than taxol, laulimalide and isolaulimalide,[31] WS9885B,[32] and polyisoprenylated benzophenones such as guttiferone E.[33] The naturally occurring 3(2*H*)-furanone derivative geiparvin has been found to counteract the microtubule-assembly effects of taxol, suggesting that it is a competitive inhibitor at the taxolbinding site of tubulin.[34]

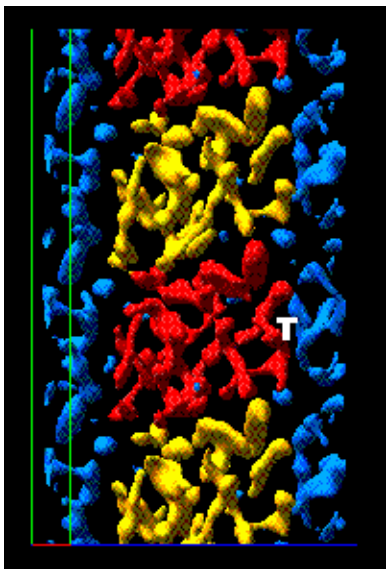


Figure-3: This image shows the site where the anti-cancer drug taxol interacts with tubulin proteins to prevent cell division. "T" marks the approximate position of the taxol binding site, which is shown at a resolution of about 6.5 angstroms (Nogales, E.; Whittaker, M.; Milligan, R. A.; Downing, K. H. *Cell*, **1999**, *96*, 79.)

1.1.3 Structure-Activity Relationship of Taxol:

The structure activity relationship (SAR) of Taxol has been studied by large number of researcher from academia as well as industries. The detailed study on this topic has been included in several comprehensive reviews[35] and books.[36] However a birds eye view on some major findings of groups involved is presented.

In 1979 Kingston initiated work on SAR of Taxol, as a consequence several analogues varying peripheral oxygenated functionality of skeleton and side chain of parent Taxol had been prepared and tested. The results are summarized in figure-4.[37]

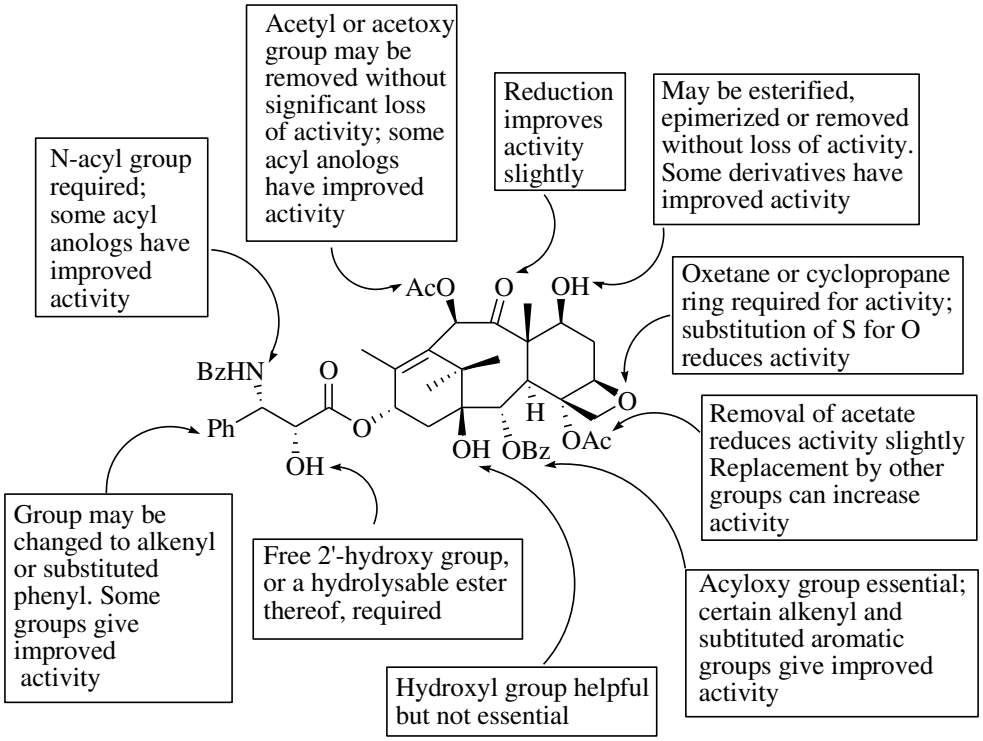
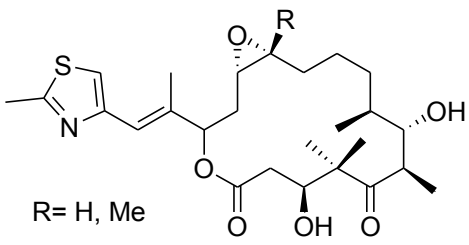


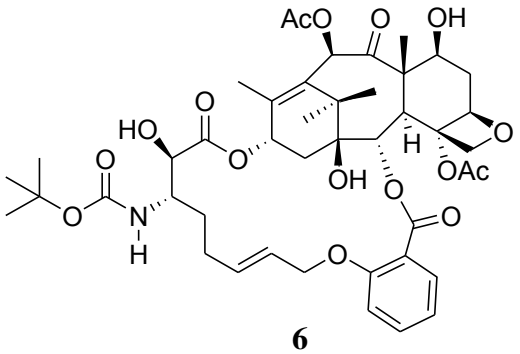
Figure-4: Kingston's model: SAR of Taxol (Kingston, D. G. I. *Chem. Commun.* **2001**, 867.)

The discovery of taxol resulted in different way of delineating the pharmacophore of taxol. Many groups have compared the taxol structures with that of taxol mimicking molecule i.e. epoithilones.

In one approach various bridged analogs of taxol such as **6** were prepared by olefin methathesis.[38] Three related analogs were found to be cytotoxic to the human breast cancer cell line MDA-435/LCC6-WT with IC50 values of less than 1 mM. These activities are significantly less than that of taxol in the same cell line (0.0031 mM), but the compounds also showed tubulin assembly activity that was only slightly less than that of taxol, so they are presumably binding to the same binding site as taxol. These data were used to support a model of the pharmacophore in which the aryl sector of



Epothilones **5**



6

epothilone overlaps the C-13 acyl side chain of taxol and in which the baccatin portion of the taxol molecule is relatively non-essential.

A second approach, developed by Giannakakou and his collaborators, was based on a comparison of the effects of taxol and various epothilone analogs on the polymerization of native tubulin and of modified tubulins carrying β-tubulin mutations near the taxol-binding site.[39] Two possible common overlaps of the epothilones and taxol were found. In the first the C-2 benzoyl group of taxol overlapped with much of the 1-methyl-2-thiazolyl side chain of the epothilones, while in the second the thiazole portion of the epothilones overlapped with the side chain of taxol.

A third approach deduced a different binding based on the finding that the side chain of taxol is not as essential for activity as was previously thought, since 2-(*m*-azidobenzoyl)baccatin III is significantly active as a promoter of tubulin polymerization and is a competitive inhibitor of the binding of taxol to microtubules.[40] These studies led to the proposal of a pharmacophore model similar to the first binding mode of Giannakakou *et al.* A perceptive evaluation of the various models has been published.[41] A different approach was taken by Snyder, who developed a minireceptor model for the binding of taxol and epothilone to the microtubule based on an analysis of tubulin-assembly data.[42] This model places the thiazole ring of the epothilones in the same region of the receptor as the side chain of taxol, consistent with the second binding mode of Giannakakou *et al*.[39] It also predicts much of the SAR data for taxol and the epothilones and appears to be an interesting first step towards the development of a full binding site model.

In nutshell, the taxol pharmacophore is still under development, with at least two rather different competing hypotheses, and further work will be needed to clarify the situation. It is reasonable however to expect that a final model of the taxol pharmacophore will eventually be developed and will be used in a predictive way to create new and improved taxol analogs.

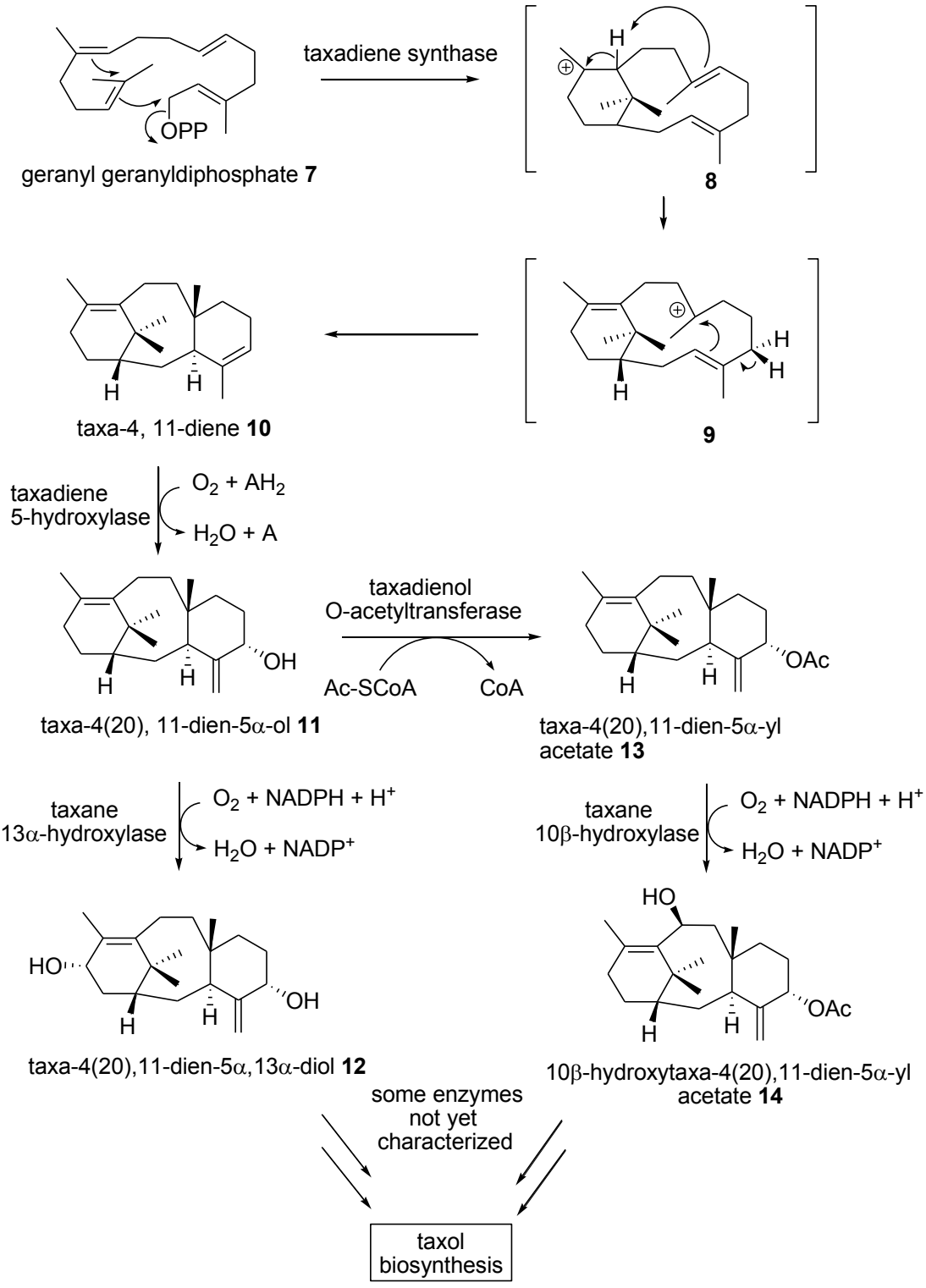
1.1.4 Biosynthesis of Taxol:

Great progress has been made in the biosynthetic mechanism of Taxol in Taxus (yew) due to dozens of researchers' fundamental work, especially in the past ten years.[43] Except for a few undefined steps, the Taxol biosynthetic pathway has been elucidated (Scheme-1) and many genes encoding certain enzymes, which regulate Taxol biosynthesis pathway, have been cloned and characterized.[43] The Taxol biosynthetic pathway is considered to require 19 enzymatic steps from the universal diterpenoid precursor geranylgeranyl diphosphate.[44] The fundamental building blocks of all isoprenoids, including terpenes such as geranylgeranyl diphosphate, are isopentyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP). These are biosynthesized via acetoacetyl-CoA, 3-hydroxy 3-methyl glutaryl-CoA (HMG-CoA) and mevalonic acid (MVA). Following this first committed step in taxol biosynthesis, taxadiene 5-hydroxylase, a cytochrome P-450-dependent enzyme, regioselectively hydroxylates **10** with allylic rearrangement, to taxa-4(20),11(12)-dien-5R-ol **11**. Taxadienol-*O*-acetyltransferase subsequently acylates **11** to provide the acetate **13**, which further selectively is oxidized at C-11 by taxane 10β-hydroxylase to 10β-hydroxytaxa-4(20),11-dien-5a-yl acetate **14,** further steps converting enzymes are not yet characterized. Alternately, taxa-4(20), 11-dien-5α-ol **11** was selectively oxidized at C-13 position by an cytochrome P-450-dependent enzyme taxane 13α-hydroxylase to obtained taxa-4(20),11-dien-5α,13α-diol **12**.

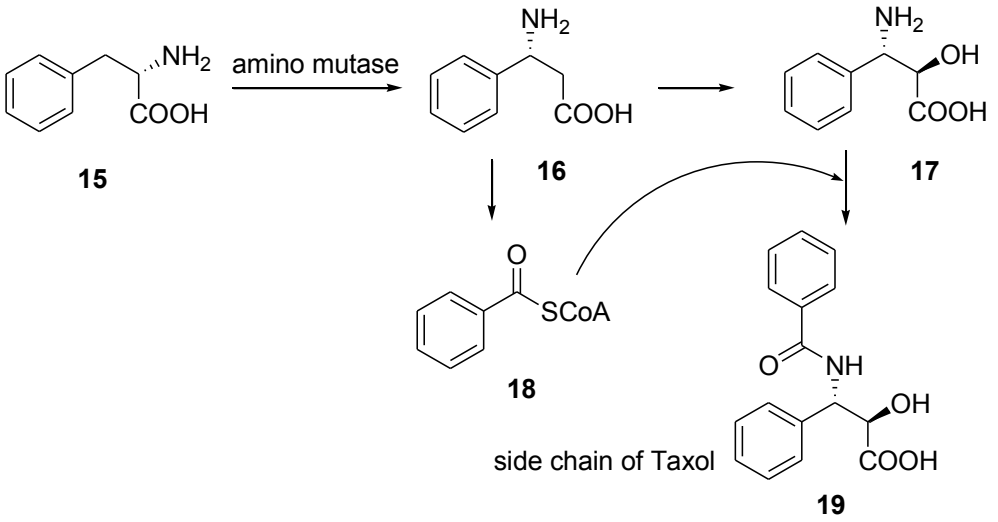
The side chain of Taxol is formed from phenylalanine via β-phenylalanine, catalysed by an aminomutase enzyme, followed by hydroxylation of C-2 and acylation of the nitrogen. The benzoyl moiety is also formed via β-phenylalanine (Scheme-2).[45]

The enzyme 2α-hydroxytaxane 2-*O*-benzoyltransferase which selectively benzoylate at C-2 hydroxyl group of 10-deacetyl-2-debenzoylbaccatin III in presence of benzoyl-CoA and further selectively acylation at C-10 to form baccatin III is catalysed by an enzyme 10-deacetylbaccatin III 10-*O*-acetyltransferase in the presence of acetyl-CoA had been reported (Scheme-3).[46] The final stages of biosynthesis, appending of side chain to Baccatin III have not been understood yet.

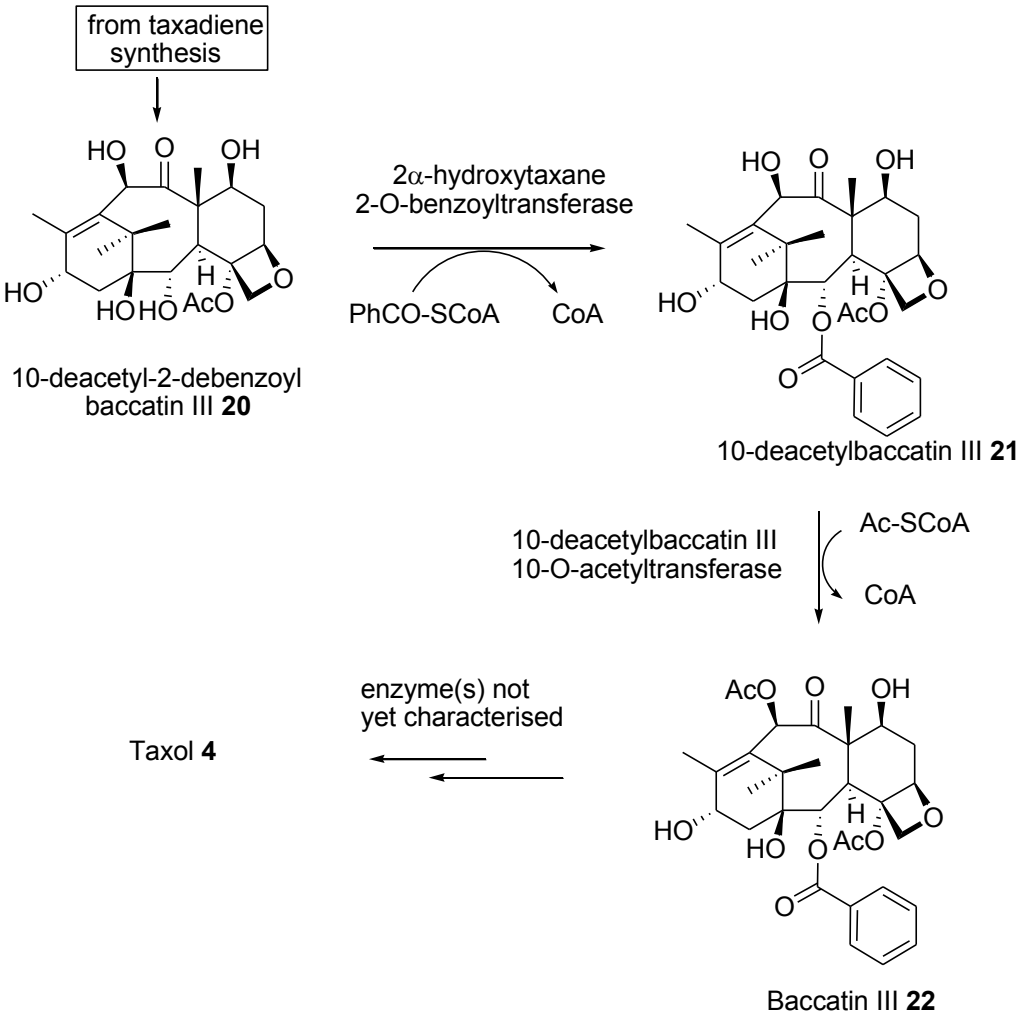
Scheme-1: Guo, B. H; Kai, G. Y.; Jin, H. B.; Tang, K. X. *Afr. J. Biotechnol* **2006**, *5*, 15.



Scheme-2: Fleming, P. E.; Mocek, U.; Floss, H. G. *J. Am. Chem. Soc.* **1993**, *115*, 805.



Scheme-3: Walker, K. and Croteau, R. *Proc. Natl. Acad. Sci. USA* 97 (2000) 13591.

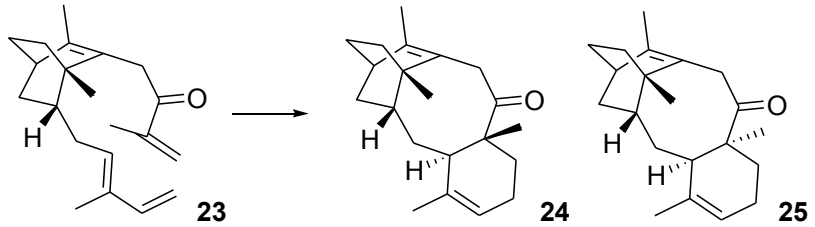


1.1.5 A brief literature survey of synthesis of AB, BC & ABC skeleton of Taxol:

Taxol was one of anti-cytotoxic agent isolated then as part of programme of NIH (USA) widespread screening of substances from various origins for antineoplastic activity. But as soon as its unique mode of action towards tumor cells was discovered, legions of synthetic organic chemist around the world embarked on its synthesis. As a consequence, 1980's and 1990's witnessed flood of publications in literature. Owing to its unique structure, almost all the researcher developed AB, BC and ABC ring system focusing on central eight membered B-ring as part of strategy and tactics before venturing directly to the total synthesis. As the theme of dissertation centers around the development of ABC ring systems models, a brief summary of the reported route till date is presented herein.

First paper in literature for skeleton work was carried out in 1983 by Sakan and Craven,[47] who utilized intramolecular Lewis acid catalysed Diels-Alder reaction as the key step to furnish the major desired diastereomer product **25** (Scheme-4).

Scheme-4: Sakan, K.; Craven, B. M. *J. Am. Chem. Soc.* **1983**, *105,* 3732.



23 **24** **25**

Me_2AlCl, PhH, 25°C (90%)	1	:	19
$B(OMe)_3$, PhMe, 160°C (70%)	4	:	1

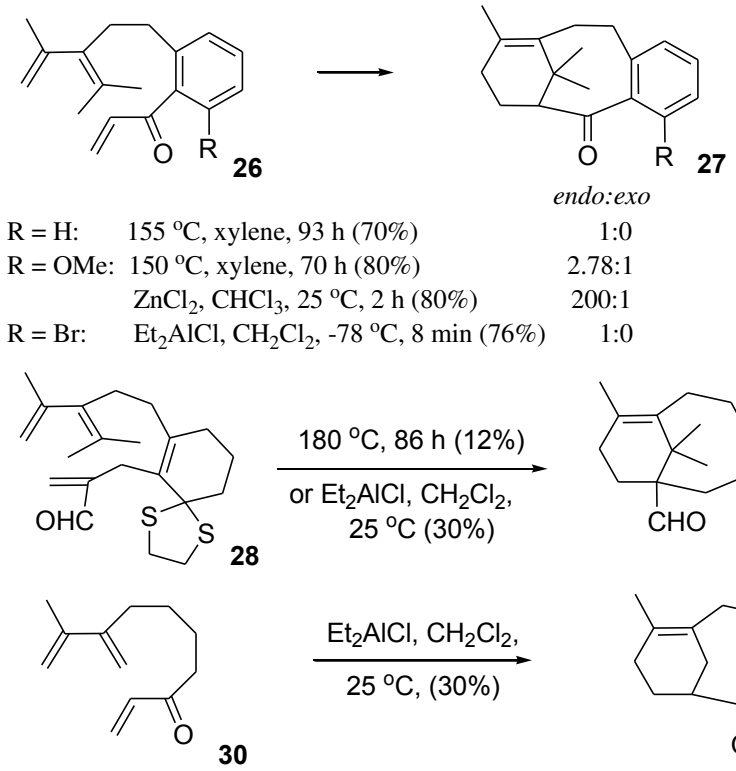
Similarly but independently, Shea and his collaborators developed a number of intramolecular versions of the Diels-Alder reaction starting with **26**, **28**, and **30** and leading to taxol skeleton models **27**, **29**, and **31** as shown in Scheme-5.[48]

In a similar fashion Jenkin concurrently devised intramolecular Diels-Alder reaction to obtain ABC ring skeleton as depicted in Scheme-6.[49]

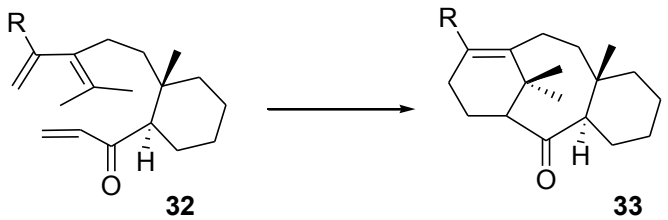
Wender group have disclosed their synthetic strategy of AB and BC ring model systems **35**, **37**, and **39** (Scheme-7) using nickel catalyzed direct [4+4] cycloaddition process.[50]

Two clever approaches to taxol model systems were reported by Trost *et al.* In the first approach, shown in Scheme-8, a fragmentation reaction of hydroxy sulfones **42**

Scheme-5: Shea, K. J.; Sakata, S. T. *Tetrahedron Lett.* **1992**, *33,* 4264.



Scheme-6: Bonnert, R. V.; P. R. Jenkins, *J. Chem. Soc. Chem. Commun.* **1989**, 413.

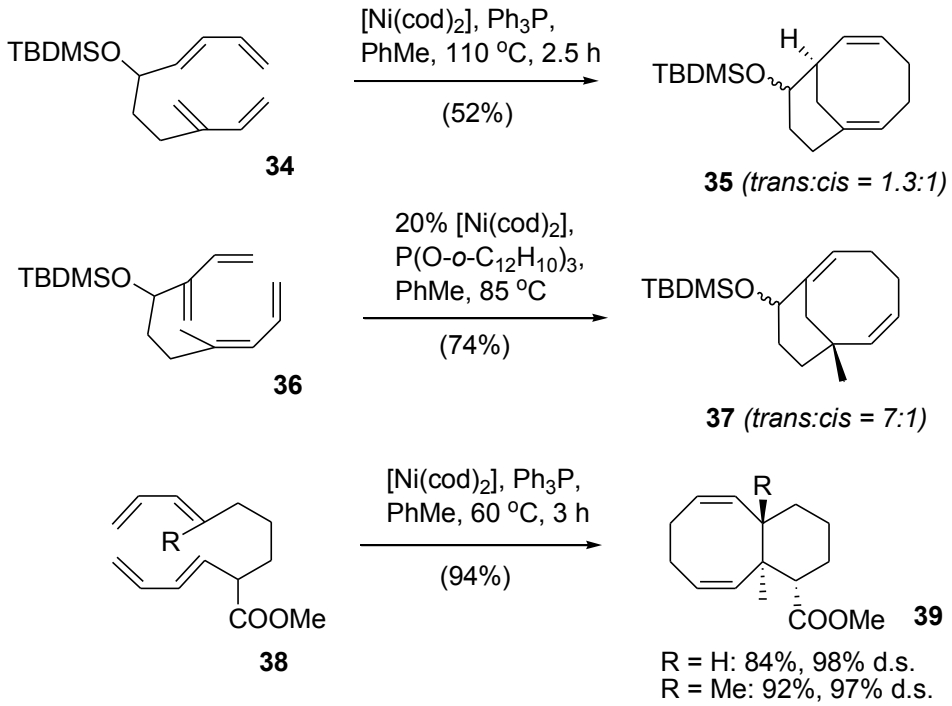


lead to the eight-membered ring system **44** was utilized.[51] This reaction takes advantage of the stabilization, provided by the sulfone group, of the carbanion intermediates involved. In the second approach, depicted in Scheme-9, an oxidative cleavage of diols **48** and **49** led to the formation of a similar bicyclic skeleton **50**.[52]

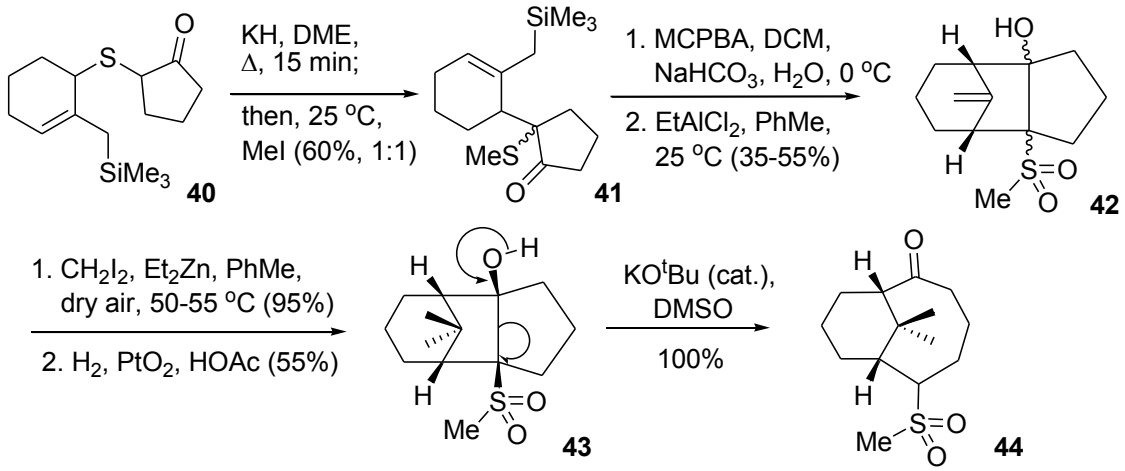
An approach based on a retroaldol type fragmentation was reported by Pattenden in 1983 (Scheme-10).[53] In this strategy, β-acetoxy ketones **52 a,b,** derived from the intramolecular [2+2] photocycloaddition of **51,** were converted into **53** and **54,** respectively, under the influence of KOH. Unfortunately, the nonregioselective nature of the photocycloaddition reaction led to a mixture of products.

Retroaldol and oxidative ring expansion were also utilized by Blechert *et al.* in the synthesis of a number of interesting taxoids with biological activity (Schemes 11-13). Substrates **58**[54] and **65,**[55] derived from intermolecular [2 + 2] photocycloaddition reactions and subsequent manipulations, were subjected to basic conditions to afford tricyclic model system **59** (Scheme-11), and **67** (Scheme-12), respectively, on retroaldol-type fragmentations. In an alternative approach, oxidative cleavage of compounds **62**[56] and **68** gave **63** (Scheme-12) and **69** (Scheme-13), respectively.

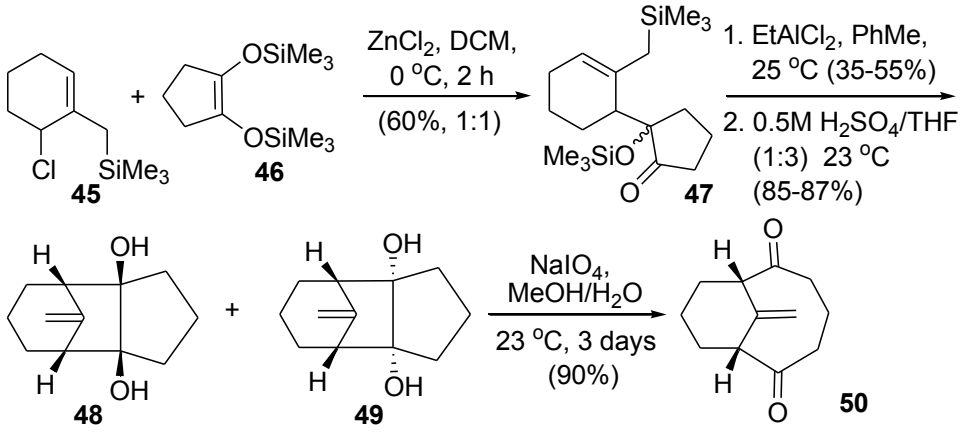
Scheme-7: Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, 1089.



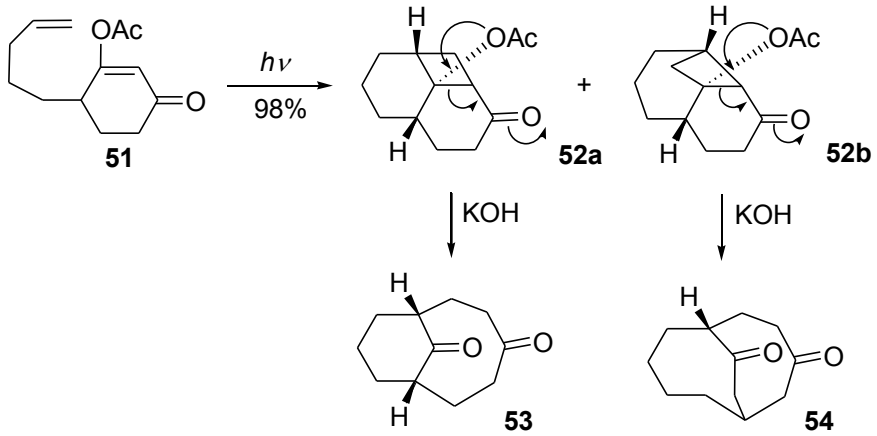
Scheme-8: Trost, B. M.; Hiemstra, H. *J. Am. Chem. Soc.* **1982**, *104*, 886.



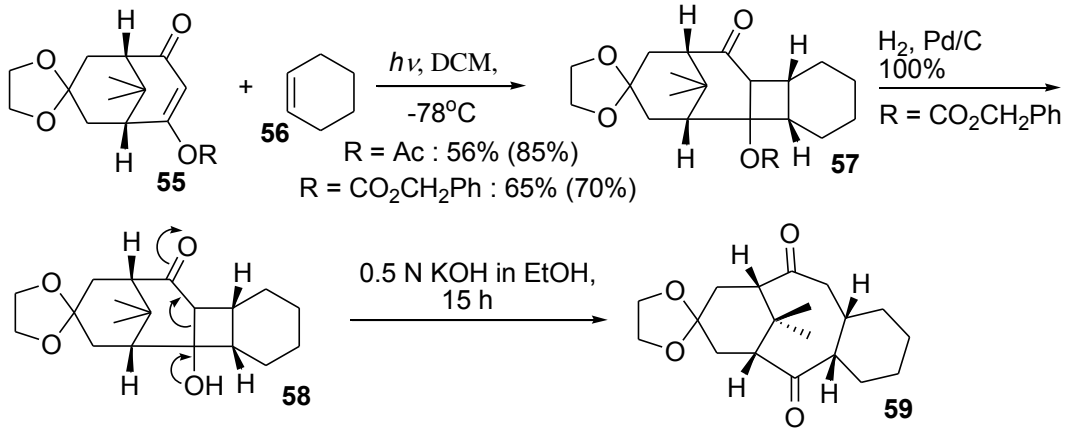
Scheme-9: Trost, B. M.; Fray, M. J. *Tetrahedron Lett.* **1984,** *25,* 4605.



Scheme-10: Begley, M. J.; Mellor, M.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1905.



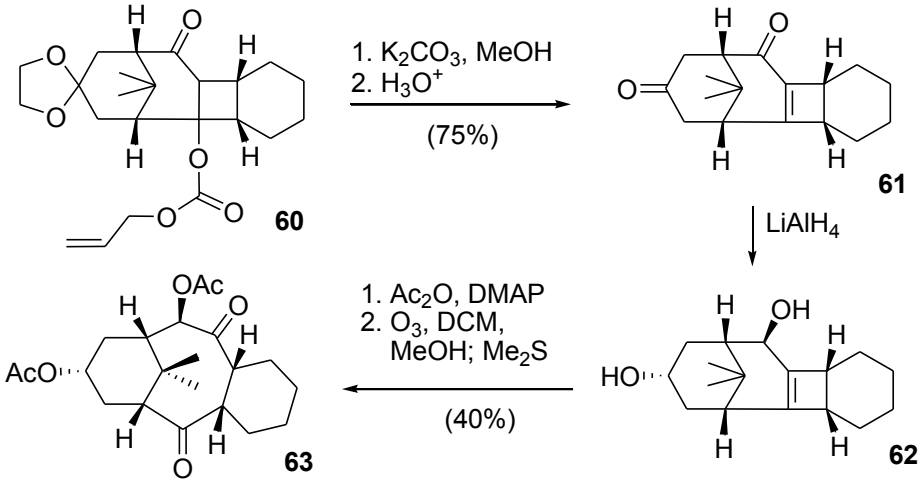
Scheme-11: Blechert, S.; Kleine-Klausing, A *Angew. Chem. Int. Ed. Engl.* **1991**, *30,* 412.



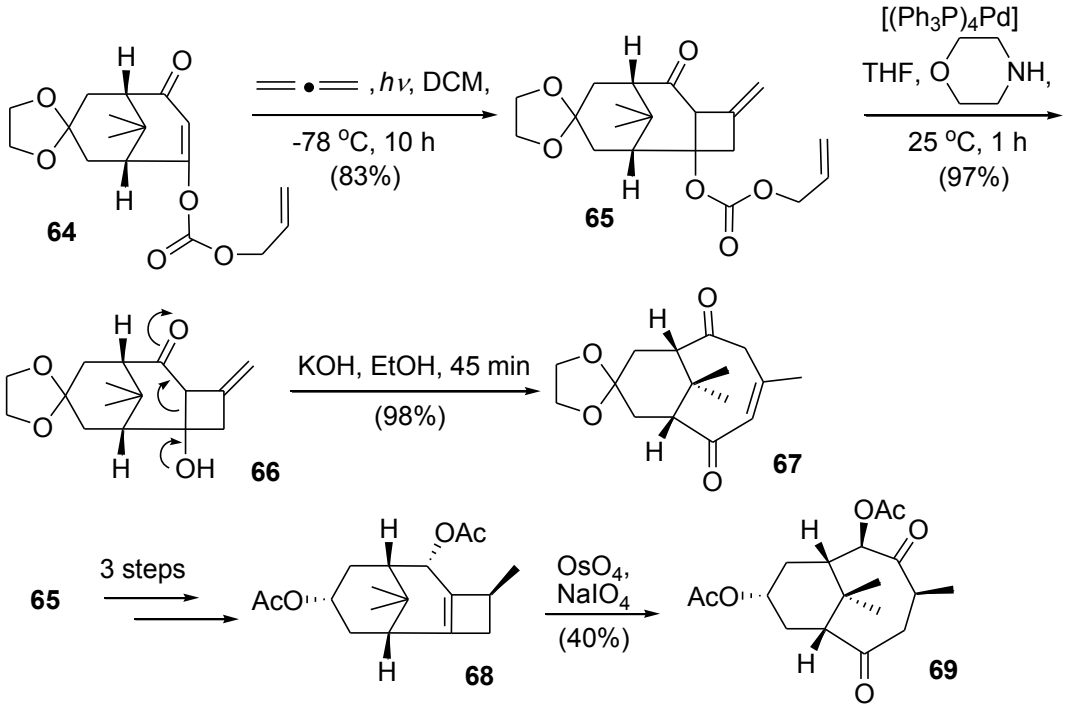
Berkowitz *et al.* also provided examples of the approach through photocycloaddition-retroaldol reactions for the construction of taxol model systems **73** and **77,** starting from **70** and **75** (Schemes 14 and 15).[57] These models have 5-membered A-ring frameworks that, while not functionalized appropriately for conversion to the

cyclohexene ring present in the natural product, could provide interesting biological mimics of taxol.

Scheme-12: Kaczmarek, R.; Blechert, S. *Tetrahedron Lett.* **1986,** *27,* 2845.

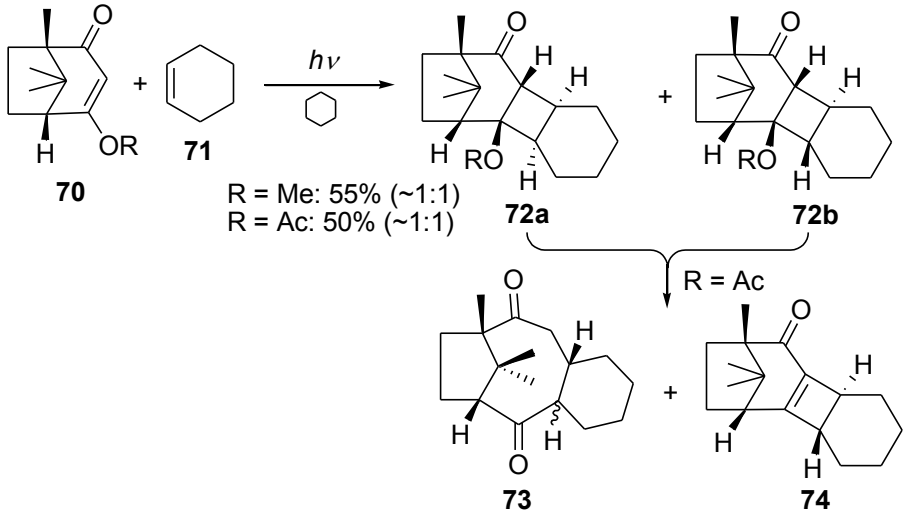


Scheme-13: Blechert, S.; Muller, R.; Beitzel, M. *Tetrahedron* **1992**, *48*, 6953.

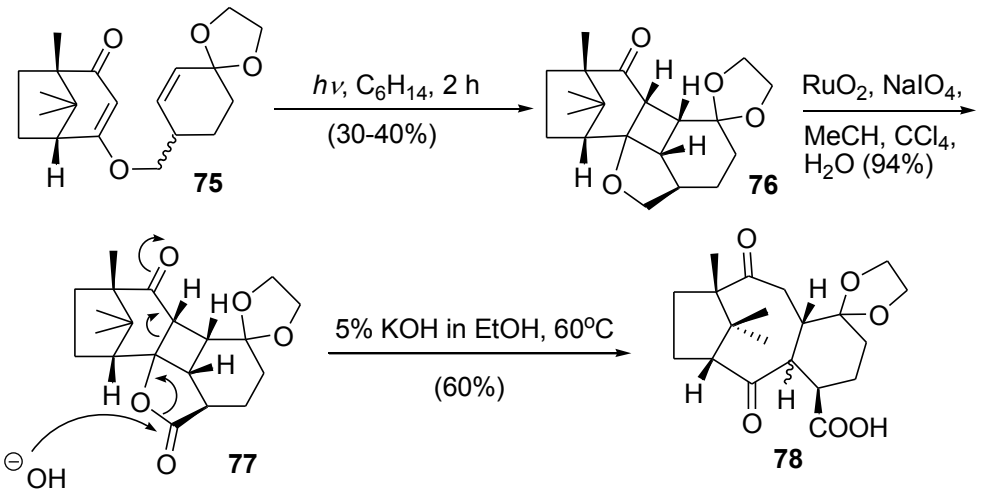


A further example of a synthesis of the taxoid skeleton through photocycloaddition - retroaldol reactions was reported by Inouye's group (Scheme-16).[58] This study could prove particularly useful because of its success in the difficult step of installing the tertiary methyl group and proper functionality for further elaboration, even though the synthesized model **82** lacked the gem dimethyl groups of taxol.

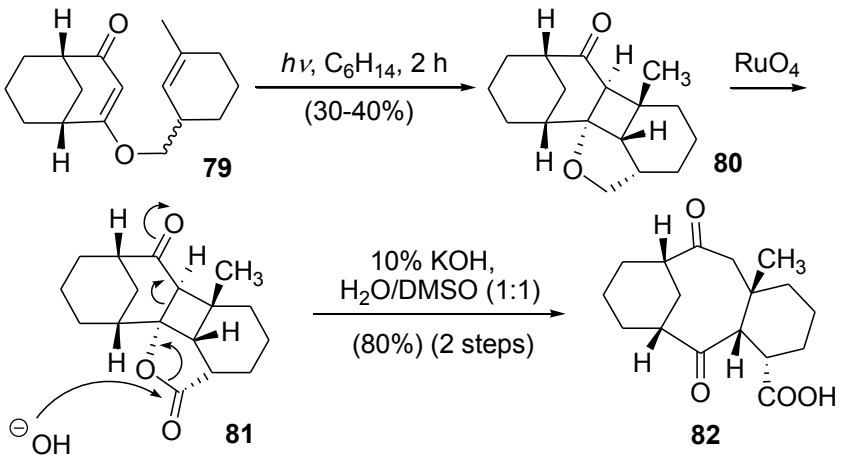
Scheme-14: Berkowitz, W. F.; Perumattam, J.; Amarasekara, A. *Tetrahedron Lett.* **1985**, *26*, 3665.



Scheme-15: Berkowitz *et al. Tetrahedron Lett.* **1985**, *26*, 3665.

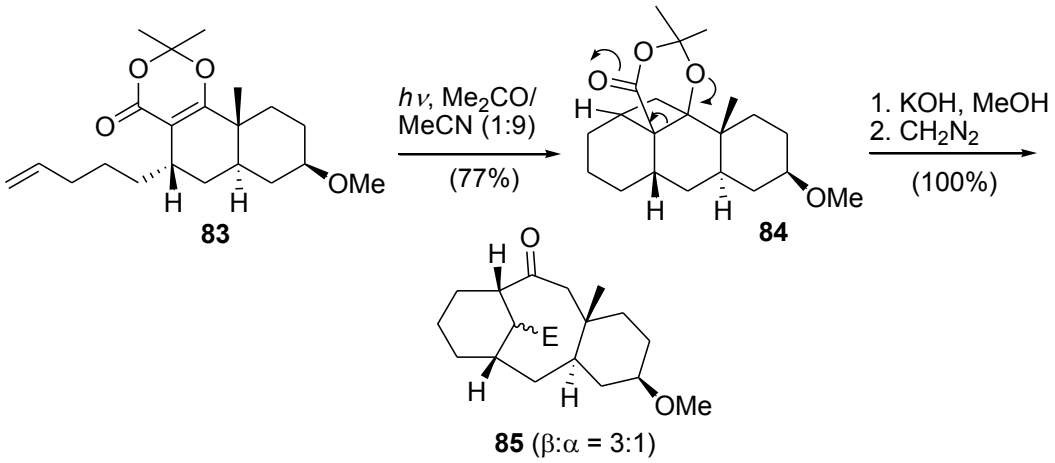


Scheme-16: Kojima, T.; Inouye, Y.; Kakisawa, H. *Chem. Lett.* **1985**, 323.



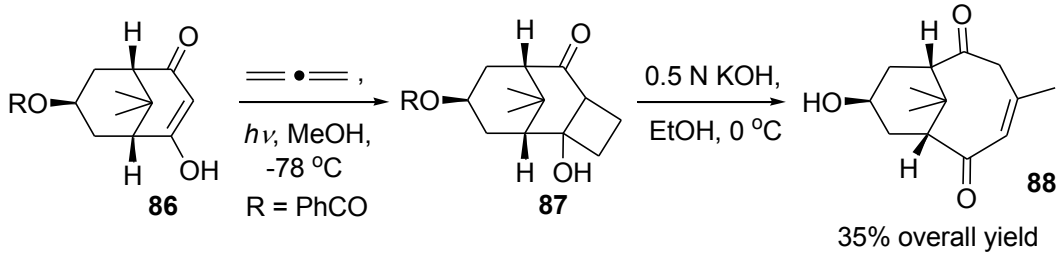
The Winkler group's studies were also based on photocycloaddition/retroaldol strategies and led to interesting and promising results.[59] As shown in Scheme-17 treatment of compound **84** with base provided, after esterification, taxol framework.

Scheme-17: Winkler, J. D.; Hey, J. P.; Williard, P. G. *J. Am. Chem. Soc.* **1986,** *108*, 6425.



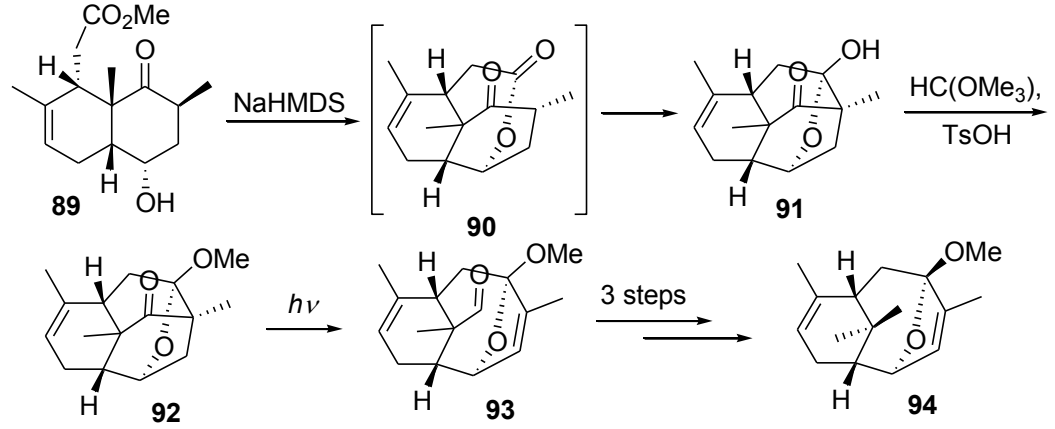
The work of the Fetizon laboratory, depicted in Scheme-18, also involved a combination of photocycloaddition and retroaldo1 reactions and provided rapid access to interesting taxoid skeletons **88**.[60] Additionally, ketoester condensation of **90** (Scheme-19)[61] followed by methylation furnished product **92**, which was further elaborated to the AB ring framework by a Norrish II photolytic reaction to provide **94** via **93**.

Scheme-18: Benchikh le-Hocine, M.; Do Khac, D.; Fetizon, M.; Hanna, I.; Zeghdoudi, R. *Synth. Commun.* **1987**, *17*, 913.

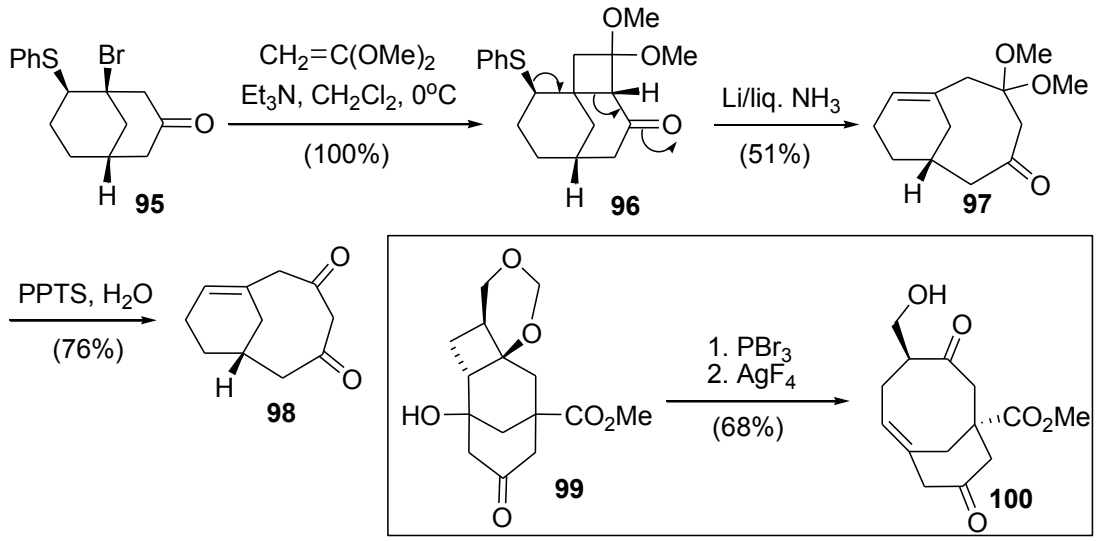


Kraus *et al.* have reported two photocycloaddition–reductive cleavage approaches to the AB ring model systems (Scheme-20). The first method[62] involves *in situ* generation of an enone from **95** followed by trapping as **96** with ketene dimethyl acetal. Treatment of **96** with Li/liquid ammonia gave the ring-opened product **97**, which upon deprotection led to **98**. In the second approach,[63] the tetracycle **99** is fragmented by generation of the bridgehead bromide followed by Lewis acid treatment to give bicycle **100**.

Scheme-19: Benchikh le-Hocine, M.; Do Khac, D.; Fetizon, M.; Guir, F.; Guo, Y.; Prange, T. *Tetrahedron Lett.* **1992,** *33,* 1443.



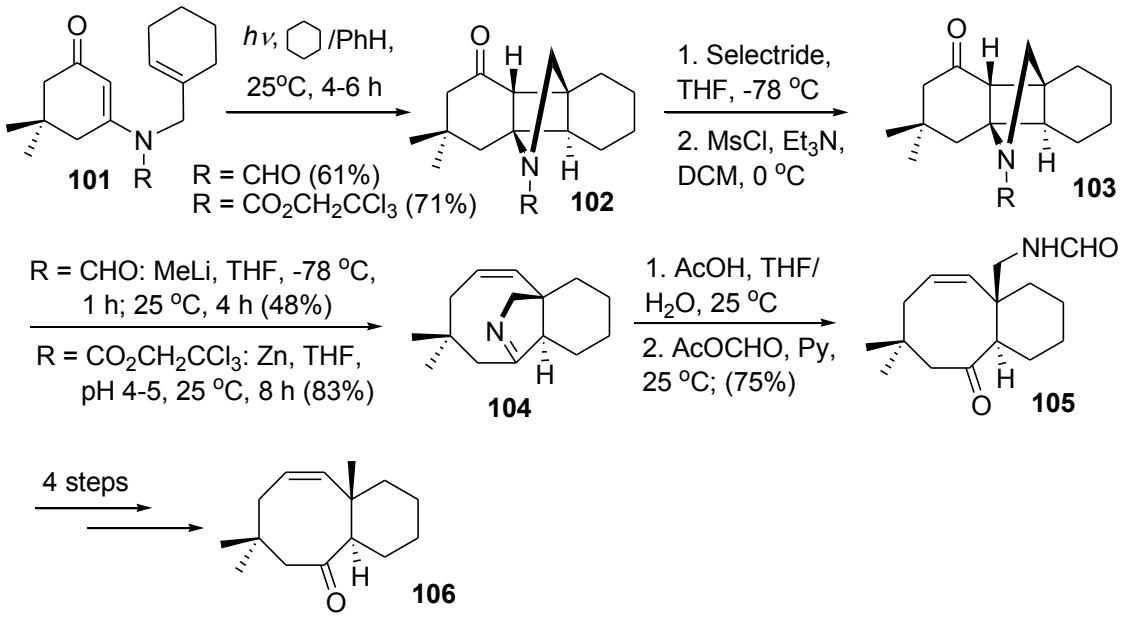
Scheme-20: Kraus, G. A.; Zheng, D. *Synlett* **1993**, 71.



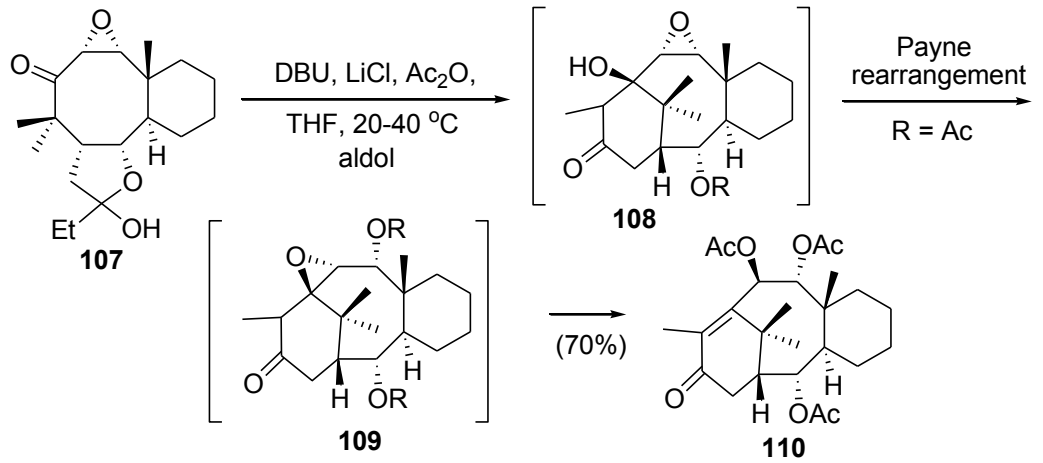
Swindell group initially made BC-ring system.[64] As shown in Scheme-21 polycyclic system was made by photochemical reaction, which on further fragmentation delivered eight membered ring and subsequent functional group manipulation, gave taxoid BC-ring system. A highly advanced functionalized taxane ABC skeleton (Scheme-22) were constructed by photoaddition, amide fragmentation, and aldol condensation.[65]

A reductive fragmentation reaction was used by Ghosh *et al.* to establish the eight-membered ring compound **112** (Scheme-23) starting with compound **111**.[66] Subsequent ring expansion of **113,** derived from **112,** gave the AB ring skeleton **114**.

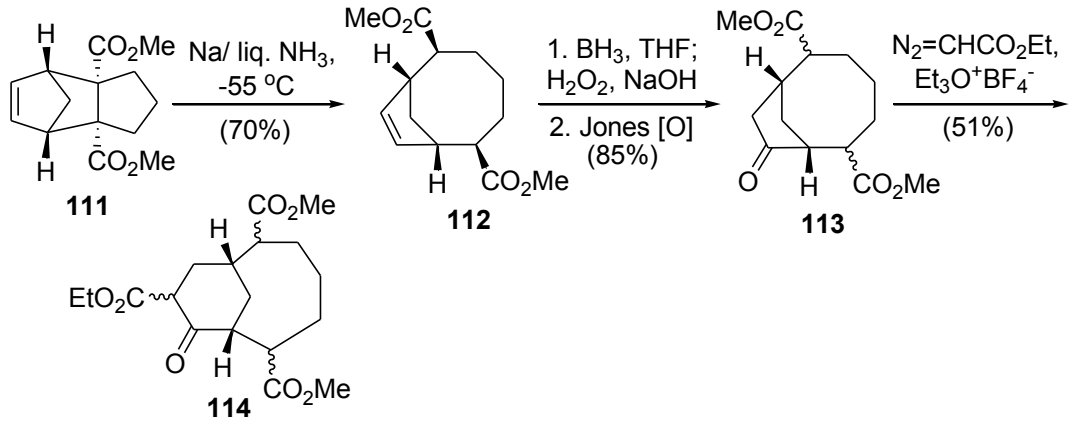
Scheme-21: Swindell, C. S.; Patel, B. P.; deSolms, S. J.; Springer, J. P. *J. Org, Chem.* **1987**, *52*, 2346.



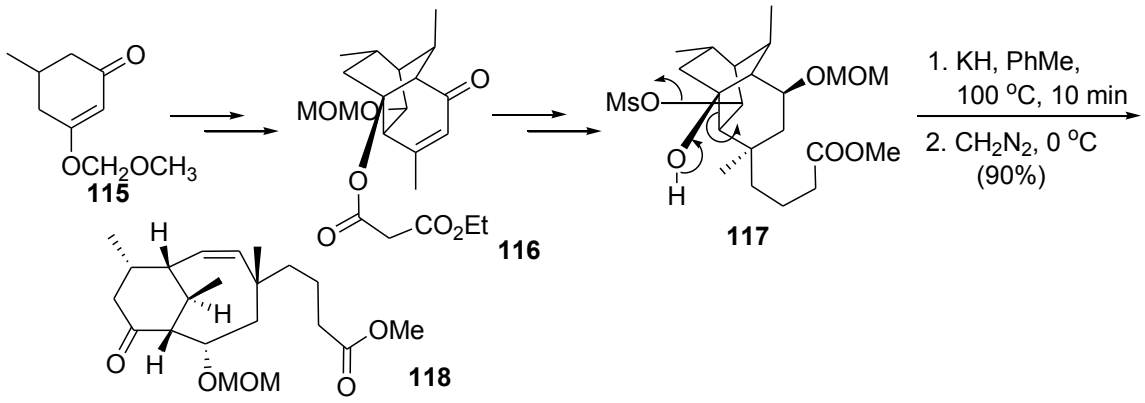
Scheme-22: Swindell, C. S.; Patel, B. P. *J. Org. Chem.* **1990**, *55*, 3.



Scheme-23: Saha, G.; Bhattacharya, A.; Roy, S. S.; Ghosh, S. *Tetrahedron Lett.* **1990**, *31*, 1483.

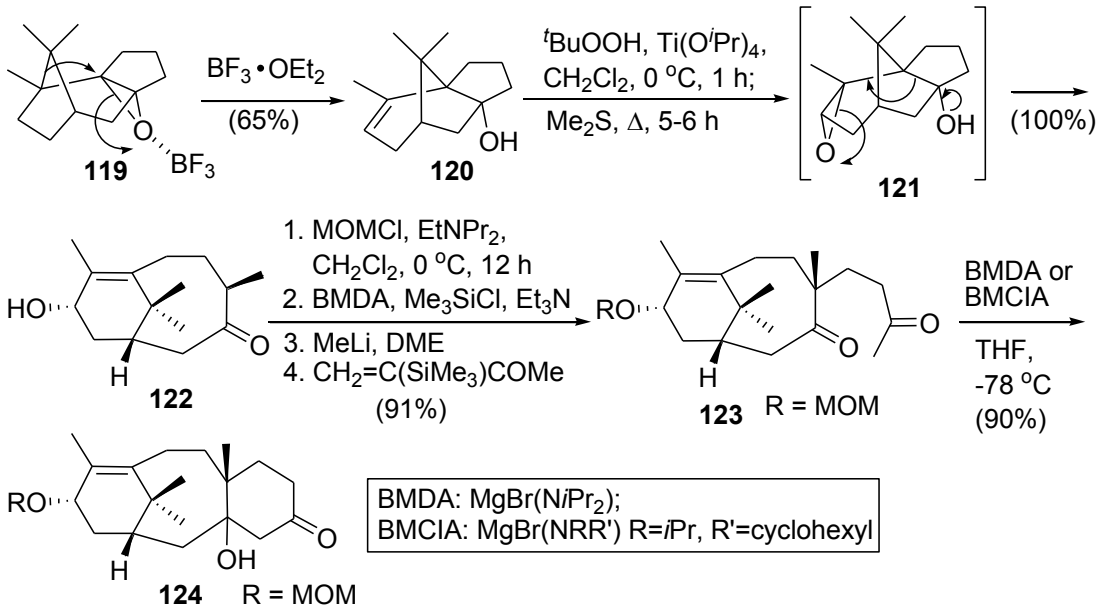


Scheme-24: Nagaoka, H.; Ohaawa, K.; Takata, T.; Yamada, Y. *Tetrahedron Lett.* **1984**, *25*, 5389.



An interesting application of the Grob fragmentation for the synthesis of an AB ring system was devised by Yamada *et al.* (Scheme-24).[67] In this study, tricyclic substrate **116**, derived from **115** in 17 steps, was converted in eight steps into hydroxyl mesylate **117**. Treatment of **117** with potassium hydride followed by methylation furnished **118** in high yield.

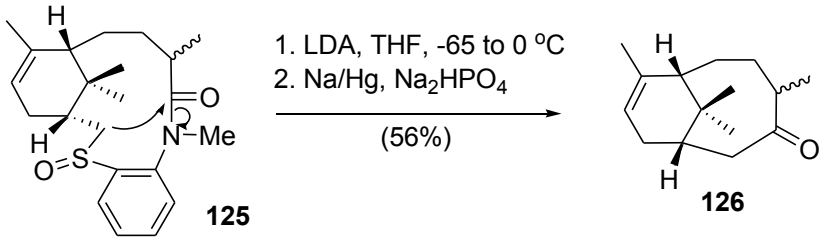
Scheme-25: Holton, R. **A**.; Juo, R. R.; Kim, H. B.; Williams, A. D.; Harusawa, S.; Lowenthal, R. E.; Yogai, S. *J. Am. Chem. Soc.* **1988**, *110*, 6558.



The Holton laboratory has reported a number of advanced studies concerning taxol, including a total synthesis of taxusin **(1,** see Fig. l), in which they employed the naturally occurring β-patchouline oxide as the starting material. They have used a hydroxyepoxide mediated fragmentation process involving an epoxide intermediate as the key step to secure **AB** ring system. As delineated in Scheme-25, patchouline oxide

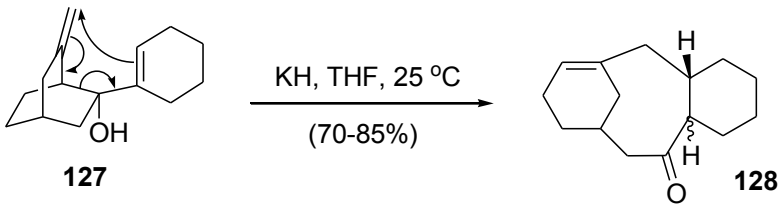
119 is subjected to Lewis acid mediated epoxide opening/rearrangement, and the resulting hydroxyl alkene is epoxidized to give **122**. An intramolecular aldol condensation within **123** derived from **122** established the ABC ring framework **124** of taxol.[68] The same strategy were applied to a total synthesis of the nonnatural enantiomer of (–)-taxusin[69] and later on the first total synthesis of Taxol was accomplished,[12] a milestone in the history of synthetic organic chemistry.

Scheme-26: Ohtsuka, Y.; Oishi, T. *Chem. Pharm. Bull.* **1988,** *36*, 4711 and 4722.



An elegant ring-contraction method has been applied to the synthesis of taxol model systems **126** by Ohtsuka *et al.*[70] As shown in Scheme-26, this approach involves a base-induced rearrangement after which a sulfoxide moiety is excised by reductive C-S bond cleavage, leading to the eight membered ring.

Scheme-27: Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47***,** 3190.

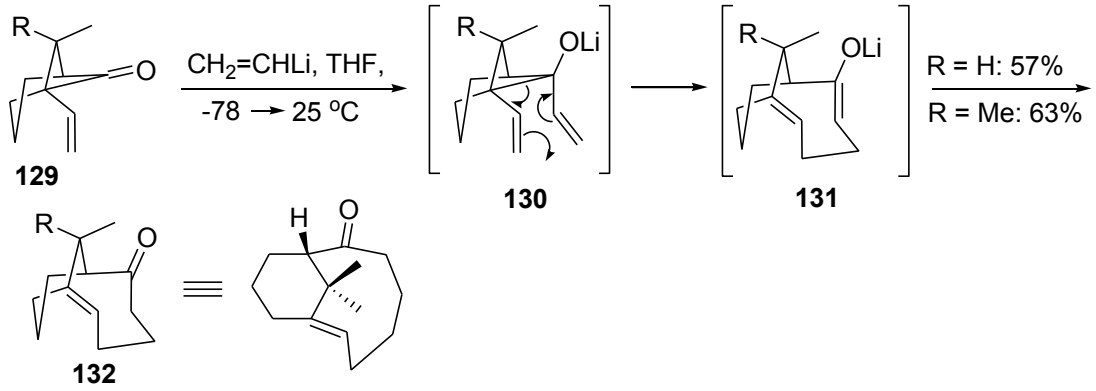


An interesting approach to the taxol skeleton **128** based on an oxy-Cope rearrangement reaction of **127** was published by Martin *et al.* in 1982 (Scheme-27).[71] The most important point in this approach is establishment of the **ABC** ring system in four steps from readily available (3-oxocyclohexyl)acetic acid.

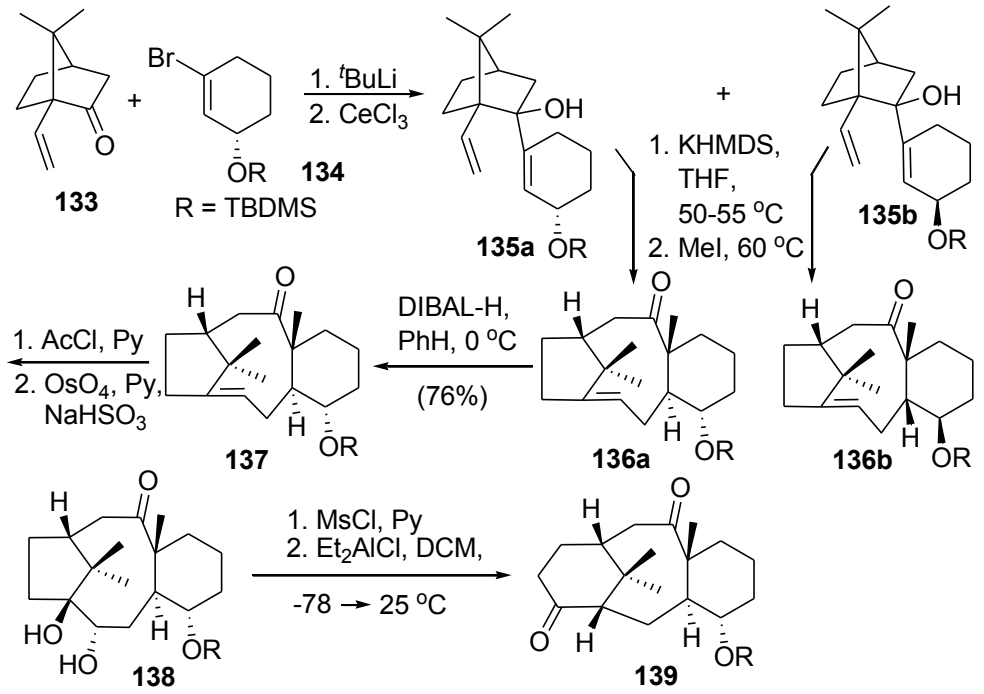
The approach of Snider *et al.* to model system **132** also involved oxy-Cope rearrangement (Scheme-28).[72]

Paquette's group reported a particularly interesting anionic oxy-Cope rearrangement route to the taxol skeleton (Scheme-29). Base treatment of isomers **135 a,b** gave rearrangement products **136 a,b**; **136 a** was converted into diol **138** via **137**. Pinacol-type rearrangement of **138** afforded the ABC ring skeleton **139**.[73]

Scheme-28: Snider, B. B.; Allentoff, A. J.; *J. Org. Chem.* **1991**, *56*, 321.



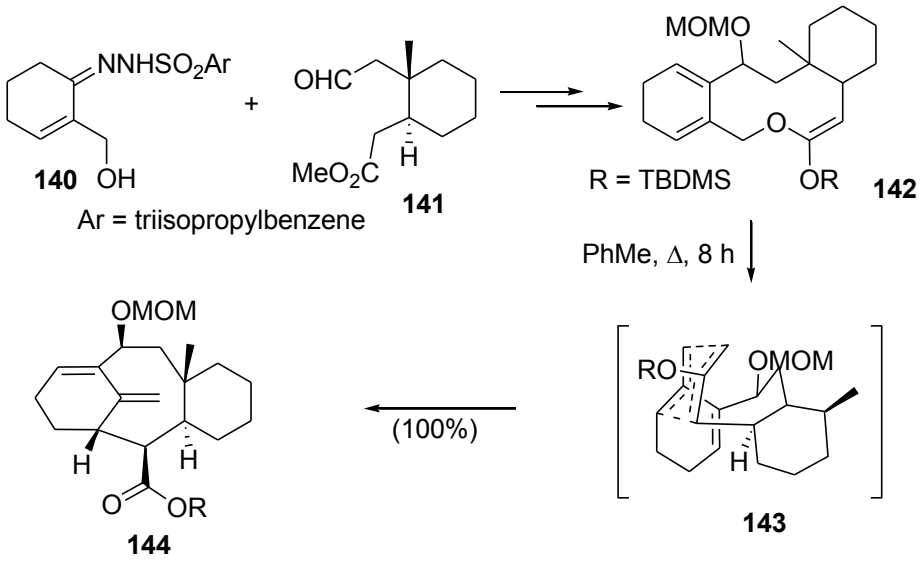
Scheme-29: Paquette, L. A.; Combrink, K. D.; Elmore, S. W.; Rogers, R. D. *J. Am. Chem. Soc.* **1991,** *113*, 1335.



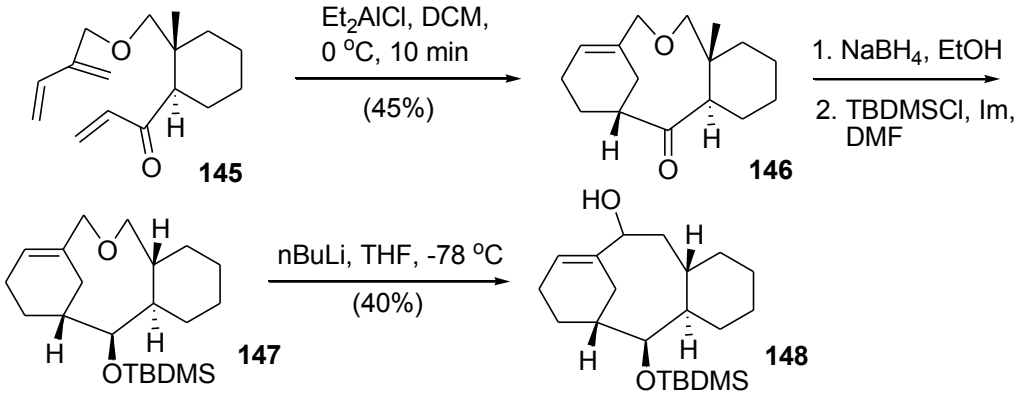
A clever approach to the taxol skeleton based on an intramolecular Claisen rearrangement in which a 10-membered ring is contracted to an eight-membered ring was reported by Funk (**142→143→144**, Scheme-30). The ten-membered ring was synthesized from **140** and **141** in seven steps.[74] This method provides the ABC system with the troublesome angular methyl group already installed

Another interesting strategy towards the taxol skeleton (Scheme-31) based on a Wittig rearrangement was published by Yadav's group.[75] This approach began with an intramolecular Diels-Alder reaction to construct the A ring model system **146,** which was converted into **147** by standard chemistry. Treatment of **147** with base resulted in a contraction of the nine-membered ring to the eight-membered ring **148**.

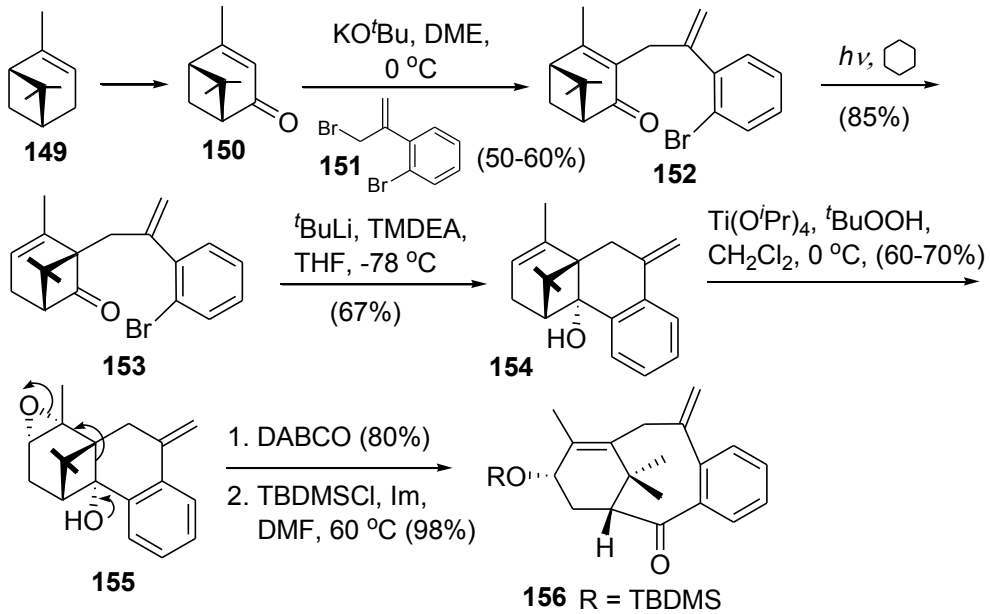
Scheme-30: Funk, R. L.; Daily, W. J.; Parvez, M. *J. Org. Chem.* **1988**, *53*, 4141.



Scheme-31: Yadav, J. S.; Ravishankar, R. *Tetrahedron Lett.* **1991**, *32*, 2629.

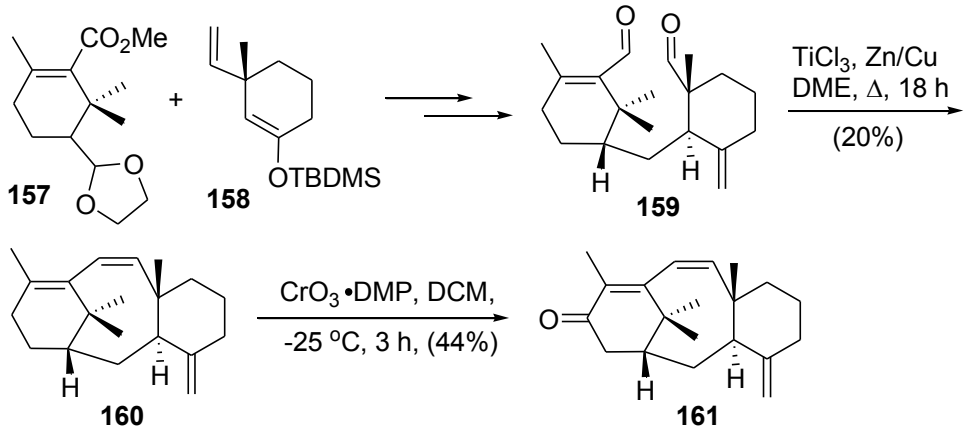


Scheme-32: Wender, P.A.; Mucciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114,* 5878.

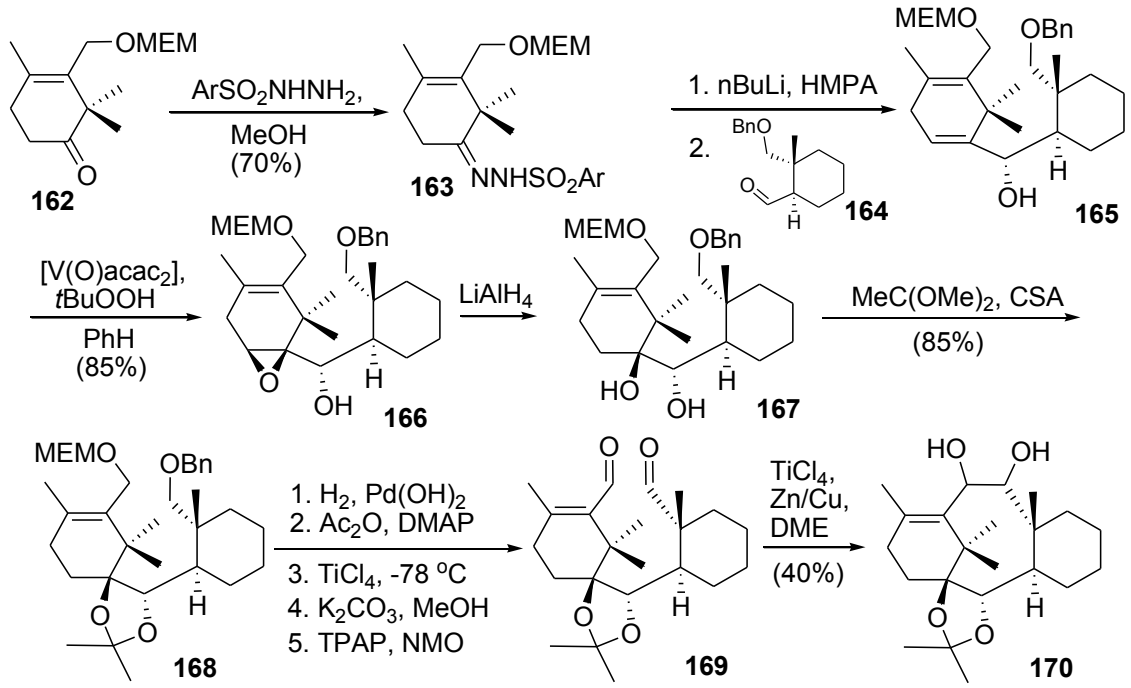


An elegant strategy towards the taxol skeleton was reported by the Wender group (Scheme-32). In this sequence, (+)-pinene **(149)** was utilized as a cheap starting material for hydroxyepoxide the synthesis of **155**, which then underwent base-induced fragmentation to afford the tricyclic system **156**.[76] Further elaborations led to the successful total synthesis of Taxol,[15] which is popularly known in the synthetic organic chemist world as pinene approach to Taxol.

Scheme-33: Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am Chem. Soc.* **1986**, *108*, 3513.



Scheme-34: Nicolaou, K. C.; Yang, Z.; Sorensen, E.; Nakada, M. *J. Chem. Soc. Chem. Commun.* **1993,** 1024.

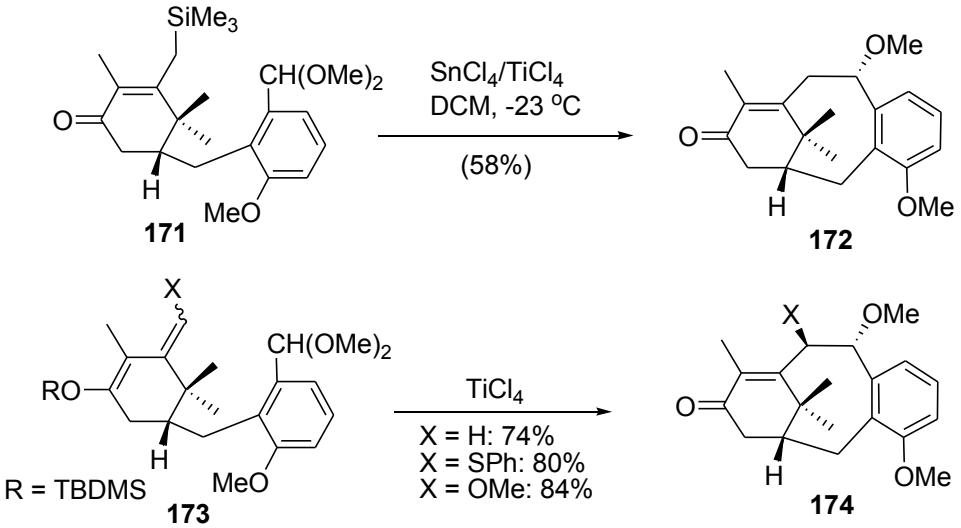


In the pioneering work of Kende *et al.*, a McMurry cyclization reaction was successfully applied to form the B ring system **160** from the dialdehyde **159,** obtained

from **157** and **158** in twelve steps, as shown in Scheme-33.[77] The low yield of the intramolecular coupling reaction was attributed primarily to competing intramolecular 1 ,4-addition of the intermediate diketyl.

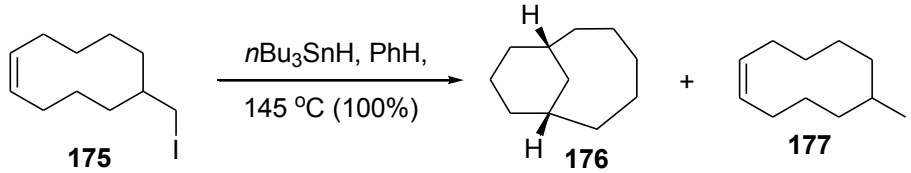
An elegant approach was used by Nicolaou's laboratory for synthesis of taxanes. The hydrazone-vinyllithium chemistry, illustrated in Scheme-34, was found to be exceptionally efficient in coupling A ring and C ring fragments.[78] Addition of the vinyllithium species, generated from **163**, to the aldehyde **164** gave **165**, which was converted into the diol **167** by regioselective epoxidation and subsequent regioselective reduction. Protection of the diol as **168** and further standard chemistry provided the dialdehyde **169**. An intramolecular McMurry coupling reaction within **169** gave the diol **170**. Utilizing above developed chemistry and well-functionalized C ring, conquered[13] Taxol in almost same day with Holton group, thus the race for the first total synthesis was ended up in a tie.

Scheme-35: Kataoka, Y.; Nakamura, Y.; Morihira, K.; Arai, H.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1992**, *33,* 6979.



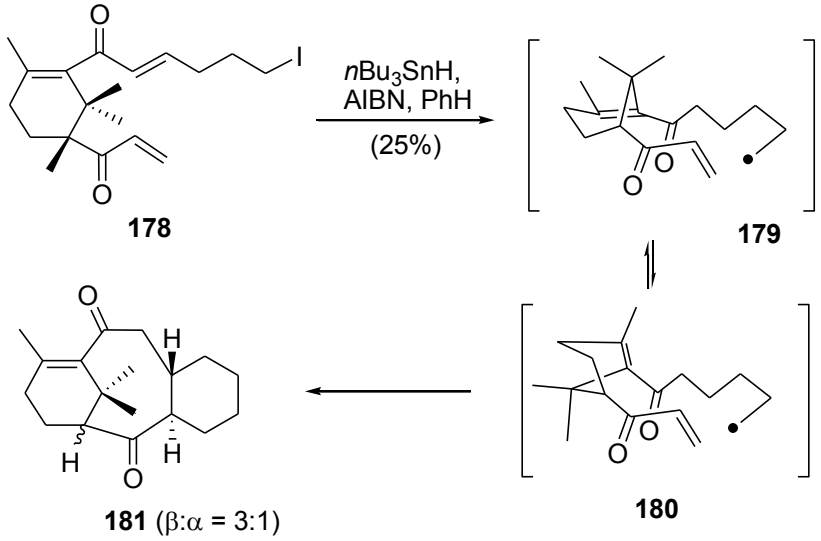
Kuwajima's elegant studies in the taxol area employing acid promoted intramolecular alkylation reactions culminated in the synthesis of several advanced intermediates (Scheme-35). These workers have carried out careful surveys of the appropriate conditions for these cyclizations and prepared taxoids such as **172** and **174**.[79]

Scheme-36: Winkler, J. D.; Sridar, V.; Siegel, M. G. *Tetrahedron Lett.* **1989,** *30*, 4943.

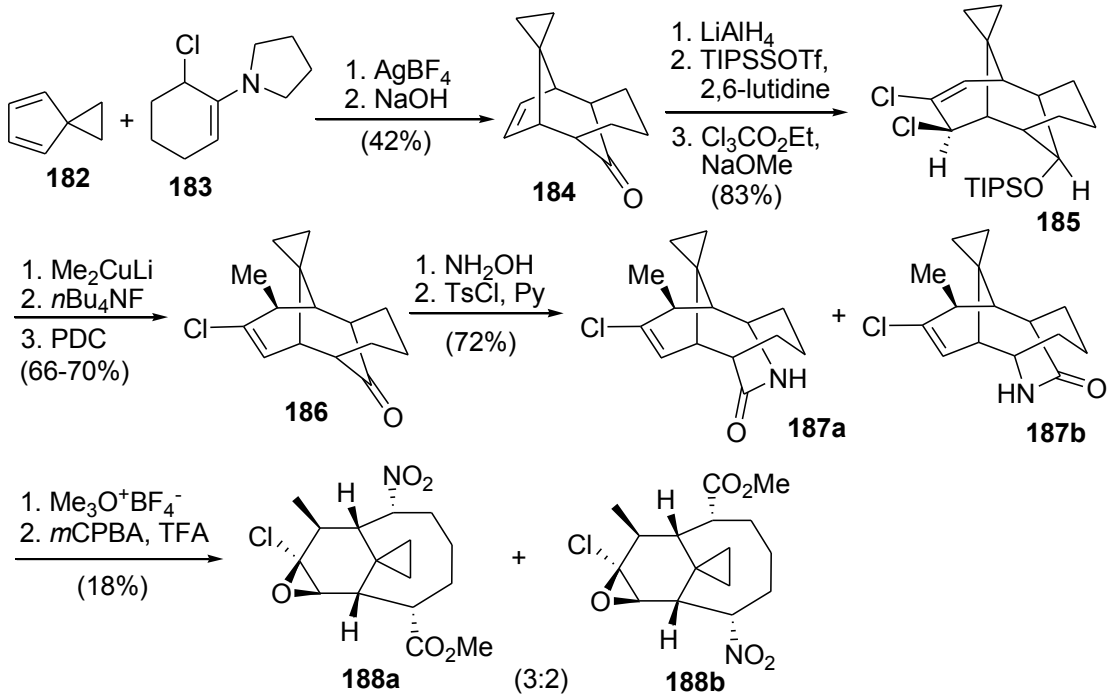


Radical-based approaches to taxol model systems have also been reported. In an attempt by Winkler *et al.*,[80] a simple cyclic iodoalkene **175** was used to form the AB ring fragment **176** (Scheme-36). Pattenden *et al.*, on the other hand, were able to prepare the ABC ring skeleton **181** through a tandem radical sequence as shown in Scheme-37.[81]

Scheme-37: Hitchcock, S. A.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 7448.



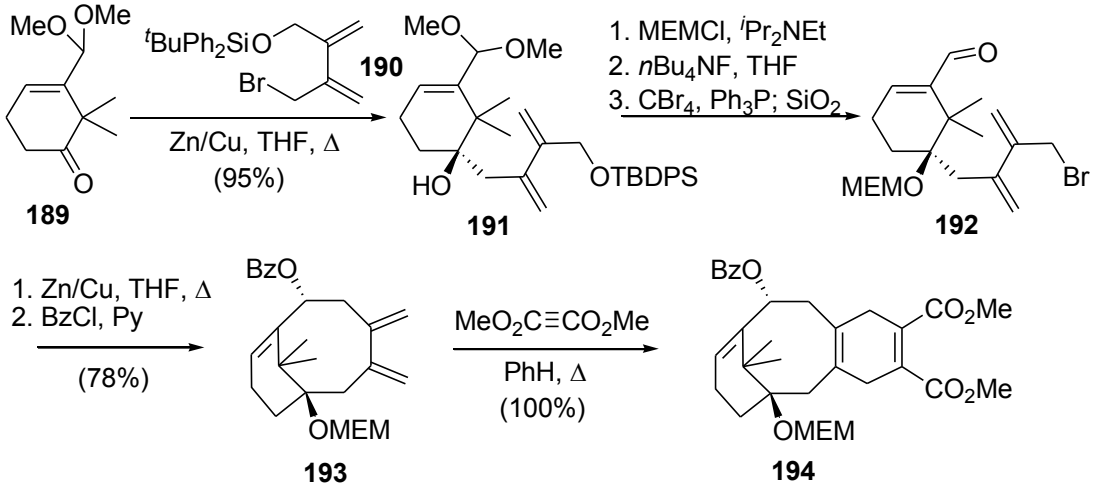
Scheme-38: Oh, J.; Choi, J. R.; Cha, J. K. *J. Org. Chem.* **1992**, *57*, 6664.



Cha's group delineates the synthesis of taxol AB ring model compounds **188 a,b** based on a formal [4 + 3] diene-oxyallyl cycloaddition reaction as shown in Scheme-38.[82] The adduct **184**, obtained from **182** and **183**, was subjected to ring expansion (**184** →**185** for A ring), followed by further manipulation to give ketone **186**. Beckmann rearrangement then led to compounds **187 a,b** which were converted into the targeted

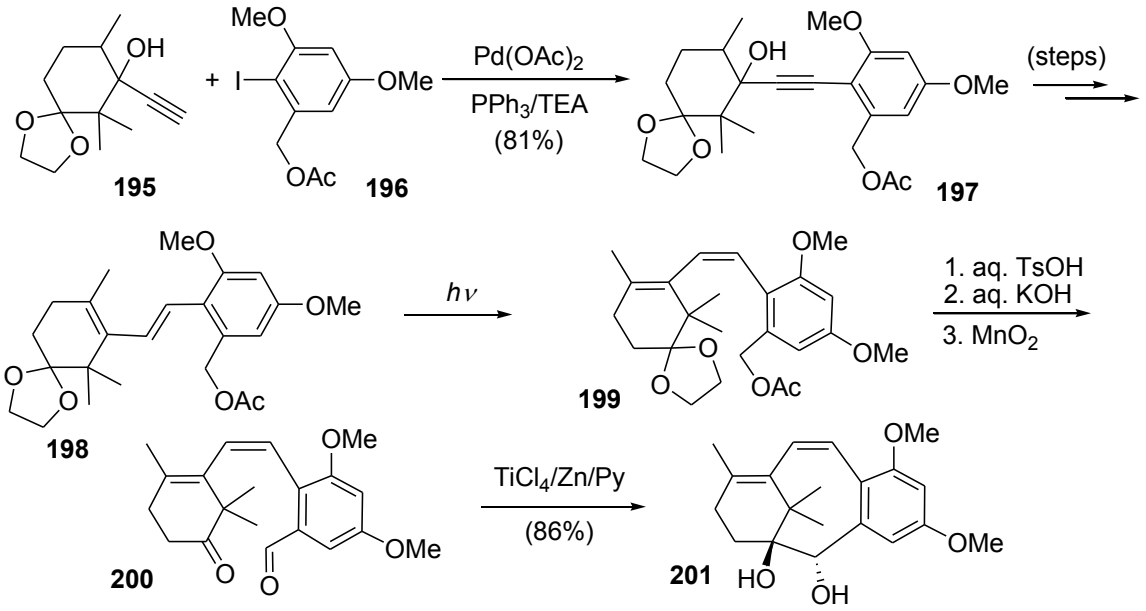
intermediates **188 a,b**. Even though the efficiency of the last step was poor, the strategy certainly provides a novel approach to the bicyclic AB system.

Scheme-39: Wang, Z.; Warder, S. E.; Perrier, H.; Grimm, E. L.; Bernstein, M. A.; Ball, R. G. *J. Org. Chem* **1993**, *58*, 2931.



Wang's group disclosed a sequential anionic condensation strategy for establishing the B ring (Scheme-39).[83] Thus, A ring model **189** was condensed with the zinc cuprate formed from **190**. After manipulation, the B ring was closed by applying an intramolecular version of the same method to give **193**. Finally, the C ring was added with a Diels-Alder reaction to give **194**.

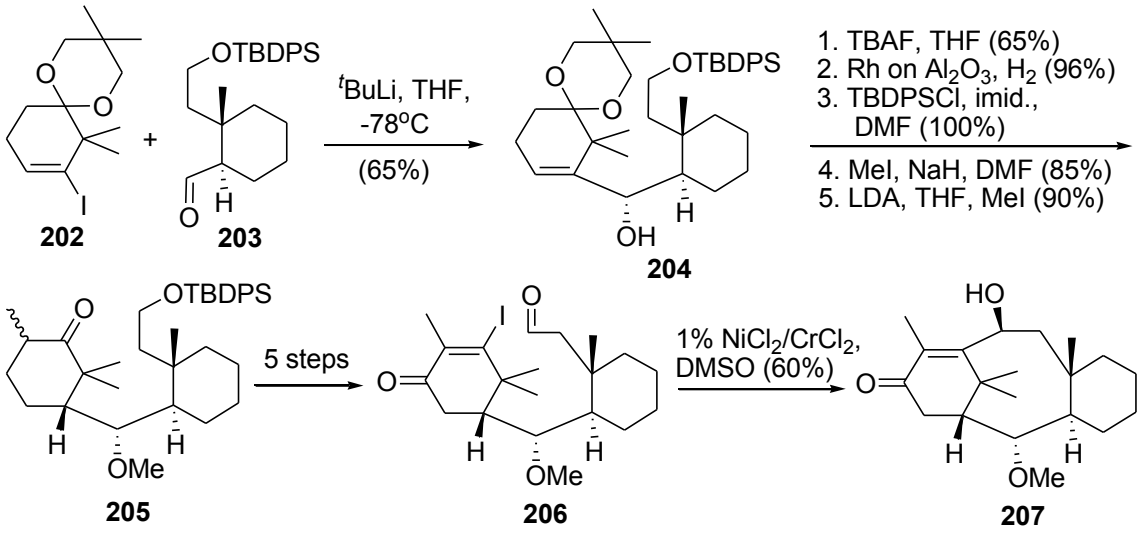
Scheme-40: Swindell, C. S.; Chander, M. C.; Heerding, J. M.; Klimko, P. G.; Rahman, L. T.; Venkat Raman, J.; Venkataraman, H. *Tetrahedron Lett.* **1993**, *34*, 7005.



In an another approach from Swindell laboratory as depicted in Scheme-40,[84] the propargylic A-ring **195** was coupled with aryl iodide C-aromatic unit **196** in the presence

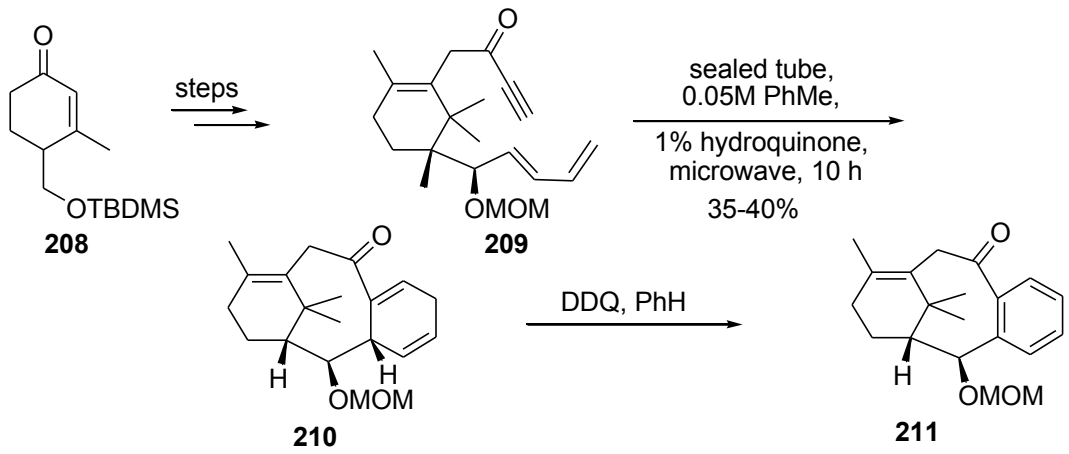
of $Pd(OAc)_2$ to get coupled product **197**. After failing to reduce triple bond of **197** to double bond in *cis*-form, it was initially converted to *trans*-form and later was isomerized to *cis*-form, photochemically. The keto-aldehyde **200** treated with low valent Ti complex resulted in a stereoselective intramolecular pinaccol coupling that produces ABC skeleton of taxane.

Scheme-41: Kress, M. H.; Ruel, R.; Miller, W. H.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 5999.



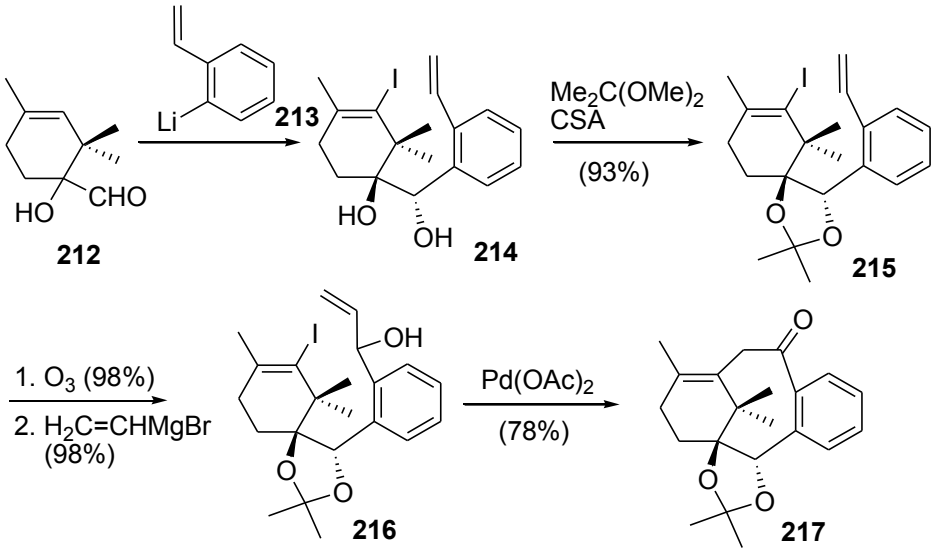
Kishi group used their own Ni/Cr developed chemistry for the synthesis of ABC taxane system (Scheme-41).[85] The lithiated A-ring model **202** was coupled with C-ring aldehyde part **203** resulted in an alcohol **204** in a separable diastereomeric mixture in the ratio 7:1. On further using standard chemistry, **206** were obtained as a key precursor. Thus, on treatment of **206** with Ni(II)/Cr(II) reagent gave tricyclic ABC skeleton of taxane in 60 % yield.

Scheme-42: Lu Y.; Fallis, A. G. *Tetrahedron Lett.* **1993**, *34*, 3361.



An intramolecular Diels-Alder reaction was utilized by Fallis group for formation of BC ring of ABC taxane skeleton (Scheme-42).[86] Thus, the prerequisite precursor **210** which was prepared in 11 steps from **208**, on microwave irradiation in a sealed-tube furnished ABC ring on further oxidation with DDQ afforded C-aromatic ABC taxane skeleton.

Scheme-43: Masters, J. J.; Jung, D. K.; Bornmann, W. G.; Danishefsky, S. J. *Tetrahedron Lett*. **1993**, *34*, 7253.

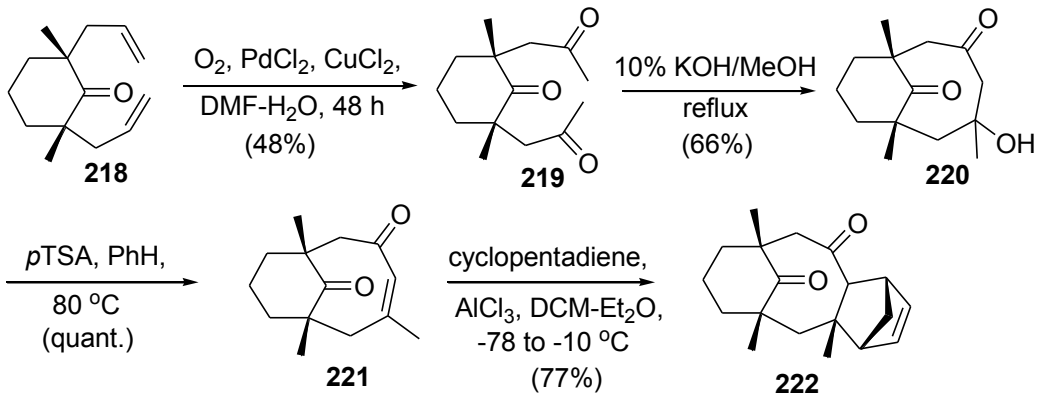


Intramolecular Heck reaction of **216** has been successfully achieved by Danishefsky group for the construction of baccatine III bearing an aromatic C-ring **217(**Scheme-43).[87] Stereoselective addition of 2-lithio styrene (**213)** to ring-A aldehyde **212** afforded racemic alcohol **214**. Protection of vicinal diol **214** followed by the ozonolysis of the styryl moiety of **215** and reaction of the resultant aldehyde with vinylmagnesium bromide resulted **216** as a single diastreomer. Regioselective intramolecular cyclization of **39** employing Heck reaction condition offered desired C-aromatic taxane **217** in 78% yield. After securing ABC ring, utilizing Heck coupling as a key step total synthesis was accomplished.

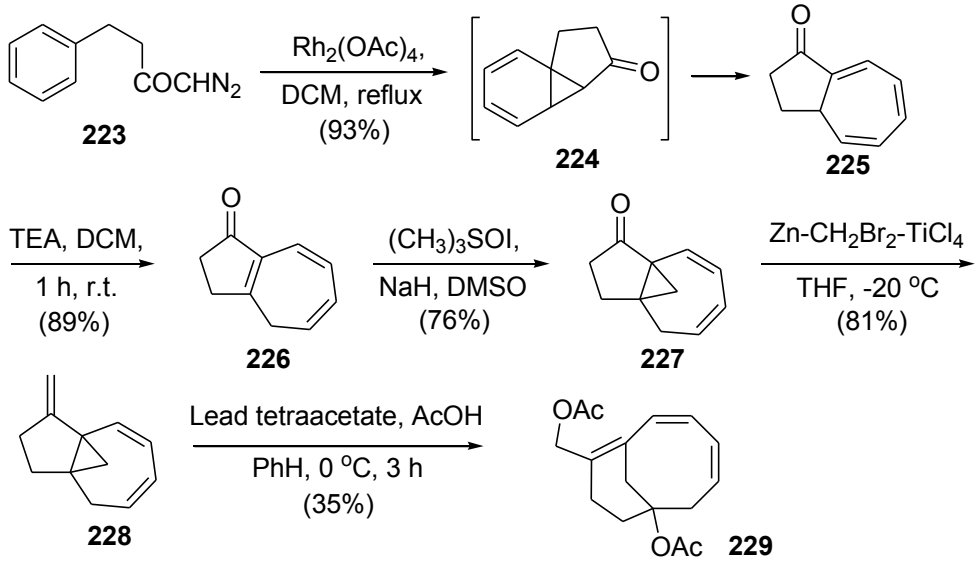
Direct intramolecular aldol condensation was utilized by Romero *et al.* to get BC pattern of taxane (Scheme-44).[88] C-ring was formed by Diels-Alder reaction to form ABC taxane skeleton which lacks gem-dimethyl.

Kumar group have disclosed their synthesis of AB ring framework by utilizing lead tetraacetate mediated oxidative cyclopropyl ring cleavage of propellane intermediate **228** to deliver fused 6-8 ring **229** as depicted in Scheme-45.[89] Simplicity and cheaper starting material were claimed by the authors.

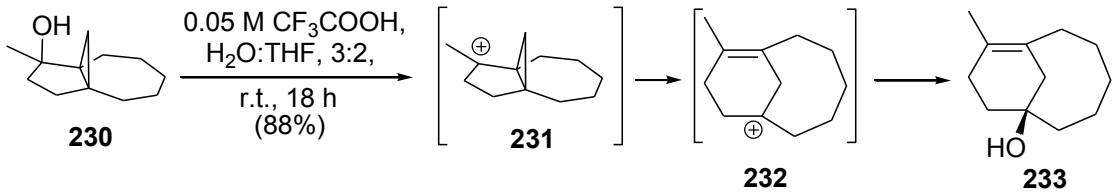
Scheme-44: Romero, M. A.; Franco, R. P.; Cruz-Almanxa, R.; Padilla, F. *Tetrahedron Lett*. **1994**, *35*, 3255.



Scheme-45: Kumar, P.; Rao, A. T.; Saravanan, K.; Pandey, B. *Tetrahedron Lett*. **1995**, *36*, 3397.



Scheme-46: Thielemann, W.; Schafer, H. J.; Kotila, S. *Tetrahedron* **1995**, *51*, 12027.

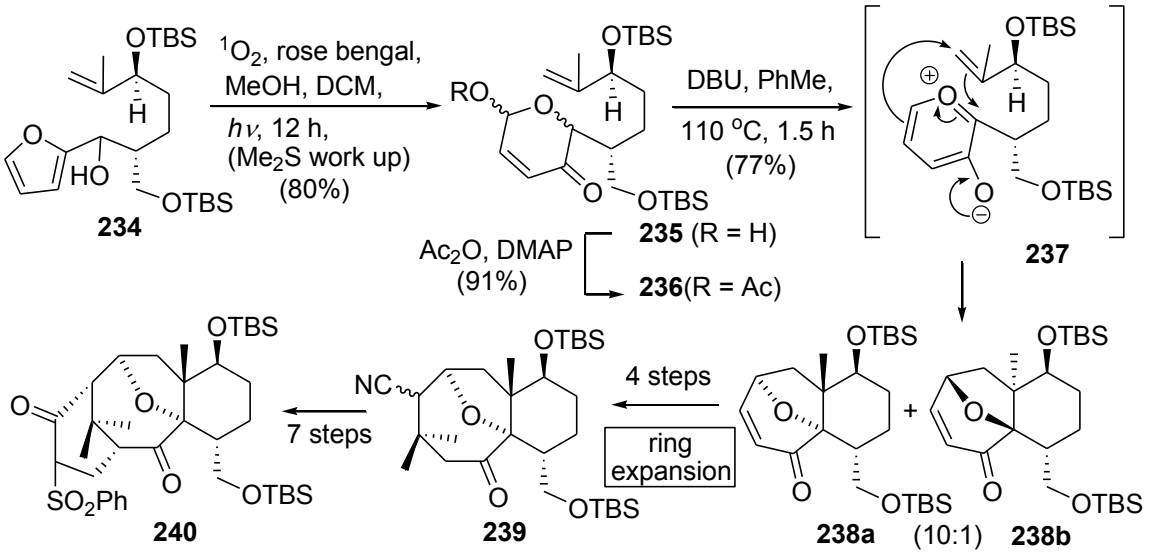


Similar but independently another acid catalyzed-carbinyl rearrangement of cyclopropyl ring cleavage was reported by Schafer's group (Scheme-46).[90]

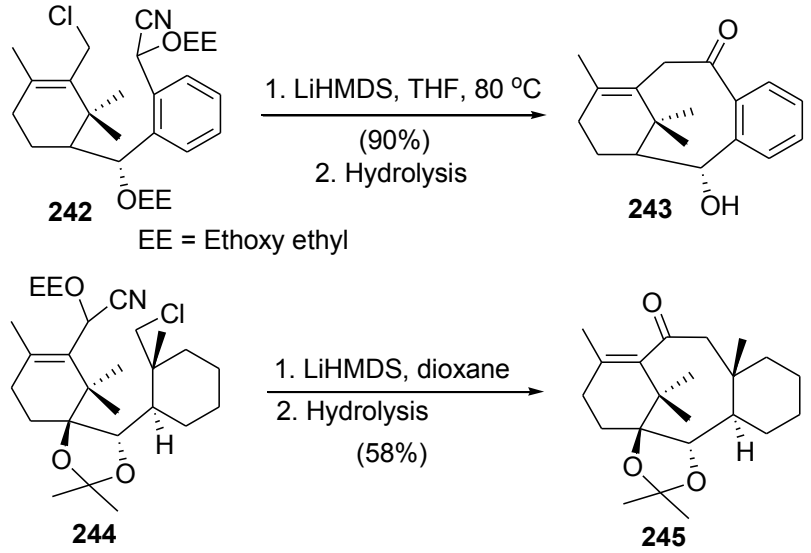
Magnus devised an elegant route for construction of highly functionalized ABC pattern of taxoids (Schme-47).[91] Initially, BC ring **238a,b** was formed by an intramolecular [5+2]-pyrylium ylide-alkene cyclization. The seven membered B-ring **238a** was transformed to eight membered **239** by reductive cleavage of cyclopropyl ring

in 4 steps. Further A-ring was formed over seven steps by ester-sulfone condensation resulting in ABC skeleton **240**.

Scheme-47: Magnus, P.; Booth, J.; Magnus, N.; Tarrant, J.; Thom, S.; Ujjainwalla, F. *Tetrahedron Lett*. **1995**, *36*, 5331.



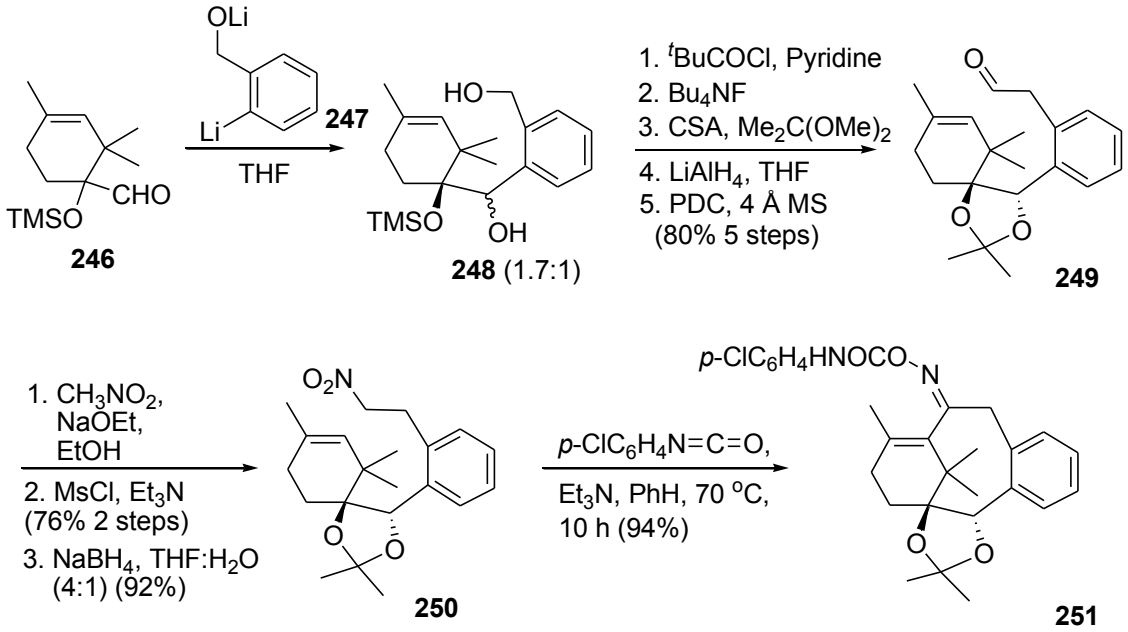
Scheme-48: Takahashi, T.; Iwamoto, H.; Nagashima, K.; Okabe, T.; Doi T.; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1319.



Intramolecular alkylation of cyanohydrin ethers were judiciously used by Takahishi *et al.* for the formation of central eight membered B-ring in their synthesis of taxoid system; taking C-ring aromatic as well as alicyclic as shown in Scheme-48.[92]

Nagaoka & Hirai devised a formation of a taxane carbon framework utilizing the intramolecular 1,3-dipolar cycloaddition of nitrile oxide as depicted in Scheme-49. It was to be noted that, after key eight membered ring cyclization double bond was present in bridgehead position, which is present in naturally occurring taxanes.[93]

Scheme-49: Hirai, Y.; Nagaoka, H. *Tetrahedron Lett.* **1997**, *38*, 1969.

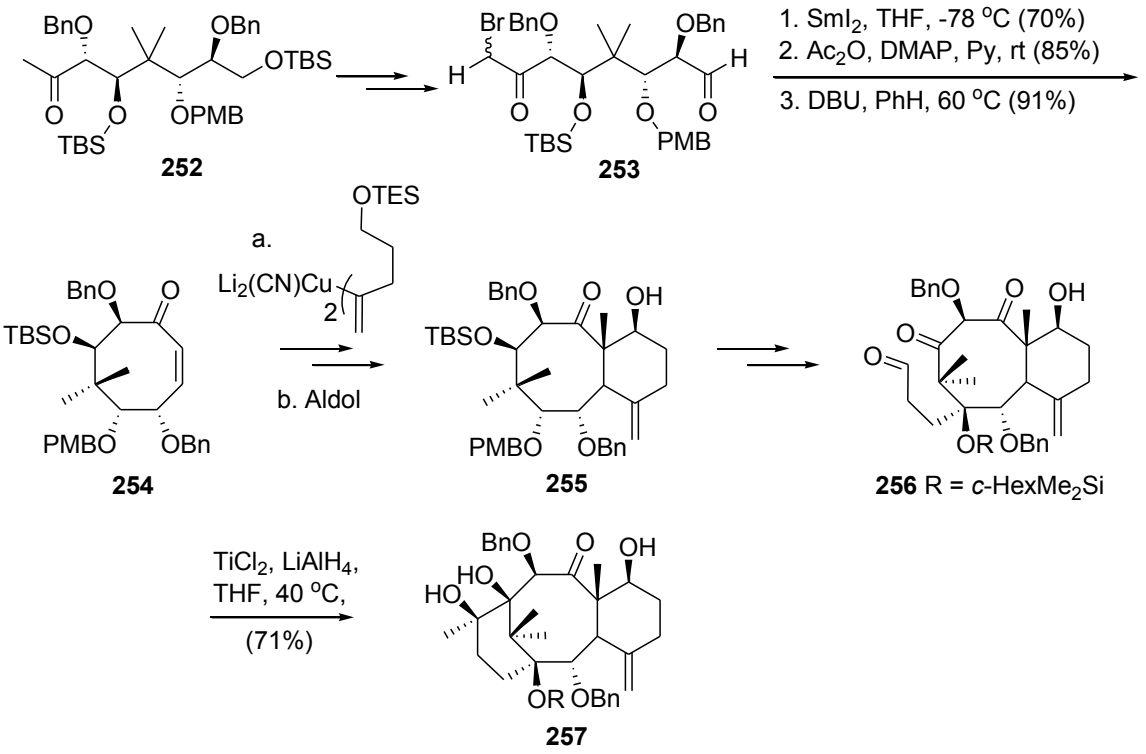


Mukaiyama team delivered a unique approach (Scheme-50) for synthesis of ABC skeleton of Taxol. Initially they made eight membered B-ring by SmI_2-mediated intramolecular aldol cyclization from optically active polyoxy compound.[94a] The interesting point to be noted is that all the functionalities there in eight membered of natural taxol were present in their eight membered enone ring **254**. Later, BC ring **255** was formed *via* Michael addition and successive intramolecular aldol cyclization. To this BC ring A ring was made by Ti mediated pinacol coupling reaction to get ABC skeleton **257** of Taxol as shown in Scheme-50.[94b] Using same ABC skeleton they were successful in making D-ring and later on attachment of side chain to finish the fifth total synthesis of Taxol in a linear fashion (B→BC→ABC→ABCD).[16]

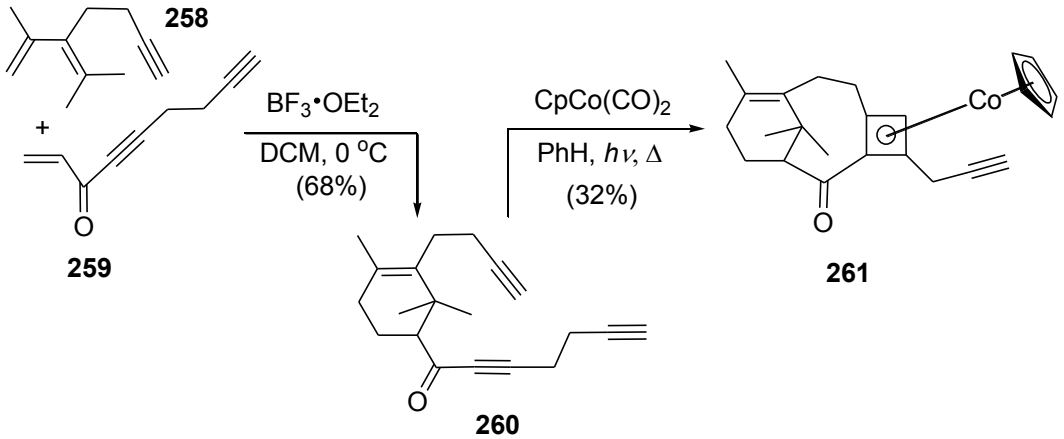
Malacria have demonstrated their AB skeleton work by using acid catalysed Diels-Alder [4+2] reaction to obtain A-ring and further cobalt(I) mediated complex catalyzed cycloaddition as depicted in Scheme-51.[95]

Cohen and coworkers have obtained AB frame work by radical based ring expansion strategy.[96] The key bicyclic intermediate **262** intermediate when subjected to flash vacuum pyrolysis at 470 ^oC led to a formation of 8-6 ring system of taxanes as mechanistically explained in Scheme-52.

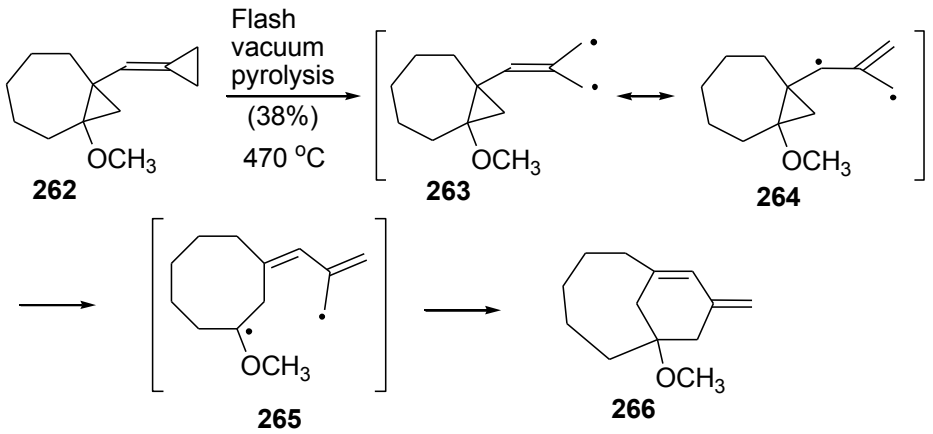
Scheme-50: Shiina, I.; Iwadare, H.; Sakoh, H.; Hasegawa, M.; Tani, Y.; Mukaiyama, T. *Chem. Lett.* **1998**, 1.



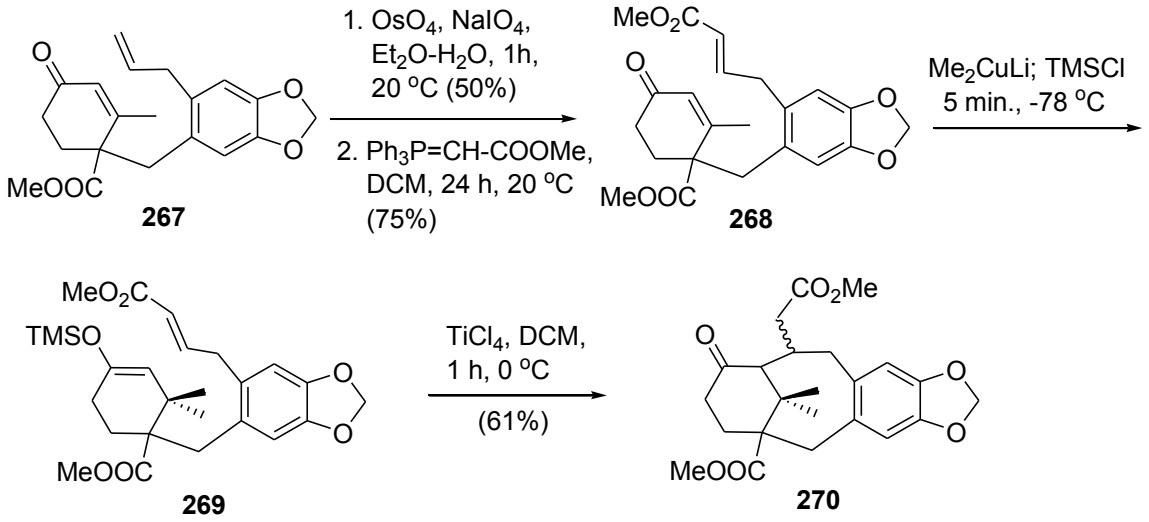
Scheme-51: Phansavath, P.; Anbert, C.; Malacria, M. *Tetrahedron Lett.* **1998**, *39*, 1561.



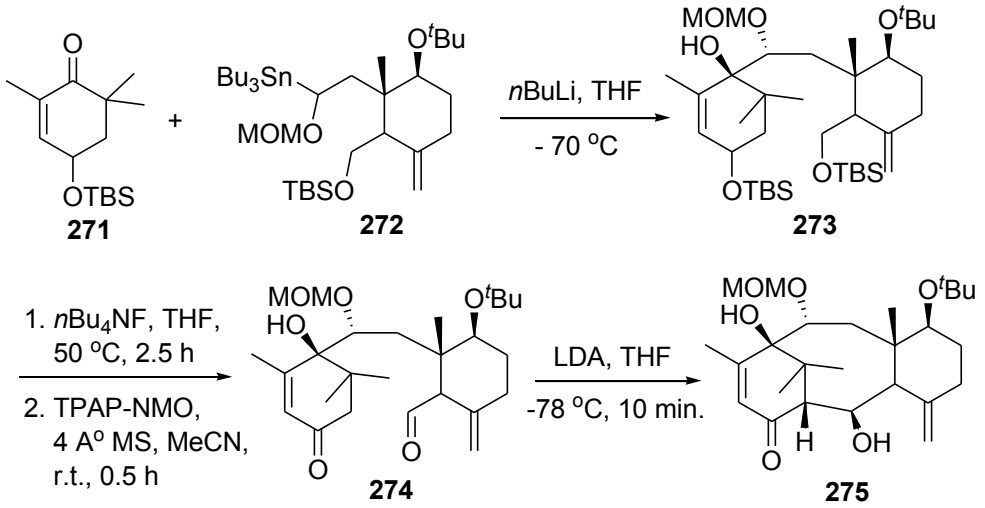
Scheme-52: Liu, H.; Shook, C. A.; Jamison, J. A.; Thiruvazhi, M.; Cohen, T. *J. Am. Chem. Soc.* **1998,** *120*, 605.



Scheme-53: Cave, C.; Valancogne, I.; Casas, R.; d'Angelo, J. *Tetrahedron Lett.* **1998**, *39*, 3133.



Scheme-54: Martín Hernando, J. I.; Quílez del Moral, J.; Rico Ferreira, M.; Candela Lena J. I.; Arseniyadis, S. *Tetrahedron: Asymmetry* **1999**, *10*, 783.



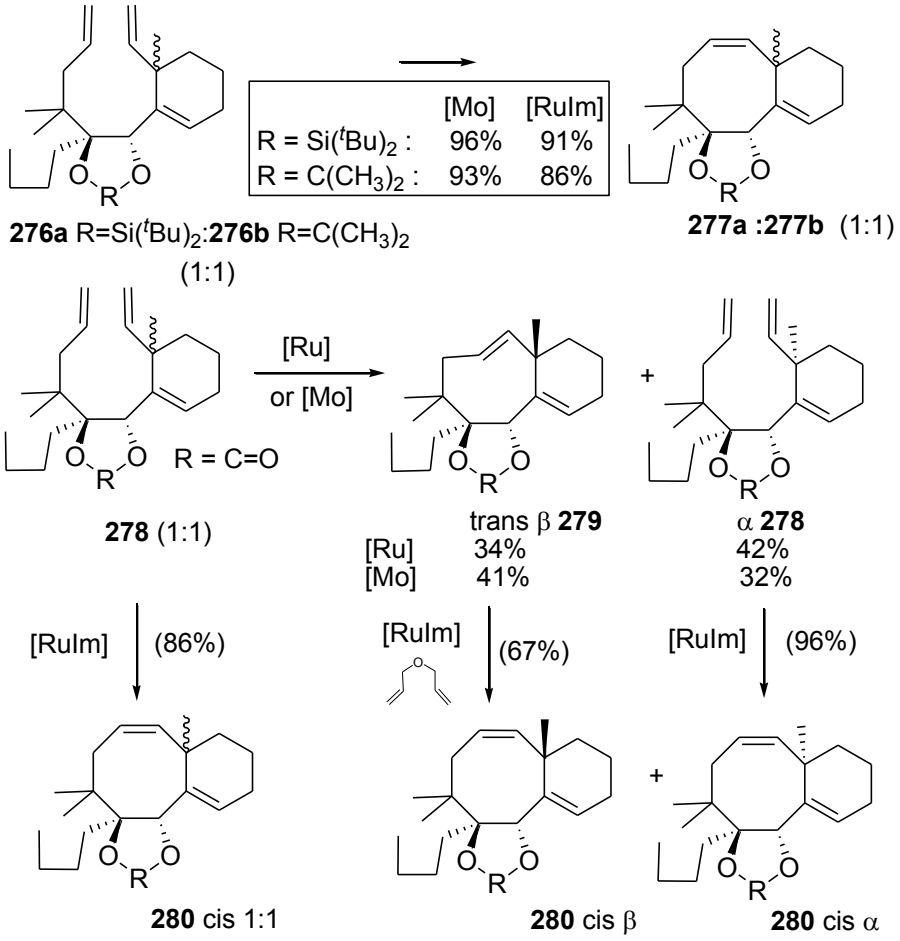
d'Angelo and co-worker's synthesized substituted Hagemann's ester **267** as shown in Scheme-53, which on further using standard chemistry was converted to **269**, a key precursor for Mukaiyama-type cyclization reaction. Thus, $TiCl_4$ were added to **269** afforded cyclized product **270** nothing but an ABC taxane system.[97]

In a convergent approach from Arsenyadis laboratory for the construction of ABC skeleton of taxane, both A-ring **271** and C-ring **272** were prepared from Hajos-Parrish ketone, a chiral building block. Authors elegantly utilized their methodology involving Lead tetraacetate mediated chemistry for the preparation of C-ring part. Thus two rings were coupled by butyl lithium chemistry to get the alcohol **273**, which was subsequently converted, into di-keto compound **274** as portrayed in Scheme-54. Base

catalyzed intramolecular aldol reaction was used for formation of central eight membered B-ring.[98]

Ring-closing metathesis (RCM) was used as a pivotal step by Nolan and Prunet and their collaborators for the synthesis of BC taxane frame work.[99] As outlined in Scheme-55, silylene **276a** and acetonide **276b** precursors underwent cyclooctene formation, using Schrock's [Mo] catalyst and Ruthenium complex [RuIm] developed by authors, in high yields. In carbonate **278** case, trans β-**279** octene was formed and whereas other starting α-**278** isomer did not undergo RCM reaction when Grubb's catalyst [Ru] were used, indicating that RCM does not always proceed to completion of thermodynamic equilibrium. However using author's own catalyst they were able to carry out RCM of carbonates **278** and α-**278** respectively and isomerization of *trans* β-**279** compound as well.

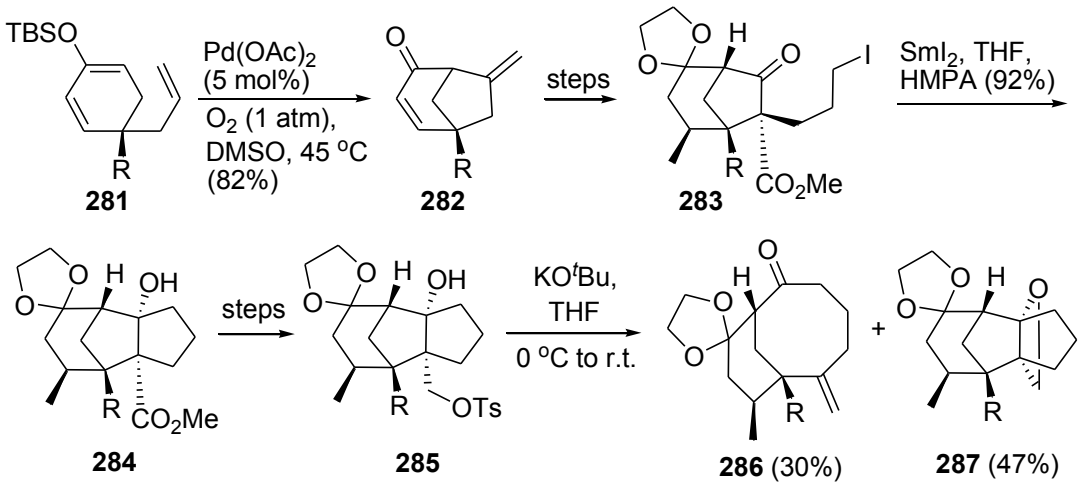
Scheme-55: Bourgeois, D.; Mahuteau, J.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *Synthesis* **2000**, 869.



Toyota and Ihara have applied Grob-type fragmentation to obtain AB pattern of taxane which lacks geminal dimethyls.[100] They began with bicycle [3.2.1] octane ring

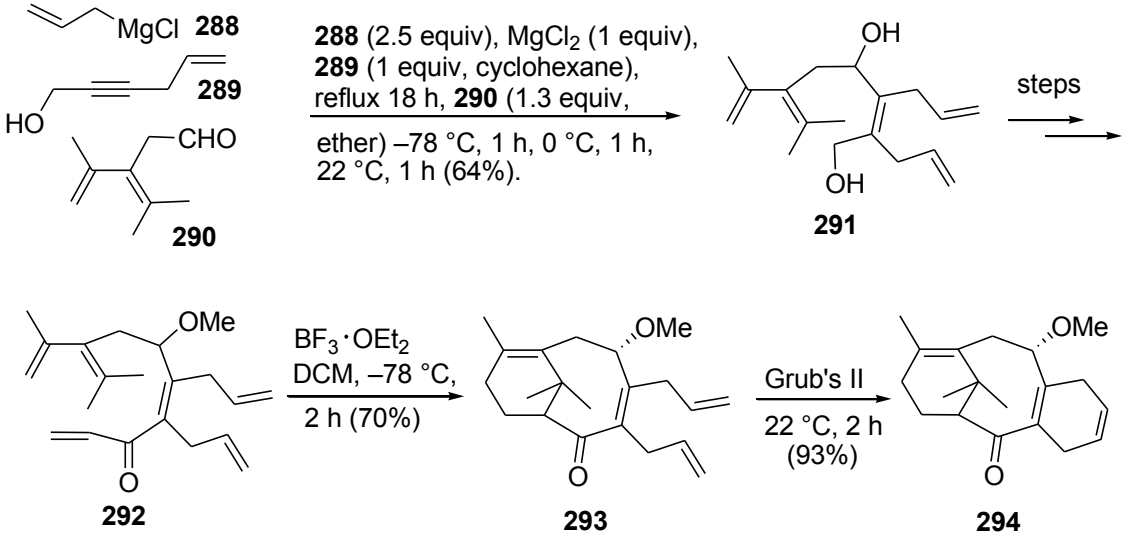
system **282**, prepared from cross conjugated silyl enol ether employing palladium catalyzed cyclo alkenylation reaction. Further steps led to a key tricycle [$5.3.1^{2,6}$] precursor **284**, which on treatment with base afforded fragmented bicycle[5.3.1] undecane **286** as a minor compound as delineated in Scheme-56.

Scheme-56: Toyota, M.; Rudyanto, M.; Ihara, M. *Tetrahedron Lett.* **2000**, *41*, 8929.



In another approach from Fallis group of synthesis of ABC ring system of taxane (Scheme-57), AB ring was generated by sequential carbometallation of a propargyl alcohol **289**, followed by a *cis*-alkene **290** tether controlled stereoselective intramolecular Diels–Alder reaction to generate the AB-ring system **293** and subsequent ring closing metathesis (RCM) of the pendant allyl substituents to construct the C ring (**293**→**294**).[101]

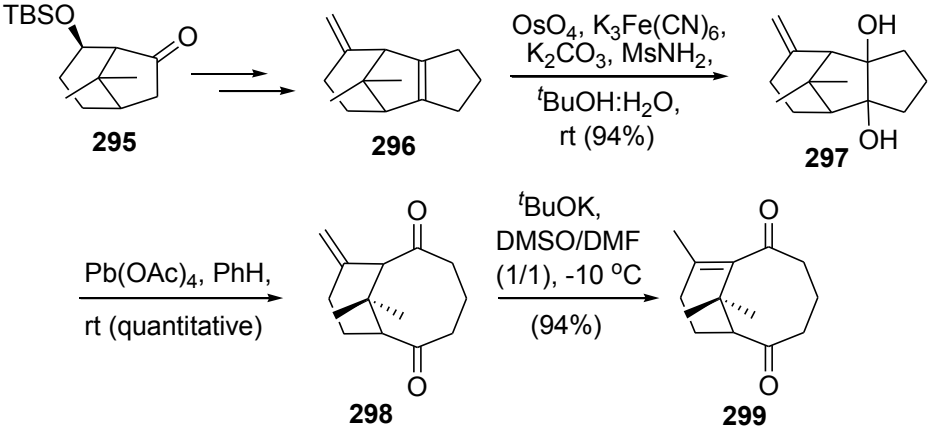
Scheme-57: Smil, D. V.; Laurent, A.; Spassova, N. S.; Fallis, A. G. *Tetrahedron Lett.* **2003**, *44*, 5129.



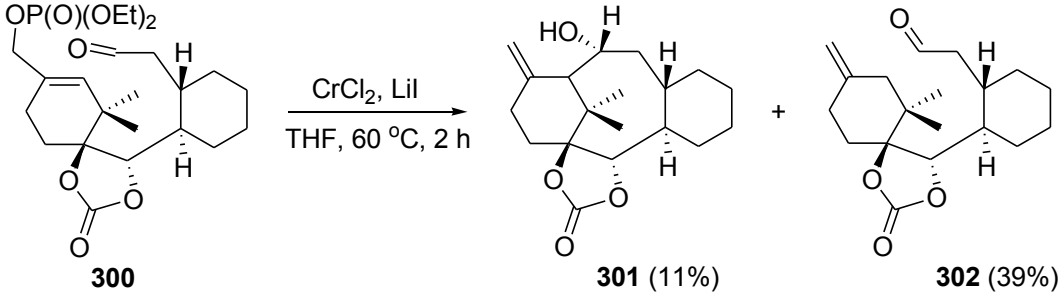
Oxidative ring expansion strategy was used by Kakichis laboratory to get AB frame work.[102] Thus bicyclic compound **295** was converted to tricyclic compound **296** by

Suzuki coupling. The stepwise oxidation of inner double bond resulted in AB core of taxol as depicted in Scheme-58. Later the exocyclic double bond was isomerized under kinetically controlled conditions, resulted in Anti-Bredt's fashion to form AB core **299** of taxane family.

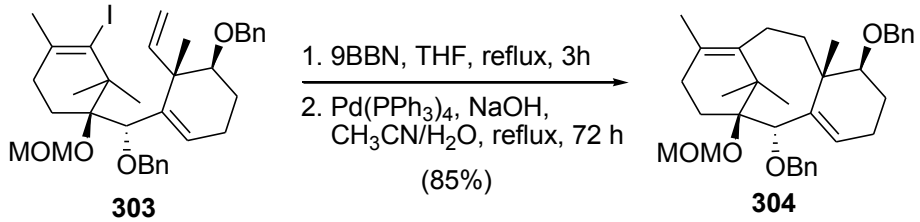
Scheme-58: Shimada, Y.; Nakamura, M.; Suzuka, T.; Matsui, J.; Tatsumi, R.; Tsutsumi, K.; Morimoto, T.; Kurosawab, H.; Kakiuchi, K. *Tetrahedron Lett.* **2003**, *44*, 1401.



Scheme-59: Iwamoto, M.; Miyano, M.; Utsugi, M.; Kawada, H.; Nakada, M. *Tetrahedron Lett.* **2004**, *45*, 8653.

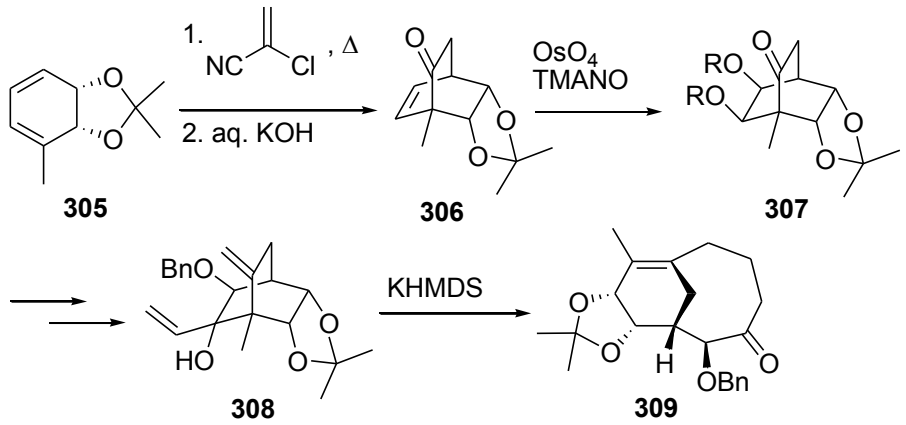


Scheme-60: Kawada, H.; Iwamoto, M.; Utsugi, M.; Miyano, M.; Nakada, M. *Org. Lett.* **2004**, *6*, 4491.



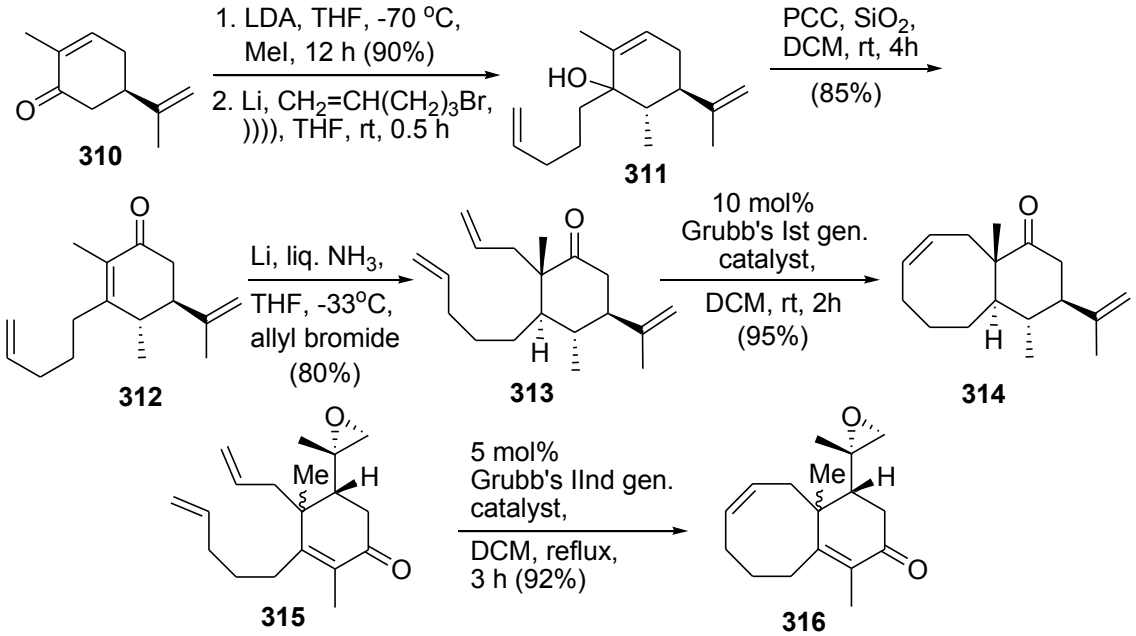
Another direct method of eight membered ring formation was reported by Nakada and co-workers.[103] As depicted in Scheme-59, the allyl phosphate and aldehyde group were coupled intramolecularly by using a protocol developed by Nozaki-Hiyama to obtain ABC core of taxane **301** in poor yields. In an another approach[104] from same group the central eight membered B-ring was formed by intramolecular B-alkyl Suzuki-Miyaura cross coupling reaction as shown in Scheme-60 in high yields.

Scheme-61: Banwell, M. G.; Mcleod, M. D.; Riches, A. G. *Aust. J. Chem.* **2004**, *57*, 53.



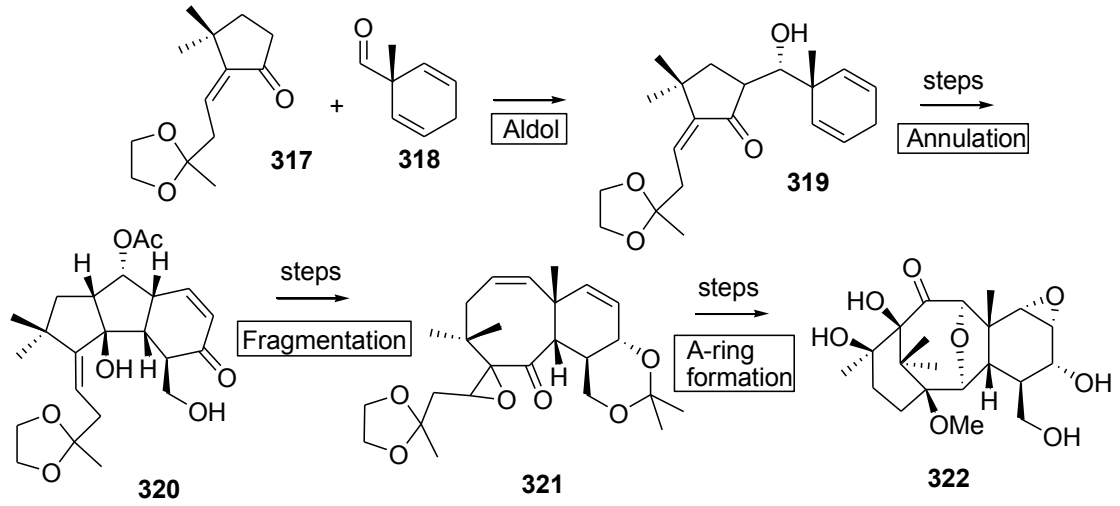
Anionic oxy cope rearrangement strategy was applied by Banwell to construct AB ring of taxane.[105] Thus microbially derived chiral cis-1,2-dihydroxycatechol **305** was converted to bicyclic[2.2.2] octene **306** by [4+2] reaction (Scheme-61). Further functional group manipulation led to precursor, allyl and homoallylic alcohol **308**. On treatment with KHMDS it underwent smooth anionic oxy-Cope rearrangement to get desired AB core of taxane.

Scheme-62: Srikrishna, A., Dethe, D. H.; Ravi Kumar, P. *Tetrahedron Lett*. **2004**, *45*, 2939.



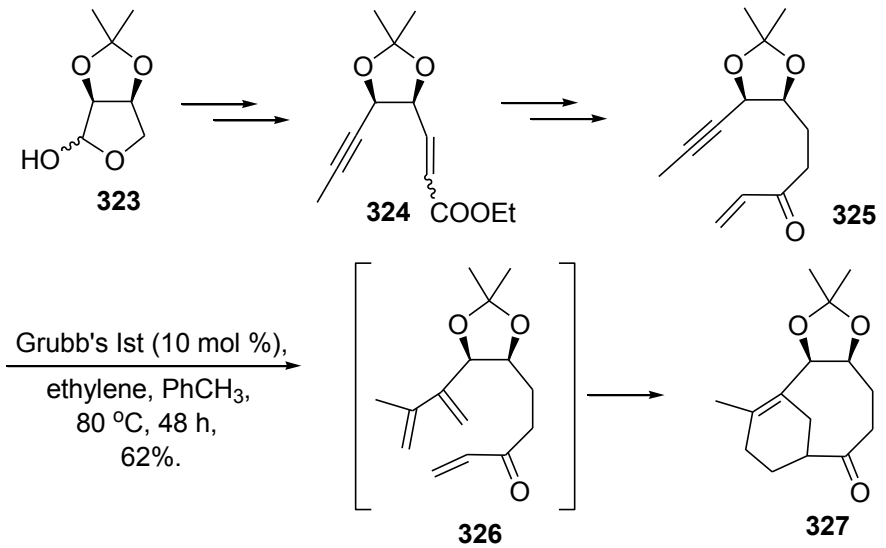
Two alternative approaches from same synthons were reported by Srikrishna *et al.* for the construction of BC taxane framework (Scheme-62).[106] As a part of their ongoing programme of utilization of carvone as a chiral pool, they have elegantly synthesized C-ring from the same. After few steps precursor olefins **313** & **315** were synthesized which subsequently were closed by RCM using Grubbs' catalyst to obtain eight membered B-ring compounds (**314** & **316**) respectively.

Scheme-63: Hamon, S.; Birlirakis, N.; Toupet, L.; Arseniyadis, S. *Eur. J. Org. Chem.* **2005**, 4082.



In another elegant approach from Arsenyadis team has led to synthesis of highly oxygenated functionalized carbon centers containing all 20-carbon of taxane ABC system.[107] The team has devised a protocol i.e. aldol-annulation-fragmentation as portrayed in Scheme-63 to get BC-ring **321**. Later A-ring was formed by samarium iodide mediated pinacol coupling to get ABC taxoid **322**.

Scheme-64: Kaliappan, K. P.; Ravikumar, V.; Pujari, S. A. *Tetrahedron Lett*. **2006**, *47*, 981.



Recently Kaliappan group demonstrated a domino cross-enyne metathesis/intramolecular Diels–Alder reaction for the construction of AB ring system **327** of taxane outlined in Scheme-64.[108]

1.1.6 References:

1. (a) Shi, Q.; Kiyota, H. *Chemistry and Biodiversity* **2005**, *2*, 1597. (b) Baloglu, E.; Kingston, D. G. I. *J. Nat. Prod.* **1999**, *62*, 1448. (b) Eisenhauer, E. A.; Vermorken, J. B. *Drug* **1998**, *55*, 5. (c) Kobayashi, J.; Hosoyama, H.; Shigemori, H.; Koiso, Y.; Iwasaki, S. *Experientia* **1995**, *51*, 592. (d) Kobayashi, J.; Hosoyama, H.; Wang, X. X.; Shigemori, H.; Sudo, Y.; Tsuruo, T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1555. (e) Kobayashi, J.; Hosoyama, H.; Wang, X. X.; Shigemori, H.; Koiso, Y.; Iwasaki, S.; Sasaki, T.; Naito, M.; Tsuruo, T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3. (f) Kobayashi, J.; Shigemori, H. *Heterocycles* **1998**, *47*, 1111. (g) Kobayashi, J.; Shigemori, H. *Med. Res. Rev.* **2002**, *22*, 305.
2. (a) Cragg, G. M. *Med. Res. Rev.* **1998**, 315. (b) http://www.taxol.com.
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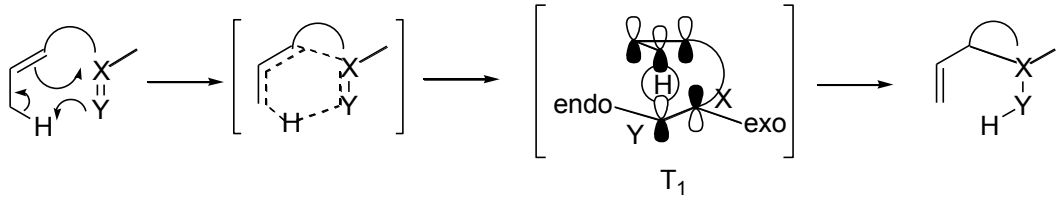
Section-II

Attempted synthesis of ABC skeleton of C-aromatic taxane

1.2.1 Introduction:

Reactions involving the activation of C-H bond for the formation of C-C bond are clue to synthetic exploitation in organic synthesis for the last several years.[1] In this regard, the ene reaction[2] which converts readily available alkenes into a more functionalized products may be considered one of the simplest (Figure-1). The ene–reaction may be defined as a six-electron pericyclic process in which a reaction between an alkene bearing an allylic hydrogen (ene) and an electron deficient multiple bond (an enophile) leads to the formation of two new σ-bonds with the migration of π-bond. The ene-reaction is mechanistically related to Diels-Alder reaction[3] since both reactions can be considered proceeding through six-membered cyclic transition state involving six electrons. In the ene reaction; involving a suprafacial orbital interaction (T_1), two electrons of the allylic C-H σ bond replace two π- electrons of the diene in the Diels-Alder reaction which necessitates the higher energy of activation (thus, higher reaction temperature) compared to the Diels-Alder reactions.

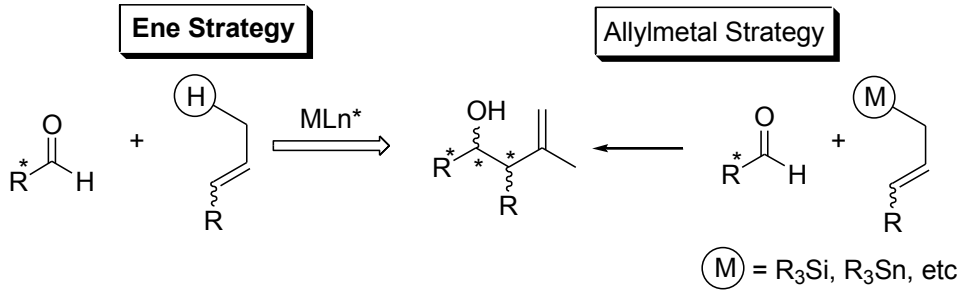
Figure-1



X = Y : C=CH$_2$, C=O, C=N-, C=S, C≡C—

Ene reaction proceeds most readily when the ene part is electron rich and the enophile counter part is electron deficient. The exact order of ene part depends upon the enophile and the reaction conditions. The relative reactivity of alkenes as ene component has typically been found to be 1,1-di> tri-> tetra-> mono-> 1,2 disubstituted. The ene reaction encompasses a vast number of variants in terms of the enophile used.[4] Olefins are relatively unreactive as enophiles; acetylenes are more enophilic. Under high pressure, acetylene reacts with a variety of simple alkenes to form 1,4-dienes. When carbonyl compounds are used as enophiles, alcohols, rather than ethers, are formed exclusively. From the synthetic point of view, the carbonyl-ene reaction should in principle constitute a more efficient alternative to the carbonyl addition reaction of allylmetals which has now become one of the most useful methods for carbon skeletal construction with stereocontrol featuring acyclic stereocontrol (Figure-2). The synthetic

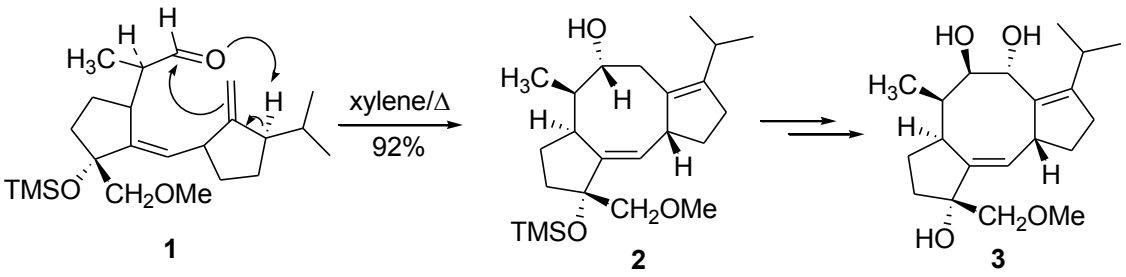
Figure-2



utility of the carbonyl-ene products depends heavily on the functionalities of the enophiles employed. The rate of carbonyl-ene reaction has been shown to dramatically increase on Lewis acid catalysis. Complexation of a Lewis acid with the carbonyl group makes the carbonyl group more electrophilic and thereby accelerating the ene reaction which enables this reaction more useful synthetically. Recent investigations have suggested that Lewis acid catalyzed ene reactions are stepwise rather than concerted but the intermediate bears more resemblance to a π-complex than to a zwitterionic intermediate[5].

The most difficult eight-membered ring annulation by carbonyl-ene reaction has been successfully demonstrated by Kato's group[6] in Cotylenol synthesis **3** starting from **1**. The synthesis essentially utilized thermal carbonyl-ene cyclization protocol as the key step from **1** to produce **2** in high yield. (Scheme-1)

Scheme-1: Kato, N.; Okamoto, H.; Takeshita, H. *Tetrahedron*. **1996**, *52*, 3921.

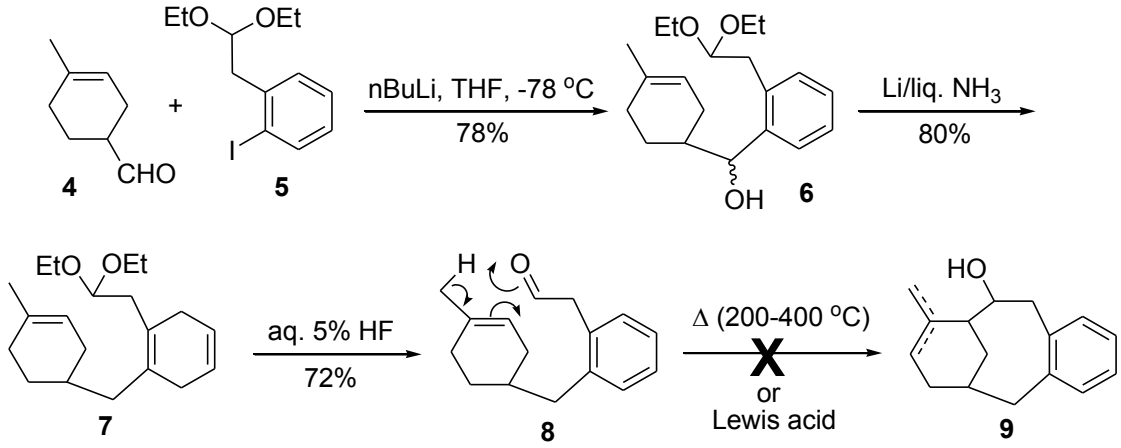


The application of intramolecular carbonyl-ene reaction in the synthesis of **3** appears to be the sole example reported in the literature, for the construction of 8-membered carbocylic ring system.

It was considered worthwhile to exploit this methodology for cyclooctane ring unit of taxol.

Sonawane's group is actively engaged in the synthesis of taxoids for last one decade. Described herein are earlier efforts[7] from this laboratory for the synthesis of ABC skeleton of taxol utilizing carbonyl-ene cyclization as a pivotal step.

Scheme-2: Maji, D. K. Ph. D. Dissertation, University of Pune, Pune, 1999.



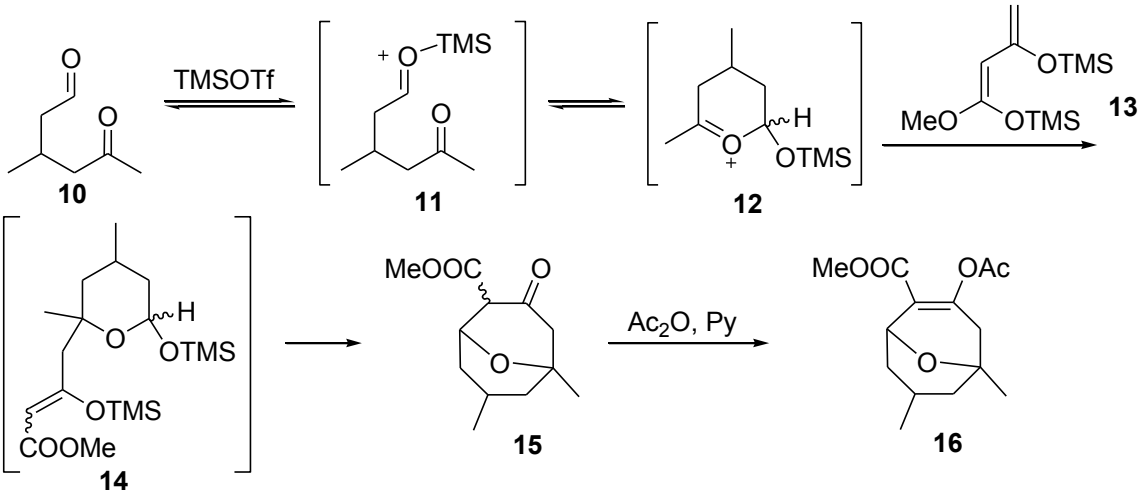
As outlined in Scheme-2, intermediate **8** failed to undergo carbonyl-ene cyclization reaction, surprisingly when compared to Cotylenol **3** synthesis where it worked in excellent yields.

After unsuccessful attempts it was decided to employ its modified version to this effect oxonium-ene cyclization.[8] It was soon realized that direct eight-membered ring annulation with bridgehead carbon may not be possible by an intramolecular carbonyl-ene reaction. In this regard, it was envisioned that the oxonium-ene cyclization[8] would be of lower energy process as compared to that of direct carbonyl ene process. And it is also likely to circumvent the well-documented difficulties[9] (entropy and enthalpy) of direct cyclization approach for cyclooctanoid moiety, therefore an indirect protocol for the synthesis of masked eight-membered carbocycle (six membered fused with another six-membered with an oxygen bridgehead atom) was adopted.

However, before describing Sonawane's group achievements it would be pertinent to present a brief note on cyclooctanoid annulation using oxonium-ene cyclization reaction.

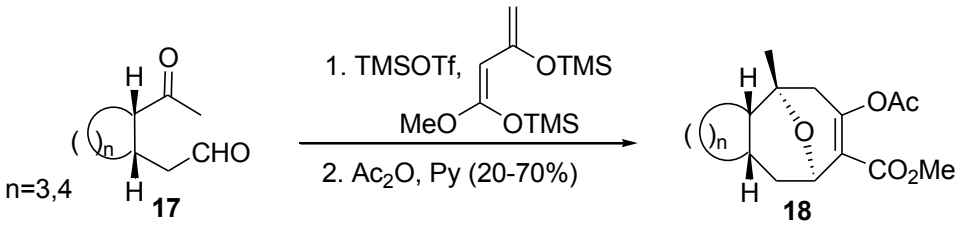
Molander's group[10] have conceptually developed a new approach to furnish cyclooctanoid bicyclic ethers **16** in good yields by the Lewis acid catalyzed reaction between masked β-ketoester **13** and 1,5-dienone **10** as shown in Scheme-3. The cyclization is reported to proceed through the regioselective generation of oxonium ion **12** and subsequent attack of the more nucleophilic terminal carbon of **13** on to the second carbonyl group generating the intermediate **14** which finally produces **15** via the intermediacy of another oxonium ion generated from **14**.

Scheme-3: Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc*. **1993**, *115*, 830.



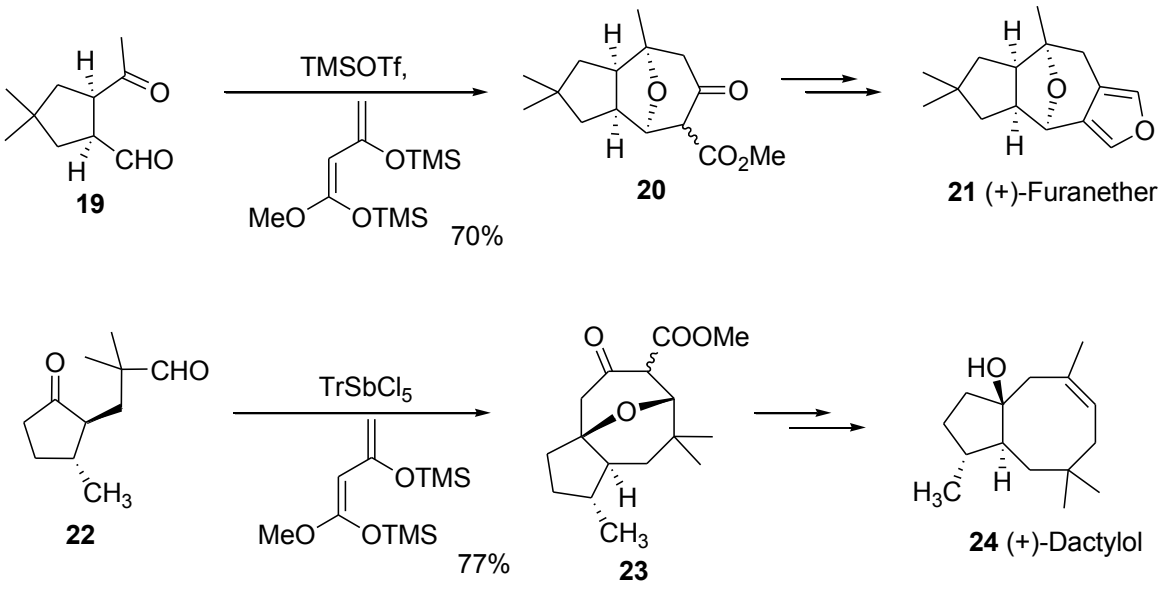
This intramolecular oxonium-ene cyclization method was shown to be quite general and varieties of cyclooctanoids[11] **18** were prepared (Scheme-4).

Scheme-4: Molander, G. A.; Cameron, K. O. *J. Org. Chem*. **1993**, *58*, 5931.

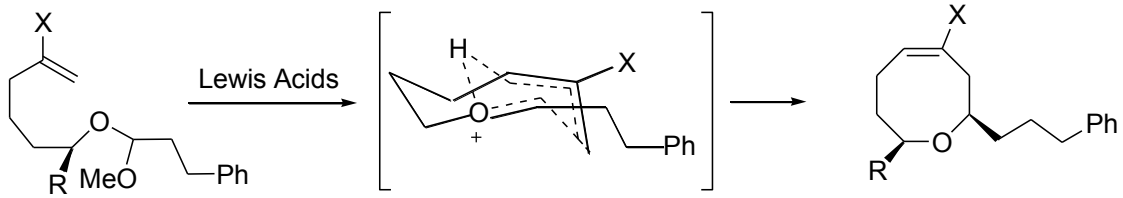


These annulation reactions were further extended for the stereocontrolled synthesis of tricyclic ether, for example, the synthesis of natural product i.e. Furanether B[12] **21** and (+)-Dactylol[13] **24** as represented in Scheme-5.

Scheme-5: (a) Molander, G. A.; Carey, J. S. *J. Org. Chem*. **1995**, *60*, 4845. (b) Molander, G. A.; Eastwood, P. R. *J. Org. Chem*. **1995**, *60*, 4559.



Scheme-6: Blumenkopf, T. A.; Bratz, M.; Castaneda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D. Thompson, A. S. *J. Am. Chem. Soc*. **1990**, *112*, 4386.



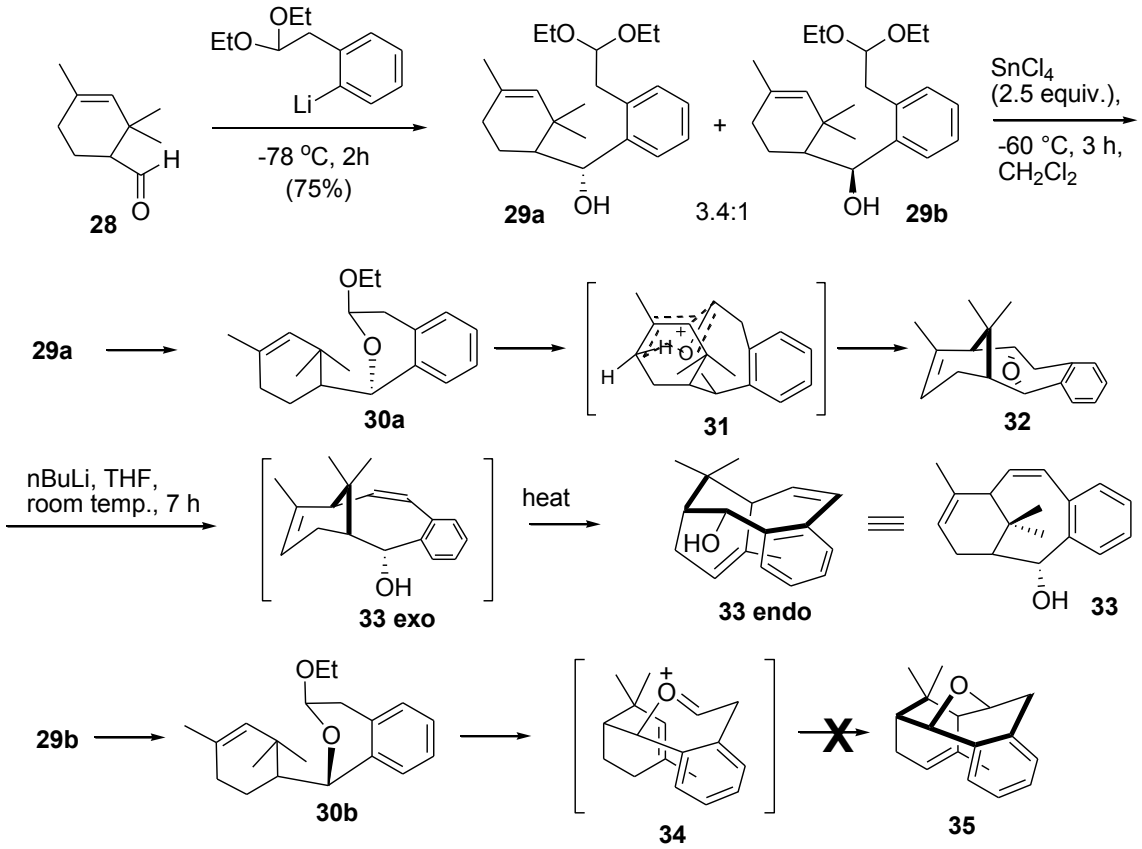
25 **26** **27** Δ^4-Oxocene

X	Reaction conditions	Δ^4-oxocene(**27**),yield
H	$EtAlCl_2$, CH_2Cl_2 , – 60 ^oC	11% (R=H)
$SiMe_3$	$SnCl_4$, CH_2Cl_2, – 60 to 20 ^oC	31% (R= Me)
SPh	$BF_3.OEt_2$,t-BuOMe, –78 to 30 ^oC	78% (R= Me)

It has been shown that the yield of **27** increases as the vinylic substitution varies from H to $SiMe_3$ to SPh;[15] notably electron-rich vinylic moiety offers high yields (75-80%) under non-high-dilution conditions (Scheme-6). A concerted oxonium-ene cyclization was proposed to be involved in this facile transformation. A highly stereocontrolled and enantioselective synthesis of (–)-Laurenyne[16] has been achieved by the application of this methodology.

Oxonium-ene cyclization was utilized by Sonawane's group for the construction of ABC skeleton of taxol as shown in Scheme-7.[17] Thus, precursor compound **29a** & **29b** were readily assembled by the reaction of aryllithium reagent **5a** (prepared *via* the reductive metalation of the diethylacetal of 2-iodophenylacetaldehyde **5** using nBuLi) with compound **28**. The substrate **29** (75%) was found to be a inseparable diastereomeric mixture as a **29a** (1*R**, 2*R**) and **29b** (1*R**, 2*S**) in the ratio of 3.4:1. Addition of $SnCl_4$ (2.5 equiv.) to **30a**, afforded cyclized product **32** in 32% yield, which is nothing but oxo-bridged ABC skeleton of taxol, which was subsequently unmasked by treatment with nBuLi delivered 6-8-6 taxane system (**33**). Mechanistically, in analogy with Overman's proposal[8], a concerted oxonium-ene cyclization may well be visualized in the formation of *exo*-**32** from oxonium ion **31**, derived from the major isomer **29a** involving a favorable six membered transition state. The lack of such transition state possibility from the minor isomer **29b** due to the unfavorable geometry of the oxonium ion **34** precludes it from undergoing an analogous type of cyclization that would lead to taxane system **35**.

Scheme-7: Sonawane, H. R.; Maji, D. K; Jana, G. J.; Pandey, G. *Chem. Commun*. **1998**, 1773.

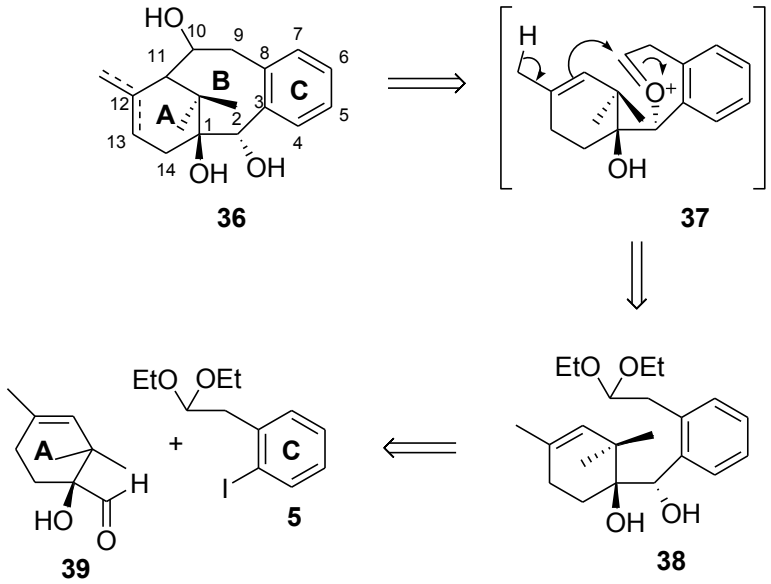


1.2.2 Present Work:

Synthesis of C-1 hydroxyl C-Aromatic ABC taxane system:

After achieving ABC skeleton of taxol by oxonium ene strategy by our group, it was thought to incorporate C-1 hydroxyl group in A-ring, which is present in naturally occurring taxol and to examine its effect on oxonium-ene cyclization reaction a pivotal step in the construction of C-1 hydroxy C-aromatic ABC taxane system.

Scheme-8:



Towards fulfilling the goal of synthesizing C-1 hydroxy-C-aromatic ABC taxane system **36** by following the retrosynthetic route (Scheme-8), involving C10-C11 bond formation step through oxonium-ene cyclization, compound **38** was evaluated as the precursor. It was envisaged that the compound **38** could be prepared by Barbier-type coupling reaction of **5** with **39**. The synthesis of all components and the attempt to synthesize **36** are described sequentially below.

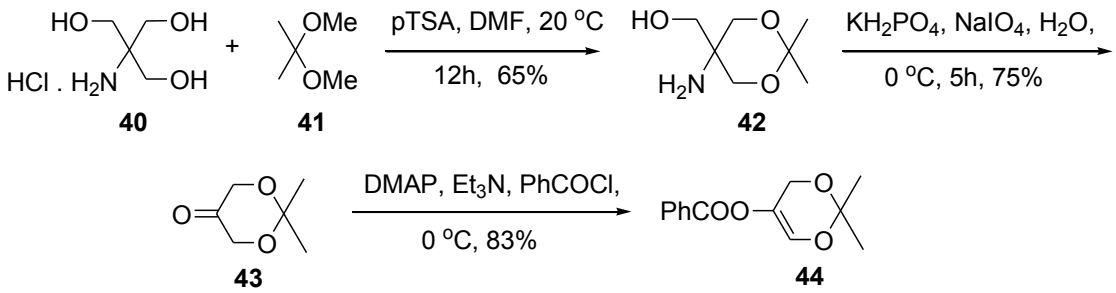
Preparation of compound 38

Synthesis of **38** as perceived through the retrosynthetic strategy (Scheme-8) was initiated with the preparation of **39** and **5**.

Preparation of 1-hydroxy-2,2,4-trimethylcyclohex-3-enecarbaldehyde (39)

A-ring unit was prepared by classical Diels-Alder reaction and therefore the dienophile and diene were prepared accordingly as described below. The protocol developed by Funk and Yost for the preparation of α-benzoyloxy dioxin was used.[18] As delineated in Scheme-9, the acetonide protection of tris-buffer **40** was carried out with 2,2-dimethoxy propane in DMF catalyzed by *para*-toluenesulfonic acid, resulted

Scheme-9:

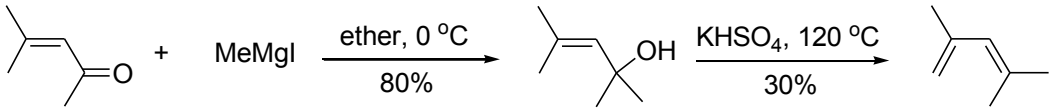


40 **41** **42** **43** **44**

5-amino-5-hydroxymethyl-2,2-dimethyl-1,3-dioxane **42** in 65% yield. The product **42** formed was confirmed by matching data of IR, ^{1}H NMR and Mass spectra taken with the values of reported. The reductive cleavage of β-amino alcohol **42** was carried out by treating it with aq. sodium periodate in the presence of potassium hydrogen phosphate at 0 ^{o}C for 5h to furnish 2,2-dimethyl-5-oxo-1,3-dioxane **43** in 75% yield. IR spectrum of **43** indicated the absence of hydroxyl or amino group but showed prominent absorption band at 1752 cm^{-1} owing to presence of carbonyl group. ^{1}H NMR spectrum of **43** shows two singlet peaks at δ 4.14 and 1.44, integrating in the ratio 2:3 respectively. The values appeared in spectrum are almost similar position with the reported. The mass spectrum of **43** also revealed the presence of molecular ion peak along with sodium ion at 153.

The O-benzoylation was performed with benzoyl choride instead of benzoic anhydride used by Funk and Yost.[18] Thus, addition of benzoyl choride to a solution of **43** in DCM along with catalytic amount of 4-DMAP and triethyl amine afforded dienophile precursor **44**.

Scheme-10:



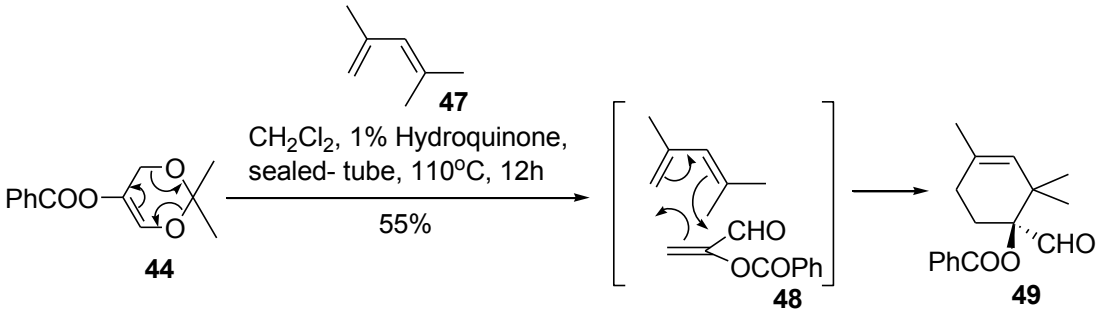
45 **46** **47**

The diene; 2,4-dimethyl-1,3-pentadiene **47** was prepared by reaction of methyl magnesium iodide with mesityl oxide **45**, and the resulting tert. alcohol was subsequently dehydrated by potassium hydrogen sulphate (Scheme-10).[19]

The Diels-Alder reaction was carried out by mixing DCM solution of diene **47**, dienophile precursor **44** and trace of hydroquinone in a sealed-tube, which was kept in protective steel-bomb and further kept in an oven at temperature 110 °C for 12h. Thus, as depicted in Scheme-11 initially compound **44** undergoes retro Diels-Alder reaction to form *in-situ* dienophile *i.e.* α-benzoyloxy acrolien **48** and acetone molecule and

subsequently undergoes cycloaddition with diene **47** to afford regioselective adduct **49** in 55% yield.

Scheme-11:



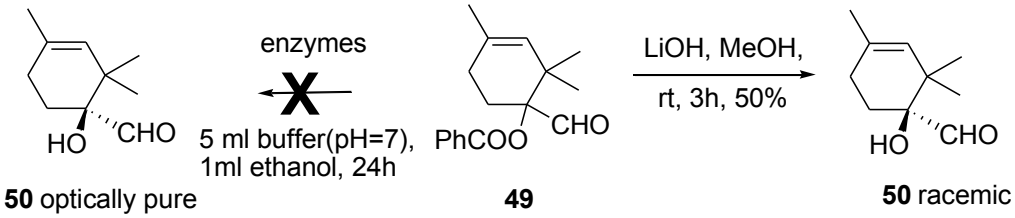
IR spectrum of **49** displayed a strong broad band at 1705 cm^{-1}, indicating the presence of benzoate carbonyl group.

^{1}H NMR spectrum of **49** revealed following pattern. A singlet peak at δ 9.86 corresponds to aldehyde proton. The multiplets at δ 8.04, 7.60 and 7.46 were attributed to aromatic protons. A singlet at δ 5.08 integrating for one proton corresponds to olefinic groups. The three sharp singlets at δ 1.69, 1.27 and 1.03, integrating for three protons corresponds to methyl on double bond and geminal dimethyls respectively.

^{13}C NMR spectrum of **49** along with DEPT spectrum revealed following pattern. The five quaternary signals present at δ 199.0, 165.1, 130.0, 129.0, 86.3 and 37.9 correspond to benzoate carbonyl, aromatic, olefinic, carbon attached to benzoate and the carbon where gem dimethyls present accordingly. Methine signals at δ 170.5, 132.9, 132.8, 129.4, 129.0, 128.9, 127.9 and 127.7 correspond to aldehyde carbonyl, six aromatic and olefin carbon. The two methylenes carbon present in the molecule appeared at δ 25.6 and 21.5. The methyl signals appear at δ 25.9, 23.7 and 22.3 were ascribed to vinylic methyl and geminal dimethyl respectively.

The mass spectrum of **49** revealed molecular ion peak along with sodium ion at 273 and the other major peaks appeared at 238, 233, and 177.

Scheme-12:



The benzoate group in compound **49** was hydrolyzed by aqueous lithium hydroxide in methanol to form α-hydroxy A-ring unit **50** in 50% yield (Scheme-12).

IR spectrum of **50** displayed a strong broad band at 3500 & 1717 cm^{-1}, indicating the presence of hydroxyl and carbonyl group respectively.

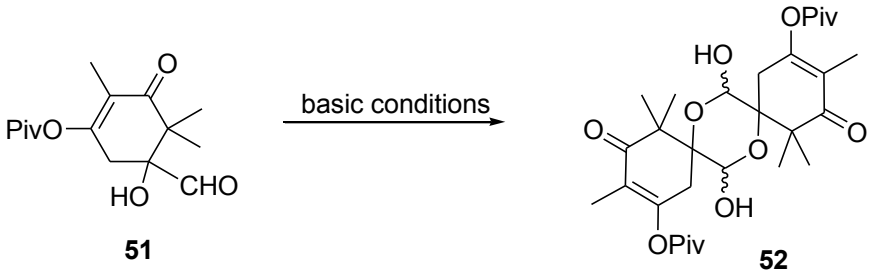
^{1}H NMR spectrum of **50** displayed the following pattern. A singlet peak at δ 9.86 corresponded to aldehyde proton. A singlet at δ 5.23 integrating for one proton corresponded to olefinic protons. The methylene protons appeared as multiplets at δ 2.90–1.80. The three sharp singlets at δ 1.71, 1.03 and 0.97, integrating for three protons corresponded to methyl on double bond and geminal dimethyls respectively.

^{13}C NMR spectrum of **50** revealed the following pattern. The most downfield signal appeared at δ 205.9 was assigned to aldehydic carbonyl group. The signals that appeared at δ 130.9 & 130.4 were attributed to olefinic carbons. The signals at δ 79.4 & 37.7 corresponded to carbons bearing hydroxyl & gem. dimethyl groups respectively. The signals at 28.1, 27.7, 2 x 24.7 & 22.8 were assigned to methylenes and methyls.

The mass spectrum of **50** revealed molecular ion peak at 168 and the other prominent peaks appeared at 150 ($M–H_2O$), 140 (M–CO), 139 (M–CHO), 122, 107, 96, 91, 81, 67, 55.

The compound **50** was found to be unstable even after keeping in freezer. Similar situation were also experienced by Kuwajima group in their development of ABC skeleton of taxol,[20] where they reported formation of dimer product **52** when α-hydroxy carbonyl compound **51** was handled in basic conditions (Scheme-13).

Scheme-13:



51 **52**

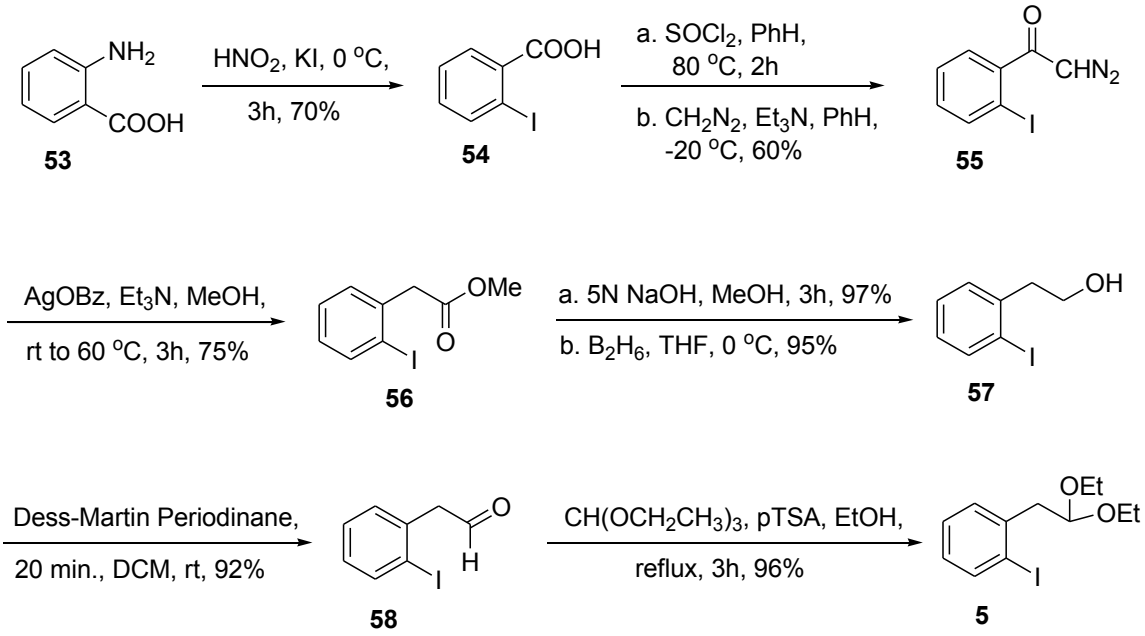
Since racemic A-ring alcohol **50** was obtained by alkaline hydrolysis of **49** it was decided to obtain optically pure A-ring unit by kinetic hydrolysis of racemic benzoate **49**. In this context enzymatic kinetic resolution byhydrolysis of benzoate A-ring unit **49** to deliver optically pure A-ring alcohol **50** (Scheme-12) was explored as an option. So the substrate **49**was subjected to various commercially available hydrolase enzymes (Table-1) for selective hydrolysis but to unfortunately none of them worked and staring material **49** recovered as such.

Table-1:

	Amount of **49** (mg)	Enzyme used (Purchased from Sigma)	Buffer (phosphate pH=7) (mL)	Ethanol used (mL)	Time (h)
1	50	Chirazyme	5	1	24
2	50	Lipase	5	1	24
3	50	Pig Liver Esterase	5	1	24
4	50	Candida Antarctica Lipase	5	1	24
5	50	Candida Cylindricia Lipase	5	1	24

Preparation of C-ring unit 5.

Scheme-14:



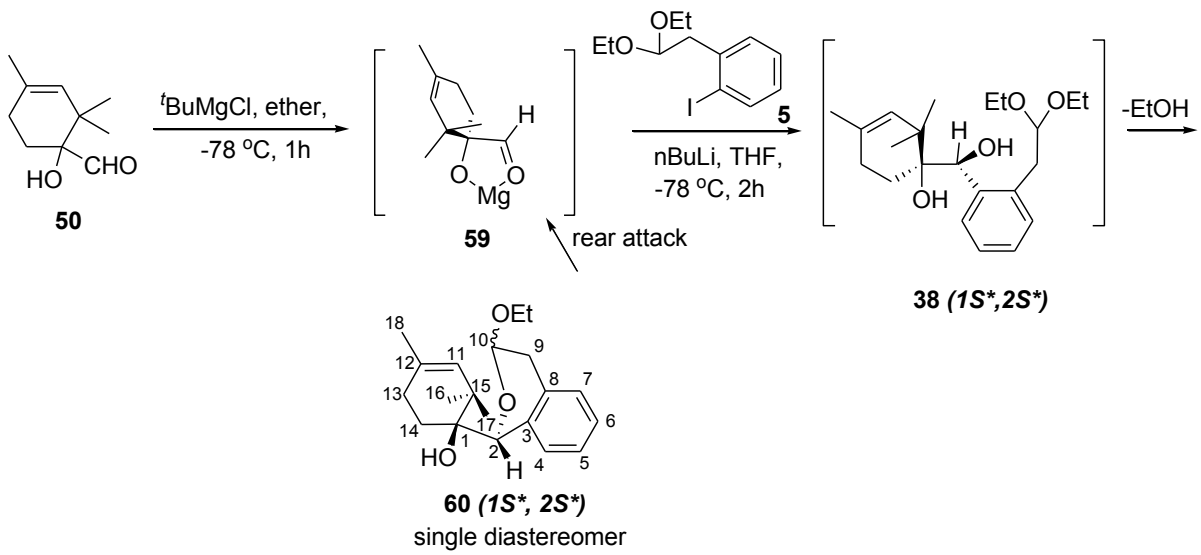
The C-ring unit was prepared in six steps[21] and 26% overall yield from commercially available cheap material *i.e.* anthranilic acid **53**, which was *in-situ* diazotized and substituted with KI to get *o*-iodobenzoic acid **54**. Arndt-Eistert one carbon homologation protocol was used to get **56** from **54** in two steps as delineated in Scheme-14. *o*-Iodo benzoyl chloride formed by reaction with thionyl chloride, which was further added to a yellowish cold (–20 °C) ethereal diazomethane solution afforded *o*-iododiazoketone **55**. Wolff-rearrangement was carried out by Newman and Beal's reagent[22] *viz.* silver benzoate and triethyl amine, which forms silver nanoclusters, recently discovered and reported from this group.[23] Thus homologated methyl ester **56**

was obtained by treating α-diazoketone **55** in methanol with silver nanoclusters. The methyl ester **56** was hydrolyzed by 5N NaOH to get 2-iodophenylacetic acid, which was further reduced by diborane to get 2-(2-iodophenyl)ethanol **57** and further partially oxidized by Dess-Martin periodinane afforded 2-(2-iodophenyl)acetaldehyde **58** in 92% yield. And lastly aldehyde functionality was protected by triethyl orthoformate in ethanol to get C-ring unit **5**.

Coupling of A-ring unit 50 and C-ring unit 5

A ^{t}BuMgCl was added to a solution of cold (–78 °C) ethereal solution of A-ring unit **50**, which forms spiro Mg(II) ion A-ring complex (**59**) as shown in Scheme-15 Simultaneously, metal halogen exchange of C-ring unit **5** was carried out separately by nBuLi at –78 °C and subsequently added to above prepared Mg (II) ion complex (**59**) *via*

Scheme-15:



canula at same temperature yielded coupled product [**38**(***1S*, 2S****)], however during work-up it underwent trans acetalization by loss of a ethanol molecule and hemi acetal was isolated **60**(***1S*, 2S****) as a single diastereomer in 70% yield.

IR spectrum of **60** displayed a sharp band at 3454 cm^{-1}, indicating presence of hydroxyl functionality in the compound.

^{1}H NMR spectrum of **60** showed following pattern. The most downfield signals *i.e.* a doublet of doublet appearing at δ 7.26 with coupling constants 5.16 and 12.32 Hz, doublet of doublet at δ 7.16 with coupling constants 7.15 and 13.51 Hz integrating for two protons and doublet at δ 7.03 with coupling constant 7.15 Hz belong to aromatic protons. The singlet appearing at δ 5.16 was attributed to olefin proton. Another singlet at δ 5.01 was attributed to H-2 proton. The spectrum displayed ABX pattern. Where the

H-10 trans acetal proton appeared as a doublet at δ 5.84 ($J_{H10,H9a}$ = 3.6 Hz). An AB type quartet at δ 3.17 ($J_{H9a,H9b}$ = 17.08 Hz and $J_{H10,H9a}$ = 3.6 Hz), integrating for one proton, could be assigned to one of the benzylic proton while the other appeared at δ 2.85 ($J_{H9a,H9b}$ = 17.08 Hz) presence of only geminal coupling indicated that this proton is at angle of 90° with vicinal H-10 proton and hence no vicinal coupling occured. The triplet-quartet appearing at δ 3.74 and 1.50 with J = 5 Hz were assigned to ethoxy groups. A sharp singlet at δ 1.60 integrating for three protons corresponded to vinylic methyl group. The multiplets at δ 1.97-1.83 and 1.20-1.16 were attributed to H-13, H-14 and H-1 respectively. A sharp singlet at δ 1.14 integrating for six protons was ascribed to geminal dimethyl groups.

^{13}C NMR spectrum of **60** coupled with DEPT spectrum revealed five quaternary carbons: the three down field signals appeared at δ 136.7, 131.7 and 130.7 were assigned to two aromatic and one olefin carbons, while the other two that appeared at δ 89.2 and 38.7 were attributed to C-1 and C-15 respectively. The down field methines at δ 131.9, 128.6, 127.0, 125.1 and 124.9 were assigned to four aromatic and one olefin carbons respectively. The other two methine carbons appeared at δ 100.3 and 77.8 were attributed to C-10 and C-2 carbons respectively. The upfield signals present at δ 26.8, 25.8, 22.7 and 18.1 correspond to four methyls. The four methylene signals appeared at δ 58.0, 36.3, 28.1 and 26.8 were attributed to –O<u>C</u>H$_2$CH$_3$, benzylic, C-13 and C-14 carbons respectively.

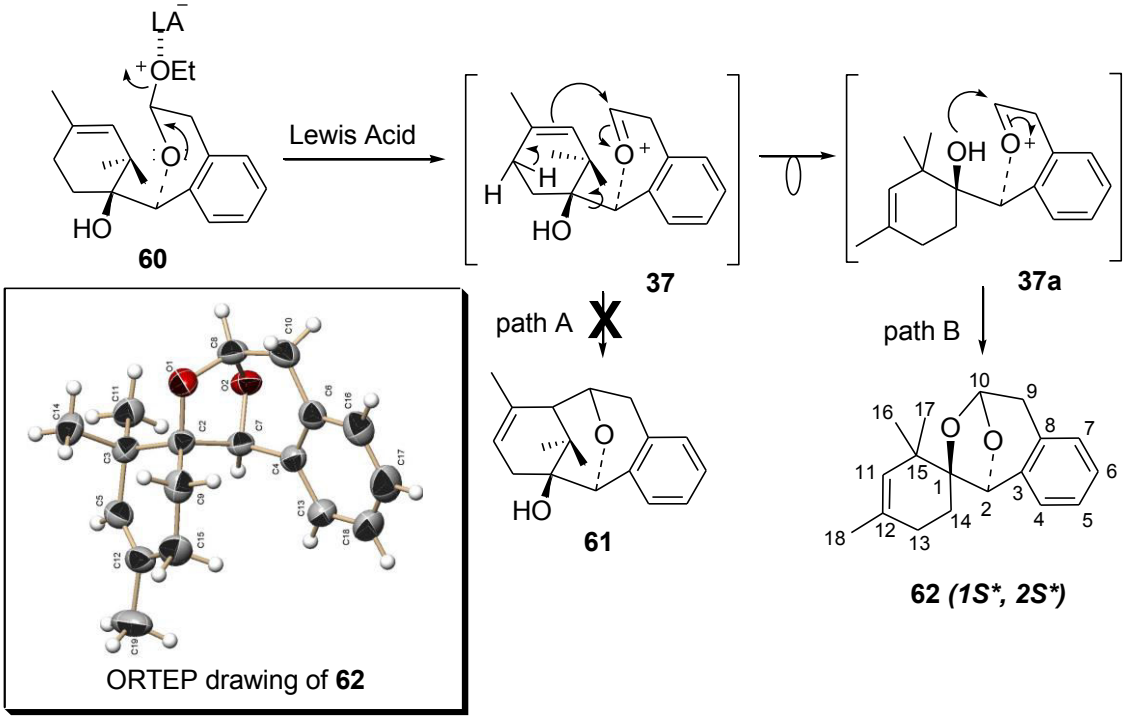
The complex formed **59** restricts the carbon-carbon bond rotation of aldehyde moiety and directs incoming nucleophilic attack from only one face i.e. opposite to bulky geminal dimethyls as shown in Scheme-15

It is pertinent to mention that geminal dimethyls play a crucial role in formation of a single diastereomer. This may be contrasted with the case of nor-geminal dimethyls A-ring coupling 1:1 mixture of diastereomers (previous studies).[7]

$SnCl_4$ promoted cyclization of AC-coupled product 53

After having B-seco-taxane (**60**) in hand it was subjected to oxonium-ene reaction in dichloromethane using various Lewis acids ($BF_3.OEt_2$, Ti[Cl_2(^{i}PrO)$_2$], $TiCl_4$ and $SnCl_4$) and at temperatures ranging from –60 °C→0 °C→50 °C led to the formation of the same product and in almost same yield. Instead of formation of the desired oxonium-ene cyclized product **61** (path A) it formed undesired spiro compound **62** (path B) as shown mechanistically in Scheme-16.

Scheme-16:



IR spectrum of **62** neither shows any band in the 3000-5000 cm^{-1} region nor any other intense band.

^{1}H NMR spectrum of **62** displayed following pattern. The multiplet ranging from δ 7.29-7.0 corresponded to four aromatic protons. The broad singlet present at δ 5.16, integrating for one proton was due to olefin proton. One sharp singlet at δ 4.99 integrating for one proton was attributed to H-2 proton. The spectrum displayed ABX pattern, where the H-10 bridged proton appeared as a doublet at δ 5.83 with coupling constant $J_{H10,H9a}$ = 3.42 Hz. AB type quartet appeared at δ 3.21 ($J_{H9a,H9b}$ = 17.09 Hz and $J_{H9a,H10}$ = 3.42 Hz), integrating for one proton, could be assigned to one of benzylic proton and the other appears at δ 2.86 ($J_{H9a,H9b}$ = 17.09 Hz). Here also one of the benzylic proton is situated at an angle of about 90° with H-10 proton. The multiplets' appearing at δ 1.91, 1.65-1.50 and 1.29 correspond to four methylene protons of A-ring. Two sharp intense singlets appearing at δ 1.69 and 1.13, integrating for three and six proton each correspond to vinyl methyl and geminal dimethyl respectively.

^{13}C NMR spectrum of **62** along with DEPT spectrum revealed the presence of five quaternary carbons, among which three downfield signals appearing at δ 136.7, 131.8 and 130.8 were assigned to two aromatic carbons and one olefin carbon. The other two quaternary carbons appearing at δ 89.1 and 38.7 corresponded to C-1 spiro and C-15 carbons respectively. The methine signals at δ 132.0, 28.6, 127.4, 125.1 and 124.9 were

attributed to four aromatic carbons and one olefin carbon and the other two methine signals at δ 100.2 and 77.7 were attributed to C-10 and acetal and C-2 carbons respectively. The three methylene signals at δ 36.3, 28.2 and 26.7 could be assigned to C-9, C-14 and C-15 accordingly. Lastly the upfield methyls at δ 26.7, 26.0 and 22.7 were attributed to vinyl methyl and geminal dimethyl groups respectively.

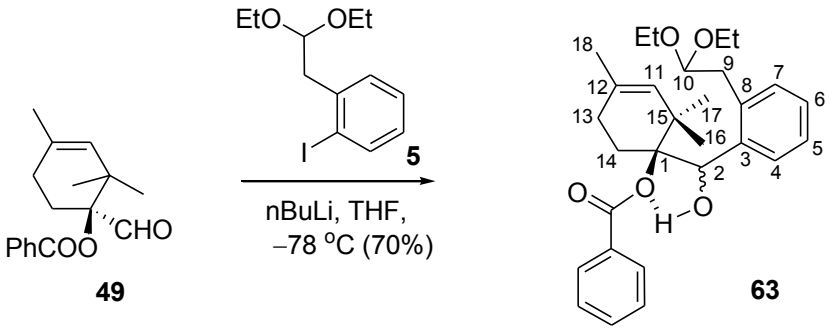
The mass spectrum of **62** showed molecular ion peak at 270, along with base peak at 131. The other major fragmentation peaks were at 255 (M–CH_3), 242, 227, 209, 165 and 145.

Finally the structure was confirmed by X-ray analysis. Crystal structure of **62** reveaed relative configuration as *1S** and *2S** which is present in naturally occurring taxol and also it firmly supports the proposed model for formation of single diastereomer in Scheme-15 and the assigned relative configuration of coupled product **60** (*1S*, 2S**).

Attempts to construct C-1 benzoate ABC skeleton of taxane

It is clear now, the C-1 hydroxyl attacks the oxonium-ion species generated instead of olefin (Scheme-16). So it was thought to protect the hydroxyl functionality in A-ring part and then do further coupling reaction and finally oxonium-ene cyclization. Since α-hydroxyl A-ring compound **50** was unstable and it is well known that tertiary alcohols need strong bases to protect them but the problem of dimerizations of α-hydroxy aldehyde under strong basic conditions experienced by Kuwajima group (Scheme-13), and therefore idea of protection was abandoned and it was thought to use in hand benzoate **49**, (Scheme-17) and then attempt the synthesis of C-1 hydroxyl ABC taxane system.

Scheme-17:



Thus, metallation of **5** using nBuLi in THF at –78 °C followed by the slow addition *via* canula to **49** in THF at –78 °C delivered a single diastereomers in 70% yield.

IR spectrum of **63** displayed a broad band at 3500 cm^{-1} and a sharp band at 1750

cm^{-1} indicative of the presence of hydroxyl and carbonyl functionality respectively in the molecule.

^{1}H NMR spectrum of **63** showed following pattern. A doublet at δ 8.12 (J = 8 Hz) integrating for two protons, multiplets at δ 7.8-7.6 integrating for six protons were assigned to aromatic protons. A singlet appearing at δ 6.54 integrating for one proton was attributed to carbinol proton. The vinylic proton appeared as a singlet at δ 4.97. The spectrum revealed ABX pattern. An acetal proton appeared at δ 5.13 as a doublet of doublet with coupling constants J_{XB} = 7.8 Hz and J_{XA} = 2.9 Hz. One of benzylic proton appeared at δ 3.04 as a doublet of doublet with coupling constants J_{AB} = 14.6 and J_{AX} = 2.9 Hz and the other one resonated at δ 3.04 as a doublet of doublet with coupling constants J_{AB} = 14.6 and J_{BX} = 7.8 Hz. The decoupling experiments confirmed ABX pattern assigned above. Thus irradiating at δ 4.96, AB quartets at δ 3.34 and 3.06 collapsed to a doublet, indicated coupling of H-10 with H-9A and H-9B. Another irradiation at δ 3.04, the AB quartet at δ 3.34 and 4.96 collapsed into a doublet thus revealing geminal and vicinal couplings.

^{13}C NMR of **63** along with DEPT spectra revealed the presence of five quaternary carbons; the most downfield signal which appeared at δ 164.5 was assigned to carbonyl carbon, the intense down field signal at δ 136.4 was attributed to two aromatic carbons and a signal at δ 135.9 was assigned to olefin carbon, while the last two peaks appearing at δ 74.3 and 40.2 correspond to C-1 and C-15 carbons respectively. The methine signals at δ 132.6, 132.3, 130.4, 129.4, 128.1, 127.3 and 126.1 were attributed to aromatics and one olefin carbon. The methine signal appeared at δ 102.7 was assigned to acetal (C-10) carbon. The carbinol (C-2) carbon appeared at δ 75.9. The two methylene carbons of ethoxy group resonated at δ 62.6 and 61.6 respectively. The signal that appeared at δ 37.5 could be assigned to benzylic carbon. The two upfield methylenes at δ 27.9 and 25.7 correspond to C-13 and C-14 respectively. The methyl carbons appeared at δ 26.7, 25.0, 22.5, 15.1 and 14.8 correspond to vinyl methyl, two methyls of $-OCH_2\underline{C}H_3$ and geminal dimethyls accordingly.

The mass spectrum of **63** revealed molecular ion peak at 466 and the other prominent peaks were observed at 420 (M–OEt), 375 (M–2xOEt), 298, 282 and 236.

Thus the ^{1}H NMR, ^{13}C NMR and mass spectra unambiguously prove the formation of a single a diastereomer of **63**.

Surprisingly the coupled product obtained here do not loose ethanol molecule to form trans hemiacetal product, which was observed in the previous coupling (Scheme-15). The reason may be due to hydrogen bonding of C-2 hydroxyl with adjacent benzoate carbonyl or there may exist a rotational barrier (C-1 and C-2), which prohibits C-2 hydroxyl and acetal groups coming closer.

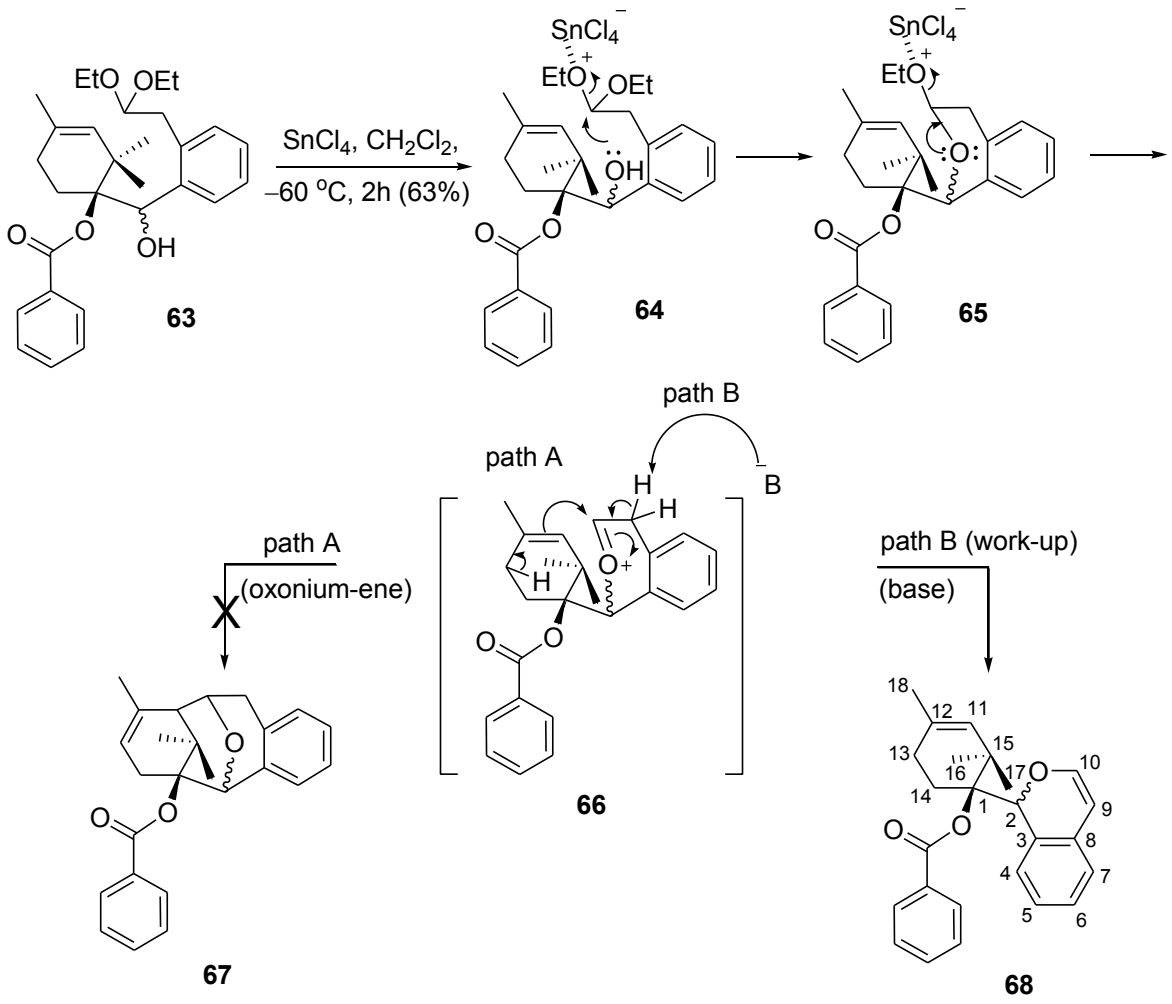
The coupled product **63** was subjected to react with freshly distilled $SnCl_4$ in CH_2Cl_2 at –60 °C to afford compound **68** instead of oxonium-ene cyclized product **67**. The structure was assigned by interpreting ^1H and ^{13}C NMR spectral data of product obtained. The formation of compound **68** may be explained as shown mechanistically in Scheme-17. After step-wise elimination of ethoxy moiety, oxonium ion (**66**) was generated but there was no attack of olefin to it (path-A) and therefore during work-up base abstracts a proton α to oxonium and forms 6-membered cyclic enol ether (path-B). The same result was obtained by performing the reaction at reflux temperature. The reason for failure of oxonium-ene cyclization may be due to unfavored transition state because of bulky C-1 benzoate group.

The ^1H NMR spectrum of **68** displayed following pattern. A doublet appeared at δ 7.99 (J = 8 Hz) and multiplets at δ 7.50-7.00 were attributed to aromatic protons. A doublet appeared at δ 6.61 with coupling constant (J = 8 Hz) was ascribed to C-10 olefin proton and it coupled with C-9 olefinic proton at δ 5.50 (J = 8 Hz). A sharp singlet appeared at δ 6.30 integrating for one proton corresponding to carbinol proton. An olefinic proton of A-ring part appeared at δ 5.11. A sharp singlet was observed at δ 1.70 integrating for three proton was assigned to vinylic methyl. And the singlets at δ 1.21 and 1.12, integrating for three protons each were assigned to the geminal dimethyls.

^{13}C NMR spectrum of **68** along with DEPT spectrum of compound displayed seven quaternary carbons. The signal that appeared at δ 164.8 corresponds to benzoate carbonyl. Four down field quaternary signals at δ 136, 132, 130.4 and 129.7 correspond to three aromatic and olefin carbon. Another two quaternary signals appeared at δ 82.3 and 40.5 were attributed to C-1 and C-16 respectively. The most down field methine carbon that appeared at δ 143.2 could be ascribed to C-10 olefin carbon. The other down field methine signals appeared at δ 132.2, 131.6, 130.7, 130.7, 130.5, 128.5, 128.2, 128.0 and 124.8 were attributed to aromatic and olefin carbons. The methine signals at δ 104.3 and 77.5 correspond to C-9 and C-2 carbons. The two methylene carbons appeared at δ

27.3 and 25.5 were assigned to C-13 and C-14 carbons. The methyl signals at δ 26.5, 26.0 and 22.7 could be ascribed to three methyl groups present in molecule.

Scheme-18:

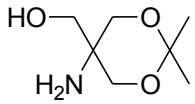


1.2.3 Conclusion:

The failure of oxonium-ene cyclization reaction in the construction of C-1 hydroxyl C-aromatic ABC taxane skeleton in the present work is surprising particularly when compared with earlier successful studies in the case of C-1 hydroxy-less B-seco taxane. It proves that C-1 hydroxyl certainly plays crucial role in the course of oxonium-ene cyclization step. However, it is believed that it could be executed with protected C-1 and C-2 hydroxyl group simultaneously, and the protecting group should withstand acidic conditions. Thus it is felt that boronate ester of AC coupled product may cyclize. The boronate ester formation not only will withstand in acidic conditions but also restrict rotation of C-1 and C-2 bond and facilate ene cyclization reaction. This hypothesis could not be ascertained due to paucity of time.

1.2.4 Experimental:

1.2.4.1 Preparation of (5-amino-2,2-dimethyl-1,3-dioxan-5-yl)methanol (42):[18]



42

To a solution of tris(hydroxymethyl)aminomethane hydrochloride (20.0 g, 125 mmol) in anhydrous DMF (140 mL) was added *p*TSA (1.8 g, 6 mmol) followed by 2,2-dimethoxy propane (16.9 mL, 138 mmol) in one portion. The resulting clear and colourless solution was allowed to stir overnight (12 h) at which time Et_3N (1.0 mL, 7.0 mmol) was added and allowed to stir for an additional 10 min. The mixture was concentrated *in vacuo* and treated with Et_3N (13.7 mL, 98.0 mmol) and EtOAc (500 mL). The white precipitate which was formed upon addition of the base was removed by filtration and the filtrate was concentrated *in vacuo* to afford **42** as a gum.

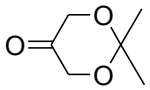
Chemical Formula: $C_7H_{15}NO_3$, 161

Yield: 13.331 g (65 %)

IR ($CHCl_3$): 3351 cm^{-1}

MS (m/z): 161(M^+), 143, 121

1.2.4.2 Preparation of 2,2-dimethyl-1,3-dioxan-5-one (43):[18]



43

To a cold (5 ^oC) solution containing (5-amino-2,2-dimethyl-1,3-dioxan-5-yl)methanol **42** (9.7 g, 60 mmol) and KH_2PO_4 (8.2 g, 60 mmol) in water (200 mL) was added dropwise *via* addition funnel a solution of $NaIO_4$ (12.8 g, 60.0 mmol) in water (175 mL). Upon completion (approx. 3 h) the reaction mixture was allowed to stir for an additional hour at 5 ^oC and then at room temperature. $Na_2S_2O_3$ (14.8 g, 60.0 mmol) was added, and resulting solution was allowed to stir for approximately 15 min. and extracted with CH_2Cl_2 (15 x 50 mL). The organic phases were dried (anhydrous Na_2SO_4), filtered, concentrated *in vacuo*, and purified by distillation to afford **43** as a clear and colouress oil.

Chemical Formula: $C_6H_{10}O_3$, 130

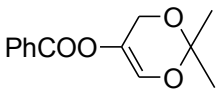
Yield: 5.874 g (75%)

IR ($CHCl_3$): 1752 cm^{-1}

MS (m/z): 153 $(M+Na)^+$, 138, 130

^{1}H NMR ($CDCl_3$, 200 MHz): 4.14 (s, 4H), 1.44 (s, 6H).

1.2.4.3 Preparation of 2,2-dimethyl-4*H*-1,3-dioxin-5-yl benzoate (44):[18]



44

To a cold (0 ^oC) solution of 2,2-dimethyl-5-oxo-1,3-dioxane **43** (5.0 g, 38.46 mmol) and DMAP (9.384 g, 76.92 mmol), in CH_2Cl_2 (50 mL) was added benzoyl chloride (6.7 mL, 57.69 mmol). The resulting mixture was stirred for 10 minutes and triethylamine (21.40 mL, 153.84 mmol) was added. The reaction mixture was stirred for 36 hours at room temperature. The reaction mixture was extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the crude residue on silica gel (95:5 pet. ether-EtOAc) yielded **44** as a yellow oil.

Chemical Formula: $C_{13}H_{14}O_4$, 234

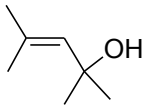
Yield: 7.470 g (83 %)

IR ($CHCl_3$): 1711 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.10 (d, 2H, *J* = 7.1 Hz), 7.62 (t, 1H, *J* = 7.1 Hz), 7.47 (t, 2H, *J* = 7.1 Hz), 6.64 (t, 1H, *J* = 1.5 Hz), 4.36 (d, 2H, *J* = 1.5 Hz), 1.50 (s, 6H).

MS (m/z): 373 $(M+Na)^+$, 238, 233, 177

1.2.4.4 Preparation of 2,4-dimethylpent-3-en-2-ol (46):[19]



46

Methyl magnesium iodide was freshly prepared from magnesium turnings (6.00 g, 250 g. atom), pinch of iodine (0.02 g) and methyl iodide (35.5 g, 250 mmol) in dry ether (100 ml). The organomagnesium reagent was diluted with ether (150 ml) and chilled to 0 ^oC. Mesityl oxide **45** (24.5 g, 250 mmol) was added in such away that temperature did not exceed 2 ^oC. After addition was over (3 h), the reaction mixture was stirred for additional 6 h at room temperature and refluxed for 2 h and left overnight at room temperature. The reaction was quenched by pouring reaction mixture slowly to a

cold saturated NH_4Cl solution (18 ml) and was extracted with ether (250 ml x 3). After concentration, the compound **46** was purified by distillation.

Chemical Formula: $C_7H_{14}O$, 114

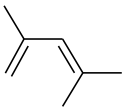
Yield: 20.52g (72%)

B.P.: 132-135 ^oC

IR (Neat): 3450, 2850, 1420, 1310, 1250, 1110 cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz): δ 5.20 (bs, 1H), 1.80 (s, 3H), 1.60 (s, 3H), 1.30 (s, 6H).

1.2.4.5 Preparation of 2,4-dimethylpenta-1,3-diene (47):[19]



47

Into a two necked 250 ml round bottom flask fitted with distillation condenser having a flow of ice cold water and a dropping funnel, was taken potassium hydrogen sulfate (30 g). The flask was heated to 120 ^oC in an oil bath and the compound **46** (117.0 g) was dropped into the flask at a rate of 1 ml per min. The diene **47** was collected in another flask along with water and it was separated from water by separating funnel and dried over anhydrous Na_2SO_4. It was purified by distillation (92-98 ^oC) over sodium to furnish **47** as clear oil.

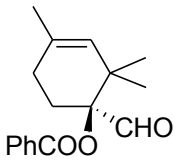
Chemical Formula: C_7H_{12}, 96

Yield: 87.0 g (60%)

IR (Neat): 3000, 1600, 1450, 1380, 900 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ 5.40 (s, 1H), 4.80 (s, 1H), 4.60 (s, 1H), 1.85 (s, 9H).

1.2.4.6 Preparation of 1-formyl-2,2,4-trimethylcyclohex-3-enyl benzoate (49):



49

To a solution of 2,2-dimethyl-4*H*-1,3-dioxin-5-yl benzoate **44** (5 g, 21.26 mmol) in CH_2Cl_2 (10 mL) at room temperature was added 2,4-dimethyl-1,3-pentadiene (5 mL, 32.04 mmol). The resulting solution was sealed in a seal-tube, which was further kept in

a steel bomb in an oven at 110 ^{o}C for 12 h. The solvent was removed by distillation. Purification of the crude residue by high vacuum distillation afforded **49** as a clear oil.

Chemical Formula: $C_{17}H_{20}O_3$, 272

Yield: 3.196 g (55 %)

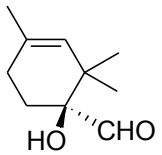
IR (Neat): ν 1705 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.86 (s, 1H), 8.04-8.00 (m, 2H), 7.64-7.57 (m, 1H), 7.46 (m, 2H), 5.08 (s, 1H), 2.50-2.20 (m, 2H), 2.00-1.90 (m, 2H), 1.69 (s, 3H), 1.27 (s, 3H), 1.03 (s, 3H)

^{13}C NMR ($CDCl_3$, 50 MHz): 199.0 (C), 170.5 (CH), 165.1 (C), 132.9 (CH), 132.8 (CH), 130.0 (C), 129.0 (C), 129.05 (CH), 127.9 (CH), 127.7 (CH), 86.3 (C), 37.9 (C), 25.9 (CH_3), 25.6 (CH_2), 23.7 (CH_3), 22.3 (CH_3), 21.5 (CH_2).

MS (m/z): 273 $(M+1)^+$, 238, 233, 177

1.2.4.7 Preparation of 1-hydroxy-2,2,4-trimethylcyclohex-3-enecarbaldehyde (50):



50

To a solution of 1-formyl-2,2,4-trimethylcyclohex-3-enyl benzoate (**49**) (0.666 g, 2.45 mmol) in methanol (50 mL) was added $LiOH.H_2O$ (0.154 g, 3.67 mmol) and the reaction mixture was stirred for 3 h at room temperature. After completion of the reaction it was concentrated *in vacuo*, extracted with ether (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* and the residue obtained was purified by flash column chromatography (230-400 mesh silica gel, 97:3 pet. ether-EtOAc) afforded **50** as a colourless oil.

Chemical Formula: $C_{10}H_{16}O_2$, 168

Yield: 0.350 g (50 %)

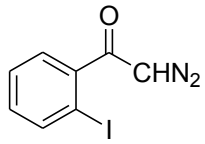
IR (Neat): ν 3500, 1717 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.81 (s, 1H), 5.22 (s, 1H), 2.9-1.8 (m, 4H), 1.71 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 205.9, 130.9, 130.4, 79.4, 37.7, 28.1, 27.7, 2 x 24.7, 22.8.

MS (m/z): 168 $(M)^+$, 150, 140, 139, 122, 107, 96, 91, 81, 67, 55.

1.2.4.8 Preparation of 2-Iodo-α-diazoacetophenone (55):



55

To a suspension of **54** (4.90 g, 20 mmol) in benzene (20 ml) at 0 ^{o}C was added thionyl chloride (3.6 ml, 30 mmol) dropwise. After completion of the addition, the reaction mixture was refluxed for 3 h. The excess thionyl chloride and benzene were removed by distillation. This acid chloride solution in benzene (10 ml) was added to ethereal solution of diazomethane (40 mmol in 100 ml ether) at –20 ^{o}C. After being stirred for 3 h, the mixture was allowed to warm to room temperature and stirred over night to remove excess diazomethane. The solid obtained was removed by filtration and the filtrate was concentrated *in vacuo*, and the residue obtained was purified by silica gel column chromatography using 12 % ethylacetate and pet. ether mixture as eluent afforded **55** as a pale yellowish solid.

Chemical Formula: $C_8H_5IN_2O$, 272

Yield: 4.40 g (81%)

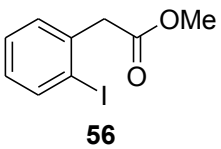
M.P.: 59-60 ^{o}C (Lit[21] 61-62 ^{o}C).

IR (Neat): 3103, 2103, 1618, 1461, 1350, 1216, 1098 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.90 (d, *J* = 7.9 Hz, 1H), 7.50-7.30 (m, 2H), 7.20-7.10 (m, 1H), 5.60 (s, 1H).

MS (m/e): 272 (3), 244 (43), 127 (14), 89 (100), 76 (19), 63 (41).

1.2.4.9 Preparation of methyl 2-(2-iodophenyl)acetate (56):



56

To a warm solution of **55** (5.44 g, 20 mmol) in methanol (100 ml) at 60 ^{o}C was added a solution of silverbenzoate (0.182 g, 0.8 mmol) in triethyl amine (2 ml) during 15 min and was refluxed for 45 min. After completion of reaction (1 h), it was filtered through a small pad of celite and the resultant filtrate was concentrated under reduced pressure. Purification of the residue by column chromatography with 5% ethylacetate in pet. ether gave **56** as colourless oil.

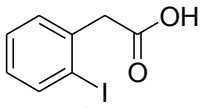
Chemical Formula: $C_9H_9IO_2$, 276

Yield: 4.35 g (75%)

IR (neat): 2950, 1730, 1570, 1450, 1340, 1220, 1160, 1040 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz,): δ 7.85 (d, *J* = 8.3 Hz, 1H), 7.30-7.25 (m, 2H), 7.00-6.90 (m, 1H), 3.76 (s, 2H), 3.4 (s, 3H).

1.2.4.10 Preparation of 2-(2-iodophenyl)acetic acid (56a):



56a

A solution of **56** (5.80 g, 20 mmol) with 2.40 g of NaOH in 2:1 water ethanol (30 ml) was refluxed for 3 h. After cooling to room temperature, the reaction mixture was neutralized by dilute HCl and the aqueous layer was extracted with chloroform (30 ml x 3). The organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* to furnish **56a** as a pale yellow solid.

Chemical Formula: $C_8H_7IO_2$, 262

Yield: 5.10 g (97%)

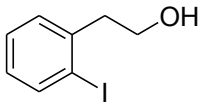
M.P.: 115-116 ^oC, (Lit[21] 117-119 ^oC)

IR ($CHCl_3$): 2900, 1697, 1450, 1220 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.85 (d, *J* = 7.8 Hz, 1H), 7.40-7.30 (m, 2H), 7.05-6.95 (m, 1H), 3.90 (s, 2H).

MS (m/e): 262 (M^+, 43), 217 (44), 135 (76), 107 (42), 90 (100).

1.2.4.11 Preparation of 2-(2-iodophenyl)ethanol (57):



57

To a solution of **56a** (2.62 g, 10 mmol) in THF (5 ml) was slowly introduced borane.THF complex in THF (6 ml, 2M) over a period of 20 min. After vigorous stirring for 2 h at room temperature, the excess hydride was carefully destroyed with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 25 mL) and combined layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and solvent was removed *in vacuo* to yield **57** as a pale yellow solid.

Chemical Formula: C_8H_9IO, 248

Yield: 2.36 g (95%)

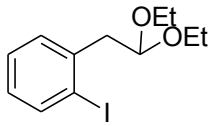
M.P.: 63-64 ^oC, (Lit[21] mp 65 ^oC)

IR ($CHCl_3$): 3338, 2947, 1585, 1561, 1465, 1434, 1164 cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz): δ 7.85 (d, *J* = 7.8 Hz, 1H), 7.30-7.20 (m, 2H), 6.95-6.85 (m, 1H), 3.90 (t, *J* = 6.8 Hz, 2H), 3.05 (t, *J* = 6.7 Hz, 2H).

MS (m/e): 248 (M^+, 30), 217 (47), 121 (100), 91 (84).

1.2.4.12 Preparation of 1-(2,2-diethoxyethyl)-2-iodobenzene (5):



5

To a solution of Dess-Martin reagent (4.24 g, 10 mmol) in CH_2Cl_2 (50 ml) was added solution of **57** (2.48 g, 10 mmol) dissolved in CH_2Cl_2 (20 ml) during a period of 5 min and the contents were allowed to stir for additional 1 h. The reaction mixture was concentrated and purified by column chromatography using 4% ethylacetate and pet. ether mixture as eluent to furnish 2-iodophenylacetaldehyde (2.00 g, 92%) as a pale yellow oil and was subjected to further reaction without characterization.

A mixture of 2-iodophenylacetaldehyde (2.00 g, mmol), triethylorthoformate (20 ml, mmol) and ethanol (10 ml) were refluxed for 2 h in presence of *p*TSA (0.10 g). Excess ethanol and triethylorthoformate were removed by distillation under reduced pressure. The residue was diluted with $CHCl_3$ (20 ml) and neutralized by aqueous saturated $NaHCO_3$ solution (10 ml). After concentration, the residue was purified by flash column chromatography (230-400 mesh size silica gel) 2% ethyl acetate and pet. ether mixture as mobile phase to give **5** as light yellow oil.

Chemical Formula: $C_{12}H_{17}IO_2$, 320

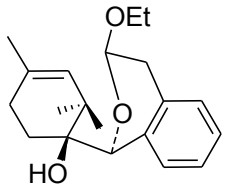
Yield: 2.50 g (96%)

IR (Neat): 2973, 2927, 1562, 1437, 1372, 1118, 1062 cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz): δ 7.80 (d, *J* = 8.6 Hz, 1H), 7.35-7.25 (m, 2H), 6.95-6.85 (m, 1H), 4.70 (t, *J* = 5.7 Hz, 1H), 3.75-3.60 (m, 2H), 3.50-3.40 (m, 2H), 3.10 (d, *J* = 5.7 Hz, 2H), 1.25-1.10 (m, 6H).

MS (m/e): 306 (5), 275 (100), 261 (38), 247 (54), 217 (88), 119 (99).

1.2.4.13 Coupling of 5 with 50: Synthesis of 60



60

Magnesium alkoxide **59** was prepared by treatment of **50** (0.100 g, 0.6 mmol) in ether (25 mL) with *t*-butylmagnesium chloride (0.070 g, 0.6 mmol) at –78 ^{o}C for 1 h. In a separate two neck 100 mL RB flask, nBuLi (0.0768 g, 1.2 mmol) was added to a mixture of 2-Iodophenylacetaldehyde diethyl acetal (**5**) (0.384 g, 1.2 mmol) in THF (15 mL) at –78 ^{o}C and the mixture was stirred for 1 h and was added *via* canula to magnesium alkoxide **59** –78 ^{o}C. The mixture was stirred for 2 h at –78 ^{o}C. The reaction was quenched with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The resultant residue was purified by flash column chromatography (230-400 mesh size silica gel, 5% EtOAc/pet. ether, gradient elution) to afford alcohol **60** as a white solid.

Chemical Formula: $C_{20}H_{28}O_3$, 316

Yield: 0.163 g (70%)

M.P.: 170-172 ^{o}C

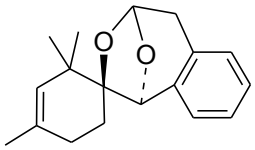
IR ($CHCl_3$): ν 3271, 1455, 1398 cm^{-1}

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.26 (dd, *J* = 12.32, 5.16 Hz, 1H), 7.16 (dd, *J* = 13.51, 7.15 Hz, 2H), 7.03 (d, *J* = 7.15 Hz, 1H), 5.84 (d, *J* = 3.57 Hz, 1H), 5.16 (s, 1H), 5.01 (s, 1H), 3.74 (q, *J* = 5 Hz, 2H), 3.17 (dd, *J* = 17.08, 3.18 Hz, 1H), 2.85 (d, *J* = 17.09 Hz, 1H), 1.97-1.83 (m, 2H), 1.60 (s, 3H), 1.50 (t, *J* = 5 Hz, 3H), 1.20-1.16 (m, 1H), 1,14 (s, 6H)

^{13}C NMR ($CDCl_3$, 125 MHz): δ 136.7 (C), 131.9 (CH), 131.7 (C), 130.9 (C), 128.6 (CH), 127 (CH), 125.1(CH), 124.9 (CH), 100.3 (CH), 89.2 (C), 77.79 (C), 58 (CH_2), 38.7 (C), 36.3 (CH_2), 28.1 (CH_2), 26.8 (CH_2), 26.8 (CH_3), 25.8 (CH_3), 22.7 (CH_3), 18.1 (CH_3)

MS (m/z): 316 $(M)^+$, 298, 280, 270, 254, 227, 209, 195, 177, 164.

1.2.4.14 Oxonium-Ene Reaction: Formation of 62



62

To a stirring solution of acetal **60** (0.100 g, 0.3 mmol) in CH_2Cl_2 (50 ml) under nitrogen atmosphere at –60 ^oC was added a solution $SnCl_4$ (1 ml, 1M) in CH_2Cl_2. During the addition of $SnCl_4$ solution, the reaction mixture developed a dark reddish color. After stirring for 2 h, triethyl amine (3 ml) was added and stirred for additional 1 h. After completion of reaction, it was quenched by adding saturated aqueous NH_4Cl solution (5 ml) and was extracted with CH_2Cl_2 (2 x 10 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* and the residue obtained was purified by flash column chromatography (230-400 mesh size silica gel, using 3% ethyl acetate in pet. ether as eluent to yield **121** as white crystalline solid.

Chemical Formula: $C_{18}H_{22}O_2$, 270

Yield: 0.072 g (85%)

M.P.: 165-168 ºC

IR ($CHCl_3$): ν 2850, 1420, 1350, 1200, 1040 cm^{-1}

^{1}H NMR (200 MHz): δ 7.29-7.00 (m, 4H), 5.83 (d, *J* = 3.42 Hz, 1H), 5.16 (s, 1H), 4.99 (s, 1H), 3.21 (dd, *J* = 17.09, 3.42 Hz, 1H), 2.86 (d, *J* = 17.09 Hz, 1H), 1.91 (m, 2H), 1.69 (s, 3H), 1.65-1.50 (m, 1H), 1.29 (m, 1H), 1.13 (6H)

^{13}C NMR (50 MHz): δ 136.7 (C), 132.0 (CH), 131.8 (C), 130.8 (C), 128.6 (CH), 127.4 (CH), 125.1 (CH), 124.9 (CH), 100.2 (CH), 89.1 (C), 77.7 (CH), 38.7 (C), 36.3 (CH_2), 28.2 (CH_2), 26.7 (CH_2), 26.7 (CH_3), 26.0 (CH_3), 22.7 (CH_3)

MS (m/z): 270 $(M)^+$, 255, 242, 227, 145, 131, 104, 95, 81

Anal. Calcd. For $C_{18}H_{22}O_2$: C, 79.96; H, 8.20; O, 11.84 Found C, 79.63; H, 8.01%

Crystal Data of 62

Table 1. Crystal data and structure refinement for **62**

Identification code	62
Empirical formula	C_{18} H_{22} O_2
Formula weight	270.36
Temperature	297(2) K
Wavelength	0.71073 Å

Crystal system, space group	Monoclinic, C2/c
Unit cell dimensions	a = 29.288(4) Å alpha = 90º.
	b = 5.6744(8) Å beta = 122.440(2)º.
	c = 21.006(3) Å gamma = 90º.
Volume	2946.2(7) $Å^3$
Z, Calculated density	8, 1.219 Mg/m^3
Absorption coefficient	0.078 mm^{-1}
F(000)	1168
Crystal size	0.58 x 0.30 x 0.27 mm
Theta range for data collection	1.65 to 25.00º.
Limiting indices	-34<=h<=34, -6<=k<=6, -24<=l<=24
Reflections collected / unique	13174 / 2596 [R(int) = 0.0265]
Completeness to theta = 25.00	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9794 and 0.9564
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2596 / 0 / 184
Goodness-of-fit on F^2	1.086
Final R indices [I>2sigma(I)]	R1 = 0.0459, wR2 = 0.1204
R indices (all data)	R1 = 0.0507, wR2 = 0.1245
Largest diff. peak and hole	0.239 and -0.194 e. $Å^{-3}$

Table 2. Bond lengths [Å] and angles [deg] for **62**

O(1)-C(10)	1.4244(18)
O(1)-C(1)	1.4475(17)
O(2)-C(10)	1.4124(19)
O(2)-C(2)	1.4374(16)
C(1)-C(15)	1.527(2)
C(1)-C(11)	1.554(2)
C(1)-C(2)	1.5558(19)
C(2)-C(3)	1.5093(19)
C(2)-H(2)	0.9800
C(3)-C(4)	1.387(2)
C(3)-C(8)	1.394(2)
C(4)-C(5)	1.381(2)
C(4)-H(4)	0.9300
C(5)-C(6)	1.372(3)
C(5)-H(5)	0.9300
C(6)-C(7)	1.383(3)
C(6)-H(6)	0.9300

C(7)-C(8)	1.388(2)
C(7)-H(7)	0.9300
C(8)-C(9)	1.517(2)
C(9)-C(10)	1.507(2)
C(9)-H(9A)	0.9700
C(9)-H(9B)	0.9700
C(10)-H(10)	0.9800
C(11)-C(12)	1.510(2)
C(11)-C(16)	1.536(2)
C(11)-C(17)	1.544(2)
C(12)-C(13)	1.325(2)
C(12)-H(12)	0.9300
C(13)-C(14)	1.484(3)
C(13)-C(18)	1.507(2)
C(14)-C(15)	1.523(2)
C(14)-H(14A)	0.9700
C(14)-H(14B)	0.9700
C(15)-H(15A)	0.9700
C(15)-H(15B)	0.9700
C(16)-H(16A)	0.9600
C(16)-H(16B)	0.9600
C(16)-H(16C)	0.9600
C(17)-H(17A)	0.9600
C(17)-H(17B)	0.9600
C(17)-H(17C)	0.9600
C(18)-H(18A)	0.9600
C(18)-H(18B)	0.9600
C(18)-H(18C)	0.9600
C(10)-O(1)-C(1)	108.33(10)
C(10)-O(2)-C(2)	101.52(10)
O(1)-C(1)-C(15)	108.48(12)
O(1)-C(1)-C(11)	109.44(11)
C(15)-C(1)-C(11)	109.32(11)
O(1)-C(1)-C(2)	101.05(10)
C(15)-C(1)-C(2)	114.27(12)
C(11)-C(1)-C(2)	113.80(11)
O(2)-C(2)-C(3)	107.56(11)
O(2)-C(2)-C(1)	101.75(10)
C(3)-C(2)-C(1)	112.99(11)
O(2)-C(2)-H(2)	111.4
C(3)-C(2)-H(2)	111.4
C(1)-C(2)-H(2)	111.4
C(4)-C(3)-C(8)	119.97(14)
C(4)-C(3)-C(2)	122.47(14)
C(8)-C(3)-C(2)	117.56(13)
C(5)-C(4)-C(3)	120.41(17)
C(5)-C(4)-H(4)	119.8
C(3)-C(4)-H(4)	119.8
C(6)-C(5)-C(4)	119.84(17)
C(6)-C(5)-H(5)	120.1

C(4)-C(5)-H(5)	120.1
C(5)-C(6)-C(7)	120.16(17)
C(5)-C(6)-H(6)	119.9
C(7)-C(6)-H(6)	119.9
C(6)-C(7)-C(8)	120.80(17)
C(6)-C(7)-H(7)	119.6
C(8)-C(7)-H(7)	119.6
C(7)-C(8)-C(3)	118.71(15)
C(7)-C(8)-C(9)	122.02(15)
C(3)-C(8)-C(9)	119.22(14)
C(10)-C(9)-C(8)	111.26(13)
C(10)-C(9)-H(9A)	109.4
C(8)-C(9)-H(9A)	109.4
C(10)-C(9)-H(9B)	109.4
C(8)-C(9)-H(9B)	109.4
H(9A)-C(9)-H(9B)	108.0
O(2)-C(10)-O(1)	105.89(12)
O(2)-C(10)-C(9)	110.52(12)
O(1)-C(10)-C(9)	110.34(13)
O(2)-C(10)-H(10)	110.0
O(1)-C(10)-H(10)	110.0
C(9)-C(10)-H(10)	110.0
C(12)-C(11)-C(16)	109.14(12)
C(12)-C(11)-C(17)	108.75(12)
C(16)-C(11)-C(17)	107.13(12)
C(12)-C(11)-C(1)	108.66(11)
C(16)-C(11)-C(1)	112.70(12)
C(17)-C(11)-C(1)	110.39(12)
C(13)-C(12)-C(11)	125.68(15)
C(13)-C(12)-H(12)	117.2
C(11)-C(12)-H(12)	117.2
C(12)-C(13)-C(14)	121.55(15)
C(12)-C(13)-C(18)	121.95(18)
C(14)-C(13)-C(18)	116.48(16)
C(13)-C(14)-C(15)	114.82(13)
C(13)-C(14)-H(14A)	108.6
C(15)-C(14)-H(14A)	108.6
C(13)-C(14)-H(14B)	108.6
C(15)-C(14)-H(14B)	108.6
H(14A)-C(14)-H(14B)	107.5
C(14)-C(15)-C(1)	112.14(13)
C(14)-C(15)-H(15A)	109.2
C(1)-C(15)-H(15A)	109.2
C(14)-C(15)-H(15B)	109.2
C(1)-C(15)-H(15B)	109.2
H(15A)-C(15)-H(15B)	107.9
C(11)-C(16)-H(16A)	109.5
C(11)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(11)-C(16)-H(16C)	109.5

H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
C(11)-C(17)-H(17A)	109.5
C(11)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
C(11)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
C(13)-C(18)-H(18A)	109.5
C(13)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(13)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5

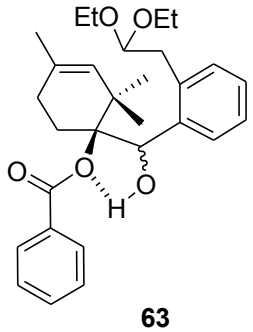
Symmetry transformations used to generate equivalent atoms

Table 3. Torsion angles [deg] for **62**

C(10)-O(1)-C(1)-C(15)	127.21(13)
C(10)-O(1)-C(1)-C(11)	-113.58(12)
C(10)-O(1)-C(1)-C(2)	6.76(14)
C(10)-O(2)-C(2)-C(3)	-73.58(13)
C(10)-O(2)-C(2)-C(1)	45.39(13)
O(1)-C(1)-C(2)-O(2)	-31.94(12)
C(15)-C(1)-C(2)-O(2)	-148.19(12)
C(11)-C(1)-C(2)-O(2)	85.25(13)
O(1)-C(1)-C(2)-C(3)	83.09(13)
C(15)-C(1)-C(2)-C(3)	-33.17(16)
C(11)-C(1)-C(2)-C(3)	-159.72(11)
O(2)-C(2)-C(3)-C(4)	-140.72(14)
C(1)-C(2)-C(3)-C(4)	107.79(16)
O(2)-C(2)-C(3)-C(8)	40.03(16)
C(1)-C(2)-C(3)-C(8)	-71.46(15)
C(8)-C(3)-C(4)-C(5)	2.7(2)
C(2)-C(3)-C(4)-C(5)	-176.52(14)
C(3)-C(4)-C(5)-C(6)	0.1(3)
C(4)-C(5)-C(6)-C(7)	-2.2(3)
C(5)-C(6)-C(7)-C(8)	1.5(3)
C(6)-C(7)-C(8)-C(3)	1.3(2)
C(6)-C(7)-C(8)-C(9)	-176.33(15)
C(4)-C(3)-C(8)-C(7)	-3.3(2)
C(2)-C(3)-C(8)-C(7)	175.94(13)
C(4)-C(3)-C(8)-C(9)	174.33(14)
C(2)-C(3)-C(8)-C(9)	-6.4(2)
C(7)-C(8)-C(9)-C(10)	-175.71(14)
C(3)-C(8)-C(9)-C(10)	6.7(2)
C(2)-O(2)-C(10)-O(1)	-42.45(14)
C(2)-O(2)-C(10)-C(9)	77.05(13)
C(1)-O(1)-C(10)-O(2)	21.54(15)
C(1)-O(1)-C(10)-C(9)	-98.08(13)

C(8)-C(9)-C(10)-O(2)	-42.57(17)
C(8)-C(9)-C(10)-O(1)	74.21(16)
O(1)-C(1)-C(11)-C(12)	-170.13(11)
C(15)-C(1)-C(11)-C(12)	-51.44(15)
C(2)-C(1)-C(11)-C(12)	77.66(14)
O(1)-C(1)-C(11)-C(16)	68.78(14)
C(15)-C(1)-C(11)-C(16)	-172.53(12)
C(2)-C(1)-C(11)-C(16)	-43.43(16)
O(1)-C(1)-C(11)-C(17)	-50.96(15)
C(15)-C(1)-C(11)-C(17)	67.73(15)
C(2)-C(1)-C(11)-C(17)	-163.17(12)
C(16)-C(11)-C(12)-C(13)	147.18(15)
C(17)-C(11)-C(12)-C(13)	-96.27(18)
C(1)-C(11)-C(12)-C(13)	23.9(2)
C(11)-C(12)-C(13)-C(14)	-0.8(2)
C(11)-C(12)-C(13)-C(18)	-179.14(15)
C(12)-C(13)-C(14)-C(15)	6.5(2)
C(18)-C(13)-C(14)-C(15)	-175.06(14)
C(13)-C(14)-C(15)-C(1)	-36.38(19)
O(1)-C(1)-C(15)-C(14)	178.95(12)
C(11)-C(1)-C(15)-C(14)	59.66(16)
C(2)-C(1)-C(15)-C(14)	-69.19(16)

1.2.4.15 Coupling of 49 with 5: Preparation of 63



63

To a stirring solution of 2-Iodophenylacetaldehyde diethyl acetal (0.832 g, 2.601 mmol) in THF (25 ml) under nitrogen atmosphere at –78 ^{o}C was added n-BuLi (1.73 ml, 2.601 mmol, 1.5M) during a period of 15 min while stirring for 1h. In an another flask charged with 1-formyl-2,2,4-trimethylcyclohex-3-enyl benzoate **49** (0.236 g, 0.867 mmol) in THF (15 mL) and kept at –78 ^{o}C for 15 min was added above lithiated mixture *via* canula at once. The reaction mixture was kept stirring until complete consumption of the starting materials was indicated by TLC analysis (~60 min). The reaction was quenched by adding saturated aqueous NH_4Cl solution (10 mL), organic layer was separated, aqueous layer was extracted with ether (3 x 20 mL), washed with brine, dried over anhydrous Na_2SO_4, filtered concentrated *in vacuo*, and the residue thus obtained

was purified by flash column chromatography (230-400 mesh size silica gel, 10% ethyl acetate/pet. ether, gradient elution), which provided **63** as a gummy oil.

Chemical Formula: $C_{29}H_{38}O_5$, 466

Yield: 0.283 g (70 %)

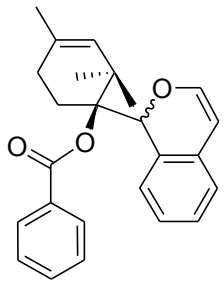
IR ($CHCl_3$): ν 3500, 1750 cm^{-1}

^{1}H NMR (200 MHz): δ 8.12 (d, *J* = 8 Hz, 2H), 7.8-7.6 (m, 1H), 7.6-7.2 (m, 6H), 6.50 (s, 1H), 5.13 (dd, *J* = 7.8, 2.9 Hz, 1H), 4.97 (s, 1H), 3.90-3.67 (m, 2H), 3.45-3.30 (m, 2H), 3.25 (dd, *J* = 14.6, 2.9 Hz, 1H), 3.04 (dd, *J* = 14.6, 7.8 Hz, 1H), 2.10 (s, 1H), 1.66 (s, 3H), (1.32-1.06 (m, 12H)

^{13}C NMR (50 MHz): δ 164.5 (C), 136.4 (C), 135.9 (C), 132.6 (CH), 132.3 (CH), 130.4 (CH), 129.4 (CH), 128.1 (CH), 127.3 (CH), 125.1 (CH), 102.7 (CH), 75.9 (CH), 74.2 (C), 63.6 (CH_2), 61.6 (CH_2), 40.2 (C), 37.6 (CH_2), 27.9 (CH_2), 26.7 (CH_3), 25.5 (CH_2), 25.0 (CH_3), 22.5 (CH_3), 15.1 (CH_3), 14.8 (CH_3)

MS (m/z): 466 (M^+), 420, 375, 298, 282, 249, 236

1.2.4.16 Oxonium-ene reaction: Formation of 68



68

To a stirred solution of **63** (0.100 g, 0.21 mmol) in CH_2Cl_2 (50 ml) under nitrogen atmosphere at –60 ^oC was added a solution $SnCl_4$ (0.75 ml, 0.75 mmol, 1M) in CH_2Cl_2. During the addition of $SnCl_4$ solution, the reaction mixture developed a dark reddish colour. After stirring for 2 h, triethyl amine (3 ml) was added and stirred for additional 1 h. After completion of reaction, it was quenched by adding saturated aqueous NH_4Cl solution (5 ml) and was extracted with CH_2Cl_2 (2 x 10 ml). Organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* and the residue obtained was purified by flash column chromatography (230-400 mesh size silica gel) using 3% ethyl acetate and pet. ether as eluent to yield **68** as a oil.

Chemical Formula: $C_{25}H_{26}O_3$, 374

Yield: 0.050 g, (62.5 %)

^{1}H NMR (200 MHz): δ 7.99 (d, *J* = 8 Hz, 2H), 7.50-7.00 (m, 7H), 6.61 (d, *J* = 8 Hz, 1H), 6.30 (s, 1H), 5.50 (d, *J* = 8 Hz, 1H), 5.11 (s, 1H), 1.75 (s, 1H), 1.70 (s, 3H), 1.65-1.40 (m, 2H), 1.31 (m, 1H), 1.21 (s, 3H), 1.12 (s, 3H)

^{13}C NMR (50 MHz): 164.8 (C), 143.2 (CH), 136.0 (C), 132.5 (C), 132.2 (CH), 131.6 (CH), 130.7 (CH), 130.5 (CH), 130.4 (C), 129.7 (C), 2x128.5 (CH), 2x128.2 (CH), 128.0 (CH), 124.8 (CH), 104.3 (CH), 82.3 (C), 77.5 (CH), 40.5 (C), 27.3 (CH_2), 26.5 (CH_3), 26.0 (CH_3), 25.5 (CH_2), 22.7 (CH_3).

1.2.5 References:

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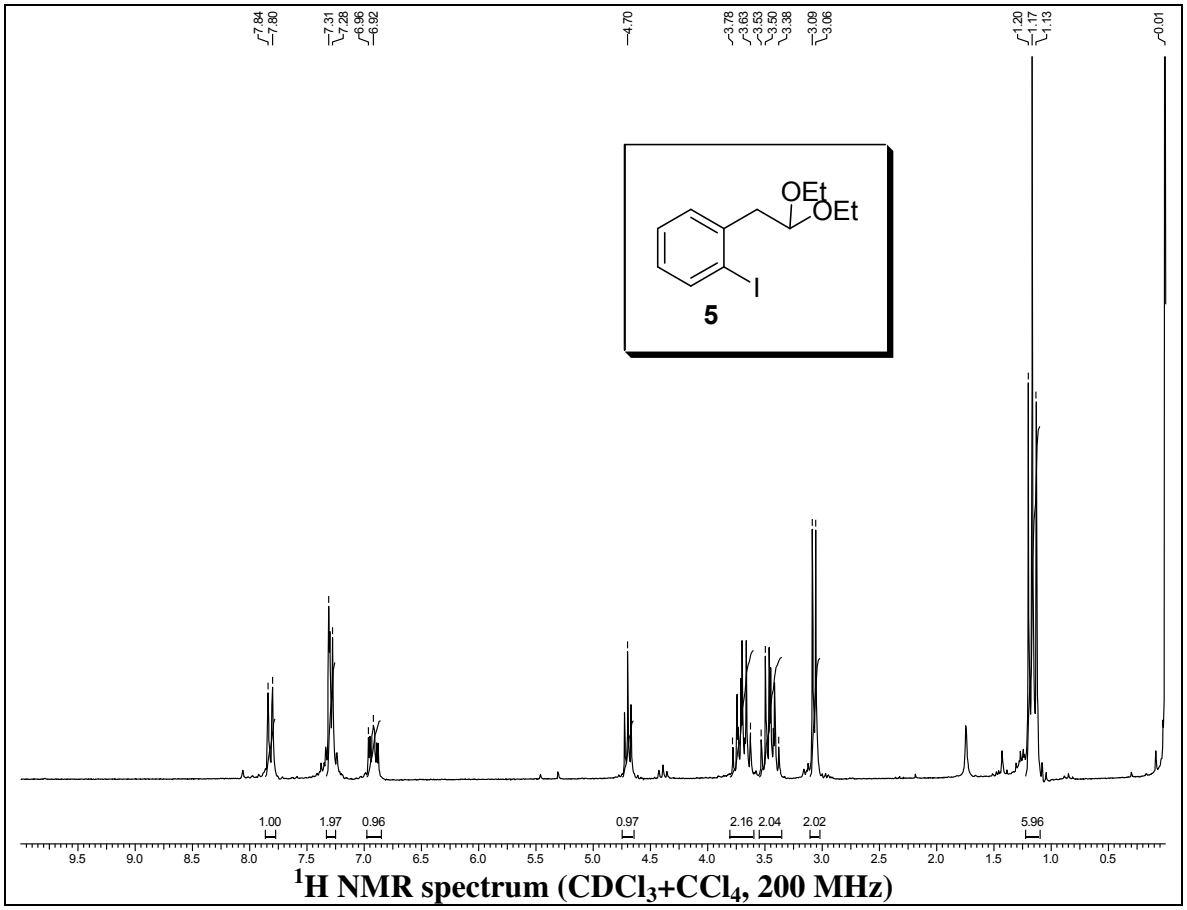
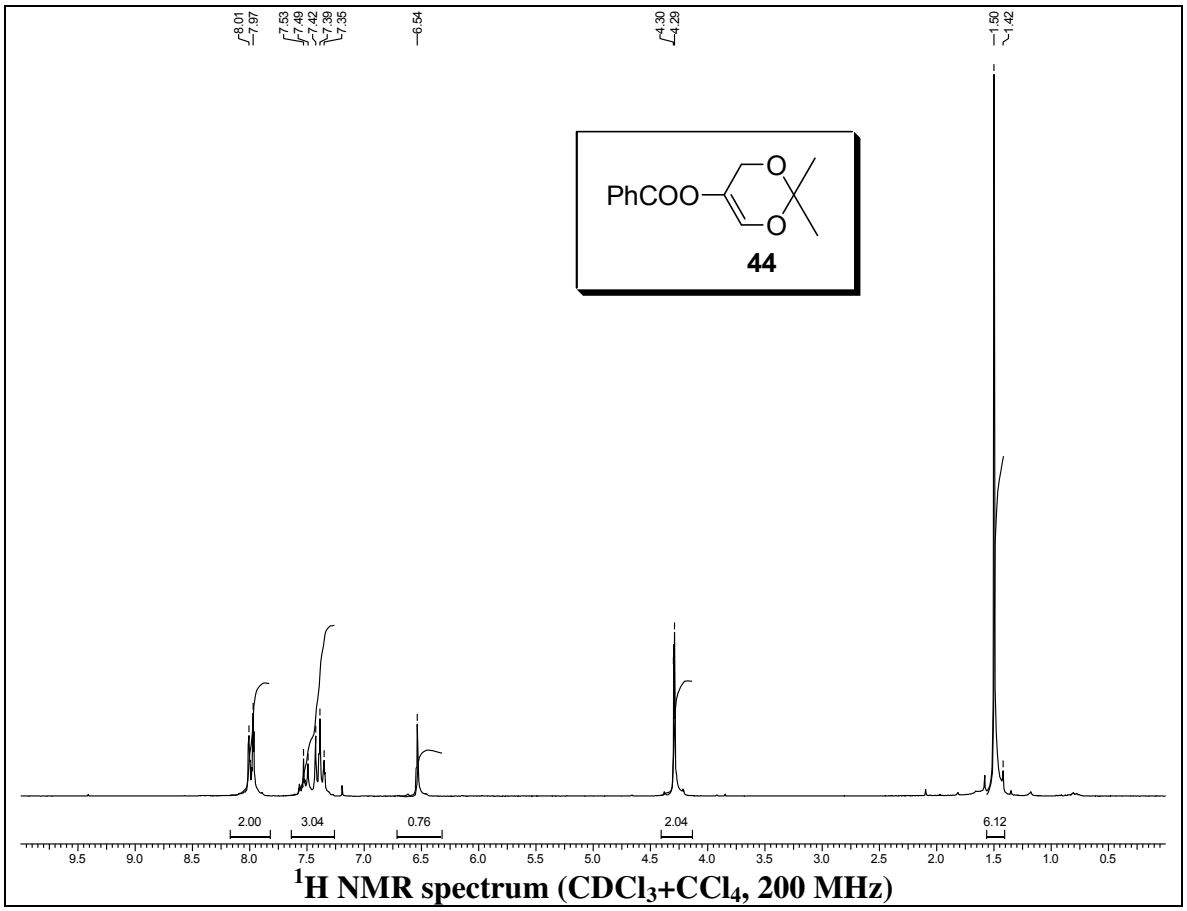
Spectra



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



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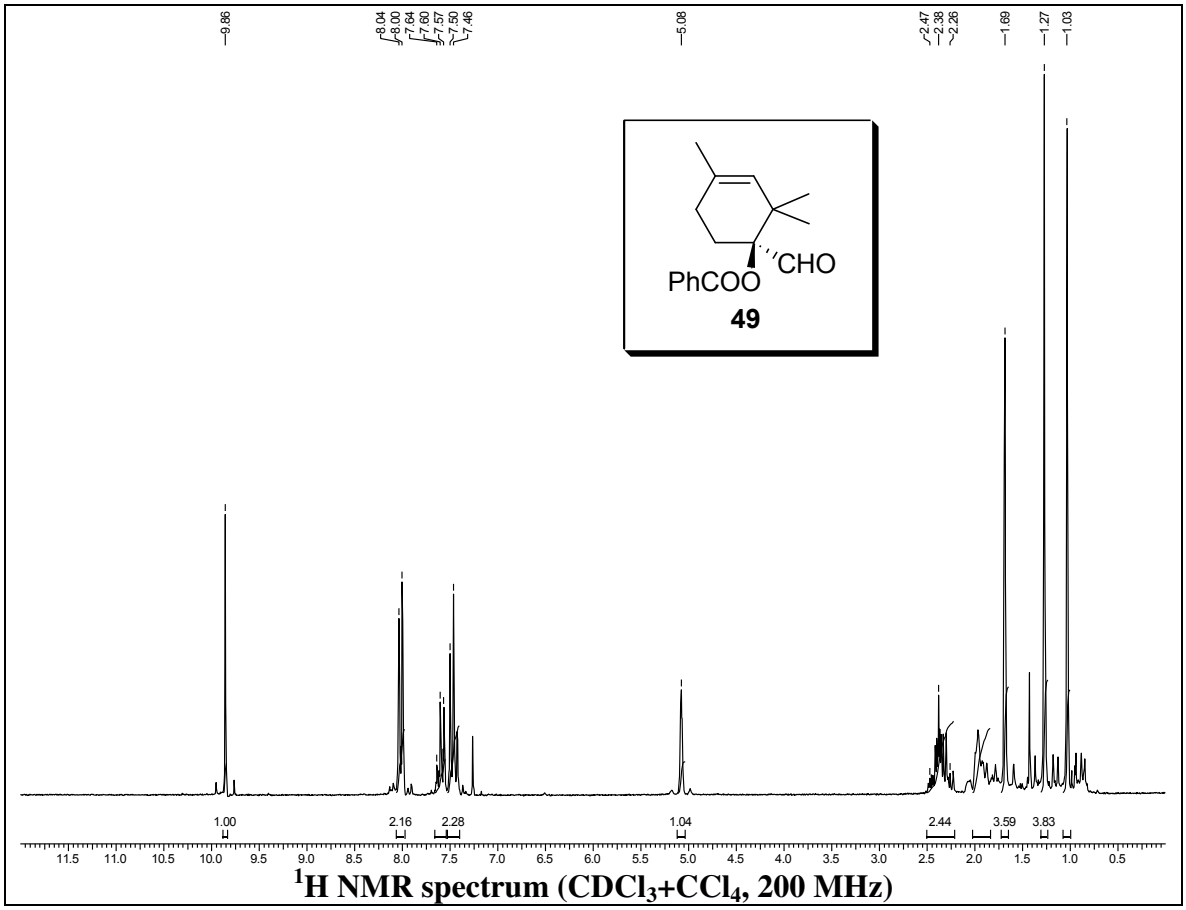

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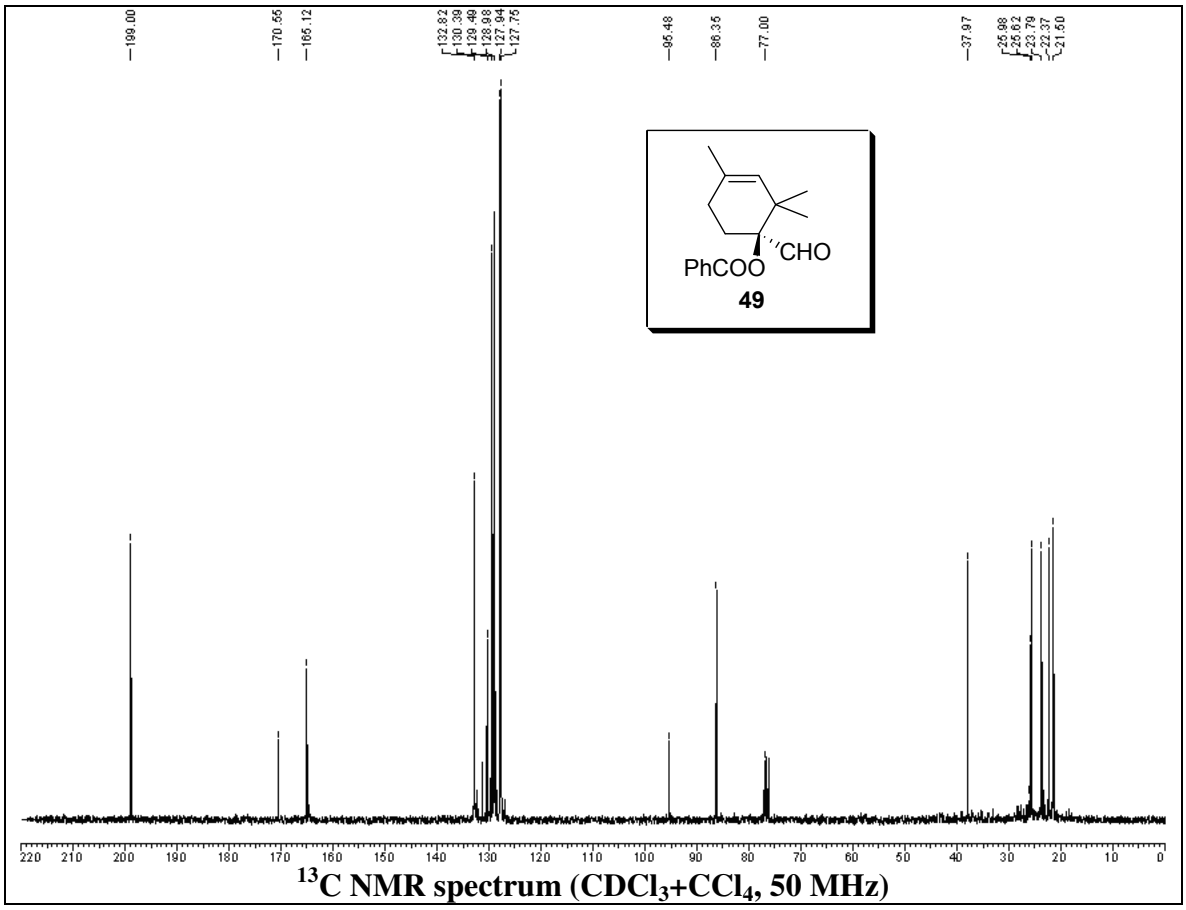

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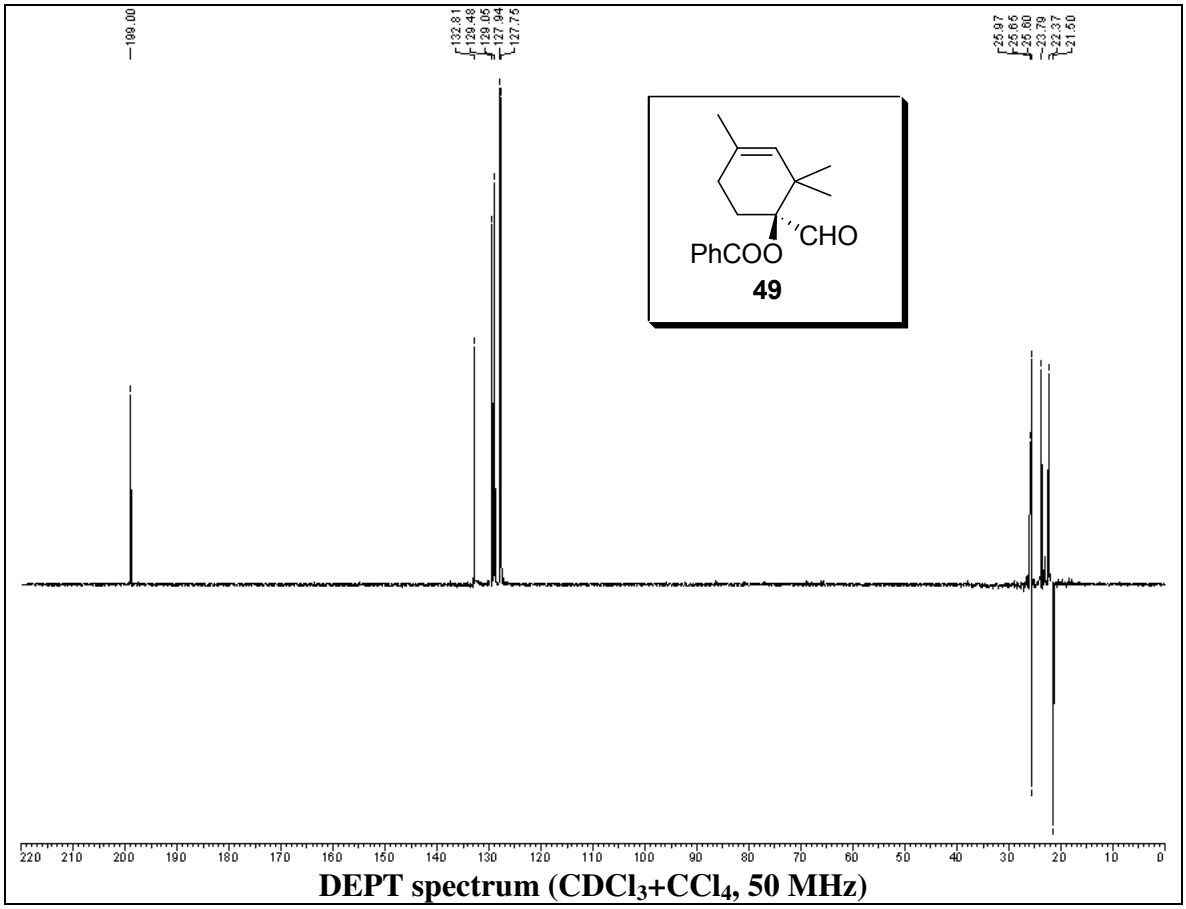

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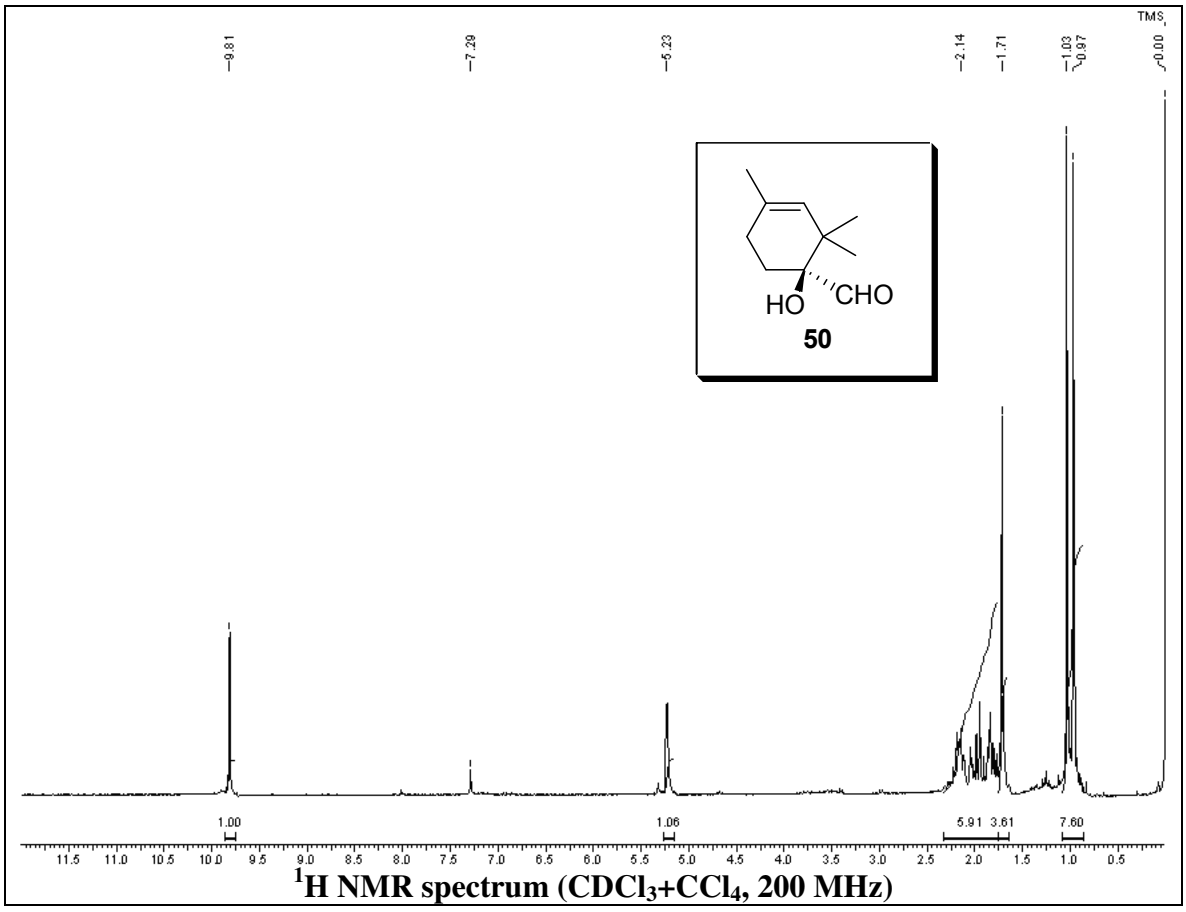
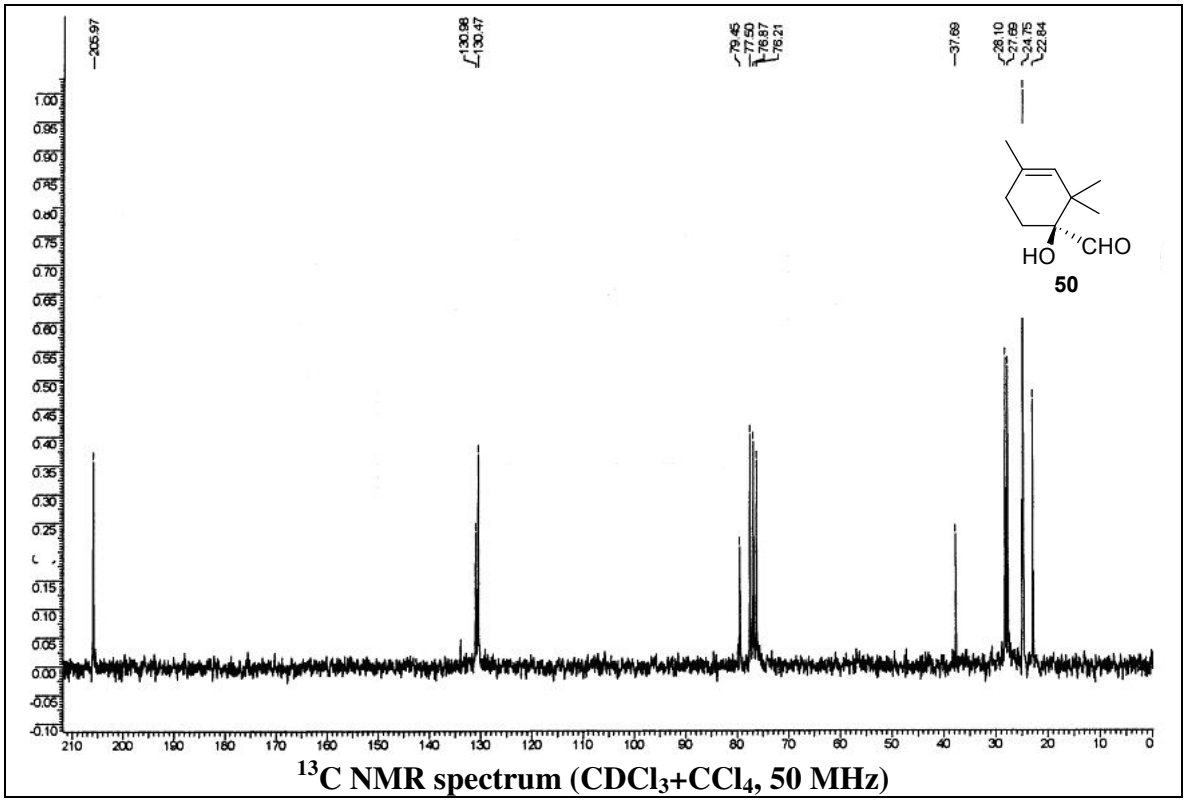
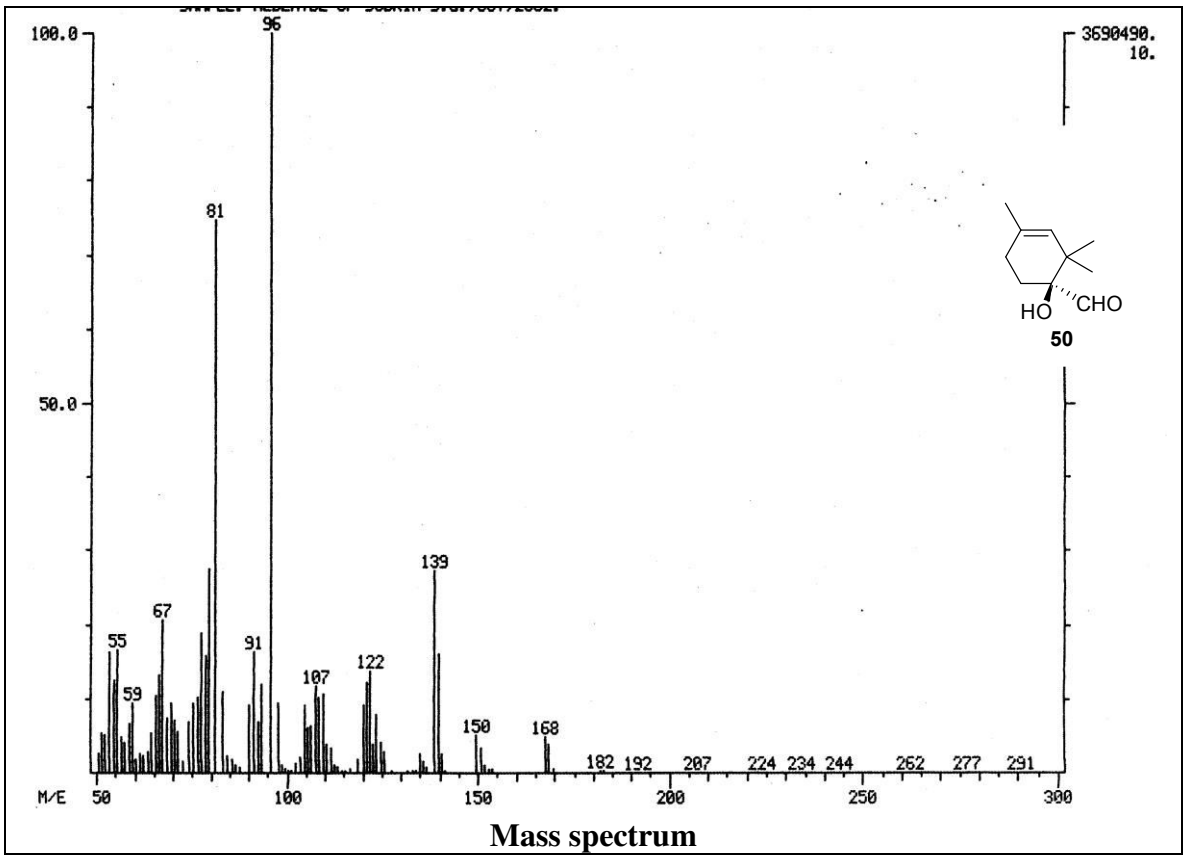


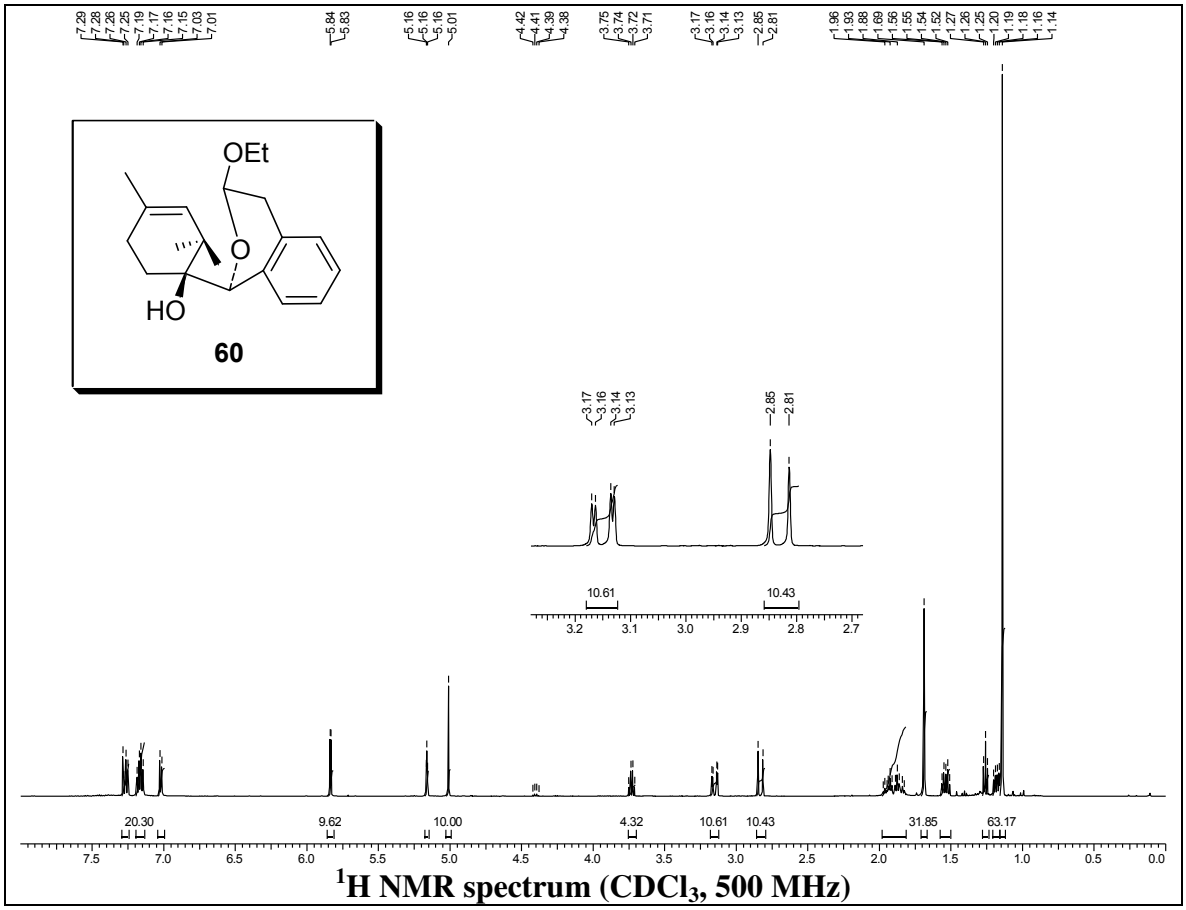
^{1}H NMR spectrum ($CDCl_3$+CCl_4, 200 MHz)



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



Mass spectrum



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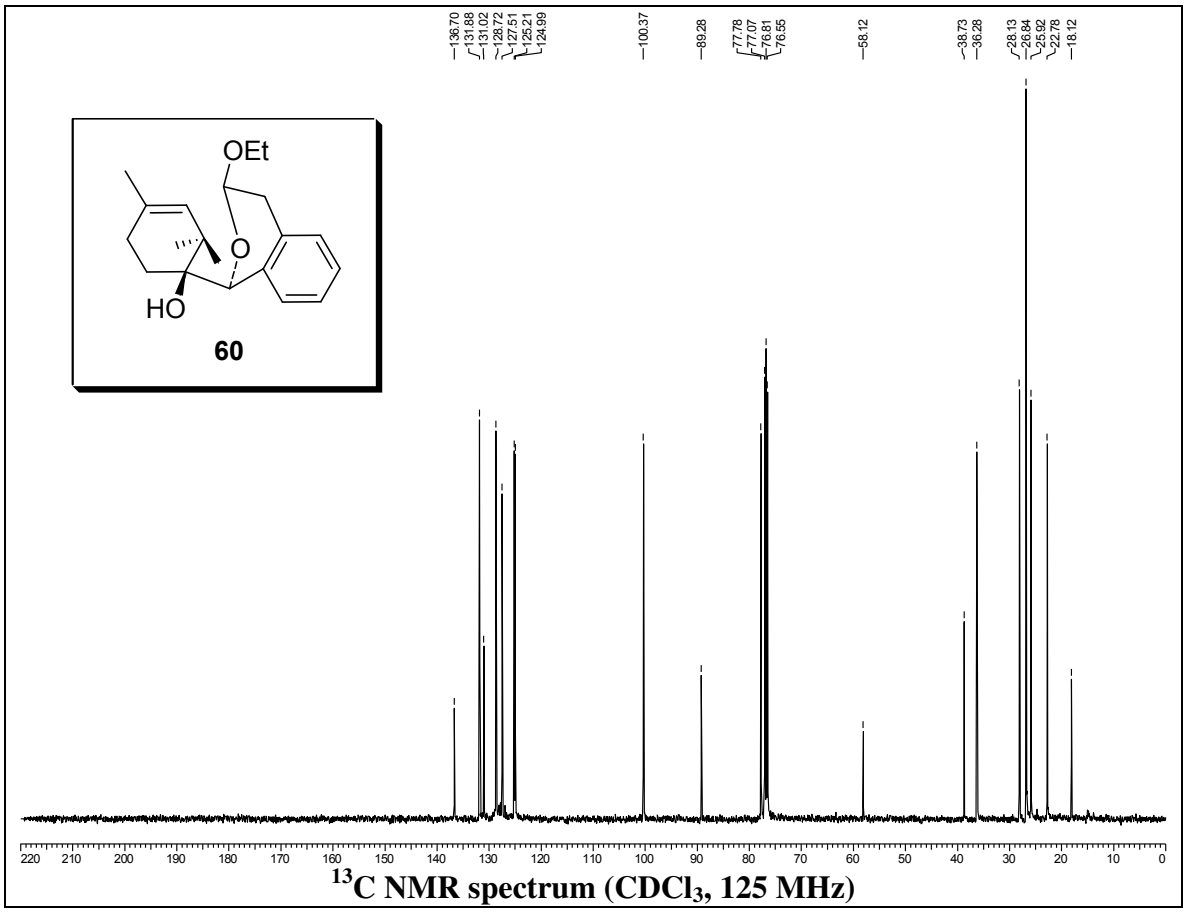

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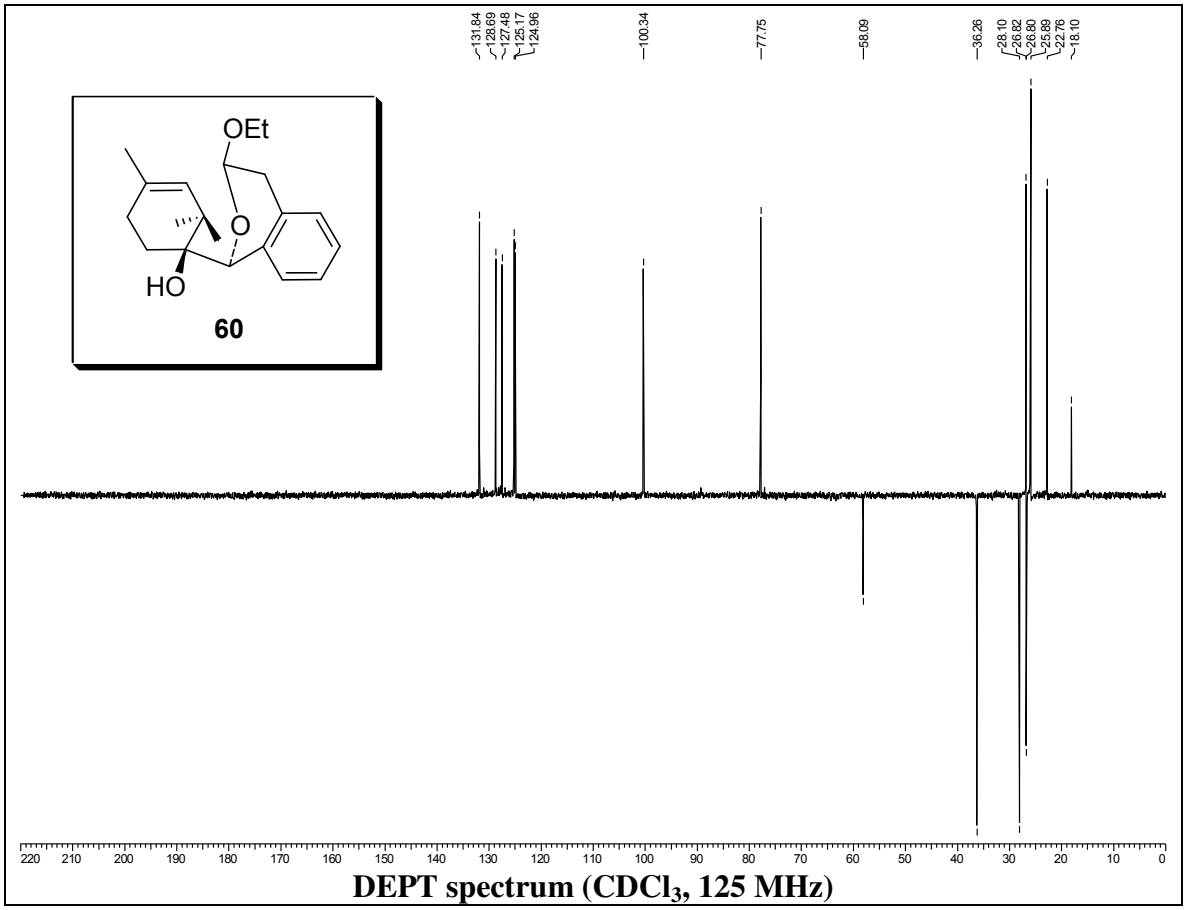
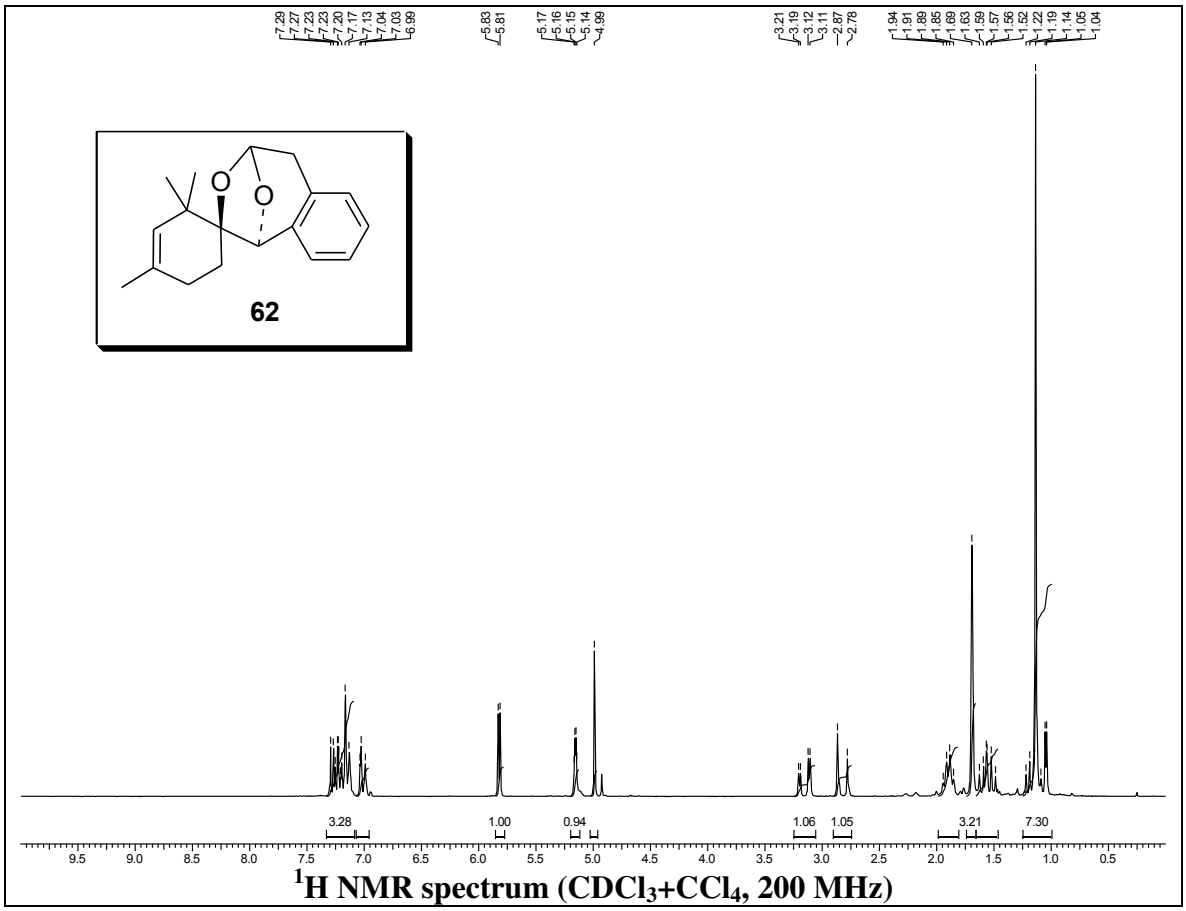


DEPT spectrum ($CDCl_3$, 125 MHz)



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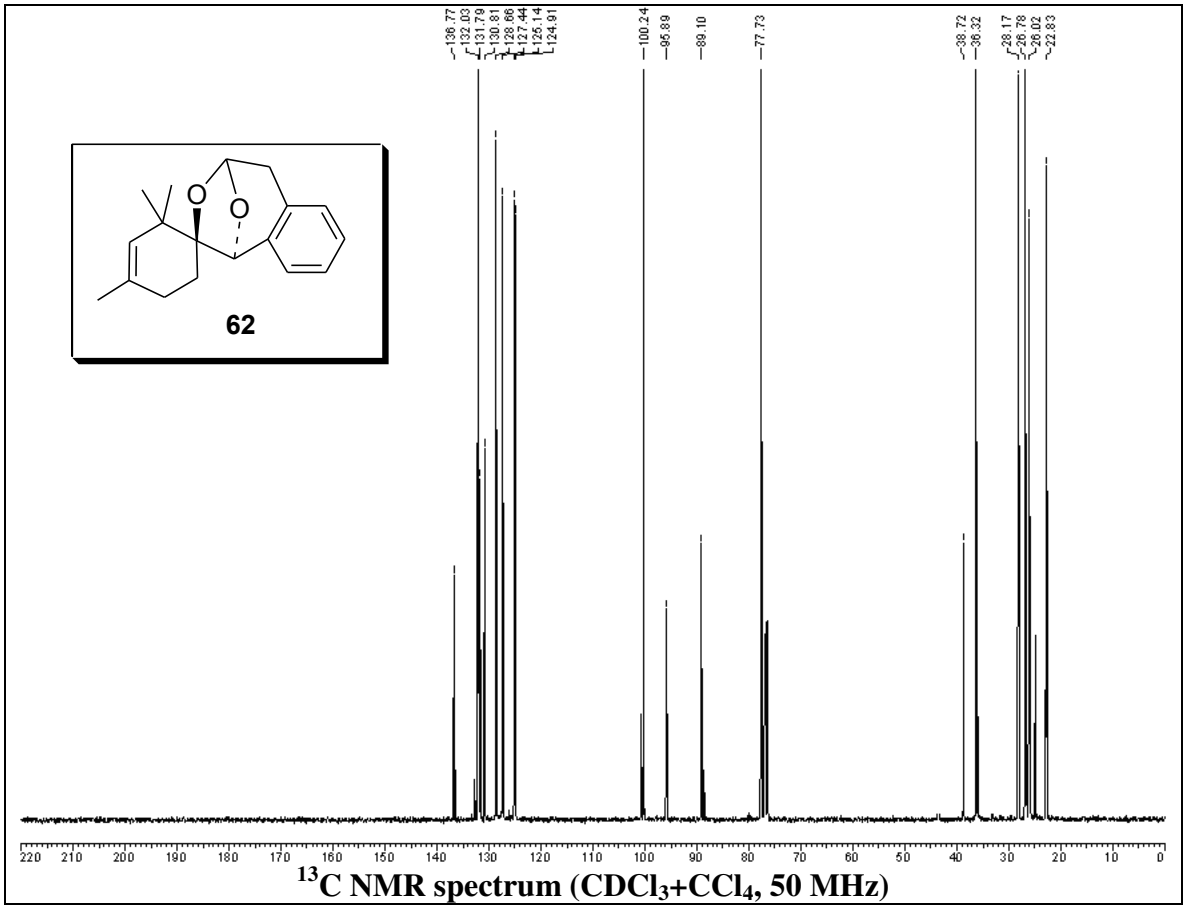
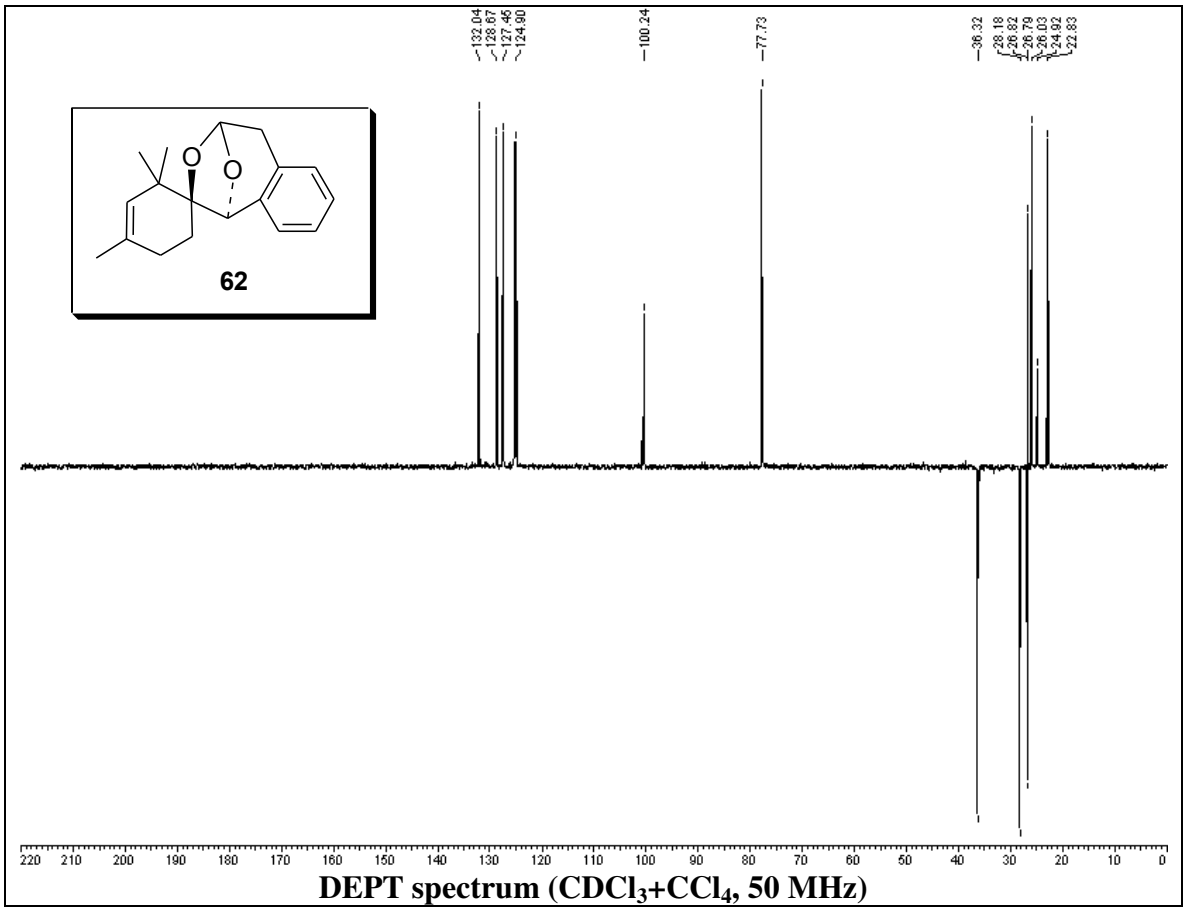
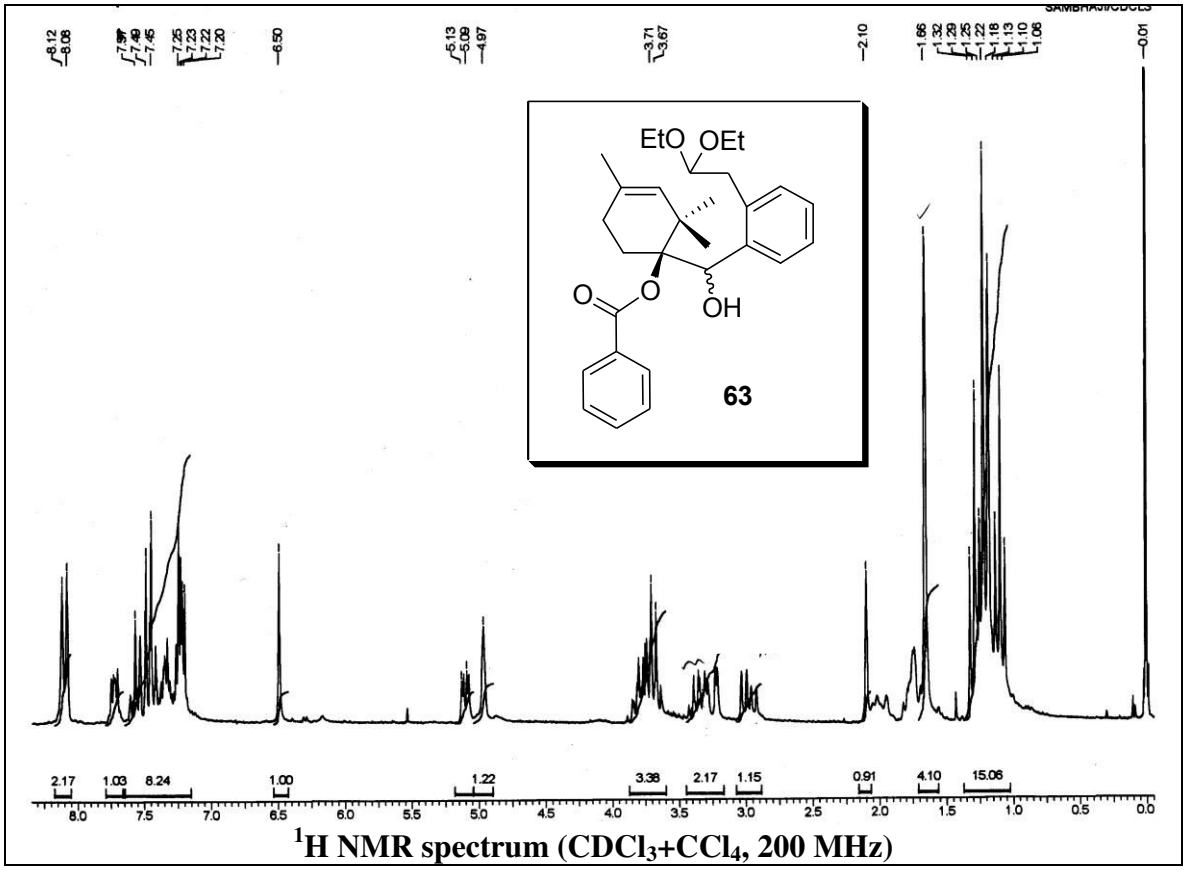


^{13}C NMR spectrum ($CDCl_3$+CCl_4, 50 MHz)



DEPT spectrum ($CDCl_3$+CCl_4, 50 MHz)



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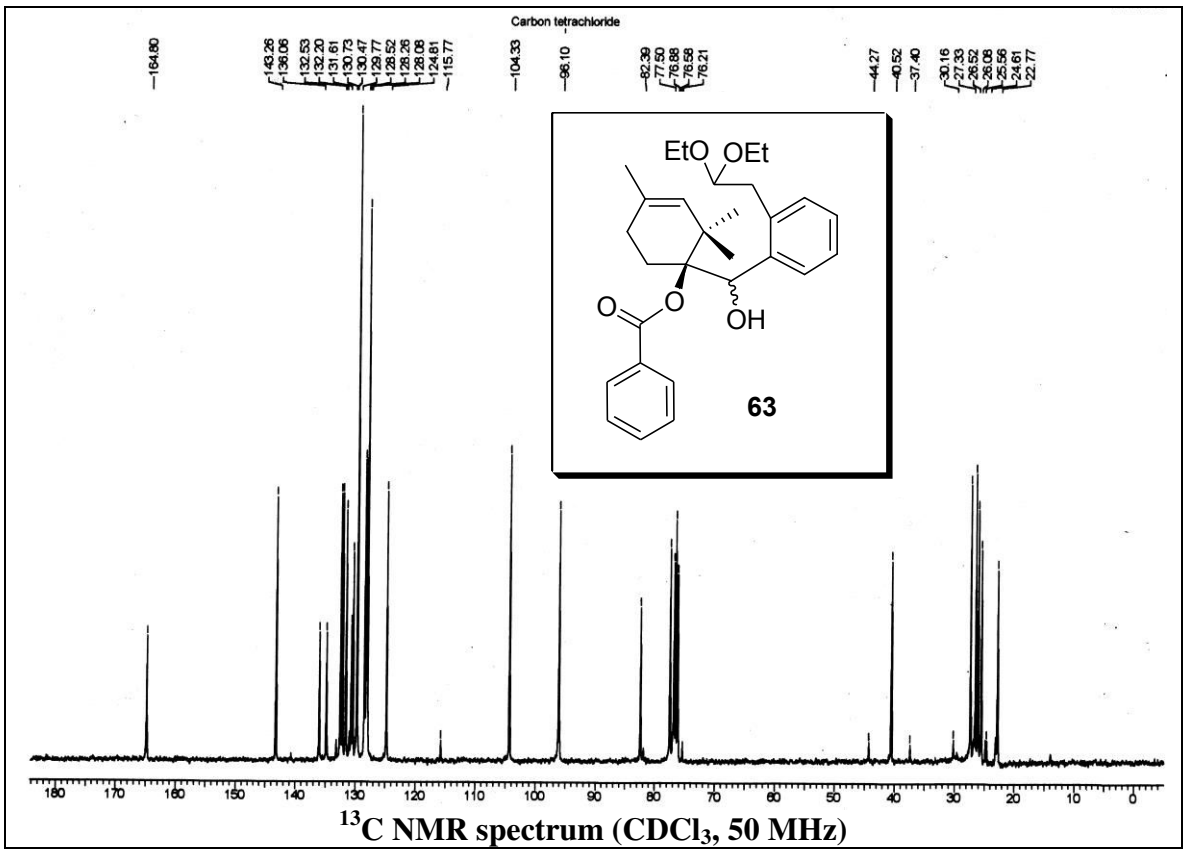
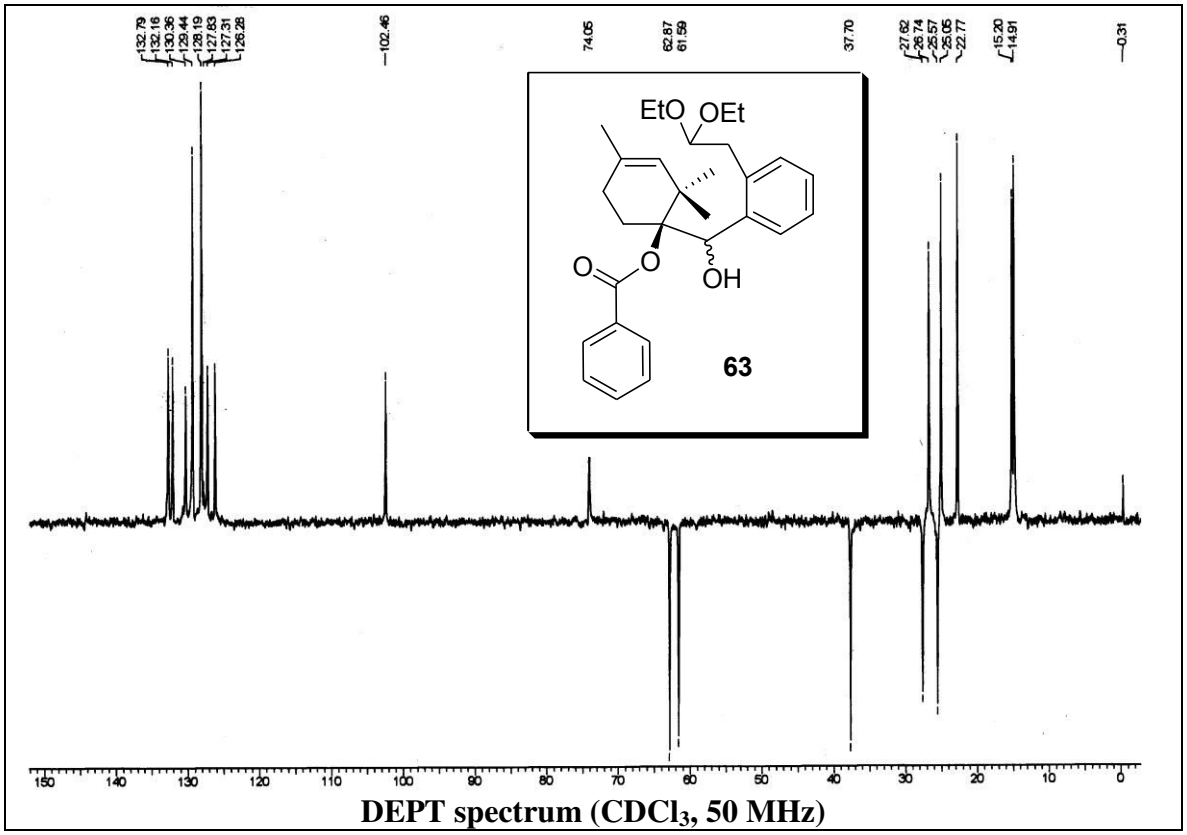
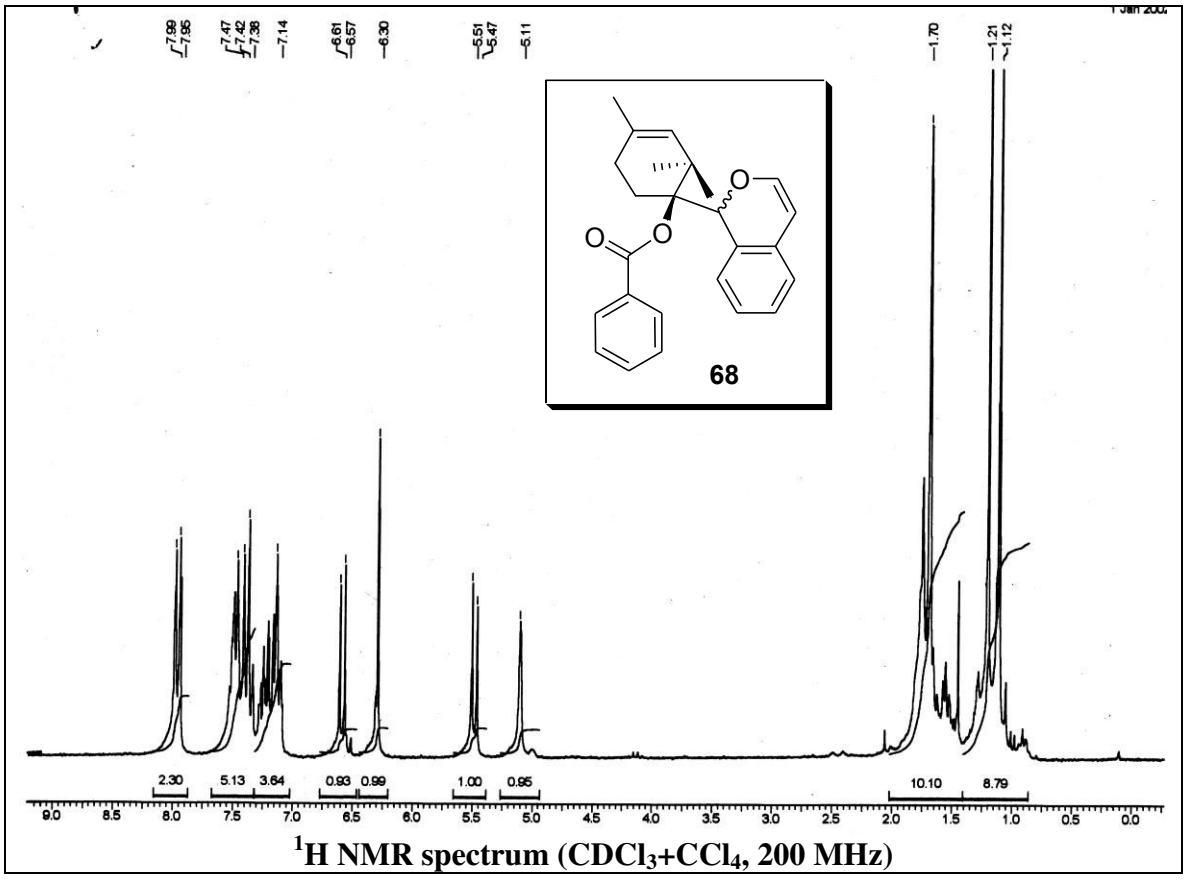


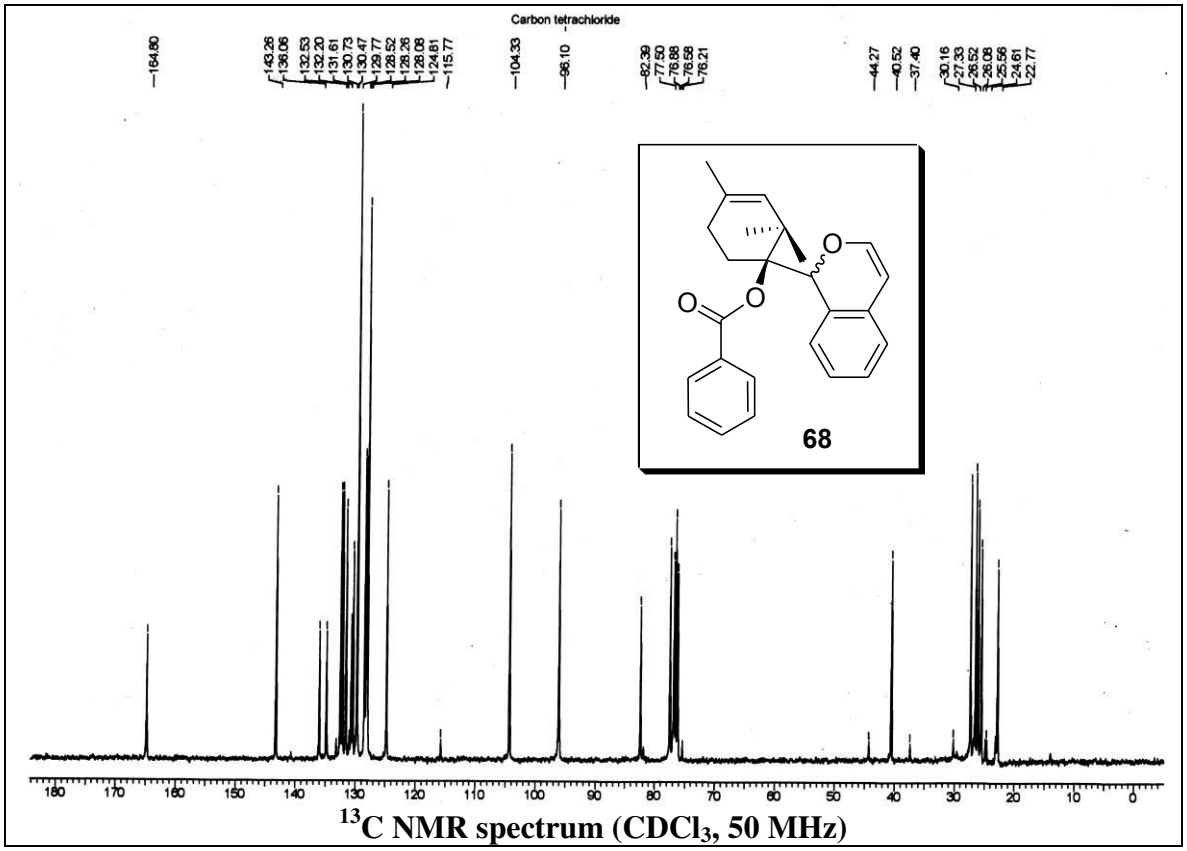
^{13}C NMR spectrum ($CDCl_3$, 50 MHz)



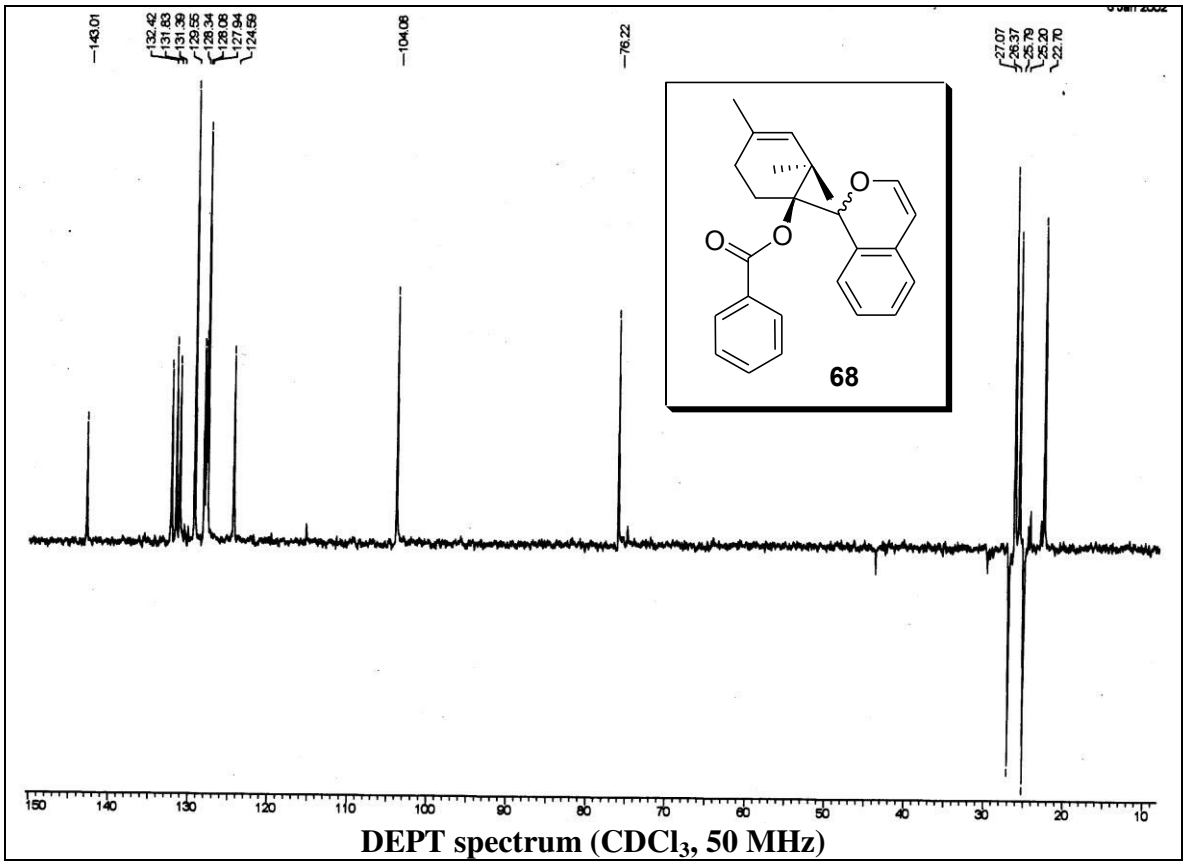
DEPT spectrum ($CDCl_3$, 50 MHz)



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



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



DEPT spectrum ($CDCl_3$, 50 MHz)

Section-III

Synthesis of C-Aromatic ABC-ring skeleton taxane system

1.3.1 Introduction:

Several methods are available to synthesize medium to large size rings, such as, Ring closing metathesis, Heck-reactions, Suzuki coupling, Nozaki coupling, radical cyclizations to name a few and also because of discovery of a new reagents, e.g. SmI_2, $Mn(OAc)_3$, Ti(0) etc. are available to synthesize them.[1] There are few drawbacks associated with them namely use of expensive catalysts, highly sensitive reagents, not general for all substrates and thus have limited large scale & industrial applications. In comparison, though fragmentation was an old arsenal for medium to large size rings construction, is even today popular because of the simplicity to perform, no designer and expensive organometallic catalyst needed for its execution, and has been used in multi-grams to industrial scale preparations. Since we have also used fragmentation reaction in our venture it is therefore pertinent to introduce a brief note on fragmentation and its few applications.

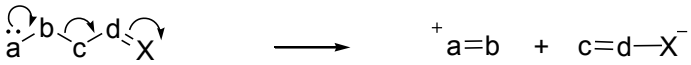
Fragmentation reactions, according to the definition of Grob,[2,3] are processes (Scheme-1) where the reacting molecule breaks into three fragments.

Scheme-1:

The electrofugal group a–b forms stable cations or neutral molecules depending on the initial charge. The middle group c–d gives an unsaturated fragment. The nuclefugal group X leaves the atom d with bonding electron pair. There are many carbon or heteroatom groups containing electrofugal, middle, and nucleofugal groups which can be combined to give fragmentable systems.[2,3]

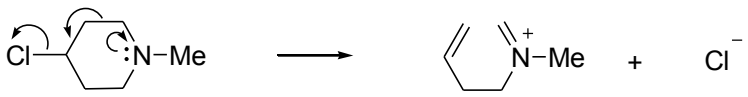
Furthermore there is a class of reactions (retroaldol, retroClaisen, oxyanion Cope etc.) which is similar to the fragmentations, but they are not to be considered as such. Here, the electron acceptor group X is double bonded to the atom d, and therefore two fragments rather than three are formed (Scheme-2).

Scheme-2:



On the other hand, there are exceptions to the rule that a reaction must lead to three fragments when the potential fragments are ring members in cyclic reactants (Scheme-3).[2]

Scheme-3:

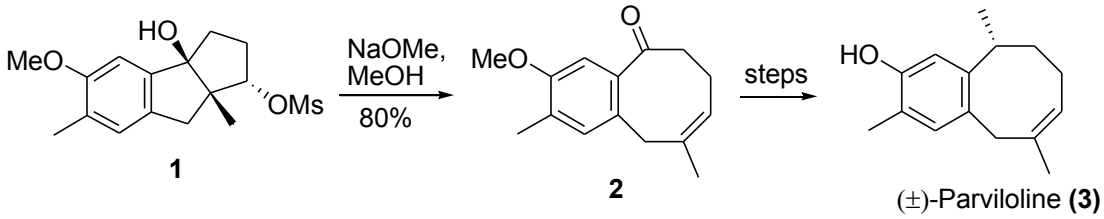


There are large number of applications of Grob fragmentation in open chains and normal rings,[3] however a few examples where medium and large size rings were synthesized will be covered. The fragmentation of cyclic 1,3-diol monotosylate were also called as Wharton-fragmentation.[4]

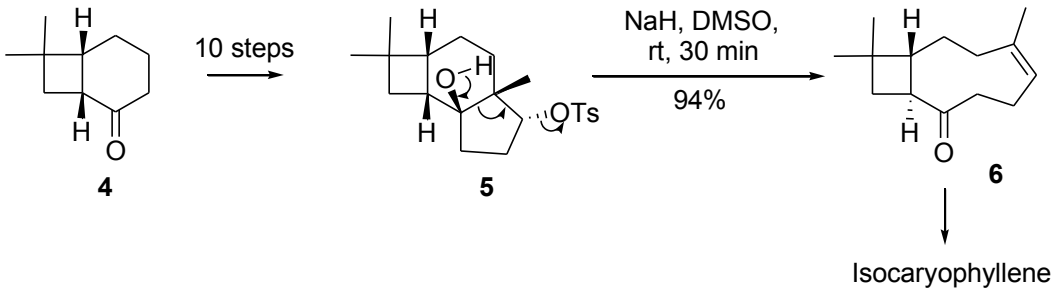
Joseph-Nathan and co-workers have elegantly employed Grob-fragmentation to generate eight-membered ring **2** for the synthesis (±)-Parvifoline (Scheme-4).[5]

Corey *et al*. utilized the fragmentation reaction of appropriately substituted 1,3-hydrindanediol monotosylates **5** for the introduction of the cyclononene moiety **6** in an elegant synthesis of caryophyllene and its isomers (Scheme-5).[6]

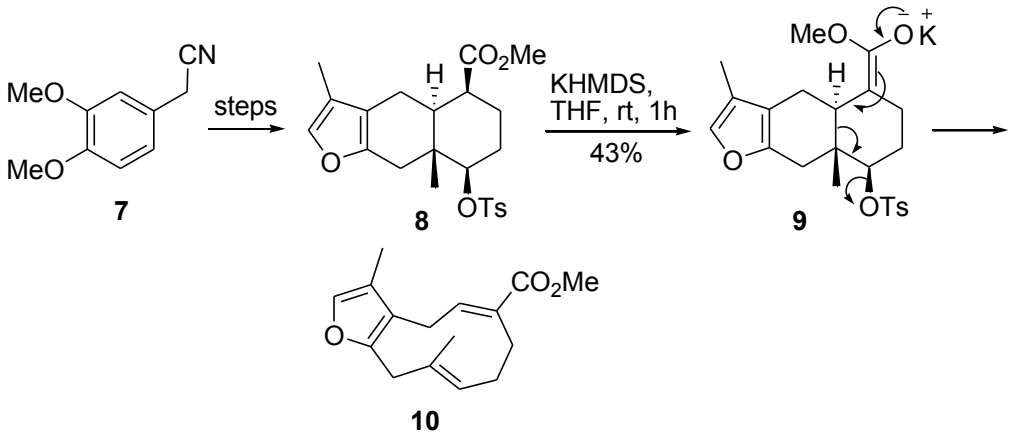
Scheme-4: (Villagomez-Ibarra, R.; Joseph-Nathan, P. *Tetrahedron Lett.* **1994**, *35*, 4771.)



Scheme-5: (Corey, R. B.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1964**, *86*, 485.)



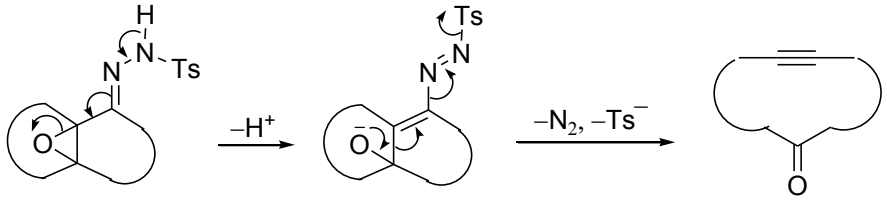
Scheme-6: (Honan, M. C.; Balasuriya, A.; Cresp, T. M. *J. Org. Chem.* **1985**, *50*, 4326.)



Enolate-assisted fragmentation has been applied to construct 10-membered ring in the last step of sericenine **10** synthesis (Scheme-6).[7] The tosyloxy ester **8** gives directly the furanogermacradiene **10**, presumably *via* the neosericenine with the *cis*-α,β-unsaturated ester group, which isomerizes to the thermodynamically favored product.

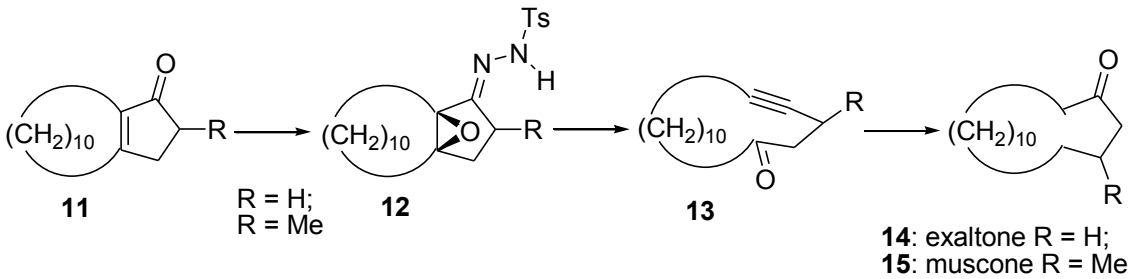
The epoxy ketone-alkynone fragmentation also called as Eschemoser fragmentation[8] is nothing but special seven center Grob-type reaction starting with the tosylhydrazone of an epoxy ketone (Scheme-7). Deprotonation leads to an alkoxide which immediately undergoes fragmentation to give four parts, a ketone, an alkyne, nitrogen and the leaving group toluenesulfinate.

Scheme-7:

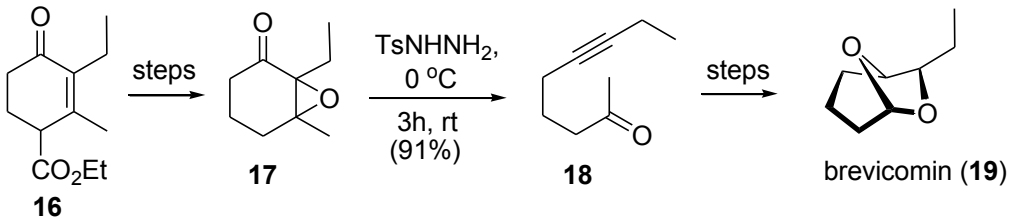


The synthetic power of this method has been elegantly demonstrated for the synthesis of exaltone **14** and muscone **15** (Scheme-8).[9] Kocienski's economical and highly stereoselective synthesis of both *endo* and *exo*-brevicomin **19** uses the alkynone **18** as an intermediate, easily accessible by fragmentation of the keto epoxide **17**, (Scheme-9).[10] Steven's have also obtained alkynone and later on converted them to key vitamin-B_{12} precursors.[11]

Scheme-8: (Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chem. Acta* **1967**, *50*, 708.)

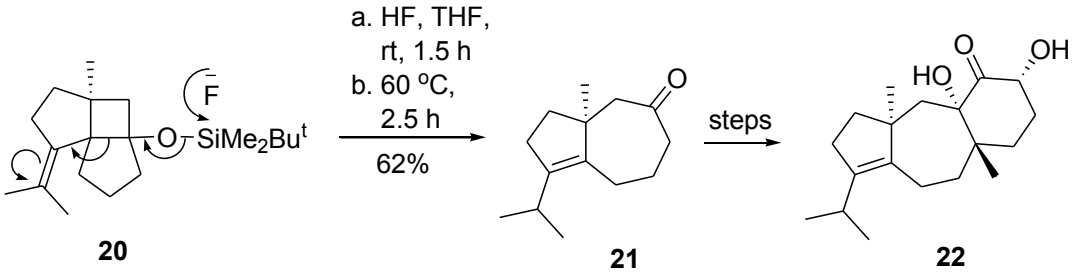


Scheme-9: (Koceinski, P.; Ostrow, R. W. *J. Org. Chem.* **1976**, *41*, 398.)



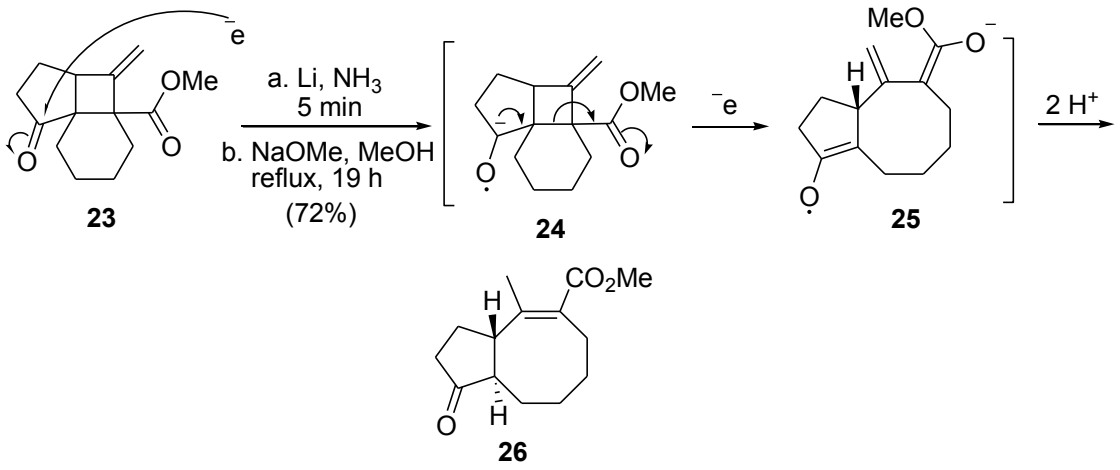
There are examples of silicon and metal assisted fragmentation reactions also.[12] Pattenden have used a photocycloaddition-fragmentation sequence (Scheme-10) for the synthesis of hydroazulenone portion **21** of **22**, which was further elaborated to Isoamijiol **22**.[12] This was the first example of a C=C bond and an Si-O bond being used as 'push-pull' partners in a fragmentation.

Scheme-10: (Begley, M. J.; Pattenden, G.; Robertson, G. M. *J. Chem. Soc. Perkin Trans.* 1, **1988**, 1085.)



The reductive fragmentation with solvated electrons (metal in liquid ammonia) of strained rings bearing carbonyl groups in a 1,4-relationship leads to dicarbonyl systems with a lower number of fused rings. This principle was elegantly used by Coates for AB rings of fusicoccin and ophiobolane natural products (Scheme-11).[13]

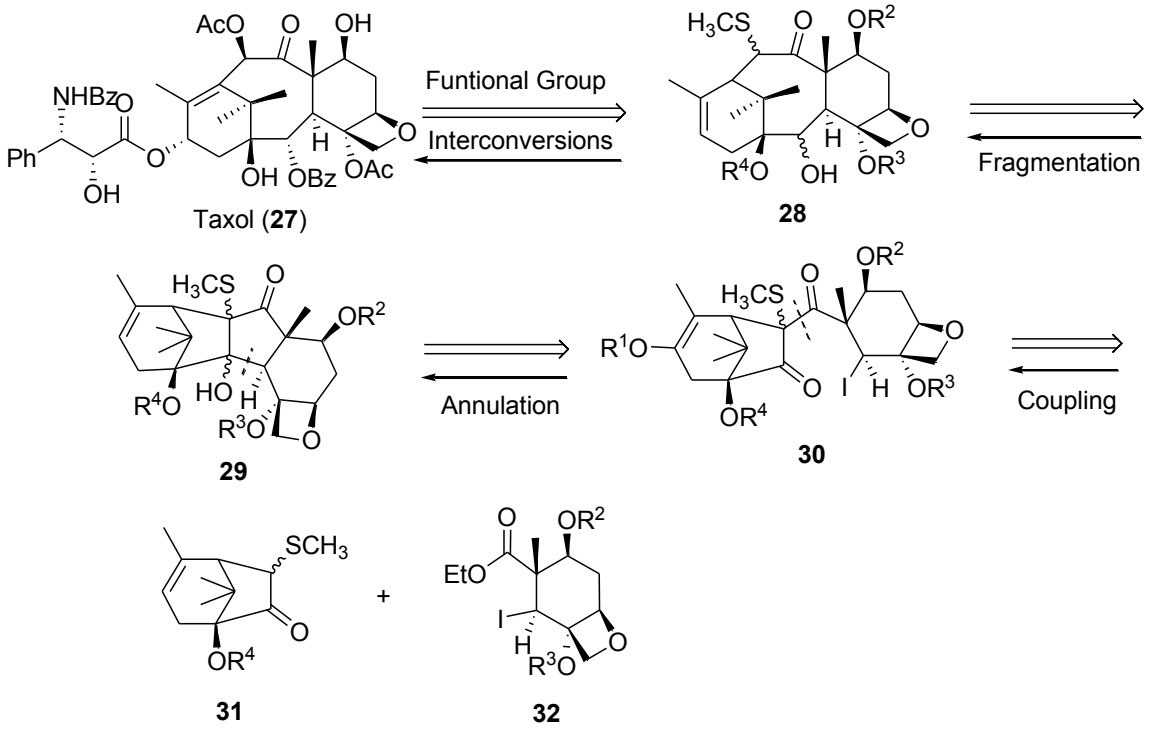
Scheme-11: (Coates, R. M.; Senter, P. D.; Baker, W. R. *J. Org. Chem.* **1982**, *47*, 3597.)



1.3.2 Present work:

Considering the simplicity and effectiveness of this fragmentation reaction, it was envisioned to utilise this strategy for the synthesis of taxol molecule as shown retrosynthetically in Scheme-12.

Scheme-12:



As delineated in retrosynthesis (Scheme-12), Taxol **27** could be visualized by multiple functional group interconversions of **28.** The ABC ring skeleton **28** could be evolved from fragmentation reaction of important precursor **29**. It was hoped that this indirect method of formation of cyclooctane ring may surpass entropy and enthalpic factors associated with direct cyclooctane annulation. Moreover fragmentation processes are thermodynamically driven, and therefore strain associated with fused system will be relieved. The multiple fused ring systems **29** could be made by annulation of **30** which in turn could be obtained by coupling of two separate entities *i.e.* **31** and **32**.

Careful examination of the structure of taxol **27** reveals that it contains fourteen carbon atoms defining the boundary of the molecule of which nine are asymmetric and seven of them bear some form of oxygenation. It indeed is an architecturally unique molecule to synthesize. Before directly embarking on total synthesis it was decided to attempt it in three stages.

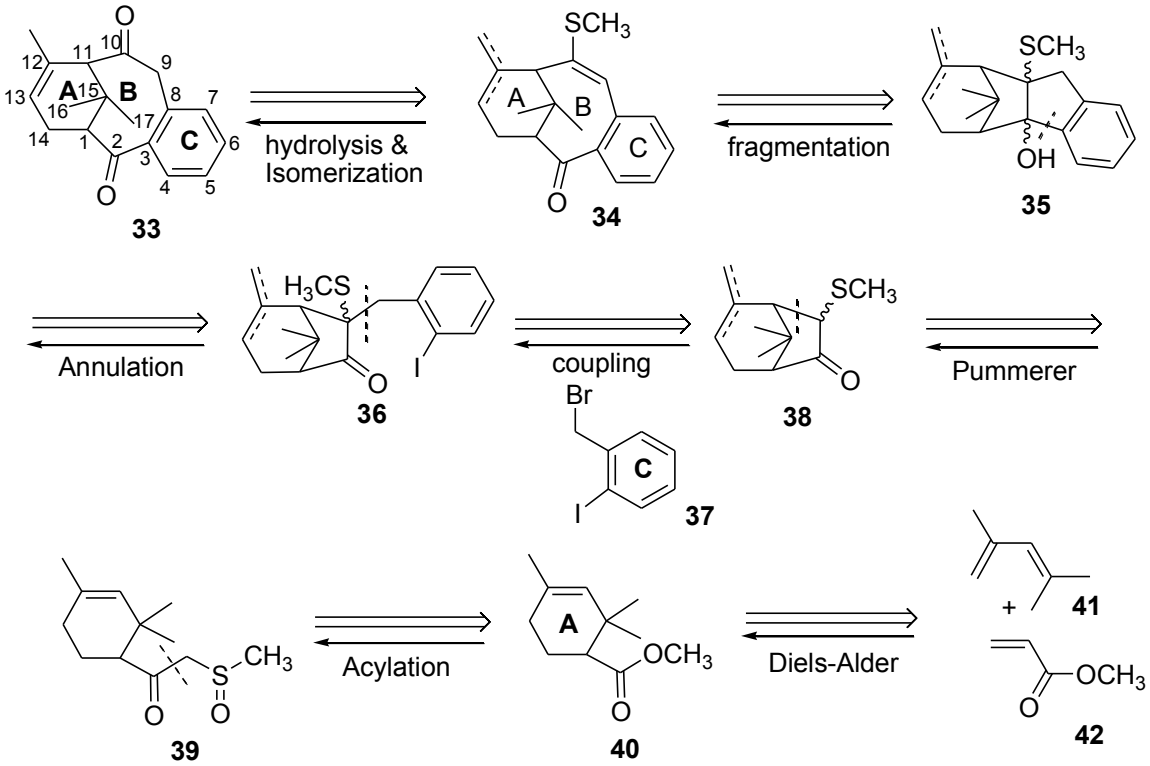
Stage-I: To undertake model study to construct ABC skeleton of taxol by taking C-ring aromatic for simplicity and generating analogues, involving fragmentation as the key step.

Stage-II: To apply methodology for synthesis of C-alicyclic ABC taxane system and if possible to functionalize AB ring portion of skeleton to resemble taxol.

Stage-III: To synthesize optically pure complicated C-ring of taxol. And further, to incorporate this C-ring with the knowledge of above developed synthetic tools in to the construction of highly functionalized ABC taxoids and ultimately leading to the total synthesis of taxol.

Synthesis of C-aromatic ABC taxane system: A model study.

Scheme-13



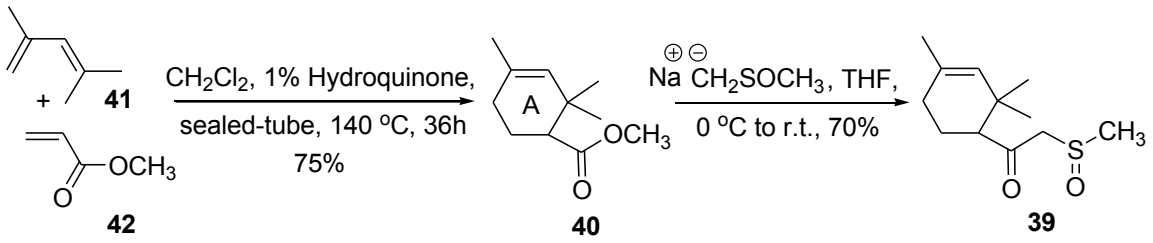
As discussed earlier, model studies taking C-ring aromatic to construct ABC ring systems of taxol was undertaken. Thus, as depicted in the retrosynthesis (Scheme-13), the taxane ABC ring skeleton **33** could be obtained by hydrolysis and isomerization of **34**. It was envisaged that 6-8-6 ring system **34** could be accessed by fragmentation of 6-5-5-6 ring systems **35**. The key precursor **35** could be made from intramolecular ring annulation of compound **36**, which in turn could be readily derived by coupling of bicyclic system **38** with C-ring unit **37**. The β-keto sulfide bicyclic unit **38** could be

obtained by Pummerer reaction of β-keto sulfoxide compound **39**, which in turn could be prepared by acylation of A-ring ester **40** with sodium dimsyl. The A-ring ester **40** would be made by Diels-Alder strategy by utilizing diene **41** and dienophile **42**.

As key synthons, A-ring ester **40** and C-ring unit **37** perceived through retrosynthesis were prepared sequentially and taken forward as described below.

Preparation of A-ring ester 40:

Scheme-14:



A-ring ester **40** was prepared by classical Diels-Alder strategy[14] (Scheme-14). The 2,4-dimethyl-1,3-pentadiene **41**, methyl acrylate **42** and trace of hydroquinone were mixed in dichloromethane in a sealed-tube, in an oil bath at temperature at 140 °C for 36h to furnish the adduct **40** in 75% yield.

IR spectrum of **40** displayed a strong band at 1732 cm^{-1}, indicating the presence of ester carbonyl group.

^{1}H NMR spectrum of **40** displayed the following pattern. A peak at δ 5.06 appearing as a singlet correspond to olefin proton. A sharp singlet appeared at δ 3.66 integrating for three protons was attributed to ester methyl group. The multiplets at δ 2.25-2.40, 1.65-2.00 and 1.00 integrating for one, three and one protons were ascribed to proton α to carbonyl and the two methylenes protons present in the molecule respectively. The three sharp singlets at δ 1.62, 1.09 and 0.89 integrating for three each corresponded to vinylic methyl and geminal dimethyls respectively.

^{13}C NMR spectrum along with DEPT spectrum of **40** revealed three quaternary carbons and they appeared at δ 174.6, 130.5 and 30.8 which were assigned to ester carbonyl, olefinic and carbon bearing gem dimethyls respectively. The methine signals at δ 131.5 and 49.5 corresponded to olefinic and α to carbonyl carbons respectively. The two methylenes carbons present in the molecule appeared at δ 28.8 and 22.0. The signals that appeared at 50.4, 29.6, 24.1 and 22.8 were attributed to carbon signals of ester methyl, methyl on double bond and geminal dimethyls respectively.

The GCMS spectrum of **40** displayed single peak with 99% purity and its corresponding mass spectrum revealed molecular ion peak at 182 and other prominent peaks at 167 (M^+–CH_3), 150 (M^+–CH_3OH), 122 (M^+–CH_3COOH), 107, 91.

In order to avoid heating boron trifluoride etherate catalyzed Diels-Alder reaction in CH_2Cl_2 at lower temperatures *i.e.* –78 and –60 °C was attempted but without any success and starting materials were recovered.

The A-ring ester **40** was treated with sodium dimsyl[15] in THF at 0 °C to afford β-keto sulfoxide **39** in 70% yield.

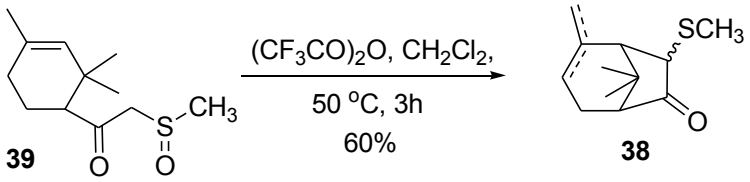
The IR spectrum of **39** displayed a strong bands at 1704 and 1030 cm^{-1} indicating the presence of carbonyl and sulfoxide functionality in the molecule respectively.

The ^1H NMR spectrum of **39** displayed the following pattern. The doublets appearing at δ 4.10 and 3.85 with geminal coupling constant J = 15 Hz integrating for one proton each were attributed to characteristic methylene protons α to sulfoxide group. The sulfoxide methyls appeared at δ 2.76 and 2.74 each integrating for 1.5 proton respectively when compared with a olefin proton singlet present at δ 5.05 integrating for one proton. The pattern illustrated here proves that the compound **39** exists as diastereomeric mixture of 1:1.

^{13}C NMR spectrum of **39** along with DEPT spectrum revealed characteristic methylene signals α to sulfoxide at δ 65.9 and 65.3 and which can be attributed to diastereomers of **39**.

The acylation of **40** with DMSO secured the entry C-10 carbon of taxol (Scheme-13).

Scheme-15



Pummerer reaction[16] on **39** was performed in DCM by using triflouro acetic anhydride at reflux to furnish a bicyclic ring system **38** in two fractions (A & B) after flash column chromatography in 60 % combined yield.

IR spectrum of fraction-A of **38** displayed a strong band at 1735 cm^{-1} indicating the presence of five membered ketone.

^1H NMR spectrum of fraction-A of **38** displayed the singlets at δ 5.17 and 1.75 integrating for one and three protons correspond to olefin and methyl on double bond

respectively. The two sharp singlets at δ 2.35 and 2.40 integrating for 1.5 each correspond to –SC<u>H</u>$_3$ group. The characteristic pattern explained here vindicates formation of a bicyclic compound with more substituted double bond and *endo* and *exo* oriented methyl sulfide group.

^{13}C NMR spectrum coupled with DEPT spectrum of fraction-A of **38** revealed two most downfield quaternary signals at δ 219.3 and 218.8 corresponding to carbonyl group. While the other downfield quaternary signals at δ 147.9 and 141.5 were attributed to olefinic carbons. The upfield quaternary signal appeared at δ 37.9 was assigned to the carbon bearing were geminal dimethyls. The most down field methine signal at δ 117.2 was ascribed to olefinic carbon while the three upfield methine signals at δ 58.1, 55.7 and 55.1 were attributed to two bridged carbons and carbon bearing –SCH$_3$ group. The only methylene signal in the molecule appeared at δ 28.9. The upfield methyl signals appeared at δ 28.6, 22.9, 21.9 and 18.5 were attributed to geminal dimethyls, vinylic methyl and –S<u>C</u>H$_3$ methyl respectively. The pattern explained further confirms the presence of more substituted double bond with –SCH$_3$ group in *exo* and *endo* orientation in the bicyclic molecule.

The GCMS spectrum of fraction-A of **38** displayed two peaks with identical molecular ion peak 210 whose mass fragmentation pattern were similar.

The fraction-B of **38** also displayed a strong band at 1735 cm^{-1} indicating the presence of five membered ketone.

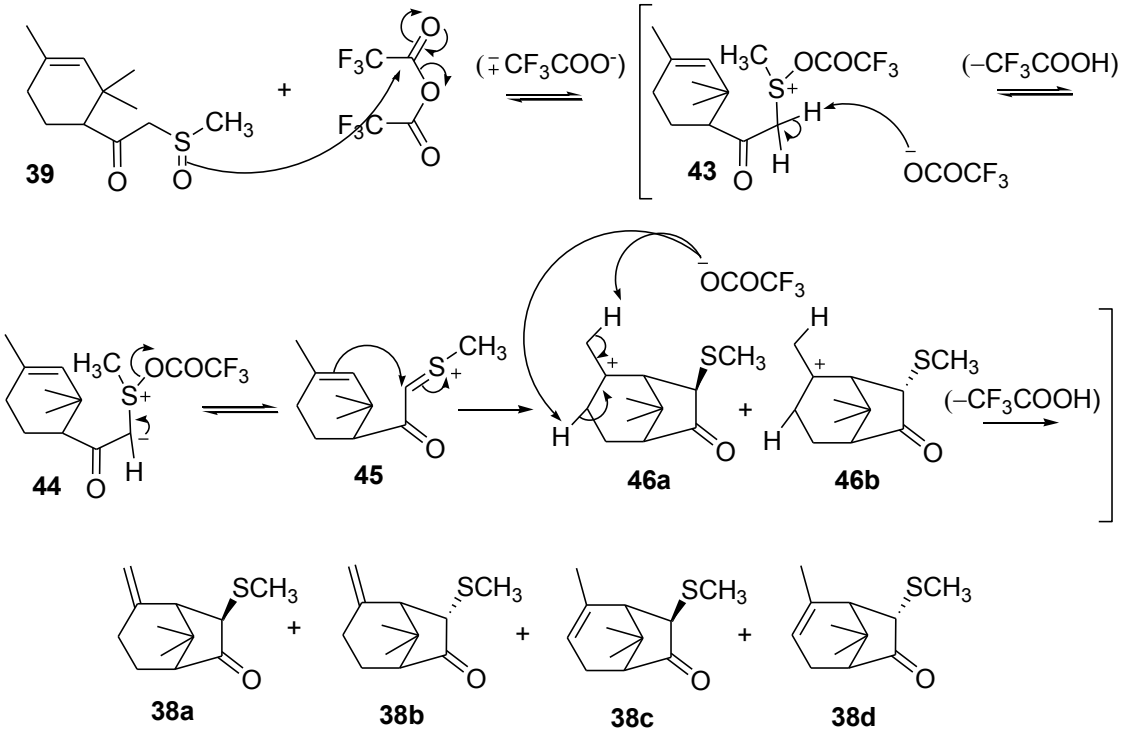
^{1}H NMR of Fraction B of **38** displayed following pattern. The mutiplets appeared at δ 4.84 and 4.74 integrating for one proton each correspond to olefin protons. The two sharp singlets at δ 2.29 and 2.27 were assigned to –SC<u>H</u>$_3$ group. The characteristic peaks observed indicated the presence of a less substituted double bond with *endo* and SCH$_3$ group in *exo* orientation in the bicyclic compound **38**.

^{13}C NMR spectrum along with DEPT spectrum of fraction-B of **38** further confirmed the structures. Thus the methylenes appeared at δ 137.3, 52.76 and 52.0 vindicates the presence of less substituted double bond in **38**.

The GCMS spectrum of fraction-B of **38** also displayed two major peaks and its corresponding mass showed similar fragmentation pattern with the molecular ion peak appeared at 210 and the other prominent peaks were observed at 195, 164, 154, 135, 122 and 107.

Although fractions-A & B were obtained by flash column chromatography but the NMR's and GC analysis revealed the presence of smaller amount of either isomers in each fractions. Silver nitrate doped silica gel column chromatography was also attempted to separate isomers but without any success.

Scheme-16:



The plausible formation of isomers is mechanistically depicted in Scheme-16. Initial attack of sulfoxide on trifluoroacetic anhydride forms acylated intermediate **43**. Acylation was followed by proton abstraction by conjugate base from α-carbon atom of the sulfoxide resulting in the formation of an ylide **44**. On further elimination of trifluoroacetic acid it formed thionium ion **45** which underwent an intramolecular attack of olefin to result in the formation of two tertiary carbocations isomers **46a** and **46b**. Further abstraction of proton from adjacent methyl and methylene from **46a** and **46b** result in the formation of four isomers **38a**, **38b**, **38c** and **38d**.

Although, four isomers were obtained, it was decided to carry forward with them since two centers would be destroyed subsequently as delineated in retrosynthesis; Scheme-13, which would lead olefinic isomers, which could be easily converted in to single isomer.

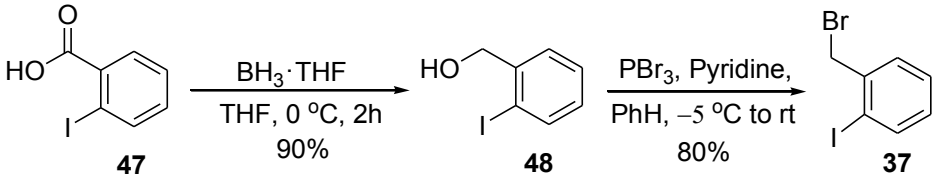
It is pertinent to mention that cation-olefin cyclizations were reported by Lewis acid catalyzed decomposition of α-diazoketones.[17] But the carbocations generated which

were α to carbonyl were not stable and were often attacked by solvent, neighbouring group and other competing nucleophiles instead of olefin and hence generally polymerization and/or tarring of substrates occurs.[18] Therefore, it was necessary to attenuate hyperactivity of carbocation in order to get desired fruitful results. In this context, hetero atom stabilized carbocations has been exploited in the synthesis of complex molecules. Utilization of thionium species for carbon-carbon or carbon-hetero atom bond formations is generally called as Pummerer reactions.[19] The other species *i.e.* oxonium ion has been already discussed in previous section while another category called as *N*-acyliminium ion and its synthetic potential which falls beyond the purview of this thesis has been reviewed elsewhere in details.[20]

Thus C-10 and C-11 carbon of ABC taxane system (Scheme-13) were coupled with the help of sulfur.

Preparation of C-ring unit 37:

Scheme-17:

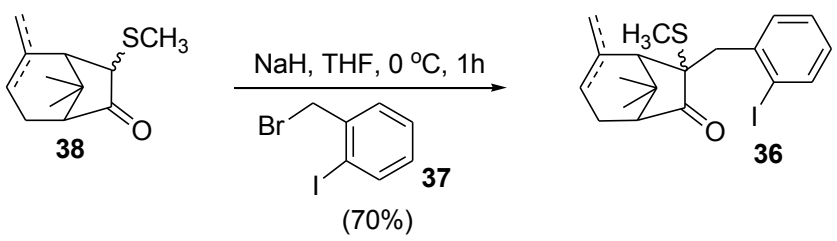


The C-ring unit **37** was prepared in a straight forward manner in two steps from *o*-iodo benzoic acid. The *o*-iodo benzoic acid **47** was reduced by borane tetrahydrofuran complex at 0 °C to afford *o*-iodo benzyl alcohol **48** in 90% yield. On further treatment with phosphorus tribromide it yielded *o*-iodo benzyl bromide **37**.[21]

Coupling of bicyclic unit 38 with C-ring unit 37:

Sodium enolate of **38** was generated by treating it with sodium hydride in THF at 0 °C for 1h. To this enolate, *o*-iodo benzyl bromide **37** was added slowly to yield coupled product **36** in 70% yield.

Scheme-18:



IR spectrum of **36** displayed strong band at 1735 cm^{-1} indicating the presence of five membered ketone.

^{1}H NMR spectrum of **36** revealed following pattern. The presence of multiplet at δ 7.87-8.04, 7.25-7.37 and 6.66-6.96 indicated incorporation of *o*-iodo benzyl moiety in bicyclic unit. The singlets at δ 5.36, 4.92 and 4.85 integrating in the ratio 1:0.5:0.5 were attributed to olefinic protons which indicate the presence of endo and exo cyclic double bonds. The sharp singlets at δ 1.62 and 1.60 were attributed to $–SCH_3$ group in endo and exo orientation. And the above characteristic pattern, indicated the presence of four isomers of **36**.

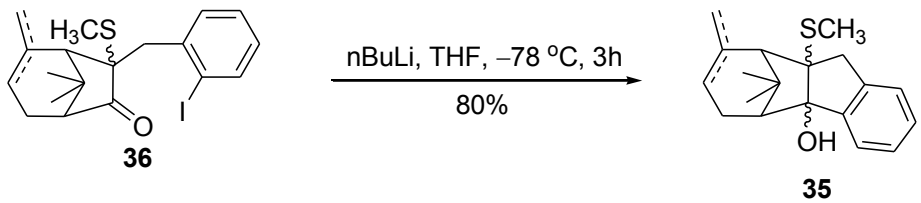
^{13}C NMR spectrum along with DEPT spectrum of **36** displayed two downfield quaternary signals at δ 219.1 and 216.5 which correspond to carbonyl carbons. The appearance of methylene signals at δ 112.7, 43.4, 42.7, 30.9, 27.2, 26.2 and 23.6 furhter indicates the possibility of four isomers of **36**.

In this step C-9 and C-10 carbons were connected (Scheme-13). Here too, sulfur played a key role in facilating C-alkylation by stabilizing carbanion.

After assembling total number of carbons required for skeleton formation, the next task was ring annulation, fragmentation and isomerization and they were executed sequentially as described below.

The next step involved, C-2 and C-3 carbon connection i.e. five membered ring annulation and it was carried out by metal halogen exchange methodology. To a cold (–78 °C) solution of **36** in THF was added nBuLi slowly to afford tetracyclic compound **35** in 80% yield.

Scheme-19:



36 **35**

IR spectrum of **35** displayed a strong band at 3400 cm^{-1} indicating the presence of hydroxyl group in the molecule.

^{1}H NMR spectrum of **35** displayed following pattern. The multiplets that appeared at δ 4.64 and 4.79 were attributed to olefinic protons. Sharp singlets at δ 2.04 and 2.14 were assigned to $–SCH_3$ group. The above characteristic pattern explained indicates the existence of isomers of **35**.

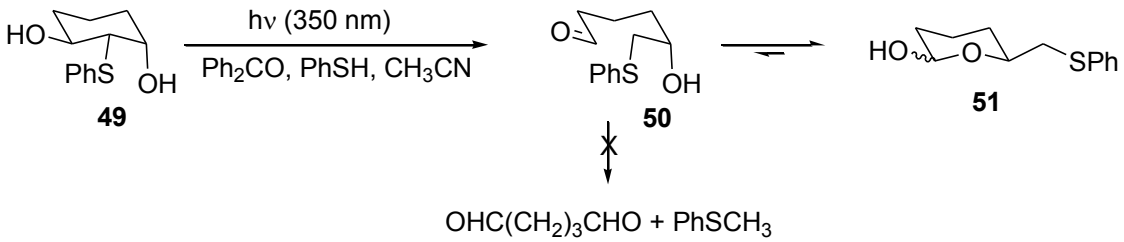
^{13}C NMR spectrum along with DEPT spectrum of **35** displayed following pattern. The two quaternary signals at δ 99.0 and 92.3 were assigned to carbinol carbon while the other two quaternary signals at δ 77.4 and 70.8 were assigned to carbon where –SCH_3 group. The spectrum also revealed six methylene signals at δ 110.3, 48.9, 43.8, 30.9, 29.7 and 23.1. The above characteristic signals supported presence of isomers of **35**.

The mass spectrum of **35** revealed molecular ion peak at 301 (M^++1) and other prominent peaks appeared at 284 (M^+–H_2O), 277, 183, 181.

Having secured the requisite 6-5-5-6 skeleton, the next task was to unmask the eight membered ring i.e. convert it to 6-8-6 skeleton. Here this could be achieved by cleaving the bond shared by two five membered rings bearing heteroatoms as the handle. The obvious choice of cleaving the vicinal thio ether alcohol was a photochemical reaction.

In this context, it was decided to exploit the photo-induced electron transfer fragmentation reactions of 2-phenyl-thioalcohols reported by Gravel *et al* (Scheme-20).[22]

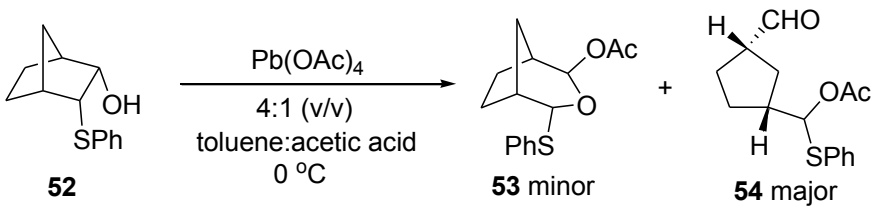
Scheme-20:



Therefore, the tetracyclic β-methylsulfidealcohol **35** and benzophenone as a photosensitizer were mixed in acetonitrile and subjected to UV irradiation using wave length of 350 nm. However even after 24 h of irradiation no change in starting material was observed, which was further confirmed by ^{1}H NMR analysis of recovered starting material.

Having failed to cleave the bond, the next option available was cleavage with Lead tetracetate.

Scheme-21:

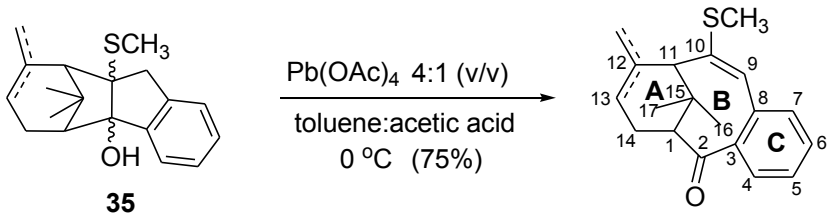


Lead tetraacetate mediated cleavage of 2-phenyl-thiols was elegantly used by Trost group. Thus as depicted in Scheme-21, β-phenylthioalcohol moiety in a norbornane

system **52** was cleaved by lead tetraacetate which afforded fragmented compound **54** as the major product.[23]

This elegant methodology largely remained unexplored and was never used for synthesis of any medium to large size rings. Therefore it was decided to exploit this methodology for the synthesis of cyclooctane ring, to this effect fragmentation of tetracyclic compound **35**.

Scheme-22:



35 **34**

Thus, the compound **35** was dissolved in toluene:acetic acid (4:1) (v/v) and cooled to 0 °C in an argon atmosphere. The Lead tetraacetate in toluene was added *via* syringe to above solution and further stirred for 6h at 0 °C to afford fragmented product **34** in 75% yield.

IR spectrum of **34** displayed a strong band at 1681 cm^{-1} which indicated the presence of conjugated carbonyl group.

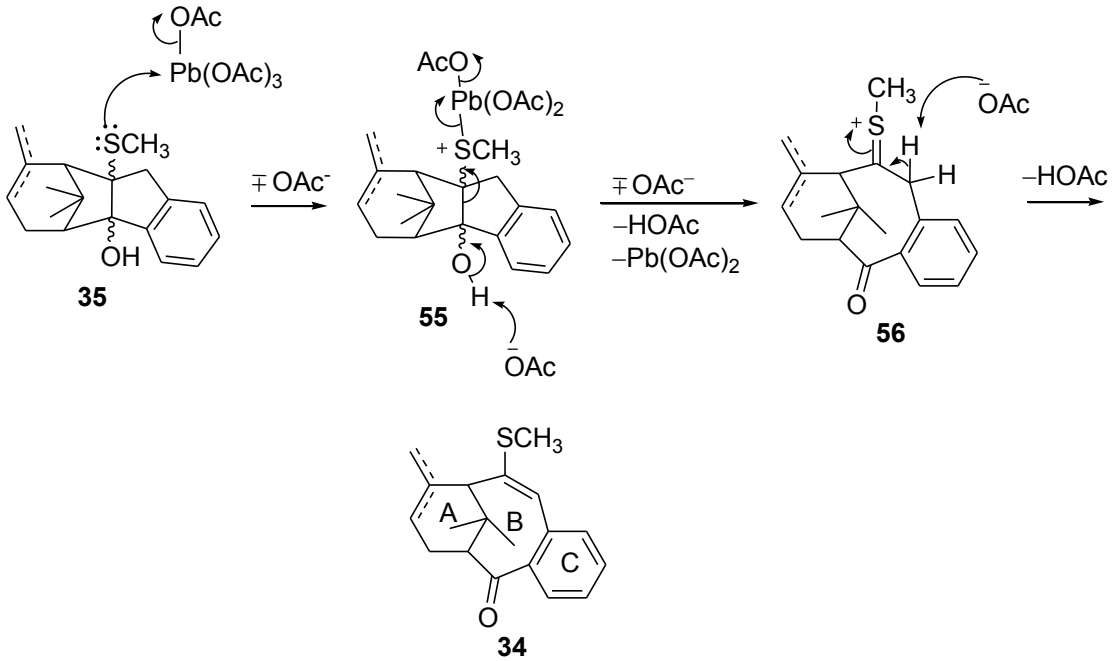
^{1}H NMR spectrum of **34** displayed following pattern. The singlets at δ 6.03, 5.91, 4.88, 4.83 and 4.73 integrating in the ratio 1:1:1:0.5:0.5 correspond to olefin protons and therefore indicate formation of the fragmented product **34** which existed as the mixture of olefinic isomers in the ratio 1:1.

^{13}C NMR along with DEPT spectra of **34** displayed most downfield quaternary signal at δ 213.0 which corresponded to carbonyl carbon. The appearance of three methylenes at δ 113.3, 25.3 and 22.4 indicated the formation of two isomers of fragmented product **34**.

GCMS spectrum of **34** displayed two peaks in the ratio 1:1, and its corresponding mass revealed similar fragmentation pattern with molecular ion peak at 298 and other prominent peaks at 283 (M^+–CH_3), 270 (M^+–CO), 251 (M^+–SCH_3), 223, 201, 174 and 77.

The plausible formation of ABC ring skeleton **34** of taxane system as a result of fragmentation of **35** can be explained mechanistically as shown in Scheme-23. Initially sulfide group attacks the lead tetraacetate to form positively charged intermediate **55.**

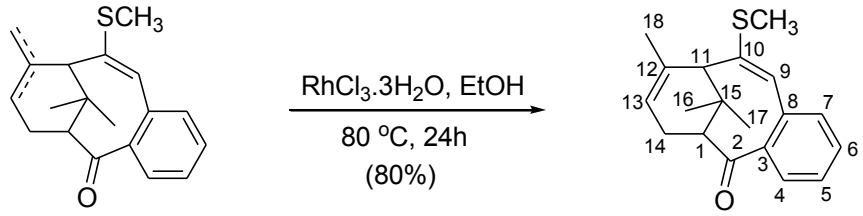
Scheme-23:



Further acetate takes hydroxyl proton and lone pair of electron moves towards Lead as a result, fragmented products namely thionium ion **56** and lead diacetate are formed. Fragmentation reaction in this case can be dubbed as metal assisted Grob-type fragmentation. Analogous to Grob fragmentation as explained in Scheme-1, here tertiary alcohol moiety acted as electrofugal group (a-b), the middle group (c-d) forms thionium ion and the nucleofugal group (X^-) *i.e.* $Pb(OAc)_2$ leaves with bonding pair of electron. Since it's a cyclic fragmentation, only two products were obtained similar to Scheme-2. The fragmentation reaction was thermodynamically favorable because of relief of ring strains and secondly due to high affinity of sulfur atom to Lead (hard soft acid base principle), where Lead literally pulls electrons and gets reduced to form Lead diacetate and substrate **35** gets oxidized (loss of two hydrogen atom). And hence the reaction may be called as oxidative fragmentation. And lastly, the eliminated second acetate anion instead of attacking thionium ion **56**, abstracts α acidic benzylic proton to form vinyl sulfide group. Alternately the formation of **34** can also be explained by attack of tertiary alcohol on to $Pb(OAc)_4$ followed by cleavage of C-C bond assisted by the lone pair of electrons on the sulfur moiety. A third possibility of formation of a cyclic intermediate by simultaneous attack of S and O may also be operative.

Here again, it is important to emphasize that sulfur played a crucial role in fragmentation step.

Scheme-24:



34 **57**

Though success was achieved in getting ABC skeleton of taxane system but it was obtained as a mixture of *exo* and *endo* olefinic isomers. Therefore, compound **34** was subjected to isomerization by refluxing it with catalytic amount of Rhodium trichloride in ethanol. After 24h, GC analysis revealed the presence of a single peak and therefore product **57** was purified by filtration column chromatography (silica gel) to yield thermodynamically more stable product.

IR spectrum of **57** displayed a strong band at 1681 cm^{-1} due to the presence of a carbonyl group.

^{1}H NMR spectrum of **57** displayed following pattern. The triplets at 7.25 (J = 7.33 Hz) & 7.16 (J = 7.33 Hz) and doublets at 7.09 (J = 7.33 Hz) & 7.18 (J = 7.33 Hz) each integrating for one proton and were assigned to aromatic protons at C-4, 5, 6 & 7 respectively. A singlet that appeared at δ 6.16 integrating for one proton corresponded to olefinic proton at C-9 position. A singlet at δ 4.84 integrating for one was ascribed to C-13 olefinic proton. The multiplets appeared at δ 2.10-2.37 integrating for four protons were attributed to methylene protons (C-14) and ring juncture (C-1 and C-11) methine protons respectively. The three sharp singlets appeared at δ 1.43, 1.22 & 1.12 integrating for three, three and six protons corresponded to $–SCH_3$, vinylic methyl and geminal dimethyls respectively.

^{13}C NMR spectrum of **57** along with DEPT spectrum revealed six quaternary signals. The most downfield signal at δ 211.1 was attributed to carbonyl. The downfield signal at δ 140.6, 140.0, 132.2 & 131.7 were assigned to carbons at C-10, 8, 12, & 3 respectively. While the upfield quaternary signal appeared at δ 33.0 corresponded to C-15 carbon. The down field methines at 127.0, 125, 124 and 119.4 were ascribed to aromatic and olefinic carbons respectively. While the upfield methines at δ 56.3 & 53.9 correspond to ring junction (C-1 and C-11) carbons. The only methylene signal appeared at δ 24.8 was assigned to C-14 carbon. The upfield methyls that appeared at δ 29.8, 26.6, 21.9 & 16.0 which were ascribed to C-16, 17, 18 and $–S\underline{C}H_3$ carbons.

GCMS spectrum of **57** displayed single peak and its corresponding mass revealed molecular ion peak at 298 and other major peaks appeared at 283, 270, 251, 223, 153 & 77.

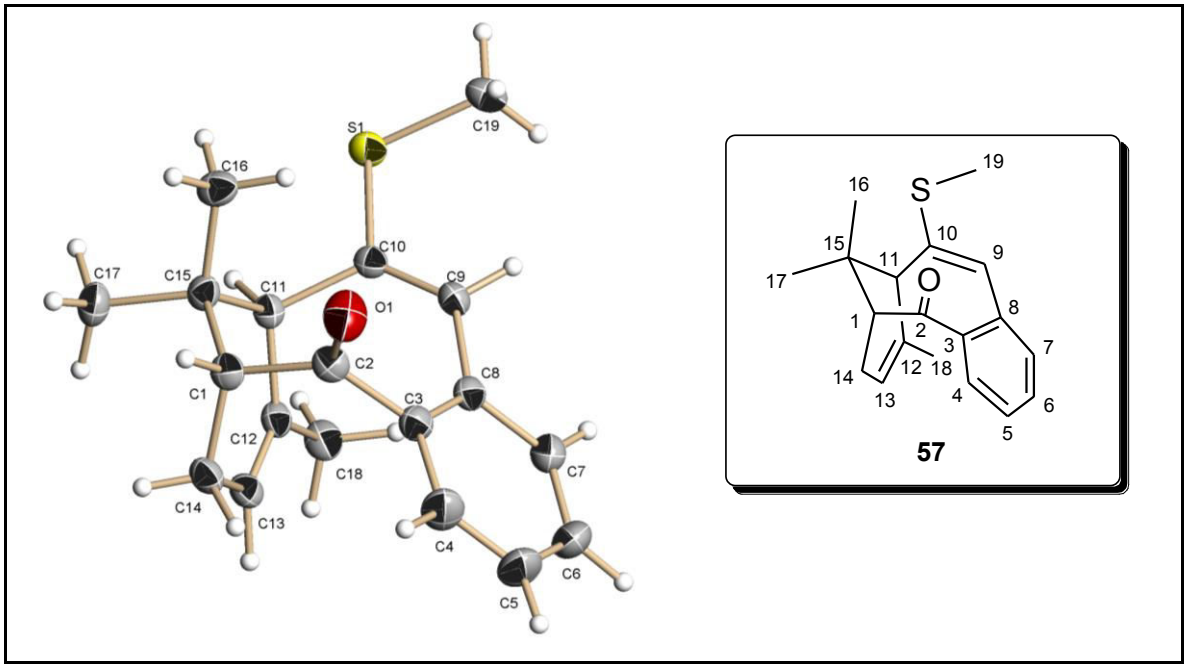


Figure-1: ORTEP drawing of ABC ring system (**57**) of taxol

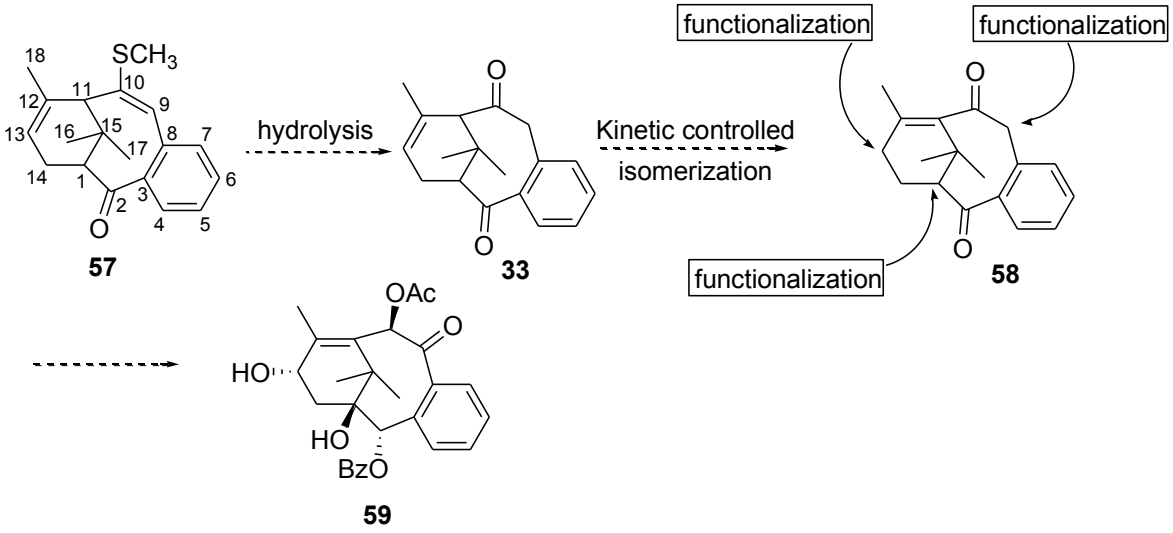
Finally, single crystal X-ray crystallography of compound **57** as shown in Figure-1 provided the unambiguous evidence and vindicated assigned structure. The crystal structure also revealed that **57** exists in *endo*-form. Shea and co-workers shown that a 6-8-6 bridged fused systems can adopt two atropisomeric conformations namely *endo* & *exo*-forms depending upon substituents.[24] *Endo*-form means, where the A-ring and C-ring are closer and nearly parallel to each other and *exo*-form means the A-ring and C-ring away from each other and are linear. The naturally occurring taxol and other taxanes exist in *endo*-form.

The primary goal was to construct ABC ring system of taxol was accomplished. However it was decided to move further and attempt functionalization of AB part of obtained skeleton as delineated in Scheme-25. It is pertinent to mention that Kuwajima team converted C-aromatic ABC taxane system to the total synthesis of taxol, a unique approach among all six total syntheses reported. In this connection as portrayed in Scheme-25, it was envisioned that hydrolysis of vinyl sulfide moiety would unmask the ketone at C-11 position (**33**→**57**) and by kinetic controlled enolization double bond can be brought in the right position i.e. at C-11 and C-12 bridgehead position (**57**→**58**).

Further oxygenation at C-1, C-9 and C-13 would furnish lead to complete AB functionalized C-aromatic taxol **59**.

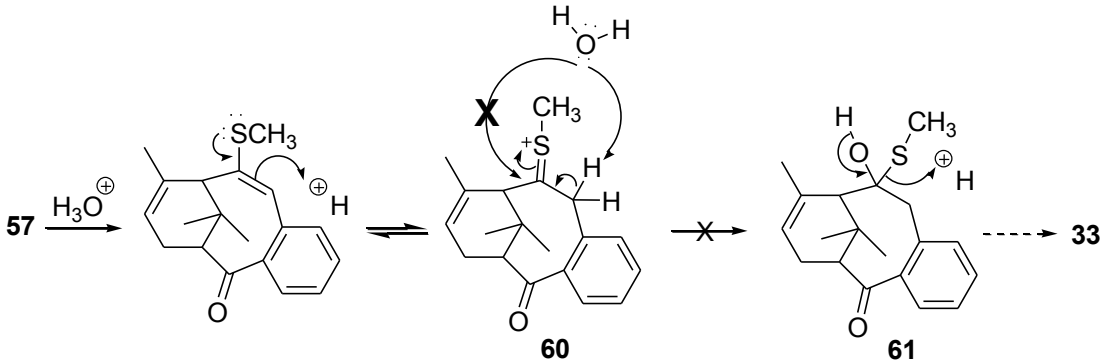
Actually vinyl sulfide moiety present in ABC skeleton after fragmentation is nothing but a masked ketone group. Again it was recognized the help of sulfur even after key fragmentation step. Hydroxyl functionality at C-1 could be introduced on **33** or **34**, and there are several methods available to do the job. Moreover since many researchers have reported the introduction of C-1 hydroxylation without any difficulty in their course of taxol synthesis, therefore the attention was directed to isomerisation of double bond *i.e.* to shift at bridgehead position. Therefore it was required to hydrolyze vinyl sulfide first as discussed earlier.

Scheme-25:



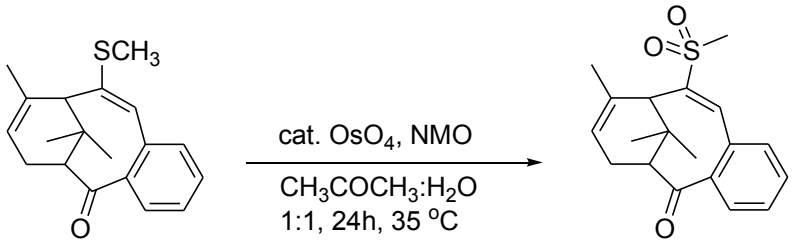
Thus, the compound **57** was subjected to several methods known for the hydrolysis of vinyl sulfide group. Accordingly, **57** was treated with $HgCl_2$, $Hg(OAc)_2$, CF_3COOH, dil. H_2SO_4, $BF_3.OEt_2$, $SnCl_4$ and $TiCl_4$. However none of acidic conditions were able to unmask the carbonyl group and the starting material recovered back.

Scheme-26:



The reason for failure of acidic hydrolysis of **57** can be explained mechanistically in Scheme-26. In presence of acid **57** gets protonated to form intermediate **60** i.e. thionium ion species, a similar kind generated in fragmentation step. But instead of Markovnikov's addition, conjugate base abstracts benzylic proton because of its high acidity and as a result starting material is recovered back.

Scheme-27:



33 **62**

After failure of hydrolysis it was thought to attempt dihydroxylation at vinyl sulfide moiety and then attempt hydrolysis. Therefore, compound **57** was treated with catalytic amount of Osmium tetraoxide and co-oxidant *N*-methylmorpholine *N*-oxide (NMO) using acetone:water (v/v) 1:1 as a binary solvent system and the reaction mixture was stirred for 24 h at 35 °C to afford vinyl sulfone **62** in 90% yield (Scheme-27).

IR spectrum of **62** displayed strong band at 1678 cm^{-1} corresponding to conjugated carbonyl group and the bands at 769 and 669 cm^{-1} correspond to sulfone group.

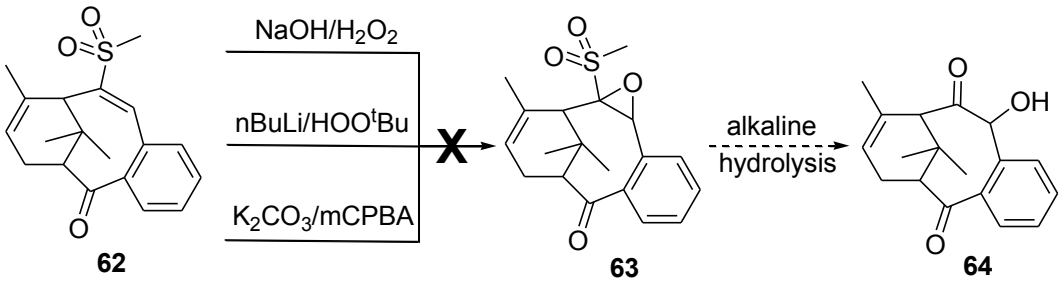
^{1}H NMR spectrum of **62** displayed following pattern. The presence of singlets at δ 7.50 & 4.74 integrating for one proton each were attributed to two olefinic protons present in molecule, indicated no dihydroxylation occurred and only oxidation of sulfur to sulfone occured.

Mass spectrum of **62** revealed molecular ion peak at 331 (M^++1) and other prominent peak at 301, 277, 263, 150, 102.

Addition of excess of OsO_4 and stirring the reaction mixture further for 8 days failed to deliver any dihydroxylation product.

It was thought to attempt nucleophilic epoxidation of obtained vinyl sulfone compound **62** which on hydrolysis may deliver **64** (Scheme-28). Thus, compound **62** was subjected to various nucleophilic epoxidizing reagents *i.e.* $NaOH/H_2O_2$, $nBuLi/HOO^tBu$, and K_2CO_3/*m*CPBA, however none of the attempted methods worked and starting material was recovered.

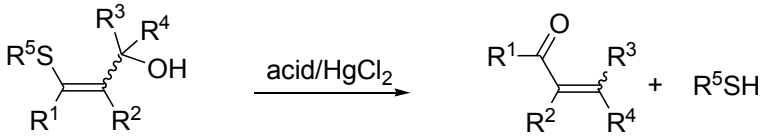
Scheme-28:



62 **63** **64**

Having failed to hydrolyse the sulfide or sulfone it was decided to look for alternative methods. Literature survey revealed the hydroxyl group assisted hydrolysis of thioenol ether.

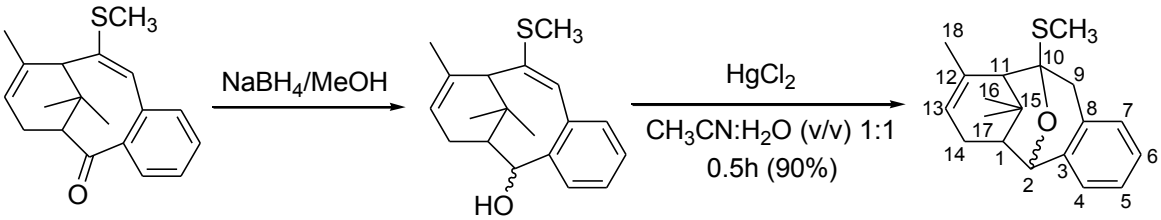
Scheme-29:



65 **66**

The β-alkyl thio allylic alcohols **65** on treatment with acid or with mercuric chloride in neutral or acidic medium gives α-ethylenic carbonyl compound **66**, a methodology reported by Pellet and Huet (Scheme-29).[25]

Scheme-30:



57 **67** **68**

Since in substrate **57** there is one more conjugated π bond of benzene ring, it was thought to utilize this methodology on substrate **67**. Thus, initially the compound **57** was reduced with sodium borohydride in methanol to get alcohol **67** and this alcoholic compound **67** was further treated with mercuric chloride in $CH_3CN:H_2O$ (v/v) 1:1 for half an hour to afford bridged ether compound **68** in 90% yield.

^{1}H NMR spectrum of **68** displayed following pattern. The multiplets at δ 7.22 & 7.06 integrating for two protons each correspond to aromatic protons. A doublet at δ 5.50 integrating for one proton with coupling constant J = 10 Hz corresponded to carbinol proton. A broad singlet at δ 4.93 integrating for one was assigned to olefinic proton. The spectrum displayed AB pattern. The doublet at δ 3.50 with coupling constant $J_{H9,H10}$ = 18

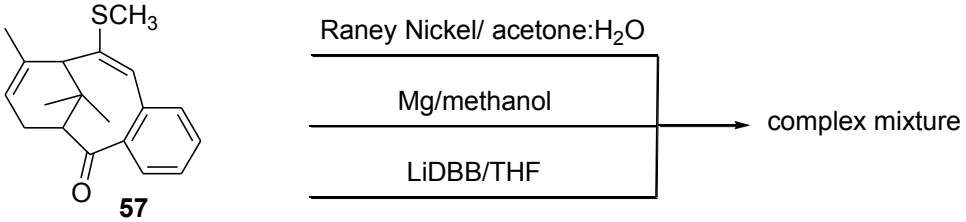
Hz corresponded to one of benzylic proton and the other proton appeared at δ 3.00 with coupling constant $J_{H9,H10}$ = 18 Hz. A singlet at δ 2.33 integrating for three protons was ascribed to $–SCH_3$ group. Three sharp singlets at 1.91, 1.82 and 1.09 integrating for three protons each were assigned to vinylic methyl and geminal dimethyls respectively.

^{13}C NMR spectrum of **68** along with DEPT spectrum revealed five quaternary signals at δ 135.7, 135.0, 134.7, 82.5 and 26.3, the first three downfield signals were attributed to aromatics and olefinic carbons while the last two upfield signals were assigned to C-10 and C-15 carbons respectively. The five downfield methines appeared at δ 126.8, 126.3, 126.1, 123.8 & 122.2 were ascribed to four aromatic and one olefinic carbon while the upfield methines at δ 76.1, 54.8 & 38.4 were assigned to C-2, C-1 and C-11 respectively. The two methylenes appeared at δ 35.6 and 28.7 corresponded to C-9 and C-14 respectively. The four methyls that appeared at δ 31.8, 29.9, 27.9 & 11.6 were assigned to C-18, C-16, C-17 & -S<u>C</u>H_3.

GCMS spectrum of **68** displayed single peak and its corresponding mass revealed molecular ion peak at 300 and other major peaks appeared at 285 ($M^+–CH_3$), 252 ($M^+–CH_3SH$), 220, 209, 181, 121, 105 and 91.

The formation of bridged ether compound **68** can be explained by initial protonation of **67** resulting in thionium species and which further gets intramolecularly trapped by C-2 hydroxyl moiety leading to the formation of compound **68**. Actually it was expected that substrate **64** should follow push pull mechanism in similar line with the reported methodology as depicted in Scheme-29. It is believed that instead of protonation of alcohol and further pushing of electrons by sulfur to eliminate alcohol, vinyl sulfide gets protonated first to form thionium ion and intramolecularly gets trapped by hydroxyl group to form bridged ether compound **68**.

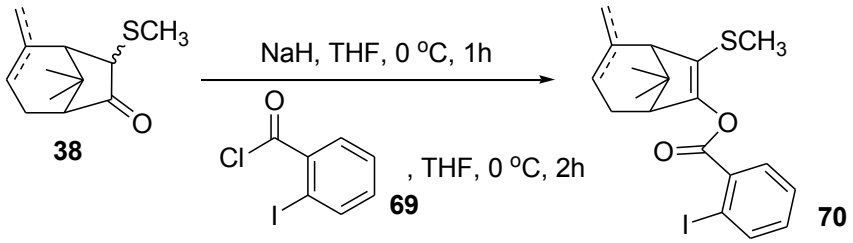
Scheme-31:



Attempted removal of $–SCH_3$ group by subjecting compound **57** to Raney-Nickel catalyst, led to complex reaction mixture as seen by TLC analysis. In addition, attempted removal of $–SCH_3$ group by subjecting compound **57** either to Mg in methanol or Lithium di-*tert*-butyl-biphenyl (Li-DBB), led to the formation multiple spots (TLC) and therefore further analysis was abandoned (Scheme-31).

After failure of hydrolysis by utilizing large number of methods it was decided to take a detour. Therefore, instead of C-alkylation of bicyclic unit **38**, C-acylation was envisioned as a result of it, after crucial fragmentation step there will not be vinyl sulfide moiety.

Scheme-32:



Therefore compound **38** was enolized by treating with sodium hydride in THF at 0 °C. To this enlolate, *o*-iodo benzoyl chloride was added slowly at 0 °C affording O-acylated product instead of desired C-acylated compound (Scheme-32).

IR spectrum of **70** displayed a strong band at 1740 cm^{-1} which indicates the presence of conjugated carbonyl.

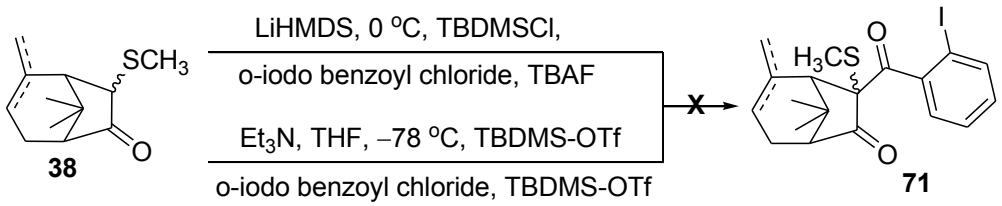
^{1}H NMR spectrum of **70** displayed following pattern. A broad singlet at δ 5.0 and multiplet at δ 4.6 integrating in the ratio 1:2 were ascribed to olefinic protons, vindicates *exo* cyclic and *endo* cyclic double bond in the molecule. The two sharp singlets at δ 2.12 and 2.35 were attributed to $–SCH_3$ group.

^{13}C NMR spectrum of **70** along with DEPT spectrum displayed following pattern. The most downfield signals at δ 163.4 & 163.7 were assigned to characteristic signals of ester carbonyl and hence formation of O-acylated product was confirmed, followed by additional evidence of the presence of ten quaternary and four methylenes carbons. This confirmed O-acylation and not the desired C-acylation. The presence of two isomers was due to the fact that the starting compound was used as a mixture of isomers.

The use of lithium enolate of **38** with o-iodo benzoyl chloride at –78 °C also led to the formation of O-acylated product.

There was a sole example reported in literature where kinetically favoured O-acylated compound was converted into thermodynamically favoured C-acylated compound catalyzed by 4-(dimethylamino)pyridine (DMAP)[26]. Hence, in order to rearrange the O-acylated product to C-acylated one, compound **70** was mixed with DMAP in THF and refluxed it for several days, but there was no change in starting material as was confirmed by GC analysis.

Scheme-33



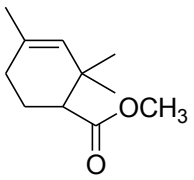
The formation of O-acylated compound instead of desired C-acylated product might be due to mismatch pairing (hard-soft acid-base principle). We believe that sodium or lithium form tight ion pairs with enolate and hence it was necessary to separate them so that there will be some negative charge on carbon. To this perspective, instead of metal ions usage of bulky positive charged counter ions would be helpful. Accordingly, compound **38** was enolized by LiHMDS in THF at 0 °C followed by addition of TBDMSCl in THF slowly and reaction mixture was stirred for 2h at 0 °C and then cooled to –78 °C and to it *o*-iodo benzoyl chloride was added slowly. To above reaction mixture tetrabutyl ammonium fluoride (TBAF) was added and stirred for three hours (Scheme-33). However, TLC analysis revealed no new product formation. Consequently reaction mixture was warmed to 0 °C and 25 °C stepwise, again TLC analysis showed no new product was formed and starting materials were recovered. In an another attempt, silyl enol ether of **38** was made *in-situ* by using triethyl amine and *tert*-butyl dimethyl silyl triflate (TBDMSOTf) at 0 °C in THF and stirred for 2 h and to it was slowly added *o*-iodo benzoyl chloride in THF and stirred at same temperature. Further, TBDMSOTf was added as a Lewis acid, to above reaction mixture at 0 °C and stirred for 3 h but TLC analysis showed neither any C-acylation nor O-acylation of **38** and starting materials were recovered. It is believed and hoped that selective C-acylation could be done by softening electrophile, instead of *o*-iodo benzoyl chloride to this effect, *o*-iodo benzoyl cyanide. However due to time constraints it was not attempted.

1.3.3 Conclusion:

In conclusion, we have demonstrated a concise, simple, practical and convenient route to access C-aromatic ABC ring system of Taxol with differentiated carbonyl groups for further elaborations, using cheap and readily available starting materials. No functional group protection-deprotection steps were required in the synthetic sequence. The salient feature of this protocol is the versatile role played by sulfur in C–C bond formation and cleavage in its various oxidation state *viz.*, (i) sulfoxide stabilized anion in C-C bond formation to furnish β-keto sulfoxide, (ii) sulfoxide mediated intramolecular Pummerer cyclization forming bicyclic compound (C-10 and C-11 bond), (iii) as α-keto sulfide, stabilizing enolate, in forming coupled product during alkylation (C-9 and C-10 bond) and (iv) lastly pivotal lead tetraacetate cleavage of β-methylsulfide alcohol (C-2–C-10 bond) leading to the formation of vinyl sulfide group (masked ketone). Literally sulfur acted as a vehicle for vital connections of C-C bond and fragmentation of C-C bond to deliver ABC ring skeleton of Taxol. We believe that using this practical five step protocol *i.e.* condensation-Pummerer-coupling-annulation-fragmentation will deliver a large number of advanced taxoids as well as fused ring systems whose further elaboration may lead to complex fused natural products. The success of the above protocol will provide impetus for the synthesis of more complicated CD ring and its conversion to more advanced taxoids.

1.3.4 Experimental:

1.3.4.1 Preparation of methyl 2,2,4-trimethylcyclohex-3-enecarboxylate (40):[14]



40

To a solution of methyl acrylate (2 mL, 0.0155 mmol) and hydroquinone (10 mg) in CH_2Cl_2 (10 mL) at room temperature was added 2,4-dimethyl-1,3-pentadiene (1.40 mL, 0.0186 mmol). The resulting solution was sealed in seal-tube, and then kept in a steel-bomb which further placed in an oil bath at 140 ^oC for 36h. The solvent was removed by distillation. Purification of the crude residue by high vacuum distillation (1 torr, oil bath temp. 100 ^oC) afforded ester **40** as a clear oil.

Chemical Formula: $C_{11}H_{18}O_2$, 182

Yield: 2.16 g (75 %)

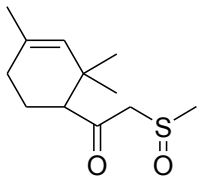
IR ($CHCl_3$): ν 1732 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.06 (s, 1H), 3.66 (s, 3H), 2.40-2.25 (m, 1H), 2.00-1.65 (m, 3H), 1.62 (s, 3H), 1.09 (s, 3H), 1.00 (m, 1H), 0.89 (s, 3H)

^{13}C NMR ($CDCl_3$, 50 MHz): δ 174.6 (C), 131.5 (CH), 130.5 (C), 50.4 (CH_3), 49.5 (CH), 30.8 (C), 29.6 (CH_3), 28.8 (CH_2), 24.1 (CH_3), 22.8 (CH_3), 22.0 (CH_2)

MS (m/z): 182 (M^+), 167, 150, 122, 107, 91

1.3.4.2 Preparation of 2-(methylsulfinyl)-1-(2,2,4-trimethylcyclohex-3-enyl)ethanone (39):[15]



39

Dimethyl sulfoxide (0.7 mL, 10 mmol) was dissolved in 10 mL of THF in an argon-purged flask, and sodium hydride (0.395 g, 8.24 mmol) as 50 % dispersion in mineral oil, was added all at once. The reaction mixture was refluxed for 2 h at 65 ^oC, and then cooled to 0 ^oC. A solution of methyl 2,2,4-trimethylcyclohex-3-enecarboxylate **40** (1 g, 5.5 mmol) in THF (20 mL) was added slowly to above prepared grey coloured sodium dimsyl solution over a period of 1 h and left over night at room temperature. The

reaction mixture was poured on a mixture of 10 M hydrochloric acid (10 mL) and ice. The organic layer was separated and aqueous layer was extracted with ether (3 x 20 mL). The combined organic layers were washed dilute sodium bicarbonate solution and then with brine solution, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and the residue obtained was purified by the column chromatography (silica gel, 2 % methanol/dichloromethane, gradient elution), which provided **39** as a gummy oil.

Chemical Formula: $C_{12}H_{20}O_2S$, 228

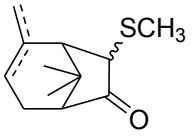
Yield: 0.870 g (70 %)

IR (neat): ν 1704, 1030 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.05 (s, 1H), 4.10 (d, *J* = 15 Hz, 1H), 3.85 (d, *J* = 15 Hz, 1H), 2.76 (s, 3H), 2.74 (s, 3H), 2.75-2.55 (m, 1H), 2.15-1.70 (m, 2H), 1.63 (s, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 1.10 (m, 1H), 0.98 (s, 3H), 0.98 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 206.3 (C), 131.5 (CH), 130.6 (C), 65.9 (CH_2), 65.3 (CH_2), 57.1 (CH), 38.6 (CH), 38.2 (CH), 34.6 (C), 29.9 (CH_3), 28.6 (CH_2), 24.2 (CH_3), 22.8 (CH_3), 21.2 (CH_2)

1.3.4.3 Preparation of bicyclic unit (38):[16]



38

Trifluoroacetic anhydride (5.45 mL, 0.039 mmol) was added at once to a stirred solution of β-ketosulfoxide **39** (7.500 g, 0.032 mmol) in anhydrous dichloromethane (300 mL) at room temperature under an atmosphere of argon. The reaction mixture was refluxed, after consumption of starting material as indicated by TLC analysis (3h). It was quenched by slow addition of aqueous saturated sodium bicarbonate solution (50 mL) at 0 ^oC. The organic layer was separated and aqueous layer was extracted with dichloromethane (3 x 25 mL), combined organic layers were washed with brine solution, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and the residue obtained was purified by flash column chromatography (230-400 mesh size silica gel, 0.5-1.0 % EtOAc/pet. ether gradient elution) afforded fraction-A R_f 0.50 (pet. ether/ethyl acetate, 8:2) & fraction-B R_f 0.45 (pet. ether/ethyl acetate, 8:2) of **38** respectively.

Chemical Formula: $C_{12}H_{18}OS$, 210

Fraction-A:

Yield: 2 g (30%)

IR (neat): ν 1735 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.17 (s, 1H), 2.9 (s, 1H), 2.35 & 2.40 (s, 3H), 2.40-2.00 (m, 3H), 1.75 (s, 3H), 1.25 & 1.20 (s, 3H), 1.06 & 1.05 (s, 3H)

^{13}C NMR (CDCl3, 50 MHz): δ 219.3 (C), 218.8 (C), 147.9 (C), 141.5 (C), 117.2 (CH), 108.8 (CH_2), 96.2 (C), 58.1(CH), 55.7(CH), 55.1(CH), 37.0 (C), 28.9 (CH_2), 28.6 (CH_3), 22.9 (CH_3), 21.9 (CH_3), 18.5 (CH_3)

MS (m/z): 210 (M^+), 195, 164, 154, 135, 122, 107, 91, 77

Fraction-B:

Yield: 2.0 g (30 %)

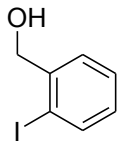
IR (neat): ν 1735 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.84 (m, 1H), 4.74 (m, 1H), 3.57 (m, 2H), 2.29 and 2.27 (s, 3H), 2.25-2.00 (m, 2H), 1.80-1.60 (m, 2H), 1.11 (s, 3H), 1.07 (s, 3H), 1.02 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 218.4 (C), 217.7 (C), 144.1 (C), 137.4 (C), 117.9 (CH), 111.4 (CH_2), 57.9 (CH), 55.6 (CH), 54.9 (CH), 53.4 (CH), 52.4 (CH), 50.7 (CH), 37.7 (C), 36.4 (C), 29.4 (CH_2), 27.0 (CH_3), 26.9 (CH_3), 26.1 (CH_2), 24.4 (CH_3), 21.8 (CH_3), 19.4 (CH_3), 15.3 (CH_3), 15.3 (CH_3), 14.9 (CH_3).

MS (m/z): 210 (M^+), 195, 164, 154, 135, 122, 107, 91, 77.

1.3.4.4 Preparation of (2-iodophenyl)methanol (48):[21]



48

To a solution of 2-iodo-benzoic acid (2.48 g, 10 mmol) in THF (5 ml) was introduced slowly borane.THF complex in THF (5 ml, 2M) over a period of 20 min. After vigorous stirring for 2 h at room temperature, the excess hydride was carefully destroyed with water, the organic layer was separated and aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with dilute sodium bicarbonate solution and then with brine solution, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and the crude product **48** obtained was used as such for further reaction.

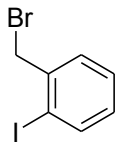
Chemical Formula: C_7H_7IO, 234.

Yield: 2.1 g (90%)

M. P.: 86-88 ^{o}C

IR ($CHCl_3$): 3338, 2947, 1585, 1561, 1465, 1434, 1164 cm^{-1}

1.3.4.5 Preparation of 1-(bromomethyl)-2-iodobenzene:[21]



37

To a stirred solution of phosphorus tribromide (4.240 g, 15.66 mmol) in benzene (27 mL) at –5 ^{o}C was added slowly a solution of pyridine (0.84 mL, 10 mmol) and benzene (5 mL). To the reaction mixture maintained below 10 ^{o}C, solid (2-iodophenyl)methanol **48** (10.0 g, 42.73 mmol) was added over 10 min. The mixture was then left for two days at room temperature, was heated at 50 ^{o}C for 1 h. cooled and decomposed with 200 mL 5 % HCl and extracted with chloroform. The extract was quickly washed with ice-cold saturated solution of $NaHCO_3$ and then with brine, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and the lachrymatic crude product **37** obtained used as such for further reaction.

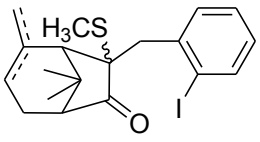
Chemical Formula: C_7H_6BrI, 296

Yield: 10.15 g (80%)

M. P.: 53-55 ^{o}C

^{1}H NMR: δ 7.80 (d, *J* = 7.9 Hz, 1H), 7.40 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.25 (m, 1H), 6.90 (td, *J* = 7.9, 1.5 Hz, 1H), 4.51 (s, 2H)

1.3.4.7 Preparation of 36:



36

The ketosulfide (**38**) (2 g, 9.523 mmol) in THF (20 mL) was added slowly over a period of 15 min to stirred a solution of NaH (50% dispersion in oil) (0.548g, 11.4 mmol) in THF (25 mL) at 0 ^{o}C under argon atmosphere. The reaction mixture became dark brown in colour after 1 h. 1-(Bromomethyl)-2-iodobenzene (**37**) (4.242 g, 14.28 mmol) in THF was added slowly (25 min) to sodium enolate and reaction mixture was stirred

for 3 h at 0 ^{o}C and then left overnight. The reaction mixture was poured in cold dilute hydrochloric acid solution, organic layer was separated, aqueous layer was extracted with ethyl acetate (3 x 25 mL), combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and the residue obtained was purified by flash column chromatography (230-400 mesh size silica gel, 0.5 % EtOAc/pet. ether gradient elution) which provided **36** as a gummy oil.

Chemical Formula: $C_{19}H_{23}IOS$, 426.0514

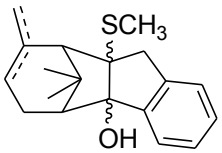
Yield: 2.840 g (70 %)

IR (neat): ν 1735 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.04-7.87 (m, aromatic-H), 7.37-7.25 (m, aromatic-H), 6.96-6.66 (m, aromatic-H) 5.36 (s, 1H), 4.92 (s, 1H), 4.85 (s, 1H), 3.54-2.98 (m, benzylic-H), 2.47-2.19 (m, benzylic-H), 1.98 (s, 3H), 1.62 and 1.60 (s, 3H), 1.43 and 1.40 (s, 3H), 1.16 (s, 3H), 0.99 (s, 3H)

^{13}C NMR ($CDCl_3$, 50 MHz): δ 219.1 (C), 216.5 (C), 146.4 (C), 140.8 (CH), 139.9 (CH), 139.6 (CH), 139.3 (CH), 130.4 (CH), 129.5 (CH), 128.5 (CH), 128.1 (CH), 127.6 (CH), 122.7 (CH), 120.4 (CH), 112.7 (CH_2), 103.3 (C), 59.7 (CH), 59.5 (C), 57.9 (CH), 56.0 (CH), 55.5 (CH), 54.5 (C), 43.4 (CH_2), 42.7 (CH_2), 38.6 (CH), 38.0 (CH), 31.3 (CH), 30.9 (CH_2), 29.7 (CH), 27.2 (CH_2), 26.9 (CH_3), 26.2 (CH_2), 24.1 (CH_3), 23.6 (CH_2), 23.3 (CH_3), 13.9 (CH_3), 12.4 (CH_3)

1.3.4.7 Preparation of 35:



35

A two necked 100 mL round bottom flask charged with alkylated compound (**36**) (0.426 g, 1.0 mmol) and THF (50 mL) was kept at –78 ^{o}C under argon atmosphere. nBuLi (1 mL, 1.5 mmol, 1.5 M) was added slowly over a period of 10 min to above stirred solution and the reaction mixture was stirred for 5 h. After completion of the reaction (TLC analysis) it was quenched with saturated aqueous ammonium chloride solution (1 mL), allowed warming to room temperature. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered,

concentrated *in vacuo*, and residue obtained was purified by column chromatography (silica gel, 5 % EtOAc/pet. ether gradient elution) provided **35** as a pale yellow solid.

Chemical Formula: $C_{19}H_{24}OS$, 300

Yield: 0.240 g (80 %)

M.P.: 210-215 °C

IR (neat): ν 3400 cm^{-1}

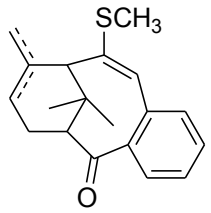
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.40-7.00 (m, aromatic-H), 4.79 (m, olefinic-H), 4.64 (m, olefinic-H), 3.9-2.5 (benzylic-H), 2.40-1.75 (m, CH_2), 2.14 and 2.04 (s, SCH_3), 1.71 and 1.65 (s, allylic-CH_3), 1.43 (s), 1.09 (s, CH_3), 0.92 (s, CH_3), 0.68 (s, CH_3)

^{13}C NMR ($CDCl_3$, 50 MHz): δ 150.8 (C), 150.2 (C), 145.8 (C), 142.0 (C), 141.4 (C), 138.5 (C), 128.7 (CH), 127.9 (CH), 126.8 (CH), 125.2 (CH), 124.5 (CH), 124.3 (CH), 119.7 (CH), 110.3 (CH_2), 99.0 (C), 92.3 (C), 77.4 (C), 70.8 (C), 66.4 (CH), 66.3 (CH), 54.3 (CH), 48.9 (CH_2), 44.0 (C), 43.8 (CH_2), 41.8 (C), 30.9 (CH_2), 29.7 (CH_2), 27.9 (CH_3), 27.5 (CH_3) , 27.0 (CH_3), 26.0 (CH_3), 25.3 (CH_3), 23.1 (CH_2), 14.2 (C), 13.2 (C).

MS (m/z): 331 (M^++1), 284, 183, 277, 181

Anal. Calcd. For $C_{19}H_{24}OS$: C, 75.95; H, 8.05; O, 5.32; S, 10.67 found C, 76.07; H, 7.43; S, 10.99 %

1.3.4.8 Preparation of 34:



34

A 100 mL two-neck RB flask was charged with Lead tetraacetate (0.886 g, 2.0 mmol) along with glacial acetic acid (5 mL) and toluene (20 mL) under argon atmosphere. The mixture was cooled to 0 ^oC and β-hydroxy sulfide **35** (0.300 g, 1.0 mmol) in toluene was added slowly and reaction mixture was stirred at 0 ^oC for 6 h. The reaction was quenched with saturated aqueous ammonium chloride solution (10 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 25 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate until neutralization and then with brine, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and the residue obtained was purified by column chromatography (silica gel, 5 % EtOAc/pet. ether gradient elution) which provided **34** as a white solid.

Chemical Formula: $C_{19}H_{22}OS$, 298

Yield: 0.223 g (75 %)

M.P.: 150-160 ^{o}C

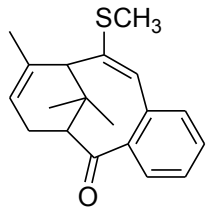
IR (neat): ν 1681 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.35-6.91 (m, 10H), 6.03 (s, 1H), 5.91 (s, 1H), 4.83 (m, 1H), 4.73 (s, 1H), 2.81 (s, 1H), 2.60-2.30 (m, 2H), 2.31 (s, 3H), 2.29 (s, 3H), 2.25-1.50 (m, 2H), 1.44 (s, 3H), 1.23 (s, 3H), 1.19 (s, 3H), 1.14 (s, 3H), 1.13 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 213 (C), 145.5 (C), 142.2 (C), 140.9 (C), 140.6 (C), 139.0 (C), 133.6 (C), 132.7 (C), 132.2 (C), 130.1 (CH), 129.5 (CH), 128.8 (CH), 128.0 (CH), 128.0 (CH), 127.8 (CH), 126.8 (CH), 125.8 (CH), 125.8 (CH), 124.9 (CH), 120.2 (C), 119.6 (CH), 116.8 (CH), 113.9 (C), 113.3 (CH_2), 72.5 (C), 61.3 (CH), 56.7 (CH), 55.8 (CH), 54.5 (CH), 34.1 (C), 33.5 (C), 30.8 (CH_3), 30.2 (CH_3), 27.1 (CH_3), 25.3 (CH_2), 23.2 (CH_3), 22.4 (CH_2), 17.1 (CH_3), 16.6 (CH_3).

MS (m/z): 298 (M^+), 270, 283, 251, 223, 201, 174, 165, 153, 115, 77

1.3.4.9 Preparation of 57:



57

A mixture of compound **34** (0.298 g 1.0 mmol), $RhCl_3.3H_2O$ (0.023 g, 0.1 mmol) in ethanol (25 mL) was refluxed in 100 mL single-neck RB flask under argon atmosphere. After 24 h (GC analysis) the reaction mixture was quenched by adding triethyl amine (1 mL). The solvent was removed *in vacuo*, solid material was directly adsorbed on silica gel and passed through a column of silica gel using 5 % ethyl acetate/pet. ether as eluent, furnished **57** as a white solid.

Chemical Formula: $C_{19}H_{22}OS$, 298

Yield: 0.238 g (80%)

M.P.: 150-152 ^{o}C

IR (neat): ν 1681 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.20 (t, *J* = 6 Hz, 1H), 7.09 (t, *J* = 6 Hz, 1H), 7.18 (d, *J* = 4 Hz, 1H), 7.16 (d, *J* = 6 Hz, 1H), 6.00 (s, 1H), 4.84 (s, 1H), 2.37-2.10 (m, 4H), 2.27(s, 3H), 1.43 (s, 3H), 1.22 (s, 3H), 1.12 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 211.2 (C), 140.6 (C), 140.0 (C), 132.2 (C), 131.7 (C), 2x127 (CH), 125.0 (CH), 2x124.5 (CH), 119.4 (CH), 56.3 (CH), 53.9 (CH), 33.0 (C), 29.8 (CH_3), 26.6 (CH_3), 24.8 (CH_2), 21.9 (CH_3), 16.0 (CH_3).

MS (m/z): 298 (M^+), 270, 283, 251, 223, 201, 174, 165, 153, 115, 77

Anal. Calcd. For $C_{19}H_{22}OS$: C, 76.46; H, 7.43; O, 5.36; S, 10.74%. Found C 76.74, H 7.79%.

Crystal Data of 57

Table 1. Crystal data and structure refinement for **57**.

Identification code	**57**
Empirical formula	C_{19} H_{22} O S
Formula weight	298.43
Temperature	297(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 6.788(3) Å alpha = 86.270(6)º. b = 7.439(3) Å beta = 84.471(6)º. c = 16.277(7) Å gamma = 82.023(7)º.
Volume	809.2(6) $Å^3$
Z, Calculated density	2, 1.225 Mg/m^3
Absorption coefficient	0.197 mm^{-1}
F(000)	320
Crystal size	0.74 x 0.59 x 0.26 mm
Theta range for data collection	1.26 to 25.00º.
Limiting indices	-8<=h<=8, -8<=k<=8, -19<=l<=19
Reflections collected / unique	7174 / 2758 [R(int) = 0.0207]
Completeness to theta = 25.00	96.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9500 and 0.8678
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2758 / 0 / 278
Goodness-of-fit on F^2	1.097
Final R indices [I>2sigma(I)]	R1 = 0.0373, wR2 = 0.1085
R indices (all data)	R1 = 0.0455, wR2 = 0.1208

Largest diff. peak and hole 0.244 and -0.143 e. $Å^{-3}$

Table 2. Bond lengths [Å] and angles [deg] for **57**

O(1)-C(10)	1.4244(18)	O(2)-C(2)-H(2)	111.4
O(1)-C(1)	1.4475(17)	C(3)-C(2)-H(2)	111.4
O(2)-C(10)	1.4124(19)	C(1)-C(2)-H(2)	111.4
O(2)-C(2)	1.4374(16)	C(4)-C(3)-C(8)	119.97(14)
C(1)-C(15)	1.527(2)	C(4)-C(3)-C(2)	122.47(14)
C(1)-C(11)	1.554(2)	C(8)-C(3)-C(2)	117.56(13)
C(1)-C(2)	1.5558(19)	C(5)-C(4)-C(3)	120.41(17)
C(2)-C(3)	1.5093(19)	C(5)-C(4)-H(4)	119.8
C(2)-H(2)	0.9800	C(3)-C(4)-H(4)	119.8
C(3)-C(4)	1.387(2)	C(6)-C(5)-C(4)	119.84(17)
C(3)-C(8)	1.394(2)	C(6)-C(5)-H(5)	120.1
C(4)-C(5)	1.381(2)	C(4)-C(5)-H(5)	120.1
C(4)-H(4)	0.9300	C(5)-C(6)-C(7)	120.16(17)
C(5)-C(6)	1.372(3)	C(5)-C(6)-H(6)	119.9
C(5)-H(5)	0.9300	C(7)-C(6)-H(6)	119.9
C(6)-C(7)	1.383(3)	C(6)-C(7)-C(8)	120.80(17)
C(6)-H(6)	0.9300	C(6)-C(7)-H(7)	119.6
C(7)-C(8)	1.388(2)	C(8)-C(7)-H(7)	119.6
C(7)-H(7)	0.9300	C(7)-C(8)-C(3)	118.71(15)
C(8)-C(9)	1.517(2)	C(7)-C(8)-C(9)	122.02(15)
C(9)-C(10)	1.507(2)	C(3)-C(8)-C(9)	119.22(14)
C(9)-H(9A)	0.9700	C(10)-C(9)-C(8)	111.26(13)
C(9)-H(9B)	0.9700	C(10)-C(9)-H(9A)	109.4
C(10)-H(10)	0.9800	C(8)-C(9)-H(9A)	109.4
C(11)-C(12)	1.510(2)	C(10)-C(9)-H(9B)	109.4
C(11)-C(16)	1.536(2)	C(8)-C(9)-H(9B)	109.4
C(11)-C(17)	1.544(2)	H(9A)-C(9)-H(9B)	108.0
C(12)-C(13)	1.325(2)	O(2)-C(10)-O(1)	105.89(12)
C(12)-H(12)	0.9300	O(2)-C(10)-C(9)	110.52(12)
C(13)-C(14)	1.484(3)	O(1)-C(10)-C(9)	110.34(13)
C(13)-C(18)	1.507(2)	O(2)-C(10)-H(10)	110.0
C(14)-C(15)	1.523(2)	O(1)-C(10)-H(10)	110.0
C(14)-H(14A)	0.9700	C(9)-C(10)-H(10)	110.0
C(14)-H(14B)	0.9700	C(12)-C(11)-C(16)	109.14(12)
C(15)-H(15A)	0.9700	C(12)-C(11)-C(17)	108.75(12)
C(15)-H(15B)	0.9700	C(16)-C(11)-C(17)	107.13(12)
C(16)-H(16A)	0.9600	C(12)-C(11)-C(1)	108.66(11)
C(16)-H(16B)	0.9600	C(16)-C(11)-C(1)	112.70(12)
C(16)-H(16C)	0.9600	C(17)-C(11)-C(1)	110.39(12)
C(17)-H(17A)	0.9600	C(13)-C(12)-C(11)	125.68(15)
C(17)-H(17B)	0.9600	C(13)-C(12)-H(12)	117.2
C(17)-H(17C)	0.9600	C(11)-C(12)-H(12)	117.2
C(18)-H(18A)	0.9600	C(12)-C(13)-C(14)	121.55(15)
C(18)-H(18B)	0.9600	C(12)-C(13)-C(18)	121.95(18)
C(18)-H(18C)	0.9600	C(14)-C(13)-C(18)	116.48(16)
C(10)-O(1)-C(1)	108.33(10)	C(13)-C(14)-C(15)	114.82(13)
C(10)-O(2)-C(2)	101.52(10)	C(13)-C(14)-H(14A)	108.6
O(1)-C(1)-C(15)	108.48(12)	C(15)-C(14)-H(14A)	108.6
O(1)-C(1)-C(11)	109.44(11)	C(13)-C(14)-H(14B)	108.6
C(15)-C(1)-C(11)	109.32(11)	C(15)-C(14)-H(14B)	108.6
O(1)-C(1)-C(2)	101.05(10)	H(14A)-C(14)-H(14B)	107.5
C(15)-C(1)-C(2)	114.27(12)	C(14)-C(15)-C(1)	112.14(13)
C(11)-C(1)-C(2)	113.80(11)	C(14)-C(15)-H(15A)	109.2
O(2)-C(2)-C(3)	107.56(11)	C(1)-C(15)-H(15A)	109.2
O(2)-C(2)-C(1)	101.75(10)	C(14)-C(15)-H(15B)	109.2
C(3)-C(2)-C(1)	112.99(11)	C(1)-C(15)-H(15B)	109.2

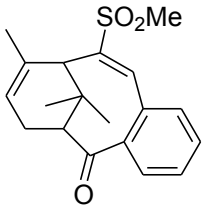
H(15A)-C(15)-H(15B)	107.9	C(11)-C(17)-H(17C)	109.5
C(11)-C(16)-H(16A)	109.5	H(17A)-C(17)-H(17C)	109.5
C(11)-C(16)-H(16B)	109.5	H(17B)-C(17)-H(17C)	109.5
H(16A)-C(16)-H(16B)	109.5	C(13)-C(18)-H(18A)	109.5
C(11)-C(16)-H(16C)	109.5	C(13)-C(18)-H(18B)	109.5
H(16A)-C(16)-H(16C)	109.5	H(18A)-C(18)-H(18B)	109.5
H(16B)-C(16)-H(16C)	109.5	C(13)-C(18)-H(18C)	109.5
C(11)-C(17)-H(17A)	109.5	H(18A)-C(18)-H(18C)	109.5
C(11)-C(17)-H(17B)	109.5	H(18B)-C(18)-H(18C)	109.5
H(17A)-C(17)-H(17B)	109.5		

Table 3. Torsion angles [deg] for **57**

C(10)-O(1)-C(1)-C(15)	127.21(13)
C(10)-O(1)-C(1)-C(11)	-113.58(12)
C(10)-O(1)-C(1)-C(2)	6.76(14)
C(10)-O(2)-C(2)-C(3)	-73.58(13)
C(10)-O(2)-C(2)-C(1)	45.39(13)
O(1)-C(1)-C(2)-O(2)	-31.94(12)
C(15)-C(1)-C(2)-O(2)	-148.19(12)
C(11)-C(1)-C(2)-O(2)	85.25(13)
O(1)-C(1)-C(2)-C(3)	83.09(13)
C(15)-C(1)-C(2)-C(3)	-33.17(16)
C(11)-C(1)-C(2)-C(3)	-159.72(11)
O(2)-C(2)-C(3)-C(4)	-140.72(14)
C(1)-C(2)-C(3)-C(4)	107.79(16)
O(2)-C(2)-C(3)-C(8)	40.03(16)
C(1)-C(2)-C(3)-C(8)	-71.46(15)
C(8)-C(3)-C(4)-C(5)	2.7(2)
C(2)-C(3)-C(4)-C(5)	-176.52(14)
C(3)-C(4)-C(5)-C(6)	0.1(3)
C(4)-C(5)-C(6)-C(7)	-2.2(3)
C(5)-C(6)-C(7)-C(8)	1.5(3)
C(6)-C(7)-C(8)-C(3)	1.3(2)
C(6)-C(7)-C(8)-C(9)	-176.33(15)
C(4)-C(3)-C(8)-C(7)	-3.3(2)
C(2)-C(3)-C(8)-C(7)	175.94(13)
C(4)-C(3)-C(8)-C(9)	174.33(14)
C(2)-C(3)-C(8)-C(9)	-6.4(2)
C(7)-C(8)-C(9)-C(10)	-175.71(14)
C(3)-C(8)-C(9)-C(10)	6.7(2)
C(2)-O(2)-C(10)-O(1)	-42.45(14)
C(2)-O(2)-C(10)-C(9)	77.05(13)
C(1)-O(1)-C(10)-O(2)	21.54(15)
C(1)-O(1)-C(10)-C(9)	-98.08(13)
C(8)-C(9)-C(10)-O(2)	-42.57(17)
C(8)-C(9)-C(10)-O(1)	74.21(16)
O(1)-C(1)-C(11)-C(12)	-170.13(11)
C(15)-C(1)-C(11)-C(12)	-51.44(15)
C(2)-C(1)-C(11)-C(12)	77.66(14)
O(1)-C(1)-C(11)-C(16)	68.78(14)
C(15)-C(1)-C(11)-C(16)	-172.53(12)

C(2)-C(1)-C(11)-C(16)	-43.43(16)
O(1)-C(1)-C(11)-C(17)	-50.96(15)
C(15)-C(1)-C(11)-C(17)	67.73(15)
C(2)-C(1)-C(11)-C(17)	-163.17(12)
C(16)-C(11)-C(12)-C(13)	147.18(15)
C(17)-C(11)-C(12)-C(13)	-96.27(18)
C(1)-C(11)-C(12)-C(13)	23.9(2)
C(11)-C(12)-C(13)-C(14)	-0.8(2)
C(11)-C(12)-C(13)-C(18)	-179.14(15)
C(12)-C(13)-C(14)-C(15)	6.5(2)
C(18)-C(13)-C(14)-C(15)	-175.06(14)
C(13)-C(14)-C(15)-C(1)	-36.38(19)
O(1)-C(1)-C(15)-C(14)	178.95(12)
C(11)-C(1)-C(15)-C(14)	59.66(16)
C(2)-C(1)-C(15)-C(14)	-69.19(16)

1.3.4.10 Preparation of 62:



62

A mixture of **57** (0.298 g, 1 mmol), OsO_4 (0.025 g, 0.1 mmol), 4-methylmorpholine 4-oxide (0.129 g, 1.1 mmol) and acetone: water (v/v) 10: 10 were stirred in an argon atmosphere until complete consumption of the starting materials was indicated by TLC analysis (~45 min). The reaction was quenched by addition of saturated solution of sodium sulfite (5 mL) and stirred for 30 min. The solvent was removed *in vacuo* and the resulting residue was dissolved in dichloromethane and washed with water (2 x 15 mL). The aqueous layer was extracted with dichloromethane (2 x 25 mL) and combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and the residue obtained was purified by column chromatography (silica gel, pet. ether/ethyl acetate, 4:1) which provided **62** as a yellow solid.

Chemical Formula: $C_{19}H_{22}O_3S$, 330

Yield: 0.297g (90%)

M.P.: 220-225 °C

IR ($CHCl_3$): ν 3019, 1678, 1215, 769, 669 cm^{-1}

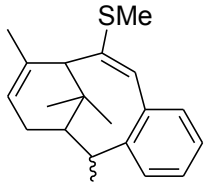
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.50 (s, 1H), 7.0 (m, 2H), 6.92 (m, 1H), 6.75 (m, 1H), 4.74 (s, 1H), 3.00 (s, 1H), 2.77 (s, 3H), 2.17-1.85 (m, 3H), 1.10 (s, 3H), 0.92 (s, 6H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 209.7 (C), 142.9(C), 140.0 (C), 139.5 (CH), 128.8 (C), 127.6 (CH), 127.0 (CH), 124.0 (CH), 120.6 (CH), 52.4 (CH), 46.8 (CH), 41.7 (CH_3), 32.5 (C), 28.2 (CH_3), 25.6 (CH_3), 23.6 (CH_2), 21.7(CH_3).

MS (m/z): 331 (M^++1), 301, 277, 263, 150, 102

Anal. Calcd. For $C_{19}H_{22}O_3S$: C, 69.06; H, 6.71; O, 14.53; S, 9.70% Found C, 69.15; H, 6.46; S, 10.66 %

1.3.4.11 Preparation for 67:



67

To a cold (0 ^oC) solution of **57** (0.298g, 1mmol) in methanol (50 mL) was added solid $NaBH_4$ (38g, 1mmol) and reaction mixture was stirred until complete consumption of the starting materials was indicated by TLC analysis (~3 h). The solvent was removed *in vacuo* and residue was poured slowly into ice cold 2N HCl solution and extracted with ethyl acetate (3 x 15 mL). The organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and crude product obtained **62** used as such for further reaction.

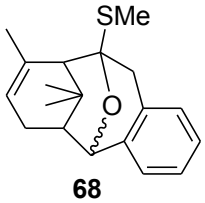
Chemical Formula: $C_{19}H_{24}OS$, 300

Yield: 0.270g (90%)

IR ($CHCl_3$): ν 3434.8, 1216 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.25-6.90 (m, 4H), 6.23 (s, 1H), 4.88 (d, *J* = 6 Hz, 1H), 4.60 (bs, 1H), 2.39 (s, 3H), 2.29 (s, 3H), 2.00-2.46 (m, 3H), 1.42 (s, 3H), 1.26 (s, 3H), 1.07 (s, 3H).

1.3.4.12 Preparation of 68:



68

A mixture of **67** (0.300 g, 1 mmol), $HgCl_2$ (0.272 g, 1 mmol), HCl (1mL, 2N), acetonitrile:water (v/v) 10:10 mL was stirred at room temperature until complete consumption of the starting materials was indicated by TLC analysis (~1 h). The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (50 mL) and washed with water (3 x 20 mL) and with saturated sodium bicarbonate solution and then with brine solution, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and residue obtained was purified by column chromatography (silica gel, pet. ether/ethyl acetate, 95:5) which provided **68** as a yellow solid.

Chemical Formula: $C_{19}H_{24}OS$, 300

Yield: 0.225g (75%)

M.P.: 187-189 °C

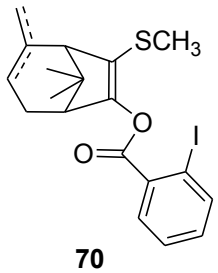
IR ($CHCl_3$): ν 995, 875 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.22 (m, 2H), 7.06 (m, 2H), 5.52 (d, *J* = 18 Hz, 1H), 4.93 (s, 1H), 3.52 (d, *J* = 18 Hz, 1H), 3.07 (d, *J* = 17. 43 Hz, 1H), 2.33 (s, 3H), 2.30 (s, 1H), 2.12 (s, 1H), 1.91 (s, 3H), 1.82 (s, 3H), 1.64 (m, 2H), 1.09 (s, 3H)

^{13}C NMR ($CDCl_3$, 50 MHz): δ 135.7 (C), 135 (C), 134.7 (C), 126.8 (CH), 126.3 (CH), 126.1 (CH), 123.8 (CH), 122.2 (CH), 82.5 (C), 76.1 (CH), 54.8 (CH), 38.4 (CH), 35.6 (CH_2), 31.8 (CH_3), 29.9 (CH_3), 28.7 (CH_2), 27.9 (CH_3), 26.3 (C), 11.6 (CH_3).

MS (m/z): 300 (M^+), 285, 272, 252, 220, 209, 181, 121, 105, 91

1.3.4.13 Preparation of 70:



70

A solution of ketosulfide **38** (0.210 g, 1.0 mmol) in THF (5 mL) was slowly to added slowly over a period of 15 min to stirred solution of NaH (50% dispersion in oil) (0.050 g, 1.1 mmol) in THF (10 mL) at 0 ^oC under argon atmosphere. The reaction mixture developed dark brown colour after 1 h. o-Iodobenzoyl chloride (0.293 g, 1.1 mmol) in THF (10 mL) was added slowly (5 min) to the above reaction and reaction mixture stirred for 3 h at 0 ^oC and then left overnight. The reaction was poured in cold dilute hydrochloric acid solution. The organic layer was separated, aqueous layer was

extracted with EtOAc (3 x 25 mL), combined organic layer were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and the residue obtained was purified by column chromatography (silica gel, 3 % EtOAc/pet. ether gradient elution) provided **70** as a gummy oil.

Chemical Formula: $C_{19}H_{21}IO_2S$, 440

Yield: 0.352 g (80 %)

IR ($CHCl_3$): ν 1740, 1215, 1238 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.78-7.88 (m, aromatic-H), 7.20-7.40 (m, aromatic-H), 6.90-7.10 (m, aromatic-H), 5.00 (bs, olefinic-H), 4.60 (m, olefinic-H), 2.20-2.40 (m, 1H), 2.60 (s, 1H), 2.11 (s, -SC$\underline{H}_3$), 2.09s, -SC$\underline{H}_3$), 1.90-2.00 (m, 2H), 1.60 (m, 3H), 1.50-1.60 (m, 1H), 1.23 (s, 1.5H), 1.17 (s, 1.5H), 0.94(s, 1.5H), 0.80 (s, 1.5H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 163.7 (C), 163.4 (C), 149.7 (C), 148.6 (C), 145.2 (C), 141.5 (CH), 139.9 (CH), 134.2 (C), 133.9 (C), 132.4 (C), 129.4 (C), 127.9 (CH), 121.6 (C), 117.9 (CH), 109.8 (CH_2), 94.5 (CH), 60.0 (CH), 55.1 (CH), 49.5 (CH), 48.2 (CH), 44.0 (C), 42.3 (C), 27.0 (CH), 25.8 (CH_2), 25.7 (CH_2), 24.3 (CH_3), 22.1 (CH_3), 21.1 (CH_3), 20.9 (CH_2), 14.9 (CH_3), 13.9 (CH_3).

1.3.5 References:

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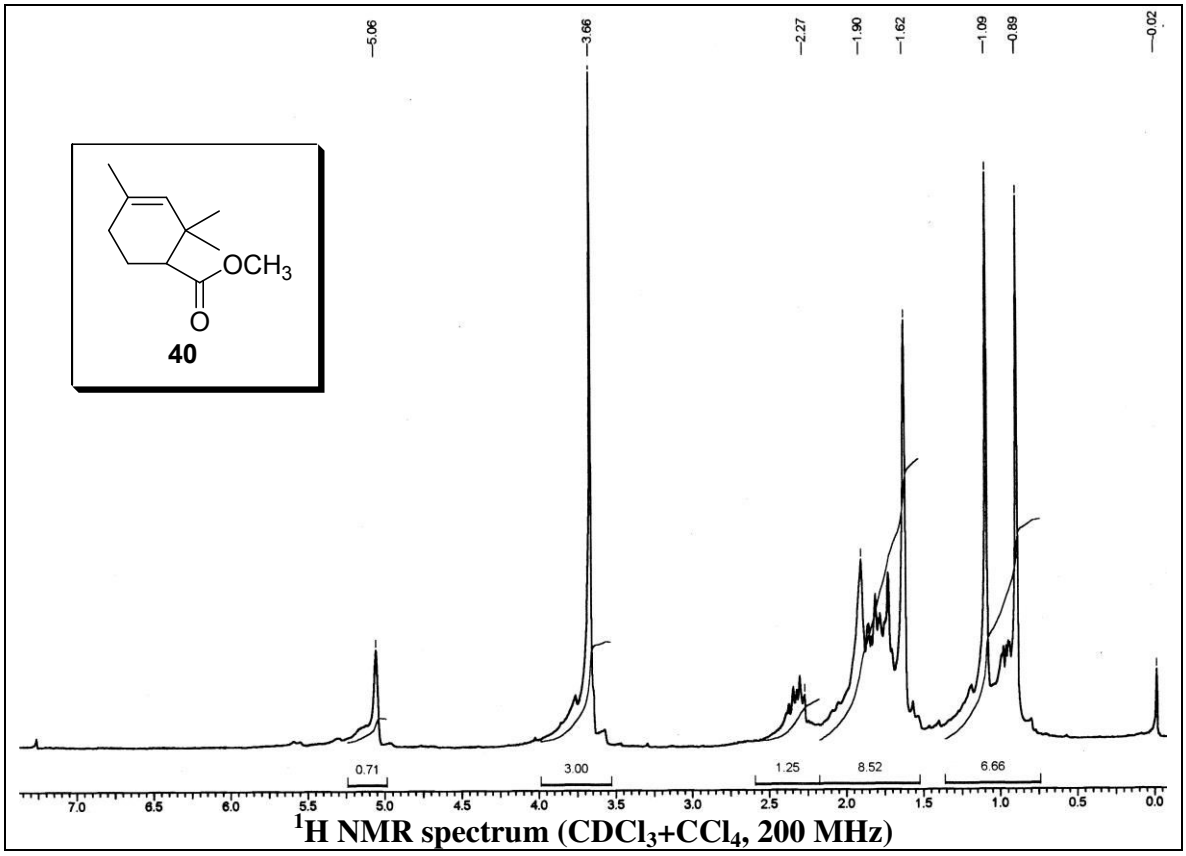
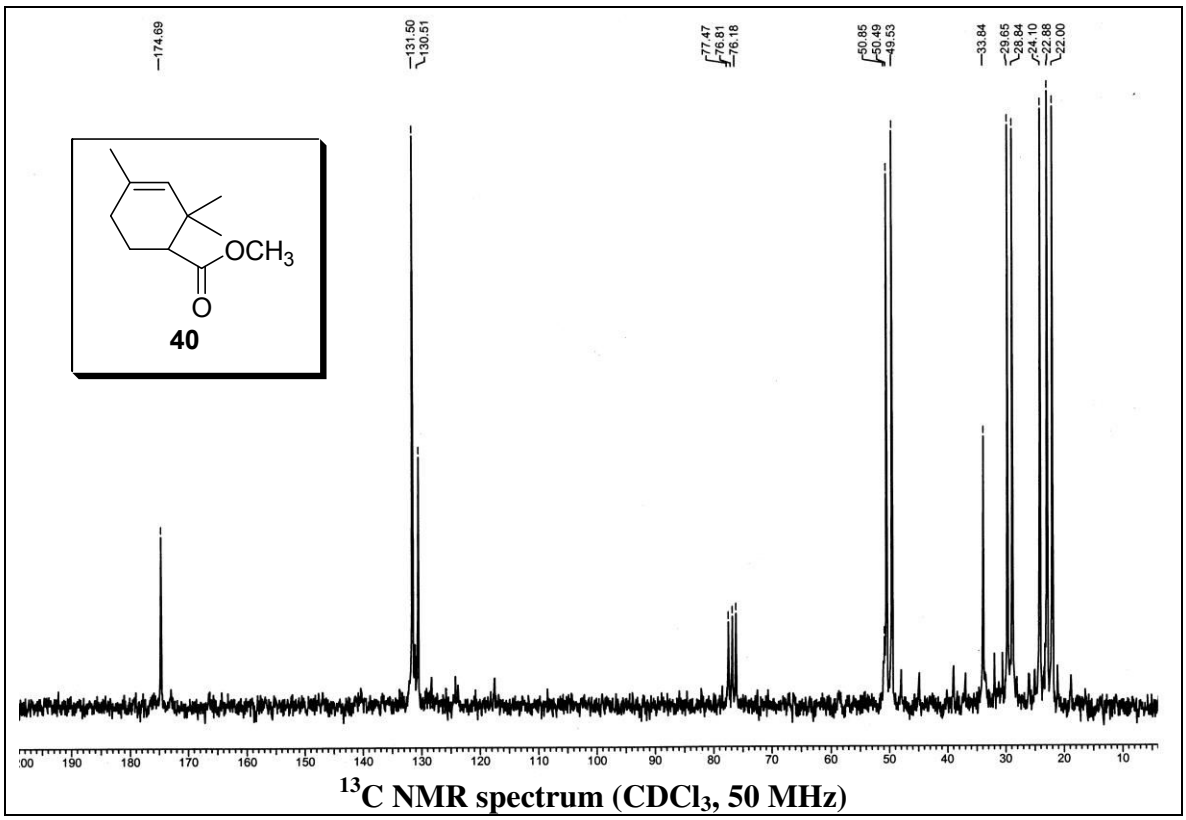
Spectra



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



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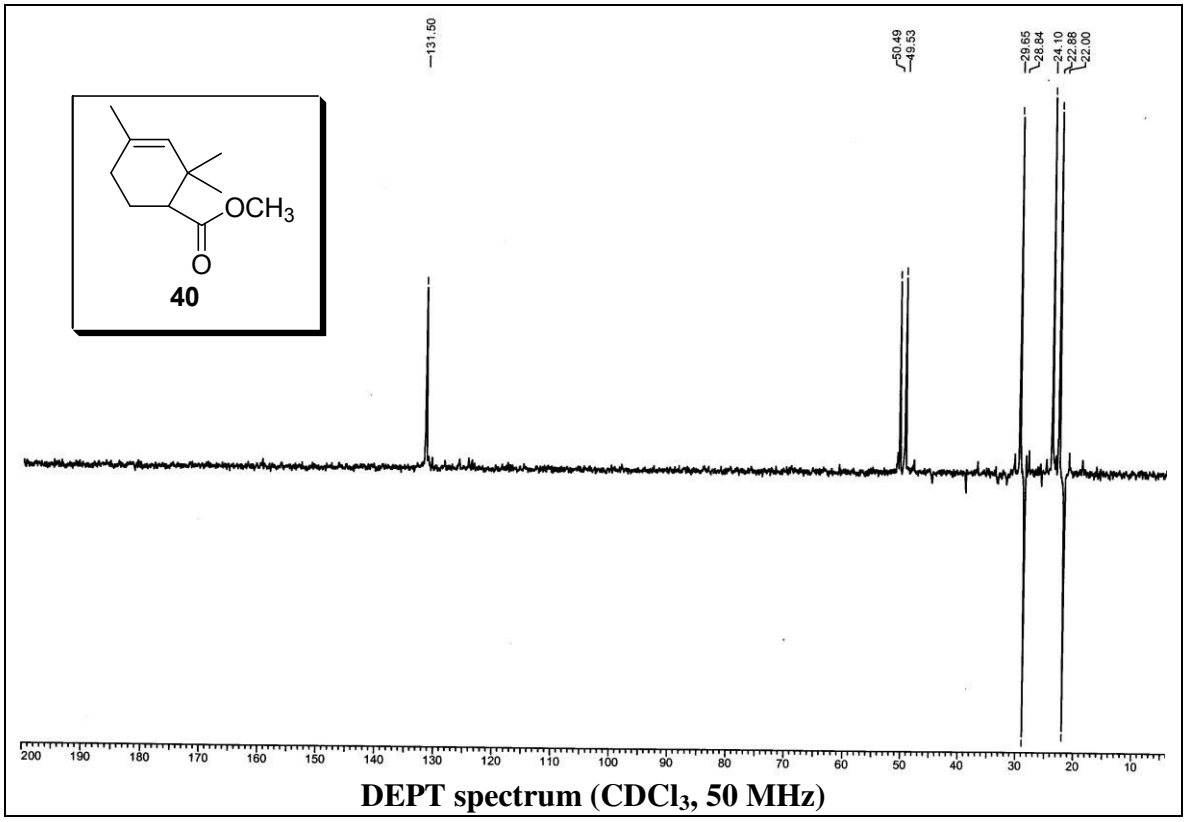

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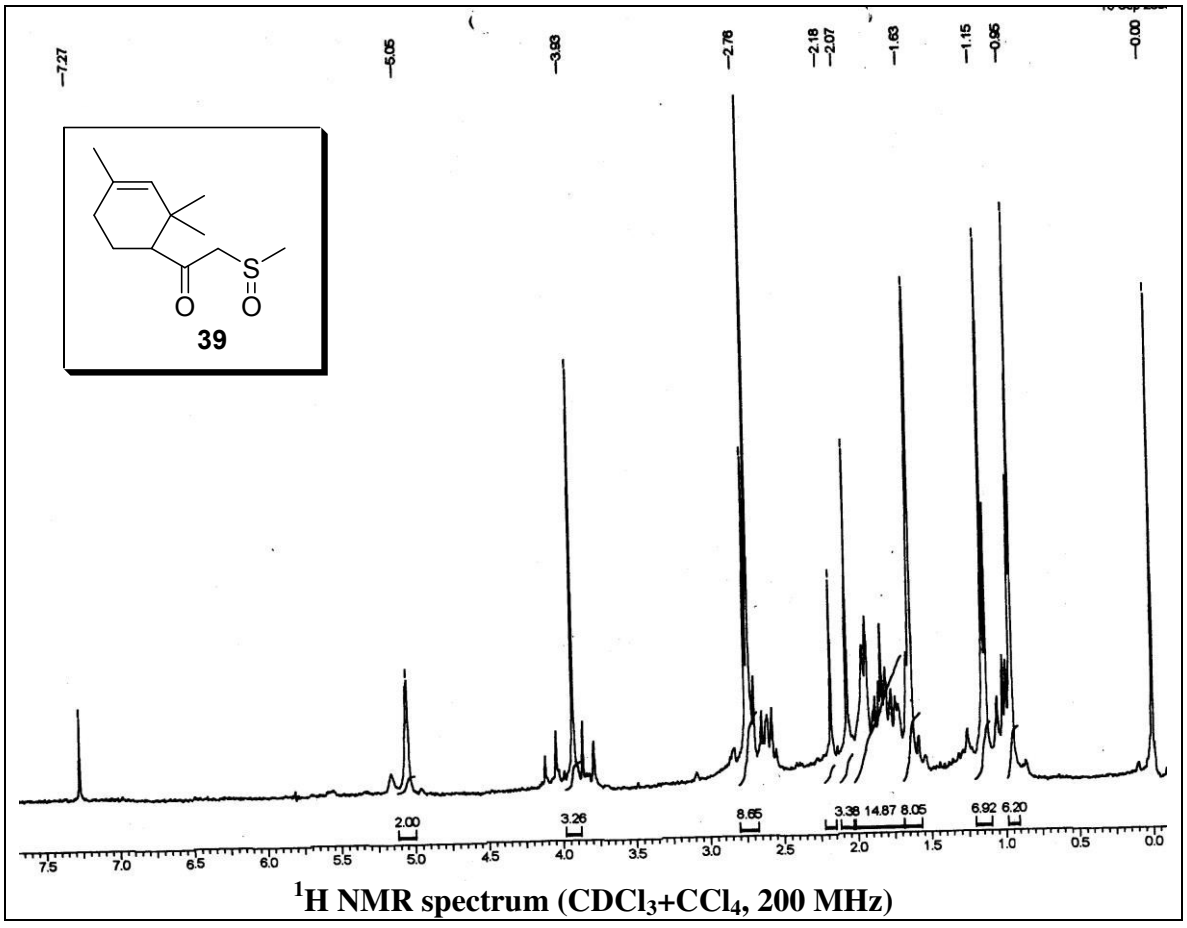

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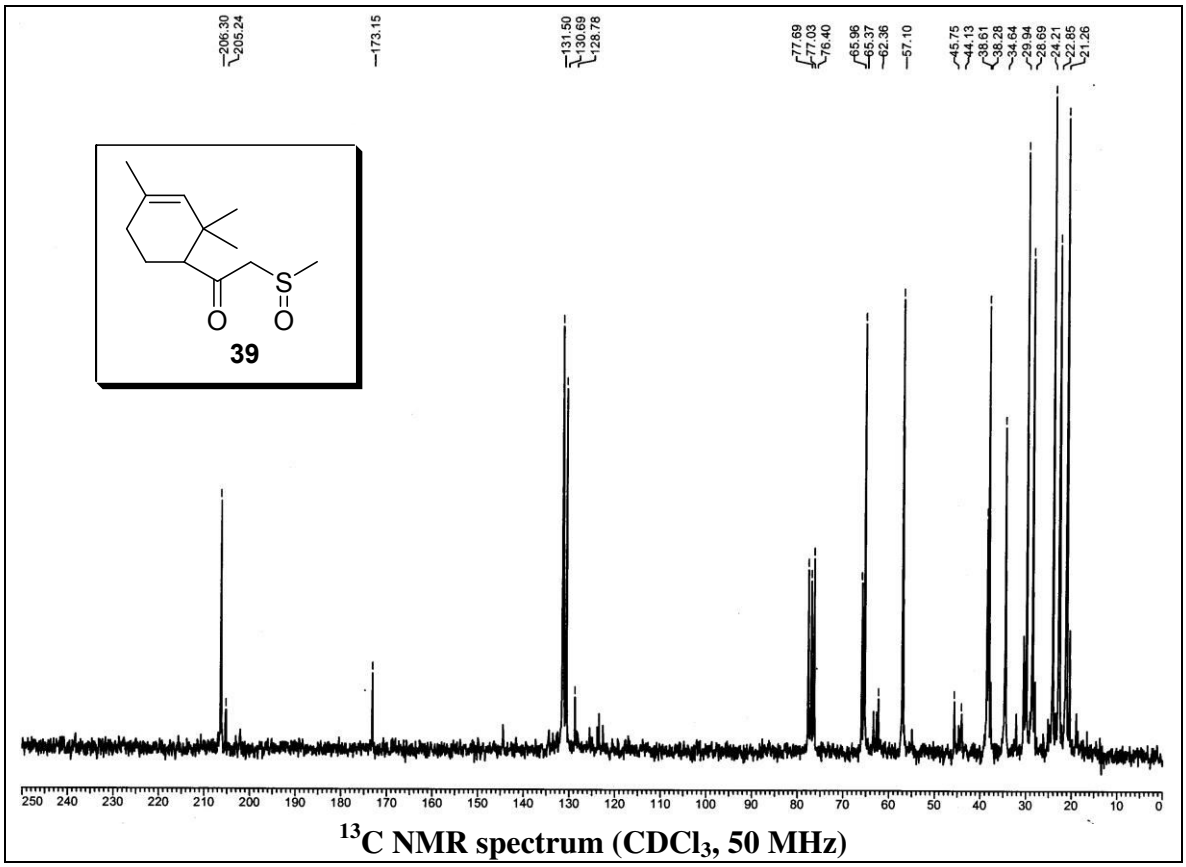

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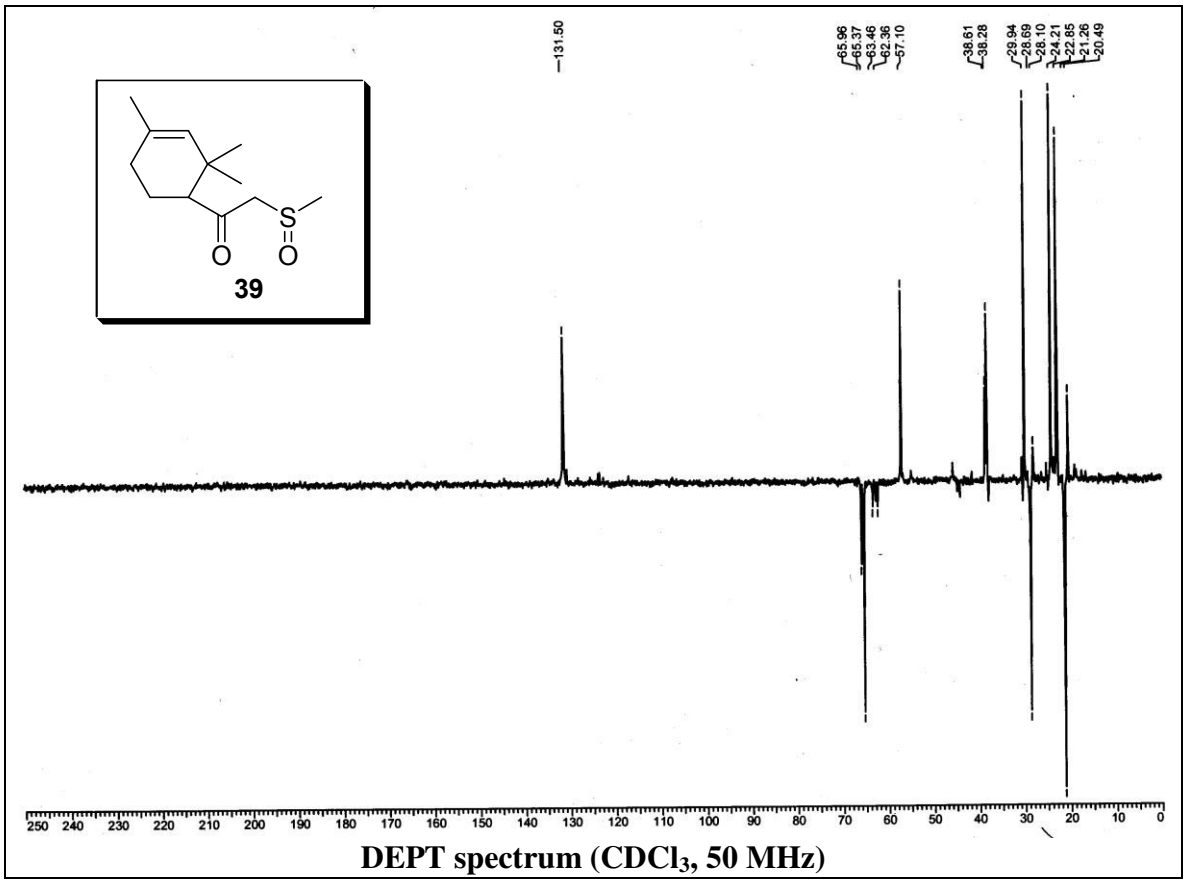
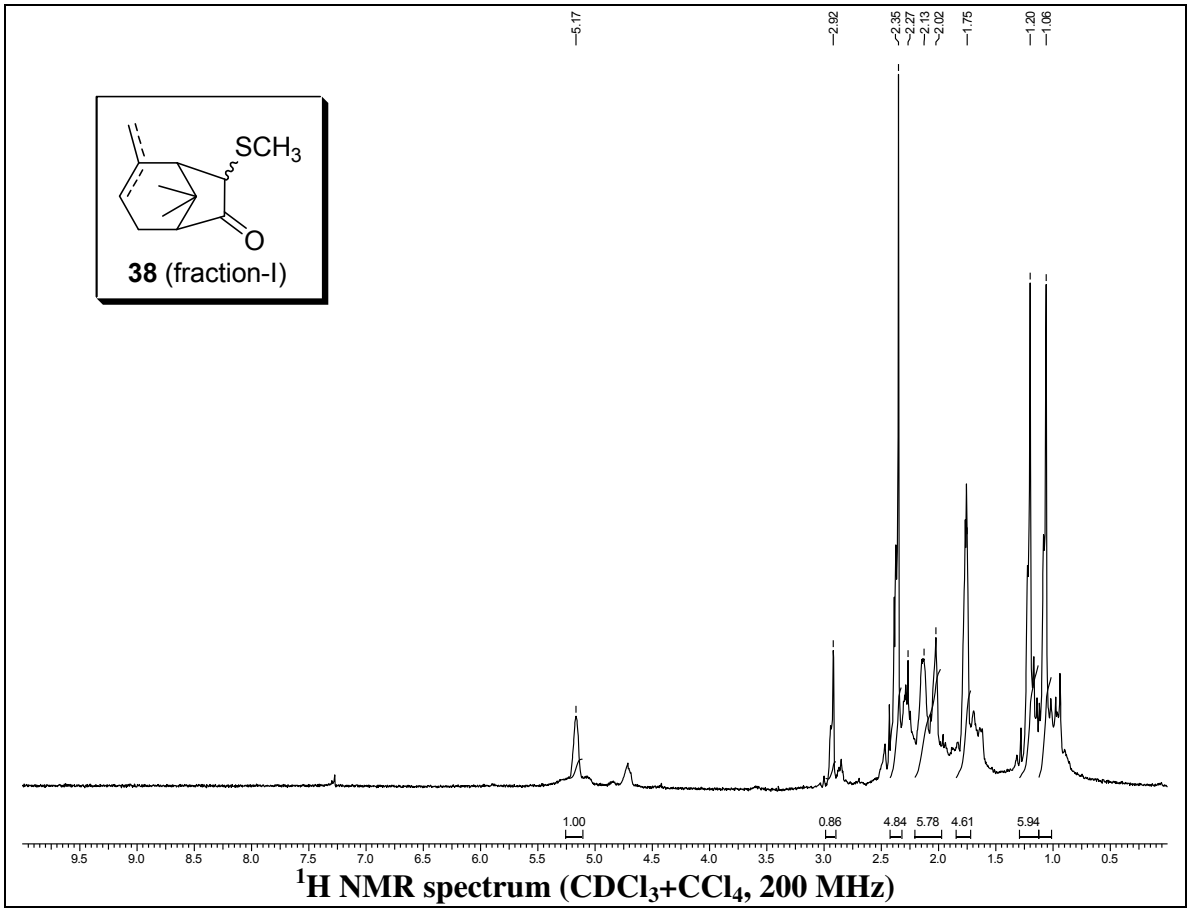
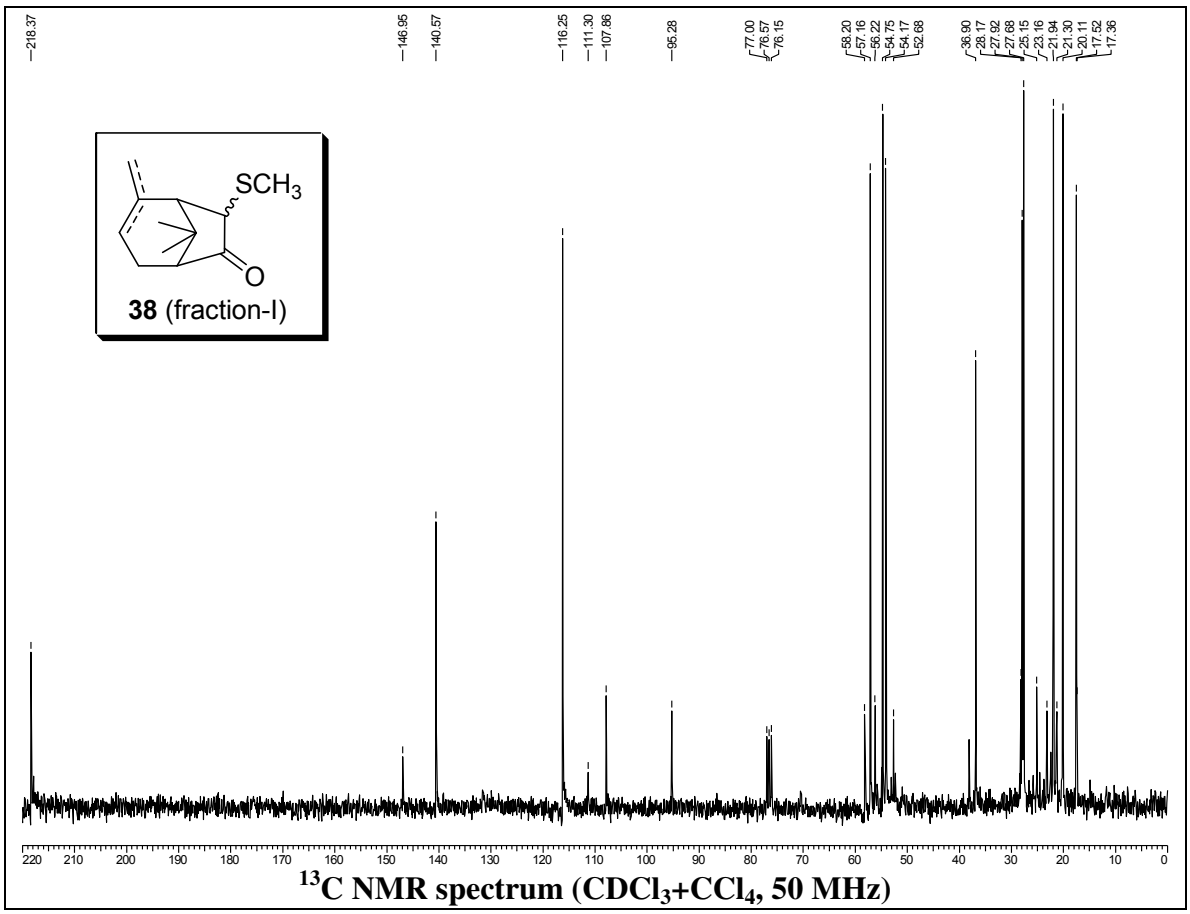


DEPT spectrum ($CDCl_3$, 50 MHz)



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



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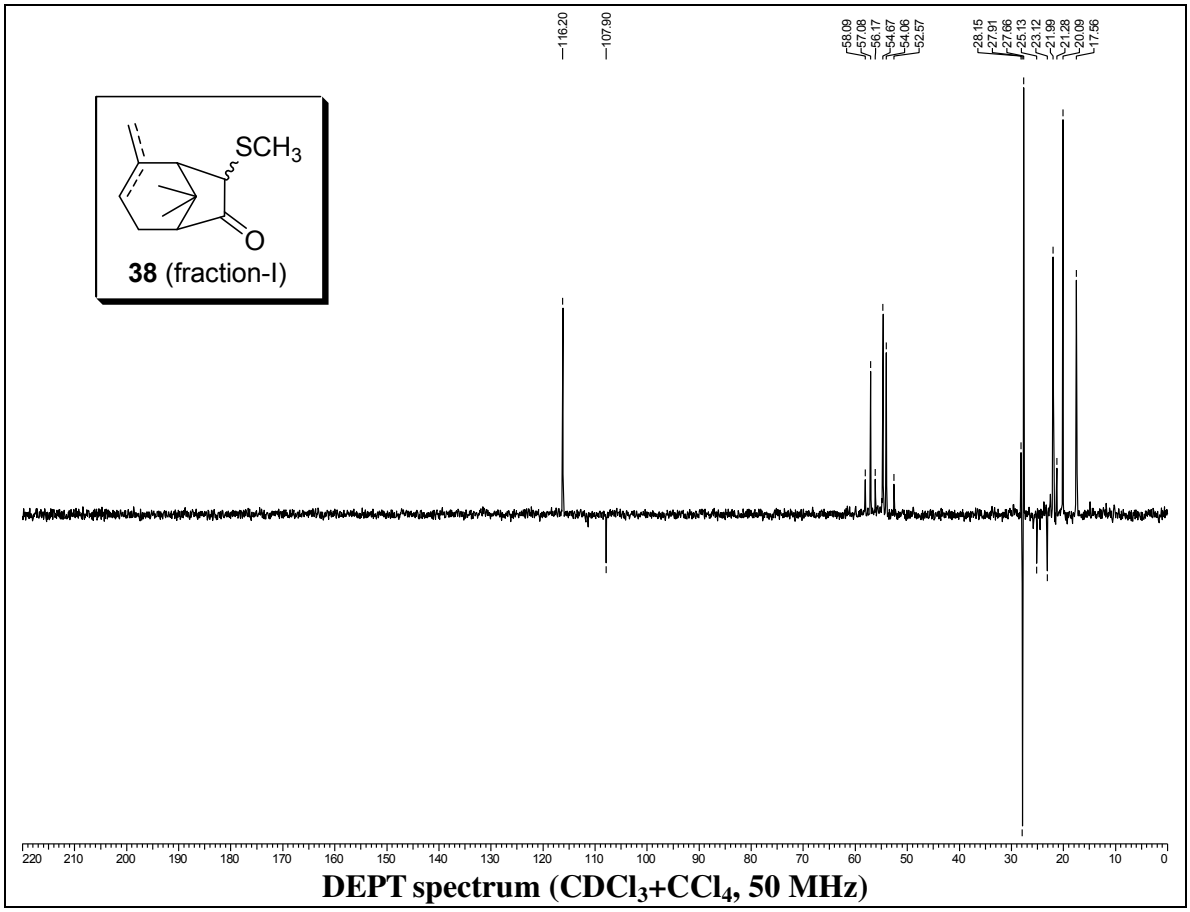
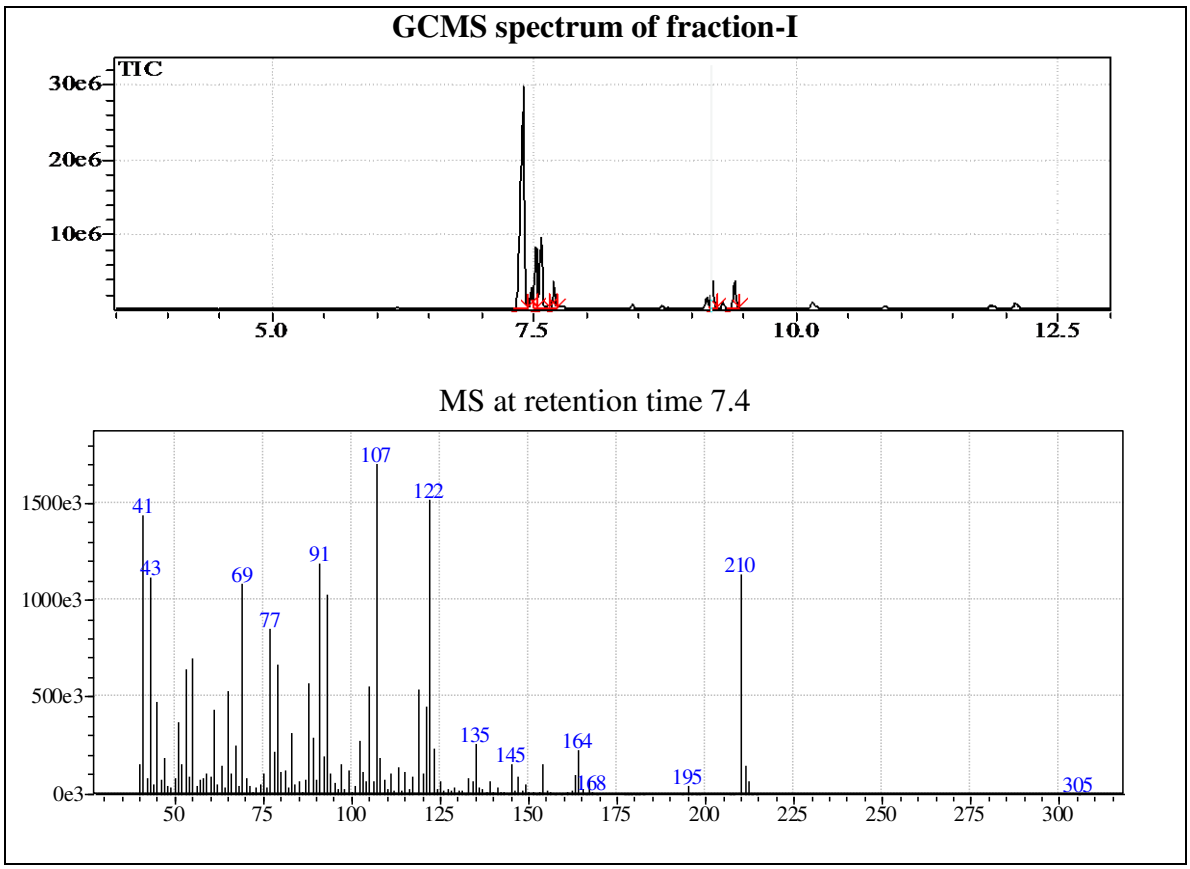
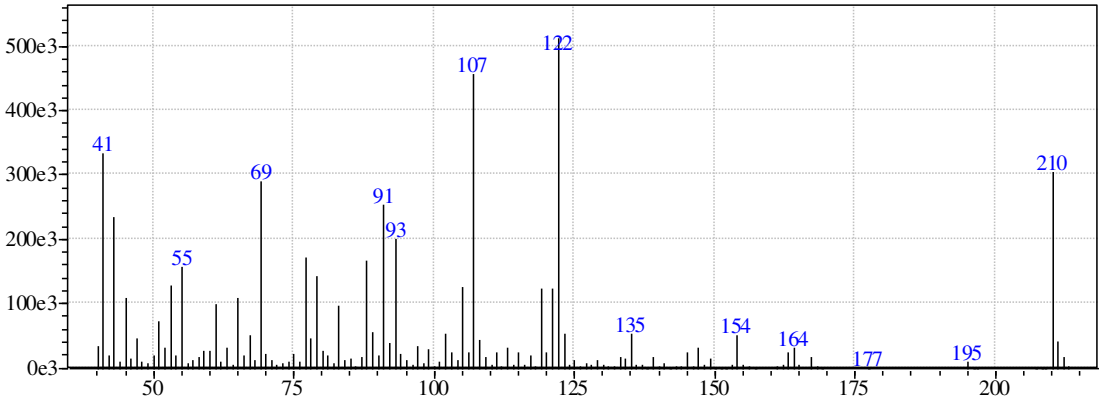


DEPT spectrum ($CDCl_3$+CCl_4, 50 MHz)

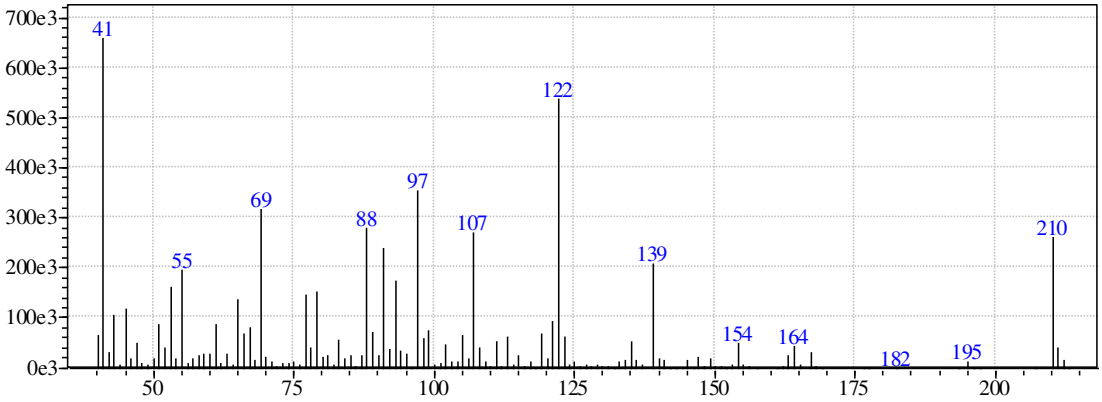
GCMS spectrum of fraction-I



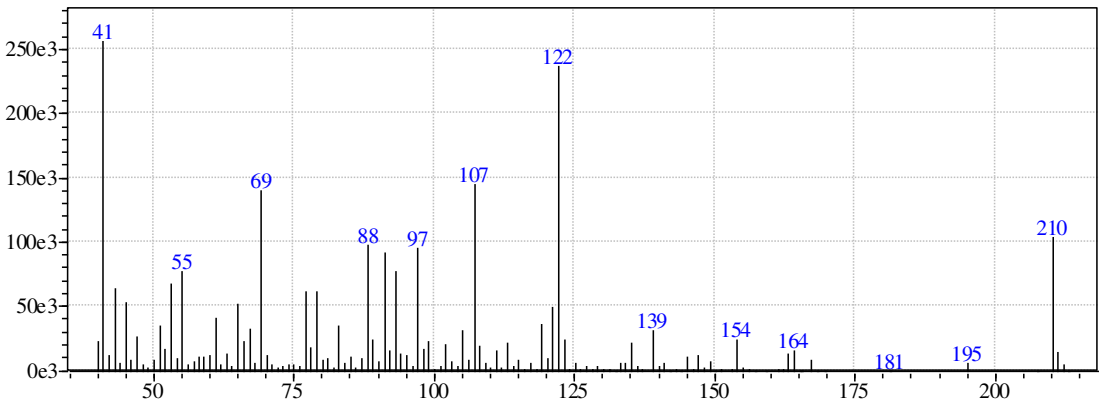
MS at retention time 7.5

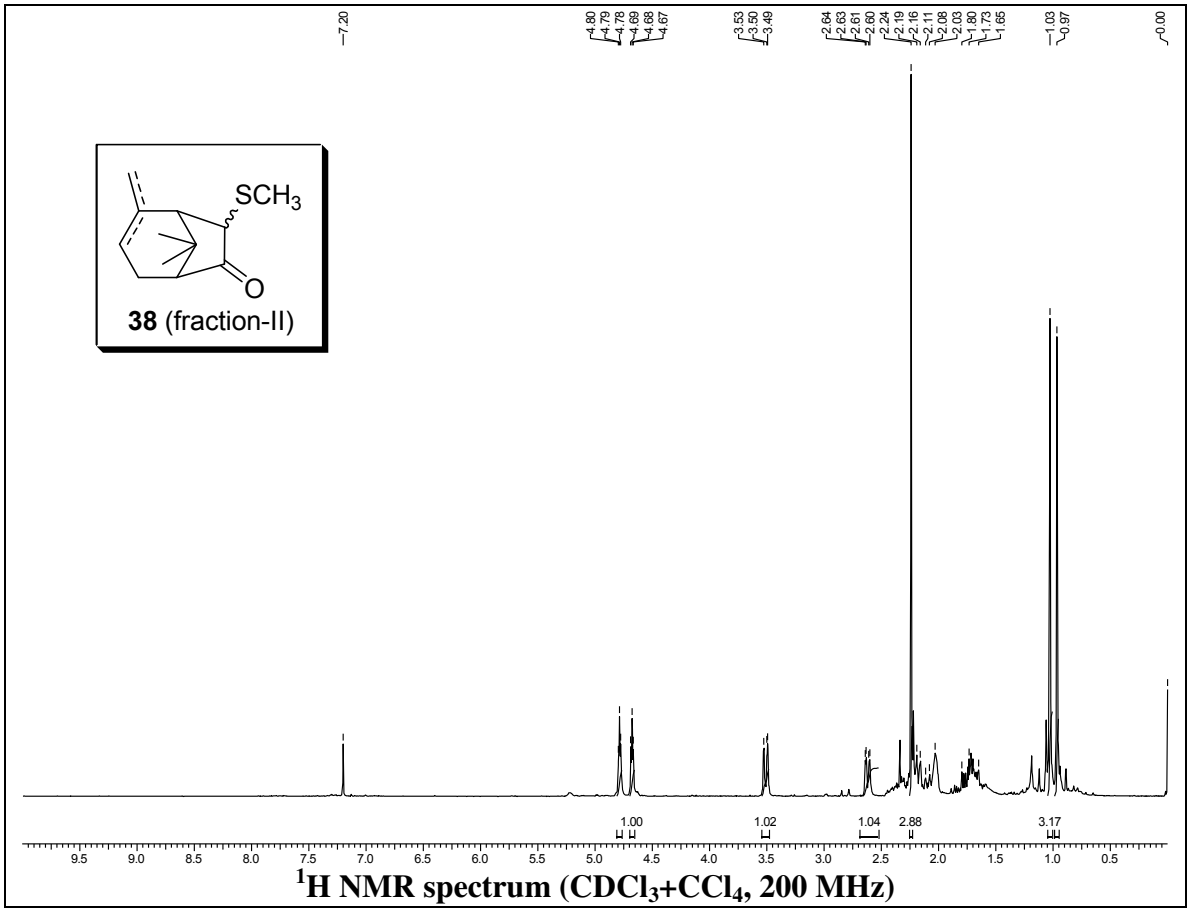


MS at retention time 7.6

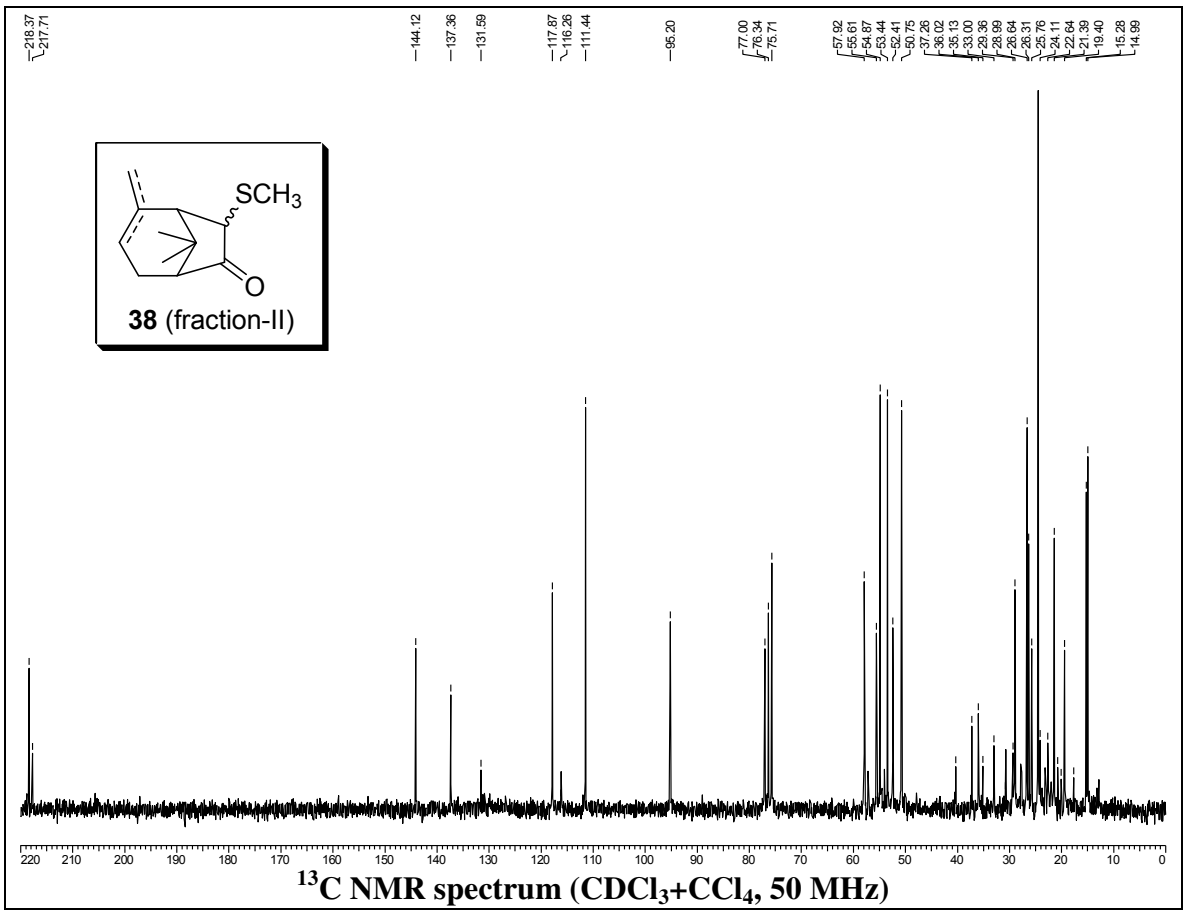


MS at retention time 7.7

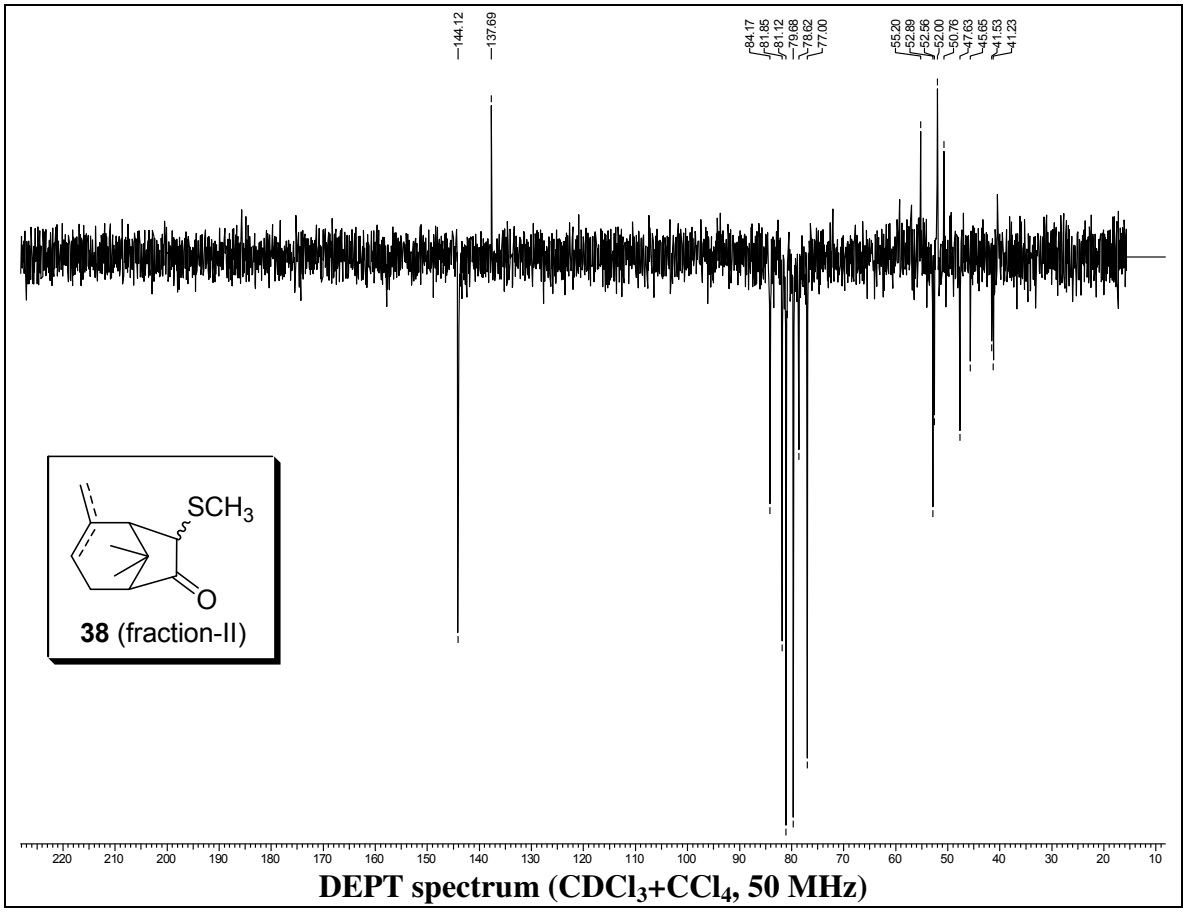




^{1}H NMR spectrum ($CDCl_3$+CCl_4, 200 MHz)

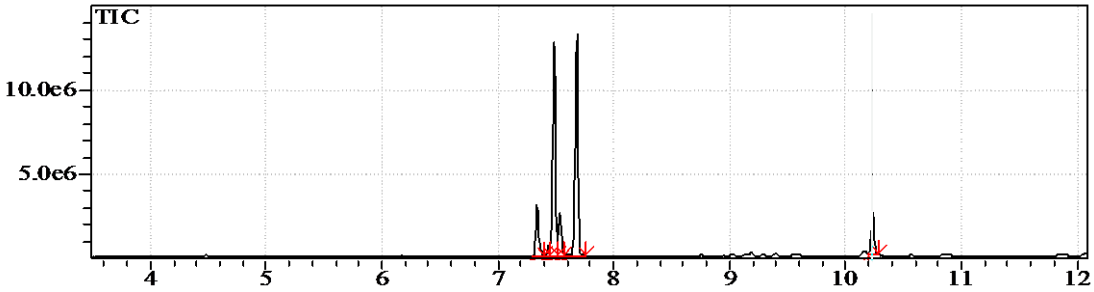


^{13}C NMR spectrum ($CDCl_3$+CCl_4, 50 MHz)

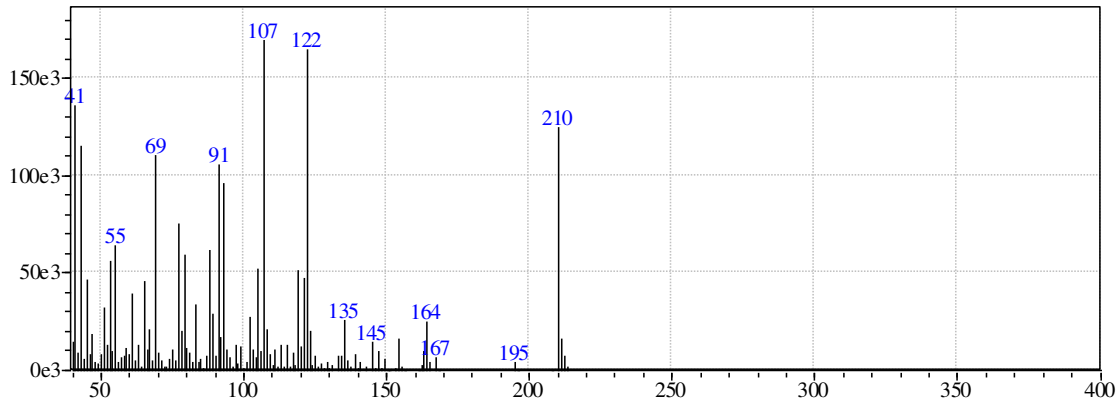


DEPT spectrum ($CDCl_3$+CCl_4, 50 MHz)

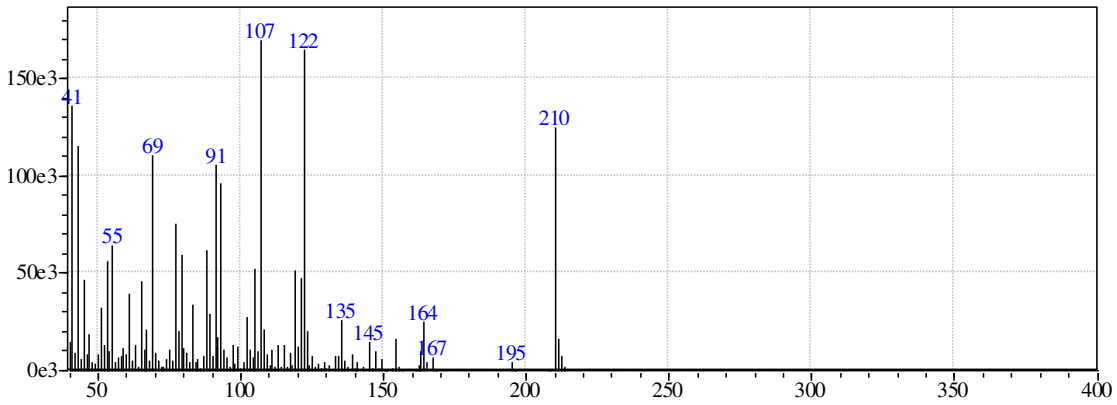
GCMS spectrum of fraction-II



MS at retention time 7.4



MS at retention time 7.5



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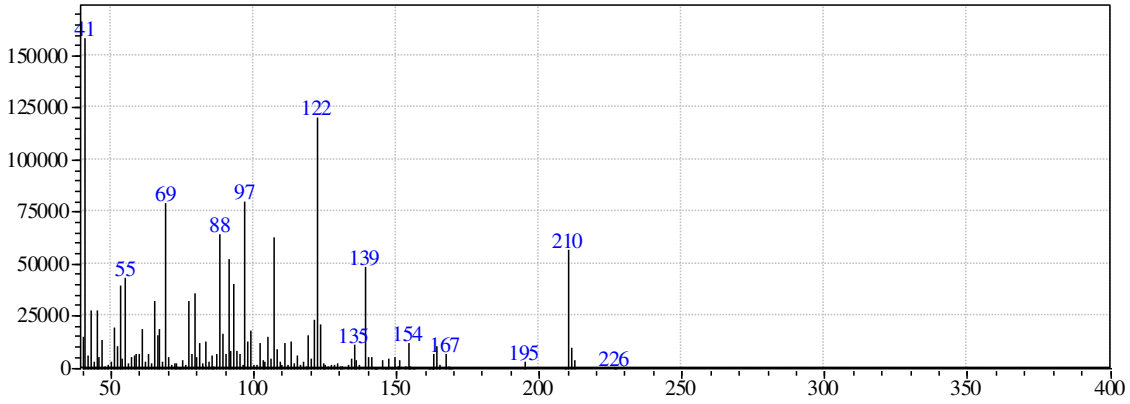
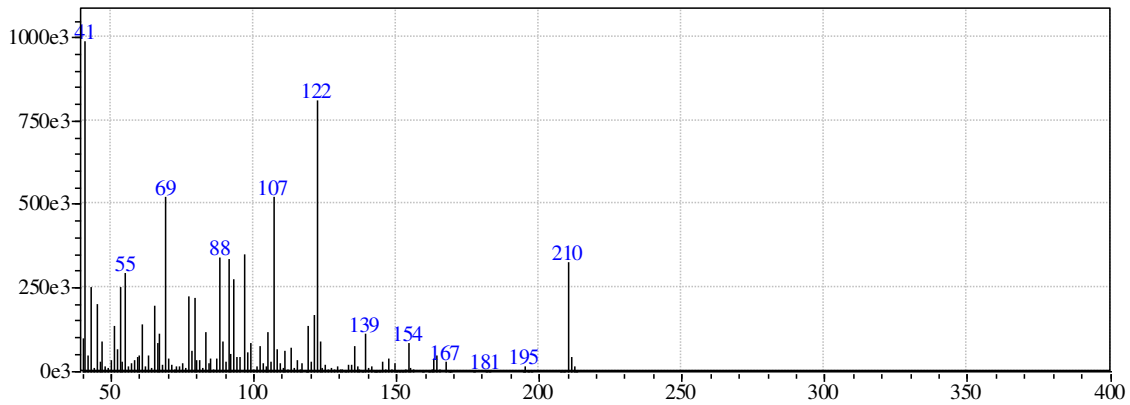
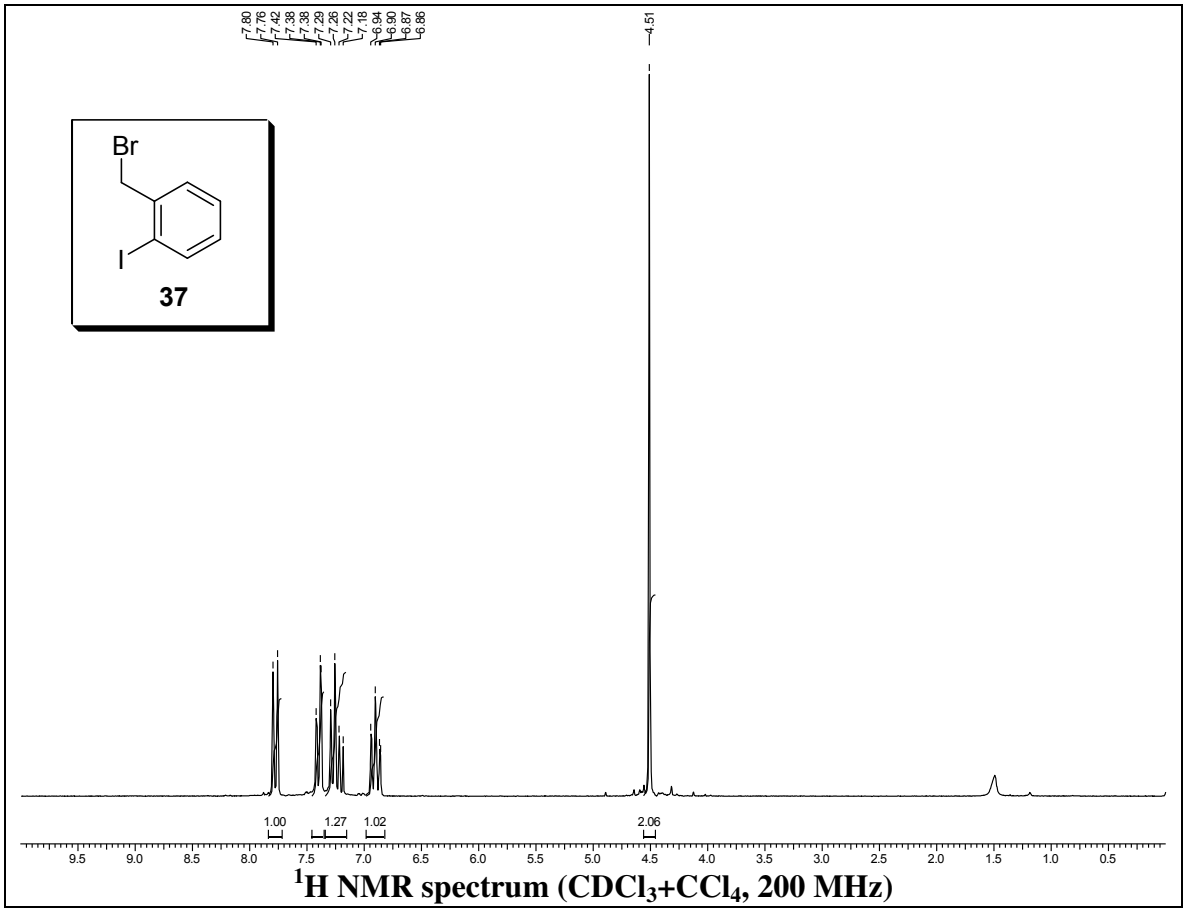
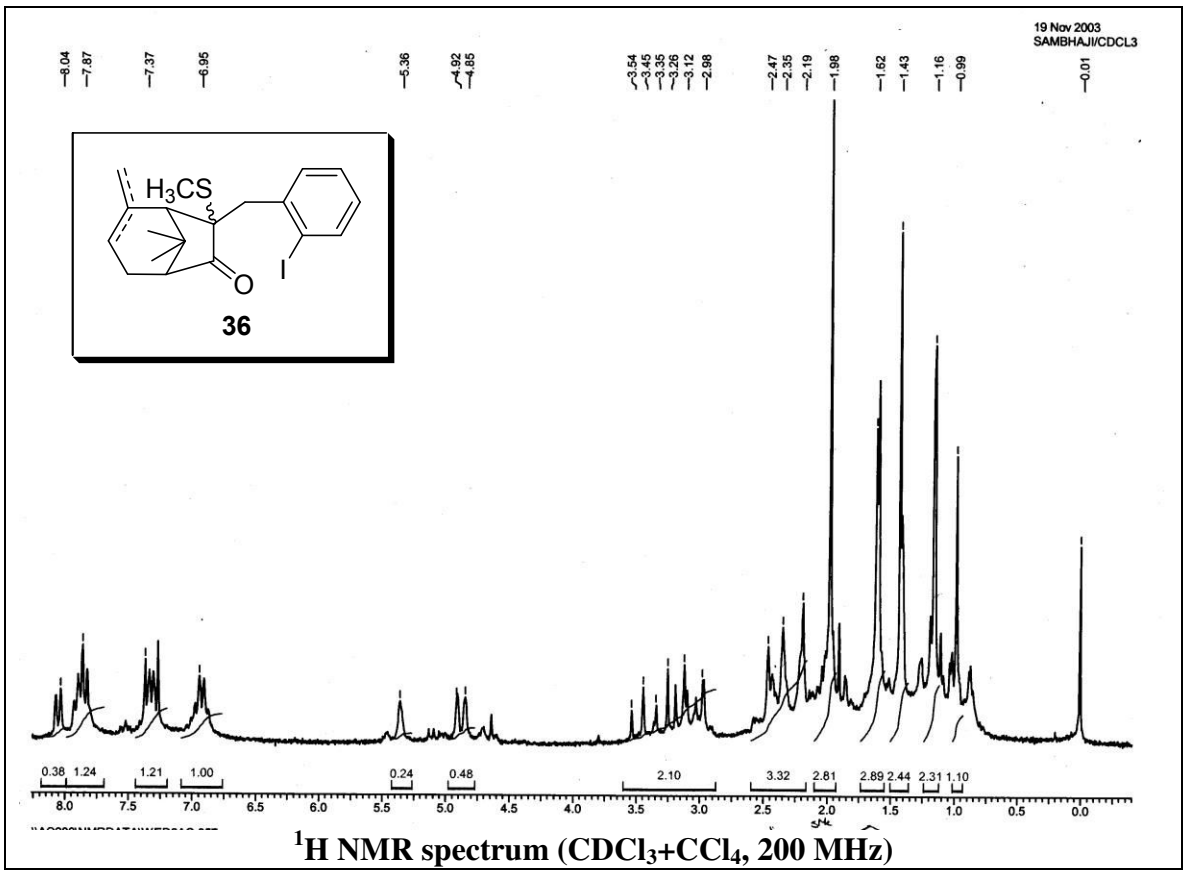


MS at retention time 7.7





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



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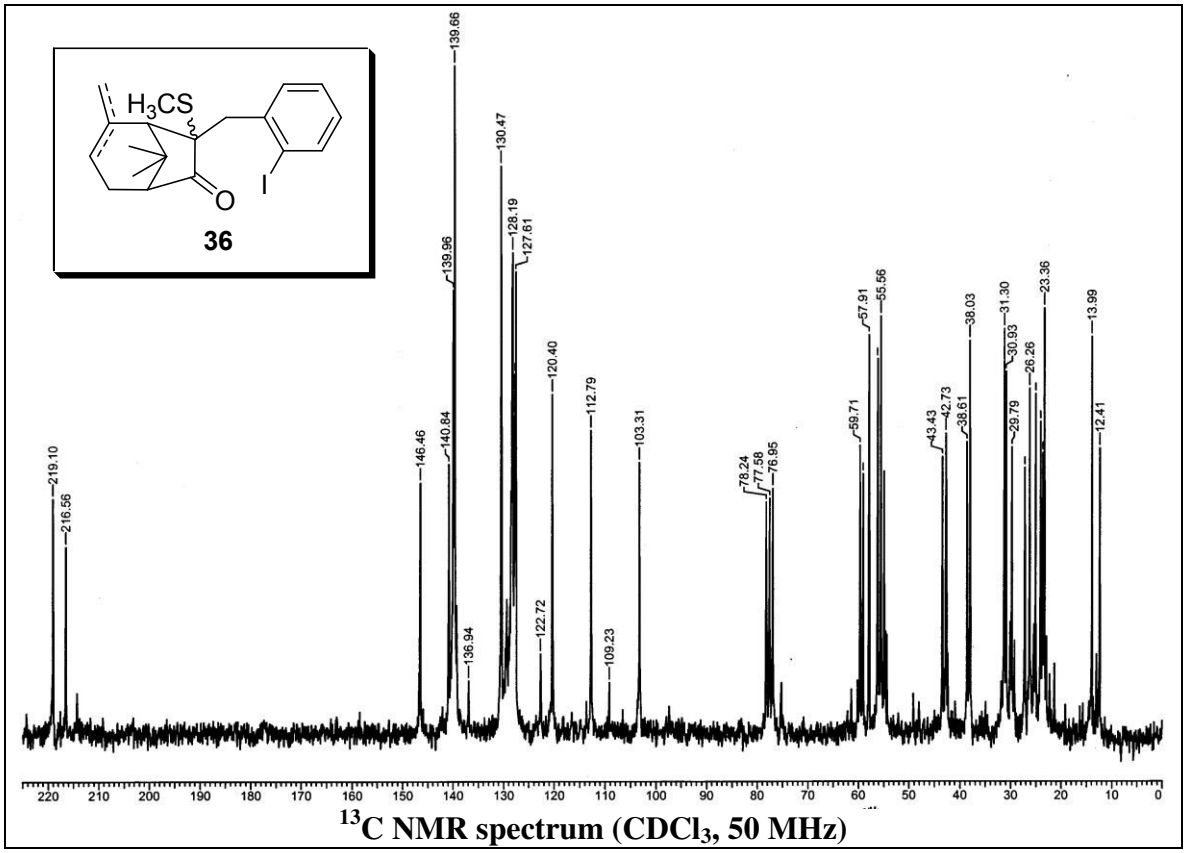

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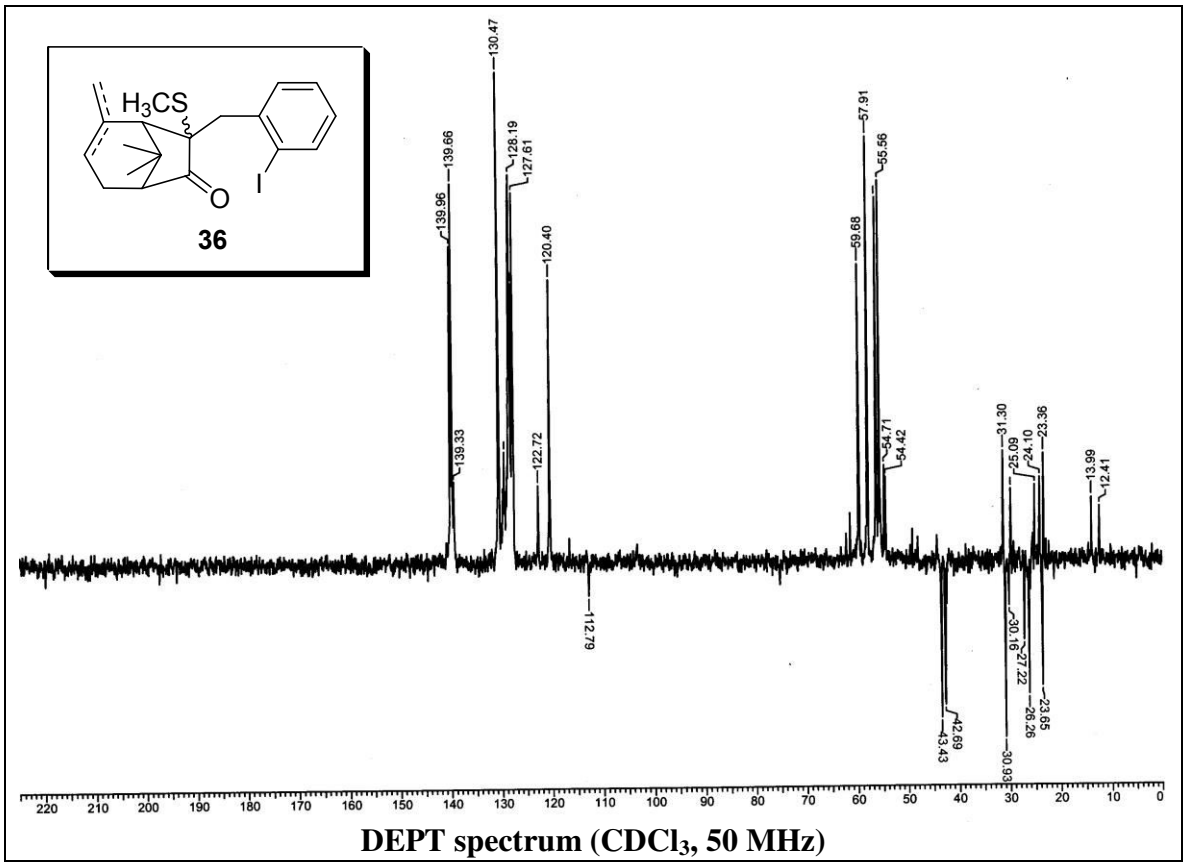
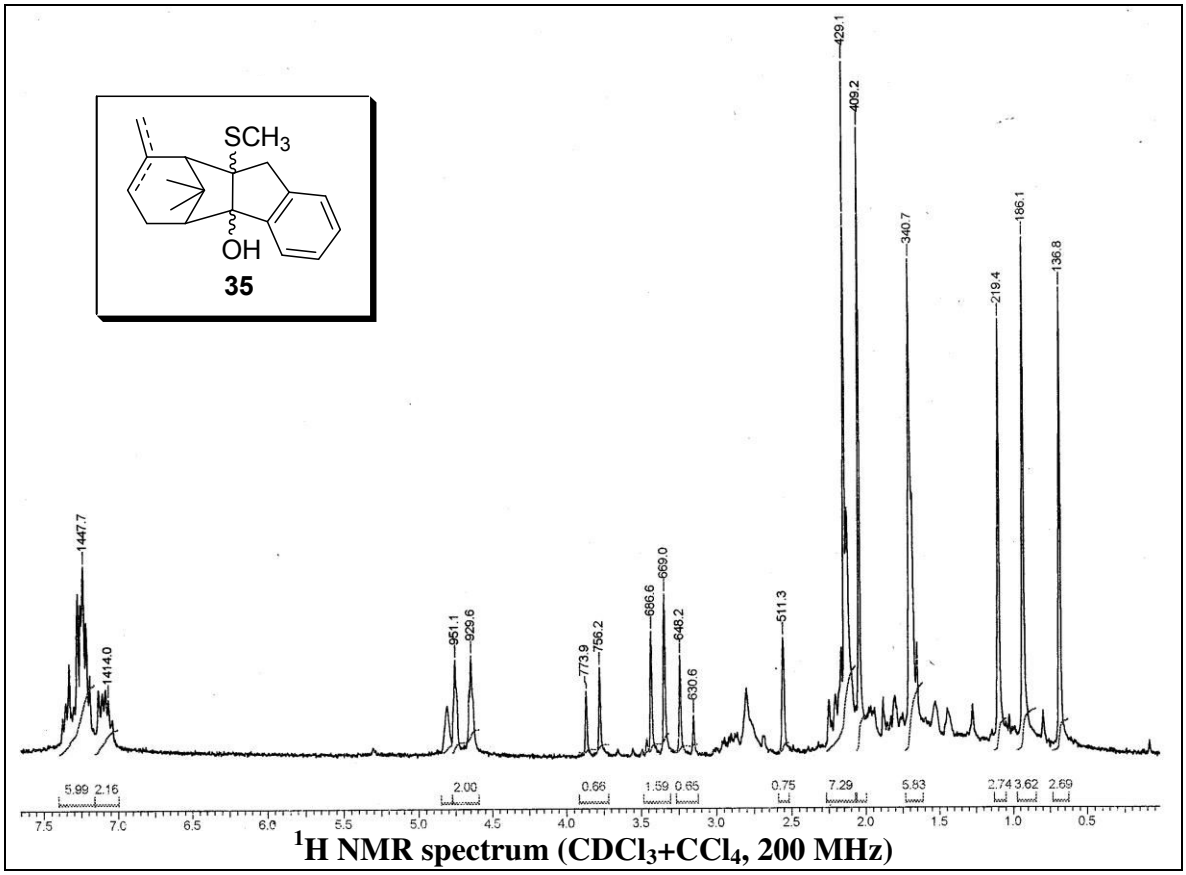
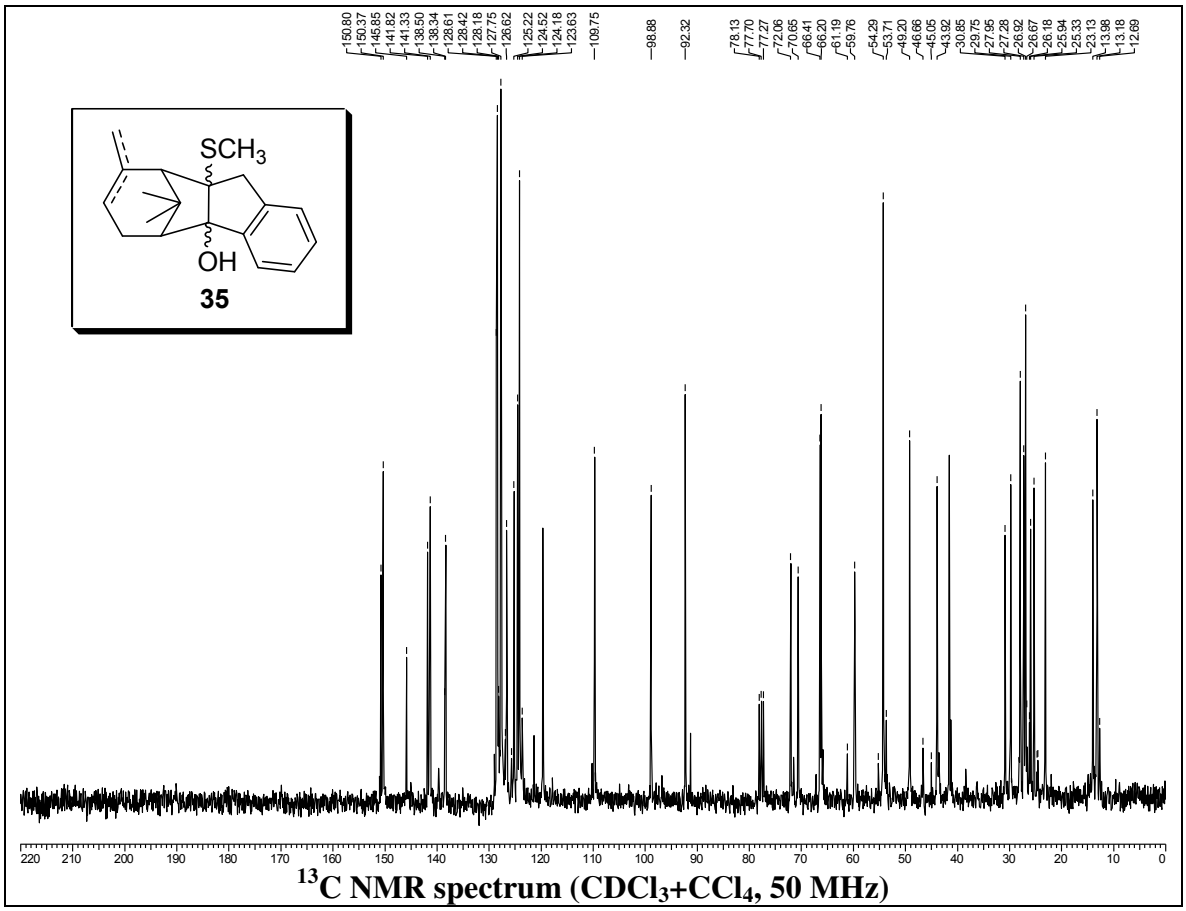


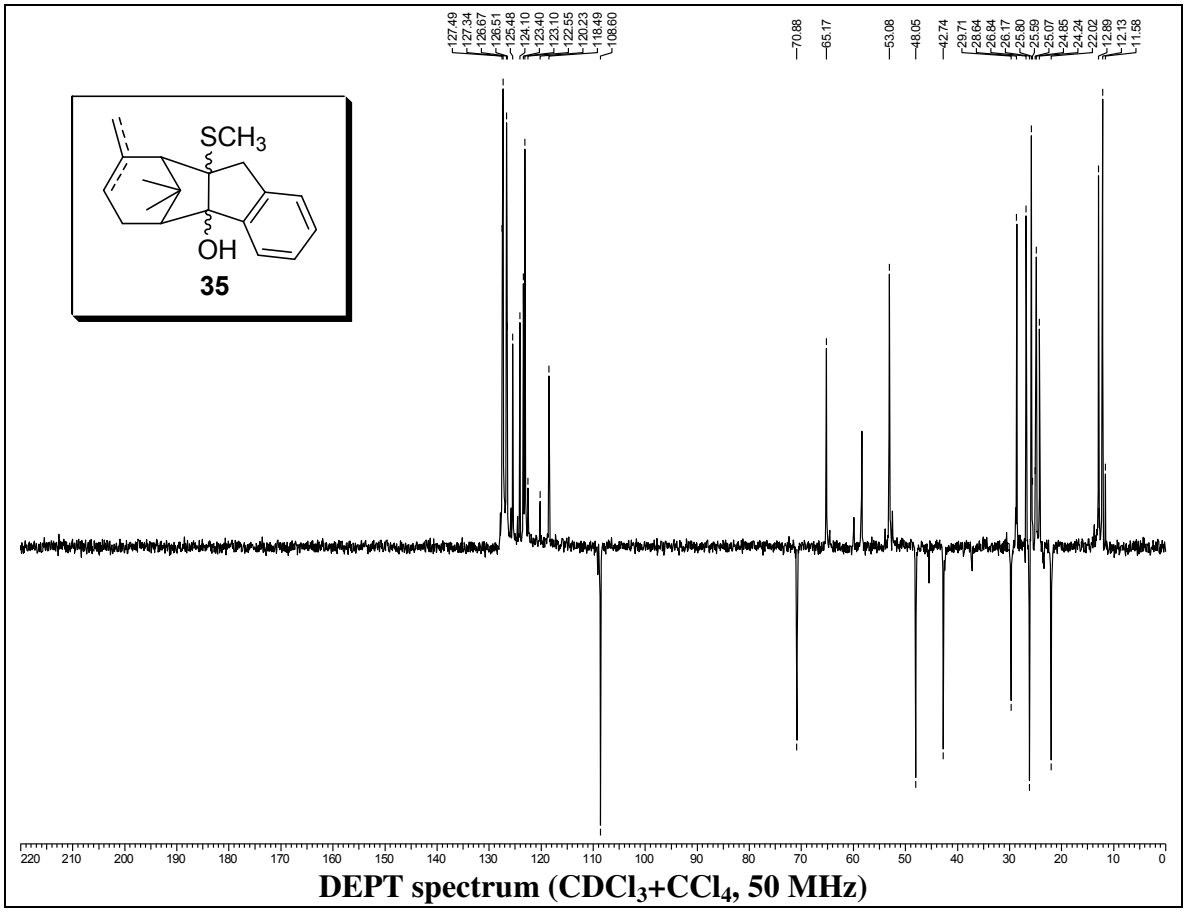
DEPT spectrum ($CDCl_3$, 50 MHz)



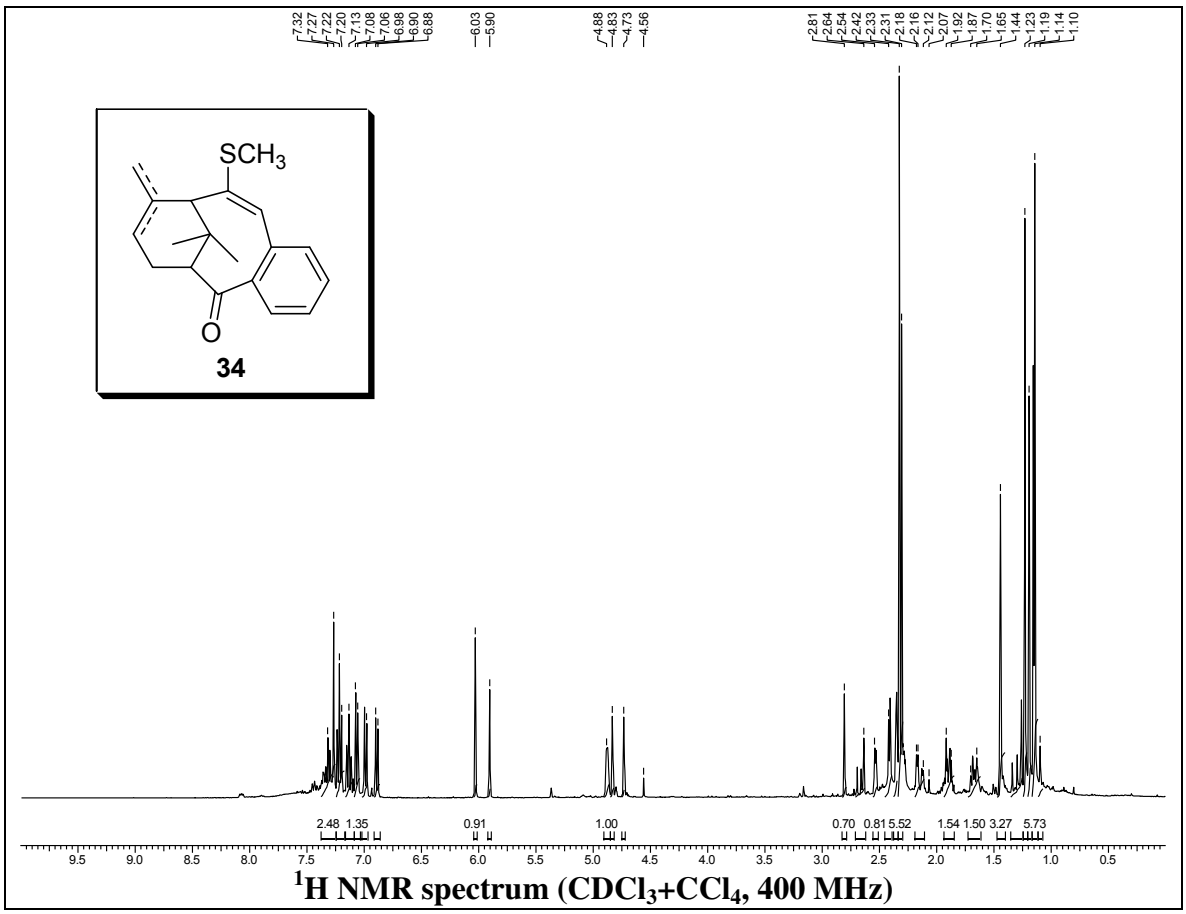
^{1}H NMR spectrum ($CDCl_3$+CCl_4, 200 MHz)



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



DEPT spectrum ($CDCl_3$+CCl_4, 50 MHz)



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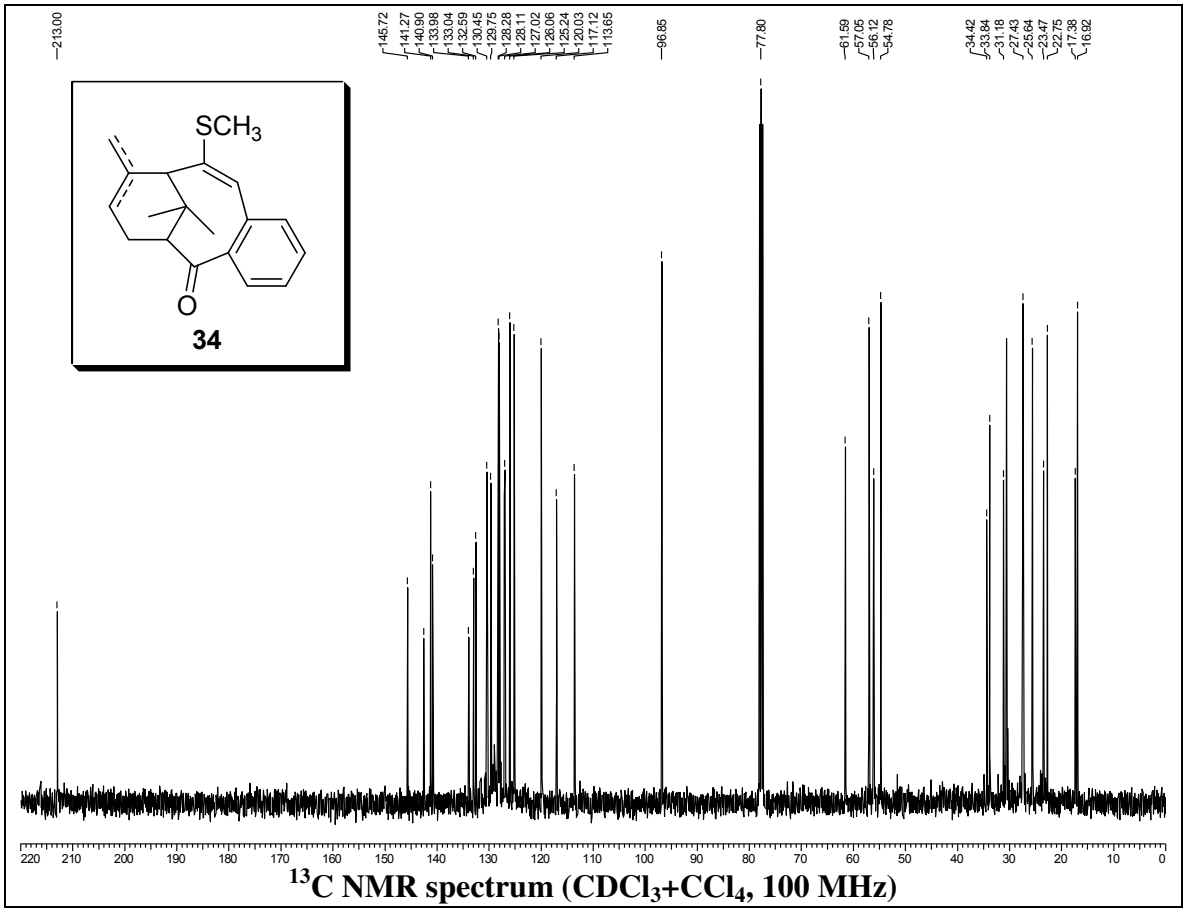

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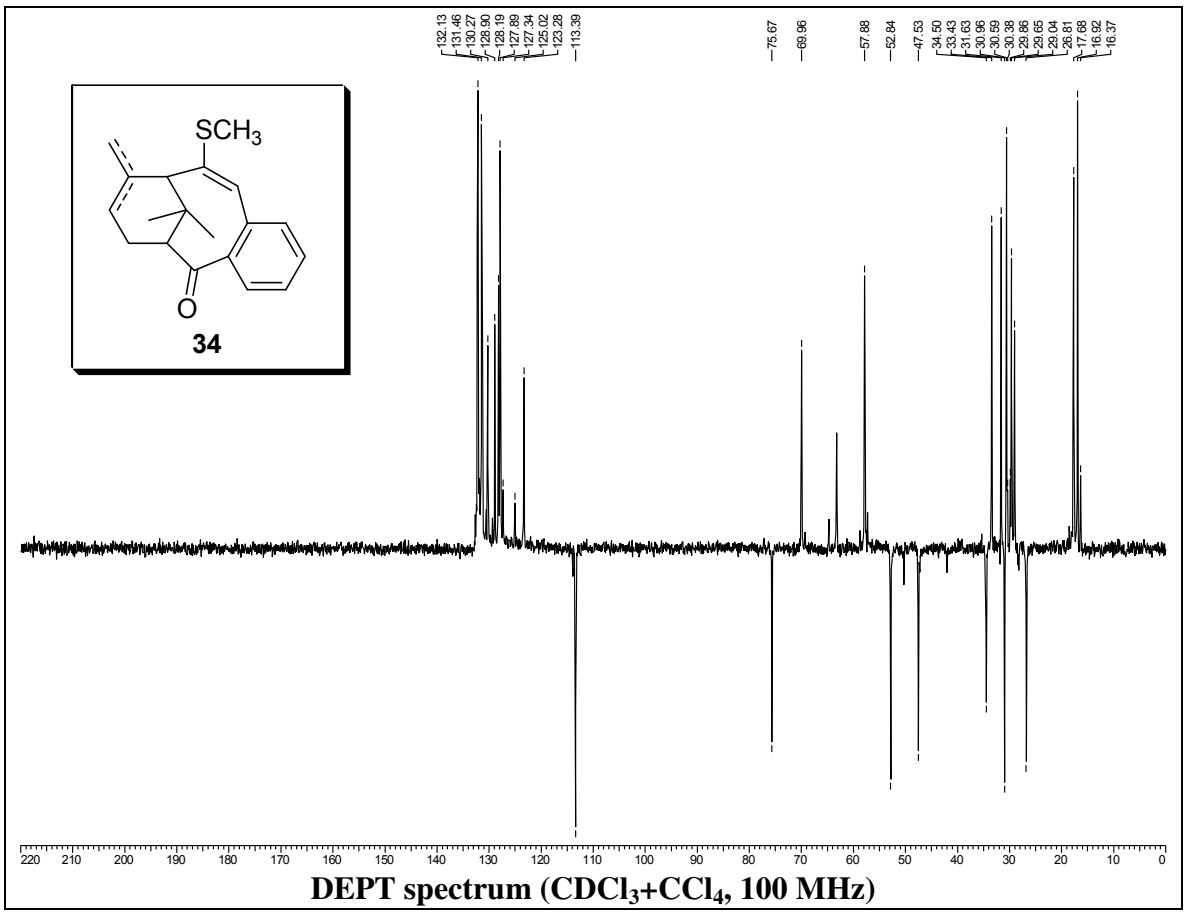
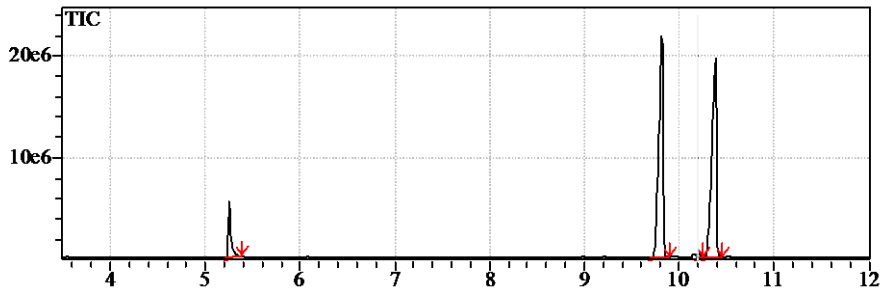


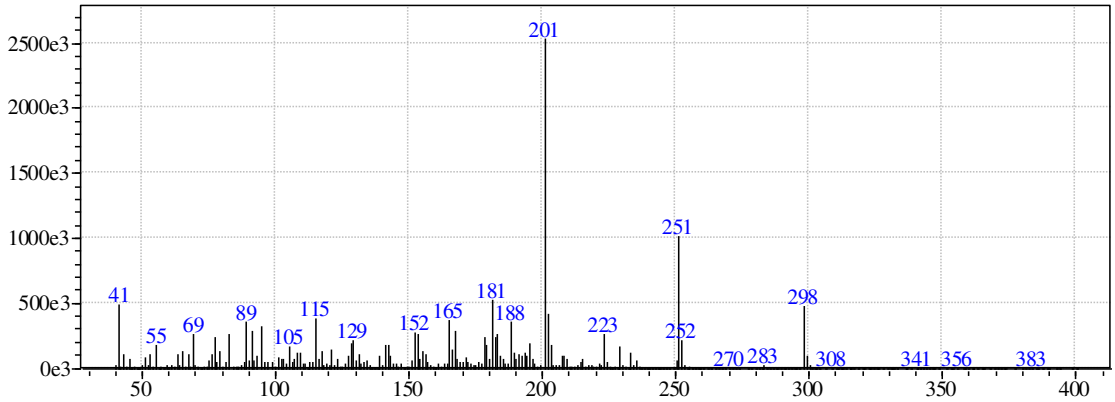
DEPT spectrum ($CDCl_3$+CCl_4, 100 MHz)

GCMS spectrum of 34

GC chromatogram



MS at retention time 9.9



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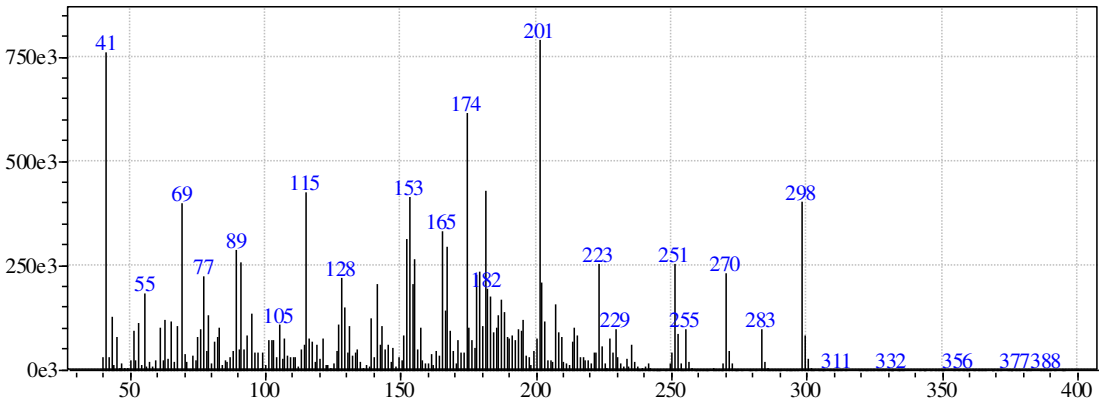
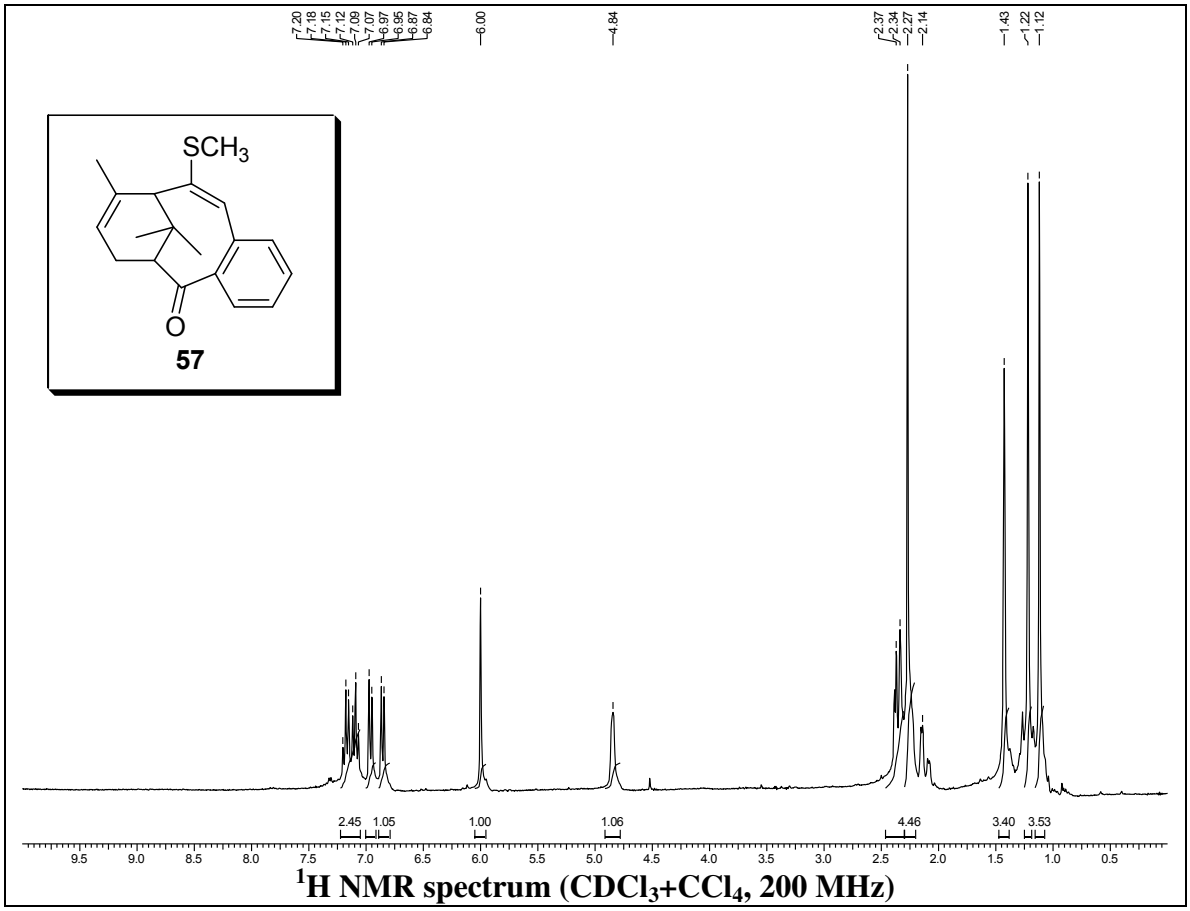
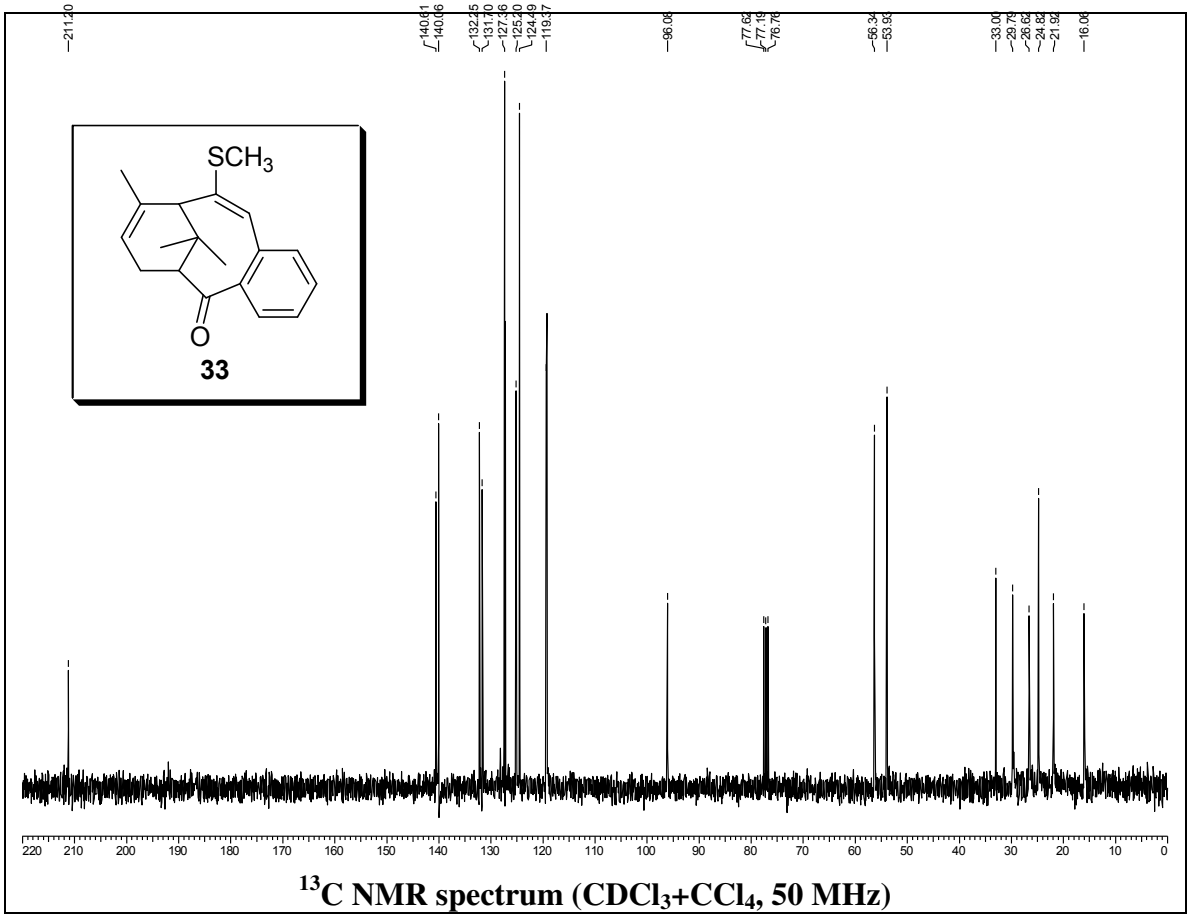
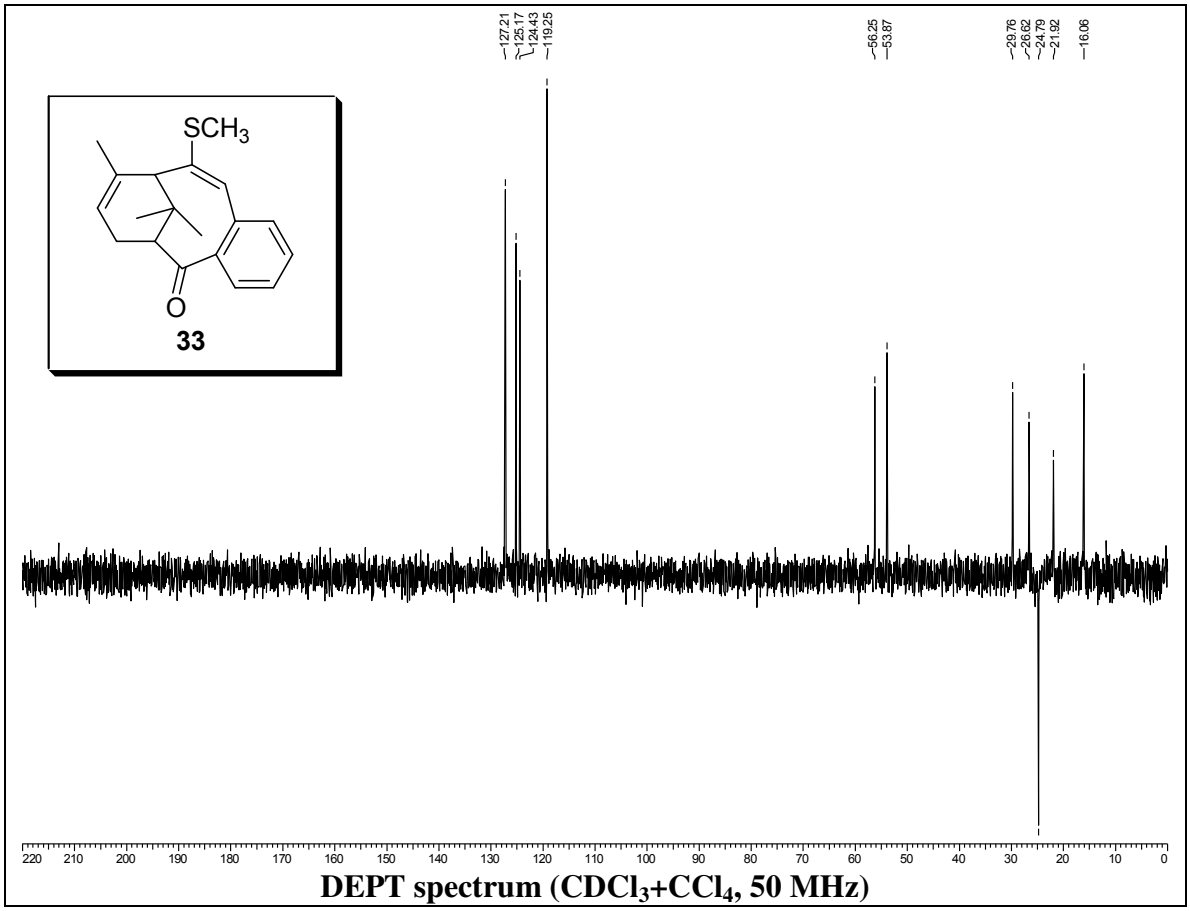




^{1}H NMR spectrum ($CDCl_3$+CCl_4, 200 MHz)

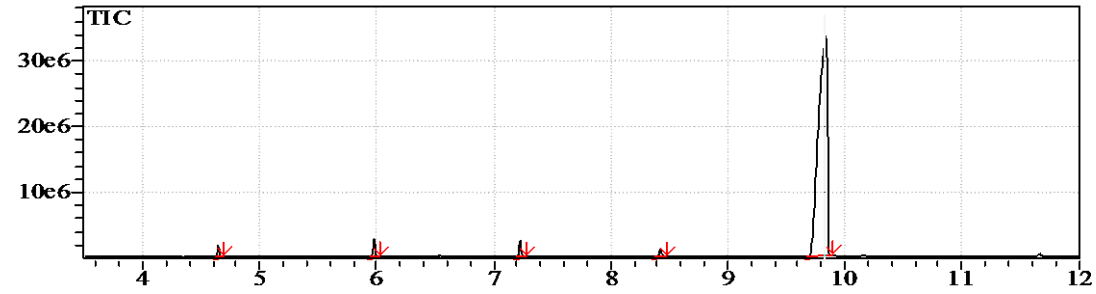


^{13}C NMR spectrum ($CDCl_3$+CCl_4, 50 MHz)



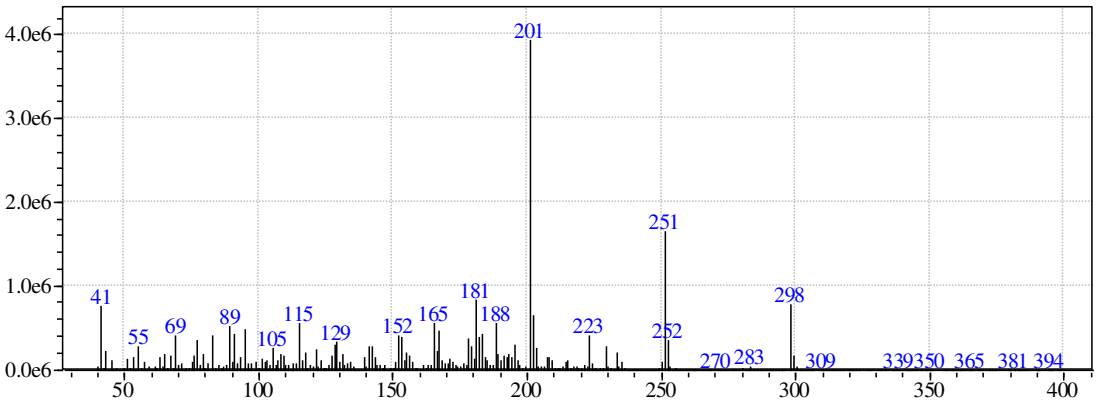
DEPT spectrum ($CDCl_3$+CCl_4, 50 MHz)

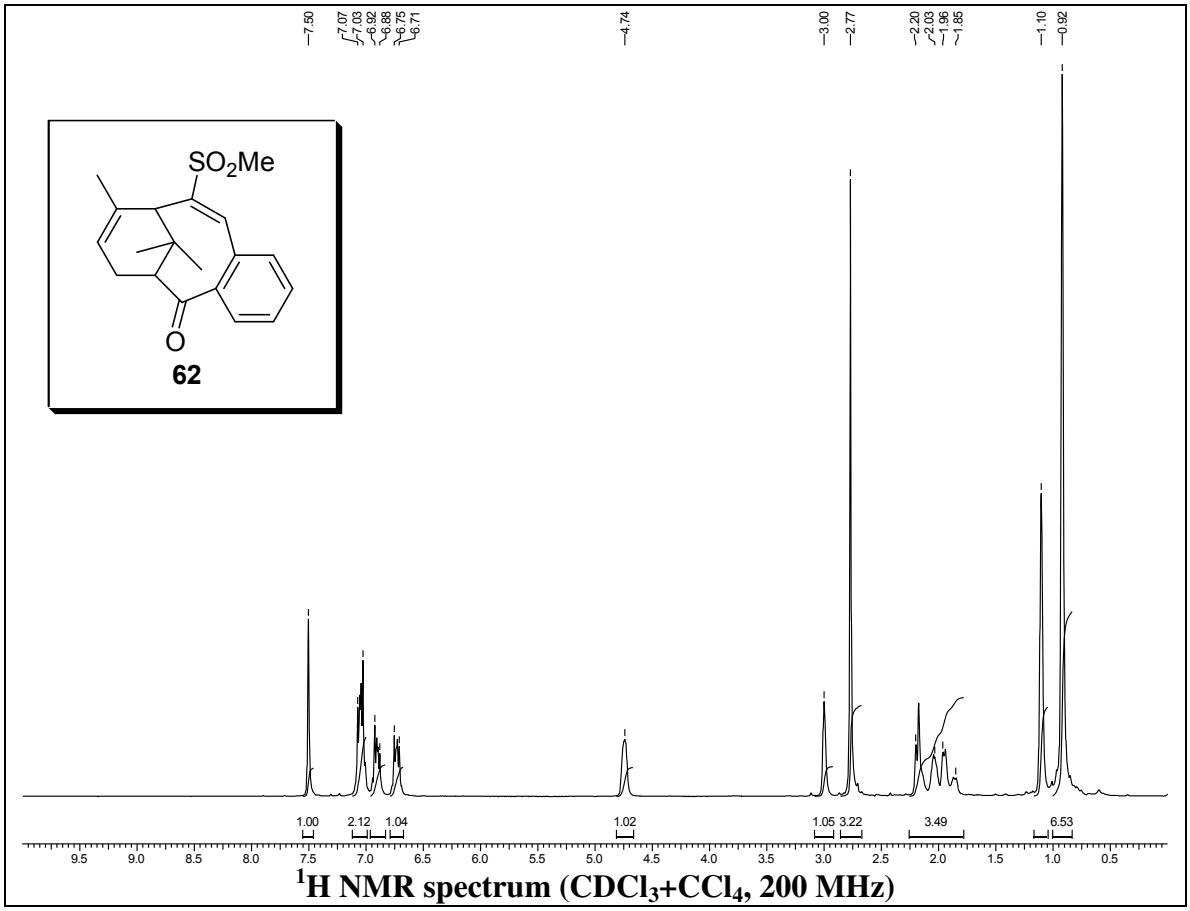
GCMS spectrum of 57



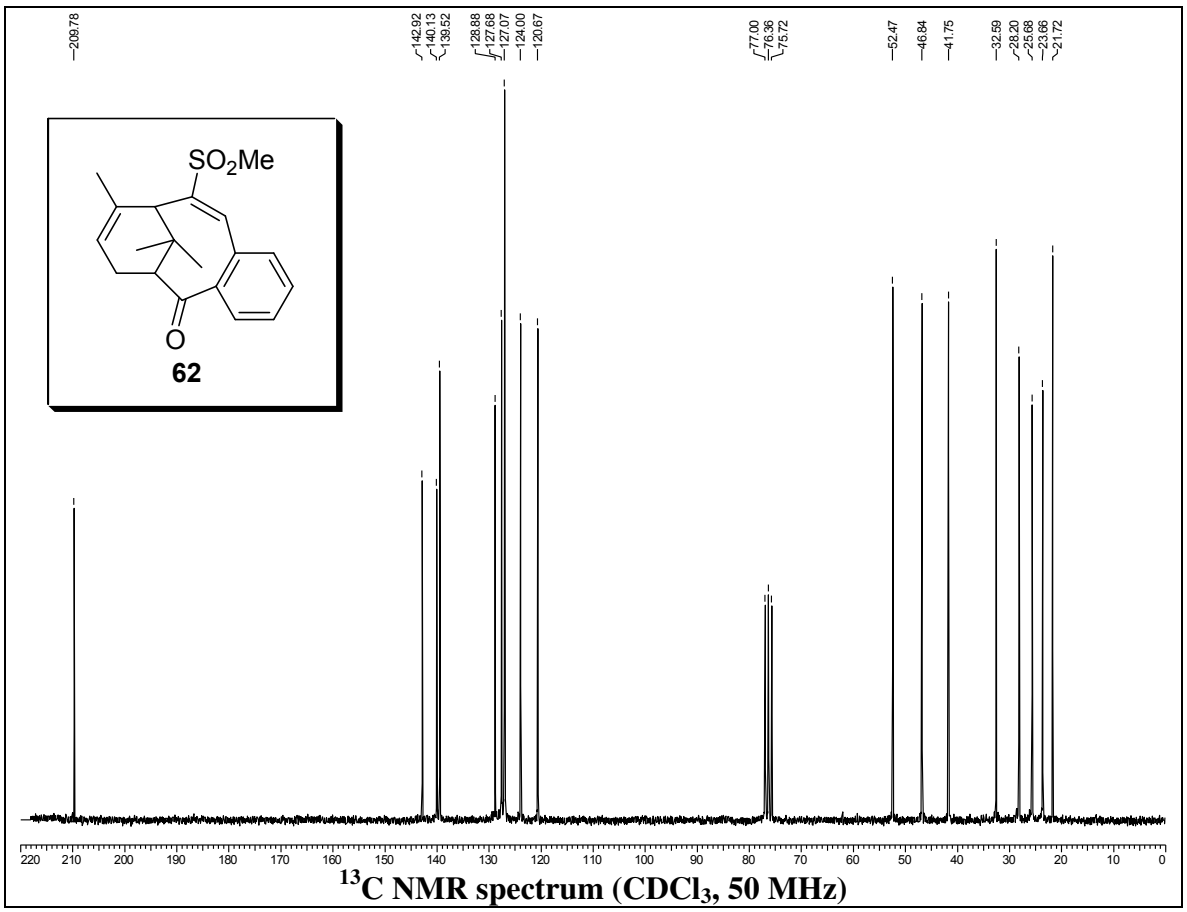
GC chromatogram

Mass spectrum at retention time 9.9

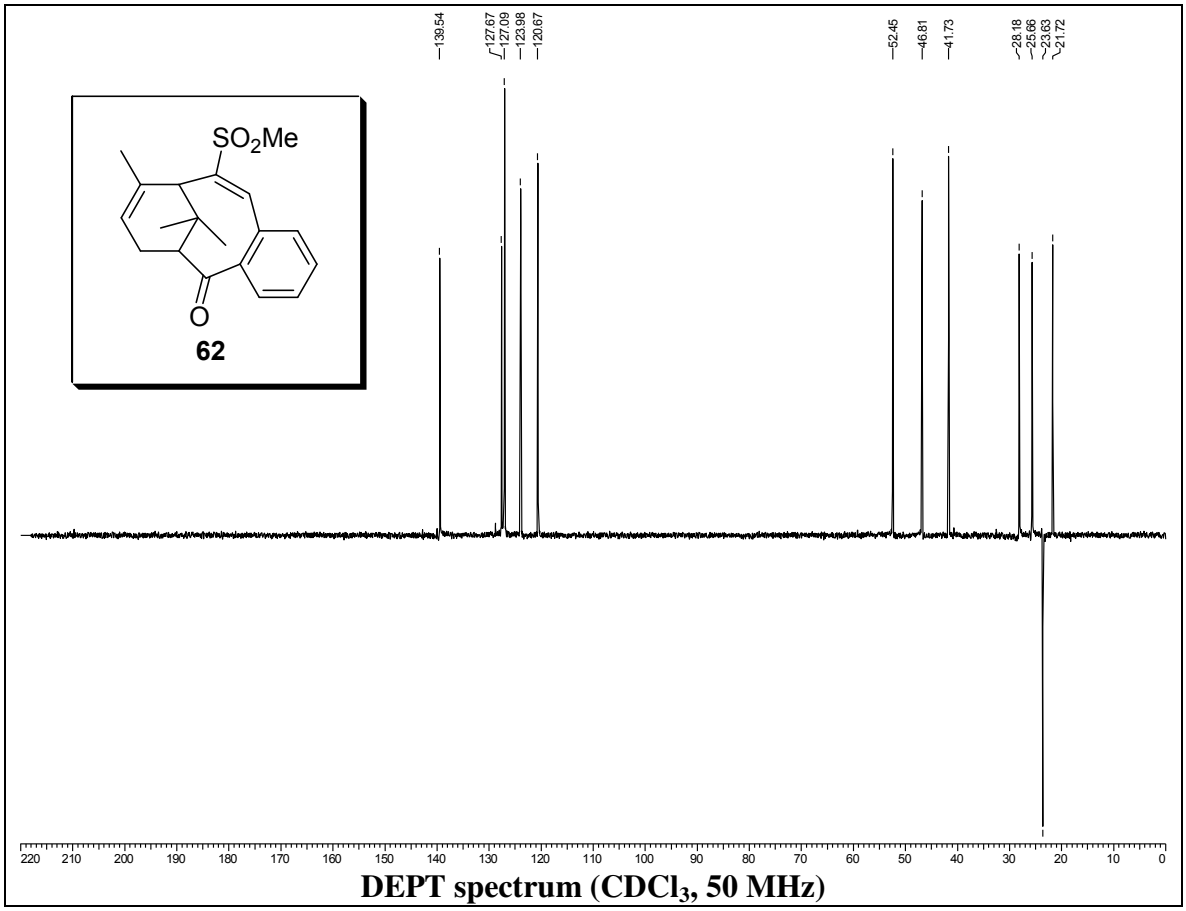




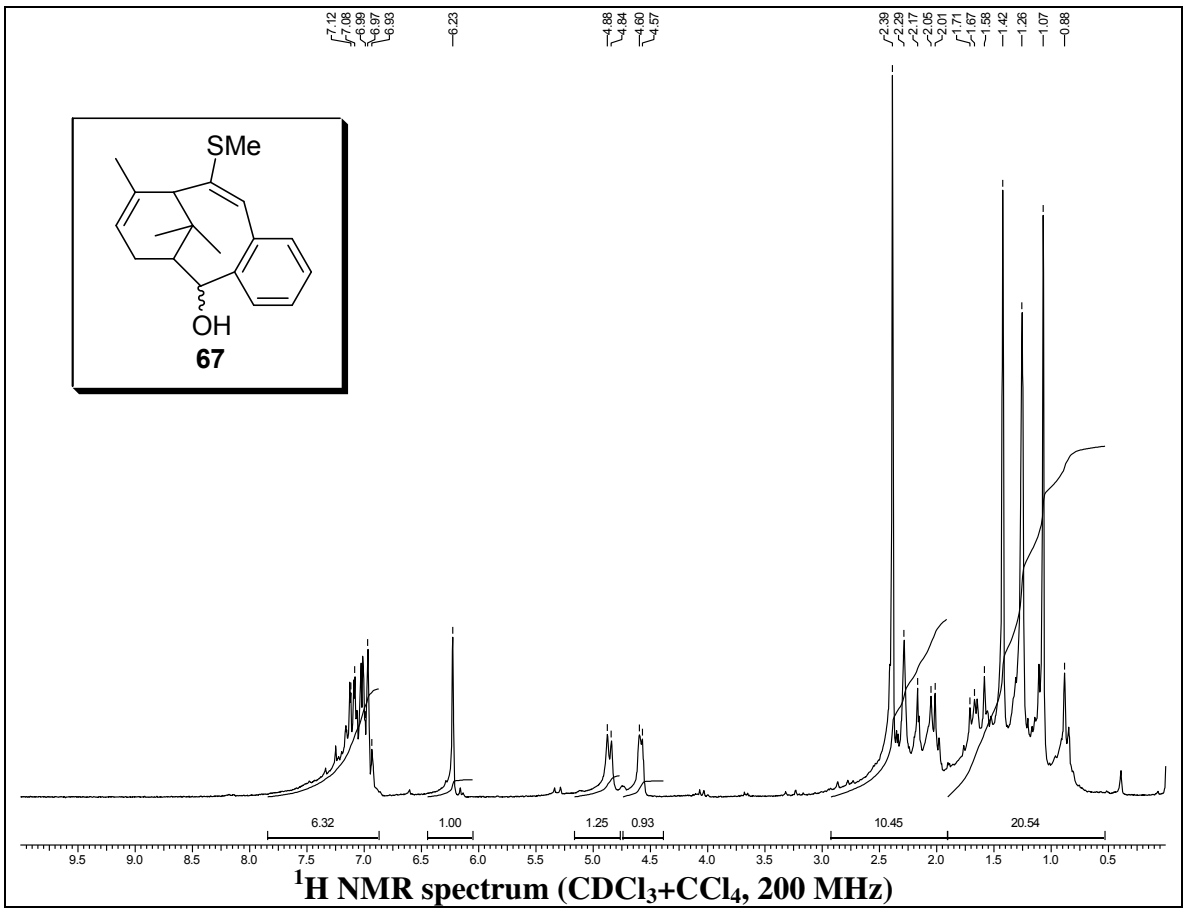
^{1}H NMR spectrum ($CDCl_3$+CCl_4, 200 MHz)



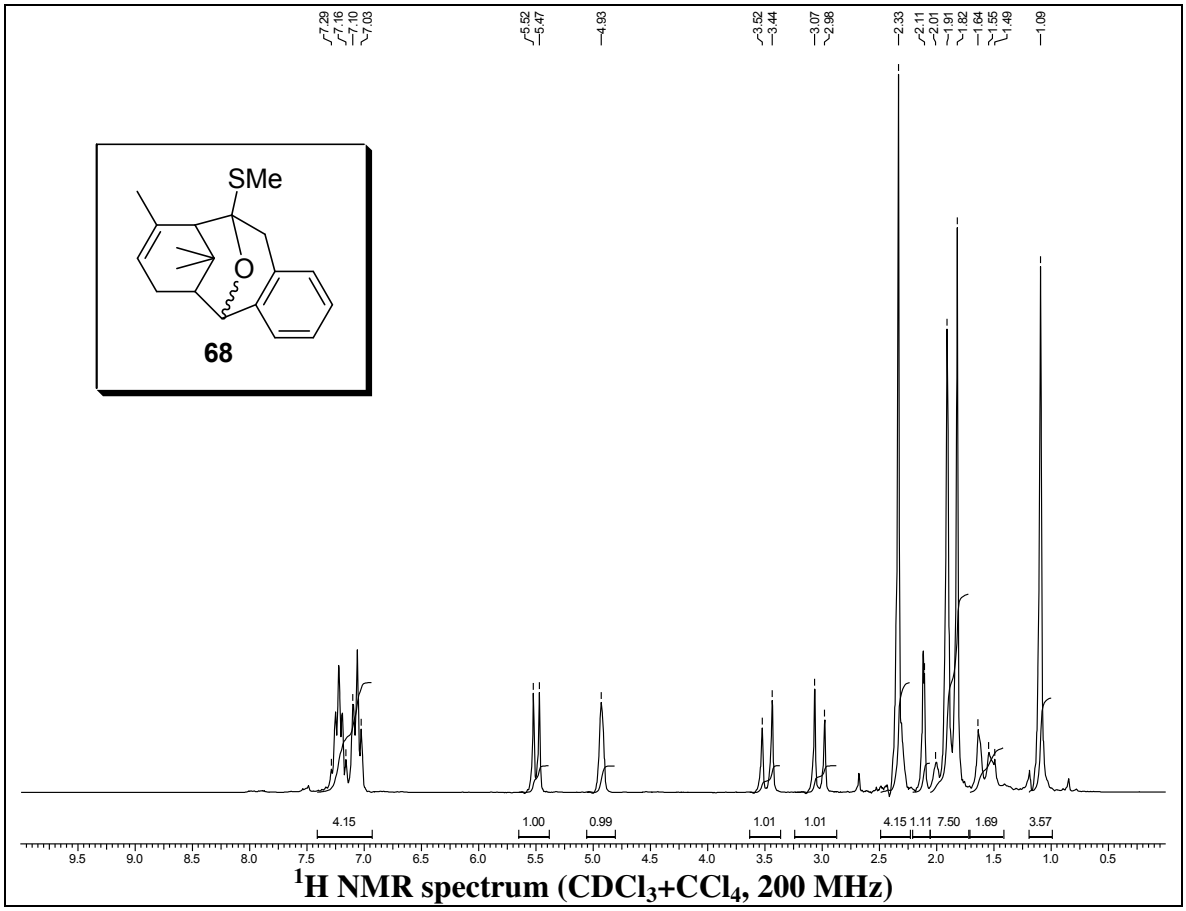
^{13}C NMR spectrum ($CDCl_3$, 50 MHz)



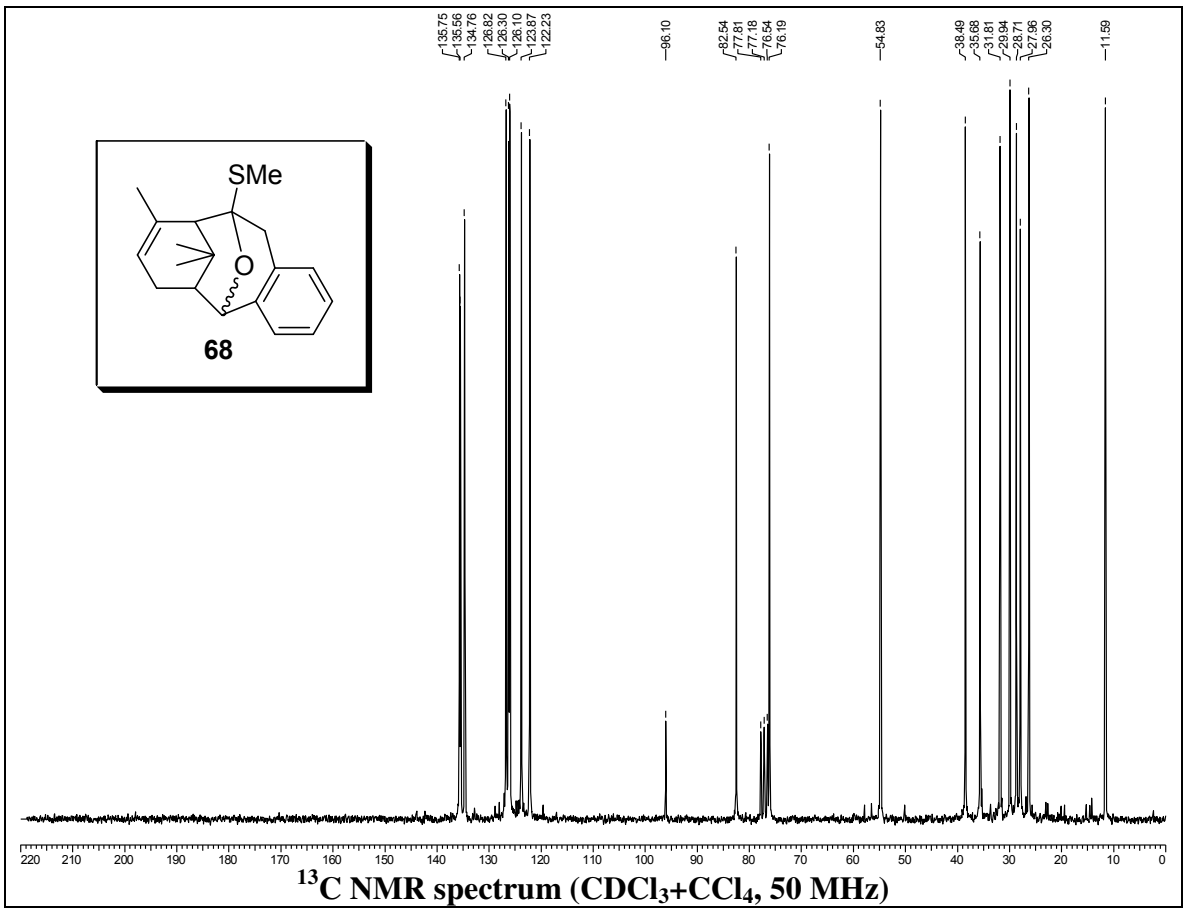
DEPT spectrum ($CDCl_3$, 50 MHz)



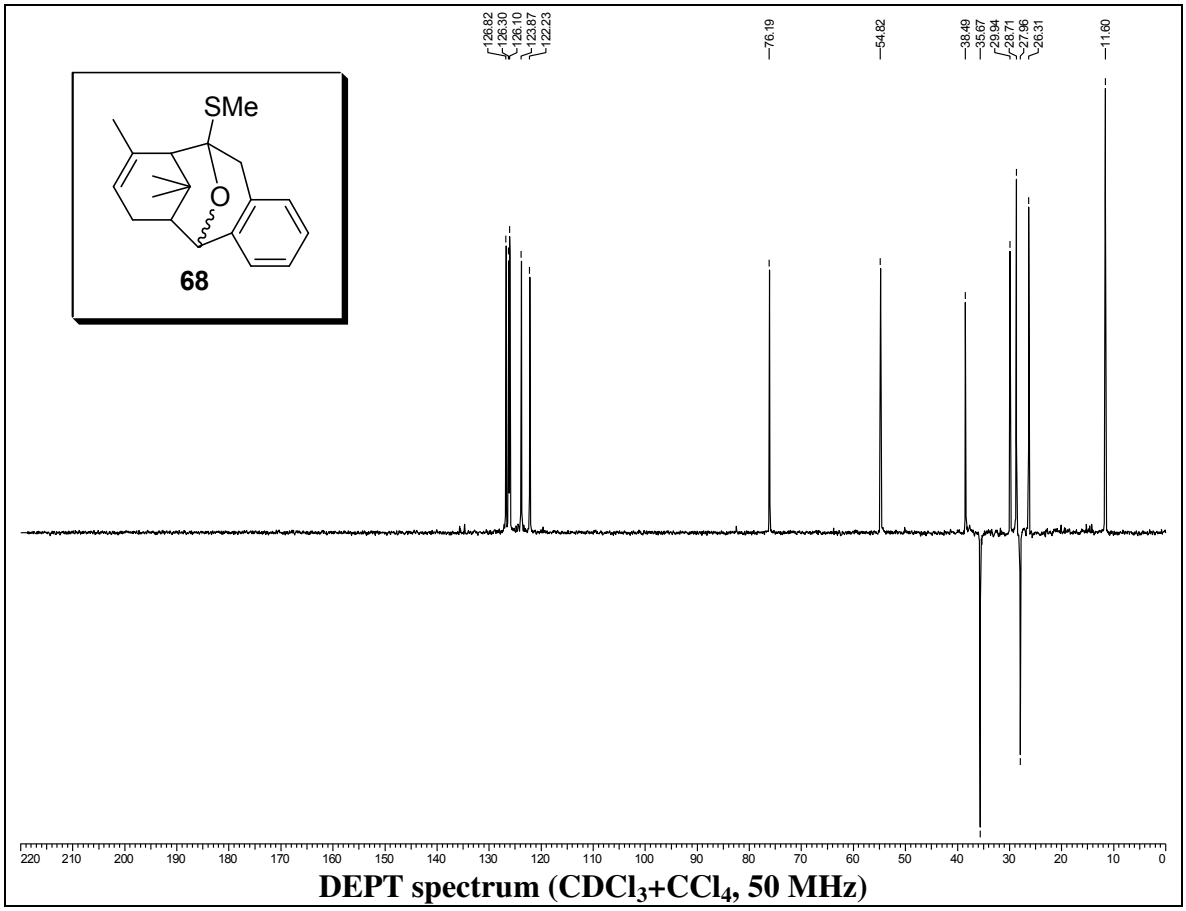
^{1}H NMR spectrum ($CDCl_3$+CCl_4, 200 MHz)



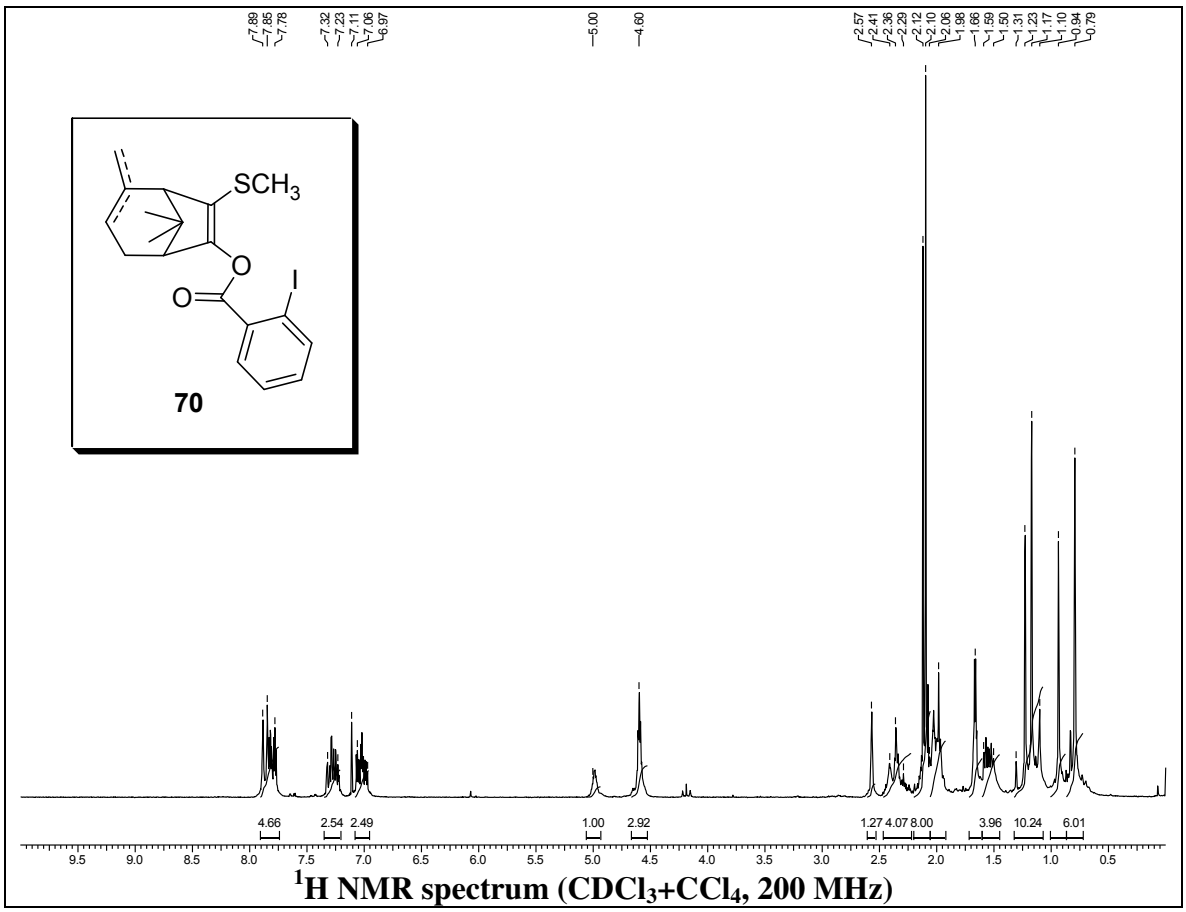
^{1}H NMR spectrum ($CDCl_3$+CCl_4, 200 MHz)



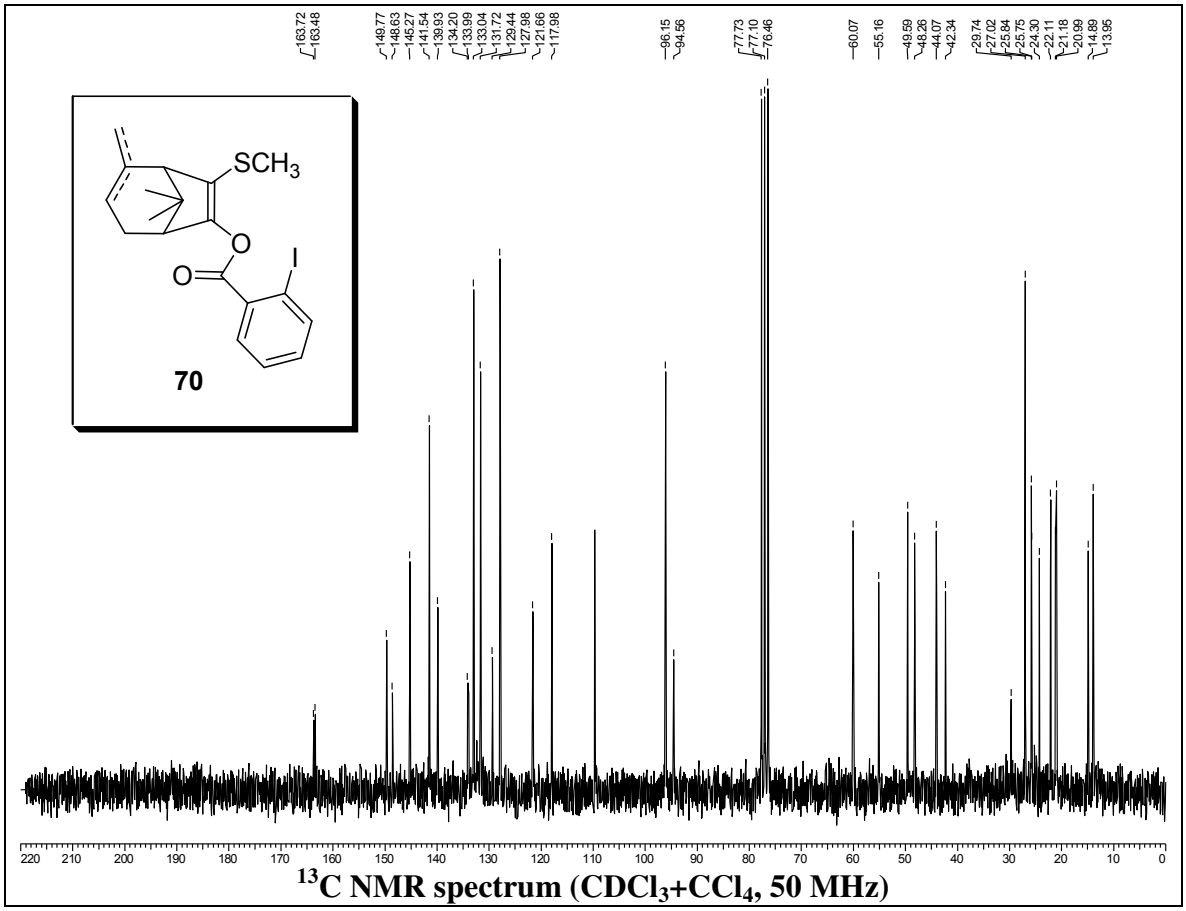
^{13}C NMR spectrum ($CDCl_3$+CCl_4, 50 MHz)



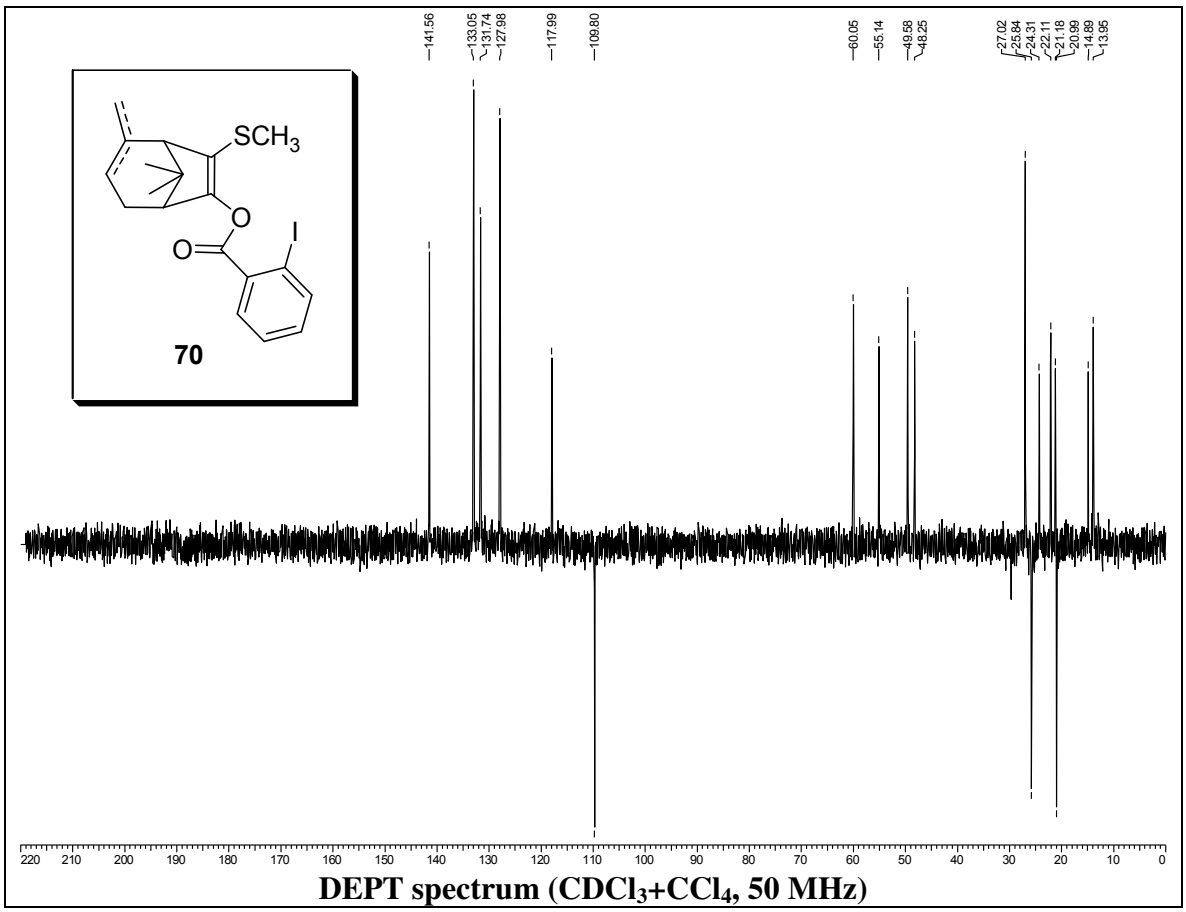
DEPT spectrum ($CDCl_3$+CCl_4, 50 MHz)



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



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



DEPT spectrum ($CDCl_3$+CCl_4, 50 MHz)

Section-IV

Synthesis of C-Alicyclic ABC-ring skeleton taxane system

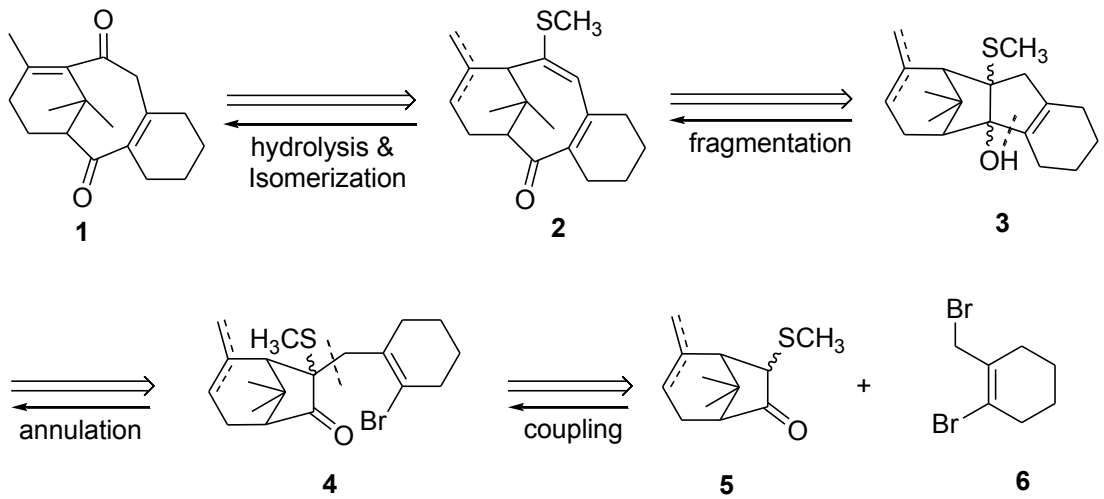
1.4.1 Introduction:

After successful synthesis of C-aromatic ABC skeleton system it was planned to apply sulfur assisted developed methodology for the synthesis of more advanced taxoids to this effect, C-alicyclic ABC skeleton of taxane system as per planned strategy.

1.4.2 Present Work:

The retrosynthetic analysis revealed that C-alicyclic ABC taxane system **1** could be accessed from hydrolysis and isomerization of **2**, which in turn could be evolved from fragmentation reaction of key precursor β-alkylsulfide alcohol **3**. It was envisaged that tetracyclic intermediate **3** could be obtained from **4** by intramolecular coupling between vinyl bromide and ketone groups either by ionic or by radical method. The intermediate **4** in turn could be prepared from anionic coupling of bicyclic unit **4** with C-ring unit **5**.

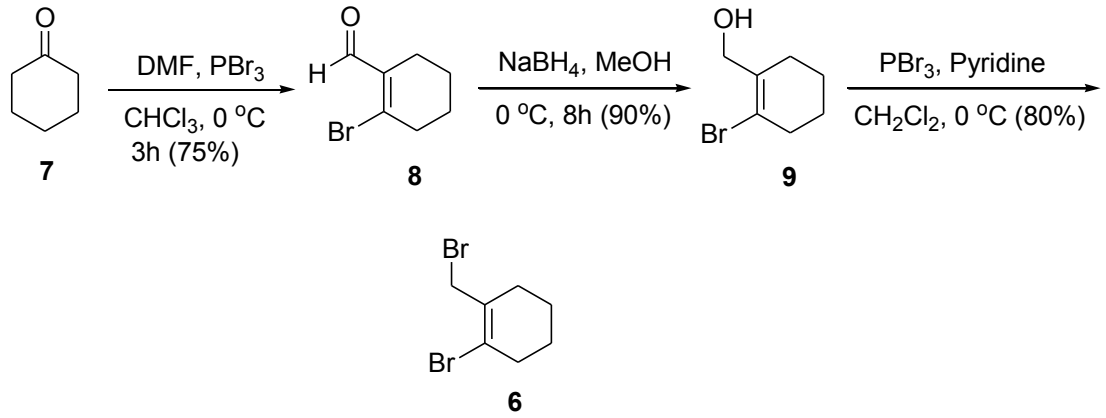
Scheme-1:



Thus, retrosynthesis revealed two synthons **5** and **6**, but synthon **5** was already prepared and used in earlier section for the synthesis of C-aromatic ABC taxane system and therefore synthon **6** was prepared accordingly as described below.

The 1-bromo-2-(bromomethyl)cyclohex-1-ene **6** was prepared in three steps from cyclohexanone as reported by Balasubramanian *et al.*[1] Thus, as delineated in Scheme-2, the formylating agent was prepared from *N*,*N*-dimethyl formamide and excess of phosphorus tribromide in chloroform at 0 ^{o}C, to this reaction mixture, cyclohexanone **7** was added and reaction mixture was refluxed at 60 ^{o}C for 3 h, to furnish 2-bromocyclohex-1-enecarbaldehyde **8** in 75% yield. Due to instability of **8** it was immediately used as such for further reduction.

Scheme-2:



IR spectrum of **8** displayed strong bands at 2939 and 1670 cm^{-1} which corresponded to aldehyde and conjugated carbonyl functional group respectively.

^{1}H NMR spectrum of **8** revealed following pattern. A singlet at δ 10.0 integrating for one proton corresponded to aldehydic proton. The multiplets at δ 2.73, 2.25 and 1.72 integrating for two, two and four protons respectively were attributed to methylene protons.

Mass spectrum of **8** revealed molecular ion peak at 190 and 188 in the ratio 1:1 and the other prominent peaks appeared at 161, 159, 109, 81, 79.

The compound **8** was thus reduced by addition of sodium borohydride to the methanolic solution of **8** at 0 °C for 6 h to furnish alcoholic compound **9** in 90% yield.

IR spectrum of **9** displayed a strong band at 3333 cm^{-1} which indicated the presence of hydroxyl functional group.

^{1}H NMR spectrum of **9** displayed a sharp singlet at δ 4.21 integrating for two protons was attributed to C<u>H</u>$_2$ α to hydroxyl group. The multiplets at δ 2.50, 2.25 and 1.68 integrating for two, two and four protons respectively were assigned to four methylene groups.

The alcohol group in **9** was substituted by bromide by reacting it with DCM solution of phosphorus tribromide and pyridine at 0 ºC for 3 h, which afforded bromide **6** in 92% yield.

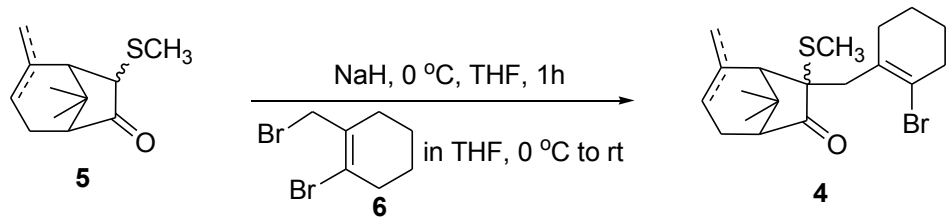
^{1}H NMR spectrum of **6** displayed a sharp peak at δ 4.12 integrating for two proton which corresponded to methylene group α to bromide and the multiplets appeared at δ 2.51, 2.28 and 1.69 integrating for two, two and four protons respectively were attributed to methylenes of the cyclohexane.

Mass spectrum of **6** revealed molecular ion peaks at 255, 254, 253 and 252.

After preparation of C-ring unit **6**, it was coupled with bicyclic unit **5** as follows (Scheme-3). Sodium enolate of β-keto sulfide **5** was prepared using sodium hydride in THF at 0 ºC and to this enolate formed, the C-ring unit **6** was slowly added and the reaction mixture was stirred at 0 ºC for 3 h to afford coupled product **4** in 70% yield.

IR spectrum of **4** displayed a strong band at 1731 cm^{-1} indicated the presence of five membered ring ketone group.

Scheme-3:



^{13}C NMR spectrum of **4** along with DEPT spectrum displayed the following pattern. The two down field quaternary signals at δ 217.9 and 215.6 were attributed to carbonyl groups. While the quaternary signals appearing at 158.1, 147.1, 146.3, 138.7, 133.7, 133.3, 121.2, 121.0 were assigned to olefinic carbons α and β to bromide and double bond present in isomeric form. The spectrum displayed 24 methylene signals. The above characteristic signals clearly indicate the existence of isomers.

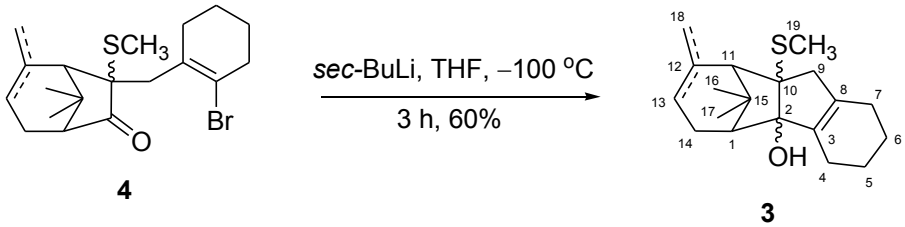
The mass spectrum of **4** displayed molecular ion peak along with sodium at 405 and 403 in the ratio 1:1.

Silver nitrate doped silica gel column chromatography was attempted to separate isomers but without any success. So it was decided to carry forward the isomers on similar line as described in the previous section, as all the isomers would eventually be converted into single product at later stages.

The next step, five membered ring annulation was carried out by using metal-halogen exchange methodology. Barbier coupling reaction was attempted as follows[2]; to a cold (0 ºC) solution of **4** in THF, lithium metal was added and stirred for 1 h, however TLC analysis of reaction mixture showed complex pattern and therefore further analysis was abandoned. Similarly, to a cold (0 ºC) solution of *tert*-butyl magnesium chloride in diethyl ether substrate **4** was added and reaction mixture was stirred for 2 h, here too TLC analysis revealed complex pattern.[3] Having failed to get five membered ring annulation by old methods it was decided to use transition metal catalysed ring annulation and therefore literature survey revealed Nozaki-Takai-Hiyama-Kishi coupling mediated by Cr(II)/Ni(II) complex could be used.[2] Thus, to a DMF solution of excess of

chromiun(II) chloride and catalytic amount of nickel(II) chloride, substrate **4** was added in THF and reaction mixture was stirred for several days but TLC analysis revealed no new product formation and starting material was recovered back. One could infer from the failure of this experiment that either the reagent has not formed or the reaction did not proceed in the desired direction.

Scheme-4:



4 **3**

After failure of the above reaction the substrate **4** was subjected to similar conditions used in previous case. Thus, to a cold (–78 ºC) and dilute solution of **4** in THF nBuLi was slowly added, but TLC analysis after 1 h revealed a complex pattern. Therefore the reaction was repeated by lowering temperature to –100 ºC, again TLC showed complex pattern and further analysis was abandoned. After failing to get desired annulation by normal butyl lithium then the next choice remained was the use of secondary butyl lithium. Thus, to a cold (–100 ºC) solution of substrate **4** in THF, *sec*-BuLi was slowly added and the reaction mixture was stirred for 3 h to and to delightfully afforded a ring annulated compound **3** in 60% yield (Scheme-4).

IR spectrum of **3** displayed a strong band at 3500 cm^{-1} indicated the presence of hydroxyl group.

^{1}H NMR spectrum of **3** displayed following pattern. A singlet at δ 4.67 and multiplet at δ 4.56 were attributed to olefinic protons. A singlets at δ 2.39 and 2.35 were assigned to H-1 protons. A sharp singlet at δ 2.02 was due to methyl sulfide group. Singlets at δ 1.11, 1.06, 1.01 and 0.89 were ascribed to geminal dimethyls. The above characteristic signals revealed that compound **3** existed as isomers.

^{13}C NMR spectrum of **3** along with DEPT spectrum displayed following pattern. The most down field quaternary signals at δ 150.2, 141.1, 137, 136.9, 136, 135.5 corresponded to carbons at 3, 8, and 12 positions. The quaternary signals at δ 93.8 and 98.2 were attributed to carbinol carbon. The upfield quaternary signals at δ 68.6 and 63.8 corresponded to carbon bearing methylsulfide group. The most upfield quaternary signals at δ 46.7, 44.7, 43.7 and 41.3 were assigned to C-15 carbon. The methylene signals appeared at 112.5, 109.1, 52.1 and 40.5, the first two signals were attributed to olefinic

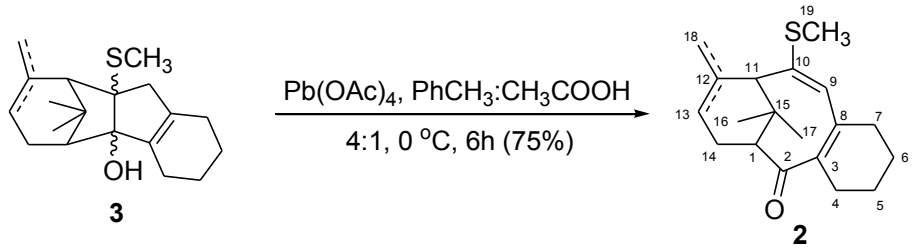
carbons while the latter corresponded to C-9 methylene group. The aliphatic methylene signals appeared at δ 29.6, 27.0, 25.6, 24.7, 23.3, 23.1, 22.8, 22.7, 22.5, 22.4 and 22.0 which correspond to C-4, 5, 6, 7, 13 and 14 methylene groups. The down field methine signals at δ 121.0 and 119.2 were assigned to C-18 carbon while the methine signals at 64.9, 58.9, 51.6 and 47.6 were attributed to ring junctures carbons at C-1 and C-11 positions. The methyl carbons at 29.4, 29.2, 25.9, 25.4, 25.0, 13.5, 13.3, 12.6, and 11.9 were ascribed to vinyl methyl, sulfide methyl and geminal dimethyls. The above spectral data establishes the existence of **3** as isomers.

The GCMS spectrum of **3** displayed four peaks each of which exhibited mass spectrum of similar pattern with molecular ion peak at 304 $(M)^+$ and the base peak at 182 while the other prominent peaks appeared at 289 $(M–CH_3)^+$, 271 $(M–CH_3OH)^+$, 256 $(M–CH_3SH)^+$, 241$(M–SCH_3OH)^+$, 227, 213, 200, 182, 123 and 105

It was therefore confirmed that **3** existed in four isomeric forms with olefin as *endo* & *exo* cyclic and hydroxyl & methylsulfide groups in *endo* and *exo* oriented. Even careful flash chromatography of **3** was unable to separate the isomers while the TLC showed a single spot. GC chart also revealed very close peaks of four isomers.

After success in getting five membered ring annulation to form 6-5-5-6 fused system then the next task was to unmask the eight membered ring.

Scheme-5:



The key fragmentation reaction was performed with lead tetraacetate as follows (Scheme-5); to a cold (0 ºC) solution of β-methylsulfide alcohol **3** in toluene:acetic acid (4:1) (v/v), lead tetraacetate in toluene was added at once and reaction mixture was stirred for 6 h at 0 ºC to afford fragmented product **2** in 75% yield.

IR spectrum of **2** displayed a strong band at 1674 cm^{-1} indicative of the presence of conjugated carbonyl functional group.

^1H NMR spectrum of **2** displayed following pattern which was relatively simple as compared to the starting material. The mulitplet at δ 5.70, the singlets at δ 5.50, 5.10, 4.95, 4.76, 4.75 and broad singlet at δ 5.40 were attributed to olefinic protons. The

singlets at δ 2.64 and 2.22 corresponded to ring junctions protons at C-11 and C-1 positions. The singlets at δ 2.13 and 2.11 were assigned to methylsulfide group. The multiplets ranging from 2.00 to 1.50 were ascribed to methylene protons. The singlets that appeared at 1.04, 1.02, 0.97 and 0.88 were attributed to geminal dimethyl groups. The above described pattern revealed that **2** exist as isomeric mixture of olefins.

^{13}C NMR spectrum of **2** along with DEPT spectrum displayed following pattern. The most down field quaternary signals at δ 213.1 & 213.0 were attributed to carbonyl group while the other quaternary signals at δ 145.7, 138.9, 137.2, 135.4, 135.1, 131.0, 130.0, 127.8, 120.7, 118.9, 118.0, 33.0 and 32.0 were assigned to C-10, 8, 12, 3 and 15 respectively. The methine signals at δ 120.7, 118.9, 118.0, 64.4, 56.4, 54.8 and 53.4 were ascribed to C-13, 9, 1 and 11 respectively. The most upfield methylene signal at δ 112.5 was due to C-18 carbon. While the other methylenes appeared at δ 30.7, 29.7, 29.5, 29.3, 27.5, 22.4 22.3, 21.5 were attributed to C-7, 6, 5, 4, 13 and 14 respectively. The methyl signals at δ 29.9, 29.4, 21.9, 16.2 and 15.9 were assigned to C-18, 19, 16 and 17 respectively. The above pattern revealed that **2** existed as a mixture of isomers.

GCMS spectrum of **2** displayed two peaks in the ratio of 1:1 and its corresponding mass fragmentation showed similar pattern with molecular ion peak at 302 and the other peaks appeared at 287 (M^+–CH_3), 274 (M^+–CO), 255 (M^+–SCH_3), 227, 191, 157, 144, 129 and 83.

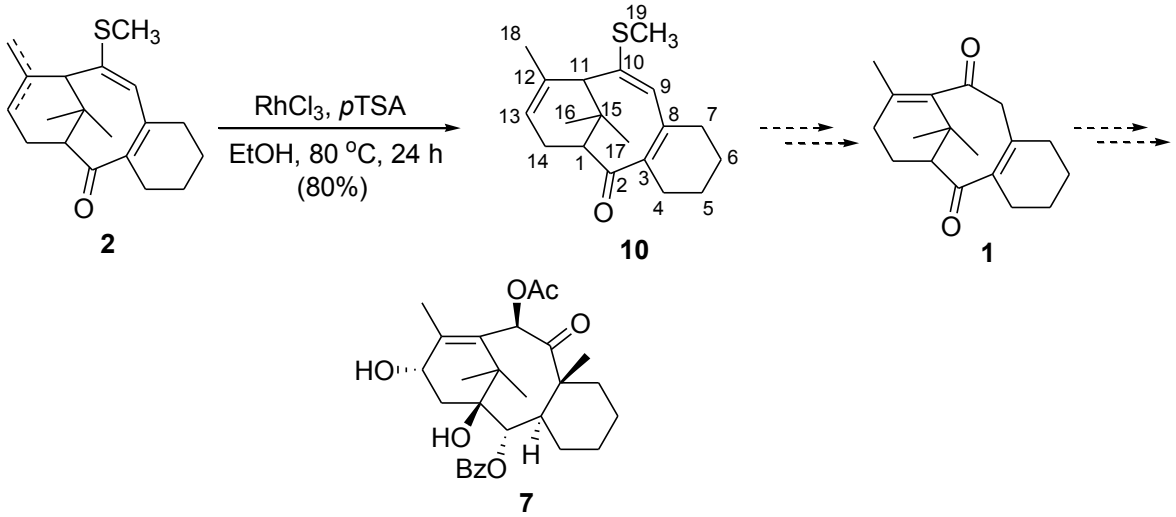
The C-alicyclic ABC taxane system **2** obtained here exists as a mixture of *exo* & *endo* double bond isomers. Therefore **2** was mixed with catalytic amounts of rhodium trichloride and *para*-toluenesulfonic acid in ethanol and heated to reflux. After 24 h, GC revealed single peak and afforded **10** in 80% yield.

IR spectrum of **10** displayed a strong band at 1674 cm^{-1} indicated the presence of conjugated carbonyl functional group.

^{1}H NMR spectrum of **10** displayed the following pattern. Singlets at δ 5.40 and 5.12 integrating for one proton each corresponded to olefinic protons at 9 and 13 positions respectively. A singlet at δ 2.21 integrating for one proton was assigned to ring junction proton at 11 position. The mutiplets at 2.21-2.10 were attributed to allylic protons. A sharp singlet at δ 2.14 integrating for three protons corresponded to –S<u>CH</u>$_3$ group. Another sharp singlet at δ 1.58 integrating for three protons was assigned to vinylic methyl. The multiplets at δ 1.55-1.40 were attributed to 5 and 6 positions

methylene protons. The sharp singlets at δ 1.03 and 1.00 integrating three protons each were ascribed to geminal dimethyl groups.

Scheme-6:



^{13}C NMR spectrum of **10** along with DEPT spectrum revealed following pattern. The most downfield quaternary signal at δ 213.7 was assigned to carbonyl group. While the downfield quaternary signals at δ 137.3, 135.1, 130.5 and 127.9 were assigned to carbons at C-10, 8, 3 and 12 respectively the upfield quaternary signal at δ 32.3 was ascribed to carbon bearing geminal dimethyls. The down field methine signals at δ 120.8 and 118.9 were attributed to the olefinic C-13 and C-9 carbons respectively. While the upfield methine signals at δ 56.4 and 53.5 were ascribed to C-11 and C-1 ring junctions carbons respectively. The aliphatic methylene signals at δ 30.0, 29.4, 24.0, 22.1 and 21.9 were assigned to C-7, 6, 5, 4, and 14 respectively. The methyl signals at 29.6, 26.4, 22.4 and 15.9 were vinylic methyl, geminal dimethyls and methyl sulfide respectively.

GCMS spectrum of **10** revealed a single peak and its corresponding mass showed molecular ion peak at 302 while the other prominent peaks appeared at 287 (M^+–CH_3), 274 (M^+–CO), 255 (M^+–SCH_3), 227, 191, 157, 144, 129 and 83.

Finally the structure assigned was unambiguously ascertained by X-ray crystallography of **10**. Interestingly the crystal structure (Figure-1) revealed that C-alicyclic ABC system of taxol exists in *endo* form.

After successfully synthesizing C-alicyclic ABC skeleton of taxol as per proposed scheme, the next chore was to functionalise. AB-ring of **10** in order to resemble taxol as portrayed in Scheme-6. Therefore as discussed in previous section what remaine to be done was just unmasking of the ketone group. Accordingly, **10** was subjected to various hydrolytic conditions namely $HgCl_2$, $Hg(OAc)_2$, CF_3COOH, dil. H_2SO_4,

$BF_3.OEt_2$, $SnCl_4$ and $TiCl_4$, unfortunately none of the above conditions worked and the starting material was recovered back.

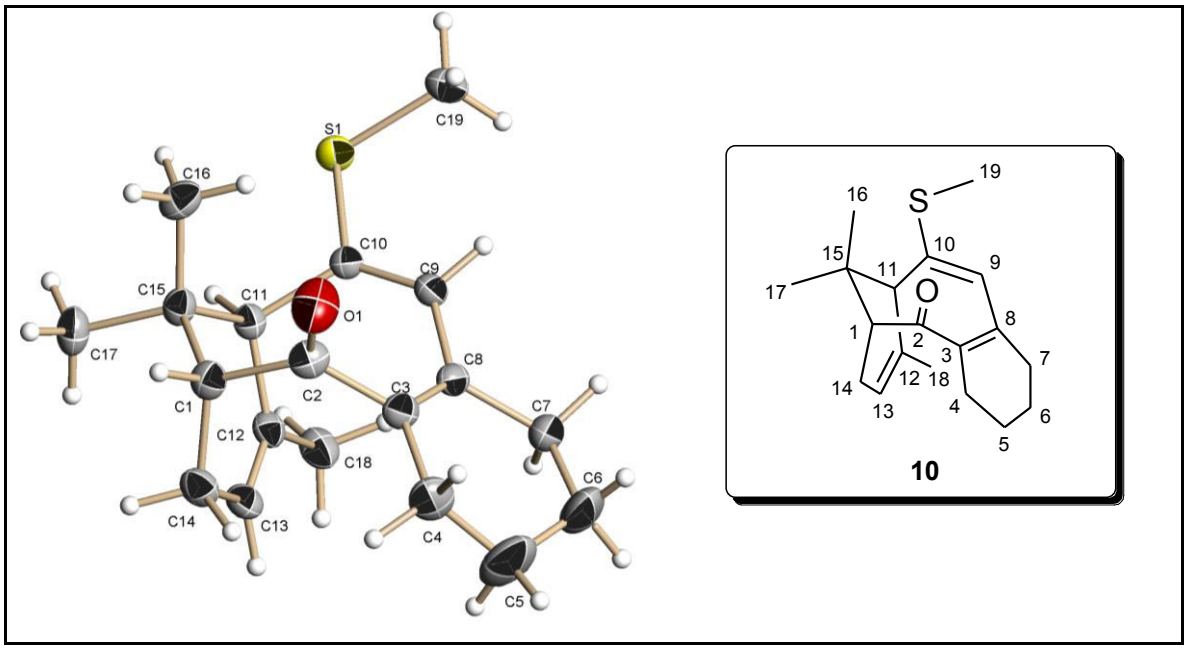


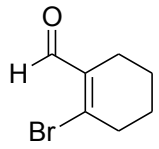
Figure-1: ORTEP view of C-alicyclic ABC ring system of taxol (**10**)

1.4.3 Conclusion:

In conclusion, C-alicyclic ABC ring skeleton of taxol was successfully synthesized from cheap and readily available starting materials. All 19 carbons in the developed core of taxol were assembled using very simple and commonly available cheap compounds *viz* mesityl oxide (6), methyl iodide (1), methyl acrylate (3), dimethyl sulfoxide (2), *N*,*N*-dimethyl formamide (1) and cyclohexanone (6) as the starting materials as carbon source and the figures in the bracket indicates number of carbons. It is believed that using this five-step protocol *i.e.* condensation-Pummerer-coupling-annulation-fragmentation a large number of advanced taxoids could be prepared and may give better biological activity than taxol. Since the structure activity relationship of taxol is under development, certainly the above-developed methodology may be helpful because large number of analogs could be accessed from simpler starting materials.

1.4.4 Experimental:

1.4.4.1 Preparation of 2-bromocyclohex-1-enecarbaldehyde (8):[1]



8

To a dry DMF (44.0 g, 0.6 mol) in chloroform (160 mL) was slowly added a freshly distilled PBr_3 (136.0 g, 0.5 mmol) at 0 ^oC. To this formylating reagent, was added cyclohexanone (19.6 g, 0.2 mmol) in dry chloroform (80 mL) at 0 ºC. After complete addition, the reaction mixture was refluxed at 60 ^oC for 3 h. After TLC analysis revealed consumption of starting material the solvent was evaporated *in vacuo*. The residue was carefully decomposed by pouring into crushed ice, neutralized with saturated $NaHCO_3$ solution and extracted with hexane (3 x 100 mL). The combined organic extracts were initially washed with saturated aqueous potassium carbonate (2 x 25 mL) and then with brine solution (2 x 50 mL) and finally dried over anhydrous Na_2SO_4. Evaporation of the solvent at room temperature *in vacuo* gave the 2-bromocyclohex-1-enecarbaldehyde **8** as colourless oil. Due to instability of this product it was used as such for the reduction.

Chemical Formula: C_7H_9BrO

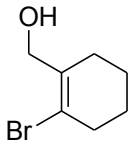
Yield: 19.0 g

IR ($CHCl_3$): ν 2939, 1670 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 10.0 (s, 1H), 2.73 (m, 2H), 2.25 (m, 2H), 1.72 (m, 4H)

MS (m/z): 190 & 188 (1:1) (M^+), 161, 159, 109, 81, 79

1.4.4.2 Preparation of (2-bromocyclohex-1-enyl) methanol (9):[1]



9

Solid $NaBH_4$ (1.4 g, 37.5 mmol) was slowly added to a stirred solution of 2-bromocyclohex-1-enecarbaldehyde **8** (14.2 g, 75 mmol) in methanol (100 mL) at 0 ^oC. The reaction was slightly exothermic. The reaction mixture was further stirred for 6 h, after consumption of starting material (TLC analysis) the solvent was evaporated *in vacuo*. The residue was poured into crushed ice, neutralized with 2N HCl solution and extracted with of dichloromethane (3 x 50 mL). The combined organic extracts were

washed with saturated brine solution (2 x 25 mL), dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent *in vacuo* furnished the (2-bromocyclohex-1-enyl) methanol **9** as a pale yellow oily liquid.

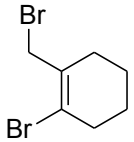
Chemical Formula: $C_7H_{11}BrO$

Yield: 13.0 g (91 %).

IR (neat): ν 3333 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.21 (s, 2H), 2.50 (m, 2H), 2.25 (m, 2H), 1.68 (m, 4H).

1.4.4.3 Preparation of 1-bromo-2-(bromomethyl) cyclohex-1-ene (6):[1]



6

To a solution of (2-bromocyclohex-1-enyl)methanol **9** (4.78 g, 25 mmol) in dichloromethane (15 mL) was added pyridine (200 mg) and the reaction mixture was cooled to 0 ^oC. To this reaction mixture was slowly added phosphorus tribromide (3.39 g, 12.5 mmol). After the addition was over the reaction mixture was further stirred for 3h at room temperature and poured into crushed ice. It was extracted with pet ether (3 x 30 mL) and the combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (25 mL) and finally with saturated brine (2 x 25 mL). It was dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent *in vacuo* yielded crude product which was further distilled under high vacuum (2 Torr, 40-50 ^oC oil bath temp.) provided a 1-bromo-2-(bromomethyl) cyclohex-1-ene **6** as colourless oil.

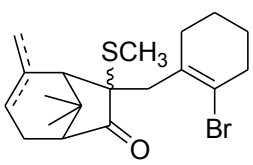
Chemical Formula: $C_7H_{10}Br_2$

Yield: 5.8 g (92 %)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.1 (s, 2H), 2.51 (m, 2H), 2.28 (m, 2H), 1.69 (m, 4H).

MS (m/z): 254 (M^+), 252 (M^+), 173, 171

1.4.4.4 Coupling reaction of 5 & 6: preparation of 4



4

To solution of ketosulfide **4** (0.210 g, 1.0 mmol) in THF (5 mL) was added slowly over a period of 15 min to stirred solution of NaH (50% dispersion in oil) (0.050 g, 1.1 mmol) in THF (10 mL) at 0 ^{o}C under argon atmosphere. The reaction mixture developed a dark brown colour after 1h. A solution of 1-bromo-2-(bromomethyl)cyclohex-1-ene **5** (0.381 g, 1.5 mmol) in THF was added slowly over a period of 5 min to sodium enolate and reaction mixture stirred for 3 h at 0 ^{o}C and then left overnight. The reaction mixture was poured in to a cold dilute hydrochloric acid solution. The organic layer was separated and the aqueous layer was extracted with ether (3 x 25 mL). The combined combined organic layers were washed with brine solution, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and the residue obtained was purified by flash column chromatography (230-400 mesh size silica gel, 2 % EtOAc/pet. ether gradient elution) provided **4** as a gummy oil.

Chemical Formula: $C_{19}H_{26}BrOS$

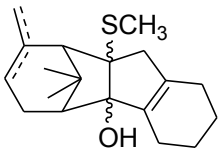
Yield: 0.272 g (71 %)

IR ($CHCl_3$): ν 2929, 1731 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.33 (s, olefin), 4.66 (s, olefin), 4.59 (s, olefin), 4.53 (s, olefin), 2.54-1.85 (m, methylenes), 2.17 (s, –S$\underline{C}H_3$), 1.85-1.45 (m, methylenes), 1.69 (s, allylic methyl), 1.10 (s, –C$\underline{H}_3$), 1.10 (s, –C$\underline{H}_3$), 0.95 (s, –C$\underline{H}_3$), 0.87 (s, –CH_3).

MS (M/Z): 404.9 $(M+Na)^+$, 402.9 $(M+Na)^+$, 399, 397, 383, 381, 373.

1.4.4.5 Ring annulation: preparation of 3



3

A two neck 100 mL RB flask charged with coupled product **4** (0.384 g, 1.0 mmol) and THF (50 mL) was kept at –100 ^{o}C under argon atmosphere. *sec*BuLi (3.3 mL, 5.0 mmol, 1.5 M) was slowly added over a period of 10 min to the above stirred solution and reaction was further stirred for 3 h. After disappearance of the starting material (TLC analysis) it was quenched with saturated aqueous ammonium chloride solution (1 mL), allowed warming to room temperature, organic layer was separated, aqueous layer was extracted with ether (3 x 25 mL). Combined organic layers were washed with brine solution, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and the residue

thus obtained was purified by flash column chromatography (230-400 mesh size silica gel, 3 % EtOAc/pet. ether gradient elution) which provided **3** as a gummy oil.

Chemical Formula: $C_{19}H_{27}OS$, 304

Yield: 0.180 g (60 %)

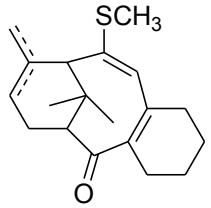
IR ($CHCl_3$): ν 3500 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.67 (s, 1H), 4.58 (m, 1H), 3.50 (s, 1H), 3.05 (s, 1H), 2.96 (s, 1H), 2.39 (s, 1H), 2.35 (s, 1H), 2.02 (s, 3H), 2.20-1.50 (m, -CH_2-), 1.01 (s, 3H), 0.89 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 150.2 (C), 141.1 (C), 137.4 (C), 136.9 (C), 136.0 (C), 135.5 (C), 121.0 (CH), 119.2 (CH), 109.1 (CH_2), 109.0 (CH_2), 100.3 (CH_2), 98.2 (C), 93.8 (C), 68.6 (C), 64.9 (CH), 63.8(C), 58.9 (CH), 52.8 (C), 52.1 (CH_2), 51.7 (CH), 47.6 (CH), 46.7 (CH_2), 46.5 (CH_2), 44.7 (C), 43.7 (C), 41.3 (C), 29.6 (CH_2), 29.4 (CH), 29.2 (CH), 28.0 (CH), 27.0 (CH_2), 26.4 (CH), 26.2 (CH), 25.9(CH), 25.6 (CH_2), 25.4 (CH), 25.3 (CH_2), 25.0 (CH), 24.7 (CH_2), 23.3 (CH_2), 23.1 (CH_2), 22.8 (CH_2), 22.7 (CH_2), 22.5 (CH_2), 22.5(CH_2), 22.4 (CH_2), 22.0 (CH_2), 13.5 (CH_3), 13.3 (CH_3), 12.6 (CH_3), 11.9 (CH_3).

MS (m/z): 304 (M^+), 289, 271, 256, 241, 227, 213, 200, 182, 123, 105.

1.4.4.6 Fragmentation reaction: preparation of 2



2

A 100 mL two-neck RB flask was charged with lead tetraacetate (0.886 g, 2.0 mmol) along with glacial acetic acid (5 mL) and toluene (20 mL) under argon atmosphere. The mixture was cooled to 0 ^oC and β-hydroxy sulfide **3** (0.304 g, 1.0 mmol) in toluene was slowly added and the reaction mixture was stirred for 6 h at 0 ^oC. The reaction was quenched with saturated aqueous ammonium chloride solution (10 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 25 mL). The combined organic layer were washed with saturated aqueous sodium bicarbonate solution until neutralization and further with brine, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and the residue obtained was purified by column

chromatography (silica gel, 5 % ethyl acetate/pet. ether gradient elution) which provided **2** as a yellowish solid.

Chemical Formula: $C_{19}H_{25}OS$

Yield: 0.226 g (75 %)

M.P.: 175-180 ºC

IR ($CHCl_3$): ν 1674 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.70 (m, olefin), 5.50 (s, olefin), 5.40 (bs, olefin), 5.10 (s, olefin) 4.95 (s, olefin) 4.75 (s, olefin), 2.65 (s, 1H), 2.18 (s, S-CH_3), 2.16 (s, S-CH_3), 2.15 (s, S-CH_3), 2.13 (s, S-CH_3), 2.25-1.40 (m, -CH_2-), 1.58 (s, allylic-CH_3), 1.57 (s, allylic-CH_3), 1.18 (s, Me), 1.03 (s, Me), 1.02 (s, Me), 1.00 (s, Me), 0.97 (s, Me), 0.95 (s, Me), 0.88 (s, Me), 0.76 (s, Me).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 213.3 (C), 213.1 (C), 145.7 (C), 138.9 (C), 137.2 (C), 135.4 (C), 135.1 (C), 131.0 (C), 130.0 (C), 127.8 (C), 120.7 (CH), 118.9 (CH), 118.0 (CH), 112.5 (CH_2), 60.4 (CH), 56.4 (CH), 54.8 (CH), 53.4 (CH), 33.0 (C), 32.0 (C), 30.7 (CH_2), 29.9 (CH_3), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_3), 29.3 (CH_2), 27.5 (CH_2), 26.4 (CH_3), 23.9 (CH_2), 22.4 (CH_2), 22.3 (CH_2), 22.1 (CH), 21.9 (CH_3), 21.5 (CH_2), 16.2 (CH_3), 15.9 (CH_3).

MS (m/z): 302 (M^+), 287, 274, 255, 227, 191, 157, 144, 129, 83.

1.4.4.7 Isomerization reaction: preparation of 10

10

A mixture of compound **2** (0.302 g, 1.0 mmol), $RhCl_3.3H_2O$ (0.025 g, 0.1 mmol), and *p*TSA.H_2O (0.019 g, 1 mmol) in ethanol (25 mL) was refluxed in 100 mL single-neck RB flask under argon atmosphere. After 24 h (GC analysis) the reaction mixture was quenched by adding triethyl amine (1 mL). The solvent was removed *in vacuo*, solid material obtained was directly absorbed on silica gel and passed through a column of silica gel using 5 % EtOAc/pet.ether as eluent, furnished **10** as a yellowish solid.

Chemical Formula: $C_{19}H_{26}OS$, 302

Yield: 0.235 g (80%)

M.P.: 175-180 ºC

IR ($CHCl_3$): ν 1674 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.40 (s, 1H), 5.12 (s, 1H), 2.21-2.10 (m, 4H), 2.14 (s, 3H), 1.75-1.80 (m, 4H), 1.58 (s, 3H), 1.40-1.55 (m, 4H), 1.03 (s, 3H), 1.00 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 213.7 (C), 137.3 (C), 135.1 (C), 130.5 (C), 127.9 (C), 120.8 (CH), 118.9 (CH), 56.4 (CH), 53.5 (CH), 32.3 (C), 30.0 (CH_2), 29.6 (CH_3), 29.4 (CH_2), 26.4 (CH_3), 24.0 (CH_2), 22.4 (CH_3), 22.1 (CH_2), 21.9 (CH_2), 15.9 (CH_3).

Anal. Calcd. For $C_{19}H_{26}OS$: C, 75.45; H, 8.66; O, 5.29; S, 10.60%. Found C 75.16, H 8.75%.

Crystal data of 10:

Table 1. Crystal data and structure refinement for **10**.

Identification code	**10**
Empirical formula	C_{19} H_{26} O S
Formula weight	302.46
Temperature	297(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 6.972(3) Å alpha = 86.298(8)º.
	b = 7.465(4) Å beta = 85.217(8)º.
	c = 16.427(8) Å gamma = 80.673(8)º.
Volume	839.6(7) $Å^3$
Z, Calculated density	2, 1.196 Mg/m^3
Absorption coefficient	0.190 mm^{-1}
F(000)	328
Crystal size	0.44 x 0.42 x 0.16 mm
Theta range for data collection	2.49 to 25.00º.
Limiting indices	-8<=h<=8, -8<=k<=8, -19<=l<=19
Reflections collected / unique	7539 / 2945 [R(int) = 0.0224]
Completeness to theta = 25.00	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9709 and 0.9206
Refinement method	2945 / 0 / 194
Goodness-of-fit on F^2	1.011

Final R indices [I>2sigma(I)]	R1 = 0.0492, wR2 = 0.1287
R indices (all data)	R1 = 0.0549, wR2 = 0.1350
Largest diff. peak and hole	0.483 and -0.292 e. $Å^{-3}$

Table 2. Bond lengths [Å] and angles [deg] for **10**.

S(1)-C(10)	1.765(2)	C(17)-H(17C)	0.9600
S(1)-C(19)	1.790(2)	C(18)-H(18A)	0.9600
O(1)-C(2)	1.213(3)	C(18)-H(18B)	0.9600
C(1)-C(2)	1.522(3)	C(18)-H(18C)	0.9600
C(1)-C(14)	1.535(3)	C(19)-H(19A)	0.9600
C(1)-C(15)	1.552(3)	C(19)-H(19B)	0.9600
C(1)-H(1)	0.9800	C(19)-H(19C)	0.9600
C(2)-C(3)	1.504(3)	C(10)-S(1)-C(19)	104.84(10)
C(3)-C(8)	1.326(3)	C(2)-C(1)-C(14)	112.53(18)
C(3)-C(4)	1.518(3)	C(2)-C(1)-C(15)	113.96(17)
C(4)-C(5)	1.475(5)	C(14)-C(1)-C(15)	109.84(17)
C(4)-H(4A)	0.9700	C(2)-C(1)-H(1)	106.7
C(4)-H(4B)	0.9700	C(14)-C(1)-H(1)	106.7
C(5)-C(6)	1.404(5)	C(15)-C(1)-H(1)	106.7
C(5)-H(5A)	0.9700	O(1)-C(2)-C(3)	119.0(2)
C(5)-H(5B)	0.9700	O(1)-C(2)-C(1)	120.3(2)
C(6)-C(7)	1.522(4)	C(3)-C(2)-C(1)	120.48(18)
C(6)-H(6A)	0.9700	C(8)-C(3)-C(2)	123.22(19)
C(6)-H(6B)	0.9700	C(8)-C(3)-C(4)	123.2(2)
C(7)-C(8)	1.515(3)	C(2)-C(3)-C(4)	113.5(2)
C(7)-H(7)	0.9700	C(5)-C(4)-C(3)	112.8(2)
C(7)-H(7B)	0.9700	C(5)-C(4)-H(4A)	109.0
C(8)-C(9)	1.470(3)	C(3)-C(4)-H(4A)	109.0
C(9)-C(10)	1.335(3)	C(5)-C(4)-H(4B)	109.0
C(9)-H(9)	0.9300	C(3)-C(4)-H(4B)	109.0
C(10)-C(11)	1.525(3)	H(4A)-C(4)-H(4B)	107.8
C(11)-C(12)	1.511(3)	C(6)-C(5)-C(4)	116.0(3)
C(11)-C(15)	1.559(3)	C(6)-C(5)-H(5A)	108.3
C(11)-H(11)	0.9800	C(4)-C(5)-H(5A)	108.3
C(12)-C(13)	1.319(3)	C(6)-C(5)-H(5B)	108.3
C(12)-C(18)	1.507(3)	C(4)-C(5)-H(5B)	108.3
C(13)-C(14)	1.497(3)	H(5A)-C(5)-H(5B)	107.4
C(13)-H(13)	0.9300	C(5)-C(6)-C(7)	116.1(3)
C(14)-H(14A)	0.9700	C(5)-C(6)-H(6A)	108.3
C(14)-H(14B)	0.9700	C(7)-C(6)-H(6A)	108.3
C(15)-C(16)	1.522(3)	C(5)-C(6)-H(6B)	108.3
C(15)-C(17)	1.540(3)	C(7)-C(6)-H(6B)	108.3
C(16)-H(16A)	0.9600	H(6A)-C(6)-H(6B)	107.4
C(16)-H(16B)	0.9600	C(8)-C(7)-C(6)	113.0(2)
C(16)-H(16C)	0.9600	C(8)-C(7)-H(7)	109.0
C(17)-H(17A)	0.9600	C(6)-C(7)-H(7)	109.0
C(17)-H(17B)	0.9600	C(8)-C(7)-H(7B)	109.0

C(6)-C(7)-H(7B)	109.0	C(16)-C(15)-C(1)	110.72(18)
H(7)-C(7)-H(7B)	107.8	C(17)-C(15)-C(1)	108.17(18)
C(3)-C(8)-C(9)	125.03(19)	C(16)-C(15)-C(11)	112.27(17)
C(3)-C(8)-C(7)	121.54(19)	C(17)-C(15)-C(11)	108.03(17)
C(9)-C(8)-C(7)	113.39(19)	C(1)-C(15)-C(11)	109.63(16)
C(10)-C(9)-C(8)	129.53(19)	C(15)-C(16)-H(16A)	109.5
C(10)-C(9)-H(9)	115.2	C(15)-C(16)-H(16B)	109.5
C(8)-C(9)-H(9)	115.2	H(16A)-C(16)-H(16B)	109.5
C(9)-C(10)-C(11)	127.01(18)	C(15)-C(16)-H(16C)	109.5
C(9)-C(10)-S(1)	123.11(16)	H(16A)-C(16)-H(16C)	109.5
C(11)-C(10)-S(1)	109.74(13)	H(16B)-C(16)-H(16C)	109.5
C(12)-C(11)-C(10)	111.19(16)	C(15)-C(17)-H(17A)	109.5
C(12)-C(11)-C(15)	113.66(17)	C(15)-C(17)-H(17B)	109.5
C(10)-C(11)-C(15)	114.96(16)	H(17A)-C(17)-H(17B)	109.5
C(12)-C(11)-H(11)	105.3	C(15)-C(17)-H(17C)	109.5
C(10)-C(11)-H(11)	105.3	H(17A)-C(17)-H(17C)	109.5
C(15)-C(11)-H(11)	105.3	H(17B)-C(17)-H(17C)	109.5
C(13)-C(12)-C(18)	122.6(2)	C(12)-C(18)-H(18A)	109.5
C(13)-C(12)-C(11)	121.73(19)	C(12)-C(18)-H(18B)	109.5
C(18)-C(12)-C(11)	115.66(18)	H(18A)-C(18)-H(18B)	109.5
C(12)-C(13)-C(14)	125.1(2)	C(12)-C(18)-H(18C)	109.5
C(12)-C(13)-H(13)	117.4	H(18A)-C(18)-H(18C)	109.5
C(14)-C(13)-H(13)	117.4	H(18B)-C(18)-H(18C)	109.5
C(13)-C(14)-C(1)	112.69(17)	S(1)-C(19)-H(19A)	109.5
C(13)-C(14)-H(14A)	109.1	S(1)-C(19)-H(19B)	109.5
C(1)-C(14)-H(14A)	109.1	H(19A)-C(19)-H(19B)	109.5
C(13)-C(14)-H(14B)	109.1	S(1)-C(19)-H(19C)	109.5
C(1)-C(14)-H(14B)	109.1	H(19A)-C(19)-H(19C)	109.5
H(14A)-C(14)-H(14B)	107.8	H(19B)-C(19)-H(19C)	109.5
C(16)-C(15)-C(17)	107.89(19)		

Symmetry transformations used to generate equivalent atoms:

Table 3. Torsion angles [deg] for **10**

C(14)-C(1)-C(2)-O(1)	-142.6(2)
C(15)-C(1)-C(2)-O(1)	91.5(3)
C(14)-C(1)-C(2)-C(3)	31.9(3)
C(15)-C(1)-C(2)-C(3)	-94.0(2)
O(1)-C(2)-C(3)-C(8)	-100.9(3)
C(1)-C(2)-C(3)-C(8)	84.5(3)
O(1)-C(2)-C(3)-C(4)	75.0(3)
C(1)-C(2)-C(3)-C(4)	-99.6(2)
C(8)-C(3)-C(4)-C(5)	-16.1(4)
C(2)-C(3)-C(4)-C(5)	168.0(3)
C(3)-C(4)-C(5)-C(6)	39.3(5)
C(4)-C(5)-C(6)-C(7)	-50.0(6)
C(5)-C(6)-C(7)-C(8)	34.4(5)
C(2)-C(3)-C(8)-C(9)	1.3(3)
C(4)-C(3)-C(8)-C(9)	-174.2(2)
C(2)-C(3)-C(8)-C(7)	178.70(19)

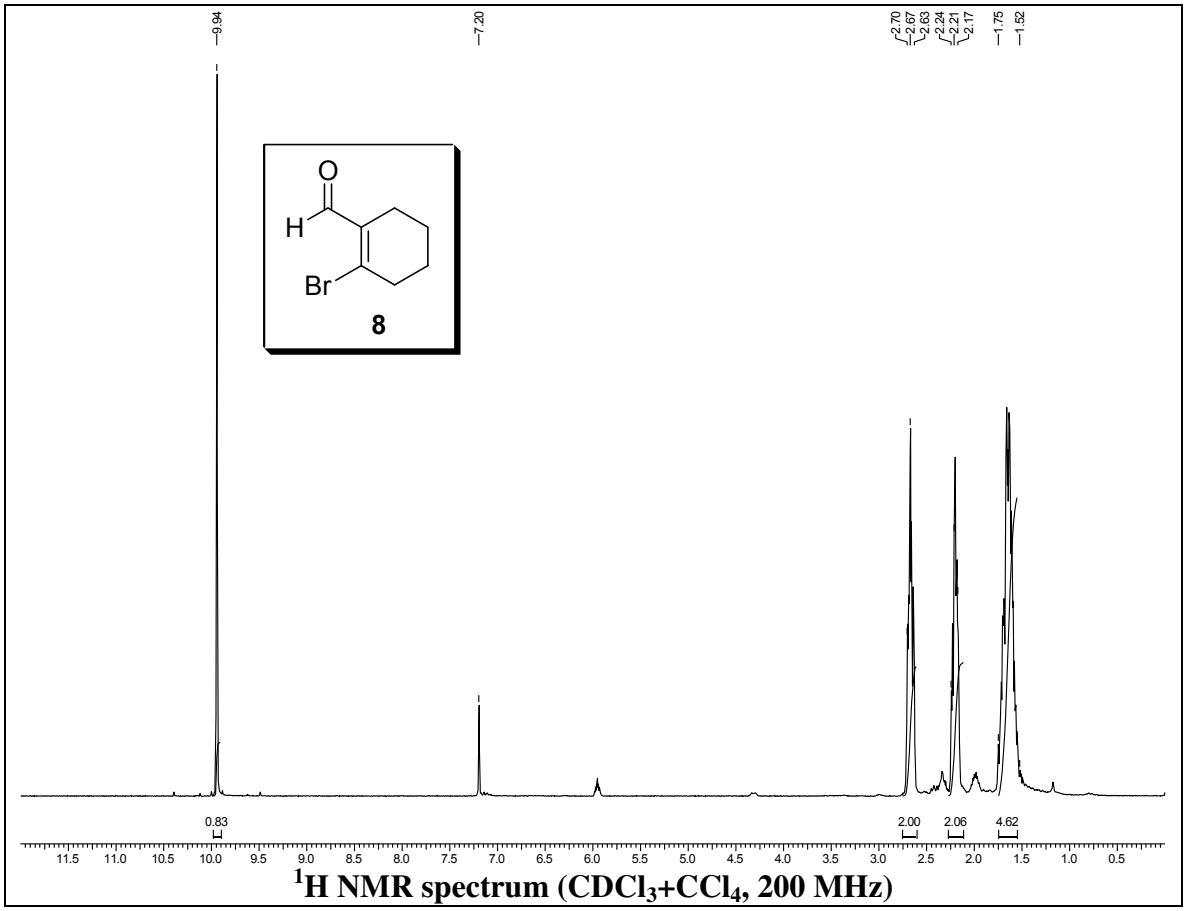
C(4)-C(3)-C(8)-C(7)	3.2(3)
C(6)-C(7)-C(8)-C(3)	-11.1(3)
C(6)-C(7)-C(8)-C(9)	166.5(2)
C(3)-C(8)-C(9)-C(10)	-53.2(3)
C(7)-C(8)-C(9)-C(10)	129.2(2)
C(8)-C(9)-C(10)-C(11)	-2.2(4)
C(8)-C(9)-C(10)-S(1)	-177.50(17)
C(19)-S(1)-C(10)-C(9)	-10.9(2)
C(19)-S(1)-C(10)-C(11)	173.12(14)
C(9)-C(10)-C(11)-C(12)	-45.1(3)
S(1)-C(10)-C(11)-C(12)	130.64(15)
C(9)-C(10)-C(11)-C(15)	85.8(2)
S(1)-C(10)-C(11)-C(15)	-98.43(17)
C(10)-C(11)-C(12)-C(13)	118.7(2)
C(15)-C(11)-C(12)-C(13)	-12.9(3)
C(10)-C(11)-C(12)-C(18)	-60.0(2)
C(15)-C(11)-C(12)-C(18)	168.38(17)
C(18)-C(12)-C(13)-C(14)	176.7(2)
C(11)-C(12)-C(13)-C(14)	-1.9(3)
C(12)-C(13)-C(14)-C(1)	-15.2(3)
C(2)-C(1)-C(14)-C(13)	-82.4(2)
C(15)-C(1)-C(14)-C(13)	45.7(2)
C(2)-C(1)-C(15)-C(16)	-56.9(2)
C(14)-C(1)-C(15)-C(16)	175.76(18)
C(2)-C(1)-C(15)-C(17)	-174.95(18)
C(14)-C(1)-C(15)-C(17)	57.7(2)
C(2)-C(1)-C(15)-C(11)	67.5(2)
C(14)-C(1)-C(15)-C(11)	-59.8(2)
C(12)-C(11)-C(15)-C(16)	166.82(17)
C(10)-C(11)-C(15)-C(16)	37.1(2)
C(12)-C(11)-C(15)-C(17)	-74.3(2)
C(10)-C(11)-C(15)-C(17)	155.93(18)
C(12)-C(11)-C(15)-C(1)	43.3(2)
C(10)-C(11)-C(15)-C(1)	-86.4(2)

Symmetry transformations used to generate equivalent atoms:

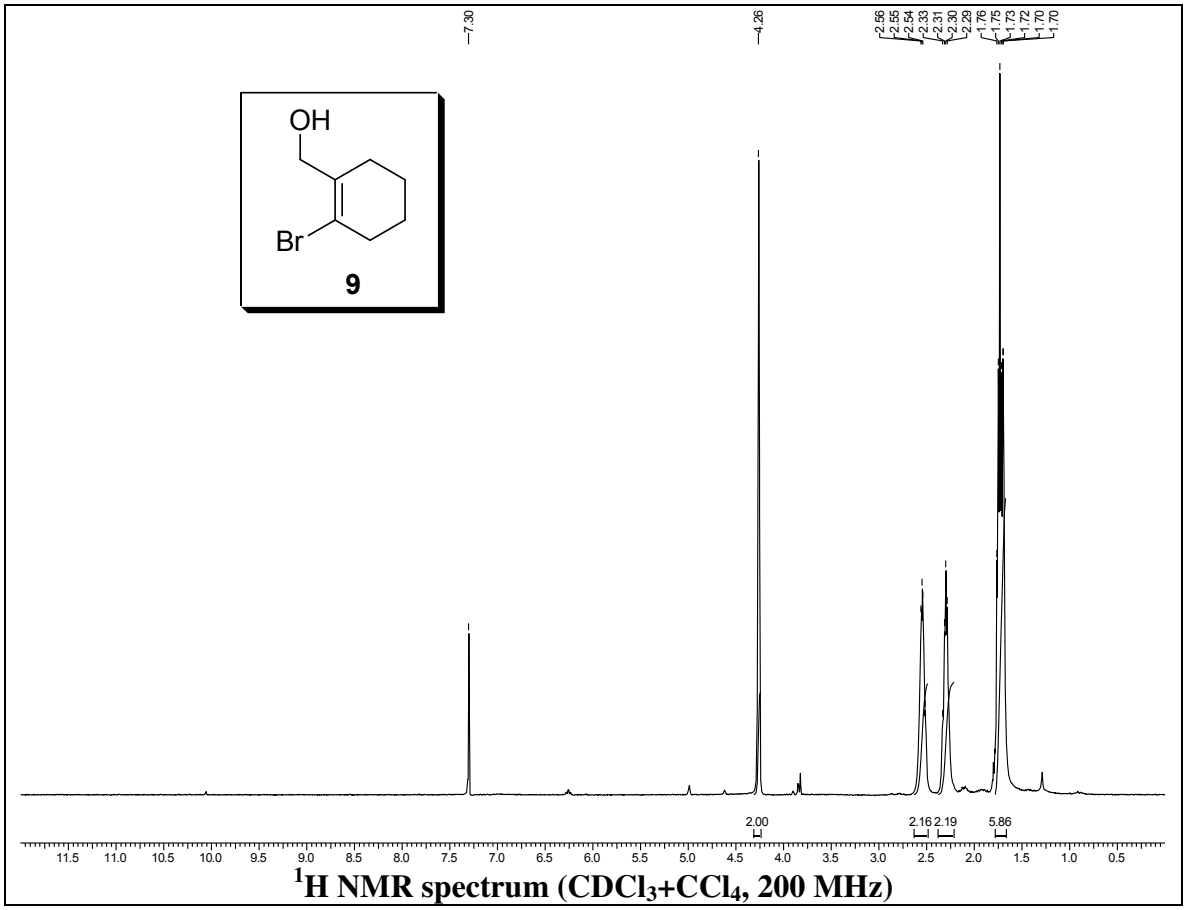
1.4.5 References:

1. Rajamannar, T.; Balasubramanian, K. K. *Tetrahedron Lett.* **1988**, *29*, 5789.
2. Briner, K. In *Encyclopedia of Reagents for Organic Synthesis*, Eds.; Paquette, L. A., Wiley: Chechester, **1995**, Vol 5, p 3003.
3. Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302.
4. (a) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561. (b) Halterman, R. L.; Zhu, C. *Tetrahedron Lett.* **1999**, *40*, 7445.

Spectra



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



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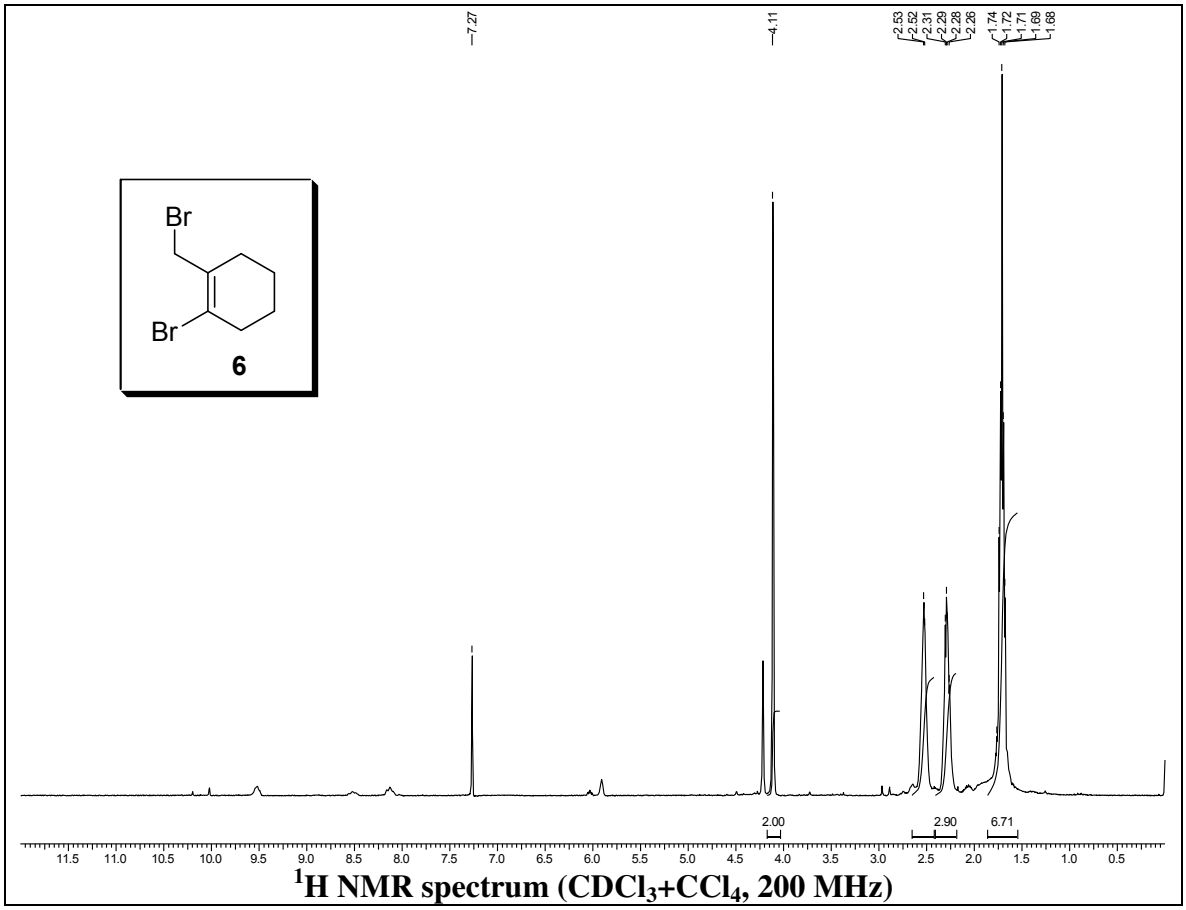

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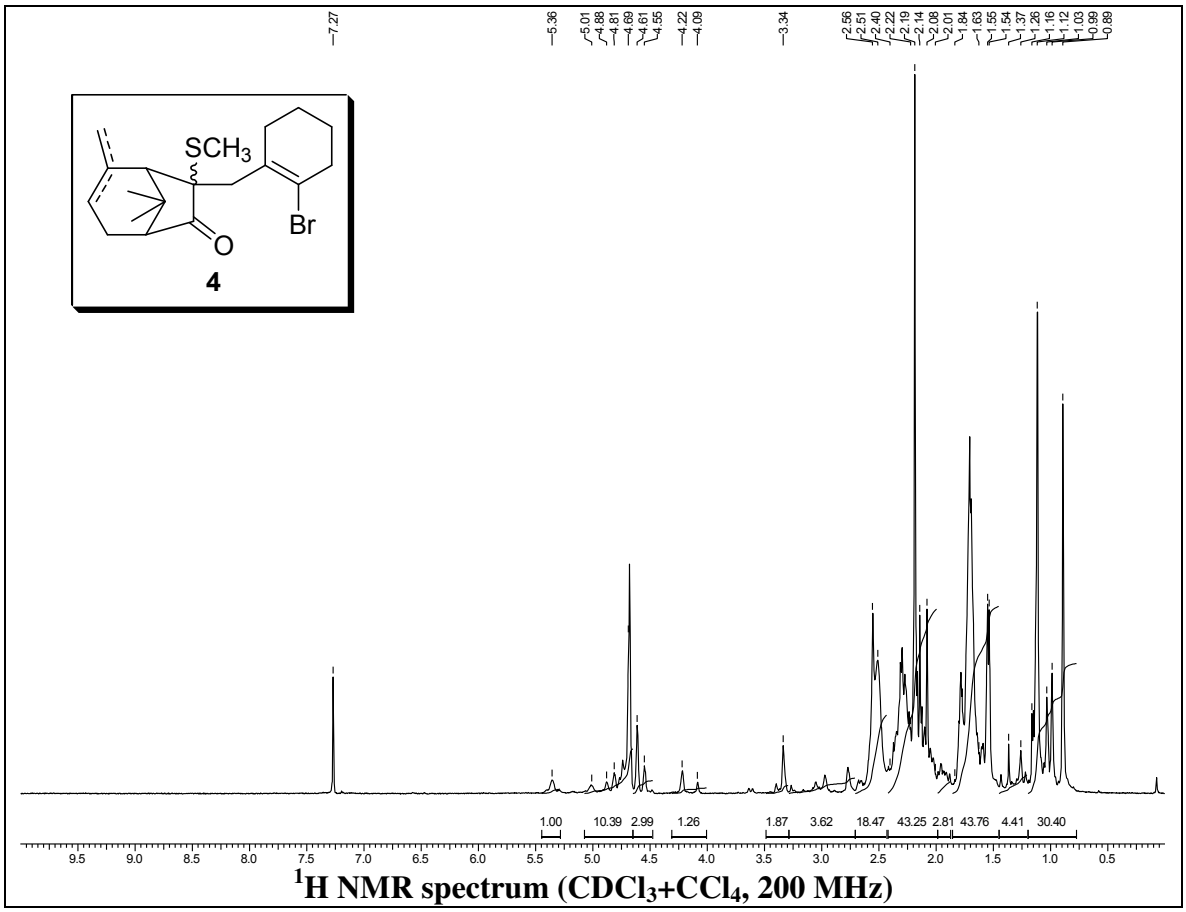

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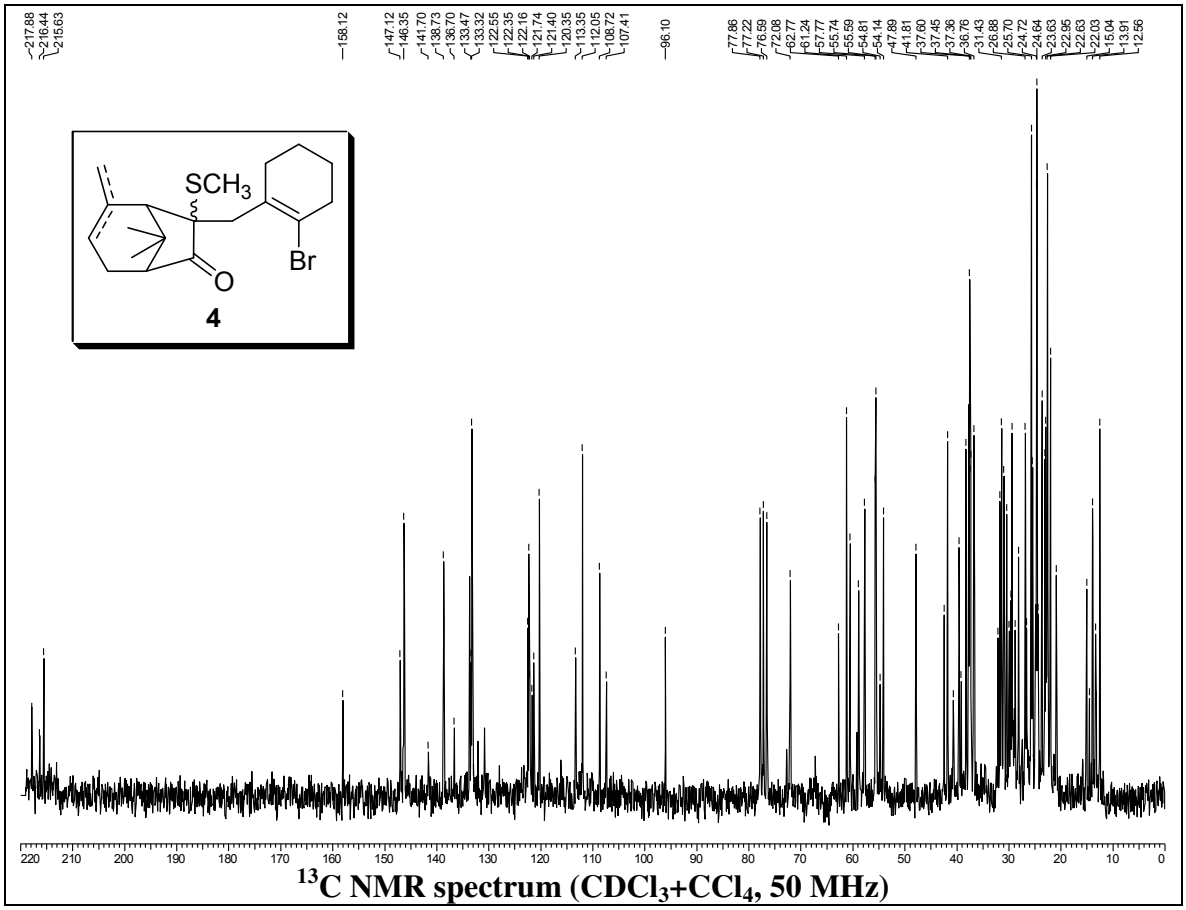

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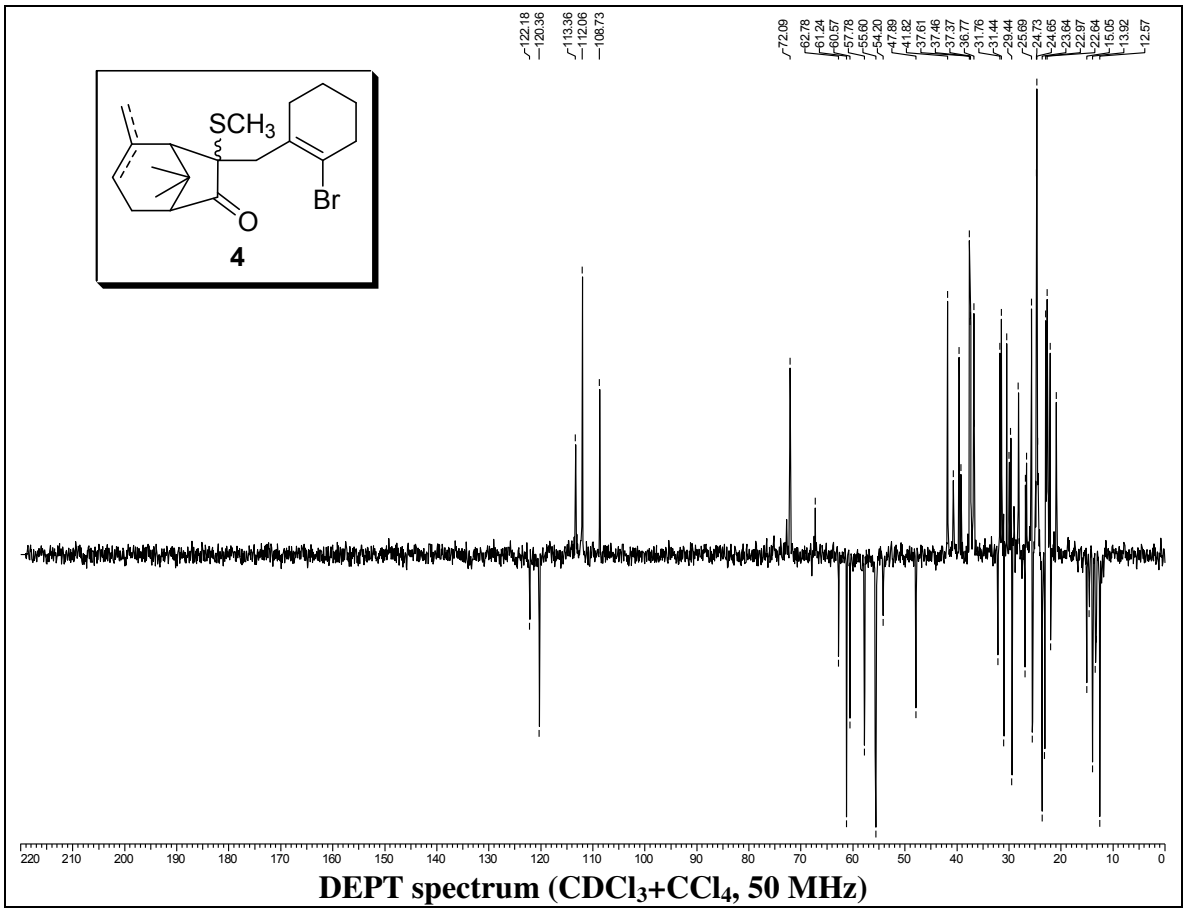
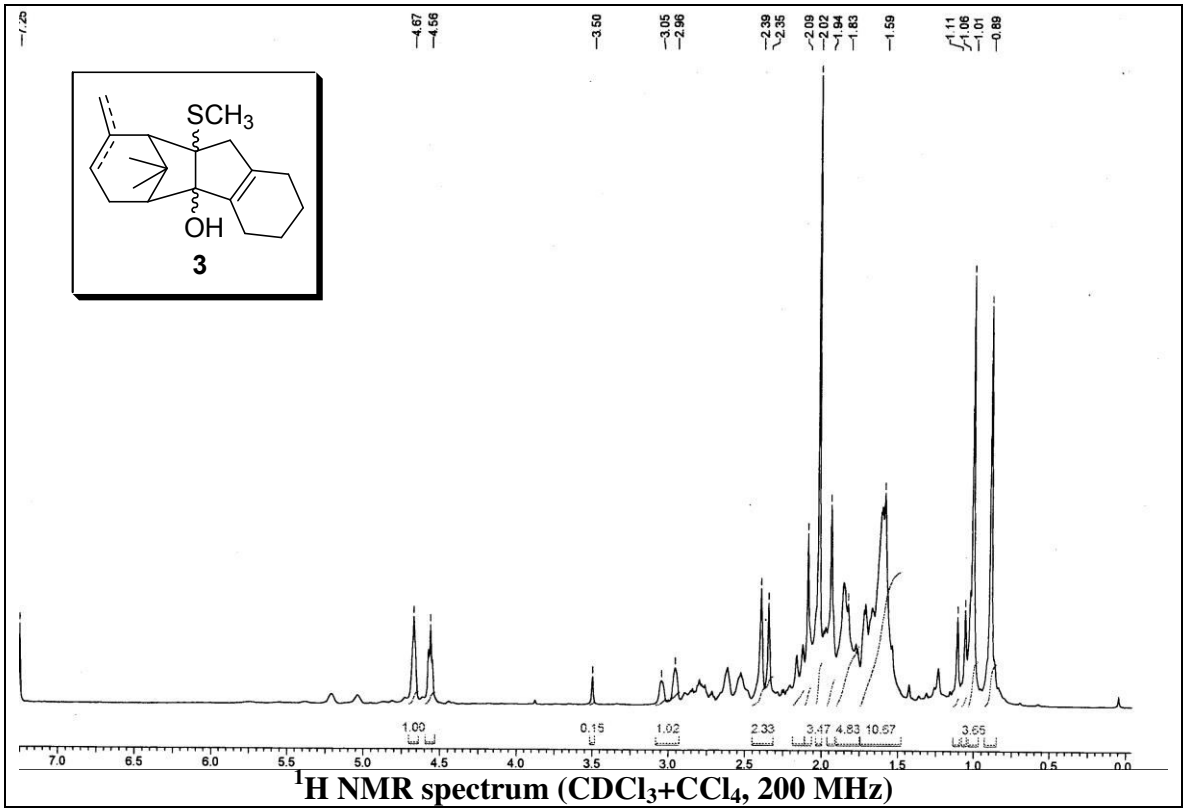


DEPT spectrum ($CDCl_3$+CCl_4, 50 MHz)



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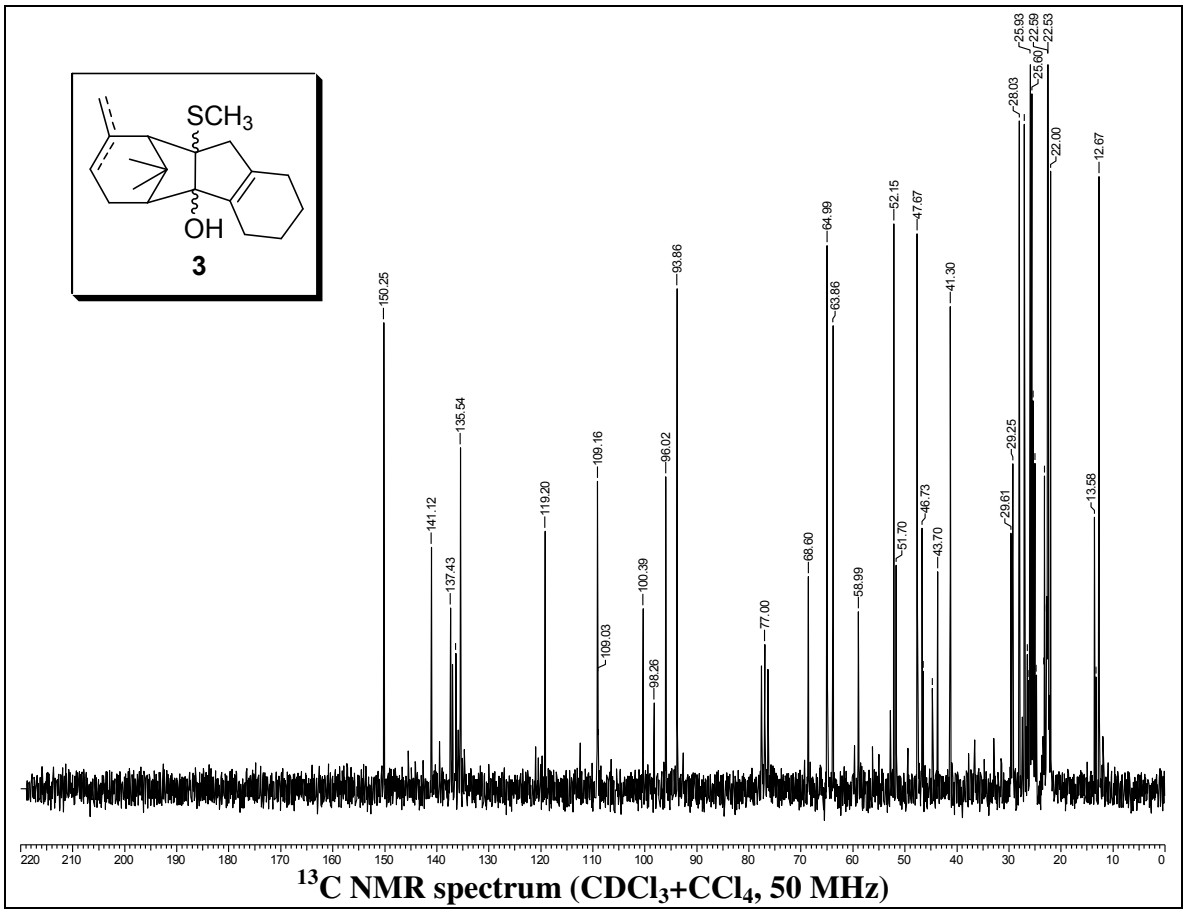

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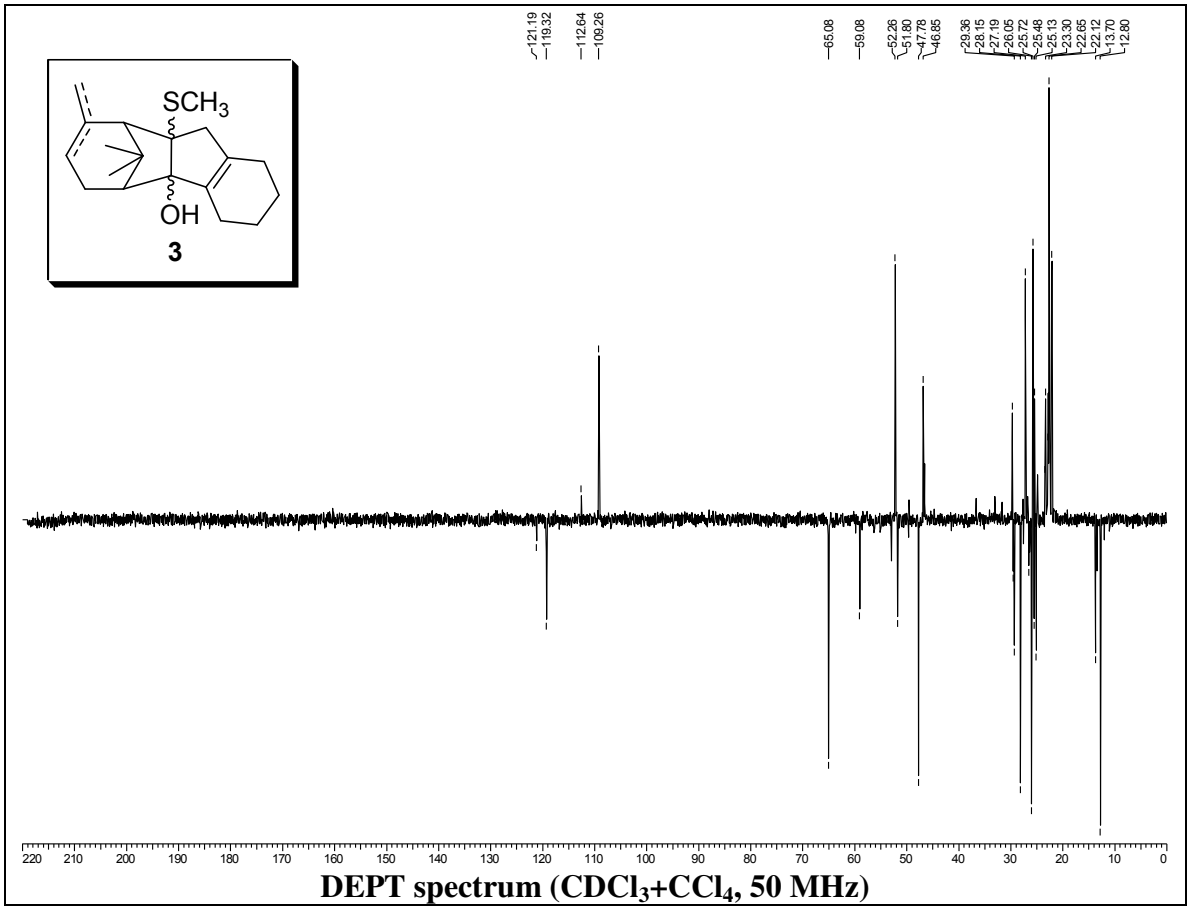
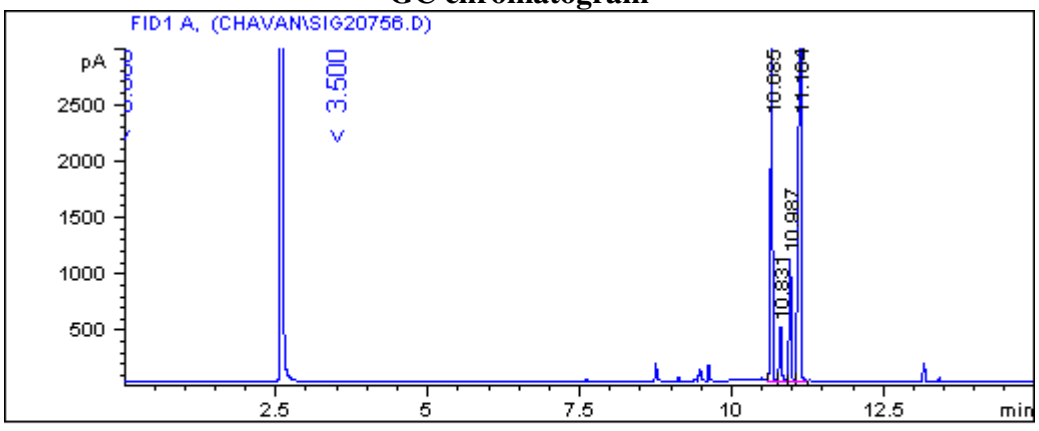


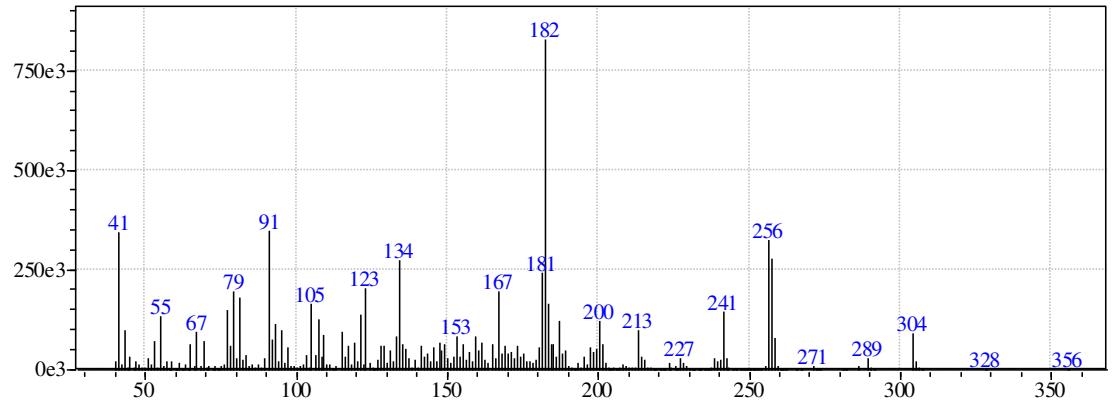
DEPT spectrum ($CDCl_3$+CCl_4, 50 MHz)

GCMS of 3

GC chromatogram



MS at retention time 10.6



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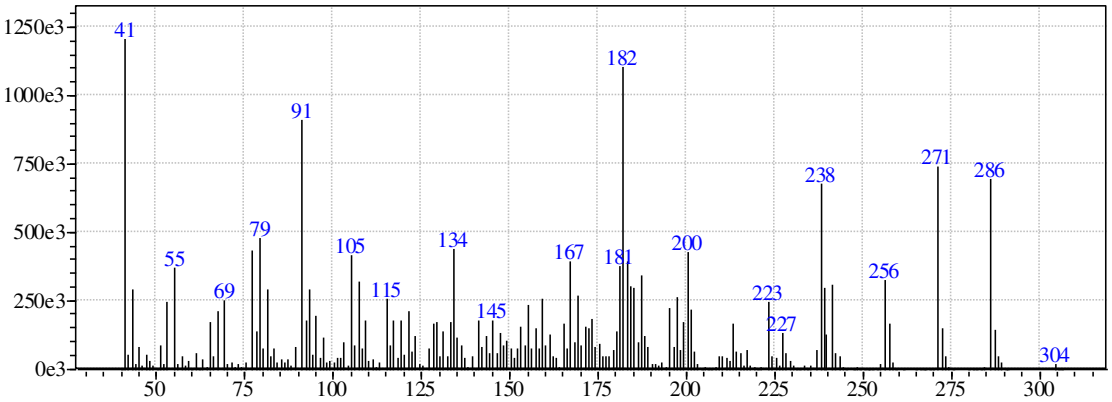

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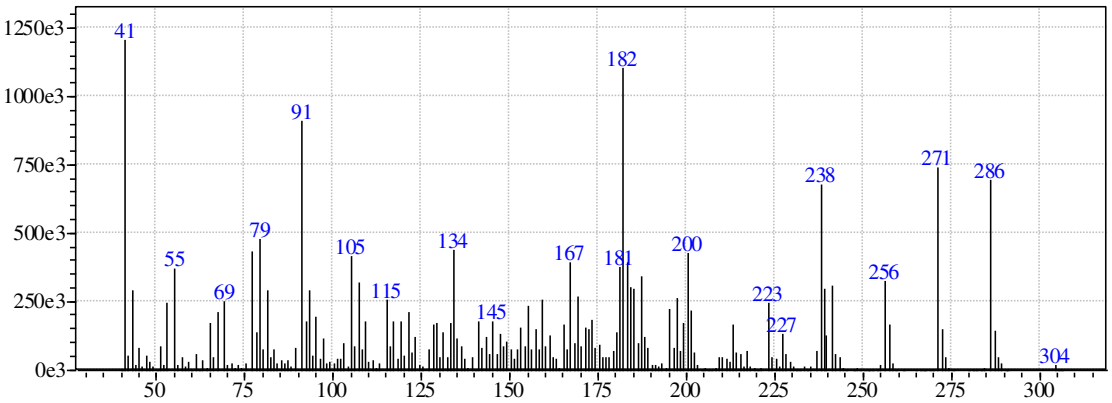
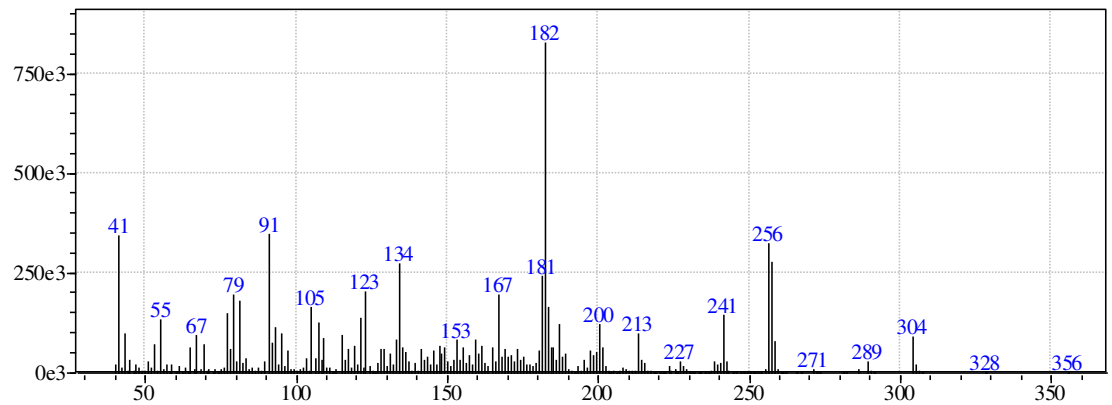
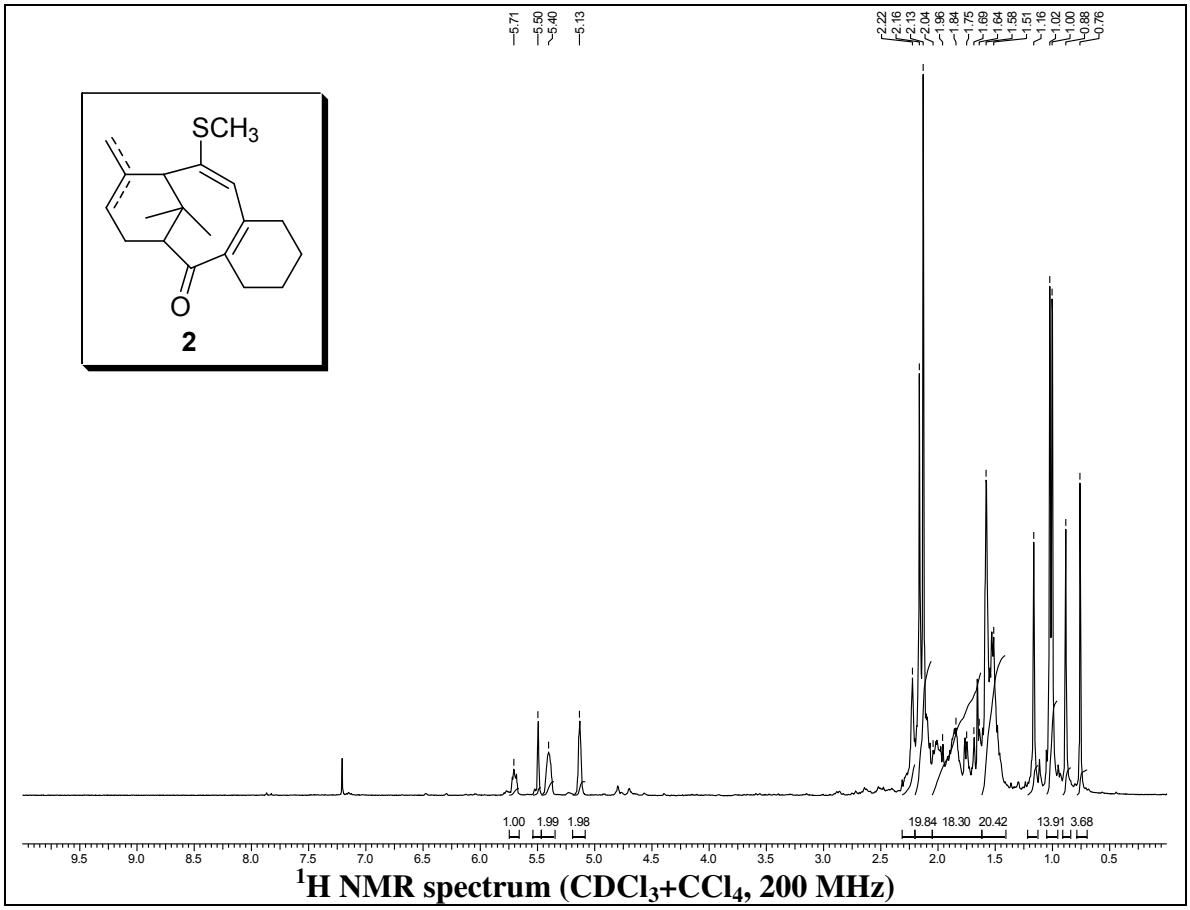
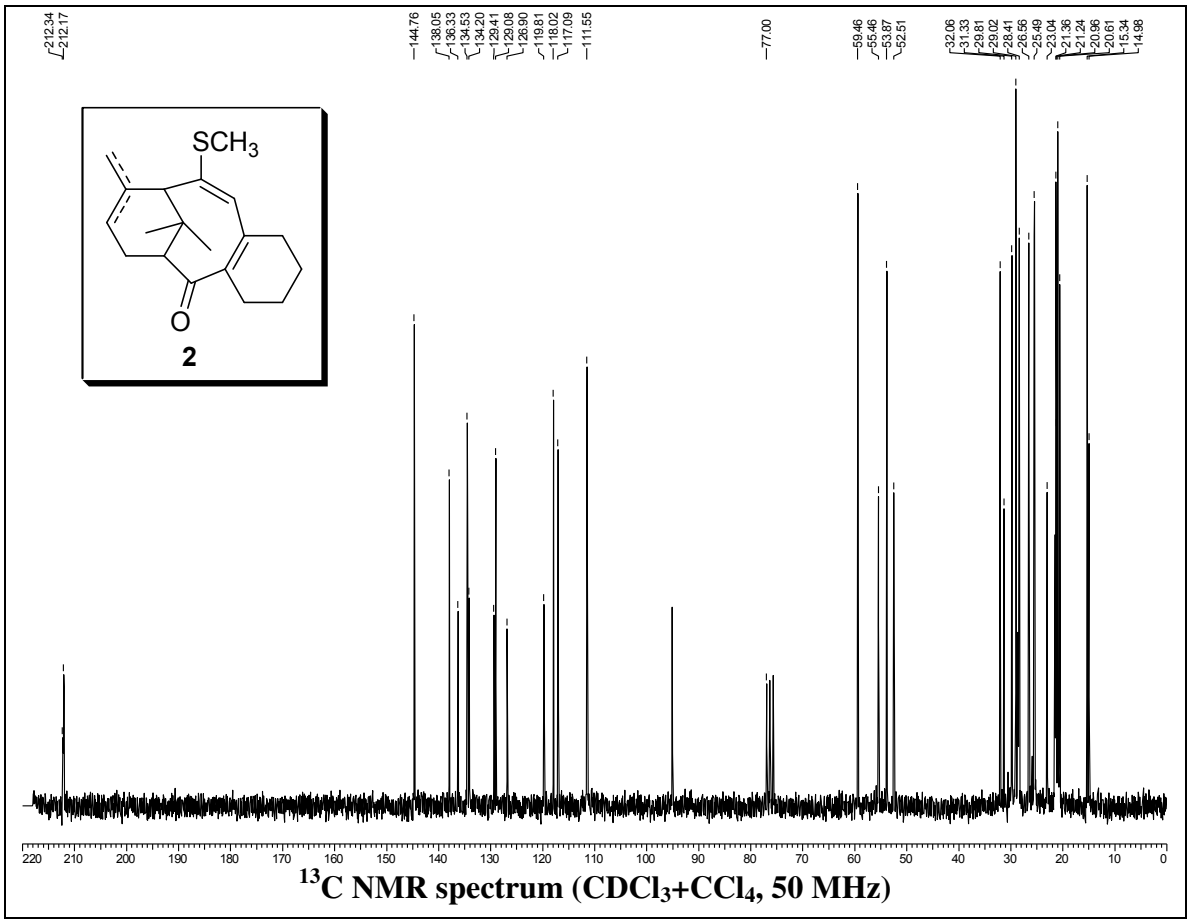


MS at retention time 11.1

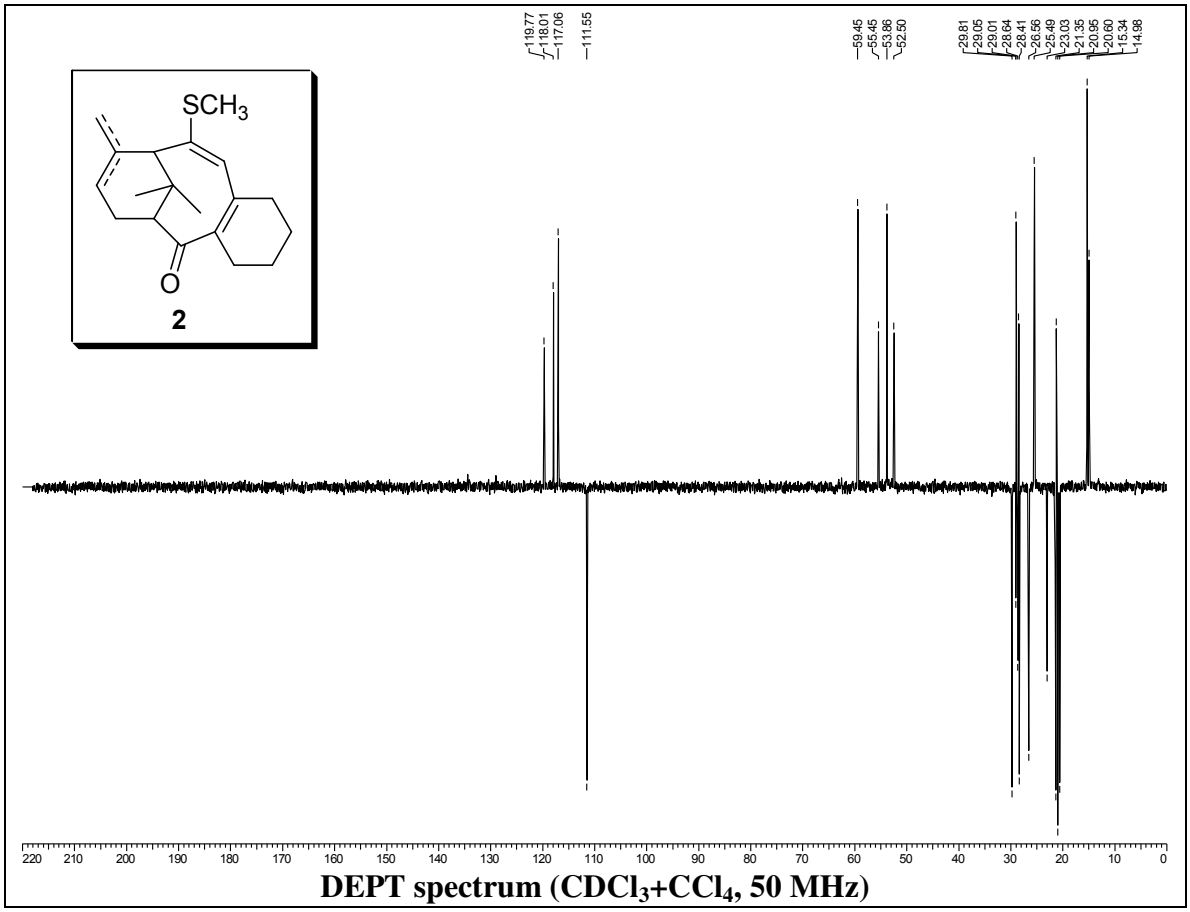




^{1}H NMR spectrum ($CDCl_3$+CCl_4, 200 MHz)



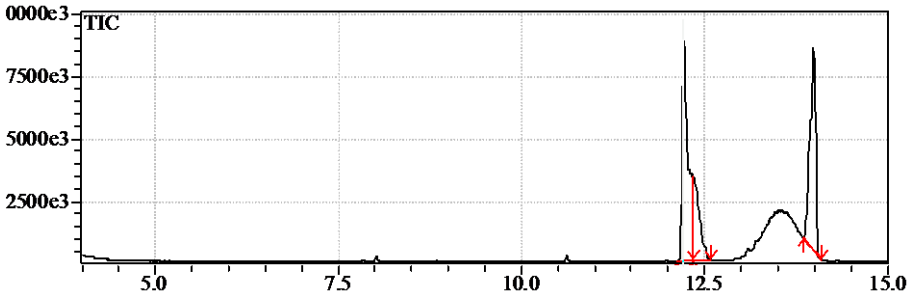
^{13}C NMR spectrum ($CDCl_3$+CCl_4, 50 MHz)



DEPT spectrum ($CDCl_3$+CCl_4, 50 MHz)

GCMS of 2

GC chromatogram



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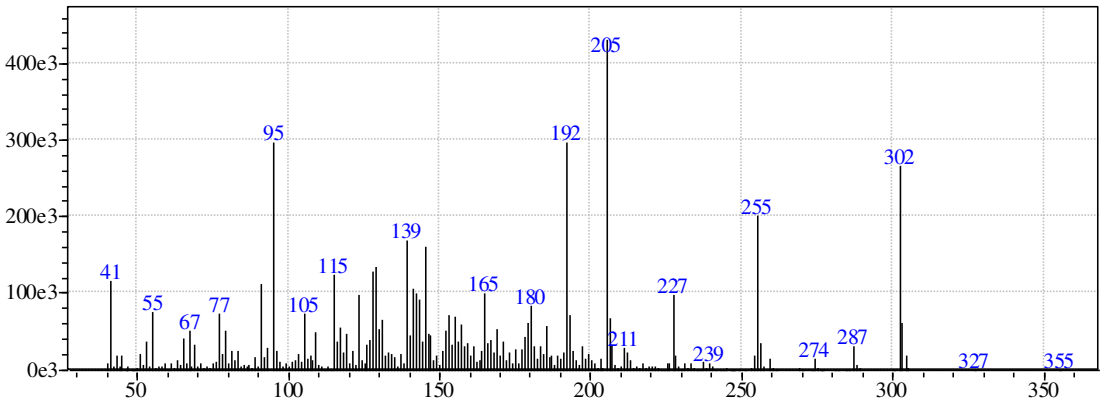
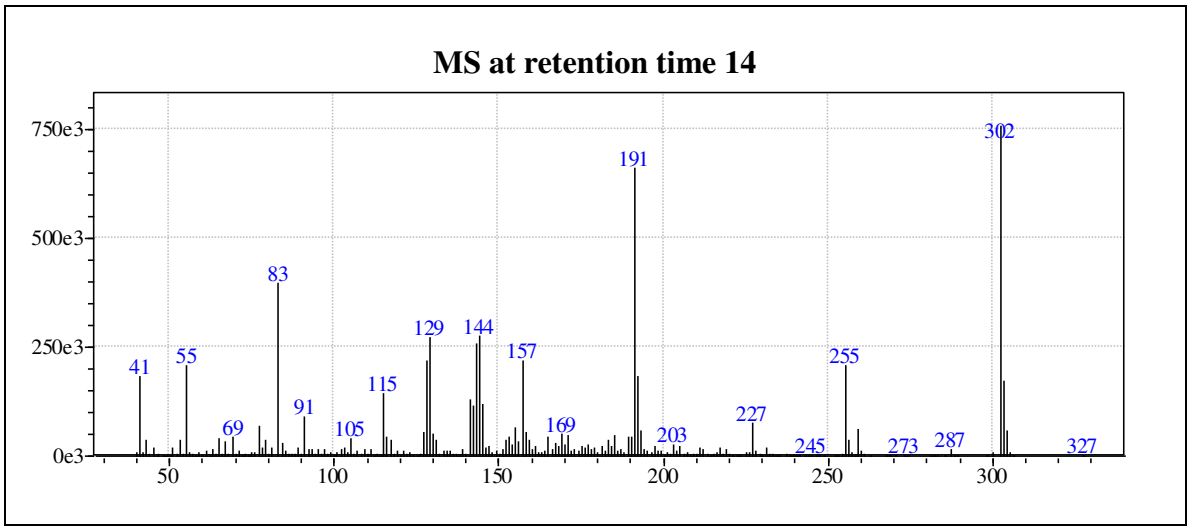
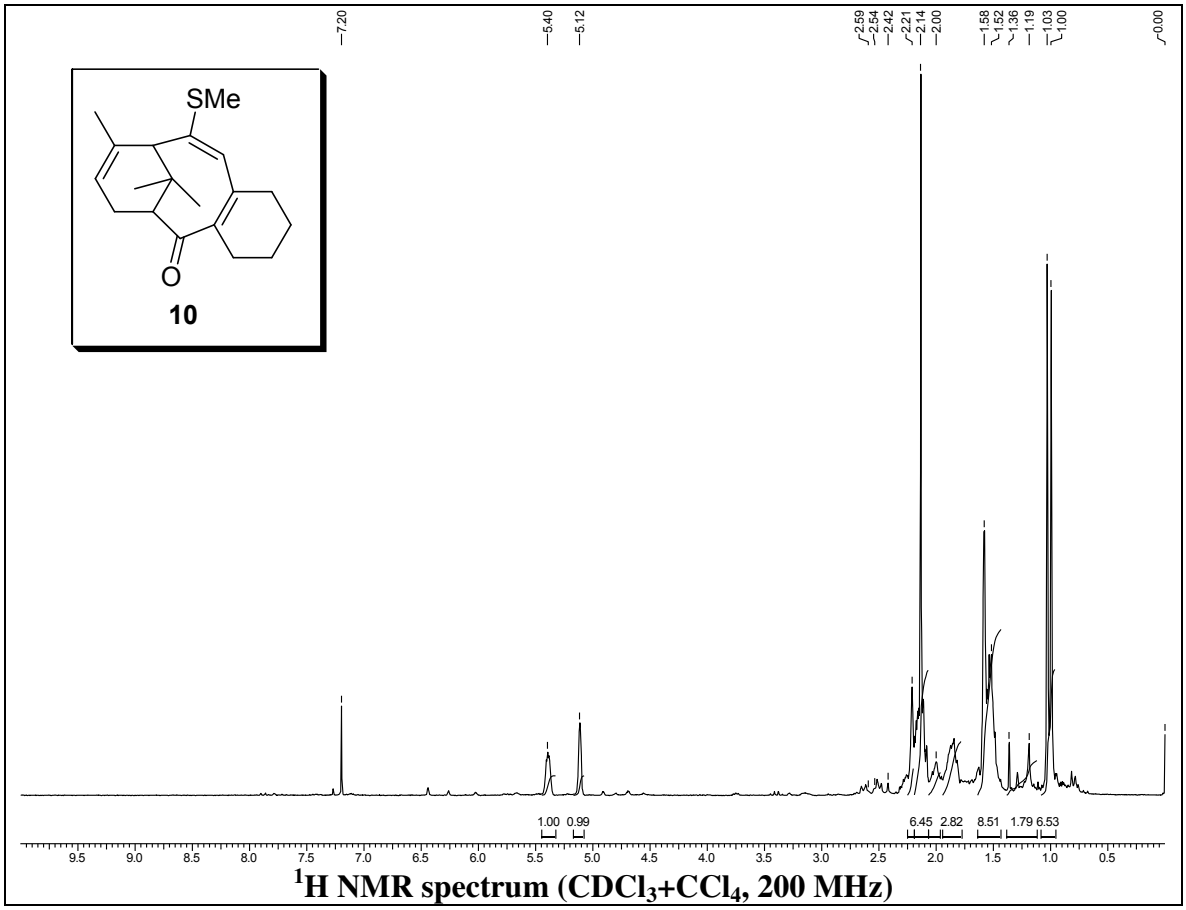
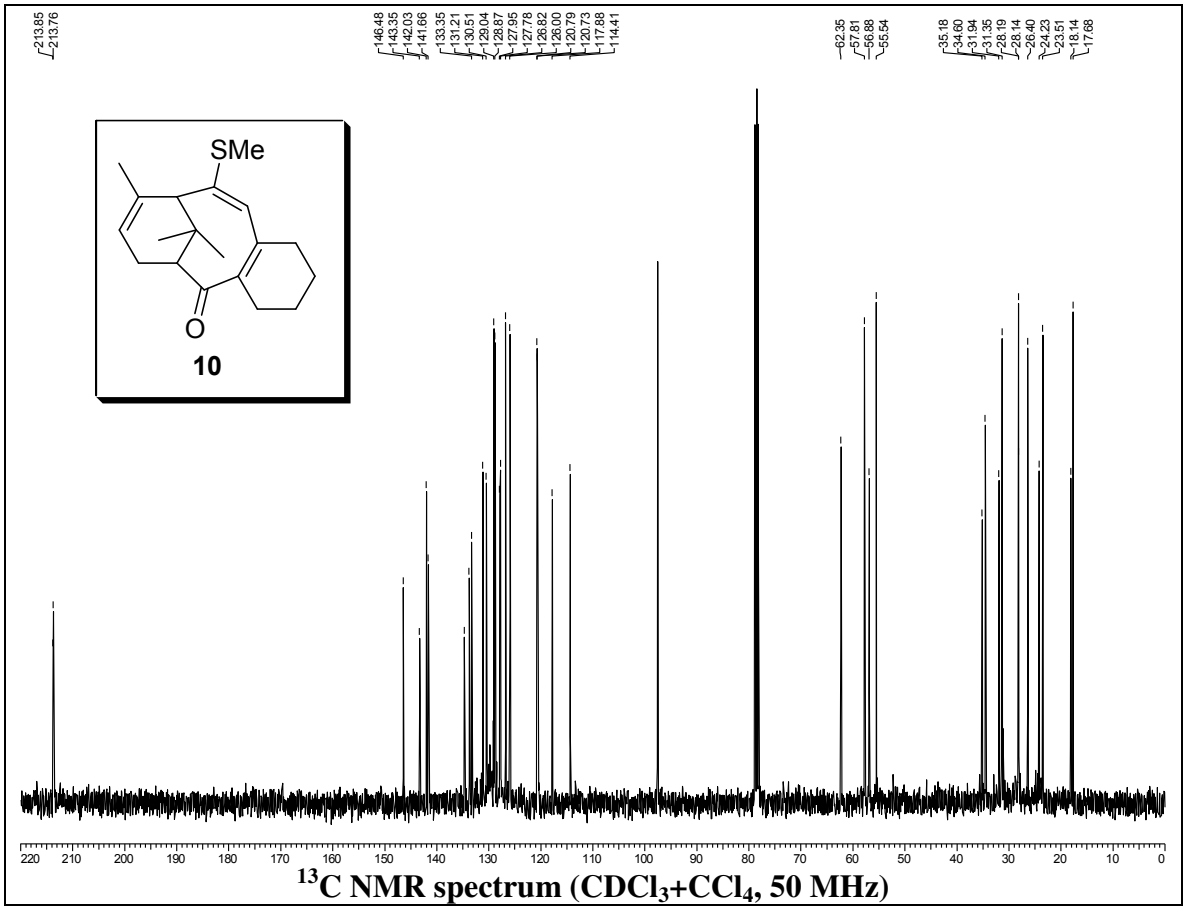


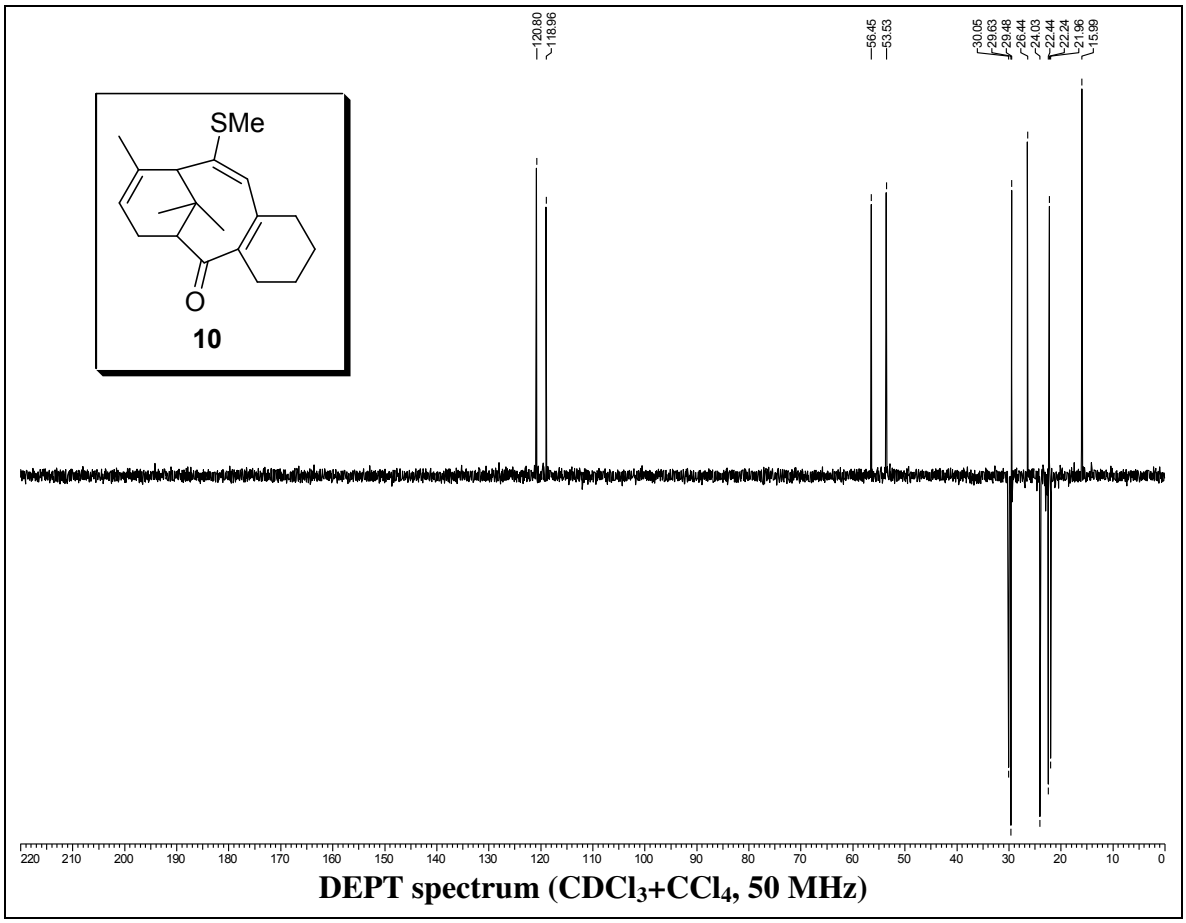




^{1}H NMR spectrum ($CDCl_3$+CCl_4, 200 MHz)



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



DEPT spectrum ($CDCl_3$+CCl_4, 50 MHz)

Chapter-II

Microwave Specific Wolff-rearrangement of α-diazoketones and its Relevance to the Non-thermal and Thermal Effect

2.1 Introduction:

A microwave is a form of electromagnetic energy that falls at the lower frequency end of the electromagnetic spectrum, and is defined in the 300 to about 300,000 MHz frequency range, corresponding to wavelength of 1 cm to 1 m. The microwave region of the electromagnetic spectrum therefore lies between infra red and radio frequencies. Wavelengths between 1 cm and 25 cm are extensively used for RADAR transmission and the remaining wavelength is used for telecommunications. All the domestic "kitchen" microwave ovens and all dedicated microwave reactors for chemical synthesis that are commercially available today operate at a frequency of 2.45 GHz (corresponding to the wave length of 12.25 cm) in order to avoid interference with telecommunications and cellular phone frequencies. Microwave energy consists of an electric field and a magnetic field, though only the electric field transfers energy to heat a substance. Magnetic field interactions do not normally occur in chemical synthesis. Microwave moves at the speed of light (300,000 km/s). The energy in microwave photons (0.037 kcal/mole) is very low relative to the typical energy required to cleave molecular bonds (80-120 kcal/mole); thus, microwave will not affect the structure of an organic molecule and therefore absorption is purely kinetic.[1]

As discussed above microwaves are electromagnetic waves which consist of an electric field and magnetic field component. The electric component of an electromagnetic field causes heating by two main mechanisms: dipolar polarization and ionic conduction. The interaction of an electric field component with the matrix is called the dipolar polarization mechanism. For a substance to be able to generate heat when irradiated with microwaves must possess a dipole moment. When exposed to the microwave frequencies, the dipoles of the sample align in the applied electric field. As the applied field oscillates, the dipole field attempts to realign itself with the alternating electric field and, in the process, energy lost in the form of heat through molecular friction and dielectric loss. The amount of heat generated by this process is directly related to the ability of the matrix to align itself with the frequency of the applied field. If the dipole does not have enough time to realign (high frequency irradiation) or reorients too quickly (low frequency irradiation) with the applied field, no heating occurs. The allocated frequency of 2.45 GHz used in all commercial system lies between these two extremes and gives the molecule dipole time to align in the field, but not to follow the alternating field precisely. Therefore, as the dipole reorients to align itself with the

electric field, the field is already changing and generates a phase difference between the orientation of the field and that of dipole. This phase difference causes energy to be lost from the dipole by molecular friction and collisions, giving rise to dielectric heating. In summary, field energy is transferred to the medium and electrical energy is converted into kinetic or thermal energy, and ultimately into heat. The second major heating mechanism is the ionic conduction mechanism. During ionic conduction, as the dissolved charged particles in a sample (usually ions) oscillate back and forth under the influence of the microwave field, they collide with their neighboring molecules or atoms. These collisions cause agitation or motion, creating heat. Such ionic conduction effects are particularly important when considering the heating behavior of ionic liquids in a microwave field. The conductivity principle is a much stronger effect than the dipolar rotation mechanism with regard to the heat generating capacity.

The heating characteristics of a particular material (for example, a solvent) under microwave irradiation conditions are dependent on its dielectric properties. The ability of a specific substance to convert electromagnetic energy into heat at a given frequency and temperature is determined by so-called loss factor tan δ. This loss factor is expressed as the quotient tan $\delta = \epsilon''/\epsilon'$, where ϵ'' is the dielectric loss, which is indicative of the efficiency with which electromagnetic radiation converted into heat, and ϵ' is the dielectric constant describing the ability of molecules to be polarized by electric field.

Traditionally, organic synthesis is carried out by conductive heating with an external heat source (e.g. an oil bath or heating mantle). This is comparatively slow and inefficient method for transforming energy into the system since it depends on convections currents and on the thermal conductivity of the various materials that must be penetrated, and results in the temperature of the reaction vessel being higher than that of the reaction mixture. In addition, a temperature gradient can develop with in the sample and local overheating can lead to product, substrate or reagent decomposition.

In contrast, microwave irradiation produces efficient internal heating (in core volumetric heating) by direct coupling of microwave energy with the molecules (solvents, reagents, catalysts) that are present in the reaction mixture.

Historically, the development of microwave technology was stimulated by World War II, when magnetron was designed to generate fixed frequency microwaves for RADAR devices. Percy LeBaron Spencer of the Raytheon Company accidentally discovered that microwave energy could cook food when a candy bar in his pocket

melted while he was experimenting with radar waves. This ultimately led to the introduction of the first commercial microwave oven for home use in 1954. Application to the industrial use of microwave was started in the late 1950s and has continued to the present. The applications in the chemical and related industries are food processing, drying and in polymer industries. Other applications range from analytical chemistry (microwave digestion, ashing, extraction) to biochemistry (protein hydrolysis, sterilization), pathology (histoprocessing, tissue fixation) and medical treatments (diathermy). The first report on the microwave accelerated organic synthesis (MAOS) was published by the groups of Richard Gedye[2] and Raymond J. Giguere/ George Majetich[3] in 1986. However upto 1990s MAOS were carried out in a domestic ovens. The drawbacks of using household appliances are (1) the irradiation power is generally controlled by on-off cycles of the magnetron and is not possible to measure real temperature, (2) non-reproducibility was observed from machines to machines, (3) lack of pressure and stirring control, (4) the major concerns is the safety, heating organic solvent in open vessel lead to a fire and explosion and on the other hand heating in a sealed vessel leads to thermal runaway and accidents, (5) even by modifying domestic oven by piercing for reflux condenser and thermo couples and magnetic stirring utility were also harmful since chances of microwave leakages are more and danger to operator and also risk of explosion are there because walls of oven are not explosion-proof. Growing interest in MAOS during the mid 1990s led to development of more dedicated microwave reactors for organic synthesis and today many companies are offering microwaves and their collective salient features are (1) continuous power regulation, (2) built-in magnetic or mechanical stirring, (3) accurate temperature measurements by using either immersed probe (fiber-optic or gas-balloon thermometer) or outer surface of vessels by IR sensors, (4) pressure controls, (5) facility to perform anhydrous reactions, (6) facility of combine using UV and microwaves (7) facility for performing low temperature reactions, (8) availability of doing combichem, parallel and high throughput synthesis, (9) efficient post-reaction cooling, (10) explosion proof cavities, and (11) computer aided method programming. The main drawbacks of this dedicated microwave reactors are its cost, which is the only reason why oil baths and heating mantles are not replaced in laboratory.

Due availability of new and reliable microwave reactors the publications relating microwave chemistry has been shot-up exponentially from the year 2000. One of pioneer

scientist in this field, Rajender S. Varma stated 'microwaves are green chemistry' because they performed reactions in the solvent free conditions in 1990s.[10] Another dedicated scientist in this field A. K. Bose called microwave reactors are 'Bunsen burners of the 21st century' because it is believed that sooner all laboratories will be equipped with dedicated microwave reactors. Large number of examples of MAOS reactions has been described in organic synthesis.[11-18] Several reviews have been published on the application of microwave to solvent-free reactions,[19] cycloadditions reactions,[20] the synthesis of radioisotopes,[21] fullerene chemistry,[22] polymers,[23] heterocyclic chemistry,[24] carbohydrates,[25] homogenous and heterogeneous catalysis,[26] medicinal and combinatorial chemistry[27] and green chemistry.[28] It is not possible to cover all MAOS reactions, however in order to compare our findings, few examples of microwave assisted organic reactions and its relevance to its thermal and non-thermal effects will be discussed.

2.2 Thermal effects:

The thermal effects are nothing but kinetics effect where inverted heat transfer occurs this is nothing but selective absorption of microwave radiations by polar compounds in the reaction mixture and because of this temperature shoots-up instantly in a few seconds and therefore rate enhancements is observed.

Mingos and Baghurst[29] have compared same reaction in oil-bath conditions (heating to reflux) to microwave irradiations. They simply applied Arrhenius law [k = A exp($-E_a$/RT)], a transformation that requires 68 days to reach 90 % conversion at 27 ºC will show the same degree of conversion within 1.61 seconds when performed at 227 ºC. They emphasized that for these thermal effects, the pre-exponential factor A and the energy term (activation energy E_a) in the Arrhenius equations are not affected, and only the temperature term changes.

Klan[30] successfully evaluated MW superheating effects in polar solvents by studying a temperature-dependent photochemical reaction. Klan described the Norrish type II reaction of valerophenones in microwave photochemistry (Scheme-1). Equimolecular mixtures of both ketones were irradiated at 280 nm in various solvents; such an experimental arrangement guaranteed identical photochemical conditions for both compounds. The fragmentation-cyclization ratio varied from 5 to 8 and was characteristic for given reaction conditions (Table-1). The photochemical efficiency R (Table-1) is temperature-dependent and the magnitude is most likely related to the

solvent basicity. The authors consider that superheating by microwave irradiation is most likely responsible for the modification of selectivity observed.

Scheme-1: Klan, P.; Literak J.; Relich, S.; *J. Photochem. Photobiol. A* **2001**, *143*, 49.

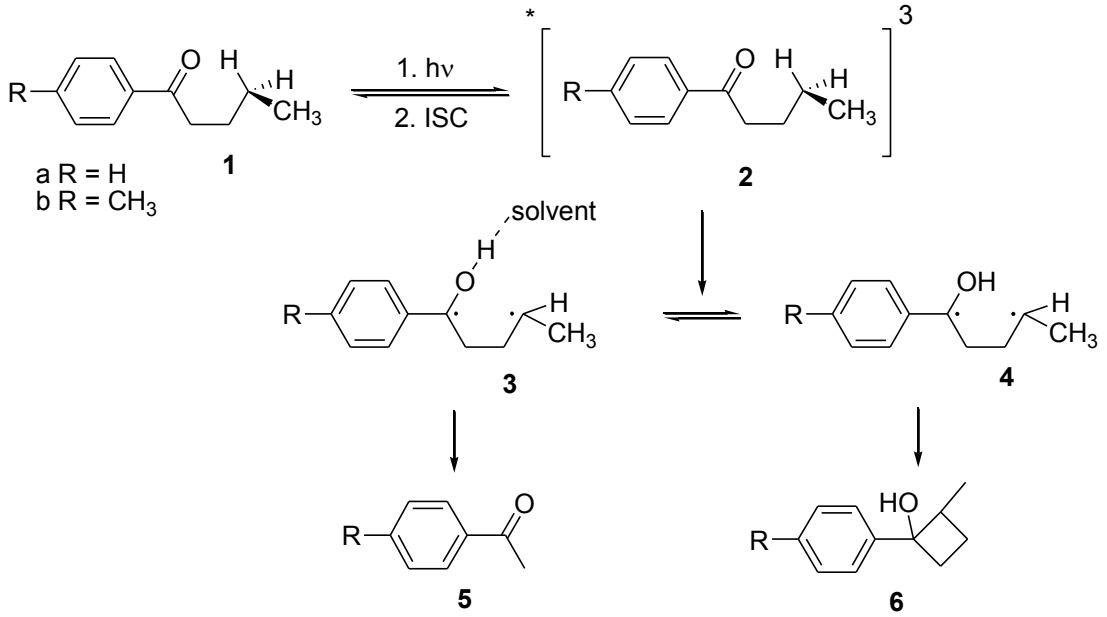


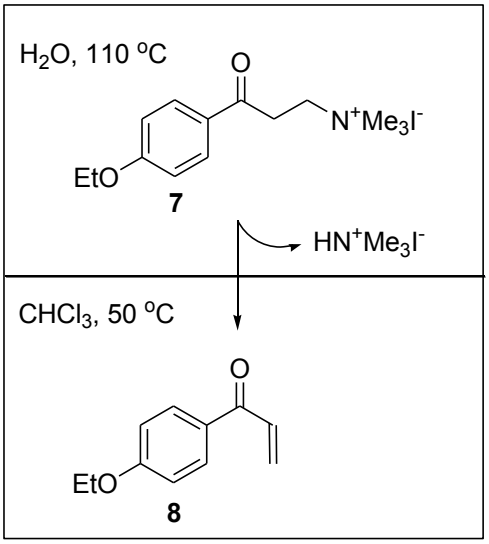
Table-1: Product distribution in the Norrish type II reaction of valerophenone

Solvent	Conditions	R^a	T/ºC	Overheating/ºC
Methanol	CH	2.25	20	—
	CH	1.52	65	—
	MW	1.34	75	11
Acetonitrile	CH	2.12	20	—
	CH	1.12	81	—
	MW	0.98	90	9

[a] Fragmentation-cyclization ratio.

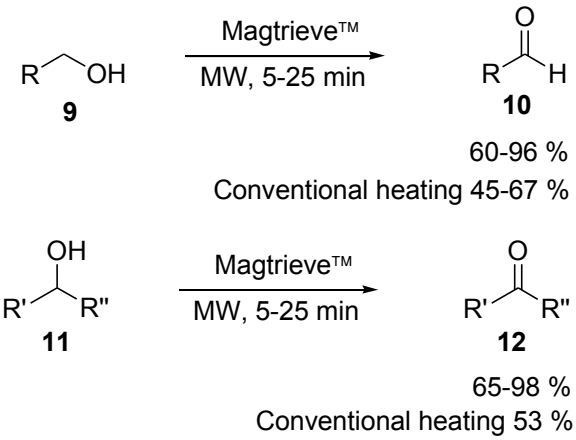
Strauss[31] performed a Hoffmann elimination using a two-phase water/chloroform system (Figure-1). When the reaction was performed in water at 105 ºC it led to polymerization of the final product. However, the reaction proceeds nicely under microwave irradiation in a two phase water/chloroform system. The temperatures of the aqueous and organic phases were 110 and 50 ºC, respectively, due to differences in the dielectric properties of the solvents. This difference avoids the decomposition of the final product. Comparable conditions would be difficult to obtain by traditional heating methods. A similar effect was observed by Hallberg in the preparation of β,β-diarylated aldehydes by hydrolysis of enol ethers in a two phase (toluene/aq. HCl) system.[32] These are the examples of selective solvent heating.

Figure-1:



Selective heating has been exploited efficiently in heterogeneous reactions to heat selectively a polar catalyst. For example, Bogdal[33] described the oxidation of alcohols using Magtrieve™ (Scheme-2). The irradiation of Magtrieve™ led to rapid heating of the material up to 360 ºC within 2 minutes. When toluene was introduced into the reaction vessel, the temperature of Magtrieve™ reached ca. 140 ºC within 2 minutes and was more uniformly distributed. This experiment showed that the temperature of the catalyst can be higher than the bulk temperature of the solvent, which implies that such a process might be more energy efficient than other conventional processes.

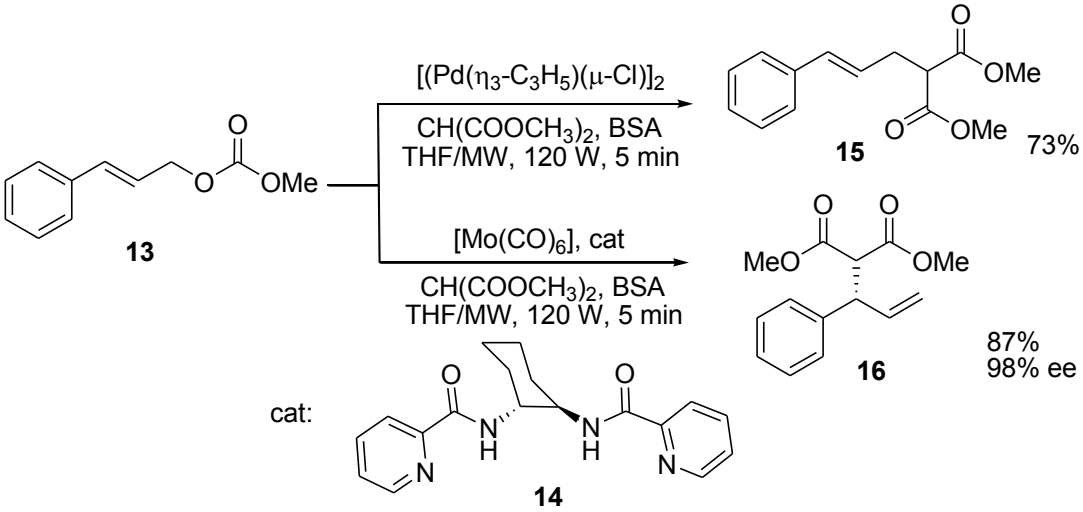
Scheme-2: (a) Bogdal, D.; Lukasiewicz, M.; Pielichowski, J.; Miciak, A.; Bednarz, Sz. *Tetrahedron* **2003**, *59*, 649. (b) Lukasiewicz, M.; Bogdal D.; Pielichowskia, J. *Adv. Synth. Catal*. **2003**, *345*, 1269.



Larhed[34] described the molybdenum-catalysed allylic alkylation of (*E*)-3-phenyl-2-propenyl acetate. The reaction occurs with good reproducibility, complete conversion,

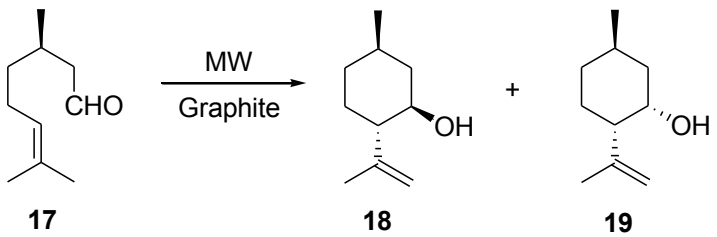
high yields and excellent ee in only a few minutes (Scheme-3). In the standard solvent (THF), and with an irradiation power of 250 W, a yield of 87% was obtained and high regioselectivity and enantiomeric excess (98%) were achieved. The high temperature obtained (220 ºC) is not only due to increased boiling points at elevated pressure, but also to a significant contribution from sustained overheating. The yields from the oil bath experiments are lower than those for the corresponding microwave-heated reactions. It's an example of a "molecular radiators" whereas substrate channeling energy from microwave radiation to bulk heat and their reactivity is enhanced.

Scheme-3: Kaiser, N. F. K.; Bremberg, U.; Larhed, M.; Moberg C.; Hallberg, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3595.



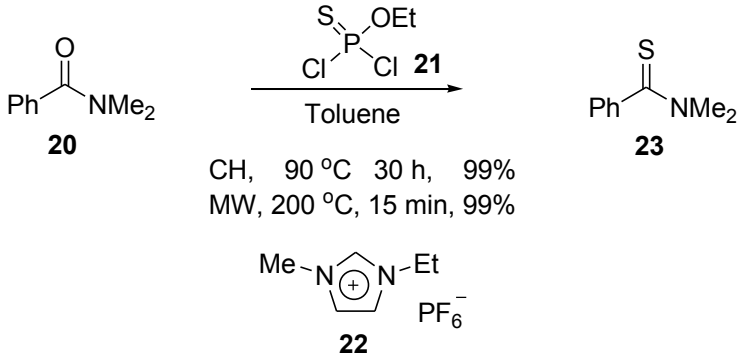
A susceptor can be used when neither substrates/solvents nor catalyst absorbs microwave radiations. They are inert and only thermal energy is transformed to the reaction medium. Garrigues[35] described the cyclization of (+)-citronellal to (–)-isopulegol and (+)-neoisopulegol on graphite, an inert susceptor. The stereoselectivity of the cyclization can be altered under microwave irradiation (Scheme-4). (–)-Isopulegol is always the principal diastereoisomer regardless of the method of heating, but the use of microwaves increases the amount of (+)-neoisopulegol up to 30 %.

Scheme-4: Garrigues, B.; Laurent, R.; Laporte, C.; Laporterie A.; Dubac, J. *Liebigs Ann. Chem.* **1996**, 743.



Ionic liquids are also utilized as a susceptor, for example Ley[36] described the preparation of thioamides from amides. Although the reaction under classical conditions occurs in excellent yield, however due to presence of small amount of ionic liquid the reaction time was be shortened using microwave irradiation (Scheme-5) using toluene as a solvent, which is microwave transparent. Leadbeater studied in detail Diels-Alder cycloaddtions, Michael additions and alkylation reactions in the presence of ionic liquids and using nonpolar solvents (hexane, THF, toluene and dioxane) under microwave irradiations. He concluded that 0.2 mmol of ionic liquid is the optimum quantity needed to heat 2 mL of solvent to deliver fruitful results.[37]

Scheme-5: Ley, S. V.; Leach A. G.; Storer, R. I. *J. Chem. Soc., Perkin Trans. 1* **2001**, 358.

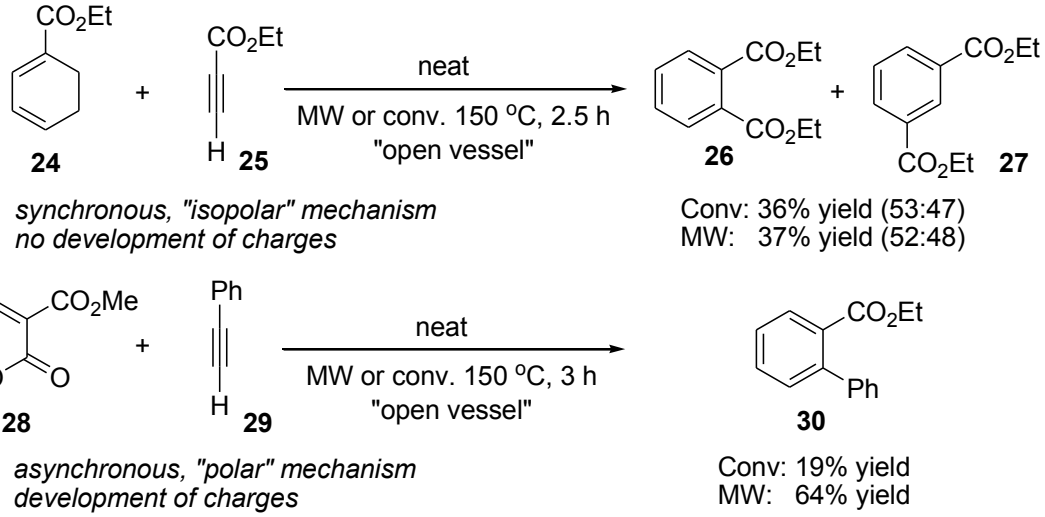


2.3 Non-Thermal effects:

It is defined as acceleration of chemical transformations in a microwave field that cannot be rationalized in terms of either purely thermal/kinetic or specific microwave effects. Essentially, most non-thermal effects result from a proposed direct interaction of the electric field with specific molecules in the reaction medium. It has been argued, for example, that the presence of an electric field leads to orientation effects of dipolar molecules and hence changes the pre-exponential factor A[38] or the activation energy[39] (entropy term) in the Arrhenius equation. Furthermore, a similar effect should be observed for polar reaction mechanisms, where the polarity is increased on going from the ground state to the transition state, resulting in an enhancement of reactivity through a lowering of the activation energy. Many publications in the literature use arguments like this to explain the outcome of a chemical reaction carried out under microwave irradiation. A study by Loupy and coworkers illustrates this point.[40] In the example shown in Scheme-6, two irreversible Diels-Alder cycloaddition processes were compared. In the first example (Scheme-6), no difference in either yield or selectivity

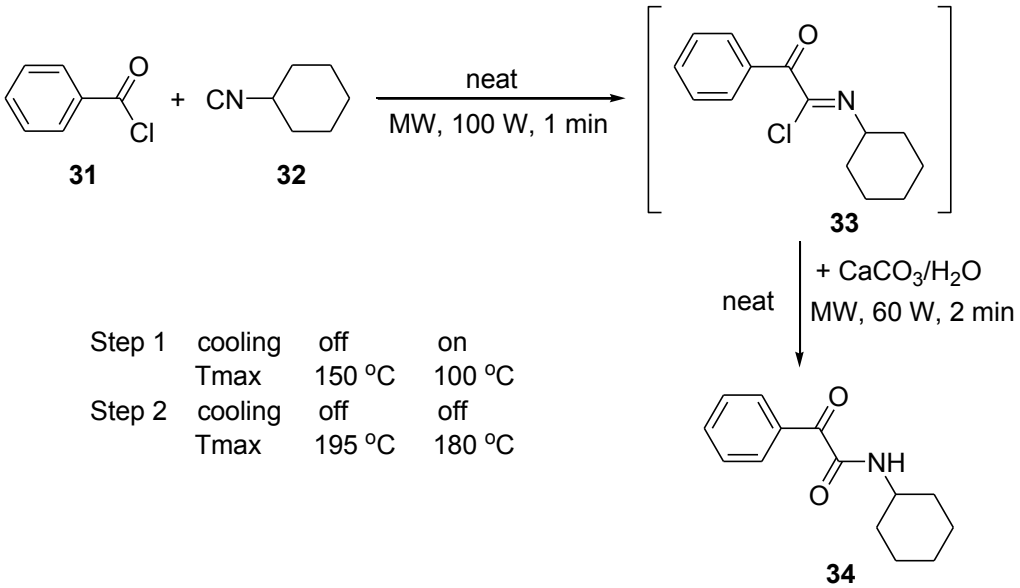
was observed between the conventionally and the microwave heated reactions. Detailed ab initio calculations on the cycloadditions processes revealed that here a synchronous, isopolar (concerted) mechanism is operational, in which no charges are developed on going from the ground state to the transitional state. On the contrary, in the second example, a significant difference in product yield was observed on comparing the

Scheme-6: Loupy, A.; Maurel, F.; Sabatie-Gogova, A. *Tetrahedron* **2004**, *60*, 1683.



thermally and microwave-heated runs. Here, ab initio calculations on transition-state geometries and dipole moments revealed a significant degree of charge development on going from ground state to transition state. The authors take these experimental results as a clear evidence for the involvement of non-thermal microwave effects arising from electrostatic interactions of polar molecules with the electrical field, that is, for the stabilizations of the transitions state and thereby a decrease of the activation energy.[40]

Scheme-7: Chen, J. J.; Deshpande, S. V. *Tetrahedron Lett.* **2003**, *44*, 8873.



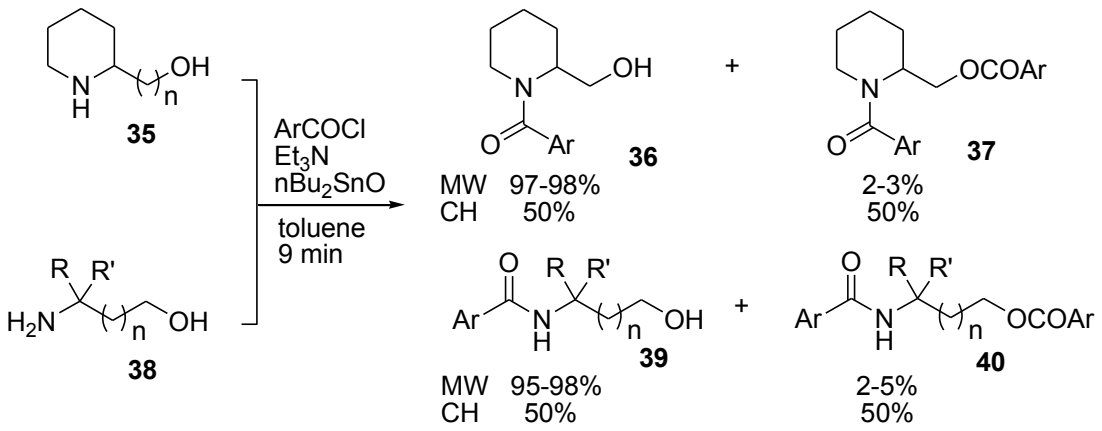
In an another claim, the researcher's compared the outcome of the condensation of an acid chloride with an isonitrile followed by hydrolysis of the intermediate to an α-ketoamide under microwave heating with and without external cooling of reaction vessel by cooled air. While irradiation at a constant 100 W for 1 min (step 1) without cooling (measured temperature 150 ºC) led only to black tar-like product, the same reaction with the cooling feature turned on (100 ºC) provided a 69 % isolated yield of the target compound. Here the microwave irradiation with simultaneous cooling of vessel by compressed air was utilized, due to this latent heat was removed and higher level of microwave power was directly administered to the reaction mixture to gain fruitful results.[41]

In a similar kind of experiment, Collins group reported examples of aqueous Suzuki coupling reactions of aryl chlorides using palladium-on-charcoal as the catalyst, where yields were significantly increased from 40% to 75% using the simultaneous cooling technique.[42]

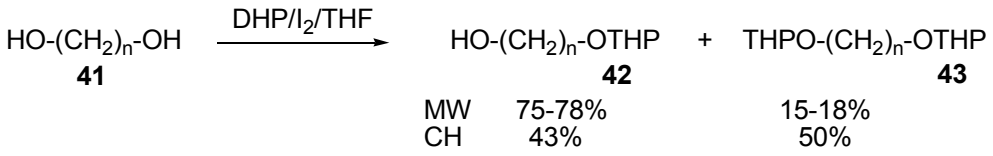
Chemoselective *N*-acylation of 1, 2 & 1, 3-amino alcohols using aryl acid chloride catalyzed by dibutyltin oxide using non-polar solvent such as toluene were reported by Morcuende et al.[43] Whereas under conventional heating they observed mixture of products *viz.*, *N*-acylation, *O*-acylation, *N*,*O*-diacylation along with starting material (Scheme-8).

In a selective reaction reported by Deka and Sharma,[44] a symmetrical diols where one of hydroxyl was mono protected as a tetrahydropyranyl ether using dihydropyran catalyzed by iodine in good yields, whereas, conventional heating method led to almost equimolar mixture of mono and di-ether products (Scheme-9).

Scheme-8: Morcuende, A.; Ors, M.; Valverde, S.; Herradon, B. *J. Org. Chem.* **1996,** *61,* 5264.



Scheme-9: Deka, N.; Sharma, J. C. *J. Org. Chem.* **2001**, *66,* 1947.



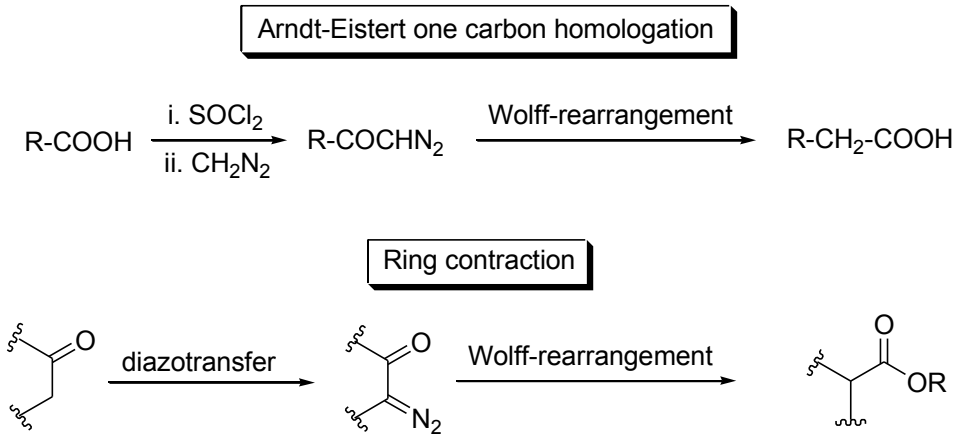
However despite many claims, microwave specific non thermal effects are subject of considerable current debate and controversies.[45] Many researchers consider that microwaves has no effect at all on a chemical reaction. For example, it has been postulated that "while the existence of a "specific microwave effect" cannot be completely ruled out, the effect appears to be a rarity and of marginal synthetic importance".[46]

Indeed, microwave radiation can be judiciously used to improve processes and modify selectivities in relation to conventional heating. It is possible to take advantage of both thermal and non-thermal effects to obtain the desired results. Overheating of polar solvents and hot spots in solvent free conditions can be used to accelerate reactions and also to avoid decomposition of thermally unstable compounds. The increased mobility in solids has been used to obtain less harsh reaction conditions under microwave irradiation. Also, the selective heating induced by microwave irradiation can be exploited to heat polar substances in the presence of apolar ones and, in this way, to modify the selectivity of a given reaction or to avoid decomposition of thermally unstable compounds.

One of dedicated researcher in this field stated that "microwave chemistry should not only be used as a last resort when all other options have failed (as is still the case in many laboratories) but rather as a first choice for all transformations that require heating." [47] This was well demonstrated by his group for the synthesis of a 4-arylquinolin-2-one derivative in which all six steps of the synthesis were successfully carried out using high-speed microwave conditions.[48]

2.4 Present Work:

Figure-2:



The origin of this work came from chapter-I section-II in the synthesis of C-ring unit, required for construction of ABC skeleton of Taxol, Arndt-Eistert one carbon homologation protocol was utilized.

The Wolff-rearrangement[49] of α-diazoketones is an integral part of the well-known Arndt-Eistert one carbon homologation of carboxylic acids as well as it provides an efficient route to the ring contracted compounds from cyclic α-diazo carbonyl compounds (Figure-2). Literature is replete with its application in organic synthesis. [49,50] The rearrangement involves specific 1,2-carbon shift, accompanying or following loss of dinitrogen, to ketene via transient free keto-carbene intermediate. The reaction can be initiated thermally,[51] photochemically,[52] by transition metal catalysis[53,54] or by ultrasound in the presence of silver ions.[55] Among these, thermolysis is used less frequently than the other techniques in spite of simplicity in operational conditions due to the several disadvantages associated with conducting the reaction at higher temperature (in the vicinity of 180 ^{o}C) such as thermal instability of the ring contracted products or ketene intermediates and other competing side reactions of carbene occurring at higher temperatures, resulting in the overall poor yield of the rearranged products. These disadvantages are largely overcome by the photolysis of the diazocarbonyl functional group in the ultraviolet region (λ ~ 300 nm), however, a limit is reached when either the product or diazocarbonyl substrates contain other photolabile groups. Among, transition metal catalysis, an efficient procedure developed by Newman et al.[53] comprising of silver ion catalysis in the presence of triethyl amine under homogenous conditions is generally preferred.

With the view to harness the above mentioned advantages associated with microwave irradiation it was thought to investigate the facility of the Wolff-rearrangement using continous mode of irradiation.

The α-diazoketones **44–52** as shown in Table-1 were prepared by acylation of diazomethane following the standard organic synthesis procedure.[56] Initially carboxylic acid was treated with thionyl chloride to obtain acid chloride, in turn, treated with cold (0 ºC) yellowish ethereal solution of diazomethane leading to the formation of respective α-diazoketones.

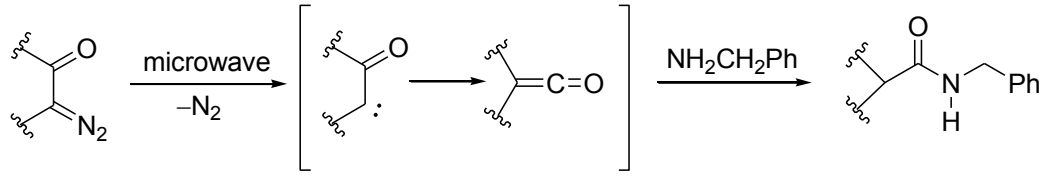
These substrates exhibited a bathochromic shift for the diazocarbonyl group in the IR spectra of **44–52** around 1600–1640 cm^{-1} due to conjugation with diazo function. The latter function showed a strong absorption band around 2000–2200 cm^{-1} due to azo stretching.

^{1}H NMR spectra of **44–52** displayed a singlet peak in the region of δ 5.00–6.00 a characteristic signal of proton attached to a carbon carrying diazo function (–CO–C<u>H</u>N_2).

The α-diazoketones **53–55** were prepared by a deformylative diazotransfer protocol as follows.[57] Initially starting ketones were formylated with ethyl formate using sodium hydride in THF at 0 ºC. Further, formylated ketones were treated with a solution of mesyl azide and triethyl amine in DCM at –15 ºC for 3 h to furnish α-diazoketones **53–55**. These substrates also displayed similar IR characteristic features.

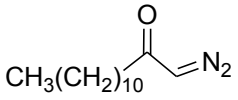
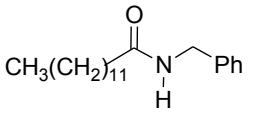
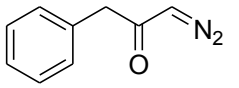
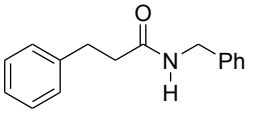
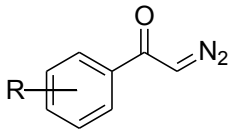
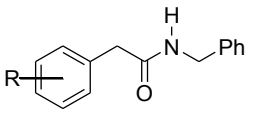
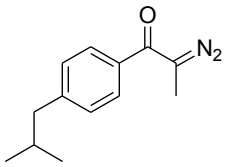
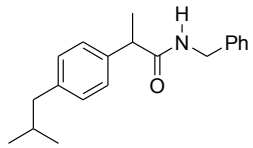
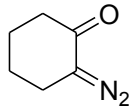
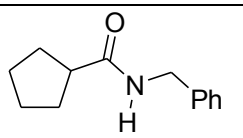
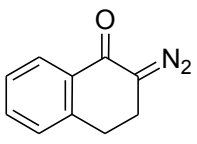
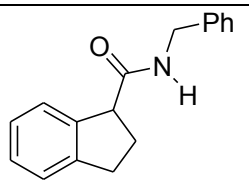
After preparing α-diazoketones **44–55** they were subjected to Wolff-rearrangement for comparison purpose in thermal conditions i.e. refluxing α-diazoketones in benzyl amine at ~ 180 ºC for 15 min to afford Wolff-rearranged amides **56–67** in moderate yields and are summarized in Table-1.

Scheme-10:



As discussed earlier in order the reaction to be microwave active either substrate, reagents, catalyst, solvent or mediator should be microwave active i.e. any one should have high dielectric constants or permanent dipolar charged. Literature survey revealed that α-diazocarbonyl compounds have high dipole moments.[58] Additionally, the dipole moments of all conformers of α-diazoketone **44a** were calculated theoretically through semi-empirical methods (PM3) by using HYPERCHEM software, and the geometry

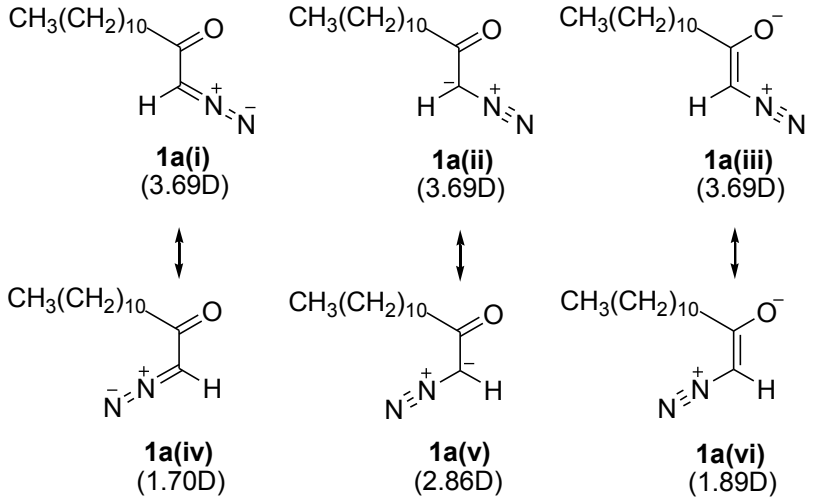
Table-1:

Entry	α-Diazoketones	Benzylamides	Yield (%)		Dipole moments (Debye)	
			MW	Δ	Z	E
(a)	 **44**	 **56**	75	45	3.69	1.89
(b)	 **45**	 **57**	92	56	3.42 (3.31)	1.75
						
(c)	R = H **46**	R = H **58**	74	54	3.65 (3.66)	1.78
(d)	R = 2-Me **47**	R = 2-Me **59**	93	52	3.3	1.82
(e)	R = 2-Cl **48**	R = 2-Cl **60**	68	48	4.1 (3.56)	2.24
(f)	R = 2-Br **49**	R = 2-Br **61**	74	38	4.19	2.35
(g)	R = 2-I **50**	R = 2-I **62**	82	41	3.75	1.93
(h)	R = 4-Me **51**	R = 4-Me **63**	74	36	3.9 (4.1)	2.5
(i)	R = 4-OMe **52**	R = 4-OMe **64**	87	74	4.75 (3.62)	3.37
(j)	 **53**	 **65**	86	32	4.0	1.93
(k)	 **54**	 **66**	90	57	3.71	--
(l)	 **55**	 **67**	72	55	3.87	--

optimization of *Z* and *E* conformers of **44a** are shown in Figure-3. The results clearly revealed that *Z* conformers **44a (i-iii)** have higher dipole moment than *E* conformers **44a (iv-vi)**. Additionally, dipole moments of *E* and *Z* conformers of all α-diazoketones **45–55**

were calculated and results are summarized in Table-1. Thus, theoretical calculations revealed that all α-diazoketones **45–55** have higher dipole moments in general and *Z*-conformer has higher dipole moment than *E*-conformer in particular. The figures in the parentheses indicate literature[58] experimental values of *Z*-conformers of α-diazoketones (Table-1). Therefore the electric field of microwaves will preferably aligned with *Z*-conformer than any other conformation of α-diazoketones. Now there is a choice to observe chemistry arises from direct substrate microwave interaction (non-thermal effect) or through using solvent heating which has higher dipole moment (thermal effect).

Figure-3:



To test the hypothesis a wide range of α-diazoketones **44–55** were successively subjected to continuous mode of microwave irradiation using dry benzyl amine (having lower dipole moment than α-diazoketones, vide infra) as a solvent (Scheme-10). The progress of the microwave-promoted reaction was monitored by following change in solution temperature and reactor pressure with respect to time (Figure-4 and Figure-5). The graph 1(B) (Figure-4) recorded showed that a maximum temperature of 99 ºC was reached in 10 min and then remained constant. The liberation of nitrogen gas during the course of reaction (Scheme-10) was advantageously used in monitoring the completion of the decomposition of α-diazoketones **44–55**. The microwave irradiation was continued till the change in reactor pressure became constant (~ 25 minutes, Figure-5). Thus, aliphatic **44**, benzylic **45** and substituted aromatic **46–52** α-diazoketones gave excellent yields of the Wolff-rearranged benzyl amides as well as, the cyclic α-diazoketones **53–55** underwent an efficient ring contraction reaction. The yields are summarized in Table-1. It

is pertinent to mention that under the influence of microwave irradiation the non-linear α-diazoketones **53** furnished exclusively the benzyl amide of ibuprofen (**65**, Table-1) whereas silver oxide catalyzed decompositions of α-diazopropiophenones are known to give Wolff-rearranged product as well as β-elimination product enone in the ratio 2:3.[59]

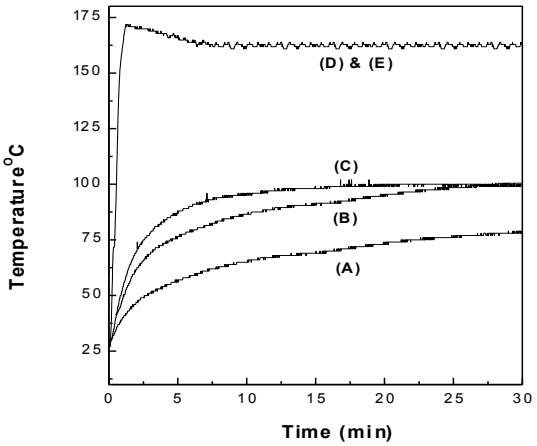


Figure-4: Temperature profile with respect to time during the microwave irradiation (300 W) of (A) anhydrous benzyl amine, 10 ml. (B) 0.1 M solution of α-diazoketone **44–55** in benzyl amine, 10 ml. (C) 0.1 M solution of the 3-diazocamphor **68** in benzyl amine, 10ml. (D) Aqueous dioxan solution (H_2O:dioxan, 1:1 vol/vol), 10 ml. (E) 3-Diazocamphor **68** in aqueous dioxan (H_2O:dioxan, 1:1 vol/vol), 10 ml.

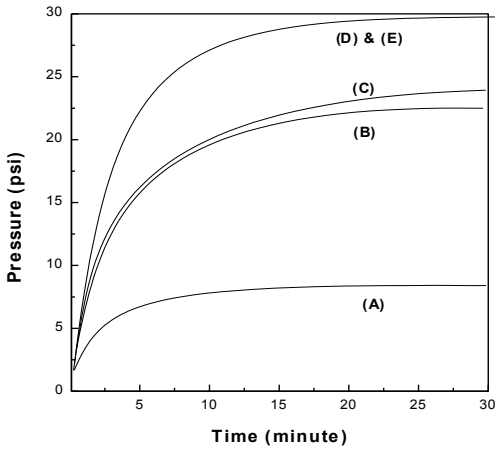


Figure-5: Pressure profile with respect to time during the microwave irradiation (300 W) of (A) anhydrous benzyl amine, 10 ml. (B) 0.1 M solution of α-diazoketone **44–55** in benzyl amine, 10 ml. (C) 0.1 M solution of the 3-diazocamphor **68** in benzyl amine, 10 ml. (D) Aqueous dioxan solution (H_2O:dioxan, 1:1 vol/vol), 10 ml. (E) 3-Diazocamphor **68** in aqueous dioxan (H_2O:dioxan, 1:1 vol/vol), 10 ml.

The reason for choosing benzylamine solvent was that it is reported in literature that amines have small dipole moments as compared to alcohols, water, nitriles, sulfoxides etc.[60] As a consequence they are weak absorbers of microwaves. Therefore, it

is expected microwaves should directly couple with α-diazoketones and not with solvent. It was further confirmed by microwave irradiation of benzylamine. Thus, the graph 1(A) (Figure-4) generated during the microwave irradiation of benzylamine at the irradiation power of 300 W shows that rate of heating is faster in the initial period of time and it decreases and eventually becomes constant with increase in length of time. A maximum solution temperature of 77 ºC was reached after irradiating for 26 minutes. Whereas using solvents which have higher dipole moments known to shoot temperature above their boiling points (critical temperature) within few seconds. Comparison between the graph 1A and graph 1B (Figure-4) clearly shows effective coupling of microwaves with α-diazoketones. A control experiment further supports this effective coupling. The solution of the α-diazoketone **44** in anhydrous benzyl amine (0.1 M, 10 mL) is heated using an oil bath around 100 ºC for twenty minutes. The infra-red analysis of the solution revealed the presence of the starting α-diazoketone. This was further confirmed from the near quantitative recovery of the **44** after work-up.

After realizing successful transformation of conformationally mobile α-diazoketones it was decided to choose conformationally restricted substrate such as 3-diazocamphor **68**, known for its distinct behaviour on thermolysis[61] or transition metal catalysis[62] it gives intramolecular C–H insertion product a tricyclic ketone, while on photolysis in methanol yields methyl ester of Wolff-rearranged product.[63]

Conventional heating of 3-diazocamphor **68** using benzylamine at reflux temperature (180 ºC) for 15 min provided the reported intramolecular C–H insertion product **69** in 43% yield (Scheme-11).

IR spectrum of **69** displayed a strong band at 1746 cm^{-1} indicative of the presence of five membered carbonyl group.

^{1}H NMR spectrum of **69** displayed following pattern. The multiplets at δ 1.90-2.10, 1.70-1.80 and 1.45-1.55 integrating for three, one and one protons respectively were assigned to three methines and one methylene group. The sharp singlets at δ 0.96, 0.89 & 0.80 corresponded to geminal dimethyls and bridgehead methyl group.

^{13}C NMR spectrum of **69** along with DEPT spectrum displayed following pattern. The most downfield quaternary signal appeared at δ 215.5 and was assigned to carbonyl group, while the upfield quaternary signal appeared at δ 48.2 and 43.5 were assigned to carbons were bridgehead methyl group and geminal dimethyls is attached respectively.

The three methines and three methyls in the molecule appeared at δ 33.7, 2 x 21.2, 20.7, 20.3 and 5.6. And the only methylene present in molecule appeared at δ 36.0.

Mass spectrum of **69** revealed molecular ion peak at 150 and the other prominent peaks appeared at 135, 122, 107, 95 and 67.

In order to investigate the microwave effect in this substrate, 3-diazocamphor **68** was subjected microwave irradiation using benzylamine as the solvent. The graph C, Figure-4 generated showed a rapid heating and maximum temperature of 97 ºC was reached, irradiation was continued till the graph C, Figure-5 showed a constant pressure (30 min) to furnish surprisingly, the Wolff-rearranged benzyl amide **70** in 73% yield in contrast to the C-H insertion product under thermal conditions as mentioned above.

IR spectrum of **70** displayed a strong band at 3309, 1634 cm^{-1} indicated the presence of an amide functional group.

^{1}H NMR spectrum of **70** displayed following pattern. The multiplets at δ 7.45-7.25 intergrating for ten protons corresponded to aromatic protons. The broad singlets at δ 5.79 & 5.51 integrating for one proton each was ascribed to NH protons. The doublets at δ 4.46 & 4.45 with coupling constant of J = 6 Hz integrating for two protons each were attributed to benzylic protons. The singlets at δ 2.71 & 2.36 integrating for one each corresponded to proton α to carbonyl group. The broad singlets at δ 2.27 & 2.07 intergrating for one proton each were assigned to bridgehead proton. The multiplets at δ 1.80-1.40 integrating for eight protons corresponded to two methylene groups. The sharp singlets at δ 1.19, 1.12, 1.11, 0.74 & 0.73 were assigned to geminal dimethyls and bridgehead methyl.

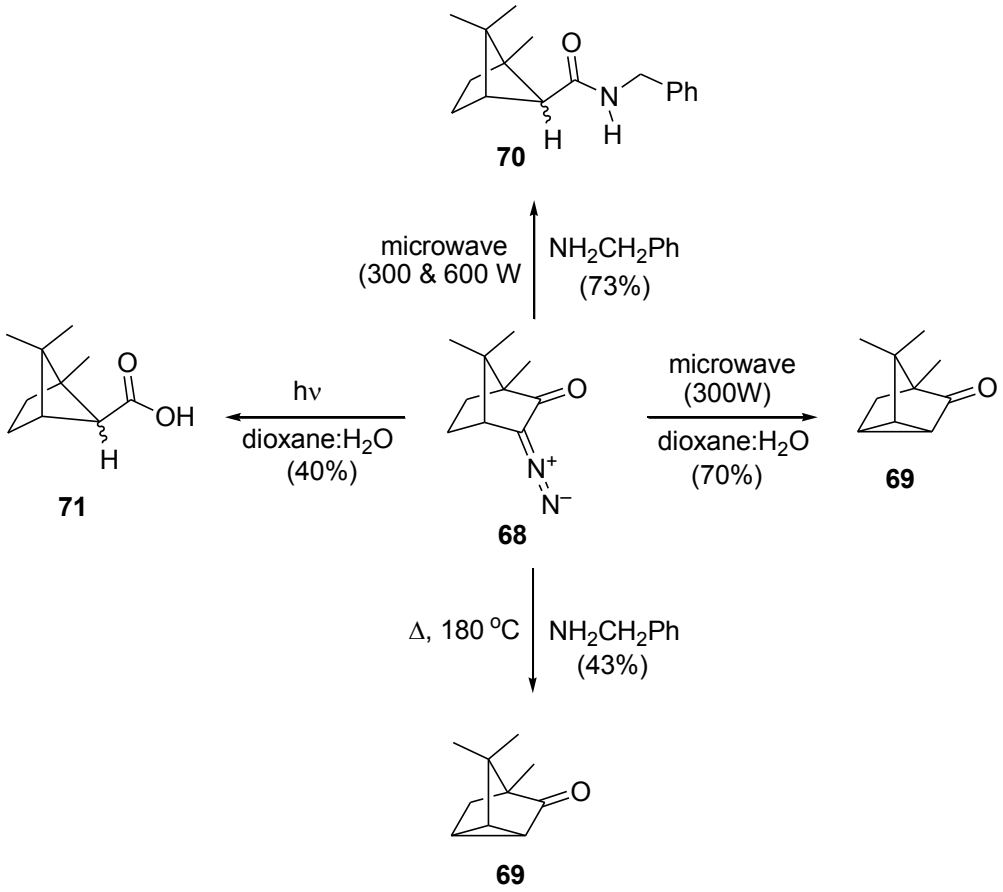
^{13}C NMR spectrum of **70** along with DEPT spectrum displayed the following pattern. The most downfields quaternary signals at δ 173.6 & 173.0 corresponded to amide carbonyls. And the downfield quaternary signals at δ 138.5 & 138.3 were assigned to aromatic carbons. While the upfield quaternary signals at δ 53.0, 52.5, 46.0 & 43.0 were attributed geminal dimethyl attached and bridgehead carbon. The intense methine signals at δ 128.4, 127.6, 127.5 & 127.1 were assigned to aromatic carbons. The upfield methines at δ 56.7, 50.6, 47.0 & 46.3 were ascribed to C-H α to carbonyl group and bridgehead C-H group. The downfield methylene signals at δ 43.0 and 42.6 corresponded to benzylic carbons while the other methylene signals at δ 34.0, 28.8, 25.1 & 23.5 attributed to $-CH_2-CH_2-$ group present in the ring. The methyl signals at δ 20.2, 19.6, 18.3, 16.7, 13.2 & 12.5 were assigned to geminal dimethyls and bridgehead methyl

group. The above NMR's pattern revealed that the amide **70** existed in a diastereomeric ratio of 1:1.

The mass spectrum of **70** displayed molecular ion peak at 257 and the other prominent peaks appeared at 242, 214, 202, 185, 174, 160 and 91.

The Wolff-rearranged benzyl amide **70** was further confirmed by comparison of data with authentic sample prepared by a known two step protocol. At first the aqueous dioxane solution of 3-diazocamphor was photolysed (λ = 300 nm) to obtain Wolff-rearranged carboxylic acid **71** in 40% yield (Scheme-11). The acid was successively treated with thionyl chloride and benzylamine to deliver authentic compound. The physical and spectroscopic data of **70** was in excellent agreement with the authentic sample.

Scheme-11:



The authentic Wolff-rearranged carboxylic acid **71** by photolysis exhibited following spectral characteristics.

IR spectrum of **71** displayed a broad bands at 3500-2600 and 1692 cm^{-1} indicated the presence of carboxylic acid functional group.

^{1}H NMR spectrum of **71** displayed the following characteristic pattern; a broad singlet at δ 2.75 & a singlet at δ 2.45 integrating for 0.15 and 0.85 protons respectively corresponded to proton α to carboxylic group.

^{13}C NMR spectrum of **71** revealed two most downfield carbon signals at δ 181.5 as a major & 179.5 as a minor are characteristic peaks of carboxylic acid group.

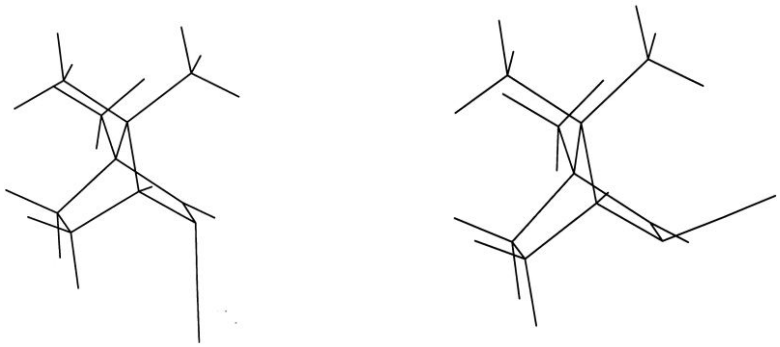
Mass spectrum of **71** displayed a molecular ion peak at 168 and the other prominent peaks appeared at 153, 135, 125, 107, 100 and 91.

Interestingly, microwave irradiation of aqueous dioxane solution of 3-diazocamphor **68**, the solvent used during photolysis, led to the formation of the product obtained during conventional heating, namely a tricyclic ketone **69**.

In order to find out reason for the observed distinct behavior of 3-diazocamphor by performing microwave reactions in two different solvents benzylamine and water. It was decided to perform theoretical calculations to predict dipole moments and thermodynamic stability of two resonating conformers of 3-diazocamphor **68** *i.e.* endo **(68*E*)** and exo **(68*Z*)** (Figure-5), because it was postulated in the literature that ground state conformation was a major factor in controlling the direction of decomposition of α-diazoketones.[64] Initially it was attempted by semi empirical method using HYPERCHEM software but without any success. Therefore calculations were performed with the help of ab initio technique by using the GAMESS program[65] and the initial geometries were generated using MOLDEN software.[66] The geometries were optimized with the use of split-valence basis sets, 3-21G, 3-21G(d,p), 6-31G and 6-31G(d,p) without any symmetry constraints. The stationary point energy calculation using the polarization and diffusion functions on the structures optimized at the level of 3-21G(d,p) and 6-31G(d,p) was also performed. The energy and dipole moment of the endo **(68*E*)** and exo **(68*Z*)** conformers of the 3-diazocamphor **68** are given in the Table-2. It is seen that the thermodynamic stability of the endo **(68*E*)** conformer is greater than the exo **(68*Z*)** conformer where as the dipole moment order is seen to be reversed. The usage of polarization and the diffuse functions actually improves the difference in the value of the dipole moment of endo and exo conformers, significantly. However, the predicted energy difference values for the both conformers are slightly reduced with the use of polarization or diffuse functions. In all cases, one can see the dipole moment of the Z-conformer is higher than that of E-conformer and the latter conformer is thermodynamically more stable than that the former conformer. Thus it is observed that the difference of dipole moments of endo

(68*E*) and exo **(68*Z*)** conformers is supported by *ab initio* calculations with a sufficiently large basis set.

Figure-5:



68*E* **68*Z***

Table-2: The dipole moment and energy of the endo (**68*E***) and exo (**68*Z***) conformers of 3-diazocamphor **68**

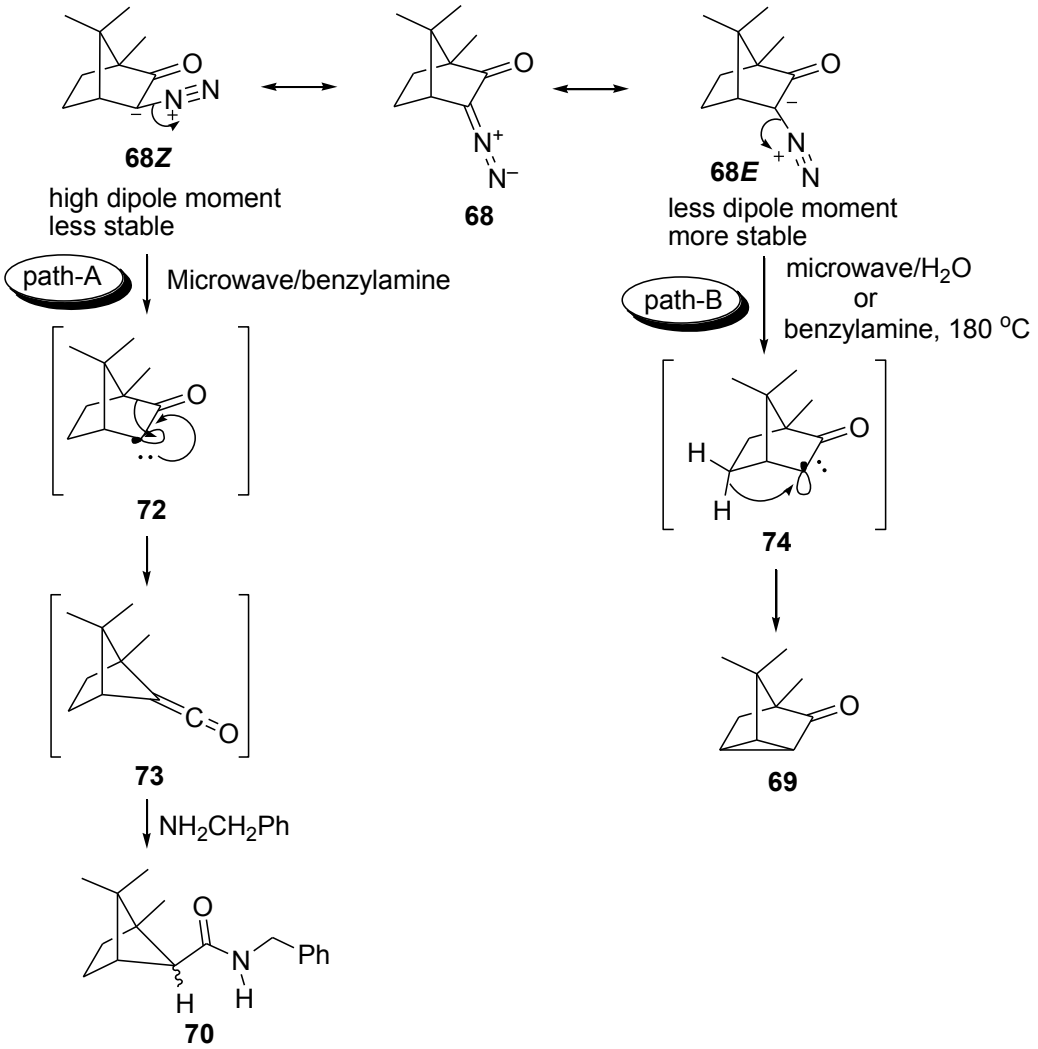
Basis Set	Dipole moment[a]		Energy[b]	
	endo (68E)	exo (68Z)	endo (68E)	exo (68Z)
3-21G	3.9397	3.9565	–567.2162894	–567.2124763
3-21G(d,p)	3.7980	3.9130	–567.3791993	–567.3776416
3-21G++(d,p)	4.6353	4.7345	–567.4402857	–567.4392741
6-31G	4.4126	4.5283	–570.2245033	–570.2242355
6-31G(d,p)	3.8529	3.9429	–570.5171595	–570.5163425
6-31G++(d,p)	4.1220	4.2123	–570.5272696	–570.5265600

[a] in Debye units; [b] in Hartree units

Therefore it is presumed that due to the dielectric field of the microwaves all the resonating conformers of 3-diazocamphor are oriented in exo form **(68*Z*)** since it has higher dipole moments and plausible mechanism of formation of Wolff-rearranged product is depicted in Scheme-12 (path-A). On elimination of nitrogen molecule, a carbene species **72** is formed and is endo oriented while the vacant orbital is exo oriented. Due to this there is 1,2-carbon shift takes place to form ring contracted ketene intermediate **73** which reacts with benzylamine to form an amide **70**.

In the case of water under microwave irradiation of 3-diazocamphor, since water couples more effectively with microwaves than α-diazoketones, causes rapid heating (compare plot 1B and 1E, Figure-4) and is transferred to substrate and reaction occurs. The reason for formation of C-H insertion product may be the reaction is occurring through thermodynamically more stable conformer i.e. endo form **68*E*** and plausible mechanism is depicted in Scheme-12 (path-B). Thus on elimination of nitrogen

Scheme-12:



molecule, a carbene specis **74** is generated and which is exo oriented and the vacant orbital is endo oriented and therefore C-H insertion takes place. The similar mechanism (via *Z*-conformation) may be operating in other conformationally mobile α-diazoketones **44–55** as can be judged from the enhanced yields of the rearrangement products **56–67**, as well as from the formation of the sole product namely benzyl amide of ibuprofen **65** from the non-linear α-diazoketone **53** (Table-1). In nutshell, it appears that in conventional thermolysis reaction occurs predominantly through the thermodynamically more stable conformer, while the conformer possessing highest dipole moment is preferred in the microwave irradiation.

Concurrently, Linder and Podlech disclosed[67] that decomposition of α-diazoketones derived from *N*-CBz protected α-amino acids under microwave irradiation forms a ketene, in turn, reacts further with imines to afford β-lactams exclusively *trans* substituted equivalent to its photolysis conditions. Whereas using solvent *o*-

dichlorobenzene and refluxing at 180 ºC afforded a mixture of *trans* and *cis* substituted β-lactams in the ratio of 64:36.

2.5 Conclusion:

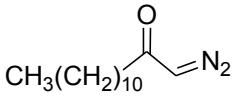
In conclusion, it has been clearly demonstrated that microwave irradiation of the α-diazoketones promotes efficient Wolff rearrangement of tremendous synthetic utility and the product selectivity depends on the dielectric properties of the solvent used. Formation of the ring-contracted bicyclic amide, a nonthermal reaction product from 3-diazocamphor most probably due to the combined solvent and microwave effect.

2.6 Experimental:

2.6.1 General procedure of preparation of α-diazoketones 44–52 from acylation of diazomethane methodology:[56]

A single-neck round-bottom flask equipped with reflux condenser and calcium chloride guard tube its outlet was connected to water trap. An acid (1 mmol), benzene (1 mL), and a freshly distilled colourless thionyl chloride (2 mmol) were placed and the reaction mixture was refluxed for 3 h at 60 ºC. After completion of reaction the excess of thionyl chloride and benzene were removed under pressure and crude acid chloride obtained was used as such for further reaction. To a cold (0 ºC) yellowish ethereal solution of diazomethane (2 mmol) and triethyl amine (1 mmol) a solution of acid chloride (1 mmol) in benzene (2 mL) was slowly added over a period of 30 min and the reaction mixture was stirred for 3 h at 0 ºC and then left overnight at room temperature. The next day, reaction mixture was warmed for 1h in order to remove excess diazomethane and then cooled. The triethylamine hydrochloride precipitated was filtered and washed with ether (3 x 25 mL). The yellowish filtrate was then concentrated *in vacuo*, and the residue obtained was purified by silica gel column chromatography to afford α-diazoketones **44–52** as a yellowish compounds. The solid obtained were recrystalised in aqueous ethanol.

2.6.1.1 1-diazotridecan-2-one (44):



44

Chemical Formula: $C_{13}H_{24}N_2O$, 224

Nature: Yellowish solid

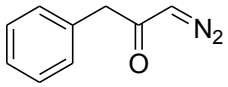
M.P.: 41 ºC [Lit[68] 44 ºC]

IR ($CHCl_3$): ν 2106, 1640 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.24 (br.s, 1H), 2.30-2.45 (m, 2H), 1.60-1.80 (m, 2H), 1.20-1.45 (m, 16 H), 0.88 (t, J = 6 Hz, 3H).

MS (EI) *m/e* (rel. intensity): 224 (M^+, 3), 196 (1), 183 (5), 167 (1), 153 (2), 125 (4), 111 (18), 97 (75), 84 (100), 69 (55).

2.6.1.2 1-diazo-3-phenylpropan-2-one (45):



45

Chemical Formula: $C_9H_8N_2O$, 160

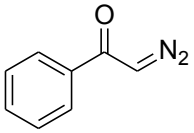
Nature: Yellowish oil

IR ($CHCl_3$): ν 2094, 1626 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.2-7.5 (m, 5H), 5.15 (s, 1H), 3.62 (s, 2H).

MS (EI) *m/e* (rel. intensity):160 (M^+), 118 (12), 104 (95), 119 (3), 91 (100).

2.6.1.3 2-diazo-1-phenylethanone (46):



46

Chemical Formula: $C_8H_6N_2O$, 146

Nature: Yellowish solid

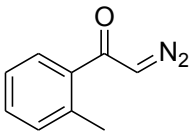
M.P.: 48 ºC [Lit[69] 48 ºC]

IR ($CHCl_3$): ν 2100, 1606 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.35-7.9 (m, 5H), 5.95 (s, 1H).

MS (EI) *m/e* (rel. intensity): 146 (M^+, 40), 118 (12), 105 (52), 90 (100), 77 (58), 63 (95).

2.6.1.4 2-diazo-1-*o*-tolylethanone (47):



47

Chemical Formula: $C_9H_8N_2O$, 160

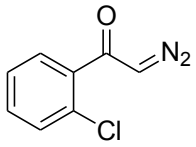
Nature: Yellowish oil

IR ($CHCl_3$): ν 2100, 1620 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.2-7.45 (m, 4H), 5.58 (s, 1H), 2.49 (s, 3H).

MS (EI) *m/e* (rel. intensity): 160 (M^+, 46), 132 (55), 131 (100), 119 (94), 104 (94), 104 (22), 103 (70), 91 (60), 78 (25), 77 (20).

2.6.1.5 1-(2-chlorophenyl)-2-diazoethanone (48):



48

Chemical Formula: $C_8H_5ClN_2O$, 180

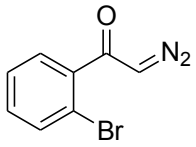
M.P.: 48 ºC [Lit[70] 50-51 ºC]

IR ($CHCl_3$): ν 2107, 1619 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.2–7.6 (m, 4H), 5.83 (s, 1H).

MS (EI) *m/e* (rel. intensity): 182 (M^+, 6), 180 (M^+, 20), 152 (M^+–N_2, 38), 139 (76), 124 (30), 111 (30), 189 (100), 75 (15), 63 (10).

2.6.1.6 1-(2-bromophenyl)-2-diazoethanone (49):



49

Chemical Formula: $C_8H_5BrN_2O$, 224

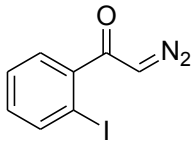
Nature: Yellowish oil

IR ($CHCl_3$): ν 2105, 1620 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.5–7.6 (d, J = 10 Hz, 1H), 7.15–7.45 (m, 3H), 5.70 (s, 1H).

MS (EI) *m/e* (rel. intensity): 226 (M^+, 4), 224 (M^+, 8), 198 (28), 196 (54), 185 (40), 183 (50), 170 (16), 157 (20), 155 (24), 89 (100), 75 (3).

2.6.1.7 2-diazo-1-(2-iodophenyl)ethanone (50):



50

Chemical Formula: $C_8H_5IN_2O$, 272

Nature: Yellowish solid

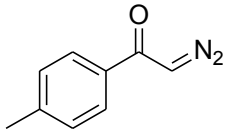
M.P.: 60 ºC [Lit[71] 62 ºC]

IR ($CHCl_3$): ν 2101, 1612 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.8–7.9 (m, 1H), 7.3–7.5 (m, 2H), 7.05–7.15 (m, 1H), 5.71 (s, 1H).

MS (EI) *m/e* (rel. intensity): 272 (M^+, 4), 244 (M^+–N_2, 72), 231 (12), 203 (10), 127 (20), 90 (10), 89 (100), 74 (15), 63 (95).

2.6.1.8 2-diazo-1-*p*-tolylethanone (51):



51

Chemical Formula: $C_9H_8N_2O$, 160

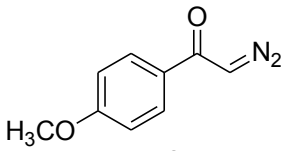
Nature: Yellowish solid

M.P.: 43 ºC [Lit[72] 44 ºC]

IR ($CHCl_3$): ν 2104, 1608 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.64 (d, *J* = 9 Hz, 2H), 7.22 (d, *J* = 9 Hz, 2H), 5.88 (s, 1H), 2.38 (s, 3H).

2.6.1.9 2-diazo-1-(4-methoxyphenyl)ethanone (52):



52

Chemical Formula: $C_9H_8N_2O_2$, 176

Nature: Yellowish solid

M.P.: 90 ºC [Lit[73] 90 ºC]

IR ($CHCl_3$): ν 2104, 1608 cm^{-1}

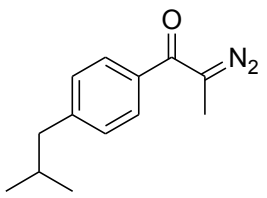
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.73 (m, 2H), 6.91 (m, 2H), 5.85 (s, 1H), 3.86 (s, 3H).

MS (EI) *m/e* (rel. intensity): 176 (M^+, 50), 148 (M^+–N_2, 18), 135 (90), 120 (38), 105 (20), 91 (80), 89 (40), 77 (100), 63 (36).

2.6.2 General procedure of preparation of α-diazoketones 53–55 & 68 by deformylative diazo-transfer:[57]

A flame dried, two-necked round bottom flask equipped with a septum and a argon balloon and was charged with sodium hydride (1 mmol) (50% dispersion in mineral oil), THF (5 mL) and one drop of absolute ethanol. Further this mixture was stirred at 0 ºC. Then ketone (1 mmol) and ethyl formate (2 mmol) in an additional THF (2 mL) was slowly added. The reaction mixture was then stirred at 0 ºC for 3h and left overnight at room temperature. The reaction was quenched with addition of water and the solution was acidified by adding dilute hydrochloride solution. The organic layer was separated and aqueous layer was extracted by ethyl acetate (3 x 10 mL). The combined organic layer was washed with water (5 mL), then with brine, dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo* and the residue obtained used as such for further reaction. A two-necked round-bottom flask equipped with pressure equalizing addition funnel was charged with formylated ketone (1 mmol), dichloromethane (10 mL) and triethyl amine (2 mmol). The flask was stirred at –15 ºC and mesyl azide (1.5 mmol) was slowly added at such a rate that the reaction temperature of reaction mixture does not rise above –5 ºC. Stirring was continued for 3 h. And the reaction was quenched with addition of a solution potassium hydroxide (1 M, 10 mL) and the mixture was stirred for 15 min at room temperature. The layers were separated and aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined DCM layer was successively washed with dilute potassium hydroxide solution, water and brine. The solution was dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo* and residue obtained was purified by flash column chromatography (230-400 mesh size silica gel) which provided α-diazoketones **53–55** & **68**.

2.6.2.1 2-diazo-1-(4-isobutylphenyl)propan-1-one (53):



53

Chemical Formula: $C_{13}H_{16}N_2O$, 216

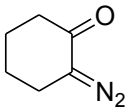
Nature: Yellowish oil

IR ($CHCl_3$): ν 2065, 1607 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.5 (d, *J* = 8 Hz, 2H), 7.19 (d , *J* = 8 Hz, 2H), 2.51 (d, *J* = 6 Hz, 1H), 2.15 (s, 3H), 1.88 (m, 1H), 0.9 (d, *J* = 6 Hz, 6H).

MS (EI) *m/e* (rel. intensity): 216 (M^+, 4), 188 (M^+–N_2, 12), 161 (30), 145 (72), 117 (100), 91 (35), 77 (8), 65 (8).

2.6.2.2 2-diazocyclohexanone (54):



54

Chemical Formula: $C_6H_8N_2O$, 124

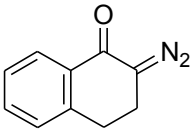
Nature: Yellowish oil

IR ($CHCl_3$): ν 2077, 1617 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.6–2.7 (m, 2H), 2.2.3–2.4 (m, 2H), 1.7–1.9 (m, 4H).

MS (EI) *m/e* (rel. intensity): 124 (M^+, 38), 96 (M^+–N_2, 45), 68 (100), 65 (15), 55 (10).

2.6.2.3 2-diazo-3,4-dihydronaphthalen-1(2*H*)-one (55):



55

Chemical Formula: $C_{10}H_8N_2O$, 172

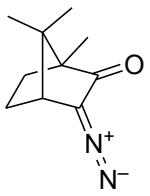
Nature: Yellowish oil

IR ($CHCl_3$): ν 2078, 1619 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.96–8.04 (m, 1H), 7.15–7.48 (m, 3H), 2.8–3.1 (m, 4H).

MS (EI) *m/e* (rel. intensity): 172 (M^+, 8), 144 (M^+–N_2, 18), 116 (32), 115 (100), 89 (48), 74 (15), 63 (42).

2.6.2.4 3-diazo-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (68):



68

Chemical Formula: $C_{10}H_{14}N_2O$, 178

Nature: Yellowish solid

M.P.: 72 ºC [Lit[74] 73 ºC]

IR ($CHCl_3$): ν 2069, 1671 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.96 (d, *J* = 4 Hz, 1H), 2.0–2.2 (m, 1H), 1.45–1.78 (m, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H).

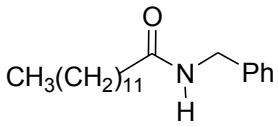
^{13}C NMR ($CDCl_3$, 50 MHz): δ 202.4, 61.1, 49.6, 58.1, 48.5, 30.6, 27.0, 20.0, 18.5, 9.4.

MS (EI) *m/e* (rel. intensity): 179 (M^++1, 4), 178 (M^+, 5), 150 (M^+–N_2, 10), 135 (30), 122 (10), 107 (96), 105 (40), 93 (35), 91 (94), 81 (12), 79 (100), 77 (20), 66 (35), 65 (30), 55 (10).

2.6.3 General Procedure of microwave irradiations of α-diazoketones 44–55:

A solution of α-diazoketone **44–55** in anhydrous benzyl amine (0.1 M, 10 mL) is charged in a sealed teflon reactor (100 ml) equipped with temperature and pressure sensors and subjected to the continuos mode of microwave irradiations (ν = 2450 MHz) with irradiation power of either 300W or 600W using Microwave Assisted Reactor System-5 [MARS-5 (CEM Corpn., USA)] till the change in the reactor pressure became constant (~15-30 minutes). The excess benzyl amine was distilled out under reduced pressure and the residue obtained was column chromatographed over silica gel using pet. ether:ethyl acetate gradient to obtain the Wolff-rearranged products **56–67**. The solid compounds obtained were recrystallized from aqueous ethanol and the literature melting points are noted in parentheses.

2.6.3.1 *N*-benzyltridecanamide (56):



56

Chemical Formula: $C_{20}H_{33}NO$, 303

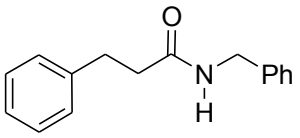
Nature: Yellowish oil

IR ($CHCl_3$): ν 3280, 1638 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.15-7.4 (m, 5H). 5.75 (br.s, 1H), 4.5 (d, *J* = 8 Hz, 2H), 2.2-2.4 (m, 2H), 1.55-1.8 (m, 2H), 1.15-1.45 (m, 18H), 0.8-1.0 (t, *J* = 6 Hz, 3H).

MS (EI) *m/e* (rel. intensity): 303 (M^+, 42), 218 (8), 204 (10), 176 (8), 162 (54), 149 (100), 148 (50), 106 (35), 91 (55).

2.6.3.2 *N*-benzyl-3-phenylpropanamide (57):



57

Chemical Formula: $C_{16}H_{17}NO$, 239

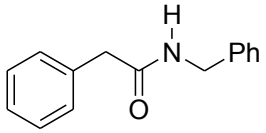
Nature: Yellowish oil

IR ($CHCl_3$): ν 3275, 1634 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.1–7.45 (m, 10H) 5.79 (br.s, 1H), 4.4 (d, *J* = 6 Hz, 2H), 3.01 (t, *J* = 7 Hz, 2H), 2.53 (t, *J* = 7 Hz, 2H).

MS (EI) *m/e* (rel. intensity): 240 (M^++1, 9), 239 (M^+, 52), 148 (60), 107 (50), 106 (48), 105 (55), 104 (25), 91 (100), 77 (30).

2.6.3.3 *N*-benzyl-2-phenylacetamide (58):



58

Chemical Formula: $C_{15}H_{15}NO$, 225

Nature: Yellowish solid

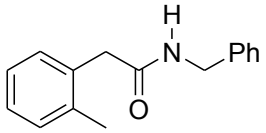
M.P.: 117 ºC [Lit[75] 119 ºC]

IR ($CHCl_3$): ν 3271, 1630 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.55–7.15 (m, 10H), 5.9 (br.s, 1H), 4.4 (d, *J* = 6 Hz, 2H), 3.62 (s, 2H).

MS (EI) *m/e* (rel. intensity): 225 (M^+, 46), 104 (5), 91 (100), 77 (10), 65 (20).

2.6.3.4 *N*-benzyl-2-*o*-tolylacetamide (59):



59

Chemical Formula: $C_{16}H_{17}NO$, 239

Nature: Yellowish solid

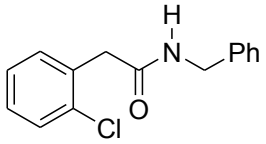
M.P.: 110 ºC [Lit[76] 115 ºC]

IR ($CHCl_3$): ν 3274, 1640 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.15–7.4 (m, 9H), 5.72 (br.s, 1H), 4.46 (d, *J* = 6 Hz, 2H), 3.7 (s, 2H), 2.34 (s, 3H).

MS (EI) *m/e* (rel. intensity): 239 (M^+, 78), 106 (48), 105 (100), 91 (72), 77 (12).

2.6.3.5 *N*-benzyl-2-(2-chlorophenyl)acetamide (60):



60

Chemical Formula: $C_{15}H_{14}ClNO$, 259

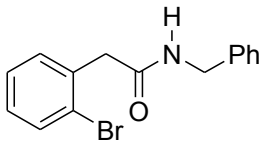
Nature: Yellowish oil

IR ($CHCl_3$): ν 3311, 1665 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.15–7.4 (m, 9H), 5.93 (br.s, 1H), 4.42 (d, *J* = 6 Hz, 2H), 3.72 (s, 2H).

MS (EI) *m/e* (rel. intensity): 261 (M^+, 4), 259 (M^+, 12), 224 (35), 139 (35), 125 (42), 91 (100), 77 (5).

2.6.3.6 *N*-benzyl-2-(2-bromophenyl)acetamide (61)



61

Chemical Formula: $C_{15}H_{14}BrNO$, 303

Nature: Yellowish solid

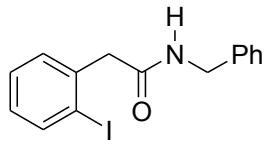
M.P.: 130 ºC [Lit[77] 132 ºC]

IR ($CHCl_3$): ν 3267, 1637 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.15–7.4 (m, 9H), 5.93 (br.s, 1H), 4.42 (d, *J* = 6 Hz, 2H), 3.72 (s, 2H).

MS (EI) *m/e* (rel. intensity): 304 (M^+, 2), 303 (M^+, 3), 224 (26), 135 (34), 91 (100), 85 (35).

2.6.3.7 *N*-benzyl-2-(2-iodophenyl)acetamide (62):



62

Chemical Formula: $C_{15}H_{14}INO$, 351

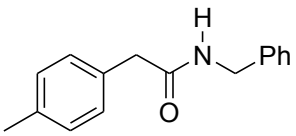
Nature: Yellowish oil

IR ($CHCl_3$): ν 3267, 1630 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.91 (d, *J* = 9 Hz, 1H), 7.2–7.5 (m, 7H), 6.9–7.1 (m, 1H), 5.75 (br.s, 1H), 4.48 (d, *J* = 6 Hz, 2H), 3.8 (s, 2H).

MS (EI) *m/e* (rel. intensity): 351 (M^+, 2), 224 (85), 223 (40), 217 (55), 181 (12), 165 (5), 104 (22), 91 (96), 90 (100), 77 (5).

2.6.3.8 *N*-benzyl-2-*p*-tolylacetamide (63):



63

Chemical Formula: $C_{16}H_{17}NO$, 239

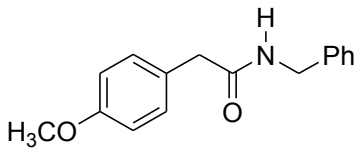
Nature: Yellowish solid

M.P.: 136 ºC [Lit[76] 137 ºC]

IR ($CHCl_3$): ν 3283, 1645 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.1–7.4 (m, 9H), 6 (br.s, 1H), 4.4 (d, *J* = 6 Hz, 2H), 3.62 (s, 2H), 2.4 (s, 3H).

2.6.3.9 *N*-benzyl-2-(4-methoxyphenyl)acetamide (64):



64

Chemical Formula: $C_{16}H_{17}NO_2$, 255

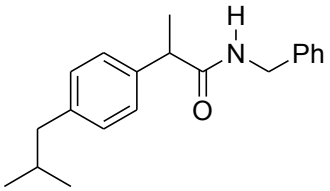
Nature: Yellowish solid

M.P.: 136 ºC [Lit[76] 137 ºC]

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.17–7.36 (m, 7H), 6.88 (d, *J* = 12 Hz, 2H), 5.71 (br.s, 1H), 4.4 (d, *J* = 6 Hz, 2H), 3.8 (s, 3H), 3.58 (s, 2H).

MS (EI) *m/e* (rel. intensity): 255 (M^+, 48), 122 (40), 121 (100), 106 (10), 91 (46), 77 (25), 65 (12).

2.6.3.10 *N*-benzyl-2-(4-isobutylphenyl)propanamide (65):



65

Chemical Formula: $C_{20}H_{25}NO$, 295

Nature: Yellowish oil

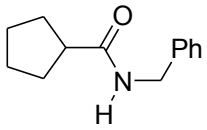
IR ($CHCl_3$): ν 3287, 1646 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.05–7.4 (m, 9H). 6.4 (br.s, 1H), 4.34 (d, *J* = 6 Hz, 2H), 3.64 (q, *J* = 6 Hz, 1H), 2.5 (d, *J* = 8 Hz, 2H), 1.84 (m, 1H), 1.53 (d, *J* = 6 Hz, 3H), 0.89 (d, *J* = 6 Hz, 6H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 174.7 (C), 2x140.7 (C), 138.5 (C), 2x129.6 (CH), 128.6 (CH), 127.4 (CH), 127.4 (CH), 127.3 (CH), 46.6 (CH), 44.8 (CH_2), 43.26 (CH_2), 30.0 (CH_3), 22.2 (CH_3), 18.3 (CH_3).

MS (EI) *m/e* (rel. intensity): 295 (M^+, 20), 162 (40), 161(65), 119 (65), 117 (38), 105 (42), 91 (100), 77 (18), 65 (12).

2.6.3.11 *N*-benzylcyclopentanecarboxamide (66):



66

Chemical Formula: $C_{13}H_{17}NO$, 203

Nature: Yellowish solid

M.P.: 94 ºC [Lit[78] 95 ºC]

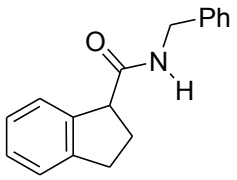
IR ($CHCl_3$): ν 3283, 1626 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.2–7.4 (m, 5H), 6.0 (br.s, 1H), 4.41(d, *J* = 6 Hz, 2H), 2.45–2.65 (m, 1H), 1.5–1.95 (m, 8H),

^{13}C NMR ($CDCl_3$, 50 MHz): δ 176.3 (C), 138.6 (C), 128.0 (CH), 126.9 (CH), 126.9 (CH), 126.6 (CH), 45.0 (CH), 42.7 (CH_2), 42.7 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 27.6 (CH_2), 27.6 (CH_2).

MS (EI) *m/e* (rel. intensity): 204 (M^++1, 12), 203 (M^+, 98), 175 (12), 162 (30), 91 (90), 77 (10), 69 (35), 65 (12).

2.6.3.12 *N*-benzyl-2,3-dihydro-1*H*-indene-1-carboxamide (67):



67

Chemical Formula: $C_{17}H_{17}NO$, 251

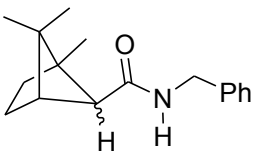
Nature: Yellowish oil

IR ($CHCl_3$): ν 3236, 1631 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.1–7.4 (m, 9H), 5.93 (br.s, 1H), 4.45 (d, *J* = 6 Hz, 1H), 4.02 (t, *J* = 6 Hz, 1H), 2.88–3.16 (m, 2H), 2.36–2.5 (m, 2H).

MS (EI) *m/e* (rel. intensity): 252 (M^++1, 7), 251 (M^+, 35), 118 (100), 116 (43), 91 (60), 77 (5), 65 (10).

2.6.3.13 data of 70:



70

Chemical Formula: $C_{17}H_{23}NO$, 257

Nature: Yellowish oil

Yield: 73 %

IR ($CHCl_3$): ν 3309, 1634, 1516 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.25-7.45 (m, 10 H, both diastereoisomers), 5.79 (br.s, 1H, NH), 5.51 (br.s, 1H, NH), 4.46 (d, *J* = 6 Hz, 2H), 4.45 (d, *J* = 6 Hz, 2H), 2.36 (s, 1H), 2.71 (s, 1H), 2.27 (br.s, 1H), 2.07 (br.s, 1H), 1.4-1.8 (m, 8H, -CH_2-CH_2-, both diastereoisomers), 1.19 (s, 3H, CH_3), 1.12 (s, 6H, CH_3), (both diastereoisomers) 1.11 (s, 3H, CH_3), 0.74 (s, 3H, CH_3), 0.73 (s, 3H, CH_3).

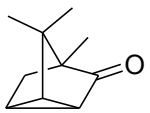
^{13}C NMR ($CDCl_3$, 50 MHz): δ 173.6 (C), 173.0 (C), 138.5 (C), 138.3 (C), 128.4 (CH), 127.5 (CH), 127.1 (CH), 56.7 (CH), 53.0 (C), 52.5 (C), 50.6 (CH), 47.0 (CH), 46.3 (CH), 46.0 (C), 43.0 (C), 42.9 (CH_2), 42.6 (CH_2), 34.1 (CH_2), 26.89 (CH_2), 25.15 (CH_2), 23.6 (CH_2), 20.2 (CH_3), 19.6 (CH_3), 18.3 (CH_3), 16.7 (CH_3), 13.2 (CH_3), 12.5 (CH_3).

MS (EI) *m/e* (rel. intensity): 258 (M^++1, 2), 257 (M^+, 14), 242 (10), 214 (8), 202 (6), 185 (8), 174 (30), 160 (22), 149 (14), 123 (30), 122 (35), 106 (75), 91 (100), 81 (40), 69 (20), 55 (5).

2.6.4 General procedure for the conventional thermolysis:

A mixture α-diazoketones **44–55 & 68** (1 mmol) and anhydrous benzyl amine (5 ml) was refluxed at 180 ºC. Infra-red spectral analysis indicated the total disappearance of the starting α-diazoketones (~10 minutes). The solvent was removed under reduced pressure and the residue obtained was column chromatographed over silica gel using pet. ether/ethyl acetate gradient as eluent which provided an amides **56–67** and **70**.

2.6.4.1 data of 69:



69

Chemical Formula: $C_{10}H_{14}O$, 150

Yield: 43 %

Nature: Yellowish solid

M.P.: 165 ºC [Lit[79] 167 ºC]

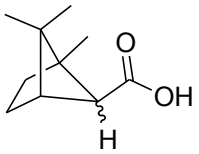
IR ($CHCl_3$): ν 1746 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.9–2.1 (m, 3H), 1.7–1.8 (m, 1H), 1.45-1.55 (m, 1H), 0.96 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 0.80 (s, 3H, CH_3),

^{13}C NMR ($CDCl_3$, 50 MHz): δ 215.5 (C), 48.2 (C), 43.5 (C), 36 (CH_2), 33.7 (CH), 21.2 (CH), 21.2 (CH), 20.7 (CH_3), 20.3 (CH_3), 5.6 (CH_3).

MS (EI) *m/e* (rel. intensity): 150 (M^+, 12), 135 (30), 122 (20), 107 (100), 95 (32), 91 (72), 79 (58), 67 (10).

2.6.5 data of 71:



71

Chemical Formula: $C_{10}H_{16}O_2$, 168

Yield: 62 %

Nature: Yellowish solid

M.P.: 100 ºC [Lit[80] 111 ºC]

IR ($CHCl_3$): ν 3500-2600, 1692 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.75 (bs, 1H, minor diastereoisomer), 2.45 (s, 1H, major diastereoisomer), 2.29 (bs, 1H, minor diastereoisomer), 2.16 (s, 1H, major diastereoisomer), 1.5-1.8 (m, 8H of both diastereoisomer), 1.21(s, 3H, minor diastereoisomer), 1.17 (s, 3H, major diastereoisomer), 1.12 (s, 3H, minor diastereoisomer), 1.10 (s, 3H, major diastereoisomer), 0.78 (s, 3H, minor diastereoisomer), 0.77 (s, 3H, major diastereoisomer).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 181.5, 179.5, 55.8, 54.0, 53.6, 50.2, 47.6, 46.9, 46.5, 43.3, 34.2, 29.3, 25.3, 23.6, 20.4, 19.7, 18.6, 16.9, 12.9, 12.4.

MS (EI) *m/e* (rel. intensity): 168 (M^+), 153, 135, 125, 107, 100, 91.

2.7 References:

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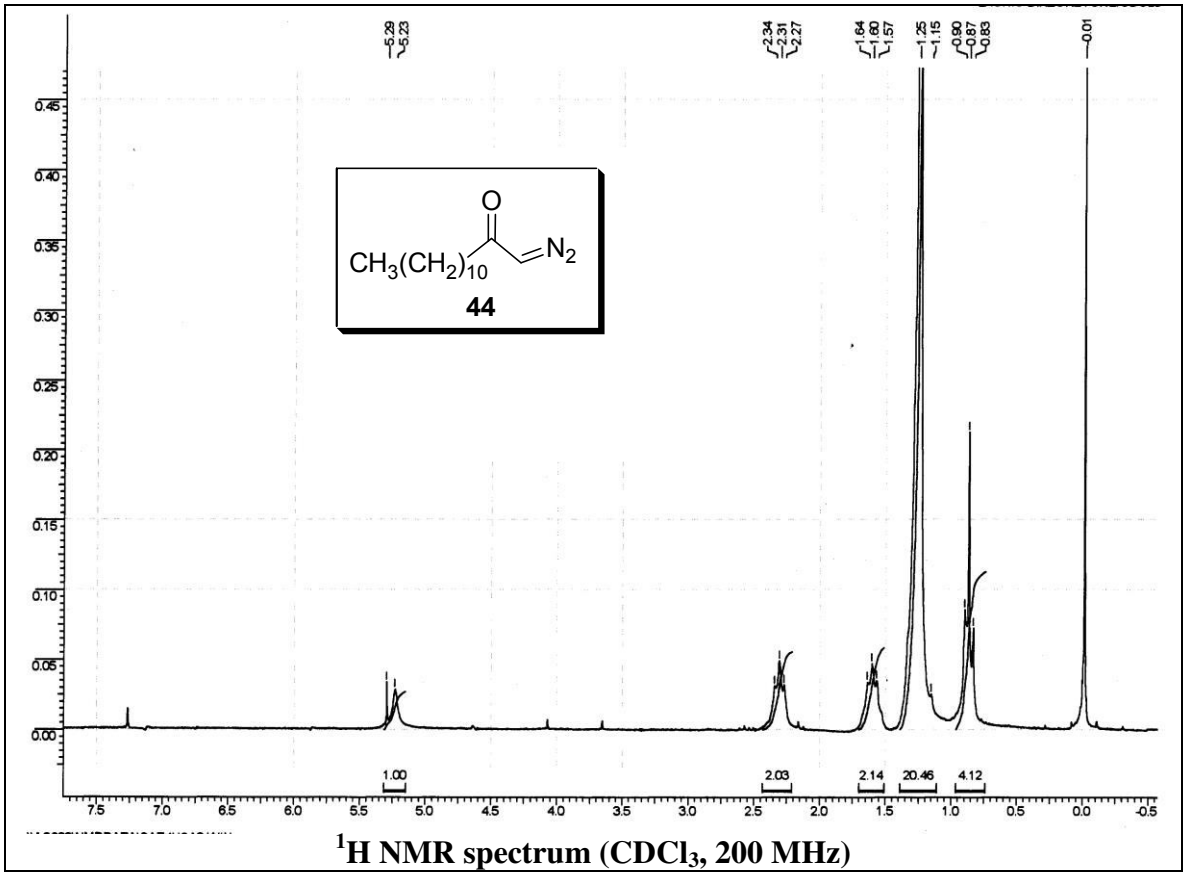
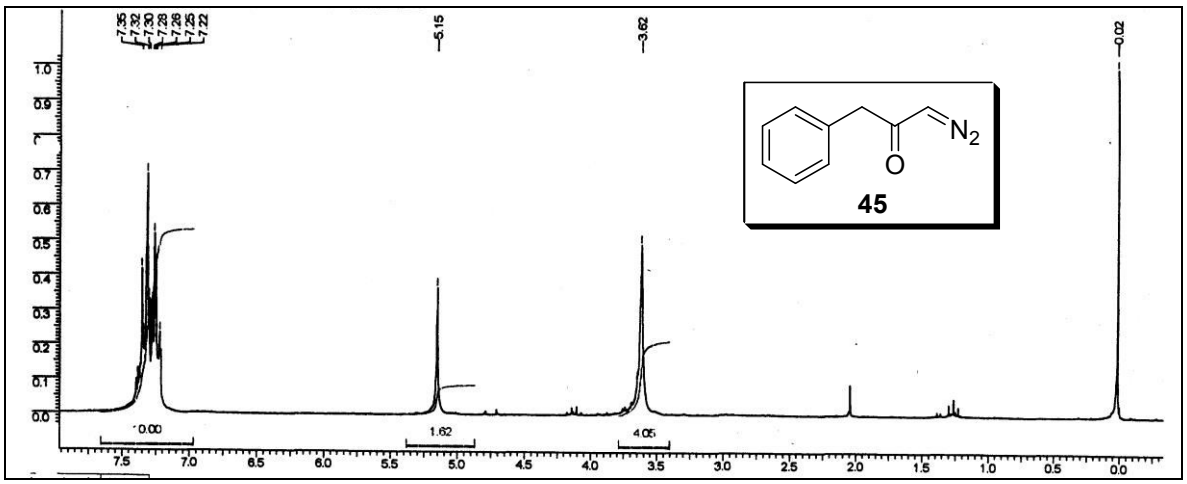
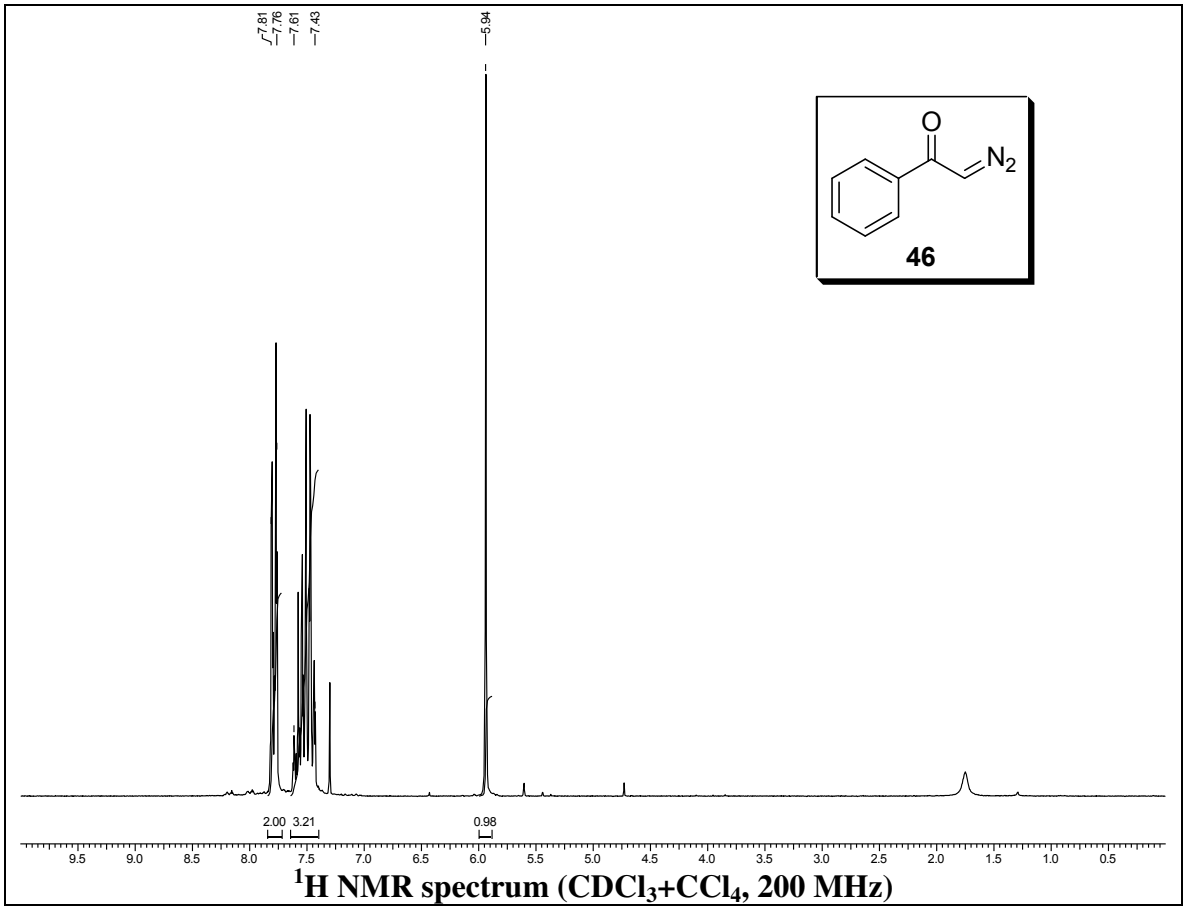
Spectra



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





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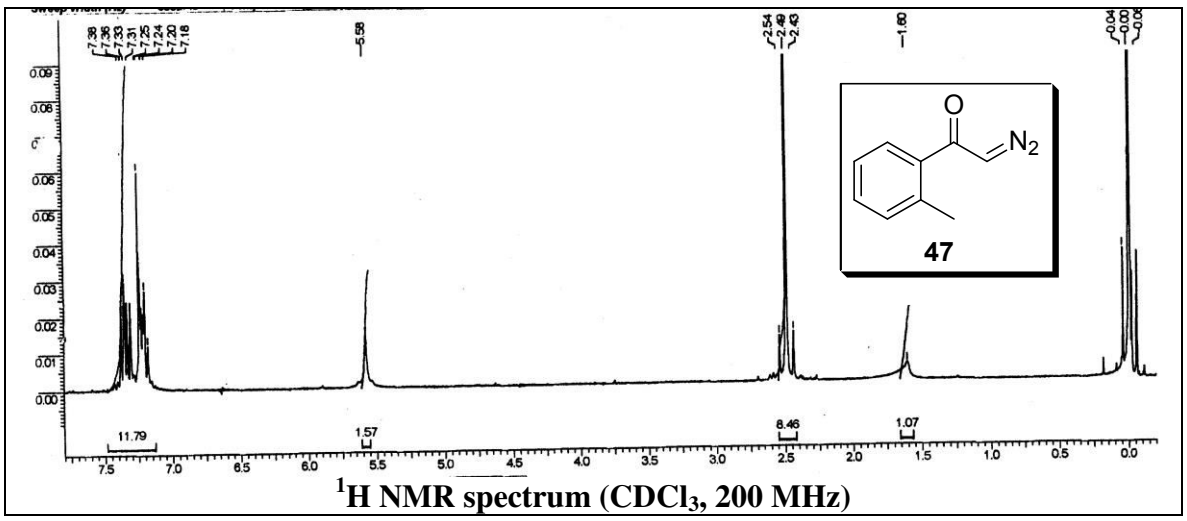

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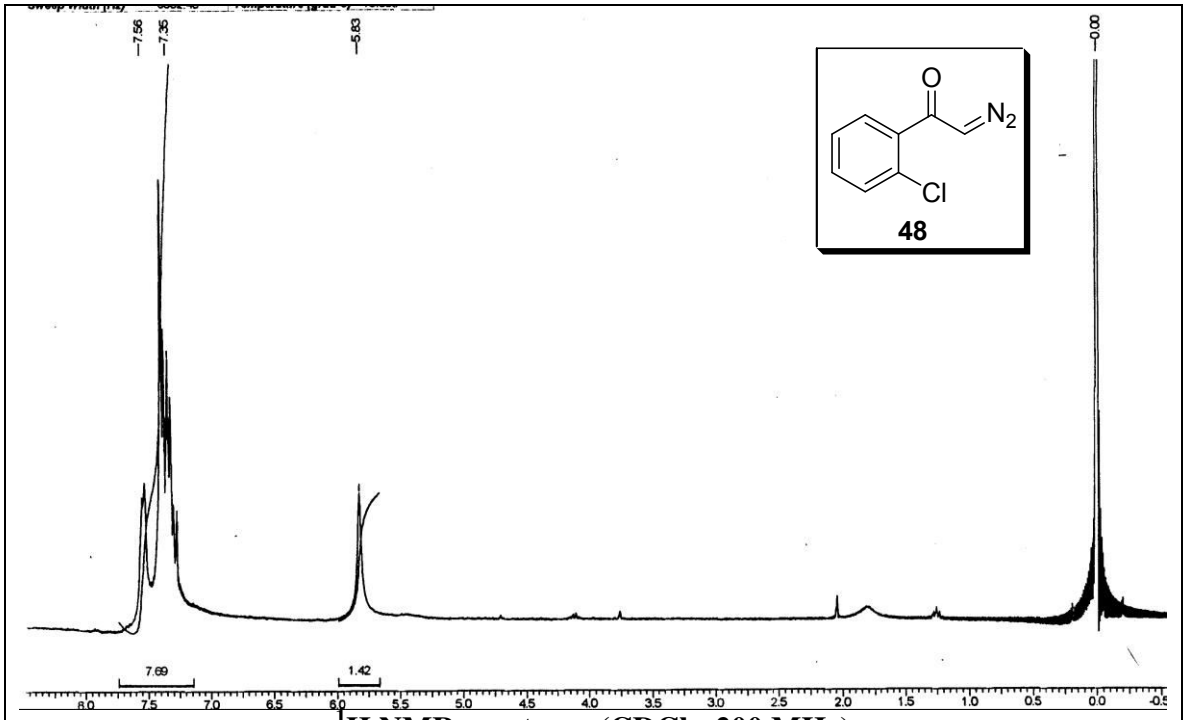

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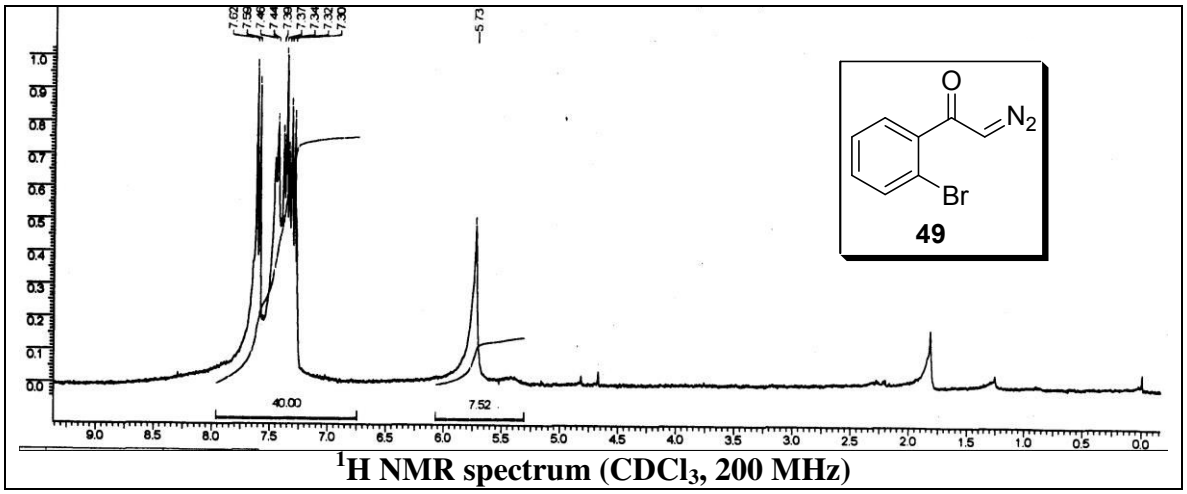

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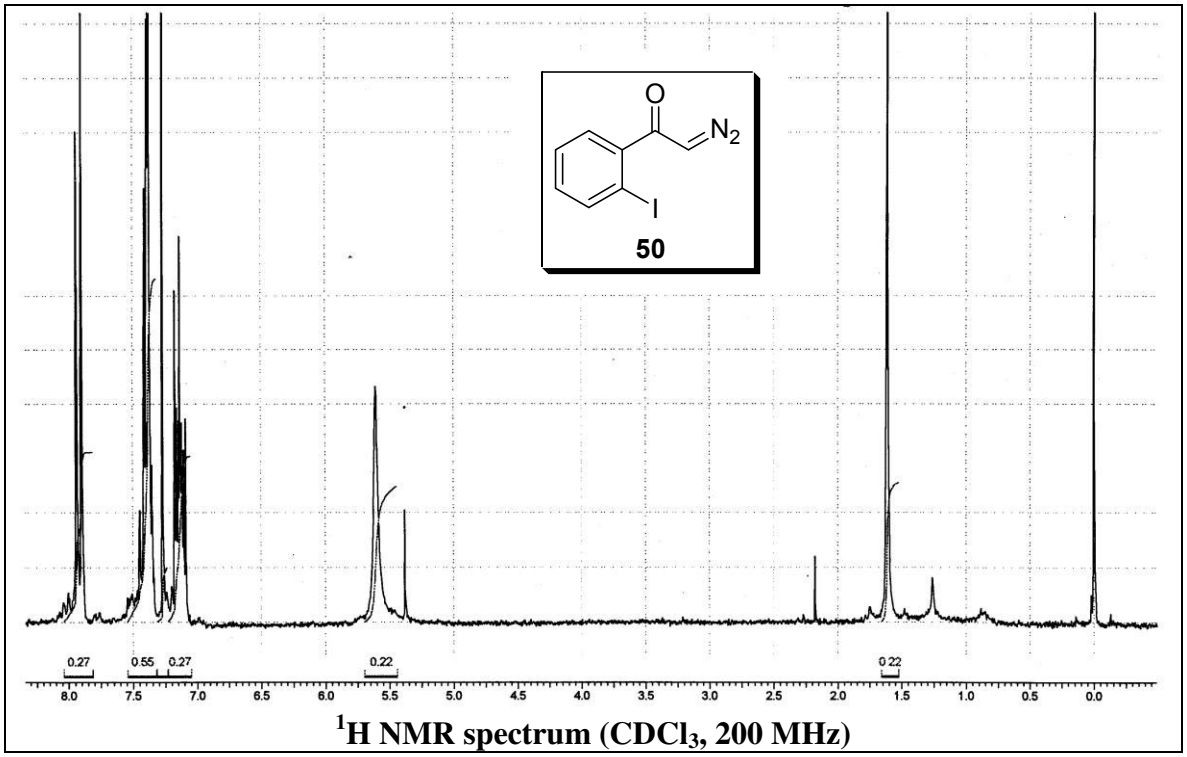

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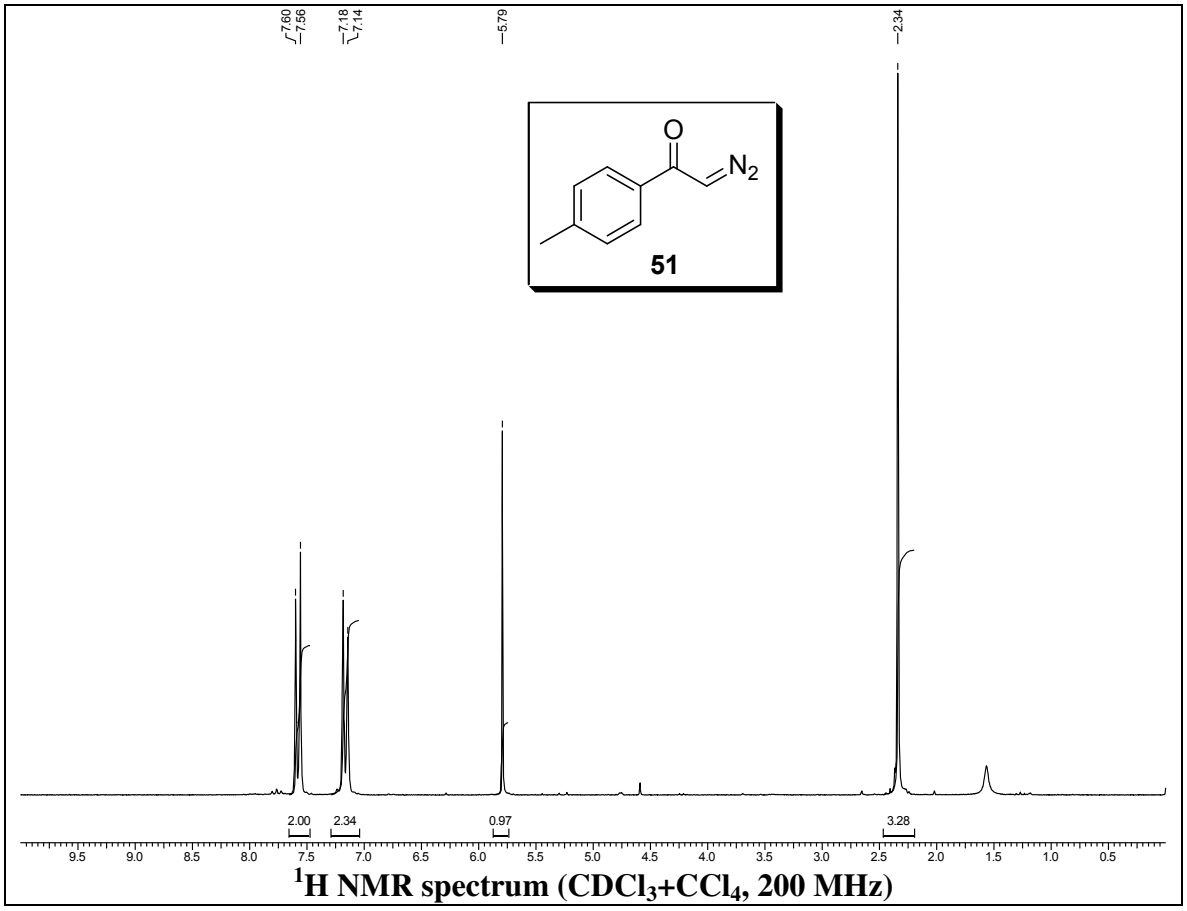

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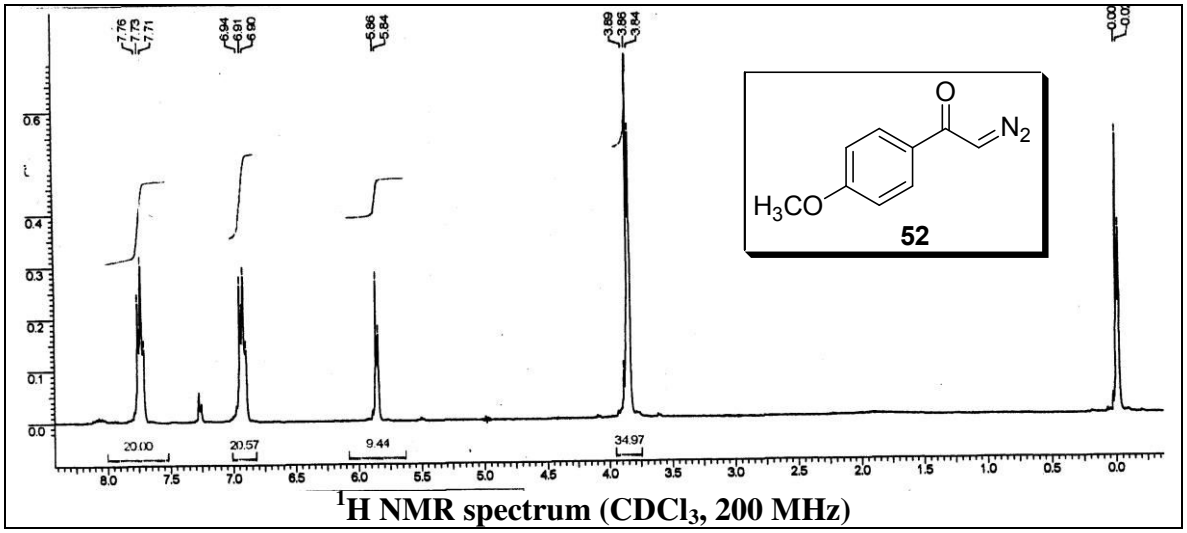

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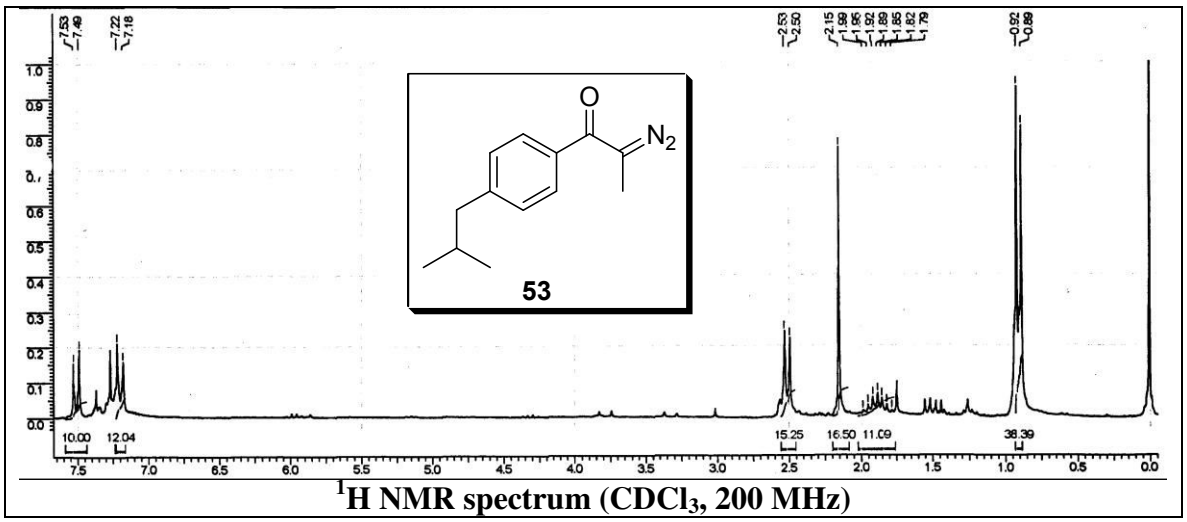

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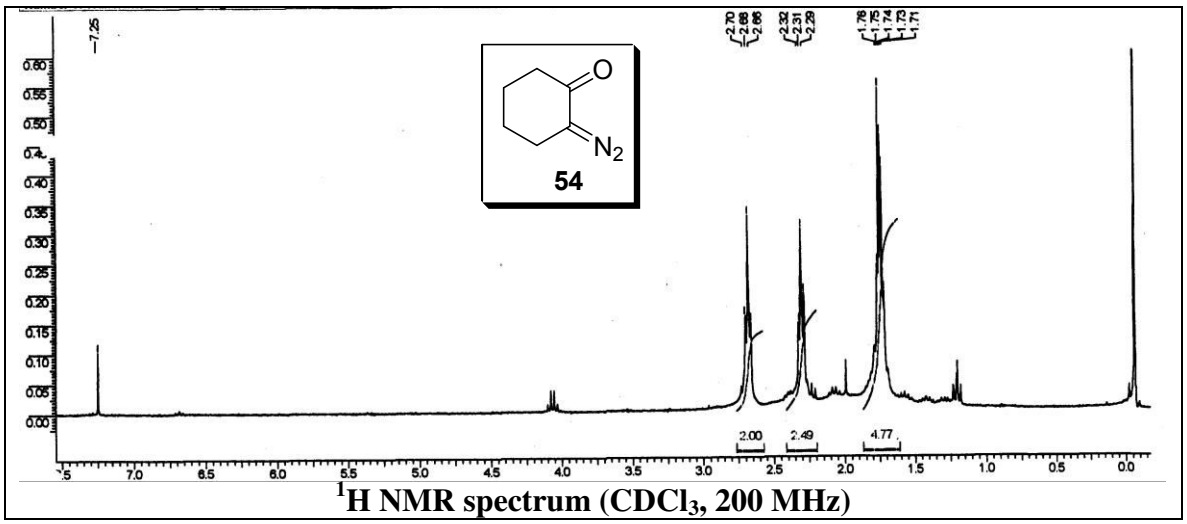

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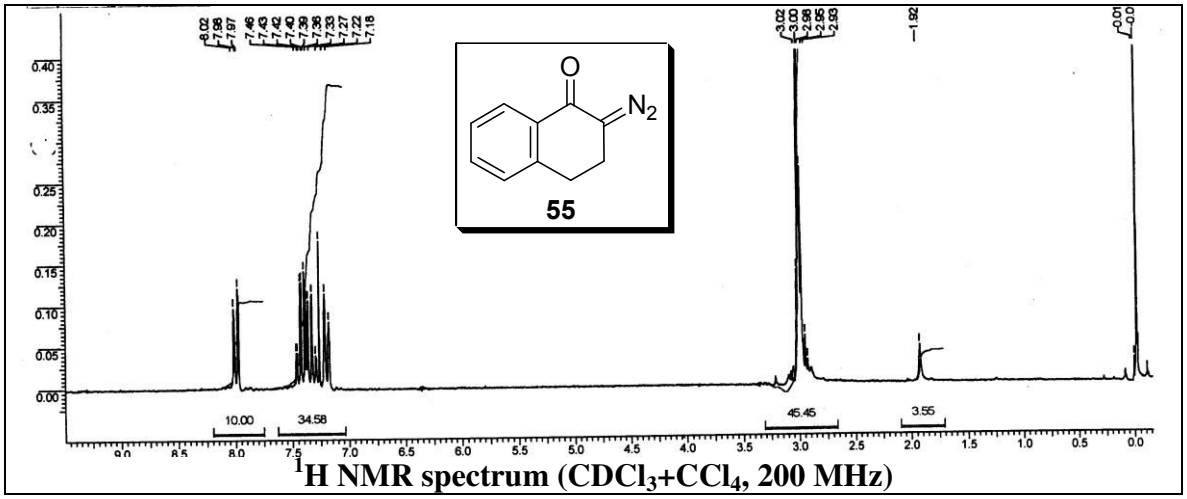

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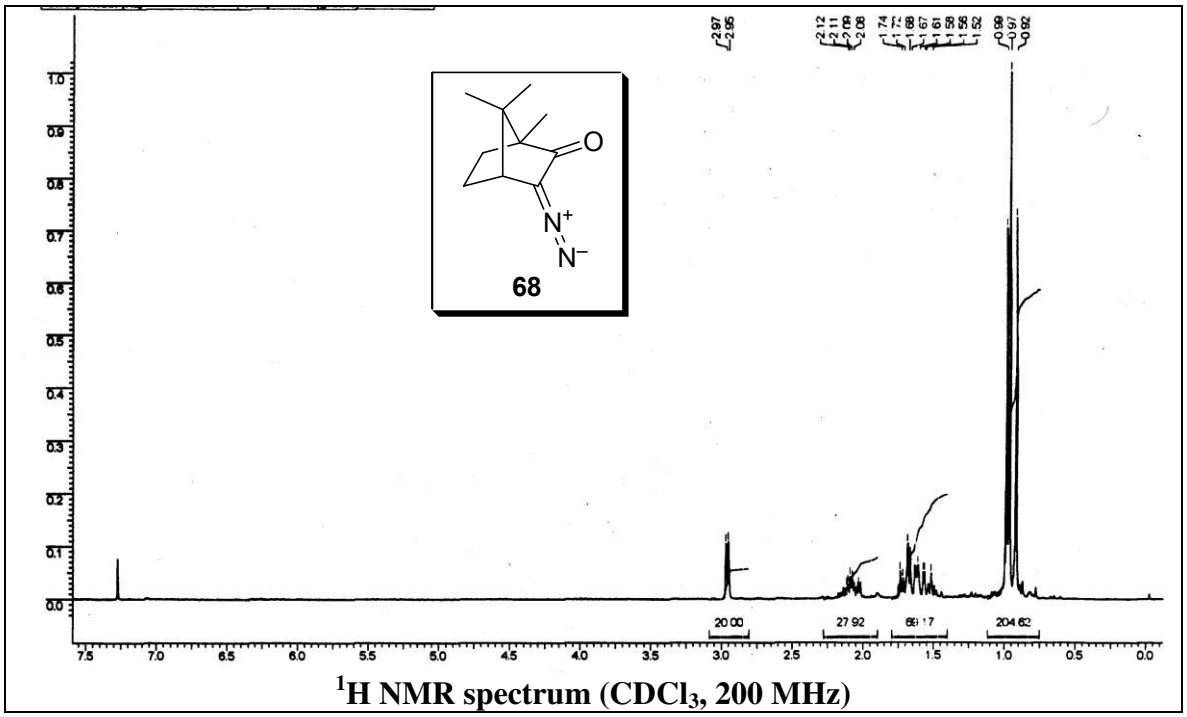

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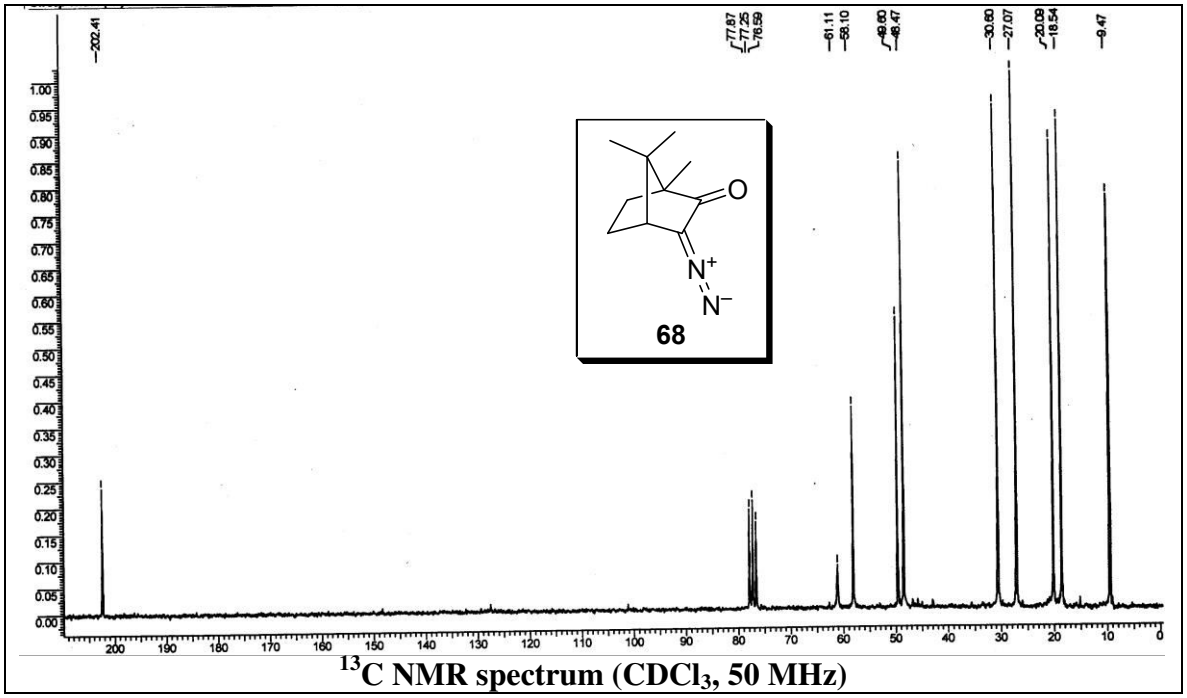

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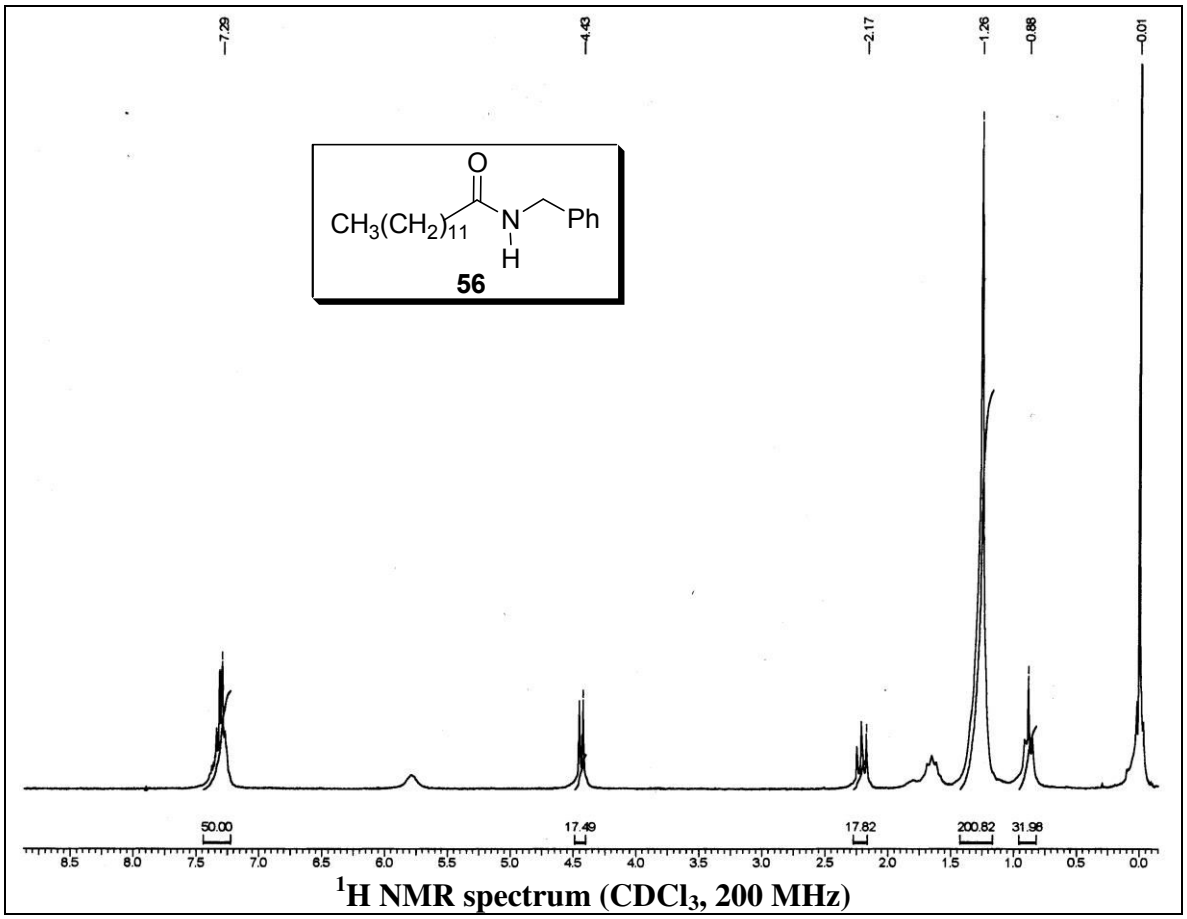

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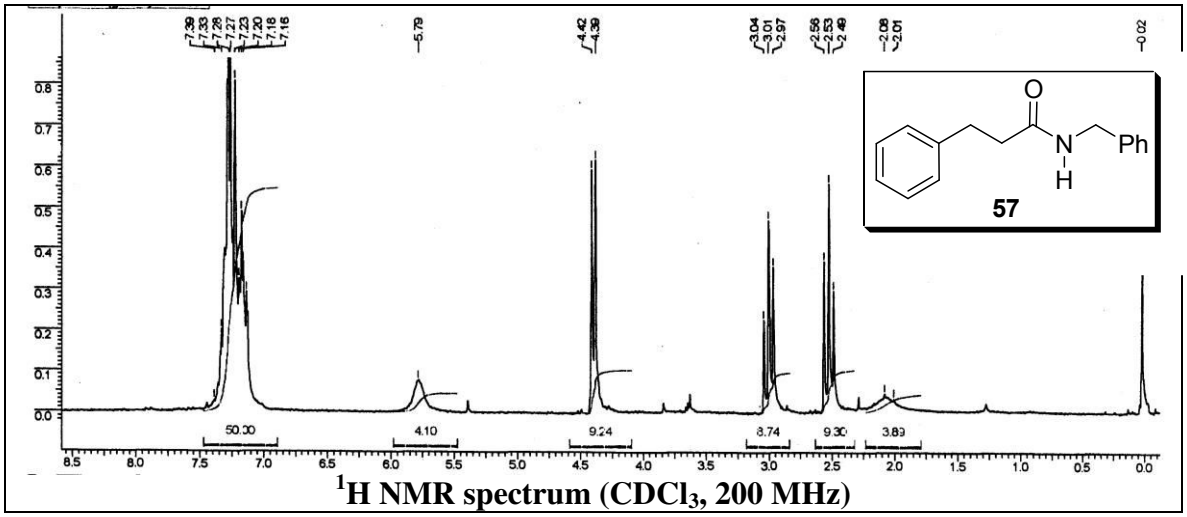

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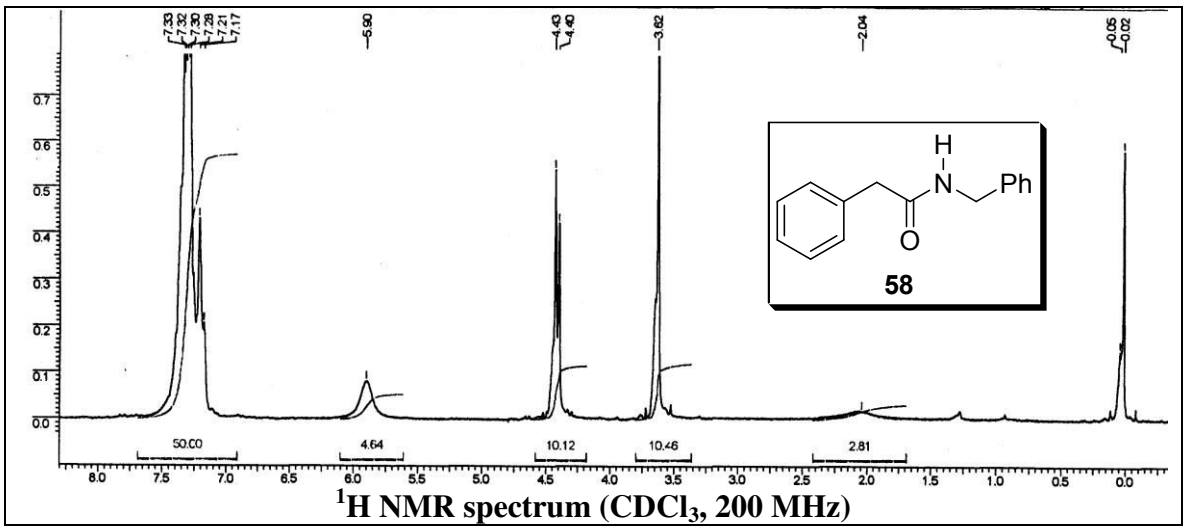

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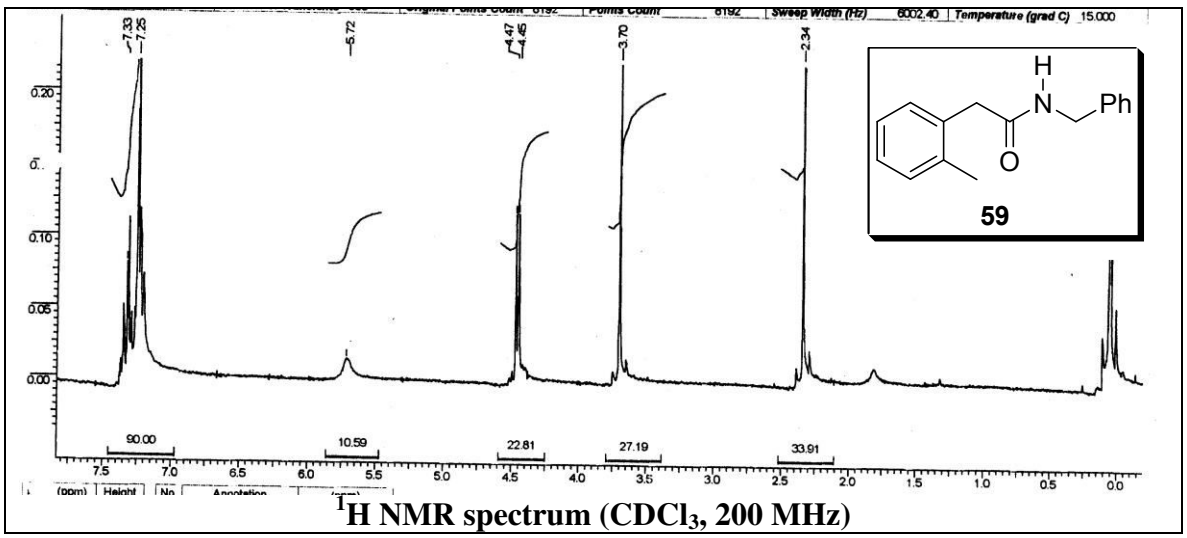

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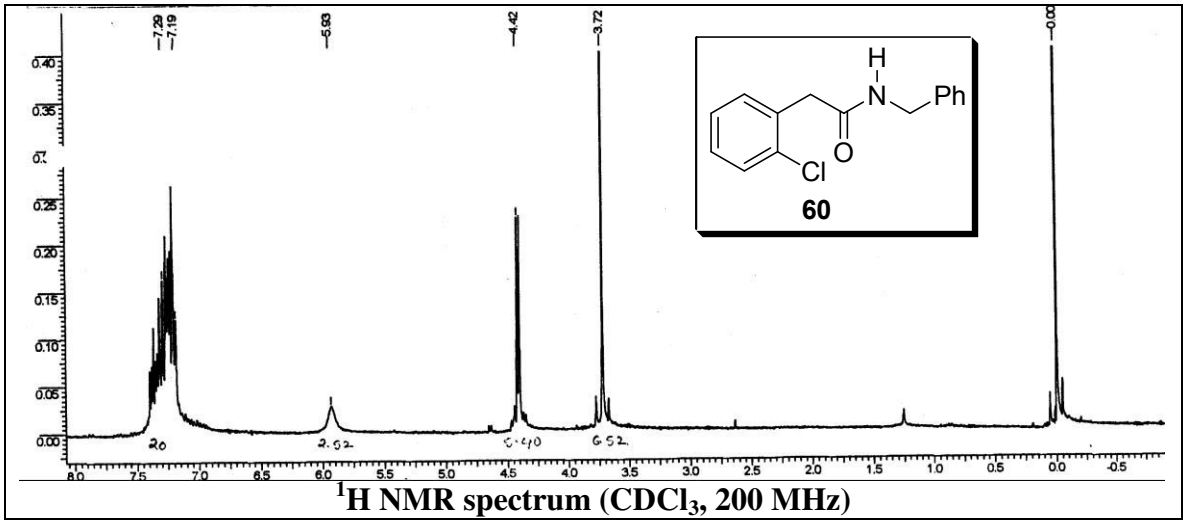

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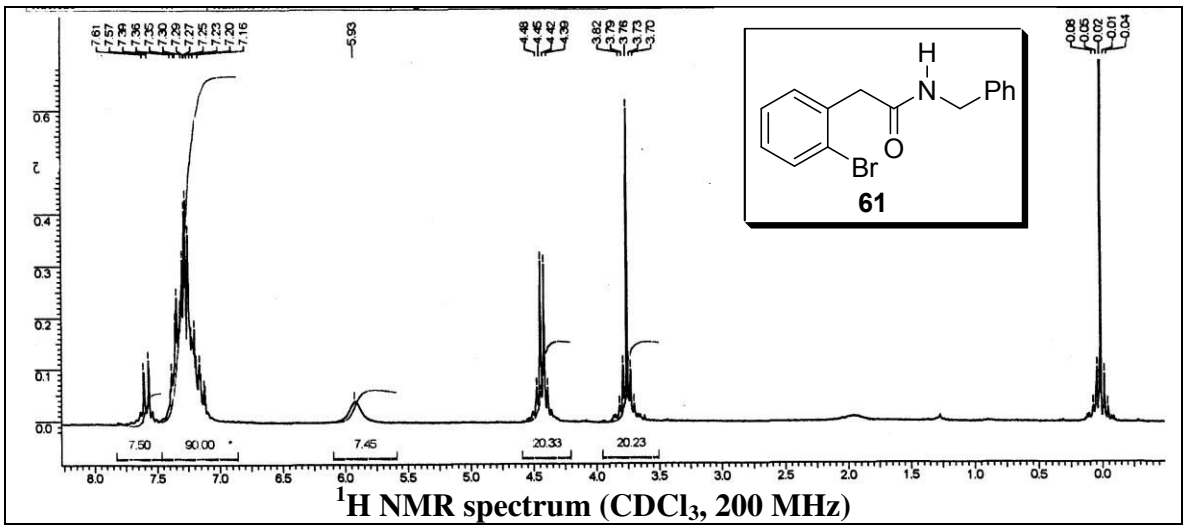

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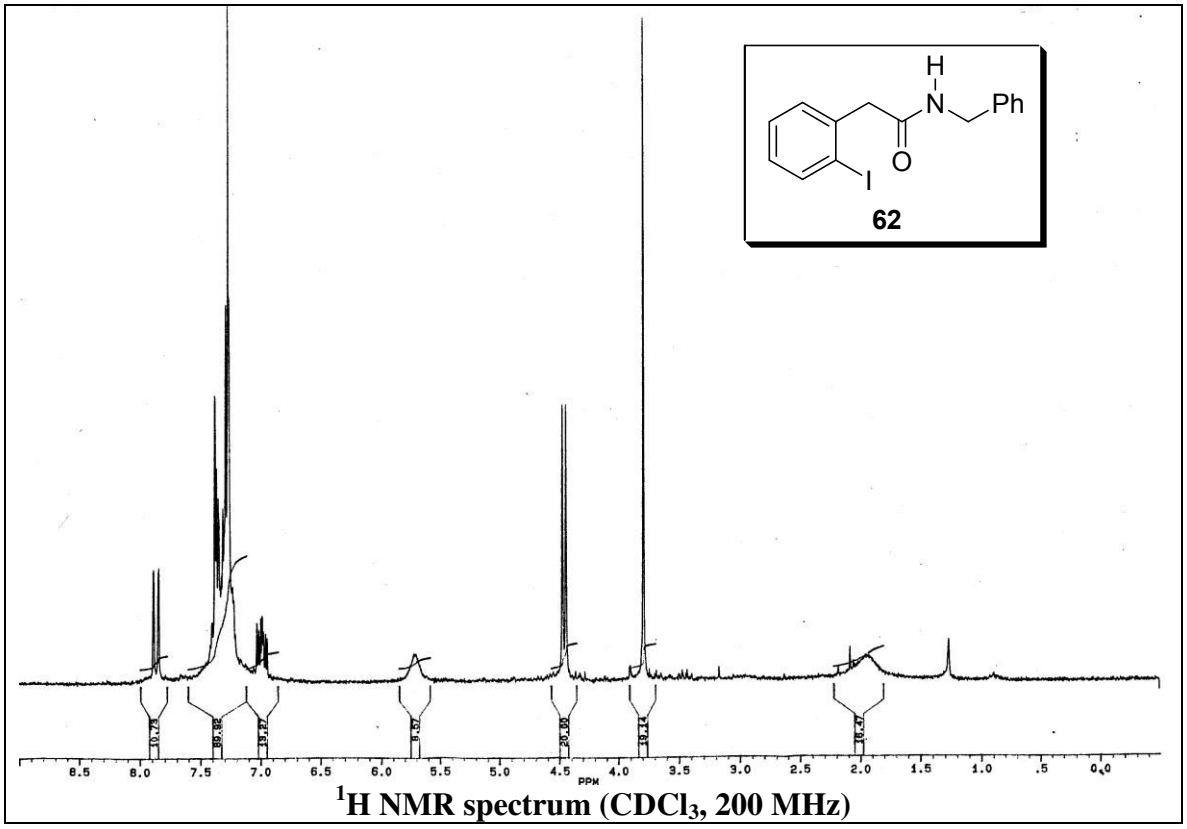

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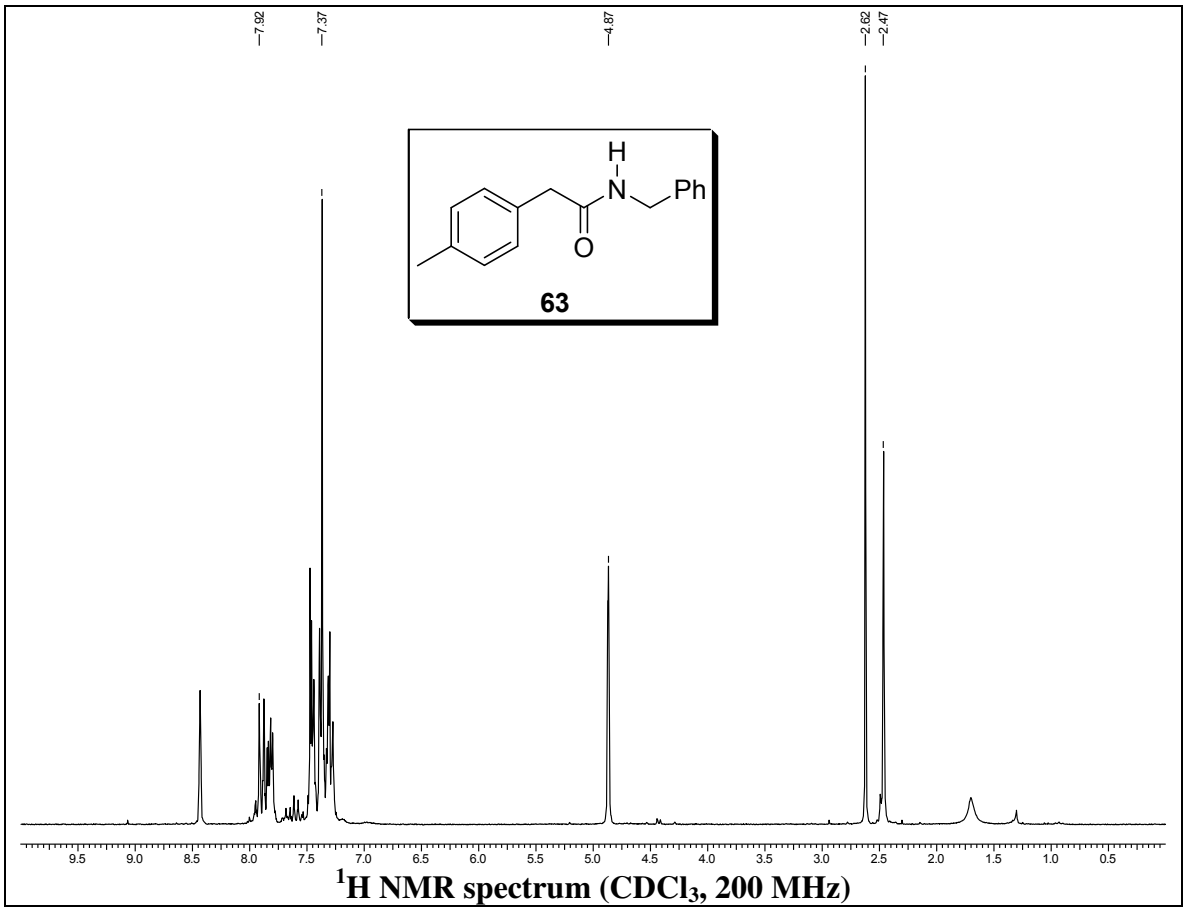

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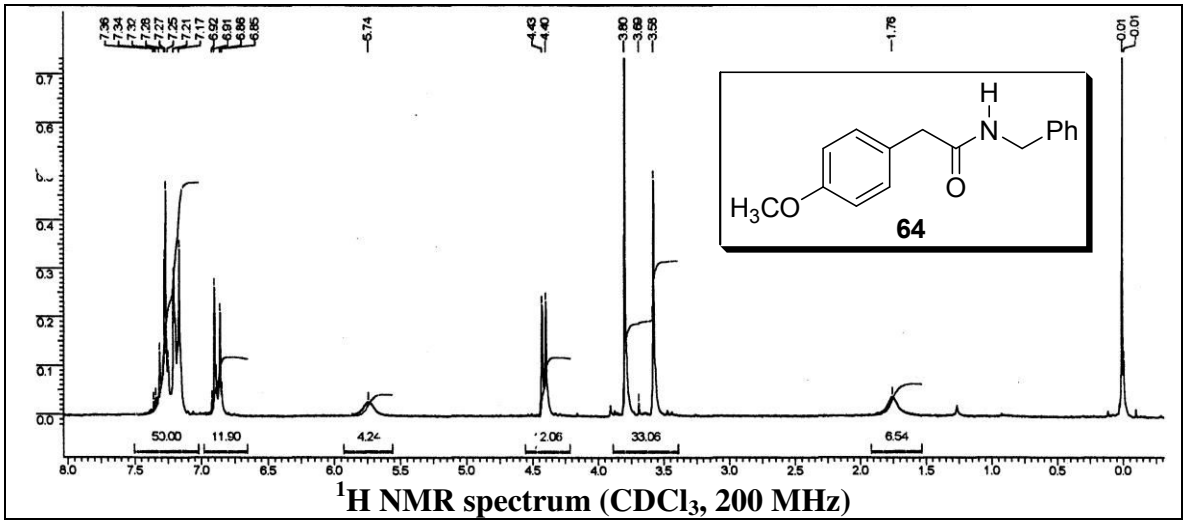

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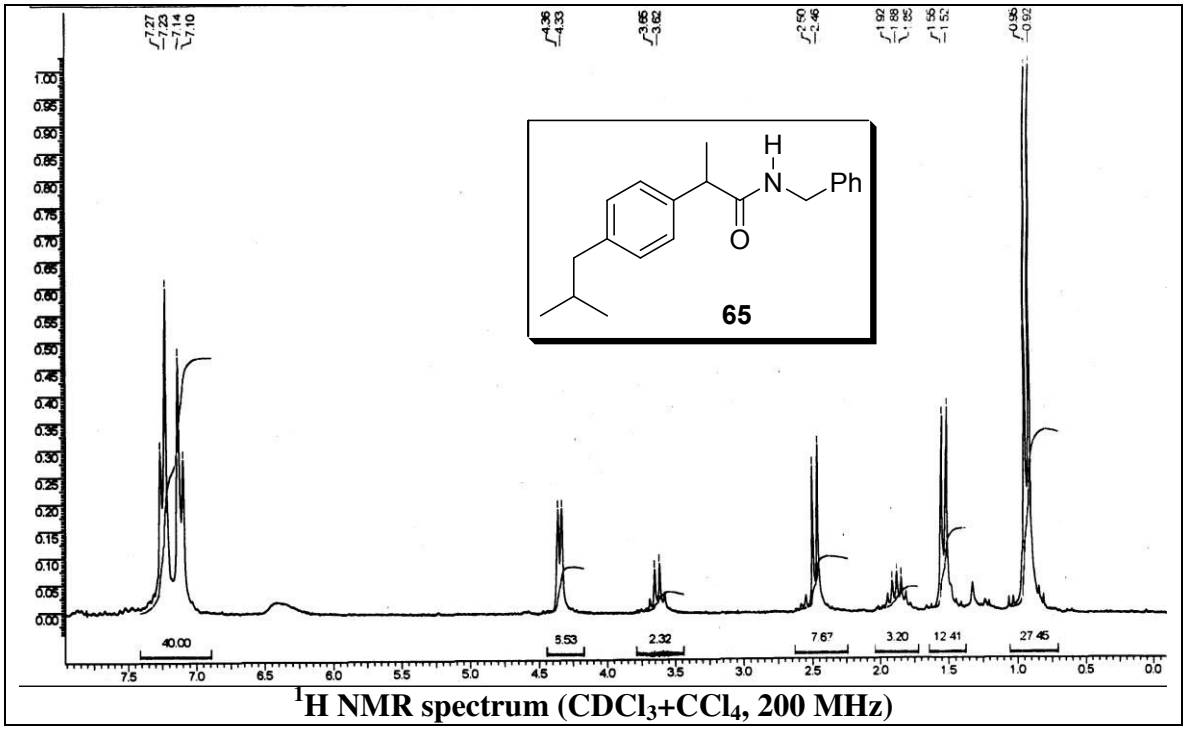

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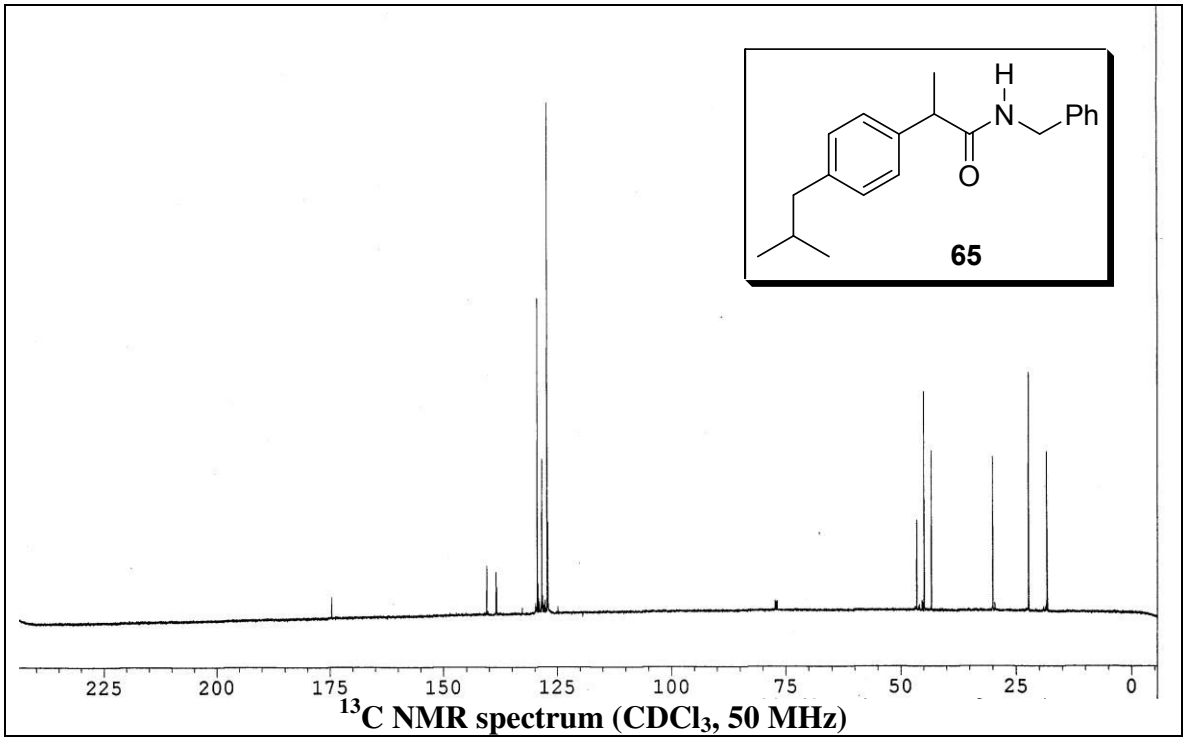

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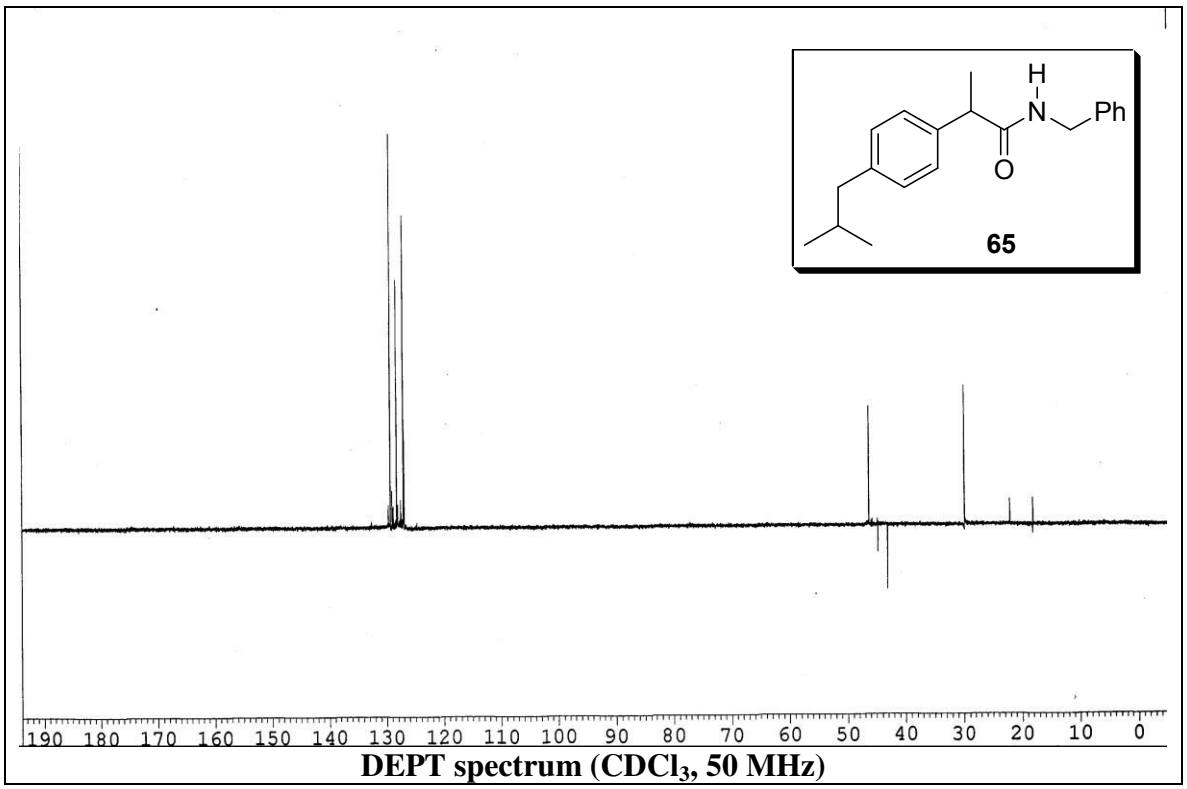
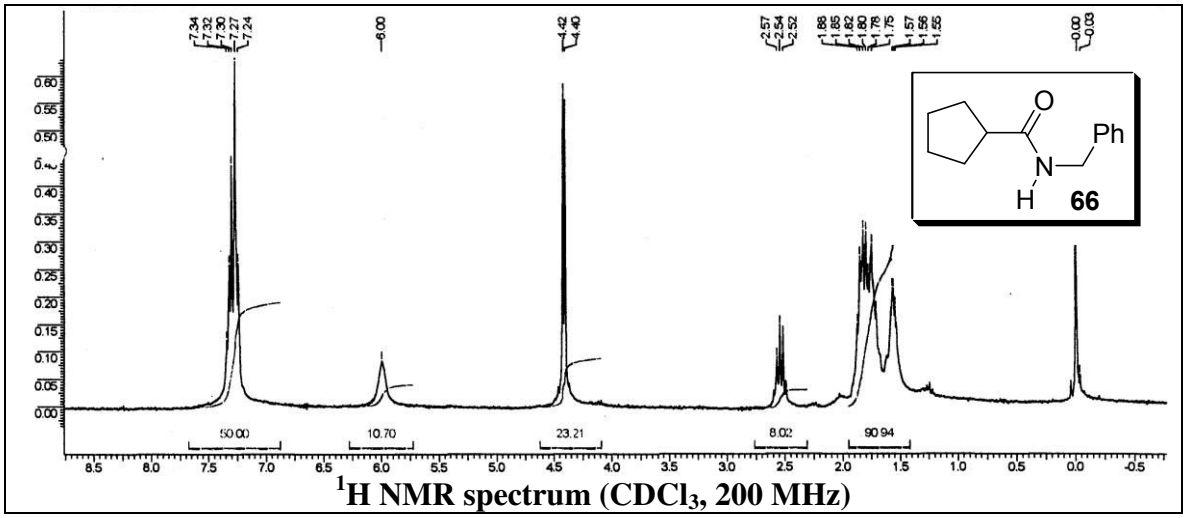
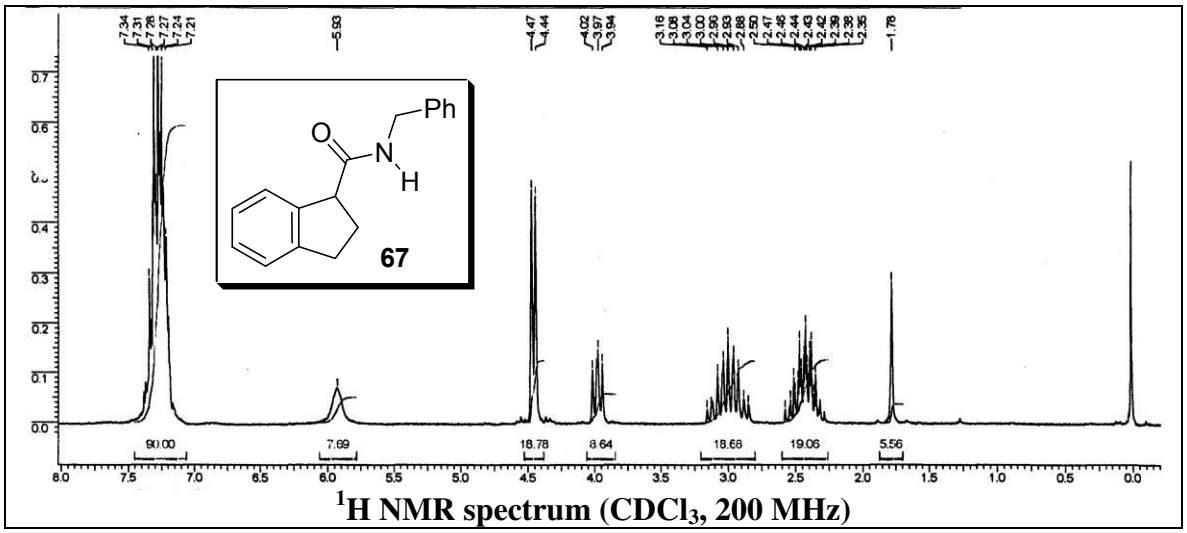


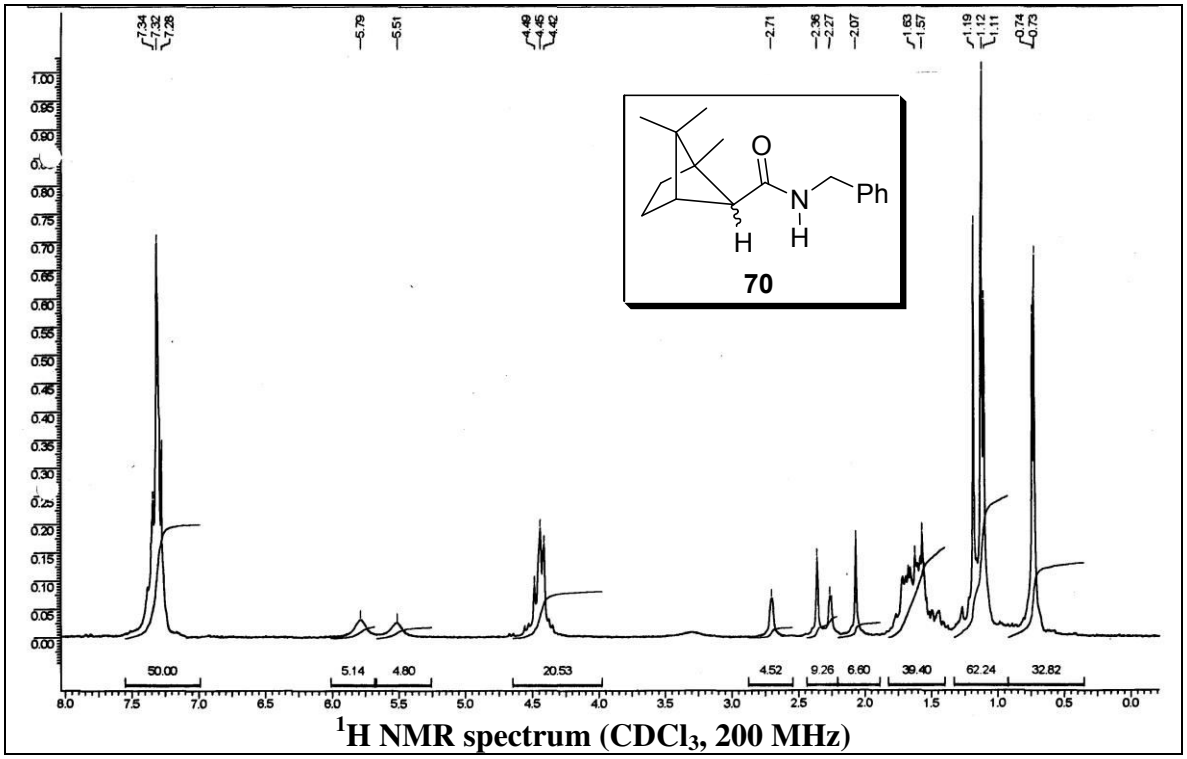
DEPT spectrum ($CDCl_3$, 50 MHz)



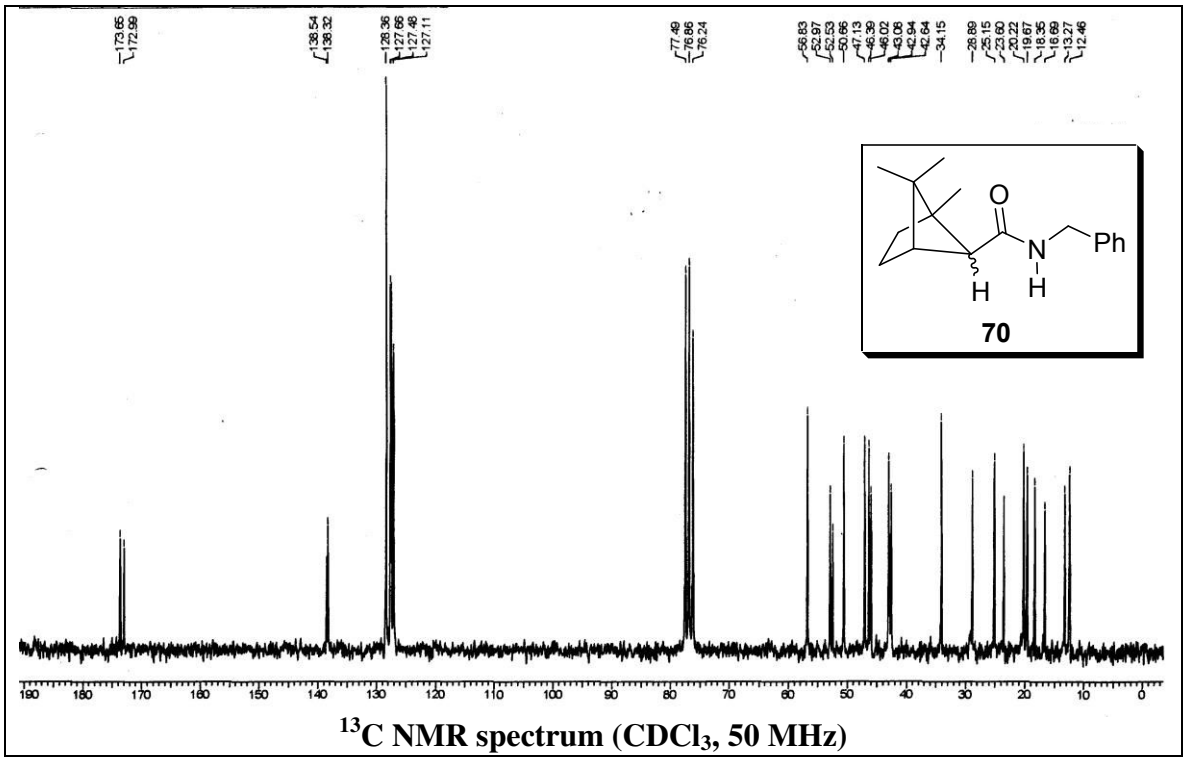
^{1}H NMR spectrum ($CDCl_3$, 200 MHz)



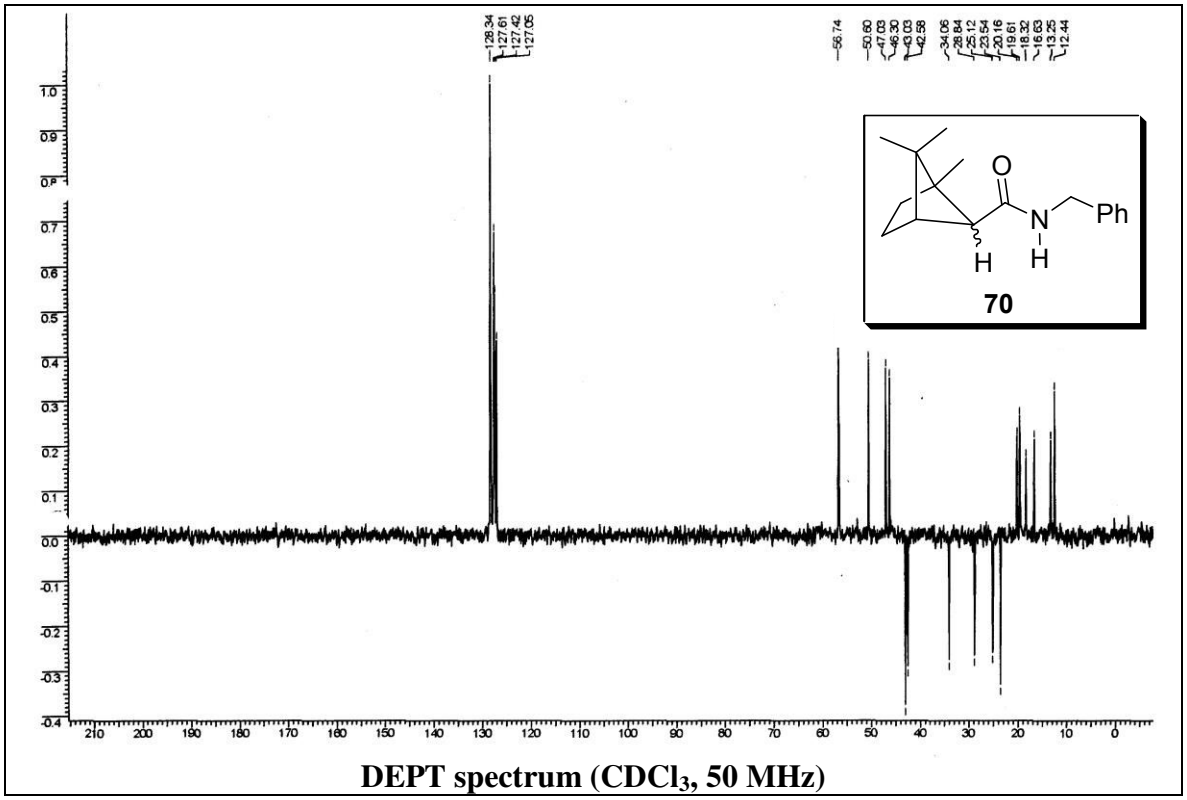
^{1}H NMR spectrum ($CDCl_3$, 200 MHz)



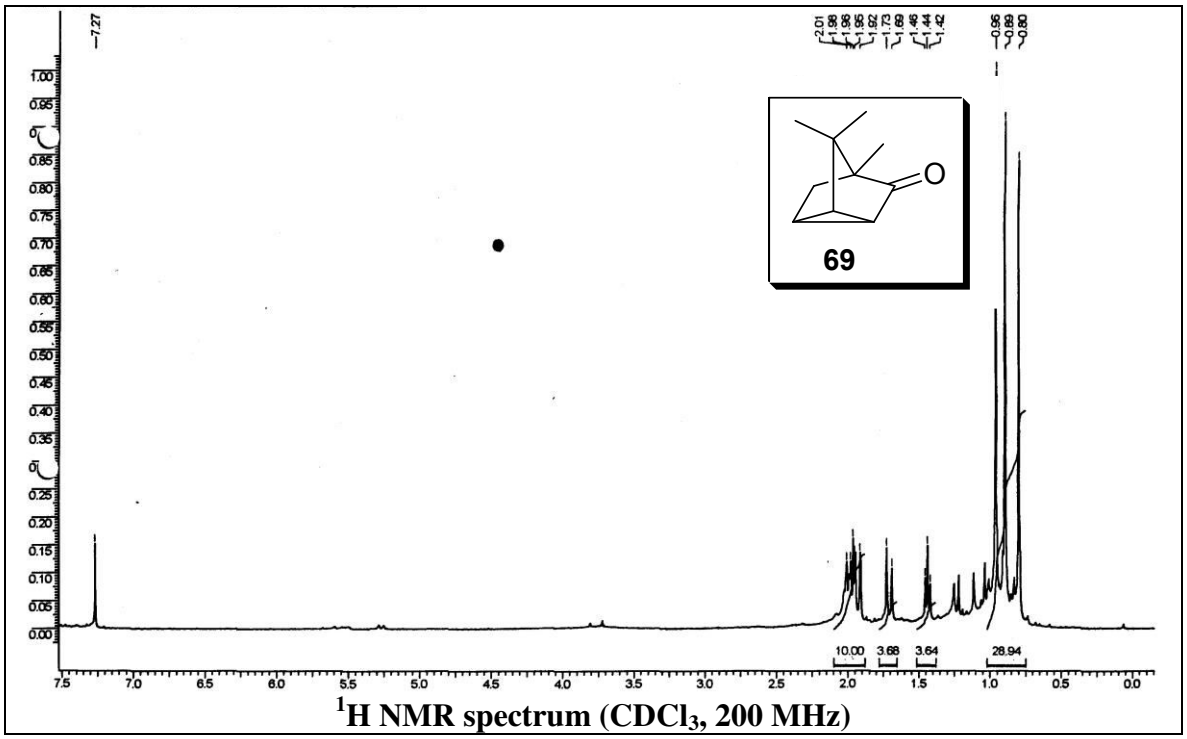
^{1}H NMR spectrum ($CDCl_3$, 200 MHz)



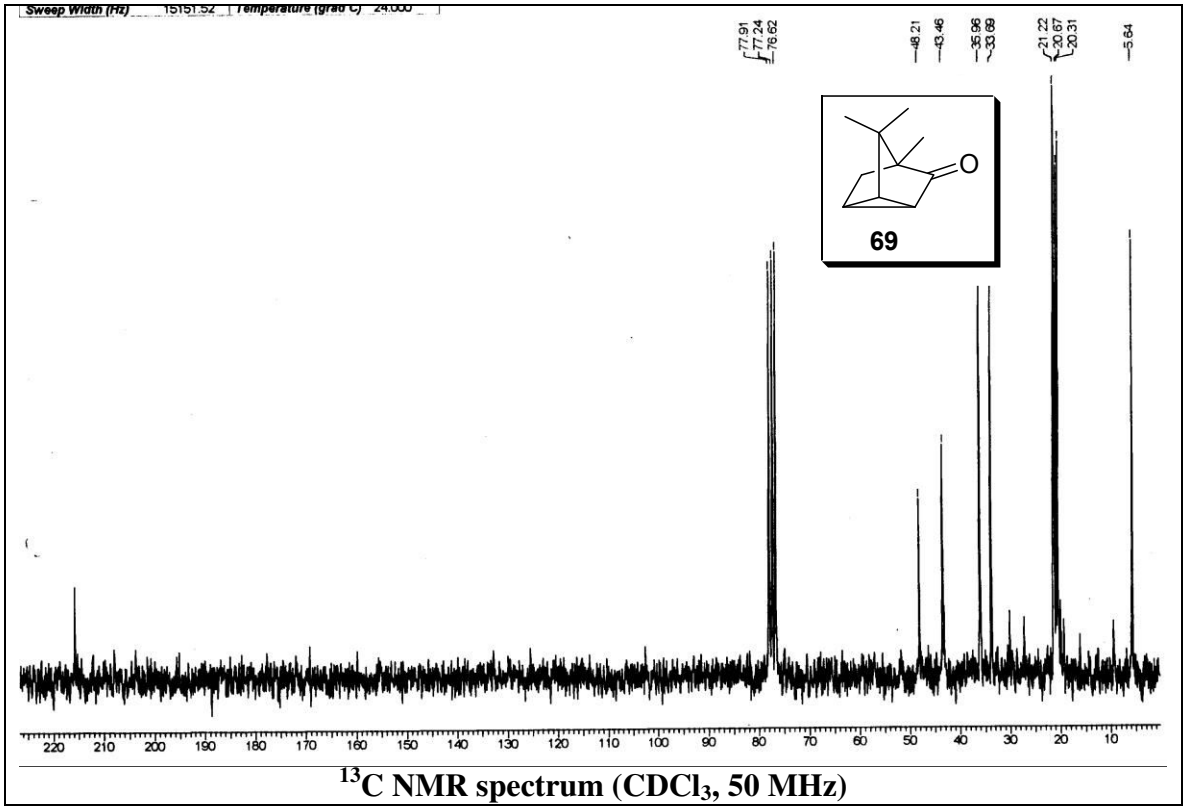
^{13}C NMR spectrum ($CDCl_3$, 50 MHz)



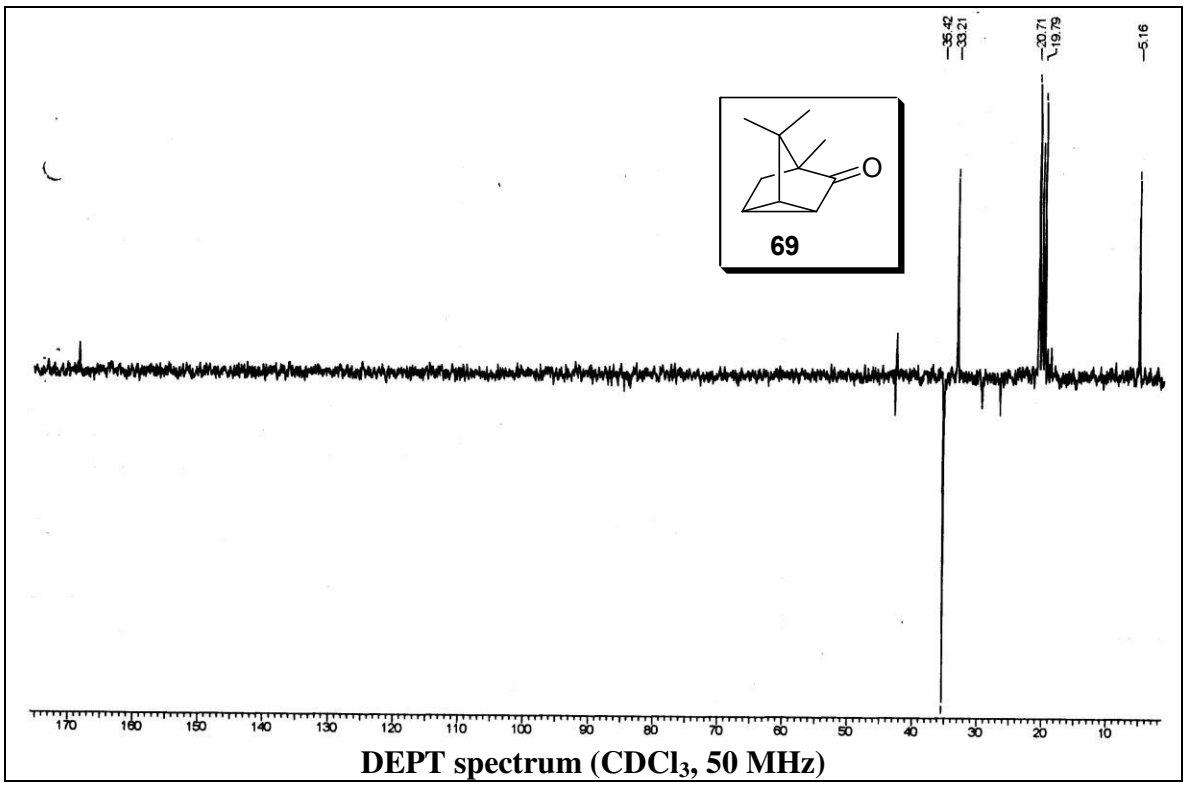
DEPT spectrum ($CDCl_3$, 50 MHz)



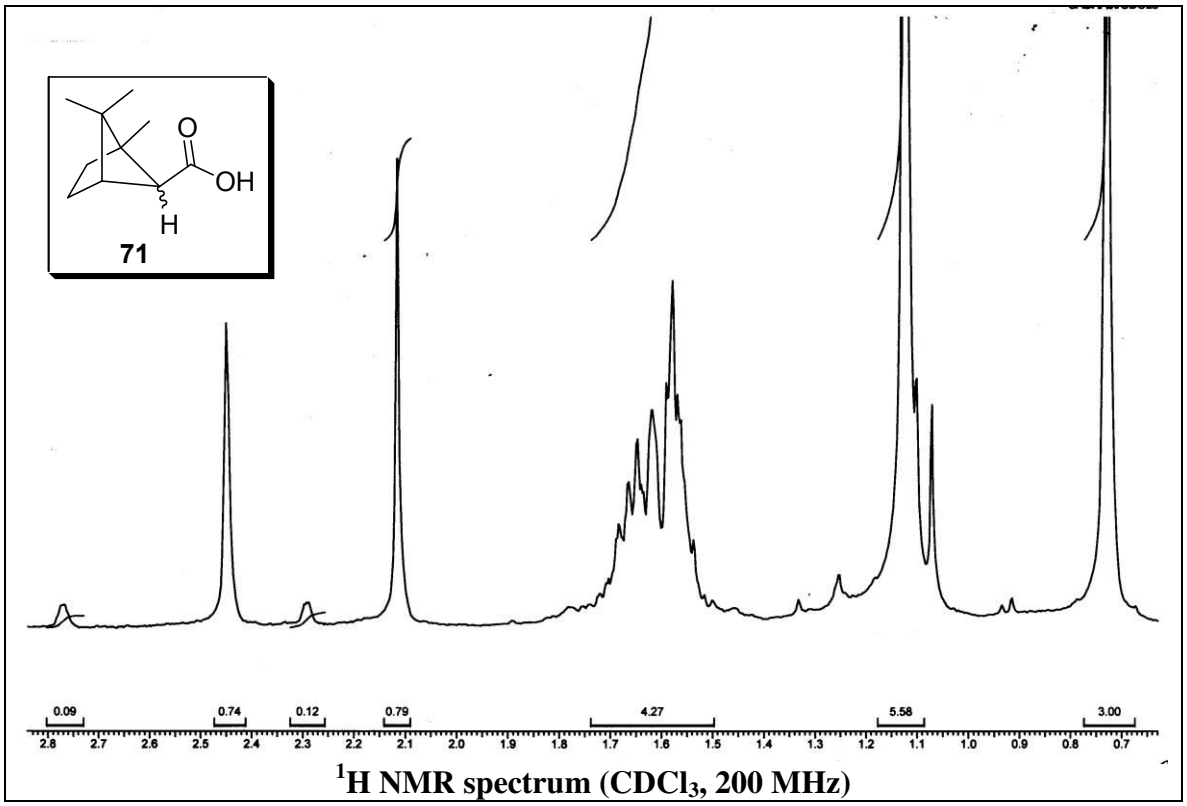
^{1}H NMR spectrum ($CDCl_3$, 200 MHz)



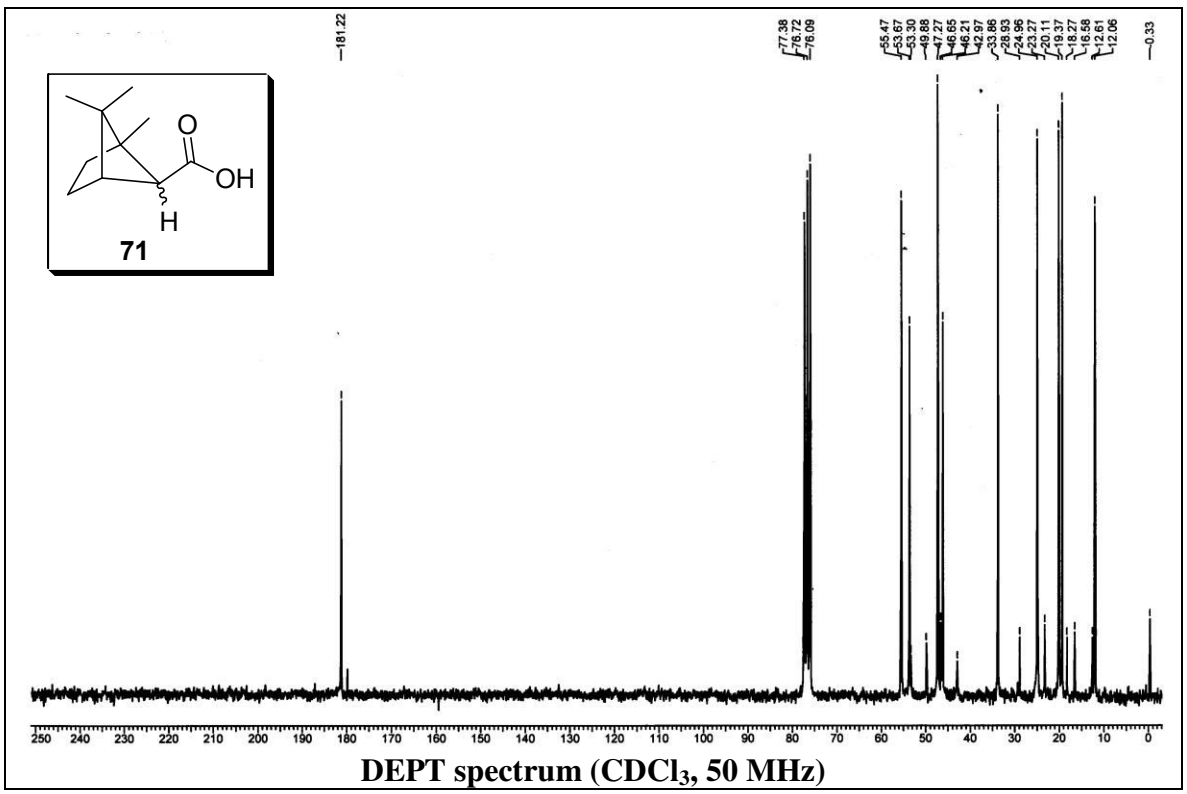
^{13}C NMR spectrum ($CDCl_3$, 50 MHz)



DEPT spectrum ($CDCl_3$, 50 MHz)



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



DEPT spectrum ($CDCl_3$, 50 MHz)