PHOTOINDUCED ELECTRON TRANSFER (PET) PROMOTED CARBOANNULATION STRATEGY: ARENE RADICAL CATION IN CARBON-CARBON BOND FORMATION REACTION

A THESIS

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IN CHEMISTRY

BY

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Photoinduced Electron Transfer (PET) promoted carboannulation strategy: Arene radical Cation in carbon-carbon bond formation reaction**" submitted by Mr. M. Karthikeyan was carried out by him under my supervision at National Chemical Laboratory, Pune, India. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

Date: 09/01/98

(Ganesh Pandey)
Research Guide

DECLARATION

I hereby declare that the thesis entitled "**Photoinduced Electron Transfer (PET) promoted carboannulation strategy: Arene radical cation in Carbon-Carbon bond formation Reaction**" submitted for Ph. D. degree to the University of Poona has been carried out at National Chemical Laboratory, under the supervision of Dr. Ganesh Pandey. The work is original and has not been submitted in part or full by me for any degree or diploma to this or any other University.

M. Karthikeyan

Date: January 09, 1998

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M. Karthikeyan.

TO

MY PARENTS,

BROTHER

&

ALL MY TEACHERS

"Thinking is Easy, Acting is Difficult,
and to put one's Thoughts into Action is
the most difficult thing
in the world" - Gothe.

CONTENTS

GENERAL REMARKS

1. All melting points and boiling points are recorded on the Celsius scale and are uncorrected.
2. IR spectra were recorded as nujol mull or neat, on a Perkin-Elmer Infrared Spectrometer Model 599-B, Model 1620 FT-IR and ATI Mattson, UK, Model-RS-1 FT-IR, using sodium chloride optics. IR bands are expressed in frequency (cm^{-1}).
3. ^1H NMR spectra were recorded using tetramethylsilane as internal reference on Bruker MSL-300, Bruker AC-200, Bruker WH-90, Bruker FT-80A. Chemical shifts were recorded in parts per million (δ). Abbreviations, *viz.*, s = singlet, d = doublet, t = triplet, dd = doublet of doublet, dt = doublet of a triplet, bs = broad singlet, br = broad peak and m = multiplet have been used. $CDCl_3$ was used as the solvent unless otherwise mentioned.
4. ^{13}C NMR spectra were recorded on Bruker MSL-300 and Bruker AC-200 instrument operating at 75 MHz and 50 MHz respectively.
5. Mass spectra were recorded on a Finnigan-Mat 1020C mass spectrophotometer at 70 eV.
6. Elemental analyses (C, H) were obtained on a Carlo - Erba 1100 automatic analyser.
7. Photoirradiations were performed using 450W Hanovia medium pressure lamp.
8. The progress of the reaction was monitored by analytical thin layer chromatography (TLC) and/or high pressure liquid chromatography (HPLC). Analytical TLC was performed using precoated silica gel 60 F_{254} (Merck, Germany) plates. GC analysis was done using Perkin Elmer, Model 8700.
9. Known compounds were characterised by their boiling points, melting points, IR and ^1H NMR.
10. Pet-ether refers to the fraction boiling between 60-80 °C.
11. Room temperature (r.t.) refers to the temperature 30 ± 5°C.
12. NMR and Mass Spectra for the compounds discussed in the text are appended at the end of the chapters.
13. The number assigned to the compounds, charts, figures and schemes in each chapter of the thesis refer only to that particular chapter.

LIST OF ABBREVIATIONS

AIBN	α, α'-Azo bis(isobutyronitrile)
Ar	Aryl
BET	Back electron transfer
B.P.	Boiling point
n-BuLi	n-Butyllithium
CH_3CN	Acetonitrile
$CHCl_3$	Chloroform
CIP	Contact ion pair
CO_2	Carbon dioxide
m-CPBA	meta-chloro perbenzoic acid
CT	Charge transfer
$CuSO_4$	Copper(II) sulfate
DCA	9,10-Dicyanoanthracene
DCB	1,4-Dicyanobenzene
DCN	1,4-Dicyanonaphthalene
DCM	Dichloromethane
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
DMT	N,N-Dimethyltoludine
EtOH	Ethanol
ET	Electron transfer
Et_3N	Triethyl amine
ENC	Encounter complex
EtOAc	Ethyl acetate
EXI	Exciplex
FM	Fredericamycin
FRIP	Free radical ion pair
HMDS	Hexamethyldisilazane
ImH	Imidazole
K_2CO_3	Potassium carbonate
KCN	Potassium cyanide

MP	Melting point
MeOH	Methanol
NaBH4	Sodium borohydride
NaH	Sodium hydride
$NaHCO_3$	Sodium bicarbonate
Na_2SO_4	Sodium sulfate
NBS	N-Bromosuccinimide
Nu	Nucleophile
PET	Photosensitized electron transfer
Ph	Phenyl
r.t.	Room temperature
SSIP	Solvent separated ion pair
t-BuLi	*tert*-Butyllithium
TBDMS	*tert*-Butyldimethylsilyl
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TCNE	Tetracyanoethylene
TLC	Thin layer chromatography
THF	Tetrahydrofuran
TMSCl	Trimethylchlorosilane
TMN	Tetranitromethane

SYNOPSIS OF THE THESIS

The thesis entitled **"Photoinduced Electron Transfer (PET) promoted carboannulation strategy: Arene radical cation in Carbon-Carbon bond formation Reaction"** is divided into three chapters. The title of each chapter and brief discussion about the chapters are as follows.

CHAPTER - 1

Photoinduced Electron Transfer (PET) reactions of Alkyl Aromatics

Chapter - 1 begins with an introduction on the importance of PET reactions and provides a concise account of electron transfer processes, the effect of photoexcitation on donor-acceptor (DA) redox properties by HOMO-LUMO concept, thermodynamic criteria of electron transfer in accordance with Weller equation and stability of incipient intermediates generated in the electron transfer processes.

The primary aim of this chapter is to provide a review of the chemistry of PET generated aromatic radical ions in solution. The emphasis in particular has been directed mainly on the literature concerning the generation and utilization of aromatic radical cation in the nucleophilic substitution reactions.

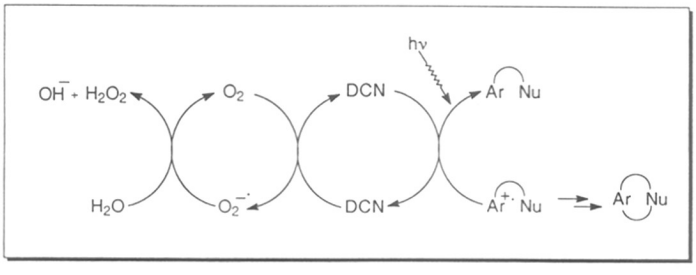
Aromatic radical ions have a chemistry of their own, and in many cases react efficiently, offering access to novel and useful synthetic processes. They show, infact; a double reactivity, behaving both as radicals as well as ions. PET generated arene radical cations have found significant applications in organic synthesis.

CHAPTER - 2

Intramolecular arylation of silyl enol ethers via PET generated arene radical cations: New carbo annulation strategy.

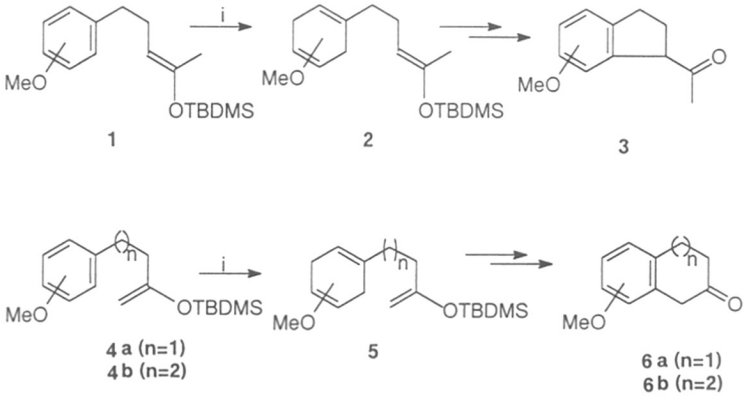
This chapter introduces briefly the utilization of direct nucleophilic substitution reaction of aromatic ring, via to PET generated arene radical cation intermediate, with O and N nucleophiles.

SCHEME - I



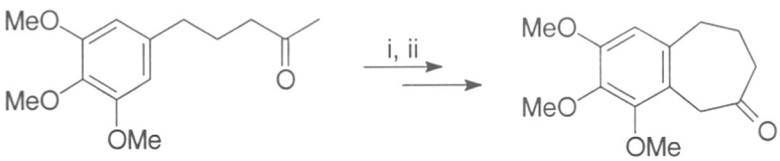
This chapter, the main objective of the thesis, presents in detail the intramolecular addition of silyl enol ether to PET generated arene radical cations and reports the construction of five (**3**) , six, seven and eight membered aromatic annulated products (**6, 8** and **10**) as shown in SCHEME - II.

SCHEME - II



i) DCN, hν, $CH_3CN:H_2O$ (4:1)

The importance of this cyclization strategy has been highlighted as it provides direct access to arene substituted β-tetralones which are very important precursors in the synthesis of many biologically and medicinally active compounds. Generally, β-tetralones are prepared with difficulty *via* 1,2-transposition of a- tetralones or alternatively prepared by ring expansion reactions. Other homologues of this series, irrespective of the number of methylene groups or the position of silyl enol ether group; provided corresponding annulated products. For illustration thermodynamically generated silyl enol ether from substrates with n=2 (**1**) provided indane system (**3**), while kinetically produced enol ether n=2 (**4b**) gave benzocycloheptanone (**6b**) framework. Selecting suitably substituted substrate (**7**), carbocyclic compound (**8**) has been prepared which has previously been used as precursor for the synthesis of a anti-mitotic agent colchicine.

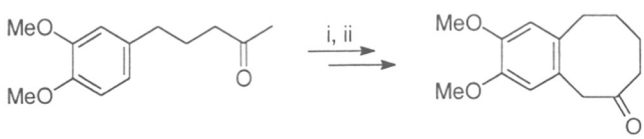


7 **8**

i) LDA, TBDMSCl, -78 °C (Kinetic enolization)

ii) PET reaction, DCN, CH3CN:H2O (4:1), hν, 3 - 4h

Having established the viability of forming polycycles, we turned to the issue of eight membered ring (benzocyclooctane ring system) construction employing this methodology.



9 **10**

i) LDA, TBDMSCl, -78 °C (Kinetic enolization)

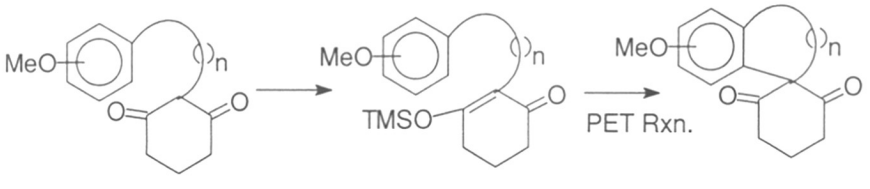
ii) PET reaction, DCN, CH3CN:H2O (4:1), hν, 3 - 4h

We suceeded in extending this methodology to construct benzocyclooctane **10** from substrate **9,** as these types of frameworks are present in many biologically active natural products and is often most difficult to prepare because of entropic factors and transannular interactions, which disfavor such process from occurring. The ease observed in the cyclization of silyl enol ether has been explained by considering the proximity between arene radical cation and enol silyl ethers in polar medium due to self-coiling .

CHAPTER - 3

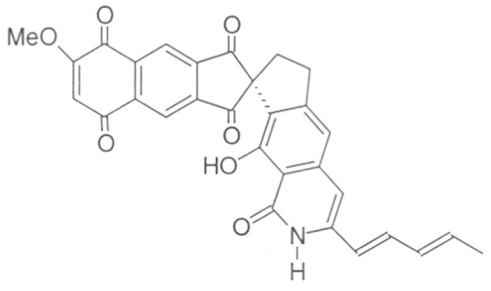
Spirocyclization reactions using photochemically generated arene radical cations:

This chapter further explores the synthetic application of arene radical cation in the construction of spiroannulated products. These spiro annulated structures are either the part of biologically active *cannabis spirans* or they were utilized for the synthesis of other biologically important molecules. As per our synthetic plan the starting compounds **11** required for the construction of **13** was prepared, and by following the standard thermodynamic enol silyl ether preparation procedure from diketones **11** and PET reaction gave corresponding spirocyclic compounds of type **13** in good yields.



11 **12** **13**

We describe also our attempts to construct the core spiro structure **19** of antitumor antibiotic *Fredericamycin A* **(14),** by the cyclization of **16.**



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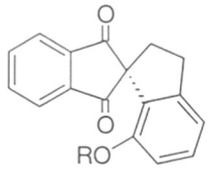

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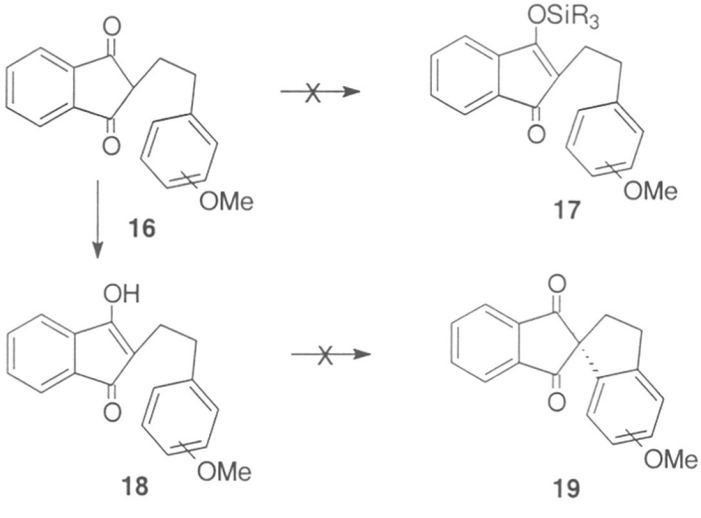
Fredericamycin - A

However the scheme was abandoned due to the failure to make corresponding silyl enol ether of type **17** required for the spiroannulation.

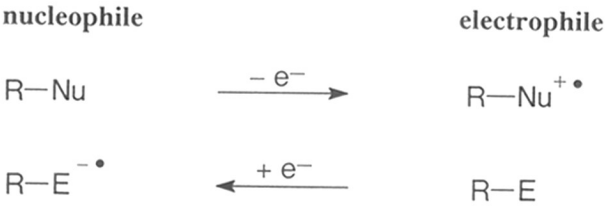


Chapter-I

Photoinduced Electron Transfer (PET) reactions of Alkyl Aromatics

1. INTRODUCTION

Addition or removal of an electron determines the chemical fate of the molecular entities to a large extent, although, at the primary stage bonds are neither broken nor formed. Photoexcitation, which renders well defined redox potential difference between two interacting species, facilitates transfer of an electron to generate radical ions; a new type of reactive intermediates from neutral substrates[1-6]. An important consequences of the chemical reactivity associated with the generation of radical ions is that an electrophilic substrate by the gain of an electron (reduction) is transformed into a nucleophile and a nucleophilic substrate by the loss of an electron (oxidation) enhances its electrophilic character (Scheme-1). Electron transfer, therefore, leads to "umpolung" with all its consequences for ensuing reactions.[7]



Scheme-1

The contents of this dissertation concerns with the generation of arene radical cation from an electron rich aromatics by one electron transfer from its excited state to the ground state of 1,4-dicyanonaphthalene (DCN) and its intramolecular

nucleophilic substitution reaction with silyl enol ethers. However, a dispel discussion on the concept of electron transfer (ET) and precedented literature reports concerning the chemistry of arene radical cation is appended here to put the forth coming discussion of the thesis in total perspectives.

2. Concept of Electron Transfer

Photoexcitation of an electron acceptor (A) or electron-donor (D) substrate leads to well defined changes in their redox properties. For example,the donor

$$IP(D^{\bullet}) = IP(D) - \Delta E(D^{\bullet}) \quad \text{..... Eq. 1}$$

$$EA(A^{\bullet}) = EA(A) + \Delta E(A^{\bullet}) \quad \text{..... Eq. 2}$$

properties of D increases proportionally to the excitation energy ($\Delta E(D) = h\nu$); *i.e.*, the ionization energy, IP (D), is reduced by the promotion of an electron from the HOMO to LUMO [Eq. 1].

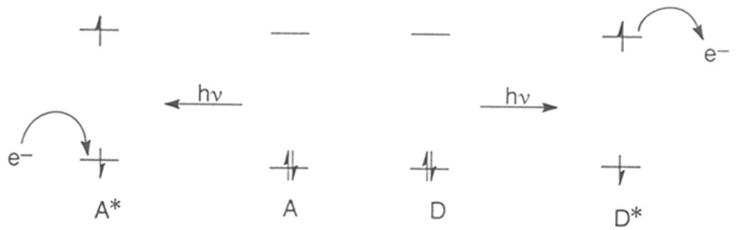


Fig.1

The electron affinity of the acceptor, EA (A), behaves accordingly [Eq. 2][8,9]. Electron transfer between donor and acceptor substrates should, therefore, occur more easily

after photoexcitation (Fig. 1) of one of the reacting species[8] if either IP (D*)< EA (A) or IP (D)< EA (A*) holds true (Fig. 2). Simple energy considerations such as these

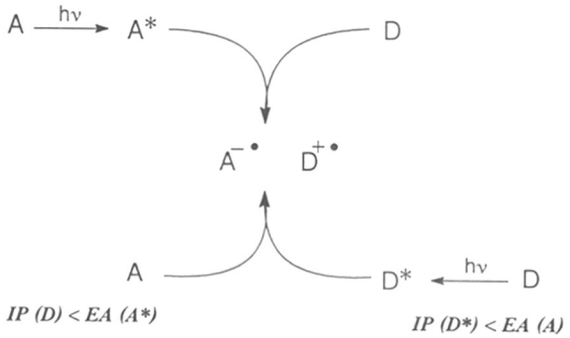


Fig.2

parameters clarify the dependence of electron transfer on electronic conditions in the participating substrates. IP and EA parameters are valid only for the gas phase . However, since the oxidation and reduction potentials [$E^{ox}_{1/2}$(D) and $E^{red}_{1/2}$ (A)], the corresponding parameters in the solution [easily obtainable experimentally[10]] are linearly related to IP and EA[11], respectively, the conditions for electron transfer between D and A after irradiation is formulated by Weller[12] as follows:

$$\Delta G\,(A_s^{-\bullet} D^{+\bullet}) = F[E_{1/2}^{ox}(D) - E_{1/2}^{red}(A)] - \Delta E_{excit} + \Delta E_{coul} \quad \text{..... Eq.3}$$

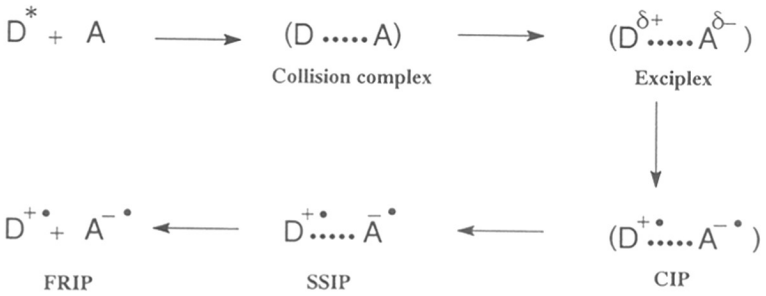
In the above equation (Eq. 3) $E^{ox}_{1/2}$(D) and $E^{red}_{1/2}$ (A) are the oxidation potential of the donor and reduction potential of the acceptor, respectively, measured in acetonitrile; ΔE_{excit} is the excitation energy of the electronically excited species, and ΔE_{coul} is the Coulomb interaction energy of the two radical ions at a distance from one another in a given solvent[12,13].

The Weller equation[12], therefore, allows to estimate, to a first approximation, whether electron transfer within a donor - acceptor pair is thermodynamically allowed (ΔG, negative exergonic process) or not (ΔG positive, endergonic process). In addition, it also indicates that the electron transfer processes can be decisively influenced by the polarity of the solvent as well as by the electronic properties of the reacting species. This knowledge has provided chemist a number of ways to direct reactions involving radical ions in a desired fashion. Rates of ET have been correlated with the ΔG_{ET} and were found to increase as ΔG becomes more exothermic until the Marcus inverted region is reached, where the rate of electron transfer decreases with increasing exothermicity[14-16].

In PET processes, the interaction between an excited and a ground state molecule creates a series of short lived intermediates by the dissipation of excitation energy through reactants and solvent molecules as each ion pair intermediate is successively transformed into another intermediate of lower energy.

Electrostatic and solvent effects may stabilize each ion pair intermediate depending on its structure, separation distance and polarity of the medium. Thus, in solution, the nature of the ET pathways leading to radical ions is dictated to a large extent by the polarity of the solvent as well as on the shape of the excited and ground state reactants besides electronic properties of the reacting species[17,18]. The quenching pathways for the ET processes are represented in Scheme-2. The pioneering work of Weller[12,13,19] has suggested exciplexes as key intermediates in ET processes

possessing charge transfer character. These intermediates can be either light emitting exciplexes (charge transfer complex) or non-emitting entities (contact ion pair). The yields and the life time of these intermediates are strongly dependent on the polarity of the solvent. Thus, in polar solvents, a non-emitting exciplex, which has strong contact ion pair (CIP) character, is expected to lead the complete transfer of an electron due to greater solvation energy.



Scheme- 2

A number of experimental techniques such as laser flash spectroscopy[20], chemically induced nuclear polarization[21], resonance Raman spectroscopy[22] and time resolved microwave conductivity[23] have allowed to chart out the dynamics of PET in homogenous solutions as well as in solid states.

The electronic properties of these intermediates are very much dependent upon the solvent polarity. Study of solvent effects reveal interesting features in product distribution; arising out of solvent-induced change of electronic properties

of an exciplex or from switching off an exciplex mechanism in polar solvents (Fig. 3 & 4).

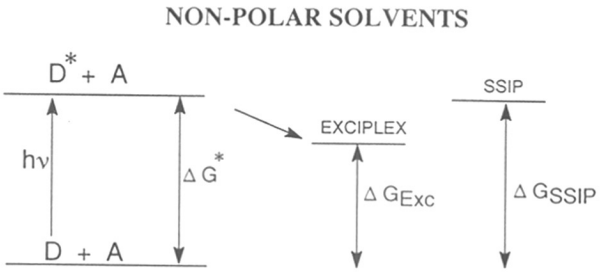


Fig. 3

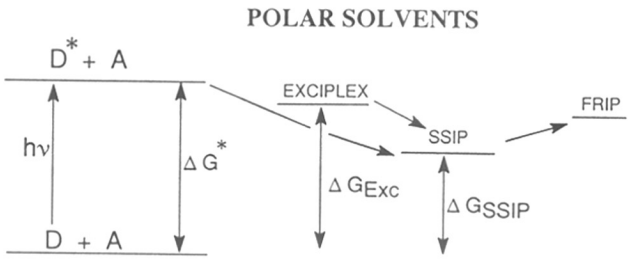
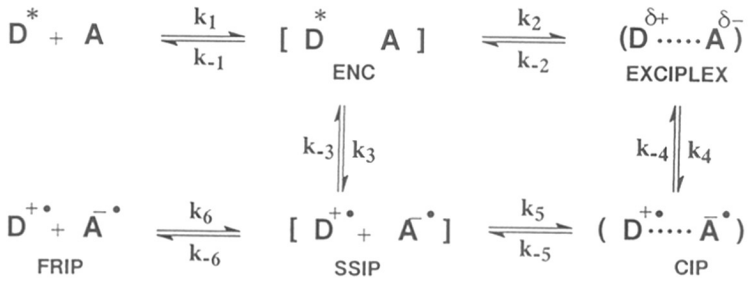


Fig. 4

It is commonly assumed that solvent reorganisation dominates electron transfer kinetics and reorganisation energy in the same medium is constant within a series of closely related redox partners (donor-acceptor pairs). The decay of redox partners in the exergonic region of electron transfer[12] ($\Delta G < 0$) directs the formation of radical ion pairs and, thus, allowing to study the quenching kinetics involved in non-bonding electron transfer processes (Scheme-3). The path characterised by k_3 shows the direct formation of solvent separated ion-pair (SSIP) from encounter

complex (ENC) in the exergonic region. However, the electron transfer is also possible *via* exciplex intermediates k_2, k_4, and k_5.



Scheme- 3

This was supported by the observation that, in contrast to expectations based on Marcus theory[16], reduction in the rate constant for electron transfer in highly exergonic regions have not been observed[24,25]. However, Miller *et al* found clear evidence for the so called "Marcus inverted region" in intramolecular electron transfer processes[26].

Attention towards PET reactions has been advanced dramatically due to the development of modern spectroscopic methods. Several pioneering studies emphasizing PET reaction involving organic and inorganic substrates are reviewed[2-4]. According to fig. 3 & 4, it is quite apparent that in polar solvents, SSIP and free ion-pairs (FRIP) are predominant. Therefore, the understanding of such solvent effect provides a clue to explore mechanism of photoreaction and the product formation [4,5,17].

3. Reactions of Arene Radical Cations

Arene radical cations may be generated by electron transfer either by collision between the excited state and a quencher or by excitation (eq. 4) of a preformed ground state complex (eq. 5)

$$Ar + h\nu \longrightarrow Ar^* + Q \longrightarrow Ar^{+\cdot} + Q^{-\cdot} \quad \text{-- (4)}$$

$$(Ar\text{------}Q) + h\nu' \longrightarrow Ar^{+\cdot} + Q^{-\cdot} \quad \text{-- (5)}$$

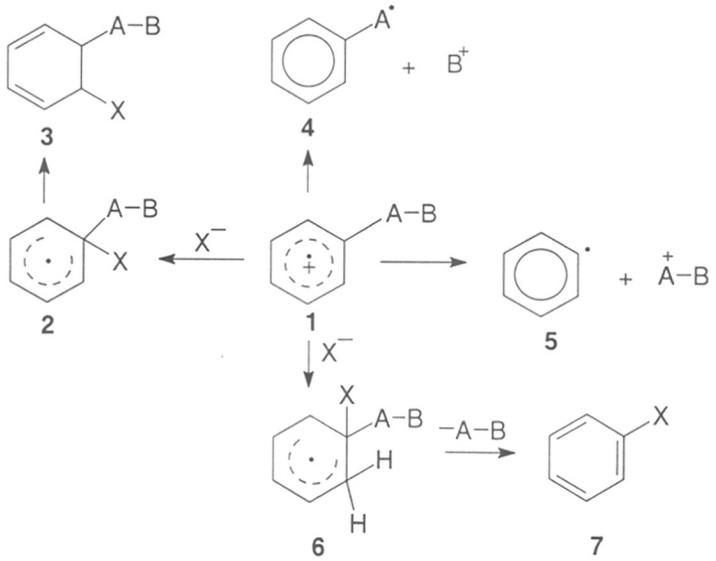
Since our proceeding discussion pertains to the case as mentioned in eq. 4, a brief insight concerning the photochemical mechanism is mentioned here.

As electronic excitation of flat aromatic molecules is localized on the "exposed" π-system, they readily interact with acceptors and either yield excited complexes of more or less pronounced charge transfer character or undergo electron transfer reactions. The initial encounter complex between the excited aromatic (Ar*) and another molecule (Q) in the ground state evolves toward an essentially covalent exciplex, initially held tightly in solvent cage and, under the proper conditions, eventually dissociates to "free" solvated radical ions.

Radical cations are stabilised due to delocalisation over an aromatic system and therefore, back electron transfer becomes the dominant process and the life time of these species is dramatically shortened. This severely limits the type of reactions available. Obviously any mechanism providing an escape from the solvent cage will

make chemical reactions easier. One such mechanism could be considered the fast chemical deactivation of radical cation or a molecular vibrations. Details of all these mechanisms are beyond the scope of this dissertation. Excellent reviews[27] are available on this subject, for detailed study.

In general the chemistry arising out of arene radical cation may be divided into i) fragmentation of a bond α-to the aromatic ring. ii) fragmentation of a bond β to the aromatic ring. iii) addition and substitution reactions directly on the aromatic ring (Scheme-4).

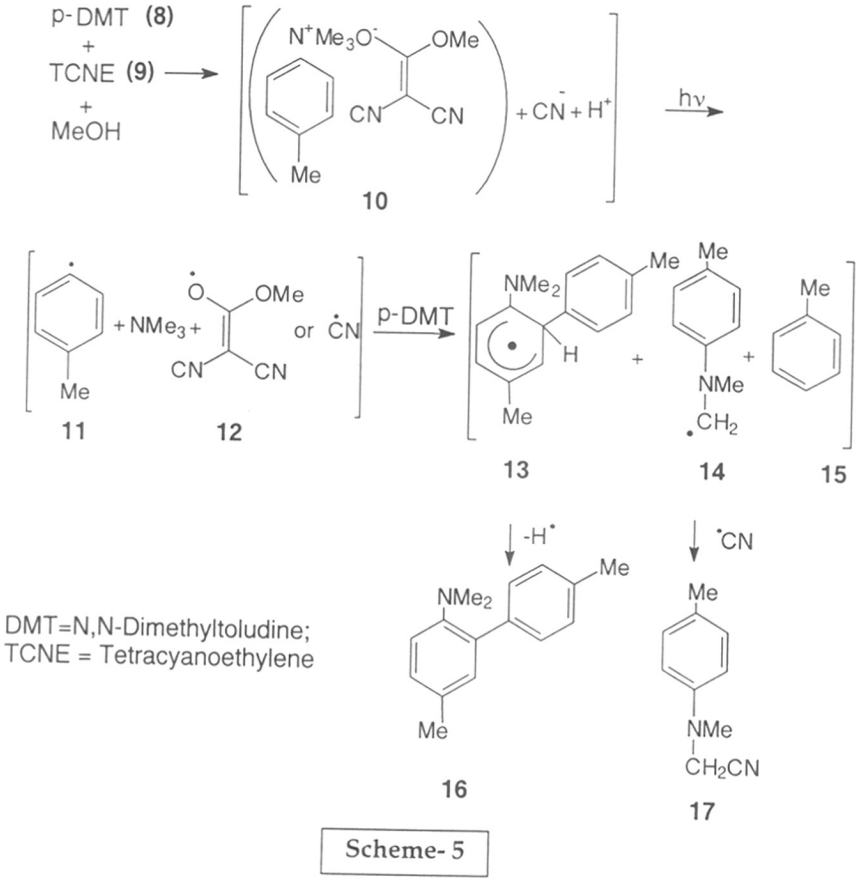


Scheme- 4

3.1. α-Fragmentation

Examples pertaining to α-fragmentation of a bond from a PET generated arene radical cation is scarce. A representative example in this context may be

catagorised by citing[28] the formation of biphenyls (Scheme-5) by the irradiation of a CT complexe between N,N'-dimethyl toludine (**8**) and tetracyanoethylene (**9**) in methanol.



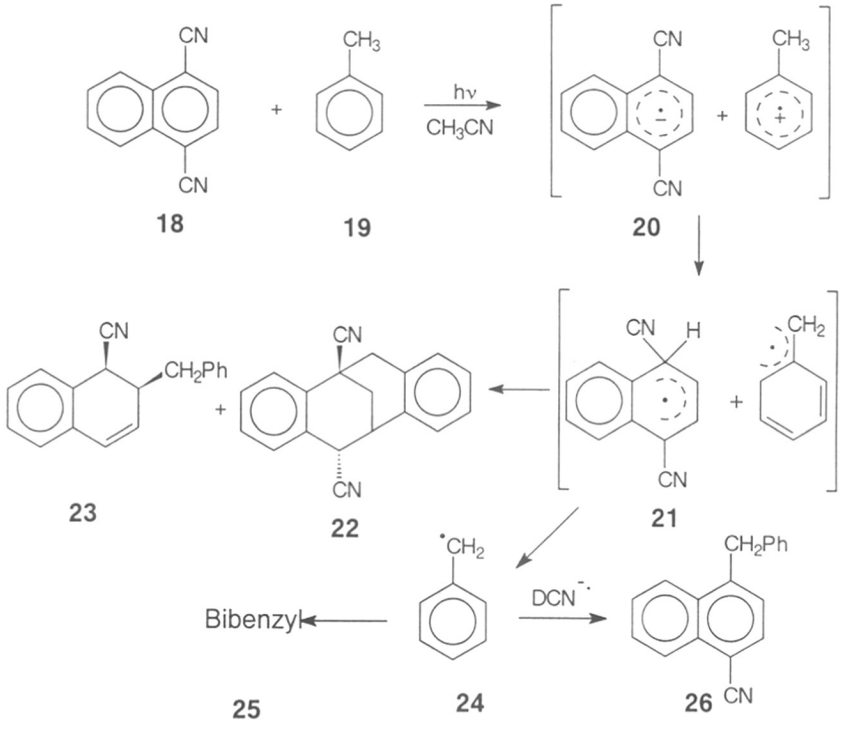
Scheme- 5

3.2 β- fragmentation

Several examples concerning the β-fragmentation from an aryl radical cation involving the cleavage of either a -C-H or a -C-C- bond to yield benzyl radical or cations are known. In majority of the cases, the proton transfer takes place between radical cation /radical anion pairs with the net result of the bimolecular coupling

product. However, during sensitized PET reactions, deprotonation from radical cation is associated either with the unilateral radical reactions or their further oxidation to produce carbocationic species. Normally, the rate of proton transfer depends upon the kinetic acidity of the cation radical and the basicity of the anion radical.

Efficient deprotonation from the benzylic position of an alkyl benzene radical-cation, formed by the electron transfer to excited DCN, **(18)** to counter anion ($DCN^{-\cdot}$)



Scheme- 6

is reported from Albini's group[29] to produce benzylic radical and DCN· which upon mutual coupling yields photoaddition products (**22**, **23** and **26**).

Trace amount of bibenzyl **25** is also formed by the dimerisation of benzylic radical. This reaction is shown to involve water mediated proton transfer with in the exciplexes and in cage coupling of the resultant radical pairs forms **22** and **23** while bibenzyl (**25**) and **26** are suggested to arise from the escaped benzyl radical and coupling with $DCN^{\cdot-}$.

The detailed study of quantum yield dependence on the solvent polarity and upon the oxidation potentials of the alkyl benzenes has led Lewis[30] *et al* to suggest the involvement of FRIP in these reactions rather than initially produced CIP (non emitting exciplex) or SSIP[31].

Santamaria's group[32] have shown the selective reaction of benzylic radical, formed by the deprotonation of alkyl arene radical cation generated by the sensitized PET reaction to singlet excited state of 9,10-dicyanoanthracene ($^1DCA^*$)-an electron acceptor and methyl viologen (MV^{++}) as an electron relay, with molecular oxygen to produce corresponding hydroperoxide in 57-100 % yield as depicted through eqs. 6-10 in Fig. 5.

$$ArCH_2R + {}^1DCA^* \longrightarrow Ar\dot{C}H_2R^{+} + DCA^{\cdot-} \quad \text{------- (6)}$$

$$DCA^{\cdot-} + MV^{++} \longrightarrow DCA + MV^{\cdot+} \quad \text{------- (7)}$$

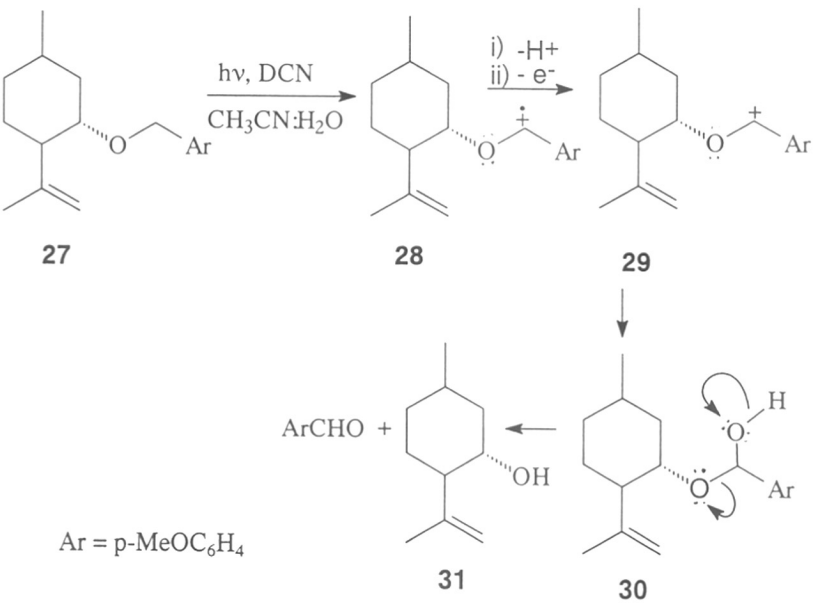
$$MV^{\cdot+} + O_2 \longrightarrow MV^{++} + O_2^{\cdot-} \quad \text{------- (8)}$$

$$ArCH_2R^{\cdot+} + O_2^{\cdot-} \longrightarrow Ar\dot{C}HR + HO_2^{\cdot} \quad \text{------- (9)}$$

$$Ar\dot{C}HR + HO_2^{\cdot} \longrightarrow ArCH(R)\text{-}OOH + HO_2^{\cdot} \quad \text{------- (10)}$$

Fig. 5

Photosensitized ET generated arene cation radical from the excited *p*-methoxy benzyl protected ethers **27** in the presence of the ground state of DCN as an electron acceptor in wet acetonitrile has been shown[33] to undergo efficient deprotonation reaction to produce benzyl radical which gets further oxidised to a benzyl cation **29**

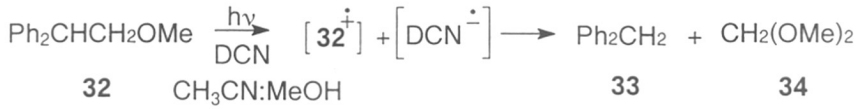


Scheme-7

by thermal ET to DCN. The hydroxylation of **29** and ensuing reaction pathway as shown in Scheme-7 leads to net debenzylation product **31**. An independent study by Nishida *et al*[34] has corroborated this photodebenzylation strategy.

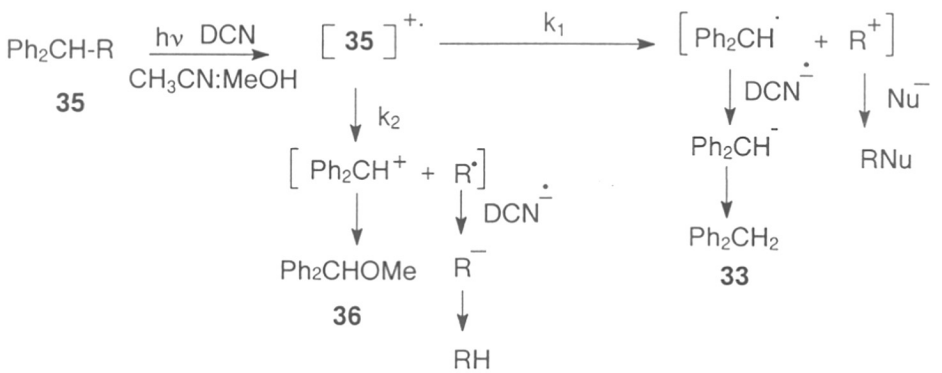
Arnold's pioneering work[35-37] of oxidative C-C bond cleavage effected by ET to excited cyanoaromatics is well recognized. Photosensitized irradiation of 2,2-diphenylether (**32**) in presence of DCN in CH_3CN:MeOH leads to the fragmentation products (**33**) and (**34**). Photophysical and electro-oxidative studies have indicated

the reaction initiated by ET from (**32**) to DCN followed by cleavage of $32^{+\cdot}$ as shown in Scheme-8.



Scheme- 8

In an analogous study[35] C-C bond fragmentation of (**35**) by photosensitized electron transfer is also reported. Product analysis of the reaction mixture confirmed the cleavage process as outlined in Scheme-9.



Scheme- 9

Further, it has been observed that fragmentation of C-C bond is governed by radical and cation stabilities to compete with other possible deactivation pathways such as proton loss, nucleophilic addition or further electron transfer etc. However, the

results obtained in the gas phase[35] are in sharp contrast (Scheme-10) to that obtained in the solution medium.

$$\underset{\mathbf{32}}{Ph_2CHCH_2OMe} \xrightarrow{\text{Gas Phase}} Ph_2CH^+ + \dot{C}H_2OMe$$

Scheme- 10

From Scheme-10 it is evident that the formation of **34** is not a dominant process in gas phase. This has been explained by reasoning that delocalized cation is more stable in gas phase but solvation serves to stabilize the more localized carbocation in solution. Thermochemical calculations have explained the regioselectivity of radical / cation. which depends on the relative oxidation potentials of fragment radicals. The fragment with lower oxidation potential has been proved to react as carbocation.[36,37]

In continuation of their studies[37], Arnold has explained all the possible products by considering the dual cleavage of unsymmetrically substituted alkane radical cation ($\mathbf{37}^{+\cdot}$) as shown in Scheme-11

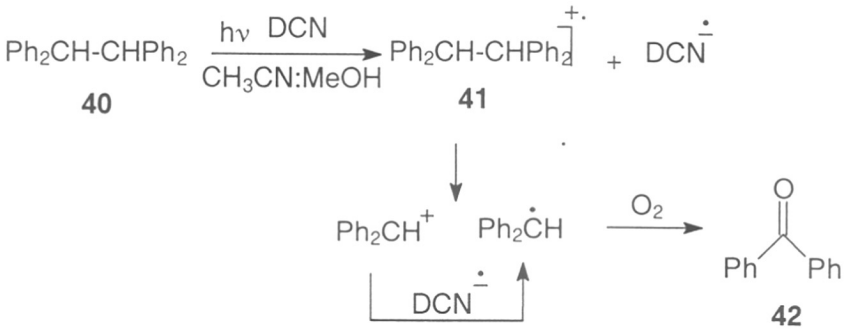
$$\underset{\mathbf{37}}{Ph_2CH\text{-}C(CH_3)_2\,(4\text{-}C_6H_4CF_3)} + DCN \longrightarrow \left[\mathbf{37}\right]^{+\cdot}$$

$$\longrightarrow \mathbf{33} + \mathbf{36} + \underset{\mathbf{38}}{(4\text{-}C_6H_4CF_3)\,(CH_3)_2C(OMe)} + \underset{\mathbf{39}}{(4\text{-}C_6H_4CF_3)\,(CH_3)_2CH}$$

Scheme- 11

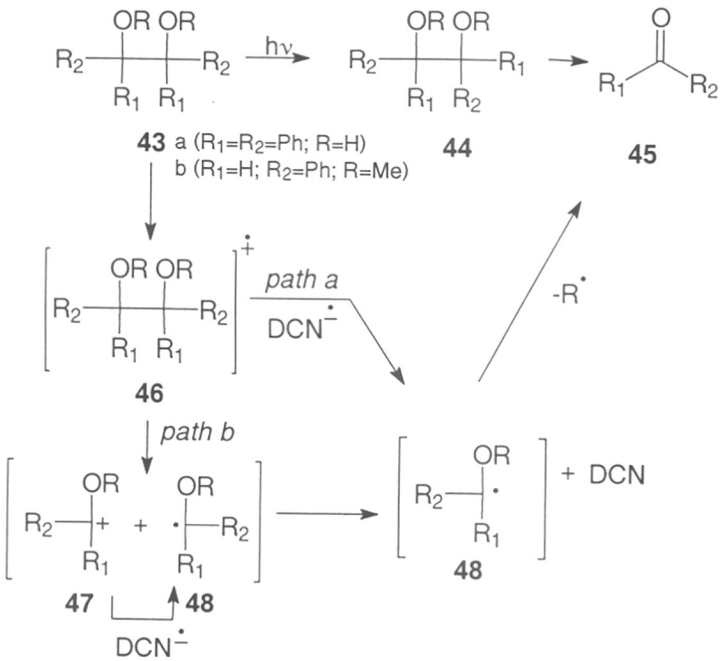
Unusual product formation has been attributed to the equilibiration of radical / cation in dual mode of fragmentation before separation from CIP. Moreover it has been conclusively shown that relative yields of products are governed by the redox properties of two radical fragments.

Simultaneously, C-C bond cleavage was also reported by Griffin *et al*[38,39] from the PET reaction of **40** and DCN in acetonitrile as shown in Scheme-12.



Scheme- 12

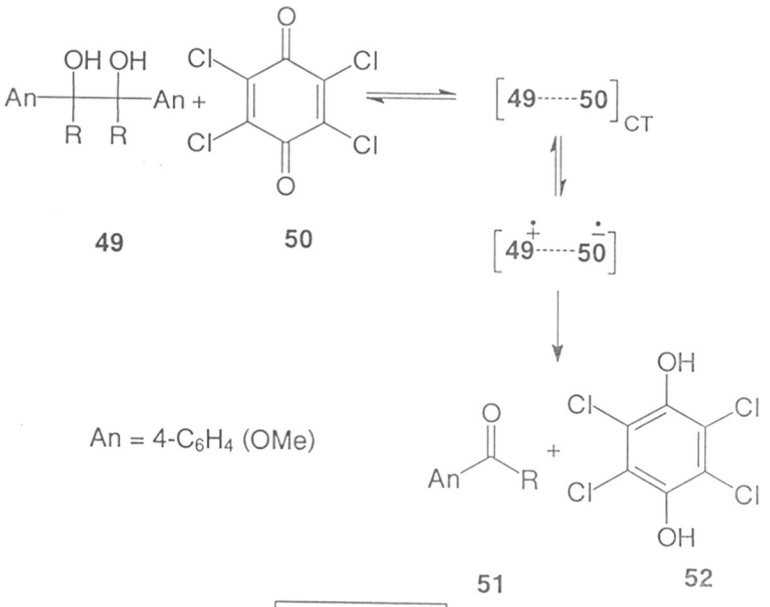
A strong evidence for SET mechanism in these systems is inferred from laser flash photolysis studies. However, in case of benzpinacols (**43a**) and benzpinacol ethers (**43b**), transient absorption studies[38], reflected different reaction sequence. It has been proposed that the fast back-electron transfer from $DCN^{-\cdot}$ to short lived radical cation $\mathbf{43}^{+\cdot}$ (path a) in the geminate pair prior to fragmentation leads to the generation of radical (**47**) instead of cation **46** (path b) as shown in Scheme-13.



Scheme- 13

Transient absorption studies[39] have not detected the presence of **47** . However, above outlined mechanism is confirmed experimentally when photostable racemic ether (**43**) afforded **44** due to radical recombination in the geminate ion pair upon irradiation in the similar conditions.

Dissociation of the activated pinacols (**49**) to generate corresponding ketones (**51**) is reported by Kochi *et al*[40] from the photolysis of CT-complex of pinacols (**49**) with chloranil (**50**).

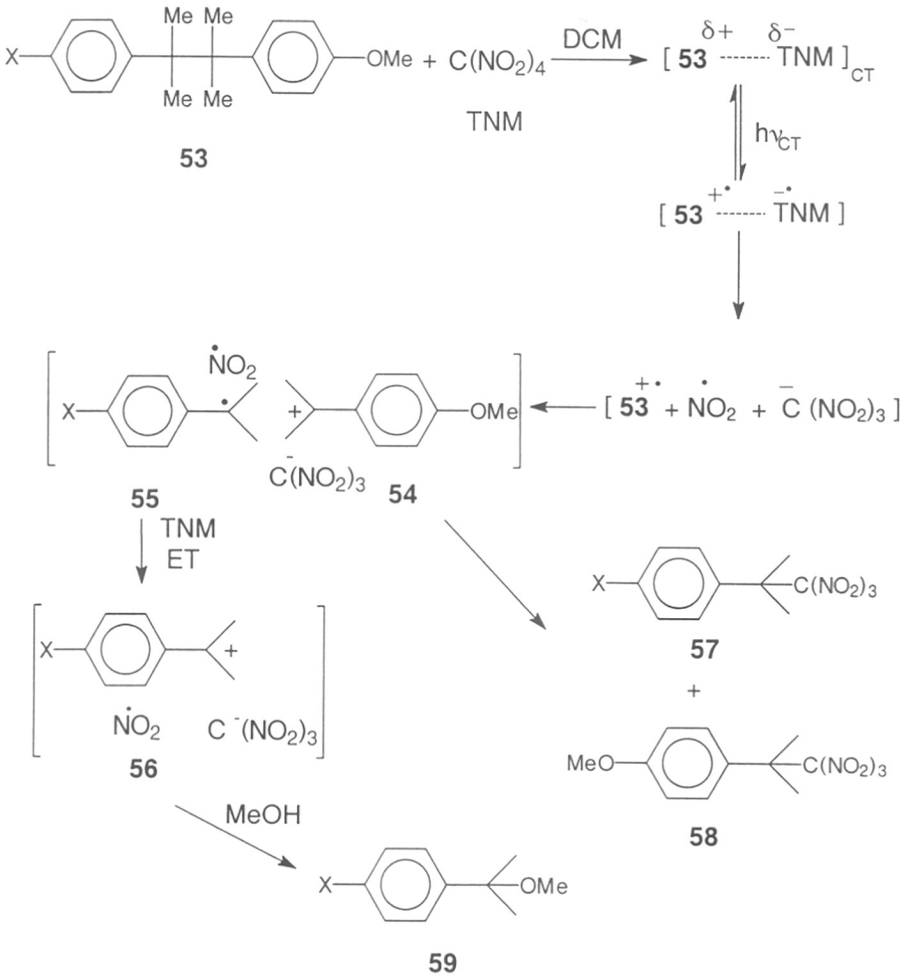


49 50 51 52

Scheme- 14

Analogous cleavage of the methoxy bicumins is also demonstrated[41] from the photolysis of CT - Complex of bicumins and chloranil.

Photolysis of the CT-complex of 4-methoxy-4',X-bicumines 53 (X = Me, Cl, CF_3, CN) with tetranitromethane (TNM) is reported[42] to lead to the formation of 57 and 58 *via* -C-C- bond scission of the initially formed $(53)^{+\cdot}$ and -C-NO_2 bond dissociation of $TNM^{-\cdot}$ followed by radical coupling reactions as shown in Scheme-15. The nature of the X and the solvent polarity greatly influences the fragmentation processes.

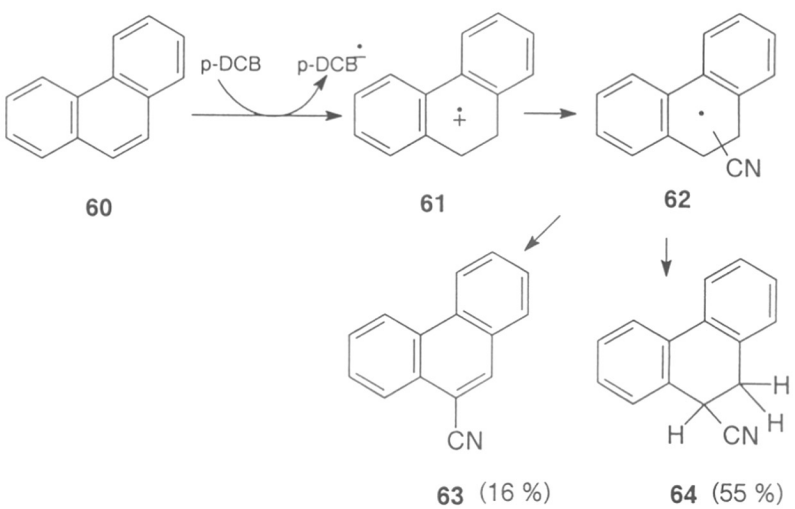


Scheme- 15

Cumyl cation **54** produced by the cleavage of (**53**)+· undergoes trinitromethylation at CIP where as **56** produced from the thermal oxidation of **55** is trapped at SSIP.

3.3 Nucleophilic Substitution Reaction

A typical reaction of an arene radical cation includes the addition of a charged or neutral nucleophile leading ultimately to a substituted aromatics (or its dihydroderivative). Many useful chemistry have been developed by the addition of a nucleophile, both inter- as well as intramolecular, to the PET generated aromatic radical cation. In this context, photocyanation of the arenes may be cited[43-45] as the representative example of an electron transfer initiated nucleophilic aromatic photosubstitution reaction where hydrogen served as the group undergoing displacement. For illustration, when phenanthrene **60** is photolysed using 1,4-dicyanobenzene (DCB) as an electron acceptor in CH_3CN containing KCN, cyano phenanthrene **63** (Scheme-16) is produced.

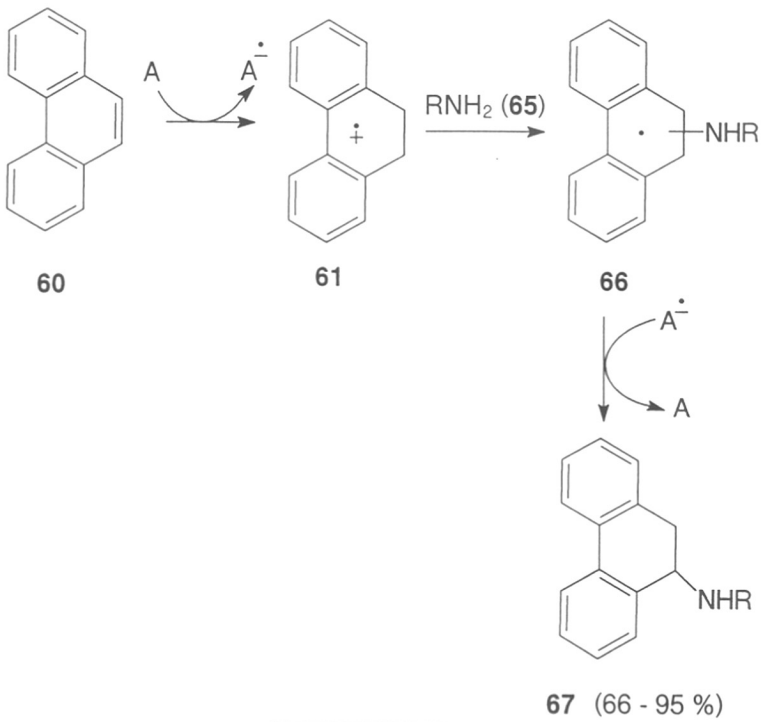


60 **61** **62**

63 (16 %) **64** (55 %)

Scheme- 16

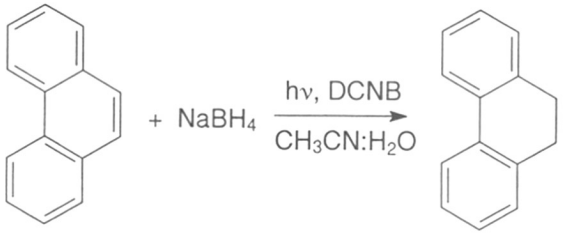
The same concept has further been utilised for the direct amination[46] of polynuclear aromatic hydrocarbons with ammonia or primary amines by irradiating the arene (e.g. phenanthrene) in the presence of DCB (Scheme-17).



60 **61** **66** **67** (66 - 95 %)

Scheme- 17

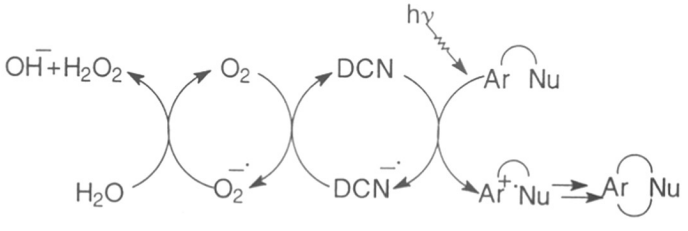
Another potentially useful application of this methodology is reported for the reduction of electron rich arenes to corresponding dihydro derivatives[47] (Birch type reduction) using $NaBH_4$ as hydride donor to arene radical cation (Scheme-18). An important aspect of this methodology is the selective reduction of electron donating substituted rings of unsymmetrically substituted arenes in contrast to Birch type procedures which favors reduction of less electron rich aromatic ring.



60 **68** (50 %)

Scheme- 18

Pandey *et al*[48] have generated arene radical cations by photosensitised electron transfer (PET) from various electron-rich aromatic rings. The photoreaction is apparently initiated by the single-electron transfer from the excited state of the arenes to the ground state of DCN in an aerated aqueous solution of acetonitrile.

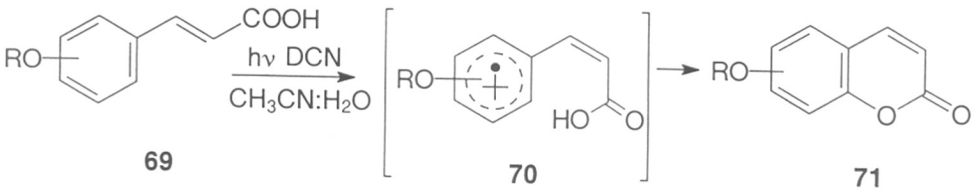


Ar= methoxy substituted benzene rings.

Scheme- 19

Intramolecular reaction with a nucleophiles leads to the annulated products regiospecifically. The regiospecificity of the cyclization is suggested by the FMO theory according to calculated electron densities at different carbon atoms of the HOMO of the radical cation (Huckel and MNDO programmes)

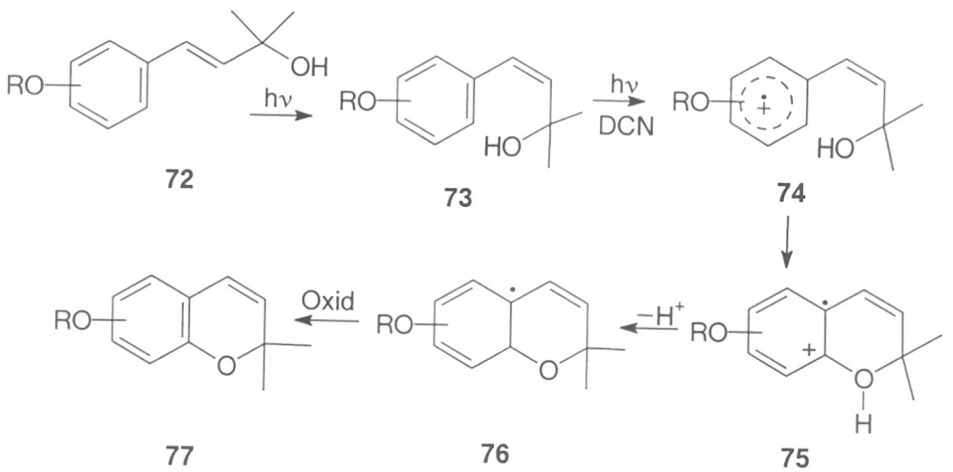
Using hydroxyl groups as nucleophiles, coumarins (**71**) are synthesized starting from the corresponding substituted cinnamic acids **69** in yields of 70 -90 %.[49]



69 **70** **71**

Scheme- 20

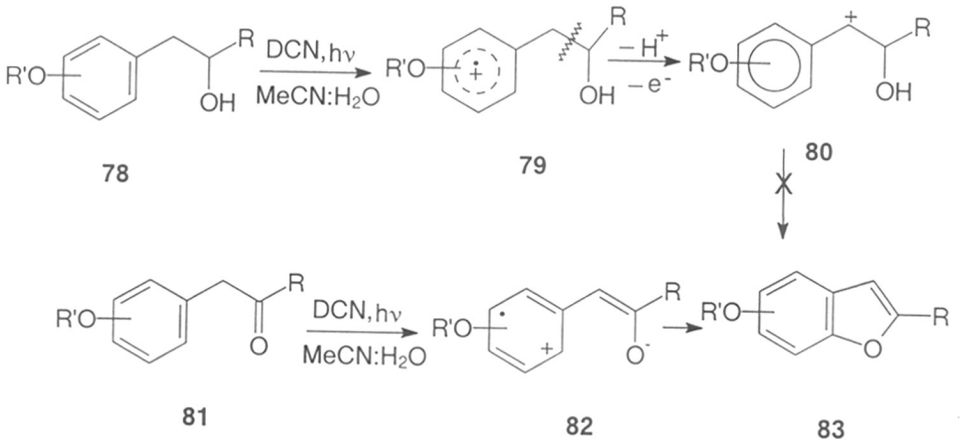
This method is further extended for the synthesis of Precocenes-I (77), a potent antijuvenile hormone compound[50].



72 **73** **74** **75** **76** **77**

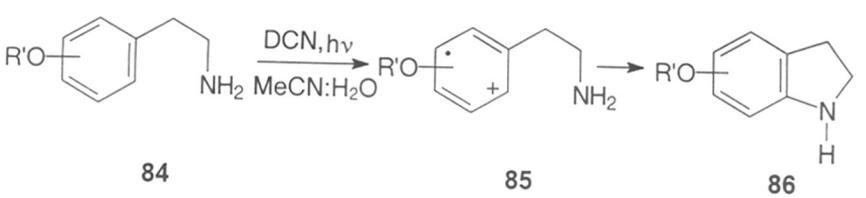
Scheme- 21

Cyclization of 2-aryl-1-alkyl-ethane-1-ol (78) failed because of competitive proton loss from the benzylic position of the arene radical cation (79) followed by fragmentation. When the benzylic position is blocked by using the enolates **82** of 2-aryl-1-alkyl-ethane-1-ones **81,** 2-substituted benzofurans **83** are formed effectively.[51]

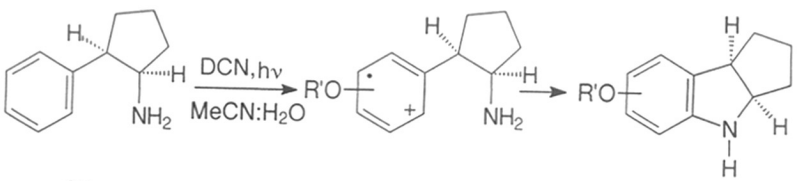


Scheme- 22

Using amines as nucleophiles, N-heterocycles are built efficiently as shown in Scheme-23. For illustration, cyclisation of β-arylethylamines (**84**) leads to the formation of highly substituted dihydroindoles (**86**)[52] (82 % yield) (Scheme-23). This methodology is also utilized to construct the aromatic tricyclic N-heterocycles (**89**) from the PET reaction of **87** (Scheme-24).

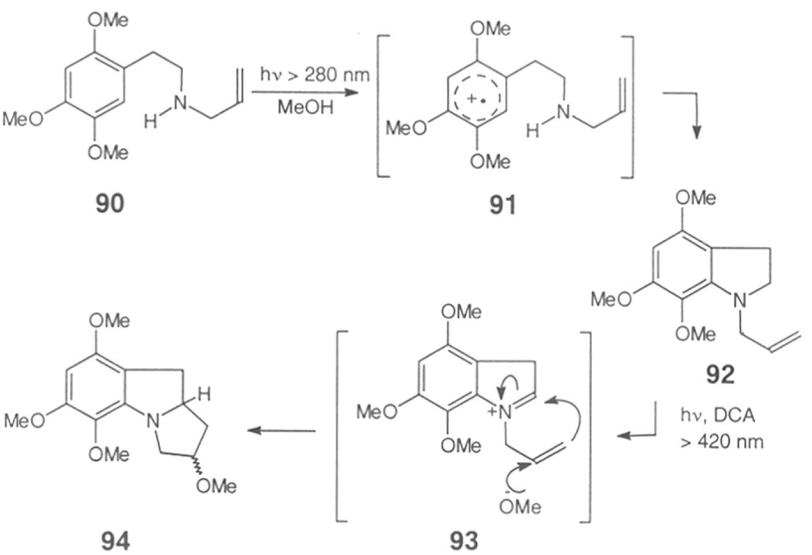


Scheme- 23



Scheme- 24

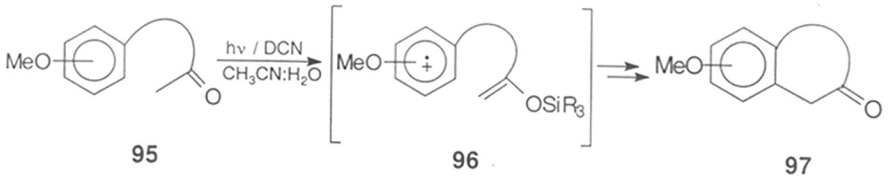
A unique combination of two independent PET operating reactions by "wavelength switch" have been developed to achieve one-pot synthesis[52] of benzopyrrolizidine **94**, possesing similar structural framework as of mitomycine (Scheme-25) from the sequentuak reaction of **90.**



Scheme- 25

From the above illustrations, it is apparent that arene radical cations can be generated by single electron transfer from the excited state of an electron rich aromatics to a suitable electron acceptor such as cyanoaromatics, and these arene radicals cations can be trapped by a nucleophile both inter- as well as intramolecularly. Our broad and ongoing research interest in this area[48] led us to explore the possibility of an intramolecular reaction of highly polarised silyl enol ether to methoxy substituted arene radical cation, generated by electron transfer to

DCN, in order to develop a novel α-arylation reaction of a ketone and a benzannulation strategy (Scheme - 26).



95 96 97

Scheme- 26

The proceeding chapters delinate our success in this context.

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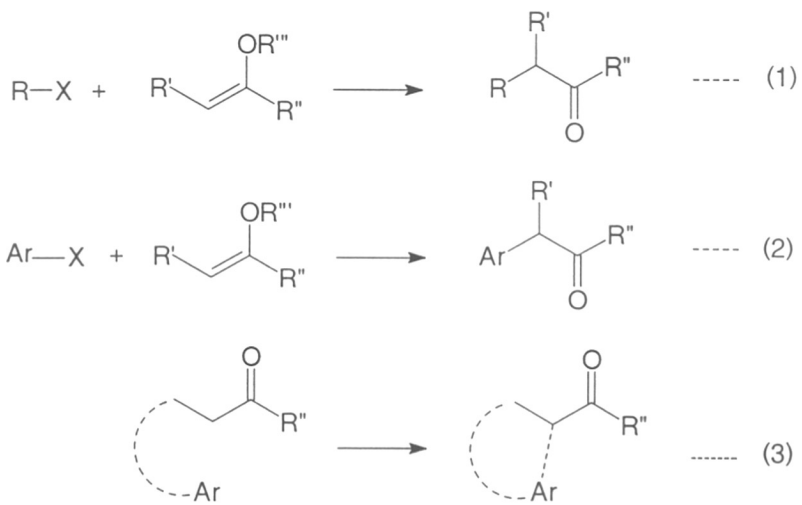
Chapter-II

Intramolecular arylation of silyl enol ethers via PET generated arene radical cations: New carbo annulation strategy

1. INTRODUCTION

Carbon-Carbon bond formation reaction adjacent to carbonyl group is one of the most important transformations in organic synthesis. These bonds are often formed by the reaction of enol silyl ethers with the activated alkyl halides (Eq..1), however, the extension of the same approach for α-arylation reaction (Eq..2) is not achievable by simple means.



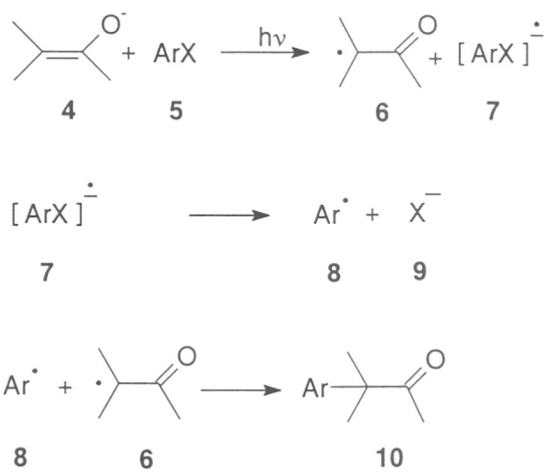
Scheme-1

α–Arylation reaction of ketones, although infrequently used, is an important C-C bond formation strategy which could be used for the rapid access of otherwise inaccessible molecules.[1-10] Particularly, intramolecular arylation of a ketone could provide an easy access to benzannulated carbocyclic compounds (Eq..3). Carboannulation processes are among the most important reactions in organic synthesis.[11-13]

Since the forgoing discussion in this chapter concerns with the development of a strategy for the intramolecular α–arylation reaction of ketones, it is pertinent to mention briefly the important methodologies reported in literature for the α–arylation reactions of ketone to put this study in total perspective.

Known α-arylation Methodologies of Ketones

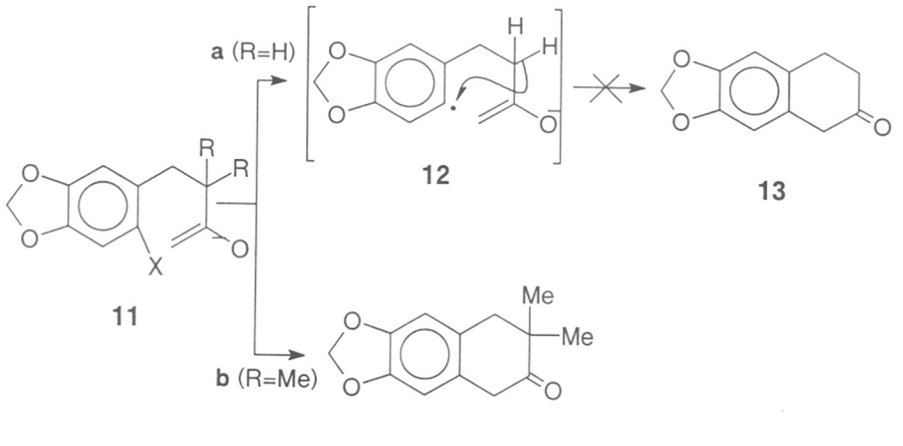
One of the earliest and most cited approach for the α-arylation reaction of ketones is the Bunnett's photochemical arylation[14] reaction. The arylation reaction is believed to occur by the $S_{RN}1$ mechanism as shown in Scheme-2.



Scheme-2

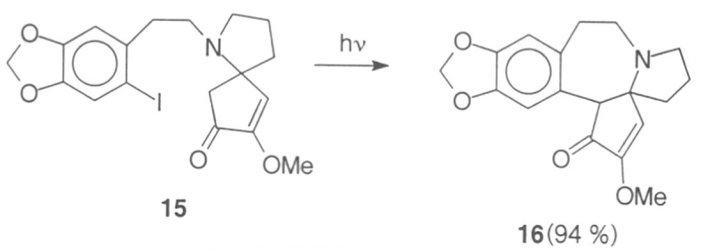
The reaction is reported to fail with the enolate ions of acetophenone and β-dicarbonyl compounds. When there is a nucleophilic site on the side chain, ring closure through intramolecular $S_{RN}1$ reaction has become a possibility, however, the intramolecular arylation reaction of **11a** (R′=R″=H), has failed to provide **13** because of competitive γ-H migration. However, with a ketone where internal H-migration

from γ-position of a ketone is blocked, for example, substrate **11b** (R=Me) on subjection to arylation reaction, efficient cyclization reaction occurs to produce **14** .



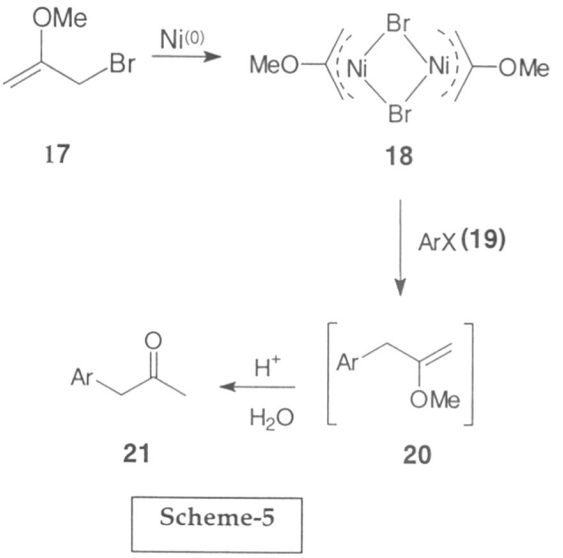
Scheme-3

This cyclization strategy has further been explored by Semmelhack and co-workers[15-17] for the synthesis of cephalotaxine **16.** (Scheme-4).



Scheme-4

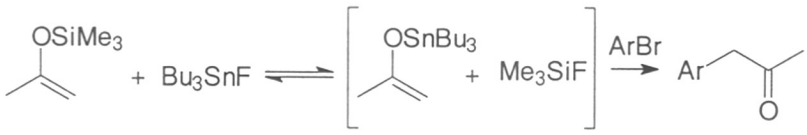
A novel α-arylation strategy for ketones is reported by utilising the reaction of *p*-2(methoxy allyl)nickel bromide complex (**18**) and aryl halide (**19**), by Hegedus *et al*,[18] under mild and neutral reaction conditions. (Scheme-5). In this approach the



Scheme-5

required complex **18** is prepared by the reaction of 2-methoxy allyl bromide (**17**) with the excess of nickel carbonyl in refluxing benzene.

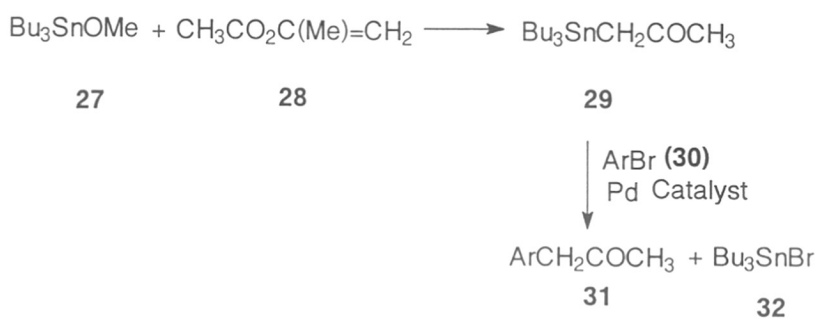
Kuwajima *et al*[19] have achieved α-arylation reaction of ketones by the coupling of aryl bromide with α-stannyl ketones (**24**) using a palladium catalyst [$PdCl_2(p(o\text{-}CH_3C_6H_4)_3)_2$]. The α-stannyl ketones are *insitu* generated by the silyl/stannyl exchange as shown in Scheme-6.



Scheme-6

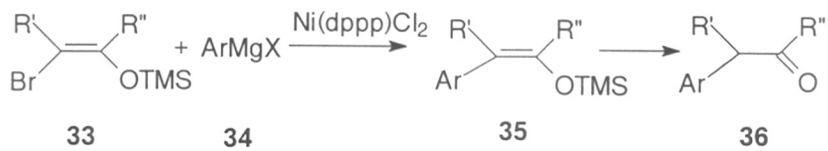
Arylacetones (**31**) are prepared[20,21] in good yield by the reaction of acetonyl tributyltin (**29**), prepared *insitu* by reacting tributyltin methoxide (**27**) and

isopropenyl acetate (**28**) with aryl bromide in the presence of a catalytic amount of $PdCl_2(o\text{-}CH_3\text{-}C_6H_4)_3)_2$.(Scheme-7)



Scheme-7

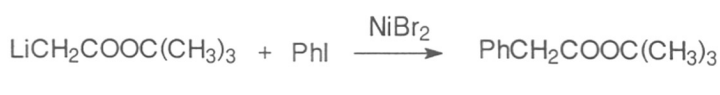
Tamao *et al*[22] have effected α–arylation reaction of a ketone, to afford **36** *via* an intermediate **35,** prepared by the coupling of *vic*-bromotrimethyl siloxy alkenes (**33**) with aryl Grignard reagent (**34**) using $Ni(Ph_2P(CH_2)_3PPh_2)Cl_2$ as a catalyst. (Scheme-8)



[dppp = $Ph_2P(CH_2)_3PPh_2$]

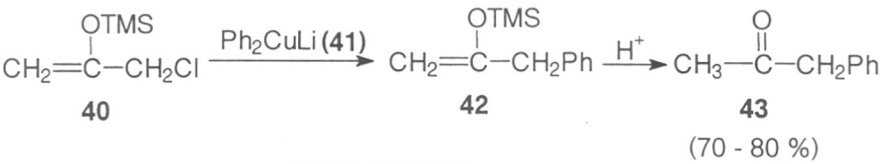
Scheme-8

α-Arylation of esters is also reported[23] by the reaction of lithium enolate of an ester (**37**) with aryl halide (**38**) using $NiBr_2$ as catalyst.



Scheme-9

A novel α-arylation reaction[24] involving nucleophilic displacement of C-Cl moiety from 2-trimethylsilyoxyallyl halide (**40**) with lithium diaryl cuprate (**41**) is reported to give α–arylated ketone **43** in 70-80 % yield.

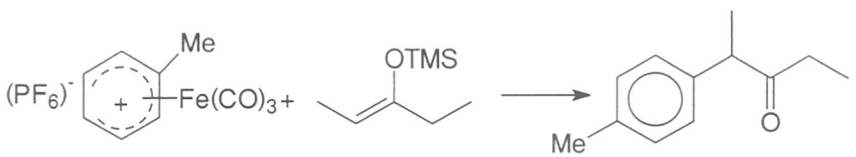


40 **42** **43**

(70 - 80 %)

Scheme-10

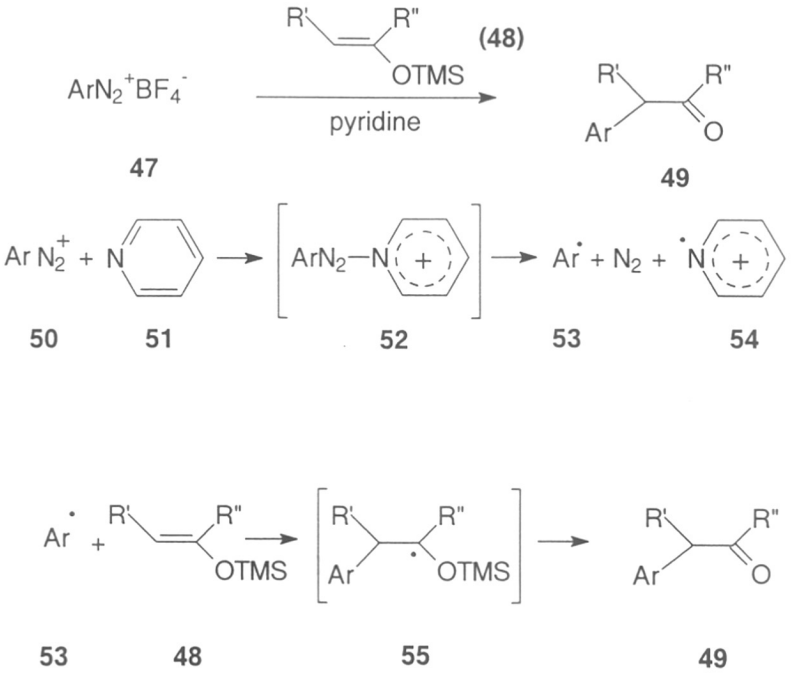
Birch *et al*[25] have utilised tricarbonyl cyclohexadienylium iron salt (**44**), as specifically substituted phenyl cation equivalent, for the arylation reaction of ketones by reacting with silyl enol ethers (**45**).



44 **45** **46**

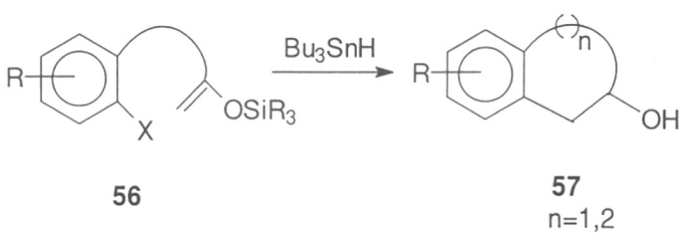
Scheme-11

α–Arylation has also been achieved[26] in good yields (72 %) by the reaction of silyl enol ethers **48** with benzene diazonium tetrafluoroborate (**47**). This reaction is believed to involve the addition of the arene radical (**53**), generated from the arenediazonium salts *via* decomposition of azo-type adducts (**52**) involving pyridine (**51**), to the silicon enolate **48** as shown in Scheme-12.



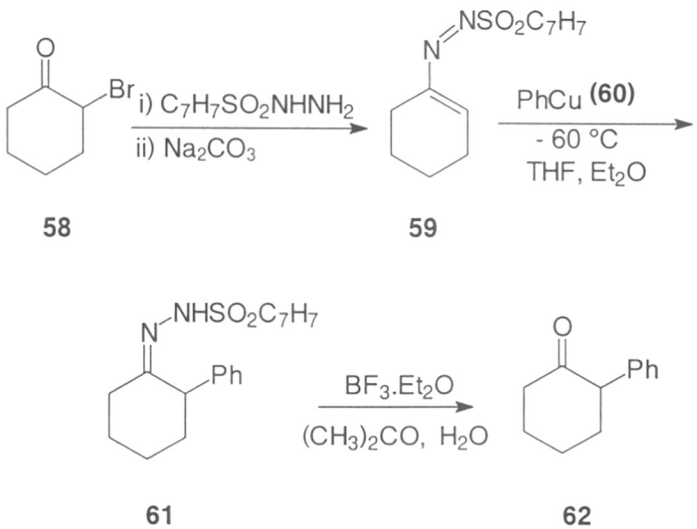
Scheme-12

Intramolecular arylation approach of a ketone, reported by Urabe *et al*,[27] has also utilised the addition of an arene radical, generated by the reaction of Bu_3SnH with an aromatic bromide of type **56**, to its tethered enol silyl ether double bond, to produce cyclic products of type **57** in 70-72 % yield (Scheme-13).



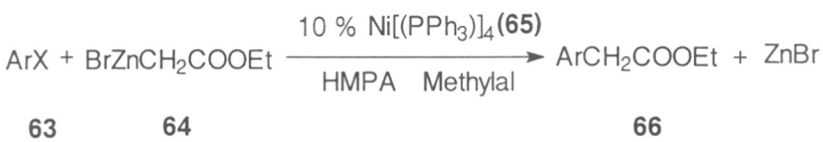
Scheme-13

α-Arylation of cyclohexanone is reported[28] in 75-80% yield by the conjugate addition of lithium diphenyl cuprate (**41**) or phenyl copper (**60**) to the *p*-toluenesulphonylazocyclohex-1-ene (**59**), prepared from tosylhydrazone of α-bromocyclohexanone (**58**) as shown in Scheme-14.



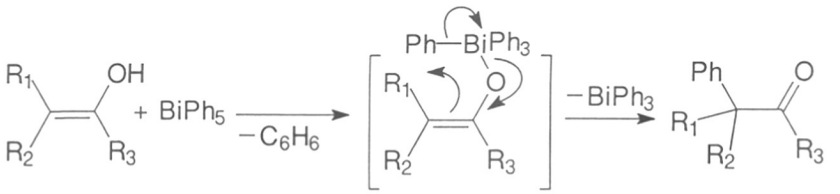
Scheme-14

Arylation of esters is also reported[29] by the reaction of a Reformatsky reagent (**64**) with an aromatic halide (**63**) to produce (**66**) in the presence of $Ni^{(0)}$ catalyst (**65**) in dipolar aprotic solvents such as HMPA, DMF, DMSO etc. (Scheme-15)



Scheme-15

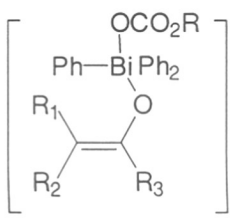
Barton's[30] group have studied the arylation of enols and enolate anions of ketones, β–diketones and keto esters using a range of Bismuth reagents. For example, the reaction of enols **67** with $BiPh_5$ **(68)** have produced **70** *via* an intermediate **(69)** possessing a covalent Bi-O bond.



67 **68** **69** **70**

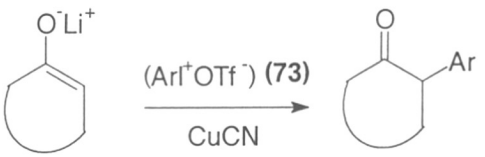
Scheme-16

The same group have also reported[31] the utilization of triphenyl bismuth carbonate for C-phenylation of enols and enolate anions *via* intermediate **71.**



71

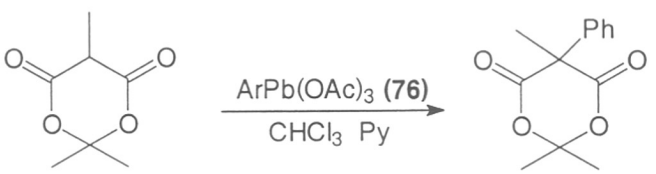
Recently, direct α–arylation[32] reaction of cyclic ketones (e.g., **74**) is reported by the reaction of a stable diphenyliodonium triflates (**73**) (ArI^+ OTf^-) with the ketone lithium enolates (**72**) in the presence of stoichiometric quantities of copper cyanide. (Scheme-17).



72 74

Scheme-17

Morgon *et al*[33] have utilized *p*-methoxy phenyl lead triacetate (**76**) for the arylation reaction of ketones of type **75**. It is reported that the reaction proceeds well at tertiary as well as at secondary α–carbons due to the activation caused by the presence of a phenyl group, however, it fails where the secondary center is unactivated (Scheme-18).



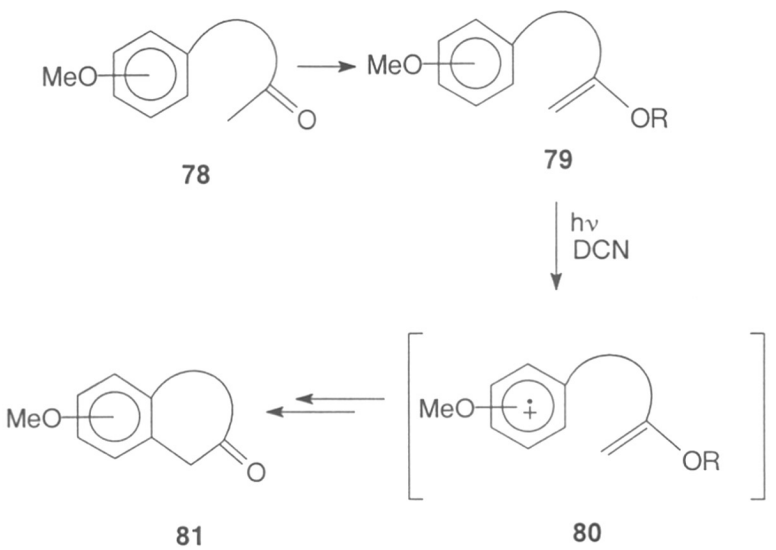
75 77

Scheme-18

2. RESULTS AND DISCUSSIONS

From the above introductory remarks, it is apparent that α–arylation of ketones are of interest from both mechanistic as well as from synthetic points of view. Therefore, we envisaged to achieve α-arylation reaction of a ketone,

particularly intramolecular, by utilizing the nucleophilic reaction of a silyl enol ether from substrate **79** to a PET generated arene radical cation **80**, affording benzannulated product (**81**) as shown in Scheme-19. This concept has originated from the successful demonstration of the nucleophilic substitution reaction of an arene moiety, observed earlier from this group, by the reaction of a nucleophile to a PET generated arene radical cations[34-38]. Generation of arene radical cation has involved an electron transfer reaction from the excited states of arene moiety to the ground state of 1,4-dicyanonaphthalene.

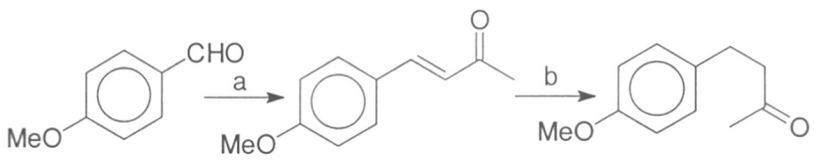


Scheme-19

2.1 Photoinduced Electron Transfer Reaction of 4-(4-methoxy-phenyl)-butan-2-one (85)

In order to evaluate the concept, as depicted in the Scheme-19, initially substrate 4-(4-methoxy-phenyl)-butan-2-one (**85**) was selected. The methoxy

substitution on the benzene ring was essential, as observed earlier[34-38], for making the arene ring capable of participating in PET processes. Compound **85** was easily obtained in 90 % yield (Fig. 1, ^{1}H NMR of **85**) by the catalytic hydrogenation of **84**, prepared by the reaction of 4-methoxy benzaldehyde (**82**) and acetone (**83**) using aqueous 10% NaOH solution as base.

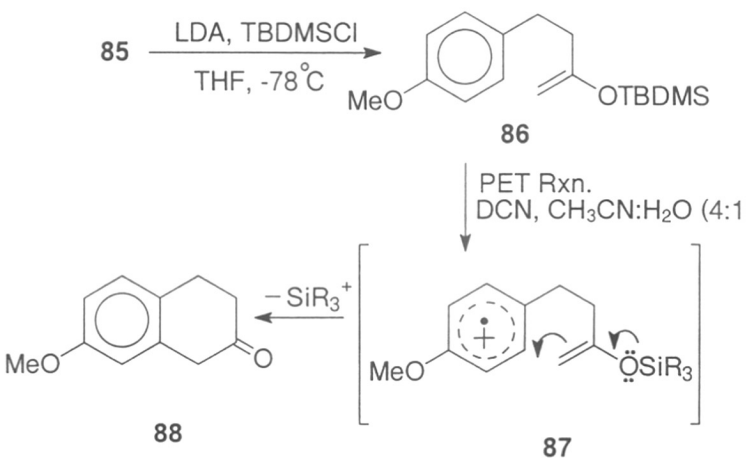


82 **84** **85**

Reagents: a) 10% NaOH, acetone (**83**), HCl, b) H_2, Pd/C, EtOH

Scheme-20

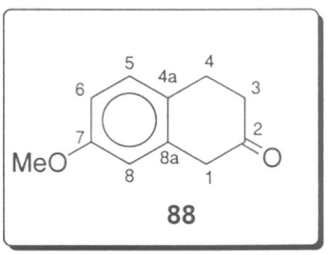
Silyl enol ether **86** was prepared quantitatively[39,40] by the reaction of TBDMSCl (6 mmol) on the lithium enolate of **85**, generated by the reaction of LDA (5 mmol) at -78 °C. Compound **86** was sufficiently pure enough to proceed to the photolysis reaction.



Scheme-21

Compound **86** (2 mmol) was dissolved into a solution of 250 mL CH_3CN:H_2O (4:1) containing DCN (0.34 mmol). The solution was placed into a immersion type photochemical reactor fitted with 450 - W Hanovia medium pressure lamp in a Pyrex filter jacket. The solution was irradiated without removing the dissolved air in it. It was ascertained by comparative UV spectroscopy that almost all the light (> 99 %) is absorbed by **86** under these experimental conditions. The irradiation was continued and the progress of the reaction was monitored by TLC for the disappearance of starting silyl enol ether (**86**). After the reaction was complete, (approximately 4 h), the solvent was evaporated under reduced pressure. Purification over silicagel column chromatography using pet.ether:EtOAc (9:1) as eluent gave **88** in 72% yield as the major product. Minor amount of ketone **85** was also isolated (approximately 10%). DCN was recovered quantitatively (~ 98 %).

IR showed a characteristic keto carbonyl peak at 1716 cm^{-1} along with other absorption bands at 2949, 1612, 1504, 1448, 1261, 1037 and 732 cm^{-1}.



88

In the ^1H NMR spectrum of **88,** (Fig. 2) one of the aromatic proton (C_{5H}) appeared as a doublet at δ 7.05 (J = 9.75 Hz) while C_{6H} proton appeared as doublet of a doublet at δ 6.75 (J_1 = 9.75, J_2 = 2.43 Hz) C_{8H} appeared as broad singlet. The singlet appearing at δ 3.75 is assigned to three protons of OMe group attached to aryl ring. The C_1 methylene protons, a characteristic for the cyclised product,

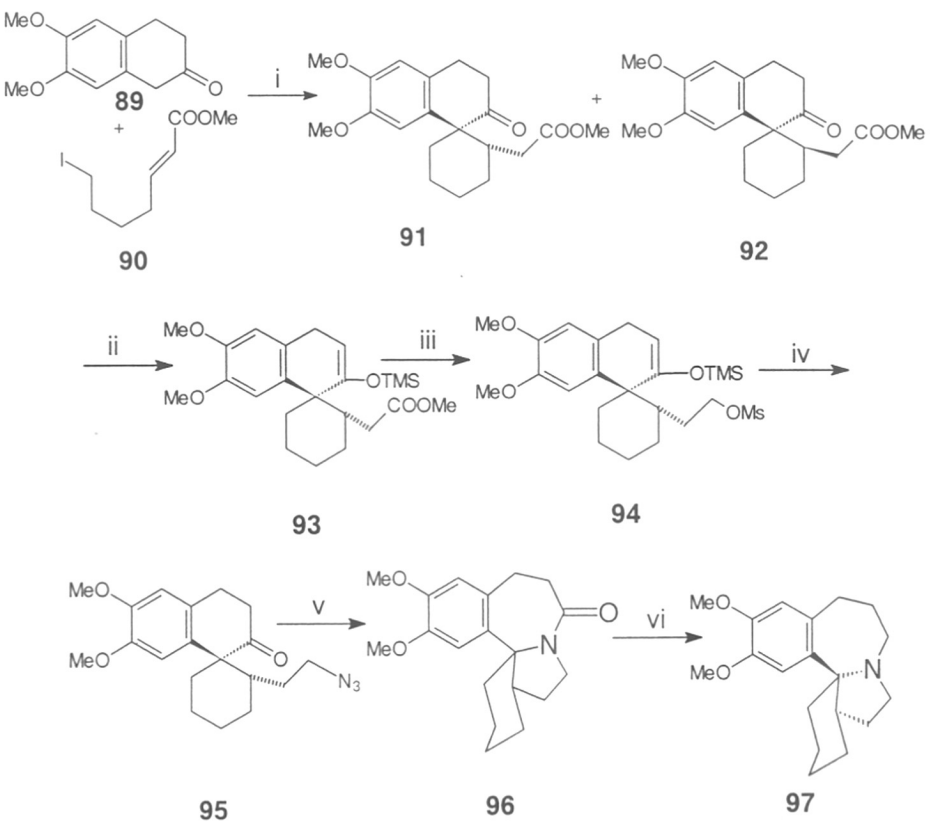
appeared as a singlet at δ 3.50. The other two sets of triplets appearing at δ 2.55 (J = 7.31 Hz) and 2.90 (J = 7.31 Hz) are assigned to the methylene protons attached to C_3 and C_4 carbons, respectively.

The ^{13}C NMR of **88** (Fig. 3a&b) showed eleven signals. The keto carbon (C_2) appeared at δ 210.23 ppm. Aryl carbon (C_7) bearing -OMe group appeared at δ 158.39. Other three aromatic carbon signals (C_6, C_8 and C_5) appeared at δ 112.16, 113.37 and 128.46, respectively. Remaining two quaternary aromatic carbons (C_{4a} and C_{8a}) appeared at δ 128.20 and 134.24, respectively. The signal appearing at δ 44.76 is assigned to the C_1 carbon. Methoxy carbon appeared at δ 54.98. The remaining two methylene carbons (C_4 and C_3) appeared at δ 27.20 and 38.23, respectively.

The mass spectrum of **88** (Fig. 4) showed molecular ion peak at 176 along with base peak at 134. Other prominent fragments were observed at 161 (5), 147 (10), 103 (17), 91(25) and 77 (17).

The formation of **88** could be explained by considering the nucleophilic reaction of silyl enol ether[36-41] to the arene radical cation (**87**), produced by an electron transfer from the excited state of **86** to ground state of DCN.(Scheme-21). The regioselectivity as observed during the cyclisation of **86** is in conformity with the earlier calculated electron densities (Huckel or MNDO) at different carbons of the HOMO of the arene radical cation[38].

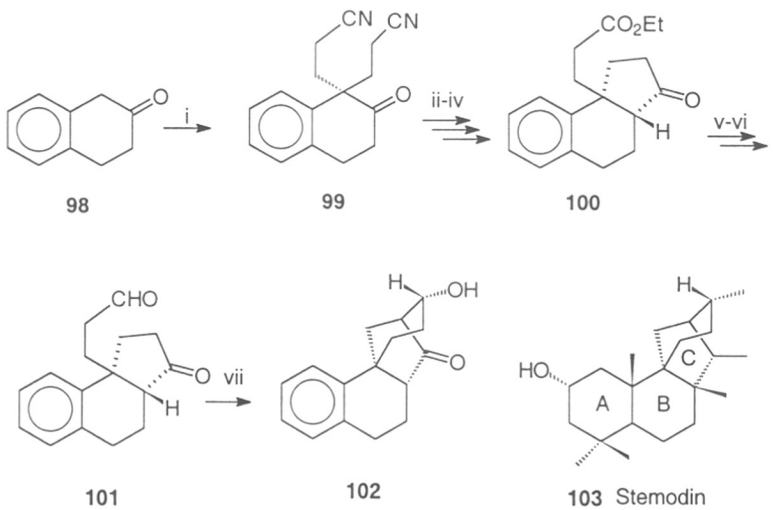
It may be visualised from the above reaction that β–tetralones can be synthesized in good yield by the PET reaction of the corresponding silyl enol ether from the ketones of type **85.** β–Tetralones are very important precursors which have been frequently utilsed during the synthesis of various kinds of biologically active compounds[45-48]. For example, substituted β–tetralone (**89**) has been utilized to prepare a crucial intermediate (**94**) during the synthesis of *homoerythirina* alkaloids (**97**) by Dreau *et al*[49] (Scheme-22).



Reagents: I) Cs_2CO_3, DMF, 20 °C; ii) TMSOTf, DCM, Et_3N, 20 °C, 48 h; iii) $LiAlH_4$, MsCl, TMS, iv) NaN_3, 53 %; v) TFA, DCM, 20 °C, 6h; vi) $LiAlH_4$, THF, 20 °C, 18h

Scheme-22

Tetracyclic skeleton (**102**), related to diterpene stemodin (**103**) also been synthesized in seven steps starting from corresponding β–tetralone **98**.



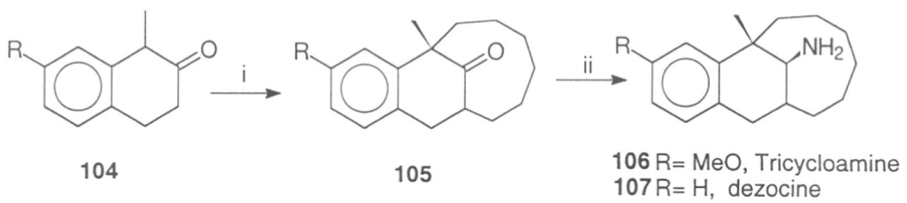
98 **99** **100**

101 **102** **103** Stemodin

Reagents: 1) Cat. Triton-B; 2 eq. CH_3CN; t-BuOH, 80 %; ii) 7 eq. Zn, 7 eq. Mg, 6 eq. TMSCl, THF reflux, iii) H_2SO_4, EtOH, reflux, 50 %, iv) H_2, Pd-C, EtOH, 80 %, v) $LiAlH_4$, ether, 65 %, vi) PCC, NaOAc, DCM, vii) pTSA, toluene, 60 °C, 37 %,

Scheme-23

Several biologically active bridghead aminotetralins[51] such as tricycloamine (**106**) and dezocine (**107**) are synthesized starting from β–tetralones **104** as shown in Scheme-24



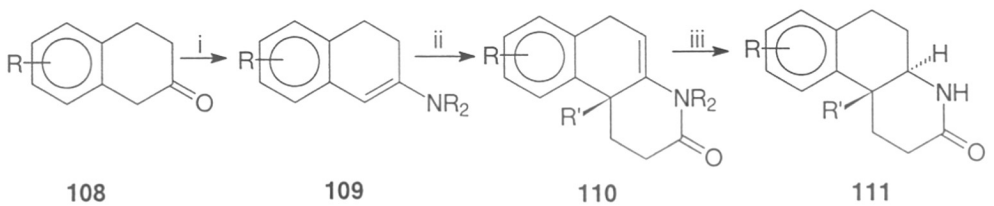
104 **105**

106 R= MeO, Tricycloamine
107 R= H, dezocine

Reagents: i) $Br(CH_2)_6Br$, NaH/DMF; ii) NH_2OH; iii) Ni / H_2

Scheme-24

Angular benzoquinolinone[52] (**111**), a potent non-competitive type-I inhibitor of 5-α–reductase; are prepared from the reaction of enamine **109,** prepared from β–tetralone (**108**), with an appropriate electrophile followed by a cyclisation protocol as shown in Scheme-25.

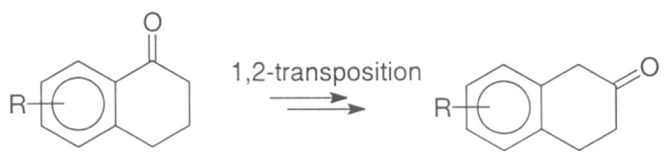


108 **109** **110** **111**

Reagents: i) R_2NH, $-H_2O$ ii) CH_2=CHCOX; iii) TES-TFA (Triethylsilane-Trifluroacetic acid.

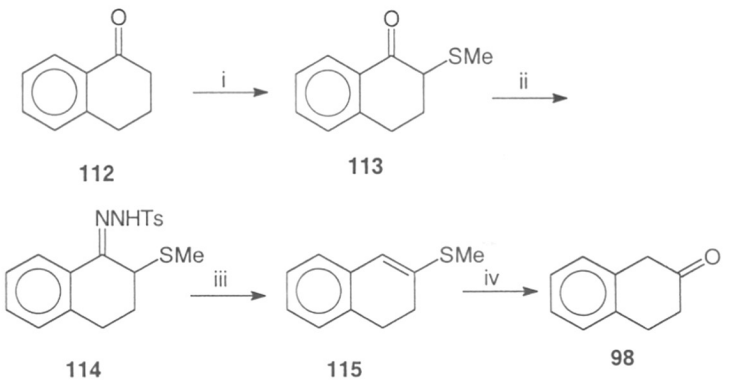
Scheme-25

In spite of the great synthetic utility of β–tetralones in the synthesis of biologically active natural products, the most common approach to access these substrates are generally *via* 1,2-transposition[53] of α–tetralones (Scheme-26). Some of the important 1,2-transposition methodologies are described as follows:



Scheme-26

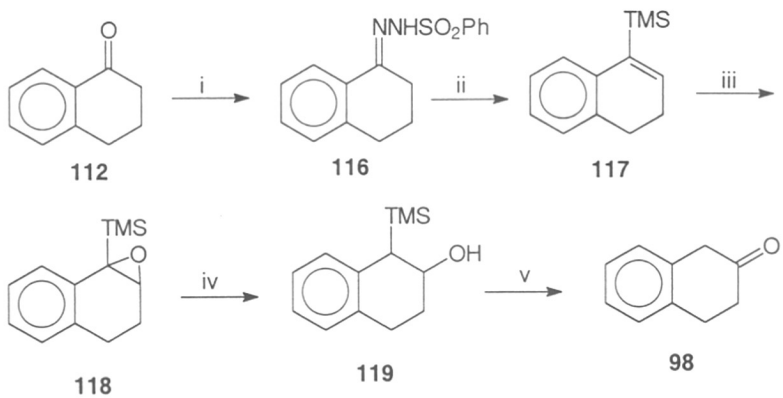
One of the important methodology[54] utilised for the 1,2-transposition of α-tetralones to β-tetralones has employed a multistep sequence involving the treatment of a crucial intermediate β–keto sulfide (**115**) with $HgCl_2$ as shown in Scheme-27. Precursor **115** is prepared in several steps from **112** (Scheme-27).



Reagents: i) LDA, MeSSMe, -78 °C ii) H_2NNHTs, iii) BuLi, iv) $HgCl_2$, MeCN, H_2O

Scheme-27

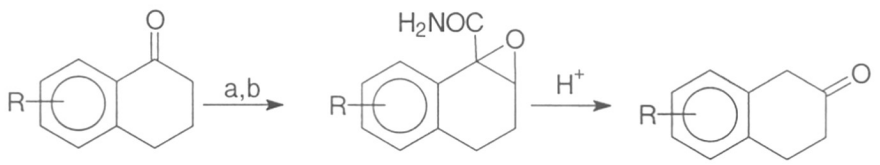
Paquette and his coworkers[55,56] have utilized another multistep sequence to achieve 1,2-ketone transposition *via* regioselective ring opening of an epoxy silane (**118**) to a β–silyl alcohol (**119**) with lithium aluminium hydride followed by its oxidation to **98** as shown in Scheme-28.



Reagents: i) H_2NNHSO_2Ph; ii) TMEDA-nBuLi, TMSCl, iii) m-CPBA, iv) $LiAlH_4$, THF, v) CrO_3-Et_2O-H_2O, H_2SO_4.

Scheme-28

Acid catalysed rearrangement of epoxy amides (**121**) is also utilized by Meyer *et al*[57] for the 1,2-transposition reaction as shown in Scheme-29.



120 **121** **122**

Reagents: a) TMSCN, ZnI_2, $POCl_3$, Py; b) n-Bu_4NHSO_4, NaOH, H_2O_2.

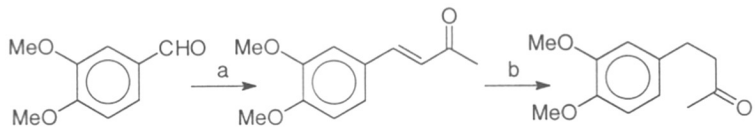
Scheme-29

From the above discussion it is apparent that β-tetralones are important precursors in natural product synthesis and are very difficult to prepare. In this context, it may be worth emphasising that our one step cyclization strategy for the synthesis of β-tetralones appear novel and far superior than the contemporary approaches known in the literature[58].

To elucidate the generality of β–tetralone formation by the direct PET initiated intramolecular α–arylation reaction, cyclisation of 4-(3,4-dimethoxy-phenyl)butan-2-one **125** was also initiated.

2.2 PET Reaction of 4-(3,4-dimethoxyphenyl)butan-2-one (125)

The precursor ketone **125** was obtained in 96% yield (Fig. 5, ^{1}H NMR of **125**) by the catalytic hydrogenation of **124**, prepared in an identical manner as described for **85** by the reaction of 3,4-dimethoxy benzaldehyde **123** and acetone in the presence of 10 % NaOH solution, as shown in Scheme-30.



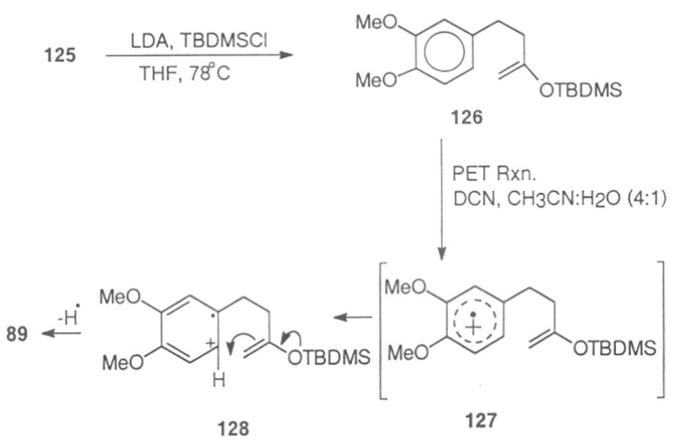
123 124 125

Reagents: a) 10% NaOH, acetone, HCl, b) H_2, Pd-C, EtOH.

Scheme-30

Silyl enol ether **126** was obtained quantitatively by the reaction of TBDMSCl (6 mmol) on the lithium enolate of **125** generated by the reaction of LDA (5 mmol) at -78 °C as described earlier for **86**.

Usual PET activation of **126**, as described for compound **86**, by irradiating a mixture of **126** (0.652 g, 2 mmol) with DCN (0.34 mmol) in CH_3CN:H_2O (4:1) using Pyrex filtered light followed by the purification of the crude reaction mixture over silica gel column chromatography using EtOAc:pet.ether (15:85) as eluent gave essentially **89** (72%) and minor amount of **125** (~10 %) as noticed in earlier case. DCN was recovered quantitatively as usual.

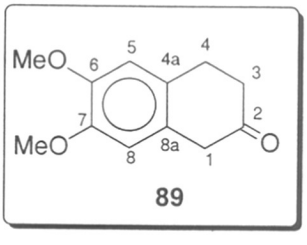


128 127

Scheme-31

IR spectrum of **89** showed a characteristic keto carbonyl peak at 1716 cm^{-1} along with other strong absorption frequencies at 2939, 1610, 1510, 1247, 912 and 731 cm^{-1}.

^1H NMR of **89** (Fig.6) showed two singlets at δ 6.75 (1H) and 6.60 (1H), characterised for the protons attached to C_5 and C_8 , respectively of the aromatic ring. The two singlets appearing at δ 3.80 and 3.85 corresponds to -OMe groups attached to the arene ring. A singlet appearing at δ 3.50 corresponds to C_1 methylene group confirming the structure of cyclization product. Other two ring methylene protons, attached to C_3 and C_4 appeared as triplet at δ 2.55 (J = 7.32 Hz) and 3.00 (J = 7.32 Hz), respectively.



89

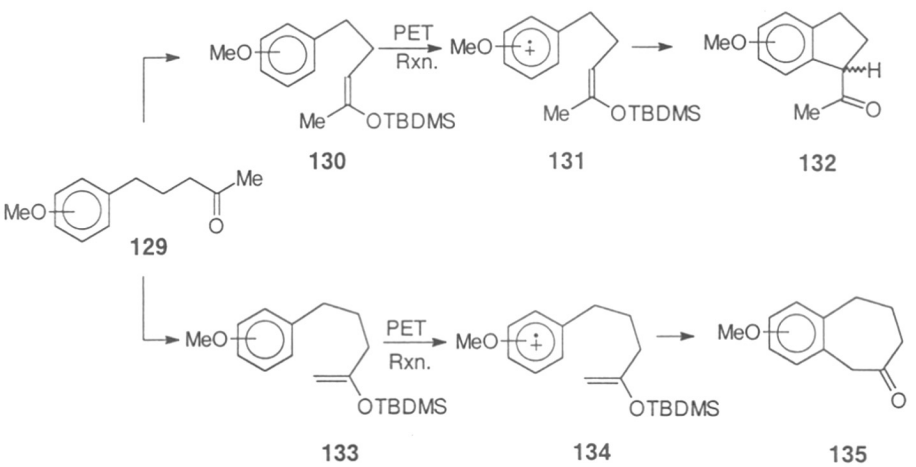
The ^{13}C NMR of **89** (Fig. 7a&b) spectrum showed eleven signals. The keto carbon (C_1) appeared at δ 209.92. The aryl carbons (C_6 and C_7) substituted with -OMe groups appeared at δ 148.19 and 147.99, respectively. Two signals appearing at δ 128.57 and 125.26 are assigned to quaternary carbons (C_{4a} and C_{8a}). Remaining other two aromatic methine (CH) carbons (C_5 and C_8) appeared at δ 111.96 and 111.67, respectively. Methoxy carbons appeared at δ 56.08. The characteristic C_1 methylene carbon appeared at δ 44.03. The other two remaining methylene ring carbons (C_3 and C_4) appeared at δ 38.41 and 28.09, respectively.

The mass spectrum of **89** (Fig. 8) showed molecular ion peak at 206 as the base peak.

Based on the above spectral data, the formation of **89** could be explained through the reaction sequence as depicted in Scheme-31.

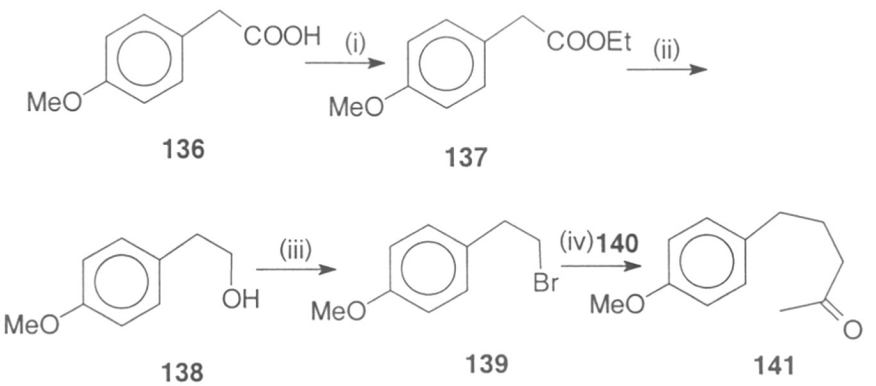
2.3. Evaluation of the present cyclization strategy for the construction of other types of benzannulated structures.

Because we hoped to maintain the versatility of this cyclisation reaction, irrespective of the number of methylene groups or the position of silyl enol ether group; cyclization reaction of respective enol silyl ethers from substrate **129** was envisioned. It was obvious to us at the beginning itself that two different types of silyl enol ethers **130** (thermodynamic) and **133** (kinetic) could be obtained from ketone **129**. Therefore, the arylation of these enol silanes was expected to produce two different types of annulated compounds **132** and **135**, respectively.



Scheme-32

To realise the above objective, substrate **141** was envisioned which was synthesised in 88 % yield (Fig. 9: ^{1}H NMR of **141**) by the alkylation of N,N-dimethyl acetone hydrazone (**140**) with **139** using n-BuLi in anhydrous THF, followed by the removal of the hydrazone moiety through a oxidation step using $NaIO_4$. The required bromide **139** was obtained from the 4-methoxy phenyl acetic acid **136** employing simple chemical steps as shown in the Scheme-33.



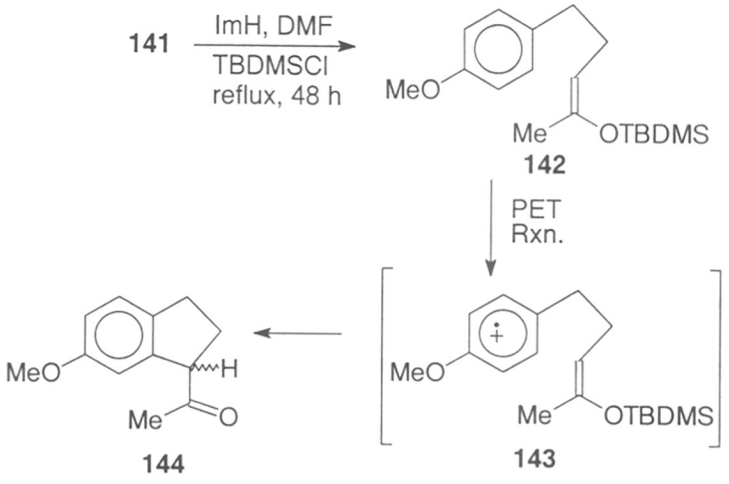
Reagents: i) EtOH/H^+, benzene, reflux; ii) $LiAlH_4$, THF, reflux; iii) PBr_3 , pyridine, benzene, reflux; iv) **140**, n-BuLi, THF, -78 °C, $NaIO_4$, THF/MeOH;

Scheme-33

2.3.1 PET transformation of 141 into corresponding 1-(2,3-dihydro-1H-1-indenyl)-1-ethanone derivative (144).

In order to evaluate the feasibility of transforming **141** into corresponding indane system **144,** first silyl enol ether **142** was prepared in 83 % yield by heating a mixture of **141** (5 mmol), TBDMSCl (6 mmol) and imidazole (12 mmol) in DMF (10 mL) for 48 h. (Scheme-34)

Usual PET activation of **142**, as described for **86**, afforded indenyl product **144** in 65 % yield along with quantitative recovery of DCN and minor amount (< 8 %) of starting ketone **141**. Compound **144** was characterised by the spectral analysis as illustrated below:

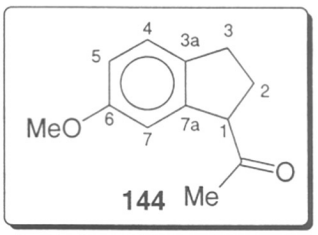


Scheme-34

IR spectrum of **144** showed a characteristic keto carbonyl peak at 1710 cm^{-1} along with other strong absorption frequencies at 2950, 1610, 1500 and 1160 cm^{-1}.

^1H NMR of **144** (Fig. 10) showed a doublet for the proton attached to C_4 at δ 7.20 (J = 9.75 Hz), integrating for one proton. A doublet of doublet appearing at δ 6.70 (J_1 = 9.75, J_2 = 2.81 Hz) corresponds to protons attached to C_5 and proton attached to C_7 appeared as a broad singlet at δ 6.75. A triplet appearing at δ 5.75 (J = 6.94 Hz) corresponds to one proton attached to C_1. The methoxy group protons appeared as a singlet at δ 3.80 integrating for total three protons. Another triplet at δ 2.75 (J = 7.31 Hz, 2 H) corresponds to (C_3) benzylic protons and another multiplet

appearing between δ 2.20-2.30 corresponds to C_2 methylene protons. A singlet at δ 2.05 corresponds to three protons of keto methyl moiety.



The ^{13}C spectrum **144** (Fig. 11) showed twelve signals. The keto carbon signal appeared at δ 206.23. The aromatic carbon signal substituted with -OMe group (C_6) appeared at δ 158.07. Three aryl methine (CH) carbons (C_4, C_5 and C_7) appeared at δ 128.23, 114.03 and 111.50, respectively. Other two aromatic quaternary carbons C_{3a} and C_{7a} appeared at 137.66 and 131.38, respectively. The methine carbon (C_1) signal appeared at δ 61.73. The methoxy carbon appeared at δ 55.20. The signal appearing at δ 31.45 corresponds to keto methyl carbon. Other two methylene carbons (C_2 and C_3) appeared at δ 28.26 and 23.45 respectively.

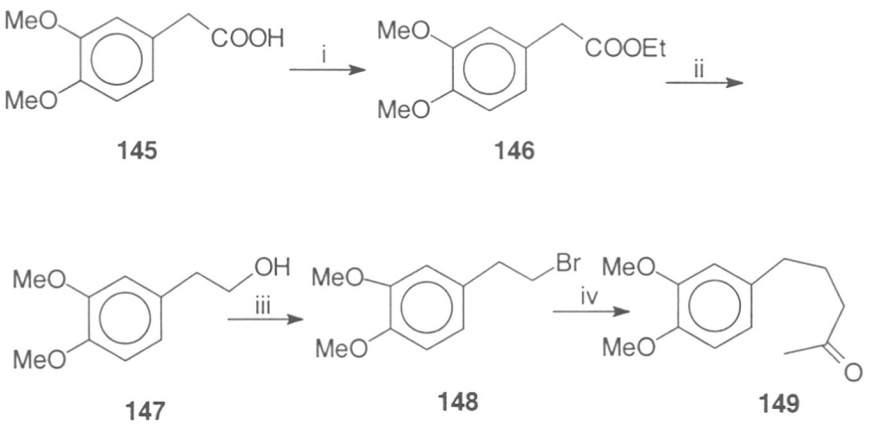
The mass spectrum (Fig. 12) showed molecular ion peak at 190 with other prominent fragmentations at 174, 159, 144, 128, 115, 103.

From the above spectral data the product structure was confirmed as **144** .

The compounds containing indane frame works have musk like aroma and are used in perfumery industries as additives to intensify the perfume fragrance[59]. Indanes are also important substructures in natural products and other related biologically active counterparts[60] . Therefore, it may be mentioned that our strategy

provides an easy route for the construction of indane related compounds in very good yields.

To test the generality of such cyclization reactions, compound **149** was also included in our study. Compound **149** was prepared, (Fig. 13, ^1H NMR of **149**) starting with commercially available 3,4-dimethoxy phenylacetic acid **145**, employing the steps as depicted in Scheme-35.



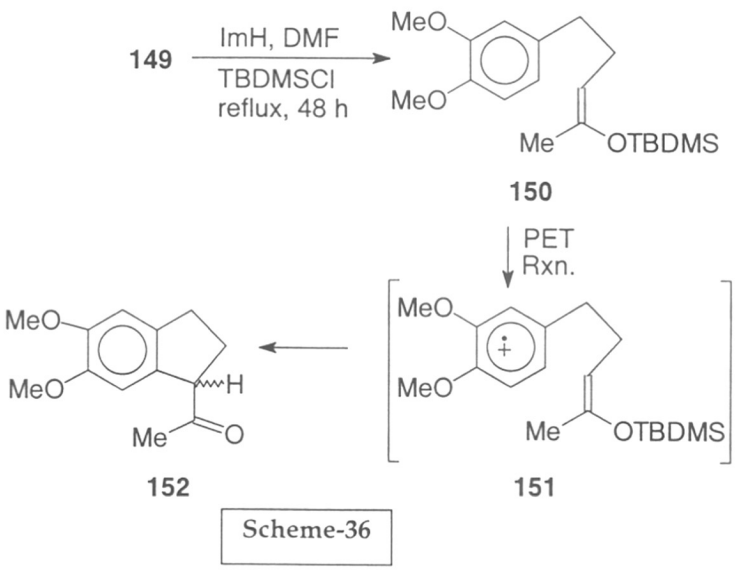
Reagents: i) EtOH / H^+, benzene, reflux; ii) $LiAlH_4$, THF, reflux; iii) PBr_3, pyridine, benzene, reflux; iv) **140**, n-BuLi, THF, -78 °C, $NaIO_4$, THF / MeOH;

Scheme-35

2.3.2 PET initiated Reaction of 150 to prepare 1-(5,6-dimethoxy-2,3-dihydro-1H-1-indenyl)-1-ethanone (152).

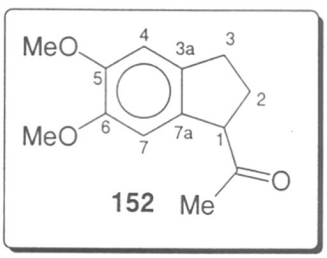
Corresponding silylenol ether **150**, required for the construction of indane framework, was obtained from **149** by following the reaction sequences as described for **142.** The cyclisation of **150** to **152** was achieved in 74 % yield, by photolysing a

mixture of **150** (2 mmol) and DCN (0.34 mmol) in CH_3CN:H_2O (4:1) in an identical manner as described for **86**. The spectral characterisation of **152** is described below:



Scheme-36

IR spectrum of **152** showed a characteristic peak of a ketone at 1710 cm^{-1} along with other strong absorption frequencies at 2930, 1590, 1495, 1250 and 1150 cm^{-1}.



^1H NMR spectrum (Fig. 14) showed two singlets appearing at δ 6.85 and δ 6.70 for the aromatic protons attached at C_4 and C_7, respectively. A triplet for methine proton (attached to C_1) was observed at δ 5.75 (J = 6.94 Hz). Two sets of methoxy protons appeared as singlets at δ 3.90 and 3.85. Another triplet at δ 2.70 (J

= 7.32 Hz) corresponds to benzylic methylene (C_3) protons. A multiplet appearing at δ 2.20 is assigned to C_2- methylene protons. Keto methyl protons appeared as singlet at δ 2.05.

The ^{13}C NMR (Fig. 15) showed thirteen signals. The keto carbon signal appeared at δ 206.26. The aromatic carbons (C_5 and C_6) bearing methoxy groups appeared at δ 148.35 and 146.99, respectively. Another two aromatic carbons (C_4 and C_7) appeared at 106.95 and 110.86, respectively. Two quaternary aryl carbons (C_{7a} and C_{3a}) appeared at δ 136.33 and 132.43, respectively. The C_1 carbon appeared at δ 62.17. Two methoxy carbons appeared at δ 55.65 and 54.78. Keto methyl carbon appeared at δ 30.43. Carbons C_3 and C_2 appeared at δ 26.95 and 22.60, respectively.

The mass spectrum of **152** (Fig. 16) showed molecular ion peak at 220 with a base peak at 204 along with other prominent fragments at 173, 121, 91 and 77.

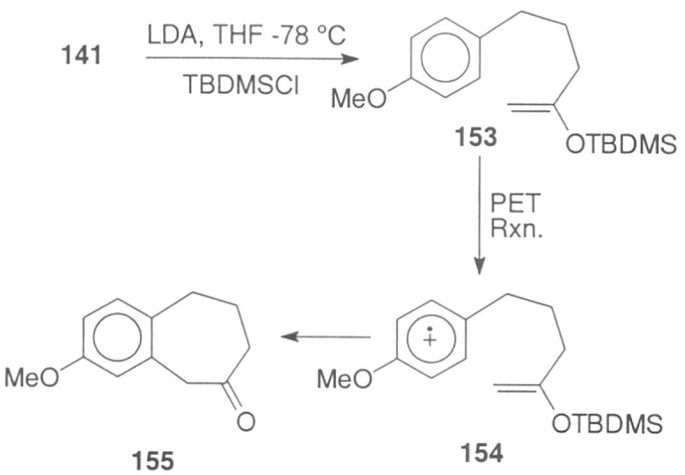
From the above spectral evidences the structure of **152** was confirmed.

2.3.3 PET initiated cyclisation of 153 to 3-methoxy-6,7,8,9-tetrahydro-5*H*-benzo[a]cyclohepten-6-one (155)

In order to evaluate the feasibility of transforming **141** into corresponding 3-methoxy-6,7,8,9-tetrahydro-5*H*-benzo[a]cyclohepten-6-one (**155**), silyl enol ether **153** was prepared in good yield (95%) by the reaction of TBDMSCl on the lithium

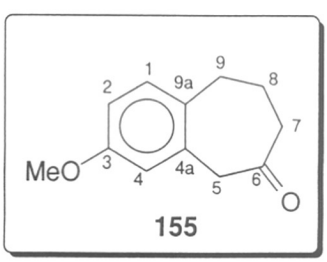
enolate of **141,** generated by the reaction of LDA at -78 °C in an identical manner as described from **85**.

Photolysis of a mixture of **153** (2 mmol) and DCN (0.34 mmol) in $CH_3CN:H_2O$ (4:1) in an identical manner as described for **86,** gave **155** as the major product (74 %). The spectral characterisation of **155** is described as follows:



Scheme-37

IR spectrum of **155** showed a characteristic C=O peak at 1700 cm^{-1} along with other strong absorption bands at 2940, 2260, 1610, 1500 and 940 cm^{-1}.



^{1}H NMR (Fig. 17) showed a doublet at δ 7.05 (J = 9.75 Hz), assigned to C_1 aryl proton while protons attached to C_2 appeared as a doublet of doublet (J_1 = 9.75, J_2 = 2.82 Hz) at δ 6.75 and protons attached to C_4 appeared as a broad singlet at δ 6.70. A sharp singlet appearing at δ 3.75 (3H) corresponds to methoxy protons. Another singlet, characteristics of cyclized product, integrating for two protons ($C_{5\text{-}H}$) appeared at δ 3.65. The remaining other three methylene group protons, attached to C_9, C_8 and C_7, appeared at δ 2.90 (t, J = 7.31 Hz), 2.05 (m) and 2.55 (t, J = 7.31 Hz), respectively.

The ^{13}C NMR spectrum (Fig. 18a&b) showed a total of twelve signals. Characterization of each signal for corresponding carbons is suggested by INEPT experiment, which are as follows: The signal appearing at δ 208.95 is assigned to keto carbon. The aromatic carbon C_3 bearing -OMe group appeared at δ 159.01. The two aromatic quaternary carbons (C_{4a} and C_{9a}), appeared at δ 130.39 and 125.64, respectively. Three remaining aromatic carbon signals appeared at δ 141.81, 115.35 and 111.56, respectively. The methoxy carbon signal appeared at δ 55.21. The characteristic methylene carbon signal for C_5 appeared at δ 49.19. Remaining three methylene carbon signals for C_1, C_2 and C_3 appeared at δ 33.25, 26.23 and 43.54, respectively.

Mass spectrum (Fig. 19) showed molecular ion peak at 190 (42%) along with base peak at 134.

Based on the above spectral data the structure of **155** was confirmed.

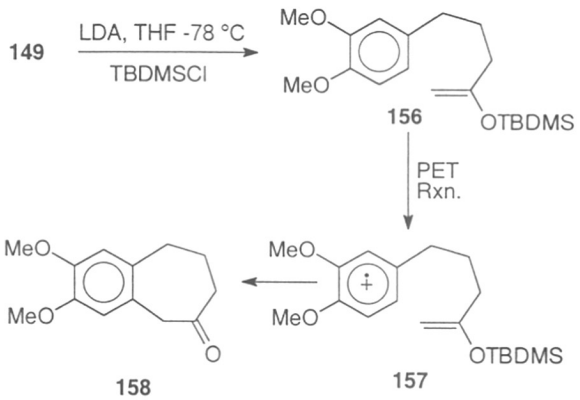
In comparison to five and six membered ring forming reactions, relatively few methods exist for the direct construction of seven and eight membered rings. Therefore, our strategy developed for the construction of benzocycloheptane framework (**135**) is an important achievement in synthetic organic chemistry. Moreover, there are many biologically important compounds possessing benzocycloheptane framework[62] and the application of this methodology would have wider scope.

To test the generality of these reactions, identical PET reaction from substrate **156** was also studied.

Substrate **156** was obtained by the usual kinetic silyl enolisation of ketone **149** as described above for **85.**

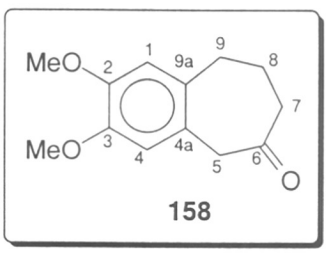
2.3.4 PET initiated cyclisation of 156 to 3,4-dimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[a]cyclohepten-6-one (158)

Photolysis of a mixture of **156** (2 mmol) and DCN (0.34 mmol) in CH_3CN:H_2O (4:1), in an identical manner as described for photolysis of **86**, gave **158** as the major product (74 %). (Scheme-38). The spectral characterisation of **158** is described below:



Scheme-38

IR spectrum of **158** showed a characteristic peak at 1700 cm^{-1} indicating the presence of keto carbonyl functionality in the product.



^{1}H NMR spectrum of **158** (Fig. 20) showed two singlets at δ 6.73 (1H) and δ 6.70 (1H) corresponding to the aromatic protons attached to C_1 and C_4, respectively. Two signals appearing as singlets at δ 3.90 and 3.87, respectively, can be assigned to the MeO- protons. A singlet, integrating for two protons and assignable to the protons attached to C_5 appeared at δ 3.65. The remaining other three methylene group protons, attached to C_9, C_8 and C_7, appeared at δ 2.90 (t, J = 7.07 Hz), 2.00 (m) and 2.55 (t, J = 7.07 Hz), respectively.

The ^{13}C NMR spectrum of **158** (Fig. 21a&b) showed a total of thirteen signals. Characterization of each of the carbon signal is suggested by the INEPT experiment

which are described as follows: The signal appearing at δ 208.97 corresponds to C_6 keto carbon. The aromatic carbons (C_2 and C_3) bearing two -OMe groups appeared at δ 148.12 and 147.79, respectively. Two aromatic quaternary carbons C_{4a} and C_{9a} appeared at δ 132.93 and 125.48, respectively. Carbons C_1 and C_4 appeared at δ 113.51 and 113.24, respectively. The two methoxy carbons appeared at δ 56.21 and 55.91, respectively. The characteristic C_5 methylene carbon signal appeared at δ 49.81. Remaining three methylene carbon signals corresponding to C_9, C_8 and C_7 appeared at δ 32.95, 26.93 and 44.05, respectively.

Mass spectrum of **158** (Fig. 22) showed molecular ion peak (m/z) at 220 along with other prominent fragments at 192 , 177 , 164, 149, 121 and 91.

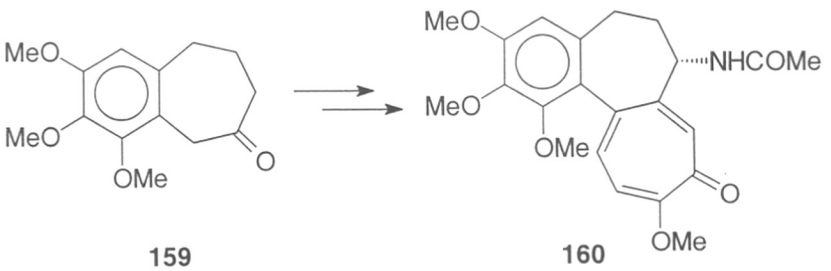
Based on the above structural elucidations the structure of **158** was confirmed.

2.4 Synthesis of 1,2,3 - trimethoxy - 6,7,8,9 - tetrahydro - 5*H* -benzo [a] cyclohepten-6-one (166): A Colchicine precursor

Since above cyclization protocol gave compounds of type 6,7,8,9-tetrahydro-5*H*-benzo[a]cyclohepten-6-one (**155** and **158**) in good yield, we became interested to extend the scope of this methodology for the synthesis of 1,2,3-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[a]cyclohepten-6-one (**159**), widely used as a precursor for the synthesis of a potent mitotic inhibitor colchicine[61-63].

Colchicine **160,** the principal alkaloid of the autumn crocus *(Colchicum autumnale L.)* was isolated and characterised in the early part of the nineteenth

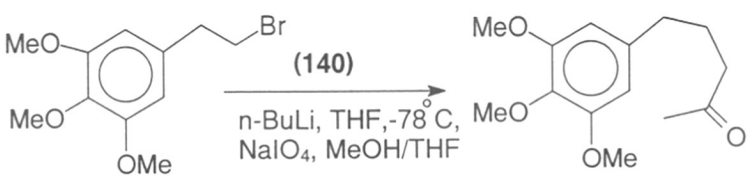
century and since then this compound has been an object of study for the chemical, biological and medical properties. Apart from its long standing use in the treatment of gout, the potential of colchicine as an anti-cancer agent is noteworthy[63].



159 **160**

Colchicine

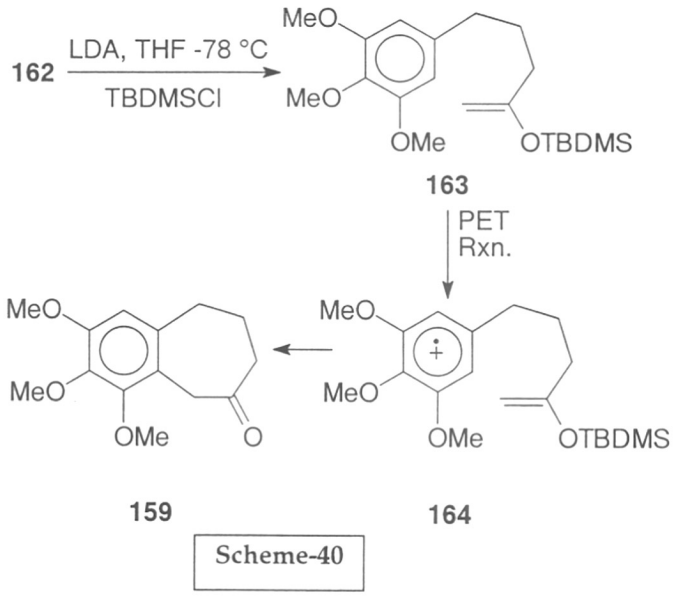
The ketone (**162**), required for the synthesis of **159** - a colchicine precursor, was prepared (Fig. 23, ^1H NMR of **162**) by the reaction of 2,3,4-trimethoxy phenylethyl bromide (**161**) with **140**, by following the reaction condition as described for **149** (Scheme-39).



161 **162**

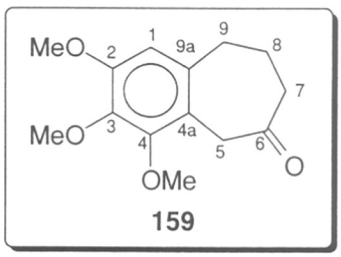
Scheme-39

Kinetic silyl enolisation, by following the exact reaction protocol as reported for **86**, of ketone **162** gave corresponding silyl enol ether **163**. PET cyclisation by irradiating a mixture of **163** (2 mmol) in the presence of DCN (0.34 mmol) in CH_3CN:H_2O (4:1), in an identical manner as described for **86**, gave **159** as the major product (72 %). The spectral characterisation of **159** is described as follows:



Scheme-40

IR spectrum of **159** showed a characteristic keto carbonyl band at 1706 cm^{-1}. The other prominent absorption bands were observed at 2938, 1492,1410, 1120 cm^{-1}.



159

^1H NMR spectrum of **159** (Fig. 24) showed one singlet at δ 6.50 (1H) corresponding to $C_{1\text{-}H}$ aromatic proton. Three -OMe group protons appeared as two singlets δ 3.90 (6H) and 3.85 (3H). The characteristic singlet for the $C_{5\text{-}CH2}$ was observed at δ 3.75 (2H). The remaining other three methylene protons (i.e. $C_{9\text{-}CH2}$, $C_{8\text{-}CH2}$ and $C_{7\text{-}CH2}$) appeared at δ 2.85 (t, J = 7.1 Hz), 1.95 (m) and 2.55 (t, J = 7.10 Hz), respectively.

The ^{13}C NMR spectrum (Fig. 25a&b) showed a total of fourteen signals. Characterization of each carbon signal is suggested by INEPT experiment which are as follows: The signal appearing at δ 209.84 corresponds to C_6 keto carbon. The aryl carbons bearing three -OMe groups appeared at δ 152.35, 151.58 and 141.21, respectively. Two aromatic quarternary carbons, C_{4a} and C_{9a}, appeared at δ 136.49 and 119.88, respectively. Methine carbon C_1 appeared at δ 108.96. The three methoxy carbons appeared at δ 61.57, 61.05 and 56.23, respectively. The characteristic C_5 methylene carbon signal appeared at δ 43.36. Remaining other three methylene carbon signals for C_9, C_8 and C_7 appeared at δ 33.34, 26.67 and 41.47, respectively.

Mass spectrum (Fig. 26) showed molecular ion peak (m/z) at 252, along with other peaks at 219, 190, 161, 147, 134, 105, 91 and 77.

The spectral values as observed for **159** was found comparable with the spectral values reported in literature[61].

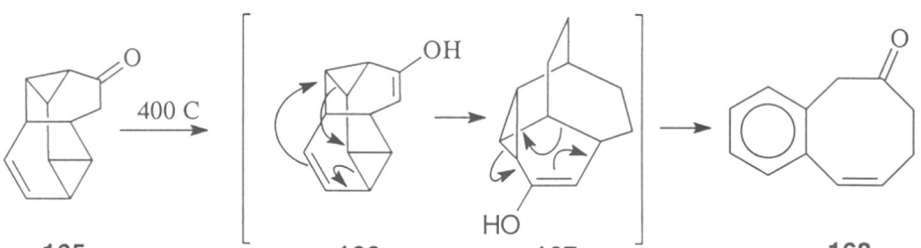
2.5 Synthesis of 2,3 - dimethoxy - 6, 7, 8, 9, 10 - pentahydro - 5*H* - benzo [a] cycloocten-7-one (185):

From the preceding discussion it is clear that our methodology of intramolecular cyclisation of enol silyl ether to the PET generated arene radical cation can afford benzannulated (five, six and seven membered) product efficiently. The spectacular success of this strategy, encouraged us to explore the application of this strategy for the construction of benzene fused eight membered ring compound

owing to their importance and synthetic challenge. The construction of eight membered rings is often most difficult task because of entropy factors and transannular interactions[64-66]. Excellent review on the various methods of constructing cyclooctane ring system is written by Patasis[67].

Before dwelling into the attempt and success of our methodology for the construction of benzocyclooctanone ring system by the above methodology, it would be appropriate to discuss briefly the literature methodologies in this context.

Miyashi *et al* have reported[68] a remarkable one pot thermal rearrangement strategy to obtain benzocyclooctenone (**168**) from a polycyclic ketone (**165**) involving a series of homo-Cope, retro Diels-Alder and 1,5 hydrogen shift reactions (Scheme-41).

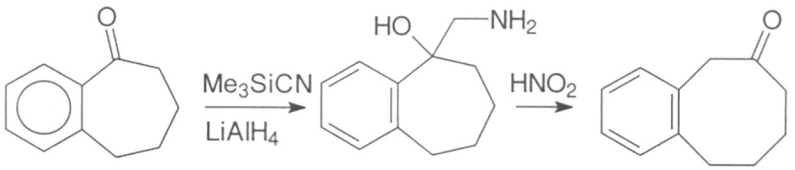


165 **166** **167** **168**

Scheme-41

Thies *et al*[69,70] have utilized Tiffeneu-Demyanov ring expansion reaction[71] from the aminoalcohol (**170**) for the synthesis of benzene fused cyclooctanone moiety (**171**) in 80 % yield. The precursor **170** is obtained by the reaction of

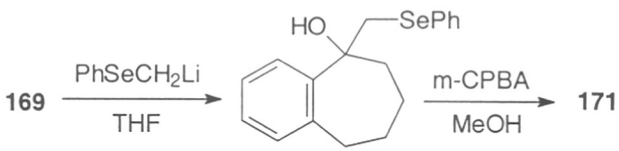
benzocycloheptanone (**169**) with TMSCN followed by reduction with $LiAlH_4$ (Scheme-42).



169 **170** **171**

Scheme-42

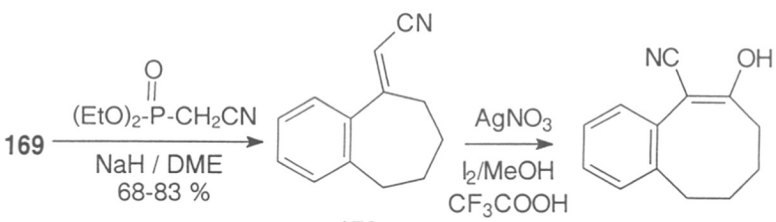
One carbon homologation strategy for the synthesis of **171** is also reported[72] *via* the addition of phenyl seleno methyl lithium to **169** followed by the oxidative rearrangement as shown in Scheme-43.



172

Scheme-43

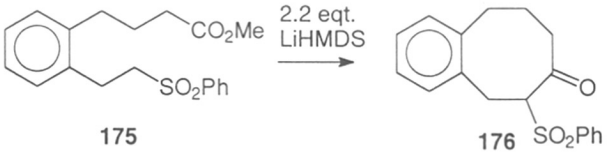
Silver nitrate mediated olefination-ring expansion sequence from **169** is utilised[73] to synthesise **174** as shown in Scheme-44.



173 **174**

Scheme-44

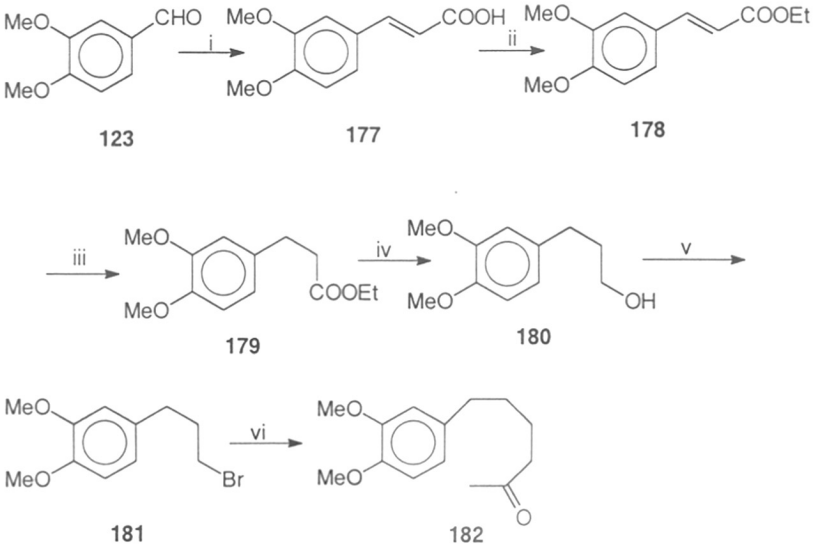
Recently Grimm[74] *et al* have reported a novel synthetic approach to construct (**176**) *via* intramolecular cyclization of a sulfone stabilized carbanion, generated by the reaction of sulfone ester **175** and lithium bis(trimethylsilyl)amide (LiHMDS) in THF (Scheme-45).



175 **176**

Scheme-45

In order to evaluate the application of arene radical cation based intramolecular cyclisation strategy for the construction of benzofused cyclooctanone skeleton, compound **182** was prepared (80 % yield) (Fig. 27, ^{1}H NMR of **182**) from **123** by following the sequence of chemical reactions as depicted in Scheme-46.



123 **177** **178**

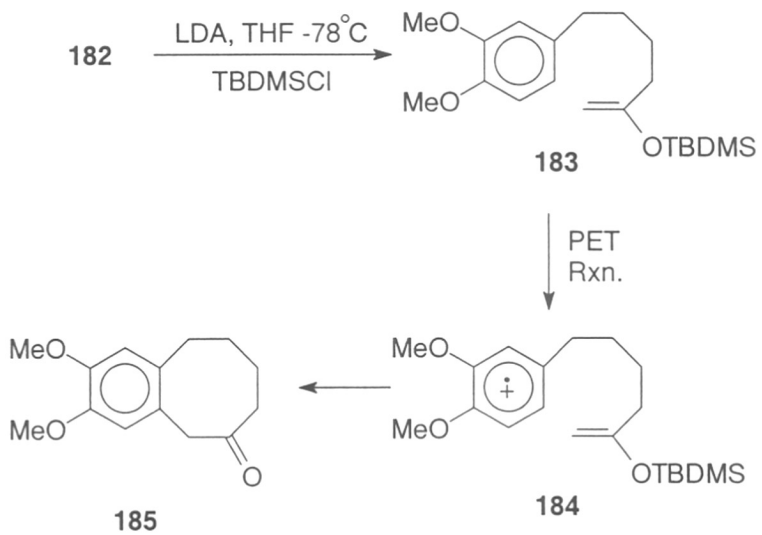
179 **180**

181 **182**

Reagents: i) Malonic acid, pyridine, piperidine, reflux, H^+; ii) EtOH/H^+; iii) H_2, Pd-C, EtOH; iv) $LiAlH_4$, THF, reflux; v) PBr_3,pyridine (cat), Benzene; reflux; vi) **140**, n-BuLi, THF, -78 °C, MeOH/THF, $NaIO_4$.

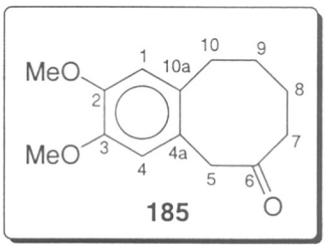
Scheme-46

Enol silyl ether (**183**) was obtained by the usual kinetic silyl enolisation reaction, as described for **86**, from the corresponding ketone **182**. PET activation of a mixture of **183** (2 mmol) and DCN (0.34 mmol) in CH_3CN:H_2O (4:1), in an identical manner as described for the synthesis of **88**, gave **185** (60 %, m.p. 85-86.5 °C) as the major product (Scheme-47). Some amount of starting ketone (10 %) was also recovered in this case too. The spectral characterisation of **185** is described below:



Scheme-47

IR spectrum of **185** showed an intense peak at 1700 cm^{-1}, suggesting the presence of keto carbonyl group in the product. The other major absorption frequencies were observed at 3040, 2960, 1620, 1450, 1230, 1120 cm^{-1} .



185

^{1}H NMR spectrum of **185** (Fig. 28) showed two singlets at δ 6.65 (1H) and 6.70 (1H) for the protons attached to aromatic carbons C_1 and C_4 , respectively. Other two singlets observed at δ 3.90 and 3.85, integrating for three protons each, are assigned to -OMe groups. A sharp singlet appearing at δ 3.70 (2H) corresponds to methylene protons (C_5-CH_2) confirming the cyclization reaction. Methylene group protons attached to C_7 and C_{10} appeared as triplets at δ 2.35 (J = 6.94 Hz) and 2.80 (J = 6.94 Hz), respectively. A multiplet at δ 1.80 (4H) corresponds to C_8 and C_9 methylene protons.

The ^{13}C NMR spectrum of **185** (Fig. 30a&b) showed thirteen signals and characterization of each carbon signal is suggested by the INEPT experiment which are as follows: The signal appearing at δ 211.76 corresponds to C_6 keto carbon. The aromatic carbons C_2 and C_3, bearing -OMe groups, appeared at δ 148.68 and 147.69, respectively. Two aromatic quarternary carbons C_{4a} and C_{10a}, fused with cyclooctanone moiety, appeared at δ 133.13 and 125.63, respectively. C_1 and C_4 methine carbon signals appeared at δ 113.38 and 113.15, respectively. Both of the methoxy carbons appeared at δ 56.03. The characteristic C_5 methylene carbon signal appeared at δ 48.19. Other four methylene carbons (C_{10}, C_9, C_8 and C_7) appeared at δ 32.94, 31.33, 24.71 and 41.12, respectively.

Mass spectrum of **185** (Fig. 30) showed molecular ion peak (m/z) at 234, along with other fragmentation peaks at 206 , 191 , 175 , 165, 121 , 107 , 91.

From the above spectral evidences the structure of **185** was confirmed.

Conclusion

From the above study it is concluded that we have successfully established a new α–arylation methodology involving the reaction of silyl enol ether to PET generated arene radical cations. Further studies for the synthetic utility of these reactions are under progress.

3. EXPERIMENTAL SECTION

3.1 General

Melting points were determined in open capillaries with a Metler FP 51 melting point apparatus. IR data were obtained either on a Pye Unicam SP3-200 spectrophotometer or Perkin-Elmer Model 283 spectrophotometer either as neat or in $CHCl_3$. ^1H NMR data were obtained on a varian FT-80A spectrophotometer or Jeol FX-90Q or AC-200 Bruker Spectrophotometer in $CDCl_3$ using tetramethylsilane as internal standard. Mass spectral data were obtained on VG micromass 7070H spectrophotometer. UV spectra were recorded on a Shimadzu UV-240 spectrometer in pure acetonitrile solvent. Vapour pressure chromatography analysis were carried out by HP 5890 system or Perkin Elmer 8700 system. All the compounds were purified by recrystalization or distillation under vacuum or column chromatography either over Silica Gel or over Basic / Neutral Alumina. The purity of the compounds were checked either by TLC or VPC.

3.2 General Procedure for Photolysis Reaction

All the compounds were photolysed in an immersion well type photoreactor with a Pyrex-Water jacket filter (>280 nm) using either 450-W Hanovia medium pressure immersion lamp.

3.3. Preparation of 4-(4-methoxy-phenyl)-buten-2-one (84)

A solution of 4-methoxy benzaldehyde (**82**), (6.8 g, 50 mmol) in 8 mL of acetone was placed into a 100 mL round bottomed (RB) flask. The flask was cooled to 0 °C, 10 mL of aqueous sodium hydroxide solution (10 %) was added slowly from a dropping funnel into the flask while stirring. The rate of addition was adjusted in such a way that the temperature of the reaction mixture was maintained at 25 - 30 °C. The solution was stirred at r.t. for further 2 h. The reaction mixture was made slightly acidic by the addition of dil. HCl, and extracted twice with 20 mL portions of toluene. The organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed by distillation at atmospheric pressure and the residue was purified by silica gel column chromatography (pet.ether:EtOAc = 95 : 5), to get 7.31 g (83 %) of pure compound **84**.

Yield 83 % (7.31 g), colourless oil.

^{1}H NMR 7.60 (d, J = 16.67 Hz, 2H), 7.40 (d, J= 9.52 Hz, 1H), 6.90 (d, J = 9.52 Hz, 2H), 6.60 (d, J = 16.67 Hz, 1H), 3.85 (s, 3H), 2.35 (s, 3H).

3.4. Preparation of 4-(3,4-dimethoxy-phenyl)-buten-2-one (124)

8.3 g of **123** (50 mmol) and 10 mL of acetone (140 mmol) were reacted in the presence of 10 % NaOH (10 mL) solution by following the identical reaction conditions as mentioned for **84**, to afford 7.4 g (83 %) of **124**.

Yield 83 % (7.40 g) , thick oil.

^{1}H NMR 7.50 (d, J = 16.67 Hz, 1H), 7.20-7.10 (m, 2H), 6.90 (d, J = 9.52 Hz, 1H), 6.60 (d, J = 16.67 Hz, 1H), 3.95 (s, 6H), 2.40 (s, 3H)

3.5 Preparation of 4-(4-methoxy-phenyl)-butan-2-one (85)

A solution containing 5 g of **84** (28 mmol) in 15 mL of ethyl alcohol and 0.1 g of 10 % Pd on activated charcoal was placed into a thick glass hydrogenation bottle, and was hydrogenated using 50 lbs of hydrogen pressure at r.t. The progress of the reaction was monitored by thin layer chromatography. The reaction was continued until the uptake of hydrogen had ceased. Catalyst was filtered off and the solvent was removed under vacuum. The purification of the reaction mixture over silca gel column chromatography, using pet.ether:EtOAc (9:1) as eluent, gave 4.5 g (90 %) of **85.**

Yield 90% (4.50 g), thick oil.

IR (neat) 2935, 1716, 1612, 1514, 1247, 1035, 910 cm^{-1}.

^{1}H NMR δ 7.15 (d, 2H, J = 9.52 Hz) , 6.85 (d, 2H, J = 9.52 Hz) , 3.75 (s, 3H) , 2.70-2.85 (m, 4H) , 2.20 (s, 3H)

^{13}C NMR δ 207.73, 158.30, 133.32, 129.45, 114.15, 55.25, 45.41, 30.03, 29.10

Mass (m/e) 178 (M^+), 163 (5), 135 (13), 121 (100), 108 (17), 91 (25), 77 (19), 65 (13)

3.6 Preparation of 4-(3,4-dimethoxy-phenyl)-butan-2-one (125)

Hydrogenation of **124** (5 g, 24 mmol), using 0.1 g of 10 % Pd/C catalyst in EtOH, in the identical manner as described for the synthesis of **85,** afforded 4.2 g (84 %) of **125**.

Yield	84%(4.2 g), colorless oil.
IR (neat)	2937, 1716, 1591, 1456, 1236, 1028, 912 cm^{-1}.
^{1}H NMR	δ 6.65 - 6.80 (m, 3H), 3.85 (s, 3H), 2.65-2.90 (m, 4H), 2.15 (s, 3H)
^{13}C NMR	δ 208.01, 149.15, 147.64, 133.89, 120.30, 112.09, 111.72, 56.09, 55.99, 45.47, 30.16, 29.55
Mass (m/e)	208 (M^+), 193 (5), 165 (57), 151 (100), 135 (15), 119 (17), 107 (26), 91 (25), 77 (25), 65 (15)

3.7. Preparation of 4-methoxy phenyl ethyl bromide (139)

4-Methoxy phenyl ethyl alcohol **138** (3.8 g, 25 mmol) dissolved in a 50 mL of dry benzene was placed into a two neck RB flask. Pyridine (1 mL) was added to the flask fitted with an argon balloon, stiring bar and reflux condenser. Freshly distilled PBr_3 (7.44 g) was added to the flask while stirring at 0 °C. The progress of the reaction was monitored by the formation of a white precipitate. After complete

addition of PBr_3, the cold bath was removed and the flask was kept on an oil bath and heated to reflux for 3h. The flask was allowed to cool and water was carefully added dropwise while stirring at 0 °C. The benzene layer was separated and aqueous layer was extracted twice with 20 mL portions of benzene. The combined organic layers were concentrated under reduced pressure and purified by passing through a pad of silica gel, to get 4.67 g (87 %) of **139**.

Yield 87 % (4.67 g), pale yellow oil.

IR (neat) 2950, 1610, 1515, 1240, 1150, 1020, 820 cm^{-1}.

^{1}H NMR δ 7.15 (d, 2H, *J* = 9.75 Hz) , 6.85 (d, 2H, *J* = 9.75 Hz), 3.75 (s, 3H), 3.55 (t, *J* = 7.31 Hz, 2H) , 3.15 (t, *J* = 7.31 Hz, 2H) .;

3.8 Preparation of 3,4-dimethoxy phenyl ethyl bromide (148)

Compound **147** (5g, 27 mmol) was brominated using 10.8 g of PBr_3 (40 mmol) in an identical manner as described above for the preparation of **139**, to afford 5.6 g (85 %) of **148.**

Yield 85 % (5.60 g), pale yellow oil.

IR (neat) 2950, 1600, 1510, 1450, 1250, 1030, 800 cm^{-1}.

^{1}H NMR δ 6.80 (m, 3H) ,3.90 (s, 3H), 3.85 (s, 3H), 3.55 (t, *J* = 7.5 Hz, 2H) , 3.15 (t, *J* = 7.5 Hz, 2H)

3.9. Preparation of 2,3,4-trimethoxy phenyl ethyl bromide (161)

Yield 80 % (5.06 g), thick oil.

IR (neat) 2940, 1610, 1500, 1455, 1250, 1150, 760 cm^{-1}.

^{1}H NMR δ 6.60 (s, 2H) , 3.90 (s, 6H), 3.85 (s, 3H), 3.55 (t, J = 7.36 Hz, 2H) , 3.10 (t, J = 7.36 Hz, 2H) .

3.10 Preparation of Acetone-N,N-dimethylhydrazone (140)

A solution of acetone (12 g, 0.2 mol) and N,N-dimethyl hydrazine (15g, 0.25 mol) in 170 mL of anhydrous benzene were placed into a 250 mL R.B. flask and were refluxed azeotrpically to remove the water formed. When no more water was formed, benzene was distilled off and fractional distillation at 92-94 °C gave 18.2 g (91 %) of **140**.

Yield 91 % (18.2 g), colourless liquid.

IR 2900, 1650, 1480, 1450, 1370, 1210, 1030 cm^{-1}.

^{1}H NMR δ 2.50 (s, 6H), 2.0 (s, 3H), 1.95 (s, 3H).

3.11 Preparation of 5-(4-methoxy-phenyl)-pentan-2-one (141)

To a previously dried 100 mL two neck RB flask, equipped with a magnetic bar and argon balloon, 1.5 g of **140** (15 mmol) dissolved in 20 mL of anhydrous THF

was introduced. The contents were cooled to -78 °C. n-BuLi (2.20 M, in hexane, 6.8 mL) was introduced slowly to the flask while stirring. A pale red colour appeared after the complete addition of n-BuLi. After stirring for about 30 minutes, 3.23 g (15 mmol) of 4-methoxy-phenyl-ethylbromide **139** dissolved in 15 mL of THF was added over a period of 5 min. Stiring was allowed to continue for additional 30 min. After warming the reaction mixture to r.t., it was quenched with 10 mL of saturated solution of NH_4Cl. The organic layer was extracted with 20 mL of ethyl acetate. The organic layers were combined and concentrated. The crude hydrazone, thus, obtained was dissolved in 20 mL of MeOH:THF (1:1) and poured into a phosphate buffer (Na_2HPO_2:NaH_2PO_3) solution (10 mL) maintaining pH at 7.5-8.0. 3.2 g (15 mmol) of $NaIO_4$ was added to the reaction mixture and the whole content was stirred at r.t. for 2-3 h. After complete oxidation of hydrazone to the ketone, the reaction mixture was extracted with ethyl acetate, concentrated and purified over silicagel column, using EtOAc:pet.ether (1:9) as eluent to give 2.53 g (88 %) of **141** as a pale yellow oil.

Yield 88% (2.53 g), pale yellow oil.

IR (neat) 2945, 1720, 1610, 1510, 1350, 1240, 1030 cm^{-1}.

^{1}H NMR δ 7.1(d, 2H, *J* = 9.80 Hz), 6.7 (d, 2H, *J* = 9.80 Hz), 3.75 (s, 3H), 2.55 (t, 2H, *J* = 7.31 Hz), 2.40 (t, 2H, *J* = 7.31 Hz), 2.10 (s, 3H), 1.85 (m, 2H)

3.12 Preparation of 5-(3,4-dimethoxy-phenyl)-pentan-2-one (149)

Reaction of **148** (3.67 g, 15 mmol) and **140** (1.5 g, 15 mmol) in the presence of n-butyl lithium (2.20 M, in hexane, 6.8 mL) at -78 °C followed by the oxidation using $NaIO_4$ in MeOH:THF (1:1) in phosphate buffer (Na_2HPO_2 : NaH_2PO_3) and usual purification as described in **3.11,** gave **149** (2.66 g, 80 %).

Yield 80 % (2.66 g), viscous liquid.

IR (neat) 2900, 1710, 1515, 1420, 1360, 1260, 1020 cm^{-1}.

^{1}H NMR δ 6.60-6.75 (m, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 2.65 (t, 2H, J = 7.5 Hz), 2.45 (t, 2H, J = 7.5 Hz), 2.20 (s, 3H), 1.90 (m, 2H).

3.13 Preparation of 5-(3,4,5-trimethoxy-phenyl)-pentan-2-one (162)

Usual alkylation of **140** with **161** (4.10 g, 15 mmol) in the presence of n-butyl lithium (2.20 M, in hexane, 6.8 mL) at -78 °C gave 3.1 g (82 %) of **162.**

Yield 82% (3.10 g), viscous liquid

IR 2945, 2262, 1700, 1612, 1510 1045, 950 cm^{-1}

^{1}H NMR δ 6.45 (s, 2H), 3.90 (s, 6H), 3.85 (s, 3H), 2.65 (t, 2H, J = 7.42 Hz), 2.45 (t, 2H, J = 7.10 Hz), 2.20(s, 2H), 1.85 (m, 2H).

3.14 Preparation of 3,4-dimethoxycinnamic acid (177)

A mixture containing pyridine (40 mL), piperidine (1 mL), 3,4-dimethoxy benzaldehyde (15.0 g, 90.3 mmol) and 20.4 g (196 mmol) of malonic acid was refluxed for two hours on a water bath. During the course of the reaction rapid evoluation of CO_2 was observed. The progress of the reaction was monitored by TLC (pet.ether:ethyl acetate = 1:3). After the reaction was complete, the solution was allowed to cool down to r.t. and poured onto a ice-cold water containing 60 mL of conc. HCl. The crude cinnamic acid was filtered off at the pump, washed three times with cold water, dried and recrystallised from aqueous ethanol to furnish 16.52 (88 %) of **177**.

Yield 88 % (16.52 g), crystalline solid.

M.Pt 184-185.5 °C

^{1}H NMR 7.61 (d, 1H, J =16.8 Hz) 7.03- 7.34 (m, 3H), 6.39 (d, 1H, J =16.8 Hz), 3.85 (s, 6H).

3.13 Preparation of Ethyl-(3,4-dimethoxy phenyl) propionate (179)

To a 3,4-dimethoxy cinnamic acid (10.4 g, 0.05 mol) solution in 30 mL of anhydrous ethanol was added 10 % Pd (0.1 g) on activated charcoal. The mixture was hydrogenated at 60 lbs at r.t until the uptake of hydrogen had ceased (5-6 h). The catalyst was filtered off from the reaction mixture, and solvent was removed under vacuum to result 3,4-dimethoxyhydrocinnamic acid as an oil, which

solidified on standing. The crude acid thus obtained, was dissolved in 100 mL of toluene and 10 mL of ethanol, catalytic amount of p-toluene sulphonic acid was added to the flask. The contents were refluxed using Dean-Stark water separator. When no more water separation was observed, the contents were cooled, washed with sufficient amount of water and the organic layer was concentrated under reduced pressure to yield the crude product, which was purified by silica gel column chromatography using pet.ether:EtOAc (90:10) as eluent to give 9.60 g (81 %) of pure **179**.

Yield 81 % (9.6 g), colourless liquid.

IR (neat) 2955, 1720, 1600, 1515, 1460, 1020, 810 cm^{-1}.

^{1}H NMR 6.70-6.90 (m, 3H), 4.10 (q, 2H, *J* = 8.2 Hz), 3.85 (s, 3H), 3.80 (s, 3H), 2.60 (t, *J* = 7.42 Hz, 2H), 2.30 (t, *J* = 7.42 Hz, 2H), 1.25 (t, *J* = 8.2 Hz, 3H).

3.16 Preparation of 3,4-Dimethoxyphenylpropanol (180)

A 250 mL RB flask equipped with a reflux condenser and magnetic stir bar was charged with $LiAlH_4$ (1.14 g, 30 mmol) and 40 mL of absolute anhydrous THF under an inert argon atmosphere. To the stirring suspension, a solution of **179** (6.0 g, 25 mmol) in 30 mL of dry THF was added dropwise. After completion of the addition, the reaction mixture was refluxed for 30 min. The reaction was quenched by dropwise addition of aqueous NaOH (10 %) solution followed by the solid addition of Na_2SO_4. The organic layer was decanted and washed with additional 20

mL of ether. The combined organic layers were concentrated. Purification of the reaction mixture over silicagel column chromatography using pet.ether:EtOAc (80:20) as eluent gave **180** (4.35 g).

Yield 88 % (4.35 g), viscous liquid.

IR (neat) 3355, 2950, 2250, 1600, 1440, 1175, 925 cm^{-1}.

^{1}H NMR δ 7.25 (m, 1H), 6.75 (m, 2 H), 3.90 (s, 3H), 3.85 (s, 3H), 3.70 (t, *J* = 7.32 Hz, 2H), 2.65 (t, 2H, *J* = 7.32 Hz), 2.45 (s, 1H), 1.95 (m, 2H).

3.17 Preparation of 3,4-dimethoxy phenyl propyl bromide (181)

Compound **180** (5 g, 33 mmol) was brominated, using 10.8 g (40 mmol) of PBr_3 in benzene in the presence of catalytic amount of pyridine by following an identical reaction condition as described for **139,** to get 6.50 g (76 %) of **181**.

Yield 76 % (6.50 g), viscous liquid.

IR (neat) 3440, 2960, 1600, 1520, 1460, 1340, 1220, 1130, 750 cm^{-1}.

^{1}H NMR δ 6.60 (m, 3H) ,3.90 (s, 3H), 3.85 (s, 3H), 3.35 (t, *J* = 7.35 Hz, 2H) , 2.67 (t, *J* = 7.35 Hz, 2H) , 2.10 (m, 2H)

3.18 Preparation of 6-(3,4-dimethoxy-phenyl)-hexan-2-one (182)

Usual alkylation of **140** (1.5 g, 15 mmol) with **181** (3.9 g, 15 mmol) using n-butyl lithium (2.20 M in hexane, 6.8 mL) at -78 °C followed by the oxidation with

$NaIO_4$ in MeOH:THF (1:1) in phosphate buffer (Na_2HPO_2 : NaH_2PO_3). Standard work-up, as described earlier for **141** in **3.11**, gave 2.90 g (82 %) of **182**.

Yield 82 % (2.90 g), thick liquid.

IR (neat) 2920, 1710, 1590, 1500, 1440, 1420, 1355, 1260, 1160, 1030, 850, 800, 770, 740 cm^{-1}

^{1}H NMR δ 6.75 (m, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 2.55 (t, 2H, J = 7.25 Hz), 2.45 (t, 2H, J = 7.25 Hz), 2.10 (s, 3H), 1.50 (m, 4H).

3.19 General procedure for the synthesis of kinetic silyl enol ethers (86, 126, 153, 156, 163 and 183). This is exemplified by taking 86 as an example.

A solution of **85** (2.67 g, 15 mmol) in anhydrous THF (10 mL) was added to a stirring solution of LDA (prepared by the addition of n-BuLi to a solution of diisopropyl amine in THF (25 mL) at - 78 °C. TBDMSCl (17 mmol) was introduced into the flask through a syringe. The solution was stirred for 1 h at -78 °C and allowed to warm to r.t. After 3h of stirring, n-pentane (100 mL) was added and the precipitated LiCl was removed by filtration through celite. Concentration in vacuo followed by distillation under reduced pressure (96 °C / 2 mm Hg) gave **86** as essentially a single regio isomer. This silylenol ether was used immediately for the photochemical reaction without further purification.

3.20 General procedure for the preparation of Silyl enol ethers (Thermodynamic) 142 and 150. This is exemplified by taking 142 as an example.

A solution of ketone **141** (10 mmol) in 25 mL of DMF containing imidazole (ImH) (100 mmol) was charged into a 100 mL RB flask; equipped with a magnetic stirring bar, reflux condenser, under inert argon atmosphere. A solution of TBDMSCl (30 mmol) in 20 mL of DMF was added dropwise to the flask with stirring. The contents were refluxed for 48 h. On cooling it was diluted with ether (50 mL) and washed with cold saturated $NaHCO_3$ solution. The aqueous phase was re-extracted with ether (30 mL). After drying the ether layer over anhydrous Na_2SO_4, it was concentrated and distilled to give 2.43 g (83 %) of **142** in an enriched 88:12 regio isomeric ratio.

3.21 Photoinduced Electron Transfer (PET) activation reaction of 86

A 500 mL pyrex irradiation vessel containing mixtures of silyl enol ether **86** (0.580 g, 2 mmol) and DCN (0.06 g , 0.34 mmol) in 250 mL of CH_3CN:H_2O (4:1) was irradiated for 4 h through a Pyrex filtered light (> 280 nm, all light absorbed **86** only) using 450 W Hanovia lamp without removing the dissolved oxygen from the reaction mixture. The progress of the reaction was monitored by TLC (pet.ether: ethyl acetate = 8:2). After the significant disappearance of **86** (≈ 80 %), the solvent was evaporated under reduced pressure and the residue was purified by silicagel column chromatography using pet.ether:EtOAc (85:15) as eluent to give 0.25 g (72 %) of **88**. DCN was recovered quantitatively (98%) at the end of the reaction. During

the irradiation of silyl enol ethers minor quantity (~ 10 %) of starting ketone was also formed which was shown to be formed by the thermal reversion of the enol silyl ethers by adequate control experiments.

Yield 72% (0.253 g), viscous liquid.

IR ($CHCl_3$) 2949, 1716, 1612, 1504, 1261, 1037, 732 cm^{-1}.

^1H NMR δ 7.05 (d, 1H, J = 9.75 Hz), 6.75 (dd, J_1 = 9.75 Hz, J_2 = 2.43 Hz), 1H), 6.60 (bs, 1H), 3.75 (s, 3H), 3.50 (s, 2H), 2.95 (t, 2H, J = 7.31 Hz), 2.45 (t, 2H, J = 7.31 Hz)

^{13}C NMR δ 210.23, 158.39, 134.24, 128.46, 128.20, 113.37, 112.16, 54.98, 44.76, 38.23, 27.20

Mass (m/e) 176 (M^+), 161 (5), 147 (10), 134 (100), 103 (17), 91 (25), 77 (17).

3.22 PET activation of 126

A solution containing mixtures of **126** (0.650 g, 2 mmol) and DCN (0.06 g, 0.34 mmol) was photolysed for 4 h utilizing the similar irradiation setup as described for **86.** Usual workup and purification gave **89** (0.305 g, 74 %).

Yield 74 % (0.305 g), very thick viscous liquid.

IR ($CHCl_3$) 2939, 1716, 1514, 1465, 1338, 1247, 912 cm^{-1}.

^1H NMR δ 6.75 (s, 1H), 6.60 (s, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.50 (s, 2H), 3.00 (t, 2H, J = 7.32 Hz), 2.55 (t, 2H, J = 7.32 Hz)

^{13}C NMR δ 209.92, 148.19, 147.99, 128.57, 125.26, 111.96, 111.67, 56.08, 44.03, 38.41, 28.09.

Mass (m/e) 206 (M^+), 191 (5), 178 (13), 164 (55), 147 (13), 135 (17), 121 (25), 107 (40), 91 (34)

3.23 PET activation of 142

Identical irradiation of a mixture containing **142** (0.610 g, 2 mmol) and DCN (0.06 g , 0.34 mmol), as described for **86,** followed by usual workup and purification using pet.ether:EtOAc (80:10) as eluent gave 0.266 g (74 %) of **144.**

Yield 70% (0.266 g), thick liquid.

IR 2950, 1710, 1610, 1500, 1420, 1250, 900 cm^{-1}.

^{1}H NMR δ 7.20 (d, J = 9.75 Hz, 1H), 6.80 (dd, J_1 = 9.75 Hz, J_2 = 2.80 Hz, 1H), 6.75 (s, 1H), 5.75 (t, J = 6.94 Hz, 1H), 3.80 (s, 3H), 2.75 (t, J = 7.31 Hz, 2H), 2.30-2.20 (m, 2H), 2.05 (s, 3H).

^{13}C NMR δ 206.23, 158.07, 137.66, 131.38, 128.23, 114.03, 111.50, 61.73, 55.20, 31.45, 28.26, 23.45.

Mass (m/e) 190 (M^+), 174 (68), 159 (100), 144 (38), 128 (46), 115 (51), 103 (13), 91 (23), 77 (19)

3.24 PET activation of 150

Similar photoactivation of a mixture containing **150** (0.670 g, 2 mmol) and DCN (0.06 g , 0.34 mmol) in CH_3CN:H_2O (4:1) solution as described for **86** and normal work up of the reaction mixture and purification using pet.ether:EtOAc (8:2) as eluent gave 0.308 g (70 %) of **152.**

Yield 70% (0.308 g), viscous liquid.

IR 2910, 1700, 1590, 1510, 1350, 1250, 1150 cm^{-1}.

^{1}H NMR δ 6.70 (s, 1H), 6.80 (s, 1H), 5.75 (t, *J* = 6.94 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 2.70 (t, *J* = 7.32 Hz, 2H), 2.20 (m, 2H), 2.05 (s, 3H)

^{13}C NMR 206.26, 148.35, 146.99, 136.33, 132.43, 106.95, 110.86, 62.17, 55.65, 54.78, 30.43, 26.95, 22.60

Mass (m/e) 220 (M^+), 204 (100), 189 (74), 173 (15), 161 (16), 146 (15), 121 (20), 115 (40), 91 (20), 77 (18)

3.25 PET activation of 153

Analogous photochemical irradiation of a mixture of **153** (0.610 g, 2 mmol) and DCN (0.06 g , 0.34 mmol) in CH_3CN:H_2O (4:1) followed by purification as described above for **86,** gave 0.247 g (65 %) of **155.**

Yield 65 % (0.247 g), thick viscous liquid.

IR ($CHCl_3$) 2940, 2260, 1700, 1610, 1500, 1050, 940 cm^{-1}

^{1}H NMR δ 7.05 (d, *J* = 9.75 Hz, 1H), 6.75 (dd, J_1= 9.75 Hz, J_2 = 2.82 Hz, 1H), 6.70 (bs, 1H), 3.75 (s, 3H), 3.65 (s, 2H), 2.90 (t, 2H, *J* = 7.31 Hz), 2.55 (t, 2H, *J* = 7.31 Hz), 2.05(m, 2H).

^{13}C NMR δ 208.95, 159.01, 141.81, 130.39, 125.64, 115.35, 111.56, 55.21, 49.19, 43.54, 33.25, 26.23.

Mass (m/e) 190 (M^+), 176 (4), 162 (24), 147 (22), 134 (100), 115 (11), 105 (18), 91 (49), 77 (39)

3.26 PET activation of 156

Silyl enol ether **156** (0.670 g, 2 mmol) dissolved in CH_3CN:H_2O (4:1) containing DCN (0.06 g , 0.34 mmol) was irradiated in an identical manner as described earlier for **86.** Normal work up of the reaction mixture followed by purification using pet.ether:EtOAc (85:15) as eluent gave 0.325 g (74 %) **158.**

Yield 74% (0.325 g), viscous liquid.

IR 2950, 1700, 1615, 1520, 1460, 1360, 1270, 1120 cm^{-1}.

^{1}H NMR δ 6.73 (s, 1H), 6.70 (s, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.65 (s, 2H), 2.90 (t, J = 7.07 Hz, 2H), 2.55 (t, J = 7.07 Hz, 2H), 2.00 (m, 2H)

^{13}C NMR δ 208.97, 148.12, 147.79, 132.93, 125.48, 113.51, 113.24, 56.21, 55.91, 49.81, 44.05, 32.95, 26.93.

Mass (m/e) 220 (M^+), 192 (27), 177 (51), 164(72), 149 (51), 121 (60), 107 (68), 91 (74), 77 (78).

3.27 PET activation of 163

Usual irradiation of a mixture of **163** (0.740 g, 2 mmol) and DCN (0.06 g, 0.34 mmol) in CH_3CN:H_2O (4:1) solution, followed by column chromatographic purification of the reaction mixture using pet.ether:EtOAc (75:25), as described above for **86,** gave 0.363 g (72 %) of **159.**

Yield 72% (0.363 g), viscous liquid.

IR 2938, 1706, 1492, 1410, 1120 cm^{-1}

^1H NMR δ 6.5 (s, 1H), 3.90 (s, 6H), 3.85 (s, 3H), 3.75 (s, 2H), 2.85 (t, 2H, *J* = 7.10 Hz), 2.55 (t, 2H, *J* = 7.10 Hz), 1.95 (m, 2H).

^{13}C NMR δ 209.84, 152.35, 151.58, 141.21, 136.49, 119.88, 108.96, 61.57, 61.05, 56.23, 43.40, 41.47, 33.34, 26.67.

Mass (m/e) 252 (M^+), 190 (43), 161 (27), 147 (22), 134 (100), 105 (57), 91 (70), 77 (72).

3.28 PET activation of 183

Photoirradiation of a mixture of **183** (0.7 g, 2 mmol) and DCN (0.06 g, 0.34 mmol) in CH_3CN:H_2O (4:1) solution followed by purification using pet.ether:EtOAc (80:20) as eluent, as described for **86,** gave 0.328 g (70 %) of **185.**

Yield 60% (0.328 g), colourless solid.

M.P. 85 - 86.5 °C

IR 3040, 2960, 1700, 1620, 1530, 1450, 1230, 1120 cm^{-1}

^1H NMR δ 6.70 (s, 1H), 6.65(s, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.70 (s, 2H), 2.80 (t,*J* = 6.94 Hz, 2H), 2.35 (t, *J* = 6.94 Hz, 2H), 1.80 (m, 4H).

^{13}C NMR δ 211.76, 148.68, 147.69, 133.13, 125.63, 113.38, 113.15, 56.03, 48.20, 41.12, 32.95, 31.33, 24.71.

Mass (m/e) 234 (100% M^+), 206 (63), 191 (54), 175 (68), 165 (46), 151 (24), 131 (24), 121 (44), 107 (37), 91 (49).

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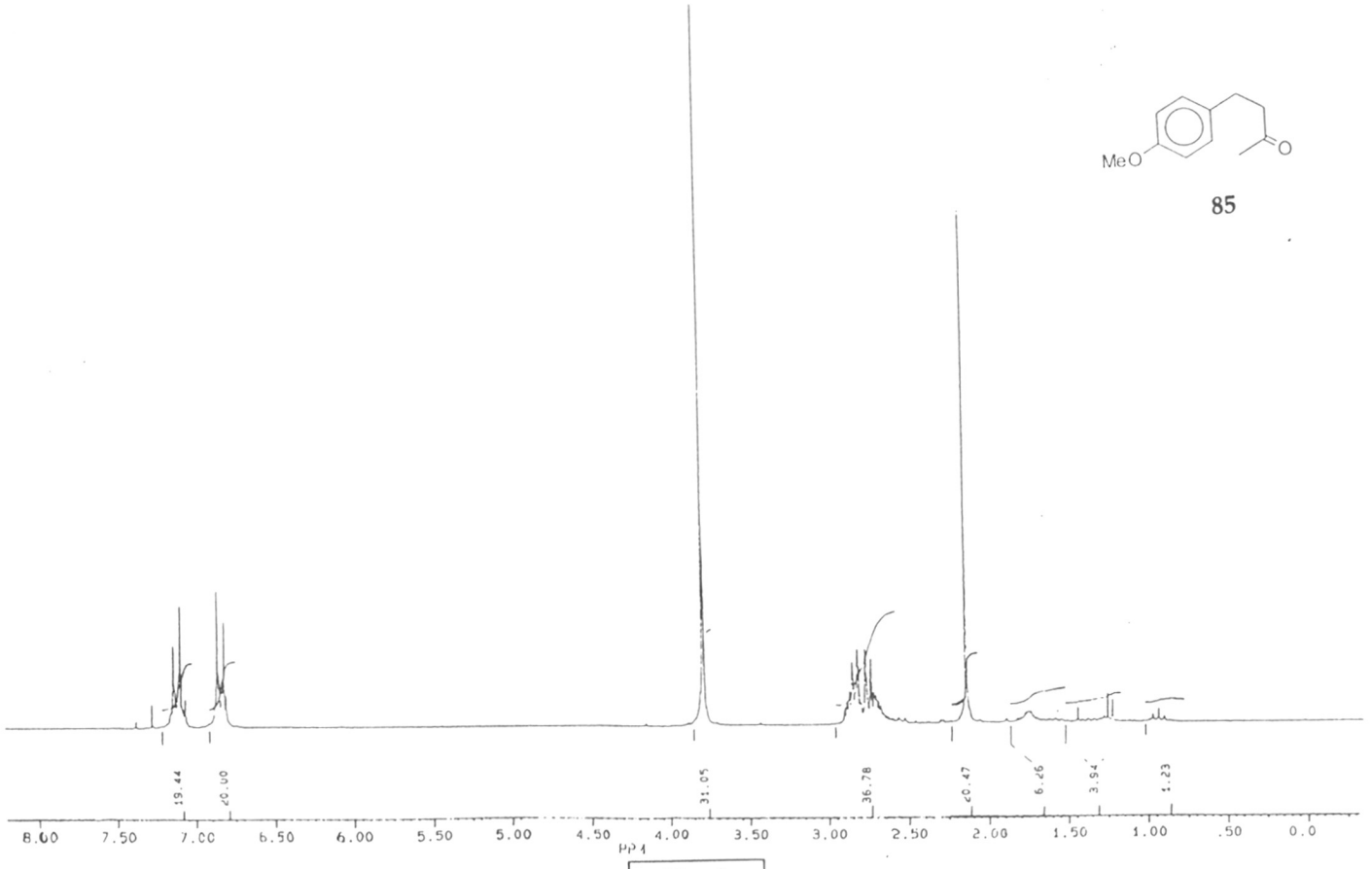
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Fig. 1

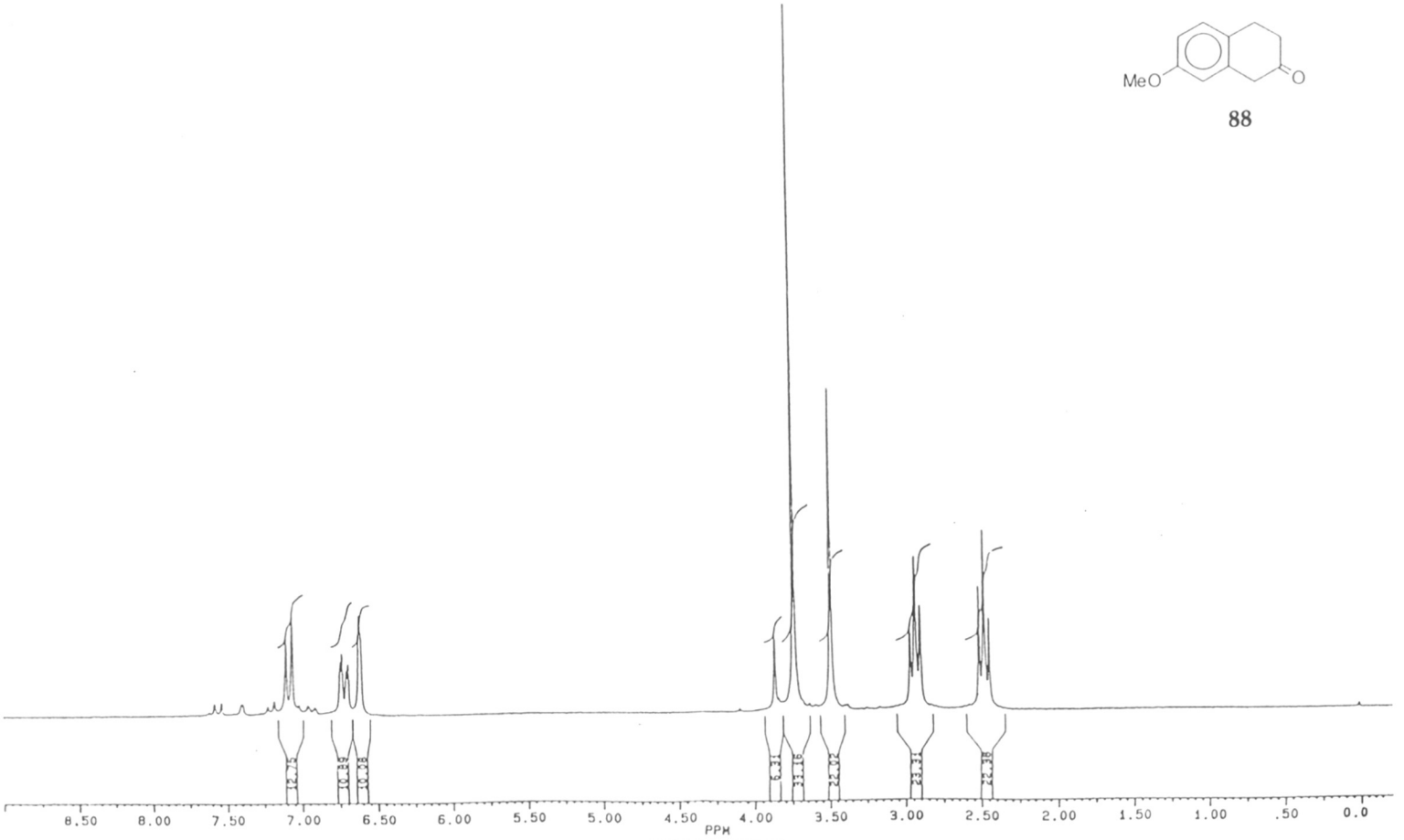
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Fig. 2


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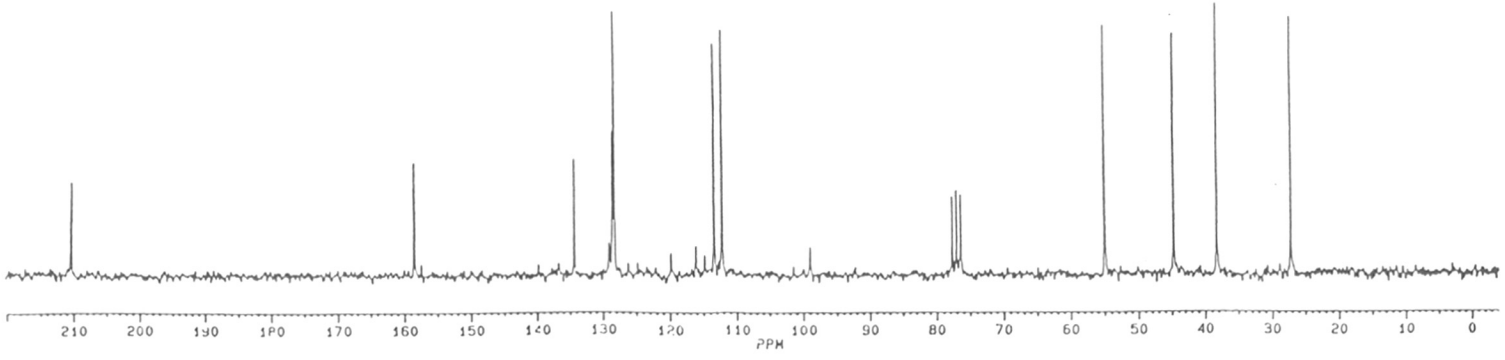
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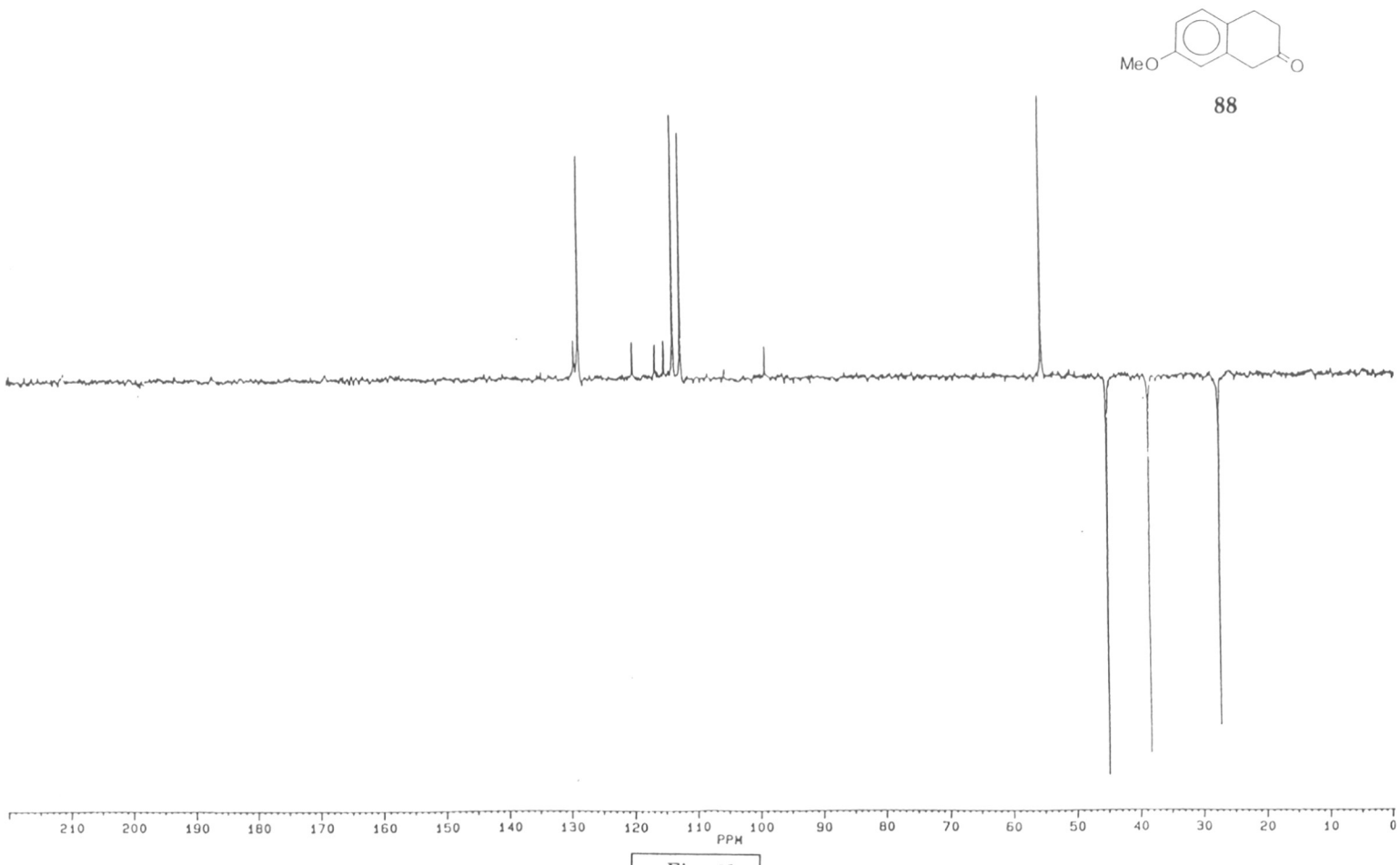
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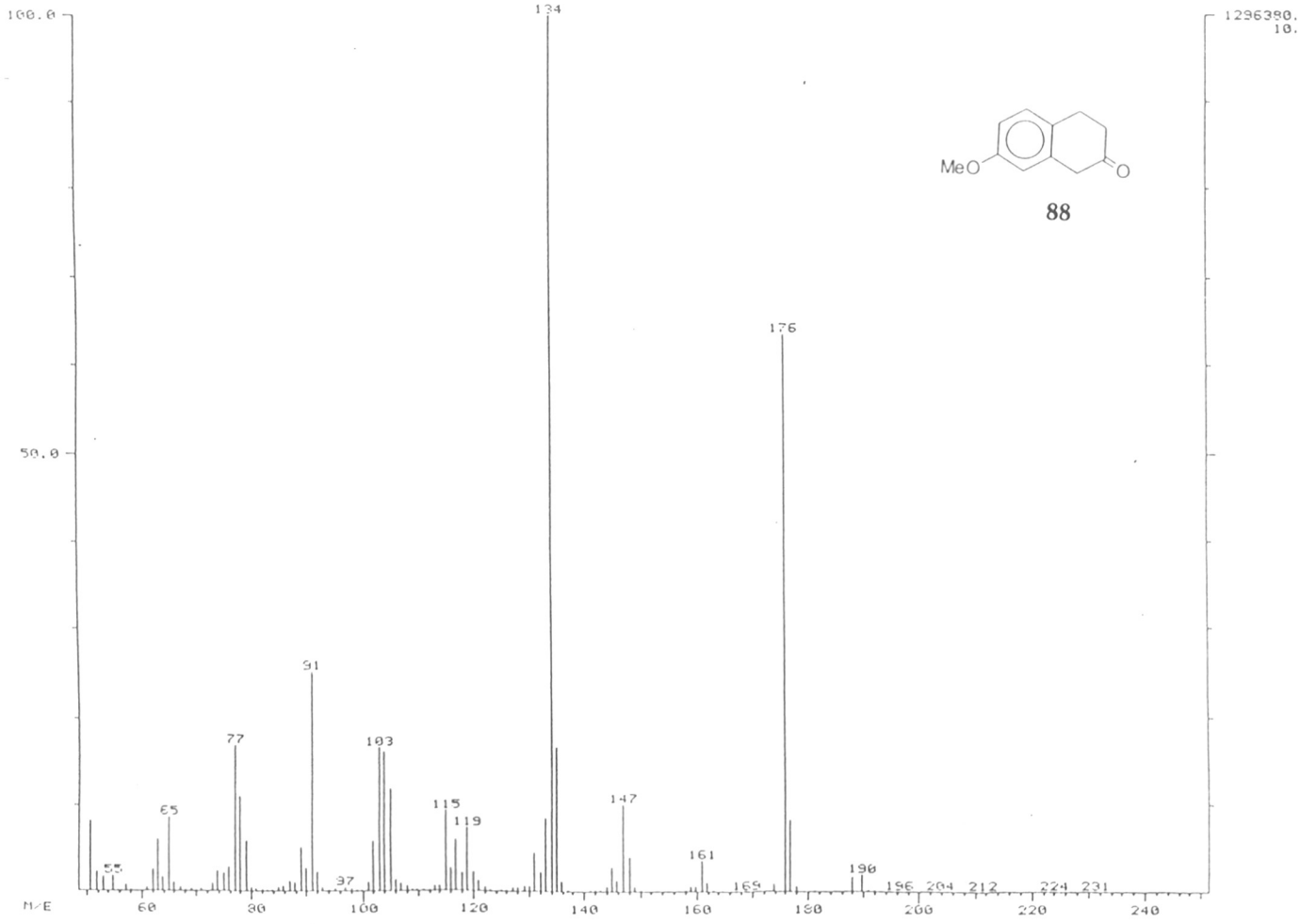
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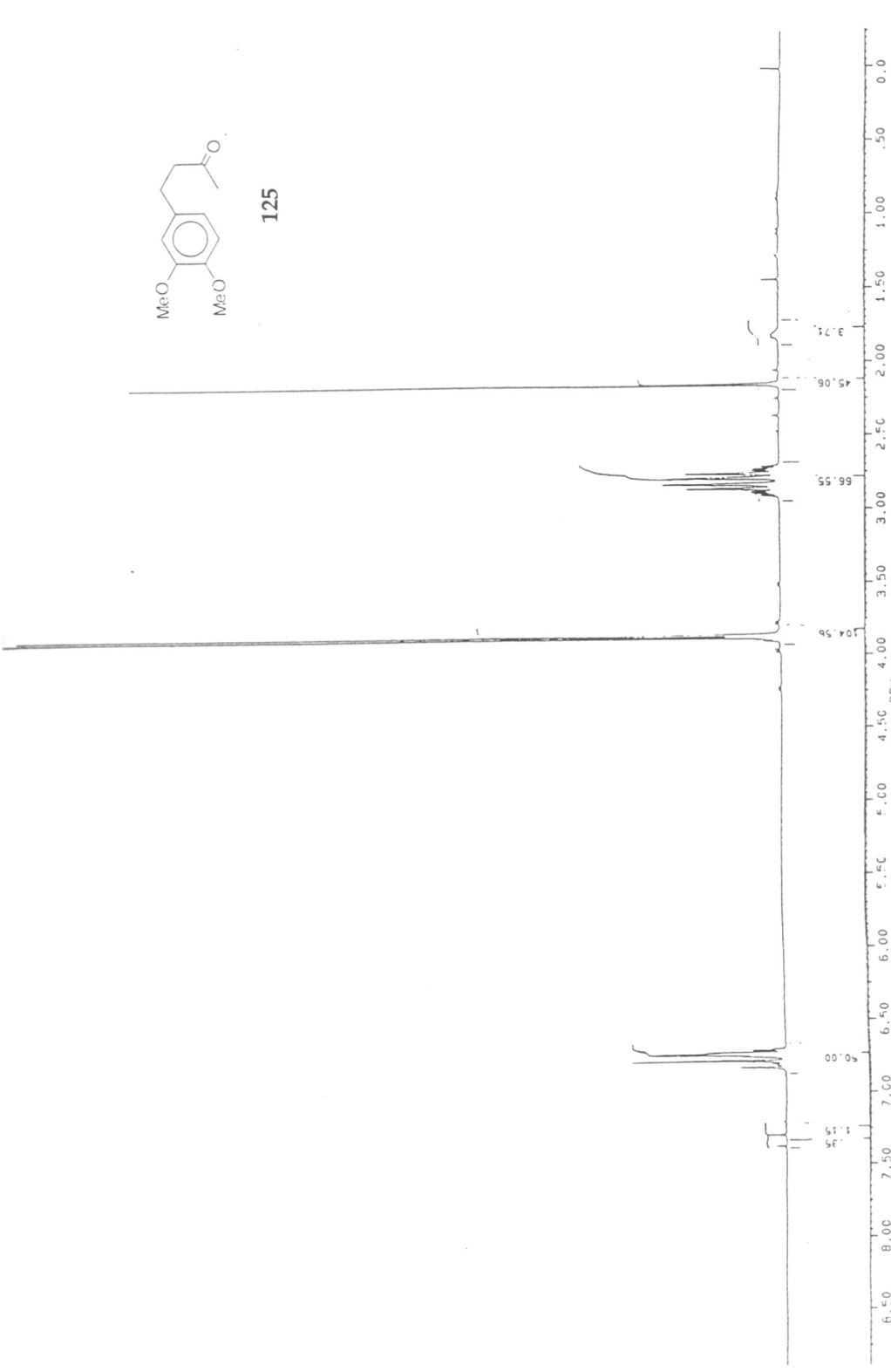
88

Fig. 4



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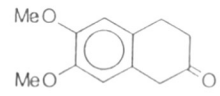
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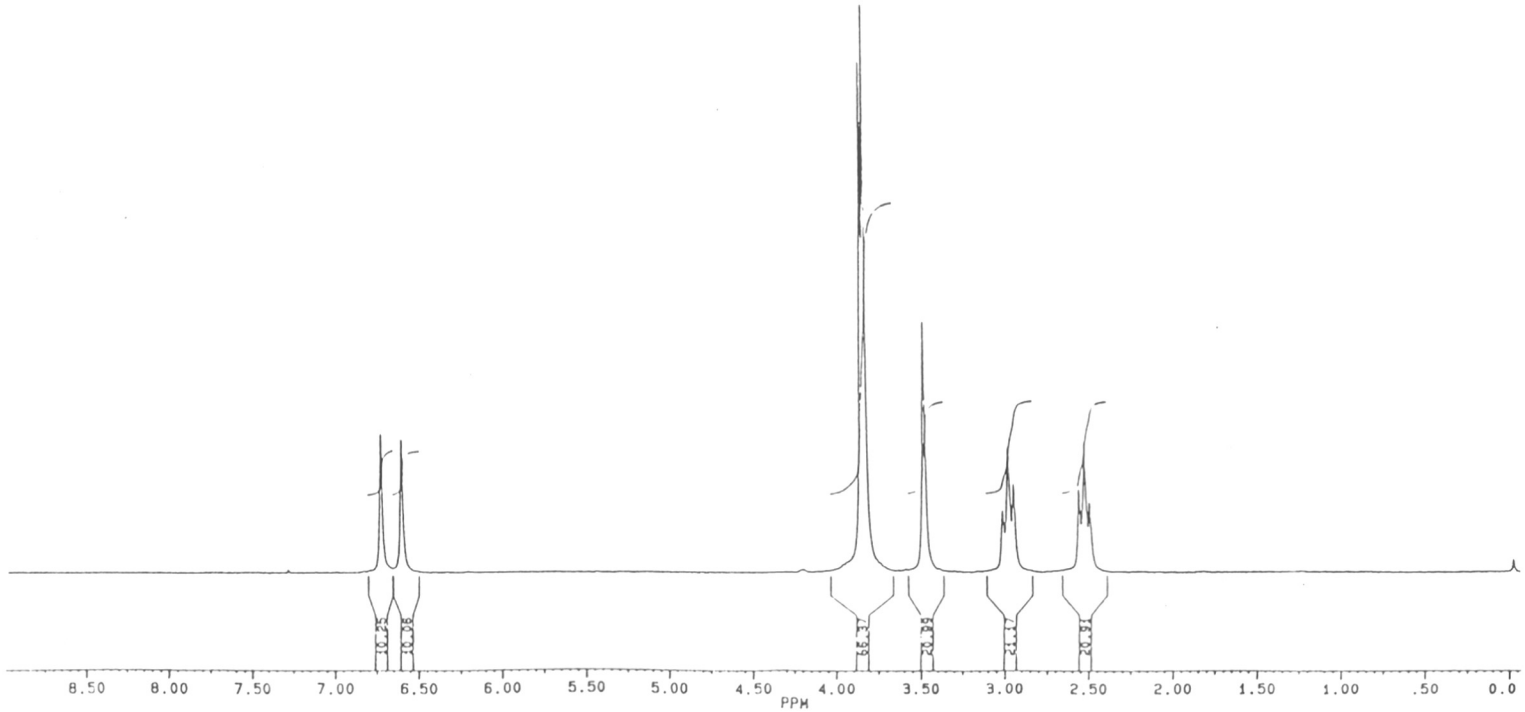
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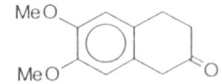
Fig. 6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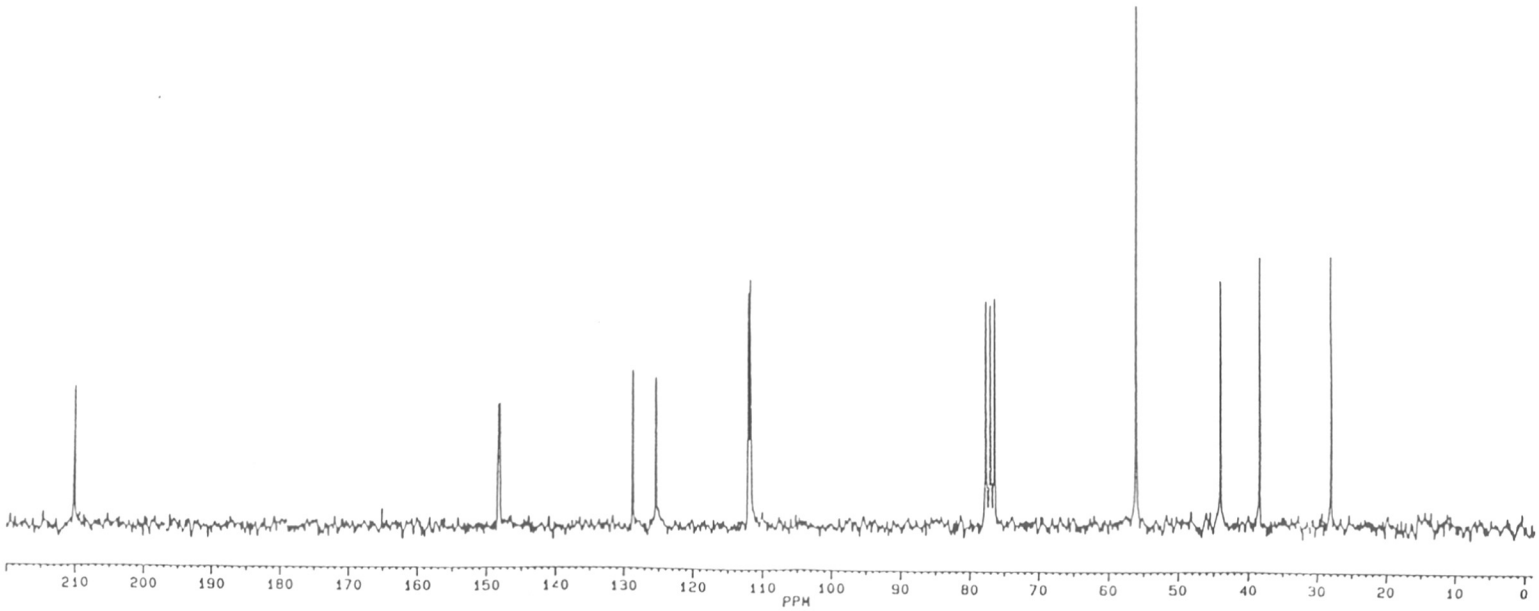
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Fig. 7a

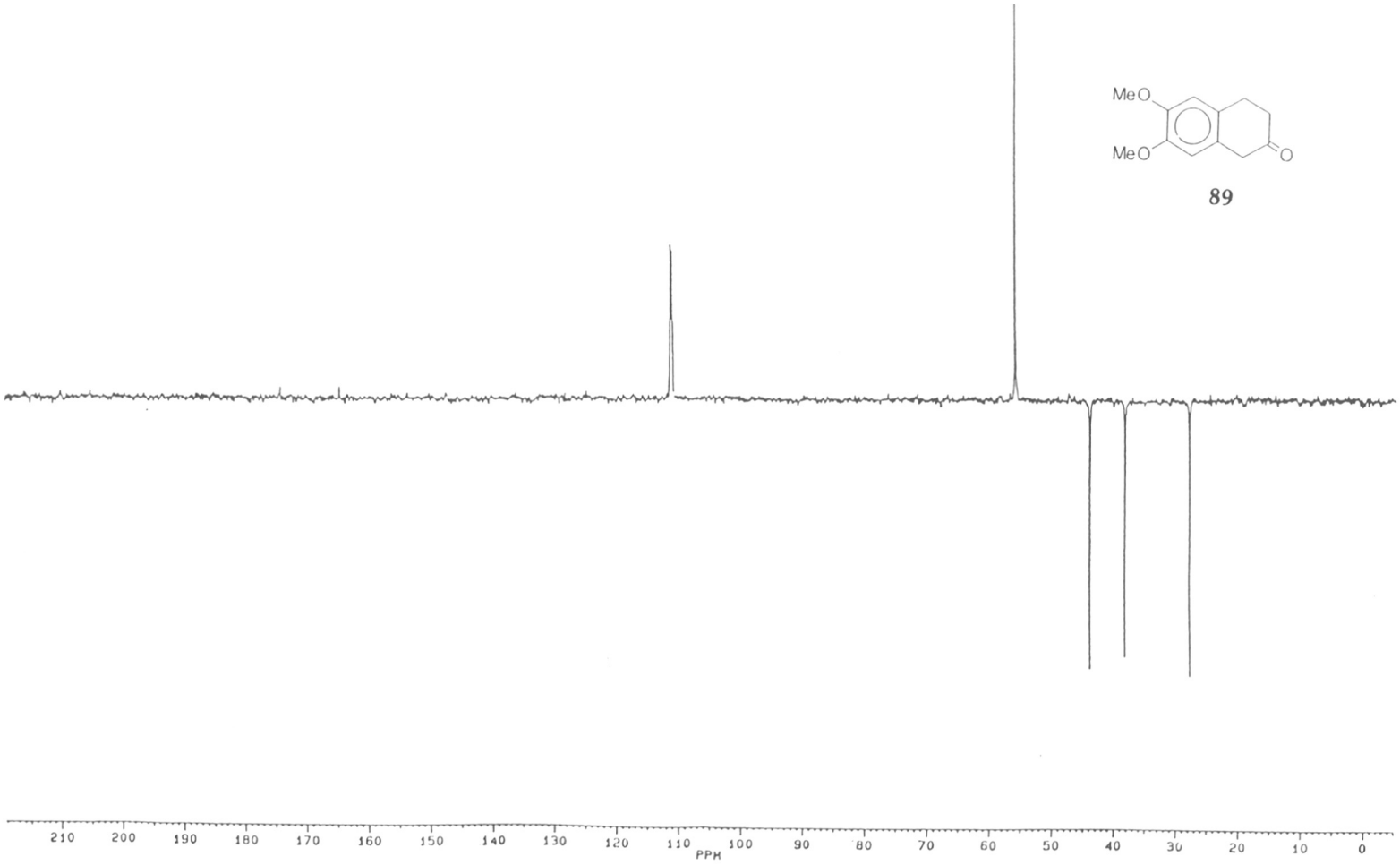
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Fig. 7b

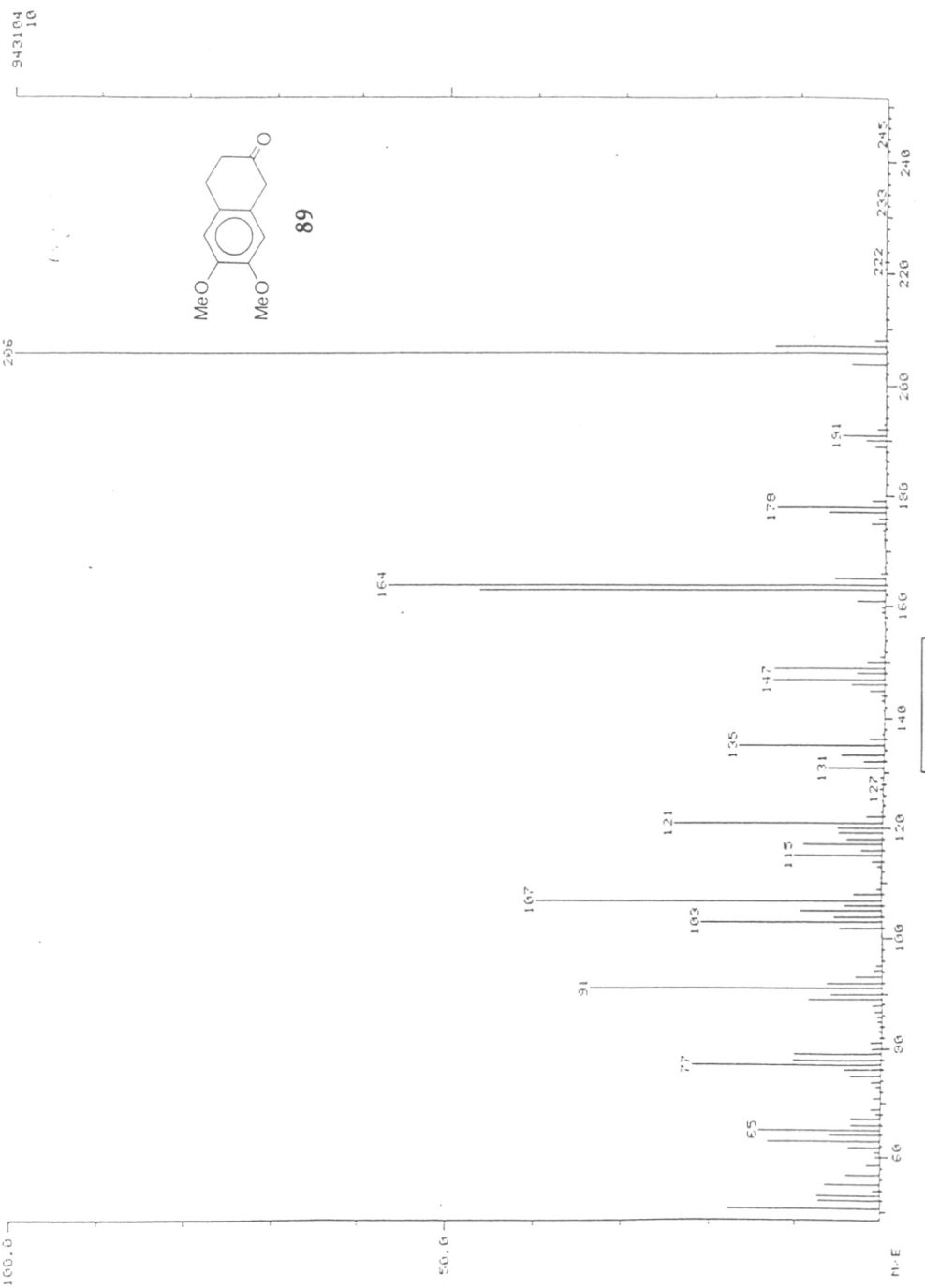
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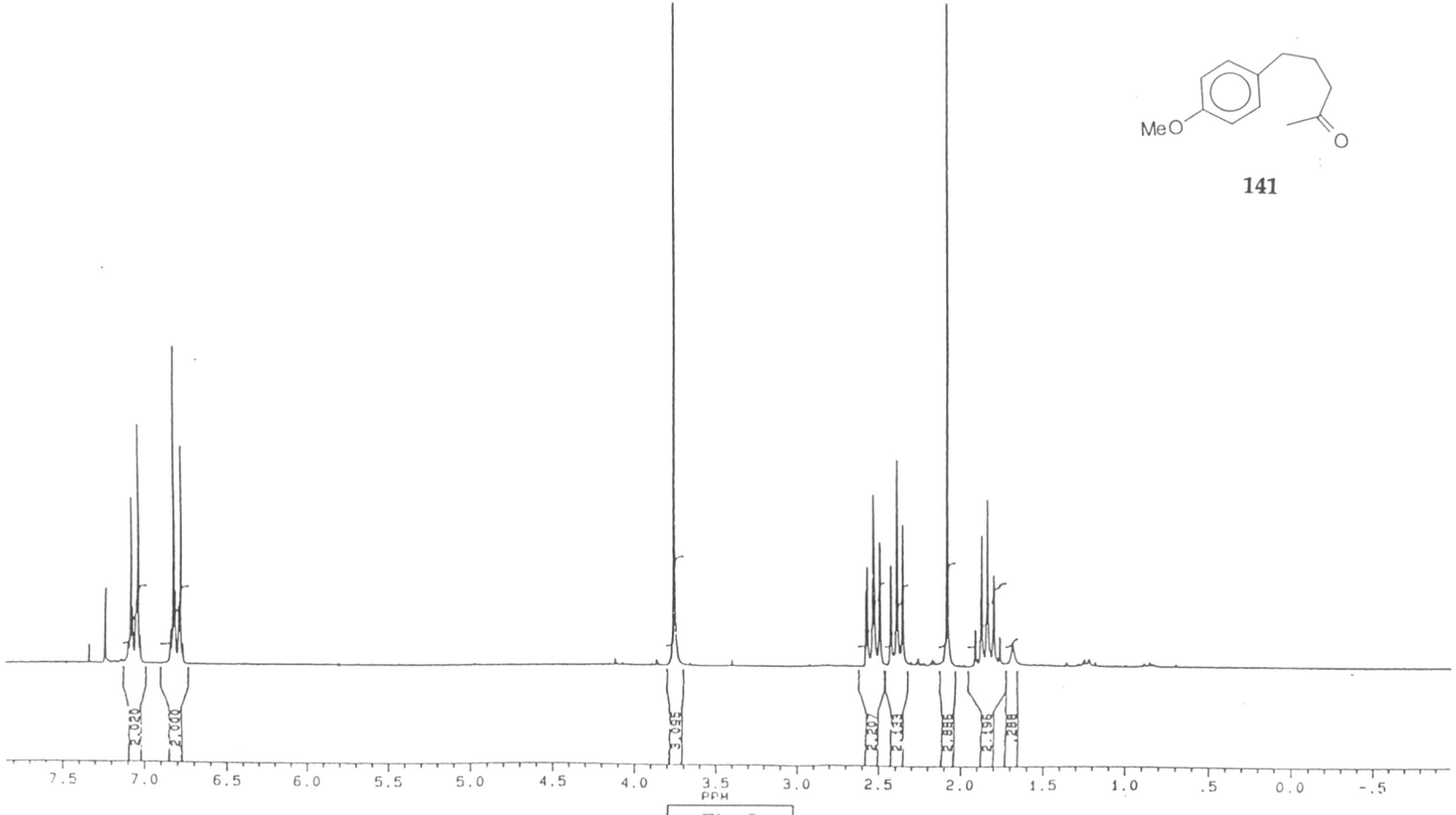
Fig. 8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6.0
5.5
5.0
4.5
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3.5
PPM
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2.5
2.0
1.5
1.0
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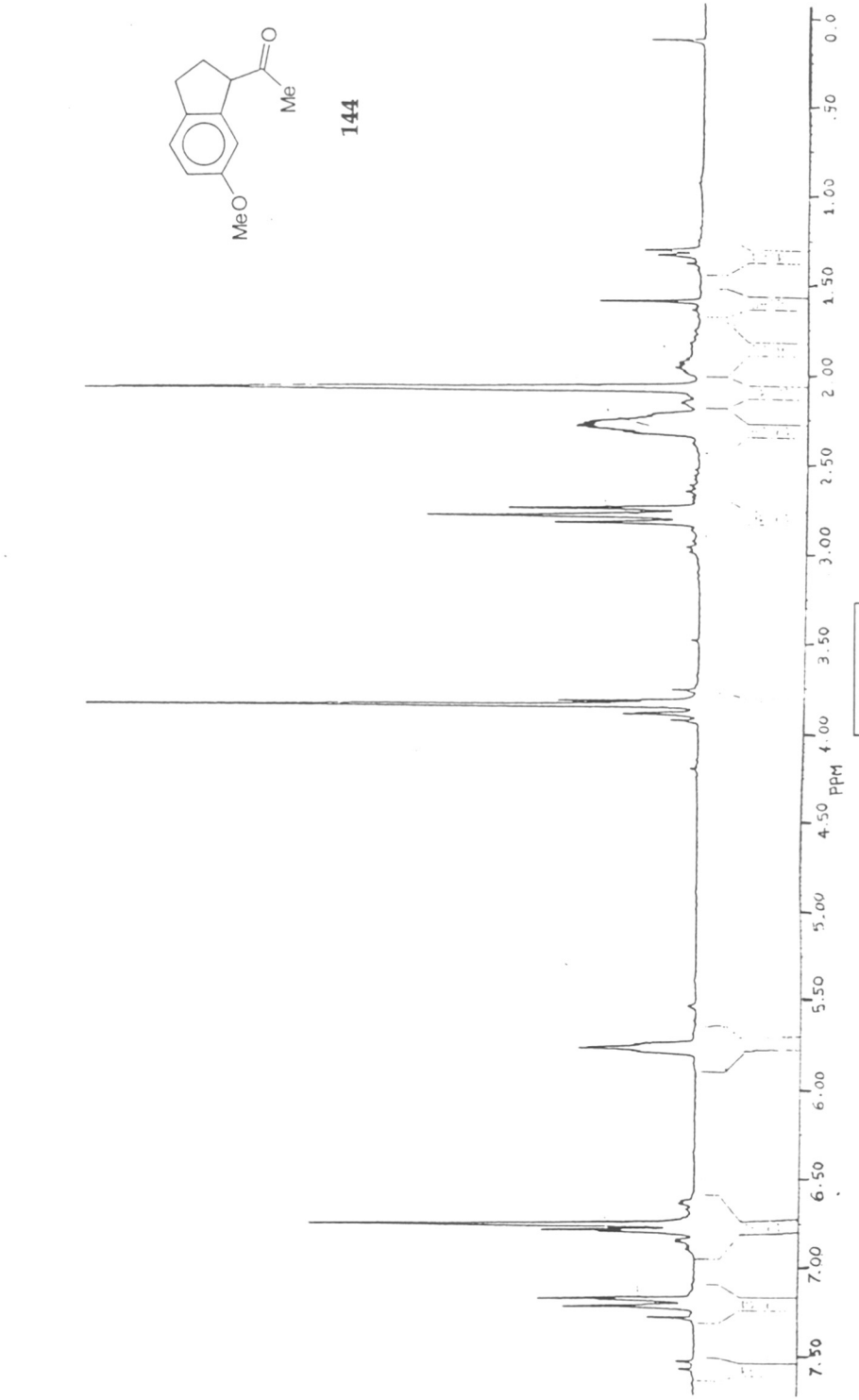
Fig. 9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Me
O
144
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6.50
6.00
5.50
5.00
4.50
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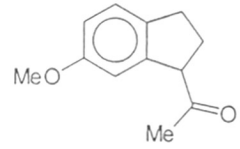
2.50
2.00
1.50
1.00
.50
0.0
PPM

Fig. 10



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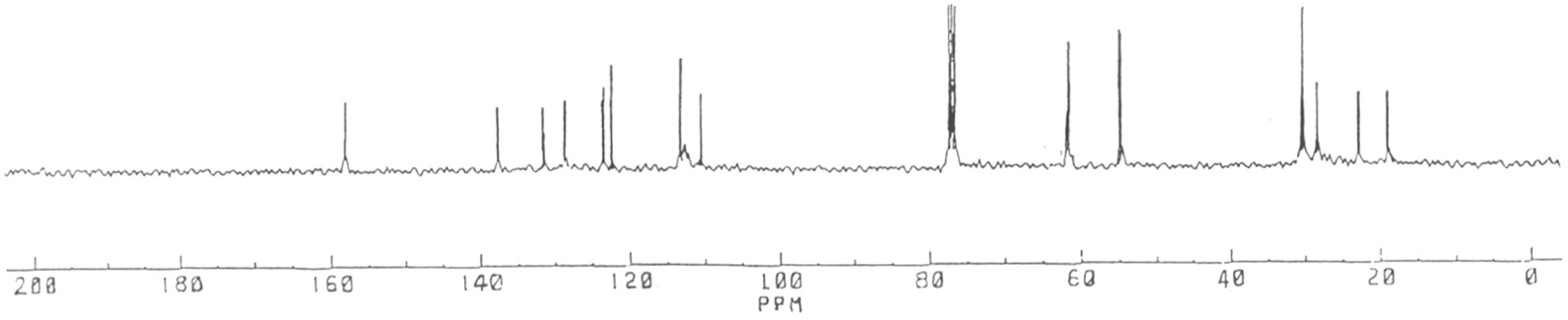

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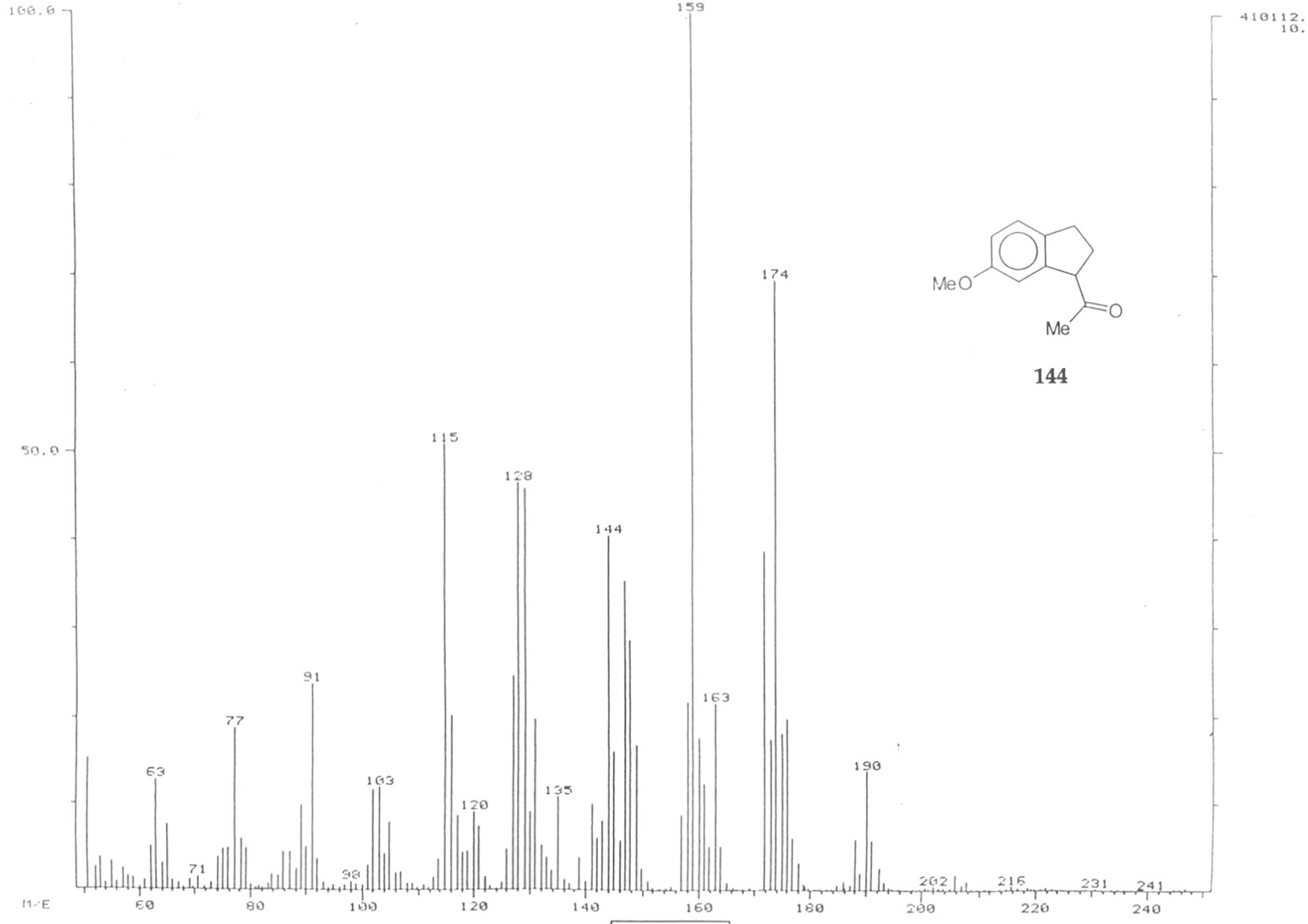
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M/E
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115
128
144
91
77
63
103
120
135
163
190
71
38
202
216
231
241
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80
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120
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200
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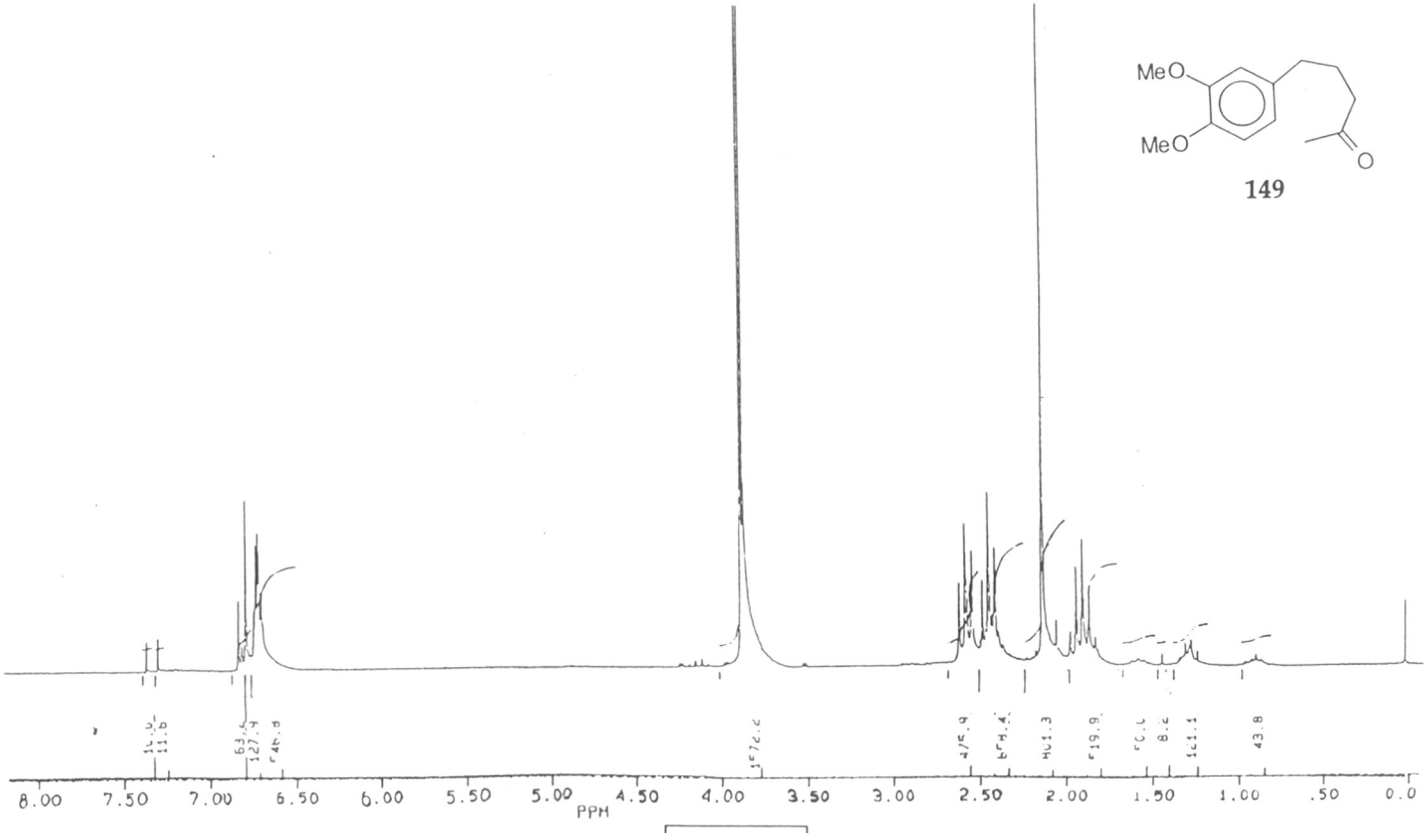
MeO
Me
O

144

Fig. 12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MeO
O
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6.50
6.00
5.50
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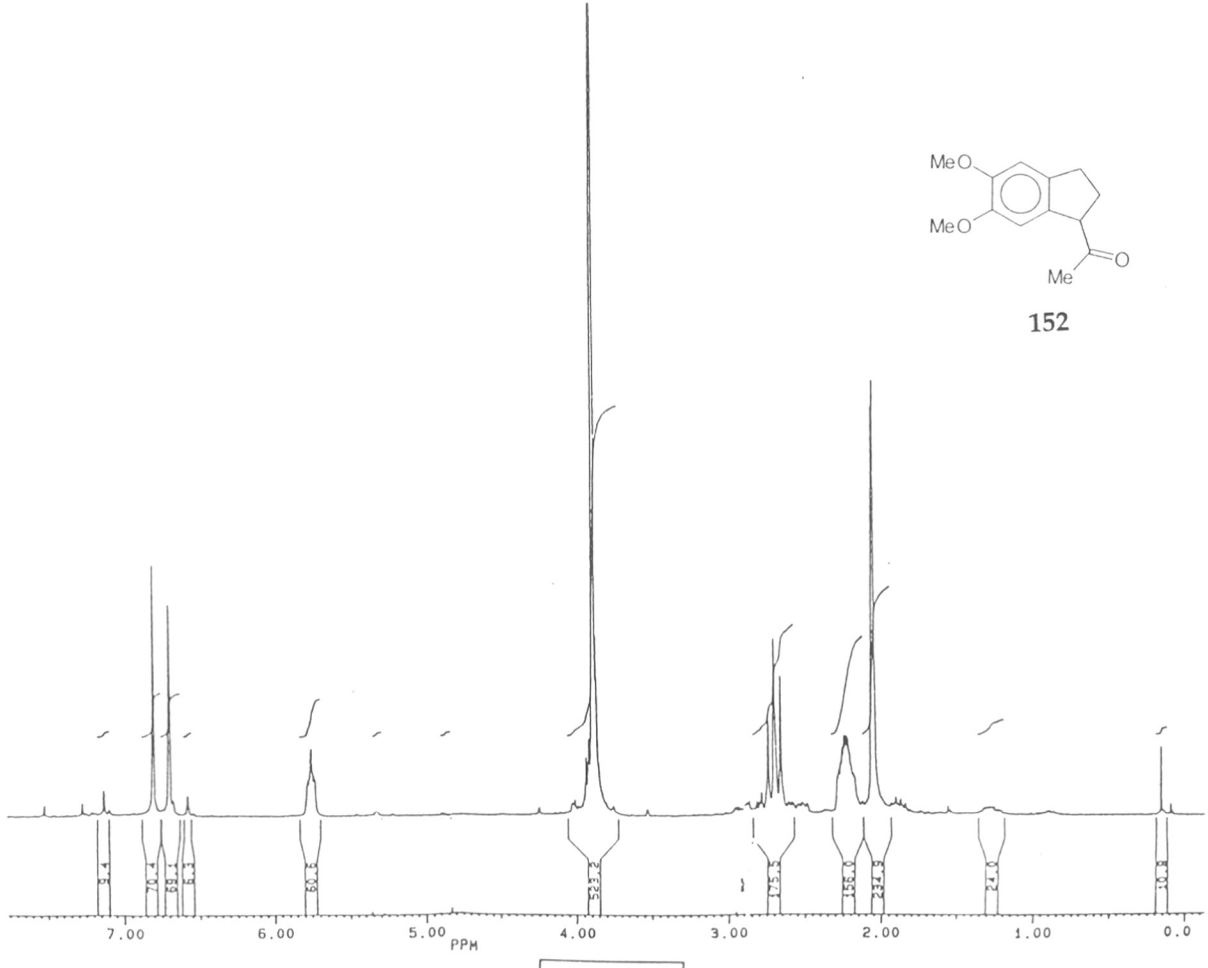
3.00
2.50
2.00
1.50
1.00
.50
0.0
PPM

Fig. 13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O
Me
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6.3
60.8
523.2
175.5
158.0
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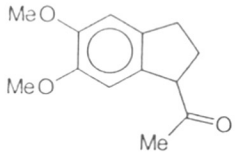
7.00
6.00
5.00
PPM
4.00
3.00
2.00
1.00
0.0

Fig. 14



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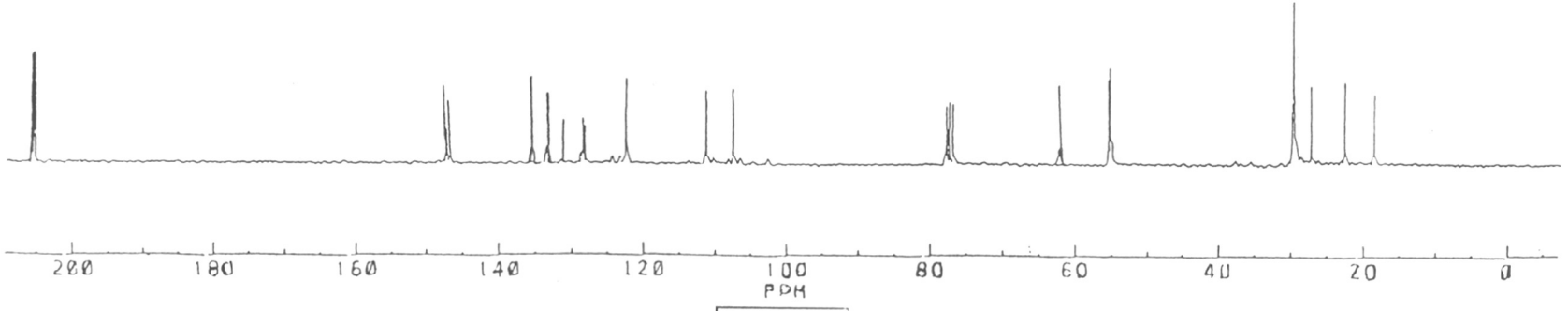
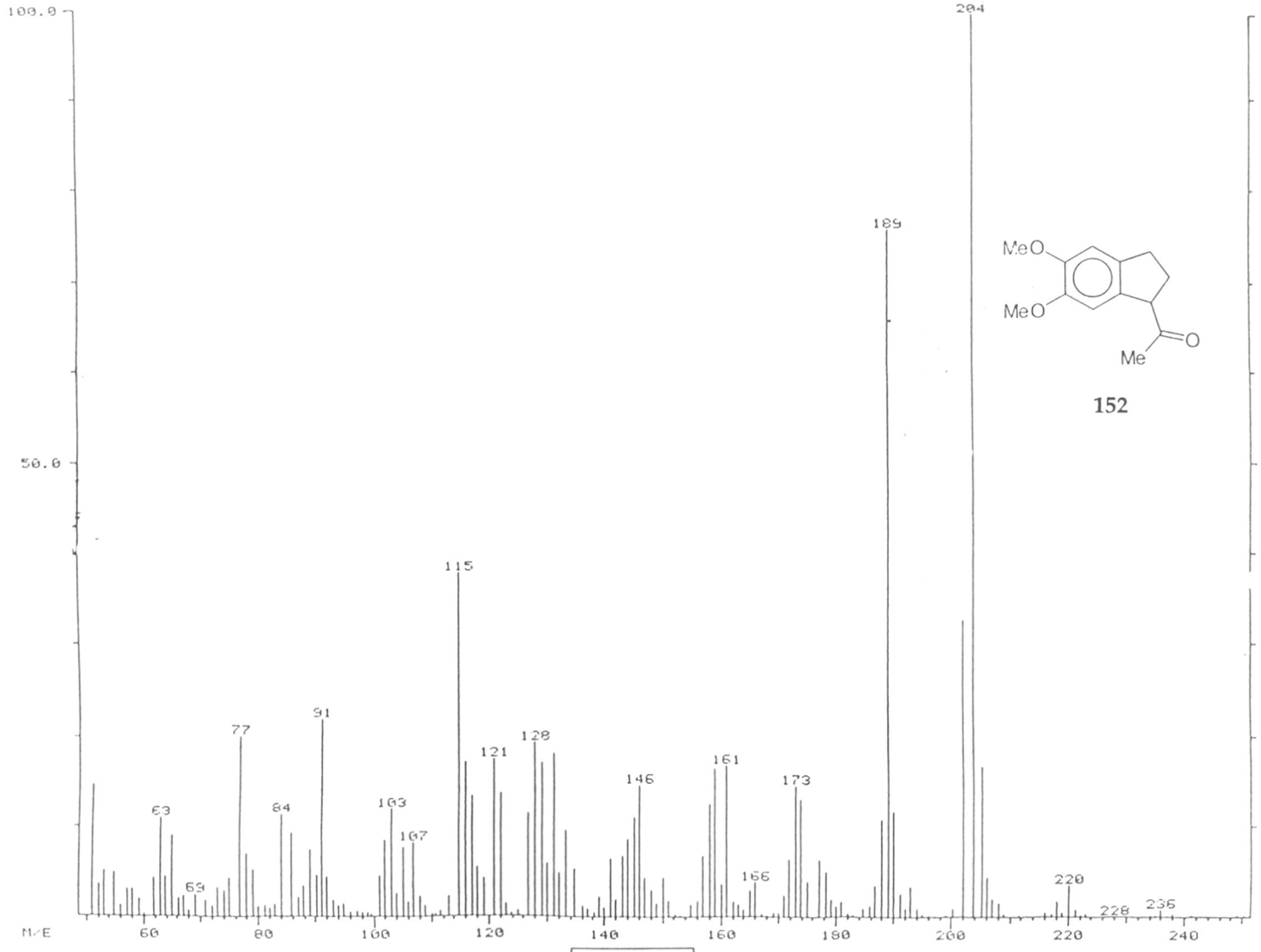


Fig. 15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M/E
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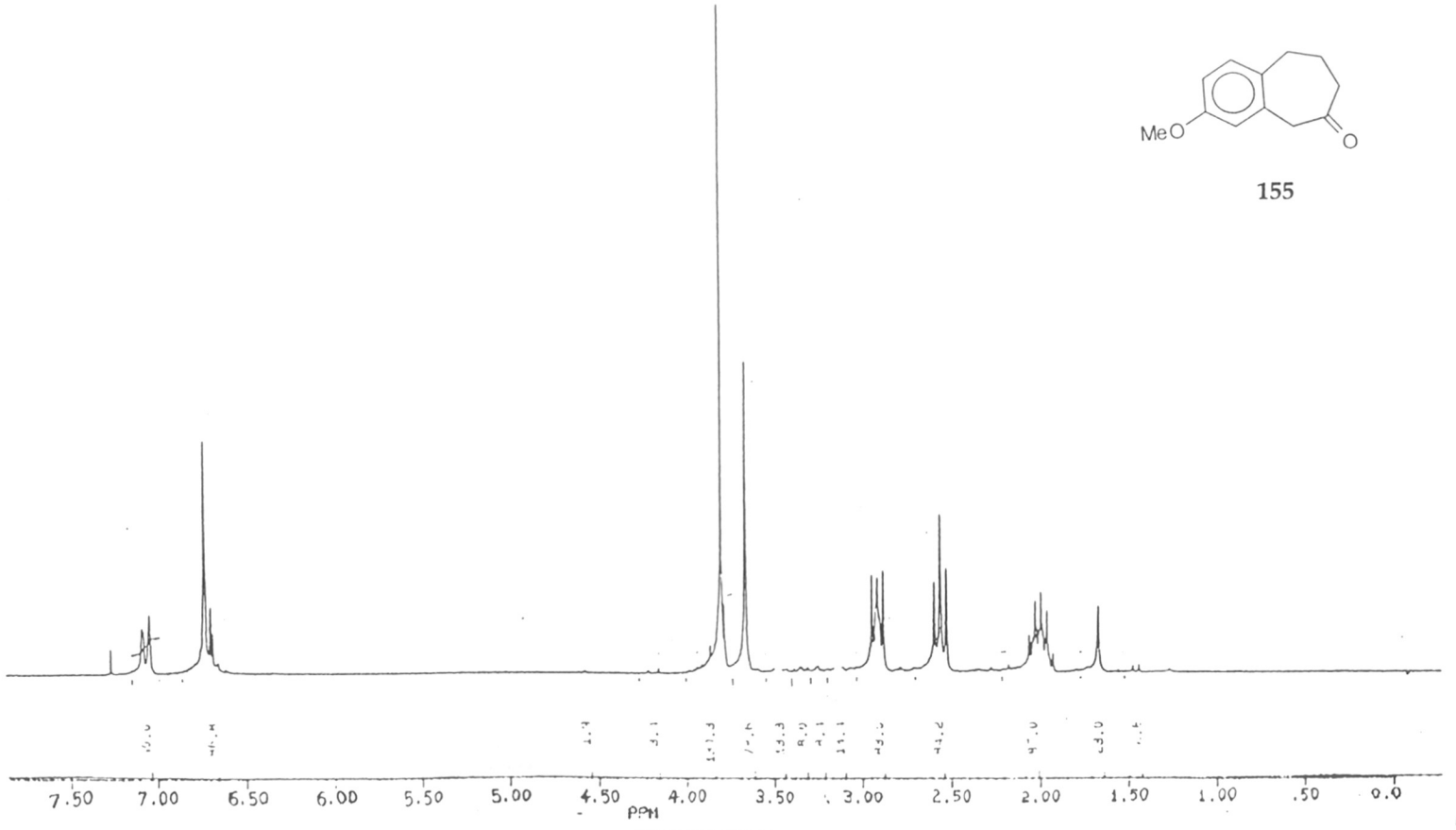
80
100
120
140
160
180
200
220
240
63
69
77
84
91
103
107
115
121
128
146
161
166
173
189
204
220
228
235
MeO
MeO
Me
O

152

Fig. 16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O
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7.00
6.50
6.00
5.50
5.00
4.50
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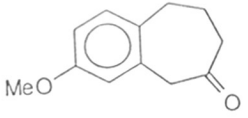
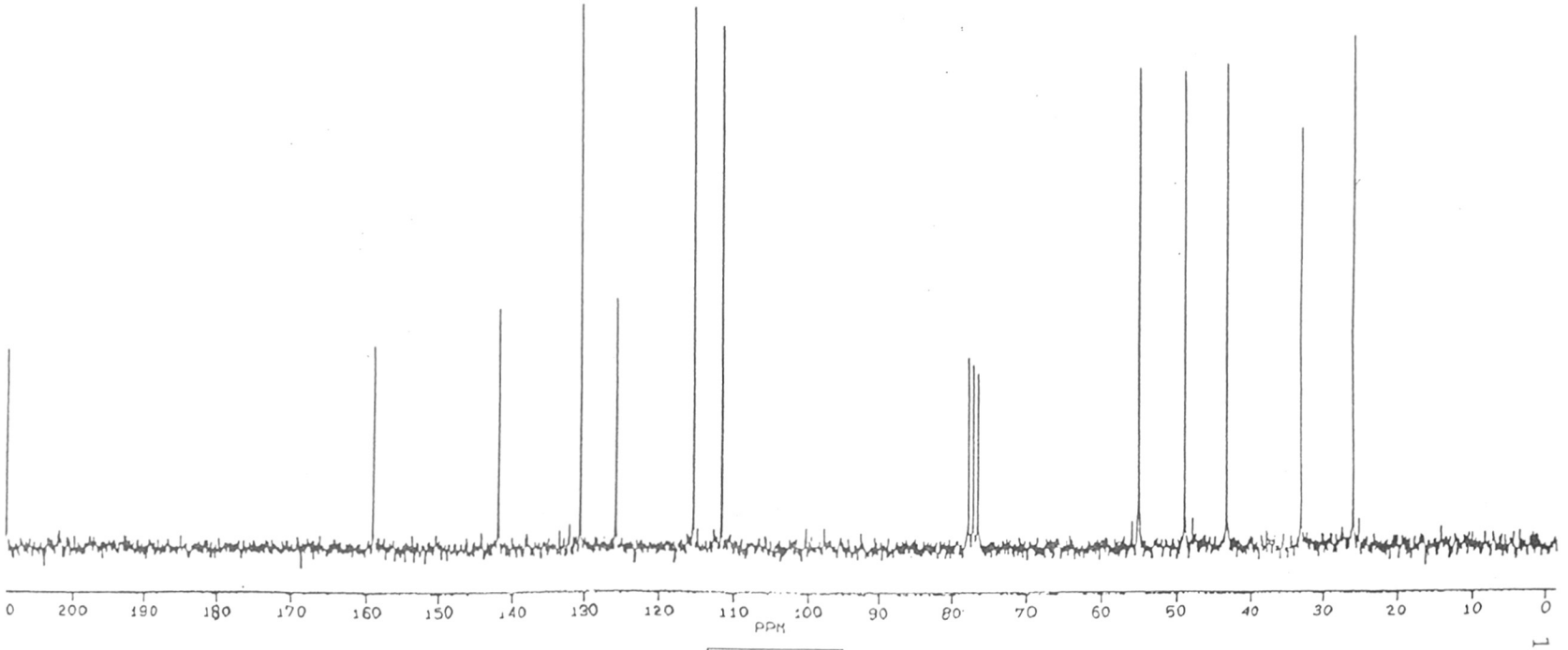
3.50
3.00
2.50
2.00
1.50
1.00
.50
0.0
PPM

155

Fig. 17


MeO
O

155


0
200
190
180
170
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150
140
130
120
110
PPM
100
90
80
70
60
50
40
30
20
10
0

Fig. 18a

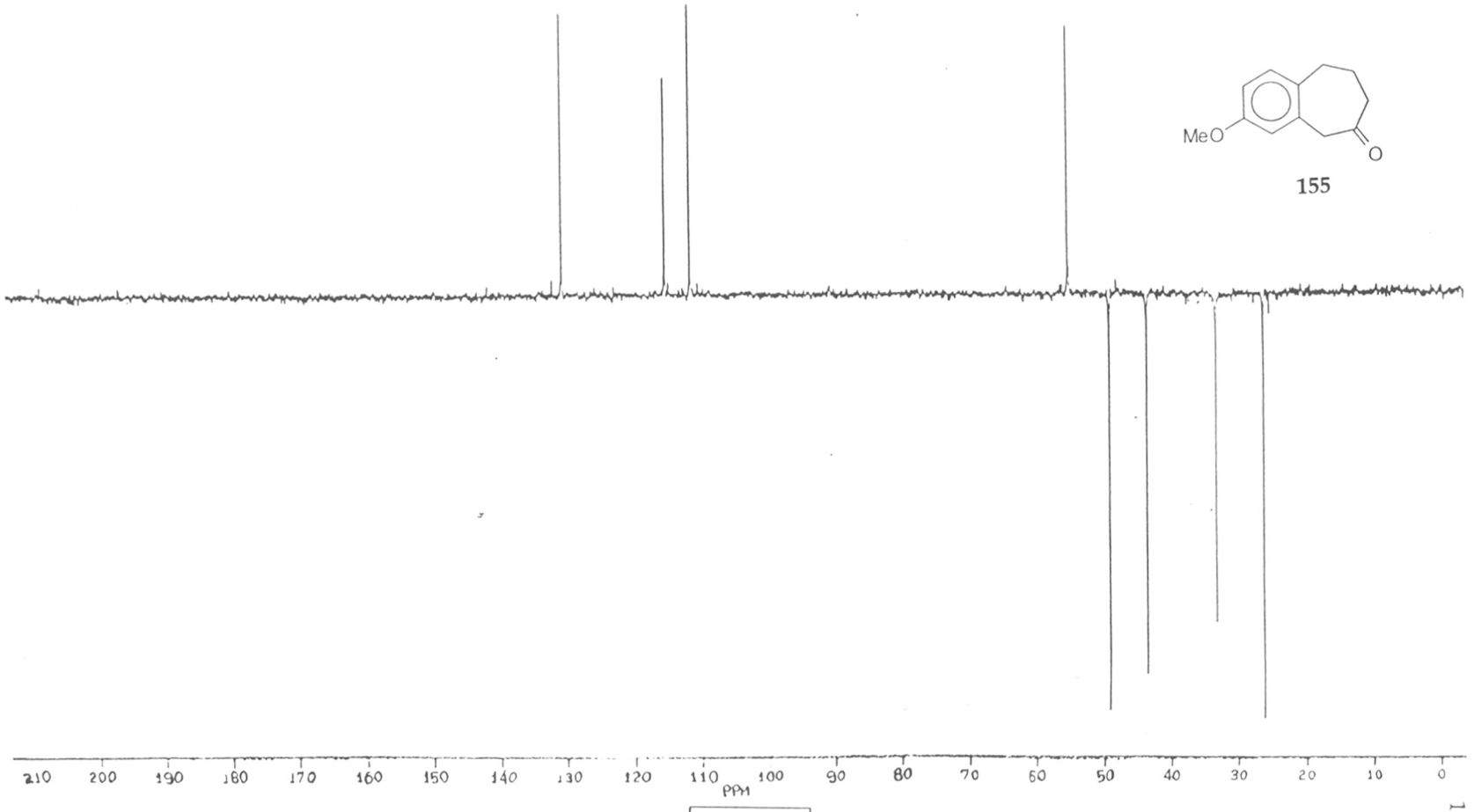
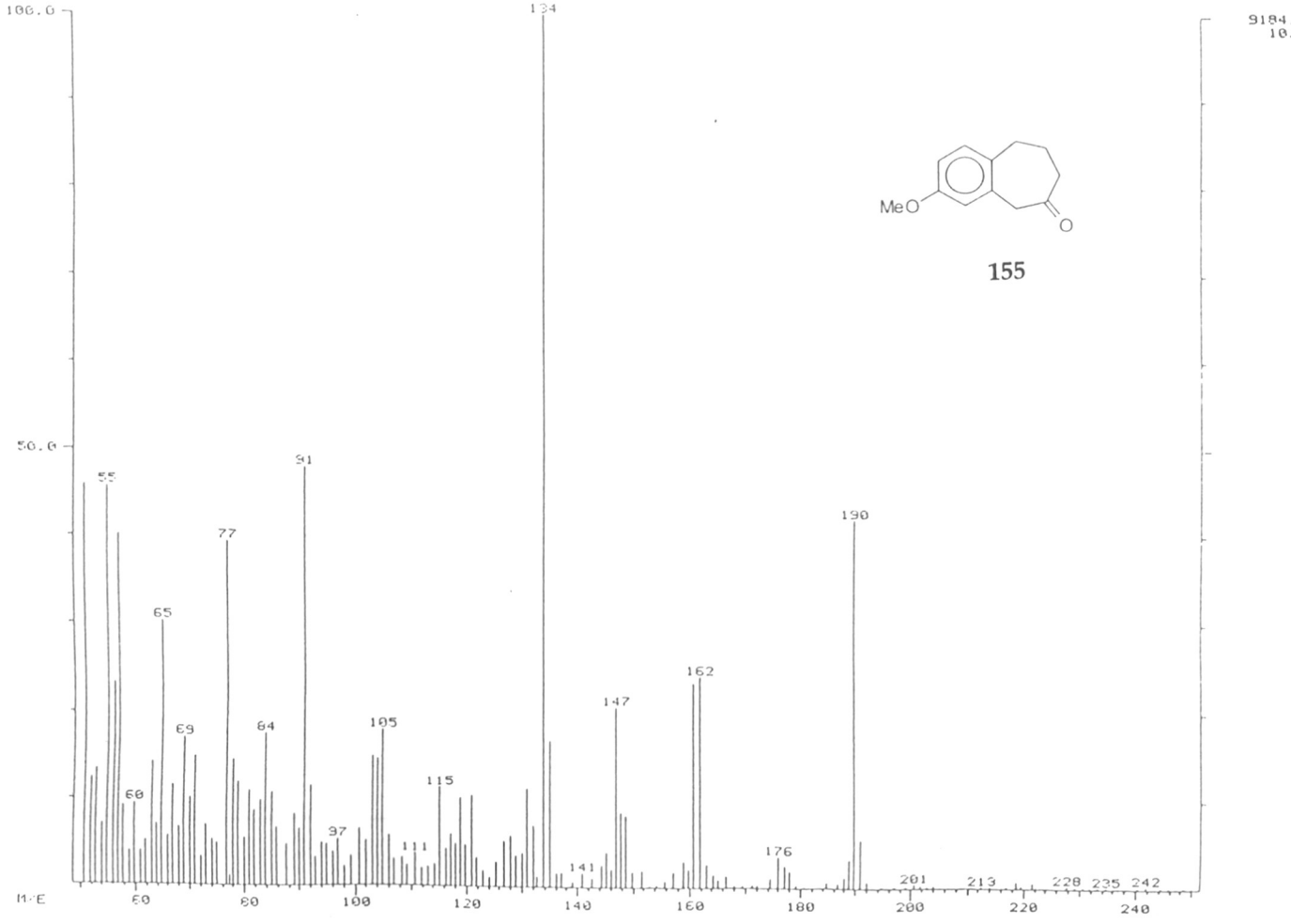

MeO
O
155
210
200
190
180
170
160
150
140
130
120
110
PPM
100
90
80
70
60
50
40
30
20
10
0

Fig. 18b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50.0
M/E
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10.
134
91
55
77
65
69
84
60
105
97
115
111
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147
162
176
190
201
213
228 235 242
MeO
O
155

Fig. 19

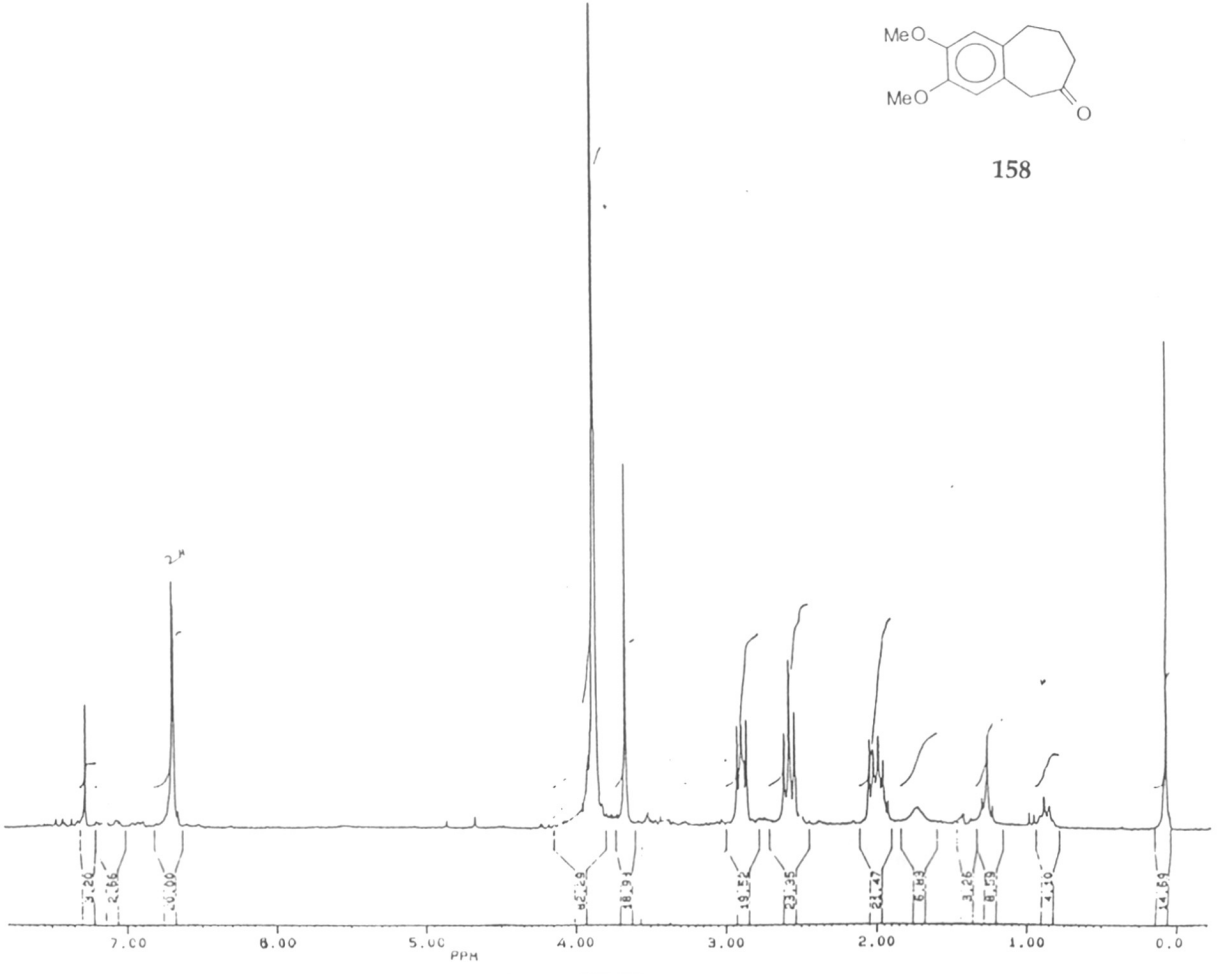
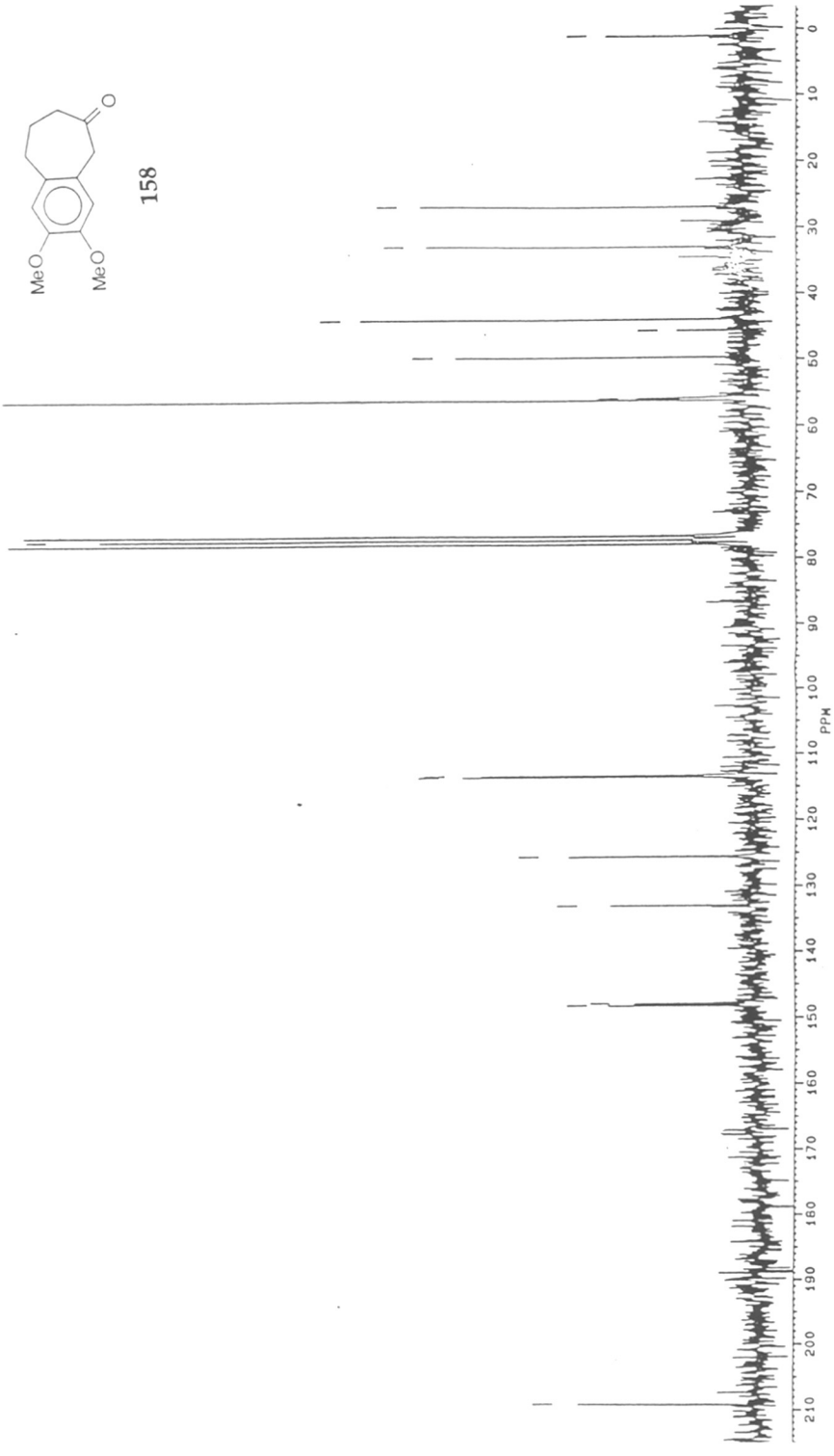


Fig. 20



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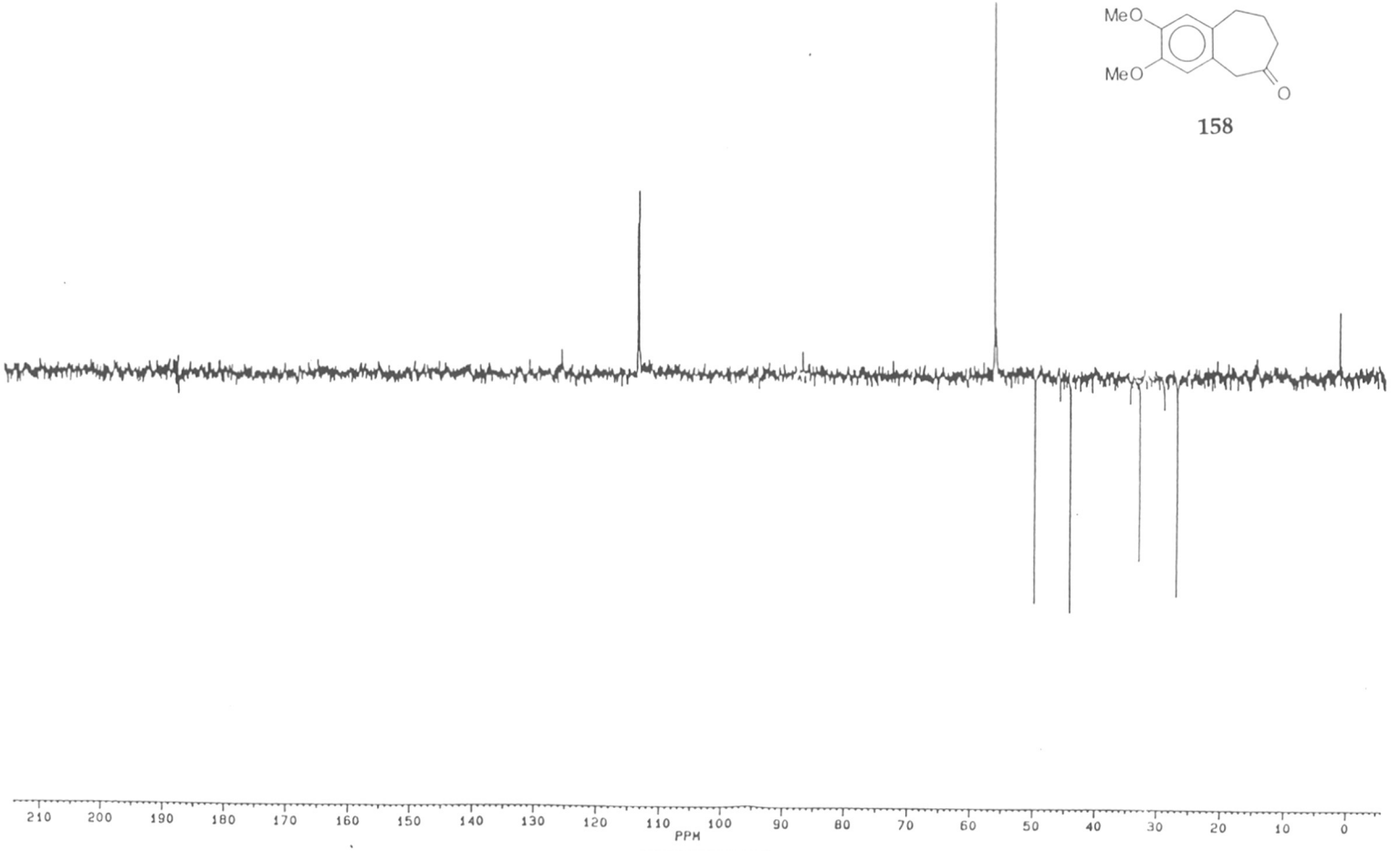
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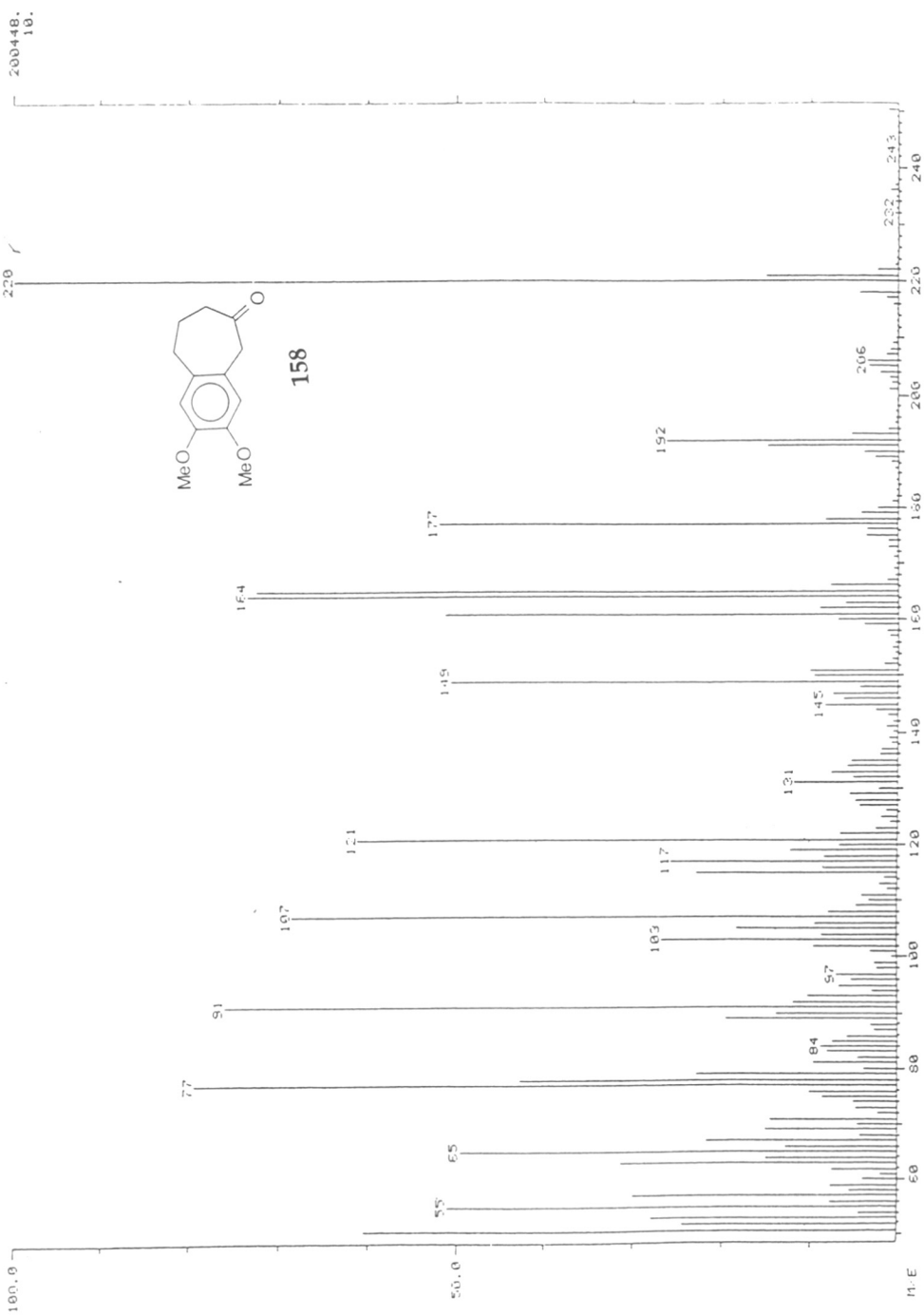
MeO
O
158
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM

Fig. 21b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50.0
0.0
220
240
232
243
206
192
177
164
149
145
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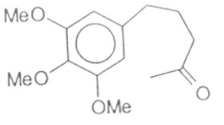
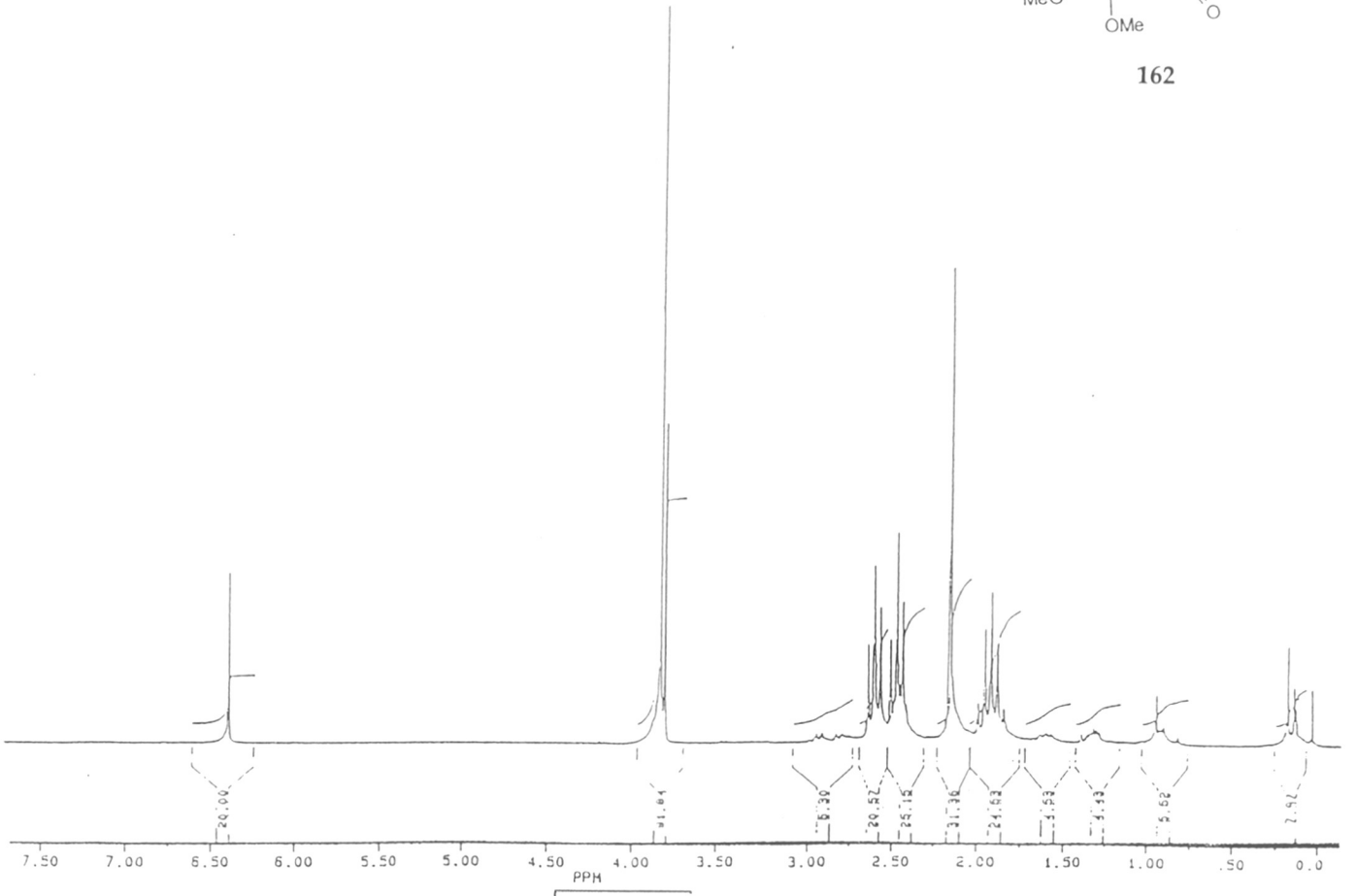
121
117
107
103
97
91
84
77
65
55
MeO
MeO
O
158

Fig. 22


MeO
MeO
OMe
O

162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6.39
20.82
25.15
31.36
24.63
3.93
3.93
5.62
2.92
7.50
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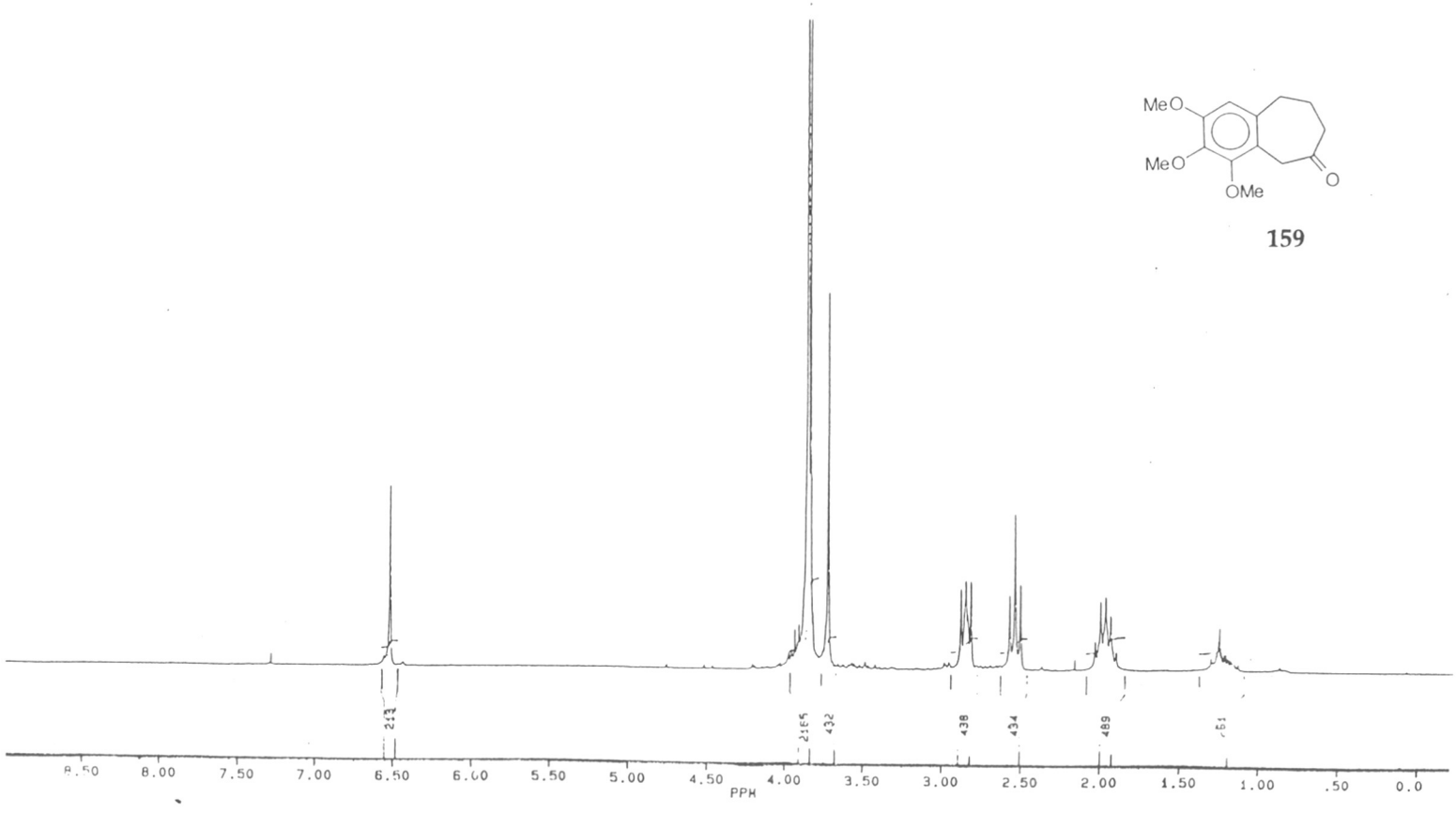
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
.50
0.0
PPM

Fig. 23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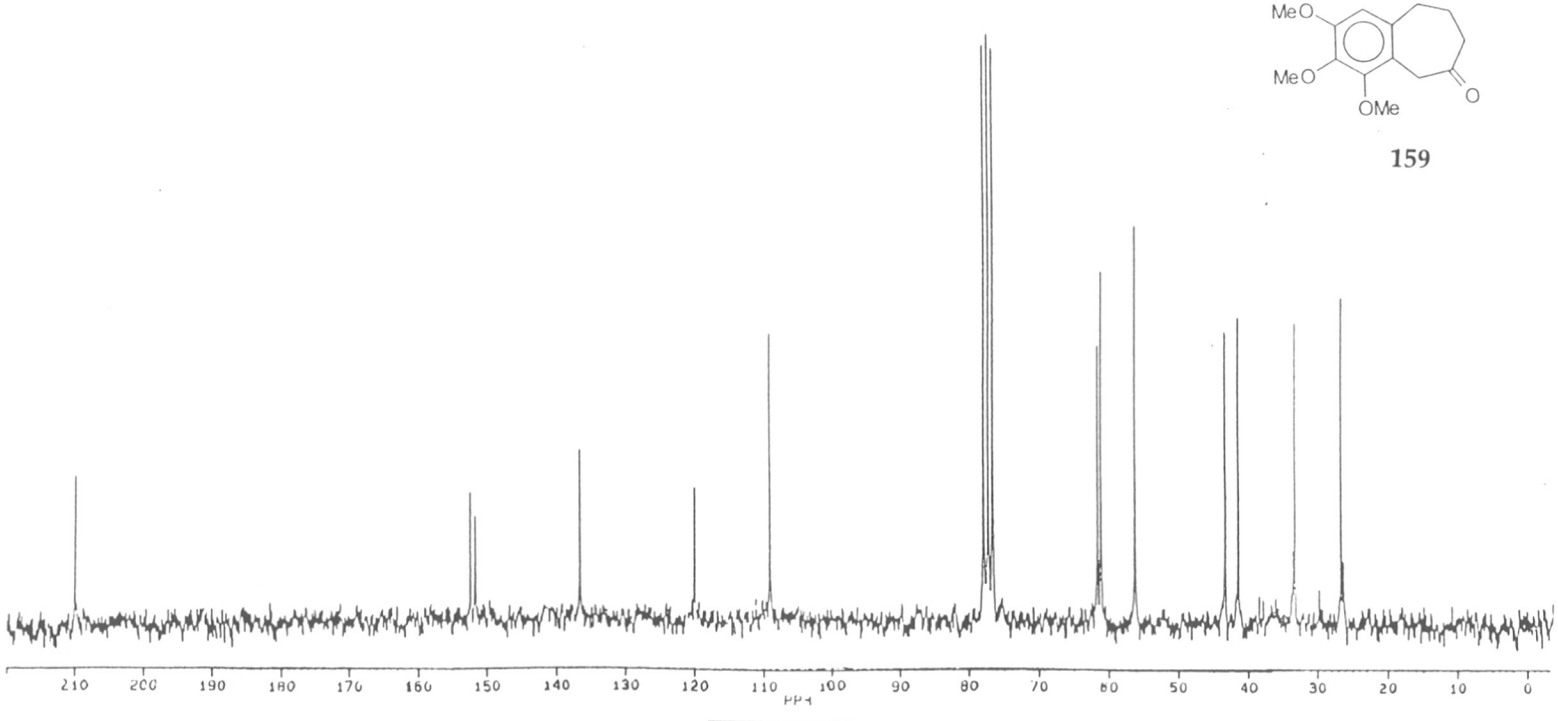
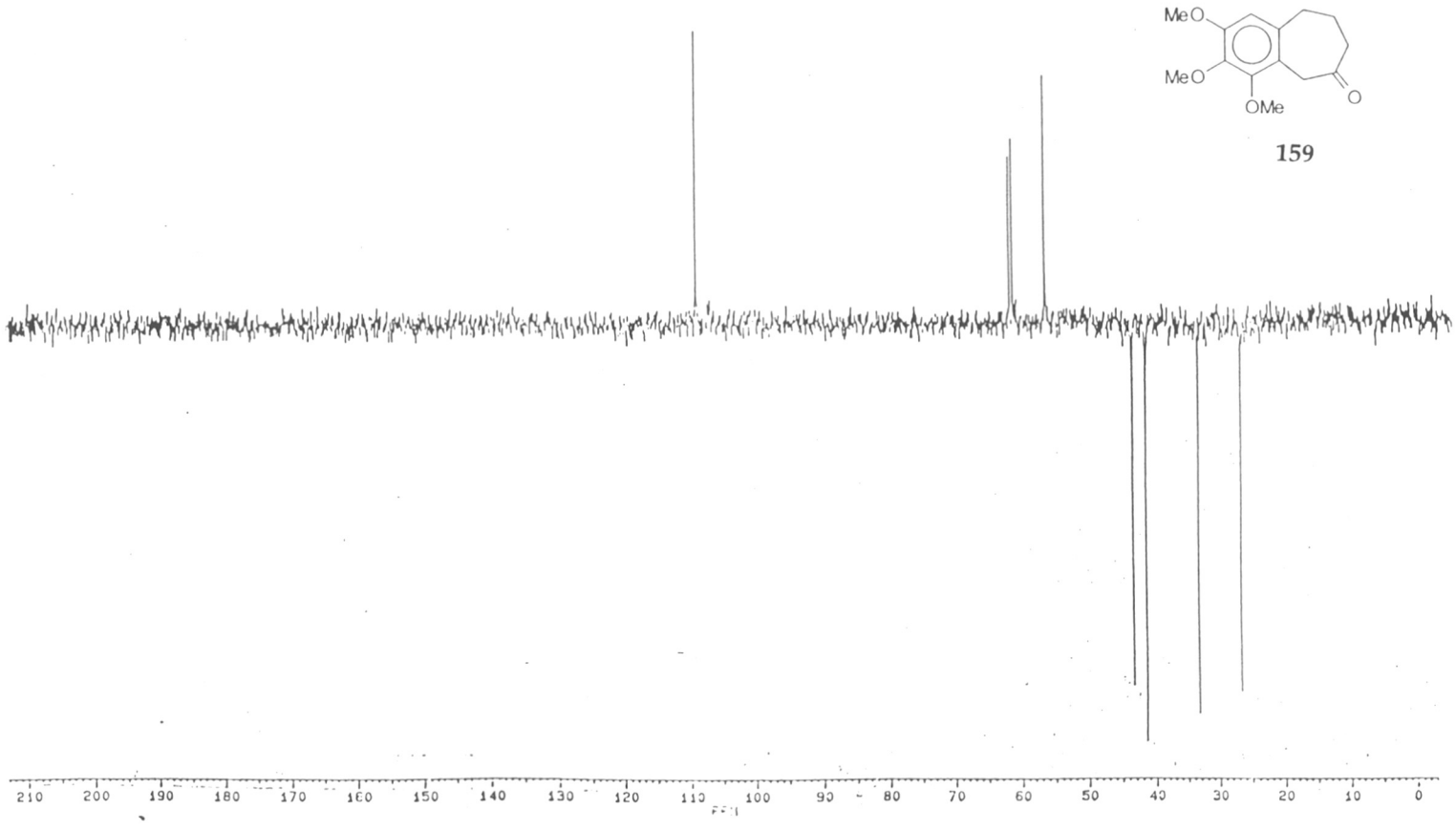
MeO
OMe
O
159
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
PPM
4.00
3.50
3.00
2.50
2.00
1.50
1.00
.50
0.0
2.13
2.15
4.32
4.38
4.34
4.89
1.61

Fig. 24


MeO
MeO
OMe
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

159

Fig. 25a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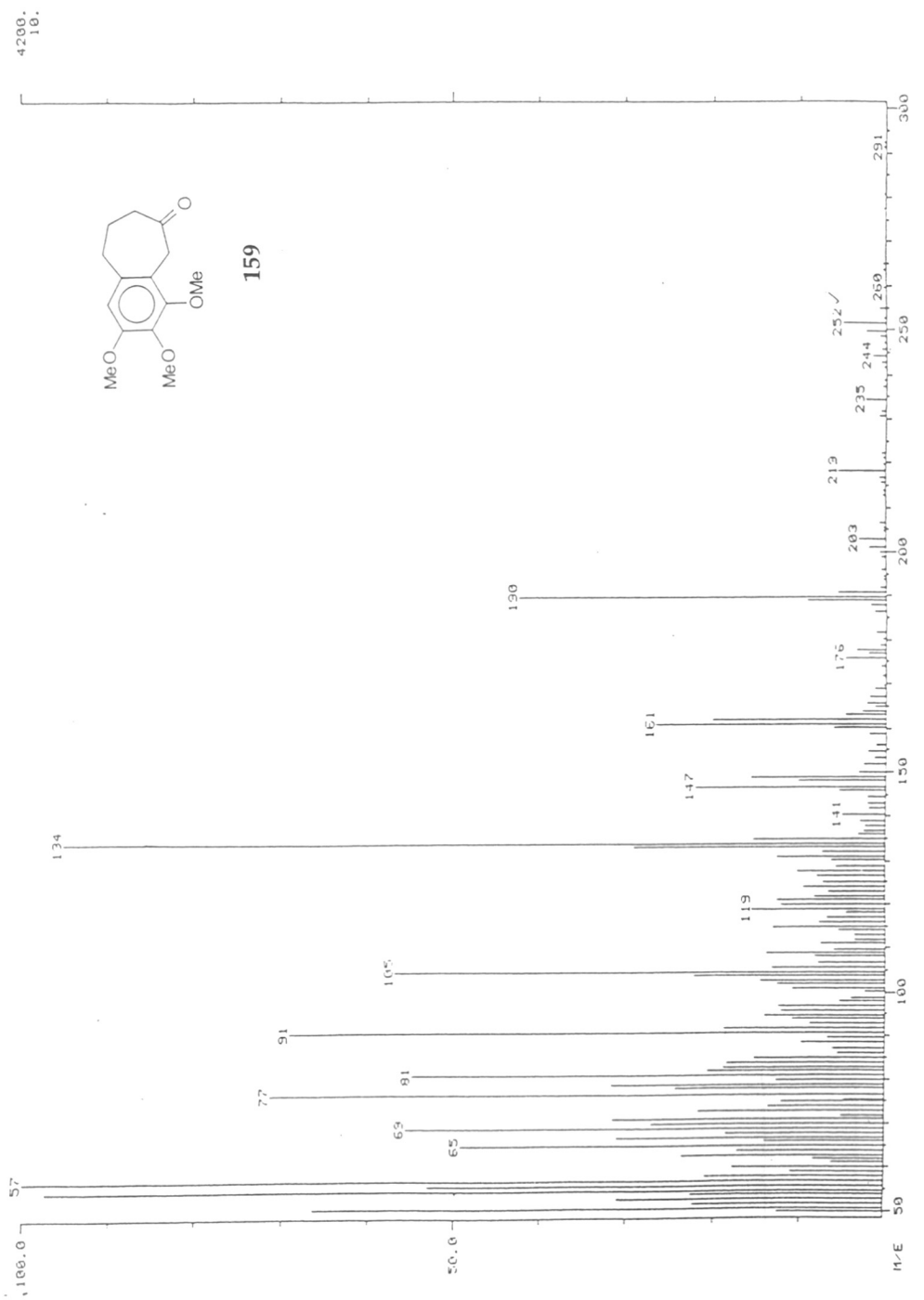
MeO
OMe
O
159
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Fig. 25b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MeO
MeO
OMe
O
4200.
10.
100.0
50.0
M-E
50
57
65
69
77
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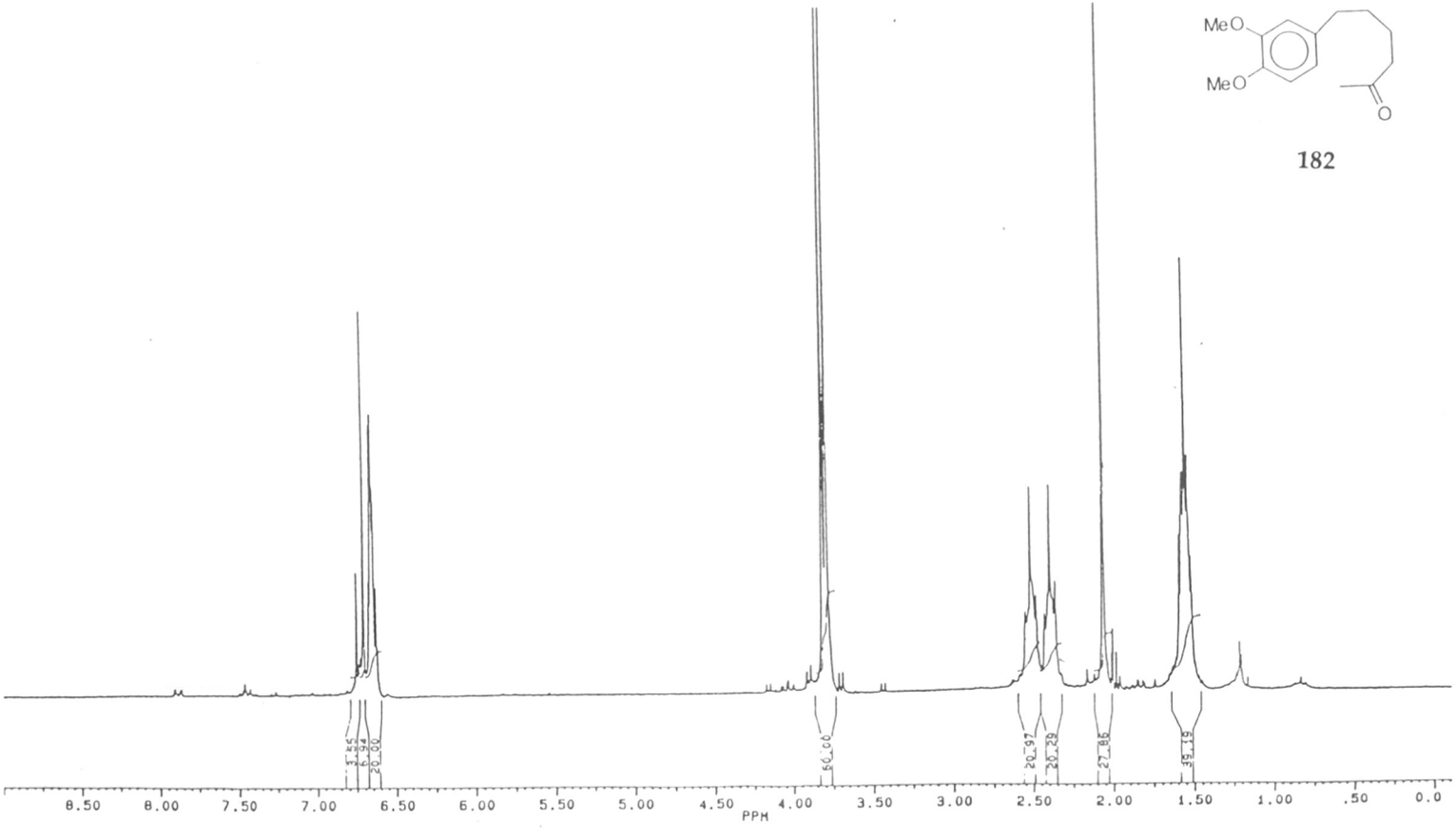
91
105
119
134
141
147
161
175
190
203
219
235
244
252
260
291
300

Fig. 26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MeO
O
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60.00
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27.86
35.19
8.50
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7.50
7.00
6.50
6.00
5.50
5.00
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3.50
3.00
2.50
2.00
1.50
1.00
.50
0.0
PPM

Fig. 27

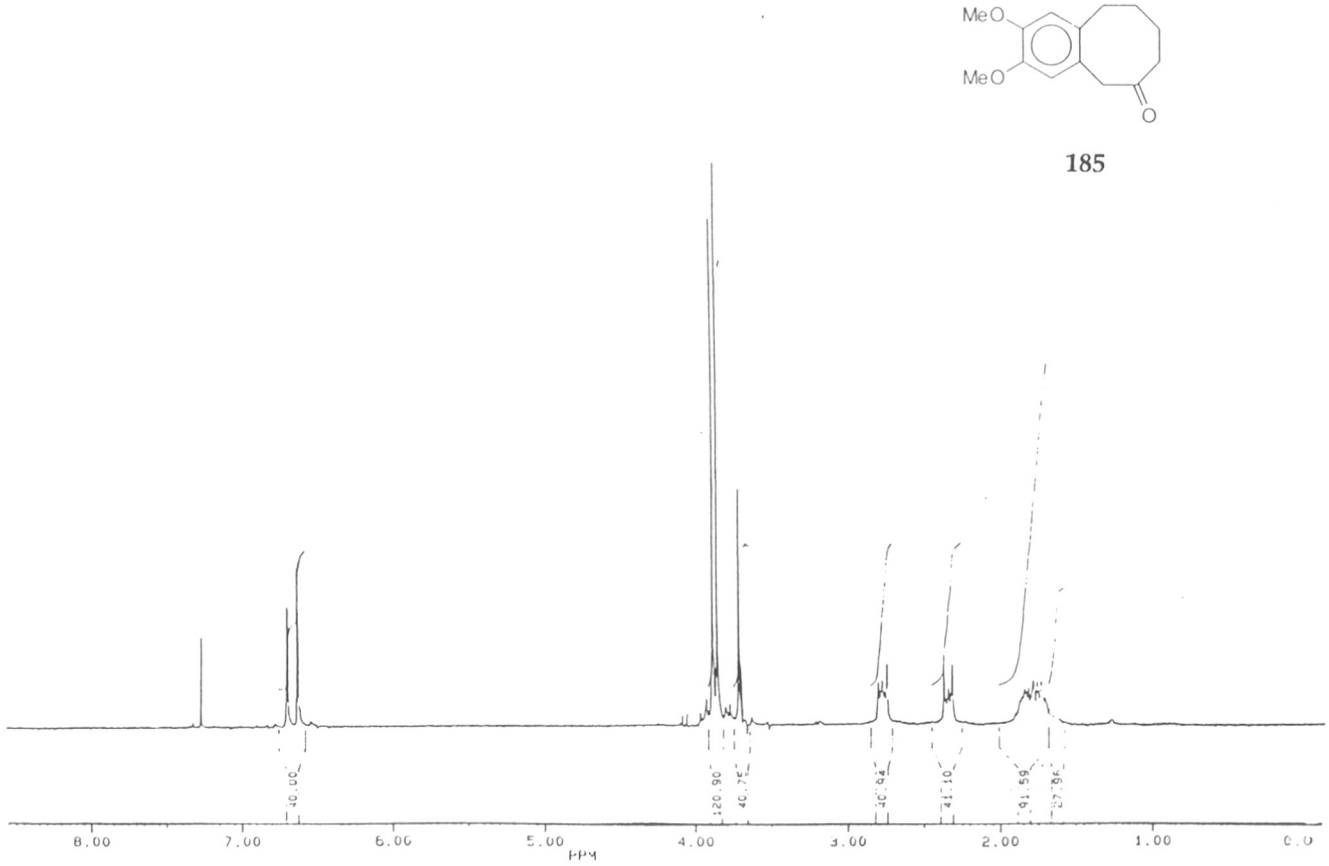
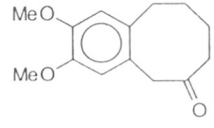


Fig. 28


MeO
MeO
O

185

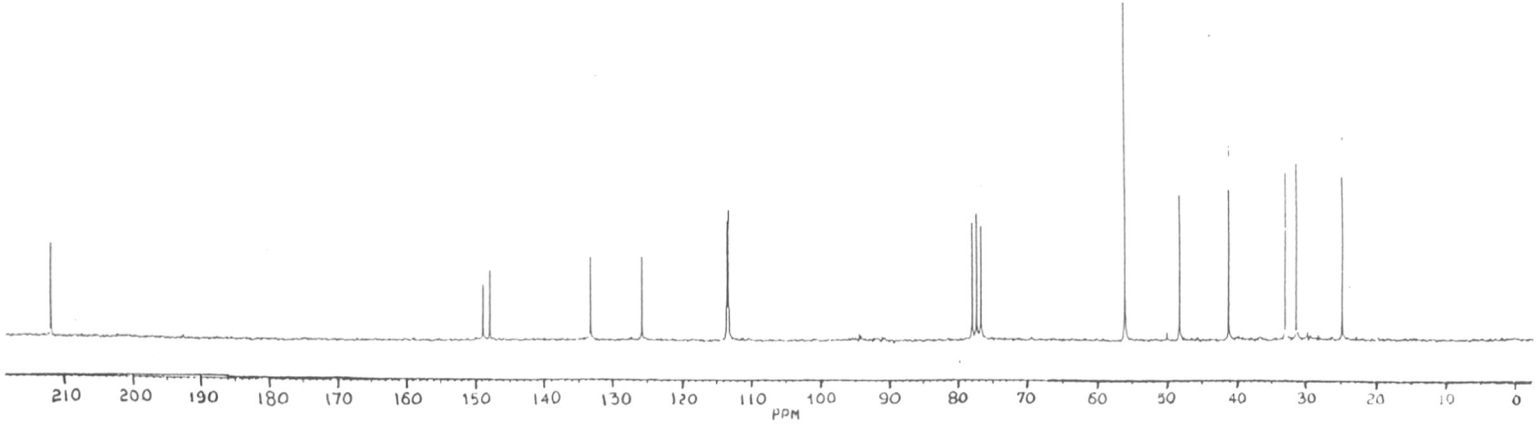

210
200
190
180
170
160
150
140
130
120
110
PPM
100
90
80
70
60
50
40
30
20
10
0

Fig. 29a

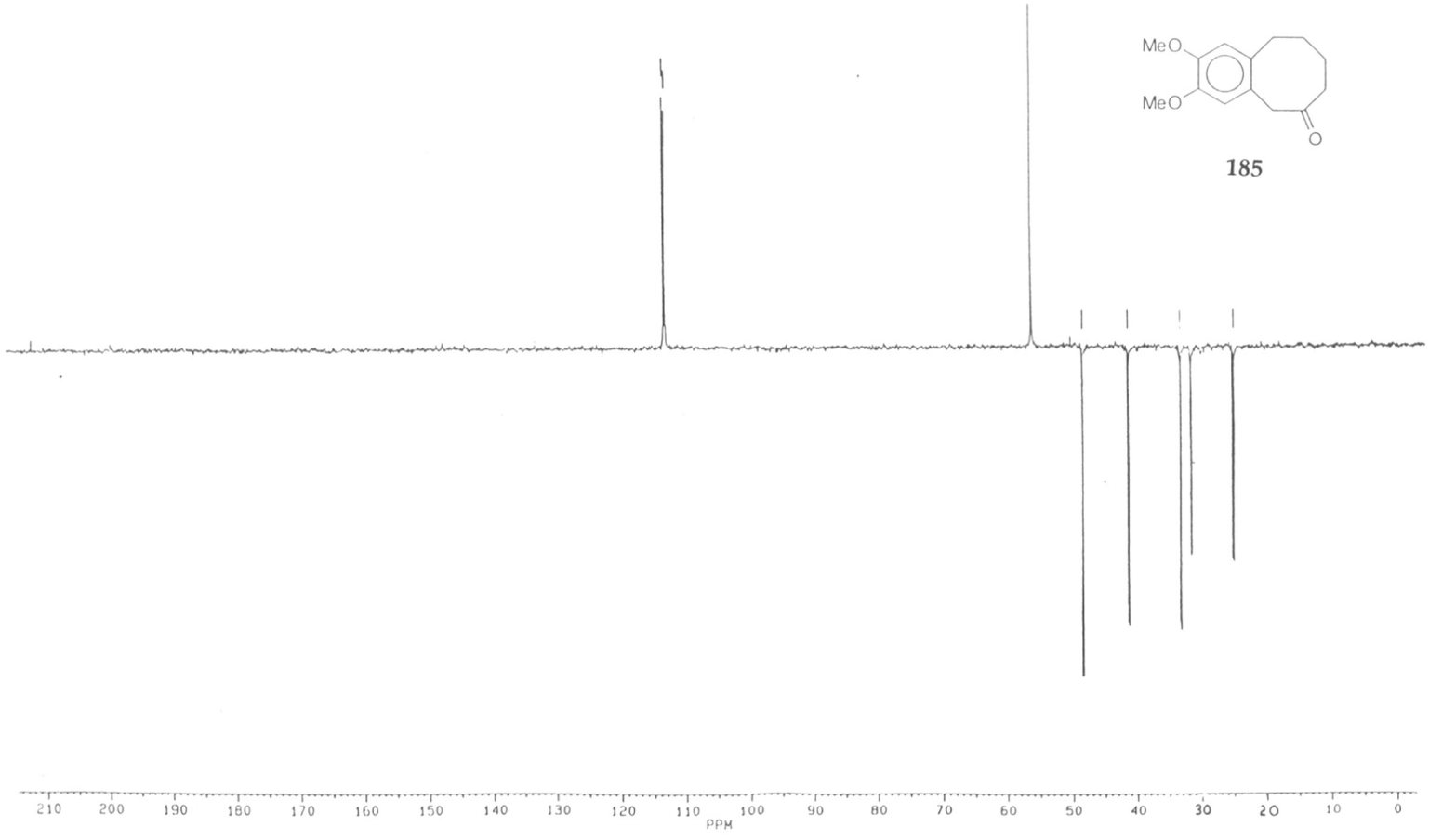
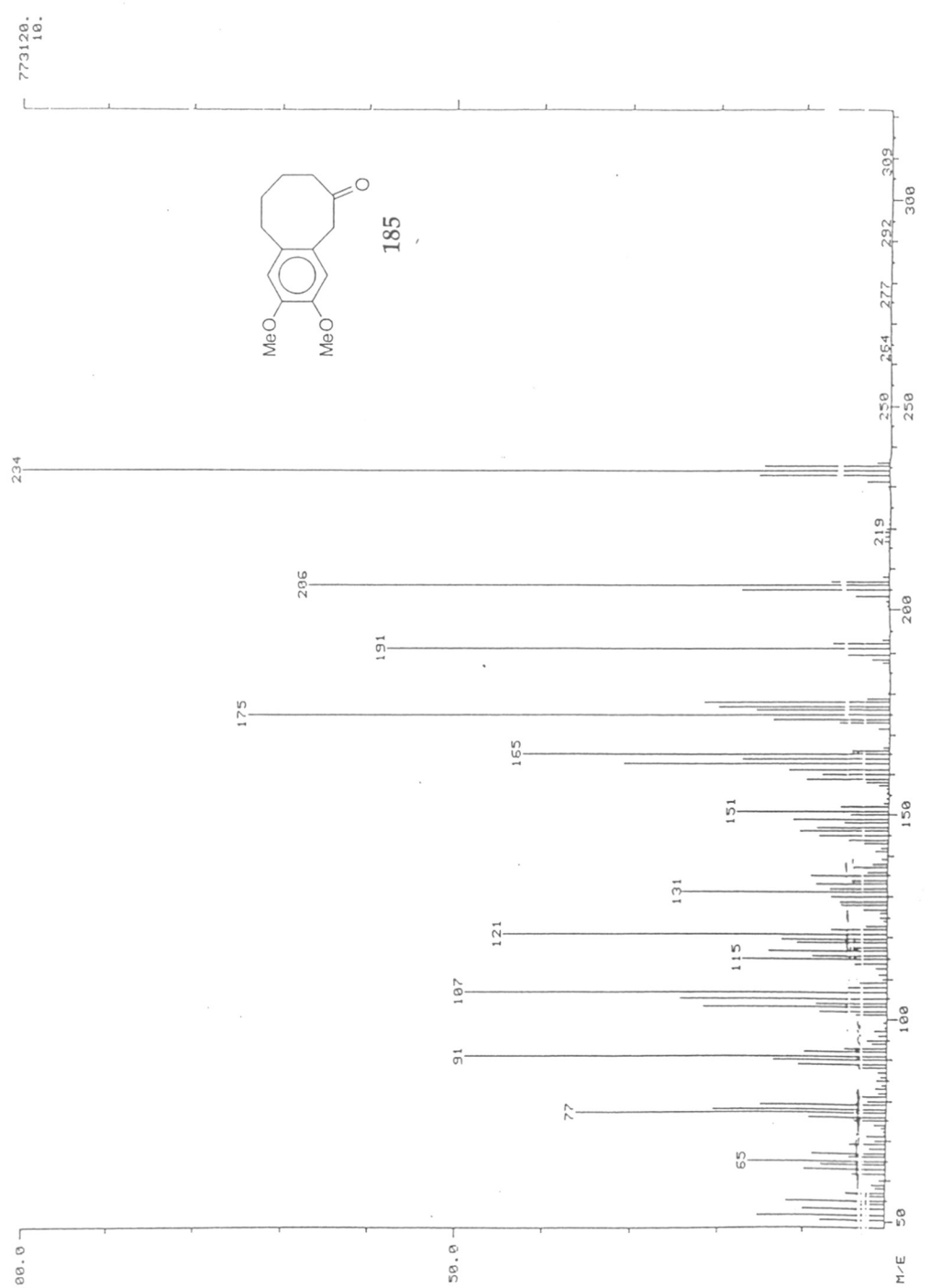

MeO
MeO
O
185
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM

Fig. 29b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10.
MeO
MeO
O
185
234
206
191
175
165
151
131
121
115
107
91
77
65
100.0
50.0
M/E
50
100
150
200
250
300
219
254
277
292
309

Fig. 30

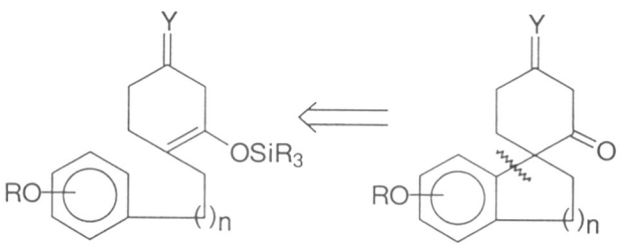
Chapter-III

Spirocyclization reactions using photochemically generated arene radical cations

1. INTRODUCTION

Benzospiroannulation strategy:

The spectacular success of intramolecular arylation reaction of ketones by the reaction of silyl enol ether to the PET generated arene radical cation, as discussed in chapter-2, led us to envisage the possible exploitation of this strategy for the construction of benzospiro[n.5]alkanes (**2**) through the strategy as shown in the Scheme-1.



1 **2** a (n=1)
b (n=2)

Scheme-1

Spiro annulated structural framework of type **2** represent either as the integral part of some biologically active natural products or are utilised as intermediates for the synthesis of some of the important biologically active compounds. For illustration, **2a** (n=1), represents the basic skeleton of Cannabinoids[1], known for their estrogenic activity[2]. Some of the important molecules of this class, possessing benzospiro[4.5]decane framework, are Cannabis spiradienone (**3**)[3], Cannabis spirenone-A (**4**)[4], Cannabis spirone (**5**)[5], and Cannabis spiranol(**6**)[6].

Similarly, skeleton **2b** (n=2) is known to be the main structural unit of naturally occurring terpenoid stemodine[7]. This type of skeleton has also been used in the synthesis of homoerythirina alkaloids[8].

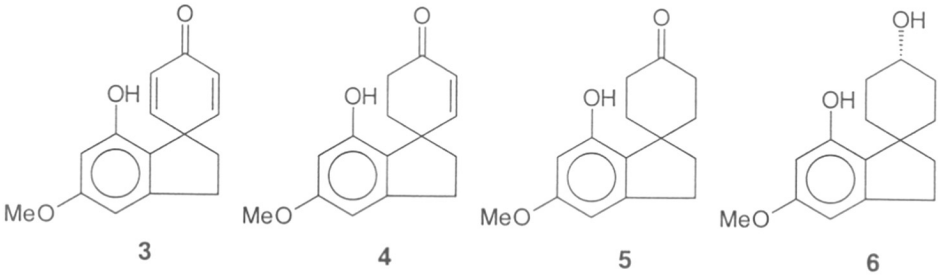
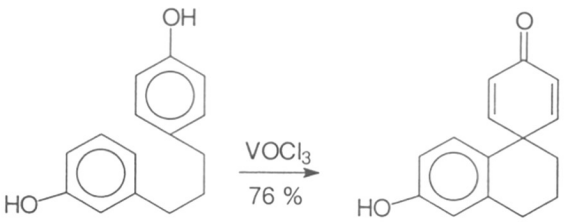


Fig.1

Due to the unique structural features associated with these spiroannulated frameworks and remarkable pharmacological activity exhibited by some of the compounds possessing such structures, many synthetic attempts have been made to construct these structural entities. It would be pertinent to briefly mention, few of the important strategies reported in literature for the construction of benzospiroannulated compounds to put the forthcoming discussions in proper perspectives.

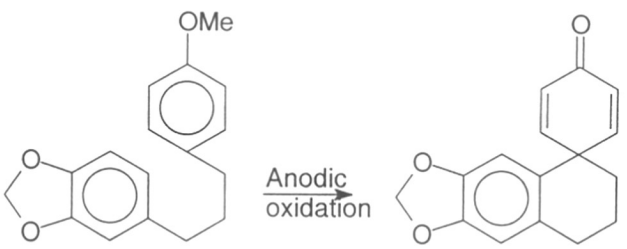
Generally, benzospiroannulated structural frameworks are constructed by the oxidative phenolic coupling reactions using a variety of oxidising reagents[9]. For example, Schwartz *et al*[10] have utilized $VOCl_3$ as two electron oxidant to bring about the transformation of **7** to **8** in 76 % yield. Later the same group[11] and also others[12] have screened a variety of other oxidising reagents for such transformations.



7 8

Scheme-2

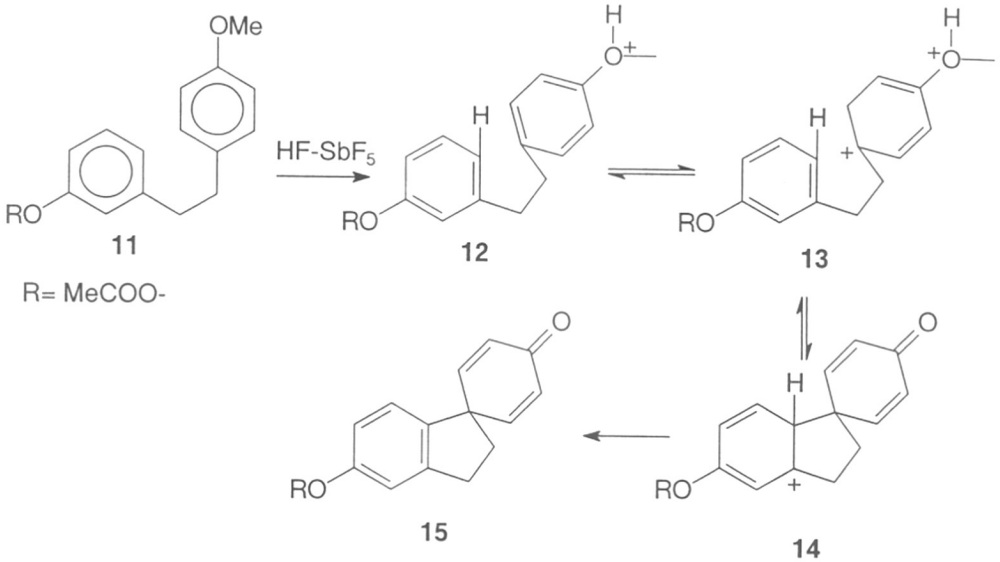
Similar strategy have been utilised by Kotani *et al*[13] for the synthesis of related spirocyclic compound **10** from **9** utilising either $[Fe(DMF)_3Cl_2][FeCl_4]$ complex as an oxidising reagent or by anodic oxidation reactions.



9 10

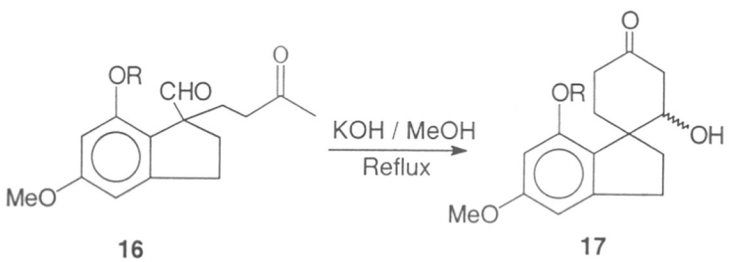
Scheme-3

Benzospirocyclic compounds **15** are also prepared[14] (46 % yield) by the coupling reaction of **11** utilising HF-SbF_5 as super acid reagent. The details of the reaction sequence is shown in Scheme-4. However, due to many other competitive reactions associated with such couplings *viz.* polymerisations and over oxidations, very poor yield of spiroannelated products are obtained.



Scheme-4

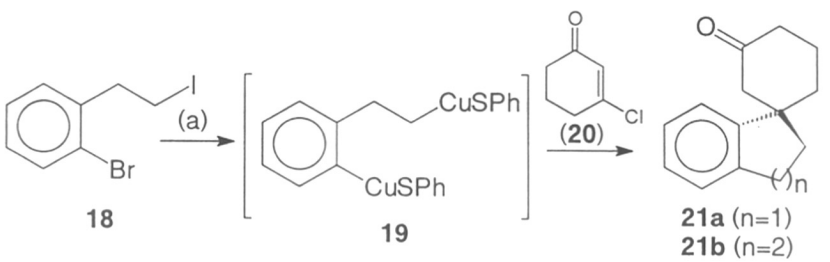
Crombie *et al*[15,16] have achieved the spiroannulation of **16** in 53 % yield by the intramolecular Aldol condensation reaction carried out by heating in MeOH solution containing KOH as base (Scheme-5).



Scheme-5

Similar Aldol condensation methodology is also reported[17,18] by Novak *et al* for the synthesis of *o*-methyl cannabis spirenone.

Wender *et al*[19] have reported an one-pot spiroannulation strategy for the synthesis of spiro[4.5]decanes **21a** (n=1) as well as for spiro[5.5]undecanes **21b** (n=2), by the reaction of 3-chloro-cyclohex-2-enone (**20**) with **19,** prepared by the reaction of **18** with copper thiophenoxide in the presence of t-BuLi at -78 °C (Scheme-6).

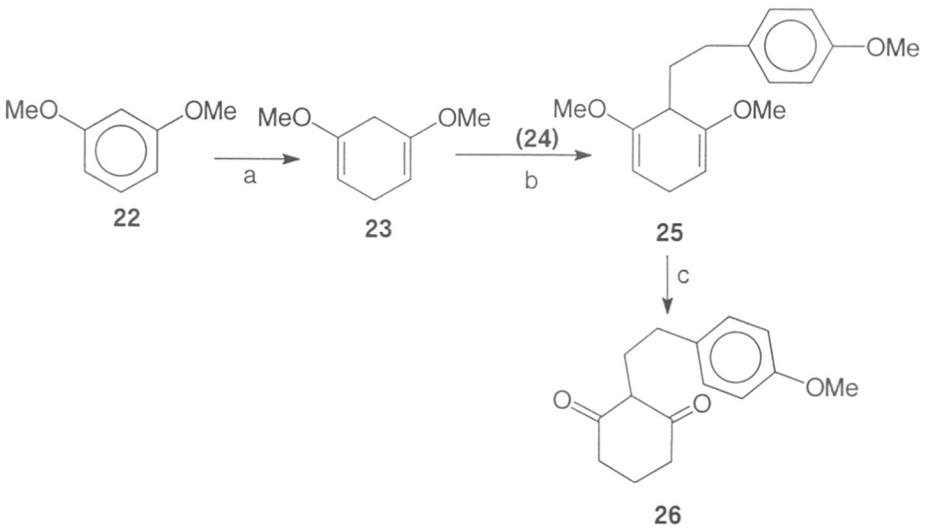


Reagents: a) t-BuLi, pentane, CuSPh, -78 °C

Scheme-6

2. RESULTS AND DISCUSSION

In order to achieve our planned strategy for the construction of benzospiroannulated structure as depicted in Scheme-1, we began our attempt by synthesising required starting diketone (**26**) at first. Compound **26** was prepared (Scheme-7) (Fig. 2, ^{1}H NMR of **26**) by the alkylation of 1,5-dimethoxy-1,4-cyclohexadiene[20] (**23**) with 2-(4'-methoxy phenyl)ethyl bromide (**24**) using t-BuLi / THF at -78 °C followed by the demethylation of the alkylated product (**25**, 82 % yield) by refluxing with HCl / acetone.



Reagents: a) Na/NH_3, $EtOH\text{-}Et_2O$, b) t-BuLi, 4-methoxy-phenylethylbromide (**24**), THF, -78 C, c) Acetone, HCl reflux;

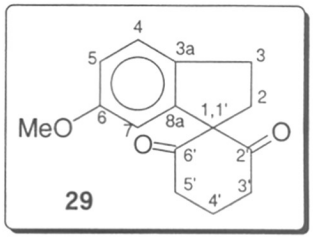
Scheme-7

2.1. PET initiated activation of 27:

Silylation of compound **26** (1.30 g, 5 mmol) was achieved in 85 % yield by refluxing with hexamethyldisilazane (HMDS) (10 equivalents) in the presence of Imidazole (1.2 equivalents) - a reaction protocol reported[21] in literature for the silylation of 1,3-diketones. PET activation of the **27;** brought about by irradiating a mixture of (**27,** 2 mmol) dissolved in 250 mL of (4:1) $CH_3CN:H_2O$ solution containing DCN (0.3 mmol), using 450-W Hanovia lamp, as described in previous chapter for compound **86,** followed by the purification of crude reaction mixture

over silicagel column chromatography using pet.ether:EtOAc (65:35) as eluent, gave 6′-methoxyspiro[cyclohexane-1,1′-(2′,3′-dihydro indene)]-2,6-dione (**29**) as the major product (71 % yield). The product **29** was characterised by detailed spectral analyses which are described as follows:

IR spectrum of (**29**) showed a prominent peak at 1700 cm^{-1} corresponding to keto carbonyl functionality. The other major absorption frequencies observed were at 2940, 1600, 1250, 1080 cm^{-1}.



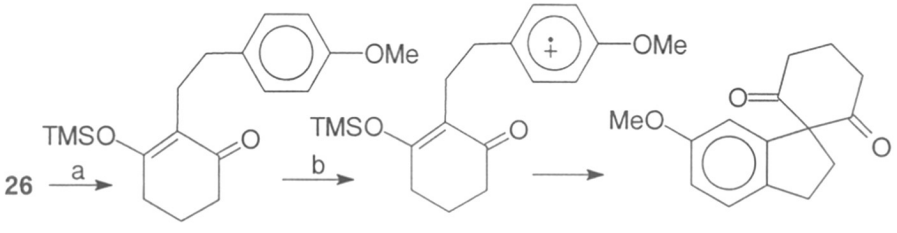
^{1}H NMR of **29** (Fig. 3) showed a doublet at δ 7.10 (J = 8.78 Hz) integrating for one proton which may be considered corresponding to the proton attached to the C_4 carbon. A doublet of doublet observed at δ 6.70 (2H) (J_1 = 8.78 Hz and J_2 = 1.95 Hz) corresponds to the proton attached to C_5. $C_{7\text{-}H}$ appeared as a broad singlet at δ 6.65. Methoxy group protons appeared as a singlet at δ 3.80. Two triplets appearing at δ 3.05 (J = 7.32 Hz ,2H) and 2.60 (J = 7.32 Hz , 2H) corresponds to methylene protons attached to C_3 and C_2, respectively. A multiplet appearing at δ 2.85 (4H) corresponds to CH_2 of $C_{3'}$ and $C_{5'}$. Another multiplet observed at δ 2.15 (2H) may be assigned to methylene protons attached to $C_{4'}$.

^{13}C NMR spectrum of **29** (Fig. 4a&b) showed thirteen signals. Keto carbonyl signals appeared at δ 207.34. Aromatic carbon attached to methoxy group (C_6) appeared at δ 160.19 and other two quaternary carbons (C_{8a} and C_{3a}) appeared at 146.70 and 132.52, respectively. Remaining other aromatic carbons, C_4, C_5 and C_7, appeared at δ 125.31, 112.89 and 110.48, respectively. The spiro quaternary carbon ($C_{1,1'}$) appeared at δ 77.89. Methoxy carbon appeared at δ 55.47. Methylene carbons $C_{3'}$, $C_{5'}$ appeared at 38.38 (2C), and other three remaining methylene carbons C_2, C_3 and $C_{4'}$ appeared at δ 33.57, 31.66 and 17.85, respectively.

The mass spectrum (Fig. 5) showed molecular ion peak at 244.

From the above spectral data the structure of the compound **29** was confirmed.

The formation of the **29** could be explained by considering the nucleophilic reaction of the silyl enol ether to the PET generated arene radical cation as shown in Scheme-8.



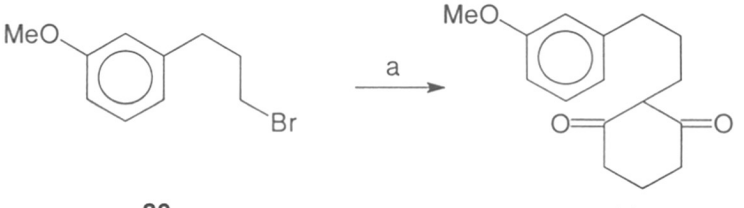
27 **28** **29**

Reagents: a) HMDS, ImH, reflux, 4h; b)PET reaction, DCN, CH_3CN:H_2O; 4h;

Scheme-8

Encouraged by the above success of spirocyclization reaction, we decided to extend the applicability of this methodology for the construction of spiro structure of type **2b** too.

To this end, the required starting diketone **31** was prepared in 68% yield (Scheme-9), (Fig. 6, ^{1}H NMR of **31**) by the alkylation of 1,5-dimethoxy-1,4-cyclohexadiene[20] (**23**) with 3-(3′-methoxy phenyl)propyl bromide (**30**) in the presence of t-BuLi/THF at 78 °C, in an identical manner as described for **26** (Scheme-9).

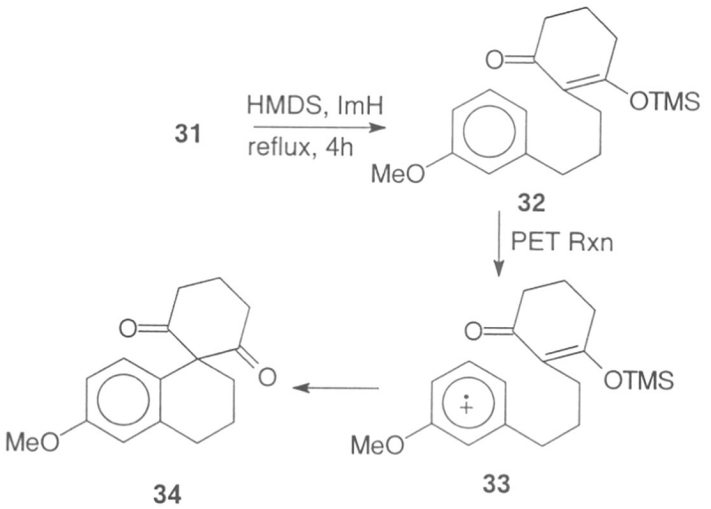


30 **31**

Reagents: a) **23,** t-BuLi, THF, -78 °C, acetone-HCl reflux;

Scheme-9

Compound **31** was enolized and silyated[21] (80 % yield), in an identical manner as described for **26,** by heating a mixture of **31** (5 mmol) with HMDS (10 eq) containing ImH (1.2 eq).

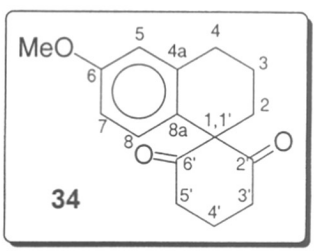


Scheme-10

2.2. PET initiated activation of 32:

PET activation of **32**, in an identical reaction condition as described for **27**, afforded spirodiketone **34** as the major product (71% yield) (Scheme-10). The structural characterisaton of **34** is illustrated as follows:

The IR spectrum of **34** showed a prominent peak at 1720 cm^{-1} along with other characteristic peaks at 2950, 1700, 1620, 1510, 1120, 920 and 740 cm^{-1}.



In the ^1H NMR spectrum of **34**, (Fig. 7) $C_{7\text{-}H}$ appeared as a double doublet at δ 6.70 (J_1 = 8.78, J_2 = 1.95), $C_{5\text{-}H}$ appeared as a broad singlet at δ 6.65 and $C_{8\text{-}H}$ aromatic proton appeared as a doublet at δ 6.50 (J = 8.78). The OMe group protons appeared at δ 3.80 as a singlet. A multiplet observed at δ 2.97 is assigned to the protons attached to C_4 and a multiplet appearing between δ 2.50-2.20 (6H) is characterised for the methylene protons attached to C_2 , $C_{3'}$ and $C_{5'}$, respectively. Another multiplet appearing between δ 1.85-1.70 (4H) corresponds to methylene protons attached to C_3 and $C_{4'}$.

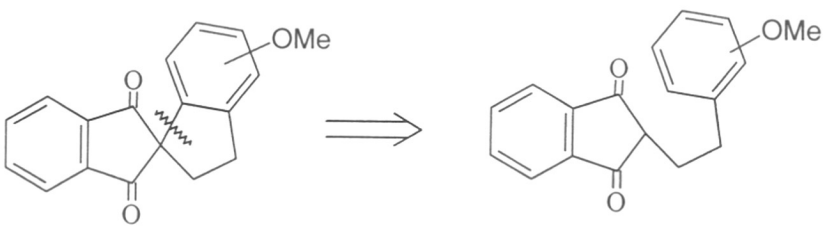
The ^{13}C NMR spectrum (Fig. 8a&b) showed fourteen signals. The carbonyl group carbon signals appeared at δ 209.85. The aromatic signal corresponding to C_6 appeared at δ 158.38. The other two quarternary carbons C_{4a} and C_{8a} appeared at δ 139.64 and 125.31, respectively. Methine carbon signals for C_8, C_7 and C_5 appeared at δ 131.30, 113.41 and 112.59, respectively. The characteristic quarternary spiro carbon C_1 appeared at δ 70.66. The methoxy group carbon appeared at δ 55.04. All other six methylene carbons such as $C_{3'}$, $C_{5'}$ (2C) , C_4, C_2, C_3 and $C_{4'}$ appeared at δ 38.06 (2C), 34.14, 29.47, 18.88 and 17.55, respectively.

The mass spectrum of the compound **34** (Fig.9) showed molecular ion peak at 258, and base peak at 174.

From the above spectral data the structure of **34** was confirmed.

2.3. Synthetic attempt towards the construction of the core spiro structure of antitumour antibiotic Fredericamycin - A:

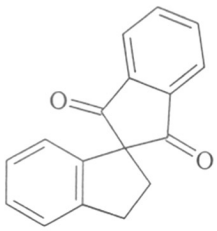
The success of benzospiroannulation reactions, as described in the preceding sections, encouraged us to expand the scope of our methodology for the construction of the core spiro skeleton (**35**) of Fredericamycin-A (**38**)[22] through the retrosynthetic route as depicted in Scheme-11.



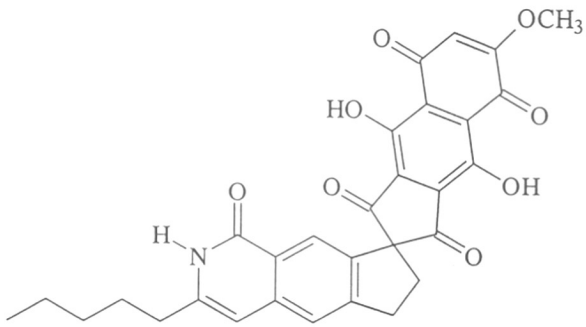
35 **36**

Scheme-11

Fredericamycin-A (**38**), (NSC-305263), a quinone antitumor antibiotic, is the major component isolated from a fermentation broth of the strain Streptomyces griseus (FCRC-48) by Pandey and coworkers[23] in 1981.



37

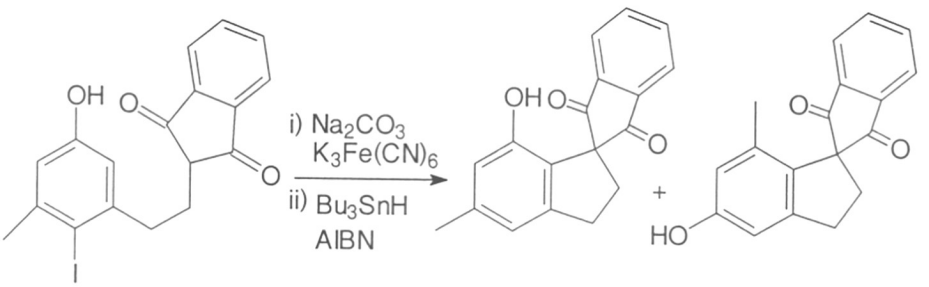


38

While dealing with the synthesis of Fredericamycin-A, the main objective has been towards the construction of the unusual spiro[4.4]nonane system (**37**). The synthetic efforts to date have been generally focused on the creation of this spirocenter or its closely related derivatives.

It would be appropriate here to discuss in brief, few strategies reported for the construction of core spiro[4.4]nonane system of FM-A, before dwelling upon our own efforts in this context.

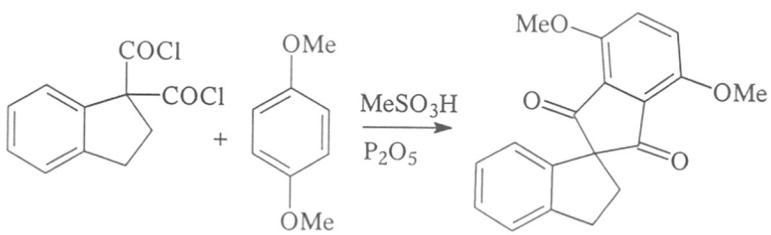
The spirocyclic structures (**40** and **41**), related to the core spiro structure of Fredericamycin-A, are constructed by Kende *et al*[24] by the ferricyanide promoted oxidative intramolecular phenoxy-enoxy radical coupling of the dianions of phenolic β-diketone **39** as shown in Scheme-12.



39 40 41

Scheme-12

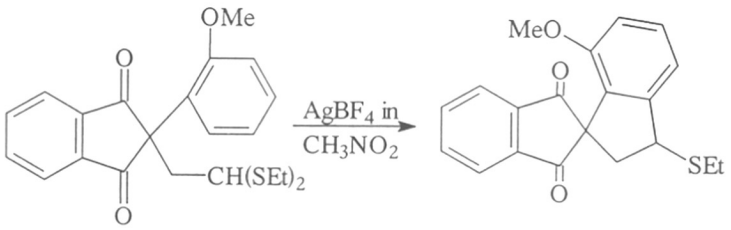
Spirocyclic structure **44** is also synthesised[25] in very poor yield (10 %) by the condensation of 1,1-indane dicarboxylic acid derivative (**42**) with 1,4-dimethoxy benzene (**43**) in the presence of Me_2SO_3H-P_2O_5 (Scheme-13).



42 43 44

Scheme-13

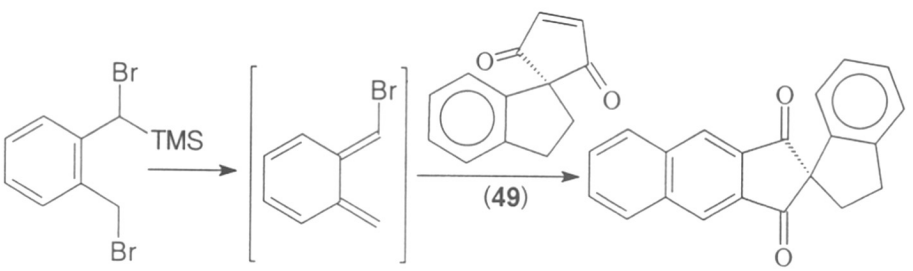
Braun *et al*[26] have reported the construction of spirocyclic framework **46** by the intramolecular Friedel-Crafts type reaction of the thioacetal **45** using $AgBF_4$ as Lewis acid in anhydrous CH_3NO_2 (Scheme-14).



45 **46**

Scheme-14

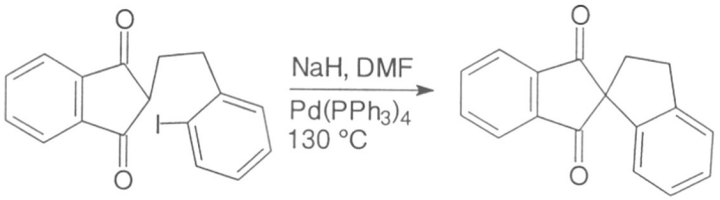
An interesting strategy reported[27] for the construction of skeleton **50** involves Diels-Alder cycloaddition reaction of an α-bromo-o-quinodimethane (**48**) intermediate with the carbon-carbon double bond of a preformed spiro dienophile **49** (Scheme-15). The quinodimethane intermediate **48** is generated by the reaction of tetraalkylammoniumfluoride with **47**.



47 **48** **50**

Scheme-15

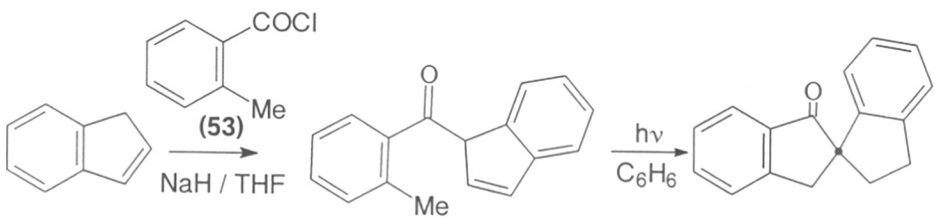
Spirocyclisation of **51** to **38** has also been effected[28] by palladium promoted intramolecular arylation of β-diketone moiety as shown in Scheme-16.



51 37

Scheme-16

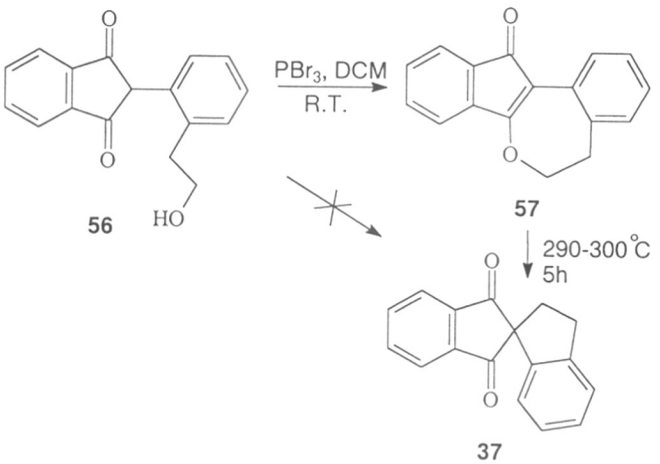
Mehta *et al* have reported[29] an elegant protocol for the spiroannulation of **54** to **55**, using an intramolecular H-abstraction as key step from **54** promoted by a photochemical reaction step (Scheme-17).



52 54 55

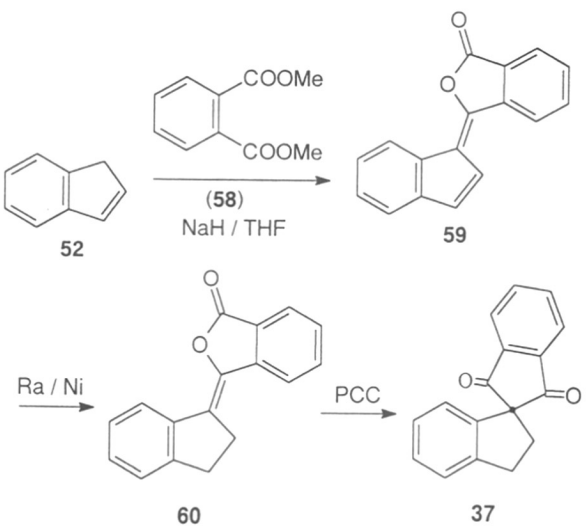
Scheme-17

Spiro[4.4]nonane system **37**, present in FM-A, has also been constructed by the conventional thermal isomerisation[30] reaction of **56** (Scheme-18).



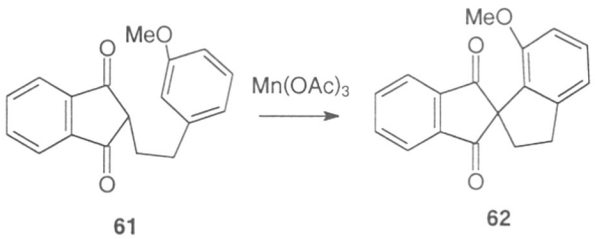
Scheme-18

Kelly *et al* have reported[31] the synthesis of parent spirosystem **37** of FM-A by the reductive rearrangement followed by the oxidation of **59.** Compound **59** is prepared by the reaction of dimethyl phthalate (**58**) and indenyl anion.



Scheme-19

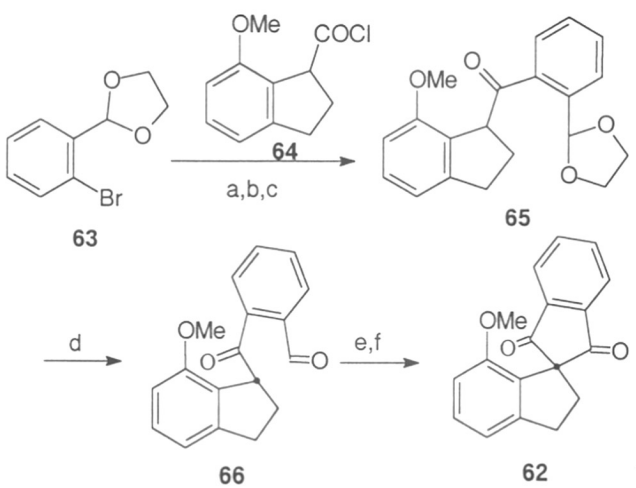
Intramolecular arylation reaction promoted by the $Mn(OAc)_3$ mediated radical cyclisation from **61** is also reported[32] to give spiro[4.4]none skeleton **62**, in 32 % yield (Scheme-20).



61 **62**

Scheme-20

Recently Evans *et al*[33] have reported the construction of spiro[4.4]nonane **62** by the $[Pd(PPh_3)_4]$ catalyzed cross-coupling of the organozinc reagent, derived from 2-bromobenzaldehyde ethylene ketal **63**, with the 7-methoxy-1-indanecarbonyl chloride **64**.

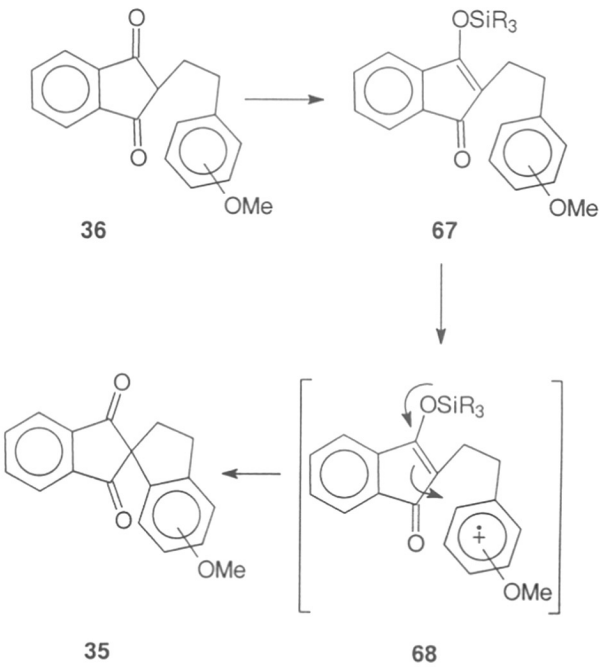


63 **65** **66** **62**

Reagents: a) n-BuLi, Et_2O, -65 °C; b)$ZnCl_2$, -55 °C-R.T.; c) $Pd(PPh_3)_4$ (cat.); **64**, 0 °C - R.T.; d) PPTS, acetone, H_2O, heat, 2h; e) NaOMe, MeOH, 0 °C - R.T.; f) PCC, DCM, 0 °C-RT, 16h

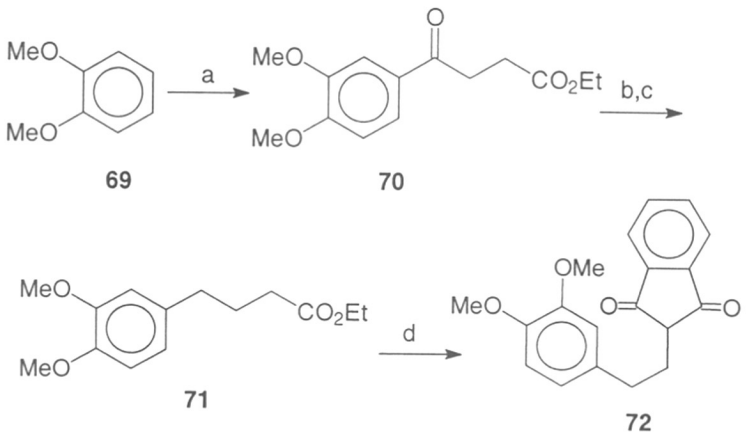
Scheme-21

Considering the synthetic challenge associated with the construction of spirocyclic core structure of Fredericamycin-A and to extend the scope of our success of benzospiroannulation strategy, we envisaged to construct the structural framework **35** by the intramolecular cyclisation of the silylenol ether **67** from **36** to PET generated arene radical cation **68** as shown in Scheme-22.



Scheme-22

In order to construct the spiro structure of type **35**, as shown in Scheme-22, the required starting compound **36** was prepared starting with veratrole (**69**) employing the steps as shown in Scheme-23.



Reagents: a) $AlCl_3$, succinic anhydride, DCM, reflux (78 %); b) Zn-Hg, HCl, toluene, c) EtOH, H^+; d) Diethyl phthalate, NaH, DMF, reflux, 3h (81 %).

Scheme-23

Commercially available veratrole (**69**) was acylated with succinic anhydride using $AlCl_3$ as Lewis acid to give **70** in 78 % yield. Compound **70** was subjected to reduction with amalgamated zinc in toluene followed by esterification by heating with EtOH in the presence of PTSA to obtain corresponding ester **71**. Compound **71** was reacted with diethylphthalate in the presence of NaH in DMF to give the desired diketone **72** (Fig. 10, ^1H NMR of **72**) in reasonably good yield (81 %).

In order to bring about the cyclisation of **72** to its corresponding spiro structure **74** we attempted the conversion of **72** into its corresponding silyl enol ether **73** by following conventional silylation procedures[21, 34-36], however all our efforts have failed. However, the attempts described below gave enolised product **75** instead of **73.** The following strategies were tried to bring about the conversion of **72** to **73.**

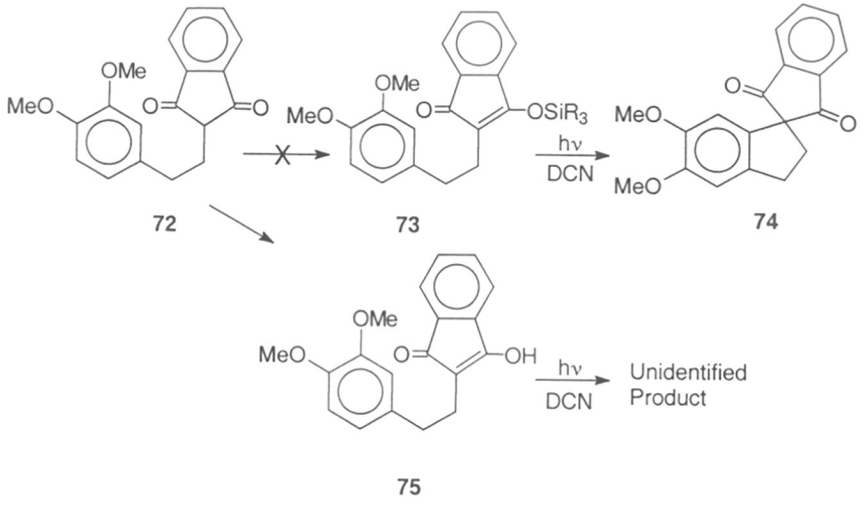
i) HMDS, ImH. (Ref. 21)

ii) TMSCl / Et_3N / NaI / CH_3CN; (Ref. 34)

iii) Et_3N/ $ZnCl_2$ / TMSCl; (Ref. 35)

iv) LDA, DME, TMSCl; (Ref. 36)

v) DMF, TMSCl, Et_3N (Ref. 36)



Scheme-24

Since all our attempts to prepare silyl enol ether **73** from **72** failed, we evaluated to irradiate **72** itself in its enolic form **75** (Fig. 11. ^1H NMR of **75**).

Usual PET reaction of enolic compound **75** involving the irradiation of a mixture **75** (0.50 g) (2 mmol) with DCN (0.34 mmol) in CH_3CN:H_2O (4:1), in an identical manner as described earlier for **27**, indicated very poor conversion of this

compound to any product. A very small amount of new product formation was noticed on TLC analysis of the irradiated mixture. Normal workup and purification gave a thick viscous liquid in very minute quantity. The spectral characterisaton of this product couldn't be realised due to its very poor yield. Further effort in this direction is in progress in this laboratory.

3. Conclusion.

In conclusion, we have developed a practical and efficient spiroannulation strategy by the intramolecular nucleophilic reaction of silylenol ethers to PET generated arene radical cation. Attempt have also been made to construct the core spirocyclic structure FM-A, however, it has failed so far.

3. Experimental

3.1. Preparation of 1,5-dimethoxy-1,4-cyclohexadiene (23)

A two neck RB (250 mL) flask equipped with ammonia condenser, was charged with a solution of 1,3-dimethoxy benzene (2.80 g, 20 mmol) in ethanol (8 mL) and liquid ammonia (50 mL). Metallic sodium (1.5 g) in small pieces were added very slowly to the reaction flask while stirring. Stirring was continued until all the sodium was dissolved and a blue colored solution was obtained. The condenser was removed from the flask and ammonia was allowed to evaporate. The remaining mixture was diluted with brine (100 mL) very carefully and thoroughly extracted with 1:1 mixture of ether and petroleum ether. The combined extracts were washed with brine and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure followed by distillation of the crude oil (b.p. 96 °C / 12 mm Hg) afforded 1,5-dimethoxy 1,4-cyclohexadiene as a clear colourless oil in 95 % yield.

Yield 95 % (2.66 g), colourless oil.

IR 3010, 2960, 1690, 1590, 1440, 1230, 920, 760 cm^{-1}

^{1}H NMR 4.58 (t, J = 3 Hz, 2H), 3.47 (s, 6H), 2.66-2.86 (m, 4H)

3.2. 3-(3′methoxy phenyl)propyl bromide (30)

Yield 87 %, viscous liquid.

IR 2950, 2250, 1600, 1450, 1280, 1170, 1050, 910, 740

^{1}H NMR 7.20 (m, 1H), 6.75(m, 3H), 3.80 (s, 3H), 3.40 (t, J = 7.35 Hz, 2H), 2.75 (t, J = 7.35 Hz, 2H), 2.15 (m, 2H)

3.3 Preparation of 2-(4′-methoxy-phenyl)ethyl)-1,3-cyclohexane dione (26)

To a cooled solution 1.98 g (14 mmol) of 1,5-dimethoxy-1,4-cyclohexadiene in THF (10 mL) at -78 °C was introduced 9.7 mL of t-BuLi (1.6 M in n-pentane, , 1.11 eq.) while stirring. After 1 h HMPA (1.2 equiv., freshly distilled from $LiAlH_4$) was added and stirring was continued for an additional 10 min. Addition of 2-(4-methoxyphenyl)ethylbromide 3.87 g (18 mmol, 1.31 equiv.) (freshly filtered through a short column of neutral alumina) in THF (10 mL) resulted in an immediate change in the colour of the reaction mixture (maroon to light brown). The reaction mixture was allowed to warm to room temperature, diluted with 5 mL of brine and then thrice extracted with 50 mL portions of pentane. The combined pentane extracts were washed twice with brine and dried over $MgSO_4$. Removal of the solvent followed by concentration at reduced pressure gave thick pale yellow oil which was subsequently dissolved in acetone (20 mL of spectrograde, previously purged with a stream of N_2 for 15 min). With vigorous stirring, 1N hydrochloric acid (4 mL, previously purged with a stream of N_2 for 15 min) was added to the solution. The resultant solution was stirred for additional 1 h. The acetone was removed under reduced pressure, the residue was diluted with 10 mL of brine, and the mixture was extracted four times with 10 mL portions of CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$. Removal of the solvent afforded (2.82 g, 82 %) of 2-(4′-methoxy-phenyl)ethyl)-1,3-cyclohexane dione as a white solid, m.p. 142-143.5 °C.

Yield 82 % (2.82 g), white solid, m.p. 142-143.5 °C

IR 2960, 2230, 1650, 1620, 1520, 1480, 1385, 1260, 1240, 1200, 1160, 930;

^{1}H NMR δ 7.15 (d, 2H, *J* = 9.47 Hz), 6.85 (d, 2H, *J* = 9.47 Hz), 5.35 (s, 1H), 4.00 (t, 2H, *J* = 7.37 Hz), 3.80 (s, 3H), 3.00 (t, 2H, *J* = 7.37 Hz), 2.35 (m, 4H), 1.95(m, 2H);

^{13}C NMR δ 199.78, 177.88, 158.60, 129.99, 129.61, 114.15, 102.98, 69.29, 55.37, 36.88, 34.24, 29.12, 21.33;

3.4. Compound 2-(3'-methoxy-phenyl)propyl)-1,3-cyclohexane dione (31)

1.41 g (10 mmol) of 1,5-dimethoxy-1,4-cyclohexadiene was alkylated with 3-(3-methoxy phenyl)propylbromide (**30**) 2.67 g (10 mmol, 1.2 equiv.) in the presence of t-BuLi in THF followed by demethylation using HCl/acetone; as described above for the preparation of **26**, gave 2.03 g (78 %) of **31.**

Yield 78 % (2.03 g), white solid, m.p. 153-154.5 °C

IR 2960, 1650, 1500, 1460, 1440, 1380, 1260, 1240, 1190, 1050, 920;

^{1}H NMR δ 7.25(dd, *J* = 9.75 Hz, 1H), 6.75(m, 3H), 5.35 (s, 1H), 3.90 (t, *J* = 7.31, 2H), 3.80 (s, 3H), 2.70 (t, *J* = 7.31, 2H), 2.40 (m, 4H), 2.00 (m, 4H);

^{13}C NMR δ 199.35, 177.88, 159.68, 142.30, 129.24, 120.54, 114.10, 111.20, 102.49, 67.42, 54.85, 36.48, 31.88, 29.71, 29.79, 21.01;

MS 260 (2, M+), 228 (3), 208 (4), 166 (26), 148 (10), 135 (9), 122 (100), 107 (14), 91 (41), 84 (25), 77 (28), 55 (56)

3.5. General procedure for the preparation of Silyl enol ethers 27 and 32. This is exemplified by taking 27 as an example.

Compound (**26**) (1.30 g, 5 mmol) was refluxed with hexamethyldisilazane (HMDS) (10 equivalents) in the presence of Imidazole (1.2 equivalents) for 24 h. The excess HMDS was distilled out and the crude residue was purified by passing through a pad of neutral alumina, using pentane:EtOAc (95:5) as the eluant, to give **27** in in 85 % yield. This compound was used as such for photochemical reaction without further purification.

3.6. PET initiated reaction of 27.

Compound **27** (2 mmol) was irradiated in 250 mL of (4:1) CH_3CN:H_2O solution containing DCN (0.3 mmol) using 450-W Hanovia lamp, as described in previous chapter for compound **86**, usual workup and purification of crude reaction mixture over silicagel column chromatography using pet.ether:EtOAc (65:35) as eluent, gave 6'-methoxyspiro[cyclohexane-1,1'-(2',3'-dihydro indene)]-2,6-dione (**29**) as the major product (71% yield).

Yield 71%, pale yellow solid, m.p. 72-73.5 °C.

IR 3020, 2940, 1700, 1600, 1430, 1320, 1250, 1210, 1080, 1020 cm^{-1}

^{1}H NMR δ 7.10 (d, J = 8.78 Hz, 1H), 6.70 (dd, J_1= 8.78, J_2=1.95, 1H), 6.65 (bs, 1H), 3.80 (s, 3H), 3.05 (t, J = 7.32 Hz, 2H), 2.85 (m, 4H), 2.60 (t, J = 7.32 Hz, 2H), 2.15 (m, 2H).

^{13}C NMR δ 207.34, 160.19, 146.70, 132.52, 125.21, 112.89, 110.48, 77.89, 55.47, 38.38, 33.57, 31.66, 17.85.

Mass(m/e) 244 (M^+), 162 (15), 141 (3), 127 (4), 111 (7), 97 (13), 91 (15), 85 (36), 71 (60), 57 (100).

3.7 PET initiated reaction of 32.

Usual PET activation of compound **32** (2 mmol), as described for **27**, followed by purification gave 6'-methoxyspiro[cyclohexane-1,1'-(3',4'-dihydro-2'H-naphthalene)]-2,6-dione (**34**) in 69% yield.

Yield 69%, pale yellow solid, m.p. 77-78.5 °C.

IR 2950, 1720, 1700, 1620, 1510, 1480, 1250, 1180, 1120, 920, 740. cm^{-1}

^{1}H NMR δ 6.70 (dd, J_1 = 8.78, J_2 = 1.95 Hz, 1H), 6.65 (bs, 1H), 6.50 (d, J = 8.78 Hz, 1H), 3.80(s, 3H), 2.97 (m, 2H), 2.50-2.20 (m, 6H), 1.85-1.70 (m, 4H).

^{13}C NMR δ 209.85, 158.38, 139.64, 131.30, 125.31, 113.41, 112.59, 70.66, 55.04, 38.06, 34.14, 29.47, 18.88, 17.55.

Mass (m/e) 258 (M^+), 174 (100), 159 (28), 126 (15), 115 (22), 91 (15), 84 (86), 71 (22), 55 (61).

3.8. Preparation of 70

A three neck RB (250 mL) flask, equipped with a mechanical stirring rod, condenser and solid addition funnel, was charged with a mixture of 1,2-dimethoxy benzene (**69**) (20 g, 145 mmol) and succinic anhydride (15 g, 150 mmol) in 30 mL of dichloromethane. $AlCl_3$ (25 g, 0.187) was added in 2 g portions each slowly through the solid addition funnel while stirring vigorously at 0 °C. The colour change of

reaction mixture from light brown to deep violet indicated the progress of the reaction. After completion of $AlCl_3$ addition, the reaction mixture was allowed to warm to r.t. The reaction mixture was quenched with dropwise addition of ice cold water. The compound was washed with water, filtered through sintered funnel, and air dried. The compound was esterfied with EtOH in the presence of 0.5 ml of Conc H_2SO_4 in benzene under Dean-Stark conditions. After normal work up and purification resulted 26 g (64 %) of **70**.

Yield 64 %, thick liquid.

^{1}H NMR 7.70 (dd, J_1 = 9.73, J_2 = 1.89 Hz, 1H), 7.50 (d, J =1.89, 1H), 6.90 (d, J = 9.73 Hz, 1H), 4.2 (q, J = 8.10 Hz, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 3.30 (t, J = 7.29 Hz, 2H), 2.75 (t, J = 7.29 Hz, 2 H), 1.25 (t, J = 8.10 Hz, 3H)

3.9. Preparation of 71

Compound **70** (10 g, 38 mmol) was dissolved 50 mL of toluene and refluxed with Zn / Hg (prepared *in situ* by stirring a mixture of $HgCl_2$ (approx. 1 g) and 15 g Zn powder, in 5 % HCl for 5-10 min.). Concentrated HCl was added to the reaction mixture dropwise through the addition funnel. After complete addition of HCl the contents were cooled and toluene layer was separated and the aqueous layer was extracted with toluene. The combined organic layers were concentrated and the crude product containing major amount of acid was further reesterified with EtOH as usual to give 7.3 g of **71** (78 % yield)

Yield 78 %, thick liquid.

IR 2950, 1720, 1600, 1510, 1460, 1230, 1030, 850, 810, 750

^{1}H NMR 6.7 6.90 (m, 3H), 4.1 (q, 2H, J = 7.5 Hz), 3.85 (s, 3H), 3.80 (s, 3H), 2.60 (t, J = 8 Hz, 2H), 2.30 (t, 2 H, J = 8 Hz), 1.90 (q, 2H, J = 7.5 Hz), 1.20 (t, 3H, 7.5 Hz)

3.10. Preparation of 72

A 100 mL 3 neck RB flask equipped with a stopper, reflux condenser, magnetic stir bar and a pressure equalizing dropping funnel were flame dried under a dry stream of nitrogen. Into this flask were placed 3.32 g, 50 % NaH dispersed in oil (70 mmol of NaH), diethyl phthalate (5.2 g, 23 mmol) and 20 mL of freshly distilled anhydrous DMF. The mixture was stirred under N_2 at 0 °C. Ethyl (3,4-dimethoxy phenyl butanoate (**71**) (4.6 g, 19.3 mmol) in 10 mL of dry DMF was added dropwise. After the additional stirring at room temperature for 10 min, the flask was immersed in an oil bath and heated to 110 °C until gas evolution had ceased (approx. 20 min). After cooling, the orange red reaction mixture was poured into ice water acidified with dil. HCl. The reaction mixture was extracted once with dichloromethane. The orange layer was washed with water and concentrated. The crude product was purified by silicagel column chromatography using 10 % ethyl acetate in Pet.Ether as eluant, to afford 4.84 g of **72** in 81 % yield.

Yield 81 %, pale yellow solid, m.p. 82-83.5 °C

IR 3000, 1700, 1660, 1520, 1450, 1390, 1250, 1160, 1030

^{1}H NMR 8.90 (m, 2H), 7.85 (m, 2H), 6.75 (m, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 3.05 (t, J = 7.07 Hz, 1H), 2.75 (t, J = 7.07 Hz, 2H), 2.30 (m, 2H)

^{13}C NMR 200.31, 148.33, 146.92, 141.67, 135.09, 132.92, 122.44, 120.27, 111.75, 111.02, 55.32, 55.20, 51.80, 31.47, 28.25

MS 310 (M+)

3.11. PET initiated reaction of 75.

Compound **75** (0.5 g, 2 mmol) and DCN (0.34 mmol) dissolved in 250 mL of CH_3CN:H_2O (4:1), was irradiated in an identical manner as described earlier for **27** followed by normal workup and purification through column chromatography using pet.ether:acetone (80:20) as the eluant gave a thick viscous liquid in very minute quantity.

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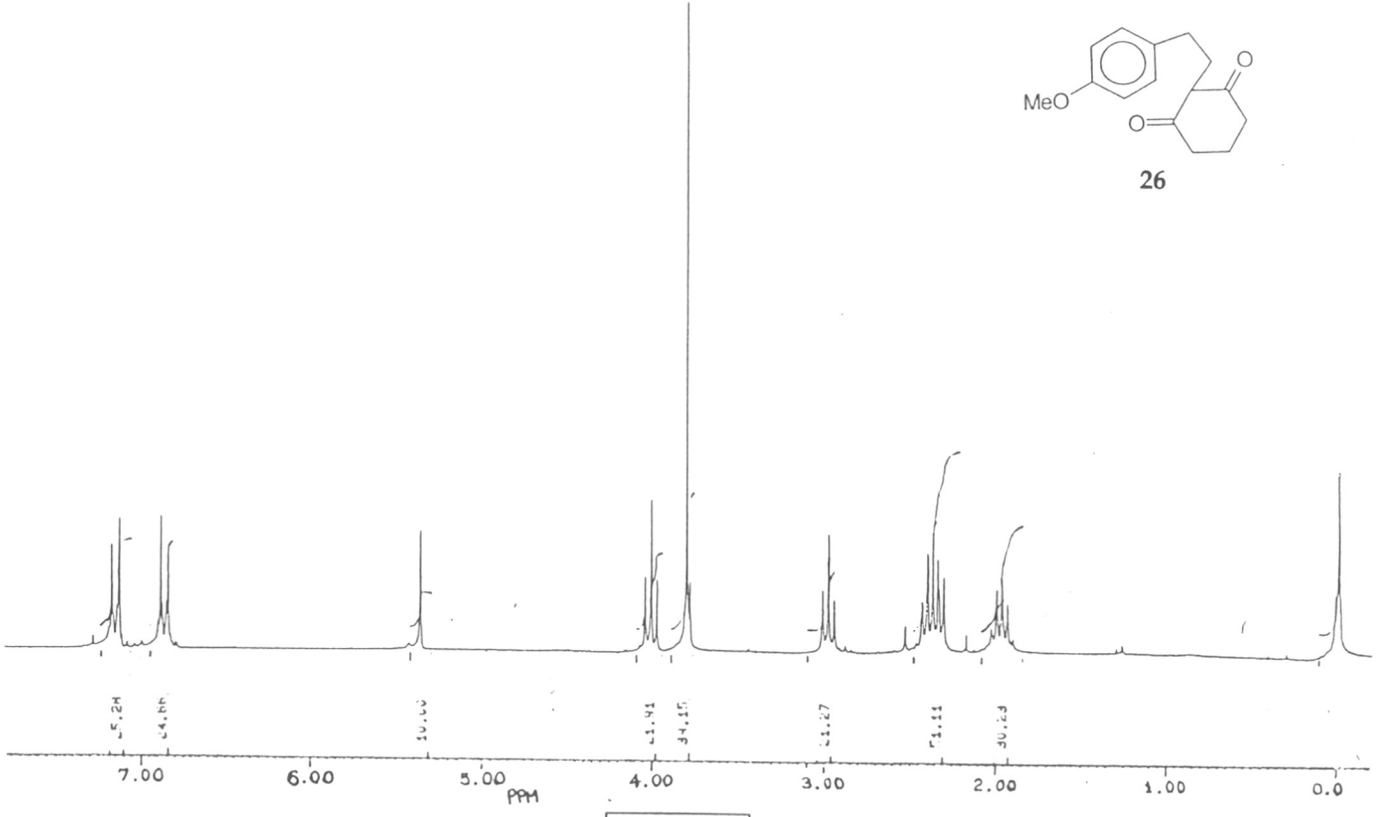

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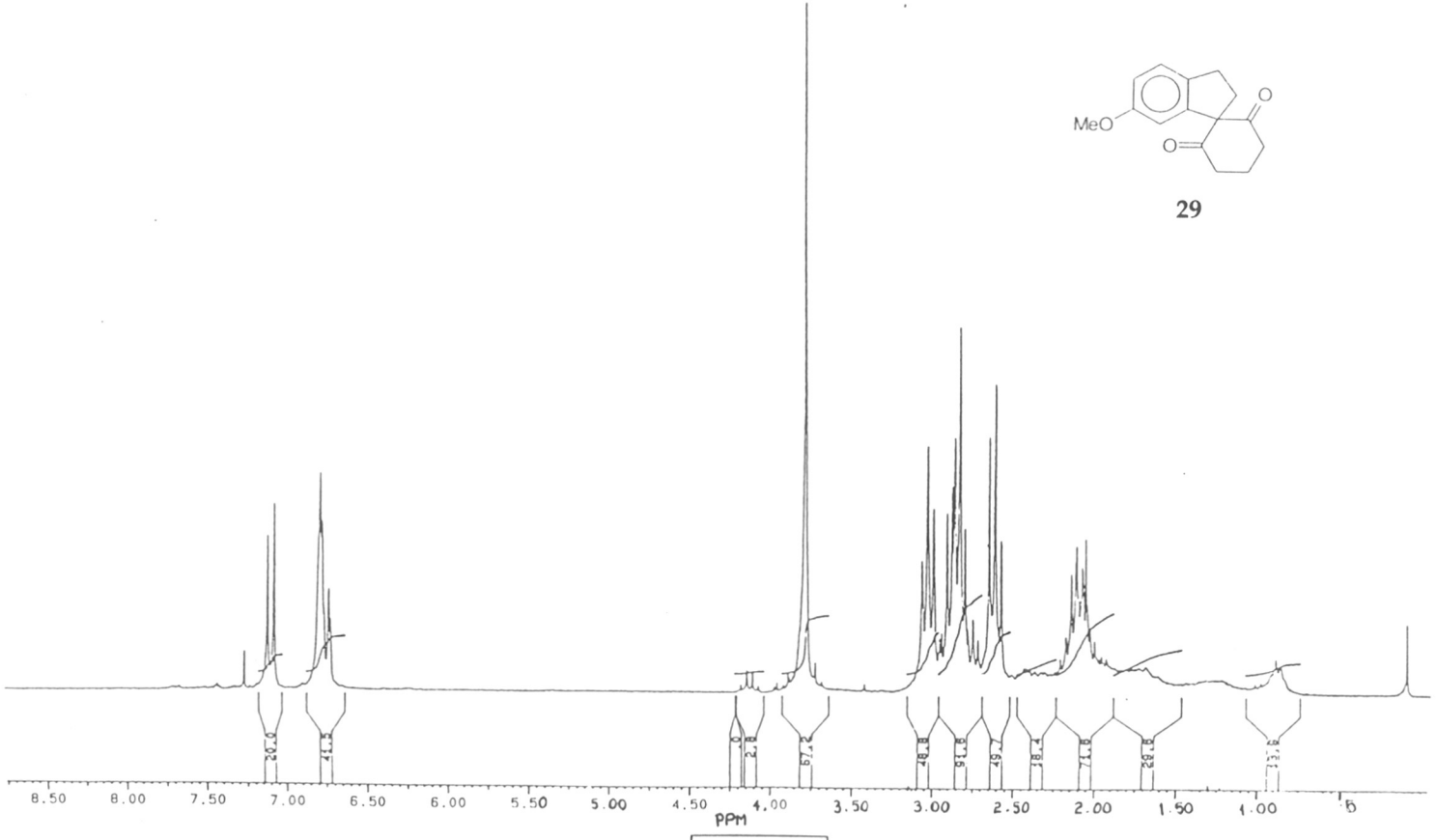
Fig. 2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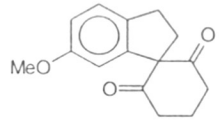
29

Fig. 3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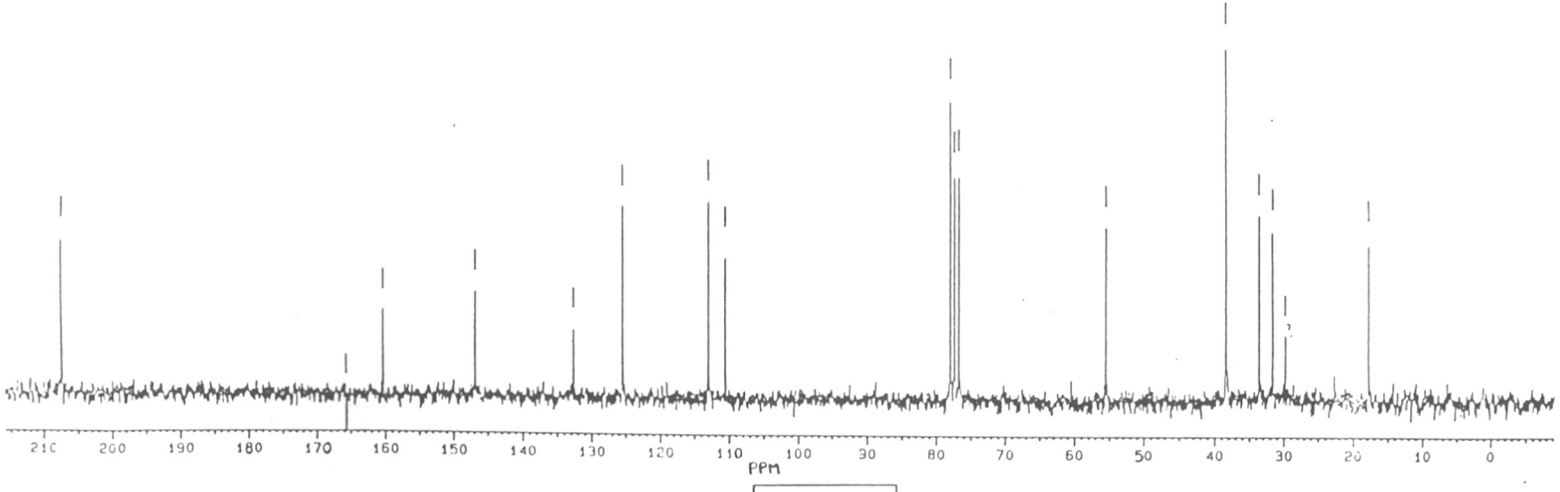
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Fig. 4a

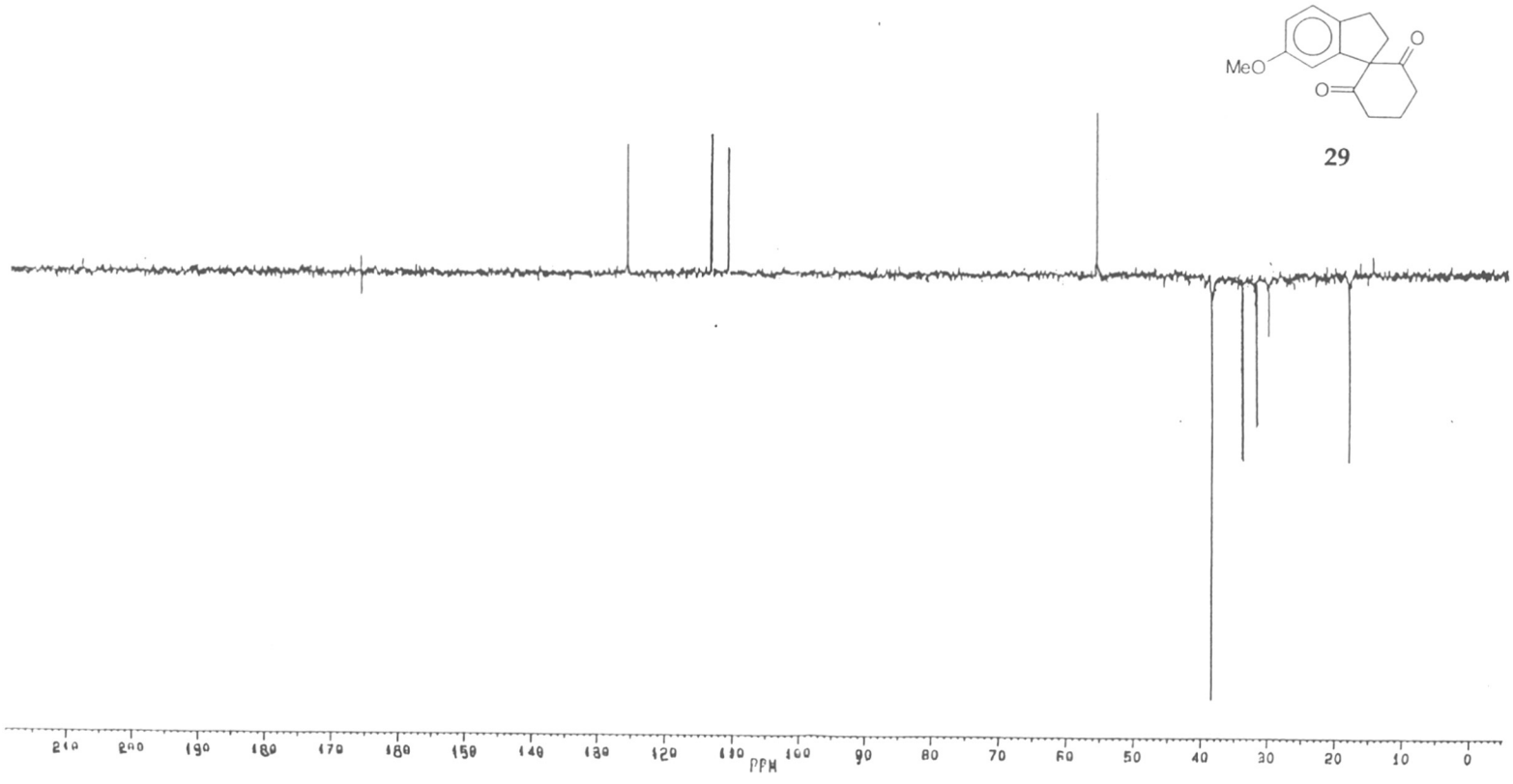
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Fig. 4b

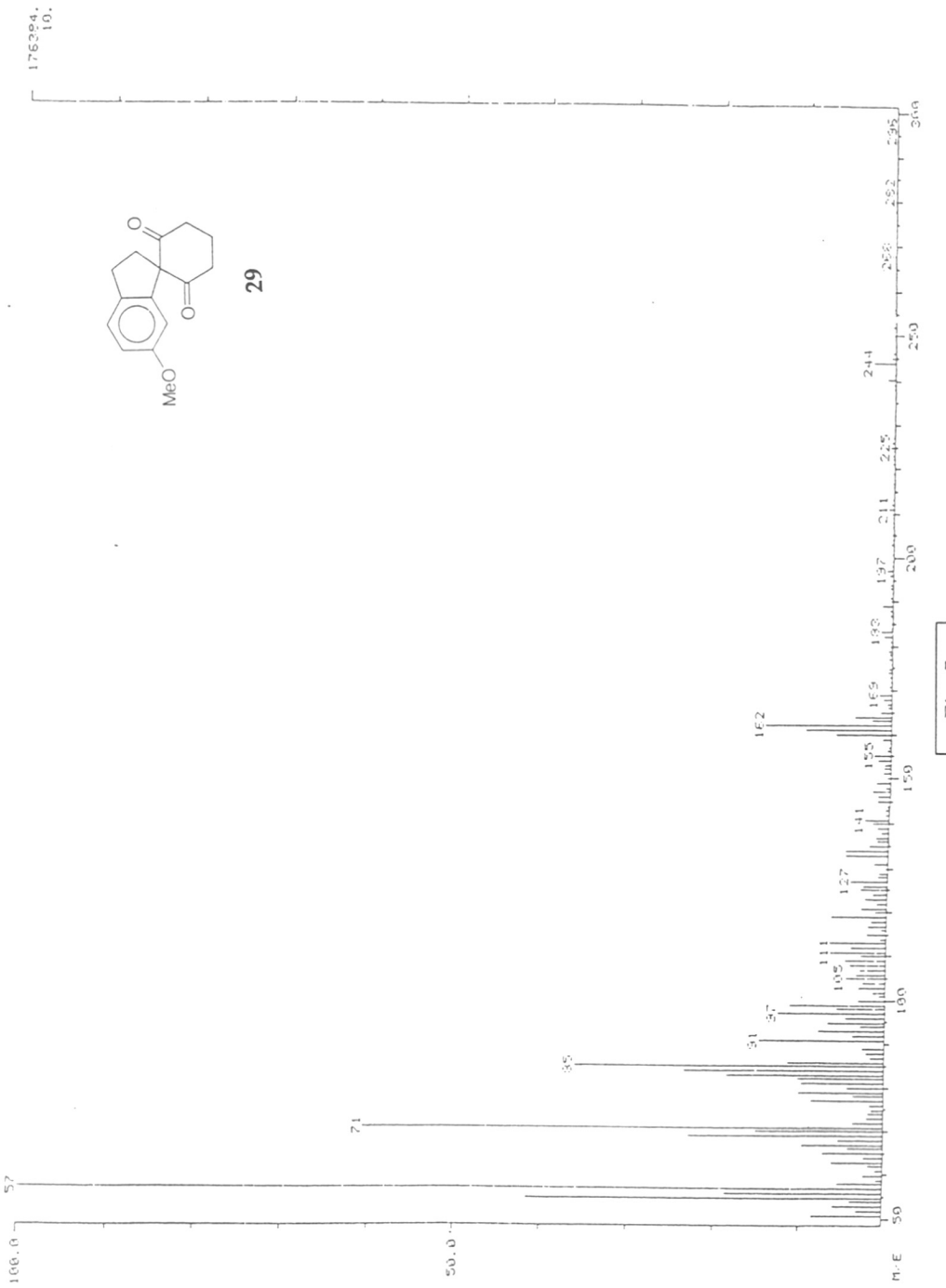
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Fig. 5

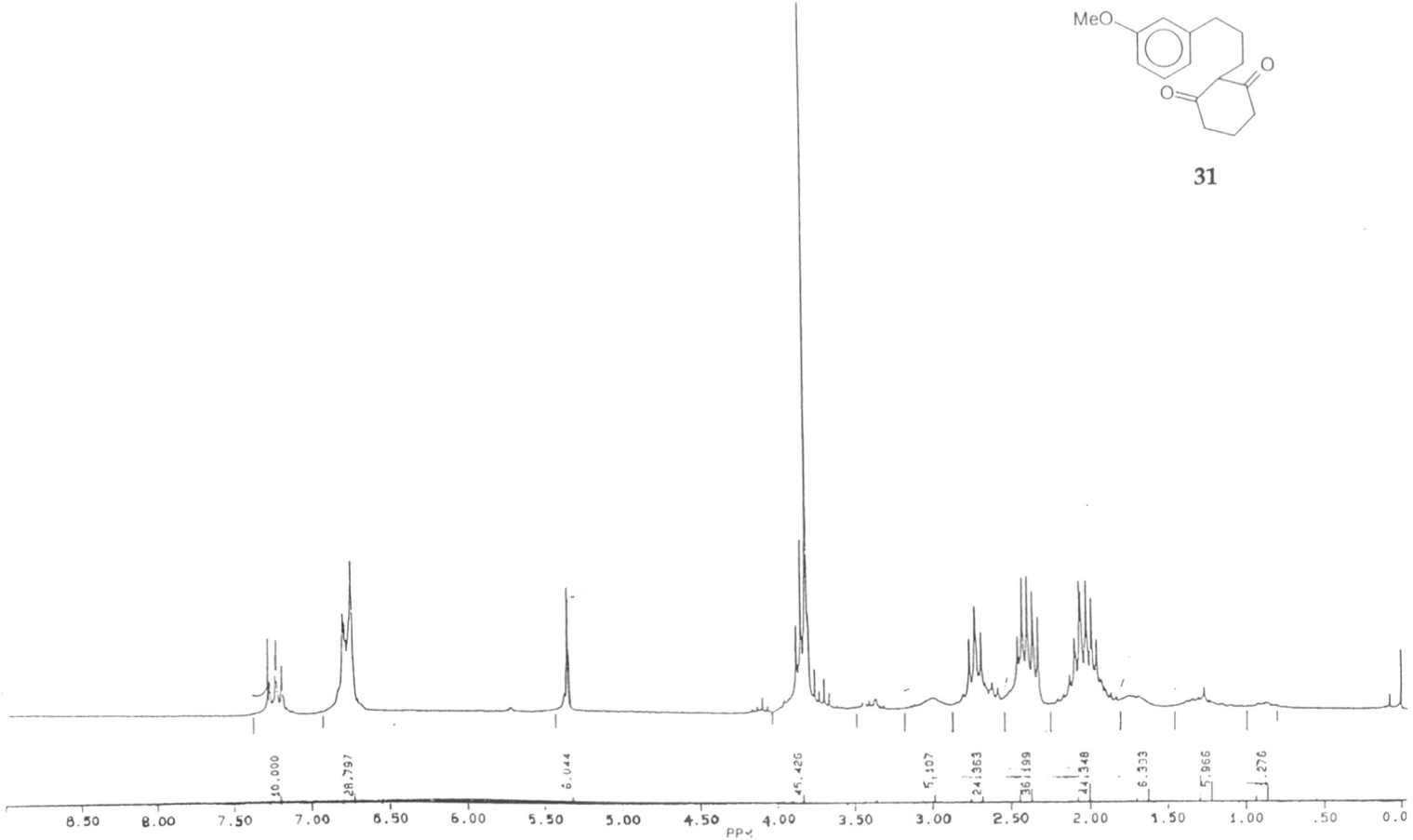
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Fig. 6

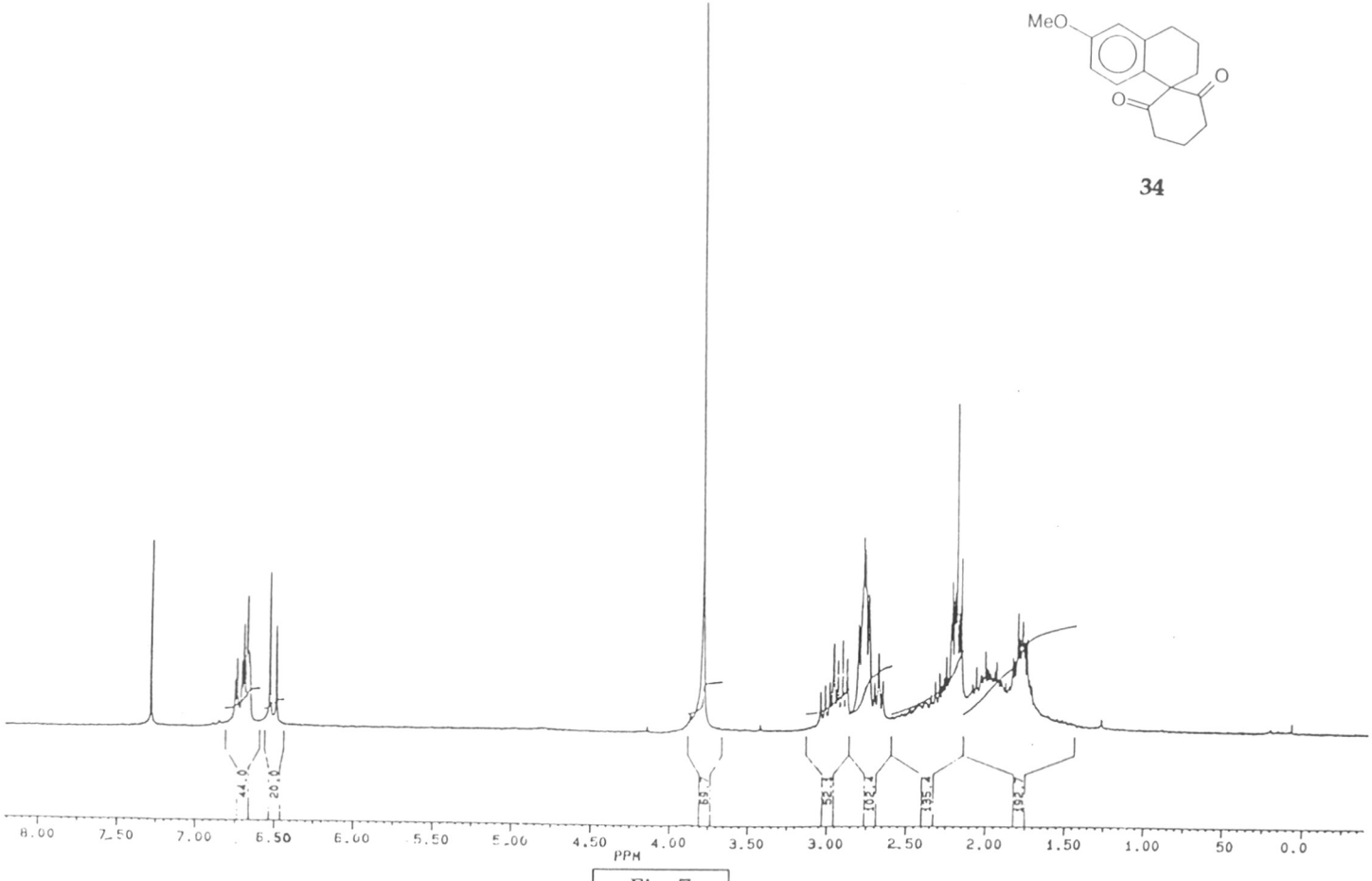
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Fig. 7

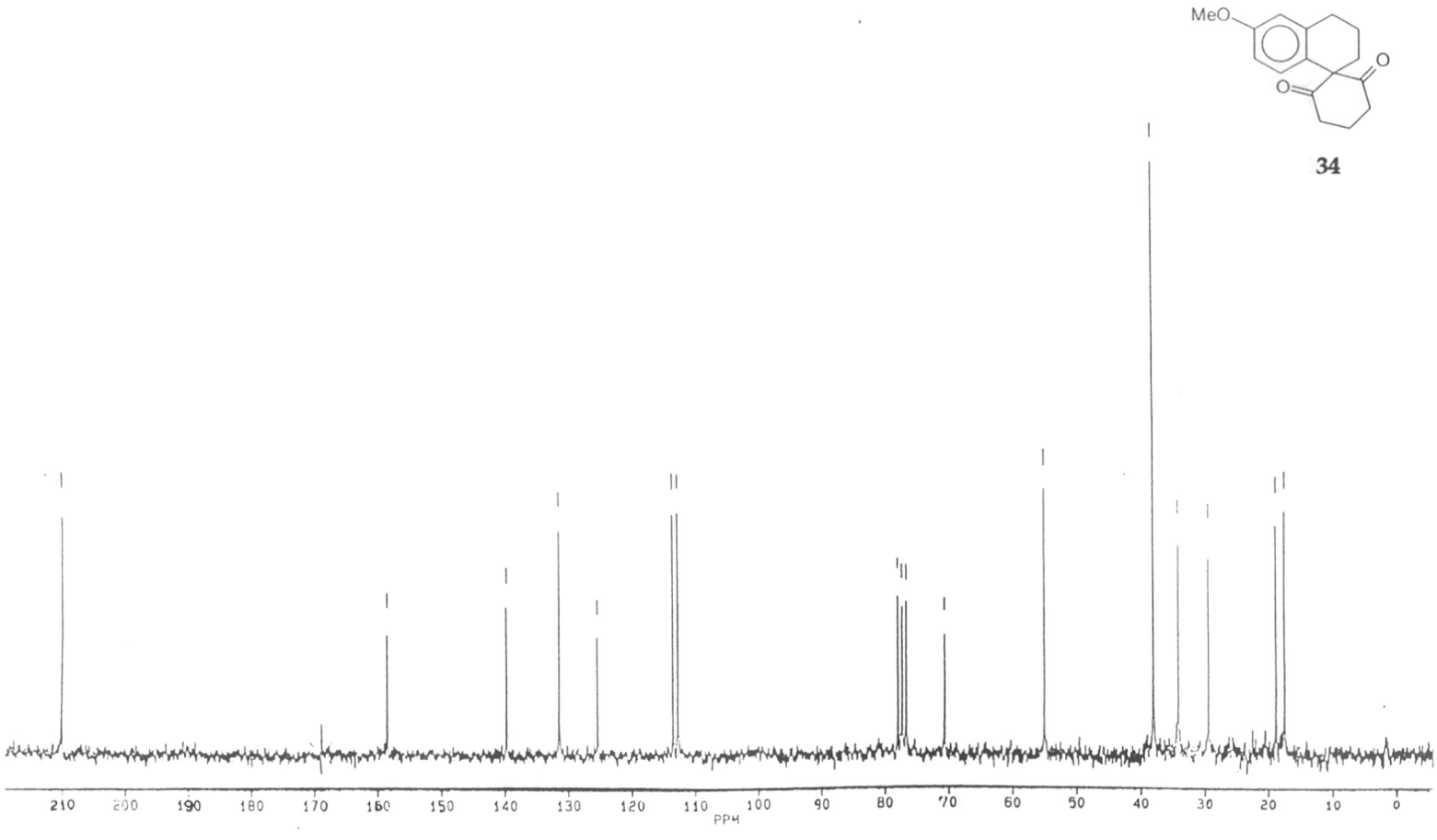
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Fig. 8a

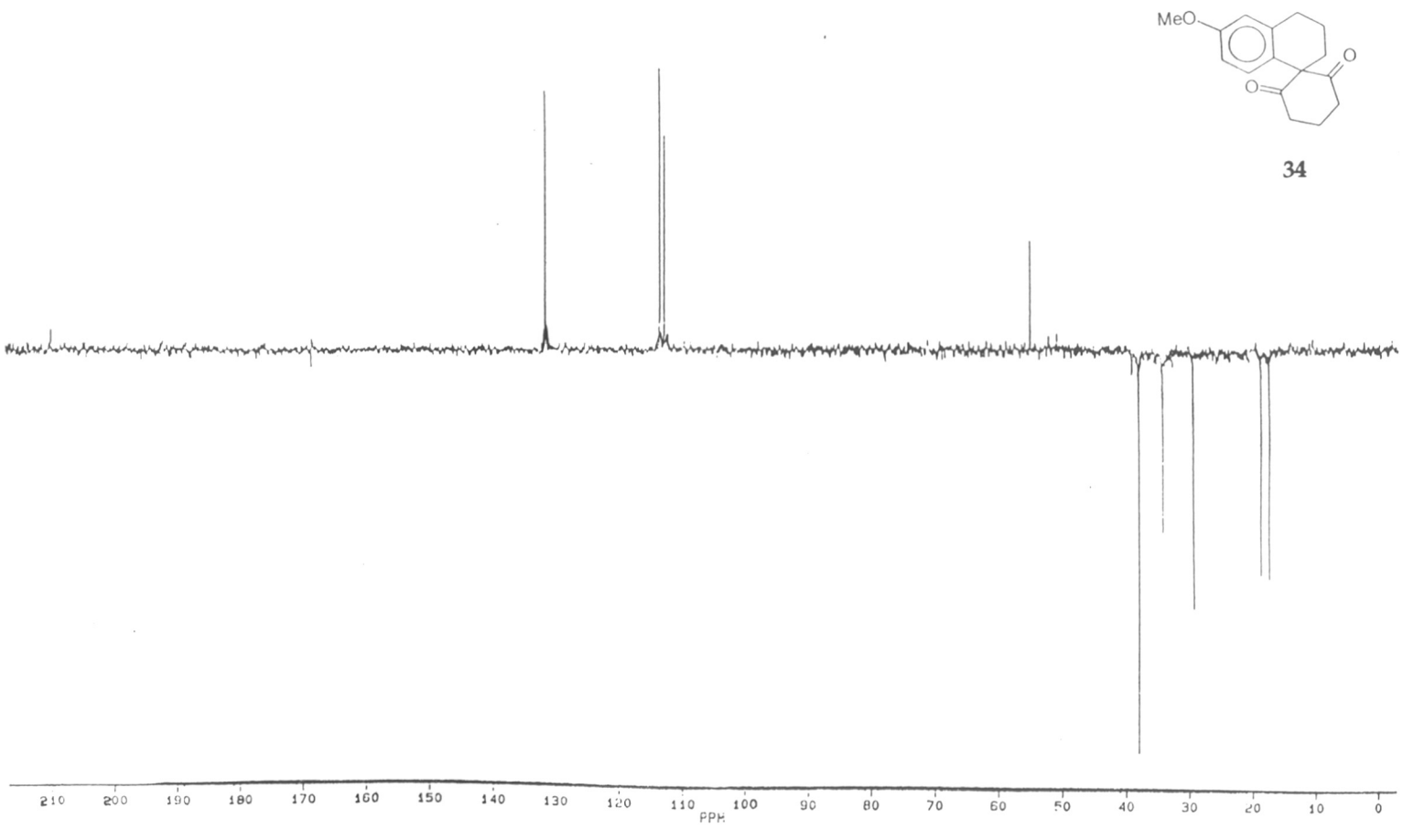
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Fig. 8b

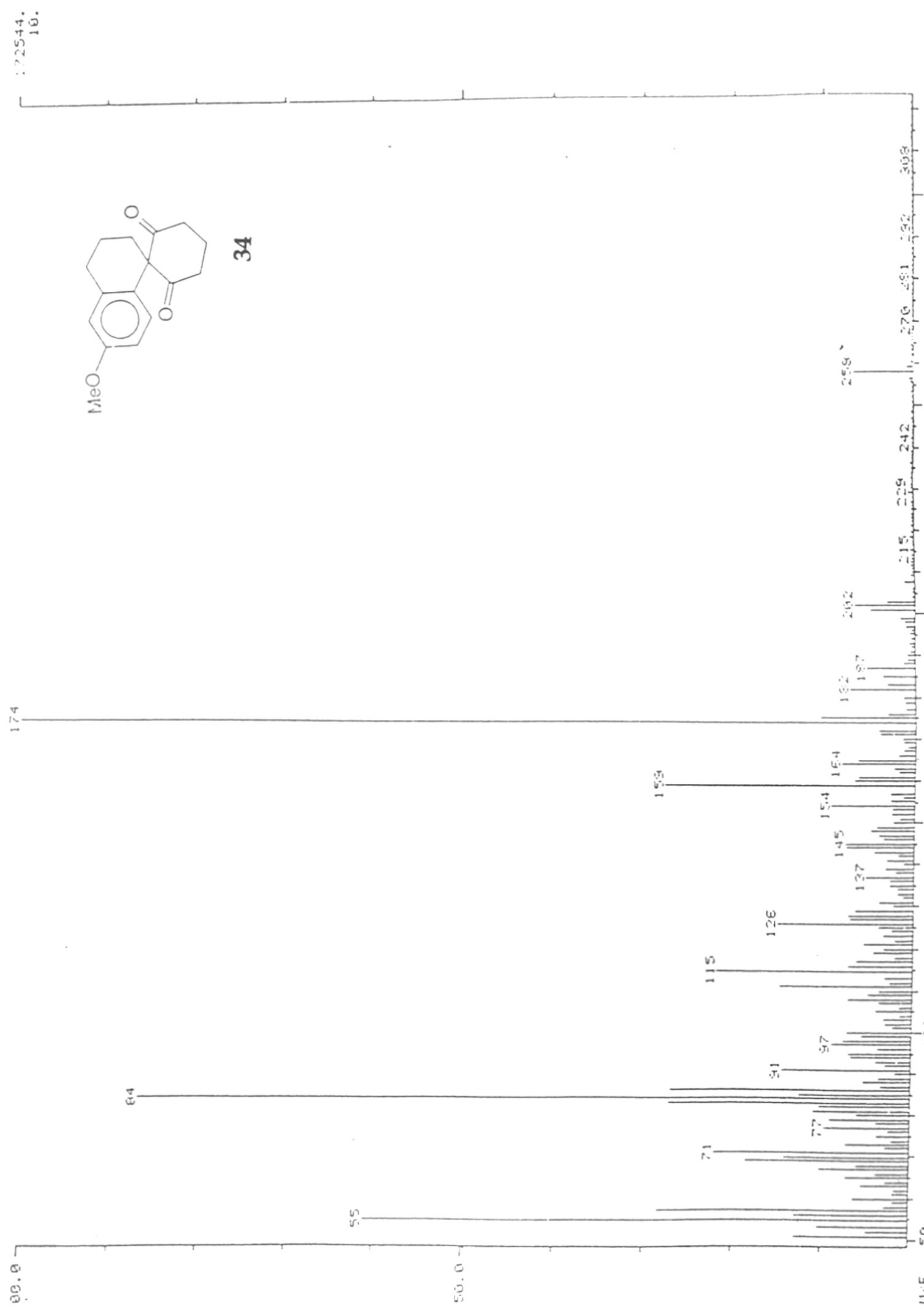
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Fig. 9

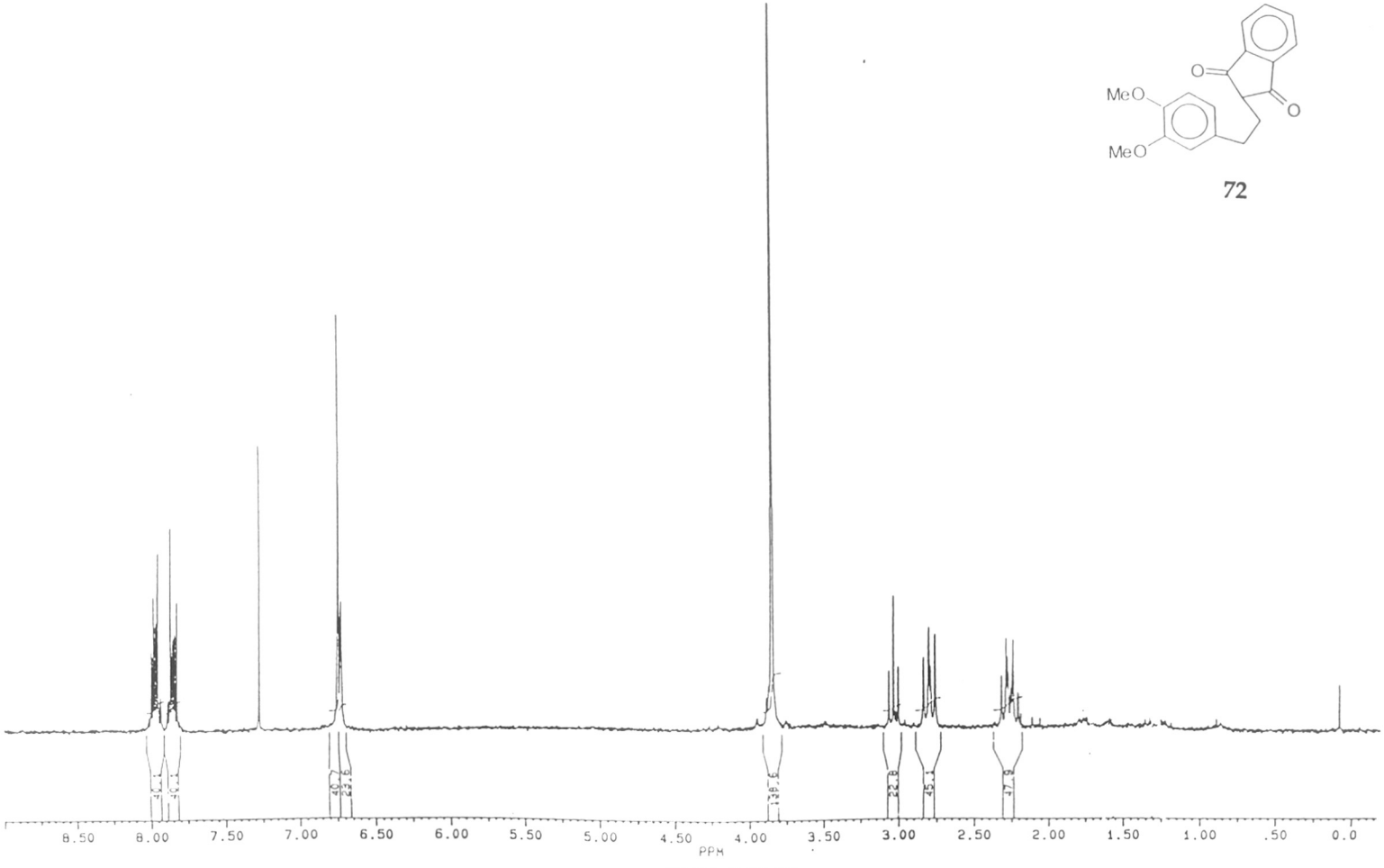
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Fig. 10

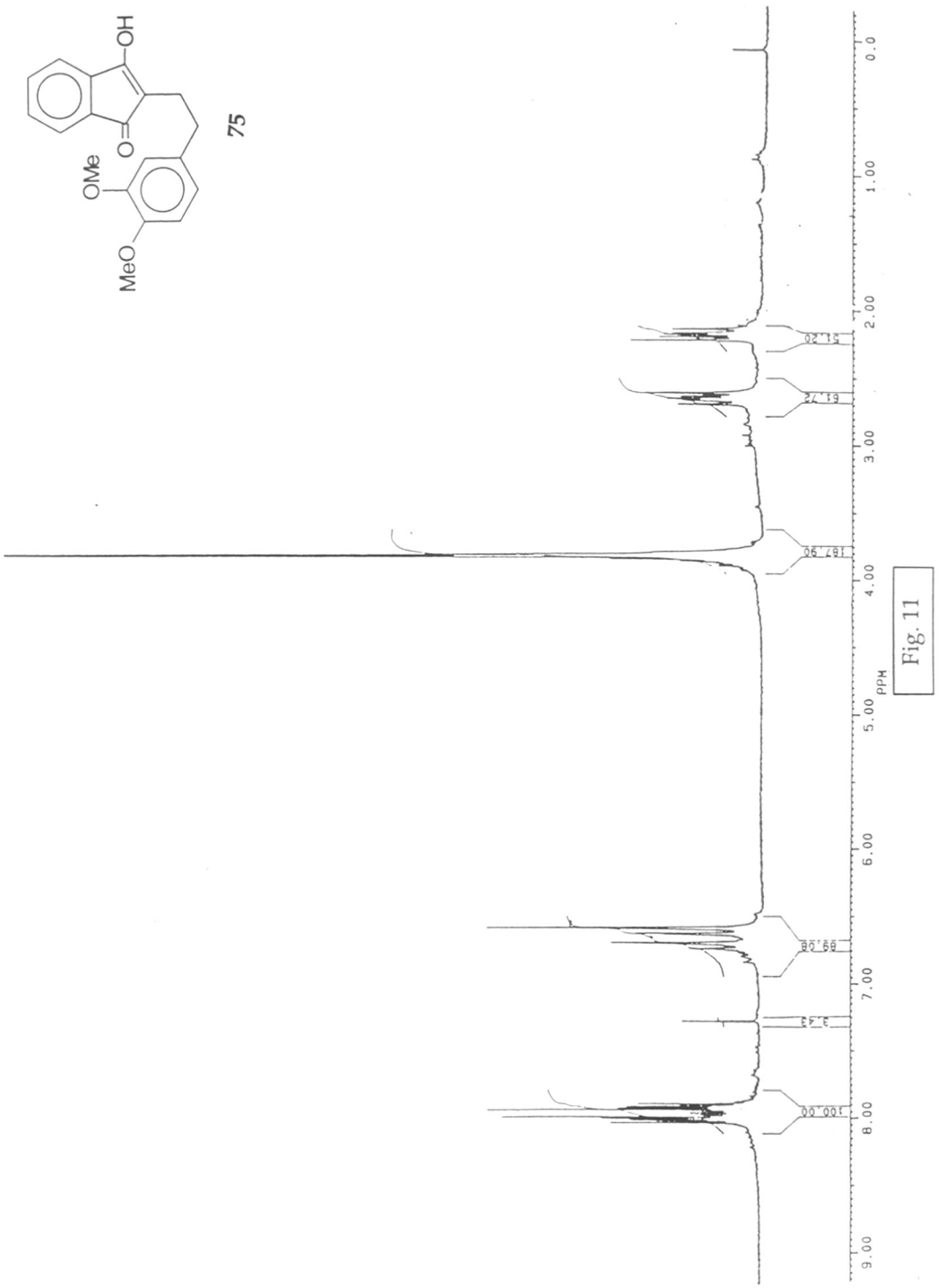
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Fig. 11

The ultimate measure of a man is not where he stands in the moments of comfort and convenience but where he stands at times of challenge and controversy . .

- Martin Luther King .