SYNTHETIC PERSPECTIVES OF PHOTOREDUCTIVE β-ACTIVATION OF α, β-UNSATURATED CARBONYLS FOR RADICAL REACTIONS

A THESIS

SUBMITTED TO THE

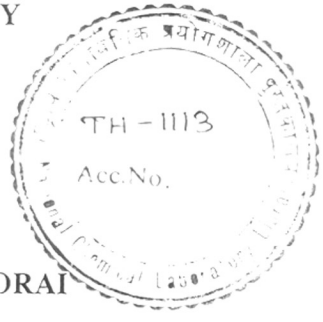
UNIVERSITY OF POONA

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY



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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Synthetic Perspectives of Photoreductive β-Activation of α,β-Unsaturated Carbonyls for Radical Reactions**" submitted by Manas K. Ghorai was carried out by him under my supervision at the National Chemical Laboratory, Pune. Material that has been obtained from other sources is duly acknowledged in the thesis.

Date May 5th 1998

(Ganesh Pandey)
Research Guide

DECLARATION

I hereby declare that the thesis entitled "**Synthetic Perspectives of Photoreductive β-Activation of α,β-Unsaturated Carbonyls for Radical Reactions**" 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.

Ghoraimn

(Manas K. Ghorai)

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Whatever I am and whatever I intend to be in future is because of the goodwill and unstinted support that I have received from my parents, late paternal grand-father, in-laws, sisters, sister-in-law and my other family members. Their kind cooperation helped me in pursuing the Ph.D. study and no words are enough to acknowledge them.

At the doorsteps of procuring the highest degree of the land I would like to fondly remember the admonition of my maternal grandmother who had brought me up and taught me the ABC's of life.

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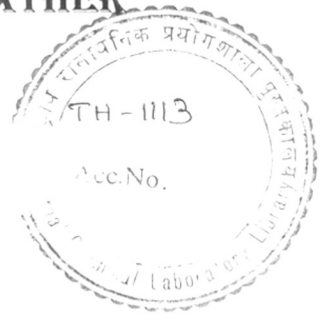
Manas K. Ghorai.

DEDICATED TO THE MEMORY OF
MY MATERNAL GRANDFATHER



Contents

GENERAL REMARKS

1. All melting points and boiling points were recorded on the Celsius scale and 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. ^{1}H 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, brs = 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. X-ray crystal diffraction data were obtained from Siemens R3m/V diffractometer and crystallographic calculations were carried with the laid of the SHELXTL Plus program package.
7. The progress of the reaction was monitored by analytical thin layer chromatography (TLC) and/or gas chromatography (GC). Analytical TLC were performed using precoated silica gel 60 F_{254} (Merck, Germany) plates. GC analysis was done using Perkin Elmer, Model 8700.
8. Exact product ratios were determined by GC analysis (Perkin Elmer, model 8700) using capillary column SP-1000 or Methyl silicon or Phenyl silicon 50m, 0.25mm.
9. Cyclic Voltametric experiments were carried out with a three electrode assembly on a Bioanalytical system, model CV-27 or PAR 175 Universal programmer and PAR RE0074 XY recorder.
10. Quantum Yield measurements were performed using Applied Photophysics Quantum Yield reactor, model QYR-20.
11. High resolution mass spectra (HRMS) were taken on a VG AUTOSPEC-M mass spectrometer with OPUS V3.IX software.

12. Photoirradiations were performed using 450W Hanovia medium pressure lamp.
13. Known compounds were characterised by their boiling points, melting points, IR and ^{1}H NMR.
14. All optical rotations were measured on a JASCO-181 digital polarimeter using Na light (4893 Å). Concentrations are expressed in g/100 ml.
15. Pet-ether refers to the fraction boiling between 60-80 °C.
16. Room temperature (r.t.) refers to the temperature 30±5°C.
17. 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

Ac	Acetyl
aq	aqueous
AIBN	α, α'-Azo bis(isobutyronitrile)
Bn	benzyl
bp.	boiling point
Bu	butyl
Bu_3SnH	Tributyltin hydride
CH_3CN	Acetonitrile
CH_2Cl_2	Dichloromethane
CIP	Contact ion pair
$(COCl)_2$	Oxalyl chloride
$CuSO_4$	Copper(II) sulfate
DCA	9,10-Dicyanoanthracene
DCM	dichloromethane
DMF	N, N-dimethyl formamide
DMN	1,5-Dimethoxynaphthalene
DMSO	Dimethyl sulfoxide
ED	Electron doner
ET	Electron transfer
Et_3N	Triethyl amine
Et_2O	Diethyl ether
EtOAc	ethyl acetate
EtOH	Ethanol
FRIP	Free radical ion pair
HMPA	Hexamethyl phosphoric triamide
g	gram
h	hour
i-PrOH	*iso*-Propanol
ImH	Imidazole
IR	infrared
K_2CO_3	Potassium carbonate

$KMnO_4$	Potassium permanganate
KOH	Potassium hydroxide
M	molar
LAH	Lithium aluminium hydride
mL	millilitre
mmol	millimole
mp	melting point
MeOH	Methanol
n-BuLi	n-Butyl lithium
NaH	Sodium hydride
$NaHCO_3$	Sodium bicarbonate
Na_2SO_4	Sodium sulfate
$Na_2S_2O_3$	Sodium thiosulfate
NH_3	Ammonia
NMM	N-Methyl morpholine
PCC	Pyridinium chlorochromate
PET	Photosensitised electron transfer
Ph_3P	Triphenyl phosphine
$Ph_3P=O$	Triphenyl phosphine oxide
Py	Pyridine
rt	room temp
SCE	Standard calomel electrode
SmI_2	Samarium(II) iodide
t-Bu	*tert*-Butyl
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
TsOH	*p*-Toluene sulfonic acid
TMSCl	chlorotrimethylsilane

SYNOPSIS OF THE THESIS

SYNOPSIS OF THE THESIS

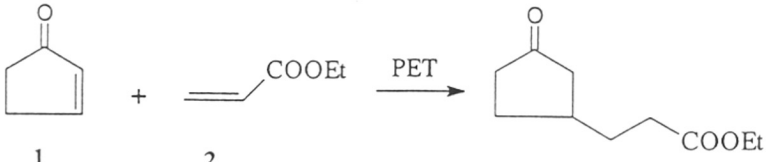
Investigations embodied in the thesis entitled "**Synthetic Perspectives of Photoreductive β-Activation of α,β-Unsaturated Carbonyls for Radical Reactions**" is divided into three chapters which are as follows:

Chapter I. Development of Photosystem for Sequential ET Reaction.

This chapter presents a concise description on the secondary electron transfer processes with earlier literature reports and a brief discussion on the development of two photosystems for sequential ET reactions. Detailed photophysical parameters regarding electron transfer are provided. More emphasis is given on the concept, background and its applications for C-C- bond formation reaction.

ChapterIII. Intermolecular coupling of cyclic enones with activated alkenes or alkynes : Attempts towards the synthesis of chiral PG analogue.

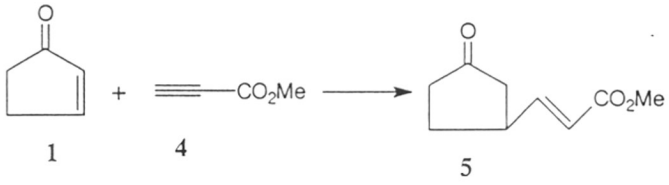
This chapter describes the applications of electron harvesting concept through sequential ET processes for promoting intermolecular addition of activated alkenes and alkynes to cyclic enones as a new strategy for C-C- bond formation reactions. The α,β-unsaturated ketone moiety of cyclic enones, upon PET activation, generates a radical center at



1 2 3

its β-position which eventually adds to an activated alkene or alkyne to give coupling products. For illustration, when a mixture of cycloalkenone 1 and ethyl acrylate 2 is subjected to PET activation reaction, leads to the unprecedented coupling product 3 in moderate yield.

The coupling of methyl propiolate **4** with **1** gives thermodynamically more stable *trans*-isomer **5**. Compound **6**, when subjected to coupling reaction with **4**, using PET activation condition, furnished compound **7** with a very high 2,3-*trans*-diastereoselectivity.



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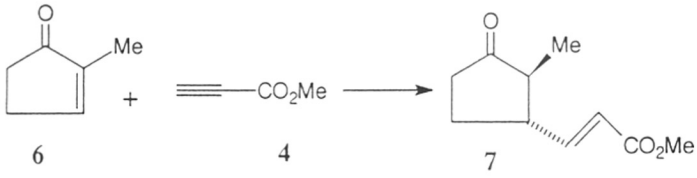
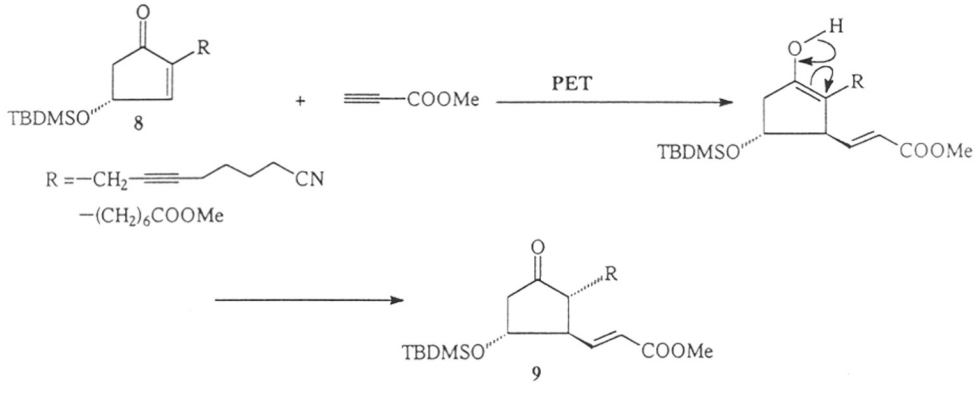


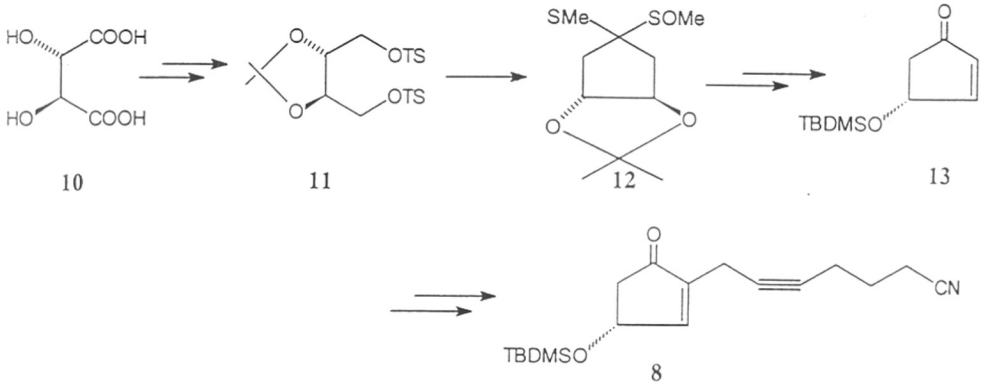
6 4 7

Encouraged by the excellent stereoselectivity observed during the coupling of **6** and **4**, the same methodology is extended for the synthesis of biologically active prostaglandin analogue (**9**).

Present approach:



Results from the above approach including preparation of the chiral prostaglandin precursor **8** starting from D-tartaric acid are presented.



10 11 12 13 8

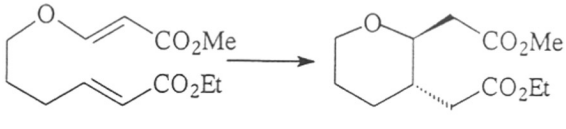
Chapter II.

a) Intramolecular coupling of activated dienes for medium size ring synthesis.

A new strategy is developed for the β-activation of α,β-unsaturated esters by sequential ET processes, Reductive activation of α,β-unsaturated ester moiety generates a radical centre at it's β-position which efficiently cyclises to tethered activated olefin to give *trans*-1,2-disubstituted carbocyclic compound in very good chemical yield. When compound 14 is subjected to PET activation, cyclized product **15** is obtained .

14 **15**

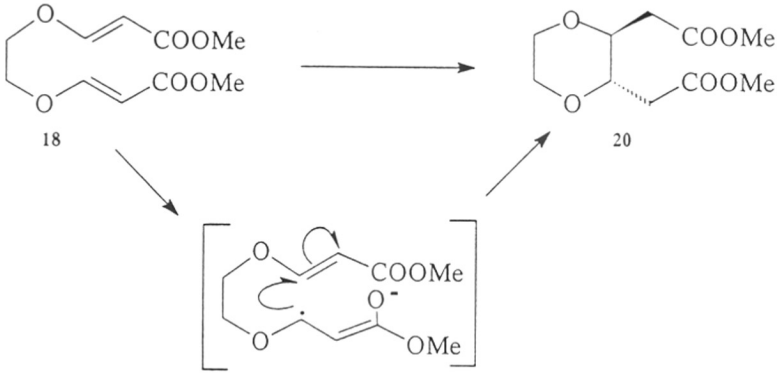
This strategy has been further extended for the stereoselective synthesis of 2,3-disubstituted hydropyran sub-units by the intramolecular cyclization of **16** as shown below.



16 **17**

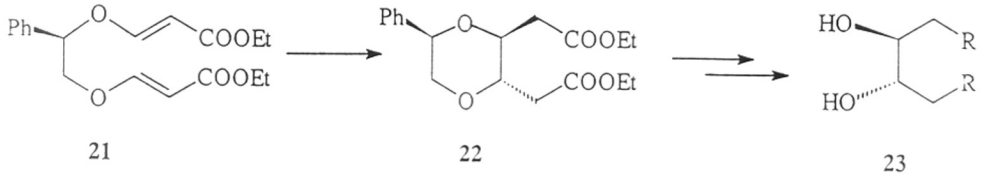
b) Generation of α-alkoxy radical, and it's application for the synthesis of chiral dioxane.

This part of chapter **III** describes results from the coupling of bis-β-alkoxy acrylate to form 1,2 disubstituted dioxane. When compound **18** is subjected to PET activation, cyclized product **19** is formed in very good yield with excellent diastereoselectivity (>95%).



19

Chiral dioxane **22**, a precursor for trans 1,2 - diol, has been synthesized by the PET activation of chiral compound **21** in good yield as a single diastereomer. The synthesis of C_2-symmetric 1,2-diol **23** from **22** is also described.



Chapter-I

Designing a New Photosystem for Harvesting Photons into Electrons by Sequential Electron-Transfer Processes: One Electron Reductive β-Activation of α,β-Unsaturated Ketones as Carbon Radical Precursor

1. Introduction

Photochemical reactions occupy principal position in the field of chemistry. One of the remarkable achievement of several decades of intense research activities in this area has been the recognition that photoexcitation renders well defined redox potential differences whereupon molecules either become powerful electron donors or acceptors. This property of photoexcitation has become increasingly useful tool in initiating electron exchange processes to generate radical ions:- a new type of reactive intermediates[1-4]. The importance of this phenomenon, known as photoinduced electron transfer (PET), has grown rapidly during the last one decade and that have attracted the attention of not only organic chemists but also inorganic chemists[5] and molecular biologists[6] as well.

The importance of PET phenomena, particularly in organic chemistry, may be imparted to the unique features of these transformations as the key reactive intermediates are radical ion species rather than the initially populated excited states. The knowledge over the years in this area concerning with the physical and mechanistic aspects has rapidly enhanced its scope in organic synthesis[7-9] .

The PET processes are initiated by the interaction of a donor (D) molecule with an acceptor (A) upon photoexcitation which results either in partial charge transfer (exciplex formation) or electron transfer (radical ion formation) depending upon the nature of the donor, acceptor and solvent polarity[10] (**Eq. 1**) .

$$D + A \underset{}{\overset{h\nu}{\rightleftharpoons}} D^{+\bullet} + A^{-\bullet} \qquad \text{.....} Eq.\ 1$$

Generally, the feasibility of producing radical ions *via* PET reactions is predicted by estimating the free energy change (ΔG_{et}) associated with their formation by using Weller[11] equation (**Eq. 2**)

$$\Delta G_{D S}^{+\bullet}{}_{AS}^{-\bullet} = E_{1/2}^{ox.} \text{ of } D - E_{1/2}^{red.} \text{ of } A - E_{exc.} \text{ of } A \quad \text{.....} Eq.2$$

$\Delta G_{DS}^{+\bullet}{}_{AS}^{-\bullet}$ = *Gibbs free energy change for the formation of FRIP.*

$E_{1/2}^{ox}$ *of D* = *Oxidation potential of the donor*

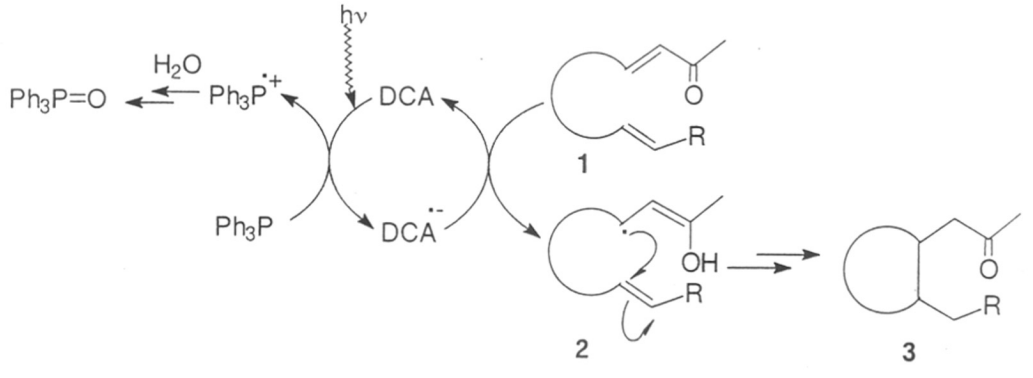
$E_{1/2}^{red}$ *of A* = *Reduction potentials of the acceptor*

E_{exc} *of A* = *Singlet state excitation energy of acceptor.*

which employs experimentally derivable parameters such as oxidation potential of the donor ($E_{1/2}^{ox}$ of D), reduction potential of acceptor ($E_{1/2}^{red}$ of A) in the given solvent.

Although, several new and synthetically important organic photoreactions are discovered[12-15] employing PET concept, the competive back electron transfer and the strong influence of the nature of primary intermediates [*viz* contact ion pair (CIP), solvent separated ion pair (SSIP) and free radical ion pair (FRIP)] on the reactivity profiles of the radical ions have raised some restrictions in the designed application of these reactions in organic synthesis. While partial solution to retard the impact of BET is suggested[16], the later issue which is primarily the function of donor-acceptor redox properties have remained rather unmanipulable except in playing with the solvent polarity. Earlier effort from our group[17a-b] have tried to solve this problem by directing the PET generated primary free radical ion, obviously possessing sufficiently large redox potential differeneces in comparison to other neutral substrates, for initiating secondary dark ET reaction to produce another radical ionic species. This concept has been realised through a photosystem (photosystem-A, **PS-A**) comprising of Ph_3P as sacrificial electron donor and DCA as visible light harvesting electron acceptor in deoxygenated atmosphere, to drive a secondary ET from $DCA^{\cdot-}$ to α, β-unsaturated ketones as shown in **Fig. 1**.

Fig. 1



Upon accepting an electron the α, β-unsaturated moiety of **1** is activated at its β-position as carbon centered radical that cyclises with the tethered olefin to produce 1,2-disubstituted cycloalkanoids (**3**). The thermodynamic feasibility of ET from $DCA^{\cdot-}$ to **1** in

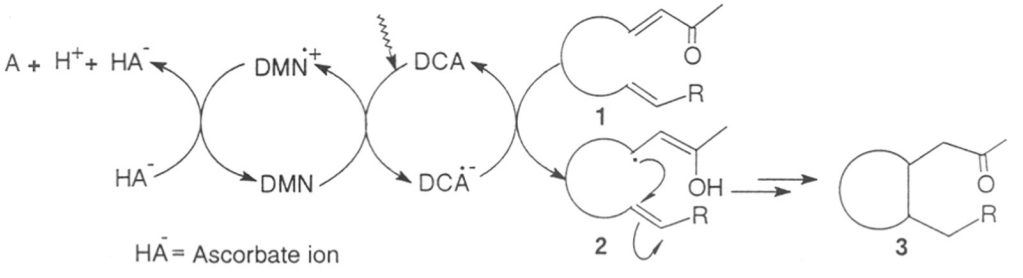
the above photosystem is evaluated by estimating the Gibb's free energy change (-11.29 Kcals mol^{-1}).

Although, the photosystem-A as shown in **Fig-1** represents the success of our basic concept of harvesting photons into electrons and its utilization for initiating one electron reductive β-activation of α, β-unsaturated ketones for radical reactions, it was realized that this photosystem may not be considered ideal for synthetic purposes owing to the constant build up of $Ph_3P=O$. To overcome this problem an alternative photosystem (photosystem-B, **PS-B**) that could have wider acceptability as a synthetic methodology was considered[17c].

2. Results and Discussions

The design of another photosystem, named here afterwords **PS-B** consisted of DCA as visible-light absorbing electron acceptor as usual, 1,5-dimethoxynaphthalene (DMN) as primary electron donor and ascorbic acid as sacrificial electron donor. The concept of this improved photosystem (**Fig. 2**) is also based on the thermodynamic feasibility of electron transfer (ET) between each interacting partners which are described as follows:

Fig. 2



2.1. Evaluation of ET feasibility between interacting components of PS-B:

(a) Evaluation of photophysical parameters for ET processes from DMN to $^1DCA^*$ (Fluorescence quenching study) :

To establish the PET phenomenon between DMN and excited state of DCA (DCA*), first the fluorescence quenching of DCA was studied at varying concentrations of DMN. Fluorescence measurement of DCA was made in acetonitrile at room temperature. Gradual decrease in the fluorescence intensity of DCA (λ_{ex}= 430 nm, λ_{em}= 461 nm) with the increase of quencher (DMN) concentration, while keeping the DCA concentration constant, was observed.

$I_0/I = 1 + Kqf\ \tau\ [Q]$ *Eq.3*

$K_{qf}\ \tau$ = *Slope*

I_0 = *Intensity of fluorescence without quencher*

I = *Intensity of fluorescence with quencher*

K_{qf} = *Rate constant of fluorescence quenching*

$[Q]$ = *Concentration of quencher (DMN)*

τ = *Singlet life time of donor (DCA)*

Treatment of quenching data to Stern-Volmer analysis (**Eq. 3**) plot (I_0/I *versus* quencher concentration) resulted in a straight line passing through 1 (**Fig. 3**) from which the slope (0.253) was measured . Substituting the τ (singlet lifetime of DCA)[19] with a value of 19.6 ns in **Eq. 2**, the fluorescence quenching rate constant (K_{qf} = 1.27×10^{10} n^{-1} s^{-1}) was calculated and was found to be near diffusion[18] (K_{diff} = 2.30×10^{10} M^{-1} S^{-1}) controlled rate constant.

Exciplex emission between DCA* amd DMN are not noticed either in polar or in non-polar solvents. Excitation and absorption spectra of DCA are unaffected in the presence of maximum concentration of quencher (DMN). Therefore, the quenching observed can not be attributed to the ground state complexation between DCA and DMN. Thus, the possibility of thermal electron transfer could be eliminated. The quenching process due to the singlet energy transfer from DCA (Es = 66.4 Kcal M^{-1})[4] to DMN could

also be ruled out as UV-absorption spectum of DMN extends up to 270-330 nm in acetonitrile. Therefore, it is imperative to assume that fluorescence quenching in these systems is *via* single electron transfer (SET) mechanism involving CT stabilized exciplex intermediate.

(b) Evaluation of thermodynamic parameters :

(i) Electron transfer from DMN to DCA :*

To provide further evidence of PET generation of radical-ion pairs between DMN and ^{1}DCA*, the thermodynamic feasibility of ET between DMN and excited state of DCA was established by estimating Gibb's free energy change (ΔG_{et}) for radical ion formation using Weller equation[11] (**Eq. 1**). Substituting **Eq. 1** with appropriate values of oxidation potential of DMN (1.28 eV),[21] reduction potential of ^{1}DCA* (-0.89 eV)[18] and excitation energy of DCA (2.88 eV)[18], an exergonic value of -16.37 kcals mol^{-1} was obtained.

(ii) Electron transfer from ascorbic acid to DMN$^{+\bullet}$:

To establish ET feasibility from the ascorbic acid to DMN$^{+\bullet}$, oxidation potential ($E^{1/2}$ox) of ascorbic acid (1.084 eV *vs* SCE) was measured first. Oxidation potential of ascorbic acid was measured by cyclic voltameter consisting of three-electrode assembly on a PAR-173/175 Potentiostat Universal programmer instrument equipped with PAR RE0074 XY recorder. The cell consisted of a ultra micro electrode (UME) as working electrode and Pt foil as counter electrode. The peak potential values of degassed solution at a sweep rate of 200 mVS^{-1} was measured in water solution employing potassium chloride as supporting electrolyte. The potential was referred to standard calomel electrode (SCE) and was uncorrected for liquid junction potential. The reduction potential of ascorbic acid was found to be -1.084 eV.

ET feasibility from the ascorbic acid to DMN$^{+\bullet}$ is evaluated by estimating the ΔG_{et} value employing the electrochemical equation, **Eq. 4**. Substituting **Eq. 4** with appropriate values of reduction potential of DMN (1.28 eV)[20] and oxidation potential of ascorbic acid (1.048 ev) an exergonic value of -4.5 kcals mol^{-1} was obtained.

$$\Delta G = E_{1/2}^{ox.} - E_{1/2}^{red.} \quad \text{.....Eq.4}$$

$E_{1/2}^{ox}$ = *Oxidation potential of donor.*

$E_{1/2}^{red.}$ = *Reduction potentials of acceptor*

The oxidative transformation of ascorbate ion to the dehydroascorbic acid and proton, as shown in **Fig. 2** is precedented from the literature report.[21]

(iii) Electron transfer from $DCA^{-\bullet}$ to ethyl-9-oxo-7(E), 2(E)-decadienoate (7) :

Similarly, the feasibility of ET from $DCA^{\cdot-}$ to α, β-unsaturated ketone (**7**) is evaluated by estimating the Gibb's free energy change ΔG_{et} employing **Eq. 4**. For this purpose the reduction potential of **7** was estimated by cyclic voltameter consisting of a three electrodes assembly on a Bioanalytical system, model CV- 27. The cell consisted of a Pt inlay working electrode, Ag/AgCl reference electrode and Pt wire as an auxiliary electrode. Tetraethylammoniumperchlorate was used as a supporting electrolyte in DMF solution. The observed cyclic voltammograms were irreversible and therefore, the point of inclination of the curves were considered[22] as approximate reduction potential value of **7**. This value were changed to standard calomel electrode (SCE) by adding[22] -0.045 to the values obtained by Ag/AgCl.

Substituting **Eq. 3** with appropriate values of redox potentials of $DCA^{\cdot-}$ (-0.89 ev) and reduction potential of **7** (-0.40 ev) an exergonic value of -11.29 kcals mol^{-1} was obtained.

2.2. Evaluation of Synthetic Perspectives of Photosystem-B :

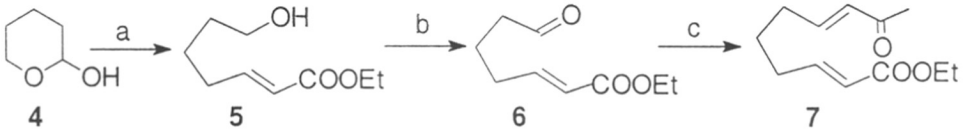
To evaluate the suitability of photosystem-B (**Fig. 2**) for triggering sequential ET reaction, one electron reductive activation of ethyl-9-oxo-7 (E), 2 (E)-decadienoate (**7**) was undertaken using DMN and ascorbic acid in an exactly similar manner as described earlier for PS-A activation reaction[17]. It was expected that like PS-A activation, α, β-unsaturated ketone moiety of **7** upon accepting an electron from $DCA^{\cdot-}$ would generate a radical center at its β-position (**9**) which would immediately add to the tethered olefinic functionality and following radical termination step by H-abstraction would result a cyclic product **10** (**Scheme-2**).

2.2.1. Preparation of ethyl-9-oxo-7 (E), 2 (E)-decadienoate (7):

Substrate **7** was easily synthesized in 90 % yield by the Wittig olefination[23] of **6** by stirring with 1-triphenylphosphoranylidene-2-propanone in CH_2Cl_2 at r.t. for 30 h.

Compound **6** was obtained by the Swern oxidation[24] of ethyl-7-hydroxy-2 (E)-heptenoate (**5**) which was prepared by the reaction of 2-hydroxypyran[25] (**4**) with ethyl triphenylphosphoranylidene acetate (**Scheme- 1**).

Scheme 1



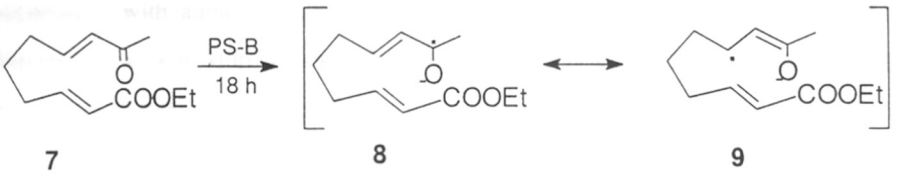
Reagents: (a) Ph_3P=CHCOOEt, CH_2Cl_2, r. t., 2d, 83 %; (b) $(COCl)_2$, DMSO, ET_3N, -78 °C, 100 %; (c) Ph_3P=CHCOOEt, CH_2Cl_2, r. t., 1d, 90 %;

2.2.2. PET Activation of 7:

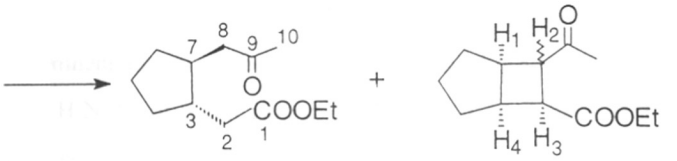
PET activation of **7** involved the irradiation (λ = 405 nm) of a solution of 7 (2.38 mmol) containing DMN (0.52 mmol), ascorbic acid (2.6 equiv. of enone) and DCA (0.57 mmol) in DMF: *i*-PrOH: H_2O (88: 10: 2) in a specially designed photoreactor which consisted of three chambers. The first and outermost chamber contained the irradiation solution and the second one was charged with $CuSO_4.5H_2O$: NH_3 filter[26] solution. 450W Hanovia medium pressure mercury lamp was housed into a water cooled double jacketed chamber which was immersed into the second one. The whole photoreactor was made of Pyrex glass. The *i*-PrOH functioned as hydrogen donor. The 405 nm wavelength light was obtained by using $CuSO_4.5H_2O$: NH_3 solution filter[26] from 450-W Hanovia medium pressure mercury lamp. All the light under this experimental setup was absorbed by DCA only. Before the irradiation, the solution was deoxygenated by bubbling argon for 2 h. After 18 h of irradiation, when 7 was almost consumed (98 %, monitored by GC), the solvents were removed under vacuo and the concentrate was purified by column chromatography over silica gel using petroleum-ether/ethylacetate as an eluent to afford **11** (70 %) as major product with small amount of **10** (< 20 %).

IR spectrum of **10** indicated the loss of conjugated double bonds. It showed prominent absorption bands at 1715, 1729 cm^{-1} corresponding to keto and ester carbonyl group, respectively.

Scheme 2



7 8 9



10 (18 %) **11** (1.6: 1, 70 %)

(ϕ = 0.058)

^{1}H NMR spectrum of product **10** (**Fig. 4**) displayed a quartet at δ 4.15 (two protons, J = 7.2 Hz) assigned as the methylene protons of ester group. A multiplet appearing between δ 2.68-2.17 (four protons), corresponds to methylene protons of -CH_2CO- and -CH_2COO-, respectively. A singlet at δ 2.12 (three protons) is assigned to the ketomethyl (CH_3CO-). Protons of cyclopentane ring appeared as a bunch of multiplets at δ 1.9 (four protons), 1.6 (two protons) and 1.25 (two protons), respectively. Methyl protons of the ester moiety appeared as a triplet at δ 1.25 (J = 7.2 Hz).

The ^{13}C NMR spectrum of **10** (**Fig. 5**) showed twelve carbon signals whose characterization was suggested by INEPT experiment. Two down field quaternary carbons appearing at δ 208.57 and 173.27, correspond to -CO- and -COO-, respectively. Two methine carbons appeared at δ 42.25 and 41.02. Methylene carbons appearing at δ 60.32, 49.08 and 39.50, were assigned to OCH_2, CH_2CO, CH_2COO, respectively. Remaining three methylene carbon signals of cyclopentane ring were observed at δ 32.50, 32.23 and 23.60. A signal at δ 30.32 was assigned as methyl carbon attached to -CO- while methyl carbon of ester moiety appeared at δ 14.40.

Mass spectral analysis (**Fig. 6**) gave expected molecular ion peak at 212 with 3% intensity and base peak at 124. The other prominent fragmentation peaks are found at 167 (59%, M^+-$COCH_3$), 155 (90%, M^+-CH_2COCH_3), 154 (72%) 139 (16%, M^+-COOEt), 109 (71%), 81 (85%) and 67 (45%) were also observed.

The structure of **10** as well as it's *trans*-stereochemistry was further confirmed by comparing it with authentic sample of **10** prepared by Enholm's procedure[27]. **10** was characterised as a mixture of two diastereomers (1.6:1) by GC/MS analysis (capillary column, phenyl methyl silicone, 25 m).

The diastereomeric mixture of **11** could be resolved into pure diastereomers by careful column chromatography.

IR spectrum of major isomer of **11** indicated the loss of conjugated double bonds. It showed prominent absorption bands at 1730 (COO), 1715 (-CO-) cm^{-1}.

In the ^1H NMR of major isomer of **11** (**Fig. 7**), methylene protons of ester moiety appeared as usual a quartet at δ 4.12 (two protons, J = 7.2 Hz). A multiplet at δ 2.95 (three protons) and a doublet of doublet at δ 2.83 (one protons, J = 9.8, 4.9 Hz) could be assigned to four protons of cyclobutane ring. The singlet appearing at δ 2.1 (three protons), corresponds to $-COCH_3$. Remaining protons of cyclopentane ring are observed as multiplets at δ 1.85 (three protons), 1.60 (three protons). A triplet at δ 1.25 (three protons, J = 7.2 Hz) could be ascribed to the methyl protons of ester moiety.

The ^{13}C NMR spectrum (**Fig. 8**) displayed two down field quaternary carbons at δ 207.34 and 173.50, assigned for the carbons of the keto-carbonyl and ester carbonyl, respectively. Signals at δ 50.66, 43.65, 39.05 and 38.66 corresponds to the four methine carbons. Methylene carbon of ester moiety appeared at δ 60.54. Another three methylene carbons of cyclopentane ring were observed at δ 32.35, 32.14, 25.09. Methyl carbon attached to -CO- appeared at δ 28.76 and methyl carbon of ester moiety showed up at δ 14.14. These characterization of signals were suggested by INEPT experiments of decoupled ^{13}C spectrum.

GC-MS analysis (**Fig. 9**) exhibited molecular ion peak at 210 (4 %) and base peak at 167 (M^+-$COCH_3$) besides other fragmentation peaks at 195 (47 %, M^+-CH_3), 165 (31 %, M^+-OEt), 155 (32 %), 137 (54 %, M^+-COOEt), 121 (30 %), 109 (12 %), 97 (28 %), 81 (20 %), 67 (12 %), 55 (8 %).

IR spectrum of minor isomer of **11** indicated the loss of conjugated double bonds. It showed prominent absorption bands at 1732 (COO), 1718 (-CO-) cm^{-1}.

The ^1H NMR of minor isomer of **11** (**Fig. 10**) displayed a quartet at δ 4.12 (two protons, J = 7.2 Hz) corresponding to methylene protons of ester moiety. H-$_2$ appeared as doublet of doublet at δ 3.62 (J = 8.7, 8.2 Hz) whereas H-$_1$ and H-$_3$ are noticed as

multiplets at δ 3.08 (two protons). A doublet of doublet at δ 2.88 (J = 13.2, 8.2 Hz) is ascribed as *H-4*. Another singlet at δ 2.1 (three protons) could be assigned as CH_3CO-. The ester methyl protons appeared as triplet at δ 1.25 (J = 7.2 Hz). Other six protons of cyclopentane ring are observed in two bunches of multiplets at δ 1.70 (three protons) and δ 1.48 (three protons). Assignment of first four protons are made by ^{1}H NMR COSY experiments (**Fig. 11**).

The ^{13}C NMR spectrum (**Fig. 12**) showed twelve carbon signals and characterization of each carbon signal is suggested by INEPT experiment which are as follows: δ 205.47 (-CO-), 174.3 (-COO-), 60.29 (OCH_2), 47.40 (CH), 40.23 (CH), 40.0 (CH), 38.54 (CH), 31.85 (CH_2), 28.12 (CH_3), 27.75 (CH_2), 25.36 (CH_2), 14.08 (CH_3).

Mass spectrum showed molecular ion peak (m/z) at 210 with 2 % intensity and 143 as a base peak along with other peaks at 167 (15 %, M^+-$COCH_3$), 165 (16 %, M^+-OEt), 137 (14 %, M^+-COOEt), 121 (11 %), 97 (10 %) and 67 (11 %). HRMS (EI) showed 165.0917 [(M^+-OEt), calcd. for $C_{10}H_{13}O_2$; 165.0915].

2.2.3.Quantum Yield Determination of 11 :

The quantum yield for the formation of **11** was estimated by Applied Photophysics Quantum Yield reactor (Model QYR-20) using 200-W Mercury Lamp. Samples for the quantum yield estimation were prepared by pipetting out quantitative volume from the stock solution into the Pyrex tube. The stock solution contained the enone **7**, DMN (15 mol % of enone), ascorbic acid (2.6 equiv.) and DCA (20 mole %) in DMF : *i*-PrOH : H_2O (88 : 10 : 2) solution. The sample was irradiated in the above mentioned Quantum Yield reactor for a short interval of time (2 h) to bring about 8-12 % of conversion. Uranyl oxalate actinometer[28] was used to monitor the intensity of light. Quantitative formation of cyclized product **11** was estimated by HPLC (Perkin Elmer 135C, Diode-array detector; C_8-reversed phase column) using CH_3CN : H_2O as eluent system. The quantum yield for product formation was obtained by utilizing equation **eq. 5**.

$$\phi = \frac{C \times P \times V \times A.N.}{I \times t} \quad \text{..... eq. 5}$$

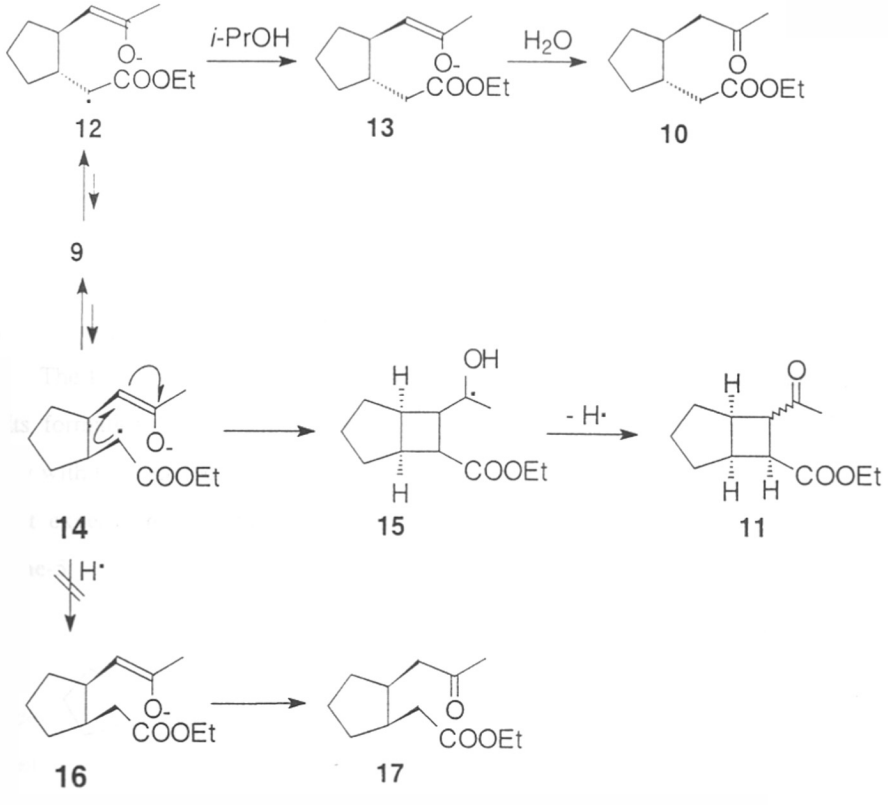
where, C = concentration of compound; P = % of formation of cyclized product; V = volume of solution pipetted out for irradiation; A.N. = Avogadro no.; I = light intensity and t = time of irradiation.

Substituting **Eq. 5** with appropriate values of C = 0.00407619, P = 0.1251235, v = 4 mL, t = 2h, I = 0.302×10^{16} photons/sec, quantum yield for the formation of **11** from **10** was obtained as ($\phi = 0.058$). The quantum yield for the formation of **11** ($\phi = 0.058$) clearly indicated that its formation did not involve radical chain reaction.

2.2.4. Mechanism for the formation of 10 :

Though Beckwith's model[29] suggests that under kinetic control the cyclization of intermediate **9** should give cyclized compound with *syn*-appendages (**17**), **10** is obtained with *anti*-stereochemistry from **9**. It may be postulated that initially produced *syn*-intermediate (**14**) being less stable, gets transformed into thermodynamically more stable *anti*-intermediate (**12**) due to the resonance stabilization of enolate ketyl radical as shown in **Scheme 3**.

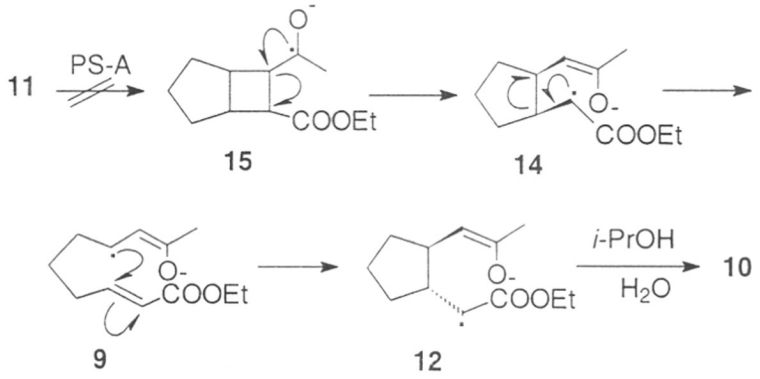
Scheme 3



Thermodynamic control in radical cyclizations are known in literature,[30, 31] though the examples pertaining to this observation have involved the formation of six membered rings only.

Another possibility[32] for the formation of **10** by further PET reaction of **11** (**Scheme-4**) is ruled out from a controlled PET activation experiment of **7** where the ratios of **10** and **11** remained same throughout the entire period of irradiation. Further support to this aspect was obtained by irradiating **11** independently, under identical PET activation conditions as discussed for **7**, showed negligible conversion to **10**.

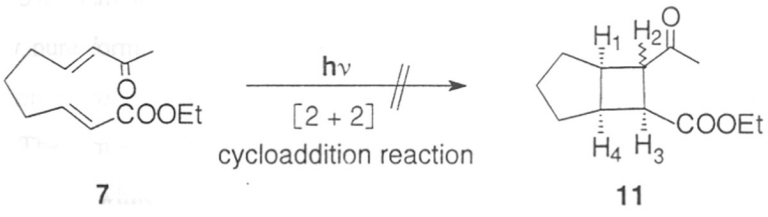
Scheme-4



2.2.5. Mechanism for the formation of 11:

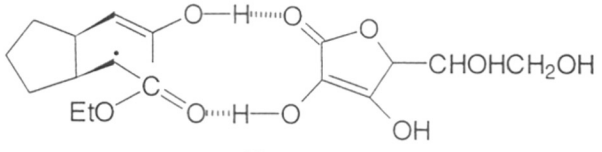
The formation of **11** in this reaction, as the major product, was quite surprising to us. Its formation by the intramolecular [2+2]-cycloaddition reaction of excited enone moiety with the tethered alkene is easily ruled out as **7** does not absorb any light under the present experimental conditions (**Scheme-5**).

Scheme-5



Although at this stage we are not sure about the exact mechanistic role of the ascorbic acid for the formation of **11** in the above reaction, it appears that ascorbic acid is somehow stabilizing the *syn*-intermediate (**14**) that retards the equilibration towards the thermodynamically stable *anti*-isomer (**12**). One of the possibilities for this stabilization may be due to the itermolecular hydrogen bonding (**18**) between **14** and ascorbic acid as shown in the **scheme-6**. Therefore, the plausible route for the formation of **11** could likely be by the efficient cyclization of electrophilic

Scheme-6



18

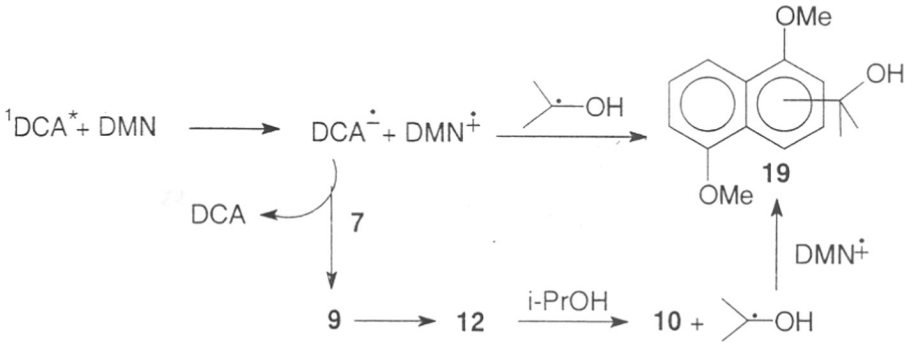
radical of *syn*-intermediate **14** to electron rich enolate double bond[33] due to their geometrical proximity (**Scheme-3**). This could be possible only if the rate of the termination of radical species in intermediate **14** by H-abstraction is slower than its further cyclization to enolate double bond.

In order to pin-point either DMN or ascorbic acid responsible for producing **11** in this experiment, a controlled irradiation[34] experiment using stoichiometric amount of DMN to **7** and without ascorbic acid, was performed which indicated the similar ratio (3.2: 1) of **10** and **11** as obtained earlier using **PS-A**, though the combined chemical yields were found to be much reduced (40%). This experiment suggests that ascorbic acid is definitely playing a role in the formation of **11**. To rule out the possibility of ascorbic acid changing the UV spectral pattern of the mixtures of DMN-DCA-7, detailed spectral analysis of the mixture at varying concentrations of ascorbic acid were also carried out which showed no significant change in UV spectral behavior.

During this experiment, fast degradation of DMN to a mixture of products (not more than 5% each) were observed. Although, none of the products could be isolated in sufficiently pure form, based on the ^{1}H NMR spectra of at least two isolated products, incorporation of *iso*-propoxy as well as 2-hydroxy-*iso*-propyl moiety in the DMN may be suggested. The former product could be considered to arise by the nucleophilic addition of *i*-PrOH to $DMN^{+\cdot}$ while the formation of the later (**19**) could be explained by the coupling of $DMN^{+\bullet}$ with 2-hydroxy-*iso*-propyl radical, produced after the $H^{\bullet}$ donation to terminate

intermediate **12**. This observation further supports the involvement of radicaloid intermediate of type **9**, during the PET activation of **7** (**Scheme-7**).

Scheme-7



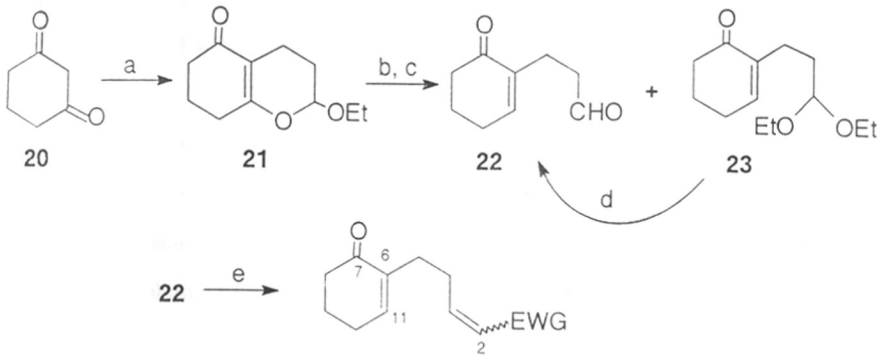
2.3. Support for the cyclisation of syn radicaloid intermedia (14) to enolate double bond:

To provide convincing evidence that the cyclization of **9** initially produces *syn*-intermediate (**14**) which undergoes further cyclization to the enolate double bond to produce **11**, in competition with its thermodynamically equilibrated *anti*-intermediate (**12**), the cyclization of **24** was considered. It was envisaged that the corresponding enolate ketyl radicals from **24** is expected to produce *cis*-cyclized product (**28**) only, as its reversal to corresponding *anti*-intermediate would be energetically unfavorable (**Scheme 9**).

2.3.1. Preparation of 2-(4-Carboethoxy-3-butenyl)-2-cyclohexene-1-one (24a) :

Substrates **24a** (E-isomer) was prepared in 85% yield by Wittig olefination of **22** by stirring with the ethyl triphenyphosphoranylidene acetate in CH_2Cl_2 at r.t. for 30 h (**Scheme-8**). Precursor **22** itself is obtained in three steps starting from 1,3-cyclohexadione (**20**). Reaction of **20** with acrolein in presence of a catalytic amount of potassium hydroxide in refluxing absolute EtOH followed by acidification with conc. HCl gave **21** (64%) as a thick liquid. Lithium aluminium hydride reduction[35] of **21** in Et_2O at 0°C followed by acidic hydrolysis and dehydration yielded **22** (84%) and **23** (10%). Compound **23** is further converted to **22** by treating with 5% HCl in acetone. All the intermediate compounds are well characterized by detailed ^1H NMR, ^{13}C NMR, IR and mass spectroscopic experiments.

Scheme-8



24a: EWG = COOEt (trans, 85%)

24b: EWG = CN (trans: cis = 62: 38)

Reagents: (a)(i) CH_2: CHCHO, EtOH, KOH (cat.), reflux 3h; (ii) Conc. HCl, r.t., 2 h, 64%; (b) LAH, Et_2O, 0°C, 30 min.; (c) EtOH, 5% aq. HCl, r.t., 1h; 84% (d) Aq. HCl, $(CH_3)_2CO$; (e) when EWG = COOEt; Ph_3P=CHCOOEt, CH_2Cl_2, r.t., 1d; 85% (E-isomer); when EWG = CN; Ph_3P=CHCN,CH_2Cl_2, r.t., 1d, 95% (E:Z = 62:38).

2.3.2. PET activation of 24a :

Usual PET activation of **24a** in DMF: *i*-PrOH: H_2O (88: 12: 2) solution containing DMN, ascorbic acid and DCA for 14 h gave 84% yield of **27a** as a thick liquid (**Scheme-9**).

IR spectrum of **27a** indicated the loss of conjugated double bonds. It showed prominent absorption bands at 1730, 1668 cm^{-1} corresponding to ester and keto carbonyl groups, respectively.

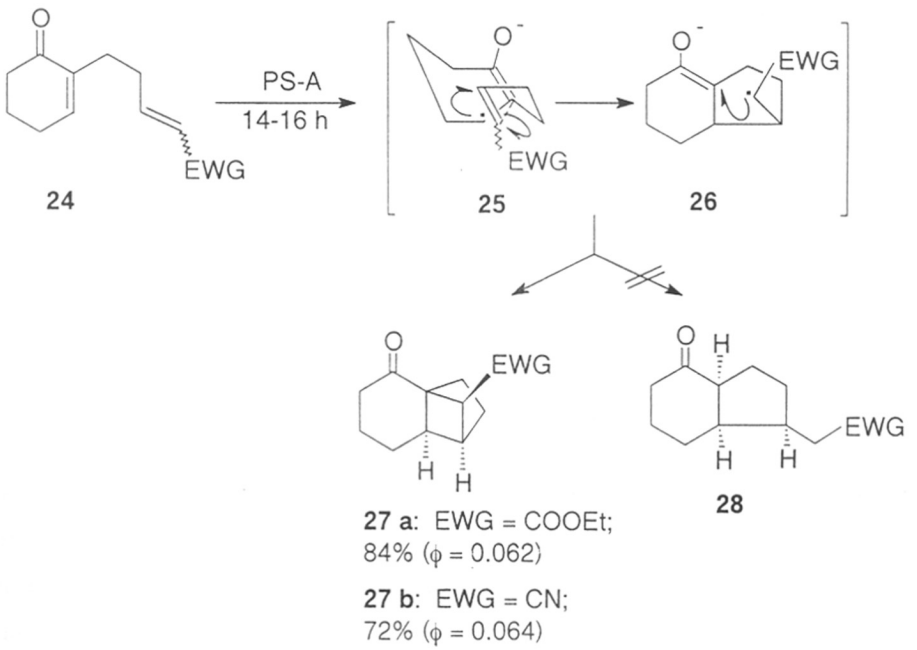
The ^1H NMR of **27a** (**Fig. 13**) displayed a bunch of multiplets at δ 4.08 (two protons), 3.38 (one proton), 2.67 (one proton), 2.35 (three protons), 2.09 (one proton), 1.88 (four protons), 1.76- 1.47 (three protons). Methyl protons of ester moiety appeared as a triplet at δ 1.21 (three protons, J = 7.2 Hz).

The ^{13}C NMR (**Fig. 14**) showed two down field quaternary carbons at δ 208.31 and 171.25 corresponding to keto and ester carbonyls, respectively. It also displayed another quaternary carbon at δ 58.90, assignable to the bridge head carbon. Three methine carbons appeared at δ 51.40, 50.52, 43.93, respectively. Methylene and methyl carbons of ester

moiety are observed appearing at δ 60.55 and 14.39, respectively. Remaining five signals at δ 39.86, 26.77, 25.27, 24.24 and 22.99 are assigned to methylene carbons. These characterization of signals have been suggested by INEPT experiments of decoupled ^{13}C spectrum.

Mass spectrum of **27a** (**Fig. 15**) gave molecular ion peak at 222 with 19% intensity as well as $M^+ + 1$ with 9% intensity and base peak at 149 (M^+ - COOEt). Other prominent fragmentation peaks are observed at 176 (72%, M^+ + 1- OEt), 131 (43%), 120 (43%), 91 (53%), 79 (49%) and 67 (35%).

Scheme-9



2.3.3. Preparation of 2-(4-Cyano-3-butenyl)-2-cyclohexene-1-one (24b) :

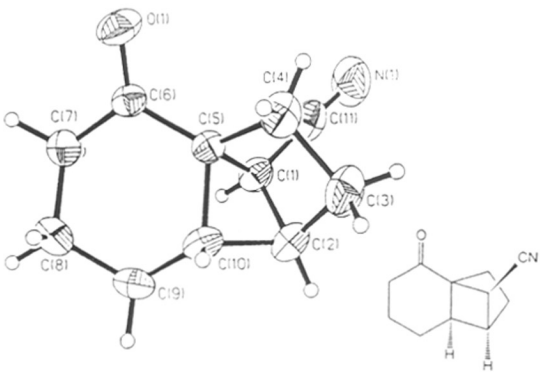
Substrate **24b** was also prepared in 95% yield as a mixture of isomers (*trans:cis* 68:32) from compound **22** by Wittig olefination reaction using triphenylphopsphoranylidene nitrile instead of ethyl triphenylphosphoranylidene acetate following identical reaction sequences as decribed for **24a** (**Scheme-8**).

2.3.4. PET activation of 24b :

Similar PET activation of **24b,** as described for **24a,** gave **27b** as a crystalline solid (m.p. 114°C) in 72% yield (**Scheme-9**).

The structure of **27b** is established with detailed ^{1}H NMR, ^{13}C NMR, IR and MS (for details see expt. section). The tricycle structure of **27b** is unequivocally confirmed by the single crystal X-ray (**Fig. 16**).

Fig. 16



It appears that tricyclic compounds **27** from **24**, are definitely formed by further cyclization of intermediate **26** to enolate double bond. This observation suggests that wherever *syn*-cyclized intermediates are thermodynamically more stable, invariably undergo further cyclization to proximate enolate double bond to produce double cyclized product before they can get terminated by the intermolecular H-abstraction. Our attempt to arrest the *syn*-monocyclized product (**17** and **28**) from both **7** as well as **24** by increasing the percentage of *i*-PrOH in the reaction mixture, however, failed. Further progress in this direction is in progress.

3. Conclusion

In conclusion, we have developed a new photosystem to drive sequential electron transfer processes, promoted by visible light, to trigger one electron reductive β-activation of α, β-unsaturated ketones to produce carbon centered radical precursor. The cyclization of these radicals to tethered activated olefins are shown to be very efficient and stereoselective. The formation of double cyclized products are demonstrated to originate

from the thermodynamic stability of *syn*-intermediates by hydrogen bonding. The application of this photosystem is expected to give a new direction in generating radical anionic species from variety of functionalities to study unexplored and interesting areas of chemistry. Moreover, this strategy would be advantageous from ecological point of view as well.

4. Experimental Section

4.1. Cyclic Voltammetry Experiments:

The reduction potential of compounds 7, **24 (a** and **b)** were measured by cyclic voltammetry experiments. These experiments were carried out with a three electrode assembly on a Bioanalytical System, model CV-27. The cell consisted of a Pt inlay working electrode, Ag/AgCl reference electrode and Pt wire as an auxiliary electrode. Tetraethylammonium perchlorate was used as supporting electrolyte in DMF solution. Before each experiment, the solution was deoxygenated by bubbling argon for 10 min. The observed cyclic voltammograms were irreversible and therefore, the point of inclination of the curves were considered[22] as approximate reduction potential values of enones. These values were changed[22] to standard calomel electrode (SCE) by adding -0.045 to the values obtained from Ag/AgCl.

4.2. Fluorescence Quenching of DCA with DMN :

Quenching of fluorescence intensity of singlet excited state of DCA with varying concentrations of DMN was studied and the details of the procedure are as follows:

A stock solution of DCA (3.0×10^{-3} M) was made by dissolving 0.0342 g (1.5 mmol) of DCA in 50 mL of acetonitrile. 1 mL of the above stock solution was distributed into eight 10 mL volumetric flasks. Similarly, stock solution of DMN (3.02×10^{-2} M) was prepared by dissolving 0.2846 g (mmol) of DMN in 50 mL of acetonitrile. From the stock solution of DMN, 0.0, 0.4, 0.6, 0.8, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, and 4.5 mL were pipetted out and added to above eight 10 mL volumetric flasks containing 1 mL solution of DCA and the volume of the resulting mixtures were made up to 10 mL with acetonitrile. The flourescence spectra of DCA solution, containing zero concentration of DMN was obtained by exciting at 430 nm (λ_{ex}) and flourescence emission intensity (I_0) was monitored at 461 nm (λ_{em}). Similarly, fluorescence intensity of the other solutions containing varying concentrations of DMN were also recorded. The details of the fluorescence intensity (I) at particular concentration of DMN are given in Table A.

Table A :Fluorescence Quenching of DCA by DMN at different concentrations of DMN

Flask No.	Vol. of stock Sol. of DMN added (mL)	Resulting conc. of DMN at final dilution ($\times 10^{-3}$M)	I_0/I
1	0.0	0.000	–
2	0.4	1.2	1.270
3	0.6	1.8	1.428
4	0.8	2.4	1.557
5	1.0	3.0	1.688
6	1.5	4.5	2.079
7	2.0	6.0	2.452
8	2.5	7.6	2.907
9	3.0	9.0	3.268
10	3.5	10.6	3.605

Analyses of the data presented in Table A, using Stern-Volmer quenching kinetic equation $\left(\frac{I_0}{I} = 1 + K_{qf}\tau\ (Q)\right)$, by plotting $\frac{I_0}{I}$ on Y-axis with corresponding concentration of DMN on X-axis gave a straight line (**Fig. 3**) with an intercept of 1.0 (±0.001) on Y-axis. The slope of the straight line ($Kq_f\tau$) was calculated and found to be 0.253 (±0.005). Incorporating singlet lifetime value of DCA (τ =19.6 ns)[19] in the slope, the rate of fluorescence quenching (Kq_f) was estimated to be ($1.27 \times 10^{10}\ M^{-1}S^{-1}$).

4.3. Estimation of quantum yields :

In order to estimate quantum yields for the formation of products from the enones **7, 24a-b**, at first lamp intensity was evaluated

a) Evaluation of lamp intensity in photons/second:

Lamp intensity was evaluated by using uranyloxalate actinometry[28]. The details of the experimental procedures are as follows:

i) Preparation of standard $KMnO_4$ solution:

2 g of $KMnO_4$ was dissolved in 200 mL of freshly distilled water and solution was boiled for 4 h. The solution was allowed to stir overnight and then filtered through a medium porosity sintered glass funnel and stored in amber colored bottles prior to standardisation.

ii) Sodium oxalate standardization:

1.655 g of dry sodium oxalate was dissolved in distilled water and diluted to 250 mL so that the normality of sodium oxalate was 0.0988 N.

iii) Titration for the standardisation of $KMnO_4$:

Two 50 mL burettes were cleaned and filled with 4 N H_2SO_4 and $KMnO_4$ solutions, respectively. Three 50 mL conical flasks were taken and in each flask 2 mL of sodium oxalate solution was delivered from a calibrated constant aliquot pipette. 10 mL of H_2SO_4 was added and the solution was warmed to 80 ^{0}C before titrating with $KMnO_4$ solution. The end point was noted when the faint pink coloured MnO_4^- did not disappear instantly but lingered on for few seconds, forming faint pink coloured solution. The titrations were repeated to give three concurrent values. The titration readings are given in Table-6.

Table-6: Standardisation of $KMnO_4$

S.No.	Vol. of $KMnO_4$		
	initial value (mL)	**final value (mL)**	**difference (mL)**
1	0	6.80	6.80
2	7	13.80	6.80
3	14	20.80	6.80

The normality of $KMnO_4$ was calculated as follows:

$$[N_{KMnO4}] \times [V_{KMnO4}] = [N_{Na2C2O4}] \times [V_{Na2C2O4}]$$

$$[N_{KMnO4}] \times 6.80 = (0.0988) \times 2.0$$

$$[N_{KMnO4}] = 0.0291\ N$$

iv) Oxalic acid actinometer:

This actinometer was prepared by dissolving 1.259 g of uranyl nitrate (2.5 mmol) and 1.579 g of oxalic acid (12.5 mmol) in 250 mL distilled water and preserved in ambered bottle .

v) Titration of actinometer:

2 mL of the above actinometer solution was delivered into 50 mL conical flask from a calibrated pipette and 10 mL of 4 N H_2SO_4 was added. The solution was warmed to 80 ^{0}C. The hot solution was titrated with standard $KMnO_4$ solution. The titration was repeated for two concurrent values.

vi) Irradiation and titration of actinometer solution :

4 mL of standard actinometer solution was added by pipette into two 10 mL pyrex tubes and irradiated for 2 h in Applied Photophysics Quantum Yield reactor (Model QYR-20) using 200 W mercury lamp at 405 nm wave length light. For the isolation of monochromatic 405 nm light, a filter solution[35] of $CuSO_4.5H_2O$-NH_3 was kept in the middle chamber of light filtration chamber placed between the UV source and the sample cells. After the irradiation, 2 mL of irradiated actinometer was pipetted out into 50 mL Erlenmeyer flask. 10 mL of 4N H_2SO_4 was added and warmed to 80 ^{0}C. The hot solution was titrated against the standard $KMnO_4$ solution. The titration was repeated to give two consecutive concurrent values. The titration values before and after the irradiation of actinometer solution and their difference (Δ ml) are given below:

Table-7: Irradiation and titration of actinometer solution

Entry	Vol. of $KMnO_4$		
	initial value(mL)	**final value (mL)**	**difference**
Unirradiated	0.00	6.85	6.85
	7.00	13.85	6.85
Irradiated	0.0	6.15	6.15
	7.0	13.15	6.15

$$\Delta ml\ KMnO_4 = KMnO_4\ (unirr) - KMnO_4\ (irr)$$

$$= 6.85 - 6.15$$

$$= 0.7\ mL$$

Calculation of the lamp intensity:

The lamp intensity (I) was calculated according to the equation as shown below :

$$I = \frac{X_{eq} \times \text{Avagadro number}}{(2_{eq/mole}) \times \phi_{AC} \times t_{sec}}$$

Where

$$X_{eq} = (\Delta mL\ KMnO_4) \times N\ KMnO_4 \times \frac{V_{AC}\ Irr.}{V_{AC}\ titrated} \times 10^{-3}$$

$$= 0.7 \times 0.0291 \times \frac{4}{2} \times 10^{-3}$$

$$= 0.04074 \times 10^{-3}$$

On incorporating the values of in the above equation the lamp intensity (I) was calculated and found to be

$$I = \frac{0.04074 \times 10^{-3} \times 6.023 \times 10^{23}}{2 \times 0.563 \times 2 \times 60 \times 60}$$

$$= 0.302 \times 10^{16}\ \ photons/sec.$$

(A.N. = 6.023×10^{23}, ϕ_{Ac} = Quantum yield for disappearance of uranyl oxalate = 0.563 at 405 nm., t = 2 h).

b) *Quantum Yield Measurements:*

The samples, prepared by pipetting out quantitative volume (4 mL) from the stock solution of respective enones [**7**, **24** (**a** and **b**], DMN (15 mol % of enones), ascorbic acid (2.6 eq.) DCA (20 mol % of enones) in DMF: *i*-PrOH: H_2O (88: 10: 2), were irradiated in the above mentioned quantum yield reactor at 405 nm light.

Irradiations were carried out for a short period (2-3 h) to bring about 8-12 % of conversion. Quantitative formation of cyclized products were estimated by HPLC (PERKIN ELMER 135C, Diode-array detector; C_8-reversed phase column) using CH_3CN:H_2O as eluent and compared with the similar analyses done with the unirradiated

solution. Mean values for the increase in the area of HPLC analyses from two consecutive experiments were considered for the purpose of calculating quantitative increase in the concentration of **11** after irradiation.

The quantum yields for product formation were obtained by utilizing the following equation

$$\phi = \frac{C \times P \times V \times A.N.}{I \times t}$$

Where, C = concentration of compound; P = % of formation of cyclized product; V = volume of solution pipetted out for irradiation; A.N. = Avogadro no.; I = light intensity and t = time of irradiation.

Quantum yield for the formation of **7** from **11** was obtained by putting V = 4 mL, t = 2 h, C = 0.00407619, P = 0.1251235; as ϕ = 0.058. Similarly, quantum yields for the formation of **27 a** and **27b** were measured 0.064, 0.062 respectively.

4.4. HRMS Analysis:

Mass spectra were taken on a VG AUTOSPEC-M mass spectrometer with OPUS V3. IX software. Samples were introduced through a gas chromatograph equipped with HP-5 fused silica capillary column of 30 M length, 0.32 mm id and 0.25 μm film thickness. Injector temperature: 280°C; Transferline temperature: 250°C; Oven temperature; Initial 100°C; initial 5 min; rate of heating 10°C/min, Final temperature 220°C. Accurate mass measurement was done at 5000RP and PFK was used as the internal reference.

Some of the compounds (**10, 11**) did not give intense molecular ion peaks. Hence, mass measurement has been done on the first intense fragmented ion from the M^+.

4.5. General Photoirradiation Procedure:

All irradiations were performed in a specially designed photoreactor which consisted of three chambers. The first and the outer chamber contained the irradiation solution and the second one was charged with $CuSO_4.5H_2O$: NH_3 filter solution. 450W Hanovia medium pressure mercury lamp was housed into a water circulated double

jacketed chamber which was immersed into the second one maintaining 1 cm path length of the filter solution. The whole photoreactor was made of Pyrex glass.

DCA (20-25 mol%) was dissolved in DMF: *i*-PrOH: H_2O (300 mL, 88: 10: 2) in a RB flask by stirring for about 2 h. Substrate DMN (15 mol%) and ascorbic acid (2.6 eq.) were introduced to the solution and stirred for an additional 5 minutes. The resultant mixture was transferred into the outer chamber of the above photoreactor and was deoxygenated by bubbling argon for 2 h and properly sealed. Irradiation was performed with light (405 nm) of 450 W Hanovia medium pressure lamp through $CuSO_4.5H_2O$: NH_3 filter solution. The progress of the reaction was monitored by GC. After 16-20 h of irradiation, when substrate was almost consumed (95-98%), the solvents were removed by distillation under reduced pressure. The concentrate was dissolved in Et_2O (50 mL) and the Et_2O layer was washed with H_2O, saturated brine solution and dried over Na_2SO_4. After evaporation of the solvent, the mixture was purified by silica gel column chromatography to give respective cyclized products.

4.6. Preparation of Ethyl-9-oxo-7(E), 2(E)-decadienoate (7): Compound **7** was prepared in three steps as described below:

(a) Ethyl-7-hydroxy-2(E)-heptenoate (5) :

In a dry 100 mL round bottom (RB) flask was added ethyl triphenylphosphoranylidene acetate (11.2 g, 32.1 mmol) and CH_2Cl_2 (60 mL) followed by 2-hydroxypyran (**4**, 2.4 g, 23.5 mmol) under argon atmosphere. The reaction mixture was allowed to stir at room temperature (r.t.) for 48 h. After concentrating, the residue was stirred with 40 mL of Et_2O: pet-ether (7:3) for 45 min. The resulting suspension was filtered and the precipitate was washed with 10 mL of the same mixed solvent. The combined filtrate was concentrated under vacuo and the mixture was separated by column chromatography on silica gel to yield 3.36 g (83%) of **5** as clear liquid ;

^{1}H NMR (200 MHz) : 6.95 (1H, dt, J =15.6, 7.0 Hz), 5.8 (1H, dt, J =15.6, 1.4 Hz), 4.17 (2H, q, J =7.2 Hz), 3.62 (2H, t, J = 6.4 Hz), 2.19 (2H, m), 2.0 (1H, br. s, OH). 1.61-1.32 (4H, m), 1.27 (3H, t, J = 7.2 Hz).

^{13}C NMR (50 MHz) : 166.94, 149.29, 121.50, 62.57, 60.29, 32.49, 32.19, 25.42, 14.32.

IR (neat) : 3400 (br), 3025, 2940, 2885, 1722, 1655, 1375, 1222, 1045, 988, 765

(b) Ethyl-7-oxo-2(E)-heptenoate (6):

Into a two necked 100-mL RB flask oxalyl chloride (0.95 mL, 11.0 mmol) dissolved in CH_2Cl_2 (30 mL) was cooled to -78°C under argon atmosphere. DMSO (1.97 mL, 27.8 mmol) in CH_2Cl_2 (8 mL) was introduced dropwise over 5 min into the flask and the gas evolution was observed. After 5 min of stirring, the alcohol (5, 1.2 g, 7.0 mmol) in CH_2Cl_2 (10 mL) was added over a period of 5 min, stirred for additional 1.5 h at -78°C, and then Et_3N (4.85 mL, 34.8 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After allowing the reaction mixture to warm to r.t., it was quenched with water (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (1×20 mL). The combined organic layers were washed with water (5×30 mL), saturated brine solution, dried over Na_2SO_4 and concentrated under vacuo. The crude aldehyde (6, 1.2 g, 100%) was used for Wittig reaction without further purification.

^{1}H NMR (200 MHz) : 9.8 (1H, t, J = 1.4 Hz), 6.94 (1H, dt, J = 15.7, 6.9 Hz), 5.85 (1H, dt, J = 15.7, 1.4 Hz), 4.2 (2H, q, J = 7.2 Hz), 2.51 (2H, td, J = 7.3, 1.4 Hz), 2.27 (2H, m), 1.84 (2H, m), 1.28 (3H, t, J = 7.2 Hz).

^{13}C NMR (75 MHz) : 201.4, 166.28, 147.37, 122.21, 60.13, 42.85, 31.15, 20.28, 14.13.

IR (neat) : 2955, 2842, 2727, 1728, 1661, 1441, 1320, 1275, 1200, 1158, 1043, 984.

(c) Ethyl-9-oxo-7(E), 2(E)-decadienoate (7):

1-Triphenyphosphoranylidene-2-propanone (2.9 g, 9.1 mmol) in CH_2Cl_2 (25 mL) was placed in a 50 mL of RB flask equipped with a magnetic stirring bar and an argon gas balloon. A solution of ethyl-7-oxo-2(E)-heptenoate (6, 1.2 g, 7.0 mmol) in CH_2Cl_2 (5 mL) was introduced with a syringe and the reaction mixture was allowed to stir for 30 h at r.t. The reaction mixture was concentrated under vacuo and the residue was stirred with 30 mL of Et_2O: pet-ether (1:1) for 20 min. The resulting suspension was filtered and was washed with 15 mL of the same mixture of solvents. The combined filtrate was evaporated and chromatographed over silica gel column to yield 7 as a clear liquid (1.3 g, 90%).

^{1}H NMR (200 MHz)	:	6.95 (1H, dt, J = 16.0, 6.9 Hz), 6.75 (1H, dt, J = 16.0, 6.9 Hz), 6.08 (1H, dt, J = 16.0, 1.5 Hz), 5.8 (1H, dt, J = 16.0, 1.5 Hz), 4.18 (2H, q, J = 7.2 Hz), 2.24 (7H, m), 1.67 (2H, m), 1.28 (3H, t, J = 7.2 Hz).
^{13}C NMR (50 MHz)	:	197.97, 166.11, 147.72, 146.88, 131.53, 121.86, 59.92, 31.48, 31.24, 26.65, 26.23, 14.05.
IR (neat)	:	2942, 1724, 1698, 1668, 1632, 1430, 1358, 1252, 1188, 1032, 976 .
MS (m/e)	:	210 (M^+, 3), 195 (4), 181 (3), 164 (71), 149 (20), 137 (77), 136 (100), 122 (36), 121 (53), 107 (36), 93 (60), 81 (58), 68 (10).

4.7. PET activation of Ethyl-9-oxo-7 (E), 2 (E)-decadienoate (7):

A solution of compound **7** (0.5 g, 2.38 mmol), DMN (0.068g, 0.36 mmol), ascorbic acid (1.1 g, 6.2 mmol) and DCA (0.13 g, 0.57 mmol) in DMF: *i*-PrOH: H_2O (700 mL, 88: 10: 2) was irradiated in especially designed photoreactor as mentioned earlier under argon atmosphere with light from a 450 W Hanovia medium-pressure lamp filtered by a $CuSO_4.5H_2O$: NH_3 solution. The progress of the reaction was monitored by GC. After considerable consumption (98%) of **7** (18 h), the solvent was removed by distillation under reduced pressure. The concentrate was dissolved in Et_2O (50 mL) and washed with H_2O and saturated brine solution. The Et_2O layer was concentrated under vacuo and the mixture was separated by column chromatography over silica-gel (100-200 mesh) using pet-ether: EtOAc as eluent to give compound **11** (0.35 g, 70 %; mixture of two isomers 1.6: 1) and **10** (0.09 g, 18 %).

trans-Ethyl 2-[2-(2-oxopropyl)cyclopentyl]ethanoate (10):

^{1}H NMR (200 MHz)	:	4.15 (2H, q, J = 7.2 Hz), 2.68-2.17 (4H, m), 2.12 (3H, s), 1.9 (4H, m), 1.6 (2H, m), 1.25 (5H, m).
^{13}C NMR (50 MHz)	:	208.57, 173.27, 60.32, 49.08, 42.25, 41.02, 39.50, 32.50, 32.23, 30.32, 23.60, 14.4.
IR (neat)	:	2953, 2871, 1729, 1715, 1368, 1183, 1168, 1030 .
MS m/e	:	212 (M^+, 3), 167 (59), 155 (90), 154 (72), 139 (16), 124 (100), 109 (71), 81 (85), 67 (45).
HRMS (EI)	:	167.1067 [($M^{+\cdot}$ - OEt), calcd for $C_{10}H_{15}O_2$ 167.1072].

*6-Acetyl-7-carboethoxybicyclo[3.2.0]heptane (**11**, major isomer):*

^{1}H NMR (200 MHz) : 4.14 (2H, q, J = 7.3 Hz), 2.95 (3H, m), 2.83 (1H, dd, J = 9.8, 4.9 Hz), 2.1 (3H, s), 1.85 (3H, m), 1.60 (3H, m), 1.25 (3H, t, J = 7.3 Hz).

^{13}C NMR (50 MHz) : 207.34, 173.50, 60.54, 50.66, 43.65, 39.05, 38.66, 32.35, 32.14, 28.76, 25.09, 14.14.

MS (m/e) : 210 (M^+, 4), 195 (M^+-CH_3, 47), 167 (M^+ - $COCH_3$, 100), 165 (M^+ - OEt, 31), 155 (32), 137 (54), 121 (30), 109 (12), 97 (28), 81 (20), 67 (12).

*6-Acetyl-7-carboethoxybicyclo[3.2.0]heptane (**11**, minor isomer):*

^{1}H NMR (200 MHz) : 4.12 (2H, q, J = 7.2 Hz), 3.62 (1H, dd, J = 8.7, 8.2 Hz), 3.08 (2H, m), 2.88 (1H, dd, J = 13.2, 8.2 HZ), 2.1 (3H, s), 1.70 (3H, m), 1.48 (3H, m), 1.25 (3H, t, J = 7.2 Hz).

^{13}C NMR (50 MHz) : 205.47, 174.3, 60.29, 47.40, 40.23, 40.0, 38.54, 31.85, 28.12, 27.75, 25.36, 14.08.

IR (neat) : 2958, 2868, 1732, 1718, 1371, 1195, 1154, 1032 .

MS (m/e) : 167 (15), 165 (16), 143 (100), 137 (14), 121 (11), 97 (10), 67 (11); [211 (M^++1, 8), 210 (M^+, 12), 195 (22), 165 (100)].

HRMS (EI) : 165.0917 [($M^{+\cdot}$-OEt), calcd for $C_{10}H_{13}O_2$ 165.0915].

4.8. Preparation of 2-(4-Carboethoxy-3-butenyl)-2-cyclohexene-1-one (24a): This was synthesized as follows:

*(a) Synthesis of compound **21**:*

Into a 100 mL RB flask, containing potassium hydroxide (2 pellets) in absolute ethanol (40 mL), 1, 3-cyclohexadione (**20**, 2.5 g, 22.3 mmol) was added while stirring. Slow addition of acrolein (1.53 mL, 22.9 mmol) followed immediately afterwards. The mixture was allowed to stir at r.t. for 2 h and refluxed for 3 h. After cooling to 0°C, it was acidified to pH-2 with conc. HCl and stirred at r.t. for additional 2 h. The mixture was diluted with water (20 mL) and extracted with Et_2O (3×30 mL). The organic layer was washed with water, $NaHCO_3$ solution (10%), water, brine and dried over Na_2SO_4. Concentration of the organic solvent followed by column chromatographic purification yielded **21** (2.8 g, 64%) as thick liquid.

^{1}H NMR (200 MHz) : 5.1 (1H, dd, J = 4.3, 2.8 Hz), 3.85 (1H, m), 3.62 (1H, m), 2.58-2.15 (6H, m), 2.05- 1.66 (4H, m), 1.22 (3H, t, J = 7 Hz).

^{13}C NMR 50 MHz : 197.72, 168.56, 111.74, 98.6, 64.33, 36.44, 28.24, 26.0, 20.68, 14.93, 13.97.

IR (neat) : 2941, 1655, 1627, 1392, 1346, 1296, 1224, 1182, 1162, 1120, 1066, 1023, 971, 946, 836 .

MS (m/e) : 196 (M^+, 2), 167 (30), 151 (23), 150 (28), 139 (78), 122 (30), 107 (68), 97 (70), 94 (68), 72 (100), 66 (30), 55 (46).

(b) 2-(3-Oxopropyl)2-cyclohexen-1-one (22):

Into a 100 mL two necked previously dried RB flask, equipped with a magnetic stirring bar and argon balloon, was placed lithium aluminium hydride (0.33 g, 8.7 mmol) and dry Et_2O (40 mL). To this suspension, a solution of **21** (2.6 g, 13.3 mmol) dissolved in dry Et_2O (10 mL) was slowly added at 0°C. After stirring for 30 min at 0°C, the reaction mixture was quenched with cold saturated aqueous NH_4Cl solution and diluted with Et_2O (20 mL). The Et_2O layer was separated and washed with water, brine, dried over Na_2SO_4 and concentrated under vacuo. The residue was diluted with ethanol (40 mL) containing 5% HCl (10 mL) solution. After stirring for 1 h at r.t., it was neutralized with 10% of $NaHCO_3$ solution and extracted with Et_2O. The Et_2O layer was washed with saturated brine solution (2×50 mL), dried over Na_2SO_4 and concentrated under vacuo. The mixture was purified by column chromatography to give 1.7 g (84%) of **22** and 0.3 g (10%) of compound **23**. A solution of **23** in 25 mL of CH_3COCH_3 was taken in a 50 mL of RB flask and 5 mL of 5% of HCl was added to it. After stirring for 3 min at r.t., the reaction was quenched with saturated brine solution. This was extracted with pet-ether (3×20 mL). The combined organic layers was dried over Na_2SO_4 and concentrated under reduced pressure to yield 0.19 g (94%) of **22**.

2-(3-Oxopropyl)2-cyclohexen-1-one (22):

^{1}H NMR (200 MHz) : 9.75 (1H, s), 6.8 (1H, t, J = 3.85 Hz), 2.55 (4H, m), 2.32 (4H, m), 1.97 (2H, m).

^{13}C NMR (50 MHz) : 201.58, 198.77, 146.40, 137.55, 42.35, 38.05, 25.68, 22.68, 22.48.

IR (neat) : 2930, 2882, 2815, 2727, 1723, 1672, 1658, 1445, 1383, 1224, 1174, 1120, 1084, 1062, 894 .

MS (m/e) : 153 (M^+ + 1, 3), 152 (M^+, 2.5), 123 (15), 111 (30), 103 (100), 95 (52), 81 (25), 67 (26).

2-(3,3-diethoxypropyl)-2-cyclohexen-1-one (23):

^{1}H NMR (200 MHz) : 6.74 (1H, t, J = 4.2 Hz), 4.50 (1H, t, J = 5.8 Hz), 3.72-3.4 (4H, m), 2.50-2.18 (6H, m), 1.98 (2H, m), 1.7 (2H, m), 1.22 (6H, t, J = 7.0 Hz).

IR (neat) : 2938, 2929, 2876, 1673, 1445, 1374, 1131, 1062 .

MS (m/e) : 226 (M+, 1), 181 (9), 152 (4), 135 (5), 103 (37), 96 (18), 85 (20), 71 (36), 67 (30), 57 (100).

(c) Preparation of 2-(4-Carboethoxy-3-butenyl)-2-cyclohexen-1-one (24a):

A 50 mL RB flask equipped with a magnetic stirring bar and argon gas balloon was charged with ethyl triphenylphosphoranylidene acetate (2.4 g, 6.9 mmol) in dry CH_2Cl_2 (25 mL). To this solution, **22** (0.8 g, 5.26 mmol) was added slowly with stirring. The stirring was continued for 30 h at r.t. The solvent was removed under vacuum and Et_2O: pet-ether (1:1, 20 mL) was added to the residue. After stirring for 15 min., the resulting suspension was filtered and the precipitate was washed with the same solvent mixture (5 mL). The filtrate was concentrated under vacuo and purified by column chromatography over silica gel to yield **24a** (1 g, 85%).

^{1}H NMR (200 MHz) : 6.9 (1H, m), 6.72 (1H, t, J = 3.9 Hz), 5.78 (1H, d, J = 15.7 Hz), 4.17 (2H, q, J = 7.2 Hz), 2.6- 2.15 (8H, m), 1.94 (2H, m), 1.27 (3H, t, J = 7.2 Hz).

^{13}C NMR (75 MHz) : 199.02, 166.46, 148.18, 145.96, 138.19, 121.62, 60.02, 38.37, 30.95, 28.31, 25.93, 22.96, 14.16.

IR (neat) : 2931, 1714, 1668, 1650, 1540, 1455, 1370, 1269, 1173, 1104, 1038 .

MS (m/e) : 222 (M^+, 1), 176 (28), 148 (72), 131 (75), 120 (100), 104 (64), 91 (89), 81 (78), 68 (39).

4.9. PET Activation of 2-(4-Carboethoxy-3-butenyl)-2-cyclohexene-1-one (24a):

To a solution of DCA (0.064 g, 0.28 mmol) in DMF: i-PrOH: H_2O (300 mL), 0.25 g (1.126 mmol) of **24a**, DMN (0.032 g, 0.169 mmol) and ascorbic acid (0.516 g, 2.93

mmol) were added and the mixture was irradiated in an analogous manner as mentioned for 7. After 14 h, irradiation was stopped and solvents were distilled off under reduced pressure. Purification of the concentrate by pet-ether: EtOAc gave 0.21 g of **27a** in 84% yield.

Compound 27a:

^{1}H NMR (200 MHz)	:	4.08 (2H, m), 3.38 (1H, m), 2.67 (1H, m), 2.35 (3H, m), 2.09 (1H, m), 1.88 (4H, m), 1.76 - 1.47 (3H, m), 1.21 (3H, t, J = 7.2 Hz).
^{13}C NMR (50 MHz)	:	208.31, 171.25, 60.55, 58.90, 51.40, 50.52, 43.94, 39.86, 26.77, 25.27, 24.24, 22.99, 14.39.
IR (neat)	:	2963, 1730, 1668, 1537, 1454, 1371, 1224.
MS m/e	:	223 (M^++1, 9), 222 (M^+, 19), 176 (42), 149 (100), 131 (43), 120 (43), 105 (34), 91 (53), 79 (49), 67 (35).
HRMS (EI)	:	222.1257 (calcd for $C_{13}H_{18}O_3$ 222.1255).

4.10. Preparation of 2-(4-Cyano-3-butenyl)-2-cyclohexene-1-one (24b):

Wittig olefination reaction of compound **22** (0.7 g, 4.6 mmol) with triphenyl-phosphoranylidene acetonitrile (1.81 g, 6.0 mmol) by following identical procedure as described for **24a** yielded 0.77 g of **24b** (95%) as a mixture of isomers (*trans : cis* 68: 32).

^{1}H NMR (200 MHz)	6.73 (1.7H, m), 6.45 (0.3H, dt, J = 10.8, 7.0 Hz), 5.32 (1H, m), 2.42 (8H, m), 1.98 (2H, m).
^{13}C NMR (50 MHz)	198.14, 154.74 (153.63), 146.21, 136.95, 116.83 (115.34), 99.47 (99.36), 37.77, 31.67 (30.40), 27.40 (27.46), 25.42, 22.45.
IR (neat)	2931, 2221, 1668, 1622, 1541, 1384, 1173, 1105, 972, 907.
MS (m/e)	175 (M^+, 32), 147 (17), 135 (14), 119 (23), 109 (40), 91 (18), 81 (100), 67 (16), 53 (27).

4.11. Photoactivation of 2-(4-Cyano-3-butenyl)-2-cyclohexene-1-one (24b):

Compound **24b** (0.25 g, 1.42 mmol) DMN (0.04 g, 0.213 mmol) and ascorbic acid (0.65 g, 3.69 mmol) were dissolved in a solution of DMF: *i*-PrOH: H_2O (300 mL) containing DCA (0.081 g, 0.355 mmol) and mixture was irradiated for 16 h as discussed

for 7. After removal of solvents and column chromatographic purification, the residue yielded 0.18 g (72%) of **27b** as a crystalline solid, which was recrystalized from CH_2Cl_2-pet-ether mixture.

Compound 27b:

Color	:	Colorless
MP	:	114°C
^{1}**H NMR** (200 MHz)	:	3.40 (1H, m), 2.78 (1H, m), 2.40 (2H, m), 2.26 (1H, m), 2.08 (3H, m), 1.94-1.53 (5H, m).
^{13}**C NMR** (50 MHz)	:	206.32, 117.24, 58.59, 51.77, 45.34, 39.54, 36.25, 25.67, 25.30, 24.13, 22.44.
IR (nujol)	:	2922, 2231, 1693, 1553, 1454, 1372, 1257, 1102, 939, 848 .
MS (m/e)	:	176 (M^+ + 1, 17), 175 (M^+, 85), 174 (M^+ - 1, 30), 146 (82), 135 (59), 119 (100), 91 (74), 81 (92), 79 (99), 67 (48), 65 (49), 53 (85).

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34. Care was taken so that under this experimental conditions the light was absorbed completely by DCA only.

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Spectra

Stern-Volmer plot for fluorescence quenching of DCA* by DMN

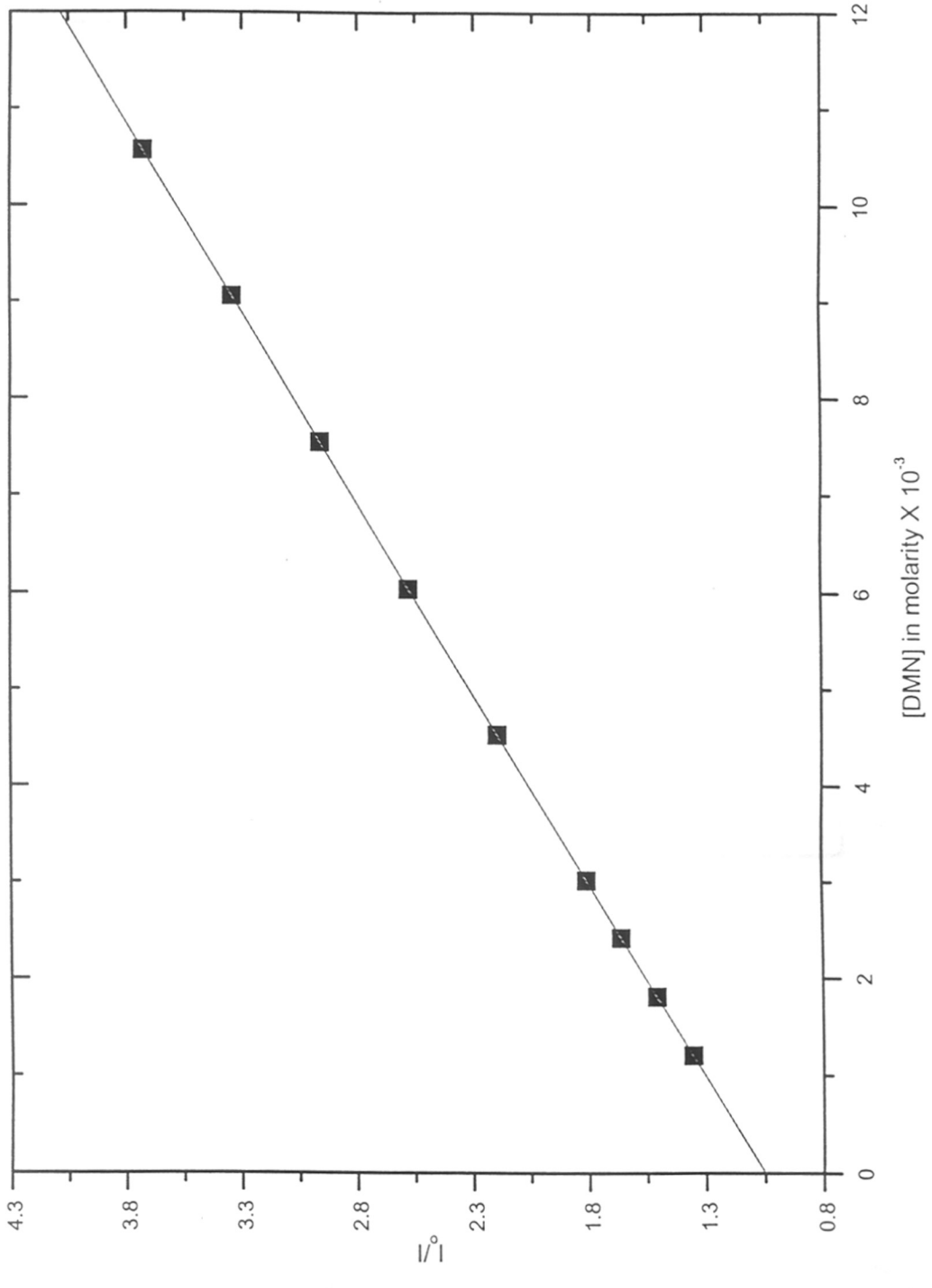


Fig. 3

Fig. 4

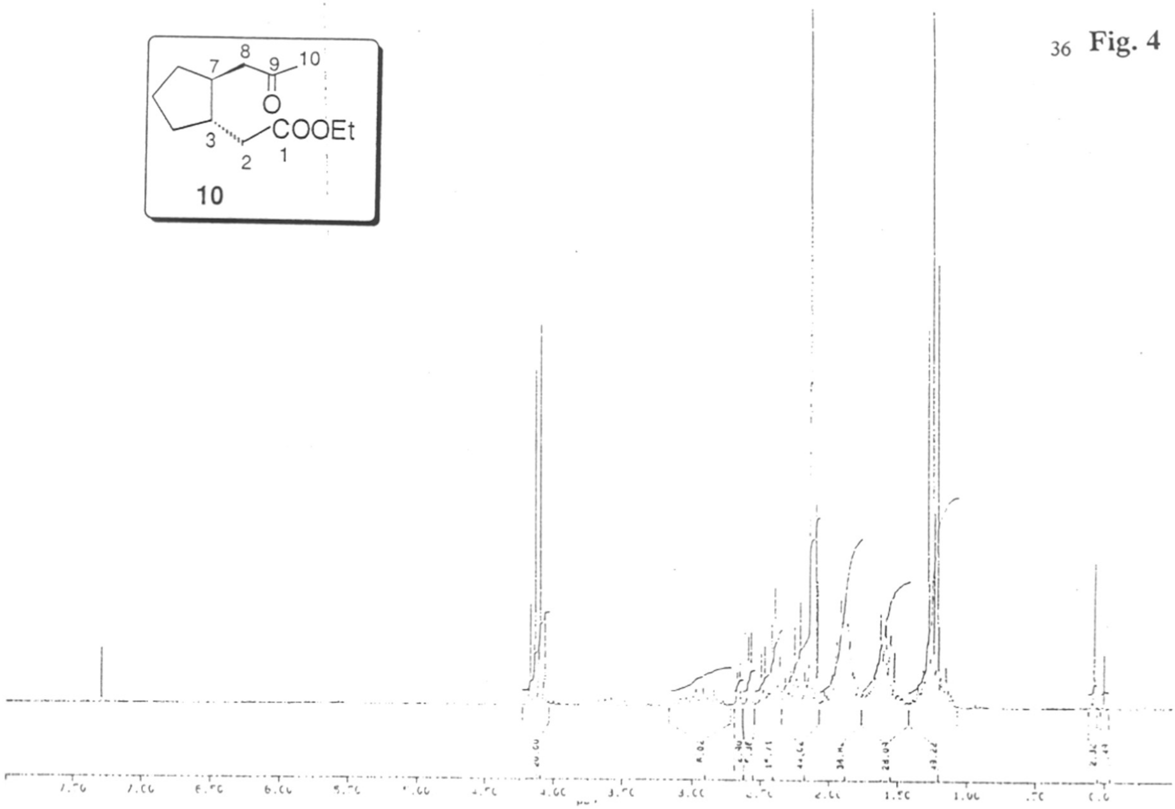
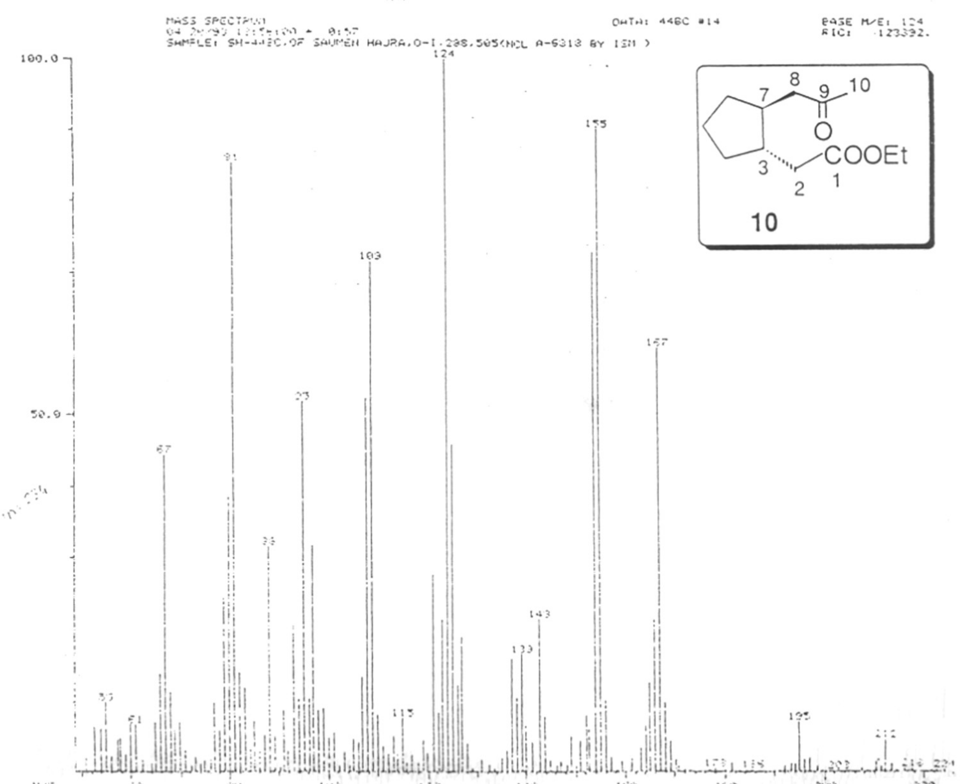

COOEt
10

Fig. 6


MASS SPECTRUM
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91
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157
143
133
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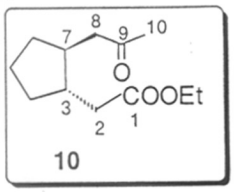
195
212
COOEt
10

Fig. 5



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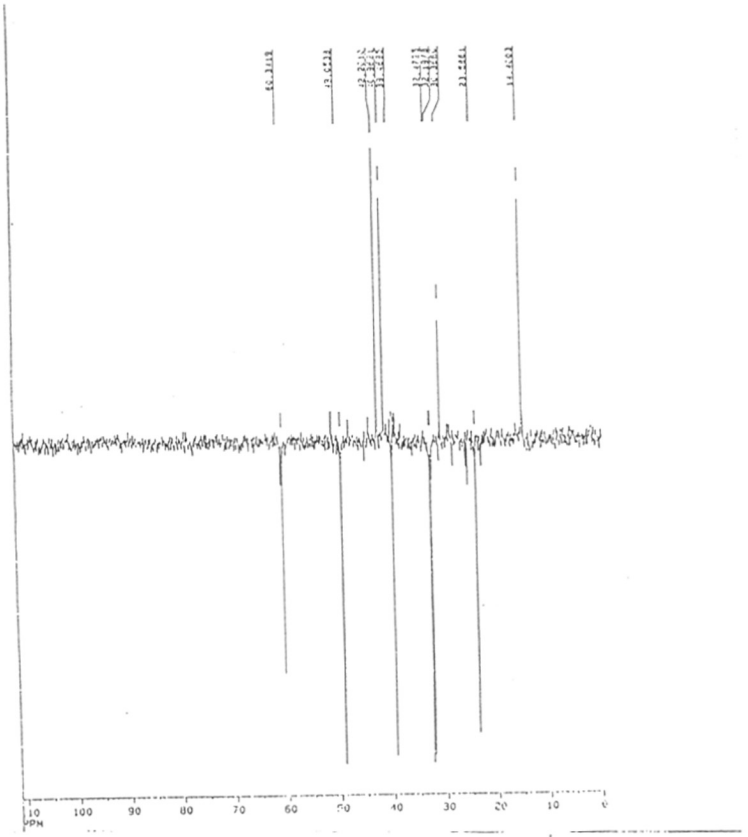
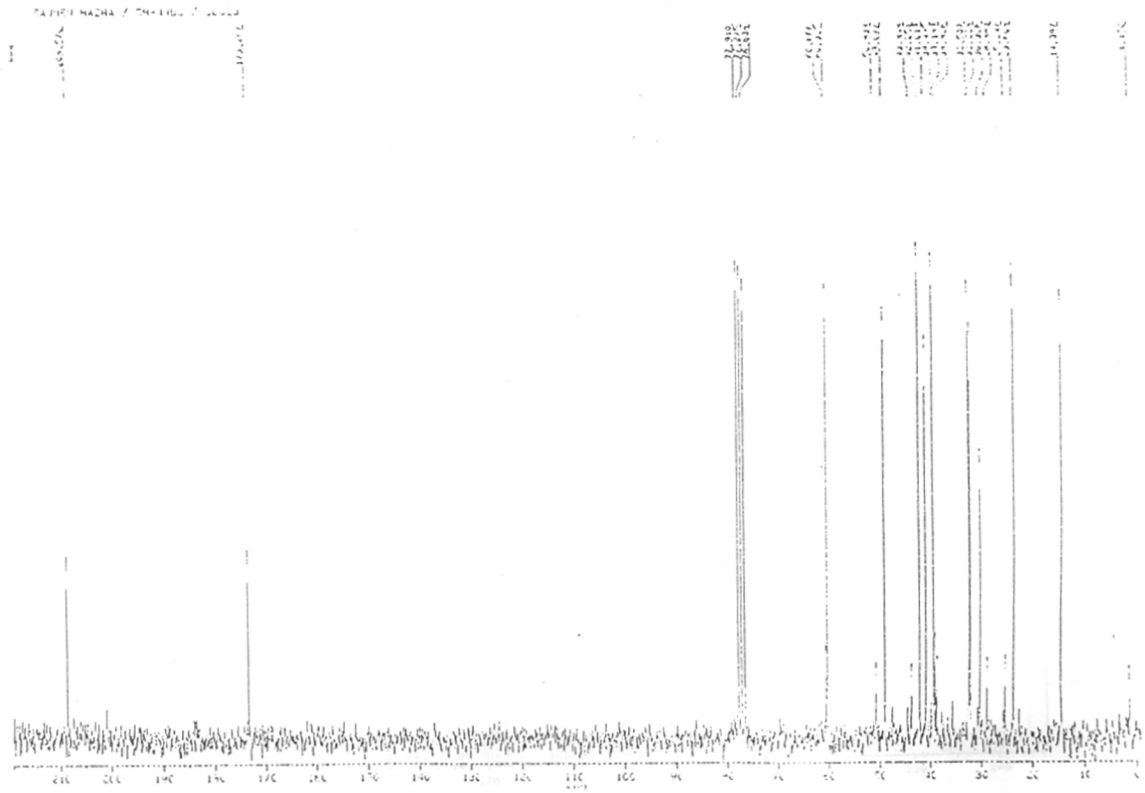




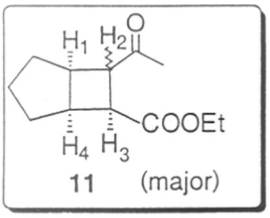
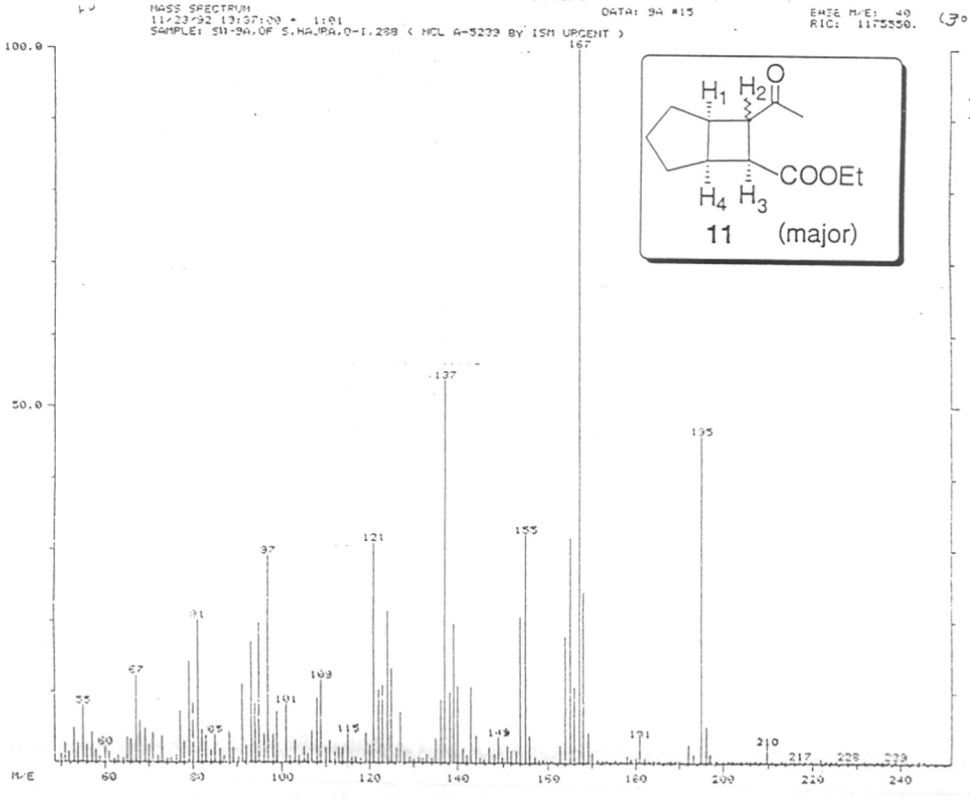

H1 H2
O
COOEt
H4 H3
11 (major)

Fig. 7

8.50
8.00
7.50
7.00
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


MASS SPECTRUM
11/23/92 13:37:00 + 1:01
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DATA: 94 #15
BASE M/E: 40
RIC: 1175350.
100.0
50.0
M/E
60
80
100
120
140
160
180
200
220
240
167
137
135
121
155
37
91
67
109
101
55
115
149
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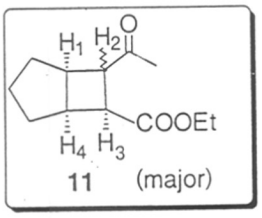
210
217
228
239

H1 H2
O
COOEt
H4 H3
11 (major)

Fig. 9

Fig. 8



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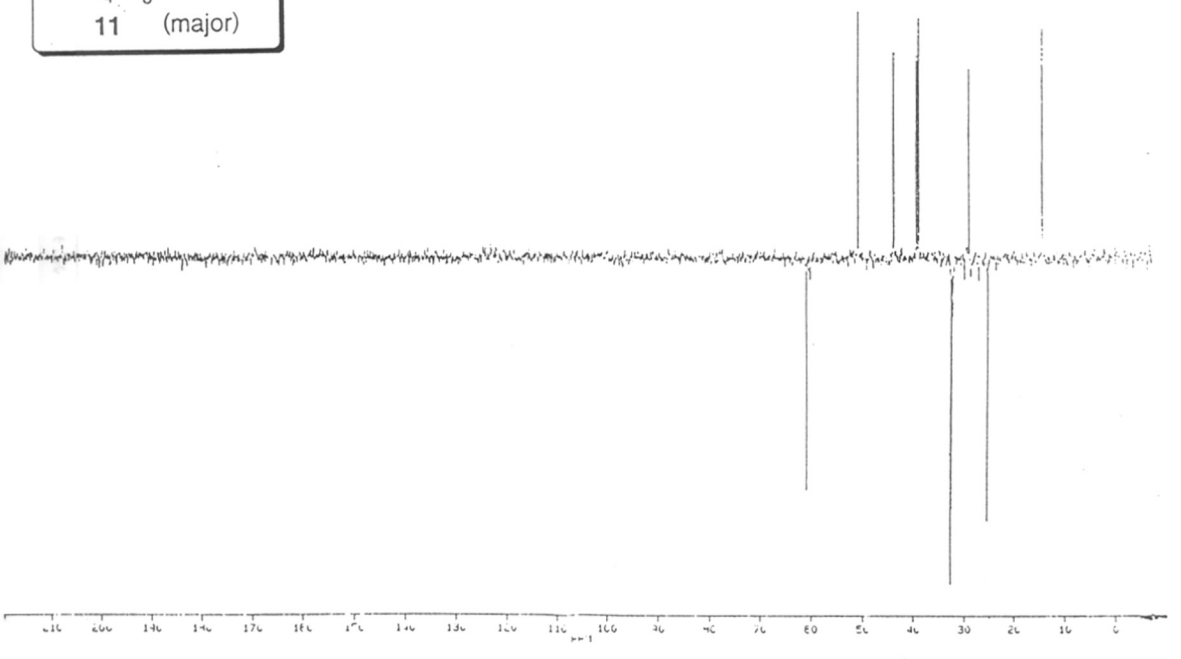


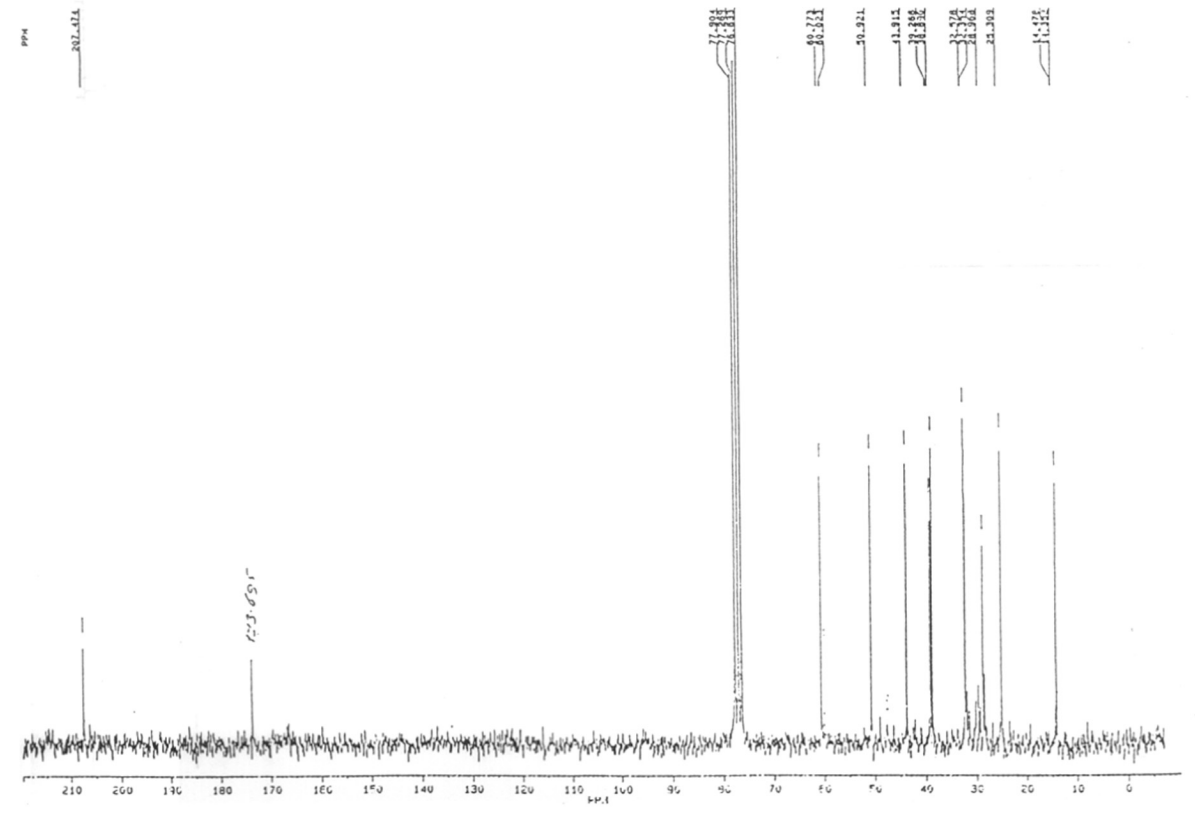
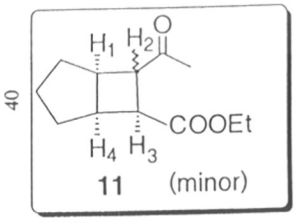
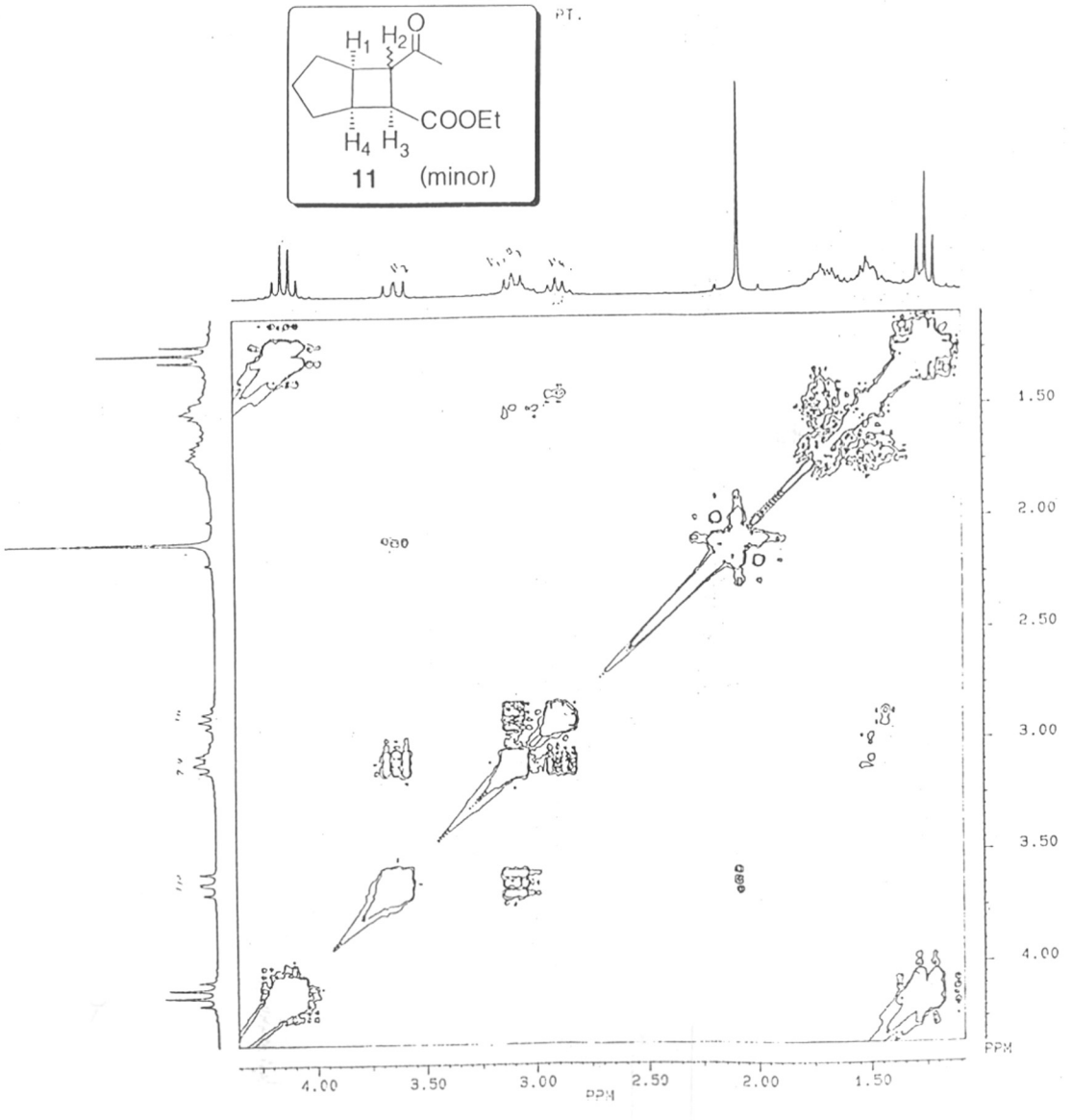


Fig. 10



11 (minor)



BRUKER

Fig. 11

```
SH44A.SMX
F1 PROJ:
 SH44APR.001
F2 PROJ:
 SH44APR.001
AU PROG:
 COSY.AU
DATE 17-4-93

SI2   1024
SI1    512
SW2  1315.789
SW1   657.895
ND0      1


WDW2     S
WDW1     S
SSB2     0
SSB1     0
MC2      M
PLIM ROW:
F1       4.360P
F2       1.065P
AND COLUMN:
F1       4.360P
F2       1.065P

D1    1.0000000
P1         7.00
D0     .0000030
P2         7.00
RD     0.0
PW         0.0
DE       477.00
NS           16
DS            2
NE          256
IN     .0007600
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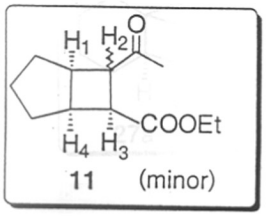
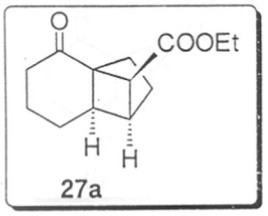


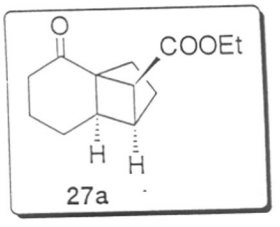
Fig. 12

Fig. 13


O
COOEt
H
H
27a

8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.0
PPM

Fig. 15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COOEt
H
H
27a

MASS SPECTRUM
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143
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67
120
131
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105
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153
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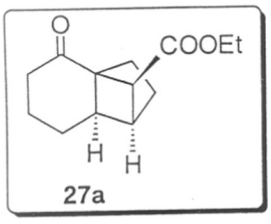
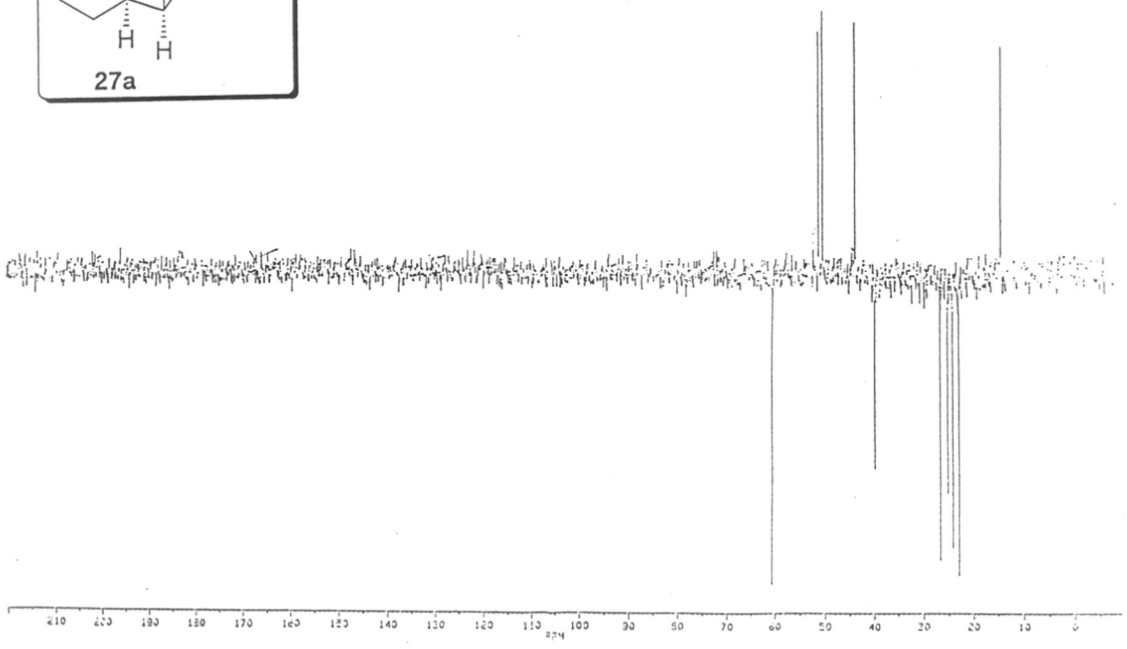
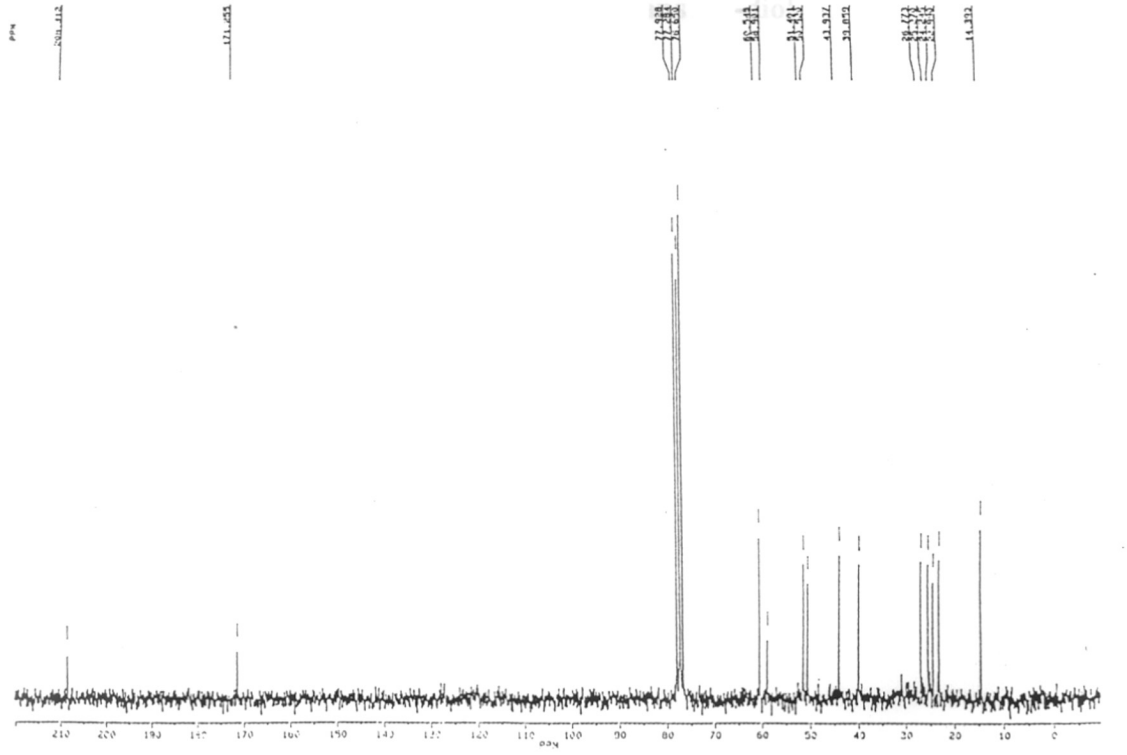
220
240

Fig. 14







Chapter-II

A New Strategy for the Construction of Carbo- and Oxycycles by Intramolecular Reductive Coupling of α,β-Unsaturated Esters : Asymmetric Synthesis of trans 1,2-diol

1. Introduction

The quest for the development of methodologies for the construction of carbocyclic frameworks is of prime importance in a synthetic strategy. Towards this endeavor, increasing attention is being given, currently, to explore the synthetic potential of one electron reductive cyclisations. In this context, our attention was drawn towards the possible utilization of our photosystem[1], **(PS-B)** as described in previous chapter, for the one electron reductive cyclisations of substrate **1** to **3** as shown in **Scheme-1.**

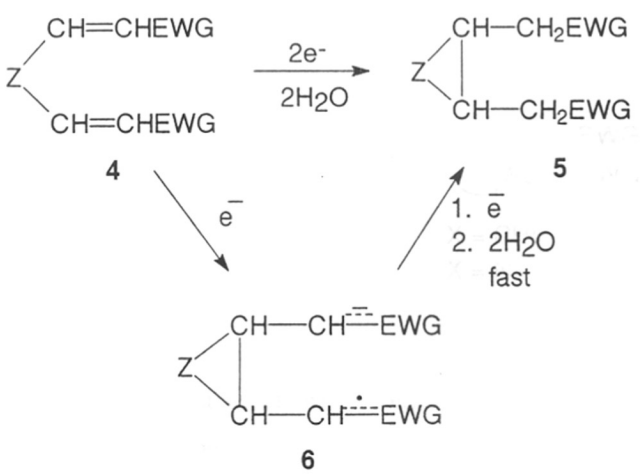
Scheme-1

1 **2** **3**

However, before we describe the success of our strategy in detail, it would be pertinent to briefly describe the methodologies reported for the reductive coupling of α,β-unsaturated esters.

One of the very early report in this context was the effort from the group of Petrovich et al[2] where intramolecular reductive coupling of bis activated olefins of the type **4** by cathodic reductions was demonstrated to produce cyclised product **5.**

Scheme-2



4 **5** **6**

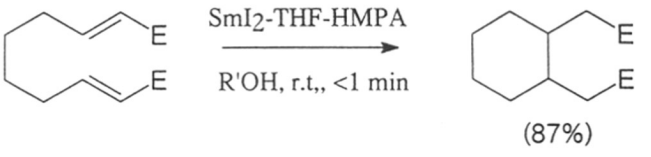
Z = (-C-)$_n$ or a heteroatom

n = 1, 2, 3, or 4

It was claimed that this strategy gave excellent results for the construction of three to six-membered carbocyclic rings (**Scheme-2**).

Surprisingly, there was no further effort in this direction for a long time till Inanaga et al[3] reported the intramolecular hydrodimerisation of conjugated ester **7** to produce **8** utilising SmI_2-THF-HMPA system as one electron reductant (**Scheme-3**). However, no effort was made to determine the diastereoselectivity of **8** in this report.

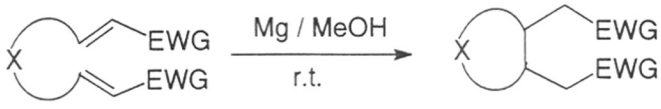
Scheme-3



7 **8**

Magnesium in methanol, a well established reducing reagent[4], has recently been extended by Chavan et al[5] for a facile intramolecular cyclization of **9** as shown in **Scheme-4**. Although, this methodology has been successful for the synthesis of three to five-membered carbocycles and heterocycles, it has failed for the construction of six membered rings due to competitive reductions.

Scheme-4



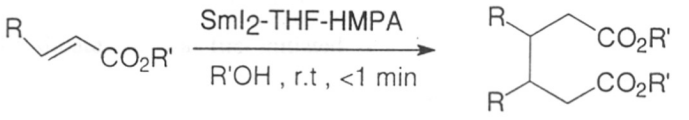
X = CH_2
x = N - CH_2 - Ph

X = CH_2
X = N - CH_2 - Ph

9 **10**

Inspite of the great potentials of the one electron reductive cyclisation for the construction of carbocycles of the type **3**, not much effort has been made to develop suitable reagent, though few scattered reports are available for the dimerisation of α,β-unsaturated esters. For example, intermolecular hydrodimerisation of **11** was reported[2] by the use of SmI_2-THF-HMPA system in the presence of R'OH. (**Scheme-5**).

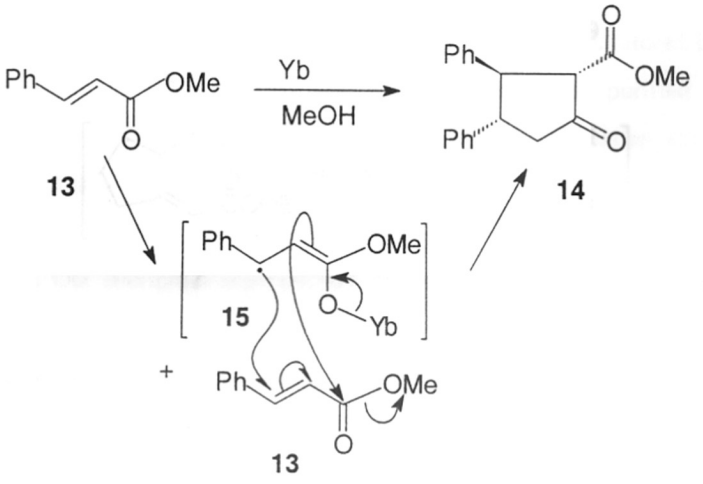
Scheme-5



11 **12**

Takaki et al[6] have reported the utilisation of Yb/MeOH as one electron reduction reagent to effect the reductive dimerisation followed by cyclisation of **13** to produce cyclopentanone derivative **14** (**Scheme-6**).

Scheme-6

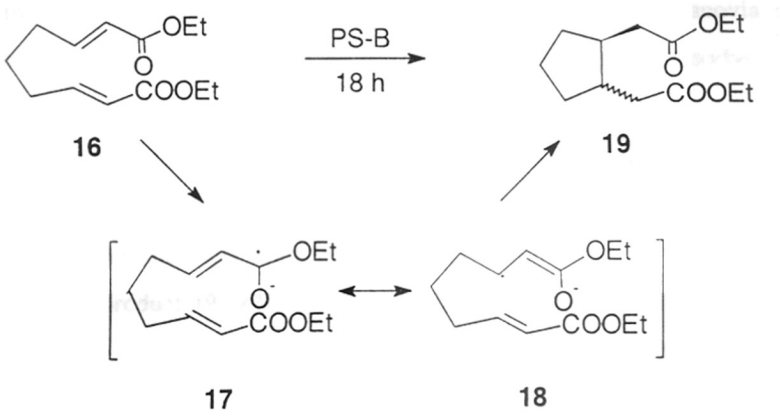


It is apparent from the above strategies that they are either too difficult to adopt in the normal synthetic laboratories[1] or involve toxic reagents[2,6] and /or dry reaction condition[5]. In the present era of increased ecological concern and increasing demand for the development of simpler and efficient synthetic methodologies using aqueous solvent, an alternative strategy to affect such types of chemistry is essential. In this endeavor, we envisaged that the application of photosystem (**PS-B**), as described in the previous chapter, could prove as an attractive strategy to realise the diastereoselective cyclizations of substrates of the type **1** by visible-light initiated photosensitized one electron reductive reactions.

2. Results and discussion

To evaluate the suitability of photosystem-B for effecting the reductive coupling of α,β- unsaturated esters, photosensitised one electron reductive activation of diethyl-2(E), 7(E)-nonene-1,9-dioate (**16**) was first initiated. It was expected that α, β-unsaturated ester moiety of **16** upon accepting an electron from $DCA^{\cdot-}$ would generate a radical center at its β-position (**18**) which would immediately add to the tethered olefinic functionality and following radical termination step by H-abstraction would result a cyclic product **19** (**Scheme 7**).

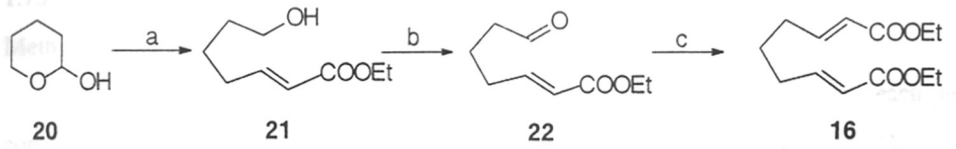
Scheme-7



2.1. Synthesis of diethyl-2(F), 7(E)-nonene-1,9-dioate (16) :

Substrate **16** was easily synthesized in 90% yield by the Wittig olefination[7] of **22** by stirring with the ethyl triphenylphosphoranylidene acetate in CH_2Cl_2 at r.t. for 30 h. Compound **22** was obtained by the Swern oxidation[8] of ethyl-7-hydroxy-2(E)-heptenoate (**21**), prepared by the reaction of 2-hydroxypyran[9] (**20**) with ethyl triphenylphosphoranylidene acetate (**Scheme-8**).

Scheme-8



Reagents : (a) Ph_3P=CHCOOEt, CH_2Cl_2, r.t. 2d, 83 % (b) $(COCl_2)$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 100 % (c) Ph_3P=CHCOOEt, CH_2Cl_2, r.t. 1d, 90 %

2.2. PET activation of 16 using PS-B :

PET activation of **16** involved the irradiation (λ = 405 nm) of a solution of **16** (2.38 mmol) containing DCA (0.57 mmol), DMN (0.36 mmol) and ascorbic acid (6.2 mmol) in DMF: *i*-PrOH: H_2O (88: 10: 2) in a specially designed photoreactor which consisted of three chambers. The first and outer most chamber contained the irradiation solution and the second one was charged with $CuSO_4.5H_2O$: NH_3 filter[10] solution. 450W Hanovia medium pressure mercury lamp was housed into a water cooled double jacketed chamber which was immersed into the second one. The whole photoreactor was made of Pyrex glass. The *i*-PrOH functioned as hydrogen donor. The 405 nm wavelength light was obtained by using $CuSO_4.5H_2O$: NH_3 solution filter[10] from 450-W Hanovia medium pressure mercury lamp. All the light under this experimental setup was absorbed by DCA only. Before the irradiation, the solution was deoxygenated by bubbling argon for 2 h. After 20 h of irradiation, when **16** was almost consumed (98%; monitored by GC), the solvents were removed under vacuum and the concentrate was purified by column chromatography over silica gel using petroleum-ether/ethylacetate as an eluent, to give expected cyclized product **19** (92%). Product **19** was characterised as a mixture of two diastereoisomers (*trans:cis* 17:3) by GC/MS analysis (capillary column, phenyl methyl silicone, 25 m). Our attempt to separate pure diastereomers by column chromatography remained unsuccessful. DCA and DMN were recovered back almost quantitatively ($\approx$ 98 %).

IR spectrum of **19** showed prominent absorption band at 1735 cm^{-1} , characteristic of a ester functionality.

^1H NMR spectrum of product **19** (**Fig. 1**) displayed a quartet at δ 4.15 (four protons, J = 7.2 Hz), assigned to the methylene protons of ester groups. A multiplet appearing between δ 2.55-2.05 (four protons), corresponds to methylene protons attached to ester groups. Protons of cyclopentane ring appeared as a bunch of multiplets at δ 2.04-1.75 (three protons), δ 1.7-1.45 (three protons) and δ 1.25 (two protons), respectively. Methyl protons of the ester moiety appeared as a triplet at δ 1.25 (J = 7.2 Hz).

The ^{13}C NMR spectrum (**Fig. 2**) showed two sets of carbon signals, each set corresponding to the respective diastereomer which further confirmed compound **19** to be a mixture of two diastereomers. Exact ratio of diastereomers are obtained by GC analysis. Since compound **19** possesses C_2-axis of symmetry (*trans* isomer) or plane of symmetry

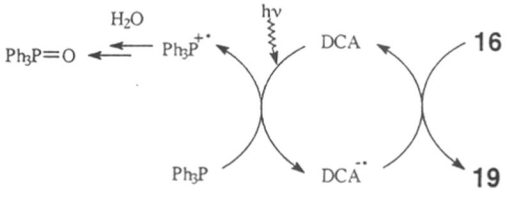
(*cis* isomers), carbon signals of the symmetrical carbons appeared at one single position. First set of carbon signals corresponding to the major isomer, showed seven signals whose characterization was obtained by INEPT experiment. Down field quaternary carbon appearing at δ 178.80 is characterised to -C̲OO- moiety of ester group (2C). Two methine carbons appeared at δ 41.84. Methylene carbons appearing at δ 60.02 and 39.19 are assigned to -OC̲H$_2$- (2C) and -C̲H$_2$COO- (2C), respectively. Remaining three methylene carbon signals of cyclopentane ring were observed at δ 32.07(2C) and 23.30. Methyl carbon of ester moiety appeared at δ 14.13.

Similarly, for minor isomer, a down field signal appearing at δ 172.80 is characterised to the quaternary carbons of -C̲OO- moieties (2C). Another signal appearing at δ 38.75 is assigned to the methine carbons (2C). Methylene carbons of -OC̲H$_2$ moieties (2C) and -C̲H$_2$COOEt moieties (2C) appeared at δ 60.02 and δ 35.08, respectively. Remaining three methylene carbon signals of cyclopentane ring appeared at δ 30.37 (2C) and δ 22.14. Methyl carbon of ester moiety is observed at δ 14.13.

Mass spectral analysis (**Fig. 3**) gave expected molecular ion peak at 242 with 1.3 % intensity along with base peak at 81 [M$^+$ - 88 (MacLaffarty fragment) - COOEt]. The other prominent fragmentation peaks were found at 197 (73 %, M$^+$ - OEt), 168 (52 %, M$^+$ - HCOOEt), 155 (82 %), 139 (4 %), 127 (14 %), 109 (35 %), 94 (31 %), 67 (37 %) and 55 (9 %)

In order to explore the effectiveness of **PS-A**, discovered from our group previously[1a], PET reductive reaction of **16** using **PS-A** (**Scheme-9**) was also undertaken. The activation essentially employed the same reaction condition as described earlier. Irradiation (405 nm) of a mixture consisting of **16** (2.38 mmol), Ph_3P (1.43 mmol) and DCA (0.57 mmol), in DMF: *i*-PrOH: H_2O (88: 10: 2) gave **19** (90 %) as a mixture of two diastereomers (*trans:cis* = 17:3).

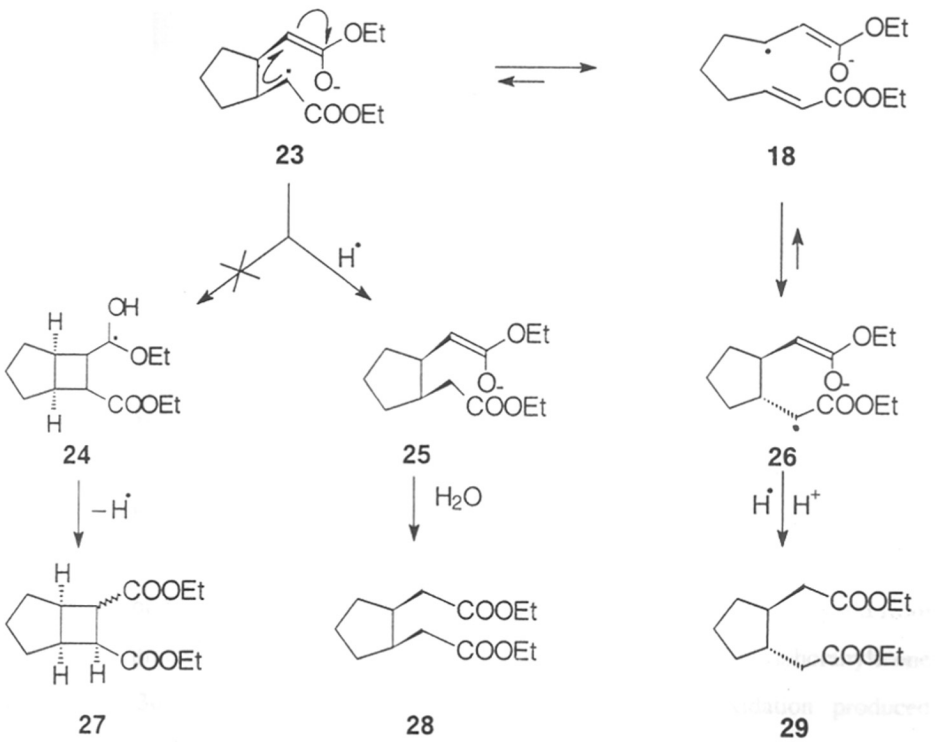
Scheme-9



2.3. Stereochemical and Mechanistic interpretations for the formation of 19:

The observed *anti*-stereochemistry of **29** appeared to be in close agreement with the general trend of *anti*-stereochemistry observed in enone-olefin radical cyclizations (chapter 1). Beckwith's model[11] suggests that under kinetic control, the cyclization of intermediate **18** should give cyclized compound with *syn*-appendages (**28**). However, the predominant *trans*-diastereoselectivity in the formation of **19** led us to postulate that initially produced *syn*-intermediate **23** is less stable that gets transformed to thermodynamically more stable *anti*-intermediate **26** due to the resonance stabilization of ester enolate ketyl radical (**18**) as shown in **Scheme-7**. In sharp contrast to the enone-olefin cyclisations, no further cyclisation from the intermediate **23** is observed in this case. Formation of minor diastereomer with *syn*-appendages (**28**) is also noticed. The formation of minor *syn*-monocyclized diastereomer could only be explained by considering the partial termination of radical intermediate **23** by H-abstraction in competition with its equilibration with *anti*-intermediate **18** (**Scheme-10**).

Scheme 10



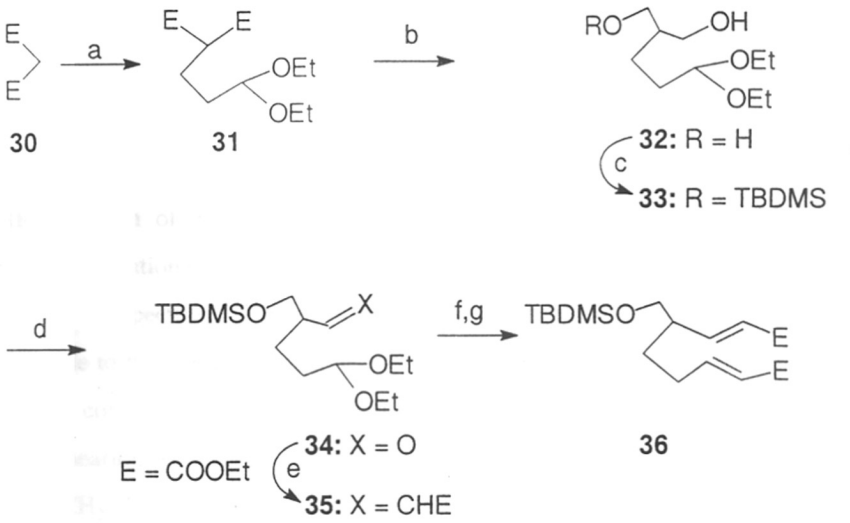
It is possible that the rate of the termination of radical species in intermediate **23** by H-abstraction is faster than its further cyclization to ester enolate double bond because of less electron density in the ester enolate double bond compared to enolate double bond (cf. Chapter-1).

To establish the generality of such cyclisations for the formation of five membered carbocycles, substrates diethyl-4-t-butyldimethylsilyloxymethyl-2(E),7(E)-nonadien-1,9-dioate (**36**) and 9-oxo, 9-carboethoxy-2(E),7(E)-nonadienenitrile (**40**) were selected.

2.4. Preparation of diethyl-4-t-butyl-dimethylsilyloxymethyl-2(E),7(E)-nonadien-1,9-dioate (36) :

Compound **36** was prepared by following the steps as shown in the **Scheme-11**

Scheme-11



Reagents : (a) K_2CO_3, $ICH_2CH_2CH(OEt)_2$, CH_3CN, reflux, 12h; (b) LAH, THF, r.t., 8h; (c) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, r.t., 6h, 70%; (d) $(COCl)_2$, DMSO, Et_3N, -78° C, 100%; (e) Ph_3P=CHCOOEt, CH_2Cl_2, r.t., 20h, 92%; (f) 5% HF, CH_3CN, 0° C, 5min, 84%; (g) Ph_3P=CHCOOEt, CH_2Cl_2, r.t., 20h, 88%

Wittig olefination of the corresponding aldehyde (**34**), obtained in 84 % yield from **33** by the treatment of 5 % aq HF in CH_3CN, with ethyl triphenylphosphoranylidene acetate gave **36** in 88 % yield. Compound **33** upon Swern oxidation produced corresponding aldehyde (**34**) which on subsequent Wittig olefination with ethyl

triphenylphosphoranylidene acetate gave **35** (92 %). Compound **31** was prepared by the alkylation of diethyl malonate (**30**) with 3,3-diethoxy-iodopropane using K_2CO_3 as a base in dry acetonitrile (70 %). LAH reduction of **31** gave corresponding diol (**32**) which on subsequent selective protection by TBDMSCl furnished **33** in 70 % yield.

2.5. PET Activation diethyl-4-t-butyl-dimethylsilyloxymethyl-2(E),7(E)-nonadien-1,9-dioate (36) :

PET activation of **36**, by following the experimental procedure as described earlier for **16**, gave cyclised products **37** as a mixture of two diastereoisomers (*trans:cis* 80:20) in 80% yield. The exact diastereomeric ratio of 37 was estimated by the GC analysis (capillary column, phenyl methyl silicone , 25 m) (**Scheme-12**).

Scheme-12

36 **37**

R = OTBDMS

IR spectrum of **37** showed prominent absorption band at 1720 (COO-) cm^{-1} confirming the retention of the ester moiety in the product.

^1H NMR spectrum (**Fig. 4**) displayed a quartet at δ 4.15 (four protons, J = 7.3 Hz), assignable to the methylene protons of ester groups. A multiplet appearing at δ 3.55 (two protons), corresponds to the methylene protons of -C<u>H</u>$_2$OTBDMS group. A bunch of multiplets appearing between δ 2.6-1.35 (ten protons) is assigned to the four methylene protons of CH_2COO- and six protons of cyclopentane ring. Remaining one proton of cyclopentane ring and six methyl protons of the ester moieties appeared as a multiplet at δ 1.2. Another singlet at δ 0.9 is attributed to the nine methyl protons of *t*-butyl group. Remaining six methyl protons of -TBDMS group appeared as a singlet at δ 0.05.

The ^{13}C NMR spectrum of 37 (major isomer) (**Fig. 5**) showed fourteen carbon signals whose characterization is based upon the INEPT experiment. Down field quaternary carbon appearing at δ 172.74, corresponds to two -<u>C</u>OO- groups. Three methine carbons appeared at δ 47.64, 44.06 and 42.65, respectively. Methylene carbons appearing at δ 65.95 and 59.97 are assigned to -<u>C</u>H$_2$OTBDMS and -COO<u>C</u>H$_2$,

respectively. Methylene carbon signals of two $\underline{C}H_2COO$- groups appeared at δ 39.40 and 38.83, respectively. Remaining three methylene carbon signals of cyclopentane ring are observed at δ 31.17, 27.47, respectively. A signal appearing at δ 14.14 is assigned to the methyl carbon of ester moieties. Another signal appearing at δ 18.20 is attributed to the quaternary carbon of TBDMS group. Methyl signals of t-butyl group are observed at δ 25.87. The other two methyl signals of TBDMS group appeared at δ -5.51.

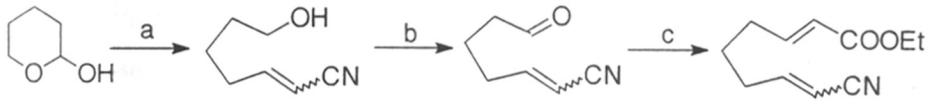
Similarly, for minor isomer, a down field signal appearing at δ 172.74 is characterised to the quaternary carbons of -$\underline{C}OO$- moieties (2C). Another three signals appearing at 45.86, 43.50 and 41.16 are assigned to the methine carbons (3C). Methylene carbons of -$\underline{C}H_2$OTBDMS and -COO$\underline{C}H_2$- groups appeared at δ 63.59 and 59.97, respectively. Another two signals appearing at δ 35.41 and 35.12 are characterised to the methylene carbons of $\underline{C}H_2COO$- (2C) moieties. Remaining two methylene carbon signals of cyclopentane ring appeared at δ 30.12 and 26.49. Methyl carbons of ester moieties and *t*-butyl group are observed at δ 14.14 and 25.87, respectively. The other two methyl signals of TBDMS group appeared at δ -5.51. Quaternary carbon of TBDMS group appeared at δ 18.20.

Mass spectral analysis (**Fig. 6**) did not show intense molecular ion peak. First intense fragment ion peak is observed at 371 (M^+ - Me) with 3% intensity and the base peak is found at 329 (M^+- *t*-Bu). The other prominent fragmentation peaks are observed at 341 (16%, M^+- OEt), 255 (7%, M^+- OTBDMS), 209 (!2%), 181 (12%), 167 (15%), 135 (19%), 107 (26%), 93 (29%), 75 (50%).

2.6. Preparation of 9-oxo-9-ethoxy-2(E),7(E)-nonadienenitrile (40):

Substrate **40** was easily obtained in 92 % yield by the Wittig reaction of **39** with ethyl triphenylphosphoranylidene acetate in CH_2Cl_2 at r.t. for 48 h (**Scheme-13**).

Scheme-13



20 **38** **39** **40**

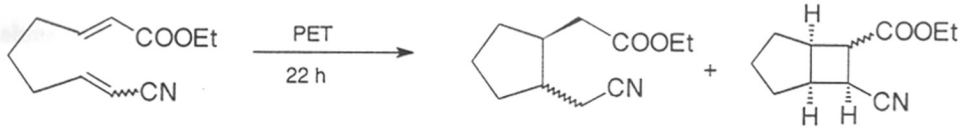
Reagent : (a) Ph_3P=CHCN, CH_2Cl_2, r.t., 48h, 96%, (E : Z = 72 : 28); (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 100%; (c) Ph_3P=CHCOOEt, CH_2Cl_2, r.t., 24h, 92%, (E : Z = 70 : 30)

Compound **39** was prepared by the Swern oxidation of 7-hydroxy-2-heptinonitrile (**38**), prepared by the Wittig olefination of 2-hydroxy pyran (**20**) with triphenylphosphoranylidene acetonitrile (96 %).

2.7. PET activation of 9-oxo-9-ethoxy-2(E),7(E)-nonadienenitrile (40):

Identical PET reductive activation of **40**, as described for **16**, resulted expected product **41** as a mixture of two diastereoisomers (*trans:cis* 80:20) in 75% yield and another minor compound **42** (10 %) also as a mixture of diastereomers (*dr* 3:2) (**Scheme-14**) .

Scheme-14



40 **41** **42**

IR spectrum of **41** indicated the loss of the conjugated double bonds. It showed prominent absorption bands at 1730 and 2360 cm^{-1} corresponding to COO- and CN groups, respectively.

The ^{1}H NMR (**Fig. 7**) confirmed the absence of conjugated double bond. It displayed a quartet at δ 4.15 (J = 7.3 Hz) integrating for two protons, assignable to the methylene protons of ester moiety. A bunch of multiplets appearing between δ 2.6-2.15 (four protons) could be assigned to the methylene protons of $-CH_2COO-$ and $-CH_2CN$ groups, respectively. Another bunch of multiplets appearing between δ 2.1-1.58 (six protons) is assigned to the six protons of cyclopentane ring. Remaining two protons of cyclopentane ring appeared as a multiplet at δ 1.5-1.2. Methyl protons of ester moiety appeared as a triplet at δ 1.3 (J = 7.3 Hz).

The ^{13}C NMR (**Fig. 8**) of **41** revealed two sets of carbon signals which indicated **41** to be a non-separable mixture of two diastereoisomers. First set corresponding to major diastereomer, displayed twelve carbon signals whose characterisations are made by INEPT experiment. Down field quarternary carbon appearing at δ 172.45 is characterised to -$\underline{C}$OO- moiety of ester group. Another signal appearing at δ 118.89 is assigned to the quarternary carbon of -$\underline{C}$N group. Methylene carbon signals of -COO$\underline{C}H_2$-, $\underline{C}H_2$COO- and

-$\underline{C}H_2CN$ groups appeared at δ 60.39, 38.04 and 32.36, respectively. Another two signals appearing at δ 41.50 and 41.21 are assigned to the methine carbons. Remaining three methylene carbon signals of cyclopentane ring are observed at δ 31.95, 23.33 and 21.78. A signal appearing at δ 14.15 is assigned to the methyl carbon of ester moiety.

Similarly for minor isomer, two signals appearing at δ 172.45 and 118.89 are characterised to the quarternary carbons of -$\underline{C}OO$- and -$\underline{C}N$ groups, respectively. Another two signals appearing at δ 38.60, 38.18 are assigned to the methine carbons. Methylene carbons of -$COO\underline{C}H_2$-, $\underline{C}H_2COO$- and -$\underline{C}H_2CN$ groups appeared at δ 60.39, 34.86 and 30.49, respectively. Remaining methylene carbons appeared at δ 29.90, 22.08 and 18.03, respectively. Methyl carbon of ester moiety is observed at δ 14.15.

Mass spectral analysis (**Fig. 9**) indicated M^+ +1 peak at 195 with 1 % intensity along with base peak at 80 [M^+ - 88 (MacLaffarty fragment) - HCN] . The other prominent fragmentation peaks are found at 155 (9 %, M^+ - CH_2CN), 150 (27 %, M^+ - OEt), 122 (9 %, M^+ - COOEt), 109 (16 %), 88 (65 %), 67 (35 %), 61 (54 %), 54 (50 %).

IR spectrum of the minor bicyclic product (**42**) showed prominent absorptions at 2236 and 1731 cm^{-1}, corresponding to -CN and COO- groups, respectively.

The proton NMR (**Fig. 10**) of **42** displayed a multiplet between δ 4.4-4.1, integrating for two protons, assigned as the methylene protons of ester group. Methine protons of -$\underline{C}HCN$, -$\underline{C}HCOOEt$ groups and another two protons of cyclopentane ring appeared as bunch of multiplets between δ 3.75-3.6 (0.5 proton) and 3.35-2.2 (3.5 protons). Remaining protons of cyclopentane ring appeared as a bunch of multiplets between δ 2.1-1.88 and δ 1.85-1.45, respectively. Methyl protons of ester moiety are observed as a multiplet between δ 1.4-1.15.

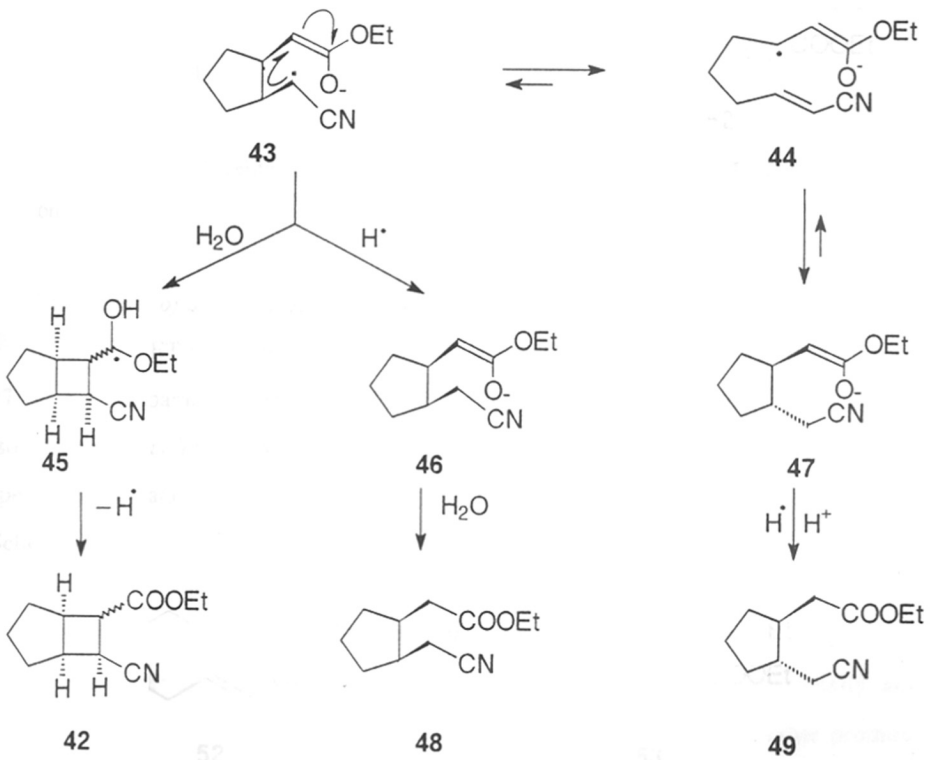
The ^{13}C NMR (**Fig, 11**) revealed two sets of carbon signals which indicated **42** to be a non-separable mixture of two diastereoisomers. It gave correct accounting of the different types of carbons for the structure corresponding to **42**. First set corresponding to the major diastereomer, displayed eleven carbon signals whose characterisation are made by INEPT experiment. Down field quarternary carbon appearing at 172.43 is characterised to the -$\underline{C}OO$- moiety of ester group. Another signal appearing at 118.56 is assigned to the quarternary carbon of -$\underline{C}N$ group. Methylene carbon signal of -$COO\underline{C}H_2$- appeared at δ 61.25. Another four signals appearing at δ 44.22, 42.02, 36.74 and 24.66 are assigned to the methine carbons. Remaining three methylene carbon signals of cyclopentane ring are

observed at δ 32.34, 29.08 and 25.03. A signal appearing at δ 14.1 is assigned to the methyl carbon of ester moiety.

Similarly, in the second set of carbon signals which corresponds to the minor isomer of **42**, two signals appearing at δ 171.2 and 119.9 could be assigned to the quarternary carbon of -COO- and -CN groups, respectively. Methine carbons (4C) appeared at δ 42.57, 41.38, 38.96 and 27.66. A signal appearing at δ 61.25 is characterised to the methylene carbon of $-COOCH_2-$ group. Remaining methylene carbons of cyclopentane ring appeared at δ 31.98, 31.77 and 24.51. Methyl carbon of ester moiety is observed at δ 14.1.

Mass spectral analysis (**Fig. 12**) gave molecular ion peak at 193 with 1 % intensity, along with base peak at 68 (M^+ - CNCHCHCOOEt). The other prominent fragmentation peaks were found at 148 (12 %, M^+ - OEt), 120 (35 %, M^+ - COOEt), 98 (33 %), 93 (44 %), 80 (24 %), 53 (27 %).

The formation of minor bicyclic diastereomer **42**, in contrast to the cyclisation as **Scheme-15**



observed from **16**, could only be explained by considering the partial cyclisation of the radical intermediate **43** in competition with its termination by H-abstraction (**Scheme-15**). Probably the rate of termination of radical species in the intermediate **43** by H-abstraction is slower than its cyclization to ester enolate double bond due to the greater electrophilic nature of the α-cyano radical compared to that of α-ester radical (**scheme-10**).

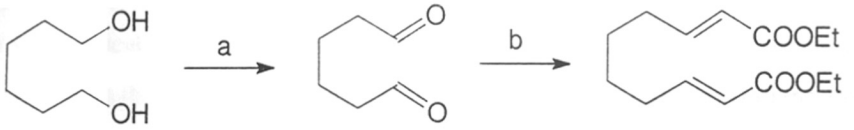
2.8. Construction of 1,2-disubstituted cyclohexane derivatives :

In order to evaluate the scope of this strategy for the construction of six-membered carbocyclic ring systems, substrate 52 was selected.

2.8.1. Preparation of diethyl-2(E), 8(E)-decadien-1,10-dioate (52):

Substrate **52** was easily synthesized in 92% yield by the Wittig olefination of adipaldehyde (**51**), prepared from the oxidation of 1,6-hexanediol (**50**) by PCC, with ethyl triphenylphosphoranylidene acetate (**Scheme-16**).

Scheme-16



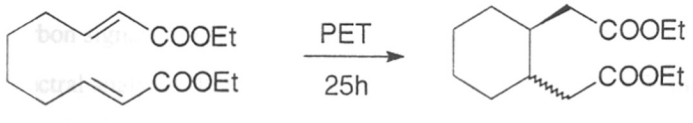
50 **51** **52**

Reagents: (a) PCC, celite, CH_2Cl_2, r.t. 80%, (b) , Ph_3P=CHCOOEt, CH_2Cl_2, r.t., 48h, E-isomer 86%

PET Activation of diethyl-2(E),8(E)-decadien-1,10-dioate (52):

Usual PET reductive activation of **52** yielded monocyclized product **53** (**Scheme-17**) as a nonseparable mixture of two diastereoisomers with *trans*-appendages as major isomer (*trans:cis* 75:25) which was characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic data

Scheme-17



52 **53**

IR spectrum of **53** indicated the loss of conjugated double bonds. It showed prominent absorption band at 1718 cm^{-1} corresponding to ester carbonyl groups.

^1H NMR (**Fig. 13**) of **53** confirmed the absence of acrylate double bonds. It displayed a quartet at δ 4.12 (four protons, J = 7.2 Hz), assigned as methylene protons of ester groups. A doublet of a doublet appearing at δ 2.5, integrating for one proton (J = 14.6, 4 Hz), is attributed to one of the methylene protons of $C\underline{H}_2COO$- group. Another doublet of a doublet at δ 2.1, integrating for one proton (J = 14.6, 8.8 Hz), corresponds to the other protons of the same $C\underline{H}_2COO$- group. A multiplet appearing at δ 2.2 (two protons) is assigned to the methylene protons of the other $C\underline{H}_2COO$- group. Protons of the cyclohexyl ring (ten protons) appeared as a bunch of multiplets between δ 1.85-1.05. A triplet at δ 1.26 (J = 7.2 Hz) integrating for six protons is assigned to the methyl protons of ester groups.

^{13}C NMR spectrum (**Fig. 14**) revealed two sets of carbon signals, each set corresponds to the respective diastereoisomer. Compound **53** having symmetry elements *viz.* C_2- axis of symmetry (*trans* isomer) or plane of symmetry (*cis* isomer), carbon signals of the symmetrical carbons appeared at one single position. First set of carbon signals corresponding to the major isomer, showed seven signals whose characterizations are done by INEPT experiment. Downfield quaternary carbon appearing at δ 172.4 is characterised to -$\underline{C}$OO- moieties of ester groups (2C). Two methine carbons appeared at δ 38.76. Methylene carbons appearing at δ 59.73, 38.82 are assigned to -O$\underline{C}H_2$- (2C) and $\underline{C}H_2COO$- (2C), respectively. Remaining four methylene carbon signals of cyclohexane ring are observed at δ 32.10 (2C) and 25.57 (2C). Methyl carbon signals of ester moieties appeared at δ 13.91 (2C).

Similarly, for the minor isomer, a down field signal appearing at δ 172.4 is characterised to the quaternary carbons of ester groups (-$\underline{C}$OO-, 2C). Another signal appearing at δ 35.12 is assigned to the methine carbons (-$\underline{C}$H-, 2C). Methylene carbons of -O$\underline{C}H_2$- (2C) and $\underline{C}H_2COO$- (2C) groups are observed at δ 59.73 and δ 35.44, respectively. Remaining methylene carbons of cyclohexyl ring appeared at δ 28.58 (2C) and δ 22.88 (2C). Methyl carbon signals of ester moieties appeared at δ 13.91 (2C).

Mass spectral analysis (**Fig. 15**) gave M^+ +1 peak at 242 with 4 % intensity, along with base peak at 95 [M^+ - 88 (MacLaffarty fragment) - COOEt]. The other prominent fragmentation peaks are found at 211 (64 %, M^+-OEt), 182 (28 %, M^+ - HCOOEt), 169

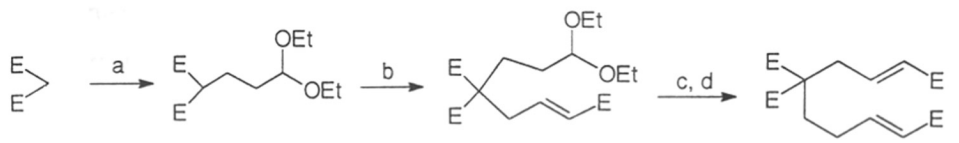
(99 %, M^+ + 1- 88), 168 (57 %), 123 (90 %), 122 (55 %), 94 (58 %), 88 (45 %), 81 (96 %), 67 (58 %) and 55 (60 %).

To establish the generality of six membered carbocyclisation reaction through this strategy , substrate **56** was also included in our study.

2.8.3. Preparation of diethyl-5,5-dicarboethoxy-2(E),8(E)-decadien-1,10-dioate (56):

Substrate **56** was prepared by the Wittig reaction of corresponding aldehyde obtained from the hydrolysis of the acetal **55** with ethyl triphenylphosphoranylidene acetate. Compound **55** was prepared by the double alkylation of diethylmalonate (**30**) with 3,3-diethoxy-iodoprpane[12] and ethylbromocrotonate (**Scheme-18**).

Scheme-18



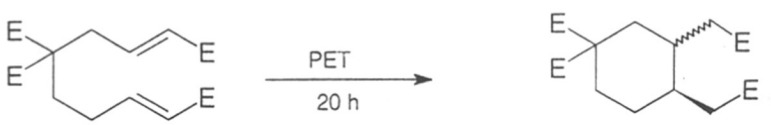
30 **54** **55** **56**

Reagents : (a) K_2CO_3, $ICH_2CH_2CH(OEt)_2$, CH_3CN, reflux, 12h; (b) NaH, THF, $BrCH_2CH$=$CHCOOEt$, 50 °C, 77%; (c) 5% aq HF, CH_3CN, 0 °C, 5min, (d) Ph_3P=$CHCOOEt$, CH_2Cl_2, r.t., 1d, 88%

2.8.4. PET Activation of diethyl-5,5-dicarboethoxy-2(E),8(E)-decadien-1,10-dioate (56):

Usual PET reductive activation of **56** yielded monocyclized product **57** (**Scheme-19**) as a nonseparable mixture of two diastereoisomers with *trans*-appendages as major isomer (*trans:cis* 70:30) which was characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic data.

Scheme-19



56 **57**

IR spectrum of **57** indicated the loss of conjugated double bonds. It showed prominent absorption band at 1720 cm^{-1} corresponding to COO- groups.

The ^{1}H NMR (**Fig. 16**) of **57** displayed a multiplet between δ 4.35-4.02, integrating for eight protons, assigned as the methylene protons of ester groups. Another multiplet appearing between δ 2.67-2.42 (2H) could be characterised to two of the methylene protons of -C<u>H</u>$_2$COO- groups. Remaining two protons of -C<u>H</u>$_2$COO- groups and another three protons of cyclohexane ring appeared as a bunch of multiplets between δ 2.4-1.98. Another bunch of multiplets appearing between δ 1.95-1.48 could be assigned to the remaining five protons of cyclohexane ring. Methyl protons of ester moieties are observed as a multiplet between δ 1.4-1.15 (12H).

The ^{13}C NMR (**Fig. 17**) revealed two sets of carbon signals which indicated **57** to be a non-separable mixture of two diastereoisomers The exact ratio of diastereomers for **57** (70:30) was obtained by the GC analysis. First set corresponding to the major diastereomer, displayed fourteen carbon signals whose characterisations are made by INEPT experiment. Two pairs of down field signals appearing at δ (172.90, 172.57) and δ (172.14, 171.91) are characterised to the quarternary carbons of -CH$_2$<u>C</u>OO- groups and that of -<u>C</u>OO- moieties. Methylene carbon signals of -COO<u>C</u>H$_2$- groups appeared at δ 61.37, 61.30 and 60.35 (2C). Another signal appearing at δ 54.90 is assigned to the C-5 quarternary carbon. Methylene carbon signals of <u>C</u>H$_2$COO- groups appeared at δ 38.68 (2C). Another two signals appearing at δ 37.94 and 35.59 are characterised to the methine carbons. Remaining three methylene carbon signals of cyclohexane ring are observed at δ 36.77, 31.76 and 28.80. A signal appearing at δ 14.22 is assigned to the methyl carbons of ester moieties.

Similarly, in the second set of carbon signals which corresponds to the minor isomer of **57**, two pairs of down field signals appearing at δ (172.14, 171.91) and δ (170.59, 170.5) correspond to the quarternary carbons of -<u>C</u>OO- moieties at C5 position and that of -CH$_2$<u>C</u>OO- groups, respectively. Methylene carbon signals of -COO<u>C</u>H$_2$- groups appeared at δ 61.17, 61.05 and 60.35 (2C). Another signal appearing at δ 54.71 is assigned to the C5 quarternary carbon. A signal appearing at δ 38.16 is attributed to the methylene carbon signals of <u>C</u>H$_2$COO- groups (2C). Another two signals appearing at δ 33.50 and 32.95 are characterised to the methine carbons. Remaining three methylene carbon signals of cyclohexane ring are observed at δ 30.71, 26.48 and 25.68. Methyl carbons of ester moieties appeared at δ 14.04 .

Mass spectral analysis (**Fig. 18**) gave molecular ion peak at 400 with 5 % intensity, along with base peak at 313 (M^+ - CH_2COOEt). The other prominent fragmentation peaks are found at 355 (28 %, M^+ - OEt), 281 (20 %), 267 (53 %), 239 (27 %), 207 (33 %), 193 (50 %), 165 (36 %), 105 (21 %), 91 (21 %) and 55 (7%).

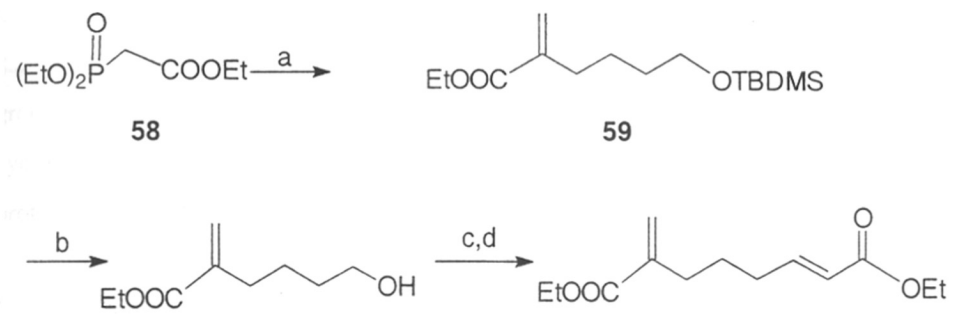
2.9. Evaluation of the cyclisation strategy for 6-Endo-trig cyclisation :

From the above examples, it is apparent that these cyclizations follow well established 5- and 6-*exo-trig* radical cyclization rules.[12] These rules also suggest that 5-*endo-trig* cyclisation is a disfavoured process which has been proved by us earlier in the case of enone-olefin cyclisations[1b]. In order to evaluate the validity of the radical intermediate in such cyclisations we further examined the 6-*endo-trig* mode of radical cyclization by selecting substrate diethyl-7-methylidene-2(E)-octen-1,8-dioate (**61**) whose 6-*endo* position is highly activated as radical acceptor.

2.9.1. Preparation of diethyl-7-methylidene-2(E)-octen-1,8-dioate (61) :

Compound **61** was prepared in three steps starting from triethylphosphonoacetate (**58**). One pot alkylation of **58** with 4-*tert*-butyldimethylsilyl-oxy-iodobutane followed by Wittig-Horner olefination of the intermediate with paraformaldehyde using NaH as base yielded 54% of 5-*tert*-butyldimethylsilyloxy-2-methylenehexanoate[13] (**59**).

Scheme-20



58 **59** **60** **61**

Reagents : (a) (i) NaH, $I(CH_2)_4OTBDMS$, C_6H_6, reflux, 9h, (ii) NaH, $(CH_2O)n$, r.t., overnight, 54%; (b) TBAF, THF, 0 °C, 94%; (c) $(COCl)_2$,DMSO, Et_3N, CH_2Cl_2, -78 °C, (d) Ph_3P=CHCOOEt,CH_2Cl_2, r.t., 1d, 91%.

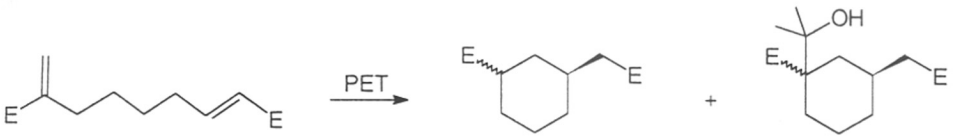
Desilylation of **59** using 48% HF solution in CH_3CN at r.t. gave ethyl-6-hydroxy-2-methylene heptanoate (**60**, 94%). Diethyl-7-methylidene-2(E)-octen-1,8-dioate (**61**) was

prepared in 91% yield by the Wittig reaction of the aldehyde obtained by the Swern oxidation of **60**, with ethyl-triphenyphosphoranylidene-acetate (**Scheme-20**).

2.9.2. PET activation of 61 :

When compound **61** was subjected to the usual PET activation using **PS-B** system, cyclized product **62** (non-separable mixture of two isomers in 3:2 ratio, 60 %) along with minor amount of product **63** (5 %) were isolated (**Scheme-21**). Compound **62** and **63** were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic data.

Scheme-21



61 **62** **63**

IR spectrum of **62** indicated the loss of conjugated double bond. It showed prominent absorption band at 1720 cm^{-1} corresponding to ester carbonyl groups.

^{1}H NMR (**Fig. 19**) of **62** displayed a multiplet at δ 4.15 (four protons), assignable to the methylene protons of ester groups. A bunch of multiplets appearing between δ 2.75-2.2 (three protons) could be assigned to the protons of -CHCOOEt and -CH_2COOEt groups, respectively. Another bunch of multiplets corresponding to seven protons of cyclohexyl ring appeared at δ 2.15-1.25. Remaining protons of cyclohexyl ring and methyl protons of ester moieties are observed as a bunch of multiplets at δ 1.3-1.05.

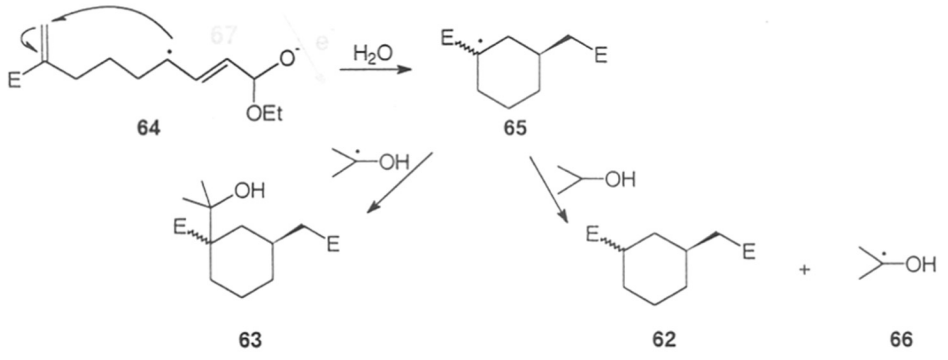
Mass spectral analysis (**Fig. 20**) gave molecular ion (M^+) peak at 242 with 8 % intensity along with base peak at 168 [M^+ - HCOOEt]. The other prominent fragmentation peaks are found at 181 (17 %), 154 (57 %), 122 (47 %), 109 (41 %), 95 (60 %), 81 (60 %), 55 (51 %).

For details of the spectral characterisation of **63**, see experimental section.

Formation of the minor product (**63**) could be explained by considering the competitive partial termination of the radical intermediate **65** by 2-hydroxy-*iso*-propyl radical (**66**) formed by donating one H· to **65** during formation of the major product **62**.

(**Scheme-22**). Formation of **63** provides further support and confirmation for the involvement of radical intermediate of the type **64** during the PET reductive cyclisation of **61**.

Scheme-22

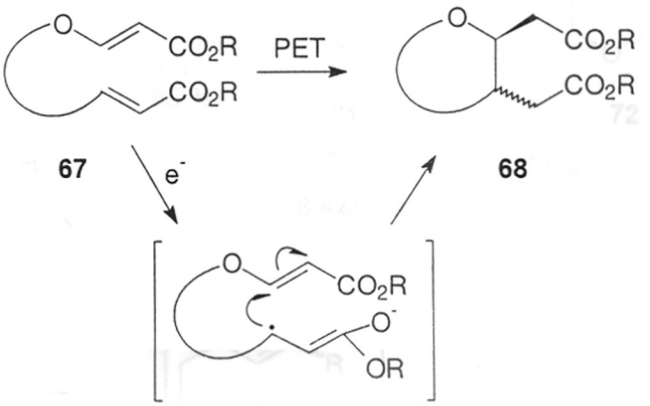


It may be worth emphasizing here that the activation of **52**, **56**, and **61** led to the smooth cyclisations to produce corresponding six-membered carbocyles in contrast to the failure reported[5] for the reaction by Mg/MeOH reduction system. This observation clearly indicates that this chemistry is operating mechanistically different than the reported[5] in the Mg/MeOH cases where anionic moiety of radical anion generated has participated. Sufficient evidence regarding the involvement of radical intermediate for the cyclisations in our case is already provided in the last chapter as well as in the preceding discussion.

3. Stereoselective Synthesis of 2,3-Disubstituted Cyclic Ethers

From the previous discussion it is apparent that we have established a new strategy for the activation of α, β-unsaturated esters as carbon centered radicals at its β-position by one electron reductive activation utilizing photosystems **PS-A** or **PS-B** which undergoes efficient intramolecular cyclizations with tethered activated olefins to provide cycloalkanoids. This expectacular succeess encouraged us to extend this methodology for the construction of some of the common subunits of naturally occurring carbocylic acid ionophores, specially, *trans*-2,3-disubstituted tetrahydrofurans and tetrahydropyrans[14], through the approach as shown in **Scheme-23**.

Scheme-23



R = Et or Me **69**

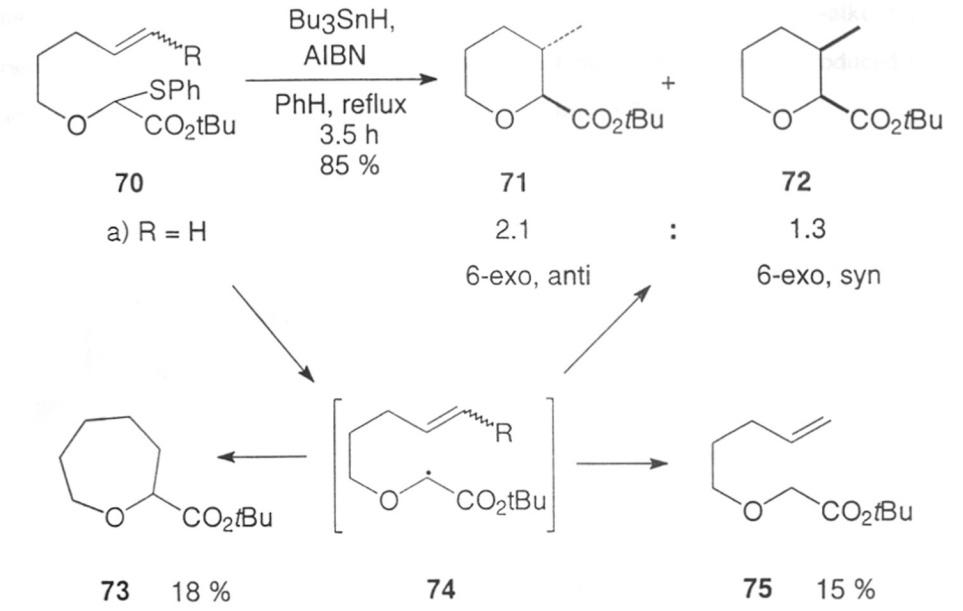
However, before dwelling upon our results, it would be pertinent to append a brief introduction concerning the importance and the methodologies known in the literature for the construction of 2,3-disubstituted cyclic ethers.

Due to the prevalence of O-heterocycles, particularly, 2,3-disubstituted hydropyran and hydrofuran subunits, in numerous polyether antibiotics[15] and ionophore natural products[16], these compounds have been the frequent and important targets for synthetic organic chemists.[17] Owing to the volumnous literature available on the syntheses of these cyclic ethers, only few and appropriate examples are presented in this section to highlight the approaches utilized in this context.

(a) ***Radical approach:***

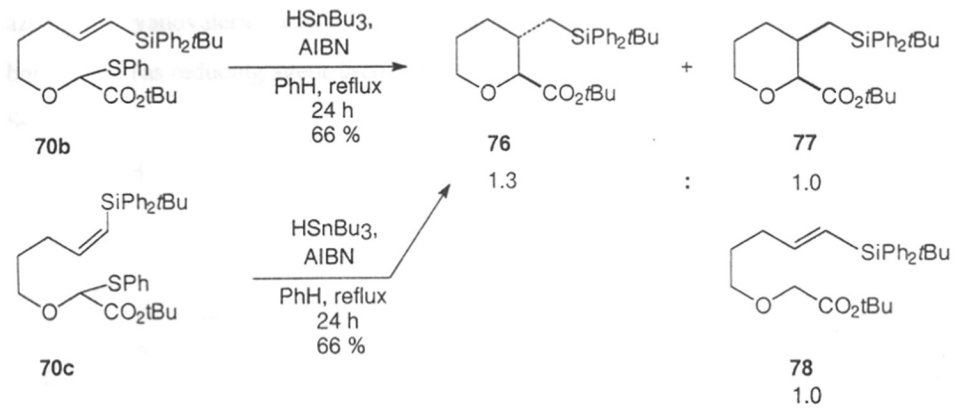
Burke and coworkers[18] have reported the synthesis of 2,3- disubstituted tetrahydropyrans by the intramolecular addition of an α-alkoxymethyl radical (**73**), generated by the C-S bond homolysis of **70** using Bu_3SnH, to the tethered olefin as shown in **Scheme-24**. The stereoselectivity of the products are dependent on the substituents as well as on the geometry (E/Z) of the olefin. For example, when R = H, (**70a**) pyrans **71** and **72** are produced in the 2.1:1.3 ratio. During this reaction small amounts of 7-*endo-trig* product (18 %) and reduced product (15 %) are also formed.

Scheme-24



The silicone substituents (R = $SiPh_2tBu$) on the olefin such as **70b** and **70c** are found to suppress the 7-*endo* mode of cyclization in comparison to **70a.** Addition of α-alkoxymethyl radical derived from (**70b**) has been shown to be relatively less selective (76:77 1.3:1) in comparison to **70c** where *anti*-diastereomer **(76)** predominates **(Scheme-25).**

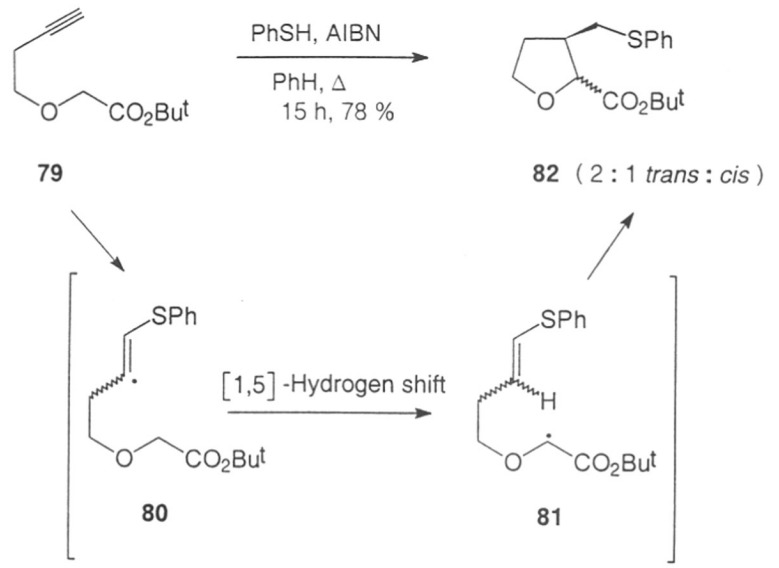
Scheme-25



Although, this report has made a valuable contribution in this regard, it can not be made general as the selectivity depends on several factors, moreover, it utilizes toxic Bu_3SnH as a reagent.

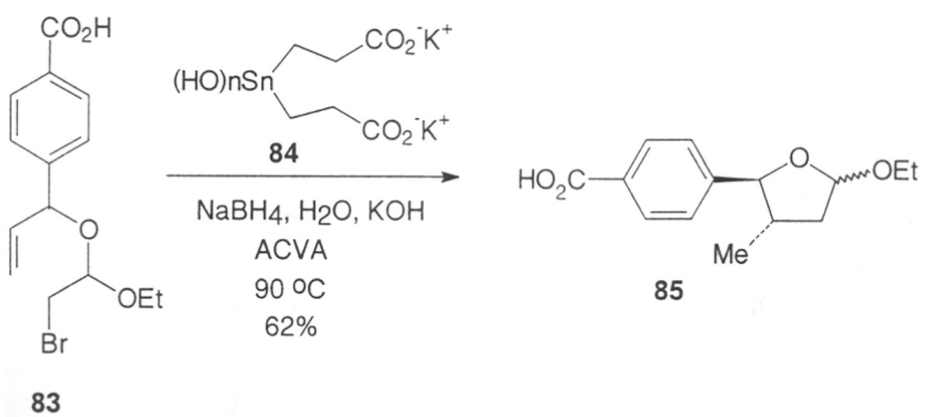
The same group have further reported[19] the diastereoselective synthesis of tetrahydrofurans **82** in a ratio of 2:1 (*trans:cis*) by the cyclisation the α-alkoxymethyl radical **81**, generated by the radical translocation of the intermediate **80** produced by the addition of thiophenoxy radical, to triple bond terminus of **79**. **(Scheme-26)**.

Scheme-26



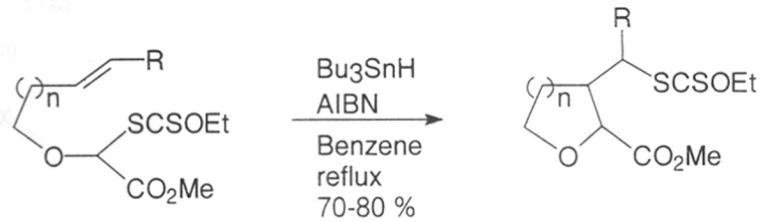
Synthesis of 5-(4-carboxyphenyl)-4-methyl-2-ethoxy-tetrahydrofuran (**85**) with *trans* stereoselectivity is reported[20] by the *endo-trig* cyclisation of a radical produced from **83**, initiated by the *in situ* generated tin radical species obtained from **84** by using 4,4′-azobis (4-cyanovaleric acid) (ACVA) as initiator and in the presence of sodium borohydride as reducing agent (**Scheme-27**).

Scheme-27



Substituted tetrahydrofurans as well as tetrahydropyrans (**87**) are also synthesised[21] by the xanthate group transfer radical cyclisation of 2-(alken-1-oxy)-2-[(ethoxythio-carbonyl)sulfanyl]acetic acid methyl esters (**86**) using di-*tert*-butyl peroxide as initiator (**Scheme-28**).

Scheme-28



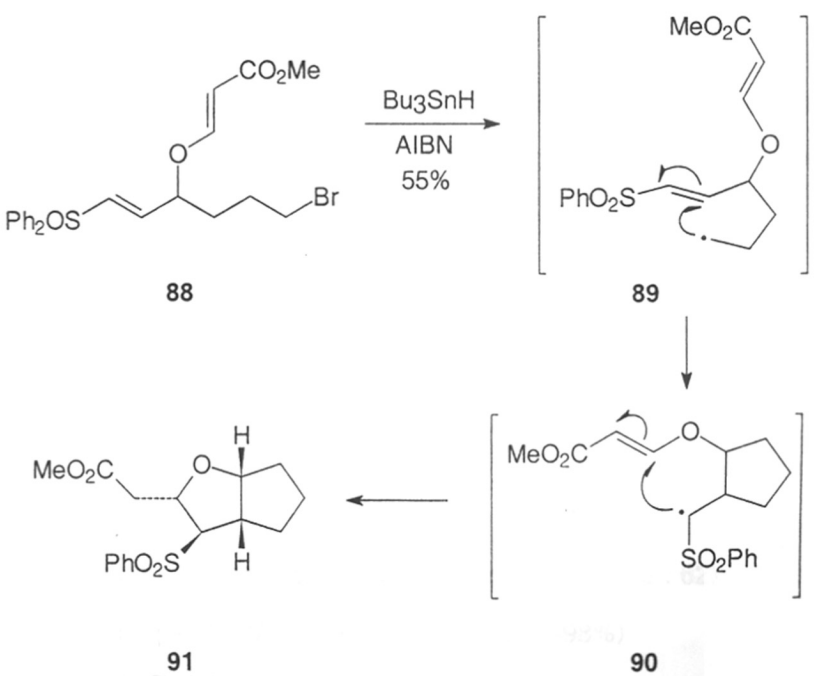
86 **87**

a) R = H, n = 1 *cis* : *trans* = 56 : 44

b) R = H, n = 2 *cis* : *trans* = 25 : 75

Although, the cyclisation of **86** (R = H, n = 2) is shown to give comparable regio- and stereoselectivity as reported by Burkey et al[18], however, the stereoselectivity, in sharp contrast, is shown not to depend on the olefin geometry.

Scheme-29



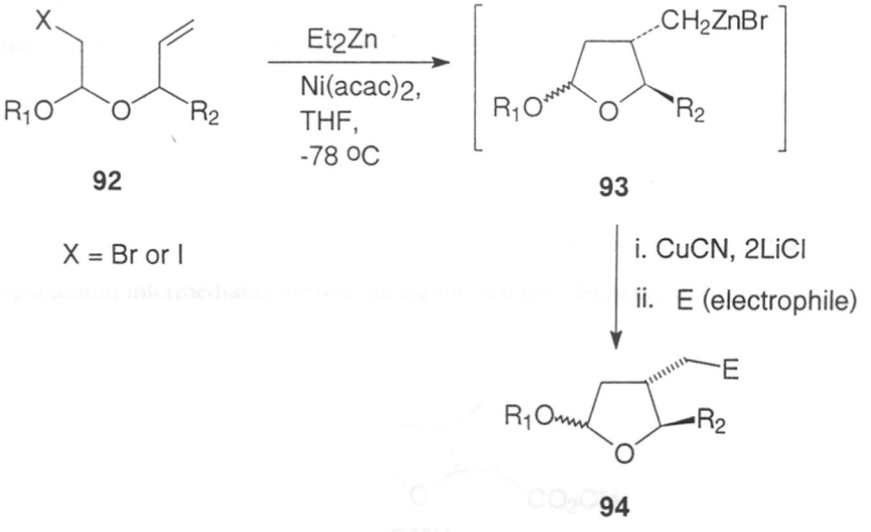
88 **89**

91 **90**

Fused tetrahydrofuran **91**, has also been synthesised[22] by the radical mediated tandem cyclisation from **88** as shown in **Scheme-29**.

Vaupel and Knochel[23] have reported the syntheses of substituted tetrahydrofurans **94** in > 99:1 ratio by the nickel catalysed carbozincation of 2-iodo and 2-bromoethyl allyl ethers of the type **92** in the presence of diethyl zinc. This cyclisation is suggested to proceed by a radical mechanism initiated by nickel catalyst (**Scheme-30**).

Scheme-30



92 **93**

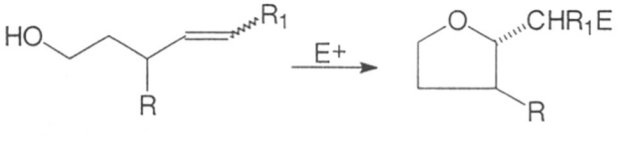
X = Br or I

94

(b) Electrophile mediated cyclisation approach:

Liotta etal[24] have reported the syntheses of substituted tetrahydrofurans **96a** and **96b** by an electrophile mediated cyclisation of γ-hydroxy alkenes utilizing a variety of electrophiles [NBS, I_2, mercury (II) acetate, $PhSe^+$ etc].

Scheme-31



95 **96**

a) R_1 = H, R = Me, E^+ = I^+ (trans : cis = 32 : 62)

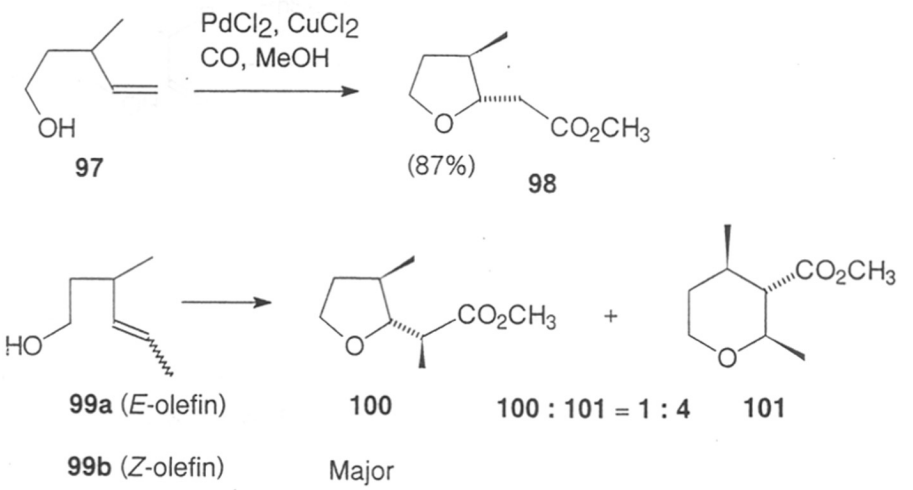
b) R_1 = R = Me, E^+ = I^+ (trans >98%)

with *Z*-olefin

It has been shown that alkyl group at allylic position does not have significant influence on the cyclisation stereochemistry (**96a**), though, the olefin geometry exerts substantial influence on the product distribution. For example, *trans* isomer **96-b** is formed exclusively from a substrate having *Z* methyl-olefin geometry (e. g. **95b**) (**Scheme-31**).

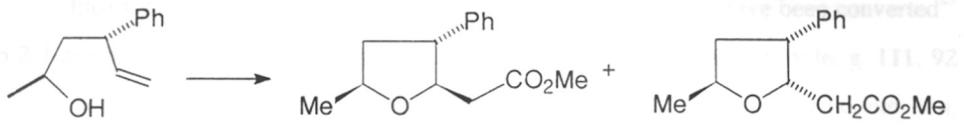
The same group[25] have further reported the syntheses of substituted tetrahydrofurans (**98**, **100**) and tetrahydropyrans (**101**) by an intramolecular alkoxy-palladation carbonylation reaction of γ-hydroxy alkenes (**97**, **99a-b**). Regio- and stereochemistry of products are demonstrated to depend upon the olefin geometry and substituent at allylic position. For example, **98** is produced exclusively from **97** having methyl group at allylic position. Substrate **99** with *E*-olefin geometry has been shown to give tetrahydropyran **101** as a major product whereas **99b** with *Z*-olefin geometry leads to the formation of tetrahydrofuran **100**. It is suggested that the regio- and stereochemistry of the major products of these reactions are determined by the relative energetics of various organopalladium intermediates formed during the reaction (**Scheme-32**).

Scheme-32



Similar oxopalladation carbonylation reaction has also been reported for the synthesis of tetrahydrofurans by Semmelhack[26] where both the 2,3-*trans* (**103**) and 2,3-*cis* (**104**) diastereomers are shown to be formed, in sharp contrast to the contemporary report by Liotta et al[25] where only 2,3-*trans* diastereomer (**103**) is suggested exclusively from the same starting olefin (**102**) (**Scheme-33**).

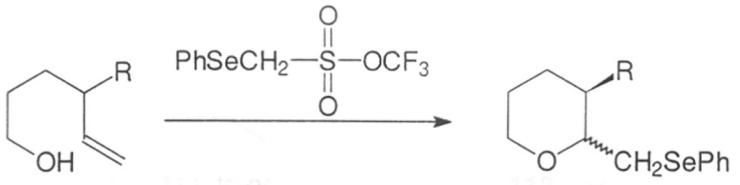
Scheme-33



102 **103** **104**

Inoue et al[27] **have** reported the syntheses of *cis* or *trans* 3-substituted, 2-(phenyl selenenyl **methyl)- tetrahydro**pyrans **106** by an electrophilic selenium, obtained from benzene selenenyl trifluoromethanesulfonate, mediated cyclisation of 4-substituted 5-hexen-1-ol (**105**), (R = Me, CMe, OH, 4-$MeOC_6H_4CO_2$- etc.). It has been shown that the *trans* isomer is favoured when the substituent at the 4-position is either alkyl or phenyl group whereas the *cis* isomer predominates when the substituents are alkoxyalkyl, alkoxy, acyl and hydroxyl groups (**Scheme-34**).

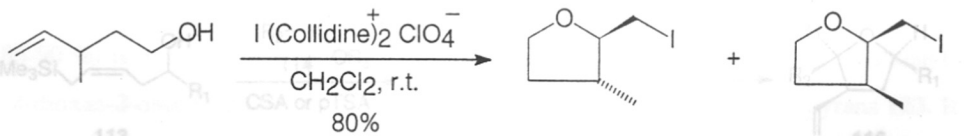
Scheme-34



105 **106**

Evans and co-workers[28] have also reported the syntheses of tetrahydrofurans **107**/ **108** (56:44) by the iodonium ion mediated cyclisation of unsaturated alcohol **91** employing bis (sym-collidine)-iodine (I) perchlorate [I $(collidine)_2^+$ ClO_4^-] as the source of iodonoium ion (**Scheme-35**).

Scheme-35



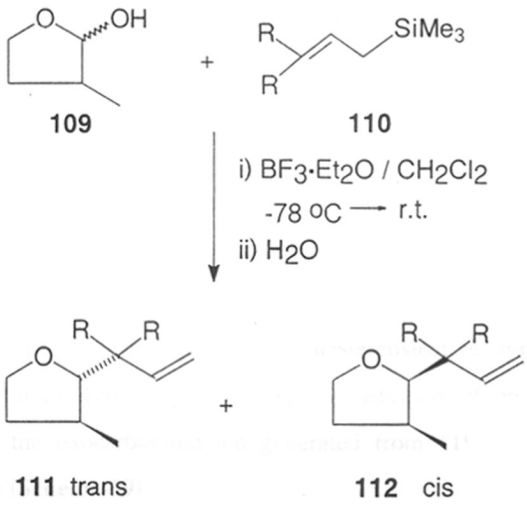
97 **107** **108**

56 : 44

(c) Oxonium ion cyclisation approach:

Easily available γ-lactols (2-hydroxy tetrahydrofurans) (**109**) have been converted[29] to 2,3-disubstituted tetrahydrofurans (**111**, **112**) in good diastereoselectivity (e. g. **111**, 92 %) by the nucleophilic addition of allyl trimethylsilanes (**110**) to the oxocarbonium ion, generated by the reaction of $BF_3.Et_2O$ on **109** (**Scheme-36**).

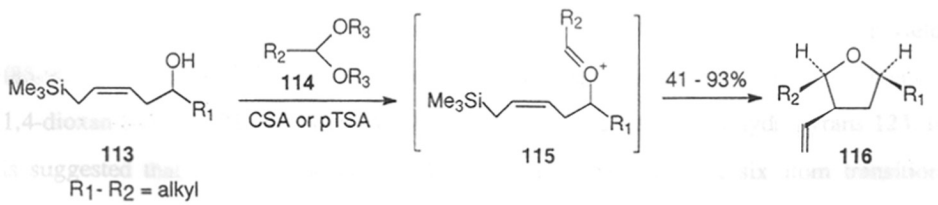
Scheme-36



a) R = H	68	:	32	(70%)
b) R = Me	96	:	4	(84%)

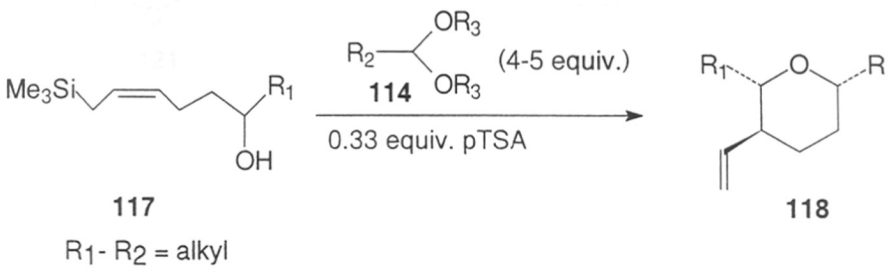
An interesting approach for the syntheses of substituted tetrahydrofurans (**116**), also reported by Mohr etal[30] by the nucleophilic reaction and cyclisation of allyltrimethyl silane moiety to the *in situ* generated oxocarbenium ion **115** as shown in **Scheme-37**.

Scheme-37



The intermediate **115** is generated by the Lewis acid catalysed addition of **113** to the acetal **114**. This strategy has produced all-*cis* tetrahydrofurans **116** in 41-93 % yield. The same strategy has further been extended[31] for the syntheses of regioselective tetrahydropyrans **118**, utilising the silanes **117**. In this case all the substituents of the pyrans (**118**) are shown to occupy equatorial orientations predominantly with > 95% diastereocontrol (**Scheme-38**).

Scheme-38

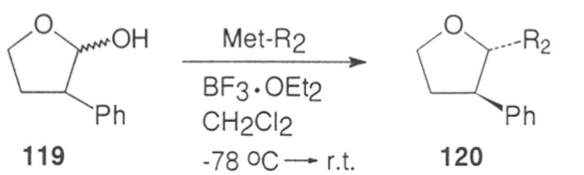


117 **114** **118**

R_1- R_2 = alkyl

Schmmit and Reiβig[32] have reported the diastereoslective syntheses of 2,3-disubstituted tetrahydrofurans **120** by the nucleophilic addition of an organometallic reagent (e.g. $ZnEt_2$) to the oxocarbonium ion generated from **119** by the reaction of borontrifluoride etherate (**Scheme-39**).

Scheme-39



119 **120**

R = Et 96%

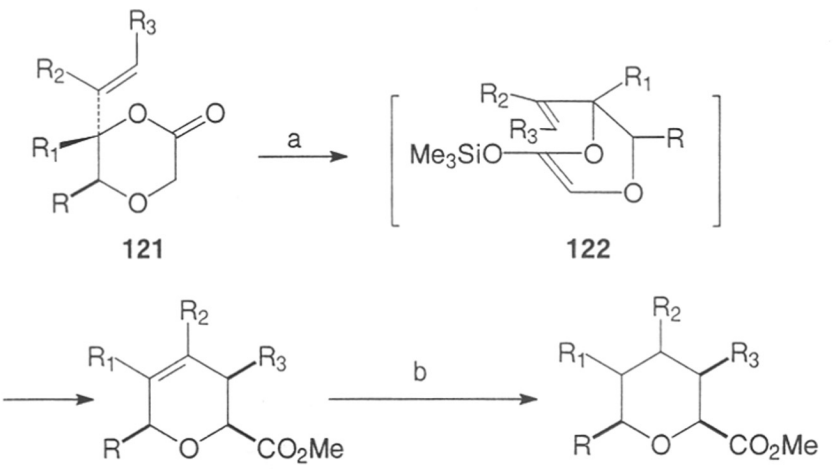
(80% de)

(d) Miscellaneous approach:

Stereoselective synthesis of all *syn*-substituted tetrahydropyrans **124** in high yield (85-90 %) is reported[33] by the Ireland ester enolate Claisen rearrangements of 6-alkenyl-1,4-dioxan-2-ones (**121**) followed by hydrogenation of the resulting dihydropyrans **123**. It is suggested that the intermediates **122** incorporates two boat like six atom transition

arrays during its pericyclic rearrangements and, thus, resulting the stereochemical orientations of the substituents at C-2, C-3 and C-6 position as shown in **Scheme-40**.

Scheme-40



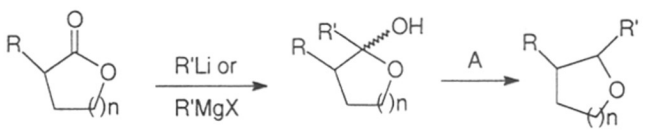
123 R, R_1, R_2, R_3 = alkyl group **124**

R = *i*Pr, R_1 = R_2 = H, R_3 = Me 91 %

a) LDA, THF, -78 °C, TMSCl, Et_3N ; -THF, + $PhCH_3$, 110 °C
5 % aq HCl, CH_2Cl_2; CH_2N_2, Ether, MeOH, -5 °C
b) H_2, 10 % Pd / C, EtOH

2,3-Disubstituted tetrahydrofurans and pyrans **127** are synthesised[34] in good yields from five- and six-membered lactones (**125**), respectively, by the addition of a R′Li or

Scheme-41



125 **126** **127**

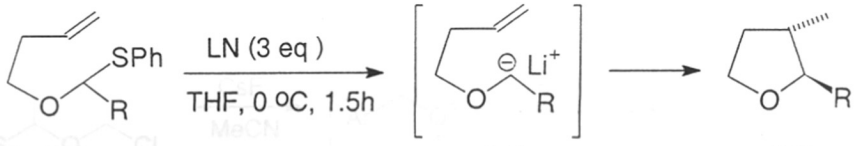
A = TFA (3 eq),
triethyl silane (3 eq)
CH_2Cl_2, -78 °C ⟶ 0 °C

R, R'	n	yield	cis : trans
R' = Ph, R = Me	1	74	1 : 1
R' = Ph, R = Me	2	75	1 : 100

R'MgX followed by the eliminative reduction of the resultant lactols **126** using $BF_3.Et_2O$ and triethylsilane as the reagents. The stereoselectivity of products is shown to depend upon the ring size of the lactones **125** (**Scheme-41**)

Intramolecular cyclisation of α-alkoxymethyllithiums (**129**) derived by the reaction of lithum naphthalenide with **128** has been shown to be an important approach for the synthesis[35] of 2,3-substituted tetrahydrofurans **130** in moderate yield. *Trans* diastereoselectivity is shown to predomominate (*trans/cis* 7:1) in such cyclizations (**Scheme-42**).

Scheme-42

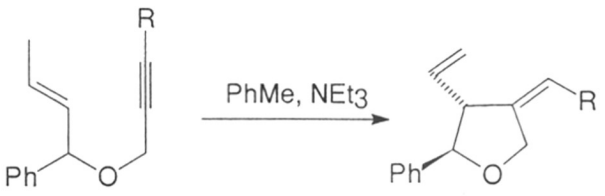


128 **129** **130**

LN = Lithium naphthalenide 50-60% (trans / cis = 7 : 1)

A stereoselective intramolecular ene reaction of allylic (γ-aryl) propergyl ethers **131** is developed by Mikami *et al*[36] for the syntheses of substituted tetrhydrofurans **132**. The *anti*-diastereoselectivity is suggested to predominate in such reactions too (**Scheme-43**).

Scheme-43

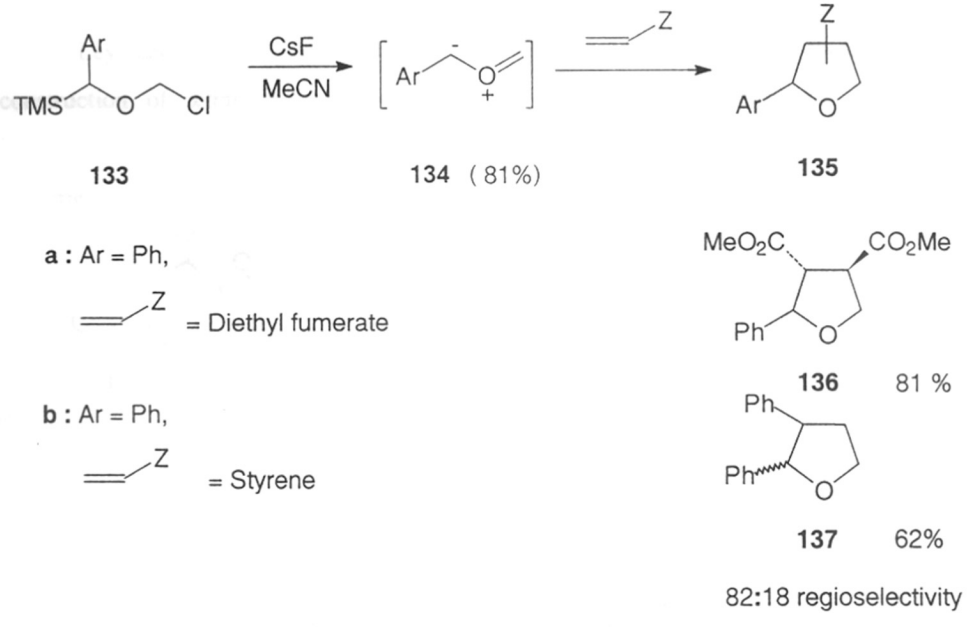


131 **132**

R = CO_2Me, 130 °C 93 % (trans)
R = *p*-MeOPh, 200 °C 100 % (trans)

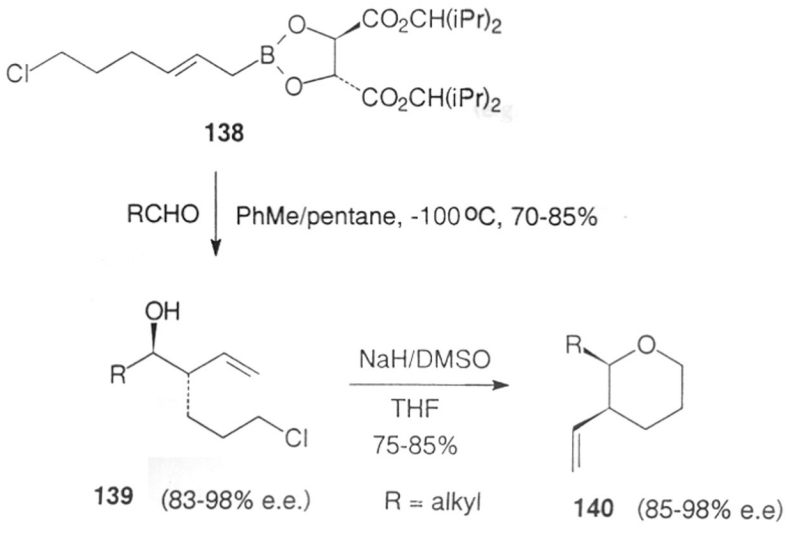
A [3 + 2] cycloaddition approach involving the addition of an activated[37a] or nonactivated[37b] multiple π-bonds to an stabilised carbonyl ylide (**134**), generated *in situ* by the 1,3-elimination of trimethylsilyl (α-aryl) methyl chloromethyl ether (**133**) by fluoride ion, has been utilised by Hojo et al[37a-b] for the syntheses of substituted tetrahydrofurans **135**. The regio- and stereochemistry of the cyloadducts are shown to depend on the nature of the dipolarophiles. For example, the tetrahydrofuran **136** is essentially produced as a 1:1 mixture of distereomers while **137**, obtained by the cycloaddition of styrene with **134**, is formed predominantly with *trans* diastereoselectivity (*trans:cis 82:*18) (**Scheme-44**).

Scheme-44



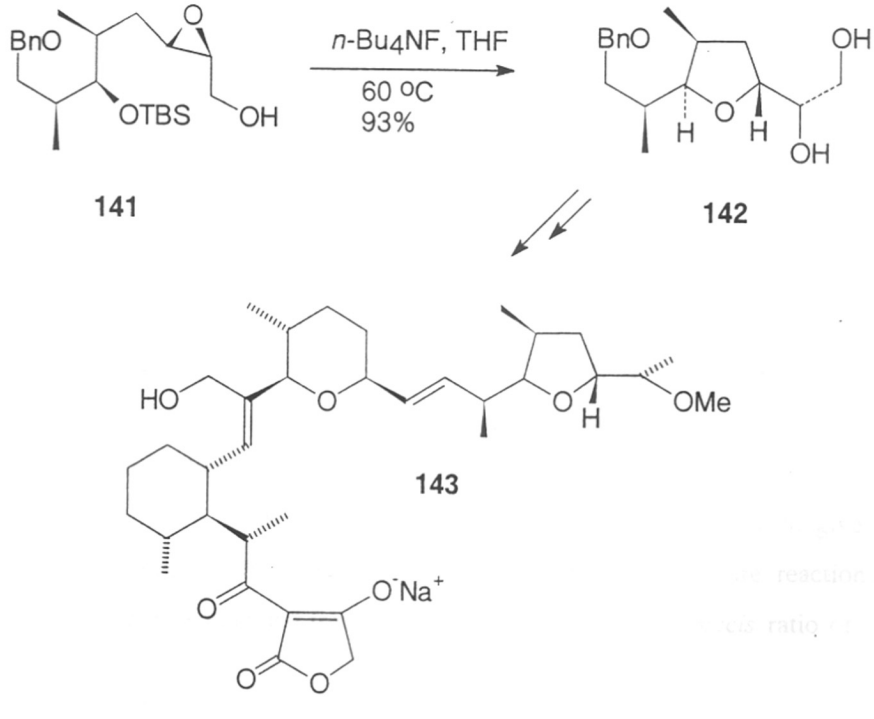
Brown et al[38] have reported the synthesis of *cis*-2,3-disubstituted tetrahydropyrans **140** in high optical purity by the intramolecular nucleophilic displacement of chloride ion by hydroxyl ion from the chlorohydrins **139**, prepared in high optical purity by the reaction of chiral allyl boronates **138** with the corresponding aldehydes (**Scheme-45**).

Scheme-45



Ley and co-workers[39] have devised an interesting synthetic route for the construction of tetrahydrofuran portion **142** of the antibiotic tetronasin (**143**) *via* intramolecular epoxide

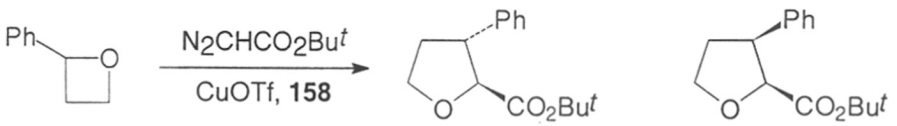
Scheme-46



ring opening of the chiral epoxide **141** by hydroxyl moiety using tetrabutylammonium fluoride as a base (**Scheme-46**).

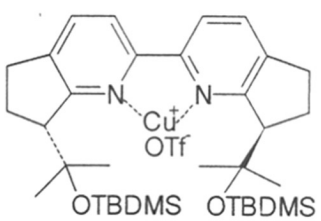
Stereoselective syntheses of tetrahydrofurans (e.g. **145** and **146**) are also reported[40] by the insertion of chiral carbene generated by the catalysis of **147** on *t*-butyl diazoaceticester to the oxetanes **144** followed by catalytic asymmetric ring expansion. In this case, each enantiomer of the oxetanes gave a single diastereomer of the tetrahydrofuran. Competing metal-free ring expansions are involved to account for the less than perfect enantioselectivity (**Scheme-47**).

Scheme-47



144 **145** **146**

21% (75% ee) 15% (81% ee)

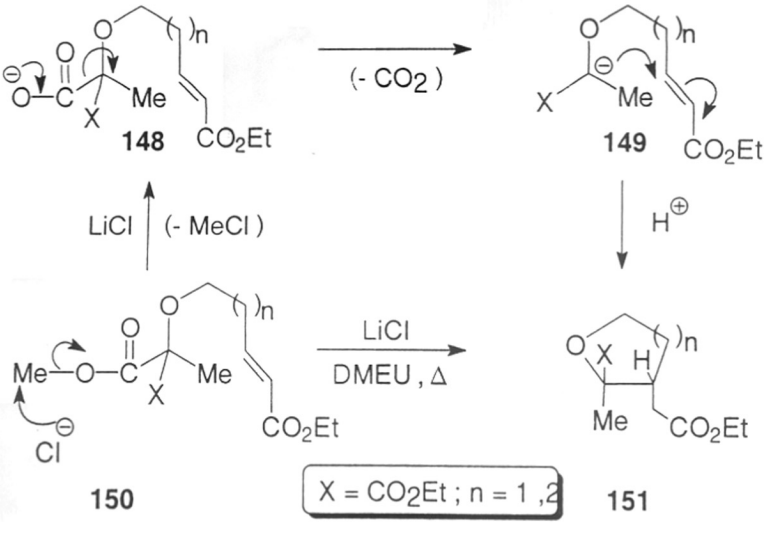


147

More recently, Bunce and coworkers[41] have utilised a known tandem demethoxycarbonylation-Michael addition reaction strategy for the synthesis of functionalised tetrahydrofurans and 2H- tetrahydropyrans (**151**) from the substrates of type **150** as shown in **Scheme-48**. Six membered cyclisations are shown to give better yield and diastereoselectivity compared to five membered ring closure reactions. For example, furan **151a** is obtained from **150a** in 60 % yield with *trans:cis* ratio of 75:25

whereas corresponding pyran **151b** is formed from the cyclisation of **150b** in 75 % yield with *dr* 82:18.

Scheme-48



Inspite of the great usefulness of this approach, it can not be generalized as it is only applicable to a particular type of substrates where decarboxylation has to proceed through a tertiary enolate intermediate for better results.

From the above introductory illustrations, it is evident that there is a need for the development of an additional strategies for the more general and practical syntheses of substituted tetrahydrofurans and pyrans.

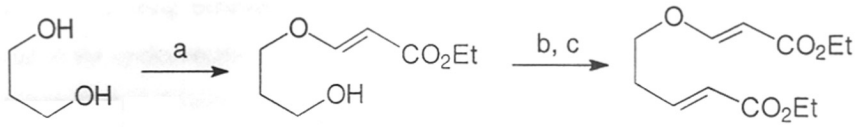
With a view to provide a new and novel strategy for the syntheses of substrates of type **68** through the strategy as proposed in **Scheme-1**, substrate **154** having both acrylate and β-alkoxy acrylate moieties was selected.

3.1. Preparation of 1-ethoxy-5(-3-ethoxy-3-oxo-1(E)-propenyloxy)-2(E)-penten-1-one (154) :

Substrate **154** was synthesised easily in 96 % yield by the Wittig olefination of the corresponding aldehyde, obtained (60%) by the Swern oxidation of the corresponding

alcohol (**152**), with ethyl triphenylphosphoranylidene acetate.. The details of its synthesis is shown in **scheme-49**.

Scheme-49



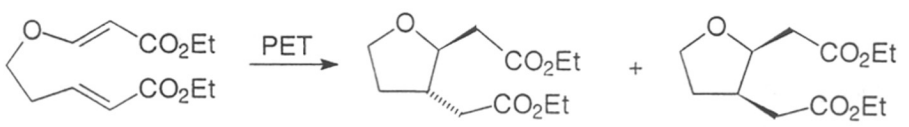
152 **153** **154**

Reagents : (a) Ethyl propiolate, NMM, CH_2Cl_2, r.t., 70 % ; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 60 %; (c) Ph_3P=CHCOOEt, CH_2Cl_2, r.t., 20 h, 96%

3.2. PET activation of the substrate 154:

PET activation of the substrate **154**, achieved by utilising an identical setup as described for **16**, using either **PS - A** or **PS - B** reaction conditions, resulted in the formation of diastreomeric mixtures of **155** and **156** in 90 % yield (*trans:cis* 75:25) (**Scheme-50**). Pure diastereomers **155** as well as **156** were separated by careful column chromatography and were characterised by ^{1}H NMR, ^{13}C NMR, IR and mass spectral data. The diastereomeric ratio was measured by capillary GC analysis using 25 mts phenylmethyl silicon column.

Scheme-50



154 **155** **156**

IR spectrum of **155** indicated the loss of the conjugated double bond and alkoxy acrylate moiety. It showed prominent absorption band at 1735 cm^{-1} corresponding to ester moiety.

^{1}H NMR spectrum (**Fig. 21**) of **155** confirmed the absence of conjugated double bond. It displayed a multiplet between δ 4.45-4.05, integrating for five protons,

characterised as the methylene protons of ester groups and H_{-5e} mehtylene proton. Mehtylene proton H_{-5a} and methine proton H_{-2} appeared between δ 3.75-4.0 as a multiplet. A bunch of multiplets appearing between δ 2.65-2.10 (five protons) are assigned to the methylene protons of -$C\underline{H}_2$COO- and the methine proton (H_{-3}). Another bunch of multiplets appearing between δ 1.8-1.6 (two protons) are attributed to the remaining protons of the cyclopentane ring. A triplet at δ 1.3 (J = 7.3 Hz), integrating for six protons is characterised to the methyl protons of ester moieties.

The ^{13}C NMR (**Fig. 22**) of **155** revealed ten carbon signals whose characterization are assigned by INEPT experiment. Down field quaternary carbon appearing at δ 172.25 and 171.28 are characterized to carbonyl moieties of ester groups. Methylene carbon signals of C-5 and methylenenes of ester groups (-COO$\underline{C}H_2$) appeared at δ 67.02 and 60.63, respectively. Another two signals appearing at δ 80.19 and 40.67 are assigned to the methine carbons C-2 and C-3, respectively. Methylene carbon signals of $\underline{C}H_2$COO- groups appeared at δ 39.89, and 37.65, respectively. Remaining methylene carbon signal of cyclopentane ring is observed at δ 32.89. A signal appearing at δ14.28 is attributed to the methyl carbons of ester moieties.

^{1}H NMR spectrum (**Fig. 23**) of minor *cis*-isomer **156** displayed a multiplet between δ 4.25-4.06, integrating for four protons, characterised as the methylene protons of ester groups. Methylene proton H_{-5a} and methine proton H_{-2} appeared between δ 4.05-3.80 as a multiplet. Another multiplet appearing between δ 3.62-3.35 is characterised to H_{-5e} mehtylene proton. A bunch of multiplets appearing between δ 2.85-2.28 (three protons) are assigned to the methylene protons of -$C\underline{H}_2$COO- and the methine proton (H_{-3}). Remaining methylene protons of -$C\underline{H}_2$COO- appeared as a multiplet between δ 2.20-1.98 (two protons). Another bunch of multiplet appearing between δ 1.95-1.55 (two protons) is assignable to the remaining protons of the cyclopentane ring. A multiplet at δ 1.3 integrating for six protons is characterised to the methyl protons of ester moieties.

Similarly **156** displayed its carbon signals (**Fig. 24**) as follows : two down field signals appearing at δ 173.11 and 170.68 are assignable to the respective quaternary carbons of ester moieties. Another two signals appearing at δ 75.04 and 47.06 are attributed to the respective C-2 and C-3 methine carbons. C-5 and -COO$\underline{C}H_2$ methylene carbons appeared at δ 67.93 and 60.33 (2C), respectively. Methylene carbon signals of $\underline{C}H_2$COO- groups (2C) and remaining one methylene carbons of cyclopentane ring are

observed at δ 39.79 (2C), 34.20 and 31, respectively. A signal appearing at δ14.07 is assigned to the methyl carbons of ester moieties.

Mass spectral analysis (**Fig. 25**) gave $M^+ + 1$ peak at 244 with 1 % intensity, along with base peak at 157 [M^+ - 87 (CH_2COOEt)] . The other prominent fragmentation peaks are found at 199 (13 %, M^+ +1 - OEt), 181 (4 %), 170 (77 %, M^+ - COOEt), 141(2 %), 129 (14 %), 115 (17 %), 97 (10 %), 83 (21 %) and 55 (11 %).

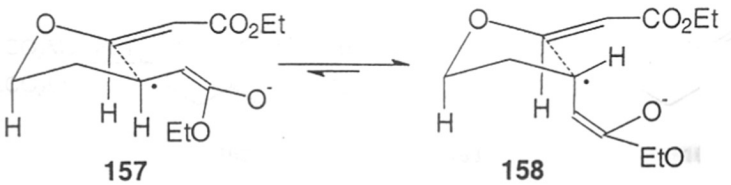
3.3. Stereochemical and mechanistic interpretation :

The stereochemical assignments of the diastereomers **155** and **156** is based on the comparison of their ^1H NMR and ^{13}C spectroscopic data.. In **155** H_{-2} and H_{-3} protons appeared at higher field due to the shielding effect of the substituent in comparison to cis isomer (**156**). Similarly, C-2 and C-3 carbons **155** appeared at lower field than those of the corresponding cis compound **156**. This argument is supported from the literature precedence[42].

The *trans* selectivity observed during the ring closure reaction of **154** merits further discussion since cyclisation in such cases are operated by a different mechanism in comparison to other approaches. Initially formed intermediate of the type (**23**) gets transformed to a thermodynamically more stable *anti*-intermediate **26** which gives more stable *trans*-product (**Scheme-10**) in contrast to Burkes[18] report, and thus allowing diastereoselectivity not to depend on the geometry of the acceptor olefinic double bond.

This logic can be further substantiated by considering the transition state conformers as shown in **Scheme-51**. The conformer **158** with enolate group in a psudo-axial position is likely to be thermodynamically favored over **157** resulting the *trans* diastereoselectivity in the product.

Scheme-51



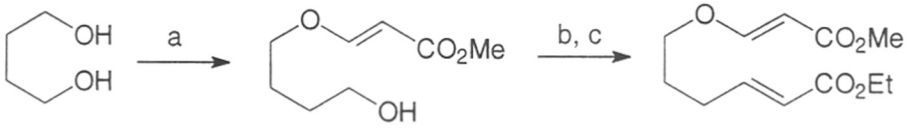
3.4. Synthesis of 2,3-disubstituteded tetrahydropyrans :

To extend the scope of the cyclisation of β-enolate allylic radical to tethered alkoxy olefin for the synthesis of 2,3-disubstituted tetrahydropyrans, substrate **161** was studied.

3.4.1. Preparation of1-ethoxy-6-(3-methoxy-3-oxo-1(E)-propenyloxy)-2(E)-hexen-1-one (161) :

Compound **161** was synthesised in 92 % yield by following the steps as shown in **Scheme-52** utilising 1,4-butanediol as starting material.

Scheme-52



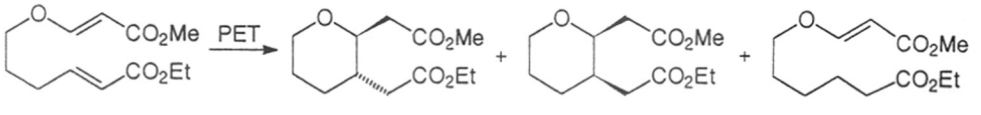
159 **160** **161**

Reagents : (a) Methyl propiolate, NMM, CH_2Cl_2, r.t., 70 % ; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 100 %; (c) Ph_3P=CHCOOEt, CH_2Cl_2, r.t., 20 h, 92 %

3.4.2. PET activation of 1-ethoxy-6-(3-methoxy-3-oxo-1(E)-propenyloxy)-2(E)-hexen-1-one (161) :

PET activation of **161**, by following the identical experimental procedure as described for **16**, furnished corresponding hydropyrans moiety **162** and **163** in the ratio of 85:15 in 60 % yield alongwith olefin reduced product (**164**, 15%). The diastereomers (**162** and **163**) could be isolated in pure forms, however **163** was not obtained in sufficient amount for detailed spectral analysis. Compound **162** was characterized by ^1H NMR, ^{13}C NMR, IR and mass spectral data (**Scheme-53**).

Scheme-53



161 **162** **163** **164**

IR spectrum of **162** indicated the loss of conjugated double bond and alkoxy acrylate moiety originally present in **161.** It showed prominent absorption band at 1730 cm^{-1} corresponding to ester group.

^1H NMR (**Fig, 26**) confirmed the absence of conjugated double bond. It displayed a quartet at δ 4.2 (J = 7.1 Hz), integrating for two protons, assigned as the methylene protons of ethyl ester group. A multiplet at δ 3.9, integrating for one proton is assigned to H_{-6eq} proton. A sharp singlet at δ 3.7, integrating for three protons is attributed to the methyl protons of -$COOCH_3$ moiety. A bunch of multiplets appearing between δ 3.62-3.3 (two protons) is assigned to the H_{-6ax} and H_{-2} protons. Another bunch of multiplets appearing between δ 2.65-2.25 (four protons) could be assigned to the mehtylene protons of -CH_2COO- groups. Remaining protons of cyclohexane ring are observed as a bunch of multiplets appearing between δ 2.1 (one proton), 1.9-1.75 (two protons), 1.7-1.35 (one proton) and 1.35-1.2 (one proton), respectively. A triplet at δ 1.2 (J = 7.1 Hz), integrating for three protons, is assigned to the methyl protons of -$COOCH_2CH_3$- group.

The ^{13}C NMR (**Fig. 27**) of **162** revealed eleven carbon signals whose characterizations are assigned by INEPT experiment A down field signal appearing at δ 172.2 is assigned to the carbonyl moieties of the ester groups (2C). Methylene carbon (C-6) and -$COOCH_2$- group appeared at δ 68.4 and 60.7, respectively. Another two signals appearing at δ 78.6 and 37.6 are assigned to the C-2 and C-3 methine carbons, respectively. Methylene carbon signals of CH_2COO- groups appeared at δ 39.3, and 37.7. Another two signals appearing at δ 51.9 and 14.4 are assigned to the methyl carbons of -$COOCH_3$ and -$COOCH_2CH_3$ groups, respectively. Remaining methylene carbons of cyclohexane ring are observed at δ 30 and 26.1.

Mass spectral analysis (**Fig. 28**) showed M^+/e at 244 (1 %) along with base peak at 157 [M^+ - 87 (CH_2COOEt)] . The other prominent fragmentation peaks were found at 213, (7 %, M^+ - OMe), 199 (9 %, M^+ - OEt), 171 (17 %, M^+ - COOEt), 125 (28 %), 115(12 %), 97 (68 %), 82 (19 %), 68 (32 %) and 55 (28 %).

3.4.3. Stereochemical and mechanistic interpretation of tetrahydropyran 162 :

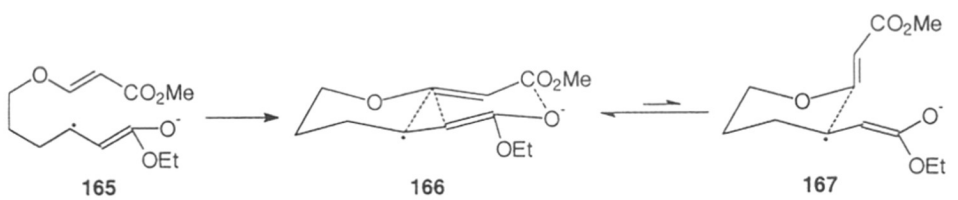
Correlation between interacting protons of **162** were established by ^1H NMR COSY experiment. The *trans* stereochemistry was confirmed by detailed decoupling experiment of its ^1H NMR spectrum and measuring the coupling constant between H_{-2} and

H_{-3} protons. In this experiment, irradiation at δ 2.5 (methylene protons of -CH_2COOMe group) simplified H_{-2} proton and it appeared as doublet indicating the coupling only with H_{-3} proron (**Fig. 29** and **30**). The observed coupling constant J = 9.6 Hz implies *trans* relationship between H_{-2} and H_{-3}.

The observed stereoselectivity in **162** is likely to be governed by the involvement of transition state **166** where *trans* diastereomer would predominate. As explained earlier in this chapter for tetrahydrofuran **155**, the kinetically produced conformer **167** expected to result *cis*-diastereomer **163** gets transformed to the the thermodynamically more stable *trans* transition state **166** (**Scheme-54**).

This argument also draws the rational provided by Bounce et al[41] by considering the dominant secondary orbital interaction and overlap involving HOMO of the enolate and LUMO of the α-alkoxy-α,β-unsaturated ester carbonyl in the transition state **166**.

Scheme-54



165 **166** **167**

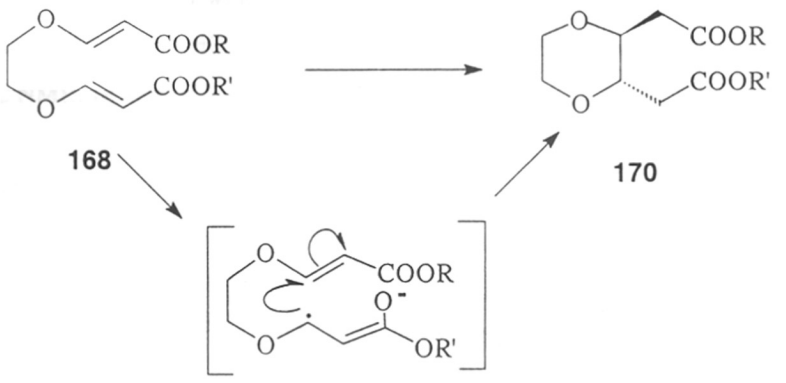
One important point worth mentioning is the observation of lower selectivity during the formation of five-membered ring over the six-members, in sharp contrast to the observation made during the formation of carbocycles. This may be postulated by considering the greater strain requirements to align the interacting π-systems for optimum orbital overlap.

4. Generation and cyclisation of α-alkoxy radical

Our continuous efforts to extend the scope of the photosystems (**PS-A**, **PS-B**) for the useful and significant synthetic transformations led us to direct our attention for the generation of the α-alkoxy carbon centered radical (**169**)[43] from the PET reductive β-activation of alkoxy acrylate moiety **168**. It was anticipated that PET reductive cyclisation of such radical species would add to tethered alkoxy acrylate moiety, providing a new approach for the construction of substituted 1,4-dioxane (**170**) framework present in many biologically active molecules[44]. Furthermore, it was realised that such radical species

(169) will enjoy further stabilization[45] by the spin delocalization on to oxygen and the stereochemical out come of this cyclisation would be governed by a late and rigid transition state where nonbonding interactions of the substituent would play a vital role (Scheme-55).

Scheme-55

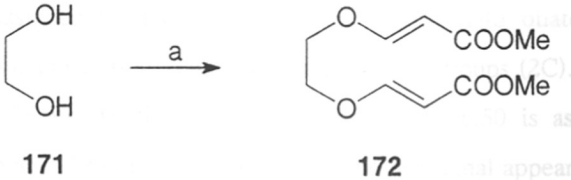


To test the viability of this concept substrate 1-methoxy-3-(2-(3-methoxy-3-oxo-(E)-1-propenyloxy)ethyloxy)-(E)-2-propen-1-one (172) was designed.

4.1. Preparation of 1-methoxy-3-(2-(3-methoxy-3-oxo-(E)-1-propenyloxy)ethyloxy)-(E)-2-propen-1-one (172) :

This compound was prepared in 70 % yield by the Michael reaction[46] of 1,2-ethandiol with methyl propiolate in the presence of N-methyl-mporpholine as shown in the **Scheme-56** .

Scheme-56



Reagents : (a) Methylpropiolate, NMM, CH_2Cl_2, 70%

4.2. PET reductive activation of 172 :

Identical PET reductive cyclisation of **172**, as described for **16**, resulted into the expected cyclised dioxane product, 1-methoxy-2-(3-(2-methoxy-2-oxoethyl) [1,4] diox-2-yl)-1-ethanone (**173**, 80 %) with excellent diastereoselectivity (*trans:cis* 95:5) along with the recovery of 15 % of starting material (**172**) (**Scheme-57**). **173** was characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic data.

Scheme-57

172 173

IR spectrum of **173** indicated the absence of conjugated double bonds. It showed prominent absorption band for ester carbonyl groups at 1740 cm^{-1}.

^{1}H NMR (**Fig. 31**) of **173** confirmed the absence of alkoxy acrylate double bonds. It displayed a bunch of multiplets between δ 3.80-3.60 integrating for twelve protons including a singlet at δ 3.7, is attributed to the methylene protons (H_{-5eq}, H_{-5ax}, H_{-6eq} and H_{-6ax}), methine protons (H_{-2} and H_{-3}) and six methyl protons of ester moieties (singlet at δ 3.7).

^{13}C NMR spectrum (**Fig. 32**) revealed two sets of carbon signals, each set corresponding to the respective diastereoisomer. Compound **173** being a symmetrical molecule, carbon signals of the symmetrical carbons appeared at one single position. First set of carbon signals corresponding to the major isomer, showed five signals whose characterizations are assigned by INEPT experiment. Down field quaternary carbon appearing at δ 170.71 is characterised to -CO- moieties of ester groups (2C). Two methine carbons appeared at δ 75.55. Another signal appearing at δ 66.50 is assigned to the methylene carbons (C-5 and C-6) of the dioxane ring. Another signal appearing at δ 51.62

(2C) is attributed to the methyl carbons of ester groups. Methylene carbons of -$\underline{C}H_2COO$- groups are observed at δ 36.77 (2C).

Similarly, for minor isomer quaternary carbons of ester groups (-$\underline{C}O$-, 2C) are observed at δ 170.71. Another two signals appearing at δ 72.32 (2C) and 50.81 (2C) are characterised to the methine and methyl carbons of ester groups, respectively. C-5, C-6 methylene and $\underline{C}H_2COO$- appeared at δ 72.32 (2C) and δ 33.76 (2C), respectively.

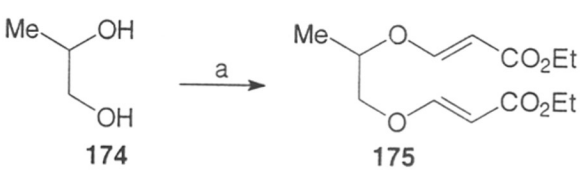
Mass spectral analysis (**Fig.** 33) showed molecular ion peak at 232 with 6 % intensity. The base peak was observed at 99 (M^+ - HCOOMe - CH_2COOMe). The other prominent fragmentations are noticed at 200 (M^+ - MeOH, 41 %), 158 (76 %), 145 (10 %,), 115 (13 %), 81 (15 %), 74 (73 %), 65 (8 %), 59 (92 %), 55 (33 %).

To establish the generality of such cyclisations for the formation of 2,3-disubstituted 1,4-dioxane framework, substrate 1-ethoxy-3-(2-(1-methyl-3-ethoxy-3-oxo-(E)-1-propenyloxy)ethyloxy)-(E)-2-propen-1-one (**175**) was also included in our study.

4.3. Preparation of 175 :

Substrate **175** was prepared from 1,2-propandiol (**174**) following the identical procedure as described for **172** (**Scheme-58**).

Scheme-58



174 **175**

Reagents : (a) Ethylpropiolate, NMM, CH_2Cl_2, 75%

4.4. PET reductive activation of 175 :

Identical PET reductive cyclisation of **175**, as described for **172**, gave cyclised dioxane, 1-ethoxy-2-(3-(1-methyl-2-ethoxy-2-oxoethyl) [1,4] diox-2-yl)-1-ethanone (**176**) as a mixture of two diastereomers (*trans*:*cis* 95:5) in 75 % yield along with the recovery of

20 % of starting material (175). Product **176** was characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic data (for details see experimental section) (**Scheme-59**).

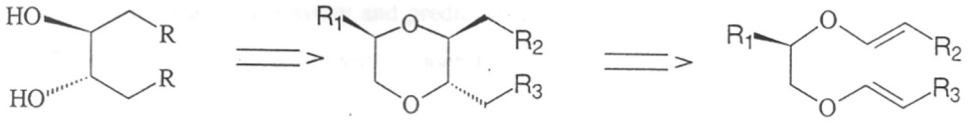
Scheme-59

175 **176**

4.5. Synthesis of optically pure C_2-symmetric diol :

Synthesis of dioxane framework of the type **176** in high diastereocontrol encouraged us to utilise this type of structure for the asymmetric synthesis of *trans*-1,2-diol (**177**) *via* the stereoselective synthesis of chiral dioxane **178.** The retrosynthetic route for our proposed plan for the synthesis of *trans*-1,2-diol is shown in **Scheme-60.**

Scheme-60



177 178 **179**

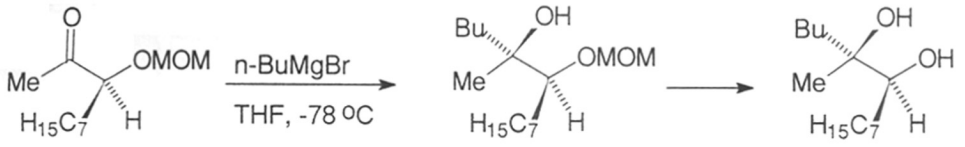
1,2-Diols are part of various biologically active natural products including pheromones[47a]. The other uses of C_2-symmetric diols as auxiliaries for asymmetric syntheses and formation of diastereomeric acetals and ketals are well known in the literature[47b-d].

The development of a stereoselective synthesis of chiral 1,2-disubstituted 1,2-diols is a very important subject in the synthetic organic chemistry and many methodologies have been devised in this context. The known approaches can be classified in the following three broad categories.

4.5.1. Stereoselective addition to the carbonyl functionality bearing a chiral α-alkoxy group:

Addition of organometallic reagents (organomagnasium, organolithium, organocopper) to aldehydes or ketones having a chiral α-alkoxy group, is an imprtant approach for the asymmetric synthesis of 1,2-diols. For example, addition of n-butylmagnesiumbromide to the carbonyl functionality of **180** is reported[48] to afford **181** in > 99 % ds (**Scheme-61**).

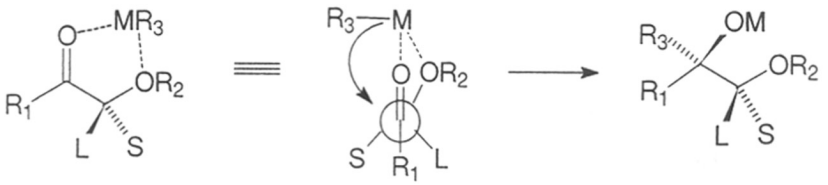
Scheme-61



180 **181** **182**

The high diastereoselectivity is explained by considering the Cram's[49] chelation controlled transition state model (**184**) as shown in **Scheme-62**. Chelation dominates all other effects which determines the conformation in acyclic aldehydes and ketones and favours high diastereoselectivity and predictability[50]. However, several factors are known to influence the diastereoselectivity of such types of additions, including solvent polarity, counter-ion, and the nature of the ligating group.

Scheme-62



183 **184** **185**

L and **S** are large and small substituents, respectively.

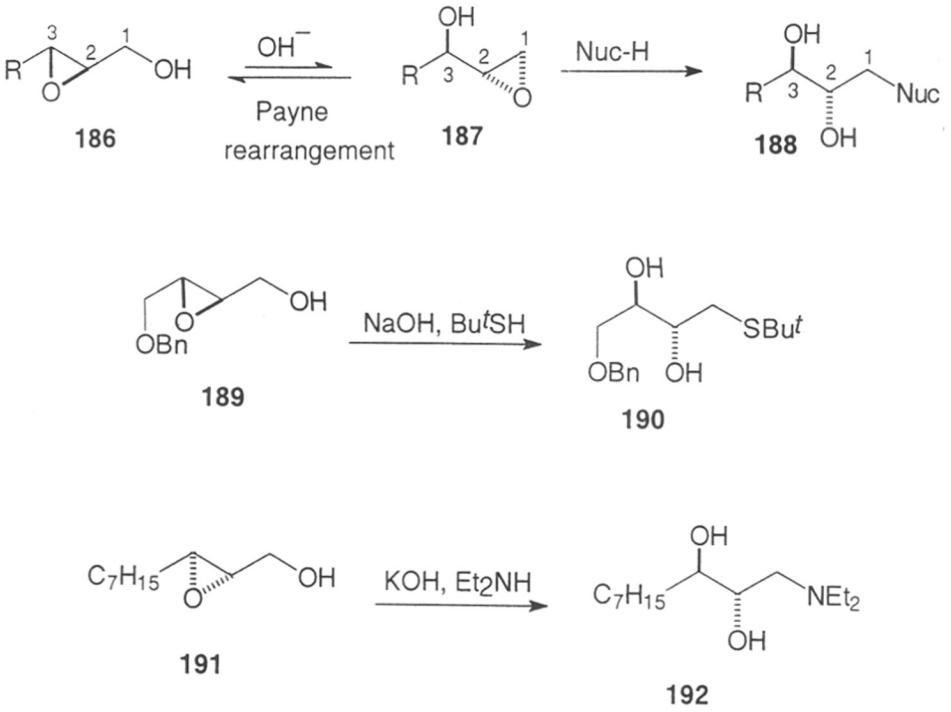
4.5.2. Nucleophilic opening of chiral epoxide :

Nucleophilic opening or hydrolysis of chiral (enantiomerically pure) epoxides, obtained either by Sharpless[51] AE reaction of olefins having alcohol/alkoxy group in

allylic position or by Jacobson's[52] method, provides an excellent approach for the synthesis of chiral 1,2-diols.

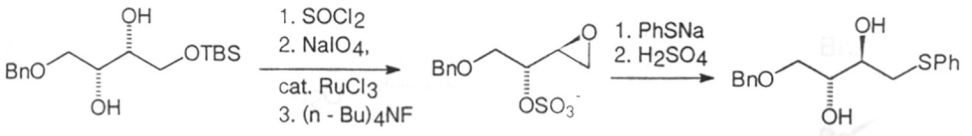
For example, diol (**190**) is obtained from the epoxide **186** by transforming it to **187** through Payne rearrangement followed by nucleophilic ring opening of the terminal epoxide[53]. The terminal epoxide (**187**) is less stable than the corresponding internal epoxide (**186**), and therefore former is normally the minor component in the reaction mixture, though, it reacts much more rapidly than the epoxide **187**[54] due to the lack of steric hindrance (**Scheme-63**).

Scheme-63



The problem of reversibility of epoxides during the Payne rearrangement step (**Scheme-63**) has led to the development of an alternate strategy involving irreversible formation of epoxide[55] as shown in **Scheme-64**.

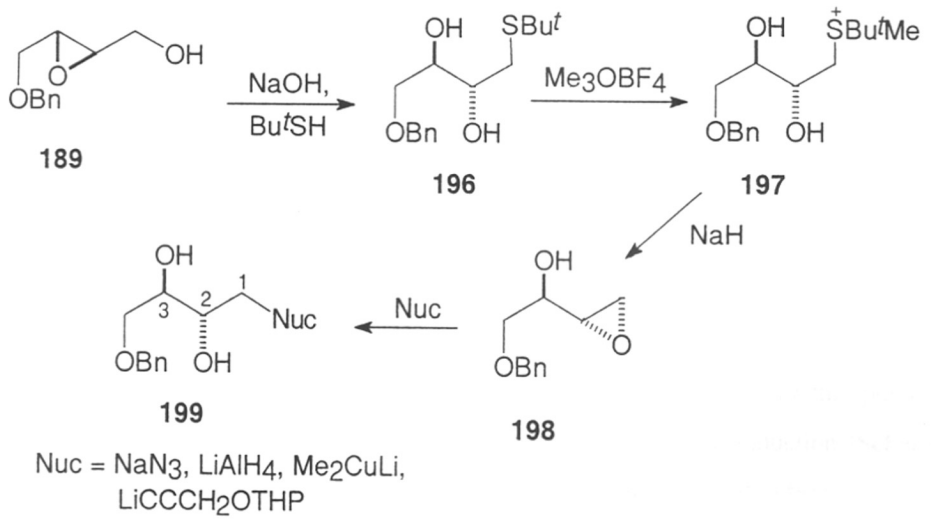
Scheme-64



193 194 195

The range of nucleophiles which can be used in this process are limited to those compatible to aqueous bases. This limitation has been, however, circumvented by the preparation of the terminal epoxide (198) as a descrete entity followed by reaction under anhydrous (non-equilibrating) conditions[56] (**Scheme-65**).

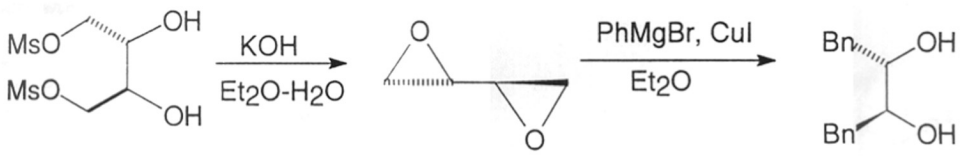
Scheme-65



189 196 197 198 199

Devine et al[57] have synthesised chiral diols **202** in good yield by the nucleophilic opening of (S,S)-1,2,3,4-diepoxybutane, obtained from the dimesylate (**200**), as shown in **scheme-66**.

Scheme-66

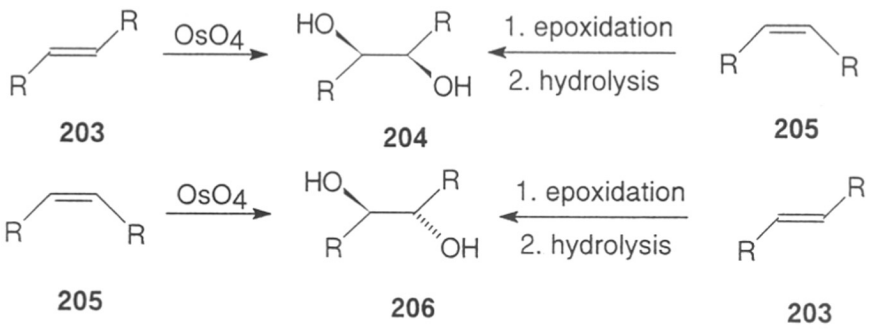


200 **201** 76% **202** 85%

4.5.3. Asymmetric dihydroxylation approach :

The development of an efficient asymmetric dihydroxylation process involving the reaction of OsO_4 with unactivated olefins pioneered by Sharpless[58], is perhaps the most reliable and general method for the oxygenation of olefines (**Scheme-67**).

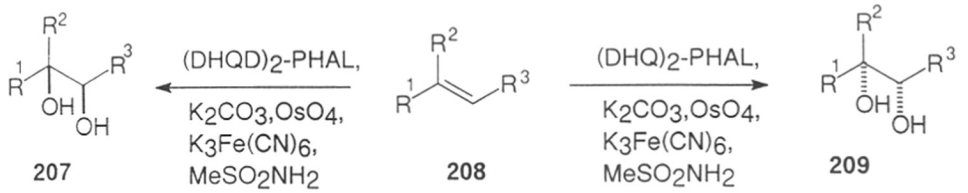
Scheme-67



A range of catalysts is available which provides *cis*-diols from various alkenes in high ee. Complexes derived from OsO_4 with phthalzine ligands of dihydroquinidine (DHQD) and dihydroquinine (DHQ) have been found to be very effective catalysts for this purpose. These two catalysts systems are shown to give opposite asymmetric induction (**Scheme-68**). However this approach suffers from the following limitations: (a) substrates having *cis*-olefins are problematic for AD reaction, and in most of the cases give poor ee (no examples exceeding 90 % ee), (b) aliphatic and acyclic substrates give even lower selectivities (~ 50 % ee), (c) few terminal olefins with a single, small substituent e. g. allyl derivatives CH_2CHCH_2X [X = H, CH3, OC(O)R, OR, halo etc.], normally give < 70 % ee, (d) OSO_4 being an electrophilic reagent, electron rich olefins give better results in

comparison to electron deficient olefins and (e) lastly, this reagent is toxic and expensive too.

Scheme-68



4.6. Present investigation :

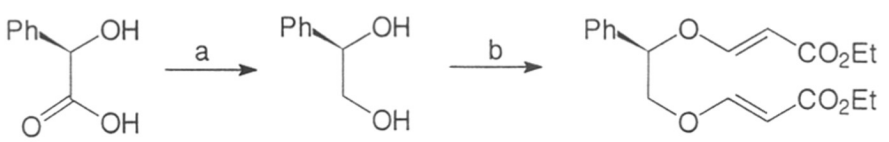
To provide an alternate strategy for the asymmetric synthesis of C_2-symmetric diols, we evaluated to synthesise and utilise chiral dioxane **213** as a precursor for the synthesis of 1,2-*trans*-diol by its stereoselective ring opening.

The synthesis of dioxane **213** was envisaged to be realised from the from the PET cyclisation of **212**.

4.6.1. Preparation of 1-ethoxy-3-(1(R)-phenyl,2-(3-ethoxy-3-oxo-(E)-1-propenyloxy) ethyloxy) -(E)-2-propen-1-one (212) :

Compound **212** was obtained in two steps starting from (R)-mandelic acid as shown in **Scheme-69**.

Scheme-69



210 **211** **212**

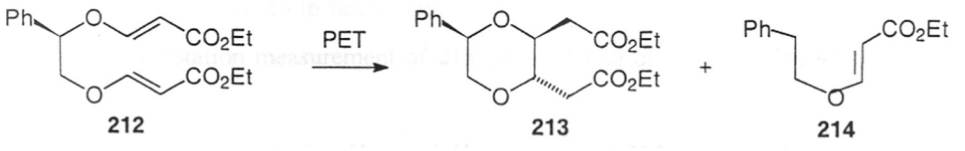
Reagents and conditions : (a) LAH, Ether, r. t., 93 %; (b) Ethylpropiolate, NMM, CH_2Cl_2, r. t., 83 %

4.6.2. PET reductive cyclisation of 1-ethoxy-3-(1(R)-phenyl, 2-(3-ethoxy-3-oxo-(E)-1-propenyloxy)ethyloxy)-(E)-2-propen-1-one (212) :

PET reductive activation of **212**, achieved by utilising **PS-A** or **PS-B** reaction condition, as described for **16**, afforded expected dioxane moiety (**213**) in 65 % yield as a

single diastereomer. Minor amount of cleavage product (**214**, 10 %) was also observed during its activation. Unreacted **212** was recovered in about 20 % yield. Products **213** and **214** were characterised by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic data (**Scheme-70**).

Scheme-70



212 **213** **214**

IR spectrum of **213** indicated the loss of alkoxy acrylate double bonds. It showed prominent absorption band at 1736 cm^{-1} corresponding to ester moiety.

The ^{1}H NMR (**Fig. 34**) of **213** displayed a multiplet between δ 7.45-7.3, integrating for five protons, assigned to the aromatic protons. A doublet of a doublet (J = 10.9, 2.4 Hz) appearing at δ 4.67, integrating for one proton, is attributed to the benzylic proton. A quartet (J = 7.3 Hz) appearing at δ 4.2 is assigned to the methylene protons of ester groups. Another doublet of a doublet (J = 10.9, 12.2 Hz) appearing at δ 3.50 is characterised to one of the H_{-5} methylene proton. A bunch of multiplets appearing between δ 4.1-3.8 (three protons) could be assigned to the remaining H_{-5} and two other methine protons (H_{-3} and H_{-4}). Methylene protons of $C\underline{H}_2COO$- moieties appeared at δ 2.55 as a multiplet while methyl protons of ester moieties are observed as a multiplet at δ 1.25.

The ^{13}C NMR (**Fig. 35**) of **213** showed only one set of carbon signals which indicated **213** to be an optically pure diastereomer. It revealed fifteen carbon signals whose characterization were assigned by INEPT experiment. Down field quaternary carbons appearing at δ 170.63 and 170.56 are characterized to carbonyl moieties of ester groups. Another downfield signal appearing at δ 137.91 is assigned to the quaternary carbon of aromatic benzene ring. Three signals appearing at δ 128.47, 128.07 and 126.19, are attributed to the *ortho*, *para* and *meta* carbons of benzene ring, respectively. C-5 methylene carbon appeared at δ 72.43. Methylene carbon signals of $-COO\underline{C}H_2$ groups are observed at δ 60.95 and 60.85, respectively. A pair of signals appearing at δ 37.54 and 37.24 are characterised to the methylene carbons of $\underline{C}H_2COO$- groups (2C). Another three

signals observed at δ 77.65, 76.06 and 75.54 are assigned to the methine carbons. A signal appearing at δ14.28 is assignable to the methyl carbons of ester moieties.

Mass spectral analysis (**Fig. 36**) showed $M^+ + 1$ peak at 337 with 1 % intensity along with base peak at 104 (M^+ -). The other prominent fragmentation peaks are found at 291 (M^+ - OEt, 3 %), 216 (10 %), 184 (7 %,), 170 (28 %), 143 (17 %), 129 (9 %), 125 (5 %), 97 (8 %), 91 (20 %), 85 (6 %), 77 (19 %), 69 (6 %), 55 (18 %).

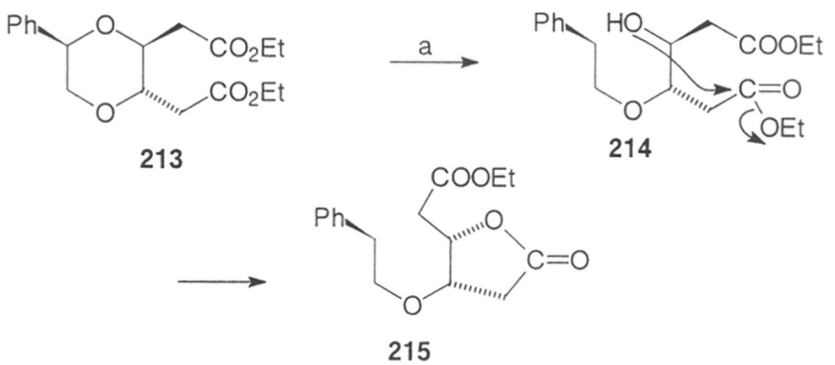
Optical rotation measurement of **213** gave a value of $[\alpha]_D^{22}$ = -66.90 (C = 0.94, MeOH).

Stereochemistry of H_{-2}, H_{-3}, and H_{-6} protons of **213** were confirmed by NOE, NOESY and decoupling experiments of its ^1H NMR spectrum.

4.6.3. Synthesis of (-)-1,8-di(-t-butyldimethylsilyloxy)l-4 (S),5(S)-octanediol (218):

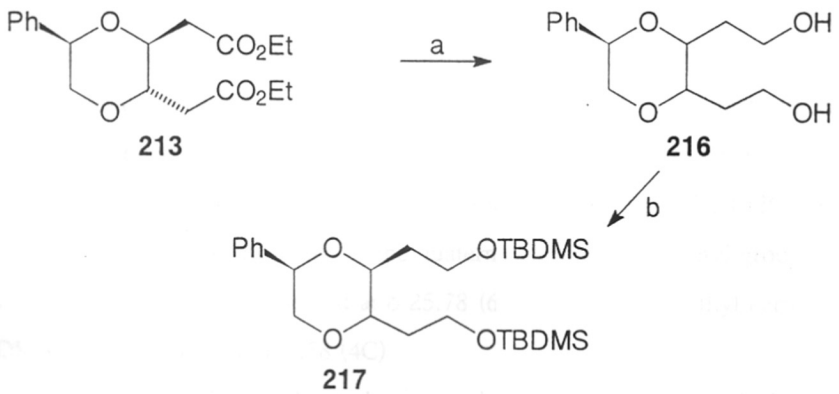
Initially we tried to open the dioxane ring of **213** by hydrogenation, however, hydrogenation employing Pd/C or $Pd(OH)_2$ remained unsuccessful. Our attempt to open the dioxane **213** by using Na/liq NH_3 gave a mixture of products with **215** as major as shown in **Scheme-71**.

Scheme-71



Formation of **215** led us to realise that stereoselective ring opening of **213** could be made possible by using Na/liq NH_3 if the ester groups are in reduced form. For this purpose dioxane **213** was transformed to **217** by LAH reduction followed by protection of the hydroxyl groups by TBDMSCl as shown in **Scheme-72**.

Scheme-72

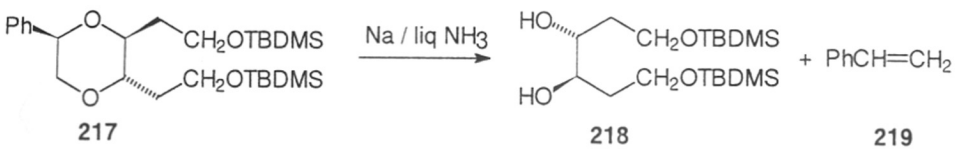


213 216 217

Reagents : (a) LAH, ether, r. t., 98 %; (b) TBDMSCl, imidazole,CH_2Cl_2, 98%

Subjecting **217** with Na/liq NH_3 reduction gave **218** with the formation of styrene molecule (**219**) (**Scheme-73**). Diol **218** was characterised by ^1H NMR, ^{13}C NMR, IR and mass spectroscopic data.

Scheme-73



217 218 219

$[\alpha]_D^{22}$ = - 24.5 (C = 0.24, MeOH)

IR spectrum (**Fig. 37**) showed a broad absorption band at 3471 cm^{-1} corresponding to the hydroxyl groups.

The 1H NMR (**Fig. 38**) displayed a multiplet between δ 3.98-3.82 integrating for four protons, assigned as the methylene protons of -CH_2OTBDMS groups. Another multiplet appearing between δ 3.80-3.65 (two protons) is characterised to the α-hydroxy methine protons. Remaining methylene protons appeared as a bunch of multiplets between δ 1.85-1.72. Protons of hydroxyl groups are observed as broad singlets at δ 3.55 and 1.65. Another singlet at δ 0.92 is attributed to the eighteen protons of *t*-butyl groups. Remaining twelve methyl protons of -TBDMS group appeared as a singlet at δ 0.10.

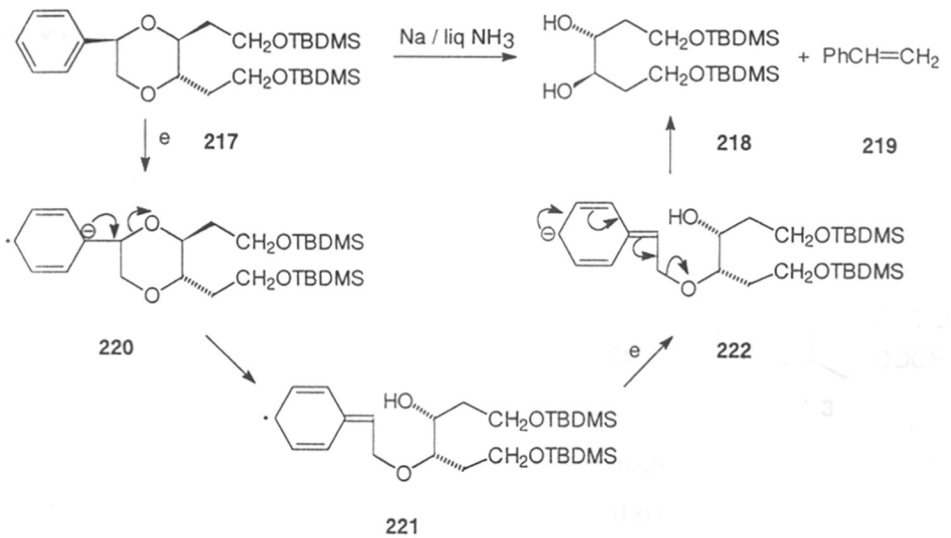
The ^{13}C NMR spectrum (**Fig. 39**) of the diol (**218**) showed six carbon signals whose characterisation was assigned by INEPT experiment. Compound **218** being a C_2-symmetric molecule carbon signals of the symmetrical carbons appeared at one single position. A signal appearing at δ 73.30 (2C) is characterised to the methine carbons. Another signal appearing at δ 61.51 (2C) is assigned to the methylene carbons of -$\underline{C}H_2$OTBDMS group. Remaining methylene carbons appeared at δ 35.18 (2C). A signal appearing at δ18.10 (2C) is attributed to the quaternary carbons of *t*-butyl groups. Methyl carbons of *t*-butyl groups are observed at δ 25.78 (6C). Remaining methyl carbon signals of TBDMS group appeared at δ -5.58 (4C)

Mass spectral analysis did not show prominent molecular ion peak. First intense peak from M^+ is found at 321 [M^+ - 57 (*t*-Bu)] with 5 % intensity and the base peak is observed at 75. The other prominent fragmentation peaks appeared at 312 (1 %), 304 (3 %), 229 (3 %), 189 (37 %), 171 (38 %), 159 (10 %), 133 (13 %), 115 (20 %), 105 (28 %), 97 (51 %), 89 (63 %), 69 (12 %) and 59 (8 %).

This one step ring opening of dioxane ring of **217** (**Scheme-73**) is a new strategy of its own kind. The plausible mechanism of dioxane ring opening is shown in **Scheme-74.**

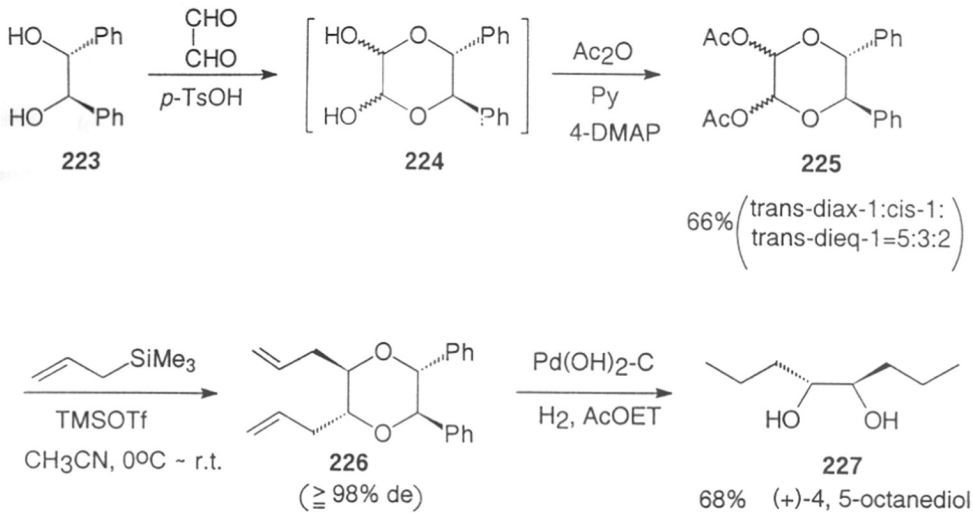
4.6.4. Mechnism of ring opening of 217 :

Scheme-74



It may be important to cite a related work here[59] for the synthesis of chiral diol **227** by the double nucleophilic addition to the dioxane (**224**) using chiral hydrobenzoin (**223**) as an auxiliary. However, it is apparent that this approach involves longer reaction sequence compared to ours as detailed out in **Scheme-75**.

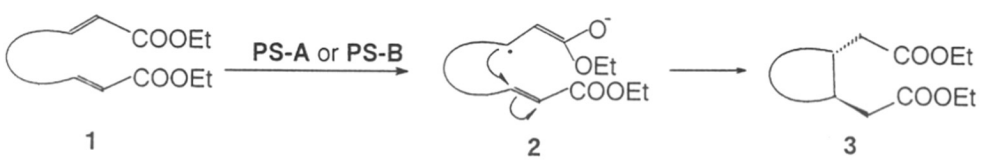
Scheme-75



5. Conclusion

The work presented in this chapter can be summarised as follows :

(a) we have developed a new strategy for the reductive β-activation of α, β-unsaturated esters to produce carbon centered radical precursor. The cyclization of these radicals to tethered activated olefins are shown to be very efficient and stereoselective for carbocyclic ring formation.



The 1,2-*anti*-stereochemistry observed in the cyclized products are suggested to originate from the thermodynamic equilibration of kinetically favored *syn*-intermediates.

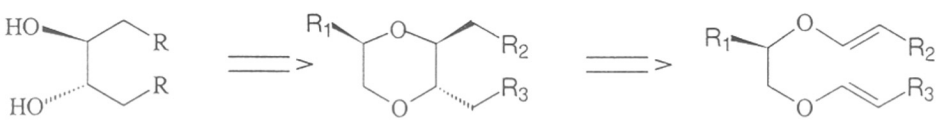
(b) The application of this strategy has been demonstrated by the stereoselective synthesis of *trans* 2,3-disubstituted tetrahydrofuran and tetrahydropyran as a simple and new methodology.

67 **68**

(c) Generation of α-alkoxy radical from the β-activation of alkoxy acrylate moiety and its cyclisations have been shown to provide an attractive route to substituted 1,4-dioxane systems.

168 **170**

(d) Synthetic significance of this approach has been utilised for the asymmetric synthesis C_2-symemetric 1,2-diol.



177 178 **179**

6. Experimental Section

6.1. General Photoirradiation Procedure:

All irradiations were performed in a specially designed photoreactor as described in chapter-1 using either **PS-A** or **PS-B** reaction conditions. **PS-A** reaction conditons involved the photolysis of mixture containing DCA (20-25 mol %), substrate (1 equiv.) and Ph_3P (0.7-0.8 equivalent) in DMF: *i*-PrOH: H_2O (88: 10: 2) using 405 nm light. Details of the procedure has been described in chapter-1.

6.2. Preparation of Diethyl-2(E),7(E)-nonadien-1,9-dioate (16): Compound **16** was prepared in the three steps starting from **20** :

(a) Preparation of Ethyl-7-hydroxy-2(E)-heptenoate (**21**) and (b) Ethyl-7-oxo-2(E)-heptenoate (**22**) has already been described in chapter-1.

(c) Preparation of diethyl-2(E),7(E)-nonadien-1,9-dioate (16):

Ethyl triphenyphosphoranylideneacetate (3.18 g, 9.1 mmol) in CH_2Cl_2 (25 mL) was placed into a 50 mL RB flask equipped with a magnetic stirring bar and an argon gas balloon. A solution of ethyl-7-oxo-2 (E)-heptenoate (**22**, 1.2 g, 7.0 mmol) in CH_2Cl_2 (5 mL) was introduced with the help of a syringe into the flask and the reaction mixture was allowed to stir for 30 h at r.t. The reaction mixture was concentrated under vacuo and the residue was stirred with 30 mL of Et_2O: pet-ether (1:1) for 20 min. The resulting suspension was filtered and was washed with 15 mL of the same mixture of solvents. Evaporation of the combined filtrate under vacuo followed by column chromatographic purification over silica gel afforded 1.51 g (90 %) of **16** as a clear liquid .

^{1}H NMR (200 MHz)	:	6.95 (2H, dt, *J* = 15.6 Hz, 2.4 Hz), 5.8 (2H, dt, *J* = 15.6, 7.0 Hz), 4.2 (4H,q, *J* = 7.3 Hz), 2.35-2.2 (4H, m), 1.75-1.55 (2H, m), 1.3 (6H, t, *J* = 7.3 Hz)
^{13}C NMR (50 MHz)	:	165.89 (2C), 147.62 (2C), 121.70 (2C), 59.71 (2C), 31.07 (2C), 26.08, 13.89 (2C)

IR (neat) : 2982, 2935, 1720, 1655, 1368, 1268, 1183, 1097, 1042, 979

MS m/e : 241 (M^+ + 1, 3), 240 (M^+, 8), 195 (31), 166 (36), 149 (21), 138 (17), 121 (24), 99 (32), 93 (56), 86 (23), 81 (100), 68 (28), 55 (24)

6.3. PET activation of Diethyl-2(E),7(E)-nonadien-1,9-dioate (16):

A solution of compound **16** (0.571 g, 2.38 mmol), DCA (0.13 g, 0.57 mmol), DMN (0.034 g, 0.18 mmol) and ascorbic acid (0.55 g, 3.1 mmol) dissolved in a mixture of DMF: *i*-PrOH: H_2O (700 mL, 88: 10: 2) solvent was irradiated in especially designed photoreactor, as mentioned earlier in chapter I, under argon atmosphere with the light emanating from a 450 W Hanovia medium-pressure lamp filtered through a $CuSO_4.5H_2O$: NH_3 solution. The progress of the reaction was monitored by GC. After considerable consumption (98%) of **16** (18 h), the solvents were removed by distillation under reduced pressure. The concentrate was dissolved in Et_2O (50 mL) and washed with H_2O and saturated brine solution. The Et_2O layer was concentrated under vacuo and the mixture was separated by column chromatography over silica-gel (100-200 mesh) using pet-ether: EtOAc as eluant to give compound **19** (0.526 g, 92%) as a mixture of two isomers (*trans:cis* 17 : 3).

Ethyl 2-[2-(carboethoxymethyl)cyclopentyl]ethanoate (19):

^{1}H NMR (200 MHz) : 4.15 (4H, q, J = 7.2 Hz), 2.55-2.05 (4H, m), 2-1.75 (3H, m) 1.7-1.45 (3H, m), 1.45-1.05 (8H, m , including 6H, t, J = 7.2 Hz at 1.25)

^{13}C NMR (50 MHz) : (major) 172.80, 60.02, 41.84, 39.19, 32.07, 23.30, 14.13.
(minor) 172.80, 60.02, 38.75, 35.08, 30.37, 22.14, 14.13

IR (neat) : 2979, 2956, 1735, 1390, 1280, 1200, 1170, 1050

MS m/e : 243 (M^+ + 1, 5), 242 (M^+, 13), 197 (73), 168 (52), 155 (82), 139 (4), 127 (14), 109 (35), 94 (31), 81 (100), 67 (37), 55 (9)

6.4. PET Activation of Diethyl-2(E),7(E)-nonadien-1,9-dioate (16) using PS-A :

PET activation of **16** using **PS-A** involved the irradiation of a solution of **16** (0.57g., 2.38 mmol), Ph_3P (0.375 g, 1.43 mmol) and DCA (0.13 g, 0.571 mmol) in DMF: i-PrOH: H_2O (700 mL) utilising the same setup and procedure using **PS-B**. After 18 h, irradiation was stopped and solvents were distilled off under reduced pressure. Column chromatographic purification of the crude concentrate over silica-gel using pet-ether: EtOAc as eluent afforded 0.515 g of **19** (90%) as a mixture of diastreomers.

6.5. Preparation of Diethyl-4-t-butyldimethylsilyloxymethyl-2(E),7(E)-nonadien-1,9-dioate (36):

Compound **36** was prepared in seven steps starting from diethylmalonate (**30**) as described below.

(a) Preparation of **31** :

(i) *3,3-diethoxy-iodopropane*[60]*:* To a solution of NaI (18 g, 120 mmol) and acrolein (5.6 g, 100 mmol) in acetonitrile (250 mL) was rapidly added chlorotrimethylsilane (15.3 mL, 120 mmol) with vigorous stirring. The resulting suspension was stirred for 4 min and ethanol (14 mL, 238.8 mmol) was added. After stirring for 5 min, the reaction mixture was poured onto a 5% aq solution of $NaHCO_3$ (100 mL) overlaid with hexane (300 mL). After thorough mixing three distinct liquid phases were produced. The bottom aqueous layer was removed and the remaining top and middle organic phases were washed with 5% aq solution of $Na_2S_2O_3$ (100 mL) and subsequently with saturated NaCl solution (8×100 mL) until only a single organic phase was formed. The hexane layer was dried over anhydrous K_2CO_3. Solvent removal at reduced pressure gave 22.2 g (86 %) of 3,3-diethoxy-iodopropane as a pale yellow liquid.

^{1}H NMR (90 MHz) : 4.7 (1H, t, J = 5.6 Hz), 3.8-2.2 (4H, m), 3.16 (2H, t, J = 7.3 Hz), 2.15 (2H, td, J = 7.3, 5.6 Hz).

(ii) Into a dry 250 ml RB flask, fitted with reflux condenser, an argon gas balloon and a magnetic stirring bar, was placed K_2CO_3 (37.6 g, 271.8 mmol) and dry acetonitrile

(80 ml). Neat diethylmalonate (14.5 g, 90.6 mmol) was added to the above stirring mixture at r.t. A solution of 3,3-diethoxy-iodopropane (23.38 g, 90.6 mmol) in acetonitrile (20 ml) was added and the resultant reaction mixture was refluxed in an oil bath for 12 h. After cooling to r.t., the reaction mixture was filtered and the filtrate was concentrated under vacuo. Purification of the crude concentrate by column chromatography over silica-gel yielded 18.4 g of **31** (70 %) as a viscous liquid.

^{1}H NMR (90 MHz) : 4.44 (1H, t, J = 6 Hz), 4.10 (4H, q, J = 7 Hz), 3.70-3.18 (4H, m), 2.13-1.44 (5H, m), 1.40-1.02 (12H, m)

(b) Preparation of 33 :

(i) Lithium aluminium hydride (0.68 g, 17.9 mmol) and dry THF (50 mL) were placed in a 100 mL two neck RB flask equipped with a magnetic stirring bar, reflux condenser and argon gas balloon. Compound 31 (4 g, 13.8 mmol) dissolved in THF (15 mL) was slowly added to the suspension through a syringe. The whole content was refluxed for 10 h. After cooling, the reaction mixture was quenched with conc. NaOH solution. The organic layer was separated from the precipitate and the precipitate was washed with Et_2O (2×50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuo. The concentrate was purified by silica-gel column chromatography to yield 2.72 g (96 %) of the corresponding diol (32).

^{1}H NMR (90 MHz) : 4.4 (1H, t, J = 6.1 Hz), 3.88-3.08 (8H, m), 1.95-1.30 (4H, m), 1.15 (6H, t, J = 7 Hz)

(ii) To a stirring solution of **32** (2 g, 9.7 mmol), triethylamine (1.49 mL, 10.6 mmol) and DMAP (0.12 g, 0.97 mmol) in 30 mL of CH_2Cl_2 was slowly added a solution of *t*-butyldimethylsilylchloride (1.46 g, 9.7 mmol) in 15 mL of CH_2Cl_2 at 0 °C by addition funnel and the stirring was continued at r.t. for 4 h. The reaction mixture was filtered and the filtrate was washed with H_2O (2×30 mL), saturated brine solution, dried over Na_2SO_4 and concentrated under vacuo. Silica-gel column chromatographic purification of the concentrate afforded 2.19 g (70 %) of **33** as a clear liquid.

^{1}H NMR (200 MHz) : 4.45 (1H, t, J = 6.0 Hz), 3.80-3.25 (8H, m), 1.80-1.30 (4H, m), 1.22 (6H, t, J = 7.1 Hz), 0.89 (9H, s), 0.05 (6H, s).

IR (neat) : 3450, 2953, 2858, 1257, 1132, 1097, 835.

(c) Preparation of **34** :

Swern oxidation of **33** (2 g, 6.2 mmol) by following the identical procedure as described earlier from **21** gave the corrresponding aldehyde (1.99 g, 100 %).

^{1}H NMR (200 MHz) : 9.7 (1H, d, J = 2.7 Hz), 4.48 (1H, t, J = 5.4 Hz), 3.85 (2H, m), 3.72-3.35 (4H, m), 2.45 (1H, m), 1.85-1.35 (4H, m), 1.22 (6H, t, J = 7.5 Hz), 0.88 (9H, s), .08 (6H, s)

Wittig olefination of the crude aldehyde with ethyl triphenylphosphoranyledene acetate (2.8 g, 6.2 mmol) by following the identical reaction procedure as described for **22** furnished 2.22 g (92 %) of **35** as a clear liquid.

^{1}H NMR (200 MHz) : 6.8 (2H, dd, J = 15.85, 8.5 Hz), 5.85 (1H, d, J = 15.85 Hz), 4.45 (1H, t, J = 6.0 Hz), 4.21 (2H, q, J = 7.2 Jz), 3.8-3.35 (8H, m), 2.35 (1H, m), 1.75-1.36 (4H, m), 1.35-1.20 (9H, m), 0.9 (9H, s), 0.05 (6H, s)

(d) Preparation of **36** :

To a solution of **35** (2 g, 5.15 mmol) in 30 ml of acetonitrile was added 4.4 mL of a 5 % solution of HF(48 %) in acetonitrile at 0 °C with stirring. Progress of the reaction was monitored by TLC. After 3 min, the reaction was quenched by adding $CHCl_3$ (10 ml). The reaction mixture was washed with aq $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was dried over Na_2SO4 and concentrated under vacuo to yield 1.36 g of crude aldehyde (84 %). This crude aldehyde was used for the Wittig reaction using ethyl triphenyl phosphoranyledene acetate (1.81 g, 5.19 mmol) by following the identical reaction procedure as described for **22** to give 1.47 g (88 %) of **36** as a clear liquid.

^{1}H NMR (200 MHz) : δ 6.75-7.05 (2H, m), 5.85 (2H, m), 4.2 (4H, m), 3.6 (2H, d, J = 6.8 Hz), 2.5-2.05 (3H, m), 1.85-1.45 (2H, m), 1.3 (6H, t, J = 7.3 Hz), 0.9 (9H, s), 0.05 (6H, s).

^{13}C NMR (50 MHz) : δ 166.1, 165.92, 149.13, 147.92, 122.63, 121.64, 65.18, 59.91, 59.85, 44.23, 29.36, 28.50, 25.63, 18.03, 14.03, -5.67.

IR (neat) : 2929, 2857, 2360, 1721, 1656, 1465, 1368, 1260, 1100, 837, 757

MS (m/e) : 369 (M^+ - Me, 3), 339 (M^+ - OEt, 10), 327 (M^+ - *t*-Bu, 100), 253 (8), 235 (9), 207 (13), 179 (6), 161 (18), 133 (38), 105 (30), 103 (40), 89 (63), 81 (30), 75 (64).

6.6. PET activation of 36 :

PET activation of **36** involved the irradiation (20 h) of the solution of DMF: *i*-PrOH: H_2O containing **36** (0.40 g., 1.04 mmol), Ph_3P (0.22 g, 0.84 mmol) and DCA (0.064 g, 0.28 mmol) following identical irradiation procedure as described for **16**. After removal of solvents by distillation under vacuo followed by column chromatographic purification of the concentrate gave ethyl-2-[-(2-(carboethoxy)-5-(*tert*-butyldimethylsilyloxy) methyl)cyclohexyl]ethanoate (**37**, 0.32 g, 80 %) as a non-separable mixture of diastereomers (80: 20).

*Ethyl-2-[(*2-carboethoxymethyl-*5-tert*-butyldimethylsilyloxy)*cyclopentyl]ethannoate:*

^{1}H NMR (200 MHz) : δ 4.15 (4H, q, J = 7.3 Hz), 3.55 (2H, m), 2.6-1.35 (10H, m), 1.2 (6H m), 0.9 (9H, s), 0.05 (6H, s).

^{13}C NMR (50 MHz) : δ 172.74, 65.95, 59.97, 47.64, 44.06, 42.65, 39.40, 38.83, 31.17, 27.47, 25.87, 18.20, 14.14, -5.51.

IR (neat) : 2953, 2361, 1734, 1378, 1252, 1156, 1033, 838, 746

MS (m/e) : 371 (M^+ - Me, 3), 341 (M^+ - OEt, 16), 329 (M^+ - *t*-Bu, 100), 255 (7), 209 (12), 181 (12), 167 (15), 135 (19), 107 (26), 93 (29), 75 (50).

6.7. Preparation of 9-oxo, 9-carboethoxy-2(E),7(E)-nonadienenitrile (40):

This compound was prepared by following the same reaction sequence as described for diethyl-2(E), 7(E)-nonadien-1,9-dioate (**16**).

(a) Preparation of 7-Hydroxy-2-heptenonitrile (38):

It was obtained (1.18 g) in 96 % yield as a mixture of two isomers (*trans: cis* = 68: 32) by the Wittig olefination of 2-hydroxypyran (**20**, 1 g, 9.8 mmol) following the same reaction procedure as described for **21** employing triphenylphosphoranylidene acetonitrile (3.8 g, 12.6 mmol) instead of ethyl triphenylphosphoranylidene acetate.

^{1}H NMR (200 MHz) : 6.75 (0.7 H, dt, J = 16.2, 6.8 Hz), 6.51 (0.3 H, dt, J = 11.0, 7.5 Hz), 5.36 (1H, m), 3.65 (2H, m), 2.48 (0.6H, m), 2.27 (1.4H, m), 2.12 (1H, br s, OH), 1.58 (4H, m).

(b) Preparation of 7-Oxo-2-heptenonitrile (39):

Swern oxidation of 7-hydroxy-2-heptenonitrile (**38**, 1 g, 8 mmol), as described earlier for compound **21**, gave 1.0 g of crude 7-oxo-2-heptenonitrile (**39**, 100%).

^{1}H NMR (200 MHz) : 9.8 (1H, m), 6.7 (0.7H, dt, J = 16.3, 6.8 Hz), 6.48 (0.3H, dt, J = 11.1, 7.7 Hz), 5.38 (1H, m), 2.5 (2.6 H, m), 2.26 (1.4H, m), 1.82 (2H, m).

(c) *Preparation of 9-Oxo, 9-ethoxy-2 (E),7(E)-nonadienenitrile :*

Wittig reaction of the crude aldehyde (**39**, 1 g, 8 mmol) with ethyl triphenylphosphoranylidene acetate (3.34 g, 9.6 mmol) yielded 1.44 g (92%) of 9-oxo, 9-ethoxy-2 (E),7 (E)-nonadienenitrile (**40**).

^{1}H NMR (200 MHz) : δ 6.95 (1H, m), 6.7 (0.7H, dt, J =16.2, 6.7 Hz), 6.5 (0.3H, m), 5.85 (1H, dt, J = 14.8, 1.4 Hz), 5.4 (1H, dt, J = 16.2, 1.4 Hz), 4.2 (2H, q, J = 7.2 Hz), 2.8-2.4 (1H, m), 2.35-2.1 (3H, m), 1.9-1.5 (3H, m), 1.3 (3H, t, J = 7.2 Hz)

^{13}C NMR (50 MHz) : (major isomer) δ 201.35, 165.98, 154.74, 147.27, 121.97, 100.16, 59.88, 32.22, 30.93, 25.71,13.95

IR (neat) : 2938, 2223, 1719, 1655, 1640, 1445, 1191, 1042, 979, 864

MS (m/e) : 193 (M^+, 1), 148 (M^+ - OEt, 50), 127 (56), 120 (300), 99 (69), 93 (37), 81 (96), 53 (100).

6.8. PET Activation of 9-oxo, 9-ethoxy-2(E),7(E)-nonadienenitrile (40):

To a solution of DCA (0.11 g, 0.48 mmol) in DMF: i-PrOH: H_2O (500 mL), 0.50 g (2.59 mmol) of **40**, DMN (0.68 g, 0.36 mmol) and ascorbic acid (1.18 g, 6.7 mmol) were added and the mixture was irradiated in an analogous manner as mentioned earlier for **16**. After 22 h, irradiation was stopped and solvents were distilled off under reduced pressure. Column chromatographic purification of the concentrate yielded **41** (0.379 g, 75 %) as a non-separable mixture of isomers (*trans:cis* 80: 20; ratio obtained from GC analysis) along with a minor compound **42** (0.05 g, 10 %) also as a mixture of diastereomers (*dr* 3:2).

2-[2-(carboethoxymethyl)cyclopentyl]ethanenitrile (41):

^{1}H NMR (200 MHz) : 4.15 (2H, q, J = 7.3 Hz), 2.6-2.15 (4H, m), 2.1-1.58 (6H, m), 1.5-1.2 (5H, m, including 3H, t, at 1.3, J = 7.3 Hz)

^{13}C NMR (50 MHz) : 172.45, 118.89, 60.39, 41.50, 41.20, 39.04, 32.36, 31.95, 23.33, 21.78, 14.15.

IR (neat) : 2957, 2360, 1730, 1183, 1027.

MS (m/e) : 195 (M^+, 1), 155 (9), 150 (27), 122 (9), 109 (16), 88 (65), 80 (100), 67 (35), 61 (54), 54 (50).

GC/MS (m/e) : (major) 155 (24), 150 (99), 122 (40), 88 (100), 81 (84), 60 (43), 53 (41), 41 (68).
(minor) 155 (5), 150 (27), 88 (83), 81 (100), 67 (52), 53 (41), 41 (69).

Minor bicyclic compound 6-cyano-7-carboethoxy-bicyclo[3.2.0] heptane (42):

^{1}H NMR (200 MHz) : 4.4- 4.1 (2H, m), 3.75-3.6 (0.5H, m), 3.35-2.2 (3.5H, m), 2.1-1.88 (2H, m), 1.65-1.45 (4H, m), 1.4-1.15 (3H, m).

^{13}C NMR (50 MHz)	:	(major) 172.43, 118.56, 61.25, 44.22, 42.02, 36.74, 32.34, 29.08, 5.03, 24.66, 14.10. (minor) 172.12, 119.9, 61.25, 42.57, 41.38, 38.96, 31.98, 31.77, 7.66, 24.51, 14.1.
IR (neat)	:	2957, 2236, 1731, 1374, 1262, 1184, 1047, 1036.
MS (m/e)	:	193 (M^+, 0.5), 148 (M^+ - OEt, 12), 120 (35), 98 (33), 93 (44), 80 (24), 68 (100), 53 (27).
GC/MS (m/e)	:	(major) 166 (M^+ - HCN, 22), 164 (29), 148 (18), 120 (38), 98 (41), 93 (37), 80 (18), 68 (100), 41 (39). (minor) 166 (29), 148 (28), 120 (63), 98 (85), 93 (64), 80 (43), 68 (100), 67 (87), 53 (27), 41 (61).

6.9. Preparation of Dithyl-2(E),8(E)-decadien-1,10-dioate (52): This compound was synthesized in two steps starting from 1,6-hexanediol (**50**).

Dry pyridinium chlorochromate (22.84 g, 106 mmol) and celite (23 g) were placed in a 500 mL RB flask equipped with a magnetic stirring bar and an argon gas balloon. Dry CH_2Cl_2 (150 ml) was introduced in to the flask by a canulla. A solution of 1, 6-hexanediol (**50**, 5 g, 42.4 mmol) in CH_2Cl_2 (160 mL) was added very fast to the reaction mixture at r.t. by a an addition funnel. The suspended mixture was continued to stir for another 2 h. Et_2O (100 mL) was added to the reaction mixture. The resulting mixture was passed through a silica gel column and eluted with EtOAc: pet-ether to give 3.38 g (70 %) of adipaldehyde[61] (**51**) as a clear oil. Wittig reaction of **51** (1.0 g, 8.77 mmol) with ethyl triphenyl phosphoranylidene acetate (7.33 g, 21 mmol) by following the identical reaction condition as described for **22** gave dithyl-2 (E), 8 (E)-decadien-1,10-dioate (**52**; 1.92 g, 86 %) as an oil.

^{1}H NMR (200 MHz)	:	6.96 (2H, dt, J = 16.8, 5.8 Hz), 5.84 (2H, dt, J = 16.8, 2.4 Hz), 4.18 (4H, q, J = 7.1 Hz), 2.2 (4H, m), 1.48 (4H, m), 1.3 (6H, t, J = 7.1 Hz)
^{13}C NMR (50 MHz)	:	166.52 (2C), 148.25 (2C), 121.45 (2C), 59.78 (2C), 31.57 (2C), 27.26 (2C), 13.98 (2C).
IR (neat)	:	2980, 1720, 1655, 1460, 1367, 1263, 1045.
MS (m/e)	:	255 (M^+1, 3), 254 (M^+, 3), 209 (M^+ - OEt, 13), 208 (M^+ - EtOH, 12),

180 (42), 163 (54), 162 (37), 140 (37), 135 (87), 134 (73), 122 (18), 107 (85), 99 (44), 95 (52), 86 (37), 68 (70), 67 (77), 55 (100).

6.10. PET activation of Dithyl-2(E),8(E)-decadien-1,10-dioate (52):

PET activation of **52** involved the irradiation (25 h) of solution of DMF: *i*-PrOH: H_2O (300 mL) containing **52** (0.28 g., 1.1 mmol), Ph_3P (0.23 g, 0.88 mmol) and DCA (0.064 g, 0.28 mmol) by adopting the identical procedure as described for **16**. Usual work up and purification of the reaction mixture yielded 0.24 g (85 %) of ethyl-2-[2-(carboethoxymethyl)cyclohexyl]ethanoate (**53**) as a mixture of two isomers which were characterised as diastereomers (*trans:cis* 75:25) by GC/MS analysis.

Ethyl-2-[2-(carboethoxymethyl)cyclohexyl]ethanoate (53):

^{1}H NMR (200 MHz) : 4.12 (4H, q, J = 7.2 Hz), 2.5 (1H, dd, J = 14.6, 4 Hz), 2.2 (2H, m), 2.1 (1H, dd, J = 14.6, 8.8 Hz), 1.85-1.05 (16H, m, including 6H, t, at 1.26, J = 7.2 Hz)

^{13}C NMR (50 MHz) : (major) 172.4 (2C), 59.73 (2C), 38.82 (2C), 38.76 (2C), 32.10, 25.57 (2C), 13.91 (2C),
(minor) 172.4 (2C), 59.73 (2C), 35.44 (2C), 35.12 (2C), 28.58 (2C), 22.88 (2C), 13.91 (2C).

IR (neat) : 2928, 2856, 1718, 1477, 1465, 1421, 1367, 1301, 1240, 1159, 1032.

MS (m/e) : 257 (M^+ + 1, 4), 211 (M^+ - OEt, 64), 182 (28), 169 (99), 168 (57), 123 (90), 122 (55), 95 (100), 94 (58), 88 (45), 81 (96), 67 (58), 55 (60).

6.11. Preparation of 56: This compound was prepared in four steps starting from diethyl malonate (**30**) as described below:

(a) Preparation of compound (54):

Compound **54** was prepared (2.29 g,) in 70 % yield from diethyl malonate (**30**, 2 g, 12.5 mmol) by following the exactly same reaction procedure as described for **31** using 3,3-dimethoxy-iodopropane (2.87 g, 12.5 mmol) instead of 3,3-diethoxy-iodopropane.

(b) Preparation of Compound 55:

Into a dry 100 mL RB flask, fitted with reflux condenser, argon gas balloon and a magnetic stirring bar, was placed paraffin free NaH (0.35 g, 50%) and dry THF (30 mL). A solution of **54** (1.9 g, 7.25 mmol) dissolved in THF (5 mL) was added dropwise to the above stirring mixture at r.t.. The stirring was continued till the solution became clear (~45 min.). Solution of ethyl bromocrotonate (1.4 g, 7.25 mmol) in THF (5 mL) was added slowly to the reaction mixture and the whole content was heated in an oil bath at 45-50°C for 40 h. After cooling to r.t., water (15 mL) was added and diluted with Et_2O (50 mL). The organic layer was separated and the aqueous layer was further extracted with Et_2O (2×20 mL). The combined organic layer was washed with water, saturated brine solution and dried over Na_2SO_4. After evaporation of the solvent, the residue was column chromatographed over silica-gel to give 2.1 g (77%) of **55**.

^{1}H NMR (200 MHz)	:	6.8 (1H, dt, J = 16.2, 7.6 Hz), 5.87 (1H, d, J = 16.2 Hz), 4.35 (1H, t, J = 5.4 Hz), 4.30-4.05 (6H, m), 3.32 (6H, s), 2.72 (2H, d, J = 7.6 Hz), 2.02-1.80 (2H, m), 1.62-1.40 (2H, m), 1.35-1.15 (9H, m)
IR (neat)	:	2982, 2832, 2360, 1728, 1670, 1284, 1160, 1050, 980.
MS (m/e)	:	359 (M^+ - Me, 1), 343 (5), 329 (3), 271 (20), 255 (12), 141 (8), 225 (19), 183 (24), 123 (7), 107 (9), 91 (10), 85 (24), 79 (14), 75 (100), 71 (95), 58 (39), 55 (30)

Preparation of Compound 56:

To a solution of the compound **55** (1 g, 2.67 mmol) in 30 mL of acetonitrile was added a 5 % solution of HF(48 %) in acetonitrile (2.1 mL) at 0 °C with stirring. Progress of the reaction was monitored by TLC. After 3 min, the reaction was quenched by adding $CHCl_3$ (10 mL) and H_2O (10 mL). The reaction mixture was washed with aq $NaHCO_3$ and extracted with $CHCl_3$.The organic phase was dried over Na_2SO_4 and concentreted under vacuo to yield 0.84 g of crude aldehyde. This aldehyde was used as such for the Wittig reaction using ethyl triphenylphosphoranyledene acetate (1.16 g, 3.34 mmol) by following the identical reaction procedure as described for **22** to give 0.86 g of **56** as a clear liquid in 81 % overall yield starting from **55**.

^{1}H NMR (200 MHz)	:	6.9 (1H, dt, J = 15.6, 6.17 Hz), 6.80 (1H, dt, J = 15.6, 7.7 Hz), 5.9 (1H, dt, J = 15.6, 1.3 Hz), 5.84 (1H, dt, J = 15.6, 1.4 Hz), 4.3-4.1 (8H, m), 2.80 (2H, dd, J = 7.7, 1.3 Hz), 2.25-1.95 (2H, m), 1.40-1.20 (12H, m)
^{13}C NMR (50 MHz)	:	169.92 (2C), 165.85, 165.31, 146.81, 142.03, 124.96, 121.90, 61.32 (2C), 60.03, 59.86, 56.54, 35.46, 31.07, 26.63, 13.96 (2C), 13.77 (2C)
IR (neat)	:	2983, 1728, 1656, 1371, 1184, 1023.
MS (m/e)	:	398 (M^+, 2), 353 (14), 325 (10), 307 (16), 272 (12), 233 (21), 226 (29), 205 (51), 197 (17), 180 (49), 167 (17), 133 (25), 108 (41), 97 (52), 81 (80), 75 (47), 71 (84), 68 (73), 55 (100)

6.12. PET activation of 56:

0.318 g (0.80 mmol) of **56** and 0.168 g (0.64 mmol) of Ph_3P were dissolved in 300 mL solution of DMF: *i*-PrOH: H_2O (300 mL) containing 0.048 g (0.21 mmol) of DCA and mixture was irradiated for 20 h, as described for **16**. After removal of solvents and subsequent column chromatographic purification of the residue yielded 0.256 g (80 %) of 57 as a mixture of diastereomers (*trans:cis* 70:30) which were identified by GC/MS analysis.

Ethyl 2-[4,4-dicarboethoxy-2-(carboethoxymethyl)cyclohexyl]ethanoate (57):

^{1}H NMR (200 MHz)	:	4.35-4.02 (8H, m), 2.67-2.42 (2H, m), 2.40-1.98 (5H, m), 1.95-1.48 (5H, m), 1.4-1.15 (12H, m)
^{13}C NMR (50 MHz)	:	major 172.90, 172.57, 171.14, 171.91, 61.37, 61.30, 60.35 (2C), 54.90, 38.68 (2C), 37.90, 36.77, 35.59, 31.76, 28.80, 14.22 (4C) minor 172.14, 171.91, 170.59, 170.5, 61.17, 61.05, 60.35 (2C), 54.71, 38.16 (2C), 33.50, 32.95, 30.71, 26.48, 25.68, 14.04 (4C)
IR (neat)	:	2982, 2936, 2362, 1731, 1250, 1180, 1175
MS (m/e)	:	355 (28), 313 (100), 281 (20), 267 (53), 239 (27), 207 (33), 193 (51), 165 (36), 105 (21), 91 (21), 55 (7) [400 (M^+, 5), 355 (100), 341 (15), 337 (17), 326 (33)]

6.13. Synthesis of Diethyl 7-methylidene-2(E)-octen-1,8-dioate (61):

Compound **61** was prepared in four steps starting from triethylphophonoacetate (**58**) as described below:

(a) Preparation of 5-tert-butyldimethylsilyloxy-2-methylene hexanoate (59):

i) *4-tert-butyldimethylsilyloxy iodobutane:* To a stirred suspension of KI (26.9 g, 162.3 mmol) in 60 mL of dry THF, $BF_3.OEt_2$ (20 mL, 161.8 mmol) was added dropwise. The reaction mixture was stirred at r.t. for 12 h. Saturated $NaHCO_3$ solution (50 mL) was added to the solution and extracted with $CHCl_3$ (2×60 mL). The combined organic layer was washed with $Na_2S_2O_3$ solution (50 mL) followed by water (2×150 mL) and finally dried over anhydrous Na_2SO_4. Concentration of the dry organic layer under vacuo yielded 23.6 g (73%) of crude iodobutanol.[62]

To a stirred solution of the above alcohol (10.0 g, 50 mmol) and imidazole (7.5 g, 110 mmol) in CH_2Cl_2 (120 mL), *t*-butyldimethylsilylchloride (8.3 g, 55 mmol) was added at r.t. and stirring was continued for an additional 4 h. Reaction mixture was filtered and the filtrate was washed with H_2O (2×40 mL), saturated brine solution, dried over anhydrous Na_2SO_4 and concentrated under vacuo. Silica-gel column chromatographic purification of the concentrate afforded 15.1 g (95%) of 4-tert-butyldimethylsilyloxy iodobutane.

^{1}H NMR (90 MHz) : 3.65 (2H, t, J = 7.2 Hz), 3.23 (2H, t, J =7.8 Hz), 1.73 (4H, m), 0.88 (9H, s), 0.06 (6H, s).

ii) A previously dried 100 mL two neck RB flask fitted with a reflux condenser was charged with paraffin free NaH (1.07 g, 50%) and dry C_6H_6 (30 mL). Ttriethylphosphonoacetate (**58**, 5 g, 22.3 mmol) was added to the flask slowly under argon atmosphere at r.t. The mixture was stirred until it became clear (~30 min.). 4-*tert*-butyldimethylsilyloxy iodobutane (5.6 g, 17.85 mmol) in C_6H_6 (5 mL) was added dropwise to the mixture and the whole content was refluxed for 8 h. After cooling to 0°C,

an additional amount of NaH (1.07 g, 50%) was added at a time and the resulting mixture was allowed to stir for 45 min at r.t. Solid paraformaldehyde (1.0 g) was introduced portionwise by a solid addition flask and the reaction mixture was left stirring overnight at r.t. The mixture was diluted with 100 mL of Et_2O, suction filtered through small celite pad and washed with Et_2O (25 mL). The filtrate was concentrated under vacuo and subsequently purified by column chromatography over silica-gel to give ethyl 5-*tert*-butyl-dimethyl-silyloxy-2-methylenehexanoate (**59**, 2.76g, 54%)

^{1}H NMR (200 MHz)	:	6.15 (1H, s), 5.54 (1H, m), 4.22 (2H, q, J = 7.2 Hz), 3.67 (2H, m), 2.35 (2H, m), 1.52 (4H, m), 1.35 (3H, t, J = 7.2 Hz). 0.9 (9H, s), 0.05 (6H, s).
IR (neat)	:	2836, 2832, 1714, 1649, 1466, 1378, 1365, 1272, 1193, 1075, 1043, 982 .

*(b) Preparation of Ethyl 5-hydroxy-2-methylene hexanoate (**60**):*

To a stirred solution of **59** (1.5 g , 5.24 mmol) in CH_3CN (20 mL), was added aqueous solution of 48% HF (0.5 mL, 10.5 mmol) at r.t. and the progress of the reaction was monitored by TLC. After 30 min, 10% $NaHCO_3$ solution (5 mL) was added and the mixture was extracted with Et_2O (3×25 mL). The combined organic layer was washed with water, saturated brine solution and dried over anhydrous Na_2SO_4. Concentration under vacuo followed by column chromatographic purification of the residue on silica gel gave alcohol **60** (0.85 g, 94 %).

^{1}H NMR (200 MHz)	:	6.15 (1H, d, J = 1.35 Hz), 5.5 (1H, m), 4.22 (2H, q, J = 7.1 Hz), 3.68 (2H, t, J = 6 Hz), 2.35 (2H, t, J = 6.5 Hz), 1.75 (1H, s, OH), 1.6 (4H, m), 1.32 (3H, t, J = 7.1 Hz).
^{13}C NMR (50 MHz)	:	167.54, 140.84, 124.68, 62.35, 60.75, 32.18, 31.62, 24.74, 14.24.
IR (neat)	:	3428 (br., OH), 2936, 1716, 1648, 1372, 1274, 1188, 1042, 982 .
MS (m/e)	:	173 (M^+ + 1, 7), 155 (4), 142 (12), 126 (99), 111 (57), 98 (95), 81 (100), 67 (58), 55 (56).

(c) Preparation of diethyl 7-methylidene-2(E)-octen-1,8-dioate (61) :

This compound was prepared (0.76 g, 91%) by Wittig reaction of ethyl-5-oxo-2-methylene hexanoate (0.59 g, 3.47 mmol), obtained by Swern oxidation of alcohol **60** (0.6 g, 3.49 mmol), with ethyl triphenylphosphoranylidene-acetate (1.45 g, 4.16 mmol) in an analogous manner as described for **22**.

^{1}H NMR (200 MHz)	:	6.95 (1H, dt, J = 15.6, 6.9 Hz), 6.15 (1H, d, 1.2 Hz), 5.8 (1H, dt, J = 15.6, 1.7 Hz), 5.50 (1H, m), 4.15 (4H, m), 2.25 (4H, m), 1.60 (2H, m), 1.25 (6H, m)
^{13}C NMR (50 MHz)	:	(major) 166.84, 166.37, 148.32, 124.69, 121.74, 60.51, 60.0, 31.47, 26.77, 14.16 (2C)
IR (neat)	:	2981, 2890, 1718, 1652, 1440, 1370, 1027.
MS (m/e)	:	240 (M^+, 6), 241 (3), 194 (30), 167 (50), 148 (66), 126 (81), 121 (51), 98 (81), 92 (94), 80 (100), 68 (54), 54 (50)

6.14. PET Activation of Diethyl 7-methylidene-2(E)-octen-1,8-dioate (61):

0.25 g (1.04 mmol) of **61** and 0.273 g (1.04 mmol) of Ph_3P were dissolved in solution of DMF: *i*-PrOH: H_2O (300 mL) containing of DCA (0.068 g, 0.30 mmol) and mixture was irradiated for 28 h in an identical reaction setup as discussed for **16**. After removal of solvents and column chromatographic separation, the crude mixture yielded 0.15 g (60 %) of ethyl-3-(carboethoxy)methyl-cyclohexanecarboxylate (**62**) as a non-separable mixture of two isomers (3:2) along with 0.016 g (5 %) of Ethyl-1-(2-hydroxypropyl)-3-(carboethoxy)methyl-cyclohexanecarboxylate (**63**).

Ethyl-3-(carboethoxy)methyl-cyclohexanecarboxylate (62):

^{1}H NMR (200 MHz)	:	4.15 (4H, m), 2.75-2.20 (3H, m), 2.15-1.35 (7H, m), 1.30-1.05 (8H, m)
IR (neat)	:	2920, 2860, 1730, 1472, 1320, 1015.
MS (m/e)	:	242 (M+, 8), 181 (17), 168 (100), 154 (57), 122 (47), 109 (41), 95 (60), 81 (60), 55 (51)

Ethyl-1-(2-hydroxypropyl)-3-(carboethoxy)methyl-cyclohexanecarboxylate (63):

^{1}H NMR (200 MHz)	:	4.2 (4H, q, J = 7,2 Hz), 2.6-2.45 (2H, m), 2.35-1.60 (10H, m), 1.45 (6H, s), 1.3 (6H, t, J = 7.2 Hz).
^{13}C NMR (75 MHz)	:	180.72, 171.78, 81.14, 60.49 (2C), 53.67, 43,52, 41.59, 40.36, 35.71, 31.01, 29.70, 29.28, 22.37, 14.01 (2C)
IR (neat)	:	3420, 2956, 1720, 1465, 1430. 1350, 1120, 1070.
MS (m/e)	:	254 (M^+ - EtOH, 10), 239 (13), 221 (4), 213 (34), 167 (31), 154 (15), 136 (24), 122 (100), 107 (76), 93 (54), 81 (56), 67 (41), 55 (37)

6.15. Preparation of1-ethoxy-5 (3-ethoxy-3-oxo-1(E)-propenyloxy)-2(E)-penten-1-one (154) :

This compound was prepared in three steps starting from 1,3-propanediol as described below :

(a) *Preparation of 3(3-hydroxypropyloxy)-1-ethoxy-2 (E)-propen-1-one (153):*

N-Methylmorpholine (1.06 g, 10.5 mmol) and dry CH_2Cl_2 (20 mL) were placed in a 100 mL two necked RB flask equipped with a magnetic stirring bar and an argon gas balloon. Methylpropiolate (1.03 g, 10.5 mmol) in CH_2Cl_2 (5 mL) was slowly added to the stirring solution at 0 °C and stirring was continued for 5 min for the completion of the complex formation between ethylpropiolate and NMM. This cold reaction mixture was then added by a syringe to a solution of 1,3-propandiol (1 g, 13.14 mmol) in CH_2Cl_2 (20 mL) kept in an another two neck RB flask fitted with magnetic stirring bar and argon gas balloon at 0 °C. After continuous stirring at r.t. for another 10 h, the reaction mixture was washed with water (3 x 40 mL), brine solution and dried over anhydrous Na_2SO_4 and finally concentrated under vacuo. Column chromatographic purification of the concentrate over silica-gel gave 1.6 g of **153** (70 %) as a thick liquid.

^{1}H NMR (200 MHz)	:	δ 7.6 (1H, d, J = 12.2 Hz), 5.2 (1H, d, J = 12.2 Hz), 4.15 (2H, q, J = 7.3 Hz), 4.01 (2H, t, J = 6.1 Hz), 3.8 (2H, t, J = 6.1 Hz), 1.95 (2H, m), 1.3 (3H, t, J = 7.3 Hz).

IR (neat) : 3400 (br), 2980, 2887, 1708, 1625, 1329, 1239, 1141, 1048

(b) Preparation of 1-ethoxy-5 (-3-ethoxy-3-oxo-1 (E)-propenyloxy)-2(E)-penten-1-one (154) :

Compound **154** was prepared (0.81 g, 96 %) by the Wittig reaction of the corresponding aldehyde, (0.6 g, 3.48 mmol), obtained by Swern oxidation of alcohol **153** (1.01 g, 5.8 mmol), with ethyl triphenylphosphoranylidene-acetate (1.58 g, 4.53 mmol) following the same reaction procedure as described for **21**.

^{1}H NMR (200 MHz) : δ 7.55 (1H, d, J = 12.2 Hz), 6.9 (1H, dt, J = 15.6 Hz, J = 6.1 Hz), 5.9 (1H, dt, J = 15.6 Hz, J = 1.4 Hz), 5.2 (1H, d, J = 12.2 Hz), 4.2 (4H, q, J = 7.3 Hz), 3.95 (2H, t, J = 6.1 Hz), 2.6 (2H, m), 1.25 (6H, m).

^{13}C NMR (75 MHz) : 167.45, 165.96, 166.77, 143.36, 123.95, 97, 68.60, 60.30, 59.74, 31.48, 14.28, 14.18.

IR (neat) : 2929, 2360, 1712, 1626, 1368, 1136, 1041

MS (m/e) : 242 (M^+, 1), 197 (25), 168 (100), 140 (28), 127 (30), 99 (78), 81 (72), 71 (41).

6.16. PET Activation of 154:

PET activation of **154** involved the irradiation (18 h) of the solution of DMF: *i*-PrOH: H_2O containing **154** (0.2 g., 0.826 mmol), Ph_3P (0.173 g, 0.66 mmol) and DCA (0.064 g, 0.28 mmol), in an identical manner as described for **16**. Usual work up and purification of the reaction mixture yielded 0.137 g (68%) of *trans* 1-ethoxy-2 (2-(2-ethoxy-oxoethyl)perhydro3-furanyl)-1-ethanone **(155)** along with minor amount of **156** (0.044 g, 22 %). Minor product was observed in GC analysis of the reaction mixture which could be assigned as *cis* diastereomer **156** by GC/MS fragmentation pattern and NMR spectroscopic experiments.

trans 1-Ethoxy-2 (2-(2-ethoxy-oxoethyl) perhydro3-furanyl)-1-ethanone (155) :

^{1}H NMR (200 MHz)	:	δ 4.45-4.05 (5H m), 4.0-3.75 (2H, m), 2.1-2.65 (5H, m), 1.6-1.8 (2H, m), 1.25 (6H, t, J = 7.2 Hz)
^{13}C NMR (50 MHz)	:	δ 172.25, 171.28, 80.19, 67.02, 60.63 (2C), 40.67, 39.89, 37.65, 32.89, 14.28 (2C).
IR (neat)	:	2956, 1735, 1372, 1253, 1154, 1032.
MS (m/e)	:	244 (M^+, 1), 199 (13), 181 (4), 170 (77), 157 (100), 141 (2), 129 (14), 115 (17), 97 (10), 83 (21), 55 (11).

cis-1-Ethoxy-2 (2-(2-ethoxy-oxoethyl) perhydro3-furanyl)-1-ethanone (156):

^{1}H NMR (200 MHz)	:	4.25-4.06 (4H, m), 4.05-3.80 (2H, m), 3.62-3.35 (1H, m), 2.85-2.28 (3H, m), 2.20-1.98 (2H, m), 1.95-1.55 (2H, m), 1.25 (6H, t, J = 7.0 Hz)
^{13}C NMR (75 MHz)	:	173.11, 170.68, 75.04, 67.93, 60.33 (2C), 47.06, 39.79, 27.29, 24.72, 14.07 (2C)
IR (neat)	:	2933, 2855, 1733, 1407, 1376, 1177, 1110, 1031, 750
GC/MS	:	198 (M^+ - EtOH, 38), 170 (43), 157 (28), 153 (53), 128 (23), 100 (49), 83 (24), 55 (100), 43 (50).

6.17. Preparation of 1-ethoxy-6-(3-methoxy-3-oxo-1(E)-propenyloxy)-2(E)-hexen-1-one (161): This compound was prepared from 1,4-butanediol following the same reaction sequence as described for **154**.

(a) Preparation of 3(4-hydroxybutyloxy)-1-methoxy-2(E)-propen-1-one :

It was obtained (1.35 g) in 70% yield from 1,4-butanediol following the same reaction procedure as **154** using methylpropiolate (0.75 g, 8.92 mmol) instead of ethylpropiolate.

^{1}H NMR (300 MHz)	:	δ 7.65 (1H, d, J = 13.4 Hz), 5.15 (1H, d, J = 13.4 Hz), 3.85 (2H, t, J = 6.2 Hz), 3.69, (3H, s), 3.65 (2H, t, J = 6.1 Hz), 1.95 (2H, m), 1.88-1.75 (2H, m), 1.73-1.60 (2H, m).

IR (neat) : 3417 (br), 2952, 2361, 1710, 1625, 1439, 1335, 1214, 1145, 1048, 825

(b) 1-ethoxy-6-(3-methoxy-3-oxo-1(E)-propenyloxy)-2(E)-hexen-1-one (161):

Swern oxidation of **160** (0.7 g, mmol) as described earlier for compound **16** gave crude aldehyde (0.7 g, 100%). Wittig reaction of the crude aldehyde (0.7 g, 4.06 mmol) with ethyl triphenylphosphoranylidene acetate (1.84 g, 5.28 mmol) yielded 0.9 g (92%) of **161**.

^{1}**H NMR** (200 MHz) : δ 7.58 (1H, d, J = 12.6 Hz), 6.93 (1H, dt, J = 15.6 Hz, J = 6.9 Hz), 5.84 (1H, dt, J = 15.6 Hz, J = 1.56 Hz), 5.20 (1H, d, J = 12.6 Hz), 4.2 (2H, q, J = 7.25 Hz), 3.85 (2H, t, J = 6.2 Hz), 3.7 (3H, s), 2.3 (2H, m), 1.85 (2H, m), 1.3 (3H, t, J = 7.25 Hz).

^{13}**C NMR** (50 MHz) : δ 167.52, 165.78, 161.98, 146.89, 121.98, 96, 69.59, 59.78, 50.53, 27.98, 27, 13.88.

IR (neat) : 3020, 2952, 1713, 1653, 1626, 1510, 1500, 1466, 1390, 1295, 1095, 956, 823.

MS (m/e) : 242 (M^+, 1), 243 (M^+ +1, 1), 211 (M^+ - OMe, 19), 197 (M^+ - OEt, 9), 182 (27), 168 (32), 155 (8), 141 (21), 127 (30), 113 (68), 95 (100), 84 (83), 71 (48), 67 (84).

6.18. PET Activation of 161 :

To a solution of DCA (0.07 g, 0.307 mmol) in DMF: i-PrOH: H_2O (300 mL), 0.29 g (1.2 mmol) of **46** and Ph_3P (0.25 g, 0.953 mmol) were added and the mixture was irradiated in an analogous manner as mentioned for **16**. After 30 h, irradiation was stopped and solvents were distilled off under reduced pressure. Column chromatographic purification of the concentrate yielded **62** (0.140 g, 48%),), 0.35 g as a mixture of **162** and **163** along with reduced product (**164**, 0.044 g, 15 %).

trans 1-Ethoxy-2-(2-(2-methoxy-2-oxoethyl) perhydro-3-pyranyl)-1-ethanone (162):

^{1}H NMR (200 MHz)	:	δ 4.2 (2H, q, J = 7.1 Hz), 3.9 (1H, m), 3.7 (3H, s), 3.6-3.3 (2H, m), 2.65-2.25 (4H, m), 2.1 (1H, m), 1.90-1.75 (2H, m), 1.70-1.45 (1H, m), 1.35-1.20 (4H, m, including a triplet at 1.2, J = 7.1 Hz).
^{13}C NMR (50 MHz)	:	δ 172.23, 78.60, 68.40, 60.73, 51.93, 39.27, 37.72, 37.60, 30.01, 26.11, 14.42.
IR (neat)	:	3020, 2855, 2400, 1731, 1439, 1217, 1024, 756
MS (m/e)	:	244 (M^+, 1), 213 (M+ - OMe, 7), 199 (M^+ - OEt, 9), 171 (17), 157 (100), 125 (28), 115 (12), 97 (68), 82 (19), 68 (32), 55 (28).

Product (**164**) :

^{1}H NMR (300 MHz)	:	δ 7.52 (1H, d, J = 12.5 Hz),), 5.20 (1H, d, J = 12.5 Hz), 4.15 (2H, q, J = 7.3 Hz), 3.82 (2H, t, J = 6.3 Hz), 3.68 (3H, s), 2.30 (2H, t, J = 6.25 Hz), 1.80-1.35 (6H, m), 1.30 (3H, t, J = 7.3 Hz).
^{13}C NMR (75 MHz)	:	172.59, 167.42, 161.94, 95.45, 70.21, 59.50, 50.22, 33.38, 27.94, 24.69, 23.89, 13.56

6.19. Preparation of 1-methoxy-3-(2-(3-methoxy-3-oxo-1(E)-propenyloxy)-2(E)-propen-1-one (172) :

This compound was prepared in three steps from 1,2-ethanediol (**171**) as described below.

N-methylmorpholine (1.26 g, 12.5 mmol) and dry CH_2Cl_2 (10 mL) were placed in a 50 mL two necked RB flask equipped with a magnetic stirring bar and an argon gas balloon. Methylpropilate (1.05 g, 12.5 mmol) in CH_2Cl_2 (5 mL) was slowly added to the stirring solution at 0 °C and stirring was continued for 5 min. A solution of 1,2-ethanediol (**171**, 0.37 g, 5.97 mmol) in CH_2Cl_2 (10 mL) was slowly added by an addition funnel to the stirring solution at 0 °C and the reaction mixture was allowed to stirr at r.t. for another 10 h. The reaction mixture was washed with water (3 x 40 mL), brine solution and dried over anhydrous Na_2SO_4 and finally concentrated under vacuo. The concentrate was purified by column chromatography over silica-gel to give 0.96 g of **172** (70 %) as a thick liquid.

^{1}H NMR (200 MHz) : δ 7.6 (2H, d, J = 12.7 Hz), 5.25 (2H, d, J = 12.7 Hz), 4.1 (4H, s), 3.7 (6H, s).

^{13}C NMR (75 MHz) : δ 167.42 (2C), 161.53 (2C), 96.92 (2C), 68.49 (2C), 50.88 (2C).

IR (neat) : 3098, 2955, 2366, 1711, 1625, 1449, 1344, 1244, 1192, 1141, 1130, 1111, 1045, 984, 858, 827.

MS (m/e) : 199 (7), 171 (11), 129 (43), 97 (16), 85 (36), 73 (56), 69 (58), 59 (100), 55 (17)
[230 (M^+, 3), 199 (64), 187 (3), 171 (100), 167 (26), 155 (18), 145 (47), 139 (29)].

6.20. PET Activation 172:

PET activation of **172** involved the irradiation (32 h) of a solution of DMF: *i*-PrOH: H_2O (700 mL) containing **172** (0.7 g., 3.04 mmol), Ph_3P (0.64 g, 2.44 mmol) and DCA (0.192 g, 0.84 mmol) in an analogous manner as described for **16**. Usual work up and purification of the reaction mixture yielded 0.564 g (80 %) of 1-methoxy-2 (3 (2-methoxy-2-oxoethyl) [1,4] diox-2-yl)-1-ethanone (**173**) as a mixture of two diastereomers (dr 95:5). Minor product was observed in GC analysis of the reaction mixture which could be assigned as the *cis*-diastereomer of **173** by GC/MS analysis.

1-Methoxy-2 (3 (2-methoxy-2-oxoethyl) [1,4] diox-2-yl)-1-ethanone (173)

^{1}H NMR (200 MHz) : δ 3.80-3.60 (12H, m, including 6H, s, at 3.7), 2.45 (4H, d, J = 6.1 Hz)

^{13}C NMR (75 MHz) : δ (major) 170.71, (2C), 75.55 (2C), 66.50 (2C), 51.62 (2C), 36.77
(minor) 170.71, (2C), 72.32 (2C), 63.09 (2C), 50.81 (2C), 33.76

IR (neat) : 2957, 2861, 2361, 1740, 1627, 1440, 1385, 1309, 1271, 1252, 1157, 1119, 926, 895

MS (m/e) : 232 (M^+, 6), 200 (41), 158 (67), 145 (10), 129 (37), 115 (13), 99 (100), 81 (15), 74 (73), 65 (8), 59 (92), 55 (33)

6.21. Preparation of 1-ethoxy-3-(1-methyl-2-(3-ethoxy-3-oxo-1 (E)-propenyl) ethyloxy)-2 (E)-propen-1-one (175):

Compound **175** was obtained (1.07 g) in 75 % yield from 1,2-propanediol (**174**, 0.4 g, 5.26 mmol) by following the same reaction procedure as described for **172**.

^{1}H NMR (200 MHz)	:	δ 7.58 (1H, d, *J* = 12.65 Hz), 7.48 (1H, d, *J* = 12.7 Hz), 5.38 (1H, d, *J* = 12.65 Hz), 5.2 (1H, d, *J* = 12.7 Hz), 4.35 (1H, m), 4.2 (4H, q, *J* = 7.2 Hz), 3.88 (2H, d, *J* = 5.1 Hz), 1.33 (3H, d, *J* = 6.7 Hz), 1.26 (3H, q, *J* = 7.2 Hz)
^{13}C NMR (75 MHz)	:	δ 167.3, 166.99, 161.5, 161.1, 97.99, 97.28, 76.7, 73, 59.5, 59.4, 16.1.
IR (neat)	:	2982, 1708, 1642, 1625, 1133.
MS (m/e)	:	227 (M^+ - OEt, 6), 199 (5), 185 (18), 157 (19), 129 (9), 111 (10), 100 (25), 87 (92), 71 (100), 59 (18), 55 (28).

6.22. PET Activation of 175:

A solution of **175** (0.3 g, 1.1 mmol), DCA (0.07 g, 0.307 mmol), and Ph_3P (0.23 g, 0.88 mmol) in DMF: i-PrOH: H_2O (300 mL) was irradiated in an analogous manner as mentioned for **16**. After 32 h, irradiation was stopped and solvents were removed by distillation under reduced pressure. Column chromatographic purification of the concentrate yielded **176** (0.227 g, 75 %) as a non-separable mixture of isomers (*dr* 95:5; ratio estimated from GC analysis).

^{1}H NMR (200 MHz)	:	δ 4.11-4.22 (4H, q, *J* = 7.2 Hz), 3.6-3.8 (4H, m), 3.25 (1H, dd, *J* = 11.6, 10.9 Hz), 2.4 (4H, m), 1.25 (6H, t, J = 7.1 Hz), 1.05 (3H, d, *J* = 6.2 Hz)
^{13}C NMR (75 MHz)	:	δ 170.16 (2C), 75.47, 75, 71.92, 71.26, 60.32, 60.26, 37, 36.75, 16.26, 13.86 (2C)
IR (neat)	:	2980, 2875, 3261, 1738, 1374, 1160, 1094, 1026, 950, 830.
MS (m/e)	:	274 (M+, 3.4), 275 (M^+ +1, 2.5), 229 (M^+ - OEt, 34), 170 (92), 143 (59), 125 (17), 113 (63), 97 (29), 75 (10), 71 (100), 59 (33), 55 (36).

6.23. Preparation of 1-ethoxy-3-(1(R)-phenyl-2(3-ethoxy-3-oxo-1(E)-propenyloxy) ethyloxy)-2(E)-propen-1-one (212) :

This compound was prepared in two steps starting from (R)-mandelic acid as described below.

(a) Preparation of (R)-(-)-1-phenyl-1,2-ethanediol:

To a refluxing suspension of lithium aluminium hydride (1 g, 26.35 mmol) in Et_2O (50 mL) was introduced slowly mandelic acid (**210**, 2 g, mmol) by a solid addition flask with continued stirring under argon atmosphere at such a rate that gentle reflux was maintained. The contents were refluxed for another 6 h. After cooling, the reaction was cautiously quenched by conc NaOH solution. The Et_2O layer was separated and the precipitate was washed with Et_2O (2×25 mL). The combined organic layer was washed with saturated brine solution, dried over Na_2SO_4 and concentrated under vacuo to give **211** as a white solid (1.67g, 93 %).

MP : 66-69 °C

$[\alpha]_D^{22}$: -68 ° (C = 1, $CHCl_3$)

(b) Preparation of 212:

Compound **212** was obtained (1 g) in 83 % yield from **211** (0.5 g, 3.62 mmol) by following the same reaction procedure as described for **172**.

$[\alpha]_D^{22}$: -34.52 °(C = 0.84, MeOH)

^{1}H NMR (200 MHz) : 7.55 (1H, d, *J* = 12.5 Hz), 7.50 (1H, d, *J* = 12.6 Hz), 7.45-7.25 (5H, m), 5.30 (1H, d, *J* = 12.6 Hz), 5.25 (1H, d, *J* = 12.5 Hz), 5.15 (1H, dd, *J* = 10.8, 5.4 Hz), 4.25-3.95 (4H, m), 1.35-1.15 (6H, m)

^{13}C NMR (75 MHz) : 166.98, 161.51, 160.64, 135.31, 128.91, 128.80, 126.31, 99.20, 97.48, 81.72, 77.93, 77.28, 76.65, 73.53, 59.53, 14.08

IR (neat) : 2982, 1708, 1642, 1628, 1370, 1326, 1288, 1194, 1173, 1097, 1048, 757

MS (m/e) : 289 (1), 219 (17), 191 (10), 173 (7), 163 (5), 145 (100), 129 (27), 117 (47), 104 (83), 91 (33), 77 (29), 71 (25), 57 (9)

6.24. PET Activation of 212:

To a solution of DCA (0.175 g, 0.77 mmol) in DMF: i-PrOH: H_2O (700 mL), **212** (0.60 g, 1.80 mmol) and Ph_3P (0.47 g, 1.80 mmol) were added and the mixture was irradiated in an analogous manner as mentioned for **16**. After 35 h, irradiation was stopped and solvents were distilled off under reduced pressure. Column chromatographic purification of the concentrate yielded 0.398 g of (2*S*, 3*S*, 6*R*) 2,3-dicarboethoxymethyl-6-phenyl-1,4-dioxan (**213**) (65 %) as a single diastereomer along with a cleavage product (**214**, .060 g, 10 %).

(2*S*, 3*S*, 6*R*) 2,3-dicarboethoxymethyl-6-phenyl-1,4-dioxan (**213**) :

$[\alpha]_D^{22}$: -66.90 °(C = 0.94, MeOH).

^{1}**H NMR** (200 MHz) : 7.45-7.3 (5H, m), 4.67 (1H, dd, *J* = 10.9, 2.4 Hz), 4.2 (4H, q, *J* = 7.3 Hz), 4.1-3.8 (3H, m), 3.5 (1H, dd, *J* = 10.9, 12.2 Hz), 2.55 (4H, m), 1.25 (6H, m)

^{13}**C NMR** (75 MHz) : 170.63, 170.56, 137.91, 128.47, 128.07, 126.19, 77.65, 76.06, 75.54, 72.43, 60.95, 60.85, 37.54, 37.24, 14.28

IR (neat) : 2982, 2902, 2362, 1736, 1251, 1112, 755

MS (m/e) : 337 (M^+ + 1, 1), 291 (M+ - OEt, 3), 216 (10), 184 (7), 170 (28), 143 (17), 129 (9), 125 (5), 104 (100), 97 (8), 91 (20), 85 (6), 77 (19), 69 (6), 55 (18)

Cleavage product **214** :

^{1}**H NMR** (200 MHz) : 7.6 (1H, d, *J* = 13.4 Hz), 7.4-7.15 (5H, m), 5.2 (1H, d, *J* = 13.4 Hz), 4.25-3.95 (4H, m), 3.05 (2H, t, *J* = 7.3 Hz), 1.28 (3H, t, *J* = 7.3 Hz).

6.25. Preparation of(2S, 3S, 6R)-6-phenyl-2,3-di-(2-hydroxy)ethyl-1,4-dioxan (216) :

Compound **216** was obtained (0.13 g, 98 %) by LAH (0.025 g, 0.66 mmol) reduction of **213** (0.18 g, 0.535 mmol) by following exactly the same procudure as described for **211**.

^{1}**H NMR** (200 MHz) : 7.42-7.25 (5H, m), 4.65 (1H, dd, J = 10.6, 2.4 Hz), 3.68-3.40 (8H, m), 2.48 (br, s, OH), 1.98-1.42 (4H, m)

6.26. Preparation of(2S, 3S, 6R)-2,3-di-(2-t-butyldimethylsilyloxy)ethyl-6-phenyl-1,4-dioxan (217):

To a stirred solution of **216** (0.10 g, 0,4 mmol) and imidazole (0.12 g, 1.76 mmol) in CH_2Cl_2 (15 mL), *t*-butyldimethylsilylchloride (0,133g, 0.88 mmol) was added at r.t. and stirring was continued for another 4 h. Reaction mixture was filtered and the filtrate was washed with H_2O (2×10 mL), saturated brine solution, dried over Na_2SO_4 and concentrated under vacuum. Silica gel column chromatographic purification of the concentrate afforded 0.187 g of **217** (98 %) as a gummy liquid.

^{1}**H NMR** (200 MHz) : 7.40-7.18 (5H, m), 4.68 (1H, dd, J = 10.6, 2.4 Hz), 3.70-3.42 (8H, m), 1.98-1.45 (4H, m), 0.9 (18H, s), 0.1 (12H, s).

6.27. Preparation of trans (-)-(3S, 4S)-1,6-di(t-butyldimethylsilyloxy)-3,4-hexanediol (218) :

To a dry and distilled liquid ammonia (10 mL) collected in a 25 mL two neck RB flask equipped with a magnetic stirring bar and a cold finger condenser, was added Na (0.05 g, 2.2 mmol) at -78 °C under argon atmosphere and stirring was continued for 10 min. A solution of **217** (0.1 g, 0,21 mmol) in dry THF (2 mL) was added slowly by a syringe and the reaction mixture was allowed to stir at -78 °C for another 20 min. The

reaction was quenched by adding solid ammonium chloride (1 g) and the cooling bath was removed. Ammonia was distilled off by allowing the reaction mixture to come to r.t. and residue was washed with ethyl acetate (2 × 10 mL). Removal of solvent followed by column chromatographic purification yielded 0.078 g of **218** (100 %).

$[\alpha]_D^{22}$	:	-24.5 (C = 0.24, MeOH).
^{1}H NMR (200 MHz)	:	3.98-3.82 (4H, m), 3.80-3.65 (2H, m), 3.55-3.45 (br, s, 1H), 1.85-1.72 (4H, m), 1.70-1.55 (br, s, OH), 0-9.2 (18H, 3), 0.10 (12H, S)
^{13}C NMR (75 MHz)	:	73.30, 61.51, 35.18, 25.78, 18.10, -5.58.
IR (neat)	:	3471 (br, OH), 2930, 2858, 2362, 1471, 1256, 1090, 836, 758.
MS (m/e)	:	321 [M^+ - 57 (t-Bu), 5], 312 (1), 304 (3), 229 (3), 189 (37), 171 (38), 159 (10), 133 (13), 115 (20), 105 (28), 97 (511), 89 (63), 75 (100), 69 (12), 59 (8).

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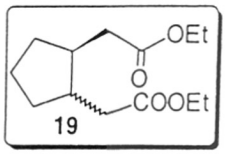
Spectra

Fig. 1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O
COOEt
19

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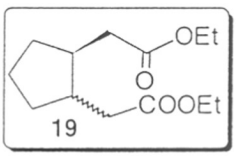
6.00
5.00
PPM
4.00
3.00
2.00
1.00
0.0

Fig. 3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COOEt
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50.0
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155
197
168
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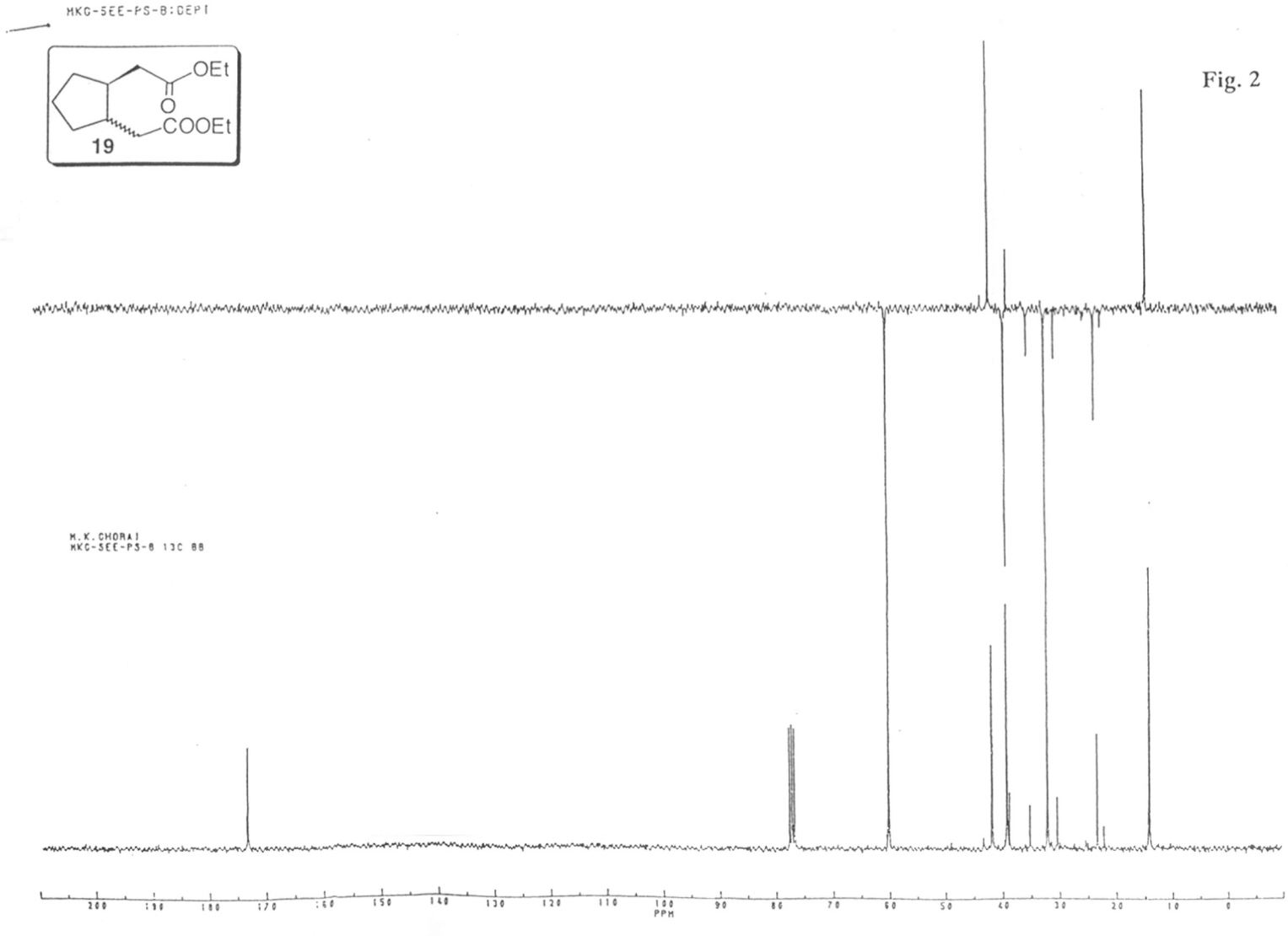
94
98
127
55
99
139
243
179
188
213
229
263
271
282
291

Fig. 2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COOEt
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M.K.CHORAI
MKG-5EE-PS-8 13C BB
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190
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100
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60
50
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30
20
10
0
PPM

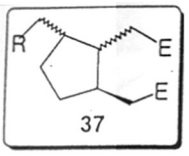
R
E
E
37

Fig. 4

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7.50
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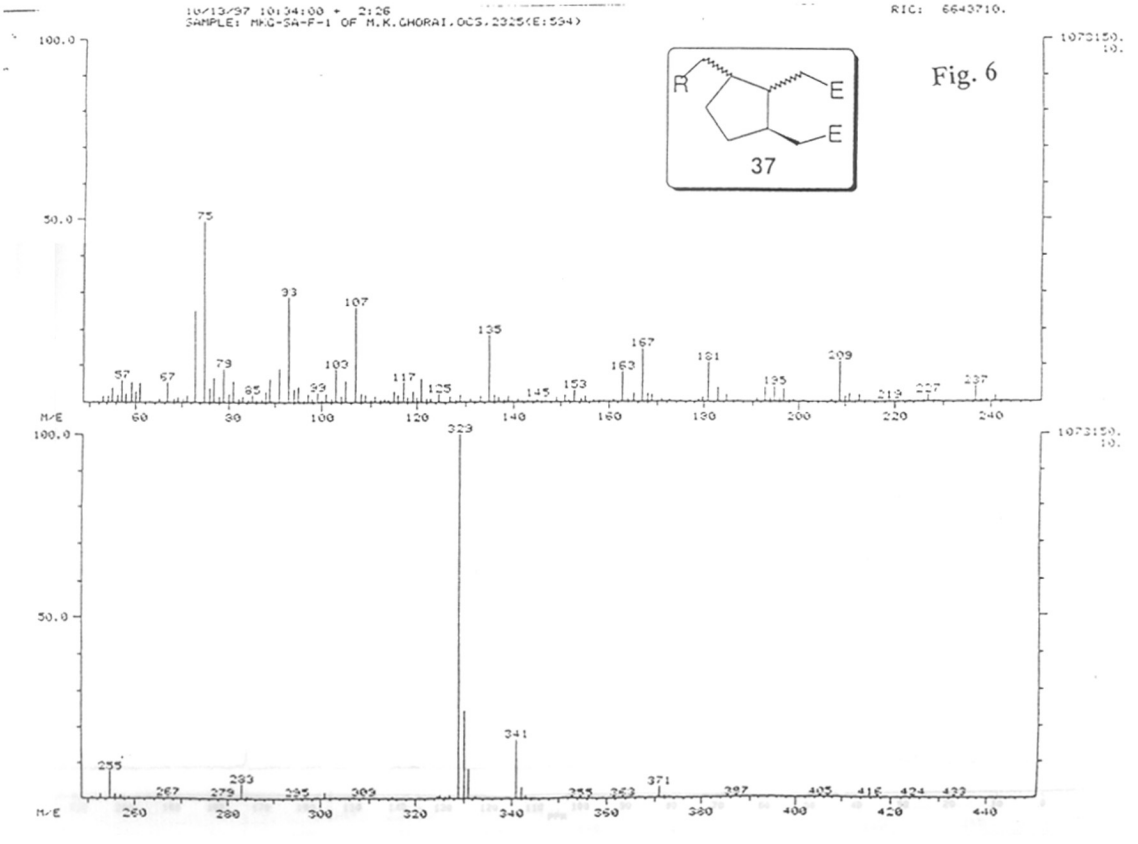
PPM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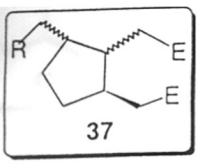
50.0
M/E
75
93
107
135
167
163
181
209
323
341
295
371

R
E
E
37

Fig. 6

Fig. 5



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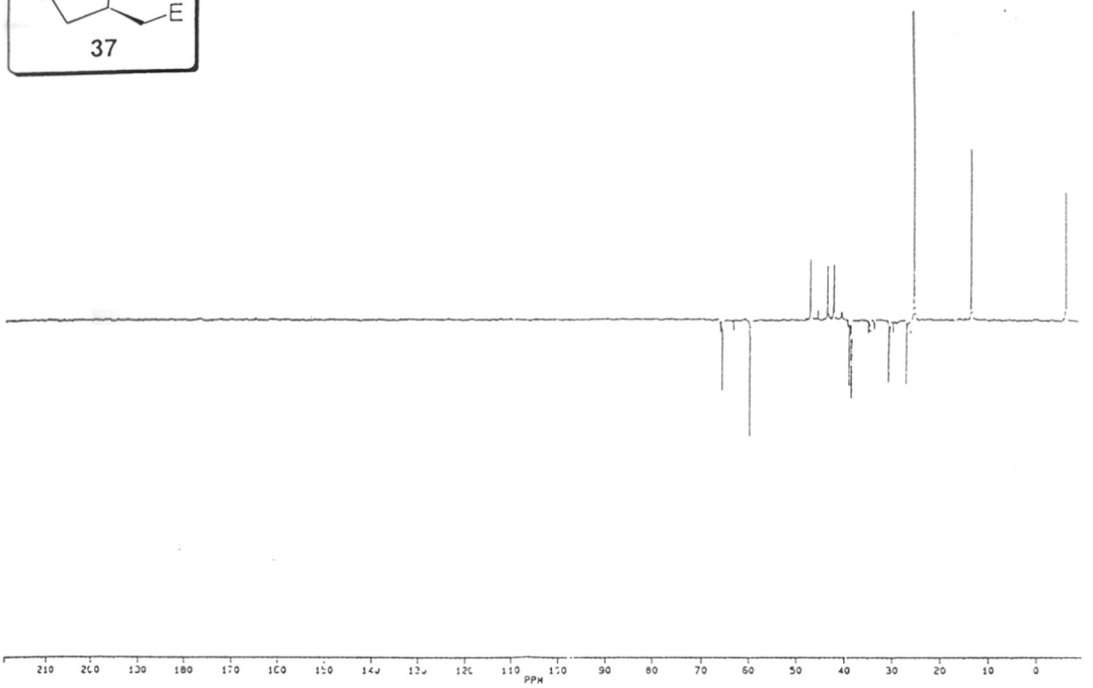

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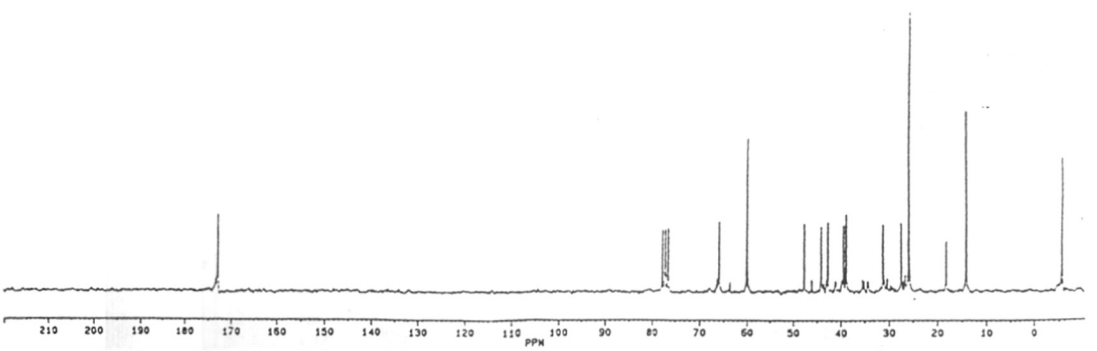

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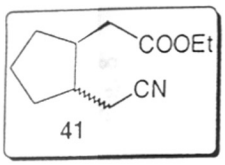
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CN
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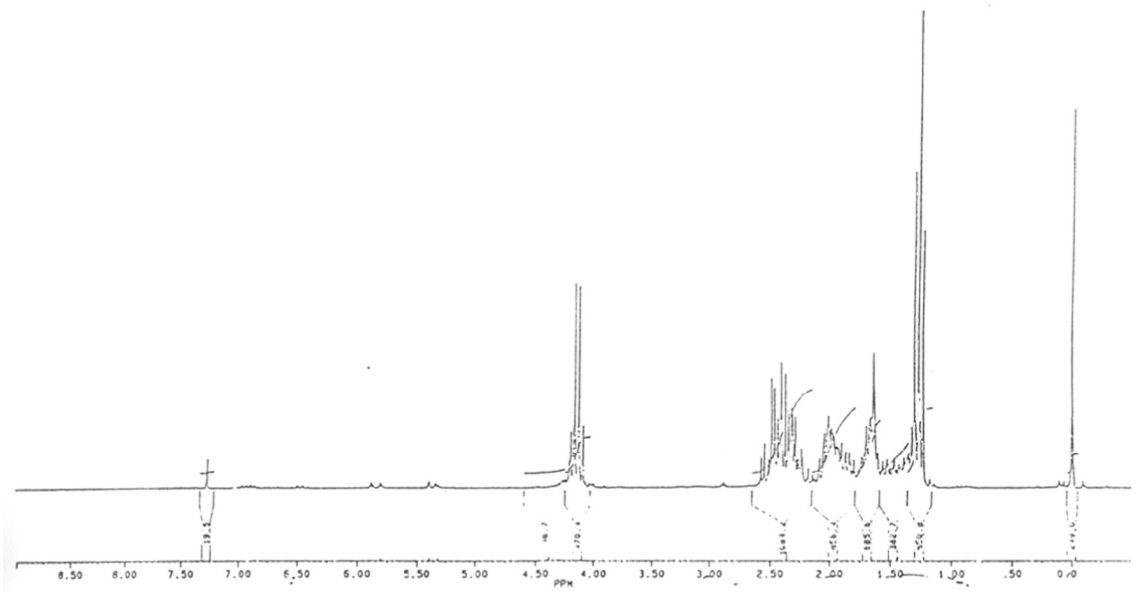
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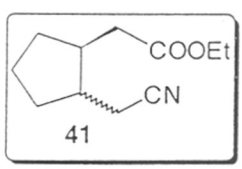
PPM

Fig. 9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CN
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54
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67
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77
65
94
109
113
122
127
136
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153
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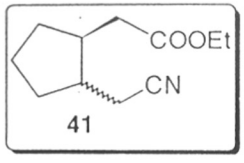
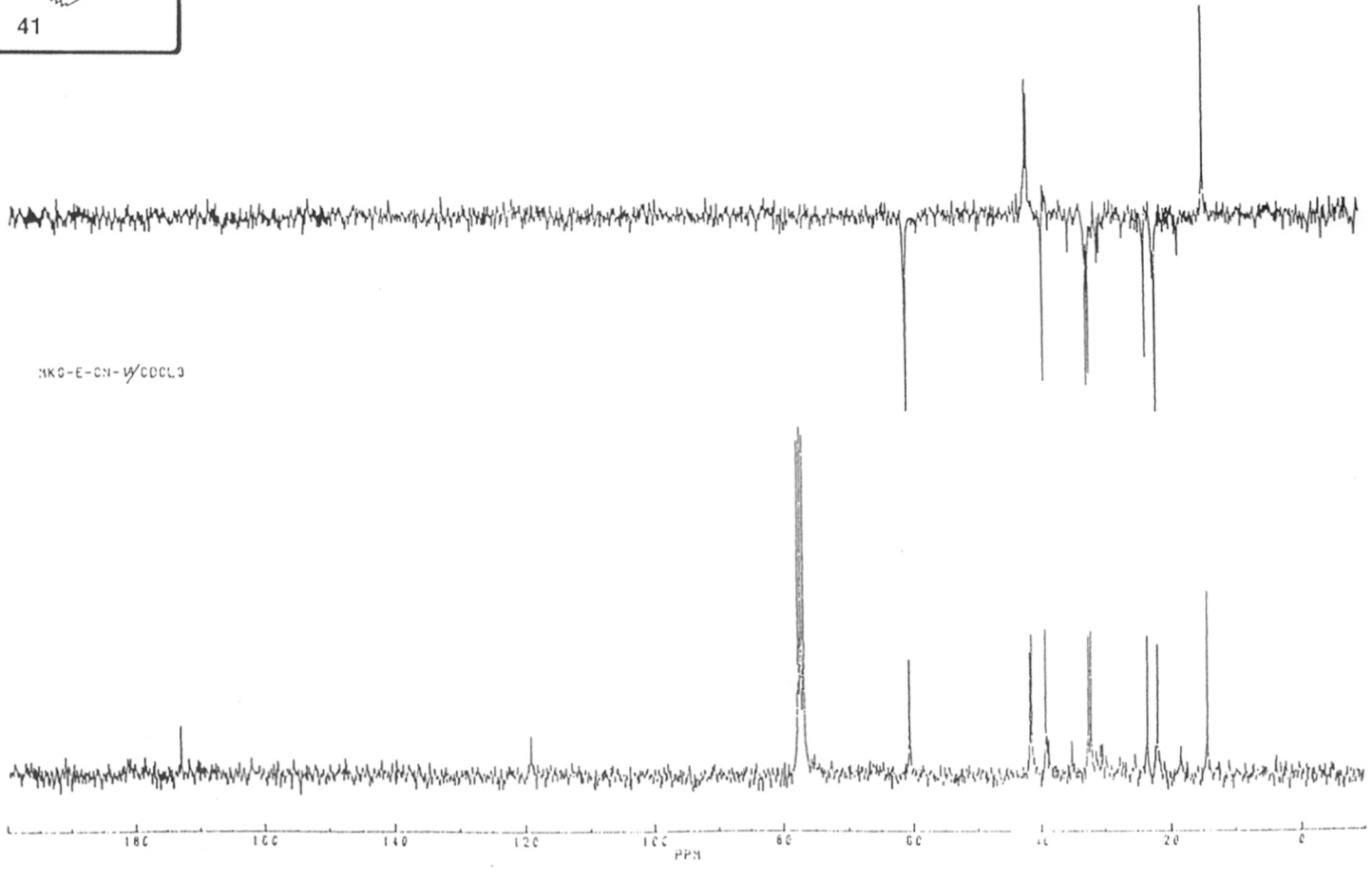
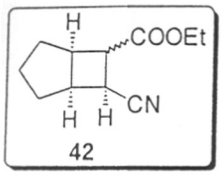


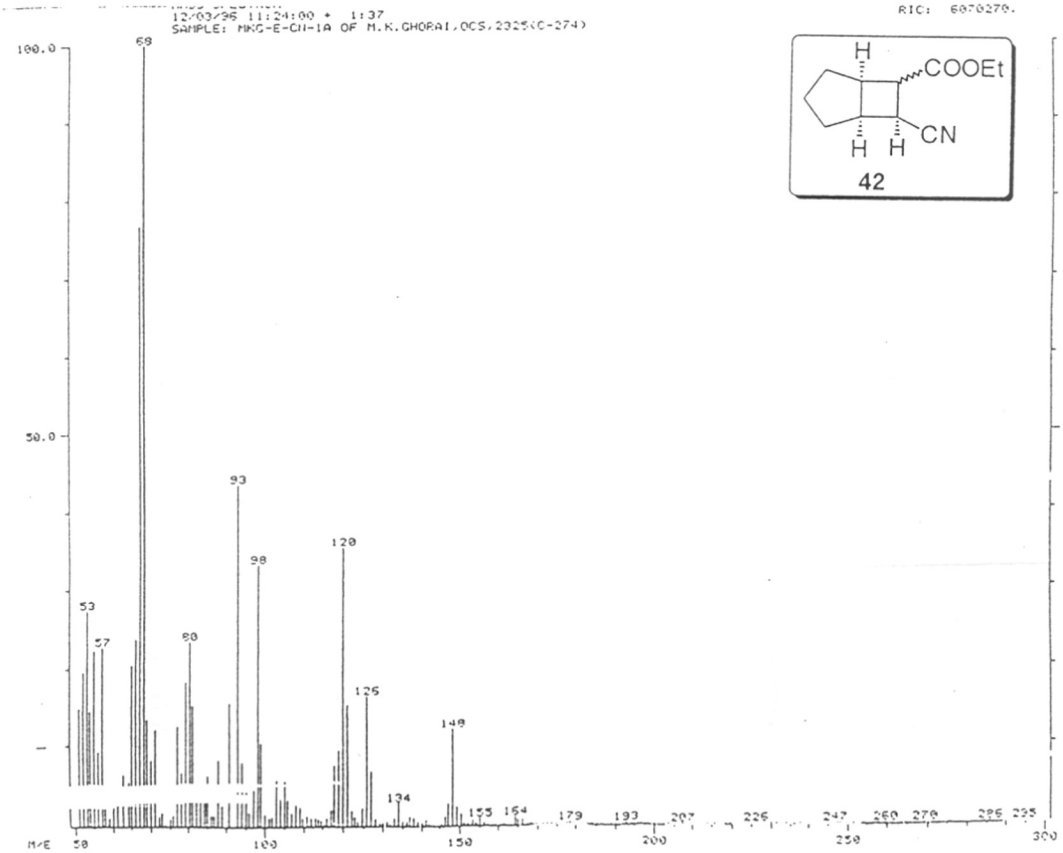
Fig. 8





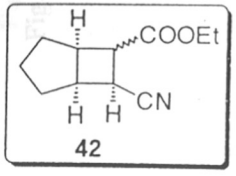
42

Fig. 10



42

Fig. 12



42

Fig. 11

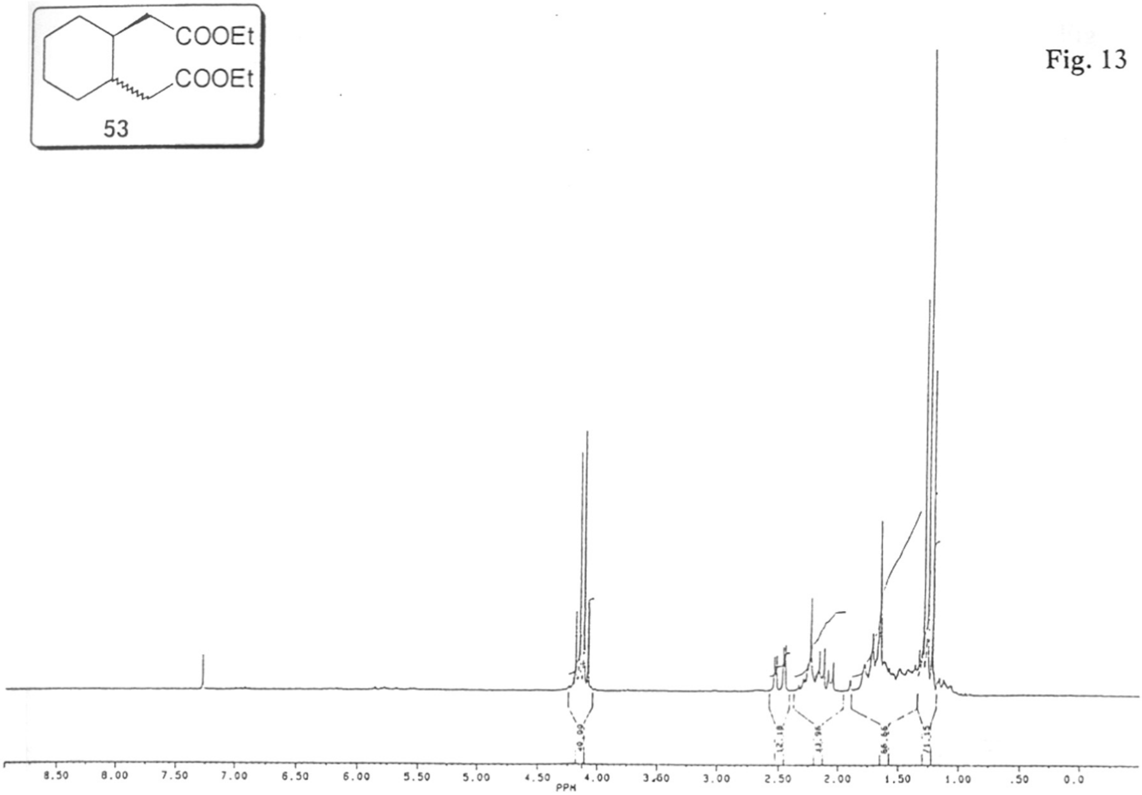


Fig. 13

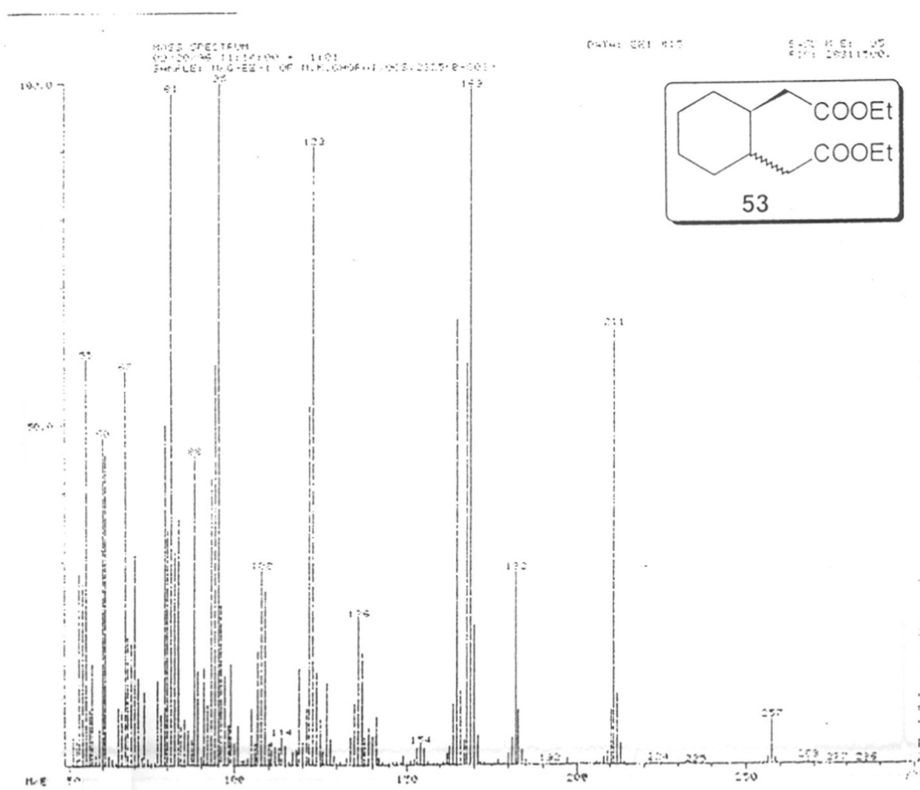
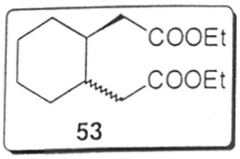


Fig. 15

Fig. 14



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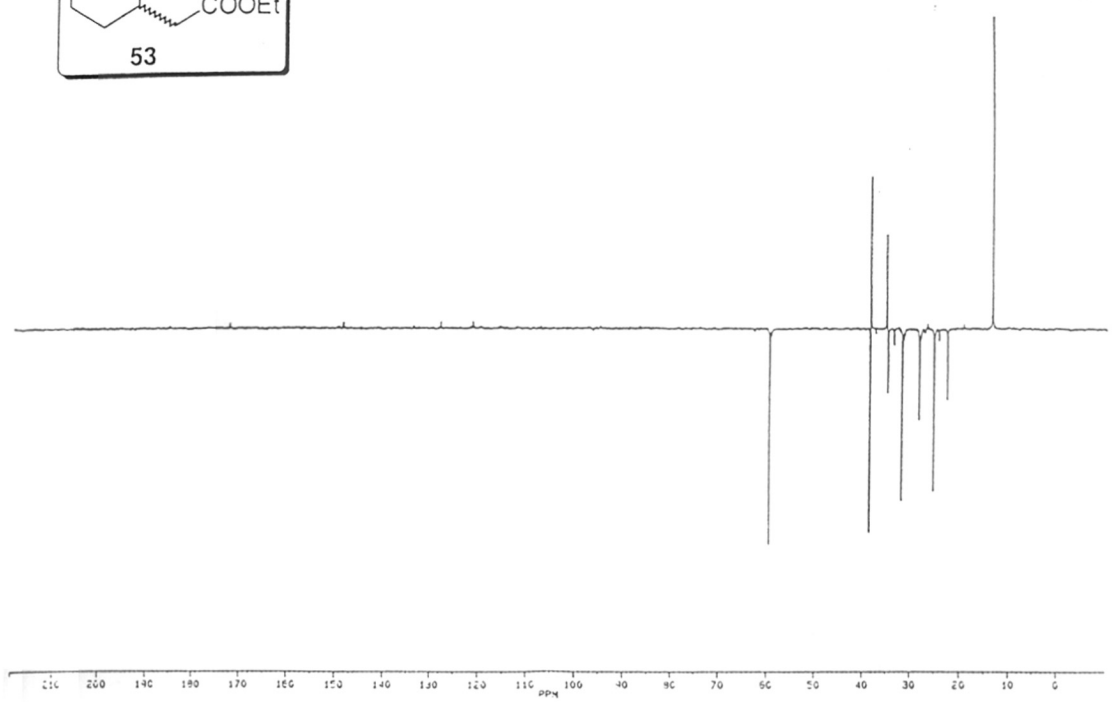

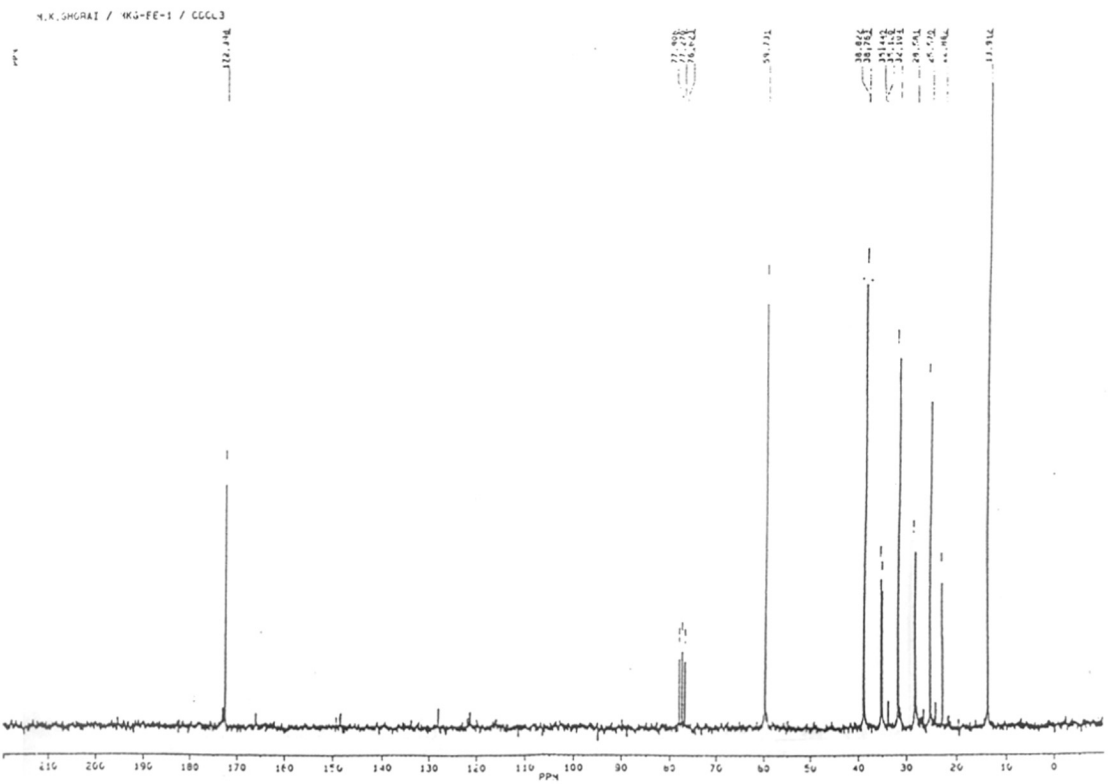

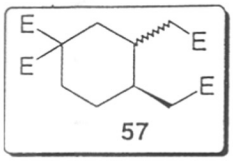
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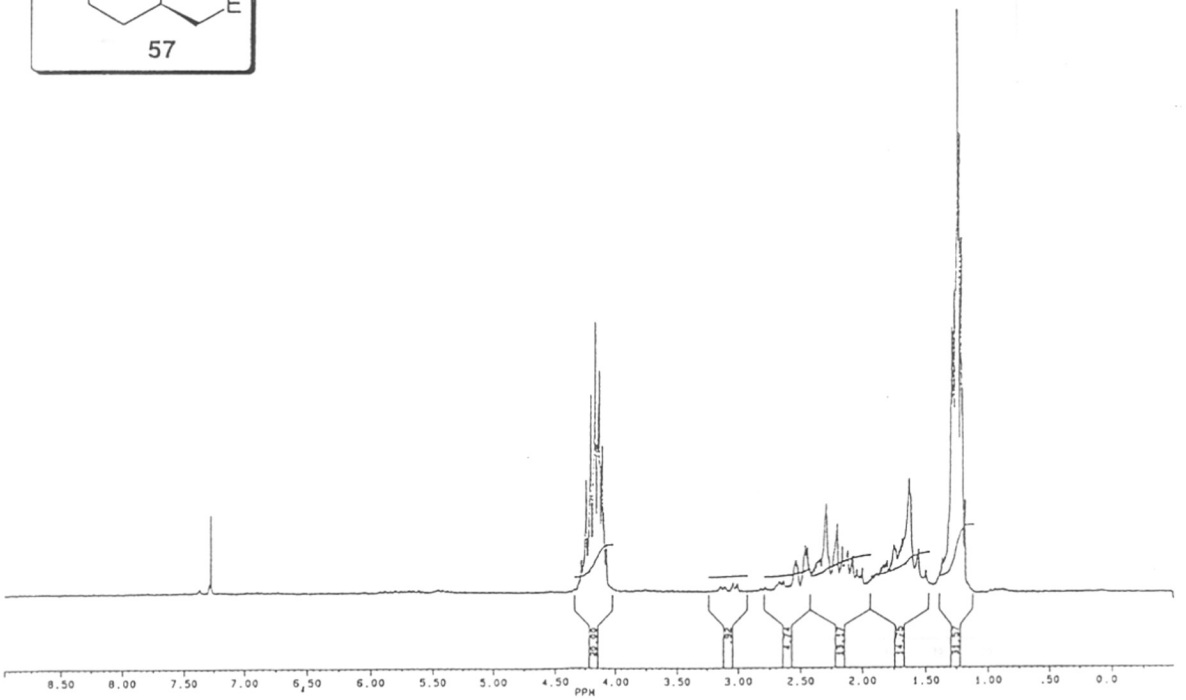
E
E
E
57

Fig. 16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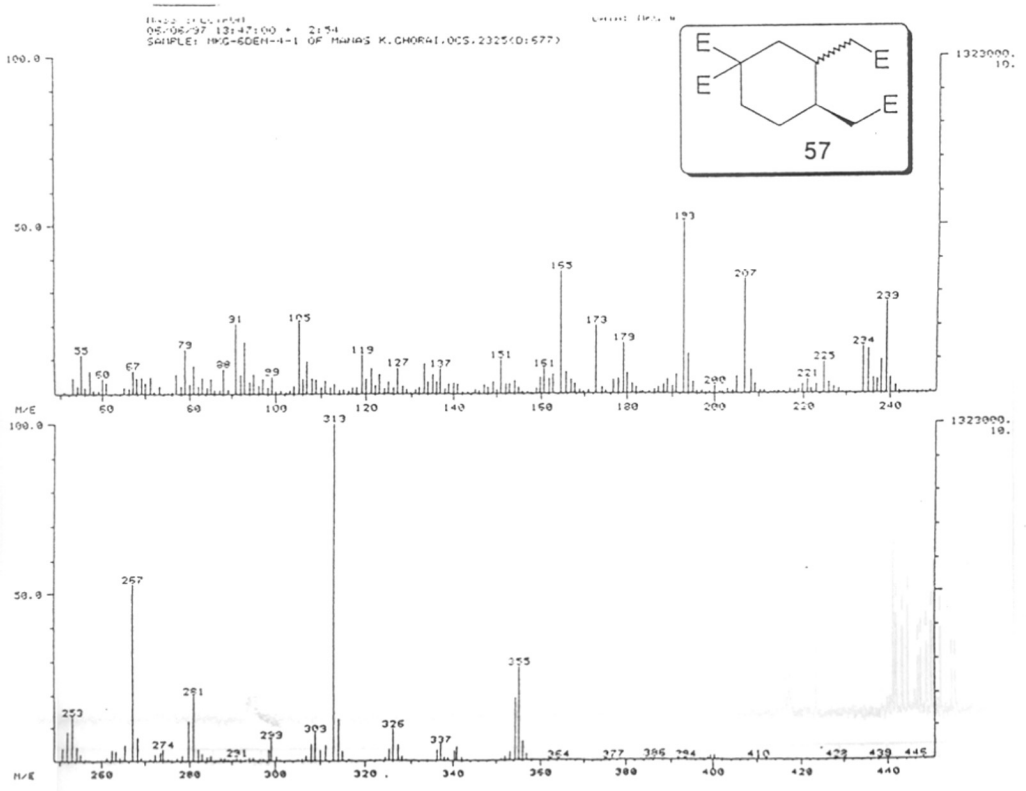
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119
127
137
151
161
223
234
1323000.
10.

Fig. 18

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253
274
293
303
326
337
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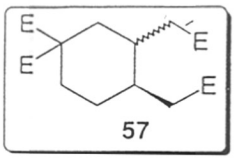
10.

Fig. 17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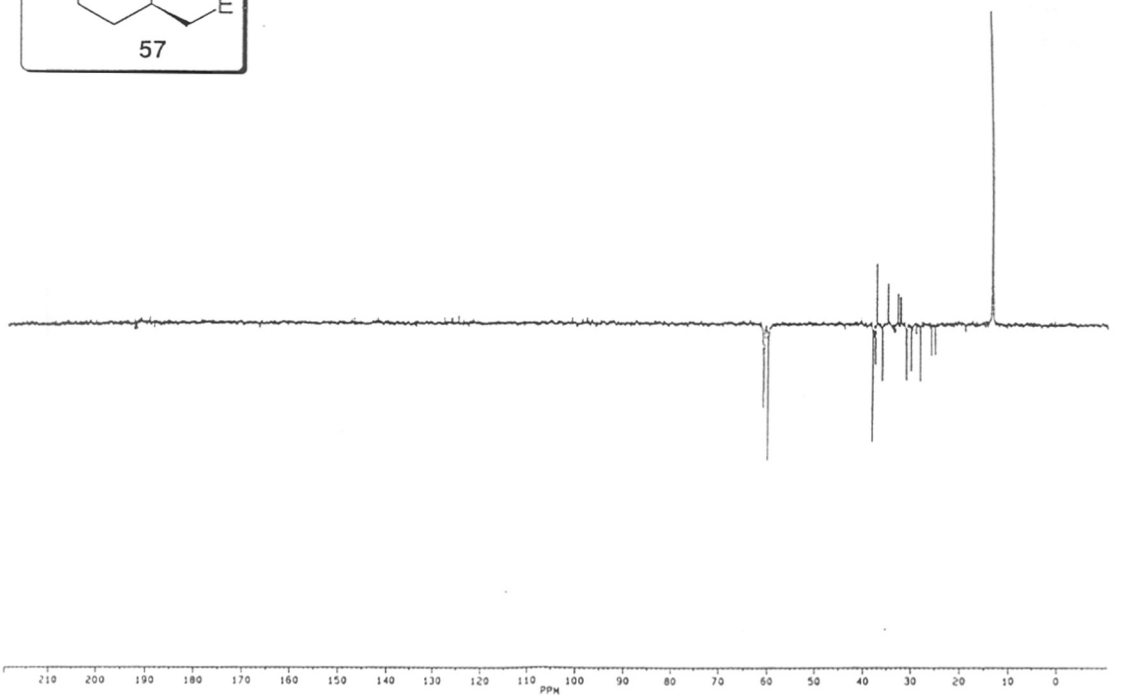
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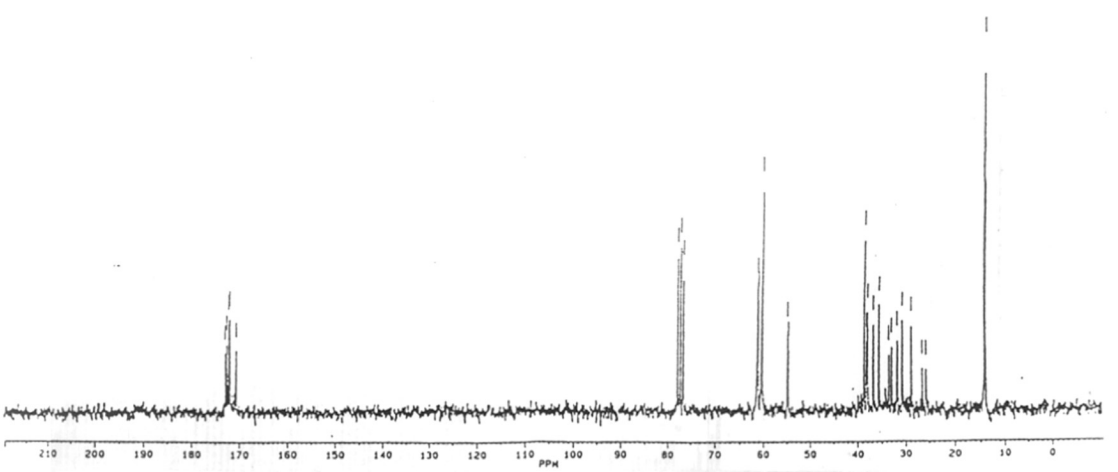
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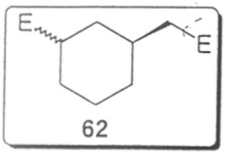
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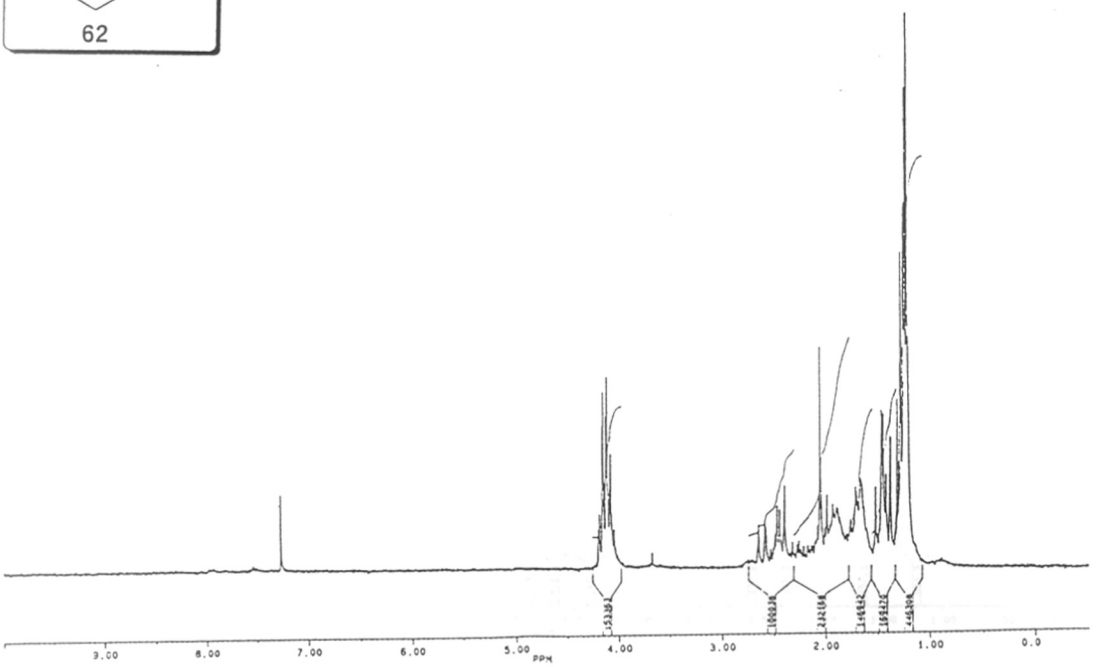
62

Fig. 19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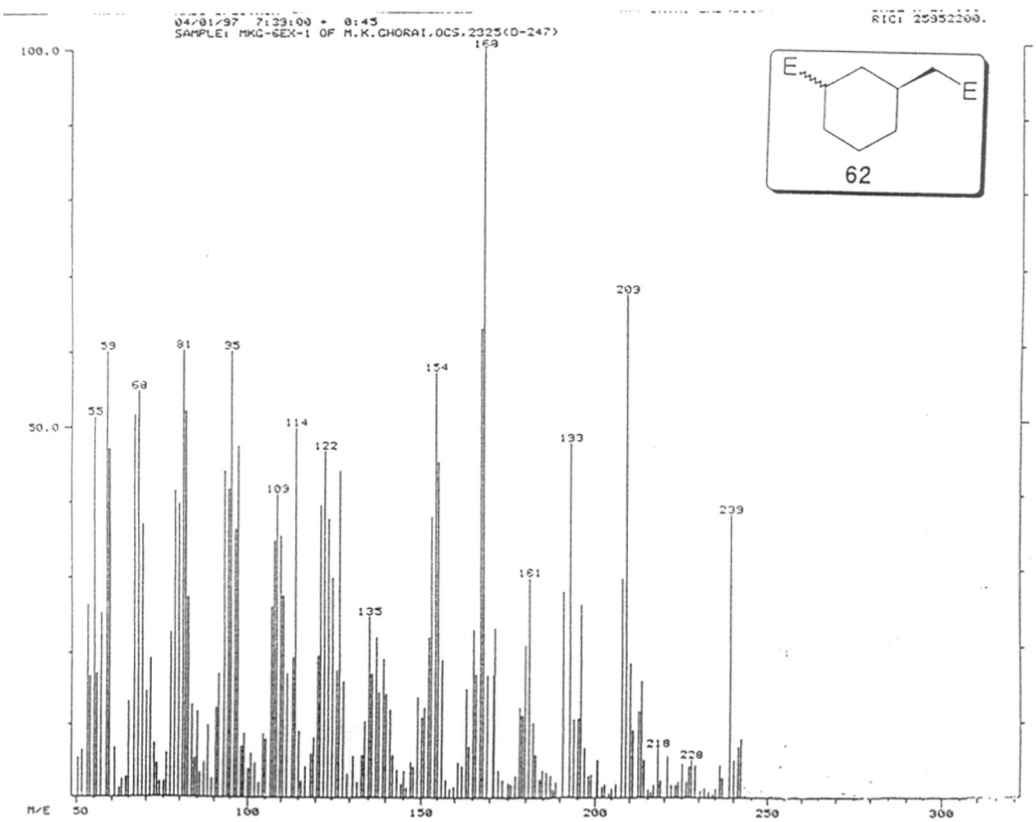
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300
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81
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122
193
109
239
161
135
218
228

E
E
62

Fig. 20

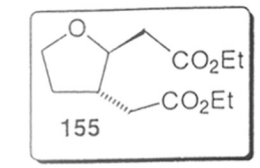
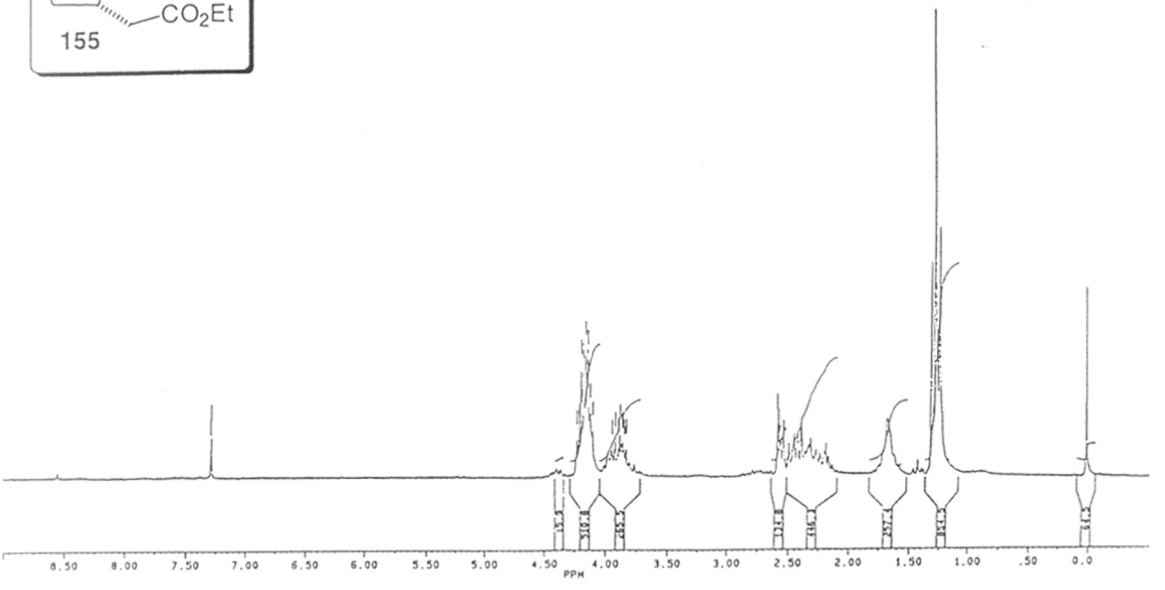

CO2Et
CO2Et
155

Fig. 21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7.00
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6.00
5.50
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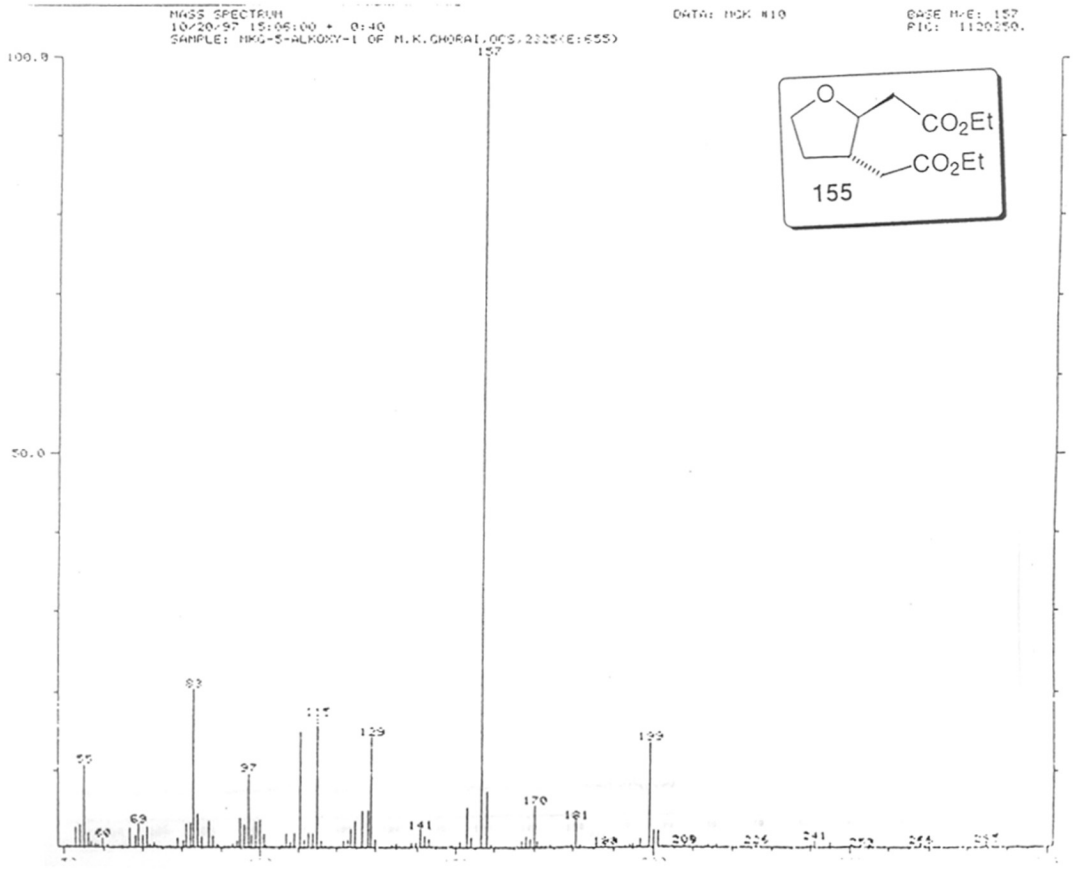
PPM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DATA: NGK #10
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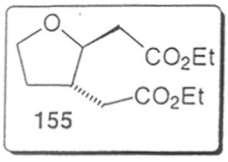
PIC: 1120250.
100.0
50.0
157
83
115
129
139
55
97
170
181
141

CO2Et
CO2Et
155

Fig. 23

Fig. 22



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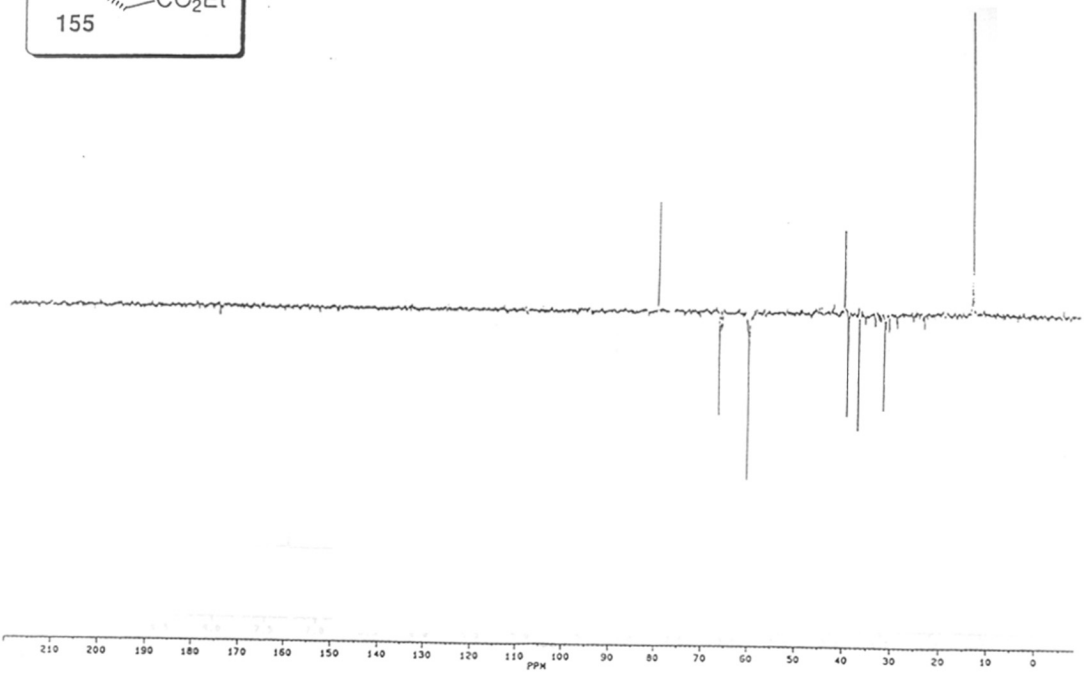
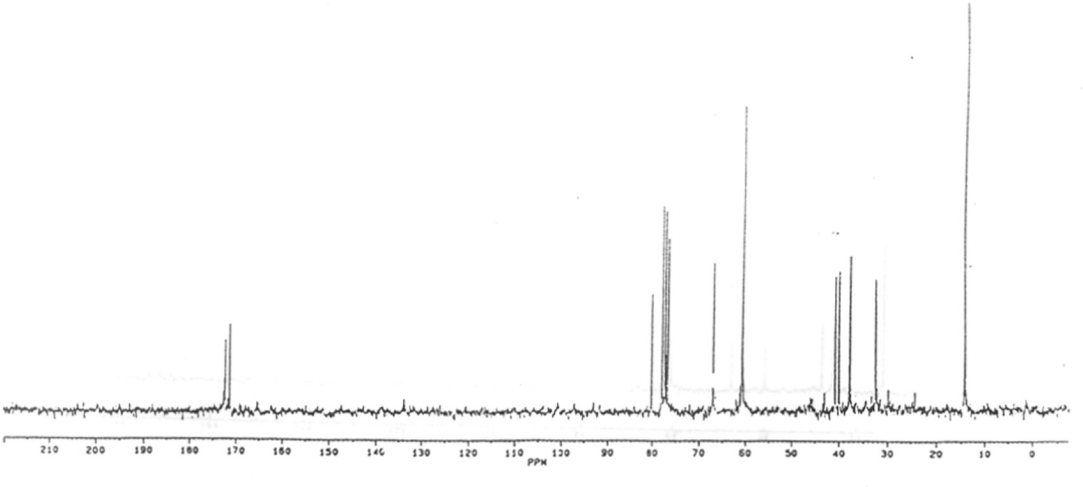


M.K. GHORAI/ C13/MKG-5-ALKOXY-1/CDCL3/ **



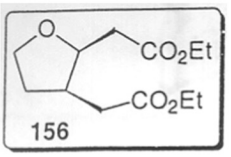


Fig. 24

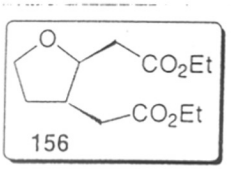


Fig. 25

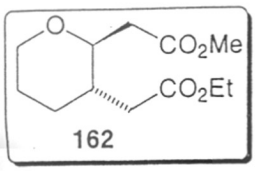
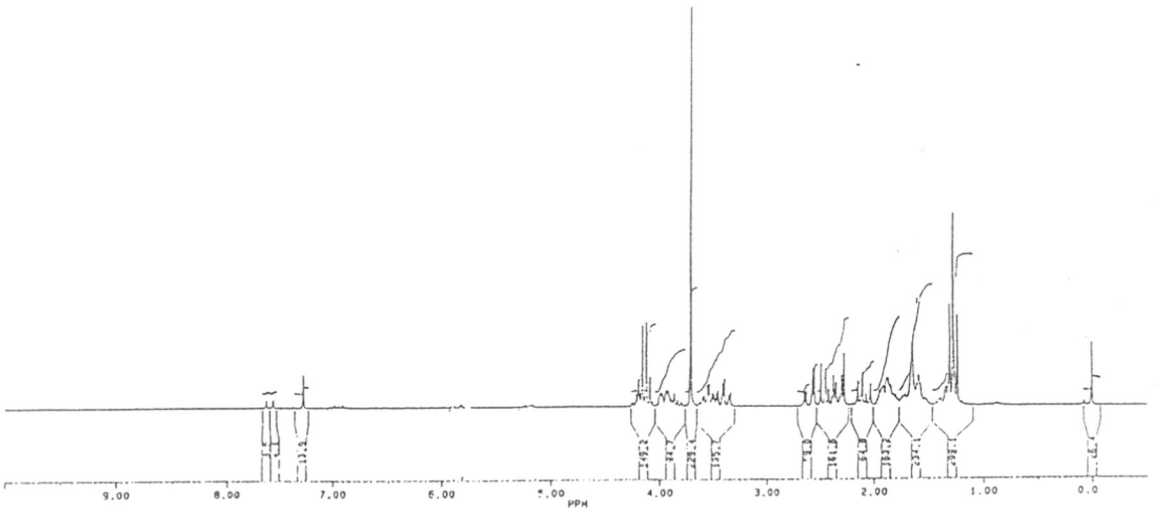

O
CO2Me
CO2Et
162

Fig. 26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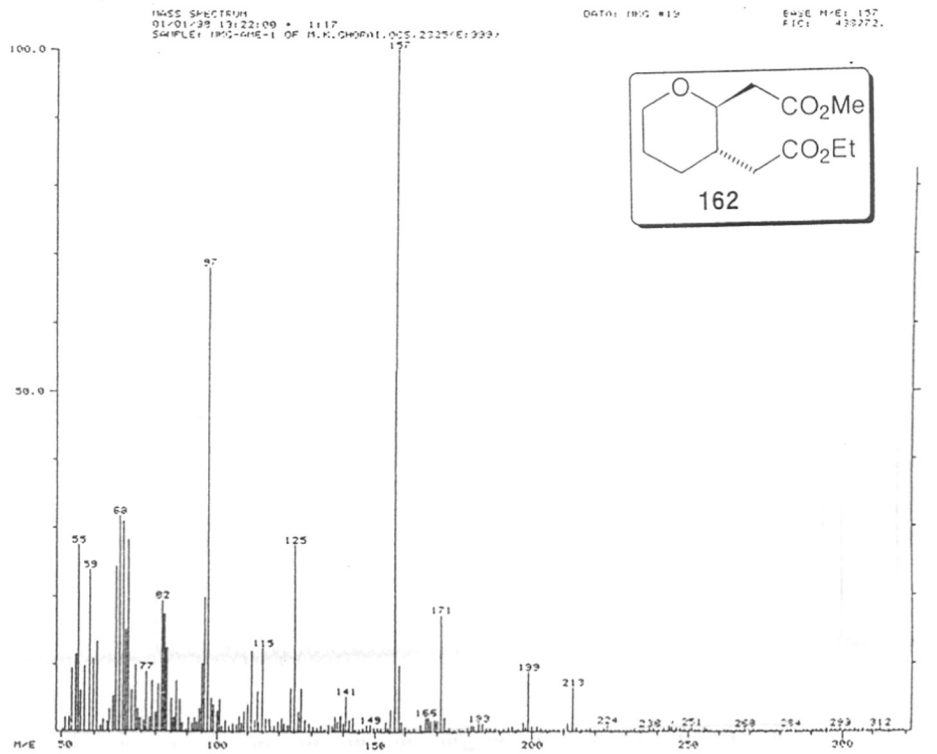
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M/E
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97
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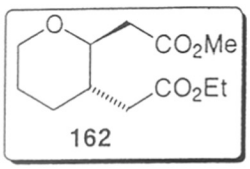
55
59
82
125
115
77
171
141
199
213

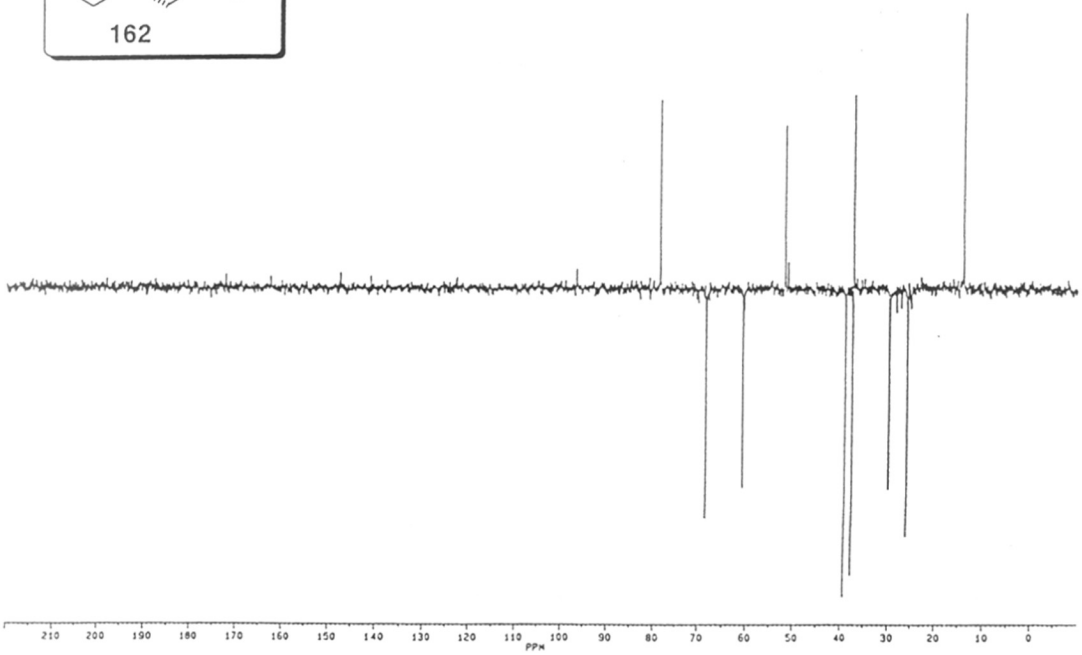
O
CO2Me
CO2Et
162

Fig. 28

Fig. 27


O
CO2Me
CO2Et

162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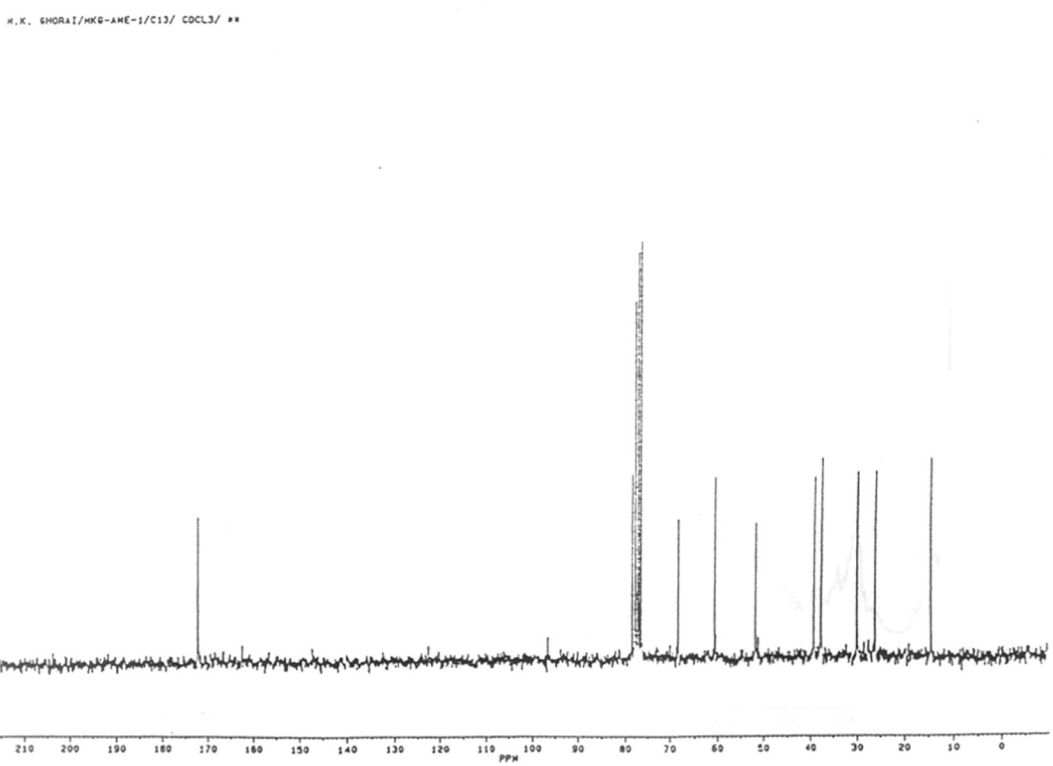
PPM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PPM

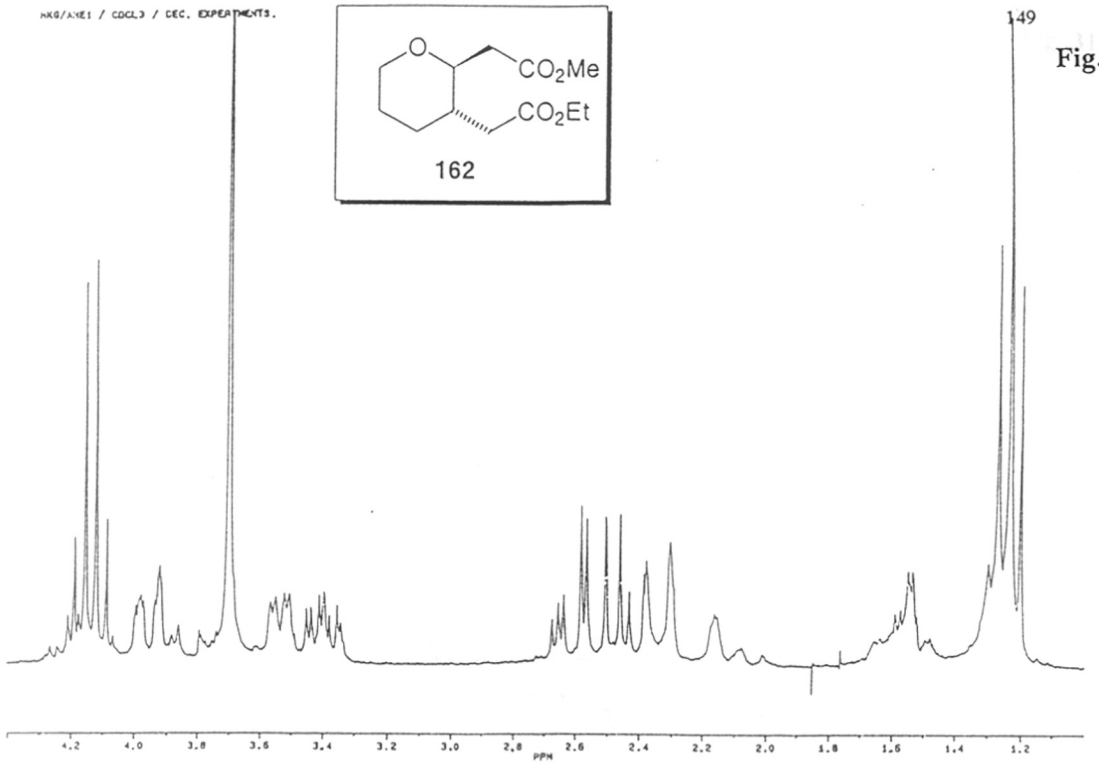


Fig. 29

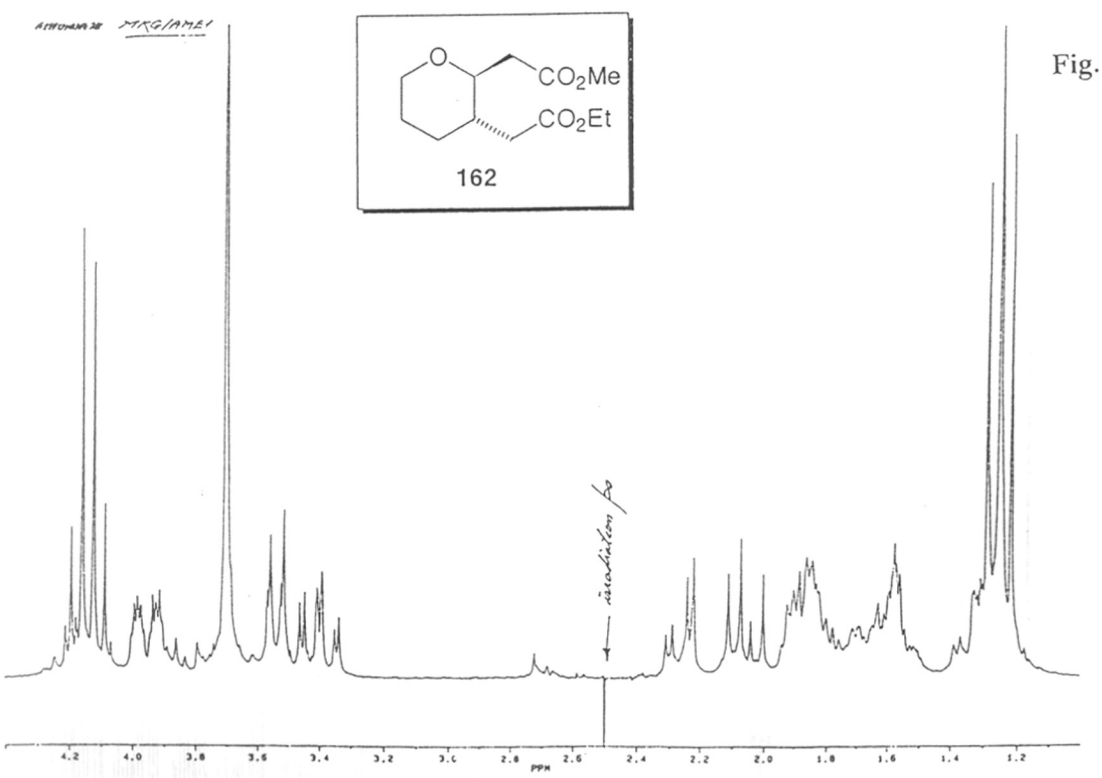
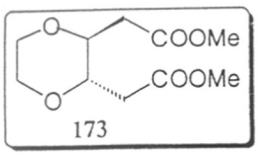
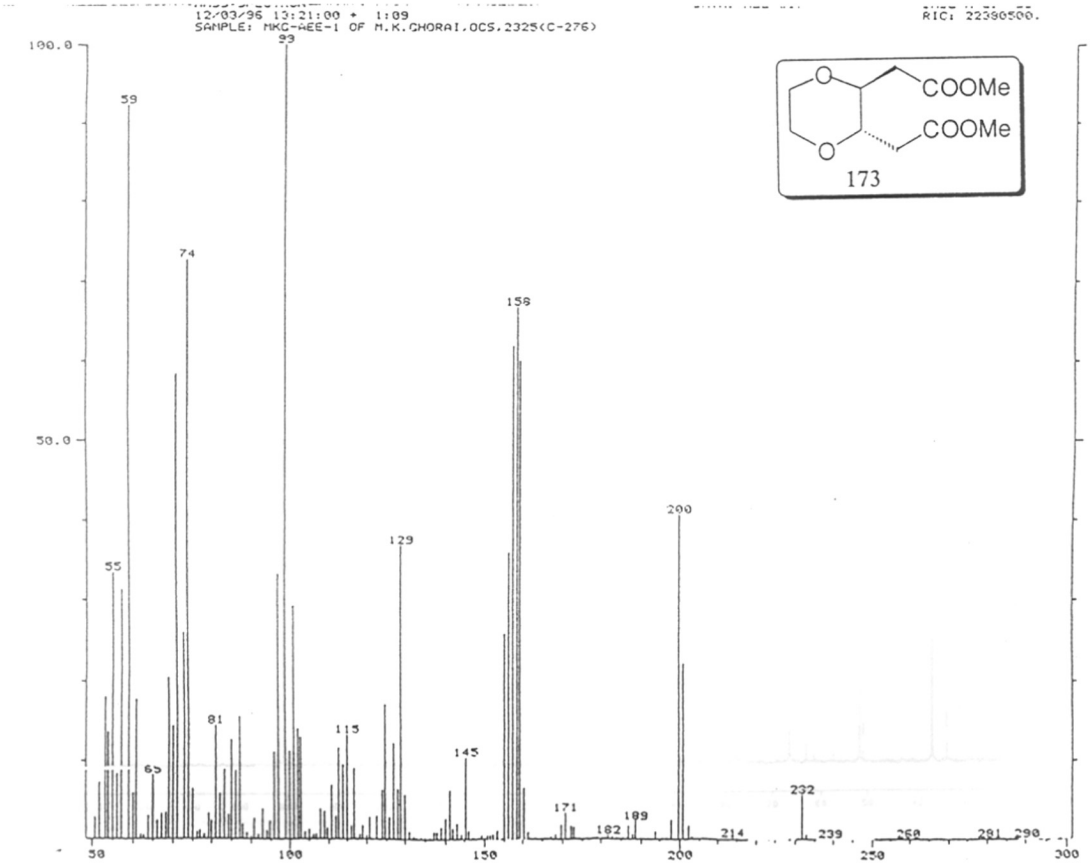


Fig. 30



173

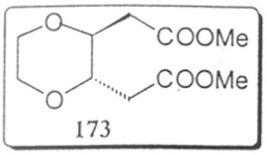
Fig. 31



173

Fig. 33

Fig. 32



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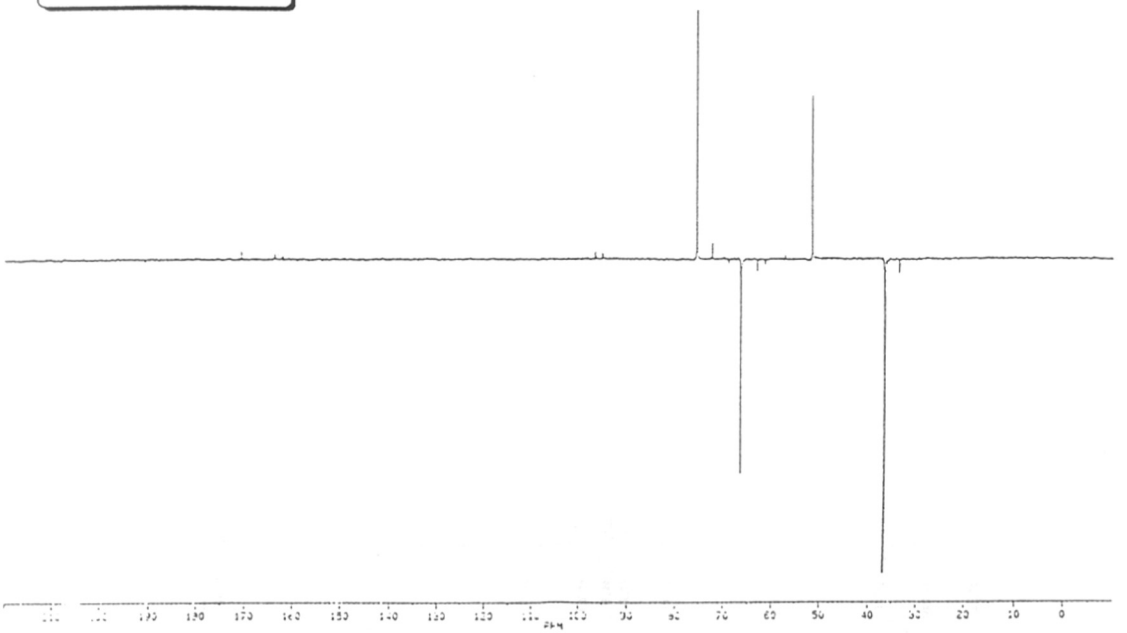


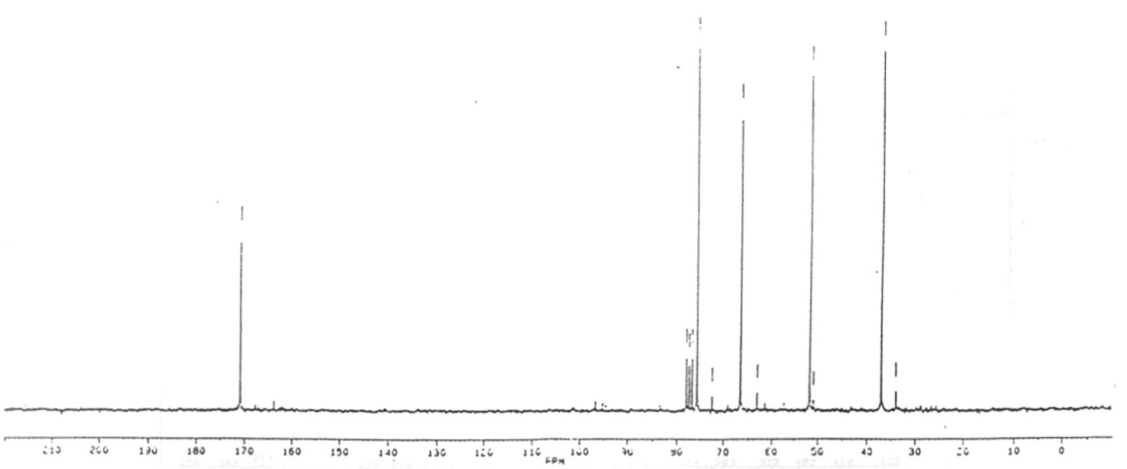
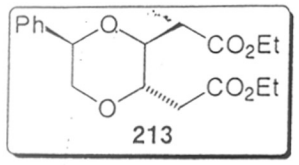


Fig. 34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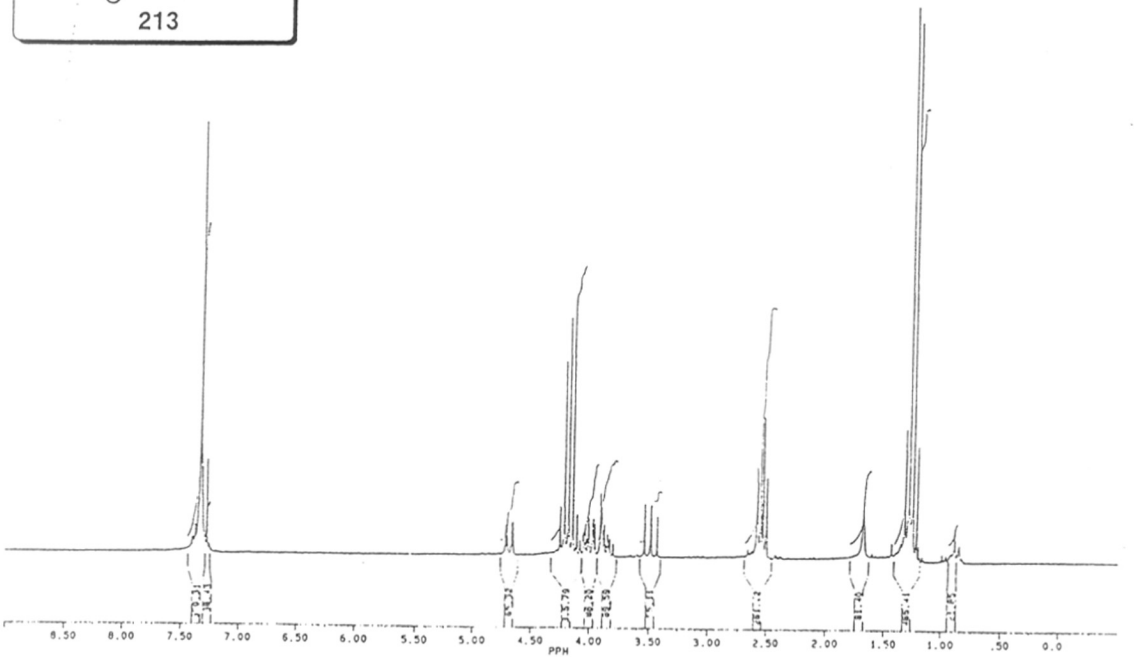
O
CO_2Et
CO_2Et
O
213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8.00
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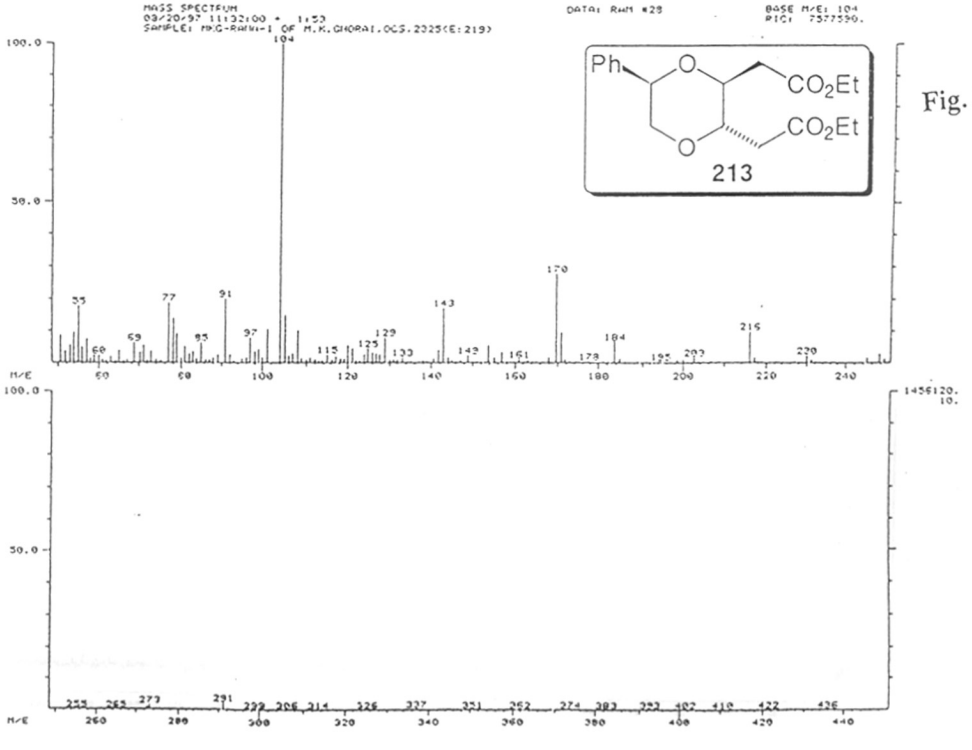
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
.50
0.0
PPM

Fig. 36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PIC: 7577590.
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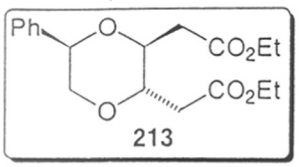
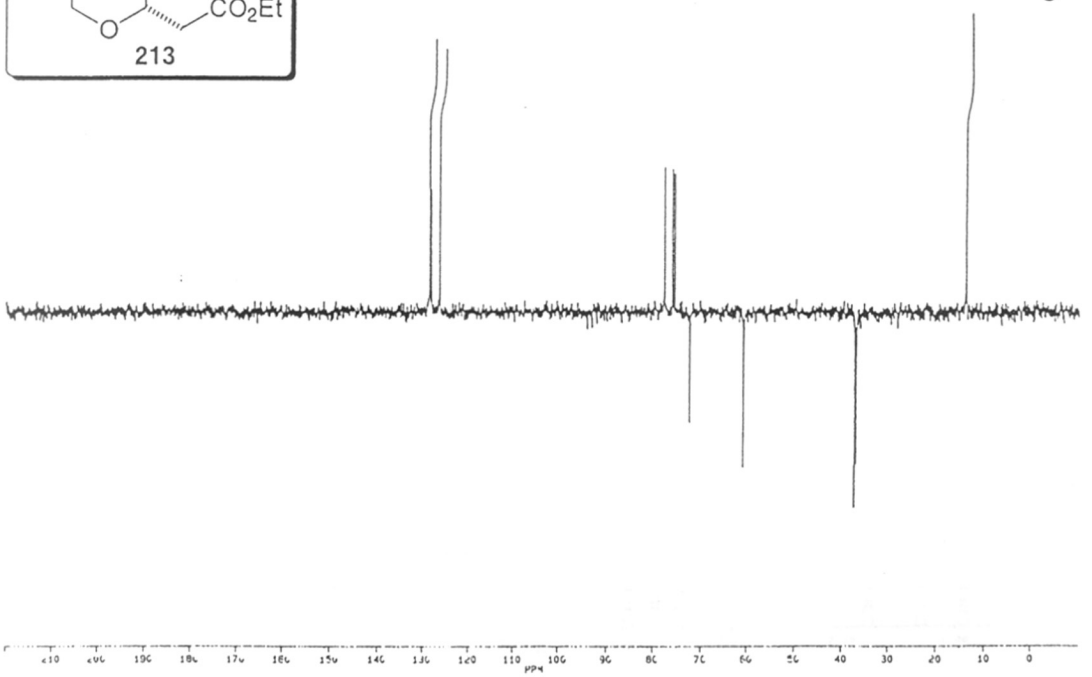
50.0
104
170
143
216
M/E
1456120.
10.
291

Ph
O
CO_2Et
CO_2Et
O
213

Fig. 35


Ph
O
CO2Et
CO2Et
O

213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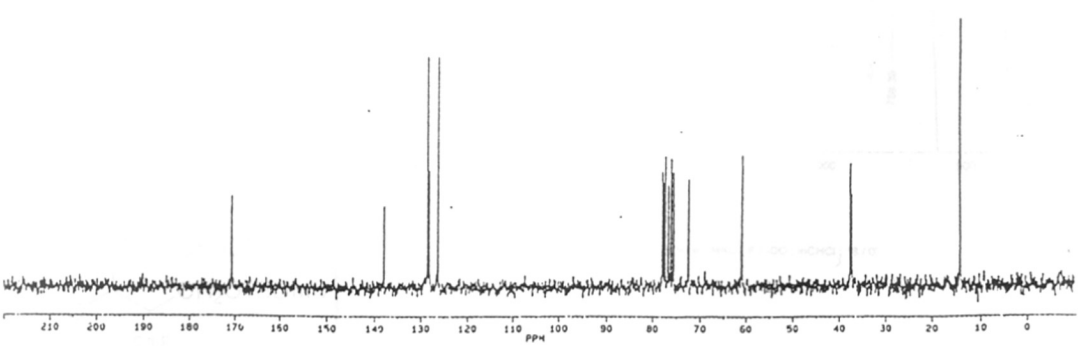
ppm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ppm

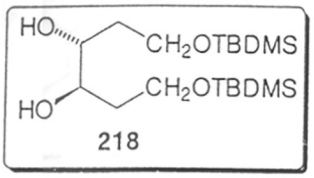


Fig. 38

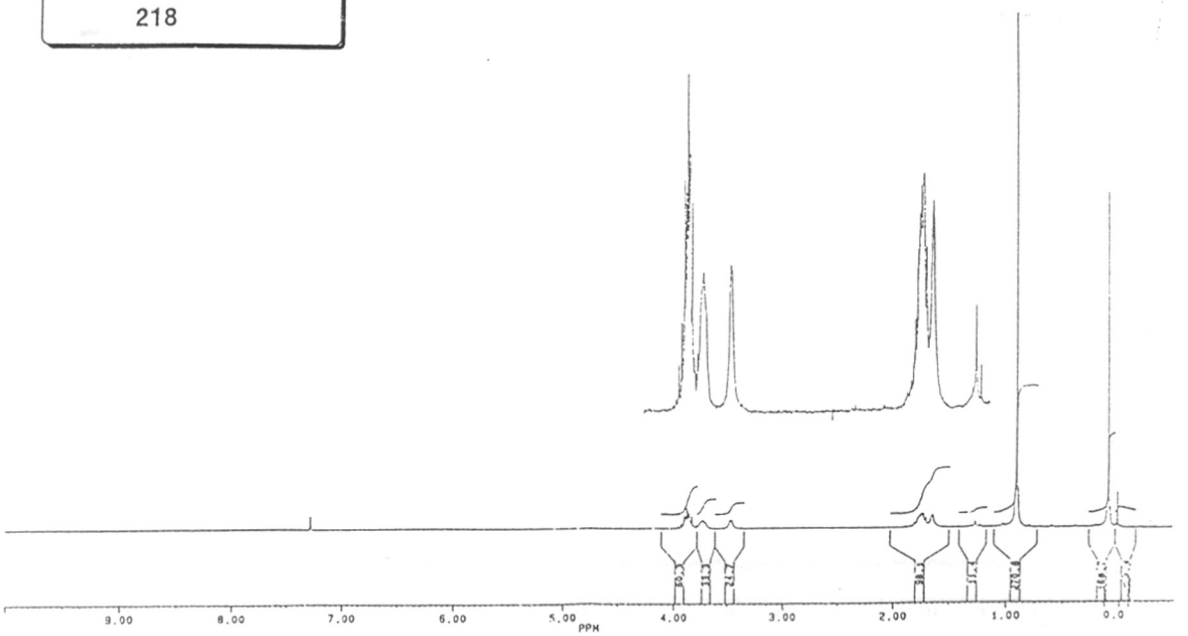
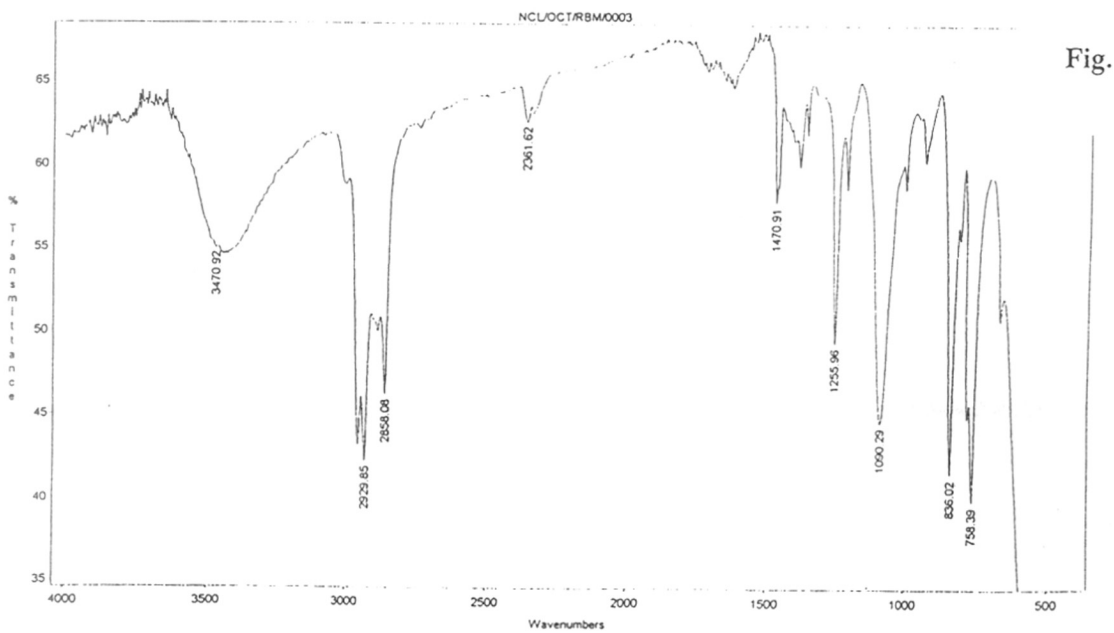
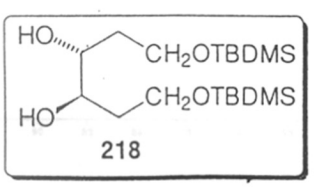


Fig. 37

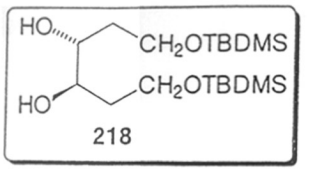




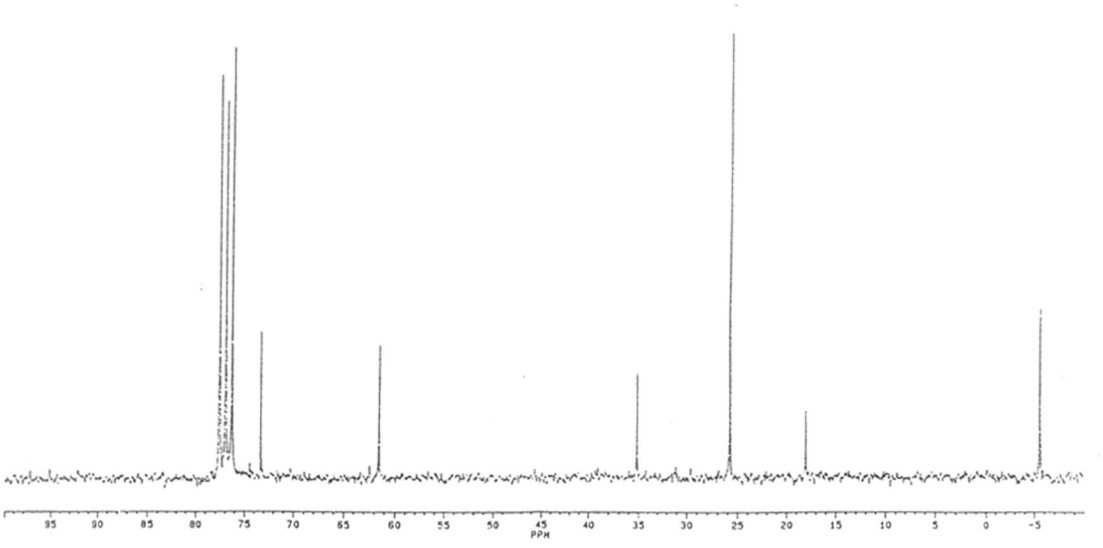
Ghorai ; MKG (R) -DO ; InCHCl ; 18 / 0

N.G. Ghosh Tech

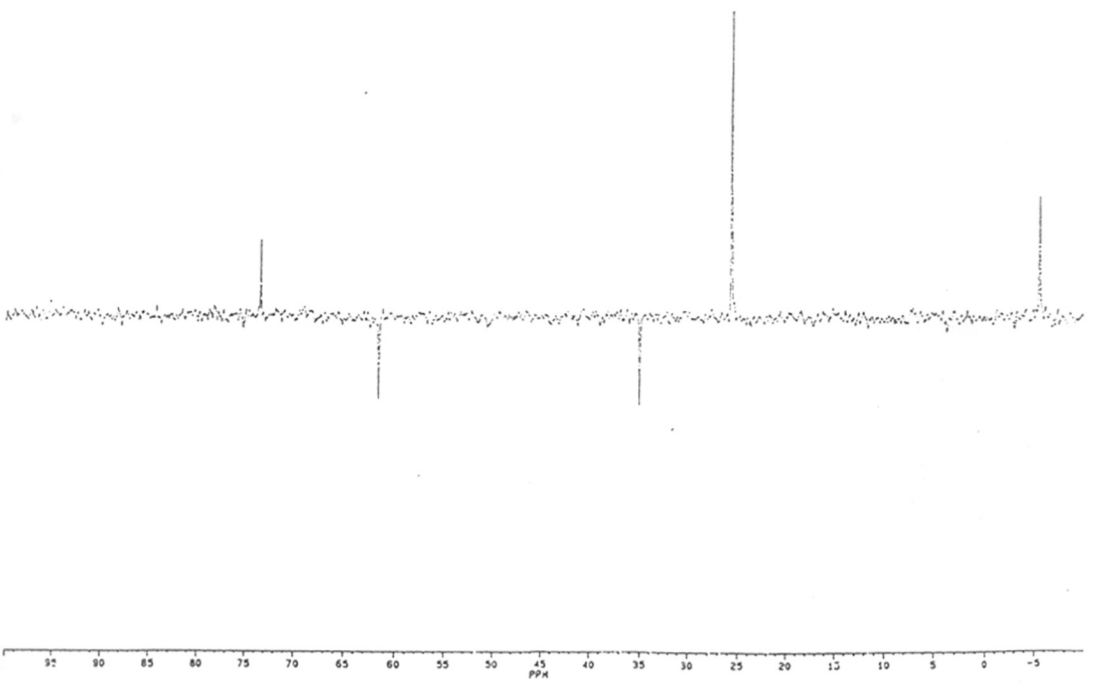
Fig. 39



218



DEPT SPECTRUM FOR - CH2 SIGNALS WITH -VE PHASES



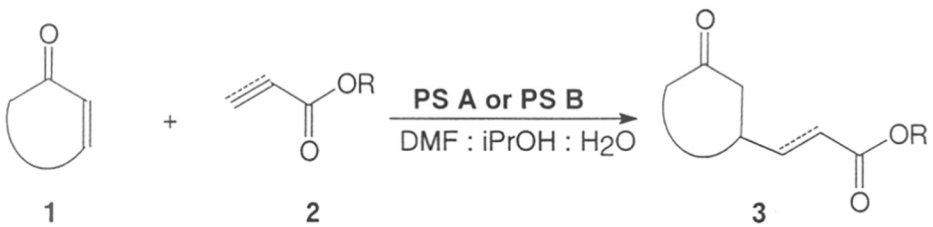
Chapter-III

A New Carbon -Carbon Bond Formation Strategy by the Intermolecular β-Coupling of Cyclic Enones with Activated Alkenes and Alkynes : Efforts Towards the Synthesis of Optically Pure Prostaglandin Analogue

1. Introduction

We have described in the early part of this dissertation the development of a novel strategy to activate β-position of α, β-unsaturated ketones (enones) to carbon centered radicals employing either of the photosystems, **PS-A** or **PS-B**[1,2]. Intramolecular addition of these radicals to tethered activated olefins have provided an unique opportunity to construct stereoselective *trans* 1,2-disubstituted cycloalkanes and *cis* fused bicycloalkanes[2]. Since developing a carbon-carbon bond forming strategy at the β-position of enones is an important endeavor in organic synthesis, it occurred to us that activation of a α, β-unsaturated ketones in the presence of an activated olefin or alkyne might result into a new strategy for carbon-carbon bond formation at the β- position of enones as shown in **Scheme-1**.

Scheme-1



Generally, the -C-C- bond formation at the β-position of α, β-unsaturated ketones are achieved either by the conjugate addition of a carbon nucleophile or by the addition of a radical species.

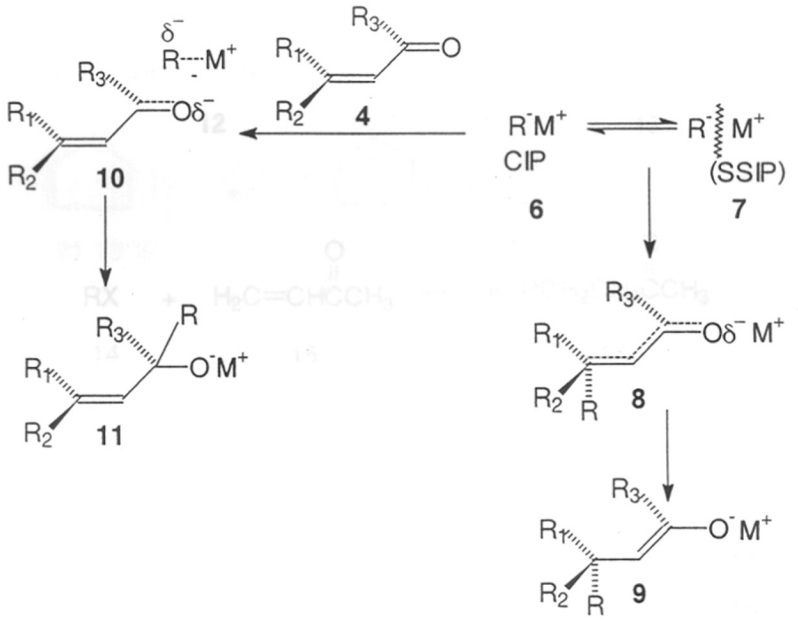
1.1. Conjugate additions :

Conjugate addition is the one of the best known method for carbon-carbon bond formation reaction at the β-position of enone (**Scheme-2**) and vast literature is available on this subject[3].

Scheme-2

However, the main problem in this approach lies in the competitive 1,2-carbonyl addition reaction (**Scheme-3**). Initially efforts were centered around to enhance the kinetic 1,4-addition product over 1,2-addition by carrying out the reaction at low temperature, but subsequently significant improvement could be achieved in changing the ratio of 1,4 addition *vs* 1,2-addition by changing the solvent polarity as organometallic reagent were assumed to add *via* contact ion pair (CIP) in a 1,2 fashion whereas solvent separated ion pairs (SSIP) underwent only 1,4-conjugate additions. Soft and hard acid-base concept has also been utilized to control the reaction.

Scheme-3



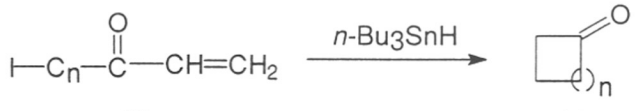
In general, for soft nucleophiles, including π-stabilised carbanions, conjugate addition (1,4-addition) is favoured. For example, organolithium gives 1,2- addition product whereas organomagnesium gives both 1,2- and 1,4- additions and organocopper gives only 1,4-addition product. It is also known that effects of polar solvent, larger counter-ion, increasing steric hindrance in either reactant (except at the β-carbon of the conjugate acceptor), increasing delocalisation or stabilisation of the carbanion, higher temperature and longer reaction time have a strong influence on 1,4- *vs* 1,2-additions.

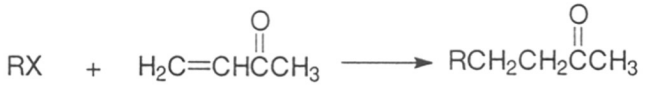
Further development in this area have been made by introducing a variety of new soft organometallic reagents utilising different metals *viz* copper[4], zinc[5], aluminium[6], manganese[7] etc.

1.2. Free radical additions :

Alkyl radicals are well known to undergo 1,4-addition (conjugate addition) to α, β-unsaturated ketones or aldehydes and are well documented in literature.[8] Examples of both intra[9] as well as intermolecular[10] additions are utilised in many synthetic strategies (**Scheme-4**) .

Scheme-4





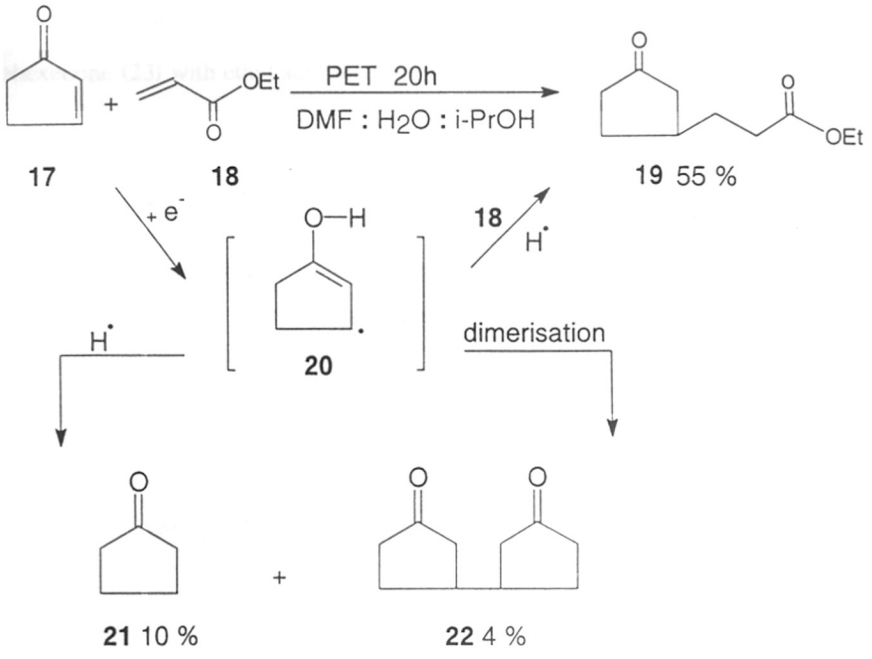
2. Results and discussion

In order to evaluate the intermolecular coupling as shown in **Scheme-1**, PET activation of a mixture of cyclopentenone (**17**) with ethyl acrylate (**18**) was first studied.

2.1. PET initiated coupling of cyclopentenone (17) with ethyl acrylate (18) :

The coupling between **17** and **18** involved the irradiation of a mixture containing DCA (20 mol %), **17** (1 equiv.), Ph_3P (0.8 equiv.) and **18** (2.5 equiv.) in DMF:iPrOH:H_2O (88:10:2) using 405 nm light[11]. Evaporation of the solvent under reduced pressure followed by purification gave **19** (55 %) along with enone reduced product (**21**, 10 %), dimer (**22**, 4 %) and some polymeric material (**Scheme-5**). DCA was recovered almost quantitatively (>98 %).

Scheme-5



IR spectrum of **19** showed prominent absorption bands at 1710 and 1728 cm^{-1} indicating the presence of keto-carbonyl and ester-carbonyl groups, respectively.

^1H NMR spectrum displayed a quartet at δ 4.15 (2H, J = 7.3 Hz), assignable to the methylene protons of ester group. A triplet (2H, J = 6.3 Hz) appearing at δ 2.42 is characterised to the methylene protons of -$C\underline{H}_2$COO- group. A multiplet appearing between δ 2.40-1.96, is assigned to the four keto methylene protons of cyclopentanone ring. Another multiplet appearing between 1.95-1.35 (four protons) could be assigned to the remaining two methylene protons, one methine proton of cyclopentanone ring and another β-proton to the ester group. Remaining protons appeared as a bunch of multiplet between δ 1.3-1.10.

Mass spectral analysis revealed expected molecular ion peak at 184 with 2 % intensity along with base peak at 55. The other prominent fragmentation peaks were found at 138 (M^+ - EtOH, 30 %), 127 (3 %), 110 (18 %), 111 (11 %), 97 (12 %), 82 (28 %), 83 (27 %), 67 (24 %).

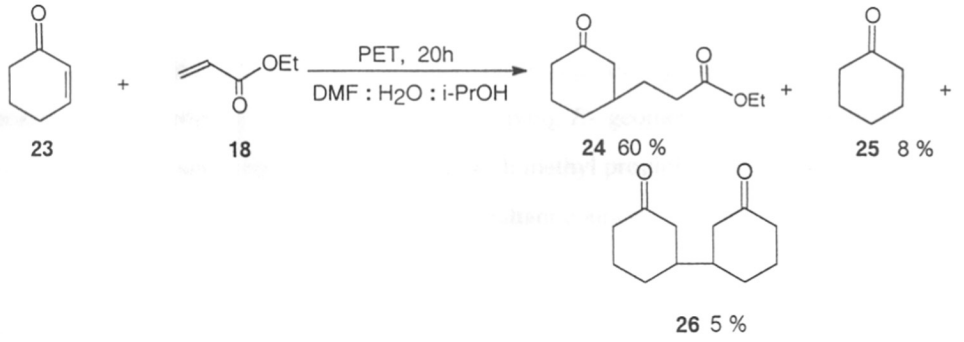
Compound **21** and **22** have been characterised by ^{1}H NMR spectrum and compared with authentic samples (for details see experimental section).

To establish the generality of this coupling reaction, PET reductive activation of cyclohexenone (**23**) with ethyl acrylate (**18**) was also studied.

2.2. PET initiated coupling of cyclohexenone(23) with 18:

Identical PET activation of a mixture of **23** and **18**, as described for **17**, yielded coupling product **24** along with reduction product (**25**, 8 %) and dimer (**26**, 5 %) (**Scheme-6**). All the compounds were characterised by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic data.

Scheme-6



23 + **18** → **24** 60 % + **25** 8 % + **26** 5 %

IR spectrum of **24** showed prominent absorption bands at 1720 and 1710 cm^{-1} corresponding to ester and keto-carbonyl functionalities, respectively.

The ^{1}H NMR spectrum (**Fig. 1**) displayed a quartet at δ 4.15 (two protons, J = 7.3 Hz), assignable to the methylene protons of ester group. A multiplet appearing between δ 2.5-2.25 is characterised to the two methylene protons of -C$\underline{H}_2$COO- group and two keto-methylene protons of cyclohexanone ring. Remaining two keto-methylene protons and methine proton of cyclohexanone ring appeared between δ 2.22-1.85 as a bunch of multiplets. Remaining protons are observed as bunch of multiplets between δ 1.84-1.55 (four protons), δ 1.50-1.10 (two protons). Methyl protons of ester moiety appeared as a triplet at δ 1.26 (J = 7.3 Hz)

^{13}C NMR (**Fig. 2**) showed eleven signals whose characterisations were assigned by INEPT experiment. Down field quaternary carbons appearing at δ 211.16 and 173.45 are

characterised to -C=O- moiety of keto-carbonyl and -C=OO- moiety of ester-carbonyl groups, respectively. Another two signals appearing at δ 60.57 and 47.88 are assigned to the methylene carbons of -O$\underline{C}H_2$- and -$\underline{C}H_2$COO- groups, respectively. A signal appearing at δ 36.66 is characterised to the methine carbon. Methylene carbons of -$\underline{C}H_2$CO- groups appeared at δ 41.50 and 31.82 respectively. Remaining methylene carbons appeared at δ 31.64, 31.14 and 25.24, respectively. Methyl carbon signal of ester moiety is observed at δ 14.39.

Mass spectral analysis **(Fig. 3)** showed molecular ion peak at 198 with 24 % intensity along with base peak at 152 (M^+ - EtOH). The other prominent fragmentation peaks are found at 141 (9 %), 124 (61 %), 111 (25 %), 98 (46 %), 99 (53 %), 88 (18 %), 81 (27 %), 67 (28 %), 55 (95 %).

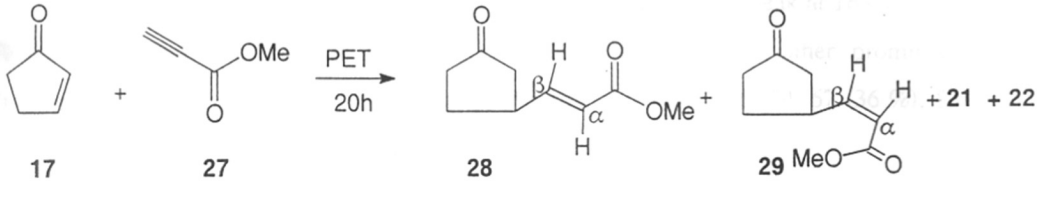
Compound **25** and **26** are characterised by ^{1}H NMR spectrum (for details see experimental section).

Since there are several naturally occurring biologically active compounds possessing 3-alkenyl cyclopentanone moiety having *E*- geometry (e. g. prostaglandins[12] etc.), PET activation of cyclopentenone (17) with methyl propiolate (**27**) was considered in order to evaluate the olefin geometry of the resultant coupling product.

2.3. PET initiated coupling of cyclopentenone (17) with methyl propiolate (27) :

PET coupling of **17** with **27**, employing **PS-B** photolyses reaction conditions, gave coupled product **28** and **29** (*trans:cis* 5:1) along with the usual reduction and dimerisation product **21** and **22**, respectively (**Scheme-7**). It may be mentioned here that coupling of **17** and **27** was found much cleaner using **PS-B** irradiation condition than **PS-A.**

Scheme-7



17 **27** **28** **29**

65 % (***28*** /**29** 5:1)

Although **28** and **29** could be isolated in pure form by careful column chromatography for complete spectral characterisation, the *cis* isomer (**29**) could not be obtained in sufficient amount.

IR spectrum of **28** indicated a strong band at 1653 cm^{-1} indicating the presence of a conjugated double bond. It also showed prominent absorption bands at 1739 and 1724 cm^{-1} corresponding to ester carbonyl and keto-carbonyl groups, respectively.

The ^1H NMR spectrum (**Fig. 4**) of **28** displayed a doublet of a doublet (J = 15.6, 7.8 Hz) at δ 6.98 (one proton) for the β proton of α,β-unsaturated olefin. Another doublet of a doublet (J = 15.6, 0.8 Hz) at δ 5.83, integrating for one proton, is attributed to the α proton of the same α, β-unsaturated ester. A sharp singlet appearing at δ 3.75 (three protons) is characterised to the methyl protons of ester group. Allylic methine proton (H_{-3}) of cyclopentanone ring appeared as a multiplet between δ 3.15-2.80 (one proton). A bunch of multiplets appearing between δ 2.65-2.02 is assignable to the five protons of cyclopentanone ring. Remaining one proton of the cyclopentanone ring appeared as a multiplet between δ 1.98-1.70.

The coupling constant of J = 15.6 Hz between α and β protons of α,β-unsaturated ester moiety suggested it to have *E*- geometry.

^{13}C NMR (**Fig. 5**) revealed nine carbon signals whose characterisation are assigned by INEPT experiment. Two down field quaternary carbons appearing at δ 207.05 and 166.88, correspond to -CO- and -COO- groups, respectively. A pair of signals appearing at δ 149.92 and 121.02 is assigned to the β carbon and α carbon of the α, β-unsaturated ester group, respectively. Another two signals appearing at δ 51.77 and 39.46 are characterized to the methyl carbon of the ester group and methine carbon (C-3), respectively. Keto-methylene carbons of cyclopentanone ring appeared at δ 43.84 and 38.04. Remaining methylene carbon of cyclopentanone ring is observed at δ 29.03.

Mass spectral analysis (**Fig. 6**) showed expected molecular ion peak at 168 with 40 % intensity. The base peak is observed at 153 (M^+ - Me). The other prominent fragmentation peaks are at 137 (24 %), 109 (59 %), 97 (22 %), 81 (89 %), 67 (36 %), 53 (76 %), 39 (59 %).

2.4. Coupling of 2-alkyl cyclopentenone with methyl propiolate (27) :

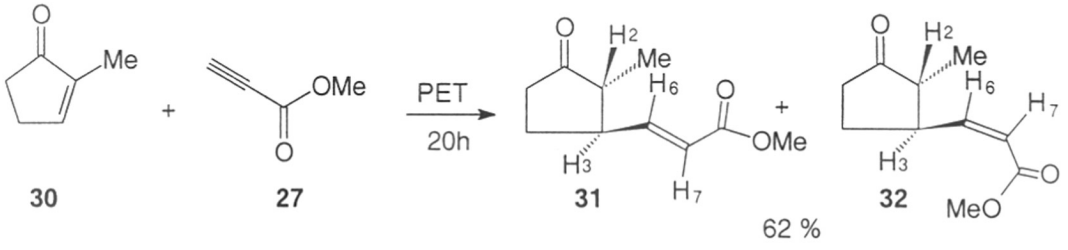
There are many important biologically active molecules possessing stereoselective 2,3-disubstituted alkylated cyclopentanone moiety, for example, jasmone[13],

prostaglandins[12] etc. Therefore, in order to determine the relative stereochemistry between H_{-2} and H_{-3} in the resultant products coupling between 2-alkyl cyclopentanone with **27** was studied.

2.4.1. PET initiated coupling of 2-methyl cyclopentenone (30) with 27 :

Usual PET reductive activation of a mixture of **30** and **27** in an analogous manner as described above, led to the coupling products **31** and **32** in 62 % yield, with each of the product as a mixture of two diastereomers (**Scheme-8**). Diastereomeric ratio was measured by ^{1}H NMR spectrum by comparing the integration of the methyl protons (attached to C-2). *E* and *Z* isomers were separated by column chromatography.

Scheme-8



IR spectrum of *E*-isomer (**31**) indicated the characteristic absorption band of α,β-unsaturated olefinic double bond at 1662 cm^{-1}. It showed prominent absorption bands at 1743 and 1716 cm^{-1} also confirming the retention of ester and keto-carbonyl moieties, respectively, in the product.

^{1}H NMR (**Fig. 7**) displayed a doublet of a doublet (J = 15.8, 8.1 Hz), integrating for one proton, characterised to the β proton of α, β-unsaturated ester group (H_{-6}). Another doublet of a doublet (J = 15.8, 0.76 Hz) at δ 5.93, integrating for one proton, is attributed to the α-proton of the same α, β-unsaturated ester group (H_{-7}). A sharp singlet at δ 3.75, integrating for three protons, is assigned to the methyl protons of ester group. The allylic proton (H_{-3}) and another proton (H_{-5eq}) are observed as a bunch of multiplets between δ 2.65-2.30. Another bunch of multiplets appearing between δ 2.28-2.06 (two protons) could be assigned to the remaining H_{-5ax} and H_{-4eq}, respectively. H_{-4ax} proton is observed as a multiplet between δ 1.82-1.50. Another multiplet between δ 2.05-1.86 (one proton) is

characterised to the methine proton (H_{-2}) . Another doublet (J = 6.98 Hz) at δ 1.10, integrating for three protons, is assignable to the methyl protons attached to C-2 carbon.

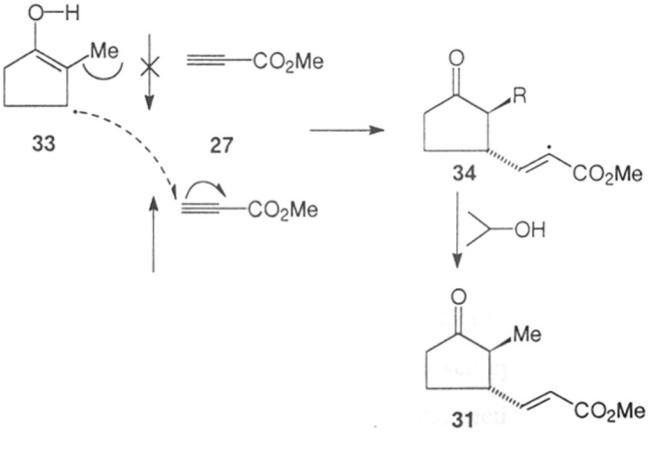
The ^{13}C NMR (**Fig. 8**) showed ten carbon signals whose characterisation are assigned by INEPT experiment. A pair of down field signals appearing at δ 218.20 and 166.69 are characterised to the quaternary carbon of keto-carbonyl and estercarbonyl groups, respectively. Another pair of signals appearing at δ 149.76 and 121.64 are characterised to the β-carbon and α-carbon of α, β-unsaturated ester group, respectively. Methyl carbon of ester group and methyl carbon attached to C-2 carbon, appeared at δ 15.61 and δ 12.15, respectively. Another pair of signals appearing at δ 49.47, 47.76 are assigned to the methine carbons. Methylene carbons of cyclopentanone ring (C-5 and C-4) are observed at δ 36.84 and 26.95, respectively.

Mass spectral analysis (**Fig. 9**) showed molecular ion peak at 182 with 18 % intensity along with base peak at 55. The other prominent fragmentation peaks are observed at 167 (M^+ - Me, 14 %), 150 (M^+ - MeOH, 15 %), 151 (M^+ - OMe, 15 %), 123 (74 %), 111 (48 %), 95 (61 %), 81 (60 %), 67 (88 %).

(Z) isomer (**32**) was characterised by ^1H NMR spectrum (for details see experimental section).

The structural assignment of **31** was confirmed by ^1H COSY (**Fig. 10**), NOE and detailed decoupling experiment (**Fig. 11** & **12**). The relative stereochemistry between H_{-2} and H_{-3} was assigned as *trans* from the decoupling experiment and measuring the coupling constant (J = 10.8 Hz) between these two protons.

Scheme-9



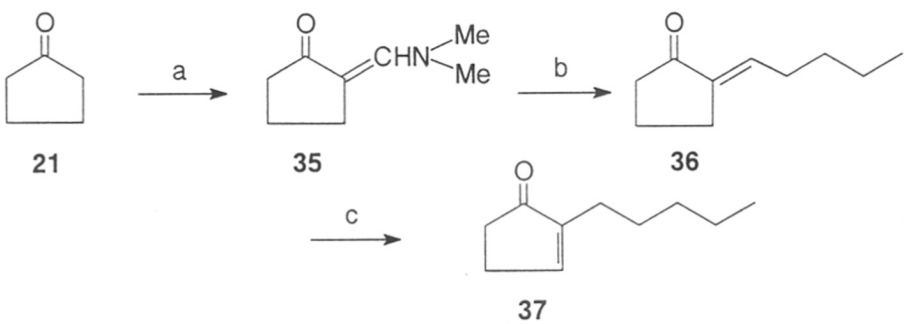
The *trans* relationship between H_{-2} and H_{-3} in **31** is likely to emerge by the predominant *anti* addition of the resultant β-centered radical **33** to **27** owing to the shielding[14] of the *syn* face of **33** by the substituent present at 2-position as depicted in **Scheme-9**.

To establish the generality of the reaction and stereochemistry for the 2,3-disubstituted cyclopentanone, PET reductive coupling of 2-pentyl cyclopentenone (**36**) with **27** was also studied.

2.4.2. Preparation of 2-pentyl cyclopentenone (37) :

Substrate **37** was prepared[15] from **21** in three steps as shown in **Scheme-10.** Compound **21** upon treatment with N,N-dimethylformamide dimethyl acetal gave **35** (88 %), which on subsequent conjugate addition of n-butyl group, using n-butyllithium as a nucleophile, followed by elimination of N,N-dimethylamide produced **36** (77 %). Acid catalysed isomerisation of the endocyclic olefinic double bond of **36** gave **37** in 75 % yield (**Scheme-10**).

Scheme-10



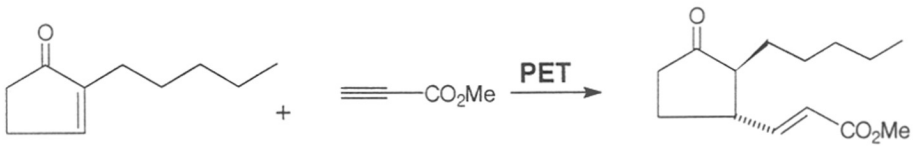
Reagents and conditons: (a) $CH(OMe)_2NMe_2$, 110 °C, 12 h; (b) n-BuLi, -30 °C, (c) 12N HCl, n-BuOH, 100 °C.

2.4.3. PET initiated coupling of 37 with 27:

Usual PET activation of **37** in the presence of **27** furnished **38** in 55 % yield (*trans:cis* 5:1) (**Scheme-11**). Compound **38** was characterised by ^1H NMR, ^{13}C NMR, IR and mass spectroscopic data. (for details see experimental section). Diastereomeric ratio

was measured by ^1H NMR spectrum by comparing the integration of methoxy protons and further confirmed by GC analysis (Capillary column, methyl phenyl silicone, 25m).

Scheme-11

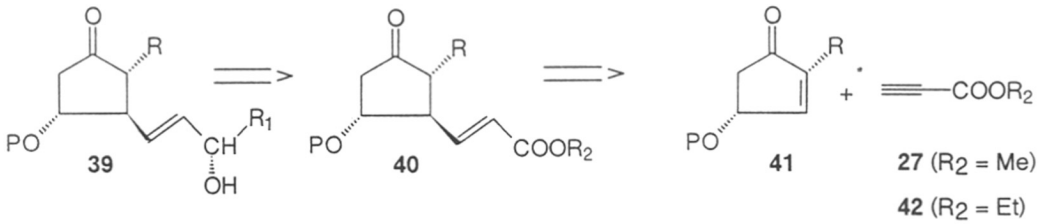


37 **27** **38**

3. Attempts towards the synthesis of prostaglandin analogues :

The successful coupling between **30** or **37** and **27** and the observed 1,2-*trans* stereochemistry and *E*-olefin geometry in **31** and **38** encouraged us to attempt the synthesis of optically pure PG analogue **40** through the retrosynthetic route as shown in **Scheme-12**. The transformation of **40** to **39** was planned to be achieved by following the reported procedure of Otera et al[16].

Scheme-12



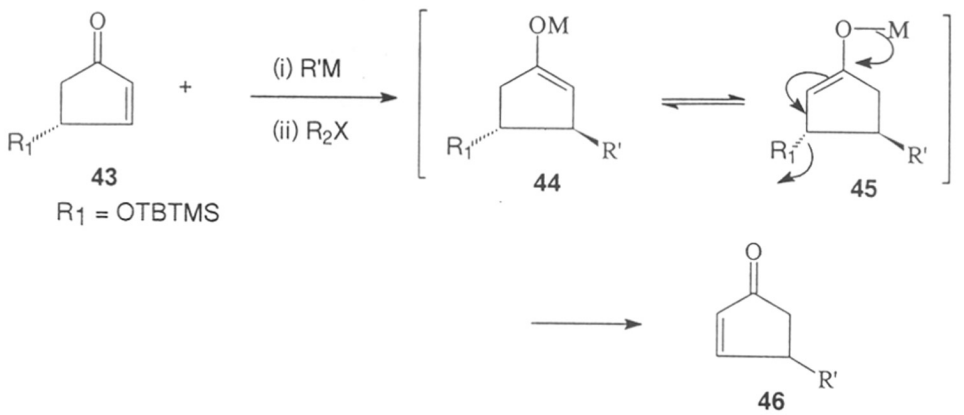
a R = CH_2—≡—$(CH_2)_6$CN , P = TBDMS, R_1 = Amyl

or

b $(CH_2)_6COOMe$

Despite the attractiveness of three component coupling approach[17] for the assembling of **39**, serious limitations *viz*: enolate isomerisation [e.g. **44** → **45**] and β-alkoxide elimination [e.g. **45** →**46**] from **44** (**Scheme-13**) has rendered two component coupling approach[18] still a highly studied and valuable route.

Scheme-13



This background led us to attempt the above proposed strategy (**Scheme-12**) as an alternative to the classical two-component coupling approach. Since our photolysis reaction is performed in aqueous solvent, it was envisaged that it might help in restricting the offending enolate equilibrium step [e.g. **44** → **45**] due to the quenching of the initially formed intermediate by the proton, easily available from water. It was also envisioned that our approach might become attractive as it avoids the use of sensitive organometallic reagents and dry reaction conditions.

Towards this goal we initiated our effort by studying the coupling of **41a** & **41b** with **27** and **42**, respectively, by following the PET activation conditions as described earlier. Prostaglandin precursor **41a** was synthesised starting from 4(R)-*tert*-butyldimethyl-silyloxy-cyclopenten-2-one (**43**).

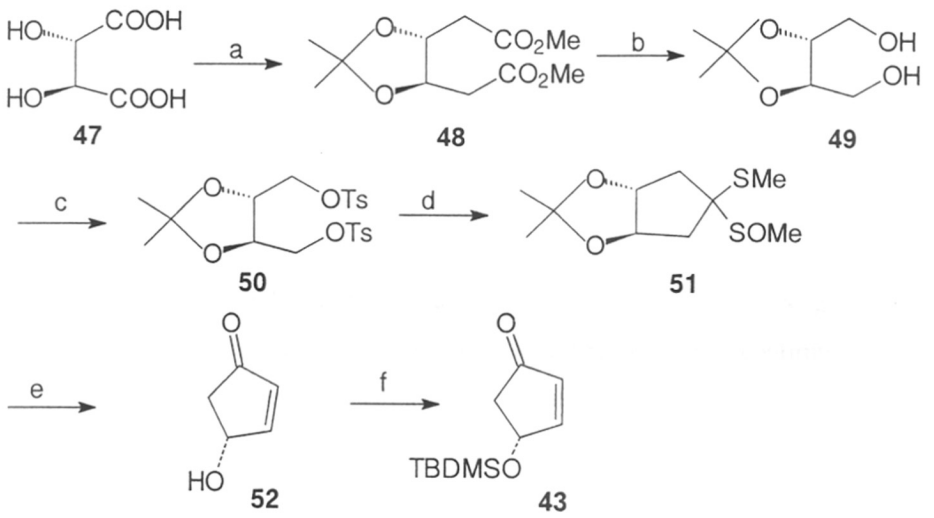
3.1. Preparation of 4(R)-Hydroxycyclopent-2-enone (43):

43 was obtained from D-tartaric acid (**47**) with little modification of the known procedure[19] in six simple steps as shown in **Scheme-14**.

47 was converted to dimethyl 2,3-O-isopropylidene-D-tartarate (**48**) by heating with 2,2-dimethoxy propane in presence of p-toluene sulphonic acid (TsOH) which on reduction by lithium aluminium hydride afforded 2,3-O-isopropylidene-D-threitol (**49**) in quantitative yield. Tosyl protection of the hydroxyl groups of **49** by tosyl chloride/pyridine gave ditosylate (**50**, 90 %) as a solid, mp 89 °C (lit.[20] mp 91.7-92.7 °C). Condensation of

lithio derivative of methyl methylsulfinyl sulfide with **50** afforded cyclic sulfoxide **51** which on subsequent acid hydrolysis produced **52** as a colorless oil. Protection of the hydroxyl moiety of **52** as TBDMS ether by stirring with *t*-butyldimethylsilylchloride in DMF at r.t in the presence of imidazole afforded **43** in 90 % yield.

Scheme-14



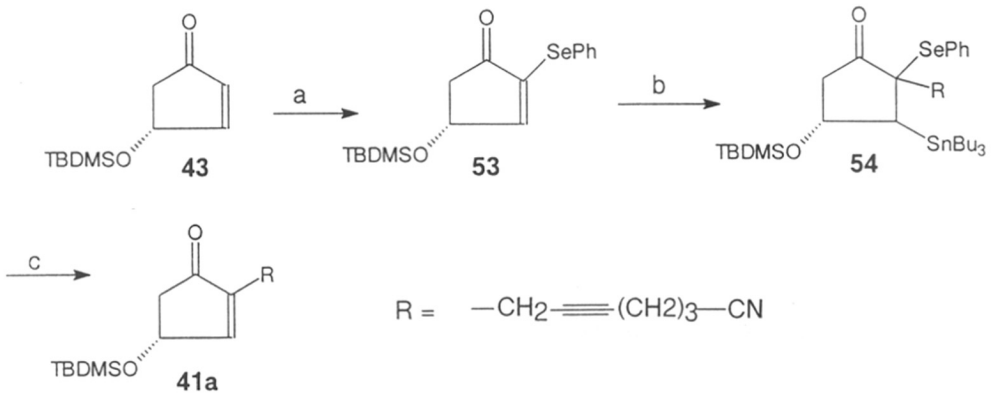
Reagents and conditions: (a) 2,2-dimethoxypropane, TsOH, (b) LAH, THF, reflux, 99 %, (c) TsCl, Pyridine, 0 °C, 90 %, (d) $MeSCH_2SOMe$, n-BuLi, THF, -78 °C, 75 %, (e) 1N H_2SO_4, 50 %, (f) TBDMSCl, imidazole, DMF, r. t., 90 %.

3.2. Preparation of substrate 41a :

Precursor **41a** was obtained[21] from **43** in four steps as shown in the **Scheme-15**.

Treatment of **43** with phenylselenyl chloride in the presence of pyridine at r.t. afforded 2-phenylseleno-4(R)-*tert*-butydimethylsilyloxy-cyclopent-2-en-1-one **(53)**. Conjugate addition of tributylstannyl group to **53** using tributylstannyllithium as nucleophile followed by trapping of the resultant lithium enolate by 7-iodo-hept-5-yne-1-nitrile at -78 °C in THF gave **54**. Subsequent deselenostanyllation by tetrabutylammonium fluoride furnished **41a** in 70 % yield.

Scheme-15



Reagents and conditions: (a) PhSeCl, Py, CH_2Cl_2, r. t., 90 %; (b) Bu_3SnLi, RI, THF, -78 °C, 80 %; (c) TBAF, THF, -20 °C, 90 %.

IR spectrum of **41a** indicated the characteristic absorption band of -CN- group at 2343 cm^{-1}. It showed prominent absorption bands at 1708, 1647 cm^{-1} confirming the retention of keto-carbonyl moiety and olefinic double bond, respectively.

The ^1H NMR (**Fig. 13**) displayed a multiplet between δ 7.36-7.30 integrating for one proton, assigned as the vinylic proton (H_{-12}). Another multiplet between δ 4.99-3.87 is characterised to the methine proton (H_{-11}), attached to -OTBDMS group. Another multiplet between δ 3.15-3.02 integrating for two protons, is assigned to the methylene protons α to CN group. A doublet of a doublet (J = 17.5, 5.4 Hz) at δ 2.85, integrating for one proton is attributed to the H_{-10eq} proton. Methylene protons attached to C-2, C-4 and remaining one methylene proton (H_{-10ax}) appeared as a bunch of multiplets between δ 2.65-2.22 (five protons). A multiplet appearing between δ 1.98-1.78 (two proton) is attributed to the methylene protons β to CN group. Protons of *t*-Bu-group (nine proton) appeared as a singlet at δ 0.95. Protons of the remaining two methyl group of TBDMS moiety are observed as two singlets at δ .13 (three proton) and 0.12 (three protons), respectively.

The ^{13}C NMR (**Fig. 14**) and its INEPT experiment suggested the characteristics of carbon signals as well as the correct accounting of different carbons. It displayed fifteen carbon signals. Two down field carbon signals appearing at δ 203.98 and 157.90 corresponds to the keto-carbonyl and the methine carbon (C-12). The C-8, C-6, and C-5 quaternary carbons appeared at δ 118.88, 79.63 and 77.02, respectively. Another signal

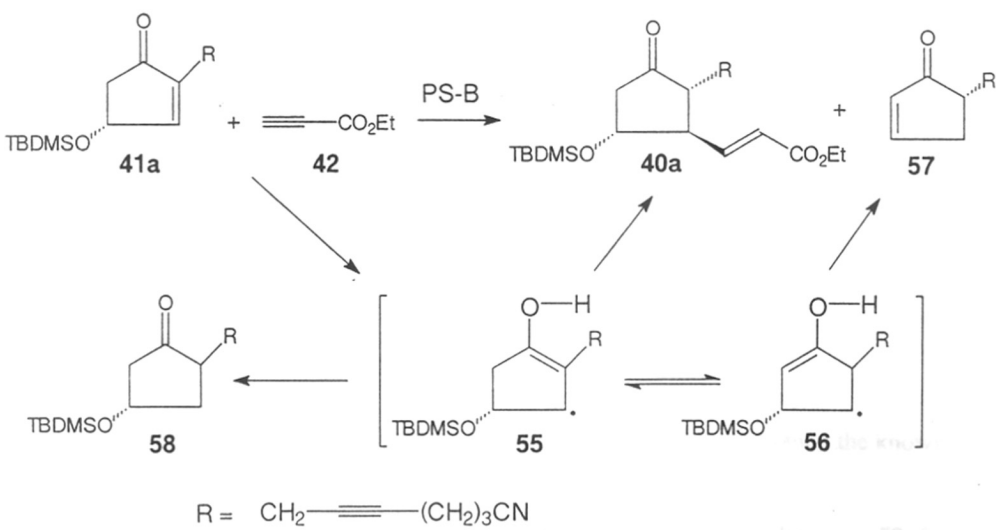
appearing at δ 68.50 is characterised to the methine carbon (C-11). Methylene carbons (C-7, C-9, C-4, C-3 and C-2) are observed at δ 45.46, 25.55, 24.50, 17.85 and 15.87 respectively. A signal appearing at δ 17.64 is attributed to the quaternary carbon of *t*-Bu moiety. Methyl carbon signals of *t*-Bu group (2C) and the remaining two methyl carbon signal of TBDMS moiety are observed at δ 15.09 and -4.90 respectively.

Mass spectral analysis (**Fig. 15**) did not show prominent molecular ion peak. First intense peak is found at 260 (M^+ - *t*-Bu) with 21 % intensity along with a base peak at 75. The other prominent fragmentation peaks are found at 232 (44 %), 218 (91 %), 205 (6 %), 186 (8 %), 175 (5 %), 157 (6 %), 115 (17 %), 103 (11 %), 91 (23 %), 77 (21 %), 74 (30 %), 57 (29 %).

3.3. PET reductive coupling of 41a with 42 :

PET reductive coupling of **41a** with **42** involved the irradiation of a mixture of chiral enone (**41a**) and ethyl propiolate (**42**) using **PS-B** reduction conditions in an identical fashion as described for **17**.

Scheme-16



Usual workup followed by purification of the reaction mixture afforded the expected coupling product **40a** in very poor yield (<15 %) along with β-alkoxide elimination product **57** (yield 40 %) and reduced product **58** (yield 20 %) (**Scheme-16**).

Formation of **40a** as a minor product was quite surprising to us. Formation of **57** and **58** dominated the reaction mixture. Much effort was not made to isolate the coupling product **40a** in very pure form. However, **57** and **58** could be isolated in pure form and were characterised by ^{1}H NMR spectral analysis (see details in experimental section).

Compound **40a** was always isolated as a mixture with **57**. The ^{1}H NMR spectrum (**Fig. 16**) of the mixture clearly provides sufficient information regarding its presence in the mixture. For example, it displayed the absence of vinylic double bond present in **41a**., a doublet of doublet at δ 6.95 (J = 15.2, 8.1 Hz), and a doublet at δ 5.92 (J = 15.2 Hz), characteristics of the β and α protons of acrylic double bond, respectively, suggested its presence in the reaction mixture.

3.4. Mechanism of the reaction :

Upon acceptance of an electron from $DCA^{\bullet-}$, α, β-unsaturated ketone moiety of **41a** is transformed into enolate radical ion which on protonation by H_2O is converted to **55**. The formation of **57** suggests that **55** isomerises to **56** reversibly by intermolecular deprotonation/protonation of the intermediates **55** and **56** even in aqueous medium. Due to the isomerisation of **55** to **56**, the carbon centered radical (**55**) looses its stabilisation, as no longer it remains conjugated with the olefinic double bond and before it gets trapped by the propiolate, it is terminated by H-donation from iso-propanol, followed by β-elimination to form **57**. Formation of **58** could be explained by partial termination of the intermediate **55** by iso-propanol followed by the quenching of the enol by H_2O.

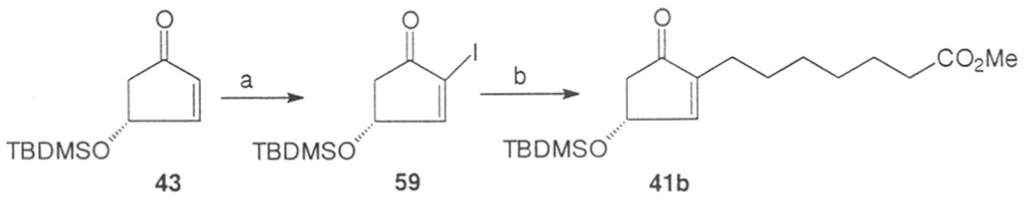
3.5. Preparation of substrate 41b :

Precursor **41b** was prepared in three steps starting from **43** by following the known procedure[22] (**Scheme-17**).

α-Iodination of **43** by the reaction of iodine in the presence of pyridine gave **59** (77 %) which upon Pd(0) catalysed Suzuki cross coupling with 9-(7-oxo,7-ethoxy) heptyl-9-BBN, obtained by the hydroboration of methyl-6-heptenoate with 9-BBN, gave **41b** (25 %). Methyl-6-heptenoate was prepared (55 %) by the Grignard reaction of 5-hexenyl

magnesium bromide and methyl chloroformate. Although the coupling yield of **41b** is reported[22] to be 77 %, in our hand we could not achieve more than 25 % yield.

Scheme-17

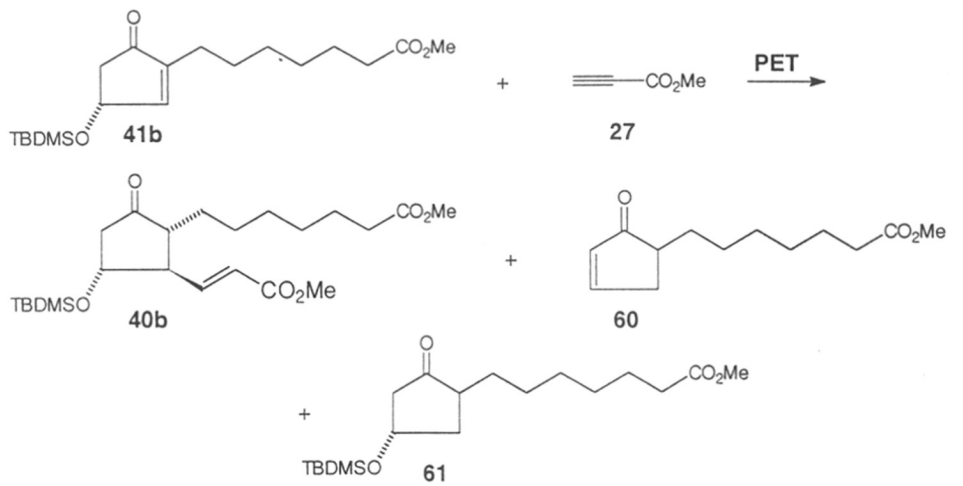


Reagents and conditions : (a) I_2, CCl_4/Py, r. t., 77 %; (b) 9-BBN, methyl-6-heptenoate, $PdCl_2$(dppf), Ph_3As, Cs_2CO_3, DMF/THF/H_2O, 25 °C, 25 %.

3.6. PET initiated coupling of 41b with 27 :

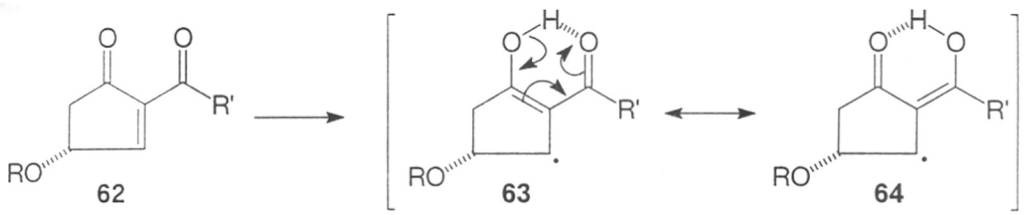
PET activation of **41b** by following analogous reaction condition as described for **41a** yielded **40b** in 12 % yield along with **60** (40 %) and **61** (20 %) (**Scheme-18**). Due to the poor yield for the formation of **40b,** we did not attempt its isolation from the reaction mixture in the pure form, however, its formation has been confirmed by analysing the ^{1}HNMR spectrum of the crude reaction mixture as described earlier.

Scheme-18



Our above frustrating effort to achieve a meaningful synthesis of PG analogue through the strategy developed by us has been dropped at the moment at this stage. It is proposed that the same will be tried through the modified approach as shown in **Scheme-19**

Scheme-19



Further development in this direction is in progress.

4. Conclusion :

In summary, we have developed a new and simple strategy for the intermolecular coupling of α,β-unsaturated ketones at its β-position with activated alkenes or alkynes. This methodology presents a new concept in -C-C- bond formation reaction. An attempt has been made to extend this methodology towards the synthesis of optically pure PG analogues as an alternative strategy to two component coupling approach. New observation of β-enolate radical intermediate isomerisation in aqueous medium is also described .

4. Experimental

4.1. General Photoirradiation Procedure:

All irradiations were performed in a specially designed photoreactor as described in chapter-1. Details of the reaction procedure has also been described in chapter-1 and chapter-2. **PS-A** reaction conditions involved the photolysis of a mixture containing DCA (25 mol %), enone (1 equiv.), Ph_3P (0.7-0.8 equiv.) and alkene or alkyne (2-4 equiv.) in DMF:*i*-PrOH:H_2O (88:10:2) using 405 nm light.[11] Similarly, the reactions utilizing **PS-B** were carried out by photolysing a mixture of DCA (25 mol %), enone (1 equiv.), DMN (15 mol %), ascorbic acid (2.6 equiv.) and alkene or alkyne (2-4 equiv.) under similar irradiation conditions.

4.2. PET initiated coupling of cyclopentenone (17) with ethyl acrylate (18) using PS-A :

A solution of compound **17** (0.25 g, 3.04 mmol), **18** (0.76 g, 7.6 mmol), Ph_3P (0.637 g, 0.2.43 mmol) and DCA (0.173 g, 0.76 mmol) in DMF: *i*-PrOH: H_2O (300 mL, 88: 10: 2) was irradiated in a specially designed photoreactor as mentioned in chapter-1 under argon with light from a 450 W Hanovia medium-pressure lamp filtered by a $CuSO_4.5H_2O$: NH_3 solution. The progress of the reaction was monitored by GC. After considerable consumption (98%) of **17** (25 h), the solvent was removed by distillation under reduced pressure. The concentrate was dissolved in EtOAc (50 mL) and washed with H_2O and saturated brine solution. The EtOAc layer was concentrated under vacuo and the mixture was separated by column chromatography over silica-gel (100-200 mesh) using pet-ether: EtOAc as eluant to give compound **19** (0.31 g, 55 %) along with dimer (**22**, 0.021 g, 4 %). **22** was characterised by GC/MS analysis.

3-(3-ethoxy-3-oxo)propyl-cyclopentanone (19):

^{1}H NMR (200 MHz) : 4.15 (2H, q, J = 7.3 Hz), 2.42 (2H, t, J = 6.3 Hz), 2.40-1.96 (4H, m), 1.95-1.35 (4H, m), 1.30-1.10 (4H, m, including, 3H, t, J = 7.3 Hz).

IR (neat) : 2968, 2822, 1730, 1715, 1428, 1361, 1340 1231. 1140, 1062.

MS (m/e) : 184 (M+, 2 %), 138 (M+ - EtOH, 30 %), 127 (3 %), 110 (18 %), 111 (11 %), 97 (12 %), 82 (28 %), 83 (27 %), 67 (24 %), 55 (100 %).

4.3. PET initiated coupling of cyclohexenone (23) with ethyl acrylate (18) using PS-A:

To a solution of DCA (0.148 g, 0.65 mmol) in DMF: *i*-PrOH: H_2O (300 mL), **23** (0.25 g, 2.6 mmol) , **18** (0.65 g, 6.5 mmol) and Ph_3P (0.546 g, 2.08 mmol) were added and the mixture was irradiated in a similar manner as described above. After 28 h, irradiation was stopped and solvents were distilled off under reduced pressure. Column chromatographic purification of the concentrate yielded 3-(3-ethoxy-3-oxo)propyl-cyclohexanone (**24**, 0.31 g, 60 %) and dimer 3,3′-bicyclohexanone (**26**, 0.025 g, 5 %).

*3-(3-ethoxy-3-oxo)propyl-cyclohexanone (**24**):*

^{1}H NMR (200 MHz)	:	4.15 (2H, q, J = 7.3 Hz), 2.55-2.25 (4H, m), 2.22-1.85 (3H, m), 1.84-1.55 (4H, m), 1.50-1.10 (5H, m, including 3H, t, at 1.26, J = 7.3 Hz).
^{13}C NMR (50 MHz)	:	211.16, 173.45, 60.57, 47.88, 41.50, 38.66, 31.82, 31.64, 31.14, 25.24, 14.39.
MS (m/e)	:	198 (M^+, 24 %), 152 (M^+ - EtOH, 100 %), 141 (9 %), 124 (61 %), 111 (25 %), 98 (46 %), 99 (53 %), 88 (18 %), 81 (27 %), 67 (28 %), 55 (95 %).
IR (neat)	:	2980, 1732, 1712, 1478, 1340, 1221, 1050

3,3′-bicyclohexanone (**26**) was characterised by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic experiment and compared with reported data [23].

4.4. PET initiated coupling of cyclopentenone (17) with methyl propiolate (27) using PS-B:

To a solution of DCA (0.173 g, 0.76 mmol) in DMF: *i*-PrOH: H_2O (300 mL), 0.25 g (3.04 mmol) of **17**, **27** (0.894 g, 10.64 mmol), DMN (0.086 g, 0.457 mmol) and ascorbic acid (1.39 g, 7.8 mmol) were added and the mixture was irradiated in an analogous manner as mentioned for **17** using **PS-A**. After 29 h, irradiation was stopped and solvents were distilled off under reduced pressure. Purification of the concentrate by pet-ether: EtOAc gave 0.3 g of **28** (54 %).

3-[(3-ethoxy-3-oxo)-2(E)-propenyl]-cyclopentanone (28):

^{1}H NMR (200 MHz)	:	6.98 (1H, dd, J = 15.6, 7.8 Hz), 5.83 (1H, dd, J = 15.6, 0.8 Hz), 3.75 (3H, s), 3.15-2.80 (1H, m), 2.65-2.02 (5H, m), 1.98-1.70 (1H, m).
^{13}C NMR (50 MHz)	:	217.05, 166.88, 149.92, 121.02, 51.77, 43.84, 39.46, 38.04, 29.03.
IR (neat)	:	2955, 1739, 1724, 1653, 1274, 1200, 1155, 979, 861.
GC/MS (m/e)	:	168 (M^+, 40 %), 153 (M^+ - Me, 100 %), 137 (M^+ - OMe, 24 %), 109 (59 %), 97 (22 %), 81 (89 %), 67 (36 %), 53 (76 %), 39 (59 %).

4.5. PET initiated coupling of 2-methylcyclopentenone (30) with methyl propiolate (27) using PS-B:

PET initiated coupling of **30** involved the irradiation (28 h) of the solution of DMF: *i*-PrOH: H_2O (300 mL) containing **30** (0.3 g, 3.12 mmol), **27** (0.92 g, 10.95 mmol), and DCA (0.178 g, 0.78 mmol), DMN (0.088 g, 0.468 mmol) and ascorbic acid (1.43 g, 8.1 mmol) following the identical irradiation procedure as described earlier. After removal of solvents by distillation under vacuo followed by column chromatographic purification of the concentrate gave **31** (0.29 g, 52 %) and **32** (0.058 g, 10 %).

Trans-2-methyl-3-[(3-ethoxy-3-oxo)-2(E)-propenyl]-cyclopentanone (31):

^{1}H NMR (200 MHz)	:	6.95 (1H, dd, J = 15.6, 8.1 Hz), 5.93 (1H, dd, J = 15.6, 0.76 Hz), 3.75 (3H, s), 2.65-2.32 (2H, m), 2.28-2.06 (2H, m), 2.05-1.85 (1H, m), 1.82-1.50 (1H, m), 1.10 (3H, d, J = 6.98 Hz).
^{13}C NMR (50 MHz)	:	218.20, 166.69, 149.76, 121.64, 51.61, 49.47, 47.76, 36.84, 26.95, 12.15.
IR (neat)	:	2957, 2877, 2361, 1743, 1716, 1662, 1446, 1311, 1277, 1149.
MS (m/e)	:	182 (M^+, 18 %), 167 (M^+ - Me, 14 %), 150 (M^+ - MeOH, 15 %), 151 (M^+ - OMe, 15 %), 123 (M^+ - COOMe, 74 %), 111 (48 %), 95 (61 %), 81 (60 %), 67 (88 %), 55 (100 %).

Cis-2-methyl-3-[(3-methoxy-3-oxo)-1(E)-propenyl]-cyclopentanone (32):

^{1}H NMR (200 MHz) : 6.14 (1H, dd, J = 9.7, 7.9 Hz), 6.0-5.85 (1H, m), 3.75 (3H, s), 3.35-2.28 (2H, m), 2.55-2.1 (2H, m), 2.05-1.75 (1H, m), 1.45-1.20 (1H, m), 1.03 (3H, d, J = 6.8 Hz).

4.6. Preparation of 2-pentyl cyclopentenone (37) :

Compound **37** was prepared from **21** in three steps as described below :

(a) preparation of 2-[(Dimethylamino) methylene]cyclopentane (35):

To a 8.4 g (109.64 mmol) of cyclopentanone was added 11.9 g (100 mmol) of N,N- dimethyl formamide dimethyl acetal and the mixture was refluxed under argon at 110 °C for 12 h. Methanol was distilled off and the concentrate was distilled in a **Kugelrohr** apparatus at 120-130 °C / 0.4-0.6 mm to afford 12.2 g of **35** (88%) as an reddish oil which was used without further purification.

^{1}H NMR (200 MHz) : 7.2 (1H, t, J = 0.76 Hz), 3.08 (6H, s), 2.85 (2H, t, J = 7.6 Hz), 2.22 (2H, t, J = 8.1 Hz), 1.95-1.45 (2H, m).

(b) To a solution of **35** (4 g, 28.78 mmol) in THF(120 mL) at -30 °C was added 3M solution of n-BuLi (10.55 mL, 32,65 mmol) dropwise over a period of 30 min. The reaction mixture was stirred to r.t. over 2 h. The excess n-BuLi was destroyed by the addition of water (5 mL) and the solvent was removed under vacuo. The residue was treated with 50 mL of water and extracted 5 times with 50 mL portion of Et_2O. The Et_2O layer was washed with water, dried over anhydrous $NaSO_4$ and evaporated under vacuo to give 3.37 g of **36** (77%).

BP 95-102 °C /8 mm

^{1}H NMR (200 MHz) : 6.5-6.40 (1H, m), 2.65-2.40 (2H, m), 2.35-2.22 (2H, t, J = 6.8 Hz), 2.20-2.02 (2H, m), 1.98-1.75 (2H, m), 1.70-1.15 (4H, m), 0.85 (3H, t, J = 7 Hz)

(c) Into a solution of **36** (1 g, 6.58 mmol) dissolved in 10 mL of n-BuOH was added 2 mL of 12 N HCl and the mixture was stirred at 100 °C for 1 h. The mixture was poured into water and extracted with Et_2O. The Et_2O solution was dried over anhydrous Na_2SO_4 and solvent was removed to give 0.75 gm (75 %) of **37** as a mobile, colourless, fragrant liquid.

^{1}H NMR (200 MHz) : 7.45-7.25 (1H, m), 2.65-2.50 (2H, m), 2.48-2.35 (2H, m), 2.25-2.05 (2H, m), 1.80-1.10 (6H, m), 0.92 (3H, t, J = 6.5 Hz).

^{13}C NMR (50 MHz) : 209.93, 157.29, 146.47, 34.56, 31.57, 27.42, 26.42, 24.72, 22.40, 13.94.

IR (neat) : 2987, 2837, 1715, 1639, 1446, 1351, 1267, 1049.

4.7. PET initiated coupling of 2-pentyl cyclopentenone (37) with methyl propiolate (27) using PS-B:

Compound **37** (0.3 g, 1.97 mmol), **27** (0.58 g, 6.9 mmol), DMN (0.056 g, 0.30 mmol) and ascorbic acid (0.51 g, 2.9 mmol) were dissolved in a solution of DMF: *i*-PrOH: H_2O (300 mL) containing DCA (0.063 g, 0.28 mmol) and mixture was irradiated for 20 h. After removal of solvents and column chromatographic separation of the residue yielded 0.258 g (55 %) of **38**.

Trans-2-pentyl-3-(3-methoxy-3-oxo-1(E)-propenyl)-cyclopentanone (38):

^{1}H NMR (200 MHz) : 6.96 (1H, dd, J = 16.1, 8.1 Hz), 5.95 (1H, d, J = 16.1 Hz), 3.76 (3H, s), 2.95-2.82 (1H, m), 2.60-1.82 (6H, m), 1.80-1.05 (7H, m), 0.9 (3H, t, J = 6.1 Hz)

^{13}C NMR (50 MHz) : 218.1, 166.05, 149.58, 120.43, 50.9, 43.56, 39.5, 35.87, 35.23, 29.98, (2C), 25.27, 22.19, 13.14.

IR (neat) : 2927, 2842, 1740, 1718, 1656, 1466, 1291, 1262, 1047.

MS (m/e) : 238 (M^+, 2 %), 236 (67 %), 221 (89 %), 207 (16 %), 193 (7 %), 177 (100 %), 175 (20 %), 168 (26 %), 167 (37 %), 161 (10 %), 153 (23 %),

149 (12 %), 147 (16 %), 153 (23 %), 149 (12 %), 147 (16 %), 135 (6 %), 91 (5 %), 79 (3 %).

4.8. Preparation of 2,3-O-Isopropylidene-D-tartarate (48):

D- tartaric acid (**47**, 50.5 g, 336.5 mmol), 2,2-dimethoxypropane (80 g, 770 mmol), PTSA (0.2 g) and dry MeOH (25 mL) were charged into a 500 mL RB flask fitted with magnetic stirring bar and reflux condenser. The whole content was warmed gently on an oil bath for 1.5 h. To the dark red solution was added an additional 40 g, (385 mmol) of 2,2-dimethoxypropane and 225 mL of cyclohexane. The resulting two layer solution was refluxed with stirring with azeotropic removal of cyclohexane-acetone (53 °C) and methanol-cyclohexane (54.5 °C). After 48 h, 240 mL distillate was collected. Anhydrous K_2CO_3 (1 g) was added to neutralise PTSA. The solvent and unreacted 2,2-dimethoxypropane were removed under reduced pressure to give 74 g (~ 100 %) of **48**.

BP : 90-100 °C/0.5 mm (Lit.[24] 82-90 °C/0.02 mm).

^{1}H NMR : 4.76 (2H, s), 3.82 (6H, s), 1.48 (6H, s).
(200 MHz)

4.9. Preparation of 2,3-O-Isopropylidene-D-threitol (49):

Compound **49** (22 g, 90 %) was prepared by the LAH (7.3 g, 192.6 mmol) reduction of **48** (33 g, 151.38 mmol) by following the identical procedure as described earlier.

BP : 110-120 °C/0.5-0.6 mm (Lit.[20] 91-93 °C/0.01-0.02 mm).

^{1}H NMR : 4.02-3.90 (2H, m), 3.82-3.57 (4H, m), 2.4-2.1 (2H, broad s), 1.39 (6H, s)
(200 MHz)

4.10. Preparation of 1,4-Ditosyl-2,3-O-Isopropylidene-D-threitol (50):

To a solution of 20 g (123.4 mmol) of **49** in 150 mL of dry pyridine at - 10 °C was added 58.8 g (308.4 mmol) of freshly crystallised TsCl in one portion. The mixture was stirred till it became homogeneous and it was kept at 0 °C for 12 h. The product was crystallised from the reaction mixture by the slow addition of water and crystallisation was

permitted to continue at 0 °C for few hour. The product was washed with 95 % EtOH. Recrystallisation of the product from pet ether/EtOAc gave (52 g, 90 %) of **50**.

MP : 86-88 °C (Lit.[20] 91.7-92.7 °C)

^{1}H NMR (200 MHz) : 7.75 (2H, d, J = 8.1 Hz), 7.32 (2H, d, J = 8.0 Hz), 4.05 (4H, d, J = 1.3 Hz, 4.1 Hz), 3.98-3.90 (2H, m), 2.45 (6H, s), 1.32 (6H, s).

4.11. Preparation of (3R,4R)-3,4-O-Isopropylidene-L-threitolcyclopentanone Dimehtyldithioketal S-Oxide (51) :

To a cooled solution of methyl methylsulfinyl sulfide (15 g, 120.47 mmol) in dry THF (400 mL) was added 4 M solution of n-BuLi (30.2 mL, 110.24 mmol) at -78 °C dropwise over a period of 2 h. The reaction mixture was stirred at -78^0 C for 2 h and then allowed to warm slowly to room temperature for 2.5 h after which the solution turned yellow. The reaction mixture was cooled to -78 °C and a solution of **50** (24.62 g, 52.50 mmol) in dry THF (150 mL) was added dropwise over a period of 2 h. It was stirred at -78^0 C for 2 h and then allowed to stir at room temperature for 2 days. Saturated aqueous ammonium chloride (100 mL) and triethylamine (1 mL) were added to the reaction mixture. The THF layer was separated, and the aqueous layer was extracted with methylene chloride (2 × 100 mL). The combined organic extracts were evaporated at reduced pressure, and the residue obtained was loaded on a silica gel column, pretreated with 1 % triethylamine in hexane and eluted with 20 % acetone in ethyl acetate containing 1 % triethylamine to give the 9.84 g of pure **51** (75 %).

^{1}H NMR (200 MHz) : 4.3-4.1 (1H, m), 4.0-3.85 (1H, m), 2.65 (3H, two singlet), 2.25 (3H, two singlet), 2.1-1.95 (2H, m), 1.85-1.75 (2H, m), 1.5 (6H, two singlet)

4.12. Preparation of (4R)-hydroxy-cyclopent-2-en-1-one (52) :

To a solution of **51** (9.5 g, 38.32 mmol) in ether (500 mL) was added 1N H_2SO_4 (7.3 mL) at 0 °C and the resulting mixture was allowed to stir at r. t. for 3 days. The reaction mixture was neutralised by adding solid $NaHCO_3$ and dried over anhydrous Na_2SO_4. Removal of insoluble material by filtration followed by evaporation of the solvent under reduced pressure afforded 1.88 g, (50 %) of **52** as an oil.

$[\alpha]_D^{25}$: + 68.8 ° (C = 2.46, $CHCl_3$)

^{1}H NMR (200 MHz) : 7.57 (1H, dd, *J* = 5.8, 2.6 Hz), 6.16 (1H, dd, *J* = 5.8, 1.5 Hz), 5.02-4.98 (1H, m), 3.92 (1H, m), 2.76 (1H, dd, *J* = 18.1, 6.0 Hz), 2.26 (1H, dd, *J* = 18.1, 2.0 Hz)

^{13}C NMR (75 MHz) : 207.41, 163.93, 134.88, 70.14, 44.12.

IR (neat) : 3395 (OH), 2986, 1712, 1596.

4.13. Preparation of (4R)-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one (43) :

Compound **43** (2.1 g, 90 %) was prepared from **52** (1.08 g, 11.02 mmol) by stirring with TBDMSCl (2 g, 13.26 mmol) in the presence of imidazole (1.9 g, 27.94 mmol) in DMF (10mL).

^{1}H NMR (200 MHz) : 7.45 (1H, m), 6.20 (1H, d, *J* = 7 Hz), 5.01 (1H, m), 2.70 (1H, dd, *J* = 18, 6 Hz), 2.25 (1H, dd, *J* = 18, 1.2 Hz), 0.9 (9H, s), 0.15 (6H, s).

4.1.4. 7-[(3R)-3(tert-butyldimethylsilyloxy-5 oxo-1-cyclopentenyl]-5 heptynonitrile (41a):

(a) Preparation of 53[25] *:*

To a magnetically stirred solution of benzeneselenyl chloride (0.526 g, 2.61 mmol) in CH_2Cl_2 (5 mL), kept in 25 mL two neck RB flask, was added pyridine (0.22 mL, 2.75 mmol) at r. t under argon atmosphere. After 15 min, the mixture was added in one portion to a stirred solution of **43** (0.37 g, 1.74 mmol) in CH_2Cl_2 (2 mL) placed in another 25 mL RB flask fitted with argon gas balloon. The reaction mixture was stirred at r. t. for 3 h. The resulting yellow solution was washed with 5 % HCl (3 mL), brine (3 mL) and finally dried over anhydrous Na_2SO_4. Removal of the solvent followed by flash column chromatography (silicagel, 20 % CH_2Cl_2/pet ether and then 20 % EtOAc/pet ether) afforded **53** (0.58 g, 90 %).

^{1}H NMR (200 MHz) : 7.6 (2H, d, *J*= 5.7 Hz), 7.45-7.25 (3H, m), 6.7 (1H, d, *J* = 2.4 Hz), 4.9 (1H, m), 2.9 (1H, dd, *J* = 18.3, 5.8 Hz), 2.4 (1H, dd, *J* = 18.3, 1.3 Hz), 0.9 (9H, s), 0.2 (3H, s), 0.19 (3H, s).

(b) Preparation of 7-iodo-5-heptynonitrile :

This compound was prepared by following the reported[26,27] reaction sequences as follows :

Propargyl tetrahydropyranyl ether (15 g, 107.1 mmol) was converted into 6-chloro-2-octyn-1-ol-tetrahydropyranyl ether (18 g, 80 %), using n-BuLi (34 mL, 107.1 mmol, 3.15 M) as a base and 1-chloro-3-bromo propane (16.87 g, 107.1 mmol) as alkylating agent.

6-chloro-2-octyn-1-ol-tetrahydropyranyl ether (10 g, 46.17 mmol) on subsequent reaction with NaCN (3.16 g, 64.64 mmol) in DMSO (75 mL) gave 6-cyano-2-octyn-1-ol-tetrahydropyranyl ether (9 g, 94 %).

6-cyano-2-octyn-1-ol-tetrahydropyranyl ether:

^{1}H NMR (200 MHz)	:	4.85 (1H, broad, s), 4.3-4.15 (2H, m), 3.95-3.8 (1H, m), 3.62 (2H, t, J = 7.3 Hz), 3.6-3.55 (1H, m), 2.5-2.4 (2H, m), 2.1-1.9 (2H, m), 1.9-1.5 (6H, m)

6-cyano-2-octyn-1-ol-tetrahydropyranyl ether (3 g, 14.49 mmol) on treatment with PPTS (0.364 g, 1.45 mmol) in aq EtOH produced corresponding alcohol, 6-cyano-2-octyn-1-ol (1.25 g, 70 %) which upon subsequent treatment with PBr_3 (1.4 g, 5.18 mmol) and pyridine (0.169 g, 2.13 mmol) at 0 °C in dry ether (20 mL), afforded 7-bromo-5-heptynonitrile (1.52 g, 80 %).

Preparation of 7-iodo-5-heptynonitrile :

To a solution of 7-bromo-5-heptynonitrile (1.09 g, 5.85 mmol) in dry acetone (30 mL) was added NaI (1.317 g, 8.78 mmol). The reaction mixture was stirred for 5 min, filtered and poured into a mixture of ether (150 mL) and water (50 mL). The ether layer was separated , washed with water (3×50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuo to yield 7-iodo-5-heptynonitrile (1.363g, 100 %). The iodide was used immediately without further purification.

7-iodo-5-heptynonitrile :

^{1}H NMR (200 MHz) : 3.95 (2H, t, J = 1.7 Hz), 2.6-2.4 (4H, m), 2.0-1.85 (2H, m).

*Preparation of compound **41a** :*

(c) Into a 25 mL two neck RB fitted with argon gas balloon was placed 0.624 mL of diisopropyl amine in dry THF (10 mL) and the reaction mixture was stirred at 0 °C while n-BuLi (1.65 mL, 3.9 mmol, 2.36 M) was added dropwise. The resulting solution was stirred for an additional 5 min and tributyltinhydride (1.02 mL, 3.9 mmol) was added *via* syringe. After 15-20 min at stirring at 0 °C, the formation of Bu_3SnLi was completed. The reaction mixture was cooled to - 78 °C and a solution of (4R)-4 [tert butyldimethyl silyl)]-2- (phenyl seleno)-2-cyclopentenone **53** (0.72 g, 1.95 mmol) in THF (2 mL) was added. The mixture was stirred for an additional 10 min, and 7-iodo-5-heptynonitrile (1.363 g, 5.85 mmol) and HMPA (2 mL) were added. The mixture was stirred for 1 h, during which time the bath temperature was increased to -20 °C. Completion of the allylation was confirmed by TLC. A solution of tetrabutylammonium fluoride (1.0 M, 2.34 mL, 2.34 mmol) in THF was added at - 20 °C and the cooling bath was removed. The mixture was stirred at r. t. for another 30 min. Additional tetra (1.95 mL, 1.95 m mol) was added and stirring was continued for 1.5 h. The reaction mixture was directly subjected to column chromatography over silica gel using pet ether/EtOAc as eluant to give **41a** (0.432 g, 70 % yield)

$[\alpha]_D^{22}$: + 11.5 (C = 0.9, MeOH).

^{1}H NMR (200 MHz) : 7.36-7.30 (1H, m), 4.99-3.87 (1H, m), 3.15-3.02 (2H, m), 2.85 (1H, dd, J = 17.5, 5.4 Hz), 2.65-2.22 (5H, m), 1.98-1.78 (2H, m), 0.95 (9H, s), 0.15 (3H, s), 0.12 (3H, s).

^{13}C NMR (50 MHz) : 203.98, 157.90, 142.60, 118.88, 79.63, 77.02, 68.50, 45.46, 25.55, 24.50, 17.85, 17.64, 15.87, 15.09, -4.90

IR (neat) : 2925, 2343, 2248, 1708, 1422, 1045.

MS (m/e) : 274 (2 %), 260 (M^+ - *t*-Bu, 21 %), 232 (44 %), 218 (91 %), 205 (6 %), 186 (8 %), 175 (5 %), 157 (6 %), 115 (17 %), 103 (11 %), 91 (23 %), 77 (21 %), 75 (100 %), 74 (30 %).

4.15. PET initiated coupling of (41a) with ethyl propiolate (42) using PS-B:

PET initiated coupling of **41a** with **42** involved the irradiation (28 h) of the solution of DMF: *i*-PrOH: H_2O (300 mL) containing **41a** (0.2 g., 0.63 mmol), **27** (0.189 g, 2.52 mmol), and DCA (0.036 g, 0.158 mmol), DMN (0.018 g, 0.095 mmol) and ascorbic acid (0.288 g, 1.638 mmol), following the same procedure as described earlier. After the removal of solvents by distillation under vacuo followed by column chromatographic purification of the concentrate, gave 0.60 g of a mixture of **40a** and **57** along with pure **57** (0.023 g, 20 %) and pure **58** (0.040 g, 20 %). Ratio of **40a**, **57** and **58** in the crude mixture was measured by GC analysis (capillary column, methyl phenyl silicone, 25 m).

4.16. Methyl 7-((3R) - 3(tert-Butyldimethyl silyloxy)-5 oxo-1- cyclopentenyl)-heptenoate (41b) :

Preparation of substrate 59[28] *:*

(a) Iodine (1.5 g, 5.91 mmol) dissolved in 20 mL of CCl_4/Pyridine (1:1) was added dropwise to a solution of **43** (0.5 g, 2.36 mmol) in 20 mL of CCl_4/Pyridine (1:1), kept in a 100 mL RB flask fitted with argon gas balloon, at 0 °C. The mixture was stirred for 24 h during which time the temperature was allowed to reach to r. t. The mixture was diluted with ether (100 mL) and washed successively with H_2O (40), 1N HCl (2×40 mL), H_2O (40 mL), 20 % $Na_2S_2O_3$ (40 mL) and dried over anhydrous Na_2SO4. Solvent evaporation followed by column chromatographic purification yielded 0.61g of **59** (77 %).

^{1}H NMR (200 MHz) : 7.8 (1H, d, J = 2.5 Hz), 5.0-4.9 (1H, m), 2.85 (1H, dd, J = 18.5, 6.3 Hz), 2.35 (1H, dd, J = 18.1, 1.9 Hz), 0.9 (9H, s), 0.14 (3H, s), 0.15 (3H, s)

(b) Preparation of methyl-6-heptenoate :

To a 100 mL two neck RB flask containing a solution of methyl chloroformate (5.8 g, 61.32 mmol) and Et_2O (20 mL) at 0 °C was added dropwise the Grignard reagent, prepared in Et_2O (40 mL) from magnesium (0.75 g, 30.97 mmol) and 6-bromo-1-hexene (5 g, 30.67 mmol) at 10°-15°C. The mixture was stirred for 2 h. at r.t. Afterwards, the

mixture was poured onto an ice-cold saturated aqueous NH_4Cl solution and extracted with Et_2O (2×100 mL). The organic layer was washed with water, saturated brine solution, dried over anhydrous Na_2SO_4 and concentrated under vacuo. The concentrate was distilled to yield methyl-6-heptenoate as a clear oil (2.39 g, 55 %).

^{1}**H NMR** (200 MHz) : 5.9-5.8 (1H, m), 5.1-4.9 (2H, m), 3.65 (3H, s), 2.3 (2H, t, J = 7.2 Hz), 2.15-2.0 (2H, m), 1.75-1.55 (2H, m), 1.5-1.35 (2H, m).

(c) To a flame dried RB flask were added methyl-6-heptenoate (0.631 g, 4.44 mmol) and dry THF (4 mL). The solution was cooled to -10 °C and a THF solution of 9-BBN-H (0.5 M, 8.9 mL, 4.44 mmol) was added dropwise over 15 min. The solution was allowed to warm to r. t. and stirring was continued for an additional 4 h. 50 % of the THF was removed from the reaction mixture under reduced pressure. A solution of the α-iodoenone (**59**, 1 g, 2.96 mmol) in DMF (10 mL) was added to a mixture of Cs_2CO_3 (1.74 g, 5.34 mmol), $PdCl_2$ (dppf) (0.065 g, 3 mol %) and Ph_3As (0.054 g, 10 mol %) kept in a separate RB flask. Water (0.64 mL, 12 equiv) was added to the reaction mixture with vigorous stirring, followed by addition of the above THF solution of the borane. After stirring for 1.5 h, the contents of the flask were poured into 100 mL of water and extracted with ether (150 mL). The organic phase was washed with 1 N HCl (1×50 mL), 10 % NH_4OH (1×50 mL), water (1×50 mL), and brine (1×50 mL) and dried over anhydrous Na_2SO_4. Removal of the solvents under vacuo followed by column chromatographic purification of the concentrate afforded 0.26 g of **41b** (25 %) as an oil.

$[\alpha]_D^{25}$: + 20.2 (C = 0.68, MeOH), Lit.[29] $[\alpha]_D^{21}$ + 22.8 (C = 0.404, MeOH)

^{1}**H NMR** (200 MHz) : 7.2-6.98 (1H, m), 4.97-4.79 (1H, m), 3.68 (3H, s), 2.75 (1H, dd, J = 17.5, 5.4 Hz), 2.42-2.02 (5H, m), 1.80-1.18 (8H, m), 0.92 (9H, s), 0.15 (6H, s)

MS (m/e) : 323 (M^+ - OMe, 1), 297 (M^+ - t-Bu, 57), 265 (34), 247 (10), 237 (6), 191 (15), 173 (24), 169 (32), 163 (41), 145 (28), 131 (29), 107 (23), 95 (42), 89 (20), 79 (26), 75 (100), 67 (31), 55 (32).

4.17. PET initiated coupling of (41b) with methyl propiolate (27) using PS-B:

Compound **41b** (0.2 g, 565 mmol), **27** (0.22 g, 2.24 mmol), DMN (0.016 g, 0.085 mmol) and ascorbic acid (0.259 g, 1.47 mmol) were dissolved in a solution of DMF: *i*-PrOH: H_2O (300 mL) containing DCA (0.032g, 0.14 mmol) and mixture was irradiated for 20 h. After removal of solvents and column chromatographic separation of the residue yielded a mixture of **40b** and **60** (0.055 g) along with pure **60** (0.025 g, 20 %) and pure **61** (0.039 g, 20 %). Ratio of **40b**, **60** and **61** in the initial mixture were measured by GC analysis (capillary column, methyl phenyl silicone, 25 m)

5. References

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Spectra

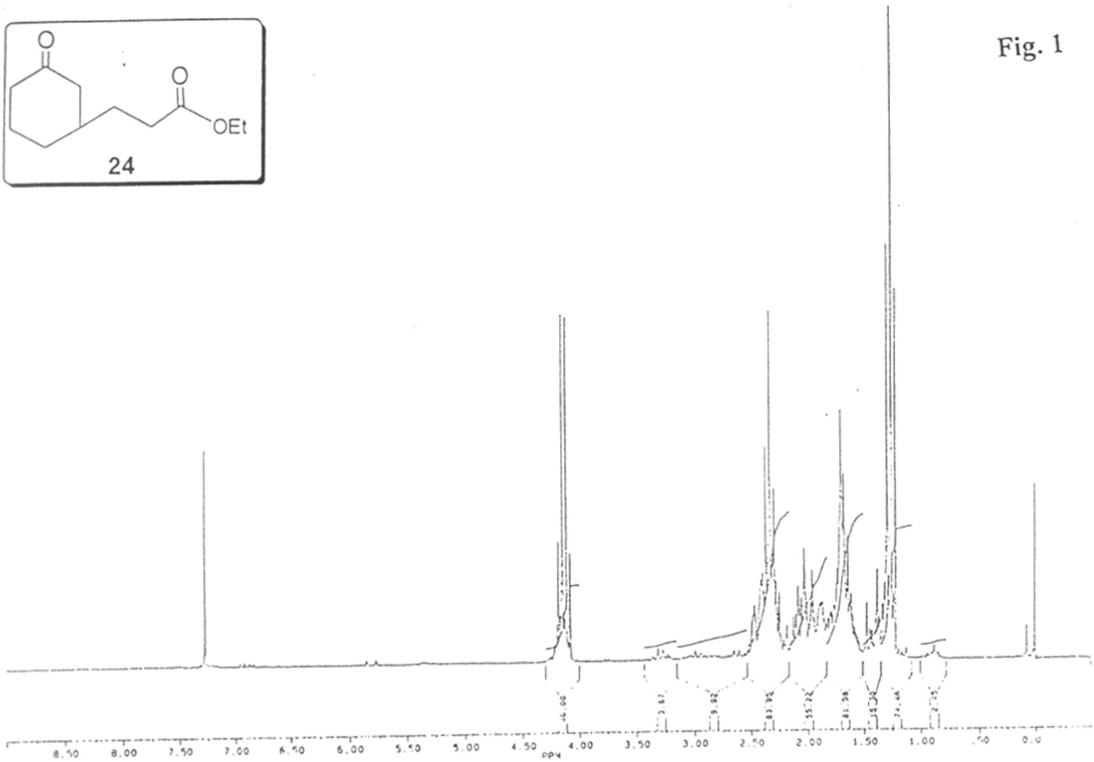


Fig. 1

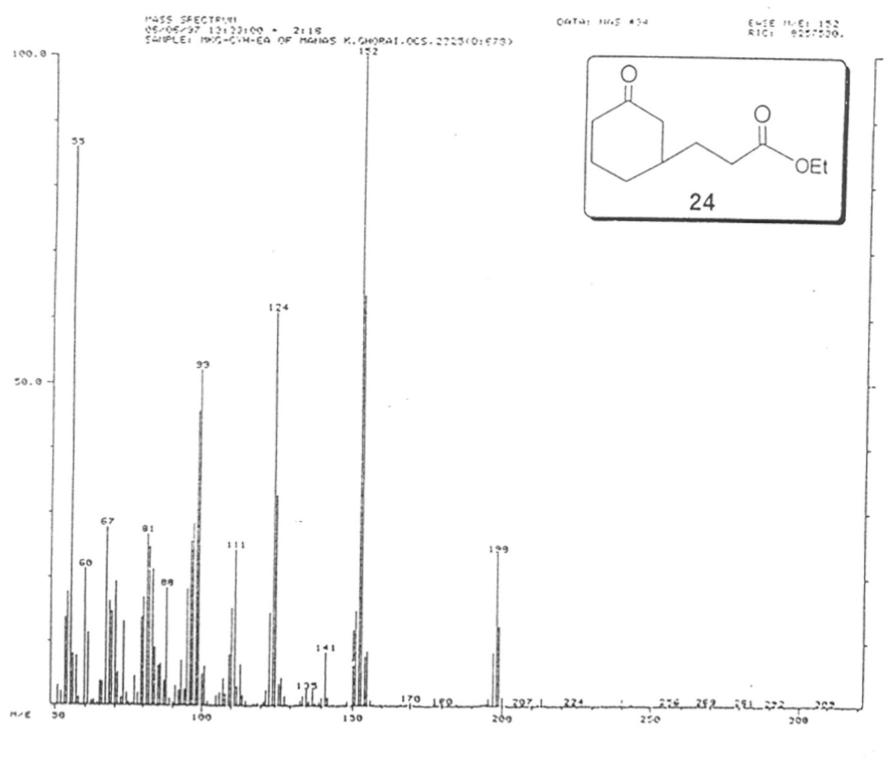


Fig. 3

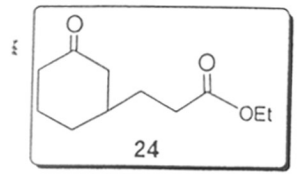
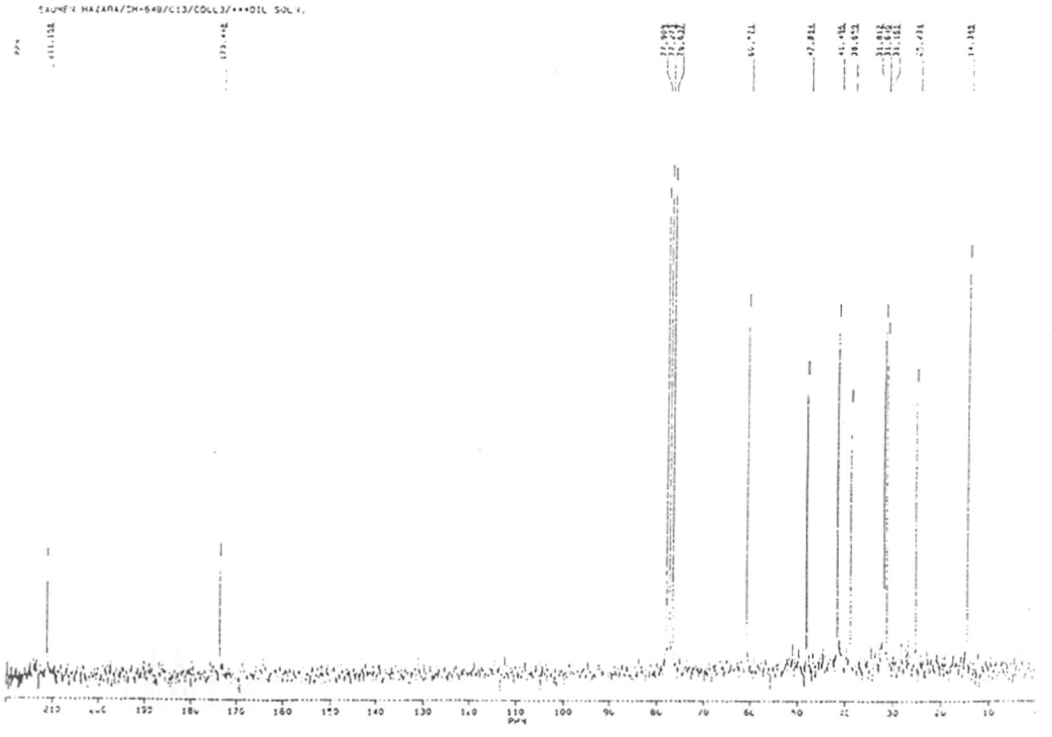


Fig. 2



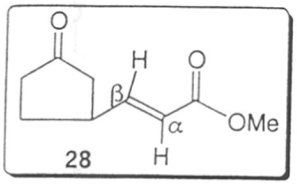

O
H
O
β
α
OMe
28
H

Fig. 4

8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
PPM

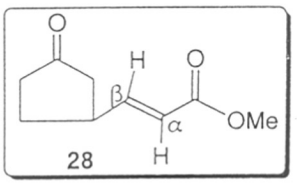
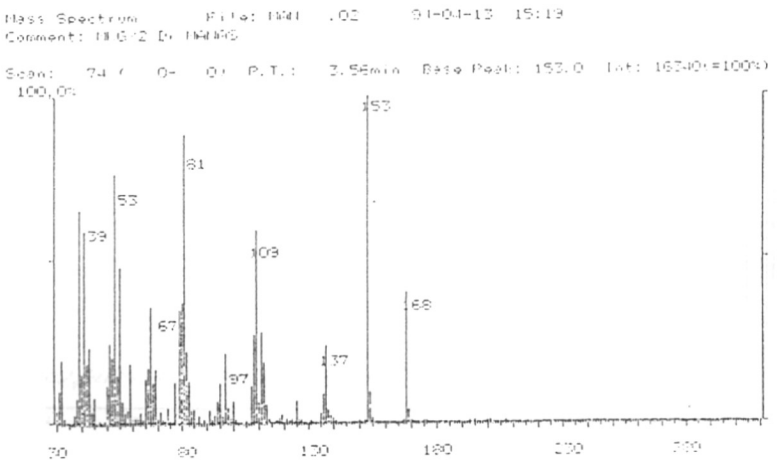

O
H
O
β
α
OMe
28
H

Fig. 6


Mass Spectrum
100.0%
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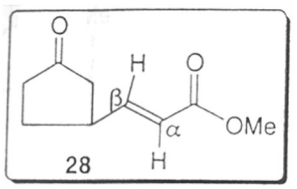
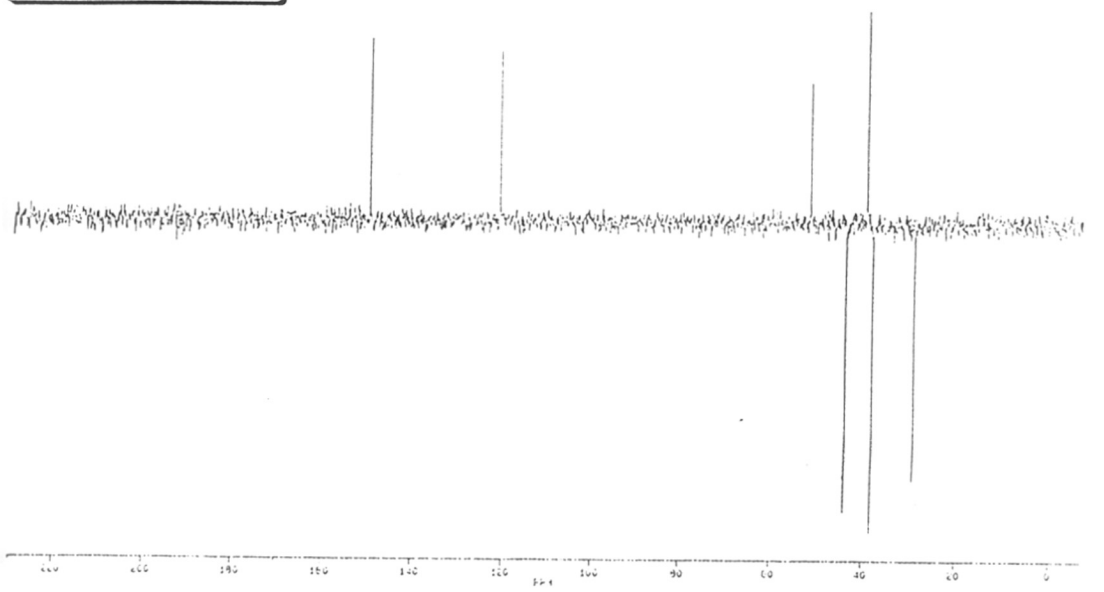
81
53
39
109
68
67
137
97
30
80
130
180
230
280

Fig. 5





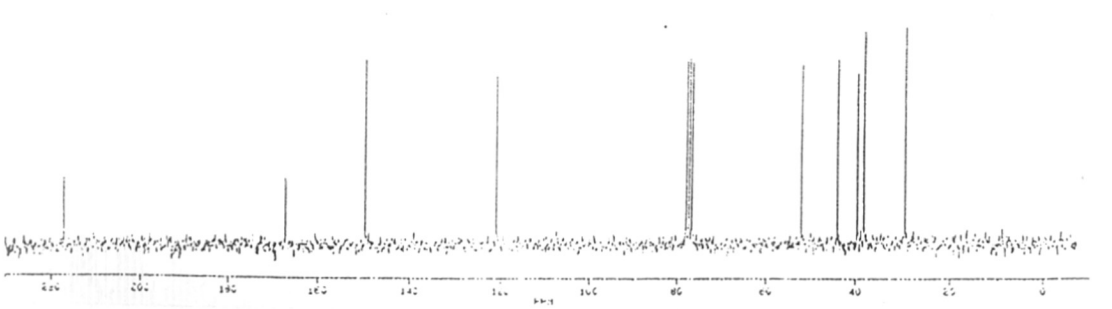


Fig. 7

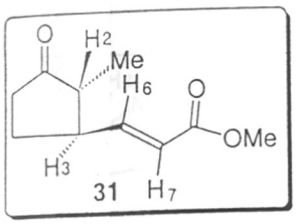
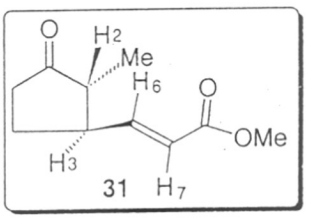
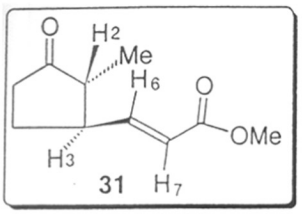

O
H2
Me
H6
O
OMe
H3
31
H7

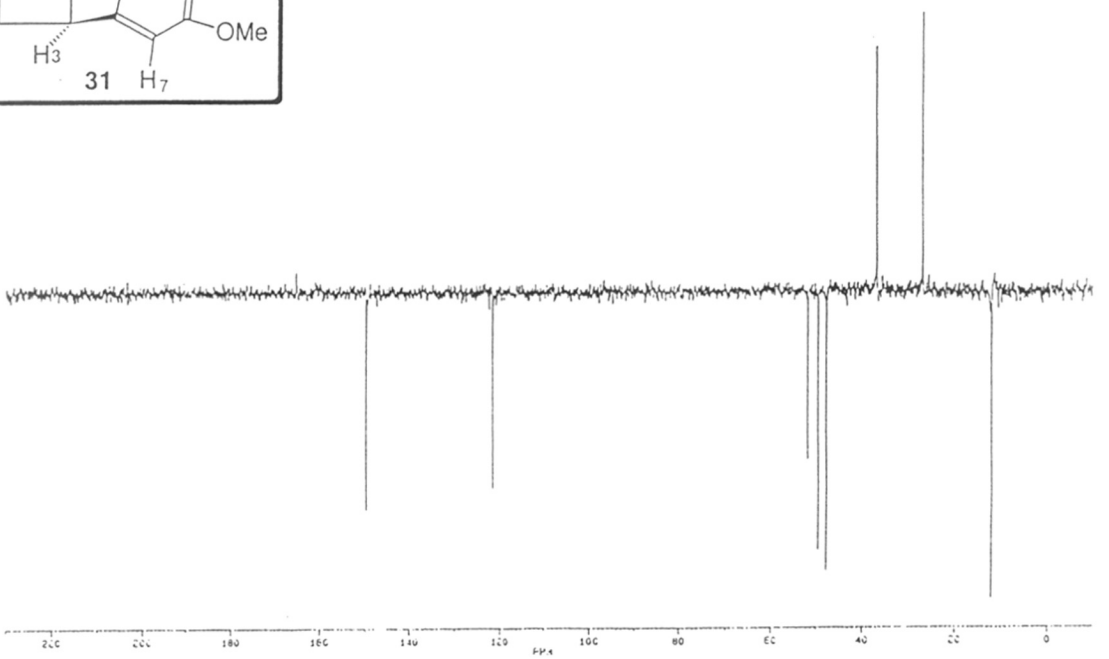
Fig. 9


O
H2
Me
H6
O
OMe
H3
31
H7

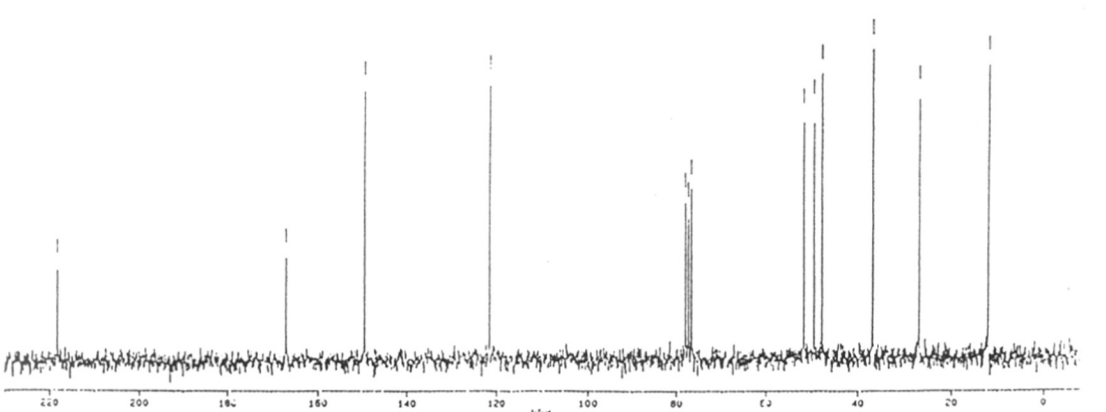
100.0
50.0
55
67
81
95
111
123
139
150
167
182
196
213
228
244
257
268
279
282
311
M/E
50
100
150
200
250
300

Fig. 8


O
H2
Me
H6
O
OMe
H3
31
H7


220
200
180
160
140
120
100
80
60
40
20
0
PPM


M.K. GHORAI/C13/MKG-MC-1/CDCL3
PPM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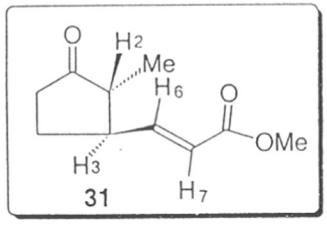
200
180
160
140
120
100
80
60
40
20
0
PPM


O
H2
Me
H6
O
OMe
H3
H7
31

M.K. GHORAI/MKG-MC-1/1H-1H-COSY-EXPT
BRUKER
MKGMCH.SMX
F1 PROJ:
INTERNAL
F2 PROJ:
INTERNAL
AU PROG:
COSY.AU
DATE 9-3-98
SI2 1024
SI1 512
SW2 1461.988
SW1 730.994
ND0 1
WDW2 S
WDW1 S
SSB2 0
SSB1 0
MC2 M
PLIM ROW:
F1 7.807P
F2 .516P
AND COLUMN:
F1 7.807P
F2 .515P
D1 1.0000000
P1 6.00
D0 .0000030
P2 6.00
RD 0.0
PW 0.0
DE 430.00
NS 16
DS 2
NE 1
IN .0006840
1.0
2.0
3.0
4.0
5.0
6.0
7.0
PPM
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM

Fig. 10

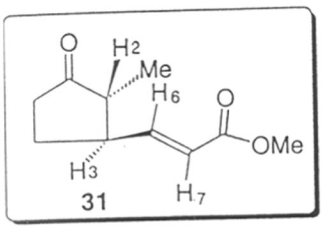


Fig. 11

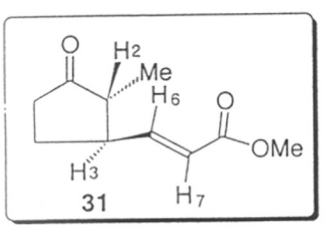
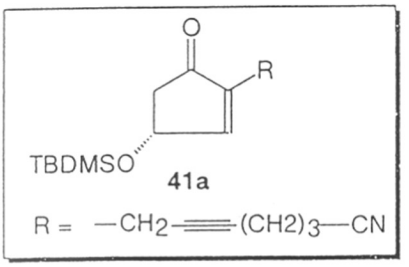


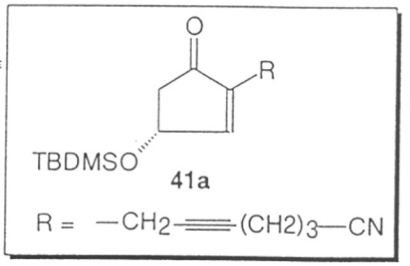
Fig. 12

Fig. 13


O
R
TBDMSO
41a
R = —CH2—≡—(CH2)3—CN

9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.0
PPM

Fig. 15


O
R
TBDMSO
41a
R = —CH2—≡—(CH2)3—CN

100.0
50.0
73
57
55
85
91
97
103
111
115
129
141
149
157
175
196
205
218
233
245
M/E
60
80
100
120
140
160
180
200
220
240

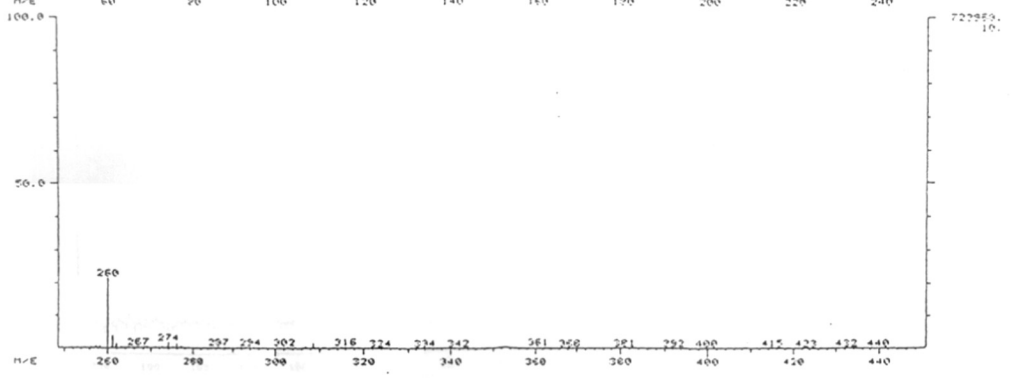
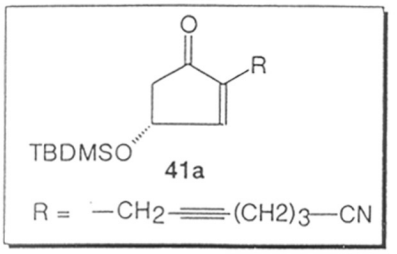
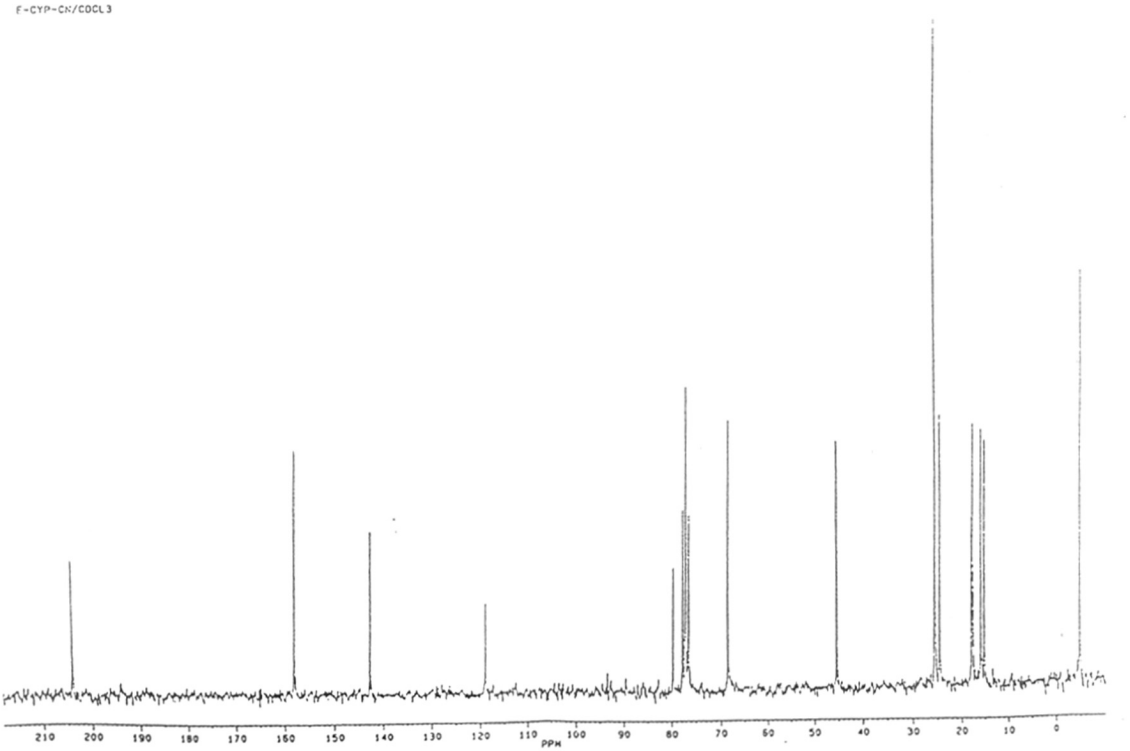

100.0
50.0
260
267
274
297
294
302
316
324
334
342
361
356
381
392
400
415
423
432
440
M/E
260
280
300
320
340
360
380
400
420
440

Fig. 14


O
R
TBDMSO
41a
R = —CH2—≡—(CH2)3—CN

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


E-CYP-CN/CDCL3
210 200 190 180 170 160 150 140 130 120 110 PPM 100 90 80 70 60 50 40 30 20 10 0

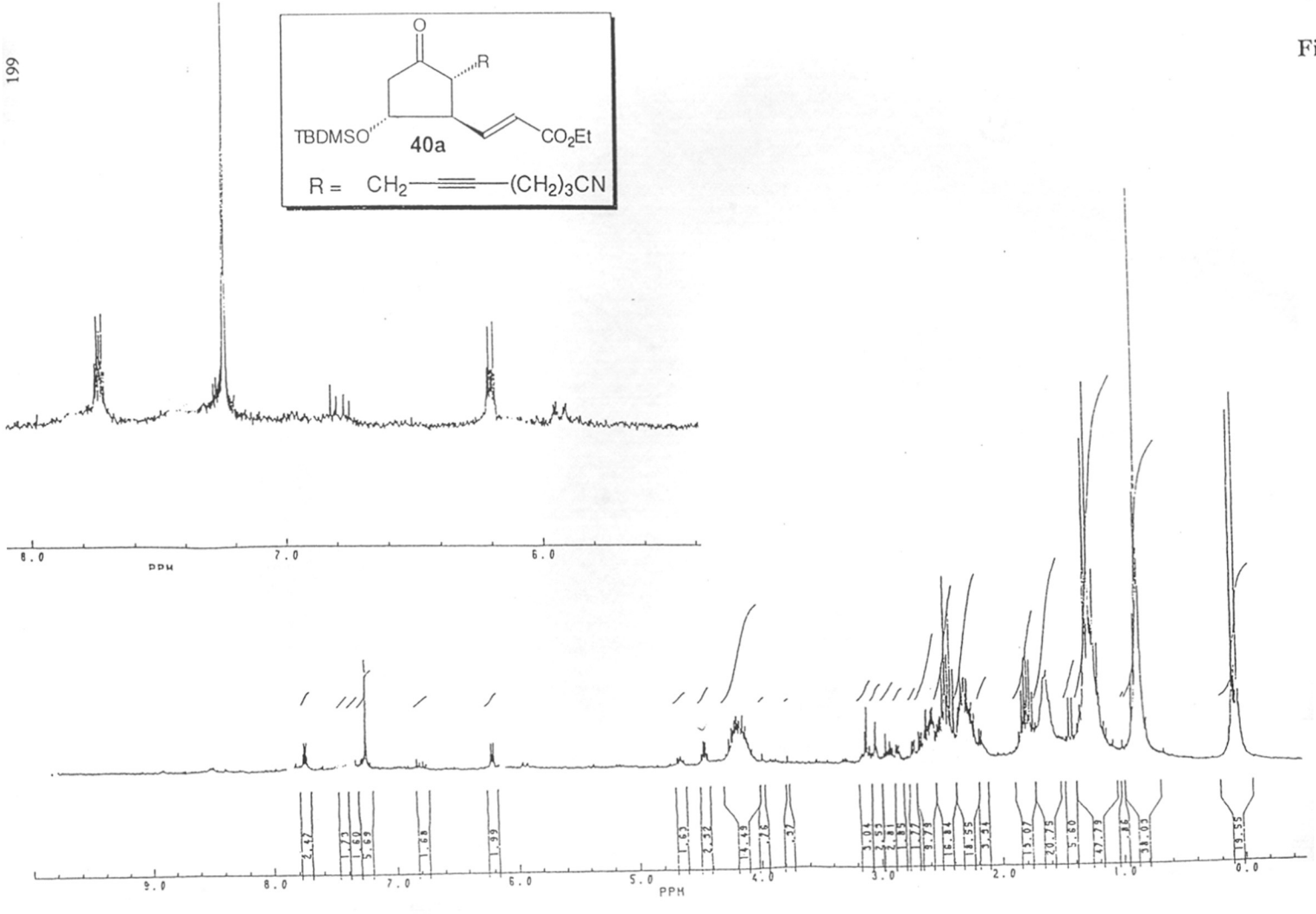

O
R
TBDMSO
CO2Et
40a
R = CH2—≡—(CH2)3CN
8.0
7.0
6.0
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

Fig. 16

LIST OF PUBLICATIONS:

1. Visible-Light Initiated Photosensitized Electron Transfer (PET) Reductive β-Activation of α,β-Unsaturated Ketones for Radical Cyclization: A new Concept in Promoting Radical Reactions.
   Ganesh Pandey, Saumen Hajra and **Manas K. Ghorai** ***Tetrahedron Lett.*** **1994**, *35*, 7837.

2. Design of a Photosystem to Harvest Visible-Light into Electrons: Photosensitized one Electron Redox Reactions in Organic Synthesis.
   Ganesh Pandey, **Manas K. Ghorai** and Saumen Hajra ***Pure & Appl. Chem.*** **1996**, *68*, 653.

3. Designing Photosystems for Harvesting Photons into Electrons by Sequential Electron-Transfer Processes: Reversing the Reactivity Profiles of α,β-Unsaturated Ketones as Carbon Radical Precursor by One Electron Reductive β-Activation.
   Ganesh Pandey, Saumen Hajra, **Manas K. Ghorai** and K. Ravi Kumar ***J. Am. Chem. Soc.*** **1997**, *119*, 8777.

4. Visible-Light Initiated Photosensitized Electron Transfer (PET) Cyclization of Aldehydes and Ketones to Tethered α,β-Unsaturated Esters: Stereoselective Synthesis of Optically Pure C-Furanoside.
   Ganesh Pandey, Saumen Hajra, **Manas K. Ghorai** and K. Ravi Kumar ***J. Org. Chem.*** **1997**, *62*, 5966.

5. A New Strategy for the Construction of Carbo- and Oxycycles by Intra-molecular Reductive Coupling of α,β-Unsaturated Esters:
   Ganesh Pandey, **Manas K. Ghorai** and Saumen Hajra ***Tetrahedron Lett.,*** **1998**, *39*, 1831.