Synthetic Studies Towards Taxoids and Reaction of Diazoester with Carbon-Carbon/ Heteroatom Bonds Catalyzed by Transition Metal Exchanged Clay

Thesis

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by

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DEDICATED TO THE

MEMORY OF MY FATHER

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CERTIFICATE

Certified that the work incorporated in the thesis entitled "**Synthetic Studies Towards Taxoids and Reaction of Diazoester with Carbon-Carbon/Heteroatom Bonds Catalyzed By Transition Metal Exchanged Clay**" submitted by Mr. Madan Mohan Jakkam was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

NCL, Pune
August 1998

Dr.T.Ravindranathan
(Research Supervisor)

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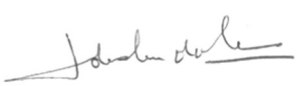

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August 1998

Jakkam Madan Mohan

GENERAL REMARKS

1. All melting points and boiling points temperatures are in centigrade scale.
2. The compound numbers, scheme numbers and reference numbers given in each chapter refers to that particular chapter only.
3. All solvents were distilled prior to use. Petroleum ether refers to the fraction collected in the boiling range 60-80 °C.
4. Organic layers were dried over anhydrous sodium sulfate (Na_2SO_4)
5. TLC analysis were carried out on glass plates using silica gel; GF-254 and the plates were developed by iodine stain.
6. In cases where chromatographic separations were done, SiO_2 was used as the stationary phase.
7. The IR spectra were recorded on Perkin-Elmer spectrophotometer model 683B or 1605 FT-IR and absorptions are expressed in cm^{-1}.
8. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker WH-90 and Bruker AC-200 instruments using tetramethylsilane as the internal standard.. The following abbreviations were used. s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet.
9. The mass spectra were recorded on Finnigan MAT-1020-B-70eV mass spectrometer.
10. The optical rotations were carried out on JASCO-181 digital polarimeter at 25 °C using sodium D light.

C O N T E N T S

Abbreviations

Ac	Acetyl
TBDMS	*tert*-Butyldimethyl silyl
DMSO	Dimethyl sulfoxide
DMAP	4-Dimethyl aminopyridine
DMS	Dimethyl sulphide
PPTS	Pyridinium *p*-Toluene Sulphonate
MOMCl	Methoxy methyl chloride
DIBAL-H	Diisobutylaluminium hydride
DME	Ethylene glycol dimethyl ether
TMEDA	N,N,N',N'-Tetramethyl ethyl diamine
DABCO	1,4-Diazabicyclo[2,2,2]octane
DMF	N,N-Dimethylformamide
TMS	Trimethyl silane
MEM	2-Methoxy ethoxy methyl
*m*CPBA	3-Chloroperbenzoic acid
LTA	Lead tetraacetate
$BF_3 \cdot OEt_2$	Born trifluoride diethyl etherate
LDA	Lithium diisopropyl amide
*P*TSA	Paratoluene sulfonic acid
B_2H_6	Diborane
$SnCl_4$	Stannic chloride
MTO	Methyl Rhenium Trioxide
Al_2O_3	Aluminium oxide
SiO_2	Silicon dioxide
$Cu(OTf)_2$	Copper (II) trifluoromethane sulfonate
$Cu(acac)_2$	Copper (II) acetyl acetonate
Ag_2O	Silver oxide

ABSTRACT

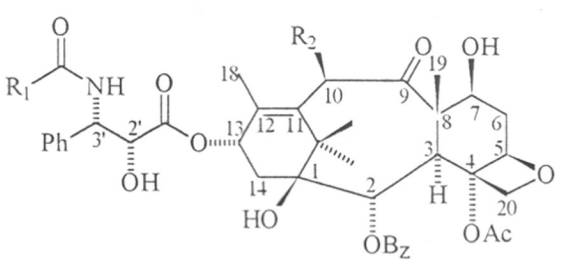
The thesis entitled "**Synthetic Studies Towards Taxoids and Reaction of Diazo Ester with Carbon-Carbon/Hetero Atom Bonds Catalysed by Transition Metal Exchanged Clay**" is divided into the following four chapters -

Chapters I and II of this thesis describe the development of methodologies for the construction of AB and ABC ring systems of Taxoid skeleton.

Chapters III essentially deals with the reactions of α-diazoesters with a variety of olefins and imines, utilizing Rhodium/K_{10} montmorillionite as a catalyst. This investigation resulted in the development of methodologies for aziridination and cyclopropanation. In addition, reactions of methyl diazoacetate with various aromatic and aliphatic aldehydes and with different aromatic amines under Cu/K_{10} montmorillionite catalysis have been discussed in Chapter-IV. The latter study led to development of a good methodology for the synthesis of β-ketoesters and β-amino esters.

Chapter-I: Synthetic Studies Towards Construction of AB Rings of Taxoid Molecules

Section-I: Taxol-I



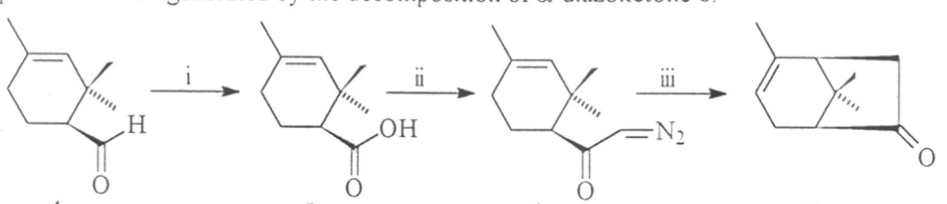
1: Taxol R_1 = Ph, R_2 = OAc
2: Taxotere R_1 = *t*BuO, R_2 = OH

Taxol (I) is a natural product isolated from the bark of the pacific yew, Taxus brevifolia nutt. Use of taxol has been recently approved for the treatment of refractory

ovarian,[1] and metastatic breast cancers.[2] Large scale clinical trials with taxol have been deterred by relatively low supply of the drug. The tedious extraction procedures and extremely low availability of taxol from the natural sources have triggered frenetic synthetic efforts not only towards a total synthesis of this molecule, but also towards development of methodologies to realise the ABC framework of taxoid skeleton. This Section has presented a brief review of literature methods reported during the past decade. This account besides providing a background to appreciate the present work, places it in a proper perspective.

Section-II:

The bicyclic [3.2.1] heptanone **7** (*Scheme-I*) has been recognised as a key synthon with a potential to generate the ABC framework of Taxol. A methodology has been developed to synthesize **7** from 2,2,4-trimethylcyclo hexene-3-aldehyde-4. Intramolecular nucleophilic participation of an olefinic π-bond with an electrophilic carbenoid centre constitutes the key step in this protocol. The necessary carbenoid species has been generated by the decomposition of α-diazoketone **6**.



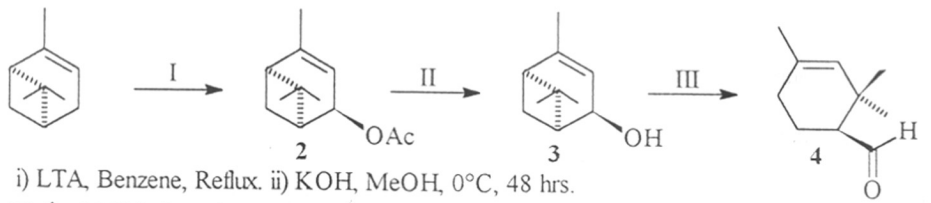
4 **5** **6** **7**

i)Ag_2O, ether, RT, 6 h ii) $SOCl_2$, CH_2N_2, ether, 0°C, 6 h. iii) BF_3OEt_2,·EDC, 0°C- RT

Scheme-I

A convenient method for the preparation of **4** from naturally occurring monoterpen-α-pinene has been developed, based on a known reaction.[3] Flash vacuum pyrolysis of *trans*-verbenol **2** afforded the required aldehyde-4 in moderate yields. This

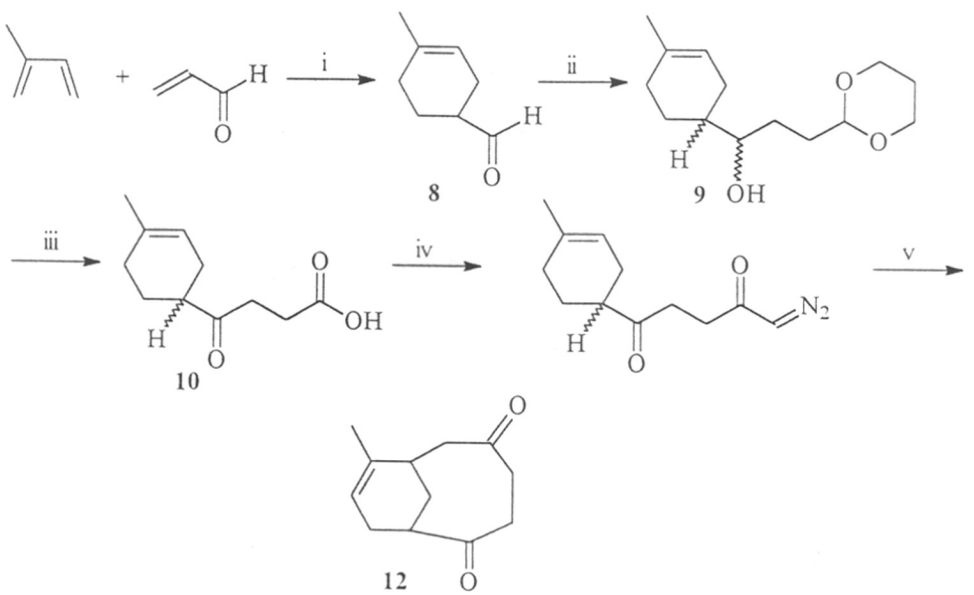
reaction, which involves a 1,5-sigmatropic hydrogen shift, results in the retention of the chirality of the starting material (*Scheme-II*).

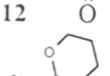


i) LTA, Benzene, Reflux. ii) KOH, MeOH, 0°C, 48 hrs.
iii) △, 350°C, Petroleum ether.

Scheme-II

The carbenoid reaction that led to the synthesis of 7 has been successfully utilised in the construction of the AB framework (*Scheme-III*) of taxoid molecules. The feasibility of this reaction was initially checked with an aldehyde corresponding to **8** lacking the gem dimethyl groups; with the success realized the protocol was extended to the aldehyde **8** to obtain the bicyclic dione **12**.



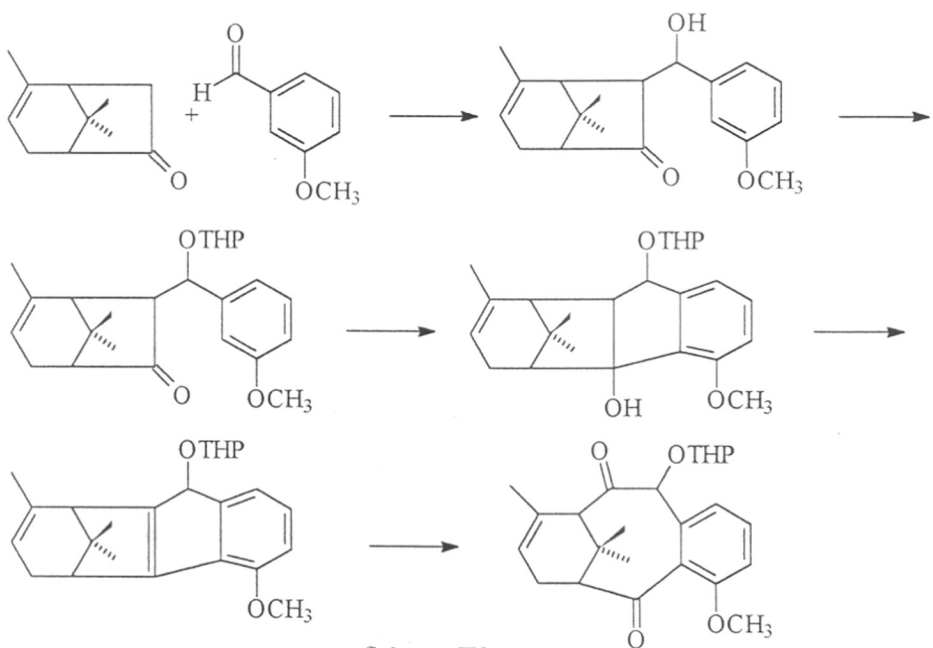
i) BF_3OEt_2, CH_2Cl_2, -78°C. ii)  , THF. iii) CrO_3, H_2SO_4, H_2O, 0°C-RT
iv) $SOCl_2$, CH_2N_2, CH_2Cl_2 v) BF_3OEt_2, EDC; 0°C-RT

Scheme-III

It may be added that a metal-carbene reaction has been used for the first time in the synthesis of Taxoid skeleton or its intermediates.

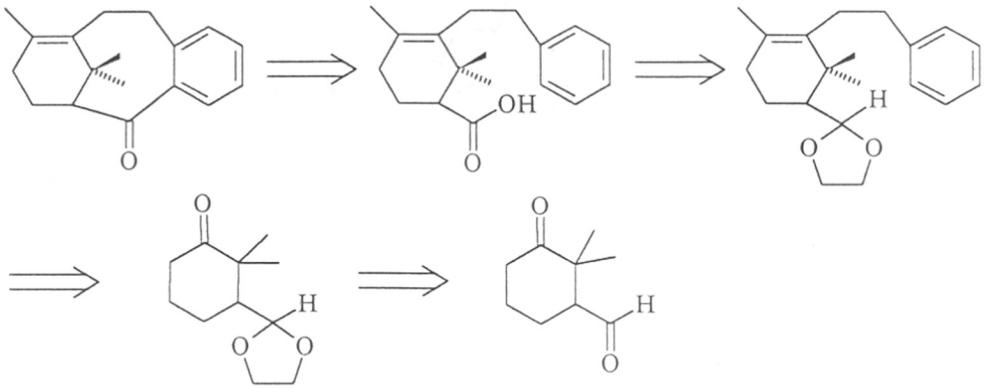
Chapter-II: Synthetic Efforts Towards Construction of ABC Rings of Taxoid Molecules

The synthetic potential of the bicyclic ketone 7 to generate the ABC ring system has been explored; even though the initial reactions (*Scheme-IV*) were successful, the non-occurrence of methoxy-mediated lithiation and subsequent cyclization despite various modifications, led to the abandonment of the strategy (*Scheme-IV*).



Scheme-IV

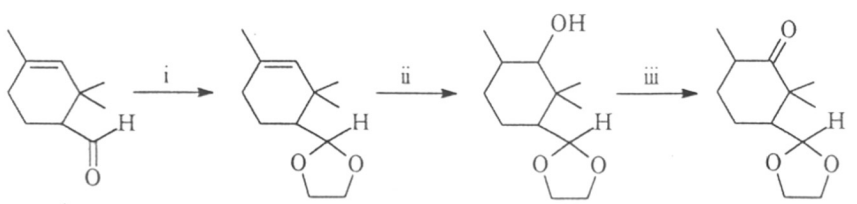
An alternate strategy to realize the ABC system was envisaged, the key feature of which is the building up of A and C fragments with required number of carbon atoms for the formation of central ring and a final coupling reaction between A and C with concomitant formation of the central B ring (*Scheme-V*).



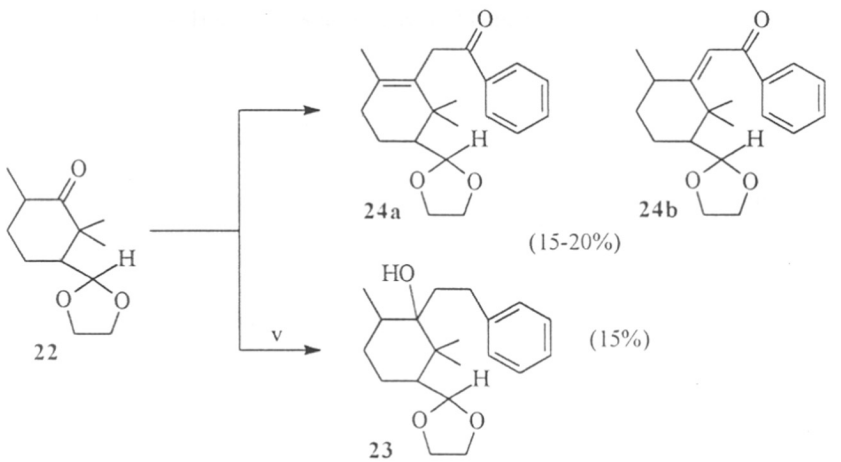
Scheme-V

Accordingly, the execution of the plan was done, as shown in the following *Schemes (VI* and *VII*).

Grignard reaction of 2-phenylethylbromide with the ketone **22** afforded the corresponding product **23** in a low yield. With the objective of realizing higher yields of this type of product, aldol condensation of substituted acetophenones with ketone **22** was also explored. However, the yields in this reaction also were low.The low yield in both the reactions was attributed to the steric hindrance offered by the gem-dimethyl groups in **22**. Therefore, aldol condensation of substituted acetophenones with the ketone **27** lacking gem dimethyl groups was carried out, realising a significant increase in the yields of the products (*Scheme-VI*).

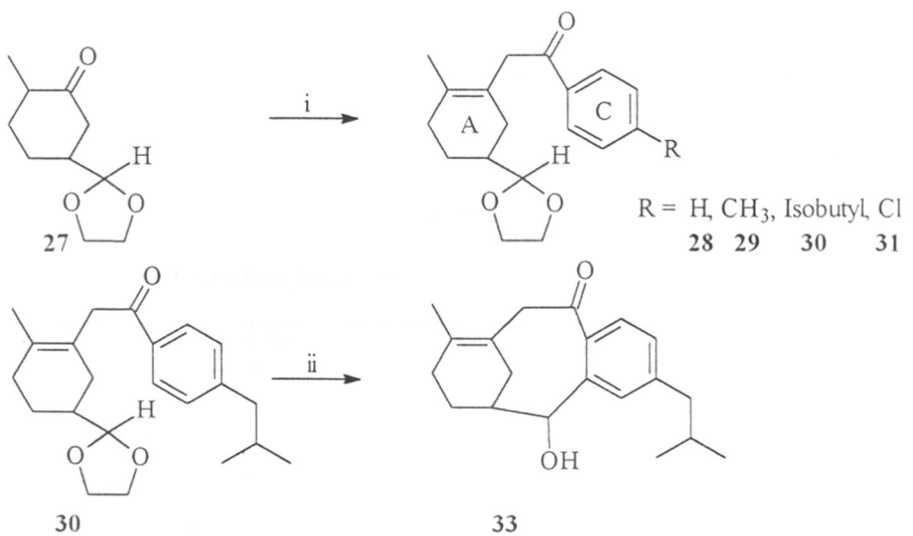


4 **20** **21** **22**



Scheme-VI i)$HOCH_2CH_2OH$, PTSA, C_6H_6 ii) B_2H_6, NaOH / H_2O_2, THF iii) PDC, CH_2Cl_2 iv) NaH, $PhCOCH_3$, C_6H_6 v) Mg, $PhCH_2CH_2Br$, THF

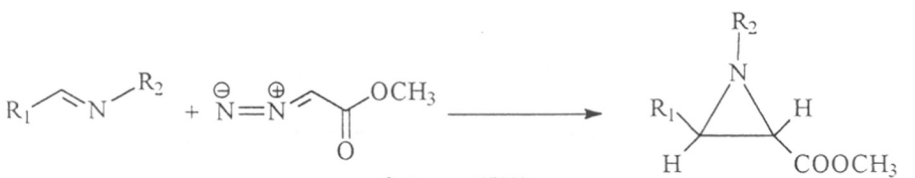
The final coupling reaction between A and C rings could be conveniently achieved by a $SnCl_4$-catalysed cyclization.[4] (*Scheme-VII*).



Scheme-VII i) $RPhCOCH_3$, NaH, $PhCH_3$ ii) $SnCl_4$, CH_2Cl_2, 0-25°C

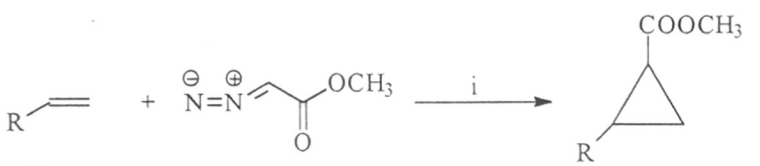
Chapter-III: New Heterogeneous Catalytic Method for the Synthesis of Aziridines and Cyclopropanes

Section-I: This Section describes the results from the reaction of methyl diazoacetate with numerous aromatic imines and three alicyclic/aliphatic imines under Rhodium-clay catalysis. A preferential formation of *trans*-aziridines in 40-57% was observed. This study led to the development of a convenient methodology for the synthesis of *trans* aziridines (*Scheme-VIII*).



Scheme-VIII

Section-II: The results obtained from the reaction of methyl diazoacetate with different types of olefins under Rhodium/K-10 mont morillionite catalysis are presented in this Section (*Scheme-IX*).



i = Rh / Clay, Benzene

Scheme-IX

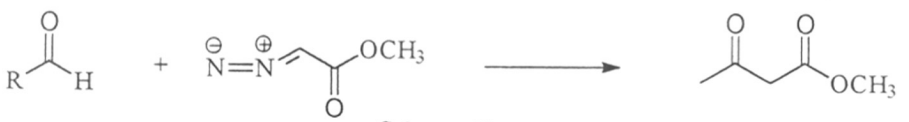
The following Table summarises the results.

Sr.No.	Substrate	Yield (%)	*Trans/cis*
1	Styrene	87	1:1
2	Ethyl cinnamate	84	3:1
3	Diethyl fumerate	74	2.5:1
4	Norbornene	82	1:1 (Syn/Anti)
5	Cholestrol	32	2:1
6	Mesityl oxide	70	1.5:1

An advantage of these methodologies for both aziridination and cyclopropanation is the observation that the Rhodium/K-10 catalyst can be reused without affecting the yields of the reaction.

Chapter-IV: A New Heterogeneous Catalytic Method for the Synthesis of β-keto esters and β-amino esters

Section-I: The reaction of methyl diazoacetate under Cu/clay catalysis has been extended to numerous aromatic and aliphatic aldehydes. This study resulted in the development of a convenient methodology for the synthesis of β-keto esters (*Scheme-X*). It may be added that β-ketoesters constitute important organic synthetic intermediates.[5]



Scheme-X

Section-II: The reaction of methyl diazoacetate under Cu/clay catalysis with numerous primary and secondary aromatic amines has been studied. This investigation led to a convenient method for the synthesis of β-amino esters (*Scheme-XI*). This class of compounds find application in the synthesis of pharmaceutical compounds such as thienamycin.[6]

$$R\text{-}NH_2 + N_2CHCOOCH_3 \rightarrow R\text{-}NH_2\text{-}CH\text{-}COOCH_3$$

Scheme-XI

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CHAPTER - I

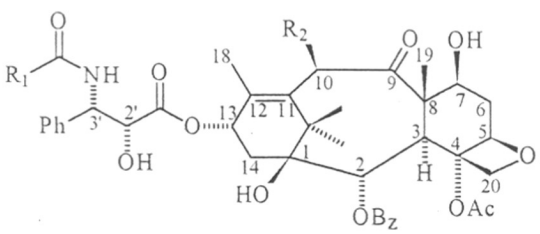
Synthetic Studies Towards Construction of AB Rings of Taxoid Molecules

Chapter-I: Synthetic Studies Towards Construction of AB Rings of Taxoid Molecules

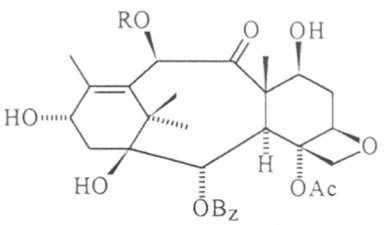
Section-I

1.1.0 INTRODUCTION:

The biological profile and the complex structure of Taxol[1,2] (**I**) have served for the past three decades as a stimulus for the development of radically new advances in synthetic chemistry, biology and medicine. It has been recently approved for the treatment of refractory ovarian,[3] and metastatic breast cancers.[4] This molecule is also in clinical trials for the treatment of lung, head and neck and other cancers.[1,5] From this point of view, availability of taxol in substantial quantities becomes crucial, not only for further development of this medicinal lead, but also to elucidate its novel mode of action at the molecular level.[1,6]



1: Taxol R_1 = Ph, R_2 = OAc
2: Taxotere R_1 = *t*BuO, R_2 = OH



3: Baccatin III, R = Ac
4: 10-Deacetylbaccatin III, R = H

Taxol (**I**) is a natural product isolated from the bark of the pacific yew, *Taxus brevifolia* Nutt. Large scale clinical trials with Taxol have been deterred for a long time by relatively low supplies of the drug. For example, one has to sacrifice about 3000 yew trees and process 10,000 Kgs. of the bark to obtain one kilogram of taxol. An attractive alternative to obtain taxol in quantities appears to consist of the coupling of a suitable side chain equivalent with a 7-protected baccatin intermediate (III) obtainable in large quantities from *T.baccata*. For example, Taxotere (II) is currently produced by coupling a synthetic side chain to 10-deacetyl baccatin-III, which is readily available from an European yew, T.baccata in considerable yields. The same species of taxus are also

available in some tracts of Himalayas. It may be mentioned that Taxotere has also been shown to be active against a wide range of tumor cells.[7]

The tedious extraction procedures and extremely low availability of taxol from the natural sources have triggered hectic synthetic efforts of organic chemists towards a total synthesis of this molecule. An examination of the taxol molecule presents a wide range of potential problems in its chemical synthesis. The most obvious is the challenge posed by the central eight-membered carbocycle. The difficulties to be encountered in realizing this carbocycle are listed below -

1. Formation of eight-membered ring is generally hindered by entropic factors.
2. The normally high transannular strain of an eight-membered ring is further increased by the presence of the geminal dimethyl groups which project into the interior of the central ring.
3. In addition, the trans fused C-ring with its angular methyl group and another six-membered A-ring which is a 1,3 C_3 bridge must also be introduced.
4. The other difficult features of the molecule are the construction of the ring-A with a problematic bridgehead alkene formally forbidden in a 6-membered ring by Bredts rule and introduction of a high degree of oxygenation.

Besides these, some of the functionalities are quite sensitive to common reaction conditions. For example, the oxetane ring can open under acidic or nucleophilc conditions and 7-hydroxyl group when unprotected will epimerise under basic conditions.

1.2.0 LITERATURE METHODS:

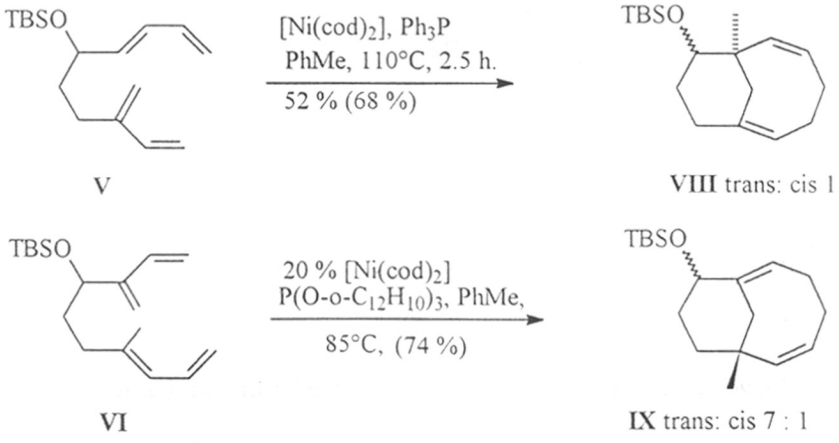
As the work presented in the first two chapters of the thesis concerns itself with development of two synthetic methods for A, B and A, B, C ring systems of the taxol framework, it is both pertinent and useful to present briefly various methods reported in literature for realizing the taxol skeleton. Such an introduction, besides providing the known synthetic routes, places the work described in the thesis in the right perspective. However, various excellent reviews on taxol have been published.[8] In addition, there have been four reported total syntheses of Taxol.[9] The available literature has been classified on the basis of key reactions utilized.

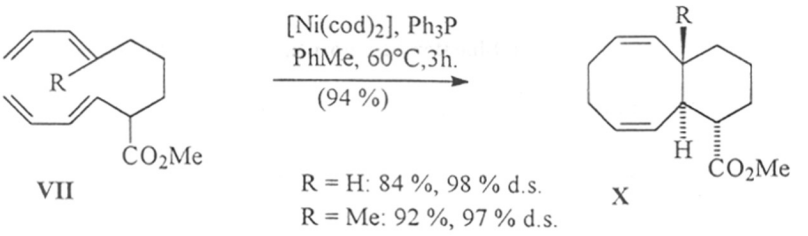
1.2.1 APPROACHES BASED ON INTRAMOLECULAR CYCLOADDITION REACTIONS

1. Wender's approach (1987) :

[4+4] cycloaddition .

Wender *et al.*[10] demonstrated the feasibility of constructing the central ring of taxol by a Nickel-catalyzed direct (4+4) cycloaddition process.





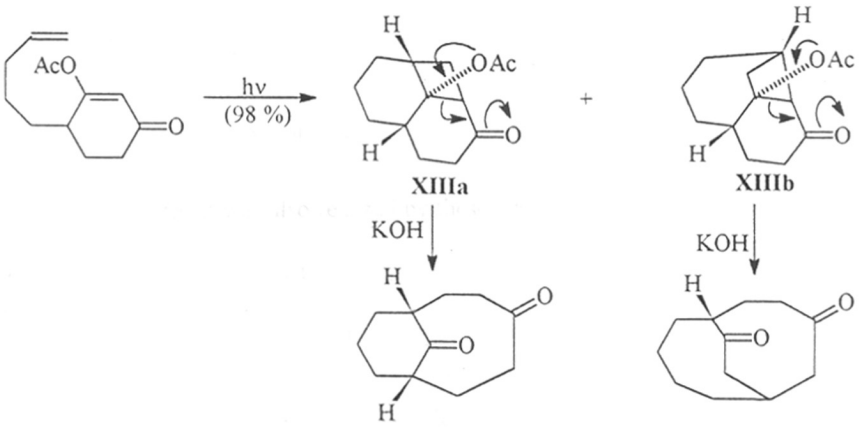
Scheme-1.1

With this strategy, they transformed the bisdienes **V**, **VI** and **VII** into the corresponding bicyclic products **VIII**, **IX** and **X** comprising the eight membered carbocycle respectively (*Scheme-1.1*)

2. Pattenden's approach (1983) :

Photochemical [2+2] cycloaddition and retroaldol fragmentation .

A retroaldol type fragmentation was employed by Pattenden *et al*[13] to obtain the AB ring system (*Scheme 1.2).*



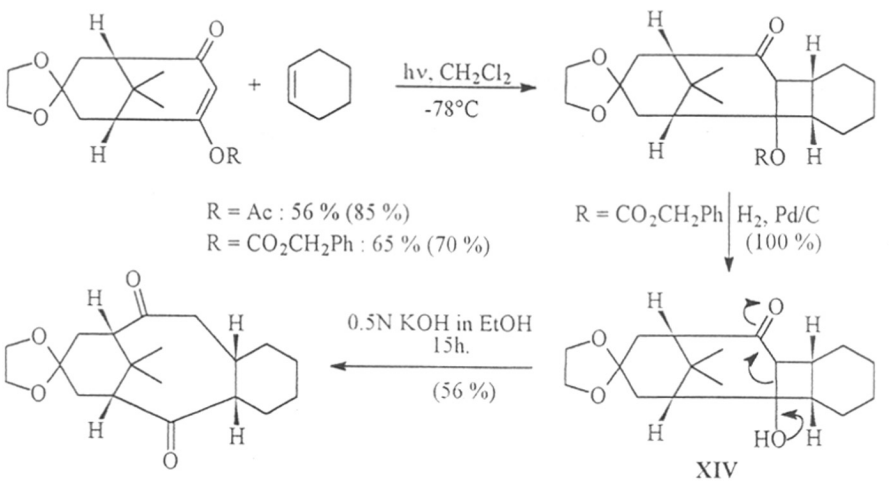
Scheme-1.2

2. The necessary β-acetoxy ketones **XIIIa** and **XIIIb** were obtained by a [2+2] photo cycloaddition. However, the non-regioselective nature of the photoprocess led to a mixture of two products. The starting material for the photoreaction was obtained by a multi-step sequence of reactions.

3. Blechert's approach (1984) :

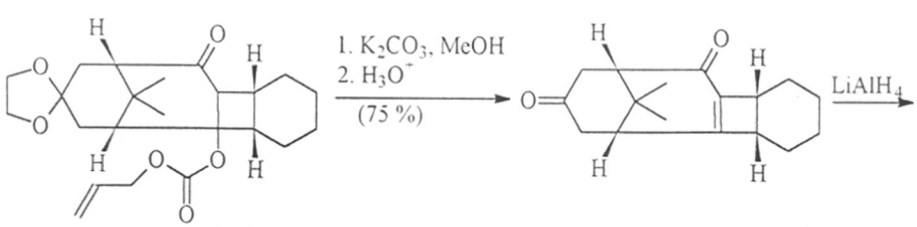
Photochemical [2+2] cycloaddition and retroaldol.

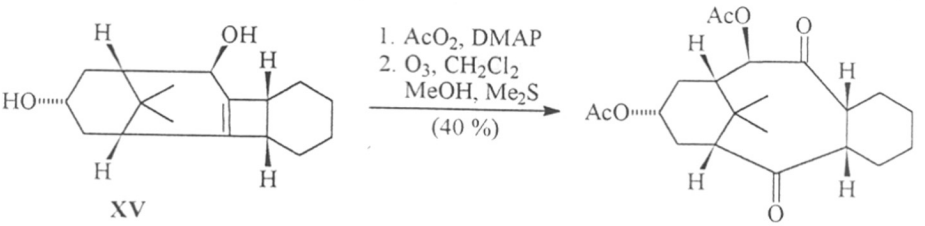
It is interesting to note that a retroaldol fragmentation reaction was elegantly employed by Blechert *et al*[14] in the synthesis of the total tricyclic framework of a number of taxoids. Treatment of the intermediate hydroxyketone **XIV** *(Scheme-1.3)* with base led to the desired framework. It can be seen that a low temperature photo[2+2] addtion is a key step in their protocol for the synthesis of the intermediate **XIV**.



Scheme-1.3

A similar result was also realized by these authors by an oxidative ring expansion reaction.[15] (*Scheme 1.4*). It can be seen that the ozonalysis of the intermediate, **XV**, furnished the eight-membered carbocycle in a moderate yield.



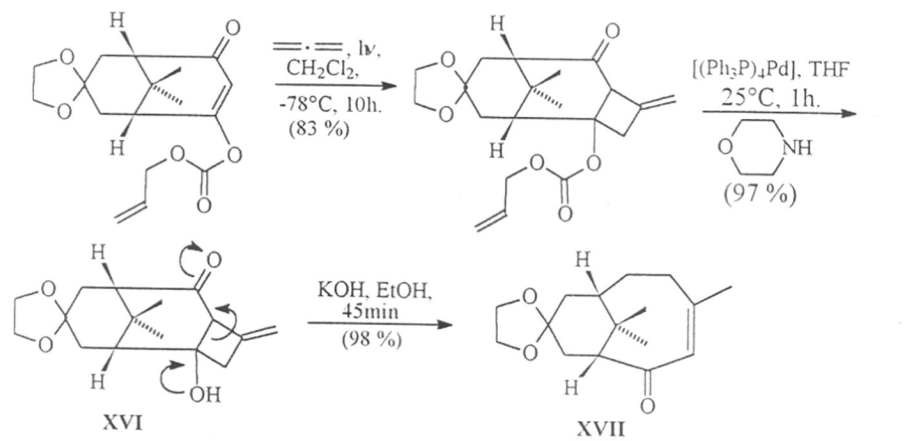


XV

Scheme-1.4

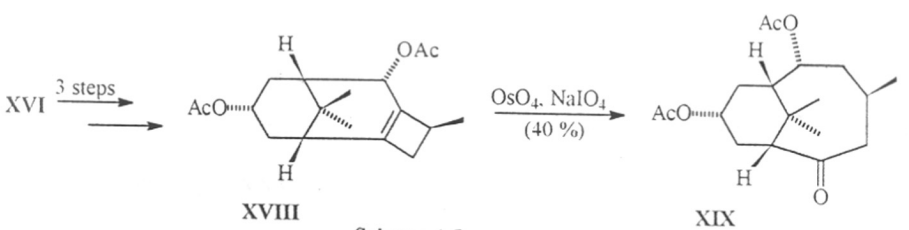
Retro-aldol rection coupled with an oxdative cleavage

Blechert's group have successfully ulitized both the retro-aldol reaction and oxdative cleavage in realizing the AB ring system of taxoids (*Scheme 1.5*). Their synthetic protocol involved a photo[2+2] cycloaddition of allene to a substituted cyclohexenone and a subsequent hydrolysis to get the required hydroxy ketone intermediate **XVI**. A retro aldol fragmentation in the latter led to the required bicyclic AB system **XVII**.



XVI

XVII



XVIII

XIX

Scheme-1.5

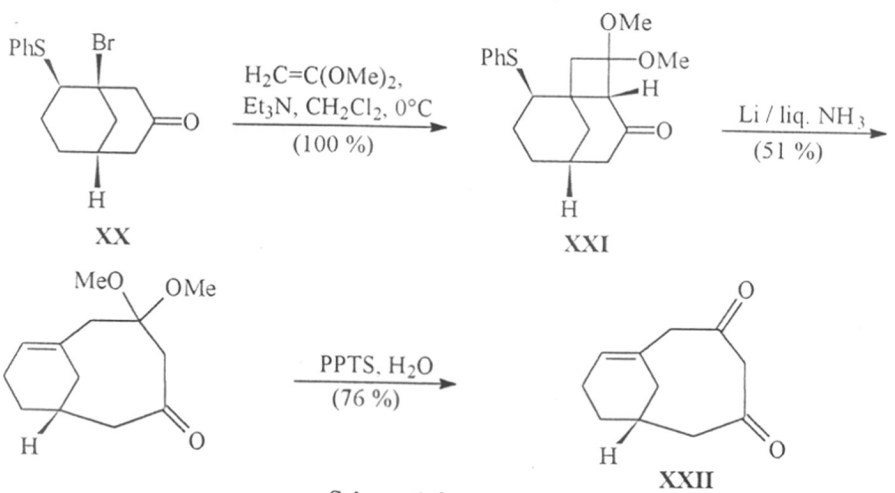
Alternatively, the hydroxy ketone **XVI** was transformed into the cyclobutene

intermediate **XVIII** which on oxidative cleavage furnishied the bicyclic dione **XIX** Similarly, the strategy of photocycloaddition and retroaldol reaction has been utilized by other researchers in the construction of both A, B and A, B, C ring systems.[16-21]

4.. Krau's approach (1987) :

[2+2] Photocycloaddition and γ-carbanion initiated α, β-cleavage of lactone.

Kraus *et al.* have realized[22] the AB ring system **XXII** by a reductive cleavage of a cyclobutane bond in the intermediate **XXI**, which was obtained by a *insitu* generation of an enone from **XX** (*Scheme 1.6*) and its subsequent photoaddition with ketene dimethyl acetal.

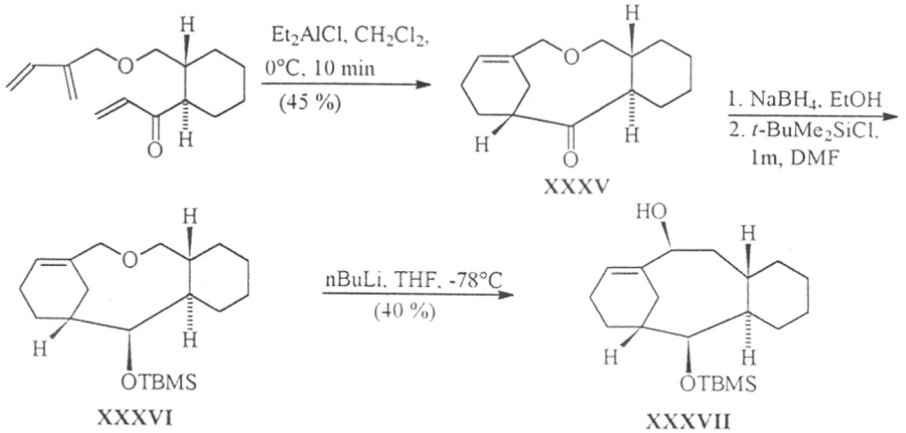


Scheme-1.6

5. Yadav's approach (1991) :

Intramolecular Diels-Alder and Wittig Rearragenment.

Ring contraction ensuing a Wittig rearrangement has been interestingly utilized by Yadav *et al.*[27] in realizing the tricyclic framework of taxol (*Scheme 1.7*). The larger nine membered ring **XXXV** was prepared by a lewis acid catalyzed intramolecular Diels-Alder reaction; The Wittig rearrangement of the intermediate silyl ether **XXXVI** furnished the tricyclic skeleton **XXXVII**.



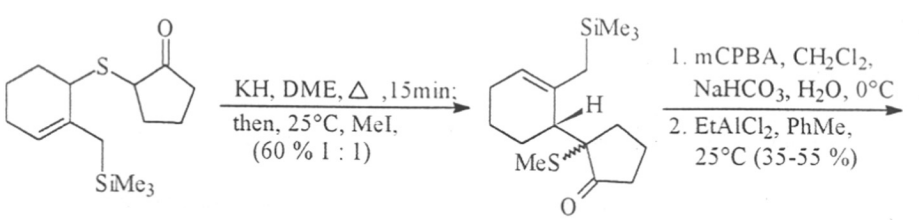
Scheme-1.7

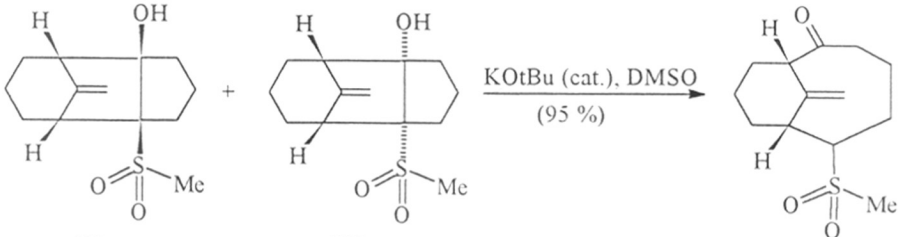
1.2.2 APPROACHES BASED ON REARRANGEMENT REACTIONS

10. Trost's approach (1982) :

Rearrangement and fragementation reaction of hydroxy sulfone.

The AB ring system of taxol was realized by Trost *et al*[11] utilizing a fragmentation reaction in the hydroxy sulfones **XIa** and **XIb**, *(scheme-1.8)* taking advantage of the stabilization of the carbanion intermediate by the sulfone group. A sequence of reactions starting with S-methylation and its futher oxidation by mCPBA to SO_2Me functionality and finally Ethyl $AlCl_2$ catalysed cyclization, is involved in the generation of **XIa** and **XIb**; the latter reaction occurs by the particitation of the C=C with the electrophilic carbonyl carbon with concomitant formation of an exo olefinic linkage, stabilizing the incipient tertiary carbocation.

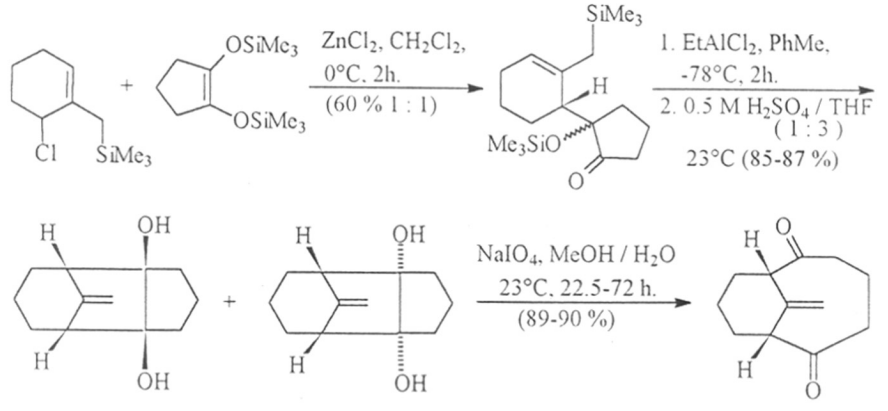




XIa XIb

Scheme-1.8

In an alternative approach(1984),the same authors utilized the oxidative cleavage of the diol intermediates[12] **XIIa, b** in getting the central B-ring(*Scheme*-1.9) Here again, a lewis acid-promoted cyclization generates the intermediates **XIIa** and **XIIb.**



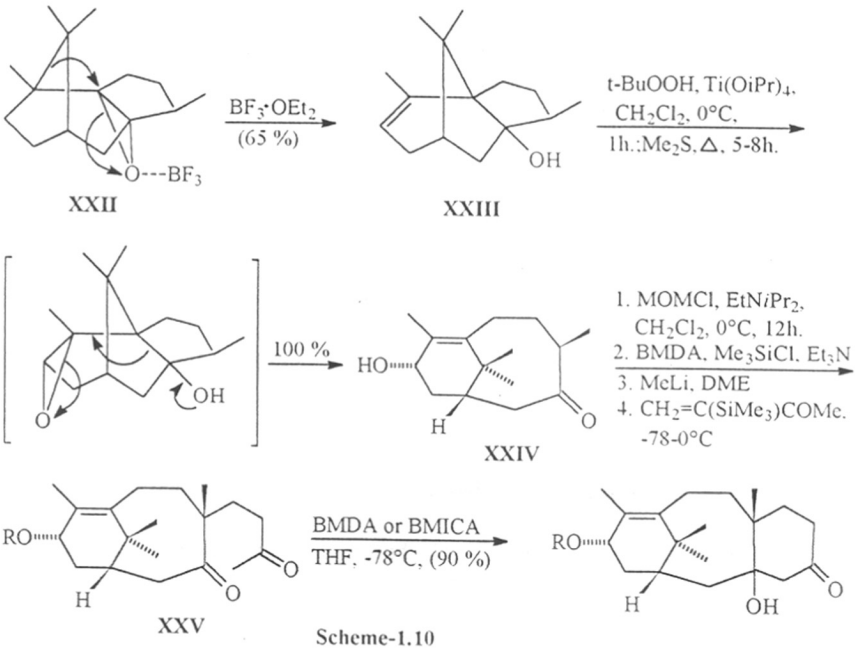
XIIa XIIb

Scheme-1.9

2. Holton's approach (1984) :

Lewis acid-catalyzed opening and rearrngement andfrgamentation of hydroxy epoxide.

Holton *et al.* not only achieved[23] the total framework of Taxol, but also carried out the total synthesis of taxusin, the non-natural enantiomer of (-) taxusin, by the combination of a fragmentation reaction and an intramolecular aldol condensation (*Scheme 1.10*).



XXII XXIII XXIV XXV

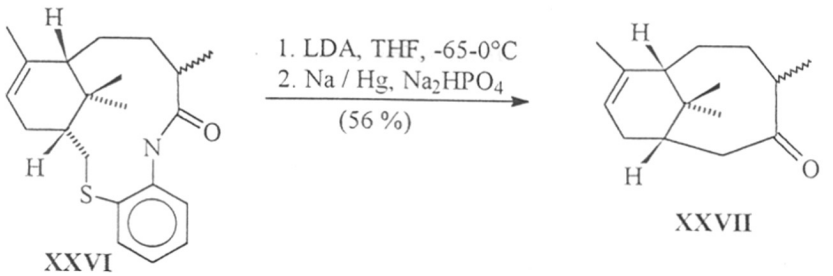
Scheme-1.10

It can be seen that a lewis acid catalyzed epoxide opening, followed by a rearrangement in the natural product patchouline epoxide **XXII** furnished the hydroxy olefinic intermediate **XXIII** and the epoxide of the latter underwent a fragmentation reaction leading to the bicyclic AB framework **XXIV**. Addition of four more carbon atoms to **XXIX** by an alkylation reaction to get the diketone **XXV** and an intramolecular aldol condensation in the latter led to the ABC ring system.

3. Ohtsuka's approach (1984-86) :

Rearrangement and Ring contraction.

The AB ring system has also been realized by a Ohtsuka's et al. by a base- induced intramolecular cyclization in 12-membered lactam sulfoxide XXVI which was prepared in a multi step (15-steps) synthesis starting from α-ionone. Thus, treatment of the lactam XXVI with LDA followed by desulfurization of the cyclized product furnished the required bicyclic system XXVII in a moderate yield of 56%. *(Scheme-1.11)*



XXVI

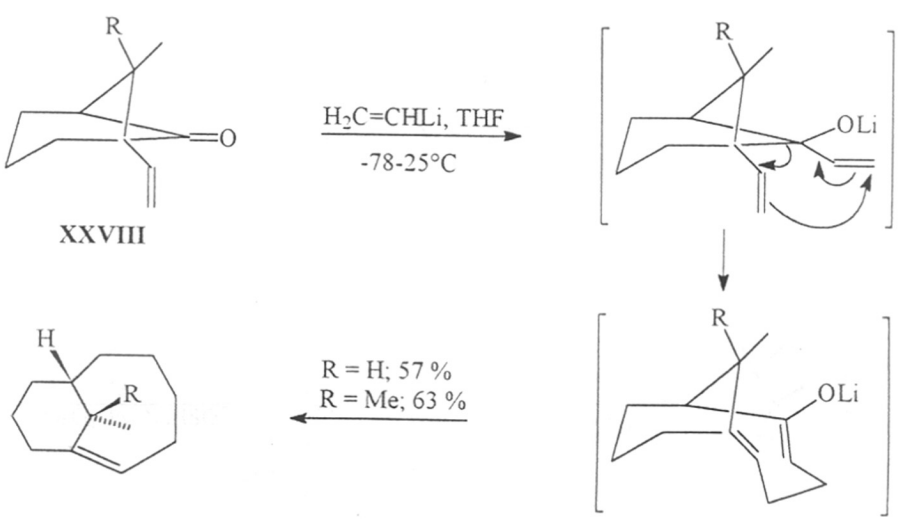
XXVII

Scheme-1.11

4. Snider's approach (1991) :

Oxy-Cope rearrangement.

Oxycope rearrangement has been utilised by quite a few groups of researchers in the construction of AB ring system and also for proper functionalization at the ring junctures. Snider *et al.*[25] reported that the anionic oxy-cope rearrangement in the intermediate XXIX furnished the desired bicyclic system XXX (*Scheme-1.12*). The bicyclic (3.1.1) heptane-based starting material XXVIII was obtained by six steps from 5-methyl hex-4-enyl iodide and methyl crotonate and the strategy involved a vinyl lithium low temperature reaction.



XXVIII

XXX

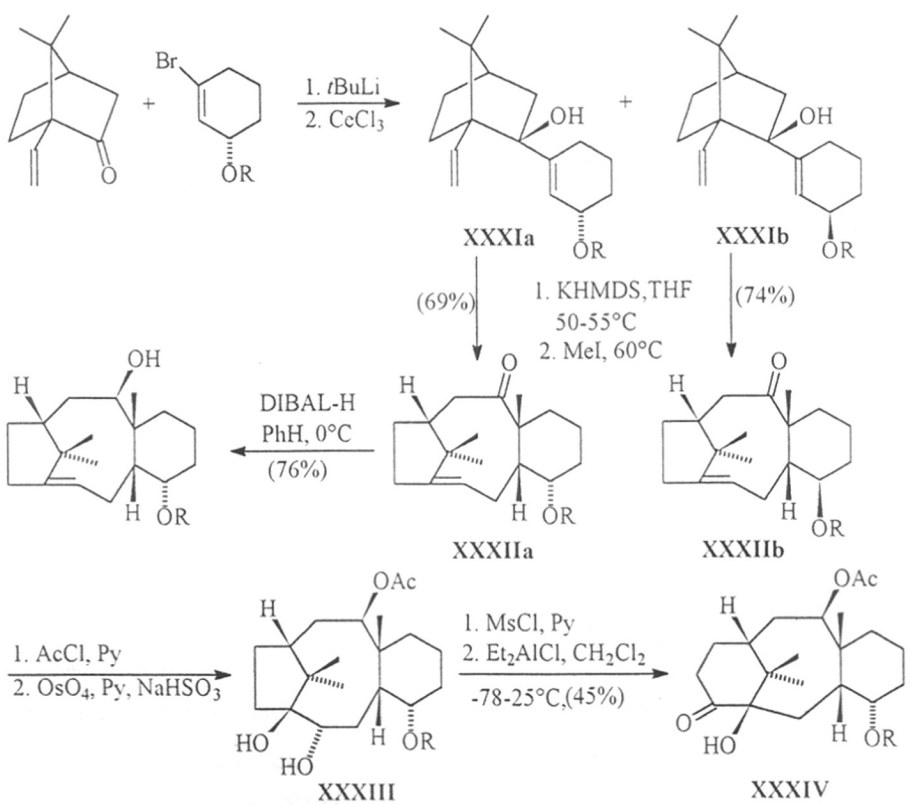
XXIX

Scheme-1.12

5. Paquette's approach (1989-1991) :

Oxy-Cope / pinacol-pinacolone rearragement.

Taxol skeleton was achieved by Pacquette et al. [26]employing oxy-cope and pinacol-pinacolone type rearrangement as key reactions.While the first reaction led to the nine membered central ring, the second rearrangement resulted in ring expansion of a five membered cycle to a six membered one with concomitant ring contraction of the nine membered ring to an eight membered cycle. Base treatment of the isomeric 1,5 dienes XXXI a and b offered the rearrangement products XXXII a and b. The intermediate XXXII a was subjected to a few routine operations to furnish the required vicinal diol XXXIII which on pinacol-pinacolone type rearrangement furnished the desired tri cyclic frame work XXXIV *(Scheme 1.13)*.

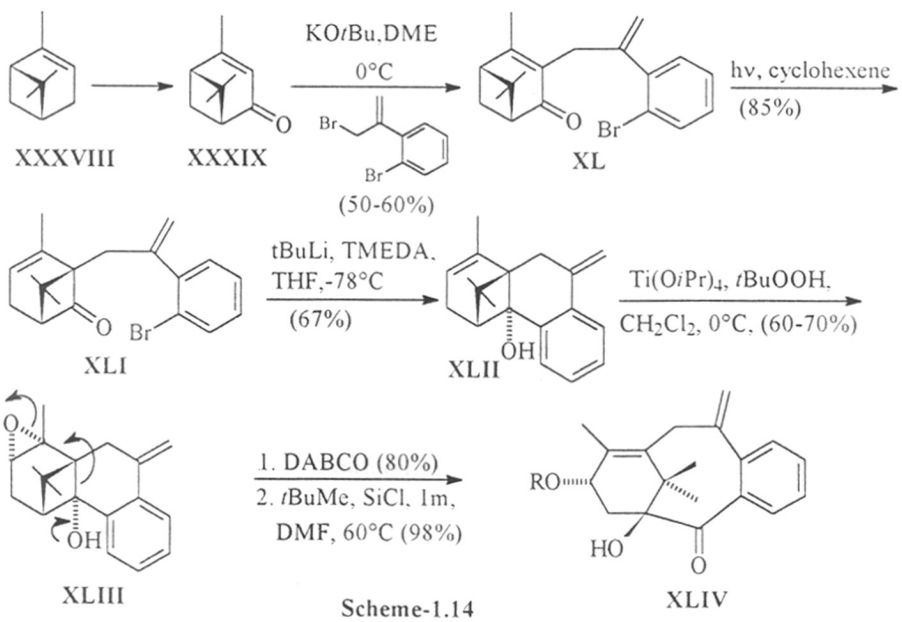


Scheme-1.13

6. Wender's approach (1992) :

{[3,3] sigmatropic photorearrangement} base catalysed fragmentation.

An elegant approach not only for realization of the taxol skeleton, but for the total synthesis of taxol molecule was reported by Wender *et al.*[28] The choice of the monoterpenic natural product α-pinene, **XXXVII** as the starting material offered many conspicuous advantages; α-pinene is abundantly and cheaply available from turpentine oil, provides 10-carbon atoms to the target molecule, besides lending the core chirality. The key reactions of the strategy are a photorearrangement and a base-catalysed fragmentation (*Scheme 1.14*).



XXXVIII XXXIX XL XLI XLII XLIII XLIV

Scheme-1.14

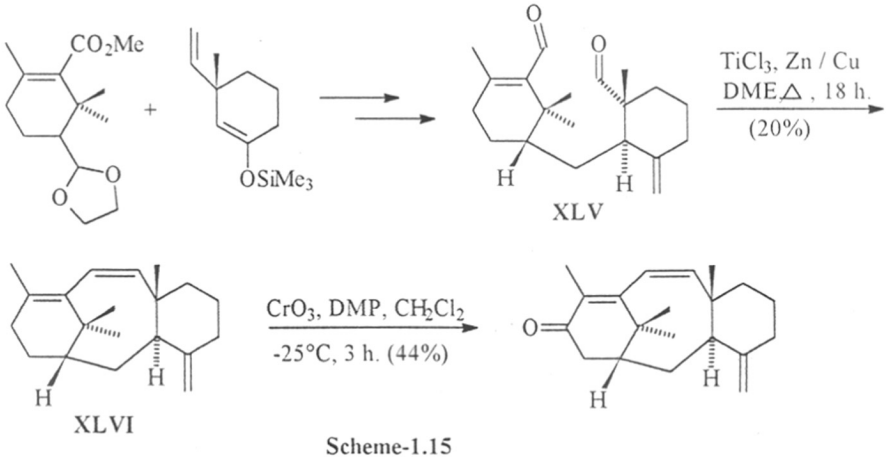
Verbenone **XXXIX** was alkylated *via* its dienolate by suitable alkylating agent to **XL**, which on a photo rearrangement involving a 1,3-sigmatropic carbon shift afforded the product **XLI** with suitable carbon placement for the A-ring of taxol. Lithium-mediated cyclization of **XLI** to **XLII** and a regio and stereoselective epoxidation in the latter gave the epoxy alcohol **XLIII**. Base-catalyzed fragmentation of **XLIII** afforded the desired tricyclic framework **XLIV**.

1.2.3 APPROACHES BASED ON McMURRY COUPLING

1 Kende's approach (1986) :

Vinyl carbanion alkylation via hydrozone.

McMurry coupling reaction has been employed by a few groups of workers to realize the AB and AB&C rings of taxol. Pattenden *et al.* employed this reaction to realize a B.C. secotaxol[29] skeleton, while the total ring system of Taxol utilizing the reaction was achieved by Kende's group[30] (*Scheme-1.15*). The intermediate dialdehyde **XLV** obtained in 12 steps, on an intramolecular $TiCl_3$-catalyzed McMurry coupling reaction led to the tricyclic product **XLVI** in a low yield.



Scheme-1.15

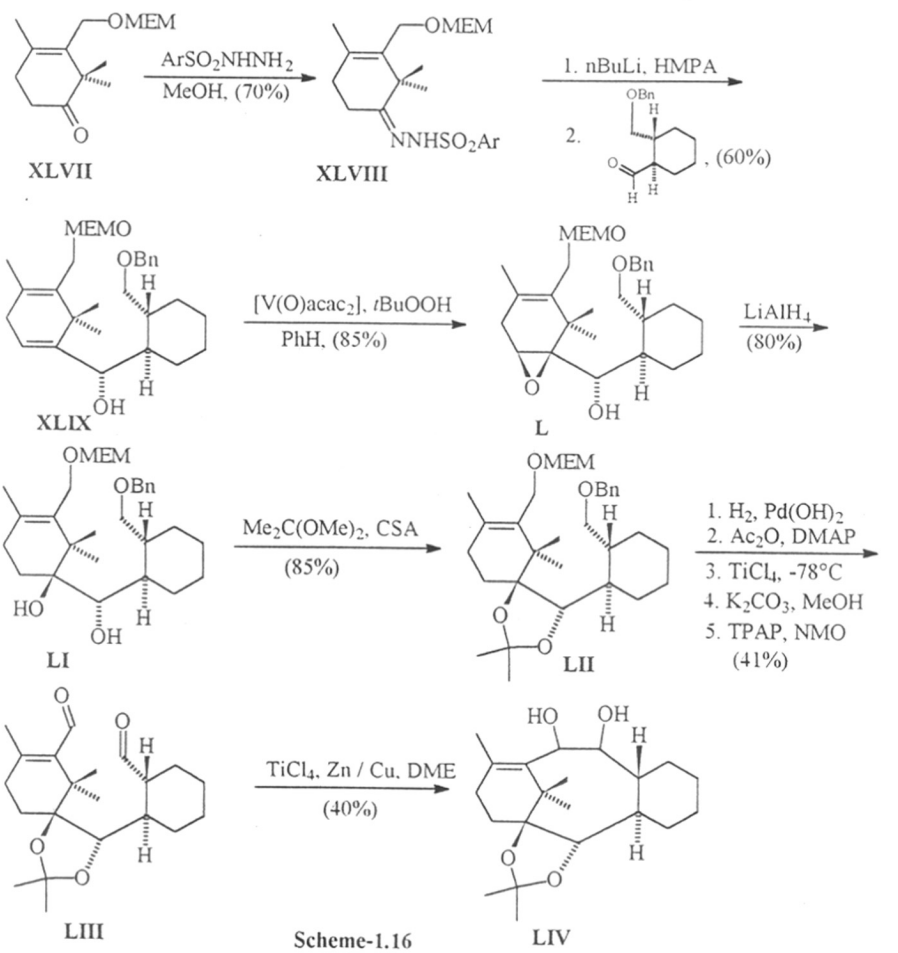
2 Nicolaou approach (1993-94) :

Vinyl carbanion alkylation via hydrozone.

Nicolaou *et al.* have reported an elegant total synthesis of taxol recently.[31] Prior to this total synthesis, these researchers had tried various coupling reactions such as Dithiane and Stille reactions to bridge A and C-rings with the formation of the central carbocycle. Among these reactions, one involving hydrazone-vinyllithium chemistry[32] was found to be very efficient. It can be seen (*Scheme-1.16*) that base-catalyzed condensation of the hydrazone **XLVIII** derived from **XLVII** with a suitable aldehyde

furnished the secondary alcohol **XLIX**, which was regio and stereoselectively epoxidized to **L**. The vicinal diol **LI** was protected as the acetonide **LII** and the latter through a sequence of reactions shown in the scheme led to the dialdehyde **LIII**. The final step of joining the A and C rings was accomplished by a McMurry coupling reaction. This strategy described in the scheme was employed by these authors for the total synthesis of taxol.

TH 1155



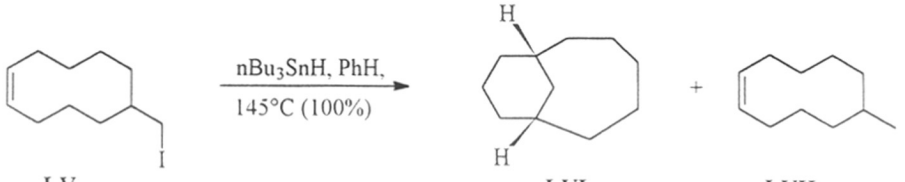
Scheme-1.16

1.2.4 INTRAMOLECULAR RADICAL CYCLIZATION REACTIONS

1. Winkler's approach (1989) :

Radicals via alkyl iodide cyclisation.

Radical reactions have also been utilized in the construction of both AB and AB&C ring systems. Winkler *et al.*[33] could synthesize the bicyclic compound **LVI** from an iodo compound **LV** by an intramolecular radical addition to the olefinic linkage. This reaction was also accompanied by the reduction of the C-I bond *(Scheme 1.7)* leading to **LVII**.



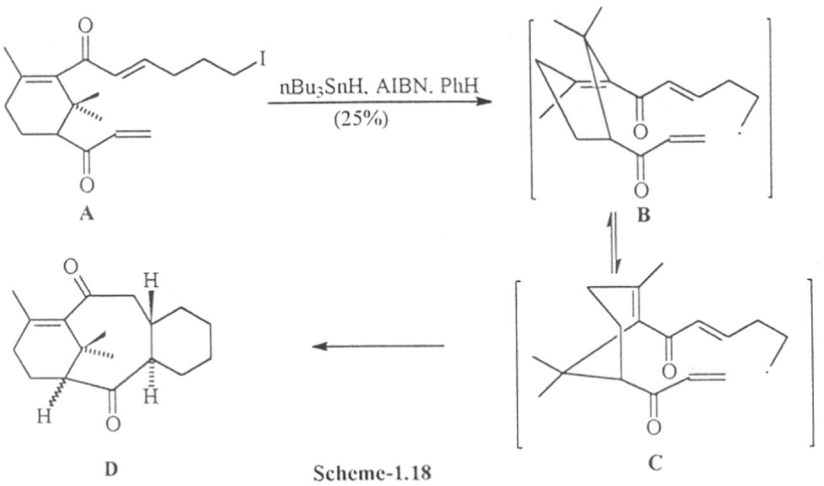
LV LVI LVII

Scheme-1.17

2. Pattenden's approach (1992) :

Radicals via alkyl iodide , tandem cyclization.

Tandem radical cyclization has been elegantly utilized by pattenden for a simultaneous realization of three rings of the taxol frame work. The necessory iodo compound-A for cyclization was produced in five steps from a suitably substituted cyclohexene aldehyde. AIBN-initiated free radical cyclization of A in the presence of n-Bu_3SnH led to a mixture of epimers of D in a 25% yield. The formation of epimers was attributed to the different conformations B and C of the intermediate radical.*(Scheme 1.18)*.



A B C D

Scheme-1.18

The foregoing survey of literature regarding the construction of the basic AB and ABC rings of Taxoid system has been presented as Table I and Table II with specific remarks followed by a few lines as highlights.

1.2.5 Highlights of literature methods: Construction of AB and ABC Ring System of Taxoid Molecules - Table-I and Table-II

Table-I

AB Ring System of Taxoid Molecules

S.No.	Key Reaction	Remarks	Reference
1.	Nickel-catalysed {4+4] Cycloaddition $Ni(COD)_2Ph_3P$	i) Starting material is got in 5 steps plus additional one step ii) Use of expensive catalysts	Wender *et al.*[10]
2.	Fragmentation reaction utilising a sulfone group for anion stabilization	3+4 = 7 Steps with poor yields	Trost *et al.*[11]
3.	Retro aldol fragmentation	3+2 = 5 Steps, involves a photo {2+2] cycloaddition leading to regio isomers	Pattenden *et al.*[13]
4.	Reductive cleavage of cyclobutane bond	4+3 = 7 Steps, includes a {2+2] photoaddition	Krau's *et al.*[22]
5.	Ring contraction involves a base induced rearrangement	15+2 = 17 Steps	Ohttnka *et al.*[24]
6.	Oxy-Cope rearrangement	6+1 = 7 Steps, involves a vinyl lithium, low temperature reaction	Snider *et al.*[25]
7.	Intramolecular radical cyclization (Radical addition into the olefinic linkage)	Number of steps to realize the starting material is not mentioned	Winkler *et al.*[33]

I) Wender *et al.* utilized a convenient Nickel-based catalyst for an intramolecular {4+4] cycloaddition.

II) A fragmentation reaction in which stabilization of a carbon anion by a sulfone group is used by Trost *et al.*

III) A retro aldol fragmentation constitutes the key step in the approach of Pattenden and their scheme also involves a photo {2+2] cycloaddition.

IV) Similarly, a reductive cleavage of cyclobutane bond and a {2+2] photo cyclo addition are the key features of the strategy employed by Kraus *et al.*

V) A base catalysed ring contraction is the key reaction employed by Ohtsuk *et.al.*

VI) While oxy-cope rearrangement constitutes the key reaction in the protocol of Snider, intramolecular radical cyclization is the main feature of the approach Winkler *et.al.*

Table-II

ABC Ring System of Taxoid Molecules

S.No.	Key Reaction	Remarks	Reference
1.	Retro aldol fragmentation	Low temperature, {2+2] photoaddition	Blecherts *et al.*[14]
2.	Fragmentation and Intramolecular retro-aldol condensation	2+8 = 10 Steps	Holten *et al.*[23]
3.	Oxycope and pinacol-pina colone type rearrangement	~ 10 steps	Paquett *et al.*[26]
4.	Ring contraction by Wittig Rearrangement of an ether		Yadav *et al.*[27]
5.	Photo rearrangement, base-catalysed ring fragmentation	Starting material is naturally occurring α-pinene, 9 steps, chiral framework	Wender *et al.*[28]
6.	Intramolecular McMurry coupling	12+3 = 15 Steps, Low yields	Kende *et al.*[30]
7.	i) Base catalysed vinyl lithium addition to an aldehyde function		
	ii) McMurry (Intramolecular) coupling	2+12 = 14 Steps	Nicolaou *et al.*[31]
8.	Intramolecular tandem radical addition (n-Bu_3SnH-mediated)		Pattenden *et al.*[34]

The above tabular data is again summarized.

I) A retro aldol fragmentation has been employed by Blecherts *et al.* to realise the ABC ring system and their protocol involves a low temperature {2+2] addition also.

II) A fragmentation reaction coupled with an intramolecular retro-aldol condensation is the main strategy utilised by Holton *et al.*

III) Paquette *et al.* employed oxy-cope and a pinacol-pinacolone type rearrangement in their strategy.

IV) An isolated ring contraction method involving a Wittig rearrangement was

utilised by Yadav *et al.*

V) McMurry coupling as the key reaction is the feature of the strategies reported by Kende and Nicolaou.

VI) An intramolecular tributyltin hydride-mediated tandem radical addition is the key reaction of Pattenden's approach.

It may be mentioned that most of the strategies involve starting materials obtained by a multi-step sequence of reactions, thereby reducing the overall yields. The photoaddition has led to mixture of regioisomers.

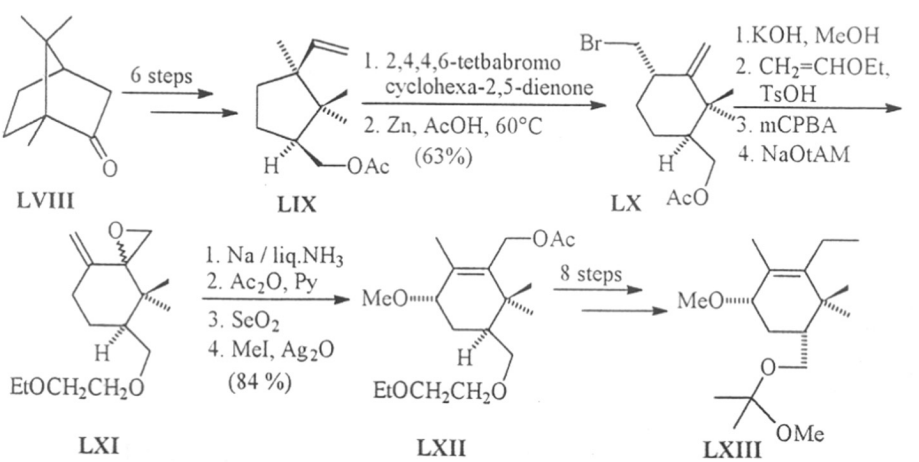
Synthesis of A-ring

Many strategies for the construction of the AB ring system of Taxoid framework have already been outlined and their merits and demerits brought out; However, even the construction of the A-ring with suitable substituents for further elaboration into AB system does not appear to be simple. Many researchers have made successful attempts in this direction and survey of these methods is both informative and relevant to this chapter

1.2.6 Literature Methods:

1. Kitagowa's approach (1980-84) :

One of the earliest approaches by Kitagawa[35] *et al.* involved a Wagner-Meerwein arrangement in **LIX** induced by a bromonium ion and which led to the substituted cyclohexane ring **LX**. A few standard organic transformations converted **LX** to the epoxide **LXI** which in turn was converted to **LXII** as shown in the *Scheme–1.20* The latter intermediate was finally transformed to **LXIII** in sequence of a reactions involving eight steps. It may be seen that **LXIII** possesses most of the structural features of A-ring of taxol.

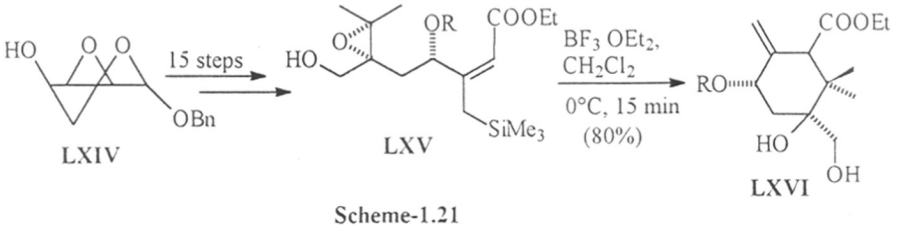


Scheme-1.20

2. T. Frejd approach (1987) :

Rearrangement of allyl silane.

T. Frejd *et al.* have elegantly utilized lewis-acid catalysed eletrophilic polyene cyclization of epoxy allyl silane as a key reaction in generating a percursor to A-ring of taxol. These authors obtained the chiral epoxy alcohol **LXIV** from cheaply available sugar, arabinose, in five steps; this epoxy alcohol was transformed into the epoxy allyl silane **LXV**, well set for the cyclization, in reaction sequence of fifteen steps. $BF_3.OEt_2$-catalysed cyclization of **LXV** afforded the key precursor of ring-A in an excellent yield. It can be seen that **LXVI** contains the required substituents in the right stereochemistry for transformation into A-ring of taxol *(Scheme-1.21)*.

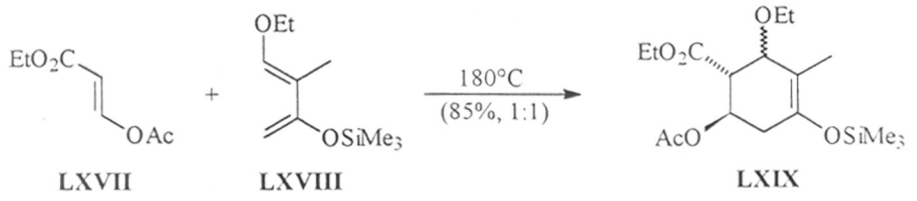


Scheme-1.21

3. Clark's approach (1987) :

Diels-Alder [4+2] cycloaddition.

A traditional Diels-Alder approach has been reported by Clark et al. for the construction of A-ring fragment of taxol skeleton. The reaction of 1-ethoxy-3-[(trimethyl silyl) oxy]-2-methyl-1,3-butadiene **LXVIII** with ethyl (E)-2-acetoxy acrylate **LXVII** afforded the epimeric cycloaduct **LXIX** in a high yield. However, it may be mentioned that this method required the preparation and use of unstable starting materials. In addition, the cycloadduct **LXIX** requires quite a few transformations in realising the actual A-ring of taxol *(Scheme-1.22)*.

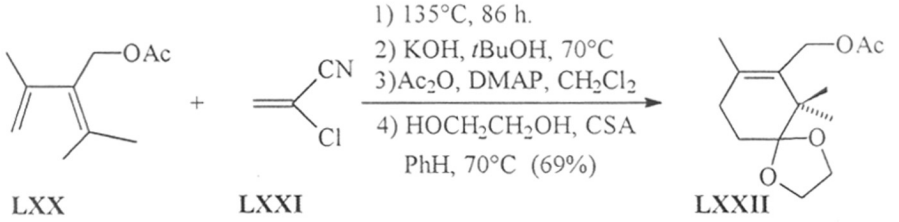


LXVII LXVIII LXIX

Scheme-1.22

4. Nicoloau's approach (1992) :

A short and efficient route to the A-ring system of taxol has been reported by Nicoloau et al. These authors prepared enantiomerically pure A-ring fragment of taxol utilizing a Diels-Alder reaction and Corey's oxazaboralidine reduction The cycloadduct **LXXII** was subjected to allylic oxidation with SeO_2 and the reduction of the enone with chiral oxazaborolidine furnished the corrsponding chiral allylic alocohol.



LXX LXXI LXXII

Scheme-1.23

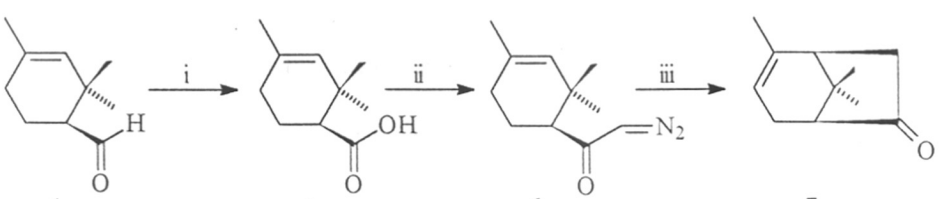
Section-II

1.3.0 Introduction

The methods so far reported in literature for realising the skeletal framework of taxoid systems involve cycloaddtion and base-catalysed carbonanion reactions and a few radical reactions. It is conspicuous that there has not been a single strategy which is based on carbene chemistry. Therefore, development of a synthetic protocol involving the reactions of carbenoid species would be both novel and interesting.

1.4.0 Present work

Owing to certain advantages offered by α-pinene molecule *(vide infra)*, we envisaged that this molecule would be the most suitable starting material in realizing the A-B ring system of taxoid framework. An analysis of the structural features of the target molecule-I suggests useful clues in terms of selecting not only the starting materials, but the key reactions as well. We conceived that the synthon 4 (*Scheme-1.24*) would serve as an ideal substrate for the required chemical transformations leading to the key bicyclic intermediate 7.

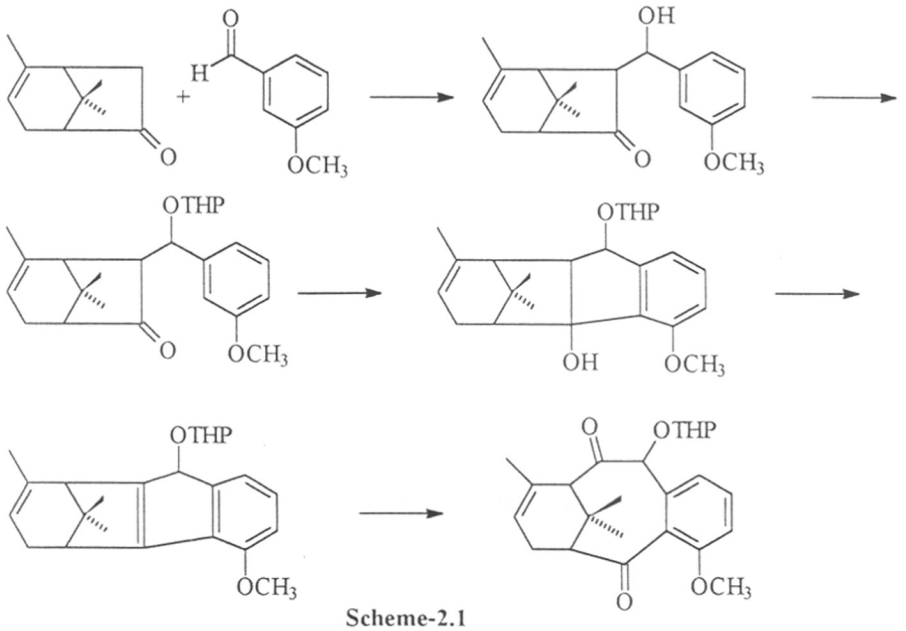


4 5 6 7

i)Ag_2O, ether, RT, 6 h ii) $SOCl_2$, CH_2N_2, ether, 0°C, 6 h. iii) BF_3OEt_2,·EDC, 0°C- RT

Scheme-1.24

The latter has the potential to generate the 8-membered carbocycle based on a strategy described in the second chapter; this aspect can be seen by a perusal of the scheme shown below; the scheme is self explanatory *(Scheme-2.1)*.



Scheme-2.1

The attractive features of our first target synthon **4** are the following:

(1) The *gem*-dimethyl as well as the olefinic methyl groups as needed in I are already present.

(2) The olefinic linkage can be utilized for introduction of the hydroxyl functionality at C-13 of I.

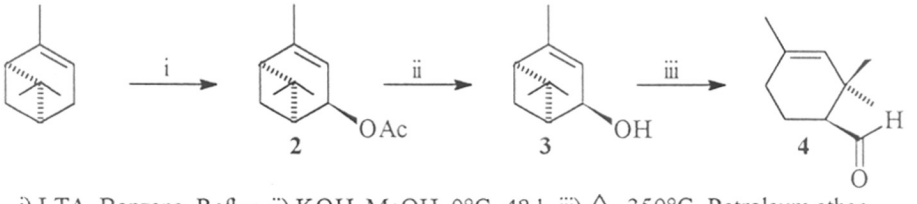
(3) Extension of the aldehyde by one more carbon and linkage of the added centre to carbon-3 of **4** would result in a cyclopentane annulation on the existing 6-membered ring leading to framework of 7.

1.5.0 Results and Discussion

As our immediate object was to fuse a cyclopentane ring on to the existing six-membered ring, various strategies were checked from this point of view; excellent review articles are available, describing methods for cyclopentane annulation.[39,40] An examination of the reported methods revealed that these strategies lead to cyclopentane formation on vicinal carbons of a carbocycle. We did not come across a single method,

wherein a three carbon unit could be annulated to an existing carbocycle in a 1,3 manner. We have such a situation which required annulation of six membered ring to lead to the desired bicyclic system **7**.

We contemplated that an α-diazoketone obtainable from **5** could easily generate a α-ketocarbene precursor **6**, the addition of which to the trisubstituted carbon of the olefinic linkage can lead to **7**. Surprisingly enough, we found that Erman and Stone[41] have utilized this intramolecular addition of diazoketones to olefins in their synthesis of α--patchoulane sesquiterpenes. Therefore, this reaction appeared quite promising for the required cyclopentane annulation. The initial target was to obtain the aldehyde **4** from α-pinene. The synthetic plan that we intended to follow is shown in *Scheme-1.25*



i) LTA, Benzene, Reflux. ii) KOH, MeOH, 0°C, 48 h. iii) △, 350°C, Petroleum ether.

Scheme-1.25

Preparation of *trans*-Verbenol 3:

The authenticity of α-pinene was ensured by its GLC and the PMR spectrum. The latter (Fig-1) showed resonances well in agreement reported for α-pinene and the significant features of this spectrum were three 3-H singlet at 0.85 δ, 1.27 δ, 1.60 δ and a multiplet at 5.15δ. Reaction of α-pinene with LTA afforded a homogeneous product in a quantitative yield, which could be readily characterized as *trans*-verbenol acetate,2. The *trans* stereochemistry of the acetate function was deduced from the well known preference for bulky and electrophilic reagents to approach the pinene molecule from the less hindered side. The PMR spectrum *(Fig-2)* of the product besides showing three singlets for the geminal dimethyl and olefinic methyl groups, displayed a 3-H singlet at

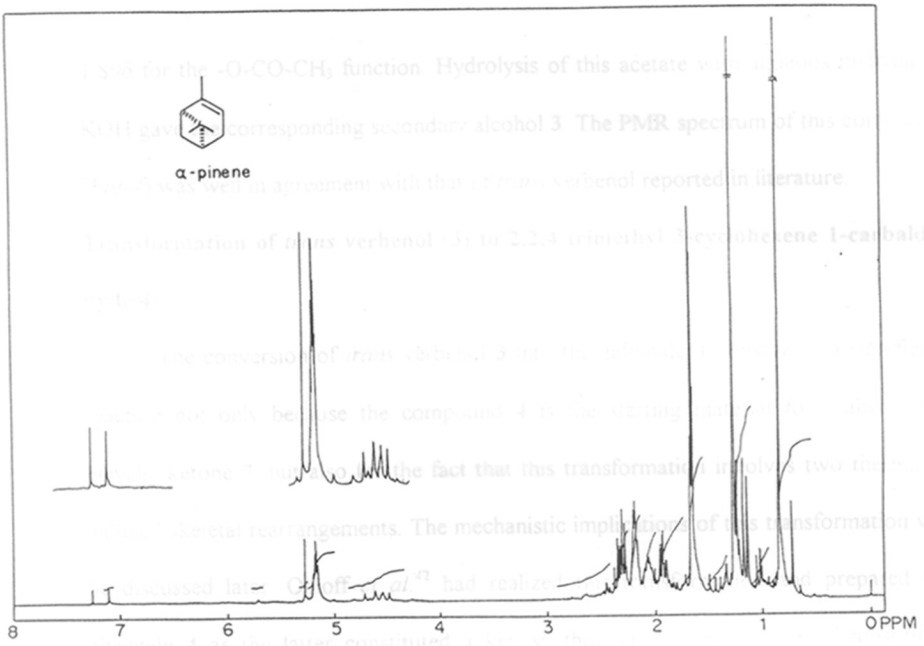


FIG. 1: PMR SPECTRUM OF α-PINENE

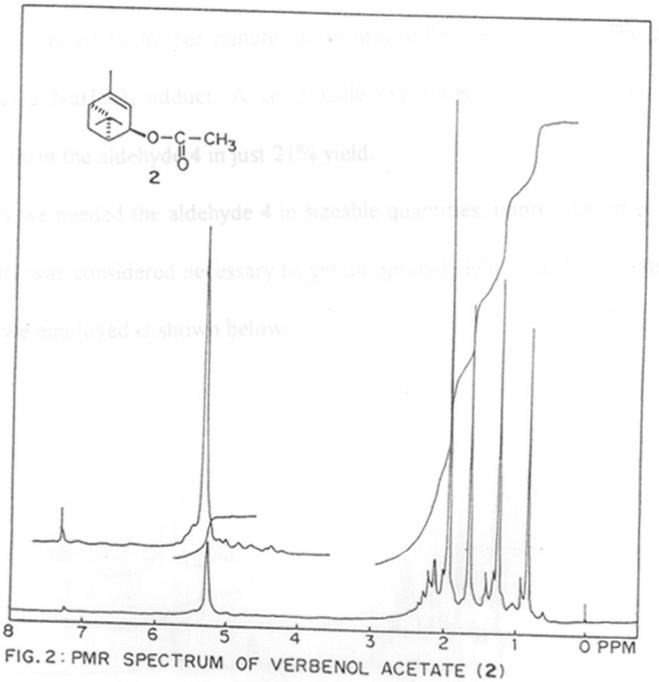


FIG. 2: PMR SPECTRUM OF VERBENOL ACETATE (2)

1.89δ for the -O-CO-CH_3 function. Hydrolysis of this acetate with aqueous methanolic KOH gave the corresponding secondary alcohol **3**. The PMR spectrum of this compound (*Fig-4*) was well in agreement with that of *trans* verbenol reported in literature.

Transformation of *trans* verbenol (3) to 2.2.4 trimethyl 3-cyclohexene 1-carbaldehyde 4:

The conversion of *trans* verbenol **3** into the aldehyde **4** constitutes a significant reaction not only because the compound **4** is the starting material for realizing the bicyclic ketone **7**, but also for the fact that this transformation involves two thermally-induced skeletal rearrangements. The mechanistic implications of this transformation will be discussed later. Ohloff *et al.*[42] had realized this transformation and prepared the aldehyde **4** as the latter constituted a key synthon in the preparation of substituted ionones. The pyrolysis unit employed by them consisted of a quartz reactor packed with sintered quartz rings. *Trans*-verbenol was introduced into the reactor maintained at 350°C at a rate of 30 ml per minute, in an atmosphere of nitrogen. The product was isolated as a $NaHSO_4$ adduct. A large scale experiment (95.0 g. of *trans* verbenol) furnished them the aldehyde **4** in just 21% yield.

As we needed the aldehyde **4** in sizeable quantities, improvisation of the reaction parameters was considered necessary to get an optimal yield. The flash vacuum pyrolysis unit that we employed is shown below.

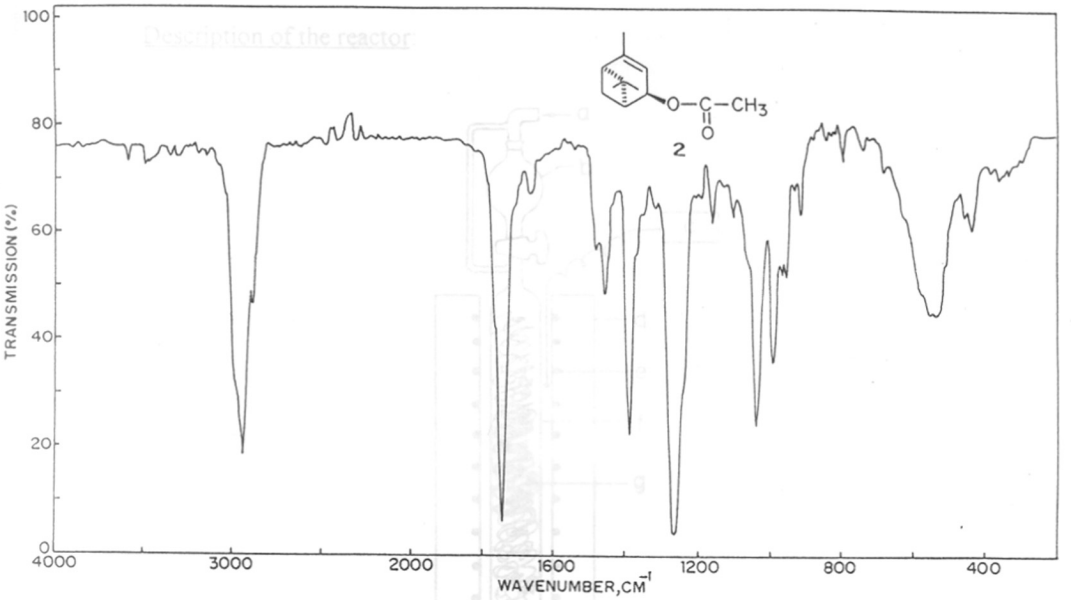


FIG. 3: IR SPECTRUM OF VERBENOL ACETATE (2)

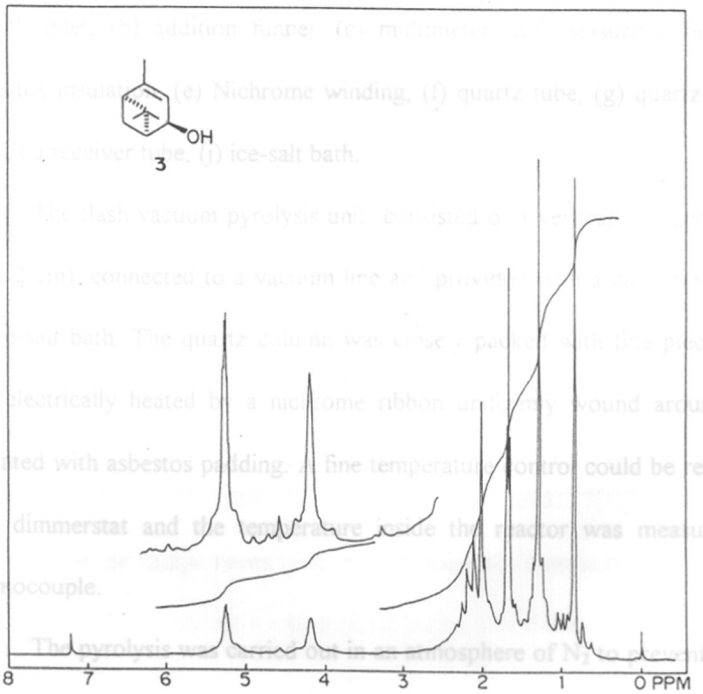
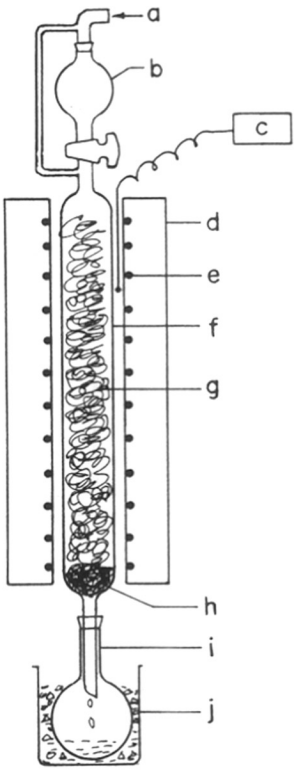


FIG. 4: PMR SPECTRUM OF TRANS VERBENOL-3

Description of the reactor:



(a) N_2 inlet, (b) addition funnel, (c) multimeter, for measuring the temprature (d) Asbestos insulation, (e) Nichrome winding, (f) quartz tube, (g) quartz pieces, (h) glass wool, (i) receiver tube, (j) ice-salt bath.

The flash vacuum pyrolysis unit consisted of a vertically placed quartz tube (35 cm x 2 cm), connected to a vacuum line and provided with a collection flask housed in an ice-salt bath. The quartz column was closely packed with fine pieces of quartz and was electrically heated by a nichrome ribbon uniformly wound around it which was insulated with asbestos padding. A fine temperature control could be realized by the use of a dimmerstat and the temperature inside the reactor was measured using Cr-Al thermocouple.

The pyrolysis was carried out in an atmosphere of N_2 to prevent oxidation of the

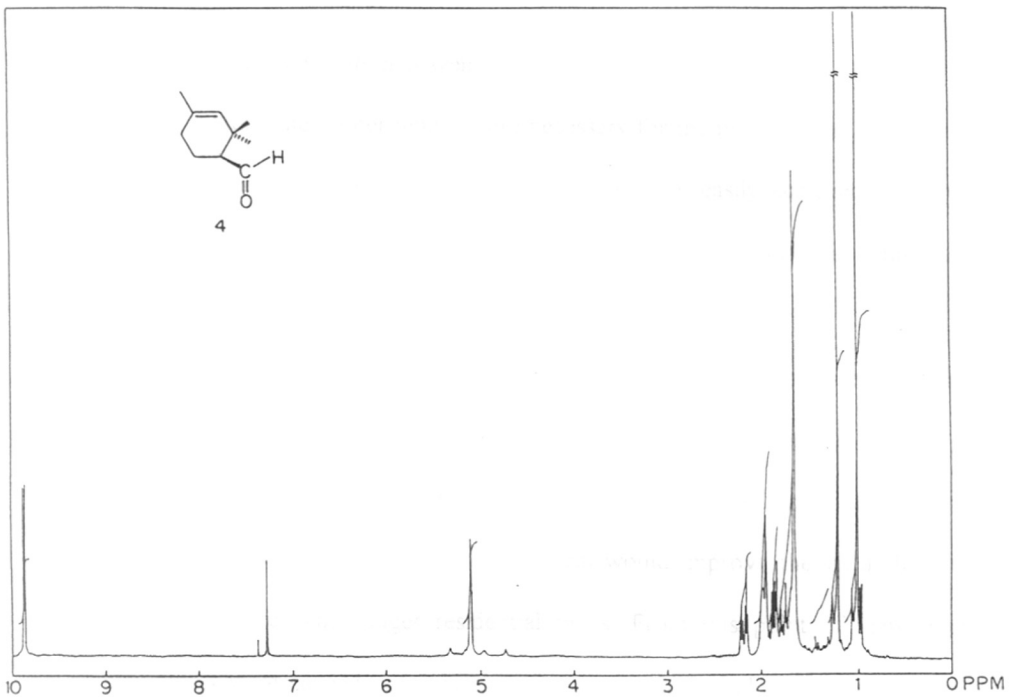


FIG. 6: PMR SPECTRUM OF 2·2·4 TRIMETHYL CYCLOHEXENE CARBALDEHYDE-4

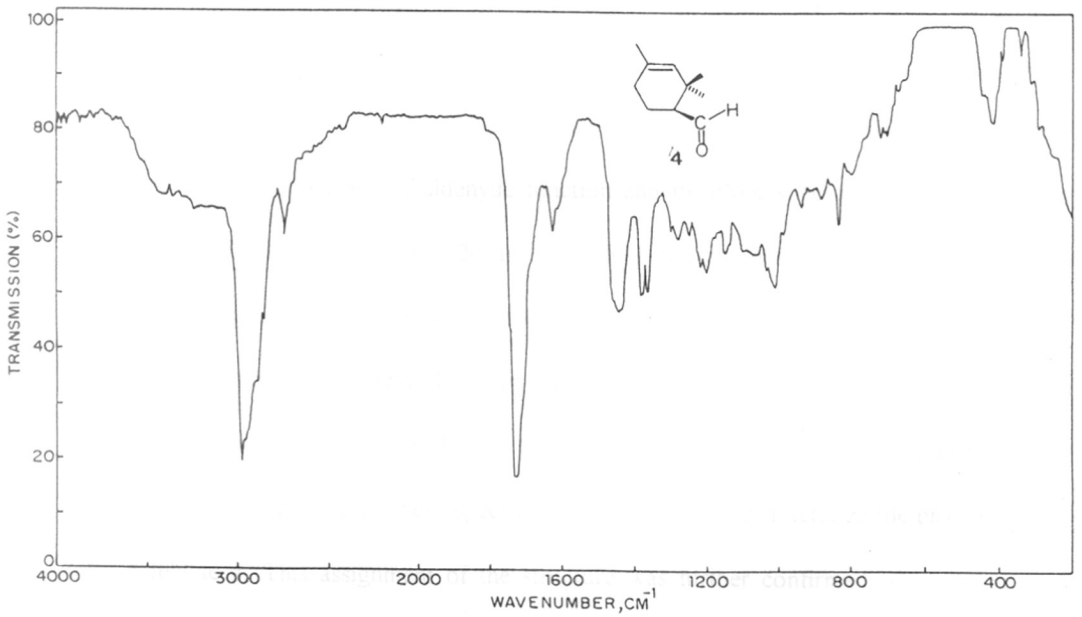


FIG. 7: IR SPECTRUM OF 2,2,4 TRIMETHYL CYCLOHEXENE-3 CARBALDEHYDE-4

products and polymerization as well.

To attain the proper temperature necessary for the pyrolysis, an initial calibration on the heating system was to be done. This could be easily achieved by varying the dimmerstat settings over a span of about 250-350°C. This resulted in a fine setting to realize the temperature with a variance of ± 5°C.

It can be seen that the thermal reactor employed by us was essentially similar to that described by Ohloff.[42] A significant feature of Ohloff's method is that the alcohol was introduced in a neat form and its addition was rather very fast. It was thought that a slow addition of the alcohol in a diluted form would improve the yields by providing more surface area and longer residential times. From this point of view, numerous experiments were carried out varying the concentration of alcohol in petroleum ether, and also employing different rates of addition.

The GLC of the total pyrolysate revealed that it comprised at least 4 to 5 components with the required aldehyde **4** as a major one. This aldehyde was isolated pure by a column chromatography of the total material on silica gel (see experimental). The IR spectrum (*Fig.7*) of the product displayed bands at 1730 and 2720 cm^{-1} indicating the presence of aldehyde function and its PMR spectrum (*Fig.6*) displayed three 3-H singlets at 1.00, 1.20 and 1.55 δ, indicating the presence of two geminal dimethyl groups and a methyl on the double bond. It can be noticed that one of the methyl groups appearing at 1.30δ in verbenol (*Fig.4*) has shifted now to 1.20. Besides these features, the spectrum showed the olefinic proton and the aldehydic proton at 5.10 and 9.85 δ respectively. These spectral data enabled us to characterize the product as the aldehyde **4**. This assignment of the structure was further confirmed when the IR and PMR data of **4** matched well with those reported for this compound.[42] It should be mentioned that the product **4** was optically active (see *Experimental*).

As mentioned earlier, many experiments were conducted varying the concentration of alcohol **3** in petroleum ether and also the rate of addition. However, the temperature of the reaction was maintained at 350°C. The results obtained from ten such experiments are shown in Table.1. It can be seen that addition of neat alcohol gave 13% yield of the aldehyde **4**; a dilution to 50% enhanced the yield to 19%. A concentration of 2% and 1% led to yields of 35 to 38%. This was in conjunction with reduced rate of addition, the rate being about 10 ml/min. Thus, it can be concluded that 1 to 5% concentration of verbenol in petroleum ether when pyrolysed at 350°C over a period of 25 to 50 min. gave an optimal yield of 35 to 38% of the required aldehyde. This exercise made a considerable improvement over the conditions of Ohloff *et al.*[42] which resulted in a mere 21% yield. The reaction carried out at tempareture highar than 350°c led to decomposition of the products.

Pyrolysis of *trans* Verbenol - Optimization of Reaction Parameters

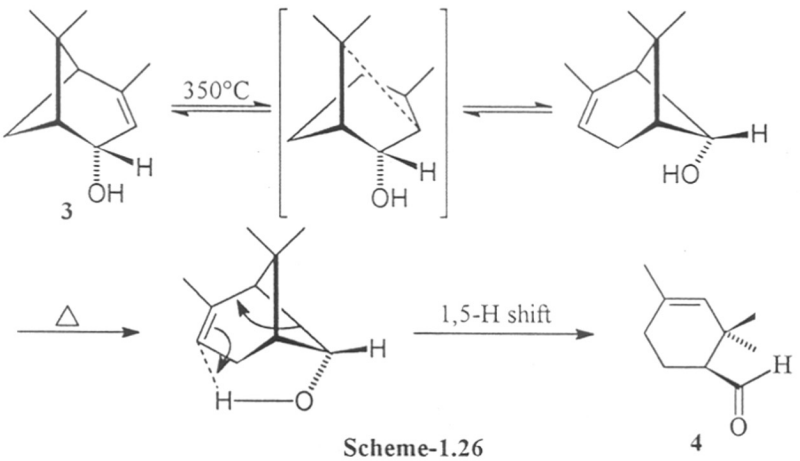
Table. 1

S.No.	Concentration of Verbenol in pet.ether	Temperature of the Column	Duration of Addition	Isolated Yield (%)
1.	*100%	350°C	10 min.	13
2.	50%	350°C	20	19
3.	20%	350°C	20	22
4.	15%	350°C	3	25
5.	15%	300°C	5	20
6.	10%	350°C	5	28
7.	5%	350°C	10	32
8.	2%	350°C	25	35
9.	1%	350°C	50	35-38
10.	1%	250°C	50	27%

*g/100ml

In this context, as mentioned earlier,it may be added that the thermal transformation of *trans* verbenol **3** to aldehyde **4** involves two rearrangement reactions. This isomerization of *trans* verbenol and related pinene derivatives was first observed by Ohloff[42] *et al. (Scheme-1.26)* They postulated the skeletal rearrangement of *trans* verbenol to *trans* chresanthenol to involve a [3,3]-sigmatropic carbon shift; the primary product of this rearrangement being a homoallylic alcohol and also with the right orientation of the hydroxyl group bringing it into the proximity of the double bond is

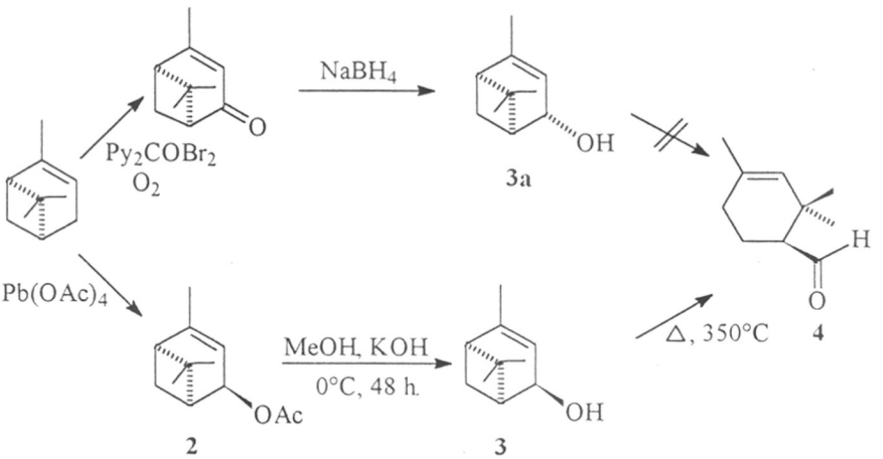
very well set for a [1,5] sigmatropic hydrogen shift and undergoes the rearrangement leading to the aldehyde **4**.



Scheme-1.26

In this context, it is pertinent to mention that this [3,3]-sigmatropic carbon shift was realized by Wender *et al.*[43] by a photoreaction to get the proper skeletal arrangement of the taxol A-ring. It is also interesting to note in the present case that the chirality of the starting material α-pinene has been retained in the product even after four transformations. This chiraliy of aldehyde **4** has also been carried forward to the bicyclic ketone 7, to be described later.

The specific requirement of the *trans* geometry of the hydroxyl group with respect to the cyclobutane ring in the alcohol **2** for the rearrangement to occur was further confirmed by us when *cis* verbenol **3a** did not yield the aldehyde **4** on pyrolysis. The sequence of reactions employed to prepare the *cis* alcohol is shown in (*Scheme-27*). It involved the $NaBH_4$ reduction of verbenone prepared from the oxidation of α-pinene with oxygen in presence of Py_2CoBr_2.



Scheme-1.27

Preparation of [3.2.1] bicyclooctenone 7

The potential of the bicycloketone 7 in generating the AB ring system of taxoid skeleton has been just mentioned (vide infra) and would be discussed further in the next chapter. The protocol that we intend to follow to realise this ketone 7 has also been indicated (*Scheme-1.24*). It can be seen that the aldehyde 4 has a chiral centre and drastic conditions of acid or base can racemise the aldehyde. Although various methods are available for the transformations R-CHO to R-COOH,[44] we were on the lookout for a mild and an efficient reagent for the oxidation without effecting epimerization. From this point of view, silver oxide appeared the most suitable and thus, was used for this transformation. Oxidation of 4 with silver oxide (see Experimental) furnished a homogeneous product in almost a quantitative yield. The IR spectrum of the product showed the carbonyl band at 1690 cm^{-1} and a weak OH stretching band at ~ 2700 cm^{-1}. In addition, the aldehydic band that appeared at 1730 cm^{-1} in 4 had disappeared. The PMR spectrum (*Fig-8*) besides showing three 3H signals at 0.92, 1.12 and 1.56δ for three methyl groups and a 1H signal for olefinic proton at 5.04δ, showed a broad 1H signal for carboxylic acid proton at 9.50δ, contrasting with the fine doublet observed for

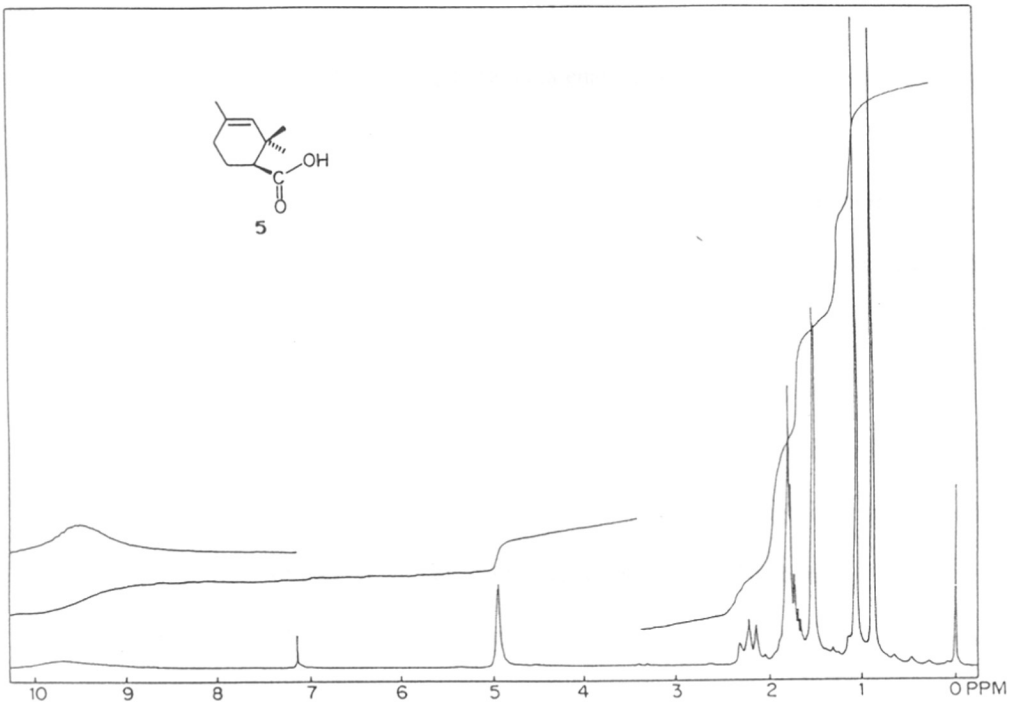


FIG.8: PMR SPECTRUM OF 2,2,4 TRIMETHYL CYCLOHEXENE-3 CARBOXYLIC ACID-5

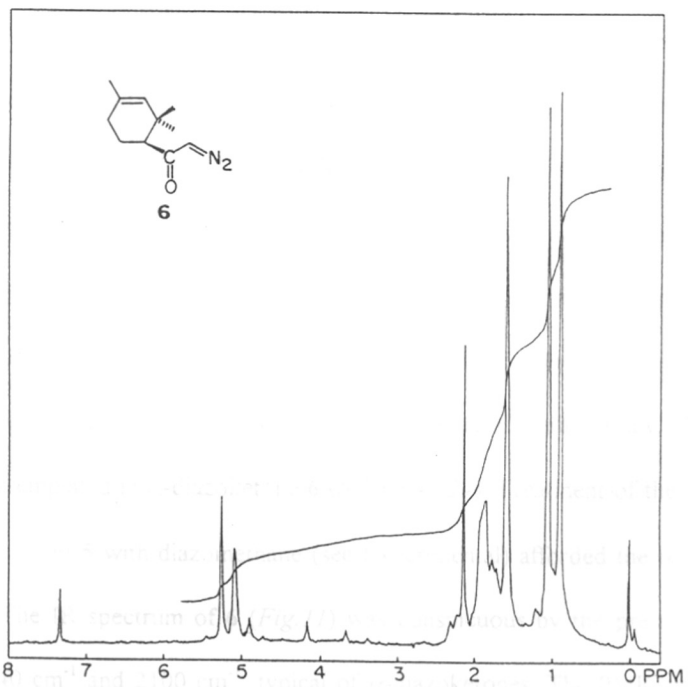


FIG. 10: PMR SPECTRUM OF 2,2,4 TRIMETHYL CYCLOHEXENE-3 DIAZO KETONE-6

the aldehydic proton of **4**. These spectral data enabled us to recognize the product as the acid 5.

It was intended to utilize a carbenoid reaction to achieve a C-C bond formation. Generally, the methods employed for C-C bond formation make use of ionic, free radical and well known pericyclic reactions and these necessitate the activation of both the carbon atoms. However, recent years have witnessed the development of a new and efficient methodology in which an activation of one carbon centre is sufficient. It involves an electron deficient metal carbenoid as a reactive enough intermediate which can undergo bond formation with even an unactivated remote C-H bond.

With the advent of Rh-acetate as a superior catalyst to generate transient electrophilic metal carbenoids,[45] from α-diazo carbonyl compounds, intramolecular carbenoid insertion reaction into unactivated C-H bonds has assumed strategic importance. These reactions of diazo compounds have been amply reviewed.[46] However, the reaction we contemplated to use in realizing the bicyclic ketone 7 was a nucleophilic reaction on an electrophilic carbenoid species. Cyclization processes in which a new C-C bond is formed by nucleophilic addition to an ionizing centre provide efficient pathways to carbocycles and heterocycles. α-diazoketones with suitably situated internal nucleophile are known to display this type of reaction under acid catalysis. Although the nucleophiles range from olefinic, acetylenic and aromatic groups to hetero atoms, π-route cyclization of alkenes and aromatics have been very well used for cyclization; this topic has been reviewed.[47] With this background of literature, a C-C bond formation was contemplated in α-diazoketone **6** (*Scheme-1.24*). Treatment of the acid chloride derived from acid **5** with diazomethane (see Experimental) afforded the required α-diazoketone **6**. The IR spectrum of **6** (*Fig.11*) was conspicuous by the presence of sharp bands at 1640 cm^{-1} and 2100 cm^{-1}, typical of α-diazoketones. The PMR spectrum (*Fig.10*) was

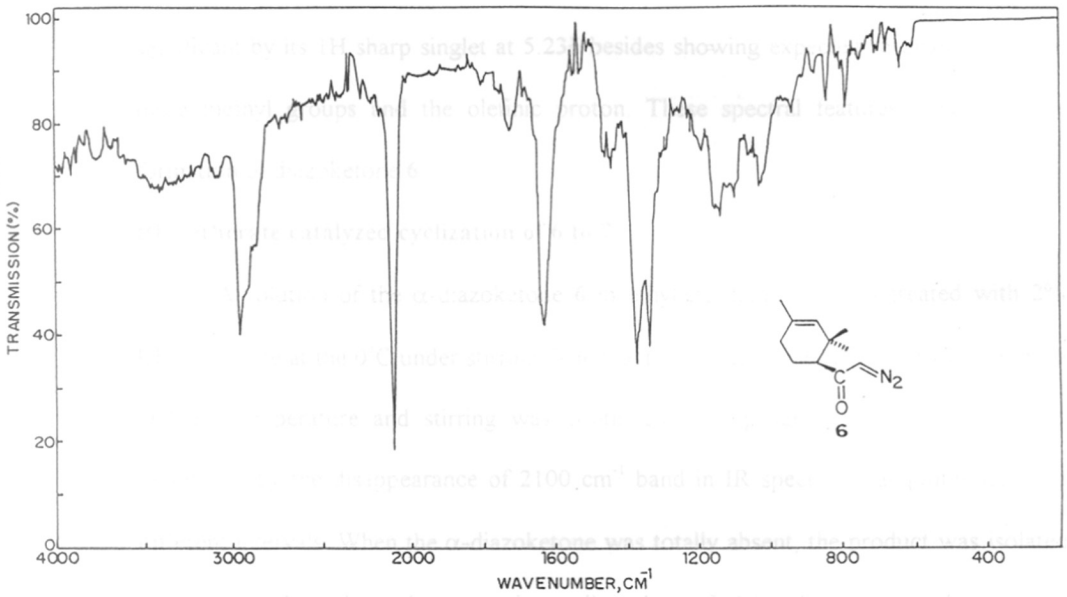


FIG. 11: IR SPECTRUM OF 2,2,4 TRIMETHYL CYCLOHEXENE-3 DIAZOKETONE-6

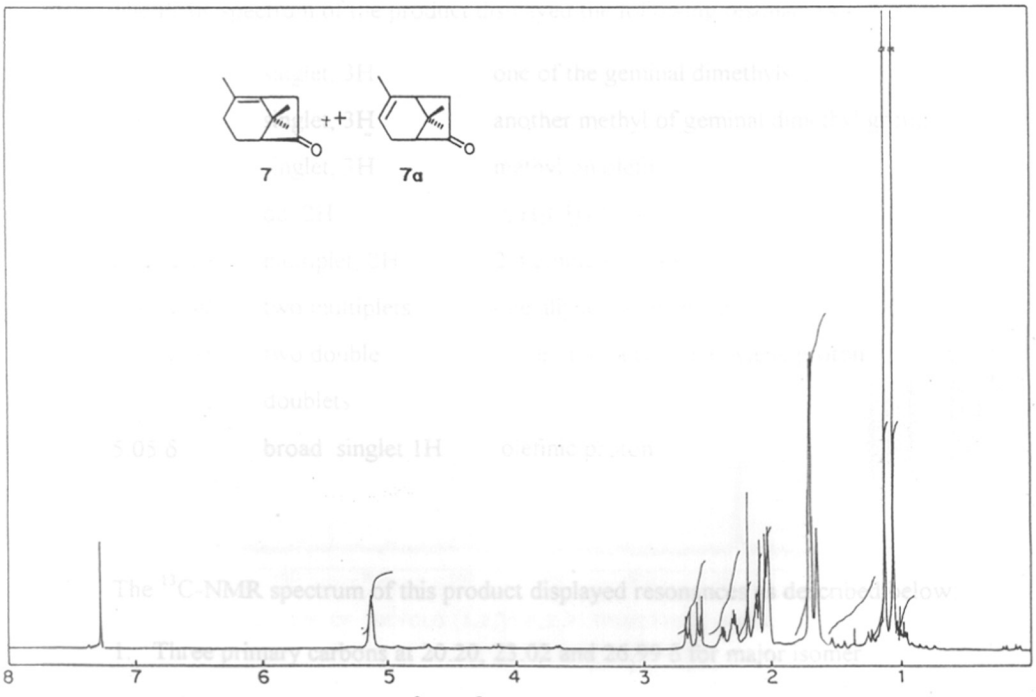


FIG. 12: PMR SPECTRUM OF BICYCLO [3,2,1] 2,2,4 TRIMETHYL CYCLO OCTANONE-7

significant by its 1H sharp singlet at 5.23δ besides showing expected resonances for the three methyl groups and the olefinic proton. These spectral features confirmed the formation of diazoketone **6**.

BF_3 etherate catalyzed cyclization of 6 to 7

A solution of the α-diazoketone **6** in ethylene dichloride was treated with 2% BF_3 etherate at the 0°C under stirring. The reaction mixture was allowed to warm up to ambient temperature and stirring was continued. The progress of the reaction was monitored by the disappearance of 2100 cm^{-1} band in IR spectra of aliquotes taken at different intervals. When the α-diazoketone was totally absent, the product was isolated by a standard work-up (see experimental) and purified by distillation under reduced pressure, a good yield of 56% was realized (112-113°C/5mm). The first evidence for the occurrence of cyclopentane annulation was a conspicuous band at 1745 cm^{-1} in the IR spectrum (*Fig.13*) of the product. The PMR spectrum *(Fig.12)* displayed the following resonances.

The PMR spectrum of the product displayed the following resonances -

1.10	singlet, 3H	one of the geminal dimethyls
1.30	singlet, 3H	another methyl of geminal dimethyl group
1.60	singlet, 3H	methyl on olefin
2.10	dd, 2H	$-CH_2\underline{CH_2}-CO-$
2.15-2.20	multiplet, 2H	2 methine protons
2.30-2.40	two multiplets	one allylic methylene proton
2.55-2.65	two double doublets	The other allylic methylene proton
5.05 δ	broad singlet 1H	olefinic proton

The ^{13}C-NMR spectrum of this product displayed resonances as described below:

1. Three primary carbons at 20.20, 23.02 and 26.99 δ for major isomer

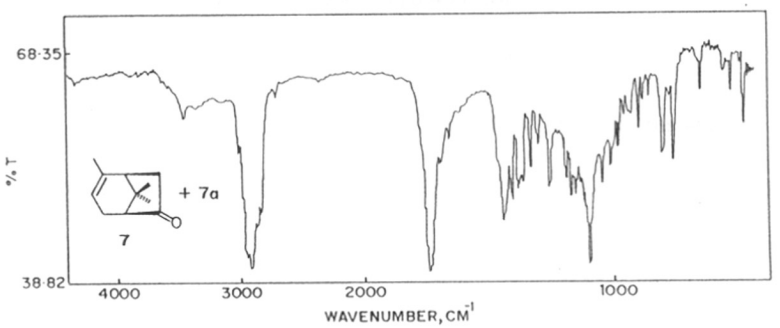


FIG.13: IR SPECTRUM OF BICYCLO [3,2,1] 2,2,4 TRIMETHYL CYCLO-OCTANONE-7

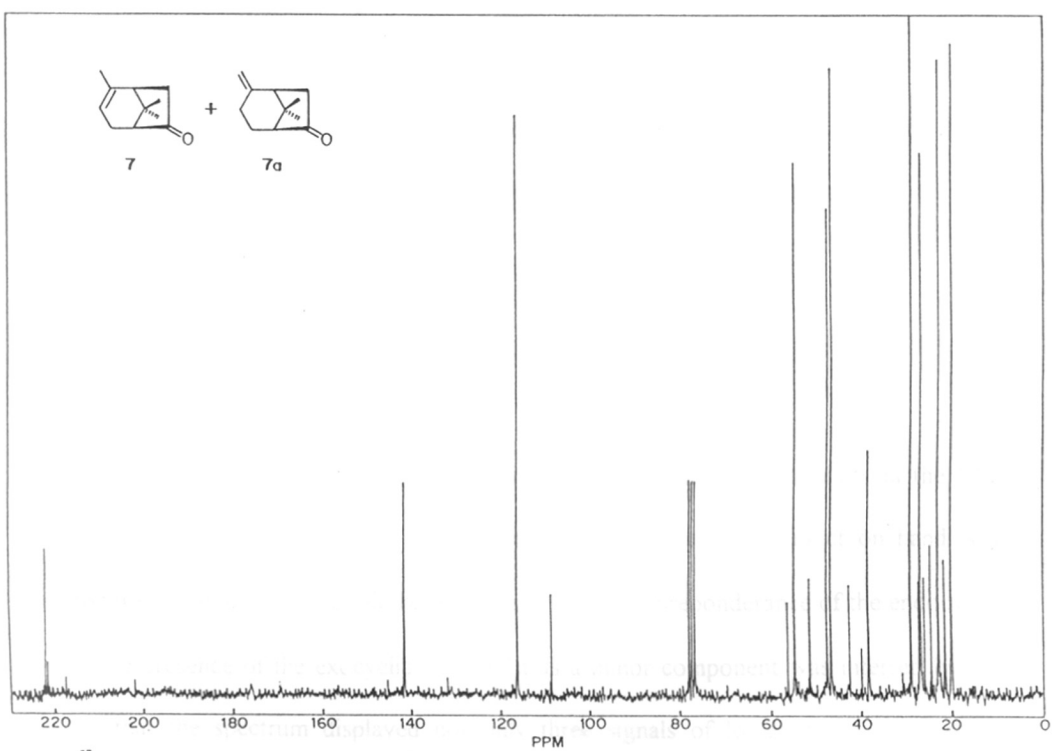


FIG. 14: ^{13}C-NMR SPECTRUM OF BICYCLO [3,2,] 1 2,2,4 TRIMETHYL CYCLO OCTANONE-7

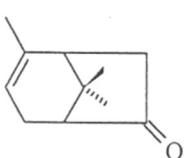
2. Two secondary carbons at 29.12 and 46.61 δ for major isomer

3. Three tertiary carbons at 47.45, 54.70 and 116.45 δ for major isomer

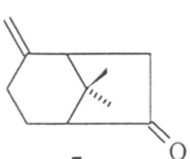
4. Three quarternary carbons at 38.40, 141.57 and 221.74 δ

It was interesting to note that the secondary carbon resonances were accompanied by two resonances of lower intensities at 27.26 and 42.47 δ. Similarly, the three tertiary carbon resonances were also accompanied with resonances of lower intensity at 51.31, 55.94 and 108.67 δ. Again, three quarternary carbon resonances of lower intensity were observed at 39.85, 148.37 and 221.23 δ. The data clearly suggested the product to be a mixture of two isomeric compounds. However, signals for the minor isomer were not clearly seen in the PMR spectrum of the product *(Fig.12)* except that two signals of low intensity (amounting to about 10% of the product) were seen at 4.65 and 4.80 δ, suggesting the presence of exo methylene protons.

The product from the BF_3-etherate catalyzed reaction of the diazoketone **6** was expected to arise from the nucleophilic attack of the olefinic bond on the electrophilic carbene centre leading to cyclopentane annulated cation intermediate **7b**.The latter could stabilize by a proton loss leading to either of the following two structures (**7** or **7a**)



7



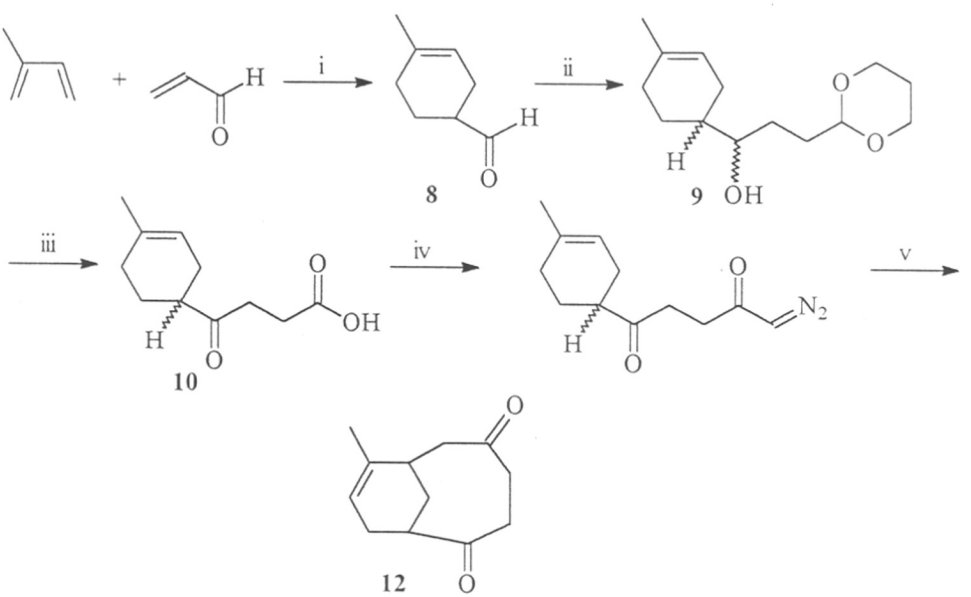
7a

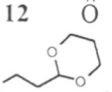
An examination of both the signal features and the chemical shifts in the ^{13}C-NMR spectrum data described above clearly indicates that the product on hand is a mixture of the isomeric bicyclic ketones **7** and **7a** with a preponderance of the endocyclic **7**. The presence of the exocyclic ketone **7a** as a minor component was inferred by the fact that the spectrum displayed not only three signals of lower intensity for three

methylene groups, but also a low intensity resonances at 42.47 δ for the exomethylene in its ^{13}C spectrum. Thus, from the PMR and ^{13}C-NMR data and also from the expected mode of reaction of the olefinic bond in **6** with the incipient carbon, the product was characterized as the required bicyclic ketone **7** with minor amounts of **7a**.

Construction of AB ring system

With the success realized in cyclopentane annulation using intramolecular nucleophilic addition of olefin to the electrophilic carbene centre in realizing the bicyclic octenone **7**, we were prompted to utilize this reaction to get the bicyclic AB ring system, starting from a suitable α-diazoketone. The sequence of reactions that we envisaged to follow is shown in the (*Scheme-1.28).*



i) BF_3OEt_2, CH_2Cl_2, -78°C. ii)  , THF. iii) CrO_3, H_2SO_4, H_2O, 0°C-RT
iv) $SOCl_2$, CH_2N_2, CH_2Cl_2 v) BF_3OEt_2, EDC; 0°C-RT

Scheme-1.28

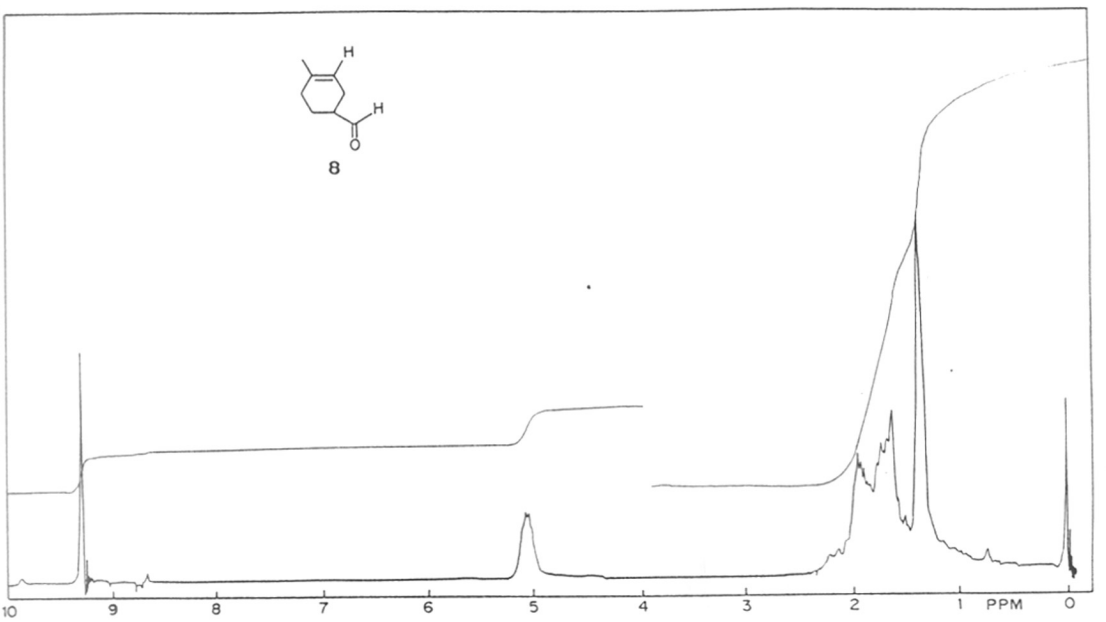


FIG. 16 : PMR SPECTRUM OF 4-METHYL CYCLOHEXENE-3 CARBALDEHYDE-8

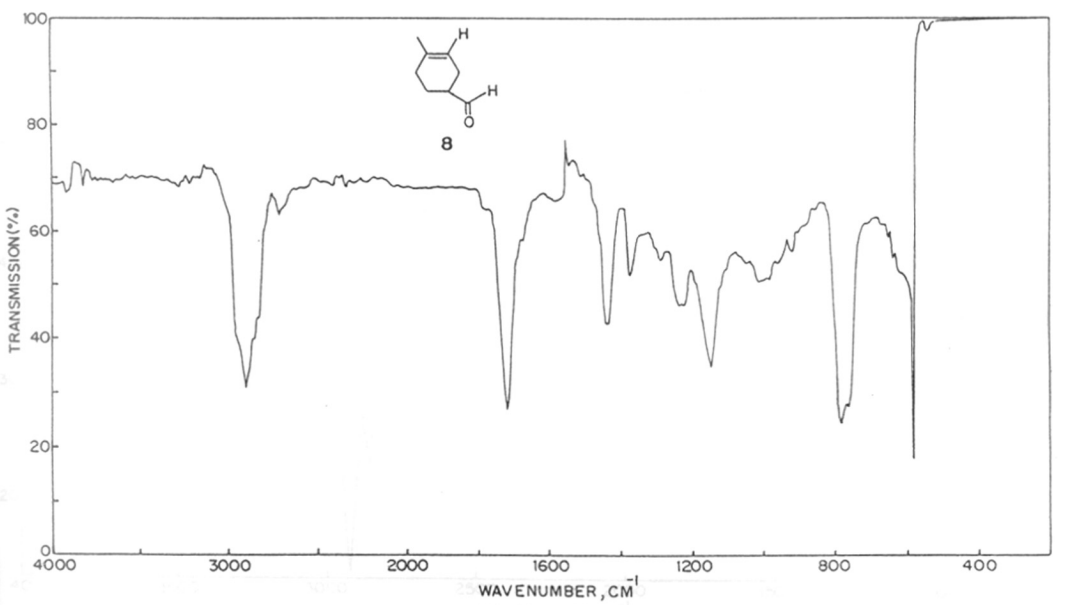


FIG. 17 : IR SPECTRUM OF 4-METHYL CYCLOHEXENE-3 CARBALDEHYDE-8

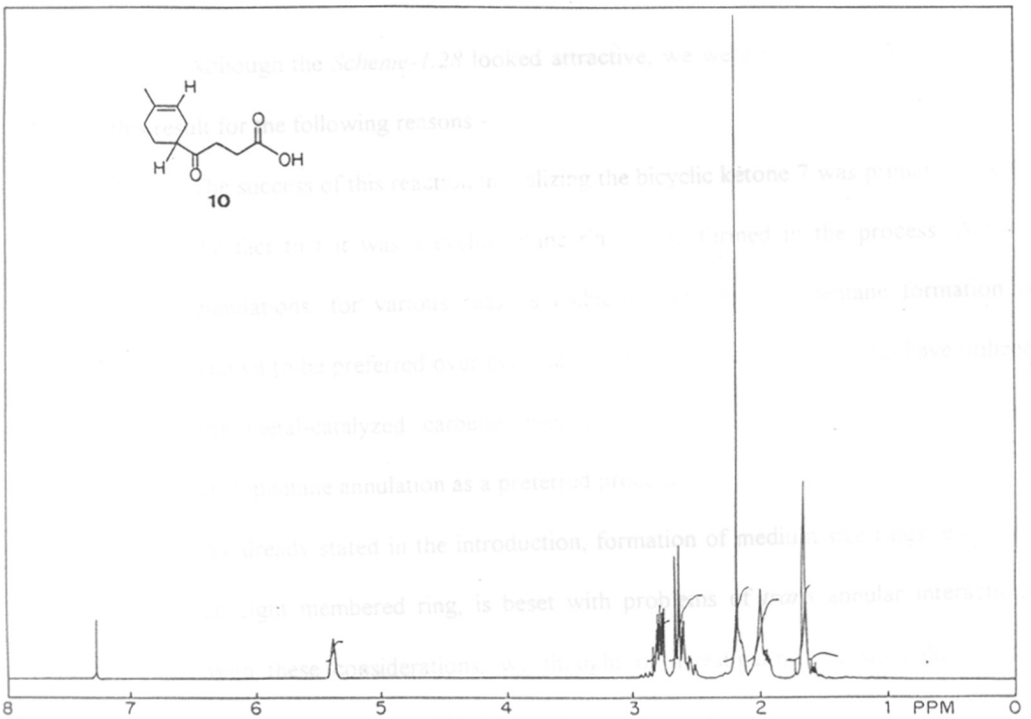


FIG. 18 : PMR SPECTRUM OF 4-(4-METHYL CYCLOHEXENE-3) 4-KETO BUTANOIC ACID - 10

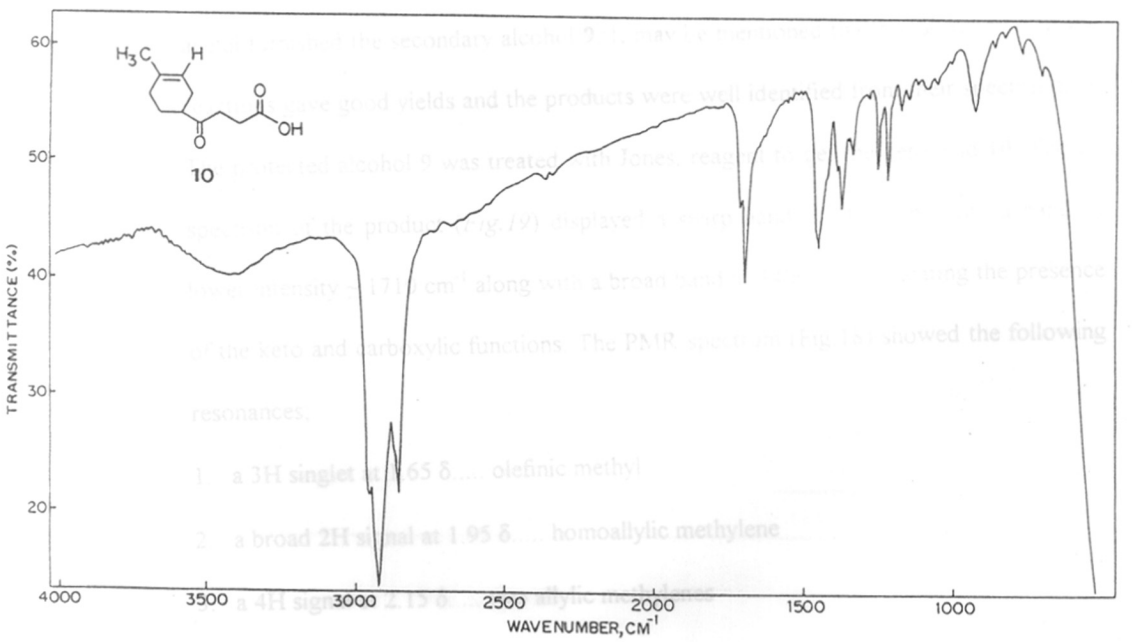


FIG. 19: IR SPECTRUM OF 4-(4'-METHYL CYCLOHEXENE-3) - 4 KETO BUTANOIC ACID-10

Although the *Scheme-1.28* looked attractive, we were not very sure of realizing this result for the following reasons -

1. The success of this reaction in realizing the bicyclic ketone **7** was primarily due to the fact that it was a cyclopentane ring being formed in the process. Among annulations, for various reasons including entropy cyclopentane formation is known to be preferred over cyclooctane. Most of the workers, who have utilized the metal-catalyzed carbene insertion into C-H bonds, have observed the cyclopentane annulation as a preferred process.
2. As already stated in the introduction, formation of medium size rings, especially an eight membered ring, is beset with problems of *trans* annular interactions. With these considerations, we thought of investigating the suitability of this reaction for getting AB ring system initially with a model lacking the gem-dimethyl groups.

Diels-Alder reaction of isoprene with acrolein readily afforded the aldehyde **8** *(Scheme-1.28,* see Experimental). The Grignard reaction of **8** with 3-bromopropanal acetal furnished the secondary alcohol **9**. It may be mentioned that the above two of the reactions gave good yields and the products were well identified from their spectral data. The protected alcohol **9** was treated with Jones, reagent to get the keto acid **10**. The IR spectrum of the product (*Fig.19*) displayed a sharp band at 1699 cm^{-1} and a band of lower intensity $\simeq$ 1710 cm^{-1} along with a broad band at 3400 cm^{-1} indicating the presence of the keto and carboxylic functions. The PMR spectrum (Fig.18) showed the following resonances;

1. a 3H singlet at 1.65 δ..... olefinic methyl
2. a broad 2H signal at 1.95 δ..... homoallylic methylene
3. a 4H signal at 2.15 δ..... two allylic methylenes

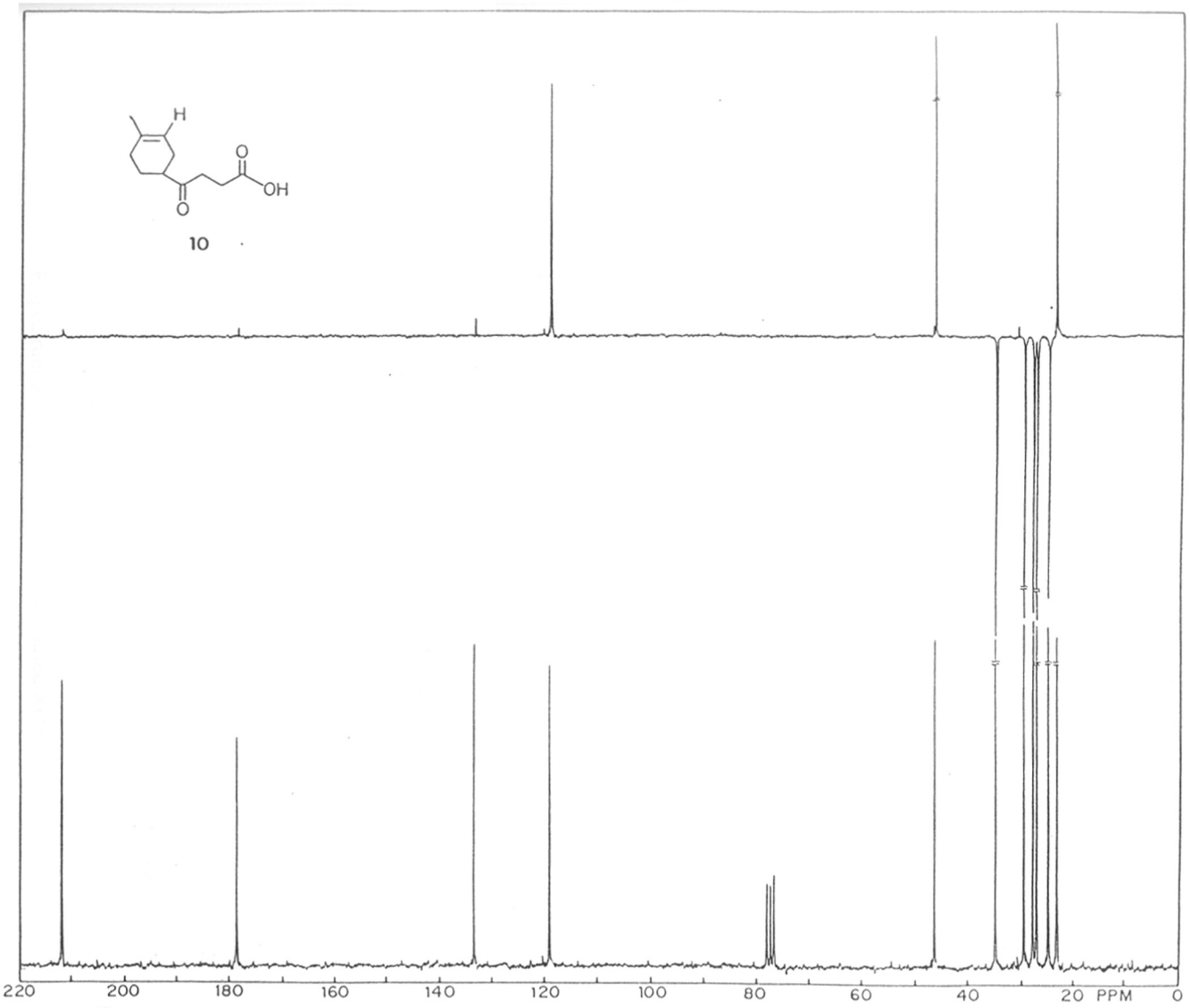


FIG. 20: ^{13}C-NMR SPECTRUM OF 4-(4'-METHYL CYCLOHEXENE-3)-4-KETO BUTANOIC ACID-10

4. a 3H multiplet at 2.65 δ..... one of the methylenes adjacent to the carbonyl group and a methine proton
5. a 2H multiplet at 2.85 δ..... the other methylene adjacent to the carbonyl group
6. a 1H multiplet at 5.40 δ..... olefinic proton.

The above spectral data clearly indicated that the compound on hand was the keto acid **10** and this was further confirmed by the ^{13}C-NMR spectrum. The ^{13}C-NMR spectrum of the keto acid **10** *(Fig.20)* clearly indicated all the carbon atoms in terms of the following:

(a)	113.61, 178.60 and 211.00 δ	... Three quarternary carbons
(b)	119.00 and 46.30 δ	... Two tertiary carbons
(c)	24.86, 27.03, 27.69, 29.35 and 34.82 δ	... Five secondary carbons
(d)	23.24 δ	... One primary carbon

Treatment of the acid chloride of **10** with diazomethane gave the required α-diazo ketone **11** The diazoketone displayed the characteristic band at 2100 cm^{-1} in its IR spectrum and also a broad 1H signal at 5.12 δ in the PMR spectrum.

$BF_3.OEt_2$ catalyzed intramolecular reaction of the olefinic α-diazoketone 11 to 12

The diazoketone **11** taken in ethylene dichloride was treated with 2% $BF_3.OEt_2$ at 0°C under stirring. The reaction mixture was allowed to warm up to room temperature and stirring was continued for 3 hours. The product obtained on a standard work-up, showed to comprise a few less polar impurities/side products along with a major more polar product. The major product was brought out by elution with 10% Ethylacetate in petroleum ether on a column of silica (see Experimental).

The IR spectrum of the product *(Fig.23)* displayed bands at 1700 and 1740 cm^{-1} indicating two ketonic functions. The PMR spectrum *(Fig.22)* was quite conspicuous by

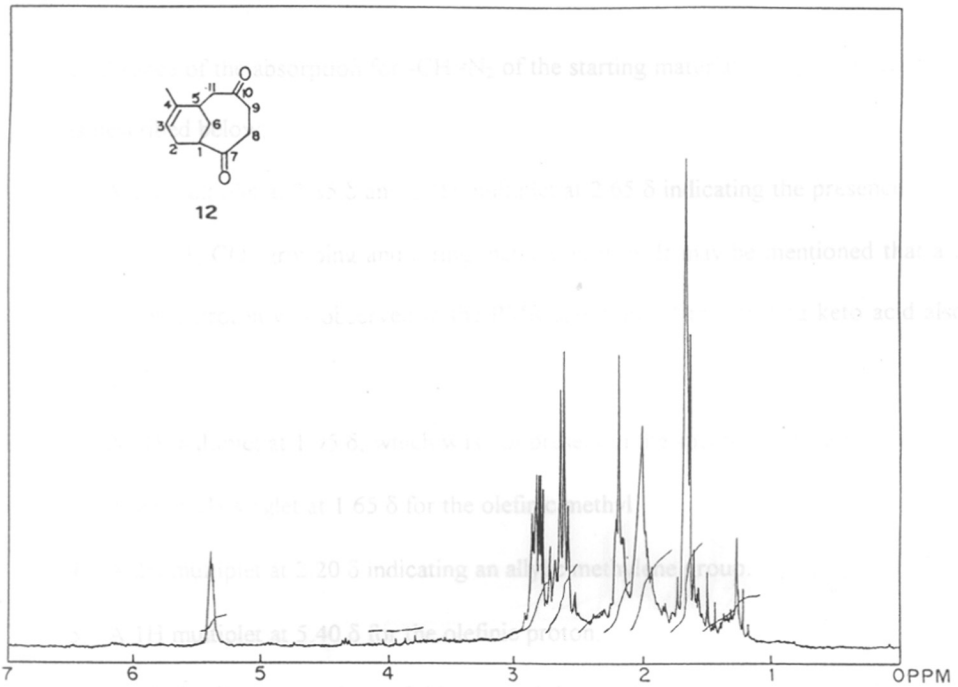


FIG.22 : PMR SPECTRUM OF BICYCLO (5,3,1) 4-METHYL DODECA-7, 10 DIONE - 12

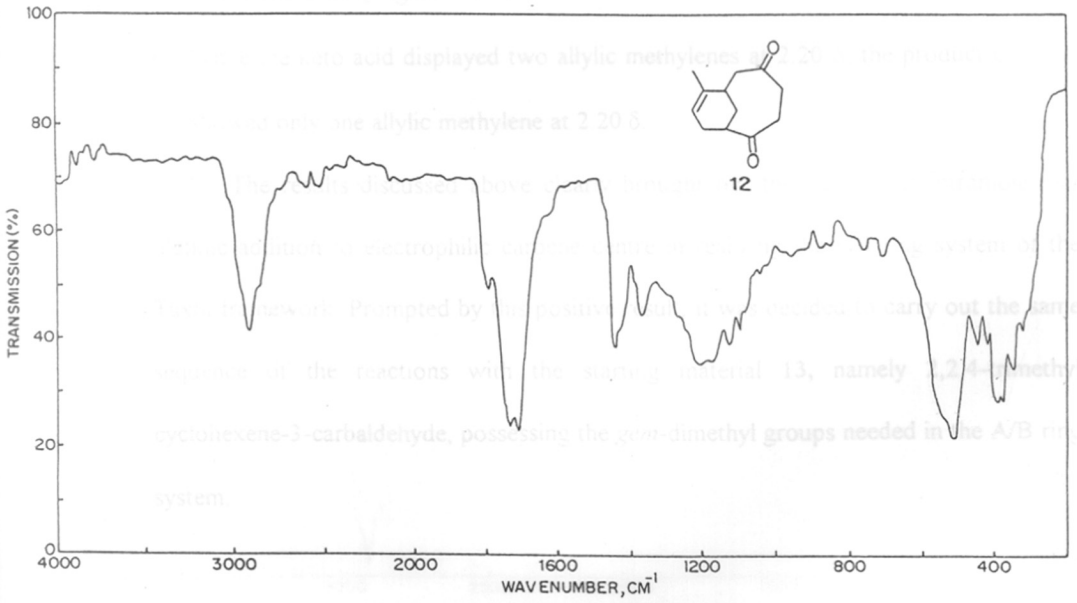


FIG.23: IR SPECTRUM OF BICYCLO (5,3,1) 4-METHYL DODECENE-3-7, 10 DIONE - 12

its absence of the absorption for -CH=N_2 of the starting material and showed resonances as described below;

1. A 2H multiplet at 2.85 δ and a 3H multiplet at 2.65 δ indicating the presence of -CO-CH_2-CH_2-CO- grouping and a ring methine proton. It may be mentioned that a ring methine proton was observed in the PMR spectrum of the starting keto acid also at 2.65 δ.
2. A 3H multiplet at 1.95 δ, which was not present in the spectrum of starting acid.
3. A sharp 3H singlet at 1.65 δ for the olefinic methyl
4. A 2H multiplet at 2.20 δ indicating an allylic methylene group.
5. A 1H multiplet at 5.40 δ for the olefinic proton.

A detailed comparison of this spectral data with that of the keto acid brings forth ample evidence for the occurrence of cyclization yielding the desired bicyclic system. The observations are as follows:

- Occurrence of an additional 1H methine signal at 1.95 δ, so also an additional methylene C-CH_2-signal at 1.95 δ
- While the keto acid displayed two allylic methylenes at 2.20 δ, the product on hand showed only one allylic methylene at 2.20 δ.

The results discussed above clearly brought out the success of intramolecular olefinic addition to electrophilic carbene centre in realizing the AB ring system of the Taxol framework. Prompted by this positive result, it was decided to carry out the same sequence of the reactions with the starting material **13,** namely 2,2,4-trimethyl cyclohexene-3-carbaldehyde, possessing the *gem*-dimethyl groups needed in the A/B ring system.

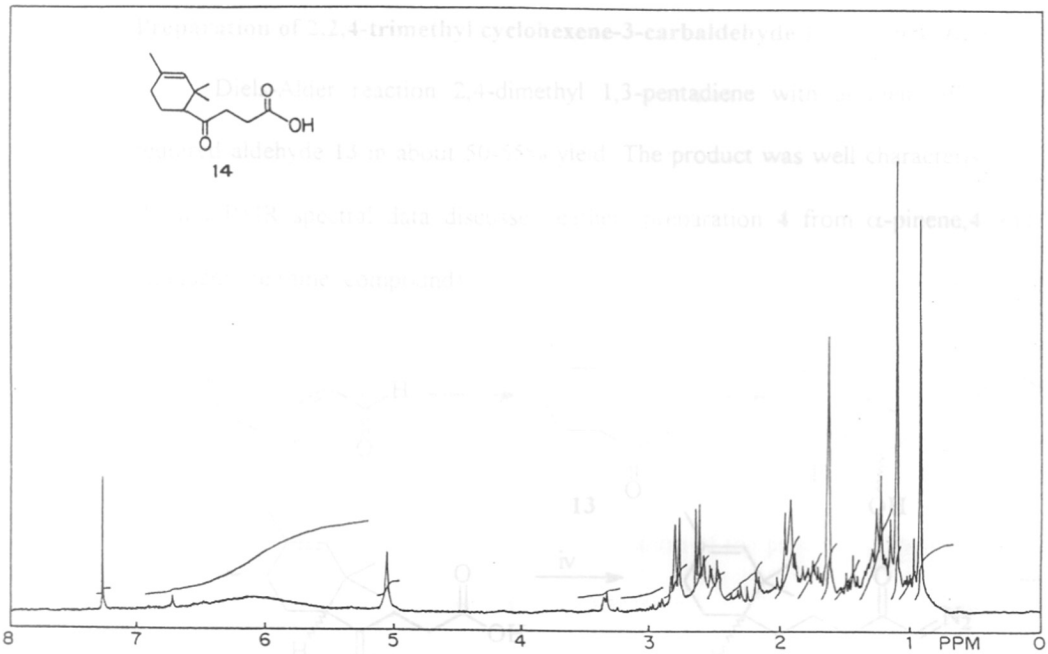


FIG.25 : PMR SPECTRUM OF 4-(2',2',4'-TRIMETHYL CYCLOHEXENE-3)4-KETO BUTANOIC ACID - 14

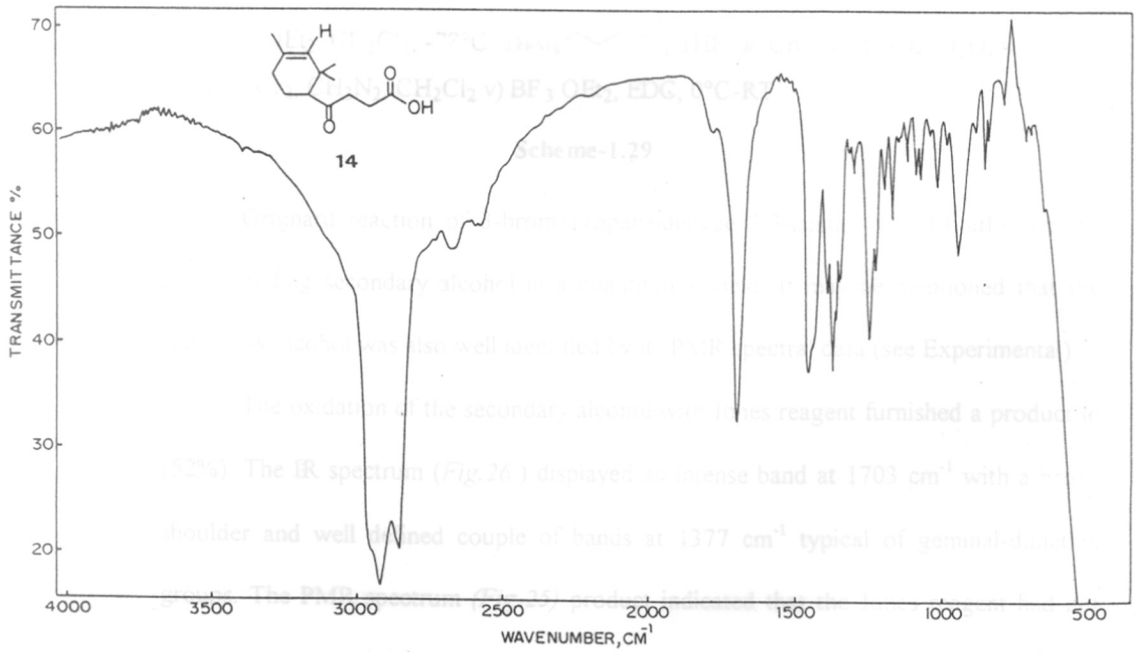
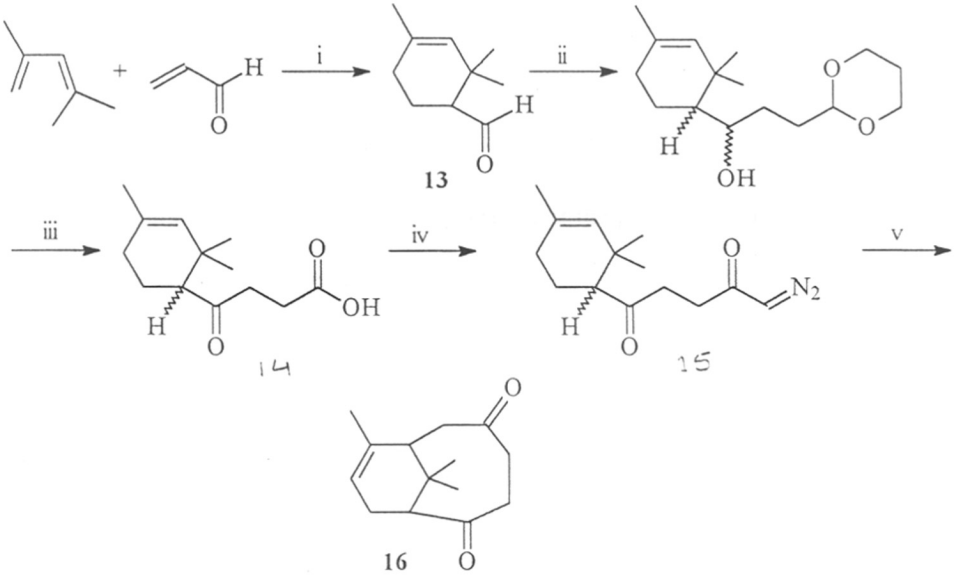
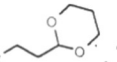


FIG.26 : IR SPECTRUM OF 4-(2',2',4'-TRIMETHYL CYCLOHEXENE-3)4-KETO BUTANOIC ACID - 14

Preparation of 2,2,4-trimethyl cyclohexene-3-carbaldehyde 13 *(Scheme-1.29)*

Diels-Alder reaction 2,4-dimethyl 1,3-pentadiene with acrolein afforded the required aldehyde **13** in about 50-55% yield. The product was well characterised by its IR and PMR spectral data discussed earlier (preparation **4** from α-pinene,**4** and **13** represent the same compound).



i) BF_3OEt_2, CH_2Cl_2, -78°C. ii) BrMg  , THF. iii) CrO_3, H_2SO_4, H_2O, 0°C-RT
iv) $SOCl_2$, CH_2N_2, CH_2Cl_2 v) BF_3OEt_2, EDC, 0°C-RT

Scheme-1.29

Grignard reaction of 3-bromopropanaldehyde 1,3-acetal with **13** afforded the corresponding secondary alcohol in a quantitative yield. It may be mentioned that the secondary alcohol was also well identified by its PMR spectral data (see Experimental).

The oxidation of the secondary alcohol with Jones reagent furnished a product in (52%). The IR spectrum (*Fig.26.*) displayed an intense band at 1703 cm^{-1} with a broad shoulder and well defined couple of bands at 1377 cm^{-1} typical of geminal-dimethyl groups. The PMR spectrum *(Fig-25)* product indicated that the Jones reagent had not

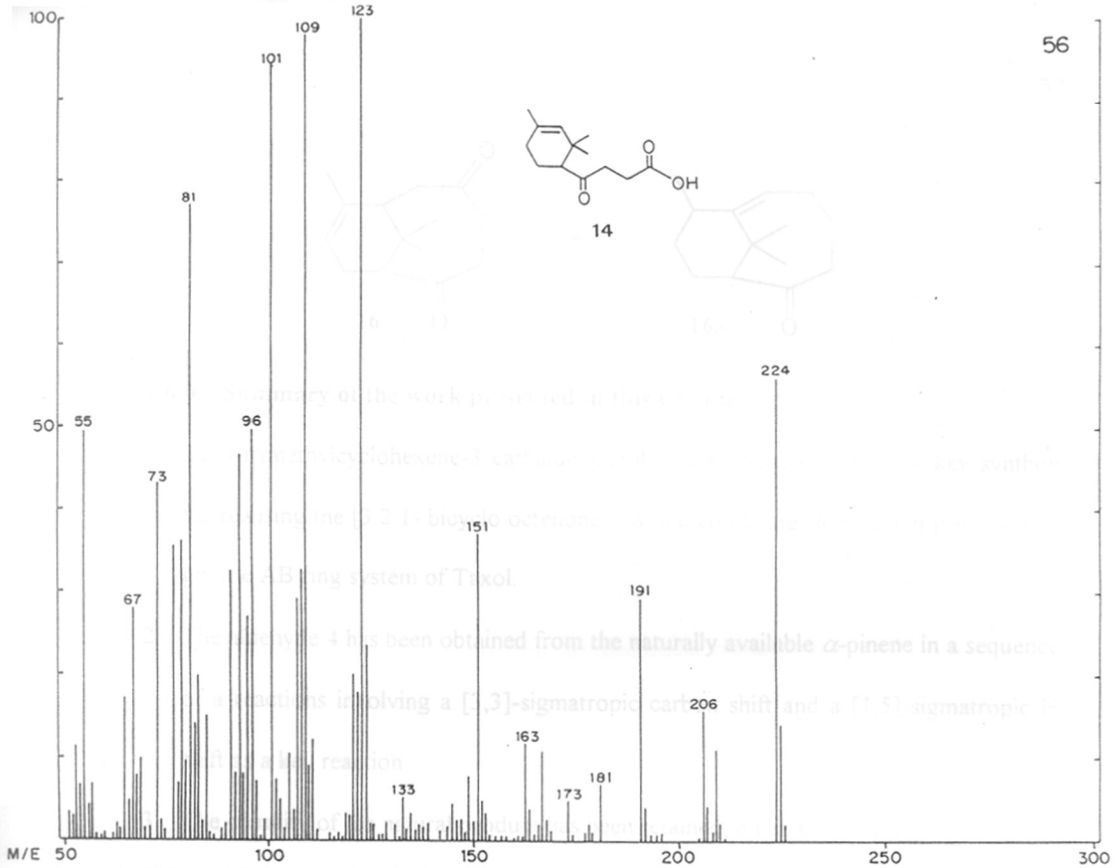
only oxidised the secondary alcohol to the corresponding ketone but also oxidised the protected terminal aldehyde to the corresponding acid. The spectrum displayed 3H singlets at 0.90 δ, 1.10 δ and 1.65 δ for the gem-dimethyl and olefinic methyl groups. A remarkable feature of spectrum was two 2H double doublets at 2.56 δ and 2.75 δ, suggesting the presence of $-CO-CH_2-CH_2-CO$ group; a well defined double doublet centered at 2.50 δ integrating for a proton was observed attributable to the methylene proton adjacent to the carbonyl group. Two more 2H multiplets were noticeable at 1.20 δ and 1.95 δ, ascribable to a methyl group and a allylic methylene groups respectively. The above spectral data enabled the characterization of the product as the keto acid **14**. In addition, the compound showed a molecular ion m/z = 224 needed for $C_{13}H_{20}O_3$ in its mass spectrum.

Intramolecular cyclization reaction with carbenoid centre leading to cyclo octane ring:

The acid chloride of **14** was treated with an etherial solution of diazomethane to get the corresponding α-diazoketone **15**. Into a solution of this diazoketone in ethylene dichloride, was slowly introduced a 2% solution of BF_3 etherate at 0°C. The reaction mixture was stirred and allowed to warm up to the ambient temperature. The progress of the reaction was monitored by TLC and when the starting diazo compound totally disappeared, the product was isolated by a standard work-up.

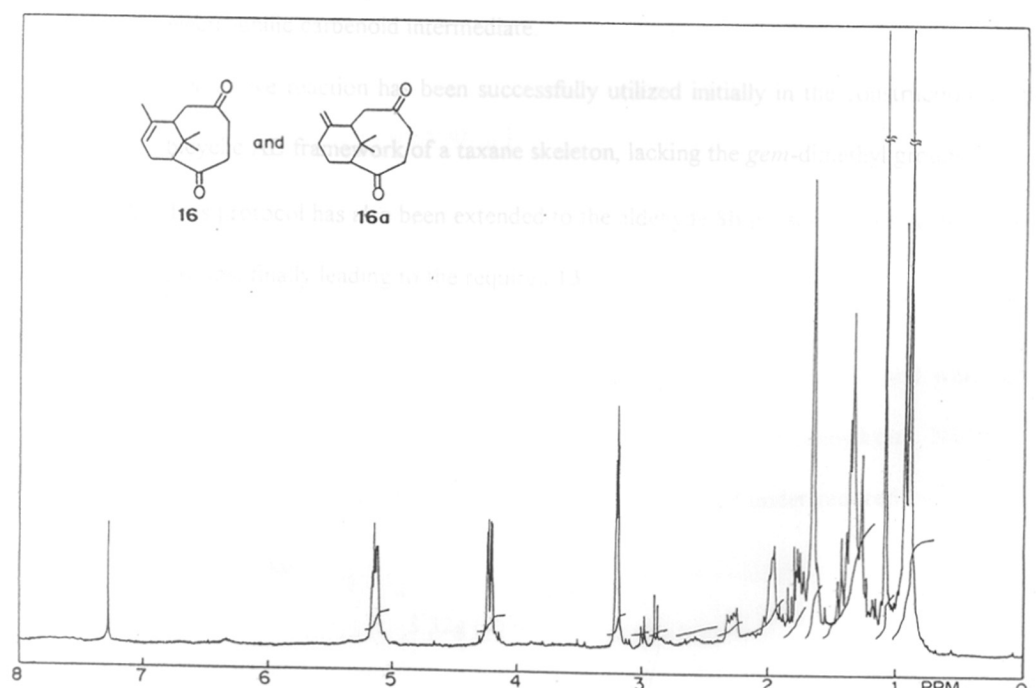
The PMR spectrum of the product *(Fig.28)* was conspicuously different from that of the starting keto acid. The spectrum displayed two 3H singlets at 0.90 δ and 1.10 δ for the *gem* dimethyl groups and a sharp 3H singlet at 1.65 δ for the olefinic methyl group, in addition to the 1H multiplet at 5.15 δ for the olefinic proton. An interesting feature of the spectrum was the occurrence of two additional singlets at 0.95 δ and 1.00 δ and a 2H double doublet centered at 4.25 δ indicating the presence of the isomeric *exo*-methylene product. Another remarkable feature of this spectrum was the occurrence of a double doublet centered at 2.95 δ integrating for a proton and which could be attributed to the ring methine adjacent to a carbonyl group. Similarly, a double doublet integrating for a proton was noticeable at 2.30 δ. While one of the methylenes adjacent to the carbonyl group could be observed at 1.95 δ, the other similarly situated methylene and the allylic methylene could not be precisely located, although multiplets were noticed between 1.25 δ and 1.60 δ.

From the above spectral data, it could be deduced that the product on hand was a mixture of the endocyclic olefinic bicyclo diketone (**16**) and its *exo*-olefinic isomer (**16a**) with the predominance of the former.



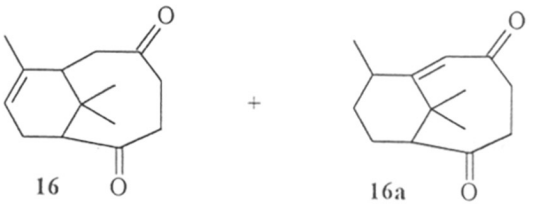
14

FIG. 27: MASS SPECTRUM OF 4-(2,2,4-TRIMETHYL CYCLOHEXENE-3) 4-KETO BUTANOIC ACID - 14



16 16a

FIG. 28: PMR SPECTRUM OF BICYCLO (5,3,1) 2,2,4 TRIMETHYL DODECENE - 16



16 16a

1.6.0 Summary of the work presented in this Chapter:

1. 2,2,4-trimethylcyclohexene-3 carbaldehyde-**4** has been recognised as a key synthon for realising the [3.2.1- bicyclo octenone **7** which constitutes a potential precursor to get the AB ring system of Taxol.
2. The aldehyde **4** has been obtained from the naturally available α-pinene in a sequence of a reactions involving a [3,3]-sigmatropic carbon shift and a [1,5]-sigmatropic H shift as a key reaction.
3. The chirality of the natural product has been retained in the aldehyde **4**.
4. The bicyclo octenone **7** has been realized starting from aldehyde **4** employing the key reaction of intramolecular BF_3 etherate catalysed nucleophilic addition to an electrophilic carbenoid intermediate.
5. The above reaction has been successfully utilized initially in the construction of the bicyclic AB framework of a taxane skeleton, lacking the *gem*-dimethyl groups.
6. This protocol has also been extended to the aldehyde **8b** possessing the *gem*-dimethyl groups, finally leading to the required **13**.

1.8.0 Experimental

1. Preparation of (-) verbenol acetate: (2)

This compound was prepared according to the literature procedure.

To a stirred solution of α-pinene (5.00 g, 0.036 mol) in dry benzene was added lead tetraacetate (16.27 g, 0.04 mol) in one lot; the reaction mixture was stirred under reflux. The progress of the reaction was monitored by GLC and when the starting α-pinene was totally absent (6 h.), the reaction mixture was cooled to room temperature and filtered. The filtrate was washed with water, dried over anhydrous sodium sulphate and was concentrated. The residue was distilled under reduced pressure (6.00 g.).

Yield : 6.00 g. (85%)

BP : 110°C / 2mm of Hg

IR*(Fig .3)* : 1710 cm^{-1}

PMR($CDCl_3$200 MHz, *Fig .2*) δ : 0.96 (s, 3H), 1.40 (s, 3H), 1.80 (s, 3H), 2.12 (s, 3H), 2.30 (m, 5H), 5.30 (s, 1H).

$[\alpha]_D^{20}$: -101 (neat)

2. Preparation of (-) verbenol: (3)[42]

To a solution of verbenol acetate (5.0 g, 0.025 mol) in methanol was added 10% aqueous KOH (0.5 g in 5ml H_2O) and stirred at 0°C. The reaction was monitored by TLC and when the starting material was absent (48 h.), the solvent was removed under reduced pressure. The crude product was taken in dichloromethane and washed with water until neutral. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give crude verbenol, which was distilled under reduced pressure to get pure verbenol.

Yield : 3.32g (85%)

BP	:	120°C/7 mm, Reported 108°C /7mm
IR(*Fig-5)*	:	3400, 1640, 1420, 1380, 900, 800
PMR(80 MHz,	:	0.85 (s, 3H), 1.30 (s, 3H), 1.70 (s, 3H), 1.9 to 2.40 (m, 5H),
$CDCl_3$,)δ		4.20 (brs, 1H), 5.27 (brs, 1H)
(Fig.4)		
$[\alpha]_D^{20}$	:	−98° Reported $[\alpha]_D^{20}$ = -101°, neat

3. Preparation of 2,2,4-trimethyl hex-3-ene aldehyde (4) by pyrolysis of (3)

The flash pyrolysis unit employed is depicted in *Fig 1* It consisted of a vertically placed quartz tube (35 cm x 1 cm) with a dropping funnel for addition, connected to a vacuum line and provided with a collection flask housed in a cold bath. The quartz tube was closely packed with fine pieces of silica and was electrically heated by a nichrome ribbon uniformly would around it, which was insulated with asbestos padding. A fine temperature control could be realized by the use of dimmerstat and the temperature inside the reactor was measured using a Cr-Al thermocouple.

The pyrolysis was carried out in an atmosphere of N_2 to prevent oxidation of the products and polymerization as well.

To attain the proper temperature necessary for the pyrolysis, an initial calibration on the heating system was to be done. This could be easily achieved by varying the dimmerstat settings and recording the internal temperature over a wide range and covering a span of about 250-350°C. This resulted in a fine setting to realise the temperature with a variance of 5-10°C.

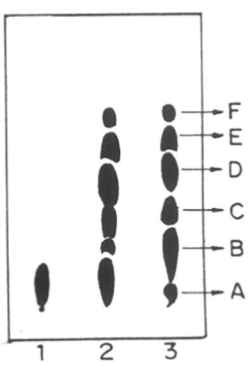
Pyrolysis of Verbenol:

A 1% solution of (S)-verbenol in dry petroleum ether was added dropwise (12 ml per minute) under the atmosphere of nitrogen gas, through the quartz tube which was preheated to 350°C (8 min). The pyrolysed product was collected at the bottom of the

reactor in a receiver which was cooled by ice-salt mixture. The TLC of pyrolysate showed five spots. The pyrolysate was concentrated, the crude product (0.9 g) was chromatographed using SiO_2 (40 g) using petroleum ether, ethyl acetate as eluents on a column length of 35 cm and internal diameter 2 cm. The analysis of the chromatographed product is given in Table-I.

Table-I: Chromatography of the pyrolysate

Fraction No.	Eluent	Volume ml.	Remarks	TLC of the crude product
1	Pet ether	400	No compound appeared	
2	1% EtOAc in pet.ether	400	Mixture of E & F	
3	4% of EtOAc	200	Single spot of E	
4	- do -	200	- do -	
5	- do -	200	- do -	
6	- do -	200	Mixture of E & D	
7	- do -	200	Mixture of C, C & D	
8	- do -	200	Mixture of A, B & C	
9	- do -	200	Mixture of A & B	
10	- do -	200	No spot is seen	



The fractions 3-5 were pooled and concentrated. Distillation under reduced pressure gave a pure product 3-5. 3,4.

The same experiment was repeated on a large scale, starting with 5.0 g of (S)-verbenol. The crude product was chromatographed on silica gel as described above and the pure aldehyde (1.70 g, 37%) was obtained. The IR and PMR data were identical with those described above. This large scale experiment was repeatedly carried out to obtain multigrams of the aldehyde.

Yield	:	1.70 g, 37%
BP	:	80°C/18mm , Reported 68 c/12mm [42]
IR (cm^{-1}) (*Fig*-7)	:	2990, 2640, 1730, 1640, 1450, 1390, 1380, 1200, 1010, 830
PMR (200 MHz	:	1.10 (s, 3H), 1.20 (s, 3H), 1.62 (s, 3H), 1.7-2.4 (m, 5H), 5.02
$CDCl_3$ *Fig-6*) δ		(s, 1H), 9.80 (d, 1H).
$[\alpha]_D^{20}$	:	-53°C (neat)

Preparation of 2,2,4-trimethyl cyclohex-3-ene carboxylic acid (5)

The aldehyde (0.5 g, 3.28 mmol) was dissolved in ether and treated with freshly prepared silver oxide (0.760 g, 0.40 mmol). The reaction mixture was stirred and the reaction was monitored by TLC; when the starting material totally disappeared (3h.). The reaction mixture was filtered, concentrated and the crude product purified by passage through a column of SiO_2 to obtain 550 mg of the product.

Yield	:	98%
mp	:	80°C , Lit[42] = 72°C
I.R. (neat,*Fig-9)*	:	2990, 1700, 1440, 1370, 1200, 1090, 1020, 880, 820 cm^{-1}
PMR (80 MHz	:	0.92 (s, 3H), 1.12 (s, 3H), 1.56 (5, 3H), 1.62-2.2 (m, 5H), 5.0
$CDCl_3$*Fig 8*) δ		(brs, 1H), 9.80 (bs, 1H).

Preparation of Diazoketone (6):

The acid **5** (5.00 g, 0.029 mol) in ether at 0°C and the reaction mixture was taken in dry ether at 0°C and the reaction mixture was allowed to warm upto room temperature. When an aliquote of the reaction mixture showed the absence of 1700 cm^{-1} band and appearance of a band at 1800 cm^{-1} (2 h) in the IR spectrum, excess $SOCl_2$ was distilled out and the residue was taken in dry ether. This solution was added in a dropwise manner to an etheral solution of freshly prepared diazomethane containing

triethylamine (5.00 g, 0.034 mol). The reaction mixture was stirred till the disappearance of the 1800 cm^{-1} band and appearance of a clear 2100 cm^{-1} band. The crude product obtained after filtration and evaporation of the solvent was passed through a column of silica gel, when a clear yellow liquid product ensued.

Yield : 314g. (60%)

IR (neat,*Fig 11)* : 2980, 2100, 1630, 1450, 1370, 1340, 1130, 940, 840, 740 cm^{-1}

PMR (80 MHz : δ 1.04 (s, 3H), 1.16 (s, 3H), 1.72 (s, 3H), 1.80-2.00 (m, 4H),

$CDCl_3$ *Fig 10)* δ 2.20 (s, 1H), 5.12 (s, 1H), 5.32 (s, 1H).

Preparation of bicyclo [3.2.1] heptenone (7)

To a cooled solution of diazoketone (3.00 g, 1.56mmol) in dry ethylene dichloride was added a 2% $BF_3{\cdot}OEt_2$ solution in ethylene dichloride in a dropwise manner with stirring. The progress of the reaction was monitored by IR spectra of reaction aliquotes which showed a gradual disappearance of the 2100 cm^{-1} band and the appearance of a new band at 1745 cm^{-1}. When the diazoketone band completely disappeared (3 h), the reaction mixture was washed with saturated sodium bicarbonate (20 ml x 3), followed by washing with water. The crude product obtained on usual work was passed through a short column of silica gel and distilled (1.43 g.).

Yield : 1.43 g. (56%)

BP : 112°C/5.0 mm of Hg

IR (neat,*Fig 13)* : 2925, 1745, 1447, 1415, 1387, 1337, 1309, 1265, 1198, 1177, 1105, 1055, 1018, 909, 811, 766, 660 cm^{-1}

PMR (80 MHz : 1.10 (s, 3H), 1.30 (s, 3H), 1.65 (s, 3H), 2.20 (m, 2H), 2.35

$CDCl_3$ *Fig .12)* δ (m, 2H), 2.60 (m, 2H), 5.10 (bs, 1H).

^{13}C-NMR (50MHz) *(Fig 14)*	:	221, 141, 116, 54, 47, 46, 38, 29, 26, 23 and 20
Mass	:	m/z 164 (M^+, 50), 149(7), 135(7), 121(20), 107(100), 93(80), 77(40)
$[\alpha]_D^{20}$	:	-5.8° (c=1.12, MeOH)

Preparation of 4-methyl cyclohex-3-ene carbaldehyde (8)

To a cooled and stirred solution (-78°C) of isoprene (20 g, 0.293 mol) and acrolein (16.8 g, 0.3 mol) in dry CH_2Cl_2, a 2% solution of $BF_3.OEt_2$ (0.854 ml) in dry CH_2Cl_2 was added drop by drop and the reaction mixture was slowly warmed up to room temperature and further stirred for 5 h. The reaction mixture was taken in CH_2Cl_2 (150 ml) and washed successively with sodium bicarbonate (50 ml x 3) and water (50 ml x 2) and the organic extract was dried over anhydrous sodium sulphate. After removal of solvent, the crude product was distilled under reduced pressure.

BP	:	50°C / 0.3mm of Hg
Yield	:	18.2 g. (50%)
I.R. (neat,*Fig 17)*	:	2900, 1720, 1440, 1350, 1240, 1150, 790 and 580 cm^{-1}
PMR 60 MHz	:	1.34 (brs.3H), 1.64 (s, 3H), 2.00 (m, 4H), 5.10 (d, 1H) and
CCl_4 *Fig-16*) δ		9.34 (s, 1H).

Preparation of 4-(4'-methyl 3'-cyclohexene)-4-ketobutanoic acid (10)

i) Grignard reaction:

To a pre-synthesised Grignard reagent from 3-bromopropanaldehyde (1,3-acetal (25.35 g, 0.13 mol) and Magnesium (3.12 g, 0.13 mol), a solution of the aldehyde **4a** (15.0 g, 0.12 mol) in dry THF, was added dropwise. The reaction mixture was refluxed under stirring for 30 minutes and when it cooled to room temperature, it was quenched with ice-cold water, addition of 150 ml of ether effected the separation of layers. The

aqueous layer was extracted with ether (100 ml x 3) and combined organic layer was washed with water and brine. Removal of solvent afforded a crude alcoholic product, 26.5 g. (92%)

IR (neat, cm^{-1}) : 3400

PMR ($CDCl_3$) δ : 1.60 (s, 3H), 1.92 (s, 3H), 2.00 (brs, 5H), 2.62 (m, 3H), 2.85 (m, 2H), 3.53-4.08 (5 multiplets, 6H), 4.46 (d, 1H) and 5.20 (m, 1H).

ii) Oxidation of the secondary alcohol (9) with Jone's reagent to 4, (4'-methyl-3-cyclohexyl)4-ketobutanoic acid (10)

The above crude alcohol **(9)** (20.0 g, mol) was taken in ether and cooled to 0°C to -5°C, was slowly treated with Jone's reagent (100.0 ml) (Jones reagent was synthesised by using 20.0 g of CrO_3 was dissolved in 50 ml cold water and 14.0 ml of H_2SO_4 was treated slowly and make the total volume to 100 ml). The reaction mixture was stirred for 32 h at room temperature. The organic layer was separated and the aqueous layer was washed with ether (100 ml x 5). The combined organic layer was washed with water, brine and dried over anhydrous sodium sulphate. Evaporation of the solvent afforded the keto acid (**10**) (6.4 g, 40% yield). The crude product was passed through a column of SiO_2, using pet.ether and Ethylacetate (96:4) as a solvent to obtain pure product(**10**)in 40 % yield.

Mp : 42°C

IR (neat,*Fig 19)* : 2923, 2853, 2673, 1699, 1710, 1458, 1377, 12.58 and 936.

PMR(200MHz $CDCl_3$ *Fig 18*) δ : . 1.65 (s, 3H), 1.95 (bs, 3H), 2.15 (bs, 4H), 2.65 (m, 3H), 2.85 (m, 2H) and 5.40 (m, 1H).cm^{-1}

^{13}C-NMR (53Mhz) : 23.24, 24.86, 27.03, 27.69, 29.35, 34.82, 46.30, 119.19,

(*Fig* –20) 133.61, 178.60, 211.75

Mass : m/z 196 (M^+, 5). 178(30), 163(15), 135(10), 123(55), 118(75), 105(20), 101(50), 95(95), 85(15), 79(50), 73(70), 67(95), 60(10), 55(100).

Preparation of bicyclic ketone (12)

i) Preparation of Diazoketone**(11)** from 4(4'-methyl 3'-cyclohexene) 4-ketobutanoic acid **(10)**

To a cooled solution of keto acid **(10)** (4.0 g, 0.02 mol) in dry ether; $SOCl_2$ (3.56 g, 0.03 mol) was added in a dropwise manner. The reaction mixture was stirred for 8.0 hr. at room temperature. The completion of reaction was confirmed by disappearance of carbonyl band of acid at 1699 cm^{-1} and appearance of new acid chloride band at 1800 cm^{-1}. After removal of solvent and excess $SOCl_2$, the residue was taken in dry ether and added to a freshly prepared solution of diazomethane in dry ether containing $(C_2H_5)_3N$ (3.0 g, 0.03 mol) drop by drop. The progress of reaction mixture was monitored by IR spectra of aliquots, wherein the complete disappearance of acid chloride band at 1800 cm^{-1} and appearance of new band at 2100 cm^{-1} ensured the completion of the completion of the reaction. The reaction mixture was filtered through celite and solvent was removed to obtain the diazoketone **(10a)**

Yield 1.70 gm (38%).

IR : 2100 cm^{-1}

PMR (200 MHz $CDCl_3$), δ : 1.70 (s, 3H), 2.00 (m, 3H), 2.20 (m, 3H), 2.65 (t, 3H), 2.80 (m, 2H), 5.25 (s, 1H), 5.40 (s, 1H).

ii) Boron trifluoride catalysed intramolecular cyclization reaction of the olefinic α-diazoketone to bicyclo nonane (12)

To a cooled solution of diazoketone (1.7 g, 0.007 mol) in dry EDC, a solution of $BF_3.(OEt)_2$ in EDC (0.2 ml/5ml EDC) was added drop by drop under stirring. The reaction mixture was allowed to reach the room temperature. The progress of the reaction was monitored by IR spectroscopy, wherein the complete disappearance of 2100 cm^{-1} band of diazoketone and appearance of a new band at 1740 cm^{-1} ensured the completion of the reaction. The reaction mixture was washed with saturated sodium bicarbonate, water and dried over anhydrous sodium sulphate. Removal of solvent gave the crude product (0.723 g, 49%). Passage of the product through a column of SiO_2 and elution with a mixture of petroleum ether and ethyl acetate (92:8) gave a pure product.

Yield		0.512 g (34%)
IR ($CHCl_3$) (*Fig –23*)	:	2920, 1740, 1700, 1450, 1380, 1210, 1170, 1140, 1100 cm^{-1}
PMR (200 Mhz $CDCl_3$ *Fig –22*) δ	:	1.65 (s, 3H), 1.95 (bm, 3H), 2.20 (br s, 2H), 2.40 (d, 1H), 2.65 (t, 3H), 2.85 (m, 2H), 5.40 (m, 1H)
Mass	:	192 (M^+, 5)

Preparation of 2,2,4-trimethyl 3-cyclohexene carbaldehyde (13)

To a cooled and stirred solution (-78°C) of 2.4 dimethyl 1,3-pentadiene (20.0 g, 0.20 mol) and acrolein (12.0 g, 0.21 mol) in dry CH_2Cl_2, a 2% solution of $BF_3.(OEt_2)$ (0.8 ml) was slowly warmed up to room temperature and further stirred for 5 hrs. The reaction mixture was taken in CH_2Cl_2 (200 ml) and washed successively with sodium bicarbonate (50 ml x 3) and water (50 ml x2) and the organic extract was dried over anhydrous sodium sulphate. After removal of solvent, the crude product was distilled

under reduced pressure.

B.P.	:	80°C/18mm
Yield	:	15.0 g (50%)
IR (neat)	:	2990, 2640, 1730, 1640, 1450, 1390, 1380, 1200, 1010 and 830 cm^{-1}
PMR (200 MHz $CDCl_3$,) δ.	:	1.10 (s, 3H), 1.20 (s, 3H), 1.62 (s, 3H), 1.70 to 2.40 (m, 5H), 5.02 (s, 1H), 9.80 (d, 1H)

Preparation of 4-(2',2',4'-trimethyl-3'-cyclohexyl)4-keto butanoic acid (14)

However, the carboxylic proton is not observable as the spectrum was not scanned in that region.

(i) Grignard reaction

To a previously prepared Grignard reagent from 3-bromopropanaldehyde 1,3-acetal (10.2 g, 0.10 mol) and magnesium (2.4 g, 0.1mol), a solution of the aldehyde **4** (13.68 g, 0.09 mol) in dry THF, was added dropwise. The reaction mixture was refluxed under stirring for 2.0 hrs and when it cooled to room temperature, it was quenched with ice cold water. Addition of 200 ml of ether effected the separation of two layers. The aqueous layer was extracted with ether (100 ml x 3) and the combined organic layer was washed with water and brine, removal of solvent afforded a crude alcoholic product.

Yield		22.0 g (92%)
IR	:	3500, 1365, 1390 cm^{-1}
PMR (200 MHz) $CDCl_3$, δ	:	0.9 (br s, 6H), 1.20 (4H, br s, 2(CH_2)), 1.37 (s, 2H), (allylic methelene), 1.57 (s, 3H, methyl on double bond), 1.60 to 2.00 (m, 5H), 3.53 to 4.08, five multiplets, 3 methylenes), 4.46 (d, 1H, methylene of acetal) and 4.92 (s, 1H).

(ii) Conversion of alcohol (13) to ketoacid (14)

To a solution of alcohol (**13**) (21.0 g, 0.07 mol) in ether (200 ml) was cooled to 0°C and Jones reagent (synthesized from CrO_3: 15.6 gm, H_2SO_4: 10.6 gm, and water: 54 ml) drop by drop. The reaction mixture was slowly warmed up to room temperature, with continued stirring. Progress of the reaction was monitored by TLC. After the disappearance of the starting alcohol (40 h), the organic layer was separated. The aqueous layer was repeatedly extracted with ether, the combined organic layer was washed with water, brine and dried over anhydrous sodium sulphate. The organic extract was concentrated and passed through a column of SiO_2 and eluted initially with 5% ethylacetate with gradual increase of ethylacetate concentration to 10% ethylacetate in petroleum ether. The keto acid (**14**) showed the following data:

Yield		4.80 g (31%)
IR *(Fig-26)*	:	3400, 2970, 2820, 2650, 1703, 1459, 1377, 1252, 1175 and 951 cm^{-1}
PMR(200MHz $CDCl_3$,*Fig.25*) δ	:	0.90 (s, 3H), 1.10 (s, 3H), 1.20 (m, 2H), 1.65 (s, 3H), 1.95 (m, 2H), 2.50 (dd, 1H), 2.65 (dd, 2H), 2.75 (dd, 2H), 5.10 (s, 1H) and 6.10 (br s, OH)
Mass *(Fig-27)*	:	224 (60, M^+)

Preparation of diazoketone(15)

The acid chloride of the ketoacid (14) (4.0 g, 0.017 mol) on treatment with etherial solution of diazomethane by a procedure, as described earlier, afforded the diazoketone.

Yield		1.6g. (38%)
IR	:	2100 cm^{-1}
PMR	:	Essentially same as that of the corresponding ketoacid without the *gem* dimethyl group (**10a**) but with resonances for the Geminal dimethyl group

Cyclization of the diazoketone (15) to bicyclic dione (16)

To a cooled solution of diazoketone (15) (1.5 g) in dry CH_2Cl_2 was added a cooled solution of $BF_3.(OEt)_2$ in CH_2Cl_2 drop by drop. The reaction mixture was warmed up to room temperature and the progress of reaction mixture was monitored by IR spectroscopy. When the 2100 cm^{-1} of diazoketone band disappears with appearance of new carbonyl band at 1740 cm^{-1} (5 h), the crude product was isolated as previously described.

Yield		0,220 g (15%)
IR (neat)	:	1710 and 1740 cm^{-1}
PMR (200 MHz $CDCl_3$,*Fig-28*) δ	:	0.90 (s, 3H), 1.10 (s, 3H), 1.25-1.60 (m, 4H), 1.65 (s, 3H), 1.95 (m, 2H), 2.30 (m, 1H), 2.95 (dd, 1H), 4.25 (dd, 2H), 5.15 (m, 1H).

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CHAPTER - II

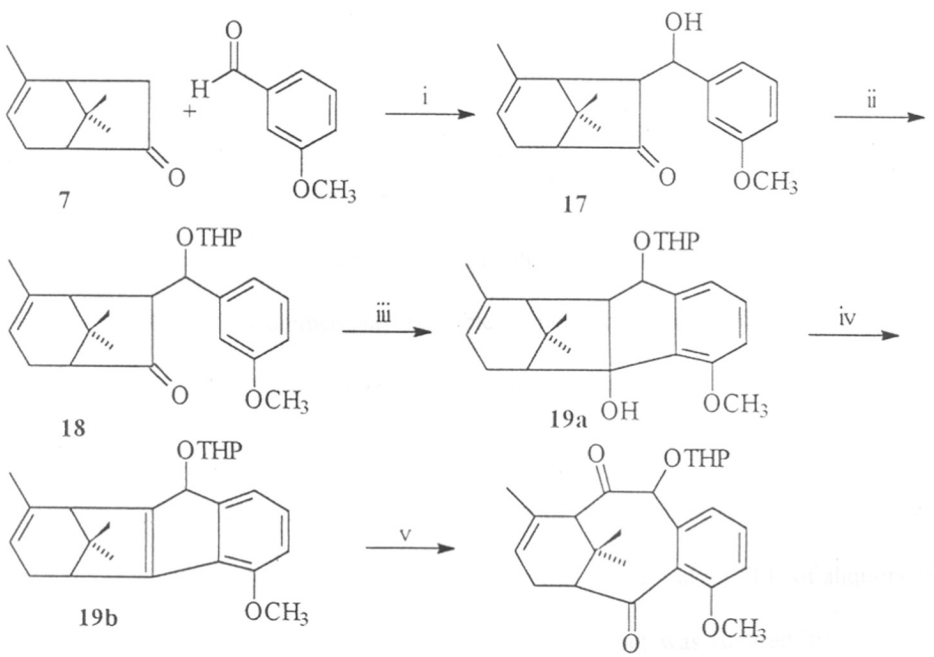
Synthetic Studies Towards Construction of A B C Rings of Taxoid Molecules by use of Bicyclo(3.2.1) octanone

Chapter-II: Synthetic Studies Towards Construction of ABC Rings of Taxoid Molecules

2.1.0 INTRODUCTION:

The previous Chapter described our synthetic efforts towards the construction of 2,2,4-trimethyl cyclohexene-3-carbaldehyde **4** possessing all the structural features of the A-ring of Taxol (1) and a method was described for the construction of the A B framework of taxoid molecules.

In addition, the bicyclo[3.2.1]octanone 7 was synthesized utilising an intramolecular nucleophilic reaction with an electrophilic carbene centre. This ketone was considered to be a potential synthon for the realization of the A B framework of taxoid system. However, this was not realised for A B rings of Taxoids as described in the last Chapter. The present Chapter indicates a retrosynthetic strategy to generate the A B C framework and also our attempts to execute the synthetic protocol. Such a strategy has been shown in *Scheme-2.1* below:



i) LDA, THF, -78-0°C ii) DHP, pTSA, CH_2Cl_2, 0°C
iii) n-BuLi, THF, -30 to -78°C

Scheme-2.1

2.2.0 RESULTS:

Aldol condensation of the bicyclic ketone **7** with readily available *m*-methoxy benzaldehyde should easily generate the secondary alcohol **17** which could be protected as tetrahydropyranyl ether **18**.The selection of *m*-methoxy-benzaldehyde for the condensation had the rationale of realizing heteroatom-directed regioselective lithiation. The ortho-lithiated protected alcohol **18** appeared attractive enough to realize an intramolecular condensation reaction at the carbonyl carbon leading to the tetracyclic intermediate **19a**; a dehydration reaction in the latter should lead to the bridged alkene **19b**. An oxidative cleavage of the olefinic linkage inturn could generate a 1,5-dione with concomitant formation of the required ABC skeleton **19c**, possessing the eight membered central ring. In fact, such an oxidative cleavage in a bicyclic bridged alkene system has been utilized by H.R.Sonawane *et al.*[1] to realize medium and large-sized 1,5-diones, a class of potentially useful synthetic intermediates.

At the outset, the above retrosynthetic *Scheme-2.1* appeared quite feasible and, therefore, its execution was undertaken.

The bicyclic ketone **7** has already been described along with its spectral data in the previous Chapter. Commercially available *m*-methoxybenzaldehyde, the authenticity of which was confirmed by its PMR spectrum, was utilized in the condensation. A solution of the bicyclic ketone **7** in THF was treated with an equimolar amount of LDA at -30°C and a solution of an equimolar quantity of the aromatic aldehyde in THF was introduced at -78°C. The progress of the reaction was monitored by TLC of aliquots and when the ketone totally disappeared (30 min), the product was isolated by a standard procedure (See *Experimental*). The crude product on passage through a column of SiO_2 afforded a pure homogeneous material in a good yield of 76%. Its IR spectrum displayed

bands for both carbonyl and the secondary hydroxyl functionalities and also showed bands typical of the aromatic system. The PMR spectrum of the product (*Fig. 1*) clearly indicated the occurrence of the desired condensation; the spectrum was similar in many ways to that of the starting ketone with the addition of the aromatic system and a secondary alcoholic functionality. This spectrum showed a typical meta-disubstituted aromatic pattern in the region 6.80 to 7.50 δ, besides showing two singlets in a 7:3 ratio at 3.80 δ and 3.85 δ, indicating the OCH_3 on a aromatic ring group. It also showed a one H multiplet at 3.40 δ suggesting the presence of a -CH-OH group, which was also accompanied by a similar resonance of lower intensity. This spectrum displayed two singlets in a similar ratio at 1.60 δ and 1.75 δ for the olefinic methyls. However, three singlets were observed at 0.90, 1.10 and 1.20 δ, suggesting the overlap of one of the methyl group resonance with the corresponding methyl resonance of an isomeric compound. Similarly, the olefinic resonance at 5.0 δ was also accompanied by a similar multiplet at 5.20 δ. The above mentioned spectral features and the data indicated the occurrance of condensation leading to a mixture of diastereomeric products. However, although all the resonances of the methylenes and the methine groups of the starting ketone portion were seen, they were not clearly discernable. From the above PMR data, the product could be characterized as **17**.

As the next reaction was a heteroatom directed lithiation of aromatic ring, it was necessary to protect the hydroxyl function and, therefore, its tetrahydropyranyl ether was prepared. The latter derivative showed satisfactory spectral data.

Intramolecular cyclization *via* lithiation and subsequent reaction at the carbonyl carbon:

The protected alcohol **18** appeared very well set for methoxyl group-directed

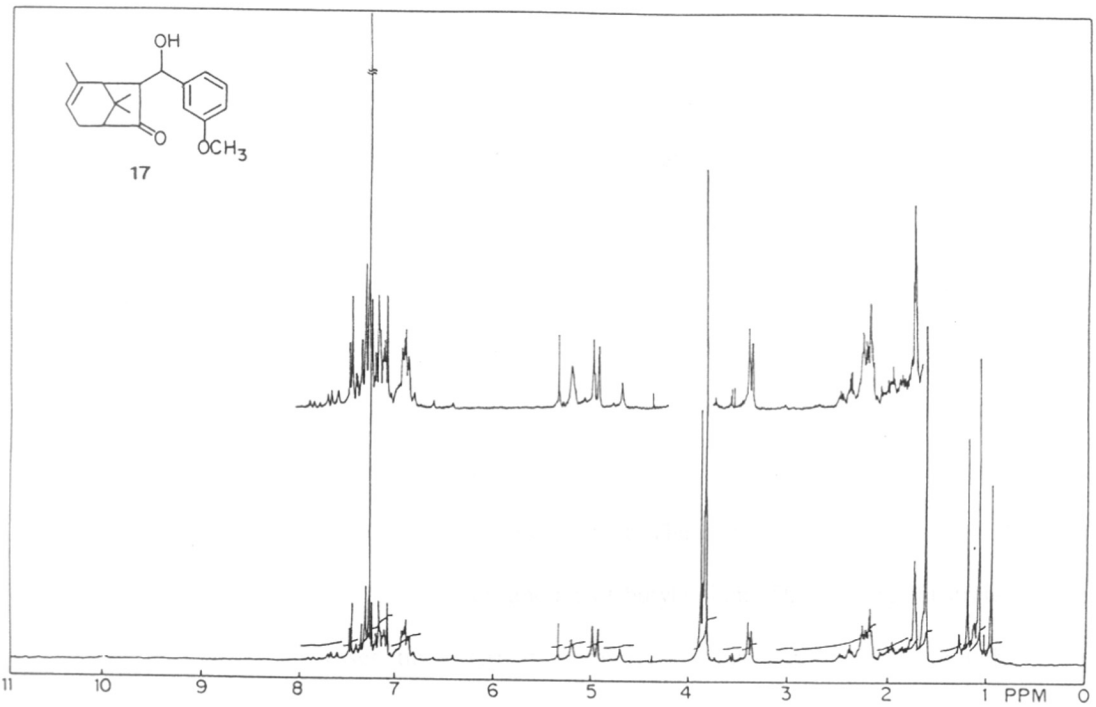


FIG. 1: PMR SPECTRUM (200 MHz) OF **17**

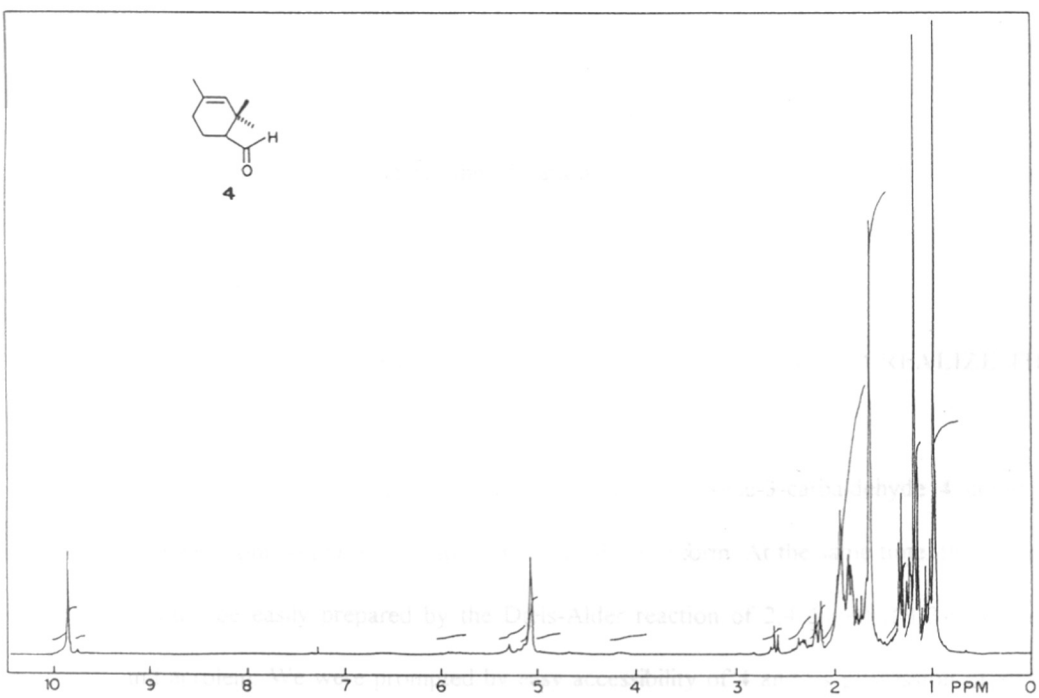


FIG. 2: PMR SPECTRUM (200 MHz) OF **4**

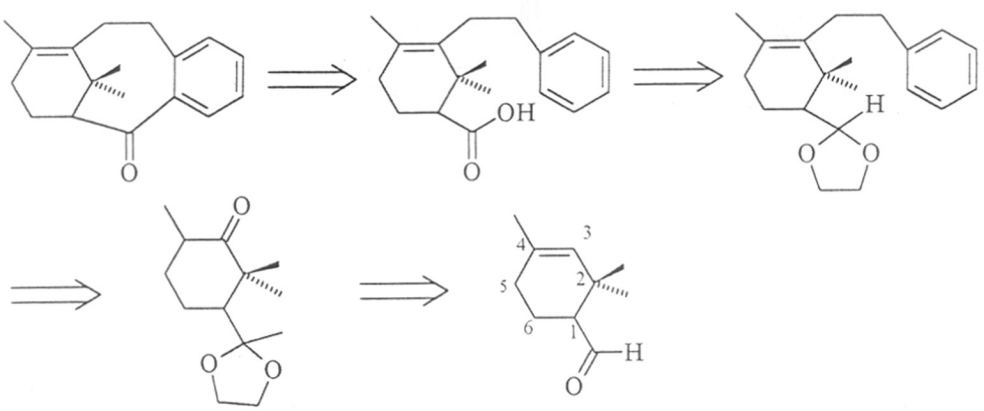
ortho lithiation and reaction of the lithio derivative with the electrophilic carbon centre and was expected to result in cyclopentane annulation.

A solution of the protected alcohol **18** in THF was cooled to -30°C and into it was introduced an equimolar amount of butyllithium and the reaction mixture was stirred for 30 minutes. It was further cooled to -78°C and stirred at this temperature for another 30 minutes. The progress of the reaction was monitored by TLC. However, to our disappointment, there was no reaction taking place. The starting material was observed on the TLC with no trace of a new product. The non-occurrence of the reaction was initially attributed to insufficient amount of butyllithium. The starting substrate for the cyclization possesses three tertiary carbon hydrogen bonds acidic enough to be abstracted by the base; while one of the sites could lead to a bridgehead enolate, the other would lead to an enolate without the construction of the bridgehead alkene. In addition to this, the aromatic ring possesses two protons *ortho* to the methoxyl function and thus provides two competitive sites for the attack of the base. Thus, this situation might have led to dissipatory processes without the production of the required lithiated aromatic carbon. Therefore, the reaction was repeated using four equivalents of butyllithium and prolonging the duration of the reaction for nearly two hours. Nevertheless, the reaction did not occur. This situation compelled us to abandon the strategy that we envisaged to realize the ABC system.

2.2.1 DEVELOPMENT OF AN ALTERNATE STRATEGY TO REALIZE THE ABC SKELETON:

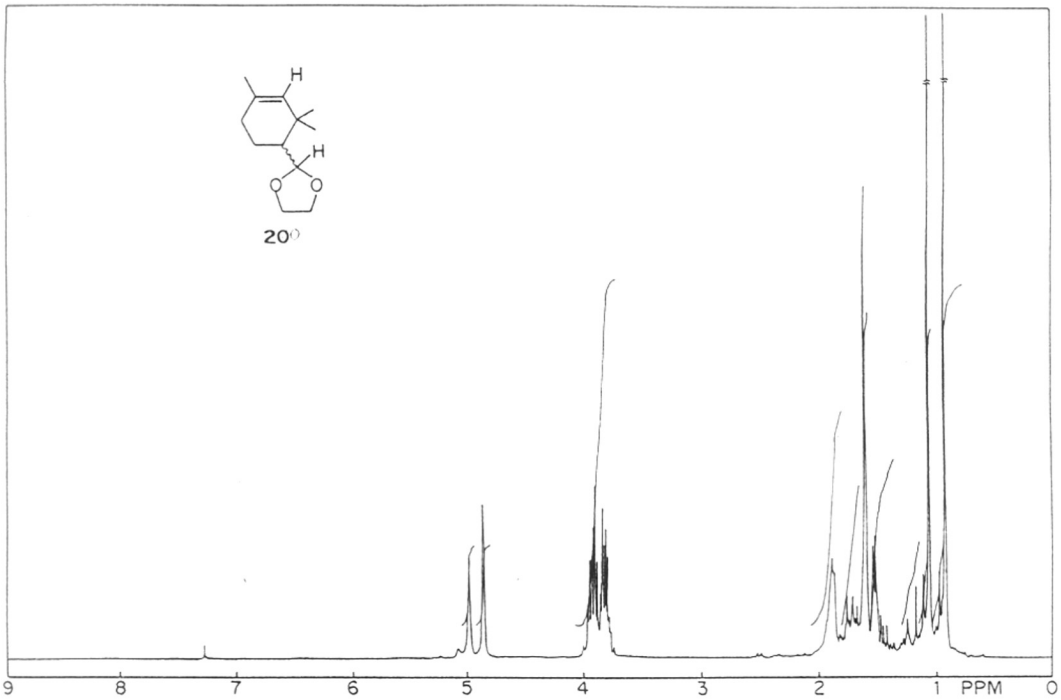
It may be recalled that 2,2,4-trimethylcyclohexene-3-carbaldehyde **4** could be obtained from (-)-*trans* verbenol in an optically pure form. At the same time, the racemic **4** could be easily prepared by the Diels-Alder reaction of 2,4-dimethyl-1,3-pentadiene and acrolein. We were prompted by easy accessibility of **4** and its possession of all the

features of A-ring of taxoid molecules to develop a methodology to build up the rings C and B in succession. Taking into consideration that a 1,3-fusion is necessary in aldehyde **4** to realize the central ring, we thought of extending the carbon chain by two carbon atoms at C-3. Therefore, it was planned to introduce a carbonyl function at C-3 and carry out a Grignard reaction with 2-phenylethylbromide. A cyclization reaction coupling the aromatic ring to the aldehyde carbon in the Grignard product preferably by a FriedelCrafts acylation was expected to result in ABC system. This retrosynthetic plan is schematically shown below (*Scheme-2.2*):



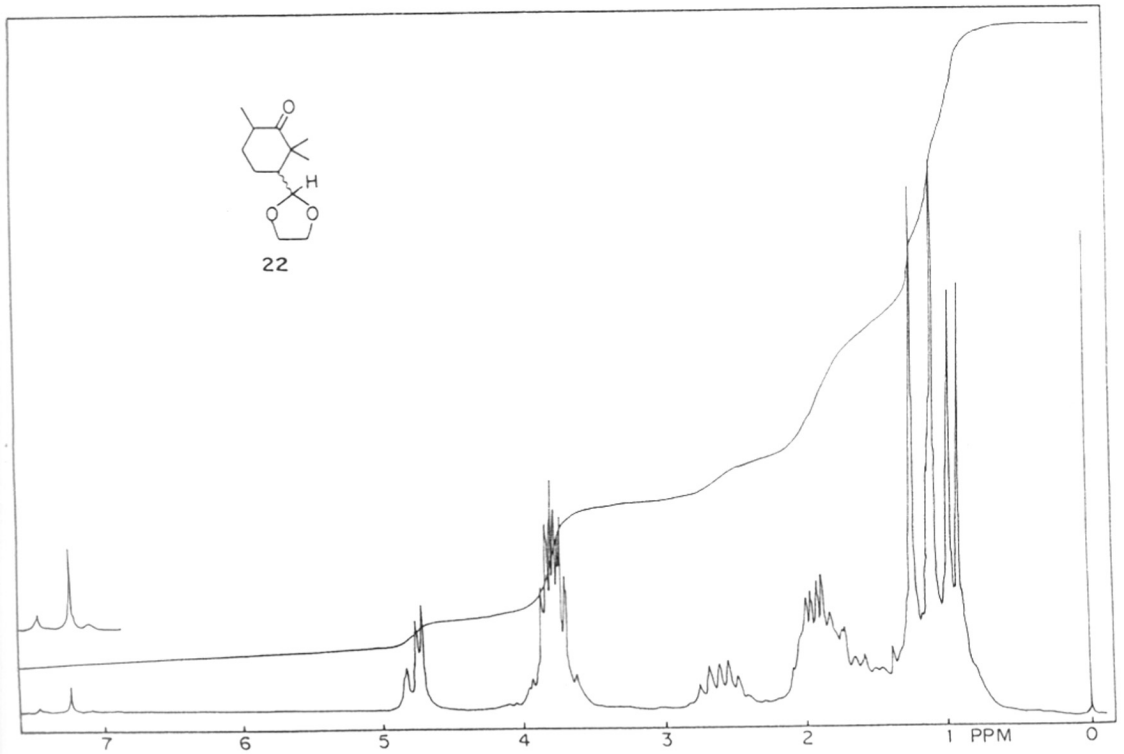
Scheme-2.2

Hydroboration was the reaction of choice for the introduction of the carbonyl group at C-3 in **4**. The authenticity of the aldehyde **4** was well ensured by its PMR spectral data (*Fig.2*). As a prerequisite to hydroboration, the aldehydic function was protected as an acetal **20**. Reaction of the aldehyde with ethylene glycol in presence of *pTSA* afforded a product in a quantitative yield. Significant features of its PMR spectrum (*Fig.3*) were two 2H multiplets centered that 3.75 and 3.95 δ and a one H doublet at 4.85 δ. The spectrum also displayed satisfactory resonances for the *gem*-dimethyl groups, the olefinic methyl, the olefinic proton and the methylenes and a methine proton. Another conspicuous feature of this spectrum was the absence of the aldehyde proton



20

FIG. 3 : PMR SPECTRUM (200 MHz) OF 20



22

FIG. 4 : PMR SPECTRUM (90 MHz) OF 22

resonance. This data enabled to identify the product as the acetal **20**. Hydroboration of the acetal with diborane, followed by an oxidative work-up afforded the required secondary alcohol **21** in an excellent yield. Both the IR and PMR spectral data were satisfactory (See *Experimental*).

In selecting a suitable oxidizing agent for the transformation of the alcohol to the ketone, especially in the presence of acid labile acetal, pyridinium dichromate was thought to be the right reagent[2]. Treatment of the alcohol with a molar equivalent of the oxidizing agent afforded a product after a standard work-up in about 65 to 70% yield. The IR spectrum of the product showed an intense band at 1710 cm^{-1} and its PMR spectrum (*Fig.4*) clearly revealed the following structural features. This spectrum displayed a secondary methyl doublet at 0.92 δ and two 3-H singlets for the *gem* dimethyl groups. It is significant to note that these two signals were shifted downfield and occurred at 1.04 and 1.20.δ The other resonances in this spectrum were a 4H multiplet at 3.77 δ and a 1H doublet at 4.71 δ. An interesting feature of this spectrum was the accompaniment of all the signals by minor signals of the same nature, indicating that the product was a diastereomeric mixture. From the above spectral data, the product could be identified as the diastereomeric ketoacetal **22**.

(a) Grignard reaction of keto acetal 22 with 2-phenyl ethyl bromide:

The Grignard reaction of the keto acetal-**22** with 2-phenylethyl bromide afforded a product which was purified by column chromatography (15% yield). The poor yield may be ascribed to the steric hindrance offered by the *gem*-dimethyl groups to the approach of the Grignard reagent to the carbonyl carbon. The IR spectrum displayed an intense broad band at 2922 cm^{-1}, suggesting the presence of a hydroxyl function. The PMR spectrum (*Fig.6*) exhibited the following resonances, suggesting the structural

features shown against them -

1.	A 3-H doublet with J=7Hz at 0.90 δ	Secondary methyl group
2.	Two 3-H singlets at 1.10 and 1.25 δ	gem-dimethyl groups
3.	A 2H triplet at 2.85 δ	benzylic-CH_2
4.	A 4H multiplet at 3.80 δ	O-CH_2-CH_2-O
5.	A 1H doublet at 4.80 δ	methine proton of acetal
6.	A 5H multiplet at 7.25 δ	aromatic protons
7.	Agroup of signals between 1.50 to 2.20δ inte greting for 6 H	3 CH_2 groups
8.	Two 1H multiplets at 2.65 δ	two methine protons

It was interesting to see that here again, as in the PMR spectrum of the keto acetal **22**, this spectrum displayed minor signals alongwith the major ones, corresponding to all the structural features detailed above, suggesting the diastereomeric nature of the product.

Thus, the IR and PMR spectral data enabled us to infer that the expected Grignard reaction had occurred, but the yield of the reaction was very poor.

This reaction was repeated in terms of varying the reaction time and the mode of addition. The reaction was tried by slow addition of previously prepared Grignard reagent into a solution of the ketoacetal in THF. However, neither enhanced reaction times nor inverse mode of addition helped in enhancement of the yield.

The low yields of this reaction were thought to be due to the steric hindrance offered by the *gem*-dimethyl groups to the adjacent reaction centre. Nevertheless, it was thought that an aldol condensation between the keto acetal and acetophenone might result in improved yields (*Scheme-3*). It was difficult to assess which reaction *viz.* the Grignard reaction of 2-phenylethyl bromide or the aldol condensation of acetophenone at the carbonyl carbon of the keto acetal is more affected by the steric effects of the *gem*

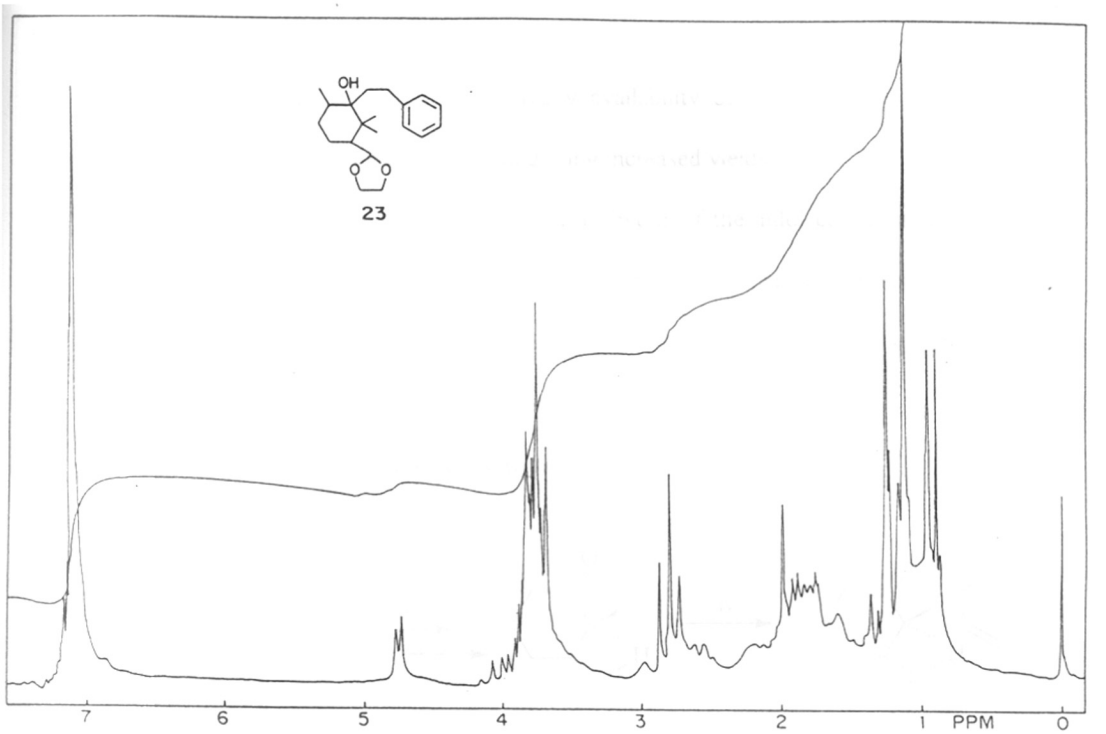


FIG. 6 : PMR SPECTRUM (90 MHz) OF 23

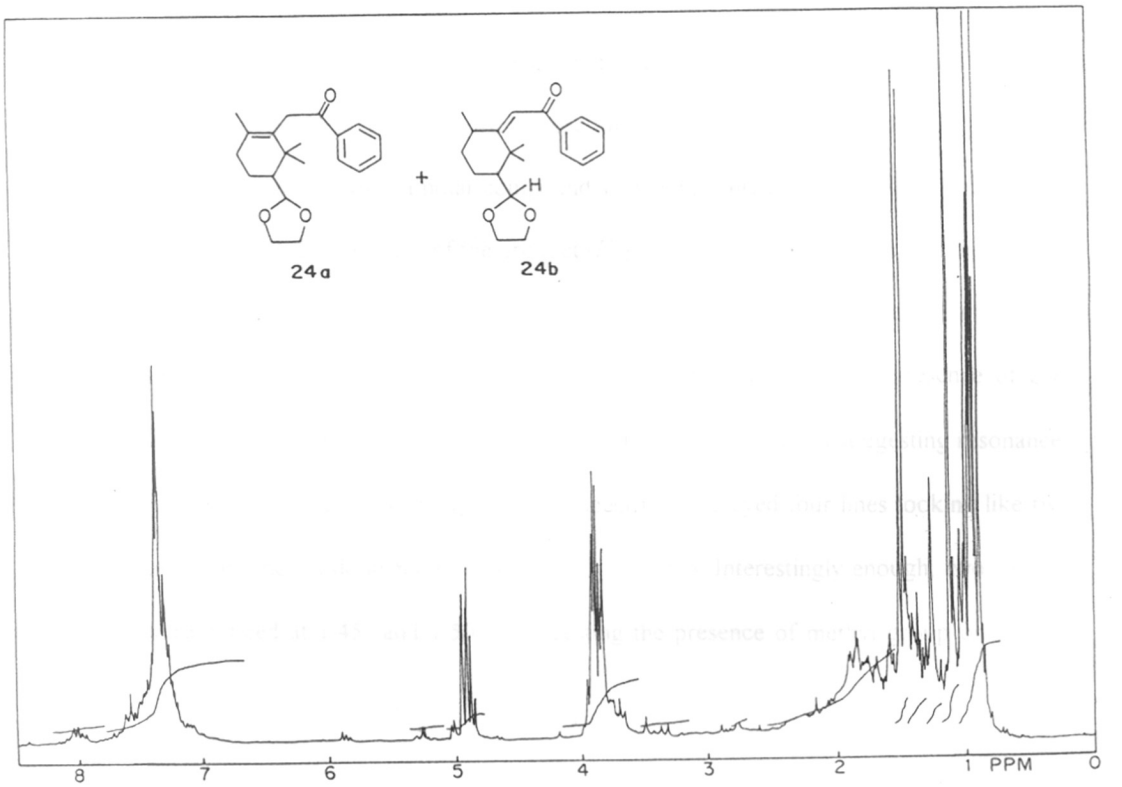
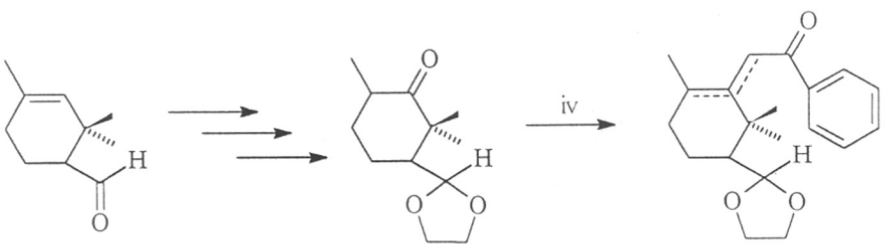


FIG. 7 : PMR SPECTRUM (200 MHz) OF 24a AND 24b

dimethyl groups. In addition, the ready availability of acetophenone prompted us to check the efficacy of this reaction in getting increased yields.

Another attractive consideration in favour of the aldol condensation was that a product obtainable from this reaction would possess the carbonyl function at the right carbon (carbon-9 of Taxol) as needed in the central ring of the ABC system of Taxoid molecule i.e. it would provide the desired functionalities.

(b) Aldol condensation of the keto acetal with acetophenone:



24

i) $HOCH_2CH_2OH$, pTSA, benzene 6 h. ii) B_2H_6, THF, H_2O_2, NaOH
iii) PDC, CH_2Cl_2 iv) NaH, acetophenone, benzene

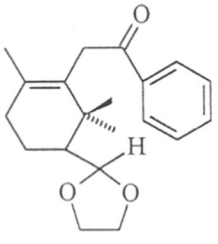
Scheme-2.3

The ketoacetal was condensed with acetophenone in the presence of sodium hydride in benzene and the crude reaction mixture was processed and purified by chromatography to yield a polar compound showing an intense band at 1680 cm^{-1}.

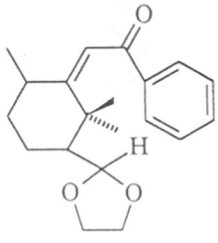
The PMR spectrum of the product (*Fig.*7) at the outset indicated that the product on hand was a mixture of two compounds and also included two diastereoisomers. The spectrum displayed two singlets at 0.90 δ and 0.95 δ indicating the presence of *gem* dimethyl groups and two more singlets at 1.00 δ and 1.30 δ again suggesting resonances of *gem*-dimethyl groups. In addition, the spectrum displayed four lines looking like two secondary methyl doublets in between 0.90 to 0.95 δ. Interestingly enough, two singlets were noticed at 1.45 and 1.50 δ, suggesting the presence of methyl group on olefinic

linkage. This spectrum showed two groups of multiplets in the region of 3.60 to 3.90 δ integrating for 6H indicating resonances of the methylenes of acetal and a $\underline{CH_2}$-CO- adjacent to a carbonyl group. Besides showing resonances of the aromatic proton between 7.10 to 7.80 δ, the spectrum showed a 2H double doublet at 4.90 δ suggesting presence of an olefinic proton and also the resonance of methine proton of the acetal.

The above described PMR spectrum in terms of the features and chemical shifts indicated that the product is a mixture of two compounds defined by the following structures.



24a



24b

Besides this, the spectrum also indicated that both the compounds were also diastereomeric mixtures.

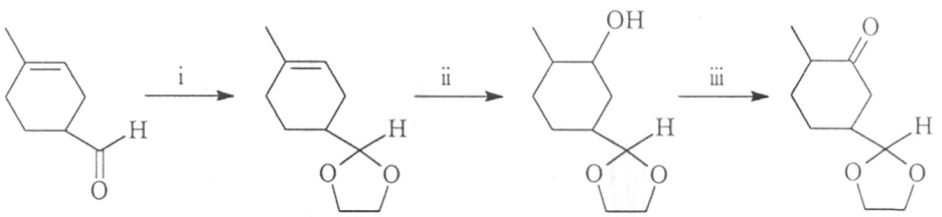
Although the reaction was successful in getting the desired product, the yield again was miserably poor. This result confirmed our conjecture that steric hindrance has been detrimental in getting good yields in both the Grignard and the aldol condensation reactions.

2.2.2 IMPROVEMENT OF THE ALDOL CONDENSATION METHODOLOGY:

It was our plan to initially build the carbon framework of A and C rings and investigate different reactions to realise the central ring. However, our attempts to build up the necessary appendages to the A ring were not very successful in terms of yields. This result was attributed to steric problems originating from the *gem*-dimethyl groups. It was, therefore, thought worthwhile to investigate the same sequence of the reactions with the substrate **8** corresponding to the substrate **4**, but lacking the *gem*-dimethyl

groups. This change was expected to result in improved yields of the aldol reaction and hopefully not alter significantly the bioactivity of the end product.

Another major reason in trying such a substrate was the expectation that the final coupling reaction between the A and C rings might also be susceptible to steric hindrance of the *gem*-dimethyl groups. Such steric problems in realizing central eight-membered ring has been noted by the previous workers.[3]



8 **25** **26** **27**

i)$HOCH_2CH_2OH$, pTSA, C_6H_6 ii) B_2H_6, NaOH / H_2O_2, THF iii) PDC, CH_2Cl_2

Scheme-2.4

The sequence of the reactions followed in the preparation of the required keto acetal **27** has been shown in *Scheme-1*. It may be mentioned that most of the reactions furnished products in good yields and all the products displayed satisfactory spectral data.

The IR spectrum of **27** (keto acetal) showed an intense band at 1710 cm^{-1} and its PMR spectrum (*Fig.8*) clearly suggested its diastereomeric composition. The significant features of this spectrum were two secondary methyl doublets centered at 0.95 and 1.05 δ. Two more or less overlapped multiplets integrating for four protons at 3.80 δ and two doublets at 4.70 and 4.75 δ together integrating for a proton. These spectral data clearly enabled us to establish the identity of the product. In addition, the ^{13}C-NMR spectrum showed all the required resonances for the structure.

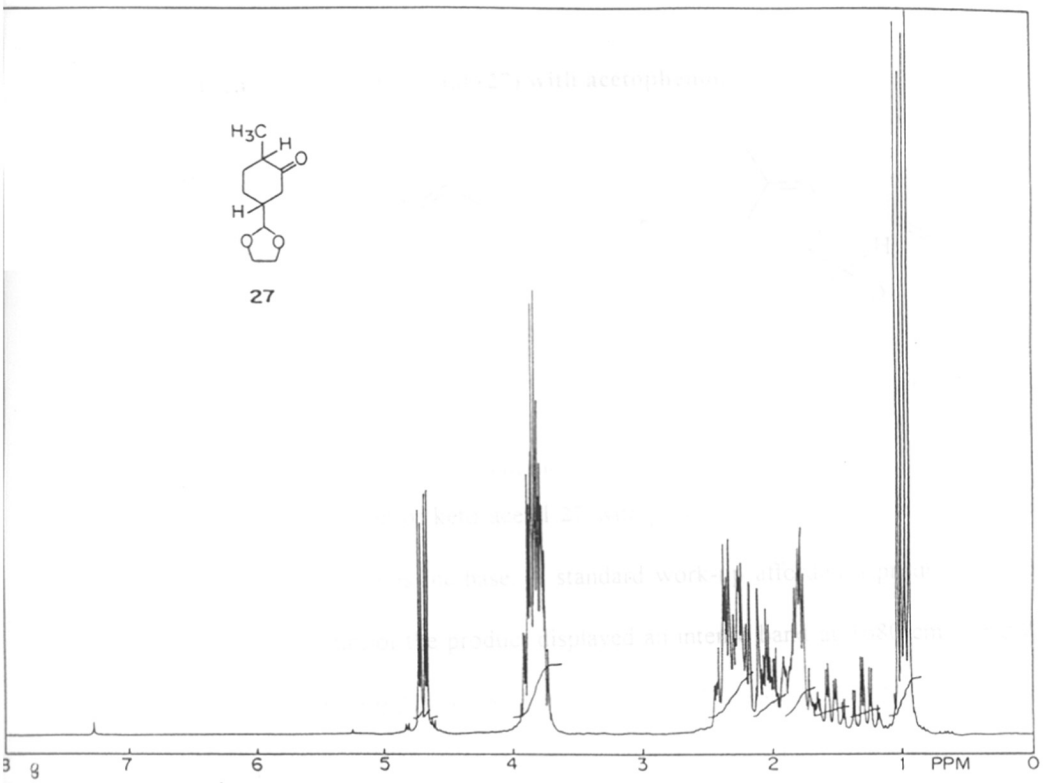


FIG. PMR SPECTRUM (200 MHz) OF **27**

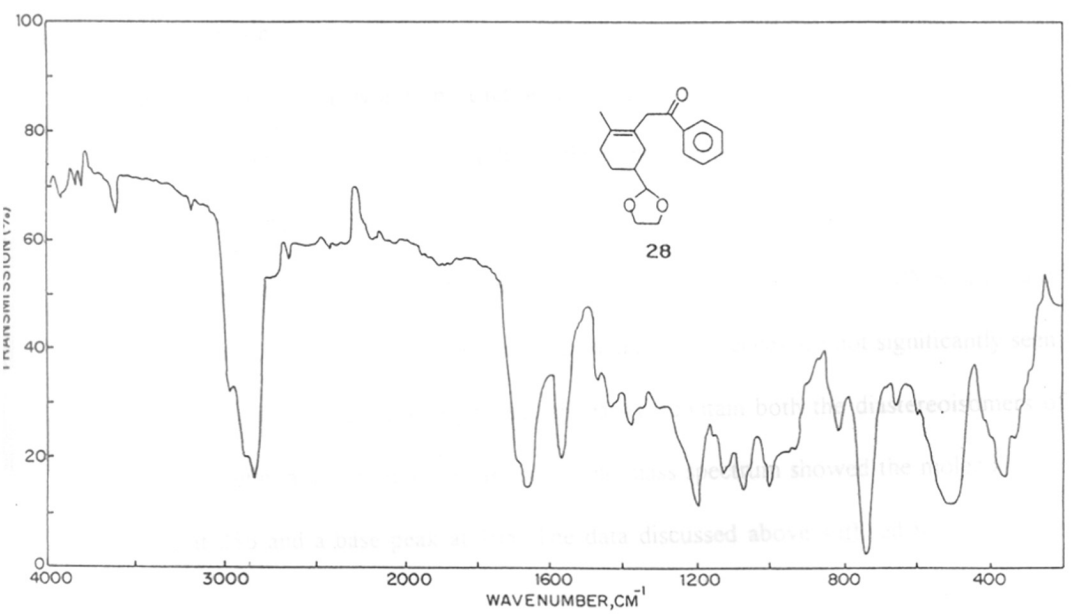
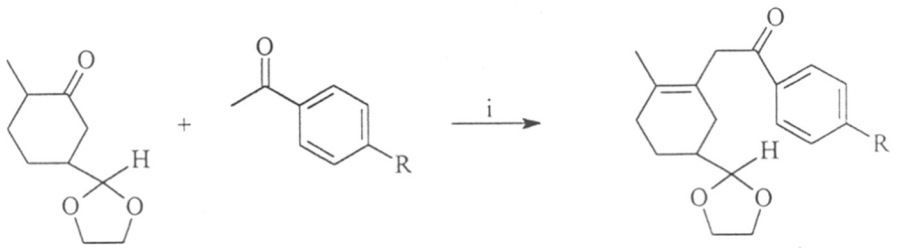


FIG. 9: IR SPECTRUM OF **28**

Aldol condensation of keto acetal (27) with acetophenone:



i) NaH, $PhCH_3$

R = H, CH_3, Isobutyl, Cl
28 29 30 31

Scheme-2.5

Aldol condensation of keto acetal **27** with *p*-isobutyl acetophenone was carried out using sodium hydride as the base. A standard work-up afforded a product in 50% yield. The IR spectrum of the product displayed an intense band at 1680 cm^{-1} (*Fig.9*). The PMR spectrum (*Fig.10*) revealed two groups of signals at δ 7.30 and 7.80 δ, integrating for 3H and 2H respectively, showing all the aromatic protons. The spectrum was conspicuous by its absence of olefinic proton resonance and also by the presence of a 3H singlet at 1.57 δ suggesting both the *endo* cyclic and tetrasubstituted nature of the olefin. The other resonances included a 4H multiplet at 3.80 δ, and 1H multiplet at 4.80 δ and a 2H singlet at 3.67 δ. These spectral data suggested that the primary aldol product had undergone a dehydration reaction leading to the *endo* olefin **28**. Although the principal product was the *endo* cyclic olefinic one, traces of *exo* cyclic olefinic product are also obtained in most of the cases (except in the case of *p*-isobutyl acetophenone) as seen by secondary methyl resonences in the region 0.90 to 1.10 δ in the PMR spectra of the products. However, the corresponding olefinic resoncences are not significantly seen. The *para*-chloroacetophenone product appears to contain both the diastereoisomers of the *exo* olefin, although in trace amounts. The mass spectrum showed the molecular ion peak at 286 and a base peak at 105. The data discussed above sufficed to identify the

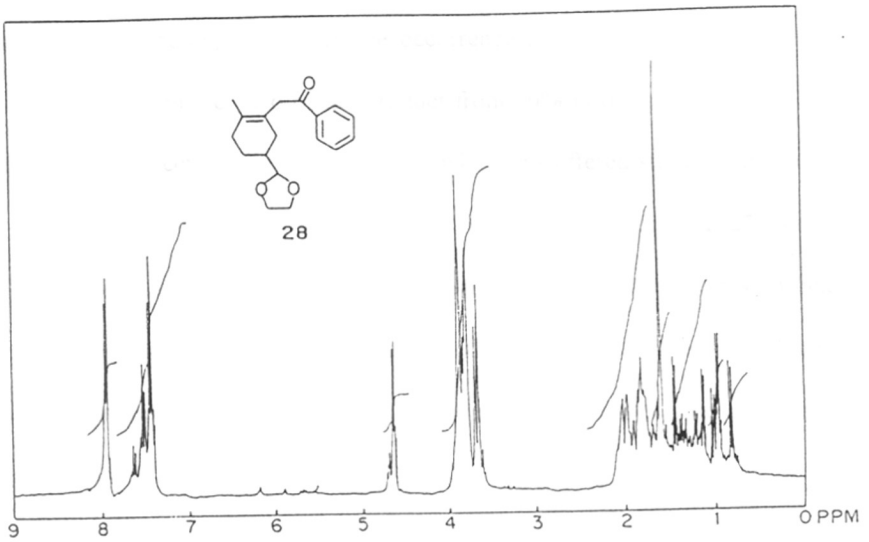


FIG. 10 : PMR SPECTRUM (200 MHz) OF **28**

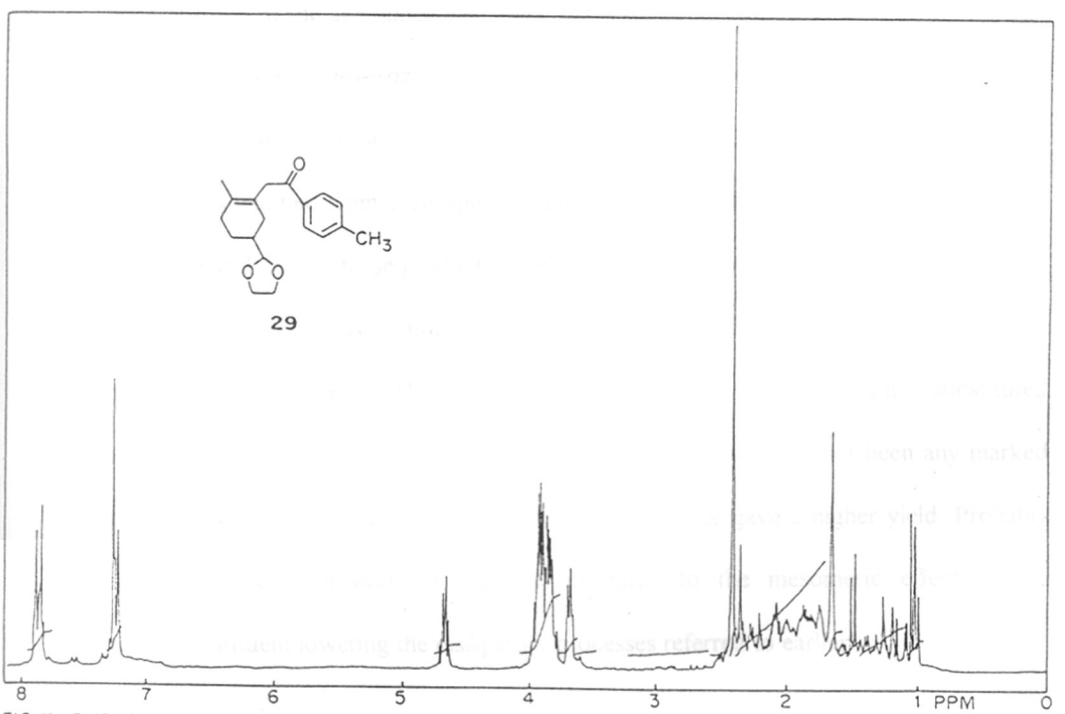
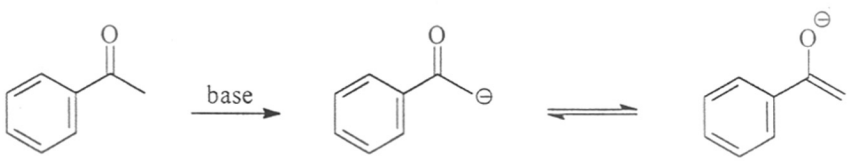


FIG. 11 : PMR SPECTRUM (200 MHz) OF **29**

product as **28**. More important than the occurrence of the reaction was the observed substantial increase in the yield of the product from 10% in the case of **4** to 50% here, confirming our conjecture that the gem-dimethyl groups offered steric hindrance. With a view to check the generality of this aldol condensation with ketoacetal **27**, some more substituted acetophenones were tried and the results therefrom are discussed below. It was also thought that the low yields of this reaction could be to some extent due to the dissipatory process of the enolate anion derived from the base treatment of acetophenone.



Such a phenomenon perhaps can be reduced by electron-donating substituents at the *para* position in the acetophenone. Thus, the aldol condensation of **27** was carried out with *para*-methyl, *para*-isobutyl and *para*-chloro acetophenones under the conditions described earlier for unsubstituted acetophenone. The products from these reactions have been well identified from their spectral data (*Experimental*). It may be noted that the PMR spectral data of these products (*Fig.10, 12* and *13*) were almost identical with that of **28** (derived from unsubstituted acetophenone), but for the resonances of the protons in the ring substituents. The % yields of this reaction with differently substituted acetophenones are shown in *Table-I*. It can be seen that there has not been any marked change in the yield except that the *p*-chloroacetophenone gave a higher yield. Probably this slight yield enhancement may be attributed to the mesomeric effect of the chlorosubstituent lowering the dissipatory processes referred to earlier.

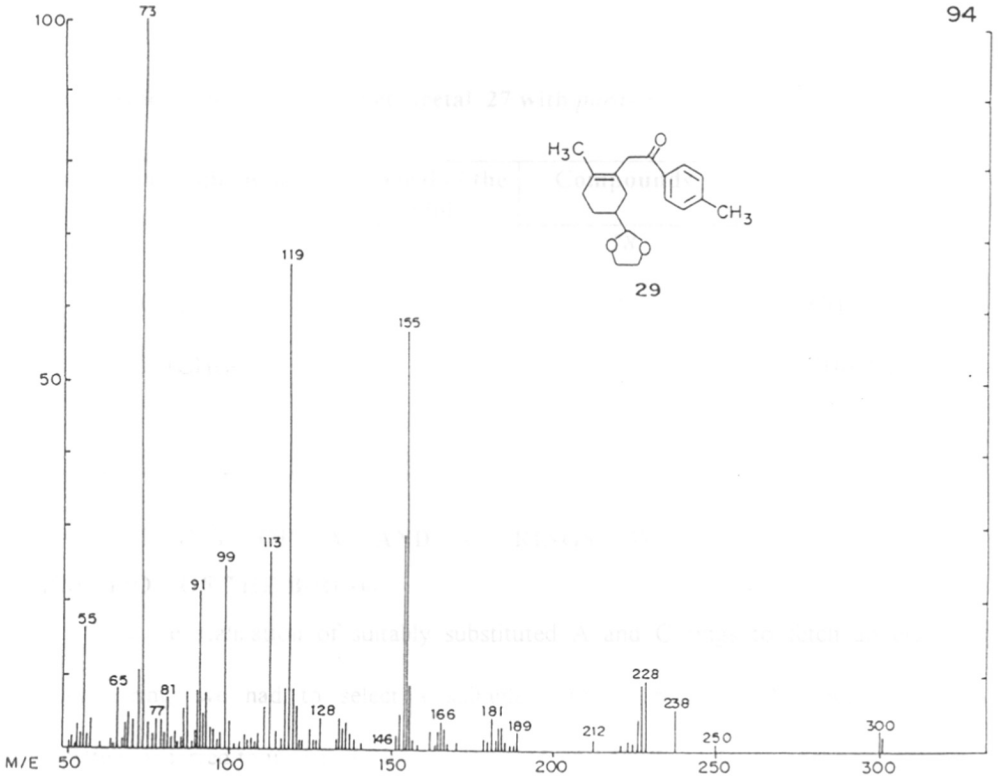


FIG. 12 : MASS SPECTRUM OF 29

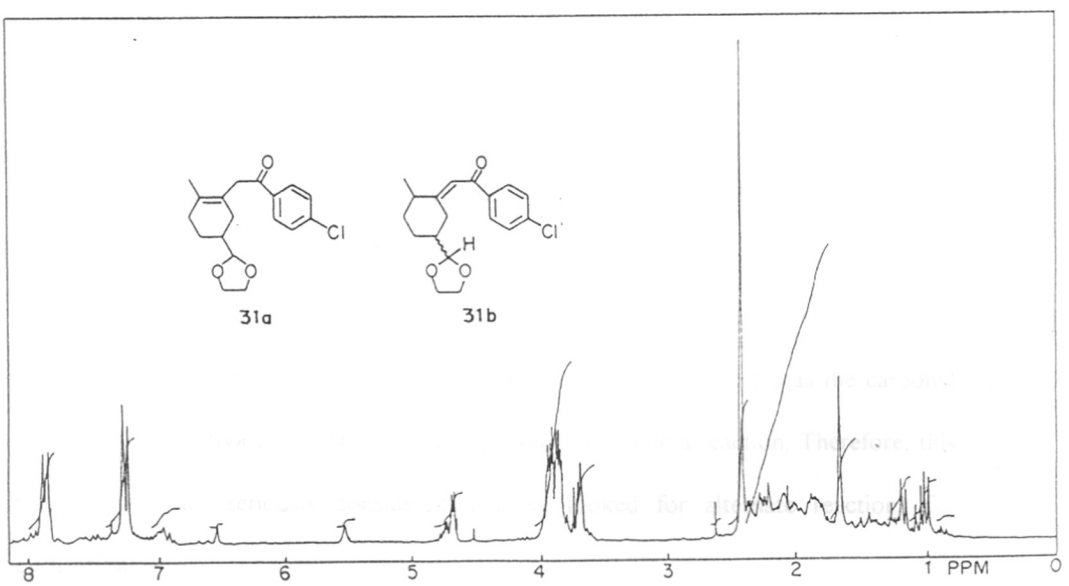


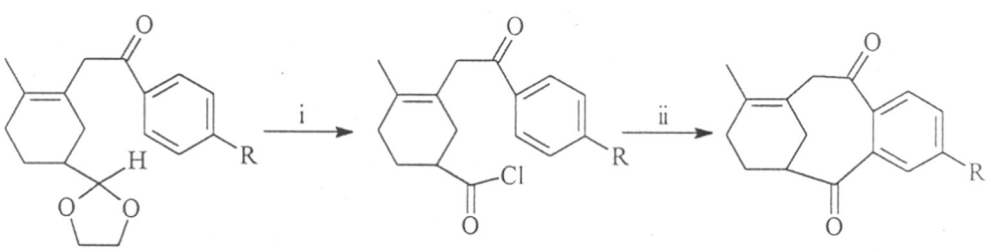
FIG. 13 : PMR SPECTRUM (200 MHz) OF 31a & 31b

Table-1: Aldol condensation of ketoacetal 27 with *para*-substituted acetophenones:

Substrate (acetophenone)	% Yield of the aldol	Compounds	R
H	50	*28*	H
CH_3	50	*29*	CH_3
$CH_2CH(CH_3)_2$	50	*30*	$-CH_2CH(CH_3)_2$
Cl	55	*31*	-Cl

2.2.3 COUPLING OF A AND C RINGS WITH CONCOMITANT FORMATION OF THE B-RING:

With the realization of suitably substituted A and C rings to fetch an eight membered ring, we had to select a suitable coupling reaction. A reaction that immediately occurred to us was the intramolecular Fridel-Crafts acylation of the aromatic ring by the initial transformation of the acetal into the corresponding acylchloride. (*Scheme*-6).

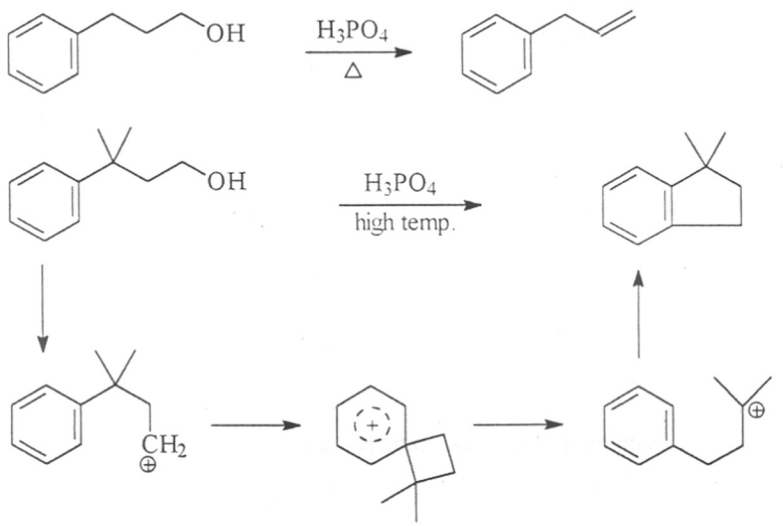


Scheme-2.6

However, due to the presence of the carbonyl function at the carbon *ortho* to the site of the electrophilic reaction, this did not appear very much feasible as the carbonyl group would deactivate the *ortho* and *para* positions for such a reaction. Therefore, this reaction was not seriously considered and we looked for alternate reactions for cyclization.

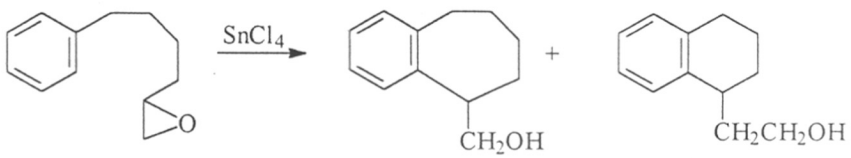
At this stage, a survey of literature to find out reactions used in the fusion of 5, 6,

7 and 8 membered rings on to an aromatic system led us to some interesting reports. A class of reactions referred to as cyclialkylations appeared attractive.



A.A.Khalaf and R.H.Roberts[4] reported some cyclialkylations of a few phenyl alkanols. These authors reinvestigated the previous work of Bogert *et al.*[5] who observed that 3-phenylpropanol on heating with phosphoric acid afforded essentially a dehydration product with no cyclization leading to indane. On the other hand, Khalaf and Roberts observed that while 3-phenylpropanol did not cyclize, 3-methyl-3-phenylbutanol underwent cyclization to a considerable extent yielding the corresponding indane. This contrasting difference in the reactivity of these two primary alcohols has been rationalized by invoking aryl participation, followed by a 1,3 phenyl shift leading to a tertiary carbonium ion intermediate which cyclizes to the observed product.

Another interesting report in Fridel-Crafts cyclialkylations that was relevant to our work, was that of Taylor *et al.*[6] who carried out $SnCl_4$-catalysed cyclialkylations of several aryl alkyl epoxides. These authors observed that cyclialkylations leading to 6-membered rings was a facile process and occurred at secondary but not at primary epoxide positions; such a reaction leading to seven membered rings also was observed.

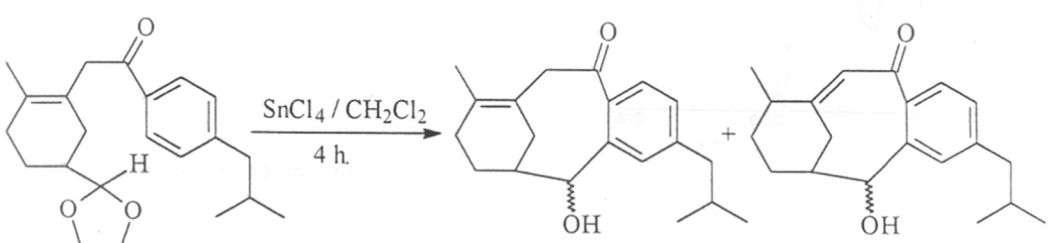


They attributed the observed regioselectivity to the moderation of electrophilicity by epoxide group. The epoxide oxygen was thought to be stabilizing an intermediate or transition state by partial bonding to the reaction centre. However, such reactions have not been reported in realizing eight membered rings. Nevertheless, we conjectured that an acetal group bearing a semblance to an epoxide might regulate the electrophilicity and promote the required cyclialkylation.

With these encouraging reports, we were prompted to try $SnCl_4$-catalysed intramolecular cyclialkylation.

2.2.4 $SnCl_4$-CATALYSED INTRAMOLECULAR CYCLIALKYLATION:

As considerable amounts of *p*-isobutyl-substituted aldol condensation product **30** was available at the moment, its reaction was performed first. Into a solution of 2% $SnCl_4$ in CH_2Cl_2 was slowly introduced a CH_2Cl_2 solution of **30** at 0°C and the reaction mixture was stirred for 3 to 4 hrs. When the starting material disappeared (TLC 4 hrs), the reaction mixture was successively washed with saturated ammonium chloride and water. The aqueous layer was repeatedly extracted with CH_2Cl_2 and the combined organic extracts was dried over sodium sulfate. The crude product obtained on removal of solvent was chromatographed over silica gel. After the initial removal of less polar biproducts, a more polar homogeneous material could be obtained in 45% yield.



Scheme-2.7

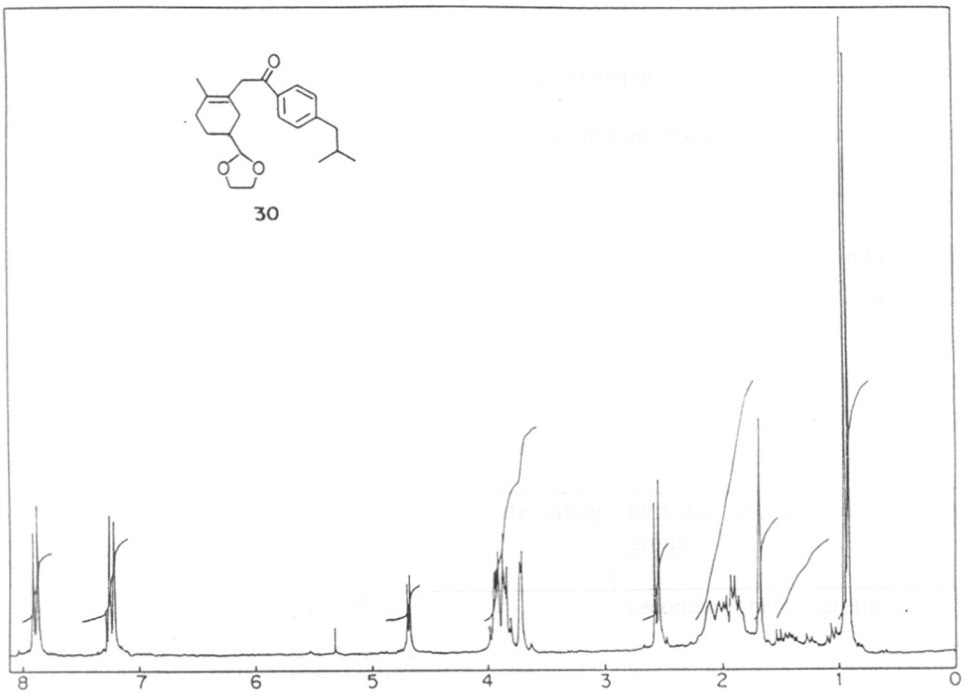


FIG. 14 : PMR SPECTRUM (200 MHz) OF **30**

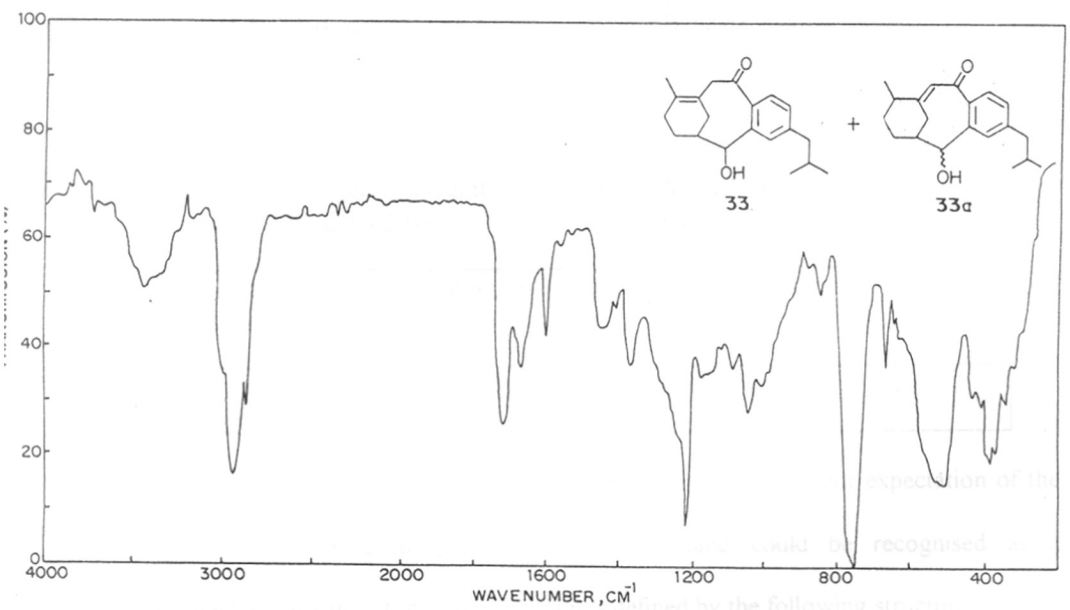


FIG. 15 : IR SPECTRUM OF **33** AND **33a**

The IR spectrum of the product *(Fig.15)* displayed a broad band at 3450 cm^{-1} and a corresponding small band at 1100 cm^{-1} indicating the presence of a secondary alcoholic group. Another interesting feature of this spectrum was the appearance of two bands at 1710 and 1680 cm^{-1}, suggesting the presence of isomeric ketones; in addition, typical aromatic pattern was observed between 1600 cm^{-1} and 1450 cm^{-1}.

The PMR spectrum (*Fig.16*) at the outset, clearly indicated the isomeric nature of the product. It showed the following resonances.

1.Two doublets together integrating for 6H centered at 0.90 δ	terminal methyls of isobutyl group
2. Two 3H doublets at 1.20 δ	secondary methyl group
3. A group of multiplets integrating for 7H between 1.20-1.90 δ	3xCH_2 and a methine proton
4. Two singlets together integrating for 3H at 2.20 δ	olefinic methyls
5. Two 2H doublets at 2.40-2.55 δ	Benzylic methylene
6. Two multiplets together integrating for a proton at 3.20 and 3.30 δ	Methine of a secondary alcohol
7. Two multiplets together integrating for two protons at 3.80 and 4.10 δ	Methylene adjacent to the carbonyl
8. 3 groups of multiplets integrating for 3 protons between 7.10 to 7.90 δ	Aromatic protons
9. Two multiplets together integrating for a 1H at 4.70 and 5.20 δ	Olefinic proton

From the above described IR and PMR spectral data and our expectation of the cyclization to have occurred, the product on hand could be recognised as a diastereomeric mixture of the two compounds defined by the following structures.

It may be added that the downfield shift of the olefinic methyl resonances in the *endo* olefin to 2.00 δ might be arising from the anisotropy of the carbonyl group. The

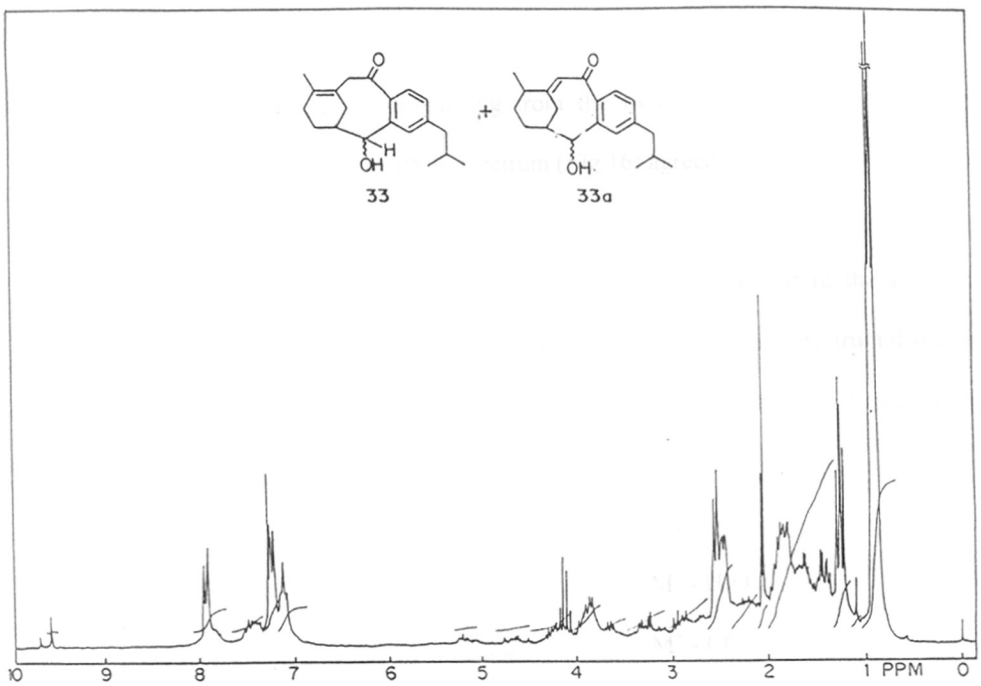


FIG. 16 : PMR SPECTRUM (200 MHz) OF 33 and 33a

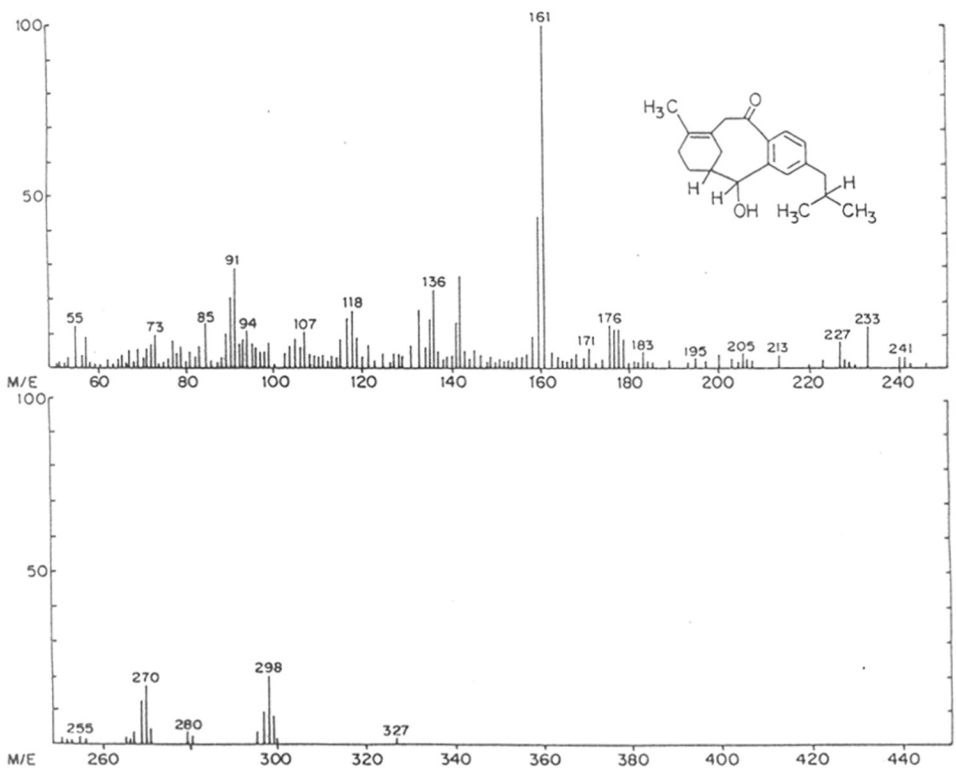


FIG. 17 : MASS SPECTRUM OF 33 AND 33a

diastereomeric nature can be originating from the two orientations of the hydroxyl group. It may be added that the PMR spectrum (*Fig.* 16) agreed very well in detail for the structural composition suggested above.

The mass spectrum of the product (*Fig.* 17) provided support to the structural assignment. Besides showing the molecular ion peak at m/e 298, this spectrum displayed major fragmentation expected from the predominant *endo* compound. Some of the observed fragments are shown below:

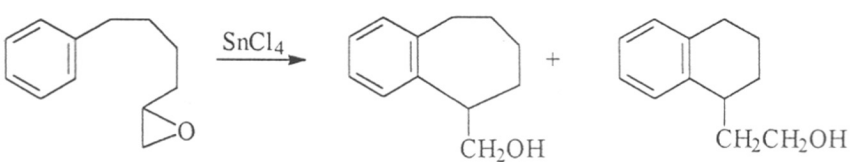
1. base peak ..... m/z 161
2. 280(5) ..... $M^+ - H_2O$
3. 270(18) ..... $M^+ - CO$
4. 241(5) ..... M^+ - isobutyl group

2.3.0 DISCUSSION

The work presented in this chapter essentially comprised the building up of the aromatic C-ring over a pre-fabricated A-ring and a coupling reaction between A and C-rings with simultaneous generation of the eight membered central ring. Grignard and Aldol condensation reactions were utilized to introduce two carbon units and both the reactions were not successful in terms of good yields. The low yield in these reactions has been attributed to the steric hindrance offered by the *gem*-dimethyl groups to the adjacent reaction centre. On the other hand, Aldol condensation of the keto acetal **27** lacking the *gem*-dimethyl groups was successful in giving the required product in considerably good yields.

2.4.0 MECHANISTIC ASPECTS

The precursor needed for the final coupling reaction was obtained by standard organic reactions. On the contrary, the final cyclization needed an altogether a different type of reaction. In this context, a brief discussion of the $SnCl_4$ catalyzed transformation of some aryl-alkyl epoxides into six-six and six-seven bicyclic products reported by Taylor *et al.*[6] (*Scheme-8*) *via* Fridel Crafts cyclialkylation becomes relevant.

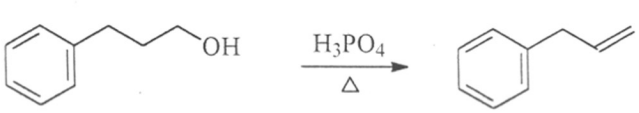


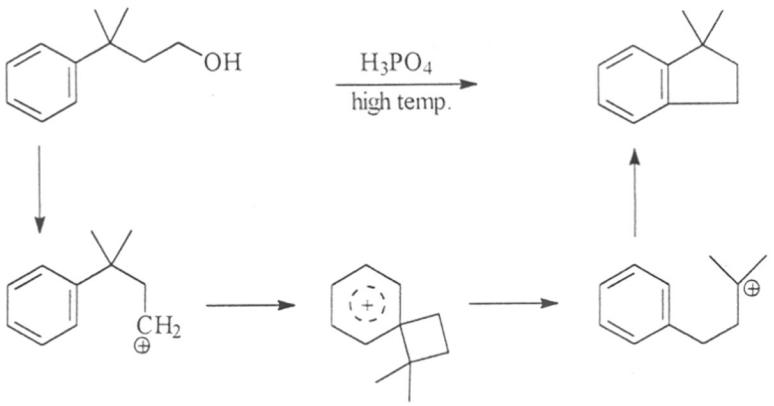
These authors reported that cyclialkylation reactions were observed essentially at the secondary carbon of the epoxide. This was especially so in a substrate leading to six and seven membered rings. The authors have rationalized these results in terms of the epoxide oxygen moderating the electrophilicity of the reacting carbon site. Such a moderation of electrophilicity reduces the rearrangement reaction and leads to more of

cyclised products.

One can see a considerable similarity between the epoxy structure referred to above and the acetal group of **30**. The incipent carbocation in the cyclialkylation has probably been stabilized by the lone pair of electrons on the oxygen atom. This may be looked upon as a case of anchimeric assistance by a neighbouring group. Nevertheless, the observed Friedel-Crafts cyclialkylation in **30** is rather surprising with the expectation that the electron withdrawing carbonyl group in **30** should deplete electron density at *ortho* and *para* positions. Thus, the mechanistic aspects of this cyclization reaction cannot be talked about with certainty.

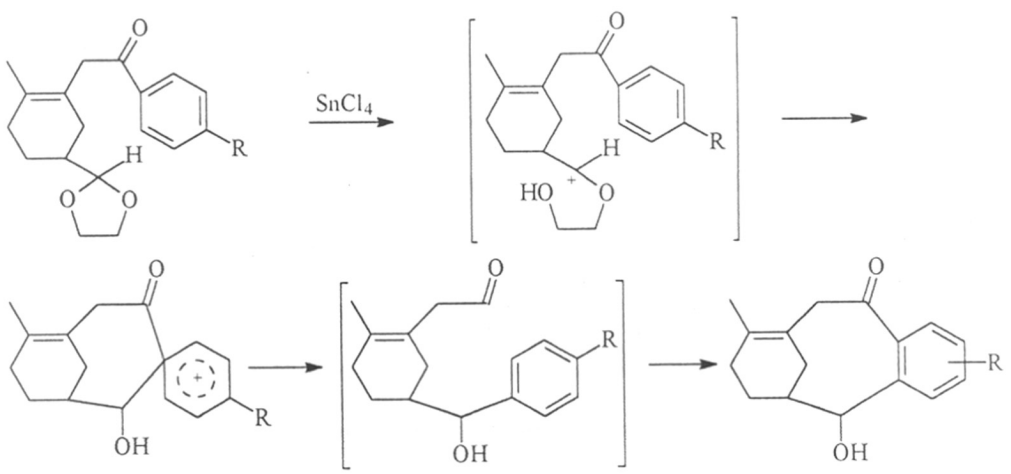
In this context, the work reported by Khalaf and Roberts on cyclialkylation of phenyl alkanols is worth being considered[4]. These authors observed that tertiary 3- and 4-phenyl alkanols underwent cyclialkylation with sulfuric acid in a facile manner to yield the corresponding indanes and tetralenes. However, primary and secondary 3-phenyl alkanols did not undergo cyclialkylation even at elevated temperatures. On the other hand, the primary alcohol namely 3-methyl-3-phenyl-1-butanol (*Scheme-9*) was mainly dehydrated and cyclised to a minor extent. These authors have invoked the participation of the aromatic ring leading to a 1,3-phenyl shift providing the necessary tertiary carbocation for cyclization.





Scheme-2.9

From this point of view, the reaction pathway of the final cyclization reaction in our case may be postulated as shown in *Scheme-10*.



Scheme-2.10

Such a mechanistic scheme appears more tenable than the mechanism in which the carbocation derived from acetal alkylates the phenyl ring at a site bearing an *ortho* electron withdrawing carbonyl group which is not very much favoured.

In the event of the operation of a mechanism in which aryl participation with the initially formed carbocation at the acetal carbon leading to a spiro intermediate is involved, the substituent on the aromatic ring in the product would be in a *meta* position

in relation to the carbon carrying the carbonyl group. A determination of exact location of the substitution in the product could not be assessed with the available NMR spectral data. However, a detailed NMR study of the cyclised product in terms of cosy experiments should resolve this issue.

2.5.0 SUMMARY AND CONCLUSION:

The total work presented in this Chapter can be summarised in terms of the following observations:

1. A very attractive retrosynthetic *Scheme-1* was taken up with the bicycloketone (7) as the starting material. The main reactions of the scheme were an aldol condensation of 7 with *meta* methoxy benzaldehyde, a hetero atom-directed ortho lithiation of the aromatic carbon, followed by an intramolecular cyclization leading to a tetracyclic bridged alkene. Oxidative cleavage of this alkene was expected to generate the desired ABC skeleton. However, the non-occurrence of lithiation / cyclization resulted in the abandoning of the scheme.
2. In an alternate strategy (*Scheme-2*), the keto acetal (22) obtainable from α-pinene as well as from a simple Diels-Alder reaction, was considered as a suitable starting material as it possessed the salient structural features of A-ring of taxoids. It was intended to build up suitable appendages to the A-ring in terms of the composition of the central B-ring and also with proper connections to a phenyl ring. It was planned to connect A and C-rings by a suitable reaction with the concomitant formation of the central ring.
3. Both Grignard and aldol condensation reactions were explored to build up the required A and C rings for the final cyclization. Although both the reactions occurred, the low yields of these reactions deterred us from using the keto acetal **22** possessing the *gem*-dimethyl groups, as the latter groups were believed to be offering steric hindrance for the reactions.
4. The Aldol condensation of substituted acetophenones with the acetal *P* **27** lacking the *gem*

2.7.0 EXPERIMENTAL

Execution of *Scheme-1*:

Aldol condensation of Bicyclo ketone-7 with m-methoxy benzaldehyde leading to 17:

To a previously prepared LDA from diisopropyl amine (1.20 g, 0.012 mol) and butyl lithium (1.28g, 0.02mol) at 0°C, a solution of bicycloketone **7** (1.64 g, 0.01mol) in dry THF was added drop by drop at -30°C. The stirred solution was cooled to -78°C and stirred for another 30 minutes. A solution of m-methoxybenzaldehyde (1.36 g, 0.01mol) in THF was added to the above reaction mixture and stirred for 30 minutes more; the reaction mixture was quenched with saturated ammonium chloride solution at -78°C. The reaction mixture was diluted with ether, the organic layer was separated and aqueous layer was extracted with ether. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of solvent, the crude product obtained was chromatographed over a column of silica gel, eluting with 5% ethylacetate in petroleum ether to get the pure product **17**.

Yield	2.20g. (74%)
IR(nujol)	2950, 1680, 1610, 1600, 1530, 1300, 1200, 1080, 900, 780, 600 cm-1
PMR (200 MHz,$CDCl_3$) δ: *Fig.1*	0.90 (s, 3H), 1.10 (s, 3H), 1.20 (s, 3H), 1.60 (s, 3H),1.75 2.40(m,1H),3.80 and 3.85(2s,3H) 5.0 and 5.20 (m, 1H), 6.80-7.50 (m, 4H).

Protection of alcohol 17 with Dihydropyran to get 18:

To a cooled solution of alcohol (2.00 g, 0.006 mol) in dry CH_2Cl_2 (100 ml) containing dihydropyran (0.6 g, 0.006 mol) a catalytic amount of *pTSA* (100 mg) was added. The progress of the reaction was monitored by IR,where the Hydroxyl function

at 3100 cm-1 got disappered (4 h.) and the reaction mixture was washed with water, brine and the organic layer was dried over anhydrous sodium sulphate. After removal of solvent, the crude product was just passed through a column of silica gel and eluted with 10-15% ethyl acetate in petroleum ether to obtain pure protected alcohal **18**.

Yield: 2.35g (92%)

IR (cm^{-1}): 2970, 1690, 1600, 1530, 1330, 1200, 1070, 950, 780, 550

PMR (200 MHz $CDCl_3$,) δ: 0.90 (s, 3H), 1.15 (s, 3H), 1.20 (s, 3H), 1.45 (m, 3H), 1.60 (s, 3H), 1.65 (m, 4H), 1.70-2.40 (m, 3H), 3.40 (m, 1H), 3.60 (t, 1H), 3.80 and 3.85 (2s, 3H), 5.0 (m, 1H), 6.80-7.45 (m, 4H).

Coupling reaction of 18 using BuLi to get 19:

Into a stirred solution of the protected alcohol, **18** (0.500g, 0.0013mol) in THF was introduced nBuLi (0.086g, 0.0013mol) in hexane at -30°C. The reaction mixture was further cooled to -78°C and stirred at this temperature for 30 minutes. A TLC of an aliquot did not show the formation of any product. The reaction mixture was stirred for another 2-3 hours; nevertheless, the TLC of an aliquot showed only the starting material without any trace of the product. The reaction mixture was quenched with a saturated solution of ammonium chloride and worked up in a standard manner. The residue obtained (0.470 g) was found by its PMR spectral data to be the unreacted starting ketone **18**.

Reaction of 18 using excess of butyl lithium:

The above reaction was performed again using four equivalents of n butyl lithium with respect to the ketone. The reaction was carried out for a prolonged duration of 5 hours. The TLC of an aliquots at different intervals just indicated the starting material. The reaction was worked up as described above. The residue obtained (450 mg) was

again found to be the unreacted starting material from its PMR data.

Execution of *Scheme-2*: Grignard reaction of keto acetal 22 with 2-phenyl ethyl bromide.

Preparation of 2,2,4,-trimethylcyclohex-3-ene carbaldehyde acetal 20 from aldehyde 4

To a stirred solution of 2,2,4-trimethyl cyclohexene-3 carbaldehyde **4** (See Experimental of Chapter-I, *Fig.2* of this Chapter for purity) (10.0g, 0.065mol) and ethylene glycol (5.58g, 0.09mol) in dry benzene (150 ml) was added pTSA (100 mg). The reaction mixture was stirred under reflux using Dean-Stark azeotropic unit. The progress of the reaction was monitored by IR; when the carbonyl frequency at 1740 cm^{-1} was absent (5 h.) in the IR spectrum, the reaction mixture was washed successively with saturated sodium bicarbonate, water and dried over anhydrous Na_2SO_4. After removal of solvent, the crude product obtained was distilled under reduced pressure to obtain pure homogeneous protected aldehyde, **20**.

Yield: 11.97g (94%)

B.P: 85°C/2mm (Lit85.7°/2mm)

IR(neat): 2970,1740,1530,1350,1225,1070,and950cm-1

PMR (80 MHz $CDCl_3$,*Fig.3*),δ : 0.90 (s, 3H), 1.20 (s, 3H), 1.60 (s, 3H), 1.70-2.00 (m, 5H), 3.80 (m, 4H), 4.90 (d, 1H), 5.00 (s, 1H).

Hydroboration of olefin 20 leading to 2,2,4-trimethyl cyclohexane 3-ol,1-carbaldehyde acetal 21:

To a stirred solution of the olefin **20** (11.0g, 0.056mol) in dry THF (100 ml) containing $NaBH_4$ (1.0g, 0.028mol), $BF_3.OEt_2$ (6.83 ml, 0.056mol) was introduced drop by drop and the reaction mixture stirred for 6 hrs at room temperature. The excess $NaBH_4$ was carefully destroyed with water (5 ml) at 0°C. After the addition of 3N NaOH

(5 ml), followed by 30% H_2O_2 (7.0 ml), the reaction mixture was kept under stirring for 6 more hours. The dilution of the reaction mixture with ether led to the fine separation of organic layer from aqueous layer. The aqueous layer was extracted with ether (3 x 100 ml). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4. After removal of solvent, the crude product obtained was filtered through a column of silica gel using 5-10% ethylacetate in petroleum ether.

Yield: 11.8g (94%)

IR(neat): 3450, 2960, 1530, 1360, 1230, 1050,and 950 cm^{-1}

PMR(200MHz,$CDCl_3$)δ: 0.90 (d, J=7Hz, 3H), 1.15 (s, 3H), 1.25 (s, 3H), 1.40-2.30 (m, 7H), 2.65 (m, 1H), 3.85 (t, 4H), 4.90 (d, 1H).

Oxidation of secondary alcohol 21 to 2,2,4 trimethylcyclohexanone-3,1-carbalde hyde acetal 22:

To a cooled and stirred solution of alcohol (11.0 g, 0.051mol) in dry ether containing celite (3.0 g), PDC (15.0 g) was added in three lots and the reaction mixture was further stirred. The progress of the reaction was monitored by IR, where the gradual disappearance of alcoholic band at 2990 cm^{-1} and appearance of new carbonyl frequency band at 1710 cm^{-1} indicated the course of the reaction. The complete disappearance of -OH band took 4 hrs. The reaction mixture was filtered through a column of silica gel containing a pad of celite, eluted with 5% ethylacetate in petroleum ether to get pure colourless homogeneous product.

Yield: 8.82g (70%)

IR (neat): 2800, 1710,1540, 1400, 1380, 1230, 1070 and 950 cm^{-1}

PMR(200MHz,CDCl3,*Fig.*4)δ : 0.95 (d, 3H), 1.04 (s, 3H), 1.20 (s, 3H), 1.53-2.15 (m, 5H), 2.40-2.60 (m, 1H), 3.77 (m, 4H), 4.71 (d,1H).

Grignard reaction of ketoacetal 22 with 2-phenylethylbromide to get 2,2,4 trimethyl cyclohexane 3-ol[3-ethylbenzene]-1-carbaldehyde acetal 23.

To a presynthesized Grignard reagent from 2-phenylethylbromide (2.6 g, 0.0141mol) and Mg turnings (0.0141 g atom) in dry THF (10 ml) was slowly introduced a solution of keto acetal **22** (2.0 g, 0.0094 mol) in dry THF (10 ml). The reaction mixture was refluxed under stirring. The progress of the reaction was monitored by TLC and when the starting keto acetal totally disappeared (24 h), the reaction mixture was quenched with saturated NH_4Cl solution. It was extracted with ether (3 x 25 ml), the combined organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was column chromatographed over SiO_2 using 20% ethyl acetate in petroleum ether to get pure product **23**.

Yield: 0.45 g (15%)

IR: (neat). 2922, 1600, 1530, 1350, 1210, 1050, 1000, and 950 cm^{-1}

PMR(200MHz)δ (*Fig.6*): 0.90 (d, J=7Hz, 3H), 1.10 (s, 3H), 1.25 (s, 3H), 1.50-2.20 (m, 6H), 2.65 (m, 1H), 2.85 (t, 4H), 3.80 (m, 4H), 4.80 (d, 1H), 7.25 (m, 5H).

Preparation of 2,2,4 trimethylcyclohex-3ene[3-ethyl-2-oxo-phenyl]1-carbaldehyde acetal 24.

To a suspension of sodium hydride (0.120 g, 0.005 mol) in dry benzene, freshly distilled acetophenone (0.60 g, 0.005 mol) was slowly introduced. After stirring for an hour, the keto acetal **22** (1.0 g, 0.0047 mol) in dry benzene was slowly introduced. The reaction mixture was heated to reflux. When the starting material disappeared (20 h) as monitored by TLC, the reaction mixture was quenched cautiously with ice-cold water. The organic layer was separated, the aqueous layer was extracted with ether (2 x 25 ml), the combined organic layer was washed with water, brine and dried over anhydrous

sodium sulphate. After removal of solvent, the crude product was chromatographed over SiO_2, using 10% ethyl acetate in petroleum ether to get a mixture of **24a** and **24b**.

Yield: 0.220 g. (15%)

IR:(neat). 1680 cm^{-1}

PMR(200MHz,$CDCl_3$) δ 0.90 (s, 3H), 0.95 (s, 3H), 1.00 (s, 3H), 1.30 (s, 3H),

Fig.7 0.90 to 0.95 (4 lines, 3H), 1.45 (s, 3H), 1.50 (s, 3H),

1.55-2.00 (m, 5H), 3.60-3.90 (m, 6H), 4.70 (dd, 2H) and

7.10-7.80 (m, 5H).

Execution of *Schemes-4 & 5*: Aldol condensation of the keto-acetal 27 with substituted acetophenones and the final cyclization to ABC ring system:

(a) Preparation of the 4 methylcyclohex 3-one 1-carbaldehyde acetal 27

(i) Preparation of the 4 methylcyclohex 3-ene carbaldehyde 8:

This compound was prepared by the Diels-Alder reaction of isoprene and acrolein, as described in the preparation of the aldehyde **4** (Chapter-I, Experimental).

b.p 80-5°C/10mm (oil bath)

Yield: 52%

IR:(neat). 1720 cm^{-1}

PMR(200MHz,$CDCl_3$)δ: 1.60 (s, 3H), 1.70-1.95 (m, 7H), 5.05 (d, 1H), 9.80(d,1H)

(ii) Protection of the aldehydic function of 8 leading to 4 methyl cyclohex 3-ene 1-carbaldehyde 25:

This derivative was prepared as described earlier for **20**.

b.p. : 60-3°C (oil bath temperature) / 5mm of Hg

Yield: 92%

PMR: (200MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.70-2.00 (m, 7H), 3.60-4.00 (m, 4H), 4.80

(d, 1H), 5.05 (d, 1H).

(iii) Hydroboration/Alkaline oxidation of the olefin 25 leading to 4-methylcyclo hexane3-ol,1-carbaldehyde acetal 26:

The experimental procedure followed has already been described for **20**.

Yield: 95%

IR:(neat) . 3460, 2950, 1530, 1350, 1210, 1060, 1000 and 950 cm^{-1}

PMR:(200MHz,$CDCl_3$)δ : 0.95(d, 3H),1.60-2.00(m,10H),3.50-3.90(m,4H),4.80(d,1H)

(iv) PDC oxidation of 26 leading to 4-methylcyclohex 3-one1-carbaldehyde acetal 27:

The experimental procedure followed for the oxidation of secondary alcohol **26** to ketoacetal (**27**) was the same as described previously for 22.

Yield: 76%

IR: (neat) 2950, 1700, 1550, 1320, 1200, 1050, 1000, and 900 cm^{-1}

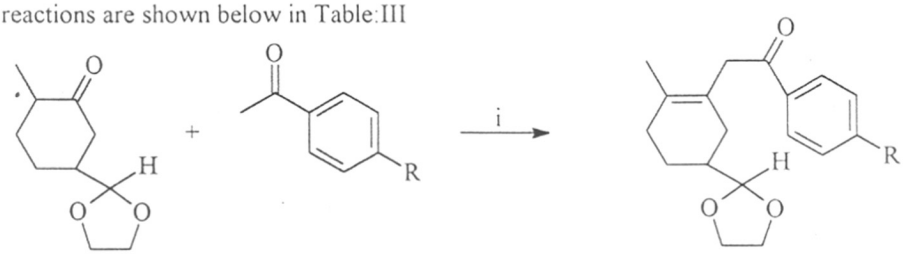
PMR (200 MHz,*Fig.8*)δ :1.0 (d, 3H), 1.40-2.50 (m, 8H), 3.80 (m, 4H), 4.70 (d, 1H)

^{13}C-NMR(50.3MHz,$CDCl_3$) δ :13.95, 25.72, 33.94, 38.94, 41.44, 44.78, 44.94, 64.66, 105.57, 211.15

(b) Aldol condensation of ketoacetal 27 with *p*-substituted aceto-phenones leading to 28 to 31 (*Scheme-5*):

To a suspension of sodium hydride (1.1 eq.) in dry toluene ,the acetophenone (1.1eq)was introduced, the acetophenone (1.1 eq.) and the reaction mixture was stirred for an hour; a solution of keto acetal **27** (1.0 eq.) in toluene was added dropwise and the reaction mixture was refluxed and the course of the reaction was monitored by TLC. After the complete disappearance of starting keto acetal **27** (4 -5 h), the reaction mixture was quenched with ice-cold water. The aqueous layer was extracted with ether (2 x 50 ml). The

combined organic layer was washed with water, brine and dried over anhydrous sodium sulphate. After removal of solvent, the crude product obtained was column chromatographed. The quantities of the ketoacetal, the reagents and the yields of the reactions are shown below in Table:III



i) NaH, $PhCH_3$

R = H, CH_3, Isobutyl, Cl
28 29 30 31

Table:III

S.No.	A (in moles)	R	In gms. B moles	in gms. NaH	in gms. C	% yield	Product No.
1.	0.500 (0.0027M)	H	0.360 (0.003M)	0.075 (0.003M)	0.390	50	28
2.	0.500 (0.0027M)	CH_3	0.365 (0.003M)	0.075 (0.003M)	0.400	50	29
3.	1.00 (0.0054M)		1.00 (0.006M)	0.145 (0.006M)	0.910	50	30
4.	0.500 (0.0027M)	Cl	0.460 (0.003M)	0.075 (0.003M)	0.480	55	31

Spectral data for aldol products:

Product 28: 4-methyl cyclohex 3-ene[3 ethyl-2-oxo phenyl]1-carbaldehyde acetal :

IR (neat,*Fig.9*): 2850,1690,1600, 1200,1100, 900 and 800 cm^{-1}

PMR (200MHz,$CDCl_3$,*Fig.10*)δ: 0.90 to 1.10 (d, 3H), 1.20-1.40 (m, 2H), 1.50 (s, 2H), 1.55 - 2.50 (m,3H), 3.55 (s, 2H), 3.70 (m, 4H), 4.55 (m, 1H), 7.40 (d, 3H), 7.88 (d, 2H).

Product 29:4 methylcyclohex 3-ene[3-ethyl-2-oxophenyl-4'methyl]1-carbaldehyde acetal:

IR:(neat) 2900 , 1680 ,1600, 1200 1050,950,and 800 cm^{-1}

PMR(200MHz, *Fig.11*):δ 1.00 (d, 3H), 1.60 (s, 3H), 1.70-2.40 (m, 7H), 2.50 (s, 3H),3.70 (m, 2H),3.90(m, 4H), 4.75 (m, 1H), 7.35 (d,2H), 7.90 (d, 2H)

Ms:m/z (rel.intencity) 300 (M^+, 5) 228(10), 181(5), 166(5), 155(50), 119(70), 91(20), 73(100), 55(17).

Product 30: 4 methyl cyclohex 3-ene[3 ethyl 2-oxo-phenyl 4'isobutyl]1-carbldehydeacetal

IR(neat) : 2850, 1690, 1600 1550, 1250, 1100,1000,and 900 cm^{-1}.

PMR(200MHz, *Fig.14*): 0.90 (d, 6H), 1.10-1.45 (m, 2H), 1.70 (s, 3H), 1.80-2.25 (m, 6H), 2.60 (d, 2H), 3.75 (d, 2H), 3.85 (m, 4H), 4.75 (d, 1H), 7.25 (d, 2H), 7.90 (d, 2H)

Product 31 and 31a: 4 methyl cyclohex 3-ene [3 ethyl-2-oxo-phenyl,4'chloro] 1-carbaldehyde acetal

IR(neat): 1600, 1700 cm^{-1}

PMR(200MHz,$CDCl_3$) δ 0.90 to 1.10 (4 lines, 3H), 1.00 (t, 1H), 1.60 (s, 3H), 1.70-

(*Fig.13*) 2.40 (m, 6H), 3.70 (m, 2H), 3.90 (m, 4H), 4.70 (d, 1H), 5.50 (s, 1H), 7.40 (d, 2H), 7.90 (d, 2H)

Cyclization of 30 leading to 33a and 33b:

To an ice-cooled and stirred solution of ketoacetal -**30** (0.340 g, 0.001mol) in dry dichloromethane (50 ml) was slowly added stannic chloride (0.520 g, 0.002 mol) in dry dichloromethane (5 ml). The reaction mixture was slowly warmed up to room temperature and the course of the reaction was monitored by TLC. The complete disappearance of

starting keto-acetal **30** took 3-4 hours. Then, the reaction mixture was successively washed with saturated sodium bicarbonate, water and brine. The organic layer was dried over anhydrous sodium sulphate. After removal of solvent, the crude product obtained was column chromatographed to get pure product 0.134 g. (50% yield).

IR (*Fig.15*): 3450, 3000, 1710, 1680, 1600, 1450, 1200, 1000, 770, 500 cm^{-1}

PMR (200 MHz, $CDCl_3$) δ: (*Fig.16*) 0.90 (two doublets, 6H), 1.20 (two 3H doublets and 2.20 (two singlets together integrating for 3H), 1.20-1.90 (m, 7H), 2.40-2.55 (d, 2H), 3.20-3.30 (m, 1H), 3.80-4.10 (m, 4H), 4.70-5.20 δ (m, 1H), 7.10-7.90 (m, 3H).

Mass (*Fig.17*): 298 (M^+, 20), 280(50), 270(18), 247(5), 233(15), 227 (15), 176(20), 161(100), 136(20), 118(15), 107(5), 94(5), 91(30), 85(10), 73(5), 55(10).

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CHAPTER - III

A New Heterogeneous Catalytic Method for the Synthesis of Aziridines and Cyclopropanes

Chapter-III: A New Heterogeneous Catalytic Method for the Synthesis of Aziridines and Cyclopropanes

3.1.0 GENERAL INTRODUCTION

This chapter and the one that follows present the development of efficient and new methodologies for the following transformations using K-10 montmorillonite to clay catalysts.

1. Aromatic and aliphatic imines into corresponding aziridines
2. Transformation of substituted olefins into the corresponding cyclopropyl derivatives
3. Realization of β-ketoesters from aliphatic/aromatic aldehydes and finally,
4. Conversion of aliphatic and aromatic amines into the corresponding β-amino esters

The methodologies developed for the above transformations involve the reaction of α-diazo esters and are catalyzed by different metal-exchanged clays. Thus, the basic theme of these two chapters is the realization of the catalytic potential of clays especially mont-morillonite-K10 in leading to useful and important organic transformations. It is, therefore, both pertinent and useful to provide an overview of clay-catalyzed organic reactions, so that the present work can be viewed in a proper perspective.

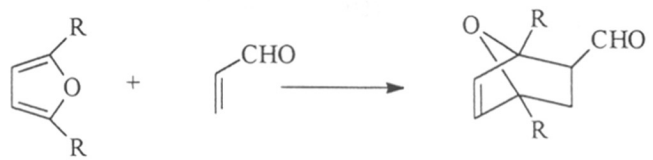
Use of aluminosilicates as catalysts in useful organic transformations is gaining importance of late. These inorganic catalysts are known to enhance the rates of the reactions in numerous ways such as stabilization of high energy intermediates and storing energy in their lattice structure and releasing it in the form of chemical energy. They often exhibit high surface acidity and this property has been harnessed to realise useful organic transformations.

The catalytic activity of clays is known to be arising from its structure as well as spacial arrangements.[R] The clay particles are organised, often into parallel plates stacked one upon another; clays are aluminosilicates in which the Al^{III} cations are bonded to an

octahedral arrangement of oxygen anions, repetition of these AlO_6 units in two dimensions forms an octahedral layer. Similarly, a tetrahedral layer is formed from silicate SiO_4 units. Generally, clays are classified according to the relative number of tetrahedral and octahedral layers. Montmorillonite clays which find extensive use in organic chemical applications, have an octahedral layer sandwitched between two tetrahedral layers. From this ideal situation, a different clays can arise by replacement of either aluminium or silicon by other atoms. A number of metallic cations usually divalent, such as Mg^{II}, Fe^{II}, Zn^{II} substitute for Al^{III} in the octahedral layer. Such replacements provide a diversity of catalysts. The catalysis offered by clay is mainly due to its surface property in terms of surface area and also due to either bronsted acidity or lewis acidity. With overall dimensions below 2 microlitres, montmorillonites have specific areas of the order of 500 square meters/gm. A distinction is made between the Lewis and Bronsted acidities by an IR spectrum of the catalyst. For example, when a base like ammonia, an aliphatic amine or pyridine, is adsorbed on the catalyst, an IR spectrum shows absorptions that can be assigned to either the metal ion coordinated base (1440 and 1465 cm^{-1}) or the protonated base at 1545 cm^{-1}. We have used a montmorillonite clay which displayed the required IR absorption characteristic of Lewis acid sites. From this point of view, an overview of recent literature pertaining to organic transformations employing clays in place of Lewis acids is presented here.

Diels-Alder reactions have been utilized to explore the Lewis acid efficacy of clay catalysts. For example, P.Laszlo and J.Leuckarti *et al.*[1] realized the cycloadducts from the Diels-Alder reactions of furan and substituted furans with acrolein and methylvinyl ketone using K-10 bentonite clay doped with Fe^{3+}; the yields varied from 20% to 80%. Such Diels-Alder reactions with aromatic dienes are difficult to realize owing to the loss of aromaticity in the reaction. These authors could access 7-oxabicyclo [2:2:1] heptane

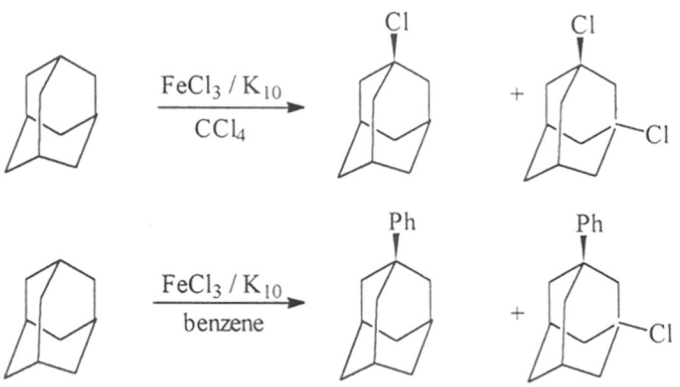
system which features in a number of natural products, by this reaction. The use of clay catalysis obviated the use of high pressures (*Scheme-1*).



R = H, CH_3 20-80% yield

Scheme-1

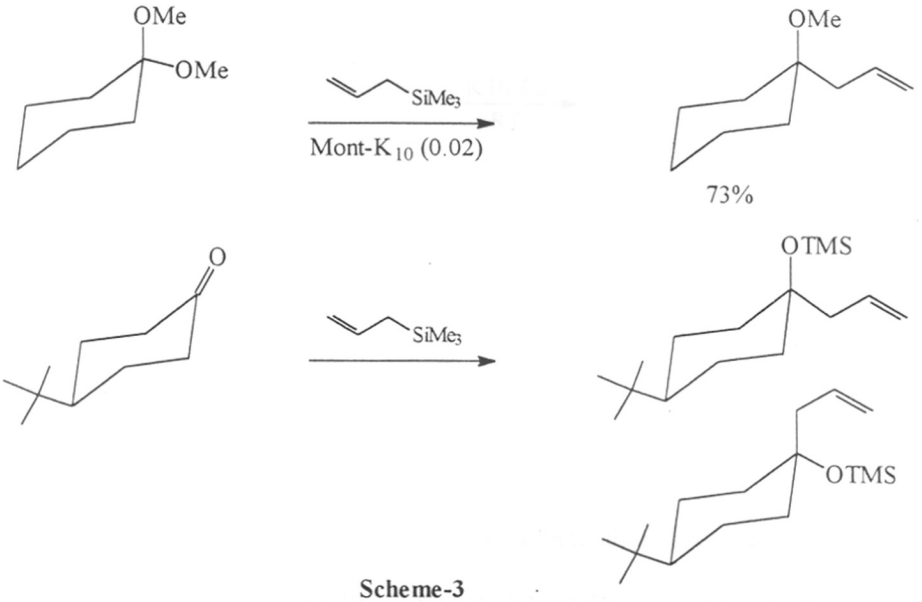
Another interesting example is the direct $FeCl_3$ doped clay-catalysed Friedel Crafts arylation and chlorination of admantane reported by P.Laszlo *et al* These authors achieved selective chlorination at the 3° position of admantane and also reported the first direct arylation of admantane by this clay catalysis (*Scheme-2*).



Scheme-2

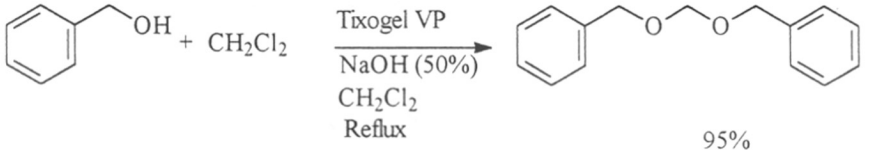
This alkylation of benzene is assumed to have arisen from the adamantyl cation generated on K-10 clay.

The efficacy of clay catalysis in C-C bond forming reactions is demonstrated by Onaka *et al.*[2] who allylated a number of acetals and carbonyl compounds with allylic trimethylsilane in 57-90% yields employing montmorillonite K-10 (*Scheme-3*).



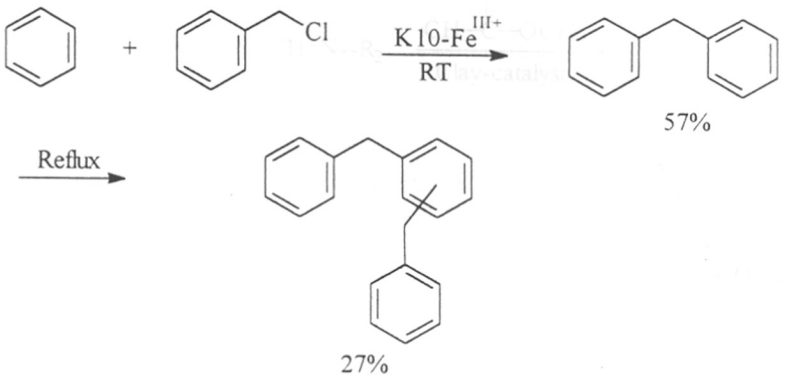
Scheme-3

Anionic reactions are efficiently catalysed by clay catalysts; for example, Laszlo[3] reported the Williamsons coupling of methylene chloride with benzyl alcohol using Tixogel V.P., a class of organophilic clays in which 3° ammonium ions with long alkyl chains are substituted for the natural Na^+ or K^+ ions.



Scheme-4

K-10 montmornillonite upon exchange with transition metal ions display an outstanding catalytic activity in Friedel-Crafts reactions (*Scheme*-4) leading to improved yields and conversions and reducing reaction times. For example, benzene is benzylated at room temperature in a very short time with K-10/Fe^{III} catalysis, while the product benzylbenzene is further benzylated at the reflux temperature.[4] (*Scheme-5*).

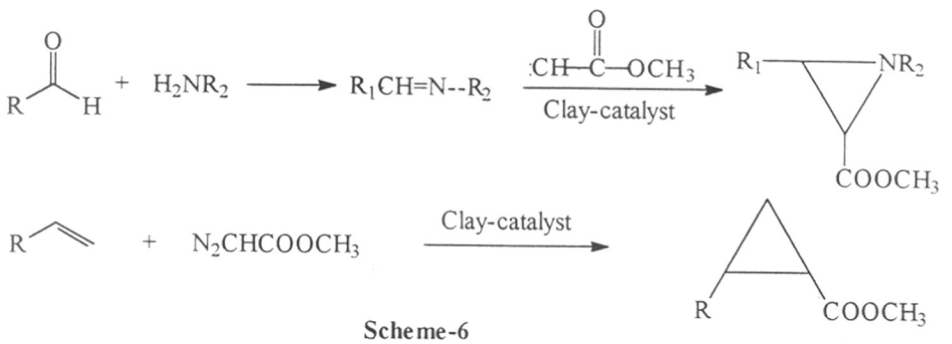


Scheme-5

The foregoing examples of clay catalysis are only illustrative and by no means exhaustive. The characteristic features of such a catalysis are short reaction times, easy separation of products and specific Lewis acid catalysis. Another important feature of clay catalysis is that such clays act as micro reactors with tremendous surface area. An overview of these examples and related work in literature revealed that clay catalysis has been employed for pericyclic reactions, and for both cationic and anionic organic reactions. Surprisingly enough, we did not come across examples of carbene reactions using clay catalysis.

3.2.0 OBJECTIVE OF THE PRESENT WORK:

As already stated before, the potential of clay catalysis in carbene addition reactions to unsaturated systems have not been explored. We, therefore, envisaged that addition of carbenes under clay catalysis to both C=C and -C=N- functionalities is worthwhile investigating in leading to useful organic transformations. Such a plan is depicted below: (*Scheme-6*)



Scheme-6

Such a scheme, when transformed into a methodology, is expected to lead to substituted aziridines and cyclopropanes.

The commercial availability of K-10 Mont morillonite and the ease with which differently substituted aliphatic and aromatic imines can be prepared and also the facile accessibility to different aliphatic and aromatic alkenes prompted us to explore the scheme outlined above. The first section of this Chapter deals with our work on aziridination, while the next section presents our efforts towards cyclopropanation. With this objective, a survey of literature was carried out for aziridination methods and for the importance of aziridines in organic synthesis and industry. Aziridines find great application as organic synthetic intermediates since the ring strain can be harnessed to realize other reactions. Besides the ring strain, aziridines act as electrophiles and thus, nucleophilic opening of this strained ring has a potential to generate different types of functionalities.

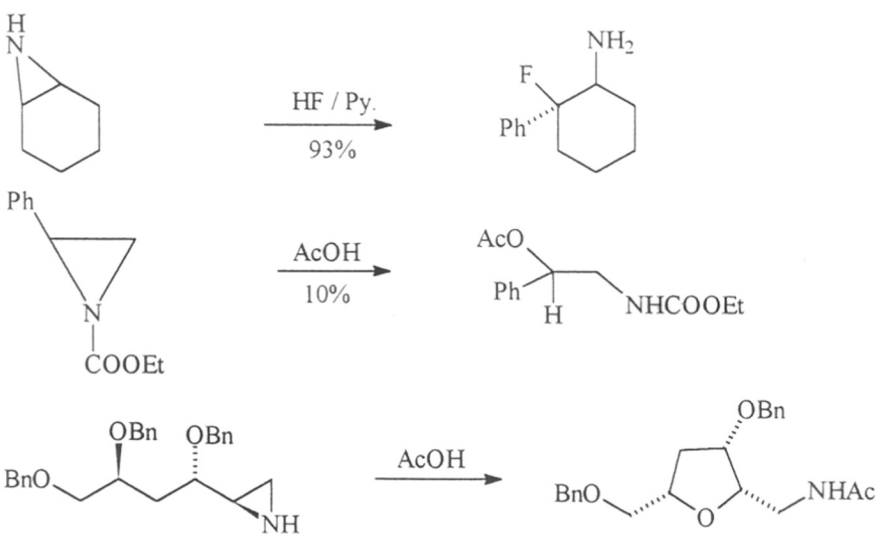
Section-I

Carbenoid Transfer to Imines: A New Heterogeneous Catalytic Synthesis of Aziridines

3.3.0 INTRODUCTION:

Aziridines as organic synthetic intermediates:

The potential of aziridines in organic synthesis owes essentially to its ring strain and the electrophilicity. Therefore, most of the applications originate from either acid catalysed or nucleophilic opening of the ring. The acid-catalysed opening generally occurs with the nitrogen unsubstituted aziridine and needs either protonation, quaternization or Lewis acid adduct formation. In a different class of activated aziridines, wherein the nitrogen atom is substituted with electron-withdrawing groups, ring opening occurs with generation of a negative charge on nitrogen which is stabilized by the substituent. Some examples of the above processes are given in *Scheme-7*.

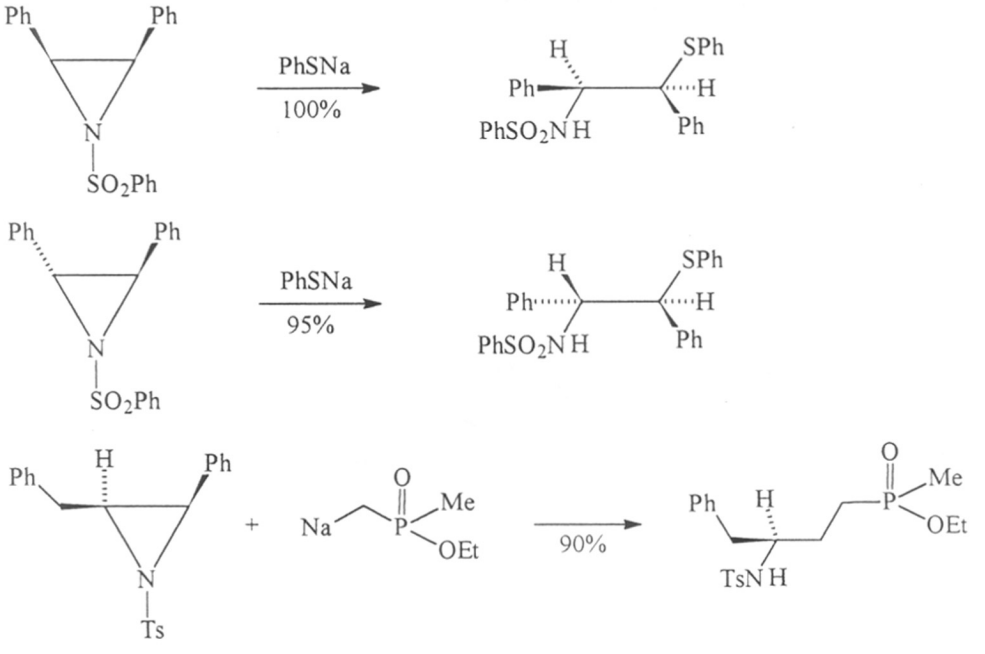


Scheme-7

The examples given above are self-explanatory.

Although acid-catalyzed ring opening leads to useful intermediates, the nucleophilic ring opening, especially when activated with electron withdrawing group on the nitrogen atom generates a plethora of useful compounds from monosubstituted aziridines. The attack occurs by a SN_2 process leading to inversion of configuration and

for mono-substituted aziridines, nucleophilic attack exclusively occurs at the methylene carbon atom. A few illustrative examples are shown in *Scheme-8*.



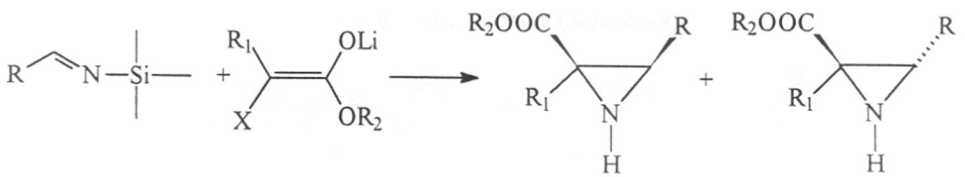
Scheme-8

Besides the opening of the basic aziridine ring, opening of aziridinoalcohols and aziridine-2-carboxylates (*Scheme*-8) have offered diverse organic intermediates which find extensive application in synthesis of natural products, for example, peptides. An excellent review on this topic is available.[7] It can be seen that aziridines, aziridine alcohols and aziridine-2-carboxylic acids are utilised to generate useful synthetic intermediates that are used in natural product synthesis. Therefore, the methods for aziridination are aimed towards getting chiral aziridines.

The potential of chiral aziridines in the treatment of cancer as alkylating agents has been recognised. The mitomicin family of anti-tumor antibiotics is the most well known class of natural products containing the aziridine ring. Aziridines are also used as affinity probes for receptors and peptides.[8]

3. Addition of enolates of 2-halocarboxylic esters to N-trimethylsilyl imines:

A method for the preparation of N-unsubstituted aziridines has been reported, in which enolates of α-haloesters were treated with N-trimethyl silyl imines prepared from different aldehydes. This reaction was carried out between -78°C to -30°C and was essentially done on α-bromotertiarybutyl esters; yields in the range of 25 to 60% were obtained. A notable feature of this method is the exclusive formation of *cis* aziridines and the authors suggest a mechanism involving an intramolecular nucleophilic displacement of the halide by the imine nitrogen (*Scheme-11*).



R = n-alkyl C_6-C_8
R_2 = *t*-butyl

Scheme-11

As the work presented in this Chapter pertains to metal-catalysed reactions, brief account of metal-catalysed aziridinations known so far is presented below. Although aziridination is realized by nitrene addition to C=C bonds, and complemented by the addition of carbenes to imines, we are restricting outselves to the latter reaction.

Catalytic methods for Aziridination:

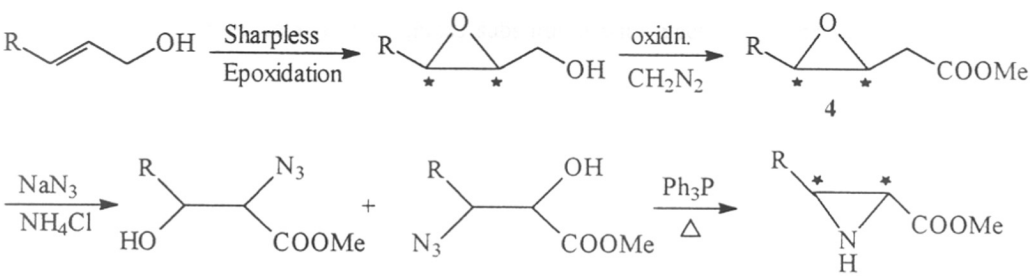
Coppertriflate catalysed group transfer from ethyldiazoacetate to differently substituted imines has been recently reported by Rasmussen and Jorgensen.[12] leading to aziridines in 35 to 95% yields. These authors observed that the substituent on the nitrogen plays a crucial role in both the yield and diastereoselectivity (*Scheme-12*). While a phenyl substituent led to a yield of 95%, bulky substituents or electron withdrawing substituents on nitrogen lowered the yields.

3.3.1 SYNTHESIS OF AZIRIDINES: A REVIEW

Classical methods for aziridination

1. Ring opening of epoxides:

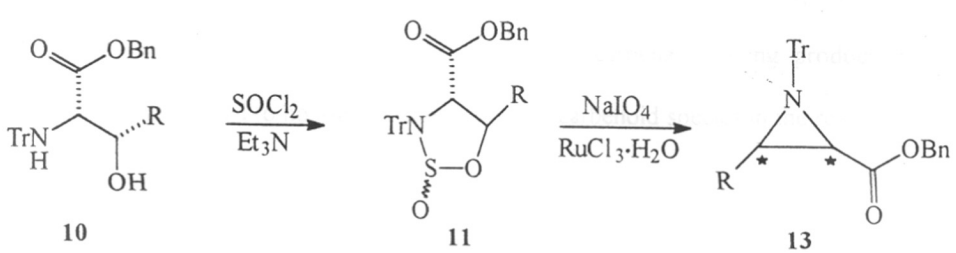
Epoxides by virtue of their electrophilicity and the ring strain are susceptible to opening and this aspect has been utilized for the synthesis of aziridines. For example, B.Zwanenburg *et al.*[9] treated the glycidic esters with sodium azide to obtain a mixture of isomeric azidoalcohols which on treatment with triphenylphosphine afforded 1H-aziridine-2-carboxylic esters (**1**). These authors prepared the required chiral glycidic esters **4** from sharpless epoxidation of allylic alcohols (*Scheme-9*).



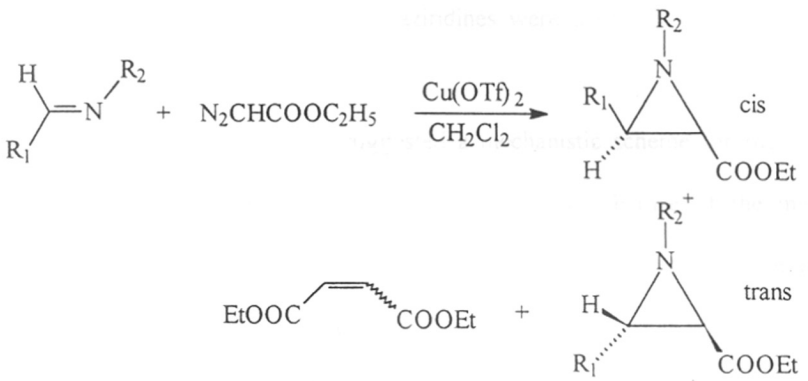
Scheme-9

2. Ring closure of α-amino alcohols:

A one-step synthesis of chiral N-trityl-L-aziridine-2-carboxylic esters was reported[10] in which N-trityl-L-serine benzyl esters was treated with sulfur chloride to obtain the cyclic sulphamidite which on oxidation with $NaIO_4/RuCl_3$ H_2O afforded the aziridine. Such a ring closure of amino alcohols to aziridines required a bulky substituent on the nitrogen (*Scheme-10*)

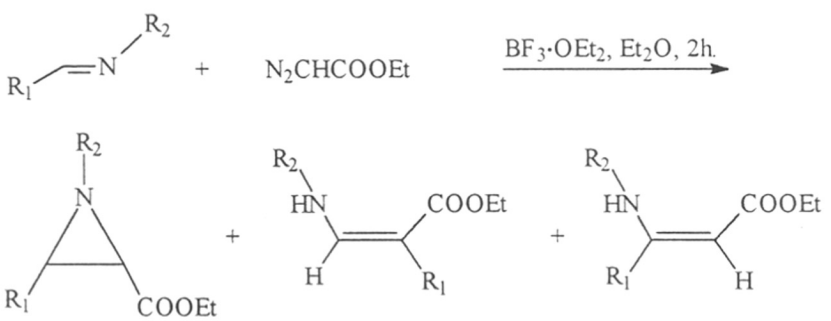


Scheme-10



Scheme-12

It may be added that with imines possessing electron donating substituents, carbene dimerization reaction was suppressed, while the dimeric products methyl maleate and fumarates were considerable with imines substituted with electron withdrawing groups (*Scheme-13*).

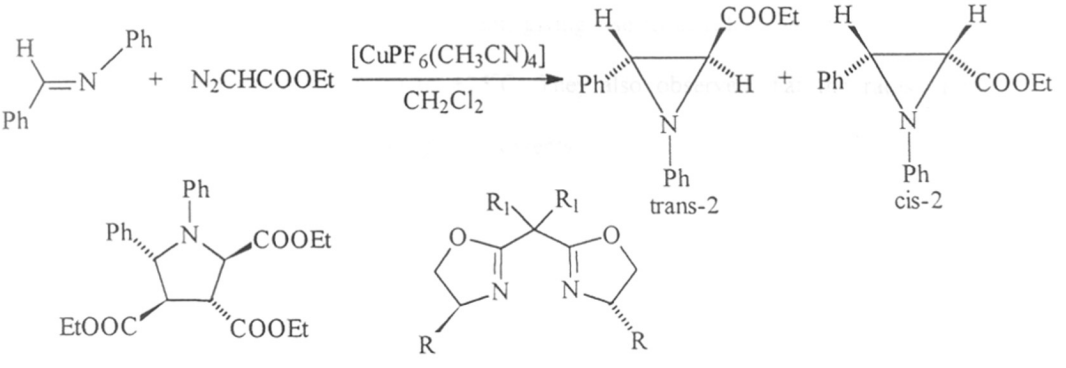


Scheme-13

There was a preponderance of *trans*-aziridine in this method. A highly interesting Lewis acid catalysed aziridination reaction has been reported by Casarrubios *et al.*[13] in which exclusively *cis*-aziridines are obtained. These authors have used different Lewis acids such as $BF_3(OEt)_2$, $AlCl_3$ and $TiCl_4$ and transferred ethyldiazo group to various substituted imines in varying yields. The absence of carbene coupling products *viz.* fumarate was attributed to non-involvement of metal carbenoid species in the reaction.

It may be mentioned that *cis*-aziridines were preponderantly formed over the *trans*-isomer.

These authors have also suggested a mechanistic scheme for the formation of aziridines as well as the side products. The essential feature of the mechanism is activation of imine by complexation with Lewis acid, followed by the nucleophilic addition of ethyldiazoacetate, leading to an intermediate shown in this *Scheme-14*. These mechanistic aspects are again discussed.



Scheme-14

Jacobson *et* al.[14] have explored various transition metal catalysts for the group transfer of ethyldiazoacetate to the imine, N-benzylidene aniline and found that Copper (I) salts in association with bis (dihydrooxazole) ligands were most effective in catalysing the aziridination. The use of Cu(I) hexafluorophosphates along with the chiral substituted oxazole furnished enantiomerically enriched diastereomeric aziridines and racemic pyrrolidine. They observed that electron donating substituents in either of the aromatic rings of the imines led to higher diastereoselectivity with lower yields of the aziridination (17-34%). These authors have proposed a ylide intermediate to rationalize the formation of aziridines and pyrrolidine.

The substituent in the chiral catalyst, bis-oxazole, appears to alter the stereoselectivity; nevertheless, the formation of *cis*-aziridines predominated.

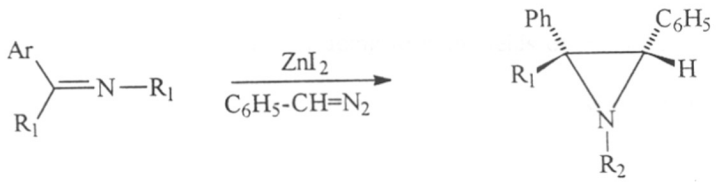
The methods so far described for aziridination involved Lewis acid-catalysed carbene addition to substituted imines. An alternate method to realise the same result is the addition of a nitrene to a substituted olefin. There has been a series of reports from Evans *et al.*[15a,b] describing the development of a copper catalysed olefin aziridination. These authors observed that soluble Cu^{I} and Cu^{II} triflates and perchlorate salts are efficient catalysts for aziridination of olefins with N-(*p*-tolylsulphonyl)imino) phenyliodinane, PhI=NTs as the nitrene precursor. Both electron rich and electron deficient olefins reacted with this reagent, giving rise to aziridines in 55-95% yields at temperatures ranging from -20 to +25°C. They also observed that the rates of the reaction were enhanced by polar aprotic solvents.

Olefin	Catalyst	Yield %
X=H	$CuClO_4$	89
X=OMe	$CuClO_4$	78
X=Me	$CuClO_4$	83
X=Cl	$CuClO_4$	90
$X=NO_2$	$CuClO_4$	89

The same authors have extended this reaction to realize enantioselective aziridination using *bis*(oxazoline)copper complexes as chiral cation.

Bartnik and Mcoston[16] studied the reaction of phenyldiazomethane with N-allylidine amines in the presence of zinc iodide and obtained N-substituted 2-aryl-3-phenyl aziridines in moderate yields. A notable aspect of this work is the attainment of the *cis*-aziridines exclusively. However, the other aliphatic carbene transfer reagents such

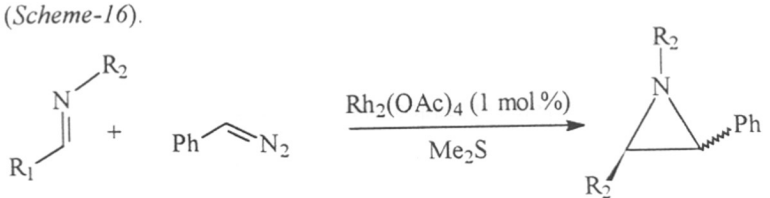
as diazomethane, ethyl diazoacetate, etc. failed to result in aziridination (*Scheme-15*). Therefore, this method does not appear to be of a general character.



15-74% yield

Scheme-15

A novel, catalytic and asymmetric process for aziridination has been recently reported by Agarwal *et al.*[17] These authors observed that a slow addition of a diazocompound to a solution of a suitable metal salt, sulfide and imine afforded the corresponding *trans* aziridines as the major products. As there was no aziridination in the absence of sulfide, these authors invoked the intermediacy of a sulfur ylide in the addition of the carbene to the imine. Electron withdrawing groups on the imine nitrogen prevented the direct reaction of the carbenoid with the imine. They obtained aziridines with a predominance of *cis* isomers when ethyldiazoacetate was the carbene source; on the other hand, use of N,N-diethyldiazoacetamide gave a higher yield of the *trans* product (*Scheme-16*).

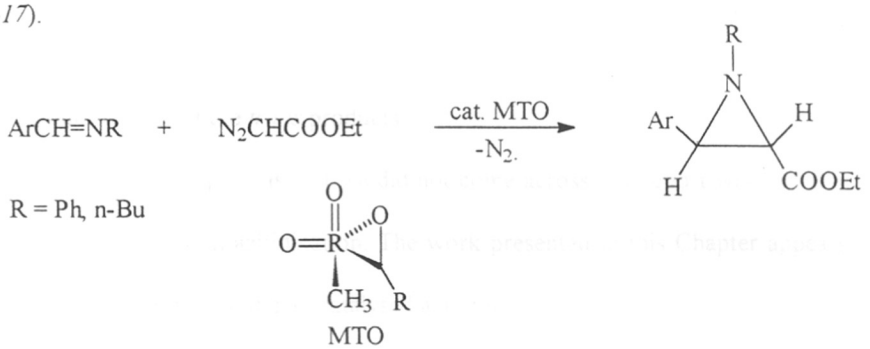


Scheme-16

R^1	R^2	Yield (%)	*trans/cis* ratio
Ph	TS	90	4:1
P-ClC_6H_4	SES	80	3:1
P-MeC_6H_4	SES	96	3:1

SES = β-(trimethylsilyl) ethane sulfonyl

Another catalytic method for aziridination was recently reported by Espenson and Zhu,[18] who observed that methylrheniumtrioxide (MTO) catalyses the reaction of ethyldiazoacetate with aromatic imines leading to high yields of *trans* aziridines. These authors suggested the involvement of a carbenoid intermediate in which the electron rich double bond attacks the :CH-COOEt group, as a possible mechanism of aziridination (*Scheme-17*).



Scheme-17

A close perusal of the results from various catalytic methods of aziridination described above reveals the following points:

1. Most of the researchers have used ethyl diazoacetate as the carbene source, while the work of Bartnik *et al.* is restricted to phenyldiazomethane and the other carbene sources failed to effect aziridination with this ZnI_2-catalysed reaction.

2. Among the metal-catalysed reactions, copper triflates, rhodium acetate and MTO have been employed with ethyl diazoacetate as the carbene source. While coppertriflates gave aziridines in 35-96% yields, Cu hexafluoro phosphates furnished yields of 17-34%.

3. The effect of ring substitution on the aromatic portion of the aldehyde appears to be inconsistent; The parachloro substituent did not yield aziridines at all with copper catalysis, while high yields of aziridines were obtained with the same substituent in rhodium acetate catalysis.

4. The substitution on the nitrogen atom and on the aromatic ring of the aniline portion appears to be crucial in determining yields of the reaction and also in diastereoselectivity. Electron donating groups on either of the rings appears to increase stereoselectivity.

5. Most of the Lewis acid catalysed aziridinations have led to higher or exclusive stereoselectivity in favour of *cis* products, while the use of transition metal catalysts has resulted in predominance of the *trans* products.

The most important point is that we did not come across any report wherein clay has been used as a catalyst in aziridination. The work presented in this Chapter appears to constitute the first examples of clay catalysed aziridination.

3.3.2 PRESENT WORK

The work concerns with the development of a methodology for *trans* aziridines based on metal-incorporated clay-catalysed group transfer of methyl diazoacetate into the C=N functionality of substituted aromatic imines.

Methodology for Aziridination

(a) Scanning of various transition metals incorporated catalysts for aziridination:

Initially, it was intended to scan the efficacy of different catalysts for aziridination in terms of the yield and stereoselectivity, utilizing 4-chloro N-benzilidine aniline (**1**) as a model compound. This study was expected to identify the most suitable catalyst for the study of substituent effects on aziridination. Therefore, the following six-catalytic systems were selected to be tried in the aziridination of the model compound -

1. Rh^{III}/ SiO_2 gel
2. Rh^{III} / Al_2O_3
3. Rh^{III} / Carbon
4. Cu^{II} / Clay
5. Mn^{II} / Clay
6. Rh^{III} / Clay

As the objective of this study was to explore the catalytic activity of transition metals such as Rhodium, Manganese and Copper incorporated in clay, it was thought necessary to do some reactions of aziridinations, with these metals supported over other solids such as silica, alumina and carbon. The results from such a study would help in ascertaining the catalytic role of clay/transition metal in the aziridination. Another important reason for selecting the catalysts Rh/SiO_2 and Rh/Al_2O_3 is that basically clays are highly ordered a*lumino silicates* and, therefore, it would be interesting to check the efficacy of these ingredients separately. While Rhodium over carbon was commercially

available, the other catalysts were prepared by a procedure exemplified below by the preparation of Rhodium/clay.

The PMR spectrum of the product (*Fig.*2) was devoid of the benzylic, olefinic proton resonance (observed at 8.40 δ in the starting imine) and showed a 3H doublet in the region between 3.50 and 3.60 δ with a coupling constant of ~ 3 Hz. A significant feature of the spectrum was the appearance of two 1H doublets with J=3.8 Hz at 3.20 δ and 3.80 δ indicating *trans* disposed aziridine protons. The aromatic region showed well separated 2H multiplets at 7.00 and 7.60 δ typical of a *para* substituted phenyl ring and a 5H multiplet at 7.20 δ. The above data clearly indicated that the reaction has led to *trans* azirinated product. The *trans* geometry assigned to the product is based on literature observation that the *cis* and *trans* vicinal protons of an aziridine ring showed a large (7 to 8 Hz) and a small (2-3 Hz) coupling respectively. The doublet observed for the OCH_3 group is perhaps attributable to the long range coupling of -OCH_3 protons with the proton adjacent to the carbonyl group. Owing to the high resolution offered by the 300 MHz instrument, minor resonances that may be arising from the other diastereoisomers are seen in the region 3.40 to 3.60 δ.

The ^{13}C-NMR spectral data (*Fig.4*) clearly accounts for the 16-carbon atoms. ^{13}C-NMR (50 MHz, $CDCl_3$): δ 45.52, 45.62, 51.92, 119.82, 122.95, 123.62, 128.17, 128.29, 128.65, 128.96, 129.91, 130.83, 130.83, 133.72, 152.0 and 167.65.

It may be added that this spectrum also showed signals for the presence of extremely minor amounts of the *cis*-compound.

The mass spectrum (*Fig.3*) showed the molecular ion peak at (m/z) 287 and various other peaks among which peaks at m/e : 256 and 228 may be mentioned arising out of the loss of OCH_3 and -COOMe moieties from the molecular ion.

Thus, aziridination of *p*-chlorophenyl N-benzilidine aniline with methyl diazoacetate in Rh-clay catalysis afforded a 57% yield of *trans* aziridine. At this point, it may be mentioned that this *p*-chloro substituted substrate failed to yield aziridines with ethyl diazoacetate and copper catalysis, Jacobson *et.al.*[14] Aziridination was carried out with the above mentioned imine with the use of five more catalysts and the results are shown in *Table-I*.

Table-I: Results from reaction of methyl diazoacetate with the 4-chloro-N-benzilidine aniline with different catalysts[a]

Entry	Catalysts	t/h	Yield of aziridination[b] (%)
1	Mn^{II}/Clay	10	46
2	Cu^{II}/Clay	10	0
3	Rh^{III}/Clay	5	57
4	Rh^{III}/SiO_2	12	52
5	Rh^{III}/Al_2O_3	12	40
6	Rh^{III}/C^c	12	0

[a]Reaction condition: imine (10 mmol), diazoester (12 mmol), catalyst (10% w/w), dry benzene, reflux, [b]Yield of isolated and purified product, [c]Commercial catalyst from Degussa.

3.3.3 RESULTS AND DISCUSSION

From the foregoing example of a typical aziridination, the data given in the *Table* on a gross analysis brings out some special features about the aziridination reaction as well as the activity of the catalysts tried. It may be noted that both Rhodium over carbon and copper over clay did not catalyze the reaction at all, and there was no aziridination. Although carbenoid insertion reactions are known to be catalysed by copper salts, the reaction has not occurred with 4-chloro-N-benzylidene aniline with Cu/clay, may be because of the electron withdrawing effect of the chlorine atom. In this context, it can be recalled that Jorgenson *et al.* similarly did not realise aziridination with copper triflate catalysed reaction of ethyl diazoacetate with the 4-chloro substituted imine.

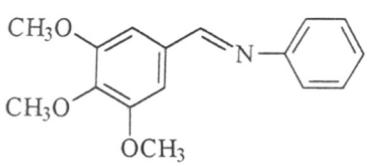
Rhodium over silica gel and Rhodium over alumina did catalyze the aziridination leading to 52 and 40% yields of products respectively, although the reactions needed longer durations. Manganese over clay, too, catalysed the reaction giving the products in a 46% yield. Surprisingly enough, this catalyst was found by us to be ineffective in the same reaction with any other differently substituted imines. Finally, the use of Rhodium over clay led to higher yields of the products in a shorter reaction time. From this study, it emerged that Rhodium over clay is better than any other catalyst that we have studied and, therefore, this catalyst was used in our investigations of substituent effects in the aziridination reaction.

A few blank experiments were carried out to ensure the need of metal incorporated clay as a catalyst for the aziridination. The reaction of methyl diazoacetate with 4-chloro-N-benzylidine aniline in benzene under reflux conditions for 8 to 10 hours in an atmosphere of N_2 without Rh/clay did not afford any product as evidenced by the total recovery of the imine.

Similarly, the above reaction was repeated using K_{10}-mont morillionite (without incorporation of any metal) and here also the unreacted imine could be totally recovered. Thus, the above experiments indicated the need of a metal incorporated clay as a catalyst for aziridination.

Effect of substituents in the aldehyde and aniline portions of the imines : A Study -

With the success realised in the aziridination of the 4-chloro-N-benzilidine aniline **1**, it was necessary to check the generality of this reaction, so that a general method for the synthesis of aziridines could emerge. With this goal, numerous aromatic aldehydes and aromatic amines substituted with both electron withdrawing and electron donating groups were condensed and the corresponding imines were obtained. In addition, two aliphatic aldehydes were condensed with aniline and the corresponding imines were utilized for aziridination. This study also included an imine derived from an alicyclic aldehyde and an alicyclic amine. The imines which were included for this study, have been shown in the *Scheme-18*.



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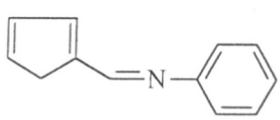

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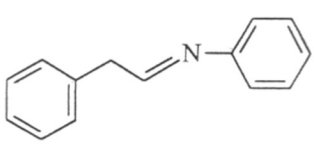
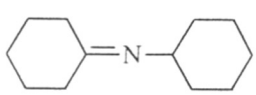


3



4

Scheme-18

1. Reaction of methyl diazoacetate with 3.4.5-trimethoxy N-benzylidine aniline:

This imine when treated with methyl diazoacetate, as described for p-Iso N-benzylidene aniline afforded a product in 75% yield, although the reaction required a longer time (10 hrs.). The PMR spectrum of the product (*Figure-6*) showed two major singlets and six signals of lower intensity together integrating for 12 protons in the region 3.60 δ to 4.00 δ indicating the presence of the three methoxy groups on phenyl ring and the carboxy methyl group on the cyclopropyl ring. In addition, this spectrum showed a two 1H multiplet at 3.60 and 4.15 δ for the aziridinyl protons, although the coupling constant could not be discerned accurately. The absence of the resonance for the imine proton and occurrence of many signals in the typical methoxyl region contrasting with a singlet looking signal for 3 methoxyl groups observed in the PMR spectrum of the starting imine (*Fig.5*) indicated that aziridination had occurred. Again, many signals in the methoxyl region were thought to have arisen by a long rang coupling between the protons of the $COOCH_3$ group and the adjacent aziridine proton and also the presence of small amounts of the diastereo-isomers along with the major, perhaps the *trans* aziridine.

A comparable result was obtained in the aziridination of 3,4-dimethoxy benzilidine aniline, as seen from the PMR spectrum (*Fig.9*) of the product, while two methoxyl groups on the aromatic ring are distinctly seen as two singlets, the carbomethoxyl group appears as two doublets of less intensity. Here again, the doublets may be arising from a long range coupling. At the same time, while one aziridinyl proton can be seen as a doublet at 4.05 δ, the other appears to be masked under the OCH_3 signals. However, the yield of the product was lower (42%) than that of the trimethoxy case.

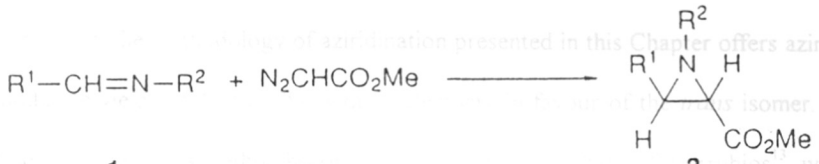
The reaction of 3-nitro-4-methyl N-benzilidine 4'-chloroaniline with methyl diazoacetate under Rh-clay catalysis offered a product in 50% yield. The PMR spectrum

of the product (*Fig.8*) showed a 1H doublet with a coupling constant of ~ 3Hz at 2.50 δ and four pairs of signals with a pair in preponderance in the region 3.75 to 3.90 δ together integrating for four protons accounting for the carbomethoxyl group and the other aziridine proton; in addition this spectrum displayed two singlets at 2.40 and 2.60 δ together integrating for three protons in a 3:2 ratio for the methyl group on the aromatic ring. The small coupling constant observed for the aziridine proton indicated the *trans* configuration of the major isomer. It may be noted that aziridination has led to a complex pattern of signals in the aromatic region contrasting with that of the starting imine (*Fig.7*).

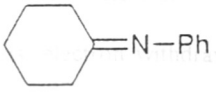
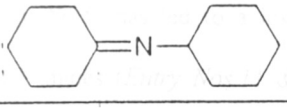
The reaction of the imine with alicyclic substituents *i.e.* N-cyclohexylidine cyclohexyl imine with methyl diazoacetate furnished a product rather in a low yield of 37%. The salient features of the PMR spectrum of this product (*Fig.10*) were two doublets with a coupling constants ~ 3-4 Hz in the region of 3.65 δ to 3.90 δ together integrating for 3 protons and two multiplets at 2.49 and 2.75 δ together integrating for a proton indicating the presence of a cyclohexyl methine proton; another significant resonance was a 1H singlet at 2.60 δ which could be attributed to the aziridine proton of one of the isomers. However, the proton of the other isomer could not be easily placed.

The reaction of methyl diazoacetate under Rhodium catalysis has been extended to various other imines and the results therefrom have been tabulated (*Table-2*), showing the duration of the reaction and the percentage yield of the product. The products from these reactions were identified from their PMR spectral data (*Experimental*) and the major isomer in all the cases has been found to be the *trans* isomer as deduced by a small coupling constant between the aziridine protons.

Table 2 Rh-clay catalysed aziridination of imines[a]



1 2

Entry	R^1	R^2	t/h	Yield[b] (%)
1	4-ClC_6H_4	Ph	5	57
2	4-$MeOC_6H_4$	Ph	3	32
3	3,4-$(OMe)_2C_6H_3$	Ph	7	42
4	3,4,5-$(OMe)_3C_6H_2$	Ph	10	75
5	4-ClC_6H_4	2,5-$Cl_2C_6H_3$	6	40
6	4-ClC_6H_4	3-NO_2-4-MeC_6H_3	9	50
7	2-Furyl	Ph	7	38
8	2-Furyl	Cyclohexyl	5.5	48
9	Bn	Ph	8	30
10	Pr^i	Ph	8	48
11			10	41
12			6	37

[a] Reaction conditions: imine (10 mmol), diazo ester (12 mmol), Rh-clay (10% m/m), dry benzene, reflux. [b] Isolated and purified yield; the selectivity was nearly 100% and no other product could be seen by TLC.

An analysis of results so far presented reveals that the general yield of aziridination ranges from 30-75% and in the majority of cases, it is around 40 to 50%. Nevertheless, the methodology of aziridination presented in this Chapter offers aziridines in moderate yields of 40 to 50% with a selectivity in favour of the *trans* isomer. From this point of view, this method becomes complementary to that of Casarrubios[13], wherein *cis* selectivity was the major feature.

Substituent effect: It is quite remarkable that the aziridination being an electrophilic reaction, has been found to be favourably influenced by increasing the electronic content of the imine double bond. It can be seen from *Table*-2 that 4-methoxy substituted imine (*Entry No.2*) furnished the corresponding aziridine in a 32% yield, while dimethoxy substitution (*Entry No.3*) has led to enhanced yield of 42%. It is remarkable that the best yield of aziridination has been obtained from the trimethoxy substituted imine (*Entry No.4*, 75%). Thus, electron rich imine double bonds have shown enhanced yields. On a similar basis, electron withdrawing chlorine substitution in both the aromatic rings of imine (*Entry No.5*) has led to a low yield of 40%; so also the cyclohexyl aryl and dicyclohexyl imines (*Entry Nos.11 & 12*). In this context, the observations made by Jorgenson *et al.*[12] are worth mentioning. These authors noticed that substitution on nitrogen plays a crucial role in the yield of aziridination; they observed that while N-phenyl substitution gave good yields of the reaction, trimethyl silyl and phenyl sulphonyl groups on the nitrogen brought down the yields.

Stereoselectivity:

A literature survey (vide infra) made on recently reported aziridinations reveals that the stereoselectivity of the reaction is a function of many parameters. For example, Brookhart *et al.*[13] reported that Lewis acid catalysed reaction of ethyl diazoacetate with various aromatic imines led to the exclusive formation of *cis* aziridines. Similarly, Jorgenson *et al.*[12] obtained predominantly *cis* aziridines from the reaction of ethyl-diazoacetate with aromatic imines using $Cu(OTf)_2$ temperatures. These authors also observed that electron withdrawing groups on nitrogen led to higher *cis* selectivity and at the same time, lowered the yields of aziridination.

A recent publication from Agarwal *et al.*[17] reports that the stereoselectivity in aziridination depends on the source of the carbene, while the use of ethyl diazoacetate furnished predominantly the *cis* products, N,N-diethyl-α-diazoacetamide gave higher yields of *trans* products under the same conditions of the reaction. However, it may be mentioned that these authors realised the aziridination not by a carbene addition, but by a nucleophilic addition of a sulphur ylide. With this background of various parameters affecting the stereoselectivity, the results presented by us in this Chapter is noteworthy. It should be emphasized that to the best of our knowledge, there has not been any report of an aziridination reaction carried out utilizing metal incorporated clay as a catalyst. However, there has been a report of a cyclopropanation reaction using copper incorporated clay as the catalyst in which a predominance of *cis* isomer was observed. The same authors[19] refer to the general trend of getting *trans* products from copper catalysed reactions, although they themselves realised the *cis* isomers preferentially. In this context, the realization of a *trans* product in the Rh/clay catalysed reactions of methyl diazoacetate with various substituted imines by us is quite remarkable. This

protocol serves as a complementary methodology to obtain *trans* aziridines to that of Brookhart's method[13] leading to *cis* products.

Mechanistic aspects of aziridination:

The mechanistic aspects of aziridination has been very briefly discussed at the end of next section along with cyclopropanation mechanism. As both aziridination and cyclopropanation involve the group transfer of methyl diazoacetate under Rhodium clay catalysis to imine and olefinic double bonds, they may be considered to be operating under similar mechanistic pathways. Therefore, they are treated together.

3.3.4 EXPERIMENTAL

Preparation of Rh/Clay catalyst:

A mixture of rhodium chloride (0.3 gm.) and clay (25 gm.) in distilled water (600 ml) was stirred vigorously at room temperature for 24 hrs. The material was centrifuged and the clay was repeatedly washed with distilled water till the filtrate was free from chloride ions. Finally, the catalyst was dried at 110°C for 12 hrs. The metal content of the catalyst was determined by electron disperse X-ray microscope connected to a JEOL, scanning electron microscope method. The analysis was carried out by (1), (2), (3) from the Department of Physical Chemistry, University of Pune, and this contribution is sincerely acknowledged. For example, copper incorporation into clay was found to be 0.39 weight %, possessing a surface area of 238 m^2/gm. However, these data for Rhodium and Manganese clays were not collected.

Preparation of N-(4-chloro)benzylidine aniline:

A solution of 4-chlorobenzaldehyde and an equimolar amount of aniline in dry methanol was stirred at room temperature for about 30 minutes for removal of the solvent and passage of residue through a column of silica gel afforded a solid product which showed satisfactory PMR data (*Fig.1*).

General procedure for aziridination

A mixture of imine (10 mmol) methyl diazoacetate (12 mmol) and Rh-clay (10% m/m) in dry benzene (30 ml) was heated under reflux for 5 to 10 h. The progress of the reaction was monitored by TLC. The catalyst was filtered off and the product purified by flash chromatography to afford the corresponding *trans*-aziridine in 37 to 75% yields, different types of imines which have been successfully aziridinated and their spectral data is given below.

Spectral data of Compound **2**:

PMR (200 Mhz $CDCl_3$,*Fig.2*):δ	3.2 (1H, d, J=3.8Hz), 3.6 (3H, s), 3.8 (1H, d, J=3.8Hz), 7.0 (2H, d, J=8Hz), 7.3 (5H, m) and 7.6 (2H, d, J=8Hz).
^{13}C-NMR (50 MHz, *Fig.4*):δ	45.52, 45.65, 51.96, 119.82, 122.95, 123.62, 128.17, 128.29, 128.65, 128.96, 129.91,130.83,133.72,133.83,152.0and 167.65
MS:(m/z,rel.intencity) *Fig.3*	286 (M^+, 25%), 256(30), 228(90), 193(55), 165(35), 155(20), 150(15), 125(35), 104(50), 89(55), 77(100), 63(25) and 59(15)

Spectral data of compound **4**:

Yield:	75%
IR:	1740 cm^{-1}
PMR (*Fig.6*):	3.60-4.00 (m, 12H), 3.65 (d, 1H), 4.15 (d, 1H), 6.45 to 7.30 (m, 7H)

Spectral data of compound **6**:

Yield:	50%
IR:	1740 cm^{-1}
PMR (*Fig.9*):	2.40-2.60 (m, 3H), 2.50 (d, 3Hz, 2H), 3.65-3.90 (m, 4H), 6.75-7.80 (m, 7H)

Spectral data of compound **7**:

Yield:	42%
IR:	1730 cm^{-1}
PMR (*Fig.7*):	3.60-4.00 (m, 10H), 4.05 (d, 1H), 6.60-7.50 (m, 8H)

Spectral data of compound **8**:

Yield:	37%
IR:	1735 cm^{-1}
PMR (*Fig.10*):	δ 1.0-1.5 (m, 10), 1.6-2.0 (m, 11), 2.30-3.0 (m, 2H), 3.65-3.90 (m, 3H)

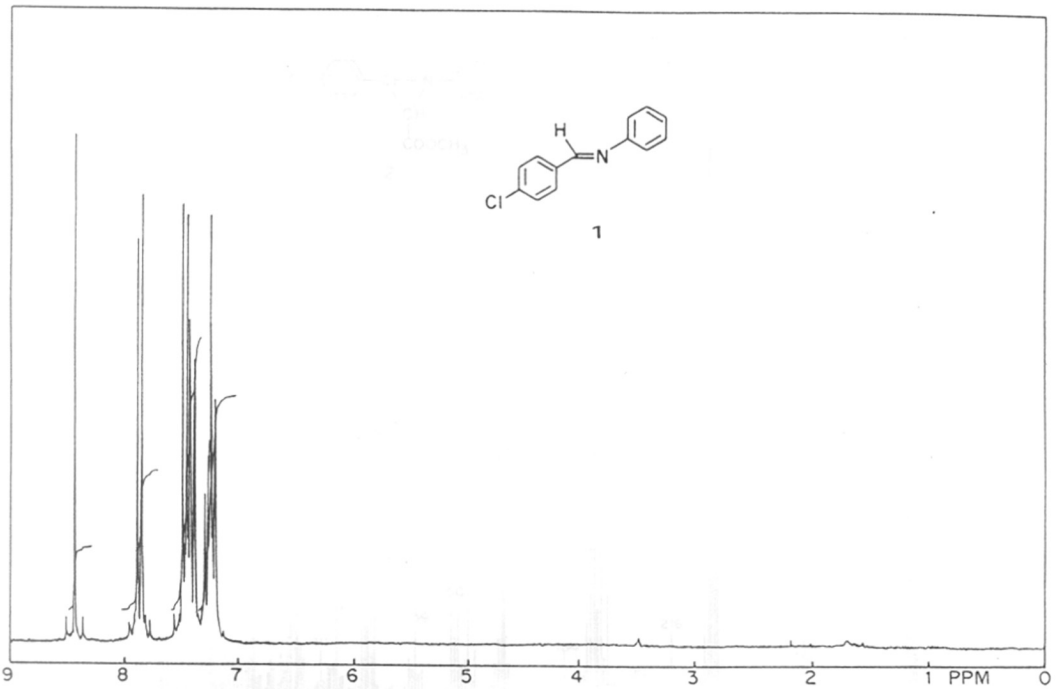


FIG.1: PMR SPECTRUM OF COMPOUND 1

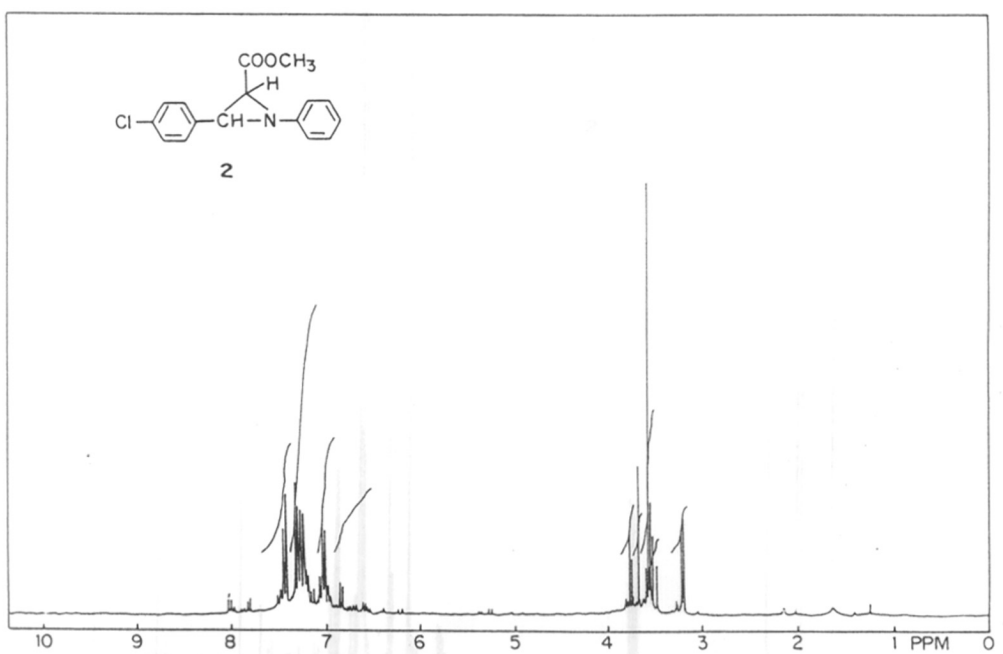


FIG.2: PMR SPECTRUM OF COMPOUND-2

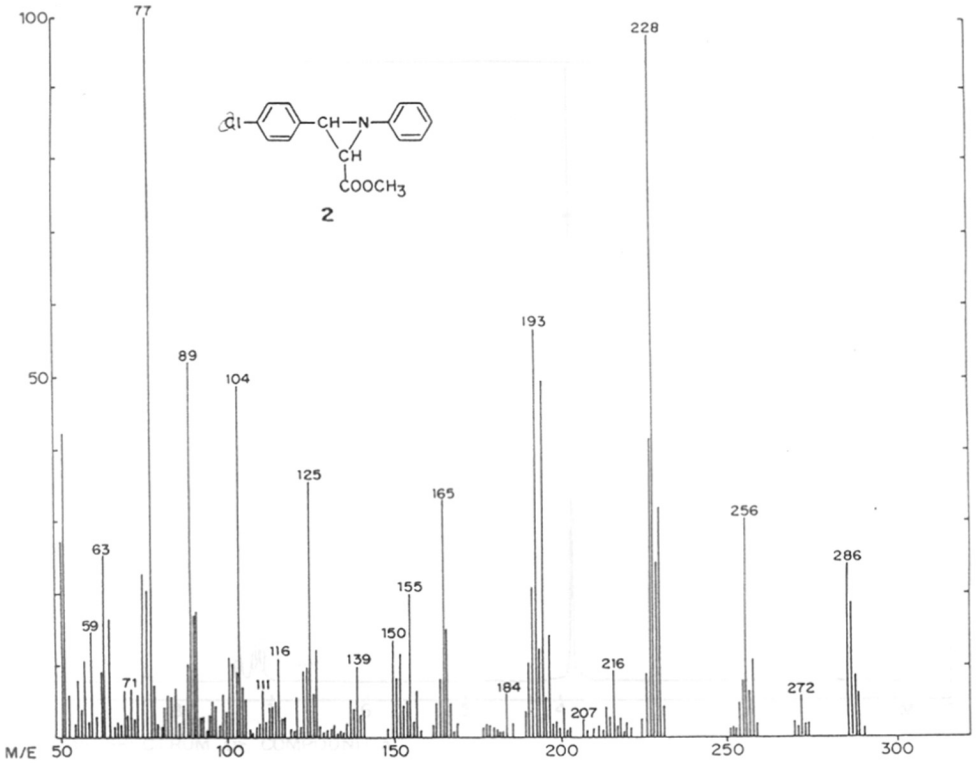


FIG. 3: MASS SPECTRUM OF COMPOUND-2

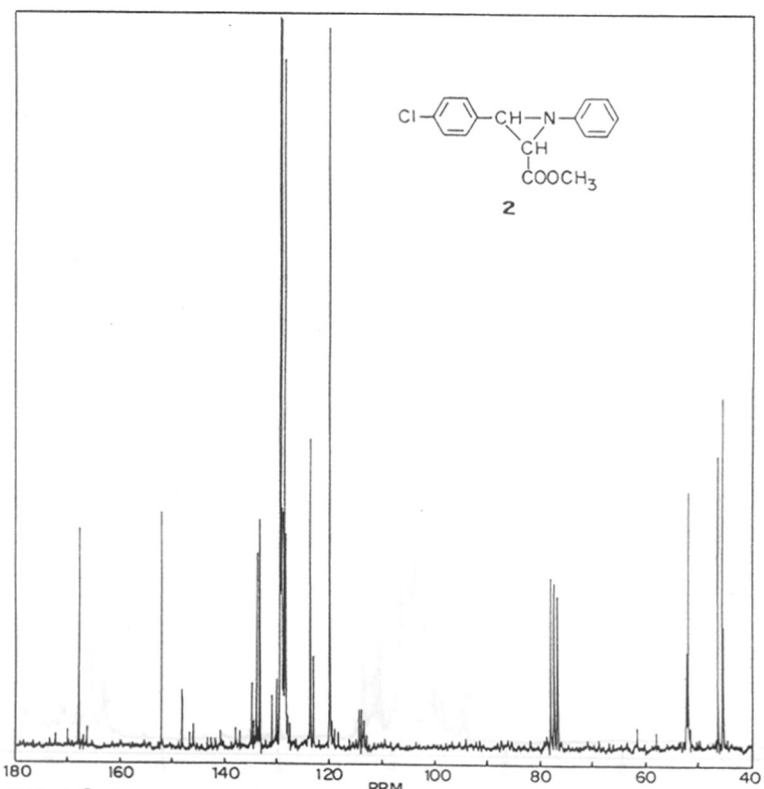


FIG. 4: ^{13}C NMR SPECTRUM OF COMPOUND-2

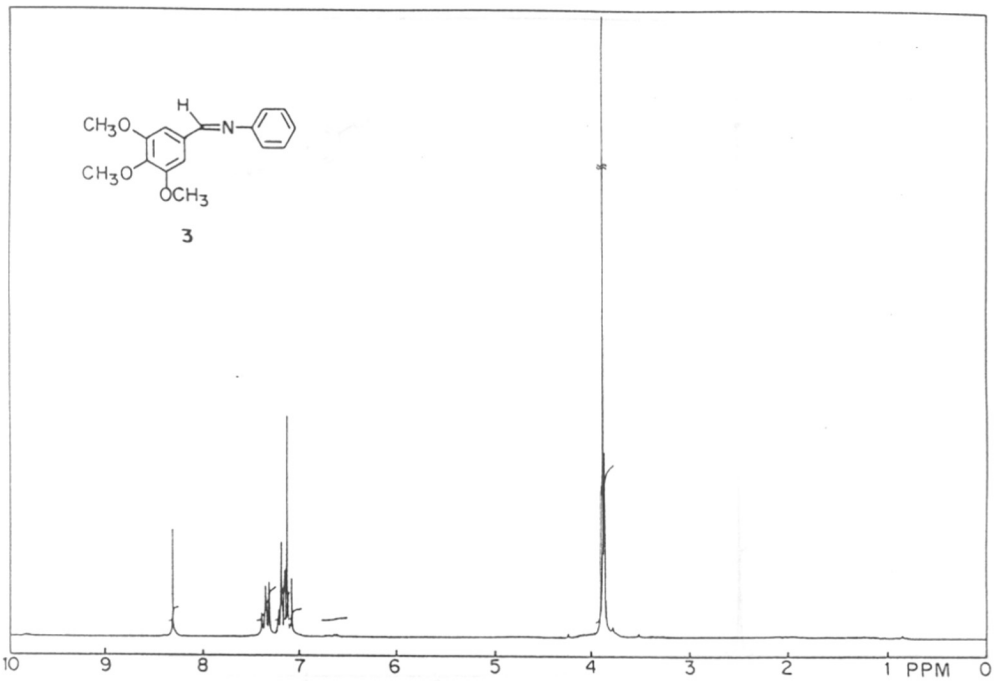


FIG. 5: PMR SPECTRUM OF COMPOUND 3

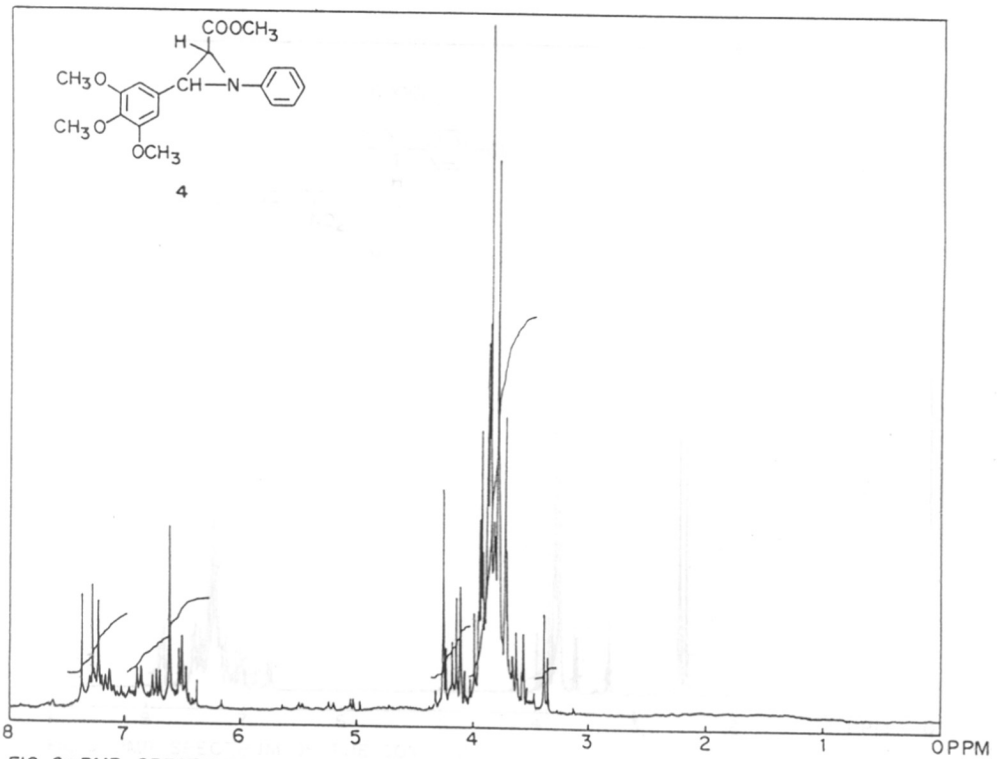


FIG. 6: PMR SPECTRUM OF COMPOUND-4

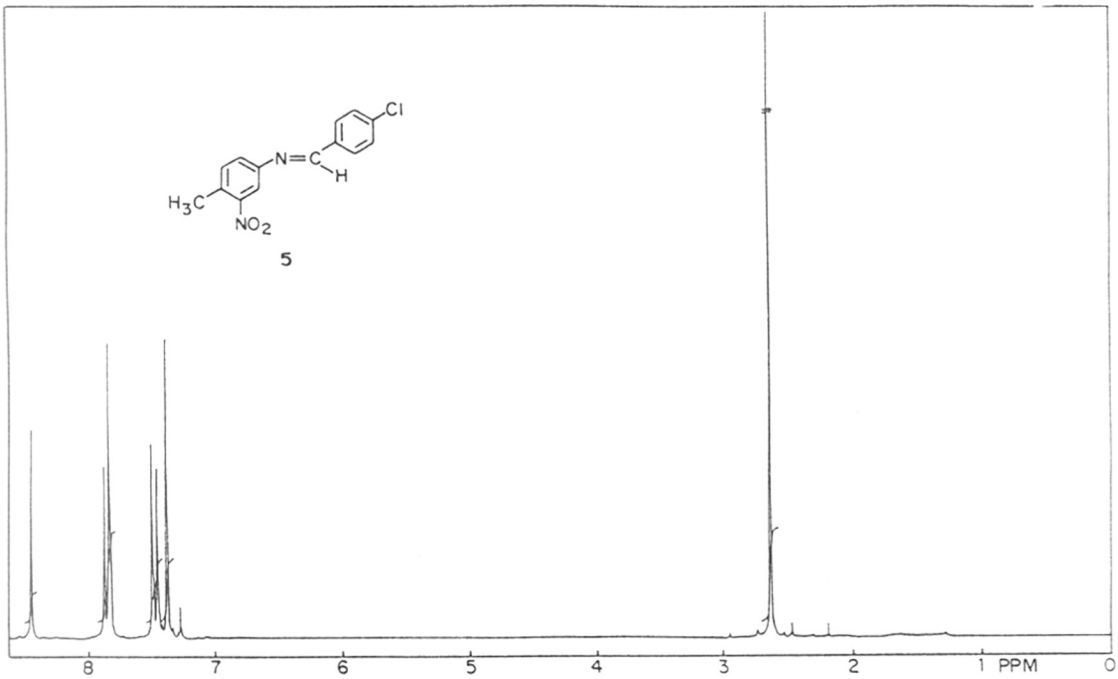


FIG. 7 : PMR SPECTRUM OF THE COMPOUND-5

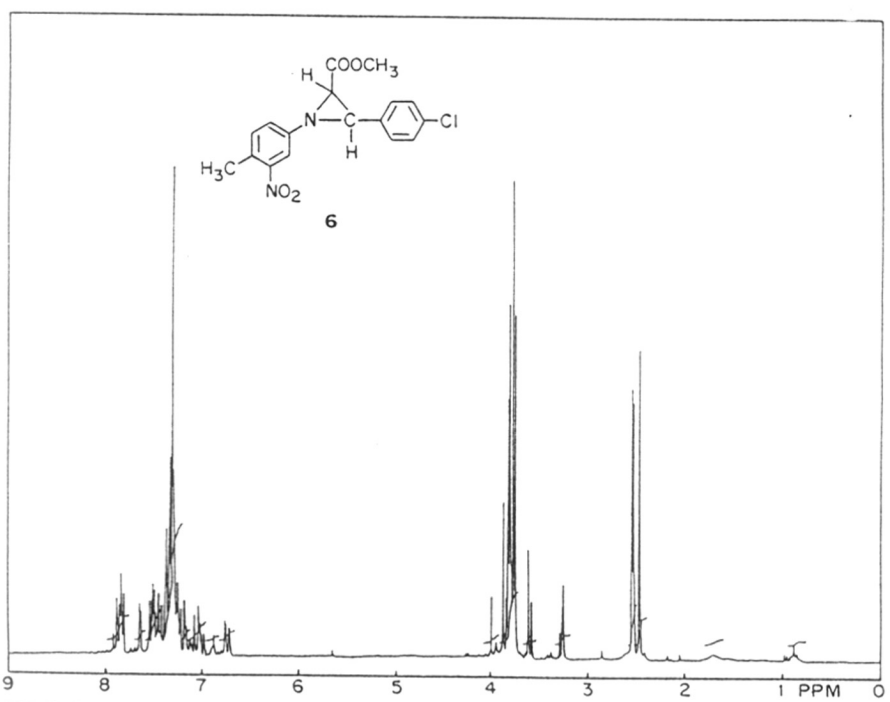


FIG. 8 : PMR SPECTRUM OF THE COMPOUND-6

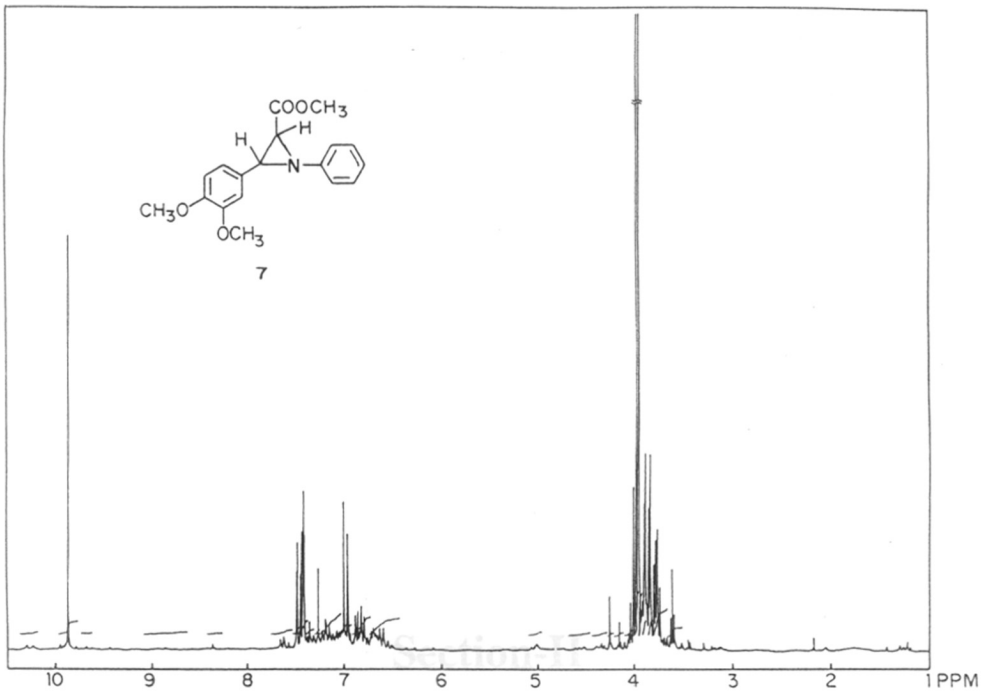


FIG.7 : PMR SPECTRUM OF THE COMPOUND 7

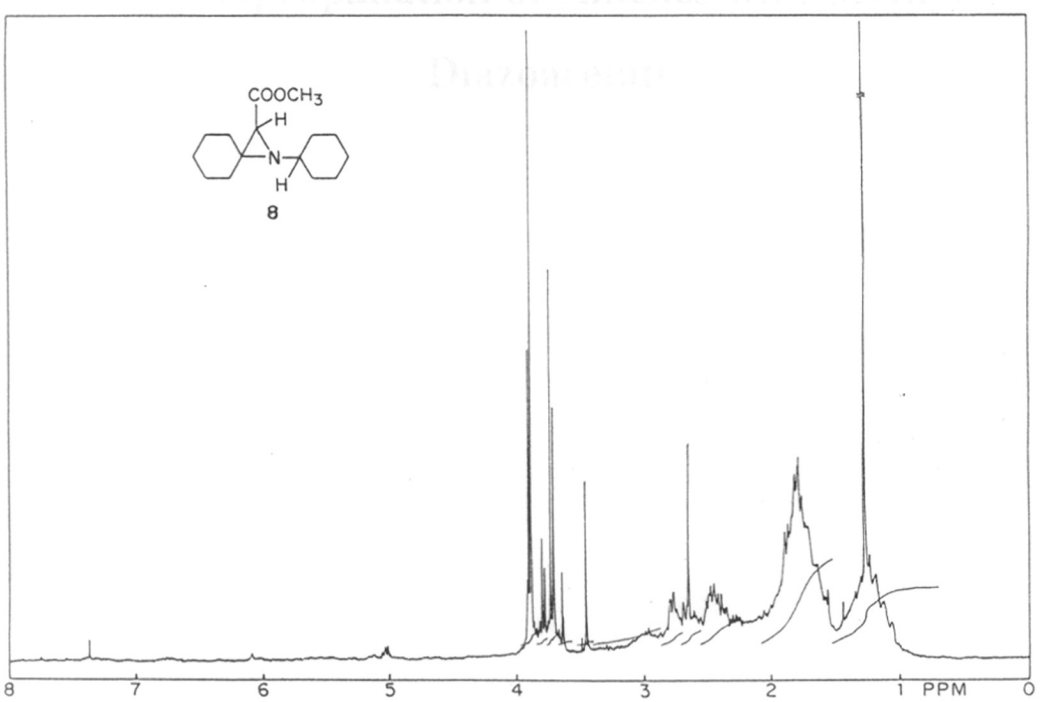


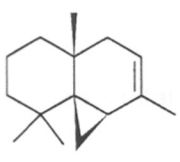
FIG. 10 : PMR SPECTRUM OF COMPOUND-8

Section-II

Cu^{II} and Rh^{III} - Exchanged K_{10} Montmorillionite: Heterogeneous Catalysts for Cyclopropanation of Alkenes with Methyl Diazoacetate

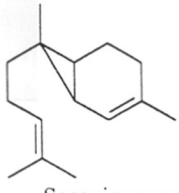
3.4.0 INTRODUCTION:

Importance of cyclopropanes: Owing to their occurrence in natural products, biological profile and synthetic utility, cyclopropanes have received great attention during the past few decades. Transition metal-catalysed decomposition of diazocarbonyl compounds in the presence of olefins constitutes a powerful method of constructing cyclopropanes. Both intermolecular and intramolecular cyclopropanation reactions along with their mechanistic aspects and choice of catalysts have been reviewed in detail by Mass *et al.*[20] A few natural products synthesized by the addition of carbenes to the olefinic bonds have been shown below:



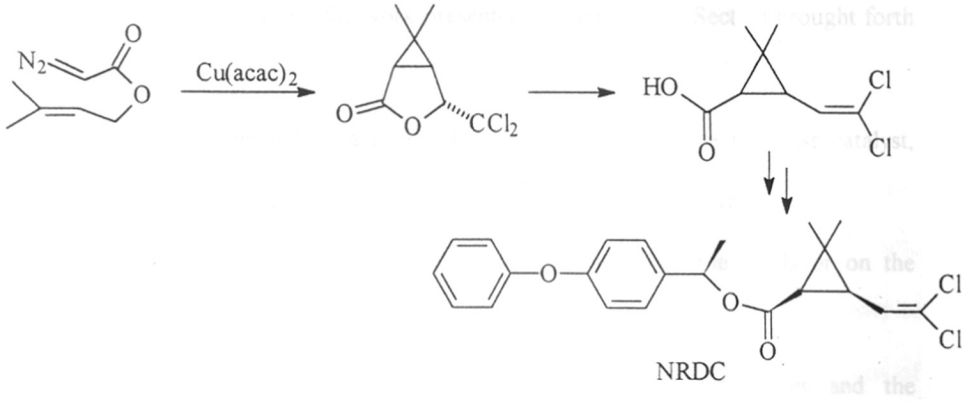
Thujopsene

Longicyclene



Sesquicarene

Just to illustrate the potential of this cyclopropanation reaction in the synthesis of commercially important products, the example of the potent synthetic pyrethroid NRDC 182 may be cited.



NRDC

The synthetic uses of cyclopropane compounds have their origin in the ring strain. In addition, cyclopropanes are also used to generate the gem dimethyl groups of

natural products.[21] As the biological activity of cyclopropane compounds originate from their chirality, most of the methods are aimed at generating chiral cyclopropanes. The following six olefins were chosen to study the cyclopropanation reaction using methyl diazoacetate as the carbene precursor. The experimental conditions of cyclopropanation have been, more or less, maintained the same, as followed in our arizidination study.

1. Styrene
2. Ethyl cinnamate
3. Diethyl fumerate
4. Mesityl oxide
5. Norbornene
6. Cholesterol

It can be seen that olefins chosen include two alkenes in conjugation with the aromatic ring and two alkenes with electron withdrawing substituents, a strained bicyclic olefin and a steroid molecule. Such a wide array of substrates may speak for the generality of the reaction, if the method is successful.

Rh^{III} exchanged Mont-morillonite K-10 clay catalysis in cyclopropanation:

It may be recalled that the work presented in the previous Section brought forth the following points:

1. Among various metal/clay catalysts, Rh/clay was found to be the best catalyst, furnishing 40-75% yields of aziridines with an almost *trans* selectivity.

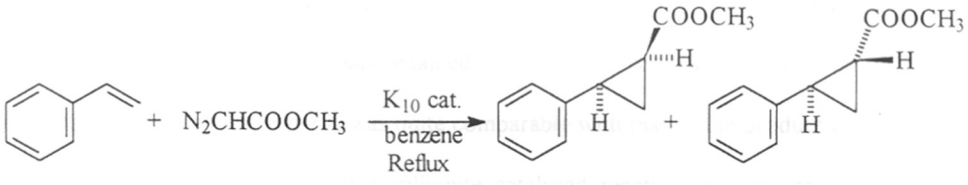
No significant olefin substituent effect was observed either on the yields or on the stereoselectivity of the reaction.

A moderate success realized with differently substituted imines and the preferential formation *trans* aziridines, led to a method for *trans* aziridination. Encouraged by these results, it was planned to investigate Rh/clay-catalysed group

transfer of methyl diazoacetate to substituted olefins with a hope of developing an efficient method for cyclopropanation.

3.4.1 RESULTS AND DISCUSSION:

The cyclopropanation procedure (*Scheme-1*) was fairly simple and comprised refluxing a mixture of olefin with another equivalent amount of methyl diazoacetate and Rhodium incorporated Mont-morrilionite K-10 catalyst (10% by weight) in dry benzene.



The reaction was monitored by TLC and when the olefin totally disappeared, the catalyst was filtered off, and the filtrate processed to obtain the crude product. Purification of the product was effected by passage through a column of silica gel. The yields are based on the olefin consumed.

The cyclopropanation with styrene carried out, as described above, offered a product in 87% yield. The IR spectrum displayed an intense band at 1710 cm^{-1} and a broad band at 3030 cm^{-1} along with bands in the region 1450-1600 cm^{-1} typical of the aromatic group (*Fig.11*). The GLC of the product showed it to comprise two components in a 1:1 ratio; the observed small difference in relative retention times and the nature of the peaks suggested the components to be isomeric in nature. The PMR spectrum (*Fig.12*) was conspicuous by the presence of two signals of equal intensity at 3.50 δ and 3.75 δ together integrating for three protons and the following groups of signals indicating the occurrance of cyclopropanation:

1. A multiplet centered at 1.30 δ integrating for one proton
2. Two multiplets centered at 1.65 δ and 1.85 δ together integrating for one proton

3. Two multiplets centered at 1.95 and 2.15 δ together integrating for one proton and

4. A multiplet centered at 2.60 δ integrating for one proton. This spectrum, of course, showed the typical 5H signals for the mono-substituted phenyl ring in the region 7.10 to 7.40 δ.

This cyclopropanation reaction of styrene with methyl diazoacetate was also carried out using copper incorporated K-10 Mont-morrilonite in the same manner, as described above, and a product was obtained in a relatively less yield (80%). The PMR spectrum of the product (*Fig.13*) was quite comparable with that of the product obtained in the Rhodium over K-10 mont-morillionite catalysed reaction, except that the two signals integrating together for three protons were observed at 3.50 δ and 3.80 δ: besides this, the more down-field signal (3.80) integrated twice of the signal observed at 3.50 δ indicating a 1:2 *cis* and *trans* isomeric mixture of the product. In this context, the PMR spectral data reported by previous workers[22] for *cis* and *trans* methyl 2-phenylcyclopropane carboxylates makes an interesting comparison.

Methyl (±)-2-phenyl cyclopropane carboxylate

PMR: 1.00-2.83 (4H, complex multiplet, cyclopropyl ring protons), 3.38 (3H, $COOCH_3$), 7.20 (5H, C_6H_5).

Methyl (±)*trans*-2-phenyl cyclopropane carboxylate

PMR: 1.03-2.06 (3H, complex multiplet), 2.36-2.70 (1H, complex multiplex, Ph-CH), 3.68 (3H, $COOCH_3$), 7.00-7.33 (5H, C_6H_5).

The *trans* compound has displayed the $-OCH_3$ signal in a more downfield position than the *cis* isomer.

A comparison of the observed PMR data of the products from Rh/clay and Cu/clay to that reported in literature clearly indicated that cyclopropanation using

Rhodium/clay afforded a 1:1 mixture of the *cis* and *trans* methyl 2-phenyl cyclopropane carboxylates, while the reaction with Cu/clay furnished the same mixture in a 1:2 ratio with the predominance of the *trans* compound. Further support for the assignment came from the ^{13}C NMR data.

The product from Rhodium catalysed reaction was insufficient to record the ^{13}C-NMR. Therefore, the product arising from styrene and methyl diazoacetate under copper catalysis has been used to record the ^{13}C-NMR data (*Fig.14*). This product displayed identical PMR data described above.

1. One primary carbon at 21.48 ppm
2. One secondary carbon at 16.66 ppm
3. Seven tertiary carbons at 25.92, 51.40, 125.96, 126.38, 127.65, 128.24, 129.98 ppm.
4. Two quaternary carbons at 139.79 and 173.23 ppm.

It is interesting to note that all the resonances but for the tertiary aromatic carbons were accompanied by minor signals in their vicinity, showing the isomeric composition of the product. From the information obtainable from the PMR spectrum of the products, it can be deduced that the major signals in the ^{13}C-NMR spectrum (*Fig.*14) correspond to the *trans* compound. In this context, asymmetric cyclopropanation of styrene reported by Krieger and Landgrebe may be mentioned. These authors decomposed the diazoacetic esters of (-) borneol, (+) borneol and (-) menthol in styrene in the presence of catalytic amount of copper (I) chloride and obtained very high yields of the corresponding chiral cyclopropane carboxylates with a *trans* to *cis* ratio of 2:3; however, this was a homogenous catalyst and in our system (Cu/clay), a predominance of the *trans* isomer was observed.[22]

2. Cyclopropanation of *trans* ethyl cinnamate:

There was no preferential formation of either *cis* or *trans* product in the case of styrene with Rh/clay catalysis, a 1:1 mixture of *cis/trans* isomers were obtained. It was thought interesting to study this reaction with α,β-unsaturated system, so that the effect of electron withdrawing group can be explored. From this point of view, ethyl cinnamate was treated with methyl diazoacetate under conditions described for styrene with Rh/clay as the catalyst. The reaction furnished a product in 84% yield. The PMR spectrum (*Fig.15*) of the product was extremely significant by the absence of absorption at 6.40 and 7.70 originally observed in the PMR spectra of the starting materials; it indicated a 1:3 isomeric nature of the product, this spectrum displayed two triplets (1:3) in the region 1.30 and 1.40 δ besides showing two quartets centered at 3.80 and 4.25 δ. Two singlets for ethyl cinnamate were observed at 3.75 and 3.85 δ, suggesting the resonenees of OCH_3 group. Two ^1H doublets with the same coupling constant were observed at 4.40 δ and 4.70 δ suggesting the presence of two methine protons adjacent to the carbonyl groups. This spectrum also displayed two multiplets in a 3:1 ratio together integrating for a proton at 2.75 δ and 3.25 δ, attributable to the benzylic cyclopropyl proton, besides showing 5H signals in the region 7.30 to 7.45 δ for the aromatic protons.

This spectral data clearly indicated that the product on hand was a 3:1 isomeric mixture of *trans* and *cis* 1-ethyl, 2-methyl, 3-phenyl cyclopropane 1,2-dicarboxylate. However, the major signal for $-OCH_3$ of the *trans* compound has been observed rather at the upfield position. This reversal could be due to the presence of carbonyl group at the adjoining carbon. Further support for the structural assignment was a direct comparison of the PMR data with that reported for this product, which agreed well with each other.[23]

In this context, it should be mentioned that a mixture of *cis* and *trans* diethyl 3-phenyl 1,2-cyclopropane dicarboxylates was obtained by Arthur G.Anderson *et al.*[24] by the reaction of ethyl diazoacetate with ethyl cinnamate. These authors obtained the mixture of esters by refluxing a mixture of ethyl cinnamate and ethyl diazoacetate at 175-180° without any use of catalyst. The identification of the *trans* and *cis* products was made by the use of NMR; the benzylic proton was relatively observed at a more upfield position in the *trans* compound compared to the *cis* isomer. Based on this observation, we think that the product derived from the reaction of methyl diazoacetate with ethyl cinnamate in our case is predominantly *trans*, as the major signal for the benzylic proton was located at 2.75 δ, while the other benzylic signal was located at 3.25 δ.

3. Cyclopropanation of diethylfumarate:

A similar diastereodistribution of products was observed in the reaction of methyl diazoacetate with diethyl fumerate with Rh/clay catalysis. The PMR spectrum of the product (*Fig.16*) showed this feature by two singlets in a 70:30 ratio together integrating for 3 protons and two 1H doublets at 4.40 δ and 4.80 δ, indicating the cyclopropyl protons. The other cyclopropyl proton appears to be embeded in the two overlapping quartets around 4.20 δ. It may be added that the product was obtained in a 74% yield with a 2:3 *trans/cis* ratio.

4. Cyclopropanation of cholesterol using Cu/clay as the catalyst:

The reaction of methyl diazoacetate with cholesterol using Cu/K-10 montmorillionite as catalyst was carried out as described for styrene and a product in a mere 32% yield was obtained. The PMR spectrum of the product (*Fig.17*) was similar to that of cholesterol in the aliphatic region, but for the appearance of a 1H doublet at 0.80 δ, a region typical for cyclopropane protons. This spectrum, of course, displayed two singlets

for gem-dimethyl groups, two singlets for two quaternary methyl groups and a doublet for a secondary methyl group in the region 0.65 to 1.05. A conspicuous feature of the spectrum was the appearance of two singlets in a 2:1 ratio integrating together for three protons at 3.75 δ and 4.20 δ; there was another 1H doublet in the vicinity of the singlet at 3.75 δ, indicating a methylene proton adjacent to the carbonyl group. From this spectral data, it could be concluded that the cyclopropanation had occurred giving rise to an isomeric product in a 2:1 ratio probably with the predominance of the *trans* compound.

5. Cyclopropanation of mesityl oxide:

The reaction of mesityloxide with methyldiazoacetate under Rh/clay catalysis afforded a product in a 70% yield. The PMR spectrum (*Fig.18*) clearly suggested the product to be an isomeric mixture of expected cyclopropyl carboxylic esters; two singlets together integrating for three protons in a 1.5:1 ratio were observed at 3.85 and 4.00 δ, while a clear ^{1}H doublet indicating a cyclopropyl proton was observed at 3.70 δ partially overlapped with the -OCH_3 signal, the other cyclopropyl proton could not be discerned; perhaps its resonance is also overlapped in the same region. The diastereomeric nature of the product was also seen by the singlets at 1.80 δ and 2.05 δ for the gem-dimethyl groups being accompanied by singlets in the same ratio as seen for the OCH_3 singlets. However, the signal for the methyl on carbonyl group was not resolved. Thus, mesityl oxide in its reaction with methyl diazoacetate afforded a 1.5:1 mixture of *trans* and *cis* cyclopropyl products in low yield.

Cyclopropanation of Norbornene:

Ring strain appears to play a crucial role in determining the stereoselectivity of this cyclopropanation reaction. The reaction of methyl diazoacetate with norbornene under Rhodium/clay catalysis afforded a mixture of two products in a high yield (82%). The PMR spectrum (*Fig.22*) of the product was devoid of olefinic signals and was conspicuous by the appearance of two 1H singlets at 2.40 δ and 2.60 δ; two 1H doublets with the same coupling constants were observed at 3.20 δ and 3.90 δ, perhaps attributable to the cyclopropyl bridge protons. This spectrum also displayed a 1H multiplet at 3.85 δ partially overlapped with a 3H singlet at 3.80 δ. This multiplet could be attributed to the cyclopropyl proton adjacent to the ester carbonyl.

Due to the steric hindrance of the caged phase of the norbornene molecule for the approach of the reagent, the cyclopropanation reaction could be expected to have occurred from the exo phase. If at all any isomeric products were to be obtained, they should be the syn and anti isomers of the exocyclopropanated products. In this connection, the reported PMR data of corresponding ethyl cyclopropane carboxylic esters derived from norbornene was extremely useful. The anti- and syn isomers of these ethyl esters were assigned their stereochemistry on the basis of singlets observed for bridge head protons at 2.37 and 2.45 δ respectively. Two singlets in a 1:1 ratio observed in the PMR spectrum of the product in our reaction of norbornene suggested that the compound on hand could be a 1:1 mixture of syn and anti isomers. However, the well defined bridge methines resonances of norbornene were moved up in the PMR spectrum of the product. At the same time, the -OCH_3 signals for the isomers were not separately seen.

The work presented in this Section is the outcome of the reactions of methyldiazoacetate with different types of olefins using Rhodium^{III} over K-10 mont-morillionite as the catalyst. The substrates included two aromatic, two simple α,β-unsaturated olefins and a bicyclic strained olefin; the study also included an isolated example of a steroid molecule. The results from these studies in terms of yields of cyclopropanation and *trans/cis* distribution of products have been tabulated below:

Table: Reactions of different olefins with methyl diazoacetate under Rhodium^{III} over K-10 mont-morillionite catalysis

Sr.No.	Substrate	Yield (%) of cyclopropanes	*trans/cis* (determined by NMR)
1	Styrene	87	1:1
2	Ethyl cinnamate	84	3:1
3	Diethyl fumerate	74	2.5:1
4	Norbornene	82	1:1 syn/anti
5	Cholesterol	32	2:1
6	Mesityl oxide	70	1.5:1

An analysis of the results tabulated above bringsforth many interesting aspects. The yields of cyclopropanation have been in the range of 70-87% with an isolated case of cholesterol furnishing a low yield.

The yields of cyclopropanation appears to have been adversely affected by an electron withdrawing group on the olefinic linkage, while styrene furnished the product in an yield of 87%, ethyl cinnamate gave the product in a slightly lower the yield; on the other hand, the yield was considerably reduced to 74% in the case of diethyl fumarate with two electron withdrawing groups on the olefinic double bond. This decreasing trend

of yields can be rationalised in terms of reduced electron density of the olefinic bond, especially towards to an electrophilic reaction of the carbene addition. However, the yield of 70% observed in the case of mesityl oxide is rather surprising as two methyl groups on the double bond should have enhanced the electron density to a larger extent than that of diethyl fumarate.

The reaction of norbornene afforded the cyclopropanated product in a high yield of 82%. This observation can be rationalised in terms of steric relief, that results from cyclopropanation as the endocyclic olefin of a bicyclic system is taken away.

The low yield observed in the cyclopropanation of cholesterol may be understood in terms of the steric hindrance afforded by two quaternary methyls and a C-8 side chain at C_{17} of cholesterol.

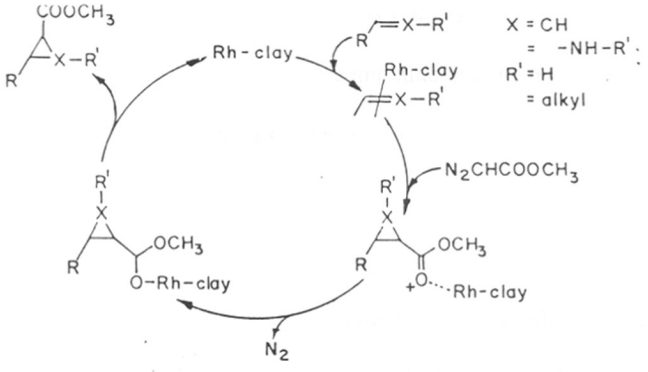
Mechanistic aspects of aziridination and cyclopropanation:

The work discussed in the previous Section and also in this Section of this Chapter involves the reaction of methyl diazoacetate (a carbene precursor) under Rhodium catalysis (Rhodium incorporated in K-10 mont-morillionite) with numerous imines and alkenes. Due to the similarity of reactions in terms of carbene addition to either a -C=N- or -C=C-, a common mechanistic picture can be envisaged.

The historic importance of copper catalysts in cyclopropanation is well recognised with the increased understanding of the mechanistic aspects of cyclopropanation. It appears that two different mechanisms might be involved, possibly as competitive pathways; one in which metal-olefin coordination is a key factor and the other a bimolecular process with metal carbenoid species attacking the uncomplexed unsaturated linkages. Reactions of copper, especially $Cu(OH)_2$ appear to involve a metal/double-bond coordination.[25]

Rhodium II carboxylates are diamagnetic species with one coordination site per metal and they form stable adducts with basic ligands but not with olefins.

A recent review of catalytic methods for metal carbene transformation deals with the mechanistic aspects of cyclopropanation reactions. With the above background and with the similarity of cyclopropanation and aziridinations, both being realized by the addition of methyl diazoacetate under Rhodium catalysis to C=C and C=N, operation of a common mechanism appears tenable. Such a mechanistic picture is shown below:



There is a general agreement that transition-metal catalysts react with diazocompounds to generate transient electrophilic metal carbenes **1**. The catalytic activity of transition-metal compounds depends on coordination unsaturation at their metal centre which allows them to react as electrophiles with diazocompounds. Electrophilic addition causes the loss of dinitrogen and production of metal-stabilized carbene-**1**. Transfer of the carbene entity to an electron-rich substrates completes the catalytic cycle. In the reactions of cyclopropanation and aziridination, methyldiazoacetate corresponds to $R_2C{=}N_2$ and the substrate **S** corresponds to either C=C or C=N. However, as the catalyst used is not just the transition metal but a metal over K-10 mont-morillionite, the mechanistic picture is not yet clear. The mont-morillionite catalyst can be acting as a Lewis acid as well.

Stereoselectivity: It can be seen that both the aziridination and cyclopropanation described in this Chapter by the reaction of methyl diazoacetate with C=N and C=C have furnished the corresponding products with *trans* stereoselectivity. Use of copper catalysis in cyclopropanation is generally known to provide high *trans* selectivity; this proclivity for *trans* product is known to be reduced with Rhodium and palladium catalysts.[26]

Stereoselectivity especially in cyclopropanation[27] appears to be governed essentially by the nature of the catalyst and also appears to be independent of catalyst concentration, the rate of addition of diazo compound and the molar ratio of olefin to the diazo compound. Stereoselectivity also appears to be dependent on the ligands bound to the metal. Such electronic effects influence carbene stabilization and thereby affect selectivity. For example, *trans* cyclopropanation is more favoured with Rhodium (II) acetamide than with even copper catalyst. These electronic effects appear to influence the closeness of the approach by the olefin to the electrophilic carbene centre.

It should be noted that this study of stereoselectivity has arisen from homogeneous catalysis. On the other hand, stereoselectivities from reactions carried out in a heterogenous manner may be totally different. To the best of our knowledge, there has been just one report of cyclopropanation catalysed by Cu(II) exchanged K-10 mont-morillionite.[26] The author of this report surprisingly enough obtained *cis* cyclopropanes in preference despite the fact that copper catalysis is known to be pre-disposed to *trans* cyclopropanation. In this background, the stereoselectivity obtained in our study of cyclopropanation leading to *trans* product constitutes a complementary method to that described by the above authors. In the absence of information on stereoselectivity from clay-catalysed reactions, parameters affecting stereoselectivity cannot be discussed with certainty.

3.4.2 EXPERIMENTAL

Spectral data of compound **9**:

Yield:	87%
IR (*Fig.11*):	3030, 1710, 1600, 1450, 1380, 1340, 1270, 1180, 1080, 1040, 900, 850, 750, 700 cm^{-1}
PMR $CDCl_3$ (*Fig.13*):	1.35 (m, 1H), 1.75 (m, 1H), 1.90 (m, 1H), 2.30 (m, 1H), 2.60 (m, 1H), 3.50 (s, 3H), 3.75 (s, 3H), 7.20-7.40 (m, 5H)
^{13}C-NMR (*Fig.14*):	16.66, 21.48, 25.92, 51.40, 125.96, 126.38, 127.65, 128.24, 129.98, 139.79, 173.23
Mass:	176 (M^+, 40), 161(5), 144(40), 133(10), 127(10), 121(35), 117(55), 116(100), 105(5), 91(35), 77(10), 65(10), 58(10)

Spectral data of compound **10**:

Yield:	70%
IR:	1710 cm^{-1}
PMR $CDCl_3$ (*Fig.18*):	1.80 (s, 3H), 2.10 (s, 3H), 2.10 (s, 3H), 3.70 (d, 1H), 3.85 (s, 3H), 4.0 δ (s, 3H)

Spectral data of compound **11**:

Yield:	74%
IR:	1710, 1700 cm^{-1}
PMR $CDCl_3$ (*Fig.16*):	1.25-1.40 (m, 6H), 3.85 (s, 3H), 4.10-4.35 (m, 5H), 4.45 (d, 1H), 4.80 (d, 1H)

Spectral data of compound **12**:

Yield:	84%
IR:	1690 cm^{-1}
PMR $CDCl_3$ (*Fig.15*):	1.30-1.40 (t, 3H), 3.80 (q, 1H), 4.25 (q, 5H), 4.40 (d, 1H), 4.70 (d, 1H), 7.30-7.45 (m, 5H)

Spectral data of compound **13**:

Yield:	32%
IR:	1680 cm^{-1}
PMR $CDCl_3$ (*Fig.17*):	1.05-1.20 (m, 7H), 1.25-1.75 (m, 14H), 1.80-2.10 (m, 5H), 2.35-2.45 (m, 2H), 3.45 (m, 1H), 3.80 (s, 2H), 4.20 (s, 1H)

Spectral data of compound **15**:

Yield:	82%
IR:	1710 cm^{-1}
PMR $CDCl_3$ (*Fig.20*):	1.10-1.70 (m, 7H), 2.40 (s, 1H), 2.60 (s, 1H), 3.20 (d, 1H), 3.80 (s, 3H), 3.90 (d, 1H)

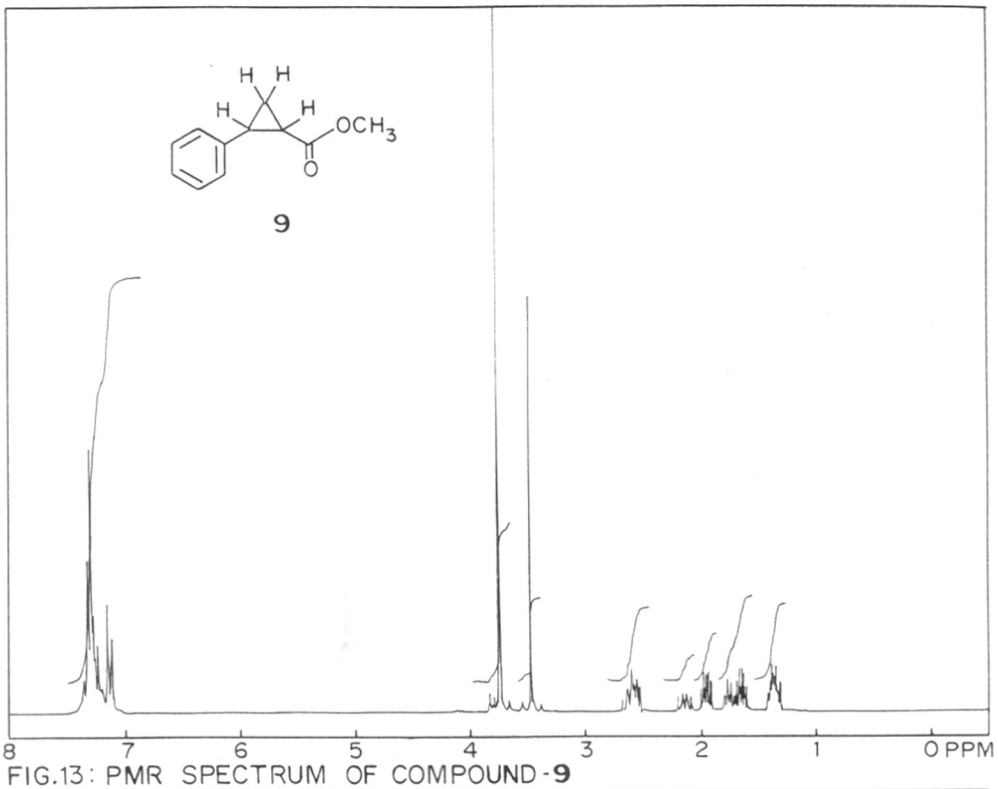


FIG.13: PMR SPECTRUM OF COMPOUND-**9**

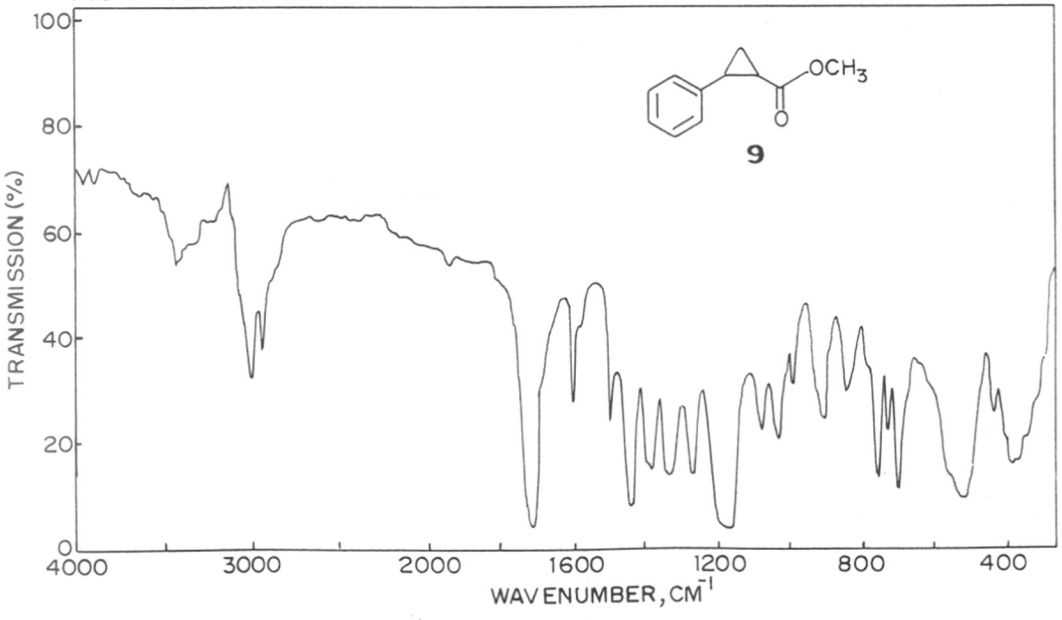


FIG.11: IR SPECTRUM OF COMPOUND-**9**

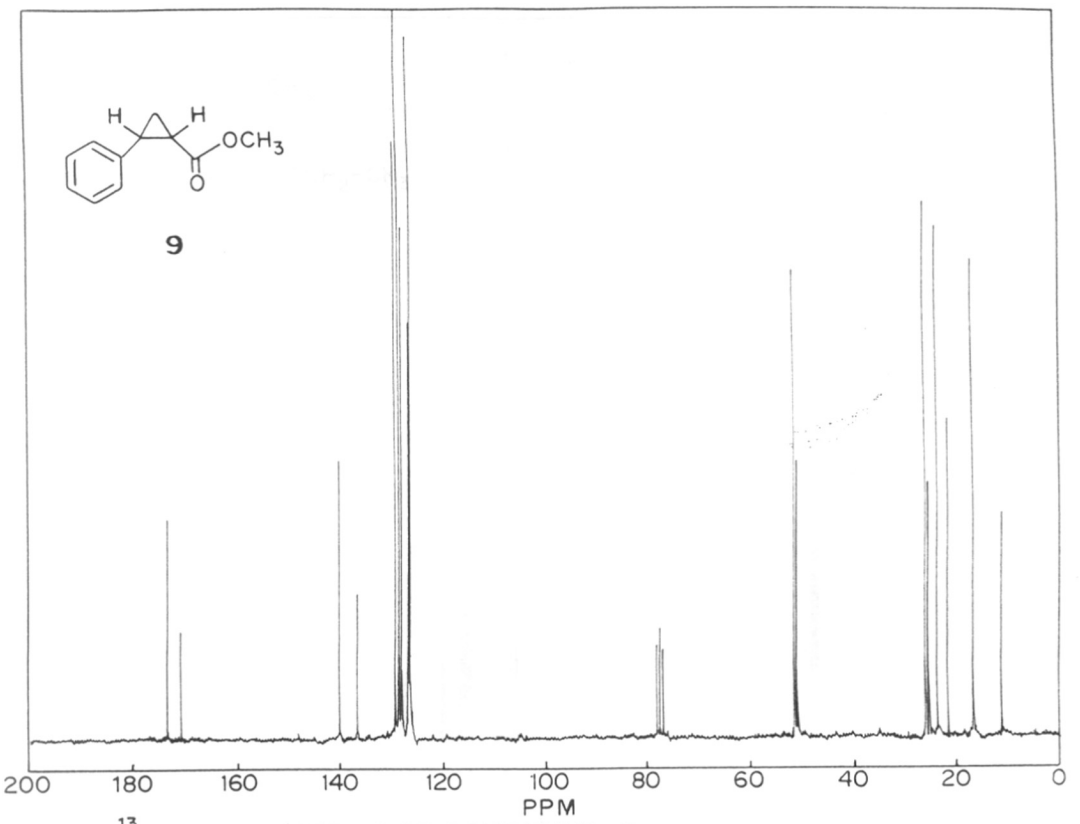
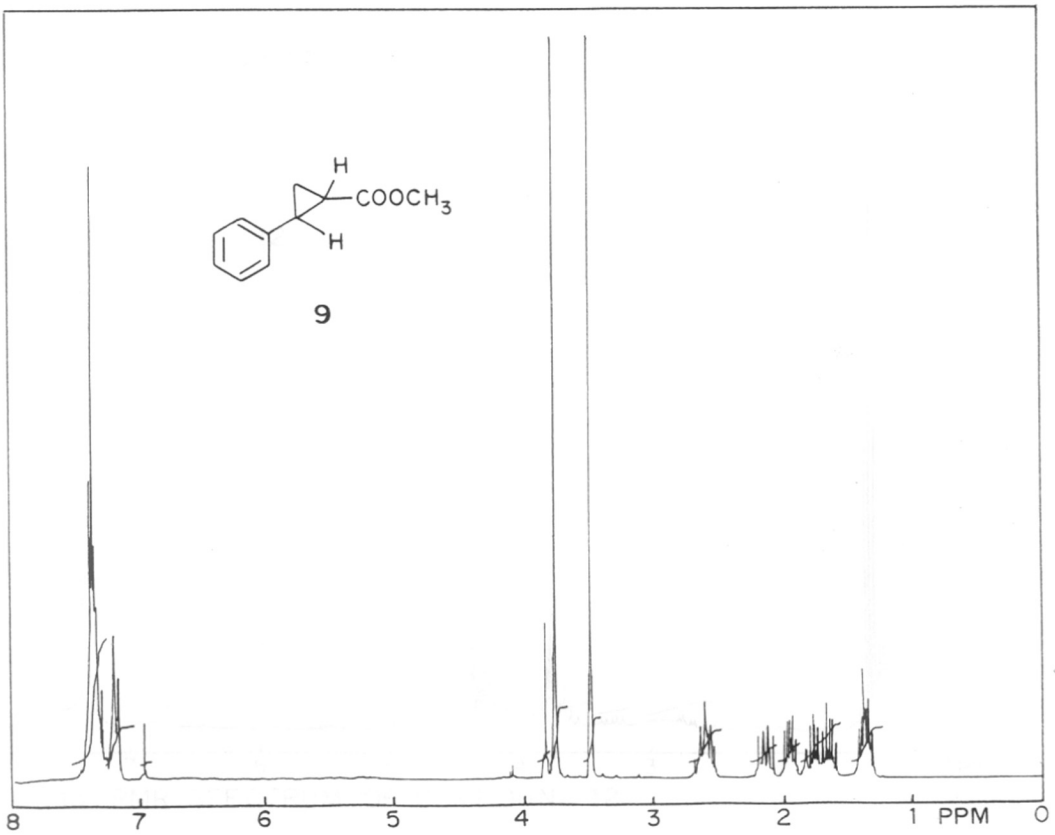


FIG. 14: ^{13}C NMR SPECTRUM OF COMPOUND-**9**



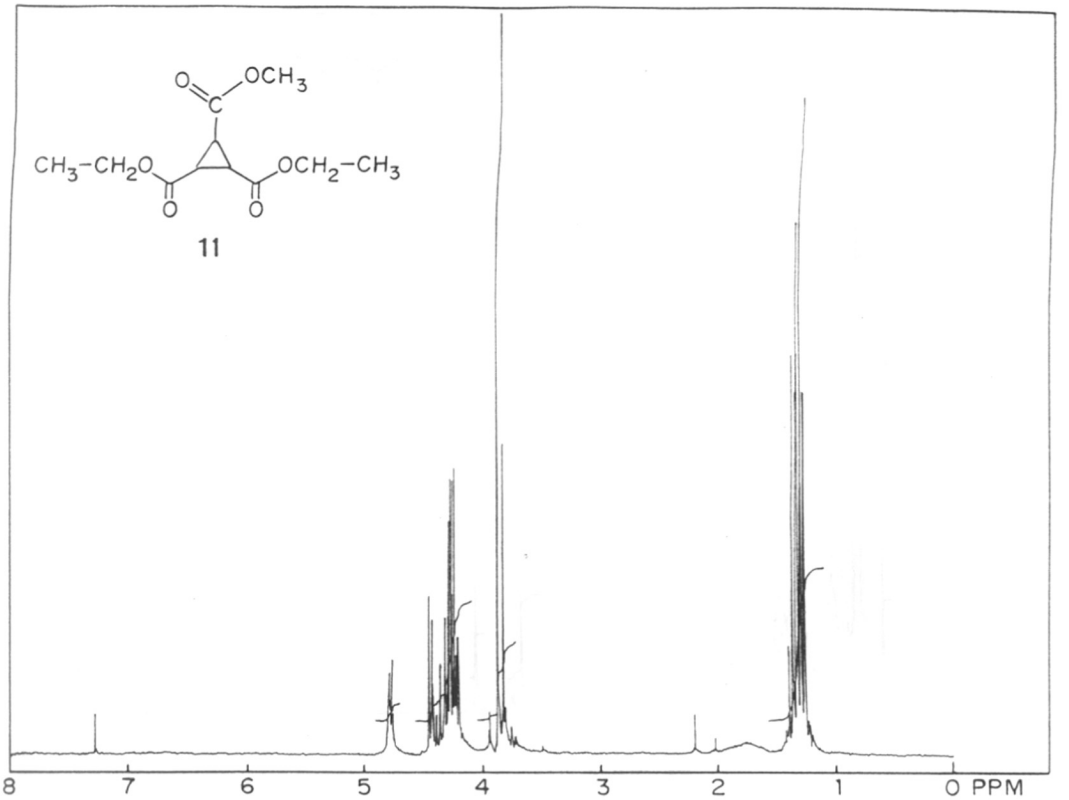


FIG.16: PMR SPECTRUM OF COMPOUND-**11**

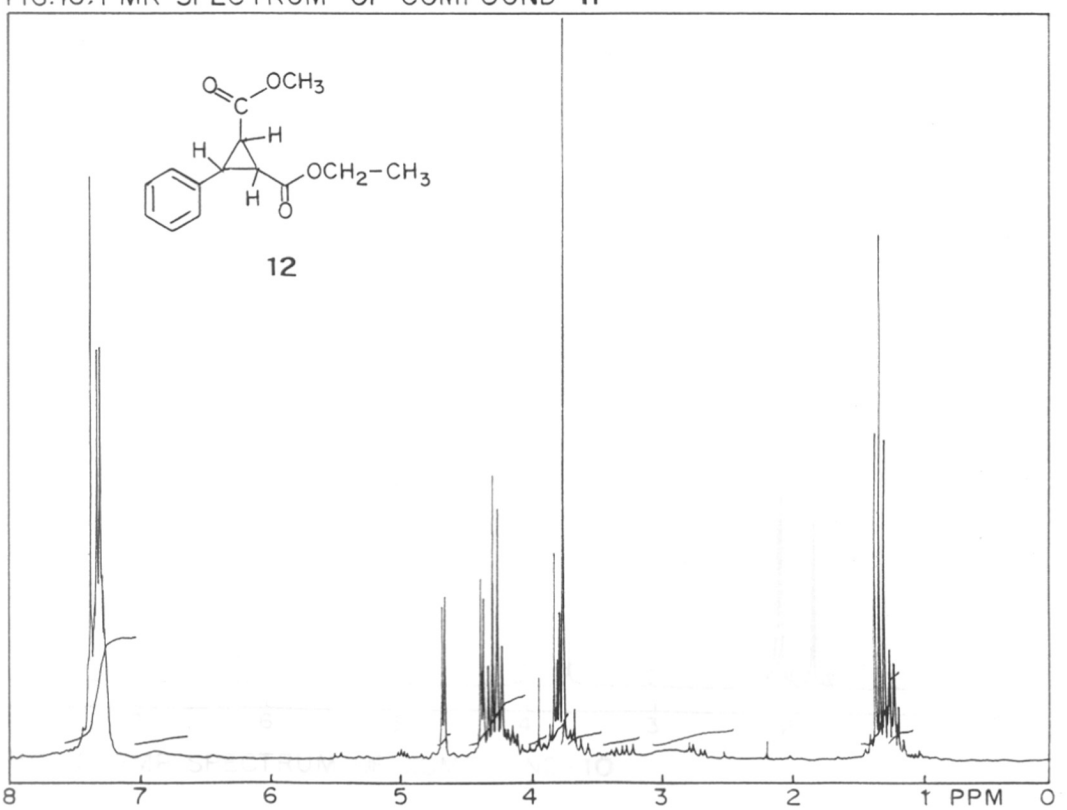


FIG. 15 : PMR SPECTRUM OF COMPOUND-**12**

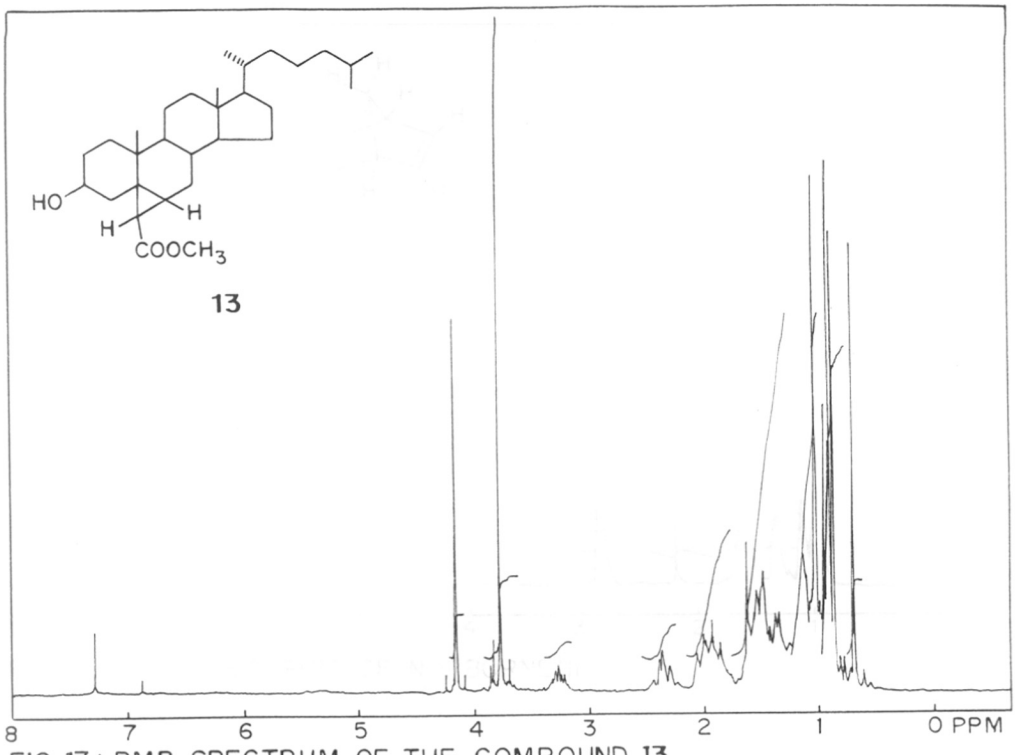


FIG. 17 : PMR SPECTRUM OF THE COMPOUND **13**

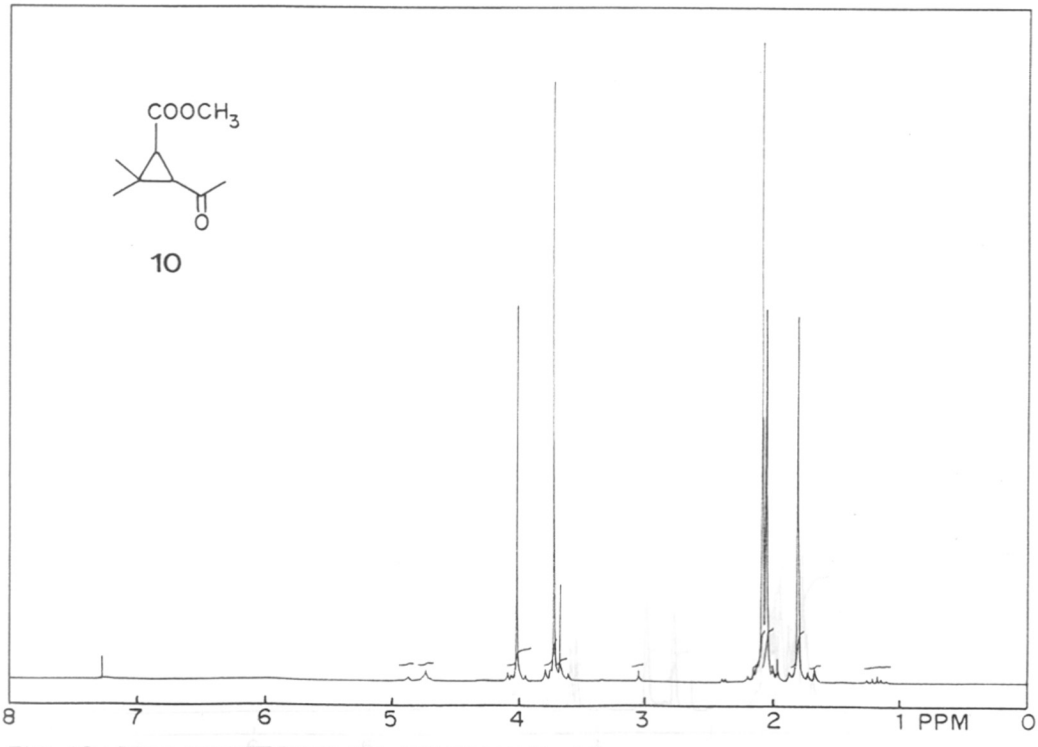


FIG. 18 : PMR SPECTRUM OF COMPOUND - **10**

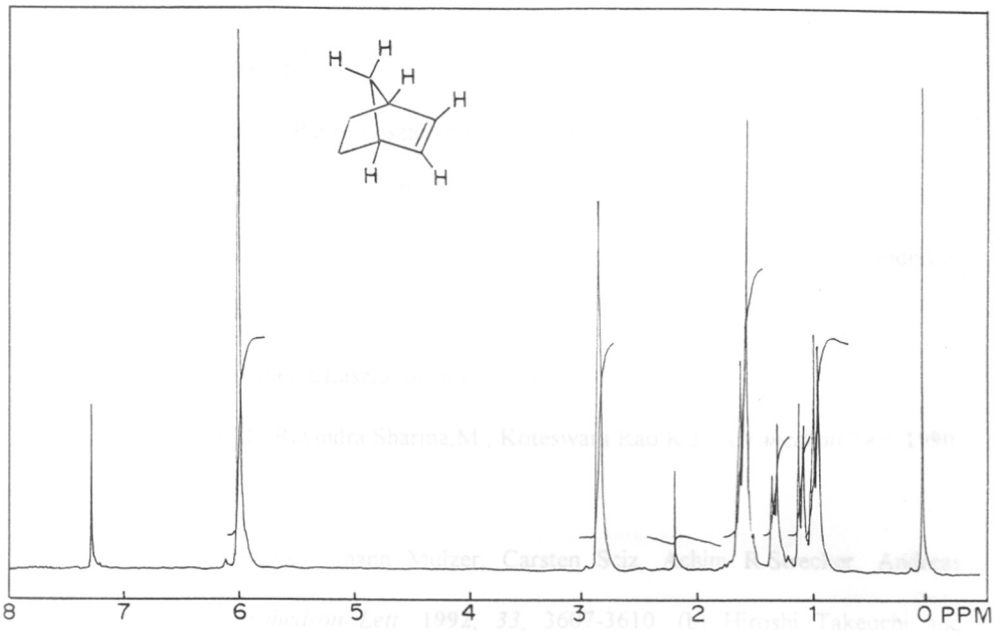
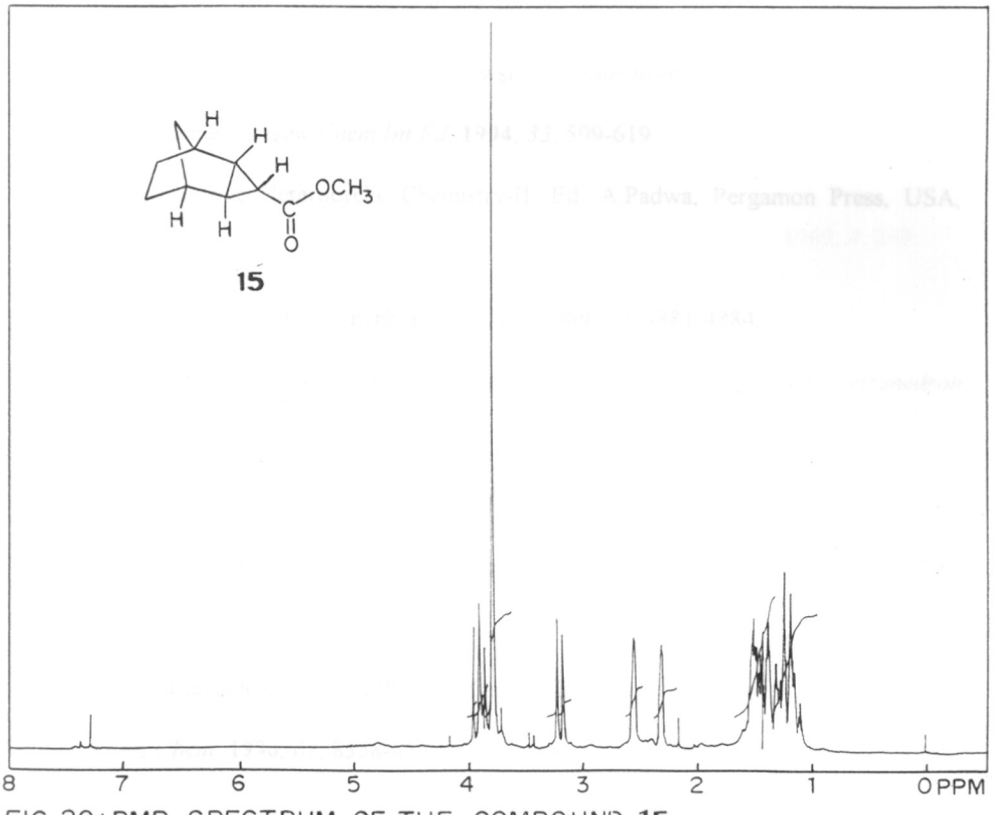


FIG. 19 : PMR SPECTRUM OF NORBORNENE



15

FIG. 20 : PMR SPECTRUM OF THE COMPOUND-**15**

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CHAPTER - IV

A New Heterogeneous Catalytic Method for the Synthesis of β-Ketoesters and β-Aminoesters

Chapter-IV: A New Heterogeneous Catalytic Method for the Synthesis of β-Ketoesters and β-Aminoesters

4.1.0 GENERAL INTRODUCTION:

The work described in the previous Chapter was the outcome of our investigation of the clay/Rhodium catalysed reactions of methyl diazoacetate with different types of C=N and C=C compounds. This study led to the development of an efficient methodology for aziridination and cyclopropanation; in both the cases, a strong procliviy for the formation of *trans*-substituted products was observed. It is obvious that these reactions involved addition of a metal carbenoid species to unsaturated linkages. Encouraged by these results, we were prompted to explore the reactions of the metal carbenoids derived from the decomposition of methyl diazoacetate with carbon heteroatom multiple bonds, specially with an aldehyde group. At the same time, another reaction of carbenes that attracted our attention was their insertion into heteroatom-hydrogen bonds. The reaction of metal carbenes with different types of aldehydes are discussed in *Section-I* of this Chapter, while the *Section-II* presents the results from metal carbenoid insertion into -N-H bonds of amines.

The above study resulted in the development of efficient methods for the synthesis of β-keto esters and β-aminoesters.

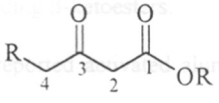
Section-I

Cu-Exchanged Mont morillionite K_{10} Clay Mediated Synthesis of β-Ketoester: Condensation of Aldehydes and Methyl Diazoacetate

4.2.0 INTRODUCTION:

Importance of β-ketoesters:

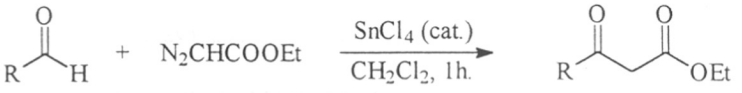
C-C bond formation constitutes the corner stone of organic synthesis. In this context, reagents possessing multiple functionalities assume importance because they can be effective and versatile species for the construction of complex organic structures from relatively simple starting materials. From this point of view, β-ketoesters serve as potential synthetic intermediates. β-ketoesters which may be represented by the following general structure possesses both electrophilic and nucleophilic sites;



in the above structure C_1 and C_3 are potential electrophilic sites while C_2 and C_4 make very good nucleophilic sites of reaction. Thus, by selection of suitable experimental conditions and proper reagents, selectivity can be realised. These features of β-ketoesters make their place unique in organic synthesis. The top of synthesis of β-ketoesters and their use in organic synthesis has been reviewed recently.[1] Synthetic routes to β-ketoesters essentially involve acylation of acetate anions, carboxylic acid derivatives and malonic anions mostly with acylhalides. However, these methods need low temperatures and use of strong bases such as lithium amides.

As the work described in this section pertains to the synthesis of β-ketoesters by a direct condensation of aldehydes with methyl diazoacetate, it is relevant to mention a few reports of this type of reactions known in literature. Although this reaction has been known for quite some time, it remained limited to a few reports. The earliest example concerns with BF_3.etherate-catalysed transformation of sugar aldehydes to the

corresponding β-ketoesters rather in low yields.[2] Roskamp and Holmquist[3] have investigated the reaction of aldehydes with ethyl diazoacetate to develop a method for β-ketoesters. Among various lewis acids, these authors found stannous chloride to be the most efficient.



However, this method was suitable only for aliphatic aldehydes; aromatic aldehydes led to poor yields of the corresponding β-ketoesters.

Dhavale *et al.*[4] recently reported activated alumina-promoted reaction of aldehydes with ethyl diazoacetate leading to β-oxoesters. The salient feature of this reaction was the absence of solvent and the use of activated alumina in large excess. The requirement of activated alumina in large quantities constitutes a limitation in the preparation of β-ketoesters on a large scale by this method.

Sonawane *et al.*[5] recently reported a synthetic method to obtain β-ketoesters from aldehydes. The method involved the reaction of ethyl diazoacetate with numerous aromatic and aliphatic aldehydes using H-β-zeolite as a catalyst.

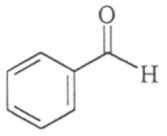
These authors also observed that aromatic aldehydes are less reactive than the aliphatic ones, while alkyl and aryl ketones were totally unreactive.

It can be seen from the brief survey of literature given above that a direct condensation of methyl diazoacetate with aldehydes has a potential to generate a practical methodology for the synthesis of β-ketoesters; nevertheless such a study has been limited.

4.3.0 RESULTS AND DISCUSSION:

With the success realized in the reaction of methyl diazoacetate with olefins and imines that led to convenient methodologies for cyclopropanation and aziridination, we were prompted to explore the reactions of methyl diazoacetate under the Cu/clay catalysis with a few aromatic aldehydes, so that a method may emerge for the synthesis of β-ketoesters. The availability of the corresponding β-ketoesters in the laboratory enabled easy characterization of the products.

The following aldehydes have been included in the study:



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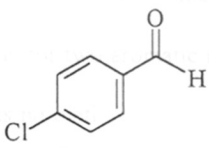

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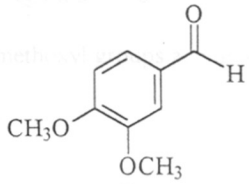

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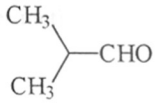

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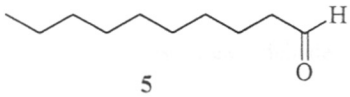

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These reactions with aromatic aldehydes with metal diazoacetate catalysed by Cu/clay-K10 montmorillionite used the following general procedure -

1. Reaction of benzaldehyde with methyl diazoacetate:

The reaction of benzaldehyde with methyl diazoacetate carried out, as described in general procedure, afforded a homogeneous product in 70% yield. The PMR spectrum of the product (*Fig.*1) displayed a 3H singlet at 3.80 δ, a 0.60 H singlet at 5.90 and two singlets between 3.9 and 4.0 δ, together integrating for 1.4H; this spectrum showed a group of signals between 7.3 to 7.50 δ, integrating together for 5 protons. This spectral

data enabled us to characterise the product as the expected β-ketoester of benzaldehyde **6** comprising the corresponding enol component to an extent of about 30%; further confirmation of structural assignment was obtained when the PMR data matched well with those reported.[6]

2. Reaction of 3,4-dimethoxybenzaldehyde **3** with methyl diazoacetate:

The product obtained from this reaction (yield 72%) displayed in its PMR spectrum (*Fig.2*) significant features showing the formation of the expected β-ketoester. This spectrum showed three singlets in the region 3.75 to 4.00 δ together integrating for nine protons accounting for two aromatic methoxyl groups and an ester methoxyl group. Surprisingly, there was no olefinic resonance and instead, two 1H singlets were noticed at 3.95 δ and 4.05 δ. This data enabled the characterization of the product as **7**. It is interesting to note that there was no enolisation in this case while the product from the *p*-OMe mono-substituted aldehyde enolised. The occurrence of enolization appears to be conformation dependent.

3. Reaction of methyl diazoacetate with n-C_{10} aldehyde **5**:

This reaction carried out, as described in general procedure, afforded a product in 90% yield. The IR spectrum of the product (*Fig.3*) showed intense bands at 1722 and 1739 cm^{-1} for the ketonic and ester carbonyl functions. This spectrum showed a band at 1438 cm^{-1} indicative of a methylene group flanked by carbonyl functions. The PMR spectrum (*Fig.4*) was devoid of the aldehydic resonance and displayed a 2H singlet at 3.50 δ and a 3H singlet at 3.70 δ indicating a methylene adjacent to the carbonyl and -$COOCH_3$ group respectively. The region between 0.85 and 2.80 exhibited satisfactory

signals for the methyl and other methylenes of the product. These spectral data sufficed to characterize the product as **8**.

A similar reaction carried out with isobutyraldehyde **4** afforded the corresponding β-ketoester **9** in (62% yield). The product exhibited satisfactory IR and PMR data (Experimental).

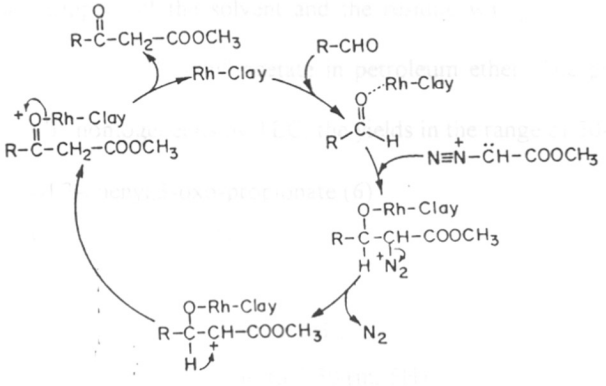
Similarly, the reaction of *p*-chlorobenzaldehyde **2** with methyl diazoacetate afforded the corresponding β-ketoester **10** which displayed satisfactory spectral data (See Experimental).

The work described in this Section include the reaction of methyl diazoacetate with three aromatic aldehydes and two aliphatic aldehydes. All the aldehydes have furnished the corresponding β-ketoesters in moderate yields of 50-80%; while some β-ketoesters are seen in their enolic forms, a few others have not enolised. This phenomenon has been understood as the conformation-dependent process. The reaction conditions in terms of different moles of methyl diazoacetate, amount of catalyst and the duration of the reaction have not been investigated. With proper optimization of reaction conditions, there is sufficient scope to enhance the yields. Therefore, this reaction has a potential to generate a practical method for the synthesis of β-ketoesters starting from both aromatic and aliphatic aldehydes.

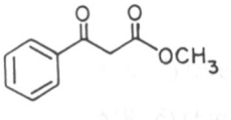
Mechanistic aspects: The formation of β-ketoesters by the reaction of methyl diazo acetate with the aldehydic group under Cu^{II}-mont morillonite catalyst can be looked upon as the carbene insertion reaction into the C-H bond of the aldehydic function. It has been observed by previous workers[1] that involvement of metal carbenoid species leads to dimerization of methyl diazoacetate furnishing a mixture of methyl fumarate and maleats.

In the present study of the reaction of methyl diazoacetate with C=N, C=C and CHO groups, no dimerization products have been observed. It, therefore, suggests that metal carbenoid species are not to be implicated in the reaction. The metal in combination with K10-mont morrillonite may be serving as a Lewis acid.

A probable mechanistic pathway for the formation of β-ketoesters is indicated below:



Coordination of the carbonyl oxygen of aldehyde with Lewis acid enhances the electrophilicity of the carbonyl carbon. A nucleophilic attack by the lone pair of electrons of the carbene generates the new C-C bond; the driving force of elimination of nitrogen as a neutral molecule triggers a 1,2-hydride shift leading to a carbonium ion which gets stabilised by ketonization, finally leading to the formation of β-ketoesters.



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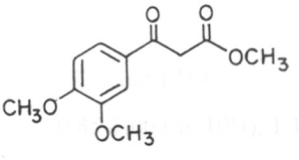

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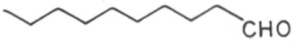

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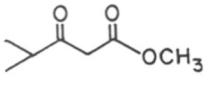

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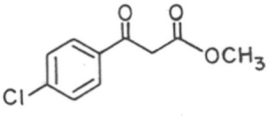

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4.4.0 EXPERIMENTAL:

General Procedure: Into a solution of the aldehyde in dry benzene were introduced 1:1 equivalent of methyl diazoacetate and Cu/clay catalyst (10% w/w). The mixture was refluxed till the disappearance of the aldehyde as monitored by TLC and till the cessation of nitrogen evolution (3-4 hrs). When the reaction mixture cooled to room temperature, the catalyst was filtered off and washed twice with benzene. The combined benzene extract was stripped off the solvent and the residue was passed through a column of silica gel eluting with 2% ethyl acetate in petroleum ether. The product thus obtained was found to be homogeneous by TLC, the yields in the range of 50-80% were obtained.

1. Methyl 3-phenyl,3-oxo-propionate (**6**)

Yield:	70%
IR (cm^{-1})	1690, 1720
PMR (δ) (*Fig.1*):	3.80 (s, 3H), 3.90, 4.00, 5.90 (three singlets, 2H)
200 MHz	7.30 to 7.50 (m, 5H).

2. Methyl-3[3',4'-dimethoxyphenyl], 3-oxo-propionate (**7**)

Yield:	72%
IR (cm^{-1}):	1700 and 1710
PMR (δ) (*Fig.2*):	3.75 to 4.00 (three singlets, 9H), 3.95 to 4.05 (two 1H
200 MHz	singlets), 6.70 to 6.90 (m, 3H).

3. Methyl, 3-oxo-dodecanoate (**8**)

Yield:	90%
IR (cm^{-1}) (*Fig.3*)	1722 and 1739
PMR (δ) (*Fig.4*):	0.85-1.00 (m, 10H), 1.10-1.30 (m, 9H), 3.50 (s, 2H),
200 MHz	3.70 (s, 3H).

4. *Methyl, 3-isopropyl-3-oxo-propionate (9)*

Yield:	*62%*
IR (cm^{-1}):	*1700, 1740*
PMR (δ):	0.95 (d, 6H), 2.0 (m, 1H), 3.70 (s, 2H).
(200 Mhz) $CDCl_3$	3.90 (s, 3H).

5. Methyl-[4'-chlorophenyl]-3-oxo-propionate (**10**)

Yield:	70%
IR (cm^{-1}):	1720, 1730
PMR (δ):	3.90 (s, 3H), 3.80, 4.10,5.80 (three singlets, 2H),
	6.80 (d, 2H), 7.20 (d, 2H).

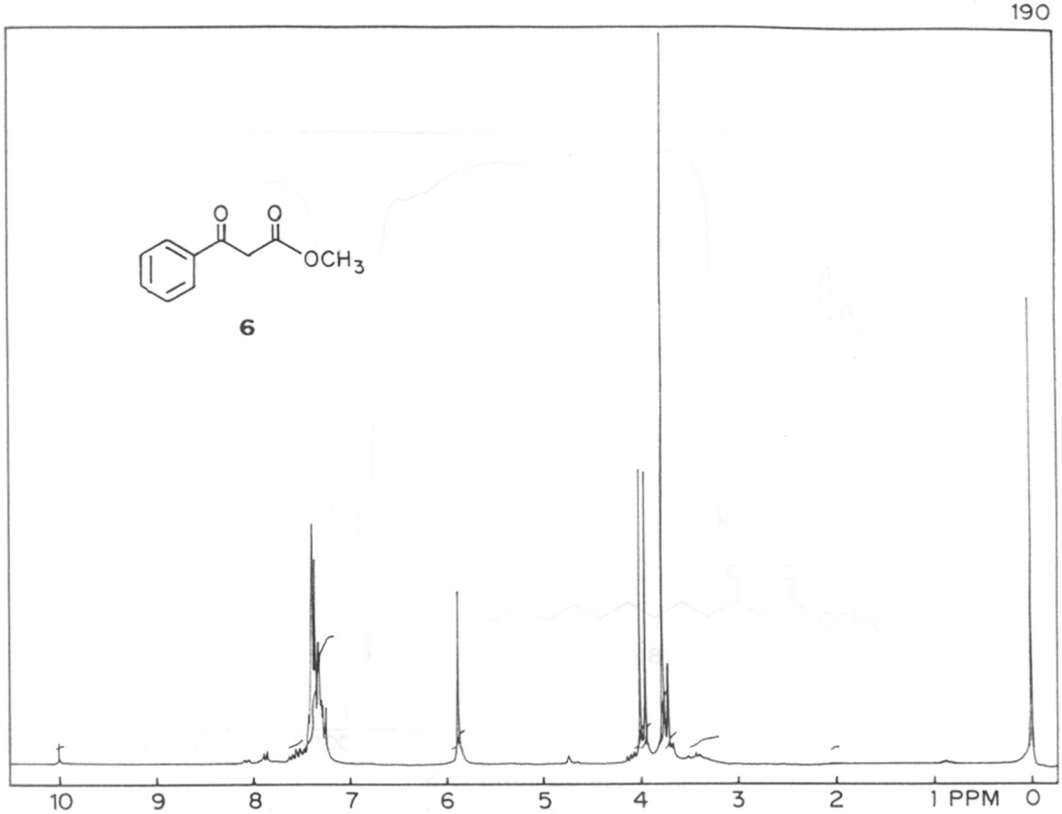


FIG. 1: PMR SPECTRUM OF COMPOUND-**6**

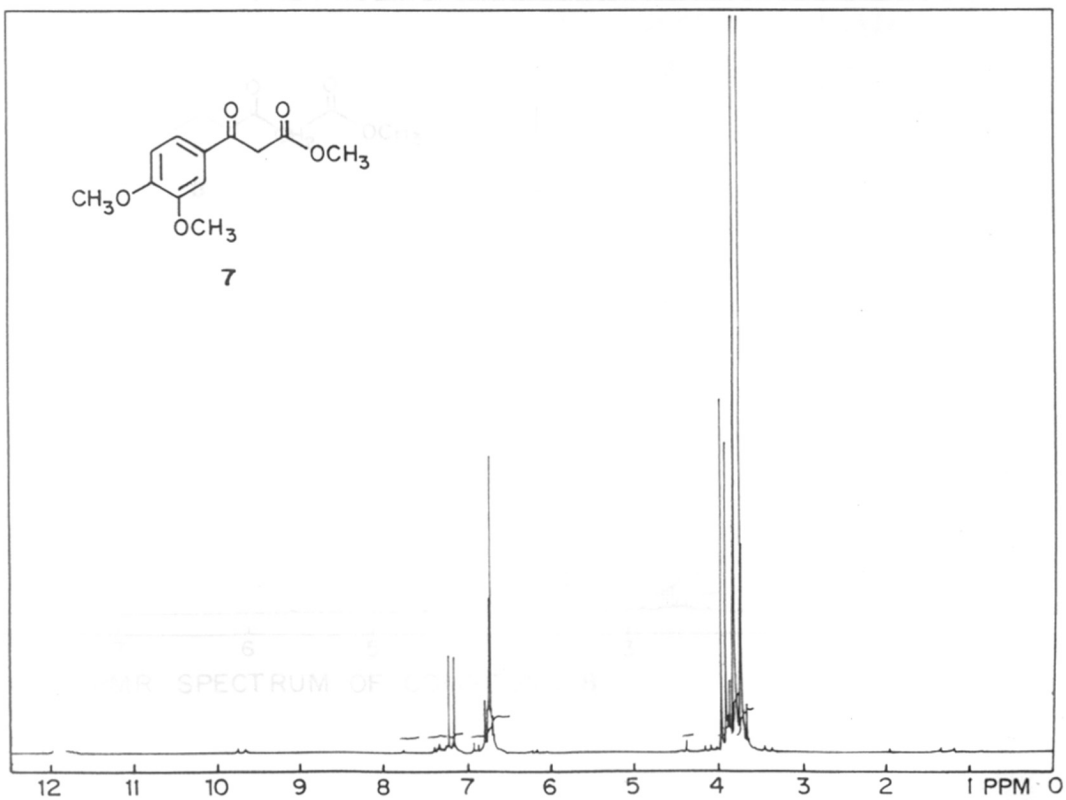


FIG. 2: PMR SPECTRUM OF COMPOUND-**7**

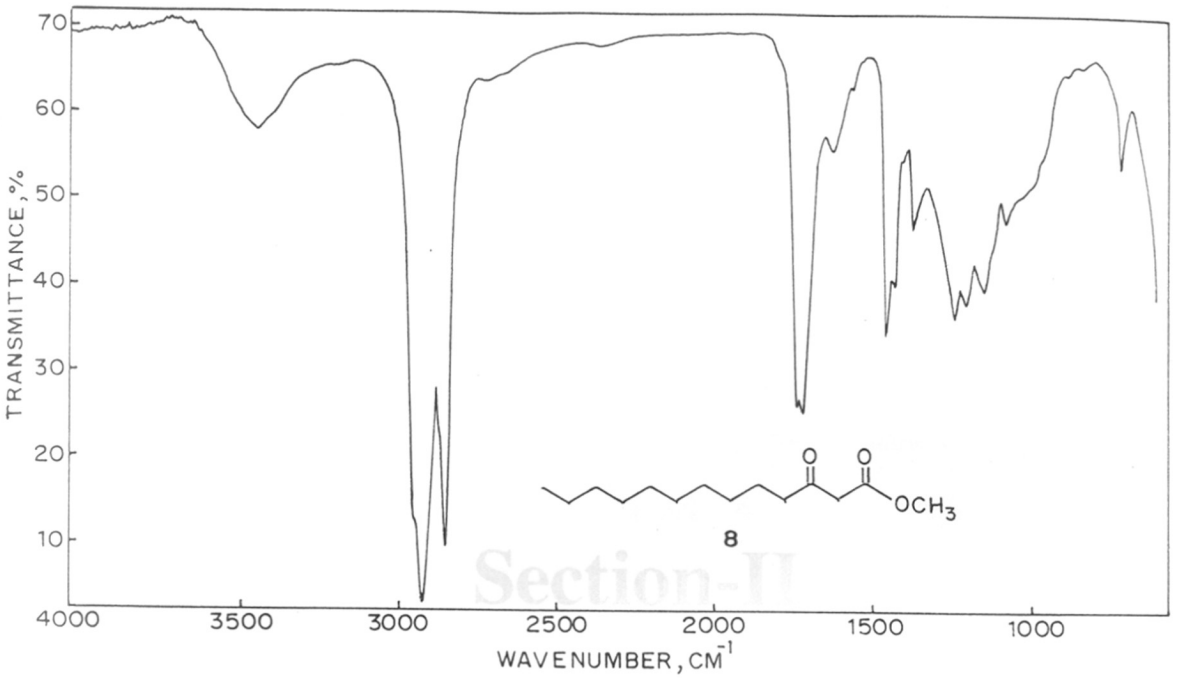


FIG. 3 : IR SPECTRUM OF COMPOUND-**8**

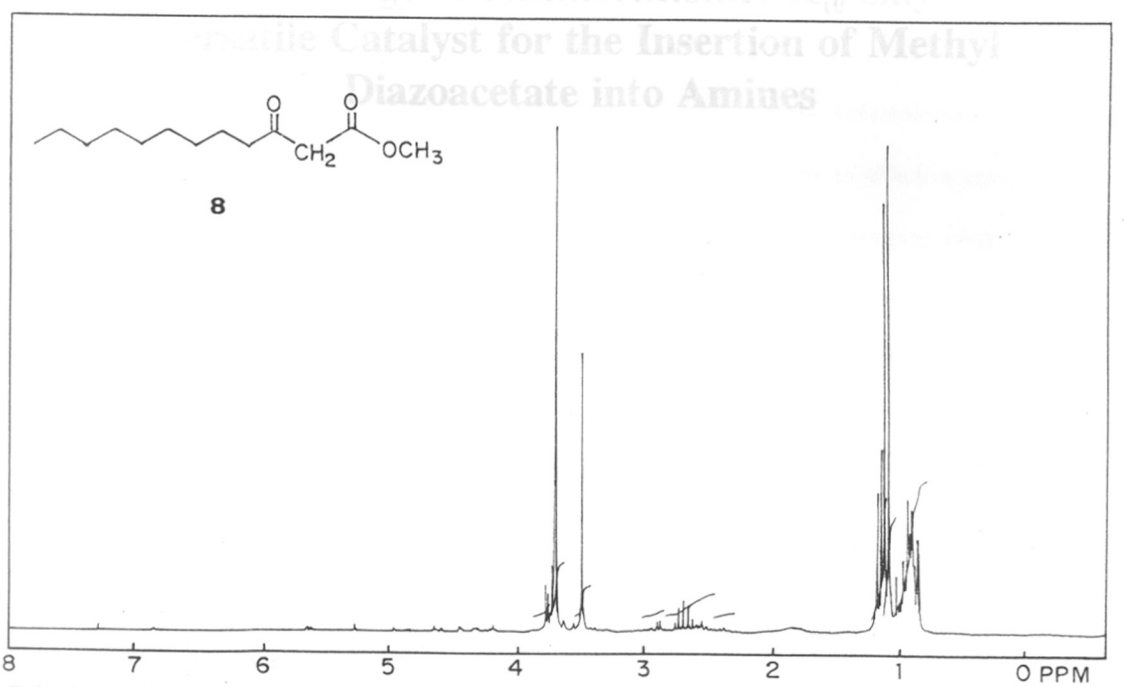


FIG. 4 : PMR SPECTRUM OF COMPOUND-**8**

Section-II

Cu-Exchanged Montmorillionite K_{10} clay: A versatile Catalyst for the Insertion of Methyl Diazoacetate into Amines

4.6.0 INTRODUCTION:

The work presented in this Section pertains to metal carbenoid insertions into N-H bonds of a few aromatic primary and secondary amines. The following amines have been included in this study -

Primary amines	**Secondary amines**
Aniline **11**	N-methyl aniline **14**
o-methyl aniline **12**	N-Ethyl aniline **15**
Cyclohexyl amine **13**	N-Propyl aniline **16**
	N-Butyl aniline **17**

In this context, it is relevant to provide a few examples of carbene insertion reactions drawn from literature into C-H bonds, O-H bonds and N-H bonds. This brief outline of literature provides a proper background in evaluation of the work presented in this *Section*. It also helps to view the work in the right perspective.

Metal-carbenoid insertions into C-H bonds:

With the advent of Rhodium acetate as a superior catalyst, intramolecular metal carbenoid insertions into unactivated C-H bonds have emerged as an effective strategy for C-C bond formation. Besides leading to good yields of cyclopentane annulated products, the methodology offers the advantage of realizing significant diastereoselectivity and enantioselectivity. This aspect has been exemplified by the recent synthesis of some important cyclopentanoid natural products such as (-) α-cuparenone, estrone, pentalenonelactone and prostaglandins.

On the other hand, the study of metal-carbenoid insertions into hetero atom-hydrogen bonds has been relatively limited; nonetheless, such reactions have led to methods for pharmaceutically important compounds.

Noels *et al.*[7] reported that Rhodium acetate catalysed insertion of carbenes derived from alkyl diazoesters into O-H bonds of various unsaturated alcohols led to high yields of the corresponding ethers.

$$\mathbf{R\text{-}OH + N_2CH\text{-}CO_2Alk \xrightarrow{Catalyst} R\text{-}O\text{-}CH_2COO\ Alk + N_2}$$

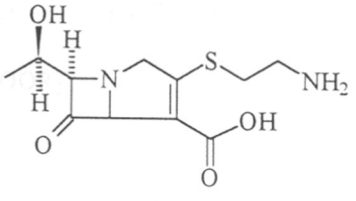
R = 1. $CH_2 = CH\text{-}CH_2$-

2. $CH \equiv C\text{-}CH_2$-

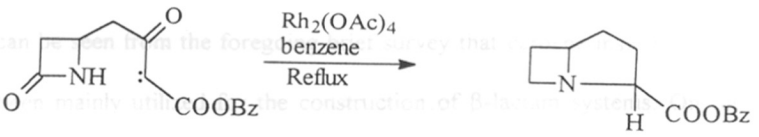
3. $CH_2 = CH\text{-}C\text{-}(CH_3)_2$-

These authors observed a highly regioselective carbene insertion into O-H bonds leading to 60-80% of the corresponding ethers along with 10 to 20% of cyclopropanated products. They observed that regioselectivity was a function of many parameters such as the nature of the catalyst and the alkoxy group of the diazoester.

The study of carbene insertion into N-H bond appears to have been triggered by a need to develop a practical methodology for the synthesis of carbopenem antibiotics such as *Thienamycin*.



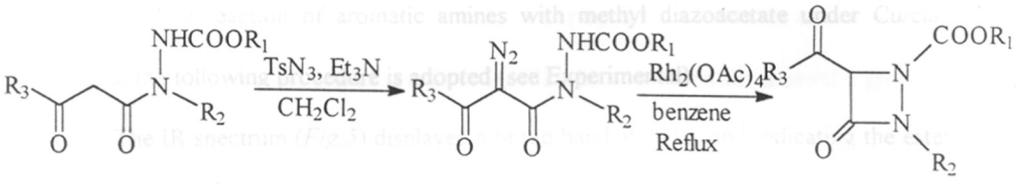
For example, Ratcliffe *et al.*[8] reported an efficient method to realize the five membered ring of thienamycin framework by the Rhodium-catalysed carbene insertion into the N-H bond.



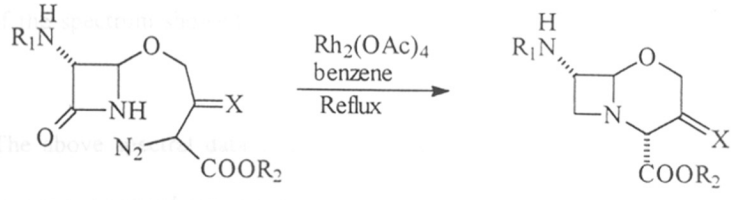
Quantitative yields

It may be added that the above mentioned carbene insertion into N-H bond constitutes the key step in the Merck synthesis of carbapenam antibiotics.

Moody and Pearson[9] have reported that Rhodium catalysed carbene insertion into a N-H bond can be utilised for the synthesis of aza-β-lactams.



Similarly, 1-oxacephem skeletons have been constructed by Yamamoto *et al.*[10] by a carbene insertion reaction into a N-H bond.



4.7.0 RESULTS AND DISCUSSION:

It can be seen from the foregoing brief survey that carbene insertion into a N-H bond has been mainly utilized for the construction of β-lactam systems. On the other hand, there does not appear any report of carbene insertion reaction into N-H bonds of aromatic amines, to the best of our knowledge. Therefore, a few aromatic primary amines and a few aromatic secondary amines were selected for such a study. The results from secondary amines would show the effect of electron donating alkyl groups on the carbene insertion reaction.

For the reaction of aromatic amines with methyl diazoacetate under Cu/clay catalysis, the following procedure is adopted (see Experimental).

The IR spectrum (*Fig.5*) displayed a broad band at 1710 cm^{-1} indicating the ester carbonyl function and another broad band at 3350 cm^{-1} suggesting the presence of a secondary amine functionality. The PMR spectrum (*Fig.6*) was significant in displaying a 3H singlet at 3.80, a 2H singlet at 3.95 and a broad 1H signal at 4.25. The aromatic region of the spectrum showed three groups of multiplets together integrating for five protons.

The above spectral data sufficed to identify the product as **18** easily. Further support for this structural assignment was provided by the mass spectrum which showed the molecular ion peak at m/e 165 ($C_9H_{11}NO_2$, 15%) with a significant base peak m/e = 106, resulting from the loss of -$COOCH_3$ from the molecular ion. The structure is too simple to need any more evidence.

Reaction of methyl diazoacetate with O-toluidine **12** when carried out as described in the case of aniline offered a clean product in 50% yield. The PMR spectrum of the product (*Fig.7*) was quite similar to that of the corresponding product from aniline

but for the extra resonance of the methyl group on the aromatic ring. From this data supported by the mass spectral features, the product could be easily identified as **19**.

Similarly, α-naphthylamine on its reaction with methyl diazoacetate furnished the N-alkylated product which could be identified as **20** on the basis of its spectral data (Experimental).

It was thought interesting to subject an alicyclic primary amine to methyl diazoacetate under the conditions previously described. The reaction of cyclohexyl amine **13** afforded a clean product in 82% yield. The PMR spectrum of the product (*Fig.8*) suggested a clean -N-H alkylation; the spectrum displayed a 1H multiplet at 2.40 δ, a 2H singlet at 3.40 δ and a 3H singlet at 3.65 δ. Besides this, the spectrum showed a group of signals integrating for five protons between 0.90-1.35 and another group of signals between 1.50-1.80 integrating for 6 protons; the latter group perhaps included the alicyclic methine resonance also. The above spectral data enabled the characterization of the product as **21**. This structural assignment was supported by its mass spectrum which showed the M^+ peak at m/e 171 and a base peak at m/e 112 arising from the loss of $COOCH_3$.

As the carbene insertion reaction can be either looked upon as an electrophilic reaction on the electron rich nitrogen atom or a nucleophilic reaction by the heteroatom on the electrophilic metal carbene centre, it was interesting to study the effect of electron donating groups on the nitrogen atom of the amines. With this view in mind, a few aromatic secondary amines were subjected to this reaction.

Thus reaction of N-methyl aniline **14** under the conditions described above furnished a clean product in 61% yield. The PMR spectrum of the product (*Fig.9*) was extremely significant by its absence of the N-H resonance originally seen in the starting

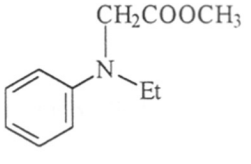
amine. This spectrum showed a 3H singlet at 3.0 δ, another 3H singlet at 3.65 δ and a 2H singlet at 4.0 δ; the spectrum, of course, displayed multiplets for 5 protons in the aromatic region. This clean spectral data was sufficient to characterize the product as **22**. Additional support for the structure was derived from its mass spectrum which showed the M^+ ion at m/e 179, a base peak at m/e 120 from a facile loss of $-COOCH_3$ and a peak at m/e 106 arising from a loss of $-CH_2COOCH_3$ from the molecular ion.

N-n-Propylaniline **16** on reaction with methyl diazoacetate yielded a clean product in 52%. The characterization of the product as **24** could be easily done on the basis of its PMR data (See Experimental). It displayed the expected 2H singlet at 4.10 and a 3H singlet at 3.75 δ indicating the occurrence of N-alkylation. The n-propyl attachment on nitrogen was clearly seen by the appearance of a 3H triplet at 1.00, a 2H multiplet at 1.75 δ and a 2H triplet at 3.40 δ. The aromatic region displayed three groups of signals together integrating for 5 protons. The mass spectrum (See Experimental) showed the molecular ion peak at 207 and peaks arising from the loss of COOMe and CH_2 COOMe.

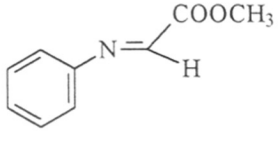
Reaction of n-butyl aniline **17** with methyl diazoacetate furnished a product in 68% yield. The PMR spectrum of the product (*Fig.10*) was interesting and revealed that the product could be a mixture of three components. A significant feature of this spectrum was a singlet at 8.15 δ integrating for half a proton. This information suggested that one of the components could be an imine constituting about 50% of the total product. The signals in the region 3.60 to 4.20 δ were extremely useful in understanding the nature of the products. A 3H singlet at 3.60 δ and 2H singlet at 4.15 δ clearly indicated the occurrence of N-alkylation leading to the expected product as observed in the case of previous secondary amines. Interestingly enough, two more singlets in a 1:2

ratio together integrating for one and a half protons were observed at 3.85 and 3.90 δ. In addition, the spectrum displayed satisfactory signals for the methyl and the methylene groups of the n-alkyl side chain. The above spectral data clearly indicated that the product on hand comprised about 50% of the expected N-alkylated product along with the cis and trans isomers of the imine (a&b) perhaps with the predominance of the trans isomer. The formation of the imines could be rationalized to arise from elimination of n-butyl side chain leading to a doubly conjugated system. The 1:2 ratio of the two extra O-CH_3 signals suggested a probable 1:2 composition of cis and trans imines.

N-ethyl aniline **15** on reaction with methyl diazoacetate under copper catalysis gave a product in 67% yield. The PMR spectrum of the product **23** showed the occurrence of the expected reaction by its resonances of a 3H singlet at 3.66 δ and a 2H singlet at 4.00 δ along with the expected resonances of the N-ethyl substituent and the aromatic protons; in addition to this, the spectrum showed a singlet at 8.0 δ indicative of an imine proton and a singlet at 3.90 δ integrating for 40:60 ratio. This spectral data indicated that the primary product had undergone elimination of the ethyl group leading to a highly conjugated imine. Thus, the product could be a 70:30 mixture of a and b.



a



b

In all probability, the imine is supposed to be in the preferred *trans* configuration. Additional support for the formation of imine was got from its mass spectrum which showed a peak at m/e 163 as required for the imine, besides showing the molecular ion

peak at m/e 193 for the alkylated primary product and a base peak m/e 134 arising from the loss of COOMe group from the molecular ion.

It can be seen from the results presented so far that the reaction of both primary and secondary aromatic amines with methyl diazoacetate under copper catalysis has furnished the corresponding N-alkylated products in moderate to good yields of 45-60%. Therefore, from this study of a few amines, it may be stated that this reaction has a potential which can be developed into a general methodology for this class of N-alkylated aromatic amines.

The effect of alkyl substitution

The results obtained in terms of yields from primary and secondary amines have been shown in the Table. The primary amines by virtue of possessing two -NH bonds have a statistical possibility of furnishing the alkylated products in double the amounts to that of the secondary amines. The yield per one -NH bond shown in the Table indicates that the yields of the alkylated products are much more from the secondary amines than that of the primary amines. These results indicate that the electron donating alkyl substituent enhances the nucleophilicity of the amine nitrogen and thereby enhances the yield.

Table: Yields of the N-alkylated products:

Primary amine	Yield (%)	Yield per N-H bond
Aniline	82	41
O-toluidine	50	25
α-Naphthylamine	93	46.5
Cyclohexylamine	82	41

Secondary amines	Yield (%)	Yield per N-H bond
N-methylaniline	61	61
N-ethylaniline	67	67
N-propylaniline	52	52
N-butylaniline	68	68

It can also be seen that none of the primary amines has given rise to dialkylated products. Such a result may be attributed to the reduced nucleophilicity of the nitrogen atom in the monoalkylated product due to the $-CH_2-COOCH_3$ grouping.

It can be seen that two secondary amines *viz*. N-ethyl and N-butyl anilines besides furnishing the expected N-alkylated products have given rise to some amounts of imines. In all probability, these imines can be looked upon as the secondary products arising from elimination of a neutral molecule of an alkane; the driving force for such a reaction can be the formation of a highly conjugated imine. Such a phenomenon has not been observed in the case of primary amines.

Mechanistic aspects:

Although the products observed from the reactions of methyl diazoacetate from various aromatic amines can be looked upon as the result of carbene insertion into the -N-H bond, there is an alternative mechanism which is more plausible. Most of the researchers in this area who obtained such apparently carbene insertion products into the -NH bonds have observed that owing to the presence of a metal carbenoid species, this reaction should be viewed as a nucleophilic reaction of the amine nitrogen on the electrophilic metal carbenoid species. However, the involvement of metal-carbenoid species is known to cause dimerization of methyl diazoacetate to a mixture of methyl fumarate and maleate. As we have not observed such dimerization products, metal carbenes may not be involved in these reactions. Thus, the mechanistic picture is not yet clear.

4.8.0 EXPERIMENTAL SECTION:

General Procedure: A solution of aniline in dry benzene was treated with 2.0 molar equivalent of methyl diazoacetate and the catalyst Cu/clay (10% by weight of the substrate) was introduced. The mixture was refluxed and the progress of the reaction mixture was monitored by TLC. When the starting material almost disappeared (3-4 hrs.), the reaction mixture was cooled to room temperature and the catalyst was filtered off. Evaporation of the solvent and passage of the residue through a column of SiO_2 yielded the product in a pure form.

[*Note*: All reactions are performed on one gram scale and the corresponding products and their yields are written in the data of each compound].

1.Methyl N-phenyl glyoxalate: 18

Yield: 1.50 gm (82%)

IR:(neat) 3350, 1710, 1600, 1500, 1420, 1200, 1000, 750, 680,500cm^{-1}

PMR ($CDCl_3$, *Fig.6*)δ: 3.80 (s, 3H), 3.95 (s, 2H), 4.25 (bs, 1H), 6.60 (d, 2H), 6.80 (t, 1H), 7.20 (t, 2H).

MS: 165 (M^+, 20), 106(100), 93(10), 77(30), 65(10), 59(10), 51(20).

2.Methyl N-phenyl 2'Methyl glyoxate 19:

Yield: 0.4 gm. (50%)

b.p: 152°C/15mm (bath temperature)

IR (neat): 3000, 2900, 1740, 1600, 1500, 1430, 1200, 750 cm^{-1}

PMR($CDCl_3$,*Fig.7*) 2.25 (s, 3H), 3.85 (s, 3H), 4.0 (s, 2H), 4.20 (bs, 1H), 6.55 (d,1H), 6.75 (t, 1H), 7.15 (t, 2H).

MS: 179 (M^+, 20). 120(100), 106(40), 91(35), 86(20), 84(30), 77(20), 65(20), 59(35), 51(15).

3.Metyl N-Nepthyl glyoxate,20:

Yield: 4.00 gm. (93%) [From 5.0 gm. of the starting amine]

M.P.: 72-74°C

IR(neat): 1720 cm^{-1}

PMR(200MHz,$CDCl_3$)δ 3.80 (s, 3H), 4.0 (s, 2H), 6.40 (bs, 1H), 7.23 (bs, 3H), 7.45 (m, 2H), 7.80 (m, 2H).

4. Methyl N-Hexyl glyoxalate 21:

Yield: 1.50 gm (82%)

b.p: 75°C/15mm (bath temperature)

IR (neat): 1730 cm^{-1}

PMR(200MHz,$CDCl_3$,*Fig 8*)δ :0.90-1.35 (m, 5H), 1.50-1.80 (m, 6H), 2.40 (m, 1H), 3.40 (s,2H), 3.65 (s, 3H).

MS : 171 (M^+, 10). 128(70), 112(100), 83(15), 68(65), 56(75).

5. Methyl N-methyl,N-phenyl glyoxalate,22:

Yield: 0.8 gm (61%)

b.p: 152°C/7mm (bath temperature)

IR (neat): 1720, 1590 cm^{-1}

PMR (200MHz,*Fig.9*): 3.0 (s, 3H), 3.65 (s, 3H), 4.0 (s, 2H), 6.6 (m, 3H), 6.9 (m, 2H)

MS: 179 (M^+, 30). 128(40), 120(100), 106(40), 91(20), 77(40), 64(10).

6.Methyl N-phenyl ,N-ethyl glyoxalate 23:

Yield: 0.72 gm (67%)

IR: 1710, 1600 cm^{-1}

PMR (200MHz,$CDCl_3$)δ: 1.20 (t, 3H), 3.37 (q, 2H), 3.60 (s, 3H), 4.00 (s, 2H), 6.52 (m,3H), 7.0 (m, 2H).

MS: 193 (M^+, 25). 178(5), 163(10), 134(100), 120(5), 105(30), 91(5), 77(10).

7.Methyl N-propyl glyoxate 24:

Yield: 0.8 gm (52%)

IR (neat): 1710, 1600 cm^{-1}

PMR(200MHz,$CDCl_3$)δ: 1.0 (s, 3H), 1.75 (m, 2H), 3.40 (t, 2H), 3.75 (s, 3H), 4.10 (s, 2H), 6.65 (d, 3H), 7.25 (d, 2H).

8. Methyl N-phenyl,N-butyl glyoxate 25 and **25a**:

Yield: 0.72 gm (68%)

b.p: 176°C/3mm (bath temperature)

IR(neat): 1710, 1600 cm^{-1}

PMR (200 MHz,*Fig.10*) δ: 1.00 (t, 3H), 1.40 (q, 2H), 1.65 (m, 2H), 3.40 (t, 2H), 3.60 (s, 3H), 3.85(s), 3.90(s), 4.20 (s, 2H), 6.70 (t, 3H), 7.25 (t, 2H), 8.15(s, 1H).

MS: 221(M^+,50),193(10),178(50), 162(100), 150(20), 134(10), 120(90), 106(45), 91(10), 77(15).

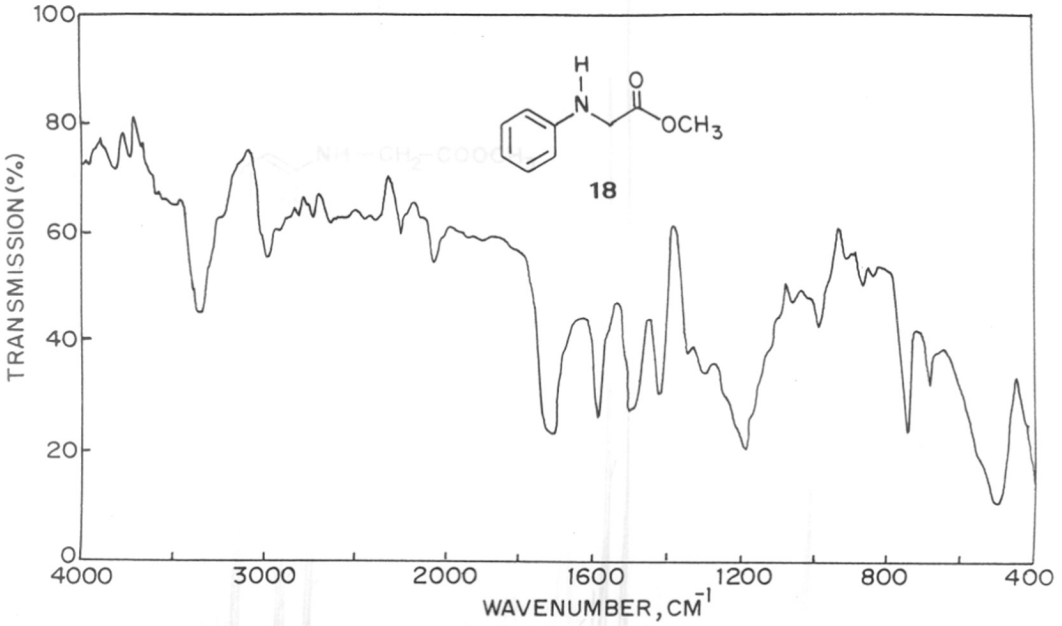


FIG. 5: IR SPECTRUM OF COMPOUND - **18**

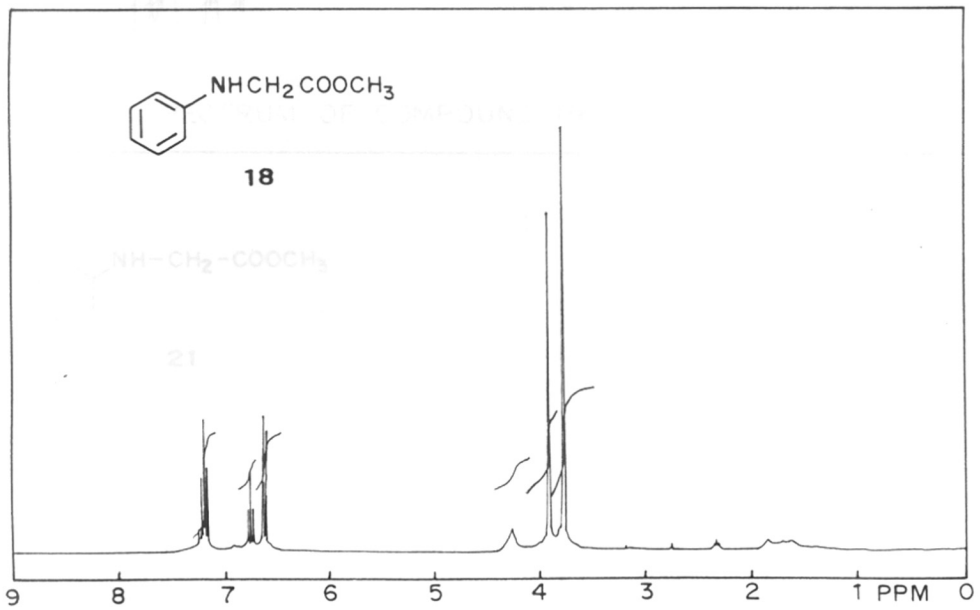


FIG. 6: PMR SPECTRUM OF COMPOUND - **18**

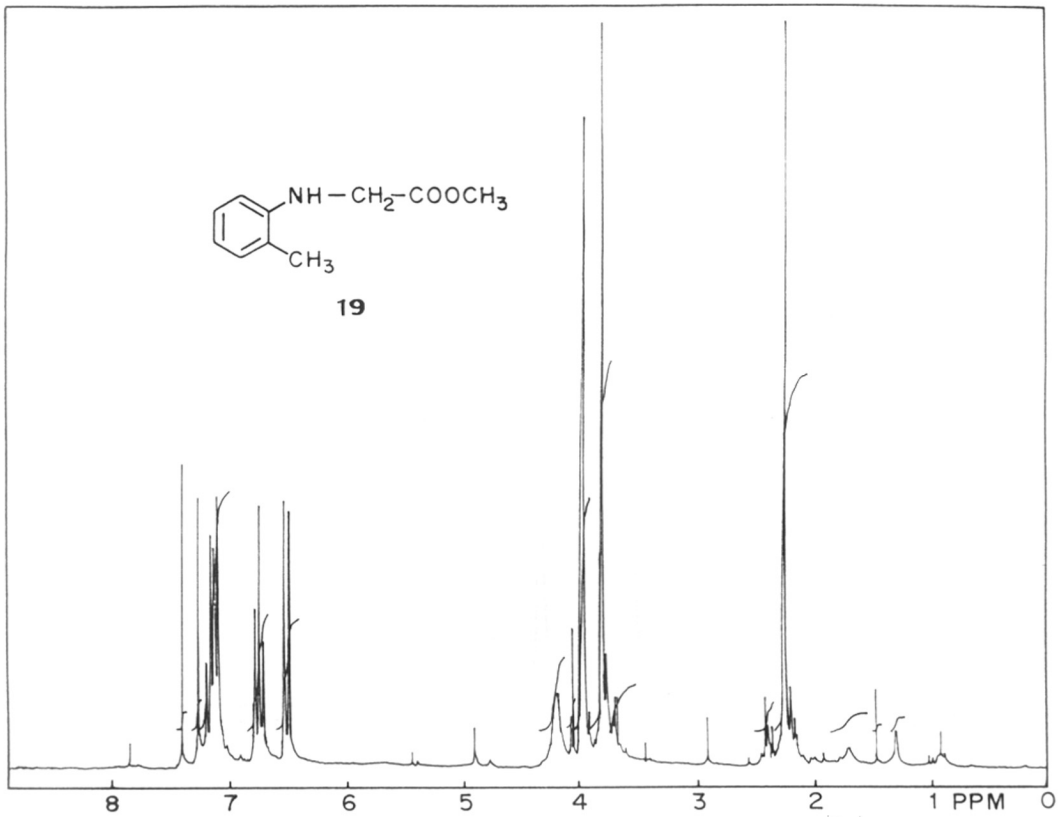


FIG. 7 : PMR SPECTRUM OF COMPOUND **19**

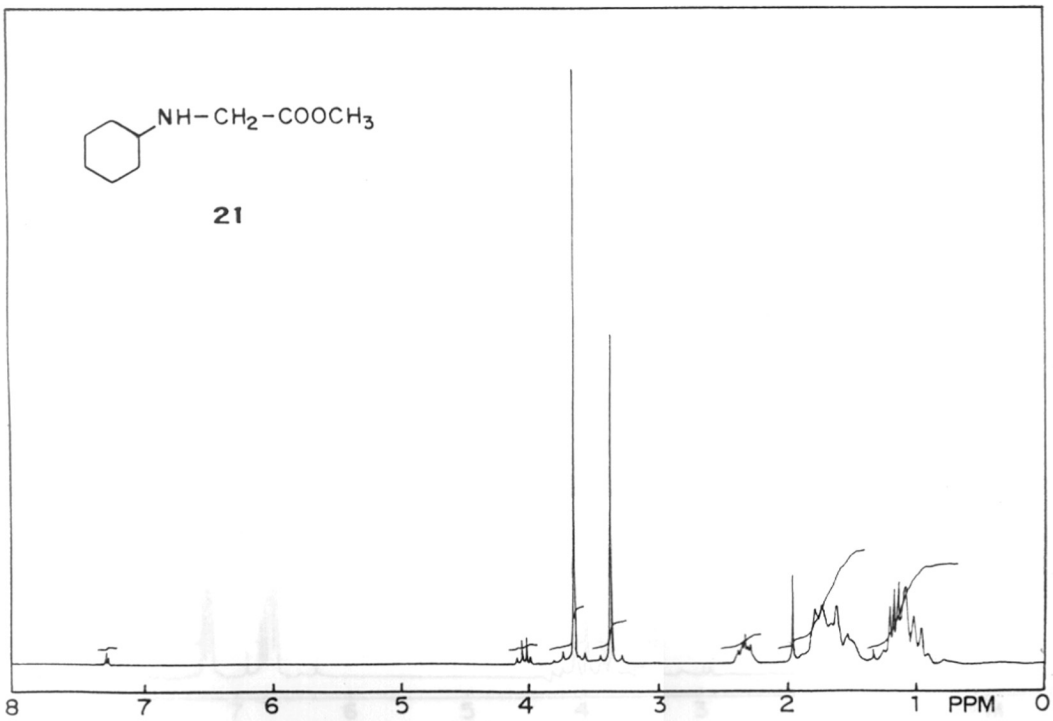


FIG. 8 : PMR SPECTRUM OF COMPOUND - **21**

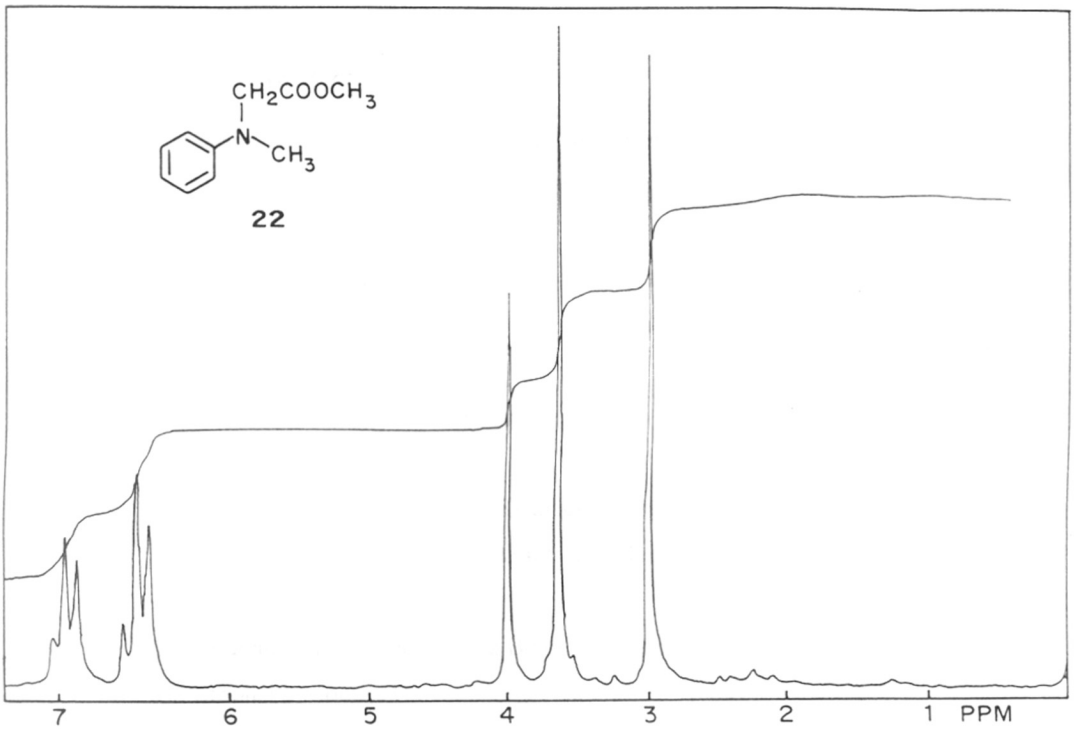


FIG. 9: PMR SPECTRUM OF COMPOUND-22

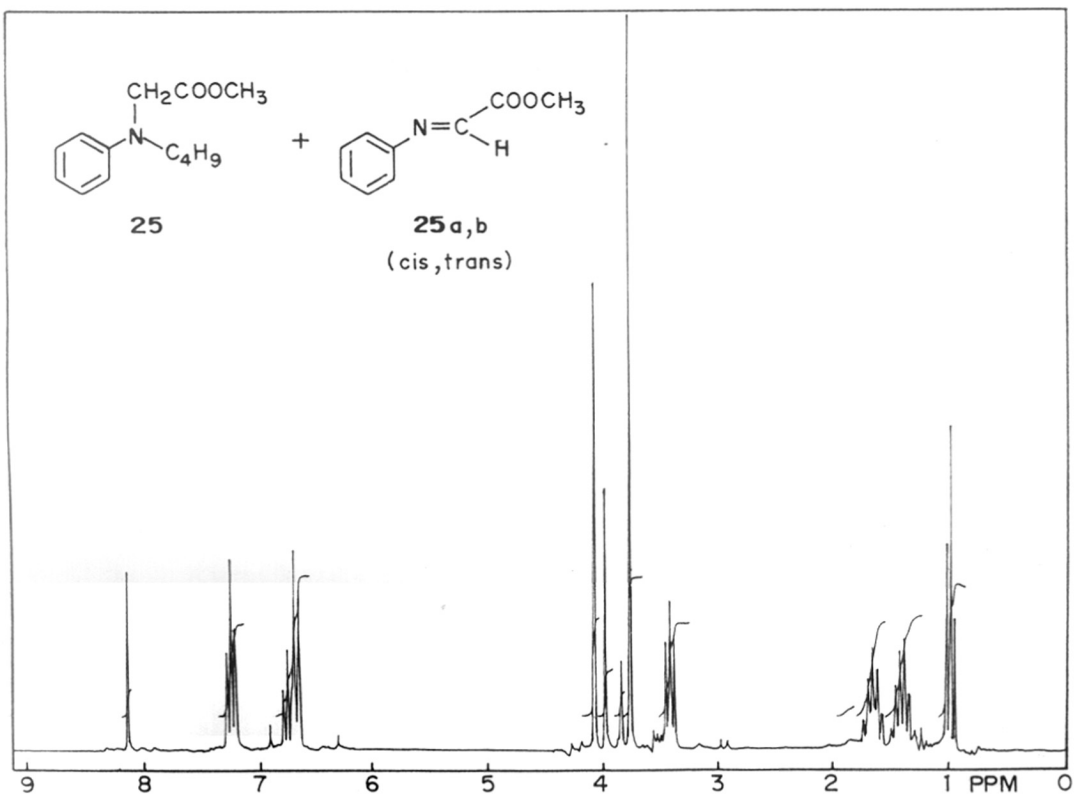


FIG. 10: PMR SPECTRUM OF COMPOUND **25** AND **25a** (Cis and trans)

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To be communicated to *Ind. J. Chem.*

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To be communicated to *Tetrahedron.*

8. Cu-Exchanged Montmorillionite K_{10}: clay mediated synthesis of keto esters: Condensation of aldehydes and methyl diazoacetate
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J. Madan Mohan, T. Ravindranathan and A. Sudalai
To be communicated to *Chemistry Letters.*