SYNTHESIS OF BIOLOGICALLY USEFUL COMPOUNDS EMPLOYING Π-FACE STEREO-SELECTION, PHOSPHACUMULENE YLIDE AND MARINE METALLOENZYME(VPO) MIMIC

A THESIS

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BY

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JULY 1996

..... MY BELOVED PARENTS

CERTIFICATE

Certified that the work incorporated in the thesis entitled "***Synthesis of Biologically Useful Compounds Employing Π-Face Stereoselection, Phosphacumulene Ylide and Marine Metalloenzyme(VPO) Mimic***" by C.U. Dinesh 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.

(DR. BIPIN PANDEY)
Research Guide

ACKNOWLEDGEMENTS

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Dinesh

(Dinesh C.U.)

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GENERAL REMARKS

1. All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.
2. All the solvent extracts were finally dried over anhydrous sodium sulphate.
3. The compound numbers, scheme numbers and references etc. given in each chapter refer to that particular chapter only and the same thing applies to the abstract.
4. All the solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80°C.
5. TLC was carried out on silica gel plates prepared by spreading the slurry (in chloroform), drying at room temperature.
6. GLC was carried out on Hewlett Packard 5890.
7. The IR spectra were recorded on Perkin-Elmer infrared spectrophotometer model 683B. The following abbreviations are used:
   s = strong, m = medium, w = weak.
8. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian FT-80A, Bruker WH-90 and Bruker AC-200 spectrometers, using tetramethylsilane as internal standard. The following abbreviations are used:
   s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.
9. The UV was recorded on Schimadzu model 240 spectrophotometer.
10. The mass spectra were recorded on Finnigan MAT - 1020-B-70eV mass spectrometer. The compounds for which only M^{+} is noted the mass spectrum was recorded on GC-MS.
11. Elemental analysis were performed by Micro analytical Lab, operated by NCL, Pune.
12. All optical rotations were measured using Sodium D lines on JASCO-181 digital polarimeter at room temperature.

ABBREVIATIONS

Ac	Acetyl
Ar	Aryl
DMSO	Dimethyl sulfoxide
eq	Equivalent/s
Et	Ethyl
g	Gram/s
h	Hour/s
IR	Infrared
L	Litre/s
Lit.	Literature
Me	Methyl
min	Minutes
m.p.	Melting point
M^+	Molecular ion
MS	Mass spectrum
MVK	Methyl vinyl ketone
NaHMDS	Sodium bis(trimethylsilyl)amide
nm	Nanometer
Pd/C	Palladium(10%) on carbon
Ph	Phenyl
PTSA	*p*-Toluenesulfonic acid
TMS	Trimethylsilyl
THF	Tetrahydrofuran
UV	Ultraviolet

ABSTRACT

The thesis entitled "***Synthesis of biologically useful compounds employing*** Π-*face* ***stereoselection, phosphacumulene ylide and marine metalloenzyme(VPO) mimic***" is divided into three chapters. The thesis has minor diversions in terms of our deep interests in several areas and also of on going research programme in our group. The main objective of the thesis was to develop synthetic methodologies to synthesize optically active skeletons (e.g., 1,2-difunctionalized bicyclic compounds, cyclopropyls etc.) based on π-face stereoselection. While marine metalloenzyme mimic work started in the beginning of Ph.D. programme, primarily to explore an unprecedented aspect of organic chemistry, the synthetic applications of phosphacumulene ylides led to novel quinolones. Simultaneously, we have also ventured into the area of synthetic methodology based on π-face stereoselection for the synthesis of optically active skeletons, which could be further employed as building blocks for bioactive compounds. Some of the results(observations) are unanticipated, especially the stability of the chiral synthon **45** (**Chapter 1, Sec. 2**) for the detachment of the chiral auxiliary after the reaction, lack of amine addition to **45** (**Chapter 1, Sec. 3**), failure of dimethyl cyclopropanation of **45** (**Chapter 1, Sec. 4**), dehydration in the case of nucleophilic reaction of **290** (**Chapter 1, Sec. 5**) etc. Many of these difficulties have been overcome by finding alternative solutions and were successful in fulfilling the main objective.

Each chapter begins with a brief overview of the respective areas followed by clear statement of objectives, results and discussion, conclusions and finally experimentals. The titles of various chapters, their subsection and a brief discussion about these chapters are as follows:

CHAPTER 1

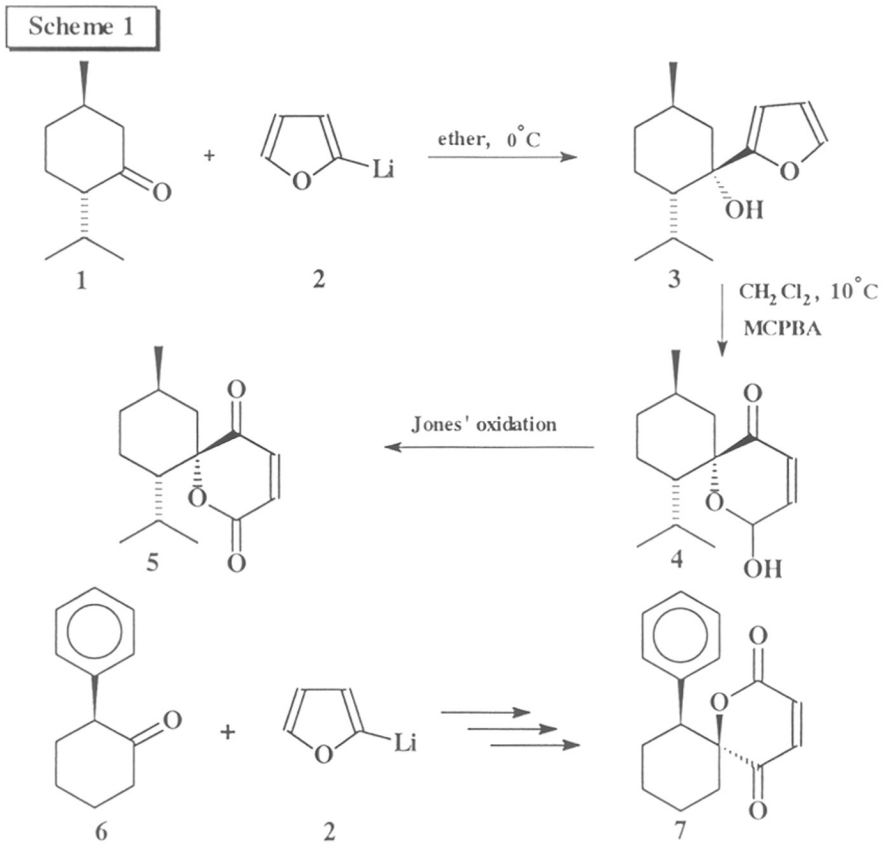
Spirodiones in Asymmetric Synthesis

Chiral auxiliary induced asymmetric synthesis is quite common because of its reliability and predictable stereocontrol. A recent report by Seebach et. al. signifies the role of Π-face stereoselection in asymmetric synthesis. In recent years, various theories e.g., Cieplak effect, nucleophilic and electrophilic surface theory, electrostatic interactions, σ-π interactions, FMO theory of stereoselection, theory of steric consideration etc. have emerged to justify the cause of stereoelectronic control in the reactions. Chiral auxiliaries such as menthol, menthone, camphor etc. have been used extensively for the efficient synthesis of optically active compounds. All these developments in the area of asymmetric synthesis prompted us for the pursuit of a new chiral antipode which can be used efficiently for the chiral induction.

This chapter is divided into five sections.

Section 1: **Synthesis and characterization of chiral spirodiones using (-)-menthone and (-)-2-phenylcyclohexanone as chiral auxiliaries**

As mentioned above, optically active menthone is an efficient chiral auxiliary because of the adjacent isopropyl group, which can exert a considerable steric effect on the incoming group. Similarly, phenyl group in 2-phenylcyclohexanone should be more steric in nature. By attaching a proactive functionality to these chiral auxiliaries, a number of reactions have been carried out. Usually the menthyl moiety attached through an ether linkage, ester, as acetals etc. have been reported in the literature. We have synthesized novel chiral spiroskeletons **5** and **7** having a unique carbon-carbon bond using the aforementioned chiral auxiliaries and furan as shown in **Scheme 1**.



X-ray crystallographic analysis of **5** has shown that the isopropyl group of menthone and the C-O ester linkage are syn to each other. On the same line the structure for **7** is also proposed. The formation of the single diastereomer by the reaction of the chiral auxiliary and furan is noteworthy.

Section 2: **Diels-Alder reactions of the spirodiones 5 and 7**

The role of Diels-Alder reactions with the control of absolute stereochemistry leading to the formation of two or more chiral centers in a single reaction is well known in the literature. Organic chemists used it advantageously for the synthesis of many complex organic molecules. Diels-Alder reactions using chiral catalysts or chiral dienes have shown to give a moderate diastereoselectivity (de). A good diastereoselectivity has been achieved in Diels-Alder reactions of chiral acrylates and sultams using Lewis acids. We have observed excellent diastereoselectivities by the reaction of chiral spirodiones with various dienes (**Scheme 2, Table-1**). The de of these reactions were measured by ^{13}C-NMR and comparing the detached (from the chiral auxiliary) product with the authentic compound.

Scheme 2

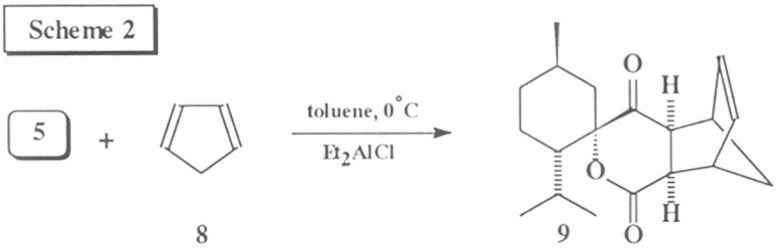


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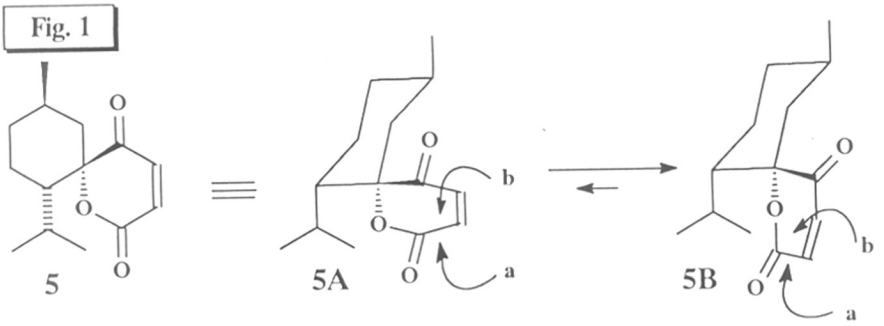
Table-1: Diels-Alder reactions of **5**

Entry	Diene	Yield (%)	de (%)
1	Cyclopentadiene	95	single diastereomer
2	2,3-dimethyl-1,3-butadiene	95	single diastereomer
3	Hexachlorocyclopentadiene	78	single diastereomer
4	2-Methyl-1,3-pentadiene	80	70
5	2-(Trimethylsilyloxy)-1,3-butadiene	82	75

Use of Lewis acids other than Et_2AlCl or variation in temperature haven't improved the diastereoselection and yield.

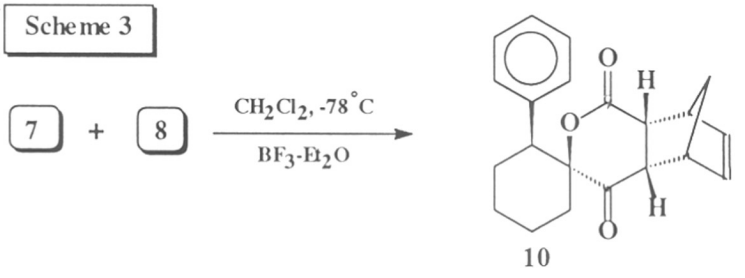
X-ray crystallographic analysis of **9** has shown that the diene has added anti to the isopropyl group of menthone. This differs significantly from the literature reports and can be explained on the basis of different facial selectivities that is exhibited by the spiroskeleton (**Fig. 1**).

Fig. 1



A remarkable π-facial stereoselection (100% preference for 'b' side to 'a' side) has been observed. One reasonable explanation is to assume that the approach of the reagent i.e., diene from 'a' side should cause appreciable steric hindrance between the isopropyl group and the diene and thus the diene attacks preferentially from 'b' side. The formation of similar product was observed from the reaction of spirodione derived from (-)-2-phenylcyclohexanone and cyclopentadiene as shown below in **Scheme 3**.

Scheme 3



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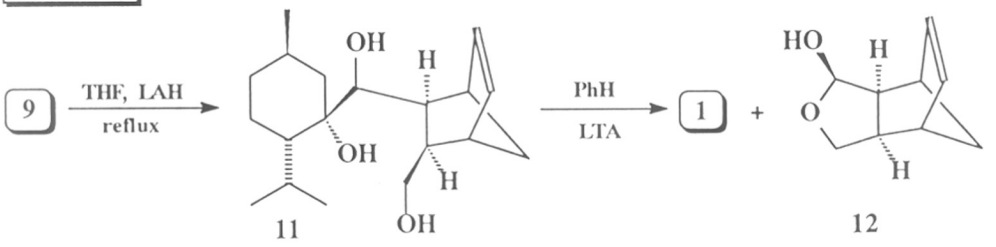
A mention of standard reactions which failed to detach the chiral auxiliary from the products of 5 will be made in this section. Finally, the detachment of the chiral auxiliary from the Diels-Alder adducts was carried out successfully using lithium aluminium hydride as shown in **Scheme 4**. The resultant products i.e., menthone and the lactols were found to be optically pure.

Scheme 4



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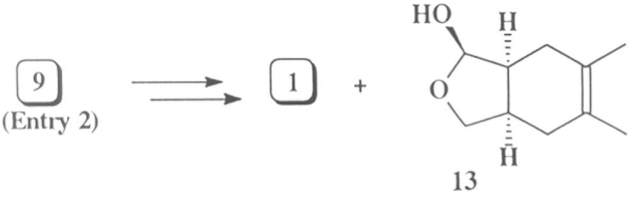

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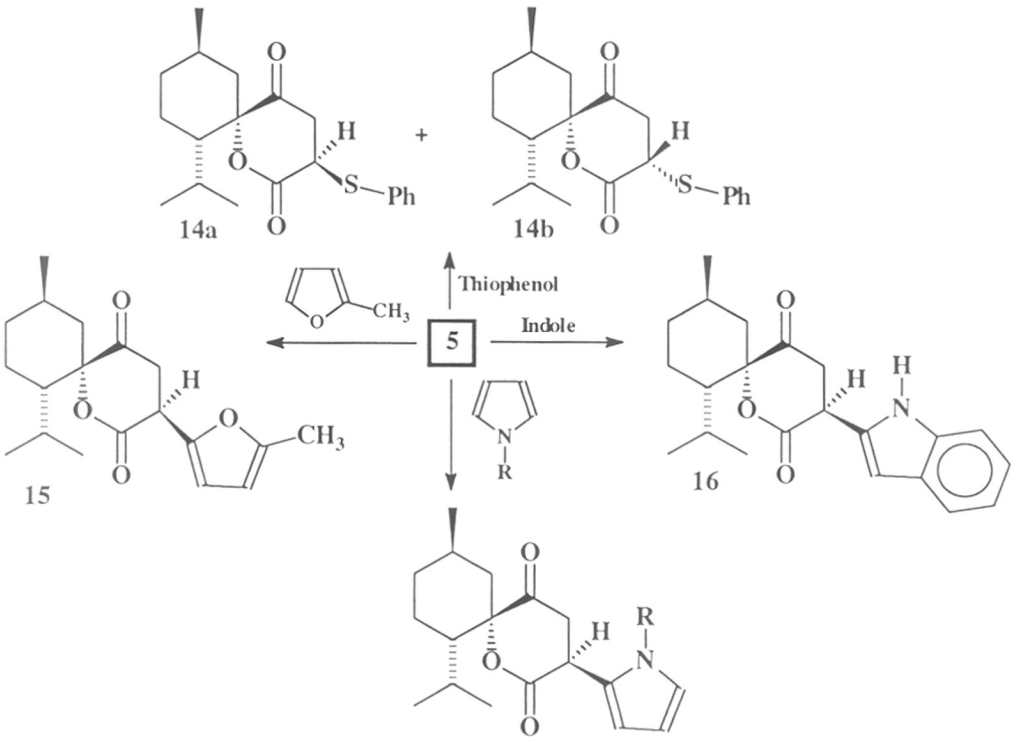
Section 3: Michael addition reactions on the spirodione 5

With a view to enhance the versatility of spiro-ketone, Michael addition reaction was attempted. In the asymmetric Michael addition reaction of a nucleophile to an activated olefin usually one of the reactant is chiral. Specifically reactions using chiral acceptors where the reactions occur at the center that is prostereogenic is known but scarce.

Amines as nucleophiles have been extensively utilized for the construction of biologically useful skeletons. In this section, we have tried to add a variety of amines to **5** with a view to synthesize optically active amino acids. While the reaction of various amines e.g., benzylamine, dibenzylamine, pyrrolidine, piperidine etc. were not encouraging. The reaction of heterocycles e.g., pyrrole, indole, substituted furan gave interesting results (**Scheme 5**, **Table-2**).

Scheme 5



Reactions of indole and N-methyl pyrrole proceeded in toluene at 0°C in the presence of diethylaluminium chloride catalyst giving single diastereomer. Reaction of pyrrole and 2-methyl furan gave a moderate diastereoselection. Variation in solvent system or reaction temperature didn't show any significant change in results. Addition of thiophenol led to a 84:16 mixture of products. Considerable chemoselectivity and de were observed in these reactions.

Table-2: Michael addition reactions of **5**

Entry	Michael donor	de (%)
1	Indole	single diastereomer
2	N-methyl pyrrole	single diastereomer
3	Pyrrole	80
4	2-Methyl furan	70
5	Furan	no reaction
6	Thiophenol	68

Section 4: Asymmetric cyclopropanation

Asymmetric cyclopropanation is one of the most important and challenging reactions in organic synthesis. Normally it is achieved by the stereoselective transfer of carbon ligands from chiral catalysts to alkenes. A few reports are also available for the chiral auxiliary based asymmetric cyclopropanation. This constitutes one of the powerful methods for preparing biologically active (insecticides) pyrethroids such as chrysanthemic acid. This section reports an excellent diastereoselectivity obtained in the reaction by the direct cyclopropanation of the spirodiones **5** and **7** using Corey's ylide and other sulphur ylides (**Scheme 6**).

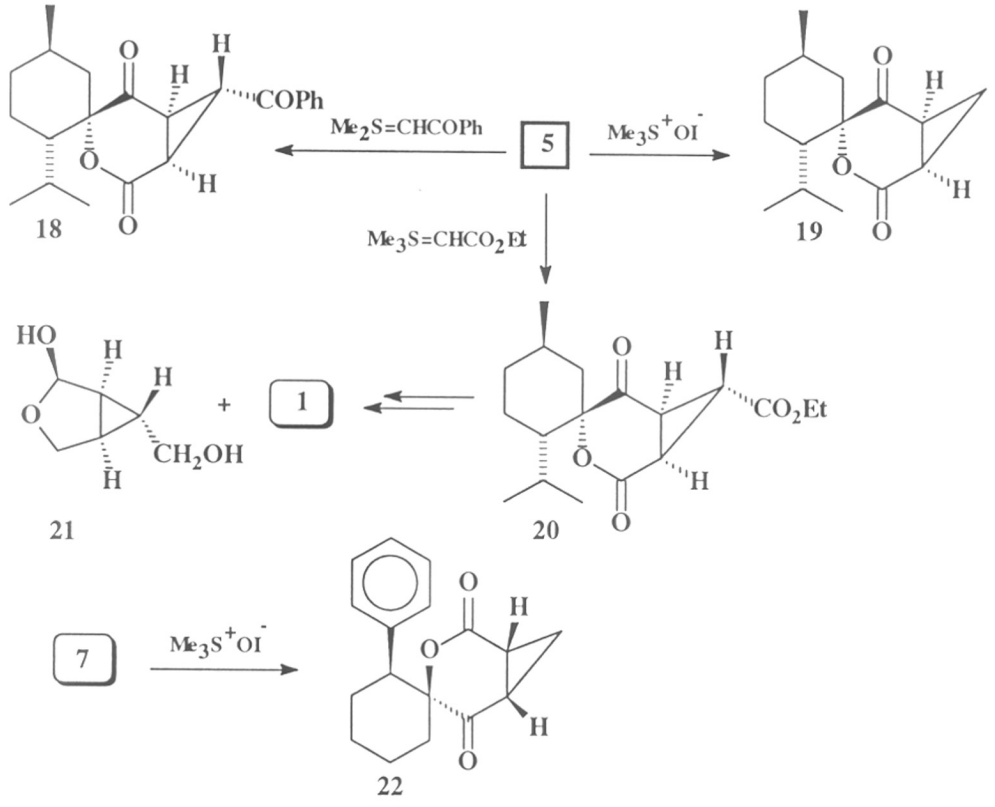
In all the cases single diastereomer is obtained where the addition is anti to the isopropyl group present α-to the spirocentre. Our studies towards synthesizing a key skeleton for chrysanthemic acid will be described (**Scheme 7**).

Section 5: Epoxidation and its cleavage

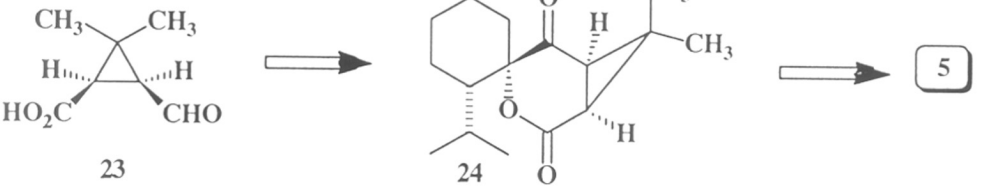
The pioneering work by Sharpless on asymmetric epoxidation and the aftermath research utilizing it for the synthesis of a vast number of organic molecules have shown the importance of the chiral epoxides in organic synthesis. The control of stereoselection in this is mainly due to the chiral ligand involved in the reaction. Here we have examined the epoxidation reaction of the spirodione **5** with a view in mind that the isopropyl group will have the significant stereoelectronic effect by the incoming oxygen atom leading preferentially to the formation of the anti product. However, a 70:30 mixture of products were obtained when H_2O_2 was used as the epoxidizing agent, but, a single diastereomer was obtained when *t*-BuOOH was used (**Scheme 8**).

It was planned to utilize the above epoxide for the synthesis of optically active amino alcohols. However, the reaction of amines with this epoxide gave unanticipated dehydrated products, perhaps due to the extended conjugation leading to a stable structure (**Scheme 9**).

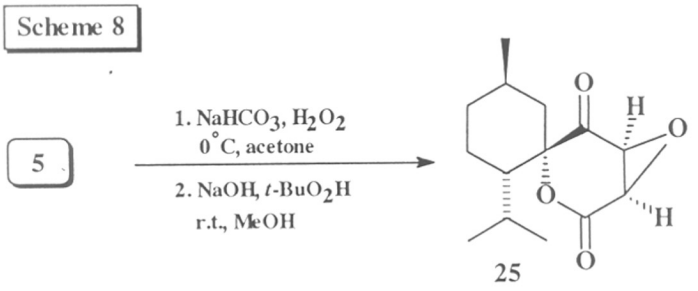
Scheme 6



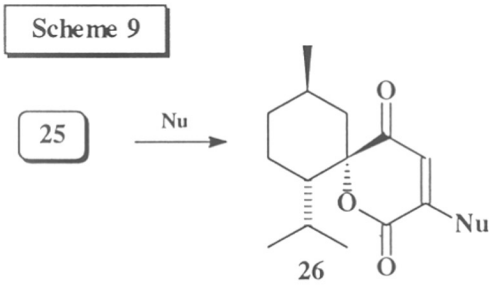
Scheme 7



Scheme 8



Scheme 9



Nu = nucleophile = N_3^-, morpholine, pyrrolidine, piperidine, diethylamine etc.

CHAPTER 2

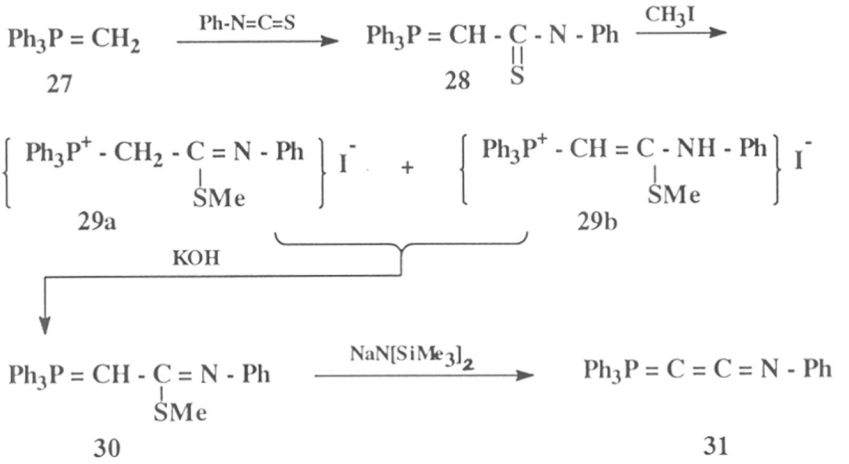
Synthesis and application of phosphacumulene ylide: N-phenyl(triphenylphosphoranylidene) ethenimine for biologically useful quinolones

Organophosphorous chemistry has made significant contribution towards the development of newer synthetic methodologies. The discovery of Wittig reaction and its varied synthetic applications constitute simply one such example. In this series of organophosphorous reagents, phosphacumulene ylides are one of the recent arrivals. They are nucleophilic and versatile reagents. The synthesis of N-phenyl(triphenylphosphoranylidene)ethenimine has been achieved by new synthetic strategy and its reaction with carboxylic acid has been investigated. Thus, in present study an attempt has been made towards development of various compounds by Wittig cyclization using N-phenyl(triphenylphosphoranylidene)ethenimine as intramolecular C-1 synthon.

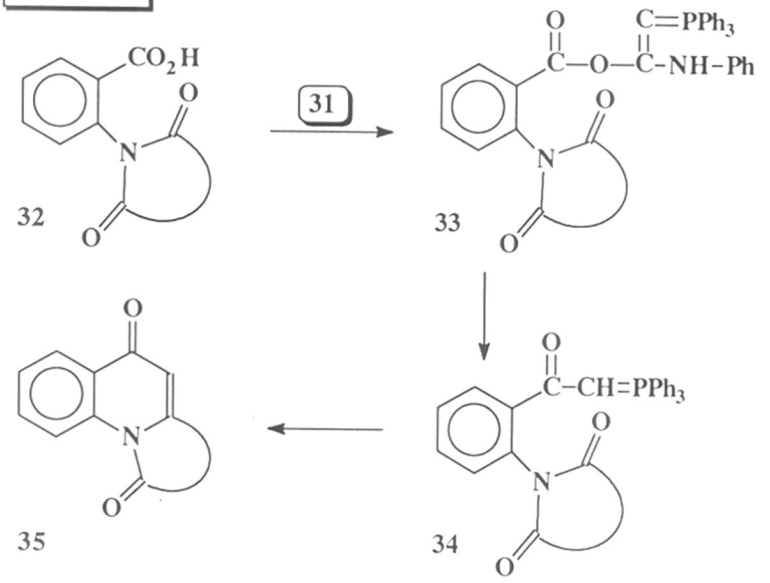
The synthesis of N-phenyl(triphenylphosphoranylidene)ethenimine was achieved as follows: Methylene triphenylphosphorane was made to react with phenylisothiocynate at 0°C to give **28** which was further methylated using methyl iodide to give a 1:1 mixture of **29a** and **29b**. This mixture was further treated with 10% KOH solution to give **30** and finally, treatment of **30** with NaHMDS yielded the required ylide N-phenyl(triphenylphosphoranylidene)ethenimine **31** in good yield (**Scheme 10**).

The coupling reaction of keto carboxylic acid with the ylide to give indenone derivative and its further extrapolation for the construction of 1-benzothiopyran-4-one have been accomplished in our group. The synthetic potential of cumulated ylide has been further extended for the biologically useful quinolone antibiotics as shown in **Scheme 11**. The reaction of ylide with various imide (prepared by heating anthranilic acid with suitable anhydrides) in stepwise fashion led to the formation of acyl phosphoranes which subsequently underwent intramolecular Wittig cyclization to an imide carbonyl to afford pyrrolo and pyrido[1,2-a] quinolones in moderate to good yield. Thus, the method provides one-pot synthesis of quinolone via intramolecular Wittig reaction using cumulated ylide as synthon.

Scheme 10



Scheme 11



CHAPTER 3

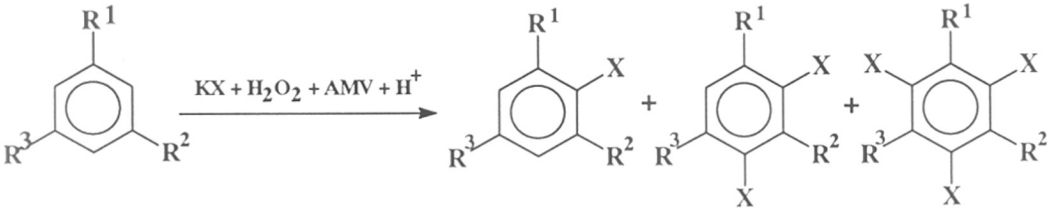
Catalytic halogenation of selected organic compounds mimicking vanadate-dependent marine metalloenzymes.

Marine natural products exhibit a considerable abundance of halogenated organic compounds compared to the natural products from the terrestrial species. Relatively, a little attention has been given to catalytic halogenation studies mimicking marine metalloenzymes while the catalytic

oxyfunctionalization of the inert C-H bonds has been attempted either by mimicking biocatalysts or using zeolites. Vanadate dependent non-haem marine metalloenzymes e.g., vanadium bromoperoxidase and iodoperoxidase which catalyze the oxidation of chlorides, bromides and iodides by hydrogen peroxide in the presence of their inorganic sodium or potassium salts are presumed to involve in the biogenesis of halogenated organic compounds. This chapter summarizes our efforts towards unprecedented use of ammonium metavanadate as catalyst for the halogenation of a variety of organic substrates from potassium halides and dilute hydrogen peroxide.

Scheme 12

$$R\text{-}H + X^- + H_2O_2 + H^+ \longrightarrow R\text{-}X + 2H_2O$$



36a-f **37a-f** **38a-f** **39a-f**

a, $R^1=R^2=R^3=OH$
b, $R^1=R^2=OH$, $R^3=H$
c, $R^1=OH$, $R^2=R^3=H$
d, $R^1=R^2=R^3=OMe$
e, $R^1=R^2=OMe$, $R^3=H$
f, $R^1=CH_2\text{-}CH(CH_3)_2$, $R^2=R^3=H$

The product ratio depends on the equivalence of the inorganic salt added.

The probable mechanism can be the oxidation of X^- to X^0 and further to X^+. The various oxidizing species involved during the oxidation could be oxyperoxides or oxovanadium (VO_2^+), peroxovanadium [$VO(O_2)^+$], diperoxovanadium {$VO(O_2)^{2-}$] and/or hydroperoxides (HO-V-O-O-H). ^{51}V-NMR studies indicate the presence of resonances at δ values corresponding to the above species and are close to the reported values.

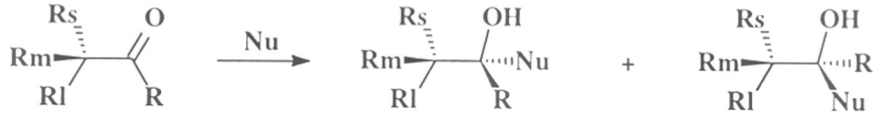
CHAPTER - 1

SPIRODIONES IN ASYMMETRIC SYNTHESIS - Π-FACE STEREOSELECTION

INTRODUCTION

Facial selectivity during addition to sp^2 carbon such as olefins, carbonyls etc. is at the heart of stereogenesis. Before realizing the importance of stereoelectronic effect, the more obvious steric effects were formulated and discussed. According to Cram's rule[1], the approach of a nucleophile (Nu) to a carbonyl flanked by three different size of groups, e.g., Rs (small), Rm (medium) and Rl (large) would be preferentially from the direction occupied by the small substituent (Rs) as shown below (**Scheme-1**).

Scheme-1



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However, the recent interest in stereoelectronic effect,[2] has contributed significantly for the explanation of π-face stereoselection. Various theories have been developed which focus on the analysis of the intrinsic ground state properties of sp^2 centers in substrates and also on the relative stabilities of diastereomeric transition states. A brief overview of some of them are discussed here.

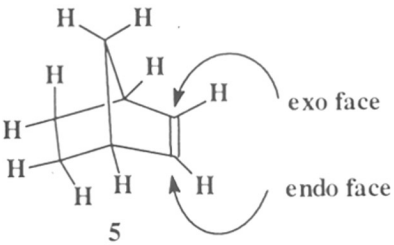
1. FMO theory of stereoselection
2. Theory of steric consideration
3. Polar group effect
4. Nucleophilic and electrophilic surface theory
5. Stabilization due to hyperconjugative interaction (Cieplak effect)
6. Theory of π-electron density distortion by σ/π-mixing
7. Electrostatic interactions
8. Torsional and steric control

1. FMO (FRONTIER MOLECULAR ORBITAL) THEORY OF STEREOSELECTION

Fukui et al.[3] developed FMO theory focussing mainly on the intrinsic inbuilt ground state properties of substrates of π-facial diastereoselection have shown that the 2p electron density is not disturbed symmetrically about the sp^2 plane of a trigonal atom which is placed in an asymmetric environment. The importance of non equivalency in frontier orbital extension is exemplified by electrophilic exo addition to norbornene and related compounds, e.g., 2-norbornyl radicals **4**[4], norbornene **5**[5], 5-substituted cyclopentadienes **6**[6] etc. Anh et al.[7] proposed non equivalent distribution of π-electron density of the carbonyl group in chiral aldehydes and ketones, **7** and **8** (**Fig. 1**).

Fig. 1

4



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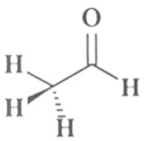

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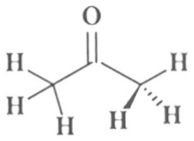
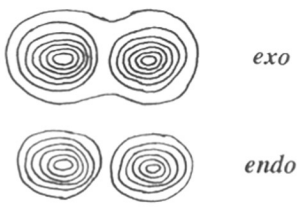


8

FMO calculations carried out by extended Huckel method propose that in reaction such as electrophilic additions to alkenes or cycloadditions of electron deficient dienophiles i.e., reactions controlled by the interaction of HOMO of the chiral substrates with LUMO of the electrophiles will occur preferentially on the SP^2 face where the HOMO is more extended. In the case of inverse electron demand cycloaddition reaction, reversal of the induction is expected.

In order to visualize the spatial extension of HOMO in norbornene a contour map of the plane perpendicular to C(1)C(2)-C(3)C(4) coplane was examined, where the nonequivalence of the exo and endo face is self evident as shown in **Fig. 2**.

Fig. 2



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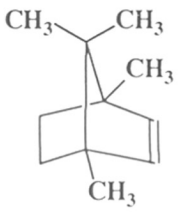

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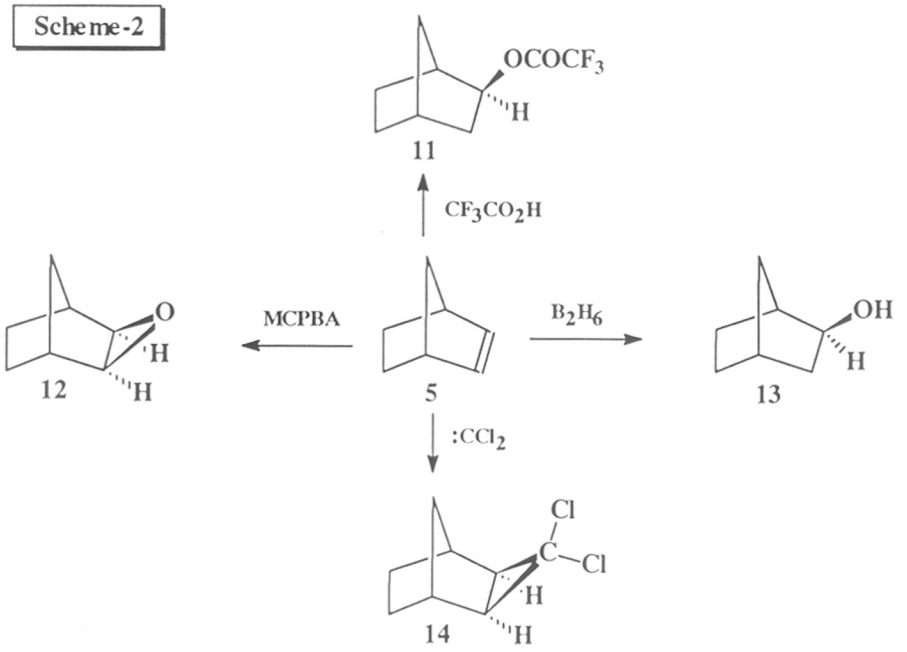
Some of the representative examples of exo-selective additions to norbornene are presented here (**Scheme 2**).

Scheme-2



2. THEORY OF STERIC CONSIDERATION

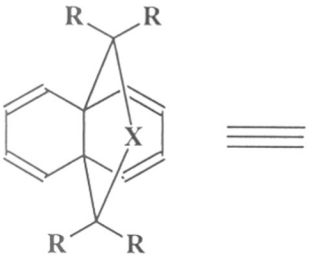
In systems such as **5** and **15**, reactions at the olefinic center exhibit preference for the exo product. Hydroboration and oxidation of **5** and **15** gave the exo:endo product ratios 99.5:0.5 and 99.9:0.1 respectively. Epoxidation gave exo epoxides predominantly (**Fig. 3**).

Fig. 3

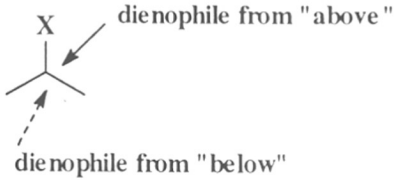
5 15

Compounds of this type have shown high degree of exo-selectivity towards a variety of reagents as shown below in the scheme. It has been proposed by Brown[8] that, steric factors contribute greatly for this observations, where C-H of methano and ethano bridge create steric congestion for the incoming groups. Thus, in **5** there is one methano C-H and two ethano C-Hs, hence the approach from ethano side will have a considerable steric hindrance thereby explaining the stereoselectivity.

Fig. 4



16 a: R,R=O, X=O
b: R,R=O, X=NMe
c: R,R=O, X=NH
d: R,R=H, X=O



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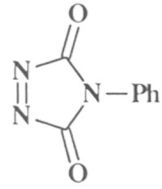

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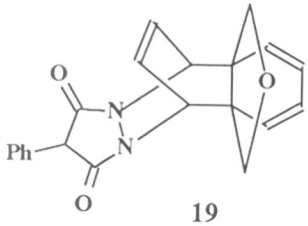
Fig. 5



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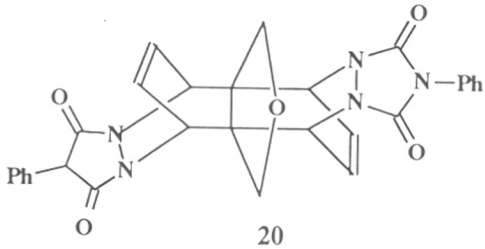

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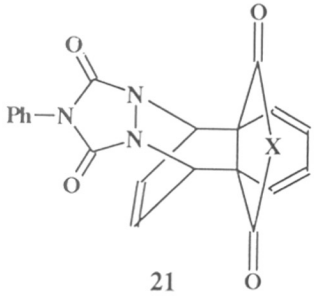

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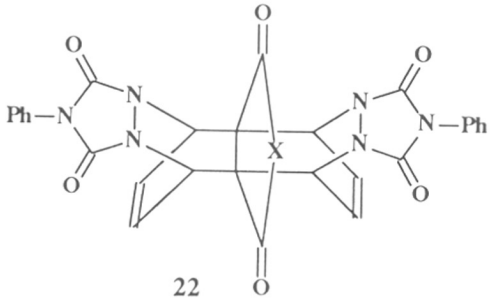

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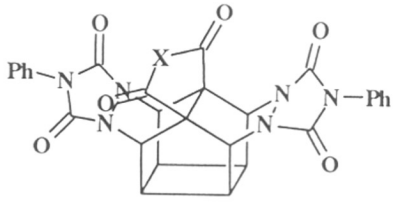


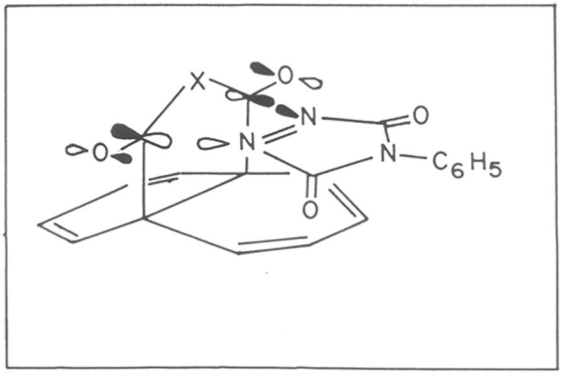
23

3. POLAR GROUP EFFECTS

Ginsburg et al.[9] observed a significant π-facial diastereoselection in the Diels-Alder reactions of a variety of tetraenic propellanes **16a-d** with 4-phenyl-1,2,4-triazoline-3,5-dione **18** (**Fig. 4**). Thus, the reactions of **16d** with **18** furnished the product **19** from the cyclohexadiene face, i.e., syn addition (**Fig. 5**). Replacement of α-CH_2 groups by carbonyls (**16a-c**) gave anti addition **21**, i.e., the dienophile approached from the carbonyl face. The addition of a second mole of dienophile **18** to **19** furnished **20** where the dienophile approached from the five membered ring face. The argument for this π-face diastereoselection of second Diels-Alder reaction could be due to steric congestion. But surprisingly contra-steric π-face diastereoselection was observed in the reaction of **21** with another molecule of **18** giving **22**, the structure of which was proved chemically by the efficient photocyclization of **22** to **23**. The formation of **22** clearly indicate the presence of factors other than steric for π-face diastereoselection.

Ginsburg interpreted these observations in terms of polar group effect. This stereochemical preference was explained in terms of relative steric contributions of the flanking bridges in **16d** when carbonyl groups of the transition state of syn attack is stabilized by interaction between n-lobes of N=N lone pairs and the anti symmetric π* orbital of the CO-X-CO bridge of **16a-c** as shown below in **Fig. 6**.

Fig. 6



Two types of electronic situations can be noticed here. The primary orbital interaction between the HOMO of the cyclohexadiene moiety and π* of **16a-c** and a secondary orbital interaction between the π-system of the anhydride or imide bridge and the n-orbitals of the azo group. The second effect operates only during the syn approach thereby stabilizing the transition state.

4. NUCLEOPHILIC AND ELECTROPHILIC SURFACE THEORY

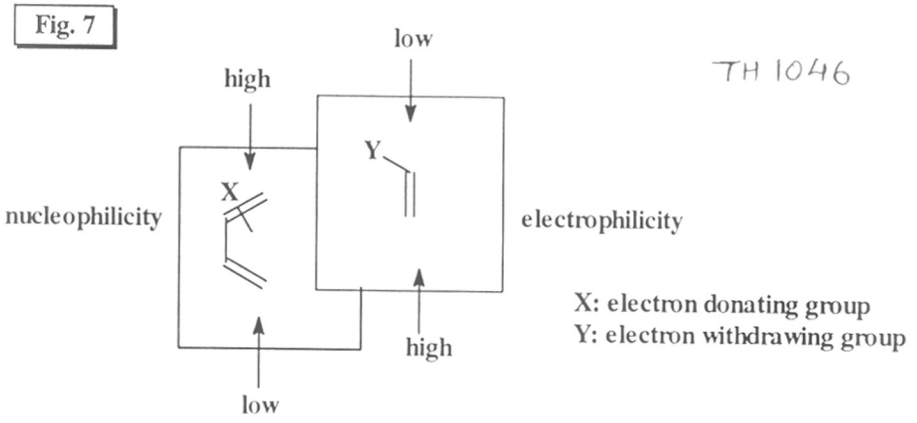
Hehre et al.[10] utilized the development of fast computational methods to probe the differences in the total electrostatic interaction on diastereofaces of a perturbed π-system. This methodology was already used by Miller & Brown[11] having the concept of total electrostatic interaction energy to evaluate the reactivity of two faces of a non-polar enamine towards electrophiles by using proton as a probe which was subsequently utilized to explain the mechanism of aldol catalysis by chiral amines.[12] Also

a hydride probe was used in the calculations of electrostatic potential on the two faces of cyclohexanone complexed by a lithium cation[13] and hydride together with proton probes were used on bicyclo[2.2.1]heptane to understand the selectivity.

Before understanding the π-face selectivity, Hehre et al.[10] established that the observed regiochemistry in Diels-Alder reactions with one partner electron rich and another electron poor could be explained by matching the atomic reactivity surfaces obtained independently for each of the molecules. In Diels-Alder reactions of electron rich dienes and electron poor dienophiles can be explained by matching the nucleophilicity of the diene and electrophilicity of the dienophile. In case of normal Diels-Alder reaction where diene's HOMO and dienophile's LUMO interaction is presumed to exert the dominant influence on regioselectivity, the diene is probed with a test electrophile, e.g., H^+ and the dienophile with a test nucleophile, e.g., H^-. Reaction regiochemistry is then determined in order to effect a best match of the complementary (electrophilic and nucleophilic) surfaces. In the case of inverse Diels-Alder reactions diene LUMO and dienophile HOMO interact, probes are reversed and comparison of the potential of the diene towards dienophiles and dienophiles towards electrophiles are effected.

Modelling studies indicate that extrapolation of the above ideas for π-face diastereoselection in the Diels-Alder reactions involving electron rich dienes and electron deficient dienophiles, addition occurs preferentially onto the face of the diene which is more reactive towards electrophiles and onto the face of the dienophile which is more reactive towards nucleophile (**Fig. 7**).

Fig. 7



These generalizations will reverse for reactions of electron deficient dienes and electron rich dienophiles (i.e., inverse electron demand reactions[14]).

5. STABILISATION DUE TO HYPERCONJUGATIVE INTERACTION (CIEPLAK EFFECT)

Of all the rationalizations for π-face diastereoselection, transition state stabilization and destabilization by electronic factors have received widest acceptance. In the case of reaction in a cyclohexane moiety where one of the carbons of the ring is involved in the reaction, the first hypothesis suggests that equatorial transition state is more stabilized than the axial one by torsional strain. In equatorial attack the incipient bond is eclipsing the axial C_2 and C_6 carbon-hydrogen bonds which is a destabilizing interaction. The second hypothesis suggests that the axial transition state is stabilized by interaction with the σ^* antibonding orbitals of the axial C_2 and C_6 carbon-hydrogen bonds. In 1981, Cieplak et al.[15] put forward a hypothesis to explain about the transition state stabilization, where the interaction with the neighbouring occupied orbitals is considered as a dominant factor.

Cieplak stereoelectronic effect is one of the recent arrivals of this category based on the nature of donor acceptor bonds and has significant predictive capabilities. In the case of an addition of an anionic nucleophile Y^- to a carbonyl group where the πCO bond is being broken and a new carbon nucleophile σCY is being formed, the factor which competes with the steric hindrance during the axial approach (both approaches are possible) originates in the non bonded interaction of the partially formed bond with neighbouring orbitals. There are three types of such interactions:

1. The four electron destabilizing interaction ($\Sigma_\#$, Σ_i) with the vicinal covalent bonds eclipsing the incipient bond with the carbon-carbon or C-H bonds may lead to a destabilization of either transition state.

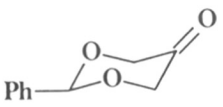
2. The two electron stabilizing interaction ($\Sigma_\#$, Σ_i^*) with the adjacent antibonding orbitals and

3. The two electron stabilizing interaction (Σ_i, $\Sigma_\#^*$) of the vicinal occupied orbitals with the antibonding orbitals of the incipient bond.

Further the Σ_i-$\Sigma_\#^*$ interaction is the dominant conjugative interaction in the bond forming process because the very definition of the incipient bond suggests that this bond is electron deficient. Thus postulating "the feature of transition state for nucleophile addition critical for the stereochemistry of the reaction is a low lying orbital $\Sigma_\#^*$ associated with the σ bond being formed in the reaction. Thus, the non equivalence of the two faces of a carbonyl group with respect to electron donating power of the neighbouring orbitals might lead to a preference for the approach which assures maximum overlap of the $\Sigma_\#^*$ orbital with the best donating orbitals. This proposition attempts to generalize the concepts of the kinetic anomeric effect[16] and according to le Noble[17] extends the concept of σ-assistance in the formation of carbonium ions to the reverse process of nucleophilic capture. Thus, the electronic nature of the antiperiplanar bonds with respect to the incipient bond (i.e., can be electron rich or poor) is important, but stabilization of the transition state by hyperconjugative interaction is expected only from the electron rich bond. Thus, on the basis of nature of the respective antiperiplanar bonds towards the approach of the reagents from both faces the π-facial differentiation can be predicted. To illustrate this in the following examples **24**, **25** and **26** the approach of the hydride towards C=O is preferred from axial, axial and equatorial sides respectively (**Fig. 8**).

Fig. 8

24



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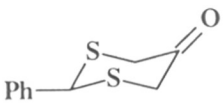


26

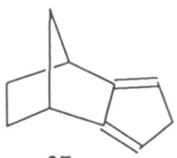
In **24** the antiperiplanar bond C-H is better donor than C-C bonds, in **25** C-H is better than C-O whereas in **26** C-S is a better donor than C-H. Cieplak has graded various bonds according to their relative donating abilities.

Si-C > C-S > C-H > C-C > C-O

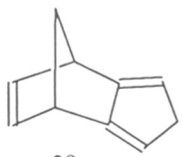
6. THEORY OF Π-ELECTRON DENSITY DISTORTION BY Σ/Π MIXING:[18]

Extension of FMO concept by introducing σ-bonds besides π-bonds in their calculations led to the development of a new concept. The observed π-face diastereoselection was exemplified by isodicyclopentadiene **27** (**Fig. 9**) by its reactivity in [4+2] cycloaddition reactions where many experiments reveal that exclusive below plane bonding occurs with all dienophiles except maleic anhydride and singlet oxygen. The cause cannot be steric in origin because the bond formation on the diene surface is *syn* to the ethano bridge. Polar interactions can also be excluded because compound **27** and similar hydrocarbons have very low dipole moment. So the observed stereoselectivity can be explained in terms of σ/π interaction.

Fig. 9



27

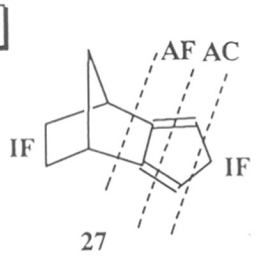


28

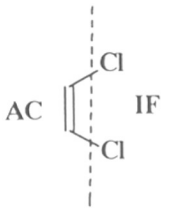
ΔE_{exo} Kcal/mol		9.91	7.02
ΔE_{endo}	-do-	5.45	3.98
$\Delta\Delta E$	-do-	4.46	3.04

Paquette and Gleiter have formulated the FMO theory by introducing σ/π interactions in their calculations. Thus, broadly the reacting diene and dienophile components were divided into easily distinguishable regions. Active centers (AC); atomic sites where the new bonds are formed, the active frame (AF); atoms which are involved in σ/π reorganization during the reaction and the inactive frame (IF); comprising the remaining molecular fragments not involved in the reaction (**Fig. 10**).

Fig. 10



27



29

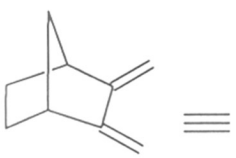
Since in this analysis the influence of σ-orbitals at the reactive centers are also considered the E_{tot} can be written as:

$$\Delta E_{tot} = \Delta E_1 + \Delta E_2 + \Delta E_P + \Delta E\sigma/\pi$$

where ΔE_1 is the energy gained or lost at the active centers, ΔE_2 is the energy gained or lost at the centers other than active centers, ΔE_P is the energy due to the polar groups present on inactive frame which may disturb the proximal π-system, and $\Delta E\sigma/\pi$ accounts for interaction of π-orbitals of active centers and active frame with π-orbitals.

For the calculations of E_{tot}, semiemperical SPINDO (EHT, modified INDO) was used together with abinito (STO -3G) computational method, where a strong mixing between lowest occupied π-orbitals (Π_s) and high lying σ-orbitals take place. The rotation Pπ lobes in the XZ plane **30** is in such a way that the lobes above the plane come closer to each other and lobes below the plane move apart as shown in **Fig. 11** (**30a**).

Fig. 11



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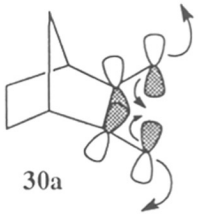
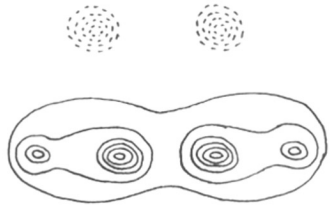


30a



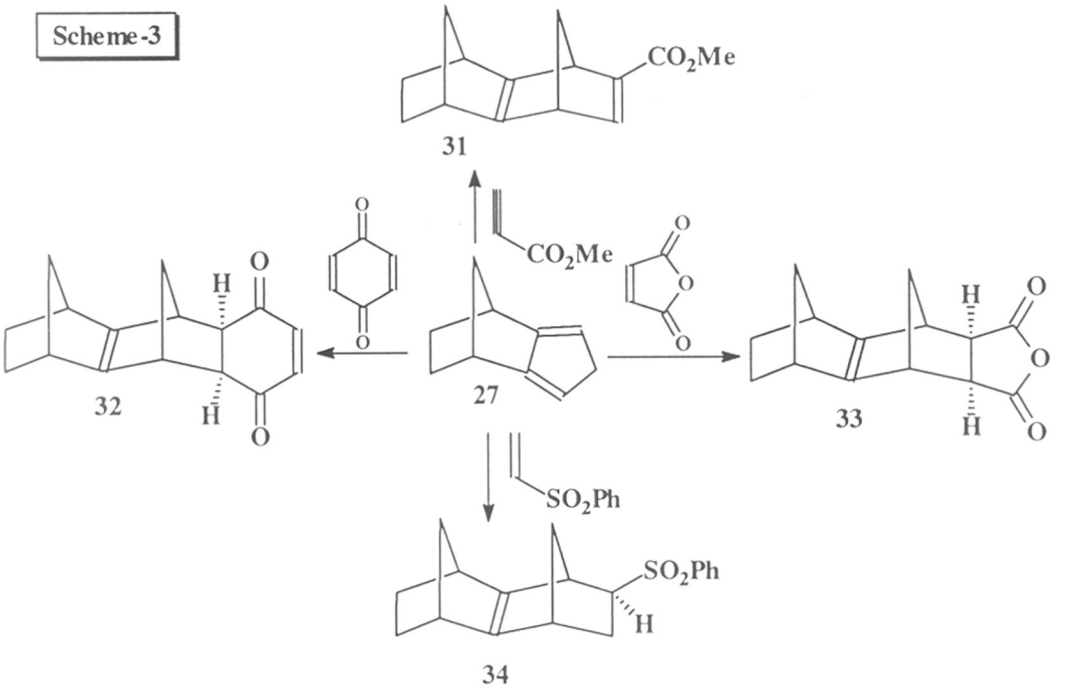
30b

This kind of tilting gives rise to significant differences in the frontier electron distribution on the *exo* and *endo* diene surfaces.

From the energy calculated for **27** and **28** it is clear that the value for the reaction from the exo face is more than that for the endo face by 4.46 kcal/mol. Therefore, endo face or bottom approach of the reagent is energetically favourable.

Some of the Diels-Alder reactions of **27** and its π-face preferences are shown in **Scheme 3**.

Scheme-3



7. ELECTROSTATIC INTERACTIONS[19]

In the reactions such as Diels-Alder, the role of solvent has been assumed to be static, i.e., its effect is roughly given through the contribution of the solvation energy to the total free energy of the reactants and the transition states. Though the direct participation of the solvent molecules in the reaction coordinate in this case is unlikely the electric field created by the solvent changes the shape of the potential energy surface and can modify the position of the stationary points.

In the case of Diels-Alder reaction of menthyl acrylate with cyclopentadiene where the diastereoselectivity of the reaction is governed by the chirality of the menthyl group, one cycloadduct is obtained in a series of solvents which requires a preferential approach of the diene on the *Si* face of the dienophile. Experimental data show that diastereomeric excess increases with solvent polarity so that one may expect the transition state of the major product is more stabilized by the solvent over the other. In all the cases parameters such as activation barriers, solvation energies, equilibrium geometries etc. have been taken into consideration.

8. TORSIONAL AND STERIC CONTROL[20]

Paquette[18] et al. proposed that the origin of π-facial selectivity is a function of orbital tilting of terminal Pπ-lobes of the diene frame work. But, Houk[20] et al. with the help of MM2 calculations, carried out on isodicyclopentadiene and related molecules argued that the π-facial diastereoselectivity

was due to torsional and steric effects. MNDO calculations predict that the double bond of *syn*-sesquinorbornene is flat and that the difference in energy between *anti* and *syn* sesquinorbornene **35a** and **35b** is 0.3kcal/mol in favour of *anti* sesquinorbornene. Experimentally derivatives of *syn*-sesquinorbornene are bent by 16-18° and several Kcal/mol stable than *anti* sesquinorbornene which has the planar alkene moiety. Because of the unsatisfactory results from MNDO calculations, MM2 calculations were tried, which predicted the *syn* and *anti* geometries clearly and obtained reasonable energy difference.

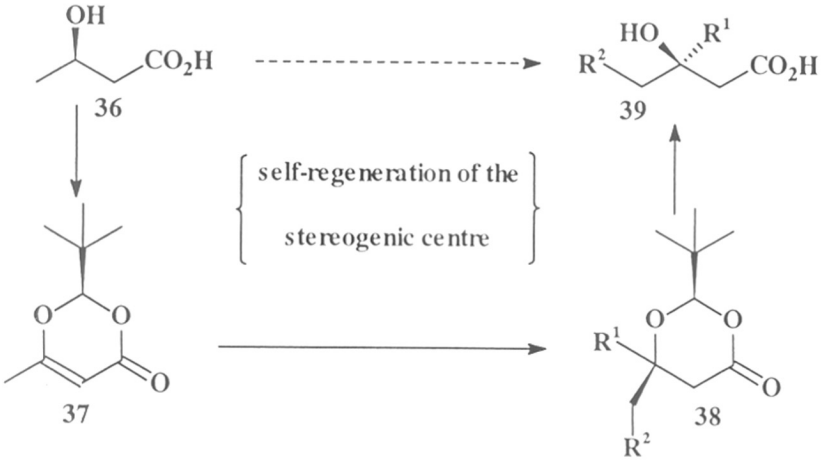
With the help of MM2 calculations on isodicyclopentadiene (**Fig. 12**), Houk et al. suggested that the π-facial selectivity is due to the torsional strain about the C1-C2 and C6-C7 bond of the diene in the Diels-Alder transitional state. For the top attack, the torsional interactions are increased due to more eclipsed arrangement. The difference in torsional strain about the C1-C2 bond is 0.3Kcal/mol and about C6-C7 bond is also 0.3Kcal/mol ultimately favouring the bottom attack of the diene skeleton.

Fig. 12

syn **35a** *anti* **35b**

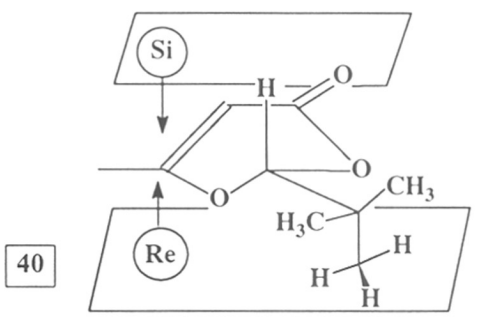
Seebach et al.'s[21] work on (*R*)-3-hydroxybutanoic acid **36** as a chiral synthetic building block, after converting it into the dioxinone **37**, shows importance of stereoelectronic effect in deciding the stereochemistry of the carbon centers (**Scheme 4**).

Scheme-4



Reactions such as 1,4-additions, catalytic hydrogenations on **37** were found to afford single diastereomer. This observed stereoselectivity of addition to the dioxinone double bond is shown not to be due to steric effects. A kinetic stereoelectronic effect [n-> $(\sigma^*)^\#$ interaction] is proposed to cause the predominance of axial attack on the rather flat dioxinone molecule. The trigonal centers of the dioxinones are pyramidalized in the same direction from which reaction occurs. It was found that all the nucleophilic addition have taken place from the face of the ring on which the acetal center carries the hydrogen and all the trigonal carbon atoms are pyramidalized in the direction of the acetal center out of plane bow. Analysis of the product of catalytic hydrogenation of the dioxinone **37** shows that it has a sofa conformation with five of the six atoms approximately in a plane and the "ether" oxygen O_1 out of plane. The two oxygens in the ring are also very different with respect to their bonding parameters which is a consequence of a large stereoelectronic effect. The *Si* attack on the t-butyl methyl dioxinone **37** is clearly more hindered by the 1,3-diaxial type neighbourhood of the hydrogen on the acetal center than is the *Re* attack by the methyl hydrogen on the *t*-Bu group as shown below in **Fig. 13**.

Fig. 13



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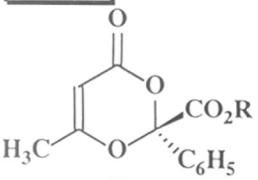
Similar to Seebach's model compound, Sato et al.[22] studied a number of compounds for the origins of sofa conformation, pyramidalization of enone function and facial selectivity by substituting the hydrogen at C_2-position with different groups. In contrast to Seebach's observation where a nucleophile attacks preferentially from the direction into which the center is pyramidalized, Sato et al. observed nucleophilic addition from the opposite side. This was explained on the basis of sofa conformation of the ring and pyramidalization of enone portion [C(4) to C(6)] of the dioxenone which has the same direction as that in which C(2) is shifted. A few model compounds of this study are given below (**Fig. 14**).

Fig. 14



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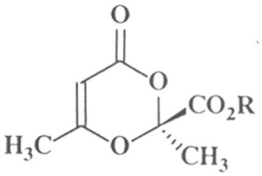
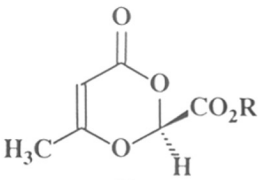


42

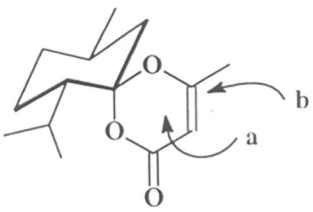


43

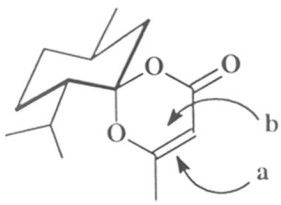
[a: R = *l*-menthyl
b: R = CH_3]

Demuth et al.[23] have synthesized spirocyclic enones using menthone as chiral auxiliary to induce chirality in [2+2] cycloaddition reactions based on the novel principle of stereofacial differentiation.

Fig. 15



44a



44b

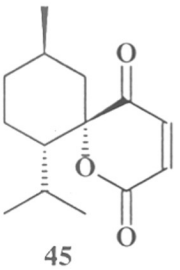
Addition of olefins occurred exclusively from 'a' side which rules out any effective shielding by the isopropyl group (**Fig. 15**). It was assumed that the dioxacyclohexenone ring could adopt a twisted boat conformation in solution, an arrangement that exposes only 'a' side.

OBJECTIVE

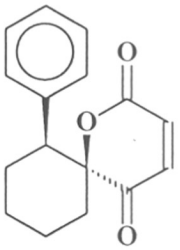
All the aforementioned theories including the concept of 'kinetic stereoelectronic effect' along with 'chiral memory centers' by Seebach[21] **37** and Demuth[23] **37** were very fascinating which influenced us to examine the π-face stereoselection in the newly developed spiro skeletons (6*S*,7*S*,10*R*)-isopropyl-10-methyl-1-oxaspiro[5.5]undec-3-ene-2,5-dione (**45**) and (6R,7R)-7-phenyl-1-oxaspiro[5.5]undec-3-ene-2,5-dione (**46**). Many novel skeletons have also been reported which exhibited chiral induction e.g., Whitesell[24] **47**, Oppolzer[25] **48**, Enders[26] **49**, Meyers[27] **50**, Evans[28] **51** etc. (**Fig. 16**). In all these studies normally an ester, amide, ether or hydrazone bonds were utilized for joining the auxiliary with the reaction site. However, in our study **45** and **46** a carbon-carbon bond was the connecting bond with chiral inducing agent. Thus, a method to cleave C-C bond to release the chiral auxiliary had to be developed. Subsequently, following synthetic transformations were examined with our substrates **45** and **46**. The de and ee were planned to be determined by the usual way. If successful, these studies should provide optically pure 1,2-bifunctionalized cyclopentanoids, cyclopropanes etc. This chapter is divided into five sections based on the type of reaction carried out to study the asymmetric induction in **45** and **46**. A brief introduction of each subsection is also presented. These subsections are as follows:

1. Synthesis and characterization of **45** and **46**
2. Asymmetric Diels-Alder reactions of **45** and **46**
3. Asymmetric conjugate addition reactions of **45**
4. Asymmetric cyclopropanation of **45** and **46**
5. Asymmetric epoxidation of **45**

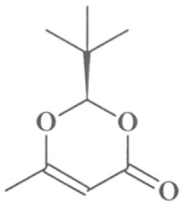
Fig. 16



45



46



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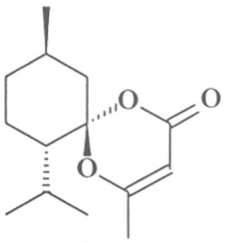

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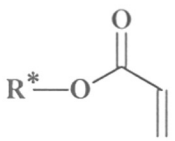

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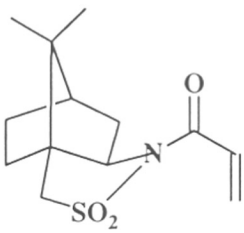

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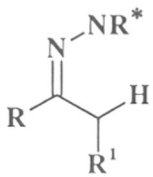

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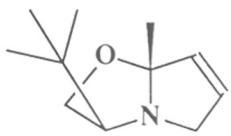

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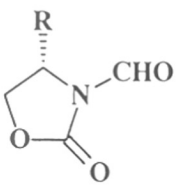


51

SECTION 1: SYNTHESIS AND CHARACTERIZATION OF NOVEL CHIRAL BIFUNCTIONAL AND HIGHLY REACTIVE COMPOUNDS 45 AND 46

INTRODUCTION

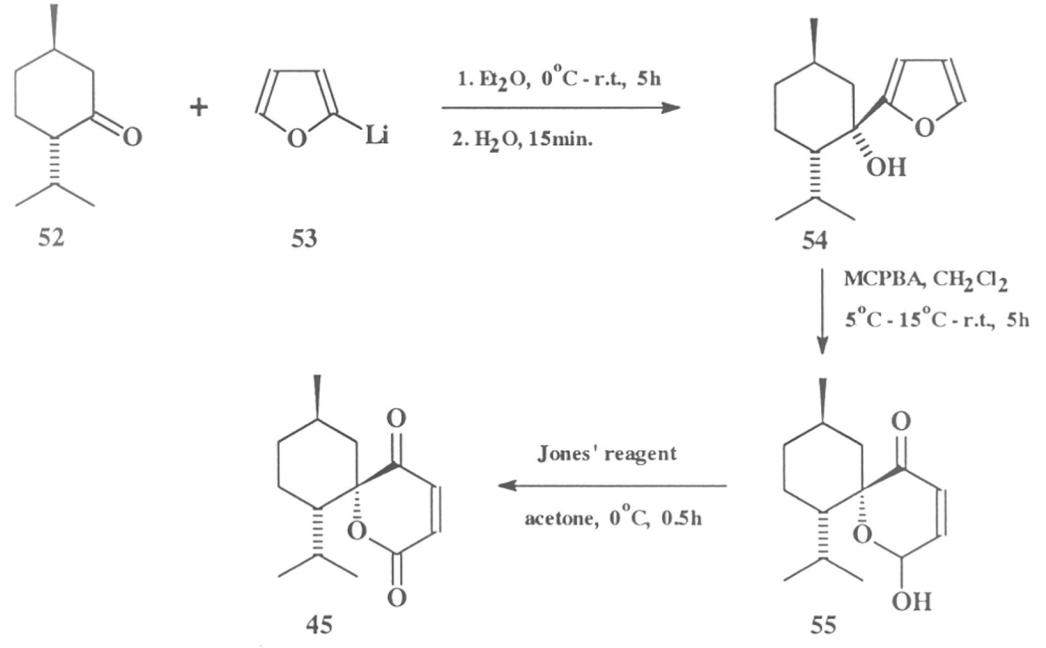
Chiral auxiliary based transformations are highly versatile because of the reliable prediction of stereochemistry that is offered in many cases.[21-28] By attaching an active functional group to the chiral auxiliaries such as menthol, menthone, 2-phenylcyclohexanol etc., efficient asymmetric synthesis was achieved by the organic chemists. In most of the cases an activated olefin was used as the functional group, on which several types of reactions have been carried out (a few of the chiral synthons have been discussed in the introductions of **Sections 2** and **3**). The attachment of this active functional group to the auxiliary is normally through an ether, ester or amide linkage. We have synthesized the chiral synthons starting from (-)-menthone and (-)-2-phenylcyclohexanone utilizing a unique carbon-carbon bond formation chemistry.

RESULTS AND DISCUSSIONS

Due to the fascinating chemistry reported in the literature using menthone or other chiral auxiliaries we wondered whether a rigid spirosystem attached to these chiral auxiliaries work as well or not. Thus, optically pure (-)-menthone **52** was treated with 2-lithiated furan **53** at 0°C to give **54** quantitatively as a single diastereomeric product. The product **54** was characterized using IR, ^{1}H-NMR, ^{13}C-NMR and mass spectrum. IR spectrum showed the presence of hydroxyl absorption at 3450cm^{-1}(s) and absorption due to furan at 750cm^{-1}(m). In ^{1}H-NMR, the signals at δ 6.22-6.30(dd), δ 6.33-6.43(dd) and δ 7.33-7.40(dd) indicate the presence of furan moiety. ^{13}C-NMR showed the presence of a single diastereomer and signals at δ 161.14, 140.61, 110.02 and 103.90 corresponding to furan carbons and signal at δ 76.21(*fu*-C-OH) clearly indicate the product. Finally, the molecular ion peak 222 (M^{+}, 8) confirmed the structure of **54**. Treatment of **54** with MCPBA at 10°C afforded **55** in 74% yield which was the consequence of a stereospecific oxidation-rearrangement sequence[29] on furan nucleus. The compound **55** was characterized by normal spectroscopic methods. Thus, in IR, the presence of strong absorptions at 3480-3280cm^{-1}(s), 1680cm^{-1} indicate the presence of hydroxyl group and enone ketone. In ^{1}H-NMR the broad signal at δ 3.25-3.40 indicates the presence of OH and peaks at δ 5.65-5.80(m), 6.05-6.17(dd) and 6.74-6.90 show the presence of olefinic protons. In ^{13}C-NMR two peaks for each carbon with equal intensity indicate the presence of a mixture 1:1 diastereomers (due to stereoisomer at anomeric center OH). In mass spectrum molecular ion peak at 238(M^{+}, 5%) finally confirmed the product. The compound **55** was then treated with Jones' reagent at 0°C to give **45** as a pale yellow solid (**Scheme 5**). The structure of **45** was confirmed by normal spectroscopic analysis and single crystal X-ray analysis (please see ^{1}H-NMR and ^{13}C-NMR spectra and X-ray structure of **45**). This compound has UV absorbance at 360nm wavelength. In IR strong absorption peaks at 1730cm^{-1} and

1690cm^{-1} indicate the presence of ester and enone. In ^{1}H-NMR, signals at δ 6.73(d) and 6.88(d) indicate the presence of olefinic protons. In ^{13}C-NMR, peaks at δ 197.30 and δ 160.80 indicate the keto and ester functionalities, signals at δ 137.62 and δ 134.79 indicate the presence of olefinic carbons and peak at δ 93.76 indicate the presence of spirocarbon with one oxygen attached to it. In mass spectrum the molecular ion peak 236(M^+, 15%) confirmed the product. Elemental analysis of the compound **45** also gave satisfactory results. Finally, the absolute configuration (6*S*,7*S*,10*R*)-7-isopropyl-10-methyl-1-oxaspiro[5.5]undec-3-ene-2,5-dione for **45** was confirmed unequivocally by single crystal X-ray crystallography.

Scheme-5

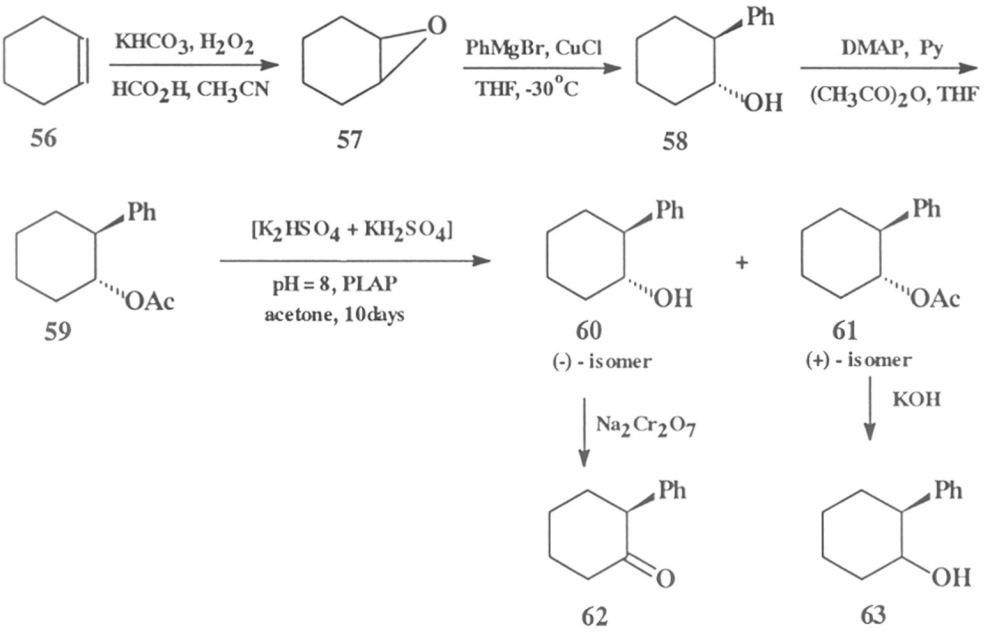


52 53 54 55 45

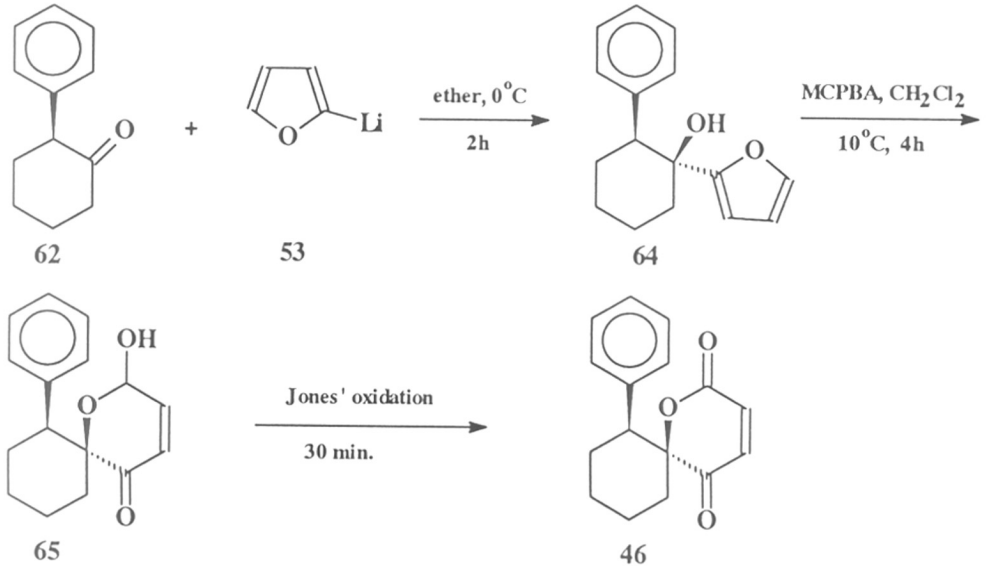
For the synthesis of **46** we required 2-phenylcyclohexanone which in turn could be prepared from cyclohexene **56** which was treated with 30% H_2O_2 in the presence of K_2CO_3 to give cyclohexene oxide **57** in 63% yield (**Scheme 6**). Treatment of **57** with phenyl magnesium bromide in presence of catalytic amount of CuCl at -30°C to 0°C for 3h gave racemic transphenylcyclohexanol **58** in excellent yield. Acetylation of **58** using acetic anhydride, pyridine and catalytic DMAP in THF afforded **59** in good yield. IR spectrum of **59** indicated the acetyl group. Treatment of **59** with freshly prepared PLAP[30a] (Pig Liver Acetone Powder, a crude form of the enzyme Pig Liver Esterase) in phosphate buffer [K_2HSO_4 + KH_2SO_4] of pH 8 at 25°C for 10 days afforded (-)-trans-2-phenylcyclohexanol **60** and (+)-trans-2-phenylcyclohexylacetate **61** in excellent enantiomeric purity and yield.[30b] The compound **61** was later hydrolyzed using KOH to obtain (+)-trans-2-phenylcyclohexanol **63** in good yield. Rotations of **60** and **63** were compared with the literature values[30c] and found to agree with

them. Oxidation of **60** with $Na_2Cr_2O_7$ afford the (-)-2-phenylcyclohexanone **62** which was further purified and the same set of reactions were performed as from **52** --> **45** to obtain **46** as a single diastereomer (**Scheme 7**).

Scheme-6

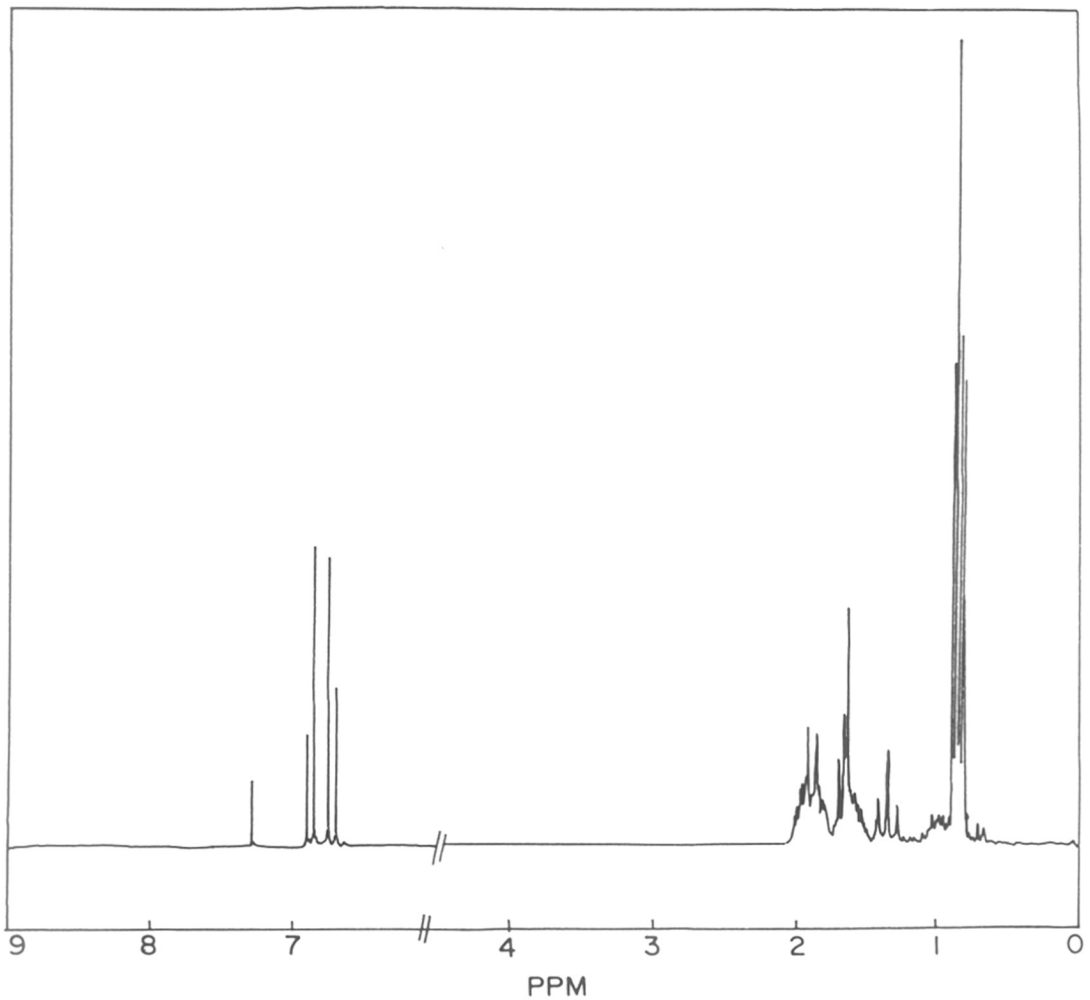


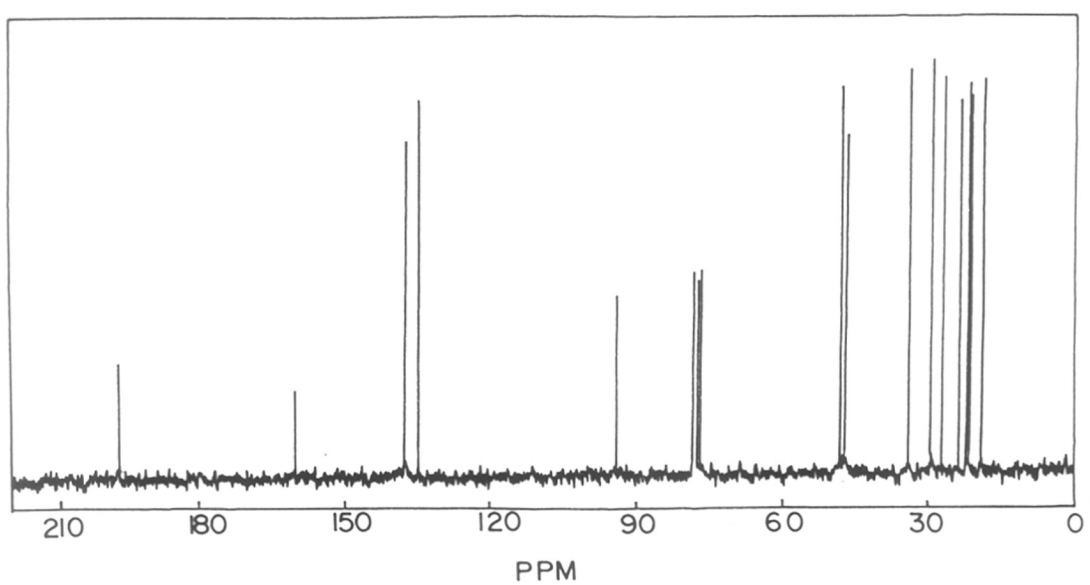
Scheme-7



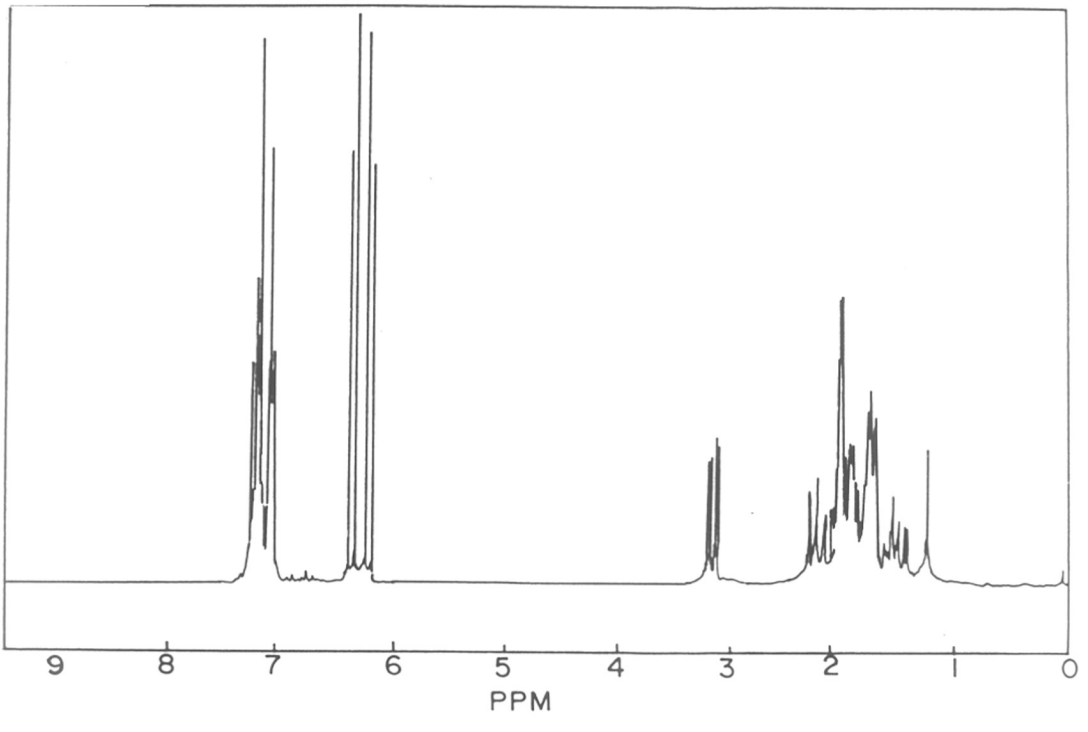
The intermediates **64** and **65** were characterized well using IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra. Compound **46** was checked thoroughly for its optical purity along with normal characterization techniques. IR showed strong peaks at 1735cm^{-1} and 1690cm^{-1} respectively for lactone and ketone carbonyls. ^{1}H-NMR showed signals at δ 3.15 (dd, 1H) for the proton on the carbon to which phenyl ring is attached, at δ6.10-6.27(d, 1H) and δ 6.35-6.42(d, 1H) for the olefinic protons. ^{13}C-NMR showed the presence of a single diastereomer. Signals at δ 137.20, 136.46, 134.39, 128.96 indicate the phenyl ring, at δ 128.79, 127.73 indicate the olefinic carbons and at δ 91.28 indicate the spiro carbon (see the ^{1}H-NMR and ^{13}C-NMR spectra of **46**). Finally the structure **46** was confirmed by molecular ion peak 256 (M+, 14%) in mass spectrum. Combustion studies showed satisfactory results.

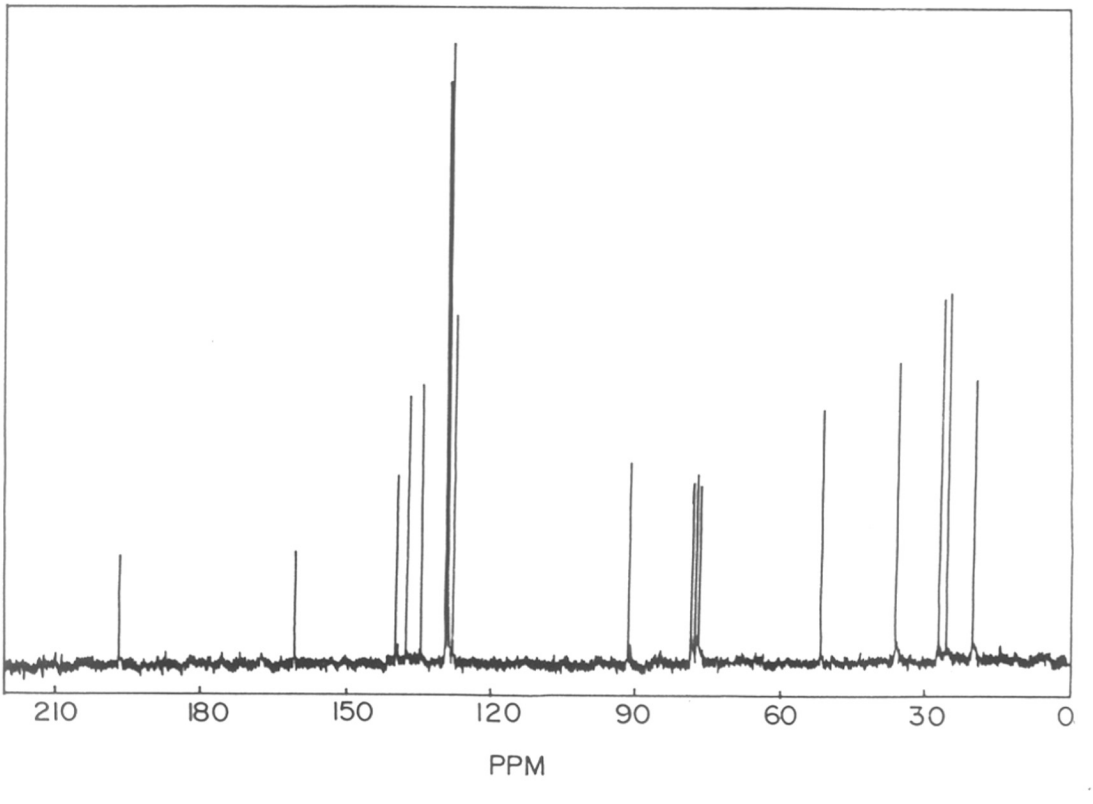
$^{1}H-NMR$ & $^{13}C-NMR$ SPECTRA OF 45

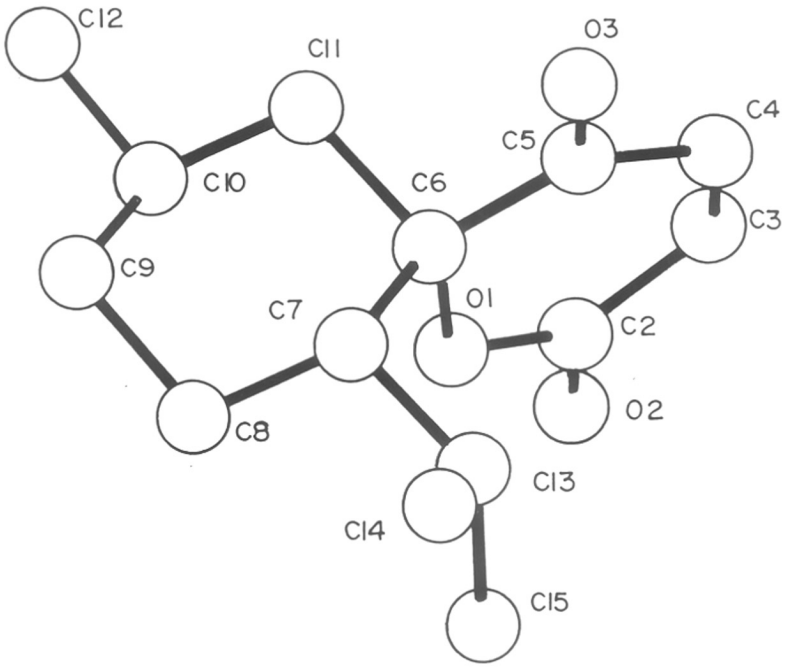




^{1}H- NMR & ^{13}C- NMR SPECTRA OF 46







X-RAY STRUCTURE OF 45

SECTION 2: ASYMMETRIC DIELS-ALDER REACTIONS

INTRODUCTION

Diels-Alder reaction, since its discovery in 1928 has become one of the most exploited and powerful reactions for carbon-carbon bond formation in organic synthesis. As far as the asymmetric synthesis is concerned in this reaction, with the formation of two bonds simultaneously, there can be a creation of up to four chiral centers at the reaction site with largely predictable relative stereochemistry.

Asymmetric Diels-Alder reactions are normally carried out by using either chiral reactants (diene and dienophile) or chiral catalysts. Quite a good number of examples are available in the literature where the use of chiral dienophile is found extensive and also a few reports for the use of chiral dienes and catalysts. As a review a few of them are discussed here briefly. We anticipated that our both skeletons **45** and **46** would be highly reactive dienophiles and give endo products.

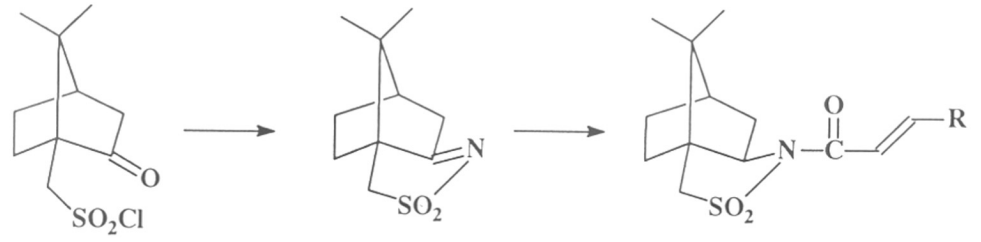
CHIRAL DIENOPHILES

A number of chiral auxiliaries have been used upon which the dienophile part was built. For example, menthol or menthone, camphor, 8-phenyl menthol etc. are the more promising and commercially available. The usual bond pattern e.g., esters/amides in which the dienophile component is attached with, the cause of the stereospecificity etc. are discussed below for each of the methods.

Camphor as chiral sultam: (W. Oppolzer et al.[25])

N-Acrolyl and N-crotonyl sultams were derived from (+)-camphor-10-sulfonyl chloride and were used for the Lewis-acid promoted Diels-Alder reactions to give good-excellent stereoselection (**Scheme 8**).

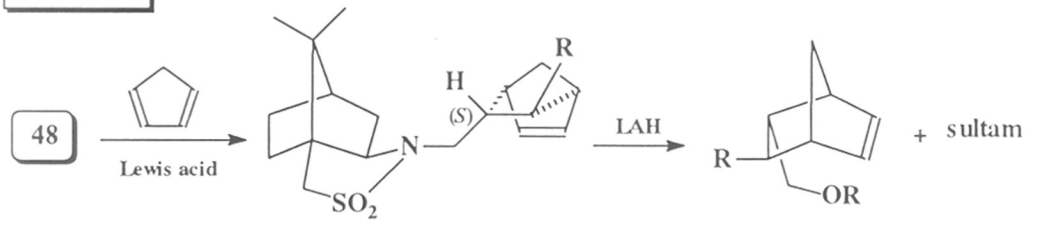
Scheme-8



66 67 48 a: R = H b: R = Me

Excellent diastereoselectivities were observed when the Diels-Alder reaction of **48** were carried out with various dienes. A number of Lewis acids such as $TiCl_4$, $SnCl_4$, BF_3-Et_2O, Et_2AlCl, $EtAlCl_2$ were used, out of which $TiCl_4$ and $EtAlCl_2$ turn out to be the best. The chiral sultam was later removed non-destructively by reducing with LAH (**Scheme 9**).

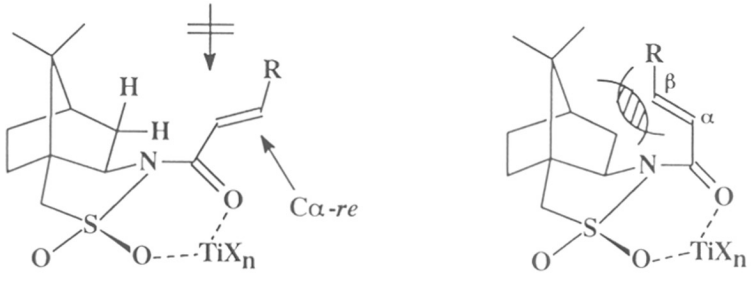
Scheme-9



68 69

X-ray crystallography of **48** showed the syn planarity of the Cα,Cβ-double bond with the carbonyl group which is anti to the SO_2 group. To rationalize this Lewis acid promoted acceleration and diastereoselection in Diels-Alder reactions it is assumed that the dienophile is chelated to the Lewis acid, which apparently restricts rotations of the C(O)N and C(O)Cα bonds (**Fig. 17**).

Fig. 17



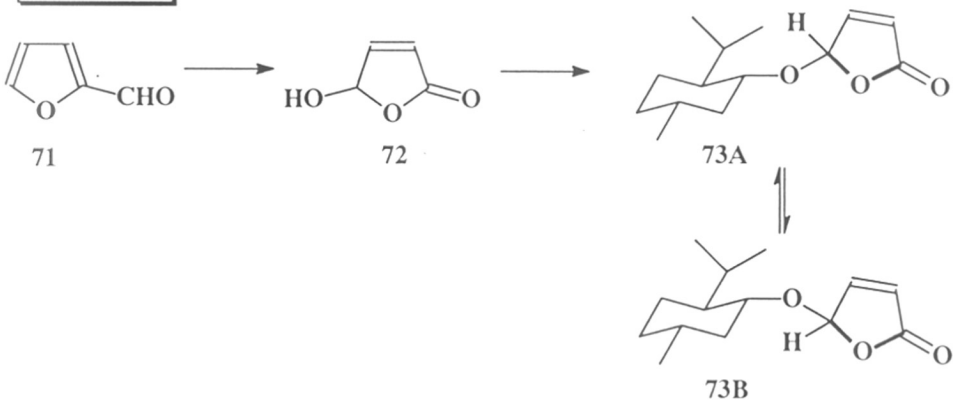
70A 70B

Conformation **70A** is favoured over **70B** (for reasons of steric repulsion between Cβ and C_3), endo attack of the diene from the less hindered face Cα-re occurs. The chiral auxiliary can be recycled and the other antipode is easily available.

Menthol as chiral 5-(1-menthyloxy)-2(5H)-furanone: (B.L. Feringa et al.[31])

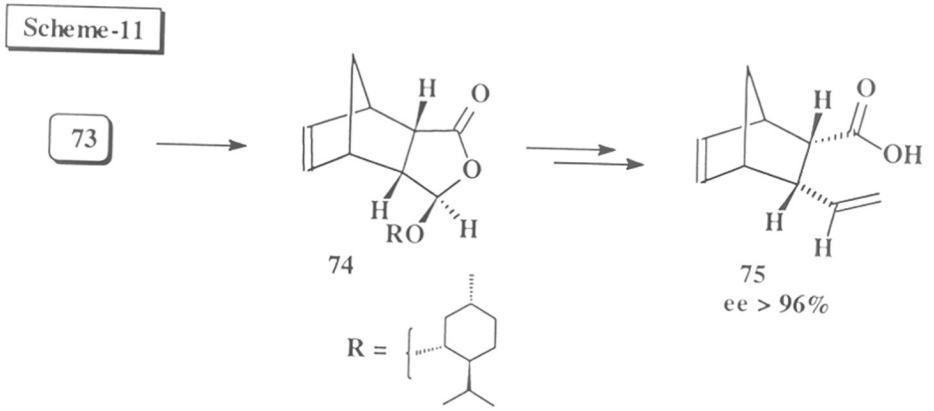
Compound of the type **73** was prepared from furfuraldehyde and l-menthol giving 60:40 ratio of epimers (**Scheme 10**).

Scheme-10



In the Diels-Alder reaction of **73** with cyclopentadiene a complete π-face selective addition takes place giving more than 97% endo isomer (**Scheme 11**).

Scheme-11

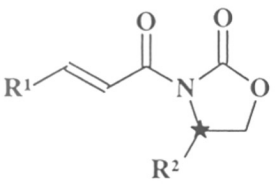


The chiral auxiliary (l-menthol) was removed non-destructively by reduction with LAH. A very useful skeleton of the type **75** was obtained by this method with more than 96% ee.

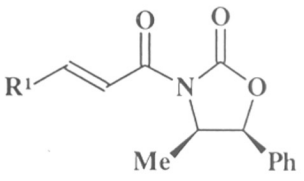
Chiral carboximides: (D.A. Evans et al.[28])

Dienophiles of the type shown below **76**, **77** and **78** were prepared by *N*-acylation of the chiral 2-oxazolidones derived from (*S*)-valinol, (*S*)-phenyl alanol or (1*R*, 2*R*)-norephedrine (**Fig. 18**). Crotonate imides **76b-78b** were obtained from lithiated 2-oxazolidones and (*E*)-2-butenoyl chloride and acrylates **76a-78a** were obtained from respective N-bromomagnesium-2-oxazolidones and propenoyl chloride.

Fig. 18



76: R^2 = *i*-Pr
77: R^2 = CH_2Ph

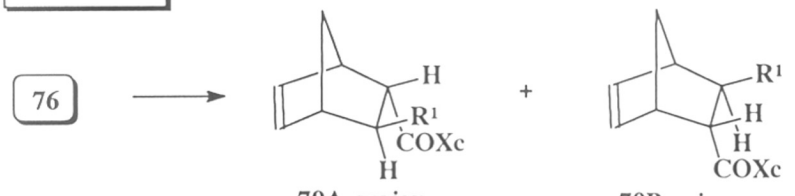


78

a: R^1 = H
b: R^1 = CH_3

Diels-Alder reaction of **76** with cyclopentadiene in the presence of 1.4equiv. of Et_2AlCl yielded 99% of the major product **79a** along with the minor isomer **79b** (**Scheme 12**). The chiral auxiliary was removed non-destructively through lithium benzyloxide transesterification.

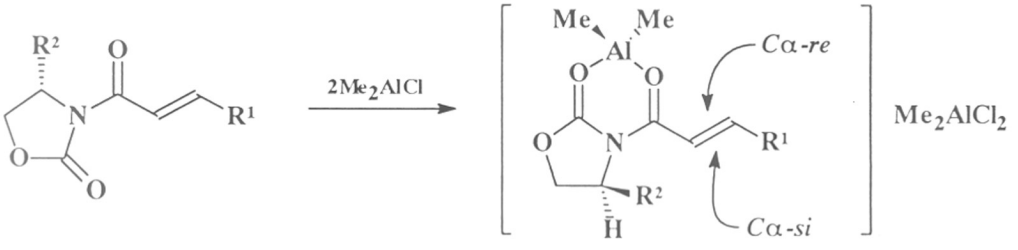
Scheme-12



79A major 79B minor

The stereochemical course of Lewis acid promoted Diels-Alder reactions of these acyloxazolidones are fully consistent with the intervention of an S-cis bidentate chelated dienophile (**Scheme 13**).

Scheme-13



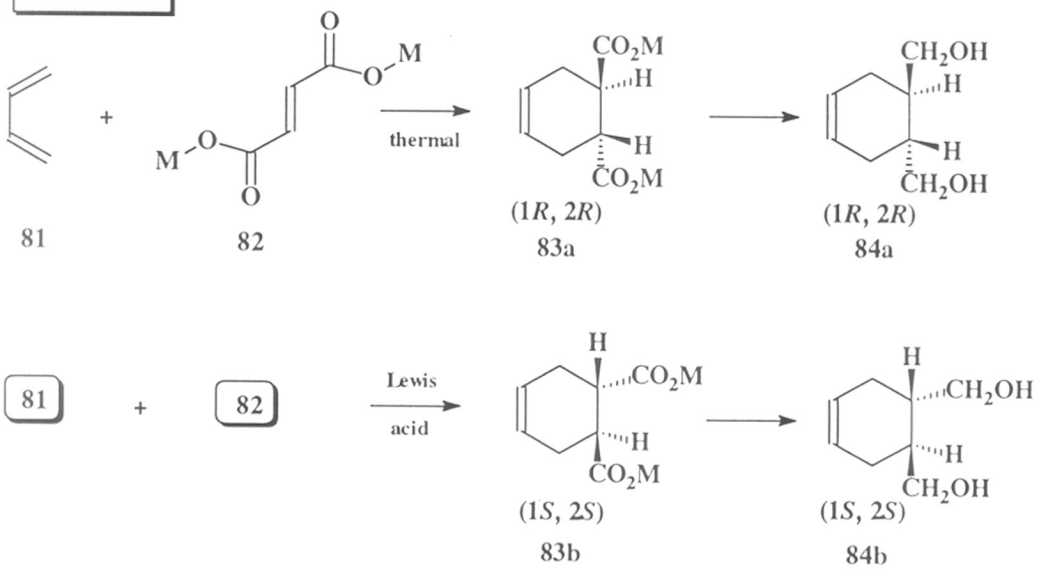
76 80

The C_4-oxazolidone substituent R^2 directs the cycloaddition process to the opposite face of the cisoid dienophile-Lewis acid complex. In the above shown complex the accessible π-face is predicted and found to be Cα-*Si*.

Menthol as dimenthyl fumarate: (H.M. Wolborsky et al.[32])

Diels-Alder reactions of (-)-dimenthyl fumarate **82** with butadiene without the Lewis acid afforded the adducts in 1-3% optical purity, but when Lewis acids such as $SnCl_4$, $TiCl_4$ or $AlCl_3$ were used optical purities up to 78% were observed (**Scheme 14**). Parameters such as solvent, temperature and catalysts were shown to have effect on the optical purity.

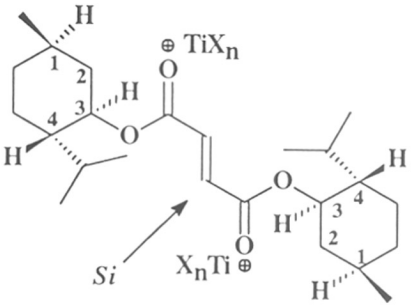
Scheme-14



81 82 83a 84a

81 + 82 83b 84b

Fig. 19



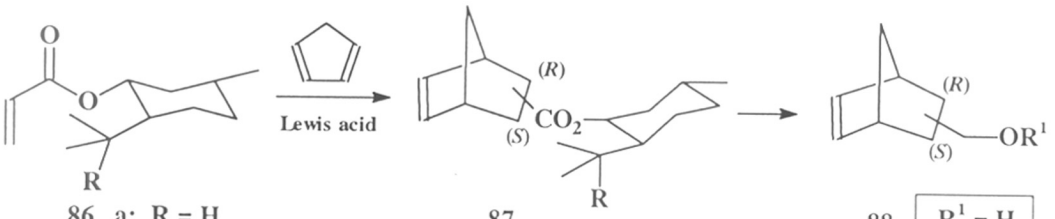
85

In the case of Lewis acid catalyzed reaction only the Si-face (complex **85** shown above in **Fig. 19**) attack is favoured thus giving the reverse stereoselection.

Chiral acrylates: (J. Sauer et al.[33a])

Initial work by Sauer et al. and the reinvestigation by W. Oppolzer et al.[33b] on chiral acrylates derived from (-)-menthol and 8-phenyl menthol show that they are quite efficient in asymmetric Diels-Alder reactions. Selectivity up to 93%ee was observed after detaching the chiral auxiliary by reduction with LAH (**Scheme 15**).

Scheme-15



86 a: R = H
b: R = Ph

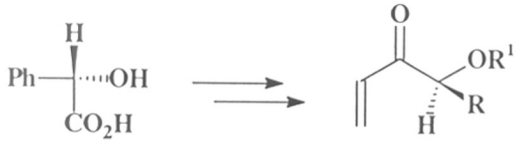
87

88 $R^1 = H$

The rate and chiral induction in the reaction are dependent completely on the Lewis acid used. In 1975 Corey et al.[33c] have used this methodology for the synthesis of lactone intermediate of prostaglandin. 8-Phenylmenthol was used as the chiral auxiliary to get the required (*1S*)-isomer.

Chiral dienophile derived from Mandelic acid: (S. Masamune et al.[34])

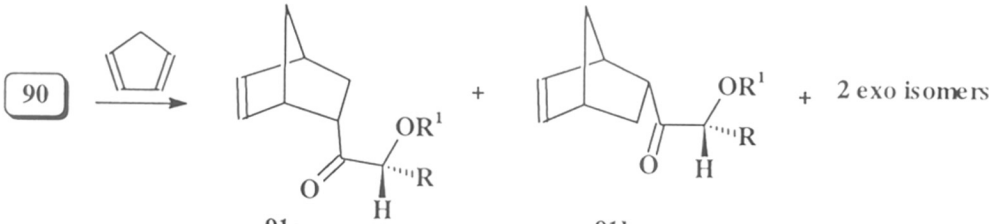
Scheme-16



89

90

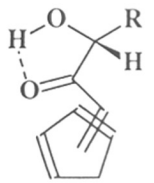
a: R = cyclohexyl, $R^1 = H$
b: R = -do- $R^1 = SMe_3$ etc.



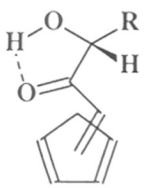
91a 91b

The reactivity in this case is attributed to the strong hydrogen bonding between the hydroxyl and ketonic functions as shown below (**Fig. 20**).

Fig. 20



92A for endo

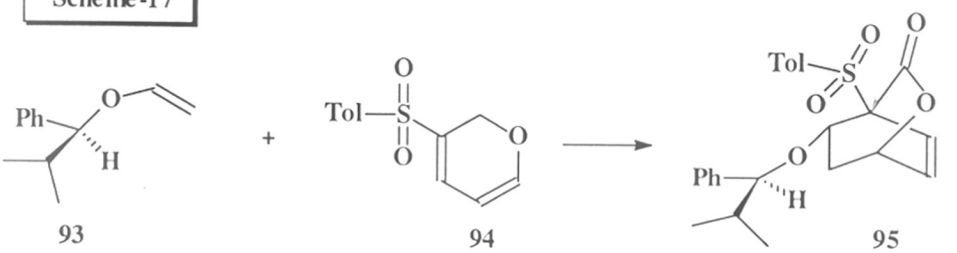


92B for exo

The formation of the five membered ring effectively freezes the free rotation along the C-(=O)-C (asymmetric) axis thus making the two diastereotopic faces of the enone system highly distinguishable. Biologically useful compounds such as Shikimic acid, (+)-pumiliotoxin have been synthesized using this chiral auxiliaries.

Chiral alkyl vinyl ethers: (G.H. Posner et al.[35a])

Scheme-17



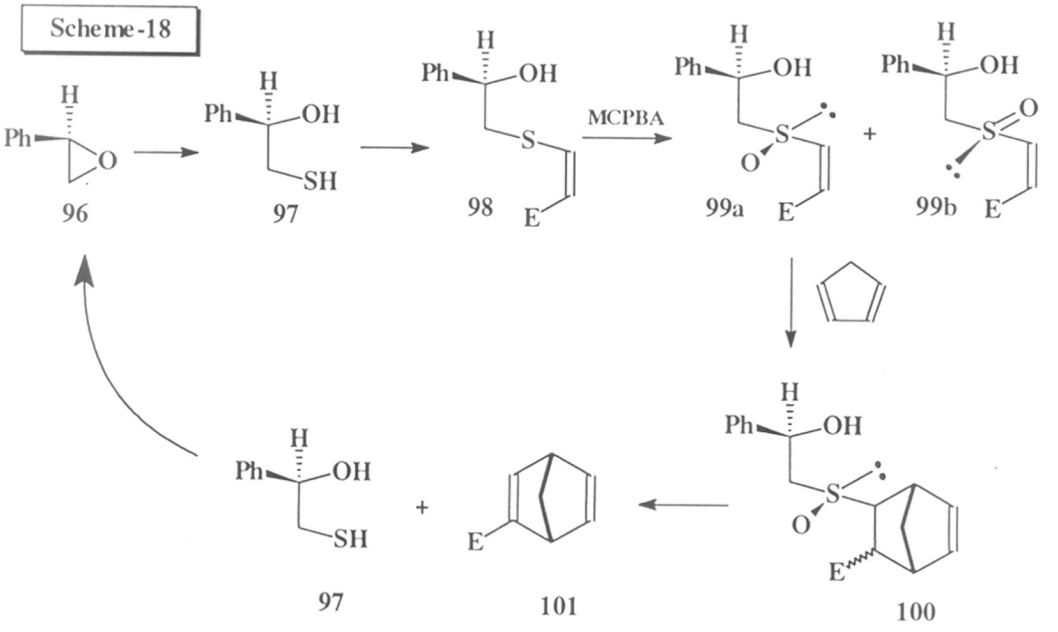
93 94 95

Inverse electron demand Diels-Alder reactions of this type (**Scheme 17**) are rarely observed in the field of organic chemistry. The product **95** was obtained in excellent yields and high diastereoselectivity (84%). When *t*-Bu phenyl ether is used 90% de was obtained. This methodology was successfully applied to the synthesis of Shikimic acid derivatives.[35b]

Chiral epoxide as the auxiliary: (O.D. Lucchi et al.[36])

Optically pure epoxides are transformed into sulfinyl dienophiles (**Scheme 18**) which were in turn utilized in Diels-Alder reactions giving high diastereoselection.

Scheme-18



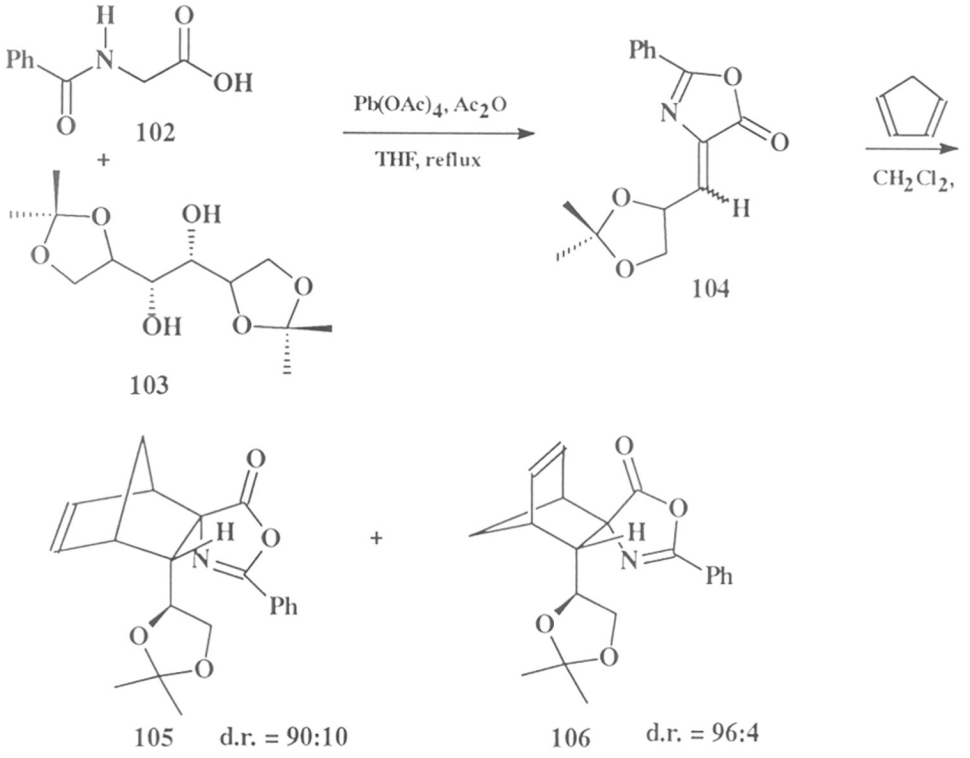
96 97 98 99a 99b 100 97 101

The compound **101** was found levorotatory (*1R,4S*) from which it was deduced that the cycloaddition of **99a** has occurred in a way such to position the lone pair of electrons below the norbornyl skeleton, the $R^{\bullet}$ group at the side of the substituted ethane bridge and the oxygen at the side of the bridge head proton.

D-Glyceraldehyde as chiral auxiliary: (C. Cativiela et al.[37])

Chiral Z-azalactone **104** was synthesized from D-mannitol diisopropylidene (cleaved to get glyceraldehyde moiety) by Erlenmeyer-Plochl method (**Scheme 19**).

Scheme-19

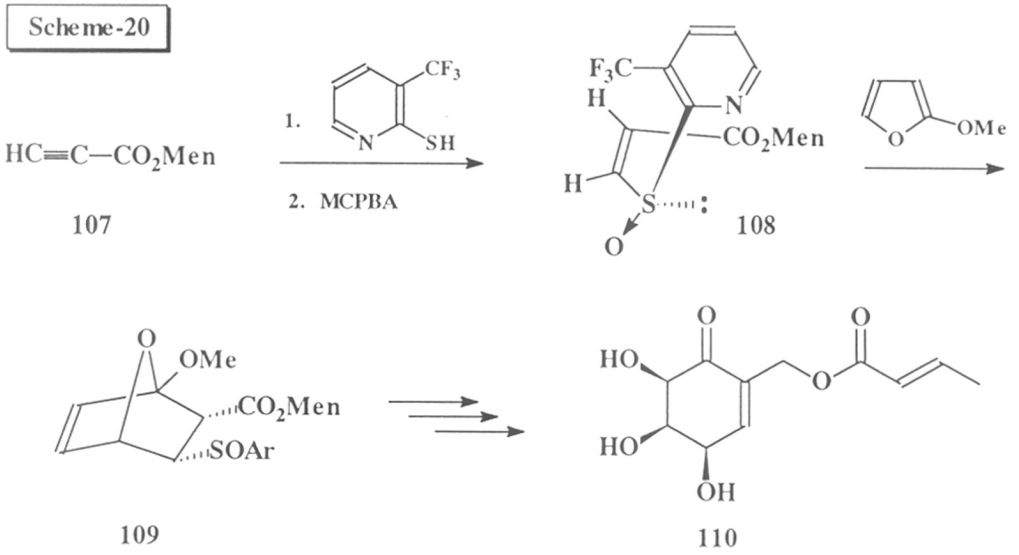


Diels-Alder reaction on **104** and analysis of the crude product by HPLC showed a slight preference for exo products (64:36) and high diastereoselectivity for both exo (90:10) and endo (96:4) adducts. X-ray structure of **105** showed that carbonyl group had in effect exo orientation and diene has added to the Cα-Re face of the double bond.

Menthyl together with sulfinyl moiety: (T. Koizumi et al.[38])

The adduct **109** was obtained almost exclusively in the reaction of (*l*)-menthyl-3-(3-trifluorimethyl pyrid-2-ylsulfinyl)acrylate with 2-methoxy furan which was later converted into **110** as shown in **Scheme 20**.

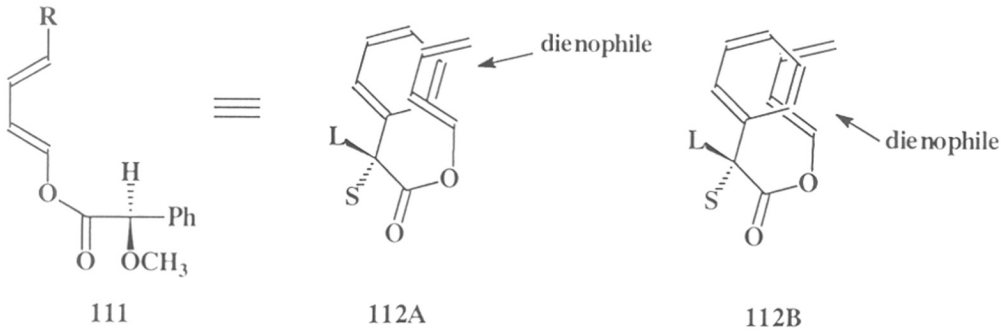
Scheme-20



CHIRAL DIENES

1. **B.M. Trost et al.**[39a]

Fig. 21

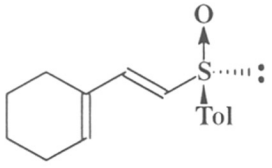


In the structure **112A** (**Fig. 21**) the large group L projects towards the diene encountering a severe non bonded interaction. Such a non bonded interaction is between the group 'S' and the diene in conformer **112B**, so the latter is favoured. The aromatic ring then serves as a steric steering group to direct the incoming dienophile to one of the two enantiotopic faces of the diene. A similar system was also used by W.G. Dauben et al[39b] for the reaction with benzoquinone at 15Kbar pressure.

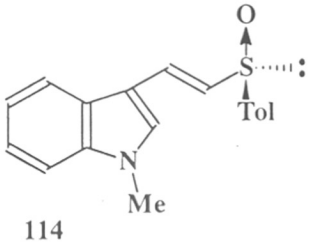
2. **M.C. Carreno et al.**[40]

1-Sulfinyl dienes with endocyclic double bond were used as chiral dienes where dienophile of the type N-methyl maleimide was used in the reaction (**Fig. 22**).

Fig. 22



113



114

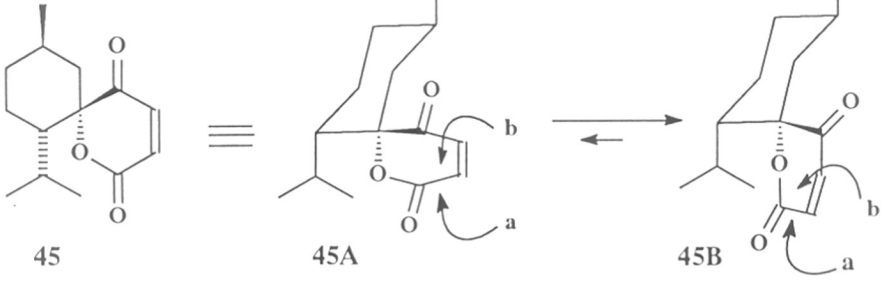
CHIRAL CATALYSTS

Recently, a large number of chiral catalysts have also been synthesized (e.g., catalysts derived from optically active alcohols,[41] Titanium complex,[42] Boron complex,[43] Lanthanide complexes,[44] and other transition metal complexes[45] etc.) and used for asymmetric Diels-Alder catalysis. But, their details are not included here, as we are more concerned with chiral induction with asymmetric dienophile.

RESULTS AND DISCUSSIONS

As mentioned in the Section 1, compounds **45** and **46** were obtained in optically pure form. Comparing these synthons with other systems studied by Oppolzer[25] **48**, Enders[28] **47**, Feringa[31] **73** etc. for Diels-Alder reaction studies we found our system very unique and rigid, with a carbon-carbon bond attached to the auxiliary as mentioned earlier. One can expect the compound **45** to have two different diastereotopic faces as reported for the similar kind of systems[46] (**Fig. 23**). Thus, reagents can approach **45** from 'a' side *cis* to the isopropyl group or from 'b' side diastereotopic face opposite to the isopropyl group as shown below. The reactivity of our dienophile was anticipated to be fairly high due to strain and two electron withdrawing groups attached to the double bond.

Fig. 23



45 45A 45B

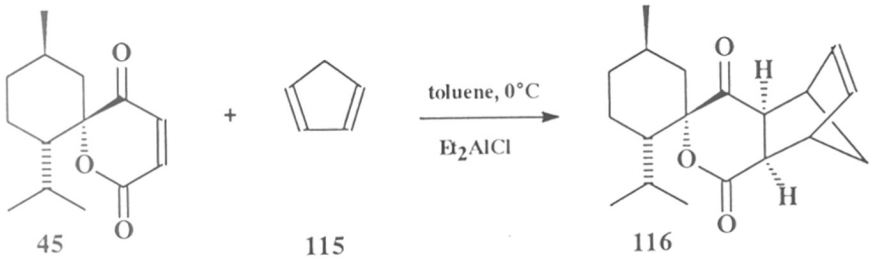
By taking advantage of the diastereotopic face differences in **45**, Diels-Alder reactions with a variety of dienes and conditions have been attempted. Thus, with freshly cracked cyclopentadiene **115** as diene, the reaction was tried at room and reflux temperatures in benzene, toluene etc. but was unsuccessful. Use of Lewis acids such as BF_3-Et_2O, $TiCl_4$ etc. also failed. However, when a mixture of **45** and **115** was heated in a sealed tube at 140°C for 10h the Diels-Alder adduct was obtained in 85% yield as 30:1 mixture of diastereomers (by ^{13}C-NMR). But, when **45** was treated with **115** in toluene at 0°C using 1.5 equiv. of diethylaluminium chloride as catalyst, the product **116** was obtained in 95% yield as a single diastereomer (**Scheme 21**). The structure of **116** was confirmed using normal spectroscopic analysis, chemical analysis and X-ray crystallography. IR spectrum showed strong peaks at 1750cm^{-1} and 1710cm^{-1} corresponding to ester and carbonyl functionalities. In ^{1}H-NMR, the two exo protons appear at δ 3.02-3.12(dd, 1H) and δ 3.35-3.45 (dd, 1H), two bridge head protons at δ 3.57(bs, 1H) and δ 3.65(bs, 1H) whereas olefinic protons appear at δ 6.16-6.21(m, 1H) and 6.30-6.36(m, 1H). ^{13}C-NMR showed the presence of a single diastereomer where the carbonyl and ester carbons appear at δ 210.05 and 169.84, signals at δ 137.36 and 136.89 correspond to olefinic carbons and the spiro carbon appears at δ 94.24 (see ^{1}H-NMR and ^{13}C-NMR OF **116**). In mass spectrum molecular ion peak 302 (M^+, 0.8%) confirmed the product. Satisfactory results are also obtained from the combustion studies. Finally the structure of **116** was confirmed by single crystal X-ray crystallography (see the X-ray structure of **116**) which shows that the diene has added *anti* to the isopropyl group of menthone.

Thus, in contrast to the literature reports,[23,31] the Diels-Alder reaction of the new chiral synthon **45** proceeded in high stereoselectivity, but in complete reverse stereofacial selectivity. The structure **45B** seems to be more favourable than **45A** under the reaction conditions employed. The reason for this unexpected reactivity is not understood. However, one reasonable explanation is to assume that the approach of the reagent, i.e., diene from 'a' side should cause appreciable steric hindrance between the isopropyl group and the diene and hence the attack occurs preferentially from 'b' side.

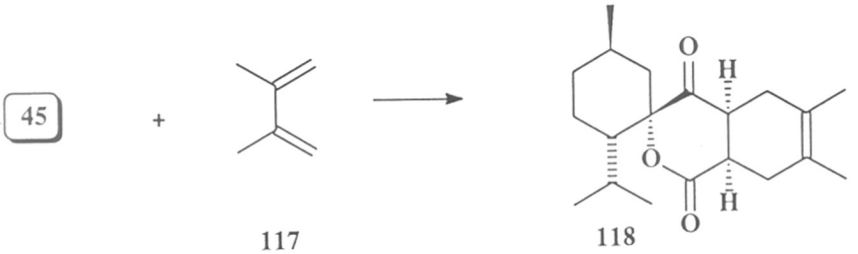
Demuth et al.[23] have reported the preferential formation of cycloadduct with similar kind of skeleton. i.e., dioxacyclohexenones in which attack of the diene preferentially occurs from 'a' side. It was assumed that dioxacyclohexenone ring could adopt a sofa conformation just as in crystallines, an arrangement that exposes 'a' side of the alkene. The stereoselectivities for thermal and photochemical addition to dioxenones were correlated with unidirectional pyramidalization of reacting centers. Similar observations were made by computational studies as well, which were experimentally verifiable.[21] It may be pertinent to mention here that complete reversal of selectivity (i.e., preferential attack from 'b' side) has been reported in the literature for hydrogenation and methylation reactions with chiral synthons like spirodioxenones.[46]

Similar to the Diels-Alder reaction of **45** with **115**, to examine the generality of the Diels-Alder cycloadditions reaction of **45** with other dienes were also attempted. Thus, the reaction of **45** with 2,3-dimethyl-1,3-butadiene **117** afforded the adduct **118** in 95% yield (**Scheme 21**). The structure of **118** was characterized by usual spectroscopic techniques. ^{13}C-NMR of **118** indicated the presence of a single diastereomer. Reaction of **45** with 2-methyl-1,3-pentadiene **119** and 2-silyloxy-1,3-butadiene

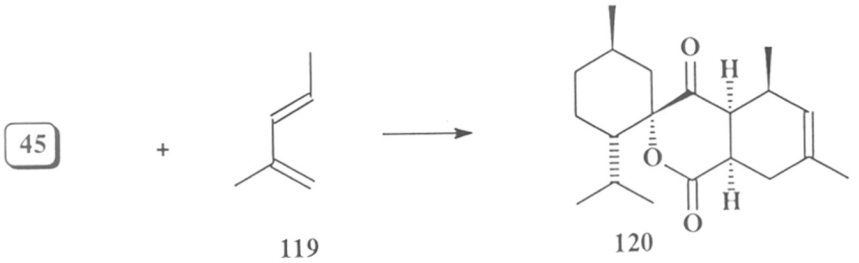
Scheme-21



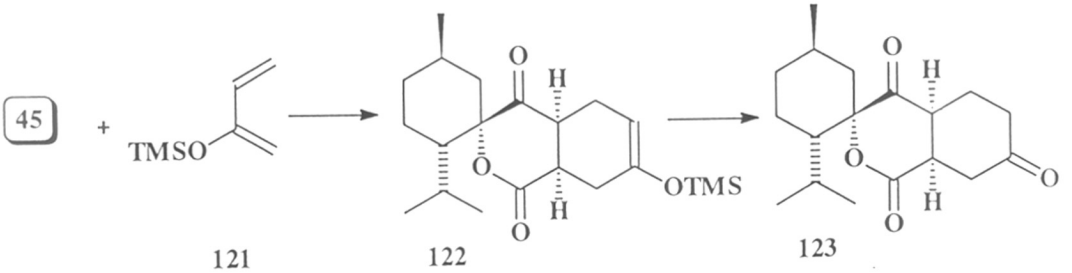
45 115 116



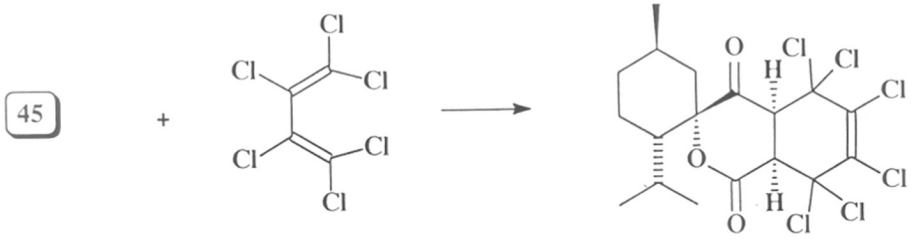
45 117 118



45 119 120

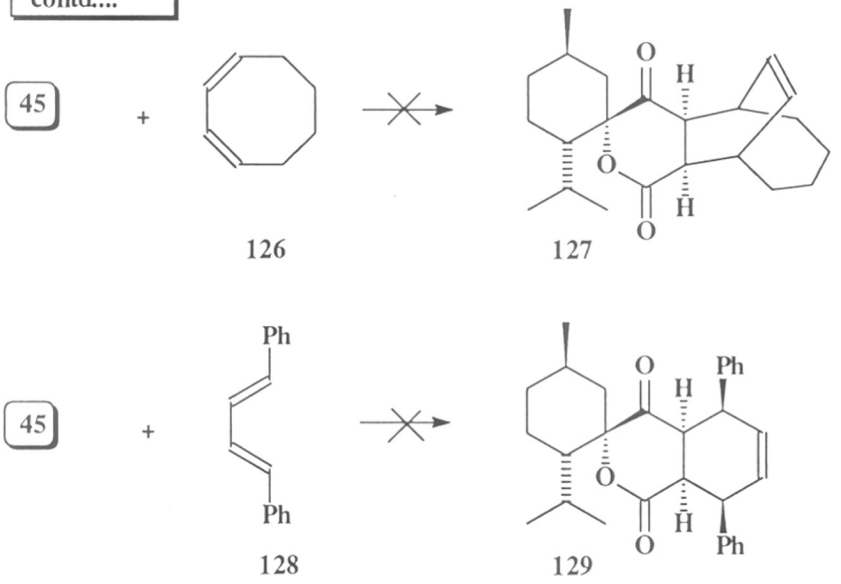


45 121 122 123



45 124 125

Scheme-21 contd....



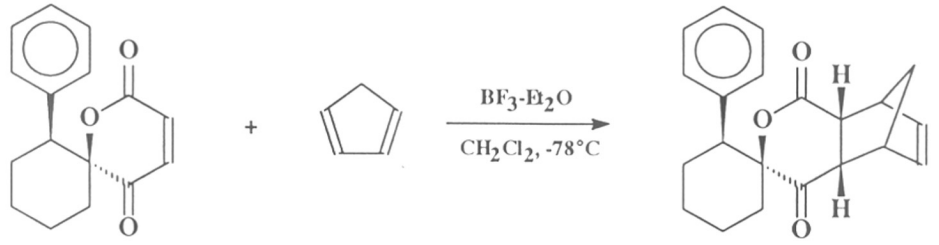
121 afforded the adducts **120** [this adduct is the most probable one according to the nucleophilic and electrophilic surface theory and the other adduct is also possible with methyl and adjacent hydrogen at the newly formed center being trans to each other (minor)] and **122** in 80% and 82% yields and 70% and 75% diastereomeric excess respectively. The compound **122** was further desilylated to get the product **123** using dilute HCl. In the similar way hexachlorobutadiene **124** reacted with **45** to afford **125** in 87% yield as a single diastereomer.

In the Diels-Alder reaction of dienes **119** and **121** a good diastereoselectivity could not be achieved. One possible explanation of the above result is to assume that the spiroskeleton **45** exists in an equilibrium mixture of **45A** and **45B** in solution.

In the Diels-Alder reaction of **45** with dienes, the major diastereomer is formed via major conformer **45B** by 'b' side approach. It may be reasonable to assume that the minor diastereomer may be formed through the less stable conformer **45A** by the approach of the diene from 'a'side which cannot be completely ignored. Thus, change of selectivity might be due to the change of structural conformations of the spiroskeleton **45** in solution.

The chiral skeleton **46** derived from (-)-2-phenylcyclohexanone also underwent Diels-Alder reaction efficiently. Thus, when **46** and freshly cracked cyclopentadiene **115** were heated at 140°C, the adduct **130** was obtained in 63% yield, whereas treatment with cyclopentadiene at -78°C in the presence of BF_3-Et_2O as catalyst gave the product **130** in 90% yield (**Scheme 22**).

Scheme-22



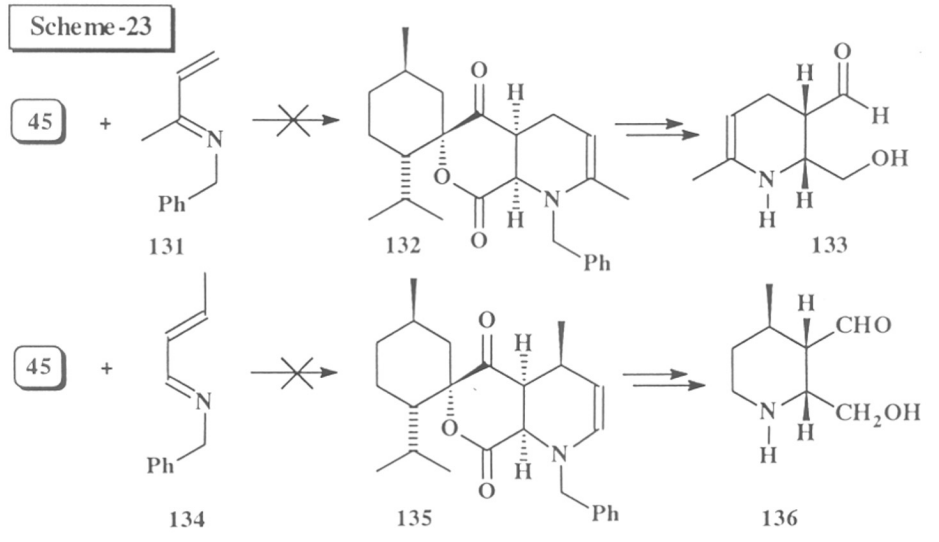
46 115 130

The compound **130** was characterized by spectroscopic and chemical analytical methods. IR spectrum showed sharp peaks at 1750cm^{-1} and 1710cm^{-1} for ester and ketone carbonyl. In ^{1}H-NMR, signals at δ 2.82-2.95 (dd, 1H) for proton on the carbon attached to the phenyl ring, at δ 3.26-3.40 (m, 2H) for proton α- to the carbonyls, δ 6.00-6.10 (m, 1H) and δ 6.14-6.22 (m, 1H) for two olefinic protons clearly indicate the product. ^{13}C-NMR showed a single diastereomer where signals at δ 136.48 (2C) for olefinic carbons and at δ 48.37 for bridge -CH_2- clearly indicate the product (see ^{1}H-NMR and ^{13}C-NMR of **130**). Finally the molecular ion peak 322 (M^+, 5%) in mass spectrum confirmed the product. Satisfactory results are also obtained from the combustion studies.

The stereochemistry of compound **130** is fixed tentatively on the basis of our investigation on the skeleton **116**, the product obtained from **45** which was unequivocally given the absolute configuration. In the reaction of **46** with cyclopentadiene also an anti addition is expected. Moreover, in the skeleton **46** the phenyl group which is present α- to the spiro center should cause a significant steric effect to the incoming reagent, if the approach is from 'a' side [similar conformations can be assumed for **46** as it was for **45** as **45A** and **45A**].

Exploration of asymmetric induction with the chiral synthon **46** is under progress in our group.

Scheme-23



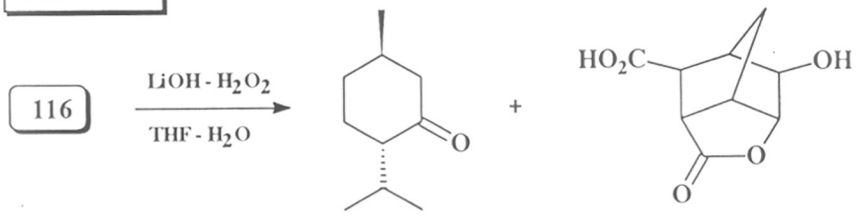
131 132 133

134 135 136

Reactions of **45** with furan, cyclooctadiene and 1,4-diphenyl-1,3-butadiene did not proceed in any of the aforementioned conditions (**Scheme 21**). No reaction was observed with heterodienes such as **131** (derived from methyl vinyl ketone) and **134** (derived from crotonaldehyde). The idea was to synthesize optically active heterocyclics of the type **133** and **136** (**Scheme 23**).

Our next objective was to detach the chiral auxiliary from the adducts obtained from the Diels-Alder reaction. A number of methods were attempted to detach the auxiliary under mild conditions. Hydrolysis using KOH or NaOH at room temperature was unable to disturb the structure, where as at reflux temperature (of methanol or ethanol) a number of unisolable products were obtained. LiOH in THF-H_2O system failed to cleave the auxiliary, but when used along with H_2O_2 it afforded the optically pure menthone **52** and the lactone **137** as shown below in **Scheme 24**. The formation of **137** can be explained in terms of epoxidation of double bond, opening and further intramolecular lactonization.

Scheme-24

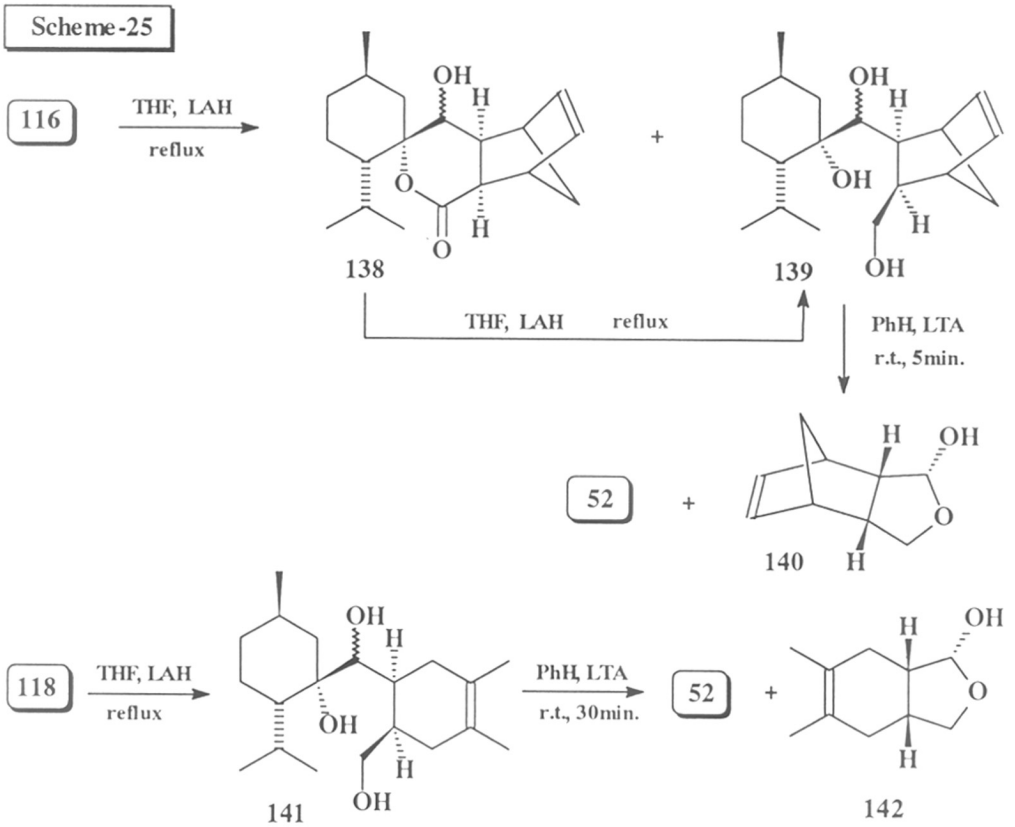


52 137

The compound **137** did not show any optical activity. The same experiment even after repeated trials did not show any optical activity. Bayer-Villiger oxidation of the ketone and the recently reported transesterification[47] using $(CH_3O)_3CH$, H_2SO_4 in dry MeOH were also unsuccessful.

Finally, we switched over the strategy to the reduction of the adducts. Thus, reduction using $NaBH_4$ in MeOH, EtOH, diglyme, THF-H_2O was unsuccessful. Reduction using lithium aluminium hydride in ether or THF at room temperature did not proceed. But, reduction of **116** in THF at reflux temperature using LAH proceeded to give a mixture of two products as shown in **Scheme 25**.

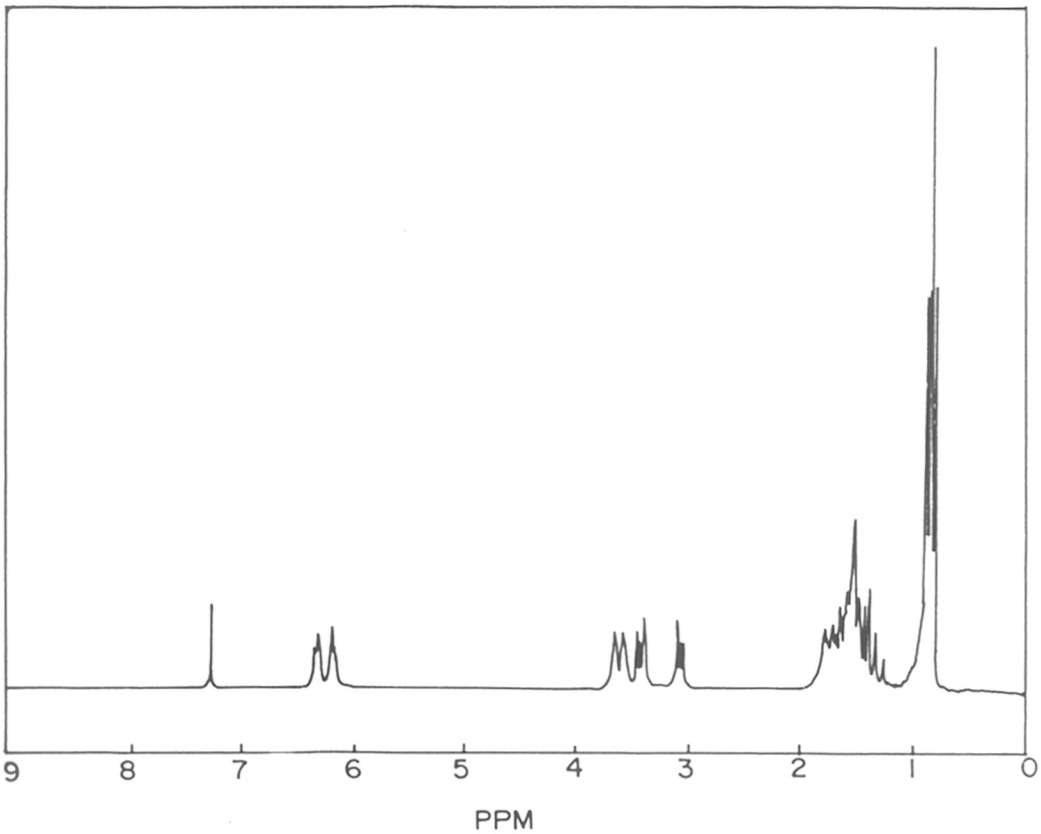
The keto reduced product **138** was further reduced to triol **139** using LAH at reflux temperature of THF. The overall yield of **139** is 87% which was fully characterized by the normal spectroscopic techniques. Thus, in IR the presence of a broad peak at 3350cm^{-1} and disappearance of all peaks in the carbonyl region indicate the complete reduction. In ^{1}H-NMR signals at δ 2.58-2.65(m, 3H), δ 2.76(bs, 1H) and δ 3.05(bs, 1H) indicate the protons on carbons attached to -OH and of -OH, signals at δ 5.97-6.05(m, 1H) and 6.20-6.28(m, 1H) indicate the olefinic protons. ^{13}C-NMR showed the presence of a single diastereomer even though two isomers are possible on the secondary -OH carbon center. Thus, signals at δ 136.10 and 134.50 indicate the olefinic carbons and signal at δ 63.50 indicate the -CH_2-OH carbon. Finally, the product was confirmed by mass spectroscopy where molecular ion peak 308(M^+, 1%) was observed. The triol **139** was then cleaved using lead tetraacetate in benzene at room temperature to give optically pure menthone **52** in 83% yield and the lactol **140** in 79% yield.

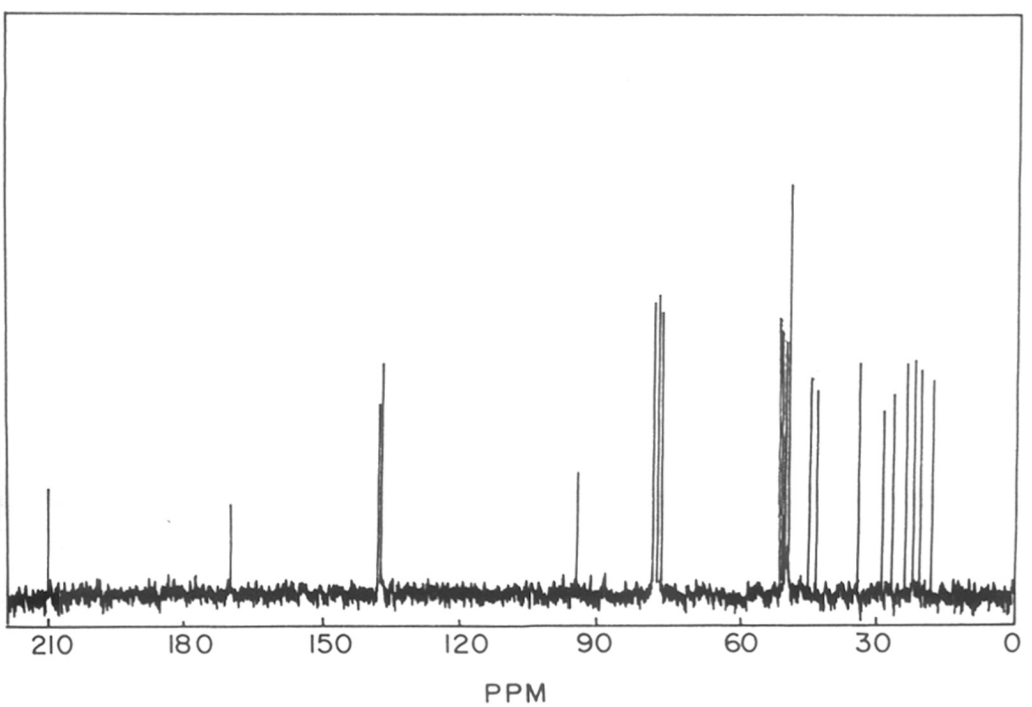


Optical rotation of menthone was compared with the authentic and found identical. The lactol **140** was characterized by spectroscopic methods. Thus, in IR spectrum a broad peak was observed at 3390cm^{-1} corresponding to the -OH group. In ^{1}H-NMR, signals at δ 3.38-3.45(dd, 2H) indicate the -CH_2-O-, at δ 3.90-4.00(q, 1H) indicate the hydrogen on carbon which is attached to -OH group, at δ 4.95 (s, 1H) for -OH proton and signals at δ 6.02-6.09(m, 1H), δ 6.14-6.20(m, 2H) correspond to two olefinic protons. ^{13}C-NMR showed a single isomer where signals at δ 136.29 and 135.51 indicate the olefinic carbons, at δ 65.06 indicate -CH_2-O- and δ 46.91 indicate the carbon attached to -OH group (see ^{1}H-NMR and ^{13}C-NMR of **140**). Finally the structure was confirmed by the presence of molecular ion peak 152 (M^+, 2%) in mass spectrum. The optical rotation is noted in the experimental section. The optical purity of the product was established by analogy, as reactions with similar experiments of cyclopropyl skeleton with chiral shift reagent Tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III) derivative showed that it did not give any diastereoisomeric mixture. The stereochemistry of lactol OH is irrelevant, as it is a cyclic form of alcohol and aldehyde. In further reaction, only open form of aldehyde would react. Besides, mechanistically LAH and LTA are known not to epimerize these kind of skeletons.

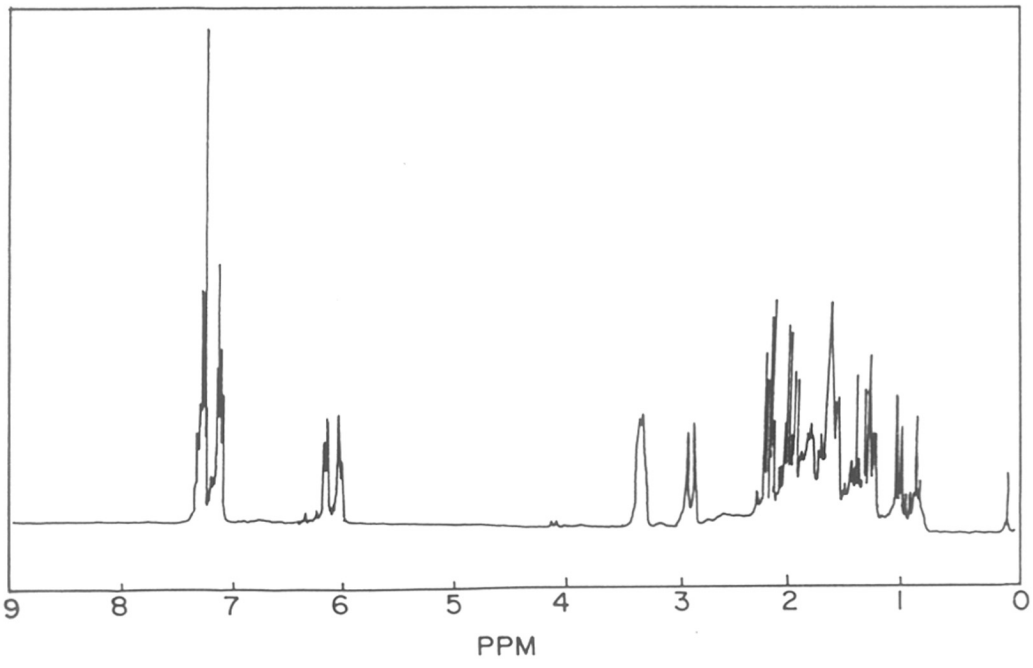
In a similar way the adduct **118** was reduced to get solely the triol **141** which was further oxidized using LTA to get optically pure menthone **52** and the lactol **142**. The compound **142** was characterized by normal spectroscopic analysis. Thus, in IR a strong peak at 3400cm^{-1} indicate the presence of OH group. In ^{1}H-NMR signals at δ 1.62(s, 6H, -CH_3), δ 3.58(t, 1H, -O-CH_2-), δ 4.10(t, 1H, -O-CH_2-) and δ 5.15(d, 1H, -O-CH-O<u>H</u>) indicate the presence of the product. ^{13}C-NMR showed the presence of only one diastereomer(at -OH carbon) and signals at δ 123.32(2C, olefinic), δ 103.37(-O-<u>C</u>H-OH), δ 72.18(-O-<u>C</u>H2-) and δ 19.03(2C, -<u>C</u>H_3) clearly indicate the product. Finally, the compound **142** was confirmed by the molecular ion peak 168(M^+, 11%) in mass spectrum. Further its optical rotation was measured as usual.

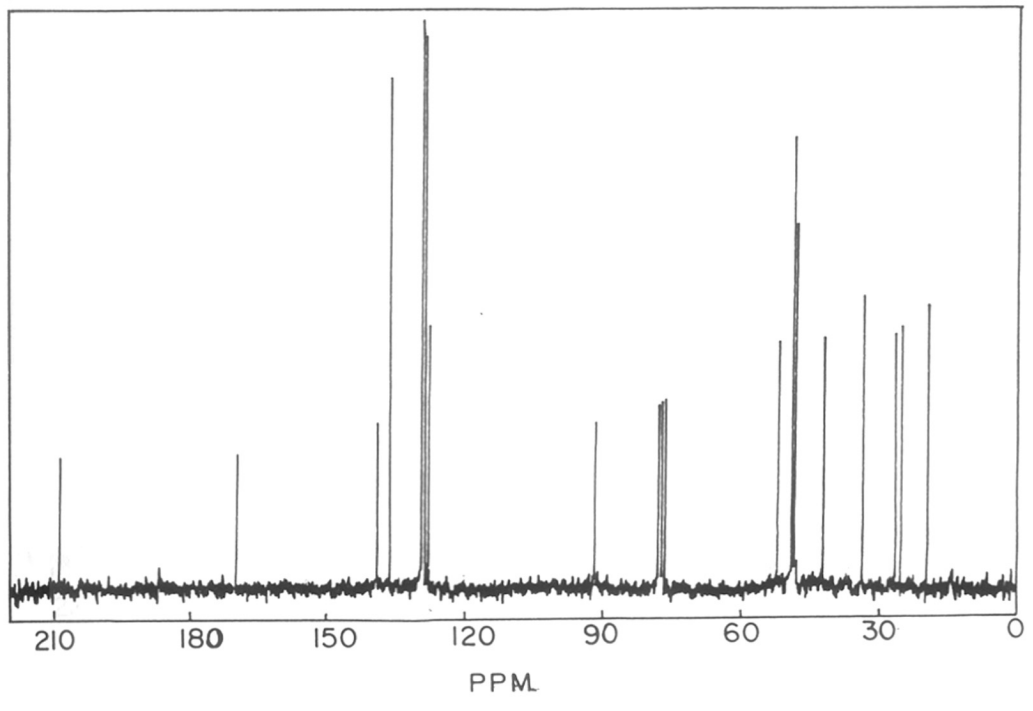
^{1}H – NMR & ^{13}C – NMR SPECTRA OF 116



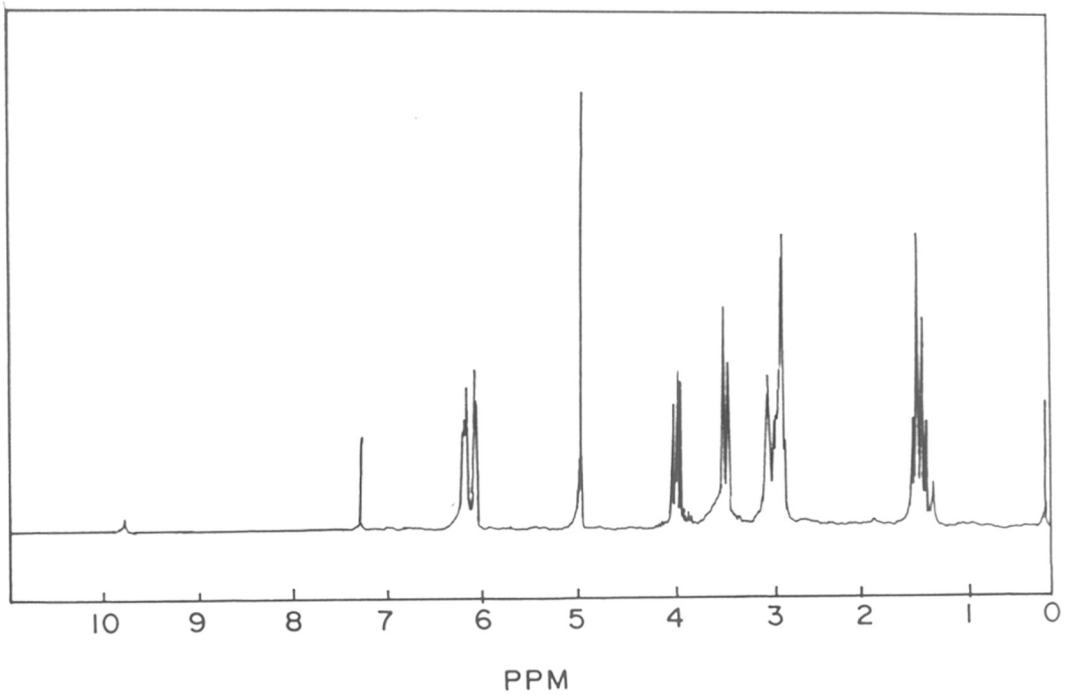


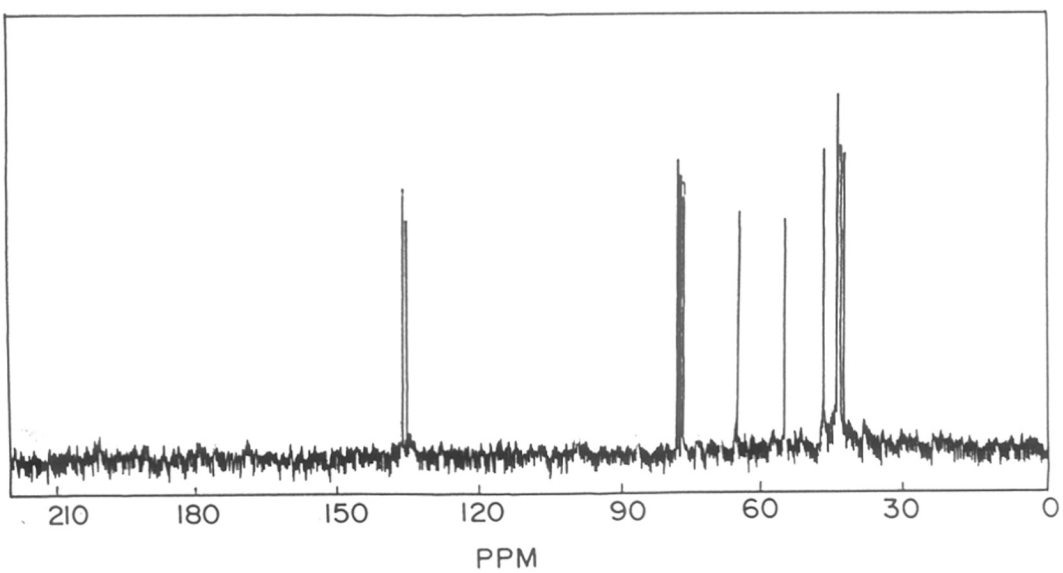
$^{1}H-NMR$ & $^{13}C-NMR$ SPECTRA OF 130

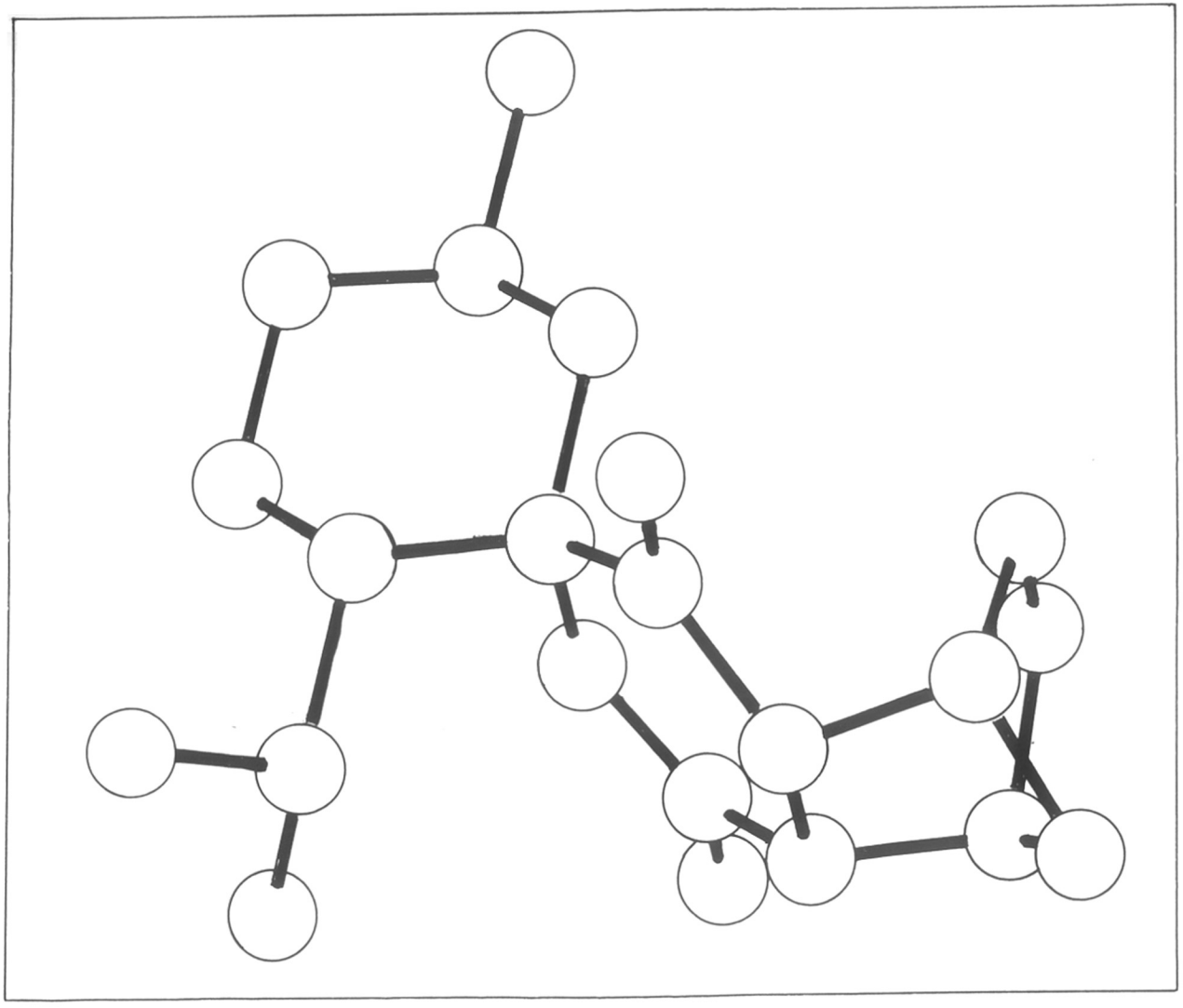




$^{1}H-NMR$ & $^{13}C-NMR$ SPECTRA OF 140







X — RAY STRUCTURE OF 116

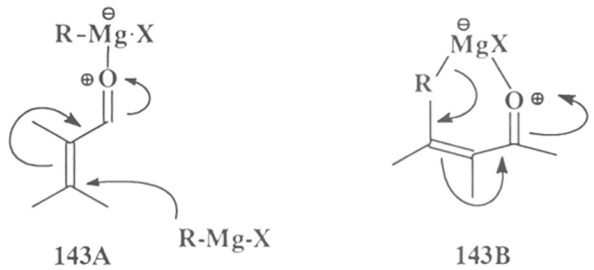
SECTION-3: ASYMMETRIC CONJUGATE ADDITION

INTRODUCTION

Conjugate addition of a nucleophile to an activated olefin leading to the construction of a carbon-carbon bond, carbon-nitrogen bond, carbon-phosphorus bond etc. is generally referred to as Michael addition. Conjugate addition of organometallic reagents to α,β-unsaturated organic substrates is an important and well known method of assembling structurally complex organic molecules.[48] Substrates used in this reaction are usually α,β-unsaturated ketones, aldehydes, esters, amides, sulfoxides or nitro compounds.

According to Munch-Peterson et al.[49] there are two types of mechanisms in the additions of Grignard reagents to conjugated esters depending on the nature of the substrates and Grignard reagent, i.e., the carbanion mechanism **143A** and the cyclic mechanism **143B** (**Fig. 24**).

Fig. 24



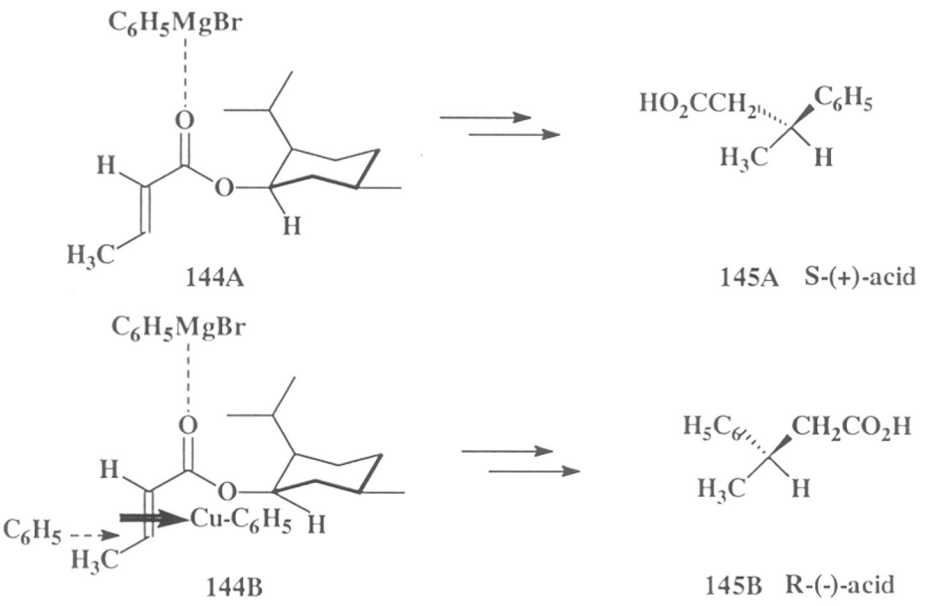
143A 143B

Both the mechanisms are irreversible. In the presence of CuCl a complex formation between the cuprous ion and the carbon-carbon double bond is expected, but still the mode of catalytic action is not completely understood. A reversal of facial selectivity was observed in the case of 1,4-addition of cuprate reagent to (-)-menthyl crotonate.

If Prelog's rule is applied to asymmetric synthesis the phenyl group would preferably enter from the least hindered side of the double bond of **144a** to give *S*-(+)-acid **145a** predominantly (**Scheme 26**). In the presence of CuCl the initial attack of phenyl copper (from CuCl & C_6H_5MgBr) would be towards the least hindered side of the double bond to form a complex **144b**, then phenyl group of Grignard reagent or phenyl copper would enter from the other side to give *R*-(-)-acid **145b** predominantly.

Elegant efforts to achieve asymmetric induction in Michael reaction involve the use of chiral basic catalysts,[50a] cosolvents[50b] and nucleophiles. However, enantioselective carbon-carbon bond closure β-to a carbonyl group has been accomplished more efficiently by 1,4-addition of organometallic reagents to α,β-unsaturated oxazolines,[50c] *t*-leucine-, *t*-butyl ester-aldemines,[50d] oxazapines,[50e] carboxylic amides derived from *l*-ephedrine,[50f] α-carbonyl-α,β-ethylenic sulfoxides.[50g] All these methods rely on a rigid substrate conformation owing to a chelation with the metal.

Scheme-26



Asymmetric Michael addition can normally be achieved by three ways:

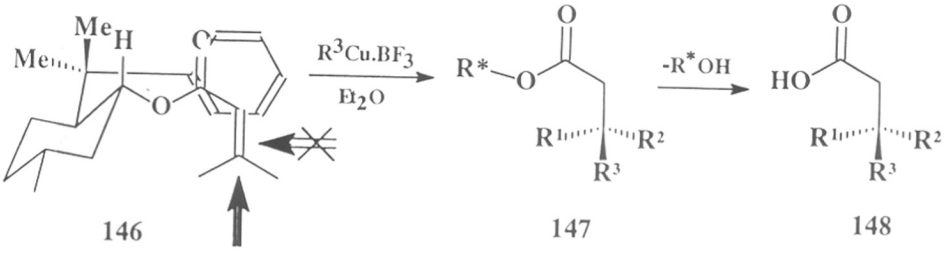
1. Using a chiral donor
2. Using a chiral acceptor
3. Using a chiral catalyst

But, in all three cases the chiral induction depends on many factors, e.g., on the nature of the chiral auxiliary, solvent, temperature etc. Many biologically useful skeletons have been built using asymmetric Michael addition as the key step. A few of the prominent reports about chiral induction in Michael addition are reviewed here.

1. Chiral acceptor

a) W. Oppolzer et al.[51]

Scheme-27



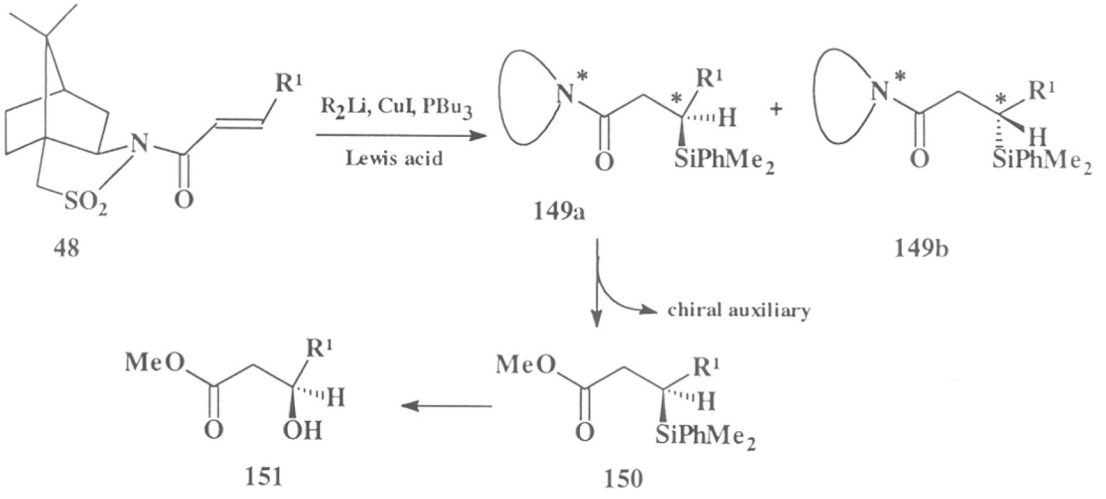
Excellent enantioselectivity was observed by the 1,4-addition of $PhCuBF_3$, *n*-$Bu.BF_3$ and $MeCu.BF_3$ to *trans*-8-phenyl menthyl enoates (**Scheme 27**).

When R^1 = H, R^2 = Me and R^3 = Ph, **148** was obtained in >99% ee.

b) W. Oppolzer et al.[52]

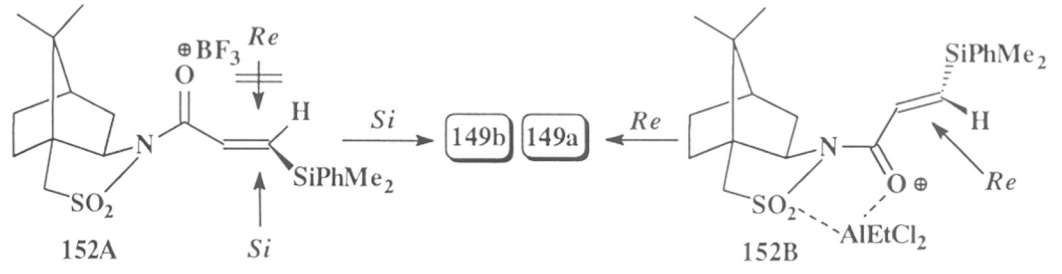
$EtAlCl_2$ promoted additions of organocopper reagents to camphor derived, conjugated N-enoyl-sultams gave saturated and olefinic β-silyl carboxyl derivatives with high diastereo differentiation (**Scheme 28**). The chiral auxiliary was later removed to get optically pure products.

Scheme-28



The stereospecific addition depends mainly on the nature of the Lewis acid used. Thus, C(β)-*Si*-face approach is favoured when BF_3-Et_2O was used and C(β)-*Re*-face approach is favoured when $EtAlCl_2$ was used as shown below in **Scheme 29**.

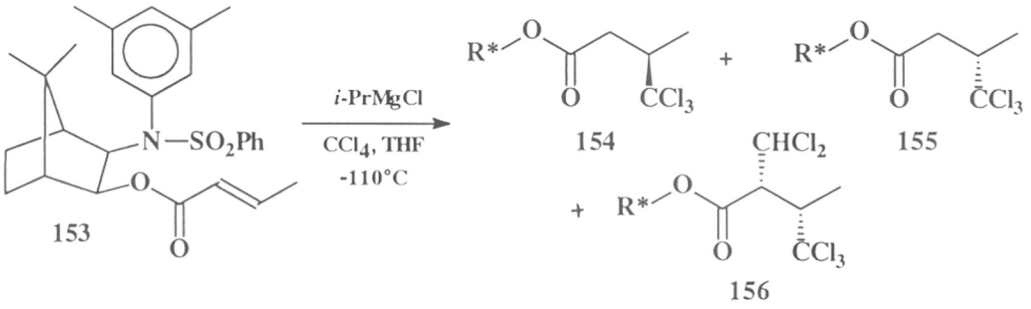
Scheme-29



c) G. Helmchen et al.[53]

Conjugate addition of Cl_3CMgCl to the crotonates of a chiral auxiliary containing sulfonylamino substituent afforded diastereoselectivities in 99% ratio which was finally utilized for the synthesis of (+)-(*S*)-3-trichloromethyl butyric acid (**Scheme 30**).

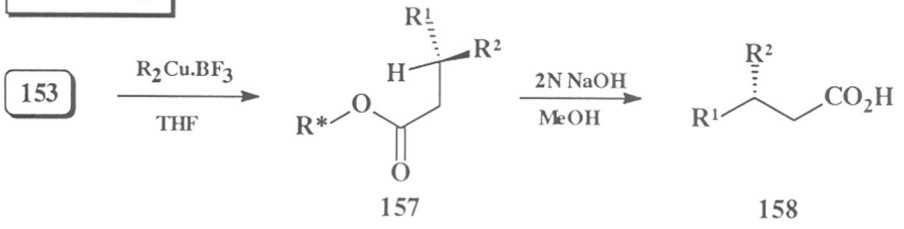
Scheme-30



When *i*-PrMgCl:CCl_4 was taken in 2.7:1 ratio exclusively the product **155** was obtained.

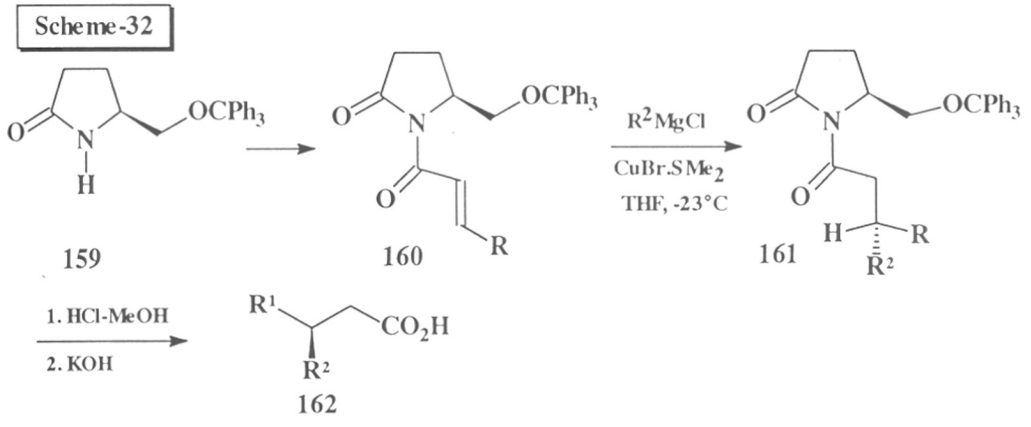
Conjugate addition of organocopper reagent $RCu.BF_3$ proceeded giving **158** in >99% ee after hydrolysis (**Scheme 31**).

Scheme-31



d) K. Tomioka et al.[54a]

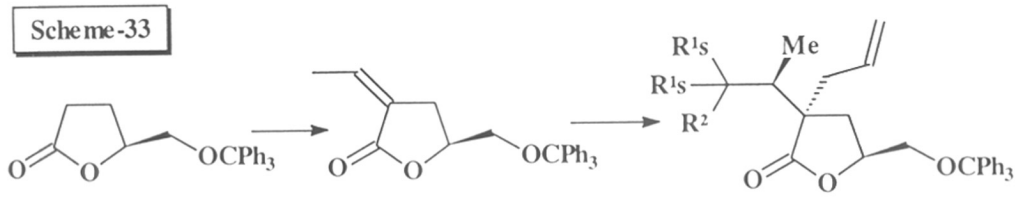
Scheme-32



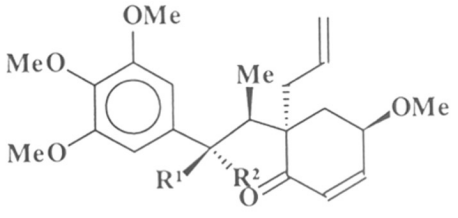
(*S*)-γ-Trityloxymethyl-γ-butyrolactam **159** serves as a chiral auxiliary in the conjugate addition reaction of the corresponding imide **160** with Grignard reagents in the presence of CuBr-SMe_2 in THF to give after hydrolysis the β,β-disubstituted carboxylic acids in high ee (**Scheme 32**).

The addition occurs anti to the trityloxymethyl group. In the similar manner enantiospecific total synthesis of (-)-megaphone[54b] **166** was achieved using conjugate addition as the key step in chiral auxiliary of the type **163** (**Scheme 33**).

Scheme-33



163 **164** **165**



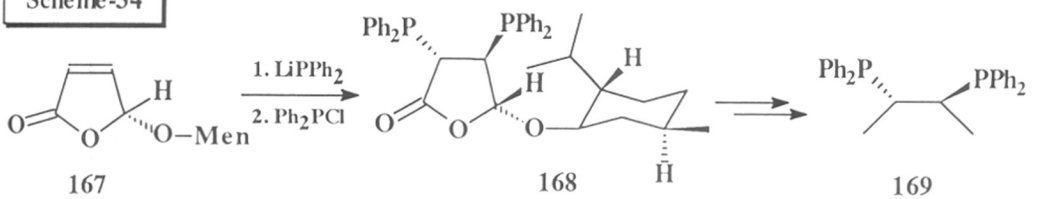
166 **(-)-Megaphone**

The compound **165** was obtained predominantly. This highly controlled production of **165** via consecutive 1,4- and 1,3-asymmetric induction is attributable to effective shielding of the β-face of **164** by the trityloxymethyl group allowing the conjugate addition and alkylation to occur from the α-face.

e) B.L. Feringa et al.[55]

Synthesis of *S,S*-chirophor **169** by the Michael addition of lithiodiphenylphosphine to menthyloxy-2[5H]-furanone **167** was achieved in 35% overall yield.

Scheme-34



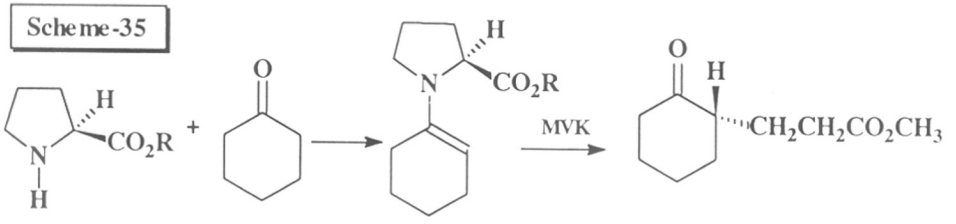
167 **168** **169**

2. Chiral donors

A good number of examples are available in the literature for the asymmetric carbon-carbon bond formation in the Michael addition of a chiral enamines to α,β-unsaturated carbonyl compounds. Normally enamines derived from a chiral primary or secondary amine and aldehydes or ketones are made to react with α,β-unsaturated carbonyl compounds where the stereoinduction is directly related to the chiral moiety present in the enamine. Chiral enamine such as α-substituted pyrrolidines, phenyl ethylamines etc. have been used as auxiliaries.

a) Optically active α-alkylcyclohexanone derivatives were prepared by using L-proline as the auxiliary[56a] (**Scheme 35**).

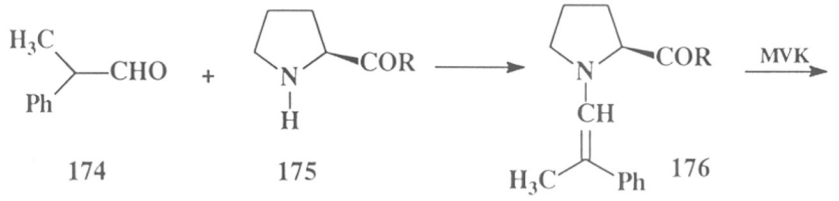
Scheme-35



170 171 172 173

The degree of asymmetric alkylation was found to increase with the bulkiness of the ester moiety. The addition occurs anti to the ester moiety of amine. When the same method is extended to aldehydes, 4,4-disubstituted-2-cyclohexenones were obtained[56b] (**Scheme 36**).

Scheme-36

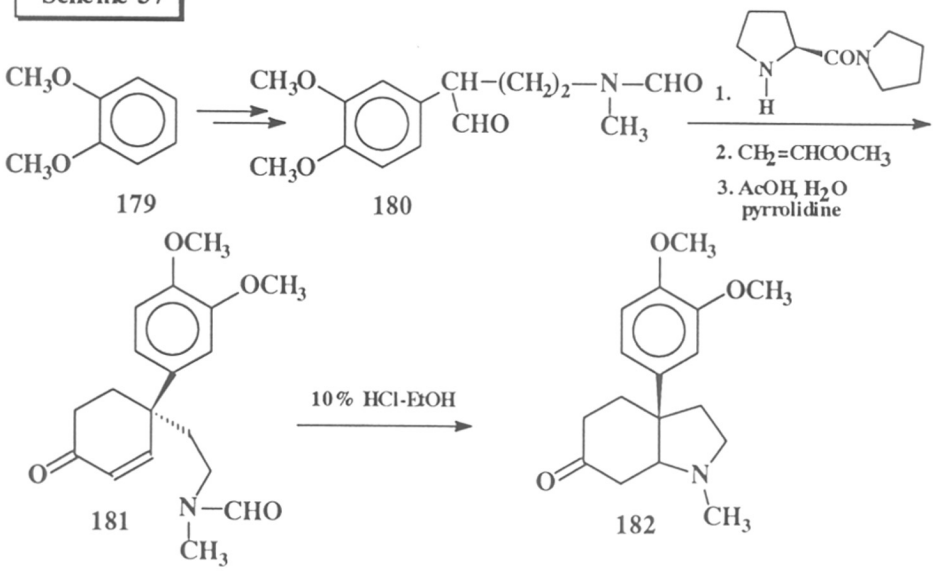


174 175 176

177 178

Optical yields of 40-50% were observed and found to have effect of the solvent used. Among alcohols, namely, MeOH, EtOH and *t*-BuOH the less bulkier alcohols increased the optical yields. Using the same strategy synthesis of (+)-Mesembrine **182** has been carried our successfully[56c] (**Scheme 37**).

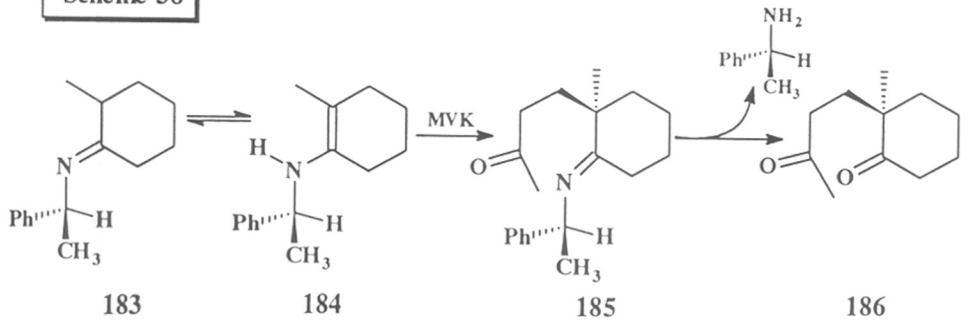
Scheme-37



b) J.D. Angelo et al.[57a]

Chiral phenyl ethylamines are used as auxiliaries where the corresponding enamines were added over enones (**Scheme 38**).

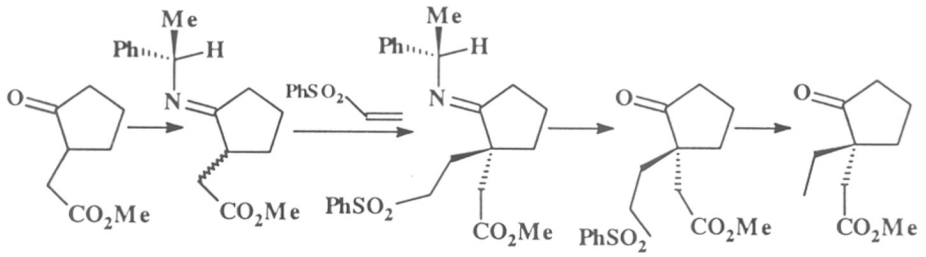
Scheme-38



Addition of similar enamines to sulfones[57b]

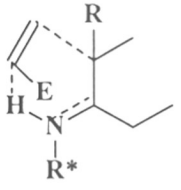
Synthesis of compounds of the type **191** (**Scheme 39**) having ethyl substituent at the quarternary center is useful in the synthesis of naturally occurring Aspidosperma and Hunteria alkaloids.[57c] The same strategy has also been used for the synthesis of ring C aromatic steroids.[57d]

Scheme-39



In all these Michael addition reactions an "aza ene synthesis like" transition state was expected, where alkylation takes place mainly on the π-face of the enamine opposite to the phenyl ring of the chiral amine moiety, where the proton from the nitrogen goes to the α-position of the Michael acceptor (**Fig. 25**).

Fig. 25



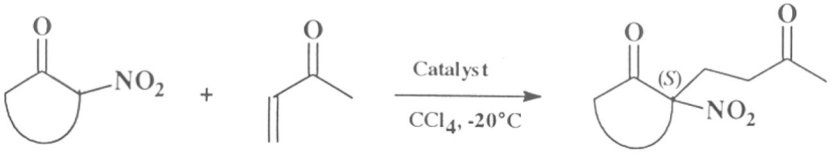
192

3. Chiral catalysts

M. Hessee et al.[58]

Michael addition reaction of 2-nitrocycloalkanones to methyl vinyl ketones catalyzed by the Cinchona alkaloid Cinchonine afforded high chemical yields and optical yields up to 60% ee (**Scheme 40**).

Scheme-40



193 194 195

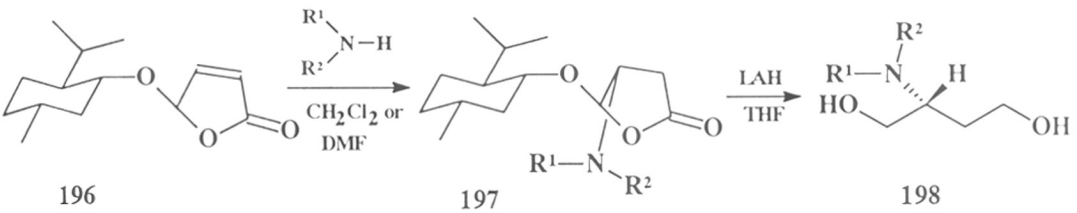
The enantioselectivity and absolute configuration of the products depends on the ring size. Six to eight membered rings gave up to 60% ee and lower in the case of larger rings. The absolute configuration in the case of larger rings is '*R*' and '*S*' in the case of smaller rings.

RESULTS AND DISCUSSIONS

The nature of our chiral synthon **45** reveals that it should be good Michael acceptor. As mentioned in the introduction, chiral enones can involve effectively in the synthesis of many useful skeletons. Compound **45**, where the double bond is conjugated with a carbonyl and an ester function can undergo regioselective 1,4-addition. Both neutral and anionic nucleophiles can be used under mild conditions, without disturbing the spirocenter.

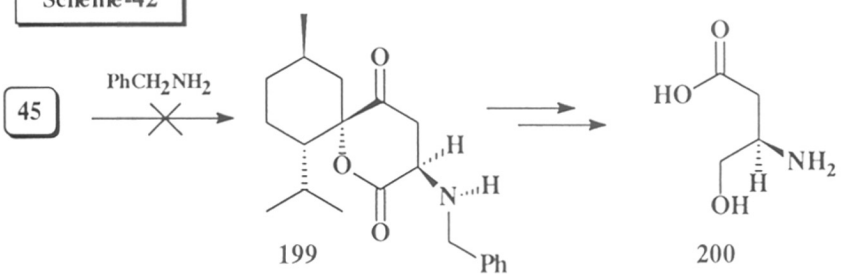
Amines (primary and secondary) have been attempted to add upon the double bond of **45** under all conditions. Thus, the treatment of **45** with morpholine at room temperature in ethanol, resulted in no reaction (**Scheme 42**). At reflux temperature a number of unisolable products were obtained. Same is the case with other amines such as pyrrolidine, piperidine, benzylamine etc. Stirring both the substrates neat by adsorbing them on neutral alumina[59] also failed to afford the product. The lack of reactivity with our synthon was puzzling, as extremely efficient addition was reported by Feringa et al.(**Scheme 41**) with similar skeletons.[60]

Scheme-41

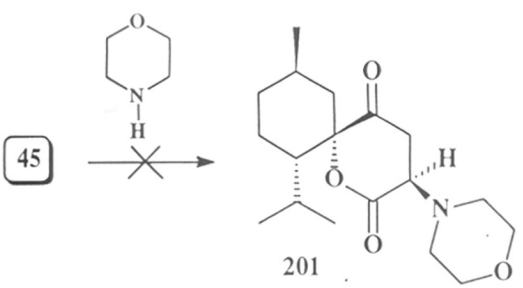


196 197 198

Scheme-42



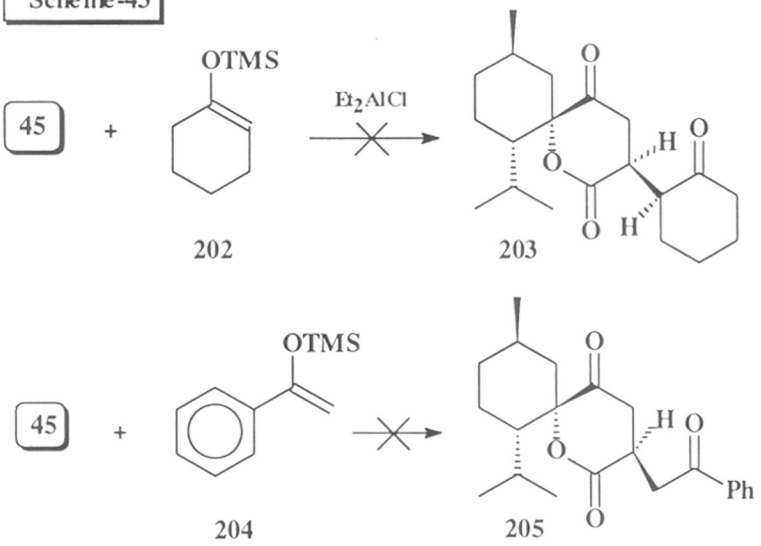
199 200



201

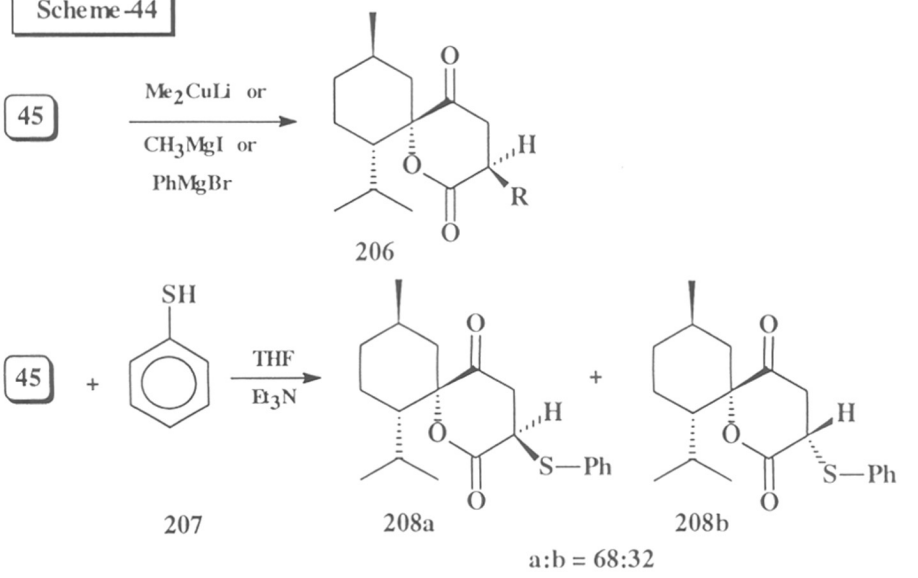
Silyl enol ethers are well known to add over conjugated double bond to give stereoselective Michael adducts.[61] When **45** was treated with silyl (trimethyl silyl) enol ethers (**202** and **204**) derived from cyclohexanone and acetophenone in the presence of diethyl aluminium chloride, no reaction was observed (**Scheme 43**). Change of solvents and temperature did not yield the desired product.

Scheme-43



We then opted for anionic nucleophiles. Thus treatment of **45** with $(CH_3)_2CuLi$ at -78°C gave a number of products. Whenever in these studies, we observed so many products, further study was discontinued. Our presumption was either selectivity is poor or reagents/workup is defective.

Scheme-44



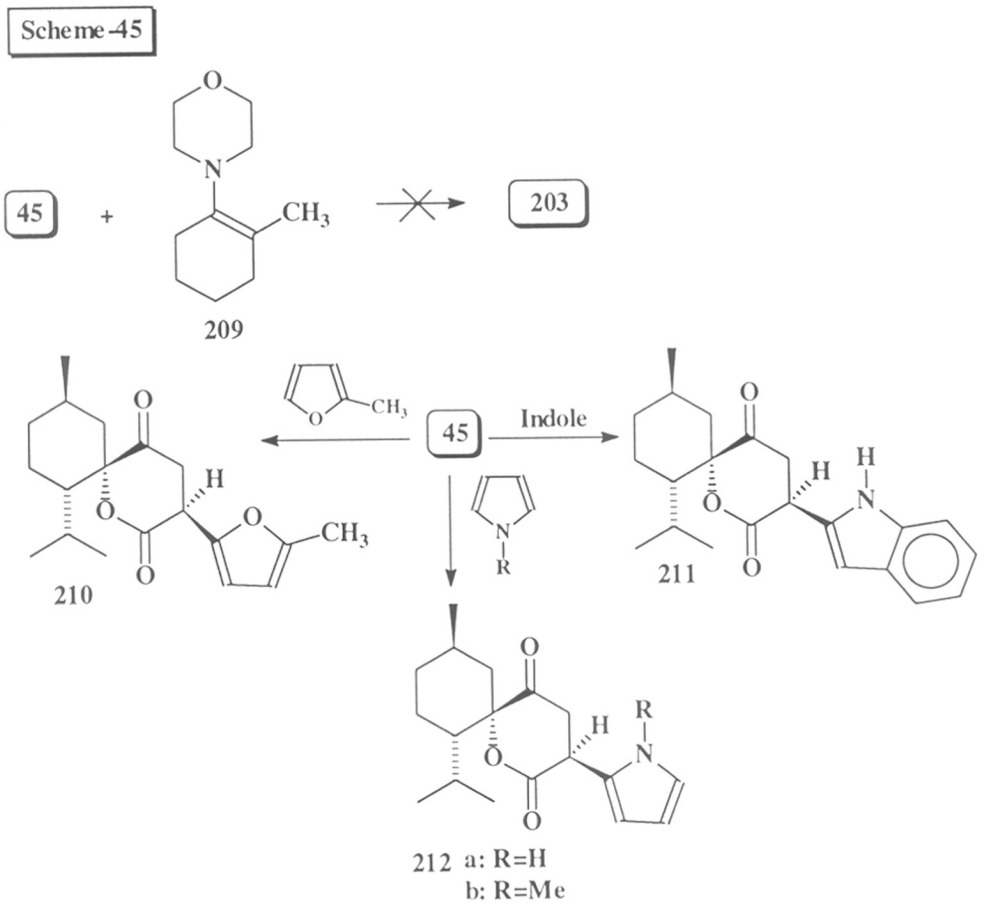
One reason for the formation of these sort of unisolable products could be that, the nucleophile attacks preferentially on the spiro center, even though it can add over the conjugated system. Similar type of reaction was observed during the addition of Grignard reagents such as CH_3MgI, $PhCH_2MgI$ etc. to **45**. But when **45** was treated with thiophenol **207** using triethylamine as the base at room temperature, the conjugate addition was observed in 86% yield with 68:32 ratio of diastereomers **208a** and **208b** (**Scheme 44**). However, no change in selectivity was observed when the reaction temperature was brought down.

Compound **208** was characterized by the usual spectroscopic techniques. In ^{1}H-NMR, a signal at δ 4.04-4.13 (m, 1H) clearly indicate the proton on the carbon to which the sulphur atom is attached. ^{13}C-NMR showed a mixture of two diastereomers in 68:32 ratio, peaks corresponding to phenyl carbons between δ 134-138, signals at 93.38 for the spiro carbon, at δ 45.70 for the methylene carbon present α- to the carbonyl, at δ 50.84 for sulphur attached carbon clearly indicate the product. Finally molecular peak 346 (M^+, 24%) in mass spectrum confirmed the product. According to our observation and prediction in Diels-Alder reaction (**Section 2**), the ratio of isomers was proposed for **208a** and **208b**.

As mentioned in the introduction for this section enamines (active olefins which are in conjugation with nitrogen) would be the suitable Michael donors for the system like this. However, when **45** was treated with enamines derived from aldehydes and ketones, no reaction was observed under normal conditions. Interestingly heterocycles such as indole, pyrrole, N-methyl pyrrole, etc. were fairly successful in conjugate addition (**Scheme 45**). Thus, when **45** was treated with indole in toluene at 0°C in the presence of diethylaluminium chloride as catalyst the addition product **211** was obtained in 66% yield. The yield and the diastereoselectivities in the reaction of **45** with other heterocycles is noted in the **Table 1**.

Table-1: Conjugate addition of heterocycles to **45**

Nucleophile	Solvent	Yield (%)	Selectivity
Indole	toluene	66	Single diastereomer
Pyrrole	-do-	75	90:10
N-Methyl pyrrole	-do-	53	Single diastereomer
Furan	toluene or ether	no reaction	----
2-Methyl furan	ether	92	85:15



Characterization of these Michael adducts revealed some interesting features. Compounds **211** and **212b** were obtained as single diastereomers (determined by ^{13}C-NMR). But, reaction with pyrrole and 2-methyl furan led to a mixture of diastereomers. All the products were characterized well. ^{1}H-NMR of **212b** showed clear signals at δ 3.47 (s, 3H) for -N-Me protons, at δ 4.17-4.25(t, 1H) for proton in the newly formed chiral center and between δ 5.90-6.70 for pyrrole moiety. In ^{13}C-NMR signal at δ 48.61 indicate the methyl attached to nitrogen and the spectrum showed the presence of a single diastereomer (see ^{1}H-NMR and ^{13}C-NMR of **212b**). Molecular ion peak 317 (M^{+}, 7.5%) in mass spectrum confirmed the product. For **211**, a strong broad peak at 3390cm^{-1} in IR, signals at δ 4.50-4.60 (t, 1H) corresponding to the proton at the new chiral center and at aromatic region in ^{1}H-NMR, signals at δ 45.26 corresponding to the methylene carbon α- to the carbon and at δ 48.88 corresponding to the new chiral center clearly indicate the product. Finally, molecular ion peak 353 (M^{+}, 9%) confirmed the structure of **211**. All other compounds showed their characteristic spectral features. It is quite surprising to see the appreciable difference in selectivity in the case of **212a** and **212b**, where

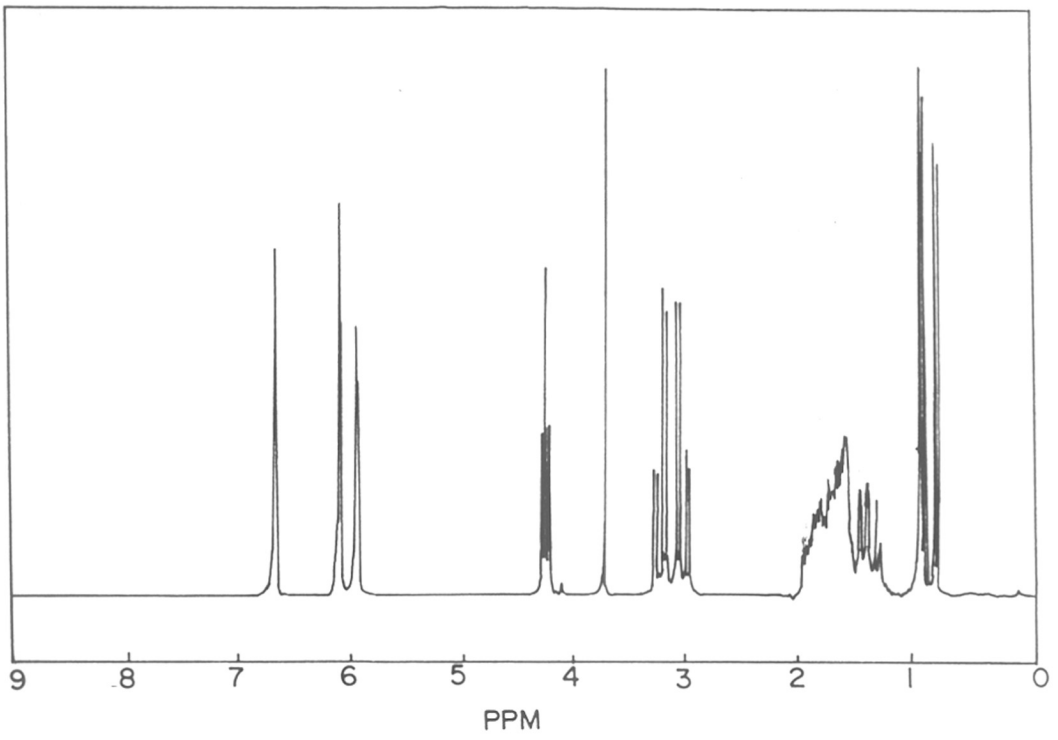
the N-substituted methyl is all the difference. Reaction with furan moiety when toluene was used as solvent did not proceed. When the reaction was carried out at -78°C (for **212a** and **210**) no significant change in selectivities were observed.

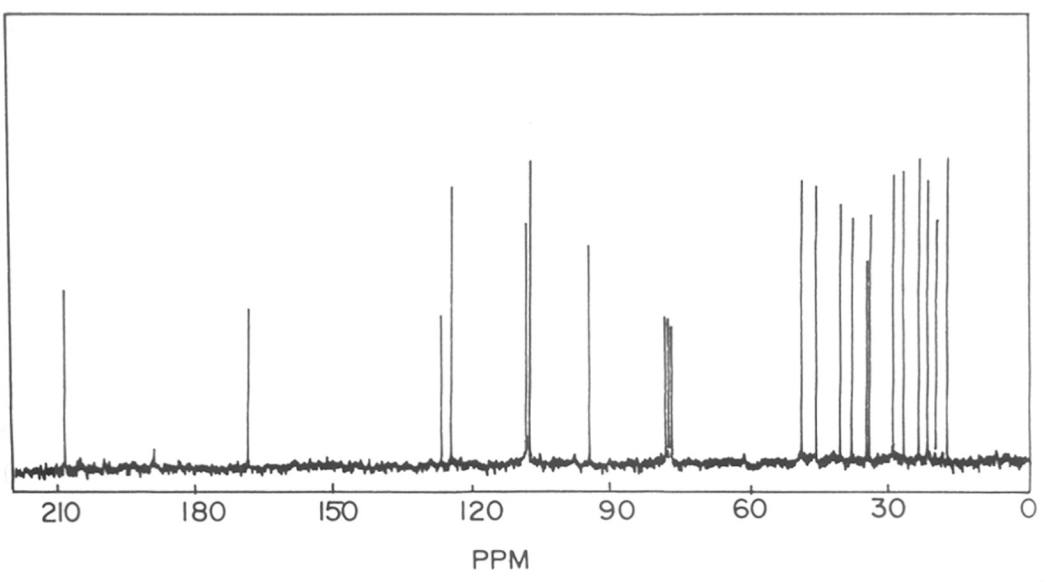
The configurations at the chiral centers were predicted based on the observation and study on the Diels-Alder reactions of the same chiral synthon.

Mechanistically, enamine and Lewis acid mediated conjugated additions are complex. The observed regiochemistry in all the above reaction could be explained on the basis of complexation of the Lewis acid with the Michael acceptor. In this case the complexation will obviously be with the ketone carbonyl.

It was presumed that the cleavage of auxiliary could be worked out similar to the cleavage of Diels-Alder adducts and cyclopropyl adducts (see **Sections 2** and **4**).

^{1}H-NMR & ^{13}C-NMR SPECTRA OF 212 b



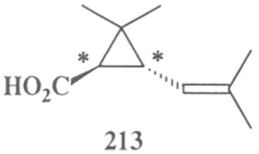


SECTION 4: ASYMMETRIC CYCLOPROPANATION

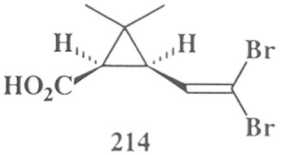
INTRODUCTION

Asymmetric cyclopropanation, i.e., either the cyclopropanation of the olefin attached to a chiral auxiliary or stereoselective transfer of carbon ligands from chiral catalysts to alkenes resulting in the asymmetric synthesis of cyclopropanes constitute the most effective methods for preparing biologically useful compounds. For example, chrysanthemic acid **213** and its analogues (**Fig. 26**).

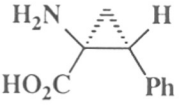
Fig. 26



213

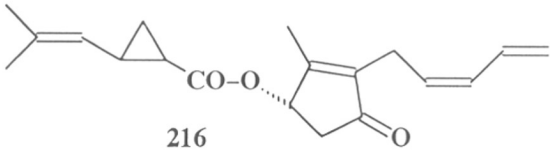


214



215

etc.



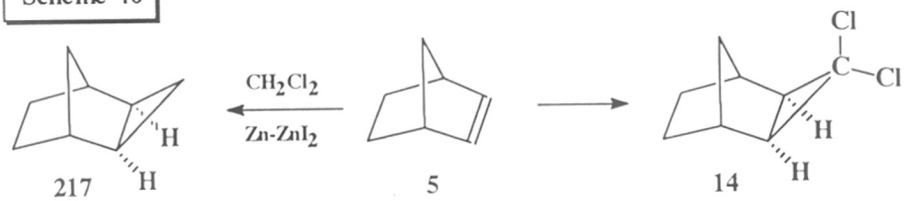
216

Apart from pyrethroids a few marine metabolites,[62] aromadendranes[63] etc. also constitute the cyclopropane ring. In all these cases the role of cyclopropane ring is considered to be major either in activity or from the stereochemical complexity view point.

Cyclopropane is unique among carbocycles in both its properties and reactions. It can for example, stabilize electron deficient centers to a much greater extent than cyclobutane or the larger carbocycles. Synthesis of this cyclopropane ring involves diversified methods. e.g., 1,3-bond formation (elimination reactions), combination of C_2 and C_1 building blocks (carbene or anionic addition to double bond), rearrangement reactions etc. In this section we have attempted asymmetric synthesis of the cyclopropyl derivatives using anionic combination of C_2 and C_1 methodology.

Addition of halocarbenes (Cl and Br) to olefinic double bond formed the nucleus of the cyclopropane ring formation.[64a] Dichloro and dibromo carbenes subjected to relative addition rate studies (in an electrophilic sense) are among the most selective carbenes known. The steric effects involved in these reactions which determines the stereochemistry of the product is discussed in the literature.[64b] For example, addition of Simmons-Smith reagent $(CH_2I)_2Zn.ZnI_2$ or dichloro carbene to norbornene occurs only in exo fashion (**Scheme 46**).

Scheme-46

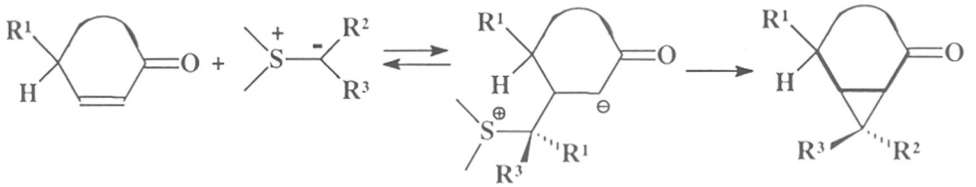


217 5 14

In the above case the opposition of the syn proton of the methano bridge provides a small barrier to the exo attack than do the opposition of the endo protons of the ethano bridge to endo attack.

Ylides cyclopropanate unsaturated system which are susceptible to Michael addition reactions, i.e., α,β-unsaturated ketones, esters, amides, nitriles, sulfones, nitro compounds etc.[65] The conjugation involved, i.e., the enhancement of electron withdrawal from carbon-carbon bond facilitates the reaction. The stereochemistry of the product can be predicted on the basis of stepwise mechanism where the intermediacy of zwitterions has been accepted (**Scheme 47**). The Michael addition of the ylide will occur predominantly from the less hindered side of the double bond and subsequent cyclization will take place in the conformation which minimizes the non bonded repulsions.

Scheme-47



218 219 220 221

Highly reactive ylides preferentially undergo carbonyl addition, whereas stabilized ylides add to carbon-carbon double bond in Michael fashion. Stabilization of the ylide by an electron-withdrawing substituent, alkyl substitutions on the ylide carbon and presence of a bulky group at the carbonyl carbon favour the cyclopropane formation. Typical ylides employed in the cyclopropanation of Michael acceptors are:

Fig. 27

222 223 224 219

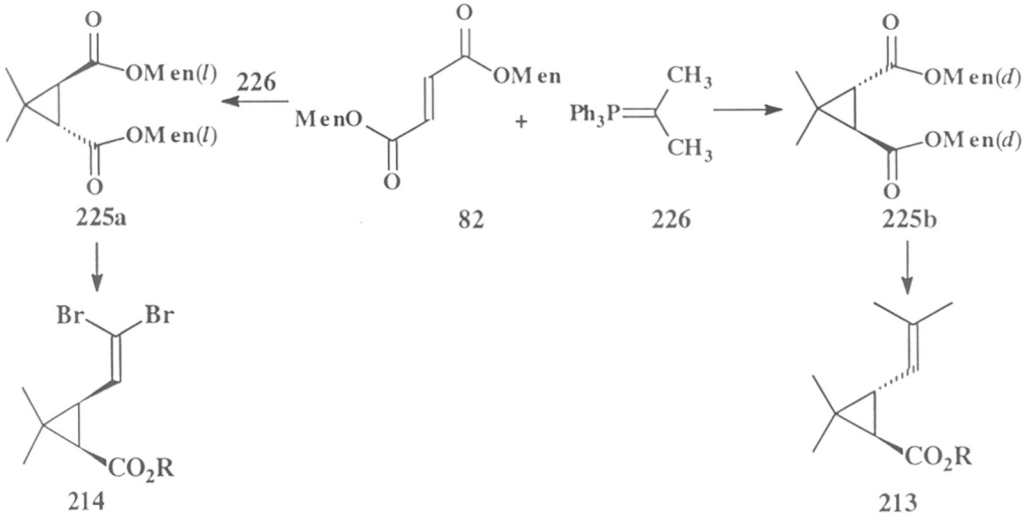
Asymmetric cyclopropanation is achieved normally by using either chiral auxiliaries or chiral catalysts. The extent of chiral induction depends directly on the chiral auxiliary or the catalyst used. Chiral synthons derived from amino alcohols, menthol etc. have been used for asymmetric cyclopropanation, whereas in the catalyst category copper is the metal which is most widely used. Other than copper, metals such as iron, rhodium have also been used. As a brief review of some of the auxiliary based and catalyst based reactions are discussed here.

CHIRAL SYNTHONS

Menthol as dimenthyl fumarate[66]

(1*R*)-*trans*-chrysanthemic acid **213** and its cis gem dibromovinyl analogue **214** were synthesized from isopropylidene triphenylphosphorane and (*d*) or (*l*) dimenthyl fumarate (**Scheme 48**).

Scheme-48



214 213

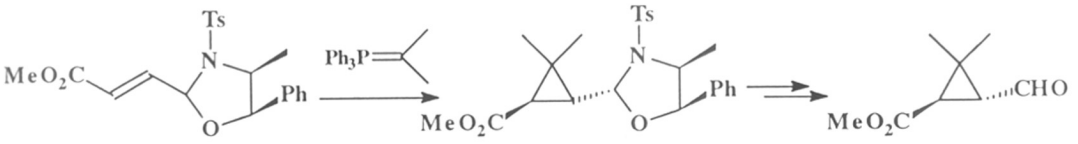
Diastereomeric excess up to 74% was obtained when the reaction was carried out at -78°C.

Amino alcohol as oxazolidine[67]

Cyclopropanation of oxazolidine of the type **227** by isopropylidene triphenylphorphorane proceeded with excellent π-face selectivity giving optically pure hemicaronic aldehyde **229** after detachment of the chiral auxiliary (**Scheme 49**).

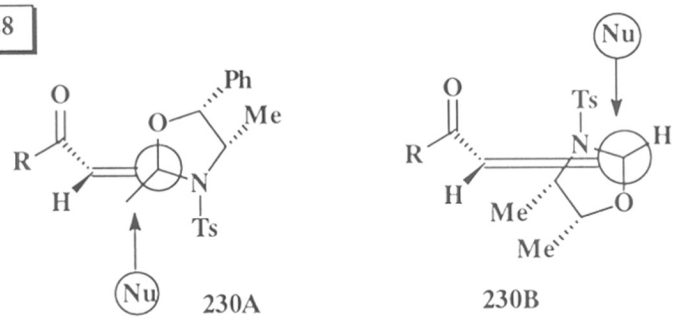
The stereochemical outcome of these reactions was rationalized using the transition structure models **230A** and **230B** (**Fig. 28**) where the very electronegative allylic substituent (oxygen) is aligned anti to the forming bond in **230A** and **230B** so that the withdrawal of electron from the π-system can be maximized. Out of the two models **230A** is favoured over **230B** for steric reasons.

Scheme-49



227 228 229

Fig. 28

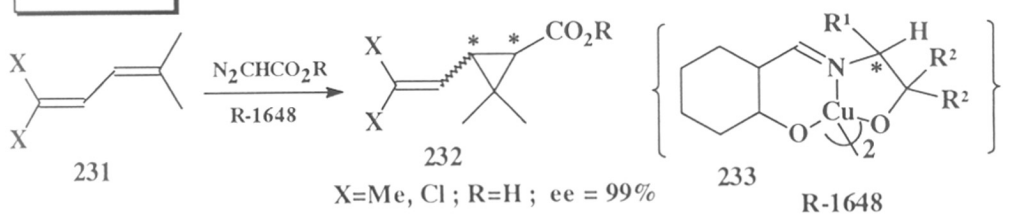


CHIRAL CATALYSTS

As mentioned before, copper in complexation with chiral compounds has been used extensively in inducing chirality in cyclopropanation. In all the cases the cyclopropanating reagents were diazo compounds. A few of the complexes with their chirality inducing capability are mentioned below:

Aratani et al.[68a] synthesized the most effective optical isomer (1*R-cis*) of permethric acid, a potent intermediate in the production of synthetic pyrethroid with high enantioselectivity (**Scheme 50**).

Scheme-50



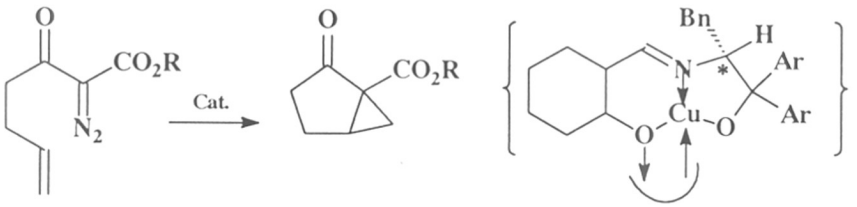
231 232 233

X=Me, Cl ; R=H ; ee = 99%

R-1648

A similar catalyst **236**[68b] was used successfully for the enantioselective (ee = 4-77%) cyclopropanation of unsaturated diazo carbonyl compounds (**Scheme 51**).

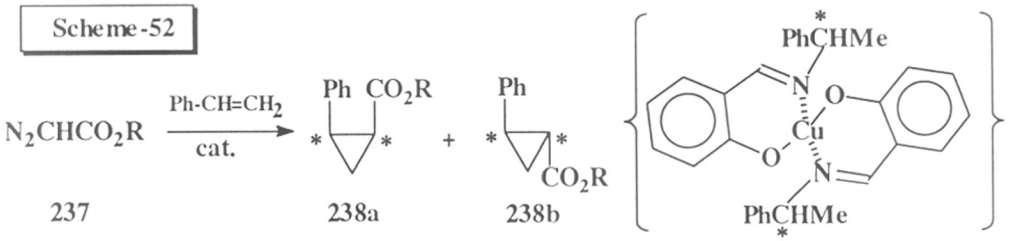
Scheme-51



234 235 236

Asymmetric cyclopropanation of styrene[69] with the diazo compound **237** using the catalyst **239** proceeded with good enantioselectivity (**Scheme 52**).

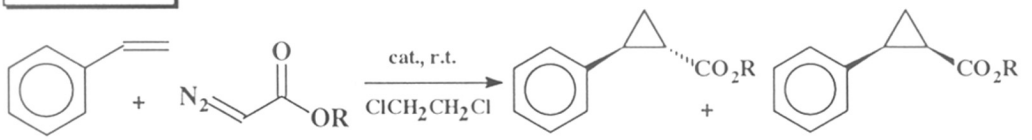
Scheme-52



237 238a 238b 239

Cu(II) complexes of bisoxazolenes[70] derived from diethylmalonate and chiral amino alcohols were used to get excellent enantioselectivity (up to 99%) (**Scheme 53**).

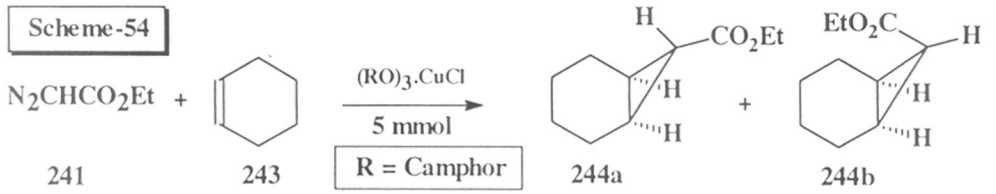
Scheme-53



240 241 242a 242b

Asymmetric cyclopropanation using ethyl diazoacetate and (trialkyl phosphite) copper(I)chloride complexes[71] was achieved, where the cyclopropane product distribution is found as a function of the steric bulk of the ligand on copper which proves the intermediacy of the carbene-metal olefin complex in the irreversible cyclopropane ring forming step (**Scheme 54**).

Scheme-54

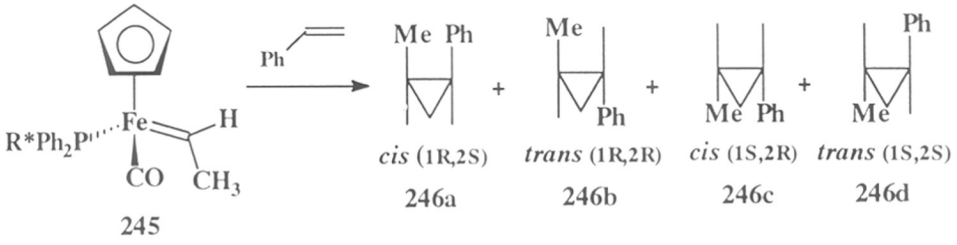


241 243 244a 244b

It has been later proved that the electronic factors are mainly responsible for the stereoselectivity observed.

Brookhart et al.[72] utilized optically active transition metal carbene complexes for the enantioselective cyclopropane synthesis (**Scheme 55**).

Scheme-55

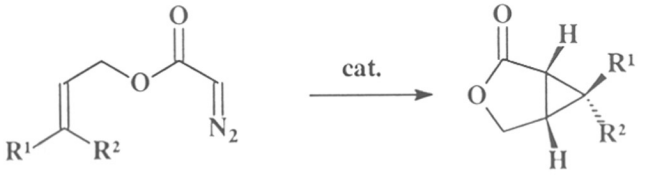


245 246a 246b 246c 246d

All the products were obtained with optical yields ranging between 84% to 90%.

A good enantioselectivity (94%) was observed in the intramolecular cyclopropanation of the diazo compound **237** in the presence of rhodium based catalyst[73] Rh_2(55-MEPY)$_4$ (**Scheme 56**).

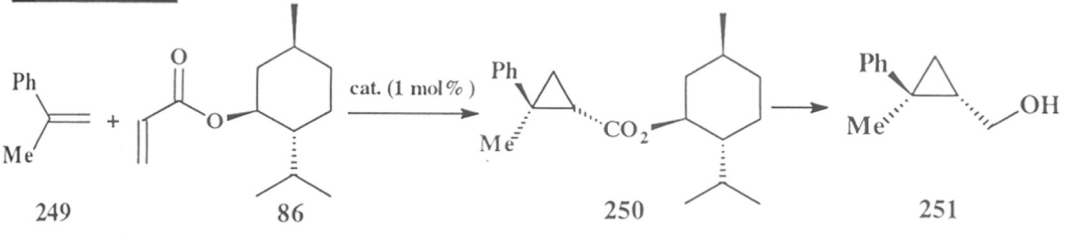
Scheme-56



247 248

More recently, a novel dirhodium (II) carboxamidate catalyst[74] was used for the asymmetric cyclopropanation of diazoacetates (**Scheme 57**).

Scheme-57



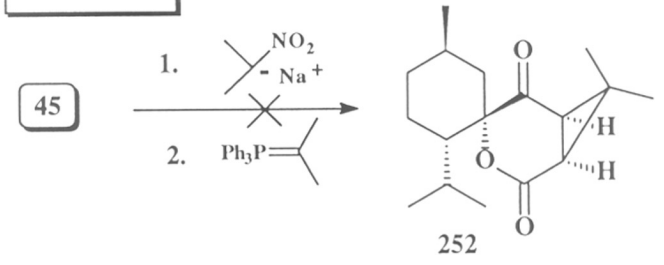
249 86 250 251

RESULTS AND DISCUSSION

A comparison of the chiral synthons **45** and **46** which are under study with other synthons used in the literature[66,67] revealed some interesting features. The unsaturated system unlike earlier reports is not only suitable for the stereospecific cyclopropanation but also throws some light on the stereoelectronic effects involved in the system. The activated double bond can easily be cyclopropanated using sulfur or phosphorus ylides i.e., the C_1 and C_3 connecting approach through the carbanion.

As mentioned in the introduction, the asymmetry involved in the pyrethroids (e.g., chrysanthemic acid and its analogues) drew our attention which influenced us to utilize the chiral systems **45** and **46** for the synthesis of intermediates involved in the synthesis of these compounds. Thus, all attempts to cyclopropanate **45** failed to afford the desired dimethylcyclopropyl product (**Scheme 58**).

Scheme-58



252

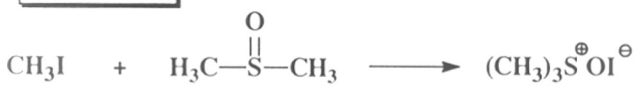
Treatment of **45** with sodium salt of 2-nitropropane in DMSO at room temperature failed to afford the product [this sodium salt was prepared by 2-nitropropane and sodium in dry ethanol[75]]. Then we opted for phosphorus ylides. When the compound **45** was treated with isopropylidene triphenyl phosphorane prepared by the treatment of $(CH_3)_2CHP^+Ph_3I^-$ with *n*-BuLi in benzene or hexane at room temperature cyclopropanation did not proceed to give the desired product. The change of base from *n*-BuLi to $NaNH_2$ or NaHMDS etc. also failed to give the product. The same set of reactions were tried on **46** which consequently showed the negative results.

Sulphur ylides developed by Corey and other groups cyclopropanate the activated olefins quite efficiently. We tried to prepare a few of the ylides which were later utilized to cyclopropanate the compounds **45** and **46** (**Scheme 59**).

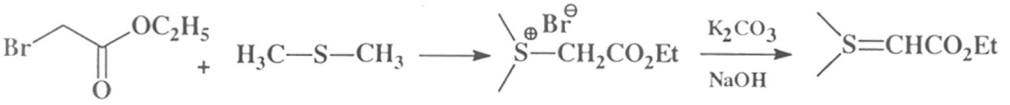
Both the compounds **45** and **46** underwent stereospecific cyclopropanation with **255** in DMSO at 80°C giving moderate yields (**Scheme 60**). Characterization of the products revealed the presence of single diastereomer in both the cases.

The compound **264** was characterized by normal spectroscopic techniques. Thus, in ^{1}H-NMR, signals at δ 0.70(s, 1H) and δ 1.20(s, 1H) clearly indicate the -CH_2- of cyclopropane ring. ^{13}C-NMR showed a single diastereomer with the signal at δ 35.61 for -CH_2- of cyclopropyl group (see ^{1}H-NMR

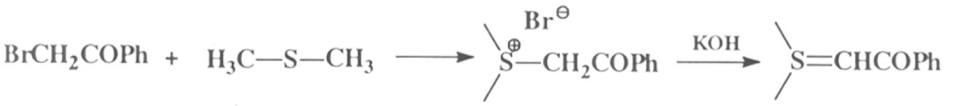
Scheme-59



253 254 255

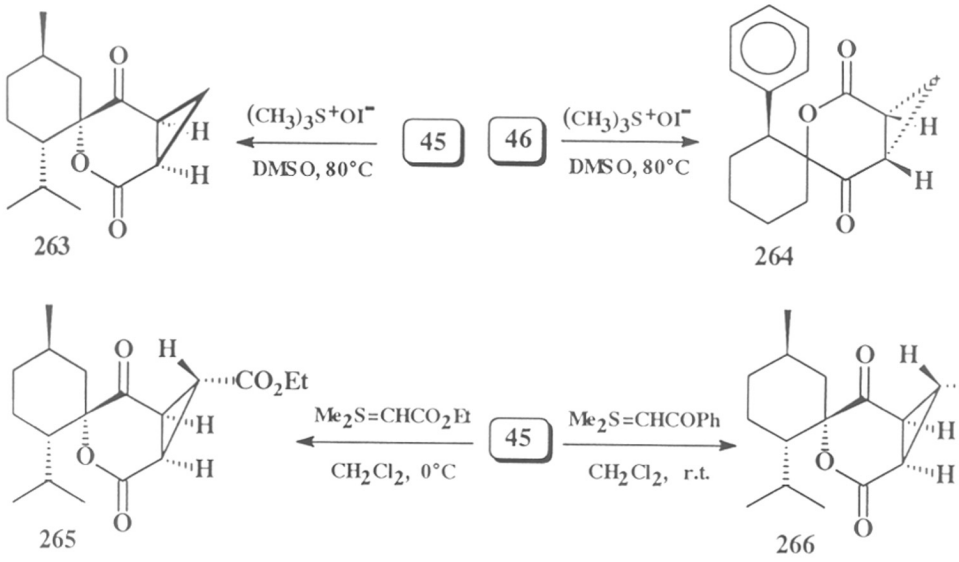


256 257 258 259



260 257 261 262

Scheme-60



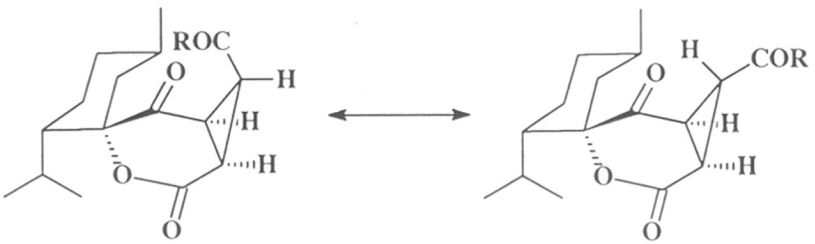
263 264 265 266

and ^{13}C-NMR of **264**). Finally molecular ion peak 270 (M^+, 9%) confirmed the product. Elemental analysis also showed satisfactory values. Once again the stereochemistry at the newly formed chiral centers was assumed on the basis of our study on the Diels-Alder adducts of the chiral synthon **45**.

When **45** was treated with ylides **259** and **262** in CH_2Cl_2, the cyclopropyl adducts were formed in good yields. ^{13}C-NMR of both the adducts showed the presence of single diastereomer.

The stereochemistry at the C2 carbon can be fixed on the basis of the conformation of the compound **265** in the reaction medium and on the stability of the product for steric reasons as shown below in **Fig. 29**.

Fig. 29

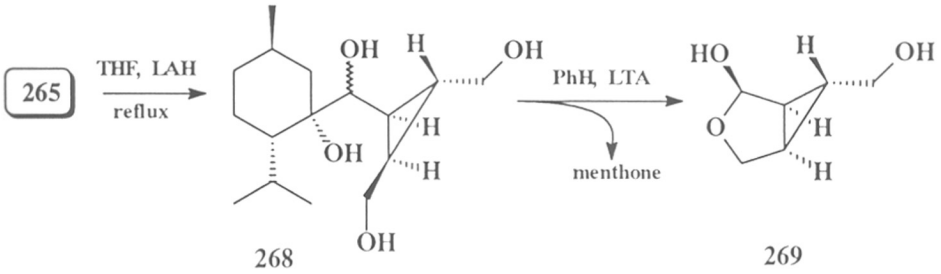


267A 267B

As it is discussed in the **Section 2** the addition will be anti to the isopropyl group. If we look at the possible conformations of the cyclopropanated product **267A** and **267B** it is very obvious that the exo compound **267B** is favoured over **267A** for steric reasons. Thus, it can be concluded that the -COR group will be *syn* to the isopropyl group of menthone.

Our next objective was to detach the chiral auxiliary to get the optically pure compounds which are similar to hemicaronic aldehyde, described in the introduction. Thus, lithium aluminium hydride reduction of **265** in refluxing THF afforded the tetrol **268**, which was further oxidized using lead tetraacetate to give menthone and the lactol **269** in good yield (**Scheme 61**).

Scheme-61



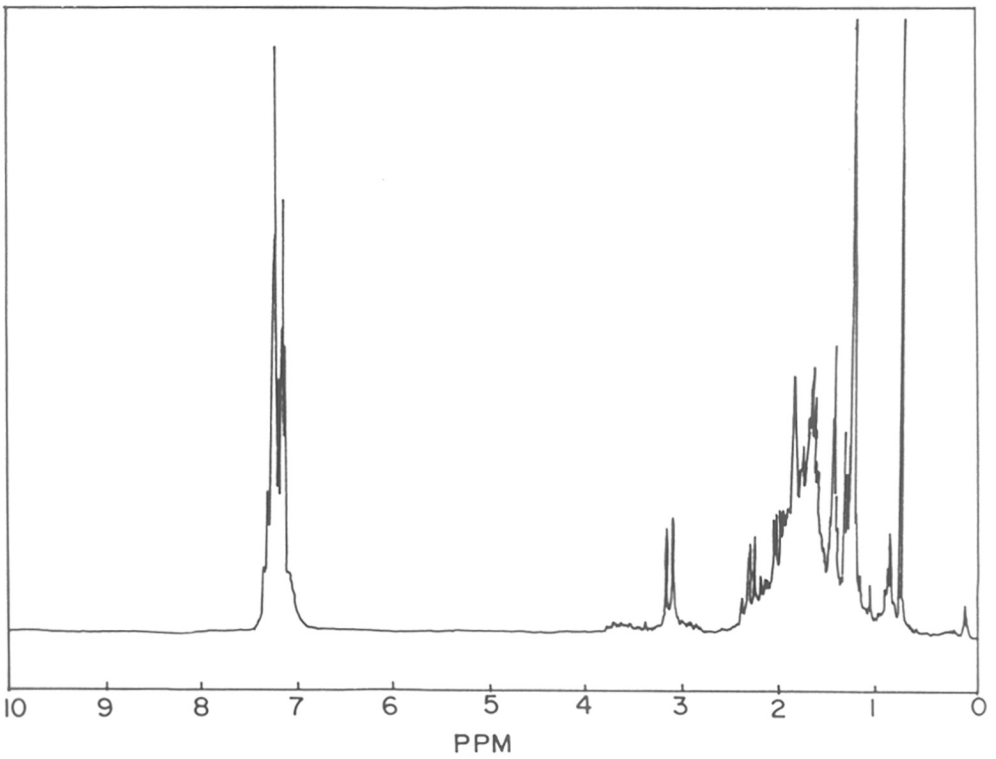
268 269

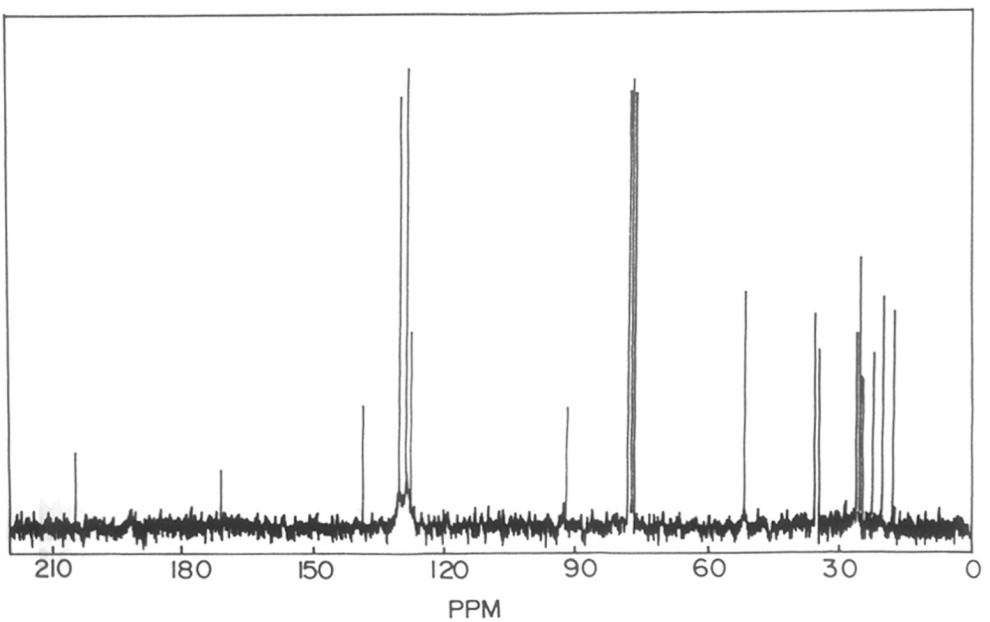
The menthone obtained was checked for its optical purity and found satisfactory. The lactol **269** was found to be insoluble in $CDCl_3$ (also in other chlorinated hydrocarbons). IR spectrum showed a strong broad peak between 3600cm^{-1} and 3015cm^{-1}. In ^{1}H-NMR (acetone-d_6), signals at δ 0.54-0.66(m, 1H) and at δ 1.27-1.43(m, 2H) indicate the cyclopropyl protons, signals at δ 3.20-3.22(m, 2H, -CH_2-OH), δ 3.42-3.50(d, 1H, -O-CH_2-), δ 3.64-3.72(dd, 1H, -O-CH_2-) and δ 4.95(s, 1H, -O-C<u>H</u>-OH) clearly indicate the presence of the product. ^{13}C-NMR showed the presence of a single

diastereomer (at -CH-OH center) where the three cyclopropyl carbons appear at δ 19.75, 21.78 and 26.92 respectively, signals at δ 61.77(-$\underline{C}H_2$-O-),δ 66.34(-$\underline{C}H_2$OH) and a signal at δ 97.15 (-O-$\underline{C}$H-OH) are indicative of the product. Molecular ion peak at 129 (M^+-1, 2%) confirms the product.

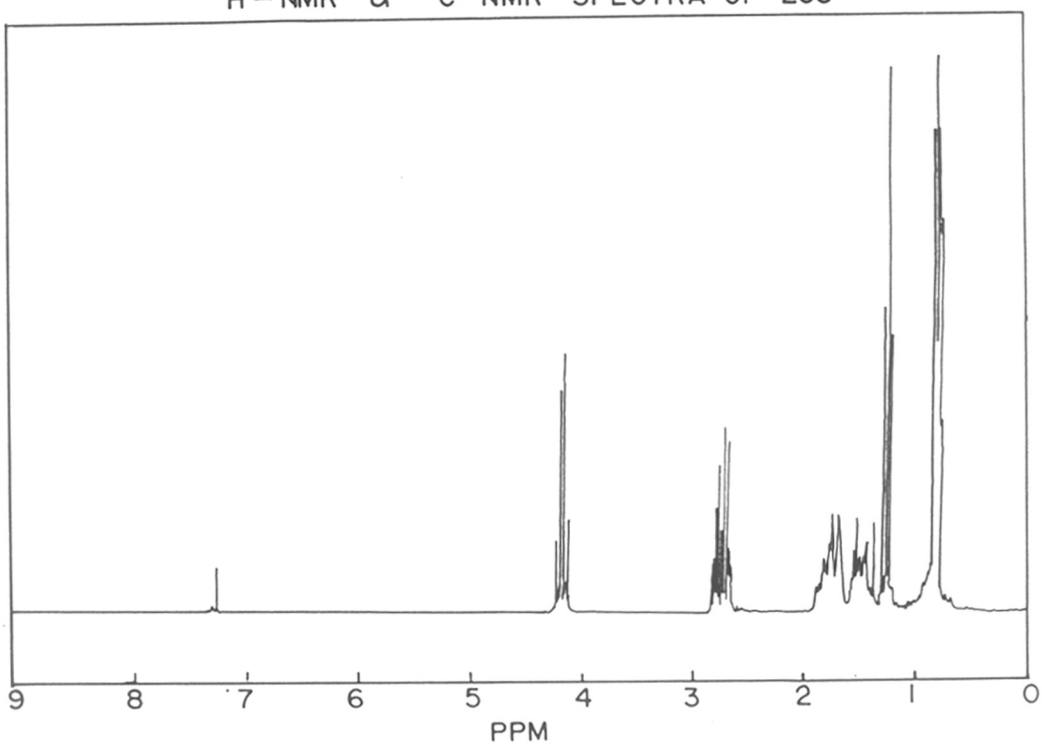
There are three chiral centers in the molecule **269** (all cyclopropyl) and also the lactol carbon which is newly formed. To check the enantiomeric purity of this molecule (also at the lactol carbon even though it is insignificant because it is merely a cyclic form of aldehyde and alcohol groups) chiral shift reagent tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium (III) derivative was used and recorded the proton NMR spectra. Addition of 0.05equiv./wt, 0.1, 0.2, 0.3, 0.4 and 0.5equiv./wt of the shift reagents were used and significant shift was observed when 0.3equiv./wt of the shift reagent was used. All the peaks remained similar with out showing any indication of the other isomer.

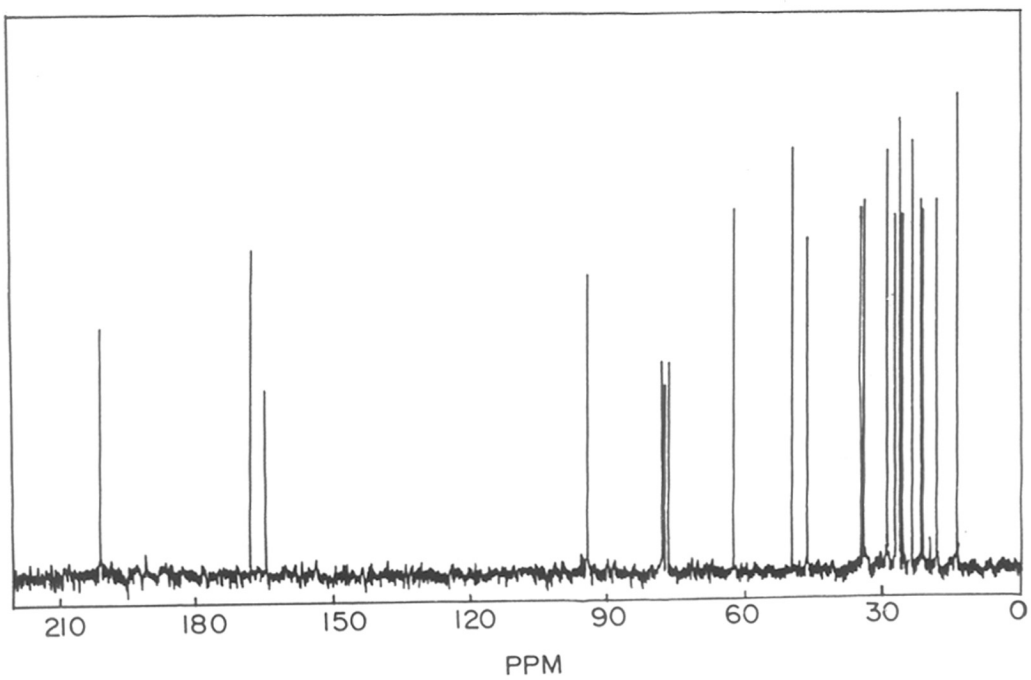
^{1}H – NMR & ^{13}C – NMR SPECTRA OF 264



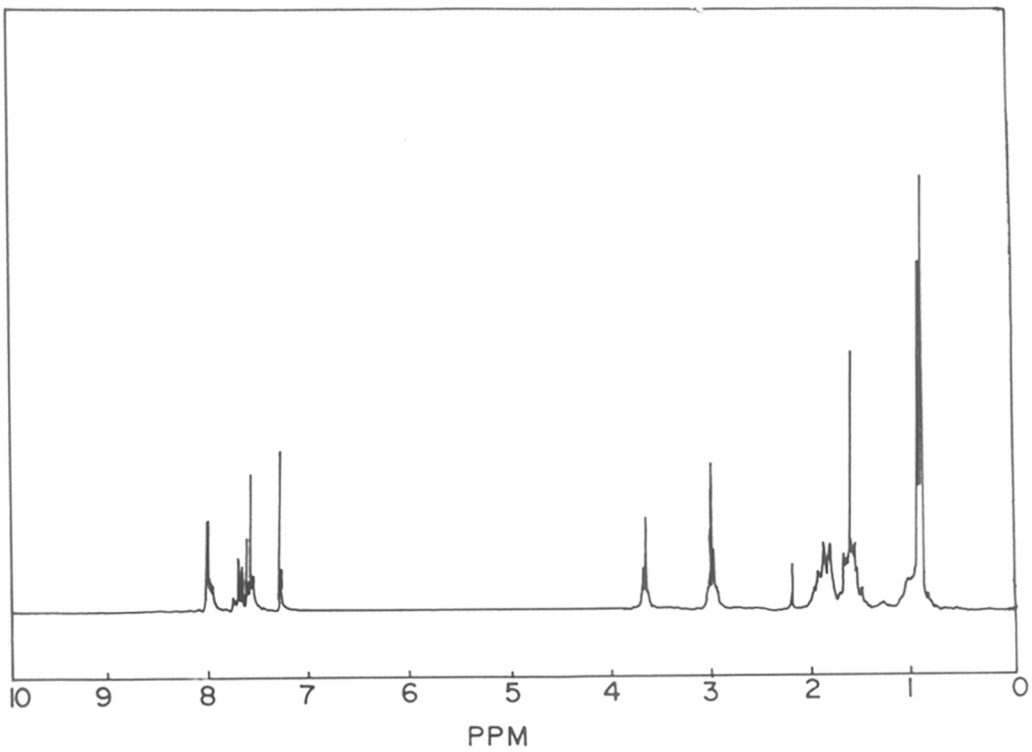


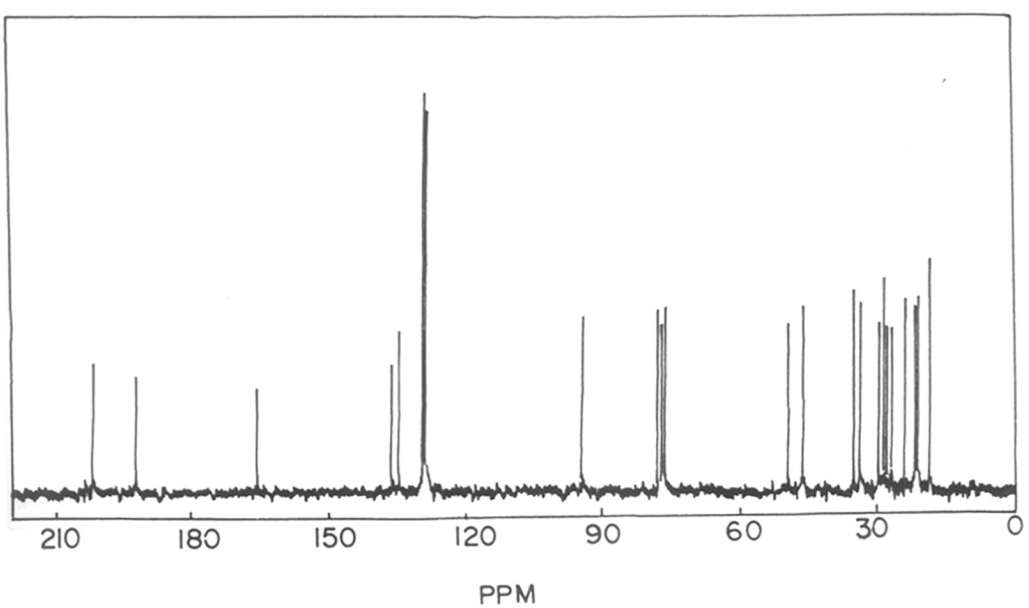
$^{1}H-NMR$ & $^{13}C-NMR$ SPECTRA OF 265



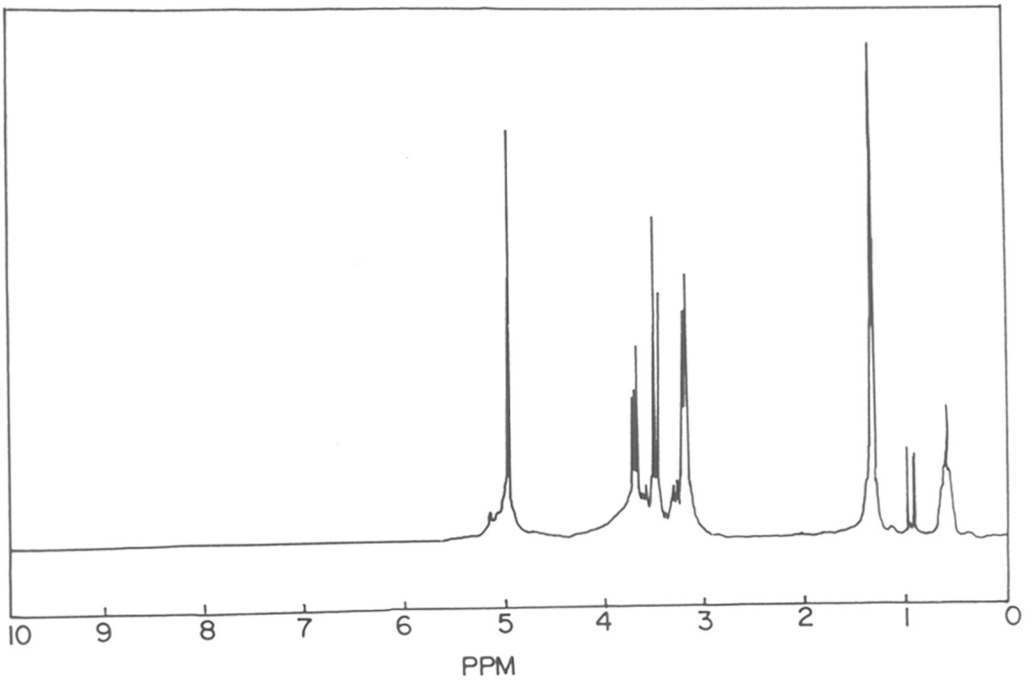


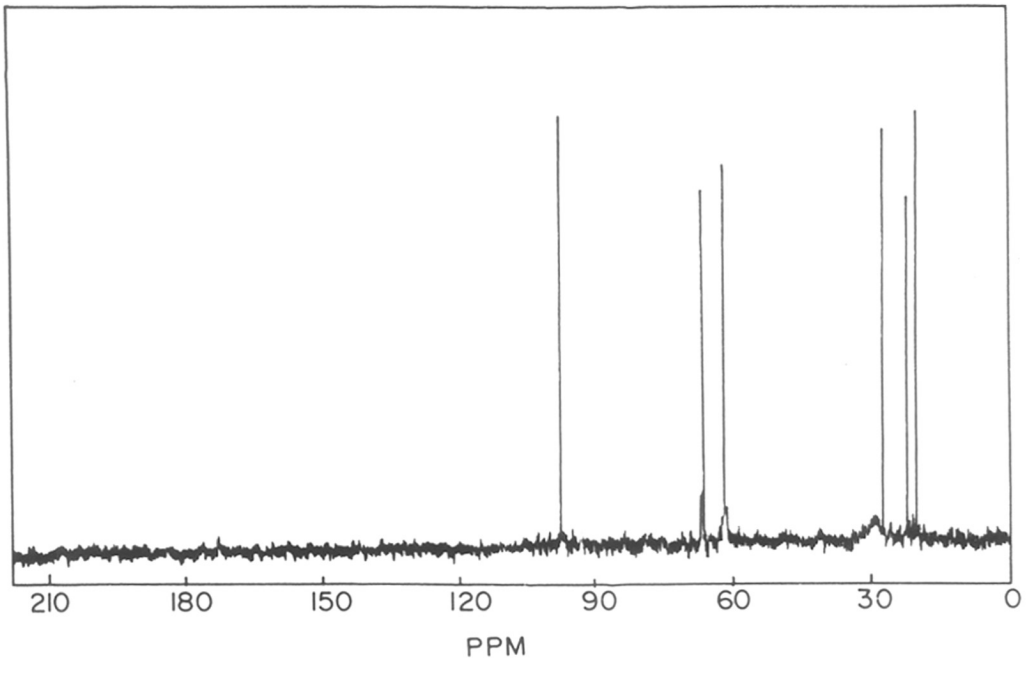
^{1}H – NMR & ^{13}C – NMR SPECTRA OF 266





^{1}H-NMR & ^{13}C-NMR SPECTRA OF 269



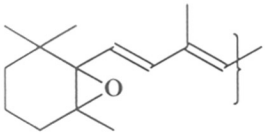


SECTION 5: ASYMMETRIC EPOXIDATION

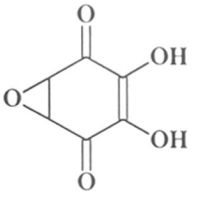
INTRODUCTION

Asymmetric epoxidation is a useful reaction in organic synthesis because the epoxide group is readily opened to produce 1,2-functionality in a stereospecific manner. The susceptibility of the epoxide to nucleophile makes it very versatile in converting it into a number of different useful skeletons. Epoxide function has been identified in many natural products of varying origins. Terpene epoxides, quinone epoxides, macrolides etc. (**Fig. 30**) are typical examples.[76a]

Fig. 30



270



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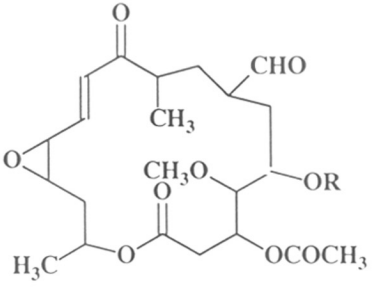
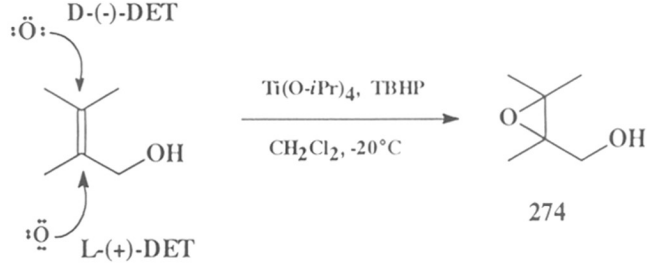


272

The epoxide function can act as a highly reactive double bond where in living systems it may possibly be involved in oxygen transport and storage and detoxification.[76b]

Sharpless et al.[77] in 1980 reported an efficient method for the stereoselective epoxidation of allylic alcohols (**Scheme 62**). D-(-)- or L-(+)-diethyl tartarate along with Ti(O-*i*Pr)$_4$ was used to epoxide the allylic alcohols where *t*-BuO$_2$H was the epoxidizing agent.

Scheme-62



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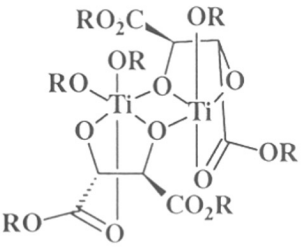
The titanium alkoxide and the chiral ligand used determine the stereochemistry of the product. According to the mechanism proposed by the same authors, the metal catalyst is a dimer consisting of two dialkyl tartarates covalently bound through the hydroxylic functions to two titaniums (**Fig. 31**). During the epoxidation reaction the allyl alcohol and the hydroperoxide are also bound to either of the two equivalent metal centers.

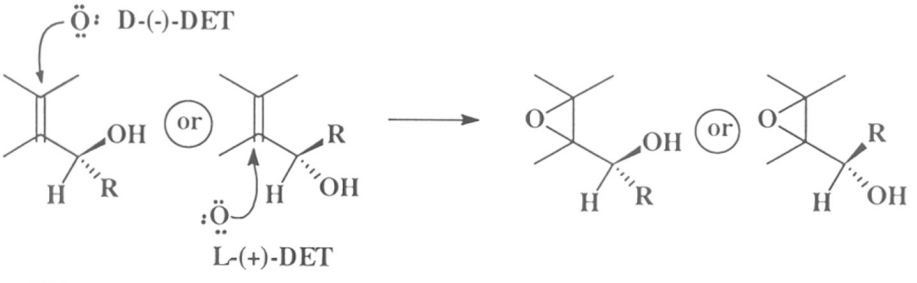
Fig. 31



275 catalyst dimer

For a given tartarate the system delivers the epoxide oxygen from the same enantioface of the olefin regardless of the olefin substitution pattern. When the olefin unit is in the plane of the drawing as shown the use of (+)-tartarate leads to the epoxidation from underside whereas use of (-)-tartarates lead to the epoxidation from the top side. The mechanism of titanium-tartarate induced asymmetric epoxidation and different types of ligands used is reviewed many times in the literature.[78] The same system was later used for the resolution of secondary alcohols kinetically (**Scheme 63**).

Scheme-63

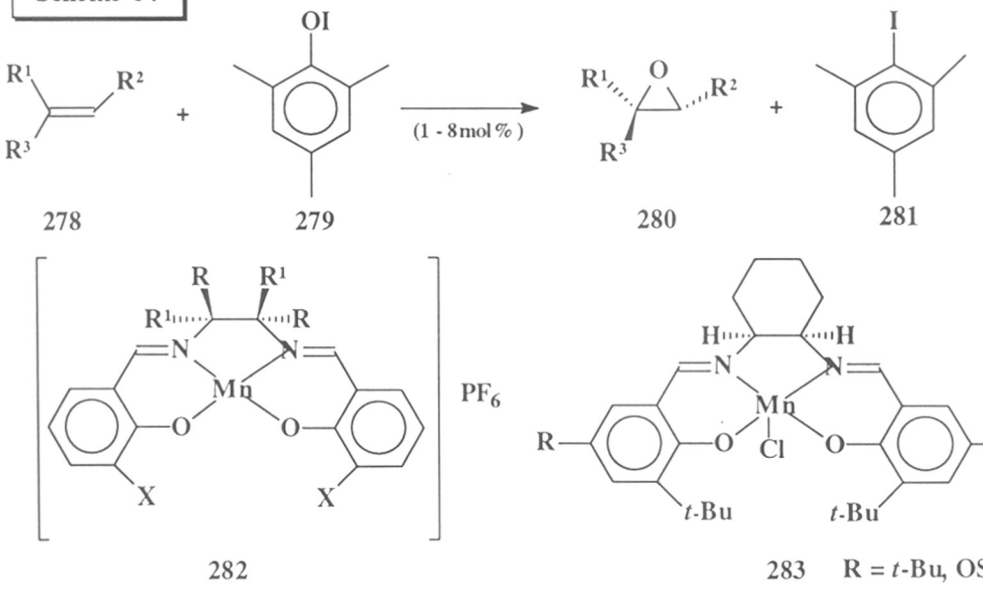


276a **276b** **277a** **277b**

Jacobsen et al.[79] reported the epoxidation of alkyl or aryl substituted olefins with the highest enantioselectivities using Mn complexes of chiral Schiffs bases e.g., **282**, **283** etc. (**Scheme 64**).

Apart from Sharpless's method a few reports are available in the literature for asymmetric epoxidation. In most of the cases a chiral auxiliary (can be catalyst) or enzymes are used to obtain the chiral epoxide. The degree of asymmetric induction depends directly on the chiral auxiliary used. A few of them are briefly mentioned below:

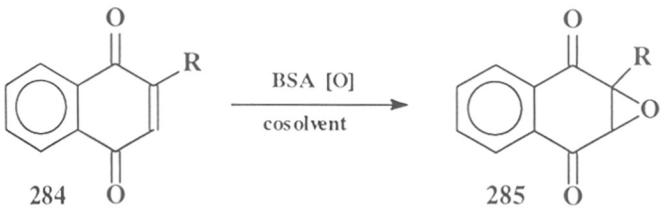
Scheme-64



a) S. Colonna et al.[80]

A strategy for increasing the enantioselectivity in reactions catalyzed by enzymes based on the use of water miscible and water immiscible organic cosolvents. The enzyme bovine serum albumen used could afford epoxides with 90% ee in an optimized solvent mixture (**Scheme 65**).

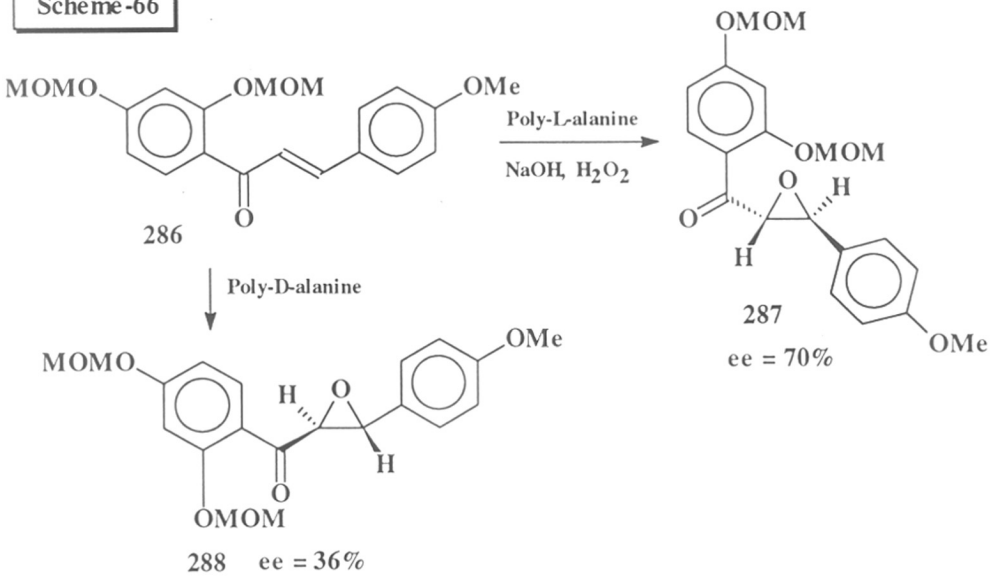
Scheme-65



b) D. Ferreira et al.[81]

Epoxidation of 4-methoxy-2',4'-dimethoxymethyl-(E)-chalcone with H_2O_2 in the presence of poly-L-amino acid catalysts afforded chiral aromatic oxygenated chalcone epoxides (**Scheme 66**).

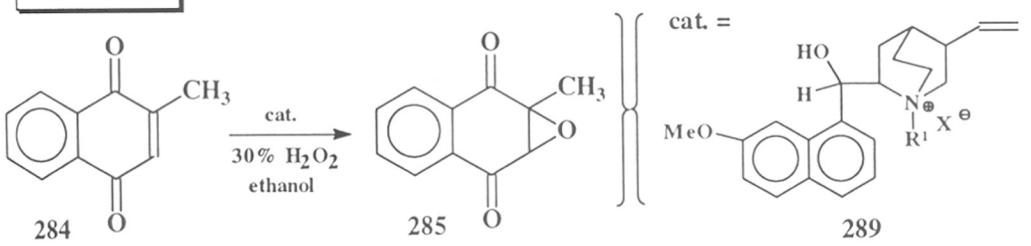
Scheme-66



c) H. Wynberg et al.[82]

Synthesis of optically active epoxides of chalcones was achieved using quaternary ammonium salts (e.g., **289**) derived from alkaloids under phase transfer conditions[82] (**Scheme 67**).

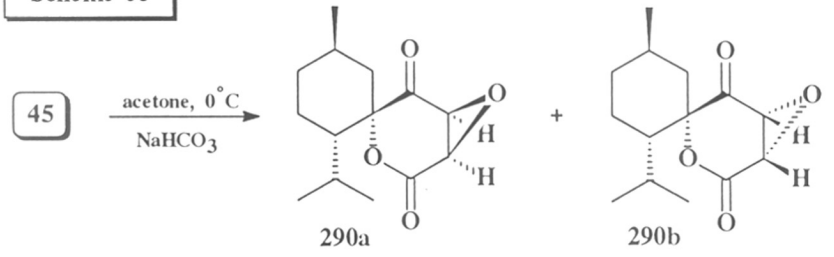
Scheme-67



RESULTS AND DISCUSSION

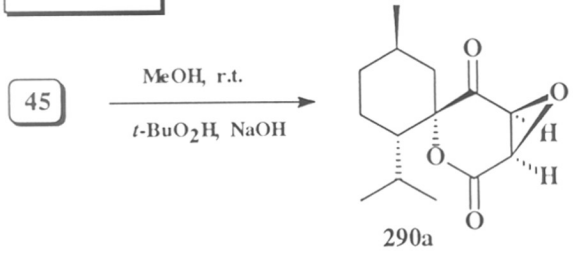
As it is clear from the introduction part that the asymmetric epoxidation involves mainly the use of chiral catalysts (Sharpless: Ti-complexes, Jacobsen: Mn-complexes etc.), where the chiral ligand used in the complexation determines the stereochemistry of the product epoxide. In the case of stereospecific epoxidation of olefins it is normally the groups in the chiral auxiliary which determines the stereochemistry of the epoxide because of many reasons (steric or stereoelectronic effects etc.). As there can be a good stereoelectronic effect by the isopropyl group in **45** with the incoming epoxide oxygen atom a stereospecific anti (to isopropyl) addition is expected. Thus, when **45** was treated with H_2O_2 in acetone using $NaHCO_3$ as the base at 0°C, a diastereomeric mixture (70:30) of products were obtained (**Scheme 68**).

Scheme-68



The compound **290a** was expected to be the major isomer (as explained in Section 2). Different reaction conditions and use of MCPBA failed to yield the product. However, when **45** was treated with *t*-BuOOH in MeOH using NaOH as base at room temperature, the epoxide was obtained as a single diastereomer (**Scheme 69**).

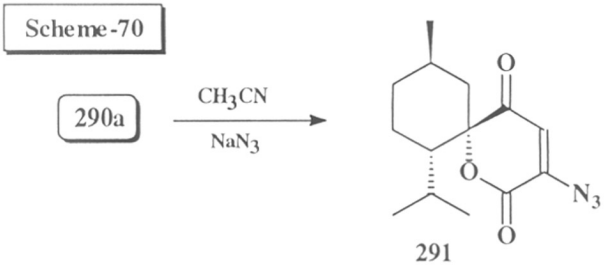
Scheme-69



The compound **290** was characterized as usual. Thus, in ^{1}H-NMR, signals at δ 3.67(d, 1H) and δ 3.90(d, 1H) indicate the epoxide protons. ^{13}C-NMR showed the presence of a single diastereomer and signals at δ 55.19 and δ 52.77 indicate the epoxide carbons (see ^{1}H-NMR and ^{13}C-NMR of **290a**). Finally molecular ion peak 252 (M^{+}, 14%) confirmed the product.

After achieving almost 100% diastereoselection in epoxidation, we attempted its opening with a variety of nucleophiles. As mentioned in the **Section 3** all anionic nucleophiles afforded unisolable products. Thus, allylmagnesium bromide treatment of the epoxide **290** in ether gave number of products. But, when **290** was treated with NaN_3 in acetonitrile at room temperature the product **291** was obtained in good yield. Opening of the epoxide by azide towards the ketone carbonyl followed by dehydration leads to the product as shown below in **Scheme 70**.

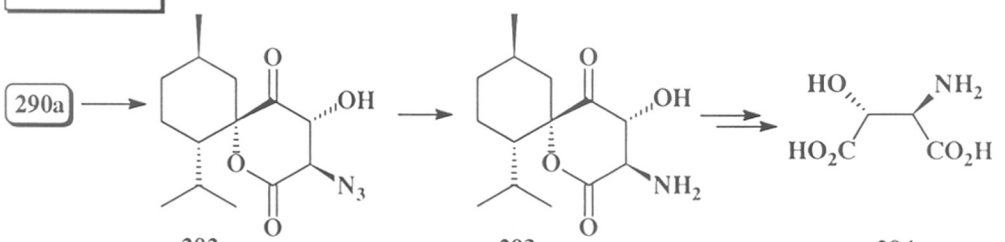
Scheme-70



This unusual dehydration was unexpected. It can be rationalized that the stability of the enone system (conjugation) favours the dehydration reaction. The product **291** was confirmed by all normal spectroscopic methods. Specifically in IR, a strong peak at 2140cm^{-1} was observed. In ^{1}H-NMR a singlet at δ 6.17 corresponding to one proton indicate the dehydrated product. In ^{13}C-NMR signals at δ 144.37(carbon attached to N_3) and δ 114.91 clearly indicate the product. Finally the molecular ion peak 263 (M^+, 15%) in mass spectrum confirmed the product.

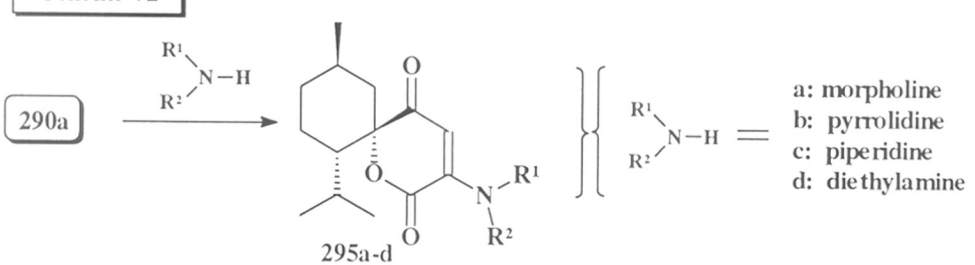
The idea behind the cleavage of the epoxide with azide was to synthesize optically active hydroxy amino acids. Opening of the epoxide with azide followed by reduction could have yielded the amino alcohol **293** and subsequent cleavage of it to α-hydroxy-β-amino acids **294** (**Scheme 71**).

Scheme-71



A number of other nucleophiles were used to cleave the epoxide so as to retain the -OH group which forms after the cleavage. However, all attempts to retain the -OH group failed (**Scheme 72**). Dehydration was found to be a highly efficient process.

Scheme-72



Alternatively, direct reaction of optically pure epoxide with amines was explored. These amine additions were expected finally to afford α-hydroxy-β-amino acids as mentioned earlier. However, all the secondary amines afforded the dehydrated products. Benzylamine, however yielded a mixture of unisolable products. All products **295a-d** were characterized well. Characterization of a typical example of these skeletons is as follows: For **295a**, in IR spectrum strong peaks at 1735cm^{-1}, 1695cm^{-1} and 1610cm^{-1} show the presence of the product. In ^{1}H-NMR, signals at δ 3.10-3.35(m, 4H), δ 3.50-3.70(m, 4H), δ 5.56(s, 1H) clearly indicate the product. In ^{13}-NMR signals at δ 150.75, δ 104.53,

δ 66.39(2C, $-CH_2-N-CH_2-$), δ 48.19 (2C, $-CH_2-O-CH_2-$) are indicative of the product. Finally the molecular ion peak 321(M^+) confirmed the product. In the similar way all other compounds were characterized. The advantage of this dehydration has been taken to synthesize the optically active side chain of taxol and the work is currently under progress in our group. Hydrogenation of these azides and amines, if diastereofacially selective, could lead to interesting optically active skeletons.

CONCLUSIONS

As described in the objectives of this chapter the following conclusions can be drawn.

1 Synthesis of optically pure **45** and **46** was achieved.

2. High reactivity of **45** and **46** towards asymmetric Diels-Alder reactions, Michael additions, cyclopropanations and epoxidation reactions are established.

3. High regio, stereo and enantioselectivities were observed in the above reactions.

4. The structure of some of the key compounds have been confirmed by X-ray studies. Chiral purity was established by mechanistic, optishift reagent and optical rotation arguments. The de was determined by ^{13}C-NMR.

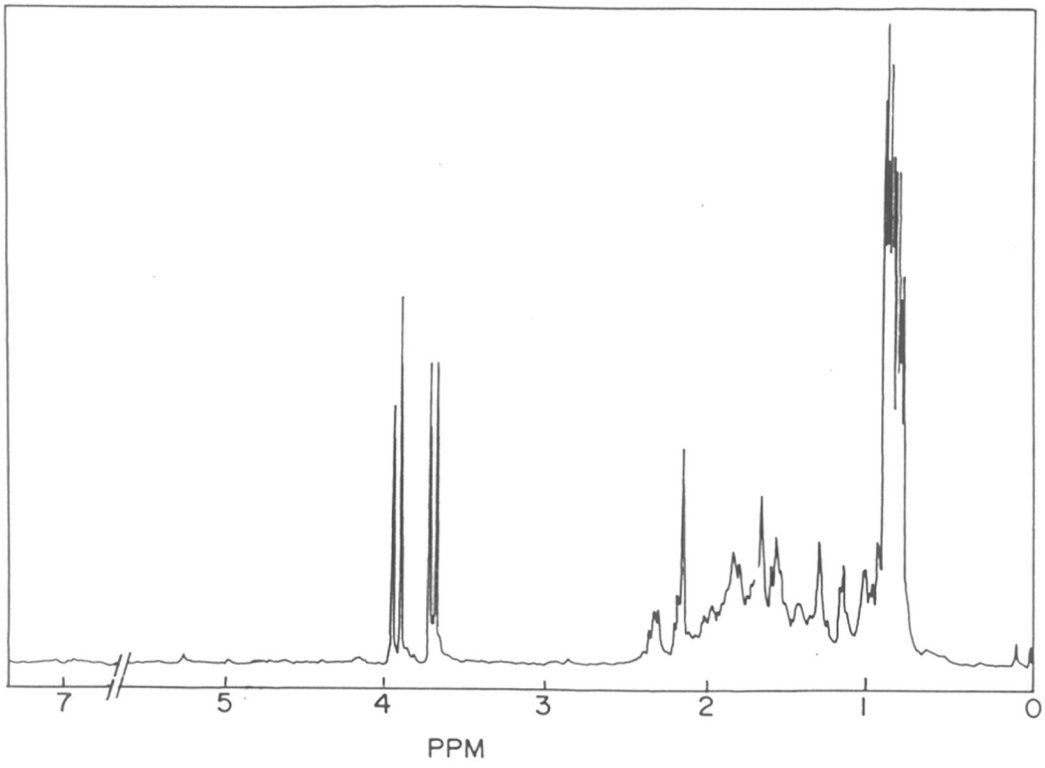
5. A method of releasing the chiral auxiliary was developed.

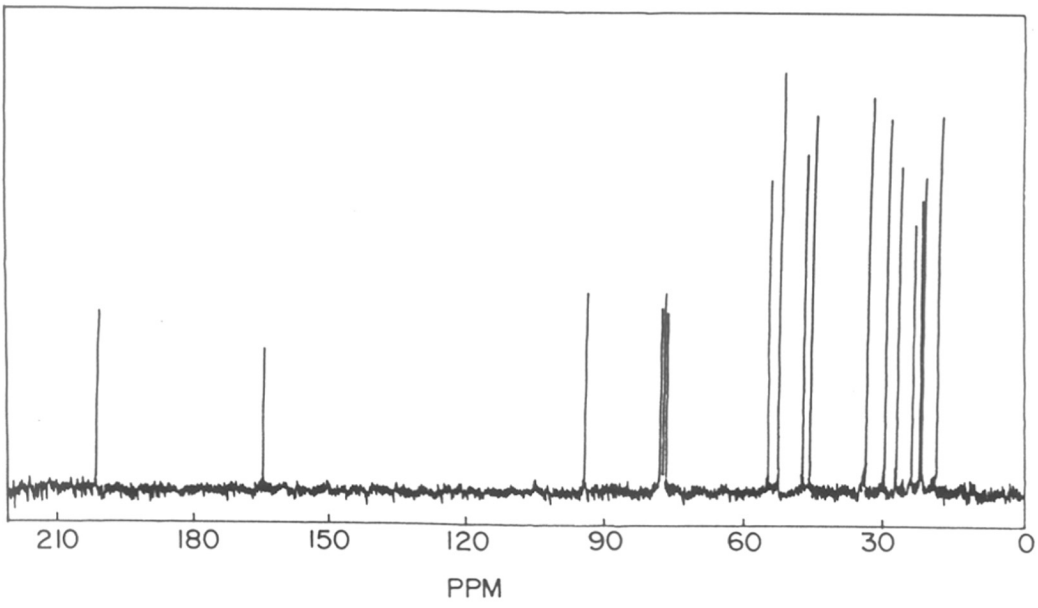
6. Contrary to Feringa's studies unanticipated lack of addition of amines to our system **45** was observed.

7. Unanticipated phenomenon of instability of α-hydroxy azides and α-hydroxy amines was discovered with our skeleton.

8. Chiral skeletons e.g., **140**, **142**, **269** can be synthesized by the above studies.

^{1}H-NMR & ^{13}C-NMR SPECTRA OF 290





EXPERIMENTAL SECTION

SECTION-1

Preparation of *trans*-1-(2-furyl)-menthan-1-ol (54)

To a solution of 4.21ml(58mmol) of freshly distilled furan in anhydrous ether (30ml), was added 29ml(2.0M in *n*-hexane) of *n*-BuLi dropwise under argon atmosphere at a temperature maintained between -10°C to -5°C. The reaction temperature was then allowed to come to room temperature and stirred for 1h. The temperature was then brought down to 0°C and 8.9g(58 mmol) of (-)-menthone **52** was added in 30ml of anhydrous ether dropwise over a period of 30 minutes. The reaction temperature was gradually brought up to room temperature and stirred for 4h. The contents of the flask were then poured into a beaker containing 20ml of saturated ammonium chloride solution and stirred for 15 min. The organic layer was then separated and washed with brine and water (20ml each) and dried over anhydrous Na_2SO_4. Concentration under reduced pressure and column chromatography on silica gel using 98:2 pet. ether:ethyl acetate afforded 11.66g of **54** as an yellow oil.

Yield	95%.
IR (neat)	cm^{-1} 3450(b), 1460(m), 1400(s), 1170(s), 750(m).
^{1}H-NMR (200MHz)	δ 0.77-0.84(d, 3H), 0.86-1.00(m, 6H), 1.05-1.15(m, 1H), 1.47-1.74(m, 5H), 1.75-1.98(m, 3H), 2.41(s, 1H), 6.22-6.30(dd, 1H), 6.33-6.43(dd, 1H), 7.33-7.40(dd, 1H).
^{13}C-NMR (300MHz)	δ 161.14(s), 140.61(d), 110.02(d), 103.90(d), 76.21(s), 48.91(t), 48.77(d), 34.93(t), 27.66(d), 27.39(d), 23.34(q), 22.05(q), 21.17(t), 18.61(q).
MS	m/z 222 (M^+, 8%), 154(6), 137(100), 123(28), 110(27), 99(40), 95(85), 86(21), 81(96), 71(81), 69(48), 55(21).

Preparation of 2-hydroxy-7-isopropyl-10-methyl-1-oxaspiro[5.5]undec-3-en-5-one (55)

To a stirred solution of 3g(19.75mmol) of **54** in anhydrous dichloromethane (40ml) maintained around 10°C, 5.2g(30mmol) of *m*CPBA was added in small portions and stirring was continued at room temperature for 5h. The progress of the reaction was monitored by TLC. The mixture was then cooled to 0°C and the precipitated solid was removed by filtration. The filtrate was washed successively with 25ml of 20% aqueous KI, 30ml of 30% aqueous $Na_2S_2O_3$, 40ml of saturated aqueous $NaHCO_3$ and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was chromatographed on silica gel using 90:10 pet. ether:ethyl acetate to yield 2.37g of **55** as a viscous liquid.

Yield	74%.

IR (neat)	cm^{-1} 3400-3280(b), 1680(s), 1640(s), 1460(s), 1380(m), 1280(m), 1220(w).
^{1}H-NMR (200MHz)	δ 0.80-1.00(m, 9H), 1.02-1.32(m, 1H), 1.44-1.70(m, 4H), 1.72-2.05(m, 3H), 2.20-2.35(m, 1H), 3.25-3.40(br, 1H), 5.65-5.80(m, 1H), 6.05-6.17(dd, 1H), 6.79-6.90(dd, 1H).
^{13}C-NMR (200MHz)	δ 201.27(s), 200.55(s), 147.69, 143.64, 128.21, 126.48, 87.54(s), 87.28, 85.70, 47.46, 46.25, 46.17, 39.94, 34.71, 29.66, 29.40, 27.90, 26.97, 23.76, 22.21, 22.15, 22.08(q), 19.76(q), 19.53(q).
MS	m/z 238 (M^+, 5%), 155(18), 137(20), 111(8), 95(34), 84(100), 81(51), 69(14), 55(8).

Preparation of (6*S*,7*S*,10*R*)-7-Isopropyl-10-methyl-1-oxaspiro[5,5]undec-3-ene-2,5-dione (45)

To an ice cold stirred solution of 2.25g(9.5mmol) of **55** in 40ml of acetone, was added 2.5ml of Jones' reagent [prepared by dissolving 2.7g of CrO_3 in 7ml of water followed by the careful addition of 2.3ml of conc. H_2SO_4] dropwise. After stirring for an additional 30min the inorganic materials were filtered off. The filtrate was concentrated on rotavapor and partitioned between 75ml of ether and 50ml of water. The organic layer was separated, washed with water (3x20ml) and dried over anhydrous Na_2SO_4. Removal of the solvent and subsequent column chromatography on silica gel using 96:4 pet. ether:ethyl acetate afforded 2.20g of **45**. It was further recrystallized from *n*-hexane to give the compound as yellow needles.

Yield	97%.
$[\alpha]_D^{25}$	-53.34 (c=10, $CHCl_3$).
m.p.	107°C.
UV(MeOH)	λ_{max} 360 nm.
IR (Nujol)	cm^{-1} 1730(s), 1690(s), 1630(s), 1470(m), 1380(s), 1320(m), 1260(s), 1250(m).
^{1}H-NMR (200MHz)	δ 0.85(d, 3H), 0.90(d, 3H), 0.93(d, 3H), 0.98-1.15(m, 1H), 1.31-1.48(t, 1H), 1.52-1.75(m, 3H), 1.78-2.05(m, 4H), 6.73(d, 1H), 6.88(d, 1H).
^{13}C-NMR (200MHz)	δ 197.30(s), 160.80(s), 137.62(d), 134.79(d), 93.76(s), 47.97(d), 46.84(t), 34.09(t), 29.45(d), 27.05(d), 23.66(q), 21.81(q), 21.44(t), 18.87(q).
MS	m/z 236 (M^+, 15%), 218(18), 203(16), 190(15), 175(16), 153(22), 137(100), 126(88), 109(50), 99(28), 96(31), 95(88), 91(26).
Analysis	$C_{14}H_{20}O_3$ Calculated C 71.18%, H 8.47%
	Found C 71.13%, H 8.41%

Preparation of Pig Liver Acetone Powder(PLAP)[30a]

Fresh pig liver (1Kg) was homogenized in 4L of cold acetone by using a mixer and the residue was collected by filtration. The residue was further washed with cold acetone (2L) to remove the fatty material as cleanly as possible. The acetone powder thus obtained was dried at room temperature, powdered and sieved to obtain 300g of the fine PLAP.

Cyclohexene oxide (57): This compound was obtained as a colourless liquid and was prepared according to the literature procedure.[83]

Yield	62%.
b.p.	130°C.
^{1}H-NMR (80MHz)	δ 0.90-1.53(m, 4H), 1.86(brs, 4H), 3.10(s, 2H).

Racemic 2-phenylcyclohexanol (58): This compound was prepared according to the literature procedure.[30b]

Yield	89%.
m.p.	56-57°C [Lit.[30b] 57-58°C].
^{1}H-NMR (80MHz)	δ 1.26-1.53(m, 4H), 1.63(s, 1H), 1.76(m, 1H), 1.84(m, 2H), 2.12(m, 1H), 2.43(dt, 1H), 3.64(dt, 1H), 7.13-7.39(m, 5H).

Racemic 2-Phenylcyclohexyl acetate (59): This compound was prepared according to the literature procedure.[30b]

Yield	93%.
IR(neat)	cm^{-1} 3070(s), 2940(s), 1730(s), 1610(s), 1490(m).
^{1}H-NMR (90MHz)	1.25-1.70(m, 4H), 1.8(s, 3H), 1.85-2.05(m, 3H), 2.10-2.20(m, 1H), 2.60-2.77(td, 1H), 4.95-5.07(m, 1H), 7.15-7.35(m, 5H).

Enzymatic hydrolysis of Racemic 2-phenylcyclohexyl acetate (59)

In a 2L round bottomed flask 13g of 2-phenylcyclohexyl acetate **59** was taken in 65ml of acetone along with 500ml of buffer [Na_2HPO_4 + NaH_2PO_4] of pH 8 and stirred for 1h. To this, was added 2g of PLAP and the mixture was stirred for 5 days at room temperature (~25°C). The stirring was continued for another 5 days with 0.6g of additional amount of PLAP. Added 300ml of diethyl ether and enough sodium chloride to the above mixture and stirred for 15min. PLAP was filtered through cotton, the organic layer separated and the aqueous layer was extracted repeatedly with ether. The organic layer

was dried over anhydrous Na_2SO_4 and concentrated. The column chromatography on silica gel using 95:5 pet. ether:ethyl acetate afforded 5.05g(96%) of pure (-) isomer **60** and 5.91(91%) of the acetate **61**. The acetate was then hydrolysed using KOH to give 4.29g(90%) of the (+) isomer **63**.

(-)-(1*R*,2*S*)-*trans*-2-phenylcyclohexanol (60)

$[\alpha]_D^{25}$	-58.02 (c=10, MeOH)
m.p.	63-65°C [Lit.[30b] 64-65°C]

(+)-(1*S*,2*R*)-*trans*-2-phenylcyclohexanol (63)

$[\alpha]_D^{25}$	+57.43 (c=10, MeOH)
m.p.	60-61°C [Lit.[30b] 60-62°C]

(-)-2-Phenylcyclohexanone (62)

In a round bottomed flask 5.28g(17.6mmol) of $Na_2Cr_2O_7$ and 18ml of water was taken. Added slowly 4.5ml of conc. H_2SO_4 and the flask was cooled to 15°C. Added in portions 4.5g(25mmol) of (-)-2-phenylcyclohexanol **60** at 15°C with stirring. The reaction mixture was stirred for an additional 30min at room temperature. Added 100ml of water and extracted the reaction mixture with CH_2Cl_2 repeatedly. The extract was washed repeatedly with water and dried over anhydrous Na_2SO_4. Column chromatography on silica gel using 97:3 pet. ether:ethyl acetate afforded 3.7g of **62** as colourless low melting solid.

Yield	83%.
m.p.	37-38°C (lit.[84] 38-39°C).
$[\alpha]_D^{25}$	-112.8 (c=0.5, C_6H_6).
IR(nujol)	cm^{-1} 1700(s), 1450(s).
^{1}H-NMR (80MHz)	δ 1.75-2.40(m, 6H), 2.46-2.65(m, 2H), 3.07-3.71(dd, 1H), 7.13-7.18(m, 2H), 7.25-7.45(m, 3H).

Preparation of 1-(2-furyl)-2-phenylcyclohexan-1-ol (64)

(For procedure see **54**) Reaction time: 5h., the crude product was chromatographed using 80:20 pet. ether:ethyl acetate solvent mixture to obtain the pure product as a brown oil.

Yield	85%.
IR(neat)	cm^{-1} 3540(b), 3025(m), 2940(s), 2860(m), 1620(m), 1500(s), 1450(s).
^{1}H-NMR (80MHz)	δ 1.20-2.33(m,8H), 2.90-3.20(dd, 1H), 5.66-5.78(dd, 1H), 6.00-6.10(dd, 1H), 6.80-7.30(m, 6H).

MS m/z 242(M^+, 53%), 224(18), 165(25), 151(23), 130(50), 123(100), 110(50), 95(21).

Preparation of 2-hydroxy-7-phenyl-1-oxaspiro[5.5]undec-3-en-5-one (65)

(For procedure see **55**) Reaction time: 6h., the crude product was chromatographed using 70:30 pet. ether:ethyl acetate solvent mixture to obtain the pure product as a highly viscous liquid.

Yield 84%.

IR(neat) cm^{-1} 3420(b), 3020(s), 2940(m), 1690(s), 1615(w), 1450(m), 1240(s).

^{1}H-NMR (200MHz) δ 1.45-1.95(m, 8H), 3.10-3.35(bm, 2H), 5.65-5.75(m, 1H), 5.77-5.90(dd, 1H), 6.60-6.75(dd, 1H), 7.10-7.45(m, 5H).

MS m/z 258(M^+, 11%), 240(8), 212(7), 175(14), 130(34), 110(40), 91(53), 84(100), 55(62).

Synthesis of (6*R*, 7*R*)-7-phenyl-1-oxaspiro[5.5]undec-3-en-2,5-dione (46)

(For procedure see **45**) Reaction time: 30min., the crude product was chromatographed on silica gel using 95:5 pet. ether:ethyl acetate to obtain the pure product as pale yellow solid.

Yield 95%.

m.p. 97°C.

$[\alpha]_D^{25}$ +74.9 (c=10, $CHCl_3$).

IR(nujol) cm^{-1} 2910(s), 2860(s), 1735(s), 1690(s), 1625(m), 1470(s), 1385(m), 1330(s), 1310(s).

^{1}H-NMR (200MHz) δ 1.45-1.65(m, 1H), 1.68-1.80(m, 2H), 1.85-2.10(m, 4H), 2.12-2.22(dd, 1H), 3.10-3.20(dd, 1H), 6.20-6.27(d, 1H), 6.35-6.42(d, 1H), 7.05-7.15(m, 2H), 7.17-7.29(m, 3H).

^{13}C-NMR (200MHz) δ 196.31(s), 160.57(s), 139.46(s), 137.20(d), 134.39(d), 128.96(d), 128.79(d), 127.73(d), 91.28(s), 51.46(d), 35.80(t), 26.82(t), 25.51(t), 20.02(t).

MS m/z 256 (M^+, 14%), 212(86), 165(20), 139(92), 131(76), 126(100), 117(68), 104(23), 91(53), 82(27).

Analysis $C_{16}H_{16}O_3$ Calculated C, 75; H, 6.25

Found C, 75.13; H, 6.27

SECTION-2

General procedure for Diels-Alder reaction of 45

To a stirred solution of 1g(4.23mmol) of **45** in dry toluene was added 0.6g(8.46mmol) of cyclopentadiene **115** and the solution was cooled to 0°C. Added 6.35ml of 1M solution of Et_2AlCl in toluene dropwise to the above solution and the reaction mixture was stirred for 3h followed by dropwise addition of 50ml of saturated NH_4Cl and stirred for 10min. The organic layer was separated and the aqueous layer extracted with 20ml of ether. The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. Concentration on rotavapor and column chromatography on silica gel using 93:7 pet. ether:ethyl acetate afforded 1.23g of **116**. It was further recrystallized using pet. ether to give colourless crystals.

Yield	96%.
$[\alpha]_D^{25}$	-61.3 (c=10, $CHCl_3$).
m.p.	154°C.
IR(nujol)	cm^{-1} 2910(s), 2860(s), 1750(s), 1710(s), 1460(s), 1380(s), 1240(m).
^{1}H-NMR (200MHz)	δ 0.80-0.90(m, 9H), 1.25-1.80(m, 1H), 3.02-3.12(dd, 1H), 3.35-3.45(dd, 1H), 3.57(bs, 1H), 3.65(bs, 1H), 6.16-6.21(m, 1H), 6.30-6.36(m, 1H).
^{13}C-NMR (200MHz)	δ 210.05(s), 169.84(s), 137.36(d), 136.89(d), 94.24(s), 49.95(d), 49.62(d), 49.27(d), 49.09(d), 48.92(t), 44.52(t), 42.97(d), 34.12(t), 28.82(d), 26.50(d), 23.81(q), 21.99(q), 20.72(t), 18.08(q).
MS	m/z 302 (M^+, 0.8%), 274(0.5), 236(2), 148(42), 120(100), 91(71), 55(55).
Analysis	Calculated C, 75.50% H, 8.60%
	Found C, 75.54% H, 8.63%

118: Reaction time: 2h, the crude product was chromatographed on silica gel using 96:4 pet. ether:ethyl acetate to obtain **118** as colourless crystals.

Yield	95%.
$[\alpha]_D^{23}$	-41.84 (c=5, $CHCl_3$).
m.p.	134°C.
IR(nujol)	cm^{-1} 1740(s), 1730(s), 1450(s), 1380(s), 1280(m), 1260(s), 1240(m).
^{1}H-NMR (200MHz)	δ 0.85-0.95(m, 9H), 1.53-1.70(m, 12H), 1.70-1.88(m, 7H), 2.92-3.02(q, 1H), 3.14-3.25(q, 1H)
^{13}C-NMR (200MHz)	δ 209.83(s), 171.21(s), 123.32(d), 122.78(d), 93.59(s), 49.63(d), 46.13(t), 44.64(d), 38.16(d), 34.20(t), 30.67(t), 28.65(d), 28.50(t), 26.84(d), 23.62(q), 21.85(q), 19.86(t), 18.88(q, 2C), 17.43(q).

MS m/z 318 (M^+, 5.5%) 275(10), 181(3.5), 165(4), 152(35), 123(41), 108(100), 93(93), 55(83).

120: Reaction time: 3h, the crude product was chromatographed on silica gel using 95:5 pet. ether:ethyl acetate to obtain **120** as colourless crystals.

Yield 80%.

m.p. 100-102°C.

IR($CHCl_3$) 1745(s), 1720(s). 1465(s), 1380(s), 1280(m), 1240(s).

^{1}H-NMR (200MHz) δ 0.85-1.00(m, 9H), 1.35(d, 3H), 1.52-1.90(m, 13H), 2.30-2.50(m, 2H), 3.06(td, 1H), 3.25-3.40(m, 1H), 5.35(d, 1H).

^{13}C-NMR (200MHz) δ 209.33(s), 172.25(s), 128.61(d), 126.19(d), 92.63(s), 50.18(d), 47.90(d), 45.05(t), 40.98(d), 34.27(t), 30.94(d), 29.61(t), 28.27(d), 26.88(d), 23.44(d), 23.06(d), 21.93(q), 19.79(q), 18.09(t), 17.41(q).

MS 319 (M^+, 2%), 275(12), 260(4.5), 232(7), 138(18), 109(99), 84(99), 69(83), 55(100).

123: Reaction time: 1.5h, the crude product was chromatographed on silica gel using 93:7 pet. ether:ethyl acetate to obtain **123** as colourless viscous liquid.

Yield 82%.

IR($CHCl_3$) cm^{-1} 1745(s), 1735(s), 1715(s), 1450(m), 1365(s), 1325(s), 1205(m).

^{1}H-NMR (200MHz) δ 0.72(d, 3H), 0.80-0.88(m, 6H), 1.45-1.67(m, 3H), 1.70-2.05(m, 4H), 2.28-2.52(m, 4H), 2.56(d, 1H), 2.63(t, 1H), 2.75(t, 1H), 2.82-2.88(m, 1H), 2.95(t, 1H), 3.02(t, 1H).

^{13}C-NMR (200MHz) δ 207.01(s), 206.78(s), 168.93(s), 94.40(s), 46.84(d), 46.13(t), 42.50(d), 41.55(t), 40.63(d), 38.71(t), 33.86(t), 29.31(d), 26.99(d), 23.90(t), 23.79(q), 21.63(q), 20.12(t), 17.40(q).

MS m/z 306 (M^+, 6%), 278(9), 155(62), 112(90), 90(100), 83(53), 69(51), 55(97).

125: Reaction time 5h, the crude product was chromatographed on silica gel using 90:10 pet. ether:ethyl acetate to obtain **125** as colourless viscous liquid.

Yield 87%.

IR(neat) cm^{-1} 1740(s), 1720(s), 1470(m), 1450(m), 1370(w), 1200(m), 1140(m).

^{1}H-NMR (200MHz) δ 0.76-0.90(m, 9H), 1.45-1.70(m, 4H), 1.70-2.00(m, 5H), 2.67(d, 2H).

^{13}C-NMR (200MHz)	δ 208.74(s), 171.27(s), 137.64(d), 134.81(d), 94.06(s), 47.81(d), 45.94(t), 40.06(d), 38.91(t), 34.21(t), 29.15(d), 27.04(d), 24.52(t), 23.88(q), 21.90(d), 20.25(t), 17.70(q), 11.05(q).
MS	m/z 496 (M^+).

Cleavage of the Diels-Alder adduct 116

To a suspension of 0.251g(6.63mmol) of LAH in 100ml of anhydrous THF was added a solution of 1g(3.31mmol) of **116** in anhydrous THF at room temperature. The reaction mixture was refluxed for 3h and subsequently quenched with ethyl acetate followed by dropwise addition of water. The upper liquid layer was decanted and the separated solid was removed. The organic layer was separated and the aqueous layer was extracted repeatedly with ether (3x25ml). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. Concentration on rotavapor and column chromatography on silica gel using 88:12 pet. ether:ethyl acetate afforded 0.89g of **139** as white solid. It was further recrystallized using 98:2 pet. ether:ethyl acetate to give colourless crystals.

Yield	87%.
$[\alpha]_D^{27}$	-13.8 (c=5, $CHCl_3$).
m.p.	114°C.
IR(Nujol)	cm^{-1} 3350(b), 2950(b), 1465(s), 1445(s), 1220(w).
^{1}H-NMR (200MHz)	δ 0.80-0.95 (m, 9H), 1.32-1.80 (m, 11H), 2.58-2.65 (m, 3H), 2.76 (bs, 1H), 3.05 (bs, 1H), 3.65-3.83 (d, 2H), 5.97-6.05 (m, 1H), 6.20-6.28 (m, 1H).
^{13}C-NMR (200MHz)	δ 136.10(d), 134.50(d), 77.51(d), 63.50(t), 49.68(t), 47.50(d), 46.79(d), 46.22(d), 46.13(d), 45.79(d), 35.07(t, 2C), 28.35(d), 25.69(d), 23.63(d), 22.83(q), 20.60(t), 18.41(q, 2C).
MS	m/z 308 (M^+, 1%), 167(1.34), 155(92), 137(40), 124(21), 106(12), 95(55), 81(100), 69(52), 55(42).

Cleavage of the triol 139

To a stirred solution of 0.5g(1.62mmol) of triol **139** in dry benzene was added 0.899g(2.03mmol) of lead tetraacetate portionwise at 0°C. The reaction mixture was stirred for an additional 5min. The precipitate formed was filtered and the benzene solution was concentrated. Column chromatography on silica gel using 85:15 pet. ether:ethyl acetate gave 0.21g (83.46%) of optically pure menthone and 0.195g of the lactol **140** as colourless viscous liquid.

Yield	79%.
$[\alpha]_D^{25}$	+23.44 (c=2.5, $CHCl_3$).
IR($CHCl_3$)	cm^{-1} 3390(b), 2900(s), 2870(m), 1251(w), 1085(m), 1045(s), 995(s).

^{1}H-NMR (200MHz)	δ 1.30-1.45(m, 2H), 2.80-3.02(m, 4H), 3.38-3.45(dd, 2H), 3.90-4.00(q, 1H), 4.95(s, 1H), 6.02-6.09(m, 1H), 6.14-6.20(m, 1H).
^{13}C-NMR (200MHz)	δ 136.29(d), 135.51(d), 65.06(t), 55.45(d), 46.91(t), 44.30(d, 2C), 44.20(d), 43.71(d).
MS	m/z 152 (M^+, 2%), 135(4), 122(3), 105(3.8), 91(15.4), 66(100).

Cleavage of the adduct 118

The triol **141** obtained after the LAH reduction of **118** was directly subjected LTA oxidation. The crude product obtained was chromatographed on silica gel using 94:6 pet. ether:ethyl acetate to obtain the product **142** as viscous colourless liquid.

Yield	97.5%.
$[\alpha]_D^{27}$	-59.47 (c=9.5, $CHCl_3$).
IR(neat)	cm^{-1} 3400(b), 2900(b).
^{1}H-NMR (200MHz)	δ 1.62(s, 6H), 1.74-1.92(m, 2H), 2.05(t, 1H), 2.14-2.26(m, 3H), 2.56-2.75(m, 1H), 3.58(t, 1H), 4.10(t, 1H), 5.15(d, 1H).
^{13}C-NMR (200MHz)	δ 123.32(s, 2C), 103.37(d), 72.18(t), 42.64(d), 33.94(d), 30.48(t), 29.93(d), 19.03(q, 2C).
MS	m/z 168 (M^+, 11%), 150(17), 121(26), 107(100), 91(94), 79(78), 67(42), 55(30).

Cleavage of 116 using LiOH-H_2O_2 system[85]

Dissolved 0.20g(0.64mmol) of **116** in 10ml of 5:1 mixture of THF:H_2O and cooled to 0°C. LiOH (15mg, 0.64mmol) and H_2O_2 (73μl, 30%, 0.64mmol) were added dropwise at 0°C to the above solution and the mixture was stirred for 30min. Reaction was brought to room temperature and stirred for additional 1h. The solvent was removed and the residue was extracted repeatedly with chloroform. The organic layer was dried over anhydrous Na_2SO_4. Column chromatography on silica gel using 80:20 $CHCl_3$:MeOH afforded 90mg(90%) of optically pure menthone and 104mg of **137** respectively.

Yield	88%.
IR(nujol)	cm^{-1} 3500(b), 2940(s), 2860(s), 1780(s), 1725(s), 1650(m), 1480(s), 1370(s).
^{1}H-NMR (200MHz, acetone-d_6)	δ 1.60-1.80(m, 2H), 2.20-2.35(dd, 2H), 2.55-2.65(dd, 1H), 2.77-2.91(m, 1H), 4.05(d, 1H), 4.25(d, 1H).
^{13}C-NMR (200MHz, acetone-d_6)	δ 175.51(s), 171.08(s), 86.24(d), 58.69(d), 47.50(d), 46.81(d), 46.58(d), 39.03(d), 33.48(t).

MS m/z 198(M^+).

Diels Alder reaction of 46 with cyclopentadiene 115

In a dry two necked 50ml round bottomed flask with septum and nitrogen balloon placed 0.11g(0.43mmol) of **46** and 0.172g(2.14mmol) of **115** in 10ml of CH_2Cl_2. The flask was cooled to -78°C (chloroform and liq. nitrogen) and 0.05ml of BF_3-Et_2O in 3ml of CH_2Cl_2 was added to the above solution dropwise. The reaction mixture was stirred for 1h at -78°C and for 2h at room temperature. The saturated $NaHCO_3$ solution was then added to the above solution and stirred for 5min. The solution was extrated repeatedly with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4 and concentrated on rotavapour. Column chromatography on silica gel using 94:6 pet. ether:ethyl acetate yielded 0.13g of **130** as colourless oil.

Yield	90%.		
$[\alpha]_D^{25}$	+16.6 (c=11, $CHCl_3$).		
IR(neat)	cm^{-1} 1750(s), 1710(s), 1455(s), 1350(m), 1250(s).		
^{1}H-NMR (200 MHz)	δ 0.98-1.08(dd, 1H), 1.22-1.47(m, 2H), 1.55-1.73(m, 4H), 1.75-2.05(m 4H), 2.12-2.25(dt, 1H), 2.82-2.95(dd, 1H), 3.26-3.40(m, 2H), 6.00-6.10(m 1H), 6.14-6.22(m, 1H), 7.07-7.18(m, 2H), 7.21-7.35(m, 3H).		
^{13}C-NMR (200 MHz)	δ 208.83(s), 169.81(s), 139.22(s), 136.48(2C, d), 129.52(2C, d), 128.82(2C, d), 127.91(d), 91.51(s), 52.01(d), 48.90(d), 48.37(t), 42.27(d), 33.91(t), 26.76(t), 25.38(t), 19.78(t).		
MS	m/z 322 (M_+, 5%), 256(29), 212(85), 165(20), 148(33), 139(71), 130(100), 120(71), 91(98).		
Analysis	$C_{21}H_{22}O_3$	Calculated	C, 78.2; H, 6.83
		Found	C, 78.31; H, 6.78

SECTION 3:

Typical procedure for the Michael addition of heterocycles to 45

To a stirred solution of 0.2g(0.847mmol) of **45** and 0.136g(1.69mmol) of *N*-methylpyrrole in dry toluene, was added 1.3ml of 1M (in toluene) diethylaluminium chloride dropwise at 0°C. The reaction was slowly brought to room temperature and stirred for 2h. Added 10ml of saturated ammonium chloride solution cautiously and the organic layer was separated. The aqueous layer was extracted with 20ml of ether. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. Column chromatography on silica gel using 95:5 pet. ether:ethyl acetate afforded 140mg of **212b** as viscous yellow liquid.

Yield 53%.

$[\alpha]_D^{25}$	-7.2 (c=10, $CHCl_3$).
IR ($CHCl_3$)	cm^{-1} 2950(s), 1730(s), 1710(s), 1440(m), 1290(s), 1120(s).
^{1}H-NMR (200MHz)	δ 0.77-0.84(dd, 3H), 0.90-1.00(dd, 6H), 1.36-1.46(dd, 1H), 1,53-1.90(m, 8H), 2.95-3.25(dq, 2H), 3.74(s, 3H), 4.17-4.25(t, 1H), 5.90-5.95(dd, 1H), 6.05-6.10(dd, 1H), 6.64-6.70(t, 1H).
^{13}C-NMR (200MHz)	δ208.53(s), 168.23(s), 126.39(s), 124.08(d), 107.99(d), 107.23(d), 94.37(s), 48.61(q), 45.61(t), 40.39(t), 37.73(d), 34.62(d), 34.09(t), 29.00(d), 26.93(d), 23.72(q), 21.81(q), 19.92(t), 17.66(q).
MS	m/z 317 (M^+, 7.5%), 134(2), 123(2.5), 107(100), 95(12), 81(8), 69(6), 55(13).

211: Reaction time: 2h., the crude product was chromatographed on silica gel using 88:12 pet. ether:ethyl acetate to obtain **211** as colourless needles.

Yield	66%.
$[\alpha]_D^{25}$	-30.8 (c=5.6, $CHCl_3$).
IR ($CHCl_3$)	cm^{-1} 3390 (bs),2940(s), 1710(s), 1680(s), 1630(m), 1440(m), 1270(w), 1210(s), 1120(s), 900(s).
^{1}H-NMR (200 MHz)	δ 0.65-0.70(d, 3H), 0.90-1,03(m, 6H), 1.25-1.37(m, 1H), 1.45-1.90(m, 7H), 2.30-2.55(m, 1H), 3.03-3.35(dq, 2H), 4.50-4.60(t, 1H), 6.95-7.00(d, 1H), 7.15-7.40(m, 3H), 7.83-7.90(d, 1H), 8.40-8.50(bs, 1H).
^{13}C-NMR (200MHz)	δ 209.78(s), 169.66(s), 136.64(s), 126.17(s), 122.93(d), 122.59(d), 120.36(d), 119.88(d), 111.66(d), 110.78(s), 84.25(s), 48.88(d), 45.26(t), 41.52(t), 37.97(d), 24.16(t), 29.09(d), 26.09(d), 26.94(d), 23.84(q), 22.79(q), 21.81(t), 20.08(q).
MS	m/z 353 (M^+, 9%), 259(1), 143(100), 130(3), 115(10).

212a: Reaction time: 3h., the crude product was chromatographed on silica gel using 97:3 pet. ether:ethyl acetate to obtain **212a** as brown oil.

Yield	75%.
IR ($CHCl_3$)	cm^{-1} 3400(b), 2950(b), 1730(s), 1715(s), 1635(m), 1550(m), 1420(m).
^{1}H-NMR (200MHz)	δ 0.65-1.10(m, 9H), 1.40-1.95(m, 10H), 3.00-3.30(m, 2H), 6.05(d, 1H), 6.12-6.27(m, 1H). 6.86(t, 1H), 8.71(bs, 1H).

^{13}C-NMR (200MHz)	δ207.97(s), 169.77(s), 124.08(s), 118.73(d), 108.13(d), 106.52(d), 93.95(s), 47.32(d), 44.53(t), 39.48(t), 37.20(d), 33.90(t), 28.73(d), 26.72(d), 23.52(q), 21.58(q), 19.99(t), 17.84(q).
MS	m/z 303 (M^+, 2%), 137(2) 123(4), 93(100), 67(11), 55(17).

210: Reaction time: 2.5h., the crude product was chromatographed on silica gel using 98:2 pet. ether:ethyl acetate to obtain **210** as colourless oil.

Yield	92%.
IR ($CHCl_3$)	cm^{-1} 1780(s), 1760(s), 1600(m), 1490(s), 1410(m), 1340(m), 1310(m), 1230(s).
^{1}H-NMR (200MHz)	δ0.72-1.00(m, 9H), 1.22-1.50(m, 2H), 1.50-1.67(m, 3H), 1.70-1.90(m, 4H), 2.27 (d, 3H), 2.87-3.23(m, 2H), [4.10(dd), 4.26(t), 1H)], 5.90-5.96(m, 1H), 6.15(dd, 1H).
^{13}C-NMR (200MHz)	δ207.56(s), 166.77(s), 152.51(s), 146.07(s), 108.99(d), 106.74(d), 93.96(s), 48.44(d), 44.52(t), 39.71(d), 39.44(t), 33.88(t), 28.71(d), 26.57(d), 23.50(q), 21.63(q), 19.96(t), 17.69(q), 13.29(q).
MS	m/z 318 (M^+, 7.5%), 231(4), 178(4), 162(14), 155(17), 137(27), 123(93), 108(100), 55(26).

Addition of thiophenol to 45

To a stirred solution of 0.1g(0.4237mmol) of **45** and 0.093g(0.8474mmol) of thiophenol in anhydrous THF, was added 4 drops of triethylamine at room temperature. The reaction mixture was stirred for 10h at room temperature. The solvent was removed under reduced pressure and to the residue 20ml of CH_2Cl_2 and 20ml of 2N NaOH solution were added and the organic layer was separated. The organic layer was repeatedly washed with 2N NaOH, dried over anhydrous Na_2SO_4 and concentrated. Column chromatography on silica gel using 95:5 pet. ether:ethyl acetate afforded 0.125g of **208** as colourless oil.

Yield	86%.
IR(neat)	cm^{-1} 1750(s), 1725(s), 1590(w), 1450(s), 1370(w), 1280(m), 1240(m), 1140(s).
^{1}H-NMR (200MHz)	δ0.82-0.97(m, 9H), 1.53-1.97(m, 9H), 2.75-3.26(m, 2H), 4.04-4.13(m, 1H), 7.30-7.40(m, 3H), 7.45-7.55(m, 2H).
^{13}C-NMR (200MHz)	δ202.78(s), 166.87(s), 134.12(d), 133.24(d, 2C), 129.38(d, 2C), 128.76(s), 93.38(s), 50.84(d), 48.04(d), 45.70(t), 34.46(t), 34.02(t), 29.16(d), 27.04(d), 23.67(q), 21.74(q), 19.79(t), 17.64(q).

MS m/z 346 (M^+, 24%), 218(14), 185(2), 109(36), 82(100), 69(31), 55(33).

SECTION 4:

Corey's ylide 255 was prepared according to the literature procedure.[86]

Preparation of dimethylphenacyl sulfonium bromide[87] (261)

To a solution of 9.95g(0.05mol) of phenacyl bromide **260** in 25ml of acetone, 3.7g(0.06mol) of dimethylsulphide **257** was added and the mixture was kept at 20°C for 24h. The white solid separated was filtered and dried (10.5g, 80%).

Preparation of dimethylsulfonium phenacylide (262)

To an ice cold solution of 20g sodium hydroxide in 250ml of water, 26g(0.1mol) of dimethylphenacylsulfonium bromide **261** was added in portion. The mixture was stirred at the same temperature until all the solid dissolved. Then it was extracted with chloroform and the organic layer washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave colourless solid which was crystallized from 1:2 mixture of $CHCl_3$:CCl_4 to give the ylide **262** as colourless solid (13.3g, 74%, m.p. 79°C).

Preparation of carbethoxymethyl dimethylsulfonium bromide (258)

A solution of 16.7g(0.1mol) of ethyl bromoacetate **256** and 7.75g(0.125mol) of dimethylsulphide **257** in 50ml of acetone was allowed to stand at room temperature for 72h with occasional stirring. The white solid separated was filtered, washed with acetone and dried to get 19.4g (81%) of **258**. m.p. 77-79°C (lit.[87] 78-80°C).

Preparation of ethyl(dimethylsulfuranilidene)acetate (259)

A solution of 11.45g(0.05mol) of sulfonium bromide **258** in 50ml of chloroform was stirred vigorously at 5-10°C and treated in one portion with a mixture of 42ml of super saturated K_2CO_3 solution and 4.5ml of 12.5N NaOH solution. The reaction mixture was stirred at that temperature for an additional 15min at 20°C. The salt formed was filtered, the chloroform upper layer separated and dried over anhydrous K_2CO_3. Removal of the solvent at 20°C gave 6.85g(92%) of the ylide **259** as light yellow liquid.

Cyclopropanation of 46 using 255

In a 100ml two necked round bottomed blask with a septum and nitrogen balloon placed 1.03g(4.68mmol) of Corey's ylide **255** and 0.057g(2.34mmol) of NaH. Added 10ml of dry DMSO with stirring at room temperature. A vigorous reaction was observed and it was stirred till a clear solution was formed. Added dropwise a solution of 0.4g(1.56mmol) of **46** in 5ml of DMSO while a change of colour from colourless to dark red was observed. The reaction mixture was heated for 6h at 75°C and poured into 100g of ice in a beaker. Added 10g of NaCl and the reaction mixture was

extrated repeatedly with chloroform. Chloroform layer was washed repeatedly with water to remove DMSO completely, dried over anhydrous Na_2SO_4 and concentrated. Column chromatography on silica gel using 90:10 pet. ether:ethyl acetate afforded 0.23g of **264** as brown oil.

Yield	40%.
$[\alpha]_D^{25}$	+15.28 (c=4.2, $CHCl_3$).
IR($CHCl_3$)	cm^{-1} 3025(m), 2960(s), 2880(m), 1750(s), 1715(s), 1502(m), 1460(s), 1350(s), 1295(s).
^{1}H-NMR (200MHz)	δ 0.70(s, 1H), 1.20(s, 1H), 1.35-1.45(m, 2H), 1.50-2.02(m, 7H), 2.17-2.28(dd, 1H), 3.02-3.14(dd, 1H), 7.05-7.30(m, 5H).
^{13}C-NMR (200MHz)	δ204.31(s), 170.78(s), 138.08(s), 130.08(d), 128.61(d), 127.71(d), 91.92(s), 51.59(d), 35.61(t), 34.77(d), 26.18(t), 25.54(t), 22.28(t), 20.15(t), 17.74(d).
MS	m/z 270 (M^+, 9%), 186(18), 175(54), 130(100), 115(35), 104(17), 91(41).
Analysis	$C_{17}H_{18}O_3$ Calculated C, 75.5; H, 6.66
	Found C, 75.67; H, 6.73

263: Reaction time: 1h, the crude product was chromatographed on silica gel using 95:5 pet. ether:ethyl acetate to afford **263** as colourless viscous liquid.

Yield	60%.
IR(nujol)	cm^{-1} 1740(s), 1710(s), 1380(m).
^{1}H-NMR (200MHz)	δ 0.65-1.10(m, 9H), 1.26-1.96(m, 11H), 2.30-2.55(m, 2H).
^{13}C-NMR (200MHz)	δ 203.58(s), 167.81(s), 93.69(s), 49.04(d), 46.14(t), 33.66(t), 28.66(d), 27.99(d), 26.63(d), 23.70(d), 21.55(q), 21.26(t), 20.41(q), 18.41(q), 14.83(t).
MS	m/z 250 (M^+, 7%), 178(4), 165(4), 155(100), 137(30), 112(6).

Cyclopropanation of 45 using 259

Dissolved 0.3g (1.27mmol) of **45** in 5ml of anhydrous CH_2Cl_2 and was cooled to 0°C. Added dropwise 0.235g(1.59mmol) of **259** in 3ml of anhydrous CH_2Cl_2 and stirred the reaction mixture at 0°C for 2h. Removal of the solvent on rotavapor and column chromatography on silica gel using 95:5 pet. ether:ethyl acetate afforded 0.318g of **265** as colourless viscous liquid.

Yield	78%.
$[\alpha]_D^{25}$	-22.08 (c=13.5, $CHCl_3$).
IR($CHCl_3$)	cm^{-1} 1745(s), 1700(s), 1445(m), 1270(s), 1190(s).

^{1}H-NMR (200MHz)	δ 0.77-0.87(m, 9H), 1.20-1.30(t, 3H), 1.36-1.60(m, 4H), 1.66-1.89(m, 5H), 2.65-2.85(m, 3H), 4.13-4.25(q, 2H).
^{13}C-NMR (200MHz)	δ 200.68(s), 167.57(s), 164.61(s), 94.09(s), 62.29(t), 49.30(d), 45.92(t), 33.69(t), 33.59(d), 28.75(d), 27.20(d), 26.64(d), 26.40(d), 23.76(q), 21.57(q), 21.32(t), 18.44(q), 13.89(q).
MS	m/z 322 (M^+).

266: Reaction time: 3h, the crude product was chromatographed on silica gel using 96:4 pet. ether:ethyl acetate to afford **266** as colourless oil.

Yield	90%.
m.p.	176°C.
$[\alpha]_D^{25}$	-43.85 (c=8, $CHCl_3$).
IR(nujol)	cm^{-1}1470(s), 1725(s), 1680(s), 1600(s), 1450(s), 1280(s), 1225(s).
^{1}H-NMR (200MHz)	δ 0.75-1.10(m, 9H), 1.46-1.67(m, 5H), 1.74-1.97(m, 4H), 2.92-3.06(m, 2H), 3.60-3.68(t, 1H), 7.52-7.74(m, 3H), 7.95-8.00(d, 2H).
^{13}C-NMR (200MHz)	δ 201.42(s), 191.94(s), 165.28(s), 136.07(s), 134.44(d), 129.16(d, 2C), 128.62(d, 2C), 94.43(s), 49.76(d), 46.36(t), 35.37(d), 33.93(t), 29.83(d), 28.90(d), 28.21(d), 26.93(d), 24.04(q), 21.90(q), 21.47(t), 18.69(q).
MS	m/z 354 (M^+).

Cleavage of 265

Followed the procedure as mentioned in **Section 2** (for **140**). The triol obtained was oxidized further to menthone and **269** using LTA in benzene. The product **269** was obtained as viscous colourless liquid.

Yield	91%.
$[\alpha]_D^{25}$	-62.15 (c=13, MeOH).
IR(neat)	cm^{-1} 3660-3015 (bs).
^{1}H-NMR (200MHz, acetone-d_6)	δ 0.54-0.66(m, 1H), 1.27-1.43(m, 2H), 3.10-3.22(m, 2H), 3.42-3.50(d, 1H), 3.64-3.72(dd, 1H), 4.95(s, 1H).
^{13}C-NMR (200MHz, acetone-d_6)	δ 97.15(d), 66.34(t), 61.77(t), 26.92(d), 21.78(d), 19.75(d).
MS	m/z 129 (M^+, 2%), 113(3), 99(19), 83(44), 69(70), 55(100).

SECTION 5:

Epoxidation of 45

1. Using H_2O_2

Dissolved 1g(4.23mmol) of **45** in 50ml of acetone and cooled to 0°C. To this, was added 3ml of 20% $NaHCO_3$ solution followed by 1ml(8.5mmol) of 30% H_2O_2 and the reaction mixture was stirred at 0°C for 30min. Acetone was removed on rotavapor, 20ml of $NaHSO_3$ solution was addded and extracted with ether (20ml x 3). Removal of the solvent and column chromatography on silica gel using 90:10 pet. ether:ethyl acetate afforded 1.030g of the epoxide (**290a+290b**) as colourless viscous liquid.

Yield	96%.
IR(neat)	cm^{-1} 1750(s), 1710(s), 1485(s), 1380(s), 1260(m).
^{1}H-NMR (90MHz)	δ 0.76-0.90(m, 9H), 0.95-1.18(m, 1H), 1.22-1.45(m, 1H), 1.47-1.73(m, 3H), 1.75-2.00(m, 3H), 2.10-2.35(m, 1H), 3.67(d, 1H), 3.90(d, 1H).
^{13}C-NMR (200MHz)	δ 200.98(s), 164.32(s), 93.95(s), 55.19(d), 52.77(d), 47.37(d), 45.83(t), 33.85(t), 29.77(d), 27.21(d), 23.90(q), 21.87(t), 21.80(q), 18.80(q).
MS	m/z 252 (M^+, 14%), 208(48), 165(43), 154(45), 139(99), 112(100).

2. Using *t*-BuOOH

To a stirred solution of 0.2g(0.8474mmol) of **45** in 10ml of MeOH was added 1.7ml of 0.05M solution of NaOH followed by 0.2ml of 70% *t*-BuOOH dropwise at room temperature and stirred the reaction mixture for 4h. The solvent was removed and the residue was extracted with ether repeatedly, dried over anhydrous Na_2SO_4 and concentrated. Column chromatography on silica gel using 95:5 pet. ether:ethyl acetate afforded 0.225g of **290a** as colourless viscous liquid.

Yield	96%.
$[\alpha]_D^{25}$	+ 41.97 (c=8, $CHCl_3$).

Cleavage of the epoxide **290a** with NaN_3

To an ice cold solution of 0.2g(0.79mmol) of epoxide **290a** in 10ml of dioxane, was added 0.103g(1.58mmol) of NaN_3 in 3ml of water dropwise with stirring. The reaction mixture was stirred for 5h and concentrated. Added 20ml of water, extracted the reaction mixture with ether (3x20ml) and dried over Na_2SO_4. Concentration on rotavapor and column chromatography on silica gel using 98:2 pet. ether:ethyl acetate afforded 0.185g of **291** as yellow viscous liquid.

Yield	77%.
IR($CHCl_3$)	cm^{-1} 2140(s), 1735(s), 1700(s), 1620(s), 1460(m), 1370(s), 1270(s), 1255(s), 1235(s).

^{1}H-NMR (200MHz)	δ 0.76-0.95(m, 9H), 1.15.1.40(m, 1H), 1.45-1.66(m, 4H), 1.70-2.05(m, 4H), 6.17(s, 1H).
^{13}C-NMR (200MHz)	δ 193.90(s), 160.95(s), 144.37(s), 114.91(d), 92.10(s), 48.28(d), 47.28(t), 34.02(t), 29.76(d), 27.34(d), 23.69(d), 21.90(t), 21.74(q), 19.02(q).
MS	m/z 277 (M^+, 11%), 260(26), 232(42), 154(59), 109(95), 84(95), 55(100).

Typical procedure for amine addition to 290a

The epoxide **290a** (0.15g, 0.59mmol) and morpholine (0.094g, 1.19mmol) were stirred neat for 20h.[88] Added 15ml of saturated NH_4Cl solution and the reaction mixture was extracted with ether (3x10ml), washed with water and dried over anhydrous Na_2SO_4. Concentration on rotavapour and column chromatography on silica gel using 80:20 pet. ether:ethyl acetate afforded 0.135g of **295a** as yellow oil.

Yield	72%.
IR($CHCl_3$)	cm^{-1} 1740(s), 1700(s), 1600(s), 1455(m), 1400(w), 1290(s), 1249(m).
^{1}H-NMR (80MHz)	δ 0.65-0.87(m, 9H), 1.10-1.30(m, 3H), 1.40-1.95(m, 6H), 3.10-3.35(m, 4H), 3.50-3.70(m, 4H), 5.56(s, 1H).
^{13}C-NMR (200MHz)	δ 195.12(s), 163.36(s), 150.75(s), 104.53(d), 90.88(s), 66.39(t, 2C), 48.19(t, 2C), 47.41(d), 46.80(t), 34.25(t), 29.55(d), 27.64(d), 23.80(q), 21.96(q), 21.74(t), 19.03(q).
MS	m/z 320 (M^+).

295b: Reaction time: 5h, the crude product was chromatographed on silica gel using 90:10 mixture of pet. ether:ethyl acetate to afford pure **295b** as brown oil.

Yield	82%.
IR($CHCl_3$)	cm^{-1} 1710(s), 1690(s), 1610(s), 1480(s), 1460(m), 1360(s), 1210(s).
^{1}H-NMR (200MHz)	δ 0.73-1.00(m, 9H), 1.12-1.40(m, 4H), 1.43-1.55(m, 3H), 1.66-1.80(m, 2H), 1.85-2.13(m, 4H), 3.40-3.65(m, 4H), 5.98(s, 1H).
^{13}C-NMR (200MHz)	δ 203.42(s), 169.48(s), 164.35(s), 93.43(d), 83.53(s), 46.57(t), 45.97(d), 45.51(t), 44.40(t), 34.64(t), 29.68(d), 27.51(d), 25.92(t), 25.66(t), 24.34)q), 23.12(t), 22.30(q), 19.23(q).
MS	m/z 305 (M^+).

295c: Reaction time: 5h, the crude product was chromatographed on silica gel using 90:10 mixture of pet. ether:ethyl acetate to afford **295c** as yellow oil.

Yield	65%.
IR($CHCl_3$)	cm^{-1} 1720(s), 1690(s), 1600(s), 1460(s), 1300(m), 1240(s).
^{1}H-NMR (200MHz)	δ 0.80-1.00(m, 9H), 1.12-1.28(m, 2H), 1.40-1.80(m, 10H), 1.85-2.00(m, 3H), 3.20-3.42(m, 4H), 5.65(s, 1H).
^{13}C-NMR (200MHz)	δ 195.31(s), 164.01(s), 151.11(s), 102.56(d), 90.40(s), 49.37(t, 2C), 47.22(d), 46.79(t), 34.27(t), 29.44(d), 27.61(d), 25.60(t, 2C), 24.68(t), 24.37(q), 21.93(q), 20.90(t), 19.29(q).
MS	m/z 319 (M^+).

295d: Reaction time: 10h, the crude product was chromatographed on silica gel using 80:20 mixture of pet. ether:ethyl acetate to afford **295d** as brown oil.

Yield	87%.
IR($CHCl_3$)	cm^{-1} 1730(s), 1690(s), 1600(s), 1480(m), 1450(s), 1400(m), 1420(m), 1330(m), 1280(m), 1250(s).
^{1}H-NMR (200MHz)	δ 0.80-0.95(m, 9H), 1.10-1.30(m, 6H), 1.50-1.77(m, 4H), 1.70-1.82(m, 2H), 1.85-2.00(m, 3H), 3.30-3.45(m, 4H), 5.44(s, 1H).
^{13}C-NMR (200MHz)	δ 195.41(s), 164.23(s), 147.70(s), 96.93(d), 89.86(s), 47.21(d), 46.59(t), 45.94(t, 2C), 34.16(t), 29.31(d), 27.49(d), 23.56(q), 21.83(t), 21.79(q), 18.87(q), 12.66(q, 2C)
MS	m/z 307 (M^+).

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CHAPTER - 2

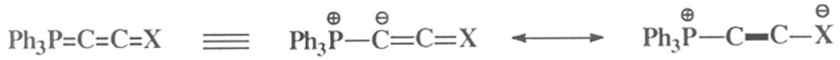
SYNTHESIS AND APPLICATIONS OF PHOSPHACUMULENE YLIDE TOWARDS BIORELEVANT MOLECULES

INTRODUCTION

PHOSPHACUMULENE YLIDES

Organophosphorus chemistry has made significant contributions towards the development of newer methodologies. The discovery of Wittig reaction followed by its varied synthetic applications exemplifies the importance of this area. In this series of organophosphorus reagents, phosphacumulene ylides are one of the recent arrivals. They are nucleophilic and versatile reagents. They can be described by the two principal resonance structures[1] **1A** and **1B** as shown below:

Fig. 1



1 **1A** **1B**

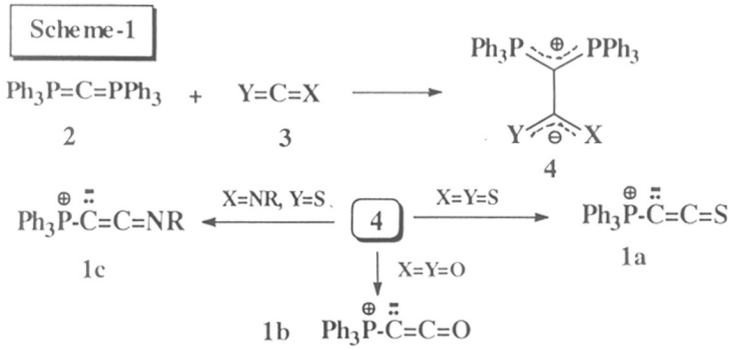
a: X=S; b: X=O; c: X=N-Ph

The disparity in the electron distribution of **1A** and **1B** changes as the electronegativity of X increases. Thus, the contribution of the structure **1B** in the resonance hybrid increases which was confirmed by the X-ray structural analysis.

Owing to this increasing contribution of structure **1B** to the resonance hybrid and the greater delocalization of the carbanion lone pair, the nucleophilic reactivity of the phosphacumulene ylides should increase along the series **1a-c** (**Fig. 1**). Literature describing the utilization of phosphacumulene ylides as synthon for the synthesis of various biologically useful compounds is rather scarce although the scope and versatility of phosphorous ylides are comparable to Grignard reagents.

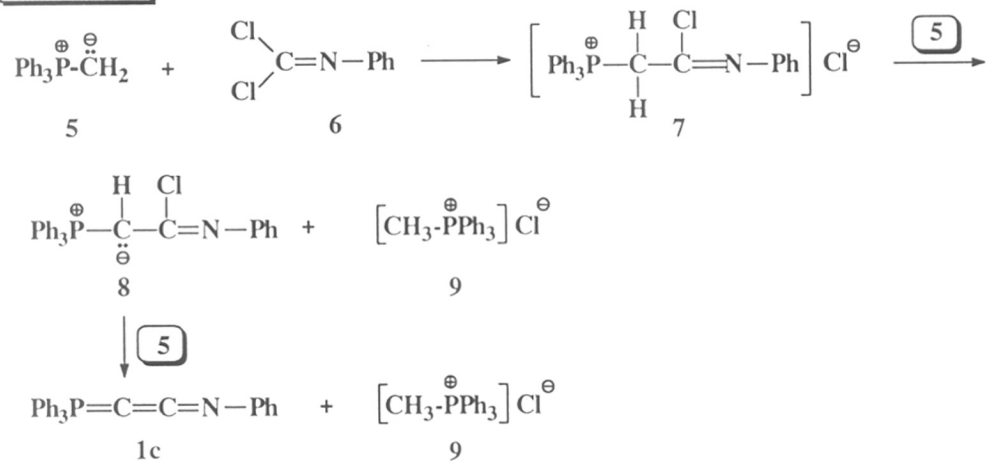
The first synthesis of these phosphacumulene ylides were achieved by Birum and Mathews[2] by the thermolysis of the product **4** obtained in the reaction of hexaphenylcarbodiphosphorane **2** and **3** as shown in **Scheme 1**.

Scheme-1



Bestmann et al.[3] synthesized N-phenyliminoketenilidene triphenylphosphorane **1c** starting from the geminal dihalo imine **6** (prepared from the chlorination of phenylisothiocyanate) and methylene triphenyl phosphorane **5** (**Scheme 2**).

Scheme-2



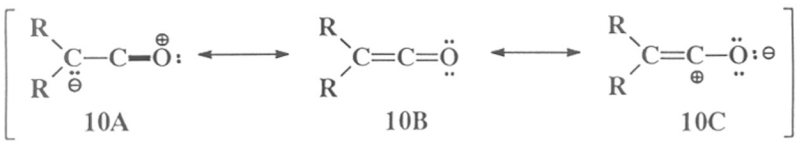
The ylide **5** and imine **6** were taken in 3:1 molar ratio initially affording the intermediate **7** subsequently removal of 2 molecules of **9** using ylide **5** afforded **1c**, which was recrystallized to get the pure product.

These phosphacumulene ylides are known to undergo nucleophilic substitution reactions with halogen compounds, with acidic functionalities e.g., NH, OH, SH, COOH etc. and are also known to form cycloaddition products. A few of the representative reactions are discussed in the next few pages.

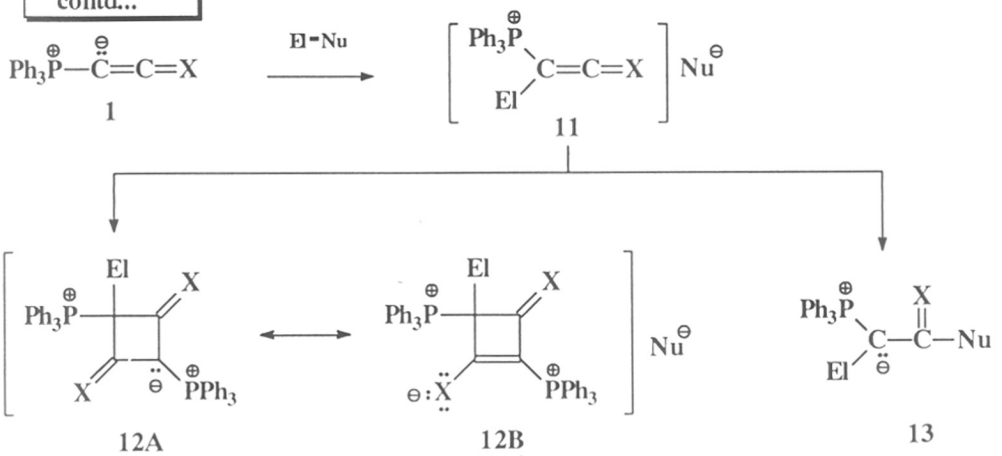
1. Nucleophilic substitution reactions:

Addition of an electrophile to the lone pair of ylides **1a-c** transforms the nucleophilic π^4-π^4 system into the dipolar π^4-π^2 system of the ketenes (**10A**, **10B** & **10C**). The resulting phosphonium ion **11** becomes a "true" dipolar ketene which reacts in a known manner[4] (**Scheme 3**).

Scheme-3



Scheme-3 contd...

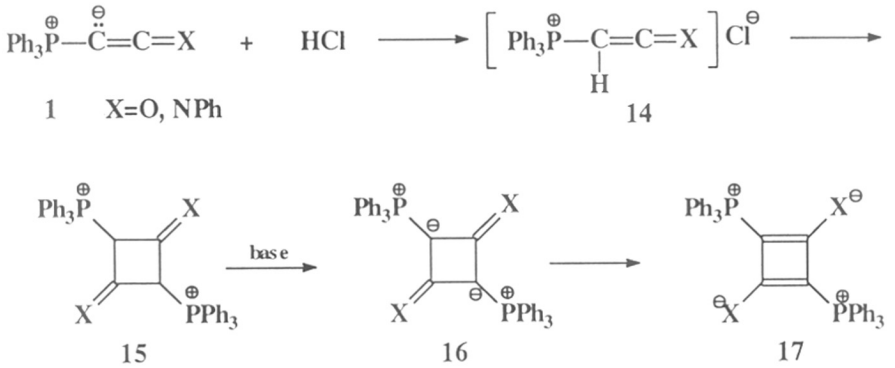


1 11 12A 12B 13

2. Reaction with halogen compounds

Phosphacumulene ylides **1b** and **1c** react with hydrogen chloride in the molar ratio 2:1 leading to 1,3-dioxo- and 1,3-diimino cyclobutane derivatives, which can be converted into stable exocyclic bisalkylidene phosphoranes by sodium bis (trimethylsilyl)amide[4] (**Scheme 4**).

Scheme--4

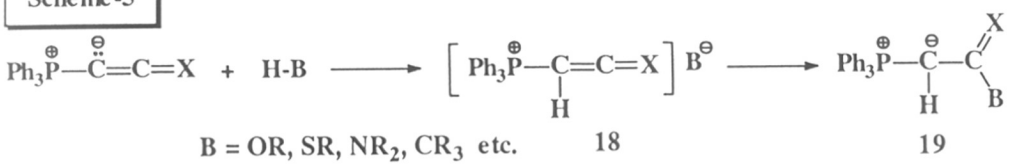


1 X=O, NPh 14 15 16 17

3. Reaction with acidic compounds

The addition of alcohols, thiols, acidic amines etc. to phosphacumulene ylides result in the formation of the phosphonium salt of the type **18** where the anion B⁻ is so nucleophilic that addition to give a new alkylidene phosphorane **19** is faster than cycloaddition of **18** to **1**[4] (**Scheme 5**).

Scheme-5

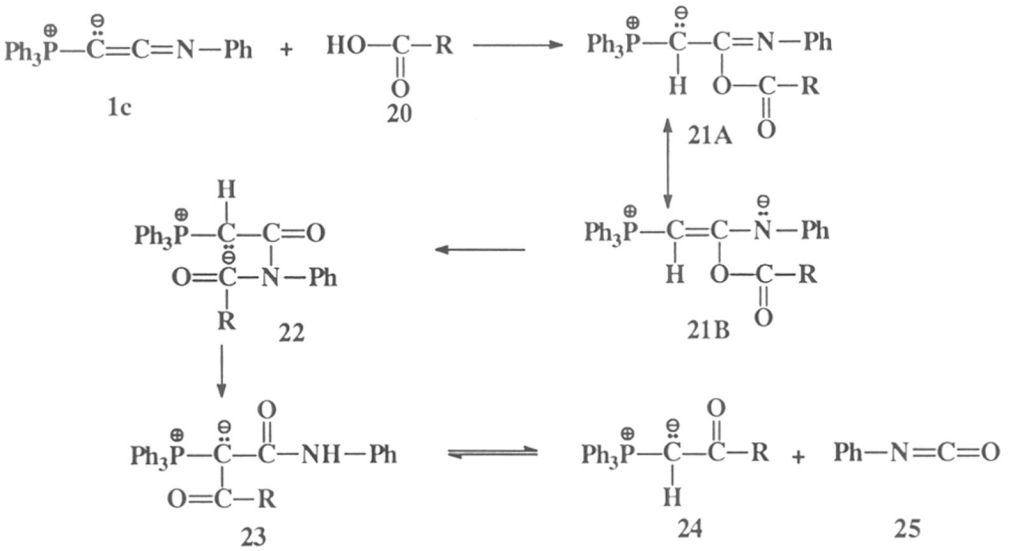


B = OR, SR, NR_2, CR_3 etc. 18 19

It has been found from the nucleophilic character of the compounds **1a-c** (**1c** > **1b** > **1a**) that iminovinylidene **1c** and oxovinylidene **1b** phosphoranes add smoothly to alcohols thiols and acidic NH compounds. While the thio ylide **1a** react readily with thiols and phenols, less rapidly with aliphatic alcohols and not with NH acids. Strongly activated CH_2 groups add rapidly to iminovinylidene phosphorane **1c**, less rapidly to oxoylide **1b** and not at all to the thio ylide **1a**.

Apart from acidic compounds of the type mentioned before, carboxylic acids react with iminovinylidene triphenylphosphorane **1c** to form the alkylidene phosphorane **22** through the intermediates **21A** and **21B**, which rearrange in an intramolecular acyl migration fashion on heating to give **24** and phenyl isocyanate **25** (**Scheme 6**).

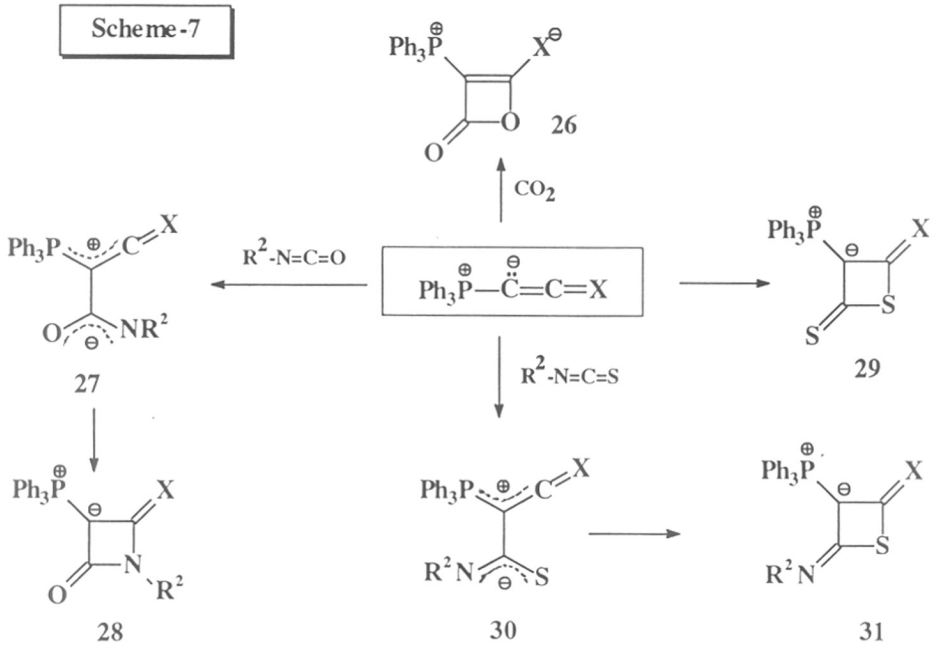
Scheme-6



4. [2+2]-Cycloadditions

[2+2] cycloaddition reactions of the phosphoranes **1a-c** with a variety of compounds yield the exocyclic ylides[4] (**Scheme 7**). In the process C=C bond of the vinylidene triphenylphosphorane involves in the bond formation. The four membered ylides formed can then be reacted with various other carbonyl compounds.

Scheme-7

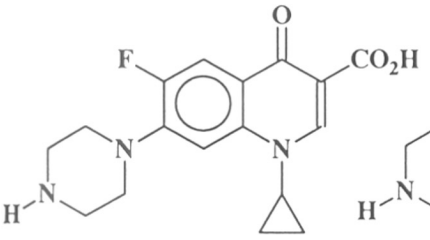


INTRODUCTION FOR QUINOLONES AND PYRROLIZIDONES

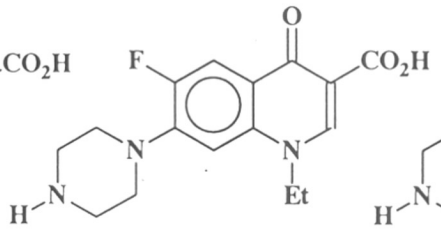
Quinolones are important class of compounds which are endowed with an array of biological activities.[5] Many of them e.g., Norfloxacin, enoxacin, ciprofloxacin, amifloxacin, ofloxacin etc. are already in the market as antibiotics (**Fig. 2**). Some of the 2-carboxyl-4-quinolone derivatives e.g., 5,7-dichlorokynurenic acid are found to exhibit anticonvulsant properties, and act as potent and selective antagonists at the NMDA-glycine site. While a variety of synthetic methodologies for quinoline ring system have been developed, the literature describing novel one pot method based on consecutive process is rather scarce. In order to explore the synthetic utility of the ylide (described in the results and discussion section) an idea for the synthesis of heterocyclics of this type was realized. So, in this chapter a methodology for the synthesis of quinolones that could be useful in designing a new and potent glycine-site-N-methyl-D-aspartate receptor antagonists[6] will be discussed. Our strategy was to use the reaction of the ylide **1c** with carboxylic acids as described in the **Scheme 6**, where the intermediate formed rearranges followed by intramolecular Wittig reaction with a relatively less reactive imide carbonyl to furnish the product.

Biopharmacological features of antibacterial quinolones have attracted the considerable attention of many major pharmaceutical companies. Early synthesis of these compounds was accomplished exclusively by a classical method starting from aniline derivatives which were condensed with diethyl ethoxymethylene malonate and the intermediates thermally condensed to the corresponding 4-hydroxyquinoline-3-carboxylates which after N-alkylation and hydrolysis provided quinolone carboxylic acids[7] (**Scheme 8**).

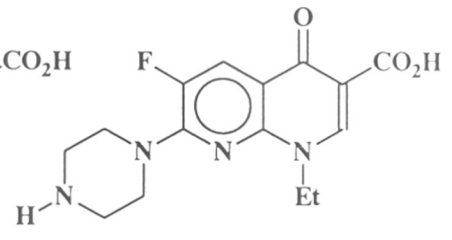
Fig. 2



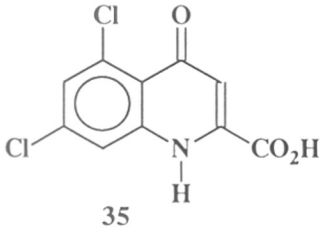
32
Ciprofloxacin



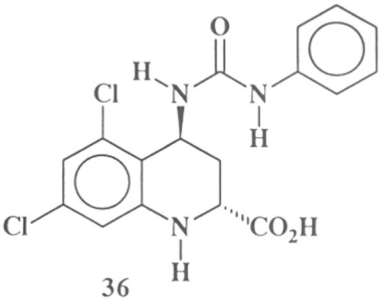
33
Norfloxacin



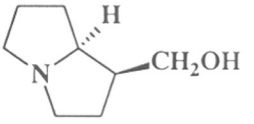
34
Enoxacin



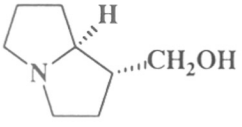
35
5,7-Dichlorokynuric acid



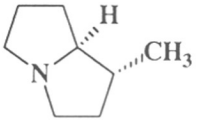
36
trans-2-carboxy-4-substituted tetrahydro quinoline



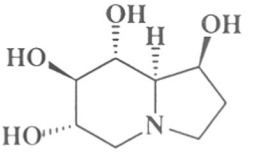
37
(-)-Isoretronecanol



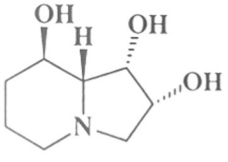
38
(+)-Trachelant thamidine



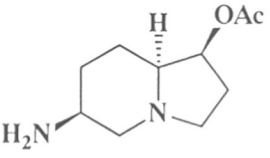
39
Psuedohelio tridane



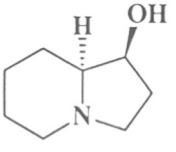
40
Castanospermine



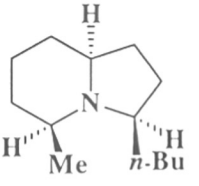
41
Swainsonine



42
Slaframine

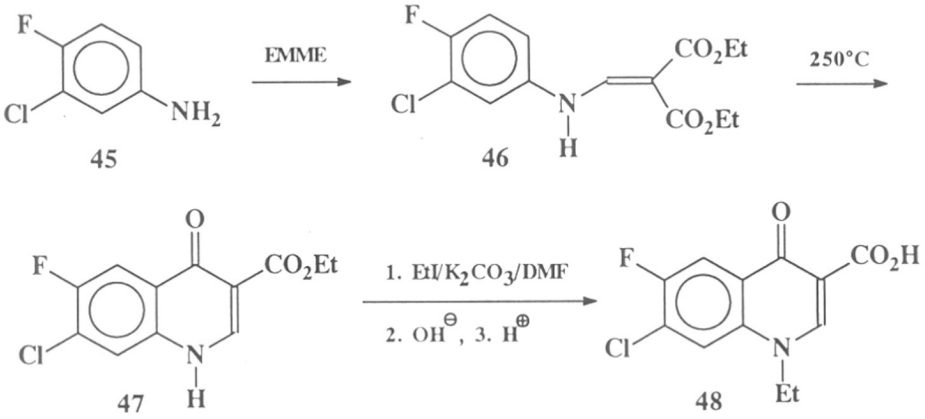


43
1-Hydroxy indolizidine



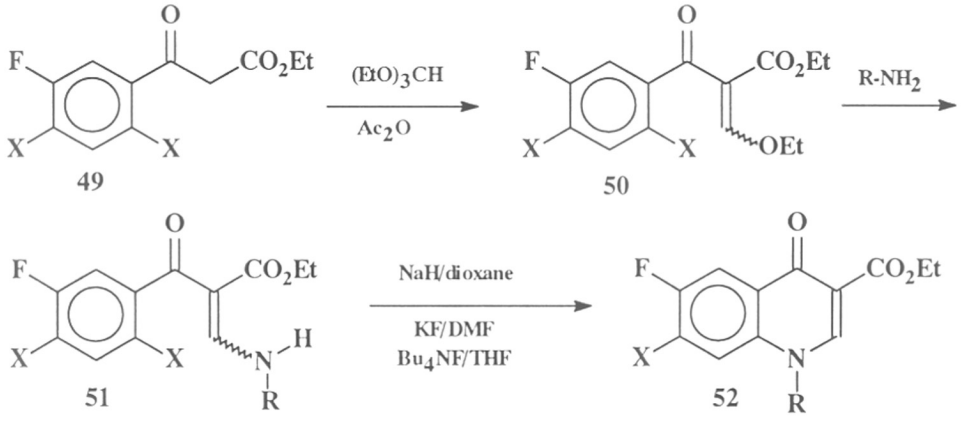
44
(+)-Monomorine

Scheme-8



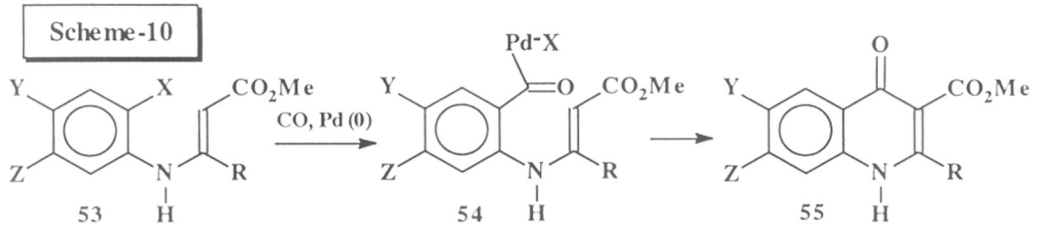
In another method a benzoyl acetate **49** was condensed with orthoformate giving the corresponding ethoxy methylene derivative **50** which when treated with the respective amine yielded the intermediate **51** (**Scheme 9**). The intermediate **51** was then cyclized to **52** using different bases.[8]

Scheme-9



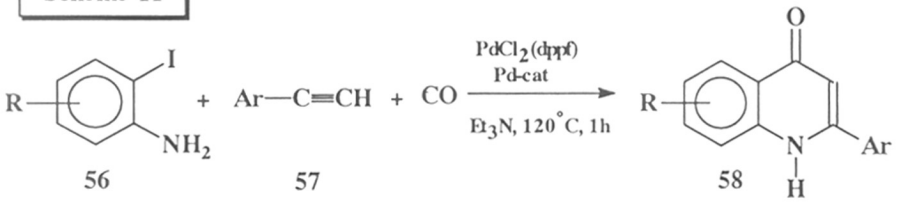
Recently, a new method based on a catalytic carbonylation reaction has been reported for the synthesis of 2-substituted quinolones[9] (**Scheme 10**).

Scheme-10



Synthesis of 2-aryl-4-quinolones was achieved via palladium catalyzed carbonylative coupling of o-iodoanilines with terminal aryl acetylenes[10] (**Scheme 11**).

Scheme-11

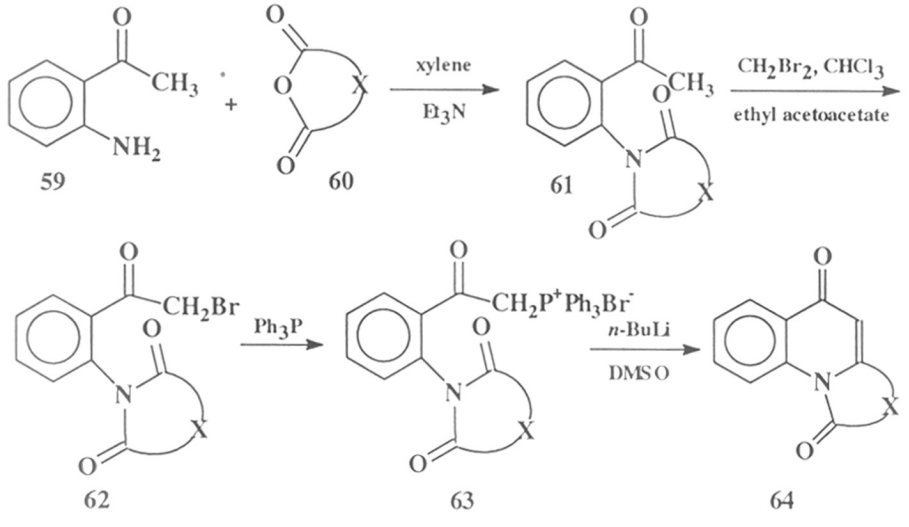


56 57 58

Similar to this work, Kundu and coworkers[11] synthesized quinolines and 2,3-dihydro-4(1H)-quinolones from o-iodoanilides and acetylenic carbinols using palladium catalyst.

More recently, intramolecular Wittig reaction of the type shown below was utilized for the synthesis of novel quinoline derivatives[12] (**Scheme 12**).

Scheme-12



59 60 61 62 63 64

Pyrrolizidine and indolizidine alkaloids having a bicyclic ring system are found in a variety of plant species[13] (**Fig. 2**). They possess potent biological properties which led to much interest in their pharmacology and synthesis. Especially polyhydroxy indolizidines were found to inhibit various glycosidases and they have been investigated as possible treatment for diabetes, cancer and viral infections (including HIV). This chapter also describes our preliminary attempts for the construction of these bicyclic systems using the strategy which was applied for quinolones.

OBJECTIVE

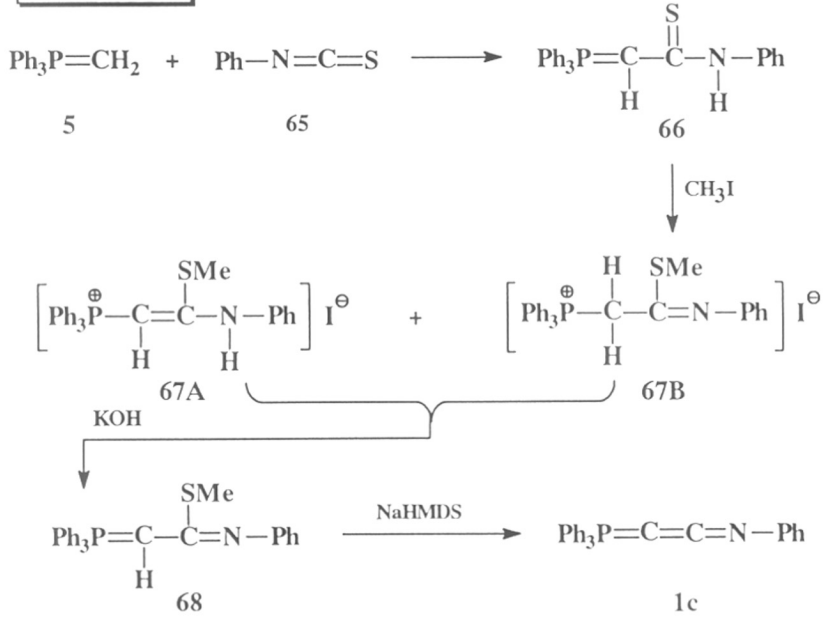
As it is mentioned in the introduction, phosphacumulene ylide of the type $Ph_3P{=}C{=}C{=}X$ can be utilized for the development of newer methodologies. This clearly indicates the need for the better yielding and facile synthesis of the ylides. The methods which are mentioned in the introduction involve either hazardous chemicals or high reaction temperatures and are not amenable for large scale preparation. Our first objective was discovering an efficient synthesis of phosphacumulene ylide. More specifically, ylides of the type **1a-c** can be used for one carbon homologations in many reactions. Therefore, an idea of using this for the construction of biologically important quinolone ring system was conceived. In continuation, we thought of extrapolating the same idea for the construction of pyrrozolidene and indolizidene ring systems, which constitute the nucleus of many biologically active compounds (**Fig. 2**).

RESULTS AND DISCUSSIONS

Synthesis of Phosphacumulene Ylide 1c

After realizing the importance and versatility of phosphacumulene ylides we chose **1c** for synthesis and application of it in various reactions. As this ylide is highly reactive and stable in an inert atmosphere, reactions can be performed with a slight skill. The reaction sequence of a methodology which has been developed in our group for the synthesis of iminovinylidene phosphorane 1c is given below in **Scheme 13**.

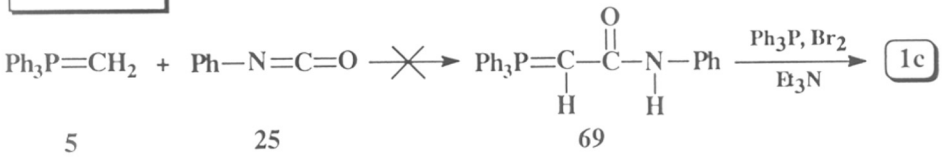
Scheme-13



The compound **5** was prepared by the reaction of triphenyl phosphine and methyl iodide and by treating the resultant phosphonium salt with sodium amide. Treatment of **5** with phenyl isothiocyanate **65** at 0°C and stirring overnight afforded **66** in 88% yield. The compound α-(*N*-phenylthiocarbamoylmethylene)-methylenetriphenylphosphorane **66** was characterized by spectroscopic analysis. The compound melted at 203°C and in ^{1}H-NMR signals at δ 1.9(bs, 1H, NH), 4.45(d, 1H, Ph_3P=C<u>H</u>-) and 7.06-7.78(m, 2H, aromatic) showed the presence of the product. Finally, molecular ion peak 411 (M^+, 9%) in mass spectrum confirmed the product. Compound **66** was further treated with methyl iodide to give a tautomeric mixture of 1:1 ratio of **67A** and **67B** which were characterized well. For **67A** ^{1}H-NMR showed signals at δ 2.12(s, 3H, S-CH_3), 5.3(d, Ph_3P=C<u>H</u>=) and 10.00(s, Ph-N<u>H</u>-) whereas for **67B** signals at δ 2.93(s, 3H, S-CH_3), 5.72(d, 1H, Ph_3P-C<u>H_2</u>-), 6.25(d, 1H, Ph_3P-C<u>H_2</u>-) and 7.02-7.97(m, 20H, Ar). Mass spectrum of **67** showed M^+ at 425(10%), which confirmed the product. This mixture (**67A** & **67B**) was converted into **68** by treating with KOH (treatment was performed in the separating funnel using chloroform and water). For **68**, in ^{1}H-NMR a signal at δ 3.04(d, 1H, Ph_3P=C<u>H</u>-) confirmed the product. Treatment of **68** with sodium hexamethyldisilazide in benzene led finally to the ylide **1c**. The structure of *N*-phenyliminoketenylidene triphenylphosphorane **1c** was confirmed by normal spectroscopic data which were compared with the literature data.[3] In IR, a strong peak at 2000cm^{-1} for C=C=N (see the IR spectrum of **1c**), in ^{1}H-NMR signal at δ 7.30-8.00(m, 20H, Ar) and molecular ion peak at 377 (M^+, 18%) are observed, which confirmed the product.

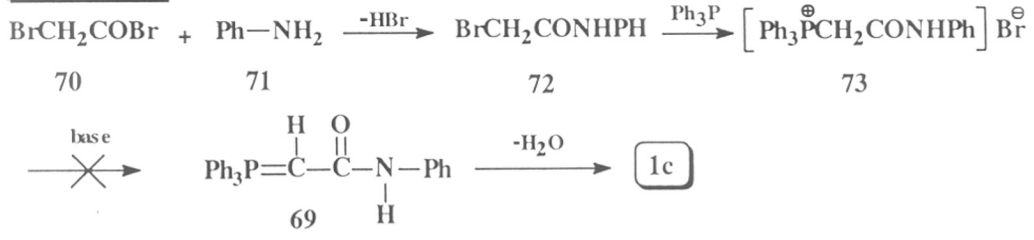
Even though the overall yield (see experimental for details) of this method is moderate, the number of steps involved are more. Therefore an idea for the synthesis of the same in less number of steps in good yield was thought of. Thus, the treatment of methylene triphenylphosphorane with phenylisocyanate (similar to phenylisothiocyanate) under different conditions failed to give the desired product **69** (**Scheme 14**).

Scheme-14



The notion behind this scheme was to get the product **69** which could further be converted to the ylide **1c** by dehydration in a single step. The synthesis of the intermediate **69** was also tried in another route shown below in the **Scheme 15**.

Scheme-15



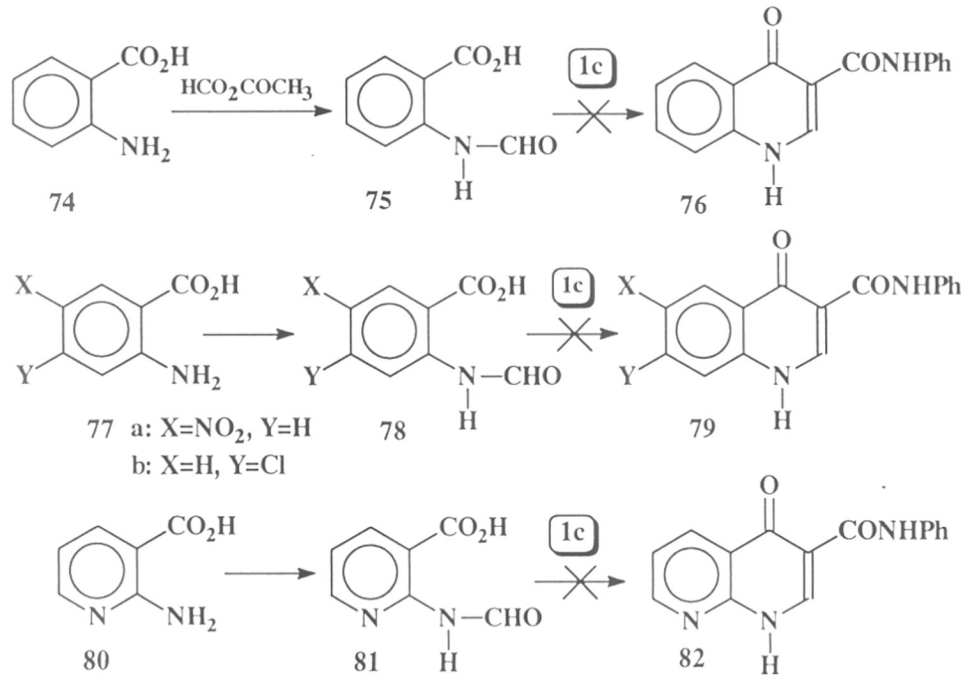
Again, we failed to synthesize the intermediate **69**. The salt obtained after the treatment of **72** with triphenylphosphine was treated with different bases such as KOH, $NaNH_2$, NaHMDS etc. to get the compound **69**, but all efforts were fruitless.

Thus, the ylide **1c** was synthesized according to the **Scheme 13**. This ylide was prepared in sufficiently bulk quantity and utilized in the attempts for the development of methodologies for heterocyclic compounds.

Synthesis of Quinolones

After synthesizing the ylide $Ph_3P{=}C{=}C{=}N\text{-}Ph$ in sufficiently good amount, we thought of using this for the synthesis of 3-substituted (-COOH) quinolones. Thus, the treatment of the ylide **1c** with the N-formyl anthranilic acid **75** [prepared by the formylation of anthranilic acid using acetic formic anhydride at 0°C] in refluxing benzene, the expected 3-carboxanilide quinolone **76** could not be obtained (**Scheme 16**). This compound forms the basic structure of quinolone antibiotics such as norfloxacin, ciprofloxacin etc.

Scheme 16

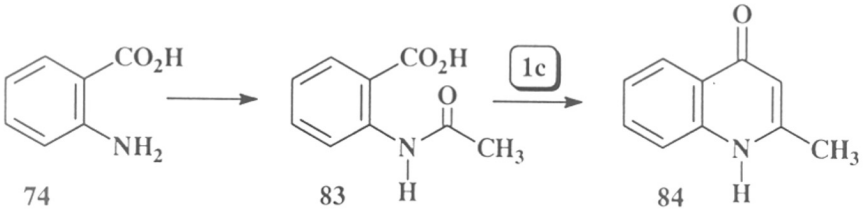


The molecule **75** is highly reactive and should react with the ylide **1c** to form the desired 3-substituted quinolone ring system at the reflux temperature where the intramolecular Wittig reaction is faster than the extrusion of phenylisocyanate, which is due to the high reactivity of the N-formyl group. But, no reaction was observed and the ylide decomposition took place. Reactions with substitutions on the aromatic ring were also tried to check the reactivity of the other *N*-formyl anthranilic

acids. However, the reaction of substituted N-formyl anthranilic acids **77** and 2-N-formyl-nicotinic acid **81** with N-phenyl(triphenylphosphoranylidene)ethenimine **1c** did not proceed under the reaction conditions. Solvents such as dioxane, diglyme were used to increase the solubility of the starting material. The idea was to hydrolyze the compound **82** to the acid and carry out further substitution reaction to obtain the enoxacin basic skeleton.

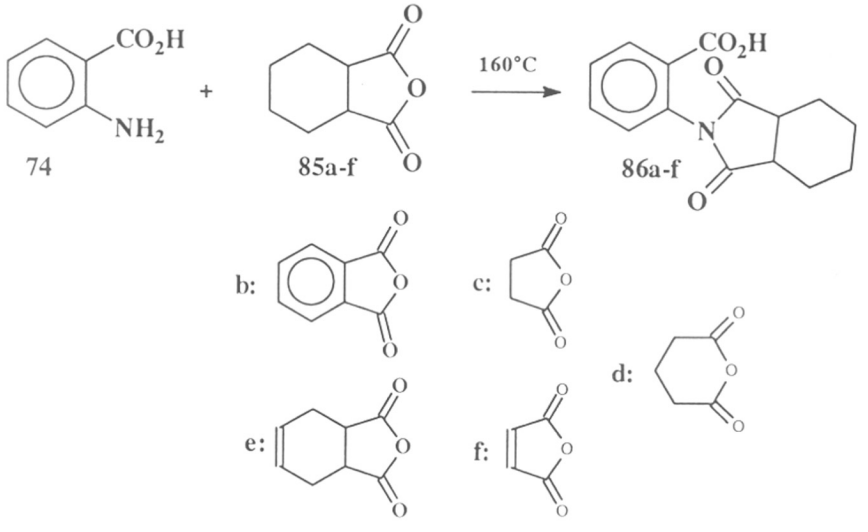
We presumed that amide carbonyls are not reacting due to low electrophilicity. This was again tested by acylating the amine group of anthranilic acid using an acid chloride. Thus, reaction of **83** with ylide **1c** did not give the require product **84** (**Scheme 17**).

Scheme-17



Thus, imides of the type **86** shown below were prepared by the condensation of anthranilic acid and the corresponding anhydrides by heating them neat above their melting points, as per the literature procedure.[14] When a mixture of imide **86** and N-phenyl(triphenylphosphoranylidene)ethenimine **1c** was heated in refluxing toluene the compound **64** was obtained in good yield.

Scheme 18



Scheme-19

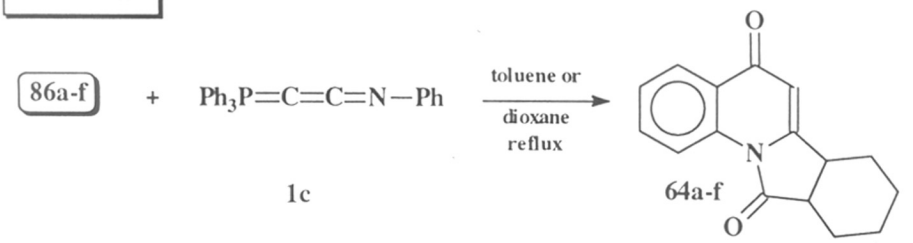


Table: Synthesis of quinolones **64** from **86** and **1c** via intramolecular Wittig Cyclization.

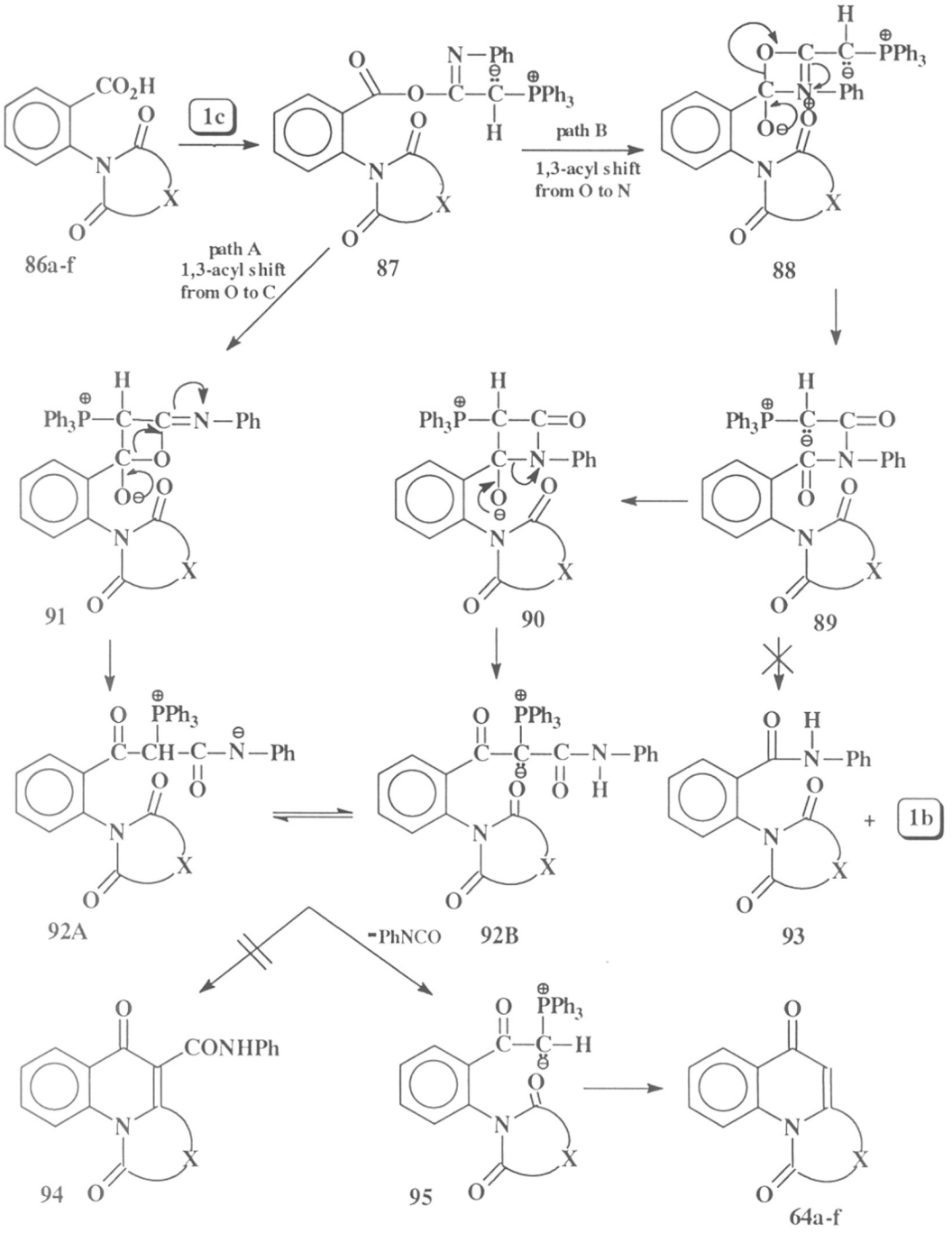
Entry	Reaction time(h)	Products	Yield (%)
1	6	**64a**	60
2	8	**64b**	70
3	6	**64c**	97
4	6	**64d**	45
5	6	**64e**	55
6	4	**64f**	75

The 2-substituted compound **64** was obtained rather than the expected 3-carboxanilide derivative. The compound **64** was characterized by the normal spectroscopic studies as usual. Thus, for **64a** in IR, peaks at 1780cm^{-1} and 1650cm^{-1} show the presence of imide and enone carbonyl. In ^{1}H-NMR, signals at δ 3.00(m, 1H) and δ 3.35(m, 1H) indicate the protons present α-to anhydride carbonyls. Signal at δ 6.25(s, 1H) indicate the ene proton and signals at δ 7.25(m, 1H), 7.70(m, 1H), 8.35(dd, 1H), 9.05(d, 1H) correspond to the aromatic protons spread over the wide range. ^{13}C-NMR gave signals at δ 179.55 (enone carbonyl), 176.99 (amide carbonyl), 158.63 (quarternary aromatic carbon present α-to N), 133.34 (tertiary ene carbon), 137.16, 126.63, 126.33, 125.69, 118.18, 108.14 represent aromatic and tertiary ene carbon, 41.78 and 36.30 (-CH- of the hexahydro moiety), 29.22, 23.51, 22.49 and 22.38 (-CH_2-) (see ^{1}H-NMR and ^{13}C-NMR of **64a**). Finally molecular ion peak 253 (M^+, 100%) confirmed the product.

In the case of compounds **86d**, **86e** and **86f** the starting materials were insoluble in toluene. Thus, to increase the solubility dioxane was used as the solvent. All the reactions were carried out under perfectly dry conditions and all the products were well characterized.

The formation of the product (rather than the 3-substituted one) can generally be explained by the reaction sequence as depicted in **Scheme 20**.

Scheme 20


CO2H
1c
86a-f
87
path B
1,3-acyl shift
from O to N
88
path A
1,3-acyl shift
from O to C
91
90
89
92A
92B
-PhNCO
93
1b
94
95
64a-f

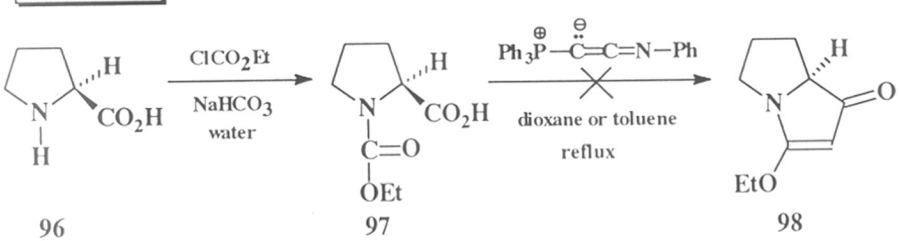
The plausible reaction mechanism can be visualized as initial protonation of N-phenyl(triphenylphosphoranylidene)ethenimine **1c** by **86** followed by the nucleophilic attack of the carboxylate ion to the resulting vinylphosphonium salt leading to the O-acyl-imidate **87**. There is then a migration of the ester carbonyl from O to C7 forming **92** followed by the extrusion of phenylisocyanate and ultimately leading to the acylphosphorane **95** which subsequently undergoes ring closure via the intramolecular Wittig reaction on one of the imide carbonyls to afford the quinolone **64**. The path B which is mentioned in the scheme is one of the other possibilities that might be occurring during the reaction. The intermediate **92** was isolated in the case of **86b** and characterized. For this the reaction was carried out at room temperature in anhydrous ethyl acetate. After stirring the reaction mixture for 5h the reaction mixture was concentrated and the solid mass obtained was recrystallized using ethyl acetate. The compound melted at 178°C. IR showed peaks at 1780cm^{-1}, 1700cm^{-1}, 1670cm^{-1} and 1610cm^{-1}. ^{1}H-NMR gave signals at δ 6.80-8.05(m, 28H) and 12.4 (s, 1H). Mass spectrum showed the presence of (M^+ - Ph_3P=O) peak at 366.

Synthesis of Pyrrolizidines

Further, to explore the utility of the phosphacumulene ylide, the important pyrrolizidine ring system was chosen. Pyrrolizidine ring system is present in a wide variety of natural products and they are known to exhibit significant biological activities e.g., antitumour, hypertensive, insect attractive etc.

To start with an example, we chose an amino acid such as proline as the precursor for the synthesis of optically active pyrrolizidine alkaloids. Thus, L-proline **96** was treated with ethylchloroformate in water using $NaHCO_3$ as base to get compound **97** in 73% yield[15] (**Scheme 21**). When compound **97** was treated with the ylide N-phenyl(triphenylphosphoranylidene)ethenimine in dioxane the expected cyclized product **98** could not be obtained.

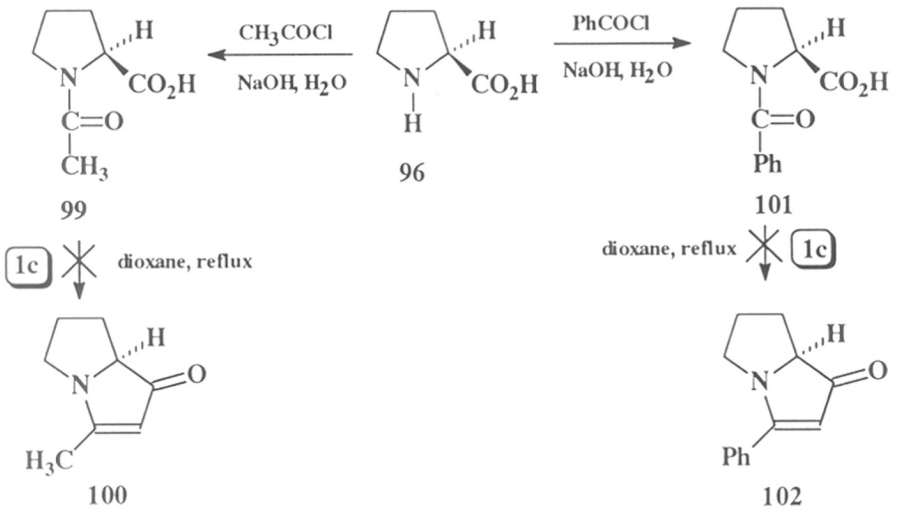
Scheme 21



96 97 98

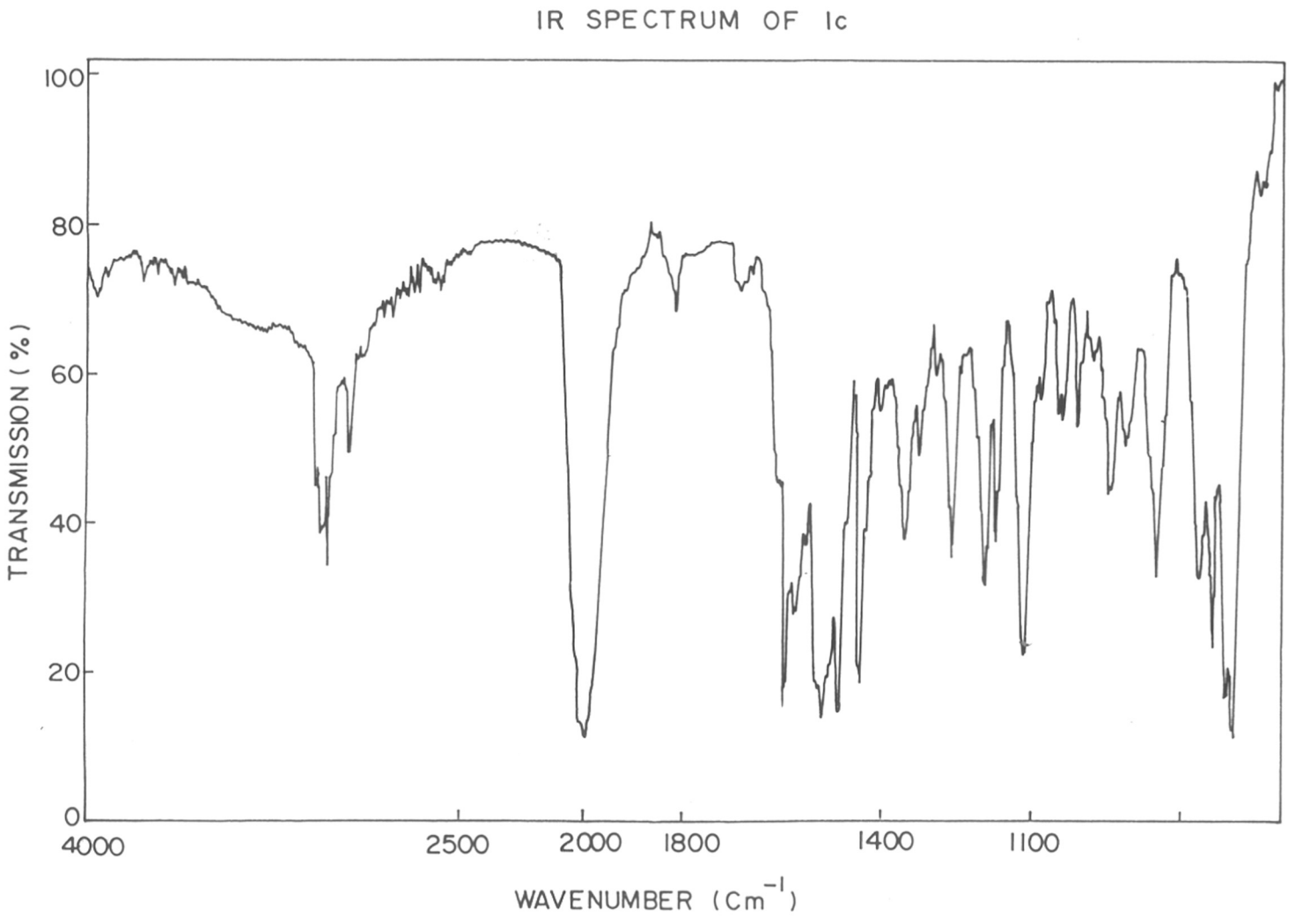
Presumably, the less reactivity of the ester carbonyl could be the reason for the failure of Wittig cyclization reaction. We then converted proline into compounds **99** and **101** by treating it with the corresponding acid chlorides and NaOH in water (**Scheme 22**). However, treatment of compounds **99** and **101** with the ylide **1c** again failed to afford the required pyrrolizidine ring system.

Scheme 22

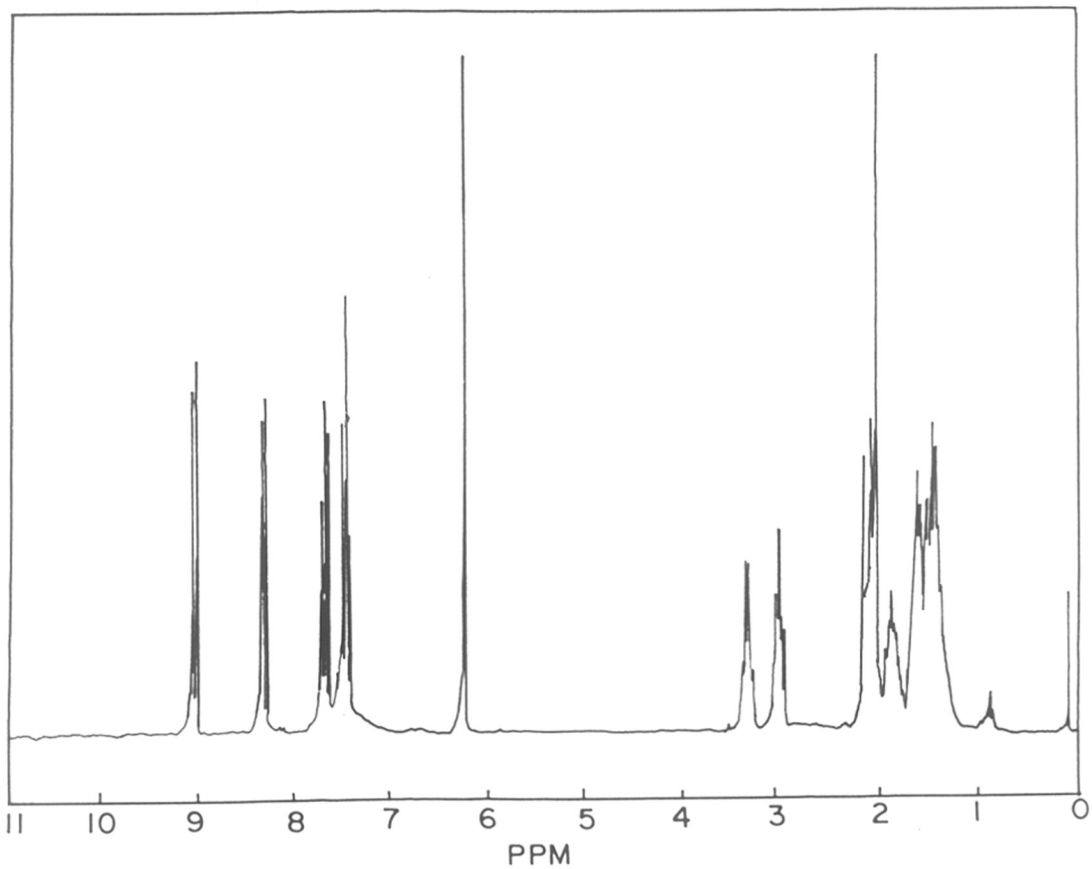


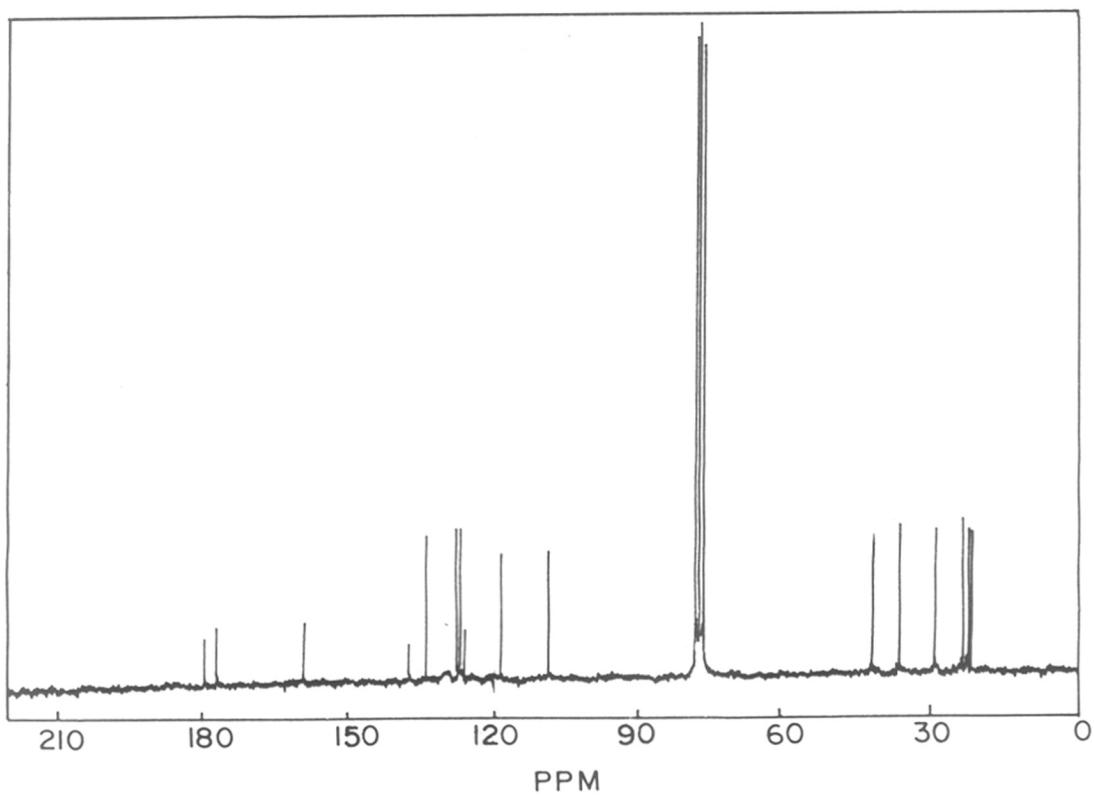
CONCLUSIONS

As mentioned in the introduction and objective section of this chapter, two of the three objectives have been successfully accomplished. An efficient synthesis of phosphacumulene ylide was devised. Secondly, application of this ylide towards the synthesis of quinolone was completed. However, usefulness of the ylide as C1 synthon for the synthesis of pyrrolizidines could not be achieved. Nevertheless, it can be concluded that phosphacumulene ylide can be an efficient C1 synthon donor.


IR SPECTRUM OF Ic
TRANSMISSION (%)
100
80
60
40
20
0
4000
2500
2000
1800
1400
1100
WAVENUMBER (Cm⁻¹)

^{1}H–NMR & ^{13}C–NMR SPECTRA OF 64a





EXPERIMENTAL

Typical procedure for the formylation of anthranilic acids

Formic acid (5.36g, 0.12mol) was added dropwise to 11.9g(0.12mol) of acetic anhydride with stirring at 0°C. The reaction mixture was heated to 50°C and stirred for 15min at that temperature. The reaction mixture was then cooled to 0°C and 2g(0.012mol) of **77b** in 5ml of formic acid was added dropwise. Stirred the reaction mixture for 1h and the precipitate formed was filtered, washed repeatedly with water and dried in high vacuum to obtain 2.05g of *N*-formyl-5-chloroanthranilic acid **78b** as colourless solid.

Yield	88%.
m.p.	212-215°C (not sharp).
IR(nujol)	cm^{-1} 3180(br), 1680(s), 1670(s), 1630(m), 1570(s), 1510(s), 1400(s).
^{1}H-NMR (90MHz)	6.56-6.70(dm, 1H), 7.46-7.58(d, 1H), 7.98-8.06(m, 1H), 8.20-8.29(m, 1H), 10.84(bs, 1H).
MS	m/z 199 (M^+).

N-formyl-4-nitroanthranilic acid (**78a**)

Yield	74%.
m.p.	150-155°C (not sharp).
IR(nujol)	cm^{-1} 3230(bm), 1710(s), 1690(s), 1640(s), 1590(m), 1430(s), 1350(s).
^{1}H-NMR (90MHz)	δ 6.60-6.69(dd, 1H), 7.34-7.40(dd, 1H), 7.84-8.05(dt, 1H), 8.08-8.33(m, 1H), 8.65-8.87(dt, 1H), 11.49(bs, 1H).
MS	m/z 210 (M^+).

N-formyl anthranilic acid (**75**)

Yield	69%.
m.p.	168-169°C.
IR(nujol)	cm^{-1} 3260(bm), 2940(s), 2860(m), 1700(s), 1660(m), 1620(m), 1540(m).
^{1}H-NMR (90MHz)	δ 4.50(bs, 1H), 7.00-7.23(m, 1H), 7.35-7.65(m, 1H), 8.00-8.10(dd, 1H), 8.45-8.75(m, 1H), 9.5(s, 1H), 11.25(bs, 1H).
MS	m/z 165 (M^+).

Synthesis of *N*-Acetyl anthranilic acid (83)

To an ice cold solution of 2g(0.015mol) of anthranilic acid and 1.63g(0.029mol) of KOH (10%), was added 20g of ice followed by 1.2g(0.018mol) of freshly distilled acetic anhydride and the resultant mixture was stirred for 30min. The product formed was precipitated by dil. HCl which was filtered, washed with water and dried. Recrystallization from ethyl acetate and petroleum ether mixture afforded 1.85g of **83** as colourless solid.

Yield	71%.
m.p.	180-182°C.
IR(nujol)	cm^{-1} 3310(bs), 3000(m), 2980(s), 1680(s), 1660(s), 1600(m).
^{1}H-NMR (90MHz)	δ 2.34(s, 3H), 3.00(bs, 1H), 7.05-7.21(m, 1H), 7.50-7.65(m, 1H), 8.05-8.15(dd, 1H), 8.72-8.85(dd, 1H).
MS	m/z 179(M^+).

Synthesis of triphenyl-methylphosphoniumiodide

Methyl iodide (8.6ml, 0.13mol) was added slowly to a cold solution of triphenylphosphine (30g, 0.11mol) in 200ml of dry benzene and the mixture was stirred at room temperature for 5h. The solid separated was filtered and washed with benzene and air dried.

Yield	>95%.
m.p.	185°C.
^{1}H-NMR (80MHz)	δ 3.00-3.20(d, 3H), 7.60-8.00(m, 15H).

Preparation of methylene-triphenylphosphorane (5)

A mixture of 40g(0.09mol) of triphenyl-methylphosphoniumiodide and 4.63g(0.11mol) of sodamide in 200ml of dry benzene was stirred at room temperature for 24h. The reaction mixture developed a pale yellow colour, the NaI precipitate formed was filtered off under an inert atmosphere and the benzene filtrate was used as such for further reaction.

Preparation of α-(*N*-phenylthiocarbamoylmethylene)-methylene triphenylphosphorane (66)

To the above solution of methylene-triphenylphosphorane was added slowly at 0°C, 13.3g(11.8ml, 0.09mol) of phenyl isothiocyanate in 30ml of dry benzene. The dark colour developed at the beginning becomes light after 15 minutes. The mixture was stirred at room temperature overnight. The solid thus obtained was filtered, washed with benzene and recrystallized from chloroform:ethylacetate to get 35g of pure product.

Yield	88%.
m.p.	203°C.
IR(nujol)	cm^{-1} 3200(bs), 2930(s), 2900(m), 1600(s), 1480(m), 1440(s).

^{1}H-NMR (80MHz)	δ 1.90(bs, 1H), 4.45(d, 1H, P=CH), 7.06-7.78(m, 20H).
MS	m/z 411 (M^+, 9%), 319(30), 302(19), 262(32), 183(100), 108(48), 77(30).

Preparation of tautomeric mixture (1-Anilino-1-methylmercapto-2-triphenylphosphonio-ethylene)-iodide (67A) and (1-Phenylimino-1-methylmercapto-2-triphenylphosphonio-ethane)-iodide (67B)

To a solution of 20g(0.048mol) of α-(*N*-phenylthiocarbamoylmethylene)-methylene triphenylphosphorane **66** in 150ml of $CHCl_3$ was added dropwise, 6.9g(3.02ml, 0.063mol) of methyl iodide at 0°C. After complete addition, the reaction mixture was stirred at room temperature overnight. Sufficient amount of ether was added to the reaction mixture. The solid thus obtained was filtered, washed and recrystallized from chloroform:ether to afford 25g of **67** as colourless crystals.

Yield	94%.
m.p.	218-220°C.
IR(nujol)	cm^{-1} 3400(bm), 1640(s), 1600(s), 1530(s), 1450(s).
^{1}H-NMR (90MHz)	**(a)** δ 2.12(s, 3H, S-C*H*$_3$), 5.3(d, 1H, Ph_3P-C*H*=), 10(s, Ph-N*H*). **(b)** δ 1.62 and 2.93(s, S-C*H*$_3$), 5.72(d, Ph_3P-C*H*$_2$-), 6.25(d, Ph_3P-C*H*$_2$), 7.02-7.97(m, Ar).
MS	m/z 425 (M^+, 10%), 378(20), 353(40), 294(26), 262(30), 183(100), 142(92), 127(54).

Preparation of 2-Phenylimino-2-methylmercapto-ethylidenetriphenylphosphorane (68)

A tautomeric mixture of **67A** and **67B** (25g, 0.045mol) was suspended in 150ml of chloroform in a separating funnel. Potassium hydroxide (3.78g, 0.068mol) was then added in 75ml of water and the mixture was shaken thoroughly for 10 minutes. The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and residue obtained was treated with toluene. The solid thus obtained was filtered, washed with toluene and recrystallized from toluene to afford 15g of the product as yellow solid.

Yield	60%.
m.p.	154-155°C.
IR(nujol)	cm^{-1} 1510(s).
^{1}H-NMR (80MHz)	δ 2.36(s, 3H, -S-CH_3), 3.04(d, Ph_3P=C*H*-), 6.59-7.74(m, 20H, Ar).
MS	296 (M^+).

Preparation of sodium bis(trimethylsilyl)amide

A mixture of 66g of hexamethyl disilazane and 12.2g of sodamide in 300ml of dry benzene was refluxed for 72h under anhydrous condition. The undissolved residue was filtered off and the solvent

was evaporated under reduced pressure. To the residue, sufficient amount of anhydrous petroleum ether was added. The solid obtained was filtered, washed with anhydrous pet. ether and dried under high vacuum to afford 35g of the product as white solid.

m.p.	165-167°C.

Preparation of N-Phenyl(triphenylphosphoranylidene)ethenimine (1c)

A mixture of 17g(0.04mol) of 2-Phenylimino-2-methylmercapto-ethylidenetriphenyl phosphorane **68** and 8.05g(0.044mol) of sodium bis(trimethylsilyl)amide in 100ml of anhydrous benzene was stirred at 60°C overnight. The sodium methyl sulphide formed during reaction was filtered off and the benzene from the filtrate was completely evaporated under reduced pressure to obtain brown solid. It was then recrystallized from anhydrous ethyl acetate to afford 11.5g of the product as yellow solid.

Yield	75%.		
m.p.	151-153°C (Lit.[3] 151-152°C).		
IR(nujol)	cm^{-1} 3800(s), 2000(s), 1600(s), 1530(s), 1450(s).		
^{1}H-NMR (90MHz)	δ 7.30-8.00(m, 20H, Ar),		
MS	m/z 377 (M^+).		
Analysis	$C_{26}H_{20}NP$	Calculated	C, 82.74; H, 5.34; N, 3.71
		Found	C, 82.43; H, 5.41; N, 3.61

Typical procedure for the preparation of amides (86a-f)

Hexahydrophthalic anhydride **85a** (3.00g, 0.0194mol) and anthranilic acid **74** (2.67g, 0.0194mol) were mixed thoroughly and heated neat up to 160°C. The solid melted and formed a clear transparent liquid. It was then cooled and the gummy mass obtained was dissolved in 10ml of ethanol at 50°C. The white solid formed after cooling was filtered and dried. The compound was then recrystallized from ethanol to afford 4.72g of **86a** as white solid.

86a:

Yield	89%.
m.p.	203-204°C.
IR(nujol)	cm^{-1} 1740(s), 1710(s), 1620(s), 1595(s), 1510(s), 1450(s), 1400(s).
^{1}H-NMR (200MHz, $CDCl_3$ + acetone d_6)	δ 1.45(bs, 4H), 1.82(bs, 4H), 2.95(bs, 2H), 7.07-7.18(dd, 1H), 7.36-7.48(m, 1H), 7.48-7.62(m, 1H), 7.95-8.08(m, 1H).
MS	m/z 255 (M^+, 9%), 229(9), 163(8), 137(52), 119(93), 81(100), 67(76), 55(42).

86b:

Yield	87%.
m.p.	176°C.
IR(nujol)	cm^{-1} 3040(b), 2850(m), 1740(s), 1695(s), 1620(s), 1600(s), 1565(s).
^{1}H-NMR (200MHz)	δ 7.80-8.00(m, 4H), 8.10-8.45(m, 4H).
MS	m/z 266 (M^+, 34%), 222(61), 194(26), 178(100), 167(21), 140(22), 104(23), 76(27).

86c:

Yield	95%.
m.p.	182-185°C.
IR(nujol)	cm^{-1} 1690(s), 1680(s), 1600(s), 1540(s), 1470(s), 1460(s).
^{1}H-NMR (200MHz, $CDCl_3$ + acetone d_6)	δ 2.70(t, 4H), 6.95-7.05(td, 1H), 7.40-7.50(td, 1H), 8.00-8.08(dd, 1H), 8.60-8.67(dd, 1H), 11.40(bs, 1H).
MS	m/z 219 (M^+, 54%), 175(73), 146(100), 119(74), 90(27).

86d:

Yield	92%.
m.p.	138°C.
IR(nujol)	cm^{-1} 1730(s), 1700(s), 1630(s), 1615(s), 1560(s), 1480(s), 1405(m).
^{1}H-NMR (200MHz, $CDCl_3$ + acetone d_6)	δ 1.80-2.00(m, 2H), 2.13-2.41(m, 4H), 6.80-7.05(td, 1H), 7.25-7.43(m, 1H), 7.80-7.95(dd, 1H), 8.40-8.56(dd, 1H), 11.25(bs, 1H).
MS	m/z 233 (M^+, 2%), 174(12), 146(20), 137(89), 119(100), 90(39).

86e:

Yield	83%.
m.p.	180-182°C.
IR(nujol)	cm^{-1} 1710(s), 1690(s), 1630(s), 1615(s), 1560(m), 1490(s), 1285(s).
^{1}H-NMR (200MHz, $CDCl_3$ + acetone d_6)	δ 2.40-2.72(m, 4H), 3.05-3.32(m, 2H), 5.68(s, 2H), 7.00-7.22(m, 1H), 7.45-7.66(m, 1H), 8.02-8.16(dd, 1H), 8.67-8.80(dd, 1H).
MS	m/z 253 (M^+, 32%), 224(10), 137(31), 119(100), 79(88).

86f:

Yield	92%.
m.p.	184-185°C.

IR(nujol)	cm^{-1} 3100(b), 1695(s), 1610(s), 1590(s), 1540(s), 1490(s), 1470(s), 1240(s).
^{1}H-NMR (200MHz, $CDCl_3$ + acetone d_6)	δ 6.17-6.36(q, 2H), 7.02-7.10(td, 1H), 7.38-7.48(td, 1H), 7.95-8.0(dd, 1H), 8.46-8.54(dd, 1H), 12.00(bs, 1H).
MS	m/z 217 (M^+, 2%), 137(65), 119(100), 92(62), 65(25), 54(52).

Typical procedure for intramolecular Wittig cyclization

To a stirred solution of 0.15g(0.55mmol) of **86a** in 5ml of dry toluene, was added 0.23g(0.61mmol) of **1c** in 3ml of dry toluene at room temperature under argon atmosphere. The reaction mixture was then refluxed for 6h. Removal of the solvent on rotavapour and column chromatography of the crude product on silica gel using 80:20 pet. ether:ethyl acetate afforded 0.097g of **64a** as brown solid.

64a:

Yield	70%.
m.p.	139°C.
IR(nujol)	cm^{-1} 3040(b), 2980(m), 2880(m), 1780(s), 1650(s), 1620(s), 1580(m), 1490(s), 1460(s), 1430(m).
^{1}H-NMR (200MHz)	δ 1.28-1.70(m, 4H), 1.74-2.15(m, 4H), 2.93-3.07(m, 1H), 3.25-3.41(q, 1H), 6.25(s, 1H), 7.40-7.57(m, 1H), 7.65-7.75(m, 1H), 8.27-8.35(dd, 1H), 9.00-9.08(d, 1H).
^{13}C-NMR (200MHz)	δ 179.55(s), 176.99(s), 158.63(s), 137.16(s), 133.34(d), 126.63(d), 126.33(d), 125.69(s), 118.18(d), 108.14(d), 41.78(d), 36.30(d), 29.22(t), 23.51(t), 22.49(t), 22.38(t).
MS	m/z 253 (M^+, 100%), 224(14), 211(20), 199(48), 159(17), 135(13), 93(47), 55(25).

64b: Solvent used: toluene; time: 8h; chromatographed using 90:10 pet. ether:ethyl acetate.

Yield	70%.
m.p.	265-267°C.
IR(nujol)	cm^{-1} 1720(s), 1650(w), 1620(s), 1585(s), 1450(s), 1230(s).
^{1}H-NMR (200MHz)	δ 6.80(s, 1H), 7.33-7.42(td, 1H), 7.55-7.80(m, 4H), 7.87-7.95(dd, 1H), 8.23-8.28(dd, 1H), 9.03-9.07(dd, 1H).
^{13}C-NMR (200MHz)	δ 181.53(s), 178.84(s), 147.20(s), 134.51(d), 134.27(s), 132.32(s), 131.91(d, 2C), 126.85(d), 125.74(d), 125.28(s), 121.80(d, 2C), 117.89(d, 2C), 107.05(s).
MS	m/z 247 (M^+, 2%), 223(100), 179(89), 168(49), 149(16), 139(43), 104(22), 76(19).

64c: Solvent used: toluene; time: 6h; chromatographed using 90:10 pet. ether:ethyl acetate.

Yield	97%.
m.p.	187-188°C.
IR(nujol)	cm^{-1} 1715(s), 1680(s), 1600(s), 1550(m), 1505(s), 1445(s).
^{1}H-NMR (200MHz)	δ 2.90-3.00(m, 2H), 3.19-3.28(m, 2H), 6.30(s, 1H), 7.67-7.75(m, 2H), 8.36-8.40(dd, 1H), 9.13-9.17(dd, 1H).
^{13}C-NMR (200MHz)	δ 177.35(s), 174.42(s), 154.42(s), 135.58(s), 131.70(d), 125.19(d), 125.15(d), 124.24(d), 116.66(d), 107.75(s), 28.03(t), 22.15(t).
MS	m/z 199 (M^+, 45%), 183(27), 152(22), 143(9), 115(5).

64d: Solvent used: dioxane; time: 6h; chromatographed using 85:15 pet. ether: ethyl acetate.

Yield	45%.
m.p.	157-159°C.
IR(nujol)	cm^{-1} 1720(s), 1685(s), 1600(s), 1560(m), 1510(s).
^{1}H-NMR (200MHz)	δ2.15-2.30(m,2H), 2.40-2.55(m, 2H), 3.68-3.80(d, 2H), 6.18-6.27(dd, 1H), 7.50-7.55(dd, 2H), 7.63-7.74(m, 1H), 8.46-8.53(d, 1H).
MS	m/z 213 (M^+).

64e: Solvent used: dioxane; time: 6h; chromatographed using 80:20 pet. ether:ethyl acetate.

Yield	55%.
m.p.	179-181°C.
IR(nujol)	cm^{-1} 3020(b), 2910(m), 1780(s), 1650(s), 1615(s), 1575(m), 1490(m).
^{1}H-NMR (200MHz)	δ 2.85-3.12(m, 4H), 3.20-3.30(m, 2H), 5.59-6.05(m, 2H), 6.30(s, 1H), 7.52-7.57(d, 2H), 8.30-8.35(dd, 1H), 9.10-9.15(d, 1H).
MS	m/z 251 (M^+).

64f: Solvent used: dioxane; time: 4h; chromatographed using 80:20 pet. ether.ethyl acetate.

Yield	75%
m.p.	138-140°C
IR(nujol)	cm^{-1} 3000(s), 1680(s), 1660(s), 1600(m), 1400(w).
^{1}H-NMR (200MHz)	δ 6.45-6.55(td, 1H), 6.58-6.65(dd, 1H), 7.05-7.20(m, 3H), 7.57(s, 1H), 7.69-7.76(dd, 1H),
^{13}C-NMR (200MHz)	δ 168.14(s), 149.78(s), 131.92(2C), 129.67(2C), 127.05, 114.76(2C), 113.13(2C), 108.45.

MS	m/z 197 (M^+, 2%), 167(3), 137(6), 119(9), 66(100).

Isolation of the intermediate 92 in the reaction of 86b

To a stirred solution of 0.1g(0.374mmol) of **86b** in 5ml of dry ethyl acetate, was added 0.176g(0.468mmol) of **1c** in 3ml of dry ethyl acetate at room temperature and the reaction mixture was stirred for 10h at the same temperature under argon atmosphere. Evaporated the solvent and crude product obtained was recrystallized from ethyl acetate to obtain 0.185g of the intermediate **92** as brown solid.

Yield	77%.
m.p.	178°C.
IR(nujol)	cm^{-1} 1780(s), 1700(s), 1670(s), 1610(m), 1580(m), 1510(w).
^{1}H-NMR (200MHz)	δ 6.80-8.05(m, 28H), 12.4(s, 1H).
MS	m/z 366 (M^+-Ph_3P=O, 1%), 352(4), 345(15), 318(31), 303(100), 277(84), 262(5), 199(11), 183(13), 152(4), 118(5), 93(6), 77(8).

Synthesis of compound 97

To a stirred solution of 1.15g(10mmol) of proline in 20ml of water, was added 0.84g(10mmol) of $NaHCO_3$, followed by 1.1g(10mmol) of ethyl chloroformate and the reaction mixture was stirred for 12h at 25°C. The reaction mixture was then extracted with ethylacetate repeatedly and the combined extracts were washed with brine. Drying over anhydrous Na_2SO_4 and evaporation of the solvent afforded the required product **97**.

Yield	73%.
IR(nujol)	cm^{-1} 1740, 1700.
^{1}H-NMR (200MHz)	δ 1.14-1.30(m, 3H), 1.80-2.30(m, 4H), 3.32-3.64(m, 2H), 4.00-4.20(m, 2H), 4.25-4.43(m, 1H), 9.55(s, 1H).
MS	m/z 187(M^+).

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CHAPTER - 3

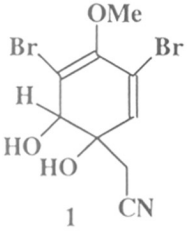
CATALYTIC HALOGENATION OF SELECTED ORGANIC COMPOUNDS MIMICKING VANADATE-DEPENDENT MARINE METALLOENZYMES

INTRODUCTION

Ocean water is rich in chloride (~0.5M), bromide (~1mM) and iodide (~1μM) and because of this, marine organisms have developed a means to incorporate halogens into their metabolites. Many of these halogenated compounds are thought to be involved in chemical diffuse roles to keep predators away from a particular organism and also these are of pharmacological interest due to their biological activities which include antifungal, antibacterial, antineoplastic, antiviral, antiinflammatory etc.

Marine natural products exhibit a considerable abundance of halogenated (Cl, Br, I) organic compounds compared to the natural products from the terrestrial species. They include volatile compounds such as hydrocarbons produced in large quantities, e.g., $CHBr_3$, CH_2Br_2, CH_3I, bromochloroanisoles etc. which are reported to be responsible for the ozone destruction comparable to the one produced from industry.[1] A variety of temperate marine microalgae (the brown algae *Ascophyllum nodosum* and *Fucus Vesiculosis*, the green algae *Enteromorpha Linza* and *Vlva Lacta* and the red alga *Gigartina Stellata*) contain these volatile halogenated organic compounds and also release them to the sea water at the rate of nanograms and micrograms of each compound per gram of dry alga per day.[2] The algae also release compounds such as ethyl iodide, isopropyl iodide, *n*-propyl iodide, 1-iodobutane, 1-iodopentane, 1-bromopropane etc. Phenolic derivatives such as **1** (**Fig. 1**) an antimicrobial metabolite from sponges[3] or 14-debromoprearaplysillin **2** from the sponge *Druinella Purpurea*[4] or the antimicrobial compound 2-(2'-bromophenoxy)-3,4,5,6-tetrabromophenol **3** from the sponge *Dysidea*,[5] terpenoids such as solenolide E **4**,[6] brominated and chlorinated indoles e.g., 5-bromo-N,N-dimethyltryptamine **5**[7] etc. were also found in the marine world. Tyrian purple **6** is one of the well known marine natural products isolated from a marine mollusk.

Fig. 1



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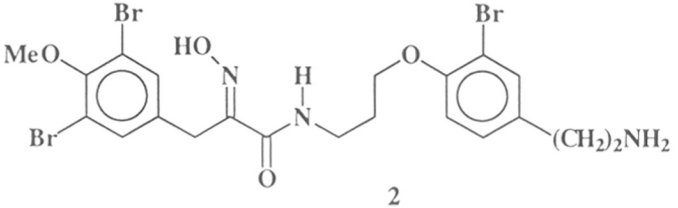

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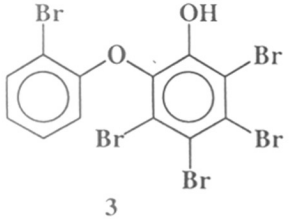

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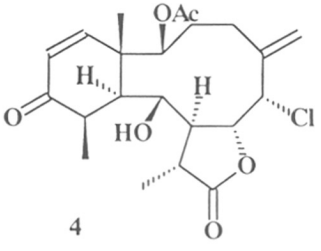

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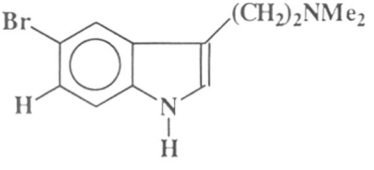

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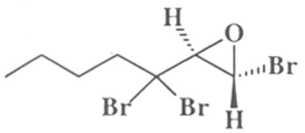
The family of marine red algae *Bounemaisoniaceae* has revealed the presence of the following compounds[8] (**Fig. 2**).

Fig. 2



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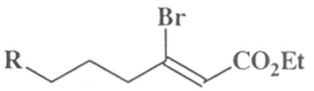

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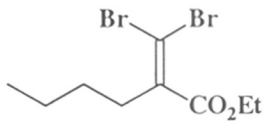

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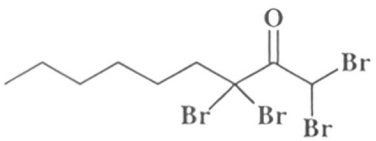

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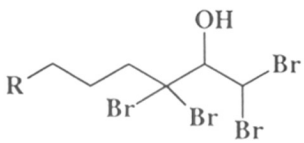

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It is becoming increasingly clear that nature produces a wide variety of halometabolites. These vary from iodinated thyroid harmones[9] in mammals to toxic fluorinated fatty acids produced by certain plants.[10] A large number of metabolites are also produced by fungi,[11] actinomycetes[12] and marine organisms as described earlier.

How do these halogenated compounds get produced in the nature or marine world?

Marine natural products chemists have long invoked the role of haloperoxidases in the biogenesis of the halogenated marine natural products. Haloperoxidases (chloro, bromo & iodo) have found virtually in all class of marine organisms. Many species of marine algae have bromoperoxidase activity e.g., *Rhodophyta* were the richest and *Pheophyta* were the poorest.

Haloperoxidases are enzymes that catalyze the oxidation of a halide (i.e., chloride, bromide & iodide) by hydrogen peroxide, a process which results in the concomitant halogenation of organic substrates (**Scheme 1**).

Scheme-1

$$Org\text{-}H + X^- + H_2O_2 + H^+ \longrightarrow Org\text{-}X + 2H_2O$$

The nomenclature for the haloperoxidases is based on the most electronegative halide which is able to be oxidized by H_2O_2 catalyzed by the enzyme. Thus, chloroperoxidase catalyses the oxidation of Cl^-, Br^-, and I^- by H_2O_2, bromoperoxidase catalyses the oxidation of Br^- and I^-, while iodoperoxidase catalyses the oxidation of only iodide.

There are mainly two types of haloperoxidases which have been isolated and characterized from marine world.

1. Vanadium bromoperoxidase (V-BrPO) - a nonheme enzyme

2. Fe-Heme bromoperoxidase (Fe-Heme-BrPO)

Terrestrial haloperoxidases such as chloroperoxidase, the Fe-Heme enzyme from the fungus *Caldaromyces fumago*,[13] mammalian haloperoxidases such as eosinophil peroxidase[14] salivary and lactoperoxidase found in saliva and tears[14] and bacterial haloperoxidases etc. have also been isolated and characterized. Recently, a new enzyme methyl transferase was isolated from a marine alga that catalyses the formation of methyl chloride[15] which uses S-adenosyl methionine as the carbon source.

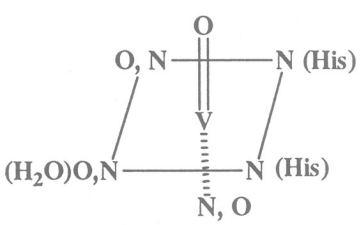
Vanadium Bromoperoxidase (V-BrPO)

1. Characteristics

Vanadium bromoperoxidases are all acidic glycoproteins with very similar amino acid composition, molecular weight, charge and vanadium content.[16] The subunit molecular weight of V-BrPO is ~65,000 and it binds approximately 1equiv. of vanadium per subunit.

The oxidation state of vanadium in V-BrPO is vanadium (V). This was found by extended X-ray adsorption fine structure (EXAFS) analysis and the vanadium is believed to be a distorted octahedron coordinated by a single terminal oxide ligand at 1.61Å, three unknown light atom donors at 1.72Å and two nitrogen donors at 2.11Å (**Fig. 3**).

Fig. 3



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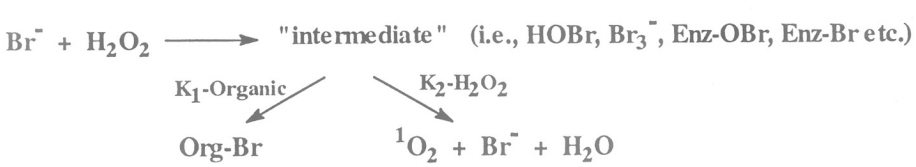
2. Reactivity

Vanadium bromoperoxidase was first discovered in the brown alga *Ascophyllum nodosum*.[17] This enzyme has been shown to catalyze the bromination of monochlorodimedone(MCD) using H_2O_2 as an oxidant of bromide. In the absence of an organic substrate V-BrPO catalyses the formation of dioxygen (**Scheme 2**). Kinetic investigations[18] of the rate of dioxygen formation and MCD bromination catalyzed by V-BrPO indicate that both reactions proceed via the formation of a common intermediate as shown below:

Scheme-2

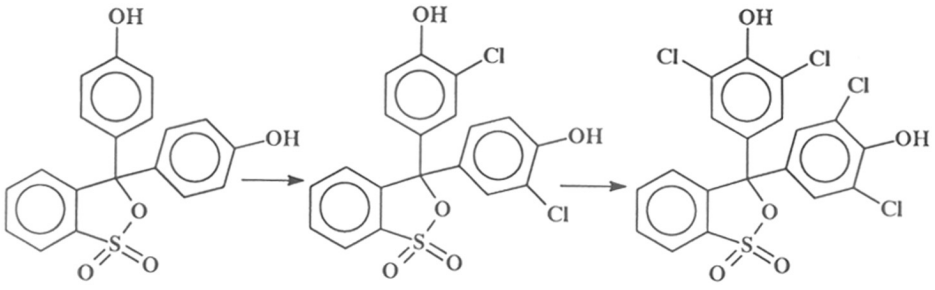


Bromoperoxidases generally catalyze the oxidation of bromide by H_2O_2 which results in the bromination of suitable organic substrates. A variety of organic substrates were brominated including ß-diketones, ß-ketoacids, phenols, nitrogen and sulphur heterocycles etc.[14] Vanadium containing bromoperoxidases are also responsible for the production of bromoform and other halogenated compounds. These are present in brown seaweeds and produce HOBr and Br_2 in solution. This enzymic activity is linked to the observed ozone destruction which is of the order of magnitude as the production by industry as mentioned earlier.

Bromoperoxidase activity was detected by soaking the bromoperoxidase sample in 35μM phenol red and subsequently in a medium containing 2mM H_2O_2, 0.1M KBr and 0.1M potassium phosphate (pH = 6.5). When bromoperoxidase activity is present phenol red is brominated as detected by the formation of brown colour.[19]

V-BrPO also catalyses chlorination reactions.[20] V-BrPO isolated from the brown alga *Ascophyllum nodosum* catalyses the conversion of 0.1mM phenol sulphonephthalein (i.e., phenol red) to the tetrachlorinated derivative as identified by electron impact mass spectral analysis under the conditions of 0.1M KCl, 2mM H_2O_2 and 0.3μM V-BrPO in 0.1M citrate buffer of pH 5 (**Scheme 3**).

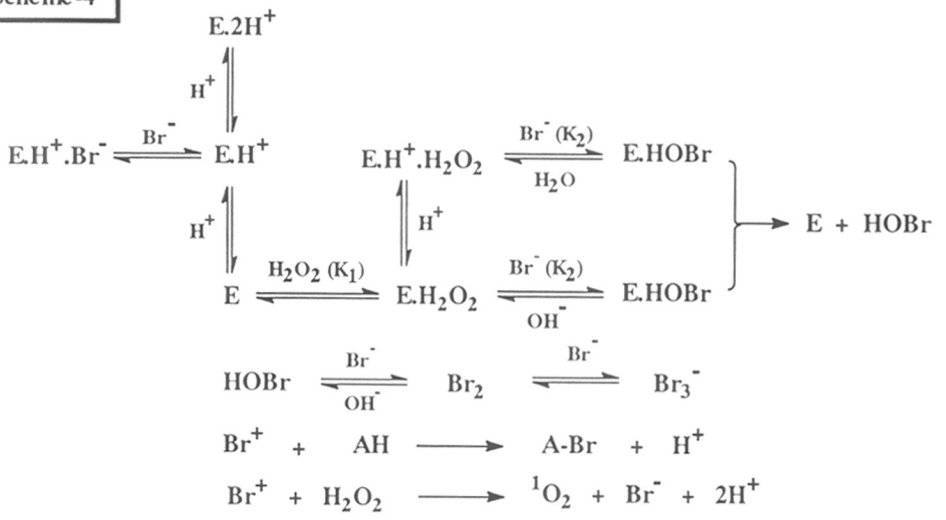
Scheme-3



3. Reaction Mechanism

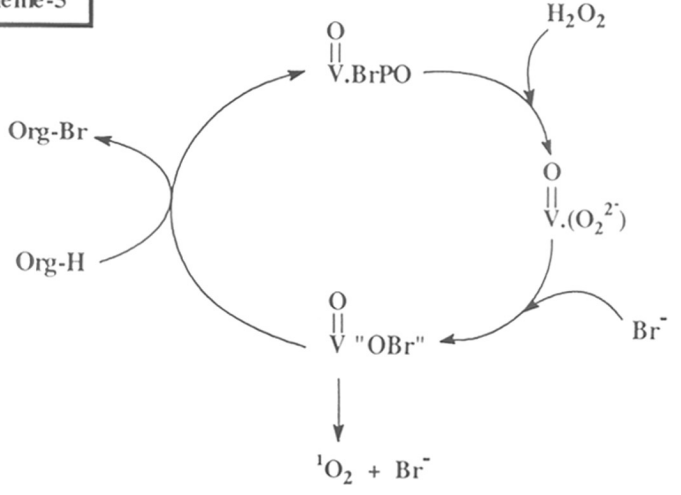
This was studied by measuring bromination rates of the nucleophile 2-chlorodimedone at a variety of concentrations of both H_2O_2 and bromide and at various values of pH. The results show that H_2O_2 and bromide (as a substrate) react with the enzyme in an ordered mechanism. Since the reaction between native bromoperoxidase and bromide is competitive with the binding of H_2O_2, it is obvious that H_2O_2 adds first to the enzyme and that bromination is the second substrate in the catalytic cycle. The mechanism can be written as follows (**Scheme 4**):

Scheme-4



Tromp et al.[21] have found by spectrophotometric analysis that during the reaction H_2O_2 binds first to V-BrPO by coordination to the vanadium. They also observed a small absorbance decrease between 300nm and 340nm upon addition of H_2O_2 to V-BrPO and the original UV spectrum reappears upon the addition of bromide. However, in a different set of experiments Butler et al.[22] observed that stoichiometric bromination of MCD does not occur by the addition of excess bromide to relative high concentrations of V-BrPO. Thus, V-BrPO does not oxidize bromide in the absence of a peroxide source. Based on these facts a cyclic mechanism where H_2O_2 coordination followed by bromide oxidation is proposed (**Scheme 5**).

Scheme-5



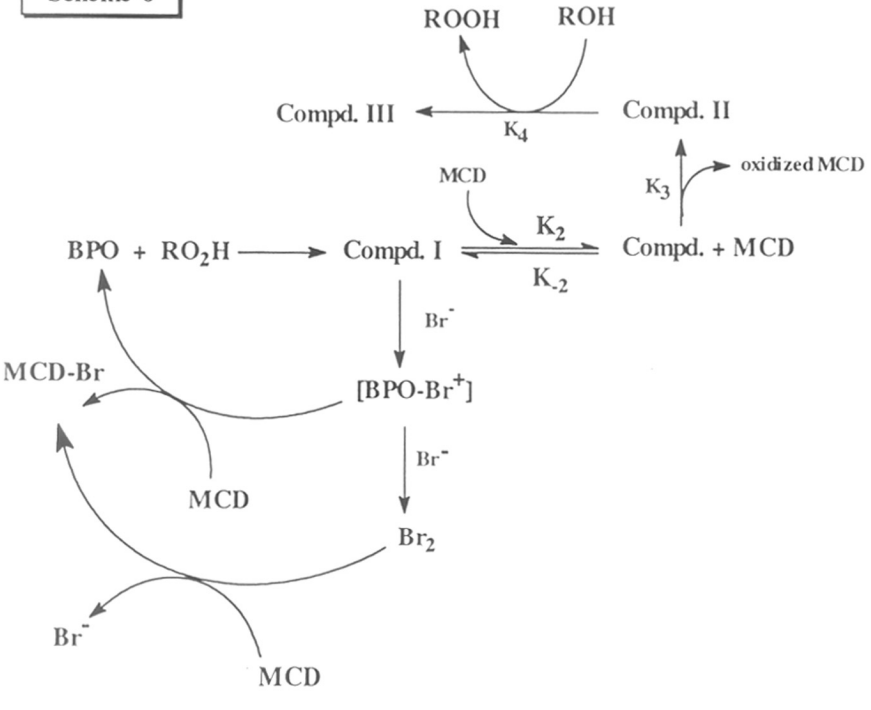
The exact role of the active site of the vanadium ion and its change of oxidation states during the reaction are not clearly understood.

Fe-Heme Bromoperoxidase

Fe-Heme BrPO is a dimeric protein (MW 97,600) comprised of two identical subunits each containing a tightly bound ferriprotoporphyrin IX moiety.[23] It has been isolated from several marine sources[24] and the most thoroughly characterized is one isolated from green alga *Penicillus Capitatus*. In Fe-Heme BrPO the Fe-Heme moiety is present in a high spin electronic configuration.[25]

In addition to the haloperoxidase activity Fe-Heme BrPO catalyses free radical peroxidation reactions[23] such as single electron oxidation of phenolic compounds (pyrogallol, hydroquinone etc.), monochlorodimedone etc. in the absence of halide. In these reactions compound I is reduced to compound II (Heme-Fe^{II}=O) by one electron and the organic radical. Compound III is also observed by the compound with excess H_2O_2[25] (**Scheme 6**).

Scheme-6



Chloroperoxidase

As mentioned earlier, chloroperoxidase, the Fe-Heme enzyme which is excreted by the fungus *Caldariomyces fumago* was found to be involved in the biosynthesis of Caldariomycine. The formation of this antibiotic either involves HOCl or an enzyme bound intermediate E-HOCl. The general mechanism can be written as follows similar to the one mentioned for V-BrPO (**Scheme 7**).

Scheme-7

$$E. + H_2O_2 \rightleftharpoons E.H_2O_2$$

$$E.H_2O_2 + H^+ + X^- \rightleftharpoons E.HOX + H_2O$$

$$E.HOX + AH \longrightarrow E. + A\text{-}X + H_2O$$

$$E.HOX \longrightarrow E. + HOX$$

where E represents the haloperoxidase, X=Cl^-, Br^-, I^- and AH a nucleophilic reagent. When X = I^- peroxidation led to the formation of elemental iodine.[13] Evidence for this anionic electrophilic substitution reaction mechanism is also reported.[26]

β-Keto adipic acid was chlorinated with Cl^- to form δ-chlorolevulinic acid using this enzyme.[27] Biological chlorination of β-keto adipate illustrates this class of reaction[28] (**Scheme 8**).

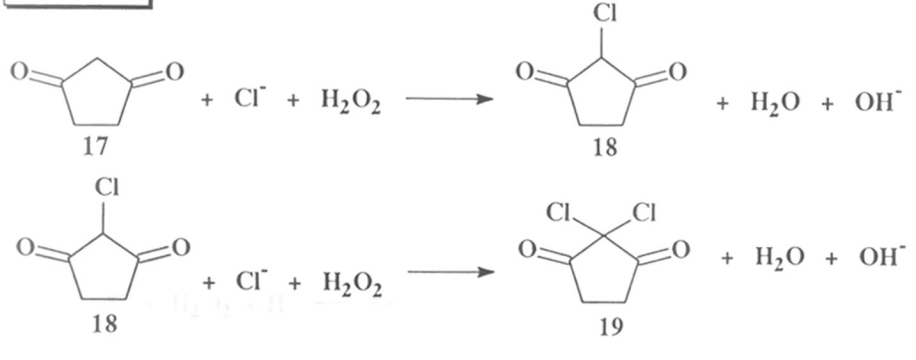
Scheme-8

$$^-O_2CCH_2CH_2COCH_2CO_2^- + Cl^- + 1/2O_2 + 2H^+ \longrightarrow CO_2 + {}^-O_2CCH_2CH_2COCH_2Cl + H_2O$$

15 16

Chlorination of 1,3-cyclopentadione was also found to be effective using chloroperoxidase[29] (**Scheme 9**).

Scheme-9



OBJECTIVE

1. Our first objective was to mimic VPO with simple vanadium compounds such as ammonium metavanadate, vanadium pentoxide etc. The idea was to take simple vanadium compounds e.g., NH_4VO_3 and stimulate marine like environment in the flask. However, to handle organic compounds, little bit of organic solvents are essential. Thus, a biphasic system was our first choice. Later, single phase reaction was attempted by using quarternary ammonium salts such as tetrapropyl ammonium bromide.
2. If we succeed then it will offer unprecedented opportunity of halogenating C-H bonds in organic chemistry in an aqueous environmentally friendly way. This study opens up opportunities for developing green chemistry and technologies. Earlier halogenation methodologies contribute to pollution.
3. The simple mimic will also help in understanding the complex active site of VPO.

RESULTS AND DISCUSSIONS

As mentioned in the introduction marine natural products exhibit a considerable abundance of halogenated organic compounds, compared to the natural products from the terrestrial species. While the catalytic oxyfunctionalization of relatively inert C-H bonds has attracted significant attention either by mimicking biocatalysts,[30-32] or via zeolites,[33] little attention has been given to catalytic halogenation studies mimicking marine metalloenzymes. The biogenesis of halogenated organic compounds is presumed to involve recently discovered vanadate dependent non-haem marine metalloenzymes.[34] For example, vanadium bromoperoxidase and iodoperoxidase which catalyze the oxidation of chloride, bromide and iodides by H_2O_2 or other peroxides in the presence of their inorganic sodium or potassium salts. Since the conventional method of halogenating the organic substrates (aliphatic or aromatic) involves hazardous chemicals such as chlorine, bromine etc., an idea was conceived based on the role of haloperoxidases in the synthesis of halogenated natural products. This method will have a lot of advantages over the conventional method if it is commercially viable. Pollution can drastically be reduced by this method. Easy handling of chemicals and abundance of inorganic salts will lead to safer and environmentally friendly chemistry.

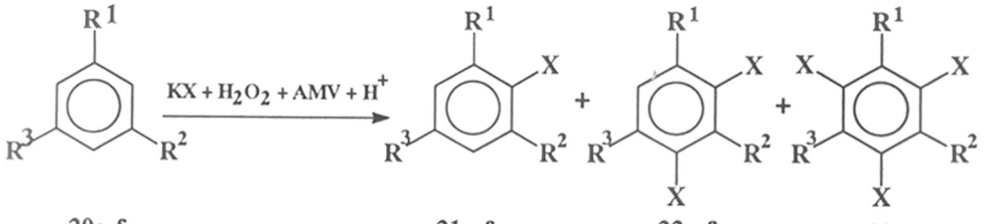
In an attempt we have used ammonium metavanadate as the catalyst for the halogenation of a variety of organic substrates from potassium halides and dilute H_2O_2 (**Scheme 10**).

Scheme-10

$$R\text{-}H + X^- + H_2O_2 + H^+ \longrightarrow R\text{-}X + 2H_2O$$

Some of the substrates examined in our studies with AMV are phloroglucinol (**20a**), resorcinol (**20b**), phenol (**20c**), 1,3,5-trimethoxybenzene (**20d**), 1,3-dimethoxybenzene (**20e**), isobutylbenzene (**20f**), with various potassium salts (KX, X = Cl, Br, I and F), including TPAB (tetraisopropyl ammonium bromide) (see **Table 1, Scheme 11**).

Scheme-11



20a-f **21a-f** **22a-f** **23a-f**

a, $R^1=R^2=R^3=OH$
b, $R^1=R^2=OH$, $R^3=H$
c, $R^1=OH$, $R^2=R^3=H$
d, $R^1=R^2=R^3=OMe$
e, $R^1=R^2=OMe$, $R^3=H$
f, $R^1=CH_2\text{-}CH(CH_3)_2$, $R^2=R^3=H$

In all the experiments the substrate concentration was kept constant(1eq) varying halide KX (1 to 6eq), H_2O_2 (1.2 to 7.2eq) and catalyst NH_4VO_3 (0.05 to 0.3eq). Normally, a 2:1 mixture of MeCN:H_2O or MeOH:H_2O were used as solvent.

Several characteristic features from the Table 1 are summarized as follows:

(a) Catalytic amount of AMV (0.03-0.1eq) can halogenate electron rich organic substrates from potassium halides (KBr and KCl, 1eq) and H_2O_2 (1.1-1.2eq) in moderate to good yields. (b) Unlike KBr and KCl, KI and KF fail to halogenate (entry 18 and 19). (c) Excess KBr, along with appropriate amount of H_2O_2 leads to di- and tribromoproducts (entry 2 and 12). However, this pattern of reactivity is also a function of nature of substrates. (d) The presence of enzyme mimic, AMV, is a must for halogenation (entry 5 and 6). (e) The presence of H_2O_2 is also necessary for the success of halogenation (entry 7). (f) It is possible to do bromination only in H_2O (entry 13). (g) The nature of counter ion is not relevant as tetraisopropyl ammonium bromide could also lead to effective bromination even in CH_2Cl_2 (entry 17). The purpose of choosing TPAB and CH_2Cl_2 was to enhance miscibility of reaction

Table 1 Catalytic halogenation mimicking marine metalloenzymes.

Entry No.	Substrate	Halide Source	Molar Ratio[a]				Solvent[b]	Durn.[c]	Convn.[d]	Product(s)(%)[e]
			Sub.	KX	H_2O_2	Cat.				
1	**20a**	KBr	1	1	1.2	0.05	A	15	90	**21a**(75)
2	**20a**	KBr	1	2	2.4	0.1	A	15	92	**21a**(24),**22a**(60)
3	**20a**	KBr	1	3	3.6	0.15	A	15	95	**22a**(75)
4	**20a**	KBr	1	6	7.2	0.3	A	15	96	**22a**(80)
5	**20a**	KBr	1	1	1.2	0.0	A	15	0	**20a**(90)[f]
6	**20a**	KBr	1	3	3.6	0.0	A	15	0	**20a**(85)[f]
7	**20a**	KBr	1	3	0.0	0.1	A	15	0	**20a**(92)[f]
8	**20b**	KBr	1	1	1.2	0.05	A	20	40	**21b**(32)
9	**20b**	KBr	1	2	2.2	0.1	A	20	45	**21b**(37)
10	**20c**	KBr	1	2	2.4	0.1	A	20	0	**20c**(90)[f]
11	**20d**	KBr	1	1	1.2	0.05	B	24	95	**21d**(90)
12	**20d**	KBr	1	3	3.6	0.1	B	24	98	**21d**(43),**22d**(20), **23d**(13)[g]
13	**20d**	KBr	1	1	1.2	0.1	H_2O	24	20	**21d**(10)
14	**20d**	KBr	1	3	3.6	0.1	B	24	55	**21d**(40)
15	**20e**	KBr	1	2	2.4	0.05	A	24	73	**21e**(65)
16	**20e**	KCl	1	2	2.4	0.1	A	24	65	**21e**(45)
17	**20e**	TPAB[h]	1	2	2.4	0.1	CH_2Cl_2	24	30	**21e**(23)
18	**20e**	KI	1	2	2.4	0.1	A	24	0	**20e**(90)[i]
19	**20e**	KF	1	2	2.4	0.1	A	24	0	**20e**(92)
20	**20f**	KBr	1	2	2.4	0.1	A	24	20	**21f**(15)
21	**20f**	KBr	1	5	6.2	0.2	A	24	50	**21f** (18)[j]

[a] Molar ratio of substrates : halide source (KX) : 30% H_2O_2 : ammonium metavanadate (catalyst and enzyme mimic) at pH = 4-5 in indicated solvents is shown. Usually 10-20% excess of H_2O_2 with respect to KX was utilized. [b] Normally a 50 ml batch of 2:1 mixture of either CH_3CN:H_2O (A) or CH_3OH:H_2O (B) was stirred at room temperature. [c] Number of hours stirred at room temperature. [d] % conversion of starting materials determined by capillary GC. [e] The % product(s) formation, as isolated by column chromatography, after appropriate work-up. Complementary observations were made by GC of reaction mixtures as well. [f] Usually in control experiments, >90% of substrate was recovered. [g] The products are confirmed by GC-MS as well. [h] Tetraisopropyl ammonium bromide was used. [i] Only iodine (I_2) was isolated. [j] Other side products were isopropylphenyl ketone (19%) and its reduced form (3%).

mixture. (h) The ortho-halogenation in all these studies is indeed unique and unprecedented (entry 8, 9, 15-17, 20-21). (i) Additionally, other probable VPO mimics e.g., $VO(SO_4)$, V_2O_5 etc. failed to do halogenation in above studies.

The probable mechanism can be visualized as oxidation of X^- to X° (may dimerize to X_2), which may be further oxidized to X^+ (as XOH). Although liberation of Br_2 is observed in the absence of organic substrates and I_2 could be even isolated (entry 18), but the absence of benzylic bromination rules out the intermediacy of long lived radicals. The various oxidizing species involved during oxidation could be oxyperoxides or oxovanadium (VO_2^+, **5**), peroxovanadium [$VO(O_2)^+$, **6**], diperoxovanadium [$VO(O_2)_2^-$, **7**] and/or hydroxyperoxides (HO-V-O-O-H, **8**). Indeed, ^{51}V-NMR studies indicate the presence of -540.13ppm (for **5**), -468.6, -486.7 (for **6**) and -654.8 (for **7**)[35] relative to $VOCl_3$, $\delta = 0$ ppm (see ^{51}V-NMR spectra). Although, these δ values are close to the reported values for the above species indicated,[35] but our reaction conditions are different. Hence, one cannot make a definitive statement as ^{51}V-NMR values are known to vary due to nature of substituents, geometry (tetrahedron, pyramidal, octahedral etc), coordination environment and solvent effects. Oxyperoxides and hydroxyperoxides are known to be the oxidizing species in titanium and vanadium containing silicate molecular sieves (TS-1, VS-1, V-NCL-1 etc.) in the presence of H_2O_2.[33,36-39] The peroxovanadium **6** has also been implicated in oxidation studies.[40] The halogenating species can be X^+ as XOH or X_3^-,[41] but extreme ortho-selectivity associated with electron rich aromatics is intriguing.[42] The absence of iodination can be understood in terms of easy reduction of oxo-vanadium **5** with iodide,[43] thereby destroying the catalyst, whereas the absence of fluorination can be explained in terms of instability of F-OH species.[44,45]

In the similar way use of novel zeolite V-NCL-1 for the selective halogenation of organic substrates is in progress in our group.

^{51}V-NMR Experiments:

All the experiments were carried out using a Teflon tube of 1cm size with D_2O lock and spin frequency of 20 rpm.

Plot no. 1 — 50mg of NH_4VO_3 in CH_3CN:H_2O(20:10ml) + $HClO_4$ (pH~4).

Plot no. 2 — no. 1 + 0.33g of 30% H_2O_2 + 0.2g of dimethoxy benzene.

Plot no. 3 — no. 2 + 0.345g of KBr.....(zero hour).

Plot no. 4 — no. 3 after 1h of ageing.

Plot no. 5 — no. 3 after 16h of ageing.

Plot no. 6 — no. 5 + H_2O_2 (excess) + $HClO_4$ (excess pH ~2.5-3.0).

Plot no. 7 — no. 1 + H_2O_2 + KBr (without the substrate).

Plot no. 8 — no. 7 after 1h.

Plot no. 9 no. 7 after 16h.

Plot no. 10 NH_4VO_3 + CH_3CN:H_2O + H_2O_2 (pH = 6.5-7).

Plot no. 11 NH_4VO_3 + distilled water (pH = 6.5-7).

The following observations were made from the ^{51}V-NMR studies:

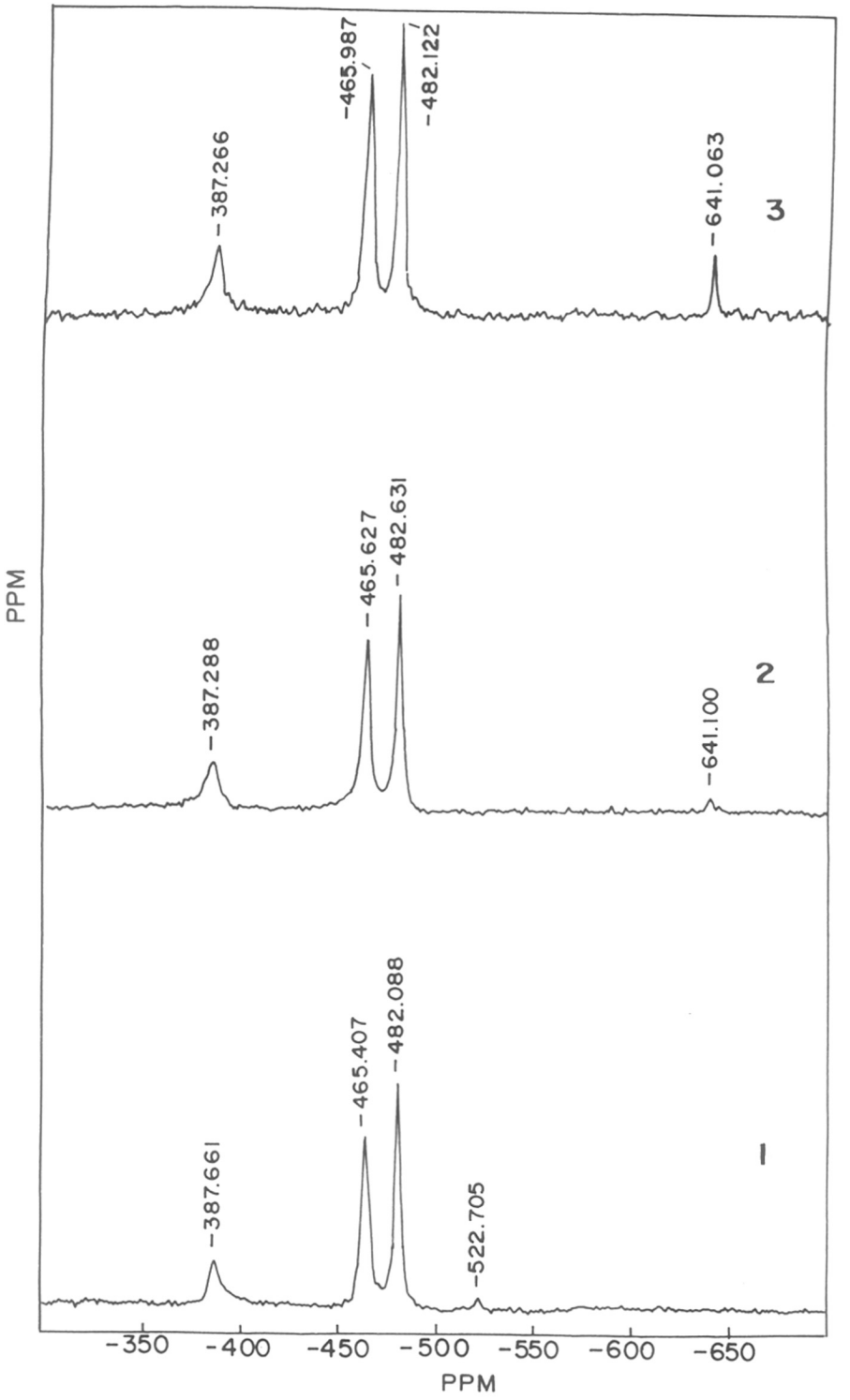
1. Ammonium metavanadate (AMV) in 2:1 mixture of acetonitrile and water at pH ~4 shows three reactive species at δ -387, -465 and -482 (plot 1).
2. All the above three species are quenched by the substrate in the presence of H_2O_2 and KBr (plots 3-5).
3. A new peak appears at δ 641 which is not reactive (or less reactive). This peak also appears in the absence of the substrate, but the other three reactive species remain throughout in the absence of the substrate (plots 7-9).
4. At neutral pH AMV and H_2O_2 give a peak at δ 654 which is unreactive (plot 10) and a peak was also observed at δ 540 for AMV in distilled water (plot 11).

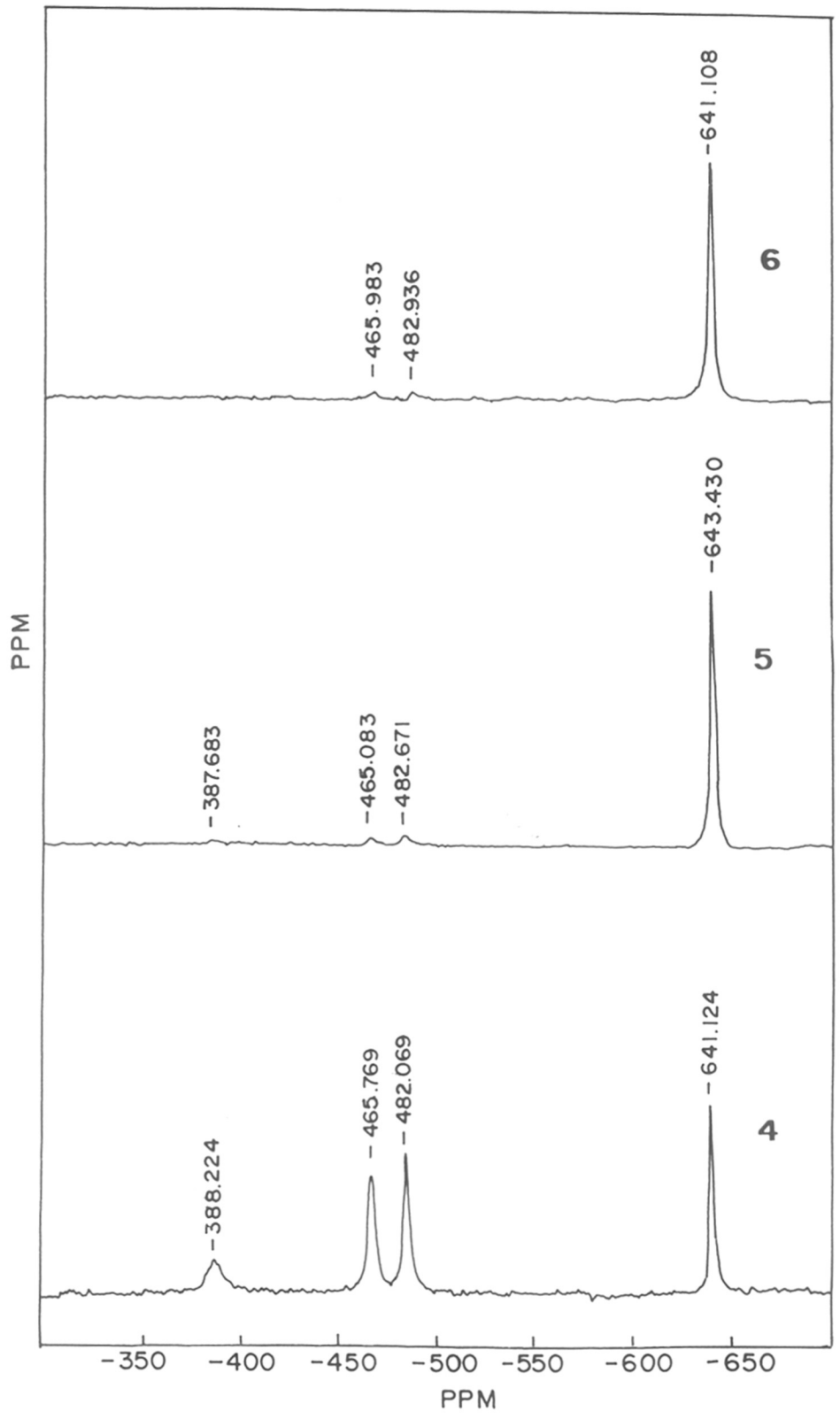
CONCLUSIONS:

The conclusion and future possibilities of preceding studies can be as follows:

A simple vanadium compound e.g., ammonium metavanadate has been shown to mimic the halogenation of aromatic substrates, similar to marine metalloenzyme VPO, in a near marine experimental conditions. Naturally, doing halogenation in an aqueous environment and utilizing both atoms of halogen during halogenation triggers hope for developing environmentally friendly halogenation technologies in future. The fact that simple vanadium compounds can halogenate organic substrates and mimic VPO, indicates the possibility of a nonenzymatic abiological route for halogenated compounds in marine world. This study is quite contemporary and of recent origin. Similar carbon-hetero bond formation can be attempted with vanadium compounds. The nature of reactive species has been verified by ^{51}V-NMR. Interestingly, similar reactive species have been proposed during vanadium molecular sieves oxidation studies (VS-1, V-NCL-1 etc.) Naturally, above halogenation studies trigger hope for developing heterogeneous halogenated methodologies of commercial significance.

^{51}V-NMR SPECTRA

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-465.983
-482.936
6
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-387.683
-465.083
-482.671
5
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-482.069
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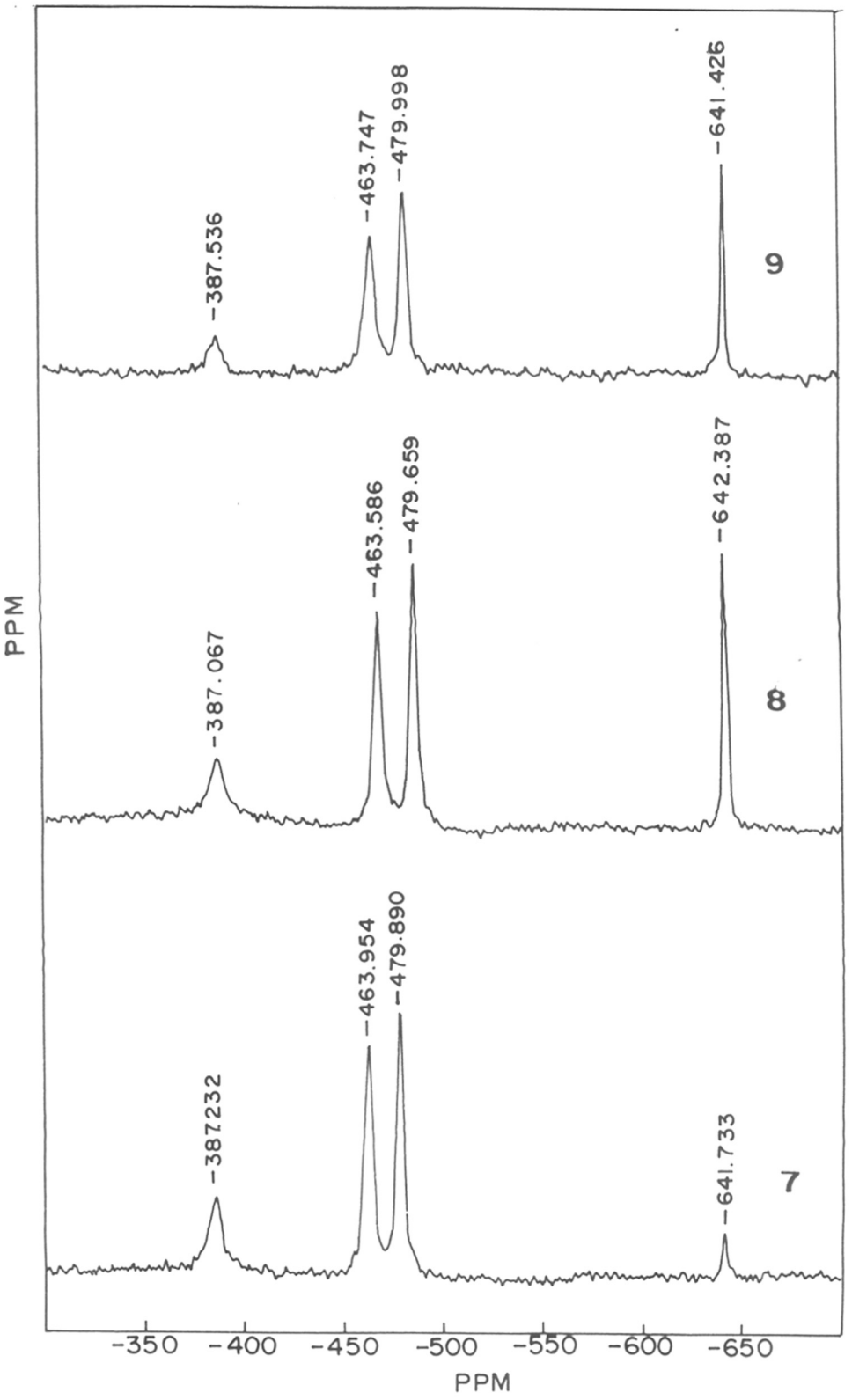
-400
-450
-500
-550
-600
-650
PPM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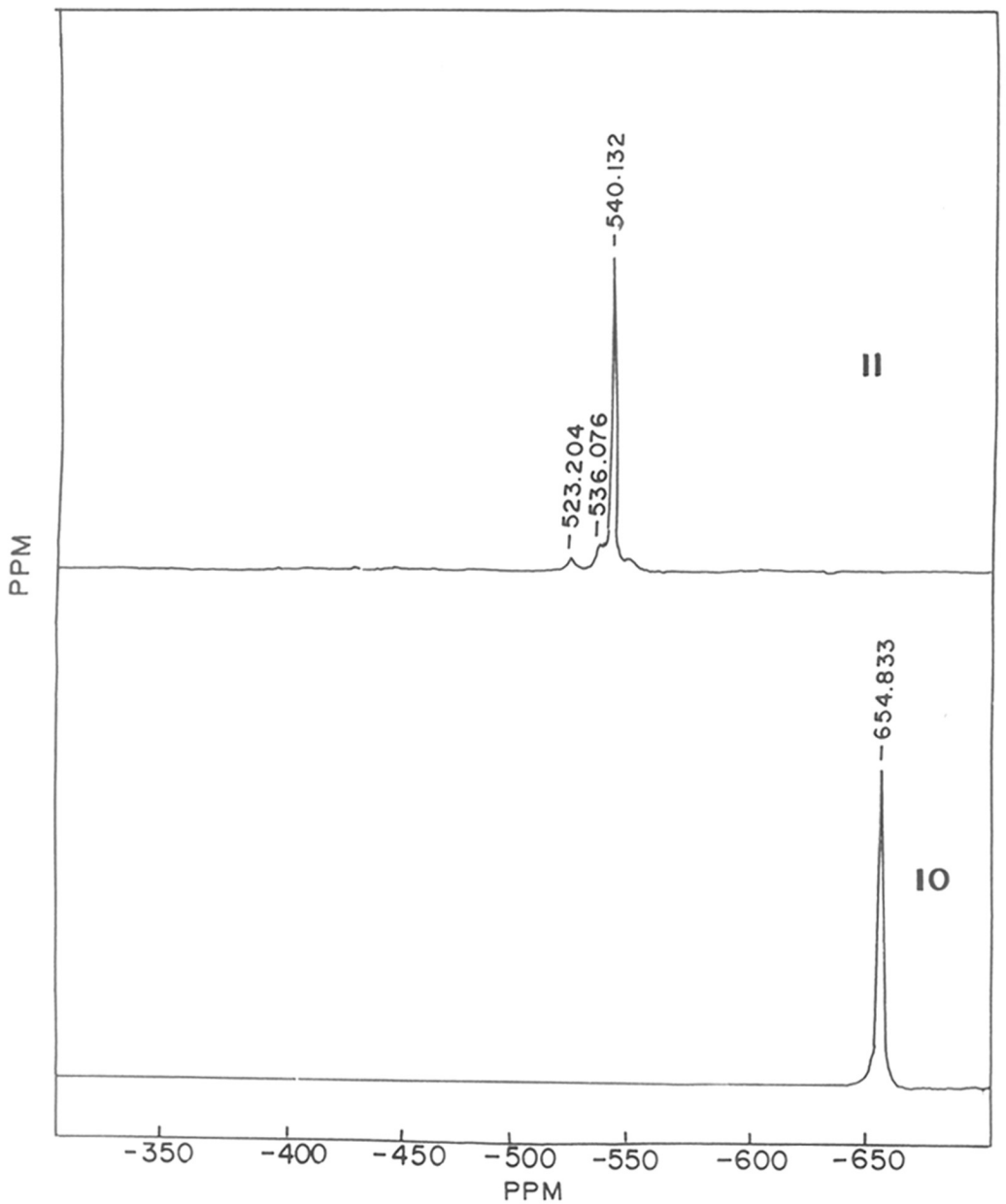
-600
-650
PPM


-540.132
-523.204
-536.076
11
-654.833
10
PPM
-350
-400
-450
-500
-550
-600
-650
PPM

EXPERIMENTAL

In all the experiments 30% H_2O_2 was used. KBr was used as the halide source. The product conversion was determined by GC and yields by isolation. In most of the cases the authentic compounds were prepared by conventional method and compared by GC analysis. GC-MS was used to confirm the products. To check the structure for orthoselectivity either ^{1}H-NMR or GC with authentic compounds were used.

General procedure for catalytic halogenation

In a typical experiment, to a solution of 0.5g (3.96mmol) of phloroglucinol, 0.944g (7.93mmol) of KBr, 0.046g (0.39mmol) of NH_4VO_3 in 50ml of MeCN:H_2O (2:1 ratio), dilute $HClO_4$ was added until pH 5. Subsequently 1.07ml (9.5mmol) of 30% H_2O_2 was added dropwise in a period of 2h during which time the colour of the reaction mixture changes from colourless to pale yellow to orange. The closed reaction mixture was stirred for 15h at room temperature. Addition of 10ml of saturated $NaHSO_3$ followed by 10ml of brine and finally the solution was extracted with ether. The ether layer was dried over anhydrous Na_2SO_4 and concentrated. Column chromatography on silica gel using 90:10 pet. ether:ethyl acetate afforded 0.195g (24%) of **2a** and 0.68g (60%) of **3a**.

Data for selected compounds are as follows: For molar ratios, solvent system and yields of the products, see the **Table 1.**

2-Bromo-1,3,5-trihydroxybenzene (21a)

m.p.	140-142°C
IR(nujol)	cm^{-1} 3460(br), 1600(s), 1490(s), 1450(s).
^{1}H-NMR (80MHz, $CDCl_3$ + acetone-d_6)	δ 6.42(s, 1H), 9.02 (brs, 3H).
MS	m/z 205 (M^+, 100%), 264(6), 253(2), 174(8).

2,4-Dibromo-1,3,5-trihydroxybenzene (22a)

m.p.	145-147°C
IR(nujol)	cm^{-1} 3445(br), 1615(s), 1500(s), 1460(s), 1065(s), 840(s), 720(s).
^{1}H-NMR (80MHz, $CDCl_3$ + acetone-d_6)	δ 6.25(s, 1H), 9.15(s, 1H), 10.05(s, 2H).
MS	m/z 284(M^+, 100%), 204(11), 175(30), 157(30), 119(32), 95(62), 69(90).

2-Bromo-1,3-dihydroxybenzene (21b)

m.p.	101-102°C.
IR(nujol)	cm^{-1} 1605(s), 1500(s), 1480(s), 1380(s), 1215(s), 1075(m), 865(w), 765(s).
^{1}H-NMR (80MHz, $CDCl_3$ + acetone-d_6)	δ 6.43-6.57(d, 2H), 6.87-6.93(t, 1H), 9.82-10.05(bs, 2H).
MS	m/z 188 (M^+, 100%), 110(33), 81(34), 69(5).

2-Bromo-1,3,5-trimethoxybenzene (21d)

m.p.	98-99°C
IR(nujol)	cm^{-1} 1600(s), 1505(s), 1370(s), 1275(s), 805(s), 700(s).
^{1}H-NMR (80MHz)	δ 3.78(s, 3H), 3.85(s, 6H), 6.56-6.63(d, 2H).
MS	m/z 247 (M^+).

2,4-Dibromo-1,3,5-trimethoxybenzene (22d)

m.p.	130-131°C
IR(nujol)	cm^{-1} 1600(s), 1510(s), 1385(s), 1260(s), 810(s), 705(s).
^{1}H-NMR (80MHz)	δ 3.87(s, 3H), 3.94(s, 6H), 6.40(s, 1H).
MS	m/z 326 (M^+).

2,4,6-Tribromo-1,3,5-trimethoxybenzene (23d)

m.p.	143-144°C.
IR(nujol)	cm^{-1} 1600(s), 1510(s), 1380(s), 1260(s), 800(s), 700(s).
^{1}H-NMR (80MHz)	δ 3.92(s, 9H).
MS	m/z 405 (M^+).

2-Bromo-1,3-dimethoxybenzene (21e)

IR(nujol)	cm^{-1} 1600(s), 1490(s), 1470(s), 1440(s), 1420(s), 1375(m), 1315(s), 1290(s), 1215(s), 1170(s), 800(s), 705(s).
^{1}H-NMR (80MHz)	δ 3.71(s, 3H), 3.78-3.85(d, 3H), 6.21-6.51(td, 2H), 7.18-7.45(t, 1H).
MS	m/z 216 (M^+, 98%), 173(100), 138(41), 107(42), 79(20).

2-Chloro-1,3-dimethoxybenzene (21e)

IR(nujol)	cm^{-1} 1600(s), 1485(s), 1460(s), 1430(s), 1320(s), 1220(s), 790(m), 710(m).

^{1}H-NMR (80MHz)	δ 3.60(s, 3H), 3.68-3.75(d, 3H), 6.14-6.40(m, 2H), 7.00-7.14(dd, 1H).
MS	m/z 172 (M^+, 100%), 138(16), 129(41), 109(9), 79(3).

2-Bromoisobutylbenzene (21f)

IR(nujol)	cm^{-1} 1600(s), 1585(s), 1455(s), 1240(s), 995(s), 750(s), 725(s).
^{1}H-NMR (80MHz)	δ 1.10-1.27(m, 6H), 2.00-2.38(m, 1H), 2.92-3.18(dt, 2H), 7.40-7.68(m, 4H).
MS	m/z 213 (M^+, 3%), 183(16), 105(100), 77(35), 51(13), 41(10).

The authentic compound for **2f** was prepared according to the literature,[47] which gave a 1:3 mixture of *ortho*- and *para*-bromoisobutyl benzenes. The GC analysis of the authentic compound and **2f** showed that the product **2f** is exclusively the *ortho* isomer.

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