

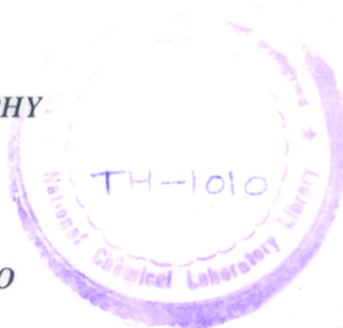
***DEVELOPMENT OF SYNTHETIC METHODOLOGIES
USING PHOTOCHEMICAL TRANSFORMATIONS AND
PHOSPHACUMULENE YLIDE CHEMISTRY AND
THEIR APPLICATIONS TOWARDS BIOLOGICALLY
ACTIVE COMPOUNDS***

NATIONAL CHEMICAL LABORATORY
R. S. P. D. E. BOOK
(NOT TO BE ISSUED)

A Thesis
Submitted to the
UNIVERSITY OF POONA

For the Degree of
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

By
TUNOORI ASHOK RAO

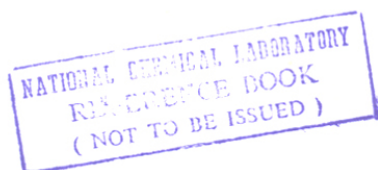


**DIVISION OF ORGANIC CHEMISTRY: TECHNOLOGY
NATIONAL CHEMICAL LABORATORY
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AUGUST 1994

COMPUTERISED

Dedicated to
My beloved Parents,
to Shri Bhoopal Rao
and
to Shri Kishan Rao



COMPUTERISED

CERTIFICATE

Certified that the work incorporated in the thesis entitled "**Development of Synthetic Methodologies Using Photochemical Transformations and Phosphacumulene Ylide Chemistry and their Applications Towards Biologically Active Compounds**" by T. Ashok Rao 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

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I wish to express my deep sense of gratitude to my Ph.D. Supervisor, Dr. Bipin Pandey, Assistant Director, National Chemical Laboratory, for his inspiring guidance, helpful suggestions and never-failing deep interest throughout the progress of this work. The unique experience of working in his group, especially through his group seminars, where whole range of organic chemistry, with particular emphasis on the recent conceptual developments and new emerging frontiers were discussed, it was indeed quite a memorable and joyfully learning experience.

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Tunoori Ashok Rao

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LIST OF PUBLICATIONS

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 reference numbers etc. given in each chapter refer to that particular chapter only.
4. All 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. ^1H -NMR and ^{13}C -NMR spectra were recorded on Varian FT-80A, Bruker WH-90, Bruker AC-200 and Bruker MSL-300 SC-FT spectrometers, using tetramethylsilane as internal standard. The following abbreviations are used :
s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.
9. The mass spectra were recorded on Finnigan MAT - 1020-B-70 ev mass spectrometer.
10. The UV was recorded on Shimadzu model 240 spectrophotometer. Photolysis was conducted in Srinivasan-Rayonet Photoreactor supplied by the Southern New England Co. Model No. RPR-100 with 254, 300 and 350 nm lamps. 200 W Hanovia high pressure lamps were used for large scale photolysis.
11. Elemental analysis were performed by Microanalytical Lab, operated by NCL, Pune.
12. All optical rotations were measured using Sodium D lines on JASCO-181-digital polarimeter at room temperatures.

ABBREVIATIONS

Ac	Acetyl
Ar	Aryl
bp	Boiling point
DABCO	1,4-Diazabicyclo[2.2.2]octane
DMSO	Dimethyl sulfoxide
Et	Ethyl
g	gram/s
HMPA	Hexamethylphosphoramide
h	Hour/s
IR	Infrared
Me	Methyl
min	Minutes
mp	Melting point
M+	Molecular ion
MS	Mass spectrum
nm	Nanometer
pd/c	Palladium (10%) on carbon
Ph	Phenyl
PPTS	Pyridinium paratoluene sulfonate
PTSA	p-Toluene Sulfonic acid
THF	Tetrahydrofuran
THE	Triethylamine
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
UV	Ultraviolet

ABSTRACT

The thesis entitled "**Development of Synthetic Methodologies Using Photochemical Transformations and Phosphacumulene Ylide Chemistry and Their Application Towards Biologically Active Compounds**" is divided into four chapters. The main objective of the thesis revolves around the on-going research programme in our group i.e. control and prediction of stereochemistry in medium cyclic rings via cage compound **1**. With a view to functionalizing the diene frame in **1**, which should ultimately give functionalized medium cyclic ring, two approaches have been employed. The first one involves functionalization of naphthoquinone fragment prior to photolysis, to get cage compound, whereas second approach targets to directly functionalize the diene by employing various concepts of π -face stereoselection. Towards our main objective of synthesizing stereocontrolled medium cyclic rings, β -cleavage studies of above mentioned cage precursors by photo-induced electron transfer (PET) have been examined. Much of the observed chemistry was unanticipated and unexpected in nature. Hence, there arose the need for generalization, mechanistic insights and comparing our observation with existing knowledge. Thus, β -cleavage of cyclobutyl ketones was compared with β -cleavage of cyclopropyl ketone. In continuation, the β -cleavage and allied chemistry was exploited for the synthesis of carbocyclic frame of antitumor Taxol. We reasoned that Taxol is not only a 8-membered ring chemistry, but it is also a chemistry of bicyclic frames with which we are involved above and 10-membered ring, a medium cyclic ring chemistry. Above perceptions have triggered novel approaches towards Taxol skeleton, which is summarized in a separate chapter.

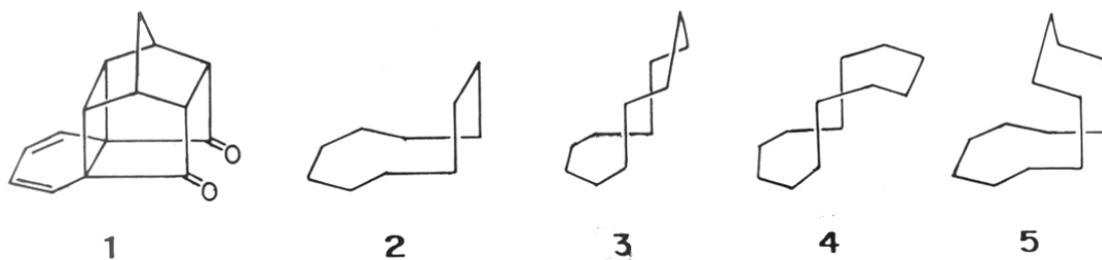
The thesis has also minor diversions in terms of our deep interests in the mechanism of π -face stereoselection and one of our curiosity regarding the relevance of the size of reagent has been addressed through optically active dithiolanes. Additionally, novel ylide chemistry has been employed to get a one-pot procedure for useful skeleton eg. quinolone and benzothiopyran-4-one which are precursors for a biologically active norfloxacin, nalidixic acid and benzothiazepin.

CHAPTER-I

Approaches towards Stereocontrolled Medium Cyclic Rings

The first chapter begins with a brief review of literature regarding the need for stereo-controlled medium cyclic rings with a view to synthesise various biologically useful compounds, describes the complexity of problems and critically assesses the various methodologies available in recent literature. The main stress has been on the recent contributions of Clark Still¹ and Vedes² group. Then our approach via readily available, locked and rigid hexacyclic frame **1**, where we perceive a latent 10, 11 and 12-membered ring is delineated by conformational protection and deprotection methodology.

Scheme 1

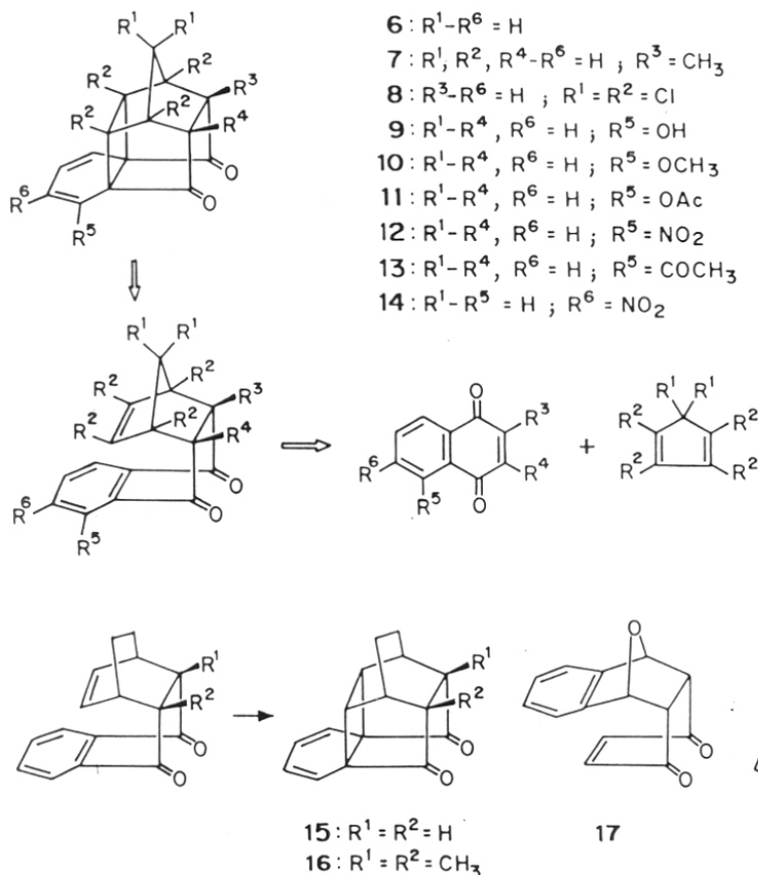


We presume that the various substituents in the norbornane frame in **1** would have predictable stereochemistry, which should remain unchanged in unlocked form as well. The cleavage of cyclobutyl ketone bonds for 11 and 12-membered rings, should be possible either via ketone photochemistry, or Baeyer-Villiger oxidation, carbene addition, lead tetraacetate (LTA) or some other synthetic manipulations. The thermolysis of **1** or its related analogues should cleave cyclobutane in Mehta's metathetic way³, which will offer additional stereocontrol to the incoming reagents to the double bonds. Further, stereocontrol in the diene frame is possible if it exhibits π -face stereoselection. Thus, one can easily visualize a great promise for highly functionalized and stereocontrolled medium cyclic rings via **1**.

SECTION-A: Approaches Towards Functionalised Caged Skeletons

Aryl-olefin *ortho*- and *meta*-photocycloadditions are of considerable interests to synthetic, mechanistic and theoretical organic chemists⁴. One of the important steps in our strategy was the efficient intramolecular aryl-olefin *ortho*-photocycloaddition in tetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13-tetraene-3,10-dione systems. With a view to obtaining functionalized diene frame in **1**, which should provide opportunities for further stereocontrol and should ultimately lead to functionalized stereocontrolled medium cyclic rings **2-5**, the photocycloaddition of various substituted aryl-olefins of similar structural frame was examined under varied experimental conditions. However, the intramolecular aryl-olefin [2+2] photocycloaddition was found to be extremely sensitive to substituent effect. The extreme pattern of reactivity i.e. 80-98% yield or no reactions at all, in these systems is unique (Scheme-2). Earlier investigations and broad generalizations mainly concentrated on olefin perturbation, whereas ours is an unprecedented effort towards perturbation of aryl group for *ortho*-photocyclization. This study defines the limits of our understanding for aryl-olefin *ortho*-photocycloaddition in structurally similar systems. During optimization studies with model system, an interesting solvent effect was observed. The synthesis of various model compounds involving Diels-Alder reaction with appropriate diene or dienophile or some other standard synthetic transformation will be described in this chapter. Some of the mechanistic arguments to support our observation will also be described.

Scheme -2

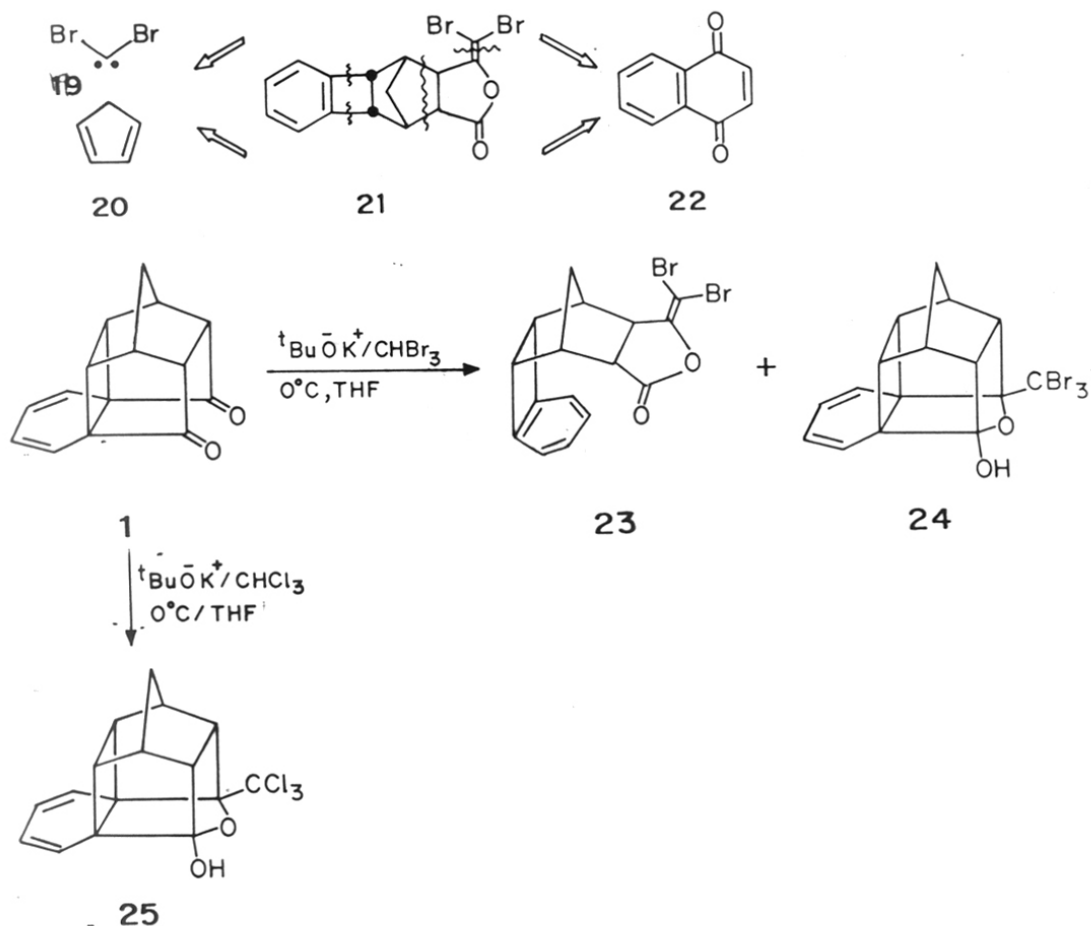


SECTION-B: π -Face Stereoselection in Cage Dione 1

After a brief overview of literature regarding various theories of π -face stereoselection and our involvement with the π -face studies with diene 1, we got interested with a recently discovered theory of nucleophilic and electrophilic surfaces⁵. Our presumption was that the diene face of carbonyl side will be electrophilic, whereas the cyclobutane face will be nucleophilic. We wondered whether such surfaces could be identified by an electrophilic reactive species eg. carbene. Thus, reaction of 1 with dichlorocarbene and dibromocarbene has been examined and an unprecedented aspect of reactivity towards carbonyl functionality has been discovered. The structure of unexpected product was characterized, besides other spectroscopic technique, by X-ray as well. Another objective of this subsection was functionalization of diene frames. As shown in Scheme-3, this study throws new light on the kinetics of carbene generation, and the nucleophilic attack of its precursor to carbonyl. Additionally, although a failure from the point

of our main objective, these developments offer opportunities for introduction of cyclopentadiene unit between the rings of naphthoquinone in a stereoselective way, which is difficult to obtain otherwise (Scheme-3).

Scheme - 3

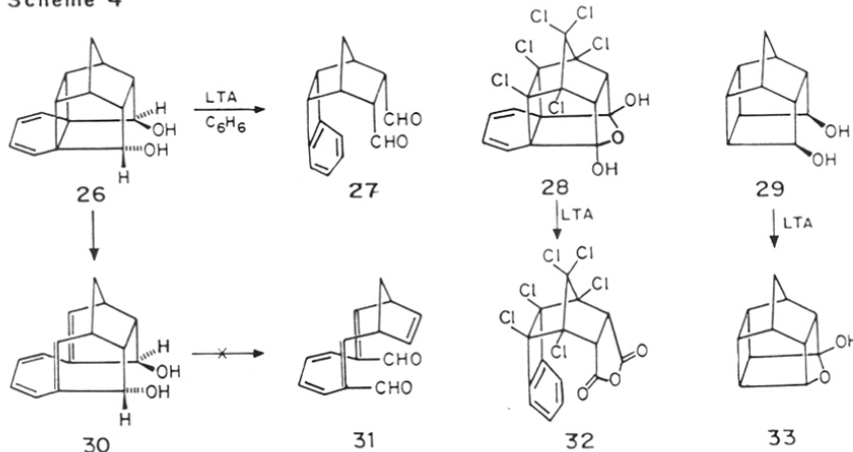


SECTION-C: Stereospecific Cleavage of 1,4-Proximate Diols by Lead Tetraacetate

As part of programme for the synthesis of stereocontrolled medium cyclic rings eg. 10, 11, 12 and 13-membered rings 2-5, the locked cage dione 1 is envisaged as an intermediate offering considerable opportunity for stereochemical manipulation^{6,7}. However, central to our synthetic strategy for transformation of 1 to 11 and 12-membered ring 3 and 4 is the cleavage of cyclobutyl carbonyl bond (Scheme-1). It would be interesting, if the desired bonds could be cleaved by reacting the proximate 1,4-diols with LTA (lead tetraacetate). We observed an unprecedented

stereospecific cleavage of proximate diols with LTA. The preparation of starting diols, its reaction with LTA and mechanistic points whether oxidation is concerted or stepwise, etc. will be described in this sub-section (**Scheme-4**).

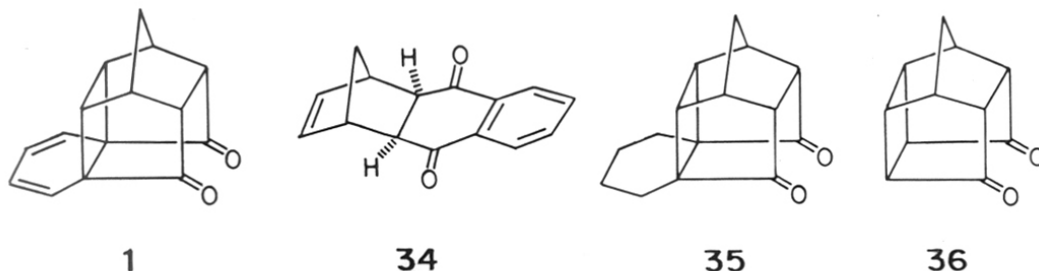
Scheme 4



SECTION-D: Cleavage of Cyclobutyl ketones under PET Conditions:

To unlock cage dione **1**, one can use carbonyl photochemistry via β -cleavage⁷ with a view to get 11 and 12-membered ring. Since the β -bonds C4-C9 and C2-C11 **1** should have more overlap with carbonyl π^* -orbital in **1**, **35** and **36** a study of photochemical electron transfer (PET) with cage dione was undertaken with a view to cleave these bonds and with a view to understand the nature of PET-generated radical anions vs. other modes of generating these species, in these systems. Initially, the reaction of **1** with triethylamine (TEA) and ethanol in photolytic conditions⁸ was examined and a quantitative conversion to *exo* **34** was accomplished. The generality of cyclobutyl bond cleavage in various substrates eg. **1**, **35** and **36** has been examined and a mechanistic rationale has been provided.

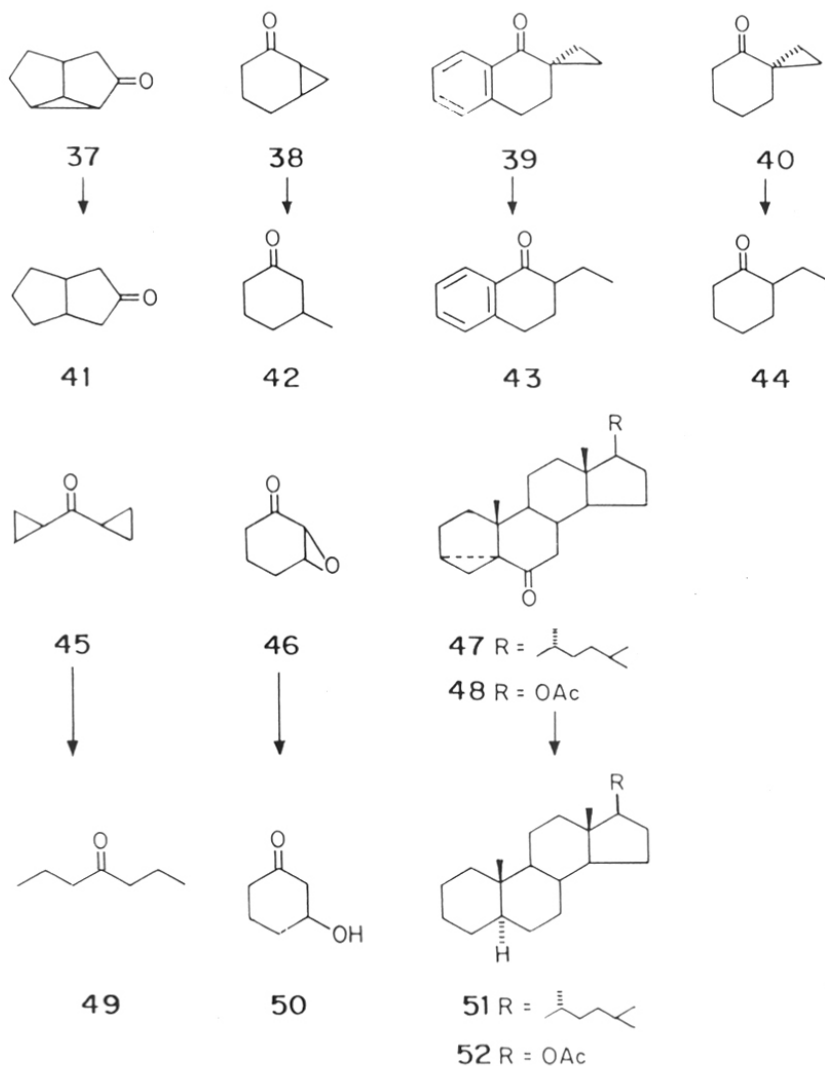
Scheme -5



Cleavage of Cyclopropyl Ketones under PET Conditions:

In continuation of previous sub-section, where the cleavage of cyclobutyl bonds adjacent to carbonyl has been examined, this sub-section reports the cleavage of cyclopropyl ketones under our new PET conditions. Some of the substrates examined and corresponding products are given in **scheme-6**. Unlike cyclobutyl ketones, the cleavage of cyclopropyl ketones and epoxy ketone under our new PET conditions is a facile process. The regiochemistry of bond cleavage is governed by the principle of maximum overlap of σ of cyclopropyl and π^* of carbonyl orbitals. Thus, exocyclic cyclopropanes could be utilized as ethyl equivalent synthon. Our studies reveal interesting wavelength dependence (254 nm vs 300 nm) phenomenon for these transformations.

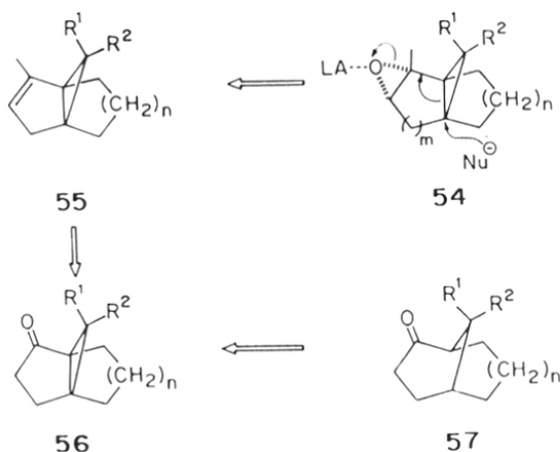
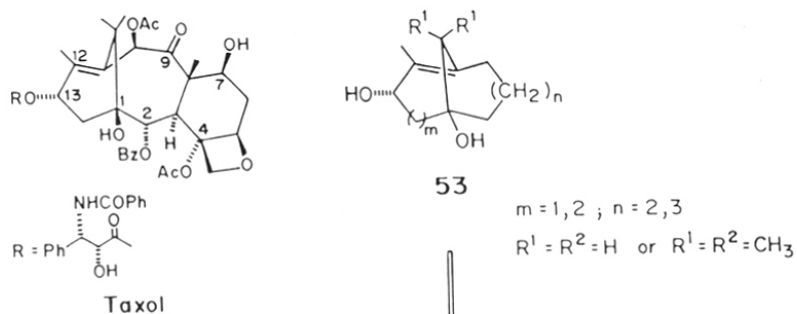
Scheme - 6



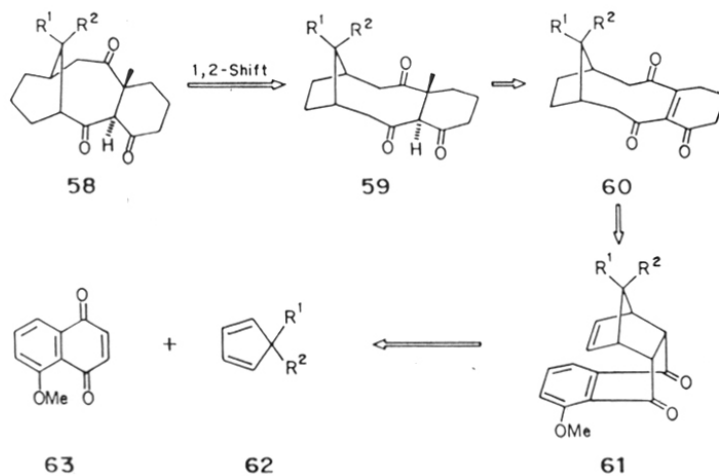
SECTION-E: Strategy for Carbocyclic Frame of Taxol

In continuation, some aspects of cyclopropyl ketone (**56**→**57**) and epoxy cyclopropane (**54**→**53**) has been exploited for the synthesis of carbocyclic frame of Taxol. For details, see Chapter-3. **Scheme-7** and **8** provides a brief overview of our retrosynthetic concepts.

Scheme - 7



Scheme - 8



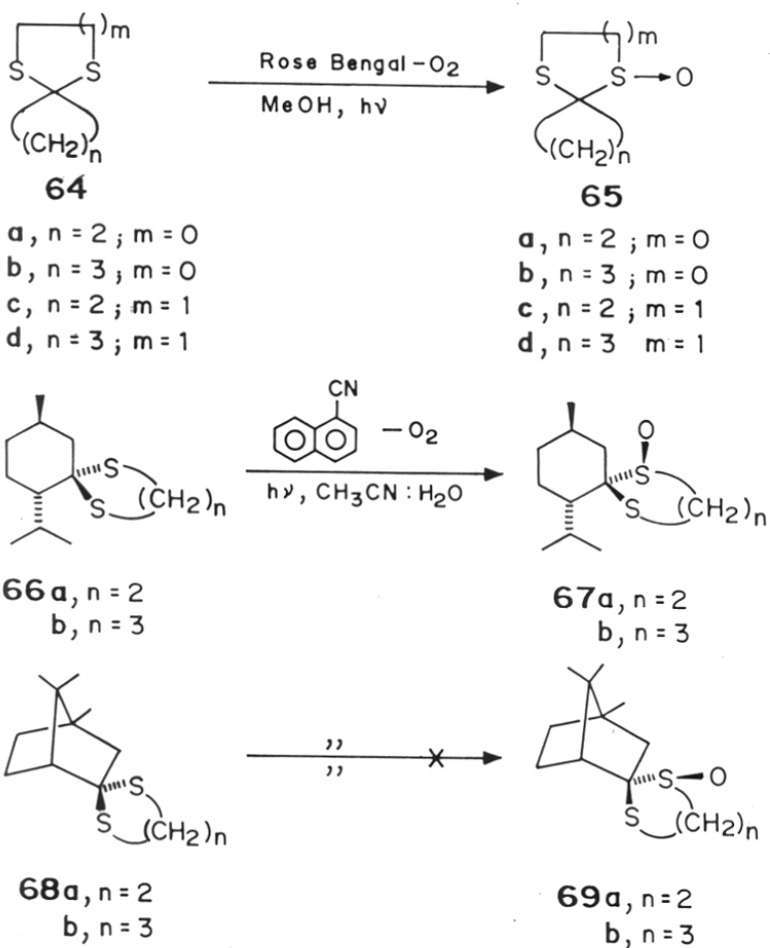
$R^1, R^2 = \text{Alkyl, TMS}$

CHAPTER-II

Stereoelectronic Effects in Oxidation of Dithiolanes

This chapter is an outgrowth of our interest in the mechanistic investigation of photochemistry and photoelectron-transfer oxidation of 1,3-dithiolanes.⁹ Some of the intermediates proposed in above studies could also be obtained by the reaction of singlet oxygen with dithiolanes. Indeed, singlet oxidation of dithiolanes gave quantitative yields of dithiolane S-->O (Scheme-9).

Scheme - 9



In continuation, we have also examined the role of size of reagent to ascertain whether stereoelectronic effect or steric effect is responsible for stereoselective oxidation of some of the optically active dithiolanes. Our presumption is that smaller reagents eg. $^1\text{O}_2$ or O_2 will encounter less steric barrier. Thus, oxidation of dithiolane **66a,b** and **68a,b** with small reagents eg. singlet oxidation and radical-cation-superoxide coupling method,⁹ was examined and product stereochemistry was compared with oxidations due to bulky reagents eg. NaIO_4 , mCPBA, etc. These studies have relevance for various theories of stereoelectronic effect eg. Cieplak effect,¹⁰ nucleophilic-electrophilic surface theory⁵ etc.

CHAPTER-III

Synthetic Studies Towards Carbocyclic Frame of Taxol

Recently, Taxol has been isolated in minute quantities from a number of *Taxus* species¹¹ and has come to the central stage as an anti-cancer chemotherapeutic lead compound. Taxol has got special significance due to successful clinical trials for the treatment of breast, head, neck and ovarian cancer. Unlike many other antitumor agents eg. adriamycin, daunomycin, *cis*-platin, etc., which work as inhibitors of nucleic acid synthesis by intercalating with DNA grooves, taxol has a unique mode of action at cell division level. Thus, Taxol is considered to be a powerful tool for biologists interested in the study of the tubulin microtubule system, proteins which play a crucial role in the construction of the mitotic spindle during cell division.^{12, 13}

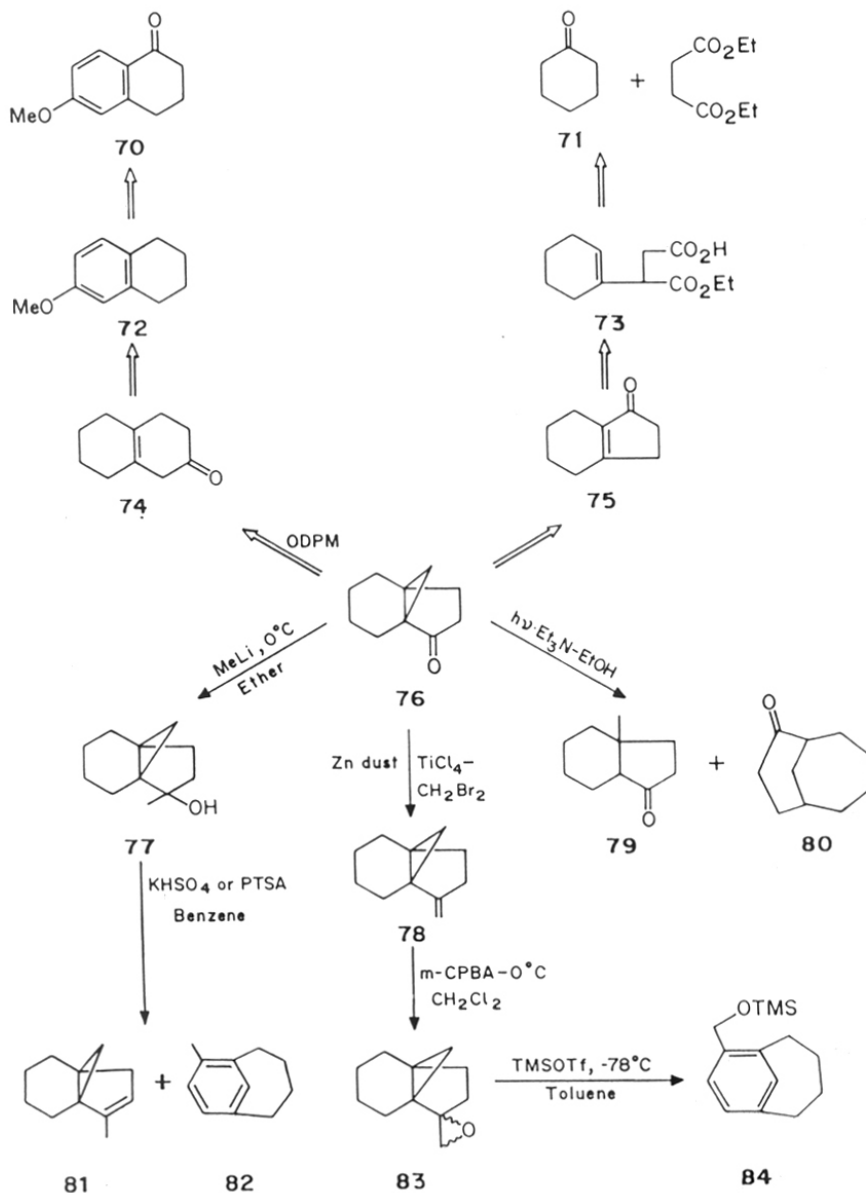
Taxol is a highly challenging and complex synthetic target. There are many aspects of Taxol synthesis eg. OH at C-1 bridgehead position, bridgehead double bond, 8-membered carbocyclic frame, bicyclic frame [5.3.1] system and C-13 ester etc. As a continuation of our involvement with cyclopropyl ketone chemistry in Chapter-1 (Section-D & E-Scheme 7 & 8), this chapter reports our preliminary investigations with cyclopropyl ketone **76** and **89** (Scheme-10 & 11). The preparation of these ketones involves known chemistry, as shown in scheme 10 & 11. Subsequently, PET-chemistry from **76** gave **79** and **80**, whereas methylation and dehydration gave **81**, a precursor for the desired epoxide. However, aromatization was found to be a favoured reaction during dehydration, which gave *m*-cyclophane **82**. Alternatively, olefination of **76** with $\text{TiCl}_4/\text{CH}_2\text{Br}_2/\text{Zn}$ -dust and epoxidation gave **83**. Although many other synthetic possibilities do arise with this epoxide to get useful carbocyclic frame of Taxol, treatment with TMS-OTf gave once again aromatized product **84**.

Subsequently, with a more closer carbocyclic model for Taxol skeleton, the chemistry with cyclopropyl ketones **89** (Scheme-11) was examined. Treatment of **89** with MeLi gave quantitative yield of **90**, which on diimide hydrogenation and subsequent dehydration gave, once again, aromatized *m*-cyclophane **94**. However, LTA oxidation of **89** and **92** gave **91** and **95** respectively, which are quite close to carbocyclic frames of Taxol.

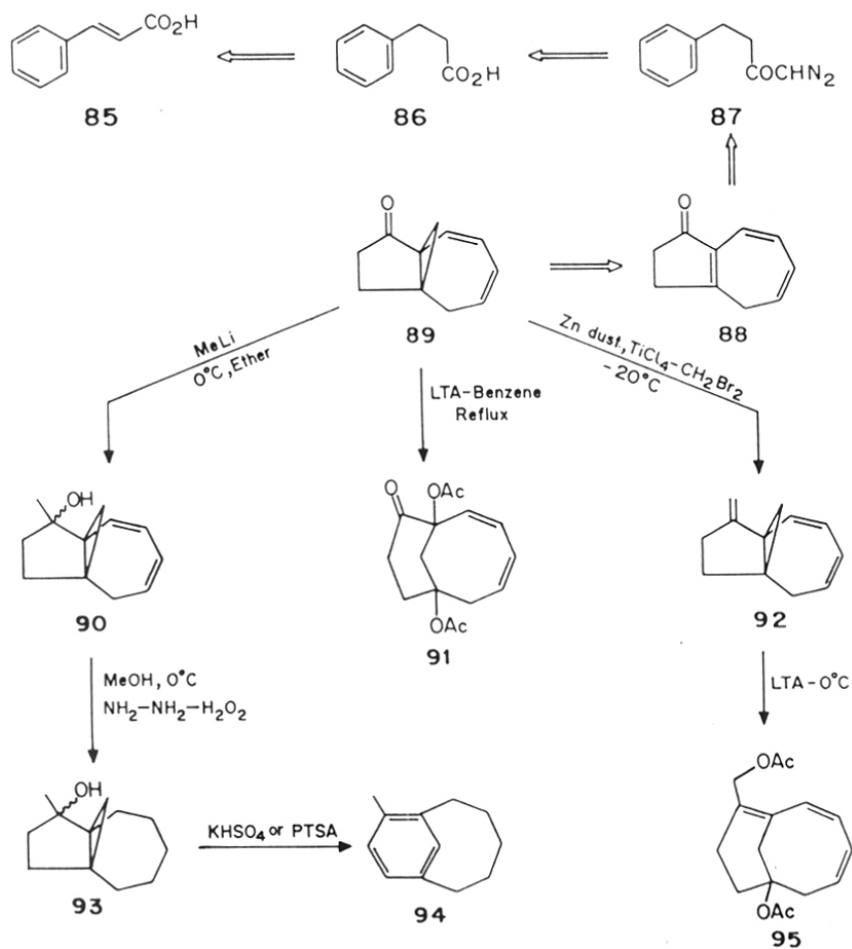
Other attempted reactions in this series and its relevance in the light of literature precedences will be described in this chapter.

Simultaneously, our deep involvement with the bicyclic systems and the realization that the cleavage of central bond in **96** could give a quick precursor for Taxol frame, has led to examine the reaction of **96** and **99** with Na/liq. NH_3/EtOH . Here also, some unprecedented aspects of Birch-reduction have surfaced (Scheme-12). Thus, an extra-carbon has been added to **98** from **96**. The structure of **98** has been unambiguously proved by X-ray. Although intriguing, some mechanistic suggestions will be made in this section.

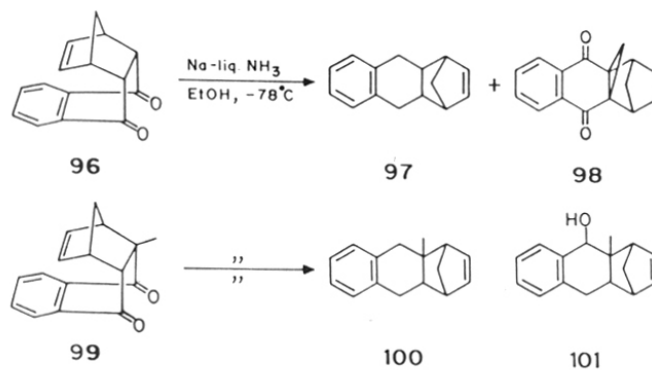
Scheme - 10



Scheme - 11



Scheme - 12



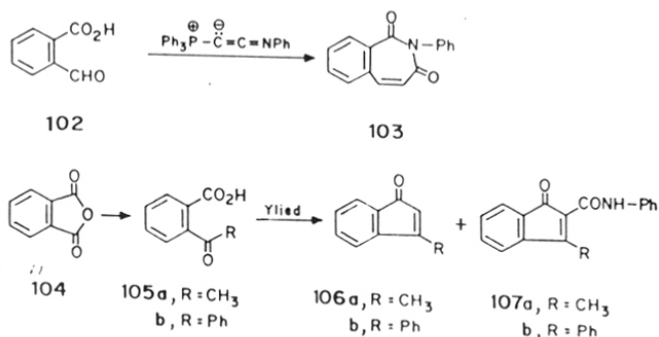
CHAPTER-IV

Synthesis of Carbocyclic and Heterocyclic Compounds Using Phosphacumulene Ylides as Synthons

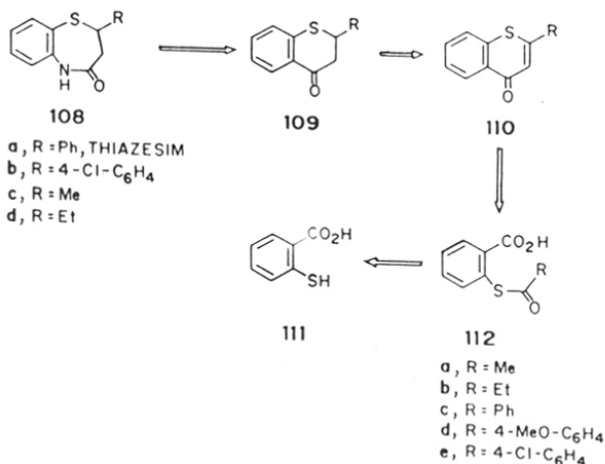
Organophosphorous chemistry has made significant contributions towards the development of newer synthetic methodologies. The discovery of Wittig reaction and its varied synthetic applications constitute simply one such example. In this series of organophosphorous reagents, phosphacumulene ylides are one of the recent arrivals.

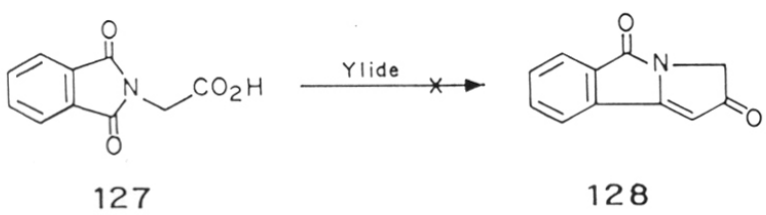
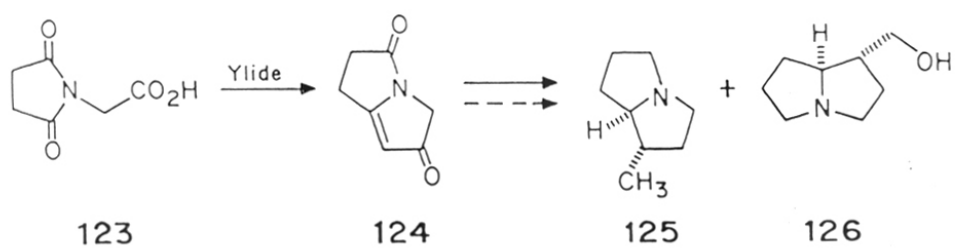
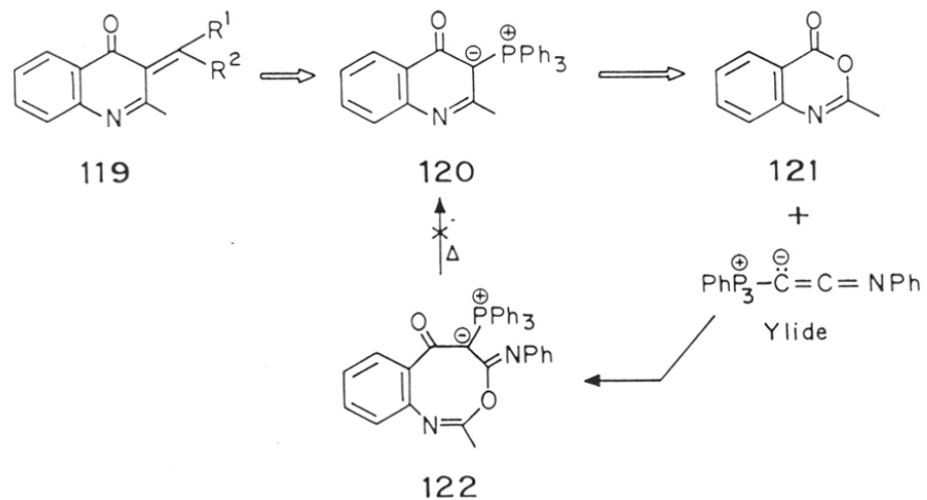
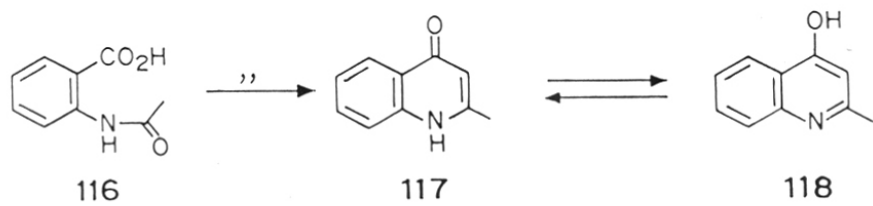
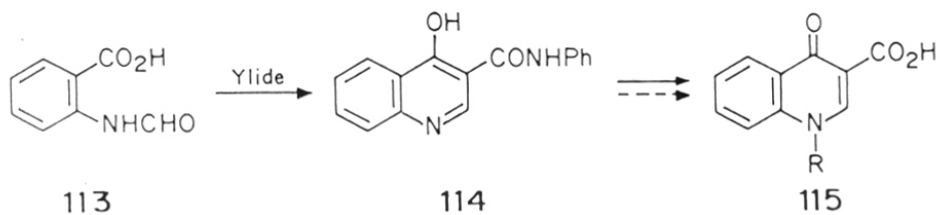
After a brief overview of literature¹⁴ pertaining to the chemistry of phosphacumulene ylides, its limitations and opportunities offered by this reagent, our attempts to exploit the ylide as intramolecular C-1 synthon has been described. The retrosynthetic analysis for biologically useful skeletons of quinolones and benzothioazepins is shown in **scheme-14 & 15**. We have also exploited these concepts for the synthesis of substituted indenones (**Scheme-13**). Currently, we are also exploring this chemistry for the synthesis of Taxol skeleton as well.

Scheme -13



Scheme -14





CHAPTER-I

**STUDIES TOWARDS STEREOCONTROLLED
MEDIUM CYCLIC RINGS**

INTRODUCTION

Medium cyclic ring compounds have attracted the attention of organic chemists, not only because they are biologically useful for numerous human diseases and they have varied commercial applications in terms of their agricultural utility, fragrances and pheromonal activity etc., but also because they offer considerable synthetic challenges to construct and manipulate the functional and orientation aspect of functionalities. In nature, such rings are scattered throughout various groups of natural products e.g., macrolides, alkaloids, sesqui- and diterpenes, etc. After a pioneering study by Ruzicka on the chemistry and structure of civetone and muscone in the beginning of this century, H.C.Brown^{1a} and V.Prelog^{1b} categorized carbocyclic and other ring compounds on the basis of heat of combustion, enthalpy and concept of 1-strain, as follows:

- i) Small rings : Three and four membered rings
- ii) Common rings : Five, six and seven membered rings
- iii) Medium rings : Eight to twelve membered rings
- iv) Large rings : More than 12-membered rings

By and large, small and medium rings have high heats of combustion. The high heat of combustion in small rings is due to Baeyer strain i.e. deviation of bond angles from optimum geometry (for example tetrahedral for sp^3 centre), whereas Pitzer strain (torsional distortion) and eclipsed conformational strain contribute for medium cyclic rings. Originally, the 12-membered rings were included in the medium ring category.² Subsequently, based on heats of combustion per methylene group data, which was closer to larger rings, they have been included in the large ring category. However, due to our combined proposed synthetic strategy for the creation of 10, 11 and 12-membered ring compounds from a single source structure, we have included 12-membered rings in the medium cyclic ring category. Sometimes, large rings and medium cyclic rings have been grouped together as macrocyclic compounds as well.

Stereocontrol in the context of relative specific configuration at remote carbon centres in a medium cyclic ring has attracted considerable attention recently.^{3a,b} Classically, stereoselection in common rings has been successfully manipulated by steric considerations.⁴

Thus, in a carbocyclic six membered ring, an equatorial substituent has pronounced preference than its axial isomer. However, the effect of a hetero atom e.g., O,S leads to reversal of stabilities, which is commonly known as anomeric effect.⁴

Comparably, the situation is complex in a medium cyclic ring, because of its fluxional nature and possibility for multiple low energy conformations, which can be visualised by the floppy necklaces of atoms produced by molecular models. Basically, three types of approaches have evolved to solve the complex stereochemical problem in medium cyclic ring. The first one involves the stereocontrolled synthesis of smaller fragments of medium cyclic ring and finally stitching them together.⁵ However, recent studies from the laboratories of Still^{3a} and Vedejs^{3b} have uncovered some new insights for stereocontrol in a medium cyclic ring. Thus, Still^{3a} advocates the importance of computational methods for the production of stable stereoisomers in a given reaction sequence in a medium cyclic ring, whereas Vedejs^{3b} emphasizes the importance of local conformations close to reaction site for stereochemical outcome.

Almost all strategies, directed towards synthesis and structure determination in a medium cyclic ring, are based on the low energy conformation of molecules involved, which are determined either by molecular mechanics computational method or by X-rays in suitable cases. In this connection, the "RING MAKER" programme developed in Still^{3a} group is noteworthy.

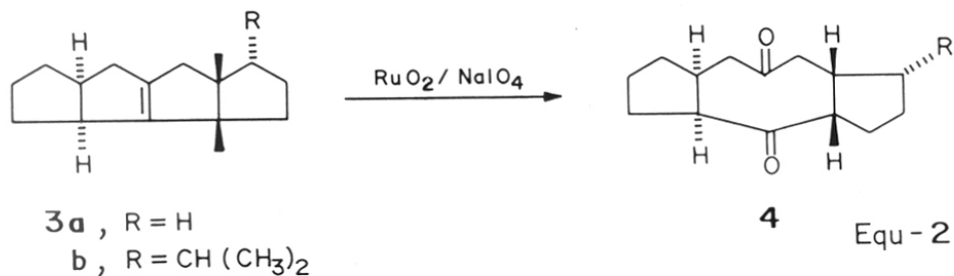
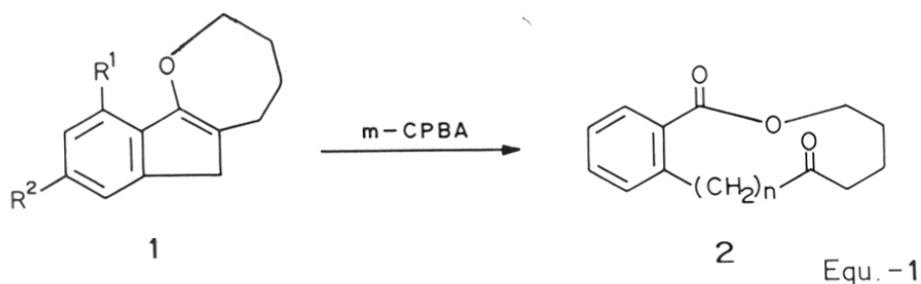
Thus, for a nine-membered ring, after minimizing initial bond length and bond angle parameters, eliminating duplicate conformations, minimizing *trans*-annular non-bonded repulsion conformations and removing high energy conformations, his modified MM2 programme brings down the number of possible conformations from 7,962,624 to five. For all medium cyclic rings and in majority of cases, they fit the conformations determined by X-ray as well, besides suggesting the possibilities of some other low energy conformations. 'Even' and 'odd' membered rings in the medium cyclic rings also offer some subtle differences. Thus, in 'even' membered rings, there is considerable symmetry and near homogeneity in its various conformers, whereas in 'odd' membered medium cyclics, low energy conformers exhibit less symmetry with smaller energy differences.

Standard Methodologies for the Synthesis of Medium Cyclic Ring Compounds:

Some of the routine methods utilized for the construction of medium cyclic ring skeleton, which have found use for the synthesis of macrocyclic rings are as follows:

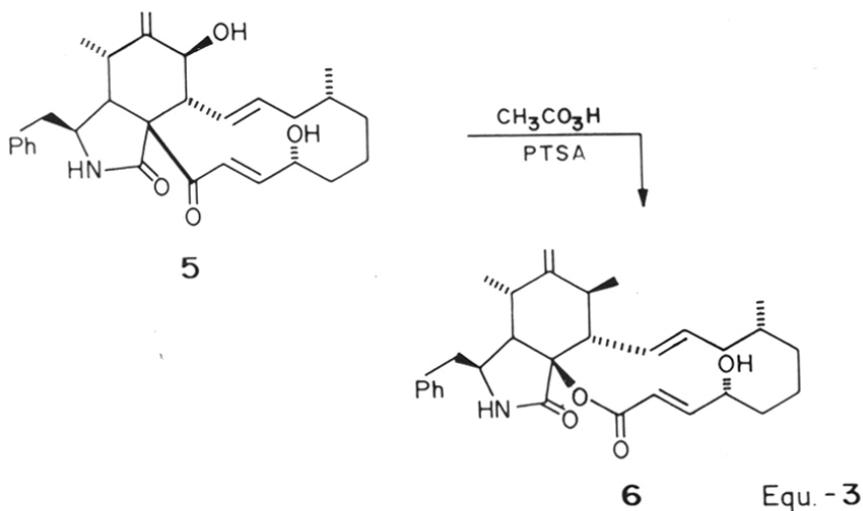
Cleavage of the Bond between Ring Junctures:

A double bond or an appropriately functionalized single bond can be cleaved at the ring junctures in a bicyclo [m:n:o] system to provide larger ring size of both rings. Immer and Bagli⁶ used *m*-chloroperbenzoic acid (*m*-CPBA) induced oxidation and subsequent cleavage of various enol ethers to give lactones, which resemble β -resorsylic acid lactone skeleton (*Equation-1*). Cleavage of central C=C bond with ozone or potassium dichromate or OsO₄/NaIO₄ is the general method of choice.⁷ Recently, Mehta et.al⁸ used RuO₂/NaIO₄ as oxidizing agent to cleave 5-5-5 ring system to 5-8 ring system (*Equation-2*).



Oxygen Insertion by Baeyer-Villiger Oxidation:

Baeyer-Villiger oxidation is the standard methodology to prepare macrocyclic lactones from corresponding ketones. Binder and Tamm⁹ have successfully employed this method to synthesize, where oxygen insertion took place with considerable regio- and stereoselection (*Equation-3*).

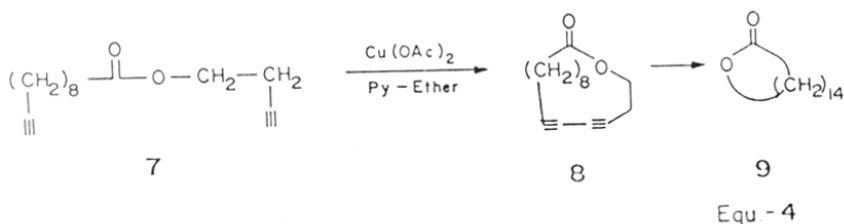


Carbon-carbon bond formation:

Various techniques e.g., acetylene coupling, allylic coupling, intramolecular Diels-Alder reaction, Dieckmann condensation and intramolecular photochemical oxetane formation have been utilized for the construction of medium cyclic rings. During ring formation, distance between the two terminus and strain involved in the transition state play an important role. In small rings closure, distance favours ring formation. Thus, in six membered ring, distance factor dominates the strain factor. However, in seven and eight membered rings, distance and strength both work opposite to the process of ring formation. After that, distance factors become constant and low ease of ring formation is encountered for 9 to 12 membered rings. One has also to be cautious about intermolecular vs. intramolecular bond formation processes, for which concentration of substrates becomes an important issue. This is why high dilution is required for the construction of intramolecular C-C bond formation in medium cyclic rings.

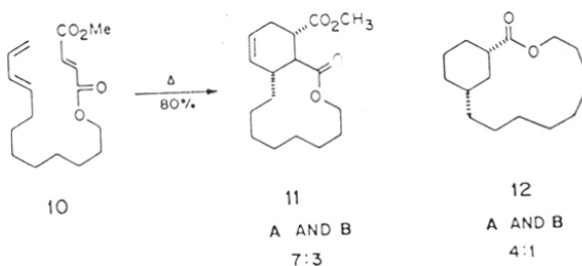
Acetylene coupling:

Oxidative coupling of diacetylenic esters with cupric acetate in pyridine-ether afforded good yields, which on reduction gave saturated sixteen membered lactone, which was ultimately transformed into Exaltolide (*Equation-4*).¹⁰



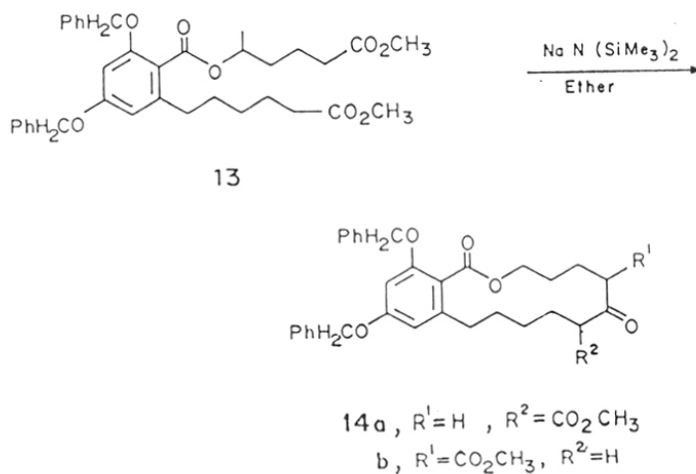
Intramolecular Diels-Alder Reaction:

Intramolecular Diels-Alder reaction (IMDA) has been used for the construction of macrocyclic lactones in a highly regio- and stereoselective manner (*Equation-5*).¹¹



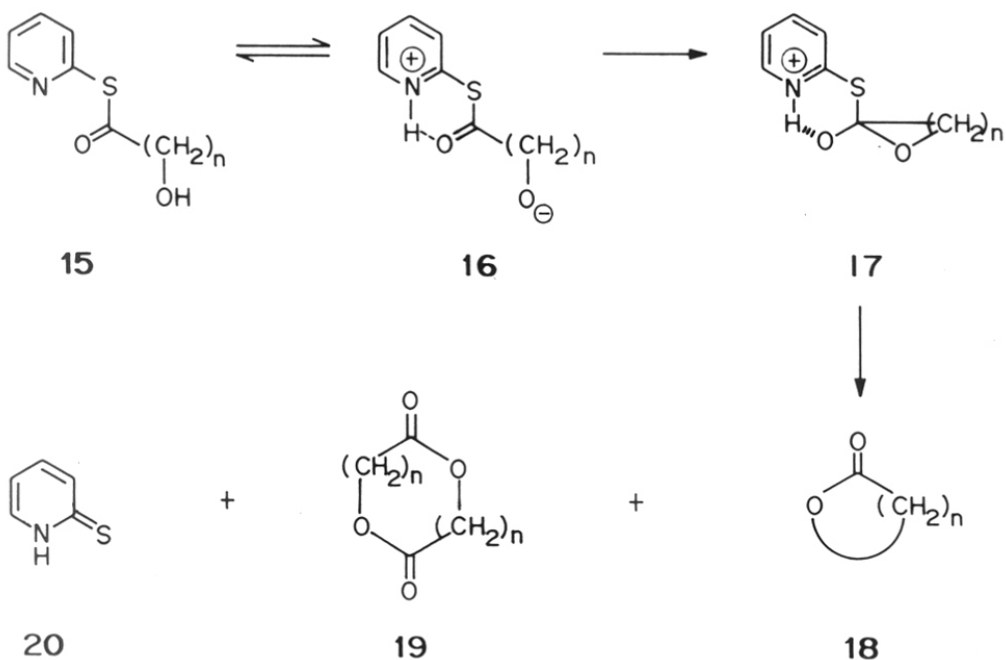
Dieckmann Condensation:

Hurd and Shah¹² have used Dieckmann condensation in synthesis of zeralenone (*Equation-6*).

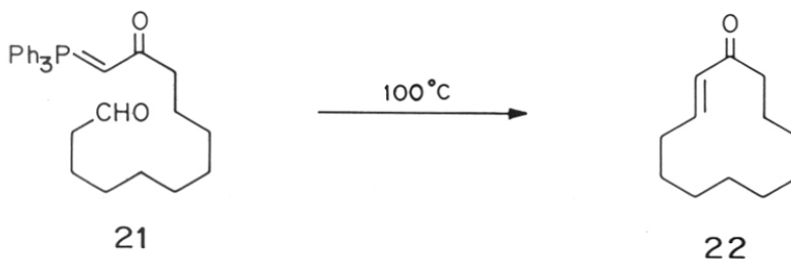


Lactonization Method:

Long open chain hydroxy acid lactonization is the most direct method in macrolide formation. In this method, activation of one or both interacting groups is utilized.¹³ For example, 2-pyridinethiol esters of hydroxy acids is lactonized in a synthetically useful yield *via* proton transfer to pyridine and subsequent activation of carbonyl for intramolecular nucleophilic attack by alkoxide, as shown in *Equation-7*. Normal reflux of hydroxy acids with *p*-toluene sulphonic acids is a low yielding and time consuming process.



Equ. - 7

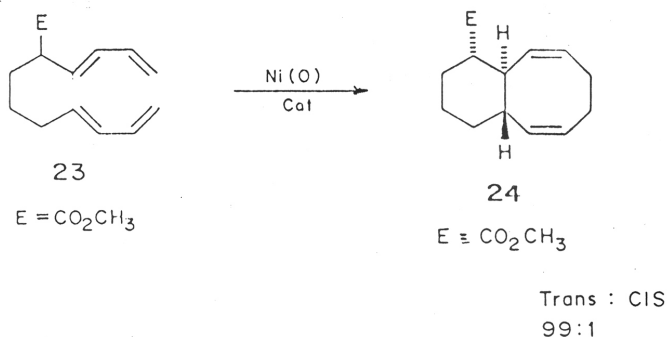


Equ. - 8

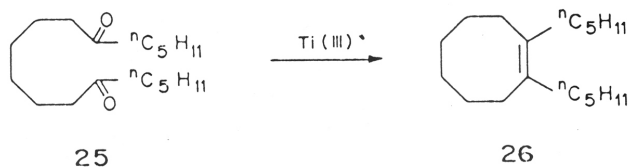
Cyclizations involving Transition Metals and Other Reagents:

Application of intramolecular Wittig reaction has been successfully employed for the construction of C=C double bond in medium cyclic rings, as shown in *Equation-8*.¹⁴

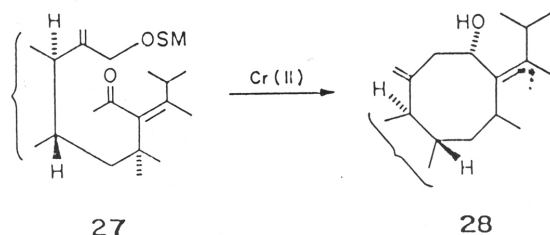
Various transition metals e.g., Ni(O), Ti(III), Cr(II) and Pd(O) have also been used for cyclization towards medium cyclic rings. Thus, tetracarbonyl nickel (O) has been used to close the diallylic bromide termini of an acyclic precursor.¹⁵ Wender¹⁶ has shown that intramolecular cyclization, with Ni(cyclooctadiene)₂ as a catalyst, is an efficient process (*Equation-9*). Titanium induced dicarbonyl coupling reactions are quite effective and have been successfully applied for the synthesis of natural products by McMurtry (*Equation-10*).¹⁷ Nozaki et.al¹⁸ have reported that the C=C bond formation, for medium cyclic ring preparation, can be achieved by chromium (II) reagent (*Equation-11*). Trost et.al¹⁹ have used Pd(O) reagent for intramolecular cyclization (*Equation-12*).



Equ.-9



Equ. - 10



Equ. 11

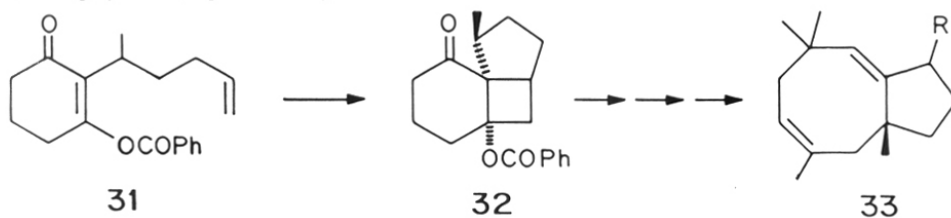


Equ. - 12

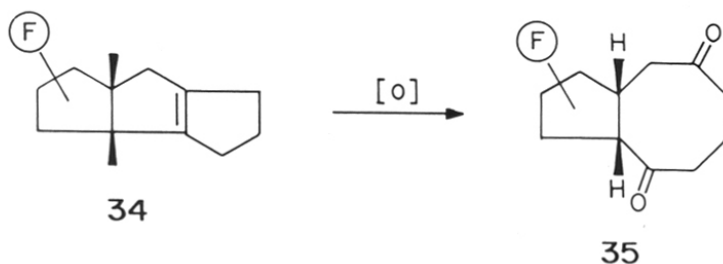
Total Synthesis of Medium Cyclic Rings/Natural Products:

Structural spectrum in macrocycles is perhaps one of the richest in natural product chemistry. Because of their high performance in clinical use, preservatives, biological activities, phomonal activity, agricultural applications, its synthesis continues to attract synthetic organic chemists throughout the world. Some of the natural products synthesis has been described in the following section. Since large number of natural products contain medium cyclic rings, their survey is beyond the scope of this chapter. However, we will be considering some representative examples of 8-12 membered ring natural products and only the latest synthesis for the compounds will be reported.

(±) precapelladiene **33**, a biosynthetic precursor containing 5,8-ring system, has been synthesized by Pattenden²⁰ and Mehta.²¹ Pattenden has reported a construction of fused 5,8-ring system which utilizes regio- and stereoselective intramolecular [2+2] photocycloaddition of **31** (Equation-13), whereas Mehta²¹ has used bicyclo [3.3.0] oct-1(5)-ene moiety present in trinquane, as a cyclooctane-1,5-dione equivalent, for the construction of 5,8-ring system (Equation-14).

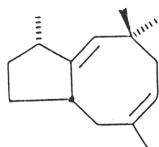


Equ. - 13

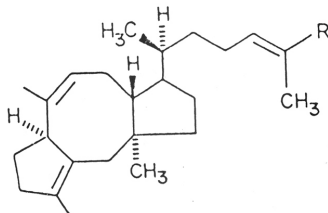


Equ. - 14

Scheme -1



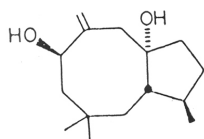
36



37

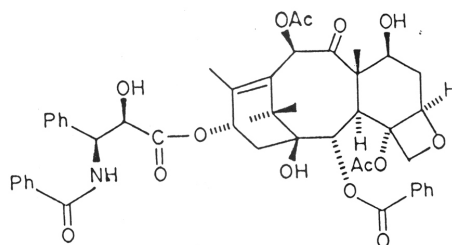
R = CO₂H , AIBOLIC ACID

R = CH₂OH , CAROPLASTOL II



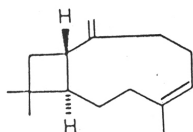
38

POITEDIOL

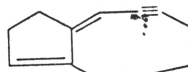


39

TAXOL

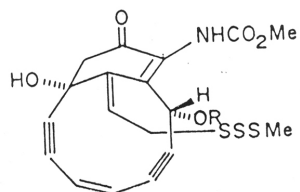


40



41

NEOCARZINOSTATIN

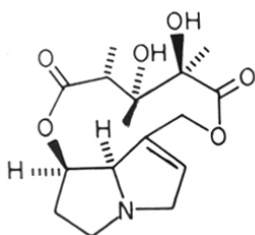


42

CALICHEMICIN

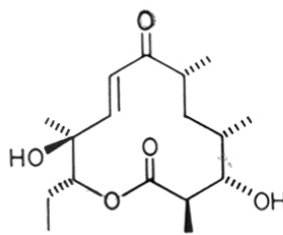
Wender²² reported the total synthesis of a subunit of Neocarzinostatin **41**, which contains an interesting 9-membered skeleton (*Scheme-1*). Recently, an interesting 10-membered skeleton has been uncovered as a core of Esperamicins and Calichecin **42**, the most potent antitumour antibiotic ever known, and its synthesis has been attempted by Schreiber,²³ Danishefsky²⁴, Magnus²⁵ and Nicolaou²⁶. Vedejs²⁷ reported a synthesis of d,l methynolide **44**. This synthesis differs from traditional method of coupling of optically pure segments to achieve stereocontrol.

Scheme - 2



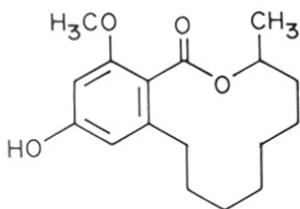
43

MONOCROTALINE



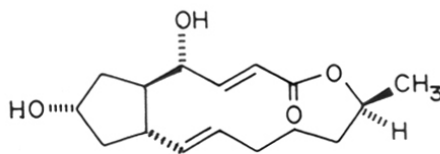
44

METHYNOLIDE



45

LASIODIPLODINE



46

BREFELDIN-A

Some important natural product skeletons containing eight to thirteen membered ring has been illustrated (*Scheme 1 & 2*). Paquette,²⁸ Takeshita,²⁹ Gadwood,³⁰ Nicolaou³¹ have reported the synthesis of 8-membered ring systems. Kende,³² Wender²² have reported 9-membered ring skeleton, whereas Nicolaou³³ has reported 10-membered natural product

(Calicheamicin). Vedejs³⁴ has reported 11-membered natural product synthesis. While 12- and 13-membered natural products have been reported by Vedejs,³⁵ Danishefsky³⁶ and Trost³⁷ respectively. Many of these targets have been shown in *Scheme-1* & 2 with their respective names.

Our Approach for Stereocontrolled Medium Cyclics:

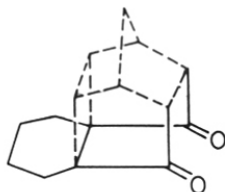
The last several pages of information should make the point clear that control and prediction of stereochemistry in medium cyclic rings is quite a complex and challenging task in current organic synthesis. Some of the earlier approaches e.g., molecular stitching suffer from cyclization problems due to extreme dilution at the final stages of synthesis, whereas the concepts advanced by Still^{3a} and Vedejs^{3b} are very much restricted to special type of starting substrates needed in their approach. The concept of determination of low energy conformations by computational methods may be true for natural substances, but it is problematic with charged or polar groups. The application of transition metals e.g., Pd, Ti, Ni, Cr etc., based reagents is not only costly, but can be effective only with very special kind of functionalities and target molecules. Thus, there is a clear-cut need for developing alternative methodologies for highly functionalized and stereocontrolled medium cyclic rings.

We visualized (note the solid lines in these structures) the presence of 10, 11 and 12-membered ring compounds (**48**, **49** and **50** respectively) in the hexacyclic cage compound **47** as shown in *Scheme-3*. Our starting cage compound can be assembled very quickly by two step thermal Diels-Alder reaction of readily available cyclopentadiene and 1,4-naphthoquinone and its subsequent photolysis. Naturally, such medium cyclic rings e.g., 10-, 11- and 12-membered ring compounds can be visualized as a subunit of **51**, where X, Y, Z can be thought of as conformational protecting groups. Conceptually, the synthetic manipulation of dotted bonds is possible, if X is a hetero atom (*Equation-15*). The manipulation of cyclobutane ring in similar cage diones by flash thermolysis has been amply demonstrated by Mehta et.al and utilized for the total synthesis of various cyclopentanoids e.g., Hirsutene **61**, Corioline **62**, Capnallane **63** and building block of Dodecahedrane **64**. Thus, it should be possible to cleave the cyclobutane ring in our hexacyclic cage dione by Mehta's metathetic way. However, **47** gave retrophoto [2+2] product **65** at 450°C on flash thermolysis, whereas

Scheme - 3

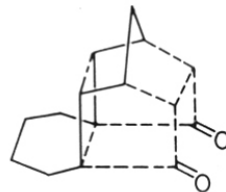


47



48

10-MEMBERED



49

11-MEMBERED

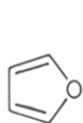


50

12-MEMBERED

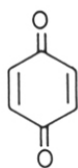


51

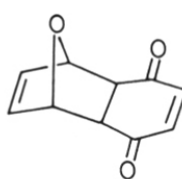


52

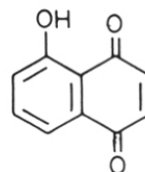
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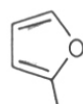
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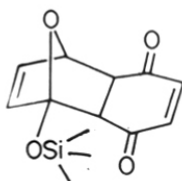
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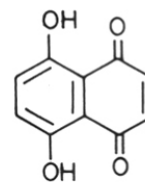
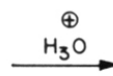
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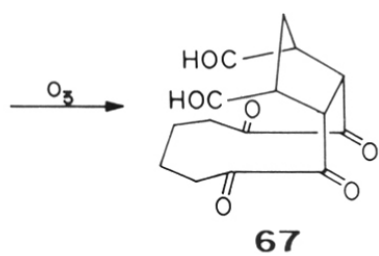
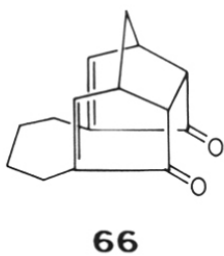
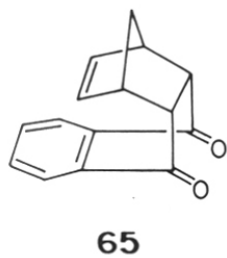
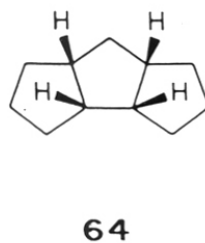
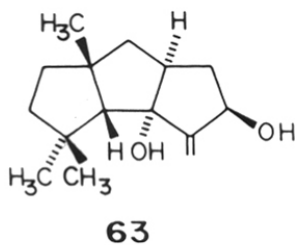
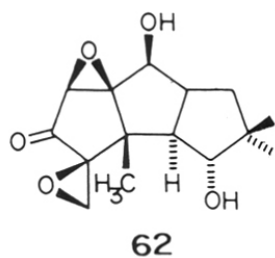
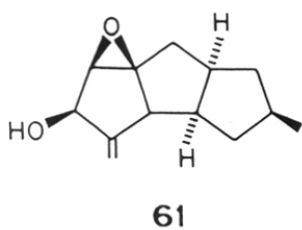
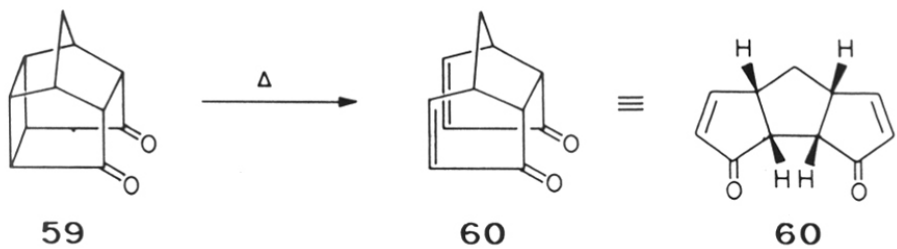
57



58

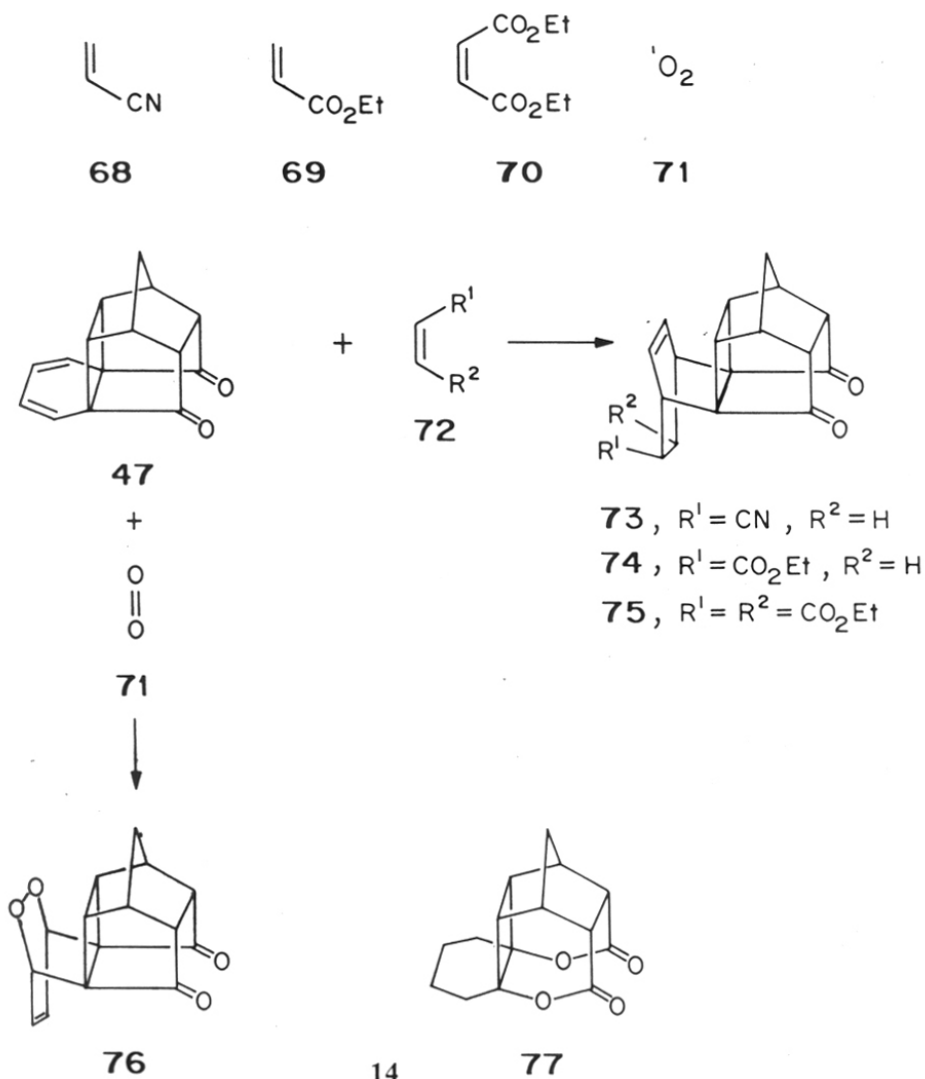
Equ.-15

Scheme -4



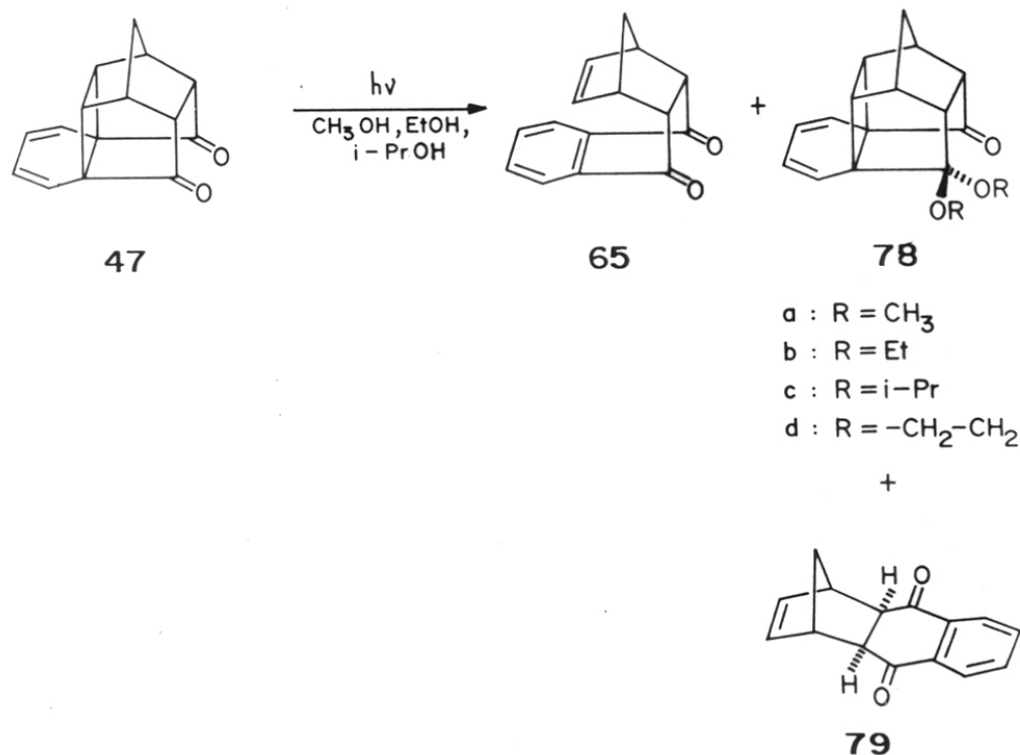
the saturated analogue gave **66** (*Scheme-4*). Earlier studies in our group has shown that **67**, a 13-membered ring, can be prepared, after ozonolysis of **66**. Needless to mention that hexacyclic frame in **47** has considerable opportunities for stereochemical manipulation. Thus, substituents adjacent to X, Y and Z and cyclobutane would have fixed orientation and it is presumed that it would be the same on opening of cage system as well. To have additional control in the diene frame, we^{38,39} and Coxon et.al⁴⁰ have shown that **47** exhibits significant amount of π -facial stereoselectivity in Diels-Alder reaction. Thus, it was shown that C=C types of dienophiles e.g., acrylonitrile, ethyl acrylate, dimethyl maleate approach from carbonyl face, whereas heterodienophiles e.g., O_2 and DEAD (Diethylazodicarboxylate) etc., approach from cyclobutane face as shown in (*Scheme-5*).³⁸

Scheme - 5



Various reasons for π -face stereoselection e.g., electrostatic interaction, product stability, π -orbital distortion due to σ/π interaction, polarizability effects, secondary orbital overlap effect, and combination of torsional and steric effects have been offered. It is assumed that steric and electronic effects are mainly responsible in the present study. Such unusual π -face stereoselection in **47** offers an additional opportunity for stereocontrol in the diene frame of **47**, which will ultimately be manifested in the formation of stereocontrolled medium cyclic rings. Besides, one can also visualize some more opportunity of stereocontrol in **66**, opened up cyclobutane derivative of saturated analogue, in which approach of reagents will be guided because of steric reasons. Marchand et.al⁴¹ have reported π -face differentiation in the ketone reduction of analogous cage dione as well. Thus, virtually, every centre of 12-membered ring can be stereochemically manipulated. We have examined the substituent effect in intramolecular photochemical [2+2] aryl-olefin cyclization step, which should offer varied substitution pattern in our cage hexacyclic dione.⁴² Similarly, cyclopentadiene can also be functionalized and synthetically manipulated. Above discussion clearly points to a

Scheme - 6



rich possibility of varied substitution pattern in hexacyclic cage systems and substituent stereochemical control. However, central to our strategy for 12-membered ring is the development of methodology for the cleavage of cyclobutyl-carbonyl bond in **47** as **50**. Initial attempts to cleave this bond by photochemical α -cleavage processes lead to unexpected---ketalization, β -cleavage and dual epimerization, as shown in (*Scheme-6*).⁴³ Extensive Baeyer-Villiger studies lead to regioselective insertion of oxygen close to cyclobutane ring, but we failed to cleave the lactones.⁴⁴

Subsequently, we have examined the possibilities for obtaining functionalized cage dione by varying either the diene (cyclopentadiene) or 1,4-naphthoquinone fragment *via* intramolecular aryl-olefin [2+2] photocycloaddition. Some aspects of π -face stereoselection with dihalocarbenes, with a view to understanding the nature of surfaces e.g., electrophilic or nucleophilic have been examined. Cleavage of cyclobutane ring by photochemical electron transfer (PET) and its subsequent generalization on 3-membered ring also constitutes part of this chapter. Ultimately, we have utilized our knowledge of cyclopropyl ketone chemistry the synthesis of carbocyclic frame of Taxol. All the above objectives have been described separately as various sub-sections in this chapter.

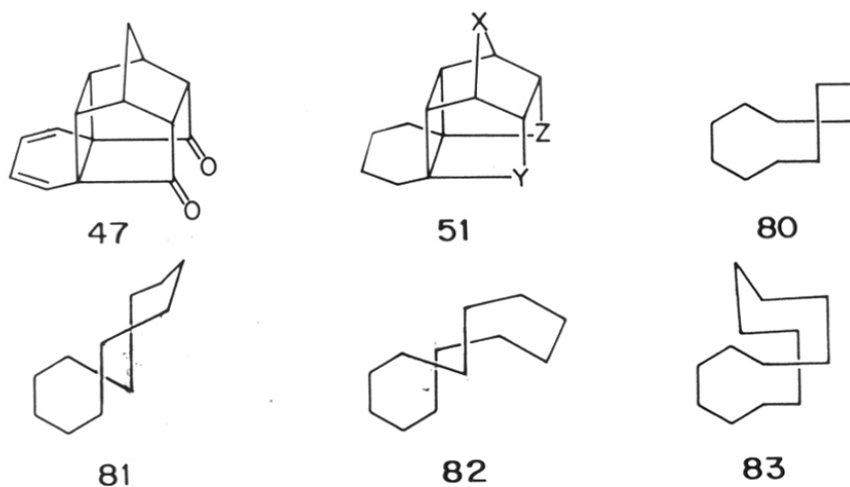
SECTION-A

APPROACHES TOWARDS FUNCTIONALISED DIENE CAGED DIONES

INTRODUCTION

Aryl-olefin *ortho*- and *meta*-photocycloadditions are of considerable interest to synthetic, mechanistic and theoretical organic chemists.⁴⁵ Recently, we initiated a programme for the synthesis of stereocontrolled medium cyclic rings e.g., 10, 11, 12 and 13-membered rings **80-83**, where the cage compound **47** was envisaged as a precursor for these rings (appropriate X, Y, Z are used as a conformational protecting groups)^{38,43,46} (see the preceding section for details). One of the important step in our strategy was the efficient intramolecular aryl-olefin *ortho*-photocycloaddition in tetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13-tetraene-3,10-di one systems. With a view to obtaining functionalized diene frame in **47**, which should provide

Scheme -7



opportunities for further stereocontrol and should ultimately lead to functionalized stereocontrolled medium cyclic rings **80-83**, the photocycloaddition of various substituted aryl-olefins of similar structural frame was examined under varied experimental conditions. Compared to the model test case, where 98% yield of photocyclization was achieved, substitution either with donor groups or acceptor groups in the aryl ring or perturbation of even olefin skeleton, failed

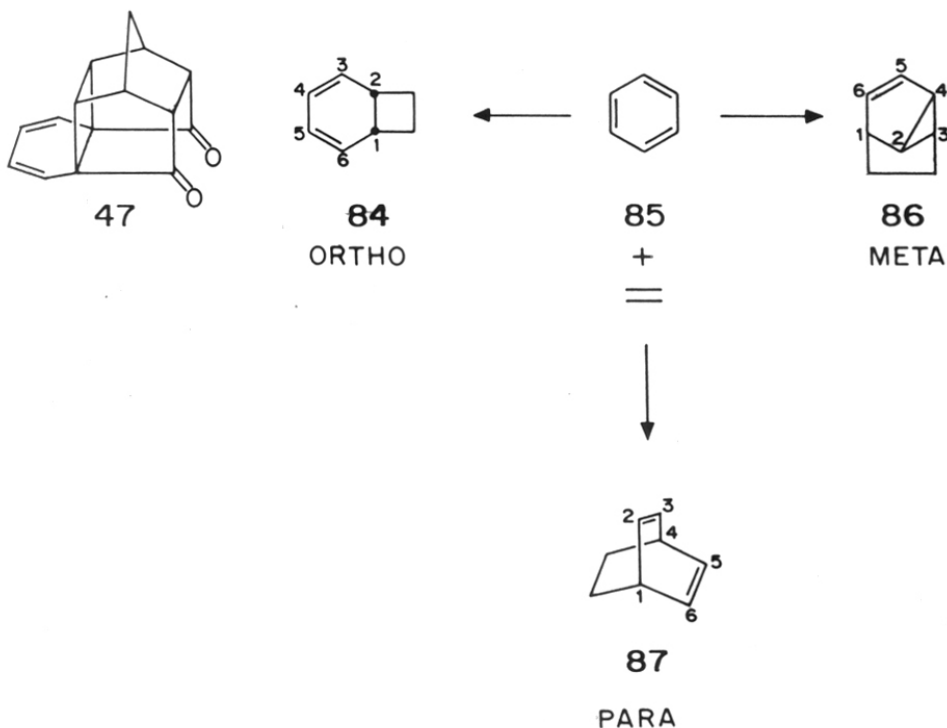
RR
547.842:541.14(043)
RAO

to give photocyclization. The extreme pattern of reactivity i.e. either 80-98% yield or no reaction at all, in these systems is unique. This study defines the limits of our understanding for aryl-olefin *ortho*-photocycloaddition in structurally similar systems. During optimization studies with model system, an interesting solvent effect was observed.

Mode of Photocycloaddition Reaction^{45,47,48}

When benzene is irradiated in the presence of an alkene, a number of processes occur. Cycloaddition reaction is one of the processes which would give *ortho*(1,2)-, *meta*(1,3)- and *para*(1,4)-photocycloaddition products (*Scheme-8*). Synthetic and mechanistic aspects of arene-alkene photocycloaddition have been discussed by a number of groups,^{47a} viz. Bryce-Smith, Buchi, Cornelisse, Gilbert, Houk, Matty, Morrison, Sheridan, Srinivasan and Yang.

Scheme-8



Because of the poor orbital overlap between the excited arene and the ground-state olefin, *para*-photocycloaddition is a relatively uncommon event. The competitive reactions are *ortho* and *meta*-photocycloadditions. The broad theoretical generalization by Bryce-Smith,^{45d,e} Houk⁴⁹ and Mattay^{45a} were mainly based on perturbations in olefin fragment. Thus, based on ionization potential of olefins, Bryce-Smith^{45d,e} et.al postulated $\phi_{ortho} < \phi_{meta}$, when $9.6 \text{ eV} < \text{I.P.} < 8.65 \text{ eV}$, employing thereby that with powerful donors and acceptor alkenes, *ortho*-photocycloaddition is preferred (*Scheme-9*). Similarly, based on HOMO-LUMO orbital interactions and their energetics, Houk⁴⁹ proposed that *ortho*-photocycloaddition is preferred either with a highly electron rich olefins or extremely electron deficient olefins, with respect to benzene. Following similar electron density pattern arguments, Mattay et.al^{45a} have invoked the relevance of free energy of enthalpy from Reim-Weller equation and proposed that *ortho* addition is feasible if $0.5 < \Delta G < \approx 1.7$.

Regio and Stereoselectivity in *ortho*-Photocycloaddition:

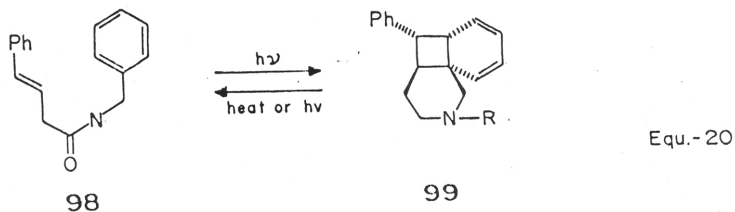
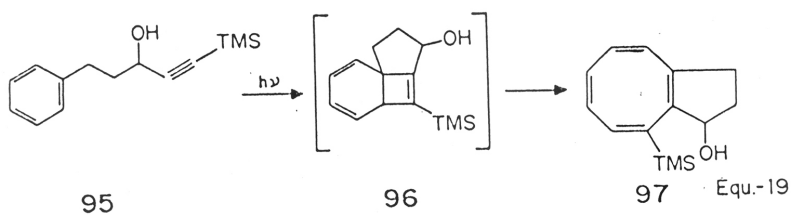
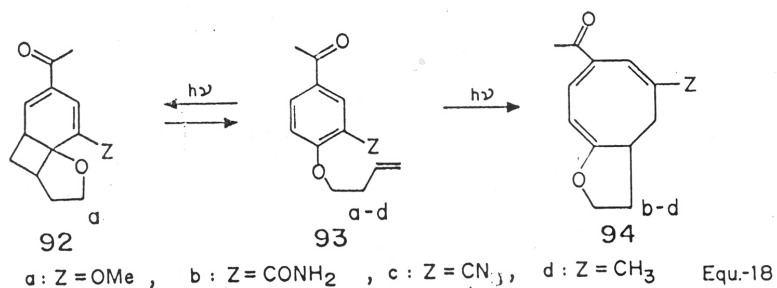
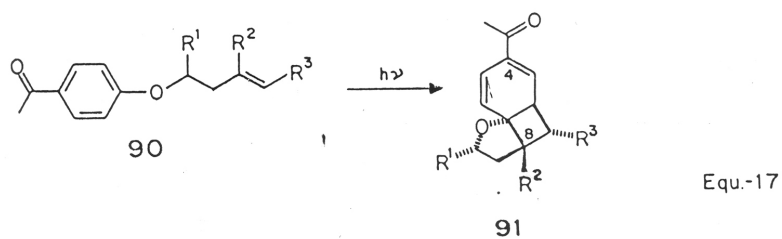
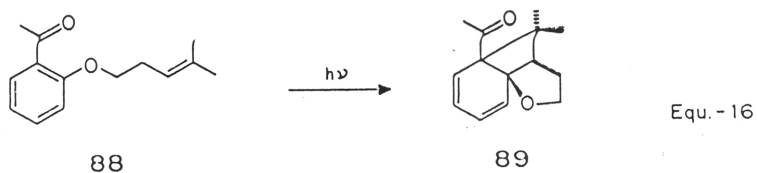
Substitution in the aromatic ring gives rise to the problem of regioselectivity. A donor substituent at C₁ position increases the orbital coefficients at C₂ and C₆ giving product of *ortho*-photocycloaddition at C₁-C₂ or C₁-C₆ centres (*Scheme-9*). Even though there is scrambling in stereoselectivity, donor olefins add stereospecifically *endo* and acceptor olefins add stereospecifically *exo* to the benzene ring.^{48a}

Very little attention has been paid to the mechanistic aspects of intramolecular photocycloaddition. It is still an evolving phenomenon. This is illustrated by the examples shown in *Scheme-9*. The compounds **88**, **90**, **93**, **95** and **98**, on photolysis give *ortho*-photocycloaddition products **89**, **91**, **92**, **97** and **99** respectively.⁵⁰ Apart from basic synthetic studies, the cycloaddition reactions are also used as key steps in the synthesis of natural products such as (±)- α -pitzol, (±)- α -isocomene, (±)-hirsutene, (±)-coriolin, (±)-silphenene, and (±)-laurenene.

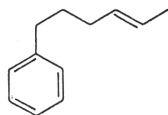
Polar solvents, e.g., acetonitrile favour *ortho*-photocycloaddition^{48a} over *meta*-photocycloaddition. Regioselectivity is also enhanced due to polar solvents.^{48d}

Scheme-9

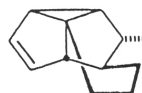
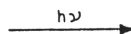
ORTHO-PHOTOCYCLOADDITION REACTIONS



META - PHOTOCYCLOADDITION

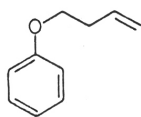


100

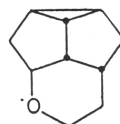
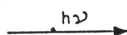


101

Equ.- 21

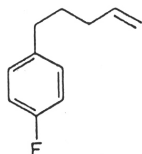


102

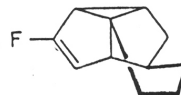
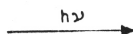


103

Equ.- 22



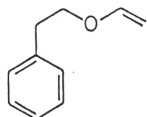
104



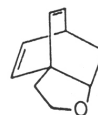
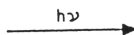
105

Equ.-23

PARA - PHOTOCYCLOADDITION

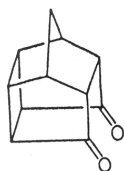


106



107

Equ.-24



59

Different groups viz. Mehta⁵¹ and Marchand⁵² have extensively studied the Cookson's ketone model **59**. Extensive literature about similar 2+2 photocycloaddition reactions is also available.⁵²

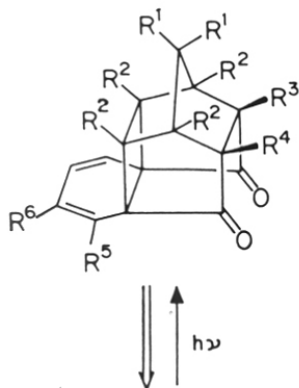
OBJECTIVE

As shown in the preceding section, the photochemical step was one of the key step for obtaining functionalized diene in cage diones. Thus, a series of functionalized 1,4-naphthoquinones were prepared, which were reacted with various dienes e.g., cyclopentadienes, cyclohexadiene, isobenzofurans in a Diels-Alder fashion and their photochemistry was examined. Various attempts e.g., sensitization, solvent variation, λ -variation, etc. were made to get efficient aryl-olefin [2+2] photocycloaddition. *Section-A* describes some of our observations in this area.

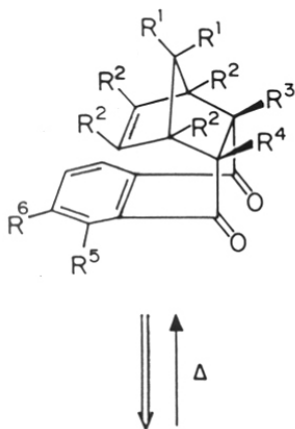
RESULTS AND DISCUSSION

Kushner et.al.⁵³ have reported photocyclization of cyclopentadiene and 1,4-naphthoquinone Diels-Alder product in 80% yield after 60 minutes of irradiation. Initially, as a model case, the optimization studies for the photocyclization of **47** from **65** with 300 nm Rayonet in various solvents (1mg/1ml) concentration in Pyrex tube e.g., EtOAc, n-hexane, benzene, cyclohexane and acetonitrile was examined and respective yields of 52%, 65%, 80%, 88% and 98% were obtained. While the effect of solvents on altering the photocyclization efficiency was an interesting observation, our best results of 98% in acetonitrile were employed for other substrates for *ortho*-photocycloaddition. For stereocontrol in norbornane ring system of **47**, substituted diene and/or dienophile can be used in Diels-Alder reaction (*Scheme-12*). Cyclopentadiene (CPD) and 1,4-naphthoquinone were refluxed (in molar ratio 1:1.3) in dry benzene for half an hour to yield a product mixture containing '*endo*' isomer **65**, a product of kinetic control as a major product (83%), and '*exo*' isomer **79**, a product of thermodynamic control, as a minor product (12%). Structure of both compounds were confirmed by chemical, spectroscopic and analytical techniques. The ¹H-NMR of *endo* isomer **65** showed characteristic signals at δ 5.8-6.2 (2H, m) for olefin and at 7.6-8.0 (4H, m) for aromatic protons. The symmetrical nature of the

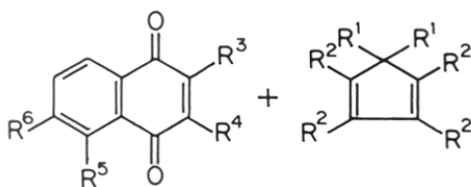
Scheme -10



- 47 : $R^1-R^6=H$
 108 : $R^1, R^2, R^4-R^6=H, R^3=CH_3$
 109 : $R^1, R^2=Cl, R^3-R^6=H$
 110 : $R^1-R^4, R^6=H, R^5=OH$
 111 : $R^1-R^4, R^6=H, R^5=OMe$
 112 : $R^1-R^4, R^6=H, R^5=OAc$
 113 : $R^1-R^4, R^6=H, R^5=NO_2$
 114 : $R^1-R^4, R^6=H, R^5=COCH_3$
 115 : $R^1-R^5=H, R^6=NO_2$

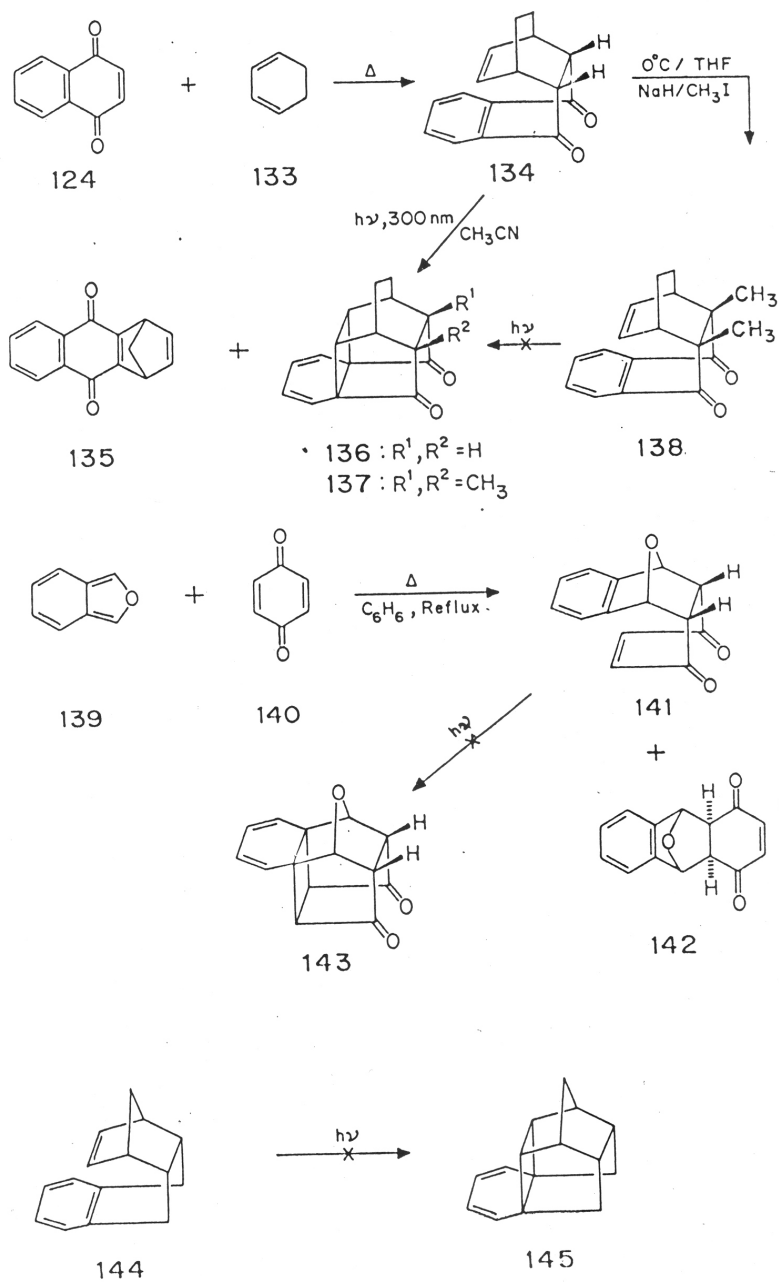


- 65 : $R^1-R^6=H$
 116 : $R^1, R^2, R^4-R^6=H, R^3=CH_3$
 117 : $R^1, R^2=Cl, R^3-R^6=H$
 118 : $R^1-R^4, R^6=H, R^5=OH$
 119 : $R^1-R^4, R^6=H, R^5=OMe$
 120 : $R^1-R^4, R^6=H, R^5=OAc$
 121 : $R^1-R^4, R^6=H, R^5=NO_2$
 122 : $R^1-R^4, R^6=H, R^5=COCH_3$
 123 : $R^1-R^5=H, R^6=NO_2$

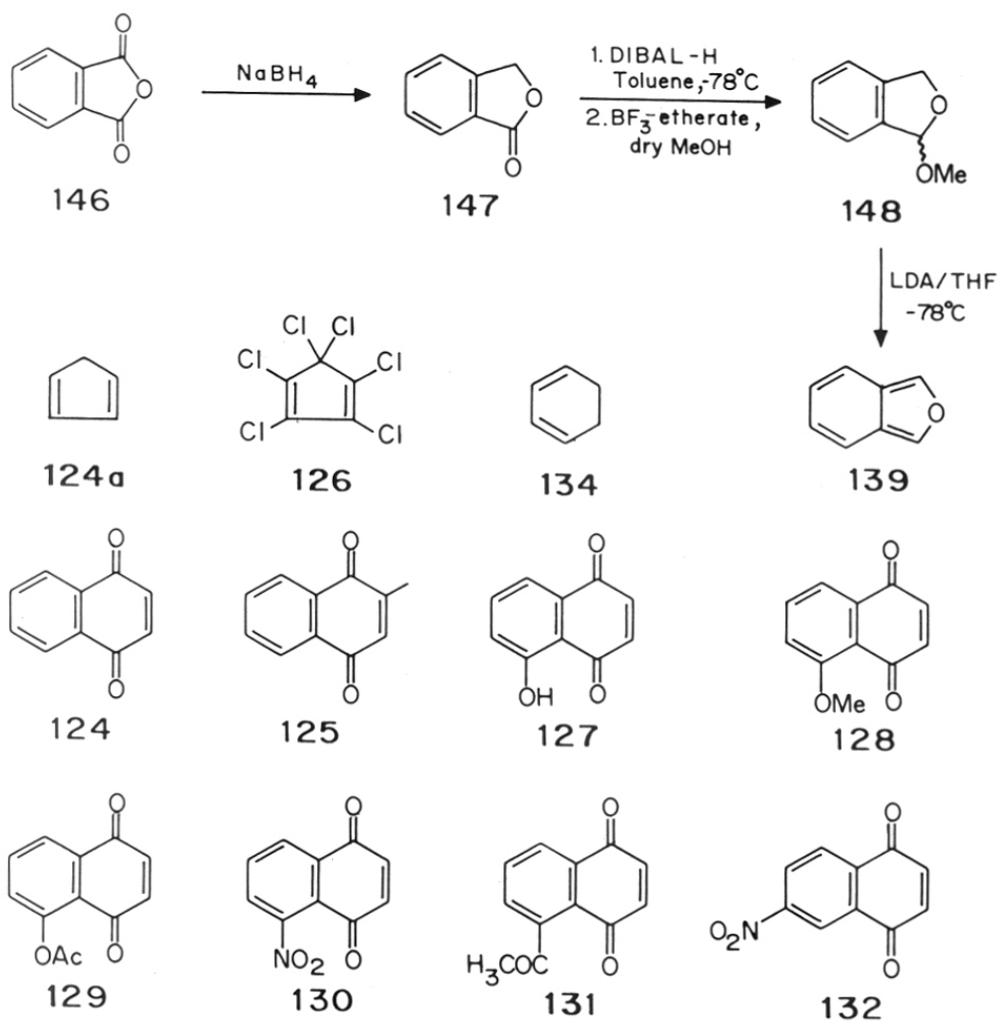


- 124 : $R^1-R^6=H$
 125 : $R^1, R^2, R^4-R^6=H, R^3=CH_3$
 126 : $R^1, R^2=Cl, R^3-R^6=H$
 127 : $R^1-R^4, R^6=H, R^5=OH$
 128 : $R^1-R^4, R^6=H, R^5=OMe$
 129 : $R^1-R^4, R^6=H, R^5=OAc$
 130 : $R^1-R^4, R^6=H, R^5=NO_2$
 131 : $R^1-R^4, R^6=H, R^5=COCH_3$
 132 : $R^1-R^5=H, R^6=NO_2$

Scheme -11



Scheme - 12

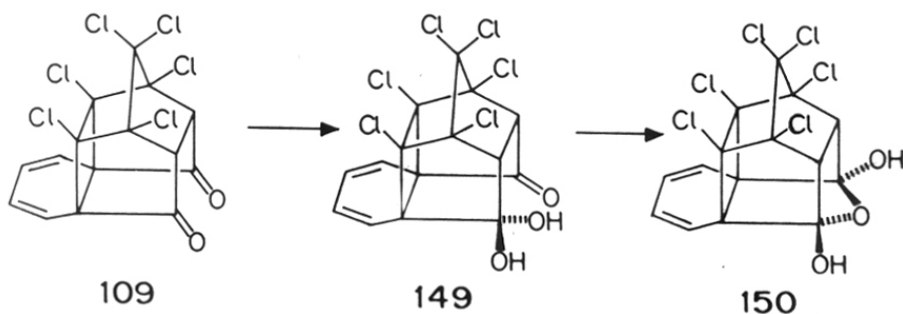


compound was confirmed on the basis of 8 lines observed in ^{13}C -NMR δ 197.12(s), 135.48(s), 135.15(d), 133.59(d), 126.39(d), 124.16(d), 49.11(d) and 48.79(t). While for 'exo' isomer, ^1H -NMR gave signal at δ 6.7-6.9 (2H, m) for olefin protons, 7.5-7.7 (2H, m), 7.9-8.1 (2H, m) for aromatic protons, ^{13}C -NMR signals appeared at δ 181.23(s), 162.66(s), 142.25(d), 132.91(d), 132.53(d), 125.82(d), 73.02(d), 48.44(t), which once again established the symmetrical nature of *exo* isomer. Synthesis of photo cage compound hexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-diene-3,10-dione **47** was accomplished by photolysis of 'endo' isomer **65** in dry CH_3CN at 300 nm. The structure of the photo cage dione **47** was confirmed by matching spectral data (IR and ^1H -NMR) with the literature data of reported compounds,⁵³ which melted at 114°C (lit. 111°C)⁵³ and exhibited peaks in IR at 1740 cm^{-1} for substituted cyclobutyl ketone. Subsequently, we prepared *endo* 2-methyltetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13-tetraene-3,10-dione **116** by Diels-Alder reaction of 2-methyl-1,4-naphthoquinone and cyclopentadiene (1:1.2) in refluxing ethanol for about 10 h. Surprisingly (94%) yield⁵⁴ of the Diels-Alder product was obtained, which was considerably more than the reported yield (57%) in the presence of micellar solution (cetyl trimethyl ammonium bromide).⁵⁵ The structure was confirmed by matching spectral data (IR and ^1H -NMR) with data of reported compound.⁵⁵ IR showed absorptions at 1680, 1670 cm^{-1} for ketone carbonyl, whereas proton NMR gave peaks at δ 1.4-1.6 (d, 2H), 2.4 (s, 3H), 3.3-3.5 (m, 2H), 3.62 (br s, 1H), 5.8-5.9 (m, 2H), 7.3-7.5 (m, 2H), 7.7-8.0 (m, 2H). The compound **116** was subsequently photolysed in CH_3CN solvent (1mg/1ml) at 300 nm to give photo cage dione **108** (75%) yield, which was characterized by spectral, analytical and chemical transformations. ^1H -NMR showed characteristic peaks of olefinic protons at δ 5.2-5.5 (m, 2H), 5.8-6.1 (m, 2H), whereas ^{13}C -NMR exhibited peaks at δ 212.63(s), 210.23(s), 124.37(d), 124.25(d), 120.01(d), 119.57(d), 61.88(d), 58.23(d), 50.65(s), 50.13(s), 49.64(d), 49.59(d), 49.24(d), 44.27(d), 37.20(t), 16.98(q).

Perturbation of olefin fragment, however, with chloro, gave reasonably good yields of photocyclised product. The *endo*-1,12,13,14,15,15'-hexachlorocyclo[10.2.1.0^{2,11}.0^{4,9}]penta deca-4,5,7,13-tetraene-3,10-dione **117** was synthesized in (60%) yield by Diels-Alder reaction

of naphthoquinone and hexachlorocyclopentadiene (HCP) by refluxing neat at 160°C for about 12h. The photolysis of endo compound **117** at 300 nm in CH₃CN (1mg/1ml) for 2.5h gave **109** (90%), which was characterized by spectral and analytical data. Thus, IR showed absorptions at 1740 cm⁻¹ for ketone carbonyl, whereas ¹H-NMR gave signals at δ 2.44-2.6 (m, 2H), 6.1-6.6 (m, 4H). The 1,12,13,14,15,15'-hexachlorohexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-diene-3,10-dione **109** was extremely moisture sensitive compound. Thus, in ¹H-NMR two prominent sets of protons α to the carbonyl group which were D₂O exchangeable were observed. Further, in IR spectra, scrambling due to peaks corresponding to carbonyl and hydroxyl groups were observed. A CH₂Cl₂ solution of the reaction mixture was stirred with a few drops of water for 2h, when clear single compound was obtained. The spectral data revealed the presence of hemiacetals (spectral data given in *Section-C*). The probable mechanism for the formation of the hemiacetals **150** is given below. In the stepwise mechanism (*Scheme-13*), antiperipheral⁵⁶ or peripheral attack⁵⁷ of lone pair of electrons of the oxygen or moisture may give the gem diol **149**, followed by an attack of antiperipheral OH group on the other carbonyl to give the compound **150**. The second attack is due to the proximity of carbonyl carbons as seen in molecular models.

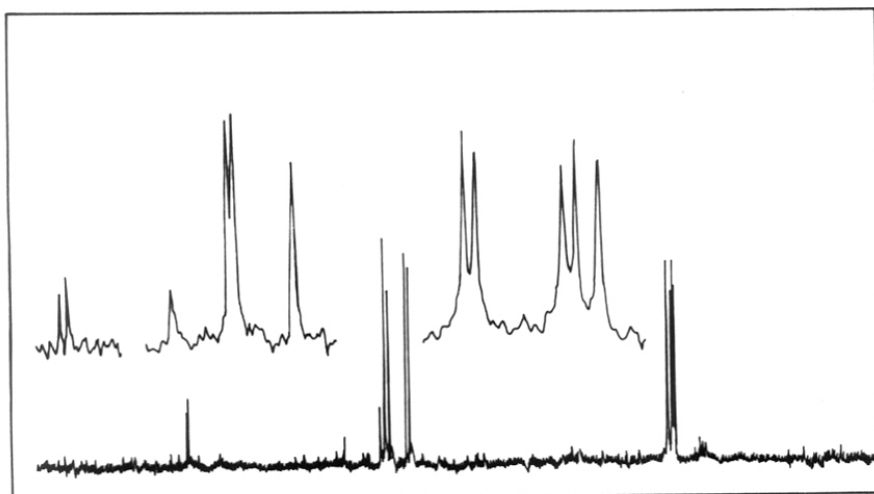
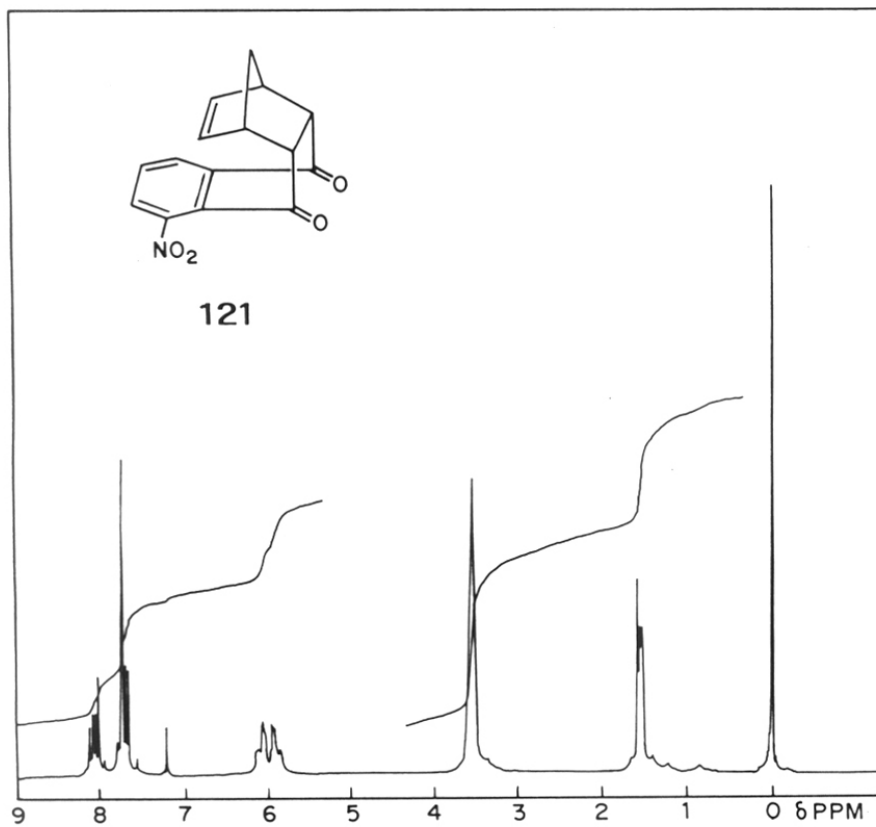
Scheme -13



Subsequently, we started with the photolysis with electron acceptor e.g., NO₂, COCH₃ or electron donor e.g., OH, OAC, OCH₃ substituents at R⁵ and R⁶ the aromatic ring in **118-123**. Surprisingly, no photocyclization occurred with either donor or acceptor substituents. The *endo*

5-hydroxytetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13-tetraene-3,10-dione **118** was synthesized by Diels-Alder reaction of 5-hydroxy-1,4-naphthoquinone⁵⁸ and CPD in refluxing benzene for 1h in (94%) yield, which was confirmed by ¹H-NMR δ 1.44-1.68 (m, 2H), 3.24-3.72 (m, 4H), 5.9-6.0 (m, 2H), 6.96-7.44 (m, 3H), 12.48 (s, 1H, OH). Similarly, the *endo* 5-methoxytetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13-tetraene-3,10-dione **119** was synthesized by Diels-Alder reaction of 5-methoxy-1,4-naphthoquinone, which in turn was prepared from 1,5-dihydroxynaphthalene by mono methylation (K₂CO₃/(CH₃)₂SO₄), followed by salcomine oxidation in the presence of molecular oxygen⁵⁸ and freshly cracked cyclopentadiene in refluxing benzene for 3h. in (92%) yield **119**. The structure **119** was confirmed on the basis of ¹H-NMR δ 1.5 (m, 2H), 3.42-3.7 (m, 4H), 4.0 (s, 3H, OCH₃), 6.1 (m, 2H), 7.32 (m, 2H, Ar), 7.72 (m, 2H, Ar). Lastly, the *endo* 5-*O*-acetyltetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13-tetraene-3,10-dione **120** was prepared from *O*-acetylation (pinch of 4-dimethylaminopyridine (DMAP), acetic anhydride and pyridine) of **118** in (83%) yield, which was confirmed by ¹H-NMR δ 1.5 (m, 2H), 2.4 (s, 3H), 3.4-3.7 (m, 4H), 6.1 (m, 2H), 7.45 (dd, 1H), 7.74 (t, 1H), 8.1 (dd, 1H), besides satisfactory mass spectral data.

Further, we wanted to study the effect of acceptor groups like NO₂ and COCH₃ at R⁵ and R⁶ position of tetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13 -tetraene-3,10-diones **121-123**. Thus, the *endo* 5-nitrotetracyclo [10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13-tetraene-3,10-dione **121** was synthesized from Diels-Alder reaction of 5-nitro-1,4-naphthoquinone with CPD in refluxing benzene for 2h. The 5-nitro-1,4-naphthoquinone itself was prepared by nitration (fuming HNO₃ and conc. H₂SO₄) of 1,4-naphthoquinone in 40% yield. The structure of Diels-Alder product **121** was confirmed by spectral data (¹H-NMR and ¹³C-NMR). Proton NMR showed δ 1.5 (m, 2H), 3.6 (m, 4H), 5.9-6.1 (m, 2H), 7.7-7.85 (m, 2H), 8.0-8.1 (m, 1H), whereas ¹³C-NMR δ 193.53(s), 193.16(s), 146.53(s), 135.52(s), 134.05(d), 133.92(d), 133.72(s), 132.61(d), 127.57(d), 126.39(d), 48.66(d), 48.49(d), 47.13(d), 46.90(d), 46.54(t). Similarly, 5-acetyltetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13-tetraene-3,10-dione **122** was synthesised by Diels-Alder reaction of 5-acetyl-1,4-naphthoquinone and CPD. The synthesis of 5-acetyl-1,4-naphthoquinone was accomplished by monoacetylation of naphthalene (84%)



($\text{CH}_3\text{COCl} + \text{AlCl}_3$) and subsequent oxidation (H^+/CrO_3)⁵⁹ (65%). Diels-Alder reaction with CPD in refluxing dry benzene for 1-2h. gave **122** which was confirmed by spectral data. Proton NMR showed signals at δ 6.05 (m, 2H), olefin protons, 7.5 (dd, 1H), 8.6-8.9 (t, 1H), 8.1-8.2 (dd, 1H) aromatic protons and ^{13}C -NMR exhibited satisfactory signals at δ 203.18 (s, COCH_3), 197.40(s), 196.38(s), 143.27(s), 135.94(s), 135.26(s), 133.48(d), 133.34(d), 130.43(d), 127.26(d), 127.08(d), 49.16(d), 49.08(d), 48.91(d), 48.76(d), 48.40(t), 29.97(q). Finally, 6-nitrotetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13-tetraene-3,10-dione **123** was synthesised by Diels-Alder reaction of 6-nitro-1,4-naphthoquinone and CPD in refluxing dry benzene for 3-4h. which was characterized by spectral data. Satisfactory proton NMR δ 1.45 (dd, 2H), 3.45-3.8 (m, 4H), 6.0 (m, 2H), 8.2 (s, 1H), 8.5-8.65 (dd, 1H), 8.88 (d, 1H) was obtained.

Additionally with a view to prepare inverse electron density pattern diene frame for π -facial selectivity,³⁸ we attempted the photocycloaddition of Diels-Alder product from isobenzofuran and benzoquinone. Our presumption was that in old cage diene frame **47** the diene surface from cyclobutane face was electron-rich (nucleophilic in nature), whereas the diene surface from carbonyl side is electrophilic in nature. Indeed, potential energy surface calculation of the diene frame by bringing a point charge e.g., H^+ , has proved our points.³⁹ However, in cage dione **143**, we presumed that these nucleophilic and electrophilic surfaces will change. The *endo* 15-oxatetracyclo[6.6.1.0^{2,7}.0^{9,14}] pentadeca-4,9,11,13-tetraene-3,6-dione **141** was synthesized by Diels-Alder reaction of isobenzofuran and benzoquinone. The ratio of *endo:exo* was (90:10). From the point of aryl-olefin photocycloaddition, aryl was substituted with donor groups, whereas olefin was attached to electron withdrawing group. However, *ortho*-photocyclisation was not observed at 300 nm (1mg/1ml) in acetonitrile. In recent years, an efficient Diels-Alder addition of substituted and unsubstituted isobenzofurans⁶⁰ has acquired a prominent place as synthons for the synthesis of polycyclic compounds. Their use as reactive dienes has been shown in many successful synthesis of natural products. The unsubstituted isobenzofuran **139** is stable enough to be isolated in solution at room temperature. It can be easily prepared by the reaction of lithium diisopropylamide (LDA) with 1-methoxy-1,4-dihydroisobenzofuran⁶¹ **148** which in turn can be prepared from phthalide⁶¹ **147** (Scheme-12).

Thus, diisobutyl aluminium hydride (DIBAL-H) reduction of **147** followed by *o*-methylation gave good yield of **148**. Treatment of **148** with LDA in dry benzene led to the formation of isobenzofuran **139**, which was used in the benzene solution itself. The addition of *p*-benzoquinone to the solution of **139** and refluxing at 70-80°C for 2-3h. Led to the formation of Diels-Alder adducts **141** and **142** (ratio 90:10, 65%). It was found to be a mixture of Diels-Alder *endo+exo* and were separated and confirmed by the proton NMR, *endo*: **141** δ 2.35 (m, 2H), 3.88 (m, 2H), 5.8 (m, 2H), 7.3 (m, 4H, Ar), *exo*: **142** δ 2.39 (m, 2H), 3.91 (m, 2H), 6.0 (m, 2H), 7.1-7.35 (m, 4H, Ar).

In yet another variation, the saturated analogue of **144** failed to give **145** either *ortho* or *meta* photocyclization. Interestingly, **144** was an ideal case for *meta* photocycloaddition.⁶² But due to geometric constraints, no *meta*-cyclization was observed. The synthesis of saturated analogue **144** is described in Chapter-3.

With a view to release the strain from [2.2.1] system to [2.2.2] systems, our next objective was to prepare higher homologue of cage dione **47**, since extrusion of 'X' would be possible by thermal means. Thus, reaction of cyclohexadiene with 1,4-naphthoquinone in ethanol at 50°C in a sealed tube afforded expected Diels-Alder reaction products **134** and more stable **135**, which were confirmed by proton NMR *endo* **134**, δ 1.35-1.8 (m, 4H), 3.1 (m, 2H), 3.15-3.22 (m, 2H), 6.05 (m, 2H), 7.7 (m, 2H, Ar), 8.05 (m, 2H, Ar), **135** δ 1.5-1.73 (m, 4H), 4.5 (m, 2H), 6.3 (dd, 2H), 7.8 (m, 2H, Ar), 8.1 (m, 2H, Ar).

Further, *endo* **134** compound on photolysis in dry acetonitrile (1mg/1ml) at 300 nm for 2.5h yielded very poor yield (35%) of expected photocage dione **136** and a side product **135** formed perhaps by autooxidation of **134**. Difficulty to obtain more yield of photocage dione **136** can be rationalised on the basis of unstability of *endo* compound **134**. Literature procedure⁶³ shows that *endo* compound **134** is highly unstable compound and on heating or air oxidation affords compound **135**. During photolysis of **134**, formation of large amount of yellow crystalline compound was observed, which was proved to be compound **135** with the help of spectral data. The structure of photo cage dione **136** was confirmed by ¹H-NMR δ 1.65 (s, 4H), 1.8-1.9

(m, 2H), 2.95-3.1 (m, 2H), 3.5 (m, 2H), 7.0-7.1 (m, 2H), 7.2-7.3 (m, 2H). To avoid autooxidation possibility of **135**, the dimethyl endo compound **138** was synthesised by reaction of **134**, with NaH and trapping the anion with CH₃I at 0°C which gave 62% yield of **138**. The structure of **138** was characterized by ¹H-NMR δ 1.68 (s, 6H), 3.9 (m, 4H), 4.45 (m, 2H), 6.5 (m, 2H), 7.44 (m, 2H), 8.25 (m, 2H). The compound **138** was subjected to photolysis. However, no photocyclization was observed.

With a view to circumvent the unanticipated photocyclization problem, we have examined the effect of different reaction parameters e.g., (i) Sensitization study, (ii) Wavelength variation effect, (iii) Photolysis under electron transfer condition, (iv) Interception of the probable dione with 2-phenyl-1,2-dehydro-1,2,4-triazol-3,5-dione (PTAD).

Sensitization study:⁶⁴ The initial absorption of a photon by the enone gives the n,π^* singlet state (S_1) which then undergoes rapid (unit efficiency) intersystems crossing into triplet (T_1). T_1 may be either n, π^* or π, π^* in nature. This excited enone interacts with alkene to give cycloaddition products in a normal way. Alternatively, in the presence of sensitizers e.g., acetone, acetophenone and benzophenone, one can excite the olefin itself, which can photocyclize with the aromatics.⁶⁴ Similarly, we irradiated a mixture of **119** and **121** (0.05M) in benzene with sensitizer (acetone or acetophenone or benzophenone) 0.5M concentration at 300 nm for 12-20 h. However, no photocyclization occurred and >90% of the starting material was recovered.

Wavelength effect: The endo compounds **119** and **121** were photolysed separately at different wavelengths e.g., 254 nm (Rayonet) irradiation, 350 nm (Rayonet) and 200W (Hanovia) with a view to examining the effect of wavelength on photocyclization efficiency. However, no photocyclized products were obtained.

Electron transfer conditions:⁶⁵ Since it is possible to generate reactive species e.g., radical cations from olefins or from electron rich aromatics by photochemical electron transfer methods, we wondered whether such methods could be exploited for our photocyclization studies. Thus,

endo compounds **119** and **121** (substrate concentration 1×10^{-3}) in benzene solution were irradiated with 1,4-dicyanonaphthalene (DCN 5×10^{-4}) either to perturb electron rich olefin in **121** or electron rich aromatic in **119** at 350 nm for 10 h. However, this strategy also failed to solve our problem.

Interception of Diene formed with PTAD:⁶⁶ One of the explanation for lack of photocyclization could be an efficient equilibration between starting materials and products, since chromophore-wise both are similar. To break this equilibrium, one could trap the diene formed by a highly reactive dienophile, which could later on be eliminated by extrusion reaction. Thus, we attempted to intercept the diene formed from **119** to **111** (1 mol) in photolysis (300 nm Rayonet, 6 h.) by 4-phenyl-1,2-dehydro-1,2,4-triazol-3,5-dione (PTAD, 0.5 mol) for 6 h. However, in our case, no D-A product with PTAD was observed. Recently, Prinzbach et.al⁶⁶ have trapped the thermally unstable diene by highly reactive dienophile PTAD during aryl-olefin intramolecular *ortho*-photocycloaddition.

CONCLUSION

This study examines the *ortho*-photocycloaddition possibility in variety of related structural frames and by and large no definite patterns could be observed.⁶⁷ Out of sixteen models examined,⁴² only five successful photocyclizations were observed. Earlier investigations and generalizations mainly concentrated on olefin perturbation, whereas ours is an unprecedented effort towards perturbation of aryl group for *ortho*-photocyclization. This study defines the limits of our understanding in structurally similar frames in this area.

SECTION-B

Π-FACE STEREOSELECTION IN CAGE DIONE 45

INTRODUCTION

After a brief overview of literature regarding various theories of π -face stereoselection and our involvement^{38,39} with the π -face studies with diene **47**, we got interested with a recently discovered theory of nucleophilic and electrophilic surfaces by Professor Hehre⁶⁸. π -Face selection in addition to sp^2 centres e.g., olefins, carbonyls, enones, dienes, etc. is at the core of stereogenesis. Cram⁶⁹ showed the importance of steric effects, that nucleophilic addition to carbonyl flanked by three different sized groups occurs from the direction of small group. However, the importance of stereoelectronic effects in stereoselection is only recently being recognized. We were interested in the π -face stereoselectivity of cage dione and various theories e.g., FMO theory of stereoselection,⁷⁰ theory of steric consideration,⁷¹ polar group effect,⁷² double bond formation, theory of π -electron density distortion by σ/π mixing,⁷³ nucleophilic and electrophilic surfaces theory,⁶⁸ torsional effect, principle of least nuclear motion,⁷⁴ torsional and steric control of diastereoselection,⁷⁵ stabilization due to hyperconjugative interaction,⁷⁶ were evaluated to explain our observations. We were particularly interested in the nucleophilic and electrophilic surface theory proposed by Hehre.⁶⁸ Our presumption was that the diene face of carbonyl side will be electrophilic, whereas the cyclobutane face will be nucleophilic. We wondered whether such surfaces could be identified by chemical reactions. Thus, a nucleophilic surface should react faster with an electrophilic species e.g., carbene. Alternatively, an electrophilic surface should react faster with a nucleophilic species. Initially, the reaction of **47** with dichlorocarbene and dibromocarbene was examined and an unprecedented aspect of reactivity towards carbonyl functionality has been discovered. Additionally, double α -cleavage of cage dione was observed, which could offer opportunities for introduction of cyclopentadiene unit between the rings of naphthoquinone in a stereoselective way (i.e. only endo-norbornane skeleton) which is difficult to obtain otherwise.⁷⁷

Thus, we carried out cyclopropanation (2+1) with highly reactive halo carbenes. Carbenes and substituted carbenes add to double bonds to give cyclopropane derivatives (2+1 cycloaddition). Hine et.al have made extensive studies related to the hydrolysis of haloforms and the formation of halomethylenes from haloforms. Initial fast attack of base on chloroform gives the trichloromethyl anion and the conjugate base. The trichloromethyl anion then slowly decomposes to give dichlorocarbene. The relative rates of formation of carbanions from haloforms is $\text{CHI}_3 \sim \text{CHBr}_3 > \text{CHBr}_2\text{Cl} > \text{CHBrCl}_2 \sim \text{CHCl}_2\text{I} > \text{CHBr}_2\text{F} > \text{CHCl}_3 > \text{CHBrClF} > \text{CHCl}_2\text{F}$, showing that α -halogen substituents facilitate carbanion formation in the order $\text{I} \sim \text{Br} > \text{Cl} > \text{F}$.⁷⁸ The kinetics of hydrolysis of a number of haloforms in dioxane-water established the following order : $\text{CHBrClF} \gg \text{CHBrCl}_2 > \text{CHBr}_2\text{Cl} \sim \text{CHCl}_2\text{I} > \text{CHBr}_3 > \text{CHCl}_3 \gg \gg \text{CHF}_3$. Halogens appear to facilitate dihalomethylene formation from CX_3 in the order $\text{F} \gg \text{Cl} > \text{Br} > \text{I}$. This order is attributed to supply of electrons to the carbon atom. The parameters for the differences between the abilities of halogen to separate as anions ($\text{Br} > \text{I} > \text{Cl}$) are smaller and probably less significant. The formation of dihalo cyclopropanes from haloform, an alkoxide, and an olefin is an excellent preparative procedure. Potassium *t*-butoxide is the base of choice. Other alkoxides can be employed, but usually with lower yields. The reaction of bromoform with potassium *t*-butoxide and an olefin leads to dibromocyclopropanes in good yields.

The principal reaction of halocarbenes with olefins is addition to form halocyclopropanes, and the order of reactivity of carbene appears to be $\text{CH}_2 > \text{CHCl} > \text{CCl}_2 > \text{CBr}_2 > \text{CF}_2$. This order is consistent with added stabilization provided by overlap of the unshared *p*-electrons of the halogen with the vacant *p*-orbital of the carbenes.

The halocarbenes are electrophilic in character, and the relative rates of their additions to carbon-carbon double bonds generally increase with increasing alkyl substitution at the olefin function. Steric factors appear to be less important in this respect than electronic factors.

Carbene addition reactions are valuable in synthetic organic chemistry. Thus carbene insertion, ring enlargement, cyclopropanation, halocarbonyl ylides and addition to carbonyl,

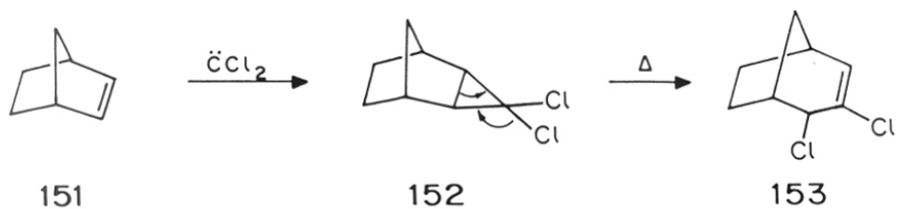
etc. are routinely employed for various synthetic strategies. A brief survey of carbene will be presented in the following section (*Scheme-14*) with a view to bring comprehension and focus to our work.

In bridged bicyclic olefins (norbornane) addition of halocarbene occurred with expansion of the six-membered ring (*Scheme-14, Equation-25*). The initial attack of carbene was stereoselective and it came from *exo*-face. Ring expansion may occur even with non-aromatic compounds, when the driving force is supplied by relief of strain.⁷⁹ The reaction of carbene with carbonyl provides carbonyl ylides, which are important class of dipolar intermediates. The thermal decomposition of phenyl (bromodichloromethyl)-mercury in presence of aryl aldehydes and dimethyl acetylene dicarboxylate leads to the formation of dimethyl 2-halo-5-aryl furan-3,4-dicarboxylates by selective trapping of the intermediate dihalocarbonyl ylides (*Equation-26*).⁸⁰ Normally, carbenes add to 1,3-dienes - as to allenes - in a 1,2-fashion. Numerous attempts have been made to achieve 1,4-addition reactions of carbenes. Most of these have either failed, are inconclusive or may be the result of rearrangement reactions subsequent to the initial 1,2-addition. But Bickelhaupt et.al⁸¹ recently observed the first case of an intermolecular 1,4-addition of a singlet carbene to a 1,3-diene (*Equation-27 & 28*).

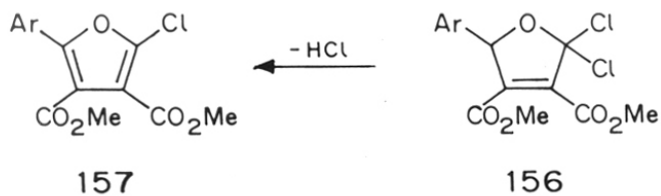
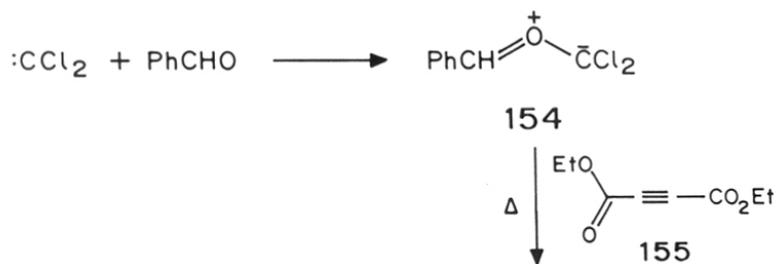
Marchand et.al⁸² recently reported the reaction of 1-X-pentacyclo [5.4.0.0^{2,6}.0^{3,10}.0^{5,9}] undecane-8,11-diones [X=CH₃, Ph, *p*-cyanophenyl and *p*-methoxyphenyl] with 1 equivalent of carbene, generated *in situ* from EDA, in the presence of BF₃.Et₂O, which gave the corresponding monohomologation product (*Equation-29*).

Many literature examples show that the reaction of a simple cyclic ketone with (dibromomethyl) lithium at -78°C, followed by low temperature hydrolysis of the resulting lithium alkoxide **168** gives the corresponding dibromomethyl alcohol. Murray et.al⁸³ found the reaction of a bicyclic or tricyclic ketone with (bromomethyl) lithium under comparable conditions provides a dibromomethyl alcohol **171** and/or an α -bromo aldehyde **172**. The latter product appears to result from an intramolecular displacement reaction in **174** to give a bromo epoxide **175** which then rearranges stereospecifically to the α -bromoaldehyde **172** (*Equation-31*).

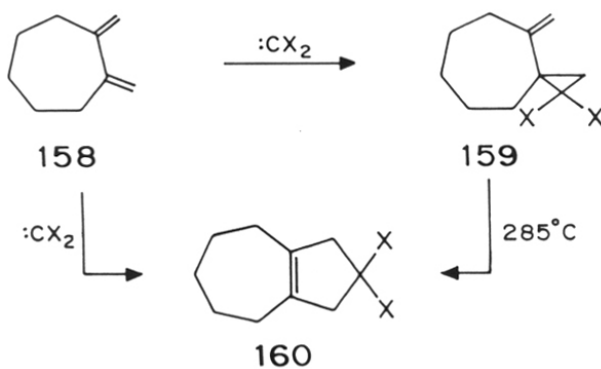
Scheme -14



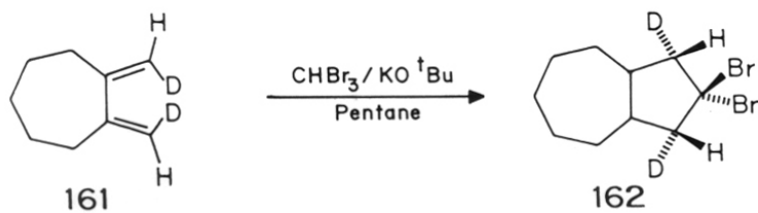
Equation- 25



Equation- 26

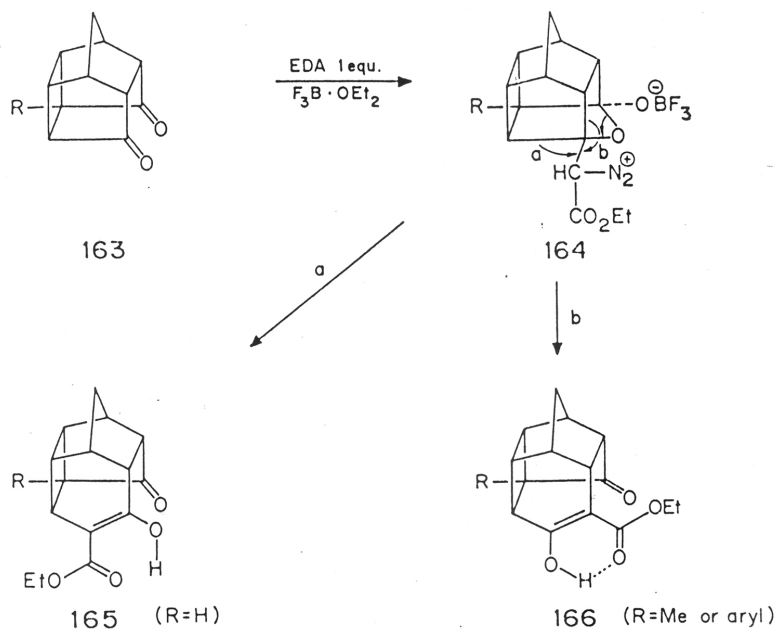


Equation- 27

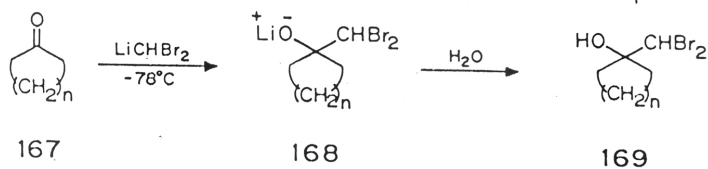


Equation - 28

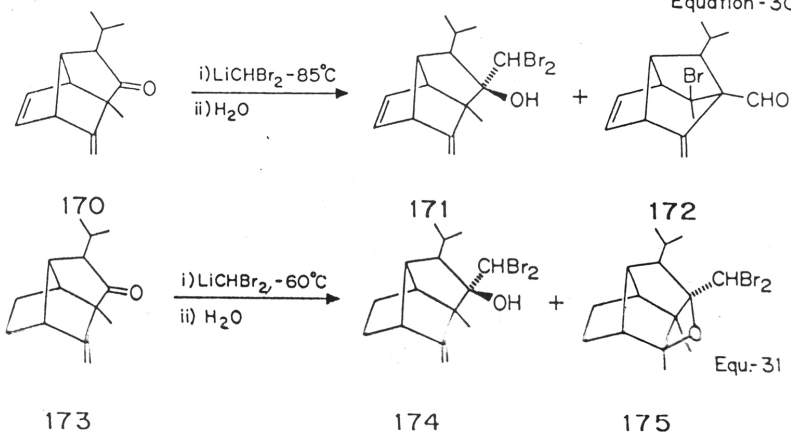
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Scheme -14



Equation - 29



Equation - 30



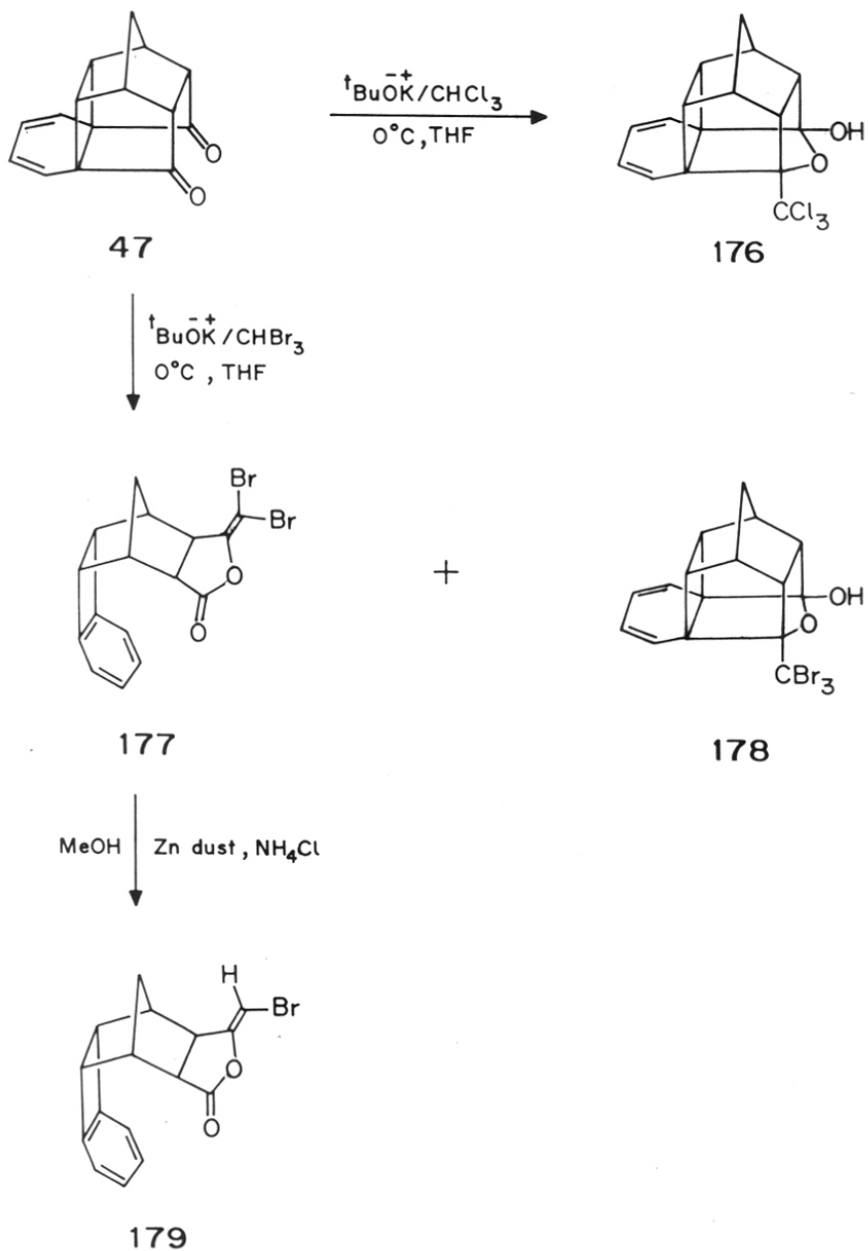
RESULTS AND DISCUSSION

With a view to chemically trapping the electrophilic and nucleophilic surfaces, as discussed earlier, we synthesised hexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-diene-3,10-dione **47** as per *Section-A* experimental conditions. Our chlorocarbene was generated from CHCl₃ and potassium tertiary butoxide in THF at 0°C, which was added to cage dione **47**. Work-up gave a clean single product **176**. The structure of the addition product **176** was proved on the basis of ¹H-NMR, ¹³C-NMR, IR, Mass spectra and satisfactory analysis of sample. ¹H-NMR showed peaks at δ 1.25-1.9 (dd, 2H), 2.55-3.0 (m, 4H), 3.2-3.55 (m, 2H), 5.4-5.6 (m, 1H), 5.65-5.9 (m, 2H), 5.91-6.0 (m, 1H), whereas IR showed strong absorption at 3460 cm⁻¹. In ¹³C-NMR δ 124.89(d), 122.67(d), 121.94(d), 119.07(d) for double bond carbons, 118.30 (s, CCl₃), 101.10(s), 97.89(s), 59.51(d), 58.86(d), 55.81 (s, 2C), 55.58(d), 54.06(d), 45.05(d), 42.96(d), 41.19(t) peaks were observed and mass spectrum gave M⁺ at 342. Finally, the structure was confirmed by single crystal X-ray, as shown in *Figure-I*.

In our second attempt i.e. the addition of dibromocarbene to cage dione **47**, bromoform (CHBr₃) in the presence of potassium tertiary butoxide in dry THF at 0°C after two hours stirring gave two products **177** and **178** (56% and 42% respectively). Compounds **177** and **178** were confirmed by ¹H-NMR, ¹³C-NMR, IR, Mass and satisfactory analytical data. IR spectrum of compound **178** revealed strong frequency at 3520 cm⁻¹ (bs) characteristic of 3° alcohol, ¹H-NMR showed signals at δ 1.3-1.95 (dd, 2H), 2.65-3.17 (m, 4H), 3.3-3.6 (m, 2H), 5.45-5.65 (m, 1H), 5.65-6.05 (m, 3H). Finally, the structure was further confirmed by molecular ion M⁺ 476 peak in mass spectrum.

The second structure **177** was confirmed by proton NMR and analytical data, m.p. 190°C, IR showed a strong band at 1800 cm⁻¹, characteristic of lactone carbonyl. Proton NMR showed signals at δ 2.0 (s, 2H), 3.0-3.6 (m, 4H), 3.78-3.95 (m, 2H, benzyl proton of cyclobutane), 7.0-7.43 (m, 4H, aromatic symmetrical protons). Mass spectrum gave M⁺ at 396 and ¹³C-NMR gave signals at δ 172.36(s) lacto ketone, 151.11(s), 146.08(s), 143.30(s), 127.85(d), 127.12(d), 126.31(d), 124.29(d), 49.50(d), 48.89(d), 48.56(t), 48.23(d), 47.72(d), 41.86(d), 41.58(d). The structure was further confirmed by single crystal X-ray structure (fig.I), which shows that ortho-disubstituted benzene ring and a tetra-endo-substituted norbornane skeleton is present in the product. The fusion of a benzocyclobutene to the

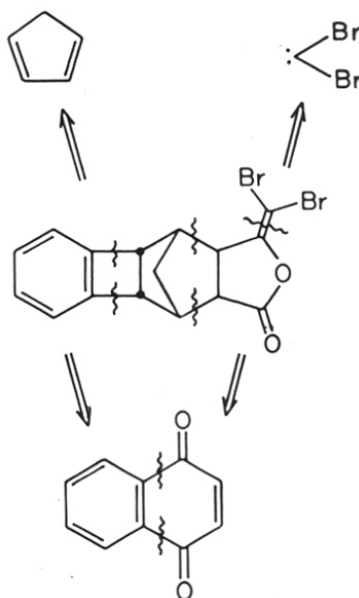
Scheme-15



norbornane skeleton results in an elongation of the C₂-C₉ bond. The structure **177** was further confirmed by chemical means by reductive debromination in the presence of saturated ammonium chloride and Zn dust in methanol. Thus, compound **177** was added to the above solution over a period of 15 minutes, which was stirred for 3h. at room temperature. Work-up of the reaction mixture gave a mono debrominated product **179** in 55% yield. The compound **179** was characterized by spectral and analytical data, m.p. 184°C, IR showed strong band at 1795 cm⁻¹. Proton NMR showed signals at δ 2.0 (s, 2H), 2.78-3.7 (m, 4H), 3.73-4.0 (m, 2H), new appearance of signal 5.2 (d, 1H, olefin proton), 7.0-7.4 (m, 4H).

Scheme -16

RETRO ANALYSIS



Based on literature precedences,⁸³ a tentative mechanism for the formation of **176**, **177** and **178** is depicted in *Scheme-17*. The first step appears to be fast addition of trihalomethyl anion to carbonyl carbon **47**, than the decomposition of trihalomethyl anion to give dihalocarbene (as described in *introduction* section).⁷⁸ Antiperipheral⁵⁶ or peripheral⁵⁷ attack of lone pair of electrons of the oxygen **180** on the carbonyl carbon gave products **176** and **178**. The second attack is due to the proximity of the carbonyl carbon. The abilities of halogen

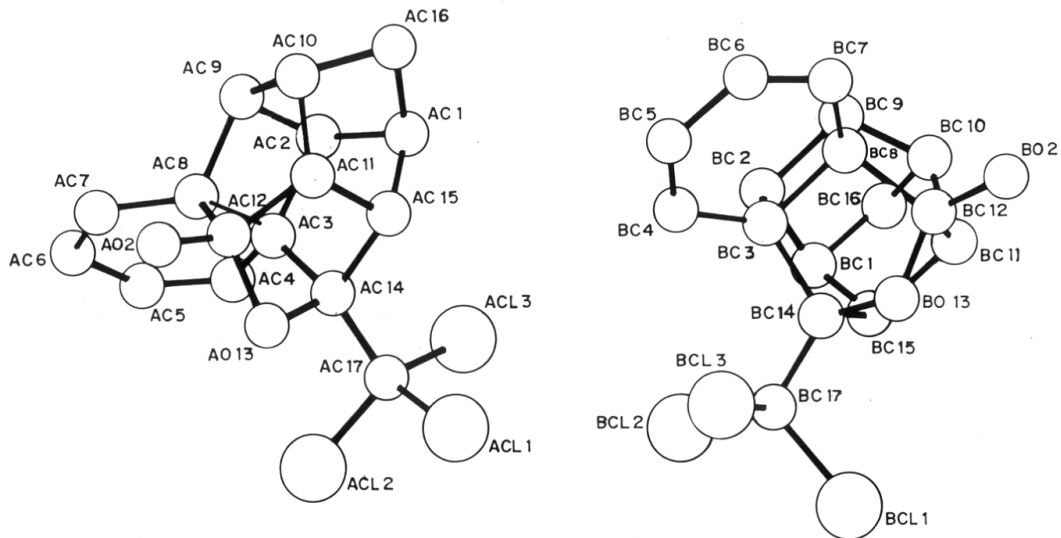
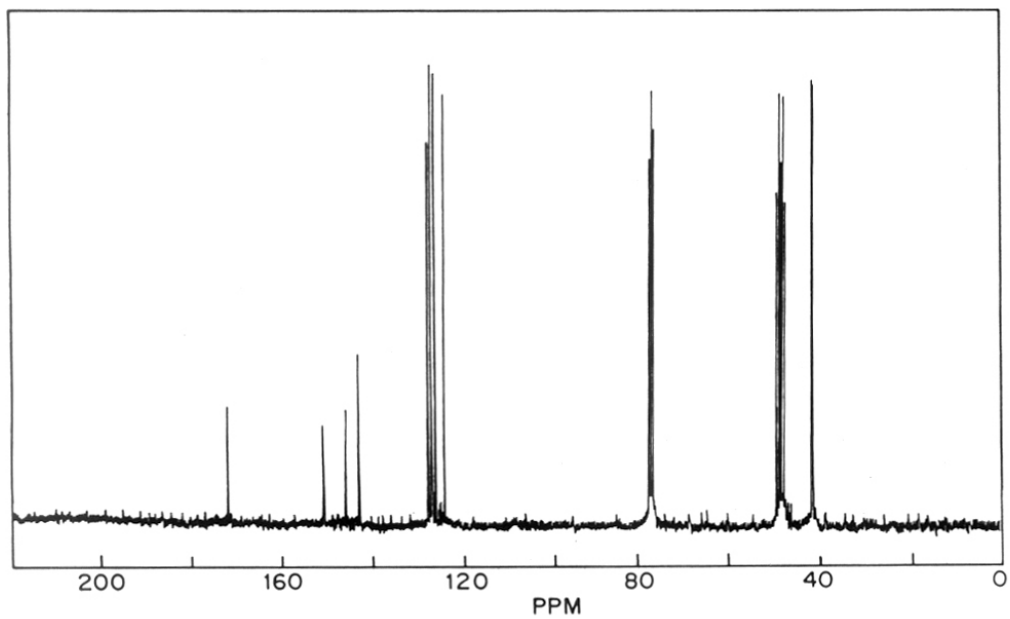
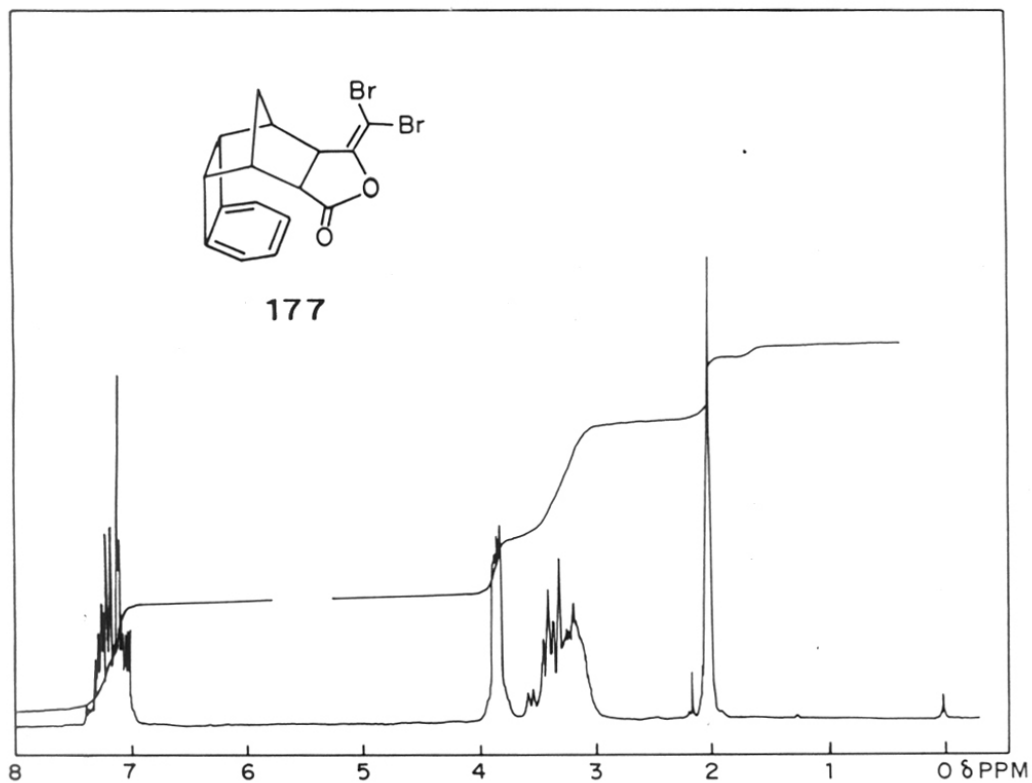
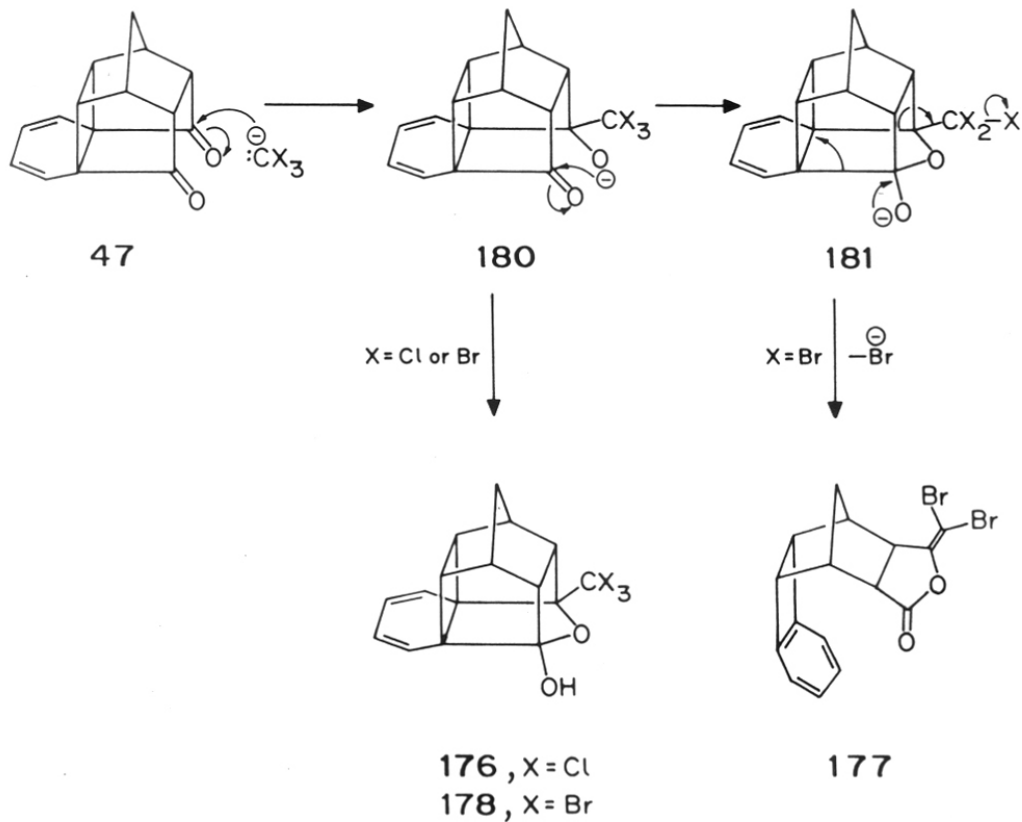


FIG.2: X-RAY STRUCTURE OF 176



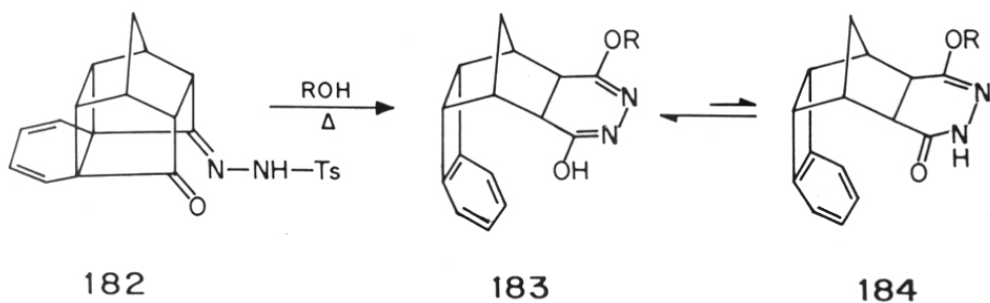
to separate as anion ($\text{Br} > \text{I} > \text{Cl}$) from tribromomethyl carbon and aromatization and rearrangement is the directive force which led to **177**.

Scheme-17
MECHANISM



Recently Coxon et.al.⁷⁷ observed (*Scheme-18*) in the course of preparing functionalised derivatives of **47** monotosyl hydrazone **182**, which undergo a novel rearrangement to the pentacyclic pyridazine derivatives **183** which was ortho-disubstituted benzene ring and a tetra-endo-substituted norbornane skeleton. This rearrangement represents a new fragmentation pathway for the PCUO skeleton and involves double α -cleavage of precursor **47**.

Scheme -18



CONCLUSION

The reaction of cage dione **47** with dichloro carbene and dibromo carbene has been examined and an unprecedented aspect of reactivity towards carbonyl functionality has been discovered. This study throws new light on the kinetics of carbene generation, and the nucleophilic attack to cage diones. Additionally although a failure from the point of our main objective i.e. to trap the nucleophilic surface, but ultimately, we were successful in cleaving the cyclobutyl carbonyl bond in this way.

SECTION-C

STEREOSPECIFIC CLEAVAGE OF 1,4-PROXIMATE DIOLS BY LEAD TETRAACETATE

INTRODUCTION

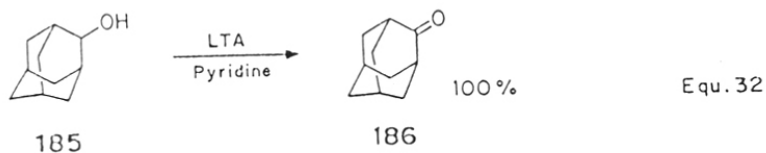
As part of our programme for the synthesis of stereocontrolled medium cyclic rings e.g., 10, 11, 12 and 13-membered rings **80**, **81**, **82** and **83**, the locked cage dione **47** is envisaged as an intermediate offering considerable opportunity for stereochemical manipulation. (see introduction of this chapter, section our approach for stereocontrolled medium cyclic on page **11**).^{38,39,42,43,46,54} However, central to our synthetic strategy for transformation of **47** to 11 and 12-membered ring is the cleavage of cyclobutyl carbonyl bond. It would be interesting, if the desired bonds could be cleaved by reacting the 1,4-diols with LTA (lead tetraacetate). If so, then it could offer a way out to cleave the much wanted cyclobutyl carbonyl bond in our system. We have been partly successful to cleave this bond like using regioselective Baeyer-Villiger oxidation **77**⁴⁶, photochemical α -cleavage **79**^{43,54} and carbene addition **178** (*Scheme-19*) [See *Section-B*], and recently Coxon et.al **183**⁷⁷ also cleaved cyclobutyl carbonyl bond via a novel rearrangement.⁷⁷ We observed an unprecedented stereospecific cleavage of proximate diols with LTA. The preparation of starting diols, its reaction with LTA and mechanistic points whether oxidation is concerted or stepwise, etc. will be described in this sub-Section-C. Subsequently, we have generalised the cleavage of proximate 1,4-diols in related systems.

Treatment of alcohols with LTA leads to the formation of acetates, aldehydes or ketones, fragmentation products and cyclizations. Oxidative cleavage of glycols is one of the well known reactions of LTA. A brief survey of LTA induced cleavage of 1,2-diols will be presented in the following section with a view to bring comprehension and focus to our work.

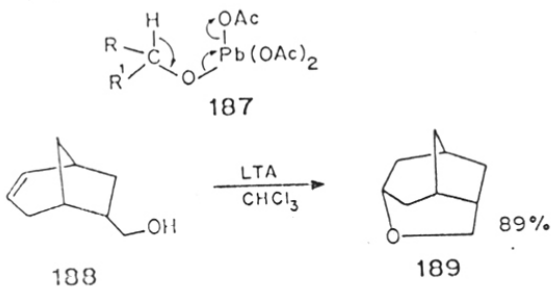
In cage compounds, LTA is known to oxidize secondary alcohols to corresponding ketones, as shown in *Equation-32*. It is suggested that formation of carbonyl functionality is from heterolytic disproportionation of intermediate **187**. In bicyclic analogue e.g., **188**, presence of a remote double bond in alcohols gives a product from neighbouring group

participation **189**.⁸⁴ 'Cis' or 1,2-diols afford aldehydes or ketones depending on the nature of the substituents. Mechanism for this oxidative cleavage was first proposed by Criegee, as outlined in *Scheme-19*.

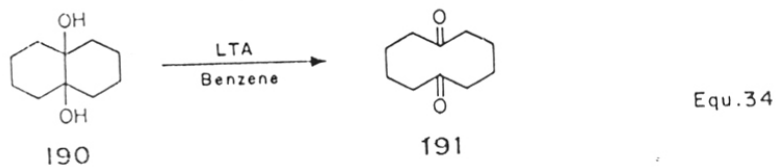
Scheme -19



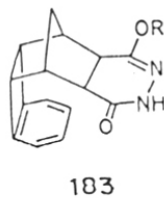
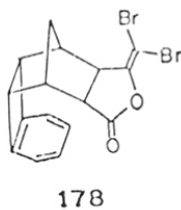
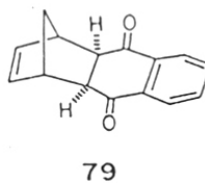
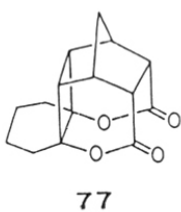
Equ. 32



Equ. 33



Equ. 34

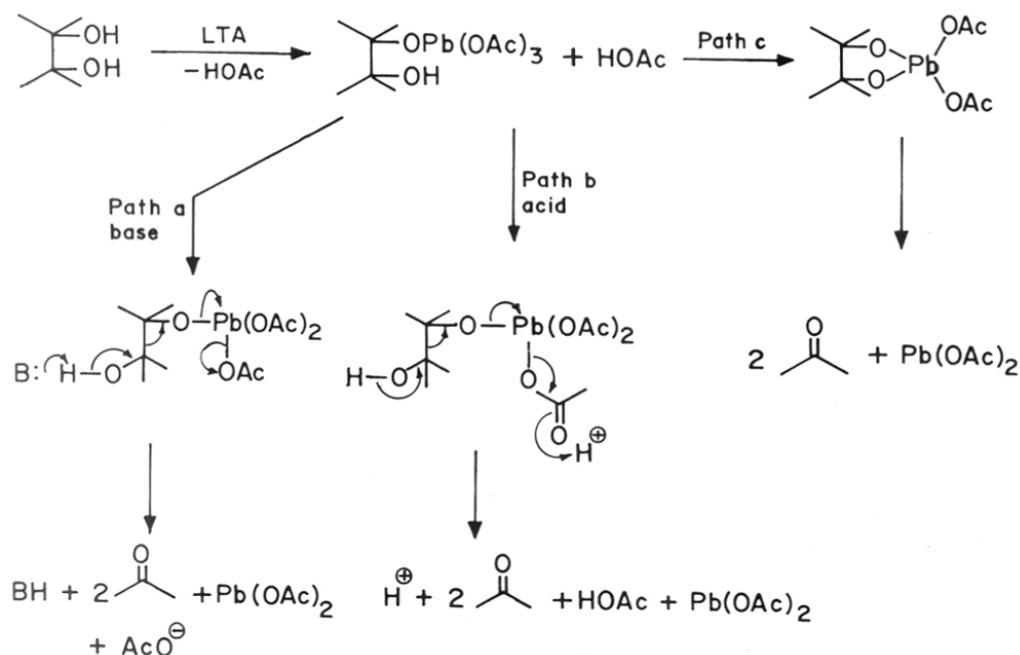


Oxidative cleavage thus, occurs through one of these three paths (*Scheme-20*). It has been proposed that, when geometry is favourable, oxidation mostly occurs *via* path 'C' by two electron process. With *trans* diols, this geometry is not possible and then it occurs either through path 'a' or path 'b'. Role of acid or base is to increase the cleavage of *trans* diols which has been explained on the basis of intermediate formation.

In a related example, cleavage of vicinal 1,2-diols, in **190** leads to formation of medium or large ring⁸⁵ **191** (*Equation-34*).

Considerable stereochemical preference has been observed in the oxidation of 1,2-diols by LTA. Thus, reaction of *cis* glycols is faster than *trans* glycols. The cases of cyclic diols, where cyclic transition state cannot form, stepwise mechanism shown by path 'b' (*Scheme-20*) operates. Although reactions of alcohols, with LTA have been studied extensively, intramolecular cyclizations are also highly important reactions in natural product synthesis.⁸⁶

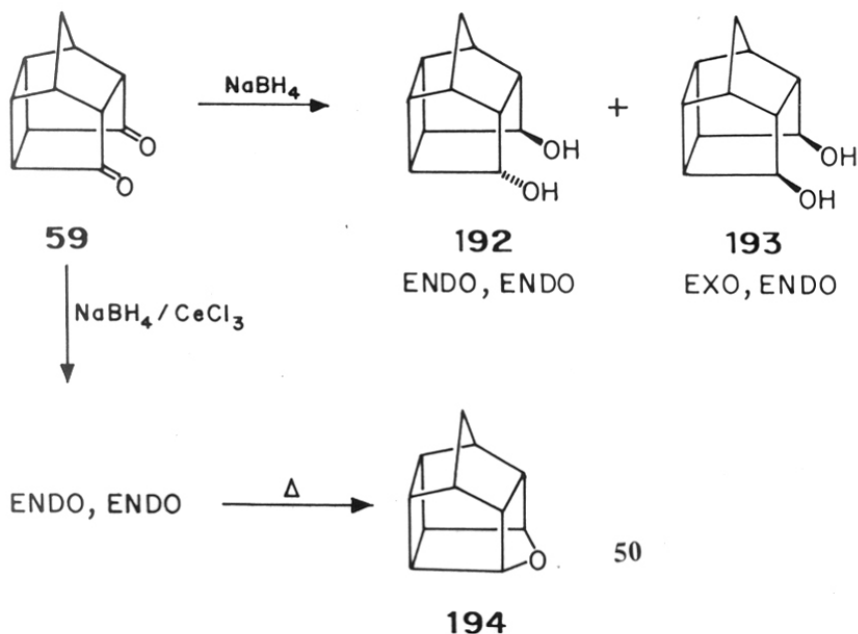
Scheme - 20



RESULTS AND DISCUSSION

For our purpose to check the validity of LTA reaction with proximate 1,4-diols, we synthesized four model compounds viz. hexacyclo[7.4.2.0^{1,9}.0^{3,7}.0^{4,14}.0^{6,15}]pentadeca-10,12-diene-*endo*-2-*endo*-8-diol **195**,⁸⁷ 7-methylhexacyclo[7.4.2.0^{1,9}.0^{3,7}.0^{4,14}.0^{6,15}]pentadeca-10,12-diene-2,8-diol **202**,⁸⁸ 1,2,9,10,16,16'-hexachloro-13-oxa-heptacyclo[8.5.1.0^{2,9}.0^{3,8}.0^{3,14}.0^{8,12}.0^{11,15}]hexadeca-4,6-diene-*exo*-12-*exo*-14-diol **150** and pentacyclo[6.2.1.0^{2,7}.0^{9,10}.0^{5,9}]undeca-*endo*-3-*exo*-6-diol **193**. Cookson and co-workers⁸⁸ reported that NaBH₄ reduction of pentacyclic cage diketone **59**, when performed in ethanol solution, afforded a mixture of the corresponding *endo, endo* and *exo, endo* diols **192** and **193** respectively. (Product ratio **192** : **193**, 38:62). It has been proposed that *trans* diol may arise by internal reduction of the second carbonyl group by the hydroborate formed from the first. Further, evidence of this transannular participation was observed in a number of standard carbonyl addition reactions with diketones.⁸⁹ Kent et.al⁹⁰ have studied reduction of photocage diones **59** with lithium aluminium hydride, aluminium 2-propoxide, NaAl(C₂H₅)₂H₂ and sodium borohydride reducing agents, where he observed that common to all reducing agents, the *endo, endo* isomer always predominates over the *exo, endo* isomer in the product mixture. Interestingly, Marchand et.al⁹¹ have reported reduction of photocage dione **59** with NaBH₄-CeCl₃ in methanol to yield *endo, endo* diol as a major product, the configuration of which was established on the basis of easy dehydration to corresponding ether **194**.

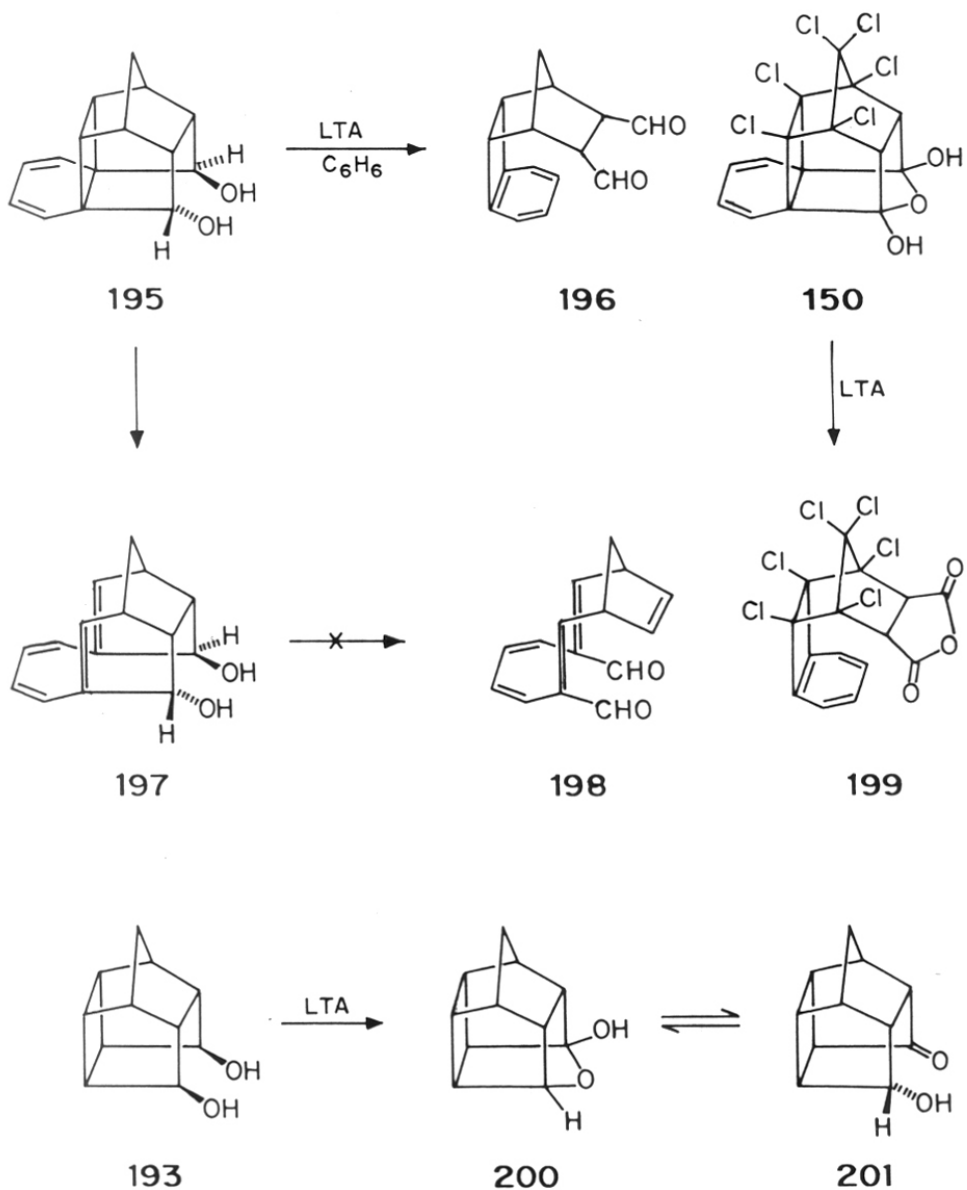
Scheme - 21



In contrast to these results, Marchand et.al.⁸⁷ reported recently solid state NaBH₄ reduction of **47** to afford exclusively the corresponding *endo, endo* diol, **195**, in quantitative yield. Compound **195** was prepared by solid state NaBH₄ reduction of **47** which afforded exclusively *endo, endo* diol **195** in quantitative yield which was confirmed by spectral data,⁸⁷ which showed appearance of broad strong band at 3200 cm⁻¹ and disappearance of carbonyl absorption in IR. Proton NMR gave signals at δ 0.9-1.52 (dd, 2H), 2.25-2.62 (m, 4H), 2.75 (s, 2H), 3.54 (s, 2H), 5.38-5.50 (m, 2H), 5.65-6.1 (m, 2H). Finally, symmetrical nature of diol was confirmed from 8 lines in ¹³C-NMR appearing at δ 32.14(t), 41.98(d), 45.58(d), 47.10(s), 53.84(d), 75.51(d), 123.70(d), 128.14(d). Similar analogue **202** were prepared by sodium borohydride reduction in ethanolic solution to give a diol mixture **202** and **203**. We faced problem in isolation of the two isomeric *endo, endo* and *exo, endo* diol and also in assigning their configurations. Besides reproducibility of solid state NaBH₄ reduction⁸⁷ was also a problem which should give an exclusively the corresponding *endo, endo* diol. The diol structure was confirmed by spectral data, broad strong band at 3440 cm⁻¹ and disappearance of carbonyl absorption in IR. Proton NMR gave significant signals at δ 3.62 (d, 1H), 4.0 (s, 1H, hydroxy group attached protons), 5.23-5.5 (m, 2H), 5.72-6.0 (m, 2H, olefin protons) and ¹³C-NMR δ 22.31(q), 31.38(t), 42.53(d), 46.78(s), 47.23(s), 48.21(d), 50.32(s), 51.84(d), 52.80(d), 53.71(d), 78.81(s), 82.71(s), 123.86(d), 124.02(d), 126.55(d), 127.10(d).

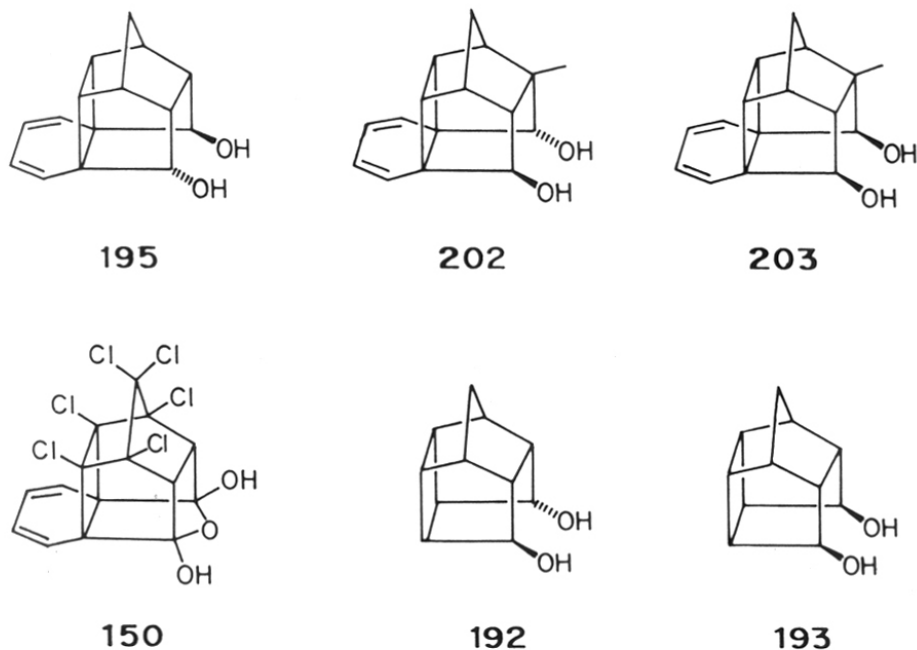
1,2,9,10,16,16'-hexachloro-13-oxa-heptacyclo[8.5.1.0^{2,9}.0^{3,8}.0^{3,14}.0^{8,12}.0^{11,15}]hexadeca-4,6-diene-*exo*-12-*exo*-14-diol **150** was obtained from the reaction of hexachloro-cage dione **109** with water by stirring in CH₂Cl₂ (see *Section-A*). The structure was established on the basis of spectral data, which showed appearance of broad strong band at 3410 cm⁻¹ and disappearance of carbonyl absorption in IR. Proton NMR gave signals at δ 6.15 (dd, 2H), 5.71 (bs, 2H, D₂O exchangeable), 5.47 (dd, 2H), 3.55 (s, 2H) and symmetrical nature of diol was confirmed from 8 lines in ¹³C-NMR appearing at δ 126.42(d), 117.26(d), 109.33(s), 97.83(s), 83.53(s), 80.41(s), 60.46(d), 60.00(s).

Scheme -22



The reaction of *endo-endo* diol **195** with LTA (1.1 eq.) in dry benzene gave 48% yield of cleaved product **196**. The structure of **196** was established based on spectroscopic and chemical evidences. It showed absorption band at 1710 cm^{-1} and 1600 cm^{-1} for aldehyde carbonyl group and aromatic ring. Proton-NMR showed the presence of aldehyde proton at $\delta\ 9.9$ (2H, s), along with aromatic protons at $\delta\ 6.7$ - 7.1 (m, 4H). Besides, ^{13}C -NMR showed peaks at $\delta\ 185.76$ (d), for aldehydic carbon, 153.50 (s), 146.12 (d), 144.20 (d), 51.94 (d), 47.33 (d), 46.07 (d), 33.48 (t), which confirmed its symmetrical nature by 8 lines in ^{13}C -NMR. Recently, Coxon et.al.⁹² have reported the acid induced (silica gel) ring opening **195** to **197** and we wondered whether compound **198** was our aldehyde. But, spectral characteristics of the product favour structure **196**. Further proof of structure **196** was derived from chemical evidences. Compound **196** in CH_2Cl_2 was mixed with 2,4-dinitrophenyl hydrazine, which gave orange red precipitate, a characteristic of aldehyde test.

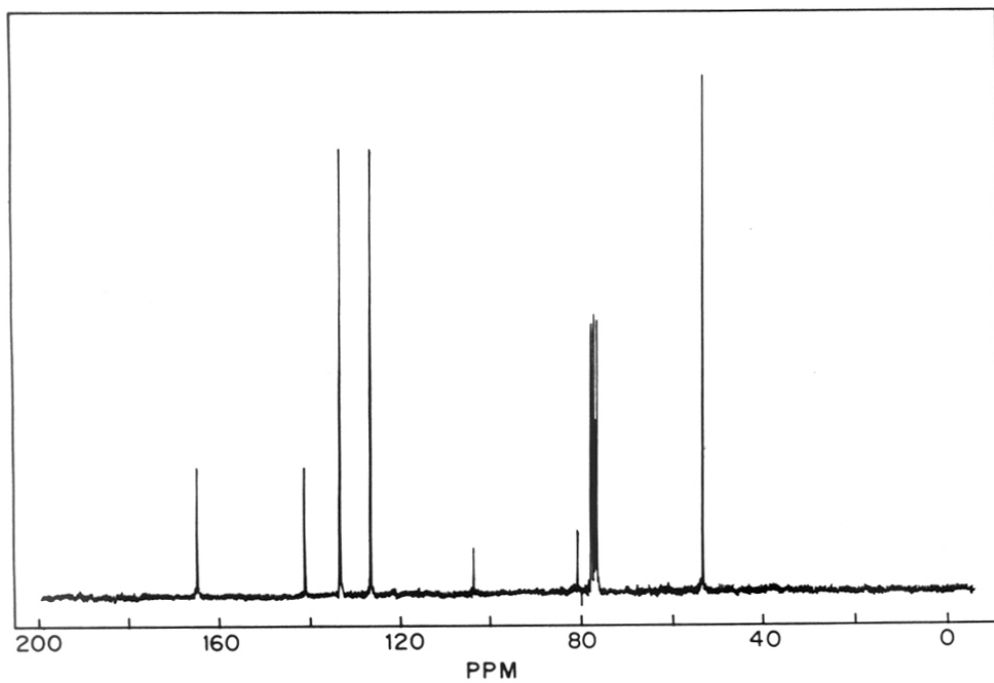
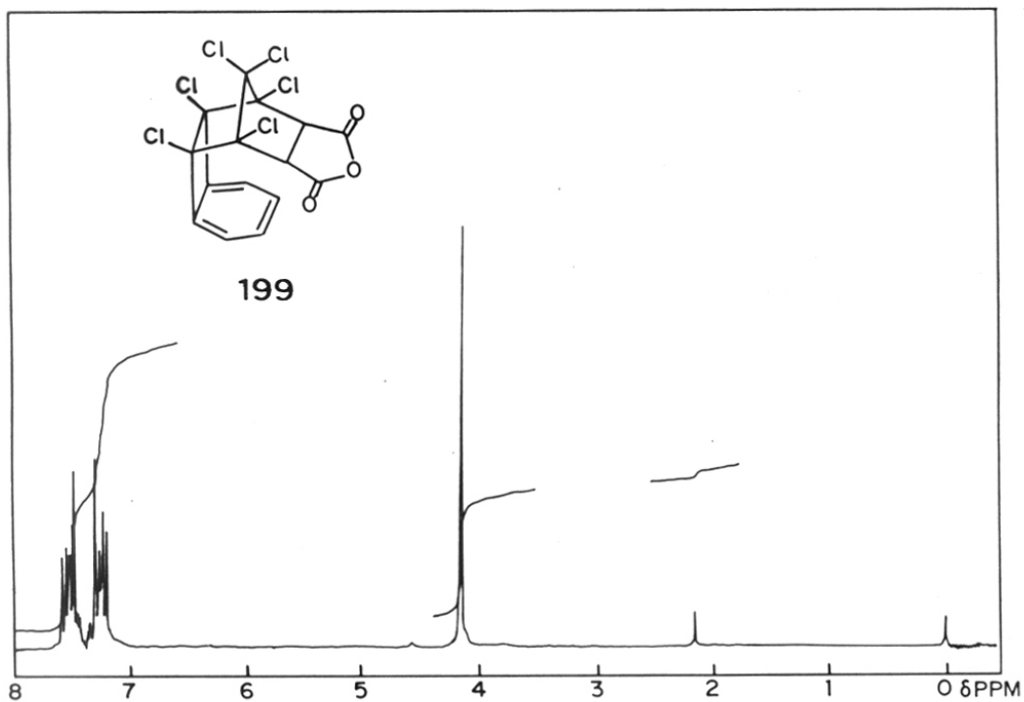
Scheme - 23



To examine the generality of 1,4-proximate diol cleavage, other diol 7-methyl hexa-cyclo [7.4.2.0^{1,9}.0^{3,7}.0^{4,14}.0^{6,15}] pentadeca-10,12-diene-2,8-diol **202** was subjected to LTA oxidation at room temperature in dry benzene. However, no change was observed. However, under drastic reaction condition (at reflux temperature) it gave considerable amount of unisolable polymeric product, and starting material could not be isolated. Additionally, the reaction of LTA with another diol 1,2,9,10,16,16'-hexachloro-13-oxa-heptacyclo [8.5.1.0^{2,9}.0^{3,8}.0^{3,14}.0^{8,12}.0^{11,15}] hexadeca-4,6-diene-*exo*-12-*exo*-14-diol **150** was examined. Thus, equimolar reactants in dry benzene at reflux for 2h. gave 70% yield of **199**. The structure was confirmed by satisfactory spectral data. It showed absorption band at 1870, 1800 cm⁻¹ in IR and appearance of anhydride carbonyl frequency. Proton NMR showed signals at δ 4.1 (d, 2H), 7.25-7.65 (m, 4H, aromatic protons) and ¹³C-NMR showed peaks at δ 165.06(s), 141.39(s), 133.39(d), 126.67(d), 103.03(s), 81.10(s), 76.93(s), 53.46(d), which confirmed its symmetrical nature.

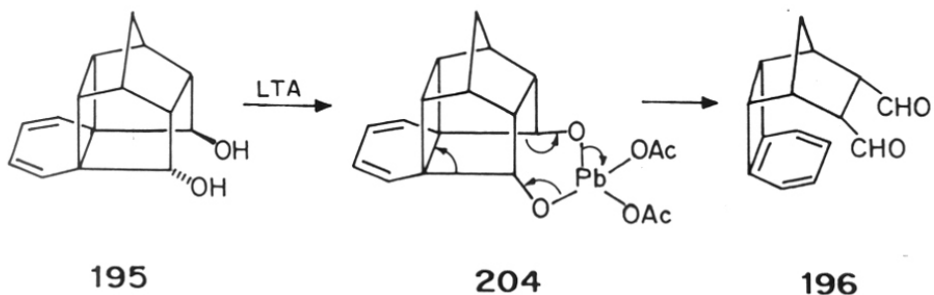
Similarly, pentacyclo [6.2.1.0^{2,7}.0^{9,10}.0^{5,9}] undecane *endo*-3-*exo*-6-diol **193** was prepared as per Cookson's procedure⁸⁸ which should give predominantly *endo-exo* product than *endo-endo* isomer. The Cookson ketone was reduced with NaBH₄ in EtOH solution to give *endo-exo* and *endo-endo* (62:38 ratio). On the contrary, the reaction of *exo-endo* diol **193** with LTA under reflux condition gave hemiketals **200** in (38%) yield along with unisolable side products. The ¹³C-NMR spectrum of the hemiketal showed a double set of signals due to 22 C's δ 211.61(s), 119.09(s), 81.9(d), 72.70(d), 56.31(d), 55.01(d), 54.4(d), 50.03(d), 45.84(d), 45.30, 43.99, 44.8, 43.4(2C), 43.18, 42.23, 42.00, 41.55(2C), 40.7, 38.48(t), 37.0(d) and characteristic resonance due to the presence of the open **201** and the cyclic hemi-acetal form **200** were discernible. This spectrum seems to represent an average between **200** and **201** caused by fast interconversion in a dynamic equilibrium between the mono hydroxy-ketone and hemi-ketal.⁹³ The ¹H-NMR spectrum confirmed by two signals at δ 4.59(t) and δ 4.07(t) due to protons attached to carbon bearing oxygen in different environment.

Mechanistically, a cyclic transition state for the oxidation of *endo-endo* and *exo-exo* 1,4-proximate diols, similar to the oxidation of 1,2-diols can be proposed,⁹⁴ which cleaves to give aromatized products **196** and **199**. Similar aromatization and rearrangement is the directive force in earlier studies in these skeletons.^{46a,47} For the oxidation of *endo-exo* diols,



apparently due to steric reasons, only *exo*-hydroxy is oxidised to ketone, which is intramolecularly trapped by *endo*-hydroxyl to give hemiketal.

Scheme - 24



CONCLUSIONS

An unprecedented stereospecific oxidative cleavage of 1,4-proximate diols with LTA has been observed. Thus, ultimately we were successful in cleaving the cyclobutyl carbonyl bond in this way. However, this cleavage reaction was successful only with specialized substrates, where aromatization possibilities were there.

SECTION-D

CYCLOBUTYL AND CYCLOPROPYL BOND CLEAVAGE BY ADJACENT KETYL RADICAL GENERATED UNDER PET CONDITIONS

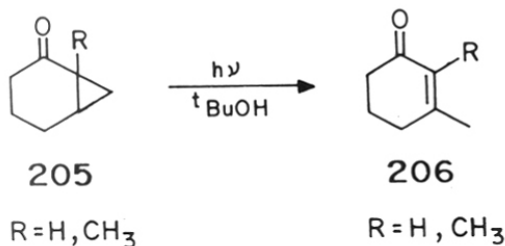
INTRODUCTION

The strain energy locked in small rings may be released by ring opening. This provides a powerful thermodynamic driving force for energy release. Photochemical excitation can initiate the cleavage of small rings, if an electronically excited chromophore is contained by the ring or if an excited chromophore nearby overlaps properly. The cleavage of strained ring systems of cyclobutane and cyclopropane conjugated to ketone has been of considerable interest, from the photochemical⁹⁵ and from electron transfer studies *via* electrochemical,⁹⁶ samarium iodide⁹⁷ and alkali metal induced transformation.⁹⁸ However, no detailed studies under photochemical electron transfer (PET) conditions are available.⁵⁴

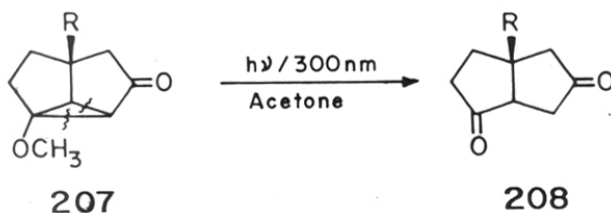
Not much information is available regarding photochemical β -cleavage of cyclopropyl and cyclobutyl ketones. Among the very few examples known, results obtained in the laboratories of Dauben et.al⁹⁹ and Demuth et.al¹⁰⁰ are noteworthy. Thus, Dauben has reported the β -cleavage in cyclopropyl ketone **205** by photolysis in *t*-BuOH, and proposed the importance of overlap of cyclopropyl σ -bonds with the π^* of C=O group (*Equation-35*). Demuth has reported regioselective β -cleavage in tricyclo [3.3.0.0^{2,8}] octane-3-one **207** in acetone (*Equation-36*).

As π^* assists cleaving of β -bond of cyclopropane, homolytic cleavage of β -CO bond of epoxides generally occurs more efficiently than cleavage of β -C-C bond¹⁰¹ (*Equation-38*). Epoxy ketones are photoepimerized *via* reversible β -cleavage (*Equation-38*). Cyclic ketones having good leaving groups like sulphonyloxy and chlorine are known to β -cleave efficiently¹⁰² (*Equation-39*). Benzoin acetate **219**. Upon UV irradiation yields 2-phenyl benzofuran¹⁰³ **220** (*Equation-40*).

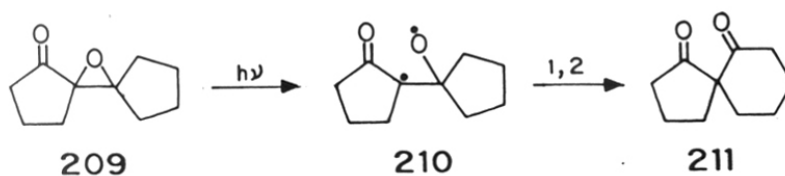
Scheme - 25



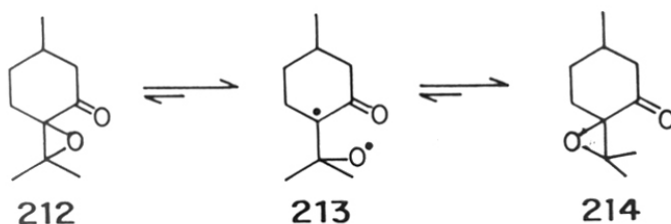
Equ. 35



Equ. 36



Equ. 37

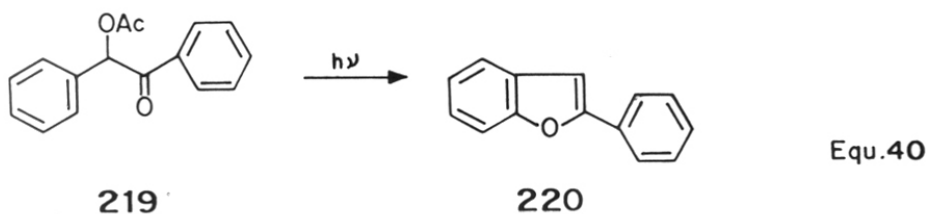
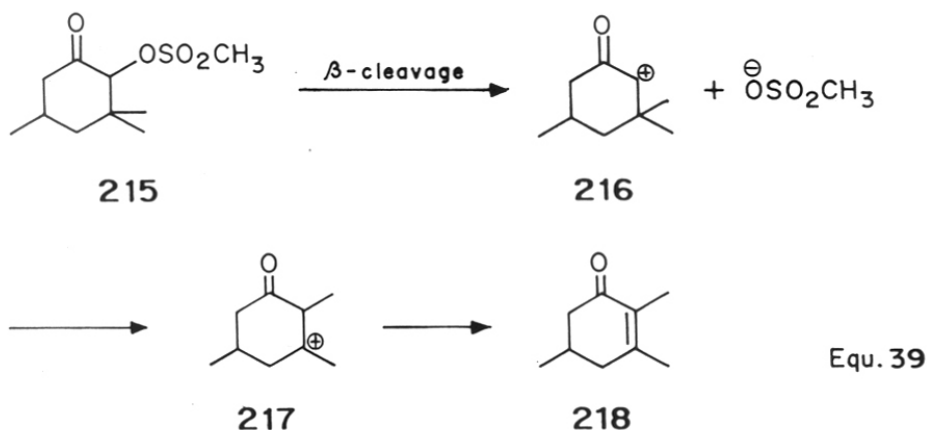


Equ. 38

Control and prediction of stereochemistry in medium cyclic rings is quite a complex and challenging concern of current synthetic organic chemists.² As part of a programme for the synthesis of stereocontrolled medium cyclic rings e.g., 10, 11, 12 and 13-membered rings **80-83**, the locked cage diones **47** and **221** are envisaged as an intermediate, offering considerable opportunity for stereochemical manipulation^{38,39,42,43,46,54} (See *Section-A, B & C* in this chapter). To unlock the cage dione,^{38,39} we and Coxon^{56a} have employed various

methods e.g., Baeyer-Villiger oxidation,^{46a} photochemical α -cleavage,^{56b} LTA and carbene (Section-B & C), etc. to cleave cyclobutyl-carbonyl bond, with limited success.

Scheme-25 contd.



Dauben et.al have proposed that during the electron transfer conditions by lithium in liquid ammonia, the regiochemistry of cyclopropane bond cleavage is governed by the concept of maximum overlap of one of the bond with the π^* -orbitals of carbonyl group.^{95,98} Since the β -bonds C₄-C₉ and C₂-C₁₁ should have more overlap with carbonyl π^* -orbital in 47 and 221, a study of photochemical electron transfer (PET) with cage dione was undertaken with a view to cleave these bonds and with a view to understand the nature of PET-generated radical anions vs. other modes of generating these species, in these systems.

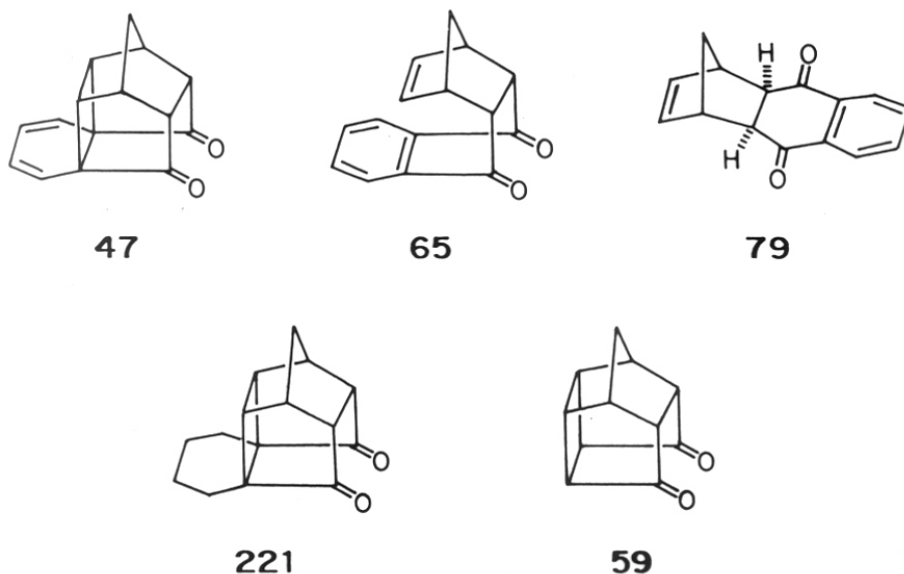
RESULTS AND DISCUSSION

During our pursuit of synthesizing stereocontrolled medium cyclic rings, photolysis of hexacyclo [10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}] pentadeca-5,7-diene-3,10-dione **47** in many reactions under different photolytic conditions leads to product of β -cleavage due to force of aromatization and strain relief. Such observations were reported later by Coxon et.al¹⁰⁴. Our group has reported photolysis of photocage dione **47** in alcoholic solvents which led to product of acetal formation, dual epimerization and β -cleavage.^{43,54} Initially, the reaction of **47** with triethylamine (TEA) and ethanol in photolytic conditions^{43,54} was examined and a quantitative conversion to exo **79** was accomplished. Understandably, the β -cleavage of unexpected cyclobutyl bond (i.e. C₄-C₁₄ and C₉-C₁₃) was triggered by adjacent PET-generated radicals leading to endo **65**, which subsequently isomerized to the exo **79**. While we preferred to examine the generality of unprecedented Diels-Alder endo-exo isomerization under PET-conditions,^{46b,c} the generality of equally important and unprecedented β -cleavage of cyclobutane ring cleavage remained to be studied. This study reports that the cleavage of cyclobutyl bonds adjacent to PET-generated ketyl radicals is a highly substrate specific reaction and not a general reaction. We also emphasize that the method of generating ketyl radicals, i.e. either by exciting TEA at 254 nm or by exciting ketone at 300 nm matters in regulating efficiency of bond cleavage. In continuation, we suggest that the nature of chemical transformations from radical anions generated by various PET reactions and by other methods, is not necessarily same.

The various cyclobutyl ketones utilized in our studies e.g. hexacyclo [10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-diene-3,10-dione **47**, hexacyclo [10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]penta-3,10-dione **221** and pentacyclo [6.2.1.0^{2,7}.0^{4,10}.0^{5,9}]undecane-3,6-dione **59** were synthesized, as per literature procedures (*Scheme-26*).

The photocage dione **47** was synthesized as per *Section-A* experimental procedure **47**, hexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-diene-3,10- dione **47** was reduced to its saturated analogue **221**, by hydrogenation over PtO₂ catalyst. By constructing molecular model of **47** and **221**, one can easily observe that **221** is less strained than **47**. The structure of saturated analogue **221** was confirmed by analytical and spectral data. It showed strong absorption band in IR at 1740 and 1720 cm⁻¹ for diketone. Proton-NMR showed peaks at

Scheme - 26



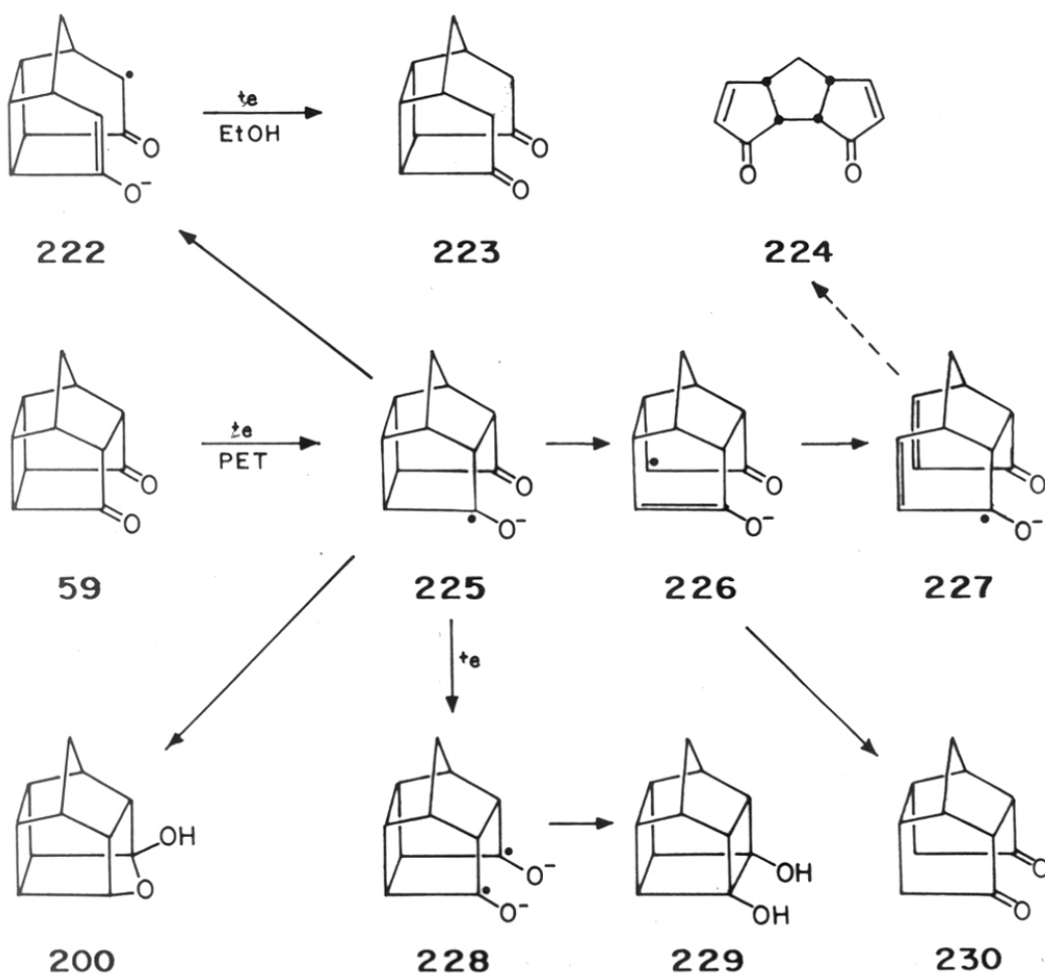
δ 1.05-2.20 (m, 10H), 2.75 (s, 2H), 2.85 (s, 4H) and mass spectrum showing molecular ion (M^+) peak at 228(100%) confirmed the structure. Further, its symmetrical nature was confirmed by ^{13}C -NMR which gave 8 signals at δ 213.29(s), 55.04(d), 49.58(s), 44.19(d), 43.54(d), 41.07(t), 22.61(t) and 19.17(t).

Pentacyclo[6.2.1.0^{2,7}.0^{4,10}.0^{5,9}]undecane-3,6-dione **59** was prepared as per literature procedure.^{51a} The compound was synthesised by Diels-Alder reaction of *p*-benzoquinone and cyclopentadiene in refluxing benzene for 15-30 minutes, followed by photolysis at 200W Hanovia medium pressure Hg lamp with, pyrex filter for 12h. which gave a quantitative yield (86%).

For the development of appropriate reaction conditions needed for PET experiments, we varied the solvent system, concentration of triethyl amine (TEA 5-20% by volume), nature of photoelectron donor e.g. HMPA (hexamethyl phosphoric triamide), DABCO (1,4-diazabicyclo [2.2.2] octane) etc., excitation wavelength and duration of photolysis, etc. To study ketyl radical anion induced β -cleavage of cyclobutyl ketones, compounds **47**, **221** and **59** were irradiated in ethanol:triethyl amine solvent system (95:5) at 300 nm in Rayonet photochemical reactor.

The successful cleavage of cyclobutane in compound **47** in above experimental conditions exclusively yielded exo compound **79**, formation of which was confirmed by spectral data (see *Section-A*). Thus, the cyclobutyl ketones accompanied by the diene frame **47** gave efficient cleavage products, but with the saturated analogues **221** and **59**, no reaction was observed. It is reasonable to assume that the cleavage of unexpected C₄-C₁₄ and C₉-C₁₃ bond, instead of C₄-C₉ or C₂-C₁₁ bond, is governed by the force of aromatization and release of strain criteria. Similar phenomenon was the driving force behind unexpected bond reorganization, during the Baeyer-Villiger oxidation studies of **47**^{46a}. The total absence of

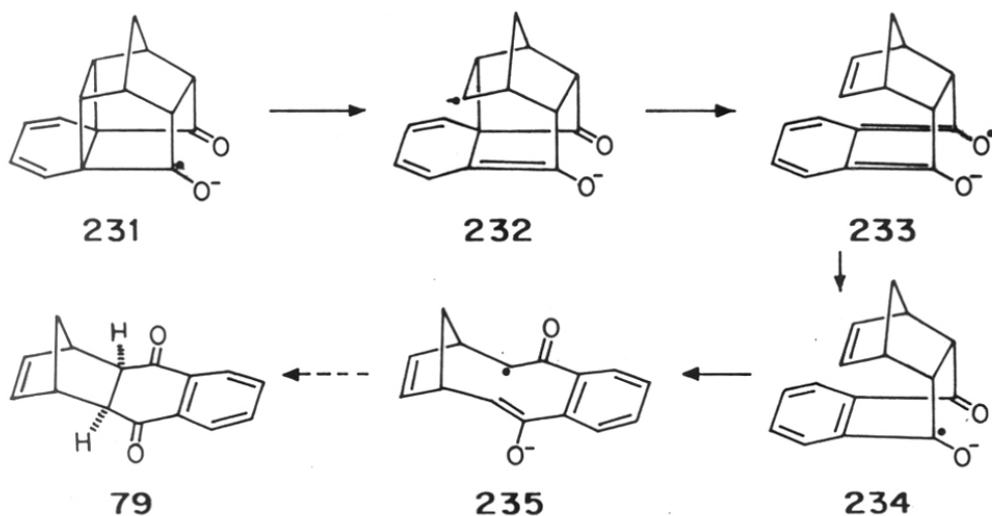
Scheme - 27



any reactivity under PET conditions in the saturated analogues e.g., **221** and **59**, was indeed very surprising to us.⁵⁴ Mechanistically, one can postulate varied interesting possibilities, as shown in *Scheme-27*. The transformation from **59** to **224** via **225**, **226** and **227** at room temperature, which is normally accomplished by flash thermolysis^{51a} would have been an interesting reaction. Although the possibility of recombination of radicaloid species e.g., **226** and **222** in cage compounds should be high, but the release of strain from **59** to **224** or **59** to **223** or **59** to **230** could as well have been the driving force for such transformation. There are precedences for the formation of cleaved β -bonds e.g., **223**^{51e} and **230**¹⁰⁵ cyclized hemiacetal **200** and coupled diol **229**¹⁰⁶ under various reductive conditions from **59**, but none of these possibilities materialized from saturated analogues under PET conditions. This clearly indicates that the nature of radical anions formed from PET-reactions and other reductive processes e.g. Zn-acetic acid^{105,106} and Na-K alloy^{51e} etc. are different.

One interesting feature of our PET experimental condition is that it does not lead to the reduction of ketones, which is a common side reaction in ground state electron transfer reactions. Similar to the cleavage of cyclopropyl¹⁰⁷ and cyclobutyl group adjacent to PET-generated ketyl radicals, one wonders whether the efficient isomerization of endo-**65** to exo-**79** was the outcome of even cyclopentane ring cleavage adjacent to ketyl radicals, as shown in *Scheme-28*. Notice the possible transformation of **234** to **235**, which can subse

Scheme - 28



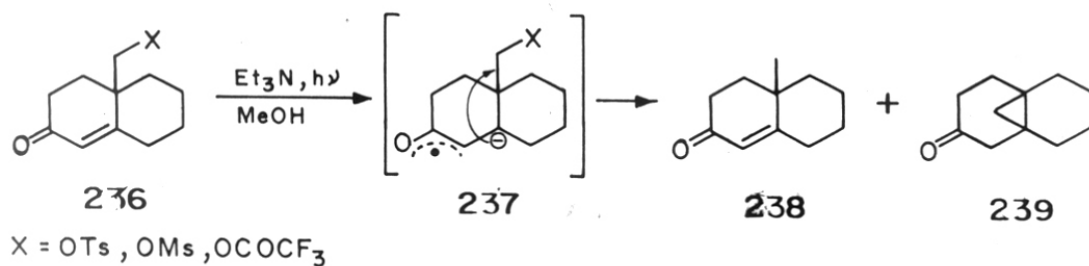
quently cyclize to give thermodynamically stable exo-**79**. In fact, similar cleavage of central bond has been indicated in lithium/liquid ammonia studies by Gassman.¹⁰⁸

Thus, in above studies, generality and limitations of cyclobutyl bond cleavage adjacent to PET (Photoinduced Electron Transfer) generated ketyl radicals have been examined.⁵⁴ Additionally, the cleavage of even cyclopentane ring in the bicyclic ring systems, during efficient isomerization of Diels-Alder endo to exo isomers has been indicated.^{46b,c} Additionally, the cleavage of PET-generated cyclopropyl ketone is described in the following section.

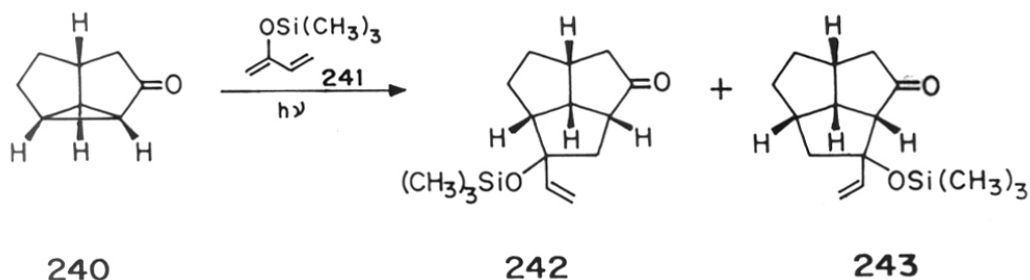
CYCLOPROPYL CLEAVAGE UNDER PET CONDITIONS

During the course of our investigation, Givens et al¹⁰⁹, have postulated cleavage of cyclopropane ring during photolysis of **236** under PET conditions and an interesting mechanism involving cyclopropyl radical formed by nucleophilic displacement of tosylate, mesylate, triflate, etc. from distonic radical anion **237** has been proposed (*Scheme-29*). Demuth et.al¹¹⁰ reported the photochemistry of a cyclopropyl ketone **240** with electron rich diene i.e. 2-silyloxy-1,3-butadiene **241**, it was tempting to presume that the initial step was an electron transfer from the diene to excited ketone **240**, which led to cleavage of cyclopropane, followed by coupling of two species. Thus, we were curious whether the cleavage of cyclopropyl ketones will be feasible under our new PET conditions i.e. photolysis in a polar and protic solvent ethanol with TEA. We observed that unlike cyclobutyl ketones,⁵⁴ the cleavage of cyclopropyl ketone and epoxy ketone under our new PET conditions is a facile process. Our studies reveal an interesting wavelength dependance (254 nm vs 300 nm) phenomenon for efficient PET cleavage.

Scheme -29



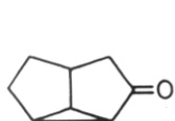
Scheme-30



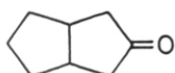
The various cyclopropyl and epoxy ketones examined in our studies e.g., **240**, **244**, **245**, **246**, **251**, **252**, **253** and **254** were prepared as per literature procedures (*Scheme-31*). The first model compound tricyclo [3.3.0.0^{2,8}] octan-3-one **240** was synthesised by oxa-di- π -methane rearrangement¹¹¹ (photolyzed at 300 nm for 72h. in acetone solvent) of bicyclo [2.2.2] oct-2-ene-5-one **261**¹¹¹, which yielded (78%) **240**. The tricyclic compound was confirmed by proton and ¹³C-NMR and by matching with literature data.¹¹¹ Proton NMR showed signals at δ 1.5 (m, 1H, C₄-endo), 1.8 (m, 1H, C₂), 1.95 (m, 1H, C₈) 1.98-2.2 (m, 4H, C₇ and C₆), 2.36 (m, 1H, C₄-exo), 2.7-3.1 (m, 2H, C₁ and C₅) and ¹³C-NMR δ 215.34(s), 46.50(t), 40.42(t), 38.39(d), 37.04(d), 35.79(d), 30.24(d), 24.19(t). The bicyclo[2.2.2]oct-2-ene-5-one **261** compound was synthesised in 65% yield by Diels-Alder reaction of chloroacrilonitrile **259** and cyclohexadiene **133**¹¹¹ followed by hydrolysis by aq. KOH in DMSO at 0°C - room temperature. The compound **261** was characterized by proton NMR and compared with literature data.¹¹¹ Proton NMR showed signals at δ 1.3-1.9 (m, 4H), 2.0 (d, 2H), 2.8-3.19 (m, 2H), 6.1-6.6 (m, 2H).

A solution of the tricyclo [3.3.0.0^{2,8}] octan-3-one **240** (0.02M) in 20% TEA in ethanol (by volume) was irradiated at suitable wavelength at 300 nm in Pyrex vessel for 6 h. and successful cleavage was achieved to bicyclo [3.3.0^{1,5}] octa-3-one **247** in 79% yield. The structure of **247** was confirmed by proton and ¹³C-NMR data and by comparison with literature.¹¹² The proton NMR showed signals at δ 1.25-2.45 (m, 10H), 2.88 (m, 2H, C₁-H and C₅-H) and ¹³C-NMR at δ 220.00(s), 44.36(d), 39.54(t), 33.17(t), 25.2(t). Subsequently, the compound bicyclo [4.1.0] heptan-2-one **244** was synthesised (CH₂I₂/Zn-Cu) as per literature procedure.⁹⁵ A solution of compound **244** (0.02M) in 20% TEA/ethanol (by volume) was

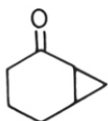
Scheme -31



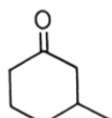
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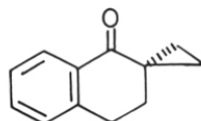
247



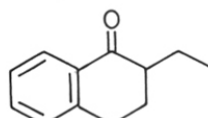
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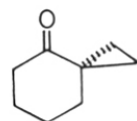
248



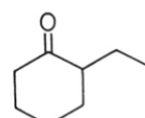
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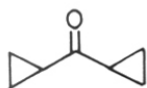
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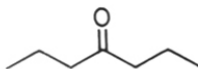
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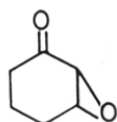
250



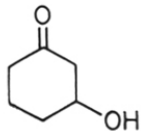
251



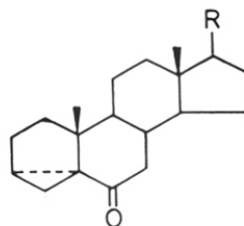
255



252

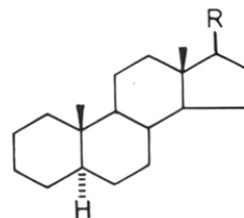


256



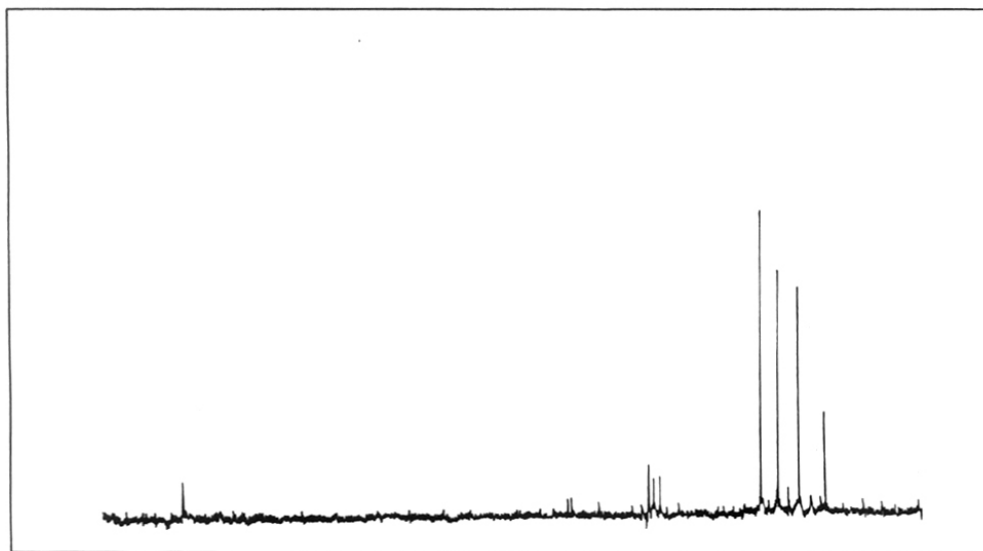
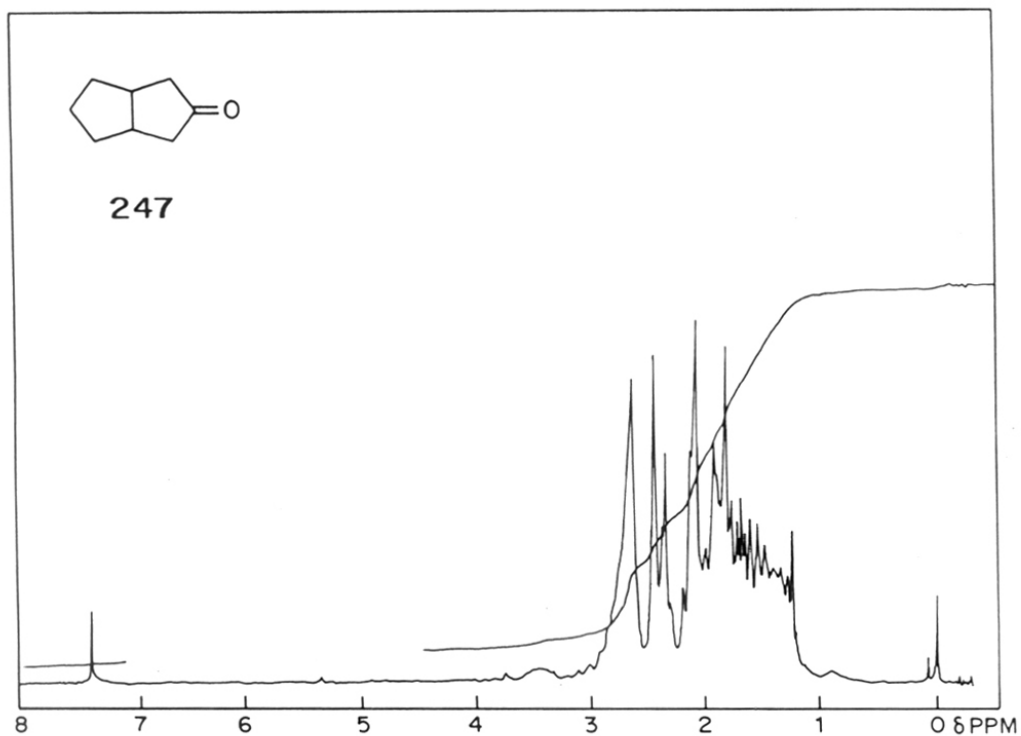
253 R =

254 R = OAc



257 R =

258 R = OAc



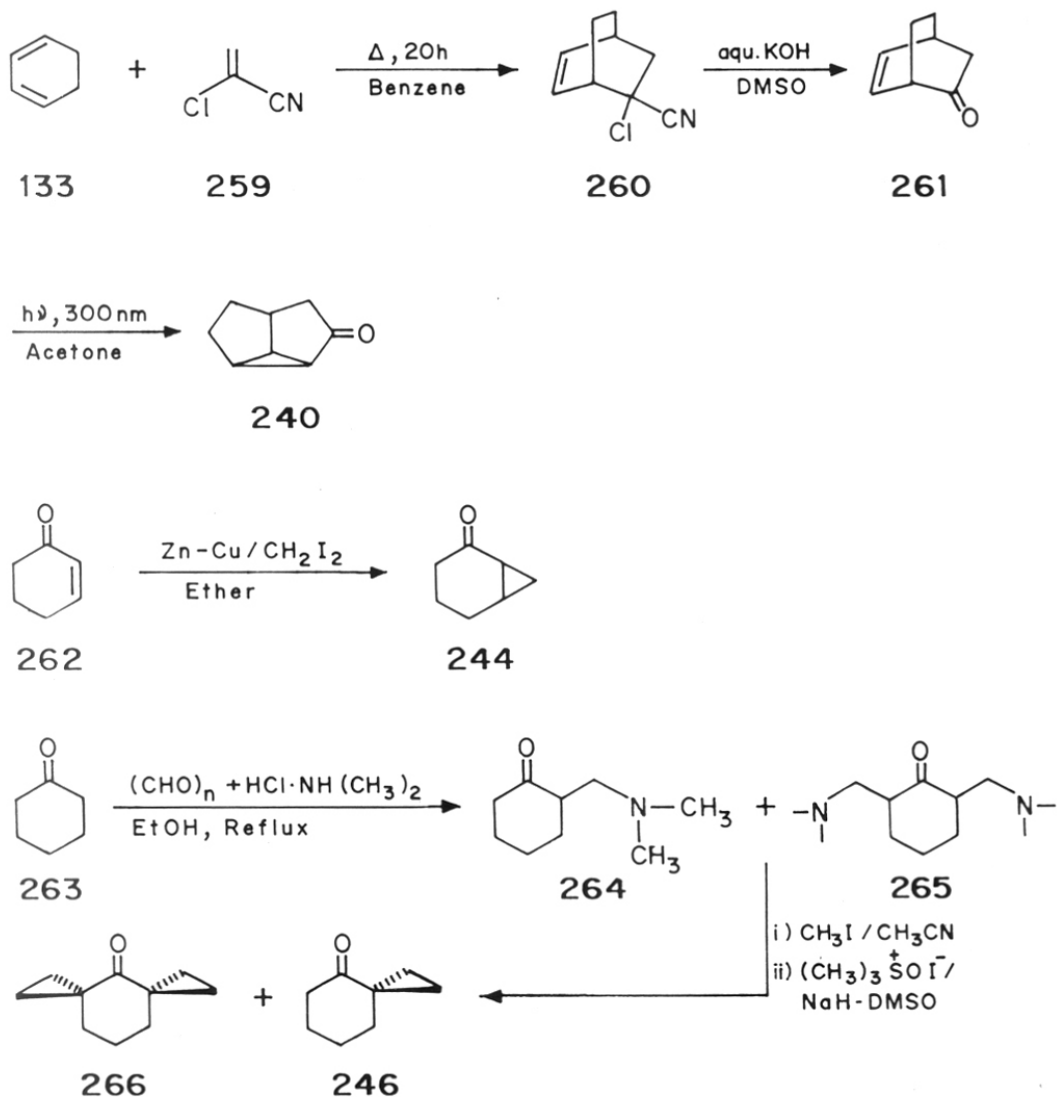
irradiated at 300 nm for 4h. to give 3-methyl cyclohexanone **248** in 55% yield, which was confirmed by authentic sample (through GLC) and proton and ^{13}C -NMR (Please see *Experimental Section*).

The exocyclic cyclopropanes could be utilized as ethyl equivalent synthon. One of the important observation is the wavelength of excitation e.g., Rayonet 254 nm vs 300 nm, in governing reactivity and selectivity, in cleavage related to cyclopropyl and epoxy ketones. The compounds 2,6-dispirocyclopropyl-1-cyclohexanone **266**, 2-spirocyclopropyl-1-cyclohexanone **246** and 2-spirocyclopropyl-1-tetralone **245** were synthesised by Mannich reaction (paraformaldehyde-dimethylamine hydrochloride) of cyclohexanone. The reaction gave 2,6-(N,N-dimethyl)methyl-1-cyclohexanone **265** and 2-(N,N-dimethyl)methyl-1-cyclohexanone **264** because of symmetrical ketone, which was subjected to methylation with excess methyl iodide in acetonitrile to give a white solid (ammonium iodide salt). The product was used for the following cyclopropanation ($\text{Me}_3\text{SO}^+\text{I}^-/\text{NaH}$ -DMSO for 3-4h.)¹¹³ without further purification, which gave two products **266** and **246** in overall (58%) yield. The compounds **266** and **246** were confirmed by ^1H -NMR and ^{13}C -NMR. The compound **266** showed proton NMR signals at δ 0.55 (q, 4H), 1.18 (q, 4H), 1.8 (m, 6H) and ^{13}C -NMR at δ 212.56(s), 34.95(t), 28.42(s), 23.60(t), 19.88(t), and compound **246** showed proton signals at δ 0.61 (q, 2H), 1.2 (m, 2H), 1.65-1.89 (m, 6H), 2.01 (m, 2H). The compounds **266** and **246** were photolysed under similar conditions, as described above. The 2,6-dispirocyclopropyl-1-cyclohexanone **266** gave a mixture of products (GC) which could not be isolated. The compound 2-spirocyclopropyl-1-cyclohexanone **246** under similar condition gave 2-ethyl-1-cyclohexanone **250** in 40% yield. The compound was characterized by proton NMR and compared with literature data.¹¹⁴ Proton NMR showed signals at δ 1.0 (m, 3H), 1.2-1.5 (m, 9H), 1.9-2.5 (m, 3H).

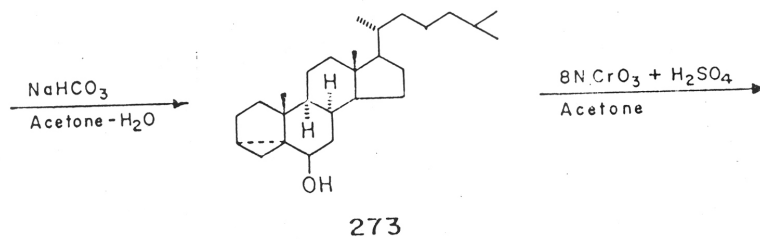
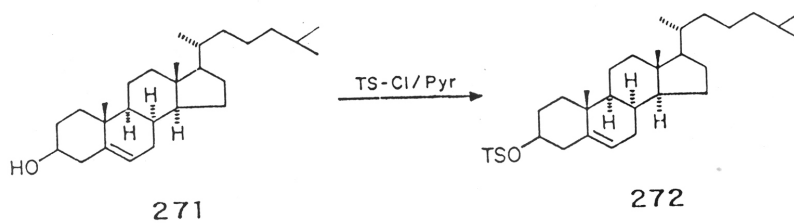
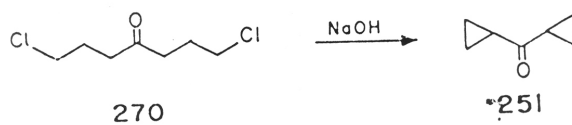
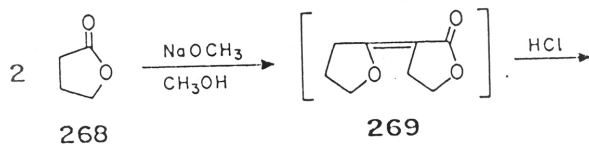
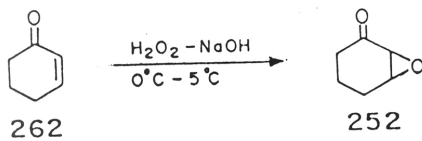
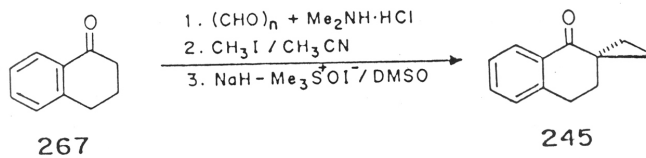
Similarly 2-spirocyclopropyl-1-tetralone **245** was synthesised by above procedure¹¹³ in 72% yield. The compound **245** was confirmed by proton NMR and Mass spectrum. The proton NMR showed signals at 0.75 (q, 2H), 1.4 (m, 2H), characteristic peaks for cyclopropyl proton, 1.95 (m, 2H), 3.0 (t, 2H), 7.1-7.55 (m, 3H, Ar), 8.0 (m, 1H, Ar) δ and mass spectrum showed molecular ion peak at M^+ 172(100%). The compound **245** (0.02M) on irradiation at 300 nm or 350 nm does not lead to any change in starting material, whereas irradiation

at 254 nm leads to complete conversion to the cleaved product 2-ethyl-1-tetralone in 79% yield. The compound **249** was confirmed by ^1H -NMR and ^{13}C -NMR. The proton NMR showed signals protons at δ 0.6-1.0 (t, 3H), 1.0-2.0 (m, 4H), 2.05-2.9 (m, 3H), 6.95-7.45 (m, 3H, Ar), 7.45-7.55 (m, 1H, Ar) and ^{13}C -NMR at δ 192.39(s), 142.81(s), 137.45(s), 128.20(d), 126.0(d), 124.74 (d, 2c), 43.71(d), 29.74(t), 26.99(t), 14.51(t), 9.9(q).

Scheme - 32



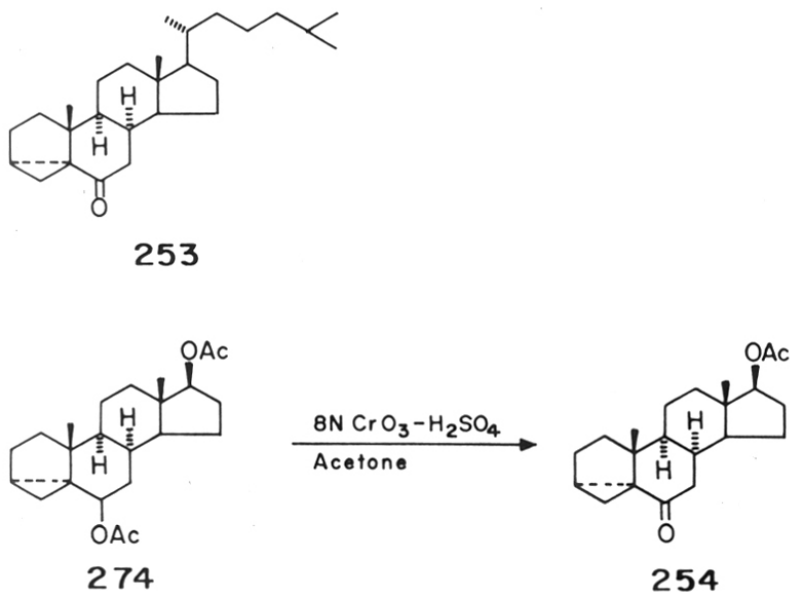
Scheme-32 contd.



Similarly, the irradiation of PET-reaction mixture of epoxy ketone **252** gives a better and cleaner yield of cleaved 3-hydroxy cyclohexanone **256** at 254 nm, than at 300 nm. The epoxy ketone was synthesised as per literature procedure,¹¹⁵ which was photolysed, a (0.02M) solution of the compound **252** in 20% TEA in ethanol (by volume) at 254 nm for 3h. Gave 3-hydroxyketone in 49% yield. The compound **256** showed IR broad peak at 3460 (bs, OH), 1720(s) cm^{-1} and proton NMR showed signals at δ 0.7-2.1 (m, 4H), 2.25-2.9 (m, 4H), 3.5-3.85 (m, 1H), 4.05 (bs, 1H, OH). The compound dicyclopropyl methanone **251** was synthesised as per literature procedure,¹¹⁶ which was confirmed by proton NMR δ 0.78-1.1 (m, 8H), 1.85-2.25 (m, 2H). The photolysis under similar conditions at 300 nm for 4h. Gave 4-heptanone **255** in 36% yield and some volatile compound which could not be isolated. The n-4-heptanone **255** was confirmed by comparison with authentic sample (GC) and with literature data.¹¹⁷ The proton NMR showed signals at δ 0.9 (t, 6H), 1.55 (m, 4H), 2.4 (t, 4H).

On the contrary, in steroidal cyclopropyl ketones e.g., **253** and **254**, no cleavage could be effected at 254 nm, whereas 300 nm irradiation led to efficient conversion to cleaved products **257** and **258**. The 3,5 α -cyclocholest-6-one **253** and 3,5 α -cycloandrostane-17 β -ol-6-one 17 β -acetate **254** were prepared as per literature procedure,¹¹⁸ the compound 3,5 α -cyclocholest-6-one was synthesised by reaction of cholesterol and *p*-toluene sulfonyl chloride-pyridine.¹¹⁸ The reaction gave quantitative tosylated product **272** which was confirmed by literature data (Please see *Experimental data*) and melting point (122°C). Solvolysis of **272** by potassium bicarbonate in H_2O -acetone under reflux for 6h. Gave 3,5 α -cyclocholest-6 β -ol **273** (75.5%) which was confirmed by literature¹¹⁸ and spectral data. The compound melted at 91°C, IR showed broad peak at 3400 cm^{-1} and proton NMR showed signals at δ 0.68 (s, 3H), 0.7-1.0 (m, 12H), 1.05-2.0 (m, 27H), 3.23 (m, 1H). The i-alcohol **273** was subjected to Jones oxidation (8N CrO_3 - H_2SO_4 at 0°C)¹¹⁸ to give 3,5 α -cyclocholest-6-one **253**, which was characterized by spectral data and compared with literature data.¹¹⁸ IR showed sharp peak at 1690 cm^{-1} for cyclopropyl ketone and proton NMR showed signals at δ 0.75 (s, 3H), 0.95 (m, 9H), 1.05-1.45 (m, 15H), 1.55 (m, 8H), 1.75-2.0 (m, 6H), 2.25 (s, 2H).

Scheme-32 contd.



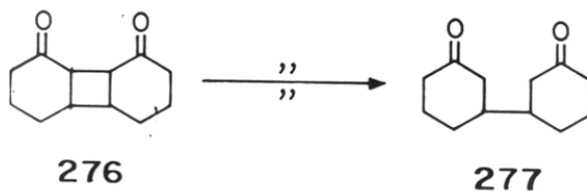
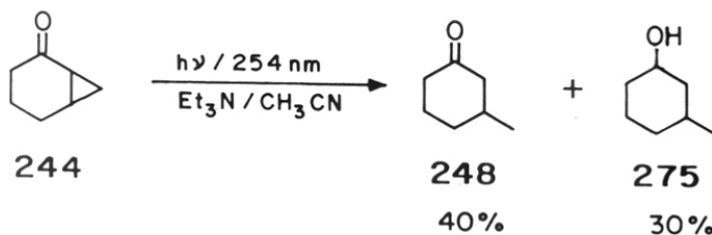
Finally, 3,5 α -cycloandrostane-17 β -ol-6-one 17 β -acetate **254** was synthesised by Jones oxidation (8N $CrO_3-H_2SO_4$)¹¹⁸ of 3,5 α -cycloandrostane-17 β -ol-6 β -acetate 17 β -acetate¹¹⁸ **274**. The compound **254** was characterized by proton and ¹³C-NMR. Proton NMR showed signals at δ 0.88 (d, 2H), 1.0-1.98 (m, 22H), 2.1 (s, 3H, COCH₃), 2.12-2.2 (m, 2H) and ¹³C-NMR at δ 210.35, 171.29(OAC), 82.60, 50.92, 49.40, 44.63, 43.55, 36.79, 31.09, 27.61, 25.45, 23.68, 22.90, 21.32, 20.99, 19.31, 18.38, 12.48. The compound 3,5 α -cyclocholest-6-one **253** was photolysed, a 0.02M solution of substrate in 20% TEA in ethanol (by volume) at 300 nm for 6 h. which gave cholestan-6-one **257** in 80% yield which was characterized by spectral data and analytical data and compared with literature data.⁹⁸ IR showed strong peak at 1720 cm⁻¹, proton NMR showed signals at δ 0.6 (s, 3H, CH₃), 0.75 (s, 3H, CH₃), 0.9 (d, 9H, 3CH₃), 1.0-2.6 (m, 31H) and ¹³C-NMR at δ 209.56(co), 56.3, 55.43, 54.99, 52.36, 45.35, 41.80, 39.96, 38.23, 36.89, 36.80, 36.07, 35.71, 34.86, 34.41, 26.71, 22.73, 22.55, 21.46, 21.22, 20.46, 17.39, 11.26, 10.75. Photolysis of 3,5 α -cycloandrostane-17 β -ol-6-one 17 β -acetate **254** under similar condition gave androstane-17 β -ol-6-one 17 β -acetate **258** in

87% yield, the structure of which was confirmed by spectral data. Thus, proton NMR showed signals at δ 0.7-0.95 (s, 6H, 2CH₃), 1.10-1.75 (m, 19H), 2.0 (s, 3H, COCH₃), 2.25-2.50 (m, 3H), 4.6 (t, 1H) and mass peak M⁺ 332 (12%), 317(40), 277(100).

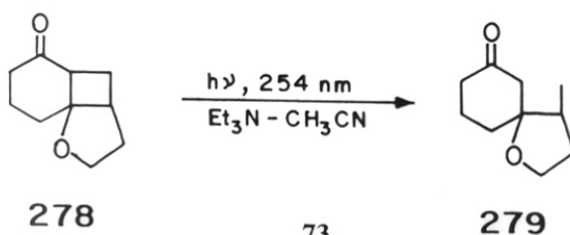
Interestingly, the cleavage of chromophorewise highly identical cyclopropyl ketones **245** and **246** was influenced by wavelength of irradiation. Thus, **246** gave efficient transformation at 300 nm, whereas **245** gave efficient cleavage at 254 nm. Comparably, for the efficient transformation of **250** to **249** without any side product e.g., reduced alcohol, under our experimental condition at 300 nm irradiation, has been found to be more suitable than 254 nm irradiation reported by Mattay^{119a} and Cossy^{119b} (Scheme-33). Thus, cleavage of cyclopropyl ketones seems to be quite wavelength specific. This specificity leads to yet another dimension in the complexity of understanding and generalizing the PET-related chemistry. Thus, the method of generating radical anions, either by exciting the donor molecule TEA or by exciting the ketone, matters in effecting chemical transformations.

Scheme - 33

Mattay

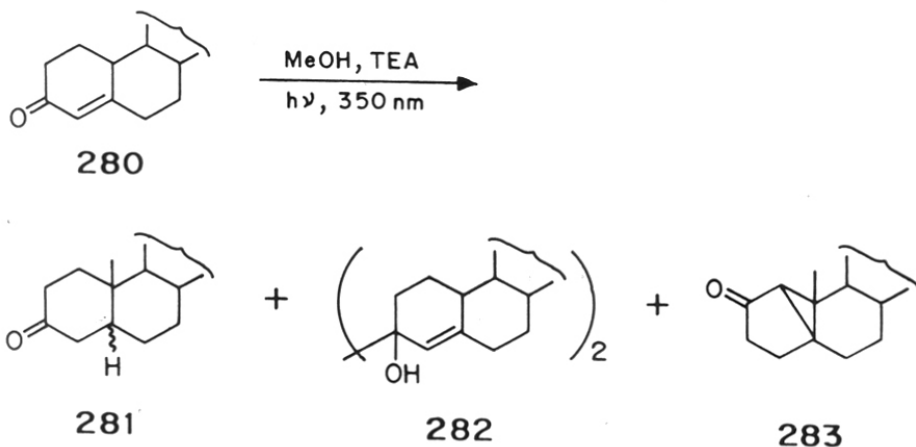


Cossy

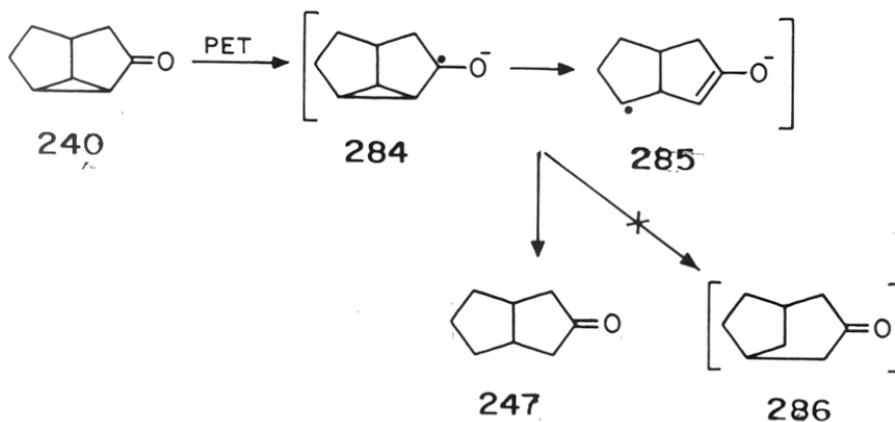


During the transformation from **240** to **247** under PET-conditions, complete regioselectivity of cyclopropyl bond cleavage was observed (*Scheme-31*). Interestingly, similar regioselectivity of bond cleavage was observed earlier during its photochemical studies and biradical was trapped by a reactive diene¹¹⁰ **241** (*Scheme-30*). Additionally, the efficient transformation of exo-cyclic cyclopropyl ketones e.g., **245** to **249**, **246** to **250** and **251** to **255** clearly indicates that cyclopropyl group can as well be thought of as synthetic equivalent of ethyl group. Normally, it is utilized as dimethyl equivalent only *via* catalytic hydrogenation. The mechanism of PET induced cleavage of cyclopropyl ketones can be visualized, as shown in *Scheme-35*. The transfer of electron from TEA to enones and ketone

Scheme - 34



Scheme-35



is well established.^{46e,54,120} Thus, the radical anion of **240** cleaves to give **285**, which is trapped by EtOH to give **247**. Interestingly, under our PET conditions, no reduction of ketones occurs either to alcohols or to deoxygenated analogues, which are common side products under ground state electron transfer reactions. Compared to Givens¹⁰⁹ (*Scheme-34*), where pinacol type products dominated, no such products were observed under our PET conditions. The regioselectivity of bond cleavage is governed by the maximum overlap principle between σ or cyclopropyl bonds and π^* or carbonyl or vice-versa.^{95,98} Thus, no products similar to **286** were observed from **240**. Whether our PET is governed by single electron transfer (SET) principle, it is difficult to decide. It is possible to get products by double electron transfer as well. During the course of our studies, Mattay and Cossy have reported efficient cleavage of cyclopropyl ketone and cyclobutyl ketone under PET condition (see *Scheme-33*). However, our experience, as discussed above, have been mixed.

CONCLUSION

This section examines the generality and limitations of regioselective cyclobutyl and cyclopropyl bond cleavage adjacent to ketyl radicals generated under a new PET-conditions in a protic solvent ethanol. Although the cleavage of cyclopropyl and epoxy bond is facile, the cleavage of cyclobutyl bonds is highly substrate specific. Thus, only those cyclobutanes, which have diene frame with a possibility of aromatization could be cleaved. Saturated cyclobutyl ketones did not lead to any product formation. In continuation, the cleavage of even adjacent cyclopentane has been proposed for efficient endo to exo isomerization under PET-conditions. The nature of chemistry generated by ketyl radicals is highly a function of methodology of generating these radicals. This phenomenon has been shown repeatedly by wavelength effect (254 nm Vs 300 nm) observed in our reactions and in comparison to other methods of ground state electron transfer reactions.

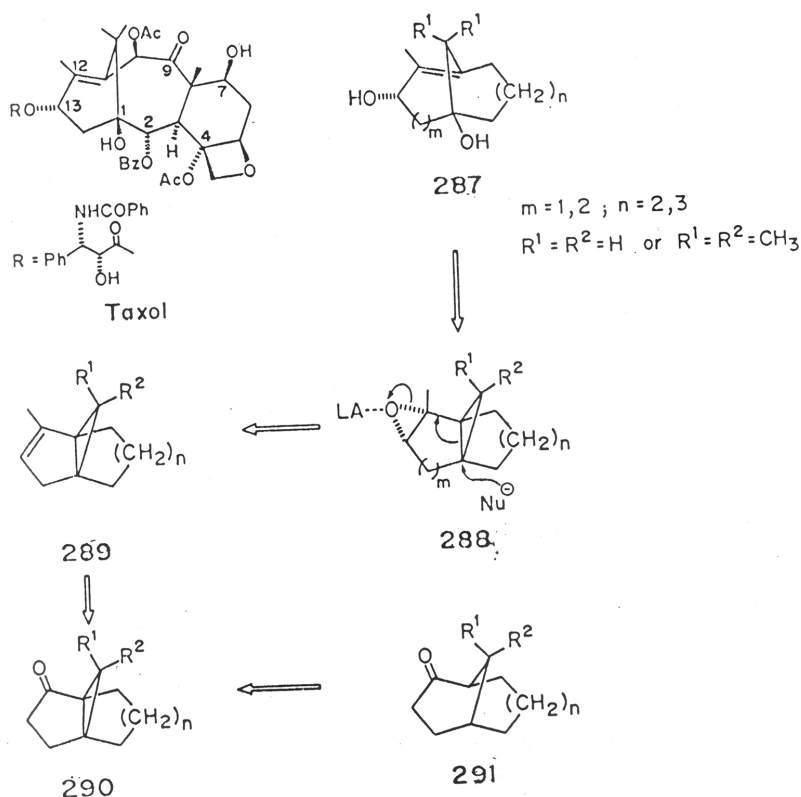
SECTION-E

STRATEGY FOR MODEL CARBOCYCLIC FRAME OF TAXOL

In continuation, some aspects of cyclopropyl ketone (**290** $\rightarrow$ **291**) and epoxy cyclopropane (**288** $\rightarrow$ **287**) chemistry has been exploited for the synthesis of carbocyclic frame of Taxol. Taxol has been demonstrated in numerous laboratories worldwide to have broad spectrum antitumour activity against many tumor models. The susceptible tumours include murine leukemias and solid tumor, and human solid tumor xenographs. Taxol has got special significance due to successful clinical trials for the treatment of breast, head, neck and ovarian cancer.¹²¹

Taxol is a highly challenging and complex synthetic target. There are many aspects of Taxol synthesis. We have utilized our understanding of cyclopropyl ketone chemistry for a synthetic strategy for carbocyclic frame of Taxol. Side by side, we have also exploited the push-pull cyclopropyl epoxide chemistry for this objective (*Scheme-36*).

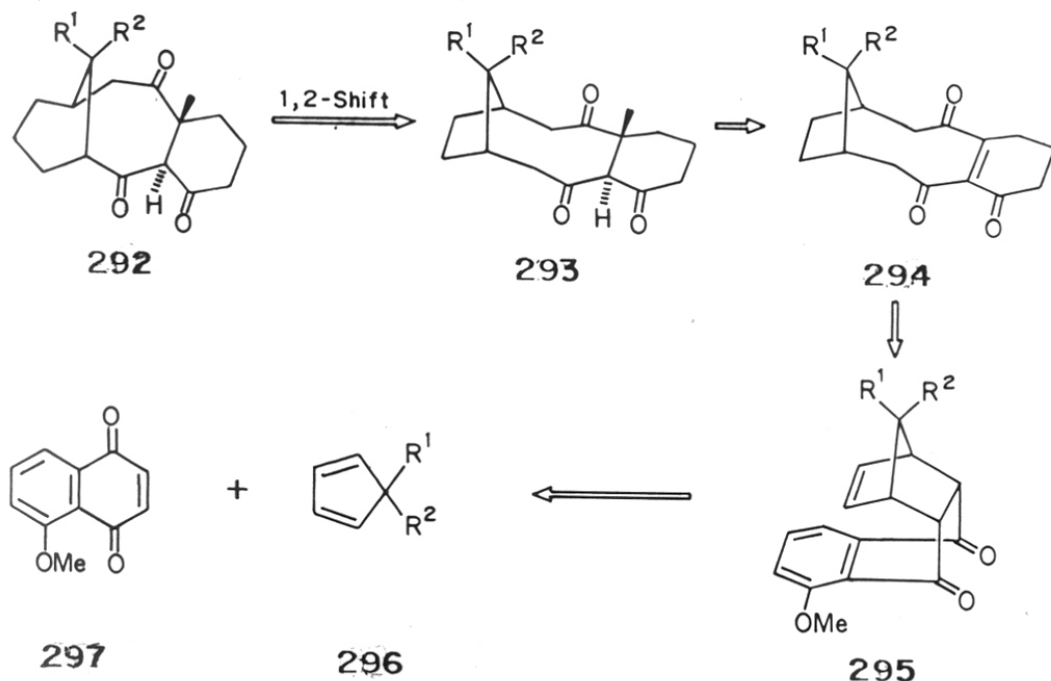
Scheme-36



Naturally, this strategy should provide appropriately functionalized C-1 with -OH, with bridge head double bond at C₁₁-C₁₂ and α -OH at C₁₃ and with a possibility of functionalization at the bridge either with dimethyl or H, Me, Cl, Br, CO₂H, etc. (numbering of the skeleton is based on the Taxol numbering). Mention must be made here that there are very few synthetic approaches which address the problem of oxidation level at C-1 i.e. C₁-OH substitution. This strategy offers an opportunity for variation with m=1,2 and n=2,3 and their permutation combination. The retrosynthesis for the cyclopropyl epoxide **288** with m=1 is shown in *Scheme-36*. Thus, stereoselective epoxidation of **288** is possible with m-CPBA, due to steric reasons, whereas **289** itself could be synthesized from **290** by treatment with MeLi and subsequent dehydration. For detailed discussion regarding this strategy and work, kindly go through *Chapter-3*.

We are also excited about the possibility of cleaving central bond in the easily obtainable bicyclic system **293** (*Scheme-37*) by electron transfer processes, in which we have considerable experience and expertise (See preceding sections). Subsequent 1,2-shift (Wagner-Meerwein type) can give advanced models of Taxol. All this and related work will be described in *Chapter-3*.

Scheme - 37



R¹, R² = Alkyl, TMS

EXPERIMENTAL

Diels-Alder reaction of cyclopentadiene with 1,4-naphthoquinone: A mixture of 1,4-naphthoquinone (5g, 0.022 mole) and cyclopentadiene (1.76g, 0.026 mole) in 100 ml of dry benzene was refluxed for half an hour and the progress of the reaction was monitored by TLC. The work-up involved removal of benzene followed by column chromatography over silica gel. Elution with pet.ether:acetone (98:2) system gave *endo* **65** and *exo* compound **79**. Recrystallization of *exo* compound **79** from methanol afforded yellow solid (0.9g, 12%).

(**79**) m.p. : 160°C.

IR (Nujol) : cm^{-1} 1650(s), 1590(s), 1320(w), 1290(w), 790(m).

$^1\text{H-NMR}$ (90 MHz) : δ 1.5 (2H, s), 2.3-2.4 (2H, m), 4.1-4.2 (2H, m), 6.7-6.9 (2H, m), 7.5-7.7 (2H, m), 7.9-8.1 (2H, m).

$^{13}\text{C-NMR}$ (80 MHz) : δ 181.23(s), 162.66(s), 142.25(d), 132.91(d), 132.53(d), 125.82(d), 73.02(d), 48.44(t).

MS : m/z 224 (M^+ , 90).

Analysis : $\text{C}_{15}\text{H}_{12}\text{O}_2$ Calculated : C, 80.35; H, 5.35.

Found : C, 80.67; H, 5.72.

Further recrystallization of *endo* compound **65** from methanol yielded white crystalline solid (5.88g, 83%).

65 m.p. : 124°C.

IR (Nujol) : cm^{-1} 2910(s), 2820(s), 1670(s).

$^1\text{H-NMR}$ (90 MHz) : δ 1.5 (2H, m), 3.11-3.26 (4H, m), 5.8-6.2 (2H, m), 7.6-8.0 (4H, m).

$^{13}\text{C-NMR}$ (80 MHz) : δ 197.12(s), 135.48(s), 135.15(d), 133.59(d), 126.39(d), 49.11(d), 48.79(t).

MS : m/z 224 (M^+ , 60%), 158(25), 66(70).

Hexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-diene-3,10-dione (47): The *endo* adduct tetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13-tetraene-3,10-dione **65** (2g, 0.008 mole) dissolved in dry acetonitrile (2 lit.) was purged with a slow stream of nitrogen gas for 15 minutes. Subsequently, the solution was stoppered and irradiated at 300 nm in Rayonet-Srinivasan photochemical reactor for 2.5 h. Progress of the reaction was monitored by TLC and/or GC. When 90% of the starting material was reacted, the solvent was removed under vacuum and product mixture was separated on silica gel column chromatography using pet.ether:acetone (95:5) solvent mixture. The pale brown compound obtained on recrystallization from methanol gave light pinkish solid (1.7g, 85%)

m.p. : 114°C (Lit⁵³. 111°C).

IR (Nujol) : cm⁻¹ 3000(s), 1740(s), 1210(m), 755(s).

¹H-NMR (90 MHz) : δ 1.6-2.1 (2H, m), 2.7-3.0 (4H, m), 3.2-3.4 (2H, m), 5.2-6.0 (4H, m).

MS : m/z 224 (M⁺, 42%).

Preparation of 11-methyltetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13-tetraene-3,10-dione (116): A solution of 2-methyl-1,4-naphthoquinone (5g, 0.029 mol) in ethanol (80 ml) was added to freshly distilled cyclopentadiene (2.3 ml, 0.034 mol) with stirring and mixture was refluxed for 8 to 10 h. After evaporation of the solvent, the resulting crude product was purified by silica gel column chromatography using pet.ether:acetone (98:2) as eluent to furnish pure *endo* adduct.

Yield : 6.5g (94%).

m.p. : 130°C.

IR (Nujol) : cm⁻¹ 2900(m), 2840(s), 1680(s), 1670(m), 1470(s), 1310(m), 1290(w).

¹H-NMR (90 MHz) : δ 1.4-1.6 (d, 2H), 2.4 (s, 3H), 3.3-3.5 (m, 2H), 3.62 (br s, 1H), 5.8-5.9 (m, 2H), 7.3-7.5 (m, 2H), 7.7-8 (m, 2H).

MS : m/z 238 (M⁺, 50%), 173(50), 118(20), 89(32), 66(100).

Preparation of 11-methylhexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-diene-3,10-dione (108): 11-Methyl tetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13-tetraene-3,10-dione (2g, 0.008 mol) was dissolved in P₂O₅ dried acetonitrile (2 lit.) and solution was purged with a slow stream of nitrogen gas for 10 minutes. The solution was irradiated in a pyrex tube with Srinivasan-Rayonet photochemical reactor at 300 nm for 2.5 h. Excess acetonitrile was removed under vacuum and product mixture was separated on silica gel column using pet.ether:acetone (94:6) solvent mixture to give solid of cage dione which on recrystallization from ethanol afforded **108**.

Yield : 75% (1.5g).

m.p. : 104°C.

IR (CHCl₃) : cm⁻¹ 3060(m), 2980(s), 2860(s), 1750(vs), 1470(m), 1390(m), 1310(w).

¹H-NMR (90 MHz) : δ 1.15 (s, 3H), 1.5-1.8 (m, 2H), 2.2-2.3 (d, 1H), 2.4-2.6 (m, 1H), 2.9-3.06 (m, 1H), 3.2-3.4 (m, 2H), 5.2-5.5 (m, 2H), 5.8-6.1 (m, 2H).

¹³C-NMR (80 MHz) : δ 212.63(s), 210.23(s), 124.37(d), 124.25(d), 120.01(d), 119.57(d), 61.88(d), 58.23(d), 50.65(s), 50.13(s), 49.64(d), 49.59(d), 49.24(d), 44.27(d), 37.20(t), 16.98(q).

MS : m/z 238 (M⁺, 12%), 173(25), 80(45), 66(100).

Analysis : C₁₆H₁₄O₂ Calculated : C, 80.67; H, 5.88.

Found : C, 80.80; H, 5.68.

Preparation of 1,12,13,14,15,15'-hexachlorohexacyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13- tetraene-3,10-dione (117): A mixture of 1,4-naphthoquinone (5g, 31.6 mmol) and hexachlorocyclopentadiene (8.64g, 31.6 mmol) was heated at 160°C for 12 h. After slow cooling to room temperature, the solid was filtered and purified by silica gel column chromatography using pet.ether:acetone (97:3) as eluent to furnish **117**.

Yield : 8.18g (60%).

m.p. : 135°C.

IR (Nujol) : cm^{-1} 2980(m), 1685(vs), 1600(m), 810(m).

$^1\text{H-NMR}$ (90 MHz) : δ 4.0 (s, 2H), 7.6-8.1 (m, 4H).

MS : m/z 430 (M^+ , 13%), 395(16), 359(11), 313(8), 272(81), 167(100), 104(60).

Analysis : $\text{C}_{15}\text{H}_6\text{Cl}_6\text{O}_2$: Calculated : C, 41.86; H, 1.39; Cl, 49.30.
Found : C, 41.68; H, 1.52; Cl, 49.09.

Preparation of 1,12,13,14,15,15'-hexachlorohexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]penta deca-5,7-diene-3,10-dione (109): Compound **109** was prepared as per procedure described for **47** from 1,12,13,14,15,15'-hexachlorotetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13-tetraene-3,10-dione (2 g, 0.004 mol). Compound was purified by silica gel column chromatography using pet.ether:acetone (92:8) as eluent to furnish pure cage compound, recrystallised from methanol.

Yield : 90% (1.8g).

m.p. : 196°C.

IR (Nujol) : cm^{-1} 2920(m), 2890(s), 1740(s), 1440(m).

$^1\text{H-NMR}$ (80 MHz) : δ 2.44-2.6 (m, 2H), 6.1-6.6 (m, 4H).

$^{13}\text{C-NMR}$ (80 MHz) : δ 213.55(s), 128.28(d), 115.90(d), 96.37(s), 83.54(s), 80.58(s), 52.23(d), 42.01(s).

MS : m/z 430 (M^+ , 6%), 272(55), 242(18), 239(48), 237(82), 167(95), 104(100), 76(86).

Analysis : $\text{C}_{15}\text{H}_6\text{Cl}_6\text{O}_2$: Calculated : C, 41.86; H, 1.39; Cl, 49.30.
Found : C, 41.98; H, 1.18; Cl, 49.11.

5-Hydroxy-1,4-naphthoquinone (Juglone, 127): To a solution of 1,5-dihydroxy naphthalene (5g, 0.028 mole) in 300 ml of acetonitrile was added salcomine (1g, 0.0033 mole) and reaction mixture was stirred at room temperature for 30 minutes, under oxygen

atmosphere. Removal of solvent led to a crude product, which was purified by silica gel column chromatography using pet.ether:ethyl acetate (90:10) to yield **127** as orange red crystalline solid (2.90g, 56%).

m.p. : 152-154°C (Lit⁵⁸. 151-153°C).

¹H-NMR (90 MHz) : δ 6.93 (s, 2H), 7.17-7.4 (m, 1H), 7.5-7.7 (m, 2H), 11.88 (s, broad, 1H, OH).

Endo 5-hydroxytetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13-tetraene-3,10-dione

(**118**): A mixture of 5-hydroxy-1,4-naphthoquinone (100 mg, 0.575 mmol) and cyclopentadiene (46 mg, 0.696 mmol) in 5 ml of dry benzene was refluxed for 1h. Benzene was removed under vacuum. The residue was chromatographed over silica gel column. Elution with pet.ether:acetone (97:3) gave *endo 118* product.

Yield : 94% (130 mg).

m.p. : 140°C.

IR (Nujol) : cm⁻¹ 1670(m), 1630(s), 1470(s), 1455(s).

¹H-NMR (80 MHz) : δ 1.44-1.68 (m, 2H), 3.24-3.72 (m, 4H), 5.9-6.0 (m, 2H), 6.96-7.44 (m, 3H), 12.48 (s, 1H, OH).

MS : m/e 240 (M⁺, 35%), 175(68), 174(100), 173(32), 146(22), 118(58), 66(88).

1-Hydroxy-5-methoxynaphthalene: A mixture of 1,5-dihydroxynaphthalene (5g, 31.25 mmol) dimethyl sulphate (1.55 ml, 1.95g, 15.6 mmol), and potassium carbonate (2.15g, 15.5 mmol) was refluxed in acetone (120 ml) for 5 h. The progress of the reaction was monitored by TLC. Acetone was then distilled off, water (80 ml) was added and aqueous layer was extracted with dichloromethane (3x25 ml). Combined extracts were washed with water (3x25 ml), brine (2x20 ml) and dried (Na₂SO₄). Removal of solvent led to a residue which was purified by silica gel column chromatography using pet.ether:acetone (9:1) to yield as a major product (1.35g, 25%), along with 1,5-dimethoxynaphthalene (400 mg, 6%).

m.p. : 142°C (Lit⁵⁸. 140-141°C)

$^1\text{H-NMR}$ (90 MHz) : δ 4.0 (s, 3H, OCH_3), 5.2 (s, broad, OH), 6.7-7.8 (m, 6H, Ar).

5-Methoxy-1,4-naphthoquinone (127): To a stirring solution of 1-Hydroxy-5-methoxynaphthalene (1.12g, 6.43 mmol) in 200 ml of CH_3CN was added salcomine (0.2g) and the reaction mixture was allowed to stir at room temperature for 2 h. under oxygen atmosphere (followed by TLC). Removal of solvent led to a crude product, which was purified on silica gel column using pet.ether:acetone (95:5) as eluent to yield **127** as orange red crystalline compound (500 mg, 42%).

m.p. : 178-180°C (Lit⁵⁸. 181-183°C).

IR (Nujol) : cm^{-1} 1660(vs), 1590(s).

$^1\text{H-NMR}$ (80 MHz) : δ 4.0 (s, 3H, OCH_3), 6.8 (s, 2H), 7.17-7.3 (m, 1H, Ar), 7.5-7.7 (m, 2H, Ar).

Endo 5-methoxytetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13-tetraene-3,10-dione

(119): A mixture of 5-hydroxy-1,4-naphthoquinone (200 mg, 1.06 mmol) and cyclopentadiene (84 mg, 1.27 mmol) in 10 ml of dry benzene was refluxed for 3h. Benzene was removed under vacuum. The residue was column chromatographed over silica gel. Elution with pet.ether:acetone (96:4) system gave *endo* **119** product.

Yield : 92% (248 mg).

IR (Nujol) : cm^{-1} 1675(s), 1600(s), 1480(m).

$^1\text{H-NMR}$ (90 MHz) : δ 1.5 (m, 2H), 3.42-3.7 (m, 4H), 4.0 (s, 3H, OCH_3), 6.1 (m, 2H), 7.32 (m, 1H, Ar), 7.72 (m, 2H, Ar).

MS : m/e 254 (M^+ 90%), 189(100), 176(20), 160(32).

5-O-Acetyltetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13-tetraene-3,10-dione (120):

Dry THF (15 ml) and juglone *endo* **118** 600 mg (2.5 mmol) were placed in a 50 ml of two neck flask. Pinch of DMAP, 3 ml of pyridine and 2.55g (2.3 ml, 25 mmol) of acetic anhydride were added to the above solution and the mixture was stirred in N_2 atmosphere at room

5-Nitro-1,4-naphthoquinone (130):

Yield : 39% (10g).

m.p. : 156°C.

IR (Nujol) : cm^{-1} 2980(s), 2850(m), 1670(vs), 1600(m).

$^1\text{H-NMR}$ (80 MHz) : δ 7.0 (s, 2H), 7.7 (dd, 1H), 7.86 (t, 1H), 8.27 (dd, 1H).

6-Nitro-1,4-naphthoquinone (132):

Yield : 32% (8.2g).

m.p. : 147-148°C.

IR (Nujol) : cm^{-1} 2980(s), 2850(m), 1680(vs), 1600(m).

$^1\text{H-NMR}$ (80 MHz) : δ 7.1 (s, 2H), 8.28 (d, 1H), 8.52 (dd, 1H), 8.9 (d, 1H).

5-Nitrotetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13-tetraene-3,10-dione (121): A mixture of 5-nitro-1,4-naphthoquinone (0.53g, 2.6 mmol) and cyclopentadiene (0.2g, 3.1 mmol) in 20 ml of dry benzene was refluxed for 2 h. and progress of the reaction was monitored by TLC. The work-up involved removal of benzene followed by column chromatography over silica gel. Elution with pet.ether:acetone (98:2) system gave *endo* compound.

m.p. : 150°C.

Yield : 70% (0.497g).

IR (Nujol) : cm^{-1} 2900(s), 1690(s), 1550(m), 1450(s).

$^1\text{H-NMR}$ (80 MHz) : δ 1.5 (m, 2H), 3.6 (m, 4H), 5.9-6.1 (m, 2H), 7.7-7.85 (m, 2H), 8-8.1 (m, 1H).

$^{13}\text{C-NMR}$ (80 MHz) : δ 193.53 (s, CO), 193.16 (s, CO), 146.53(s), 135.32(s), 134.05(d), 133.92(d), 133.72(s), 132.61(d), 127.57(d), 126.39(d), 48.66(d), 48.49(d), 47.13(d), 46.90(d), 46.54(t).

MS : m/z 269 (M^+ , 5%), 75(24), 66(100).

Analysis : $C_{15}H_{11}NO_4$: Calculated : C, 66.91; H, 4.08; N, 5.20.
 Found : C, 66.70; H, 4.20; N, 5.09.

1-Acetylnaphthalene: Acetylation in CCl_4 solution gives the 1-isomer as the major component. 21.89g (0.16 mol) of powdered anhydrous $AlCl_3$ was added to a vigorously stirred mixture of 13.09g (11.02 ml, 0.16 mol) of acetyl chloride and 25 ml of CCl_4 , the mixture which became warm, was cooled to $20^\circ C$ and then a solution of 10g (0.078 mol) naphthalene in 25 ml of CCl_4 was added dropwise. The reaction mixture was warmed to $30^\circ C$ for 30 minutes and then decomposed by slow addition of water and extracted with CH_2Cl_2 dried over anhydrous Na_2SO_4 . Evaporation of solvent gave crude compound which was purified by silica gel column chromatography using pet.ether:ethyl acetate (99:1).

Yield : 84% (11.2g).

IR (Nujol) : cm^{-1} 1695 (vs, $COCH_3$).

1H -NMR (80 MHz) : δ 2.5 (s, 3H), 7.0-7.83 (m, 7H, Ar).

5-Acetyl-1,4-naphthoquinone (131): 5g (25 mmol) of 1-acetylnaphthalene (80%, 4 ml) in acetic acid was treated with the solution of CrO_3 (16g) in water (16 ml) at room temperature for 2 h. The solution was stirred and then poured into water, the solution was extracted with ether and then dried over Na_2SO_4 . The evaporation of solvent gave the crude product which was recrystallised from methanol to give pure 5-Acetyl-1,4-naphthoquinone.

Yield : 65% (3.82g).

m.p. : $143^\circ C$ (Lit⁵⁹. 141 - $143^\circ C$).

IR (Nujol) : cm^{-1} 1700 (vs, $COCH_3$), 1670(s).

1H -NMR (80 MHz) : δ 2.47 (s, 3H, $COCH_3$), 6.9 (s, 2H), 7.3-7.5 (dd, 1H, 6-H), 7.7-7.9 (t, 1H, 7-H), 8.0-8.2 (dd, 1H, 8-H).

MS : m/z 200 (M^+ , 9%), 185(100), 157(12), 129(12).

5-Acetyltetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13-tetraene-3,10-dione (122): A mixture of 5-Acetyl-1,4-naphthoquinone (1.2g, 6.6 mmol) and cyclopentadiene 0.52g (8.0 mmol) in 35 ml of dry benzene was refluxed for 1 to 2 h. and progress of the reaction was

^{13}C -NMR (80 MHz) : δ 196.38(s), 195.94(s), 146.30(s), 138.86(s), 135.66(d),
(DMSO- d_6) 135.57(d), 133.09(s), 132.06(d), 128.64(d), 128.09(d), 49.51(d),
49.11(d), 48.69(d), 48.51(d), 46.32(t).

MS : m/e 269 (M^+ , 93%), 203(100), 157(58), 164(18), 149(17),
129(33), 66(28).

Analysis : $\text{C}_{15}\text{H}_{11}\text{NO}_4$: Calculated : C, 66.91; H, 4.08; N, 5.20.

Found : C, 66.72; H, 3.84; N, 4.98.

1-Methoxy-1,4-dihydro-isobenzofuran (148): In an oven-dried 250 ml two necked round bottom flask was placed 2g (0.0149 mol) of phthalide and the flask was flushed with nitrogen and sealed with a rubber septum. Dry toluene 30 ml was added with the help of a syringe under nitrogen atmosphere. The flask was cooled with dry-ice acetone bath, and diisobutyl aluminium hydride 15 ml (1.5 mol in toluene) was added slowly with the help of a syringe. Then, 25 ml of ether was added, stirring was continued further for 4 h, the cold bath was removed, and immediately 80 ml more of ether was added, followed by 60 ml of saturated NaCl solution. The layers were separated and the aqueous layer was extracted with ether (5x40 ml), the combined ether layers were dried over anhydrous Na_2SO_4 and the ether was evaporated. The product was dissolved in 100 ml of methanol and 1 ml of boron trifluoride etherate was added while the solution was cooled in ice. After 2 h. of stirring, the solution was poured into saturated brine solution and extracted with n-hexane (3x20 ml), which was then washed with water, dried over sodium sulphate and evaporated. The residue was purified by silica gel column chromatography using pet.ether as eluent to get a colourless liquid 1.1g (49%) of **148**.

^1H -NMR (90 MHz) : δ 3.3 (s, 3H), 4.84-5.00 (d, 1H), 5.03-5.15 (dd, 1H), 6.03 (d, 1H),
7.1-7.25 (m, 4H).

The preparation of isobenzofuran *in situ* and Diels-Alder reaction with p-benzoquinone (141): In an oven-dried 100 ml two necked round bottom flask was charged an ice-cooled solution of diisopropylamine 1.96g (2.8 ml, 20 mmol) in 20 ml of dry benzene and added 10.56 ml of 1.6M hexane solution of n-butyllithium (16.8 mmol). The lithium diisopropylamide (LDA) solution was allowed to warm to near room temperature and then

1-methoxy-1,4-dihydro isobenzofuran, 1g (6.66 mmol) in 5 ml of dry benzene was added within few minutes. After 15 minutes of stirring, the reaction mixture was turned to slightly red colour. The reaction mixture was quenched by adding 10 ml of aqueous NH_4Cl solution. The benzene layer was separated and dried over Na_2SO_4 . After 30 minutes, it was filtered into 100 ml round bottom flask and *p*-benzoquinone 0.72g (6.66 mmol) was added to it, reaction mixture was heated on an oil bath at 70-80°C for 2 hours and progress of the reaction was monitored by TLC. After completion of reaction, the solvent was then removed under diminished pressure to give a mixture of Diels-Alder adducts *endo* + *exo* (90:10) in 65% yield, which were separated by silica gel column chromatography using pet.ether:acetone (95:5) as eluent.

(141) m.p. : 220°C.

IR (Nujol) : cm^{-1} 2940(m), 1690 (vs, CO), 1480(m).

$^1\text{H-NMR}$ (90 MHz) : δ 2.35 (m, 2H), 3.88 (m, 2H), 5.8 (m, 2H), 7.3 (m, 4H, Ar).

MS : m/z 126 (M^+ , 5%), 118(100), 89(12).

(142) m.p. : 197-200°C.

$^1\text{H-NMR}$: δ 2.39 (m, 2H), 3.91 (m, 2H), 6.0 (m, 2H), 7.1-7.35 (m, 4H, Ar).

Reaction of cyclohexadiene with naphthoquinone (134): Naphthoquinone 5g (0.03 mol), cyclohexadiene 3.7g (0.047 mol), and 15 ml of ethanol were heated in a sealed tube for 6 h. at 50°C. The usual work-up and isolation gave 5.2g (69% yield) of crude crystals, which after crystallization from ethanol gave a pure compound **134**.

Yield : 69% (5.2g).

m.p. : 138°C (Lit⁶³. 134-136°C).

IR (Nujol) : cm^{-1} 2960(s), 1700(s), 1600(s), 1450(m)

$^1\text{H-NMR}$ (80 MHz) : δ 1.35-1.8 (m, 4H), 3.1 (m, 2H), 3.15-3.22 (m, 2H), 6.05 (m, 2H), 7.7 (s m, 2H, Ar), 8.05 (s m, 2H, Ar).

MS : m/z 238 (M^+ , 6%), 220(4), 158(100), 130(72), 102(79), 80(30), 76(68).

Hexacyclo[10.2.2.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]hexadeca-5,7-diene-3,10-dione (136):

Endo compound **134** 1g (4.2 mmol) was dissolved in P₂O₅ dried 1 lit. of acetonitrile and solution was purged with a slow stream of nitrogen gas for 10 minutes. The solution was irradiated in a pyrex tube with Srinivasan Rayonet Photochemical reactor at 300 nm for 2.5 h. Excess acetonitrile was removed under vacuum and product mixture was separated on silica gel column using pet.ether:EtOAc (95:5) solvent mixture to give solid of cage dione **136** and some other product **135**.

(**136**) Yield : 35% (350 mg).

m.p. : 130-132°C.

IR (Nujol) : cm⁻¹ 2980(s), 1730(s), 1470(m).

¹H-NMR (90 MHz) : δ 1.65 (s, 4H), 1.8-1.9 (m, 2H), 2.95-3.1 (m, 2H), 3.5 (m, 2H), 7.0-7.1 (m, 2H), 7.2-7.3 (m, 2H).

MS : m/z 238 (M⁺, 5%), 208(13), 152(15), 102(19), 80(100).

(**135**) Yield : 40%

m.p. : 184-186°C (Lit.⁶³. 187-188°C).

IR (Nujol) : cm⁻¹ 2940(s), 2850(m), 1670(s), 1600(w), 1450(s).

¹H-NMR (80 MHz) : δ 1.5-1.73 (m, 4H), 4.5 (m, 2H), 6.3 (dd, 2H), 7.8 (s m, 2H, Ar), 8.1 (s m, 2H, Ar).

MS : m/z 236 (M⁺, 7%), 208(56), 180(38), 160(52), 115(100).

Synthesis of 2,11-dimethyltetracyclo[10.2.2.0^{2,11}.0^{4,9}]hexadeca-4,5,7,13-tetraene-3,10-dione (138): To the well stirred solution of *endo* tetracyclo compound **134** 300 mg (1.26 mmol) in dry THF (15 ml) under nitrogen atmosphere, a suspension of sodium hydride 100 mg (2.52 mmol) in dry THF (5 ml) was added. The mixture was stirred at 0°C for 10 minutes and then methyl iodide 357 mg (2.52 mmol) was added dropwise, further stirring was continued for 2-3 h. at 0°C-rt. Then ice-water (15 ml) was added and extracted with ether

(3x20 ml). The combined organic extracts were washed with water, brine and dried over Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography using pet.ether:acetone (96:4) to give **138**.

Yield : 210 mg (62%).

m.p. : 122°C.

IR (Nujol) : cm^{-1} 2940(s), 2880(s), 1685(s), 1600(w), 1480(w).

$^1\text{H-NMR}$ (90 MHz) : δ 1.68 (s, 6H), 3.90 (m, 4H), 4.45 (m, 2H), 6.5 (m, 2H), 7.44 (m, 2H), 8.25 (m, 2H).

MS : m/z 266 (M^+ , 35%), 238(52), 223(100), 208(19), 152(50), 119(15).

Reaction of bromocarbene addition to hexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-diene-3,10-dione (47): To a cooled (at 0°C) suspension of 0.6g (5.35 mmol) potassium tertiary butoxide (freshly prepared) in dry THF (40 ml) was added dropwise 1.35g (0.46ml, 5.35 mmol) of CHBr_3 under N_2 atmosphere. It develops dark brown colour within 10 minutes. To the above solution, 0.6g (2.66 mmol) of cage compound **47** dissolved in THF solution was added using syringe over a period of 20 minutes. When the addition was complete, the resulting dark solution was stirred for 2h. at 0°C, and then it was poured into a stirred mixture of ice (20 ml) and ether (40 ml). The ether layer was separated, and the aqueous layer was extracted with ether (3x30 ml). The organic layer and extracts were combined, washed with H_2O (50 ml) and dried over Na_2SO_4 . Evaporation of the solvent at reduced pressure gave a dark crude product, which was purified by silica gel column chromatography using pet.ether:acetone (90:10) as eluent.

14-Dibromomethylidene-13-oxa-pentacyclo[8.5.1.0^{2,9}.0^{3,8}.0^{11,15}]hexadeca-3,5,7-triene-12-one (177):

Yield : 42% (450 mg).

m.p. : 190°C.

IR (Nujol) : cm^{-1} 2940(s), 2870(m), 1800(vs), 1470(s), 1400(m).

¹H-NMR (90 MHz) : δ 2.0 (s, 2H), 3.0-3.6 (m, 4H), 3.78-3.95 (m, 2H), 7.0-7.43 (m, 4H, Ar).

¹³C-NMR : δ 172.36 (s, CO), 151.11(s), 146.08(s), 143.30(s), 127.85(d), (300 MHz) 127.12(d), 126.31(d), 124.29(d), 49.50(d), 48.89(d), 48.56(t), 48.23(d), 47.72(d), 41.86(d), 41.58(d).

MS : m/z 396 (M⁺, 12%), 315(10), 287(6), 236(10), 207(30), 179(52), 141(100), 102(45), 77(28).

Analysis : C₁₆H₁₂Br₂O₂: Calculated : C, 48.48; H, 3.03; Br, 40.40
Found : C, 48.49; H, 3.29; Br, 40.64

12-Hydroxy-14-tribromomethyl-13-oxa-heptacyclo[8.5.1.0^{2,9}.0^{3,8}.0^{3,14}.0^{8,12}.0^{11,15}]hexa deca-4,6-diene (178)

Yield : 56%. (720 mg).

m.p. : 196-200°C.

IR (Nujol) : cm⁻¹ 3520 (s, OH, sharp), 2940(s), 2850(m), 1470(s).

¹H-NMR (90 MHz) : δ 1.3-1.95 (dd, 2H), 2.65-3.17 (m, 4H), 3.3-3.6 (m, 2H), 5.45-5.65 (m, 1H), 5.65-6.05 (m, 3H).

MS : m/z 476 (M⁺, 23%), 397(92), 317(50), 235(62), 195(85), 166(100), 131(80), 77(20).

Analysis : C₁₆H₁₃Br₃O₂: Calculated : C, 40.33; H, 2.73; Br, 50.2.
Found : C, 40.50; H, 2.98; Br, 49.88.

14-Bromomethylidene-13-oxa-pentacyclo[8.5.1.0^{2,9}.0^{3,8}.0^{11,15}]hexadeca-3,5,7-triene-12-one (179): To a saturated solution of ammonium chloride in dry methanol was added 0.328g (5.0 mmol) of Zn dust in portions. After 15 minutes of stirring, compound **177** 200mg (0.5 mmol) dissolved in methanol was added to the above solution and mixture was stirred for

3h. The progress of the reaction was monitored by TLC. After completion of the reaction, the insoluble material was filtered and methanol was concentrated at reduced pressure. The residue was purified by silica gel column chromatography using pet.ether:acetone (90:10).

Yield : 55% (88 mg).

m.p. : 184°C.

IR (Nujol) : cm^{-1} 2940(s), 2850(m), 1795(vs), 1670(s), 1450(s).

$^1\text{H-NMR}$ (90 MHz) : δ 2.0 (s, 2H), 2.78-3.7 (m, 4H), 3.73-4 (m, 2H), 5.2 (d, 1H, Olefin), 7.0-7.4 (m, 4H, Ar).

$^{13}\text{C-NMR}$ (200 MHz) : δ 172.71 (s, CO), 152.79(s), 146.17 (2c, s), 143.26(d), 127.60(d), 126.99(d), 126.18(d), 125.49(d), 49.67(d), 48.48(d), 48.57(t), 47.25(d), 46.12(d), 43.06(d), 41.66(d).

MS : m/z 316 (M^+ , 80%), 272(18), 237(82), 209(58), 181(63), 165(75), 141(100), 115(65), 102(15).

Analysis	: $\text{C}_{16}\text{H}_{13}\text{BrO}_2$:	Calculated	: C, 60.75; H, 4.11; Br, 25.31
		Found	: C, 60.63; H, 4.29; Br, 25.04

12-Hydroxy-14-trichloromethyl-13-oxa-heptacyclo[8.5.1.0^{2,9}.0^{3,8}.0^{3,14}.0^{8,12}.0^{11,15}]hexa

deca-4,6-diene (176): Treatment of 300 mg (1.33 mmol) of compound **47** with 0.626g (5.35 mmol) of chloroform and 0.45g (4.0 mmol) of potassium tertiary butoxide in dry THF as per the procedure described for **177** gave the crude compound **176** which was purified by silica gel column chromatography using pet.ether:acetone (95:5) as eluent.

Yield : 81% (372 mg).

m.p. : 165°C.

IR (Nujol) : cm^{-1} 3460 (s, OH), 2940(s), 2860(s), 1470(m).

$^1\text{H-NMR}$ (90 MHz) : δ 1.25-1.9 (dd, 2H), 2.55-3.0 (m, 4H), 3.2-3.55 (m, 2H), 5.4-5.6 (m, 1H), 5.65-5.9 (m, 2H), 5.91-6.0 (m, 1H).

¹³C-NMR : δ 124.89(d), 122.67(d), 121.94(d), 119.07(d), 118.30(s, CCl₃),
(300 MHz) 101.10(s), 97.89(s), 59.51(d), 58.86(d), 55.81(s, 2C), 55.58(d),
54.06(d), 45.05(d), 42.96(d), 41.19(t).

MS : m/z 342 (M⁺, 20%), 306(20), 271(46), 195(68), 179(90), 131(100).

Analysis : C₁₆H₁₃Cl₃O₂: Calculated : C, 56.14; H, 3.8; Cl, 30.70.

Found : C, 56.22; H, 4.01; Cl, 30.46.

Hexacyclo[7.4.2.0^{1,9}.0^{3,7}.0^{4,14}.0^{6,15}]Pentadeca-10,12-diene-*endo*-2-*endo*-8-diol (195):

Cage diketone **47** 0.5g (2.23 mmol) and NaBH₄ 2g. (54.05 mmol) were ground together under argon atmosphere into a fine powder, thereby producing an intimate solid mixture. The resulting powdery mixture was agitated under argon at room temperature for 7 days. Water (100 ml) was added, and the resulting mixture was extracted with CHCl₃ (4x50 ml). The combined extracts were washed with water (100 ml), dried (Na₂SO₄), and filtered, and the filtrate was concentrated in vacuo to afford pure *endo*, *endo* diol **195** yield (96%, 0.48 g.) as a colourless gummy semisolid.

IR (Nujol) : cm⁻¹ 3200(s), 2962(s), 2874(m), 1588(w), 1480(m), 1273(m),
1131(s), 1082(m).

¹H-NMR(200 MHz) : δ 0.9-1.52 (dd, 2H), 2.25-2.62 (m, 4H), 2.75 (s, 2H), 3.54 (s, 2H),
5.38-5.50 (m, 2H), 5.65-6.1 (m, 2H).

¹³C-NMR : δ 32.14(t), 41.98(d), 45.58(d), 47.10(s), 53.84(d), 75.51(d),
(200 MHz) 123.70(d), 128.14(d).

MS : m/z 228 (M⁺, 10%), 181(12), 161(53), 144(65), 128(72), 115(76),
91(66), 66(100).

Lead tetraacetate oxidation of hexacyclo[7.4.2.0^{1,9}.0^{3,7}.0^{4,14}.0^{6,15}]pentadeca-10,12-diene-*endo*-2-*endo*-8-diol (196): To a solution of diol **195** (0.25g, 1.096 mmol) in dry benzene (50 ml) was added lead tetraacetate (0.534g, 1.2 mmol) in portions over a period of 10 minutes at room temperature. Progress of reaction was monitored by TLC. Reaction mixture was stirred for 6h. at room temperature and filtered through Whatmann filter paper. Benzene

was removed under vacuo and product mixture was separated on silica gel column using pet.ether:acetone (98:2) solvent mixture, to give yellow mass. Recrystallization from methanol yielded yellow solid (119mg, 48%).

m.p. : 172°C.

IR (CCl₄) : cm⁻¹ 2940(m), 1710(w), 1600(s), 1450(w), 790(s), 750(s).

¹H-NMR (90 MHz) : δ 1.8-2.2 (m, 4H), 3.5-3.7 (m, 2H), 3.8-4.0 (m, 2H), 6.7-7.1 (m, 4H), 9.9 (s, 2H).

¹³C-NMR : δ 185.76(d), 153.50(s), 146.12(d), 144.20(d), 51.94(d), 47.33(d),
(300 MHz) 46.07(d), 33.48(t).

MS : m/z 226 (M⁺, 5%), 167(42), 141(54), 115(50), 102(100).

7-Methylhexacyclo[7.4.2.0^{1,9}.0^{3,7}.0^{4,14}.0^{6,15}]pentadeca-10,12-diene-2,8-diol (202): To a solution of cage ketone **108** 0.3g (1.136 mmol) in EtOH (30 ml) was added NaBH₄ (210 mg, 5.68 mmol), and the resulting mixture was stirred at room temperature for 2h. The reaction mixture was concentrated in vacuo, and water (50 ml) was added to the residue. The resulting mixture was extracted with CHCl₃ (4x30 ml). The combined extracts were washed with water (40 ml), dried (Na₂SO₄), and filtered, and the filtrate was concentrated in vacuo. The residue, a mixture of diols **202** and **203** (280 mg, 92%) was purified from starting ketone via column chromatography on silica gel by eluting with 30% EtOAc-pet.ether mixed solvent.

IR (Nujol) : cm⁻¹ 3440(bs), 2970(s), 2880(s), 1450(s), 1380(s), 1160(s).

¹H-NMR (90 MHz) : δ 0.85-1.0 (d, 1H), 1.2 (s, 3H, CH₃), 1.5-1.65 (d, 1H), 2.0 (bs, 1H, OH), 2.13 (m, 2H), 2.5 (bs, 1H, OH), 2.77 (m, 2H), 3.48 (m, 1H), 3.62 (d, 1H), 4.0 (s, 1H), 5.23-5.5 (m, 2H), 5.72-6.0 (m, 2H).

¹³C-NMR : δ 22.31(q), 31.38(t), 42.53(d), 46.78(s), 47.23(s), 48.21(d),
(200 MHz) 50.32(s), 51.84(d), 52.80(d), 53.71(d), 78.81(s), 82.71(s), 123.86(d), 124.02(d), 126.55(d), 127.10(d).

MS : m/z 268 (M^+ , 40%), 253(5), 203(57), 187(100), 165(18), 115(22), 66(44).

1,2,9,10,16,16'-Hexachloro-13-oxa-heptacyclo[8.5.1.0^{2,9}.0^{3,8}.0^{3,14}.0^{8,12}.0^{11,15}]hexadeca-4,6-diene-*exo*-12-*exo*-14-diol (150): Photolysis of *endo* compound **117** gave **109** 1g. residue which was dissolved in (30 ml) dichloromethane and 5 ml of water, and stirred overnight. Solvent was removed in vacuo and residue was chromatographed using silica gel column, pet.ether:acetone (90:10) solvent as eluent to give **150** (1g, ~ 93%).

m.p. : 149°C.

IR (CHCl₃) : cm⁻¹ 3410(bs), 1215(s), 1125(s), 820(m), 775(s).

¹H-NMR (90 MHz) : δ 6.15 (dd, 2H), 5.71 (bs, 2H, OH), 5.47 (dd, 2H), 3.55 (s, 2H).

¹³C-NMR (90 MHz) : δ 126.42(d), 117.26(d), 109.33(s), 97.83(s), 83.53(s), 80.41(s), 60.46(d), 60.00(s).

MS : m/z 449 (M^+ , 3%), 432(4), 430(6), 272(55), 242(18), 239(48), 237(82), 167(95), 104(100), 76(86).

Lead tetraacetate oxidation of 1,2,9,10,16,16'-hexachloro-13-oxa-heptacyclo[8.5.1.0^{2,9}.0^{3,8}.0^{3,14}.0^{8,12}.0^{11,15}]hexadeca-4,6-diene-*exo*-12-*exo*-14-diol (199): To a solution of diol **150** (0.32g, 7.12 mmol) in dry benzene (45 ml) was added lead tetraacetate (0.347g, 7.83 mmol) in portions over a period of 15 minutes at reflux temperature. Progress of reaction was monitored by TLC. Reaction mixture was refluxed for 2h. and filtered through Whatmann filter paper. Benzene was removed under vacuo and product mixture was separated on silica gel column using pet.ether:acetone (92:8) solvent mixture to give white crystals. Recrystallization from CHCl₃ yielded pure white crystals **199**.

Yield : 70% (223 mg).

m.p. : 200-202°C.

IR (Nujol) : cm⁻¹ 1870(s), 1800(s), 1600(s).

¹H-NMR (90 MHz) : δ 4.1 (d, 2H), 7.25-7.65 (m, 4H, Ar).

^{13}C -NMR : δ 165.06(s), 141.39(s), 133.39(d), 126.67(d), 103.03(s), 81.10(s),
(200 MHz) 76.93(s), 53.46(d).

MS : m/z 446 (M^+ , 5%), 197(100).

Pentacyclo[6.2.1.0^{2,7}.0^{9,10}.0^{5,9}]undecane *endo*-3-*exo*-6-diol (193): To a solution of Cookson ketone (0.5g, 2.87 mmol) in EtOH (30 ml) was added NaBH_4 (0.425g, 11.49 mmol). In order to reduce the intermediate ketol, a large excess of NaBH_4 was used, portions being added over a period of 2 days with warming. Work-up procedure followed as described for compound **202**, the product obtained in TLC shows two spots on TLC with $\text{C}_6\text{H}_6/\text{EtOAc}$ (1:1) eluent R_f 0.61 (*endo-endo*), 0.34 (*exo-endo*). The mixture can be conveniently separated by recrystallization from ether-chloroform, in which the *endo-endo* isomer (m.p. 276°C) was more soluble than the *exo-endo* isomer (m.p. 273°C).

Endo, Endo (**192**) :

^1H -NMR (90 MHz) : δ 6.05 (s, 2H), 4.31 (s, 2H), 2.23-2.80 (br m, 8H), 1.03 and 1.64 (dd, 2H).

Exo, Endo (**193**) :

^1H -NMR (90 MHz) : δ 6.55 (s, 2H), 3.76 (m, 2H), 2.58 (m, 4H), 2.30 (m, 4H), 1.32 (dd, 2H).

Lead tetraacetate oxidation of pentacyclo[6.2.1.0^{2,7}.0^{9,10}.0^{5,9}]undecane *endo*-3-*exo*-6-diol (193): To a solution of diol **193** (0.28g, 1.57 mmol) in dry benzene (30 ml) was added LTA (0.767g, 1.73 mmol) in portions over a period of 10 minutes at reflux temperature. Progress of reaction was monitored by TLC. Reaction mixture was refluxed for 3-5h. and filtered through Whatmann filter paper. Benzene was removed under vacuo and product mixture was separated on silica gel column using pet.ether:acetone (99:1) solvent mixture to give mixture of compounds **200** and **201**.

Yield : 38% (106 mg).

IR (CHCl_3) : cm^{-1} 3500 (bs, OH), 3000(s).

¹H-NMR (90 MHz) : δ 1.12-3.5 (m, 20H), 4.59 (t, 1H) and 4.07 (t, 1H) (Mono hydroxy ketone and Hemi ketol).

¹³C-NMR (80 MHz) : δ 211.61(s), 119.09(s), 81.9(d), 72.20(d), 56.31(d), 55.01(d), 54.4(d), 50.03(d), 45.84(d), 45.30, 43.99, 44.8, 43.4(2c), 43.18, 42.23, 42.00, 41.55(2c), 40.7, 38.48(t), 37.0(d).

MS : m/z 176 (M⁺, 16%), 158(10), 131(47), 117(100), 91(85).

β-Cleavage of hexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-diene-3,10-dione (47):

The dione **47** (0.1 gm, 4.46 mmol) was dissolved in ethanol:triethylamine solvent mixture (95:5) (20 ml) and purged with a slow stream of nitrogen gas for 5 minutes. The stoppered reaction mixture was irradiated in Srinivasan-Rayonet photochemical reactor at 300 nm for 2h. Ethanol was then removed under vacuo and product was separated on silica gel column using pet.ether:acetone (98:2) solvent mixture to give yellow compound. Recrystallization from methanol afforded pure yellow compound **79** (0.07g, 70%).

(Spectral data, Please see page **79**).

Catalytic hydrogenation of hexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-diene-

3,10-dione (47): A solution of unsaturated dione **47** 1g (4.46 mmol) in dry methanol (80 ml) was hydrogenated over pre-activated platinum dioxide 300 mg at a hydrogen pressure of 30 psi for 8h. The reaction mixture was filtered to remove the catalyst, and the filtrate was concentrated in vacuo to give a residue, which was chromatographed over a silica gel column using pet.ether:acetone (96:4). The purified material was recrystallized from a minimum amount of methanol to give white crystals of the reduced dione **221** 680mg (66%).

m.p. : 70°C (Lit⁴⁶. 68-69°C).

IR (Nujol) : cm⁻¹ 2900(s), 2840(s), 1740(s), 1720(s), 1450(m), 1370(m), 1100(m).

¹H-NMR (90 MHz) : δ 1.5-2.0 (m, 10H), 2.75 (2H, s), 2.85 (4H, s).

¹³C-NMR : δ 213.29(s), 55.04(d), 49.58(s), 44.19(d), 43.54(d), 41.07(t), (200 MHz) 22.61(t), 19.17(t).

MS : m/z 228 (M^+ , 100%), 200(23), 135(27), 129(29), 107(34), 91(44), 77(40), 66(33).

Analysis : $C_{15}H_{16}O_2$: Calculated : C, 78.94; H, 7.01.

Found : C, 78.76; H, 7.12.

Tricyclo[6.2.1.0^{2,7}]undeca-4,9-dien-3,6-dione: To an approximately 20% (w/v) solution of quinone (2g, 0.0185 mol) in benzene was added 1.46g (1.48 ml, 0.02 mmol) of freshly cracked cyclopentadiene. The solution was either stirred at room temperature or refluxed (for 20-60 minutes) and the reaction course was monitored by TLC. After the completion of the reaction, the solution was concentrated and the crude product obtained was directly crystallised either from the same solvent or dilution with pet.ether.

Yield : 90-95%.

m.p. : 76°C (Lit⁵¹. 75-76°C).

IR (Nujol) : cm^{-1} 3320(w), 1660(s), 1601(s), 1295(m), 1280(m), 1060(m).

¹H-NMR (80 MHz) : δ 1.48 (m, 2H), 3.28 (m, 2H), 3.52 (m, 2H), 6.02 (m, 2H), 6.52 (s, 2H).

MS : m/z 174 (M^+ , 68%), 146(27), 66(100).

Pentacyclo[6.2.1.0^{2,7}.0^{4,10}.0^{5,9}]undecane-3,6-dione (59): A solution of *endo* (4g., 0.022 mol) in ethyl acetate (150 ml) was irradiated for 12 h. with a Hanovia medium pressure Hg lamp (200W, Pyrex filter). The reaction was monitored by TLC. The solution was concentrated to give colourless, microcrystalline solid.

Yield : 3.4g (86%).

m.p. : 243°C (Lit⁵¹. 245°C).

IR (Nujol) : cm^{-1} 2990(s), 2930(m), 2870(m), 1742(vs), 1720(vs), 1185(m), 1055(s), 855(m).

¹H-NMR (80 MHz) : δ 1.86 (q, 2H), 2.6-3.0 (m, 6H), 3.05-3.22 (m, 2H).

MS : m/z 174 (M^+ , 52%), 145(20), 117(100), 91(35), 66(36).

Preparation of 1,2-dibromocyclohexane: In a 500 ml, three-necked, round bottom flask, fitted with a 50cc pressure equalizing dropping funnel, a magnetic stirrer, and a thermometer, was placed a solution of 20g (0.24 mole) of cyclohexene in a mixture of 40cc of CCl_4 and 3ml of absolute alcohol. The flask was surrounded by an ice-salt bath. The stirring was started as and when the temperature had reached -5°C , a solution of 34.14g (11 ml, 0.21 mole) of bromine (Br_2) in 20cc of CCl_4 was added from the dropping funnel at such a rate that the temperature of the reaction mixture does not exceed -1°C (Note-1). The addition requires about 20 minutes when the bromine has been added, the contents of the flask were transferred directly to other RBF, then CCl_4 and excess cyclohexene distilled on water bath. The water bath was replaced by an oil bath and the product was distilled under reduced pressure. There was a small low boiling fraction and then pure dibromo cyclohexane distilled at $99-105^\circ\text{C}/16\text{mm}$ ($108-112^\circ/25\text{mm}$) the yield was 49g (83%).

Note: Unless the temperature is controlled carefully, the yield is poor because of substitution reactions. Even at this low temperature, some substitution occurs unless the excess of cyclohexene is used.

Preparation of cyclohexadiene (133): A mixture of lithium carbonate, (27g) and lithium chloride, (17g) in hexamethyl phosphoric triamide (HMPA, 80ml) was heated in an oil bath at 160°C in 500 ml three necked flask equipped with an addition funnel and condenser set for distillation. After 30 minutes, 1,2-dibromo cyclohexane 157g (0.64 mole) was added dropwise, which resulted in an immediate distillation of 1,3-cyclohexadiene from cold water passing distillation condenser. After all the DBC had been added, a gentle stream of nitrogen was passed through the system, which resulted in an additional small amount of distillate. Yield of resulting 1,3-cyclohexadiene was 42.6g (82%).

5-Chloro-5-cyano bicyclo[2.2.2]oct-2-ene (260): A mixture of 1,3-cyclohexadiene 5g (62.5 mmol), chloroacrylonitrile, 5.43g (62.5 mmol) and 50 mg of P-hydroquinone in dry benzene (80 ml) was refluxed at 90°C strictly not more than this temperature for 20 h. Reaction was monitored by TLC and then benzene was removed at reduced pressure, crude polymeric product was washed with n-pentane or n-hexane repeatedly 4 or 5 times, and concentrated. The product was purified by silica gel column chromatography using pet.e-ther:EtOAc (99:1) to afford bicyclic adduct.

Yield : 42%, (4g.).

m.p. : 89-90°C.

IR (Nujol) : cm^{-1} 2970(s), 2880(m), 2250(s), 1470(m), 1380(m).

$^1\text{H-NMR}$ (80 MHz) : δ 1.2-1.7 (m, 4H), 1.9-2.25 (m, 2H), 2.6-2.9 (m, 1H), 3.29 (m, 1H), 6.1-6.48 (m, 2H).

MS : m/z 167 (M^+ , 10%), 141(15), 97(18), 83(42), 69(68), 55(100).

Bicyclo[2.2.2]oct-2-ene-5-one (261): A warm solution of 6.84g (0.12 mol) of 85% KOH in 5.5 ml of water was added to a solution of 4g. (0.024 mol) of chloronitrile adduct in 35 ml of DMSO. There was a gradual darkening of colour from yellow to black and a mild increase in temperature from 50-60°C. After 12 h. no more chloronitrile was present and a new peak in IR corresponding to ketone appeared. The reaction mixture was added to ice-water and extracted five times with pet.ether. The organic layer was dried over Na_2SO_4 and then concentrated. Purification by the silica gel column chromatography using pet.ether:EtOAc (98:2) afforded 1.9g of **261** (65%) yield.

m.p. : 83-85°C (Lit.¹¹¹ 84-86°C).

IR (CHCl_3) : cm^{-1} 3100(m), 2920(s), 2850(m), 1725(vs), 1470(w), 1450(m), 1410(m).

$^1\text{H-NMR}$ (90 MHz) : δ 1.3-1.9 (m, 4H), 2.0 (d, 2H), 2.8-3.19 (m, 2H), 6.1-6.6 (m, 2H).

MS : m/z 122 (M^+ , 12%), 80(100), 77(18).

Synthesis of tricyclo[3.3.0.0^{2,5}]octan-3-one (240): A solution of 1.5g (0.012 mole) of bicyclic compound **261** in acetone was purged with N_2 and irradiated in a quartz tube in a Rayonet photoreactor at 300 nm. After 72 h. 96-98% of bicyclic compound was converted into tricyclic compound **240** (no other products detected by GLC). The acetone was distilled off, and the residue was chromatographed on a column of silica gel. Pet.ether:acetone (99:1) solvent mixture eluting starting material, followed by required compound **240** 1.17g (78%) yield.

IR (Neat) : cm^{-1} 3000(w), 2900(s), 2820(m), 1700(vs), 1400(m).

$^1\text{H-NMR}$ (90 MHz) : δ 1.5 (m, 1H, $\text{C}_4\text{-endo}$), 1.8 (m, 1H, C_2), 1.95 (m, 1H, C_8), 1.98-2.2 (m, 4H, C_7 and C_6), 2.36 (m, 1H, $\text{C}_4\text{-exo}$), 2.7-3.1 (m, 2H, C_1 and C_5).

$^{13}\text{C-NMR}$ (80 MHz) : δ 215.34(s), 46.50(t), 40.42(t), 38.39(d), 37.04(d), 35.79(d), 30.24(d), 24.19(t).

MS : m/z 122 (M^+ , 9%), 80(100), 77(19).

Bicyclo[3.3.0]^{1,5}octa-3-one (247): The tricycloketone **240** (0.2g, 1.63 mmol) was dissolved in ethanol:triethylamine solvent mixture, 82 ml (80:20). The solution was purged with a slow stream of nitrogen gas for 10 minutes and then irradiated in Srinivasan-Rayonet photochemical reactor at 300 nm in pyrex tube for 6 h. The progress of the reaction was monitored by GC/TLC. The solvent and TEA were evaporated under reduced pressure and the crude product obtained was purified on silica gel column using pet.ether:acetone (99:1) as eluent to give 79% (160 mg) yield.

IR (Neat) : cm^{-1} 2930(s), 1740(vs), 1400(m).

$^1\text{H-NMR}$ (90 MHz) : δ 1.25-2.45 (m, 10H), 2.88 (m, 2H, C_1H and C_5H).

$^{13}\text{C-NMR}$ (80 MHz) : δ 220(s), 44.36(d), 39.54(t), 33.17(t), 25.2(t).

MS : m/z 124 (M^+ , 17%), 95(14), 80(100).

Analysis : $\text{C}_8\text{H}_{12}\text{O}$: Calculated : C, 77.41; H, 9.67.

Found : C, 77.08; H, 9.35.

Bicyclo[4.1.0]heptan-2-one (244): Zinc-Copper couple 4.05g (0.062 mol) in anhydrous ether (70 ml) was heated to gentle reflux, and a few drops of methylene iodide was added. After the mild exothermic reaction had been initiated, a mixture of cyclohex-2-ene-1-one, 2.17g (0.022 mol) and methylene iodide 16.97g (0.063 mole) was added dropwise over a period of 30 minutes. The mixture was heated under reflux for 36 h. and then cooled. Water (5 ml) was added dropwise and the mixture stirred for 1 h. The zinc hydroxide precipitate

was removed by centrifugation or filtration and the ether layer was washed with 10% HCl and water, dried over Na_2SO_4 and concentrated, purification by silica gel column chromatography using pet.ether:EtOAc (98:2) afforded 2g. of compound **244** in 80% yield.

IR (Neat) : cm^{-1} 2970(s), 1700(vs).

$^1\text{H-NMR}$ (90 MHz) : δ 0.98-1.35 (m, 2H), 1.5-2.05 (m, 6H), 2-2.5 (m, 2H).

MS : m/z 110 (M^+ , 22%), 81(23), 67(60), 54(100).

3-Methylcyclohexanone (248): The bicycloketone **244** (0.25g, 2.27 mmol) was dissolved in 20% TEA:EtOH (113 ml by volume) and solution was irradiated at 300 nm for 4 h. For work-up, the procedure described for compound **247** was followed. Product was purified by silica gel column chromatography using pet.ether:EtOAc (99:1) as eluent to give 55% (140 mg) yield of **248**.

IR (Neat) : cm^{-1} 1725(vs).

$^1\text{H-NMR}$ (90 MHz) : δ 0.8-1.1 (m, 8H), 2-2.05 (m, 4H).

$^{13}\text{C-NMR}$: δ 210.86(s), 49.7(t), 40.8(t), 33.8(d), 33.11(t), 24.9(t), 21.7(q).
(200 MHz)

MS : m/z 112 (M^+ , 10%).

Preparation of 2-Spirocyclopropyl-1-cyclohexanone (246):

A: 2-(N,N-Dimethyl)methyl-1-cyclohexanone (264): A mixture of cyclohexanone 5g (0.051 mole), dimethyl amine hydrochloride 31.6g (0.45 mole) and paraformaldehyde 9g (0.3 mole) in 95% ethanol (100 ml) was heated in the presence of catalytic amount of conc. HCl (2 ml) under reflux for 2.5 h. After the solution was cooled and diluted with 400 ml of acetone, the ppt was filtered (7.5g, 69.4%). Treatment of the crude product 7.5g with excess sodium carbonate in water (80 ml) gave an oil. The aqueous phase was extracted with ether. The combined organic layers were washed with water, dried, and concentrated to furnish a diamino ketone. Methylation of the amino ketone with MeI (3 ml) in CH_3CN gave a white ppt. after evaporation of solvent and excess methyl iodide. The product was used for the following cyclopropanation without further purification:

B: 2-Spirocyclopropyl-1-cyclohexanone (246): A mixture of oil-free NaH 1.12g (0.028 mole) and trimethyl oxosulfonium iodide 3.066g (0.014 mole) was treated dropwise with dimethyl sulfoxide (25 ml) at room temperature. After the solution was stirred for 1h, a solution of the crude ammonium iodide (3.4g, 7.0 mmol) was added dropwise in the same solvent (20 ml). Stirring was continued for 3-4 h. at room temperature and 1 h. at 40-50°C before the mixture was poured onto ice and extracted with ether. The organic layer was washed with water, dried and concentrated to yield liquid compound. Purification by silica gel column chromatography with pet.ether:acetone (98:2) solvent mixture eluted mono spiro cyclopropyl ketone **246**, followed by dispirocyclopropyl ketone **266** using (97:3) solvent mixture in almost equal amount (Overall yield 58%).

(**266**) IR (Neat) : cm^{-1} 3000(w), 2980(m), 1680(v s).

^1H -NMR (90 MHz) : δ 0.55 (q, 4H), 1.18 (q, 4H), 1.8 (m, 6H).

^{13}C -NMR : δ 212.56(s), 34.95(t), 28.42(s), 23.60(t), 19.88(t).
(200 MHz)

MS : m/z 150 (M^+ , 60%), 135(88), 79(100).

(**246**) IR (Neat) : cm^{-1} 1695(v s).

^1H -NMR (90 MHz) : δ 0.61 (q, 2H), 1.20 (m, 2H), 1.65-1.89 (m, 6H), 2.01 (m, 2H).

MS : m/z 124 (M^+ , 55%).

Preparation of 2-Spirocyclopropyl-1-tetralone (245):

A: 2-(N,N-Dimethyl)methyl-1-tetralone: A mixture of tetralone 2g. (0.013 mol), dimethyl amine hydrochloride 4.31g. (0.062 mmol) and paraformaldehyde 1.25g (0.041 mol) in 95% ethanol (50 ml) was heated in the presence of catalytic amount of conc. HCl (1 ml) under reflux temperature for 2.5 h. After the solution was cooled and diluted with 200 ml of acetone, the precipitate was filtered to give 2.3g (82.73%) of product. Treatment of the crude product (2.5 g) with excess sodium carbonate in water (25 ml) gave an oil. The aqueous phase was extracted with ether. The combined organic layer was washed with water, dried over Na_2SO_4 and concentrated to furnish an yellow amino ketone.

B: Methylation of the amino ketone: Methylation of the amino ketone with methyl iodide 2.28g (1 ml, 0.016 mol) in acetonitrile gave a white precipitate (3.9g) after evaporation of solvent and excess methyl iodide. The product was used for the following cyclopropanation without further purification.

C: 2-Spirocyclopropyl-1-tetralone (245): A mixture of oil-free sodium hydride (NaH) 0.9g (0.022 mol) and trimethyl oxosulfonium iodide 2.47g (0.0113 mol) was treated dropwise with dimethyl sulfoxide 25 ml at room temperature. After the solution was stirred for 1h, a solution of the crude ammonium iodide 3.9g (0.0113 mole) was added dropwise in the same solvent (25 ml). Stirring was continued for 3 h. at room temperature and 1 h. at 40-50°C before the mixture was poured into ice and extracted with ether. The organic layers were washed with water, dried and concentrated to give an yellow crude oil, which was purified by silica gel column chromatography with pet.ether:EtOAc (96:4) to furnish 1.4g (72%) of compound **245**.

2-(N,N-Dimethyl)methyl-1-tetralone:

IR (CHCl₃) : cm⁻¹ 2980(m), 1690(s), 1600(m), 1460(m).

¹H-NMR (90 MHz) : δ 2.25 (s, 6H), 2.35-3.1 (m, 7H), 7.1-7.55 (m, 3H, Ar), 8.0 (m, 1H, Ar).

MS : m/z 203 (M⁺, 16%), 158(58), 118(100).

(**245**) IR (Neat) : cm⁻¹ 2980(s), 1690(s), 1600(s), 1380(s), 1240(s).

¹H-NMR (90 MHz) : δ 0.75 (q, 2H), 1.4 (m, 2H), 1.95 (m, 2H), 3.0 (t, 2H), 7.1-7.55 (m, 3H, Ar), 8.0 (m, 1H, Ar).

MS : m/z 172 (M⁺, 100%), 144(40), 128(48), 115(40).

2-Ethylcyclohexanone (250): Procedure followed as per described for **247**. The 2-spirocyclopropyl hexanone **246** (0.12g, 0.967 mmol) was dissolved in 20% TEA:EtOH (by volume, 48 ml), irradiated at 300 nm for 4 h. Product was purified by silica gel column chromatography using n-hexane:EtOAc (98:2) as eluent to give 40% (48 mg) yield of compound **250**.

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

$^1\text{H-NMR}$ (90 MHz) : δ 1.0 (m, 3H), 1.2-1.5 (m, 9H), 1.9-2.5 (m, 3H).

MS : m/z 126 (M^+ , 42%).

2-Ethyl-1-tetralone (249): Procedure followed as per described for **247**. The 2-spirocyclopropyl-1-tetralone **245** (0.24g, 1.39 mmol) was dissolved in 20% TEA:EtOH (by volume, 70 ml), and irradiated at 254 nm for 8 h. Product was purified by silica gel column chromatography using n-hexane:EtOAc (96:4) as eluent to give (192 mg) of compound **249** (79% yield).

IR (Neat) : cm^{-1} 2980(s), 1680(s), 1600(m).

$^1\text{H-NMR}$ (90 MHz) : δ 0.6-1.0 (t, 3H), 1.0-2.0 (m, 4H), 2.05-2.9 (m, 3H), 6.95-7.45 (m, 3H, Ar), 7.45-7.55 (m, 1H, Ar).

$^{13}\text{C-NMR}$: δ 192.39(s), 142.81(s), 137.45(s), 128.20(d), 126.00(d), 124.74(d, 200 MHz) 2c), 43.71(d), 29.74(t), 26.99(t), 14.51(t), 9.9(q).

MS : m/z 174 (M^+ , 25%), 146(20), 114(25), 100(100).

Analysis : $\text{C}_{12}\text{H}_{14}\text{O}$: Calculated : C, 82.75; H, 8.04.

Found : C, 82.53; H, 7.69.

Dicyclopropyl methanone (251): A solution of sodium methoxide was prepared from 4.5g of freshly cut sodium and 60 ml of absolute methanol in a three-necked 500 ml flask placed on an oil bath and equipped with a sealed stirrer, dropping funnel and a condenser set downward for distillation. To the stirred solution was added in one portion 30g (0.34 mol) of γ -butyrolactone, and the flask was heated until methanol distills at a rapid rate. After 40 ml of methanol was collected, a filter flask or other suitable device equipped with a side arm was connected to the condenser. This receiver was surrounded by an ice bath, and reduced pressure from an aspirator was applied cautiously with continuous stirring. An additional ~ 10 ml of methanol was collected in this way. The residue presumably was dibutyrolactone.

The condenser was set for reflux and conc. HCl was added with stirring, cautiously at first because of considerable amount of CO₂ evolution. A total of 70 ml of acid was added in about 10 minutes. The mixture was heated under reflux with stirring for 20 minutes, then cooled in an ice bath. A solution of 42g. of NaOH in 55 ml of water was added to the stirred mixture as rapidly as possible, without allowing temperature to go above 50°C. The mixture was then heated under reflux for an additional 30 minutes.

The condenser was arranged for downward distillation, and a total of ketone-water mixture was collected as distillate. Sufficient potassium carbonate was added to saturate the aqueous layer and organic layer was separated. The aqueous layer was extracted with (3x50 ml) ether and combined ether and organic layer were dried over Na₂SO₄. The solvent was removed and the dicyclopropyl ketone was distilled at 72-74°C/33mm (49% yield).¹¹⁶

IR (Neat) : cm⁻¹ 3000(m), 1690(vs), 1450(w), 1420(m).

¹H-NMR (90 MHz) : δ 0.78-1.1 (m, 8H), 1.85-2.25 (m, 2H).

MS : m/z 110 (M⁺, 10%), 95(9), 84(35), 69(100), 55(28), 41(67).

4-Heptanone (255): Procedure followed as per described for **247**. The dicyclopropyl methanone **251** (160 mg, 1.45 mmol) was dissolved in 20% TEA;EtOH (by volume, 73 ml), and irradiated at 300 nm for 4h. Product was purified by silica gel column chromatography using pet.ether as eluent to afford (0.058g) 36% of the pure product.

b.p. : 148°C (Lit.¹¹⁷ 145°C).

IR (Neat) : cm⁻¹ 3100(s), 1720(s).

¹H-NMR (90 MHz) : δ 0.9 (t, 6H), 1.55 (m, 4H), 2.4 (t, 4H).

MS : m/z 114 (M⁺, 38%), 100(100).

Epoxidation of cyclohexene (252): In a 100 ml RBF equipped with a dropping funnel was placed a solution of cyclohexenone 5g. (0.052 mol) and 5.3g (0.156 mol) of 30% aqueous hydrogen peroxide in 60 ml of methanol. After the contents of the flask have been cooled to 15°C by means of an ice-bath, 1g (0.026 mol) 6N aqueous NaOH was added, dropwise with stirring over a period of 1 h. During the addition, the temperature of reaction mixture

was maintained at 15-20°C with a bath of cold water. After addition was complete, the resulting mixture was stirred for 3 h. as the temperature of the reaction mixture was maintained at 20-25°C. The reaction mixture was poured in 100 ml of water, and the resulting mixture was extracted with ether and washed with water, dried over anhydrous Na₂SO₄. After the bulk of the ether had been removed by distillation, the residue was purified by silica gel column chromatography using pet.ether:EtoAc (98:2) to afford 82% (4.8g) yield.

IR (Neat) : cm⁻¹ 2980(s), 1720(s), 1350(s), 1260(m).

¹H-NMR (90 MHz) : δ 1.43-2.7 (m, 6H), 3.15 (d, 1H), 3.55 (m, 1H).

MS : m/z 112 (M⁺, 100%), 83(23).

3-Hydroxy-1-cyclohexanone (256): Procedure followed as per described for **247**. The epoxy compound (0.2g, 1.78 mmol) was dissolved in 20% TEA:EtOH (by volume, 90 ml), and irradiated at 254 nm for 3 h. Product was purified by silica gel column chromatography using n-hexane:EtoAc (97:3) as eluent, yield 49% (0.1g).

IR (Neat) : cm⁻¹ 3460 (b s, OH), 3000(s), 1720(s), 1230(s).

¹H-NMR (90 MHz) : δ 0.7-2.1 (m, 4H), 2.25-2.9 (m, 4H), 3.5-3.85 (m, 1H), 4.05 (b s, 1H).

MS : m/z 114 (M⁺, 12%), 100(100), 88(33).

3,5α-Cycloandrostan-17β-ol-6-one-17β-acetate (254): To a cooled (10°C) solution of 3,5α-cycloandrostan-17β-ol-6β-acetate 17β-acetate (2g.) in acetone (110 ml) was added dropwise, with swirling, CrO₃-H₂SO₄ reagent (8N) 3 ml. The mixture was kept overnight at 5°C, and was then poured into ice water, and the resulting suspension was washed with water and dried to give 1.5g. of crude product with m.p. 109-111°C. Crystallization from MeOH raised the m.p. to 116-118°C Lit.¹¹⁸

IR (Nujol) : cm⁻¹ 2980(s), 1740(s), 1690(s), 1470(s), 1390(s), 1250(m).

¹H-NMR (90 MHz) : δ 0.88 (d, 2H), 1.0-1.98 (m, 22H), 2.1 (s, 3H, COCH₃), 2.12-2.2 (m, 2H).

¹³C-NMR : δ 210.35(CO), 171.29(OAc), 82.60, 50.92, 49.40, 44.63, 43.55,
(200 MHz) 36.79, 31.09, 27.61, 25.45, 23.68, 22.90, 21.32, 20.99, 19.31, 18.38,
12.48.

MS : m/z 330 (M⁺, 45%), 315(23), 301(14), 255(13), 136(52), 121(50),
107(62), 91(100), 79(100).

Tosylation of cholesterol (272): To a solution of dry cholesterol 4g (0.011 mmol) in 80 ml of dry pyridine was added 4.44g (0.023 mol) of *p*-toluenesulfonylchloride (freshly recrystallized from petroleum ether 60-70°C). The reaction mixture was allowed to stand overnight in the dark at room temperature and poured into 500 ml ice-cold 5% aqueous potassium bicarbonate solution. The resulting solid tosylate was collected by filtration, washed with water, and dried in a vacuum oven at 60°C. Recrystallization from dry acetone gave tosylated product **272** as colourless crystals.

m.p. : 122°C.

¹H-NMR (90 MHz) : δ 0.7 (s, 3H), 0.9-1.65 (m, 23H), 1.75-2.1 (m, 12H), 2.2-2.4 (m, 2H), 2.5 (s, 3H), 4.4 (m, 1H), 5.4 (m, 1H), 7.4 (d, 2H), 7.8 (d, 2H).

3,5α-Cyclocholest-6β-ol (273): A solution of 3g. of (5.7 mmol) cholesteryl tosylate and 2.5 (18.38 mmol) of potassium bicarbonate in (500 ml) acetone and 150 ml of water was refluxed for 6 h. The solvent acetone was distilled and the residue was diluted with water and extracted with ether. The ether extract was washed with water, dried over Na₂SO₄, and evaporated to dryness under reduced pressure. Crude product was purified by silica gel column chromatography using pet.ether:EtoAc (82:18), yield 1.6g. (75.5%). Crystallization from acetone and water gave a crystalline product.

m.p. : 91°C.

IR (Nujol) : cm⁻¹ 3400 (b s, OH), 2980(s), 1470(m).

¹H-NMR (90 MHz) : δ 0.68 (s, 3H), 0.7-1.0 (m, 12H), 1.05-2.0 (m, 27H), 3.23 (m, 1H).

MS : m/z 386 (M⁺, 40%), 368(82), 353(26), 331(75), 213(50), 145(88),
95(100).

3,5 α -Cyclocholest-6-one (253): Jones reagent (8N CrO₃-H₂SO₄) (1 ml) was added dropwise to a stirred and ice-cooled solution of 3,5 α -cyclocholest-6 β -ol **273** (1.5g.) in acetone (25 ml). The mixture was stirred for 15 minutes. A small amount of MeOH was added to destroy the excess CrO₃. The mixture was concentrated in vacuo. The residue was diluted with water and extracted with ether. The ether solution was washed with water, aqueous NaHCO₃ and brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was recrystallized from 99% EtOH to give (80%) of **253** as crystals.

m.p. : 98°C (Lit.¹¹⁸ 98.5-99.5°C).

IR (Nujol) : cm⁻¹ 2960(s), 1690(vs), 1460(m).

¹H-NMR (90 MHz) : δ 0.75 (s, 3H), 0.95 (m, 9H), 1.05-1.45 (m, 15H), 1.55 (m, 8H), 1.75-2.0 (m, 6H), 2.25 (s, 2H).

MS : m/z 384 (M⁺, 45%), 370(20), 243(40), 136(100), 121(60), 55(59).

Androstane-17 β -ol-6-one 17 β -acetate (258): Procedure followed as per described for **247**. The compound **254** (190 mg, 0.57 mmol) was dissolved in 20% TEA:EtOH (by volume, 30 ml), and irradiated at 300 nm for 6 h. Product was purified by silica gel column chromatography using pet.ether:EtoAc (85:15) as eluent. Yield 87% (167 mg).

IR (Nujol) : cm⁻¹ 2900(s), 2820(m), 1740(vs), 1705(s).

¹H-NMR (200 MHz) : δ 0.7-0.95 (s, 6H, 2CH₃), 1.10-1.75 (m, 19H), 2.0 (s, 3H, COCH₃), 2.25-2.50 (m, 3H), 4.6 (t, 1H).

¹³C-NMR (200 MHz) : δ 209.38(s), 170.69(s), 82.23(d), 49.21, 47.28, 44.27, 44.00, 43.27, 37.45, 36.63, 36.54, 30.83, 25.13, 23.41, 22.59, 22.00, 20.81, 20.62, 18.92, 17.96, 12.1.

MS : m/z 332 (M⁺, 12%), 317(40), 277(100).

Cholestan-6-one (257): Procedure followed as per described for **247**. The compound **253** (0.15g, 0.39 mmol) was dissolved in 20% TEA:EtOH (by volume, 20 ml), and irradiated at

300 nm for 6 h. Product was purified by silica gel column chromatography using pet.e-ther:acetone (92:8) as eluent, yield 80% (120 mg) and remaining ~8% starting material was isolated.

m.p. : 172-173°C.

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

^1H -NMR (90 MHz) : δ 0.6 (s, 3H, CH_3), 0.75 (s, 3H, CH_3), 0.9 (d, 9H, 3CH_3), 1.0-2.6 (m, 31H).

^{13}C -NMR (200 MHz) : δ 209.56, 56.3, 55.43, 54.99, 52.36, 45.35, 41.80, 39.96, 38.23, 36.89, 36.80, 36.07, 35.71, 34.86, 34.41, 26.71, 22.73, 22.55, 21.46, 21.22, 20.46, 17.39, 11.26, 10.75.

MS : m/z 386 (M^+ , 38%), 371(20), 149(100).

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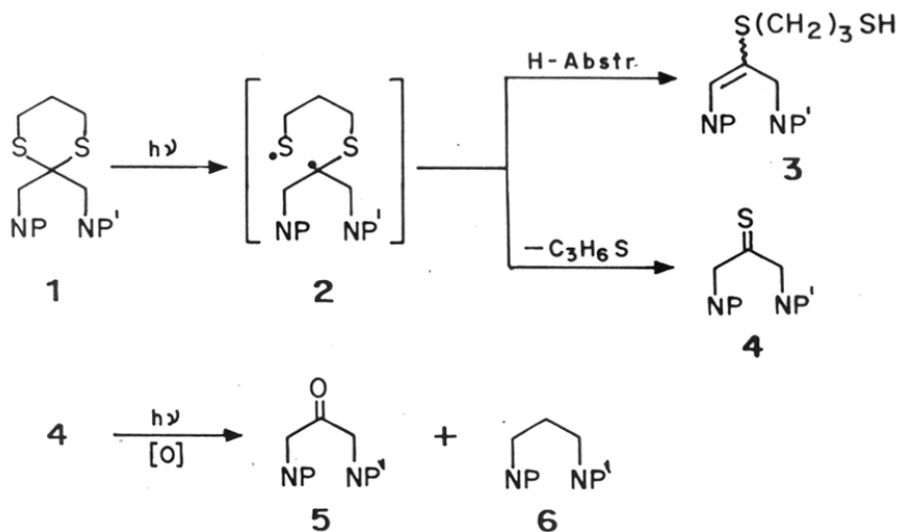
CHAPTER-II

STEREOELECTRONIC EFFECTS IN OXIDATION OF DITHIOLANES

INTRODUCTION

This chapter is an outgrowth of our interest in the mechanistic investigations of photochemistry and photoelectron transfer oxidation studies of 1,3-dithiolanes.¹ Some of the intermediates proposed could also be obtained by the reaction of singlet oxygen with dithiolanes. 1,3-Dithiolane constitutes an important functional group in organic chemistry, but its photochemistry remains underexplored. Broadly speaking, photolysis of 1,3-dithiolanes, in the absence of oxygen, lead to product(s) derived from initial C-S bond cleavage.^{2,3} The study showed the reluctance of 1,3-dithiolane to undergo photochemical change during irradiation under nitrogen atmosphere. Besides, in the literature, photodethioketalization of various 1,3-dithiolanes, in the presence of triplet sensitizers and molecular oxygen has been reported,⁴ for which no mechanistic suggestion was given.

Scheme -1

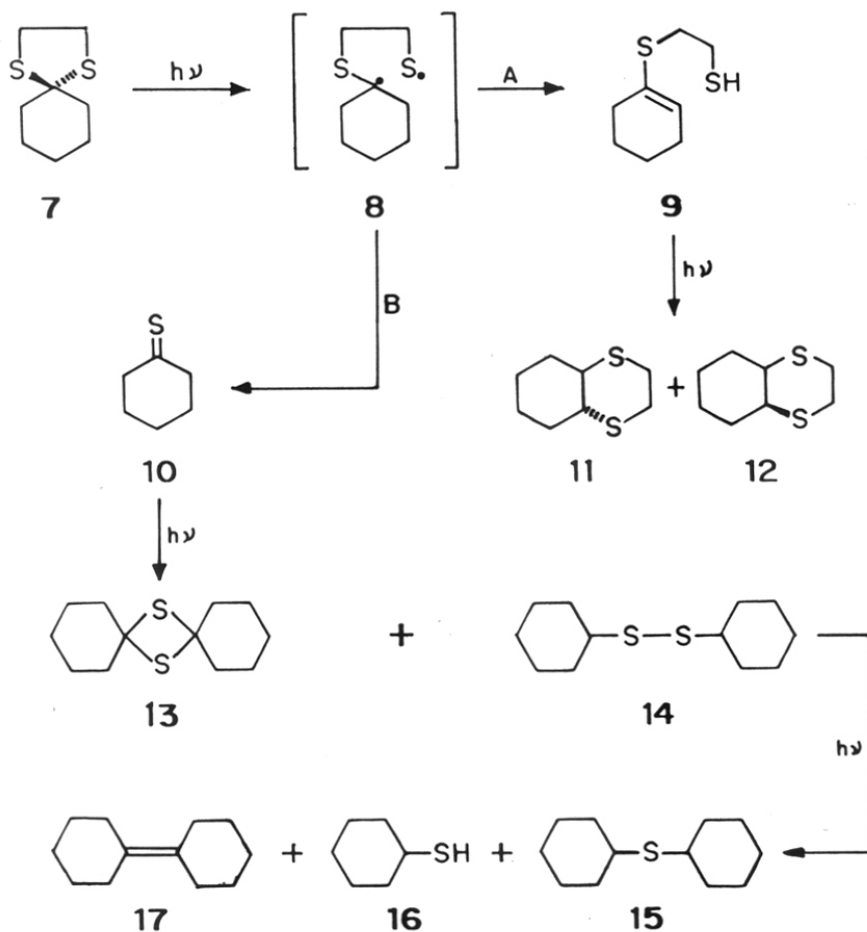


The C-S bond in the 1,3-dithiolane molecule is the weakest bond⁵ (70 Kcal/mole). Therefore, it is prone to cleave first on irradiation. Eaton et al.² have observed the breaking of C-S bond, leading to the biradical intermediate 2, during the photolysis of 2,2-bis(naphthylmethyl)-1,3-dithiolanes (Scheme-1). The biradical 2 has been shown to undergo

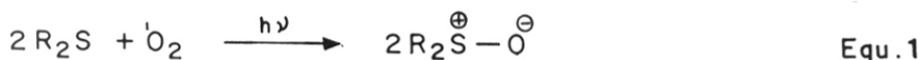
two reactions, resulting in the formation of either the olefin **3** or the thioketal **4**. Though the existence of thioketal **4** was not proved by isolation, the formation of products **5** and **6** clearly indicated the intermediacy of **4**.⁶

While studying the photochemistry of cyclic mercaptols eg. 1,3-dithiolane **7**, under various conditions, Berchtold et al.³ found the formation of various products eg. **9**, **10**, **11**, **12**, **13** and **14**, as shown in *Scheme-2*. The formation of various products can be rationalised *via* the cleavage of C-S bond, resulting in the formation of intermediate diradical **8** and an unstable species **10**.

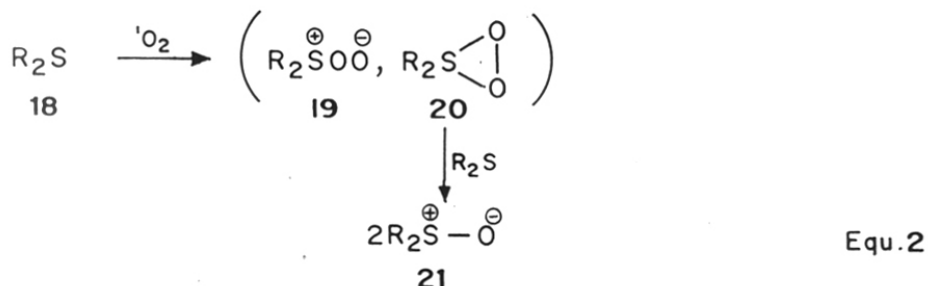
Scheme-2



Thus, the examples involving photochemistry of 1,3-dithiolanes, are scarce in literature. However, the photooxidation of dialkyl sulphides has been studied extensively, especially by Foote group.⁷ It has been shown that dialkyl sulphides undergo sensitized photooxidation to give sulfoxides in a smooth reaction^{8,9} (*Equation-1*).

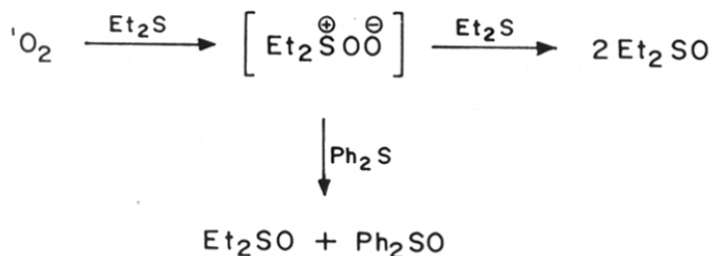


The mechanism of 1O_2 oxidation of diethylsulphide has been extensively studied by Foote et al.⁹ and is known to be highly dependent on solvent proticity and temperature. In protic solvent a single intermediate, Zwitterion (persulphoxide) **19**, has been proposed, whereas, the possibility of the involvement of two intermediates, persulphoxide **19** and cyclic sulphurane **20**, has been suggested in aprotic solvent, based on the kinetics of trapping experiments (*Equation-2*).¹⁰⁻¹³



Thus, when diphenylsulphide,¹⁰ which is unreactive towards singlet oxygen, was added to diethylsulphide 1O_2 photooxidation reaction mixture in methanol, considerable amount of diphenylsulphoxide was produced along with diethylsulphoxide, which is consistent, as shown in *Scheme-3*, with the reactive intermediate persulphoxide **19**.

Scheme-3



In the background of the above literature on photochemistry of 1,3-dithiolanes, we became curious about the nature of reactive species involved during photooxidation studies. Thus, photooxygenation of 1,3-dithiolanes was examined with singlet oxygen.

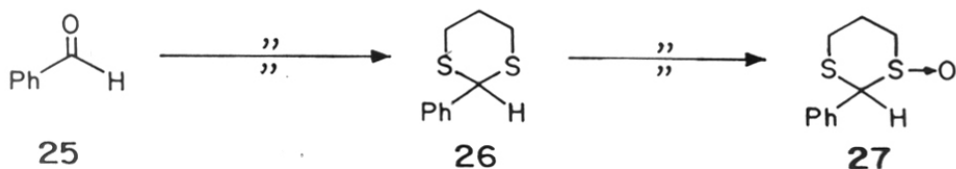
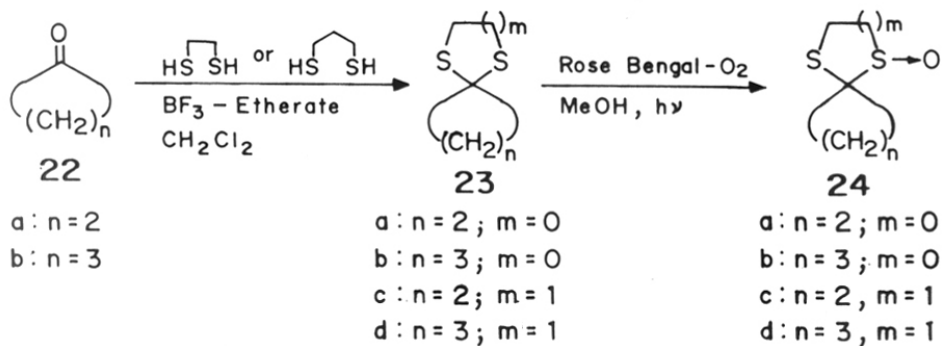
Also, our recent interest in hydroperoxide-type intermediates eg. (*Scheme-7*),¹ which could also be obtained by singlet oxidation of dithiolanes, prompted us to examine the reaction of $^1\text{O}_2$ with 1,3-dithiolanes. This study describes a synthetically useful methodology for the preparation of 1,3-dithiolane-1-oxides under neutral and mild conditions and concludes that $^1\text{O}_2$ is certainly not the species involved during Takahashi dethioketalization.⁴ Notice that one of the possibility for dethioketalization could be *via* reaction of singlet oxygen with the thioketone species e.g., **4** or **10** (*Scheme 1 & 2*).

RESULTS AND DISCUSSION

The various 1,3-dithiolanes **23a,b** and 1,3-dithianes **23c,d** and **26** (*Scheme-4*) were prepared from corresponding ketones or aldehydes by reaction with 1,3-propanedithiol or 1,2-ethanedithiol in the presence of BF_3 -etherate.¹⁴ Singlet oxidation was carried out in MeOH by O_2 bubbling and by using 350 nm lamp. Normally > 90% of dithiolane or dithiane was consumed during singlet oxidation, although the reaction was fast in the early stages of irradiation. Identical products were obtained with either Rose Bengal or Methylene Blue as sensitizers, ensuring the involvement of $^1\text{O}_2$. Although many variations in experimental conditions are possible as far as duration of irradiation, degree of O_2 -saturation/agitation, solvent variation and concentration of substrate and photosensitizer are concerned, the above reaction conditions furnished synthetically useful yields of 1,3-dithiolane-1-oxides and 1,3-dithiane-1-oxides, as shown in *Scheme-4*.

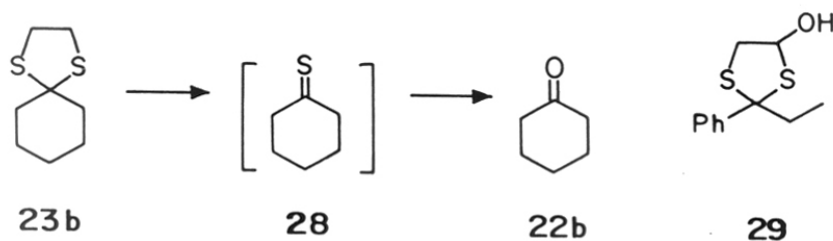
The 1,3-dithiolane and 1,3-dithiane oxides were characterised by satisfactory IR, ^1H -NMR and mass spectra. Characteristic features of the S-oxides in compound 2-phenyl-1,3-dithiane-1-oxide **27** are the strong absorption at 1040 cm^{-1} in IR spectrum, complex multiplets at δ 2.15-2.9 (m, 5H), 3.4-3.8 (m, 1H), 4.5 (s, 1H), 7.35 (m, 5H, Ar) in ^1H -NMR and in mass spectrum M^+ at 212 (100%). Similarly, in case of 1,4-dithiaspiro[4.4]nonane-1-oxide **24a** and 1,4-dithiaspiro[4.5]decane-1-oxide **24b**, characteristic features of the S-oxides are the strong absorption at 1040 cm^{-1} in IR spectrum

Scheme - 4



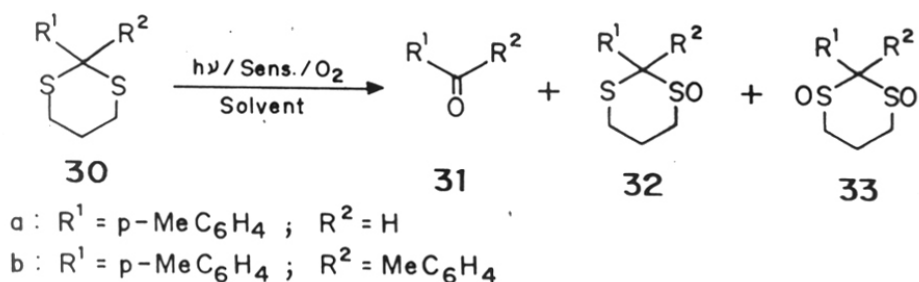
and complex multiplets between 1.6 and 3.8 δ in $^1\text{H-NMR}$ for the methylenes in dithiolane skeleton. Also, 1,5-dithiaspiro[5.4]decane-1-oxide **24c** and 1,5-dithiaspiro[5.5]undecane-1-oxide **24d** gave characteristic absorption band for S-oxide at 1040 cm^{-1} in IR spectrum. Proton-NMR of compound **24c** showed signals at δ 1.5-2.2(m, 7H), 2.2-2.9 (m, 5H), 2.95-3.15 (m, 2H) and mass spectrum gave M^+ at 190 (12%). Compound **24d** gave $^1\text{H-NMR}$ signals at δ 1.0-2.1 (m, 10H), 2.1-2.58 (m, 4H), 2.6-3.1 (m, 2H) and mass spectrum gave M^+ at 204 (20%). Interestingly, no di-S-oxides or sulphone was observed during singlet oxidation,¹⁵ and, surprisingly, no dethioketalization occurred either! Subsequently, we have examined the validity of 65% yield of **22b** from **23b** under reported experimental conditions with a 200W lamp⁴ (Scheme-5). However, we faced problems in reproducing these results and with repeated trials a maximum of only 10% dethioketalized product **22b** could be observed by GLC.

Scheme - 5



Recently, Masaki et.al reported photo-oxygenation reaction of 2-(*p*-methyl phenyl)-1,3-dithiane **30a** or 2,2-di(*p*-methylphenyl)-1,3-dithiane **30b** under various conditions and by use of the different photoelectron-transfer sensitizers such as 2,4,6-tri-(*p*-chlorophenyl) pyrylium perchlorate (TCPPCLO₄), 9,10-dicyanoanthracene (DCA), Methylene Blue (MB) and (meso-TPP). When **30a** was subjected to the photosensitized oxygenation reactions, *p*-methyl benzaldehyde **31**, 2-(*p*-methylphenyl)-1,3-dithiane-1-oxide **32a** and small amount of 2-(*p*-methylphenyl)1,3-dithiane-1,3-dioxide **33a** were also obtained (*Scheme-6*).

Scheme - 6

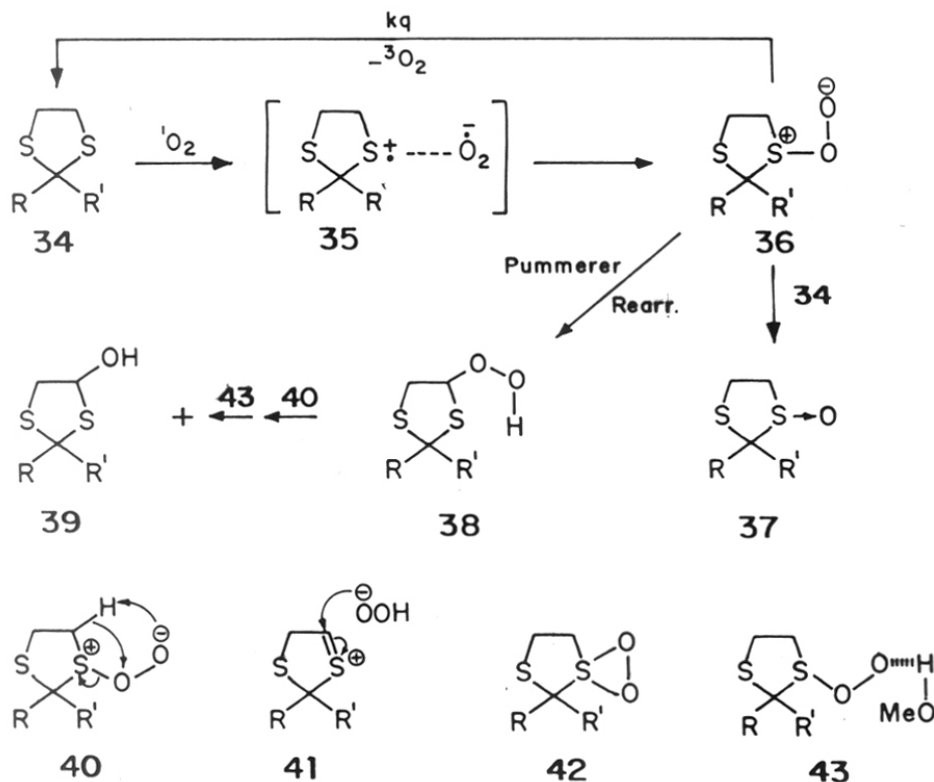


Another unusual observation during our studies was the isolation of OH insertion product **29**,¹⁶ besides 1,3-dithiolane-1-oxide during the singlet oxidation of 2-ethyl-2-phenyl-1,3-dithiolane **29** (*Scheme-5*). However, such OH-insertion products could not be observed with other substrates, even after repeated trials.

The tentative mechanism for this complex oxygenation process is shown in *Scheme-7*. Presumably, the formation of dithiolane S-oxides and OH insertion products both could be rationalized *via* peroxysulfoxide **36**, which could be formed either *via* a step-wise electron transfer process through a tight ion-pair **35** or *via* a concerted process.^{17,18} Based on detailed study by Foote et al.^{9,10} **36** could also be represented as thiadioxiranes **42** or H-bonded **43** with solvent MeOH. The reduction of **36/43** by **34** could result in the formation of S-oxides **37**. On the other hand, Pummerer rearrangement¹⁹ of **36** *via* concerted **40** or step-wise **41** could lead to **38**, which on further reduction with **34** could furnish OH insertion product

39.²⁰ The proposed mechanism explains the need for polar protic solvent (MeOH) and rationalizes the usually fast oxidation in the early stages of oxidation.

Scheme - 7



In conclusion, an efficient methodology for the synthesis of 1,3-dithiolane-S-oxide *via* singlet oxidation of 1,3-dithiolane has been described. With one of the dithiolanes, an interesting OH-insertion product **39** has been obtained. No dethioketalization occurred during singlet oxidation of dithiolanes. Thus, during Takahashi's dethioketalization (photolysis in the presence of O_2), singlet oxygen is certainly not involved.

In continuation, we have also examined the role of the size of reagent to ascertain whether stereoelectronic effect or steric effect is responsible for stereoselective oxidation of some of the optically active dithiolanes. It is commonly believed that the approach of oxidising agents e.g. NaIO_4 , *m*-CPBA, etc., which are fairly bulky, is directed due to steric

reasons and hence, asymmetric S-oxides are obtained. The argument is based on the conformational preferences for dithiolanes. The examination of its model revealed that oxidation (*Scheme-8*) should preferentially take place at S-1' **44b'** rather than S-3', since the molecule in its most stable conformation **44b'**, is sterically accessible to oxidation at S-1' rather than S-3', where approach of the reagent is inhibited due to the presence of C-2, C-1 and C-6 on the same side. Therefore, oxidation at S-1' takes place to give the more favoured equatorial sulfoxide.²¹ We were curious to know whether the above steric arguments are really true! Whether there could be any stereoelectronic reason for stereoselection. We argued that if bulky reagents are the reason for stereoselection, then with smaller oxidizing reagents such as singlet oxygen or radical cation/super oxide combination¹ developed in our earlier studies, one should get a mixture of diastereomers. Following studies explore some of these mechanistic curiosities. Thus, oxidation of optically pure dithiolane **44a** and **44b** (*Scheme-8*) with small reagents e.g. singlet oxygen and radical cation-superoxide coupling method,¹ was examined and product stereochemistry was compared with oxidations with bulky reagents e.g. NaIO₄, *m*-CPBA.²² These studies have relevance for various theories of stereoelectronic effect e.g. Cieplak effect,²³ nucleophilic-electrophilic surface theory,²⁴ etc. π -face selection during addition to trigonal carbon in olefins, carbonyls, enones, dienes, etc. or stereoselective additions (axial or equatorial) during S-oxide formation of dithiolanes are at the core of stereogenesis. While more obvious steric aspects of face selectivity was recognised early in 1952, popularly known as Cram's rule, the relevance of stereoelectronic effect was slow to come in organic chemistry. In due course, various theories of π -face stereoselection have come up in recent times. Most of these theories can be divided into two broad categories. The first group emphasizes the importance of ground state properties of starting materials, whereas the second group emphasizes the relevance of transition state properties. However, in these theories, the role of size of the reagent is rarely stressed especially, during oxidation of optically active dithiolanes, the stress on the bulkyness of the reagent is a popular reason. However, we have a suspicion for this type of explanation.

The preparation of dithiolanes **44a,b** and **46a,b** was accomplished by standard procedure from respective ketones. Singlet oxidation of dithiolanes gave optically pure S-oxides,

even with fairly small oxidizing reagents, which should not exhibit any steric bias. This clearly establishes the fact that the reason for stereoselection in spiro-optically active dithiolanes is not steric, but stereoelectronic in nature.

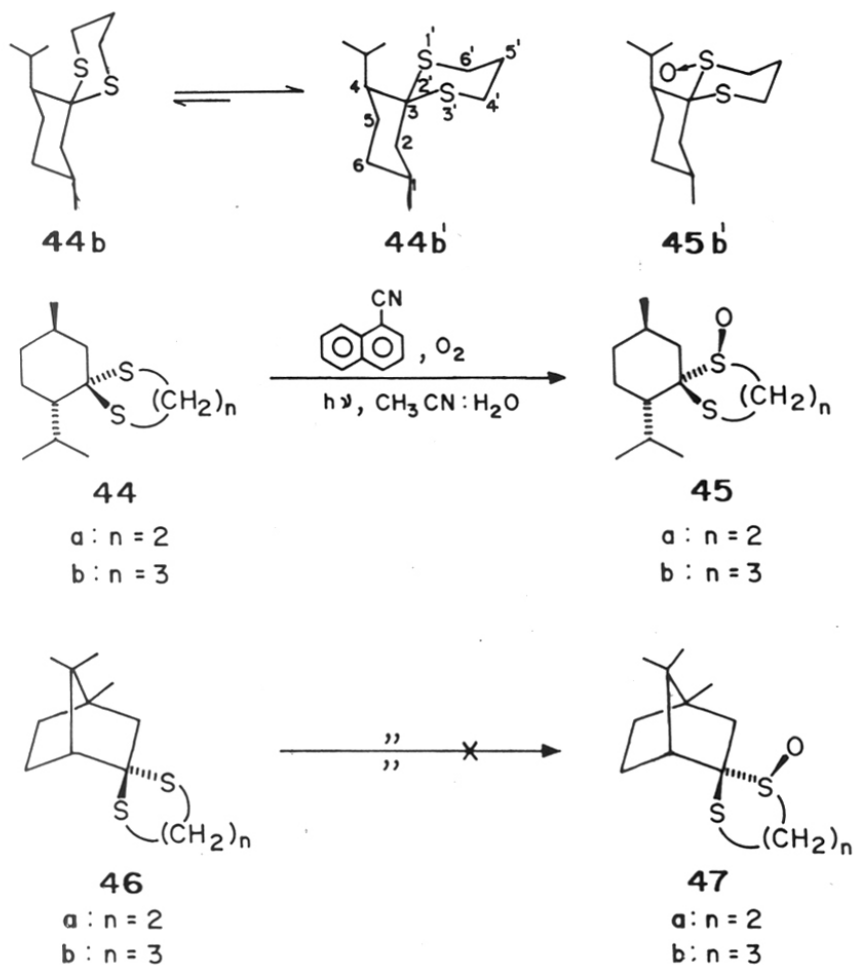
Additionally, the photochemistry of optically active spiro-dithiolanes was studied with another small reagent i.e. superoxide under electron transfer conditions, using 1-cyanonaphthalene (CNN) as photoelectron acceptor.¹ The photosensitized electron transfer oxidation was accomplished by irradiating the solution of 1,3-dithiolanes in the presence of 1-cyanonaphthalene in an oxygen saturated mixture of acetonitrile and water (3:1).

The dithiolanes of menthone **44a,b** and camphor **46a,b** were subjected to the same set of reactions of an electron transfer, as in *Scheme-5*. The spirothioketalized compounds **44a,b**, and **46a,b** were prepared by 1,2-ethanedithiol and 1,3-propanedithiol mediated by BF₃-etherate or an acid, as reported in 65-70% yield.²⁵ Compound 5-isopropyl- 8-methyl-1,4-dithiospiro (4,5) decane **44a** was oxidised by an electron transfer method (1-cyanonaphthalene-¹O₂) as per above procedure to give 65% yield of S-oxide **45a** and 8% of dethiolized menthone. The structure of compound **45a** was confirmed by spectral data and compared with authentic sample. Authentic sample of S-oxide was prepared by NaIO₄ (1.0 equ.) as per literature procedure.²² The spectroscopic and analytical data of compound **45a** matched perfectly with that of authentic compound (NaIO₄). The optical rotation of **45a** showed exclusively single regio- and stereo isomer [α]_D²⁵ - 13.70, similar to product obtained by NaIO₄. IR spectrum of **45a** gave the characteristic S-O stretching band at 1050 cm⁻¹, ¹H-NMR gave signals at δ 0.7-1.1 (m, 9H), 1.2-2.8 (m, 9H), 2.9-3.45 (m, 4H) and ¹³C-NMR at δ 86.54(s), 57.47(t), 52.19(t), 45.76(t), 34.66(d), 32.64(d), 31.55(d), 26.74(t), 26.09(t), 24.29(q), 22.41(q), 18.81(q).

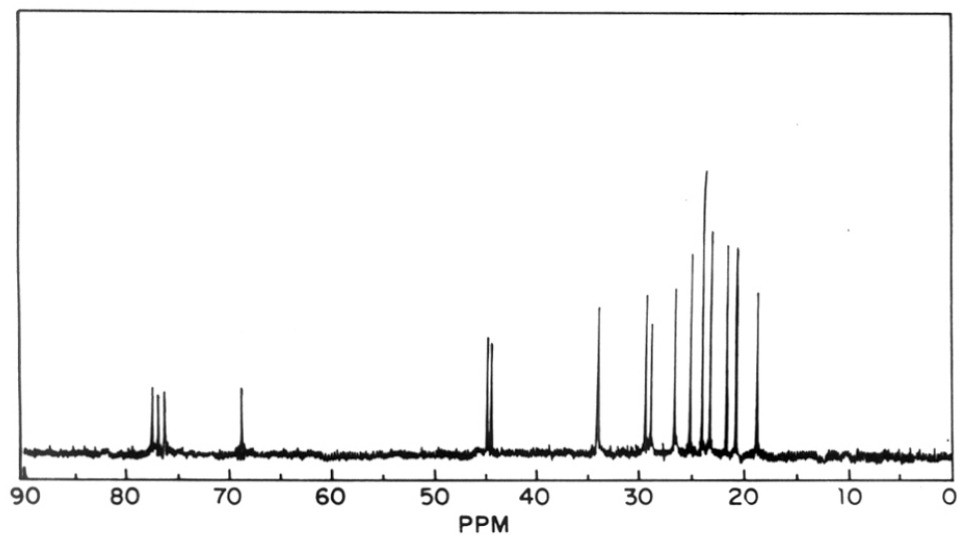
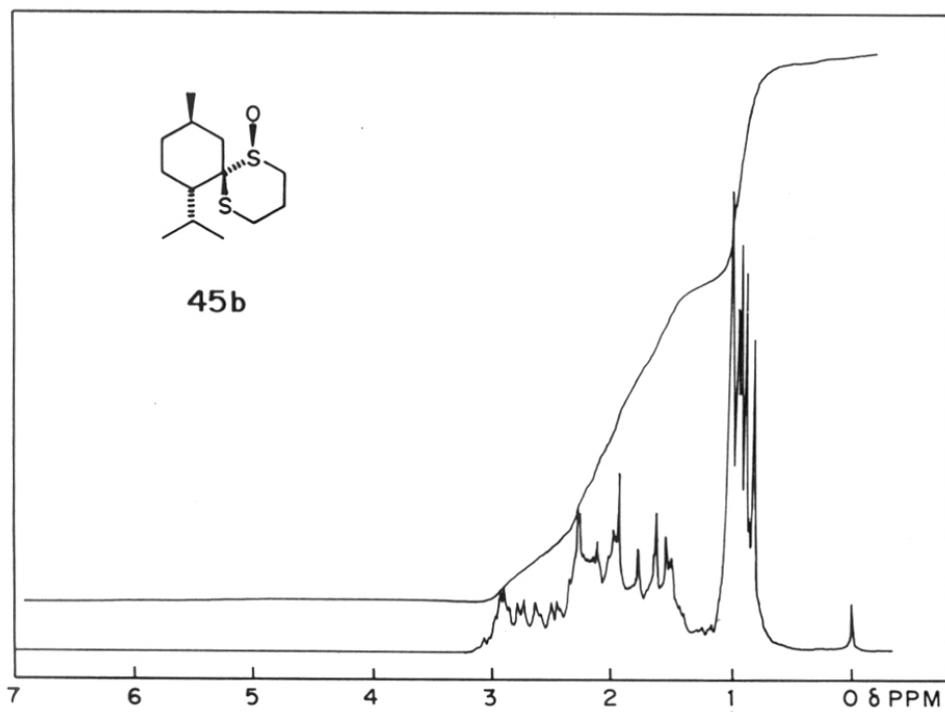
Dithiane **44b** on oxidation with 1-cyanonaphthalene in presence of oxygen (CH₃CN:H₂O) (electron transfer) and 1.0 equiv. of sodium metaperiodate (authentic) in methanol led, exclusively, to a single regio- and stereo-isomer **45b**. Compound spiro [menthane-3,2'-*m*-dithiane]-1'-oxide **45b** gave rotation [α]_D²⁵ : + 20.612, IR spectrum of which showed the characteristic S-O stretching band at 1040 cm⁻¹ and ¹H-NMR spectrum

demonstrated a downfield shift of the C-6' protons at $\delta \sim 3.0$ and ^{13}C -NMR at δ 68.87(s), 44.73(t), 44.34(t), 34.11(t), 29.53(d), 28.99(t), 26.72(d), 25.25(d), 24.05(t), 23.35(t), 21.80(q), 20.92(q), 18.83(q). Mass spectrum indicated M^+ at 260 (15%).

Scheme -8



Subsequently, we prepared dithiane of camphor, **46a,b**, which were subjected to oxidation with (1-CNN/ $^1\text{O}_2$ at 350, $\text{CH}_3\text{CN}:\text{H}_2\text{O}$) for 20 minutes, but it led to the polymeric product (white ppt.). Oxidation using sensitizer procedure (Rose Bengal- $^1\text{O}_2$, $\text{CH}_3\text{CN}:\text{H}_2\text{O}$)¹⁶ also failed to give the desired product. We concluded that camphor dithiane products under photolytic condition may not be stable.



CONCLUSIONS

1,3-Dithiolanes constitute an important functional group in organic chemistry. While studying the photochemical behaviour of this functional group, we developed two new routes for dithiolane S-oxide formation,^{1,16} both of which are neutral and mild reaction conditions. These methods should complement conventional oxidising methods like oxidation with peroxides (*m*-CPBA, NaIO₄).

The oxidation of optically active dithiolane clearly establishes the fact that the reason for stereoselection in optically active spiro-dithiolanes is not steric (earlier presumption), but stereoelectronic in nature. We presume that there are hidden stereoelectronic parameters *via* σ -bond interactions and their combinatorial effect, etc. for stereoselective oxidations.

EXPERIMENTAL

General procedure for protection of aldehyde and ketone by 1,2-Ethanedithiol or 1,3-Propanedithiol(I): A solution of aldehyde or ketone (10 mmol) in dichloromethane (15 ml) was stirred under protection of guard tube (CaCl_2) at room temperature. To the stirring solution, 1,2-ethanedithiol (15 mmol) or 1,3-propanedithiol (15 mmol) and catalytic amount of BF_3 -etherate were added successively. After following the progress of the reaction by TLC, dichloromethane layer was washed with dilute aqueous solution of potassium hydroxide (5%) (3x10 ml) to remove excess 1,2-ethanedithiol or 1,3-propanedithiol, followed by water washings (2x20 ml), solvent was dried over anhydrous Na_2SO_4 . Solvent was evaporated and thioketals were purified by silica gel column chromatography.

Following this procedure, the quantities (mol) of reactants used and the various thioketals prepared are given below:

1,4-Dithiaspiro [4.4] nonane (23a):

Cyclopentanone : 0.84g (10 mmol).

1,2-Ethanedithiol : 1.4g (15 mmol).

The crude product was purified by silica gel column chromatography using pet.ether as eluent (1.36g, 85%): (b.p. = $90^\circ\text{C}/5\text{mm}$, Lit. b.p.²⁶ = $89^\circ\text{C}/5\text{mm}$).

1,4-Dithiaspiro [4.5] decane (23b):

Cyclohexanone : 0.98g (10 mmol).

1,2-Ethanedithiol : 1.4g (15 mmol).

The crude product was purified by silica gel column chromatography using pet.ether as eluent (1.4g, 82%): (b.p. = $110^\circ\text{C}/5\text{mm}$, Lit. b.p.²⁶ = $107^\circ\text{C}/5\text{mm}$).

1,5-Dithiaspiro [5.4] decane (23c):

23c was prepared as per the procedure described for I.

b.p. : $100^\circ\text{C}/0.1\text{mm}$ (Lit.²⁶ $86-87^\circ\text{C}/0.05\text{mm}$).

$^1\text{H-NMR}$ (80 MHz) : δ 1.64-1.86 (m, 6H), 1.88-2.23 (m, 4H), 2.75-2.98 (m, 4H).

1,5-Dithiaspiro [5.5] undecane (23d):

23d was prepared as per the procedure described for **I** and the product was purified by chromatography (2% EtOAc:pet.ether) to afford 85% yield.

$^1\text{H-NMR}$ (80 MHz) : δ 1.52-1.88 (m, 8H), 1.89-2.19 (m, 4H), 2.75-3 (m, 4H).

2-Phenyl-1,3-dithiane (26):

m.p. : 73°C.

$^1\text{H-NMR}$ (90 MHz) : δ 1.64-2.34 (m, 2H), 2.73-3.38 (m, 4H), 5.15 (s, 1H), 7.15-7.6 (m, 5H).

Typical procedure for singlet oxygen oxidation of 2-substituted-1,3-dithiolanes to 1,3-dithiolane-1-oxides (II): The solution of 1,3-dithiolanes (1 mmol) in methanol with photosensitizer (either Rose Bengal or Methylene Blue) (0.5 mmol) in pyrex vessel was irradiated with 200W Hanovia lamp for 4-5 h. under continuous oxygen agitations. The ambient temperature was maintained at (+ 2°C) by continuous water circulation. The progress of the reaction was monitored by GLC. After the completion of reaction, solvent was concentrated and residue was purified by silica gel column chromatography to furnish 1,3-dithiolane-1-oxides.

1,4-Dithiaspiro [4.4] nonane-1-oxide (24a):

Yield : 80%.

b.p. : 118-120°C/0.05mm (Lit.²⁷ 122°C/0.05mm).

IR (Neat) : cm^{-1} 1040(s), 1250(m), 3000(m).

$^1\text{H-NMR}$ (80 MHz) : δ 1.8-2.0 (m, 7H), 2.6 (m, 1H), 3.1-3.8 (m, 4H).

MS : m/z 176 (M^+ , 42%), 159(10), 149(12), 77(54), 71(26), 67(100).

1,4-Dithiaspiro [4.5] decane-1-oxide (24b):

Yield : 75%.

m.p. : 87°C (Lit.²⁷ 83-85°C).

IR (Nujol) : cm^{-1} 1040(s), 1220(m).

$^1\text{H-NMR}$ (80 MHz) : δ 1.6-2.1 (m, 10H), 3.1-3.6 (m, 4H).

MS : m/z 190 (M^+ , 38%), 178(8), 153(16), 146(52), 114(24), 98(48), 81(92), 71(100), 55(73).

1,5-Dithiaspiro [5.4] decane-1-oxide (24c):

IR (CHCl_3) : cm^{-1} 2920(s), 1040(vs), 800(s).

$^1\text{H-NMR}$: δ 1.5-2.2 (m, 7H), 2.2-2.9 (m, 5H), 2.95-3.15 (m, 2H).

MS : m/z 190 (M^+ , 12%), 174(40), 121(70), 68(100).

1,5-Dithiaspiro [5.5] undecane-1-oxide (24d):

IR (CHCl_3) : cm^{-1} 2910(s), 1440(m), 1030(vs).

$^1\text{H-NMR}$ (80 MHz) : δ 1.0-2.1 (m, 10H), 2.1-2.58 (m, 4H), 2.6-3.1 (m, 2H).

MS : m/z 204 (M^+ , 20%), 188(18), 168(60), 153(55), 121(100).

2-Phenyl-1,3-dithiane-1-oxide (27):

m.p. : 141°C.

IR (CHCl_3) : cm^{-1} 2960(m), 1460(m), 1040(vs), 750(m), 695(w).

$^1\text{H-NMR}$ (80 MHz) : δ 2.15-2.9 (m, 5H), 3.4-3.8 (m, 1H), 4.5 (s, 1H), 7.35 (bs, 5H, Ar).

MS : m/z 212 (M^+ , 100%), 196(8), 163(32), 121(48), 90(70).

5-Isopropyl-8-methyl-1,4-dithiaspiro [4,5] decane (44a): 44a was prepared as per the procedure described for **I**. The product was eluted using 3% acetone in pet.ether during silica gel column chromatography.

$^1\text{H-NMR}$ (90 MHz) : δ 0.78-1.04 (m, 9H), 1.1-1.86 (m, 7H), 2.06-2.58 (m, 2H), 3.24 (s, 4H).

MS : m/z 230 (M^+ , 32%), 202(20), 102(100).

Spiro [Methane-3,2'-m-dithiane]/Menthone trimethylene mercaptole (44b): A mixture of 1.0g (6.49 mmol) of menthone and 0.70g (6.4g mmol) of 1,3-propanedithiol was cooled in an ice bath and a stream of hydrogen chloride was passed through the solution till the reaction was complete (~ 5 h.). Excess HCl was then removed in a vacuum desiccator over NaOH and the mixture was dissolved in ether, washed with 5% NaOH solution, water, brine and dried over Na_2SO_4 . After removal of ether, the residual oil was chromatographed (30% EtoAC-pet.ether) to give the pure **44b** as crystalline product in 70-75% yield.

m.p. : 41-42°C.

IR (CHCl₃) : cm⁻¹ 2980(m), 1450(m), 1400(s), 1230(m).

¹H-NMR (80 MHz) : δ 0.85-1.0 (3d, J=5.5Hz, 3CH₃), 1.0-2.2 (m, 9H), 2.3-3.4 (m, 6H).

MS : m/z 244 (M⁺, 23%), 201(11), 188(4), 170(17), 159(42), 137(30), 128(7), 114(9), 106(19), 95(31), 85(9), 81(34), 77(17), 67(23), 55(41), 43(75), 41(100).

Camphor ethylene mercaptole (46a): 46a was prepared as per the procedure described for 44b. The product was eluted using 3% acetone in pet.ether during silica gel column chromatography.

¹H-NMR (90 MHz) : δ 0.9 (s, 3H), 1.0 (s, 6H), 1.1-2.56 (m, 7H), 2.9-3.4 (m, 4H).

MS : m/z 228 (M⁺, 40%), 200(68), 185(10), 118(100).

Spiro [camphane-2,2'-dithiane]/camphor trimethylene mercaptole (46b): 46b was prepared as per the procedure described for 44b and the product was purified by chromatography using pet.ether:ethyl acetate (98:2) to afford 70-80% of the pure dithiane.

IR (CHCl₃) : cm⁻¹ 2980(s), 1480(w), 1460(m), 1400(s), 1225(s).

¹H-NMR (80 MHz) : δ 0.9 (s, 3H, CH₃), 1.1 (s, 3H, CH₃), 1.2 (s, 3H, CH₃), 1.3-2.4 (m, 7H), 2.5-3.4 (m, 6H).

MS : m/z 258 (M⁺, 67%), 240(6), 225(2), 167(35), 123(81), 93(94), 91(100).

Authentic (NaIO₄): Spiro [Menthane-3,2'-m-dithiane]-1'-oxide (45b): To a solution of 1.0g (4.098 mmol) of menthone trimethylene mercaptole 44b in 70 ml of MeOH was added dropwise, a solution of 0.96g (4.482 mmol) of NaIO₄ in 20 ml of water at -10°C. The mixture was maintained at this temperature with stirring until the reaction was complete (7-8 h.). Sodium iodate was then filtered off and methanol was removed in vacuo followed by the extraction of the aqueous phase with chloroform. The chloroform extract was washed with brine, worked up and chromatographed (40% EtOAc/PhH) to afford 0.90g (84%) of the pure white crystalline solid product.

Photochemical Route:

Spiro [Menthane-3,2'-m-dithiane]-1'-oxide (45b): The solution of menthone trimethylene mercaptole 800 mg (3.27 mmol) with 1-cyanonaphthalene (CNN) 250 mg (1.63 mmol) in an oxygen saturated mixture of $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (3:1, 187ml : 62ml) in a pyrex vessel was irradiated (Rayonet Photoreactor, 350 nm) for 12-15 h. Oxygen bubbling was repeated intermittently (every 90 min.) during photolysis. Progress of the reaction was monitored by TLC and GLC. Normally, 85-90% of reactants were consumed. Acetonitrile was removed under vacuum, water (20 ml) was added and the aqueous layer was extracted with dichloromethane (3x25 ml), washed with water (2x20 ml) and brine solution (2x20 ml). It was then dried over anhydrous sodium sulphate. Removal of solvent led to a residue which was purified by silica gel column chromatography using pet.ether:2% acetone first eluted menthone 10% and elution with pet.ether:10% acetone gave S-oxide **45b** in 70% yield (600 mg) even 4-6% starting material was also recovered.

m.p.	:	135-136°C (Lit. ²⁸ 135-137°C).
$[\alpha]_{\text{D}}^{25}$	:	+20.612 [C = 0.0049, CHCl_3] (Authentic NaIO_4). +20.477 [C = 0.0050, CHCl_3] (Photochemical).
IR (Nujol)	:	cm^{-1} 2980(s), 2880(m), 1470(s), 1040(vs).
$^1\text{H-NMR}$ (90 MHz)	:	δ 0.84 (d, J=6.5 Hz, CH_3), 0.86 (d, J=6.5 Hz, CH_3), 0.92 (d, J=6.5 Hz, CH_3), 2.4-3.4 (m, 24H).
$^{13}\text{C-NMR}$ (200 MHz)	:	δ 68.87(s), 44.73(t), 44.34(t), 34.11(t), 29.53(d), 28.99(t), 26.72(d), 25.25(d), 24.05(t), 23.35(t), 21.80(q), 20.92(q), 18.83(q).
MS	:	m/z 260 (M^+ , 15%), 244(6), 137(23), 123(100), 95(56), 81(58).
Analysis	:	$\text{C}_{13}\text{H}_{24}\text{S}_2\text{O}$: Calculated : C, 60; H, 9.23; S, 24.61. Found : C, 59.80; H, 9.15; S, 24.40.

Electron transfer method (45a):

5-Isopropyl-8-methyl-1,4-dithiaspiro (4,5)decane	:	500 mg (2.03 mmol).
Cyanonaphthalene	:	166 mg (1.13 mmol).

45a was prepared as per the procedure described for **45b**. The product was purified by column chromatography. The use of pet.ether:acetone (98:2) yielded menthone (8%), pet.ether:acetone (93:7) gave 350 mg of S-oxide (65%) and starting material recovered was (5%).

Yield	:	78% (250 mg).
m.p.	:	85°C.
$[\alpha]_D^{25}$	:	-13.70 (C = 0.026, CHCl ₃) (Authentic NaIO ₄). -13.682 (C = 0.0265, CHCl ₃) (Photochemical).
IR (Nujol)	:	cm ⁻¹ 2980(s), 2860(m), 1470(s), 1050(vs).
¹ H-NMR (90 MHz)	:	δ 0.7-1.1 (m, 9H), 1.2-2.8 (m, 9H), 2.9-3.45 (m, 4H).
¹³ C-NMR (200 MHz)	:	δ 86.54(s), 57.47(t), 52.19(t), 45.76(t), 34.66(d), 32.64(d), 31.55(d), 26.74(t), 26.09(t), 24.29(q), 22.41(q), 18.81(q).
MS	:	m/z 246 (M ⁺ , 27%), 228(10), 137(100), 95(37), 81(35).
Analysis	:	C ₁₂ H ₂₂ S ₂ O: Calculated : C, 58.53; H, 8.94; S, 26.01. Found : C, 58.41; H, 8.73; S, 25.78.

Spiro [Camphane-2,2'-m-dithiane]-1'-oxide (47b): To a solution of 1.0 mmol of dithiane **46b** in 15 ml of methanol was added dropwise a solution of NaIO₄ (1.0 mmol) in 5 ml water at -10°C. The mixture was maintained at -10°C with stirring until the completion of reaction (7-8 h.). Sodium iodate was then filtered off and methanol was removed in vacuo (< 40°C). The residue was extracted with chloroform 3-4 times, the extracts were combined, worked up and chromatographed (60% EtOAc-hexane) to afford 70-80% of the pure sulfoxide **47b**.

m.p.	:	107-109°C.
$[[\alpha]_D^{25}]$	:	+ 132.4 [C = 1.0, CHCl ₃].
IR (CHCl ₃)	:	cm ⁻¹ 1030.
¹ H-NMR	:	δ 0.75 (s, 3H, CH ₃), 0.88 (s, 3H, CH ₃), 0.94 (s, 3H, CH ₃), 1.2-3 (m, 7H), 3.0-3.9 (m, 6H).
MS	:	m/z 258 (M ⁺ , 5%), 239(7), 183(12), 107(67), 91(100).

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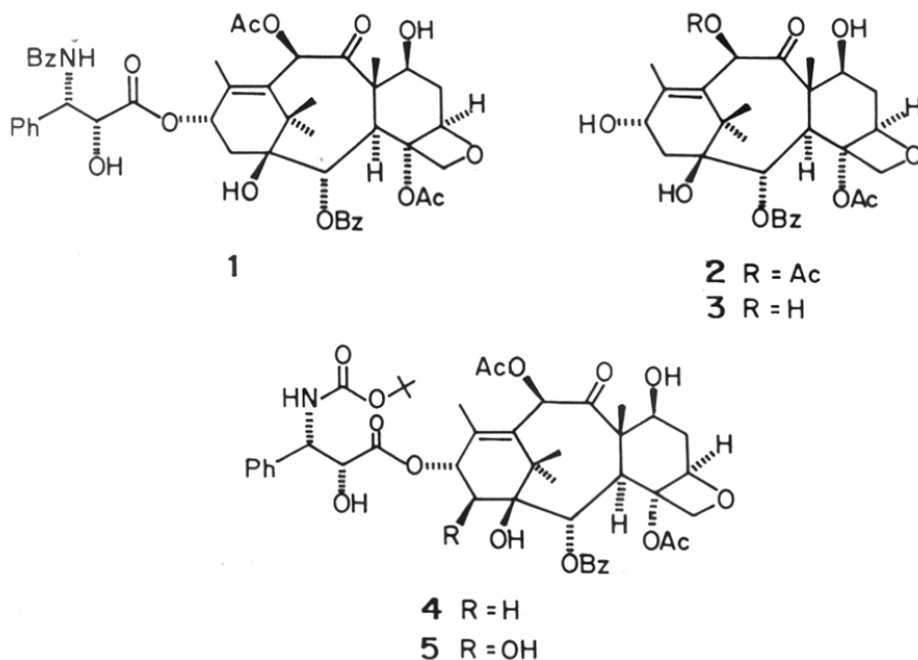
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CHAPTER-III

SYNTHETIC STUDIES TOWARDS CARBOCYCLIC FRAME OF TAXOL

INTRODUCTION

Organic molecules are the raw materials from which the principles of all-life-is delineated. The investigations into the chemistry of natural products are always fascinating because of several factors such as their biological significance and complex structures as challenging synthetic targets, etc. and many of the natural products have commercial significance as well, as drugs or agrochemicals. Prominent category of this class includes alkaloids, steroids, and terpenes, etc. The antitumour taxoids are a group of highly functionalized diterpenes, isolated from the genus *Taxus Taxacea* family. Among these, taxol **1**, an important anti-cancer drug that is demonstrating encouraging activity in human malignancies and has come to the central stage as an anti-cancer chemotherapeutic lead compound. Taxol was initially isolated¹ by Wani and co-workers in 1971 from the bark extract of the pacific yew tree, *Taxus brevifolia*. Later from the bark extract of European yew tree, baccatin III **2** with varying substituents at C-7, C-10 and/or C-13 were isolated and also from the leaves, deacetyl baccatin III **3**, a semisynthetic precursor for Taxol and Taxotere **4** was isolated.



Taxol has got special significance due to successful clinical trials for the treatment of breast, head, neck and ovarian cancers.² Unlike many other antitumor agents e.g., adriamycin, daunomycin, *cis*-platin, etc., which work as inhibitors of nucleic acid synthesis by intercalating with DNA grooves, taxol has a unique mode of action at cell division level. From its discovery until Horwitz's³ observation, no one had a clue about its mechanism of action. It enhances the polymerization of tubulin to stable microtubules and also interacts with microtubules, stabilizing them against depolymerization by cold and CaCl_2 and its ability to polymerize tubulin in the absence of any co-factors is unusual property of taxol.⁴

Taxol blocks the mitotic phase of the cell cycle and such cells are unable to replicate normally. The drug binds to cells in a specific and saturable manner with a single set of high affinity binding sites. Binding of taxol to tubulin site is quite sensitive to the conformation of the C-13 side chain and to the presence of two distinct domains. Thus, hydrophilic area includes the oxygenated functions at C-7, C-9 and C-10 and hydrophobic area involves the benzoate group at C_2 of the skeleton and amide or carbonate group at C-3' of side chain. In the binding process to tubulin, the polar area is located close to aqueous medium, whereas hydrophobic part is in direct interaction with tubulin in the core of the protein. The phenyl and hydroxyl group at carbons 3' and 2' could stabilize the drug-protein complex through direct interaction with aromatic and polar substituents of peptide residue. Drug malignancies and its development is often a factor in the success or failure of cancer chemotherapy. Taxol induces multi-drug resistance due to its hydrophobic nature and natural origin.

Horwitz^{3,4} demonstrated that taxol catalyzes rapid microtubule formation, stabilizing them against depolymerization. This gives the drug two tumour fighting mechanisms. First taxol freezes the mitotic spindle, preventing the depolymerization that pulls the chromosomes into the two halves of the rapidly dividing tumour cells. This suspends the cell at G-2 or M-phase ultimately killing it. Secondly, it inhibits cell migration i.e., prevention of the spreading of metastatic cancer cells. Taxol's hydrophobic structure suggests that it enters the cell by passive diffusion. Based on the present clinical trials, taxol constitute one of the most important discovery in the area of cancer chemotherapy. Their novel mechanism of action placed them among the spindle poisons.

Taxol is a highly challenging complex synthetic target. There are many aspects of Taxol synthesis e.g., OH at C-1 bridgehead position, bridgehead double bond, 8-membered carbocyclic frame, bicyclic frame [5.3.1] system and C-13 ester, etc. Although many approaches have been published towards partial synthesis of Taxol or its related skeletons, recently two elegant total synthesis of Taxol has come from Nicolaou⁵ and Holton⁶ groups.

Best Taxol is yet to come!

Similar to the history of drug development/improvement process in the area of β -lactam, quinolone, steroids etc., it is commonly believed that nature provides only the lead structures. However, for optimization of biological activity with high selectivity and efficiency, one has to prepare many analogues. Usually, analogues have found to have superior activity than natural compound. Similar is bound to be the case with Taxol as well. In fact, a beginning is already made with the discovery of taxotere, a small variation in the side chain of C-13 ester, which is shown to be more active *in vitro* and *in vivo* than taxol^{3,4}. Besides, recent studies from Kingston⁷ and Farina et.al⁸ show that C-7 and C-10 functionalization are not relevant for biological activity of taxols.

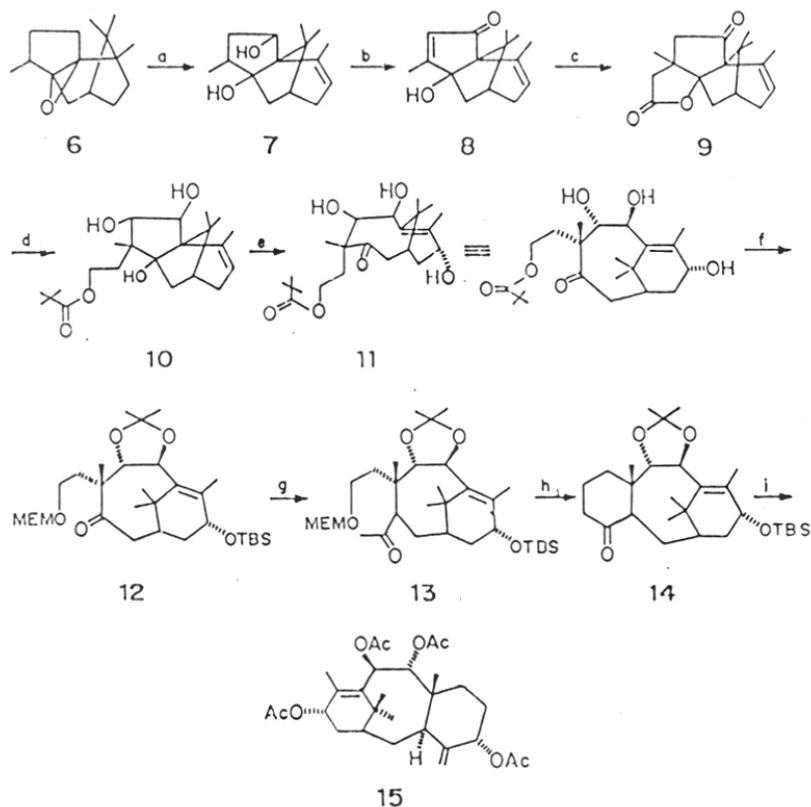
Recently, Swindell⁹ and Boa¹⁰ have reviewed the synthetic efforts towards taxanes. A brief outline of these efforts will be provided here. The synthetic strategies on taxane skeleton can be broadly classified into non Diels-Alder approaches and Diels-Alder approaches. The crucial steps involved in these approaches are mainly pinacol coupling, Claisen rearrangement, radical cyclization and 2+2 cycloaddition followed by fragmentation etc. We have concentrated on literature related to Lewis induced fragmentation approaches, as these fall under the purview of our strategy as well.

Holton's taxausin synthesis (*J. Am. Chem. Soc.*, 1988).¹¹

Synthesis of taxausin **15** begins with (-)- β -patchoulene oxide **6**. Base induced opening followed by epoxidation, exposure to Lewis acid and protic acid led to **7**. An oxidation, selenation and deselenation sequence led to **8**. *O*-alkylation of **8** and the subsequent radical cyclization and oxidation afforded **9**. Hydroxylation, reduction, protection and epoxidation provided the desired key intermediate **10**, which underwent fragmentation to **11** containing AB ring of taxausin. Protection of the hydroxyl group, saponification of pivalate ester and

MOM protection gave **12**. Addition of vinyl lithium followed by acid treatment and deoxygenation gave **13**. The completion of C-ring proceeded from **13** and begins with cleavage of MEM ether to give corresponding acetate. Saponification of the acetate and tosylation of primary hydroxyl group allowed ring closure to occur through base treatment. Finally, α -hydroxylation, deprotection and acetylation followed by Wittig olefination gave **15**.

Scheme-1



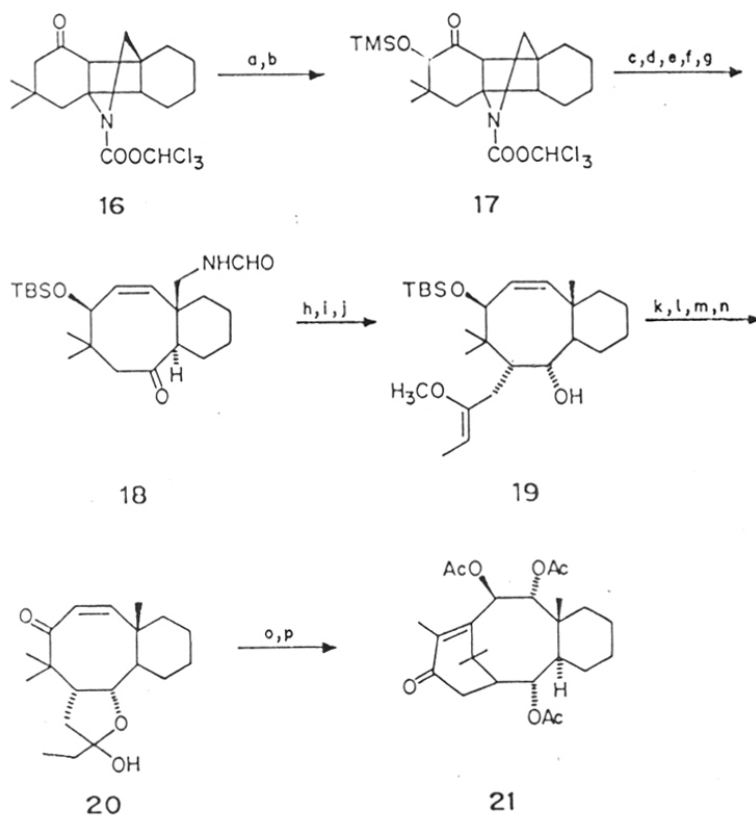
Reagents:

- a) (1) $t\text{BuLi}$ (2) $\text{Ti}(\text{OiPr})_4$, TBHP (3) $\text{BF}_3 \cdot \text{OEt}_2$; b) (1) PDC (2) LDA/TMS-Cl (3) PhSeCl (4) H_2O_2 ; c) (1) $\text{BrCH}_2\text{CH}(\text{Br})\text{OCH}_3$ (2) TBTH, AIBN (3) Jones; d) (1) LDA/TMS-Cl (2) $\text{CH}_3\text{CO}_3\text{H}$ (3) Red-Al (4) $t\text{BuCOCl}/\text{Py}$ (5) $\text{CH}_3\text{CO}_3\text{H}$; e) $\text{Ti}(\text{OiPr})_4$; f) (1) DMP/TsOH (2) TBSOTf/Py (3) $\text{K}_2\text{CO}_3/\text{MeOH}$ (4) MEM-Cl, DIPEA; g) (1) $\text{CH}_2=\text{C}(\text{OCH}_3)\text{Li}$ (2) $\text{AcOH}/\text{H}_2\text{O}/\text{THF}$ (3) SmI_2 ; h) (1) $\text{FeCl}_3/\text{Ac}_2\text{O}$ (2) NaOMe/MeOH (3) $\text{Ts}_2\text{O}/\text{Py}$ (4) $t\text{BuONa}/\text{THF}$; i) (1) LDA/TMS-Cl (2) m-CPBA (3) $\text{Bu}_4\text{N}^+\text{F}^-$ (4) $\text{HCl}/\text{H}_2\text{O}/\text{THF}$ (5) Acetylation (6) $\text{CH}_2=\text{PPh}_3$

Swindell (*J. Org. Chem.*, 1990)¹².

Swindell used intramolecular [2+2] photocycloaddition strategy to join the B and C ring and fragmentation chemistry to complete the formation of eight membered ring with required functionality to incorporate A ring, as shown in *Scheme-2*. The standard fragmentation protocol gave **18** from **17**. Alkylation, isonitrile formation and dissolving metal reduction produced **19**. A three-step deprotection sequence followed by oxidation gave **20**. Epoxidation followed by relevant annulation on **20** led to **21**.

Scheme-2



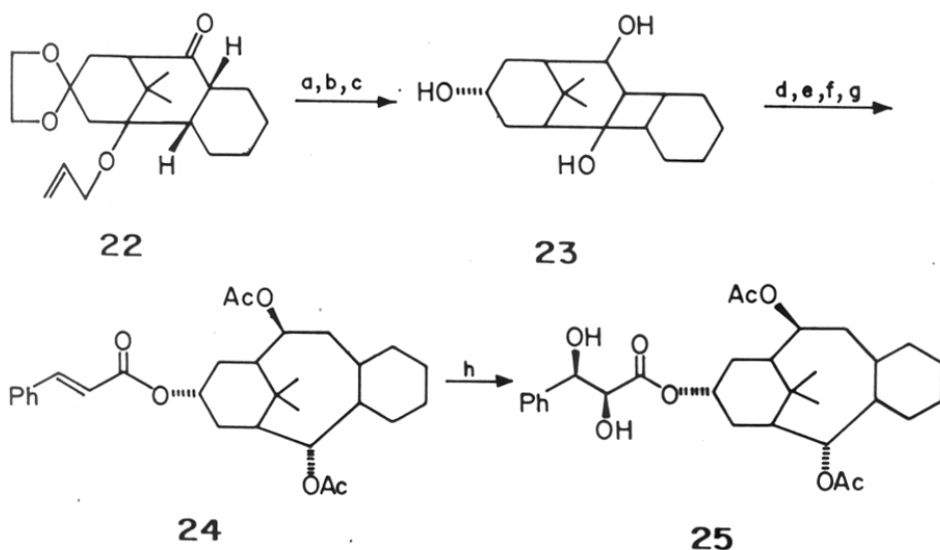
Reagents :

- a) TBSOTf / TEA b) m-CPBA c) K-selectride d) MsCl / TEA
 e) Zn f) AcOH, H₂O g) AcOCHO / Py h) CH₃CH=C(OMe)CH₂I
 i) MsCl / Py j) Na / NH₃ / NH₄Cl k) Bu₄N⁺F⁻ l) AcOH / H₂O
 m) HCl / H₂O n) MnO₂ o) TBHP / Triton-B p) DBU, Ac₂O / LiCl, THF.

Blechert (*Angew. Chem. Int. Ed. Engl.*, 1991).¹³

AB ring functionalized taxane model with a side chain on the hydroxyl group at C-13 was achieved by Blechert (*Scheme-3*). Compound **22** was converted into **23** by deallylation, ketal cleavage and reduction. A four step sequence which involves fragmentation, esterification, reduction and acetylation led to **24**, which gave **25** after *cis* hydroxylation. However, lack of functionalities on C ring and absence of one methyl group on A ring are the drawbacks in this synthetic strategy.

Scheme - 3

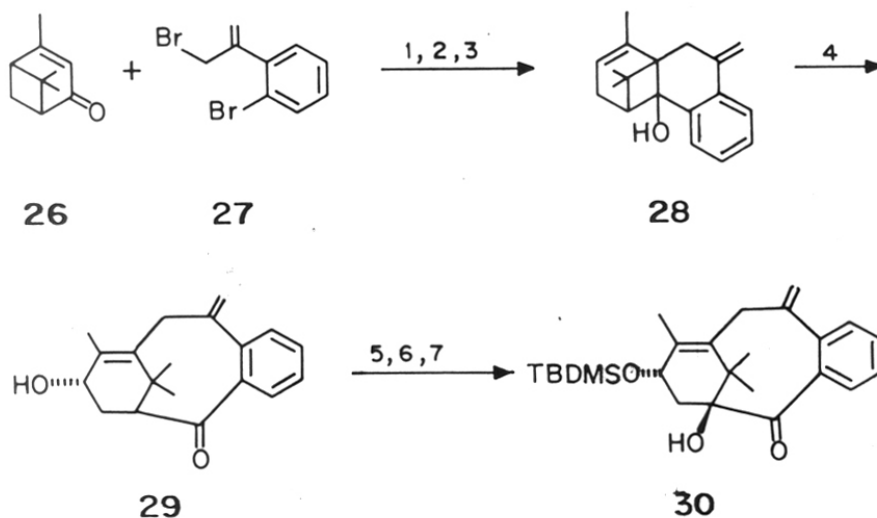


Reagents: a) Pd^0 , THF, morpholine b) THF: 2N HCl (1:1)
c) K-selectride d) $t\text{BuOK}$ / $t\text{BuOH}$, 70°C , 2h
e) Cinnamic acid, DCC, DMAP, Ph-CH_3 f) NaBH_4 , citric acid, MeOH
g) Ac_2O , Py, DMAP h) OsO_4 , NMO, Pyridine

Wender (*J. Am. Chem. Soc.*, 1992).¹⁴

A highly functionalized taxol skeleton with C ring as aromatic, which in turn can be extended to taxol and its congeners, has been developed by Wender's¹⁴ group through pinene pathway. Advantages of this approach is properly placed functionalities and required stereochemistry, as shown in *Scheme-4*.

Scheme-4



Reagents :

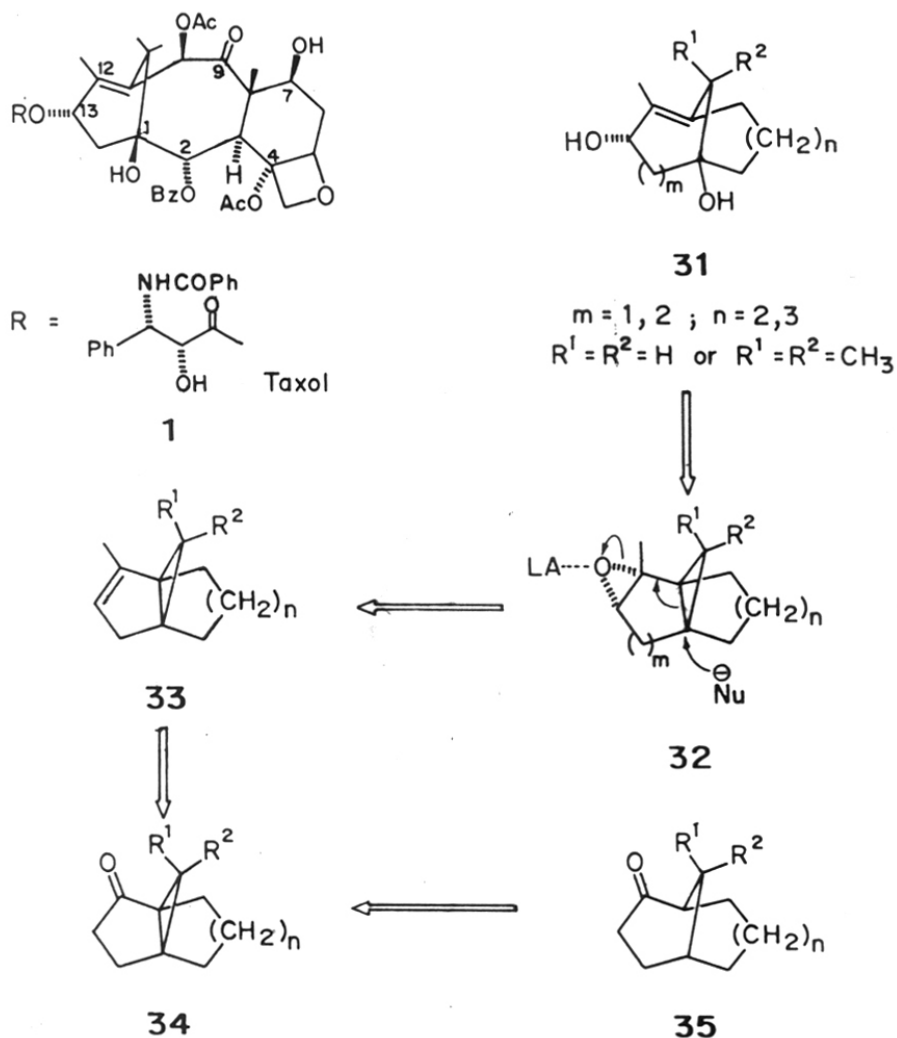
- 1) Bu^tOK ; 2) $h\nu$; 3) Bu^tLi , TMEDA ; 4) (a) $\text{Ti}(\text{O}i\text{Pr})_4$, Bu^tOOH ,
 (b) DABCO, heat ; 5) $\text{Bu}^t\text{Me}_2\text{SiCl}$, Imidazole ; 6) KO^tBu , O_2 , 60°C ;
 7) Na-EtOH

OUR APPROACH

In the background of above Lewis acid induced fragmentation related literature and as a continuation of our involvement with the cleavage of central bond in cyclopropyl ketone chemistry¹⁵ in *Chapter-1 (Section-D)*, we planned three strategies towards model carbocyclic frames of A, B ring of Taxol. The first strategy involved cleavage of central bond of cyclopropyl epoxide e.g., **32** (retro analysis, shown in *Scheme-5*) by a combination of push-pull chemistry with a variety of reagents e.g. activation by Lewis acid, followed by attack by a suitable nucleophile^{16,17} to create skeletons like **31** (*Scheme-5*). Naturally, this strategy should provide appropriately functionalized C-1 with -OH, with bridge head double bond at $\text{C}_{11}\text{-C}_{12}$ and $\alpha\text{-OH}$ at C_{13} and with a possibility of functionalization at the bridge either with dimethyl or H, Me, Cl, Br, CO_2H , etc. (numbering of the skeleton is based on the Taxol numbering in **1**). This strategy offers an opportunity for variation with $m=1,2$ and $n=2,3$ and their permutation-combination. The retrosynthesis for the cyclopropyl epoxide

37 and 41 or, reductive cleavage either by Zn-AcOH²¹ or by photoinduced electron transfer (PET)¹⁵ to give model carbocyclic frame of Taxol like 39 and 40 (Scheme-6).

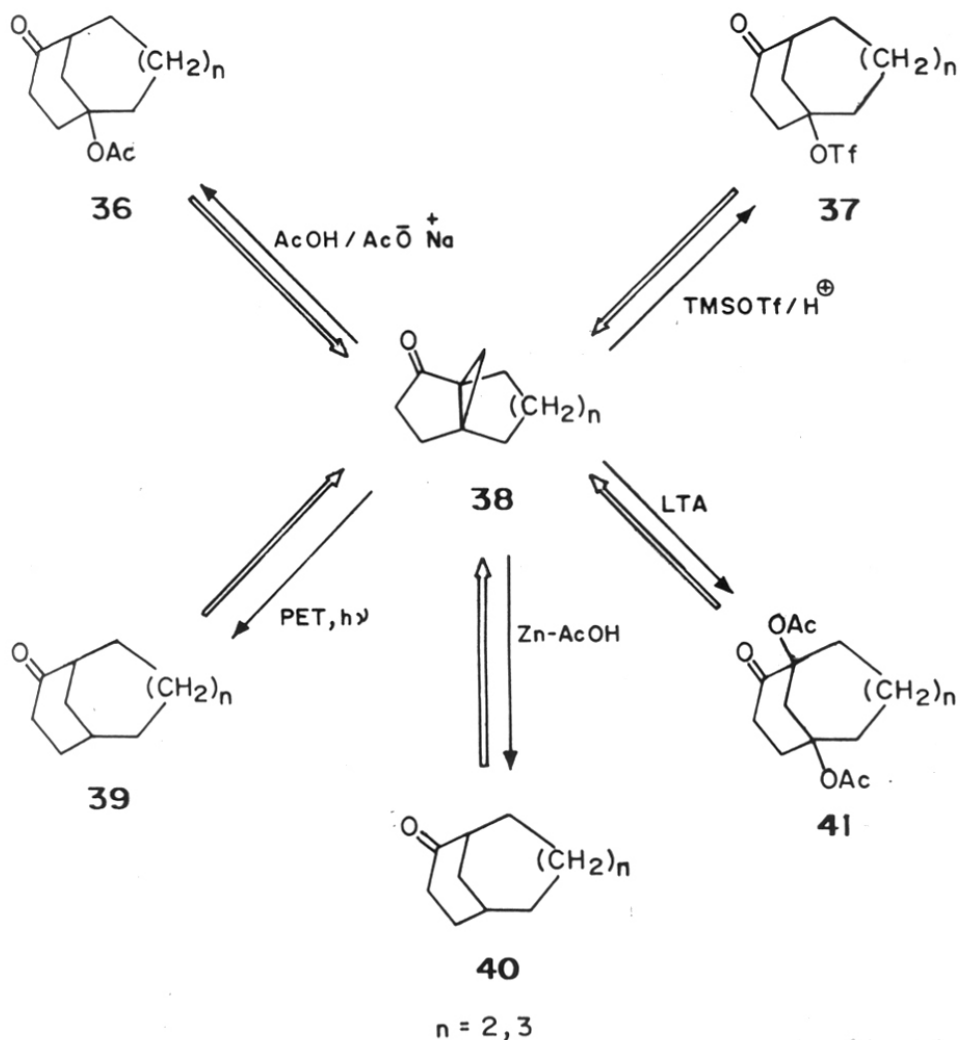
Scheme - 5



Third strategy is an outgrowth of our deep involvement with the bicyclic systems (Chapter-I) and the realization that the possibility of cleaving central bond in the easily

32 with $m=1$ is shown in *Scheme-5*. Thus, stereoselective epoxidation of **33** is possible with *m*-CPBA, due to steric reasons, whereas **33** itself could be synthesized from **34** by treatment with MeLi and subsequent dehydration.

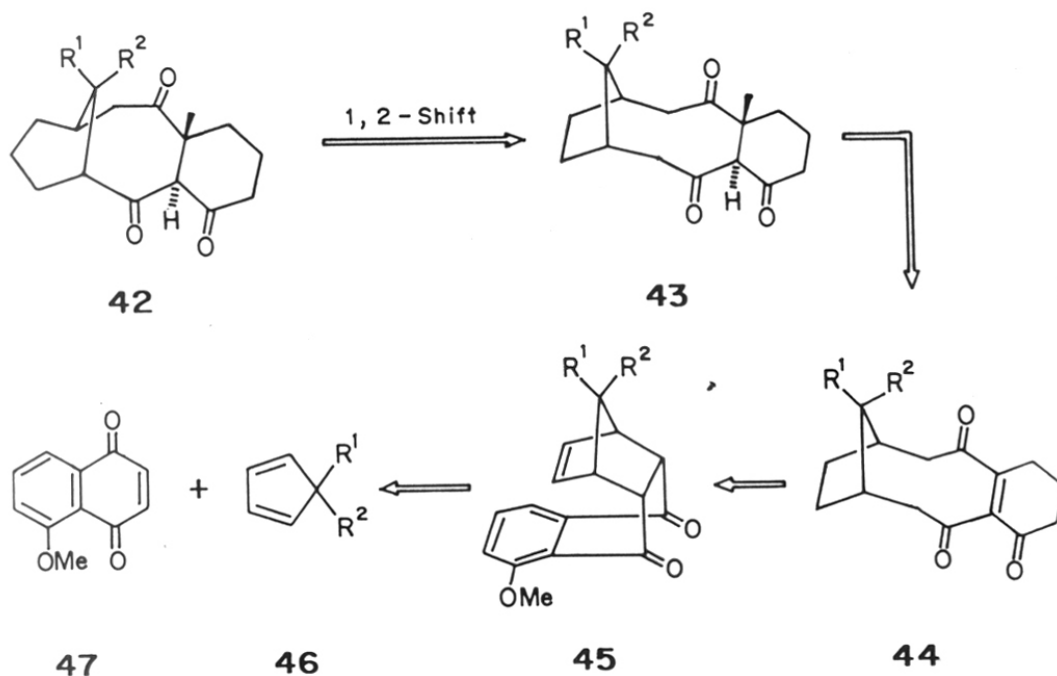
Scheme-6



Second strategy involves central cyclopropyl bond cleavage in $[n.3.1]$ propellane (*Scheme-6*), such as electrophile-assisted nucleophilic addition e.g., TMSOTf,¹⁸ LTA¹⁹ and AcOH-NaOAc²⁰, which will be appropriately functionalized at C-1 position as shown in **36**,

obtainable bicyclic system **43** (Scheme-7) by electron transfer processes, in which we have considerable experience and expertise.^{15,22} Subsequent 1,2-shift (Wagner-Meerwein type) can give advanced model of Taxol **42**.

Scheme - 7



$R^1, R^2 = \text{Alkyl, TMS}$

Some of our arguments for the proposed cleavage of cyclopropyl central bond in our new and novel strategy are given below:

Selective ring opening of activated cyclopropanes, cyclobutanes and pentanoid systems are useful tools in organic synthesis. It readily offers access to intermediates with a high degree of functionalization and with efficient stereo- and regioselection. In recent years, the synthetic potential of small rings in general^{16,23} has been increasingly exploited. Cyclopropane derivatives in particular have found widely useful applications. A severe limitation is the lack of selective general methods for cyclopropyl ring openings. However, a few applications of this reaction have been successfully exploited in the literature, as shown

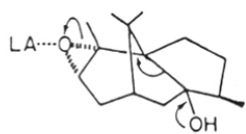
in *Scheme-8* and 9. We have also shown some of the risk factors involved with our strategy. Although some rearrangement possibilities are reported with [m.n.2] propellanes (*Scheme-10*), no such possibilities are known with [m.n.1] propallenes.

Recently, Holton et.al.¹¹ have reported fragmentation of epoxides **48** and **50** in the presence of $\text{Ti}(\text{i-PrO})_4$ to give corresponding products like **49** and **51** (*Scheme-8*). Similarly, Paul Wender¹⁴ has reported fragmentation of cyclobutyl epoxide **52** in the presence of Lewis acid and DABCO to give ring expansion compound **53**, which gave properly placed functionalities and required stereochemistry, as shown in *Scheme-8*.

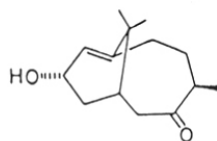
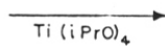
Demuth et al.¹⁸ investigated cleavage of cyclopropyl bond in tricyclic ketone **54** in the presence of $\text{AcO-Ms/Me}_4\text{N}^+\text{X}^-$ to give bicyclic compound **55** (*Scheme-8*). Similarly bicyclo [3.1.0] hex-2-one **56** in the presence of $\text{BF}_3\cdot\text{Et}_2\text{O}/\text{Ac}_2\text{O}$ gave central bond cleavage product **57**.²⁴ Solvolysis of **58** in the presence of *p*-toluenesulfonic acid in aqueous dioxane at 55°C afforded Vitamin-D₃²⁵ **59** and its *trans* isomer (*Scheme-8*). Note that this reaction also involves stereospecific and chemoselective cleavage of cyclopropane bond.

Some of the [m.n.1] propellanes, whose central bond cleavages are documented in the literature e.g., **60**, **62**, **64** and **66** are shown in *Scheme-9*. Thus, **60** under Birch reduction (Na-liq. NH_3)²⁶ conditions or **62** with bromination and dehydrobromination ($\text{Br}_2/\text{NaOCH}_3$),²⁷ or **64** with lead tetraacetate (LTA) reaction²⁸ or **66** with reductive cleavage (Zn-AcOH)²¹ gave cleavage products **61**, **63**, **65** and **67** respectively, as shown in *Scheme-9*. Thus, enough literature background was there to justify our retrosynthetic strategies (*Scheme-5* and 6). Of course, there are some risk factors involved as well. Thus rearrangement of [m.n.2] propellane is reported (*Scheme-10*). The tricyclo [4.3.2] ketone **69** in the presence of H_2SO_4 gave rearrangement product **68**,²⁹ whereas on treatment with PTSA gave tricyclo [3.3.3] ketone **70**³⁰ (*Scheme-10*). Similarly, Mehta et.al.³¹ have reported the rearrangement of hydroxy ketone **71**, in the presence of BF_3 -ether, to **72**. However, it is worth while to note that such rearrangement possibilities are reported for [m.n.2] propellanes only, and not for [m.n.1] propellanes.

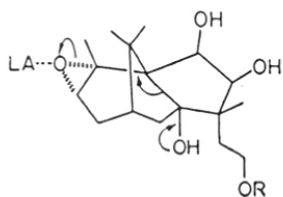
Scheme-8



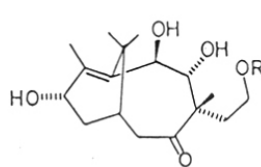
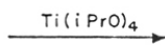
48



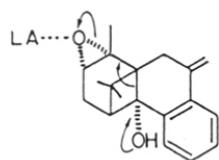
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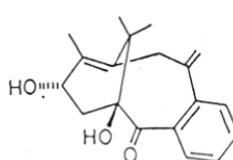
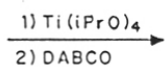
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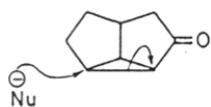
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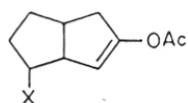
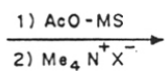
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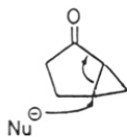
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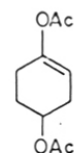
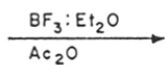
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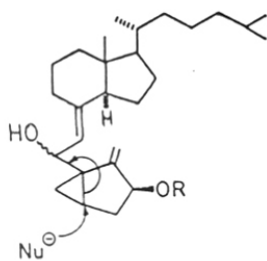
55



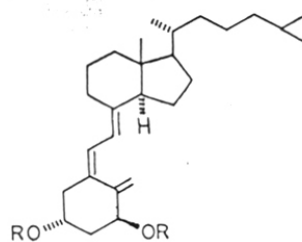
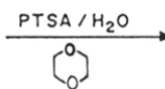
56



57



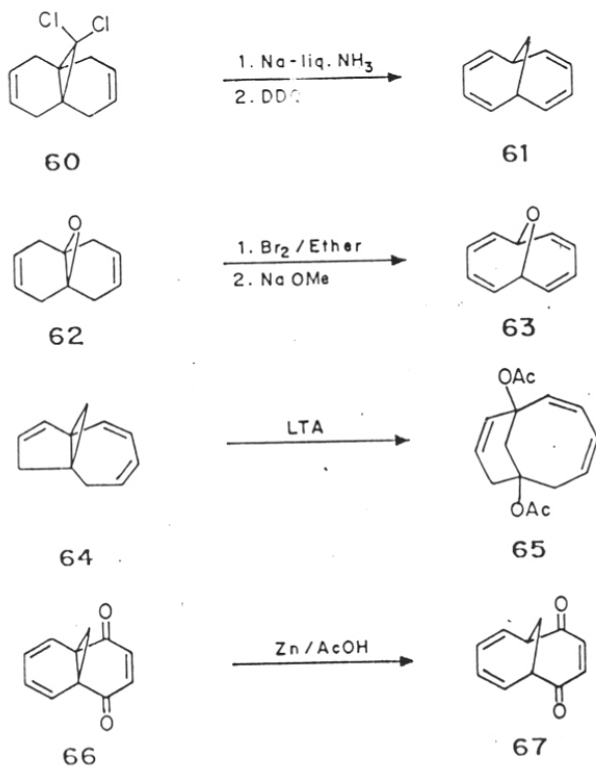
58



59

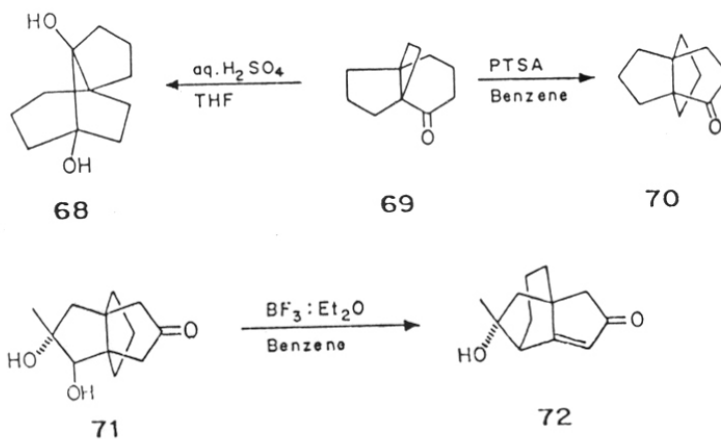
This chapter describes the synthetic strategies towards [m.n.1.] propellanes e.g., [4.3.1], [5.3.1] and [4.4.1] propellanes and various chemistry related to these skeletons for the synthesis of carbocyclic frame of Taxol.

Scheme-9

$$[m \cdot n \cdot 1] \text{ Propellanes}$$


Scheme-10

$[m \cdot n \cdot 2]$ Propellanes

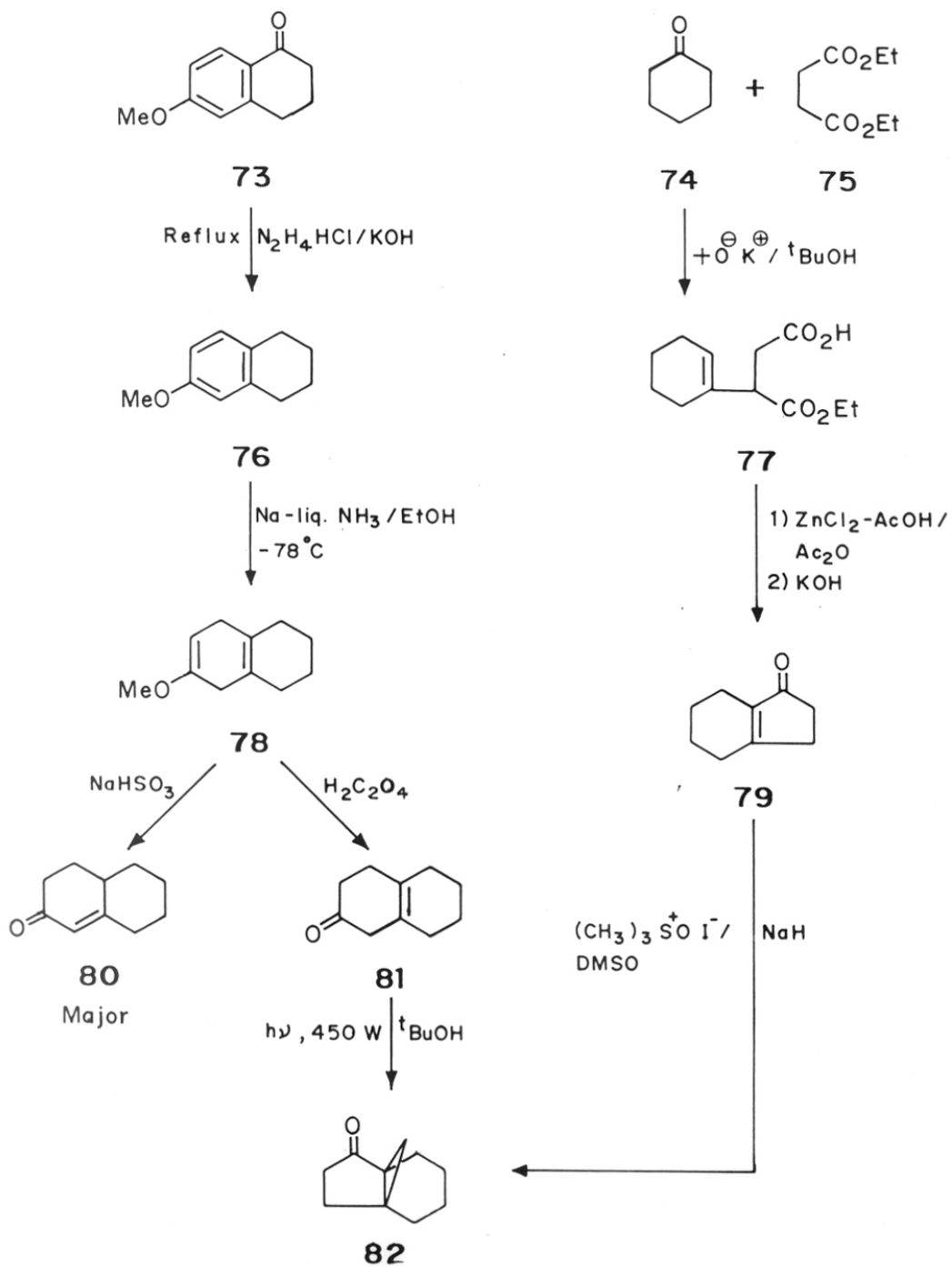


RESULTS AND DISCUSSION

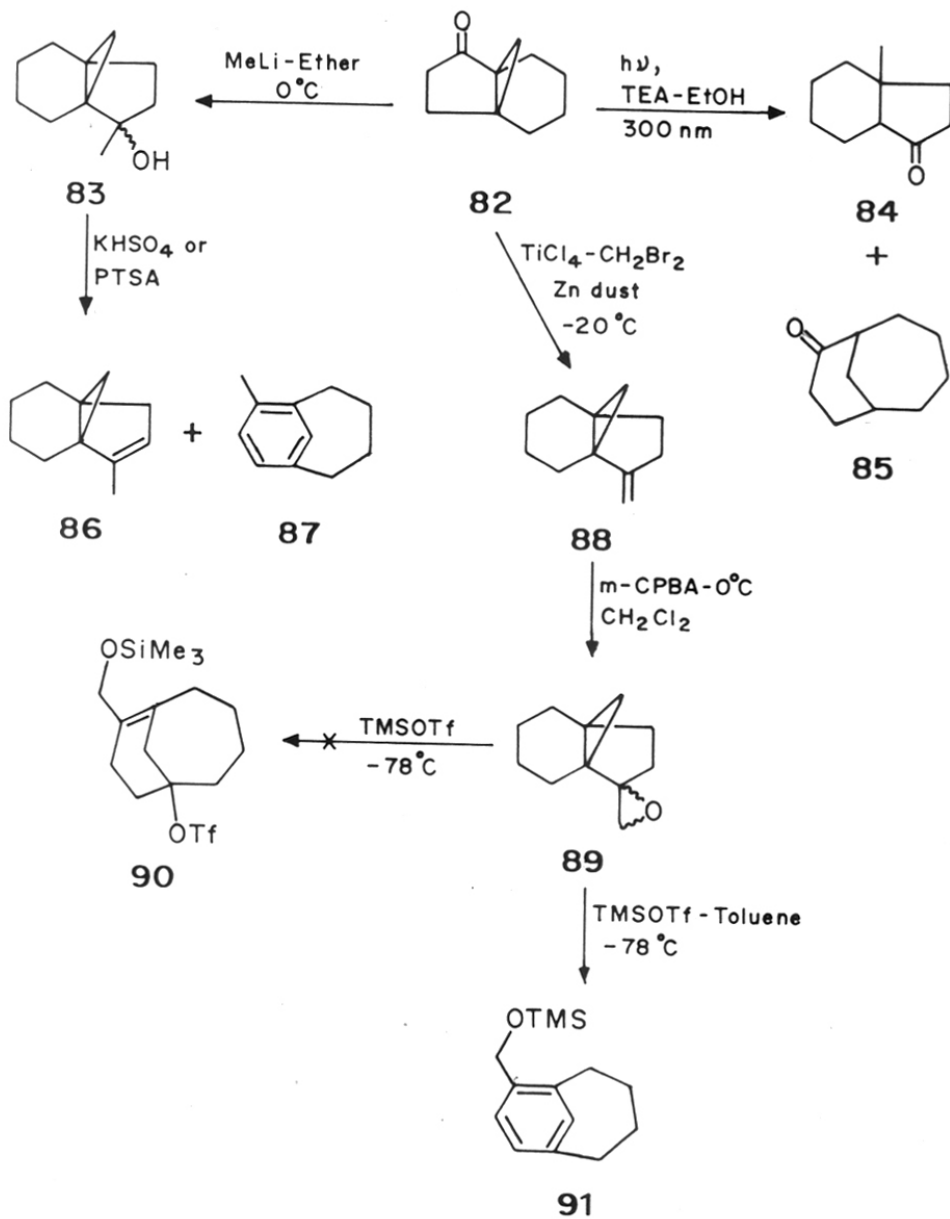
To test our strategy, we synthesized cyclopropyl ketones **82** and **115**, as shown in *Scheme-11* and *17*. Initially, we prepared tricyclo [4.3.1.0^{1,6}] decan-7-one **82**. Thus, 6-methoxytetralone **73** was subjected to Wolf-Kishner reduction (hydrazine-sodium ethoxide)³² to give 6-methoxy-1,2,3,4-tetrahydronaphthalene **76** (67%). Compound **76** was subjected to Birch reduction (Na-liq. NH₃/EtOH at -78°C)³³, followed by careful hydrolysis with aq. H₂C₂O₄ (oxalic acid)^{33b} to give 1,2,3,4,5,6,7,8-octahydro-2-oxonaphthalene **81** in 81% yield. Several other reagents e.g., (NaHSO₃ or 10% HCl)^{33a} were attempted for the hydrolysis step, which resulted in the formation of α,β -unsaturated ketone **80**. Finally, the hydrolysis step was standardized using aq. oxalic acid (H₂C₂O₄) in methanol. The structure of **81** was confirmed by spectroscopic data, besides other relevant data. Thus, IR gave absorption at 1730 cm⁻¹(vs, CO) stretching frequency of carbonyl ketone, whereas PMR gave signals at δ 1.5 (m, 4H), 1.8 (m, 4H), 2.25 (m, 2H), 2.45 (t, 2H), 2.65 (s, 2H). Finally, ¹³C-NMR showed carbonyl peak at δ 210.04(s) and double bond peaks at 128.33(s), 125.57(s), as quaternary carbons. Subsequently **81** was photolyzed in tert. butanol for 50 h. (oxa-di- π -methane (ODPM) rearrangement) at 450W Hanovia lamp through a Pyrex filter to give tricyclo [4.3.1.0^{1,6}] decan-7-one **82** in 44% yield, the structure of which was confirmed by spectral data and by comparison with literature data.^{34b} Compound **82** showed strong absorptions in IR at 1742 cm⁻¹ (CO, vs) characteristic of five membered ring strained ketone and PMR showed signals at δ 0.9-1.05 (m, 2H), 1.25-2.15 (m, 10H), 2.25-2.38 (m, 2H), whereas ¹³C-NMR gave carbonyl peak at δ 214.56 (CO, s) and M⁺ peak at 150 (52%) in mass spectrum.

Since oxa-di- π -methane rearrangement of **81** to **82** gave lower yield (44%), another route for tricyclopropyl ketone **82** was examined. The reaction of cyclohexanone and diethyl succinate in the presence of potassium tertiary butoxide gave β -carboethoxy- β -cyclohexenylpropionic acid³⁵ **77** (*Scheme-11*), which in the presence of ZnCl₂-Ac₂O reflux for 9 h. afforded the cyclized product 4,5,6,7-tetrahydro-1-indanone **79**³⁵ in 34% yield. The structure of **79** was established by spectral and chemical evidences. Thus, PMR showed signals at δ 2.25 (m, 4H), 2.5 (m, 2H). Subsequently, cyclopropanation of **79** with Corey's ylide³⁶ and sodium hydride in DMSO solvent gave 60% yield of **82**.

Scheme-11

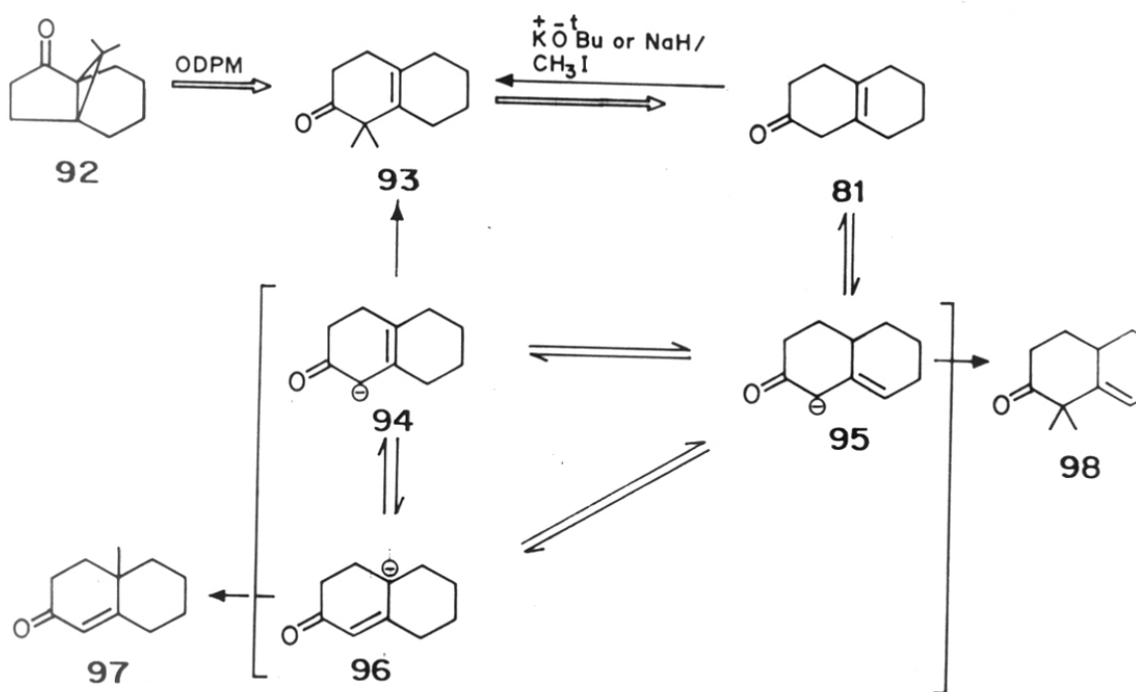


Scheme-12

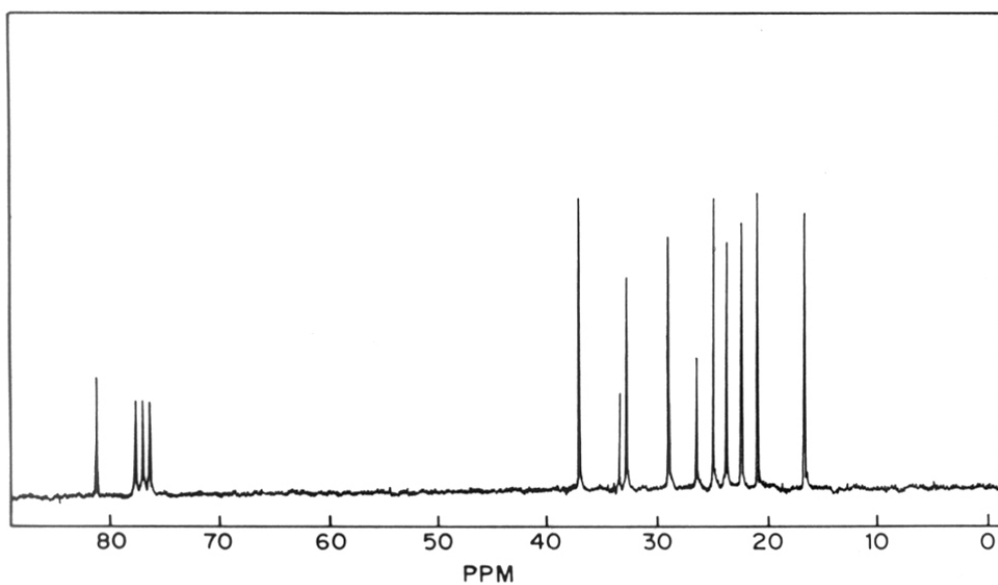
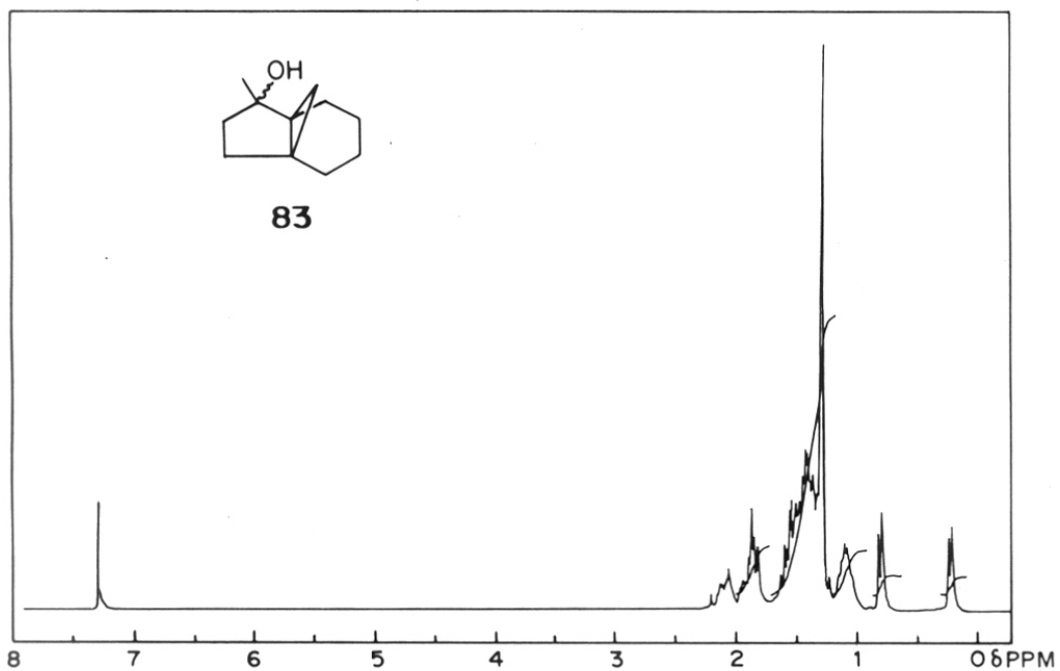


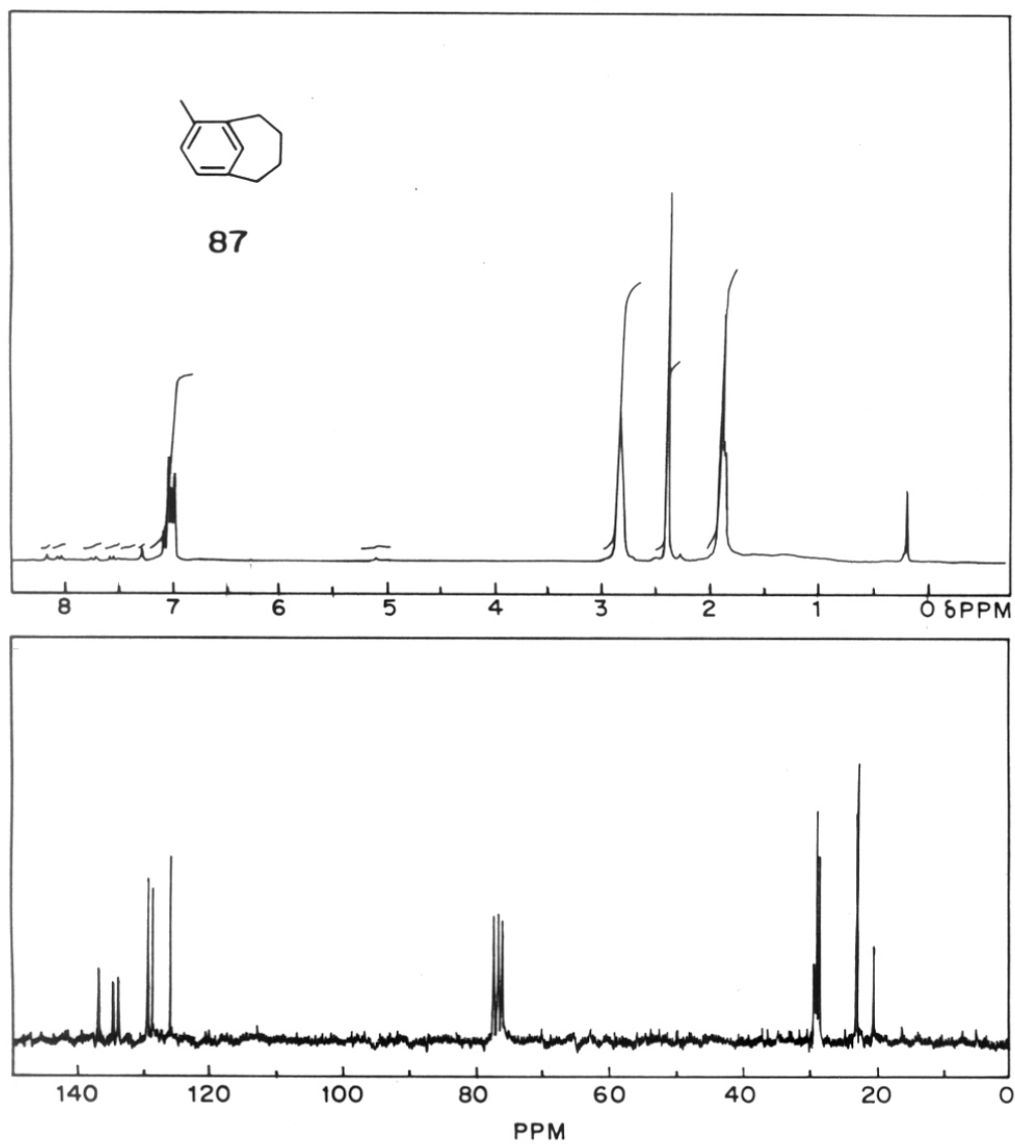
After successful synthesis of cyclopropylketone **82**, our next target was the synthesis of dimethylated β, γ -unsaturated ketone **93** from **81** in the presence of NaH or K^+O^-tBu and CH_3I , since dimethyl skeleton is needed in Taxol (Scheme-13). However, the reaction of **81** with base led to a mixture of mono and dimethylated products **93**, **97** and **98** resulting from the corresponding anions of **94**, **95** and **96** (Scheme-13),³⁷ which could not be separated by column chromatography. Above products **93**, **97** and **98** were confirmed by their mixtur's IR and 1H -NMR. Thus, IR gave absorption at 1720 cm^{-1} presumably for **93** and **98** and 1690 cm^{-1} for **97** (enone), whereas PMR gave signals at δ 1.15-1.32 (s, 6H, $2CH_3$) for dimethyl product **93**, compound **97** gave characteristic signals 2.1 δ (s, 3H, CH_3) for angular methyl, 5.93 δ (m, 1H) for olefinic proton and compound **98** characteristic signals at δ 5.65(d, 1H) for olefinic proton. Since the reaction was not clean, the strategy was abandoned.

Scheme-13



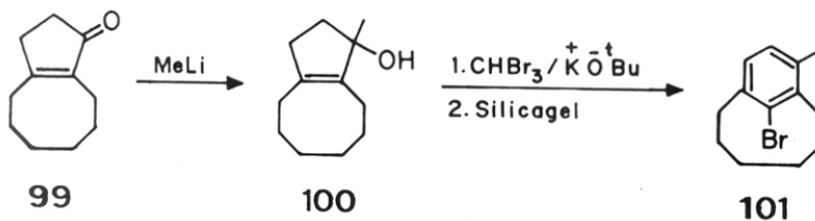
Our next target was to prepare **86** (*Scheme-12*), which is the precursor of cyclopropyl epoxide **32** ($m=1, n=2$), as shown in retroanalysis *Scheme-5*. As per our retrosynthesis, treatment of cyclopropylketone **82** with MeLi at 0°C in dry ether for 2h. gave 7-methyltri cyclo[4.3.1.0^{1,6}]decan-7-hydroxy **83** (stereoisomer 5:1 ratio) which were characterised by spectral data. PMR gave characteristic peaks of cyclopropyl protons at δ 0.2 (d, 1H), 0.75 (d, 1H) and ¹³C-NMR gave peaks at δ 81.11(s), 36.96(t), 33.32(s), 32.70(t), 28.93(t), 26.35(s), 24.80(q), 23.66(t), 22.28(t), 20.83(t), 16.58(t) (see Spectral Figure-**83**). For dehydration, cyclopropyl alcohol **83** was heated in the presence of *p*-toluenesulphonic acid, ethylene glycol and triethylorthoformate in benzene³⁸ at 60-70°C for 6 h. to give the expected product **86** in low yield (~ 8%) and an unexpected rearranged compound **87** (68%). Both the compounds were characterised by spectral data. Compound **86** gave characteristic PMR signals at δ 5.5 (m, 1H, double bond proton), 2.25 (m, 2H), 1.75-1.92 (m, 7H), 1.4 (s, 3H, CH₃), 1.0 (m, 1H) and mass spectrum gave M⁺ at 148 (22%). Similarly, the structure of **87** was confirmed based on spectral evidences. Thus PMR of compound **87** gave signals at δ 1.9 (m, 4H), 2.4 (s, 3H, CH₃), 2.85 (m, 4H), 7.0-7.1 (m, 3H) for aromatic protons and ¹³C-NMR gave peaks at δ 136.78(s), 134.65(s), 133.90(s), 129.56(d), 128.89(d), 126.17(d), 29.29(t), 28.92(t), 23.31(t), 23.25(t), 20.79(q). Mass spectrum showed M⁺ at 148 (22%) and other fragmentations 131(38), 118(47), 105(100), 91(62) (see spectra Figure-**87**). Treatment of **83** with other dehydrating reagents like KHSO₄^{38a} and acetic acid also resulted in the formation of **86** and **87** in 8% and 55% yield respectively. Perhaps aromatization is a facile process in 6-membered cationic species. Indeed, we could find one similar aromatization with brominated skeletons, which gave **101** even on silica gel (*Scheme-14*). Thus, reaction of **99** with methyl lithium furnishes alcohol **100**, which was directly subjected to dibromocarbene addition and the product was exposed to silica gel, to give 12-bromo-8-methyl [6] metacyclophane **101** (*Scheme-14*).³⁹ However, when the possibility of aromatization is not there in 7-membered ring, thermal or any other perturbation of **104** leads to a different type of chemistry. Thus, bicyclic enone **102** which was reduced to an allylic alcohol **103** with LAH and subsequent cycloaddition of dibromocarbene to **104** followed by thermolysis in vacuo, afforded 13-bromobicyclo [6.4.1] trideca-8,10,12-triene **105** (34%) along with a byproduct **106** (10%).⁴⁰ The formation of products e.g., **105** indicates



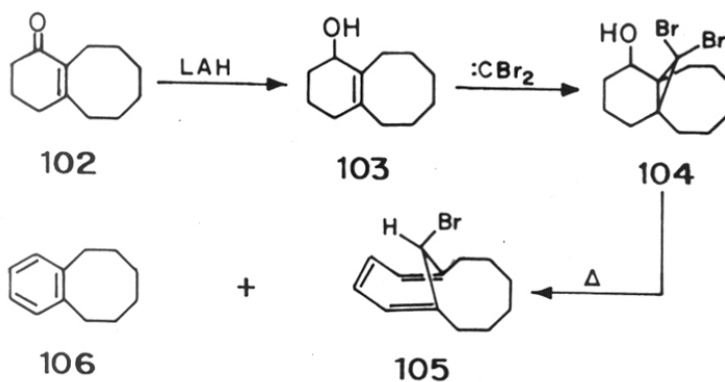


the possibility of cleaving the central bond in cyclopropyl system **104**, which is at the heart of our strategy (*Scheme-15*).

Scheme-14

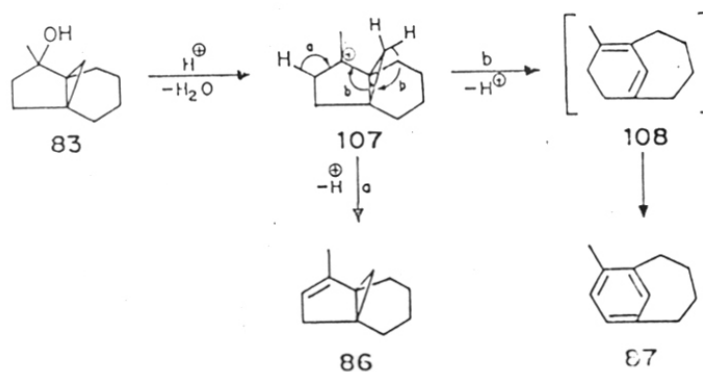


Scheme-15



The formation of aromatized product **87** and our desired olefin **86** can be explained, as shown in *Scheme-16*. Thus, thermal cleavage of the cyclopropane ring under acid-induced dehydration conditions forms initially tertiary carbocation **107**, then central (propellane bond) cyclopropyl bond shift takes place followed by proton loss to give labile compound **108**, which by air-oxidation can give aromatised product *m*-cyclophane **87** (*Scheme-16*).

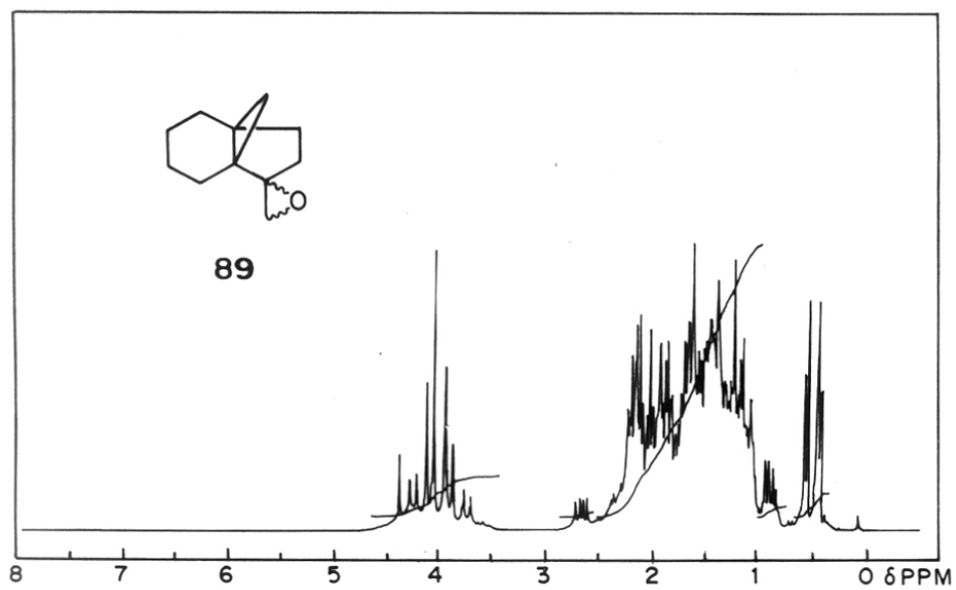
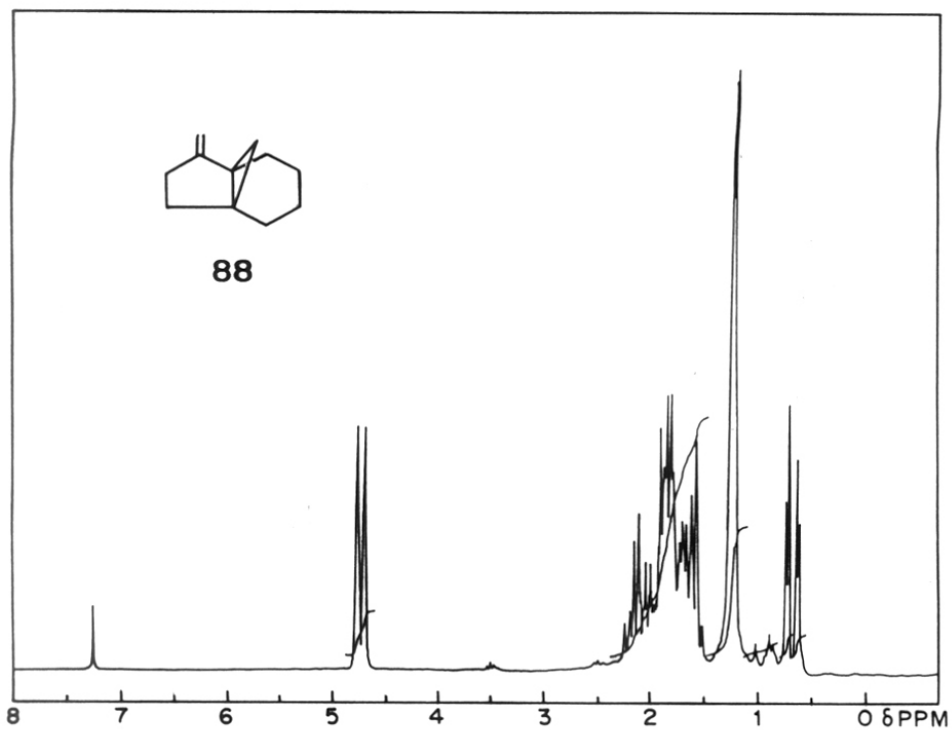
Scheme-16



Although transformation of **83** to **87** was an interesting observation, but the yield of desired olefin **86** was very low. Alternatively, one could mesylate the tertiary alcohol and treat with a base e.g., DBU or pyridine for an efficient elimination. However, we encountered problems in mesylating the alcohol, perhaps because of its tertiary nature.

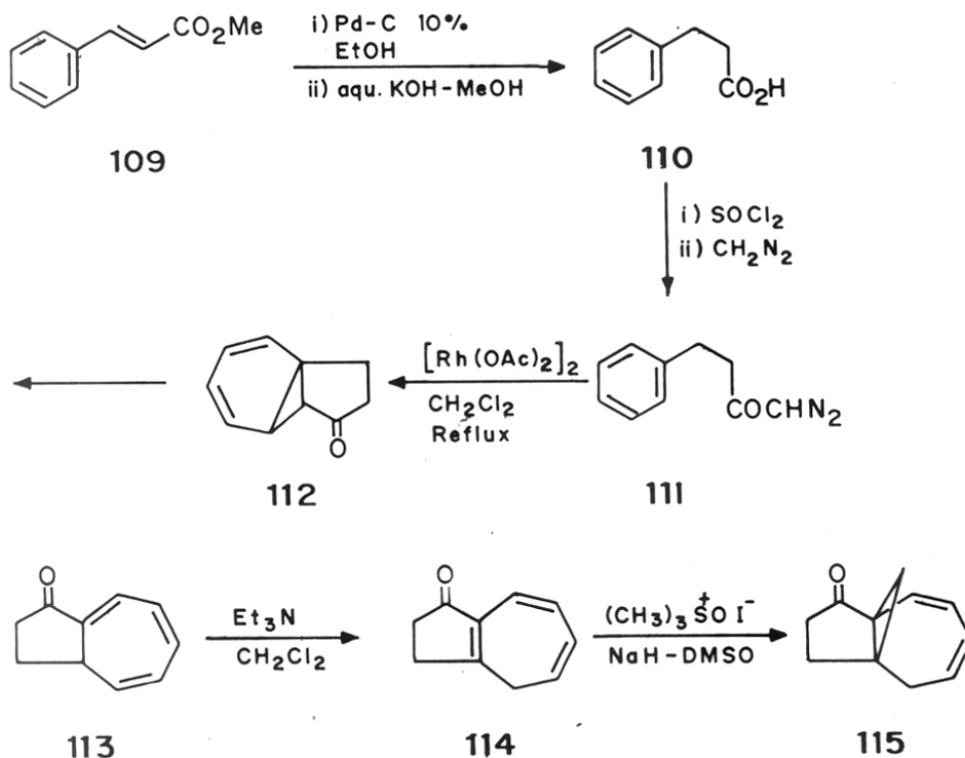
As mentioned in our strategy, our ultimate goal was to cleave the central cyclopropyl bond, which will give carbocyclic frame of Taxol, with bridgehead double bond. Although cleavage of cyclopropyl went in a desired way, but an unwanted aromatization leading to formation of **87** was a problem. Alternatively, we planned to cleave the central cyclopropyl bond in related skeletons e.g., **88** and **89**, as shown in *Scheme-12*. The reaction of cyclopropyl ketone **82** with phosphorane ($\text{Ph}_3\text{P}=\text{CH}_2$) failed to give desired product **88**, presumably because of steric reasons. Subsequently, we employed Lombardo reaction⁴¹. Thus, treatment of **82** with Zn powder, CH_2Br_2 and TiCl_4 in THF at -20°C to 0°C for 2h. gave 7-methylidene tricyclo [4.3.1.0^{1,6}] undecane **88** in 82% yield. The structure of **88** was confirmed by PMR, which showed peaks at δ 0.6-0.8 (dd, 2H), 1.3 (m, 4H), 1.55-2.2 (m, 8H) and 4.75 (d, 2H) for exocyclic double bond protons. The above exo-methylene compound **88** on epoxidation⁴² with m-chloroperbenzoic acid in CH_2Cl_2 at 0°C gave **89** in 76% yield, which was quickly purified by silica gel column. The structure of **89** was confirmed by PMR which showed signals at δ 0.45 (d, 1H), 0.55 (d, 1H) for cyclopropyl protons, 1.05-2.4 (m, 12H), 3.95-4.0 (d, 1H), 4.05-4.1 (d, 1H) for epoxide exo- CH_2 . Having prepared cyclopropyl epoxide **89**, our next target was to open epoxide concurrent with cyclopropyl opening. In the literature,⁴³ Lewis acid-assisted opening of epoxides, followed by attack with a nucleophile is well documented. Based on literature precedence,⁴³ TMSOTf was chosen for the next step. Although many other synthetic possibilities do arise with this epoxide **89** to get useful carbocyclic frame of taxol, treatment with TMSOTf in toluene at -78°C gave once again aromatized product **91**, instead of desired compound **90**. Similar to **87**, the structure of **91** was confirmed by PMR which showed signals at δ 0.1-0.18 (s, 9H, $\text{Si}(\text{CH}_3)_3$), 1.42-1.75 (m, 4H), 2.38 (m, 4H), 3.9 (s, 2H, $\text{CH}_2\text{OSi}(\text{CH}_3)_3$), 6.9-7.0 (m, 1H, Ar), 7.1-7.4 (m, 2H, Ar).

Subsequently, in accordance with our strategy employing propellanes as key compounds, instead of [4.3.1] propellane, now [5.3.1] propellane was utilised for exploratory studies. Needless to mention that [5.3.1] propellanes on ring opening would give the closest



analogue of carbocyclic frame of Taxol. This section describes a novel strategy for [5.3.1] propellanes and their chemistry (Scheme-17 and 18). We started from readily available starting material methyl cinnamate **109**, which on catalytic hydrogenation (Pd-C 10%) in ethyl acetate, followed by ester hydrolysis (aq. KOH-MeOH/reflux) gave 3-phenylpropionic acid **110**, in quantitative yield.⁴⁴ The dihydrocinnamic acid **110** was converted into acidchloride (DMF/SOCl₂ reflux)⁴⁵, followed by treatment with ethereal diazomethane⁴⁵ (Diazomethane was prepared by treatment of *N*-nitroso-*N*-methyl urea with aq. KOH in ether at ice-salt bath -10°C with appropriate precautions) to give 93% yield of diazoketone **111**. The structure of diazoketone **111** was confirmed by spectral data and by comparison with literature data⁴⁵ as well. IR spectrum gave peaks at 2090 (s, N=N), 1635 (CO, s) and ¹H-NMR gave signals at δ 2.28-2.93 (m, 4H), 5.14 (s, 1H, CHN₂), 7.1 (s, 5H, Ar). The diazoketone **111** was treated with catalytic amount of rhodium acetate in CH₂Cl₂ under mild reflux for 1 h., followed by treatment with triethylamine (TEA) to give **114** (89%). The formation of **114** can be explained via **112** by initial intramolecular carbene addition to

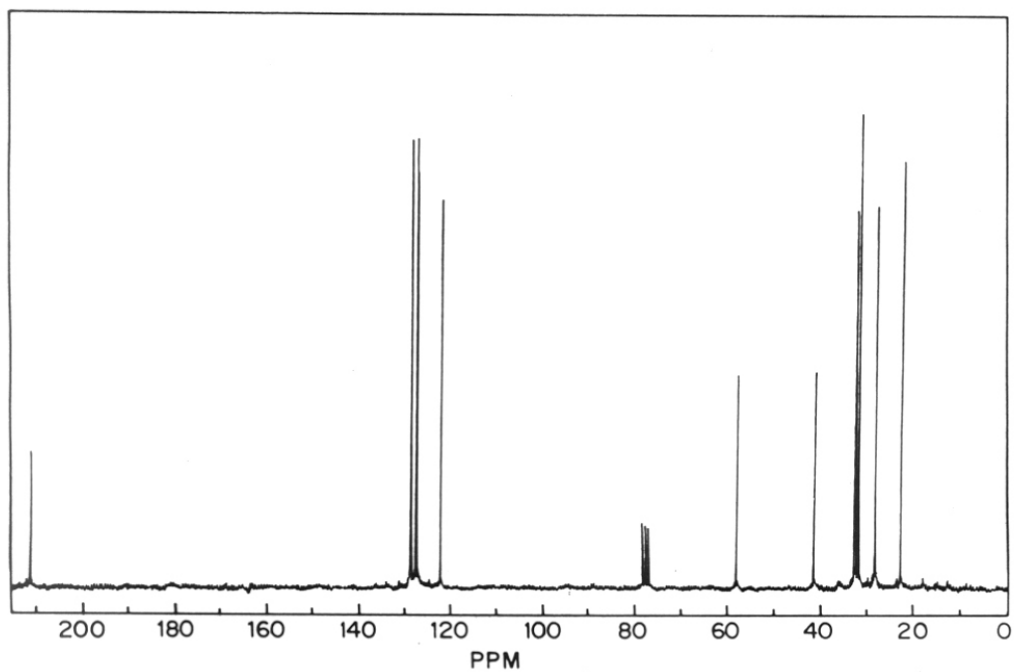
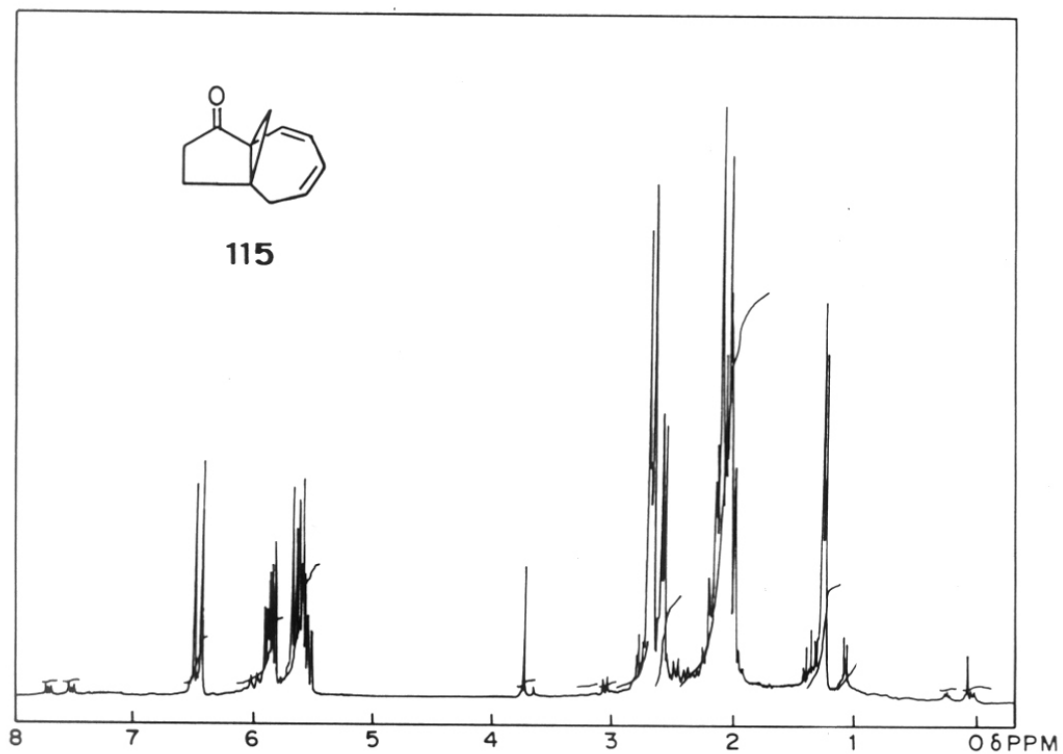
Scheme-17



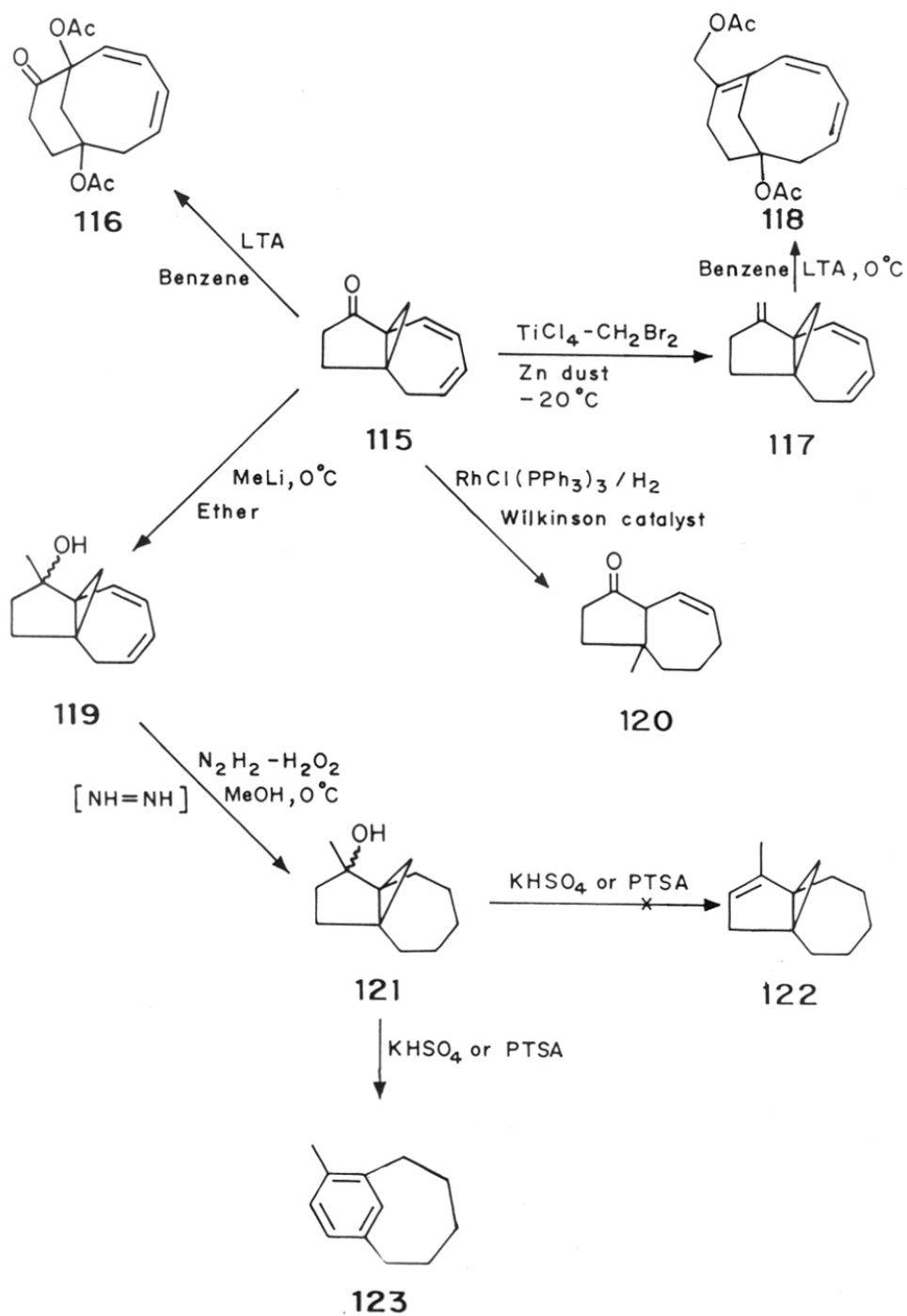
benzene, followed by base induced bond reorganisation of **113**. The structure of dihydroazulen-1(2H)-one **114** was characterised by spectral data and by comparison with literature data.⁴⁵ Thus, proton-NMR gave signals at δ 2.58 (m, 4H), 2.83 (d, 2H), 5.39 (t, 1H), 6.09 (dd, 1H), 6.48 (dd, 1H), 6.68 (d, 1H).

The trienone **114** on nucleophilic cyclopropanation³⁶ using Corey's ylide in the presence of NaH in DMSO gave tricyclo[5.3.1.0^{1,7}]undeca-2,4-dien-10-one **115** in 76% yield, the structure of which was confirmed by spectral data. Thus, IR spectrum gave carbonyl peak at 1700(s) cm⁻¹, whereas ¹H-NMR showed characteristic signals for cyclopropyl protons at δ 1.25 (d, 1H), 2.55 (d, 1H) and for double bond protons at 5.65 (m, 2H), 5.95 (m, 1H), 6.5 (d, 1H). Similarly, ¹³C-NMR gave characteristic carbonyl absorption for a strained cyclopentanone at δ 211.56(s).

Since subsequent steps needed acid induced bond reorganisation or epoxidation etc., from **115**, it was planned to prepare saturated analogues of **115**, as the double bond would create problem with either of above transformation. It is well documented that hydrogenation with heterogeneous catalysts e.g., (Pd-C) cleaves cyclopropyl ketone.⁴⁶ Hence, the Wilkinson catalyst⁴⁶ was the obvious choice, as this reagent has been used for hydrogenation of a variety of cyclic olefins in the presence of cyclopropyl group. Since with Wilkinson catalytic hydrogenation mechanism, olefins form complex with rhodium chlorotris(triphenylphosphine)[RhCl(PPh₃)₃] and transfer hydrogen to olefin, the compound tricyclo [5.3.1.0^{1,7}] undeca-3,5-triene-8-one **115** was subjected to [RhCl(PPh₃)₃] (molar ratio 1 mole percentage w.r.t. C=C) in toluene. Surprisingly, cyclopropyl bond cleaved to **120** along with saturation of one of the double bond. The unwanted cleavage of cyclopropyl bond was indeed unique and shows the labile nature of our skeleton. The structure of **120** was confirmed by IR and ¹H-NMR as usual. IR spectrum showed strong absorptions at 1745 cm⁻¹(s, CO) characteristic of five membered ring strained ketone, whereas ¹H-NMR gave signals at δ 5.4-5.6 (m, 2H) double bond protons and 1.2 (s, 3H, CH₃) methyl proton (For detailed spectral data see Experimental section). In an alternative route, cyclopropyl ketone **115** was treated with methyl lithium at 0°C to give quantitative yields of **119** (91%), which was confirmed as usual (Please see Spectra *Figure-119*). IR gave absorption at 3350 (OH) cm⁻¹ and PMR gave signals at δ 0.95 (d, 1H), 1.4 (d, 1H) for cyclopropyl protons, 1.35 (s, 3H, CH₃) for methyl



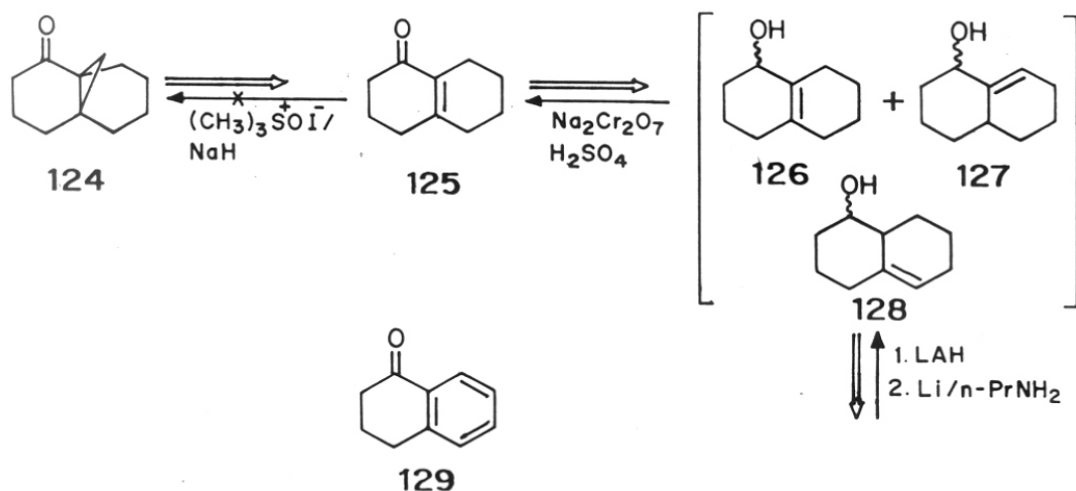
Scheme -18



protons and double bond protons 5.7 (m, 2H), 5.85 (m, 1H), 6.25 (d, 1H). The 10-methyl tricyclo[5.3.1.0^{1,7}]undeca-10-hydroxy **121** was prepared from **119** by diimide hydrogenation ($\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}_2$).⁴⁷ Initially, only one double bond was reduced (~4 h), which on prolonged hydrogenation under (~8h) similar condition gave the desired completely reduced product **121**, the structure of which was confirmed by ¹H-NMR. The characteristic signals at δ 0.5 (d, 1H), 1.2(d, 1H), 1.3(s, 3H, CH_3), 1.55-1.9 (m, 14H) were obtained, besides other spectral data. However, dehydration of alcohol **121** in the presence of KHSO_4 or PTSA ³⁸ in benzene under reflux gave once again aromatized (m-cyclophane) product **123** (42%). The structure of **123** was confirmed by ¹H-NMR and MS. Proton-NMR showed absorptions at δ 0.04-0.54 (m, 2H), 1.0-2.14 (m, 4H), 2.38 (s, 3H, CH_3), 2.4-3.1 (m, 4H), 6.75-7.23 (m, 3H) and mass spectrum gave M^+ at 160 (18%), 145(62), 131(24), 116(100), 91(63), 77(40). Although successful in some way that the central cyclopropyl bond could be cleaved, but efficient aromatization was once again a big problem (*Scheme-18*).

To avoid aromatization problem, synthesis of [4.4.1] propellane system **124** was attempted, as shown in *Scheme-19*. Thus, the reaction of α -tetralone with LiAlH_4 in dry ether gave single completely reduced ketone, which was subjected to Benkeser reduction⁴⁸ (Li-n-propylamine) for 24h at room temperature to give mixture of products **126**, **127** and **128**, which could not be separated. We argued that oxidation of these unsaturated alcohols followed by base treatment should give α,β -unsaturated product as a major product. Thus,

Scheme - 19

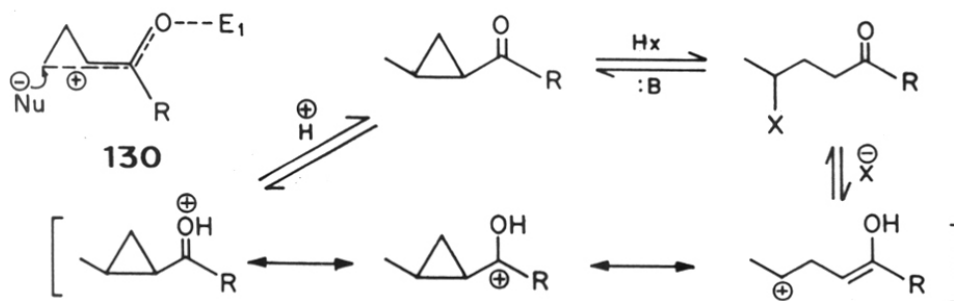


above mixture was oxidized with Brown's reagent ($\text{Na}_2\text{Cr}_2\text{O}_7/\text{H}_2\text{SO}_4$ for 0.1M alcohol oxidation)⁴⁹ to give the required bicyclic α,β -unsaturated ketone **125** in 38% yield. The structure of **125** was confirmed by spectral evidences. Proton-NMR gave signals at δ 1.5 (m, 4H), 1.85 (m, 2H), 2.15 (m, 6H), 2.35 (t, 2H) and ^{13}C -NMR showed signals at δ 198.64(s), 156.79(s), 132.16(s), 37.88(d), 31.70(d), 31.40(d), 22.46(d), 22.15(d), 21.66(d). However, our initial attempts at cyclopropanation of α,β -unsaturated ketone **125** in presence of $\text{NaH}-(\text{CH}_3)_3\text{S}^+\text{OI}^-$ under usual conditions³⁶ did not yield the expected cyclopropyl ketone [4.4.1] **124** (*Scheme-19*).

Cyclopropyl Ketone Related Chemistry

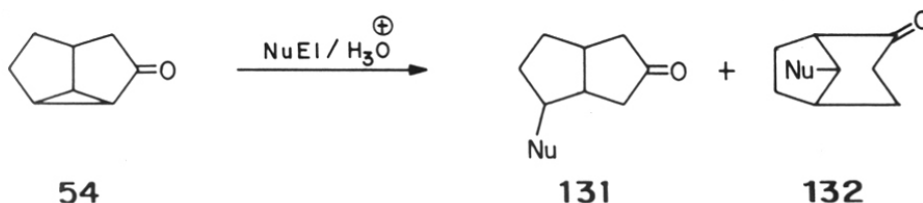
Propellane central bond cleavage of cyclopropylketone (*Scheme-6*) has been examined by electrophile assisted nucleophilic addition (TMSOTf ,¹⁸ Lead tetraacetate^{19,28} and AcOH-NaOAc),⁵⁰ reductive cleavage (Zn-AcOH)²¹ and lastly by photoinduced electron transfer (PET)¹⁵ (*Scheme-6*) methodology as well. Nucleophiles add cyclopropyl ketones in cooperative action with strong electrophiles such as various Lewis acids, acetyl R_3Si and protons. A reasonable mechanism for all these reactions would involve first an interaction of the electrophile with the carbonyl oxygen resulting in bond delocalization e.g. **130** (*Scheme-20*). Nucleophile addition now can occur in a stepwise or concerted manner. The assistance of Lewis acid to ring opening in an $\text{S}_{\text{N}}2$ mode was proposed by Stork et.al.⁵¹ proton acids, HX , add their conjugate base to cyclopropyl carbonyl compounds.⁵² The reaction presumably proceeds *via* protonation of the carbonyl group, rearrangement of the resulting cationic intermediate to the corresponding homoallyl system (*Scheme-20*) to allow the addition of the nucleophile.

Scheme - 20



Demuth et al.¹⁸ investigated the selective action modes of reagents with and without silicon (*Scheme-21*). All reagents used have in common the combination of a nucleophile (Nu) and an electrophile (El) such as $\text{CH}_3\text{SO}_2\text{OCOCH}_3$, $\text{Br}^{(-)}$, $\text{I}^{(-)}$, $\text{CF}_3\text{CO}_2\text{Si}(\text{CH}_3)_2\text{C}_4\text{H}_9$ ¹ and $\text{CF}_3\text{SO}_2\text{OSi}(\text{CH}_3)_3$ etc.

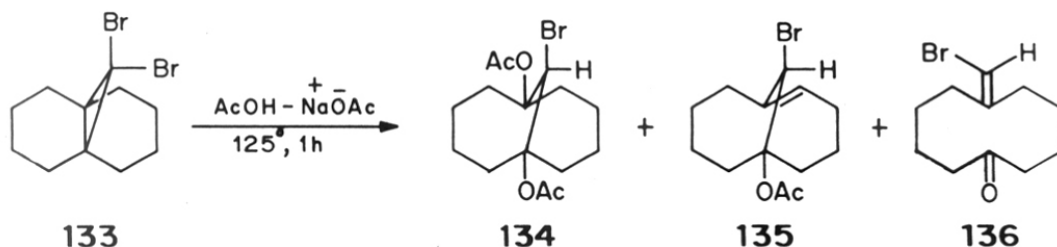
Scheme - 21



In these literature backgrounds, ring opening of our cyclopropyl ketones **82** and **115** was examined. Thus, cyclopropyl ketones **82** and **115** were subjected to treatment with TMSOTf in toluene at -78°C or room temperature for 12 h. However, the desired cleaved product could not be obtained and 45% starting material was recovered (*Retroanalysis Scheme-6*).

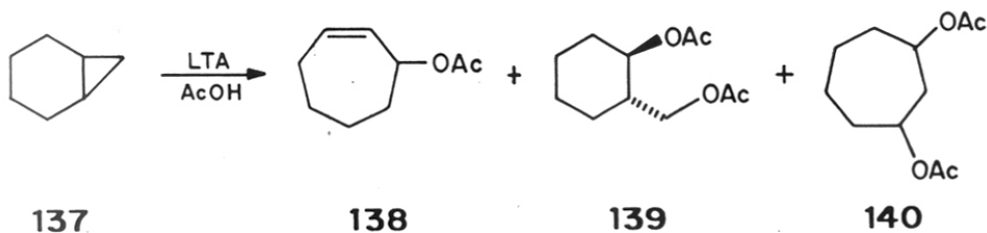
It has been well documented by Warner et.al⁵⁰ that central propellane bond can be cleaved in the presence of Br_2 , acetic acid and AcOH/NaOAc , etc. Thus, heating of 10,10-dibromo [4.4.1] propellane **133** in buffered (NaOAc) glacial acetic acid gave **134**, **135** and **136**, as shown in *Scheme-22*. Similar reaction conditions for the cleavage of central bonds in cyclopropyl ketone **82** and **115** were attempted. However, no reaction occurred even by varying reaction conditions e.g., AcOH/NaOAc for 10 h. at 125°C .

Scheme - 22

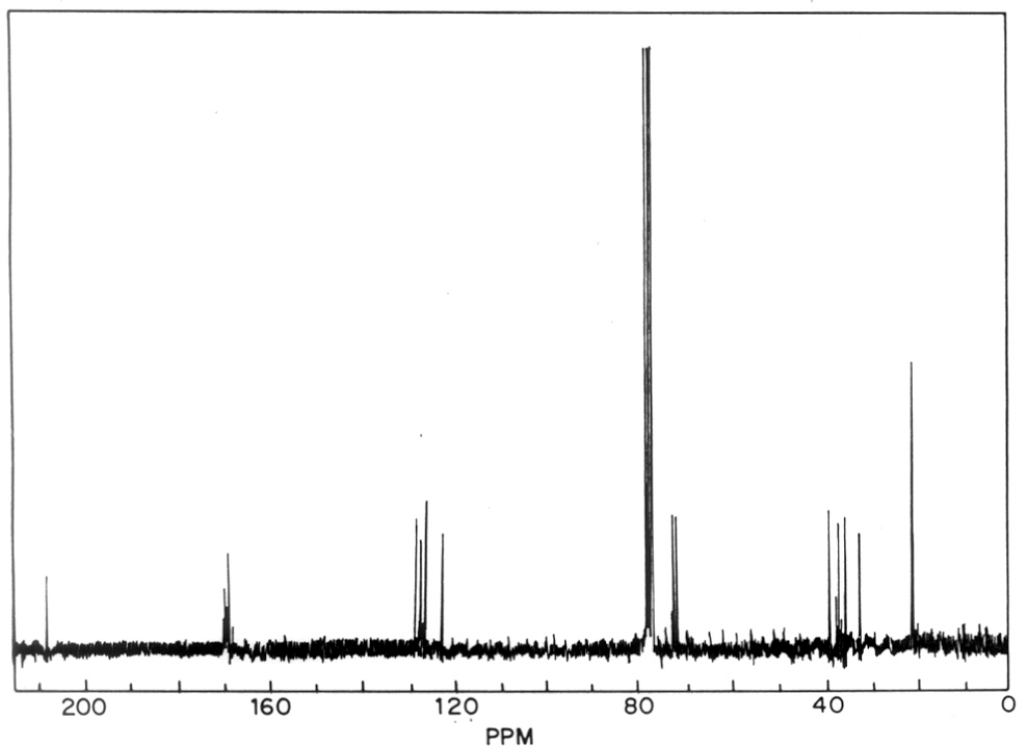
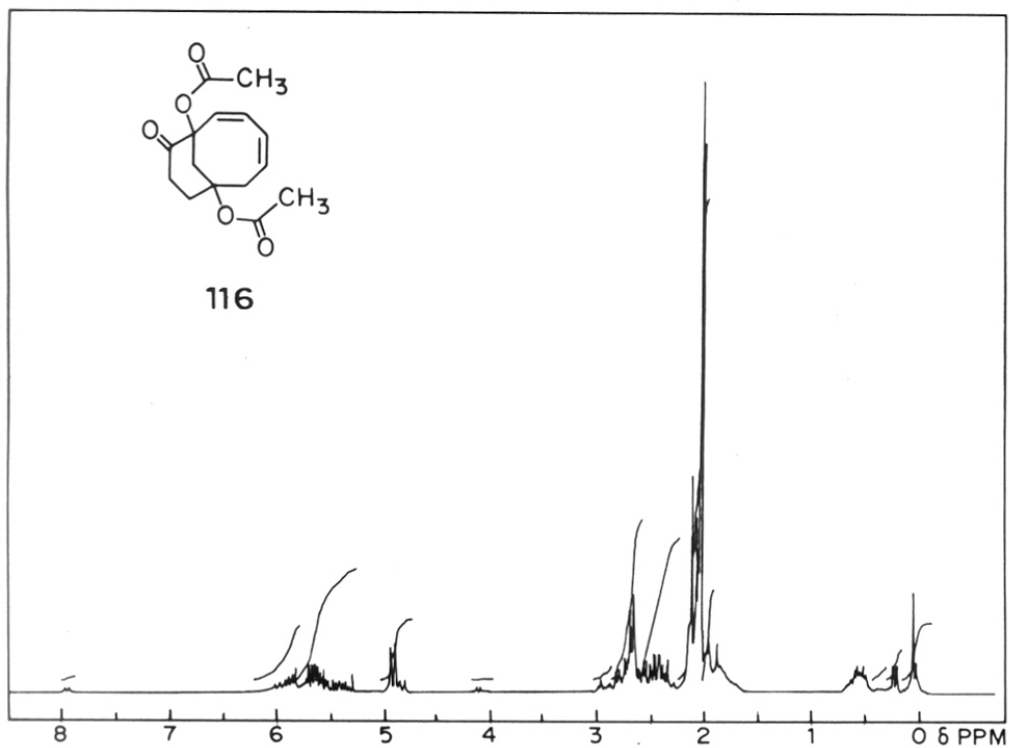


Our next choice was lead tetraacetate (LTA) reaction with above substrates. The LTA has distinguished itself as a versatile and powerful reagent in the field of organic chemistry. The mechanisms of its reaction have remained largely an enigma except for the cleavage of diols. The mode of reaction is strongly dependent on the substrate and the reaction conditions. There have been numerous product studies of oxidative processes involving LTA which unfortunately have provided little insight into the nature of the reacting species. Although LTA has found extensive use in organic chemistry, but little is known about its reactions with cyclopropane hydrocarbons. Treatment of bicyclo [4.1.0] heptane with LTA in refluxing acetic acid for 2 h. yielded a mixture of products (*Scheme-23*).

Scheme -23



Thus, we were curious whether LTA will cleave our cyclopropyl ketone. Subsequently, cyclopropyl ketone **82** (*Scheme-12*) was subjected to LTA in benzene at room temperature. However, the reaction did not show any progress on TLC. Whereas refluxing for 3 h. in benzene gave several spots on TLC. Due to non-selective nature of this reaction, further work was discontinued. Subsequently, we went ahead with [5.3.1] propellane **115**, which was earlier prepared by $[\text{Rh}(\text{OAc})_2]_2$ rhodium acetate route (*Scheme-17 & 25*). The reaction of cyclopropyl ketone **115**, with LTA and AcOH in dry benzene under reflux for 6h. gave 1,7-diacetoxy bicyclo [5.3.1]undeca-2,4-diene-10-one **116** in 38% yield, with a small recovery of starting material (10%) (*Scheme-18*). The structure of compound **116** was confirmed by spectral data (See spectra *Figure-116*). IR gave strong absorptions at 1760(s), 1730(s) cm^{-1} ester carbonyl ketone and PMR gave signals at δ 2.05 (s, 6H, 2 OAc), 2.1 (m, 2H), 2.4-2.6 (m, 4H), 2.7 (m, 2H), 4.9 (m, 1H), 5.5-5.62 (m, 2H), 5.9 (m, 1H) olefin protons,

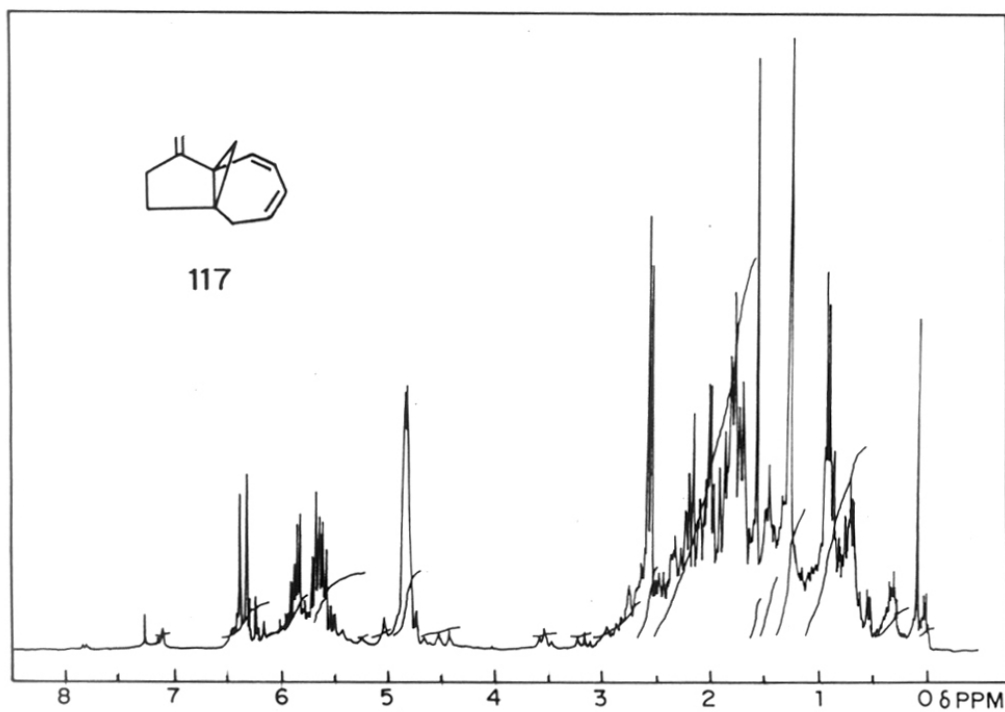
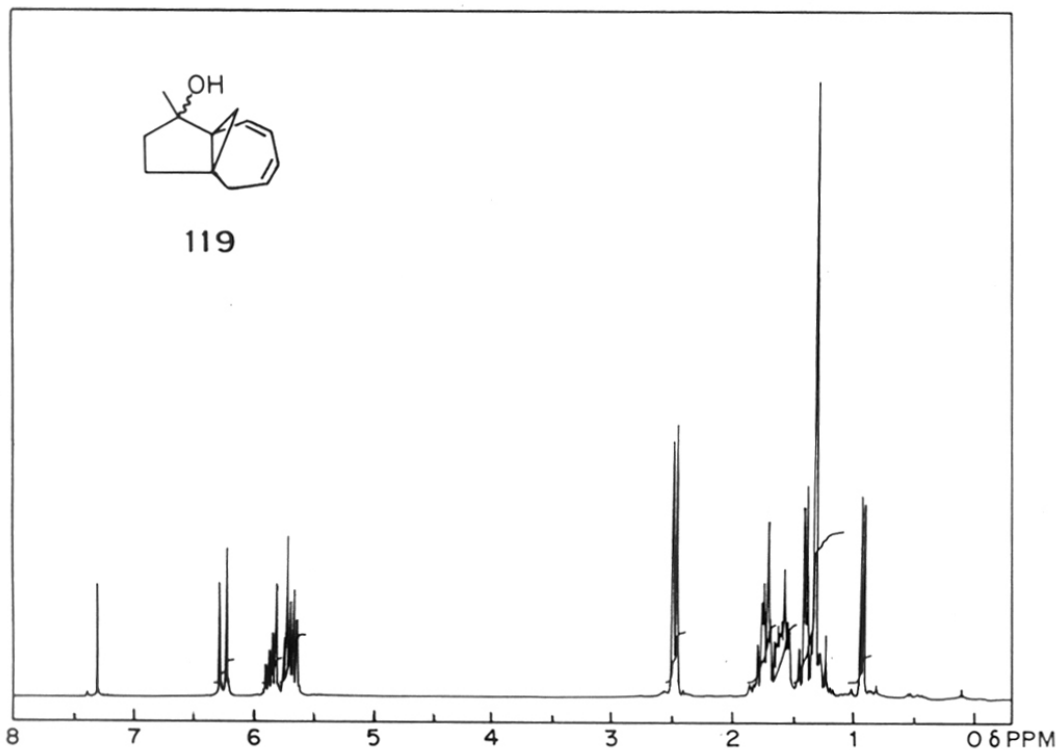


whereas ^{13}C -NMR gave peaks at δ 208.97 (CO, s), 170.36(s), 169.74(s), 129.09(s), 128.02(d), 127.00(d), 123.30(d) for olefin carbon, 72.20(s), 71.44(s), 38.64(t), 36.76(t), 35.31(t), 32.05(t), 20.94 (q, 2C, COCH₃). Mass spectrum showed 219 (5%) (M^+ -OAc) peak.

Another model 8-methylidene tricyclo [5.3.1.0^{1,7}]undeca-3,5-diene **117** (*Scheme-18*) was examined for LTA oxidation studies. The compound **117** was prepared from cyclopropylketone **115** in the presence of Zn dust, TiCl₄ and CH₂Br₂ (Lombardo reaction)⁴¹ in THF at -20°C in 81% yield. The methylidene product **117** was very unstable and was used without further purification (work-up at 0°C temperature). The structure of **117** was confirmed by ^1H -NMR (see spectra Figure-117), which showed characteristic signals at δ 0.9 (d, 1H), 1.7 (d, 1H) for cyclopropyl characteristic protons, 4.9 (d, 2H) for exocyclic double bond protons and 5.6 (m, 2H), 5.9 (m, 1H), 6.4 (d, 1H) for olefin protons. The above compound **117** was subjected to LTA oxidation in acetic acid and benzene at 0°C with stirring for 3 h. to give colourless oil of 1-acetoxy-8-methylacetoxy bicyclo[5.3.1]undeca-3,5,7-triene **118** in 21% yield. The remaining products could not be isolated. According to TLC, it showed four very close spots. These compounds could not be separated, even with repeated column chromatography. The compound **118** was characterised by IR, ^1H -NMR and Mass. IR shows strong absorption at cm^{-1} 1740 (vs) for ester carbonyl, ^1H -NMR gave signals at δ 1.95-2.1 (m, 6H), 2.15 (s, 6H, OAc), 2.4 (m, 2H), 4.55 (m, 2H, CH₂OAc), 5.5-5.8 (m, 3H), 6.25 (m, 1H) and mass spectrum gave 217 (18%, M^+ -OAc), 190(14), 157(20), 144(51), 117(100), 79(10).

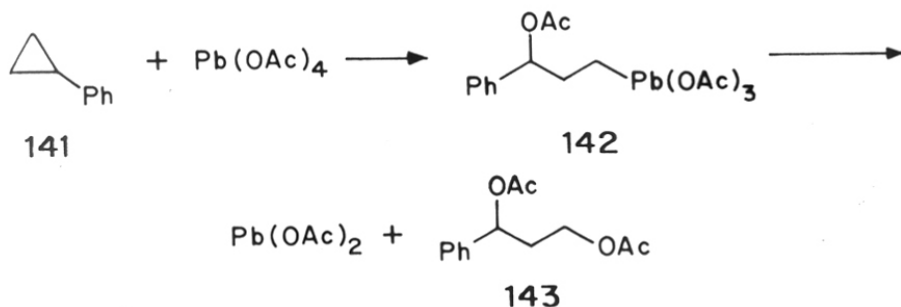
The cleavage of central cyclopropyl (propellane) bond in **115** and **117** during LTA oxidation gave **116** and **118** respectively, which are close to taxol with appropriate/oxidation state C-1.

The mechanism of the cyclopropyl bond cleavage with LTA is not yet understood, but Robins et.al⁵³ concluded that the cleavage reaction of Pb(OAc)₄ proceeds *via* the ion pair Pb⁺(OAc)₃O⁻Ac. He compared these oxidations with Hg(OAc)₂ and Ti(OAc)₃. The cleavage of aryl cyclopropanes by LTA must proceed *via* the covalent Pb(OAc)₄ which serves as the electrophile. The reaction must involve a concerted pathway similar to an S_N2 displacement mechanism in which the cyclopropane ring electron replaces an acetate ion from the coordination sphere of Pb(IV). The reaction of LTA with its loss of acetate by displacement may



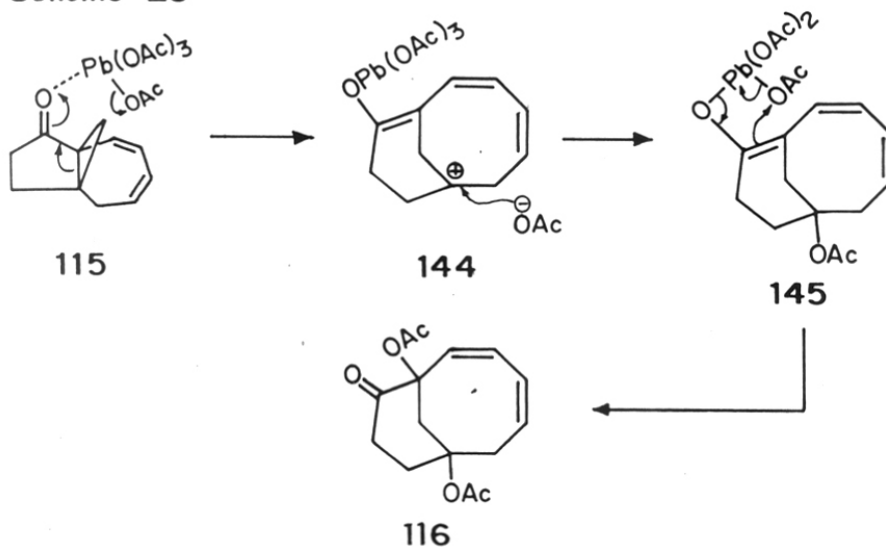
in fact be more of a concerted process in which the departing acetate ion becomes attached to the developing carbonium ion center at the benzylic carbon (*Scheme-24*).

Scheme -24



Similarly our cyclopropyl ketone **115** and **117** may proceed *via* the ketone **115** and double bond **117** covalently bound with $\text{Pb}(\text{OAc})_4$, which serves as the electrophile (*Scheme-25*). The reaction may involve a concerted pathway with **115**, similar to above cyclopropane cleavage. The reaction of LTA with its loss of acetate by displacement may in fact be more of a concerted process in which the departing acetate ion becomes attached to the developing carbonium ion center at the tertiary carbon **145** (bridgehead carbon) and back to polarization gives diacetate compounds **116** and **118** (*Scheme-25*).

Scheme -25



Doubly⁵⁴ and monoactivated⁵⁵ cyclopropanes undergo facile reductive cleavage when treated with Zn in HCl or AcOH⁵⁴ or with ZnCl₂ and shortly refluxed in ethanol.⁵⁶ The tricyclic-2,5-quinone **66** is reduced by Zn dust in 95% acetic acid at room temperature to the bicyclic-2,5-dione **67** (92%) yield (*Scheme-9*).²¹

Similar conditions were used for our cyclopropyl ketone **82** and **115** (retroanalysis *Scheme-6*) for reductive cleavage of cyclopropyl central bond. However, the reaction could not progress even under vigorous reflux conditions. Perhaps above conditions are not suitable for monoactivated ketone.

Our last attempt was made for the cleavage of the central bond in strained cyclopropyl ketone under PET (Photoinduced Electron Transfer) conditions in continuation of our previous *Chapter-I* (Sub-Section-D) work as shown in *Scheme-6*, retrosynthetic concepts (**38**→**39**). We¹⁵ and others⁵⁷ have developed the cleavage of cyclobutyl, cyclopropyl and epoxy ketones under new PET conditions, which is a facile process. The regiochemistry of bond cleavage is governed by the principle of maximum overlap of σ of cyclopropyl and π^* of carbonyl orbitals. Our initial attempts to cleave central bond in **115** under PET conditions were unsuccessful and polymeric product mixtures were observed. However, the reaction of cyclopropyl ketone **82**, 0.02M solution in 20% TEA in ethanol (by volume) was irradiated at 300 nm in pyrex vessel and successful cleavage of cyclopropyl group was achieved. However, the cleavage of cyclopropane was not selective and two products were isolated **84** (44%) and **85** (~ 10%) (*Scheme-12*). The structures of both **84** and **85** were confirmed by spectral data. IR of **84** showed peaks at 1745 cm⁻¹(CO,s) characteristic of cyclopentanone ketone. ¹H-NMR gave signals at δ 1.18 (s, 3H, CH₃), 1.25-2.0 (m, 12H), 2.25 (q, 1H) and ¹³C-NMR peaks appeared at δ 220.00(s), 47.92(d), 38.49(s), 35.21(t), 34.49(t), 33.98(t), 23.02(t), 21.85(t), 21.26(t), 21.15(q) and mass spectrum gave M⁺ at 152(100%), 137(30), 123(35), 97(78). For compound **85**, IR gave peak at 1720 cm⁻¹(vs, CO), ¹H-NMR gave signals at δ 1.2-1.96 (m, 10H), 1.99-2.15 (m, 5H), 2.25 (m, 1H) and mass spectrum gave M⁺ at 152(9%), 124(43), 110(100), 97(70), 81(15).

Thus, once again it was possible to cleave the central cyclopropyl bond by PET-method.

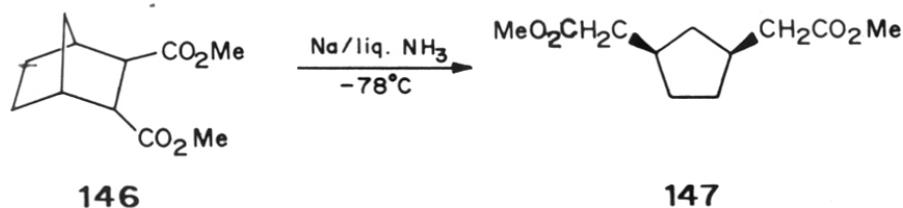
Bicyclic Route

Our third approach was the result of our deep involvement with the chemistry related to bicyclic systems and we were also excited about the possibility of cleavage of central bond in **45** (*Scheme-7*), which could lead to a quick precursor for Taxol frame **44** by electron-transfer process, in which we have considerable experience and expertise.^{15,22} A simple 1,2-shift (Wagner-Meerwein type) from **43** to **42** may give very advanced models of taxol, as shown in retrosynthetic analysis, *Scheme-7*. For the last 4-5 years, we have been involved with the chemistry of bicyclic frames,^{15,22} stereocontrol in medium cyclic rings, β -cleavage of adjacent cyclopropyl, cyclobutyl and cyclopentyl ketones (*Chapter-I*, Section-D) and this approach seems to be an outgrowth of our curiosity in this area!

Carbon-carbon bond cleavage, like C-C bond formation, is a useful transformation in organic synthesis. The cleavage is particularly advantageous over C-C bond formation in providing a variety of strategies for the synthesis of medium and large rings and in stereo-selective introduction of carbon appendages. Ring expansion *via* oxidative fission of C-C double bonds and by anion or radical induced cleavage of C-C σ bonds in bridged and small ring systems occurs smoothly. However, ring expansion through cleavage of σ bonds at the fusion of two rings larger than four membered requires either the process to be exothermic⁵⁸ or the ring expanded product be highly stabilised through an intramolecular trap⁵⁹ or a molecular geometry appropriate for continuous overlap of the participating orbitals.

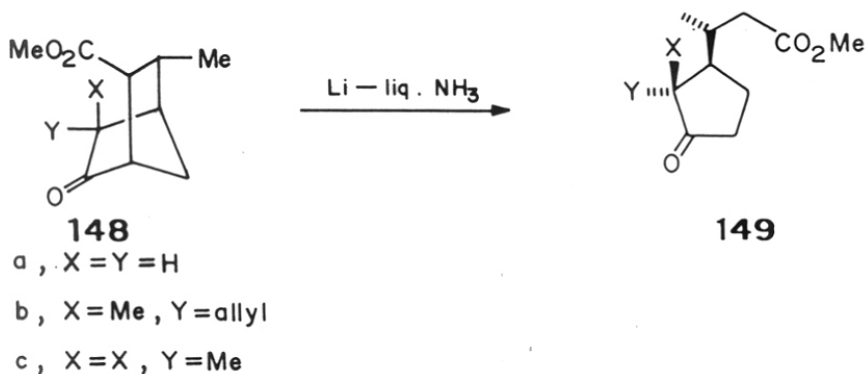
First Gassman et.al.⁶⁰ reported the Diels-Alder addition of maleic or fumaric esters to cyclopentadiene, followed by catalytic reduction and treatment with sodium in liquid ammonia at -78°C , which promotes a solvent dependent reductive cleavage of the carbon-carbon σ bond to give corresponding products (*Scheme-26*). Recently, Shimizu et.al.⁶¹

Scheme -26



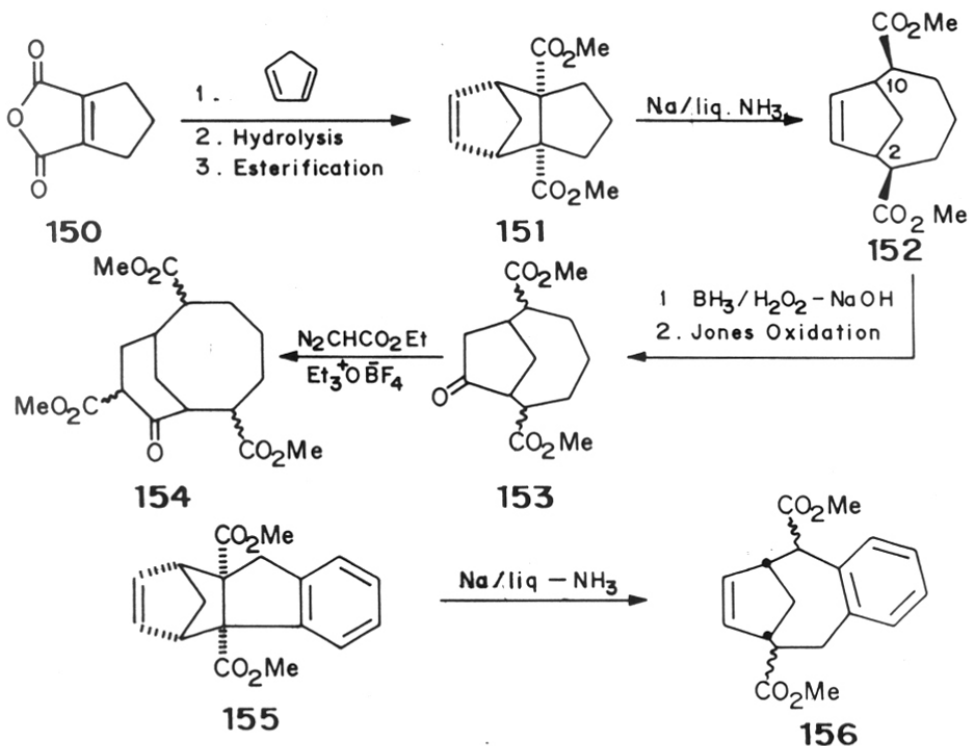
exploited above stereospecific reductive cleavage of norbornanones. Norbornanones are known to be useful precursors for cyclopentanoids, but very little is known about the reductive cleavage of norbornanones to afford cyclopentanoids (*Scheme-27*).

Scheme -27



Recently, Ghosh et.al⁶² reported a fragmentation-based strategy for taxane skeleton construction that differs from many such strategies in that a connection between C-2 and

Scheme -28

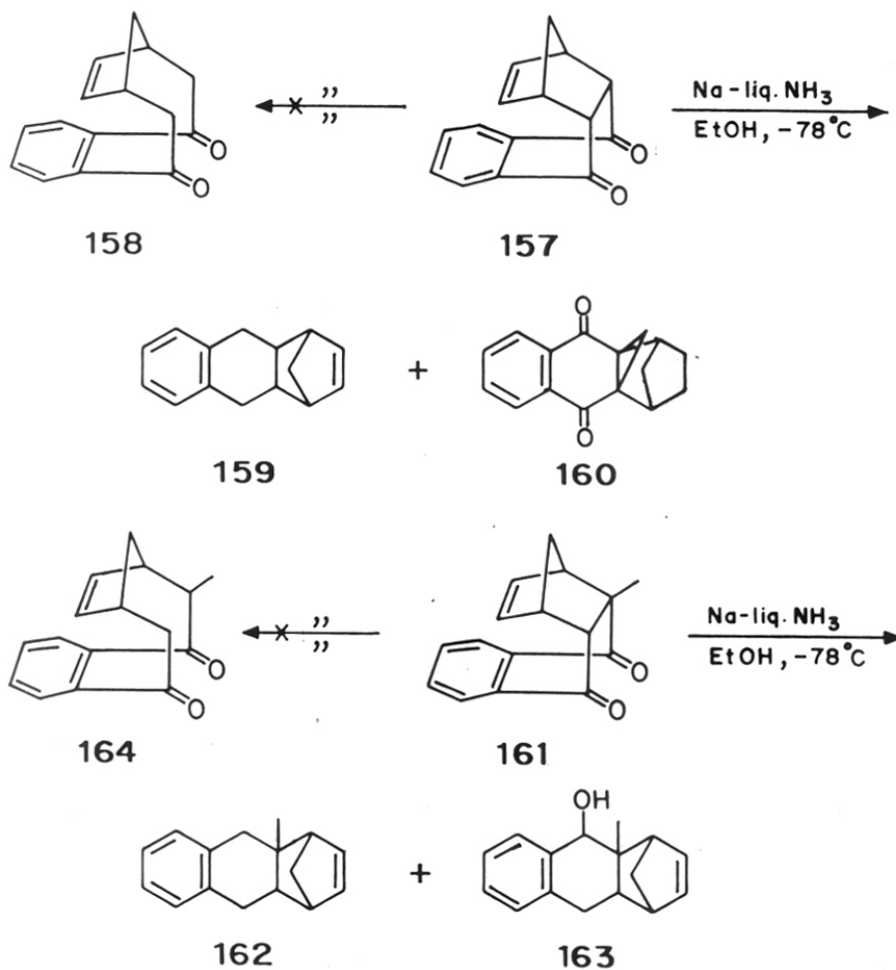


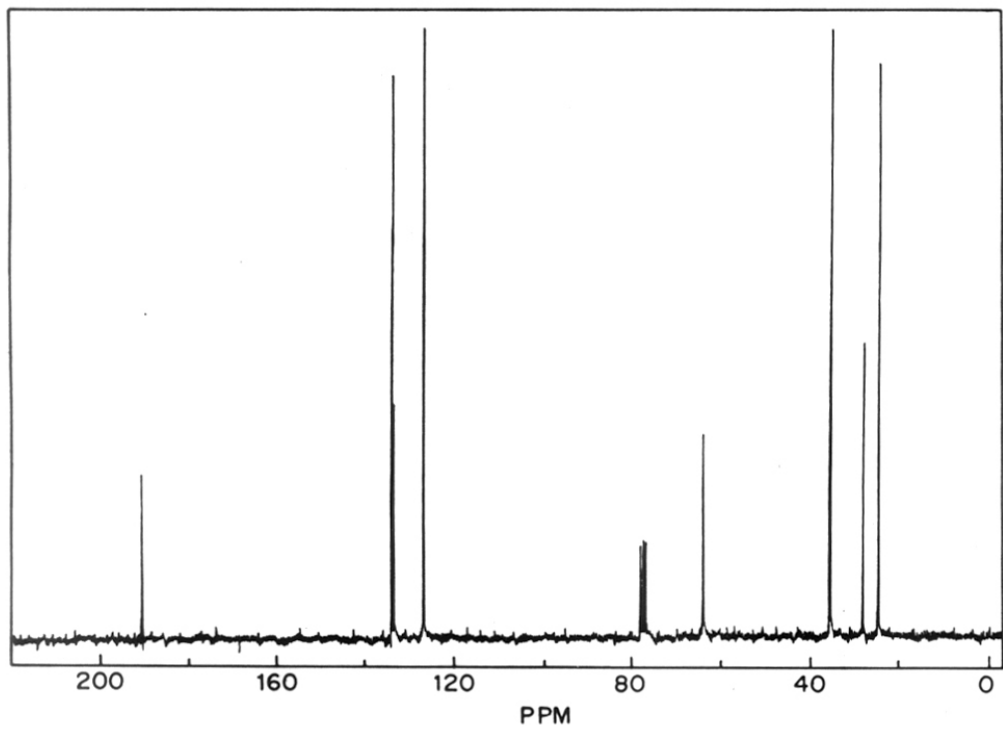
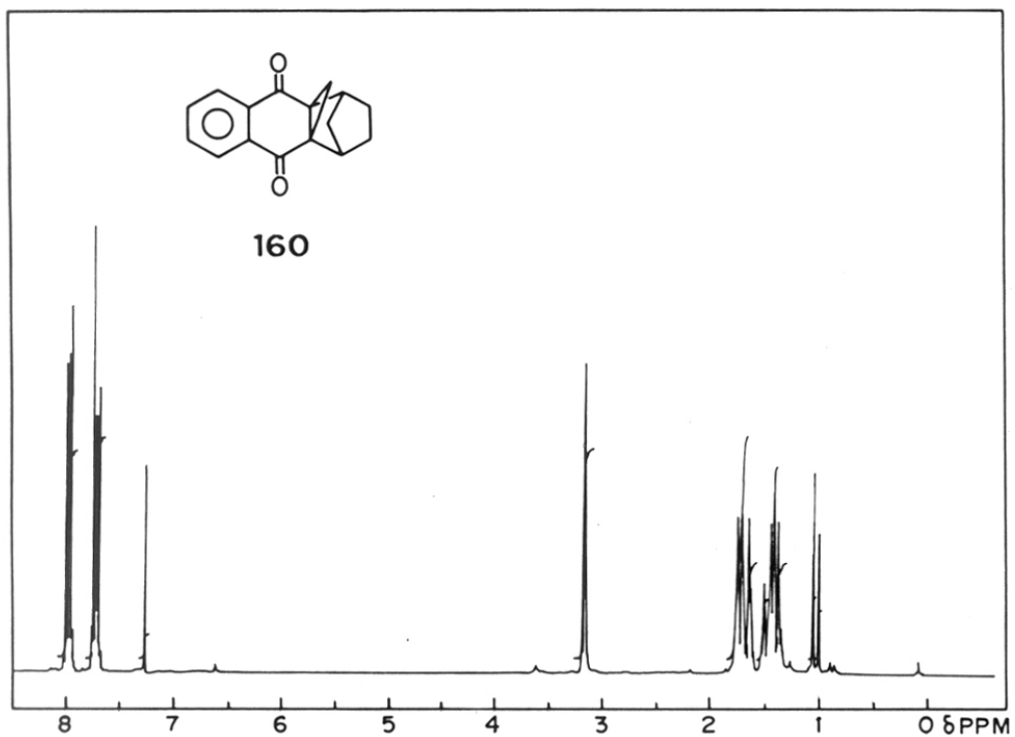
C-10 is broken in the formation of the eight-membered B-ring. Unsaturated anhydride **150** (*Scheme-28*) underwent a Diels-Alder reaction with cyclopentadiene to provide **151**, after two functional group manipulations. In the key step, diester **151** led to AB analogue **152** through reductive bond cleavage (Na-liq. NH_3/EtOH). Finally, the five-membered ring of **153** could be enlarged by way of double bond hydration and Jones oxidation followed by ring expansion with ethyl diazoacetate. An analogous sequence initiated by anhydride **155** produced tricyclic model **156**.

With our experience of efficient isomerization (β -cleavage) of endo to exo was the outcome of even cyclopentane ring cleavage adjacent to ketyl radicals, as shown in *Scheme-28*¹⁵ (Chapter-I) and by above literature precedence, we planned strategies where we could quickly enter into taxol carbocyclic frame. As part of our interest to the synthesis of the anti-cancer diterpene taxol, a simple general process for the cleavage of a ring-fusion bond in the system **157** was examined, where a 5-membered ring is fused. The tricyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13-tetraene-3,10-dione required for this investigation was obtained through D-A reaction of cyclopentadiene with naphthoquinone (See experimental, *Chapter-I*). The compound **157** was subjected to Birch reduction (Na-liq. NH_3/EtOH , -78°C) for 2 h. to give two products completely reduced **159** (37%) and an unanticipated **160** (46%) with an extra carbon. Both of the compounds were fully characterized by spectral and analytical data. Besides, the structure of **160** has been unambiguously proved by X-ray crystallography as well (See spectra-**160**, X-ray *Figure-3*). Compound **159** gave $^1\text{H-NMR}$ signals at δ 1.4-1.75 (m, 4H), 2.25-3.0 (m, 6H), 6.25 (m, 2H), 7.1-7.3 (m, 4H, Ar) whereas, in IR no carbonyl absorption occurred. However, in $^{13}\text{C-NMR}$ peaks appeared at δ 140.20(s), 136.49(d), 127.07(d), 126.11(d), 50.25(t), 46.38(d), 41.75(d), 33.98(t) and mass spectrum gave M^+ at 196 (5%). Similarly, **160** m.p. 160°C , showed strong IR absorptions at 1690 cm^{-1} (CO, s) for conjugated carbonyl and $^1\text{H-NMR}$ showed signals at δ 0.95-1.1 (dd, 2H, CH_2 , cyclopropyl), 1.3 (m, 1H), 1.45-1.55 (m, 2H), 1.65 (m, 1H), 1.75 (m, 2H), 3.2 (m, 2H), 7.75 (m, 2H, Ar), 8.0 (m, 2H, Ar). $^{13}\text{C-NMR}$ showed 8 peaks, indicating the symmetrical nature of molecule (C_2 -symmetry) δ 190.77 (s, CO), 134.08(d), 133.94(s), 126.97(d), 63.98(s, cyclopropyl carbon), 35.70(d), 28.37(t), 24.79(t) and mass spectrum gave M^+ at 238 (32%). Further methyl substituted tricyclic compound **161** was prepared as per *Chapter-I*

experimental conditions, where cyclopropanation (extra carbon) should not occur easily because of methyl substitution. The compound **161** was treated under similar Birch reaction conditions, but it failed to give desired bond cleavage **164**, while two products **162** and **163** were isolated. The structure of both the compounds was confirmed by spectral data. The compound **162** gave $^1\text{H-NMR}$ signals at δ 1.1 (s, 3H, CH_3), 1.65 (m, 2H), 2.0 (m, 1H), 2.3 (m, 2H), 2.6-3.0 (m, 4H), 6.3 (m, 2H), 7.05-7.2 (m, 4H, Ar) and $^{13}\text{C-NMR}$ gave peaks at δ 139.98(s), 139.31(s), 138.52(d), 135.90(d), 128.00(d), 126.94(d), 126.06(d), 126.00(d), 52.89(d), 49.18(d), 47.95(t), 47.21(d), 45.91(s), 40.92(t), 35.12(t), 30.54(q). The compound

Scheme - 29





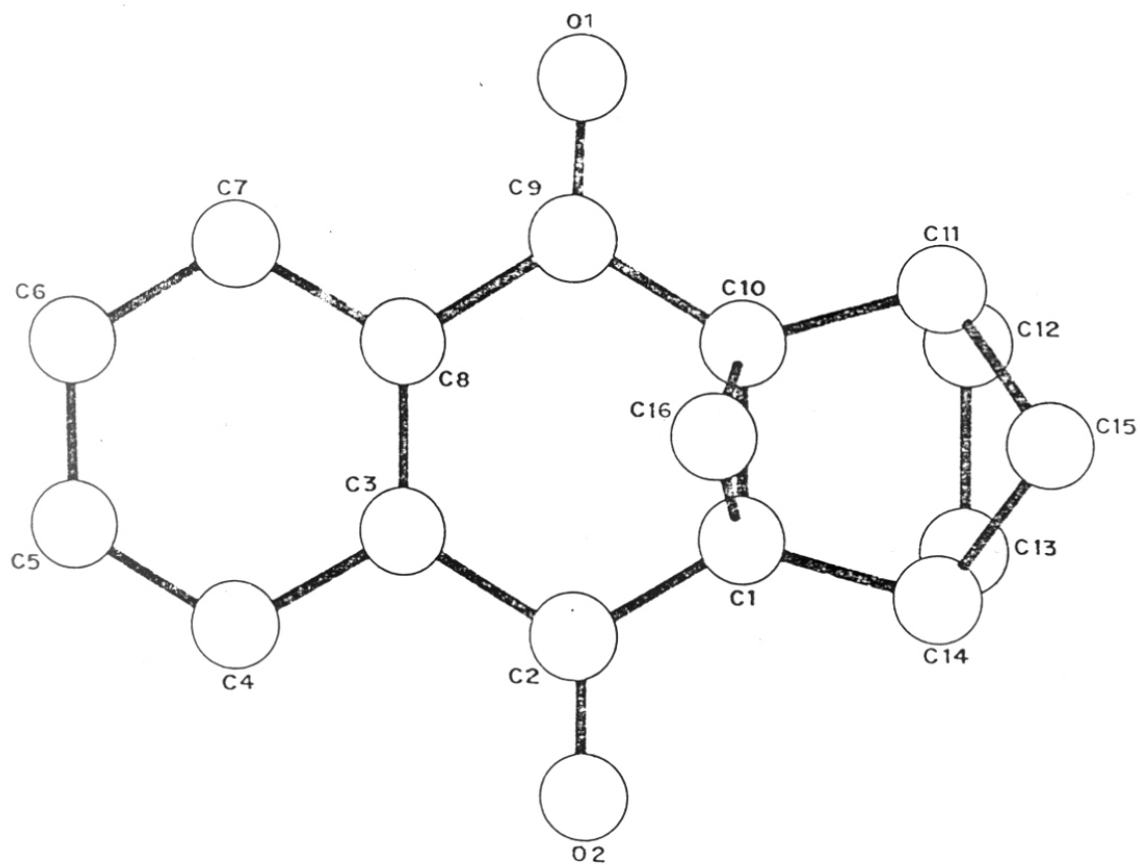


FIG. 3 : X-RAY STRUCTURE OF 160

163 showed strong absorption in IR at 3450 cm^{-1} (s, OH) whereas $^1\text{H-NMR}$ gave signals at δ 0.95 (s, 3H, CH_3), 1.65 (m, 2H), 1.8 (m, 2H), 2.0 (m, 1H), 2.65-2.9 (m, 2H), 4.65 (s, 1H, CH-OH), 6.3 (m, 1H), 6.4 (m, 1H), 7.0-7.25 (m, 3H, Ar), 7.3-7.4 (d, 1H, Ar). $^{13}\text{C-NMR}$ gave satisfactory signals at δ 141.21(s), 138.31(d), 136.85(s), 136.41(d), 126.48(d), 126.25(d), 126.06(d), 122.33(d), 74.39(d) hydroxy carbon attached, 50.52(d), 49.71(d), 47.95(t), 46.98(d), 44.99(s), 33.48(t), 22.57(q) (*Scheme-29*).

We fail to understand the mechanism of cyclopropanation (or chemistry with extra carbon) for the formation of **160**, the structure of which has been unambiguously proved by X-ray. However, central to our synthetic strategy for transformation of **157** to **158**, a precursor for carbocyclic frame of Taxol, we attempted Birch reduction. In due course, we plan to carry out reducts with SmI_2 as well. Although a failure from the point of our main objective, this study throws new light on the Birch reduction of bicyclic compounds. These developments especially the phenomenon of cyclopropanation offer new chemistry which is unanticipated. Further investigations with regard to mechanism etc. is underway in our group.

CONCLUSIONS

This chapter was an exploratory study for the creation of model carbocyclic frames of Taxol employing [m.n.1] propellanes. To conclude, this chapter covers failures and successes with regard to creation of model carbocyclic frame of Taxol. In this chapter, much of the observed chemistry was unanticipated and unexpected in nature. Hence, there arose the need for generalization, mechanistic insights and comparison of our observation with existing knowledge. Despite the efforts of three strategies (*Scheme-5, 6 and 7*), we have been only partially successful with the synthesis of carbocyclic frame of Taxol.

Mention must be made here regarding the significant potential of creating highly advanced skeletons for Taxol by our rhodium acetate strategy (*Scheme-17 and 18*) **111**, **114** and **115** including C-D ring system, if we initially start with the appropriately functionalized and substituted benzene ring at **111** itself (*Scheme-17*).

Although we were successful in cleaving the central bond in propellane, but aromatization with [m.3.1] propellane was a big problem. However, with LTA and PET studies, we were successful in creating models of Taxol, with appropriate C-1 functionalization. Of course, since our strategy is new, a lot of unprecedented and unforeseen problems were encountered in implementing these concepts. Further work is in progress to overcome above problems.

Our third approach to cleave the central bond in bicyclic system **157** under reductive conditions lead to the discovery of unprecedented and unanticipated cyclopropanation phenomenon i.e., chemistry with one extra carbon in these systems.

EXPERIMENTAL

6-Methoxy-1,2,3,4-tetrahydronaphthalene (Wolff-Kishner Reduction) (76): To a solution of 6-Methoxytetralone **73** 5 gm. (0.0284 mol) dissolved in diethylene glycol 100-120 ml, was added hydrazine 2.84g (2.75 ml, 0.05 mol) and the mixture was refluxed for 2 hrs. The hydrazone was first formed in situ, then added sodium ethoxide 9.54g (0.174 mol) and the mixture was refluxed for an additional 2 hrs. The excess of hydrazine was removed by distillation until a favourable temperature for the decomposition of the hydrazone was attained (170°C-190°C) and the solution was refluxed for 3-5 hrs longer. Reaction mixture was poured into ice water, extracted with CH_2Cl_2 , dried over Na_2SO_4 . Crude compound was purified by silica gel column chromatography with 2% EtOAc:pet.ether to afford 67% (2.9g) of the product.

IR (Neat) : cm^{-1} 2940(s), 2840(m), 1620(s), 1500(s).

$^1\text{H-NMR}$ (90 MHz) : δ 1.55-1.8 (m, 4H), 2.5-2.7 (m, 4H), 3.6 (s, 3H, OCH_3), 6.5 (m, 2H, Ar), 6.85 (m, 1H, Ar).

MS : m/z 162 (M^+ , 85%), 134(100), 115(13).

1,2,3,4,5,6,7,8-Octahydro-2-oxonaphthalene (81): Liquid ammonia (~ 625 ml) collected at -78°C was added to 10g. (0.061 mol) of the substance **76** dissolved in dry EtOH (100 ml), 10g. (0.434 mol) of freshly cut sodium metal was added in small pieces with good stirring as rapidly as possible without the reaction becoming uncontrollable (~ 2-3 h.). When the blue colour had disappeared, the pasty mass was decomposed cautiously by the addition of water (100 ml) and extraction with ether. The evaporation of solvent gave the crude compound (**78**) which was dissolved in methanol (400 ml). To this was added a solution of oxalic acid 15.6g. (0.173 mol) in 204 ml of H_2O and mixture was shaken 4-6 times and kept at room temperature for 8 h. The above solution was extracted with ether 5-6 times, then thoroughly washed with NaHCO_3 , twice with H_2O and dried over Na_2SO_4 removal of solvent and purification by silica gel column chromatography furnished 6-methoxy-1,2,3,4- dihydronaphthalene (8%) using pet.ether, pet.ether:EtOAc (98:2) and β,γ -unsaturated ketone (7.5g, 81%) using pet.ether:EtOAc (96:4) as eluent.

IR (Neat) : cm^{-1} 2950(s), 1730(vs), 1450(m).

$^1\text{H-NMR}$ (200 MHz) : δ 1.5 (m, 4H), 1.8 (m, 4H), 2.25 (m, 2H), 2.45 (t, 2H), 2.65 (s, 2H).

$^{13}\text{C-NMR}$: δ 210.04, 128.33, 125.57, 44.12, 41.25, 30.48, 29.53, 29.39, 22.66,
(200 MHz) 22.19.

MS : m/z 150 (M^+ , 100%), 122(60), 90(14).

β -Carbethoxy- β -cyclohexenylpropionic acid (77): To a refluxing solution of 5.6g. of potassium in 100 ml of dry t-butyl alcohol was added (atmosphere of nitrogen) a mixture of 11.9g. of cyclohexanone and 30.1g. of diethyl succinate, followed by 10 ml of t-butyl alcohol to complete the transfer of reagents. After refluxing for 10 minutes (atmosphere of nitrogen), the mixture was cooled in an ice-bath and acidified with a freezing mixture of 20 ml of concentrated hydrochloric acid and 20g. of ice. Most of the t-butyl alcohol was removed at reduced pressure, and the residue was extracted with ether. The ether layer was extracted thoroughly with saturated sodium bicarbonate solution. Acidification of the aqueous extracts with dilute hydrochloric acid liberated the half-ester which was taken up in ether, washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of ether, and distillation of the residue gave 23.1g (84% yield) of colourless viscous oil, b.p. 150-155°C (0.5 mmol).

IR (Neat) : cm^{-1} 3300(bs), 1840(w), 1770(m), 1740(s), 1650(w), 1230(w).

$^1\text{H-NMR}$ (200 MHz) : δ 1.2 (t, 3H), 1.55 (m, 4H), 2.0 (m, 4H), 2.5 (dd, 1H), 2.95 (dd, 1H), 3.45 (q, 1H), 4.15 (q, 2H), 5.6 (m, 1H), 10.25 (bs, 1H, OH).

MS : m/z 152 (M^+ , 12%), 136(32), 123(20), 108(26), 91(52), 79(100), 67(63).

4,5,6,7-Tetrahydro-1-indanone (79): A mixture of 4.90g. of the half-ester (77), 1.0g. of fused ZnCl_2 dissolved in 50 ml of acetic acid and 100 ml of acetic anhydride was refluxed for 9 hrs. After cooling slightly, the excess anhydride was decomposed by cautious addition of 50 ml of water, then 25 ml of conc. HCl was added and refluxing was continued for 1 hr. The solution was cooled, made strongly alkaline, and steam distilled until the distillate failed to give completely desired compound even reaction mixture also, three times extracted with dichloromethane and steam distillate also extracted with dichloromethane (3x50 ml) both

were mixed, washed with water (2x100 ml) and dried over Na_2SO_4 . Concentrated at reduced pressure then purified by silica gel column chromatography using EtOAc:pet.ether (3:97) to furnish (**79**) 34% (1 g.) yield.

IR (Neat) : cm^{-1} 2940(m), 2880(w), 1700(vs), 1650(m), 1450(m).

$^1\text{H-NMR}$ (200 MHz) : δ 1.1 (m, 4H), 2.05 (m, 2H), 2.25 (m, 4H), 2.5 (m, 2H).

MS : m/z 136 (M^+ , 41%), 121(12), 108(21), 94(100), 79(91).

Tricyclo[4.3.1.0^{1,6}]decan-7-one (82): This reaction was run in oven dried glassware under a nitrogen atmosphere. To 100 ml of dry Me_2SO were added 0.381 g. (50% in mineral oil, 7.93 mmol) of NaH and 4.84 g. (23 mmol, three fold excess) of trimethylsulfoxonium iodide. The mixture was stirred at room temperature until the solid suspension disappeared and the solution of 1 g (7.35 mmol) of enone in 15 ml of dry Me_2SO was added dropwise over 20 minutes at room temperature to the ylide solution. The dark brown reaction mixture (enolate) was then heated to 75°C for 30-45 minutes during which time the colour lightened to a clear yellow. The light yellow reaction mixture was poured into 150 ml of ice-water and extracted with four 50 ml portions of CH_2Cl_2 . The combined CH_2Cl_2 layers were washed three times with 200 ml portions of saturated NaCl solution dried over Na_2SO_4 and concentrated under reduced pressure to give 0.98 g. of crude product which was silica gel column chromatographed using pet.ether:EtOAc (97:3) solvent mixture to yield (75%, 823 mg) as a liquid.

Tricyclo[4.3.1.0^{1,6}]decan-7-one (82): A solution of 5g. (33.33 mmol) of unsaturated ketone **81** in t-BuOH (1 lit.) stirred under a stream of N_2 , was irradiated with a 450W Hanovia lamp through a pyrex filter. The reaction was complete in about 50 h., was monitored by TLC and GLC. The evaporation of the solvent at reduced pressure yielded an oil which was silica gel chromatographed using EtOAc:pet.ether (4:96) to furnish 44% (2.2 g.) of **82**, remaining thing was found to be polymeric compound and (10%) unsaturated ketone **81** was also isolated.

IR (Neat) : cm^{-1} 2980(m), 1742(vs).

$^1\text{H-NMR}$ (80 MHz) : δ 0.9-1.05 (m, 2H), 1.25-2.15 (m, 10H), 2.25-2.38 (m, 2H).

¹³C-NMR : δ 214.56, 35.93, 32.57, 32.45, 29.50, 29.17, 24.45, 21.42, 21.29,
(200 MHz) 19.82.

MS : m/z 150 (M⁺, 52%), 122(10), 108(100), 93(68), 79(48).

β-Cleavage of tricyclo[4.3.1.0^{1,6}]deca-7-one (84&85): The tricycloketone (0.180g, 1.2 mol) was dissolved in ethanol:triethylamine solvent mixture (60 ml) (80:20). The solution was purged with slow stream of nitrogen gas for 10 minutes and then irradiated in Srinivasan-Rayonet photochemical reactor at 300 nm in pyrex tube for 5 h. The progress of the reaction was monitored by GC/TLC. The solvent and TEA were evaporated under reduced pressure and the crude product obtained was purified on silica gel column using pet.ether:EtOAc (99:1) as an eluent to give (80 mg, 44%) of (84) and (18 mg, ~ 10% of (85).

(84) IR (Neat) : cm⁻¹ 2950(s), 2880(m), 1745(vs), 1450(m).

¹H-NMR : δ 1.18 (s, 3H, CH₃), 1.25-2.0 (m, 12H), 2.25 (q, 1H).

¹³C-NMR : δ 220(s), 47.92(d), 38.49(s), 35.21(t), 34.49(t), 33.98(t), 26.15(q),
(200 MHz) 23.02(t), 21.85(t), 21.26(t).

MS : m/z 152 (M⁺, 100%), 137(30), 123(35), 97(78).

(85) IR (Neat) : cm⁻¹ 2940(s), 2860(m), 1720(vs).

¹H-NMR (90 MHz) : δ 1.2-1.96 (m, 10H), 1.99-2.15 (m, 5H), 2.25 (m, 1H).

MS : m/z 152 (M⁺, 9%), 124(43), 110(100), 97(70), 81(15).

7-Methyltricyclo[4.3.1.0^{1,6}]decan-7-hydroxy (83): To a cooled solution (0°C) of 2g. (13.3 mol) of tricyclo ketone **82** in 100 ml of dry ether, 15.6 ml (1M, 15.6 mmol) of methyl lithium ether solution was added drop by drop under N₂ atmosphere, after addition, the mixture was stirred at room temperature for 2 h. An aqueous ammonium chloride solution was added, the product was taken up in ether solution dried over Na₂SO₄. The ether solution was concentrated. The crude product was purified by silica gel column chromatography using ether:n-hexane (6:94) to furnish 96% (2.13g.) of the product (83).

m.p. : 82-84°C.

IR (CHCl₃) : cm⁻¹ 3400 (bs, OH), 2940(s), 2860(m), 1230(s).

¹H-NMR (200 MHz) : δ 0.2 (d, 1H), 0.75 (d, 1H), 1.05 (m, 2H), 1.25 (s, 3H, CH₃), 1.25-1.7 (m, 8H), 1.8-1.9 (m, 2H), 2.0-2.15 (m, 1H).

¹³C-NMR (200 MHz) : δ 81.11(s), 36.96(t), 33.32(s), 32.70(t), 28.93(t), 26.35(s), 24.80(q), 23.66(t), 22.28(t), 20.83(t), 16.58(t).

MS : m/z 166 (M⁺, 33%), 151(60), 108(90), 93(100), 79(55).

Dehydration of tricyclic alcohol with p-toluenesulphonic acid (86&87): A mixture of (83) 200 mg (1.23 mmol), dry ethylene glycol (5 ml), triethylorthoformate (1 ml) and p-toluenesulphonic acid 212 mg (1.23 mmol) was heated at 60-70°C for 6 h. The progress of the reaction was monitored by TLC. After completion of reaction, the mixture was poured on ice-water and extracted with ether (4x20 ml), washed with brine solution and finally with water and dried over Na₂SO₄. Evaporation of solvent under reduced pressure gave crude material which was purified by silica gel column chromatography using pet.ether as eluent to give products (86&87).

Dehydration of tricyclic alcohol 83 with KHSO₄ (86&87): A mixture of (83) 600 mg (3.61 mmol) and KHSO₄ 983 mg. (7.22 mmol) in dry toluene was refluxed for 4 h. Progress of the reaction was monitored by TLC. After the completion of reaction, the reaction mixture was cooled and poured in water, extracted with ether (3x25 ml), dried over Na₂SO₄. The evaporation of solvent and purification by silica gel column chromatography using pet.ether as an eluent gave the products 86&87 (68%, 360 mg).

(86) ¹H-NMR (200 MHz) : δ 5.5 (m, 1H), 2.5 (m, 2H), 2.25 (m, 2H), 1.75-1.92 (m, 7H), 1.4 (s, 3H, CH₃), 1.0 (m, 1H).

MS : m/z 148 (M⁺, 22%), 131(38), 118(47), 105(100), 91(62).

(87) Yield : 63% (112 mg).

IR (Neat) : cm⁻¹ 2940(m), 1450(m), 1280(s).

¹H-NMR (200 MHz) : δ 1.9 (m, 4H), 2.4 (s, 3H, CH₃), 2.85 (m, 4H), 7.0-7.1 (m, 3H, Ar).

¹³C-NMR (200 MHz) : δ 136.78(s), 134.65(s), 133.90(s), 129.56(d), 128.89(d), 126.17(d), 29.29(t), 28.92(t), 23.31(t), 23.25(t), 20.79(q).

MS : m/z 146 (M^+ , 37%), 131(88), 128(27), 118(100), 105(54), 91(63), 77(31).

7-Methylidene tricyclo [4.3.1.0^{1,6}] decane (88): Into a 250 ml round bottom flask fitted with a pressure equalizing dropping funnel connected to a nitrogen line are placed 1.15 g. (17.58 mmol) of activated zinc powder (Zn), 60 ml of dry THF, and 1.044 g. (6.0 mmol) of CH_2Br_2 . The mixture was stirred and cooled with a $CaCl_2$ ice cooling bath at $-20^\circ C$. To the stirred mixture was added dropwise 0.91 g. (4.79 mmol) of $TiCl_4$ in dichloromethane over 15 minutes. Then reaction mixture was stirred for 45 minutes at $0^\circ C$, it becomes a dark grey slurry. To the stirred mixture was added 0.6 g. (4.0 mmol) of ketone in 15 ml of dry dichloromethane over a period of 10 minutes. The cooling bath was removed and the mixture was stirred at room temperature ($20^\circ C$) for 2 hr. The mixture was diluted with 100 ml of n-hexane and a slurry of 60 g. of $NaHCO_3$ in 25 ml of water was added cautiously over 15 minutes the clear organic solution was poured into a sintered flask and the residue was washed three times with 50 ml portions of n-hexane. The combined organic layers were dried over Na_2SO_4 . Then concentrated at low temperature ($40^\circ C$) and reduced pressure to give pure cyclopropyl exomethylene compound (88) 82% (490 mg) .

1H -NMR (200 MHz) : δ 0.6-0.8 (dd, 2H), 1.3 (m, 4H), 1.55-2.2 (m, 8H), 4.75 (d, 2H).

Epoxidation of 7-methylidene tricyclo[4.3.1.0^{1,6}]undecane (89): A solution of (88) 200 mg (1.35 mmol) in CH_2Cl_2 (25 ml) was treated with 80% *meta*-chloro perbenzoic acid (MCPBA) 581 mg (3.37 mmol) and the whole mixture was stirred at room temperature for 1-2 h. After decomposition of the excess per acid by addition of aq. saturated $NaHCO_3$ and aq. saturated $NaCl$, the organic layer was dried over Na_2SO_4 . Removal of the solvent under reduced pressure gave the product which was purified by column chromatography quickly on silica gel using EtOAc:pet.ether (2:98) to furnish epoxide (89) 76% (170 mg).

1H -NMR (200 MHz) : δ 0.45 (d, 1H), 0.55 (d, 1H), 1.05-2.4 (m, 12H), 3.95-4.0 (d, 1H), 4.05-4.1 (d, 1H).

Trimethylsilyltrifluoromethane sulfonate: 3g. (0.027 mol) of trifluoromethanesulfonic acid and 3.9g. (0.036 mol) of TMS were mixed together at room temperature. After standing

for 1 h, the evolution of methane ceased. Subsequent distillation of the reaction mixture was performed for identification purposes only, affording trimethylsilyl trifluoromethane sulfonate in ~94% yield as a colourless liquid.

b.p. : 40°C / 11 torr.

Reaction of epoxy tricyclic compound 89 with trimethylsilyltriflate (91): A solution of epoxy cyclopropyl 100 mg (0.6 mmol) in toluene (10 ml) was cooled to -78°C. Then added TMSOTf 200 mg (0.85 mmol) over a period of 10 minutes at -78°C. After being stirred for a further 10 minutes, the reaction mixture was allowed to warm gradually to room temperature, then it was stirred for an additional 20 minutes, and poured into ice-water. The mixture extracted with EtOAc dried over Na₂SO₄. The concentration of the solvent at reduced pressure and purification by the column chromatography using pet.ether:EtOAc (96:4) gave an aromatic product (91) 34% (48 mg).

¹H-NMR (90 MHz) : δ 0.1-0.18 (s, 9H, Si(CH₃)₃), 1.42-1.75 (m, 4H), 2.38 (m, 4H), 3.9 (s, 2H, CH₂OSi(CH₃)₃), 6.9-7.0 (m, 1H, Ar), 7.1-7.4 (m, 2H, Ar).

Catalytic hydrogenation of methyl cinnamate (109): A solution of 6.0g. (0.037 mol) methyl cinnamate in dry ethyl acetate (100 ml) was hydrogenated using 10% Pd-C (450 mg) at a hydrogen pressure of 30 psi for 16 h. The reaction mixture was filtered to remove the catalyst, and the filtrate was concentrated under reduced pressure to give a residue, which was chromatographed over a silica gel column using pet.ether:acetone (96:4) to give 90% (5.5 g.) of the product.

IR (Nujol) : cm⁻¹ 3000(m), 2955(s), 1745(vs), 1600(m).

¹H-NMR (200 MHz) : δ 2.65 (t, 2H), 3.0 (t, 2H), 3.7 (s, 3H, OCH₃), 7.25 (m, 5H, Ar).

3-Phenylpropionic acid (110): A mixture of 5.5g. (0.033 mol) of reduced ester in methanol (100 ml) and 50% aqueous KOH 9.39g. (0.16 mol) was refluxed for 10 h. The progress of reaction was monitored by TLC. The solution was cooled to room temperature, acidified with HCl and extracted with CH₂Cl₂ (4x50 ml) and finally washed with H₂O (2x100 ml). The evaporation of solvent gave almost pure compound 97% (4.88g). Recrystallised from pet.ether and few drops of ethyl acetate which was used for further reaction.

m.p. : 48°C

$^1\text{H-NMR}$ (80 MHz) : δ 2.6 (t, 2H), 2.9 (t, 2H), 7.05 (m, 5H).

3-Phenylpropanoyl chloride: A mixture of 10 g. (0.1 mol) of 3-phenylpropanoic acid and 12 ml (0.25 mol) of thionyl chloride was heated under reflux for 2 h. under anhydrous condition. Excess thionylchloride was removed at reduced pressure, and the residue was vacuum distilled, giving 10.87 (97%) of 3-phenylpropanoylchloride as a colourless liquid.

b.p. : 140°C (1mm) Lit.* 72°C (0.4mm).

IR (Neat) : cm^{-1} 1812

Preparation of 1-diazo-4-phenyl-2-butanone (111):

Diazomethane Generation (A): An aqueous solution of KOH (50%, 60 ml) and ether (200 ml) was placed in a conical flask and cooled in an ice-salt bath to -10°C . N-nitroso-N-methylurea 18.5g. (0.178 mol) was added portionwise and with stirring over a period of 1 h. and stirring was continued at -10°C for another 45 minutes. The contents of the flask were then transferred to a separatory funnel and the upper ether layer containing CH_2N_2 was separated and dried over KOH for 10 minutes in an ice-salt bath. The CH_2N_2 solution was filtered through a cotton plug into a 500 ml three-necked flask cooled in an ice-bath and equipped with a dropping funnel, guard tube (CaCl_2) and a N_2 inlet.

Diazoketone (B): To the above solution of CH_2N_2 , at 0°C under nitrogen atmosphere, was added dropwise a solution of the acid chloride 6g. (0.035 mol) in anhydrous ether (40 ml) over a period of 45 minutes. After stirring for 1 h. at 0°C , the cooling bath was removed and stirring was continued for 4 h. Excess CH_2N_2 was removed by bubbling dry N_2 for 20 minutes (CH_2N_2 was absorbed in a trap containing ACOH). The reaction mixture was concentrated and the residue was silica gel column chromatographed using EtOAc:pet.ether (10:90) as an eluent to yield (93%, 5.8 g.) of the product **111**. After concentration, the diazoketone was obtained as a pale yellow oil in a practically quantitative yield.

Caution: The entire operation was performed behind a safety glass shield in a fume cupboard equipped with a good exhaust.

IR (Neat) : cm^{-1} 2980(m), 2090(s), 1635(s).

$^1\text{H-NMR}$ (200 MHz) : δ 2.28-2.93 (m, 4H), 5.14 (s, 1H, CHN_2), 7.1 (s, 5H, Ar).

MS : m/z 190 (M^+ , 28%), 162(36), 120(100).

Preparation of Trienones-3,8a-dihydroazulen-1(2H)-one (113): A solution of 1-diazo-4-phenylbutan-2-one (111) 3 g. (17.2 mmol) in dry dichloromethane (50 ml) was added dropwise with stirring to a solution of rhodium (II) acetate (10 mg, 0.022 mmol) in dichloromethane (125 ml) under reflux. Reaction, which could be monitored by TLC, was complete within 1 h. The cooled solution was washed with water, dried, and concentrated under reduced pressure to afford **113** as a yellow oil (2.35g.) which was used in subsequent reactions without purification.

IR (CHCl_3) : cm^{-1} 1745(s).

$^1\text{H-NMR}$ (80 MHz) : δ 2.32-3.00 (m, 5H, 2- H_2 , 3- H_2 and 8-H), 5.00 (dd, 1H), 5.96-6.23 and 6.38-6.48 (m, 4H).

Preparation of conjugated enones-3,4-dihydroazulen-1(2H)-one (114): The diazoketone was cyclised with rhodium acetate as described above to afford (2.35g.) a dichloromethane solution of **113**. The cooled solution was treated with triethylamine (1.5 ml) and after stirring at room temperature for 1 h., the solution was washed with cold 1% hydrochloric acid (20 ml) and water (3x100 ml), and dried over Na_2SO_4 . Removal of the solvent furnished an oil which on purification by silica gel column chromatography (EtOAc-pet.ether, 15:85) furnished the trienone **114** as a yellow oil 89% (2.1 g.).

IR (Neat) : cm^{-1} 3000(s), 1700(vs), 1630(s), 1450(m).

$^1\text{H-NMR}$ (80 MHz) : δ 2.58 (Sym m, 4H), 2.83 (d, 2H), 5.39 (dt, 1H), 6.09 (dd, 1H), 6.48 (dd, 1H), 6.68 (d, 1H).

MS : m/z 146 (M^+).

Cyclopropanation of conjugated ketone-Tricyclo [5.3.1.0^{1,7}] undeca-2,4-dien-10-one (115): This reaction was run in oven dried glassware under a nitrogen atmosphere. To 600 ml of dry Me_2SO were added 1.92g. (50% in mineral oil, 40 mmol) of NaH and 24.4 g. (111 mmol, three fold excess) of trimethylsulfoxonium iodide. The mixture was stirred at room temperature until the solid suspension disappeared and the solution of 5.40g (37 mmol) of trienone in 60 ml of dry Me_2SO was added dropwise over 45 minutes at room temperature to the ylide solution. The dark brown reaction mixture (enolate) was then heated to 75°C for

30-45 minutes during which time the colour lightened to a clear yellow. The light yellow reaction mixture was poured into 600 ml of ice-water and extracted with four 200 ml portions of CH_2Cl_2 . The combined CH_2Cl_2 layers were washed three times with 200 ml portions of saturated NaCl solution dried over Na_2SO_4 and concentrated under reduced pressure to give 6.5g. of crude product which was silica gel column chromatographed using pet.ether:EtOAc (85:15) solvent mixture to yield (76%, 4.49 g.) as a pale yellow liquid.

IR (Nujol) : cm^{-1} 3000(s), 2940(m), 1700(vs), 1650(vs), 1430(m), 1290(s).

^1H -NMR (200 MHz) : δ 1.25 (d, 1H), 2.1 (m, 4H), 2.55 (d, 1H), 2.8 (d, 2H), 5.65 (m, 2H), 5.95 (m, 1H), 6.5 (d, 1H).

^{13}C -NMR (200 MHz) : δ 211.56(s), 128.81(d), 127.75(d), 127.52(d), 122.39(d), 58.19(s), 41.43(s), 32.74(t), 32.09(t), 28.37(t), 22.72(t).

MS : m/z 160 (M^+ , 51%), 133(40), 117(100), 104(78), 91(73), 77(40).

Hydrogenation of tricyclo[5.3.1.0^{1,7}]undeca-3,5-triene-8-one with $\text{RhCl}(\text{PPh}_3)_3$ catalyst (120): $\text{RhCl}(\text{PPh}_3)_3$ 22 mg. (molar ratio 1 mole percentage w.r.t. $\text{C}=\text{C}$) and (10 ml) of dry toluene were placed in a hydrogenation vessel with a magnetic bar, and the apparatus was flushed out with H_2 gas. On stirring, the solution became homogeneous in less than 1 minute, the solution was saturated with hydrogen. A toluene solution of compound (115) 200mg (1.25 mmol) was injected in reaction vessel through syringe and the hydrogenation was carried out at an atmospheric pressure for 6 h. The hydrogen gas uptake was measured at intervals to find the progress of the reaction which was monitored by TLC as well. After completion of reaction, solvent was removed and crude product was purified by silica gel column chromatography using pet.ether:EtOAc (97:3) as an eluent.

IR (Neat) : cm^{-1} 2940(s), 2850(m), 1745(vs), 1600(m), 1450(m).

^1H -NMR (200 MHz) : δ 1.2 (s, 3H, CH_3), 1.4-1.65 (m, 2H), 1.75-2.25 (m, 6H), 2.35-2.6 (m, 3H), 5.4-5.6 (m, 2H).

10-Methyltricyclo[5.3.1.0^{1,7}]undeca-2,4-diene-10-hydroxy (119): To a cooled solution (0°C) of 500 mg (3.0 mmol) of tricycloketone 115 in 30 ml of dry ether, 3.6 ml (1M, 3.6 mmol) of methyl lithium-ether solution was added drop by drop under N_2 atmosphere. After

addition was complete, the solution was stirred at room temperature for 2 h. An aqueous ammonium chloride solution was added, the product was extracted (4x30 ml) with ether then dried over Na₂SO₄. The ether solution was concentrated at reduced pressure and low temperature, the crude product was purified by silica gel column chromatography using acetone:n-hexane (4:96) as an eluent to yield alcoholic product 500 mg (91%).

m.p. : 104°C.

IR (Nujol) : cm⁻¹ 3350 (bs, OH), 3000(m), 1450(m), 800(s).

¹H-NMR (200 MHz) : δ 0.95 (d, 1H), 1.35 (s, 3H, CH₃), 1.4 (d, 1H), 1.6 (m, 2H), 1.75 (m, 2H), 2.5 (d, 2H), 5.7 (m, 2H), 5.85 (m, 1H), 6.25 (d, 1H).

MS : m/z 176 (M⁺, 47%), 161(51), 158(44), 143(100), 133(40), 128(56), 117(88), 105(30).

10-Methyltricyclo[5.3.1.0^{1,7}]undeca-10-hydroxy (121): A magnetically stirred alcoholic compound (**119**) 1g. (5.68 mmol) dissolved in a cold (0°C) mixture of THF (70 ml) and (300 ml) EtOH was treated with hydrazine 20 ml in one portion and subsequently with 30% H₂O₂ 66.6 ml over 1 h. Stirring was continued at 0°C for an additional 3 h, at room temperature overnight. After the addition of water, the solution was extracted with CH₂Cl₂ four times (4x60 ml) and combined organic layers were washed with water, dried and filtered through a short silica gel column using EtOAc:pet.ether (6:94). But reaction was not completed (¹H-NMR showing one double bond), which was repeated with same molar concentration. Overall yield 78% (800 mg) isolated.

¹H-NMR (200 MHz) : δ 0.5 (d, 1H), 1.22 (d, 1H), 1.3 (s, 3H, CH₃), 1.5-2.1 (m, 10H), 5.5 (m, 1H), 5.9 (dd, 1H) (only one double bond reduced).

IR (Nujol) : cm⁻¹ 3400 (bs, OH).

¹H-NMR (200 MHz) : δ 0.5 (d, 1H), 1.2 (d, 1H), 1.3 (s, 3H, CH₃), 1.55-1.9 (m, 14H).

MS : m/z 180 (M⁺, 25%), 165(100), 147(20), 122(48), 105(53), 91(72), 79(62).

Dehydration of 8-methyltricyclo[5.3.1.0^{1,7}]undeca-8-hydroxy (123): A mixture of **121** (80 mg, 0.44 mmol) and KHSO₄ (120 mg, 0.88 mmol) in dry toluene was refluxed for 6h. The progress of reaction was monitored by TLC. After the completion of reaction, the reaction mixture was cooled and poured in water, extracted with ether (3x20 ml), dried over Na₂SO₄. The evaporation of solvent and purification by silica gel column chromatography using pet.ether as an eluent gave the product (30 mg, 42%) and pet.ether:EtOAc (94:6) as an eluent gave starting material **121**.

¹H-NMR (200 MHz) : δ 0.04-0.54 (m, 2H), 1.1-2.14 (m, 4H), 2.38 (s, 3H, CH₃), 2.4-3.1 (m, 4H), 6.75-7.23 (m, 3H).

MS : m/z 160 (M⁺, 18%), 145(62), 131(24), 116(100), 91(63), 77(40).

1,7-Diacetoxibicyclo[5.3.1]undeca-2,4-diene-10-one (116): To 40 ml of dry benzene and 10 ml of dry glacial acetic acid, were added 500 mg (3.12 mmol) of cyclopropyl ketone and freshly prepared 1.662g. (3.75 mmol) of lead tetraacetate (LTA). The reaction mixture was refluxed for 6 h, and 100 ml of water was added. The benzene layer was separated, washed once with 100 ml of saturated NaCl and twice with 100 ml portions of saturated NaHCO₃, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was chromatographed on 70g. of silica gel with EtOAc:pet.ether (8:92) which gave semi-solid 330 mg (38%) yield, which could be stored at 0°C.

Yield : 38% (330 mg)

IR (CHCl₃) : cm⁻¹ 3000(s), 2930(m), 1760(vs), 1730(s), 1480(s), 1450(m).

¹H-NMR (200 MHz) : δ 2.05 (s, 6H, 2 OAC), 2.1 (m, 2H), 2.4-2.6 (m, 4H), 2.7 (m, 2H), 4.9 (m, 1H), 5.5-5.62 (m, 2H), 5.9 (m, 1H).

¹³C-NMR (200 MHz) : δ 208.97 (CO, s), 170.36(s), 169.74(s), 129.09(d), 128.02(d), 127.00(d), 123.30(d), 72.20(s), 71.44(s), 38.64(t), 36.76(t), 35.31(t), 32.05(t), 20.94(q, 2C COCH₃).

MS : m/z 219 (5%), 203(16), 172(35), 144(50), 129(100), 117(68), 91(27).

8-Methylidenetricyclo[5.3.1.0^{1,7}]undeca-3,5-diene (117): Into a 250 ml round bottom flask with a pressure equalizing dropping funnel connected to a nitrogen line were placed 1.79g. (27.3 mmol) of activated zinc powder (Zn), 100 ml of dry THF, and 1.63 ml (9.37 mmol) of CH₂Br₂. The mixture was stirred and cooled with a CaCl₂-ice mixture was added dropwise 0.81 ml (7.5 mmol) of TiCl₄ in dichloromethane over 15 minutes. Then reaction mixture was stirred for 45 minutes at 0°C, it becomes a dark grey slurry. To the stirred mixture was added 1g. (6.25 mmol) of ketone in 20 ml of dry CH₂Cl₂ over a period of 15 minutes. The cooling bath was removed and the mixture was stirred at room temperature at 20°C for 2 hr. The mixture was diluted with 150 ml of n-hexane and a slurry of 100 g. of NaHCO₃ in 30 ml of water was added cautiously over 15 minutes. The clear organic solution was filtered and the residue was washed four times with 75 ml portions of n-hexane. The combined organic layers were dried over Na₂SO₄. The solvent was removed at low temperature (40°C) and at reduced pressure to give pure liquid tricyclo exomethylene compound (117) 81% (800 mg).

¹H-NMR (200 MHz) : δ 0.9 (d, 1H), 1.7 (d, 1H), 1.72-2.2 (m, 4H), 2.6 (d, 2H), 4.9 (d, 2H), 5.6 (m, 2H), 5.9 (m, 1H), 6.4 (d, 1H).

MS : m/z 158 (M⁺, 34%), 143(100), 129(70), 117(27).

1-Acetoxy-8-methylacetoxy bicyclo[5.3.1]undeca-3,5,7-triene (118): To 20 ml of dry benzene and 4 ml of glacial acetic acid at 0°C were added 200 mg (1.26 mmol) of triene (117) and 673 mg (1.51 mmol) of lead tetraacetate. The reaction mixture was stirred at 0°C until it became homogeneous around 1 h. Stirring was continued for 3 h. at room temperature, and 50 ml of water was added. The benzene layer was separated, washed once with 20 ml of saturated NaCl and twice with 50 ml portions of saturated NaHCO₃, dried over Na₂SO₄, and concentrated under reduced pressure to give (~ 350 mg) of crude product. The silica gel chromatography with EtOAc:pet.ether (12:88) gave a colourless oil 74 mg (21%) (The remaining product could not be isolated), which could be stored at 0°C.

IR (CHCl₃) : cm⁻¹ 2985(s), 1740(vs), 1445(m), 1380(s).

¹H-NMR (200 MHz) : δ 1.95-2.1 (m, 6H), 2.15 (s, 6H, OAc), 2.4 (m, 2H), 4.55 (m, 2H), 5.5-5.8 (m, 3H), 6.25 (m, 1H).

MS : m/z 217 (8%, -OAC), 190(14), 157(20), 144(51), 117(100), 79(10).

Preparation of 5,6,7,8-tetrahydro-2-tetranol (126): While maintaining a nitrogen atmosphere, freshly distilled n-propylamine (180 ml) was added to a mixture of 8g, (0.054 mol) of **129** and 3.78g. (0.54g - atom) of lithium cut into small pieces. The mixture was stirred for 30 minutes in an ice bath followed by 24 h. stirring at room temperature. Solid ammonium chloride was cautiously added (cooling) until the mixture was a milky, off white colour and further addition caused no further evolution of heat. Water (300 ml) and ether (200 ml) were added and the layers were separated. The aqueous layer was shaken with three 100 ml portions of ether, and the combined ether solution was dried over Na_2SO_4 . The solvent was evaporated to get the product which was used for further reaction (oxidation) without purification.

Oxidation of 5,6,7,8-tetrahydro-2-tetranol (125): To a solution of 10g. $\text{Na}_2\text{Cr}_2\text{O}_7$ in 30 ml of H_2O was added 76 ml of conc. H_2SO_4 and further diluted with 50 ml of water. This solution was enough for 0.1M alcohol oxidation. Above reduced compound (**126**) was taken in 30 ml ether followed by addition of 40 ml of reagent dropwise with stirring. The reaction is exothermic so in condenser cold water should be circulated so that perfect condensation of ether is there. The solution was stirred for 6h., ether layer was removed, aqueous layer was washed with (3x50 ml) ether, combined ether layer was washed with saturated aqueous solution of NaHCO_3 (3x50 ml) then by water and finally by brine and then dried over Na_2SO_4 . Solvent was evaporated to give crude product which was purified by silica gel column chromatography using pet.ether:ethyl acetate (98:2) as an eluent to give complete saturated bicyclic ketone 20% and required bicyclic α,β -unsaturated ketone (38% yield).

IR (Neat) : cm^{-1} 2940(s), 2880(m), 1680(vs).

^1H -NMR (200 MHz) : δ 1.5 (m, 4H), 1.85 (m, 2H), 2.15 (m, 6H), 2.35 (t, 2H).

^{13}C -NMR : δ 198.64(s), 156.79(s), 132.16(s), 37.88(d), 31.70(d), 31.40(d),
(200 MHz) 22.46(d), 22.15(d), 21.66(d).

Birch reduction of tetracyclo [10.2.1.0^{2,11}.0^{4,9}] pentadeca-4,5,7,13-tetraene-3,10-dione (157): 2g. (8.92 mmol) of naphthoquinone adduct (**157**) and 60 ml dry ethanol were placed

in a three necked round-bottom flask. The Dewar condenser was charged with dry ice-acetone, and the flask was cooled in a dry ice-bath. Ammonia gas was then passed through a drying tube containing $\text{CaCl}_2 + \text{KOH}$. The desired amount (350 ml) of ammonia was collected at -78°C . The freshly cut sodium metal 6g. (0.26 mol) small pieces was quickly added to the reaction mixture. After 2 h., reaction mixture was quenched with ammonium chloride solution (20 ml, 10%). The quenched reaction mixture was allowed to stand for 1 h. to evaporate ammonia. To the solution was added excess of water (100 ml) and ether (50 ml) and gently poured into a separatory funnel on a ring stand (good hood, do not shake the funnel !). The ether layer was separated, then water layer was extracted with ether (3x40 ml) repeatedly, the separating funnel can be shaken without developing much pressure. The water layer was drained off. Extracted ether solution was washed with water (2x100 ml) and dried over Na_2SO_4 . Evaporation of solvent gave crude product which was purified by silica gel column chromatography using pet.ether:EtOAc (98:2).

(160) Yield : 46% (980 mg)

m.p. : 160°C

IR (Nujol) : cm^{-1} 2940(s), 2860(m), 1690(vs), 1600(s), 1470(m), 1290(s).

$^1\text{H-NMR}$ (200MHz) : δ 0.95-1.1 (dd, 2H, CH_2 , cyclopropyl), 1.3 (m, 1H), 1.45-1.55 (m, 2H), 1.65 (m, 1H), 1.75 (m, 2H), 3.2 (m, 2H), 7.75 (m, 2H, Ar), 8.0 (m, 2H, Ar).

$^{13}\text{C-NMR}$ (200 MHz) : δ 190.77 (s, CO), 134.08(d), 133.94(s), 126.97(d), 63.98(s), 35.70(d), 28.37(t), 24.79(t).

MS : m/z 238 (M^+ , 32%), 222(10), 210(81), 197(69), 181(86), 152(84), 104(100), 77(38), 66(35).

(159) Yield : 37% (650 mg)

m.p. : 63°C

IR (Nujol) : cm^{-1} 2950(s), 2860(m), 1450(s).

$^1\text{H-NMR}$ (200MHz) : δ 1.4-1.75 (m, 4H), 2.25-3.0 (m, 6H), 6.25 (m, 2H), 7.1-7.3 (m, 4H, Ar).

^{13}C -NMR : δ 140.20(s), 136.49(d), 127.07(d), 126.11(d), 50.25(t), 46.38(d),
(200 MHz) 41.75(d), 33.98(t).

MS : m/z 196 (M^+ , 5%), 129(100), 115(32), 77(4), 66(6).

Birch reduction of 11-methyltetracyclo[10.2.1.0^{2,11}.0^{4,9}]pentadeca-4,5,7,13-tetraene-3,10-dione (161): To a solution of 1.5g. (6.3 mmol) of methylnaphthoquinone adduct (**161**), dry ethanol (45 ml) and freshly cut sodium metal 2.17g. (94.5 mmol) was added ammonia solution (200 ml). Birch reduction was followed as per the procedure described for (**157**). The product was eluted using pet.ether:ethyl acetate on (97:3) silica gel column chromatography.

(**162**) Yield : 40% (530 mg)

IR (Neat) : cm^{-1} 2980(s), 2880(m), 1460(s).

^1H -NMR (200 MHz) : δ 1.1 (s, 3H, CH_3), 1.65 (m, 2H), 2.0 (m, 1H), 2.3 (m, 2H), 2.6-3.0 (m, 4H), 6.3 (m, 2H), 7.05-7.2 (m, 4H, Ar).

^{13}C -NMR : δ 139.98(s), 139.31(s), 138.52(d), 135.90(d), 128.00(d), 126.94(d),
(200 MHz) 126.06(d), 126.00(d), 52.89(d), 49.18(d), 47.95(t), 47.21(d),
45.91(s), 40.92(t), 35.12(t), 30.54(q).

(**163**) Yield : 29% (410 mg)

m.p. : 65°C

IR (Nujol) : cm^{-1} 3450 (bs, OH), 2980(s), 2890(m), 1450(w).

^1H -NMR (200 MHz) : δ 0.95 (s, 3H, CH_3), 1.65 (m, 2H), 1.8 (m, 2H), 2.0 (m, 1H), 2.65-2.9 (m, 2H), 4.65 (s, 1H, CH-OH), 6.3 (m, 1H), 6.4 (m, 1H), 7.0-7.25 (m, 3H, Ar), 7.3-7.4 (d, 1H, Ar).

^{13}C -NMR : δ 141.21(s), 138.31(d), 136.85(s), 136.41(d), 126.48(d), 126.25(d),
(200 MHz) 126.06(d), 122.33(d), 74.39(d), 50.52(d), 49.71(d), 47.95(t),
46.98(d), 44.99(s), 33.48(t), 22.57(q).

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CHAPTER-IV

SYNTHESIS OF PHOSPHACUMULENE YLIDE AND ITS APPLICATION TOWARDS BIOLOGICALLY RELEVANT COMPOUNDS

INTRODUCTION

Organophosphorous chemistry has made significant contributions towards the development of newer synthetic methodologies and their applications. Wittig reaction is one such example. In this series, phosphacumulene ylides are one of the recent arrivals. These cumulated ylides are nucleophilic and versatile reagents.¹ The last decade has witnessed considerable upsurge of interest not only for the development of new synthetic strategies for phosphacumulene ylides but also for its synthetic application towards biologically active compounds.¹

This chapter is divided into two parts. The first part deals with the synthesis of *N*-Phenyl(triphenylphosphoranylidene)ethenimine **1** through new synthetic strategies and the second part describes synthetic applications towards biologically active compounds.^{2,3}

SECTION-1

Synthesis of *N*-Phenyl(triphenylphosphoranylidene)ethenimine **1**

INTRODUCTION

Phosphacumulene ylides of type **1A** with X=NR, O and S [=1Aa, 1Ab and 1Ac, respectively] can be described by the principal resonance structures **1A** and **1B**, which differ in their geometry and electron distribution.



a: X = NPh ; **b**: X = O , **c**: X = S

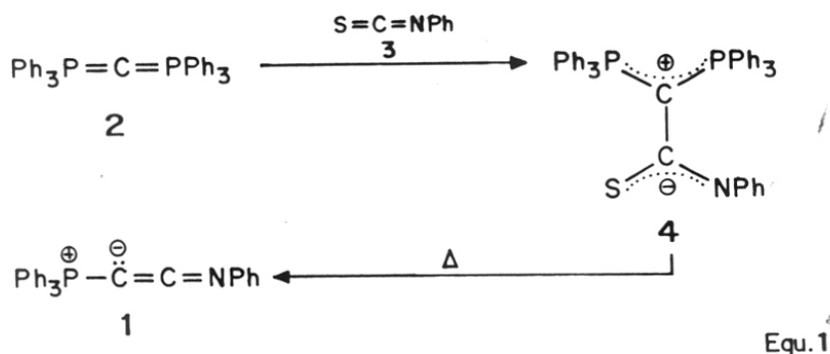
Table-1: P-C α -C β angles and P-C α -C β bond lengths in phosphacumulene ylides of type **1**.

Type	Compound	Angle P-C α -C β [°]	Distance P-C α -C β [°]
1	a, X=NC ₆ H ₅	134.0	1.248
1	b, X=O	145.5	1.210
1	c, X=S	168.0	1.204

As the electron withdrawing electron affinity or due to enhanced electro-negativity character of X increases, its tendency to participate in resonance decreases. Thus, the contribution of structure **1B** in the resonance hybrid increases. Therefore, the P-C α -C β angle should increase and the C α -C β bond length decrease in the order **1Aa**, **1Ab** and **1Ac**. These expectations are confirmed by the results of X-ray structure analysis of compound **1Aa**, R=C₆H₅¹, **1Ab**⁴ and **1Ac**⁵, which are listed in **Table-1**, together with the corresponding data.

Along the series **1Aa**, **1Ab** and **1Ac**, the PCCX grouping becomes progressively more linear, and the C α -C β distance shorter. Owing to the 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 decrease along the same series.¹ Although the nucleophilic phosphorus ylides are comparable in their scope and versatility to Grignard reagents, and their utility as synthetic strategy for a variety of biologically useful compounds has been amply demonstrated, the literature describing their synthesis are rather scarce.

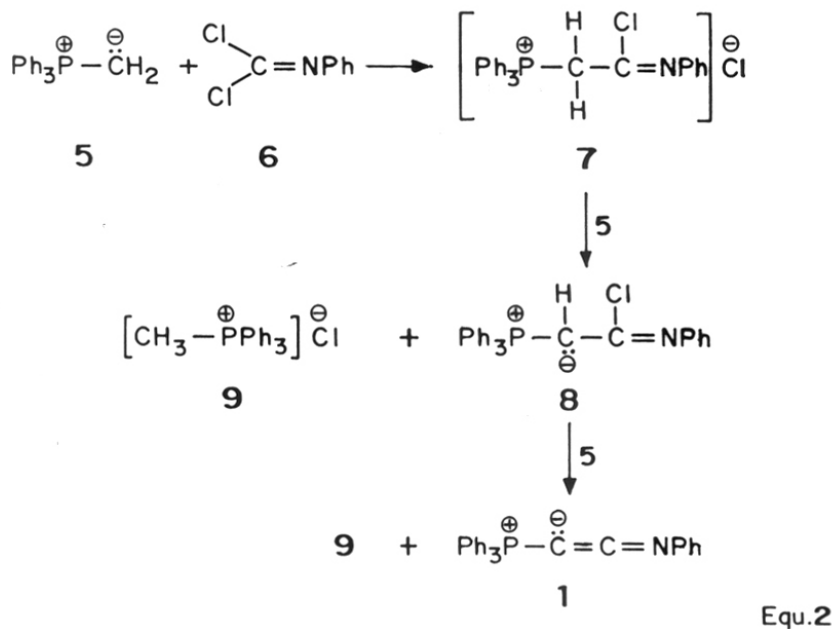
In 1961, Ramirez et.al⁶ described the synthesis of hexaphenyl carbodiphosphorane **2**, which on reaction with **3** gave betaines **4**. Thermolysis of **4** afforded N-phenylimino ketenylidene triphenylphosphorane **1** (*Equation-1*).



Bestmann et.al⁷ have developed synthesis of N-Phenyliminoketenylidene triphenyl phosphorane from methylenetriphenylphosphorane **5** and geminal dihalo compound **6**. Reaction of **5** with phenylisocyanide dichloride **6** in a molar ratio of 3:1 initially affords a

phosphonium salt **7**, primarily *via* nucleophilic substitution, which can be *trans*-ylidated with a second molecule of **5** to the phosphonium salt **9** and to the ylide **8**. The third molecule of **5** removes hydrogen chloride from **8** giving rise to the phosphacumulene ylide **1**.

The overall reaction is: 3eq (**5**) + 1eq (**6**) $\rightarrow$ 1eq (**1**) + 2eq (**9**). The phosphonium salt precipitates during the reaction. After its separation, **1** is isolated by distillative removal of the solvent and recrystallization. Compound **5** and isocyanide dichlorides **6** R=alkyl or aryl, give iminoketenylidenetriphenylphosphoranes **1** (Equation-2).



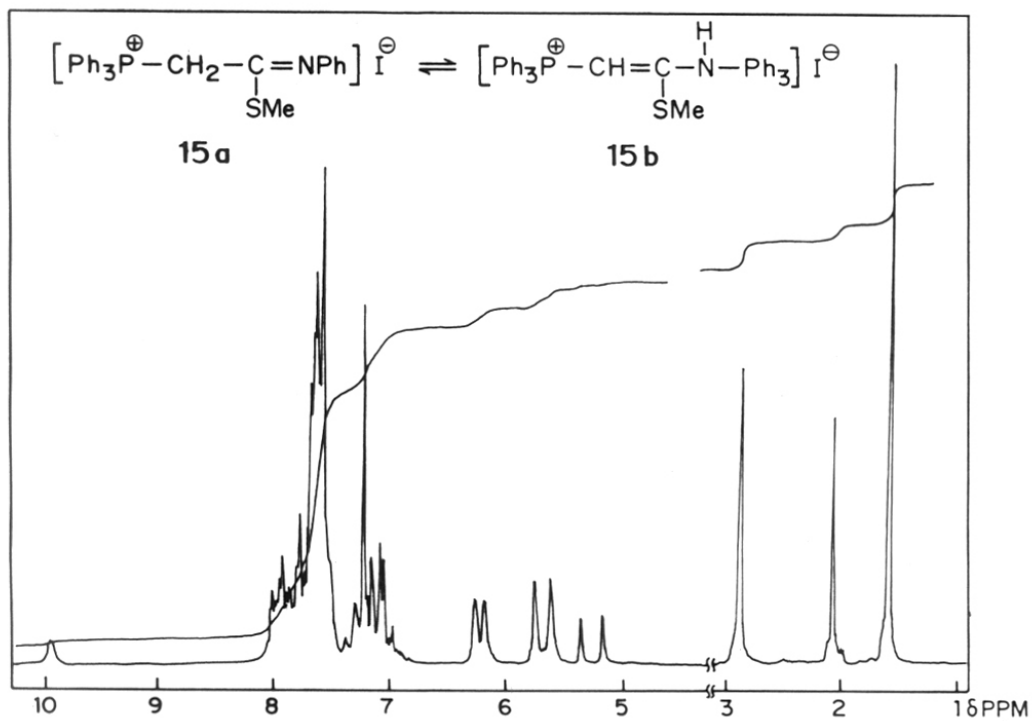
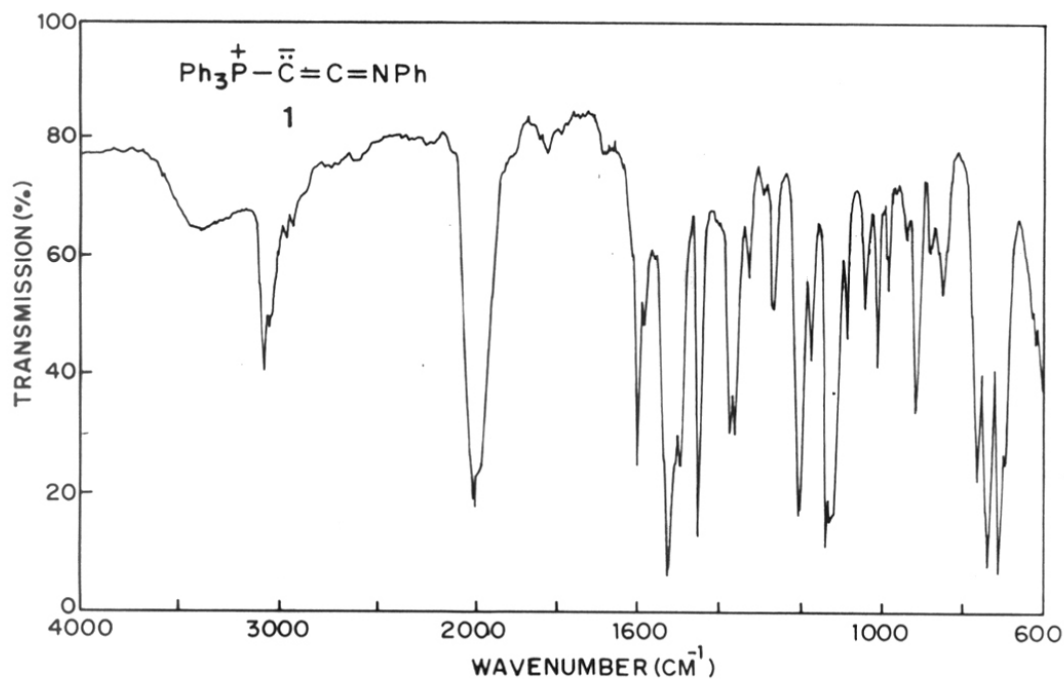
OBJECTIVE, RESULTS AND DISCUSSION

It is clear from the preceding literature that there are only two reports for the synthesis of **1**, where both the procedures involve hazardous chemicals i.e. isocyanide dichloride and isothiocyanate. The methods are also not amenable for large scale preparation. Bestmann's procedure utilises 3 moles of triphenyl phosphine and, therefore, it is not cost effective. Similarly, Birum's method involves thermolysis as one of the key steps and triphenyl

phosphine formed during reaction gives problem in separation. Thus, these methods are not easy to operate. So there is a clear-cut need to devise new methodologies for the synthesis of cumulated ylide **1**, Which is the objective of this section.

Our method of synthesis of *N*-Phenyl(triphenylphosphoranylidene)ethanimine **1** utilizes only one mole of triphenylphosphine. Thus, treatment of triphenyl phosphine **10** with CH_3I **11** gave salt **12**, which was treated with sodamide to give methylene triphenylphosphorane **5**. Benzene solution of methylene triphenyl phosphorane was added to phenyl isothiocyanate **13** slowly at 0°C for 15 minutes.⁶ The mixture was stirred at room temperature overnight. The removal of solid material by filtration yielded 88% of **14**. The structure of α -(*N*-Phenylthiocarbamoylmethylene)-methylenetriphenylphosphorane **14** was confirmed by spectral data. Compound **14** melted at 203°C and proton-NMR gave signals at δ 1.9 (bs, 1H, NH), 4.45 (d, 1H, $\text{P}=\text{CH}$), 7.06-7.78 (m, 21H, Ar) and M^+ in mass at 411 (9%). Compound **14** was treated with methyl iodide to give 93% yield of tautomeric mixture (1:1) ratio of **15a** and **15b**, which were fully characterised by spectral data. The tautomeric mixture melted at $218\text{-}220^\circ\text{C}$. Proton-NMR of (1-anilino-1-methylmercapto-2-triphenyl phosphonio-ethylene)iodide **15a** gave signals at δ 2.12 (s, 3H, $\text{S}-\text{CH}_3$), 5.3 (d, $\text{Ph}_3\text{P}=\text{CH}=\text{}$), 10.0 (s, $\text{Ph}-\text{NH}$), whereas (1-Phenylimino-1-methylmercapto-2-triphenylphosphonio-ethane)iodide **15** gave signals at δ 1.62 and 2.93 (s, $\text{S}-\text{CH}_3$), 5.72 (d, $\text{Ph}_3\text{P}-\text{CH}_2-$), 6.25 (d, $\text{Ph}_3\text{P}-\text{CH}_2-$), 7.02-7.97 (m, aromatic) and M^+ in mass at 425 (10%). The conversion of tautomeric mixture of **15a** and **15b** to 2-phenylimino-2-methylmercapto-ethylidene- triphenylphosphorane **16** was attempted by treatment with various bases eg. DBU, $\text{Na}^+\text{O}^-\text{Et}$, tBu^-OK^+ , Na_2CO_3 , TEA and the best results were obtained with 10% KOH. The structure of compound **16** was confirmed by proton-NMR, which showed signals at δ 2.36 (s, 3H, SCH_3), 3.04 (d, $\text{Ph}_3\text{P}=\text{CH}-$), 6.59-7.74 (m, 20H, Ar). Bestmann et.al⁸ have reported the synthesis of analogous cumulated ylides, by β -elimination using bistrimethylsilylamide. Similar strategy was employed here to prepare the *N*-phenylcumulated ylide **1**. Thus, treatment of **16** with sodium bis(trimethylsilyl)amide **17**⁹ led to the formation of *N*-Phenyliminoketenylidene triphenylphosphorane **1** in 74% yield by β -elimination of methane thiol. The compound was characterised by spectroscopic and analytical data and

Scheme - 1



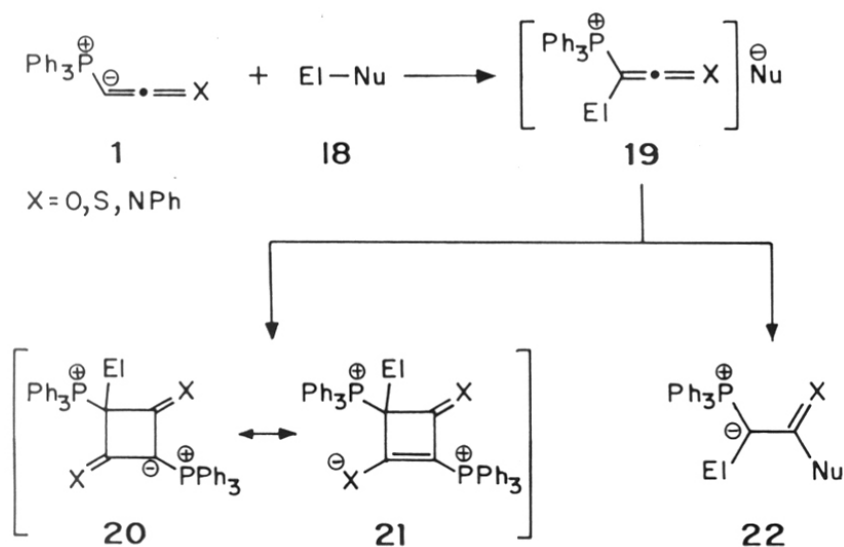
SECTION-2

SYNTHESIS OF CARBOCYCLIC AND HETEROCYCLIC COMPOUNDS USING PHOSPHACUMULENE YLIDES AS SYNTHONS

INTRODUCTION

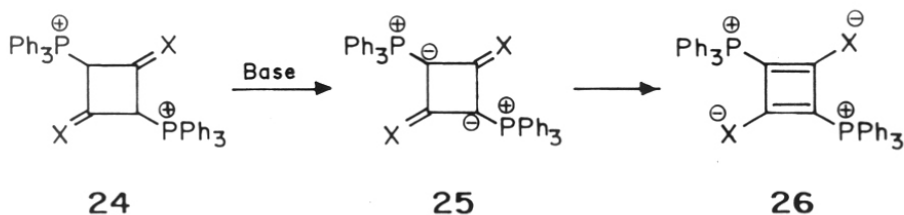
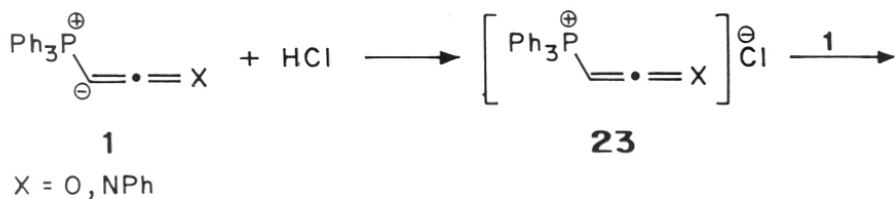
Phosphacumulene ylides are known to give nucleophilic substitutions like reactions with halogen compounds, react with acidic functionalities eg. NH, OH, SH, COOH etc. and also are known to participate in cycloaddition reactions.

i) **Nucleophilic substitution**¹: Addition of an electrophile to the lone pair of oxo-, thio- and imino-vinylidenephosphoranes transforms the nucleophilic π^4 - π^4 system into the dipolar π^4 - π^2 system of a ketene. The resulting phosphonium salt becomes a true dipolar ketene which, as such, reacts in a known manner (*Equation-3*).



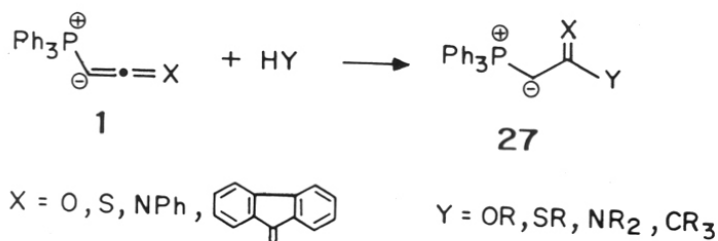
Equ.3

ii) **Reaction with halogen compounds**: Oxovinylidene- and iminovinylidene-triphenyl phosphoranes 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 (*Equation-4*).



Equ. 4

iii) **Reactions with acidic compounds:**^{1,10} In the reaction of OH-, NH-, SH- and CH-acidic compounds with phosphacumulene ylides, the anion Nu⁽⁻⁾ of the initially formed phosphonium salt is so nucleophilic, that addition of the anion to give a new alkylidenephosphorane is faster than cycloaddition of a second mole of starting ylide (*Equation-5*).

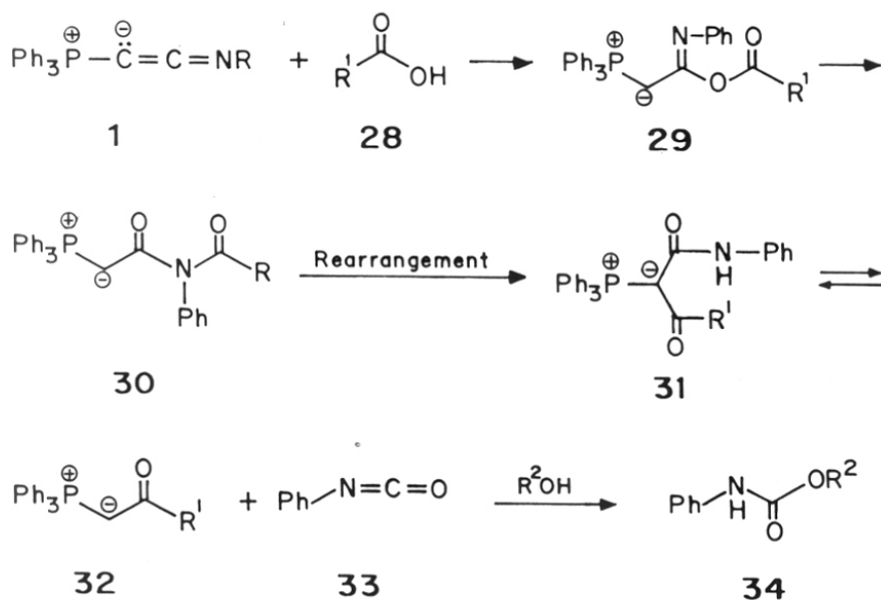


Equ. 5

According to the difference in ylides nucleophilicity (NR>O>S) iminovinylidene- and oxovinylidene-phosphorane smoothly add to alcohols, thiols and acidic NH compounds, while thioxovinylidene-phosphorane reacts readily with thiols and phenols, less rapidly with

aliphatic alcohols and does not react with NH-acidic compounds. Strongly activated CH₂ groups add readily to iminovinylidene phosphoranes, less rapidly to oxovinylidene phosphorane and not at all to thioxovinylidene phosphorane.

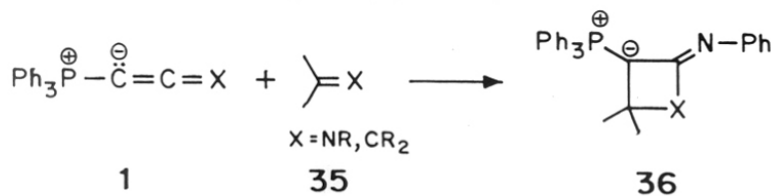
Carboxylic acids react with phenyliminovinylidene triphenylphosphorane (Equation-6) via the intermediate **29** with the formation of the alkylidene phosphoranes **30**, which on heating, rearrange in an intramolecular acyl migration to ylides **31**. By heating **30** in the presence of an alcohol, the acyl ylides **32** and *N*-phenylurethanes **34** are formed.^{10,11} The reaction sequence allows the replacement of the OH group in carboxylic acids by the ylide function.



Equ. 6

IV. Cycloaddition Reaction

A variety of compounds may undergo cycloaddition at the C=C bond of vinylidene-phosphoranes yielding exocyclic ylides.¹ [2+2] cycloadditions of *N*-phenylimino vinylidene triphenylphosphorane to electron poor double bonds of alkenes and imines lead to the formation of four-membered ylides (Equation-7).¹



Equ. 7

SECTION-2A

SYNTHESIS OF CARBOCYCLIC COMPOUNDS

INTRODUCTION

After a brief overview of literature¹ pertaining to the chemistry of phosphacumulene ylides, its limitations and opportunities offered by this reagent in the preceding section, our attempts to exploit the ylide as intramolecular C-1 synthon has been described. Although there is considerable amount of information available in the literature on intramolecular Wittig reaction, not much progress has been made towards the application of cumulated ylide in cyclization reaction through intramolecular Wittig reaction.¹² The intramolecular Wittig reaction has been reported using different reagent on carbonyl of ketone,¹³ ester¹⁴⁻¹⁶ and amide.^{17,18}

In the present study, an attempt has been made towards development of new methodology and one step synthesis of various compounds by intramolecular Wittig cyclization using phosphacumulene ylide.

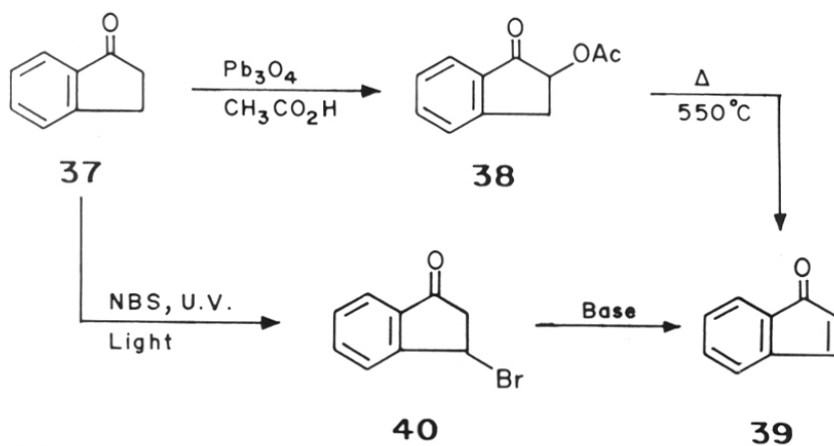
Indenone derivatives constitute the carbocyclic framework of a wide variety of natural products. There are quite a few methods available in the literature for indenone and substituted indenone.

Indenone¹⁹ can be prepared from indanone. Indanone is first converted to its 2-acetoxy derivative subsequent elimination of acetic acid by thermolysis leads to indenone. It has also been prepared by the dehydrobromination of 3-bromo indanone using suitable base, but this synthetic approach may not be very satisfactory because of the difficulty in obtaining these bromo compounds (*Scheme-2*).

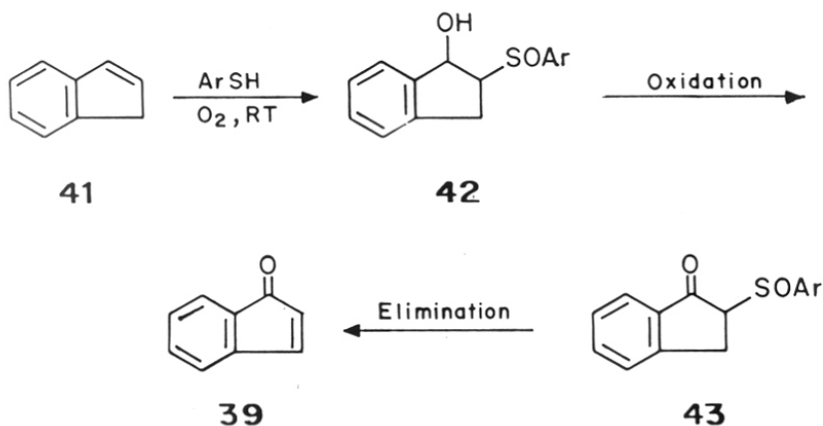
Szmant et.al²⁰ reported the facile conversion of indene by means of the thio-olefin cooxidation reaction followed by elimination (*Scheme-3*).

Substituted indenones²¹ were prepared by Reformatsky condensation of the appropriate benzaldehyde and α -bromoester followed by hydrolysis, leading to the hydracrylic acid **46**.

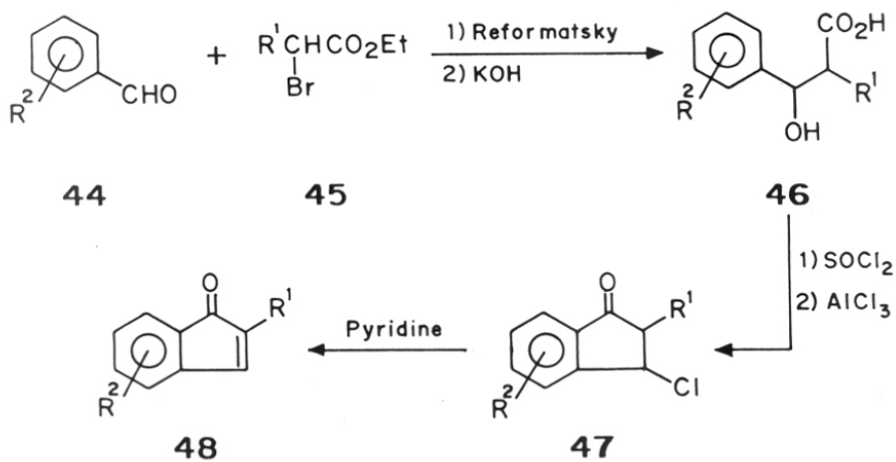
Scheme -2



Scheme -3



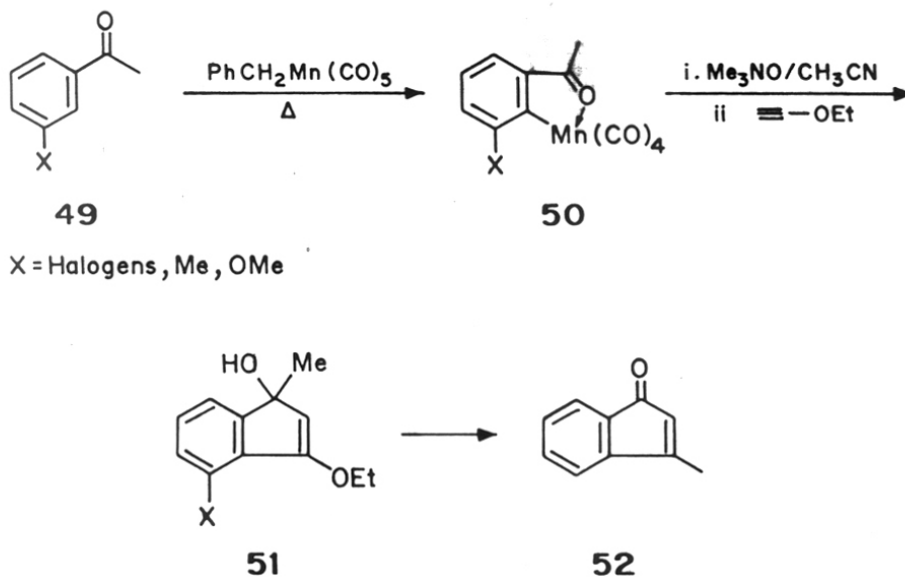
Scheme -4



The treatment of the acid with SOCl_2 followed by acylation in presence of AlCl_3 at $25\text{--}40^\circ\text{C}$ results in the formation of 3-halo indanones **47**, which were converted into the desired indenones **48** by treatment with pyridine at $70\text{--}90^\circ\text{C}$ (Scheme-4).

Recently, 3-substituted indenones²² were prepared from ortho-manganated derivatives. Arylketones are known to react with manganese reagents, $\text{RMn}(\text{CO})_5$ ($\text{R}=\text{Me}$, CH_2Ph), to provide the ortho manganated derivatives in high yields. The manganacycle **50** was activated with trimethylamino *N*-oxide (TMANO) in CH_3CN and then treated with 3-hexyne (Scheme-5). Indenol **51** was isolated in 58% yield. The compound **51** underwent acid catalyzed hydrolysis to give 3-methyl-inden-1-one **52**.

Scheme - 5



RESULTS AND DISCUSSION

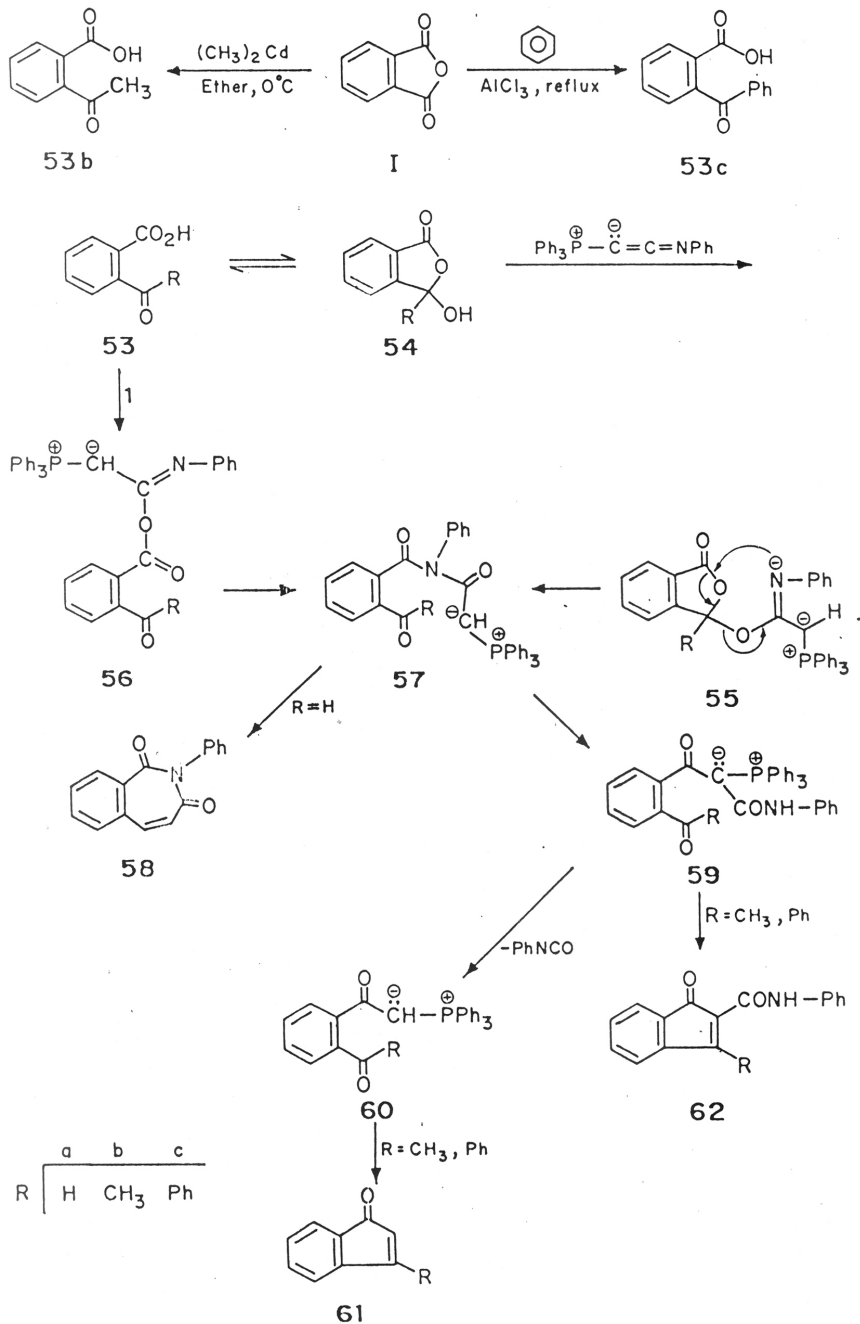
The above mentioned procedures for synthesis of indenone derivatives involve many steps, tedious reagents and drastic reaction conditions. Therefore, we thought it would be worthwhile to devise new synthetic strategies for carbocyclic framework using phosphacumulene ylides. This section constitutes a new and short one-pot synthesis of substituted indenone derivatives employing cumulated ylides. Thus, the reaction of various aromatic

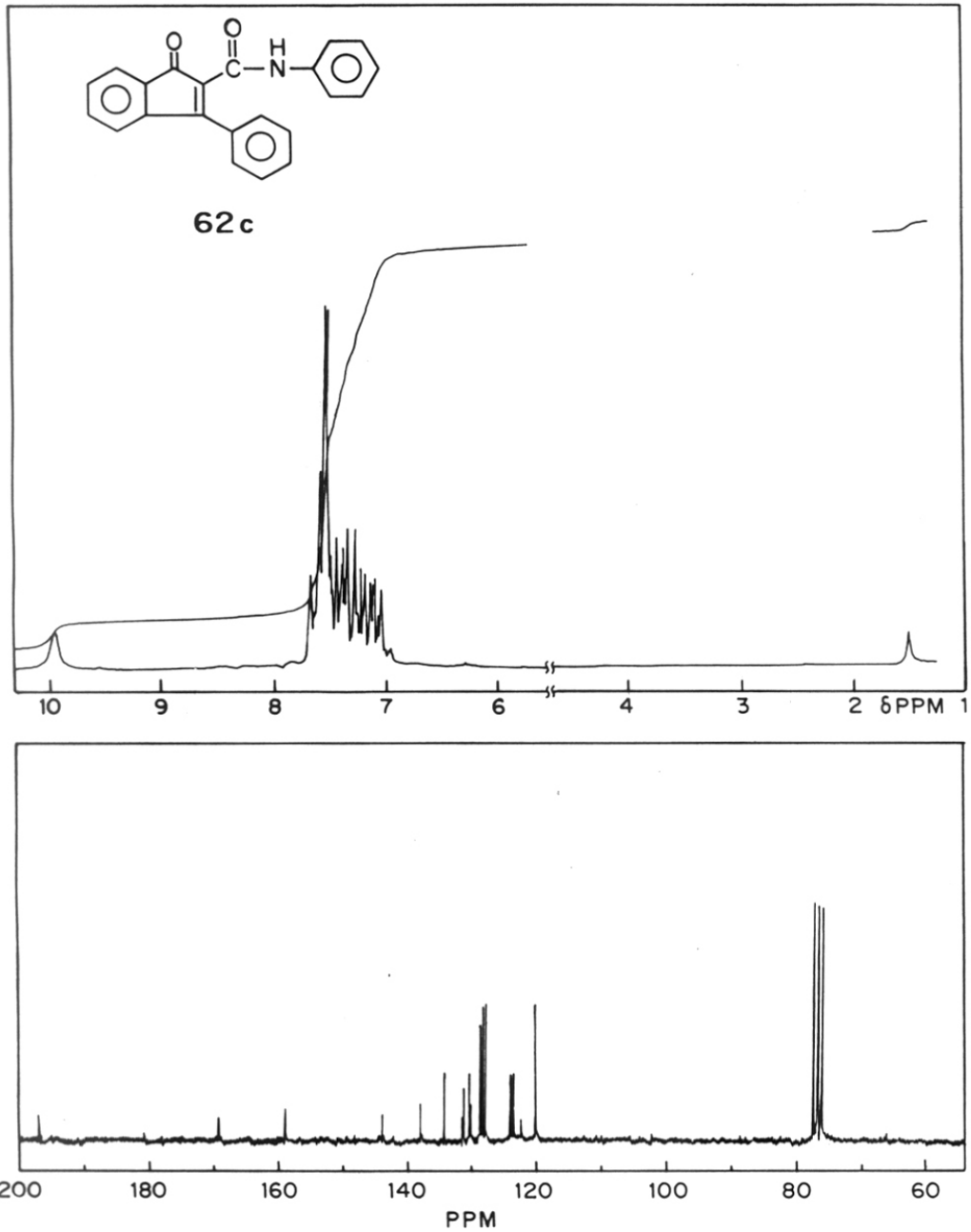
keto carboxylic acids with *N*-Phenyl(triphenylphosphoranylidene)ethanimine **1**, in order to construct the carbocyclic compounds like substituted indenones, has been studied. In our initial attempts, the reaction of phthalaldehydic acid **53a** with *N*-Phenyl (triphenylphosphoranylidene)ethanimine **1** in dry benzene at 0°C to room temperature gave 81% yield of 2-phenyl-1*H*-2-benzazepin-1,3(2*H*)-dione **58**, a seven membered cyclic product, which was unusual. The structure of 2-phenyl-1*H*-2-benzazepin-1,3(2*H*)-dione **58** was confirmed by spectral data. ¹H-NMR gave signals at δ 6.55 (d, 1H), 7.25 (m, 4H), 7.4-7.85 (m, 5H), 8.38 (dd, 1H) and ¹³C-NMR gave peaks at δ 167.9(s), 165.75(s), 140.19(s), 139.06(d), 134.06(d), 133.34(d), 132.57(s), 132.19(d), 131.08(d), 129.66(d), 128.39(d), 128.27(d), 126.32(s).

Subsequently, 2-acetylbenzoic acid **53b** was prepared as per literature procedure.²³ The reaction of dimethyl cadmium reagent (CdCl₂ + CH₃Mg⁺Br) with phthalic anhydride gave 2-acetylbenzoic acid **53b**, which on treatment with *N*-Phenyl(triphenylphosphoranylidene)ethanimine **1** gave two compounds 3-methyl-1*H*-inden-1-one **61b** in 45% yield and 3-methyl-1-oxo-1*H*-inden-2-carbox anilide **62b** in 38% yield. Both the structures were confirmed by spectral data and compared with literature data.²³ The ¹H-NMR of compound 3-methyl-1*H*-inden-1-one **61b** exhibited signals at δ 2.25 (d, 3H, CH₃), 5.75 (q, 1H, olefinic proton) and 7.0-7.5 (m, 4H, Ar). Similarly, proton-NMR of 3-methyl-1-oxo-1*H*-inden-2-carboxanilide **62b** gave signals at δ 2.86 (s, 3H), 7.0-7.9 (m, 9H), 10.1 (s, 1H, NH) whereas ¹³C-NMR gave characteristic peaks at δ 196.83 (s, CO), 172.08 (s, CONH) and 13.92 (q, CH₃).

Finally, *O*-benzoylbenzoic acid **53c** was prepared by Friedel-Crafts reaction of phthalic anhydride in the presence of AlCl₃ and benzene as per literature procedure.²⁴ The reaction of *O*-benzoylbenzoic acid **53c** and *N*-phenyl(triphenylphosphoranylidene)ethanimine **1** (1:1 ratio) under reflux condition for 6 h. gave two compounds **61c** (33%) and **62c** (42%). Compound 3-phenyl-1*H*-inden-2-carboxanilide **62c** was confirmed by spectral data. The ¹H-NMR signals of compound **61c** gave peaks at δ 5.9 (s, 1H, olefin proton) and 6.9-7.5 (m, 9H, Ar). The mass spectrum showed M⁺ peak at 206 (25%). The ¹H-NMR of compound **62c** showed signals at δ 7.0-7.87 (m, 14H, Ar) and ¹³C-NMR showed characteristic peaks at δ 197.00 (CO, s), 169.26 (CONH, s). The compound melted at 180°C.

Scheme - 6





SECTION-2B

SYNTHESIS OF NITROGEN HETEROCYCLES

INTRODUCTION

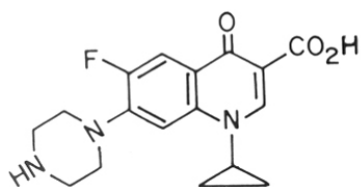
The last few years have witnessed considerable resurgence of interest in the synthesis and biological evaluation of quinolone antibiotics. Infact, some of them eg., Norfloxacin, Ciprofloxacin, Enoxacin, Amifloxacin, Ofloxacin, are already in the market as broad spectrum antibiotics.²⁵ Some quinolone antagonists to amino acid receptors eg. Kynurenic acid derivatives, etc.²⁶ are also known (*Scheme-7*). However, various synthetic methodologies described for quinoline ring system^{25,27} indicate that there is scarcity of one pot synthetic methodologies for these skeletons. Due to entropy and easy operational feasibility reasons, one-pot synthetic methodology becomes important. In order to explore the synthetic utility of the ylide, described in earlier section, we wondered whether this tandem methodology could be extended for the synthesis of other heterocycles as well. This section describes our attempts towards the synthesis of biologically relevant quinolone analogues employing phosphacumulene ylide.

The key features of the strategy involve the reaction of carboxyl group with the ylide¹¹ to give an intermediate, which on rearrangement and extrusion followed by intramolecular Wittig reaction furnishes the desired product. However, these sequential transformations are highly substrate specific and prone to reaction conditions. Also the Wittig olefination involving relatively less reactive amide carbonyl are rare and we wondered whether amide carbonyl could be olefinated under our reaction conditions.

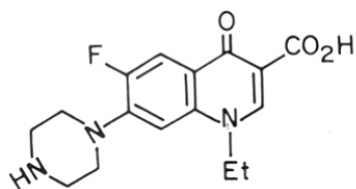
RESULTS AND DISCUSSION

Quinolones are an important class of compounds, which have been widely used as drugs. Primarily, our interest was to synthesize 2-substituted quinolone derivatives. Thus, the *N*-formylanthranilic acid **74** was prepared in 69% yield as per literature²⁸ by the reaction of anthranilic acid, 98% formic acid and acetic anhydride at 0°C. *N*-formylanthranilic acid **74** was treated with *N*-phenyl(triphenylphosphoranylidene)ethanimine **1** (1:1 ratio) in benzene under reflux for 10 h. Instead of expected product **75** as a result of extrusion of phenyl isocyanate (PhNCO), it gave 4-hydroxy-3-carboxanilide quinoline **76** in 62% yield, which is an important precursor for Norfloxacin, quinolone antibiotics (*Scheme-7&8*). This

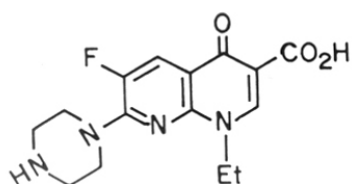
Scheme - 7



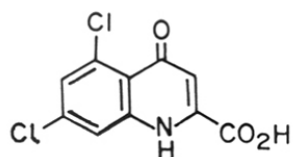
CIPROFLOXACIN
63



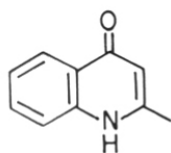
NORFLOXACIN
64



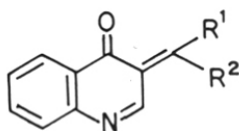
ENOXACIN
65



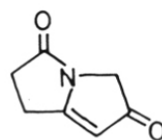
5,7-DICHLOROKYNURENIC ACID
66



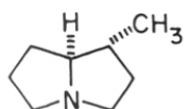
67



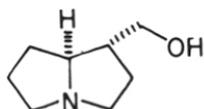
68



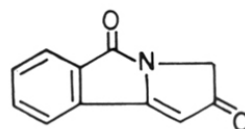
69



PSEUDOHELIO
TRIDANE
70



TRACHELANT
AMIDINE
71



72

result indicates that at higher temperature, intramolecular Wittig reaction in this particular case is faster than the cleavage of phenyl isocyanate. This could perhaps be attributed to the reactivity of the formyl group, which results in the formation of cyclised product *via* intramolecular Wittig reaction. The structure of 4-hydroxy-3-carboxanilide quinoline **76** was confirmed by spectral and analytical data. This compound melted at 145-147°C. The ¹H-NMR showed signals at δ 7.3 (d, 1H), 7.45-7.65 (m, 5H), 7.85 (m, 2H), 8.2 (s, 1H), 8.45 (d, 1H), 10.2 (s, 1H) and ¹³C-NMR gave peaks at δ 169.06 (CONH, s), 148.17, 146.26, 134.93, 129.90, 129.43, 129.11, 127.98, 127.85, 127.32, 127.22, 124.49, 120.33, 119.94.

Subsequently, *N*-acetylanthranilic acid **78** was prepared as per literature procedure.²⁹ and treated with *N*-phenyl(triphenylphosphoranylidene)ethanimine **1** in ethyl acetate under reflux for 4 h, to give 90% yield of **79**. Compound **79** melted at 220°C and was characterised by spectral data. The ¹H-NMR showed signals at δ 2.45 (s, 3H, CH₃), 3.45 (d, 1H), 6.85-7.5 (m, 17H, PPh₃, Ar), 7.8-8.0 (dd, 1H, Ar), 8.25-8.5 (dd, 1H, Ar). Mass spectrum showed M⁺ at 437 (12%). Then in our attempts from the intermediate **79** to compound 2-methylquinolone **67**, we have encountered lot of problem at the cyclization step. Due to the solubility problem of the phosphorane, all our attempts to cyclise in different solvents such as toluene, diphenyl ether, dioxane failed. Thus, the intermediate compound **79** dissolved in DMSO was refluxed for nearly 10-12 h. However, it gave a mixture of compounds **80** and cyclised product **67**. The compound **80** (*Scheme-8*) was characterised by spectral data, Proton-NMR gave signals at δ 2.1 (s, 3H, S-CH₃), 2.45 (s, 3H, SCH₃), 2.5 (s, 3H, COCH₃), 6.6-6.7 (m, 1H), 7.0-7.2 (m, 2H, Ar), 8.05-8.12 (dd, 1H, Ar), 8.6-8.72 (dd, 1H, Ar), 10.0 (b s, 1H, NH). Mass spectrum showed M⁺ at 237 (15%). Compound melted at 191-194°C. Compound 2-methyl quinolone **67** was characterised by ¹H-NMR and compared with literature data.³⁰ Proton-NMR gave signals at δ 2.45 (s, 3H, CH₃), 6.0 (s, 1H), 7.1-7.6 (m, 3H), 8.1-8.3 (m, 1H). We presume that due to the low reactivity of amide ketone, the cyclised product **67** could not be obtained in good yield. Compound **80** was the major product resulting from Wittig reaction from phosphorane and DMSO.

Our next aim was to synthesize 3-substituted quinolones (*Scheme-9*), which are an important precursors for Ciprofloxacin **63**, Norfloxacin **64**, etc. (*Scheme-7*). Thus, 2-methyl-4*H*-benzoxazin-4-one **83** (*Scheme-9*) was prepared as per literature procedure.³¹

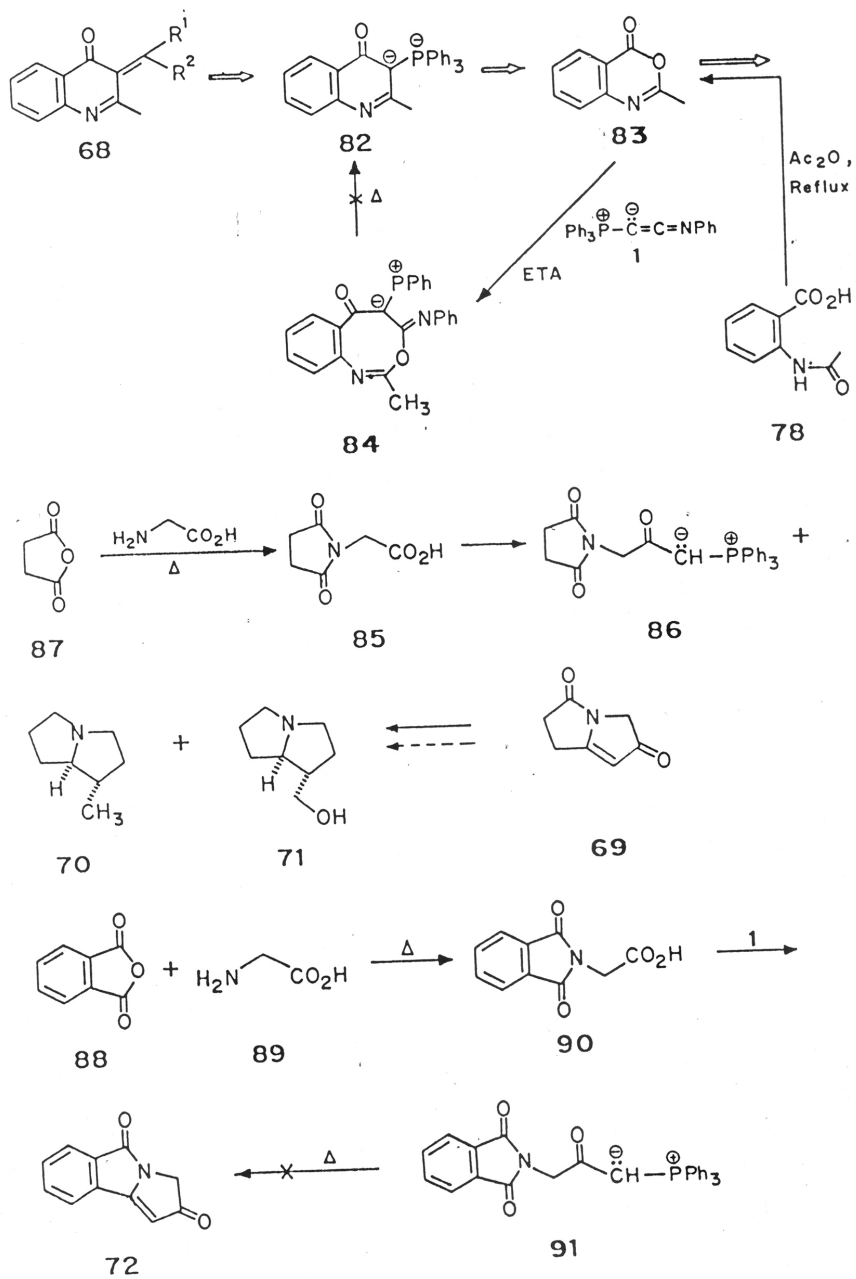
The reaction of **83** and N-phenyl ylide **1** under reflux condition in ethyl acetate for 15 h. gave the eight-membered cyclic product **84**, which on further heating in toluene did not yield the product 3-substituted phosphorane **82**. The structure of eight-membered ring heterocycle **84** was confirmed by spectral and physical data. The compound **84** melted at higher temperature 331°C. IR showed peaks at 1670 cm⁻¹ (s, CO) and ¹H-NMR δ 2.18 (s, 3H, CH₃), 6.75-7.0 (m, 5H, NPh), 7.1-7.8 (m, 18H, Ar), 8.05-8.15 (d, 1H). Mass spectrum showed M⁺ at 538(10%), 523(20%), 495(31%), 262(100%).

In continuation, we have also explored the possibility of synthesizing bicyclic pyrrolizidine ring systems *via* this strategy. Pyrrolizidine ring is present in a wide variety of complex natural products. This has triggered a great number of efforts towards synthesizing these skeletons. The pyrrolizidine alkaloids are remarkable, since they are known to exhibit an incredible range of biological activities including antitumour, hypotensive, insect attraction, etc.

The application of the above knowledge for the synthesis of pyrrolizidine alkaloids was explored, as shown in (*Scheme-7 & 9*). Our strategy involves amino acid as precursor for the synthesis of optically active pyrrolizidine alkaloids. Thus, glycine was treated with succinic anhydride to give N-succinoylamino acid³² **85**, which on reaction with N-phenyl(triphenylphosphoranylidene)ethanimine **1** (*Scheme-9*) under reflux for 18 h. in dioxane gave the intermediate **86** (40% yield) and the cyclised product **69** (23% yield). The cyclised product is valuable precursor of pyrrolizidine alkaloids like pseudoheliotridane **70** and Trachelantamidine **71** (*Scheme 7 & 9*). The structure of **69** was confirmed by spectral data. IR showed bands at 1690(s), 1590(m) cm⁻¹, ¹H-NMR gave signals at 2.45 (s, 2H), 2.75 (s, 2H), 4.15 (s, 2H), 6.75 (d, 1H) and mass spectrum gave M⁺ at 137 (100%).

Similarly, N-phthaloylglycine **90** was prepared as per literature.³² The reaction of N-phthaloylglycine **90** and ylide **1** under reflux in dioxane gave exclusively phosphorane intermediate **91** (*Scheme-9*), which under reflux in toluene did not yield the expected cyclised product **72**. We presume the reduced electrophilicity of carbonyl carbon because of extended conjugation with benzene as compared to succinic carbonyl carbon **86**, as a reason for failure of our objective.

Scheme-9



SECTION-2C

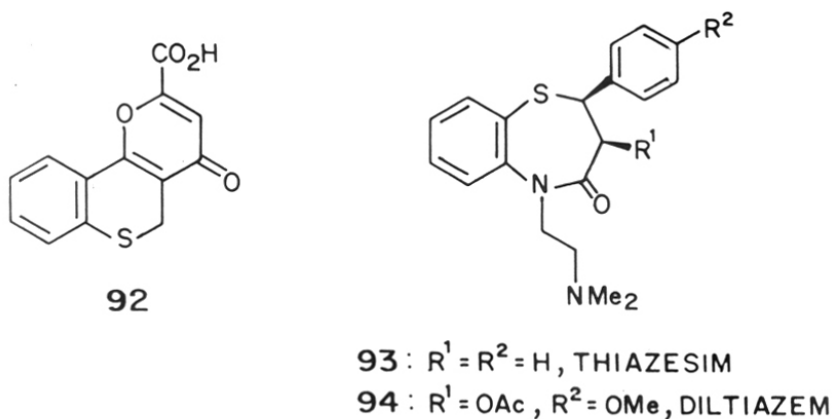
SYNTHESIS OF SULFUR HETEROCYCLES:

(Benzothiopyran and Benzothiazepin)

INTRODUCTION

The various analogues of benzothiopyrans and benzothiazepins have received considerable attention due to their biological and commercial relevance. Benzothiopyran and benzothiazepin skeletons display a wide array of biological activities such as diuretic, anti-inflammatory, anti-tuberculosis, anti-tumor, anti-depressant, coronary vasodialating activities etc. Thus, 4-oxo-4*H*,5*H*-[1] benzothiopyrano [4,3-*b*] pyran-2-carboxylic acid **92**³³ is a widely accepted drug as antianaphylatic, whereas 2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-1,5-benzothiazepin-4-(5*H*)-one **94** (*Scheme-10*) are marketed as anti-depressant and coronary vasodialating agent with a trade name *Thiazesim* **93**³⁴ and *Diltiazem* **94**³⁵ respectively. In connection with our studies on synthesis of biologically active compounds possessing benzothiopyran and benzothiazepine skeletons, we became interested in developing a suitable methodology for the synthesis of 1-benzothiopyran- 4-ones using phosphacumulene ylide.

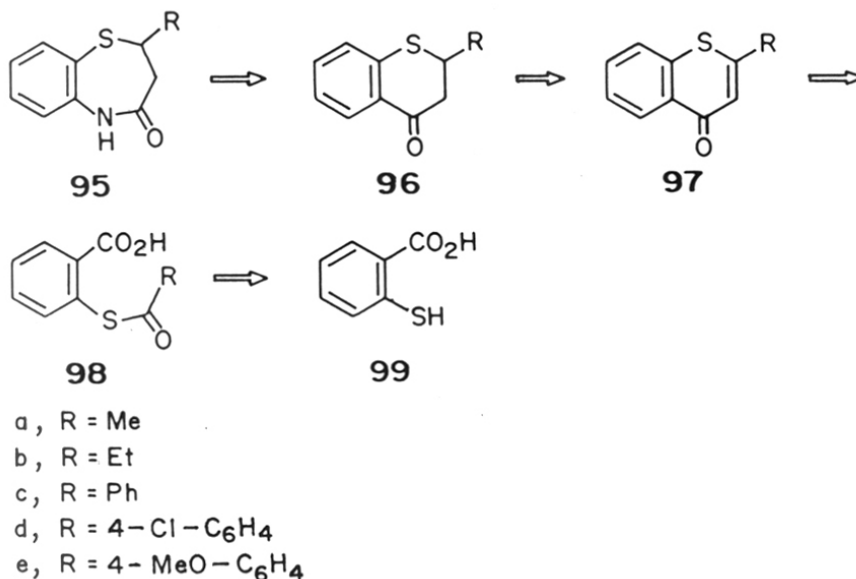
Scheme - 10



One-flask multiple bond-forming reactions are powerful tools for developing new methodologies and in the synthesis of complex molecules. We devised tandem one-pot

methodology for the synthesis of benzothiopyran ring systems which is shown in a retrosynthetic manner in *Scheme-11*. The one-pot cyclisation method is based on consecutive processes involving phosphacumulene ylide as C-1 synthon. Furthermore, the chemoselective reduction of thiochromones **97** to 2,3-dihydro-4*H*-1-benzothiopyran-4-ones (thiochromanones) **96** was examined, which is a valuable precursor for benzothiazepin **95** ring system.

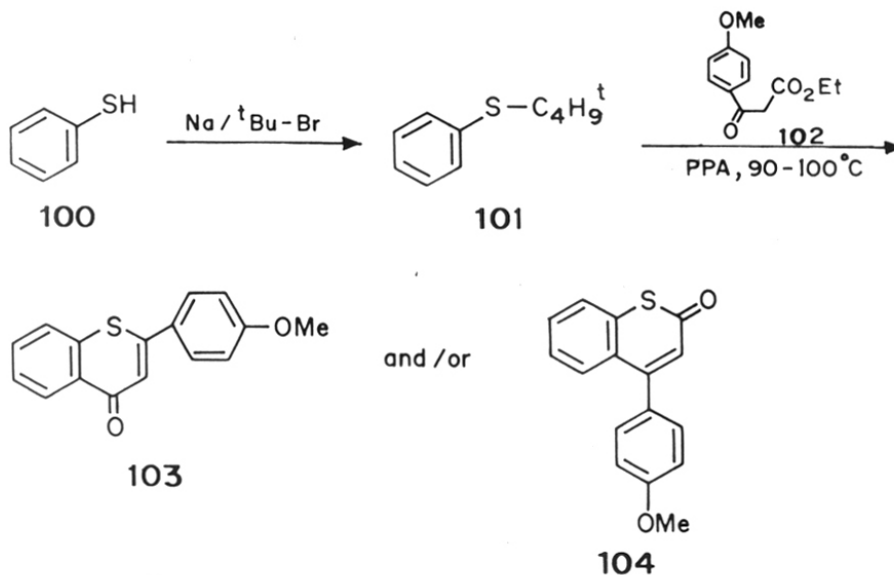
Scheme -11



RESULTS AND DISCUSSION

In general, 1-benzothiopyran-4-ones **97** are synthesised either by the condensation of a β -keto ester with a thiophenol in polyphosphoric acid³⁶ or by the cyclization of a β -substituted cinnamate, derived from the constituent thiophenol and an appropriate propiolate³⁷ (*Scheme-12*). However, these methods could not be applied for the synthesis of many target molecules,³⁸ in particular methoxy-substituted thioflavone³⁹ (*Scheme-12*). We developed² a simple, convenient and one-pot route to 1-benzothiopyran-4-ones *via* intramolecular thiolester carbonyl olefination using *N*-phenyl(triphenylphosphoranylidene) ethanimine.

Scheme - 12



Thiosalicylic acid **99** was converted into its *S*-acyl (aroyl) derivatives **98a-e** by treatment with the corresponding acid chloride or anhydride (see *Experimental Section*). The mixture of *S*-acetylthiosalicylic acid **98a** and *N*-phenyl(triphenylphosphoranylidene)ethanimine **1** (1:1 ratio) was refluxed in toluene for 10 h. to give 85% yield of 2-methyl-4*H*-1-benzothiopyran-4-one **97a**. The structure of **97a** was confirmed on the basis of satisfactory spectral data and by comparison with literature data.⁴⁰ Proton-NMR shown signals at δ 2.35-2.51 (d, 3H, CH₃), 6.8-6.9 (m, 1H, olefinic proton), 7.33-7.64 (m, 3H, Ar), 8.33-8.55 (m, 1H, Ar). Similarly, reaction of *S*-propionylthiosalicylic acid **98b** and ylide **1** under reflux for 12h. yielded 83% of 2-ethyl-4*H*-1-benzothiopyran **97b**. The Proton-NMR gave signals at δ 1.2 (t, 3H), 2.5 (q, 2H), 6.7 (s, 1H), 7.13-7.45 (m, 3H, Ar), 8.35 (m, 1H, Ar).

The reaction of *S*-benzoylthiosalicylic acid **98c** and *N*-phenyl(triphenylphosphoranylidene)ethanimine **1** under reflux condition for 8 h. gave 89% yield of 2-phenyl-4*H*-1-benzothiopyran-4-one **97c**, which was characterised by ¹H-NMR data and by comparison with literature data.⁴¹ Proton-NMR gave signals at δ 7.2 (s, 1H, S-C=CH), 7.5-7.98 (m, 8H, Ar), 8.6 (m, 1H, Ar) and IR showed band at 1635 cm⁻¹ (s, CO). The effect of electron donating and electron withdrawing group in aromatic ring was studied. Thus, reaction of *S*-(4-chlorobenzoyl)thiosalicylic acid **98d** and ylide (1:1 ratio) under reflux condition for 6h. gave

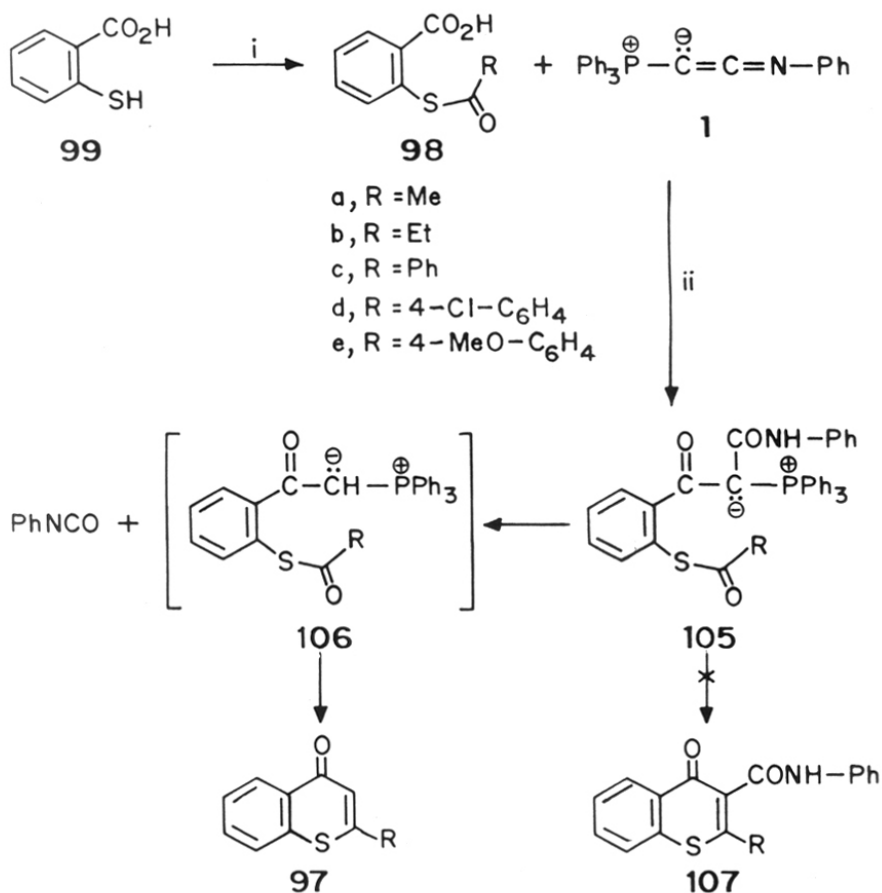
91% yield. 2-(4-chlorophenyl)-4*H*-1-benzothiopyran-4-one **97d**, the structure of which was confirmed by spectral data and by comparison with literature data.⁴² IR spectrum gave peak of carbonyl at 1640 cm⁻¹ (vs) and ¹H-NMR gave signals at δ 7.15 (s, 1H, S-C=CH), 7.48-7.98 (m, 7H, Ar), 8.6 (m, 1H, Ar).

Similarly, reaction of *S*-(4-methoxybenzoyl)thiosalicylic acid **98e** and *N*-phenyl(triphenylphosphoranylidene)ethanimine under reflux for 15h. gave 80% yield of 2-(4-methoxyphenyl)-4*H*-benzothiopyran-4-one **97e**. Once again, the structure of **97e** was confirmed by spectral data and by comparison with literature data.⁴³ Thus, proton-NMR gave signals at δ 3.9 (s, 3H, CH₃), 7.25 (s, 1H, S-C=CH), 7.05 (dd, 2H, Ar), 7.55 (m, 5H, Ar), 8.6 (m, 1H, Ar) and mass spectrum gave *M*⁺ at 268 (100%). Thus, electron withdrawing substituent accelerates the rate of Wittig reaction, while a donating substituent retards the rate of reaction. This observation can be explained on the basis of enhanced electrophilicity, due to electron withdrawing group, resulting in efficient Wittig reaction.

The formation of product **97** could be explained by a sequence of reaction, as illustrated in *Scheme-13*. A possible reaction pathway for the conversion of **98** into **97** involves protonation of *N*-phenyl(triphenylphosphoranylidene)ethanimine **1** by **98**, followed by nucleophilic attack of the carboxylate anion to the resulting vinyl phosphonium salt. There is then a migration of the ester carbonyl group from O to C forming **105**, followed by extrusion of phenyl isocyanate and ultimately leading to the acylphosphorane **106**, which subsequently undergoes ring closure *via* the intramolecular Wittig reaction on the thiolester carbonyl to form the desired 4*H*-1-benzothiopyran-4-one **97**. The extrusion of phenyl isocyanate during the reaction was detected by addition of ethanol to the reaction mixture. Thus, phenyl-isocyanate was trapped and isolated in the form of the carbamate. In none of the cases were we able to isolate 2-substituted, 4-oxo-4*H*-benzothiopyran-3-carboxanilide **107**. This result indicates that the cleavage of phenyl-isocyanate in **105** at higher temperatures is faster than the intramolecular Wittig reaction and thus eventually leads to the desired product **97**. Further, as anticipated, an electron withdrawing substituent in **97d** accelerates the rate of intramolecular Wittig reaction, whereas presence of a donor substituent in **97e** reduces the speed of reaction and hence, a slightly longer time is required for the completion of the reaction. It may be pertinent to mention here that the cyclization of cinnamate with an electron

donating substituent such as methoxy by an usual process led to the formation of the corresponding coumarin instead of the desired 1-benzothiopyran-4-one (*Scheme-12*)³⁹. Also, the reaction of methoxy-substituted benzenethiol with ethylbenzoyl acetate by a conventional method has been found to give a mixture of the corresponding thioflavone and isomeric thiocoumarin or only the thiocoumarin in very low yield (*Scheme-12*).⁴⁴ In this connection, the present methodology from **98e** to **97e** is noteworthy.

Scheme-13

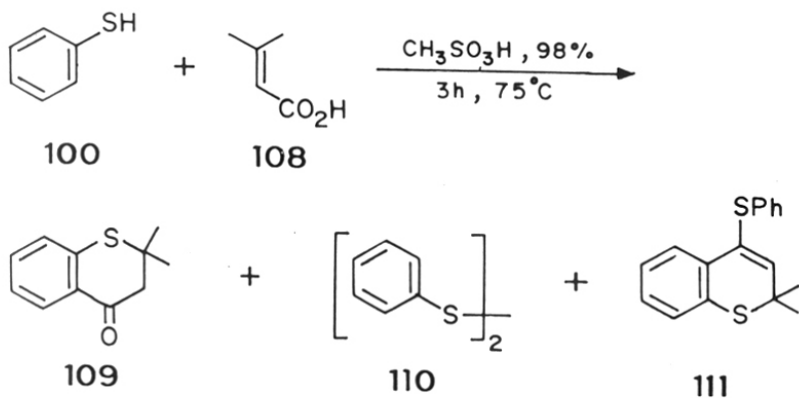


Reagents and conditions : i, RCOCl or (RCO)₂O, aqu. KOH, 0°C - r.t., 0.5 h, 60-80 %; ii, 6-15 h, in toluene or dioxane, reflux, 80-91 %.

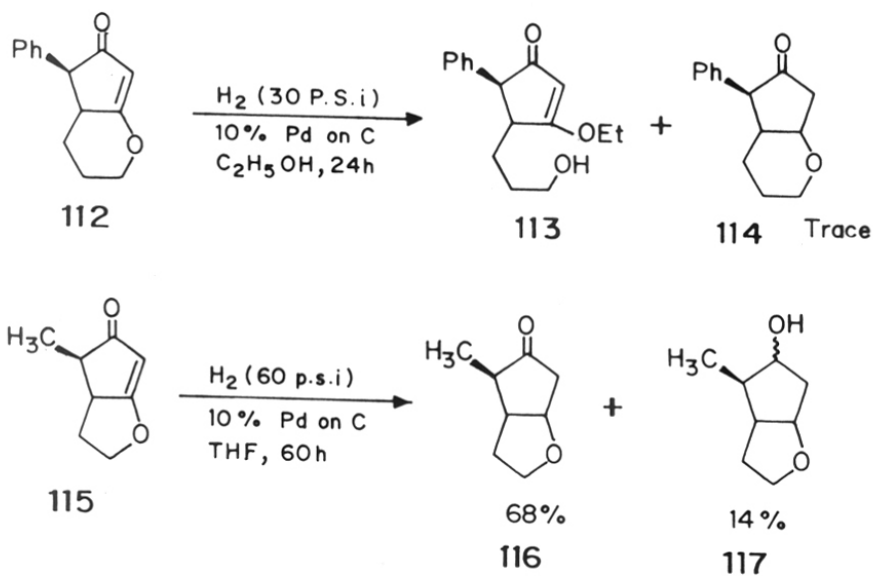
With a view to ascertaining the reaction pathway, *S*-acetylthiosalicylic acid **98a** was treated with **1** in toluene at room temperature, to give compound **105a**, which was isolated and identified by its spectral data (Please see *Experimental Section*). Compound **105a**, on heating in refluxing toluene, gave the desired 2-methyl-1-benzothiopyran-4-one **97a**. This finding indicates that compound **105a**, which results from the reaction between **98a** and **1**, is one of the intermediates which after cleavage of phenyl isocyanate, undergoes subsequent intramolecular Wittig cyclization to afford the desired product **97a**. However, the same reaction under reflux condition led to 2-methyl-1-benzothiopyran-4-one **97a** as the only product.

Having developed an efficient methodology for thiochromones, the chemoselective reduction of thiochromones into thiochromanones was examined. However, the various methods available for the chemoselective reduction of enone to ketone, eg. hydride related reagents with/without Lewis acids and various electron transfer reagents are known to create problem for even remote carbon-sulfur bonds.⁴⁵⁻⁴⁷ Perhaps, this is why, the majority of synthesis of these skeletons does not involve reductive methods.⁴⁸ Recently, Clayton et.al⁴⁹ have synthesised analogous skeletons with varied side products by conventional approach, which may not be suitable for the synthesis of 2-mono-substituted thiochromanones systems (*Scheme-14*). The complexity of chemoselective reduction of highly sensitive vinylogous esters by using various reducing agents and by varying solvent systems, has recently been reported by Herndon et.al⁵⁰ (*Scheme-14*). Presumably, vinylogous thioesters should be more sensitive than vinylogous esters as C-S bonds are known to be weaker than C-O bonds. Hence, prior to attempting any standard methods of reduction of enones to ketones, the conjugate interaction of carbon-sulfur bond to enone skeleton was visualised, which should result in an enhanced polarization of carbonyl in **97**, compared to a normal enone. Indeed, the reaction of **97** with Zn/AcOH, Li/liq. NH₃, Wilkinson's catalyst, diimide⁵¹ and cyclohexene/Pd-C 10% (catalytic hydrogen transfer)⁵² (*Scheme-16*) failed to give the desired product. Reduction with 5% Pd-C in ethyl acetate was not encouraging as it led to low yield of the desired products, even after prolonged reaction. Alternatively, catalytic hydrogenation of **97** with excess 10% Pd-C was attempted. A typical procedure involves hydrogenation of compound **97** (1 equiv.) with 10% Pd-C (30 Wt % on the basis of substrate) at 30 psi in

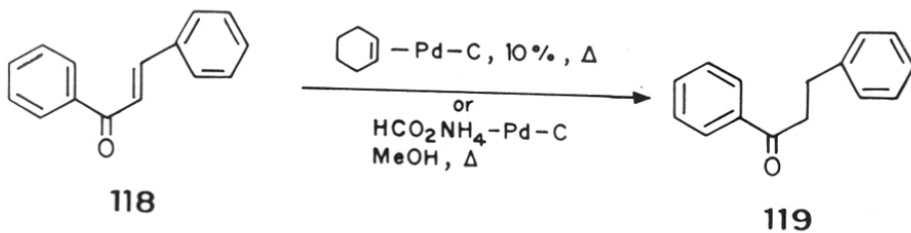
Scheme -14



Scheme-15



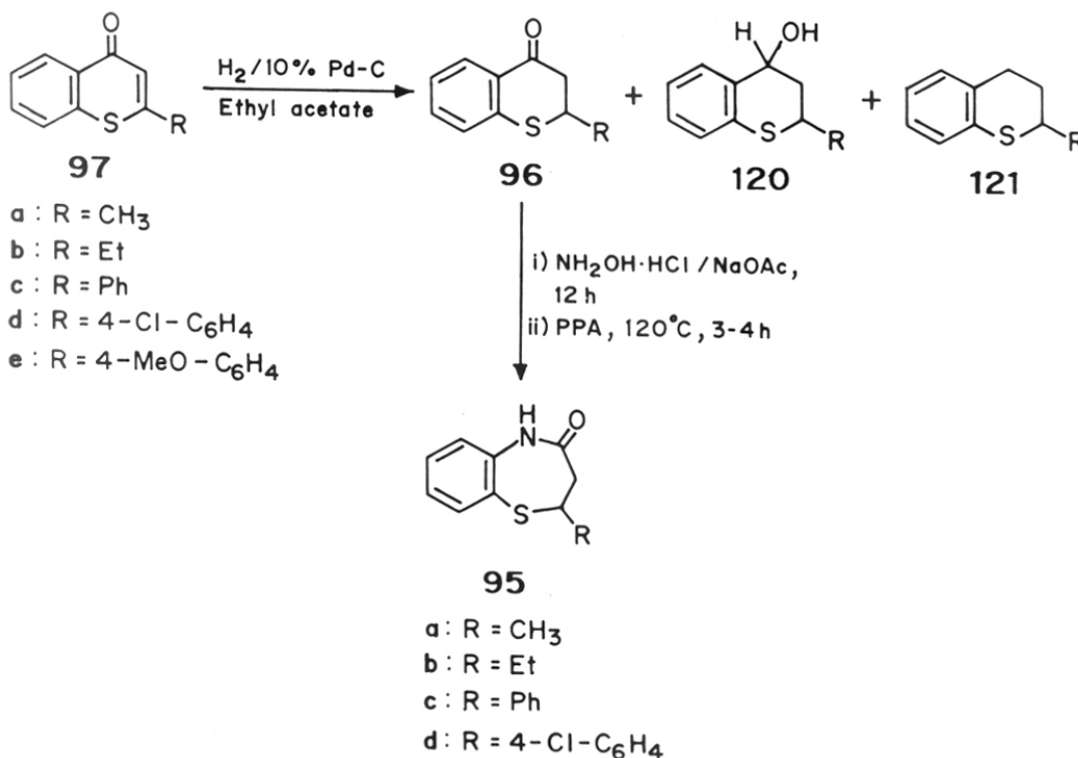
Scheme -16



ethyl acetate at room temperature (*Scheme-17*). As shown in *Scheme-17*, 2-methyl-1-benzothiopyran-4-one **97a** on catalytic reduction using 10% Pd-C in ethyl acetate gave the desired 2-methyl-thiochroman-4-one **96a**. The compound **96a** was confirmed by spectral data and compared with literature data.⁵³ IR spectrum showed peaks at 1680 cm^{-1} (CO) and $^1\text{H-NMR}$ gave signals at δ 1.46(d, 3H, CH_3), 2.75-3.0(ddd, 2H, CH_2), 3.64(m, 1H, CH), 7.16-7.4 (m, 3H, Ar), 8.1 (dd, 1H, Ar). Similarly, 2-ethyl-1-benzothio pyran-4-one **97b** furnished the desired 2-ethylthiochroman-4-one **96b** (62%), which was confirmed by spectral data. Proton-NMR gave signals at δ 1.05 (t, 3H, CH_3), 1.4 (m, 2H, CH_2), 3.45 (m, 1H, CH), 7.1-7.4 (m, 3H, Ar), 8.1 (dd, 1H, Ar). Whereas compound **97c** under similar conditions afforded a mixture of products **96c** (45%), **120c** (18%) and **121c** (31%). Compounds **96c**, **120c** and **121c** were confirmed by spectral data. Proton-NMR of compound 2-phenyl-thiochroman-4-one **96c**, gave signals at δ 3.35 (q, 2H, CH_2), 4.8 (dd, 1H, CH), 7.2-7.65 (m, 8H, Ar), 8.18 (dd, 1H, Ar) and IR spectrum showed peaks at 1680 (CO, s) , 1600(s) cm^{-1} . 2-phenyl-thiochroman-4-ol **120c** gave $^1\text{H-NMR}$ signals at δ 2.4-2.65 (m, 2H, CH_2), 4.6 (dd, 1H, $\text{CH-C}_6\text{H}_5$), 5.0 (m, 1H, CH-OH), 7.15-7.9 (m, 9H, Ar) and mass spectrum gave M^+ 249 (9%). Compound 3,4-dihydro-2-phenyl-2*H*-benzothiopyran **121c** gave $^1\text{H-NMR}$ signals at δ 2.0-2.2 (m, 2H, CH_2), 2.65-2.9 (dd, 2H, CH_2Ph), 4.18-4.38 (dd, 1H, $\text{S-CH-C}_6\text{H}_5$), 7.0-7.2 (m, 9H, Ar) and mass spectrum gave M^+ at 226 (62%). Similarly, **97d** resulted in the formation of a mixture of products **96d**, **120d** and **121d** in 10%, 25% and 40% yields respectively. Compounds **96d**, **120d** and **121d** were confirmed by spectral data. Proton-NMR of 2-(4-chlorophenyl) thiochroman-4-one **96d** gave signals at δ 3.35 (q, 2H, CH_2), 4.75 (dd, 1H, $\text{S-CH-C}_6\text{H}_4\text{-Cl}$), 7.05-7.48 (m, 7H, Ar), 8.2 (dd, 1H, Ar) and IR spectrum showed band at $1680\text{ (CO, s) cm}^{-1}$. IR spectrum of 2-(4-chlorophenyl)-thio chroman-4-ol **120d** gave peaks at $3600\text{ (b s, OH)cm}^{-1}$ and Proton-NMR gave signals at δ 1.75 (b s, OH), 2.38-2.65 (m, 2H, CH_2), 4.6 (dd, 1H, $\text{S-CH-C}_6\text{H}_4\text{-Cl}$), 5.0 (q, 1H, CH-OH), 7.2-7.9 (m, 8H, Ar) and $^1\text{H-NMR}$ of compound 3,4-dihydro-2-(4-chlorophenyl)- 2*H*-benzothiopyran **121d** gave signals at δ 2.4 (m, 2H, CH_2), 3.0 (q, 2H, benzylic CH_2), 4.5 (dd, 1H, $\text{S-CH-C}_6\text{H}_4\text{-Cl}$), 7.1 (m, 4H, Ar), 7.4 (m, 4H, Ar) and mass spectrum gave M^+ at 260 (98%). In contrast, **97e** under identical conditions furnished totally reduced product **121e** in 66% yield. The $^1\text{H-NMR}$ of compound **121e** gave signals at δ 2.0-2.2 (2H, m, CH_2), 2.95 (q, 2H, Ph-CH_2 -), 3.75 (s, 3H, OCH_3), 4.15-4.35 (ddd, 1H, $\text{S-CH-C}_6\text{H}_4\text{-OMe}$), 6.8-7.25 (m, 9H, Ar) and mass spectrum

gave peaks at 256 (M^+ , 15%), 226 (30%), 121 (100%). These results clearly indicate that the nature of substituents at 2-position in **97** influences the course of catalytic reduction and product distribution. Thus, a donor substituent such as *p*-methoxyphenyl at 2-position, eg. **97e** leads to complete reduction of carbonyl to saturated analogue **121e**, whereas an acceptor substituent, *p*-chlorophenyl eg. **97d** gives the ketone **96d** in addition to side products **120d** and **121d**. Besides, sulfur is known to deactivate the reactivity of Pd-C for enhancing selectivity.⁴⁶ Though Pd-C catalyst (10 Wt % on the basis of substrate) was useful to reduce the substrate, but due to other sequential reductions, a significant amount of starting material along with varying proportion of products was recovered. Therefore, for completion of the reaction, an adequate amount of (~ 30%) of the catalyst was needed. This could perhaps be attributed to the poisoning and deactivation of the catalyst due to its long exposure to the sulfur containing substrate. Mention must be made here that the side products formed during reaction are also useful skeletons.⁵⁴ Thus, the effect of various solvent in our reduction was

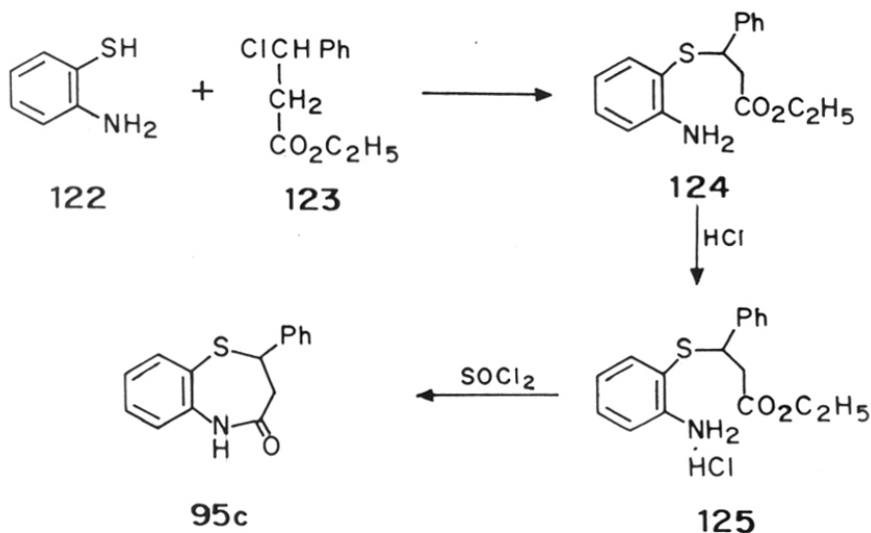
Scheme -17



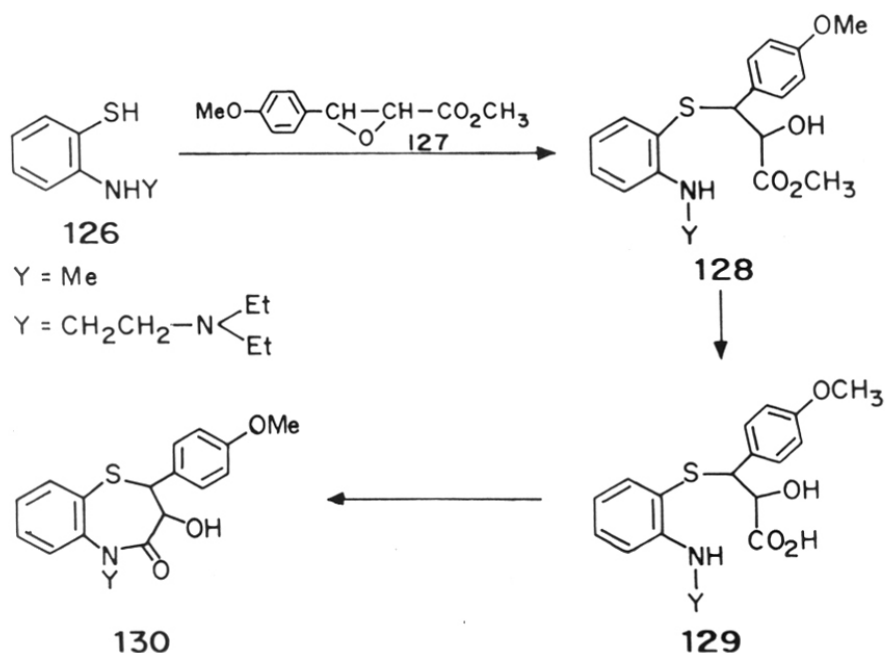
examined. However, the reduction in ethanol did not yield any product. An attempt to avoid the concomitant reduction of carbonyl function in **97** in a solvent such as dioxane⁵⁵ failed. Alternatively, one could protect the ketone prior to catalytic reduction. However, various methods available for ketone protection⁵⁶ eg. ethylene glycol/*p*-toluene sulfonic acid,⁵⁷ 2,2-diethyl-1,3-propane diol/pyridinium *p*-toluene sulfonate⁵⁸ failed with these skeletons. Once again, the conjugate, interaction of C-S bond might be reducing the electrophilicity of carbonyl carbon, ultimately creating problem for protection.

For the construction of benzothiazepin ring, various routes are available in the literature. Krapcho and co-workers⁵⁹ reported the synthesis of 1,5-benzothiazepines (*Scheme-18*), 2,3-dihydro-1,5-benzothiazepin-4-(5*H*)-ones from 2-aminobenzene thiol and the appropriate cinnamic, phenyl crotonic, or furanacrylic acid. Hiroshi et.al⁶⁰ reported the preparation of the N-substituted benzothiazepine ring. The reaction of 2-(*N*-alkylamino) thiophenols **126** with methyl 4-methoxy phenyl glycidate **127** gives methyl- 2-hydroxy-3-(4-methoxyphenyl)-3-(2-alkyl-aminophenylthio)-propionates **128**. Hydro lysis of **129** followed by cyclization of the resultant amino acid gives **130** (*Scheme-19*).

Scheme - 18

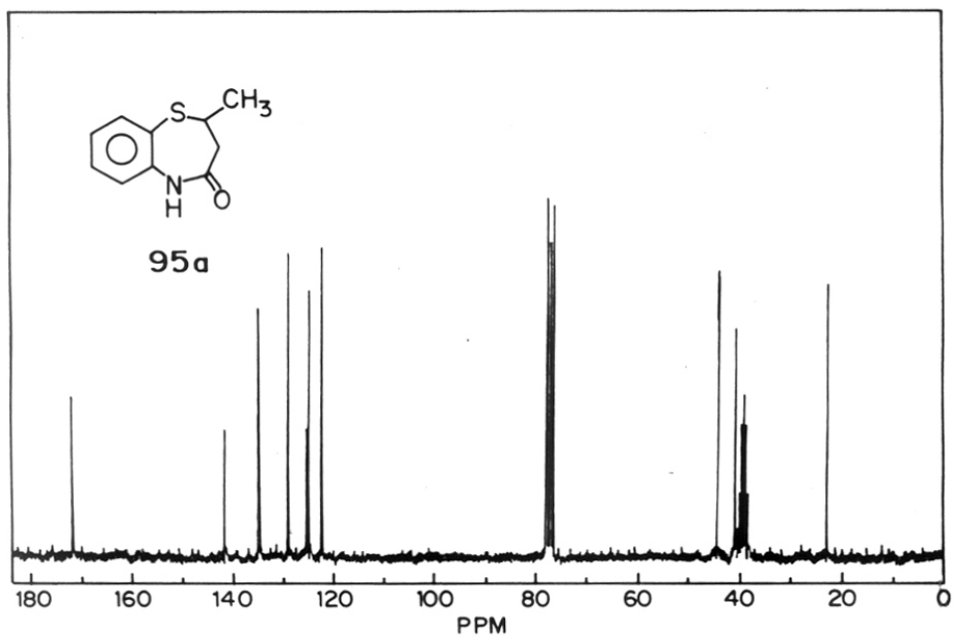
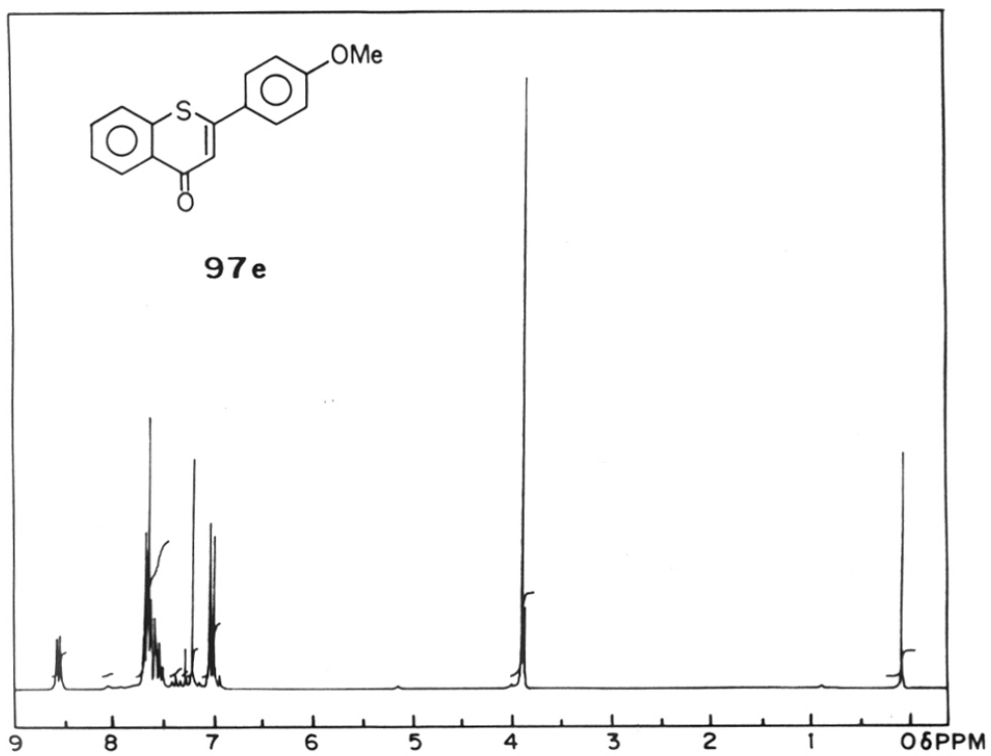


Scheme -19



For the construction of benzothiazepin ring system, the thiochromanones **96** (*Scheme-17*) were treated with hydroxyl amine hydrochloride in the presence of sodium acetate, in refluxing ethanol, to furnish the corresponding oximes,⁶¹ (Please see *Experimental Section*), which underwent regioselective Beckmann rearrangement with polyphosphoric acid, affording 2,3-dihydro-5*H*-2-substituted 1,5-benzothiazepin-4-ones **95** in 60-63% yields (*Scheme-17*).^{62,63}

As shown in *Scheme-17*, 2-methyl-1-benzothiopyran-4-one was treated with hydroxylamine hydrochloride in the presence of sodium acetate under reflux to give oxime, which was treated with polyphosphoric acid, affording 63% yield of 2-methyl benzothiazepin (2,3-dihydro-5*H*-2-methyl-1,5-benzothiazepin-4-ones) **95a**, the structure of which was confirmed by spectral data and by comparison with literature data.^{62,63} Thus, IR showed absorptions at 3340 (bm, NH), 1680 (vs, CONH) cm^{-1} , whereas $^1\text{H-NMR}$ gave signals at δ 1.34 (d, 3H, CH_3), 2.4-2.7 (ddd, 2H, CH_2), 3.8-4.1 (m, 1H, CH), 7-7.65 (m, 4H, Ar) and $^{13}\text{C-NMR}$ gave signals at δ 171.87 (CONH, s), 141.74, 134.96, 129.18, 125.63, 125.08,



122.60, 44.46, 41.03, 22.99. Similarly, compound **96b** under similar conditions afforded 60% yield of 2,3-dihydro-5*H*-2-ethyl-1,5-benzothiazepin-4-one **95b**. The compound **95b** was characterised by Proton-NMR which showed signals at δ 0.9-1.13 (t, 3H), 1.3-1.45 (m, 2H), 2.42-2.52 (q, 1H), 2.67-2.80 (dd, 1H), 3.8-4.0 (m, 1H), 7.05-7.7 (m, 4H, Ar), 8.75 (bs, 1H, NH).

Similarly, 2-phenyl-thiochroman-4-one **96c** afforded 2,3-dihydro-5*H*-2-phenyl-1,5-benzothiazepin-4-one (Thiazesim) **95c** in 62% yield. Similarly, the structure of **95c** was confirmed by spectral data and by comparison with literature data.⁶⁴ IR spectrum showed peaks at 3340 (bs, NH), 1680 (CONH, vs) cm^{-1} , ^1H -NMR gave peaks at δ 2.96 (t, 2H, CH_2), 4.65 (q, 1H, S-CH- C_6H_5), 7.34-7.92 (m, 9H, Ar), 9.36 (s, 1H, NH) and ^{13}C -NMR showed signal at δ 168.00 (CONH, s). Finally, 2,3-dihydro-5*H*-2-(4-chlorophenyl)-1,5-benzothiazepin **95d** was synthesised under similar conditions. Compound **95d** was characterised by Proton-NMR and compared with literature data,⁶² ^1H -NMR gave signals at δ 2.98 (t, 2H, CH_2), 4.59 (q, 1H, S-CH- C_6H_5), 7.33-7.94 (m, 4H, Ar), 9.36 (bs, 1H, NH) and compound melted at 202°C.⁶²

CONCLUSIONS

A facile and convenient synthesis of the *N*-phenyl(triphenylphosphoranylidene)ethanimine **1** has been developed. This method is amenable for large scale preparation.

The reaction of various aromatic carboxylic acids with *N*-phenyl(triphenylphosphoranylidene)ethanimine **1** gave useful 3-substituted indenone. Currently, we are also exploring this chemistry for the synthesis of carbocyclic frame of Taxol.

One-pot methodology for a variety of quinolone derivatives has been partially developed. Further studies on the utility of this method for the synthesis of some biologically useful quinolones with appropriate substitution are underway in our group.⁶⁵

We have synthesized² a number of 2-substituted, *4H*-1-benzothiopyran-4-ones from readily accessible starting materials in excellent yields. This method offers a more general and one-pot synthesis of 1-benzothiopyran-4-one. Some of the synthesized compounds are precursors for thiochroman-4-ones which serve as key intermediates in the syntheses of a variety of compounds of biological interest.^{33,34,63}

In continuation, chemoselective reduction of thiochromones **97** by 10% Pd-C to thiochromanones **96** has been established. The degree of chemoselectivity appears to be a function of the nature of substituent at 2-position. Subsequent regioselective Beckmann rearrangement induced ring enlargement to benothiazepines **95** has been accomplished.

EXPERIMENTAL

Triphenyl-methylphosphoniumiodide (12): 8.6ml (0.13 mol) of methyl iodide was added slowly to a cooled solution of triphenylphosphine 30g (0.11 mol) in 200ml of dry benzene and the mixture was stirred at room temperature for 5 h. The solid separated was filtered, washed with benzene and air dried.

Yield : > 90%.

m.p. : 185°C.

¹H-NMR (80 MHz) : δ 3.0-3.2 (d, 3H, CH₃) 7.6-8.0 (m, 15H, Ar).

Preparation of methylene-triphenylphosphorane (5): A mixture of triphenyl-methyl phosphoniumiodide 40g (0.09 mol) and sodamide 4.63g (0.11 mol) in 200ml of dry benzene was stirred at room temperature for 24 h. Pale yellow colour developed, the NaI preprecipitate was filtered off under an inert atmosphere (N₂) and the benzene from filtrate was evaporated to get the solid in > 90% yield. Reaction was carried out strictly under anhydrous condition.

Note: Benzene solution of methylene-triphenylphosphorane **5** was used as such for further reaction.

Preparation of α -(*N*-phenylthiocarbamoylmethylene)-methylene triphenylphosphorane (14): To above solution of methylene-triphenylphosphorane was added slowly at 0°C, 13.3g (11.8ml, 0.09 mol) of phenyl isothiocyanate dissolved in 30ml of dry benzene. Initially, a dark colour develops, which after 15 minutes becomes light. The mixture was stirred at room temperature overnight. The solid, thus obtained was filtered, washed with benzene and recrystallised from chloroform:ethyl acetate.

Yield : 88% (35g).

m.p. : 203°C.

IR (CHCl₃) : cm⁻¹ 3200(b s, NH), 2980(s), 2900(m), 1600(s), 1480(m), 1440(s).

¹H-NMR (90 MHz) : δ 1.9 (b s, 1H, NH), 4.45 (d, 1H, P=CH), 7.06-7.78 (m, 20H, Ar).

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-triphenyl phospho nio-ethylene)-iodide (15a) and (1-Phenylimino-1-methylmercapto-2-triphenylphospho nio-ethane)-iodide (15b): To a solution of α -(*N*-Phenylthiocarbamoyl)methylene-triphe nylphosphorane **14** 20g (0.048 mol) in 150ml of CHCl_3 was added dropwise, 6.9g (3.02 ml, 0.063 mol) 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 recrystallised from chloroform/ether.

Yield : 93% (25g).

m.p. : $218-220^\circ\text{C}$.

IR (CHCl_3) : cm^{-1} 3400 (b m, NH), 1640(s), 1600(s), 1530(s), 1450(s).

$^1\text{H-NMR}$ (90 MHz) : (**15a**) δ 2.12 (s, 3H, S- CH_3), 5.3 (d, $\text{Ph}_3\text{P-CH=}$), 10 (s, Ph-NH).

(**15b**) δ 1.62 and 2.93 (s, S- CH_3), 5.72 (d, $\text{Ph}_3\text{P-CH}_2-$), 6.25 (d, $\text{Ph}_3\text{P-CH}_2$), 7.02-7.97 (m, Aromatic).

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 (16): A tautomeric mixture of **15a** and **15b** 25g (0.045 mol) was suspended in 150 ml of chloroform and shaken thoroughly for 10 minutes with excess of 10% potassium hydroxide (7.56g, 0.135 mol) solution. The organic layer was separated, dried over anhydrous Na_2SO_4 . The solvent was completely evaporated under reduced pressure. The residue was treated with toluene. The solid, thus obtained was filtered, washed with toluene and recrystallised from toluene.

Yield : 60% (15g).

m.p. : $154-155^\circ\text{C}$.

IR (KBr) : cm^{-1} 1510 (s, N-C=S).

$^1\text{H-NMR}$ (90 MHz) : δ 2.36 (s, 3H, -S- CH_3), 3.04 (d, $\text{Ph}_3\text{P=CH-}$), 6.59-7.74 (m, 20H, Ar).

Preparation of sodium bis(trimethylsilyl)amide (17): A mixture of hexamethyl disilazane (66g) and sodamide (12.2g) in dry benzene (300 ml) was refluxed for 72 hours under anhydrous condition. The undissolved residue was filtered off and the solvent was evaporated under reduced pressure. To the residue, sufficient amount of dry petroleum ether was added. The solid obtained was filtered, washed with pet.ether and dried under high vacuum to yield (30g) white solid.

m.p. : 165-67°C

Preparation of *N*-Phenyliminoketenylidenetriphenylphosphorane (1): A mixture of 17g (40 mmol) 2-Phenylimino-2-methylmercapto-ethylidenetriphenyl phosphorane **16** and 8.05g (44 mmol) sodium bis(trimethylsilyl)amide in 100 ml of dry benzene was stirred at 70°C overnight. The sodium methyl sulphide formed during reaction was filtered off and the benzene from the filtrate was completely evaporated under reduced pressure. The residue was treated with ethyl acetate. The product was filtered, recrystallised from ethyl acetate.

Yield : 74% (11.11g).

m.p. : 151-153°C (Lit⁷. 151-152°C).

IR (Nujol) : cm⁻¹ 3800(s), 2000(vs), 1600(s), 1530(s), 1450(s).

¹H-NMR (90 MHz) : δ 7.3-8.0 (m, 20H, Ar).

MS : m/z 377 (M⁺).

Analysis : C₂₆H₂₀NP Calculated : C, 82.74; H, 5.34; N, 3.71.

Found : C, 82.43; H, 5.41; N, 3.61.

2-Phenyl-1*H*-2-benzazepin-1,3(2*H*)-dione (58): A mixture of phthalaldehydic acid 200mg (1.33 mmol) and *N*-Phenyl(triphenylphosphoranylidene)ethanimine 500 mg (1.33 mmol) was stirred at 0°C to room temperature for 1 h., then slowly refluxed for 3 h. in dry benzene. The progress of reaction was monitored by TLC. After the reaction was complete, the solvent was evaporated under reduced pressure to afford the crude product which was purified by silica gel column chromatography using pet.ether:acetone (95:5) as an eluent to furnish **58** in 81% yield (270 mg).

m.p. : 157°C.

IR (Nujol) : cm^{-1} 2920(s), 2870(w), 1670(s), 1630(s), 1600(s).

$^1\text{H-NMR}$ (90 MHz) : δ 6.55 (d, 1H), 7.25 (m, 4H), 7.4-7.85 (m, 5H), 8.38 (dd, 1H).

$^{13}\text{C-NMR}$ (200 MHz) : δ 167.9(s), 165.75(s), 140.19(s), 139.06(d), 134.06(d), 133.34(d), 132.57(s), 132.19(d), 131.08(d), 129.66(d), 128.39(d), 128.27(d), 126.32(s).

MS : m/z 249 (M^+ , 48%), 221(100), 208(41), 193(32), 156(15), 102(18).

Analysis : $\text{C}_{16}\text{H}_{11}\text{NO}_2$: Calculated : C, 77.10; H, 4.41; N, 5.62.
 Found : C, 76.80; H, 4.18; N, 5.26.

2-Acetylbenzoic acid (53b): A mixture of methyl iodide 5.68g (0.04 mol) and 0.96g (0.04 mol) of Mg in dry ether was stirred for 20 minutes, 3.8g (0.02 mol) of dried (200°C for 1 h.) finely powdered CdCl_2 was added to the solution of ice-cold Grignard reagent, and the mixture was refluxed slowly for 1-2 hours. Phthalic anhydride 2.8g (9.4 mmol) in diethyl ether (200 ml) was added to the cooled solution of the above mixture. The mixture was refluxed for 2 h. The crude material obtained after usual work-up was purified by silica gel column chromatography with acetone:pet.ether (1:99).

Yield : 80% (2.22g).

m.p. : $118-120^\circ\text{C}$.

IR : cm^{-1} 3300(bs), 2940(s), 2870(m), 1750(s), 1700(m), 1620(m).

$^1\text{H-NMR}$ (90 MHz) : δ 2.0 (s, 3H), 7.4-7.9 (m, 4H).

MS : m/z 164 (M^+ , 2%), 149(100), 105(50).

Reaction of 2-acetylbenzoic acid with *N*-Phenyl(triphenylphosphoranylidene)ethanimine: A mixture of 2-acetylbenzoic acid 150 mg (0.9 mmol) and *N*-Phenyl(triphenylphosphoranylidene)ethanimine 339 mg (0.9 mmol) in benzene was stirred at room temperature for 1 h. and then refluxed for 6 h. The progress of reaction was monitored by TLC. After

the reaction was complete, the solvent was evaporated under reduced pressure to afford the crude product which was purified by silica gel column chromatography using acetone:pet.ether (2:98) as an eluent.

3-Methyl-1*H*-inden-1-one (61b):

Yield : 45% (60 mg).
IR (Neat) : cm^{-1} 2900(m), 1720(s), 1600(s).
 $^1\text{H-NMR}$ (90 MHz) : δ 2.25 (d, 3H, CH_3), 5.75 (q, 1H), 7.0-7.5 (m, 4H, Ar).
MS : m/z 144 (M^+ , 61%), 114(50), 115(100), 93(20).

3-Methyl-1-oxo-1*H*-inden-2-carboxanilide (62b):

m.p. : 145°C.
Yield : 38% (92 mg).
IR (Nujol) : cm^{-1} 3300 (bm, NH), 1710(s), 1670(m), 1600(m).
 $^1\text{H-NMR}$ (90 MHz) : δ 2.86 (s, 3H), 7.0-7.9 (m, 9H), 10.1 (s, 1H, NH).
 $^{13}\text{C-NMR}$ (200 MHz) : δ 196.83(s), 172.08(s), 160.83(s), 144.16(s), 138.27(s), 134.69(d), 131.66(d), 130.18(s), 129.10(d), 124.35(d), 123.33(s), 123.08(d), 121.69(d), 120.25(d), 13.92(q).
MS : m/z 263 (M^+ , 23%), 248(26), 171(100), 115(60), 93(62).
Analysis : $\text{C}_{17}\text{H}_{13}\text{NO}_2$: Calculated : C, 77.55; H, 4.98; N, 5.32.
Found : C, 77.30; H, 4.62; N, 5.03.

Preparation of *O*-Benzoylbenzoic acid (53c): 5g. (0.033 mol) of pure phthalic anhydride was placed in a 250 ml two-necked round bottom flask equipped with a sealed mechanical stirrer and a reflux condenser connected with a gas absorption trap. To the flask was added 80 ml of sodium-dried benzene followed by addition of 10g (0.034 mol) of powdered anhydrous aluminium chloride (AlCl_3) in four portions with stirring. When the addition of AlCl_3 was complete, the evolution of HCl slackened, the reaction mixture was warmed on

a water bath and ultimately refluxed until the evolution of gas practically ceased. The flask was cooled and crushed ice was added slowly until the dark mass was completely decomposed and then conc. HCl (15 ml) was added until the solution became clear. The solution was extracted five times with benzene and washed twice with water. The solvent was evaporated and crude product was recrystallised from benzene:pet.ether.

Yield : 80% (6.15g).

m.p. : 128°C.

IR (Nujol) : cm^{-1} 3400(bs), 2980(s), 2830(m), 1680(s), 1660(s), 1600(m).

$^1\text{H-NMR}$ (80 MHz) : δ 7.3-7.8 (m, 8H), 7.95-8.15 (dd, 1H).

MS : m/z 226 (M^+ , 20%), 182(42), 149(52), 105(100), 77(51).

Reaction of benzoylbenzoic acid with *N*-Phenyl(triphenylphosphoranylidene)ethenimine: A mixture of *O*-benzoylbenzoic acid 200 mg (0.95 mmol) and *N*-phenyl(triphenylphosphoranylidene)ethenimine 0.358g (0.95 mmol) in dry benzene was stirred at room temperature, then slowly refluxed for 6 h. The progress of reaction was monitored by TLC. After the reaction was complete, the solvent was evaporated under reduced pressure to afford the crude product, which was purified by silica gel column chromatography using acetone:pet.ether (3:97) as an eluent.

3-Phenyl-1*H*-inden-1-one (61c):

Yield : 33% (60 mg).

IR (Neat) : cm^{-1} 3000(s), 1715(s), 1600(m).

$^1\text{H-NMR}$ (90 MHz) : δ 5.9 (s, 1H), 6.9-7.5 (m, 9H, Ar).

MS : m/z 206 (M^+ , 25%), 178(28), 165(39), 84(100).

1-Oxo-3-phenyl-1*H*-inden-2-carboxanilide (62c):

Yield : 42% (122 mg).

m.p. : 180°C.

IR (Nujol) : cm^{-1} 3280 (bs), 1690(s), 1660(s), 1590(s), 1540(m).

$^1\text{H-NMR}$ (90 MHz) : δ 7.0-7.87 (m, 14H, Ar).

$^{13}\text{C-NMR}$ (200 MHz) : δ 197.00 (CO, s), 169.26 (CONH, s), 159.04(s), 143.93(s), 137.96(s), 134.29(d), 131.51(s), 131.28(d), 130.35(d), 130.23(s), 128.76(d), 128.41(d), 127.95(d), 124.11(d), 123.96(d), 123.56(d), 122.38(s), 120.19(d).

MS : m/z 325 (M^+ , 10%), 296(8), 233(100), 176(66), 151(30), 93(45).

Analysis : $\text{C}_{22}\text{H}_{15}\text{NO}_2$: Calculated : C, 81.48; H, 4.61; N, 4.30.

Found : C, 81.16; H, 4.29; N, 4.50.

Preparation of *N*-formylanthranilic acid (74): Formic acid (98%) 9.6g (0.2 mol) was added dropwise to 20g (0.2 mol) of acetic anhydride with stirring at 0°C . After addition was complete, the mixture was stirred for 15 min. at 0°C and 15 min. at 50°C and then cooled to 0°C again. To this solution was added dropwise a solution of 3g (0.02 mol) of anthranilic acid in 25 ml of formic acid. The reaction mixture was stirred for 3 h. at room temperature. The solid product was collected by filtration, washed with H_2O , and recrystallised from ethyl acetate to give **74** 2.5g (69%).

m.p. : 169°C .

IR (Nujol) : cm^{-1} 3260(bm), 2940(s), 2860(m), 1700(s), 1660(m), 1620(m), 1540(m).

$^1\text{H-NMR}$ (90 MHz) : δ 4.5 (b s, 1H), 7.0-7.23 (m, 1H), 7.35-7.65 (m, 1H), 8.0-8.1 (dd, 1H), 8.45-8.75 (m, 1H), 9.5 (s, 1H), 11.25 (b s, 1H).

MS : m/z 165 (M^+ , 35%), 146(9), 137(54), 119(100), 92(56), 65(19).

4-Hydroxy-3-carboxanilide-quinoline (76): A mixture of *N*-formylanthranilic acid 0.5g (3.0 mmol) and *N*-phenyl(triphenylphosphoranylidene)ethanimine 1.13g (3.0 mmol) was refluxed in dry benzene for 10h. The progress of reaction was monitored by TLC. After the reaction was complete, the solvent was evaporated under reduced pressure to give crude product which was purified by silica gel column chromatography using acetone:pet.ether (10:90) to afford 62% of the product.

Yield : 62% (495 mg).

m.p. : 145-147°C.

IR (Nujol) : cm^{-1} 3300(bs), 2940(s), 1680(vs), 1620(m), 1600(m), 1490(w).

$^1\text{H-NMR}$ (200 MHz) : δ 7.3 (d, 1H), 7.45-7.65 (m, 5H), 7.85 (m, 2H), 8.2 (s, 1H), 8.45 (d, 1H), 10.2 (s, 1H).

$^{13}\text{C-NMR}$ (200 MHz) : δ 169.06 (CONH), 148.17, 146.26, 134.93, 129.90, 129.43, 129.11, 127.98, 127.85, 127.32, 127.22, 124.49, 120.33, 119.94.

MS : m/z 264 (M^+ , 3%), 236(8), 221(100), 194(9), 135(8), 93(28), 77(25).

Analysis : $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_2$: Calculated : C, 72.72; H, 4.54; N, 10.60.
Found : C, 72.39; H, 4.72; N, 10.22.

***N*-Acetylanthranilic acid (78):** 25g of ice followed by 1.5g (0.016 mol) of freshly distilled acetic anhydride were added to an ice-cold solution of 2.5g (0.013 mol) of anthranilic acid and 1.45g (0.026 mol) of pot.hydroxide (10%). The resulting mixture was stirred vigorously for 30 minutes. When the reaction was complete (i.e. when no odour of acid chloride be detected by smell), the solution was acidified with dil. HCl and the material which precipitated out was filtered and washed with water. Recrystallisation of the crude product from ethyl acetate and n-hexane gave the pure product in 60% yield.

m.p. : 182°C.

IR (Nujol) : cm^{-1} 3300(bs), 3000(m), 2980(s), 1680(s), 1660(s), 1600(m).

$^1\text{H-NMR}$ (90 MHz) : δ 2.35 (s, 3H, COCH_3), 3.0 (b s, 1H, OH), 7.05-7.2 (m, 1H), 7.5-7.65 (m, 1H, Ar), 8.05-8.15 (dd, 1H, Ar), 8.7-8.85 (dd, 1H, Ar).

Reaction of *N*-acetylanthranilic acid with *N*-phenyl(triphenylphosphoranylidene)ethanimine: A mixture of 0.255g (1.42 mmol) of *N*-acetylanthranilic acid, *N*-phenyl(triphenyl phosphoranylidene)ethanimine 0.538g (1.42 mmol) and 15 ml of absolute ethyl acetate was

stirred at room temperature for 2 h. and then refluxed for 4 h. The ethyl acetate was concentrated and the solid obtained was filtered, washed with ethyl acetate and dried to afford the product **79** in 90% yield.

A solution of the above solid dissolved in 40 ml dry DMSO was refluxed for 10-12 h. The progress of the reaction was monitored by TLC. When the reaction was complete, the solution was cooled, followed by addition of 50 ml of ice-water and extraction with ether (3x50 ml), the organic layer was washed with (2x50 ml) water and dried over Na₂SO₄. The solvent was evaporated and the residue obtained was purified by silica gel column chromatography using acetone:pet.ether (6:94).

- (**79**) m.p. : 220°C.
- IR (Nujol) : cm⁻¹ 2980(s), 2860(m), 1680(s), 1640(s), 1580(s).
- ¹H-NMR (90MHz, DMSO-d₆) : δ 2.45 (s, 3H, CH₃), 3.45 (d, 1H), 6.85-7.5 (m, 17H, Ar), 7.8-8 (dd, 1H, Ar), 8.25-8.5 (dd, 1H, Ar).
- MS : m/z 437 (M⁺, 12%), 422(43), 303(28), 275(33), 262(31), 183(70), 119(100), 91(33).
- (**80**) m.p. : 191-194°C.
- IR (Nujol) : cm⁻¹ 3300(bm), 2990(m), 1680(vs), 1660(s), 1600(m), 1545(m), 1435(w), 1260(m).
- ¹H-NMR (90 MHz) : δ 2.1 (s, 3H, SCH₃), 2.45 (s, 3H, SCH₃), 2.5 (s, 3H, COCH₃), 6.6-6.7 (m, 1H), 7.0-7.2 (m, 2H, Ar), 8.05-8.12 (dd, 1H, Ar), 8.6-8.72 (dd, 1H, Ar), 10.0 (bs, 1H, NH).
- MS : m/z 237 (M⁺, 15%), 236(85), 221(57), 147(31), 118(22), 77(100).

4-Hydroxy-2-methyl-quinoline (**81**):

- m.p. : 229°C (Lit²⁶. 234-236°C).
- Yield : 20%.
- IR (Nujol) : cm⁻¹ 3100 (bs), 3000(m), 2880(w), 1680(w, CO), 1650(s), 1600(m).

$^1\text{H-NMR}$ (90 MHz) : δ 2.45 (s, 3H, CH_3), 6.0 (s, 1H), 7.1-7.6 (m, 3H), 8.1-8.3 (m, 1H).

MS : m/z 159 (M^+ , 9%), 146(6), 129(15), 120(100), 106(50), 77(30).

Preparation of 2-Methyl-4H-benzoxazin-4-one (83): A solution of anthranilic acid 2g. (0.014 mol) in acetic anhydride (100 ml) was made to react at reflux temperature for 2h. The excess solvent was removed by distillation at atmospheric pressure. The residue was separated by distillation under vacuum and the fraction boiling in the range 125-132°C at 8mm Hg pressure was collected as an oil that solidified to a white solid. The solid was recrystallized from heptane to give **83** in the form of long, white, dense needles.

m.p. : 81°C (Lit²⁷. 81-82°C)

IR (Nujol) : cm^{-1} 2980(s), 1740(s)

$^1\text{H-NMR}$ (90 MHz) : δ 2.45 (s, 3H, CH_3), 7.4-7.6 (m, 2H), 7.6-7.8 (m, 1H), 8.05-8.2 (m, 1H).

MS : m/z 161 (M^+ , 100%), 146(95), 117(63), 90(51), 63(23), 50(39), 43(96).

Reaction of benzoxazinone with *N*-phenylphospha cumulene ylide (84): *N*-phenyl ylide 467 mg (1.24 mmol) was dissolved in 25 ml of dry ethyl acetate. To this, 200 mg (1.24 mmol) of benzoxazinone dissolved in ethyl acetate was added dropwise and the reaction mixture stirred at room temperature for 15h. The ethyl acetate was removed under reduced pressure. Recrystallisation from ethyl acetate-pet.ether gave around 68% of **84**.

(**84**) m.p. : 331°C.

IR (Nujol) : cm^{-1} 2980(s), 2860(m), 1670(s), 1580(s), 1530(s), 1470(s), 1380(s).

$^1\text{H-NMR}$ (90 MHz) : δ 2.18 (s, 3H, CH_3), 6.75-7.0 (m, 5H, NPh), 7.1-7.8 (m, 18H, Ar), 8.05-8.15 (d, 1H).

MS : m/z 538 (M^+ , 10%), 523(20), 495(31), 461(20), 420(18), 262(100), 217(30), 183(70), 152(18), 77(63).

Succinimidoacetic acid (85): A mixture of succinic anhydride 1.5g (0.015 mol) and glycine 1.35g (0.018 mol) was heated at 160-180°C for 30 minutes. The black crude residue was crystallised from water-ethanol to afford a pure crystalline product in 80% yield.

m.p. : 105-110°C (Lit²⁸. 117-120°C).

¹H-NMR(200 MHz) : δ 2.9 (s, 4H), 4.38 (s, 2H), 6.6 (b s, 1H, OH).

Reaction of Succinimidoacetic acid with *N*-phenyl(triphenylphosphoranylidene)ethenimine: A mixture of succinimidoacetic acid 0.3g (1.9 mmol) and *N*-phenyl(triphenylphosphoranylidene)ethenimine 0.72g (1.9 mmol) was heated in refluxing dioxane for 18 h. The progress of reaction was monitored by TLC. After the reaction was complete, the solvent was evaporated under reduced pressure to afford the crude product which was purified by silica gel column chromatography using light petroleum-acetone (97:3) as an eluent.

Yield : 23% (60 mg).

IR (CHCl₃) : cm⁻¹ 2960(s), 2860(m), 1690(s), 1590(m), 1480(m).

¹H-NMR (90 MHz) : δ 2.45 (s, 2H), 2.75 (s, 2H), 4.15 (s, 2H), 6.75 (d, 1H).

MS : m/z 137 (M⁺, 30%), 135(29), 130(11), 115(20), 66(100).

Phthalimidoacetic acid (90): A mixture of phthalic anhydride 3g (0.02 mol) and glycine 1.82g (0.024 mol) was heated at 160-180°C on an oil bath for 30 minutes. After cooling to room temperature, a semi-solid mass was obtained, which was crystallised from water-ethanol.

Yield : 60-70%.

m.p. : 174-176°C.

IR (Nujol) : cm⁻¹ 3200 (bs, OH), 2960(m), 1770(w), 1740(s), 1600(w).

¹H-NMR (90 MHz) : δ 4.5 (s, 2H), 5.0 (bs, 1H, OH), 7.7-8.0 (m, 4H, Ar).

MS : m/z 205 (M⁺, 4%), 160(100), 133(30), 104(31), 76(38).

General method for the preparation of acid chlorides: A mixture of aromatic acids (1 mol) and thionyl chloride (SOCl₂) (1.2 mol) were refluxed for 5-8 h. on an oil bath under

anhydrous condition. The completion of the reaction was confirmed by disappearance of acid peak by IR spectroscopy. Excess of thionyl chloride was distilled off. The acid chlorides were distilled under reduced pressure.

Benzoyl chloride : b.p. 198°C.

4-Methoxybenzoyl chloride : 145°C/14mm.

4-Chlorobenzoyl chloride : 140°C/2mm.

IR (Neat) : cm^{-1} 2990(s), 1780(s), 1700(s), 1600(s).

General Method for the Preparation of S-Acyl(aroyl)thiosalicylic acids (98a-e): 100g of ice followed by freshly distilled anhydride or acid chloride (0.1 mol) were added to an ice-cold solution of 12.32 g (0.08 mol) of thiosalicylic acid 11.2 g (0.2 mole) of pot. hydroxide and 112 ml of water. The resulting mixture was stirred vigorously for 30 min. After the reaction was complete (i.e. when the odour of acid chloride or anhydride could no longer be detected by smell), the solution was acidified with dil HCl and the material which precipitated out was filtered and washed with water. Recrystallisation of the crude product from C₆H₆-hexane or ethyl acetate gave the pure product 98 in 60-80% yields.

S-Acetylthiosalicylic acid (98a):

Yield : 80%.

m.p. : 120-121°C.

IR (Nujol) : cm^{-1} 3300 (bm), 1720 (s), 1680 (vs), 1600 (m).

¹H-NMR (90 MHz) : δ 2.5(s, 3H, CH₃), 7.6 (m, 3H, Ar), 8.1 (m, 1H, Ar).

MS : m/z 196(M⁺, 5%), 136 (100).

S-Propionylthiosalicylic acid (98b):

Yield : 90%.

m.p. : 55°C.

IR (Nujol) : cm^{-1} 2980(s), 1700(vs), 1670(s), 1600(w).

$^1\text{H-NMR}$ (90 MHz) : δ 1.2 (t, 3H), 2.55-2.85 (q, 2H), 7.5 (m, 3H, Ar), 8.05 (m, 1H, Ar),
8.8 (b s, 1H, OH).

MS : m/z 210 (M^+ , 4%), 136(100), 108(16), 57(35).

S-Benzoylthiosalicylic acid (98c):

Yield : 70%.

m.p. : 170°C.

IR (Nujol) : cm^{-1} 1680 (s), 1600 (m).

$^1\text{H-NMR}$ (DMSO-d_6 , 90 MHz) : δ 7.05-7.45 (m, 5H, Ar), 7.7(dd, 2H, Ar), 8.1 (dd, 2H, Ar).

MS : m/z 258(M^+ , 2%), 136(33), 105(100).

S-(4-Chlorobenzoyl)thiosalicylic acid (98d):

Yield : 68%.

m.p. : 190°C.

IR (Nujol) : cm^{-1} 2990 (m), 1690 (s), 1600 (m).

$^1\text{H-NMR}$ (DMSO-d_6 , 90 MHz) : δ 7.3-7.65 (m, 4H, Ar), 7.85-8.18 (m, 4H, Ar).

MS : m/z 171 (M^+ 4%), 156(70), 139(100).

S-(4-Methoxybenzoyl)thiosalicylic acid (98e):

Yield : 60%.

m.p. : 183°C.

IR (Nujol) : cm^{-1} 2990 (m), 1680 (s), 1600 (m).

$^1\text{H-NMR}$ (DMSO-d_6 , 80 MHz) : δ 3.84 (s, 3H, OCH_3), 6.9 (m, 4H, Ar), 8.0 (m, 4H, Ar).

MS : m/z 288 (M^+ , 6%), 152 (100).

General Method for the Preparation of 4*H*-1-Benzothiopyran-4-ones (97a-e): A mixture of S-acyl(aryl)thiosalicylic acid 98 (0.1 mol) and N-phenyl(triphenylphosphoranylidene)ethanimine 1 (0.1 mol) was heated in refluxing toluene or dioxane for 6-15h. The progress of reaction was monitored by TLC. After the reaction was complete, the solvent was evaporated under reduced pressure to afford the crude product 97 which was purified by silica gel column chromatography using light petroleum - acetone 98:2 as eluent.

Conversion of *N*-Acetylthiosalicylic acid with *N*-phenyl(triphenylphosphoranylidene)ethanimine (105a): A mixture of thioacetylsalicylic acid 200 mg (1.00 mmol) and *N*-phenyl(triphenylphosphoranylidene)ethanimine 450 mg (1.2 mmol) in dry benzene was stirred at room temperature for 10-15 h. After the reaction was complete, the solvent was evaporated under reduced pressure to give crude product, which was purified by crystallization with ethyl acetate and pet.ether (15:85).

m.p. : 90-100°C.
 IR (Nujol) : cm^{-1} 3000(m), 1685(s), 1630(s), 1600(s), 1540(m).
 $^1\text{H-NMR}$: δ 2.45 (s, 3H, CH_3), 7.0-8.0 (m, 24H, Ar).
 MS : m/z 453 (4%), 411(10), 303(100), 262(10).

2-Methyl-4*H*-1-benzothiopyran-4-one (97a):

Yield : 85%.
 m.p. : 100-101°C (Lit³⁶. 103-104°C).
 IR (Nujol) : cm^{-1} 2980 (m), 1645 (s), 1600 (s), 1450 (m).
 $^1\text{H-NMR}$ (90 MHz) : δ 2.35-2.51 (d, 3H, CH_3) 6.8-6.9 (m, 1H, S-C=CH), 7.33-7.64 (m, 3H, Ar), 8.33-8.55(m, 1H, Ar).
 MS : m/z 176(M^+ 100%), 147(86), 136 (57).

2-Ethyl-4*H*-1-benzothiopyran-4-one (97b):

Yield : 83%.
 m.p. : 47°C.

IR (Nujol) : cm^{-1} 2990(s), 2820(m), 1640(co,vs), 1600(m).
 $^1\text{H-NMR}$ (90 MHz) : δ 1.2 (t, 3H), 2.5 (q, 2H), 6.7 (s, 1H), 7.13-7.45 (m, 3H, Ar), 8.35 (m, 1H, Ar).
MS : m/z 190 (M^+ , 85%), 147(100), 136(55), 108(40), 69(32).

2-Phenyl-4*H*-1-benzothiopyran-4-one (97c):

Yield : 83%.
m.p. : 125°C (Lit³⁷. 122-123°C).
IR (Nujol) : cm^{-1} 2970 (m), 1635 (s), 1600 (s), 1400 (m).
 $^1\text{H-NMR}$ (90 MHz) : δ 7.2 (s, 1H, S-C=CH), 7.5-7.98 (m, 8H, Ar), 8.6 (m, 1H, Ar).
 $^{13}\text{C-NMR}$ (200 MHz) : δ 180.54(s), 152.62(s), 137.57(s), 136.57(s), 131.36(d), 130.99(s), 130.59(d), 129.10(d), 128.53(d), 127.56(d), 126.82(d), 126.29(d), 123.41(d).
MS : m/z 238(M^+ , 100%), 210(90), 136(48), 108(33).

2-(4-Chlorophenyl)-4*H*-1-benzothiopyran-4-one (97d):

Yield : 91%.
m.p. : 187-189°C (Lit³⁸. 192-194°C).
IR (Nujol) : cm^{-1} 2980 (m), 1640 (s), 1600 (s).
 $^1\text{H-NMR}$ (200 MHz) : δ 7.15 (s, 1H, S-C=CH), 7.48-7.98 (m, 7H, Ar), 8.6 (m, 1H, Ar).
MS : m/z 272 (M^+ , 23), 244(28), 139 (100).

2-(4-Methoxyphenyl)-4*H*-benzothiopyran-4-one (97e):

Yield : 80%.
m.p. : 126-127°C (Lit³⁹. 127-128°C).
IR (Nujol) : cm^{-1} 2980 (s), 1640 (s), 1610 (s), 1520 (s), 1340 (m).

¹H-NMR (200 MHz) : δ 3.9 (s, 3H, CH₃), 7.25 (s, 1H, S-C=CH), 7.05 (dd, 2H, Ar),
7.55-7.56 (m, 5H,Ar), 8.6 (m, 1H, Ar).

MS : m/z 268(M⁺, 100%), 240(40), 225(22).

General Method for the Catalytic Reduction of Thiochromones (97a-e): A solution of 2-substituted-4*H*-1-benzothiopyran-4-one (1 equiv.) in dry ethyl acetate was subjected to hydrogenation with 10% Pd-C (30 wt% on the basis of substrate) at 30 psi at room temp. for 10-20h (Table-2). The progress of reaction was monitored by TLC. The catalyst was filtered off and solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using Pet ether: acetone 100:0 for **121**, 98:2 for **96**; and 90:10 for **120** as eluent.

2-Methyl-1-benzothiopyran-4-one 97a on catalytic reduction gave 2-methyl-thiochroman-4-one (96a):

Yield : 65%

b.p. : 146-147°C/9 mm

IR (Neat) : cm⁻¹ 3100 (s), 2825 (m), 1680 (s), 1590 (s)

¹H-NMR (200 MHz) : δ 1.46 (d, 3H, CH₃), 2.75-3 (ddd, 2H, CH₂) 3.64 (m, 1H, CH),
7.16-7.4 (m, 3H, Ar), 8.1 (d, 1H, Ar)

MS : m/z 178(M⁺, 40%), 136(100), 108(28).

2-Ethyl-thiochroman-4-one (96b):

Yield : 62%.

IR (Neat) : cm⁻¹ 2980(s), 1680(vs), 1600(s), 1450(m).

¹H-NMR (90 MHz) : δ 1.05 (t, 3H), 1.4 (m, 2H), 2.85-3.1 (ddd, 2H), 3.45 (m, 1H),
7.1-7.4 (m, 3H, Ar), 8.1 (dd, 1H).

MS : m/z 192 (M⁺, 33%), 166(11), 162(100), 152(40), 77(23).

2-Phenyl-1-benzothiopyran-4-one 97c on catalytic reduction gave 2-phenyl-thiochroman-4-one 96c, 2-phenyl-thiochroman-4-ol 120c and 3,4-dihydro-2-phenyl-2*H*-benzothiopyran 121c:

Compound 96c

Yield : 45%.
m.p. : 50°C (Lit.⁵⁴ 51.5-52.2°C).
IR (Neat) : cm^{-1} 2960 (s), 1680 (s), 1600 (s).
¹H-NMR (200 MHz) : δ 3.35 (q, 2H, CH_2), 4.8 (dd, 1H, CH), 7.2-7.65 (m, 8H, Ar), 8.18 (dd, 1H, Ar).
MS : m/z 240(M^+ , 44%), 226(30), 136(100).

Compound 120c

Yield : 18%.
m.p. : 136-140°C (Lit.⁵⁴ 144-145°C).
IR (Nujol) : cm^{-1} 3350 (bs), 2960 (s), 1600 (m).
¹H-NMR (200 MHz) : δ 2.4-2.65 (m, 2H, CH_2), 4.6 (dd, 1H, $\text{CH-C}_6\text{H}_5$), 5(m, 1H, CH-OH), 7.15-7.9(m, 9H, Ar).
MS : m/z 242(M^+ , 9%), 233(6), 197(22), 105(100).

Compound 121c

Yield : 31%.
IR (Neat) : cm^{-1} 2940 (s), 2860 (m), 1600 (m), 1470 (m), 1280 (m).
¹H-NMR (200 MHz) : δ 2-2.2 (m, 2H, CH_2), 2.65-2.9 (dd, 2H, Benzylic), 4.18-4.38 (dd, 1H, S- $\text{CH-C}_6\text{H}_5$), 7-7.2 (m, 9H, Ar).
MS : m/z 226(M^+ , 62%), 135(100), 121(51), 91(60).

2-(4-Chlorophenyl)-1-benzothiopyran-4-one 97d on catalytic reduction gave 2-(4-chloro-phenyl)thiochroman-4-one 96d, 2-(4-chloro-phenyl)thiochroman-4-ol 120d and 3,4-dihydro-2-(4-chlorophenyl)-2H-benzothiopyran 121d.

Compound 96d

Yield : 10%.

IR (Neat) : cm^{-1} 2980 (s), 1680 (s), 1600 (m), 1500 (m).
 $^1\text{H-NMR}$ (200 MHz) : δ 3.35 (q, 2H, CH_2), 4.75 (dd, 1H, S- $\text{CH-C}_6\text{H}_5$), 7.05-7.48 (m, 7H, Ar) 8.2 (dd, 1H, Ar).
MS : m/z 274(M^+ , 5%), 244(10), 226(52), 135(100).

Compound 120d

Yield : 25%.
m.p. : 209-210°C.
IR (CHCl_3) : cm^{-1} 3600 (bs), 2960 (s), 1600 (s), 1550 (s), 1460 (m).
 $^1\text{H-NMR}$ (200 MHz) : δ 1.75 (br, OH), 2.38-2.65 (m, 2H, CH_2) 4.6 (dd, 1H, S- $\text{CH-C}_6\text{H}_5$), 5.0 (q, 1H, CH-OH), 7.2-7.9 (m, 8H, Ar).
MS : m/z 276(M^+ , 8%), 258(5), 230(53), 138(100), 111(22).

Compound 121d

Yield : 40%.
m.p. : 65-69°C.
IR : cm^{-1} 2980 (s), 1600 (s).
 $^1\text{H-NMR}$ (200 MHz) : δ 2.4 (m, 2H, CH_2), 3.0 (q, 2H, Benzylic CH_2), 4.5 (dd, 1H, S- $\text{C}_6\text{H}_4\text{-Cl}$), 7.1 (m, 4H, Ar), 7.4 (m, 4H, Ar).
MS : m/z 260(M^+ , 98%), 226(15), 191(18), 134(100), 120(25).

2-(4-Methoxyphenyl)-1-benzothiopyran-4-one 97e on catalytic reduction gave 121e as only product

Yield : 66%.
IR (CHCl_3) : cm^{-1} 2980 (s), 1600 (s), 1480 (m), 1400(m), 1280 (w).
 $^1\text{H-NMR}$ (200 MHz) : δ 2.0-2.2 (2H, m, CH_2), 2.95 (q, 2H Benzylic), 3.75 (s, 3H, OCH_3), 4.15-4.35 (ddd, 1H, S- $\text{CH}_2\text{-C}_6\text{H}_4\text{OMe}$), 6.8-7.25 (m, 9H, Ar).
MS : m/z 256(M^+ , 15%), 226(30), 121(100).

General Method for the Preparation of Oximes: A mixture of thiochromanone 6 (1 mole), hydroxylamine hydrochloride (1.6 mol) and sodium acetate (2 mol) in 80% ethanol was heated under reflux for 12h. The solvent was removed under reduced pressure and the solid thus obtained was filtered and recrystallised from aq. ethanol, yield >92%. The oximes thus prepared were characterized by comparison with their authentic samples.

2-Methyl-1-benothiopyran-4-oxime:

m.p. : 120°C.
 Yield : 92%.
 IR (Nujol) : cm^{-1} 3300 (bs, N-OH), 2980(s), 1600(s).
 $^1\text{H-NMR}$ (90 MHz) : δ 1.4 (d, 3H), 2.5-2.9 (m, 1H), 3.1-3.6 (m, 2H), 7.0-7.25 (m, 3H, Ar), 7.85 (m, 1H, Ar), 8.95 (b s, 1H, =N-OH).
 MS : m/z 193 (M^+ , 100%), 176(82), 149(38), 77(56).

1-Thioflavanone oxime:

m.p. : 195-196°C.
 Yield : 89%.
 IR (Nujol) : cm^{-1} 3280(bs), 2930(m), 1600(s).
 $^1\text{H-NMR}$ (90 MHz) : δ 3.1 (q, 1H), 3.85 (dd, 1H), 4.35 (dd, 1H, SCH-Ar), 7.4 (m, 8H, Ar), 8.0 (dd, 1H, Ar), 8.4 (b s, 1H, N-OH).
 MS : m/z 255 (M^+ , 100%), 238(98), 223(12), 149(48).

General Method for the Preparation of 2,3-dihydro-5H-2-substituted 1,5-benzothiazepin-4-one (95a-d): A mixture of oxime (1 mol) and polyphosphoric acid (prepared by heating a mixture of orthophosphoric acid and P_2O_5 at 100°C) (1.3 mol) was heated at 120°C for 3-4h. The reaction mixture was cooled, decomposed with water, and extracted with methylene chloride. The organic layer was basified to pH 9 with 25% aq. ammonia and then washed thoroughly with water, dried over anhydrous sod. sulfate. The solvent was evaporated to afford crude product which was recrystallised from ethyl acetate 2,3-dihydro-5H-2-methyl-1,5-benzothiazepin-4-one.

2,3-Dihydro-5H-2-methyl-1,5-benzothiazepin-4-one (95a):

Yield : 63%.

m.p. : 198-200°C (Lit⁵⁹. 196-198°C).

IR (Nujol) : cm^{-1} 3340 (bm), 3240 (s), 2780 (m), 1680 (s), 1575 (m), 760 (s).

¹H-NMR (200 MHz) : δ 1.34 (d, 3H, -CH₃), 2.4-2.7 (ddd, 2H, CH₂), 3.8-4.1 (m, 1H, CH), 7.0-7.65 (m, 4H, Ar).

¹³C NMR (CDCl₃ + DMSO-d₆, 200 MHz) : δ 171.87, 141.74, 134.96, 129.18, 125.63, 125.08, 122.60, 44.46, 41.03, 22.99.

MS : m/z 193(M⁺, 35%), 150(19), 69(100).

Analysis : C₁₀H₁₁NSO: Calculated : C, 62.17; H, 5.69; N, 7.25; S, 16.58.

Found : C, 62.48; H, 5.35; N, 7.03; S, 16.19.

2,3-Dihydro-5H-2-ethyl-1,5-benzothiazepin-4-one (95b):

Yield : 60%.

m.p. : 207-209°C.

IR (Nujol) : cm^{-1} 3330(bs), 3000(m), 2980(s), 1680(vs), 1580(m).

¹H-NMR (90 MHz) : δ 0.9-1.13 (t, 3H), 1.3-1.45 (m, 2H), 2.42-2.52 (q, 1H), 2.67-2.80 (dd, 1H), 3.8-4.0 (m, 1H), 7.05-7.7 (m, 4H, Ar), 8.75 (bs, 1H, NH).

MS : m/z 207 (M⁺, 32%), 165(10), 120(40), 97(23), 69(100), 63(12).

Analysis : C₁₁H₁₃NSO: Calculated : C, 63.76; H, 6.28; N, 6.76; S, 15.45.

Found : C, 63.32; H, 5.98; N, 6.38; S, 15.04.

2,3-Dihydro-5H-2-phenyl-1,5-benzothiazepin-4-one (95c):

Yield : 58%.

m.p. : 177-179°C (Lit⁶⁰. 176-177°C).

IR (CHCl₃) : cm⁻¹ 3340 (bs), 2960 (s), 1680 (s), 1600 (s).

¹H-NMR (200 MHz) : δ 2.96 (t, 2H, CH₂), 4.65 (q, 1H, S-CH-C₆H₅), 7.34-7.92 (m, 9H, Ar), 9.36 (s, 1H, NH).

¹³C NMR (200 MHz, : δ 168, 154, 137, 135, 134, 129, 129, 127, 126, 125, 123, 122, 121, CDCl₃) 96, 29.9.

MS : m/z 255(M⁺, 12%), 226(15), 149(30), 107(100), 97(38).

Analysis : C₁₅H₁₃NSO: Calculated : C, 70.58; H, 5.09; N, 5.49; S, 12.54.

Found : C, 70.21; H, 4.83; N, 5.09; S, 12.62.

2,3-Dihydro-5H-2(4-chlorophenyl)-1,5-benzothiazepin-4-one (95d):

Yield : 58%.

m.p. : 202°C (Lit⁵⁸. 204-205°C).

IR (Nujol) : cm⁻¹ 2940(s), 2880(w), 1670(vs), 1600(w).

¹H-NMR (90 MHz) : δ 2.98 (t, 2H, CH₂), 4.59 (q, 1H, S-CH-C₆H₅), 7.33-7.94 (m, 8H, Ar), 9.36 (b s, 1H, NH).

MS : m/z 289 (M⁺, 23%), 254(40), 212(10), 180(14), 105(100), 97(38), 77(30).

Analysis : C₁₅H₁₂NSClO: Calculated : C, 62.28; H, 4.15; N, 4.84; S, 11.07; Cl, 12.11.

Found : C, 62.42; H, 3.88; N, 4.52; S, 10.62; Cl, 11.79.

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