# CHEMISTRY OF POLYCYCLIC SYSTEMS

**PART I:** TC-FACE SELECTIVITIES DURING CYCLOADDITIONS TO A DISSYMMETRIC **POLYCYCLIC- 1,3-DIENE**

**PART II:** SYNTHESIS AND CHARACTERIZATION OF SOME EXCEPTIONALLY STABLE DIOZONIDES

A THESIS
SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

BY

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*To*

*My Parents*

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## STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad 500 046, India, under the supervision of **Professor Goverdhan Mehta.**

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

R. Uma

## CERTIFICATE

Certified that the work embodied in this thesis entitled **"Chemistry of Polycyclic Systems Part I: π-Face Selectivities During Cycloadditions to a Dissymmetric Polycyclic-1,3-Diene; Part II: Synthesis and Characterization of Some Exceptionally Stable Diozonides"** has been carried out by Ms. R. Uma under my supervision and that the same has not been submitted elsewhere for a decree.

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This thesis is fruitful because I have been nurtured incessantly with support and encouragement by my parents, sisters and brother.

## ABBREVIATIONS

| | |
|---|---|
| Ac | : Acetyl |
| AM1 | : Austin Model 1 |
| DCM | : dichloromethane |
| DIBAL-H | : diisobutylaluminium hydride |
| dil. | : Dilute |
| DME | : dimethoxyethane |
| DMAD | : dimethyl acetylenedicarboxylate |
| EtOAc | : ethyl acetate |
| FVP | : Flash Vacuum Pyrolysis |
| hv | : photoirradiation |
| MA | : maleic anhydride |
| Me | : methyl |
| MNDO | : Modified Neglect of Differential Overlap |
| NMM | : *N*-methylmaleimide |
| PCC | : pyridinium chlorochromate |
| PTAD | : *N*-phenyl-1,2,4-triazolinedione |
| PTSA | : p-toluenesulfonic acid |
| r.t. | : room temperature |
| THF | : tetrahydrofuran |
| tlc | : thin layer chromatography |

## PREFACE

The chemistry of novel, strained, caged, polycyclic molecules, bestowed with high symmetry continues to attract the attention of contemporary organic chemists and has aroused considerable interest during the past few decades. Their design and synthesis over the years has been actively pursued as they blend aesthetic appeal with synthetic challenge. Besides synthetic appeal, many readily available polycyclic systems, in which size, shape and symmetry are well defined have served as incisive probes for mechanistic, stereochemical and structural studies.

The thesis entitled **"CHEMISTRY OF POLYCYCLIC SYSTEMS"** is mainly concerned with utilizing polycyclic systems to address a few contemporary issues like origin of diastereoselectivity and generation of unusual structural entities and is presented in two parts. **Part I:** π-Face Selectivities During Cycloadditions to a Dissymmetric Polycyclic-1,3-Diene and **Part II:** Synthesis and Characterization of Some Exceptionally Stable Diozonides. The subject matter of each part has been organized under the headings: Introduction, Results and Discussion, Summary, Experimental. Spectra and References.

The **first part** of the thesis recounts our endeavours towards the synthesis of several derivatives of hexacyclo[7.5.1.$0^{1,6}$.$0^{6,13}$.$0^{8,12}$.$0^{10,14}$]pentadeca-2,4-diene-7,15-dione, a hexacyclic polycyclic cage dione as the probe system and the evaluation and understanding of some of the factors that govern the origin of π-face diastereoselection during Diels-Alder cycloadditions.

The recent advances in organic synthesis have been accompanied by ever-increasing pressures to attain greater levels of stereochemical control. It is therefore

important to be able to precisely predict the stereochemical outcome in a synthetic transformation for the successful design and development of an efficient synthesis. Among the commonly employed organic reactions, the synthetic utility of Diels-Alder reaction (4π+2π-cycloaddition) is very well-established. Its continued popularity and study rests, in part, on the ability to generate four new contiguous stereogenic centers in a single laboratory operation. While the regiochemistry and the topographical *viz. endo* (Alder) *vs. exo* (anti-Alder) selectivity is well understood. the third and perhaps the more subtle and important stereochemical feature namely the π-facial diastereoselection. which arises when the two faces of the reacting partners *viz.* the diene or the dienophile are non-equivalcnt, is still not fully understood and continues to be a matter of lively debate. In this context, it is important to study either newer probe systems or modify the existing ones to get better insights into the factors that control diastereoselection in Diels-Alder cycloadditions.

The issue of stereoselectivity exhibited by facially perturbed dienes in Diels-Alder reactions has been subjected to considerable theoretical and experimental scrutiny in recent years. Attempts have been made to evaluate critically the relative importance of steric, orbital and electrostatic effects in determining the π-face preferences. In this context, substrates having the 1.3-diene moieties embedded in rigid polycyclic frames are particularly useful probes, as facial discrimination due to subtle steric and electronic perturbations can be fine-tuned through distal modulation of functionalities without conformational uncertainties. In recent years, several polycyclic probes having a cyclic 1.3-diene substructure have been devised and probed for diastereoselection employing a variety of dienophiles, but among these.

hexacyclo[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]pentadeca-5,7-dien-3,10-dione system has been more enduring because of its rigidity, ready accessibility, reactivity and functional group manoeuvrability. In the hexacyclic diene, facial discrimination in the cyclohexadiene moiety is manifested through the interplay of steric effects of cyclobutyl hydrogens and the electronic interactions of the carbonyl groups. In addition, the presence of a stereogenic center in the homoallylic position of the diene, particularly a heteroatom, was expected to exert an impressively high stereo-directing influence on the facial selection. Hence, the readily available diene was the substrate of choice for our study.

An up-to-date account of important experimental and theoretical work, relevant to the ongoing debate on the origin of π-facial selectivities in [4+2]-cycloaddition provides the backdrop to the investigation and forms the introduction to the part I.

The second section deals with the synthesis of a dozen derivatives of the above mentioned diene through substitution on the diene moiety as well as through the modification of the carbonyl groups following routine synthetic transformations, their cycloaddition reactions with a variety of dienophiles *viz.* $^1O_2$, PTAD, DMAD, MA and NMM, stereochemical analyses of the addition products by unambiguous methods and interpretation of the results in the light of the various theories of stereoselection.

This section narrates the results of [4+2]-cycloaddition by converting the carbonyl groups in the hexacyclic dione to the corresponding acetals or thioacetals, which represent simple modification of a carbonyl group through a protective group.

The results described convincingly demonstrate the dramatic influence of the distal protective groups and their role as stereodirectors during [4+2]-cycloadditions. Further, these results also illustrates the role of a homoallylic heteroatom ***viz.*** oxygen and sulphur in governing the π-facial diastereoselection in [4+2]-cycloadditions. The ***endo-endo*** diol, derived from the hexacyclic dione, and its diacetoxy and dimethoxy derivatives were exploited to further segregate the role of the inside oxygen (within the cage) *vs.* the outside oxygen in the acetals.

In addition, this section also gives an account on the role of 1,4-substituents on the hexadiene moiety by modification on the diene and its remarkable influence on diastereoselection caused due to transition state geometric distortion.

The **second part** of the thesis describes the isolation and characterization of some exceptionally stable diozonides and delineation of their novel C-H…0 hydrogen bond directed solid state architecture using X-ray crystallographic technique.

Generally, ozonides, by reputation are known to decompose readily and are highly thermally labile. In our present study, all the diozonides were stable at room temperature (for months) and showed little decomposition on either moderate heating or on exposure to $Me_2S$ and $PPh_3$ under standard conditions and were isolated quite uneventfully. Two of the tetraquinane diozonides readily **furnished** single **crystals** and their X-ray crystallographic analysis shows a fascinating packing pattern and supramolecular arrangement sustained by a network of C-H…0 hydrogen bonds. The details regarding the synthesis of the tetraquinane precursors of the diozonides and their crystal packing is elaborated upon in this section.

In each part, the sections HI, IV, V and VI contain a brief summary of our experimental findings, the details of the experimental procedures, spectra of some of the key compounds and appropriate literature citations, respectively.

An appendix constitutes the last section of the thesis and describes the synthesis of some tetrasubstituted cyclobutene tectons with suitable donor and acceptor groups and their ladderane-like architecture in the solid state.

The results enumerated above constitute an important body of experimental data on the origin of rc-facial diastereoseiection in view of the conflicting theories and ongoing debate. Our efforts provide a better understanding of the interplay of various factors such as steric, electronic and electrostatic in determining the origin of π-face selectivities.

# PART I

π-FACE SELECTIVITIES DURING CYCLOADDITIONS
TO A DISSYMMETRIC POLYCYCLIC-1,3-DIENE

## I.I INTRODUCTION

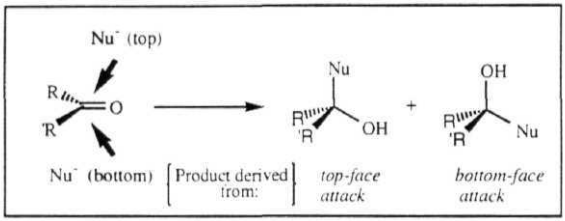
Synthesis of any complex molecule requires conceptualization of a proper strategy and implementation of a well-planned sequence. In order to execute a synthesis meticulously, it is essential to be able to predict the stereochemical outcome in the steps *en route* to the target. Generally, stereoselectivity arises when the approaching reagent has an option of adding to the substrate from two distinct faces to give two diastereomers. To achieve a diastereoselective synthesis, it is important to understand the factors that are responsible for directing the reagent predominantly from one particular face. Further, during the design of a synthetic strategy, insights gained from such studies can be applied to fine-tune the substrate or the reagent to achieve the desired selectivity.

The origin of stereoselection[1] in organic chemistry is primarily from functionalities which are planar and which can undergo addition reactions to generate tetrahcdral carbon/s. The most commonly encountered functional groups in organic chemistry which serve this purpose are carbonyl groups, olefinic bonds and 1.3-dienes etc. Studies on these functional groups have received a great deal of attention as they show satisfactory reactivity towards most of the common organic reactions.

Nucleophilic addition to carbonyl group is among the earliest studied example of creating a stereogenic center. Figure 1. Cram[2] was the first to propose an empirical rule of steric control of asymmetric induction to predict nucleophilic additions with organometallic or metal hydride reagents to acyclic ketones possessing an adjacent chiral center. Since then, a multitude of probe systems and several models to rationalize the observed diastereoselectivity have been put forward

by various groups. Particularly, last two decades have witnessed heightened response and assessment of controlling factors in diastereoselection have been a subject of ongoing debate.

Figure 1

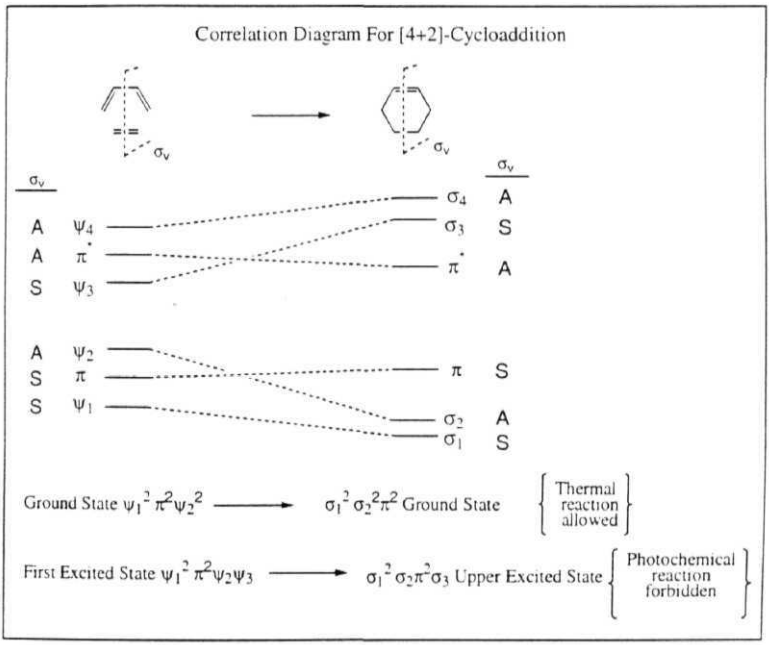



Electrophilic addition to double bonds have also received equal attention and several reactions like epoxidation, osmylation, hydroboration and oxymercuration to mention a few have been extensively investigated. While investigations on additions to either carbonyl or an olefin has received considerable attention, the mechanistic aspects of synthetically useful cycloaddition reactions remained dormant until the late sixties, when Woodward and Hoffman put forward their unifying theory[4] of pericyclic reactions.[5]

The Woodward-Hoffmann rules [a] successfully rationalize the observed stereocontrol in sigmatropic, electrocyclic and cycloaddition reactions. Among the pericyclic reactions, cycloadditions have attracted considerable attention owing to their enormous potential in organic synthesis.[6,7] Out of the various types of cycloaddition reactions *viz.* [2+2], 1,3-dipolar, [4+2], [4+4] and [6+4], the [4π+2π]-cycloaddition or more popularly known Diels-Alder reaction has attracted much

attention, as it is one of the most versatile reactions involving the union of a four component (diene) and a two component (dienophile) resulting in the generation of two new C-C bonds.

Figure 2

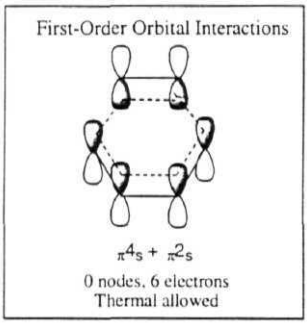



Furthermore. the synthetic utility of Diels-Alder reaction is very well established.[7] Its continued popularity and study rests, in part. on the ability to generate four new contiguous stereogenic centers in a single laboratory operation.

Subsequently, asymmetric[8] and intramolecular variants[9] of this process have come to the fore and have added to the widespread interest. The various aspects, which one needs to consider in these reactions, are (i) stereocontrol (ii) regiocontrol (iii) topographical control and (iv) diastereocontrol.

Woodward-Hoffmann rules based on orbital symmetry, see Figure 2. predict that thermal [$_{\pi}4_{s}+_{\pi}2_{s}$] cycloaddition proceeds with a retention of configuration both in diene and in the dienophile and account for the stereocontrol, Figure 3.

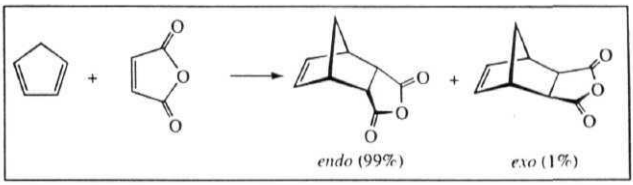
**Figure** 3



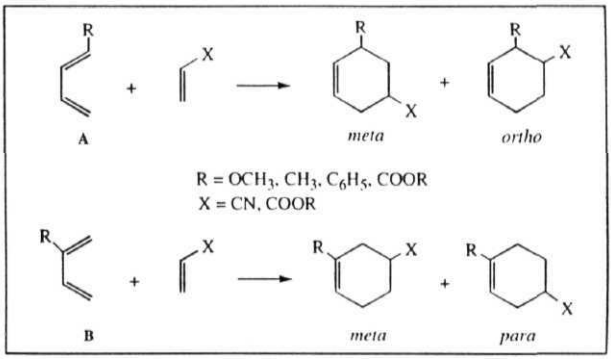

The regiocontrol and topographical control *viz. endo* (Alder) *vs.* ***exo*** (anti-Alder) selectivity is often governed by second-order orbital interactions. Thus, the frequently observed adherence of [4+2]-cycloadditions to Alder rule of *endo* addition is believed to arise from symmetry-allowed mixing of the non-primary reaction centers when *endo* oriented,[4a,10] as in the formation of ***endo***-adduct during the Diels-Alder reaction of cyclopentadiene and maleic anhydride (MA), Scheme 1. Regioselection arises when unsymmetrical dienes add to unsymmetrical dienophiles.

For electron-rich substituted 1,3-butadienes such as A and B, the formation of *ortho* and *para* cycloadducts, respectively, is strongly preferred, Scheme 2. This control

**Scheme 1**




Scheme 2




arises because the coefficients of the orbitals are strongly perturbed by substitution (donor substituent enlarging the remote coefficient in HOMO and acceptor group exerting an identical effect in LUMO), and stabilization energy is maximized when the larger coefficients overlap.[11] The fourth and perhaps the more subtle aspect is the diastereoselectivity which arises when either of the reacting partners ***viz.*** the

diene or dienophile is facially dissymmetric.[12] The facial non-equivalence may arise due to the presence of a stereogenic center in the allylic or homoallylic position. The existing center in the substrate can direct the reagent from stereochemically two distinct modes depending upon various factors. Thus, if the π-facial diastereoselectivity is controllable in such instances, the number of centers of asymmetry being simultaneously introduced is capable of growing to five or more during a [4+2]-cycloaddition; consequently, underscoring the need to gain greater insights concerning the role of controlling factors in diastereoselection.

Several probe systems have been employed to study and understand the various factors that are responsible for effecting face-selectivity in [4+2]-cycloadditions. Although a number of examples involving acyclic systems have been studied using substituted butadienes[13] and various dienophiles, the diastereoselectivities are more often controlled by dominant steric and conformational effects and therefore the outcome of such studies is not much insightful. More recently, cyclic dienes have been studied wherein conformational effects are minimal and would allow a detailed assessment of electronic factors, frequently in their myriad forms. The important factors, which determine the face-selectivity in such systems are steric effects, orbital tilting and torsional effects, complexation between the diene and dienophile, polarizability, electronic effects and electrostatic interactions.

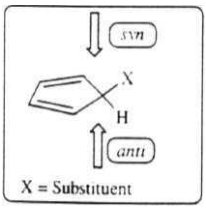
Since this thesis is concerned with diastereoselectivities during [4+2]-cycloadditions to facially dissymmetric dienes, before presenting the results of our investigations, a background review is in order. Some of the work described below

appeared during the course of this investigation but for the sake of completeness is included here and various systems, which have been studied by different groups. employing facially differentiated cyclic dienes are presented below.

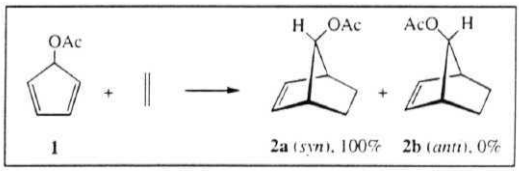
**[4+2]-Cycloadditions with 5-Substituted 1,3-Cyclopentadienes**

**One** of the very early example of cycloaddition involving a facially discriminated diene was reported by Woodward and co-workers[14] who found that 5-acetoxycyclopentadiene 1 reacted with ethylene to give rise to a single adduct 2a. with the dienophile approach exclusively from the face *syn* (Figure 4) to the substituent in a contrasteric manner. The ***anti*** addition product **2b** was not encountered. Scheme 3. The terms ***syn*** and ***anti*** in these Diels-Alder reactions refer to the mode of approach of the dienophile to the diene with respect to the substituent. Figure 4.

Figure 4




Scheme 3

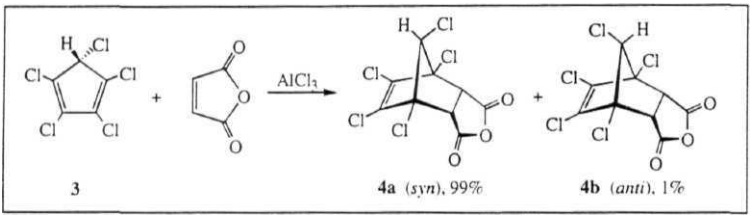



*Woodward et al.*

Williamson *et* ***al.*** later reported[1] maleic anhydride (MA) addition to pentachlorocyclopentadiene 3 and observed that the addition had taken place in a ***syn*** contrasteric fashion to furnish adduct 4a with negligible amounts of ***anti*** adduct **4b.** Scheme 4. Breslow *et* ***al.*** reported[16] the cycloaddition of 5-halocyclopentadiene with iV-phenyl-1.2.4-triazolinedione (PTAD). While iodo- 5 and bromo- 6 gave *anti*

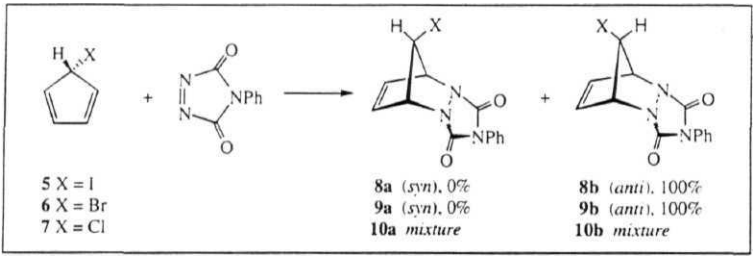
selectivity (adducts 8b and 9b. respectively), chloro derivative 7 gave a mixture **(10a,b)** with slight excess of the *anti* adduct. The *syn* adducts 8a and 9a were not formed, Scheme 5.

**Scheme** 4




*Williamson et al.*

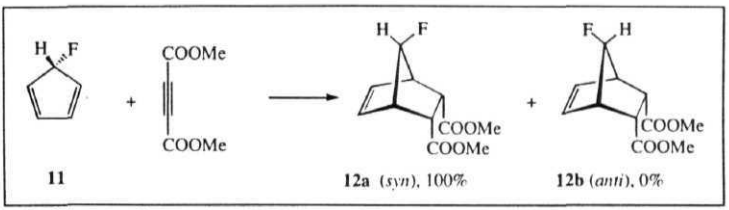
Scheme 5




*Breslow et al.*

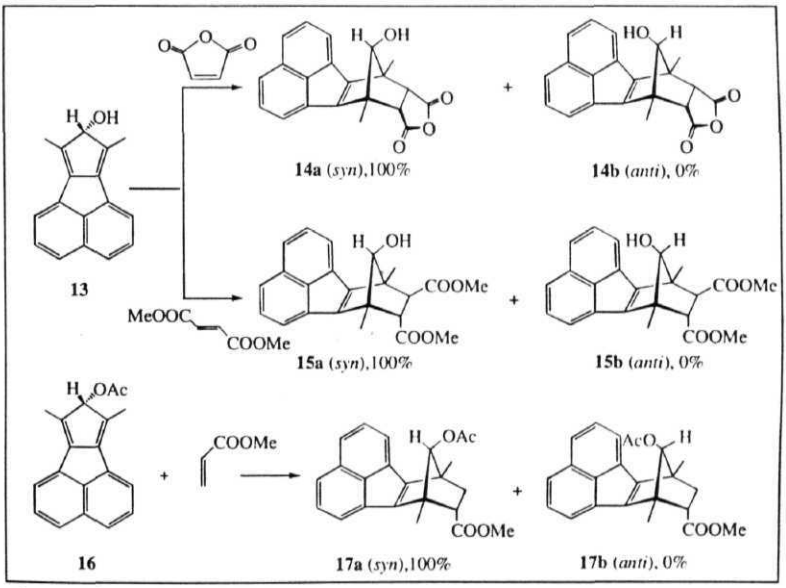
Interestingly. the fluoro derivative **11** gave ***syn*** selectivity during its reaction[17] with dimethyl acetvlenedicarboxylate (DMAD). The ***syn*** adduct **12a** was formed exclusively, with no trace of the ***anti*** addition product **12b.** Scheme 6. Jones *et al.* observed[18] that 5-substituted cyclopentadienes fused to a acenaphthene moiety exhibited uniformly ***syn*** preference when the substituent is a hydroxyl group as in 13.

Scheme 6




*McClinton et al.*

**Scheme 7**

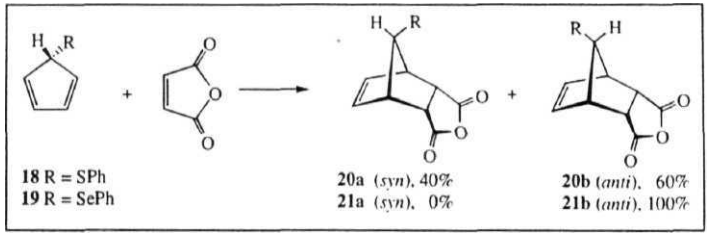



*Jones et al.*

during its reaction with MA and dimethyl fumarate resulting in the formation of **14a** and **15a,** respectively. The acetoxy derivative 16 also furnished *syn* adduct **17a** with methyl acrylate, Scheme 7. In all the three cycloadditions, the *anti* adducts **14b, 15b** and **17b** were not encountered, Scheme 7.

Ishida *et al.* have studied[19] the diastereoselectivities during MA addition to cyclopentadiene 18 with a C-5 thia substituent and selenium derivative 19, Scheme 8. In both the cases, the approach of the dienophile was found to be ***anti*** to the heteroatom resulting in the formation of **20b** and **21b** as the major adducts. While the *syn* adduct **20a** was formed in about 40%, the adduct **21a** was not at all encountered, Scheme 8.

Scheme 8



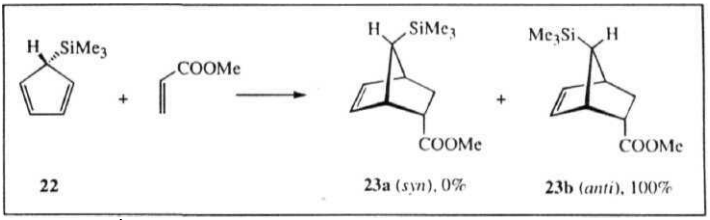

*Ishida el al.*

Fleming *et al.* have shown[20] that a trimethylsilyl group at the C-5 position (22) also directed methyl acrylate in ***anti*** fashion and resulted **in** the formation of adduct **23b.** The *syn* adduct **23a** was not observed, Scheme 9.

1,3-cyclopentadienes substituted at C-5 show an intriguing range of facial selectivity towards Diels-Alder cycloadditions. Heteroatom substituents from the first row (X = F, OH, OAc) lead overwhelmingly to reaction onto the diene face ***syn***

to the heteroatom, Figure 4. On the other hand, a heteroatom substituent from the second row (X = Cl, SPh) leads to both *syn* and *anti* adducts, but with substituent from the third or fourth rows (X = Br, SePh, I), *anti*-addition occurs exclusively.

Scheme 9

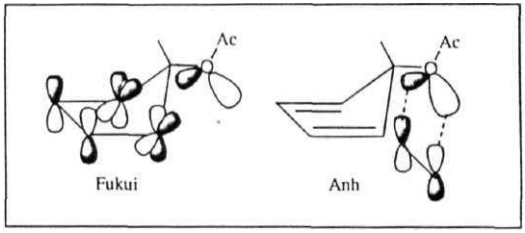



*Fleming et al.*

More often than not, the interpretation of these results is complicated as the estimation of the relative contribution and reactivity of various conformers in which the heteroatom is aligned 'inside' as predicted by electronic factors or 'outside' as favoured due to steric reasons, is very subtle. A number of theories have been advanced to explain the origin of the *syn* selectivity observed for hydroxyl, acetoxy and chloro substituents. One of the earliest proposals to be formulated was the orbital mixing rule[21] of Fukui, wherein the group X was suggested to be conducive to *syn* capture of the dienophile because of orbital mixing **interaction.** A nonequivalent extension of the diene HOMO was predicted, as the substituent with a lone-pair at C-5 position perturbed the diene HOMO and allowed mixing with low-lying σ orbitals of the carbon skeleton, thereby causing a bias (HOMO electron cloud biased towards the substituent) in the substrate, Figure 5. Alternatively, Anh suggested" the

possibility of a beneficial non-bonded interaction between the heteroatom and the dienophile that could contribute to stabilize the *syn* transition state, Figure 5.

Figure 5




Generally, when an electron acceptor bond is suitably aligned with a *n* system, the energy of both HOMO and LUMO are lowered so that the electrophilicity of the *n* system is enhanced and the nucleophilicity decreased. Kahn and Hehre later concluded[23] that electrostatic interactions are the important determinants in governing π-facial selectivity, with the more nucleophilic diene face reacting preferentially. In the latter examples ***viz,*** 18, 19 and 22 where X = SPh, SePh and $SiMe_3$, respectively, the observed stereoselectivities can be simply attributed to steric control.

More recently, Poirier and Burnell[24] have advanced an explanation based on calculations at *ab* ***initio*** HF/6-31G* level. They have found that the ranges of activation energies for ***syn*** addition are large relative to those for ***anti*** addition, which are all similar to the activation energy for cyclopentadiene itself. Partitioning the activation energy into diene deformation, dienophile deformation, and diene-

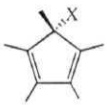
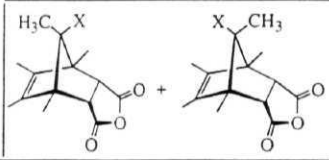
dienophile interaction energies showed that the major factor in determining facial selectivity was in the energy required to deform the diene into its transition state geometry. Deformation of 5-fluro-, 5-hydroxy-, and 5-amino-l,3-cyclopentadiene into their *syn* transition state geometries was predicted to require less energy than deformation of cyclopentadiene itself, which paralleled the experimental observation of *sxn* addition with these dienes.

Further, they attribute the facial selectivity exhibited by these dienes primarily to steric hindrance between the dienophile and the plane-nonsymmetric groups on the diene. Thus, for instance C5-C1 bond was computed to have a smaller steric factor than a C5-H bond, favouring ***syn*** addition to 5-chloro-l,3-cyclopentadiene[24c] and paralleled experimental results. However, they have identified a significant lone pair-lone pair interaction with the reacting nitrogens when the dienophile is PTAD.

The first systematic study of the effect of heteroatom[12b] on cycloaddition face selectivities on permethyicyclopentadienes was carried out[25] by Fallis *et al*. A number of substituted cyclopentadienes were subjected to Diels-Alder reactions and the results are presented in Table 1. Prior to the detailed studies of Fallis, there was hardly any effort reported on the effect of allylic sulphur and nitrogen substituents on the face selectivities. Permethylated cyclopentadienes were used to avoid the degenerate [1.5]-sigmatropic rearrangements. Cycloadditions of C-5 substituted permethyicyclopentadienes **24a-k** was carried out at room temperature with either MA or *N*-phenylmaleimide (NPM) as the dienophile partners. The overwhelming

facial preference for *syn* addition in the case of chlorine **24a,** oxygen **24b,c** and nitrogen **24d** substituent is clearly evident, Table 1.

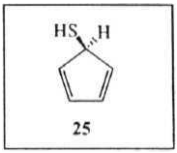
Table 1

|  | | Dienophile | Addition ratio  | |
|---|---|---|---|---|
| Compd | X | MA/NPM | (*syn*) | (*anti*) |
| 24a | Cl | MA | 100% | 00% |
| 24b | OH | MA | 100% | 00% |
| 24c | OMe | MA | 100% | 00% |
| 24d | $NH_2$ | NPM | 100% | 00% |
| 24e | NHAc | MA | 100% | 00% |
| 24f | SH | NPM | 55% | 45% |
| 24g | SMe | MA | 10% | 90% |
| 24h | $SCH_2Ph$ | MA | 10% | 90% |
| 24i | SPh | MA | 03% | 97% |
| 24j | SOMe | MA | 00% | 100% |
| 24k | $SO_2Me$ | MA | 00% | 100% |

*Fallis et al.*

There is a striking reversal in the facial selectivity encountered with sulphur substituents. When the substituent is SH **24f.** there is a modest 55:45 selectivity favoring the ***syn*** approach. Nonetheless. the results on the cyclopentadiene derivative **25**. with SH and H substituents is unknown. For compound 18. with SPh and H substituents the selectivities are 40:60 with predominant *anti* addition. The selectivities were enhanced (3:97) when the faces bore SPh and $CH_3$ substituents as

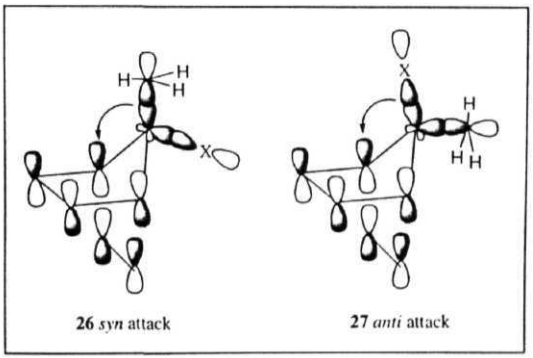
in **24i** favouring ***anti*** approach. On the other hand, sterically demanding functionalities such as sulfoxide **24j** and sulfone **24k** directed the dienophile to approach *anti,* so that addition occurred on the sterically less encumbered methyl face. Another notable reversal is that of the thiomethyl derivative **24g** as opposed to methyl ether derivative 24c.




25

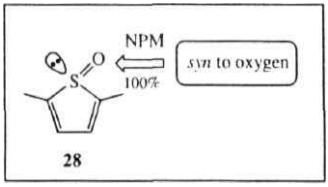
Fallis *et al.* have rationalized their results with the help of Cieplak model[26] which states that on the basis of hyperconjugation and the beneficial interaction with the incipient bond, one would expect the cycloaddition of the cyclopentadienes to display a preference for *anti* addition to the antiperiplanar σ bond that is the better donor, see Figure 6. Thus, when the choice is between a carbon-oxygen (26) and

Figure 6




**26** *syn* attack **27** *anti* attack

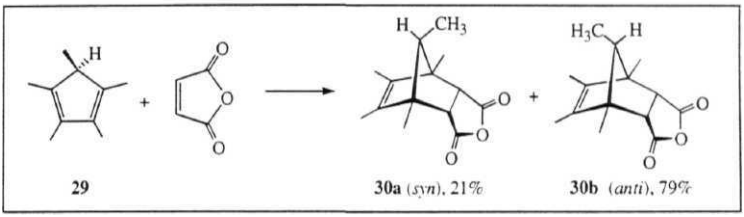
carbon-carbon bond (27) bearing face, one would expect preferential addition ***anti*** to the best **a** donor (C-C bond) and hence addition ***syn*** to C-0 is observed, see 26, Figure 6. Similarly, if the competition were between a C-C and C-S bond, cycloaddition *anti* to the C-S bond would dominate as observed. In the case of sulphoxide and sulfones, the steric interactions play a major role and direct the dienophile in *anti* fashion. However, in thiophene oxide 28, where the competition is between a lone pair and a sulfoxide oxygen, the addition was expected to be ***anti*** to the lone pair. It was confirmed experimentally[27] that addition occurred exclusively in a contrasteric manner *syn* to oxygen.




**28**

Nonetheless, the use of permethylatedcyclopentadienes **24a-k** causes an intrinsic steric bias in the probes as heteroatom is pitched against a methyl group rather than a hydrogen atom. This is supported by the fact that in the parent hydrocarbon 29, MA was captured predominantly from the face *anti* to the methyl group resulting in **30b** as the major diastereomer, which is not a contrasteric outcome,[28] Scheme 10. It is to be noted that only olefinic dienophiles *viz.* MA and NPM were used in the study, and the results with heterodienophiles are unknown.

**Scheme 10**

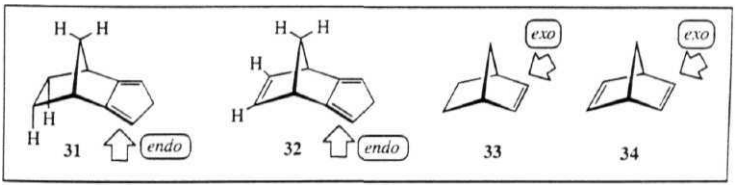



*Burnell et al.*

**[4+2]-Cycloadditions with Isodicyclopentadiene and related systems**

Paquette and Gleiter[7] have studied the cycloaddition in cyclopentadienes such as isodicyclopentadiene 31 and isodicyclopentatriene 32. which are fused to a norbornyl skeleton. Dienes 31 and 32 underwent cycloadditions preferentially from the bottom/*endo* face i.e. *syn* to the ethano/etheno bridge with a variety of dienophiles such as methyl acrylate, benzoquinone. dimethyl acetylenedicarboxylate (DMAD) and NPM.

**Scheme 11**



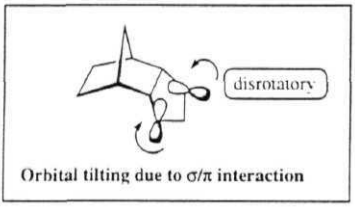

*Paquette and Gleiter*

This result was rather intriguing as norbornene 33 and norbornadiene 34 underwent cycloaddition from their more open *exo* face. The authors reasoned that the cause of this striking behaviour could not be of steric origin since the reacting

centers actually experience bond formation on the diene surface that is ***syn*** to the larger (sterically demanding) ethano bridge, Scheme 11.

Since **31,** 32 and similar hydrocarbons have **low** dipole moments, polar interactions were excluded. A comprehensive analysis of the observed stereoselectivity was made in terms of $\sigma/\pi$ interaction. On the basis of *ab initio* and semiempirical calculations, Gleiter and Paquette showed that in **31** and 32, there was mixing of high lying $\sigma$-orbitals with the lowest occupied $\pi_s$-orbitals, which resulted in disrotatory tilting[29g] of the terminal $P_\pi$-lobes, see Figure 7.

Figure 7



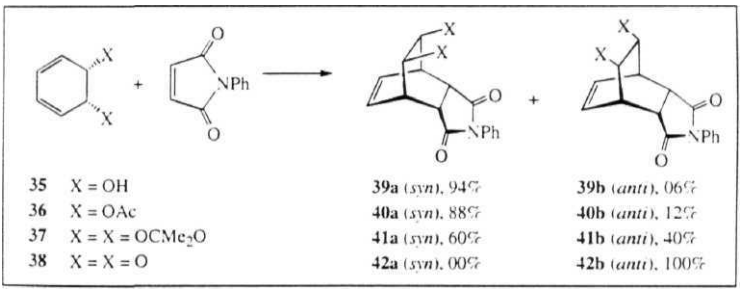

The faces of the diene are thus differentiated and antibonding interactions between the HOMO of the dienophile and the $\pi_s$-orbital of the diene were considered to be greater when reaction occured from the ***exo*** face of isodicyclopentadiene **31**, consistent with the observed *endo* preference.

**[4+2]-Cycloadditions** to **1,3-Cyclohexadienes**

Cyclohexadienes are in general less selective than the corresponding cvclopentadienes as the diene system tends to be more flexible and conformational effects often play a substantial role. Burnell *et al.* have studied[30] the selectivity of

cyclohexadienes **35-38** towards Diels-Alder reaction with NPM and the observed selectivities are indicated in Scheme 12. Addition ***syn*** to the substituent was observed uniformly in diol **35,** diacetate 36 and diacetonide 37 leading to the predominant formation of **39a**, **40a** and **41a**, respectively. On the other hand the epoxide 38 exhibited total ***anti*** selectivity leading to exclusive formation of the adduct **42b.** The sharply differing behavior of the epoxide can be attributed to steric shielding of the *sxn* trajectory in the critical mid-region.

Scheme 12

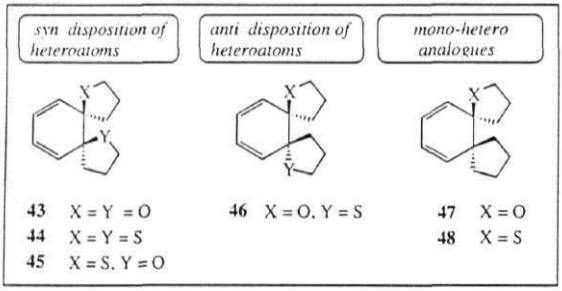



*Burnett et al.*

Paquette *et al.* have studied" the rc-face selectivities in a series of dispiro 1.3-cyclohexadienes such as **43-48.** Scheme 13. In **43-45** the heteroatoms X and Y are ***syn*** to each other and bear a structural similarity to 35-38 and at the same time, there is considerable reduction in the steric imbalance across the diastereotopic faces. Further, as the nature of the heteroatoms X and Y could be controlled, a direct comparison of the σ-donating effect of both C-0 and C-S bonds could be investigated as in **43** and **44.** On the other hand, when the heteroatoms were oriented

*anti* as in 46, it was possible to pitch two heteroatoms on either face of the diene and a direct one-on-one competition could be mapped during [4+2]-cycloaddition. Access to *mono*-hetero analogues like 47 and 48 was also possible, hence an attempt was made to investigate whether the progression from one to two heteroatom centers gave rise to additive or multiplicative effect. The dienophiles used in the study were classical $2\pi$ reagents like NPM and heterodienophile like *N*-methyltriazolinedione (MTAD). The results of the cycloaddition face selectivities are summarized in Table 2 and were rationalized as follows.

Scheme 13

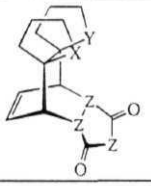
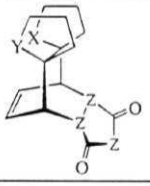



*Paquette and Gleiter*

Among the various factors that are responsible for controlling diastereoselectivities. difference in reactivity, electronic. electrostatic and steric considerations were accorded particular attention. On the basis of MO calculations[31a] Gleiter and Paquette assumed that steric and electrostatic factors dominated through out the series. NMM was considered to have a positive Mulliken partial charge on the hydrogen and carbon-carbon double bond. whereas MTAD has a slightly positive

partial charge on the doubly bonded nitrogens but a negative charge density in the region where the lone pairs are located. In contrast, NMM revealed a positive charge density at the $sp^2$ hydrogens. This region was regarded important during reaction since approach of the dienophiles would lead to electrostatic interactions with the heteroatoms in the dienes. Further, π-facial stereoselectivity of the addition of NPM was shown to be principally governed by steric and electrostatic factors.

Table 2

| Substrate | Dienophile |  | +  |
|---|---|---|---|
| 43 | NPM | *syn*, 100% | *anti*, 00% |
| 43 | MTAD | *syn*, 00% | *anti*, 100% |
| 44 | NPM | *no reaction* | *no reaction* |
| 44 | MTAD | *syn*, 00% | *anti*, 100% |
| 45 | NPM | *syn*, 100% | *anti*, 00% |
| 45 | MTAD | *syn*, 00% | *anti*, 100% |
| 46 | NPM | *syn to Oxygen*, 100% | *anti to Oxygen*, 00% |
| 46 | MTAD | *syn to Oxygen*, 59% | *anti to Oxygen*, 41% |
| 47 | NPM | *syn*, 93% | *anti*, 7% |
| 47 | MTAD | *syn*, 00% | *anti*, 100% |
| 48 | NPM | *syn*, 46% | *anti*, 54% |
| 48 | MTAD | *syn*, 9% | *anti*, 91% |

*Paquette and Gleiter*

Approach of NPM *syn* to one oxygen, 47 or two oxygens, 43 and one oxygen and one sulphur, 45 was found to be kinetically more favoured than the face consisting of $CH_2$ groups. With 46. addition of NPM ***syn*** to oxygen was observed in

order to avoid interaction with the larger sulphur atom. However, in the case of 48 the two adducts were formed in approximately equal amounts and this was attributed to the comparable size of $S/CH_2$ and $CH_2/CH_2$ array on opposite faces. The lack of reactivity of 44 towards NPM did not permit implementation of classical test of the Cieplak model. The contrasteric behaviour of MTAD was rationalized in terms of the repulsive interactions between the nonbonded electron pairs on the heteroatoms present in the dienes and on the nitrogen atoms of the dienophile.

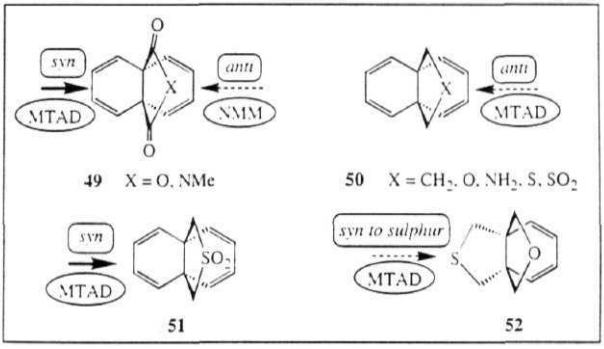
However, in **46**, the addition of MTAD was found to be predominantly from the face ***syn*** to oxygen though addition ***syn*** to sulphur was expected on the basis of electrostatic model. The authors have rationalized this result on the basis of an alternative step-wise mechanism," which involves initial formation of an aziridinium imide intermediate, which rearranges ***via*** a 1,4-zwitterion to deliver the urazole products. The authors believe that electrostatic effects dominate in *syn* dioxa system, whereas, steric factors were accorded proper consideration while accounting for the π-facial selectivity exhibited by oxa/thia and dithia compounds.

**[4+2]-Cycloadditions** to **Propella-1,3-dienes**

Ginsberg *et al.* have earlier studied a special class of cyclohexadienes embedded in a propellane skeleton. which possess homoallylic heteroatoms.[10] Scheme 14. The diene 49 underwent capture of *N*-methylmaleimide (NMM) exclusively from the face ***anti*** to the anhydride bridge. However, the major product isolated in the addition of MTAD was due to the ***syn*** approach. Ginsberg and Gleiter **have** rationalized these results by invoking stabilizing secondary orbital **interaction**[10,33c] between the electron rich heterodienophile and electron poor

anhydride functionality. In addition, as indicated in Scheme 14, the presence of neighbouring carbonyl groups and double bonds also influenced the selectivity to a large extent, see 50 and 51. Furthermore, for these homoallylic systems it was found **that** in a propelladiene containing both oxygen and sulphur bridges as in 52, cycloaddition occurred ***anti*** to oxygen and ***syn*** to sulfur, Scheme 14.

Scheme 14



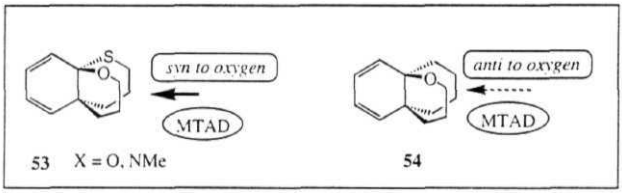

*Ginsberg et al.*

In sharp contrast. Paquette *et al.* have observed[11m] that in a related propelladiene 53. addition predominantly occurred from the direction ***syn*** to oxygen and ***anti*** to sulphur. Scheme 15. The almost complete crossover observed with the **two** closely related dienes 52 and 53 is quite remarkable. When the choice is between an oxygen and methylene[11b] as in *mono*-oxapropelladiene 54. MTAD adds exclusively *anti* to oxygen. Scheme 15.

Ginsberg *et al.* have shown that[10c] in cyclohexadienes. embedded in a propellane skeleton. dienophiles stereoselectively add to the face ***syn*** to the larger of

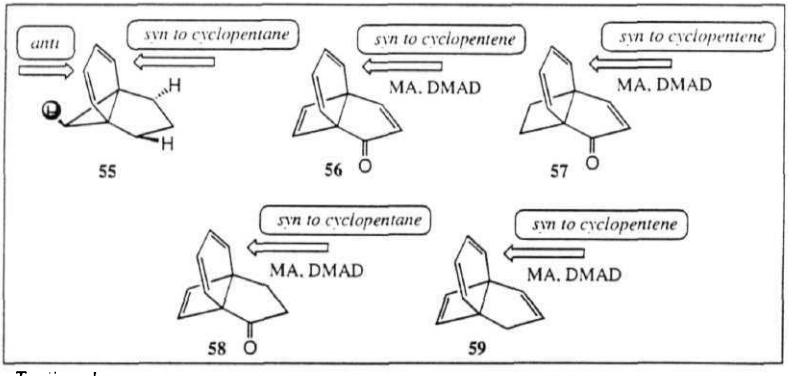
the two flanking rings unless an opposing stereoelectronic effect predominates and this outcome has been rationalized on steric grounds. Thus, it was pointed out for example, that a cyclopropane hydrogen ***syn*** to the cyclohexadiene ring in 55. disposed in the trajectory of the dienophile, effectively would exert more steric repulsion towards incoming dienophile than the cyclopentane hydrogens. which reside at the sides of the molecule, Scheme 16.

Scheme 15




*Paquette el al.*

Scheme 16

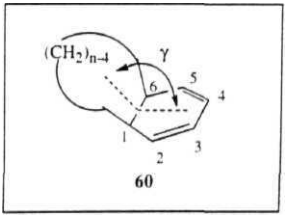



*Tsuji et al.*

Tsuji *et al.* have studied[34] the Diels-Alder addition of DMAD, methylpropiolate and MA to [4.3.2]propella-2,4,8,10-tetraene-7-one 56 and its 8,9- and 10,11-dihydro derivatives, 57 and 58 and [4.3.2]propella-2,4,7,10-tetraene 59. It was found that the addition occurred exclusively from the face *syn* to the five-membered ring, Scheme 16.

Tsuji *et al.* have rationalized their results in close conjunction with Ginsberg's interpretation. They believe that the most important factor to be considered is difference in dihedral angles between the cyclohexadiene and the two flanking rings. It was shown that in a bicyclic 1,3-cyclohexadiene 60, the smaller the size of flanking ring, the narrower is the dihedral angle *y* between the two rings. The dihedral angle *y* in the structure of 60 was evaluated with the aid of MMX calculations and was found to vary from 124° to 116° and 107° when the ring anneiated to cyclohexadiene is changed from cyclopentane to cyclobutane and cyclopropane, respectively, Figure 8.

Figure 8




**60**

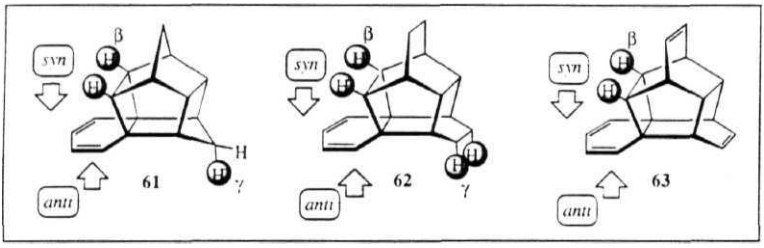
Calculations have indicated that the cyclohexadiene ring in 56 is essentially planar and the dihedral angle between the five and six membered rings would be

129°, wider by 12° than that between the four and six carbon rings. Similarly, difference in the magnitudes of corresponding dihedral angles in **59** was shown to be about 15°. Thus, in the Diels-Alder reactions of **56** and related compounds, **57-59.** the approach of dienophiles to the face of the cyclohexadiene *syn* to the five-membered ring was rationalized on steric grounds as this approach was sterically less encumbered than the *anti* approach, Scheme 16.

[4+2]-Cycloadditions to **1,3-Cyclohexadienes** Embedded in **Polycyclic** Systems

Fessner and Prinzbach have studied[35] the face selectivity exhibited by dienes **61-63** towards a variety of dienophiles. The authors' surmise was that in the rigid hydrocarbon **61**, electrostatic or extended π-interactions would be absent and would allow a detailed assessment of steric factors. Directive influences from σ/π mixing operative between olefinic and Walsh orbitals of the fused cyclobutane ring were considered to be less important. For the diene[35a] 61. a different degree of steric

Scheme **17**




*Fessner and Prinzbach*

interference between the reactants was anticipated for the two modes of attack to the dissymmetric π-faces, defined *anti* or ***syn*** relative to the four-membered ring,

Scheme 17. The studies indicated that with all the dienophiles employed, predominant *syn* addition was observed. Table 3.

Table 3

| Substrate | MA | | BQ | | PTAD/MTAD | | $^1O_2$ | | DMAD | | DCA | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *syn* | *anti* | *syn* | *anti* | *syn* | *anti* | *syn* | *anti* | *syn* | *anti* | *syn* | *anti* |
| **61** | 88% | 12% | 82% | 18% | 98% | 2% | 99% | 1% | 98% | 2% | 98% | 2% |
| **62** | 98% | 2% | 98% | 2% | 97% | 3% | 99% | 1% | 97% | 3% | 96% | 4% |
| **63** | 12% | 88% | 15% | 85% | 97% | 3% | 98% | 2% | 90% | 10% | 67% | 33% |

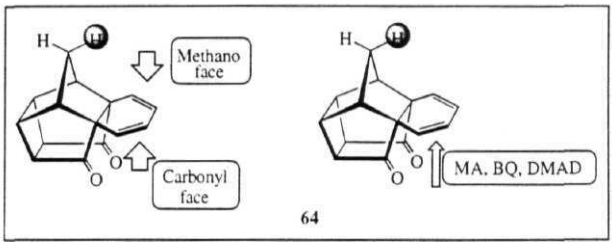
Fessner and Prinzbach have attributed the high π-facial stereoselectivity to the relative magnitude of non-bonded steric repulsions during dienophile capture from the methylene face (*anti*-trajectory) to be more effective than the cyclobutane face. In the case of dienes 62 and 63. apart from the relative steric hurdles presented to approaching dienophiles from *anti* and *syn* directions, the increment of unsaturation in 63 was also expected to enforce an electonic interaction[35b] with the adjacent π-cloud during *anti* dienophile capture; with a considerable reduction in the steric requirements. For all the dienophiles studied. cycloadditive capture in 62 occurred with an overwhelming preference for addition from the *syn* direction. This was attributed to the fact that γ-hydrogen pair exerted more pronounced steric effect than the opposite β-hydrogen pair. though spacially proximal was supposedly slightly offset of the addition trajectory. Hence, was considered less influential during *syn* dienophile approach. Further, in the case of diene 62. the steric

interactions were considered to be more demanding, particularly during addition of olefinic dienophiles, as opposed to 61 because of progressive hydrogen contacts upon change from a 'staggered' to an 'eclipsed' interaction with the hydrogens on the dienophile.

In the case of diene 63, a *syn* to *anti* reversal of face selectivity was observed for simple olefinic dienophiles *viz.* MA and p-benzoquinone (BQ), and was attributed to reduced steric interactions operative during *anti* attack. However, it was shown that heterodienophiles (*viz.* MTAD and singlet oxygen) did not differentiate the contrasting $CH_2$-$CH_2$/CH=CH environments and addition took place predominantly from the sterically demanding ***syn*** face. This was reconciled in terms of n/π and π/π repulsion among filled orbitals, which would favour ***syn*** approach. Finally, the reduced selectivities of dicyanoacetylene (DCA) relative to DMAD (Table 3) was interpreted in terms of rtHft-preorienting charge-transfer complex employing both electron depleted orthogonal 7t-bonds of the dienophile and suitably oriented π-moieties of the diene 63.

Mehta ***et*** *al.* have studied[36] the Diels-Alder cycloaddition to the diene **64**, wherein the diene moiety is flanked by a methano- and carbonyl face as shown in Scheme 18. It was observed that with dienophiles like MA. BQ and DMAD the addition was uniformly and exclusively from the carbonyl face in all cases, Scheme 18. The observed selectivities were mainly attributed to greater non-bonded steric repulsions during dienophile capture on the methano face. However. secondary orbital effects were also speculated to have cooperatively aided in the addition from the carbonvl face.

Scheme 18

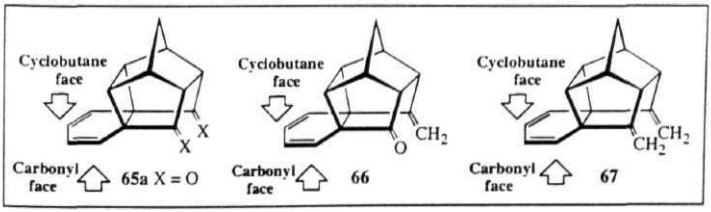



*Mehta et al.*

Coxon *et al.* have probed[37] the facial selectivity exhibited by the diene 65a and its variants 66 and 67 with a variety of dienophiles. As the 1,3-diene moiety is grafted on to a rigid polycyclic frame, the ambiguity associated with conformational uncertainty is precluded in this case and this system was also expected to complement the results on the well-studied isodicyclopentadiene **31**. Additionally, this polycyclic frame also has considerable synthetic potential in the construction of fused polycyclopentanoids (polyquinanes).

In the hexacyclic diene **65a**, the two π-faces are differentiated through the presence of a cyclobutane ring on one-face and carbonyl groups on the other.

Scheme 19




*Coxon et al.*

Scheme 19. Apart from the intrinsic non-equivalence in the steric environment, the funtionalities can also exert electronic preferences in this system. The high energy *a* bonds of the strained cyclobutane ring could also play a crucial role in directing the approach of the reagent. On the other hand, the two carbonyl groups can experience significant electrostatic interaction with a polar reagent and the insights regarding the relative importance of these effects can be studied. The diene 65a was shown to undergo reactions almost exclusively from the carbonyl face to give *endo*-addition (Alder) products with most of the dienophiles employed. Table 4. However, in actuality DMAD. PTAD and DEAD exhibited mixed selectivities.[37a]

Table 4

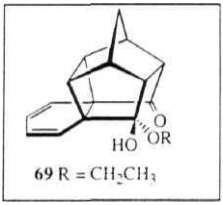
| Substrate | MA | | BQ | | PTAD | | H—≡—COOCH$_3$ | | DEAD | | DMAD | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *car** | *cyb* | *car* | *cyb* | *car* | *cyb* | *car* | *cyb* | *car* | *cyb* | *car* | *cyb* |
| **65a** | 98% | 2% | 98% | 2% | 64% | 36% | 98% | 2% | 2% | 98% | 55% | 45% |
| **66** | 100% | 0% | 100% | 0% | 78% | 22% | - | - | - | - | 25% | 75% |
| **67** | 85% | 15% | 100% | 0% | 93% | 7% | - | - | - | - | 10% | 90% |

• *car: carbonyl face; cxb:* ***cyclobutane face***

Pandey *et al.* have independently[18] reported their findings on the face-selectivity in cycloadditions to the diene **65a** and the related ***endo-endo*** diol 68a. Their results largely concur with Coxon's findings. The steric constraints due to the carbonyl groups and the cyclobutane hydrogens reinforced the intrinsic preference for ***endo***-addition (Alder) of the dienophiles and this was also reflected by the observation that the diene 65a failed to react with *trans*- and geminal disubstituted

alkenes like diethyl fumarate, (*E*)-1,2-dichloroethylene, 2-chloroacrylonitrile. No cycloaddition was observed even with the highly electron deficient dienophile like tetracyanoethylene (TCNE).

The variations in the observed facial selectivities with 65a showed some systematic trends with the olefinic dienophiles being captured exclusively from the carbonyl face of the diene. On the other hand, benzyne, alkynes and azo dienophiles showed selectivities ranging from exclusive carbonyl face attack (for methyl propiolate) to exclusive cyciobutane face attack (for DEAD).

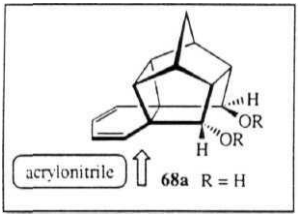



**69** R = $CH_2CH_3$

Calculations based on X-ray crystal structure parameters of the *mono*-hemiacetal[37a,e] 69 and the diene[38b] 65a indicated that for a normal Diels-Alder transition-state geometry, attack from the cyciobutane face resulted in unreasonably close interactions between the olefinic protons on the dienophile and the cyciobutane ring protons. Based on these results Coxon *et al.* have qualitatively rationalized the observed preferences (see Table 4) as an interplay of three factors.[37a] First, the azo and alkyne type dienophiles are more reactive compared to the alkenes and hence kinetic differentiation between the two transition states was expected to be reduced. Second, these dienophiles do not possess protons similarly disposed to those in the

olefinic dienophiles for steric interaction with the cyclobutane protons. In other words, the exclusive carbonyl face attack observed with olefinic dienophiles is a consequence of the steric bias inherent in the diene **65a.** Third, in the transition state for carbonyl face attack, the *n*- or nonbonding orbital electron density in the alkyne and azo dienophiles can repulsively interact with the electron density of the carbonyl oxygen atoms.

To probe the role of carbonyl groups in π-facial selectivities in the diene 65a. Pandey *et al.* have studied the facial selection in corresponding diol **68a.** resulting from $NaBH_4$ reduction of **65a,** with acrylonitrile to give the *endo*-product with addition exclusively from the hydroxy face as shown.[38a] Based on these findings, it was summarized that the carbonyl groups are unimportant in determining the face-selectivitv in **65a.**




In order to substantiate their interpretation concerning the role of carbonyl groups. Coxon *et al.* replaced the carbonyl groups by methylidene groups as in 66 and 67. thereby retaining the π-electron configuration but replacing the lone pairs of the carbonyl oxygens with hydrogen atoms, and expecting that this subtle variation

might increase the steric hindrance to the carbonyl face addition and encourage reaction from the cyclobutane-face of the diene.[37b]

It was shown that alkene dienophiles, MA and BQ, react with the dienes **66** and 67 with strong preference for the carbonyl face, whereas for DMAD, attack from this face decreases with successive methylidene substitution. In the case of PTAD the trend is reversed, Table 4. The observed selectivities were analysed by theoretical calculations.[37b] Ground state geometric distortions such as unsymmetrical pyramidalization[39] in the diene components were ruled out on the basis of single crystal X-ray structures of the *mono*-hemiacetal **69** and the parent dione **65a** wherein the diene substructure in both systems was shown to be planar. It was also shown that there was no evidence for interconversion of the diastereomers under the reaction conditions. The proposal of Vogel *et al.* based on product stabilities[40] was also considered by Coxon. The thermodynamic criterion **for** the formation of different products was examined using MMX calculations for each of the possible products resulting from reaction of these dienes with four representative dienophiles *viz.* MA, BQ, DMAD and PTAD. Based on calculated steric energy differences between the facial isomers, it was shown that the product stabilities do **not** parallel the experimentally observed selectivities. The most noteworthy being the Diels-Alder adducts of diene **65a** resulting from the **cyclobutane-face** attack were predicted to be thermodynamically more stable than the carbonyl-face addition products (observed experimentally), see Table 4. Interestingly, they have observed a trend of reduced thermodynamic driving force for the cyclobutane face attack on removal of the carbonyl groups in the diene **65a,** which was considered significant. This effect

was attributed to repulsions between the carbonyl groups and the polar dienophiles. Further, this trend was expected to be manifested in the transition states as well, which would then account for some of the observed trends in face-selectivity.

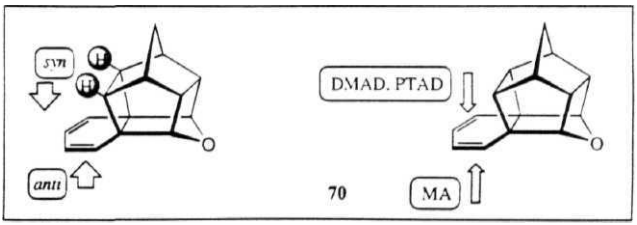
Gleiter and Paquette in their study of 31 and related systems have attributed the observed selectivities to a/n: mixing which resulted in disrotatory tilting of the $\pi$ - lobes on the basis of *ab initio* and semiempirical calculations.[29g] In a similar vein, Coxon *et al.* have probed the $\alpha/\pi$ interactions in dienes 65a, 66 and 67 at the AM 1 level. It was found that there is an inward tilting on the cyclobutane face of the terminal p lobes for the $\Psi_1$ MO of the diene unit. The degree of tilt gradually decreases from **65a** to 66-67. The inward orbital tilting was considered as a favorable factor for the carbonyl face attack by dienophiles since the antibonding interaction between the HOMO of the dienophile and the $\Psi_1$ MO of the diene were considered greater when reaction occurs from the cyclobutane face. Thus, the orbital tilt model, though previously used to rationalize observed selectivities in systems which **did** not possess any polar functionality, was found to be partly successful in explaining the greater preference for carbonyl face addition found in 65a compared to **66** and 67 **for** some of the dienophiles.

The proposal[41b] of Houk *et al.* that steric and torsional[41] interactions resulting from bending at the 'transition state' made in the context of 31 was also considered to account for the carbonyl face selectivity observed in the reactions of 65a, **66** and **67** with alkene and alkyne dienophiles. The general methodology used by Coxon *et al.* was quite similar to the one employed by Houk except in the case of alkyne cycloadditions, where a hybrid AM1/MMX procedure (a 'rigid model') was used as

MMX transition state parameters for Diels-Alder reactions involving alkynes are not available. The face-selectivities were computed from the relative steric energies for carbonyl and cyclobutane face attack of the dienophile. The modelling procedure was quite successful in predicting the absence of alkene cycloaddition to cyclobutane face of the dienes. However, the methodology incorrectly predicted exclusive carbonyl face preferences for alkyne addition to the parent dione **65a** as well. It was therefore concluded that the face-selectivities for alkene type dienophiles can be understood on the basis of steric bias in these dienes. whereas additional electronic factors have to be invoked for alkynes. especially for the diketone 65a. There was no similar model available for reactions of PTAD and hence the authors could not make any definitive comment on the behavior of this heterodienophile.

Finally. Coxon *et al.* have investigated the rc-face preferences in a related cage ether[37c] **70.** wherein a lone pair of the ether oxygen is positioned centrally so as to interact with the π-orbital of the acetylenic dienophile or n-orbitais of an azo dienophile which are disposed orthogonal. to forming σ-bonds. when reaction occurs from the face of the diene bearing the ether oxygen. Scheme 20. It was reasoned that

Scheme 20




*Coxon et al.*

if this electronic effect were important, acetylenic and azo dienophiles would react from the cyclobutane face and alkene dienophiles from the less hindered ether face. Indeed, such a variation in face-selectivities with three representative dienophiles ***viz.*** MA, DMAD and PTAD was observed. Molecular mechanics based calculations failed to rationalize these results but the authors found that MO calculations at the AM1 level could successfully reproduce the observed selectivities. Additionally, on the basis of these calculations an unfavorable interaction in the transition state between the filled π-orbital of acetylene (disposed orthogonal to the forming σ-bonds) and the lone pair on the ether oxygen was computed during the *anri* approach. see Scheme 20. Coxon *et al.* have recognized this factor for undermining addition from the ether face.

In spite of considerable experimental and theoretical scrutiny of **65a** and its derivatives 66 and 67, a number of questions have remained unresolved. It was not clear whether the carbonyl face preference of **65a** was due to orbital tilt in the substrate or a result of non-equivalent steric interactions. Alternative electronic factors can be invoked for explaining the observed preference. As suggested by Hehre[23] *et al.*, facial selectivity in Diels-Alder reaction may be directly related to the differential nature of electrophilic surfaces around the diene. The Cieplak[26] stereo-electronic model can also be invoked to rationalize the carbonyl face attack of olefinic dienophiles to **65a.** According to this model, hyperconjugative stabilization of the transition state can occur by delocalization of electrons from *anti*-periplanar **a** bonds into the a* orbital, a low-lying vacant orbital of the newly formed bonds. Although this was originally advanced for explaining nucleophilic additions to

carbonyl compounds, the concept is equally valid for pericyclic reactions[42] as well. For the present system, the cyclobutane C-C bonds are evidently more electron rich compared to the C-C bonds on the carbonyl face. As a result, the a* orbital of the newly formed bonds would be stabilized to a greater extent if the dienophile approaches from the carbonyl face. Another unresolved problem concerns the variation in face-selectivities on going to heterodienophiles. Although electronic interactions are implicated, their precise nature and generality was not studied. Further, in view of the recent investigations on the mechanistic aspect **of** PTAD addition, an alternative stepwise mechanism[32] involving the initial **formation** of an aziridinium imide intermediate, which rearranges ***via*** a 1,4-zwitterion to deliver the urazole products needs to be considered. Hence, the interpretation of the results has often been ambiguous and there is a need to study other heterodienophiles as well to gain additional insights.

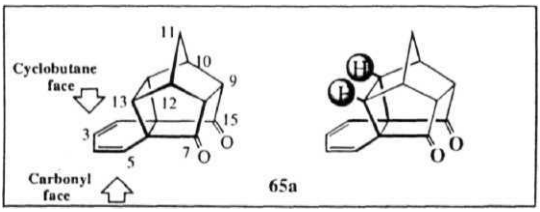
The role of carbonyl groups in 65a is still not satisfactorily explained, as conclusions of Coxon[37a,b] and Pandcy are contradictory. While Pandey *et al.* have harped on the result[37a] obtained for the diol **68a** with a single dienophile, the generality of this observation is open to question. Further, in the diol **68a** the two hydroxy groups were assumed to have a *endo-endo* configuration based **on** the topology of the system and **on** steric grounds allowing the hydride attack **from** the *exo*-face. In view of Coxon's observation[37a] **of** addition of ethanol from the *endo*-face during the hemiacetal 69 formation, the stereochemical assignment made by Pandey was questionable; in which case the *exo*-hydroxy groups can have substantial dipolar interactions in the transition state. Coxon's modification of the diene **65a**

with methylidene groups[37b] has an intrinsic flaw as the steric environment around the diene is substantially perturbed and hence it is unreasonable to implicate absence of electronic interactions involving carbonyl groups alone to explain the observed variations in π-facial selectivities of 66 and 67. Perhaps steric bias in these dienes could be overwhelmingly high; hence simple modifications of the carbonyl groups without disturbing the steric environment around the diene needs to be probed.

**Present Work:** Choice **of the** Prohe System

The background provided in the preceding sections clearly indicate that the face-selectivity encountered in Diels-Alder reactions arc in a general sense still not fully understood. Prediction and interpretation of observed diastereoselectivities continues to be a matter of lively debate. In this context, it is important to study either newer probe systems or modify the existing ones to get better insights into the factors that control diastereoselection in Diels-Alder reactions.

**Figure** 9




65a

Several polycyclic probe systems having a cyclic 1,3-diene substructure in different environments have been devised and scrutinized for diastereoselection employing a variety of dienophiles. Among these, we identified hexacyclo[7.5.1.$0^{1,6}$.$0^{6,13}$.$0^{8,12}$.$0^{10,14}$]pentadeca-2,4-diene-7,15-dione system **65a** as the

probe system for our study because of its rigidity, ready accessibility, reactivity and functional group manoeuvrability, Figure 9.

In the hexacyclic diene **65a,** facial discrimination in the cyclohexadiene moiety is manifested through the interplay of steric effects of cyclobutane hydrogens and the electronic interactions of the carbonyl groups, Figure 9. Further, facial discrimination due to subtle steric and electronic perturbations can be fine-tuned through distal modulation **of** functionalities without conformational uncertainties. In addition, the presence of a stereogenic center in the homoallylic position of the diene, particularly a heteroatom,[12b,25] **was** expected to exert an impressively high stereo-directing influence on the facial selection. Further, its ready amenability to electronic fine-tuning without altering the **steric** environment around the diene makes it a particularly attractive substrate.

In the Results and Discussion section that follows, we narrate our efforts directed towards evaluation and understanding of the origin of the π-facial diastereoselection in **65a** and related systems. Although the ring system represented by **65a** has been studied before ***(vide** supra)*, many structural issues have remained unresolved. Therefore, the need to subject **65a** to a more incisive scrutiny. In our endeavor, we have studied the Diels-Alder reaction **of** several derivatives **of 65a** through substitution on the diene moiety as well as through modification of the carbonyl groups. The dienophiles employed in our study belonged to three representative categories ***viz.*** olefinic, acetylenic and heterodienophiles. The research effort embodied here comprises of synthesis and characterization of a range of modified diene precursors based on **65a:** their reaction with various dienophiles [MA, DMAD, $^1O_2$, PTAD etc.]; determination of the product distribution in each case employing a suitable technique and isolation and unambiguous stereochemical

assignment of each of the diastereomeric addition products. In addition, a critical assessment of the various stereo-electronic factors has been made. We have recognized certain new factors, which were previously unknown, that have a dominating influence in determining face-selectivity.

## I.2 RESULTS AND DISCUSSION

We have already emphasized that evaluation of stereoelectronic effects that influence rc-face selection and control diastereoselectivity in [4+2]-cycloaddition to 1.3-dienes continues to attract considerable theoretical and experimental scrutiny. Diene moieties embedded in rigid polycyclic frames are particularly useful probes. as electronic fine-tuning of the substituents can be achieved without concomitant conformational ambiguities.

The hexacyclo[7.5.1.$0^{1,6}$.$0^{6,13}$.$0^{8,12}$.$0^{10,14}$]pentadeca-2,4-diene-7,15-dione **65a.** a unique polycycle. embodying a [4.4.2]propella-2.4-diene moiety as pan of its rigid structure. and wherein the diene moiety is desymmetrized by the presence of an electron-rich cyclobutane ring on one face and two carbonyl groups at the homoallylic position on the other provides an opportunity to study the effect of heteroatom on Diels-Alder diastereoselection and also the subtle steric and **electronic** factors associated with them. Further. in order to make our study comprehensive. we have employed dienophiles representing three important class: (a) maleic anhydride (MA) and *N*-methylmaleimide (NMM). as representative alkene dienophile. wherein. the two olefinic protons could induce a steric bias. (b) dimethyl acetylenedicarboxylate (DMAD). a representative acetylenic dienophile with filled rc-orbitals and (c) singlet oxygen ($^1O_2$) and *N*-phenyl-1.2.4-triazolinedione (PTAD) representing heterodienophiles with filled n-orbitals which can interact with the diene substrate. In order to avoid regioisomeric products only symmetrical dienophiles were studied. For the present investigation, we have devised several probes through substitution on the diene as well as through simple modification of

the carbonyl groups in **65a,** thereby effecting electronic perturbation without disturbing the steric environment or the skeletal identity of the substrate.

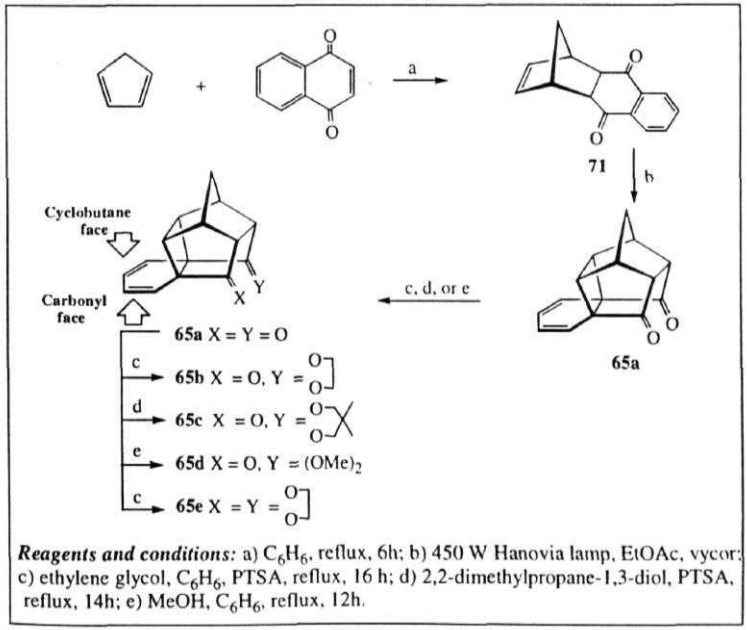
### I.2.1. Modification of the Carbonyl Groups

As enumerated **in** the introductory section, the intrinsically interesting hexacyclic dione **65a** has been shown to exhibit carbonyl-face selectivity with a variety of dienophiles in [4+2]-cycloadditions. However. Coxon ***et*** *al.* have more recently shown that in a related cage ether[37c] 70, a reversal in face selectivity is observed with acetylenic and azodienophiles in comparison to **65a** and addition from the cyclobutane-face is preponderant. They have attributed this reversal to repulsive interactions of the lone pair of the ether oxygen with these dienophiles (see Section I.1 in this thesis). Taking a cue from this interpretation. we reasoned that rehybridization of the carbonyl carbon(s) in **65a.** and strategic disposition of oxygen functionalities on the newly generated sp centens) should enable alteration of face selectivity in a profound way. In a practical sense. this expedient could be simply implemented by protecting the carbonyl groups in **65a** as corresponding acetals or thioacetals. which represent a simple modification of a carbonyl group through a protective group. Thus. without substantially altering the steric environment or sacrificing the skeletal identity of the substrate. we proposed to employ simple protective groups to function as stereodirectors by turning-on the electrostatic effects. Our expectation was that with hetero and acetylenic dienophiles the speculated repulsive interactions between the acetal oxygens and the lone pair or filled π-orbital of the dienophiles would be operative and reverse the face selectivity.

**Modification of Carbonyl Groups into Acetal Functionality**

To begin with, we selected the *mono*- **65b-d** and *bis*- acetal **65e** as the diene substrates for the present study, which were conveniently accessed from the hexacyclic dione **65a.** The dione **65a** was readily assembled following a literature procedure[43] from abundantly available cyclopentadiene and 1,4-naphthoquinone as shown in Scheme 21. Diels-Alder reaction between them furnished a single *endo*-adduct 71, which on irradiation with a 450 W Hanovia mercury vapour lamp in ethyl acetate, underwent smooth intramolecular $_{\pi}2_s + _{\pi}2_s$ photocycloaddition to afford the

**Scheme** 21




***Reagents and conditions:*** a) $C_6H_6$, reflux, 6h; b) 450 W Hanovia lamp, EtOAc, vycor; c) ethylene glycol, $C_6H_6$, PTSA, reflux, 16 h; d) 2,2-dimethylpropane-1,3-diol, PTSA, reflux, 14h; e) MeOH, $C_6H_6$, reflux, 12h.

dione **65a,** Scheme 21.

The *mono*-acetals of **65a** were readily prepared using the appropriate alcohol/diol *viz.* methanol, ethylene glycol or 2,2-dimethyl-l,3-propanediol, in benzene employing PTSA as the catalyst and using a Dean-Stark water separator. It was earlier reported[44] by Pandey *et al.* that the fois-acetal **65e** could not be made and it was attributed to over-crowding and steric congestion within the cage. During our studies, *bis*-acetal **65e** was prepared under the above mentioned reaction conditions quite uneventfully, contrary to the earlier report about its inaccessibility, Scheme 21. However, the *bis*-acetals corresponding to **65c** and **65d** were not formed under these or even slightly modified reaction conditions like using excess of the diol/alcohol or even after prolonged reaction times.

The *mono*- and *bis*-acetals **65b-e** were fully characterized and their **structures** have been secured on the basis of their $^{1}H$ NMR spectral data with signals due to **acetal** protons at 8 3.95 in **65b,** 8 3.63 and 8 3.43 in **65c,** 8 3.23 and 8 3.13 in **65d** and 8 4.10 and 8 3.84 in **65e.** The 'H NMR spectra for the series of acetals **65b-e** as compared to the dione **65a** show significant chemical shift variations: the cyclobutane hydrogens in dione **65a are** observed at 8 3.34; in **65b** at 8 3.13 and 2.98; in **65c** at 8 3.07 and 8 2.90; in **65d** at 8 2.98 and 8 2.88 and in **65e** at 8 2.84. Thus, replacement of the carbonyl oxygens by acetal groups results in a substantial (8 0.5) upfield shift for the spacially distant cyclobutane hydrogens. The $^{13}C$ NMR spectra indicated the presence of a carbonyl resonance at $\delta$ ~212 *(c.f.* 8 210.2 in **65a)** and loss of symmetry in acetals **65b-d,** whereas the *bis*-acetal **65e** exhibited 10 lines reflecting its symmetry.

**[4+2]-Cycloadditions to 65a-e with $^1O_2$, PTAD, DMAD and MA**

The heterodienophiles used in the present study were $^1O_2$ and PTAD, while DMAD and MA were employed as acetylenic and olefinic dienophiles, respectively.

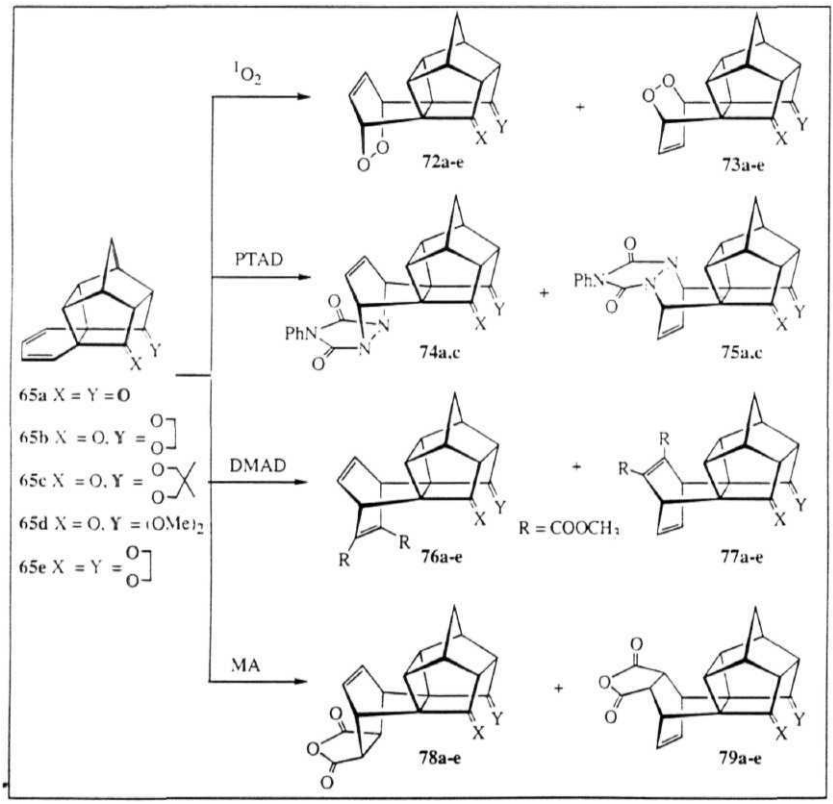
The dione **65a** and acetals **65b-e** readily underwent photooxygenation[45] when irradiated with a 500 W tungsten lamp in $CHCl_3$ under a slow stream of bubbling oxygen using methylene blue as sensitizer at ~10-15 °C to furnish endoperoxides 72a-e and 73a-e, Scheme 22. While in the dione **65a,** $^1O_2$ addition occurred predominantly from the carbonyl-face, in the acetals **65b-e,** the addition was found to be uniformly from the cyclobutane-face and the diastereomeric ratios are indicated in Table 5.

Addition of PTAD, generated by the oxidation of *N*-phenylurazole, to acetal 65c was brought about in dichloromethane at 0-5°C. Efforts to add PTAD to acetals 65b. **65d.** and 65e were unsuccessful and produced intractable products and can be discerned as follows. Preparation of PTAD involved oxidation[46] of *N*-phenylurazole with "oxides of nitogen"[47] in DCM. This mode of preparation invariably contains residual amounts of the oxidizing reagent dissolved in DCM along with PTAD and can effect other side-reactions leading to intractable products as noticed in acetals **65b. 65d.** and **65e.** Nonetheless, we have stumbled on an interesting observation in this regard and is recorded later in this thesis. It is known[37a] that PTAD is captured predominantly from the carbonyl-face in the dione **65a** to furnish adducts **74a** and 75a. Scheme 22. However, addition of PTAD to acetal **65c** follows the same trend as observed in $^1O_2$ addition and a single crystalline adduct **75c.** arising from

cyclobutane-face attack was realized. The carbonyl-face adduct **74c** could not be detected in the crude reaction mixture ($^1$H NMR spectrum), Table 5.

The acetals **65b-e** underwent smooth [4+2]-cycloaddition with DMAD in refluxing benzene to afford adducts **76b-e** and **77b-e**, with preponderant attack from

Scheme 22



the **cyclobutane-face,** in analogy with $^1O_2$ and PTAD additions, Scheme 22. In sharp contrast to this observation, the dione **65a** is **known**[37a] to afford adducts **76a** and **77a,** with modest excess of addition from the **carbonyl-face,** Table 5.

Table **5.** Product distribution (%)[a] and yield (%) in cycloadditions to 65a-e

| | Dienophile | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Singlet Oxygen [b] | | PTAD [c] | | DMAD [d] | | MA [e] | |
| Substrate | Carbonyl face | Cyclobut-ane face | Carbonyl face | Cyclobut-ane face | Carbonyl face | Cyclobut-ane face | Carbonyl face | Cyclobut-ane face |
| | **72a-e** | **73a-e** | **74a-e** | **75a-e** | **76a-e** | **77a-e** | **78a-e** | **79a-e** |
| **65a** | 78 | 22 (88) | 64 | 36 (80) | 55 | 45 (85) | 100 (98) | - |
| **65b** | 14 | 86 (92) | - | - | 17 | 83 (91) | 100 (98) | - |
| **65c** | - | 100 (98) | - | 100 (85) | 05 | 95 (92) | 100 (98) | - |
| **65d** | - | 100 (70)[f] | - | - | 06 | 94 (75) | 100 (98) | - |
| **65e** | 03 | 97 (91) | - | - | 18 | 82 (83) | 100 (98) | - |

(a) The product ratios were obtained from the analyses of the $^1H$ NMR spectra of the crude reaction mixture as well as from isolated yields of pure compounds; (b) 500W tungsten lamp, methylene blue, $O_2$, $CHCl_3$, 5-10 °C; (c) PTAD, DCM, 0-5 °C; (d) DMAD, benzene, reflux; (e) MA, benzene, reflux; (f) Yield based on recovered starting material.

As a **control,** we also studied the addition of MA to acetals **65b-e** to rule out any significant contribution from steric factors. The addition of MA to acetals **65b-e** was effected in refluxing benzene to furnish adducts **78b-e.** Scheme 22. The series of adducts **79b-e** could not be detected in the reaction mixture. We were gratified to

note that the addition indeed occurred exclusively from the carbonyl-face, effectively eliminating any steric intervention by the acetal groups, Table 5.

The yields in cycloadditions ranged between 70 to 100% and are displayed in Table 5. The product ratios were obtained from the analyses of the $^{1}H$ NMR integration of the crude reaction mixture as well as from isolated yields of pure compounds and are summarized in Table 5. The diastereomers were carefully separated using silica gel column chromatography and elution with an appropriate solvent system. Interestingly, the cyclobutane-face adducts in most of the cases eluted out first from the column and this behaviour too could be of some diagnostic value in identifying the diastereomers.

**Stereochemical Assignments of the Diastereomeric Addition Products**

Stereostructures of all the cycloadducts were determined on the basis of detailed, incisive. NMR spectral analyses, particularly 'H NMR data. chemical correlation and X-ray crystal structure determination of key compounds.

***Analyses** of $^{1}H$NMR Spectral Data:*

The formation of [4+2]-cycloaddition products was fully in consonance with the 'H and C NMR spectral data. The disappearance of signals due to cyclohexadiene moiety in the region 5 5.4 - 6.0 and appearance of signals due to bicyclo[2.2.2] moiety was forthcoming, particularly the diagnostic allylic bridgehead protons and olefinic protons in the region 5 6.4 - 6.8. The $^{13}C$ NMR data were in full agreement with the assigned structures. Further, all the cyclodditions reported herein afforded only Alder adducts. The spectra of some of the compounds are presented in Section I.5 of this thesis.

**Table 6. H NMR resonances of cyclobutane protons in carbonyl- and cyclobutane-face adducts of 65a-e**

| Substrate | H NMR resonances (6) of cyclobutane protons **in** | | | | | |
|---|---|---|---|---|---|---|
| | $^1O_2$ **adduct** | | PTAD adduct | | MA adduct | |
| | **Carbonyl face** | Cyclobut-ane **face** | Carbonyl **face** | Cyclobut-ane face | Carbonyl **face** | Cyclobut-ane face |
| | **72a -e** | **73a-e** | **74a-e** | **75a-e** | **78a-e** | **79a-e** |
| **65a** | **2.73** | 3.45 | 2.80 | **3.44** | **2.72** | |
| **65b** | **2.51-2.44.** 2.37-2.30 | 3.35-3.25. 3.12-3.04 | | | **2.49-2.44. 2.31-2.23** | |
| **65c** | | 3.37-3.23. 3.06-2.98 | | **3.27-3.20. 3.03-2.97** | **2.39-2.45. 2.27-2.19** | |
| **65d** | | 3.26. 3.08-3.00 | | | **2.44-2.36. 2.22-2.16** | - |
| **65e** | 2.15 | 2.95 | | | 2.12 | |

The stereostructures were assigned on the basis of the incisive analyses of the H NMR spectral data. In most of the adducts, the diagnostic cyclobutane protons served as a stereochemical handle as they are deshielded when the transannular heteroatom bridge is *syn* to it. On the other hand, the cyclobutane hydrogens are substantially shielded when the double bond is ***syn*** to it. The variation in the chemical shifts of the cyclobutane protons in these diastereomers provided the key to fixing their stereostructures and is mapped in the Table 6. The proton assignments were based on $^1H$-$^1H$ COSY spectra. However, in the case of DMAD addition products, the cyclobutane hydrogens were no longer of any diagnostic value and hence we resorted to other methods of fixing stereostructures.

*Results and Discussion*

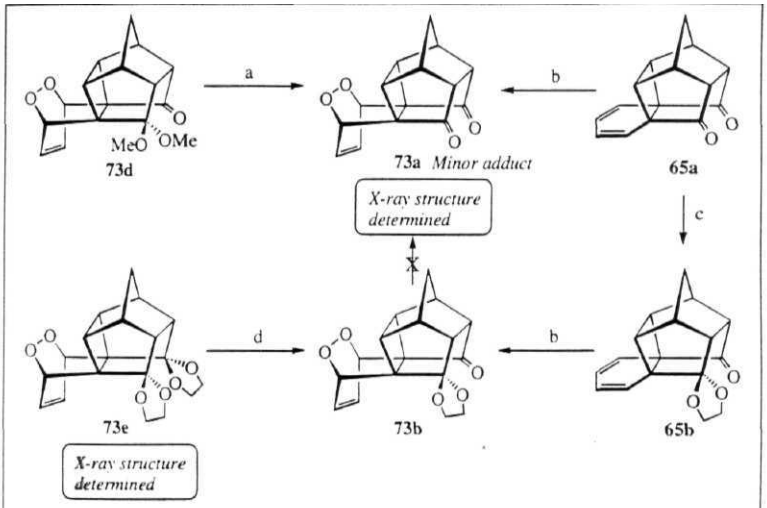
*Chemical Correlation and X-ray Crystal Structure Determination:*

**The** stereostructures were further unambiguously secured by chemical transformation of each of the diastereomer into a known compound whose structure was established by single crystal X-ray diffraction studies. This was accomplished in the following manner:

1) By unmasking the acetal groups in the adducts; thereby converting them into their respective parent (dicarbonyl) adduct whose stereostructure has been previously established.
2) By converting the parent adducts (dicarbonyl) of known stereostructures into the corresponding acetal derivatives by protecting with appropriate alcohol/diol.

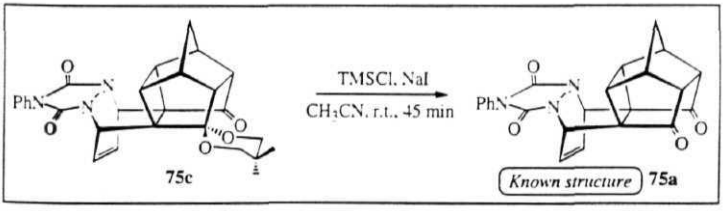
These chemical correlations involved routine protection-deprotection **protocols** and are summarized in Schemes 23-26. Thus, the endoperoxides **73d** and **73e** (X-ray structure determined) were hydrolyzed to dione **73a** (X-ray structure determined) and *mono*-acetal **73b**, respectively, Scheme 23. Likewise, the *mono*-acetal **75c** was hydrolysed[49] into the dione 75a (known[49] structure). Scheme 24. Further, the *mono*-acetals 77c. **77d** and *bis*-acetal **77e** were hydrolyzed to dione **77a** (known[37a] structure) and *mono*-acetal **77b.** respectively, Scheme 25. Alternately, the dione **76a** (known[37a] structure) was acetalized to furnish **76b.c** and **76e.** Scheme 25. In addition. *mono*-acetal **78d** and *bis*-acetal **78e** were converted to dione **78a** (known[37a] structure) and *mono*-acetal **78b.** respectively. Scheme 26. Lastly, the dione **78a** (known[37a] structure) was transformed into *mono*-acetals **78b** and **78c.** Scheme 26. The reagents and conditions employed for the above mentioned transformations are indicated in the respective Schemes 23-26.

Scheme 23

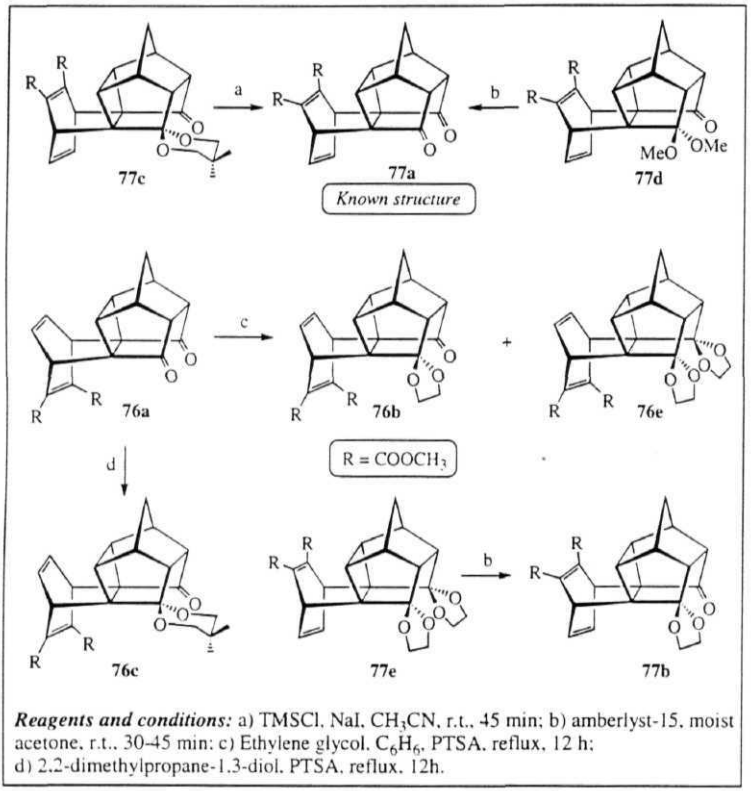



***Reagents and conditions:*** a) Amberlyst-15, moist acetone, r.t., 15 min; b) 500W tungsten lamp, methylene blue, $O_2$, $CHCl_3$, 5-10 °C; c) ethylene glycol, $C_6H_6$, PTSA, reflux, 16 h; d) CSA, moist acetone, r.t., 30min.

Scheme 24



Scheme 25



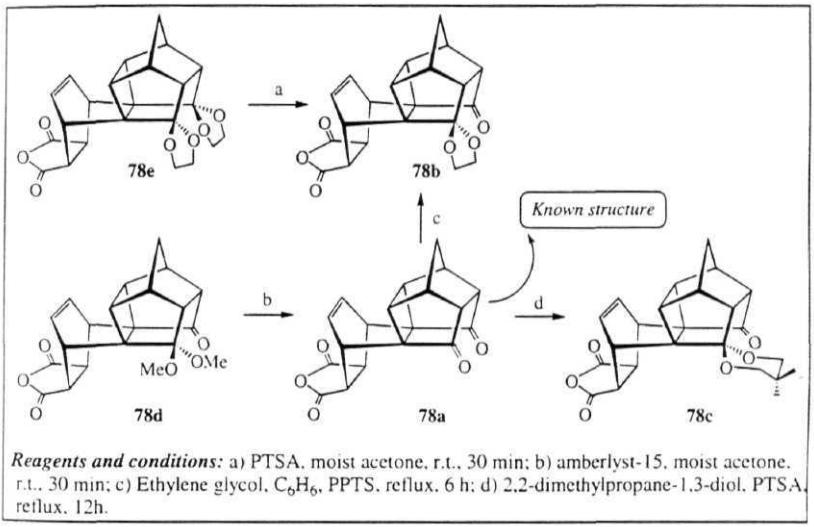

***Reagents and conditions:*** a) TMSCl, NaI, $CH_3CN$, r.t., 45 min; b) amberlyst-15, moist acetone, r.t., 30-45 min; c) Ethylene glycol, $C_6H_6$, PTSA, reflux, 12 h; d) 2,2-dimethylpropane-1,3-diol, PTSA, reflux, 12h.

StereochemicaJ assignments were further unambiguously secured through the single crystal

The crystal structure determination was carried out by Dr. M. Nethaji, Indian Institute of Science. Bangalore.

X-ray structure determination on two of the key compounds *viz.* endoperoxide 73a and 73e and the molecular structures are shown in the Figures 10 and 11, respectively.

**Scheme 26**




***Reagents and conditions:*** a) PTSA, moist acetone, r.t., 30 min; b) amberlyst-15, moist acetone, r.t., 30 min; c) Ethylene glycol, $C_6H_6$, PPTS, reflux, 6 h; d) 2,2-dimethylpropane-1,3-diol, PTSA, reflux, 12h.

**Figure 10.** Molecular Structure of **73a**

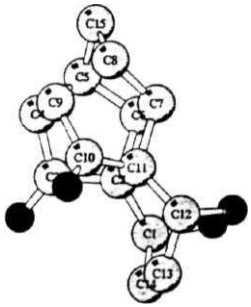
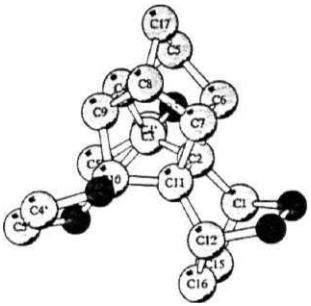


**Figure 11.** Molecular Structure of **73e**



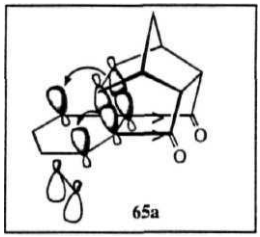

**Interpretation** of **Diastereoselectivities**

For acetals 65b-e. addition of $^1O_2$, PTAD and DM AD is overwhelmingly preferred from the cyclobutane-face in dramatic contrast to the carbonyl-face addition in **65a.** [a] There is no marked change in the π-face selectivity in addition of MA to **65b-e.** clearly indicating that the observed preferences are dienophile specific. The small **but** definitive fine-tuning of the face selectivity as a function of the acetal protecting group (Table 5) further reflects the effect of subtle variations in the positioning of the oxygen atoms on the extent of repulsive interactions. Interestingly, higher selectivities have been observed for the more flexible *mono*-acetals **65c** and **65d.** Since there is no marked change in the π-face selectivity of MA to acetals **65b-e** when compared with the parent dione **65a.** it is reasonable to rule out any steric intervention due to the acetal groups. In fact, the predominant cyclobutane-face selectivity in **65b-e** is a contrastenc outcome.

Several factors like product stability, ground state geometric distorsion. σ/π mixing and torsional interactions which have been previously considered to account

for face selectivity in [4+2]-cycloaddition are not applicable for this system as shown in the previous section. According to Cieplak model, the addition should occur from the side opposite to the most electron rich bond as shown for 65a. Figure 12.

Figure 12




65a

This model can readily rationalize the predominant carbonyl-face attack (addition opposite to electron rich cyclobutane bonds) in MA. but fails to rationalize the contrasteric approach of $^1O_2$, PTAD and DMAD in acetals 65b-e. In particular, the key hyperconjugative interaction in the cycloaddition transition state should become more important when the newly formed C-X bonds involve highly electronegative X groups. Hence, addition of $^1O_2$ or PTAD to carbonyl-face of the diene is predicted to be strongly preferred on the basis of Cieplak model, nevertheless the observed selectivities are reversed for acetals 65b-e.

The observed selectivities can be rationalized as follows: when the addition occurs from the face of the diene bearing the acetal functionality in 65b-e. repulsive electrostatic interaction between the lone pair on the acetal oxygen with the π-orbital of DMAD or n-orbitals of PTAD or $^1O_2$ (which are orthogonal to forming σ-bonds) is turned on. resulting in destabilization of the transition state. Further, the variation

in diastereoselectivity, with respect to the dienophile employed (Table 5), reaffirms our surmise that the repulsive electrostatic interactions between the incoming dienophile and the acetal oxygens in **65b-e** govern the π-facial selectivities in these systems. In addition, these results also provide an unprecedented illustration[50] of the stereodirecting[51] effect of simple remote protective groups. Since acetal protection and deprotection are fairly routine manipulations, we expect that this manoeuver could find useful synthetic applications in achieving diastereoselection in related systems.

**Modification of Carbonyl Groups into Thioacetal Functionality**

To further extend the scope of our findings[50] on the acetals **65b-e.** we directed our study to their sulphur counterparts **80a** and **80b.** expecting to gauge the effect of the change in the heteroatom on diastereoselection in these systems. Although considerable efforts have been made to understand the influence of a heteroatom on [4+2]-cycloadditions, experimental data available to illustrate the role of allylic/homoallylic sulphur substituents is rather limited. Apart from this, other distinctive features that makes studies employing sulphur as a heteroatom particularly interesting are:

1) If the Cieplak[26] hyperconjugative model is operative, it is reasonable to speculate that a preference should exist for addition *anti* to the best **a** donor (C-S bond) when the competition is between a C-C and a C-S bond. Therefore, addition *anti* to C-S bond should dominate since C-S **a** bond is a better donor as compared to **C-C a** bond.

2) If the electrostatic model is the principal determinant of face selectivity, oxygen atoms will experience greater non-bonded lone pair repulsion in the vicinity of a heterodienophile such as $^1O_2$ or PTAD because of the better match in their 2p energy levels as compared to sulphur.[3c] Hence, addition *syn* to sulphur may not be disfavoured.

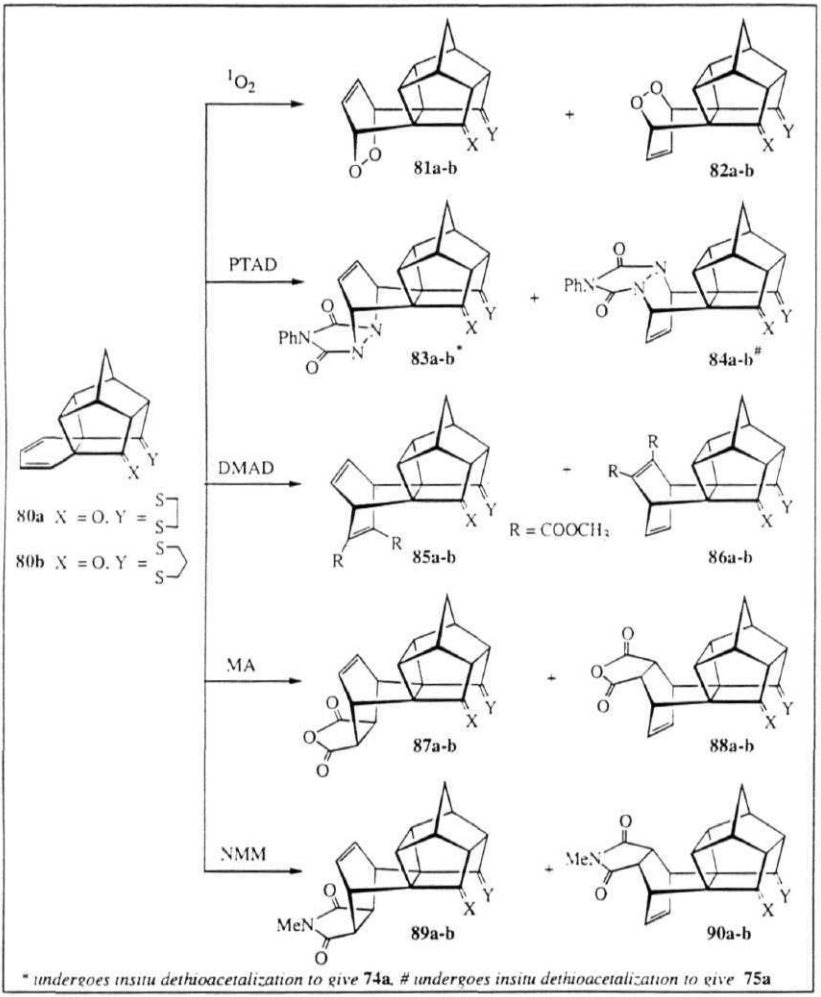
3) Admittedly, transition from oxygen to sulphur is also accompanied by a substantial steric[52] component (van der Waals radii for oxygen is 1.4 A and that of sulphur is 1.85 A).

In order to evaluate the relative contribution of the above mentioned effects, we ventured to investigate the π-facial selectivities of thioacetals **80a** and **80b** which were readily prepared employing the appropriate dithiol *viz.* 1,2-ethanedithiol or 1.3-propanedithiol. in benzene using PTSA as the catalyst. However, the *bis*-thioacetals were not formed under these reaction conditions. The crystalline thioacetals **80a** and **80b** were fully characterized on the basis of their $^1H$ and C NMR spectral data. The $^{13}C$ NMR spectra indicated loss of symmetry in consonance with the *mono*-thioacetal structure and also revealed the presence of carbonyl resonance at 8 214.1 for **80a** and 211.4 for **80b.**

**[4+2]-CycIoadditions to 80a.b with $^1O_2$, PTAD, DMAD, MA and NMM**

The thioacetal **80b** readily underwent photooxygenation to furnish a single crystalline endoperoxide **82b** in near quantitative yield. Scheme 27. However. in **80a.** photooxygenation was not clean (probably due to other competing reactions like oxidation at sulphur) and resulted in poor yield of endoperoxide **82a.** In both **80a** and

Scheme 27


$^1O_2$
PTAD
DMAD
MA
NMM
80a X = O, Y = S S
80b X = O, Y = S S
81a-b
82a-b
83a-b*
84a-b#
85a-b
86a-b
87a-b
88a-b
89a-b
90a-b
R = COOCH3
* undergoes insitu dethioacetalization to give 74a. # undergoes insitu dethioacetalization to give 75a

80b $^1O_2$ addition is uniformly, exclusively from the cyclobutane-face and the adducts (81a,b) due to carbonyl-face attack were not encountered, Table 7.

Table 7. Product distribution (%)[a] and yield (%) in cycloadditions to 80a,b

| Substrate | Dienophile | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Singlet Oxygen[b] | | PTAD[c] | | DMAD[d] | | MA[e] | | NMM[f] | |
| | *Car face | *Cyb face | Car face | Cyb face | Car face | Cyb face | Car face | Cyb face | Car face | Cyb face |
| | **81a,b** | **82a,b** | **83a,b**[#] | **84a,b**[#] | **85a,b** | **86a,b** | **87a,b** | **88a,b** | **89a,b** | **90a,b** |
| **80a** | - | 100 (15) | 09 | 91 (75) | - | 100 (92) | 100 (98) | - | 100 (98) | - |
| **80b** | - | 100 (81) | 11 | 89 (80) | - | 100 (91) | 100 (98) | - | 100 (98) | - |

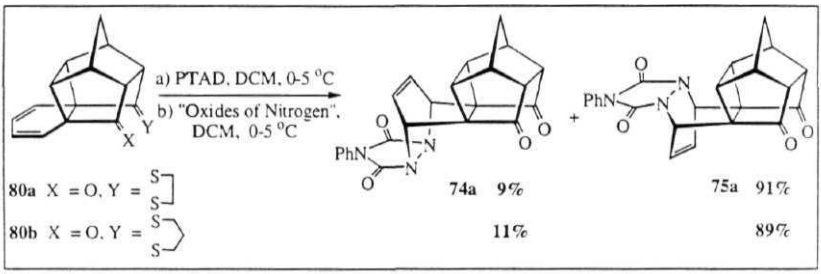
(a) The product ratios were obtained from the analyses of the $^1H$ NMR spectra of the crude reaction mixture as well as from isolated yields of pure compounds; (b) 500W tungsten lamp, methylene blue, $O_2$, $CHCl_3$, 5-10 °C; (c) PTAD, DCM, 0-5 °C; (d) DMAD, benzene, reflux; (e) MA, benzene, reflux; (f) NMM, benzene, reflux.

**Car face : Carbonyl-face; Cyb face : Cyclobutane-face; # the adducts* **83a,b** *and* **84a,b** *underwent in situ dethioacetalization to furnish* **74a** *and* **75a**, *respectively*

Addition of PTAD to thioacctals 80a,b was brought about in dichloromethane at 0-5 °C. The $^1H$ NMR spectral characteristics were not in consonance with the expected PTAD addition products of thioacetals 80a,b: *viz.* absence of signals due to thioacetal group and presence of a two fold symmetry. These spectral features clearly indicated that the adducts were in fact PTAD addition products of the parent dione 65a and their identity was further confirmed by comparing the $^1H$ and $^{13}C$ NMR spectra with authentic samples. Our speculation was

that during PTAD addition to **80a,b** the resultant [4+2]-adducts **83a,b** and **84a,b** underwent smooth *in situ* dethioacetalization to furnish adducts **74a** and 75a. respectively, corresponding to that derived from parent dione 65a, Scheme 28.

Scheme 28




The issue that needs to be settled at this juncture is whether dethioacetalization occurred *prior* to or *did it follow* the addition of PTAD to thioacetals **80a,b.** The answer was forthcoming from the fact that the major diastereomer obtained in each case was **75a** (~90%) corresponding to the cyciobutane-face addition (~36% of **75a** was observed in the case of parent dione **65a.** Table 5), which established beyond doubt that dethioacetalization followed PTAD addition. Therefore, the diastereoselectivities observed during PTAD additions reported herein correspond to that of thioacetals **80a.b** as the products **(74a** and **75a)** isolated correspond to the parent dione 65a. The concomitant dethioacetalization can be rationalized as follows. Preparation of PTAD involved oxidation[46] of *N*-phenylurazole with "oxides of nitogen"[47] in DCM. This mode of

preparation invariably contains residual amounts of the oxidizing reagent dissolved in DCM along with PTAD and could have effected dethioacetalization, Scheme 28.

This observation prompted us to explore the generality of this simple, rapid and convenient dethioacetalization procedure, which merely requires a titration of the substrate solution with "oxides of nitrogen" in DCM and has been reported by us elsewhere.[53] Addition of PTAD to thioacetals **80a,b** follow the same trend as in $^1O_2$ addition albeit with slight decrease in selectivity (Table 7) and adducts predominantly from cyclobutane-face attack were realized.

Further, thioacetals **80a,b** underwent smooth [4+2]-cycloaddition with DMAD in refluxing benzene to afford adducts **86a,b,** exclusively from the cyclobutane-face, in accord with $^1O_2$ and PTAD addition (Table 7). The crude reaction mixture did not indicate the presence of carbonyl-face adducts **85a,b.** As a control, we also studied the addition of MA and NMM to thioacetals **80a,b**, so as **to** gauge contribution from steric bias exerted by the thioacetal functionality. The addition of MA and NMM to thioacetals **80a,b** was effected in refluxing benzene to furnish adducts **87a,b** and **89a,b,** respectively (Table 7). We were pleased to note that the addition indeed occurred exclusively from the carbonyl-face, without any trace of the corresponding cyclobutane-face adducts **(88a,b** and **90a,b) in** each case, Scheme 27.

The yields in cycloaddition ranged between 90 to 100% and are displayed in Table 7. The product ratios were obtained from the analyses of the $^1H$ NMR integration of the crude reaction mixture as well as from isolated yields of pure compounds and are summarized in Table 7. The diastereomers were carefully

separated using silica gel column chromatography using an appropriate solvent system.

**Stereochemical Assignments of the Diastereomeric Cycloaddition Products**

*Analyses of $^1H$NMR Spectral Data:*

The formation of the [4+2]-cycloaddition products **81a,b-89a,l**> was fully in consonance with the $^1H$ and $^{13}C$ NMR spectral data. All the cycloadditions reported herein afforded only Alder adducts. The disappearance of signals due to cyclohexadiene moiety in the region 5 5.6 - 6.0 and appearance of signals due to bicyclo[2.2.2] moiety was readily identifiable. Particularly, allylic bridgehead and olefinic protons in the region 5 6.4 - 6.8 were diagnostic. $^{13}C$ NMR spectra reflected the lack of symmetry in the diastereomers and were supportive of the formulations. However, the stereostructures of adducts 86a,b, **87a,b, 89a,b** could not be assigned on the basis of the $^1H$ NMR spectral data alone. In most of the adducts, the diagnostic cyclobutane protons could not be identified as the signals due to thioacetal group appeared as a series of multiplets in this region. The only exception being endoperoxide **82b,** where there was a discernable downfield shift of *(c.a.* 0.3 ppm) for the cyclobutane protons indicating that the transannular peroxo bridge was *syn* to **it.** Hence, we resorted to establish the stereostructures through chemical transformations.

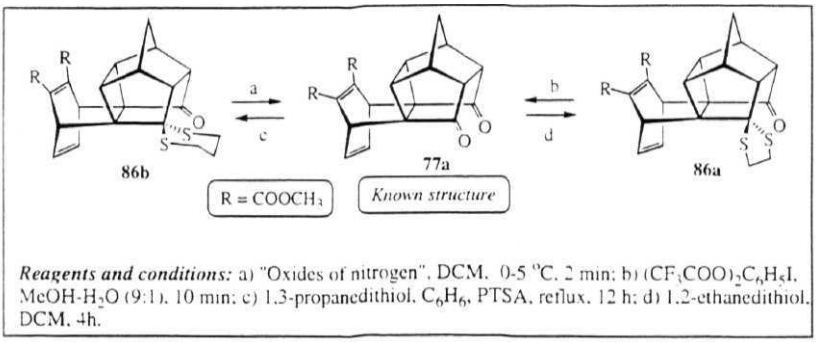
*Chemical Correlation:*

The stereostructures were unambiguously secured by chemical transformation of each of the diastereomer into a compound of known stereostructure. This was accomplished by either or both of the following techniques:

1) By unmasking the thioacetal groups in the adducts; thereby converting them into their respective parent adduct (dicarbonyl) whose stereostructure has been previously established.
2) By converting the parent adducts (dicarbonyl) of known stereostructures into the corresponding thioacetal derivatives by protecting with appropriate dithiol.

These chemical correlations involved unexceptional but tricky protection-deprotection protocols[5154] and are summarized in Schemes 29-31.

Scheme 29

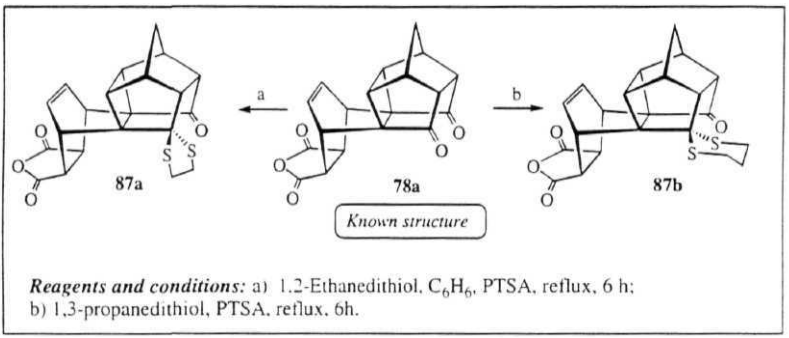



***Reagents and conditions:*** a) "Oxides of nitrogen", DCM, 0-5 °C, 2 min; b) $(CF_3COO)_2C_6H_5I$, MeOH-$H_2O$ (9:1), 10 min; c) 1,3-propanedithiol, $C_6H_6$, PTSA, reflux, 12 h; d) 1,2-ethanedithiol, DCM, 4h.

Accordingly, the *mono*-thioacetals 86a,b were dethioacetalized to the dione 77a, whose structure has been previously established.[37a] Scheme 29. Alternately, The dione 77a was converted into *mono*-thioacetals 86a and 86b. Scheme 29. Likewise, the dione 78a (known[37a] structure) was transformed into *mono*-thioacetals 87a and 87b. Scheme 30. In addition, the dione 91 (known[37a] structure) was converted into *mono*-thioacetals 89a and 89b. Scheme 31. The reagents and conditions

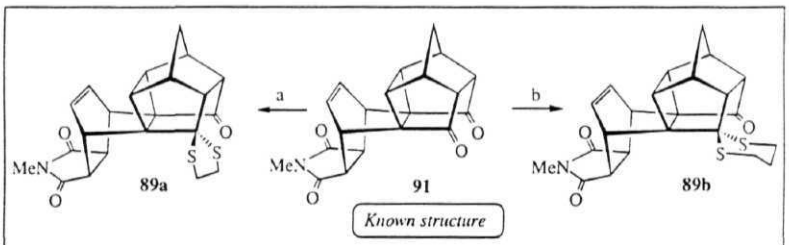
employed for the above mentioned transformations are indicated in the respective Schemes 29-31.

**Scheme 30**




***Reagents and conditions:*** a) 1,2-Ethanedithiol, $C_6H_6$, PTSA, reflux, 6 h; b) 1,3-propanedithiol, PTSA, reflux, 6h.

**Scheme** 31




***Reagents and conditions:*** a) 1,2-Ethanedithiol, $C_6H_6$, PTSA, reflux, 6 h; b) 1,3-propanedithiol, PTSA, reflux, 6h.

**Interpretation of Diastereoselectivities**

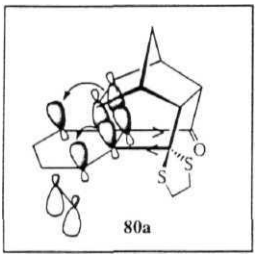
The results in Table 7 clearly indicate that the thioacetal functionality has a profound bearing on the π-facial selectivity and is generally consistent with the

observed trends in the acetals **65b-e.** Most noteworthy being total selectivity in the case of MA, NMM, $^1O_2$ and DM AD with the introduction of barely a ***single*** thioacetal functionality. The addition of $^1O_2$ and DMAD to **80a,b** occurs exclusively from the cyclobutane-face, while PTAD exhibits ~90% selectivity for this face. Lastly, MA and NMM almost exclusively add from the carbonyl-face. For olefinic dienophiles *viz.* MA and NMM, possessing an intrinsic steric bias, the addition is expected from the face of the diene which is sterically least hindered.

Considering the preferences observed for MA and NMM. it is not unreasonable to conclude that carbonyl-face is still sterically less demanding as compared to cyclobutane-face even after the introduction of thioacetal groups in dienes **80a,b.** Therefore, the observed preference for cyclobutane-face during $^1O_2$, PTAD and DMAD addition to thioacetals **80a.b** is a contrasteric outcome. Nonetheless, heterodienophiles do not have hydrogens as in the case of MA or NMM, which can experience steric interaction during the cyclobutane-face attack. Considering these factors, the observed preferences during $^1O_2$, PTAD and DMAD addition to thioacetals **8()a,b** can be attributed to electronic factors such as orbital or electrostatic interactions.

The observed preferences for hetero- and acetylenic dienophiles may be reconciled in terms of the Cieplak hyperconjugative model, according to which the preferred face of addition is *anti* to the most electron rich bond. In the substrates **80a.b.** the choice is between cyclobutane bonds and C-C bonds **a** to a thioacetal and a carbonyl group as we are dealing with unsymmetrical *mono*-thioacetals. Figure 13. Interestingly, it is evident from the trends in Table 7. that such a hyperconjugative

Figure 13




80a

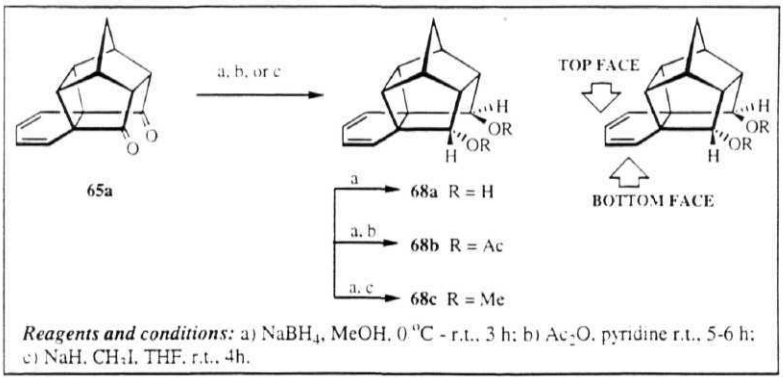
contribution should be operative. On the other hand, unfavourable electrostatic interactions between the heterodienophiles and the lone pairs on sulphur should **encourage** addition from the cyclobutane-face. However, in thioacetals **80a,b** the relative contribution from such interactions is expected to decrease as compared to their oxygen variants 65b-e where there is better match of 2p energy levels. If this were the major determining factor, it is reasonable to speculate that the observed trends for cyclobutane-face addition would be reduced or comparable with the acetal series **(60b-e.** Table 5).

In the light of these arguments, it is reasonable to consider that both electrostatic and orbital interactions act cooperatively during addition of hetero- and acetylenic dienophiles, whereas, unfavourable steric interactions between cyclobutane and the olefinic hydrogens is the principal determining factor during addition of MA and NMM to thioacetals **80a,b**. In addition, these results also further fortify our observation of unprecedented illustration of stereodirecting effect of simple remote protective groups.

**Modification of Carbonyl Groups into Hydroxy, Acetoxy and Alkoxy Functionality**

Having demonstrated that transformation of the carbonyl groups in **65a** to acetal functionality as in **65b-e** can lead to dramatic reversal of face selectivities during the addition of certain dienophiles by turning-on repulsive electrostatic interactions, we ventured to further segregate the role of ***inside*** *oxygen* (within the cage) *vs.* the *outside* ***oxygen,*** in acetals 65b-e. In order to achieve this expedient, we devised *endo,endo*-diol 68a and its diacetate **68b** and dimethoxy derivatives 68c, as diagnostic probes to investigate the role of inside oxygen by **effectively** removing the one outside.

Scheme 32




Sodium borohydride reduction of dione **65a** furnished the *endo,endo*-diol **68a** in near quantitative yield. Scheme 32. The $^{1}H$ and $^{13}C$ NMR spectra of **68a** were fully in consonance with its structure. Signals at 8 3.57 corresponding to the protons

attached to the hydroxyl group in the 'H NMR spectrum and a highly symmetrical 8 line $^{13}C$ NMR spectrum was indicative of *endo,endo* stereochemistry of 68a. Subjection of the diol 68a to acetylation with acetic anhydride and pyridine afforded diacetate 68b, Scheme 32. IR absorption at 1723 $cm^{-1}$, signals at 5 4.66 (protons attached to acetate) and a methyl singlet at 8 2.07 corresponding to the acetate methyl in the $^{1}H$ NMR spectrum and a highly symmetrical 10 line $^{13}C$ NMR spectrum with a carbon resonance at $\delta$171.3 (acetate carbonyl) secured the structure 68b. The dimethoxy derivative was obtained from diol 68a through O-methylation using sodium hydride and methyl iodide in 84% yield , Scheme 32. Signals due to protons a to the methoxy group at $\delta$ 3.21 and a methyl singlet at 8 3.33 in the 'H NMR spectrum coupled with a highly symmetrical 9 line $^{13}C$NMR spectrum secured the structure of dimethoxy derivative 68c.

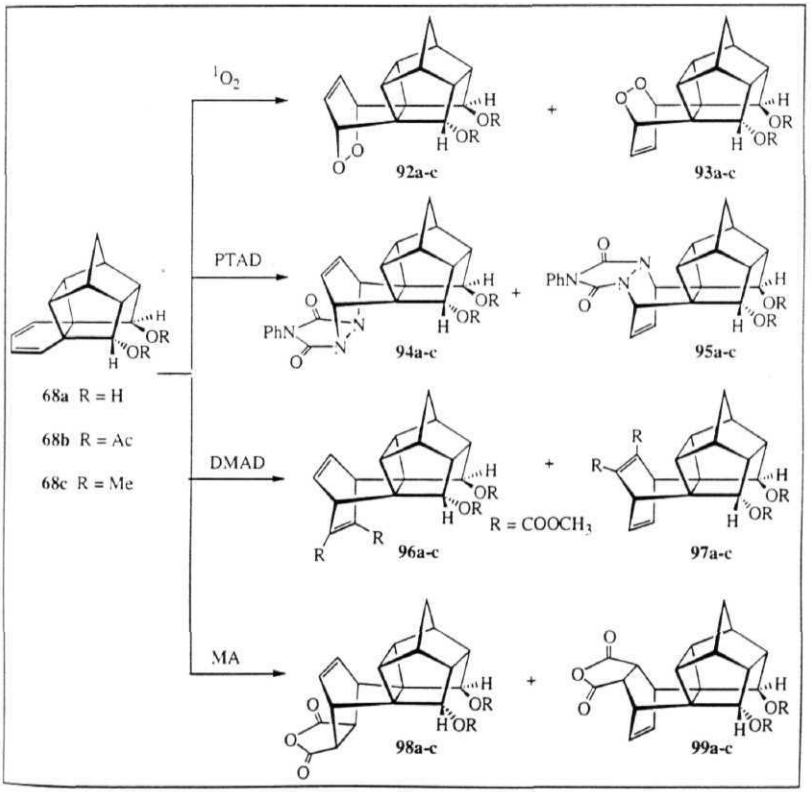
**[4+2]-Cycloadditions** to 68a-c **with $^{1}O_2$,** PTAD, **DMAD** and MA

The diol 68a, its diacetate 68b and dimethoxy 68c derivatives, readily underwent cycloaddition with $^{1}O_2$ generated in the presence of methylene blue as the sensitizer to furnish a diastereomeric mixture of endoperoxides 92a-c and **93a-c**. respectively, in 80-85% yield, Scheme 33. In diol 68a and diacetate 68b. bottom face addition was preferred, whereas, complete reversal occurred in the case of dimethyl ether 68c (top face addition) and a single crystalline endoperoxide 93c was isolated. The diastereomeric ratios obtained in the $^{1}O_2$ addition to 68a-c are indicated in Table 8.

Addition of PTAD. generated by the oxidation of *N*-phenylurazole. to **68a-c** was brought about in DCM at 0-5 °C, Scheme 33. The reaction of PTAD with **68a-c** was clean in the present case unlike the acetals 65b-e, and the face selectivities

followed the same trend as in $^1O_2$ addition and a single diastereomer due to top face attack was realised in the case of dimethoxy derivative 68c. In the case of the diol 68a and diacetate derivative 68b almost exclusively the bottom face diastereomers 94a and 94b, respectively, were obtained, Table 8.

Scheme 33



*Results and Discussion*

Substrates 68a-c underwent smooth [4+2]-cycloaddition with DMAD in refluxing benzene to afford adducts with preponderant attack from the top face in dimethoxy derivative 68c. The diol 68a furnished exclusively the bottom face adduct 96a. On the other hand, in the diacetoxy derivative 68b there was a modest 59:41 selectivity and the bottom face adduct was the major diastereomer. Scheme 33. The trends exhibited during DMAD addition is consistent with those observed in $^1O_2$ and PTAD additions. Table 8.

**Table 8. Product distribution (%)[a] and yield (%) in cycloadditions to 68a-c**

| Substrate | Dicnophile | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Singlet Oxygen [b] | | PTAD [c] | | DMAD [d] | | MA [e] | |
| | **Bottom face** | **Top face** | **Bottom face** | Top face | Bottom **face** | **Top face** | **Bottom face** | Top face |
| | **92a-c** | 93a-c | **94a-c** | 95a-c | **96a-c** | 97a-c | **98a-c** | 99a-c |
| **68a** | 79 | 21 (70) | >96 | <4 (75) | 100 (90) | | 100 (98) | |
| 6Kb | 79 | 21 (90) | >96 | <4 (78) | 59 (93) | 41 | 100 (98) | |
| **68c** | | 100 (81) | <2 | >98 (78) | 17 (77) | S3' | 100 (98) | |

(a) The product ratios were obtained from the analyses of the H N'MR spectra of the crude reaction mixture as well as from isolated yields of pure compounds: (b) 5(X)W **lungsten** lamp. methylene blue. $O_2$. CHC1,. **5-10** "C: (c) PTAD. DCM. 0-5 "C; (d) DMAD. benzene. reflux; (et MA. benzene. reflux: (f) DMAD. benzene. scaled tube.

As a control. we also studied the addition of MA to 68a-c to rule out any significant contribution from steric factors. The addition of MA to 68a-c was

effected in refluxing benzene to furnish adducts 98a-c, Table 8. We were gratified to note that the addition uniformly occurred exclusively from the bottom face, thus eliminating any significant steric intervention due to ***endo-endo*** groups, Scheme 33.

The yields in cycloaddition ranged between 70-100% and are displayed in Table 8. The product ratios were obtained from the analyses of the $^{1}H$ NMR integration of the crude reaction mixture as well as from isolated yields of pure compounds and are summarized in Table 8. The diastereomers were carefully separated using silica gel column chromatography using an appropriate solvent system.

**Stereochemical** Assignments of the Diastereomeric Cycioaddition Products

*Analyses of $^{1}H$NMR spectral data:*

The formation of [4+2]-cycloaddition products **92a-c** to 98a-c from 68a-c was fully in consonance with the $^{1}H$ and $^{13}C$ NMR spectral data. The disappearance of signals due to cyclohexadiene moiety in the region 5 5.4 - 6.0 and appearance of signals due to bicyclo[2.2.2] moiety was particularly revealing, with the diagnostic allylic bridgehead and olefinic protons in the region 5 6.4 - 6.8. The $^{13}C$ NMR spectra were in full agreement with the structures and indicated their symmetry. The spectra of some of the compounds are presented in Section I.5 of this thesis.

The stereostructures were assigned on the basis of the incisive analyses of the $^{1}H$ NMR spectral data. In most of the adducts *(viz.* 92a-c to 95a-c and 98a-c) the diagnostic cyclobutane protons served as a stereochemical handle as has been discussed previously. The variation in the chemical shifts of the cyclobutane protons

in these diastereomers provided the key to fixing their stereostructures and is displayed in the Table 9.

Table 9. $^1H$ NMR resonances of cyclobutane protons in **bottom-and** top **face** adducts of **68a-c**

| Substrate | 'H NMR resonances (5) of cyclobutane protons in | | | | | |
|---|---|---|---|---|---|---|
| | $^1O_2$ adduct | | PTAD adduct | | MA adduct | |
| | Bottom face | Top face | Bottom face | Top face | Bottom face | Top face |
| | **92a-c** | **93a-c** | 94a-c | **95a-c** | **98a-c** | **99a-c** |
| **68a** | 2.09 | 2.87 | 2.14 | | 1.88 | |
| **68b** | 2.11 | 2.97 | 2.21 | | 2.09 | |
| **68c** | | 2.84 | | 2.78 | 1.99 | |

Further, all the proton assignments were made on the basis of $^1H$-$^1H$ COSY spectra. However, in the case of DMAD addition products (96a-c and 97a-c) the cyclobutane hydrogens were no longer of any diagnostic value and hence we resorted to other methods of fixing stereostructures.

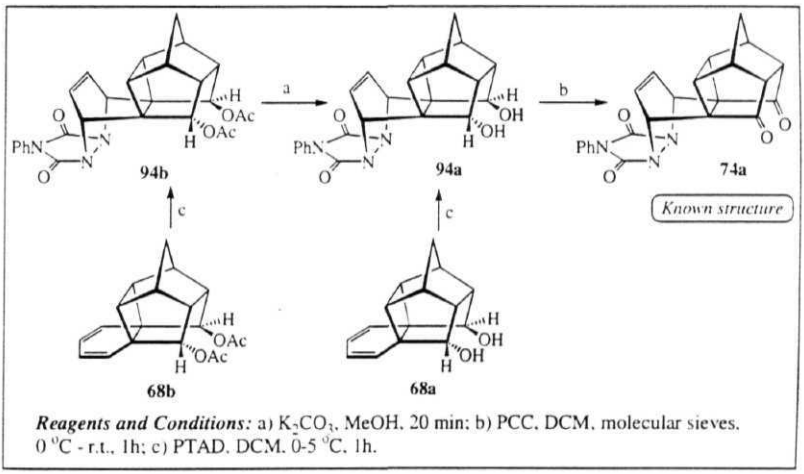
*Chemical Correlation and X-ray* ***Crystal*** *Structure* ***Determination:***

The stereostructures were further unambiguously secured by chemical transformation of each of the diastereomer into a known compound whose structure was established unambiguously in earlier studies. This was accomplished by the following techniques:

1. By unmasking the methoxy or acetoxy groups in the adducts to the diol which was further oxidized to the respective parent adducts whose stereostructure has been previously established.
2. By reducing the parent adducts of known stereostructures into diol derivatives.

These chemical correlations involved routine functional group transformations and are summarized in Schemes 34-36.

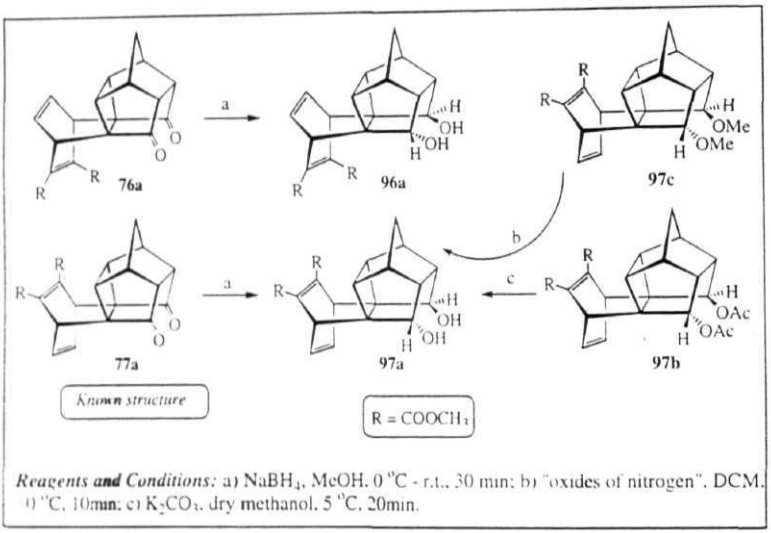
Scheme 34



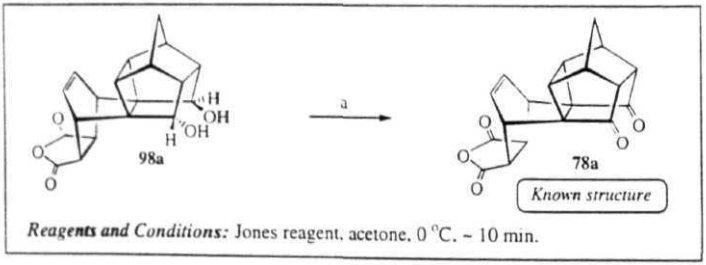

Thus, diacetate **94b** was hydrolysed to diol **94a** which was further oxidized to the dione **74a** (known[37a] structure), Scheme 34. Likewise, the diacetate **97b** and dimethoxy derivative **97c** were transformed to the diol **97a,** Scheme 35. Alternately, the dione **76a** (known[37a] structure) and **77a** (known[37a] structure) were reduced to **the**

corresponding diol 96a and 97a, Scheme 35. Further, the diol **98a** was oxidized to the **dione 78a** of known[37a] structure. Scheme 36. The reagents and conditions

Scheme 35




Scheme 36



employed for the above mentioned transformations are indicated in the respective Schemes 34-36.

Figure 14. ORTEP plot of 92b

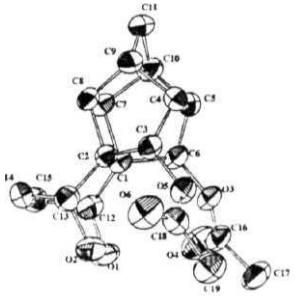
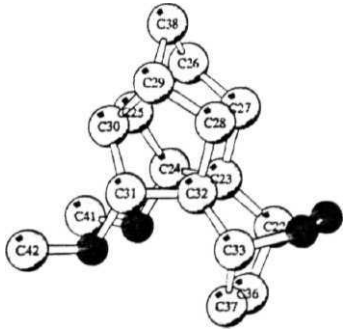


Figure 15. Molecular Structure of **93c**




Further, in two of the cases ***viz.*** endoperoxides 92b and 93c. the stereostructures were unambiguously established by single crystal X-ray structure

determination,† see Figures 14 and 15. Incidentally, the crystal structure determination also proved the ***endo-endo*** nature of the diol **68a** and its derivatives unequivocally.

**Interpretation of Diastereoselectivities**

While addition of PTAD and $^1O_2$ to diol **68a** and diacetate **68b** occurred preferentially from the bottom face, there is a complete reversal in the case of the dimethoxy derivative 68c. However, there is no marked change in the π-face selectivity during the addition of MA to **68a-c.** The results summarized in the Table 8, clearly indicate that even the simplest derivatisation can lead to a reversal in diastcreoselectivity as is observed in methoxy (top-face) **vs.** acetoxy (bottom-face). Some of the factors. which can contribute to face-selectivity in these systems. have been discussed earlier. Considering these factors and earlier studies with the acetals **65b-e,** the expectation was that repulsion between *endo*-directed oxygens in **68a-c** and the hetero/acetylenic dienophiles should uniformly favour addition from the top face. While the observed selectivity in **68c** was fully in consonance with this reasoning, the unprecedented outcome of diastereoselectivities in the case of **68a** and **68b** suggested intervention of some additional, unrecognized interactions and these needed to be probed through transition state modelling.

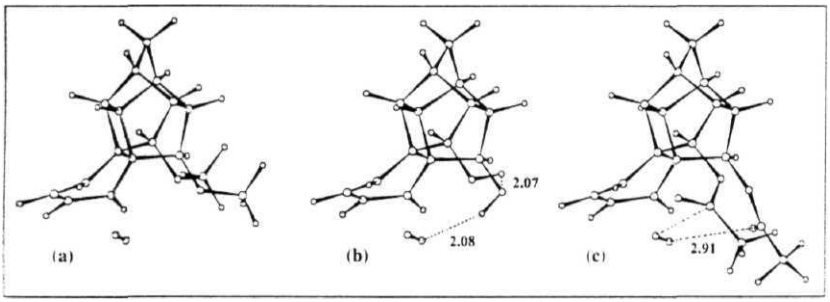
† We thank Mr. B.K. Dirghangi and Mr. S. Mondal for solving the X-ray structure of **93c and DST** for support of X-ray facilities at the University of Hyderabad and ICAS. Calcutta.

We have chosen ethylene, acetylene and (*Z*)-diimide as a model for MA, DM AD and PTAD, respectively, apart from $^1O_2$ and examined the transition states of their addition to 68a-c by AM1 calculations,[55b] Table 10. Saddle points with vanishing gradients and characterized by a single imaginary vibrational frequency were located for the top and bottom face addition. The possibility of conformational variation in the OR groups was considered by using different initial geometries, see Table 10.

While the MO calculations† are by and large consistent with the experimental trends, the computed transition state energetics for $^1O_2$ addition is particularly incisive and will be discussed in greater length and similar arguments hold good for other examples as well. For the methoxy derivative 68c, two sets of transition structures are obtained, both favouring the top face attack by varying degrees. While the energy preference is marginal (0.2 kJ $mol^{-1}$) in the structures in which the methyl groups are pointed towards the diene moiety, a strong bias (10.3 kJ $mol^{-1}$) is predicted when the methyl groups are oriented away from the diene. In the latter, repulsive interactions involving the oxygen lone pairs towards the approaching $^1O_2$ evidently come into play, Figure 16, see (a). Hence the exclusive formation of the top face adduct in 68c is entirely consistent with electrostatic control of face selection.

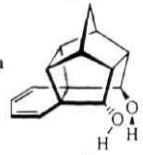
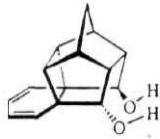
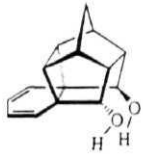
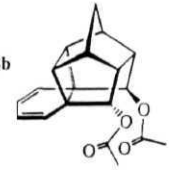
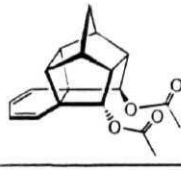
† MO calculations were done in collaboration with Prof. J. Chandrasekhar and Mr. M. N. Jagadeesh, Indian Institute of Science, Bangalore.

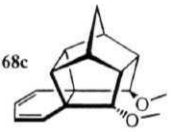
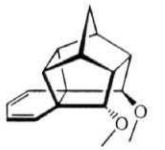
Figure 16. **AM1** Optimized Transition State Structures for the Bottom Face Addition of $^1O_2$ to (a) 68c, (b) 68a and (c) 68b




For the $^1O_2$ addition to the dihydroxy derivative. 68a. a significant bottom face preference (7.9 kJ $mol^{-1}$) is computed. qualitatively in accord with the experimental trend. The transition structures for both the top and bottom face approach lack any symmetry *(C\)* due to an intramolecular 0-H...0 hydrogen bond. In the bottom face attack saddle point. an additional hydrogen bonding interaction is evident. The second OH group in the structure interacts with one of the oxygen atoms of the approaching dienophile. Figure 16. see (b). The cyclic. cooperative hydrogen bonds seem to provide enough stabilization to overcome electrostatic repulsions noted in 68c. Additional proof for the role of hydrogen bonding with the singlet oxygen was obtained by computing the energies of transition states with *C$* symmetry constraints which led to conformations similar to those of the dimethoxy derivative. The face selectivity calculated in these high energy conformations is revealing. With both the OH groups pointing towards the diene. the bottom face

**Table 10. AM1 Heats of formation for top and bottom face addition transition states during addition of $O_2$, (*Z*)-diimide, acetylene and ethylene to 68a-c (kJ $mol^{-1}$)**

| Substrate | *Symmetry* | Dienophile | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | $^1O_2$ | | (Z)-Diimide | | Acetylene | | Ethylene | |
| | | Top face | Bottom face | Top face | Bottom face | Top face | Bottom face | Top face | Bottom face |
| 68a  | $C_1$ | 69.0 | 60.9 | 276.2 | 279.0 | 308.9 | 303.3 | 130.3 | 120.3 |
|  | $C_s$ | 96.8 | 109.4 | 293.8 | 288.3 | 324.9 | 322.0 | 145.1 | 155.6 |
|  | $C_s$ | 90.2 | 64.6 | 308.7 | 320.5 | 342.7 | 336.0 | 165.5 | 143.2 |
| 68b  | $C_s$ | -209.7 | -216.7 | -1.0 | -14.2 | 30.7 | 27.6 | -146.3 | -161.0* |
|  | $C_s$ | -208.8 | -216.7* | 0.8 | -14.2* | 31.9 | 27.6* | -145.3 | -161.0 |

| Substrate | Symmetry | Dienophile | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | $^1O_2$ | | (Z)-Diimide | | Acetylene | | Ethylene | |
| | | Top face | Bottom face | Top face | Bottom face | Top face | Bottom face | Top face | Bottom face |
| 68c  | $C_s$ | 151.0 | 161.4 | 363.6 | 373.4 | 396.6 | 392.2 | 219.4 | 199.2 |
|  | $C_s$ | 150.5 | 150.8 | 362.3 | 369.2 | 392.5 | 398.4 | 215.6 | 199.2* |

* *This conformer rearranges to the alternative conformer.*

approach of $^1O_2$ is favored by 25.6 kJ $mol^{-1}$. In this structure, the two OH groups form strong hydrogen bonds with either end of the dienophile. In the alternative transition structures in which the OH groups point away from the diene. electrostatic preference for top face attack (12.6 kJ $mol^{-1}$) similar to that calculated for the corresponding conformation of **68c** is obtained.

Transition state energies favoring the bottom face attack for the diacetoxy derivative. **68b.** are also consistent with experiment. Remarkably, the computed preference (6.9 kJ $mol^{-1}$) is similar to that obtained in the most stable transition state structures of **68a.** While the latter allows hydrogen bonding between the substituent and $^1O_2$, the origin of the selectivity in **68b** is intriguing. The calculated transition

state structure for the bottom face attack suggests a possible mode of stabilization. The oxygen atoms of the dienophile make fairly short contacts (2.9 A) with the carbonyl carbon atoms of the symmetrically oriented ester groups, Figure 16, see (c). The O...C=O angles of 91° support the possibility of a favorable interaction between the lone pairs on $^1O_2$ with the $n^*$ orbitals on the ester linkages. Similar long-range attractive interactions have been recognized, on the basis of several solid state structures, as key factors governing the nature of the reaction coordinate in nucleophilic additions to carbonyl groups. We now propose that such orbital interactions between the reagent and the remote substituent direct the approach of $^1O_2$. The attractive effects are not translated into any reaction at the substituent, but only result in the delivery of the reagent to the nearby diene face. Evidence for this model comes from calculations on a different conformation of the diester groups, with the acyl units pointing away from the diene. While the energy of the transition state for top face addition was virtually unaffected by the conformational change, in the case of the bottom face addition transition state, the ester groups reoriented to attain the conformation shown in Figure 16, see (c), implying the stabilizing interactions present in this structure.

The modest selectivity exhibited by DMAD during addition to diacetoxy **68b,** indicates that the kind of stabilizing orbital interactions described herein with heterodienophiles ($^1O_2$ and PTAD) may be diminished in DMAD. On the other hand, with dihydroxy **68a,** DMAD exhibits total bottom face selectivity suggesting hydrogen bonding interactions for this transition state. Finally, irrespective of the nature of substituents in **68a-c,** the preferred mode of addition of MA is from the

face opposite to cyclobutane, which is primarily governed by non-bonded steric interactions.

In summary, subtle change of functionality in 68 leads to remarkable variations in the face selectivities of hetero and acetylenic dienophiles. Our results[57] indicate that direct through-space interactions between remote substituents and the approaching reagent *via* three distinct modes, *viz.*, electrostatic, hydrogen bonding and stabilizing orbital interactions, need to be considered as additional stereoelectronic factors in determining face selectivity; *inter alia* caution must be exercised in extrapolating stereoselectivities, even when seemingly inconsequential functional group changes are effected at distal sites.

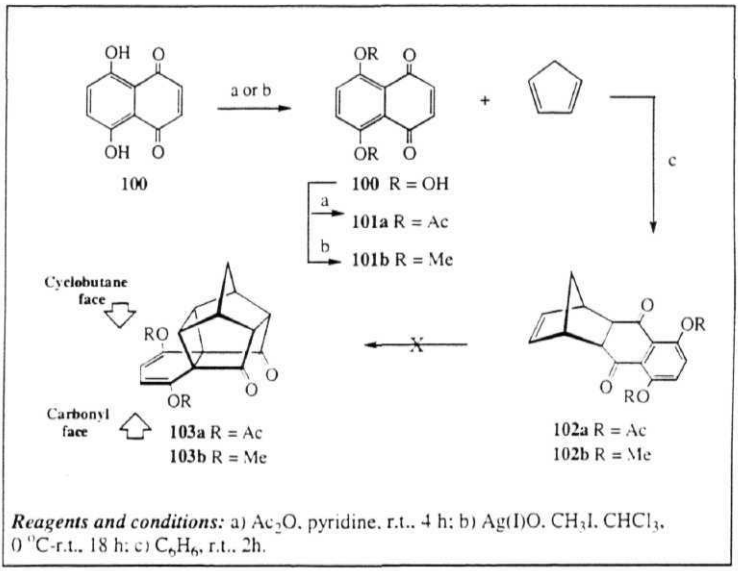
### I.2.2. Substitution on the 1,3-Cyclohexadiene Moiety

We next turned our attention to fine-tune the selectivities by introducing 1,4-substituents on the diene unit of the hexacyclic dione 65a and study its effect on the face-selectivity.

To access the 1,4-substituted dienes **103a** and **103b,** we recognized the tricyclic precursors **102a** and **102b,** respectively, which were in turn synthesized through Diels-Alder reaction of cyclopentadiene with naphthazarin derivatives **101a** and **101b,** following a similar sequence as in the case of "1,4-unsubstituted" diene **65a,** Scheme 37. The diacetate **101a,** obtained by acetylation of naphthazarin[58] **100** with acetic anhydride in pyridine, underwent facile Diels-Alder reaction with cyclopentadiene to furnish a single tricyclic *endo*-adduct **102a** in quantitative yield. The presence of two distinct carbonyl absorptions at 1769 and 1692 cm **in** the IR spectrum, appearance of signals corresponding to olefinic and bridgehead protons at 8 6.10, 3.50, respectively, in addition to a singlet at 8 2.34 (O-CO$\underline{CH_3}$) **in** the $^1$H

NMR spectrum and a 10 line $^{13}C$ NMR spectrum indicated symmetry and established the structure of **102a.**

**Scheme 37**




***Reagents and conditions:*** a) $Ac_2O$, pyridine, r.t., 4 h; b) Ag(I)O, $CH_3I$, $CHCl_3$, 0 °C-r.t., 18 h; c) $C_6H_6$, r.t., 2h.

The O-methylation[59] in naphthazarin **100** was effected with methyl iodide in the presence of silver(I) oxide to deliver the dimethoxy derivative **101b** which on Diels-Alder reaction with cyclopentadiene afforded a single tricyclic *endo*-adduct **102b** in near quantitative yield. Scheme 37. The carbonyl absorption at 1686 $cm^{-1}$ in the IR spectrum, signals corresponding to olefinic and bridgehead protons at 5 6.07 and 3.51 respectively, in addition to a singlet at 5 3.85 (O-$\underline{CH_3}$) in the 'H NMR and a 9 line $^{13}C$ NMR spectrum secured the structure **102b.**

*Results and Discussion*

Having made the tricyclic precursors **102a.b.** we now attempted to effect the intramolecular $\pi 2_s + \pi 2_s$ photocycloaddition to access the 1,4-substituted dienes, 103a.b. However, the hexacyclic diones 103a,b unlike their "1,4-unsubstituted" counterpart 65a, proved to be elusive and defied isolation and characterization. although a variety of conditions employing different reaction regimes for effecting the intramolecular [2+2]-cycloaddition were tried but only led to intractable products.

Finally, we could overcome this problem by directly subjecting their tricyclic precursors **102a.b** to photooxygenation. wherein, the unstable dienes 103a,b formed were trapped *in situ* by $^1O_2$ to furnish the endoperoxides 104a and 104b. respectively, Scheme 38. 39.

**[4+2]-Cycloaddition** to 103a,b with Singlet Oxygen

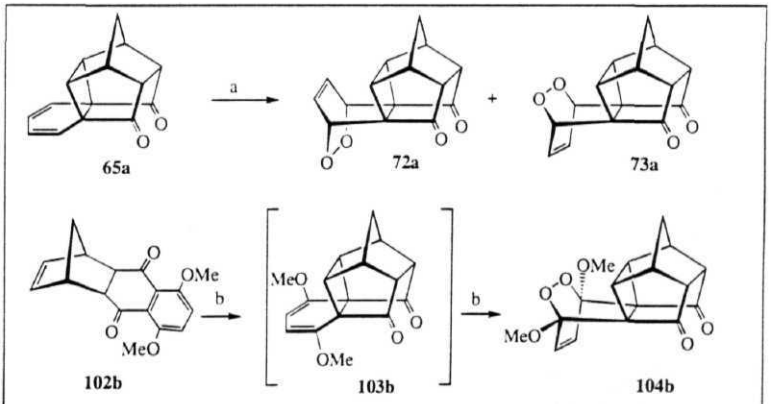
The diene 65a readily underwent photooxygenation on irradiation from a 500 W tungsten lamp to furnish two crystalline diastereomeric endoperoxides 72a and 73a in 78:22 ratio, as discussed earlier *(vide supra).* On the other hand. the tricyclic adduct 102b on irradiation with a 450 W Hanovia mercury vapour lamp in ethyl acetate using methylene blue as sensitizer at ~10-15 °C, initially underwent intramolecular $\pi 2_s + \pi 2_s$ photocycloaddition to yield the 1,4-disubstituted diene 103b. which on concomitant photooxygenation afforded a single crystalline endoperoxide. 104b. Scheme 38.

The tricyclic precursor 102a on similar irradiation led to the isolation of a crystalline endoperoxide 104a and in addition, a new product, which showed an IR absorption at 1755 $cm^{-1}$, a distinct singlet at 8 3.68 in addition to a singlet at 5 2.00

(O-CO-$\underline{CH}_3$) coupled with absence of olefinic signals in $^1H$ NMR and a 10 line $^{13}C$ NMR, with a quaternary carbon signal at 8 76.14. The forgoing spectral features led us to the formulation of a diepoxide, **105,** Scheme 39. The formation of the diepoxide **105,** was rationalized on the basis of a facile rearrangement of the labile endoperoxide **104a,** under the reaction conditions, by a homolytic cleavage of the peroxo bridge followed by addition to the double bond as shown in Scheme 39. Further, this speculation was proved by independently effecting the conversion of the pure endoperoxide **104a** to diepoxide **105** on irradiation, in near quantitative yield.

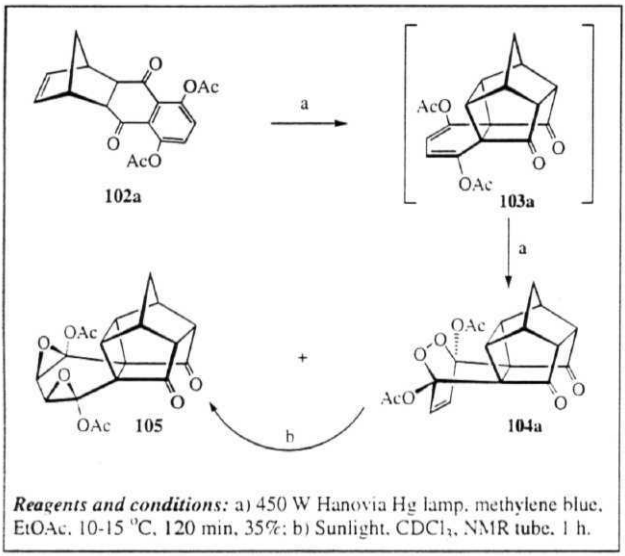
The product ratios were obtained from the analyses of the $^1H$ NMR integration of the crude reaction mixture as well as from isolated yields of pure

**Scheme** 38




***Reagents and conditions:*** a) 500 W tungten lamp, methylene blue, $O_2$, $CHCl_3$, 10-15 °C, 6h, 88%; b) 450 W Hanovia Hg lamp, methylene blue, EtOAc, 10-15 °C, 15 min, 60%.

Scheme 39




***Reagents and conditions:*** a) 450 W Hanovia Hg lamp, methylene blue, EtOAc, 10-15 °C, 120 min, 35%; b) Sunlight, $CDCl_3$, NMR tube, 1 h.

compounds. Table 11. The yields in the photooxygenation reactions ranged between 35 to 88% and are shown in Schemes 38 and 39. The diastereomers were carefully separated by silica gel column chromatography using an appropriate solvent system.

Thus, parent dione **65a** afforded a mixture of endoperoxides **72a** and 73a in the ratio 78:22, respectively, with the major diastereomer denved from carbonyl-face attack. On the other hand, the 1,4-disubstituted derivatives **103a,b** captured $^1O_2$ exclusively from the cyclobutane-face to furnish **104a** and **104b.** respectively. Table 11.

**Table 11. Product distribution (%) during photooxygenation to 65a and 103a,b**

| Substrate | Singlet Oxygen | |
|---|---|---|
| | Carbonyl-face | Cyclobutane-face |
| **65a** | 78 (**72a**) | 22 (**73a**) |
| **103a** | - | 100 (**104a**)* |
| **103b** | - | 100 (**104b**) |

• *rearranges to epoxide* 105

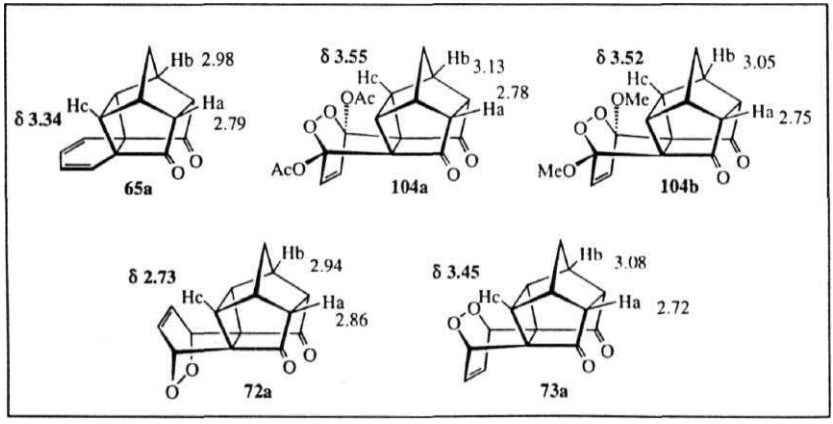
## Stereochemical Assignments of Diastereomers

The diastereomers were separated and fully characterized. Formation of the endoperoxides was forthcoming from their $^1H$ NMR spectra on the basis of absence of signals due to 1,3-hexadiene moiety and appearance of a multiplet at 8 4.7-4.9 region, characteristic of allylic bridgehead protons of cyclic endoperoxides. The stereostructures of the endoperoxides were assigned on the basis of incisive analyses of their $^1H$ NMR data. The parent dione **65a** exhibits three sets of broad singlets, at 8 2.79 (2H), 8 2.98 (2H), and 8 3.34(2H), corresponding to protons **a to** carbonyl (Ha), bridgehead protons (Hb) and cyclobutane protons (Hc), respectively. Considering this as the reference, the extent of shielding/deshielding was estimated. Initially, the proton assignments were made intuitively based on their chemical shifts (perhaps an organic chemist's instinct!) and later on verified from the $^1H$-$^1H$ COSY spectrum of each of the diastereomers. The stereochemical marker in these systems were the

diagnostic cyclobutane protons which experienced a pronounced deshielding when the transannular peroxo bridge was *syn.* On the contrary, the cyclobutane protons experienced substantial sheilding when the double bond was ***syn*** to it. In the endoperoxides **73a, 104a** and **104b,** the Hc protons are deshielded, whereas in endoperoxide **72a** the Hc proton is shielded. The chemical shifts of Ha, Hb and Hc protons in each of the diastereomer is marked on the structures, Scheme 40 and for comparison purposes the values for parent dione 65a are also listed. The spectra of some of the compounds are presented in Section I.5 of this thesis. The $^{13}C$ NMR spectra were indicative of the symmetry in each of the diastereomers although it was not of diagnostic value in elucidating the stereostructures.

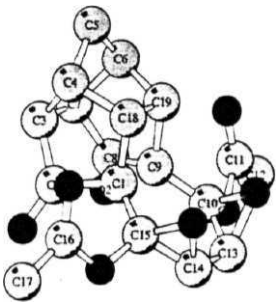
Further, stereostructures were unambiguously established through single

Scheme 40



crystal X-ray structure[†] of two of the key compounds *viz.* endoperoxide **73a** and diepoxide **105** and the molecular structures are shown in the Figures 10 and 17, respectively.

**Figure** 17. Molecular Structure of **105**




**Interpretation of Diastereoselectivities**

The ratios presented in Table 11 indicate a carbonyl-face attack of singlet oxygen on **65a** and its dramatic reversal on going to the derivatives **103a.b** bearing 1,4-disubstitution on the diene moiety. The influence of substituents on the rt-face selectivity is remarkable, since the groups are expected to remain in the rc-plane in the reactant and in the sterically neutral bridgehead positions in the product.

The crystal structure determination was carried out by Dr. M. Nethaji. Indian Institute of Science, Bangalore.

*Results and Discussion*

Several factors such as product stability, ground state geometric distortion, $\sigma/\pi$ mixing, steric and torsional interactions which have been previously considered to account for face-selectivity are not applicable for this system as discussed in the previous section. According to Cieplak model, the addition should occur from the side opposite to the most electron rich bond. This model can rationalize the predominant carbonyl-face attack (addition opposite to electron rich cyclobutane bonds) in **65a**, but fails to rationalize the contrasteric approach of $^1O_2$ in **103a,b.**

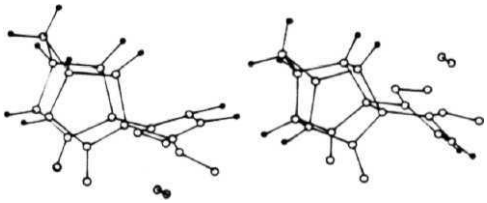
Hence, we directly probed the structure and energetics of the transition states through MNDO calculations.† First-order saddle points at the MNDO[29a] level for cycloadditions tend to be highly asynchronous. However, synchronous-constrained structures (with vanishing gradients and a hessian of 2) are quite similar to true transition state geometries obtained at *ab initio* levels. The optimized synchronized-constrained ($C_s$) transition states for $^1O_2$ addition to 65a reveal that addition to the carbonyl-face is preferred by 4.2 kJ $mol^{-1}$, consistent with the experimental trend. The reversal of face-selectivity in the dimethoxy derivative **103b** is also reproduced by MNDO calculations. The corresponding transition state energitics correspond to a preference for cyclobutane-face addition by 5.4 kJ $mol^{-1}$.

The computed geometries of these structures (Figure 18) reveal a possible reason for the reversal. The diene is twisted at the 1,4-position such that substituents move *towards* the dienophile. Thus, the O-C(1)-C(4) angle is 169°. This feature has

† MO calculations were done in collaboration with Prof. J. Chandrasekhar and Dr. A. Pramanik, Indian Institute of Science, Bangalore.

been noted in previous calculations on Diels-Alder transition states for a variety of substrates and has been suggested to be a requirement for maximizing frontier orbital interactions.[41b,60] For carbonyl-face addition **of** oxygen to **103b.** the methoxy lone pairs are brought closer to the carbonyl oxygen atoms at the transition state. The consequent repulsion would lead to relative destabilization of the corresponding transition state. The same effect should account for the face-selectivity in the diacetoxy derivative **103a.** The above interpretation was further confirmed by calculations on the corresponding dihydroxy derivative **106.** Scheme **41.**

**Figure 18. Optimized geometries of synchronous-constrained transition states for singlet oxygen addition to 103b.**

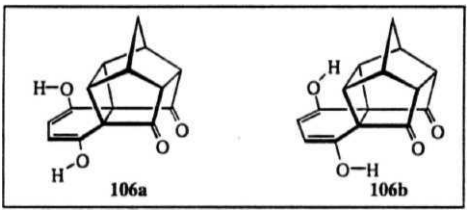


Carbonyl (cyclobutane) face addition is shown on the left (right). **The** hydrogen atoms on -OMe substituents are omitted for clarity.

In **106a.** with the lone pairs oriented in **the** same direction as in the transition state involving **103b.** cyclobutane-face addition is again favoured. by 4.6 kJ $mol^{-1}$.

An alternative conformation **106b** is conceivable, with the hydroxy hydrogens pointing towards the cage, which is not energetically accessible for **103a,b.** In this

Scheme 41




conformation, addition to the carbonyl-face no longer suffers increased lone pair repulsion. The corresponding transition state is favoured over cyclobutane-face addition by 2.5 kJ $mol^{-1}$. These results confirm the presence of interactions between the 1,4-substituents and the dione in the carbonyl-face addition transition state.[61] It may be emphasized that the critical geometric distonion (out-of-plane bending) which subtly controls face-selectivity in these systems is not present either in the reactant or the product, but is specific to the transition state. These interpretations provide an interesting complement to earlier suggestions of face-selectivity being influenced by out-of-plane bending at the 2.3-posrtions of isodicyclopentadiene[41b,60] **31.**

## I.3 SUMMARY

Employing hexacyclo[7.5.1.$0^{1,6}$.$0^{6,13}$.$0^{8,12}$.$0^{10,14}$]pentadeca-2,4-diene-7,15-dione **65a,** a unique polycycle, embodying a [4.4.2]propella-2,4-diene moiety as part of its rigid structure, we have illustrated the profound influence of heteroatoms *viz.* oxygen and sulphur on π-facial diastereoselection in these systems by exploiting the distal carbonyl groups as a handle for electronic fine-tuning. Employing this tactic, we have shown that simple modification of carbonyl groups into *mono-* or ***bis-*** acetals/thio acetals **(65b-e)** can reverse the carbonyl face-selectivity in [4+2]-cycloaddition with certain dienophiles. In other words, the reversal in diastereoselectivity in these systems has been accomplished through routine protective group manoeuver. With the demonstration of an unprecedented *stereodirecting* effect of simple, remote, protecting groups, we expect that this tactic would find useful synthetic applications in achieving diastereoselection in related systems, as acetal protection and deprotection is a fairly routine manipulation. The observed reversals in diastereoselectivities has been primarily attributed to unfavourable electrostatic interactions between acetal oxygens and filled orbitals on the dienophiles.

On replacement of oxygen by sulphur, as in the thioacetal system **(80a,b),** the expectation was that the magnitude of through-space interactions would be reduced and hence attack from the carbonyl face would be promoted. However, the total selectivity for cyclobutane face, as observed in these systems, suggest the need for Cieplak-type hyperconjugative interactions to be considered in addition to through-space electrostatic interactions.

*Summary*

In the quest for segregating the relative contribution of *inside vs. outside* oxygen in acetals **65b-e,** we have devised *endo,endo*-diol **68a** and its derivatives **68b,c** as incisive probes towards this end. While we have demonstrated that a single *endo*-directed oxygen can effect diastereoselectivities comparable to acetals **65b-e,** we have also unraveled certain key through space interactions in the transition stale which have not been recognized before as contributors to face selectivity. We interpret the reversal in selectivity exhibited in the dimethoxy **68c** as opposed to diacetoxy **68b** and diol **68a** by invoking different modes of direct through-space interactions between remote substituents and the approaching reagent **via** three distinct modes, *viz.* electostatic, hydrogen bonding and stabilizing orbital interactions as additional stereoelectronic factors.

Further, we have demonstrated a remarkable effect of 1,4-substituents on the diene moiety during singlet oxygen addition leading to reversal in selectivity **(65a** *vs.* **103a,b**). We have rationalized this reversal of face selectivity in terms of transition state geometric distortions; an effect attributed to lone pair repulsions induced by out-of-plane bending of sterically neutral substituents at the transition state.

Our findings constitute an important body of experimental and theoretical results on the origin of π-facial diastereoselection on the polycyclic 1,3-hexadiene **65a,** in particular and [4+2]-cycloadditions in general. We have electronically fine-tuned an existing probe **65a,** and critically assessed the various factors responsible for diastereoselection in related systems. In the light of our experimental and theoretical findings, we feel that the observed selectivities to be primarily governed

by through-space electronic interactions, while orbital and steric components can not be totally discounted.

In addition, we have observed a simple, rapid and convenient dethioacetalization protocol, which merely requires a titration of the substrate solution with a solution of "oxides of nitrogen" in DCM and the generality of this methodology has been established ***(vide*** *experimental).*

## I.4 EXPERIMENTAL

### Melting Points

Melting points were recorded on a Buchi SMP-20 apparatus and are uncorrected.

### Infrared Spectra

Infrared spectra were recorded on JASCO FT-IR 5300 or Perkin-Elmer 1310 spectrometers. Spectra were calibrated against the polystyrene absorption at 1601 $cm^{-1}$. Solid samples were recorded as KBr wafers and liquid samples as thin films between NaCl plates.

Nuclear Magnetic Resonance Spectra

Proton magnetic resonance (200 MHz) and carbon-13 magnetic resonance spectra (50 MHz) were recorded on Bruker AC 200 spectrometer. $^{1}H$ and $^{13}C$-NMR samples were made in chloroform-d solvent and chemical shifts are reported in 5 scale using tetramethylsilane ($Me_4Si$) as the internal standard. The standard abbreviations s. d, t. q and m refer to singlet, doublet, triplet, quartet and multiplet, respectively. Coupling constants ($J$), wherever discernible have been given in Hz. $^{13}C$-NMR assignments differing by only 1-2 ppm can in some cases be interchanged.

Mass Spectra

Mass measurements were carried out on JEOL. JMS DX-303 spectrometer.

### Elemental Analysis

Elemental analyses were performed on a Perkin-Elmer 240C-CHN analyser.

Chromatography

Analytical thin layer chromatography (tlc) were performed on (10 x 5 cm) glass plates coated with Acme's silica gel G or $G_{254}$ (250 mμ, containing 13% of calcium sulphate as binder). Visualization of the spots on tlc plates was achieved either by exposure to iodine or UV light or by spraying sulfuric acid and heating the plates at 120 °C. Column chromatography was performed using Acme's silica gel (100-200 mesh) or neutral alumina and the column was usually eluted with ethyl acetate-hexane.

General

All reactions were monitored by employing tlc technique using appropriate solvent systems for development. Moisture-sensitive reactions were carried out by using standard syringe-septum techniques under nitrogen atmosphere. Dichoromethane and chloroform were distilled over $P_2O_5$. Ethyl acetate was distilled over potassium carbonate. Benzene was distilled over sodium and stored over pressed sodium wire. Dry ether and THF were prepared by distilling them from sodium-benzophenone ketyl. All solvent extracts were washed with water. brine. dried over anhydrous $Na_2SO_4$ and concentrated at reduced pressure on a Buchi-El rotary evaporator. Yields reported are isolated yields of material judged homogeneous by tlc and NMR spectroscopy.

**Tetracyclo[10.2.1.$0^{2.11}$.$0^{4.9}$]pentadeca-4,6,8.13-tetraene-3,10-dione 71:**

To a solution of 1,4-naphthoquinone (66 g, 0.41 mol) in dry benzene (500 mL) was added freshly cracked cyclopentadiene (29.7 g, 0.45 mol). The reaction

mixture was refluxed for 6 h. After concentration, the reaction mixture was left overnight at 20 °C for crystallization. Filteration gave 71 (88 g. 94%), as pale yellow crystals.

mp : 110-112 °C (lit.[62] 115 °C)

**Hexacyclo[7.5.1.0$^{1,6}$.0$^{6,13}$.0$^{8,12}$.0$^{10,14}$]pentadeca-2,4-diene-7,15-dione 65a:**

A solution of the adduct 71 (22.4 g, 0.1 mol) in ethyl acetate (850 mL) was purged with a slow stream of dry nitrogen for 5 minutes. The solution was then irradiated with a Hanovia 450 W medium pressure mercury vapour lamp, in a quartz immersion well using vycor filter for 1.5 h. Evaporation of solvent and direct crystallization from ethyl acetate-hexane gave hexacyclic dione 65a (15.6 g, 70%).

mp : 110 °C (lit.[43] 111-112 °C)

IR : 1745. 1575 cm$^{-1}$

$^{1}$H NMR : 5 5.99-5.93 (2H. m), 5.40-5.34 (2H, m), 3.34 **(2H. bs).** 2.98 (2H. bs), **2.79(2H.bs),** 1.98 (1H, ½ ABq, *J* = 11.8 Hz), 1.74 (1H, ½ ABq. *J* = 11.0 **Hz)**

$^{13}$C NMR : 5 210.2. 124.8. 119.9. 54.6. 51.7. 50.2. 44.2. 39.0

**Acetalization** of dione 65a:

In a R.B flask fitted with a Dean-Stark water separator was placed dione 65a (500 mg, 2.23 mmol), ethylene glycol (0.75 mL. 13.2 mmol), PTSA (5-10 mg) and dry benzene (25 mL). The contents of the flask were refluxed overnight with stirring. The reaction mixture was cooled and diluted with ethyl acetate (20 mL) and washed with water (3 mL), saturated $NaHCO_3$ solution (5 mL) and dried. Removal of solvent furnished a mixture of acetals 65b and **65e,** which was charged on a silica gel

column. Elution with 30% ethyl acetate-hexane initially furnished the *mono*-acetal 65b (270 mg, 45%) and was recrystallized from DCM-hexane.

**Spiro[dihydro[1,3]dioxolane-2,7'-hexacyclo[7.5.1.$0^{1,6}$.$0^{6,13}$.$0^{8,12}$.$0^{10,14}$]pentadeca-2',4'-diene]-15'-one 65b:**

mp : 128-129 °C

IR :1734,1585 $cm^{-1}$

$^1H$ NMR : 5 5.96-5.84 (2H. m), 5.53-5.46 (2H, m), 3.96-3.93 (4H. m), 3.16-3.09 (1H, m), 3.01-2.94 (1H, m), 2.86 (1H. bs). 2.69-2.66 (1H. m), 2.57-2.55 (2H. m), 1.79 (1H, ½ ABq, $J$ = 10.8 Hz), 1.43 (1H, ½ ABq, $J$ = 11.4 Hz)

$^{13}C$ NMR : 5 212.8. 123.8(2C). 122.4. 121.0. 113.8. 66.1. 65.8. 54.6. 53.5. 51.0. 50.0. 47.4. 45.3. 42.7. 36.9

Analysis : $C_{17}H_{16}O_3$ : Calcd. : C. 76.10; H. 6.01

Found : C. 76.17; **H.** 6.11

**Dispiro[dihydro[1,3]dioxolane-2,7'-hexacyclo[7.5.1.$0^{1,6}$.$0^{6,13}$.$0^{8,12}$.$0^{10,14}$] pentadeca-2',4'-diene-15', 2''-(dihydro[1,3]dioxolane)] 65e:**

Further elution of the column with 35% ethyl acetate-hexane furnished the fc-acetal **65e** (230 mg. 33%), which was recrystallized from DCM-hexane.

mp : 148-149 °C

IR : 1581cm$^{-1}$

'HNMR : 5 5.89-5.84 (2H. m), 5.57-5.51 (2H. m), 4.12-4.07 (4H. m), 3.87-3.80 (4H, m), 2.84 (2H. bs), 2.69 (2H, bs), 2.29 (2H, bs), 1.52 (1H, ½ ABq, $J$ = 11.0 Hz), 1.07 (1H, ½ ABq, $J$ = 10.9 Hz)

$^{13}$C NMR : 5 123.6(2C), 114.6, 67.2, 63.7, 53.7, 49.3, 48.8, 45.7, 32.8

Analysis : $C_{19}H_{20}O_4$ : Calcd. : C, 73.06; H, 6.45

Found : C, 73.15; **H,** 6.49

**5,5-Dimethylspiro[dihydro-4*H*-[1,3]dioxane-2,7'-hexacyclo[7.5.1.0$^{1,6}$.0$^{6,13}$.0$^{8,12}$.0$^{10,14}$]pentadeca-2',4'-diene]-15'-one 65c:**

To a solution of dione **65a** (500 mg, 2.23 mmol), in dry benzene (35 mL) was added 2.2-dimethylpropane-l,3-diol (520 mg, 5.0 mmol) along with catalytic amount of PTSA (5-10 mg). The reaction was performed as described above for 65b and 65e. Column chromatography using silica gel as the adsorbent and elution with 30% ethyl acetate-hexane furnished the *mono*-acetal 65c (589 mg, 85%) and was recrystallized from DCM-hexane.

mp : 203 °C

IR : 1740, 1581 cm$^{-1}$

$^{1}$H NMR : 5 5.94-5.88 (2H, m), 5.74-5.69 (1H, m), 5.50-5.44 (1H, m), 3.63 (1H, ½ ABq, $J$ = 11.2 Hz), 3.46-3.40 (3H, m) 3.39 (1H, ½ ABq, $J$ = 11.4 Hz). 3.10-3.03 (1H, m), 2.94-2.86 (1H, m), 2.77-2.73 (1H, m), 2.66-2.62 (1H, m), 2.50-2.43 (1H, m), 1.76 (1H, ½ ABq, $J$ = 11.6 Hz), 1.40 (1H, ½ ABq, $J$ = 10.8 Hz), 1.07 (3H, s), 0.71 (3H. s)

$^{13}$C NMR : 5 212.5, 123.8, 123.4, 122.2, 120.8, 103.7,73.0.71.1,53.7.52.4. 49.9, 49.5. 47.0, 46.4. 45.6. 42.6, 36.7. 29.9, 22.7, 21.8

Analysis : $C_{20}H_{22}O_3$ : Calcd. : C, 77.39; H. 7.14

Found : C, 77.45; H, 7.16

**15,15-Dimethoxyhexacyclo[7.5.1.0$^{1,6}$.0$^{6,13}$.0$^{8,12}$.0$^{10,14}$]pentadeca-2,4-diene-7-one 65d:**

To a solution of dione **65a** (310 mg, 1.38 mmol), in dry benzene (25 mL) was added dry methanol (7 mL) along with catalytic amount of PTSA (5-10 mg). The reaction was performed as described above. After the removal of solvent the residue was chromatographed over a silica gel column. Elution with 30% ethyl acetate-hexane afforded the *mono*-acetal **65d** (340 mg, 91%).

mp : 88-89 °C

1R : 1734, 1580cm$^{-1}$

$^{1}$H NMR : 5 5.91 (1H, dd, $J_1$ = 9.8 Hz, $J_2$ = 4.8 Hz), 5.84-5.71 (2H, m), 5.54 (1H, d, $J$= 9.8 Hz), 3.23 (3H, s), 3.13 (3H, s), 2.99-2.96 (1H, m), 2.92-2.84 (2H. m), 2.70-2.60 (2H, m), 2.53-2.46 (1H, m) 1.72 (1H, ½ ABq, ≠ 11.4 Hz), **1.33** (1H, ½ ABq, $J$ = 11.4 Hz)

$^{13}$C NMR : 5 212.5, 125.0. 123.80, 121.2, 120.8, 105.9. 56.4. 51.9, 51.5. **50.4(2C),** 50.1. 48.2, 46.5. 44.1, 42.3. 36.2

Analysis : $C_{17}H_{18}O_3$ : Calcd. : C, 75.53; H, 6.71

Found : C. 75.66; H. 6.74

**Spiro[dihydro[1,3]dithiolane-2,7'-hexacyclo[7.5.1.0$^{1,6}$.0$^{6,13}$.0$^{8,12}$.0$^{10,14}$]pentadeca-2',4'-diene]-15'-one 80a:**

To a solution of dione 65a (300 mg, 1.34 mmol). in dry benzene (25 mL) was added 1,2-ethanedithiol (0.4 mL, 4.75 mmol) along with catalytic amount of PTSA (5-10 mg). The reaction was performed as described above. Column chromatography

using silica gel as the adsorbent and elution with 10% ethyl acetate hexane furnished the *mono*-thioacetal 80a (201 mg, 50%) and was recrystallized from DCM-hexane.

mp : 157 °C

IR :1732.1583 $cm^{-1}$

$^{1}H$ NMR : 8 5.99-5.92 (2H. series of m), 5.85-5.77 (1H. m), 5.60-5.51 (1H. m), 3.35-3.11 (4H. m), 3.08-3.01 (2H, m), 2.94-2.86 (2H. m), 2.72-2.64 (2H,m), 1.84 (1H, ½ ABq. $J$ = **11.1** Hz), 1.40 (1H. ½ ABq. / = 11.6 Hz)

$^{13}C$ NMR :5 214.1. 125.5. 124.4. 123.8. 121.4. 61.4. 56.7. 56.3. 53.4. 50.7. 49.2. 48.3. 43.2. 40.1. 39.4. 23.3

LRMS : *m/z* 300 ($M^{+}$)

Analysis : $C_{17}H_{16}OS_2$ : Calcd. : C. 67.96; H. 5.37

Found :C. 67.92; H. 5.35

**Spiro[dihydro-4*H*-[1.3]dithiane-2,7'-hexacyclo[7.5.1.$0^{1.6}$.$0^{6.13}$.$0^{8.12}$.$0^{10.14}$]pentadeca-2',4'-diene]-15-one 80b:**

A mixture of dione 65a (600 mg. 2.68 mmol), 1.3-propanedithiol (0.8 ml. 7.96 mmol) and PTSA (5-10 mg) in 30 mL of dry benzene was subjected to thioacctalization as described above. The residue was chromatographed on silica gel, using 25% ethyl acetate-hexane as eiuent to furnish mono-thioacetal 80b (656 mg, 80%).

mp : 186 °C

IR : 1723, 1583 $cm^{-1}$

$^{1}H$ NMR : δ 6.07-5.63 (4H. series of m), 3.41-3.35 (1H. m), 3.21-3.17 (2H. ml,

3.07-2.76 (5H, m), 2.71-2.59 (2H, m), 2.10-1.73 (2H. series of m), 1.81 (1H, ½ ABq, $J$ = 11.2 Hz), 1.37 (1H, ½ ABq, $J$ = 11.3 Hz)

$^{13}$C NMR : 5 211.4, 124.2, 123.9, 123.3, 122.2, 62.2, 57.6. 56.4. 55.9, 51.4, 48.9. 48.5, 48.3, 43.0, 35.1, 27.9, 27.1, 24.6

LRMS : $m/z$ 314 ($M^+$)

Analysis : $C_{18}H_{18}OS_2$ : Calcd. : C, 68.75; H, 5.77

Found : C, 68.82; H, 5.74

**Hexacyclo[7.5.1.0$^{1.6}$.0$^{6.13}$.0$^{8.12}$.0$^{10.14}$]pentadeca-2,4-diene-7,15-diol 68a:**

A solution of dione 65a (500 mg, 2.23mmol) in dry methanol (30 mL) was cooled in an ice-bath and sodium borohydride (190 mg, 5.03 mmol) was added in portions. After the addition was complete, the reaction mixture was stirred for 3 h. **Methanol** was removed at room temperature under reduced pressure and the residue diluted with water (10 mL). The aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organic layer washed and dried. Removal of solvent gave crude diol **68a** (520 mg), which was passed through a silica gel pad and on elution with 40% ethyl acetate-hexane furnished diol[38a] **68a** (469 mg, 92%) as a crystalline solid.

mp : 163-164 °C

IR : 3194. 1583. **1111** cm$^{-1}$

$^1$H NMR : 5 5.90-5.85 (2H. m), 5.41-5.36 (2H. m), 5.32 (2H, bs. $D_2O$ exchangeable), 3.57 (2H. bs), 2.78 (2H. bs), 2.44 (2H. bs), 2.39 (2H, bs), 1.54(1H, ½ ABq, $J$ = 10.7 Hz), 0.92 (1H, ½ ABq, $J$ = 10.7 Hz)

$^{13}$C NMR : 5 128.0. 124.0, 76.0, 54.1, 47.5, 45.8, 42.5, 32.4

*Experimental*

**15-methylcarbonyloxyhexacyclo[7.5.1.0$^{1,6}$.0$^{6,13}$.0$^{8,12}$.0$^{10,14}$]pentadeca-2,4-dien-7-ylacetate 68b:**

To a solution of diol **68a** (500 mg, 2.19 mmol) in dry pyridine (3 mL) was added acetic anhydride (0.7 mL, 7.40 mmol) at 0 °C. The reaction mixture was further stirred for 5-6 h at room temperature and poured into 10 mL of ice-cold water. The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic extract was successively washed with 10% HC1 (5 mL), saturated NaHCO3. water and dried. The residue obtained after the removal of solvent was charged on a silica gel column. Elution with 10% ethyl acetate-hexane furnished the diacetate **68b** (410 mg, 60%) and was recrystallized from DCM-hexane.

mp : 149 °C

1R : 1723, 1256 cm'"

$^{1}$H NMR : 5 5.85-5.79 (2H, m), 5.42-5.37 (2H, m), 4.66 (2H, bs), 2.82 (2H, bs), 2.55 (4H, bs), 2.07 (6H, s), 1.59 (1H, ½ ABq, *J* = 10.8 Hz), 0.97 (1H, ½ ABq, *J* = 11.1 Hz)

$^{13}$C NMR :S 171.3, 127.1, 123.3,74.8.53.5.45.8.43.0.42.7.32.0.21.5

LRMS : *m/z* 312 (NO

Analysis : $C_{19}H_{20}O_4$ : Calcd. : C, 73.06; H. 6.45

Found : C, 73.50: H, 7.01

**7,15-Dimethoxy hexacyclo[7.5.1.0$^{1,6}$.0$^{6,13}$.0$^{8,12}$.0$^{10,14}$]pentadeca-2,4-diene 68c:**

To a suspension of NaH (140 mg, 5.83 mmol) in dry THF (2mL), a solution of diol **68a** (520 mg, 2.28mmol) in dry THF (2ML) was added under $N_2$ blanket. The mixture was stirred for 10 minutes at room temperature during which time a white

slurry was formed. To this slurry, $CH_3I$ (0.4 mL, 6.43mmol) in dry THF (1mL) was added and the mixture was stirred at room temperature for another 4 h. The reaction mixture was cooled in an ice bath and brine (10 mL) was added and the aqueous layer was extracted with DCM (3 x 15 ml). Removal of the solvent and column purification over silica gel using 10% ethyl acetate-hexane as the eluent furnished 68c as an oil (490 mg, 84%).

IR :1209.1136 $cm^{-1}$

$^1H$ NMR : 5 5.80-5.75 (2H. m), 5.44-5.38 (2H, m), 3.33 (6H, s), 3.21 (2H, bs), 2.69 (2H. bs), 2.48 (2H. bs), 2.35 (2H. bs) 1.52 (1H, *V2* ABq, *J* = 10.6 Hz), 0.90 (1H, ½ ABq. *J* = 10.6 Hz)

$^{13}C$ NMR : 5 128.8. 122.6, 83.9. 57.8, 54.4. 46.5. 42.8. 42.1, 32.1

Analysis : $C_{17}H_{20}O_2$ : Calcd. : C. 79.65: H. 7.86

Found :C. 79.71; H, 7.42

**8-Methylcarbonyloxy-1,4-dioxo-1,4-dihydro-5-naphthalenylacetate 101a:**

A mixture of naphthazarin[58] **100** (950 mg, 5 mmol), pyridine (4 mL) and acetic anhydride (1.5 mL, 15.9 mmol) were stirred at room temperature for 4 h. The reaction mixture was poured into 15 mL of ice-cold water and the aqueous layer was extracted with ether (3 x 25 mL). The combined ethereal extract was washed thoroughly with 10% HC1, 10% $NaHCO_3$, water and dried. Removal of the solvent turnished a residue which was filtered through a silica gel pad to furnish **101a** (754 mg, 55%) and was recrystallized from DCM-hexane.

mp : 191-192 °C (lit.[58] 192-193 °C)

IR : 1770, 1670, 1200, 1100 $cm^{-1}$

*Experimental*

$^1$H NMR : 5 7.40 (2H, s), 6.81 **(2H,** s), 2.44 (6H, s)

**8-Methylcarbonyloxy-3,10-dioxotetracyclo[10.2.1.0$^{2,11}$.0$^{4,9}$]pentadeca-4,6,8,13-tetraen-5ylacetate 102a:**

To an excess of freshly cracked cyclopentadiene (193 mg, 2.92 mmol) was added to a solution of the quinone **101a** (400 mg, 1.46 mmol) in dry benzene and the reaction mixture was stirred at room temperature for 2 h. Removal of the solvent under vacuum gave a residual solid, which was washed with cold hexane to remove excess cyclopentadiene. The crude adduct was then crystallized from DCM-hexane to furnish pure **102a** (471 mg. 95%).

mp : 152-153 °C

IR : 1769. 1692. 1590. 1180 cm$^{-1}$

$^1$H NMR : 5 7.27 (2H. s), 6.10 (2H. bs), 3.50 (4H. bs). 2.35 (6H. s), 1.58 (1H. ½ ABq with **St.. *J*** = **8.8** Hz). 1.45 (1H. ½ ABq. *J* = 8.9 Hz)

$^{13}$C NMR : 8 196.3. 169.4. 146.0. 136.4. 130.3. 129.1. 52.1. 48.5. 46.9. 21.0

Analysis : $C_{19}H_{16}O_6$ : Calcd. : C. 67.05: H. 4.74

Found : C, 66.82: H. 4.55

**5.8-Dimethoxy-1.4-dihydro-l,4-naphthalenedione 101b:**

To a solution of naphthazarin[58] **100** (1.5 g, 7.89 mmol) in dry chloroform (40 mL), silver(I) oxide (2.25 g. 9.71 mmol) and $CH_3I$ (1.2 mL. 19.28 mmol) were added over a period of 15 minutes at ice-bath temperature. The cooled reaction mixture was then vigorously stirred for 18 h. The reaction mixture was filtered through celite, the filtrate was evaporated to dryness under reduced pressure and the residue was charged on a silica gel column. Elution with 15% ethyl acetate-hexane afforded

mono-methylated product (350 mg, 22%). Continued elution of the column gave the dimethylated compound **101b** (355 mg, 21%) and was recrystallized from DCM-hexane.

mp : 159 °C (lit.[59] 160 °C)

IR :1660,1269 $cm^{-1}$

$^1H$ NMR : 5 7.34 (2H, s), 6.79 (2H, s), 3.97 (6H, s)

**5,8-Dimethoxytetracyclo[10.2.1.$0^{2,11}$.$0^{4,9}$]pentadeca-4,6,8,13-tetraene-3,10-dione 102b:**

Freshly cracked cyclopentadiene (180 mg, 2.73 mmol) was added to a solution of the quinone **101b** (300 mg, 1.38 mmol) in dry benzene and the reaction mixture was stirred at room temperature for 2 h. Removal of the solvent under vacuum gave a residual solid, which was washed with cold hexane to remove excess cyclopentadiene. The crude adduct was then crystallized from DCM-hexane to furnish pure **102b** (367 mg, 94%).

mp : 158 °C

IR : 1685, 1584, 1269 $cm^{1}$

$^1H$ NMR : 5 7.11 (2H, s), 6.07 (2H.bs), 3.85 (6H,s), 3.51 (2H. bs), 3.46 (2H. bs), 1.56 (1H, ½ ABq, *J*= 10 Hz). 1.44 (1H. ½ ABq. *J* = 10 Hz)

$^{13}C$ NMR : 5 196.9, 151.4, 136.5, 128.0, 118.0, 56.9. 52.9. 48.0. 45.5

Analysis : $C_{17}H_{16}O_4$ : Calcd. : C. 71.82: H. 5.67

Found : C, 72.05; H. 5.70

**General Procedure for Photooxygenation of dienes:**

*Experimental*

In **a** small irradiation vessel fitted with an outer jacket for cold water circulation was placed diene (0.35 mmol), methylene blue (7 mg) and 25 mL of dry chloroform. The solution was irradiated with a 500 W tungsten lamp, placed about a foot away, under slow stream of bubbling oxygen for 3-6 h. Reactions were continuously monitored by tlc and continued until most of the starting material was consumed. At the end of the reaction, chloroform was removed under vacuum at room temperature to give a diastereomeric mixture of endoperoxides in good yield. The product ratios were determined by $^1H$ NMR analyses of the crude reaction mixture by comparing the integrations of appropriate protons.

**Photooxygenation** of **65a:**

The reaction was performed as described in the general procedure to furnish **72a** : **73a** (78 : 22) in 88% yield (based on starting material recovery). The minor isomer **73a** had almost the same $R_f$ as that of the starting material. Therefore. monitoring the completion of reaction and separation were done carefully. The isomers were separated by column chromatography using silica gel and elution **with** 20% ethyl acetate-hexane initially provided the minor isomer along with some starting material. Further elution with 50% ethyl acetate-hexane furnished the pure major isomer **72a.**

**72a:**

mp : 243 °C

IR : 1728, 1225, 1105 $cm^{-1}$

$^1H$ NMR (Spectrum 1) : 5 6.83 (2H, dd, $J_1$ = 4.5 Hz, $J_2$ = 3.4 Hz), 4.94 (2H, dd, $J_1$ = 4.4 Hz, $J_2$ = 3.4 Hz), 2.94 (2H, bs), 2.86 (2H, bs), 2.73 (2H, bs), 2.03 (1H.

½ ABq, $J$ = 11.3 Hz), 1.82 (1H, ½ ABq, $J$ = 11.5 Hz)

$^{13}$C NMR : δ 208.1, 131.4, 69.5, 55.4, 48.0, 43.6, 40.6, 40.4

(Spectrum 2)

LRMS : $m/z$ 256 ($M^+$)

Analysis : $C_{15}H_{12}O_4$ : Calcd. : C, 70.31; H, 4.72

Found : C, 70.22; H, 4.75

**73a:**

mp : 240 °C (decomp.)

IR : 1726, 1298, 1105, 908 cm$^{-1}$

$^1$H NMR : δ 6.78 (2H, dd as t, $J$ = 3.9 Hz), 4.70 (2H, dd as t, $J$ = 3.9 Hz),

(Spectrum 3) 3.45 (2H, bs), 3.09-3.07 (2H, m), 2.72 (2H, bs), 2.11 (2H, bs)

$^{13}$C NMR : δ 208.4, 131.6, 70.9. 55.3, 44.3,42.0. 39.2 .

(Spectrum 4)

LRMS : $m/z$ 256 ($M^+$)

Analysis : $C_{15}H_{12}O_4$ : Calcd. : C. 70.31; H, 4.72

Found : C. 69.52; H, 4.62

Photooxygenation of **65b**:

The reaction was performed as described in the general procedure to furnish **72b** : **73b** (14 : 86) in 92% yield. The two stereoisomers were separated by column chromatography using silica gel and elution with 35% ethyl acetate-hexane.

72b:

mp : 133-134 °C

IR : 1744, 1319, 1051 cm$^{-1}$

*Experimental*

$^{1}$H NMR : 5 6.88-6.73 (2H. m), 4.98-4.91 (1H, m), 4.82-4.77 (1H. m), 4.18-3.90 (4H, m), 2.75-2.71 (1H, m), 2.63 (3H, bs). 2.51-2.44(1H. m), **2.37-2.30 (lH,m),** 1.83 (1H, ½ ABq, $J$ = 11.2 Hz), 1.50 (1H, ½ ABq, $J$ = 10.8 Hz)

$^{13}$C NMR : 5 210.9. 132.5. **131.1,** 113.3, 70.9, 69.4, 66.4, 66.1, 55.6, 51.7, 48.1, 45.9.43.4(2C),42.1,39.0.38.7

LRMS : $m/z$ 300 ($M^+$)

Analysis : $C_{17}H_{16}O_5$ : Calcd. : C. 67.99; H, 5.37
Found :C. 68.15; H. 5.40

**73b:**

mp : 150-151 °C

IR : 1738. 1321, 1069 cm$^{-1}$

$^{1}$H **NMR** : 5 6.83-6.75 (1H. m), 6.67-6.59 (1H. m), 4.69 (2H. t. $J$ = 5.8 Hz), 3.96-3.77 (4H. m), 3.35-3.25 (1H. m). 3.12-3.04 (1H. m), 2.88-2.83 (1H. m), 2.78-2.73 (1H. m), 2.61-2.53. (1H. m), 2.48-2.41 (1H. m), 1.93 (1H. ½ ABq, $J$ = 10.9 Hz), 1.79 (1H. ½ ABq. $J$= 11.3 Hz)

$^{13}$C NMR : δ 211.2. 131.0. 130.9. 111.4. 71.8. 71.1. 65.8. 65.1. 54.8. 52.9. 51.5. 50.9. 43.9. 42.3. 42.1, 40.1. 36.9

LRMS : $m/z$ 300 ($M^+$)

Analysis : $C_{17}H_{16}O_5$ : Calcd. : C. 67.99: H. 5.37
Found : C. 67.85; H. 5.35

**Photooxygenation** of **65c:**

The reaction was performed as described in the general procedure to furnish 73c (single isomer) in 98% yield. The endoperoxide 73c was purified by column chromatography over silica gel with 30% ethyl acetate-hexane as the solvent system.

**73c:**

mp : 222-223 °C

IR : 1744. 1325, **1121,** 1032 $cm^{-1}$

$^{1}H$ NMR : 5 6.69 (2H, t, *J* = 3.7 Hz), 4.84-4.79 (1H, m), 4.68-4.65 (1H, m), 3.59 (1H, d, J= 11.4 Hz), 3.49-3.23 (5H, m), 3.06-2.98 (1H, m), 2.78-2.71 (2H, m), 2.40-2.32 (1H, m), 1.90 (1H, ½ ABq. *J* = 11.2 Hz), 1.76 (1H, ½ **ABq,** *J* = 10.9 Hz), 1.06 (3H. s). 0.69 (3H, s)

$^{13}C$ NMR : 5 210.6. 132.0, 129.5, 101.4, 72.9, 71.8, 71.2, 71.0, 54.6, 50.2, 48.0, 44.0, 42.0, 41.9. 39.8. 36.9. 29.8. 22.8, 21.7

Analysis : $C_{20}H_{22}O_5$ : Calcd. : C. 70.16; H, 6.48

Found : C. 70.20; H. 6.50

**Photooxygenation** of 65d:

The reaction was performed as described in the general procedure to furnish 73d (single isomer) in 70% yield (based on starting material recovery). The cndoperoxide **73d** was purified by column chromatography over silica gel with 25% ethyl acetate-hexane as the solvent system.

73d:

mp :151°C

IR : 1738, 1121, 1059 $cm^{-1}$

'H NMR : 5 6.78-6.64 (2H, m), 4.83 (1H, d, *J* = 5.7 Hz), 4.66 (1H, d with st., *J*

= 5.7 Hz), 3.26 (4H, bs), 3.16 (3H, s), 3.08-3.00 (1H, m), 2.87-2.69 **(3H, m), 2.41-2.33 (1H,** m), 1.89 (1H, ½ ABq, *J* = 10.8 Hz), 1.75 (1H, ½ ABq, *J* = 11.3 Hz)

$^{13}$C NMR : 5 210.6, 130.8, 130.5, 105.2, 72.8, 70.9, 55.6, 53.8, 52.4, 50.9, 50.5. 49.5, 44.1, 42.9, 42.0, 39.8, 36.7

Analysis : $C_{17}H_{18}O_5$ : Calcd. : C, 67.54; H, 6.00
Found : C, 67.58; H, 6.02

**Photooxygenation** of **65e:**

The reaction was performed as described in the general procedure to furnish 72e : 73e (3 : 97) in 91% yield. The two stereoisomers were separated by column chromatography using silica gel and elution with 35% ethyl acetate-hexane.

72e:

$^1$H NMR (*from mixture*) : 5 6.73 (2H. dd as t, *J* = 3.5 Hz), 4.78 (2H. dd as t. *J* = 3.5 Hz). **4.21-**4.06 (4H. m), 3.99-3.91 (4H. m), 2.57 (2H, bs), 2.38 (2H. bs). 2.15 (2H. bs), 1.63 (1H. ½ ABq, *J* = 10.7 Hz), 1.42 (1H, ½ ABq, *J* = 10.7 Hz)

73e:

mp : >230 °C (sublimes)

IR : 1316. 1157. 1026 cm$^{-1}$

$^1$H NMR (Spectrum 5) : 5 6.73 (2H. dd as t. *J* = 3.5 Hz), 4.65 (2H, dd as t, *J* = 3.5 Hz). 3.99-3.91 (4H, m), 3.87-3.73 (4H. m), 2.95 (2H, bs), 2.67 (2H, bs), 2.26 (2H,bs), 1.63 (1H, ½ ABq, *J* = 10.7 Hz), 1.42 (1H, ½ ABq, *J* = 10.7 Hz)

$^{13}C$ NMR : 5 131.1, 112.5, 72.3, 66.6, 63.1, 50.9, 48.9, 44.1, 40.4, 36.0
(Spectrum 6)

LRMS : *m/z* 344 ($M^+$)

Analysis : $C_{19}H_{20}O_6$ : Calcd. : C, 66.27; H, 5.85
Found : C, 66.35; H, 5.88

**Photooxygenation of 80a:**

The reaction was performed as described in the general procedure to furnish 82a (single isomer) in 157c yield (low yield was due to other competing reactions in the oxidative milieu). The endoperoxide **82a** was purified by column chromatography over silica gel with 25% ethyl acetate-hexane as the solvent system.

$^1H$ NMR : 8 6.78-6.74 (2H. m). 4.99-4.91 (1H, m). 4.74-4.68 (1H, m), 3.48-3.00 (8H, series of m). 2.75-2.70 (1H, m). 2.58-2.51 (1H, m). 2.00 (1H, ½ ABq, $J$ = 11.0 Hz), 1.78 (1H, ½ ABq, $J$ = 11.1 Hz)

**Photooxygenation of 80b:**

The reaction was performed as descnbed in the general procedure to furnish **82b** (single isomer) in 81% yield. The endoperoxide **82b** was purified by column chromatography over silica gel with 25% ethyl acetate-hexane as the solvent system.

mp : 213 °C

IR :1728.1277,737 $cm^{-1}$

$^1H$ NMR : δ 6.81 (2H, dd as t. $J$ = 3.8 Hz), 4.95-4.88 (1H, m), 4.78-4.75 (1H. m), 3.71-3.62 (1H, m), 3.47-3.39 (1H, m), 3.22-2.58 (8H, series of m), 2.11-2.01 (1H, m), 2.00(1H. ½ ABq, $J$ = 12.4 Hz), 1.85-1.60 (1H, m), 1.77 (1H, ½ ABq, $J$ = 10.8 Hz)
(Spectrum 7)

*Experimental*

$^{13}C$ NMR : 5 210.2. 132.0, 131.2, 73.2, 71.0, 58.1, 57.9, 52.0, 51.1, 46.9, 44.4,
(Spectrum 8) 42.1. 38.9, 36.2, 28.6, 26.5, 24.8

LRMS : *m/z* 346 ($M^+$)

Analysis : $C_{18}H_{18}O_3S_2$ : Calcd. : C, 62.40; H, 5.24
Found : C. 62.50; **H.** 5.28

**Photooxygenation of 68a:**

The reaction was performed as described in the general procedure to furnish **92a** : **93a** (79 : 21) in 70% yield. The two stereoisomers were separated by column chromatography using silica gel and elution with 35% ethyl acetate-hexane.

**92a:**

IR : 3150. 1640. 1260. 1100 $cm^{-1}$

$^1H$ NMR : 5 6.80-6.76 (2H. m), 4.81-4.77 (2H. m), 4.00 (2H. bs), 2.55 (2H. bs),
(Spectrum 9) 2.32 (2H. b.s). 2.09 (2H, bs), 1.60 (1H, ½ ABq. *J* = 10.7 Hz), 1.00
(1H. ½ ABq, *J* = 10.7 Hz)

$^{13}C$ NMR : 5 131.9. 76.2. 74.4. 46.4. 44.0. 42.1. 41.4. 34.3
(Spectrum 10)

Analysis : $C_{15}H_{16}O_4$ : Calcd. : C, 69.21; H. 6.20
Found : C, 69.52; H. 6.22

**93a:**

mp : 155-156 °C

IR : 3274. 1254, 1109, 1063 $cm^{-1}$

$^1H$ NMR : 5 6.76-6.72 (2H. m), 4.60-4.56 (2H, m), 3.74 (2H. bs), 2.87 (2H. bs),
(Spectrum 11) 2.43 (4H. bs), 1.69 (1H. ½ ABq. *J* = 10.7 Hz), 1.29 (1H, ½ ABq. *J* =

10.7 Hz)

$^{13}C$ NMR : 5 131.3, 76.1, 71.3, 50.4, 46.5, 41.3, 40.4, 35.5

(Spectrum 12)

Analysis : $C_{15}H_{16}O_4$ : Calcd. : C, 69.21; H, 6.20

Found : C. 69.28; H, 6.23

**Photooxygenation** of 68b:

The reaction was performed as described in the general procedure to furnish 92b : **93b** (79 : 21) in 90% yield. The two stereoisomers were separated by column chromatography using silica gel and elution with 10% ethyl acetate-chloroform.

92b:

mp : 236 °C

IR : 1726, 1368, 1260, 1101 $cm^{-1}$

$^1H$ NMR : 5 6.71 (2H, dd as t, $J$ = 4.0 Hz), 5.13 (2H, bs). 4.82-4.78 (2H. **m),**

**(Spectrum** 13) 2.53 (2H. bs). 2.42 (2H. bs), 2.11 (8H, s). 1.65 **(1H.** ½ ABq, $J$ = 10.8 Hz), 1.06 f 1H. ½ ABq, $J$ = 10.8 Hz)

$^{13}C$ NMR :5 171.7. 132.0. 74.1. 71.6. 43.7. 43.6. 41.9(2C). 34.1. 21.6

(Spectrum 14)

LRMS : $m/z$ 344 ($M^+$)

Analysis : $C_{19}H_{20}O_6$ : Calcd. : C. 66.27; H. 5.85

Found : C. 66.33; H, 5.55

93b:

mp : 220 °C (sublimes), 225 °C (melts)

IR : 1726. 1368. 1252. 1057 $cm^{-1}$

*Experimental*

$^1$H NMR : 5 6.53-6.50 (2H, m), 4.76 (2H, bs), 4.69-4.65 (2H, m), 2.97 (2H, bs), 2.51 (4H, bs), 2.01 (6H, s), 1.75 (1H, ½ ABq, $J$ = 10.7 Hz), 1.34 (1H, ½ ABq, $J$ = 10.7 Hz)

(Spectrum 15)

$^{13}$C NMR : 5 170.9, 131.4, 75.3, 70.6, 48.6, 43.4, 41.4, 40.5, 35.4, 21.4

(Spectrum 16)

Analysis : $C_{19}H_{20}O_6$ : Calcd. : C, 66.27; H, 5.85

Found : C, 66.32; H, 5.88

**Photooxygenation of** 68c:

The reaction was performed as described in the general procedure to furnish **93c** (single isomer) in 817c yield. The endoperoxide 93c was purified by column chromatography over silica gel with 25% ethyl acetate-hexane as the solvent system.

**93c:**

mp : 145-146 °C

IR : 1231. 1208. 1128 cm$^{-1}$

$^1$H NMR : 5 6.76-6.72 (2H, m), 4.57-4.53 (2H, m), 3.27 (8H. s). 2.84 (2H. bs). 2.56 (2H. bs), 2.37 (2H, s), 1.70 (1H, ½ ABq, $J$ = 10.4 Hz). 1.30 (1H. ½ ABq. $J$ = 10.5 Hz)

(Spectrum 17)

$^{13}$CNMR : 5 130.5, 80.0. 57.7, 49.5. 41.9, 40.9. 40.3, 35.4

(Spectrum 18)

LRMS : $m/z$ 256 ($M^+$-32)

Analysis : $C_{17}H_{20}O_4$ : Calcd. : C, 70.81; H, 6.99

Found : C, 70.88; **H,** 7.05

**General procedure for photooxygenation of 102a and 102b:**

In a small irradiation vessel was placed tricyclic adduct (0.21mmol), methylene blue (3 mg) and ethyl acetate (25 mL). After bubbling a slow stream of $O_2$ for 10 minutes, the solution was irradiated with 450 W Hanovia medium pressure mercury vapour lamp for 120 **(102a)** or 15 **(102b)** minutes using pyrex filter. Cold water was continuously circulated to maintain a temperature of 10-15 °C. The reaction was monitored by tlc and at the end of the reaction, solvent was removed under vacuum at room temperature gave the endoperoxide. The $^1H$ NMR analysis of crude reaction mixture indicated the presence of a single isomer.

**Photooxygenation of 102a:**

The reaction was performed as described in the general procedure to furnish 104a (single isomer) along with the rearranged epoxide **105** in overall 35% yield. The compounds were separated by column chromatography over silica gel with 20% ethyl acetate-hexane as the solvent system.

**104a:**

mp : 179-180 °C

IR : 1773, 1740, 1368. 1217, 1163 $cm^{-1}$

'H NMR : 5 6.79 (2H. s), 3.55 (2H. bs), 3.13 (2H. bs), 2.78 (2H, bs),

(Spectrum 19) 2.12 **(8H,S)**

$^{13}C$ NMR : 5 205.7, 167.1, 132.4. 98.2. 59.4. 55.9. 44.1. 41.2. 39.5. 21.3

(Spectrum 20)

Analysis : $C_{19}H_{16}O_8$ : Calcd. : C, 61.29; H, 4.33

Found : C, 61.34; H, 4.34

**105:**

*Experimental*

mp : 191-192 °C

IR : 1755. 1217, 1179, 1036 $cm^{-1}$

$^{1}H$ NMR : 5 3.68 (2H, s), 3.58-3.57 (2H, m), 3.04-3.03 (2H, m). 2.86-2.85 (2H. m), 2.00 (6H, s), 1.95(2H.bs)

$^{13}C$ NMR : 5 207.7. 170.8, 76.1, 57.7. 53.4, 51.6. 45.9, 43.7, 39.6. 20.7

FABMS : *m/z* 379 {[M+Li]$^{+}$}

Analysis : $C_{19}H_{16}O_8$ : Calcd. : C. 61.29; H, 4.33

Found : C. 61.21; H. 4.29

**Photooxygenation of 102b:**

The reaction was performed as described in the general procedure to furnish **104b** (single isomer) in overall 60% yield. **The** endoperoxide was separated by column chromatography over silica gel with 20% ethyl acetate-hexane as the solvent system.

mp : 204 °C

IR : 1762. 1236. 1057 $cm^{-1}$

$^{1}H$ NMR : 5 6.78 (2H. s), 3.52 (8H. s). 3.06-3.04 (2H. m). 2.75 (2H. bs). 2.10 (2H. bs)

(Spectrum 21)

$^{13}C$ NMR : 5 206.3. 132.2. 100.6. 60.1. 56.1. 53.8. 43.7. 41.7. 38.5

(Spectrum 22)

Analysis : $C_{17}H_{16}O_6$ : Calcd. : C. 64.55; H. 5.10

Found : C. 64.70; H. 5.12

**General Procedure for the [4+2]-cycIoadditions with PTAD:**

PTAD was prepared as follows: To a stirred suspension of *N*-phenylurazole (0.5 mmol) in DCM cooled in an ice-bath (0-5 °C), was added a solution of 'oxides of nitrogen' (usually regarded as a mixture of $N_2O_4$, $N_2O_3$ and NO:)[47] in DCM. This was prepared according to the literature procedure[46] by treating arsenious oxide with conc. $HNO_3$ and the resulting gaseous mixture was bubbled through a DCM solution cooled in an ice-bath (0-5 °C). The reaction mixture turned red and was stirred for additional 30 minutes to get a clear homogeneous red solution of *N*-phenyl-1,2,4-tnazoline-3.5-dione (PTAD) in DCM, which was used for the cycloadditions.

To an ice-cooled solution of diene (0.35 mmol) in DCM (10 mL) was slowly added, drop-wise, a solution of PTAD (0.40 mmol) in DCM (5 mL). The solution was stirred at 0-5 °C for 1 h until the red color had disappeared and completion of the reaction was monitored by tlc analysis. DCM was removed at room temperature under reduced pressure to give a solid residue, which was analyzed using $^1H$ NMR spectroscopy to determine the product ratios.

**PTAD addition to 65a:**

The reaction was performed as described in the general procedure to furnish **74a** : **75a** (64 : 36) in 80% yield. The diastereomers were separated by column chromatography using neutral alumina and elution with 70% ethyl acetate-chloroform.

74a:

mp : 300 °C (lit.[37a] 300-301 °C)

IR :1740.1705,1500.1400,1370 $cm^{-1}$

'H NMR : 5 7.44-7.33 (5H. m), 6.69 (2H, t. *J*= 3.0 Hz), 5.19 (2H. t, *J* = 3.0

(Spectrum 23) Hz), 3.00 (2H, bs), 2.91 (2H, bs), 2.80 (2H, bs), 2.07 (1H, ½ ABq, *J* = 10.7 Hz), 1.88 (1H, ½ ABq, *J* = 11.4 Hz)

**75a:**

mp : 311 °C (lit.[37a] 311-312 °C)

IR :1740,1710,1405,1375 cm$^{-1}$

$^1$H NMR : 5 7.47-7.42 (5H, m), 6.62 (2H, t, *J* = 4.0 Hz), 5.04 (2H, t, *J* = 4.0

(Spectrum 24) Hz), 3.44 (2H, bs), 3.12 (2H, bs), 2.79 (2H, bs), 2.13 (2H, bs)

PTAD addition to 65c:

The reaction was performed as described in the general procedure to furnish 75c (single isomer) in 85% yield and was purified by column chromatography over silica gel with 25% ethyl acetate-hexane as the solvent system.

75c:

mp : 240 °C

IR : 1750. 1715. 1399, 1125 cm$^{-1}$

$^1$H NMR : 5 7.47-7.38 (5H. m). 6.53 (2H. t. *J* = 4.0 Hz). 5.26 (1H. t. *J* = 4 Hz). 5.03 (1H. t. *J* = 4 Hz), 3.64 (1H. d. *J* = 11.2 Hz), 3.53-3.30 (4H. m) 3.27-3.20 (1H. m), 3.03-2.97 (1H. m), 2.83-2.72 (2H. m). 2.49-2.42 (1H. m), 1.94 (1H. ½ ABq, *J*= 12.8 Hz), 1.75 (1H, ½ ABq, *J*= 10.9 Hz), 1.10 (3H. s), 0.73 **(3H,s)**

$^{13}$C NMR : 5 209.1, 156.2(2C), 131.5, 130.4. 129.1(2C), 128.2. 127.8. 125.6 (2C), 101.5, 73.0, 71.1, 56.1, 51.7, 51.5. 51.0, 50.2, 47.9, 44.3. 42.8. 42.0,39.7,37.7,29.8,22.9,21.7

Analysis : $C_{28}H_{27}N_3O_5$ : Calcd. : C, 69.26; H, 5.61; N, 8.65

Found : C, 69.31; H, 5.59; N, 8.70

**PTAD addition to 80a:**

The reaction was performed as described in the general procedure to furnish **74a** : **75a** (9 : 91) in 75% overall yield. Addition of PTAD accompanied by concomitant dethioacetalization furnished **74a** and **75a,** which were separated by column chromatography using neutral alumina and elution with 70% ethyl acetate-chloroform. The two products **74a** and **75a** were found to be identical with the products obtained from PTAD addition to **65a.**

**PTAD addition to 80b:**

The reaction was performed as described in the general procedure to furnish 74a : 75a (11 : 89) in 80% overall yield. Addition of PTAD accompanied by concomitant dethioacetalization furnished **74a** and **75a.** which were separated by column chromatography using neutral alumina and elution with 70% ethyl acetate-chloroform. The two products **74a** and **75a** were found to be identical with the products obtained from PTAD addition to **65a.**

**PTAD addition to** 68a:

The reaction was performed as described in the general procedure to furnish **94a** (single isomer. >96%) in 75% yield and was purified by column chromatography over silica gel with 60% ethyl acetate-hexane as the solvent system.

**94a:**

mp : 270 °C (darkens). 272 °C (melts)

IR : 3302 (br), 1757, 1690, 1408, 1113 $cm^{-1}$

$^1H$ NMR : 5 7.45-7.37 (5H, m), 6.65 (2H, t, $J$ = 3.7 Hz), 5.01 (2H, t, $J$ = 3.6

Hz), 4.05 (2H, bs), 3.29 (2H, bs, $D_2O$ exchangeable), 2.56 (2H, bs), 2.35 (2H, bs), 2.14 (2H, bs), 1.64 (1H, ½ ABq, $J$ = 10.8 Hz), 1.06 (1H, ½ ABq, $J$ = 10.8 Hz)

$^{13}C$ NMR : 5 155.7, 130.3, 129.1, 128.2, 125.7, 74.0, 55.2, 46.5, 41.6, 41.0, 34.5

Analysis : $C_{23}H_{21}N_3O_4$ : Calcd. : C, 68.47; H. 5.25; N. 10.42

Found : C, 68.55; H. 5.28; N, 10.48

**PTAD addition to** 68b:

The reaction was performed as described in the general procedure to furnish **94b** (single isomer, >96%) in 78% yield and was purified by column chromatography over silica gel with 35% ethyl acetate-hexane as the solvent system.

**94b:**

mp : 228 °C (darkens). 244 °C (melts)

IR : 1739. 1713, 1404. 1248. 1057 cm $^{-1}$

$^1H$ NMR : 5 7.52-7.32 (5H. m), 6.62 (2H. t, $J$ = 3.6 Hz), 5.17 (2H. bs). 5.08

(Spectrum 25) **l2H.** t. $J$ = 3.6 Hz). 2.62 (2H. bs). 2.50 (2H. bs). 2.21 (2H. bs), 2.04 |6H. s), 1.69 (1H. ½ ABq, $J$ = 10.6 Hz), 1.13 **(1H.** ½ ABq, $J$= 10.9 Hz)

$^{13}C$ NMR :5 170.7. 154.7, 130.2, 128.9. 127.8, 124.9.71.8.54.1.45.8.43.4.

(Spectrum 26) 41.8.41.2.34.2.21.3

Analysis : $C_{27}H_{25}N_3O_6$ : Calcd. : C. 66.52; H. 5.17; N. 8.62

Found : C, 66.65; H. 5.12; N. 8.70

**PTAD addition to 68c:**

The reaction was performed as described in the general procedure to furnish 95c (single isomer, >98%) in 78% yield and was purified by column chromatography over silica gel with 30% ethyl acetate-hexane as the solvent system.

95c:

IR : 1769. 1713, 1404. 1119 $cm^{-1}$

$^1H$ NMR (Spectrum 27) : 5 7.47-7.32 (5H. m), 6.56 (2H. t, $J$ =3.4 Hz), 4.89 (2H. t, $J$ = 3.4 Hz), 3.43 (2H. bs), 3.30 (6H. s), 2.78 (2H, bs), 2.59 (2H. bs), 2.41 (2H. bs), 1.72 (1H, ½ABq. $J$ = 10.6 Hz), 1.29 (1H. ½ ABq, $J$ = 9.0 Hz)

$^{13}C$ NMR (Spectrum 28) :5 156.1, 129.0. 128.7. 128.1. 125.6. 80.7. 57.8. 55.9. 50.6. 42.1. 41.1,40.9,35.2

Analysis : $C_{25}H_{25}N_3O_4$ : Calcd. : C. 69.59; H. 5.84: N. 9.74

Found : C. 69.65: H. 5.86: N. 9.78

General procedure for the [4+2]-cycIoadditions with DMAD:

A solution of diene (0.30 mmol) and DMAD (0.31 mmol) in dry benzene was refluxed for 12-18 h. Benzene was removed under vacuum to give a diastereomeric mixture of adducts. The product ratios were determined by $^1H$ NMR analyses of the crude reaction mixture by comparing the integrations of appropriate protons.

**DMAD addition to 65a:**

The reaction was performed as described in the general procedure to furnish 76a : **77a** (55 : 45) in 85% yield. The diastereomers were separated by column chromatography using silica gel and elution with 30% ethyl acetate-hexane.

76a:

*Experimental*

mp : 274 °C (lit.[37a] 275-278 °C)

IR :1752,1713,1277 $cm^{-1}$

$^1H$ NMR : 5 6.65 (2H, t, *J* = 4.0 Hz), 4.07 (2H, t, *J* = 4.0 Hz), 3.80 (6H, s), 2.93 (2H, bs), 2.65 (4H, bs), 1.99 (1H, ½ ABq, *J*= 11.6 Hz), 1.87 (1H, ½ ABq, *J* = 11.5 Hz)

77a:

mp : 190 °C (lit.[37a] 188-189 °C)

IR : 1760, 1710, 1271 $cm^{-1}$

$^1H$ NMR : 8 6.57 (2H, t, *J* = 4.0 Hz), 3.99 (2H, t, *J* = 4.0 Hz), 3.82 (6H. s). 2.94 (2H, bs), 2.76 (2H. bs), 2.65 (2H, bs), 1.99 (1H, ½ ABq, *J* = 11.2 Hz), 1.89 (1H, ½ ABq. *J* = 11.2 Hz)

**DMAD addition to 65b:**

The reaction was performed as described in the general procedure to furnish **76b** : 77b (17 : 83) in 91% yield. The diastereomers were separated by column chromatography using silica gel and elution with 35% ethyl acetate-hexane.

**76b:**

mp : 184 °C

IR : 1742, 1711, 1437, 1265. 1065 $cm^{-1}$

$^1H$ NMR : δ 6.63 (2H, t. *J* = 2.7 Hz), 4.10-3.90 (6H. m), 3.82 (3H, s), 3.69 (3H. s), 2.75-2.14 (6H, series of multiplets), 1.78 (1H, ½ ABq, *J*= 10.9 Hz), 1.55 (1H, ½ ABq, *J* = 10.9 Hz)

$^{13}C$ NMR : δ 212.7, 166.3, 166.1, 143.2, 142.5, 135.2, 135.0, 112.4, 66.1, 64.9, 59.0, 56.1, 53.1, 52.2, 51.9, 50.8, 44.0, 43.0, 42.2, 40.2, 39.6. 39.3.

38.2

Analysis : $C_{23}H_{22}O_7$ : Calcd.: C, 67.31; H, 5.40
Found : C, 67.45; H, 5.40

77b:

mp :159°C

IR : 1738, 1262, 1076 $cm^{-1}$

$^1H$ NMR : δ 6.52 (1H, t, *J* = 6.4 Hz), 6.32 (1H, t. *J* = 6.4 Hz), 3.98-3.72 (6H, m), 3.77 (3H, s), 3.75 (3H, s), 2.68-2.25 (6H, series of multiplets), 1.75 (1H. ½ ABq, *J* = 10.8 Hz), 1.54 (1H, ½ ABq, *J* = 10.8 Hz)

"CNMR : δ 212.7, 166.4, 166.2. 143.7, 143.1, 133.2, 132.6, 113.0, 65.8, 65.1, 58.3, 55.5, 53.9, **52.3(2C),** 50.9, 43.7. 43.1. 42.1. 40.1, 39.7. 39.0. 38.0

Analysis : $C_{23}H_{22}O_7$ : Calcd. : C. 67.31; H. 5.40
Found : C. 67.35; H, 5.40

**DMAD addition** to 65c:

The reaction was performed as described in the general procedure to furnish 76c : 77c (5 : 95) in 92% yield. The diastereomers were separated by column chromatography using silica gel and elution with 30% ethyl acetate-hexane.

76c:

mp : 190-191 °C

IR : 1748, 1709, 1281, 1119 $cm^{-1}$

$^1H$ NMR : δ 6.70-6.59 (2H, m), 4.34 (1H, d, *J* = 4.5 Hz), 3.94 (1H, d, *J* = 4.5 Hz), 3.80 (3H, s), 3.69 (3H, s), 3.67 (1H, d, *J* = 9.3 Hz), 3.43-3.31

(4H, m), 2.62-2.57 (2H, m), 2.45 (1H, t, $J$ = 6 Hz), 2.33 (1H, dd, $J_1$ -- 10 Hz, $J_2$ = 2 Hz), 2.12 (1H, t, $J$ = 6.5 Hz), 1.77 (1H, ½ ABq, $J$ = 10.8 Hz), 1.52 (1H, ½ ABq, $J$ = 10.9 Hz), 1.05 (3H, s), 0.70 (3H, s)

$^{3}$C NMR : 5211.2, 166.7, 165.5, 144.2, 142.1, 135.9, 135.2, 102.8.73.2,70.8, 60.7. 54.8, 52.1. 51.7, 49.6. 46.6. 43.8, 43.3, 42.0. 39.7. 39.3, 39.1, 38.4. 29.5, 23.4, 22.5

Analysis $C_{26}H_{28}O_7$ : Calcd. : C, 69.01; H, 6.24
Found : C, 69.12; H. 6.28

77c

mp : 181-182°C

IR :1730.1709.1260.1082 cm$^{-1}$

$^{1}$H NMR : 5 6.51-6.41 (2H, m), 4.20 (1H, dd. $J_1$ = 4.0 Hz. $J_2$ = 2.0 Hz). 3.98-3.94 (1H, m), 3.79 (3H. s), 3.77 (3H. s), 3.61 < 1H. d. $J$ = 11.2 Hz). 3.44-3.36 (4H. m), 2.61-2.53 (3H. m), 2.34-2.27 (2H. m), 1.76 (1H. ½ ABq, $J$ = 11.1 Hz). 1.55 (1H. ½ ABq. $J$ = 10.8 Hz). 1.12 **(3H.S),** 0.70 (3H,s)

$^{13}$C NMR : 5 212.1. 166.4(2C), 143.8. 143.7. 134.0. 131.7. 102.8. 72.9. 71.0. 60.1. 54.8. 52.2(2C), 49.9. 47.1. 43.8. 43.1. 41.9. 40.0. 39.4. 38.9. 38.0.29.8.22.9.21.7

Analysis : $C_{26}H_{28}O_7$ : Calcd. : C. 69.01; H. 6.24
Found : C, 69.00; H. 6.28

DM **AD addition to** 65d:

The reaction was performed as described in the general procedure to furnish 76d : 77d (4 : 96) in 75% yield. The diastereomers were separated by column chromatography using silica gel and elution with 30% ethyl acetate-hexane.

76d:

mp :134°C

IR : 1742. 1707, 1282. 1123, 1059 $cm^{-1}$

$^{1}H$ NMR : 8 6.68-6.58 (2H. m), 4.26-4.23 (1H, m), 3.98-3.94 (1H, m), 3.81 (3H, s), 3.72 (3H. s), 3.44 (3H, s). 3.17 (3H. s). 2.78-2.69 (2H. m), 2.58-2.53 (1H, m), 2.47-2.39 (1H. m), 2.32-2.25 (1H, m), 2.13-2.04 (1H. m), 1.75 (1H, ½ ABq, $J$ = 10.9 Hz). 1.52 (1H, ½ ABq, $J$ = 11.3 Hz)

$^{13}C$ NMR : δ 211.5, 166.3(2C), 143.3. 142.5. 135.7. 135.0. 106.2.62.0.55.5. 53.1, 52.3. 52.1, 51.9, 50.8. 50.2, 44.7. 44.0. 42.0. 41.0. 39.24. 39.18, 38.1

Analysis : $C_{23}H_{24}O_7$ : Calcd. : C. 66.98: H. 5.87
Found : C, 67.00; H. 5.90

77d:

mp : 119-120 °C

IR : 1736, 1271, 1123, 1074 $cm^{-1}$

$^{1}H$ NMR : δ 6.49-6.34 (2H. m), 4.13 (1H, d. $J$ = 5.8 Hz). 3.89 (1H, d. $J$ = 5.8 Hz). 3.76 (3H, s), 3.74 (3H, s), 3.37 (3H, s), 3.10 (3H, s). 2.71-2.65 <2H, m), 2.53-2.47 (2H, m), 2.27-2.17 (2H, m). 1.71 (1H, ½ ABq, $J$ = 10.8 Hz), 1.51 (1H, ½ ABq, $J$ = 11.1 Hz)

*Experimental*

$^{13}$C NMR : 8 211.7, 166.4, 166.1, 144.8, 142.2, 133.3, 131.8, 106.4,60.4,54.7, 52.9, 52.4, 52.2(2C), 50.3(2C), 44.0(2C), 41.7, 40.9, 39.4, 38.7, 37.8

Analysis : $C_{23}H_{24}O_7$ : Calcd. : C, 66.98; H, 5.87

Found : C, 67.05; **H,** 5.90

**DMAD addition to 65e:**

The reaction was performed as described in the general procedure to furnish **76e** : **77e** (18 : 82) in 83% yield. The diastereomers were separated by column chromatography using silica gel and elution with 40% ethyl acetate-hexane.

76e:

mp : 247 °C (darkens), 253 °C (melts)

IR : 1728, 1437, 1254. 1063 cm$^{-1}$

$^1$H NMR : δ 6.63 (2H, t, *J* = 4 Hz), 4.07-3.81 (10H, series of m), 3.74 <6H. s).

(Spectrum 29) 2.53 (2H, bs), 2.14 (2H, bs), 2.07 (2H, bs), **1.51** (1H, ½ ABq. *J* = 10.8 Hz), 1.19 (1H. ½ ABq, *J*= 10.7 Hz)

$^{13}$C NMR :5 166.5, 143.7, 135.7, 113.8, 66.9, 63.4, 56.8, 51.9, 48.4, 44.1, 41.6

(Spectrum 30) 40.5, 35.7

Analysis : $C_{25}H_{26}O_8$ : Calcd. : C, 66.07; H. 5.77

Found : C, 66.14; H, 5.80

77e:

mp : 192-193 °C

IR : 1721, 1645, 1260, 1073cm$^{-1}$

$^1$H NMR : δ 6.53 (2H, t, *J* = 3.2 Hz), 4.03-3.83 (10H, series of m), 3.80 (6H, s),

(Spectrum 31) 2.55 (2H, bs), 2.19 (4H, bs), 1.51 (1H, ½ ABq, *J* = 11.0 Hz), 1.22

(1H, ½ ABq, $J$ = 11.1 Hz)

$^{13}$C NMR : 8 166.6, 144.3, 133.3, 114.1, 66.7, 63.1, 55.8, 52.2, 48.7, 44.1, 41.7

(Spectrum 32) 40.3, 35.7

Analysis : $C_{25}H_{26}O_8$ : Calcd. : C, 66.07; H, 5.77

Found : C. 66.00; H, 5.79

**DMAD addition to 80a:**

The reaction was performed as described in the general procedure to furnish 86a (single isomer) in 93% yield and was purified by column chromatography over silica gel with 20% ethyl acetate-hexane as the solvent system.

86a:

mp : 139 °C

IR : 1736, 1709, 1333. 1254. 1057 cm$^{-1}$

$^1$H NMR : 5 6.56(2H. t, $J$ = 3.6 Hz), 4.39 (1H, dd, $J_1$ = 4.6 Hz. $J_2$ = 3.1 Hz), 4.02 (1H. dd, $J_1$ = 4.6 Hz./. = 3.1 Hz), 3.84 (3H. s). 3.81 (3H. s). 3.32-3.15 (4H. m), 3.06-2.97 (1H. m), 2.92-2.86( 1H. m). 2.70-2.45 (3H,m), 2.31-2.24 (1H. m), 1.86 (1H. *V2* ABq, $J$ = 10.9 Hz). 1.58 (1H. ½ ABq, $J$ = 10.5 Hz)

$^{13}$C NMR : δ 213.7. 166.4. 166.3. 144.6, 143.3, 135.6. 131.7. 64.2, 64.0. 57.9. 52.9, 52.4(2C), 47.0. 45.9. 43.5. 42.4. 39.8, 39.3(2C). 38.9. 37.5

LRMS : $m/z$ 442 ($M^+$)

Analysis : $C_{23}H_{22}O_5S_2$ : Calcd. : C. 62.42; H, 5.01

Found : C, 62.52; **H,** 5.05

**DMAD addition to 80b:**

*Experimental*

The reaction was performed as described in the general procedure to furnish **86b** (single isomer) in 91% yield and was purified by column chromatography over silica gel with 15% ethyl acetate-hexane as the solvent system.

**86b:**

mp : 204-205 °C

IR : 1736. 1717, 1337, 1254, 1057 $cm^{-1}$

$^1H$ NMR : 5 6.61-6.56 (2H, m), 4.35 (1H, dd, $J_1$ = 5.0 Hz, $J_2$ = 1.8 Hz), 4.05 (1H. dd. $J_1$ = 5.1 Hz. $J_2$ = 2.2 Hz), 3.81 (3H, s), 3.78 (3H, s), **3.61**-3.52 (1H, m), 3.18-2.50 (8H. series of multiplets), 2.27-2.19 (1H. m), 2.11-2.01 (1H. m), 1.88-1.73 (1H. m), **1.85 (1H,** ½ ABq, *J*= 11.4 Hz), 1.56 (1H, ½ ABq, *J* = 11.3 **Hz)**

$^{13}C$ NMR : δ 211.7, 166.4. 166.0. 144.8. 142.3. 134.8. 133.1.63.7.60.9.57.3. 55.8. 52.4(2C), 51.5. 47.1. 45.7, 42.0(20. 38.9. 38.7. 37.5. 29.0. 26.6. 25.0

LR.V1S : *m/z* 456 ($M^+$)

Analysis : $C_{24}H_{24}O_5S_2$ : Calcd. : C. 63.13: H. 5.30

Found : C. 63.10: H. 5.29

**DMAD addition** to 68a:

The reaction was performed as described in the general procedure to furnish 96a (single isomer) in 90% yield and was purified by column chromatography over silica gel with 35% ethyl acetate-hexane as the solvent system.

96a:

mp : 155-156 °C

IR : 3310 (br), 1723, 1688, 1304. 1115 $cm^{-1}$

$^{1}H$ NMR : 5 6.57 (2H, t, $J$ = 4.0 Hz), 5.42 (2H, bs, $D_2O$ exchangeable), 3.85-

(Spectrum 33) 3.80 (4H, m), 3.79 (6H, s), 2.37 (2H, bs), 2.27 (2H, bs), 1.98 (2H, bs), 1.57 (1H, ½ ABq, $J$ = 10.6 Hz), 1.05 (1H, ½ ABq, $J$ = 10.4 Hz)

$^{13}C$ NMR : 5 168.5. 142.5, 134.6, 73.7, 56.3. 52.7, 45.5. 44.7, 41.9. 41.0, 35.5

(Spectrum 34)

Analysis : $C_{21}H_{22}O_6$ : Calcd. : C, 68.10: H. 5.99

Found : C. 68.15: **H.** 6.00

**DMAD addition to 68b:**

The reaction was performed as described in the general procedure to furnish 96b : **97b** (59 : 41) in 93% yield. The diastereomers were separated by column chromatography using silica gel and elution with 15% ethyl acetate-hexane.

96b:

mp : 224 °C

IR : 1725. 1262. 1053 $cm^{-1}$

$^{1}H$ NMR : 5 6.28 (2H. dd, $J_1$ = 8 Hz. $J_2$ = 4 Hz), 4.95 **(2H.** bs). 3.96 <2H. t. $J$ =

(Spectrum 35) 4 Hz), 3.79 (6H. s), 2.42 (4H. bs). 2.19 (2H, bs). 2.01 (6H. s). 1.60 (1H, ½ ABq, $J$ = 10.9 Hz). **1.13** (1H, ½ ABq, $J$ = 10.7 Hz)

$^{13}C$ NMR : δ 170.9. 166.5. 143.9. 133.2.72.6.53.0.52.3.43.8.43.0.41.7.41.6.

(Spectrum 36) 35.1, 21.6

Analysis : $C_{25}H_{26}O_8$ : Calcd. : C, 66.07; H. 5.77

Found : C, 66.07; H. 5.72

**97b:**

*Experimental*

**mp** : 200-201 °C

**IR** : 1723, 1248, 1061 $cm^{-1}$

$^1H$ **NMR** : 5 6.63 (2H, t, *J* = 4 Hz), 4.83 (2H, bs), 3.88 (2H, t, *J* = 4 Hz), 3.73 (Spectrum 37) (6H, s), 2.48 (2H, bs), 2.40 (2H, bs), 2.04 (2H, bs), 1.96 (6H, s), 1.59 (1H, ½ ABq, *J* = 10.7 Hz), 1.10 (1H, ½ ABq, *J* = 10.7 Hz)

$^{13}C$ NMR : 5 171.1, 165.9, 143.2, 135.3, 72.6, 52.9. 51.8, 44.2, 42.8, 41.6, 41.5. (Spectrum 38) 35.1,21.4

Analysis : $C_{25}H_{26}O_8$ : Calcd. : C, 66.07; H, 5.77
Found : C, 66.15; H, 5.80

**DMAD addition to 68c:**

The reaction was carried out in a sealed tube using benzene (2 mL) as the solvent andwas maintained at 75-80 °C for 12 h, removal of solvent furnished 96c : **97c** (17 : 83) in 77% yield. The diastereomers were separated by column chromatography using silica gel and elution with 15% ethyl acetate-hexane. However, only an enriched fraction of the minor isomer **96c.** could be obtained.

**96c:**

$^1H$ NMR : 5 6.57 (2H. t. *J* = 4 Hz), 3.74 (8H, s), 3.29 (2H, bs), 3.18 (6H. s), *(from mixture)* 2.39 (2H, bs), 2.23 (2H. bs), 1.91 (2H, bs), 1.55 (1H, ½ ABq, *J* = 10.5 Hz), 1.06 (1H, ½ ABq, *J* = 10.1 Hz)

$^{13}C$ NMR :5 166.5, 142.6. 135.1.82.0.57.4.54.8.51.5,45.1,42.1,41.5.40.5. *(from mixture)* 35.1

**97c:**

IR : 1738, 1375, 1254 $cm^{-1}$

$^1$H NMR : 8 6.53 (2H, t, $J$ = 4 Hz). 3.78 (8H, s), 3.38 (2H, bs), 3.28 (6H, s), 2.44 (2H, bs), 2.24 (2H, bs), 2.06 (2H, bs), 1.55 (1H, ½ ABq, $J$ = 10.5 Hz), 1.08 (1H, ½ ABq, 7 =10.1 Hz)

$^{13}$C NMR : δ 166.9, 144.0, 132.5. 82.7, 57.9, 53.8, 52.1, 44.7, 41.9, 41.8. 40.6. 35.1

LRMS : $m/z$ 398 ($M^+$)

Analysis : $C_{23}H_{26}O_6$ : Calcd. : C. 69.33; H, 6.58

Found : C. 69.42; H, 6.60

**General procedure for the [4+2]-cycIoadditions with MA:**

A solution of diene (0.40 mmol) and MA (0.41 mmol) in dry benzene was refluxed for 12-18 h. Benzene was removed under vacuum to give a single diastereomer and was funher confirmed by analyzing the $^1$H NMR of crude reaction mixture.

**MA addition to 65a:**

The reaction was performed as described in the general procedure to furnish 78a (single isomer) in near quantitative yield and was purified by crystallizing from DCM-hexane.

78a:

mp : 305 °C (lit.[37a] 304-305 °C)

IR : 1870. 1840. 1790. 1740. 1725 cm$^{-1}$

'H NMR : δ 6.50 (2H. t, $J$ = 3.3 Hz). 3.77 (2H, bs), 3.39-3.33 (2H, m), 2.96-2.94 (2H, m), 2.80 (2H. bs), 2.73-2.70 (2H. m), 2.04 (1H, ½ ABq, $J$ = 12.0 Hz), 1.86 (1H, ½ ABq, $J$ = 12.0 Hz)

*Experimental*

**MA addition to 65b:**

The reaction was performed as described in the general procedure to furnish **78b** (single isomer) in near quantitative yield and the crude adduct was directly crystallized from DCM-hexane.

**78b:**

mp : 279-280 °C

IR : 1860. 1834, 1779.1736, 1229, 1078 $cm^{-1}$

$^1H$ NMR : 8 6.55-6.41 (2H. m), 4.09-3.92 (4H. m), 3.62 (1H. dd. $J_1$ = 4.4 Hz. $J_2$ = 2.9 Hz), 3.50 (1H. dd. $J_1$ = 8.8 Hz. $J_2$ = 3.3 Hz), 3.42-3.37 (1H. m), 3.32-3.27 (1H. m), 2.70-2.59 (3H. m), 2.53-2.44 (2H. m), 2.31-2.23 (1H. m), 1.80 (1H. ½ ABq, $J$ = 11.1 Hz). 1.52 (1H. ½ ABq. $J$ = 11.1 Hz)

$^{13}C$ NMR : δ 212.5. 173.2. 172.6. 134.0. 132.6. 113.1. 65.4. 64.9. 54.2. 51.7. 51.5, 49.3. 44.3. 43.5. 42.0. 40.8, 40.3. 39.8. 39.0. 32.8. 32.4

Analysis : $C_{21}H_{18}O_6$ : Calcd. : C. 68.85: H. 4.95

Found : C. 68.90; H. 4.98

**MA addition** to **65c:**

The reaction was performed as described in the general procedure to furnish **78c** (single isomer) in near quantitative yield and the crude adduct was directly crystallized from DCM-hexane.

78c:

mp : 251 °C

IR : 1860, 1836. 1777,1738, 1227, 1086 $cm^{-1}$

$^1$H NMR : 5 6.55-6.40 (2H, m), 3.95 (1H, dd, $J_1$ = 8.8 Hz. $J_2$= 3.7 Hz), 3.70 (1H. d, $J$ = 11.6 Hz), 3.60-3.39 (6H, m), 3.32-3.26 (1H, m), 2.66-2.58 (2H, m), 2.50-2.39 (2H, m), 2.27-2.19 (1H, m), 1.80 (1H, ½ ABq, $J$ = 11.2 Hz), 1.51 (1H, ½ ABq, $J$ = 10.8 Hz), 1.18 (3H,s), 0.77 (3H, s)

$^{13}$C NMR : 5 211.7, 173.2, 172.9, 134.2, 132.5, 103.6,73.6.70.9,54.1,50.2, 48.5. 48.3, 44.3, 43.6, 41.9. 40.8, 40.5. 39.7, 38.7, 32.5, 32.4. 29.9. 23.7.21.9

Analysis : $C_{24}H_{24}O_6$ : Calcd. : C. 70.58: H. 5.92
Found : C. 70.65; H. 5.95

MA addition to 65d:

The reaction was performed as described in the general procedure to furnish 78d (single isomer) in near quantitative yield and the crude adduct was directly crystallized from DCM-hexane.

78d:

mp : 241-242 °C

IR : 1856. 1833. 1771.1738. 1231. 1086 cm$^{-1}$

$^1$H NMR : δ 6.45-6.41 (2H. m), 3.81 (1H. dd. $J_1$ = 8.8 Hz. $J_2$ = 3.1 Hz), 3.55-3.47 (2H. m), 3.46 (3H. s), 3.31 (3H. s). 3.26-3.21 (1H. m), 2.93-2.85 (1H. m), 2.77-2.72 (1H. m), 2.60-2.55 (1H. m), 2.48-2.36 (2H. m), 2.22-2.16 (1H. m), 1.77 (1H. *Vz* ABq. $J$ = 11.3 Hz). 1.49 (1H. ½ ABq, $J$ = 11.1 Hz)

$^{13}$C NMR : 5 211.9, 173.2, 172.6, 133.7, 132.7, 107.3, 56.0. 53.7. 53.4. 50.9.

50.6, 49.4, 45.1, 44.2, 41.8, 41.1, 40.5, 39.4, 38.7, 33.8, 32.1

Analysis : $C_{21}H_{20}O_6$ : Calcd. : C, 68.47; H, 5.47

Found : C, 68.55; **H,** 5.42

**MA addition to 65e:**

The reaction was performed as described in the general procedure to furnish 78e (single isomer) in near quantitative yield and the crude adduct was directly crystallized from DCM-hexane.

**78e:**

mp : 268 °C

IR : 1860, 1834, 1775, 1236, 1074 $cm^{-1}$

$^1H$ NMR : 5 6.48-6.42 (2H, m), 4.09-3.89 (8H, m), 3.77 (2H, bs), 3.35 (2H. bs).

(Spectrum 39) 2.51 (2H, bs), 2.28 (2H. bs), 2.12 (2H. bs), 1.51 (1H, ½ ABq. *J* = 10.8 Hz), 1.14 (1H, ½ ABq, *J* = 10.7 Hz)

$^{13}C$ NMR : 5 173.8, 133.6, 114.5, 66.6, 63.2, 49.4. 48.9, 43.8, 43.0, 41.0. 34.8.

(Spectrum 40) 33.3

Analysis : $C_{23}H_{22}O_7$ : Calcd. : C, 67.31; H. 5.40

Found : C, 67.25: H. 5.42

**MA addition to 80a:**

The reaction was performed as described in the general procedure to furnish **87a** (single isomer) in near quantitative yield and the crude adduct was directly crystallized from DCM-hexane.

**87a:**

mp : > 280 °C

IR : 1860, 1777, 1725, 1225, 1084 $cm^{-1}$

$^1H$ NMR : 8 6.62-6.45 (2H, m), 4.21 (1H, dd, $J_1$ = 8.8 Hz, $J_2$ = 3.9 Hz), 3.72-3.63 (2H, m), 3.43-3.27 (5H, m), 3.13-3.06 (1H, m), 2.83-2.78 (1H, m), 2.66-2.52 (3H, m), 2.24-2.17 (1H, m), 1.87 (1H, ½ ABq, *J* = 11.5 Hz), 1.49 (1H, ½ ABq, *J*= 11.7Hz)

$^{13}C$ NMR : δ 213.9, 172.9, 172.3, 134.9, 133.0, 75.0, 66.1, 56.9, 53.7, 52.5, 47.0, 46.4, 42.3, 41.4(2C), 40.4, 38.9, 38.6. 38.3, 36.1, 32.4

LRMS : *m/z* 398 ($M^+$)

Analysis : $C_{21}H_{18}O_4S_2$ : Calcd. : C, 63.29; H, 4.55
Found : C. 63.35; H, 4.58

**MA addition to 80b:**

The reaction was performed as described in the general procedure to furnish 87b (single isomer) in near quantitative yield and the crude adduct was directly crystallized from DCM-hexane.

87b:

mp :> 280 °G

IR : 1838. 1775, 1721, 1231, 1096 $cm^{-1}$

$^1H$ NMR : δ 6.58-6.45 (2H, m), 4.30 (1H, dd, $J_1$ = 8.8 Hz. $J_2$ = 3.7 Hz), 3.73-3.62 (2H, m), 3.49 (1H, dd. $J_1$ = 8.8 Hz. $J_2$ = 2.9 Hz), 3.40-3.35 (1H, m), 3.19-3.00 (3H. m), 2.84-2.57 (5H, m), 2.21-2.10 (2H, m), 1.98-1.76 (lH,m), 1.88 (1H, ½ ABq, *J*= 11.1 Hz), 1.50 (1H, ½ ABq, *J* = 11.0 Hz)

$^{13}C$ NMR : 5 210.6, 172.4, 172.2, 134.6, 132.9, 59.5, 59.0, 56.9, 52.1, 50.7,

47.2. 46.1, 42.1, 41.5, 40.6, 39.4, 37.5, 35.0, 32.1, 28.9, 26.4, 24.7

LRMS : *m/z* 412 ($M^+$)

Analysis : $C_{22}H_{20}O_4S_2$ : Calcd. : C. 64.05; H, 4.89

Found : C. 64.10; **H,** 4.87

**MA addition to 68a:**

The reaction was performed as described in the general procedure to furnish **98a** (single isomer) in near quantitative yield and the crude adduct was directly crystallized from DCM-hexane.

98a:

mp : >285 °C

IR : 3300 (br). 1860. 1838, 1771. 1236, 1111 $cm^{-1}$

$^1H$ NMR : 5 6.30 (2H, t. *J* = 4 Hz), 3.94 **(2H.** bs), 3.75 (2H. bs). 3.02 (2H. bs).

(Acetone-$d_6$) 2.28 **(2H. bs),** 2.11 **(2H. bs).** 1.88 **(2H. bs).** 1.39 (1H, ½ ABq, *J* =

(Spectrum 41) 10.6 Hz). 0.85 (1H, *V2* ABq, *J* = 10.6 Hz)

$^{13}C$ NMR :5 173.7. 133.2. 74.4. 47.5. 46.9. 43.0. 40.7. 40.3. 37.9. 34.2

(Acetone-$d_6$)

(Spectrum 42)

Analysis : $C_{19}H_{18}O_5$ : Calcd. : C. 69.93; H. 5.56

Found : C. 70.00; **H.** 5.58

**MA addition to 68b:**

The reaction was performed as described in the general procedure to furnish **98b** (single isomer) in near quantitative yield and the crude adduct was directly crystallized from DCM-hexane.

**98b:**

mp : 262 °C

IR : 1860. 1777, 1728, 1262, 1229, 1057 $cm^{-1}$

$^1H$ NMR : 5 6.50 (2H, t, *J* = 4 Hz), 4.76 (2H, bs), 3.61 (2H, bs), 3.21 (2H, bs),

(Spectrum 43) 2.66 (2H. bs), 2.42 (2H, bs), 2.09 (8H, s), 1.60 (1H, ½ ABq, *J* =

10.8 Hz), 1.07 (1H. ½ ABq. *J*= 10.9 Hz)

$^{13}C$ NMR :5 173.0. 170.2, 133.6, 74.7. 46.5, 43.0, 42.8, 41.3, 41.0. 37.4, 34.1,

(Spectrum 44) 21.7

LRMS : *m/z* **410** (NO

Analysis : $C_{23}H_{22}O_7$ : Calcd. : C. 67.31; H. 5.40

Found : C, 67.34; **H.** 5.41

**MA addition to** 68c:

The reaction was performed as described in the general procedure to furnish 98c (single isomer) in near quantitative yield and the crude adduct was directly crystallized from DCM-hexane.

**98c:**

mp : 233-234 °C

IR : 1854. 1780. 1223. 1101 $cm^{-1}$

$^1H$ NMR : 5 6.42 (2H. t. *J* = 4 Hz), 4.06 (2H. bs). 3.44 (2H. bs). 3.31 (6H. s).

'Spectrum 45) 3.12 (2H. bs), 2.55 (2H. bs). 2.22 (2H. bs). 1.99 (2H. bs). 1.57 (1H.

½ ABq. *J*= 10.6 Hz). 1.03 (1H. ½ ABq. *J* = 10.6 Hz)

"CNMR :5 174.5. 133.4, 83.1, 57.2. 47.8, 43.1, 41.6, 41.1, 40.9. 38.4, 34.3

(Spectrum 46)

LRMS : *m/z* 354 ($M^+$)

*Experimental*

Analysis : $C_{21}H_{22}O_5$ : Calcd. : C, 71.17; H, 6.26

Found : C, 71.12; **H,** 6.22

**General procedure for the [4+2]-cycloadditions with NMM:**

A solution of diene (0.30 mmol) and NMM (0.31 mmol) in dry benzene was refluxed for 12-18 h. Benzene was removed under vacuum to give a single diastereomer (> 96%) and was further confirmed by analyzing the $^1H$ NMR of crude reaction mixture.

**NMM addition to 65a:**

The reaction was performed as described in the general procedure to furnish 91 (single isomer) in near quantitative yield and the crude adduct was directly crystallized from DCM-hexane.

91:.

mp : >300 °C

IR : 1775, 1730, 1694, 1285 $cm^{-1}$

$^1H$ NMR : 5 6.32 (2H, t. $J$ = 4 Hz), 3.45 (2H, bs), 3.32-3.28 (2H, m), 2.92-2.89 (2H, m), 2.87 (3H, s). 2.76 (2H, bs), 2.67 (2H, bs), 1.99 (1H. ½ ABq. $J$= 11.1 Hz), 1.83 (1H, ½ ABq, $J$ = 11.6 **Hz)**

**NMM addition to 80a:**

The reaction was performed as described in the general procedure to furnish **89a** (single isomer) in near quantitative yield and the crude adduct was directly crystallized from DCM-hexane.

**89a:**

mp : 280 °C

IR : 1769, 1728, 1694, 1277 $cm^{-1}$

$^1H$ NMR : 5 6.44-6.27 (2H, m), 3.86 (1H, dd, $J_1$ = 7.9 Hz, $J_2$= 3.2 Hz), 3.65-3.60 (1H, m), 3.43-3.25 (6H, m), 3.09-3.03 (1H, m), 2.88 (3H, s), 2.80-2.75 (1H, m), 2.62-2.48 (3H, m), 2.20-2.13 (1H, m), 1.84 (1H, ½ ABq, $J$ = 11.3 Hz), 1.46 (1H, ½ ABq, $J$ = 11.1 Hz)

$^{13}C$ NMR : 5 214.3, 178.9, 178.5, 133.7, 132.3, 75.2, 66.0, 57.7, 53.9, 53.1, 47.0, 46.4, 42.3, 41.4, 40.5, 39.7, 38.9. 38.5, 38.3, 36.2, 32.4. 24.5

Analysis : $C_{22}H_{21}NO_3S_2$ : Calcd. : C. 64.20; H. 5.14; N, 3.40
Found : C, 64.25; H, 5.12; N. 3.98

NMM **addition to 80b:**

The reaction was performed as described in the general procedure to furnish 89b (single isomer) in near quantitative yield and the crude adduct was directly crystallized from DCM-hexane.

89b:

mp : >280 °C

IR : 1775, 1725. 1696. 1279 crn'

$^1H$ NMR : 5 6.41-6.28 (2H, m), 4.03-3.96 (1H, m), 3.73-3.58 (2H. m), 3.32-3.28 (1H, m), 3.24-2.99 (4H, series of multiplets), 2.89 (3H, s). 2.80-2.53 (5H. series of multiplets), 2.18-2.05 (2H, m), 1.96-1.81 (1H, m), 1.86 (1H, ½ ABq, $J$= 10.5 Hz), 1.48 (1H, ½ ABq, $J$ = 10.8 Hz)

$^{13}C$ NMR : 5211.1. 178.5, 178.4, 133.5, 132.3,59.8,59.0,57.5,52.3,51.3. 47.3, 46.0, 42.2, 40.5, 40.0, 39.4, 37.6, 35.2, 32.0, 28.9, 26.4. 24.8, **24.6**

LRMS : *m/z* 425 ($M^+$)

Analysis : $C_{23}H_{23}NO_3S_2$ : Calcd. : C, 64.91; H, 5.45; N. 3.29

Found : C, 65.00; **H,** 5.46; N, 3.29

**Hydrolysis of ethylene acetal of 73e; conversion of 73e to 73b:**

A mixture of to-acetal **73e** (30 mg, 0.09 mmol) and CSA (catalytic, 2 mg) in moist acetone (2 mL) was stirred at room temperature for 30 minutes. Acetone was removed under vacuum to furnish a residue which was charged on a silica gel column. Elution with 30% ethyl acetate-hexane furnished *mono*-acetal **73b** (25 mg, 95%). This was found to be identical (mp. IR. and $^1H$ NMR) to the sample **73b** derived from *mono*-acetal **65b.**

**Hydrolysis of dimethyl acetai of 73d; conversion of 73d to 73a:**

A mixture of *mono*-acetal **73d** (25 mg, 0.08 mmol) and amberlyst-15 (10 mg) in moist acetone (2 mL) was stirred at room temperature for 15 minutes. Amberlyst resin was filtered and the solvent was removed under vacuum to furnish a residue which was charged on a silica gel column. Elution with chloroform furnished dione **73a** (20 mg. 94%). This was found to be identical (mp. IR. and 'H NMR) to the sample **73a** derived from dione **65a.**

**Rearrangement of endoperoxide 104a to diepoxide 105; conversion of 104a to 105:**

Endoperoxide **104a** (5mg) in CDCh in a NMR tube was exposed to sunlight for 1 h. On recording a $^1H$ NMR at end of this period indicated (identical to diepoxide **105)** a clean rearrangement of **104a to 105.**

**Acetalisation of 76a; conversion of 76a to 76b and 76e:**

A mixture of dione 76a (60 mg, 0.16 mmol), ethylene glycol (0.03 mL, 0.49 mmol), **PTSA** (3mg) and benzene (20 mL) was refluxed for 12 h with a Dean-Stark water separator. The reaction was cooled and quenched by adding saturated $NaHCO_3$ solution (2 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic extract was washed and dried. Removal of solvent furnished a mixture of acetals. which were separated by column chromatography using silica gel. Elution with 40% ethyl acetate-hexane first furnished *mono*-acetal **76b** (30 mg, 45%) and on further elution pure to-acetal 76e (26 mg, 35%) was obtained. Both 76b and 76e were found to be identical (mp, IR, and 'H NMR ) to the sample derived from *mono*-acetal 65b and ***bis*-acetal** 65e. respectively.

**Acetalisation** of 76a; conversion of 76a to **76c:**

A mixture of dione 76a (30 mg, 0.08 mmol), 2.2-dimethylpropane-1.3-diol (25 mg, 0.24 mmol), PTSA (3mg) and benzene (10 mL) was refluxed for 12 h with a Dean-Stark water separator. Usual work-up and removal of solvent furnished a residue. which was purified by column chromatography using silica gel. Elution with 35% ethyl acetate-hexane furnished *mono*-acetal 76c (35 mg, 95%). This sample was found to be identical (mp. IR. and 'H NMR) to the sample 76c derived from ***mono*-**acetal 65c.

Hydrolysis of neopentyl acetal of 77c; conversion of 77c to **77a:**

To a stirred solution of NaI (25 mg. 0.17 mmol) in dry acetonitrile (2 mL) was added successively trimethylchlorosilane (0.02 mL. 0.16 mmol) and *mono*-acetal **77c** (30 mg, 0.07 mmol) under a dry nitrogen atmosphere. Iodine colour formation appeared instantaneously. The reaction was stirred for 45 minutes and then

quenched with water and extracted with DCM (3 x 10 mL), and the organic layer was washed successively with aqueous sodium thiosulfate, water, brine and was dried. Removal of solvent and filtration through silica gel (elution with 25% ethyl acetate-hexane) afforded the dione **77a** (17 mg, 70%). This sample was found to be identical (mp, IR, and $^1$H NMR) to the sample **77a** derived from dione **65a.**

**Hydrolysis of dimethyl acetal of 77d; conversion of 77d to 77a:**

A mixture of *mono*-acetal **77d** (33 mg, 0.08 mmol) and amberlyst-15 (10 mg) in moist acetone (2 mL) was stirred at room temperature for 30 minutes. Amberlyst resin was filtered and the solvent was removed under vacuum to furnish a residue which was charged on a silica gel column. Elution with 25% ethyl acetate-hexane furnished dione **77a** (28 mg, 95%). This sample was found to be identical (mp, IR, and $^1$H NMR) to the sample **77a** derived from dione **65a.**

**Hydrolysis of ethylene acetal** of 77e: **conversion of** 77e **to 77b:**

A mixture of *bis*-acetal 77e (35 mg, 0.08 mmol) and amberlyst-15 (10 mg) in moist acetone (3 mL) was stirred at room temperature for 45 minutes. Amberlyst resin was filtered and the solvent was removed under vacuum to furnish a residue which was charged on a silica gel column. Elution with 30% ethyl acetate-hexane furnished *mono*-acetal **77b** (30 mg, 95%). This sample was found to be identical (mp. IR. and $^1$H NMR) to the sample **77b** derived from *mono*-acetal **65b.**

**Thioacetalisation of 77a; conversion of 77a to 86a:**

**A** mixture of dione **77a** (37 mg, 0.1 mmol), 1,2-ethanedithiol (0.02 mL, 0.2 mmol), PTSA (3mg) in DCM (10 mL) was stirred for 4 h. Usual work-up and removal of solvent furnished a residue, which was purified by column

chromatography using silica gel. Elution with 20% ethyl acetate-hexane furnished *mono*-thioacetal **86a** (38 mg, 85%). This sample was found to be identical (mp, IR, and 'H NMR) to the sample **86a** derived from *mono*-thioacetal **80a.**

**Thioacetalisation of 77a; conversion of 77a to 86b:**

A mixture of dione **77a** (37 mg, 0.1 mmol), 1,3-propanedithiol (0.02 mL, 0.2 mmol), PTSA (3mg) and benzene (10 mL) was refluxed for 12 h with a Dean-Stark water separator. Usual work-up and removal of solvent furnished a residue, which was purified by column chromatography using silica gel. Elution with 30% ethyl acetate-hexane furnished *mono*-thioacetal **86b** (41 mg, 90%). This sample was found to be identical (mp, IR, and 'H NMR) to the sample **86b** derived from ***mono***-thioacetal **80b.**

**Dethioacetalisation** of **86a; conversion** of **86a to** 77a:

[Bis(trifluroacetoxy)iodo]benzene (47 mg, 0.11 mmol) was added at room temperature to a stirred solution of *mono*-thioacetal **86a** (30 mg, 0.07 mmol) in MeOH:$H_2O$ (10 mL, 9:1). The mixture was stirred for an additional 10 minutes and quenched with saturated solution of $NaHCO_3$ and extracted with DCM (3 x 5 mL). Removal of solvent and filtration through silica gel pad (elution with 25% ethyl acetate-hexane) furnished dione **77a** (15 mg, 60%). This sample was found to be identical (mp. IR. and $^1H$ NMR) to the sample **77a** derived from dione **65a.**

Dethioacetalisation of **86b; conversion** of **86b to 77a:**

To a stirred solution of the *mono*-thioacetal **86b** (30 mg, 0.07 mmol) in DCM (10 mL), cooled in an ice-bath (0-5 °C), was added drop-wise a solution of 'nitrogen oxides' in DCM until the pink colour was discharged. After stirring for 5 minutes.

the reaction was quenched with ice-cold aqueous $NaHCO_3$ and extracted with DCM (3 x 5 mL). Removal of solvent and filtration through silica gel pad (elution with 25% ethyl acetate-hexane) furnished dione 77a (17 mg, 70%). This sample was found to be identical (mp, IR, and $^1H$ NMR) to the sample 77a derived from dione 65a.

Reduction of dione 76a; conversion of 76a to 96a:

A solution of dione 76a (40 mg, 0.11 mmol) in dry MeOH (5 mL) was cooled in an ice-bath and $NaBH_4$ (8mg. 0.22mmol) was added to it. The reaction mixture was stirred for 30 minutes followed by usual work-up. Removal of solvent and filtration through silica gel pad (elution with 40% ethyl acetate-hexane) furnished diol 96a (32 mg. 80%). This sample was found to be identical (mp. IR. and $^1H$ NMR) to the sample 96a derived from diol 68a.

Reduction of dione 77a: conversion of 77a to 97a:

A solution of dione 77a (40 mg, 0.11 mmol) in dry MeOH (5 mL) was cooled in an ice-bath and $NaBH_4$ (8mg. 0.22mmol) was added to it. The reaction mixture was stirred for 30 minutes followed by usual work-up. Removal of solvent and filtration through silica gel pad (elution with 35% ethyl acetate-hexane) furnished diol **97a** (38 mg. 95%).

97a:

mp : 156-157 °C

IR : 3291 (br), 1738. 1713. 1273. 1061 $cm^{-1}$

$^1H$ NMR : $\delta$ 6.51 (2H. dd. $J_1$ =4.5 Hz. $J_2$ = 3.1 Hz), 3.83 (4H. bs). 3.80 (6H. s).

(Spectrum 47) 2.32 (4H. bs), 2.10 (2H. bs), 1.54 (1H. ½ ABq, $J$ = 10.5 Hz). 1.07

(1H, ½ ABq, $J$ = 10.6 Hz)

$^{13}$C NMR : 8 166.8, 143.7, 133.1, 74.0, 55.0, 52.3, 46.0, 44.4, 41.8, 41.3, 35.3 (Spectrum 48)

Analysis : $C_{21}H_{22}O_6$ : Calcd. : C, 68.10; H. 5.99

Found : C. 67.75; H, 5.90

This isomer could not be accessed from the DMAD addition to diol **68a.**

Hydrolysis of diacetate **97b;** conversion of 97b to 97a:

A mixture of diacetate 97b (30 mg, 0.08 mmol) and $K_2CO_3$ (14 mg, 0.10 mmol) in MeOH (3 mL) was stirred at room temperature for 20 minutes. Methanol was removed under vacuum and $H_2O$ (2 mL) was added to the mixture. The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic extract was washed and dried. Removal of solvent and filtration through a small silica gel pad (elution with *25?c* ethyl acetate-hexane) furnished the diol 97a (20 mg. 80%). This sample was found to be identical (mp. IR. and $^1$H NMR) to the sample 97a derived from reduction of dione 77a.

**Demethylation** of 97c; conversion of 97c to 97a:

To a stirred solution of the dimethyl ether **97c** (32 mg, 0.08 mmol) in DCM (10 mL), cooled in an ice-bath (0-5 °C), was added drop-wise a solution of 'nitrogen oxides' in DCM. After stirring for 10 minutes, the reaction was quenched with ice-cold aqueous $NaHCO_3$ and extracted with DCM (3 x 5 mL). Removal of solvent and filtration through silica gel pad (elution with 30% ethyl acetate-hexane) furnished diol **97a** (6 mg, 20%). This sample was found to be identical (mp. IR. and $^1$H NMR) to the sample 97a derived from reduction of dione **77a.**

**Hydrolysis** of neopentyl acetal of 75c; **conversion** of **75c** to 75a:

*Experimental*

To a stirred solution of NaI (12 mg, 0.08mmol) in dry acetonitrile (2 mL) was added successively trimethylchlorosilane (0.01 mL, 0.08 mmol) and *mono*-acetal 75c (15 mg, 0.03 mmol) under a dry nitrogen atmosphere. The reaction was stirred for 45 minutes and then quenched with water and extracted with DCM (3 x 10 mL), and the organic layer was washed successively with aqueous sodium thiosulfate, water, brine and then dried. Removal of solvent and filtration through neutral alumina (elution with 70% ethyl acetate-chloroform) afforded the dione **75a** (8 mg, 65%). This sample was found to be identical (mp, IR, and $^1$H NMR) to the sample **75a** derived from dione **65a.**

**Oxidation of diol 94a; conversion of 94a to 74a:**

To a suspension of PCC (28 mg, 0.13 mmol) and molecular sieves (4 A. 28 mg) in 5 mL of dry DCM was added diol **94a** (20 mg. 0.05 mmol) at 0 "C. The reaction mixture was further stirred for 1 h at room temperature and was filtered through a celite pad. Removal of solvent and and filtration through neutral alumina column (elution with 70% ethyl acetate-chloroform) furnished the dione **74a** (18 mg. 91%). This sample was found to be identical (mp. IR, and 'H NMR) to the sample **74a** derived from dione **65a.**

**Hydrolysis of diacetate 94b; conversion of 94b to 94a:**

A mixture of diacetate **94b** (20 mg, 0.04 mmol) and $K_2CO_3$ (8 mg. 0.06 mmol) in MeOH ( 3 mL) was stirred at room temperature for 20 minutes. Methanol was removed under vacuum and $H_2O$ (2 mL) was added to the mixture. The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic extract was washed and dried. Removal of solvent and filtration through a small neutral

alumina pad (elution with 70% ethyl acetate-chloroform) furnished the diol **94a** (13 mg, 78%). This sample was found to be identical (mp, IR, and 'H NMR) to the sample **94a** derived from diol **68a.**

**Acetalisation** of **78a; conversion** of **78a to 78b:**

A mixture of dione **78a** (33 mg, 0.1 mmol), ethylene glycol (0.01 mL, 0.20 mmol), PPTS (3mg) and benzene (10 mL) was refluxed for 6 h with a Dean-Stark water separator. Usual work-up and removal of solvent furnished a residue, which was purified by column chromatography using silica gel. Elution with 40% ethyl acetate-hexane furnished *mono*-acetal 78b (30 mg, 80%). This sample was found to be identical (mp. IR, and $^1$H NMR) to the sample 78b derived from *mono*-acetal **65b.**

**Acetalisation of** 78a; **conversion** of 78a **to** 78c:

A mixture of dione **78a** (20 mg, 0.06 mmol), 2,2-dimethylpropane-1,3-diol (8 mg, 0.08 mmol), PTSA (3mg) and benzene (10 mL) was refluxed for 12 h with a Dean-Stark water separator. Usual work-up and removal of solvent furnished a residue, which was purified by column chromatography using silica gel. Elution with 35% ethyl acetate-hexane furnished *mono*-acetal 78c (23 mg, 91%). This sample was found to be identical (mp, IR. and $^1$H NMR) to the sample **78c** derived from *mono*-acetal **65c.**

**Hydrolysis of dimethyl acetal of 78d; conversion of 78d to 78a:**

A mixture of *mono*-acetal **78d** (30 mg, 0.08 mmol) and amberlyst-15 (10 mg) in moist acetone (3 mL) was stirred at room temperature for 30 minutes. Amberlyst resin was filtered and the solvent was removed under vacuum to furnish a residue which was charged on a silica gel column. Elution with 40% ethyl acetate-hexane

furnished dione **78a** (25 mg, 96%). This sample was found to be identical (mp, IR. and $^1$H NMR) to the sample **78a** derived from dione **65a.**

**Hydrolysis of ethylene acetal of 78e; conversion of 78e to 78b:**

A mixture of *bis*-acetal **78e** (29 mg, 0.07 mmol) and PTSA (catalytic, 2 mg) in moist acetone (2 mL) was stirred at room temperature for 30 minutes. Acetone was removed under vacuum to furnish a residue which was charged on a silica gel column. Elution with 40% ethyl acetate-hexane furnished *mono*-acetal **78b** (24 mg, 93%). This sample was found to be identical (mp. IR, and $^1$H NMR) to the sample **78b** derived from *mono*-acetal **65b.**

**Thioucetalisation of 78a; conversion of** 78a **to** 87a:

A mixture of dione **78a** (29 mg, 0.09 mmol), 1,2-ethanedithiol (0.02 mL, 0.2 mmol). PTSA (3mg) and benzene (10 mL) was refiuxed for 6 h with a Dean-Stark water separator. Usual work-up and removal of solvent furnished a residue, which was purified by column chromatography using silica gel. Elution with 30% ethyl acetate-hexane furnished *mono*-thioacetal 87a (30 mg. 84%). This sample was found to be identical (mp, IR. and $^1$H NMR) to the sample **87a** derived from *mono*-thioacetal **80a.**

**Thioacetalisation of 78a: conversion of 78a to 87b:**

A mixture of dione **78a** (32 mg, 0.1 mmol), 1,3-propanedithiol (0.02 mL, 0.2 mmol). PTSA (3mg) and benzene (10 mL) was refiuxed for 6 h with a Dean-Stark water separator. Usual work-up and removal of solvent furnished a residue, which was purified by column chromatography using silica gel. Elution with 35% ethyl acetate-hexane furnished *mono*-thioacetal **87b** (37 mg, 90%). This sample was found

to be identical (mp, IR, and $^1H$ NMR) to the sample **87b** derived from *mono*-thioacetal **80b.**

**Oxidation** of **98a; conversion** of **98a** to **78a:**

To a stirred solution of the diol **98a** (33 mg, 0.1 mmol) in acetone (5 mL), cooled in an ice-bath (0-5 °C), was added drop-wise Jones reagent until a faint orange colour persisted. After stirring for 10 minutes, the reaction was quenched with ice-cold aqueous $NaHCO_3$ and extracted with ethyl acetate (3 x 5 mL). Removal of solvent and crystallization from DCM-hexane furnished dione 78a (32 mg. 98%). This sample was found to be identical (mp, IR. and $^1H$ NMR) to the sample 78a derived from dione 65a.

**Thioacetalisation** of 91; conversion of 91 to 89a:

A mixture of dione 91 (34 mg, 0.1 mmol), 1,2-ethanedithiol (0.02 mL. 0.2 mmol), PTSA (3mg) and benzene (10 mL) was refluxed for 6 h with a Dean-Stark water separator. Usual work-up and removal of solvent furnished a residue. which was purified by column chromatography using silica gel. Elution with 40% ethyl acetate-hexane furnished *mono*-thioacetal 89a (38 mg, 90%). This sample was found to be identical (mp. IR. and $^1H$ NMR) to the sample **89a** derived from *mono*-thioacetal 80a.

Thioacetaiisation of **91;** conversion of 91 to 89b:

A mixture of dione 91 (34 mg, 0.1 mmol), 1,3-propanedithiol (0.02 mL. 0.2 mmol), PTSA (3mg) and benzene (10 mL) was refluxed for 6 h with a Dean-Stark water separator. Usual work-up and removal of solvent furnished a residue. which was purified by column chromatography using silica gel. Elution with 40% ethyl

acetate-hexane furnished *mono*-thioacetal 89b (41 mg, 95%). This sample was found to be identical (mp, IR, and 'H NMR) to the sample 89b derived from *mono*-thioacetal 80b.

**CRYSTALLOGRAPHY**

**Single-Crystal X-ray Analysis of 73a:**

*Crystal data:* $C_{15}H_{12}O_4$, $M_r$ = 256.26, colourless crystals from DCM-hexane. monoclinic, space group $P2_1/n$, $a$ = 8.710(1), $b$ = 6.390(3), $c$ = 20.58(1) A, $\beta$ = 97.99(3)°, $V$= 1134.3(8) Å$^3$, Z = 4, $D_{calcd}$ = 1.501 Mg m$^{-3}$, $T$ = 295 °K, $F(000)$ = 536. crystal dimensions 0.45 x 0.20 x 0.15 mm.

*Data collection and structure solution:* Data were collected on Enraf-Nonius CAD-4 diffractometer, with graphite-monochromated Mo-K$\alpha$ radiation (A= 0.7107 A), by the $\omega/2\theta$ scan method in the range $0 < 0 < 27°$. A total of 2876 reflections were collected ($+h$, $+k$, $\pm l$), with 2464 unique reflections, of which 1008 had $F_o > 5\sigma(F_o)$, and were used in all calculations. At final convergence $R_1$ = 0.076. The structure was solved by direct methods,[63a] refined by full-matrix least-squares on $F$ with the non-H atoms anisotropic, and H atoms isotropic.[63b]

**Single-Crystal X-ray Analysis of 73e:**

*Crystal data:* $C_{19}H_{20}O_6$, $M_r$ = 344.40. colourless crystals from DCM-hexane. orthorhombic, space group $P2_12_12_1$, $a$ = 8.889(2), $b$ = 9.011(4), $c$ = 19.369(6) A, $V$ = 1551.4(9) A$^3$. Z = 4, $D_{calcd}$ = 1.731 Mg m$^{-3}$, $T$= 293 °K, $F(000)$ = 848, $\mu$(Mo-K$\alpha$) = 0.125 mm$^{-1}$.

*Data collection and structure solution:* Data were collected on Enraf-Nonius CAD-4 diffractometer. with graphite-monochromated Mo-K$\alpha$ radiation ($\lambda$ = 0.71070 A), by the $\omega/2\theta$ scan method in the range $2<d<25°$. At final convergence $R_1$ [$I > 2\sigma(I)$] =

*Experimental*

0.0517, $wR_2$ = 0.1491 for 306 parameters, GOF = 1.393, $\Delta\rho_{max}$ = 0.293 eÅ$^{-3}$, $\Delta\rho_{min}$ = -0.252 eA • The structure was solved by direct methods,[63a] refined by full-matrix least-squares on *F* with all non-H atoms anisotropic and H atoms isotropic.[63b]

**Single-Crystal X-ray Analysis of 92b:**

***Crystal data:*** $C_{19}H_{20}O_6$, $M_r$ = 344.35, colourless crystals from DCM-hexane. triclinic, space group $P\bar{1}$ *a* = 8.381(1), *b* = 8.620(1), *c* = 12.508(3) A, $\alpha$ = 87.52(1), *P* = 85.08(1), $\gamma$ = 62.32(1)°, V= 797.3(2) A *Z* = 2, $D_{calcd}$ = 1.434 Mg m$^{-3}$, *T*= 293 °K. *F*(000) = 364. $\mu$(Mo-K$\alpha$) = 0.107 mm$^{-1}$. crystal dimensions 0.14 x 0.21 x 0.16 mm.

*Data collection and structure solution:* Data were collected on Enraf-Nonius MACH-3 diffractometer. with graphite-monochromated Mo-K$\alpha$ radiation (A = 0.71073 A). by the $\omega$ scan method in the range 2 < *9* < 25°. A total of 2855 reflections were collected (+*h*, ±*k*, ±/), with 2804 unique reflections [$R_{int}$ = 0.0], of which 2213 had $F_o > 4\sigma(F_o)$, and were used in all calculations. At final convergence $R_1$ [/ > 2σ*I*)] = 0.0497. $wR_2$ = 0.1936 for 228 parameters. GOF • 1.334. $\Delta\rho_{max}$ = 0.403 eA , $\Delta\rho_{min}$ = -0.357 eA • The data were reduced using XTAL (version 3.4). solved by direct methods. refined by full-matrix least-squares on *F* with the non-H atoms anisotropic. and H atoms were placed in calculated positions and were allowed to ride on **their** parent atoms.[63c]

**Single-Crystal X-ray Analysis of 93c:**

*Crystal data:* $C_{17}H_{20}O_4$, $M_r$ = 288.3, colourless crystals from DCM-hexane, monoclinic, space group *I2/a*, *a* = 26.035(8), *b* = 8.259(3), *c* = 26.04(1) A, $\beta$ = 90.05(3)°, *V* = 5599(3) Å$^3$, Z = 16, $D_{calcd}$ = 1.372 Mg m$^{-3}$, *T*= 296 °K. *F*(000) = 2464. $\mu$(Mo-K$\alpha$) = 0.097 mm" , crystal dimensions 0.25 x 0.20 x 0.45 mm.

*Data collection and structure solution:* Data were collected on Siemens R3m/V diffractometer, with graphite-monochromated Mo-K$\alpha$ radiation (A = 0.71073 A), by the $\omega$ scan method in the range 3 < 2$\theta$ < 42°. Out of 3077 unique reflections [$R_{int}$ = 0.03], of which 1961 had *F* > 4$\sigma$(*F*), and were used in all calculations. At final convergence $R_1$ = 0.0564. $wR_2$ = 0.0588 for 309 parameters, GOF = 1.47. $\Delta\rho_{max}$ = 0.23 eA$^{-3}$. $\Delta\rho_{min}$ = -0.22 eA$^{-3}$. The stucture was solved by direct methods, refined by lull-matrix least-squares on *F*~ with all non-H atoms anisotropic. except C4-C9. C17. C25-C30 and C38 which were isotropic. The H atoms were placed in calculated positions and were allowed to ride on their parent atoms.

Single-Crystal X-ray Analysis of 105:

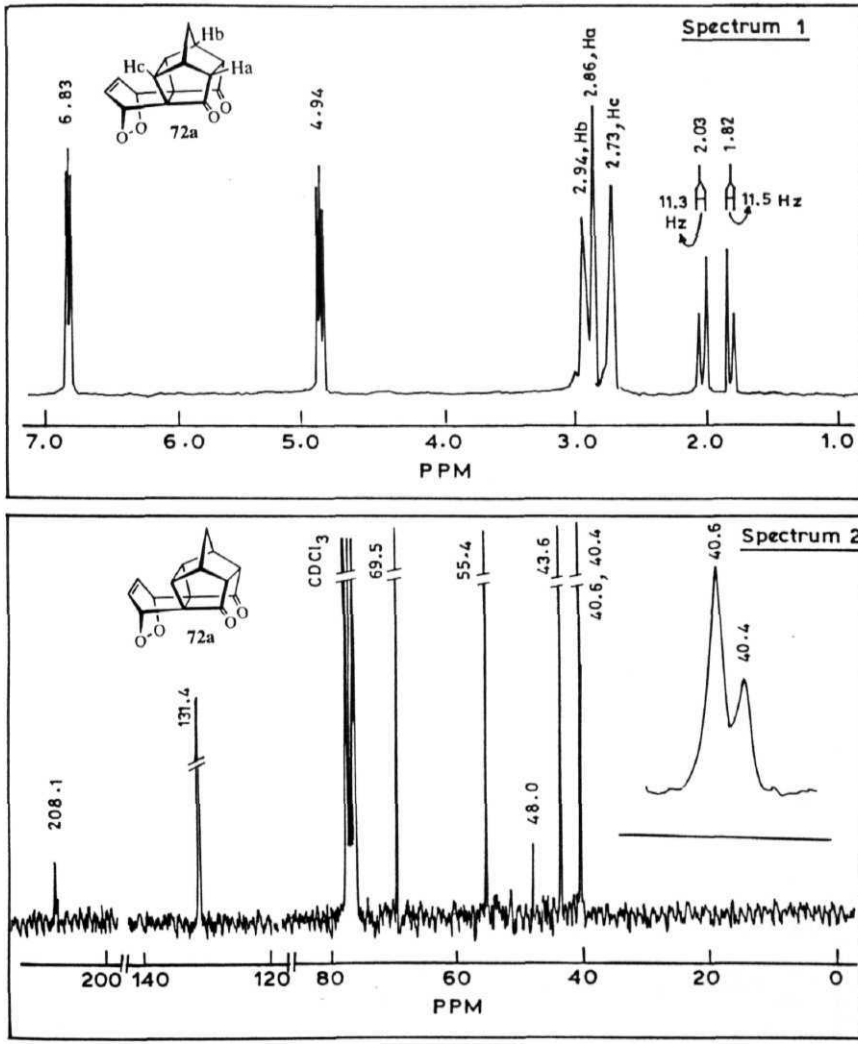
*Crystal data:* $C_{19}H_{16}O_8$, $M_r$ = 372.33. colourless crystals from DCM-hexane. triclinic, space group *P*1, *a* = 10.105(6), *b* = 14.327(2). c = 23.382(2) A. $\alpha$ = 81.06(2), 0=86.03(2), $\gamma$ = 89.17(3)°, *V* = 3336(2) Å$^3$, Z=8, $D_{calcd}$ = 1.483 Mg m$^{-3}$, *T* = 295 °K. *F*(000) = 1552. crystal dimensions 0.2 x 0.15 x 0.15 mm.

*Data collection and structure solution:* Data were collected on Enraf-Nonius CAD-4 diffractometer, with graphite-monochromated Mo-K$\alpha$ radiation (A= 0.7107 A), by the $\omega$/2$\theta$ scan method in the range *0* < $\theta$ < 20°. A total of 8852 reflections were

*Experimental*

collected ($+h$, $\pm k$, $\pm l$), with 8160 unique reflections, of which 3844 had $F_o > 5\sigma(F_o)$, and were used in all calculations. At final convergence $R_1 = 0.052$. The structure was solved by direct methods,[63a] refined by full-matrix least-squares on $F$~ with the non-H atoms anisotropic, and H atoms isotropic.[63b]

# 1.5 SPECTRA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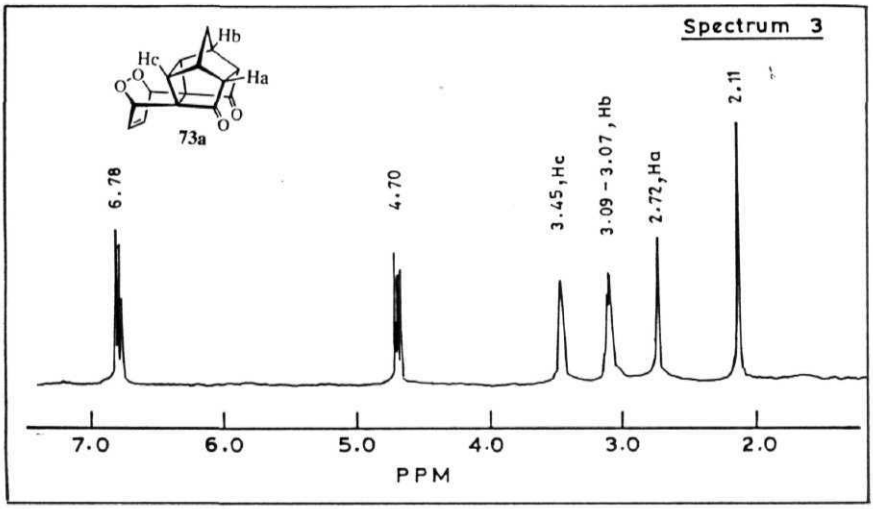
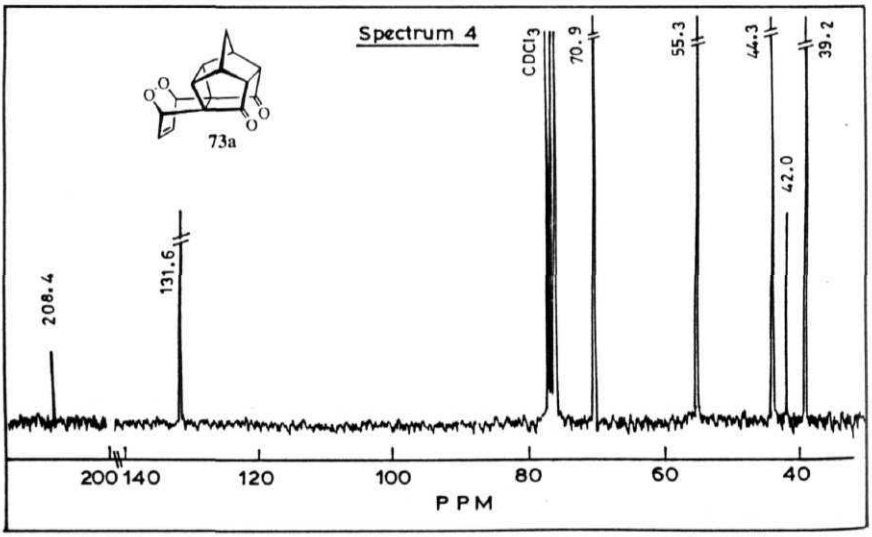
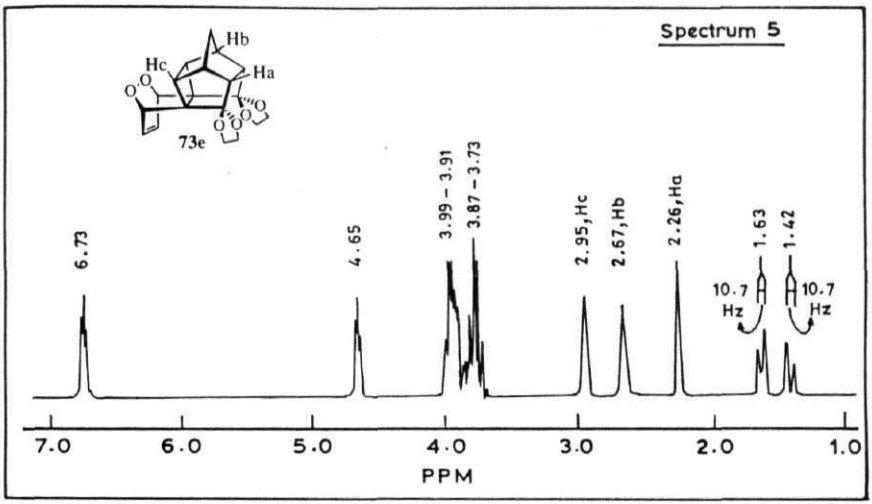
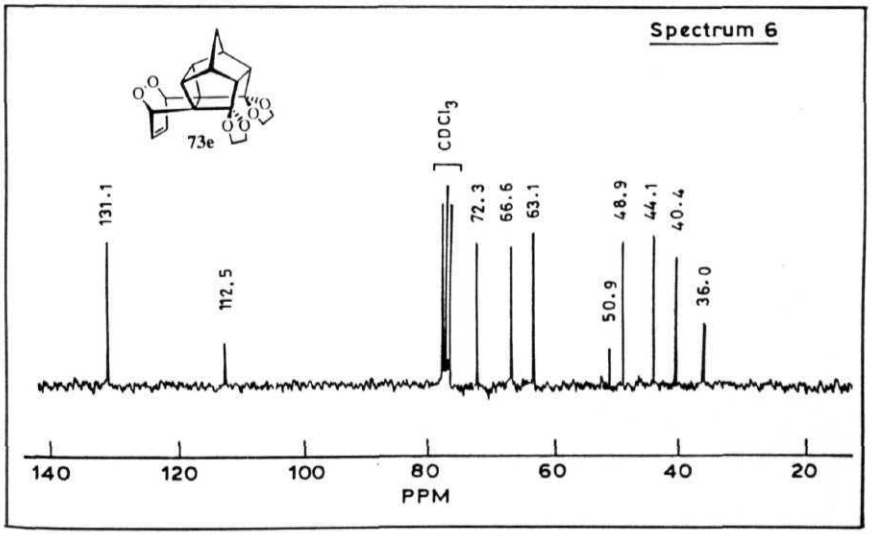
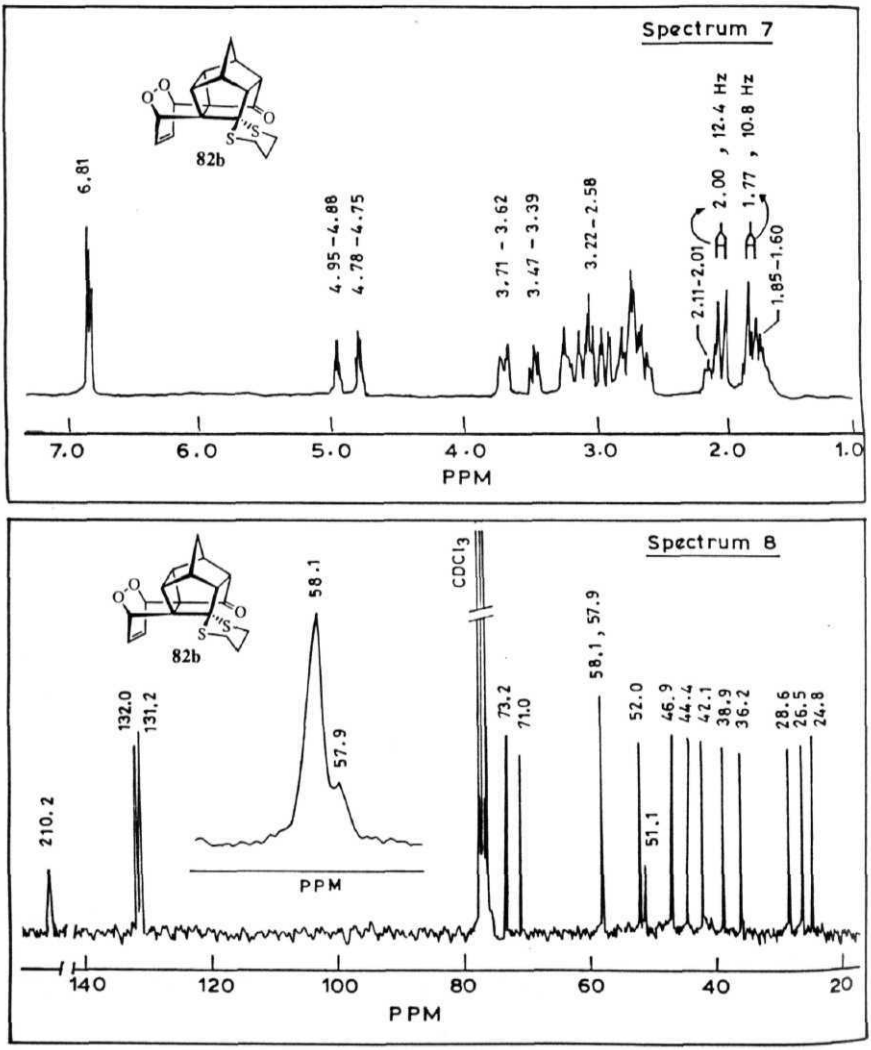
Hb
Hc
Ha
72a
6.83
4.94
2.94, Hb
2.86, Ha
2.73, Hc
2.03
1.82
11.3 Hz
11.5 Hz
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM
Spectrum 2
72a
208.1
131.4
CDCl3
69.5
55.4
48.0
43.6
40.6, 40.4
40.6
40.4
200
140
120
80
60
40
20
0
PPM

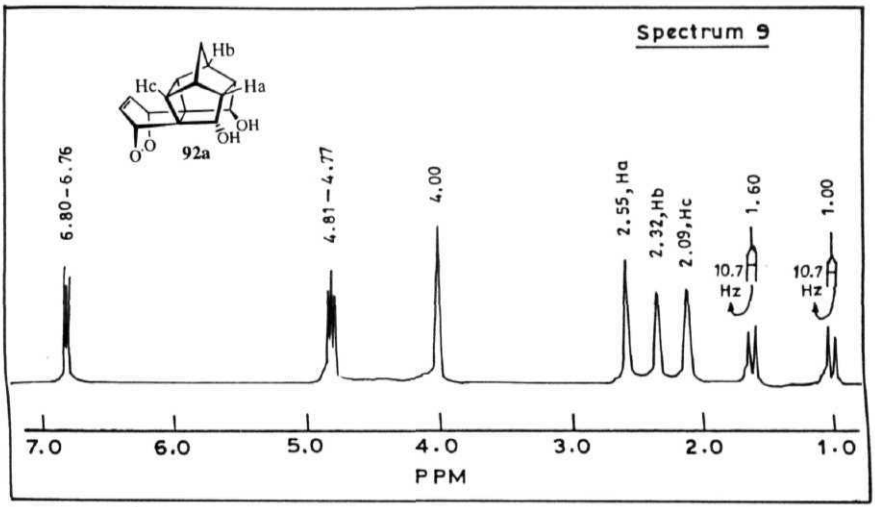

Spectrum 3
Hb
Hc
Ha
73a
6.78
4.70
3.45, Hc
3.09 - 3.07, Hb
2.72, Ha
2.11
7.0
6.0
5.0
4.0
3.0
2.0
PPM

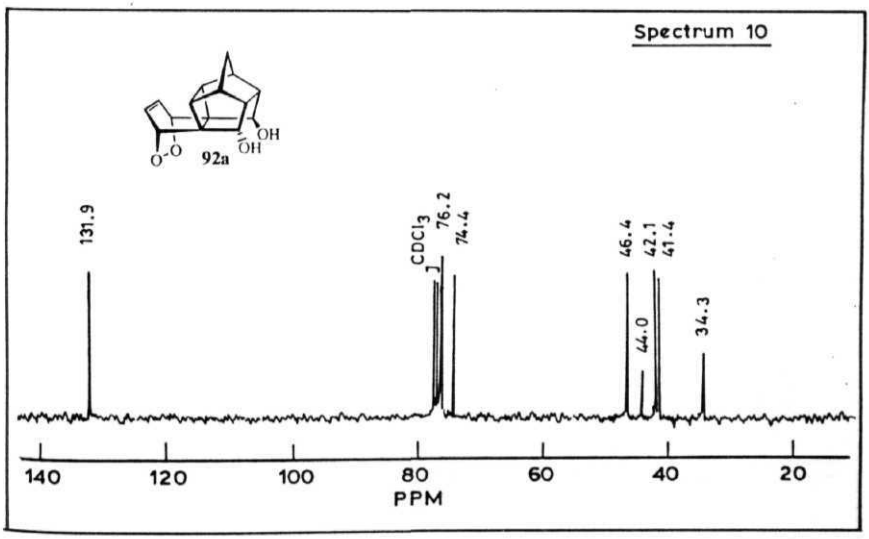

Spectrum 4
73a
208.4
131.6
CDCl3
70.9
55.3
44.3
42.0
39.2
200
140
120
100
80
60
40
PPM

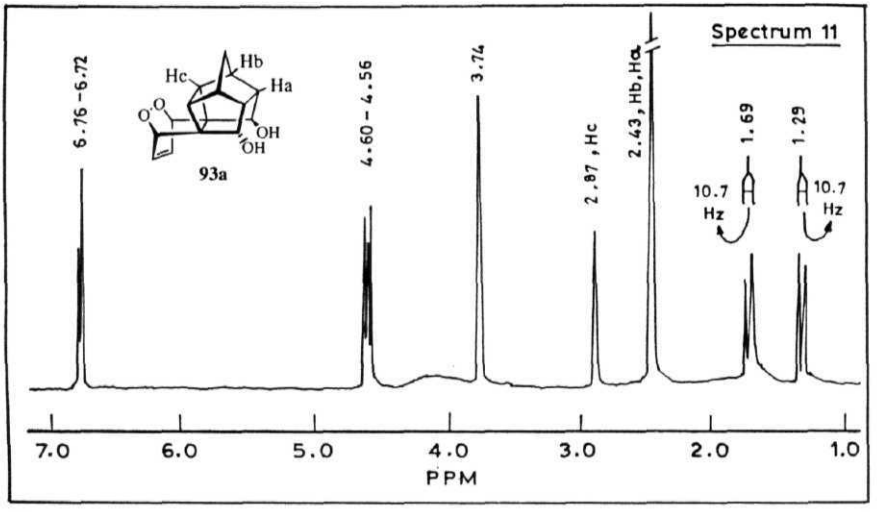

Spectrum 5
Hb
Hc
Ha
73e
6.73
4.65
3.99 – 3.91
3.87 – 3.73
2.95, Hc
2.67, Hb
2.26, Ha
1.63
1.42
10.7 Hz
10.7 Hz
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM

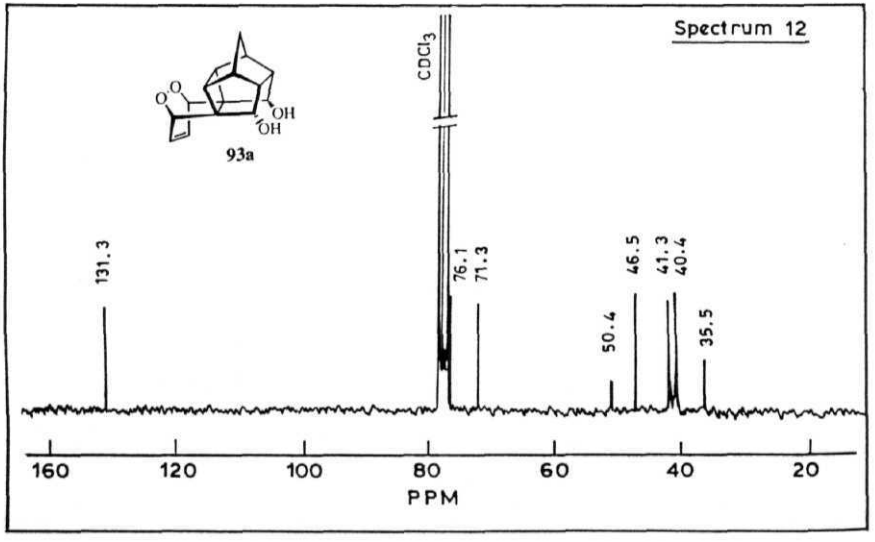

Spectrum 6
73e
CDCl3
131.1
112.5
72.3
66.6
63.1
48.9
44.1
40.4
36.0
50.9
140
120
100
80
60
40
20
PPM

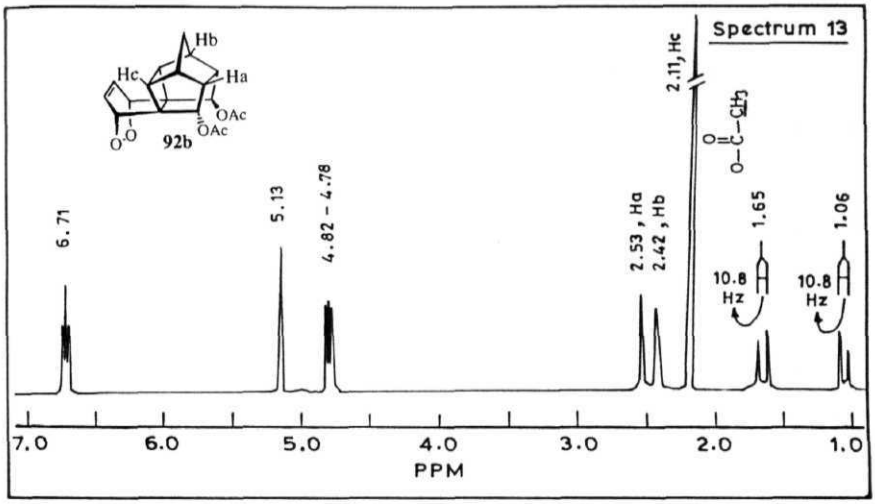

Spectrum 7
82b
6.81
4.95 – 4.88
4.78 – 4.75
3.71 – 3.62
3.47 – 3.39
3.22 – 2.58
2.11-2.01
2.00 , 12.4 Hz
1.77 , 10.8 Hz
1.85-1.60
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM
Spectrum 8
82b
210.2
132.0
131.2
58.1
57.9
PPM
CDCl3
73.2
71.0
58.1 , 57.9
52.0
51.1
46.9
44.4
42.1
38.9
36.2
28.6
26.5
24.8
140
120
100
80
60
40
20
PPM

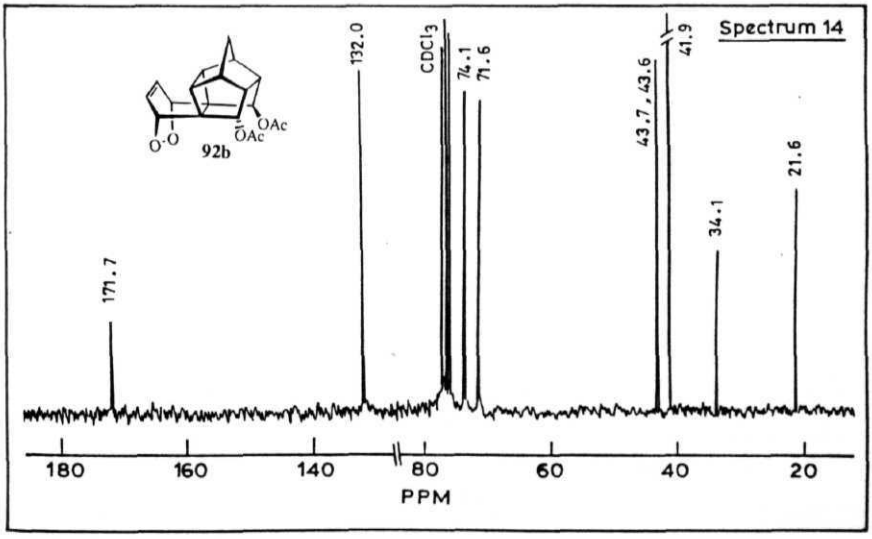

Spectrum 9
Hb
Hc
Ha
OH
OH
O
O
92a
6.80-6.76
4.81-4.77
4.00
2.55, Ha
2.32, Hb
2.09, Hc
1.60
1.00
10.7 Hz
10.7 Hz
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM

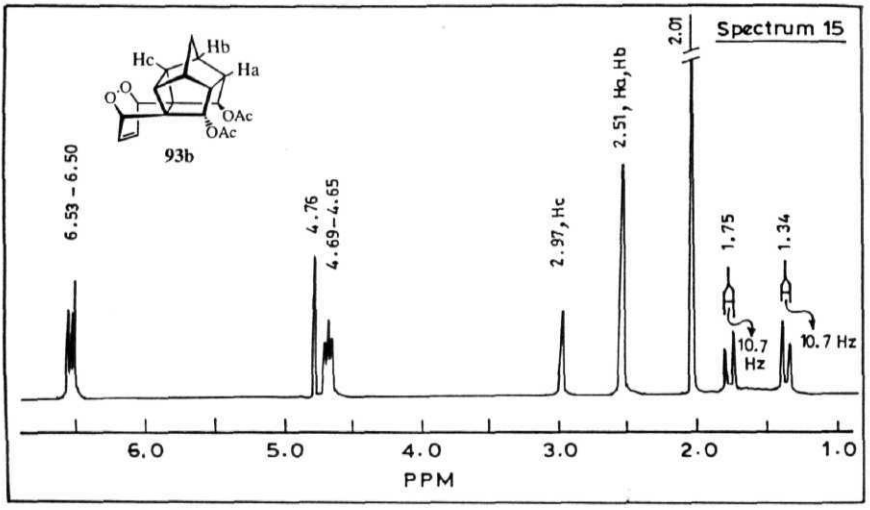

Spectrum 10
OH
OH
O
O
92a
131.9
CDCl3
76.2
74.4
46.4
42.1
41.4
44.0
34.3
140
120
100
80
60
40
20
PPM

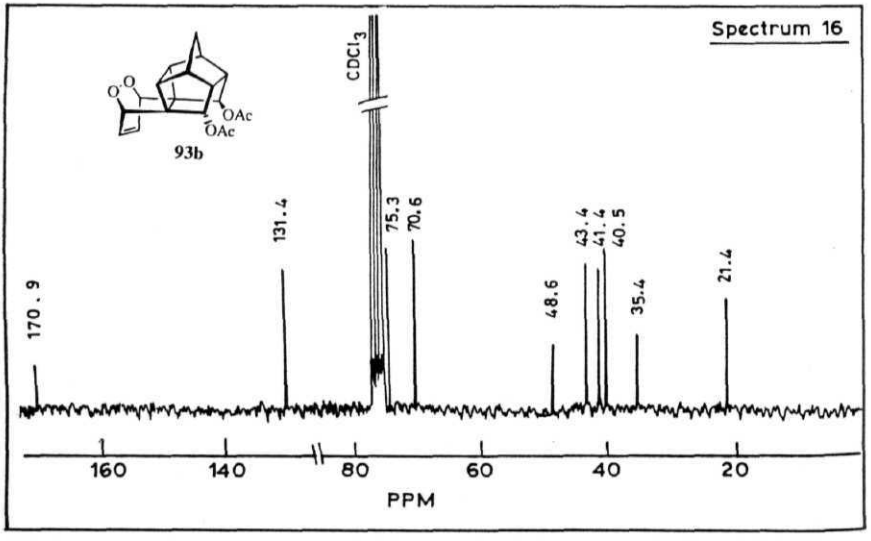

Spectrum 11
6.76 - 6.72
4.60 - 4.56
3.74
2.87 , Hc
2.43 , Hb, Ha
1.69
1.29
10.7 Hz
10.7 Hz
Hc
Hb
Ha
OH
OH
93a
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM

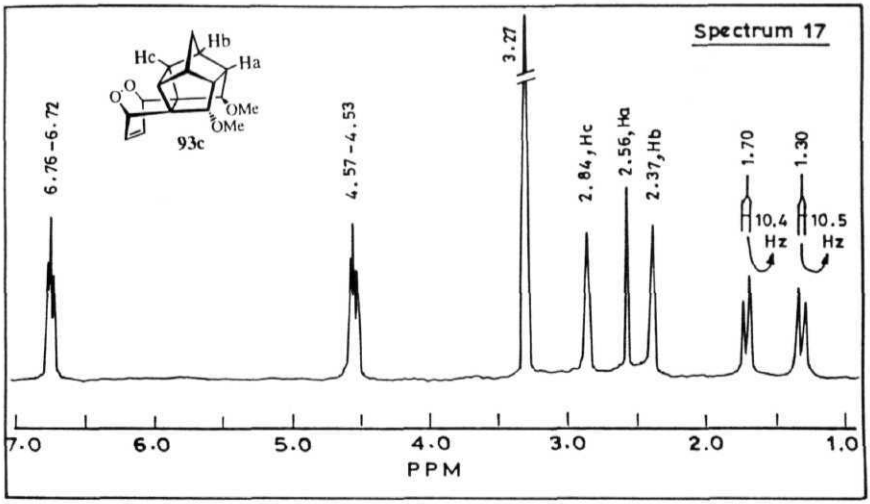

Spectrum 12
CDCl3
131.3
76.1
71.3
50.4
46.5
41.3
40.4
35.5
OH
OH
93a
160
120
100
80
60
40
20
PPM

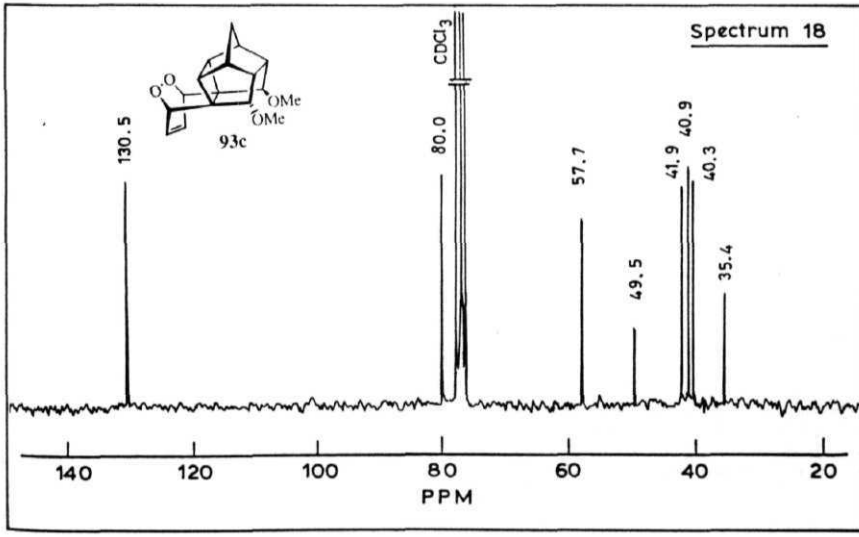

Spectrum 13
Hb
Hc
Ha
OAc
OAc
92b
6.71
5.13
4.82 - 4.78
2.53 , Ha
2.42 , Hb
2.11, Hc
1.65
1.06
10.8 Hz
10.8 Hz
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM

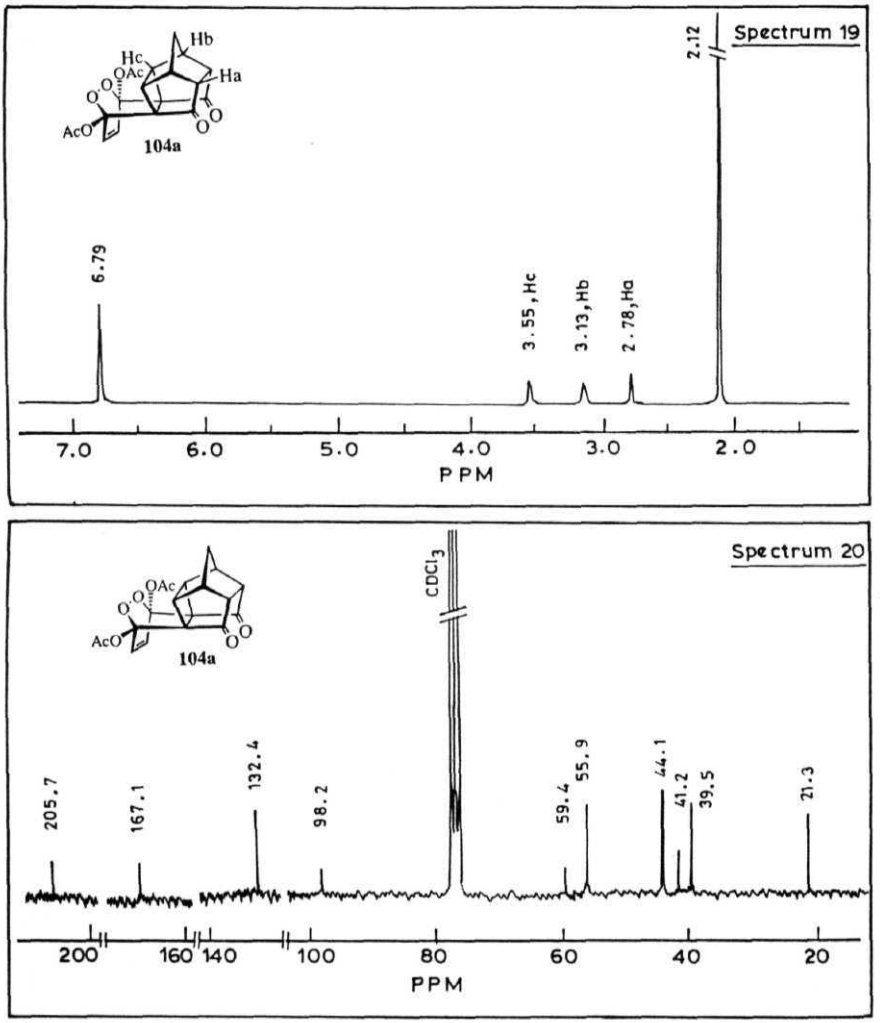

Spectrum 14
OAc
OAc
92b
171.7
132.0
CDCl3
74.1
71.6
43.7 , 43.6
41.9
34.1
21.6
180
160
140
80
60
40
20
PPM

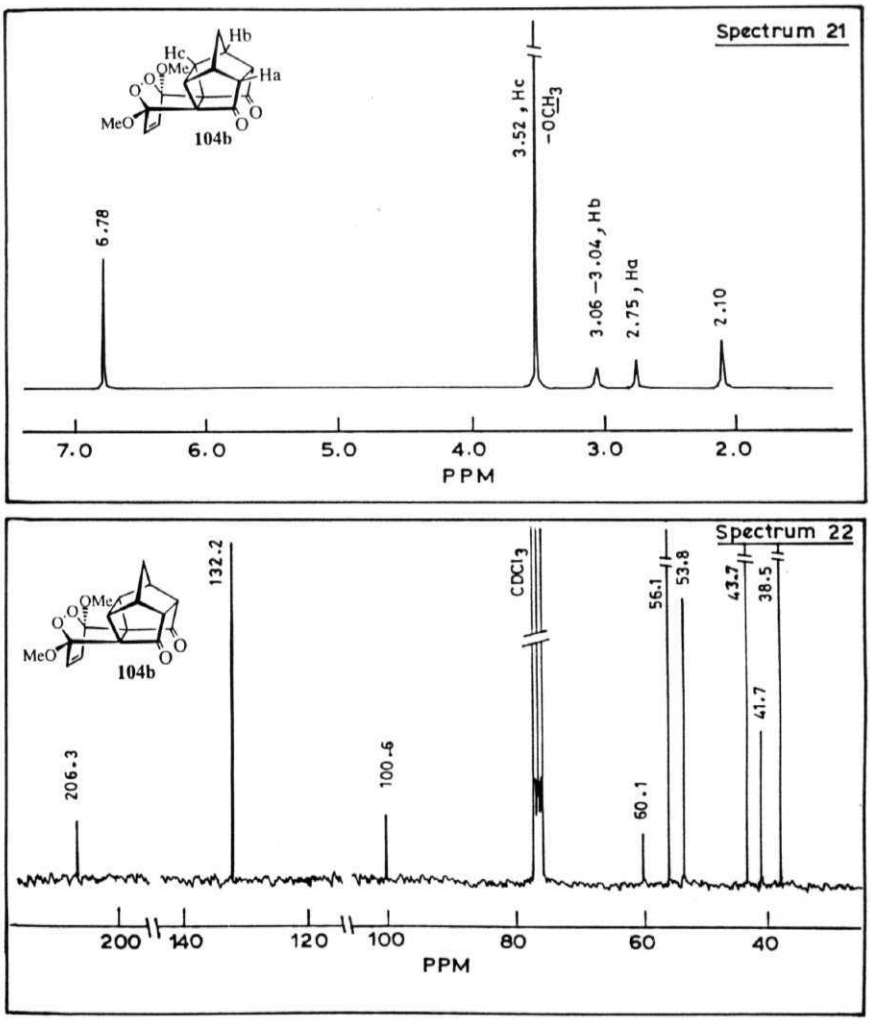

Spectrum 15
Hc
Hb
Ha
OAc
OAc
93b
6.53 – 6.50
4.76
4.69–4.65
2.97, Hc
2.51, Ha, Hb
2.01
1.75
1.34
10.7 Hz
10.7 Hz
6.0
5.0
4.0
3.0
2.0
1.0
PPM

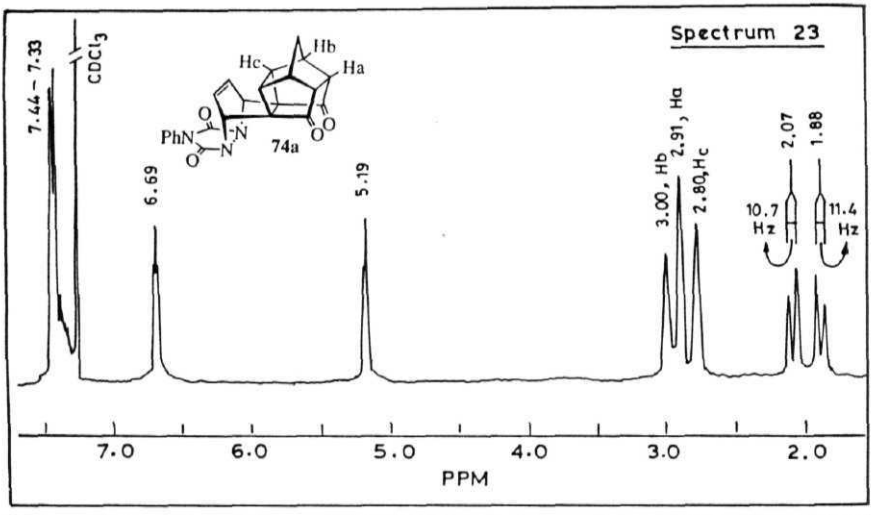

Spectrum 16
CDCl3
OAc
OAc
93b
170.9
131.4
75.3
70.6
48.6
43.4
41.4
40.5
35.4
21.4
160
140
80
60
40
20
PPM

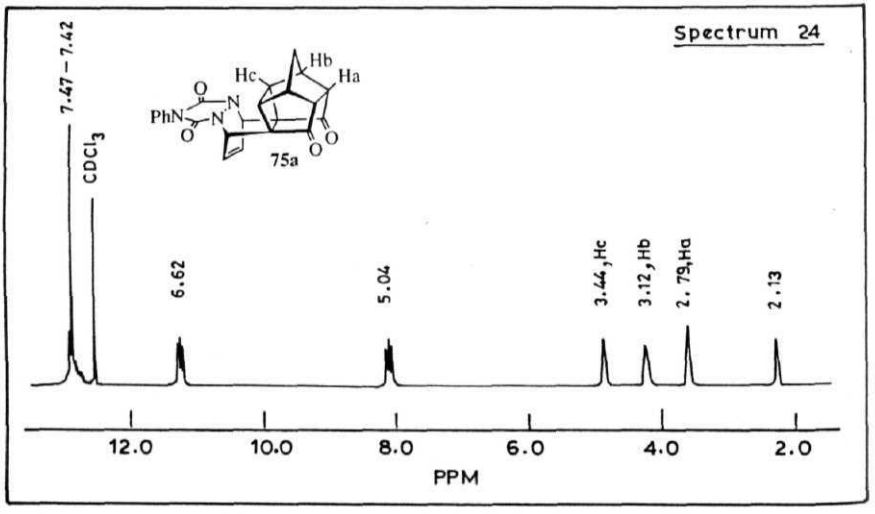

Spectrum 17
Hb
Hc
Ha
OMe
OMe
93c
6.76-6.72
4.57-4.53
3.27
2.84, Hc
2.56, Ha
2.37, Hb
1.70
1.30
10.4 Hz
10.5 Hz
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM

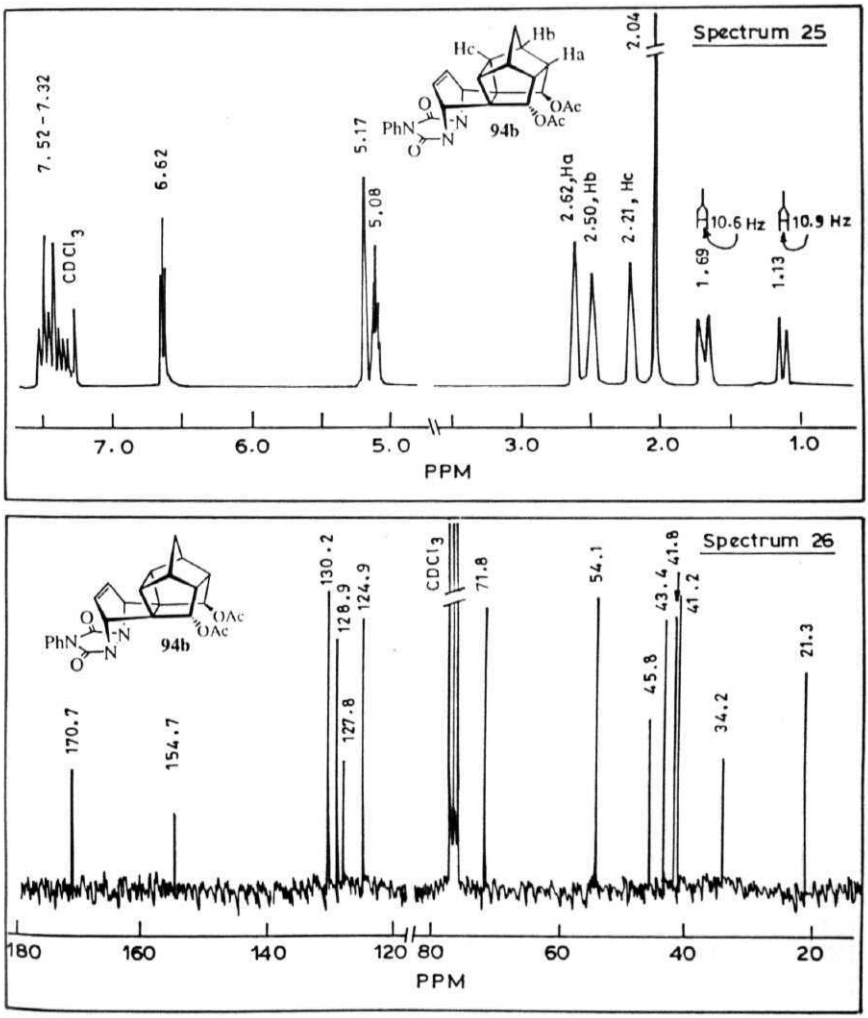

Spectrum 18
CDCl3
OMe
OMe
93c
130.5
80.0
57.7
49.5
41.9
40.9
40.3
35.4
140
120
100
80
60
40
20
PPM

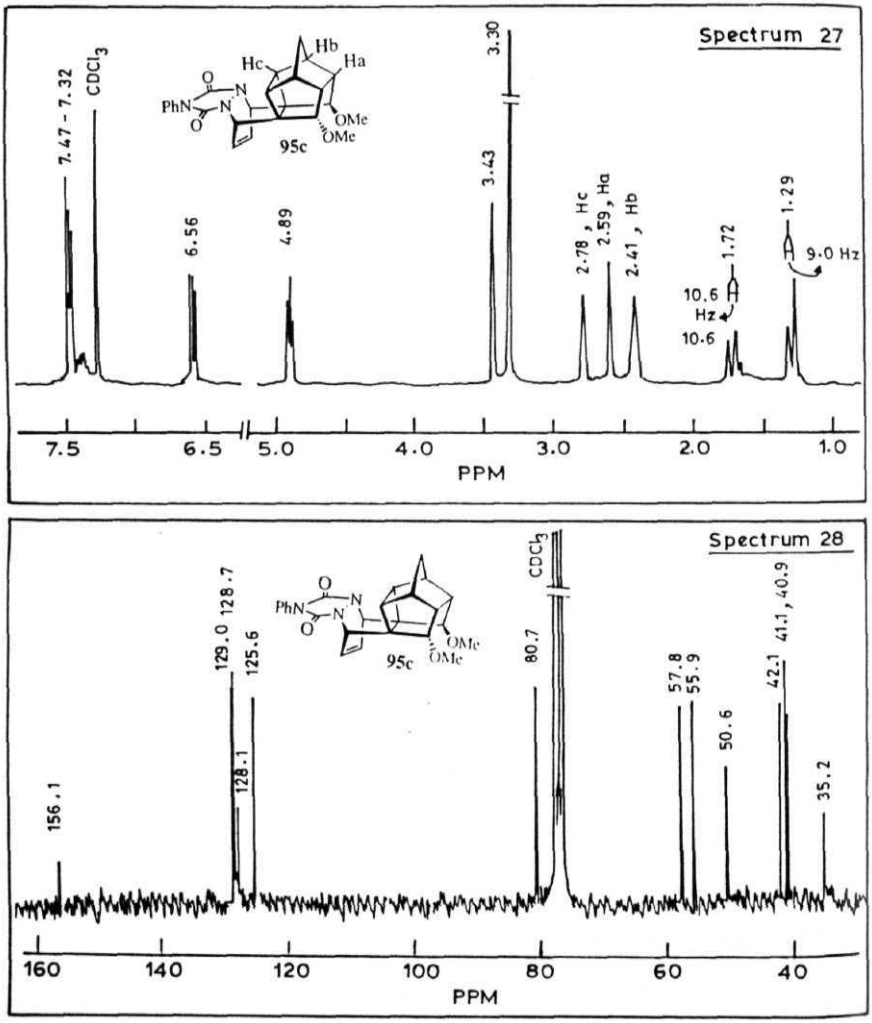

Spectrum 19
Hb
Hc
OAc
Ha
AcO
104a
2.12
6.79
3.55, Hc
3.13, Hb
2.78, Ha
7.0
6.0
5.0
4.0
3.0
2.0
PPM
Spectrum 20
OAc
AcO
104a
CDCl3
205.7
167.1
132.4
98.2
59.4
55.9
44.1
41.2
39.5
21.3
200
160
140
100
80
60
40
20
PPM

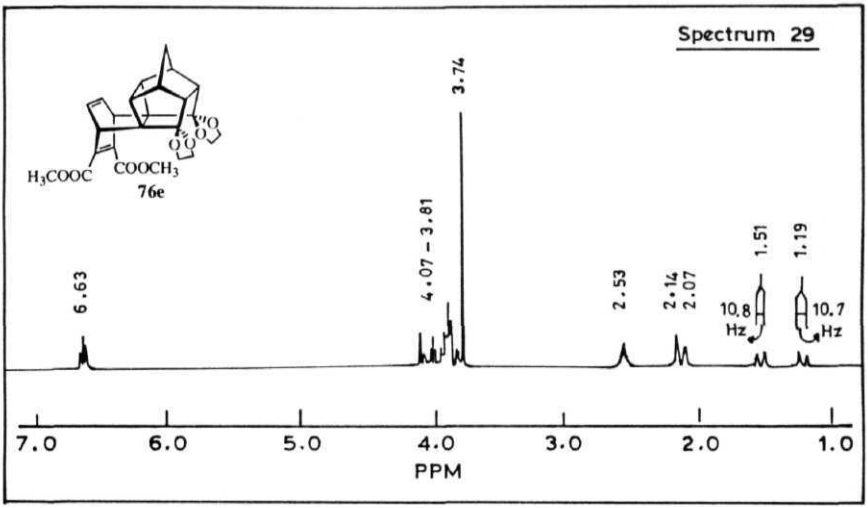

Spectrum 21
Hb
Hc
OMe
Ha
MeO
O
104b
3.52 , Hc
-OCH3
6.78
3.06 –3.04 , Hb
2.75 , Ha
2.10
7.0
6.0
5.0
4.0
3.0
2.0
PPM
Spectrum 22
OMe
MeO
104b
132.2
CDCl3
56.1
53.8
43.7
38.5
41.7
206.3
100.6
60.1
200
140
120
100
80
60
40
PPM

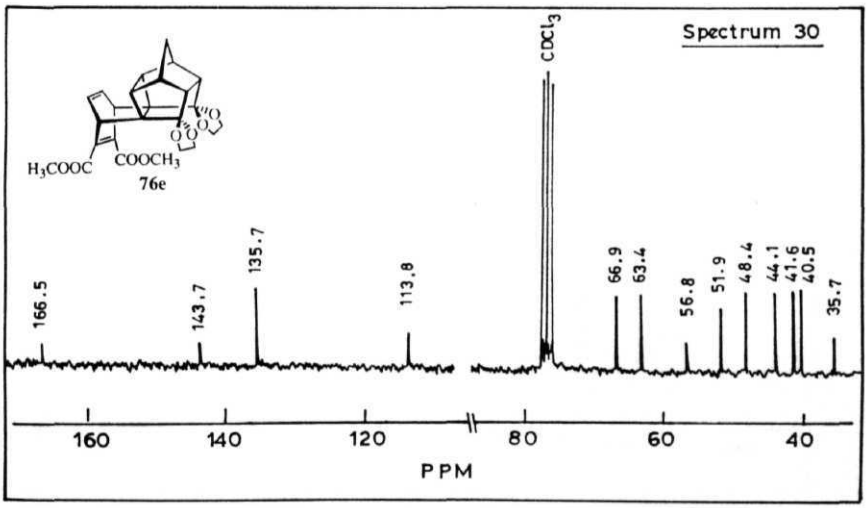

Spectrum 23
7.44 – 7.33
CDCl3
6.69
5.19
3.00, Hb
2.91, Ha
2.80, Hc
2.07
1.88
10.7 Hz
11.4 Hz
Hc
Hb
Ha
PhN
74a
7.0
6.0
5.0
4.0
3.0
2.0
PPM

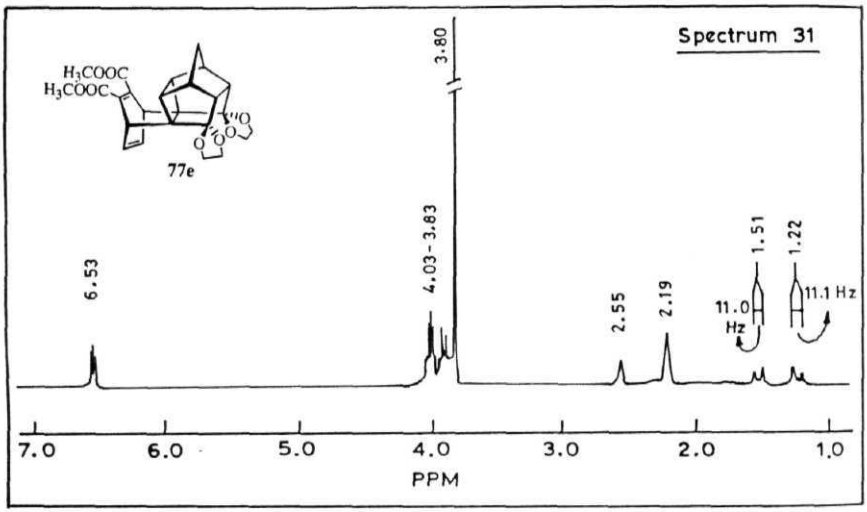

Spectrum 24
7.47 – 7.42
CDCl3
6.62
5.04
3.44, Hc
3.12, Hb
2.79, Ha
2.13
Hc
Hb
Ha
PhN
75a
12.0
10.0
8.0
6.0
4.0
2.0
PPM

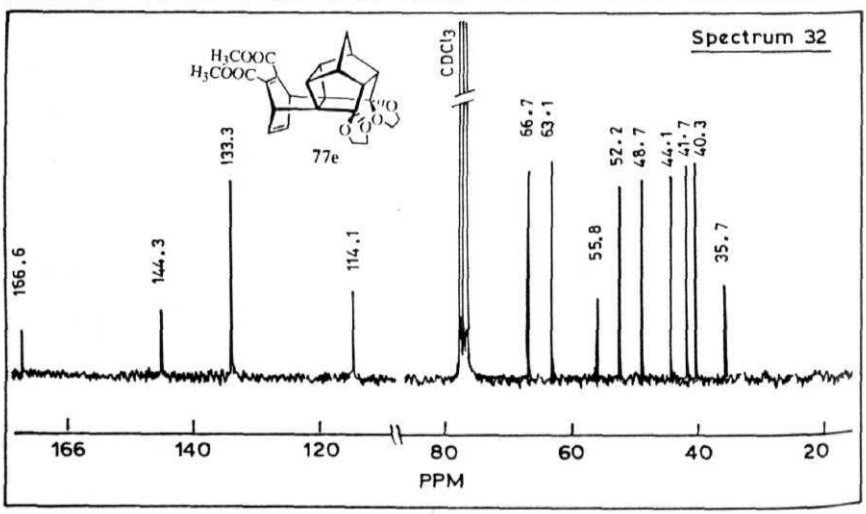

Spectrum 25
7.52-7.32
CDCl3
6.62
5.17
5.08
2.62,Ha
2.50,Hb
2.21, Hc
2.04
1.69
1.13
10.6 Hz
10.9 Hz
Hc
Hb
Ha
OAc
OAc
PhN
94b
7.0
6.0
5.0
3.0
2.0
1.0
PPM
Spectrum 26
130.2
128.9
124.9
127.8
CDCl3
71.8
54.1
43.4
41.8
41.2
45.8
34.2
21.3
170.7
154.7
94b
180
160
140
120
80
60
40
20
PPM

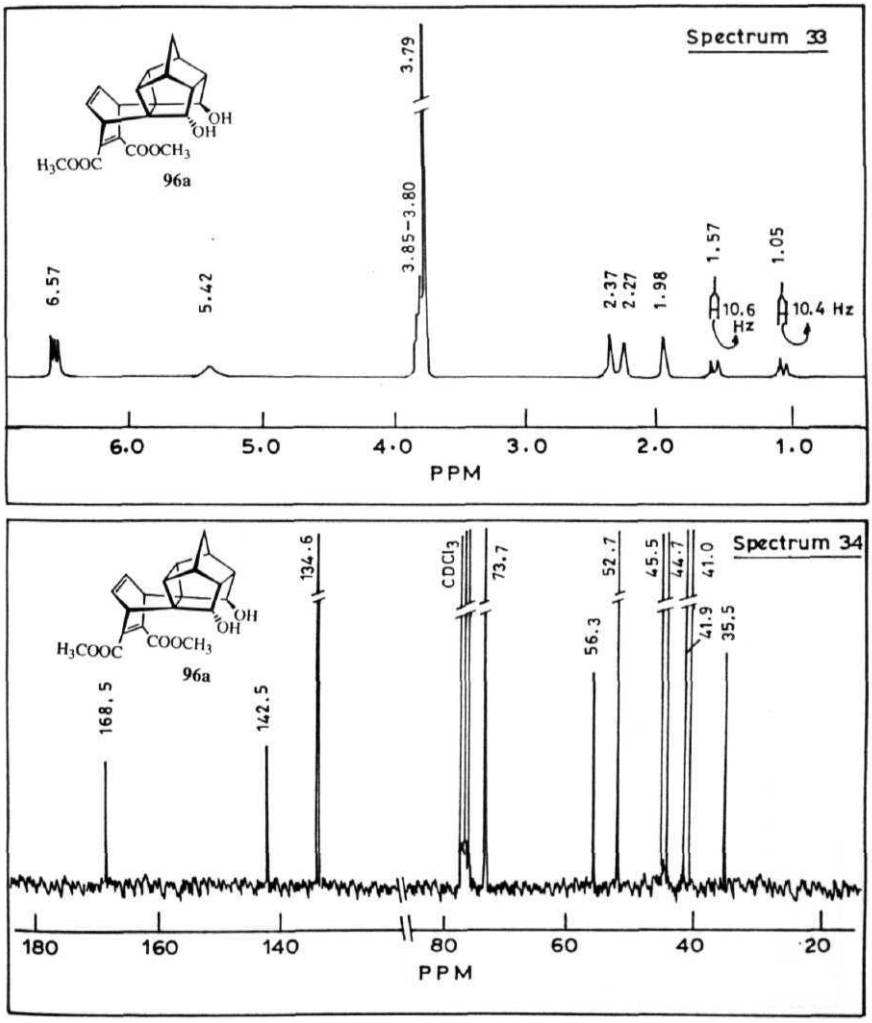

Spectrum 27
7.47 - 7.32
CDCl3
6.56
4.89
3.43
3.30
2.78 , Hc
2.59 , Ha
2.41 , Hb
1.72
10.6 Hz
10.6
1.29
9.0 Hz
Hb
Hc
Ha
PhN
OMe
OMe
95c
7.5
6.5
5.0
4.0
3.0
2.0
1.0
PPM
Spectrum 28
156 , 1
129.0
128.7
128.1
125.6
CDCl3
80.7
57.8
55.9
50.6
42.1
41.1 , 40.9
35.2
95c
160
140
120
100
80
60
40
PPM

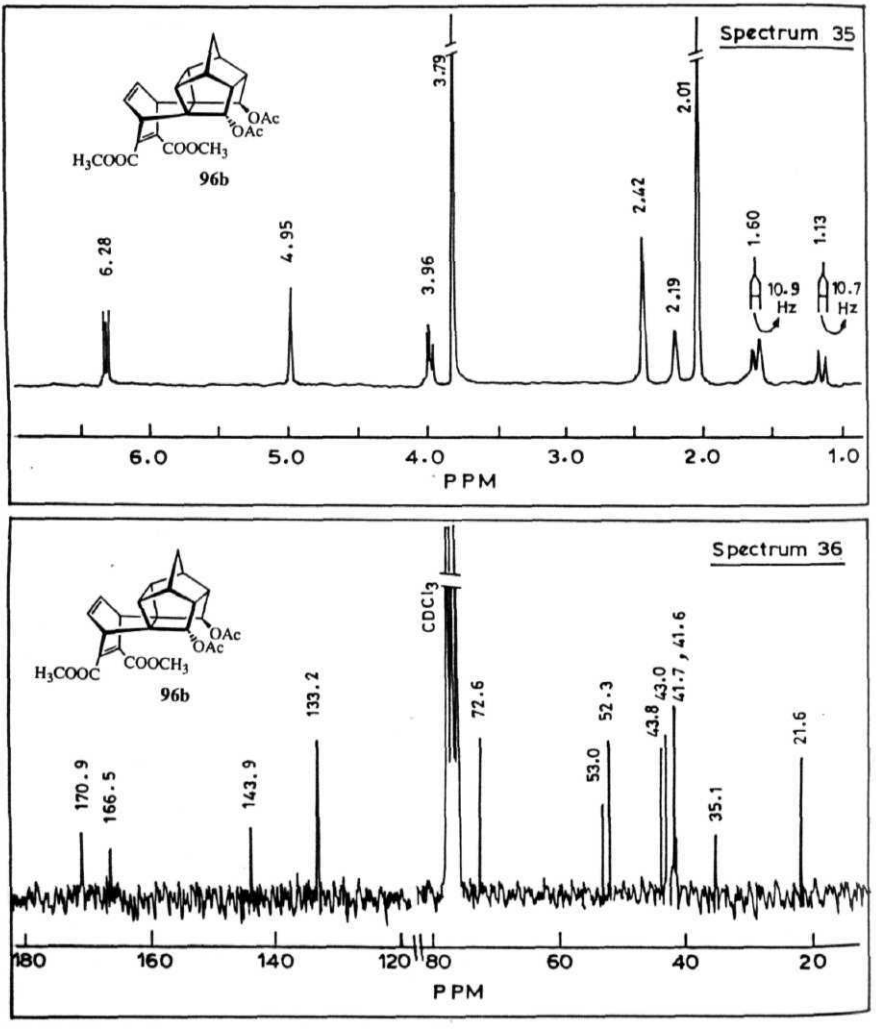

Spectrum 29
$H_3COOC$
$COOCH_3$
76e
6.63
4.07 – 3.81
3.74
2.53
2.14
2.07
1.51
1.19
10.8 Hz
10.7 Hz
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM

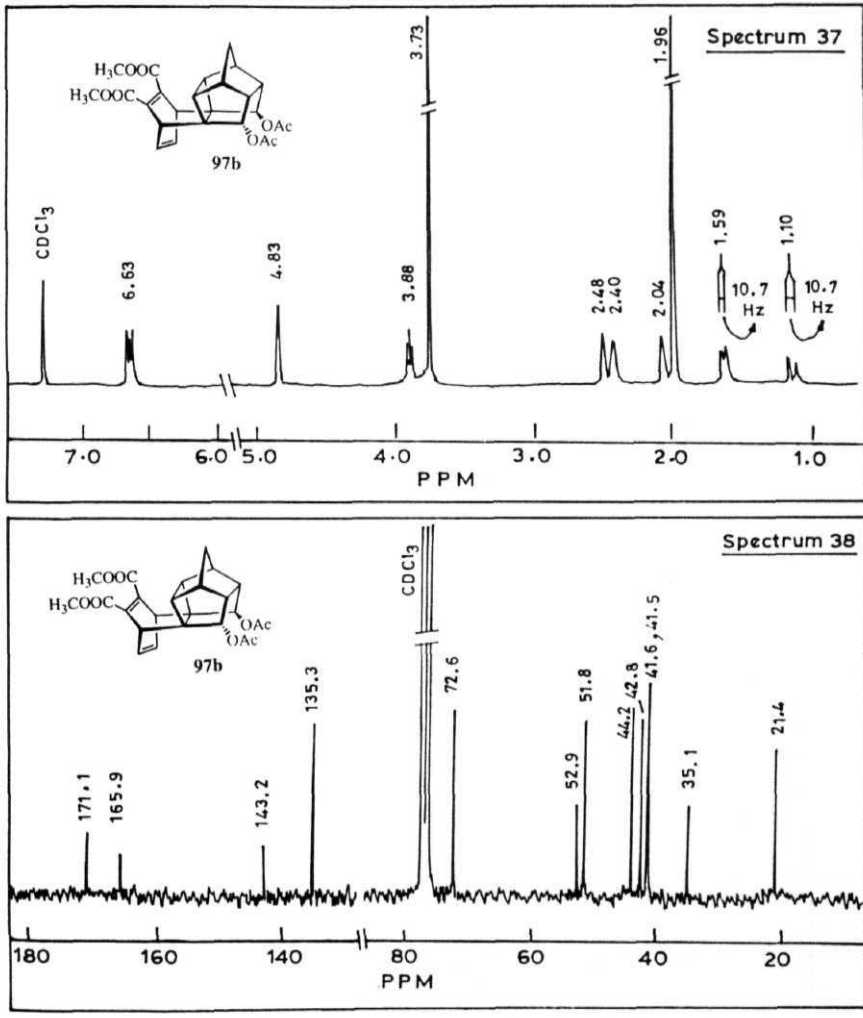

Spectrum 30
$COCl_3$
$H_3COOC$
$COOCH_3$
76e
166.5
143.7
135.7
113.8
66.9
63.4
56.8
51.9
48.4
44.1
41.6
40.5
35.7
160
140
120
80
60
40
PPM

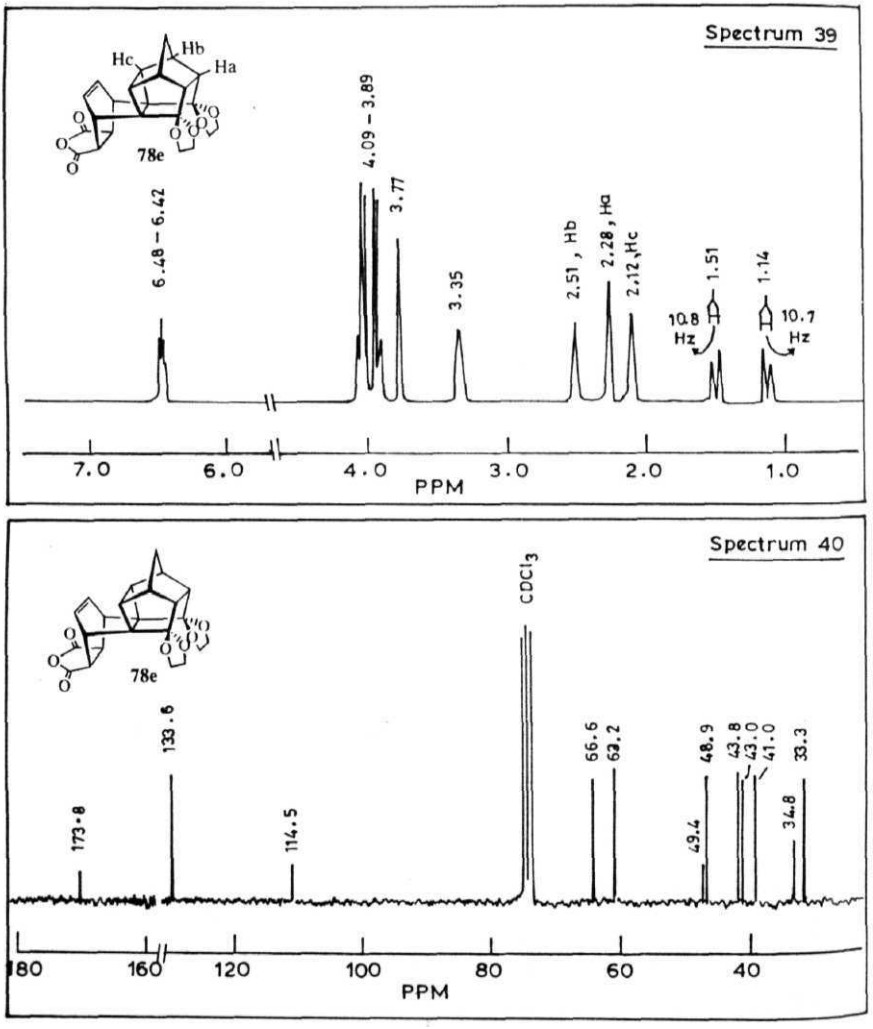

Spectrum 31
H3COOC
H3COOC
77e
3.80
6.53
4.03-3.83
2.55
2.19
1.51
1.22
11.0 Hz
11.1 Hz
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM

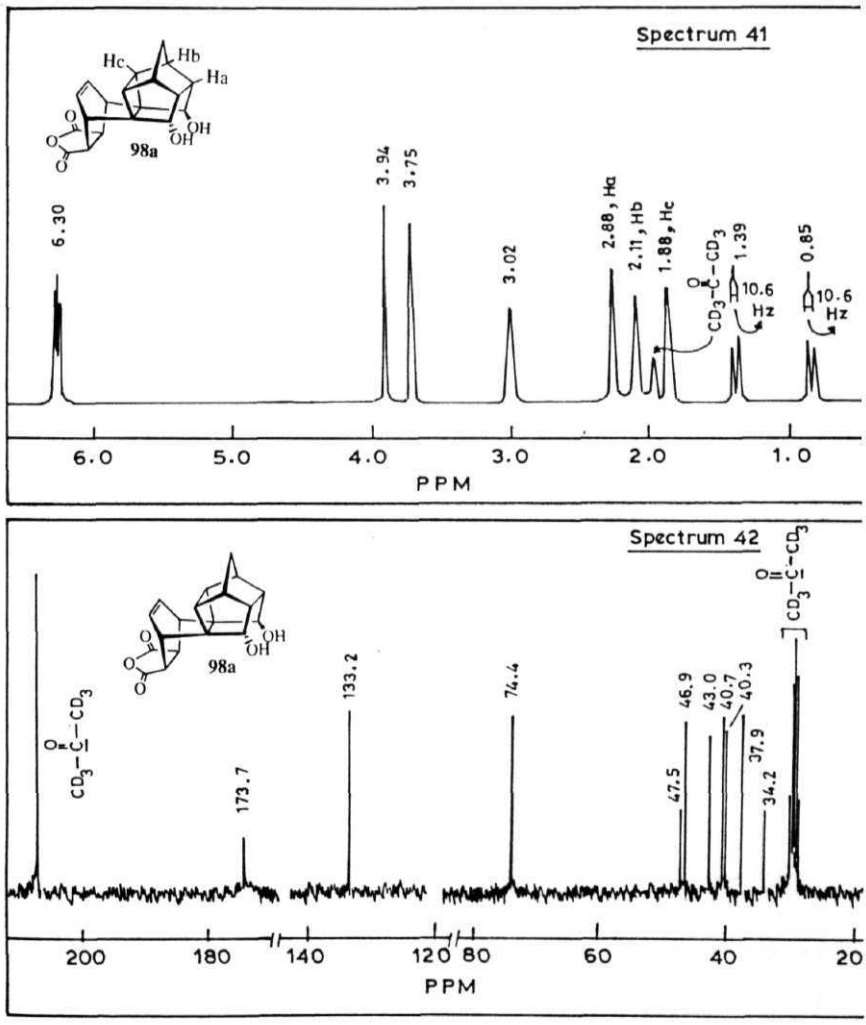

Spectrum 32
H3COOC
H3COOC
77e
CDCl3
166.6
144.3
133.3
114.1
66.7
63.1
55.8
52.2
48.7
44.1
41.7
40.3
35.7
166
140
120
80
60
40
20
PPM

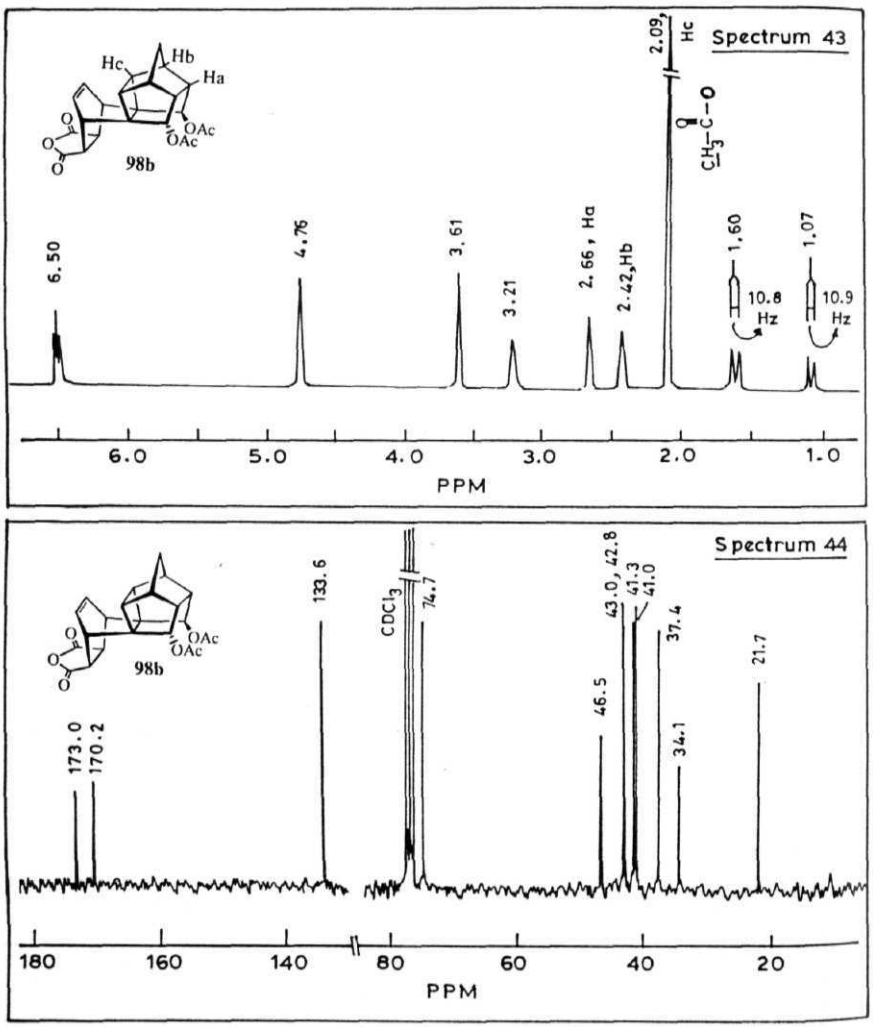

Spectrum 33
OH
OH
COOCH3
H3COOC
96a
3.79
3.85-3.80
6.57
5.42
2.37
2.27
1.98
1.57
1.05
10.6 Hz
10.4 Hz
6.0
5.0
4.0
3.0
2.0
1.0
PPM
Spectrum 34
OH
OH
COOCH3
H3COOC
96a
168.5
142.5
134.6
CDCl3
73.7
56.3
52.7
45.5
44.7
41.9
41.0
35.5
180
160
140
80
60
40
20
PPM

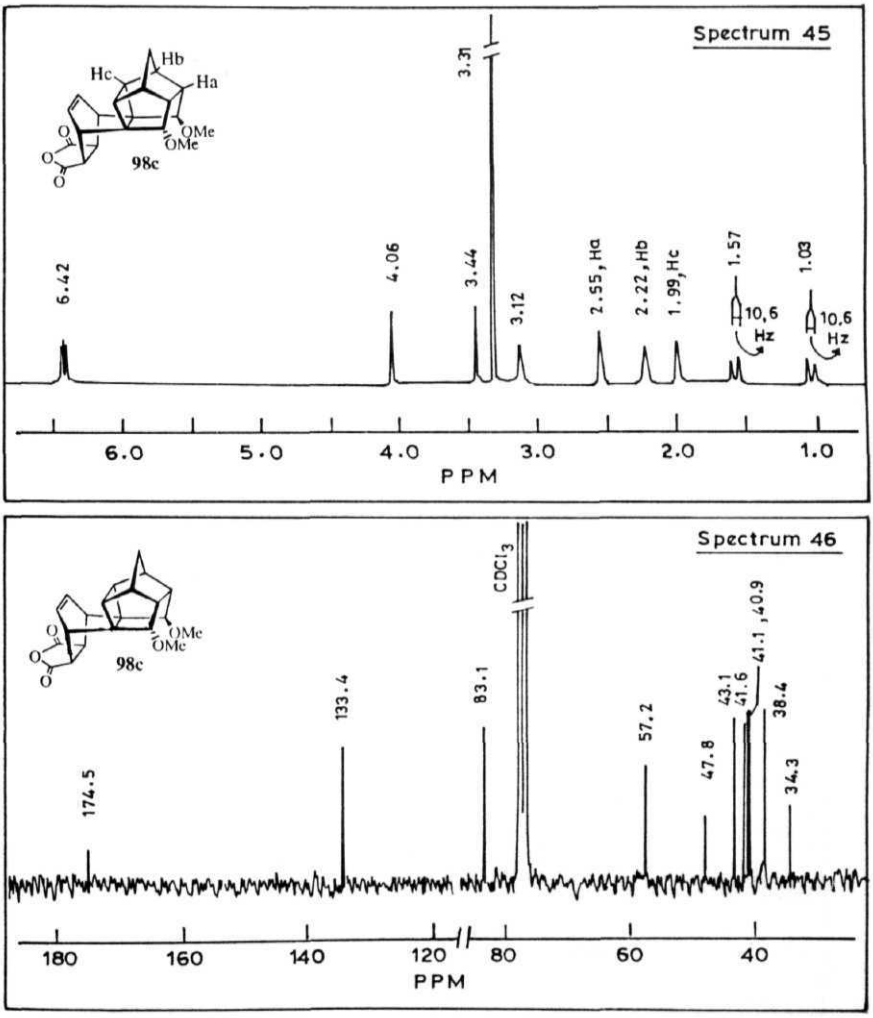

Spectrum 35
OAc
OAc
H3COOC
COOCH3
96b
6.28
4.95
3.96
3.79
2.42
2.19
2.01
1.60
10.9 Hz
1.13
10.7 Hz
6.0
5.0
4.0
3.0
2.0
1.0
PPM
Spectrum 36
OAc
OAc
H3COOC
COOCH3
96b
CDCl3
170.9
166.5
143.9
133.2
72.6
53.0
52.3
43.8
43.0
41.7 , 41.6
35.1
21.6
180
160
140
120
80
60
40
20
PPM

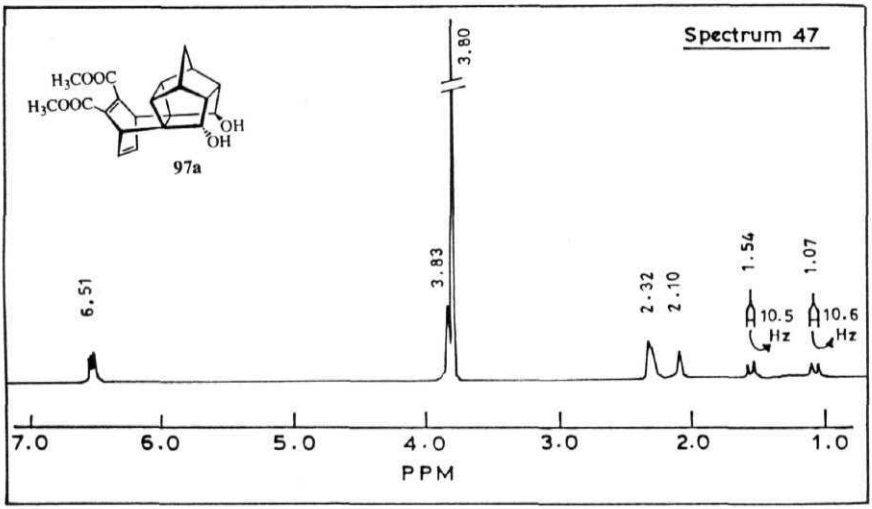

Spectrum 37
H3COOC
H3COOC
OAc
OAc
97b
CDCl3
6.63
4.83
3.88
3.73
2.48
2.40
2.04
1.96
1.59
10.7 Hz
1.10
10.7 Hz
7·0
6·0
5.0
4·0
3.0
2·0
1.0
PPM
Spectrum 38
H3COOC
H3COOC
OAc
OAc
97b
CDCl3
171.1
165.9
143.2
135.3
72.6
52.9
51.8
44.2
42.8
41.6
41.5
35.1
21.4
180
160
140
80
60
40
20
PPM

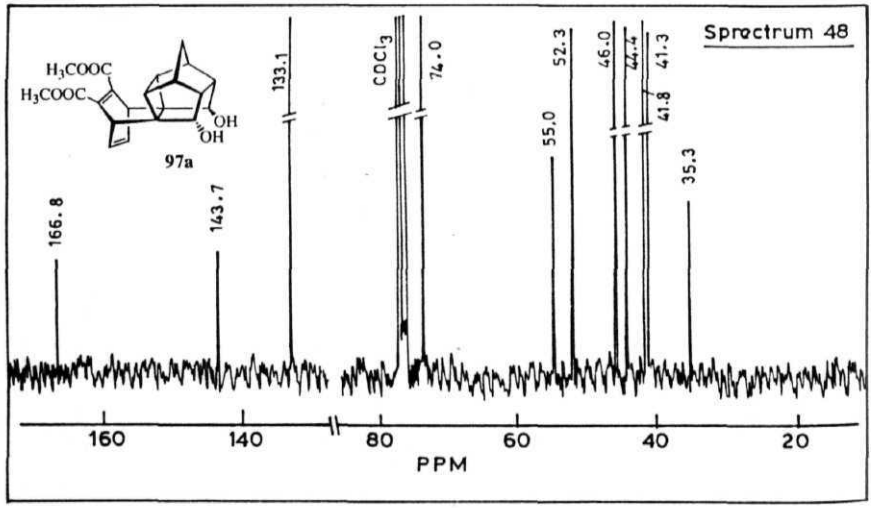

Spectrum 39
Hc
Hb
Ha
78e
6.48 – 6.42
4.09 – 3.89
3.77
3.35
2.51 , Hb
2.28 , Ha
2.12 ,Hc
1.51
1.14
10.8 Hz
10.7 Hz
7.0
6.0
4.0
3.0
2.0
1.0
PPM
Spectrum 40
78e
CDCl3
133.6
173.8
114.5
66.6
63.2
48.9
49.4
43.8
43.0
41.0
34.8
33.3
180
160
120
100
80
60
40
PPM


Spectrum 41
Hc
Hb
Ha
OH
OH
98a
6.30
3.94
3.75
3.02
2.88, Ha
2.11, Hb
1.88, Hc
1.39
0.85
10.6 Hz
10.6 Hz
6.0
5.0
4.0
3.0
2.0
1.0
PPM
Spectrum 42
98a
133.2
74.4
173.7
46.9
43.0
40.7
40.3
37.9
34.2
47.5
200
180
140
120
80
60
40
20
PPM


Spectrum 43
Hc
Hb
Ha
OAc
OAc
98b
6.50
4.76
3.61
3.21
2.66, Ha
2.42, Hb
2.09, Hc
1.60
10.8 Hz
1.07
10.9 Hz
6.0
5.0
4.0
3.0
2.0
1.0
PPM
Spectrum 44
133.6
CDCl3
74.7
43.0, 42.8
41.3
41.0
37.4
21.7
46.5
34.1
173.0
170.2
180
160
140
80
60
40
20
PPM


Spectrum 45
Hb
Hc
Ha
OMe
OMe
98c
6.42
4.06
3.44
3.31
3.12
2.55, Ha
2.22, Hb
1.99, Hc
1.57
10.6 Hz
1.03
10.6 Hz
6.0
5.0
4.0
3.0
2.0
1.0
PPM
Spectrum 46
OMe
OMe
98c
174.5
133.4
83.1
CDCl3
57.2
47.8
43.1
41.6
41.1 ,40.9
38.4
34.3
180
160
140
120
80
60
40
PPM


Spectrum 47
$H_3COOC$
$H_3COOC$
OH
OH
97a
3.80
3.83
6.51
2.32
2.10
1.54
1.07
10.5 Hz
10.6 Hz
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM


Sprectrum 48
$H_3COOC$
$H_3COOC$
OH
OH
97a
166.8
143.7
133.1
$CDCl_3$
74.0
55.0
52.3
46.0
44.4
41.8
41.3
35.3
160
140
80
60
40
20
PPM

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# PART II

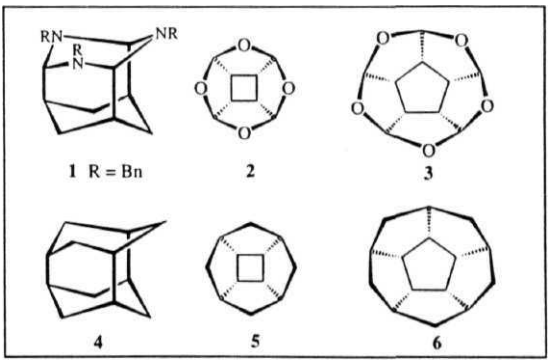
SYNTHESIS AND CHARACTERIZATION OF SOME EXCEPTIONALLY STABLE DIOZONIDES

## II.1 INTRODUCTION

The design of novel, strained polycyclic frameworks, endowed with unusual shapes and with high symmetry, is an exciting area of synthetic organic chemistry.[1,2] In recent years, chemists worldwide have made considerable progress in assembling a spectacular array of polycyclic structures among which dodecahedrane,[3a] pagodane,[3b] cubane[3c,d] and garudane[3e] are notable examples. Besides aesthetic appeal, these non-natural carbocyclic systems with unusual shape and symmetry find application in testing new structural hypotheses or to delineate new reaction pathways.

More recently, there has been considerable interest in incorporating one or

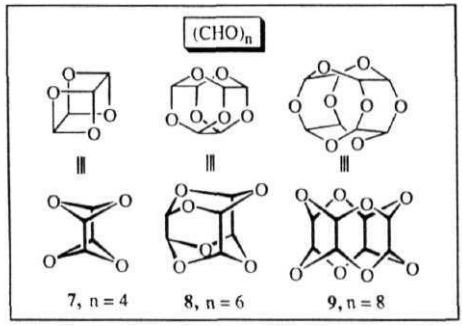
Scheme 1



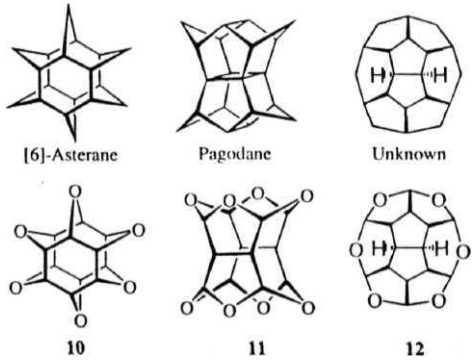

more heteroatoms in a carbocyclic framework which has led to the identification of a class of molecules, wherein, the methylene carbons of the polycyclic frame have been replaced by oxygen or nitrogen.[4] Such new entities can function as

ionophores and useful substrates for host-guest chemistry. Some of the recently synthesized compounds in this context are hetero-wurtzitanes **1**[4a] and [n]-oxaperistylanes **2**[4d] and **3**[4f] which bear close resemblance to their carba-analogues 4-6, respectively, Scheme 1.

Scheme 2

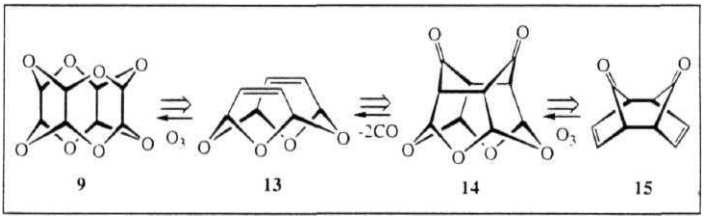



Scheme 3

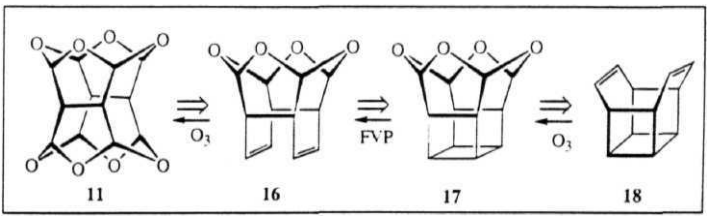


In the quest for novel molecular ensembles speckled with hetero atoms and as an offshoot of an ongoing project[4f,g] in our group towards hetero-[n]-peristylanes, we became interested in polycyclic $(CHO)_n$ oligomers e.g. 7-9, Scheme 2 and oxa-analogues **10-12.** Scheme 3, of some of the better known polycyclic hydrocarbons. It was anticipated that such entities would exhibit interesting properties besides being aesthetically pleasing and posing a formidable synthetic challenge.

Scheme 4

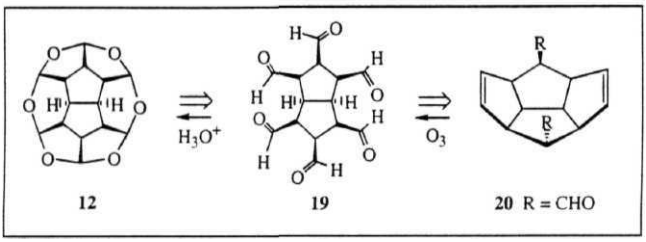



Scheme 5



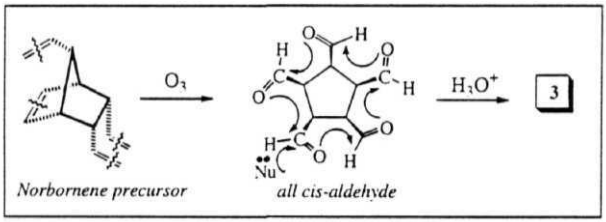

While 10 resembles oxa-variant of an asterane and 11 resembles a pagodane analogue, 12 can be regarded as a large molecular bowl with an oxygenated rim. We were particularly keen in pursuing these targets as we could readily identify a logical retrosynthetic pathway to assemble them from well-known precursors using a simple

**Scheme 6**




synthetic strategy as shown in Schemes 4-6. As can be readily perceived from these Schemes, our strategy revolves around ozonolysis of a key precursor with strategic disposition of transannular double bonds, which unfolds a set of aldehyde functionalities which can undergo an intramolecular acid catalyzed cascade acctalizations to furnish the target molecules. Our successful synthesis[4f] of pentaoxa-[5]-peristylane 3 vouches for the success of such an approach. Scheme 7, wherein, a

Scheme 7




highly functionalized norbornene precursor was ozonized to furnish the all *cis* pentaaldehyde, which underwent cascade intramolecular acetalizations to afford pentaoxa-[5]-peristylane 3, Scheme 7. Further, the ozonolytic unmasking secures the crucial *all-cis* stereochemistry of the aldehyde groups which is primarily governed

by the virtue of the in-built topology of the precursors. Our longstanding interest in polycyclic compounds enabled us to readily identify key precursors that are stereochemically well-defined, functionally embellished and amiable to intramolecular cascade cyclizations as shown in Schemes 4-6.

Thus, we proposed to access the octaoxa compound 9, from the diolefin 13. by ozonolytic scission of the transannular double bonds and by subjecting the resulting tetraaldehyde to acid catalyzed cascade acetalization to yield 9. The precursor diolefin 13 can be accessed from the dione 14 by chelotropic elimination of two molecules of CO. Further, the dione 14 can be correlated to the known [a] dimer of cyclopentadienone 15. Scheme 4. Likewise, pentacyclic dibenzene[5b] 18. can be regarded as a logical precursor of the oxa-analogue 11 of Prinzbach's pagodane.[3b] Following our strategy of ozonolysis and subsequent cascade acetalization.[4f,g] the oxa-varient 11 can be accessed from the diolefin 16. The tetraoxa-diolefin 16 can be obtained by metathetic opening of the cyclobutane ring in 17. The precursor 17 can in turn be correlated to 18 as shown in scheme 5. On the other hand, the molecular bowl 12 can be accessed from the tetraquinane precursor 20 ***via*** the intermediacy of the hexaaldehyde 19, Scheme 6.

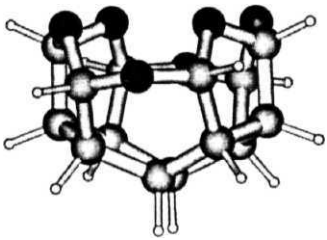
Initially, we chose **12**, an octacyclic, hexaoxa-bowl, as our target molecule. The results and discussion section that follows narrates our endeavours towards the synthesis this target molecule **12**, from a tetraquinane-based precursor 20. During our pursuit of **12**, we have encountered the formation of some exceptionally stable diozonides, which are otherwise regarded as thermally labile and decompose readily and have rarely been isolated and characterized. The work embodied in this section

mainly deals with the synthesis of several of these tetraquinane-based diozonides and their unambiguous characterization by X-ray crystallographic technique. Further, a detailed study of the packing in two of the diozonides reveals a novel C-H…0 hydrogen bond directed solid state architecture.

## II.2 RESULTS AND DISCUSSION

To begin with, we chose octacyclic hexaoxa-bowl 12, $C_{14}H_{14}O_6$, of $C_{2v}$ symmetry, a 'bowl-shaped' molecular entity, composed of a carbocyclic base and oxygen speckled rim, as our target molecule, see Scheme 6 (section **11.1).** The core carbocyclic base consists of a *cis*-diquinane moiety, and the rim is composed of alternating oxygen atoms and methine units rendering it a challenging synthetic objective. Further, in view of its interesting topology, as seen from the MMX minimized structure, we envisaged some interesting binding properties, Figure 1.

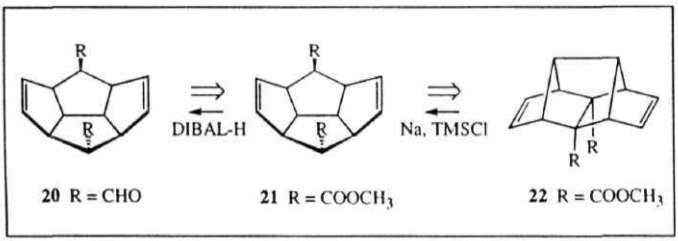
Figure 1. MMX Minimized Structure of 12



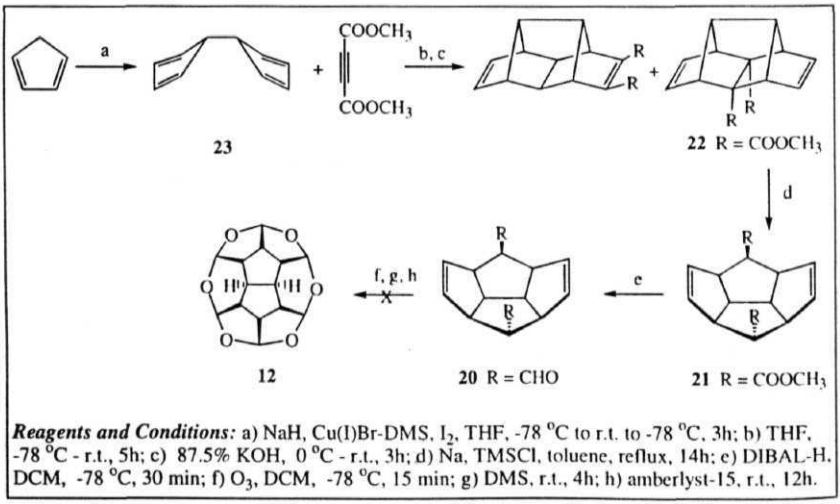
Our retrosynthetic strategy towards 12 indicated that the key hexaaldehyde 19, would be a logical precursor, which can undergo a cascade of intramolecular acetalizations on exposure to acid, to furnish the hexaoxa-bowl 12, see Scheme 6. The hexaaldehyde 19, can be correlated to the well known $C_{2v}$ symmetric tetraquinane dialdehyde 20, used as a key precursor towards the synthesis of dodecahedrane by Mehta[6,7] *et al.* and Paquette[3a] *et al.* We planned ozonolytic or equivalent oxidative scission of the suitably poised disubstituted double bonds in 20 to furnish the all *cis*-hexaaldehyde 19. Having found a stereochemically well defined

tetraquinane-based *endo,endo* dialdehyde precursor 20, our aim was to make multigram quantities of it. The *endo,endo*-dialdehyde 20, can in turn be realized from diester 21, through D1BAL-H mediated reduction. Finally, *endo,endo*-diester 21, can be readily obtained from Hedaya-Paquette ester[8] 22, through

**Scheme 8**




**Scheme 9**




***Reagents and Conditions:*** a) NaH, Cu(I)Br-DMS, $I_2$, THF, -78 °C to r.t. to -78 °C, 3h; b) THF, -78 °C - r.t., 5h; c) 87.5% KOH, 0 °C - r.t., 3h; d) Na, TMSCl, toluene, reflux, 14h; e) DIBAL-H, DCM, -78 °C, 30 min; f) $O_3$, DCM, -78 °C, 15 min; g) DMS, r.t., 4h; h) amberlyst-15, r.t., 12h.

the reductive cleavage of the C-C bond connecting the two ester moieties under acyloin conditions, see Scheme 8.

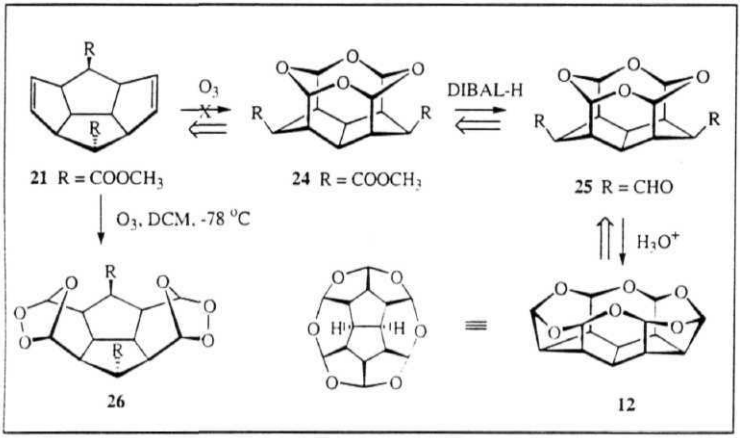
Oxidative self-coupling of cyclopentadiene directly furnished 9,10-dihydrofulvalene 23. which underwent *in situ* 'domino' Diels-Alder reaction with DMAD to furnish Hedaya-Paquette ester[8b] 22, in 8-11% overall yield. in a single pot operation, Scheme 9. Smooth scission of the 1,2-diester linkage was realized on refluxing 22 in toluene with finely dispersed sodium and TMSC1 to furnish tetraquinane *endo.endo*-diester[8a] 21 in 95% yield. On reduction with DIBAL-H. in DCM, 21 furnished *endo.endo*-dialdehyde20 in 75% yield. Scheme 9.

Having obtained the key dialdehyde 20. we ventured to unmask the four aldehyde functionalities present in the form of two disubstituted double bonds by effecting ozonolysis as per our original strategy. The expectation was that the resulting hexaaldehyde 19 will provide direct access to the hexaoxa-bowl 12, Scheme 9. But. to our disappointment, 20 did not undergo clean ozonolysis to afford 12 under a variety of reaction conditions, employing different solvents. Decomposition of the resulting ozonides with different reagents (*viz.* $PPh_3$, DMS) and subsequent exposure to acidic resin (amberlyst-15), produced a mixture of intractable products accompanied by very poor recovery.

At this stage. recourse was taken to an alternative route. wherein it was contemplated to effect the ozonolysis and acid catalysed intramolecular acetalization on the diester 21. rather than on the dialdehyde 20. This alternative approach could first furnish a tetraoxa-bowl 24. *via* the cyclization of the four aldehyde moieties. On further reduction of the two ester groups in 24 with DIBAL-H to furnish 25 and

subsequent exposure to acid should furnish the target hexaoxa-bowl 12 as shown in Scheme 10. Consequently, the diester 21 was subjected to ozonolysis in DCM and

Scheme 10




the resulting mixture was stirred with DMS and subsequently treated with amberlyst resin to furnish a highly crystalline compound 26 in 49% yield. The presence of a carbonyl absorption due to ester groups at 1726 $cm^{-1}$ in the IR spectrum, appearance of signals corresponding to cyclic acetal protons and ester methyl at 5 6.06 and 5 3.78, respectively, in the 'H NMR and a highly symmetrical 6 line $^{13}C$ NMR spectrum were indicative of the formation of the tetraoxa-bowl 24. However, we were particularly bothered about the tlc behavior of the product and there were some discrepancies in the $^{13}C$ NMR chemical shifts. Considering these observations, we sought to unambiguously establish the formulation of 26, by single crystal X-ray

diffraction, which could be accomplished as it readily furnished suitable single crystals. Slow evaporation of a DCM solution of 26 furnished beautiful long needles, which on X-ray diffraction studies revealed that our surmise was indeed, correct. The compound 26 did not turnout to be the tetraoxa-bowl 24 but was a remarkably stable diozonide. Scheme 10.

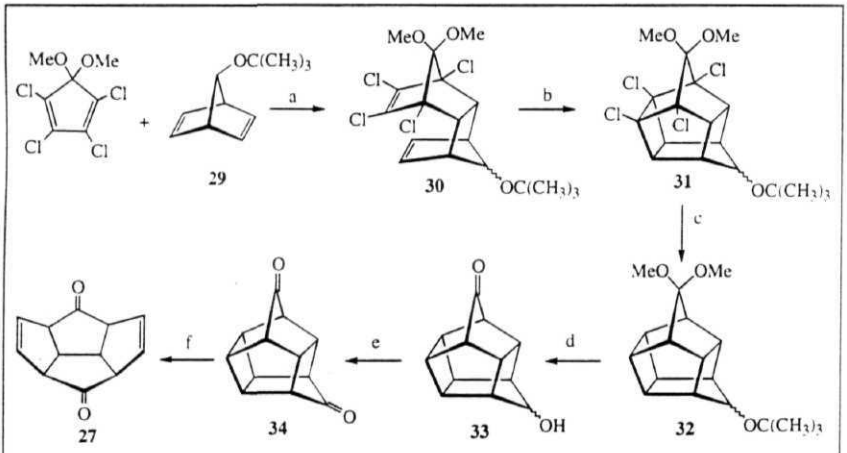
Generally, ozonides, by reputation are known to decompose readily and are highly thermally labile. Whereas, 26 was like any other organic compound amenable (o routine chromatographic purification, with a melting point of 141-142 °C, without decomposition! We were intrigued by the stability of the diozonide 26 and this gave us the impetus to explore the generality of our observation and the prospect of diozonide formation in related tetraquinane-based systems.

We chose tetraquinane 27 and its oxa-analogues **28a-d** as the substrates for additional studies. These tetraquinane precursors **27** and **28a-d** were synthesized by multi-step functional group transformation following well-known literature [a] methods reported earlier by us using photo-thermal metathesis[9] as the pivotal step as shown in Schemes 11-15. Since, all these precursors were prepared with considerable effort, although following literature procedures,[6,7,10] their preparation is detailed here.

To begin with, the adduct 30. obtained from [4+2]-cycloaddition of 29 and 1.2.3.4-tetrachloro-5.5-dimethoxycyclopentadiene. smoothly underwent $\pi 2_s + \pi 2_s$ photocycloaddition in acetone to furnish the hexacyclic system 31. Reductive dechlorination of 31 using Li/THF/t-BuOH milieu afforded **32**, which on treatment with 3N HC1 resulted in the deprotection at two centres to furnish 33. Pyridinium

chlorochromate oxidation of 33 readily resulted in the hexacyclic cage dione 34. The key metathetic step leading to the tetraquinane diketone[7a] **27**, was accomplished by slow sublimation of 34 through a quartz tube, preheated to ~580 °C and resulted in its partial conversion to 27. The pyrolysate, which contained 27 and unchanged 34 was chromatographed to furnish the tetraquinane diketone 27. in 35% yield, Scheme 11. [6a-c.7a]

Scheme 11

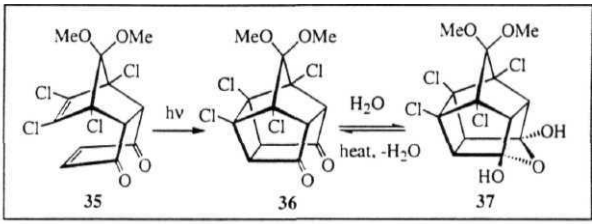



***Reagents and Conditions:*** a) $CCl_4$, 110 °C, 72h; b) 450 W mercury lamp, acetone, 1h; c) Li, t-BuOH, THF, reflux, 1h; d) 3N HCl, dioxane, reflux, 3h; e) PCC, DCM, r.t., 2h; f) FVP, ~580 °C.

Having prepared the tetraquinane diketone 27, we next turned our attention to prepare the tetraquinane diether 28a. On irradiation, **35**, obtained from the Diels-Alder reaction of l,2.3,4-tetrachloro-5.5-dimethoxycyclopentadiene and p-

benzoquinone, underwent smooth intramolecular [2+2]-photocycloaddition to give 36, in 90% yield. However, on storage 36 showed pronounced propensity towards hydration and formed a transannular hydrate 37, which on sublimation reverted back

Scheme 12

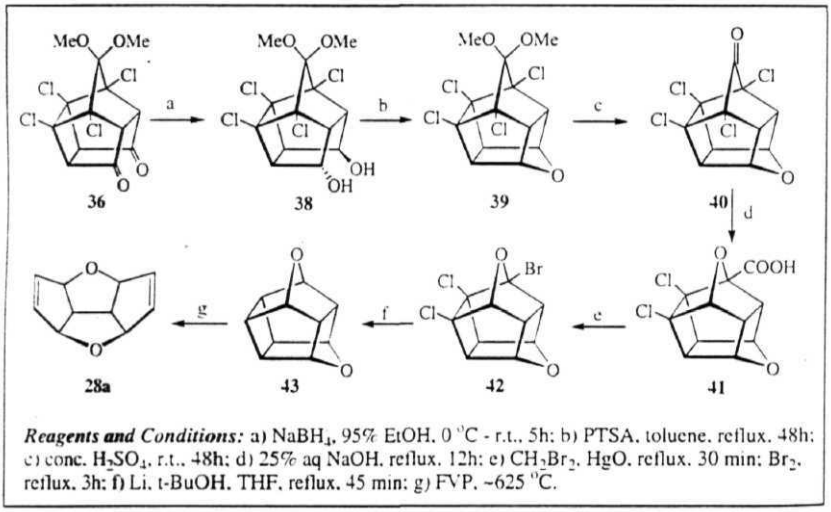



to **36**. Scheme 12. A hydrate free sample of 36, when treated with sodium borohydride in ethanol resulted in the formation of diol 38. in S0% yield. Transannular dehydration of the diol 38 was brought about by refluxing in toluene in the presence of PTSA using a Dean-Stark water separator to fumish the hexacvclic ether 39 in 75% yield. Scheme 13. In order to unmask the carbonyl functionality in 39. the dimethoxy group was deprotected on exposure to $H_2SO_4$, to provide the cage ketone 40 in 80% yield. The a-haloketone 40 was treated with 25% aqueous sodium hydroxide to furnish the acid 41, through Haller-Bauer cleavage and sequential intramolecular displacement of two chlorine atoms with carboxylate oxygen. in 85% yield.[10b] Modified Hunsdieker reaction on 41 proceeded readily to the bromo-compound 42. in 85% yield. Reductive dehalogenation of 42 with Li/THF/t-BuOH proceeded smoothly to furnish the dioxabishomopentaprismane 43. in 70% yield.[10a] Subjection to FVP. through a quartz column at 625 °C led to facile and regioselective

fragmentation of the cyclobutane ring, and dioxatetraquinane 28a was obtained in 70% yield along with some amount of unchanged 43, Scheme 13.[10]

Tetraquinane derivatives 28b and 28c were prepared from the cage dione **45**, following literature procedures.[6a,b,7a,9] Irradiation of 44, obtained through the Diels-Alder reaction of cyclopentadiene and p-benzoquinone. in ethyl acetate

Scheme 13



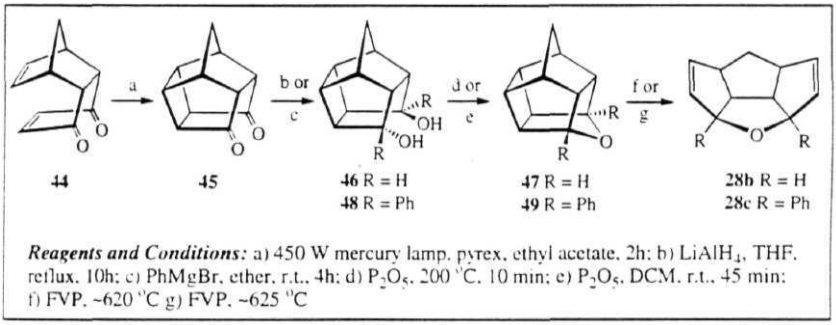

***Reagents and Conditions:*** a) $NaBH_4$, 95% EtOH, 0 °C - r.t., 5h; b) PTSA, toluene, reflux, 48h; c) conc. $H_2SO_4$, r.t., 48h; d) 25% aq NaOH, reflux, 12h; e) $CH_2Br_2$, HgO, reflux, 30 min; $Br_2$, reflux, 3h; f) Li, t-BuOH, THF, reflux, 45 min; g) FVP, ~625 °C.

gave the well characterized pentacyclic diketone 45. Reduction with $LiAlH_4$ produced the diol 46 in 90% yield. Due to the proximity of the two hydroxyl groups. 46 underwent smooth transannular dehydration on heating with $P_2O_5$ to furnish the cage ether 47 in 70% yield. The tetraquinane 28b was realized by metathetic cyclobutane ring opening following the flash vacuum pyrolysis (FVP) technique.

Slow sublimation of 47 through a quartz vigreux column at ~620 °C furnished a mixture of tetraquinane ether 28b and the unreacted hexacyclic ether 47 in a ratio of 3:1 and could be separated by column chromatography using $AgNO_3$ impregnated silica gel. Scheme 14.[7a]

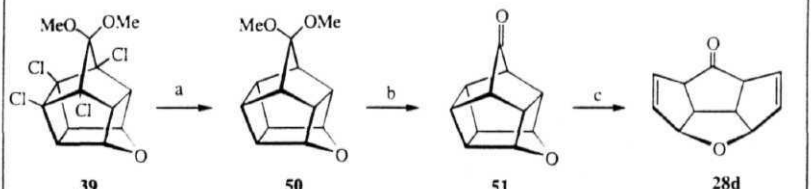
Addition of a large excess of phenyl magnesium bromide to 45. furnished the diol 48 which smoothly underwent dehydration with $P_2O_5$ in DCM to furnish the hexacyclic ether 49, in 87% yield. Flash vacuum pyrolysis of 49 at ~625 °C resulted

Scheme 14




***Reagents and Conditions:*** a) 450 W mercury lamp, pyrex, ethyl acetate, 2h; b) $LiAlH_4$, THF, reflux, 10h; c) PhMgBr, ether, r.t., 4h; d) $P_2O_5$, 200 °C, 10 min; e) $P_2O_5$, DCM, r.t., 45 min; f) FVP, ~620 °C g) FVP, ~625 °C

Scheme 15



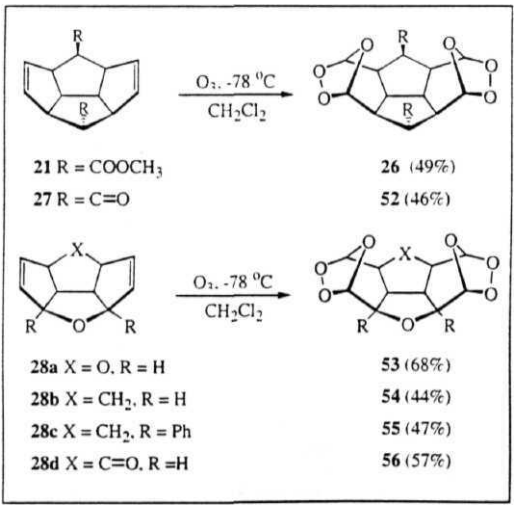

***Reagents and Conditions:*** a) Li, t-BuOH, THF, reflux, 45 min; b) 20% $H_2SO_4$,ether, 0 °C - r.t., 15 min; c) FVP, ~620 °C.

in its conversion to the tetraquinane ether **28c** along with some unreacted 49, Scheme 14.[7a]

Lastly, the keto-ether derivative **28d** was obtained starting from the cage ether 39, see Scheme 13.[7a] Reductive dechlorination of 39 was brought about by Li/THF/t-BuOH recipe to afford 50 in 80% yield.[6a-c] The carbonyl functionality was unmasked by treating with 20% $H_2SO_4$ to furnish the hexacyclic keto-ether 51 in 85% yield. On subjecting the keto-ether 51 to FVP conditions at ~620 °C the tetraquinane keto-ether **28d** was obtained, Scheme 15.[7a]

Having prepared all the tetraquinane precursors 27and **28a-d.** we decided to subject them to ozonolysis in order to investigate the generality of our observation on the diester **21**, which had furnished the diozonide **26**, quite readily and in good yield. All the tetraquinanes 27 and **28a-d** were subjected to ozonolysis in $CH_2Cl_2$ at -78 °C

Scheme 16



and on removal of solvent, a highly crystalline material was isolated in each case. Remarkably, all the tetraquinane precursors *viz.* 27 and **28a-d**, on ozonolysis uniformly afforded highly stable diozonides 52-56, respectively, and only a single stereoisomer was formed in a highly stereoselective manner in each case, Scheme 16. The gross structures of 52-56 were fully revealed through the incisive analysis of their $^{1}H$ and $^{13}C$ NMR data.

**Table 1. H NMR resonances of 1,2,4-trioxalane protons in diozonides**

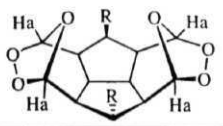
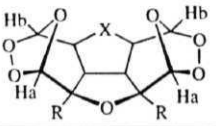
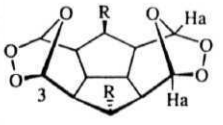
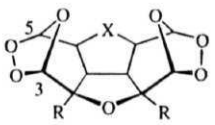
|  | Ha |  | Ha | Hb |
|---|---|---|---|---|
| **26** R = $COOCH_3$ | δ 6.06 | **53** X = O, R = H | δ 5.92 | δ 5.92 |
| **52** R = C=O | δ 6.14 | **54** X = $CH_2$, R = H | δ 5.92 | δ 5.79 |
| | | **55** X = $CH_2$, R = Ph | δ 5.91 | δ 5.84 |
| | | **56** X = C=O, R =H | δ 5.89 | δ 6.16 |

**Table 2. $^{13}C$ NMR resonances of 1,2,4-trioxalane carbons in diozonides**

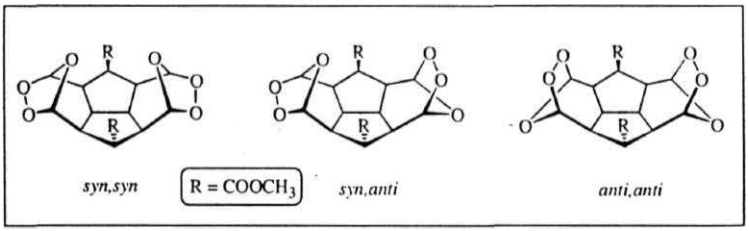
|  | $C_3$ |  | $C_3$ | $C_5$ |
|---|---|---|---|---|
| **26** R = $COOCH_3$ | δ 99.5 | **53** X = O, R = H | δ 99.1 | δ 99.1 |
| **52** R = C=O | δ 99.9 | **54** X = $CH_2$, R = H | δ 102.2 | δ 99.7 |
| | | **55** X = $CH_2$, R = Ph | δ 102.4 | δ 101.9 |
| | | **56** X = C=O, R =H | δ 99.2 | δ 99.6 |

*Results and Discussion*

Diagnostic resonances due to the bridgehead protons in the range 8 6.14-5.79 in $^{1}H$ NMR in conjunction with the symmetry exhibited by diozonides **52-56** in $^{13}C$ NMR was particularly informative. All proton assignments were made on the basis of $^{1}H$-$^{1}H$ COSY spectra and were found to be in full agreement with the diozonide structures **52-56.** The $^{1}H$ and $^{13}C$ NMR chemical shifts of the 1,2,4-trioxalane moiety of diozonides **26** and **52-56** are displayed in the Table 1 and 2, respectively. Further, their formulation was conformed by obtaining satisfactory CHN analysis on all of them.

The diozonides **26** and **52-56** can in principle occur in three diastereomeric forms, *viz. syn,syn-* wherein the two oxa-bridges are directed within the diquinane moiety, *anti,anti-* wherein the two peroxy-bridges are directed within the diquinane moiety, *syn,anti-* wherein one oxa- and one peroxy-bridge is directed within the diquinane moiety. This is shown for one of the compounds (diester 26), see Scheme 17.

Scheme 17

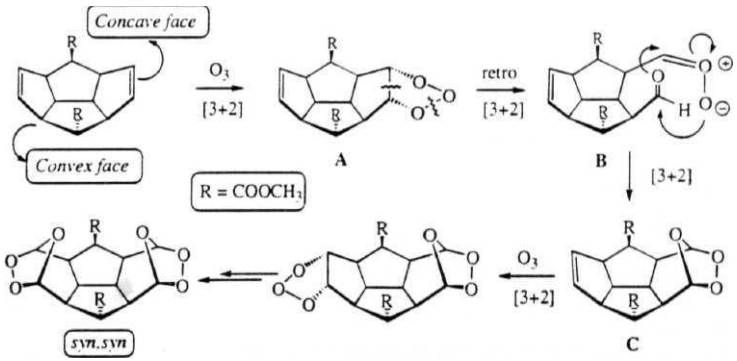



Among the three structures, MMX calculations indicated that the *syn,syn-* diastereomer was the most stable arrangement in all the diozonides ( ***viz.*** 26 and **52**-56). As the tetraquinanes **21, 27** and **28a-d** have two distinct faces *viz.* the convex and the concave, it is reasonable to presume that the attack of ozone is from the more

open convex face and the *syn,syn*-diozonide, should be favoured over the *anti,anti* or *syn,anti* isomers, Scheme 18. A tentative mechanism for the formation of diozonides **26** and **52-56** is delineated in Scheme 18. After the initial attack of ozone from the convex face of tetraquinanes **21, 27** and **28a-d. to** give the corresponding primary ozonide A, which subsequently can decompose according to the Criegee" mechanism to a carbonyloxide/carbonyl pair B. Reorientation of the sterically less hindered aldehyde group followed by recombination would give rise to a *mono*-ozonide C. The addition of a second molecuie of ozone to C on the same face as described above followed by a similar cycloreversion-recombination sequence would give rise to *syn,syn* diastereomers as was observed. Scheme 18. While the mechanism is shown for diester **26.** the same holds good for the diozonides **52-56.**

All the diozonides *viz.* **26** and **52-56** were exceptionally stable at room temperature (for months) and showed little decomposition to either moderate heating

Scheme 18



or on exposure to $Me_2S$, thiourea or triphenylphosphine under standard conditions *viz.* stirring in DCM/MeOH solution. Further, all diozonides were high melting and most of them melted without decomposition.

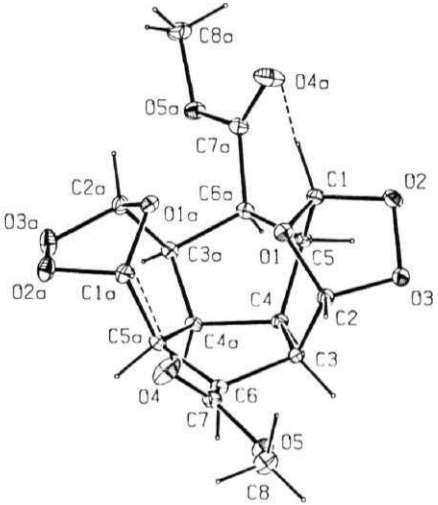
The unusual stability towards well-known ozonide decomposing agents was particularly intriguing. In addition, most of the diozonides were highly insoluble in common organic solvents. We were unable to detect any seemingly obvious reason for their unusual stability. Further, in order to establish their *syn,syn* stereochemistry unequivocally and to probe other interesting aspects as an outcome of their unusual topology, we investigated their structure in the solid state by single crystal X-ray diffraction.

**X-ray Crystal Structure of Diozonides 26 and 56**

Two **of** the tetraquinane derived diozonides 26 and 56 readily furnished crystals suitable for single crystal X-ray diffraction study. Slow evaporation of a DCM solution of the diester derived diozonide 26 furnished needle shaped crystals belonging to a centrosymmetric space group *C2/c,* an ORTEP perspective of the molecular structure is depicted in Figure 2. The details regarding the crystal. data collection and structure solution are furnished in the experimental section. There are four molecules in the unit cell and are tightly packed as reflected by a high crystal density (1.598 Mg $m^{-3}$). The bond lengths in few of the ozonides retrieved from the Cambridge Structural Database (CSD) yields the following average dimensions'": 0-O 1.473 A. C-(O-O) 1.443 A and C-0 1.418 A. These can be compared with the values obtained for the present structure: 0-0 1.469 A, mean C-(O-O) 1.440 A and mean C-0 1.404 A. The stereochemistry is *syn,syn* with the 01 and O1a oxa-bridges tilting significantly inwards (O1 and O1a distance being 2.62 A). This orientation is

facilitated by intramolecular C-H…0 hydrogen bonds between the bridgehead H1 and H1a atoms and the O4a and O4 carbonyl groups of the ester moieties **(H…O**

**Figure 2. ORTEP Plot** of 26




distance 2.21 A, C…0 2.93 A and C-H...O angle of 129.5°) as shown in Figure 2.

Before describing the details of crystal packing in diozonides 26 and 56, which is mainly governed by C-H...O hydrogen bonds, a discussion regarding the current understanding of these interactions is in order.

According to few groups, [5] weakly acidic hydrogen atoms **attached** to carbon atoms (weakly electronegative) can **act** as **a** donor in **a** C-H…O, C-H…N and C-H...CI hydrogen bonds or what has alternatively been termed as ***soft*** or ***mm-***

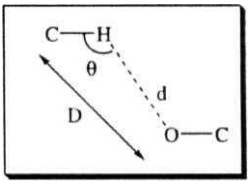
*conventional* hydrogen bonds. On the other hand, O-H...O, N-H...O and N-H...N are identified as *conventional* (classical) hydrogen bonds as the donor hydrogen atoms (O-H and N-H) are bonded to strongly electronegative atoms like oxygen and nitrogen as opposed to a carbon as in a C-H...O hydrogen bond. Nonetheless, it is *now* well documented as an important structure-directing agent and is generally accepted by the crystallographic community although its role was questioned earlier. More recently, convincing evidence in this regard has been obtained by a statistical analysis on the numerous crystal structure data available from the Cambridge Structural Database.[15a]

A recent report distinguishes van der Waals interactions and weak hydrogen bonds (*viz.* C-H...O) on the basis **of** their different directionality characteristics.[17] While van der Waal type contact are ***isotopic,*** **with** the interaction energies independent of the contact angle 9, the weak hydrogen bonds are inherently *directional,* with linear or close to linear geometries **favoured** energetically **over** bent ones.

Although it **is** difficult to define a cut-off limit for weak interactions such as C-H...O, those interactions have been considered significant in which the distance between C and H is within the sum of their van der Waals radii in addition to contact angles preferably greater than 120°. Among the **various** conventions **offered by** different groups,[15] we have generally followed the one offered by Taylor and Kennard[15a] in their seminal paper on C-H...0 hydrogen bonds, with regard to limits **of a** C-H...0 hydrogen bond. The van der Waals radii used by Taylor and Kennard are as follows: C = 1.75, H = 1.20 and O = 1.50 A. These radii were **based** on the values given by Bondi[18] and Kitaigorodsky.[19a] Accordingly, a intermolecular C-

H…0 hydrogen bond is considered significant within the following limits; C-H...O, H…0 distance (d) < 2.7 A, C…0 distance (D) < 3.5 A and C-H…0 angle > 120°, Figure 3. Nonetheless, the H…0 distance (d), in many instances, is observed to be longer than this limit and may still contribute to the structure and packing, particularly when the C-H...O angle 9 tends towards linearity.

Figure 3




The analysis of the X-ray structure in 26 reveals a fascinating packing pattern and supramolecular arrangement, sustained by a network of C-H...0 hydrogen

Table 3. Intermolecular C-H...O interactions in 26

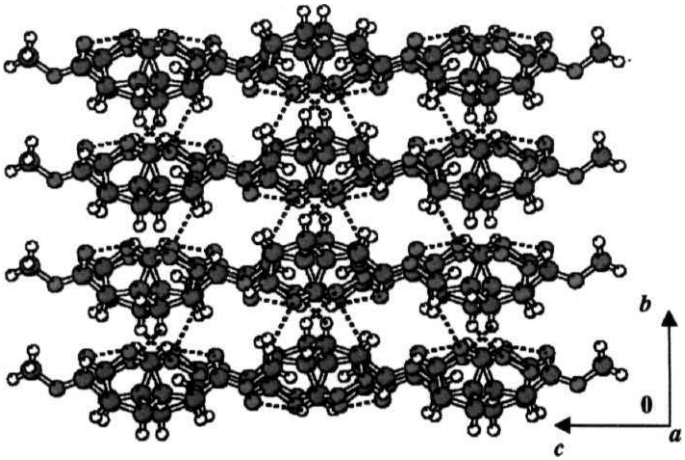
| C-H…O | d(H…O) Å | D(C…O) Å | θ(C-H…O) ° | No. of Contacts |
|---|---|---|---|---|
| C1-H1...O4* | 2.21 | 2.93 | 129.5 | 2 |
| C4-H4...O2 | 2.58 | 3.34 | 134.4 | 2 |
| C8-H8C…O1 | 2.60 | 3.18 | 119.5 | 2 |
| C6-H6…O2 | 2.70 | 3.47 | 135.1 | 2 |

* *Intramolecular interaction*

bonds and a large number of close intermolecular contacts between the molecules that are within the range of van der Waals interactions. All the notable C-H…0 hydrogen bonds and soft interactions are summarized in Table 3.

Due to the *syn,syn* arrangement with the oxa bridges protruding inwards within the diquinane moiety, the molecule attains an interesting *bowl-like* topology. The packing pattern shows a layered structure and the bowl-like molecules of 26 are stacked one over the other along the *b* axis in a columnar arrangement, Figure 4. In the *ab* plane there are arrays of unidirectional bowls piled one over the other in top-bottom fashion, with the diquinane moiety of each bowl facing the oxa-bridges of the next (i.e., the concave surface facing the convex, see Figure 4).

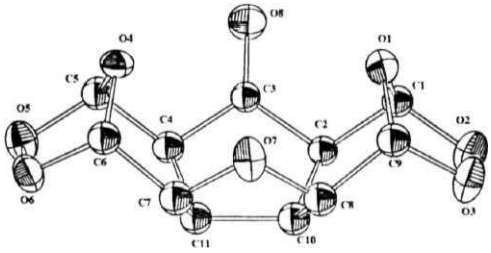
Figure 4. Crystal Packing in 26, view down *a* axis



In addition, each bowl is engaged in four C-H…O hydrogen bonds (two below and two above) to nearest neighbours through H4, H4a (ring junction protons on the diquinane moiety) and O2a, 02 oxygens of the peroxy bridge (H…0 distance 2.58 A, C…0 3.34 A and C-H…0 angle of 134.4°) along the *b* axis. The adjacent *ab* planes consist of bowls growing in opposite directions and are held by weak C-H...O contacts between the Hc protons of the ester methyl and 01 oxa-bridges of the inversion related bowls, Figure 4. Thus, there is an extensive network of C-H...O hydrogen bonding in two dimension in the *ab* plane which is further extended along the third (*i.e.* along c axis) with the ester methyl groups acting as the bridge.

The oxa-bowl 56 crystallizes from ethyl acetatc-hexane in **a** non-centrosymmetric space group *Pca2*\ and an ORTEP diagram of the molecular structure is portrayed, see Figure 5. The details regarding the crystal, data collection and structure solution are **furnished** in the experimental section. Once again, there are four molecules of 56 in the unit cell and are packed tightly[19] as indicated by its high crystal density (1.681 Mg m$^{-}$ ). The values of bond lengths obtained **for** the present structure is as follows; mean 0-0 1.463 A, mean C-(O-O) 1.424 A and mean C-0 1.395 A. In accordance with our conjecture, again the stereochemistry in diozonide **56** is ***syn,syn,*** with the two oxa-bridges protruding inwards, within the diquinane moiety. Nonetheless, there is a significant difference as compared to the earlier structure 26, with respect to the positioning of the oxa-bridges as seen in Figure 5. In the present stucture of 56, the oxa-bridges are far apart and the distance between 01 and 04 is 4.22 A. This difference **in** the case of 56 may be attributed to repulsion within the congested concave surface with O7 oxygen, see Figure 5.

Figure 5. ORTEP Plot of 56




Here again the bowls are held by numerous strong C-H...0 hydrogen bonds and the significant ones are displayed in the Table 4. Unlike **26**, where the bowls arc stacked one over the other, in 56, the bowls are slightly displaced, Figure 6. Along the *c* axis, the bowls are held by C-H...O hydrogen bonds (H...O distance 2.36 A, C...O 3.28 A and C-H...0 angle of 155.1°), between H10 (ring junction proton on the diquinane moiety) and 07 ether oxygen, defining ribbon-like **pattern,** Figure 6. There is bowl inversion (alternate convex-concave) pattern along the ***a*** axis and these bowls are held through a C1-H1...O5 contact (H...O distance 2.42 A. C...0 3.05 A and C-H...O angle of 121.4°) between H1 (bridge head proton) and O5 peroxy oxygen, along *a* axis.

The H1 proton is involved in yet another soft contact with 04 peroxy oxygen, hence is involved in a bifurcated hydrogen bonding, along the c axis. Along the *b* axis the bowls arc held by C-H...O hydrogen bonds between the H7 (α to the ether oxygen) and the 08 carbonyl oxygen (H...O distance 2.57 A. C...O 3.49 A and C-

**Table 4. Intermolecular C-H...O interactions in 56**

| C-H…O | d(H…O) Å | D(C…O) Å | θ(C-H…O) ° | No. of Contacts |
|---|---|---|---|---|
| C1-H1…O5 | 2.42 | 3.05 | 121.4 | 1 |
| C7-H7…O8 | 2.57 | 3.49 | 156.6 | 1 |
| C10-H10…O7 | 2.36 | 3.28 | 155.1 | 1 |
| C2-H2…O1 | 2.73 | 3.48 | 133.4 | 1 |
| C2-H2…O8 | 2.68 | 3.56 | 150.5 | 1 |
| C6-H6…O3 | 2.74 | 3.64 | 152.3 | 1 |
| C11-H11…O6 | 2.62 | 3.49 | 147.2 | 1 |

**Figure 6. Crystal Packing in 56, view down *b*** axis

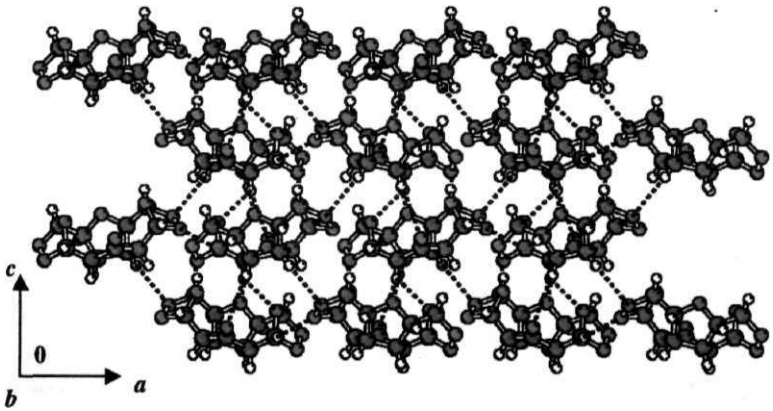
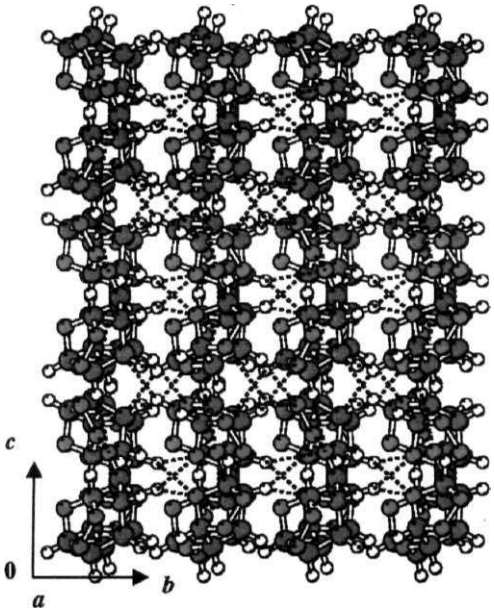


**Figure 7. Crystal Packing in 56, view down *a* axis, showing a network of C-H...O hydrogen bonds**




H…0 angle of 156.6°) to generate another ribbon-like pattern, Figure 6. The bowl-like molecules of 56 are intricately woven in a three dimensional fashion with numerous C-H...O hydrogen bonds sustaining them to result in close packing, see Figure 7. Further, the near linearity of C-H.. .0 hydrogen bonds is amazing, Table 4.

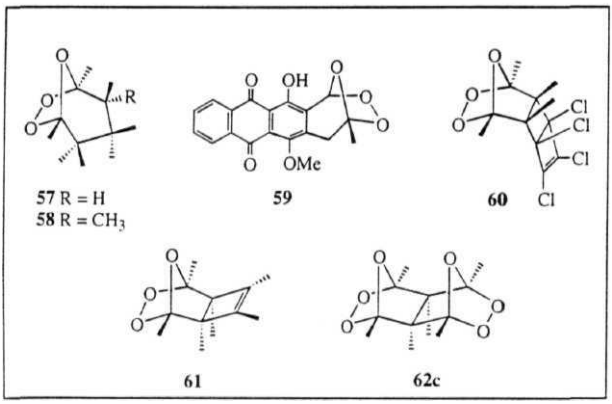
Our investigation[20] of the crystal packing in 26 and 56, shows convincing evidence for extensive C-H.. .O interactions which can contribute substantially to the

stability of the crystal lattice and eventually to the unusual stability of the diozonides. The formation of stable crystal lattice, permits the establishment of weak interactions which, when *numerous,* may affect supramolecular structure *decisively.* Admittedly, C-H...0 hydrogen bonds are much weaker than the conventional hydrogen bonds energy wise, but in the present illustration, these interactions seem to be crucial and *structure directing.* It is noteworthy that in the structures of both 26 and 56, the least acidic[21] diquinane ring junction protons are involved in the C-H...0 hydrogen bonds and this is perhaps a consequence of the bowl-like topology present in these molecules. In summary, we have described the characterization of several 'bowl-like' diozonides of exceptional stability and their X-ray structure reveals a novel architecture sustained through a network of C-H...0 hydrogen bonds.

Stable Mono- and Diozonides in the Literature

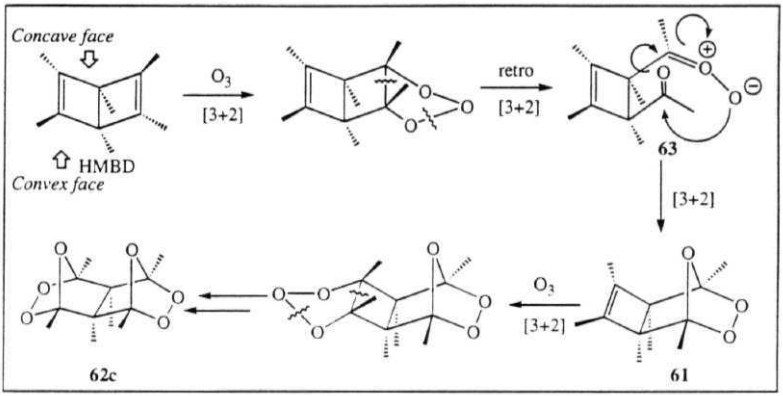
Having encountered an unusual observation of isolating and unambiguously characterizing a series of stable tetraquinane-based diozonides *viz.* 26 and 52-56. we ventured on a literature[22,23] search on mono- and diozonides. While there are several stable monoozonides (57-61) known in the literature, there is only a single stable diozonide" 62c. derived from hexamethyl(Dewar benzene) mentioned in the literature. Some examples of mono and diozonides (57-62c) known in the literature are shown in Scheme 19. Hexamethyl(Dewar benzene) [HMBD] has been reported to produce a mono- 61 and a diozonide 62c on treatment with one or two equivalents of ozone, respectively, Scheme 20. The diozonide **62c** was described to be highly stable and indeed melted without decomposition. The diozonide 62 could exist as three isomers *viz. e.xo,exo-62a. endo,e.xo-62b* and *endo,endo-***62c,** Scheme 21.

**Scheme 19**



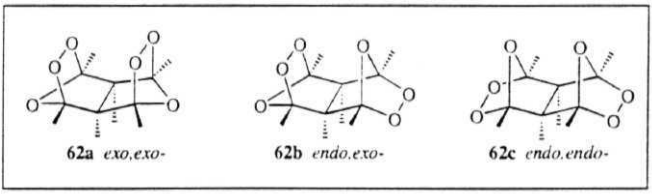

The authors" obtained a single diastereoisomer with two equivalents of ozone and the structural ambiguity was resolved by single crystal X-ray diffraction and was found to be the *endo,endo*-isomer 62c. The crystal structure revealed the existance of discrete. well-separated molecules of **62c** and did not exhibit any significant intermolecular contacts less than 3.2 A. A tentative reaction mechanism for the formation of diozonide **62c** from HMDB is outlined in Scheme 20. In order to explain the formation of **62c.** the authors proposed that the initial attack of ozone takes place from the convex face of HMDB. *syn* to the ring junction methyl groups. to give the corresponding primary ozonide which subsequently decomposed according to Criegee" mechanism to a carbonyloxide/carbonyl pair 63. Reorientation of the stencally less hindered acetyl group followed by recombination would give *endo-6l.* The addition of a second molecule of ozone to 61 on the same face as described above followed by a similar cycloreversion-recombination

Scheme 20




sequence would give rise to 62c as was observed. Scheme 20. The formation of *endo,endo*-diozonide 62c was rationalized on the basis of ease of approach of oxygen

Scheme 21




from the more open convex face than the concave face in both HMBD and 61. Funher. diozonide 62c is inherently stable like its precursor HMBD. as the activation barriers to other rearrangement processes are relatively high.

However. in all the examples reported in the literature thus far. a stable ozonide was either derived from a tri- or tetrasubstituted double bond. There is no

example of a disubstituted double bond furnishing a stable ozonide, Scheme 19. On the other hand, the per methylated diozonide 62c, derived from HMDB, acquires its stability as the methyl groups on the bridgehead cause considerable steric hindrance for the reagent approach to the peroxy bridge making it difficult to cleave.

Further, in the case of diozonide 62c, derived from HMDB, the steric crowding due to the methyl groups were implicated as the causative factor for its unusual stability. However, in the tetraquinane-based diozonides 26 and 52-56 the unusual stability may be attributed to the formation of stable crystal lattice, which seems to be an outcome of their unusual topology.

## II.3 SUMMARY

During our studies in the pursuit of 12, we have observed that tetraquinane 21 and several of its derivatives **27** and **28a-d** furnished remarkably stable topologically interesting diozonides in a highly stereoselective manner. In addition, we have established the generality of diozonide formation in half a dozen tetraquinane systems. In all the examples reported herein, only the *syn,syn* isomer is formed, thereby bestowing a 'bowl-like' topology to diozonides **26** and **52-56.** Although, ozonides by reputation are thermally labile and readily decompose, in our present study, all the diozonides **26** and **52-56.** exhibited exceptional stability (for months!) and have been isolated and fully characterized. To the best of our knowledge, only one stable diozonide [derived from hexamethyl(Dewar benzene)] is known so far. Further, the diozonides 26 and **52-56.** represent examples of ozonides derived from disubstituted double bonds which is rather unusual. Two of the diozonides 26 and 56 readily furnished single crystals and their X-ray crystallographic analysis shows a fascinating packing pattern and supramolecular arrangement, sustained by a network of C-H…0 hydrogen bonds. The remarkable stability of the diozonides **26** and **52-56** is attributed to the 'bowl-like' topology and their novel solid state architecture, woven through a network of unique C-H…0 interactions.

## II.4 EXPERIMENTAL

For a genera] write-up see the experimental section of PART I.

### Starting Materials

The adduct **30**[24.7a] and the pentacyclic diketones **36**[25.7a] and **45**[26.7a] were prepared according to literature procedures.

### General Method for Flash Vaccum Pyrolysis (FVP)

The flash thermolysis of **34, 43, 47,** 49 **and** 51 were carried out in a quartz vigreux column (30 cm x 1.5 cm) packed with quartz chips, connected to a vacuum line and adapted with a collection flask and a liquid nitrogen trap. The quartz column was heated with a nicrome coil wound around it and insulated by asbestos padding. The column temperature was controlled by a variac and measured by a thermo **couple** (Chromel-Alumel) using a Keithley digital multimeter. The column was prc-heated and equilibrated to requisite temperature (±10 °C). The hexacyclic ethers were slowly sublimed (80 -140 °C/1-7 torn through the quartz tube. The condensate. in most cases deposited in the collection flask and was carefully chromatographed.

### Dimethyl 3,3a,3b,4,6a,7a-hexahydro-3,4,7-metheno-7*H*-cyclopenta[*a*]pentalene-7,8-dicarboxylate 22:[8a,b]

To a stirred suspension of sodium hydride (10 g. 0.417 mol) in dry THF (250 mL). cooled at -78 °C (EtOAc-liq N₂ bath). was introduced neat. freshly cracked pre-cooled cyclopentadiene (27.5 g, 0.416 mol). The cyclopentadiene was added rapidly. dropwise over 30-40 minutes to the stirred slurry under argon atmosphere. After the addition was complete. the cooling bath was removed and the solution was stirred for 1 **h at** room temperature. Cuprous bromide-dimethyl sulfide complex was quickly

added under a positive sweep of argon. A solution of 53 g (0.208 mol) of sublimed iodine in dry THF (50 mL) was added dropwise to the cooled slurry over approximately 90 minutes and stirred for an additional 15 minutes at low temperature during which time a bright emerald green colour developed.

DMAD (33 g, 0.232 mol) was added rapidly dropwise over 10 minutes and the solution was stirred for 30 minutes, the cooling bath was removed, and stirring was continued for another 4 h. The reaction mixture was filtered through a celite pad, and the solid was washed repeatedly with THF (150 mL). The combined filtrates were concentrated under reduced pressure at room temperature to give a dark red oil.

The solution of the concentrate in methanol (200 mL) was cooled to -5 °C to 0 °C in an ice-salt bath. A pre-cooled (0 °C) solution containing 22 g of 87.5% KOH in 40 mL of water was added dropwise at such a rate as to keep the reaction temperature below 10 °C. The reaction mixture was stirred for an additional 2 h at 0 "C and for 1 h at room temperature prior to the addition of 10 mL of glacial acetic acid. Solid $Na_2CO_3$ was added to bring the pH to 8 and the solution was filtered through celite. Concentration of the filtrate at 35 °C and reduced pressure afforded about 100 mL of a dark liquid which was diluted with 200 mL of $H_2O$ and extracted with hexane (6 x 60 mL). The combined extracts were washed with aqueous sodium thiosulfate solution (80 mL) and dried. Removal of solvent under reduced pressure furnished a clear red liquid which was charged on neutral alumina column. Elution with 5% ethyl acetate-hexane afforded 22 (4.5-5 g, 8-11%).

mp : 62 °C (lit.[8b] 62-62.5 °C)

*Experimental*

**Dimethyl 2a,3,3a,5a,6,6a,6b,6c-octahydrodicyclopenta[cd,gh]-pentalene-3,6-endo,endo-dicarboxylate 21:**[8b]

In an oven-dried 250 mL three necked RB flask equipped with a condenser and a nitrogen inlet was placed freshly cut sodium (3.4 g, 0.148 g atom) in dry toluene (90 mL). The mixture was heated with rapid stirring until a fine dispersion was formed. TMSC1 (20 mL, 0.157 mol) was added. A solution of diester **22** (1.028 g, 3.77 mmol) in dry toluene (10 mL) was added dropwise and refluxed for 14 h, the dark solution was filtered through celite. Excess TMSC1 was removed and the concentrate (20 mL) was added to dry methanol (100 mL) dropwise under a nitrogen blanket. After dilution of the methanolic solution with water (500 mL), the layers were separated. The aqueous layer was extrated with pentane (3 x 100 mL). after which the combined organic layers were washed with water (3 x 200 mL) and dried. Removal of solvent yielded yellow oil which was chromatographed on silica gel. Elution with hexane removed silylated products and further elution with ethyl acetate-hexane afforded the pure ***endo.endo*** isomer 21 (0.98 g, *957c)* along with traces of *endo.exo* isomer.

mp : 84 °C (lit.[8a] 84-84.5 °C)

IR :1738,1195 $cm^{-1}$

**4-t-Butoxy-12,12-dimethoxyhexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecane 32:**[6a-d]

A solution of the adduct 30 (5.0 g, 11.7 mmol) in acetone (125 mL) was flushed with a slow stream of dry nitrogen and irradiated using a 450 W Hanovia medium pressure mercury vapour lamp, in a quartz immersion well for 1 h.

Evaporation of solvent under reduced pressure furnished a viscous liquid of the hexacyclic adduct 31 (5 g) which was directly used in the next step.

To a magnetically stirred solution of the tetrachlorohexacyclic adduct 31 (5 g, 11.7 mmol) in 250 mL of dry THF and 25 mL of dry t-butyl alcohol was added lithium metal (1.65 g, 0.236 g atom) in small pieces over a period of 45 minutes. The rate of addition of lithium was carefully controlled so as to retain the reaction mixture under a gentle reflux. When all the lithium had been added, the reaction was refluxed for 1 h more, the unreacted lithium was filtered off and the reaction mixture carefully quenched with water. THF was removed under reduced pressure and the crude product extracted with ethyl acetate (50 x 3). The combined organic extract was washed with water. 3% HC1 and dried. Removal of solvent furnished a residue which was chromatographed over a silica gel column to furnish pure 32 (2.71 g. 80%) and was crystallized from DCM-hexane.

mp : 117 °C (lit.[7a] 117-118 °C)

IR : 2950. 1300, 1100, 1050 $cm^{-1}$

**Hexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecane-4-ol-12-one 33:**

To a solution of 32 (2.0 g, 6.9 mmol) in 30 mL of dioxane was added 10 mL of 3N HC1 and the reaction mixture refluxed for 3 h. Dioxane was removed under reduced pressure and the product extracted with ethyl acetate (3 x 30 mL). The combined organic extract was washed with aqueous $NaHCO_3$ and dried. Removal of solvent furnished 33 (1.0 g, 80%) and was crystallized from DCM-hexane.

mp : 117 °C (lit.[7a] 182-184 °C)

IR : 3400 (br) $cm^{-1}$

## *Experimental*

**Hexacyclo[5.4.1.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$.0$^{8,11}$]dodecane-4,12-one 34:**

To a suspension of pyridinium chlorochromate (1.5 g, 0.8 mmol) in 20 mL dry DCM was added a solution of the hydroxy compound **33** (1.0 g, 5.5 mmol) in 20 mL of dry DCM. The reaction mixture was stirred at room temperature (~32 °C) for 1 h. diluted with ether and filtered through a short column of fluorisil. Removal of solvent furnished **34** (800 mg, 80%).

mp : 226 °C (lit.[7a] 227-228 °C)

IR : 1700. 1190. 1160, 1130 cm$^{-1}$

**Tetracyclo[7.2.1.0$^{4,11}$.0$^{6,10}$]dodeca-2,7-diene-5,12-dione 27:**

A sample of the hexacyclic diketone 34 (200 mg, 1.1 mmol) was slowly sublimed (130 °C/5 torr) through a quartz column preheated to 580 °C(+10 °C) as elaborated in the general procedure for FVP. The pyrolysate was charged on a neutral alumina column and eluted with 20% ethyl acetate-benzene to furnish the tetracyclic diketone 27 (60 mg, 30%).

mp : 173 °C (lit.[7a] 173-175 °C)

IR : 1720, 1630. 1160, 1180, 730 cm$^{-1}$

Further elution of the column resulted in the recovery of the hexacyclic diketone **34** (120 mg, 60%).

**4,4-Dimethoxy-2,3,5,6-tetrachloropentacyclo[5.4.0.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$]undecane-endo-8-exo-11-diol 38:**

A solution of a freshly sublimed sample of the pentacyclic diketone 36 (30g. 0.89 mmol) in 200 mL of 95% ethanol was cooled in an ice-bath and $NaBH_4$ (6 g. 156 mmol) was added to it in small portions over a period of 1 h. The reaction

mixture was stirred further for 5h and most of the ethanol was removed under reduced pressure. The residue was extracted with $CHCl_3$ (3 x 150 mL) and the combined organic extracts were washed with water and dried. Removal of solvent and crystallization from ethyl acetate-hexane furnished pentacyclic diol 38 **(24** g, 80%).

mp : 256 °C (lit.[7a,10b] 256-257 °C)

IR :3400(br)cm''

**4-Oxa-1,7,8,9-tetrachloro-12,12-dimethoxyhexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecane 39:**

A mixture of the pentacyclic diol 38 (27 g, mmol) and PTSA (2g. added in four lots of 0.5 g each after every 12 h) in dry toluene (400 mL) was **refluxed** using a Dean-Stark apparatus for 48 h. during which time 100 mL of turbid toluene was removed. The remaining solvent was evaporated under reduced pressure and the residue was extracted with $CHCl_3$ (3 x 150 mL). The combined organic extracts were washed with water. 5% aqueous $NaHCO_3$ and dried. Removal of solvent furnished a dark coloured residue which after crystallization from ethyl acetate-hexane gave the hexacyclic ether **39** (18 g, 73%).

mp : 190 °C (lit.[7a,10b] 189-190 °C)

IR :2950.1090.1025 $cm^{-1}$

**Oxa-3,5,9,10-tetrachlorohexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecane-4-one 40:**

A suspension of **39** (10.5 g, 0.03 mol) in conc. $H_2SO_4$ (50 mL) was stirred at room temperature for 48 h. The mixture was then poured into ice-water (250 mL) and the precipitated solid material was collected. washed with water and dried in

*vacuo* to furnish crude 40 (8.02 g, 87%). Recrystallization from benzene-hexane afforded 40 as colourless crystals.

mp : 199 °C (lit.[10b] 198-200 °C)

IR :1795,1260,1100,1025 $cm^{-1}$

**2-Bromo-6,7-dichlorohexahydro-2,6,3,5-ethanediylidene-2*H*,3*H*-1,4-dioxacyclopenta[*cd*]pentalene 42:**

Compound 40 (6.3 g, 20 mmol) was refluxed with 25% aqueous NaOH (100 mL) for 12 h. The mixture was then cooled to 0 °C (ice-bath) and acidified *via* dropwise addition of excess conc. HC1. The mixture was then extracted with ethyl acetate (3 x 50 mL) and the organic layer was washed with 5% aqueous $NaHCO_3$ (1 x 15 mL) and dried. Removal of solvent afforded the crude acid 41 (3.85 g, *66.59c)* which was directly used in the next step.

In a three necked RB flask, fitted with nitrogen inlet and condensor were placed acid 41 (3 g, 9.9 mmol), red mercuric oxide (2.4 g. 11.1 mmol) and $CH_2Br_2$ (30 mL). The contents were refluxed for 3 h, after which $CH_2Br_2$ was removed in *vacuo,* to give a brown solid residue. This was extracted with ethyl acetate (3 x 75 mL). The organic extract was washed with water and dried. Removal of solvent gave a viscous liquid. which was charged on a silica gel column. Elution with 15% ethyl acetate-hexane gave hexacyclic bromo-compound **42** (2.9 g, 80%) and was recrystallized from DCM-hexane.

mp : 136 °C (lit.[10a] 136-138 °C)

IR :3030,1040,790 $cm^{-1}$

**Hexahydro-2,6,3,5-ethanediylidene-2*H*,3*H*-1,4-dioxacyclopenta[*cd*]pentalene 43:**

*Experimental*

In a three-necked RB flask equipped with nitrogen inlet and condenser was placed **42** (1 g, 3.22 mmol) in dry THF (30 mL) and t-butyl alcohol (10 mL). The reaction mixture was slowly stirred, and lithium chips (180 mg, 0.026 g atom) were added in small portions over a period of 10 minutes. The reaction mixture was refluxed for 45 minutes and cooled to room temperature. The unreacted lithium metal was filtered off and the filtrate was concentrated and diluted with ether (3 x 50 mL). The ethereal solution was washed with 3% HC1, water and dried. Removal of solvent furnished a crude product, which was charged on a silica gel column. Elution with 20% ethyl acetate-hexane furnished dioxabishomopentaprismane 43 (360 mg, 70%).

mp : **271** °C (lit.[10a] 271-273 °C)

IR : 3000, 1020, 920 cm'"

**5,12-Dioxatetracyclo[7.2.1.0$^{4,11}$.0$^{6,10}$]dodeca-2,7-diene 28a:**

The dioxabishomopentaprismane 43 (250 mg, 1.54 mmol) was slowly sublimed (140 °C/4 torr), through a quartz tube filled with quanz chips and preheated and equilibrated to 625 °C (+ 10 °C). The solid residue collected in the receiver flask was carefully chromatographed over neutral alumina. Elution with 20% ethyl acetate-hexane gave the tetracyclic diether **28a** (170 mg, 70%) and was recrystallized from DCM-hexane.

mp : 136 °C (lit.[10a] 136-137 °C)

IR : 3075, 1350, 1070 cm'

**Pentacyclo[5.4.0.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$]undecane-endo,endo-8,11-diol 46 :**[6a,b]

***Experimental***

A solution of the diketone 45 (10g, 57.5 mmol) in dry THF (80 mL) was slowly added to a magnetically stirred slurry of $LiAlH_4$ (3.0 g, 79.0 mmol) in dry THF (40 mL). After the addition was over, the reaction mixture was refluxed for 10 h. cooled in an ice-bath and the excess $LiAlH_4$ was decomposed using saturated aqueous $NH_4Cl$. The precipitated lithium salts was filtered off and washed with $CHCl_3$ (3 x 15 mL). The filtrate was extracted with $CHCl_3$ (3 x 100 mL) and the combined organic extracts were washed with water and dried. Removal of solvent furnished diol 46 (9.2 g, 90%).

mp : 273 °C (lit.[7a] 273-274 °C)

1R : 3200 (br) $cm^{-1}$

**4-Oxahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecane 47:**

An intimate mixture of the diol 46 (2.37 g. 15 mmol) and $P_2O_5$ (0.6 g, 4.23 mmol) was taken in a flat bottomed flask fitted with an air condensor and healed carefully in an oil bath maintained at 200 °C for 10 minutes, during which time vigorous reaction took place. The black tarry residue was extensively extracted with DCM (4 x 20 mL). The combined organic extract was washed with aqueous $NaHCO_3$ and dried. Removal of solvent furnished the hexacyclic ether 47 (1.7 g. 80%) and sublimed to afford a pure sample.

mp : 229 °C (lit.[7a] 228-230 °C)

1R :2965.1325.1025,965 $cm^{-1}$

**5-Oxatetracyclo[7.2.1.$0^{4,11}$.$0^{6,10}$]dodeca-2,7-diene** 28b:"

47 (500 mg, 3.12 mmol) was slowly sublimed (80 °C/7 torn through a quartz tube heated to 620 °C (+10 °C) as described in the general method for FVP. The

condensate in the receiver was chromatographed over $AgNO_3$ impregnated silica gel. Elution with 20% benzene-hexane furnished the starting hexacyclic ether **28b** (125 mg, *259c).* Further elution of the column with ether afforded the tetraquinane ether 47 (350 mg, 70%).

mp : 119 °C (lit.[7a] 119-120 °C)

IR :3100,1620,740 $cm^{-1}$

**8.11-Diphenylpentacyclo[5.4.0.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$]undecane-8,11-diol 48:**

To a magnetically stirred suspension of magnesium turnings (1.05 g, 0.005 g atom) in 25 mL of dry ether was added dropwise a solution of bromobenzene (7.05 g. 4.3 mmol) in dry ether (25 mL). The reaction mixture was stirred until all the magnesium had dissolved and a solution of the diketone **45** (2.5 g, 14.4 mmol) in dry ether (50 mL) was added to it dropwise. The reaction mixture was stirred at room temperature for 4 h and quenched with saturated aqueous $NH_4Cl$. Extraction with ethyl acetate (50 mL x 4) followed by usual work up furnished the diol **48** (4 g, 87%).

mp : 272 °C (lit.[7a] 273-275 °C)

IR : 3070 (br), 2980. 1490 $cm^{-1}$

**3.5-diphenyl-4-oxahexacyclo[5.4.1.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$.0$^{8,11}$]dodecane 49:**

**To** a solution of diol **48** (700 mg. 2.2 mmol) in dry DCM (10 mL) was added $P_2O_5$ (200 mg, 1.41 mmol), the reaction mixture stirred at room temperature for 45 minutes and quenched with water, and the organic layer was separated. The aqueous layer was further extracted with DCM ( 2 x 10 mL) and the combined organic

extracts were washed with aqueous $NaHCO_3$ and dried. Removal of solvent furnished the hexacyclic ether 49 (570 mg, 87%).

mp : 70 °C (lit.[7a] 71-72 °C)

IR : 3030 , 2960, 1600, 1020 $cm^{-1}$

**4,6-Diphenyl-5-oxatetracyclo[7.2.1.0$^{4,11}$.0$^{6,10}$]dodeca-2,7-diene 28c:**

The hexacyclic ether 49 (211 mg, 0.67 mmol) was slowly sublimed (150-160 °C/1 torr) through a quartz tube pre-heated and equilibrated to 625 °C (±10 °C) as given in the general method for FVP. The solid residue collected in the receiver was chromatographed over silica gel. Elution with 3% ethyl acetate-hexane afforded the unreacted hexacyclic ether 49 (92 mg, 45%). Further elution with 5% ethyl acetate-hexane furnished the tetraquinane 28c (60 mg, 30%).

mp : 144 °C (lit.[7a] 145 °C)

IR : 3050.3020, 1600, 745 $cm^{-1}$

**4-Oxa-12,12-dimethoxyhexacyclo[5.4.1.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$.0$^{8,11}$]dodecane 50:**

In a 100 mL three necked RB flask equipped with a nitrogen inlet was placed the hexacyclic ether 39 (2 g, 5.5 mmol). dry t-butyl alcohol (8 ml) and dry THF (40 mL). The reaction mixture was vigorously stirred and lithium metal (640 mg, 0.09 g atom) was added to it as small pieces over a period of 1 h such that a gentle reflux was maintained. When the exothermic reaction had subsided, the reaction mixture was refluxed for 45 minutes and cooled to room temperature. The unreacted lithium was filtered off and the filtrate was concentrated under reduced pressure. The residue was extracted with ether (3 x 20 mL), the combined ether extracts were washed with water, 3% HC1 and dried. Removal of the solvent furnished **50** (1 g, 81%).

mp :71 °C (lit.[7a] 72 °C)

IR : 3025 , 1140, 1100 $cm^{-1}$

**4-Oxahexacyclo[5.4.1.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$.0$^{8,11}$]-dodecane-12-one 51:**

A solution of **50** (1 g, 4.95 mmol) in ether (15 mL) was cooled to ~15 °C in a cold water-bath and 20% (v/v) $H_2SO_4$ (5 mL) was added to it dropwise over a period of 25 minutes. The reaction mixture was then brought to room temperature and stirred for 15 minutes. The ethereal layer was separated and the aqueous layer extracted with ether (10 mL). The combined ether extract was washed with water, 5% aqueous $NaHCO_3$ and dried. Removal of the solvent furnished **51** (700 mg. 86%) and was recrystallized from DCM-hexane.

mp : 239 °C (lit.[7a] 239-240 °C)

IR : 3000, 1790, 1310, 1120 $cm^{-1}$

**5-Oxatetracyclo[7.2.1.0$^{4,11}$.0$^{6,10}$]dodeca-2,7-diene-12-one 31:**

The hexacyclic keto-ether **51** (500 mg, 4.85 mmol) was slowly sublimed (130-140 °C/5 torr) through a quartz tube pre-heated and equilibrated to ~620 °C as elaborated in the general procedure for FVP. The pyrolysate (250 mg) collected in the receiver was chromatographed over a silica gel column. Elution with 10% ethyl acetate removed all the less polar impurities and further elution with 35% ethyl acetate-hexane furnished oxa-tetraquinane **28d** (200 mg, 40%).

mp : 100 °C (lit.[7a] 100-101 °C)

IR : 1730. 1340, 1160 $cm^{-1}$

**General Procedure for Ozonolysis of 21, 27 and 28a-28d:**

*Experimental*

Into a solution of tetraquinane (60 mg, 0.219 mmol) in dry DCM (10 mL) at -78 °C was bubbled ozone until blue colour appeared (10-15 minutes). Excess ozone was flushed out with a slow stream of nitrogen. The solvent was removed and the residue was charged on a silica gel column (3 g) and generally elution with 70% ethyl acetate-hexane furnished the ozonides 26. 52-56 in good yields.

**Ozonolysis** of 21: Formation of ll,18-Biscarbomethoxy-7,8,14,15,16,17-**hexaoxahexacyclo[11.2.1.1$^{2,5}$.1$^{6,9}$.0$^{3,12}$.0$^{4,10}$]octadecane 26:**

The reaction was performed as described in the general procedure and the residue was chromatographed over silica gel (elution with 75% ethyl acetate-hexane) to furnish 26 in 49% yield. The ozonide was recrystallized from DCM.

mp : 141-142 °C

IR : 1726. 1219. 1126. 937. 918 cm$^{-1}$

$^{1}$H NMR (Spectrum 1) : 5 6.06 (4H. bs), 3.78 (6H. bs). 3.48-3.36 (2H. m). 3.11-2.97 (2H. m), 2.81-2.67 (4H. m)

$^{13}$C NMR (Spectrum 2) : 5 170.5 (s), 99.5 <d), 52.0 (q), 50.9 (d). 42.7 (d). 42.5 (d)

Analysis • $C_{16}H_{18}O_{10}$ : Calcd. : C. 51.89: H. 4.90

Found : C. 51.92: H. 4.92

**Ozonolysis** of 27: Formation of **7.8.14.15.16.17-Hexaoxahexacyclo[11.2.1.1$^{2,5}$.1$^{6,9}$.0$^{3,12}$.0$^{4,10}$]octadecane-11.18-dione 52:**

The reaction was performed as described in the general procedure and the residue was chromatographed over silica gel (elution with 85% ethyl acetate-hexane) to furnish **52** in 46% yield. The ozonide was recrystallized from ethyl acetate.

mp : 168-170 °C (decomp.)

IR : 1739. 1334. 1093, 922 $cm^{-1}$

$^{1}H$ NMR : 5 6.14 (4H, bs), 3.89-3.74 (2H, m), 3.01-2.95 (4H. m)

(Spectrum 3)

$^{13}C$ NMR : 5 99.9 (d), 50.6 (d). 30.7 (d) (sparingly soluble in $CDCl_3$, hence carbonyl carbon resonance did not show-up)

Analysis : $C_{12}H_{10}O_8$ : Calcd. : C. 51.07; H. 3.57

Found : C. 51.10: H. 3.56

**Ozonolysis of 28a: Formation of 7,8,11,14,15,16,17,18-Octaoxahexacyclo[11.2.1.1$^{2,5}$.1$^{6,9}$.0$^{3,12}$.0$^{4,10}$]octadecane 53:**

The reaction was performed as described in the general procedure and the residue was chromatographed over silica gel (elution with 60% ethyl acetate-hexane) to furnish 53 in 68% yield. The ozonide was recrystallized from DCM.

mp : 165 °C

IR 1157, 1097.941.896 $cm^{-1}$

$^{1}H$ NMR 5 5.92 (4H. bs). 3.93-3.91 (4H. m), 3.28-3.21(2H. m)

(Spectrum 4)

$^{13}C$ NMR 5 99.1 (d), 75.3 (d), 41.8 (d)

(Spectrum 5)

Analysis $C_{10}H_{10}O_8$ : Calcd. : C. 46.52: H. 3.90

Found : C, 46.55; **H,** 3.95

**Ozonolysis of 28b: Formation of 7,8,11,14,15,16,17-Heptaoxahexacyclo[11.2.1.1$^{2,5}$.1$^{6,9}$.0$^{3,12}$.0$^{4,10}$]octadecane 54:**

The reaction was performed as described in the general procedure and the residue was chromatographed over silica gel (elution with 60% ethyl acetate-hexane) to furnish **54** in 44% yield. The ozonide was recrystallized from DCM-hexane.

mp :122-124 °C

IR :1151, 1099, 1057, 937, 900 cm$^{-1}$

$^{1}$H NMR : 5 5.92 (2H, bs), 5.79 (2H, bs), 3.78 (2H, d, $J$ = 4.5 Hz), 3.13-2.99

(Spectrum 6) (2H. m), 2.46-2.10 (3H, m), 1.92-1.79 (1H, m)

$^{13}$C NMR : 5 102.2 (d), 99.7 (d), 76.6 (d), 42.8 (d). 41.1 (d), 29.7 (t)

(Spectrum 7)

Analysis : $C_{11}H_{12}O_7$ : Calcd. : C. 51.57; H, 4.72

Found : C, 51.62; H, 4.75

**Ozonolysis of 28c: Formation of 10,12-Diphenyl-7,8,11,14,15,16,17-heptaoxahexacyclo[11.2.1.1$^{2,5}$.1$^{6,9}$.0$^{3,12}$.0$^{4,10}$]octadecane 55:**

The reaction was performed as described in the general procedure and the residue was chromatographed over silica gel (elution with 65% ethyl acetate-hexane) to furnish **55** in 47% yield. The ozonide was recrystallized from DCM-hexane.

mp : 152-153 °C

IR : 1448, 1107, 1037, 949, 927 cm$^{-1}$

$^{1}$H NMR : 5 7.12-7.08 (5H, m), 7.00-6.94 (5H. m), 5.91 (2H, bs), 5.84 (2H, bs).

(Spectrum 8) 3.90 (2H, dd, $J_1$ = 7.1 Hz. $J_2$ = 2.6 Hz), 2.84-2.71 (2H. m), 2.48 (1H.

ABq, $J_1 = J_2$ =12.0 Hz), 2.20-2.05 (1H, m)

$^{13}$C NMR : 5 139.5 (s), 127.5 (d), 102.4 (d), 101.9 (d), 89.9 (s), 45.0 (d), 43.4 (Spectrum 9) (d), 31.3 (t)

Analysis : $C_{23}H_{20}O_7$ : Calcd. : C, 67.64; H, 4.94

Found : C, 67.70; H, 4.96

**Ozonolysis of 28d: Formation of 7,8,11,14,15,16,17-Heptaoxahexacyclo[11.2.1.1$^{2,5}$.1$^{6,9}$.0$^{3,12}$.0$^{4,10}$]octadecane-18-one 56:**

The reaction was performed as described in the general procedure and the residue was chromatographed over silica gel (elution with 85% ethyl acetate-hexane) to furnish 56 in 57% yield. The ozonide was recrystallized from ethyl acetate-hexane.

mp : 170 °C

1R : 1741. 1149. 1095.937 cm$^{-1}$

$^1$H NMR : 5 6.16 (2H, bs), 5.89 (2H. bs), 4.04-4.00 (2H. m), 3.55-3.39 (2H. m), (Spectrum 10) 2.83-2.72 (2H, m)

$^{13}$C NMR : 5 99.6 (d), 99.2 (d), 75.9 (d), 48.9 (d), 35.7 (d) (sparingly soluble in $CDCl_3$, hence carbonyl carbon resonance did not show-up)

Analysis : $C_{11}H_{10}O_8$ : Calcd. : C, 48.90; H, 3.73

Found : C, 48.95; H. 3.75

## CRYSTALLOGRAPHY

**Single-Crystal X-ray Analysis of 26:**

*Experimental*

*Crystal data:* $C_{16}H_{18}O_{10}$, $M_r$ = 370.30, colourless crystals from DCM, monoclinic, space group $C2/c$, $a$ = 11.534(6), $b$ = 9.174(9), $c$ = 14.825(19) A, $\beta$ = 101.12(8)°, $V$ = 1539(3) $A^3$, Z = 4, $D_{calcd}$ = 1.598 Mg $m^{-3}$, $T$ = 293 °K, $F(000)$ = 776, $\mu$(Mo-K$\alpha$) = 0.135 mm , crystal dimensions 0.23 x 0.11 x 0.15 mm.

*Data collection and structure solution:* Data were collected on Enraf-Nonius MACH-3 diffractometer, with graphite-monochromated Mo-K$\alpha$ radiation (A = 0.71073 A), by the *(0* scan method in the range $2 < \theta < 25°$. A total of 2745 reflections were collected ($+h$, $+k$, $\pm l$), with 1351 unique reflections [$R_{int}$ = 0.0379], of which 1211 had $F_o > 4\sigma(F_o)$,and were used in all calculations. At final convergence $R_1$ [$I > 2\sigma I$)] = 0.0447. $wR_2$ = 0.1197 for 119 parameters. GOF = 1.074. $\Delta\rho_{max}$ = 0.297 eA$^{-3}$ $\Delta\rho_{min}$ = -0.251 eA$^{-3}$. The data were reduced using XTAL (version 3.4), solved by direct methods, refined by full-matrix least-squares on $F$ with the non-H atoms anisotropic, and H atoms were placed in calculated positions and were allowed to ride on their parent atoms."[7]

**Single-Crystal** X-ray Analysis of 56:

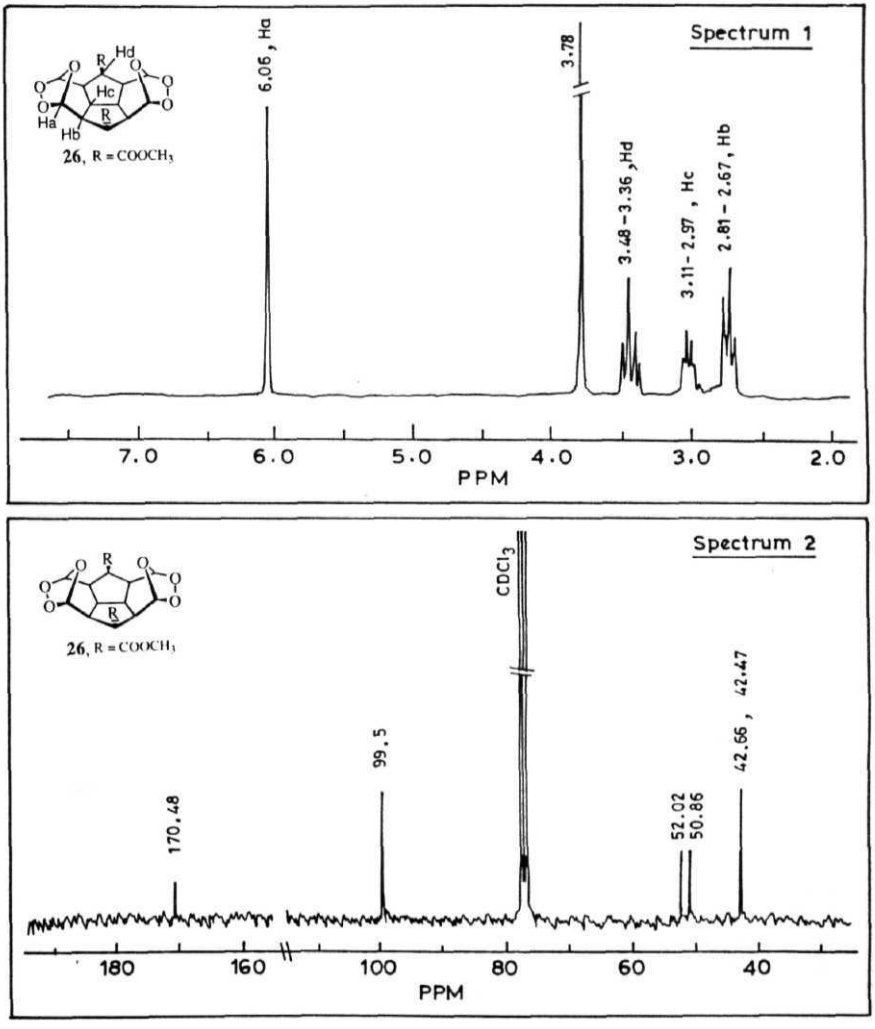
*Crystal data:* $C_{11}H_{10}O_8$, $M_r$ = 270.19, colourless crystals from ethyl acetate-hexane, orthorhombic, space group $Pca2_1$ (no. 29), $a$ = 15.547(3), $b$ = 7.584(1), $c$ = 9.052(10) A, $V$ = 1067.3(13) $A^3$, Z = 4, $D_{calcd}$ = 1.681 Mg $m^{-3}$, $T$ = 293 °K, $F(000)$ = 560. $\mu$(Mo-K$\alpha$) 0.147 $mm^{-1}$, crystal dimensions 0.20 x 0.11 x 0.13 mm.

*Data collection and structure solution:* Data were collected on Enraf-Nonius MACH-3 diffractometer, with graphite-monochromated Mo-K$\alpha$ radiation (A =

***Experimental***

0.71073 A), by the $\omega$ scan method in the range $2 < d < 30°$. A total of 1856 reflections were collected ($+h$, $+k$, $+/$), with 1648 unique reflections [$R_{int}$ = 0.0], of which 741 had $F_o > 4\sigma(F_o)$, and were used in all calculations. At final convergence $R_1$ [$/ > 2\sigma(I)$] = 0.0672, $wR_2$ = 0.1724 for 117 parameters, GOF = 1.046, $\Delta\rho_{max}$ = 0.294 eA$^{-3}$, $\Delta\rho_{min}$ = -0.283 eA$^{-3}$ • The data were reduced using XTAL (version 3.4), solved by direct methods, refined by **full-matrix** least-squares on $F$ with the oxygen atoms anisotropic. C atoms isotropic and H atoms were placed in calculated positions and were allowed to ride on their parent atoms.

# II.5 SPECTRA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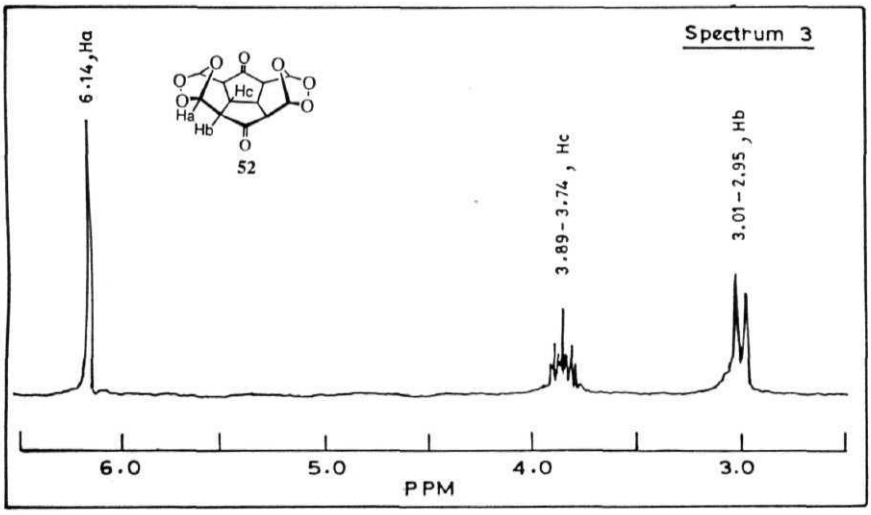
6.05 , Ha
3.78
3.48 – 3.36 , Hd
3.11 – 2.97 , Hc
2.81 – 2.67 , Hb
7.0
6.0
5.0
4.0
3.0
2.0
PPM
26, R = COOCH3
Spectrum 2
CDCl3
99.5
170.48
52.02
50.86
42.66 , 42.47
180
160
100
80
60
40
PPM
26, R = COOCH3


Spectrum 3
6.14, Ha
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3.01-2.95 , Hb
Ha
Hb
Hc
52
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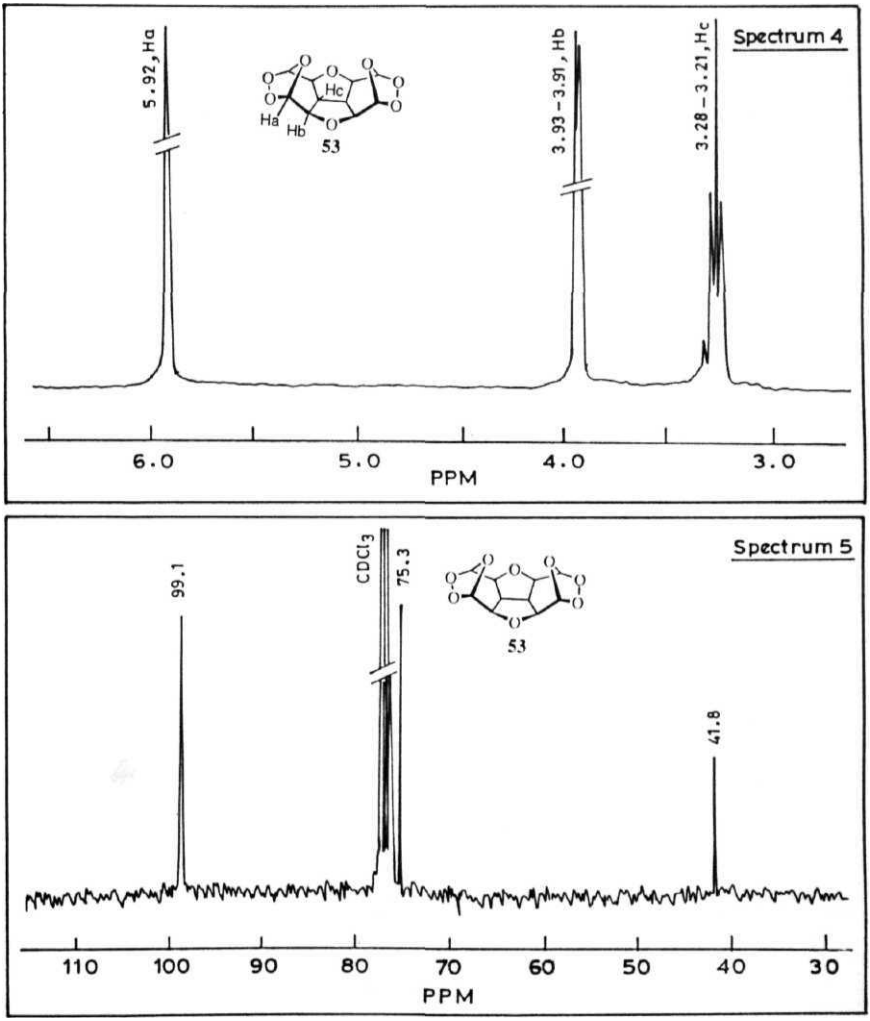
5.0
4.0
3.0
PPM


Spectrum 4
5.92, Ha
3.93 - 3.91, Hb
3.28 - 3.21, Hc
Hc
Ha
Hb
53
6.0
5.0
4.0
3.0
PPM
Spectrum 5
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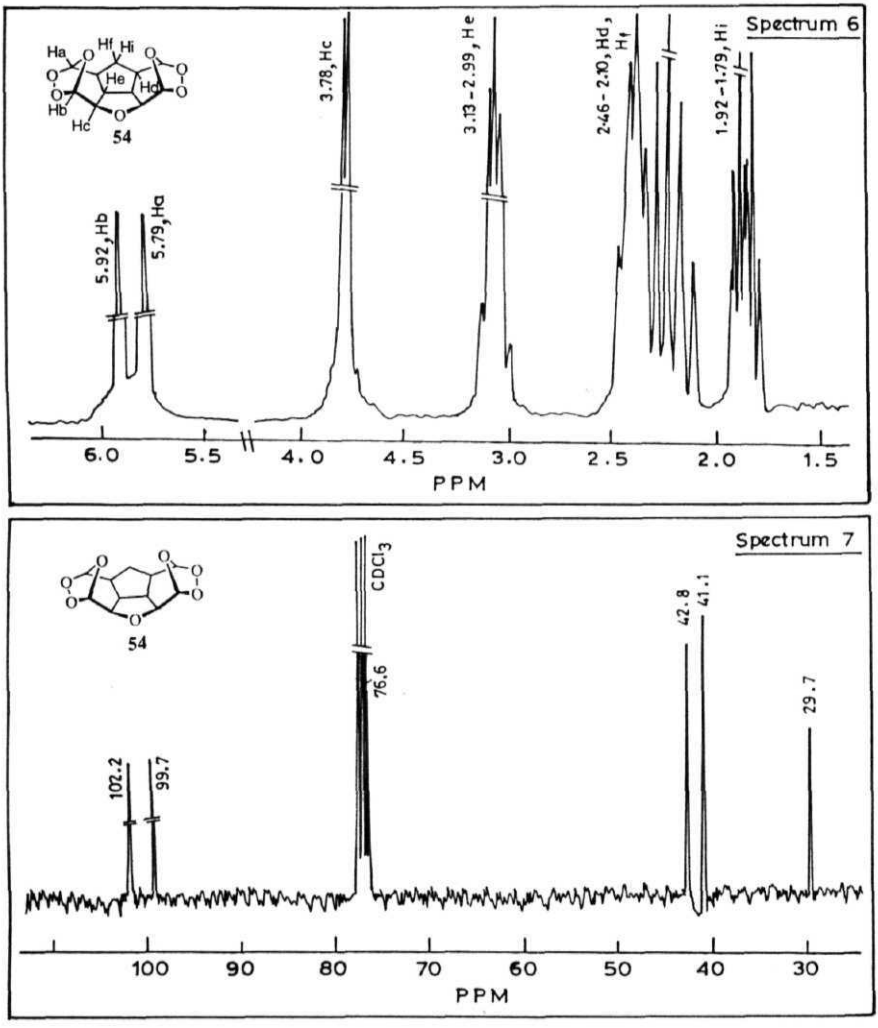
CDCl3
75.3
41.8
53
110
100
90
80
70
60
50
40
30
PPM


Spectrum 6
Ha
Hf
Hi
He
Hd
Hb
Hc
54
5.92, Hb
5.79, Ha
3.78, Hc
3.13 - 2.99, He
2.46 - 2.10, Hd, Hf
1.92 - 1.79, Hi
6.0
5.5
4.0
4.5
3.0
2.5
2.0
1.5
PPM
Spectrum 7
54
CDCl3
76.6
102.2
99.7
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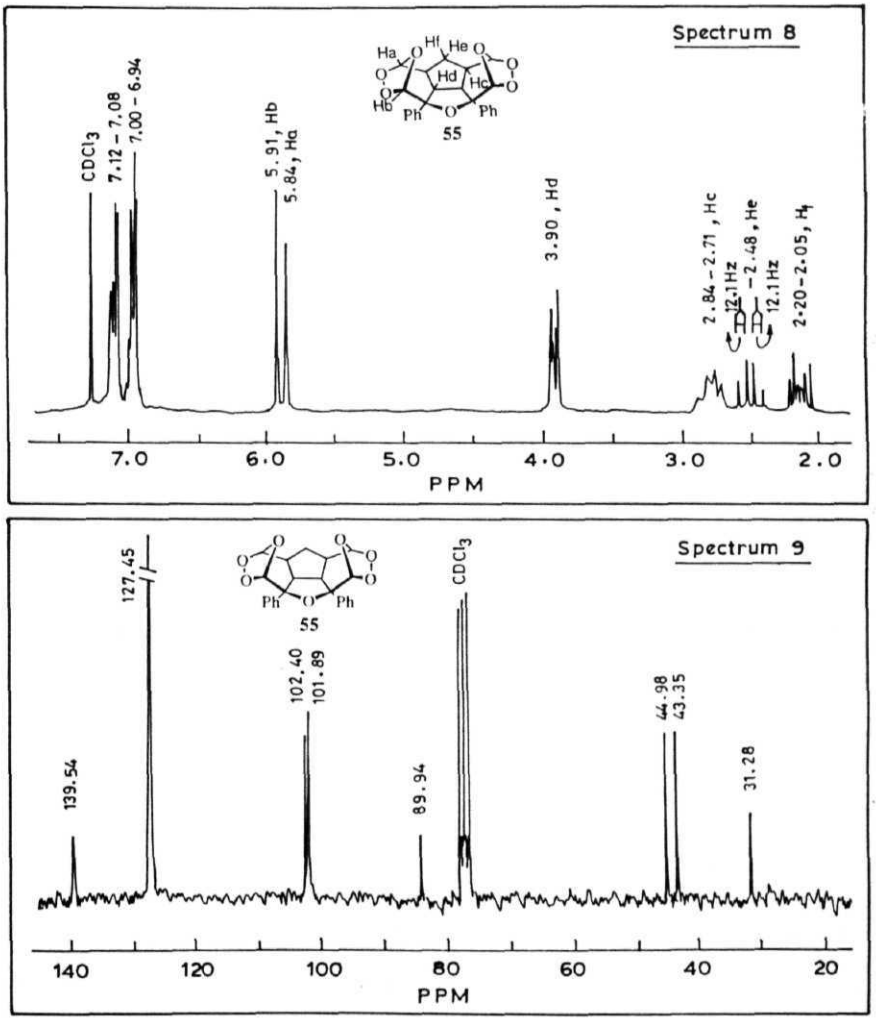
100
90
80
70
60
50
40
30
PPM


Spectrum 8
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7.12 – 7.08
7.00 – 6.94
5.91, Hb
5.84, Ha
3.90, Hd
2.84 – 2.71, Hc
12.1Hz
– 2.48, He
12.1Hz
2·20–2.05, Hf
55
7.0
6.0
5.0
4.0
3.0
2.0
PPM
Spectrum 9
127.45
139.54
102.40
101.89
89.94
CDCl3
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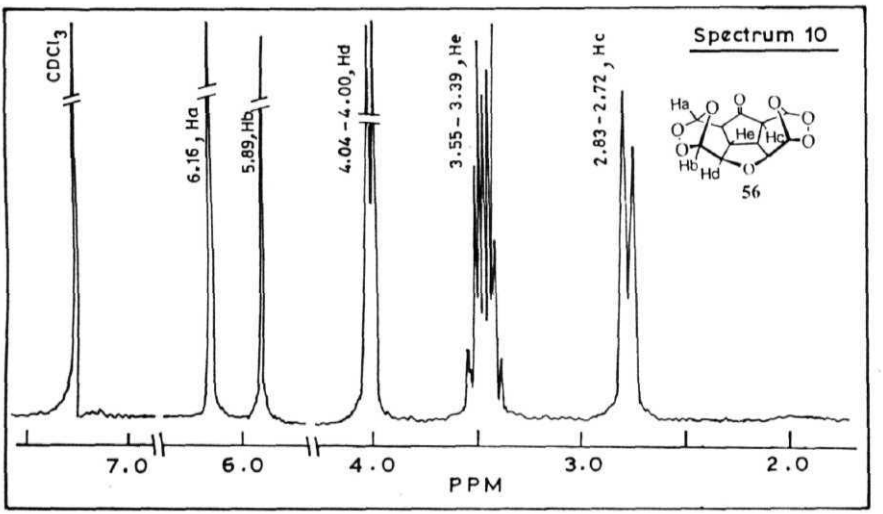
43.35
31.28
55
140
120
100
80
60
40
20
PPM


Spectrum 10
CDCl3
6.16 , Ha
5.89,Hb
4.04 - 4.00, Hd
3.55 - 3.39 , He
2.83 - 2.72 , Hc
Ha
He
Hc
Hb
Hd
56
7.0
6.0
4.0
3.0
2.0
PPM

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# APPENDIX

# Ladderane-like Motifs: Solid State Architecture of *trans*-1,2-Diphenyl-1-cyclobutene-3,4-diol Dinitrate

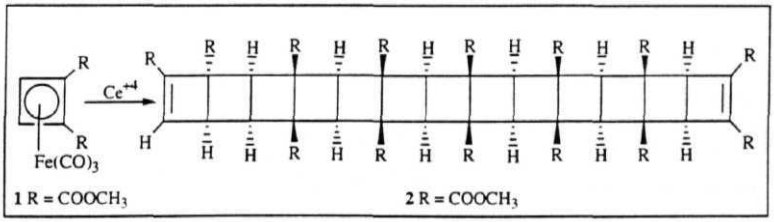
*Abstract*

$C_2$-symmetric *trans*-1,2-Diphenyl-1-cyclobutene-3,4-diol dinitrate defines a novel ladderane-like motif in the solid state through a network of C-H...O interactions between aromatic C-H donor and a weak acceptor like the nitrate ester group.

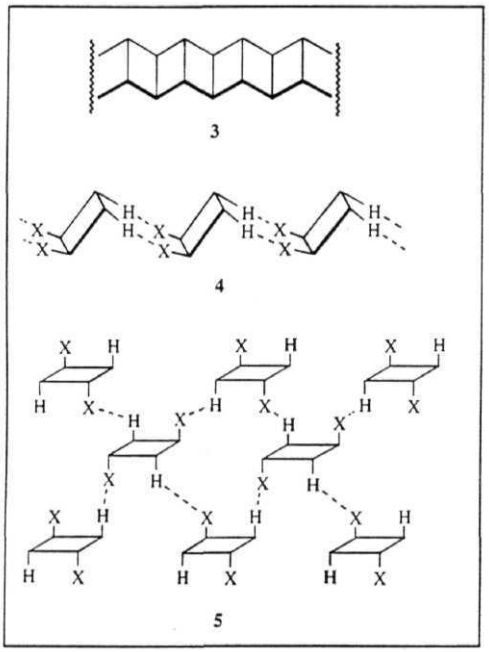
*Discussion*

[n]-Ladderanes are a class of novel molecular arrays composed entirely of linearly fused cyclobutane rings and we have recently shown that appropriately substituted cyclobutadienes e.g. 1, serve as an effective molecular building-block (synthon) for the rapid assembly of polyquadranoid frameworks through cascade cycloadditions. Employing this strategy, it has been possible to stitch together cyclobutane rings through a' bonds to unfold [n]-ladderanes e.g. 2 (n = 13) of record length and nanometric dimension in a completely regio-and stereoselective manner, Scheme 1.[lb. 2] The successful construction and characterization of such molecular

Scheme 1



Scheme 2



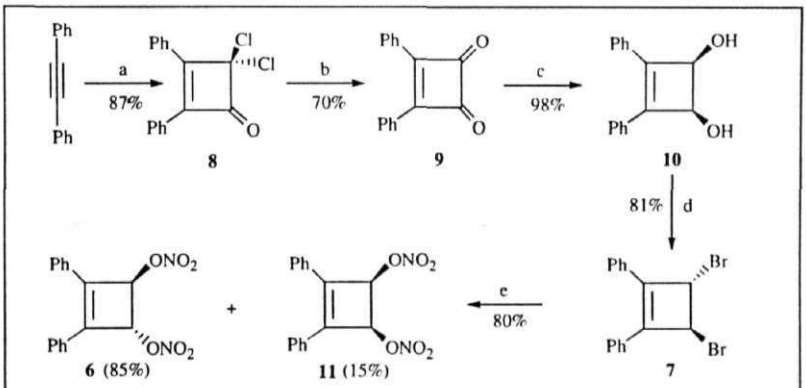

ladders through conventional covalent synthesis provided the impetus to explore the generation of such ensembles in the solid state employing non-covalent protocols.

In analogy with the term [n]-ladderanes for the covalently fused assemblies of cyclobutane rings e.g. 3. several motifs like 4 or 5 (Scheme 2), generated through weak interactions between four membered rings can be conceptualized and regarded as non-covalent ladderane motifs. In such an endeavor towards non-covalent

ladderanes, hydrogen bonds (both classical and non-conventional ) and aromatic *n-n* and related weak interactions must play an important role in promoting the molecules to self-assemble into well-defined aggregates.

Thus, a tecton having a four membered ring, preferably a square-like planar cyclobutene ring, which is appropriately embellished with functional groups at all the four corners and having positional and stereochemical complementarity, might have a prospect to self-assemble in the solid state into a ladderane-like motif. In this context, we have observed that a highly crystalline tetrasubstituted cyclobutene derivative 6, endowed with $C_2$-symmetry and readily available from the *trans*-dibromide 7,[4] as shown in the Scheme 3, exhibits ladderane-like architecture in the

**Scheme** 3

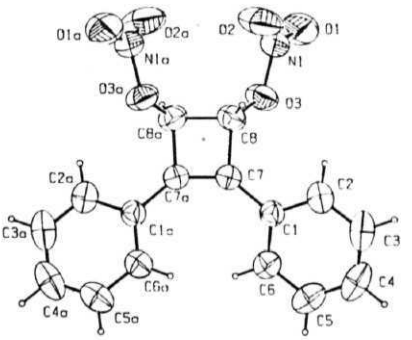



***Reagents and Conditions:*** a) Zn, $CCl_3COCl$, DME, ether, sonication, 10-15 °C, 2h; b) 90% $H_2SO_4$, 80-90 °C, 1h; c) $NaBH_4$, $CeCl_3.7H_2O$, ethanol, r.t., 90min; d) $PBr_3$, $CHCl_3$, -60 °C to r.t. to reflux, 12h; e) $AgNO_3$, $CH_3CN$, r.t., 14h

solid state.

The *trans*-dibromide 7, was obtained starting from tolan and dichloroketene in four steps.[5,6] Facile addition of dichloroketene to tolan was mediated by zinc and ultrasound, to furnish adduct 8 in 87% yield. Hydrolysis of the geminal dichloride 8 in 90% sulphuric acid at 80-90 °C provided the corresponding dione 9 in high yield.[5] Reduction of dione 9 under Luche[7] conditions, using a mixture of cerium(III)chloride and sodium borohydride in ethanol at 0 °C, afforded diol 10 in near quantitative yield. The diol 10 could be readily converted to the dibromide 7 on treatment with $PBr_3$ in 75% yield. Stirring a solution of dibromide 7 with $AgNO_3$ in acetonitrile, furnished a mixture of *trans*- and *cis*-dinitrates 6 and 11 in 85:15 ratio, respectively, see Scheme 3.

**Figure 1. ORTEP plot of 6**



The $C_2$ symmetric 6 crystallizes from ethylacetate-hexane in a centrosymmetric space group $C2/c$ and the ORTEP diagram of the molecular structure is shown in Figure 1. Analysis of the crystal packing in 6 has revealed many new and novel features that we were interested in. The crystal lattice of 6 has a layered structure and the cyclobutene rings are stacked one over the other resulting in a columnar arrangement. Within the *ab* plane, each molecule is C-H...0 hydrogen bonded to all four nearest neighbours, two above and two below through its two donor sites (H2 and H2a) and two acceptor sites (01 and O1a). These interactions, with the H...0 distance 2.72 A (C...O 3.48 A and C-H...0 angle of 140.6°) are in the generally accepted range of attractive C-H...0 contacts reported in the literature[8], see Figure 2. The functional group complementarity present in 6, coupled with suitable spatial disposition enables each unit to enter into quadruple C-H...0 interactions to weave a layered, columnar molecular array as shown in Figure 2. It is to be noted that nitrate groups, which have been generally regarded as poor acceptors, do effectively participate in C-H...0 hydrogen bonding in the present example with each monomeric unit engaged in four such interactions. Although weak, these numerous C-H...0 interactions seem to be the main directors of the self-assembly of 6 into a columnar arrangement and a ladderane-like architecture, Figure 2.

The phenyl rings in the two adjacent *ab* planes are offset from each other and the interplanar separation is ~ 3.8 A. As the molecule has a $C_s$ symmetry and is chiral, the inversion related molecules form an enantiomeric pair when viewed down the c axis, Figure 3. An interesting aspect of the crystal packing in 6 is that all the nitrate groups and the phenyl rings are aligned and when viewed down the *c* axis

appear as alternate hydrophilic and hydrophobic columns. This arrangement also leads to supramolecular host cavities with aromatic walls and nitrate group occupying periphery of the cavity, which form infinite channels, Figure 3.

**Figure 2. Packing diagram showing supramolecular ladderane-like motifs; dashed lines represent C-H...O hydrogen bonds**

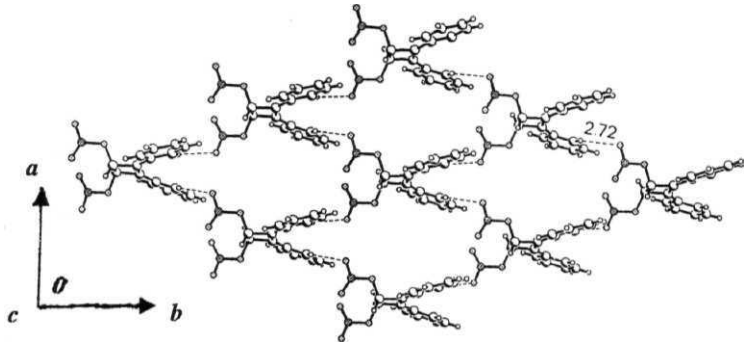
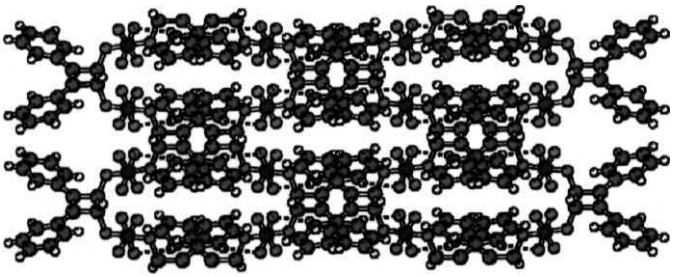



**Figure 3. Crystal packing of 6 viewed along the crystailographic *c* axis showing supramolecular cavities and nitrate group stacking**



The crystal packing in 6 is quite unique and notably different. A search of the Cambridge Structural Database for substituted cyclobutenes like 1,2 diphenyl-cyclobutene , *cis*-cyclobut-1-ene-3,4-dicarboxylic acid and cyclobut-1-ene-1,2-dicarboxylic acid [9c] failed to reveal a ladderane-like motif in any of them. The marked difference in the packing pattern of 1,2 diphenyl-cyclobutene and its dinitrate derivative 6 is clearly indicative of the ability of the *trans-disposed* nitrate groups to engineer the self-assembly in 6 in a subtle manner to generate the ladderane motif. A CSD search [10] of structures possessing organic nitrate groups, e.g. *cis*-benzocyclobutene-1,2-diol dinitrate [10b] indicated that in none of them the nitrate oxygen was involved in any significant C-H...0 interaction, thus rendering 6 as the first example.

*Summary*

In short, the crystal structure of a functionalized cyclobutene 6 has revealed a ladderane-like pattern in the solid state," which appears to be largely sustained by extensive C-H...0 hydrogen bonds. Our observations should stimulate interest in the synthesis and crystal structure determination of a range of donor-acceptor, square-shaped cyclobutenes. which are likely to exhibit interesting motifs in the solid state.

***Experimental Details***

For a general write-up see the experimental section of PART I.

**4,4-Dichloro-2,3-diphenyl-3-cyclobutenones 8:**

An oven-dried 1 L round bottom flask was centered in an ultrasound cleaning bath and charged with diphenylacetylene (23.2 g, 0.13 mol) and zinc dust (18.3 g,

0.26 mol) in 300 mL of dry diethyl ether under an argon atmosphere. The flask was fitted with dropping funnel, which contained ether (50 mL), DME (60 mL) and trichloroacetyl choride (21.8 mL, 0.195 mol). This solution was added dropwise over 45 min, while the flask was sonicated; the temperature was maintained at 10-15 °C by adding ice to the bath. The reaction mixture was sonicated for 2 h including addition time. The mixture was quenched with ether, filtered through celite, then washed with water (3 x 70 mL) and saturated $NaHCO_3$ (2 x 50 mL) solution. The organic layer was dried and removal of solvent furnished a residue which was directly crystallized from ether-hexane to give clear needles of 8 (30.2 g, 877c).

mp : 121°C (lit.[5] 120-121°C)

IR : 1772 $cm^{-1}$

**3,4-Diphenyl-3-cyclobutene-1,2-dione** 9:

The compound 8 (860 mg, 2.99 mmol) was placed in a RB flask and immersed in an oil bath maintained at 80-90 °C. 90% (v/v) $H_2SO_4$ (10 mL) was added and the mixture was stirred for 1 h. The reaction mixture was poured over ice and extracted with ether (3 x 20 mL). The ethereal layer was washed with water (2 x 20 *mL)* and saturated $NaHCO_3$ solution (3 x 20 mL). The organic layer was dried and removal of solvent afforded a residue, which was charged on a silica gel column. Elution with 25% ethyl acetate-hexane furnished dione 9 (489 mg, 70%), which was recrystallized from DCM-hexane to give yellow crystals.

mp : 97 °C (lit.[5] 97-97.2 °C)

IR : 1777, 1599, 1566. 1352, 1080 $cm^{-1}$

***cis*-3,4-Diphenyl-3-cyclobuten-1,2-diol 10:**

To a solution of 1,2-dione 9 (1.21 g, 5.15 mmol) in absolute ethanol (25 mL), cooled to 0 °C was added a solution of $CeCl_3.7H_2O$ (3.83 g, 10.31 mmol) in ethanol (30 mL). While stirring, $NaBH_4$ (418 mg, 10.99 mmol) was added in small portions. After the addition was complete, the reaction mixture was further stirred for 1.5 h and quenched with saturated $NH_4Cl$ and was extracted with ethyl acetate (3 x 70 mL). The combined organic extracts were washed and dried to give the crude diol 10 (1.21 g, 98%) and was directly crystallized from DCM-hexane.

mp : 135 °C (lit.[4] 135.5-136.5°C)

IR : 3312 (br), 1427, 1127 cm'"

$^1$H NMR : 5 7.67-7.62 (4H, m), 7.35-7.32 (6H, m), 5.00 (2H, bs), 3.45 (2H, bs, $D_2O$ exchangeable)

$^{13}$C NMR : 5 144.2, 133.2, 128.8, 128.6, 127.2, 71.0

***trans*-1,2-Dibromo-3,4-diphenyl-3-cyclobutene** 7:

To a 50 mL RB flask containing 1,2-diol 10 (238 mg, 1.0 mmol) in dry chloroform (15 mL) at –60 °C was slowly added phosphorous tribromide (0.05 mL. 0.5 mmol). The solution was stirred for 1 h, warmed to room temperature, then refluxed for 12 h. After cooling, the solution was quenched with saturated $NaHCO_3$ (30 mL) then extracted with DCM (3 x 75 mL). The combined organic extracts were washed and dried. Removal of solvent under reduced pressure afforded the crude dibromide 7 (295 mg, 81%) and was crystallized from DCM-hexane.

mp : 115 °C (lit.[4] 115-116.5°C)

IR : 1445, 1348, 1173, 1154 $cm^{-1}$

'H NMR : 6 7.63-7.58 (4H, m), 7.44-7.41 (6H, m), 5.42 (2H, s)

$^{13}C$ NMR : 5 139.0, 130.7, 129.9, 128.7, 127.8, 50.7

**Conversion of dibromide 7 to dinitrate 6 and 11:**

A mixture of trans-dibromide 7 (200 mg, 0.549 mmol), $AgNO_3$ (195mg, 1.154 mmol) in dry acetonitrile (10 mL) was stirred in dark at room temperature for 14h. The precipitated silver bromide was filtered off and washed with acetonitrile. The filtrate was concentrated under reduced pressure and the residue was taken up in $CH_2Cl_2$ (30 mL) and washed with water. Removal of solvent furnished a mixture of dinitrates 6 and 11 in 85: 15 ratio, respectively, in 80% yield. A combination of fractional crystallisation and column chromatography (neutral alumina) enabled separation of *trans*- 6 and *cis*-dinitrate 11, which were fully characterized.

***trans*-1,2-Diphenyl-1-cyclobutene-3,4-diol Dinitrate 6:**

mp : 137°C

IR :1634,1277,862 $cm^{-1}$

$^{1}H$ NMR : 5 7.59-7.51 (4H, m), 7.46-7.39 (6H, m), 6.17 (2H, s)

$^{13}C$ NMR : 5 136.3, 130.3, 129.8, 129.0, 127.4, 79.8

Analysis : $C_{16}H_{12}N_2O_6$ : Calcd. : C, 58.54; H, 3.68; N, 8.53

Found : C, 58.57; **H,** 3.66; N, 8.55

***cis*-1,2-Diphenyl-1-cyclobutene-3,4-diol Dinitrate 11:**

mp : 68°C

IR :1643,1287 $cm^{-1}$

$^{1}H$ NMR : 5 7.62-7.53 (4H, m), 7.45-7.40 (6H, m), 6.47 (2H, s)

$^{13}C$ NMR : 5 140.2, 130.7, 130.4, 129.0, 127.3, 79.8

Analysis : $C_{16}H_{12}N_2O_6$ : Calcd. : C, 58.54; H, 3.68; N, 8.53

Found : C, 58.54; H, 3.68; N, 8.56

*Crystallography*

*Single-Crystal X-ray Analysis of 6:*

*Crystal data:* $C_{16}H_{12}O_6N_2$, *M* - 328.28, colorless crystals from ethyl acetate-hexane, Monoclinic, Space group *C2/c*,*a* = 8.016(1), *b* = 17.177(2) and c= 11.334(2) A, $\beta$ = 102.19(1)°, *V* = 1525.5(4) $A^3$, Z = 4, $D_c$ = 1.429 Mg $m^{-3}$ $T$ = 293 °K, $F(000)$ = 680, $\mu$( Mo-K$\alpha$) = 0.1 1mm , crystal dimensions 0.16 x 0.13 x 0.22 mm.

*Data collection and structure solution:* Data were collected on Enraf-Nonius MACH-3 diffractometer, graphite monochromated Mo-K$\alpha$ radiation (A = 0.71073 A), by the *0)* scan method in the range 2 < $\theta$ < 25°, 1347 unique reflections [$R_{int}$ = 0.0], 979 had $F_o > 4\sigma(F_o)$, were used in all calculations. At final convergence $R_1[I > 2\sigma(I)]$=0.036, w$R_2$ = 0.0909 for 109 parameters, GOF = 1.04, $\Delta\rho_{max}$ = 0.15 eÅ$^{-3}$, $\Delta\rho_{min}$ = -0.17 eA . The data were reduced using XTAL (ver 3.4), solved by direct methods, refined by full-matrix least-squares on *F*~ with the non-H atoms anisotropic, and H atoms were placed in calculated positions and were allowed to ride on their parent atoms.[12]

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*Vitae*

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*List of Publications*

1. Singlet Oxygen Additions to Hexacyclo[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]pentadeca-5.7-dien-3,10-diones. A Remarkable Substituent Effect on π-Face Selectivity Induced by Transition state Geometric Distortions, G. Mehta, R. Uma. A. Pramanik, J. Chandrasekhar and M. Nethaji, *J. Chem. Sac, Chem. Commun.*, 1995, 677.
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3. An Exceptionally Simple and Convenient Method for Dethioacetalization. G. Mehta and R. Uma. *Tetrahedron Lett.,* 1996, *37,* 1897.

4. Oxa-Bowls: Formation of Exceptionally Stable Diozonides with novel, C-H…0 Hydrogen Bond Directed, Solid state Architecture, G. Mehta and R. **Uma,** *Chem. Commun.*, 1998, 1735.
5. Triquinane-Derived Macrocyclic Lactones and a [2]-Catenane: Synthesis and Characterisation, G. Mehta, K. Srinivas, R. Vidya, R. Uma, A.C. Kunwar, K. Ravikumar, and M. Vairamani, *Tetrahedron,* 1998, *54,* 10879.
6. New Paradigms in Cycloaddition Face-Selectivities: remarkable effect of remote substituents in singlet Oxygen Addition to Hexacyclo[7.5.1.$0^{1.6}$.$0^{6.13}$.$0^{8.12}$.$0^{10.14}$]pentadeca-2,4-diene System, G. Mehta and R. **Uma,** M.N. Jagdeesh, J. Chandrasekhar, *Chem. Commun.,* 1998, 1813.
7. Ladderane Architecture: From Molecular to Supramolecular Assemblies, G. Mehta and R. **Uma,** *J. Indian Inst. Sci.,* 1998, *78,* 177.
8. Ladderane-like Motifs: Solid State Architecture of *trans*-1,2-diphenyl-1-cyclobutene-3,4-diol dinitrate, G. Mehta and R. **Uma,** submitted for publication.
9. Molecular Structure and Reactions of l,l'-Biacenaphthylidene-2,2'-dione, G. Mehta, P.V.V.S. Sarma, R. **Uma.** S. Pogodin, S. Cohen and I. Agranat, *J. Chem. Soc., Perkin Trans. 1,* 1999, 000.