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The diastereoselectivity of the Diels-Alder reaction of dienes bearing stereogenic allylic substituents

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THE DIASTEREOSELECTIVITY OF THE DIELS-ALDER REACTION OF DIENES BEARING STEREOGENIC ALLYLIC SUBSTITUENTS

by

RABINDRANATH TRIPATHY

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

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Abstract

THE DIASTEREOSELECTIVITY OF THE DIELS-ALDER REACTION OF DIENES BEARING STEREOGENIC ALLYLIC SUBSTITUENTS

by

Rabindranath Tripathy

Advisor: Professor Richard W. Franck

The face selectivity of the Diels-Alder reaction of dienes having a stereogenic allylic carbon has been examined. For the acyclic dienes, where the allylic substituents have free rotation, the diastereoselectivity depends on the nature of the dienophile. Whereas N-phenylmaleimide and maleic anhydride afforded adducts from *like* topicity, tetracyano ethylene and 4-phenyl-1,2,4-triazolin-3,5-dione yielded products from *unlike* approach. The stereochemistries of the products have been established by NOE studies and in some cases by x-ray structure determination. Our results and those of other groups demonstrate that the dienophiles have a significant effect on the face selectivities observed. None of the recent theories are adequate to rationalize the experimental results. A new rationalization is put forward which successfully explains the observed stereodifferentiation and also serves in a predictive manner for synthetic purposes. The rationale favors two reactive diene rotamers in the transition state and the major stereodifferentiation is controlled by the relative rotamer populations and is also a function of the dienophiles.

The allylic dienes where the stereogenic center is conformationally locked showed a different trend in the face selectivity. In these cases the predominant products resulted from *anti* (*unlike*) attack irrespective of the nature of the dienophiles. Our results are also complementary to the results obtained by other workers. The stereochemistries of our products have been established by coupling constant correlations and in one case by an x-ray structure determination. The rationalization of the observed diastereoselectivity has

been based solely on the steric effect. It has also been postulated that the *A* value, a parameter used to define the steric size of different groups should not be used in intermolecular reactions. A more appropriate parameter (n) has been used to define the steric size of different groups in Diels-Alder reactions between semicyclic dienes with different dienophiles.

This work is dedicated to my wife

Anu

who has given tremendous support and encouragement for this work

Acknowledgements

I wish to express my deep sense of gratitude to Prof. R. W. Franck for his invaluable guidance, patience, inspiration and financial support throughout this work. I thank Profs. I. Fleming, K. D. Onan, and G. J. Quigley for x-ray structures and to Drs. M. Blumenstein and D. M. Frechet for their help in NMR experiments. Theoretical calculations by N. Kaila performed under the supervision of Prof. J. Dannenberg were very helpful and I am grateful for their contributions. I also thank Mr. A. Blaner and K. Chiu of the Hunter college computer center for their help in preparing this manuscript. I would like to express my gratitude to the members of Prof. Franck's group: Drs. C. S. Subramaniam, R. B. Gupta, V. Bhat, S. Ramesh and soon to be Drs. C. Soll, T. Nicolas, H. Yin, A. Choudhury, G. Grewal, N. Kaila for many helpful discussions and suggestions. Finally I wish to express my thanks to my wife Anu for her love, support and inspiration throughout this work.

Table of Contents

List of Tables

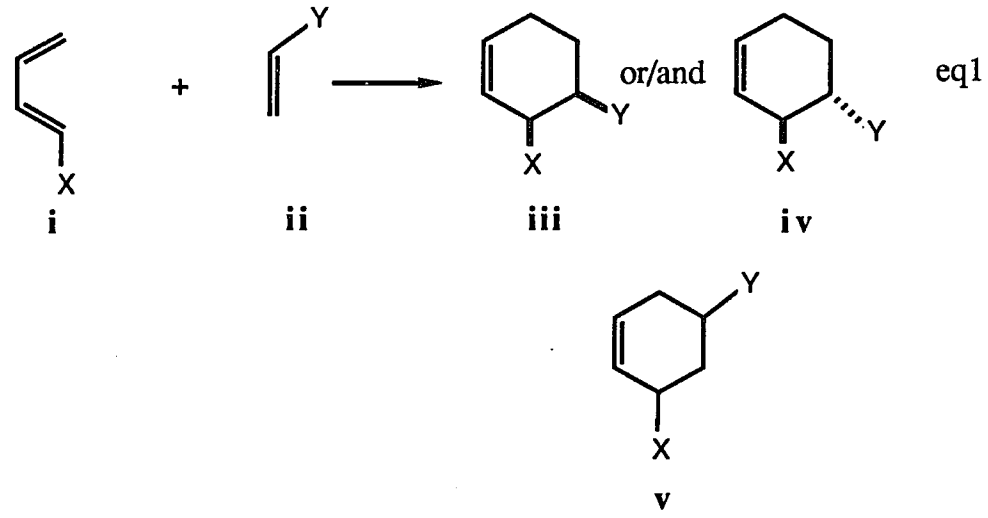
List of Figures

I. Introduction

A. Diels-Alder Reactions:

High regiospecificity and stereoselectivity along with the simultaneous creation of multiple chiral centers make the Diels-Alder reaction a very popular carbon-carbon bond forming device in organic synthesis. The outstanding potential of Diels-Alder chemistry can be understood from the numerous papers and reviews in recent years about the synthetic and mechanistic aspects of this reaction[1-6]. Discovered[7] originally in 1928, the Diels-Alder reaction (eq1) takes place between a diene (**i**) and a dienophile (**ii**) to form a six membered ring (**iii** and/or **iv**). This reaction has distinctive characteristics such as the formation of the more crowded *endo* adduct (**iii**) instead of the less encumbered *exo* product (**iv**) and formation of *ortho* (**iii, iv**) rather than *meta* (**v**) products. Steric factors certainly do not explain these preferences and alternatively FMO (Frontier Molecular Orbital) theory[8] has been popularly employed to explain regioselectivity as well as the *exo/endo* problem. FMO theory which is based on the Woodward and Hoffman rules[9] of *conservation of orbital symmetry* has gained general acceptance among organic chemists as a valid explanation of various aspects of pericyclic reactions. The essence of the Woodward and Hoffman rule is the ground state correlation of the molecular orbitals of the reactant and the product. Interaction of the molecular orbitals, of proper symmetry, of the diene and the dienophile produce the product, and those interactions between vacant and occupied orbitals are especially important as they bring a net change in energy. For simplification, only the interaction between the HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) of the reactants are considered to determine the reactivity of the Diels-Alder reaction. For a normal Diels-Alder reaction, the HOMO of the diene and the LUMO of the dienophile control reactivity and so electron donating groups on the diene and electron withdrawing groups on the dienophile enhance the reaction rate[3]. Regiochemistry has been explained in terms of this HOMO-LUMO interaction as due to pairing larger

HOMO and LUMO coefficients at the terminal position of the diene and the dienophile[10]. In contrast, another theory has been offered which involves an electrostatic approach based on the matching of complementary reactive surfaces of the two reactants[11].



The mechanism question of this reaction has been the subject of controversy, and both concerted and stepwise mechanisms have been suggested[3,12]. Dewar claims that Diels-Alder reactions must be asynchronous[12] while Houk has pointed out mistakes of the semiempirical techniques adopted by Dewar *et al*, which, Houk claims, incorrectly predicted a stepwise mechanism for concerted cycloaddition process. Houk has provided experimental and theoretical evidence which showed a synchronous concerted mechanism for the Diels-Alder reactions of butadiene and ethylene[13].

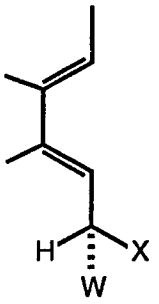
B. Stereoselectivity:

Stereocontrol is one of the most challenging problems in organic chemistry[14]. For a complex natural product synthesis it is essential to control diastereofacial selectivity. The understanding of the interactions responsible for high diastereofacial preferences is of fundamental concern to rational synthetic design. Specific identification of such interactions are highly desirable for improving the predictive utility of stereoselective reactions. Diastereoselectivity in the Diels-Alder reactions is the focal point of our current discussion

and this has been the subject of several reviews in recent years describing impressive progress in this area[15-22]. The most common approach for obtaining facial selectivity in intermolecular reactions is to hook the diene or the dienophile to a chiral auxiliary. Ideally the chiral auxiliary blocks one face of the diene or dienophile, a face-selective cycloaddition takes place, the auxiliary is removed and one obtains an adduct enriched in one enantiomer. Rationalization of relative topicity is usually based on a conformational analysis of the interaction of the auxiliary with the ground state of the substrate. The alternate approach to face selectivity is to incorporate a stereogenic center within the diene or the dienophile, usually at an allylic position[23-53]. The products of cycloaddition are diastereomers and remain so because the stereogenic center is built into the product. Usually hetero atom substitution at the allylic position exerts a pronounced effect on diastereoselectivity, an effect which has been observed in a wide range of organic reactions[54] such as : allylic epoxidation[55] , osmylation[56], hydroboration[57] etc. We were stimulated to evaluate such an effect in Diels-Alder reactions as very little attention has been paid towards studying the face selectivity of the reaction of hetero atom substituted allylic dienes or dienophiles. The present study documents an extensive survey of Diels-Alder reactions bearing chiral allylic dienes with various dienophiles, in our own and other laboratories. Attempts have been made to understand the factors responsible for the diastereofacial preferences in this reaction at the level of predictive application. Ideally three kinds of allylic dienes need to be addressed, acyclic dienes of type **1** (X = O, N) with free rotation of the allylic center, and conformationally locked cyclic and semicyclic dienes **2**, **3** and **4**.

In our work, we have used the acyclic dienes of the type **1** and the semicyclic dienes of the type **3** and we shall limit our discussion to these two classes. The cyclic dienes, the cyclopentadienes in particular, usually show abnormally high reactivity[3]. The next chapter will review the theories put forward by different groups to rationalize the experimental

results.



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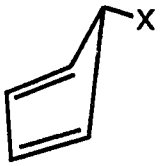

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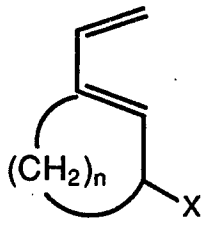

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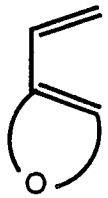


4

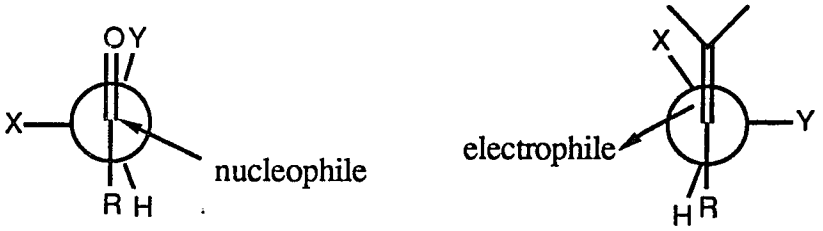
A substituted pyranose

B substituted furanose

II. Theories

A. General Theories on Diastereoselectivity:

The Greek philosopher Aristotle once said *collect the facts first, and only then relate them to each other in your mind.*. An intense look at the entire spectrum of organic chemistry brings about a wide range of theories, put forward by different groups, based on experimental facts and their predictive utility has been well exploited by synthetic organic chemists. For example, let us consider the diastereoselectivity in nucleophilic and electrophilic addition reactions where the substrate bears a hetero atom substituted chiral center next to the reactive site. Several theories have been developed to explain the observed π facial discrimination in those reactions. For nucleophilic attack, the widely accepted *Anh-Felkin model* postulates a reactive rotamer in the transition state. In most of the cases, it correctly explains the observed face selectivity (figure 1, X = O or N, Y = alkyl)[58,59]and this theory has achieved massive support in the literature[60].

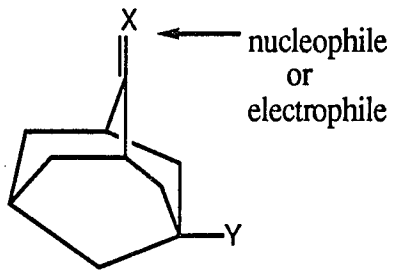


Anh-Felkin Model Houk Model

Figure 1. Anh-Felkin Model and Houk Model

The essential concept of the Anh-Felkin model is that in the transition state of nucleophilic addition the substrate adopts staggered arrangement with respect to the attacking nucleophile. Similarly, the *Houk model* also correctly predicts the observed face selectivity in electrophilic addition reactions (figure 1)[61]. It is interesting to note that the same chiral center directs two opposite faces in electrophilic and nucleophilic attacks. One of the most promising theories which needs to be addressed here is the *Cieplak theory* which had initially been put forward to explain preferential attack in the nucleophilic addition to

carbonyl groups of cyclohexanone and related ketones[62]. He proposed that electron donation from an α substituent *anti-periplanar* to the σ* orbital of the forming bond stabilizes the transition state. Recently the same theory has been further extended to explain facial discrimination in nucleophilic, electrophilic as well as in pericyclic reactions in sterically biased system like 4-substituted adamantones (figure 2) and other systems[63]. Interestingly, it has turned out that nucleophilic, electrophilic and pericyclic reactions in such a system take place preferentially opposite to the most electron rich carbon-carbon σ bond. This effect is believed to be purely electronic in nature and the most electron rich σ bond stabilizes the developing antibonding orbital in the transition state. Prof. le Noble's laboratory has contributed a significant amount of work in this field by studying different reactions including the Diels-Alder reaction and found that in sterically unbiased systems, Cieplak's theory correctly predicts the facial outcome[63d].



Cieplak model

Figure 2. Preferential Attack on Adamantone System Based on Cieplak Model

B.Theories on the Diels-Alder Reactions Bearing Allylic Substituents:

Different theories have also been suggested to explain stereoselectivity in Diels-Alder chemistry involving allylic substituents. The case of conformationally flexible acyclic diene of the type **1** will be considered first and it is essential to consider all available conformers of that diene inorder to understand the stereochemical preferences. It has been generally found for allylic compounds that energy minima correspond to conformers in which a single bond (approximately) eclipses the olefin[64]. All possible rotamers of an allylically

substituted diene are shown in figure 3. Though there is absolutely no experimental evidence regarding the thermodynamic stability or the relative equilibrium abundances of all these diene conformers in the ground state[65], it is speculated that at least one among them might be the reactive conformer in the transition state. Now let us look at the individual theories on this subject which have used such rotamers to explain stereoselectivity in Diels-Alder reactions.

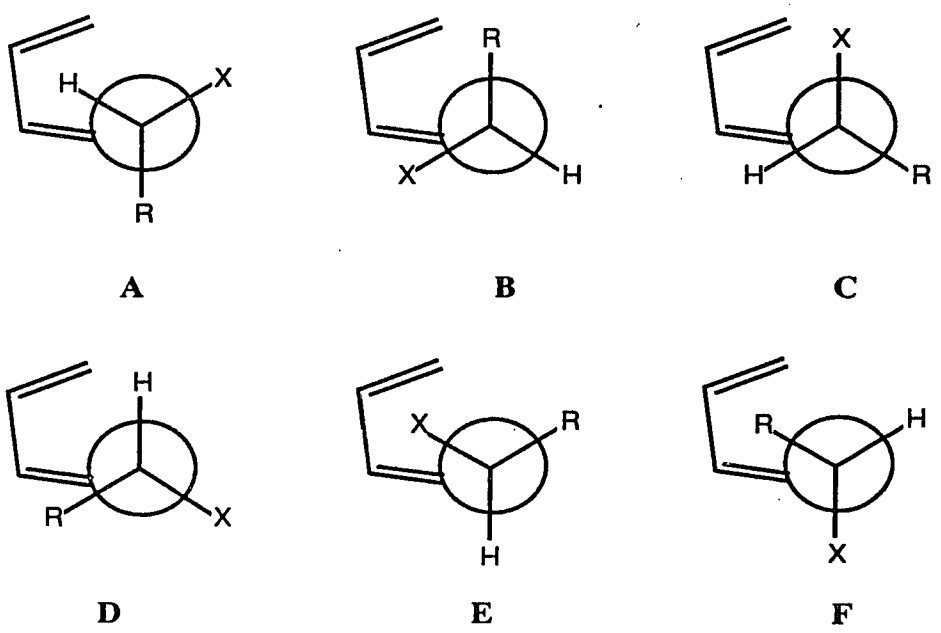
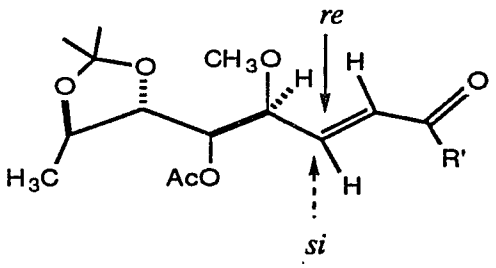


Figure 3. Different Rotamers for the Dienes Bearing Allylic Substituents

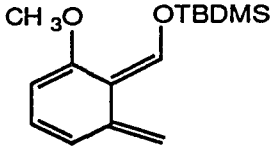
Franck's Rule:

The first rationale comes from this laboratory which has assessed the diastereofacial trend for the chiral allylic dienes and dienophiles to put forward a selection rule which allows a prediction of π facial discrimination in Diels-Alder reactions[26]. This rule was based on a Diels-Alder reaction which had been carried out in connection with the synthesis of olivin, an aglycone of the antitumor antibiotic olivomycin, by using a sugar derived chiral allylic dienophile **5** with a diene **6** generated from benzocyclobutene **7**[24]. The reaction gave rise to two products and the diastereoselectivity was rationalized by assuming an attack of the

diene on a face opposite to allylic alkoxy function of the chiral dienophile. Thus, the allylic carbon bearing an *R* chiral center directed diene approach from the *si* face of the dienophile. Subsequent work on intermolecular Diels-Alder reactions[52] and dipolar cycloaddition reactions[66] extended this trend for the dienophile (with one exception[53]) viz. an *R* derived group favored *si* face attack (*unlike*) whereas an *S* derived group favored *re* face attack (*unlike*).



5



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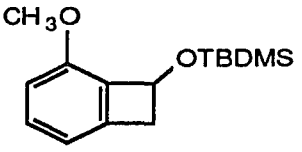
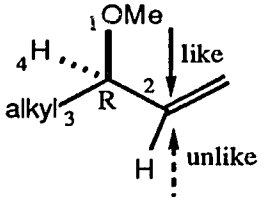
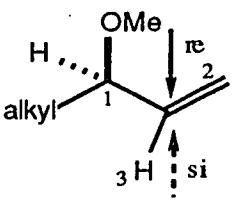


7

At this stage it is necessary to clarify the terminology used to define relative topicities of these kind of reactions since different workers have used different notations. We would like to use the Seebach-Prelog convention[67] describing the relative topicities of the approach or addition to the face of an enantiomer, e.g. addition to the *si* face of the double bond with an adjacent *R* allylic center is *unlike* . Hehre has used *anti* for *unlike* and Houk applies *erythro* for *unlike*. To be consistent, we define the configuration of the allylic center by always assigning the sp^2 carbon of the double bond a higher priority than the sp^3 carbon attached to the allylic center (shown in **8 i**). Also, in defining the facial configuration of the double bond, we always assign the priority of the allylic carbon as 1 and the vinylic carbon as 2 (shown in **8 ii**).



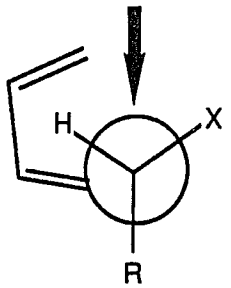
8 (i)



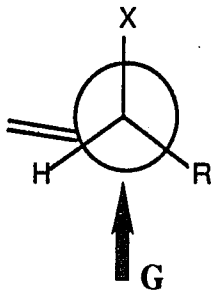
8 (ii)

The selectivity had been rationalized by invoking two different preferred conformations of the allylic group with different interactions between allylic functions and the developing transition state[24].

What will be the facial outcome of the Diels-Alder reaction when a chiral center bearing hetero atom at an allylic position is placed on a diene? The first experimental result came from French workers[28,68] and subsequently from this laboratory [26,27]which showed that the same chiral center directed opposite faces in the diene and the dienophile. Similar kinds of results have also been noted in other reactions of alkenes bearing allylic substituents. Fleming[69] and McGarvey[70] have rationalized those results by considering two different rotamers responsible, one for nucleophilic attack and the other for the electrophilic attack. McGarvey explicitly invoked a σ^* π^* interaction between the allylic group and the LUMO of the allylically perturbed system being attacked by a nucleophile; and he had called into play a σ, π interaction for the allylic effect on the HOMO of the system being attacked by an electrophile. These two different effects serve to increase the reactivity of the opposite faces in the two systems. McGarvey's argument was applied in the Diels-Alder reaction by considering the reactivity of the diene being HOMO controlled and that of the dienophile being LUMO controlled and a selection rule was proposed to rationalize the diastereoselectivity.



A



G

Two different rotamers are responsible, one for the diene and the other for the dienophile. For the case of dienophile rotamer **G**, the hetero group (X) remains *perpendicular* to the

double bond, which stabilizes the LUMO of the dienophile, and increases its reactivity. On the other hand, the same rotamer on a diene system will stabilize the HOMO (except atoms like Si), which will increase the energy gap between the HOMO of the diene and the LUMO of the dienophile resulting decrease in the reactivity of the system. Thus it would require that the hetero atom should remain orthogonal to the π system, preferably *outside* to avoid nonbonding interaction with the diene double bond whereas the alkyl group remains *antiperiplanar* to the approaching dienophile (rotamer A)[71]. Though argument regarding the reactive rotamers involves the most stable rotamer in the ground state, it has been speculated that the conformer stability in the ground state parallels the conformer reactivity in the transition state.

Franck's selection rule can be stated as : *the allylic center next to a diene and a dienophile will have opposite diastereochemical outcome in a Diels-Alder reaction* viz.

Chirality of allylic group	face selected dienophile	diene
R	(*si*)*unlike*	(*re*)*like*
S	(*re*)*unlike*	(*si*)*like*

Houk's Theory

Theoretical arguments on this subject brings Houk theory into the picture; and it has rationalized the experimental results obtained from the 1,3 dipolar cycloaddition reactions involving dipolarophiles bearing allylic oxygen substituents[72]. On the basis of molecular orbital calculations Houk has suggested a conformation of the chiral allylic group in the transition state where the alkyl group remains *anti* to the developing bond formation and the alkoxy (hetero group) group favors the *inside* position. They have argued that in an electrophilic attack on the allylic double bond, the π bond becomes electron deficient and thus electron-donor substituents on the double bond stabilize the transition state, whereas electron withdrawing substituents on the alkene destabilize the transition state. So they

think, the allylic ether group in the *anti* position will withdraw electron density through the overlap of the σ* orbital with the π orbital of the alkene and this overlap is minimized when the alkoxy group is orthogonal to the π system by staying at an *inside* position.

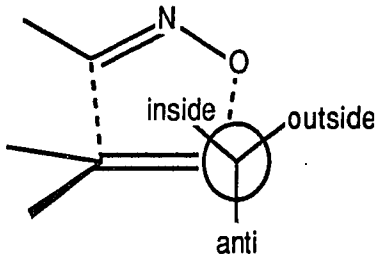
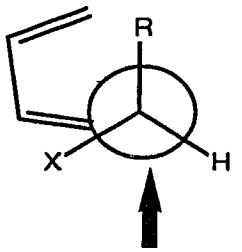


Figure 4. The calculated transition state model for the 1,3-dipolar cycloaddition reactions

Though it can remain *inside* or *outside*, the calculation showed *inside* was more favorable than *outside* position. The alkyl group remains *anti* in order to maximize the electron donation to the π bond and also to avoid the steric interaction with the incoming nitrile oxide. Our interpretation of Houk's theory brings in a second possible diene rotamer **B** into the picture. This was based on the fact that in both the cases i.e. allylic diene and dipolarophile, HOMO controls the reactivity. The essential difference between Franck's rotamer (**A**) and Houk's rotamer (**B**) is the position of the hetero atom, where in conformer **A**, it remains *outside* on steric ground and in **B**, electronic factor keeps it at *inside* position.



Houk rotamer

(B)

McDougal's support:

Another supporting rationalization in favor of Franck's rotamer (**A**) comes from McDougal

and coworkers. They have considered both of the perpendicular rotamers **A** (Franck's Rotamer) and **B** (Houk's rotamer) and speculated one to be the reactive rotamer in the transition state[35]. They have further predicted and subsequently proved that the relative population of the rotamer **A** can be increased by putting a substituent at the 2-position of the diene system (see figure 5) which will force the hetero atom to remain *outside* to avoid nonbonding steric interaction. In this way, they have shown by experiments that a complete π facial selectivity can be achieved.

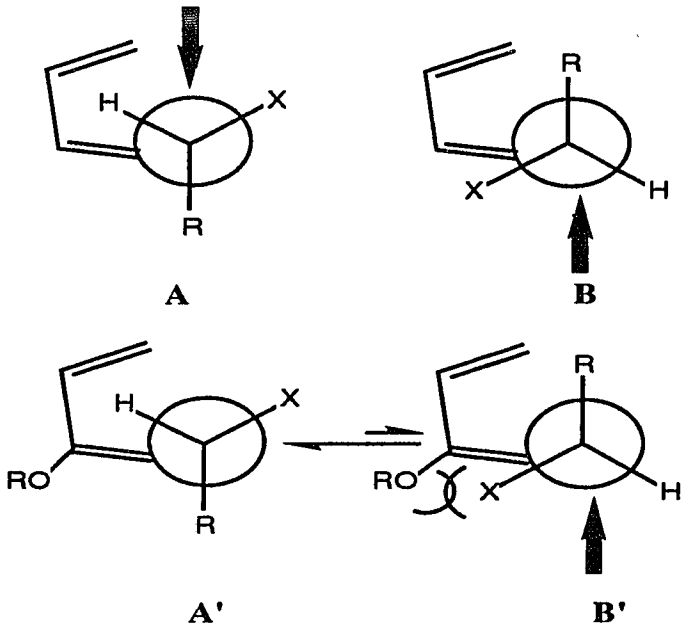
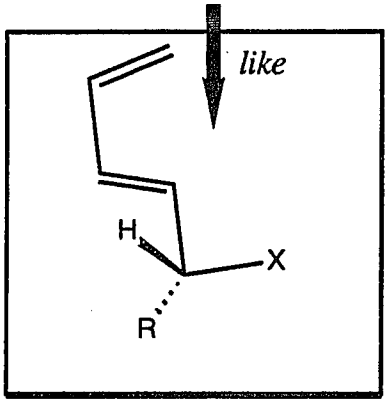


Figure 5. The Equilibrium Population of the Allylic Dienes Rotamers Bearing a Substituent at C_2 Position.

Franck-Dannenberg Theory

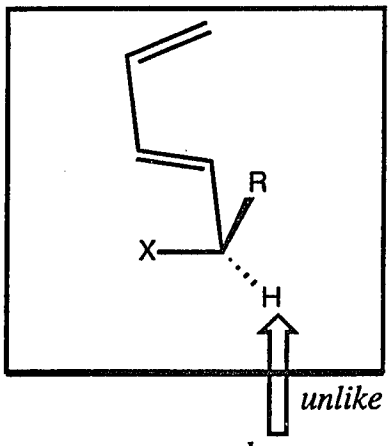
Recently the face selectivity problem in Diels-Alder reactions has been investigated by computations which bring some new insight to the subject[73]. On the basis of AM1 calculations, it has been suggest that the face selectivity induced by substituent is due to a balance of force. Thus in the transition state, the allylic substituent is rotated so that the hetero atom is essentially *coplanar* with the diene, with the *anti-coplanar* form preferred to *syn-coplanar* rotamer. Then the face approached by the dienophile is that where the

minimum steric repulsions between the diene and dienophile exist .The *anti-coplanar* rotamer (**A"**) is similar to Franck's original rotamer **A** and *syn-coplanar* rotamer (**B"**) resembles Houk's rotamer (**B**), but the essential difference is that in **A** and **B**, the alkyl group remains *perpendicular* where as in **A"** and **B"**, the hetero atom remains *coplanar* with the diene double bond. The reasons for such *coplanarity* of the hetero atom with the double bond was not readily understood.



anti-coplanar

(A")



syn-coplanar

(B")

Hehre's Theory

More recently Hehre and Cahn have totally discarded the frontier molecular orbital arguments and have proposed a theory based on electrostatic attraction and repulsion to rationalize the face selectivity problem in Diels-Alder reactions bearing allylic dienes and dienophiles[74]. They consider the fact that the diene is electron rich and should behave like a nucleophile and on the other hand the dienophile is electron poor and should be like an electrophile. Thus, they have suggested a single rotamer, responsible for the diene and dienophile bearing the allylic substituents. In their model, the alkyl and the hydrogen

substituents of the allylic group remains somewhat in the plane of the dienilic or dienophilic double bond whereas the hetero atom substituted group remains perpendicular to that plane.

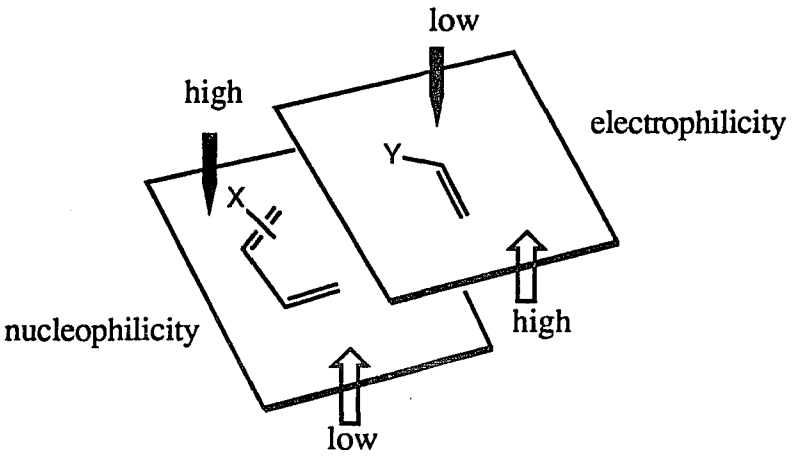
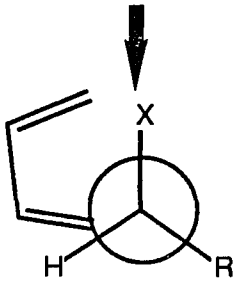


Figure 6. Two Different Reactive Surfaces for the Diene and the Dienophile based on Electrostatic Model

Thus two faces of the diene or the dienophile are electronically unequivalent and any attack from the top or bottom of the dienilic or dienophilic plane (parallel to the hetero substituted group) will be controlled by the electrostatic attraction or repulsion with the hetero substituted group.



Hehre rotamer

(C)

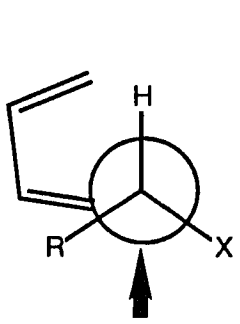
For example, if the hetero atom is electron rich (O, N) then the dienophile, being electrophilic will attack the allylic diene from a face *syn* (*like*) to hetero atom due to an electrostatic attraction between the hetero atom and the dienophile. They have also further suggested that if the hetero atom becomes electropositive then the dienophile will

approach from the face *anti* (*unlike*) to the hetero atom due to electrostatic repulsion between the electropositive hetero atom and the dienophile. Similarly, the attack of the diene on a dienophile bearing the allylic center is also controlled by the electrostatic factor and the diene being nucleophilic in nature should show opposite facial preference. Thus Hehre's theory states that , *cycloadditions involving electron rich dienes and electron poor dienophiles should occur preferentially onto the diene face which is more nucleophilic and onto the dienophile face which exhibits the greater electrophilicity.* This theory does not discriminate the nature of the hetero atom (free or conformationally locked) and can be applied to all classes of allylic dienes, summarized as follows:

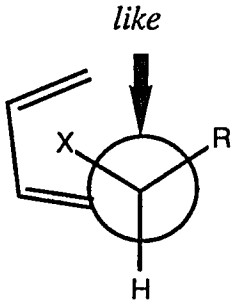
Nature of hetero atom	face *syn* or *anti* to hetero atom	
	dienophile	diene
electronegative	*anti*	*syn*
electropositive	*syn*	*anti*

Cieplak's Theory:

As mention earlier, a recent rule based on the Cieplak model proposed by le Noble can also be considered in the case of dienes bearing allylic substituents[62,63].



Rotamer **D**



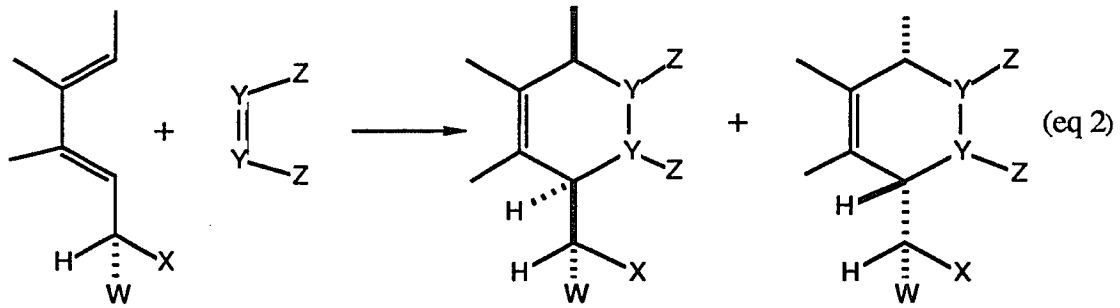
Rotamer **E**

This theory considers that favorable bond formation in the transition state which takes place from a face opposite to the most electron rich bond. For the Diels-Alder reactions bearing chiral allylic dienes or dienophiles, this rule would predict similar facial preference for the dienes and the dienophiles and our interpretation of Cieplak's theory suggests either the rotamer D or E as the reactive rotamer in the transition state based on the fact that the CH bond is the most electron rich bond.

III. Results:

A. Acyclic Dienes:

This chapter records the stereochemical outcomes of different Diels-Alder reactions carried out in our laboratory or reported in the literature where an acyclic diene of type **1** reacts with a dienophile of the type **9** (eq 2) to produce diastereomeric adducts **10** (resulting from a *like* process) and **11** (resulting from an *unlike* process).

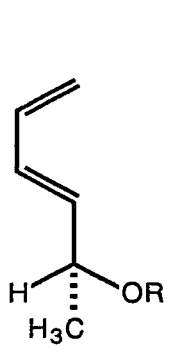


1 **9** **10** **11**

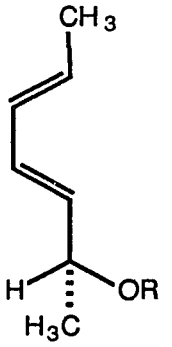
The history of Diels-Alder reactions involving the use of dienes having a chiral center at the allylic position bearing hetero atom, of the type **1** goes back to 1945, when a group of British workers reported the reactions of 2-hydroxy-3,5-hexadiene (**12a**) and its methyl derivative with maleic anhydride[75]. This interesting field remained unexplored for a long period of time until this laboratory disclosed the π facial selectivity in Diels-Alder reaction between a hetero atom substituted allylic dienophile with a diene derived from a benzcyclobutene. That work was done with a sugar derived dienophile in connection with the total synthesis of olivin. After that a number of reports appeared on π facial discrimination but exclusively on dienophiles bearing the allylic substituents.

Now the details of the Diels-Alder reactions of dienes bearing hetero atom at allylic center with different dienophiles are described here. In our work, the dienes that have been used are: (1) 2-hydroxy-3,5-hexadiene (**12a**) and its trimethylsilyl (**12b**) as well as t-butyldimethylsilyl derivatives (**12c**). (2) 2-hydroxy-3,5-heptadiene (**13a**) and it's methyl

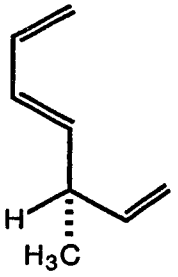
(**13b**) as well as the trimethylsilyl derivative (**13c**). (3) 3-methyl-1,4,6-heptatriene (**14**). Though the last diene (**14**) does not contain any hetero substitution at the allylic position, we were curious to evaluate the effect of a vinyl group at an allylic position of a diene on the π facial discrimination.The dienophiles used in our work are maleic anhydride (**15**), N-phenylmaleimide (**16**), dimethyl acetylenedicarboxylate (**17**) and 4-phenyl-1,2,4-triazolin-3,5-dione (**18**).



12a R = H
b R = TMS
c R = TBDMS



13a R = H
b R = Me
c R = TMS



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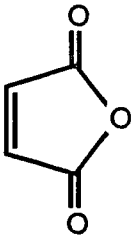

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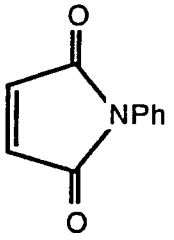

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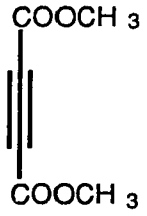

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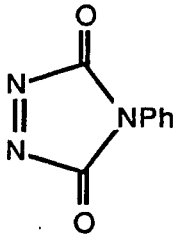
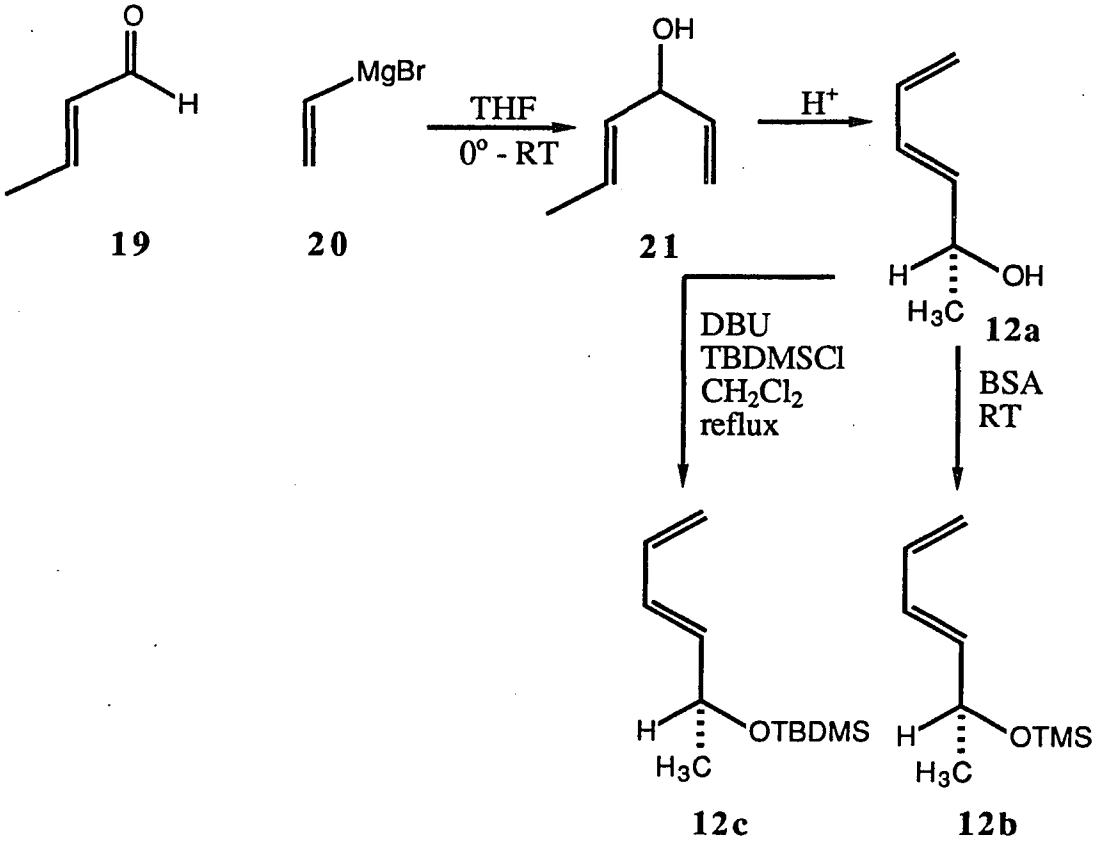


18

Preparation of the Acyclic Dienes 12-13: The acyclic diene **12a** (2-hydroxy-3,5-hexadiene) was prepared by a two step process from crotonaldehyde (**19**). The first step was the reaction of crotonaldehyde with vinylmagnesium bromide (**20**) to form 3-hydroxy-1,4-hexadiene[76] (**21**) which rearranged to the diene **12a** upon treatment with dilute acid (scheme 1)[77]. In fact it is a slight modification of the original procedure adopted by Hilborne *et al* where the precursor **21** was obtained through a two

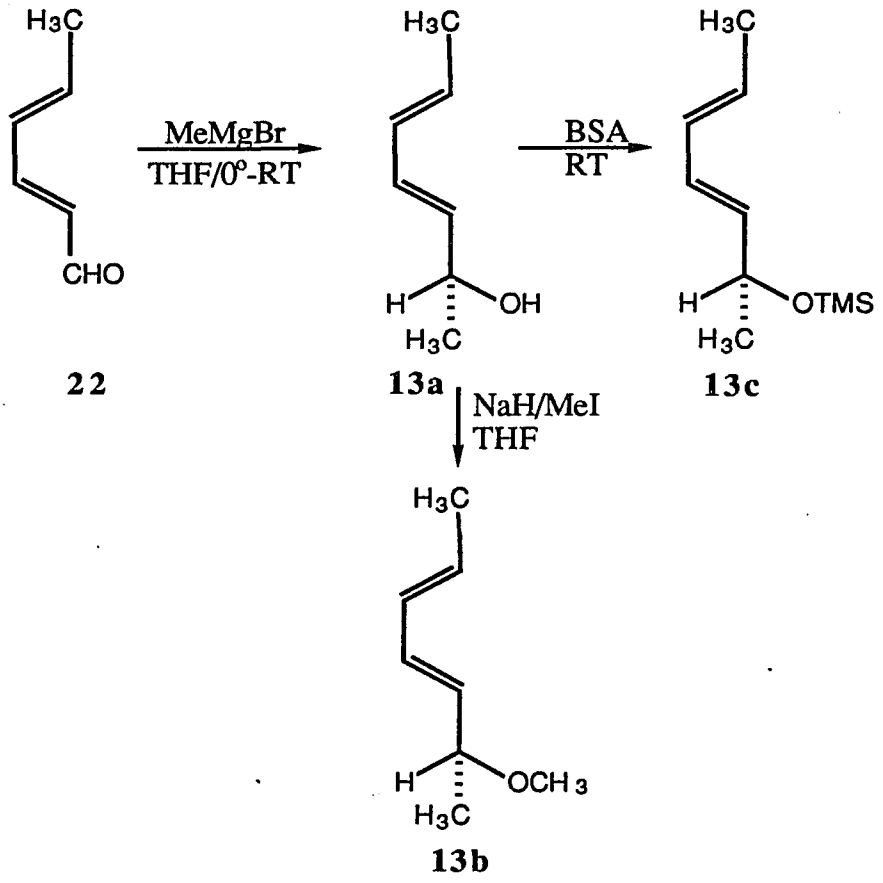
step process from crotonaldehyde (**19**)[75]. Trimethylsilyl protection of the diene **12a** was achieved by using *bis* trimethylsilylacetamide (BSA) as the silylating agent to provide the diene **12b**. Since the trimethylsilyl protection was found to be labile particularly when maleic anhydride (**15**) was used as the dienophile, the more stable t-butyldimethylsilyl group was used to protect the hydroxy diene **12a**, which was achieved by treating the diene **12a** with t-butyldimethylsilyl chloride and DBU in dichloromethane at reflux temperature[78]. The resulting TBDMS ether (**12c**) was obtained in 63.5% yield (scheme 1).



Scheme 1

The other diene **13a** (2-hydroxy-3,5-heptadiene), where both termini are substituted was prepared from the Grignard reaction of sorbic aldehyde (**22**) with methylmagnesium bromide[79] in tetrahydrofuran. The methyl and silyl protecting groups on the diene **13a** were added as per standard literature procedures to furnish the diene **13b**

(2-methoxy-3,5-heptadiene) and **13c** (2-((trimethysilyl)oxy)-3,5-heptadiene) respectively (scheme 2).



22 **13a** **13c** **13b**

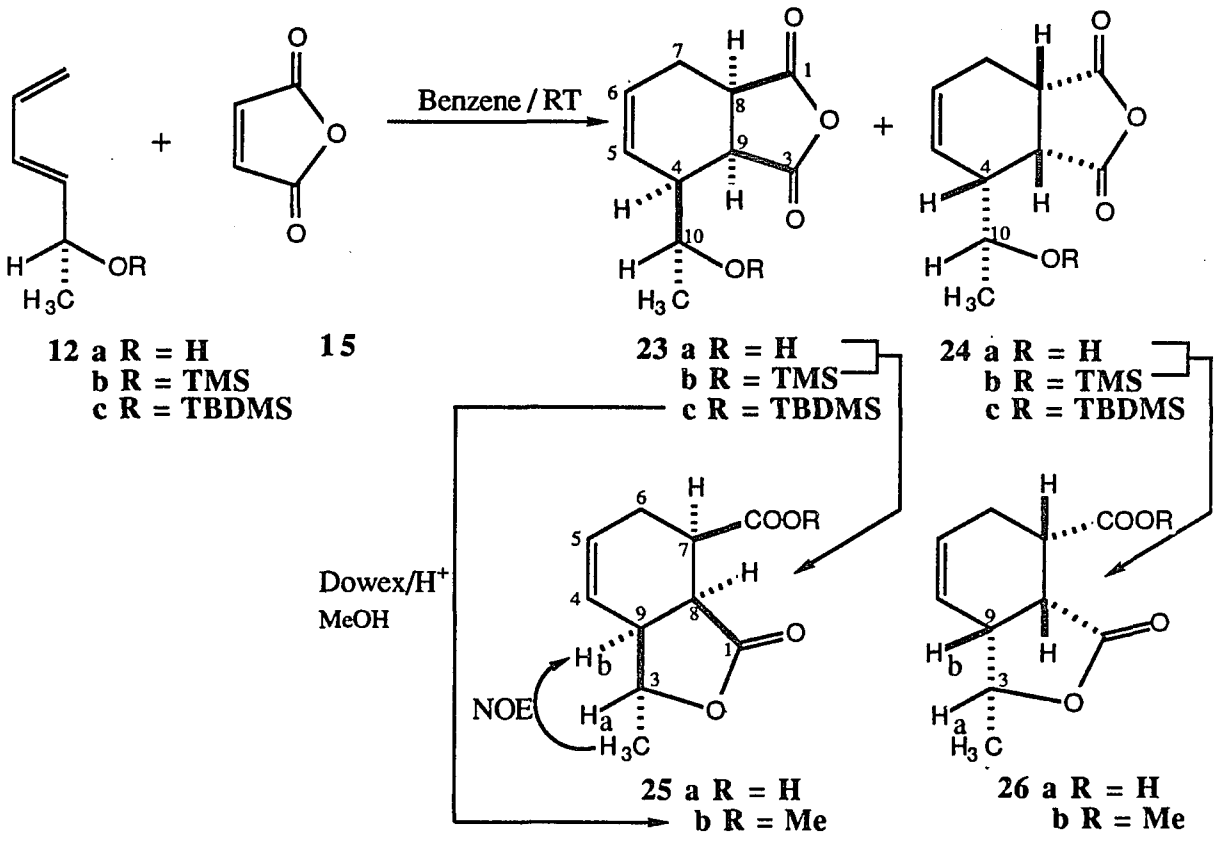
Scheme 2

Diels-Alder Reactions:

a. With Maleic Anhydride:

A series of Diels-Alder reactions have been carried out in our laboratory and by other workers and the results are recorded in table 1. The *like/unlike* ratios from our experiments were obtained from nmr spectrum. Details of the measurements are discussed in the experimental section and the spectra are reproduced in the appendix. The first entry records our repetition of the original example of a face-selective Diels-Alder reaction controlled by a chiral substituent,

namely the reactions of maleic anhydride (**15**) with (E)-2-hydroxy-3,5-hexadiene (**12a**)[75]. Due to lack of modern analytical technique, the British group reported a single adduct and our repetition of the same work showed the formation of two diastereomeric products **23a** and **24a** in a ratio of 2.7 : 1, which was concluded from the examination of the ^1H NMR (300 MHz) spectrum of the crude reaction mixture (scheme 3).



Scheme 3

The British workers had reported the formation of only one product and we guess the crystallization process might have enriched the major diastereomer.

One interesting observation was that the initial diastereomeric adducts **23a** and **24a**, formed from the Diels-Alder reaction were unstable and in both of the adducts the free hydroxy group attacks in an intramolecular fashion at the carbonyl group of the maleic anhydride moiety to form a five membered ring lactone (scheme 3). Thus, the adduct

mixtures were isolated as an inseparable mixture of lactone acids **25a** and **26a**. Attempts to separate them by chromatographic methods failed. In anticipation of the fact that the methyl esters of the lactonic acid **25a** and **26a** might be separable, we prepared successfully the lactonic esters **25b** and **26b** in 97% yield by the treatment of the purified Diels-Alder adduct mixture with diazomethane in ether (scheme 3) Unfortunately, the methyl ester mixture (**25b** and **26b**) was also homogeneous to chromatography and were inseparable. Finally fractional crystallization from water furnished the pure major lactone **25b** as a white solid.

Table 1. Relative Topicities of the Diels-Alder Reaction of a Series of Dienophiles with Acyclic Dienes Bearing a Stereogenic Allylic Carbon

Entry	Diene	Dienophile	Solvent	Temperature	Product like (%) : unlike(%)		Ref.
1	**12a**	**15**	Benzene	25°	**23a** (73)	**24a** (27)	a,b
2	**12b**	**15**	Benzene	25°	**23b** (80)	**24b** (20)	b
3	**12c**	**15**	Benzene	25°	**23c** (82)	**24c** (18)	b
4	**13a**	**15**	$CHCl_3$	25°	**29** (71)	**30** (29)	b, c
5	**12a**	**16**	Benzene	25°	**31a** (57)	**32a** (43)	b
6	**12c**	**16**	Benzene	25°	**31b** (78)	**32b** (22)	b
7	**13a**	**16**	Benzene	25°	**35a** (63)	**36a** (37)	b, d
8	**13a**	**16**	DMF	25°	**35a** (68)	**36a** (32)	b
9	**13b**	**16**	Benzene	25°	**35b** (84)	**36b** (16)	d
10	**13c**	**16**	Benzene	25°	**35c** (88)	**36c** (12)	b, d
11	**43a**	**16**	Benzene	25°	**44a** (84)	**45a** (16)	e
12	**43b**	**16**	Benzene	25°	**44b** (99+)	**45b** (0)	e
13	**46**	**16**	Benzene	25°	**47** (100)		f

14	**48a**	**16**	Benzene	60°	**49a** (18)	**50a** (82)	g
15	**48b**	**16**	Benzene	60°	**49b** (18)	**50b** (82)	g
16	**48c**	**16**	Benzene	60°	**49c** (0)	**50c**(99+)	g
17	**43b**	**51**	Benzene	50°	**52** (93)	**53** (7)	e
18	**13b**	**54**	Benzene	60°	**55a** (33)	**56a** (67)	h
19	**13d**	**54**	Benzene	60°	**55b** (15)	**56b** (85)	h
20	**13a**	**18**	THF : CH_2Cl_2	-78°-RT	**57a** (27)	**58a** (73)	b
21	**13c**	**18**	THF : CH_2Cl_2	-78°-RT	**57b** (16)	**58b** (84)	b
22	**13c**	**18**	DMF	-78°-RT	**57b** (22)	**58b** (78)	b
23	**61**	**60**	Benzene	Δ	**62** (37)	**63** (63)	i
24	**61**	**60**	CH_2Cl_2 @	25°	**62** (9)	**63** (91)	i
25	**64**	**17**	Benzene	Δ	**65** (33)	**66** (67)	j
26	**13a**	**17**	Benzene	reflux	**67** (27)	**68** (73)	b
27	**13a**	**17**	CH_2Cl_2 @	25°	**67** (28)	**68** (73)	b
28	**48a**	**17**	Benzene	-	**73** (99+)		g

@Under high pressure. (a) ref.75. (b) ref.27. (c) ref. 29. (d) ref.26. (e) ref.35. (f) ref. 36. (g) ref. 38 & 86. (h) ref.28-30 & 68. (i) ref. 31-33. (j) ref.34.

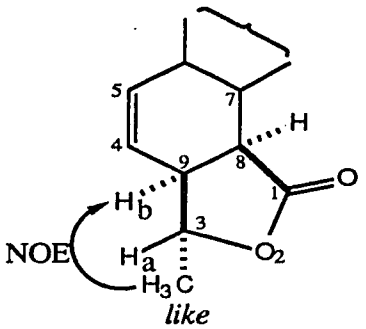
One important aspect of our study on the π facial selectivity is the stereochemical identity of the Diels-Alder adducts and our approach to structure proof is based on physical methods such as x-ray analysis; coupling constants and NOE studies from the high field NMR spectrum as well as on chemical correlation by interconversion of the adducts. Coupling constants alone do not provide any conclusive information as the J values for the methine proton H_a and the allylic proton H_b are not very much different for both the diastereoisomers for a series. For example, table 2 records the coupling constant J_{ab} for

different diastereomeric lactones obtained from various Diels-Alder adducts in our laboratory (which will be described subsequently) and it is hard to draw any conclusion regarding the relative topicities from those values.

Table 2. *J* Values for Epimeric Vicinal Protons at C_3 and C_9 on the Bicyclic Lactone Ring.

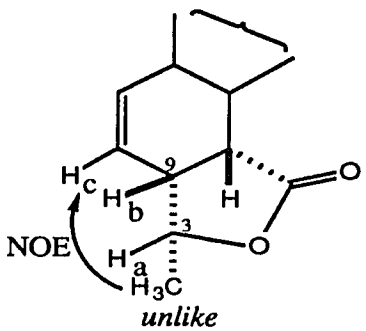
Entry	Lactone	*cis/trans*	J_{ab} (Hz)
1	**33**	t	1.71
2	**34**	c	4.81
3	**37**	t	2.44
4	**38**	c	3.66
5	**71**	t	9.15
6	**72**	c	7.93

Nuclear overhauser enhancement (NOE) difference spectra[80] provides more information for our system and helped in assigning the correct stereochemistry of the adducts. Our general approach to assign the stereochemistry involves the conversion of the adducts to their corresponding bicyclic lactones **27** and **28** (either spontaneously or by acid catalysis) and subjection of these lactones to NOE studies (See appendix for some NOE difference spectrum).



like

27



unlike

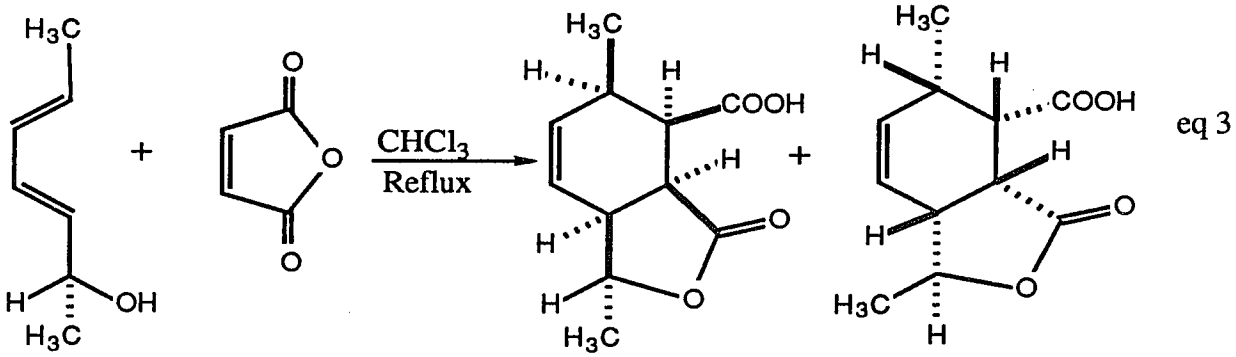
28

Due to the restricted rotation of the chiral center bearing hetero atom in bicyclic lactones, the relative spatial arrangement becomes fixed. Irradiation of the methyl group, located in the five membered ring of the bicyclic lactone either enhances the allylic proton (*like* as in **27**) or the vinylic proton (*unlike* as in **28**).

The facile conversion of the hydroxy adducts **23a** and **24a** (scheme 3) to the corresponding lactones showed that both the adducts were *endo* products. The purified major lactone **25b** showed diagnostic absorption in the infrared spectrum at 1765 and 1725 cm^{-1} for five membered ring lactone and ester carbonyl respectively. The relative topicity of the the lactone **25b** was established by an NOE study. Irradiation of the methyl group at δ1.48 enhanced the allylic proton (H_b) signal by 4.5% (table 3). Thus the major adduct **23a** resulted from a *like* process and since the minor product could not be isolated in purified form, it was assumed that it might have resulted from an *unlike* attack.

Since the reaction of the free alcohol diene **12a** provided the bicyclic lactones as the direct adducts, there might be a possibility of prior ester formation between the anhydride and free alcohol followed by intramolecular cycloaddition. This possibility obviously would require a *like* process. To rule out such a pathway as the reason for *like* process, we repeated the sequence with the silyl protected diene **12b** (scheme 3). The reaction of the silyl ether **12b** with maleic anhydride in benzene at room temperature for five days furnished a mixture of diastereomers **23b** and **24b** in the ratio of 4 : 1 (entry 2) shown by the ^1H NMR study of the crude reaction mixture. However, the products were sensitive to chromatography and attempted separation by PLC furnished the hydrolyzed product as a mixture of lactones **25a** and **26a**. The identity of the product mixture was easily established by the ^1H NMR spectrum and incidentally, an improved *like* selectivity was observed by protecting the dienol **12a**. The t-butyl dimethylsilyl protected diene **12c**, bearing a more stable silyl protection was subjected to Diels-Alder reaction with maleic anhydride (**15**) in benzene at room temperature for seven days (entry 3). The reaction was

very slow and it also formed two diastereoisomers **23c** and **24c** in a ratio of 4.5 : 1 (Scheme 3). Unlike the trimethyl silyl adducts, this mixture of diastereomers was stable to chromatographic separation. Separation by flash chromatography furnished the adducts **23c** and **24c** in pure form. A white crystalline solid, the major product showed a characteristic single carbonyl stretching at 1765 cm-^{1}. The ^{1}H NMR spectrum analysis did not provide any conclusive information regarding the relative stereochemistry due to overlapping of signals, particularly the allylic proton H_b at C_4 and the methine proton H_a at C_{10}. The hydrolysis of the major silyl adduct **23c** by Dowex/ H^+ in methanol provided the direct formation of the lactone ester **25b** (Scheme 3). This interconversion clearly showed that the adduct resulted from a *like* process. The minor silyl ether **26b**, isolated as a syrup was assumed to be an *unlike* product and its structure was not rigorously proven.



eq 3

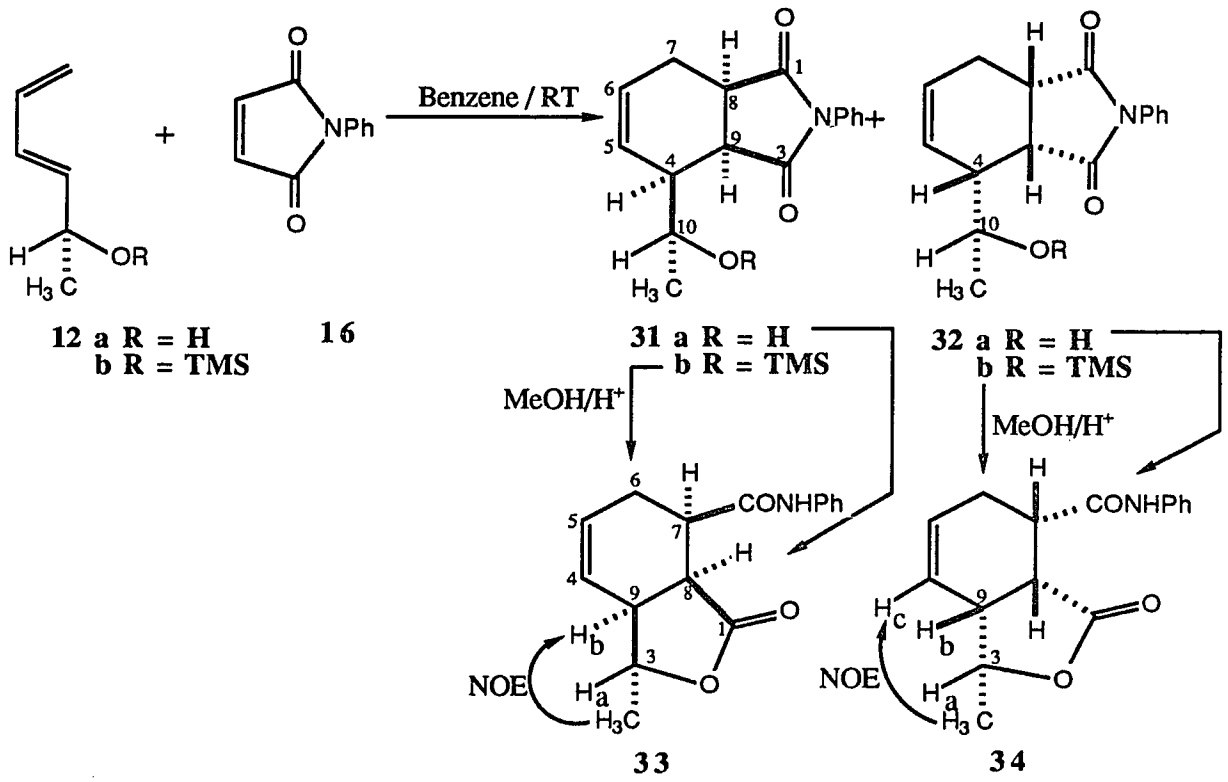
13a **15** **29** **30**

The use of 2-hydroxy-3,5-heptadiene (**13a**) in the Diels-Alder reaction also revealed *like* selectivity (entry 4). The reaction of **13a** with maleic anhydride (**15**) for 3 days at reflux temperature resulted two diastereomeric products **29** and **30** in a ratio 2.5 :1 (eq 3). This reaction was carried out in $CHCl_3$ as we were curious to verify a result reported by French workers, which was 1: 1 selectivity on the basis of isolated yield[29] for that reaction under

similar conditions. The ^1H NMR of our major product was identical to their *like* product , which had been established from the x-ray analysis[29].The mixture was not further separated.

b. With N-Phenylmaleimide (16):

We turned to N-phenylmaleimide and we have carried out several Diels-Alder reactions with this dienophiles. One specific advantage with N-phenylmaleimide (**16**) over maleic anhydride (**15**) is that the Diels-Alder adducts with dienols (**12a** and **13a**) form the lactonic amides, which , being relatively nonpolar compared to the lactonic acids, makes their work up much easier.



Scheme 4

Entry 5 records the reaction of NPM (**16**) with 2-hydroxy-3,5-hexadiene (**12a**) in benzene at room temperature for three days. As expected two products were formed in a ratio of 1.3 : 1 (scheme 4). Both of the initial adducts **31a** and **32a** are unstable and under the reaction

conditions they were converted to the lactones **33** and **34** respectively. The lactone mixture was not separable by chromatography. The reaction of the silyl protected diene **12b** with NPM (entry 6) in benzene at room temperature afforded a mixture of diastereoisomers **31b** and **32b** in a ratio of 3.5 : 1 (scheme 4). The diastereomers were separated by preparative thin layer chromatography. A colorless syrup, the major isomer showed a characteristic IR band at 1700 cm^{-1} for the carbonyl groups[81]. Its ^1H NMR spectrum also showed all expected peaks for different protons. However it was difficult to assign the relative stereochemistry as the coupling constant J for H_a and H_b is around 10.5 Hz for **31b** where the same coupling constant for **32b** could not be determined accurately from the first order analysis of the ^1H NMR spectrum due to overlapping of signals. The major adduct **31b** was easily hydrolyzed in the presence of H^+ in MeOH and the corresponding adduct alcohol **31a** was unstable and lactonized to give a crystalline solid product **33** (scheme 4). The lactone **33** showed characteristic IR bands at 1745 (five membered ring lactone) and 1670 (amide carbonyl) cm^{-1}. The ^1H NMR analysis also revealed the presence of all protons including the diagnostic NH peak at δ9.8 (broad). This NMR spectrum was also essentially identical to the peaks assigned to the major product in the NMR spectrum of the crude reaction mixture, obtained from the reaction of **12a** with NPM (**16**), which clearly established the similar stereochemical relationship between the adducts **31a** and **31b**. Convincing evidence regarding the relative stereochemistry comes from the NOE study. When the methyl proton H_a in **33** was irradiated a 8.3% enhancement (table 3) was observed at the allylic proton H_b which indicates a *like* stereochemistry for the the adducts **31a** and **31b**. Similarly, when the minor silyl adduct **32b** was hydrolyzed with MeOH/H+ the lactone **34** was obtained in 80% yield as a white crystalline solid. The structural assignment was done from spectral analysis. Like the lactone **33**, it also showed the diagnostic bands at 1745 and 1670 cm^{-1} in the IR spectrum and the ^1H NMR spectrum showed the characteristic NH proton as a broad singlet at δ10.03. The NOE experiments

established the relative stereochemistry in **34**. When the methyl group at δ1.49 was irradiated, a 6.8% enhancement at the vinylic proton H_b (C_4)) was observed. The chemical interconversion as well as the NOE experiment clearly showed the *like* stereochemical preference for the reaction of the dienes **12a** and **12b** with NPM (**16**).

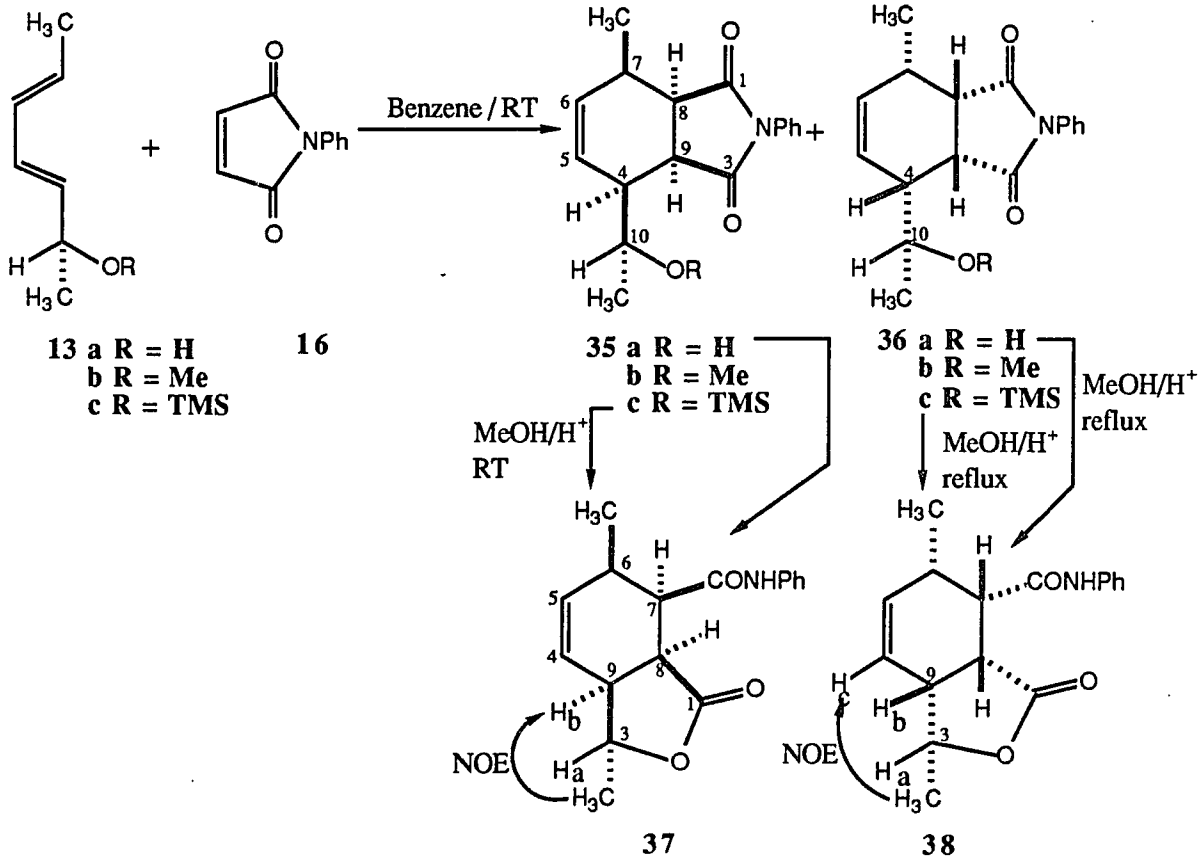
Table 3. NOE Data used to Prove Stereochemistry of the Adducts.

Entry	Lactone	Peak irradiated (δ)	Enhancement observed (%) at H_b	Enhancement observed (%) at H_c
1	**25**	1.48	4.5	--
2	**33**	1.44	8.3	--
3	**34**	1.49	--	6.8
4	**37**	1.43	11.6	--
5	**38**	1.47	--	10.3
6	**59**	1.48	--	16.4
7	**71**	1.47	7.5	--
8	**72**[a]	1.19	--	--

[a] It showed enhancement at the methine proton at C_3 only.

The reaction of N-phenylmaleimide (**16**) with the hydroxy diene **13a** at room temperature also gave a mixture of diastereoisomers (entry 7). Unlike other Diels-Alder reactions with dienol **12a** and **13a**, the most interesting feature of this particular reaction is that, only one of the diastereoisomers (**35a**) slowly cyclizes to the corresponding lactone **37** under the reaction conditions. The other diastereomer (**36a**) remains unchanged, providing a good separation of adducts by chromatography (scheme 5). However the unstable major adduct **35a** can easily be detected in the ^1H NMR spectrum but couldn't be isolated.The minor adduct **36a** is stable to chromatographic separation and could be isolated in pure form. The

major lactone **37** was isolated as a white solid, which on crystallization from EtOAc furnished colorless cubes. The IR spectrum showed the characteristic bands at 1755 and 1675 cm^{-1} for the lactone and imide carbonyls respectively. ^1H NMR also showed the diagnostic broad peak for the NH proton at δ9.98. An NOE experiment (table 3) also showed the enhancement (11.6%) of the allylic proton H_b at δ2.8 by irradiating the methyl singlet at δ1.43 (lactone ring methyl).



13 a R = H, b R = Me, c R = TMS **16** **35** a R = H, b R = Me, c R = TMS **36** a R = H, b R = Me, c R = TMS **37** **38**

Scheme 5

Finally, an x-ray[82] analysis of the lactone confirmed the structure indicating that the adduct **35a** was produced from a *like* attack (figure 7). The x-ray also confirmed the *endo* nature of the adduct **35a**. The minor isomer **36a**, a waxy solid showed the OH stretching frequency at 3450 cm^{-1} and the imide carbonyls at 1700 cm^{-1} in the IR spectrum. The ^1H NMR spectrum also revealed the presence of an exchangeable proton for the OH function

and it also showed the presence of all expected protons for the minor adduct **36a**. The lactonization of the minor adduct **36a** was also achieved by stirring in MeOH/ H^+ under reflux for 2h.

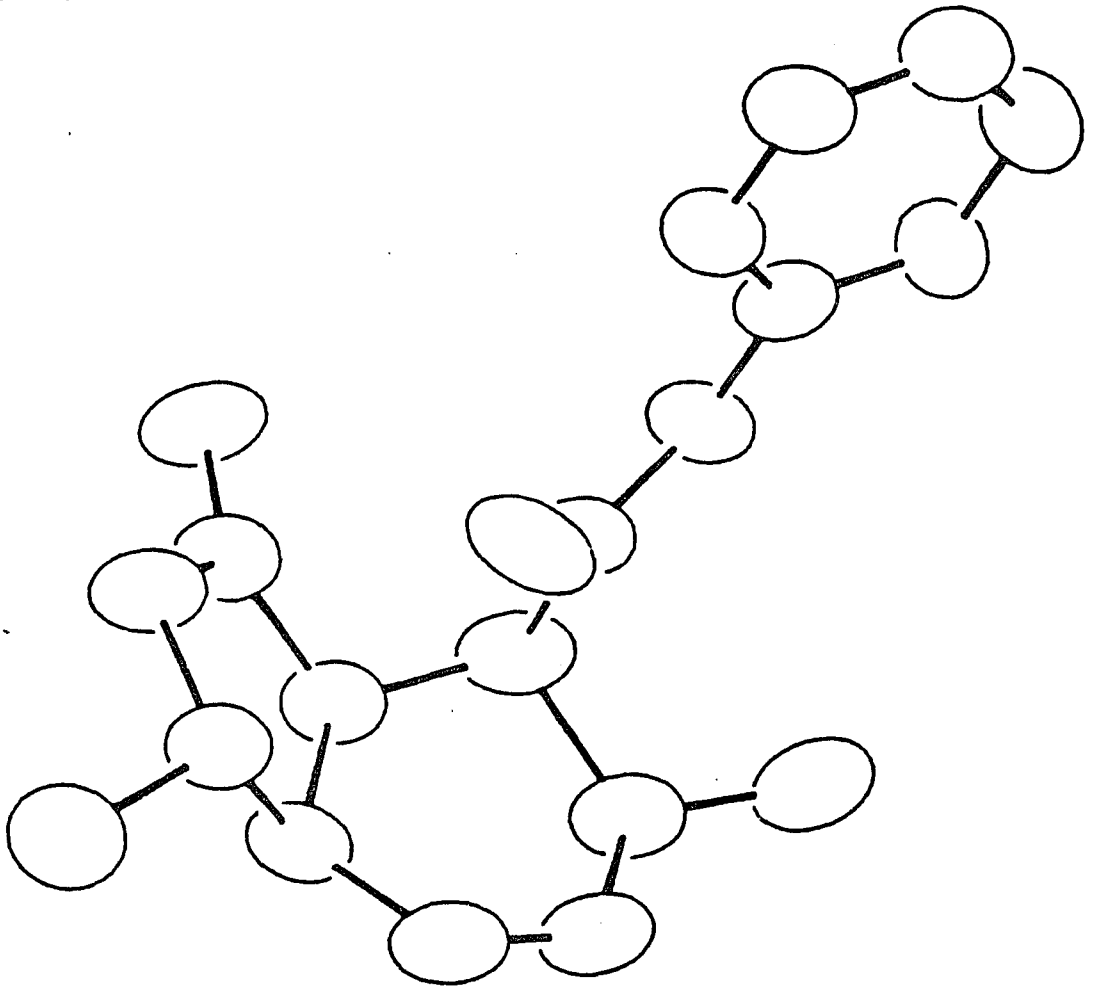


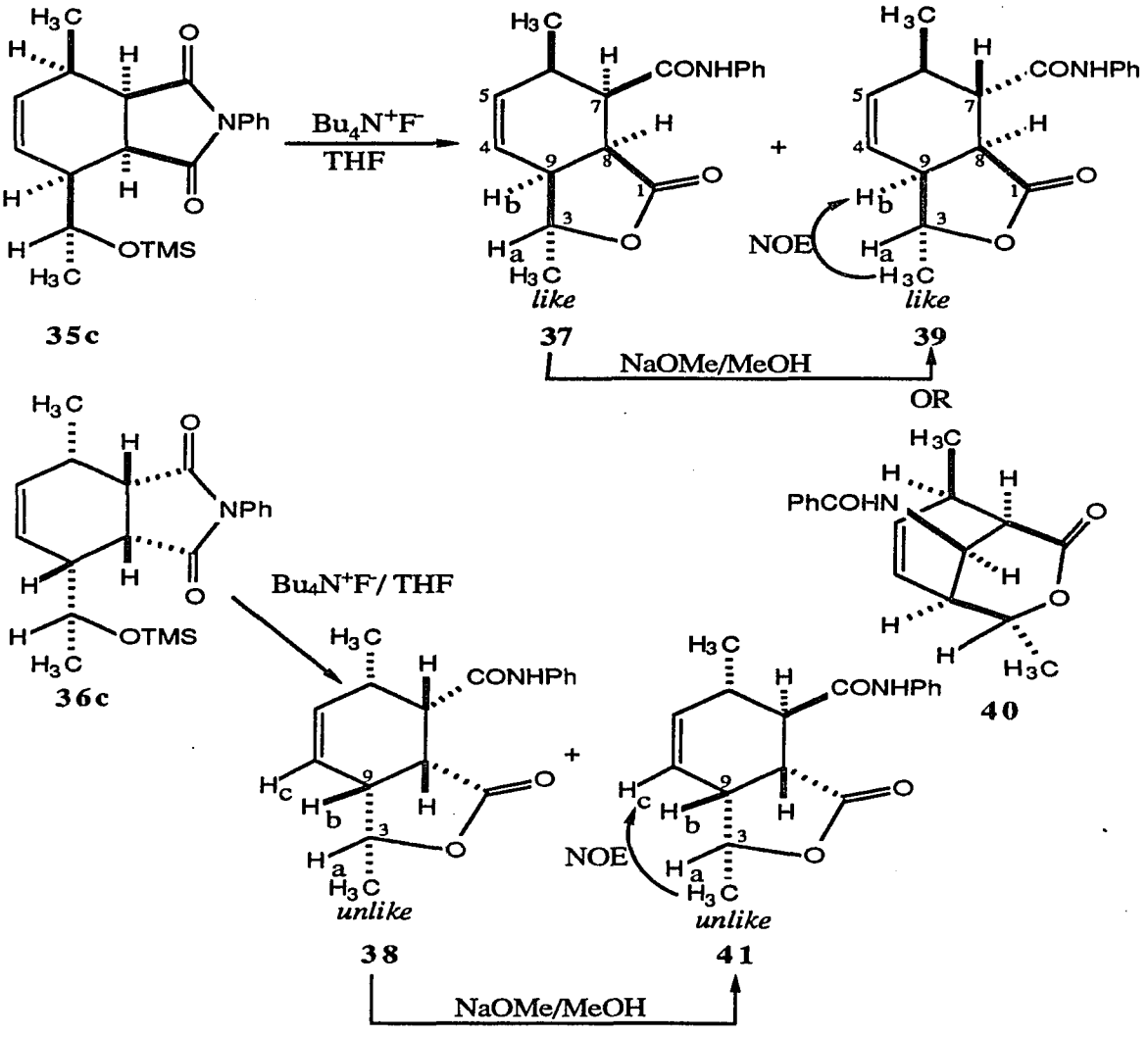
Figure 7. A perspective view of the lactone 37. Hydrogen atoms have been omitted for clarity. Thermal ellipsoids have been drawn at 50% probability.

A white crystalline solid, the minor lactone **38** showed the presence of two distinct carbonyl stretching bands at 1745 and 1660 cm^{-1}. The characteristic broad peak at δ10.77 in the ^1H NMR spectrum for the amide proton also indicated the formation of of a lactone ring. The coupling constant J_{ab} for both the lactones **37** and **38** (2.44 and 3.66 Hz respectively) are not significantly different from each other to enable assignment of stereochemistry, but the NOE experiment clearly established *unlike* stereochemistry for the

minor lactone **38**. The irradiation of the methyl signal at δ1.47 enhanced (10.3%) the vinylic proton at δ5.57 (table 3). Since Bartlett had reported that variation of solvent caused a reversal of face selectivity in the addition of "isodicyclopentadiene" and maleic anhydride[83] and Trost had observed some solvent effects in the face selectivity in his 3+2 work[84], we repeated the same reaction (entry 7) in DMF and observed small changes (entry 8). Improved stereoselectivity was noted when the protected diene **13b** was reacted with NPM (**16**) and the products **35b** and **36b** (Scheme 5) were obtained in a ratio of 5:1 (entry 9). The major product **35b** resulted from a *like* attack which was concluded from chemical conversions[26]. Trimethyl silyl protected diene **13c**, on reaction with NPM (**16**) at room temperature in benzene for 10 days gave a mixture of two diastereomers **35c** and **36c** (entry 10), which were separable by preparative chromatography and the diastereomeric ratio was significantly improved (7.4 : 1). The major diastereomer **35c** (Scheme 5) was a white crystalline solid and its IR spectrum showed only a single carbonyl frequency at 1710 cm-1. The ^{1}H NMR spectrum also showed all the expected protons. The coupling constant J_{ab} was hard to determine from the first order analysis of the spectrum due to overlapping of signals. The stereochemistry was proven by acid catalyzed hydrolysis and lactonization of the major adduct **35c** to the lactone **37**. This chemical interconversion clearly showed that *like* stereochemistry for the major silyl ether adduct **35c**. Like the 2-silyloxy-3,5-hexadienes **12b** & **c**, the protected diene **13c** also enhanced the *like* selectivity with NPM. The minor silyl adduct **36c** was isolated along with a trace of unreacted NPM (**16**) and it could not be further purified. The stereochemical identity was established by the usual acid hydrolysis followed by cyclization to the lactone **38** (Scheme 5). Thus, the minor silyl ether **36c** was produced from an *unlike* attack.

Another interesting set of results were obtained when the silyl ether adducts **35c** and **36c** were hydrolyzed with tetrabutyl ammonium fluoride. In addition to the major lactone **37** and **38**, additional compounds were also isolated by running the reaction for a long period

of time (overnight).



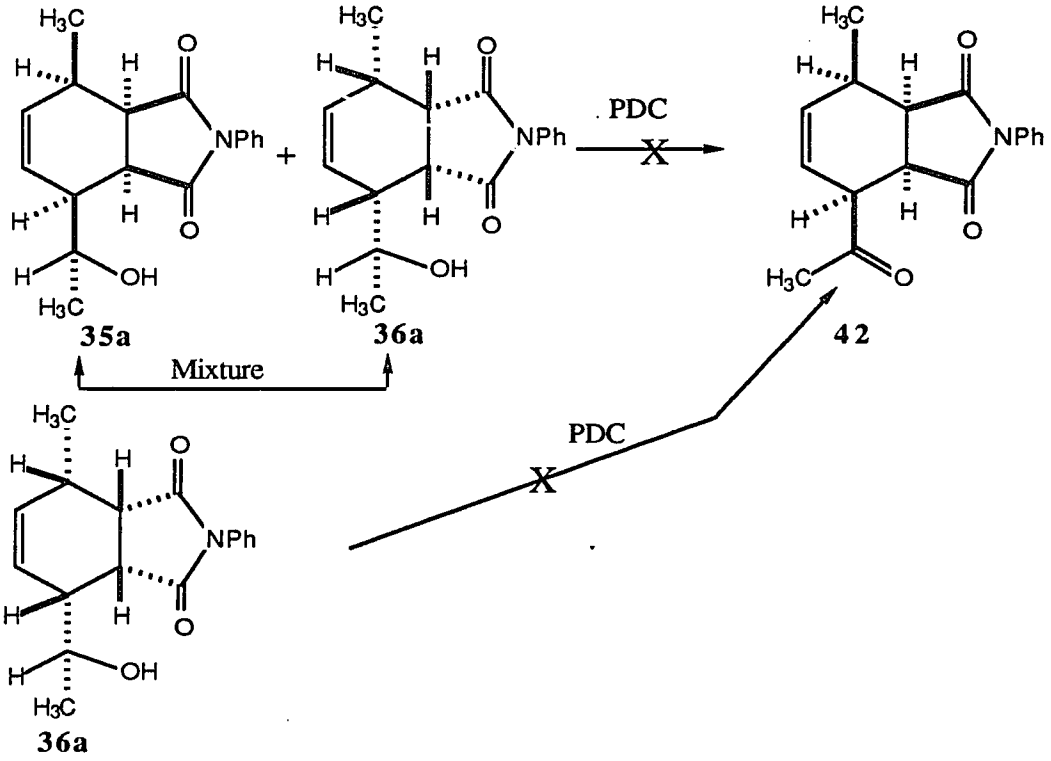
Scheme 6

The major silyl adduct **35c** gave rise to two products , one was the expected lactone **37** and the other was the unknown product which could be the epimeric lactone **39** or the six membered bicyclic lactone **40** (scheme 6). The new product **40** also showed a similar IR spectrum (1755 cm^{-1} for the lactone ring) to the major lactone **37**, which did not indicate clearly whether the two compounds differed in lactone ring size (five or six membered ring lactone). However the ^1H NMR spectrum showed a remarkable difference for the proton at C_7 (scheme 6), which being shifted upfield by 0.2 δ in the case of lactone **39** indicated

that the two compounds might be epimeric at C_7. The coupling constants also changed significantly for example J_{ab} changed from 2.44 to 6.7 Hz. In order to assign the correct relationship between the lactone **37** and **39**, we tried to interconvert both the compounds. When compound **39** was stirred in THF along with excess of tetrabutyl ammonium fluoride, there was no change. But **37** was converted to compound **39** (scheme 6), on treatment with NaOMe in absolute methanol. On the other hand, the compound **39** did not convert to lactone **37** under similar reaction condition. This experiment confirmed that the lactone **37** was a kinetic product and on treatment with a base (even tetrabutyl ammonium fluoride is basic enough), undergoes epimerization at C_7 (which is next to a carbonyl group) to afford the thermodynamically more stable product **39**. As expected, the stable product **39** did not go back to lactone **37** which is a kinetic product. The epimeric lactone **39** also showed similar NOE (see table 3) which indicated the *like* stereochemistry . A similar set of experiments for the minor lactone **38** produced the lactone **41** and it also confirmed the epimeric relationship between the lactone **38** and **41** (scheme 6). Like the other epimeric product, **41** also showed NOE similar to the minor lactone **38** (table 3) which indicated the *unlike* stereochemistry.

c. *Endo-Exo* Problem: For all these Diels-Alder adducts described so far we have assumed both the products in each case are *endo* adducts. The basis of our assumption is that the *exo* products are usually not favored and as we have already shown that both the diastereomers obtained from the reactions of NPM or maleic anhydride with the alcoholic dienes **12a** or **13a** cyclize to their corresponding lactones . White has shown that five membered ring lactones *trans* fused to a cyclohexene ring, formed by the high temperature intramolecular Diels-Alder reactions are very strained molecules. For these compounds, the ^1H NMR spectrum showed a 14 Hz coupling for the protons at the ring junction whereas in our case the *J* values are in the range of 8-9 Hz for both of the diastereomeric lactones in each series. White has further shown that the stained lactones can be easily epimerized to

the thermodynamically more stable *cis* lactones[85]. In our system, the epimerization of the diastereomeric lactones **37** and **38** to **39** and **41** respectively takes place at the carbon atom bearing the amide side chain (not at the ring junction). These evidences show that in our case, both of the diastereomeric adducts were *endo* products. More evidences for the *endo* stereochemistry comes from the NOE studies. The irradiation of the methyl group at C_3 enhanced the bridge head proton signal at C_8 for the major lactone **37**. But for the minor lactone **39**, such enhancement was not observed. Molecular model examination showed that if the minor lactone would have been *exo* product, the above enhancement would have been observed in NOE studies.

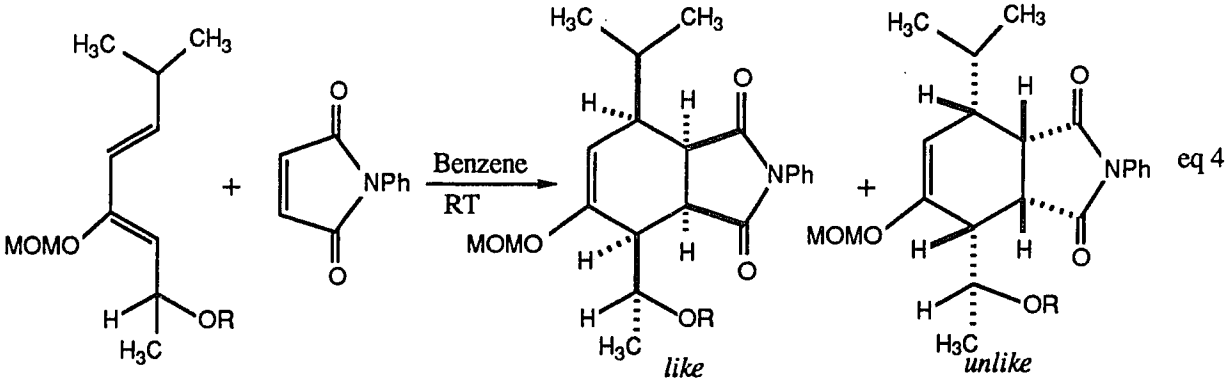


Scheme 7

Our attempt to prove the *exo-endo* nature of these adducts by a chemical method was not successful. If our assumption regarding the *endo* selectivity was correct, then by destroying the chiral center at C_{10} in either adduct should give rise to the same product. If not , then one adduct must be the *exo* and other being the *endo* product. Unfortunately, the free alcohol adducts were not stable enough to undergo such a process. The only stable

alcohol adduct **36a** was subjected to PDC oxidation, but it produced the lactone **38** rather than the expected ketone **42** (scheme 7). Our attempt to oxidize the crude reaction mixture of 2-hydroxy-3,5-heptadiene (**13a**) with NPM (as the purification of the unstable adduct alcohol **35a** leads to the lactone **37**) was not successful and only a mixture of lactone **37** and **38** was obtained.

McDougal and coworkers have carried out Diels-Alder reaction of dienes bearing an allylic substituent with N-phenylmaleimide as the dienophile. They have observed a very high diastereoselectivity for these dienes **43a** and **b** (eq 4), and the major products **44a** and **b** were the *like* products. The stereochemistry was established by the x-ray analysis (entry 11 and 12)[35]. They also observed a total face selectivity with the protected diene **43b**, a result in accordance with their prediction regarding the predominance of the Franck rotamer A in the transition state.

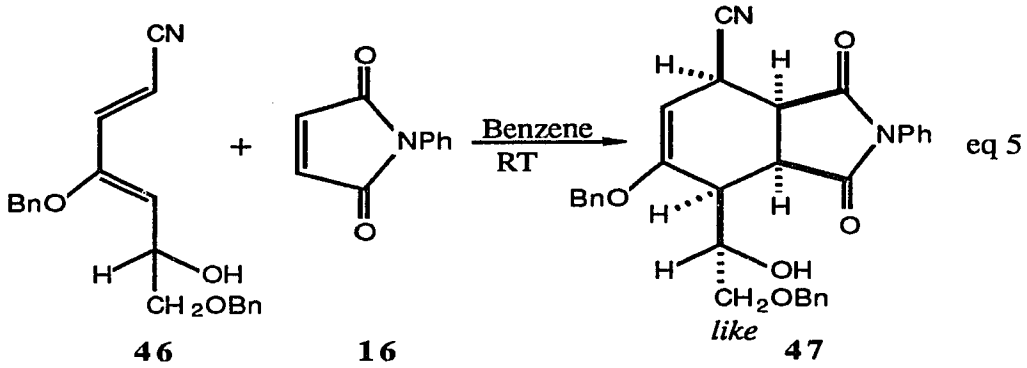


43 a R = H **16**
b R = TMS

44 a R = H 5 : 1 **45 a R = H**
b R = TMS 99+ : 0 **b R = TMS**

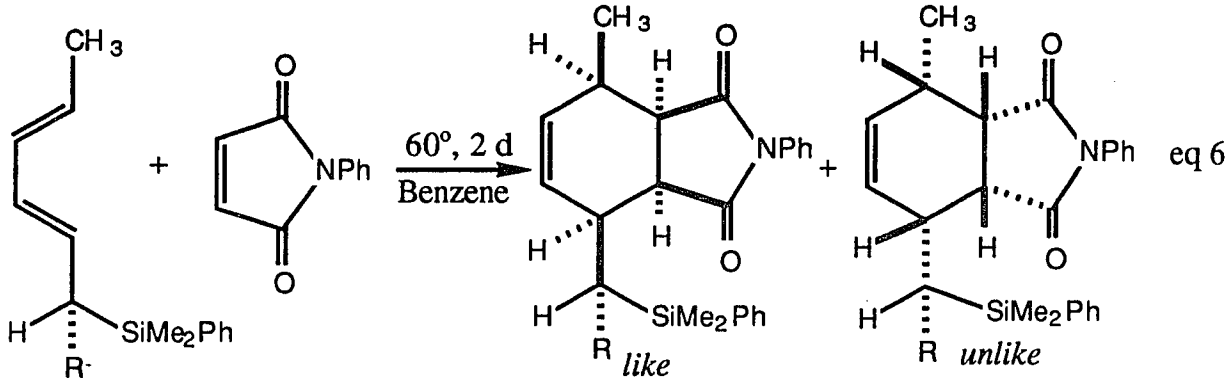
eq 4

Entry 13 shows similar work which has been reported by Reitz *et al* , they also found very high π facial selectivity using a sugar derived diene **46** bearing an allylic center (eq 5)[36]. They isolated only one diastereomer by the reaction of diene **46** with NPM (**16**). The stereochemistry, studied by x-ray and by coupling constant correlation was found to be *like* for the adduct **47**, consistent with McDougal's results.



46 16 47

Another interesting series has been done by Fleming *et al* . They have placed silicon as the hetero atom at the allylic position[38,86]. They prepared the dienes **48a,b** and **c**, and the reactions of these dienes with NPM at 60° in benzene resulted a mixture of diastereomers (**49a,b,c** and **50a,b,c**) in each case (eq 6). Entry 14-16 records the stereochemical preferences of these reactions: the face selectivity was dramatically changed (from the *like* selectivity to the *unlike* preference) by changing the nature of the hetero atom (from electronegative oxygen to electropositive silicon).

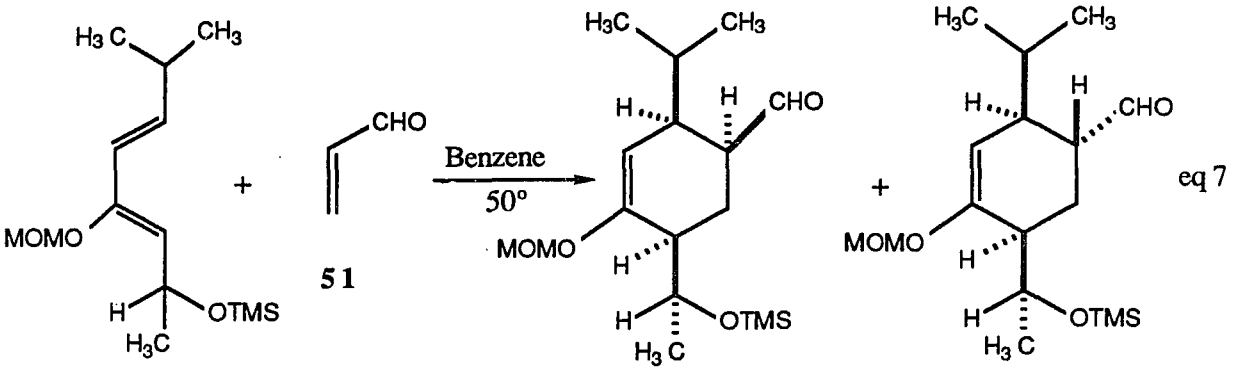


48 a R = Me 16 **49 a R = Me** 18 : 82 **50 a R = Me**
b R = Pr^n **b R = Pr^n** 18 : 82 **b R = Pr^n**
c R = Ph **c R = Ph** 0 : 99+ **c R = Ph**

d. With Acrolein (51):

McDougal observed *like* selectivity for the diene **43b** with acrolein (**51**) at 50° in benzene (entry 17)[35]. In fact, a mixture of two diastereoisomers **52** and **53** was isolated (eq 7) in

a ratio of 93 : 7 and the minor product **53** was proved to be an *exo* compound. Thus, a total *like* selectivity was observed for this diene **43b** either by using NPM (**15**) or acrolein (**51**).

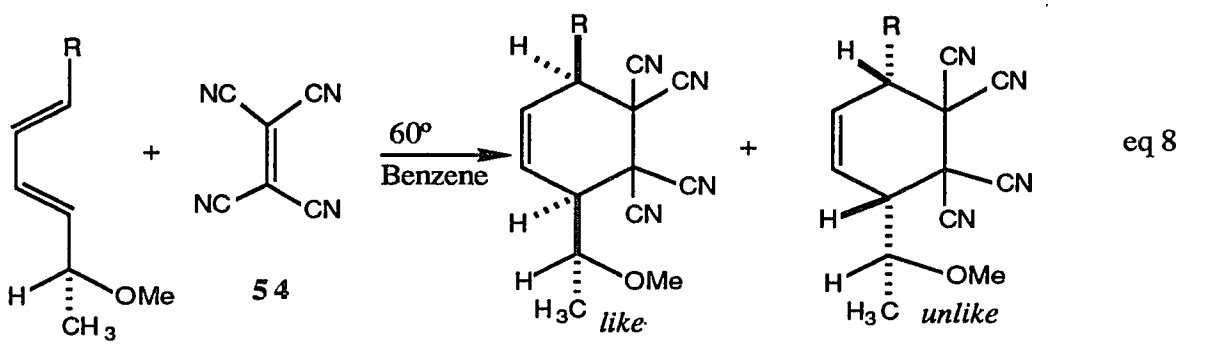


43b **52** **53**

eq 7

e. With Tetracyanoethylene (54):

In 1984, a group of French workers reported the Diels-Alder reactions of dienes (**13b** and **13d**) bearing chiral allylic methoxy substituents (mono or bis allylic centers) with tetracyanoethylene (**54**). These dienes showed *unlike* π facial preference (eq 8) , and particularly the diene **13b** (see the entry 9 and 18) showed opposite facial preference with different dienophiles (*like* for NPM and *unlike* for TCNE). The diastereomer **55a** and **56a** were formed in a ratio of 1 : 2 . The *bis* allylic diene **13d** also resulted in two diastereomers, **55b** and **56b**, in a ratio of 5.7 : 1 (entry 19). The initial report , the selectivity was reported to be *like*, but as corrected in 1986, the outcome was in fact from *unlike* approach[28,68].



eq 8

13 b R = Me
d R = CH(OMe)CH$_3$

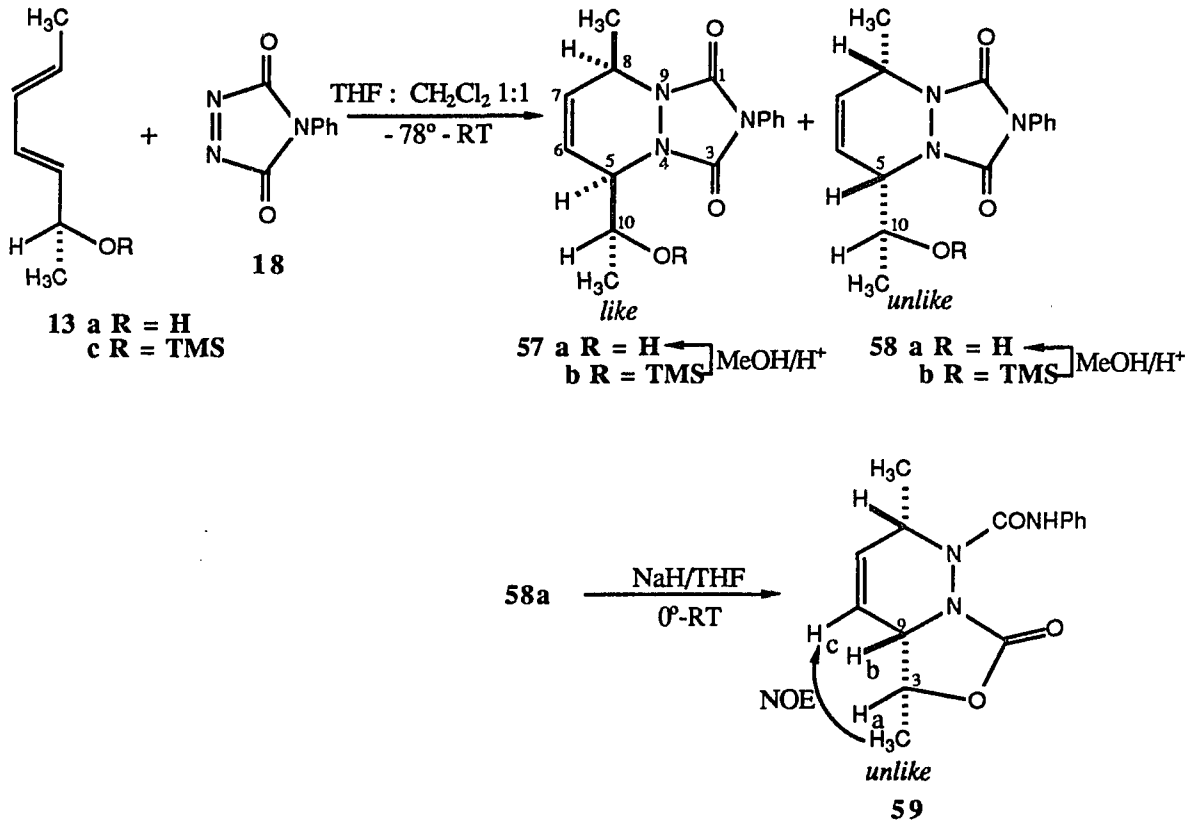
55
a R = Me
b R = CH(OMe)CH$_3$

1 : 2
1 : 5.7

56
a R = Me
b R = CH(OMe)CH$_3$

f. With 4-Phenyl-1,2,4-triazoline-3,5-dione (18):

Due to structural homology between NPM and 4-Phenyl-1,2,4-Triazoline-3,5-dione (PTAD), we thought to use PTAD (**18**) as the dienophile in our system. Unlike NPM, it is very reactive and even at very low temperature the reaction takes place within few minutes. Entry 20 shows the reaction of PTAD (**18**) with 2-hydroxy-3,5-heptadiene (**13a**) in THF : CH_2Cl_2 at -78°-RT which yielded a mixture of diastereomers (**57a** : **58a**) in a ratio of 1 : 2.8. A small amount of a third isomer was also isolated from the chromatographic separation of the adduct mixture. Unlike the NPM adducts with the free dienyl alcohols **12a** and **13a** (i.e. **31a**, **32a** and **35a**), the diastereomers **57a** and **58a** (scheme 8) did not cyclize under the reaction conditions or with H^+/MeOH (even under reflux conditions). The structure of the major product **58a** was proved by NOE studies on the corresponding carbamate **59**, which was obtained by the treatment of the adduct **58a** with NaH in THF. The carbamate **59** was isolated as white crystalline material and it showed the presence of two carbonyl stretching bands at 1785 and 1685 cm^{-1} in the IR spectrum. Irradiation of the methyl signal at δ1.48 enhanced (16.4%) the vinylic proton (H_c) signal at C_4 (table 3) and this result indicated that the major adduct **58a** was formed from an *unlike* attack of the dienophile on the face of the diene **13a**. The stereochemistry of the minor adducts were not proved rigorously and by analogy we assume *like* stereochemistry for the adduct **57a**.



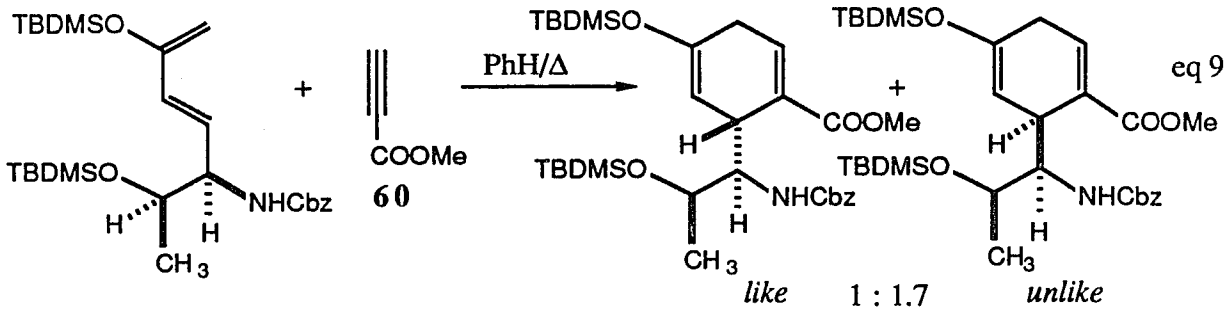
Scheme 8

The reaction of the protected diene **13c** with PTAD (**18**) gave an enhanced ratio (1: 5.5) of diastereomers under similar reaction conditions (entry 21). Like the previous case, the reaction was very clean and products (**57b** and **58b**) were easily separated by PLC . The major product **58a** (scheme 8) was isolated as a white solid and its spectral properties confirmed the structure. Stereochemistry was established by chemical conversion of the adduct **58b** to **58a** either by H^+/MeOH treatment or by fluoride ion attack. The treatment of the silyl adduct **58b** with tetrabutyl ammonium fluoride in THF furnished mainly the adduct alcohol **58a**. The expected carbamate **59** was formed as a very minor product in that reaction which was detected by the NMR analysis of the crude mixture. The minor silyl ether **57b** was also hydrolyzed to the corresponding adduct alcohol **57a** in a similar fashion. These easy correlations established the stereochemistry of the silyl adducts to be *unlike* for the major adduct **58b** and *like* for the minor adduct **57b**. Entry 22 showed the

repetition of the above reaction in DMF. A small change in the diastereomeric ratio (*unlike* preference went down from 5.5 to 3.5) was observed, which showed the formation of more *like* product in a polar solvent like DMF.

g. Methyl Propiolate (60):

Kozikowski and co-workers reported some interesting results with acetylenic dienophiles. In connection with the synthesis of actinobolin, they had carried out a Diels-Alder reaction with a diene bearing an CBz-amino allylic center (**61**) with methyl propiolate (**60**) at higher temperature in benzene[31-33].

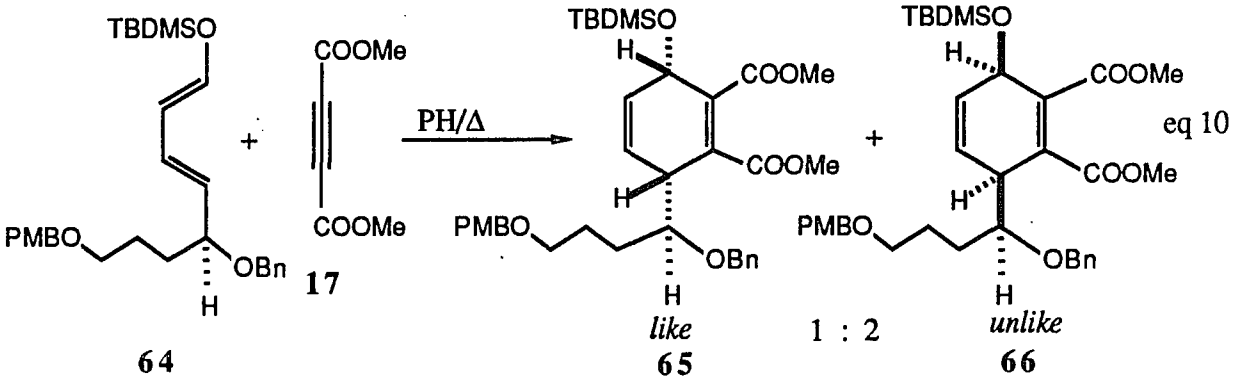


Two products **62** and **63** were produced (eq 9) in a ratio of 1 : 1.7 (entry 23) and the major product (**63**) showed *unlike* stereochemistry which was confirmed by x-ray analysis.Their program for the total synthesis of actinobolin was handicapped as the major product **63** had the undesired stereochemistry and their attempt to improve the *like* selectivity (i.e. by carrying out the reaction under pressure) also was not successful. In fact, a tremendous increase in the *unlike* selectivity was observed (1 : 10) when the same reaction was carried out under high pressure (entry 24).

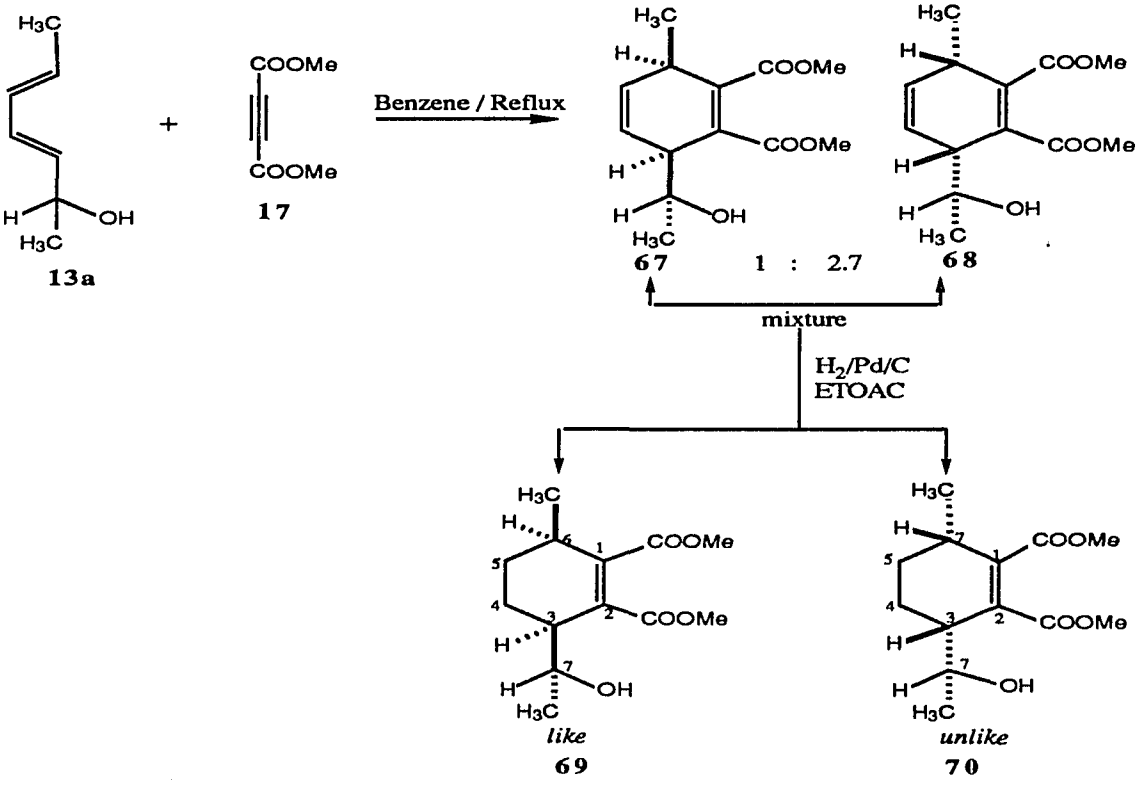
h. With DMAD (17):

In another synthetic plan for the synthesis of forskolin, the same group of workers have also shown that the *unlike* stereochemistry is consistent for the acetylenic dienophiles. This time, they used the dimethyl acetylenedicarboxylate (DMAD) as the acetylenic dienophile. As shown in eq 10 the reaction of the diene **64** and DMAD (**17**) in benzene at high reflux

yielded two products **65** and **66** in a ratio of 1 : 2 and the major product **66** exhibited *unlike* stereochemistry (entry 25)[34].



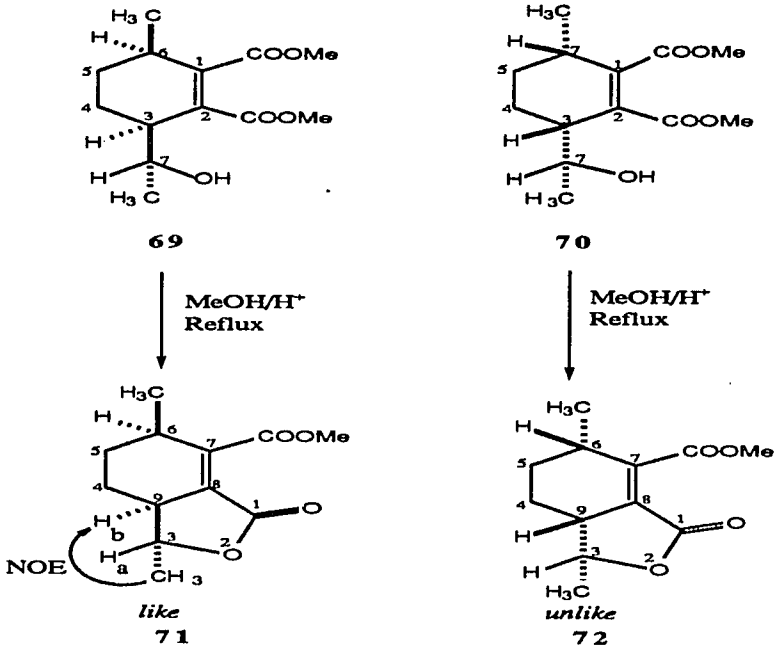
In order to acquire more information, we have done a Diels-Alder reaction of 2-hydroxy-3,5-heptadiene (**13a**) and dimethyl acetylenedicarboxylate (DMAD, **17**) in benzene under reflux (entry 26) .



Scheme 9

The reaction was extremely slow at room temperature but at elevated temperature two

diastereomeric products **67** and **68** were obtained in a ratio of 1: 2.7. A small amount of aromatic product was also observed in the ^1H NMR spectrum of the crude reaction mixture. The two diastereomers were not separable by chromatography and remains as a colorless liquid. In order to solve this problem, we tried to modify the structure of the adducts chemically. One possible modification was to hydrogenate the double bonds of the adduct. When the adduct mixture was subjected to hydrogenation in the presence of Pd/C in EtOAc, only one double bond was selectively reduced and a mixture of two products **69** and **70** was obtained. Their ^1H NMR spectra clearly showed that in both of the adducts the least hindered double was reduced, i.e. the double bond between C_4-C_5 was reduced. At this stage, the two adduct alcohols **69** and **70** were separable by PLC (petroleum ether : ether 3 : 1) and both were isolated as colorless syrups (scheme 9). The alcohols were converted to corresponding lactones **71** and **72** on treatment with acid in MeOH at reflux temperature (scheme 10).



Scheme 10

Thus, the major lactone **72** so obtained from alcohol **70** was isolated as a white crystalline

solid. Its IR spectrum shows the presence of two different carbonyl stretching band at 1755 and 1725 cm^{-1}. ^1H NMR also showed the absence of a OMe group confirming the formation of the lactone ring.

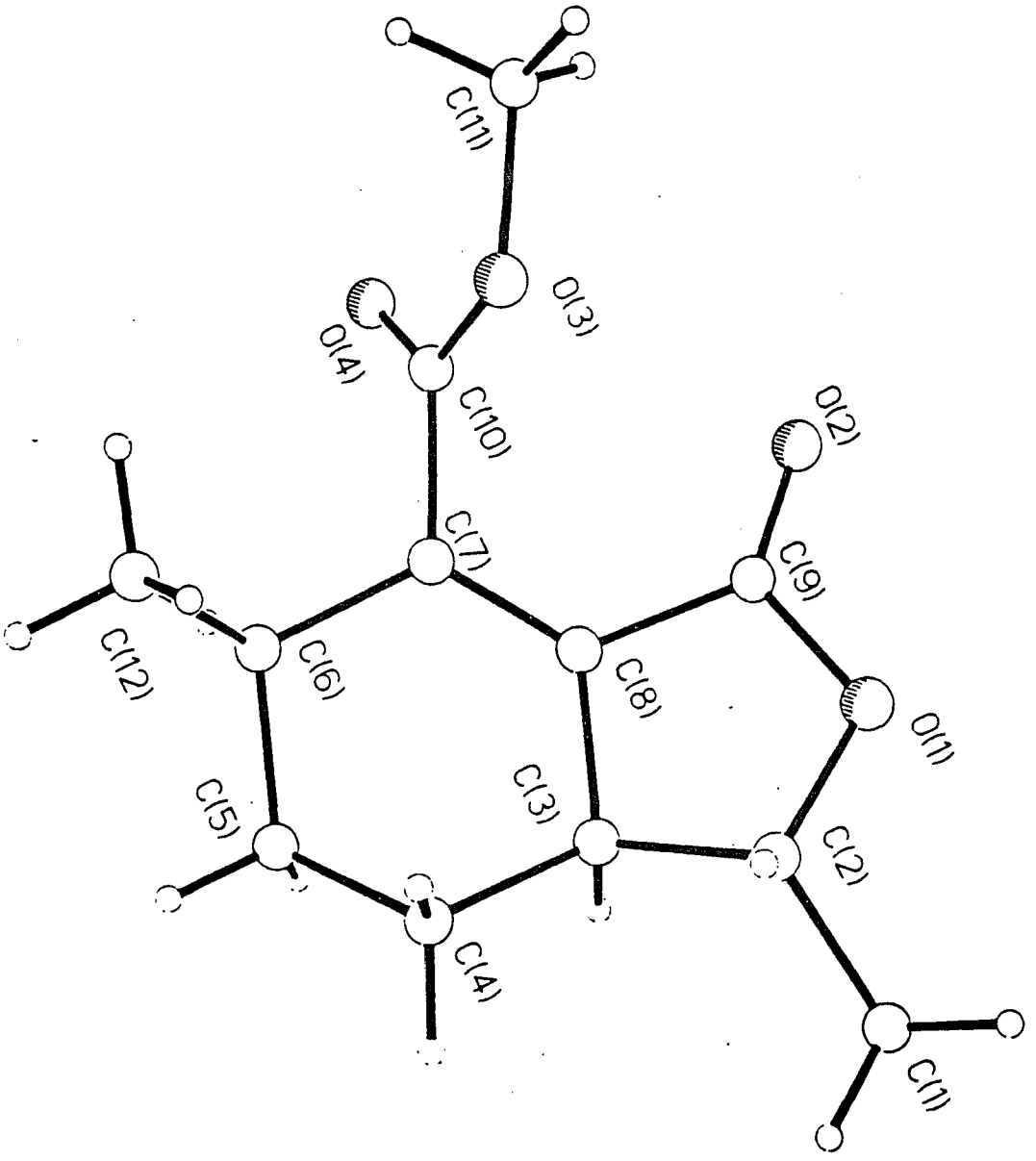
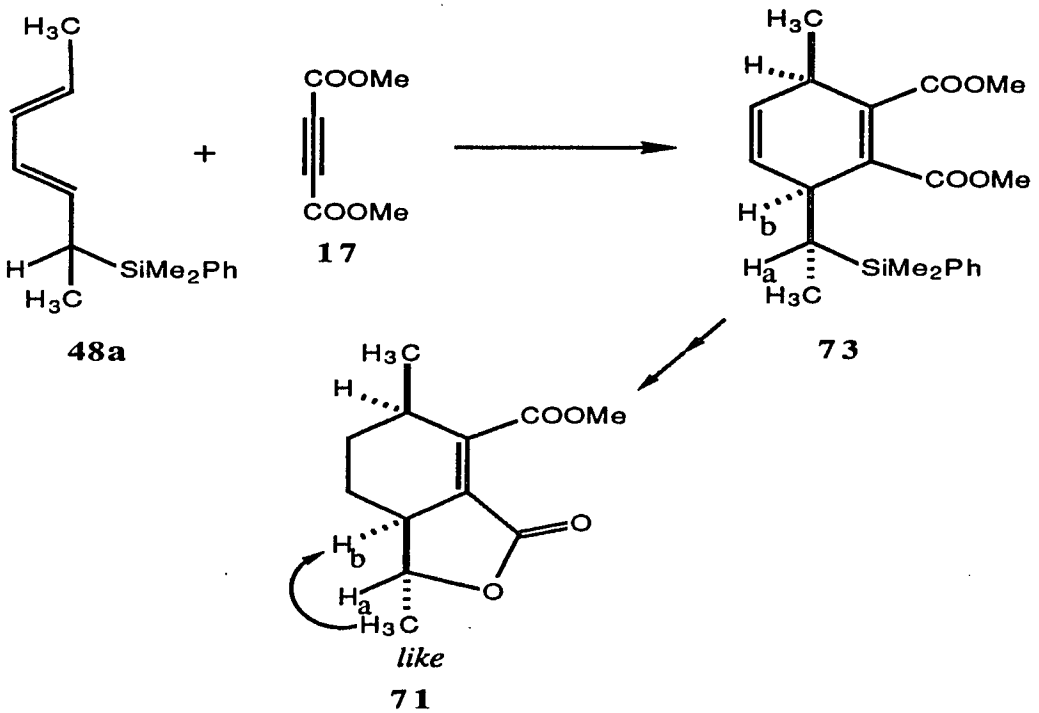


Figure 8: A perspective view of the lactone **71**.

This lactone was assumed to be the result of an *unlike* attack but it was difficult to assign the stereochemistry by ^1H NMR as the NOE does not give useful information due to the absence of the vinylic proton. This assumption was based on the fact that the minor lactone **71** showed strong evidence for the *like* stereochemistry. The minor cyclic product **71**, a white crystalline solid showed the spectral characteristics of a lactone and the stereochemistry in this case was proved by NOE studies. When the methyl signal at δ1.47 was irradiated, there was an enhancement (7.5%) of the allylic proton at C_9 (table 3). This clearly indicated that the minor adduct was a *like* product which was further proved by x-ray analysis[87]. Figure 8 shows the x-ray structure of the minor lactone **71**.Entry 27 shows the repetition of the same reaction under high pressure. The diastereomeric ratio did not change significantly and this was contrary to the observation of Kozikowski who noticed a dramatic change in the diastereomeric ratio for the acetylenic dienophiles[32,33]with his diene.



Scheme 11

Fleming has shown that the silicon substituted diene **48a** showed a dramatic reversal in face selectivity (entry 28) when the dienophile was changed from NPM (**16**) to DMAD (**17**). This result was against his expectation and a complete *like* selectivity was observed by using DMAD (**17**) as the dienophile[86]. As shown in the scheme 11, the *like* adduct **73** was obtained as the only product and its stereochemistry was proved by converting **73** to the lactone **71** through a series of steps. Thus, his results were also similar to our results, which showed that the face selectivity is a function of the dienophile.

B. Acyclic Trienes (14)

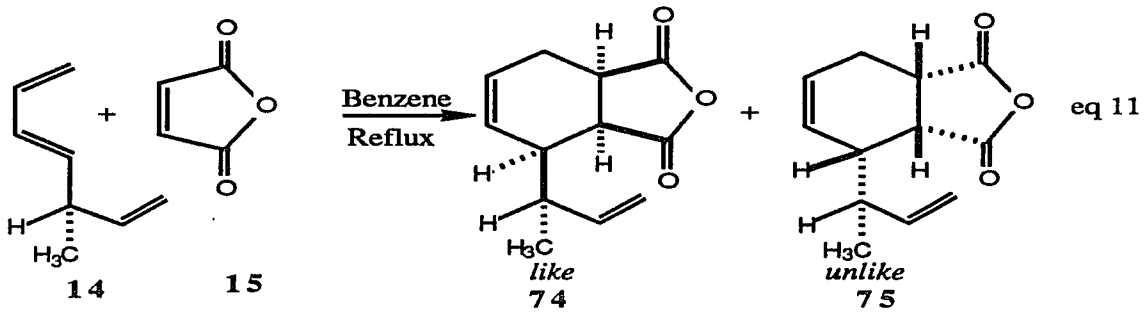
Recently Sato and co-workers have shown that a chiral center bearing a silyl substituted vinyl group next to an aldehyde has a tremendous effect on the face selectivity in the aldol reaction[88]. These results are quite interesting and can be interpreted as the stereoelectronic effect of a vinyl group controlling the face selectivity. Of course the silyl substitution of the vinyl may produce an overriding steric effect. We think that unsubstituted vinyl and methyl groups are of comparable size and a steric effect would not control the reaction. Thus some electronic effect contributed by the vinyl group might be responsible for such a discrimination and we were interested in evaluating the stereoelectronic effect of a vinyl group at a chiral allylic position in the Diels-Alder reaction. We planned to use 3-methyl-1,4,6-heptatriene (**14**) which is commercially available and we have examined the Diels-Alder reaction of this diene with three different dienophiles.

Diels-Alder Reactions:

a. With Maleic Anhydride:

The first reactions was done with maleic anhydride in benzene at reflux temperature. This reaction has also been carried out previously by polymer chemists[89] and only one product was reported. Our reaction showed the formation of two diastereomers **74** and **75** (eq 12) in a ratio of 63: 37 under similar reaction conditions. The two products could not be

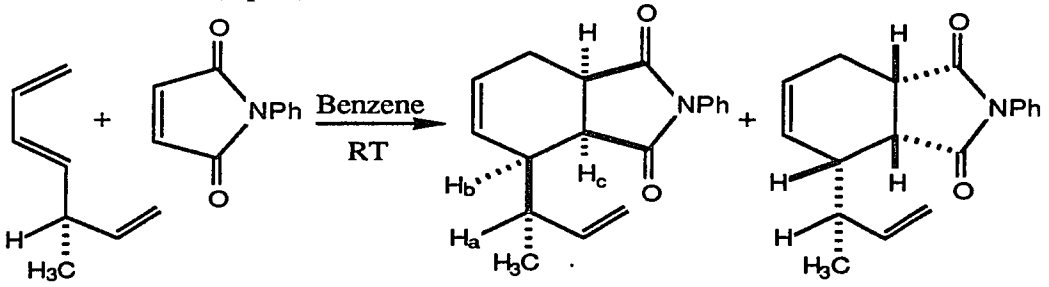
separated by chromatography. This result showed that the vinyl group makes a very small contribution towards the face selectivity. We assume that both of the adducts are *endo* adducts.



14 **15** **74** **75** eq 11

b.With N-Phenylmaleimide:

Anticipating that a phenyl group in the dienophile might have some interaction with the vinyl group at the chiral allylic center, we carried out the Diels-Alder reaction with NPM (**16**) in benzene at room temperature. This reaction also ended up with two compounds in a ratio of 55 : 45 (eq 13).

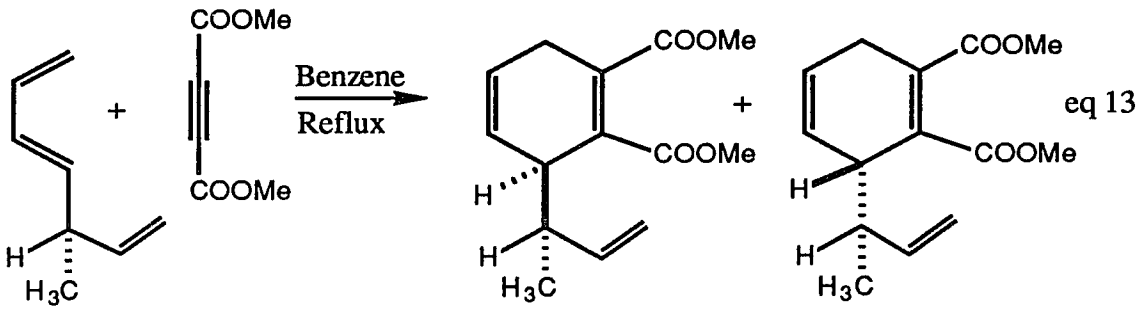


14 **16** **76** **77** eq 12

Reaction under high pressure also did not improve the selectivity (i.e. 56 : 44). The two compounds **76** and **77** were separable by PLC and the stereochemistry of the adducts was not established. However from the ^1H NMR spectrum analysis, we assume that the both the products are *endo* products (J_{bc} = 9.05 and 9.15 Hz respectively). It was hard to prove the stereochemistry on the basis of coupling constant as there was no significant difference in J values of the adducts (for example J_{ab} = 2.44 and 3.16 Hz respectively).

c. With DMAD (17):

The acetylenic dienophile, DMAD on reaction with the triene **14** at reflux temperature gave a mixture of adducts **78** and **79** in a ratio of 52 : 48. The two products were not separable by chromatography and the stereochemistry was not established (eq 13).



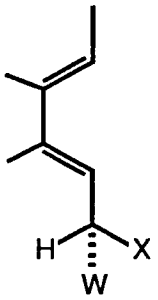
14 **17** **78** **79**

eq 13

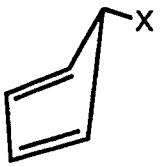
Thus the case of the triene **14**, there was no remarkable contribution of the vinyl group to the diastereoselectivity, unlike a hetero atom at an allylic position of a diene. The assignment of relative stereochemistry in each case was not established as there was no significant stereo control.

C. Semicyclic Dienes

The study of the Diels-Alder reactions of semicyclic dienes of the types **3** or **4** is also essential for better evaluation of the stereoelectronic effect exerted by a hetero atom at the allylic position. These dienes are different since the allylic group is conformationally locked; and unlike cyclic dienes (**2**), the allylic system remains external to the π system. Several Diels-Alder reactions have been reported in the recent literature which show the uses of dienes of types **2**, **3** and **4**[37,39-51]. We have also carried out several Diels-Alder reactions using semicyclic dienes of type **3** (n = 2) with different dienophiles. Here we have documented our result as well as the results obtained by other workers, all mutually consistent.



1



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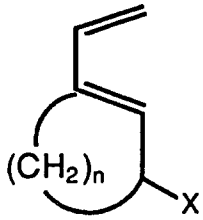

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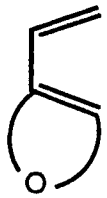


4

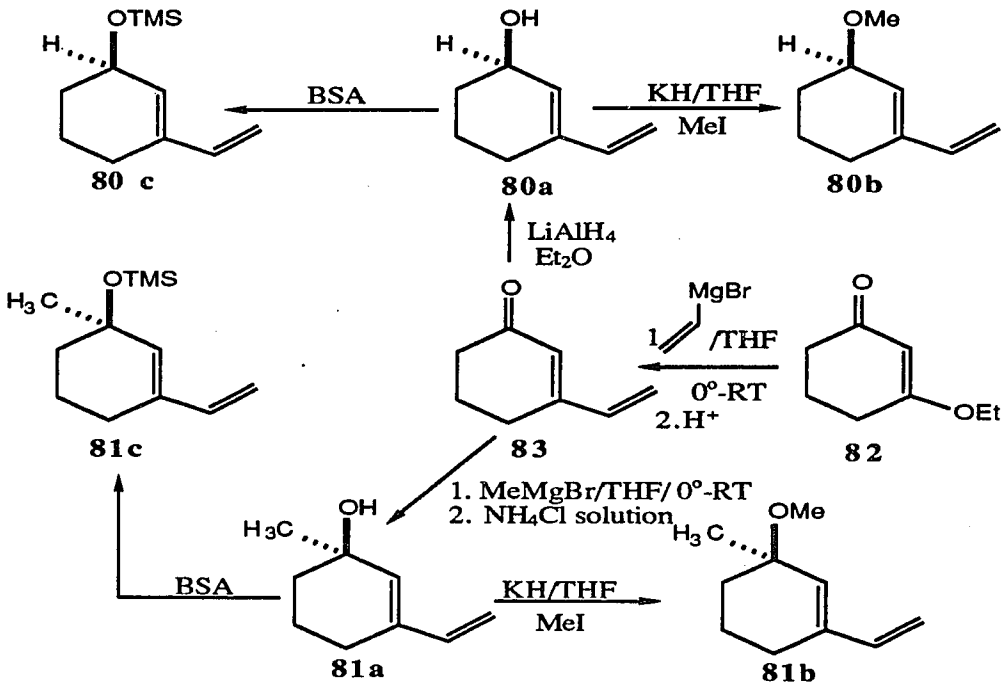
A substituted pyranose
B substituted furanose

a. Semicyclic Dienes 3 (n = 3):

Basically, we have used two type of dienes. The semicyclic diene of the type **80** having a secondary allylic center, and the heavily substituted diene of the type **81**, bearing an hetero atom at a tertiary allylic position.

Preparation of the Dienes: The reaction of vinylmagnesium bromide with 3-ethoxy-2-cyclohexenone (**82**) produced the diene, 3-vinyl-2-cyclohexenone (**83**)[90] which on $LiAlH_4$ reduction in diethyl ether furnished the semicyclic diene alcohol, 3-vinyl-2-cyclohexen-1-ol (**80a**)[91] (scheme 12) . Protection of the resulting hydroxy group

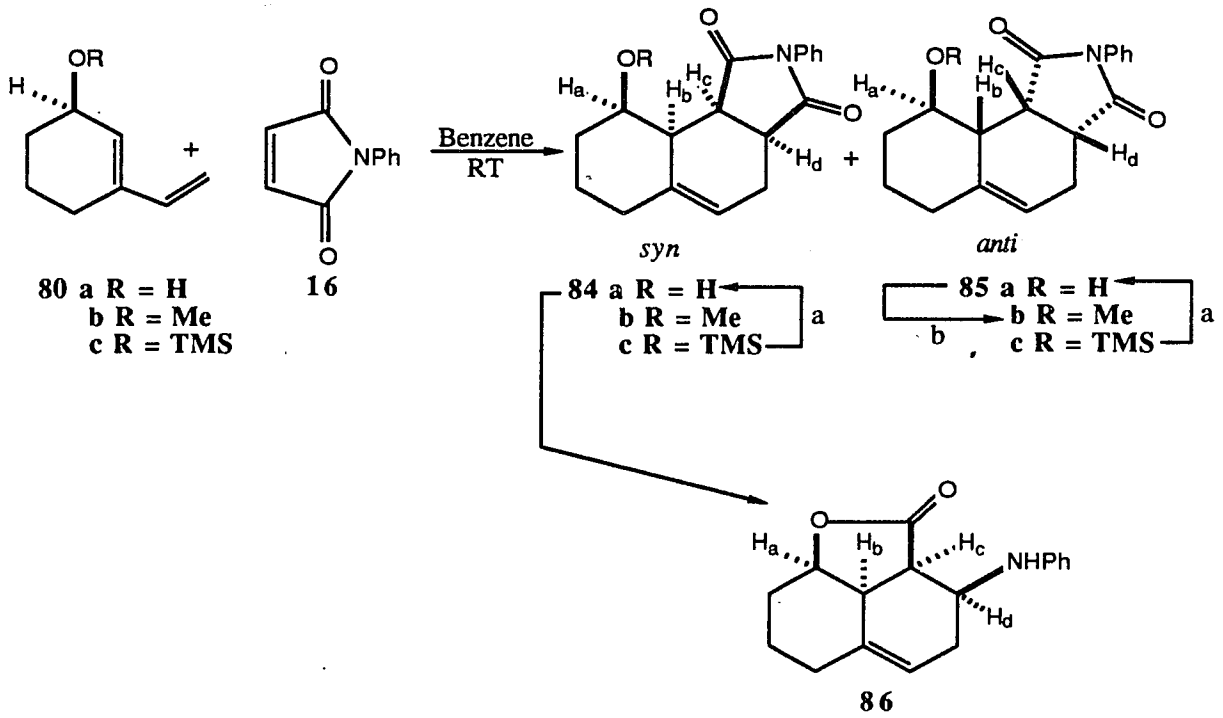
by standard methods furnished 3-methoxy -1-vinyl cyclohexene (**80b**) and 3-((trimethylsilyl)oxy)-1-vinylcyclohexene (**80c**) (scheme 12). The Grignard reaction of MeMgBr and 3-vinyl-2-cyclohexenone (**83**) afforded 3-vinyl -1-methylcyclohexenol (**81a**) and the methyl as well as the silyl protected dienes **81b** and **81c** were prepared from **81a** by standard methods (scheme 12) .



Scheme 12

Diels-Alder Reactions: A series of Diels-Alder reactions has been carried out in our laboratory by using the dienophiles N-phenylmaleimide (**16**), dimethyl acetylenedicarboxylate (**17**) and 4-phenyl-1, 2, 4- triazolin-3, 5-dione (**18**) with dienes **80a-c** and **81a-c** in different solvents and reaction conditions (see table 4). The relative topicities are termed as *syn* (*like*) and *anti* (*unlike*) for the sake of convenience in the case of the conformationally locked dienes. The first entry records the reaction of 3-vinyl-2-cyclohexen-1-ol (**80a**) with N-phenylmaleimide (**16**) at room temperature in benzene. ^{1}H NMR of the crude reaction mixture showed the formation of three products. The major product was the adduct **84a** (scheme 13) which was slowly converted into the

tricyclic lactone **86**. Similar spontaneous lactonization has also been observed earlier by us and other workers [27,37,75] when free hydroxy dienes are subjected to Diels-Alder reaction with NPM (**16**). The crude reaction mixture was refluxed in benzene to complete lactonization of the adduct **84a** and the diastereomeric ratio was determined from the ^1H NMR spectrum of the mixture and found to be 1.7 : 1. The two products **85a** and **86** were separated by chromatography. However, the adduct **84a** can be isolated by freezing the concentrated reaction mixture whereupon **84a** crystallized out as a white solid. When the adduct **84a** was treated with MeOH/H+, it underwent rapid cyclization and furnished the tricyclic lactone **86**. This cyclization clearly showed that the adduct **84a** was formed by the attack of the dienophile on the face of the diene which is *syn* to the hydroxy group. The ^{1}HNMR spectrum also provided strong evidence for the *syn* stereochemistry for the adduct **84a** which shows proton H_a resonating at δ4.34 and appearing as a broad singlet indicating a very small coupling constant between H_a and H_b.



a = H^+/MeOH, b = $Ag_2O/K2CO_3$/MeI

Scheme 13

On the other hand the same proton in the minor adduct **85a** appears as a broad multiplet indicating a trans coupling between H_a and H_b. Thus minor adduct **85a** is formed by the attack of the dienophile from the face *anti* to the hydroxy group . Adduct **85a** did not cyclize on treatment with MeOH/H^+ at room temperature or under reflux . We assign both adduct **84a** and **85a** as *endo* products because of easy cyclization of one of the adducts (**84a**) and because both have comparable coupling constants between H_b and H_c (J = 9.2 Hz for **84a** and 8.2 Hz for **85a**). A dramatic change in the diastereomeric ratio of *syn* (**84a**) : *anti* (**85a**) product was produced by changing the solvent from benzene to MeOH or DMF (entry 2 and 3). A total reversal of face selectivity was observed in the case of the more polar solvents.

Entry 4 shows that the reaction of 3-methoxy-1- vinylcyclohexene (**80b**) with NPM at room temperature in benzene also showed opposite facial selectivity to the free diene alcohol **80a**. In this case the *anti* adduct **85b** clearly predominates and the facial selectivity does not change significantly by changing the solvent from benzene to DMF (entry 5). The stereochemistries of **84b** and **85b** were proved by comparing the ^1H NMR data of **84a** and **85a** which showed a common coupling pattern for the methine proton H_a . For the *anti* adduct **85b**, the methine proton H_a showed the characteristic broad ddd (J = 4.58, 9.84, 11.0 Hz) whereas for the *syn* compound **84b**, the methine proton H_a appears as a broad singlet. Moreover methylation of the *anti* adduct alcohol **85a** with MeI/AgO/K_2CO_3 gave methyl ether **85b**.

The silyl protected diene **80c** also undergoes cycloaddition with NPM slowly and the facial selectivity remains identical to methyl ether diene **6b** (entry 6). In this case two diastereomeric products appeared as a homogeneous material when chromatographed and were not separable. ^1H NMR of the crude sample showed a clear coupling pattern for the methine proton H_a (ddd, J = 4.7, 9.4, 11.2 Hz) and again clearly indicated that the major

diastereoisomer **85c** was an *anti* adduct.

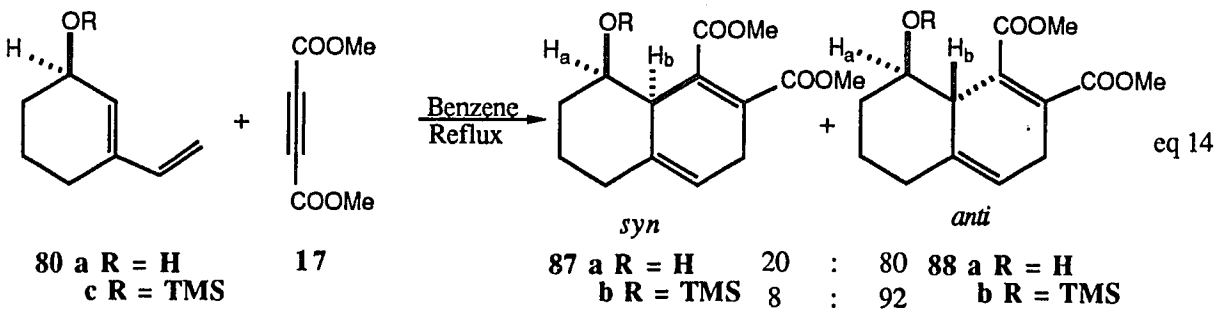
Table 4. Relative Topicities of the Diels-Alder Reaction of different Dienophiles with Semicyclic Dienes Bearing a Stereogenic Allylic Carbon.

Entry	Diene	Dienophile	Solvent	Temperature	Product *syn*(%) : *anti*(%) %				Yield
1	**80a**	**16**	Benzene	25°	**84a**	(63)	**85a**	(37)	73.5
2	**80a**	**16**	Methanol	25°		(36)		(64)	
3	**80a**	**16**	DMF	25°		(17)		(83)	
4	**80b**	**16**	Benzene	25°	**84b**	(11)	**85b**	(89)	82.4
5	**80b**	**16**	DMF	25°		(10)		(90)	
6	**80c**	**16**	Benzene	25°	**84c**	(9)	**85c**	(91)	70.5
7	**80a**	**17**	Benzene	Reflux	**87a**	(20)	**88a**	(80)	82.7
8	**80a**	**17**	CH_2Cl_2@	25°		(19)		(81)	
9	**80c**	**17**	Benzene	Reflux	**87b**	(8)	**88b**	(92)	56
10	**80c**	**17**	CH_2Cl_2@	25°		(9)		(91)	
11	**80a**	**18**	CH_2Cl_2:THF	-78°-RT	-		**89**	(100)	81
12	**81a**	**16**	Benzene	25°	**90a***	(92)	**91a**	(8)	72.2
13	**81a**	**16**	DMF	25°		(45)		(55)	
14	**81b**	**16**	CH_2Cl_2@	25°	**90b**	(26)	**91b**	(74)	65.58
15	**81b**	**16**	Benzene	50°		(25)	18b	(75)	
16	**81c**	**16**	Benzene	25°	**90c**	(23)	**91c**	(77)	50.4
17	**81c**	**16**	DMF	25°		(17)		(83)	

* Unstable, isolated as the lactone **92**.
@ under 6 Kbar pressure.

The corresponding proton for minor adduct **84c** appeared as a broad singlet. The adduct mixture was easily hydrolyzed by MeOH/H^+ to give the *anti* alcohol **85a** as the major product with a detectable amount of tricyclic lactone **86**.

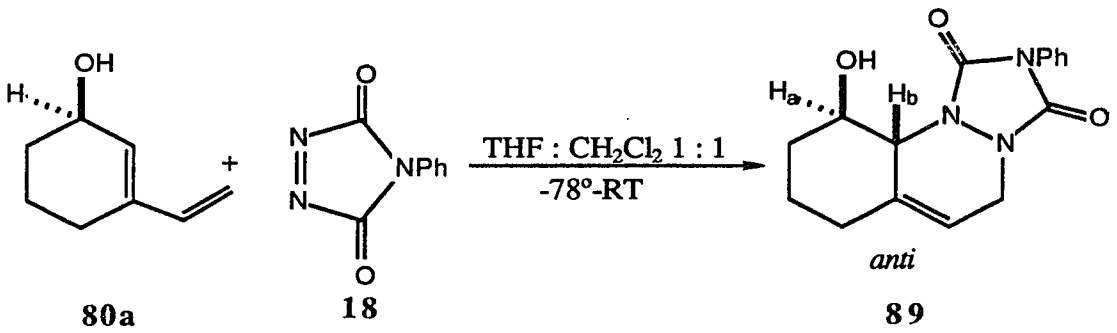
Entry 7 records the reaction of the alcohol diene **80a** with dimethyl acetylene dicarboxylate (**17**) at reflux temperature in benzene. The reactions are slow at room temperature in case of acetylenic dienophiles. However at reflux some aromatic products were observed in the ^1H NMR spectrum. When the reaction was carried out in CH_2Cl_2 under high pressure (6 Kbar), the products were clean and free from aromatic product (entry 8) and there was no significant change in the diastereomeric ratio. Two major products **87a** and **88a** (eq 14) were separated by chromatography. The stereochemistry for both the adducts were determined from their ^1H NMR spectra. The resonance of the methine proton H_a for the major adduct **88a** appears at δ3.51 as a broad multiplet, where as the the same proton resonates at δ4.11 (as a broad singlet) in the minor compound **87a**.



The silyl protection of the diene (**80c**) further increased the amount of *anti* adduct **88b** (entry 9). Stereochemistry for both the minor and major adduct **87b** and **88b** were also secured by ^1H NMR correlation with the alcoholic adduct **87a** and **88a**. The resonance for the methine proton H_a appears as a doublet of a triplet (J = 10.4, 4 Hz) for the major adduct **88b** whereas in the minor isomer **14b** the same proton appears as a broad

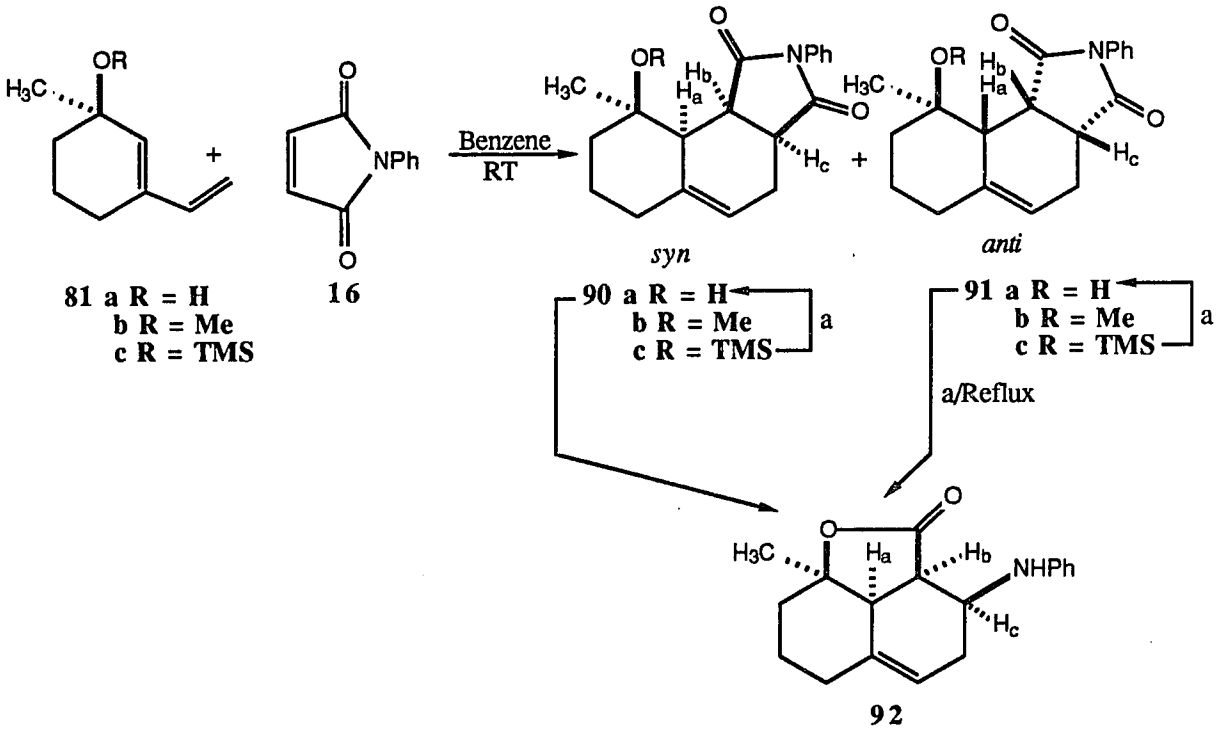
multiplet. Our ^1H NMR results are also analogous to the observations of Roush *et al* for similar kind of acetylenic adducts[92]. Moreover the major adduct **88b** was hydrolyzed by MeOH/H^+ to adduct **88a**, which shows the major product **88b** resulted from an *anti* attack.

Reaction of the diene **80a** with 4-phenyl-1, 2, 4- triazoline-3,5 -dione (**18**) in CH_2Cl_2 : THF at low temperature gave a single adduct **89** as a white solid (entry 11). The allylic proton H_b resonates as a doublet (J_{ab} = 8.8 Hz), thus indicating the adduct resulting from an *anti* attack (eq 15). The methine proton H_a also appears as a broad multiplet which is also another characteristic of the *anti* adducts.



80a **18** **89** eq15

The dienes (**81a-c**) bearing both methyl and hydroxy or alkoxy groups at the allylic position also gave interesting results. The reaction of the diene **81a** with NPM at room temperature in benzene resulted in the formation of a crystalline solid which separated out after overnight stirring (entry 12). The compound was identified as the tricyclic lactone **92** (Scheme 14) on the basis of spectral evidence and x-ray analysis (figure 9). A minor product, the *anti* alcohol **91a** (attack resulting *anti* to the hydroxy group), as shown by spectral analysis was also isolated from the mother liquor along with the tricyclic lactone **92.** Both the products were assumed to be *endo* on the basis of comparable ^1H NMR data with the adducts **84a** and **86**. Moreover when the alcoholic adduct **91a** was treated with MeOH/$H^+$and refluxed for a prolonged period of time (48 h) tricyclic lactone **92** resulted.



a = H^+/MeOH

Scheme 14

This result indicated the loss and regeneration of stereochemistry at the tertiary center (carbon bearing oxygen) by acid catalysis, and formation of the thermodynamically more stable product. This experiment also ruled out the possibility of the compound **92a** being an *exo* product. When the solvent was changed from benzene to DMF (entry 13), the diastereomeric ratio changed dramatically from 92 : 8 to 45 : 55. Thus more polar solvent favors the attack of the dienophile *anti* to the hydroxyl group.

The reaction of the diene **81b** with NPM was extremely slow in benzene at room temperature . The same reaction was carried out in CH_2Cl_2 under high pressure (6 Kbar) which gave a mixture of two products **90b** and **91b** in a ratio of 1: 3 (entry 14 and 15). The cycloadducts were separated by chromatography and the stereochemistry of both the adducts was established from the ^1H NMR spectrum. Entry 16 shows the reaction of the silylated diene **81c** with NPM and two adducts (**90c** and **91c**) resulted, in a ratio of 1 :

3.3. The products **90c** and **91c** were not separable by chromatography and the stereochemistry was elucidated on the basis of their ready conversion to tricyclic lactone **92** and alcohol **90a** respectively. Running the reaction in more polar solvent like DMF resulted in slight increase of the *anti* product **91c** (entry 17).

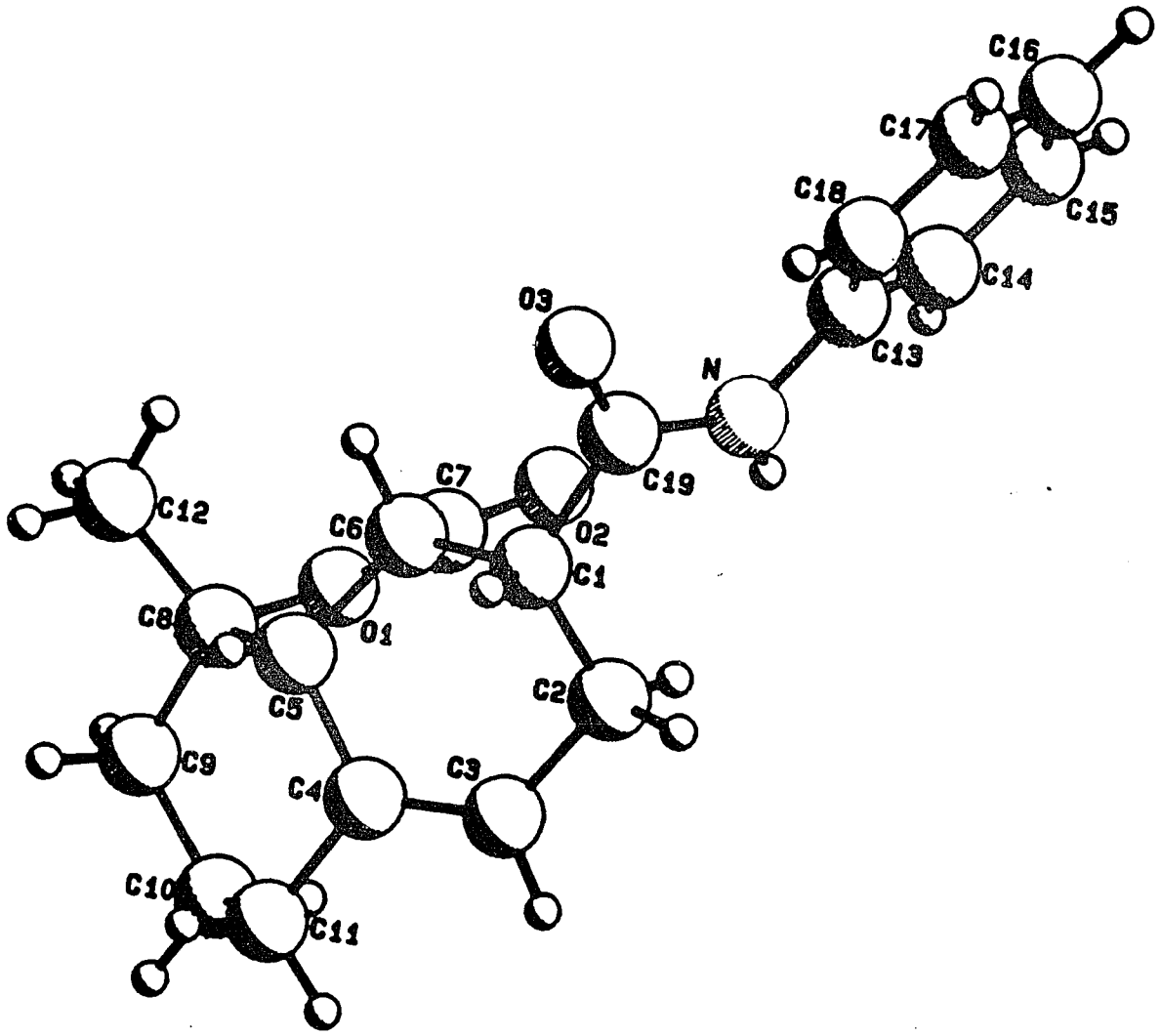
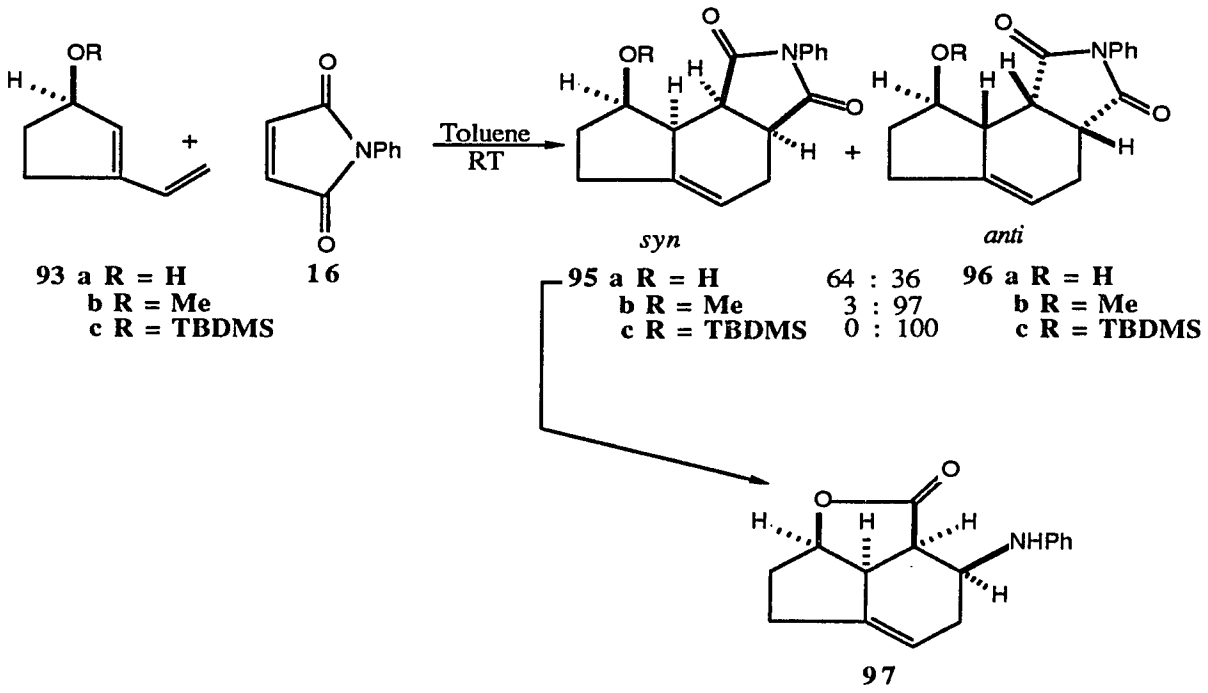


Figure 9: A Perspective View of the Tricyclic Lactone **92**.

b. Semicyclic Dienes 3 (n = 2):

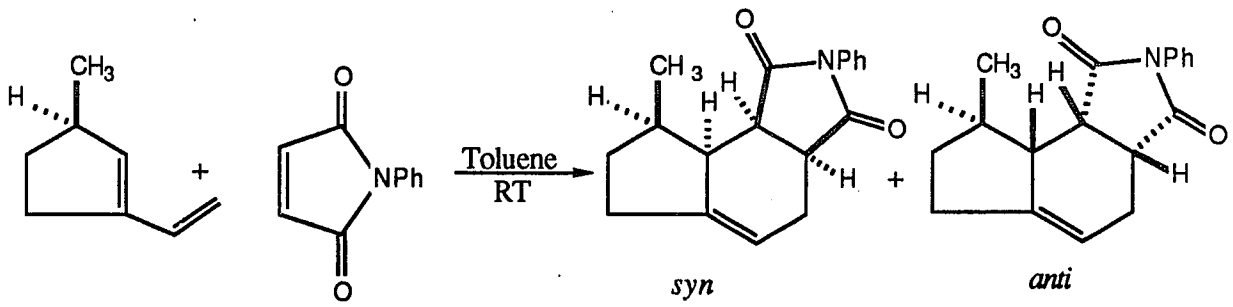
While our work was in progress, Hehre and Overman reported similar work by using the allylic diene of type **3** (n = 1) with NPM (**16**) and tetracyanoethylene (**54**)[37]. They have also modified Hehre's original theory which will be discussed later. They have used (1) 3-vinyl-2-cyclopenten-1-ol (**93a**) and it's methoxy (**93b**) as well as t-butyldimethylsilyl (**93c**) derivatives, and (2) 3-methyl-1-vinylcyclopentene (**94**) as the diene components.

The Diels-Alder reactions with the free alcohol diene **93a** with NPM in toluene at room temperature produced a mixture of diastereoisomers **95a** and **96a** in a ratio of 64 : 36 (Scheme 15) and like our case, the *syn* adduct alcohol **95a** was unstable and slowly cyclized to the tricyclic lactone **97**. This reaction showed a dramatic solvent effect. In more polar solvents like THF and MeOH the π facial preference was reversed i.e. *anti* adduct **96a** was the major product (in THF:. the ratio of **95a** : **96a** was 36 : 64, in MeOH: the ratio of **95a** : **96a** was 20 : 80). The reaction of the methylated diene **93b** with NPM in toluene gave the anti adduct **96b** predominantly.



Scheme 15

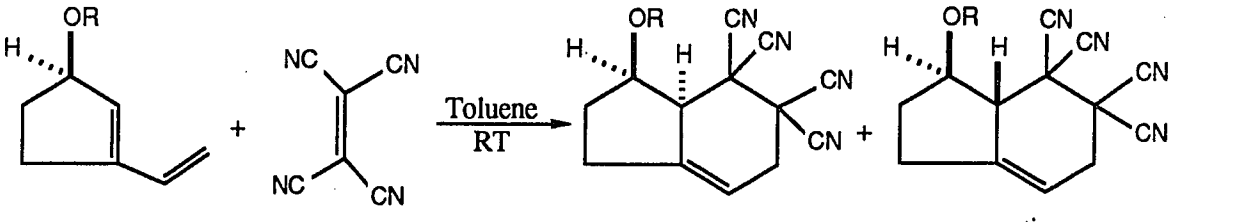
The silyl protected diene **93c** also showed exclusive formation of the *anti* adduct **96c** under similar conditions. In the case of the protected dienes, there was no significant change in the diastereomeric ratio by carrying out the reaction in THF or in MeOH. When diene **94** was reacted with NPM in toluene at room temperature, a mixture of diastereomers **98** and **99** (eq 16) was formed in a ratio of 17 : 83. There was no significant change in the diastereomeric ratio by using to more polar solvents.



94 **16** *syn* **98** 17 : 83 *anti* **99**

eq16

The use of tetracyano ethylene (**54**) as the dienophile also revealed *anti* selectivity. The reaction of TCNE (**54**) with the diene **93a** at room temperature in toluene furnished the *syn* (**100a**) and *anti* (**101a**) adducts in a ratio of 25 : 75 respectively and there was no remarkable solvent effect (In MeOH the ratio of **100** : **101** was 19 : 81).



93 a R = H
b R = Me
c R = TBDMS

54

syn

100 a R = H 25 : 75
b R = Me 17 : 83
c R = TBDMS 31 : 69

anti

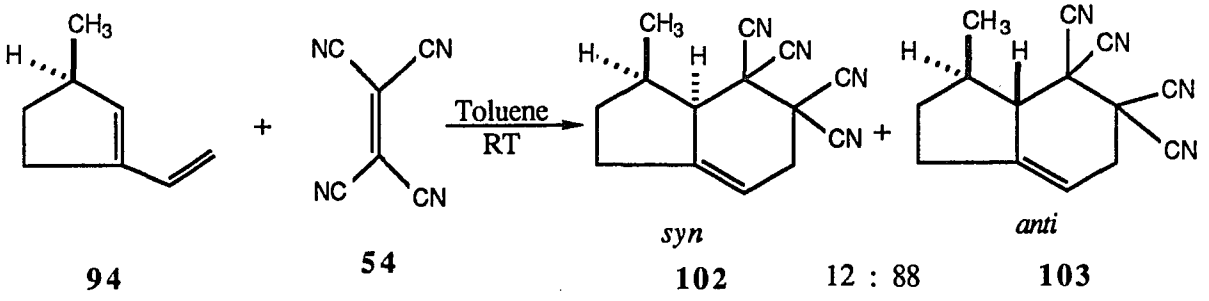
101 a R = H
b R = Me
c R = TBDMS

eq 17

A slight increase in the diastereomeric ratio was observed when the diene **93b** was employed, and in toluene the products **100b** and **101b** were formed in a ratio of 17 : 83.

There was a small decrease in the diastereomeric ratio when the t-butyldimethylsilyl protected diene **93b** was used and the reaction of this diene with TCNE in toluene at room temperature gave a mixture of the *syn* (**100c**) and *anti* (**101c**) products in a ratio of 31 : 69. The ratio changed to 25 : 75 upon changing the solvent to THF (eq 17).

The reaction of the diene **94** with TCNE in toluene at room temperature gave two products, **102** and **103** in a ratio of 18 : 82 (eq 18). The *anti* adduct **103** was the major product and the diastereomeric ratio did not change by employing a more polar solvent.



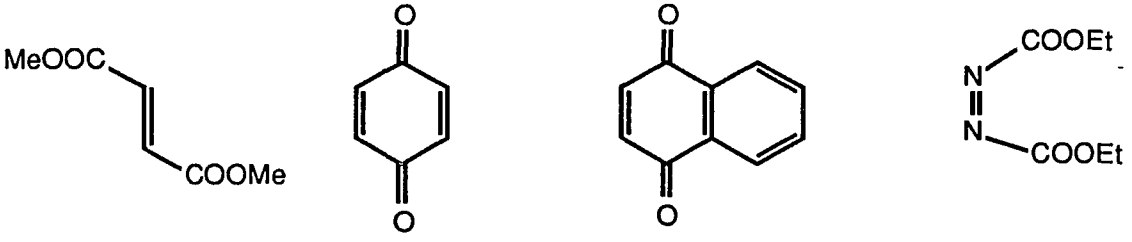
94 **54** *syn* **102** 12 : 88 *anti* **103**

eq18

c.Semicyclic Dienes 4:

Pyranosugar Derived Dienes (4A):

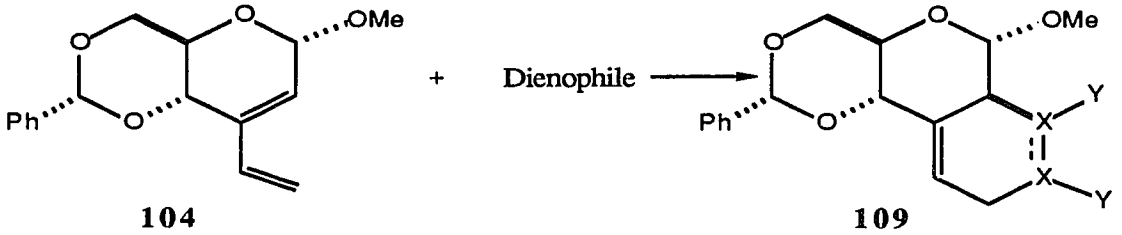
Recently two different groups[41,42] have independently carried out the Diels-Alder reactions of vinyl glycal **104** with different dienophiles such as: maleic anhydride



105 **106** **107** **108**

(**15**), DMAD (**17**), dimethyl fumarate (**105**), benzoquinone (**106**), naphthoquinone (**107**), PTAD (**18**), and DEAD (**108**). The reactions were carried out in different solvents

and in all case, only the *anti* products were isolated (eq 19). Table 5 lists the outcome of



104 **109**

a X = CH, Y = COOCO
b X = C, Y = COOMe
c X = CH, Y = COOMe
d X = CH, Y = COCH=CHCO
e X = CH, Y = COC_6H_4CO
f X = N, Y = CONPhCO
g X = N, Y = COOEt

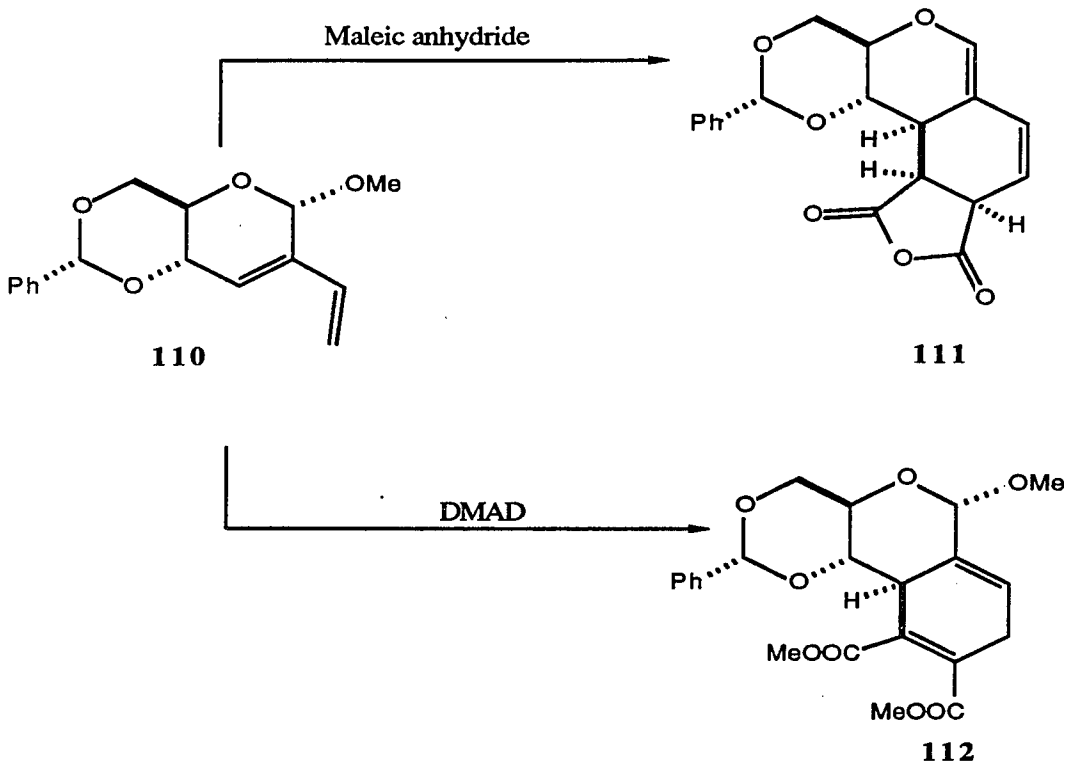
eq 19

those reactions. The reaction of **104** with dimethyl fumarate (**105**) (entry 3) gave an additional compound which was identified as a regioisomer. All the products were proved to be *endo* products except for one case (entry 5) , where the *exo* isomer was formed as a minor product (9%).

Table 5. Diels-Alder Adducts Obtained from the Vinyl glycal (**104**) with different Dienophiles.

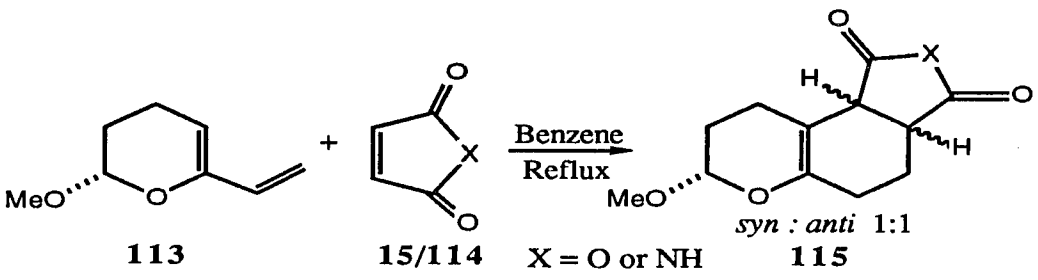
Entry	Dienophile	Solvent	*anti* Adduct	Ref.
1	**15**	CH_3CN	**109a**	41, 42
2	**17**	CH_3CN	**109b**	41, 42
3	**105**	Toluene	**109c**	41
4	**106**	Toluene	**109d**	41
5	**107**	Toluene	**109e**	41
6	**18**	CH_2Cl_2	**109f**	41
7	**108**	CH_3CN	**109g**	41

The reaction of the regioisomeric vinyl glycal **110** also furnished the *anti* adduct as the sole product. With maleic anhydride the *anti- endo* adduct **111** was formed and the *anti* adduct **112** was obtained with DMAD (scheme 16)[42].



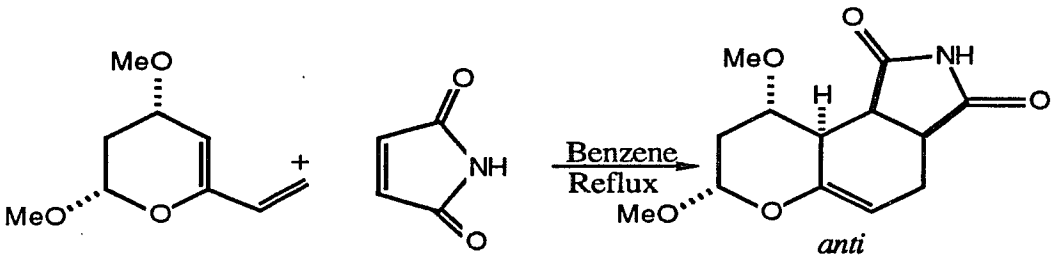
Scheme 16

Giuliano's work on the Diels-Alder reactions of the dieno-pyranosides shows that the allylic hetero atom plays a crucial role in the stereocontrol [40].



eq 20

He has shown that when the diene **113** was used there was virtually no facial selection observed either with the maleic anhydride (**15**) or maleimide (**114**) and a mixture of products (**115**) was obtained in which the double bond had migrated (eq 20). But the dieno-pyranoside **116**, possessing the allylic hetero atom gave *anti* product exclusively on reaction with maleimide (**114**) in refluxing benzene (eq 21) [40].

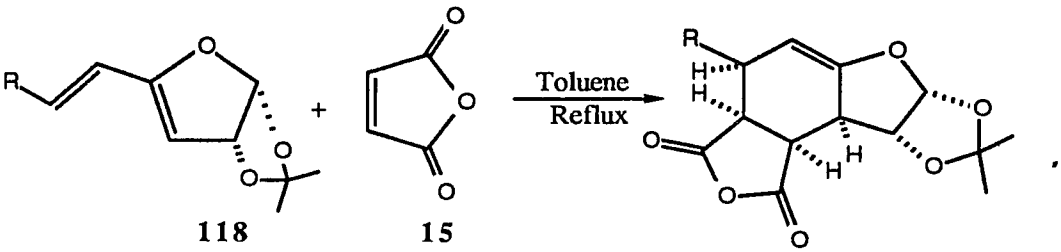


116 **114** **117**

eq 21

Furano Sugar Derived Dienes (4B):

The reactions of different dieno-furanosides (**118 a-c**) with maleic anhydride (**15**) has been reported by Fraser-Reid *et al* and in all the cases, *endo-anti* products (**119 a-c**) was isolated exclusively in refluxing toluene (eq 22) [39].



118
a R = H
b R = CH_2OH
c R = $CH_2OTBDMS$

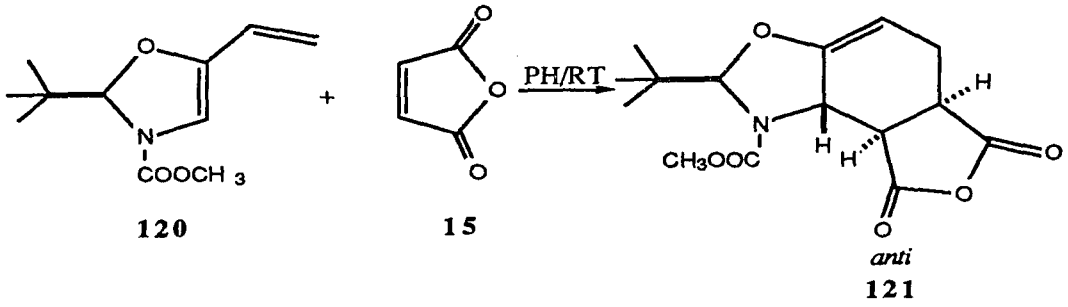
15

119
a R = H
b R = CH_2OH
c R = $CH_2OTBDMS$

eq 22

Finally, Seebach's work on the optically active t-butylhydrooxazole derived diene **120** also

shows the exclusive formation of an endo adduct (**121**), which was produced by an attack of the dienophile (maleic anhydride) on a face opposite to the t-butyl group (eq 23) [93].



120 **15** *anti* **121**

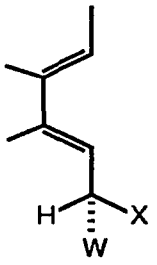
eq 23

IV. Discussion:

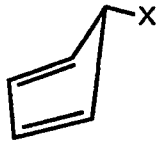
A. Summary of the Experimental Results:

The different sets of experimental results have provided suitable background to evaluate the factors responsible for the stereodifferentiation exerted by the allylic substituents. These results also provided a fertile ground for a complete discussion of the theoretical arguments put forward by different groups to rationalize the observed π facial discrimination. The experimental results can be summarized as follows:

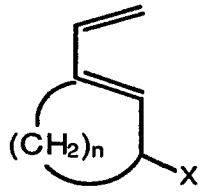
1. The reactions of the acyclic diene of type **1** bearing an electronegative heteroatom (X = O, N) exhibit a consistent *like* facial preference with the dienophiles such as: maleic anhydride (**15**), N-phenylmaleimide (**16**) and acrolein (**51**). The *like* preference increases upon blocking the allylic free hydroxy group on the diene, and it increases in the order OH> OMe> OTMS>OTBDMS. No remarkable solvent effect was observed by changing to a more polar solvent like DMF. On the contrary, dramatic enhancement in *like* preference was noted for the 2-substituted dienes.



1



2



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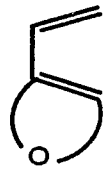


4

A substituted pyranose
B substituted furanose

2. The π facial preference was reversed (i.e.*unlike*) by using the dienophiles such as: DMAD (**17**), methyl propiolate (**60**), tetracyanoethylene (**54**) and 4-phenyl-1,2,4-triazolin-3, 5-dione (**18**) with the chiral allylic diene (**1**, X = O, N).

3. The dienes bearing electropositive groups (**1**, X = Si) at the allylic position showed opposite results to that of the allylic dienes having electronegative substituents (**1**, X = O,

N). The π facial preference is also dienophile dependent . For the dienophiles like NPM, the *unlike* preference was observed where as the uses of DMAD showed a dramatic turn around to the *like* preference.

4. For the semicyclic dienes of the type **3** or **4**, the *anti* (*unlike*) selectivity was observed predominantly in most of the cases and the dominance of *anti* selectivity was independent of the nature of the dienophiles. The semicyclic diene alcohols (**3**, n = 1 or 2) showed weak *syn* selectivity in non polar solvents and they showed a reversal in the diastereoselectivity by changing to more polar solvents. The *anti* selectivity was also improved significantly for the protected dienols. In the case of the tertiary dienes, the dienophile comes from the face opposite to the alkoxy function and *syn* to the the methyl group (we have used the term *anti* for this compound). In the same series, *syn* selectivity was observed in benzene predominantly for the hydroxy diene and there was also a remarkable solvent effect (predominant *syn* goes to weakly *anti* in DMF). The sugar derived dienes (**4 A & B**) also showed strong preference for *anti* facial attack and this preference was independent of the nature of the dienophile.

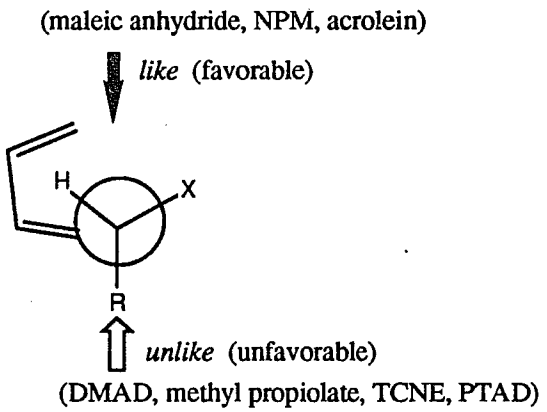
Acyclic Dienes:

a. Failure of the Theories:

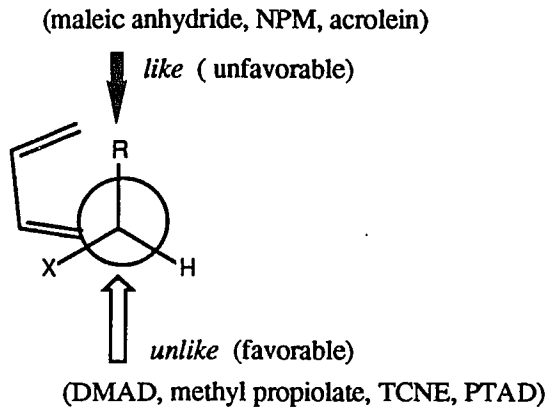
The implication from the result mentioned above is that a single stereochemical control element is not operating uniformly for both classes of dienes. The π facial discrimination for the acyclic dienes is a function of the nature of the dienophile whereas the semicyclic dienes show *anti* selectivity predominantly without showing any dependency on the dienophile.

Now, let us concentrate on the π facial preferences of the acyclic dienes (**1**) and see whether the observed experimental results can be explained by any of the rules proposed by different groups (chapter 2). As we have mentioned, Franck's selection rule [26] can explaine the *like* selectivity which is observed in the reaction of the acyclic dienes with the dienophiles such as: maleic anhydride (**15**), N-phenylmaleimide (**16**) and acrolein (**51**) but

it fails to explain the observed diastereoselectivity in DMAD (**17**), methyl propiolate (**60**), 4-phenyl-1,2,4- triazolin-3,5-dione (**18**) (see rotamer **A**).



Franck's Rotamer (**A**)

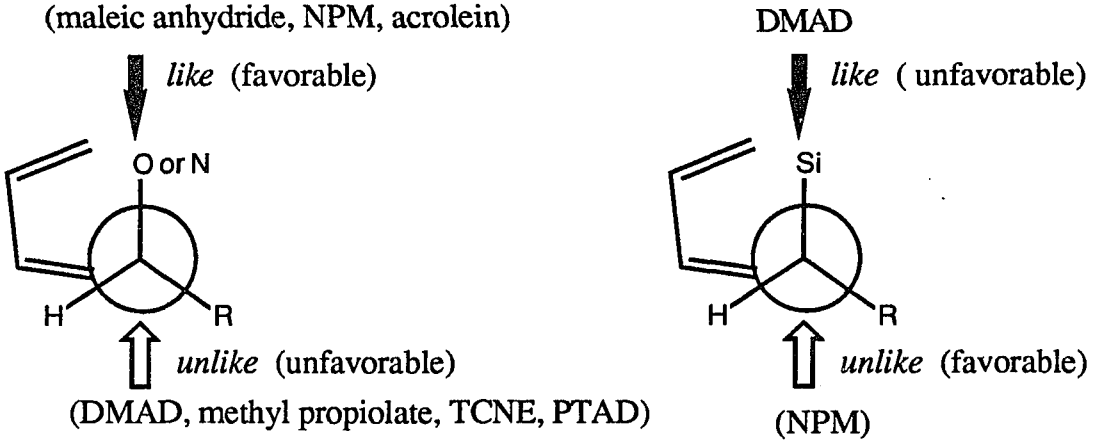


Houk's Rotamer (**B**)

Our interpretation of Houk's theory[72] is that it would uniformly predict *unlike* attack. Houk's rotamer, thus directs a opposite facial attack to Franck's rotamer (see rotamer **A** and **B**) and the observed *unlike* preference in DMAD (**17**), methyl propiolate (**60**), 4-phenyl-1,2,4- triazolin-3,5-dione (**18**) can be predicted by this theory. The *like* preference observed in the case of maleic anhydride (**15**), N-phenylmaleimide (**16**) and acrolein (**51**) can not be explained by this theory.

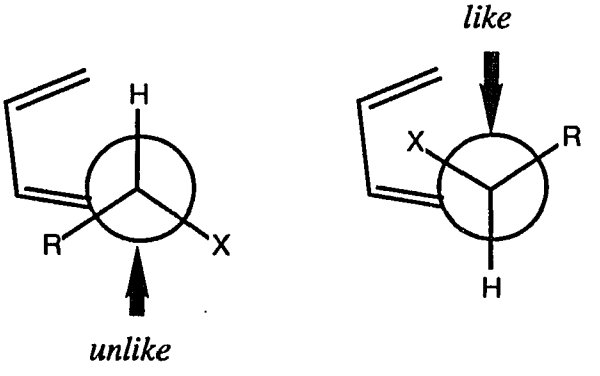
Hehre's theory[74] is based on a different concept and it uniformly predicts *like* (*syn*) selectivity irrespective of the nature of the allylic diene (acyclic or cyclic i.e. 1-4) if the hetero atom is electronegative and it predicts the *unlike* (*like*) facial attack, if the nature of the hetero atom becomes electropositive. This theory also explains the π facial preferences in the case of maleic anhydride (**15**), N-phenylmaleimide (**16**) and acrolein (**51**). But it fails to explain the observed *unlike* selectivity in the case of DMAD (**17**), methyl propiolate (**60**), 4-phenyl-1,2,4- triazolin-3,5-dione (**18**) and tetracyano ethylene (**54**) (see rotamer **C**). Though Hehre's prediction regarding the opposite facial preference (*unlike*) for the silylated dienes (i.e. bearing Si as the electropositive hetero atom) comes out to be

true when NPM was used as the dienophile, the same facial preference was not observed by changing the dienophile to DMAD (the preferred facial attack was *like*) [86].



Hehre's Rotamer C

Cieplak's theory[62,63] also can not explain the observed diastereoselectivity which is a function of the nature of the dienophile. This theory uniformly predicts similar facial preference for both, the allylic diene and the allylic dienophile. By considering the fact that the maximum electron donation from the electron rich CH single bond might stabilize the transition state, either rotamer D or E should be the reactive rotamer for both i.e. the allylic diene and the dienophile. The rotamer D will direct a *like* facial attack and rotamer E would direct a *unlike* facial attack. The observed experimental results are contrary to the this prediction as the allylic diene and dienophile direct opposite facial attack (at least in some cases).



Rotamer D Rotamer E

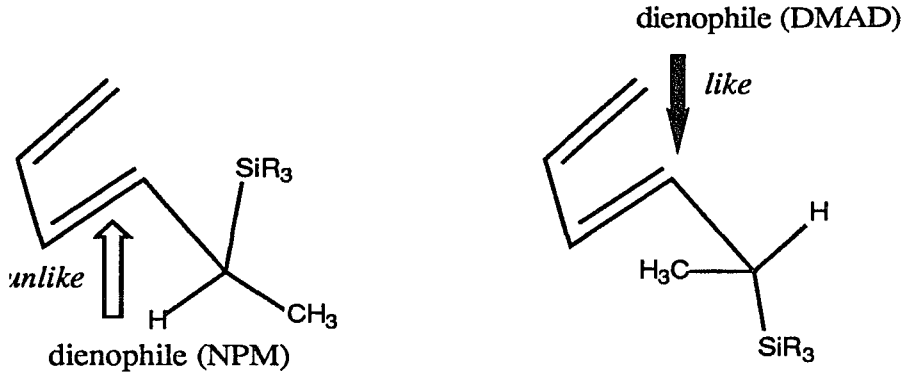
One important conclusion we can draw from the above discussion is that none of the theories put forward by different groups are adequate to explain the observed face selectivity exerted by allylic substituents. Hehre's theory in particular needs to be addressed here as we feel that the diastereochemical results do not demand the presence of an electrostatic effect as the controlling factor, due to the following reasons.

1. Hehre's theory does not explain the *unlike* selectivity observed for DMAD (**17**), methyl propiolate (**60**), 4-phenyl-1,2,4- triazolin-3,5-dione (**18**) and tetracyano ethylene (**54**).

2. Improved *like* selectivity has been observed in a series by going from the free alcoholic dienes to the protected dienes. The theory also does not explain this enhancement in *like* selectivity. It would rather be expected on the basis of Hehre's model that the facial preference should decrease by increasing the steric bulk around the hetero atom as the dienophile approaches *syn* to the hetero group.

3. Fleming's work on dienyl silanes(table 1, entry 16-19, 27) also clearly showed the failure of Hehre's theory as the π facial preference changed upon changing the dienophile (*like* for NPM and *unlike* for DMAD). Fleming was trying to verify our result (i.e. the face selectivity as a function of the dienophile) with dienes bearing silicon as the hetero atom and contrary to his expectation, the face selectivity turned round from *unlike* to *like* by changing the dienophile from NPM to DMAD. He thinks[86] that these results have some analogy to the allylsilane chemistry where nitrile oxide[94] and OsO_4[95] are anomalous among electrophiles in giving attack on the opposite surface of the double bond from the usual reaction. On the basis of that analogy he has tried to explain the observed results by considering two different reactive (see rotamer H and I) conformations which direct opposite faces and their equilibrium population depends on the nature of the dienophile. In both of the rotamers, the C-Si bond remains in conjugation with the π system in order to raise the HOMO of the diene. The reactive rotamer for NPM is the rotamer **H** where the Me group remains outside on steric ground. The preferential attack of the dienophile takes place from a face *anti* to the Si atom and the resulting product was *unlike* . On the other hand,

for the acetylenic dienophiles, the rotamer **I** becomes more populated in the transition state in order to avoid the steric repulsion between the methyl group of the diene and the carbomethoxy group of the approaching dienophile thus producing the *like* product.



H **I**

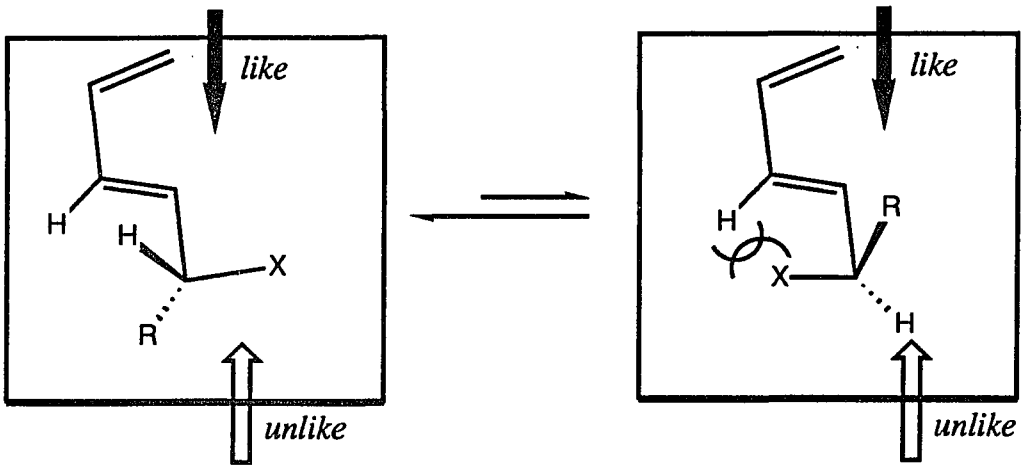
These arguments also do not involve any electrostatic nature of the hetero atom rather they consider the relative population of the reactive rotamer in the transition state on stereoelectronic grounds. Hehre had predicted the dependency of the stereoselectivity on the nature of the hetero atom. Though, his prediction was correct at least in the case of NPM as the dienophile with the silyl dienes (i.e. the usual like selectivity was changed to unlike), the results with DMAD (*like*) disproved his electrostatic concept.

4. In the case of conformationally locked dienes (cyclic and semicyclic), the observed experimental results are opposite to Hehre's prediction and this will be discussed latter.

b. Rationalization of the Experimental Results:

From the above discussion it is apparent that the factor controlling the small energy difference between the *like* and *unlike* transition states are not necessarily due to electrostatic forces. Recent calculations done at Hunter, give some important insight to the observed face selectivity induced by allylic substituents in Diels -Alder reactions[73]. As mentioned earlier, in the Franck-Dannenberg rotamer **A"** or **B"** , the hetero allylic

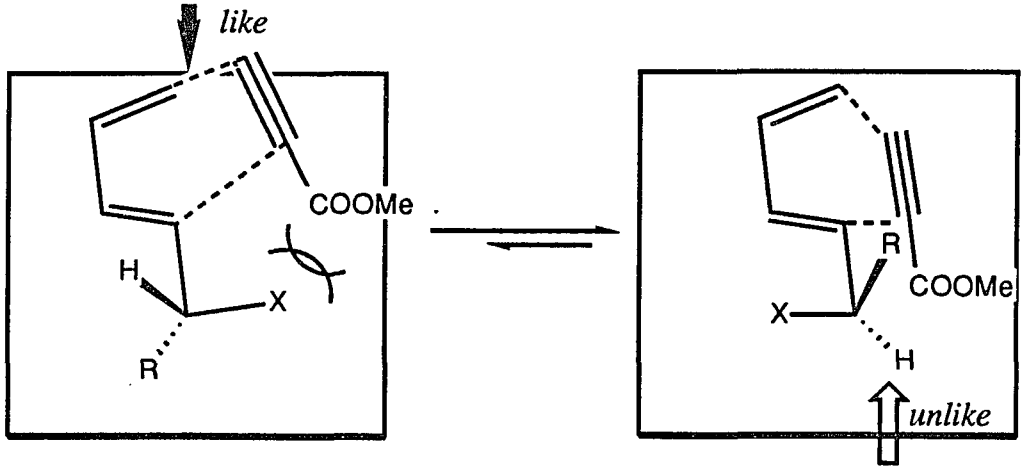
substituent prefers to remain *coplanar* with the diene, with the *anti-coplanar* form prefered to the *syn-coplanar* rotamer. The reason for coplanarity of the hetero atom with the dienilic plane is not clearly understood. However, both the rotamers are the distorted form of Franck's original rotamer (**A**) and Houk's rotamer (**B**). This calculation also showed that the ground state rotamers are not necessarily the transition state rotamers. The preferential approach by the dienophile was that where minimum steric repulsion between the diene and dienophile existed. In the *anti-coplanar* form the *like* face is favored and in the *syn-coplanar* form the unlike attack is preferred as the dienophile approaches from the side facing the hydrogen rather than the bulkier methyl group. The major factor for the stereo differentiation depends on the relative population of the *anti-coplanar* (**A"**) rotamer and the syn co-planar rotamer (**B"**) in the transition state (figure 10) and we postulate that *the important interaction responsible for stereocontrol remains in the diene rotamer itself and is due to a consequence of the interplay of the nonbonding interactions between the* C_2 *hydrogen of the diene and the hetero atom.* Our speculation regarding the steric repulsion between the hydrogen atom and the hetero atom successfully explain the *like* selectivity observed in the case of maleic anhydride (**15**), N-phenylmaleimide (**16**) and acrolein (**51**). Support for our assumption also comes from the observed increment in like selectivity by going from a free alcohol diene to the protected dienes in a particular series. Gathering the steric bulk around the hetero atom increases the nonbonding interaction and the relative population of the rotamer **A"** is further increased in the transition state which results an improved like selectivity. McDougal's experiments have convincingly shown that by increasing the steric bulk at the C_2 of a diene there is a tremendous improvement in *like* selectivity. The observed *unlike* selectivity for the acetylenic dienophiles can be explained by considering the rotamer **B"** as the reactive conformer in the transition state.



anti-coplanar (**A"**) *syn-coplanar* (**B"**)

Figure 10: The relative population of *anti-coplanar* (**A"**) and *syn-coplanar* (**B"**) rotamers in the transition state.

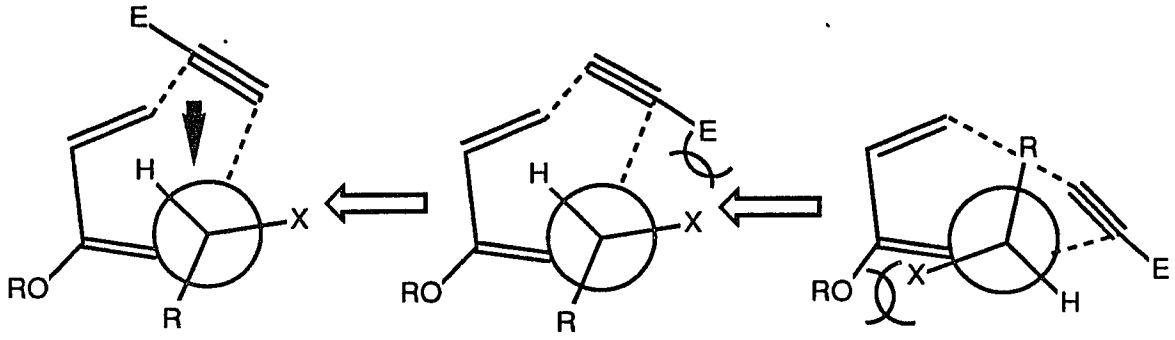
As Kozikowski suggested[34,96], the approach of the linear acetylenic dienophile to the rotamer **A"** would produce repulsions between the outside *coplanar* hetero atom and the activating group of the dienophile (COOMe), thus normally less favored *syn-coplanar* conformer **B"** would react, giving products of *unlike* attack (figure 11).



anti-coplanar (**A"**) *syn-coplanar* (**B"**)

Figure 11: The relative population of *anti-coplanar* (**A"**) and *syn-coplanar* (**B"**) rotamers in the transition state for the acetylenic dienophiles.

A prediction developing from this rationalization is that the reactivity of the McDougal-Reitz dienes, which can not readily achieve an *syn-coplanar* conformation, would greatly diminish towards DMAD (17).



like attack
(anti-coplanar) *(anti-coplanar)* *(syn-coplanar)*

Figure 12: The reactive rotamers for the McDougal-Reitz dienes favoring *like* attack for the acetylenic dienophiles in the transition state.

But a propiolate dienophile, because its opposite regiochemistry in a cycloaddition with a 2-alkoxy diene would not force the dienophile ester function against the *anti co-planar* hetero atom of McDougal-Reitz diene, might react and give *like* selectivity (figure 12). The *unlike* selectivity is also observed in the case of TCNE and PTAD (18). Vogel has reported reversal of face selectivity with the cycloaddition of deuterium-labeled 2,3-dimethylidenebicyclo[2.2.1] heptane with TCNE and PTAD on one hand and maleic anhydride, DMAD, and bezoquinone on the other[97]. Their rationalization of the data includes stereoelectronic factors, differential steric repulsive effects, and a possible change in mechanism. Their results are similar and not exactly parallel to ours; and theirs is a rigid, bicyclic system. Ginsburg, in his classic studies[98] with propellane dienes, did observe a reversal in topicity between N-phenylmaleimide and N-phenyltriazolinedione. However, in his rationale, the PTAD had a bonding interaction with the allylic group. Such a bonding interaction in our system would have favored a *like* approach, contrary to our observation. We had speculated that the PTAD and TCNE cases are not truly Diels-Alder reactions[27]. Our speculation was confirmed at least in the case of PTAD as recent work of Foote[99] and Clennan[100] shows that PTAD cycloadditions with activated dienes do, in fact, proceed via non Diels-Alder multi step pathways.

Semiyclic Dienes:

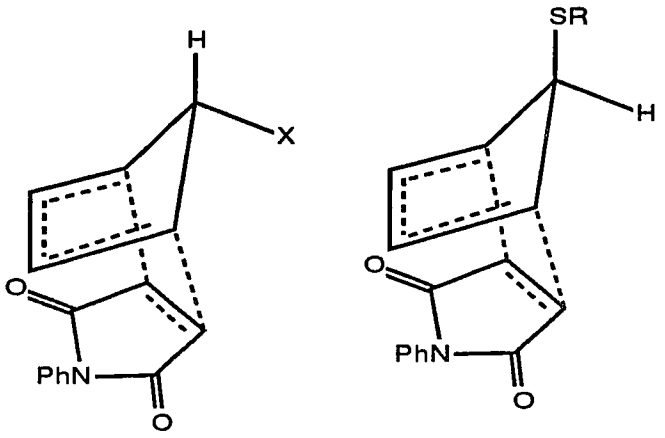
a. Failure of the Theories:

In the semicyclic case, *anti* (*unlike*) selectivity is observed except in a few cases where the semicyclic diene alcohols give weak to predominant *syn* selectivity. In recent work, Hehre and Overman have tried to modify the original version of Hehre's theory and have argued that there exists a repulsive steric interaction in the *syn* transition state as well as the repulsive electrostatic interactions between the proximal oxygen of the imide dienophile (when NPM was used as the dienophile) and the allylic hetero atom (oxygen) of the diene. Their argument is based on the fact that although the *anti* directing ability of OMe group is stronger than that of the methyl group in cycloaddition, the effect can not be explained simply by considering the steric size. They use the conventional steric measurement (*A* value) which shows that Me is bigger than the OMe group. They argue that in the case of tetracyanoethylene as the dienophile, the electrostatic effects are less important as the nitrile substituents are not directed to the allylic substituents. They have further tried to rationalize the results obtained from the substituted cyclopentadienes and say that in those cases *syn* selectivity will be observed predominantly, as the *endo* transition state for cycloaddition state of these dienes will be free of destabilizing steric and electrostatic interaction between the dienophile and the *syn* -5 substituent. The *syn* selectivity observed in their case (for the free alcohol) has been attributed to the intermolecular hydrogen bonding between the carbonyl group of the dienophile and the hydroxy group of the diene.

The new electrostatic concept put forward by Hehre and Overman,[37] as well as their idea regarding the steric size of different substituents in intermolecular reactions has several drawbacks.

1. In the case of the cyclic dienes as they say, the *endo* transition state should be free of destabilizing steric and electrostatic interactions between the dienophile and the *syn* 5-substituent, and the *syn* product should be the major product. Recent work reported by Fallis[48] shows that when sulfur was employed as the hetero atom the usual *syn* selectivity

was not observed and the *anti* compound became the major product. This result is evidence against the electrostatic theory (figure 13).

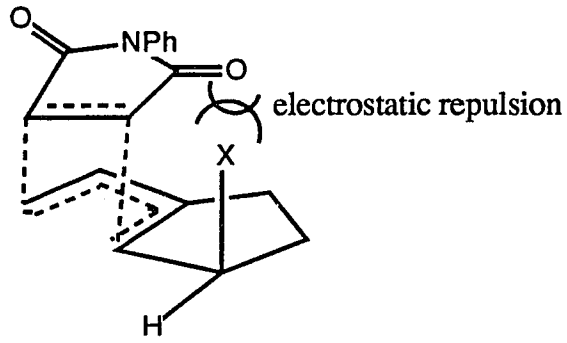


syn attack
Hehre's prediction

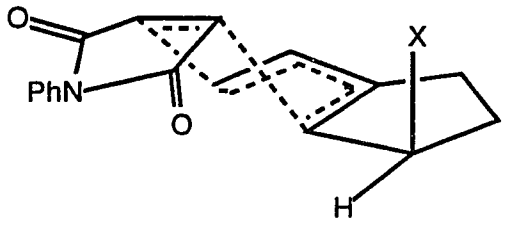
anti attack
Experimental result

Figure 13: The *syn* and *anti* transition states of the Diels-Alder reaction between the substituted cyclopentadienes and NPM.

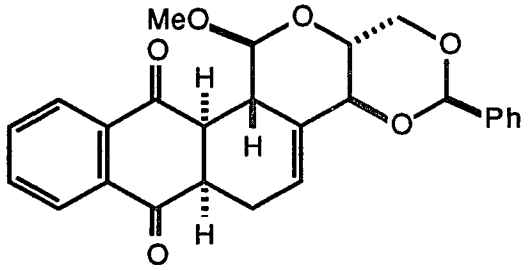
2. In the semicyclic case, they have postulated a transition state in which electrostatic repulsion between the hetero atom and the imide carbonyl oxygen plays an important role making the alkoxy group a better *anti* directing group. This would imply that in an *exo* transition state, there should be no electrostatic repulsion between the carbonyl oxygen and the hetero atom which would mean that the *exo* transition state should be more *syn* selective. Experimentally, it is hard to find any compound resulting from an *exo* transition state as it is a higher energy process than the corresponding *endo* transition state. However recent work on sugar derived dienes shows that when naphthoquinone was used as the dienophile the *exo* compound was isolated as a minor compound. The relative stereochemistry in that compound was reported to be *anti* and this result goes against the electrostatic theory (figure 14).



(**a**)*syn-endo* transition state



(**b**)*syn-exo* transition state



(**c**)*anti-exo*

Figure 14: (**a**) *syn-endo* (**b**) *syn-exo* transition states of the Diels-Alder reaction of the substituted cyclopentadienes (**c**) the observed *anti-exo* product in glycal cycloaddition.

3. They have used *A* values[101] to determine the relative size of the allylic substituents on the diene and on that basis it has been argued that the steric size of the Me group is bigger than the methoxy group[101,102]. Steric effects are popularly used by organic chemists though they are hard to evaluate quantitatively. Prof. Fraser-Reid once remarked[103]: *Just as patriotism is the last refuge of a scoundrel, steric hindrance might very well be the last resort of an organic chemist.* In our opinion the currently popular use of *A* values[37,104] which are a measure of the intramolecular size of a group interacting with a hydrogen across a chair cyclohexane ring, is inappropriate for evaluating the volume occupied by a group in blocking the approach of a dienophile in the transition state. Apart from the *A* values, there are also several parameters defining the steric size of the groups which are based on spectroscopic data, chemical methods and conformational processes. An excellent review on the subject has been provided by Vogtle and Forster, which has also discussed

the major limitations of different steric parameters including *A* values[105]. By studying sterically hindered ring inversions in bridged arenes, they have tried to evaluate the spatial requirements of different groups and have expressed them in terms of *n* values, where *n* = number of CH_2 units required for a bridge chain to adopt itself to substituents of different shapes on the aromatic ring. In our opinion, the Vogtle-Forster *n* value is a better descriptor of the volume of a group for the case of semicyclic dienes .

Table 6: Comparison of *A* values with *n* Values

Entry	Group	*A* value (in kcal.)	*n* value
1	H	0	<3
2	OH	0.5	6
3	OMe	0.6	10
4	Me	1.6	8

4. If an electrostatic effect were the major force in directing the *anti* facial attack, then the reaction should have shown a solvent effect in dipolar solvents like DMF or MeCN, since the dipolar solvent would have shielded the local electrostatic effect and more *syn* product would have been observed. But no solvent effect is observed in our case, except with dienes having a free alcoholic group, where, we guess, the *anti* preference is due to the increase in steric bulk of the OH group when it hydrogen bonds to the solvent. On those above grounds, we feel that the electrostatic might not be the cause for the π facial discrimination .

Recently, Seebach has put forward a new concept [106] on the prediction for the diastereofacial preference of a trigonal center by looking at the small degree of

pyramidalization in the ground state structure of the substrate. He has examined the ground state geometry of his dioxinone (figure 15) and of other compounds of similar type, using results of x-ray and computational analysis. He found that the trigonal center 1, 2, 3 and both of the oxygen centers are almost *co-planar* , that the acetal center is pyramidalized and that the trigonal centers (i.e carbons 1, 2 and 3) are not exactly planar, but are pyramidalized to a smaller extent in the direction of the acetal center (the deviation from planarity are in the range of 0.9-5.3°).

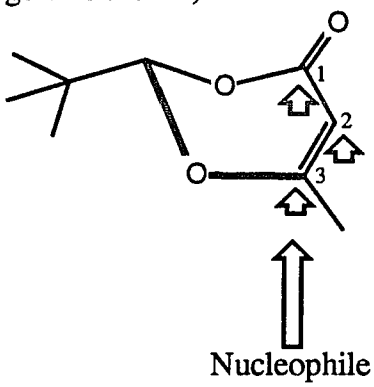


Figure 15. The small degree of pyramidalization in substituted dioxinone

The dioxinone undergoes Michael addition predominantly from the side to which the small pyramidalization of the trigonal centers has taken place. Though, this is a mere correlation and does not provide any reasoning for the diastereoselectivity, Seebach was quite optimistic for a general prediction of the face selectivity from the ground state structure of the substrate and put forward a statement : *the steric course of an attack on a trigonal center can be predicted from the direction of its pyramidalization.* In order to verify the generalization of this statement we tried to look for any such pyramidalization of the allylic substrate. Unfortunately, in our system, the starting dienes are liquids and the exact preferred geometry can not be determined. However, computational methods gave us information about the ground state. AM1 calculation on the diene **80b** showed no such pyramidalization at the trigonal atoms and they are almost coplanar (figure 16). Thus, the pyramidalization does not provide any conclusive prediction in our case.

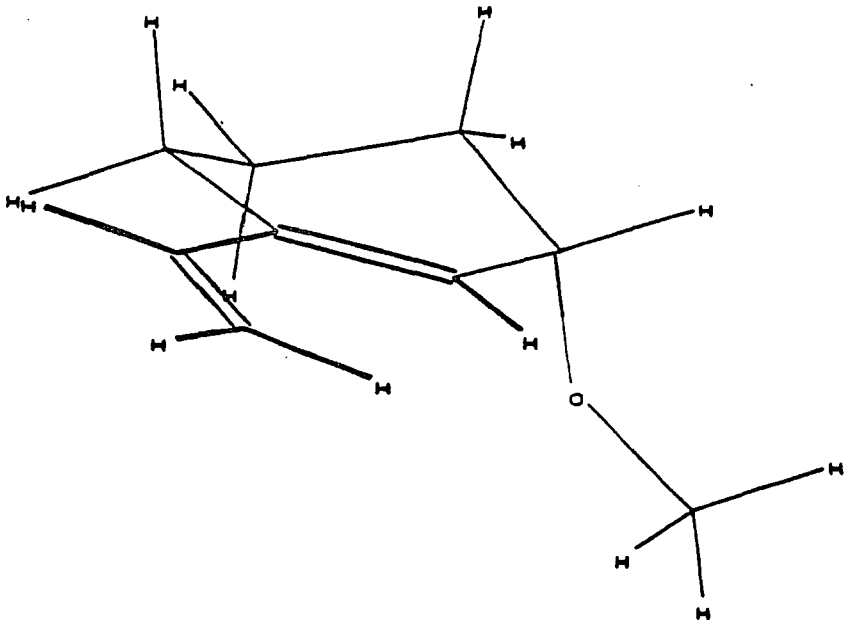
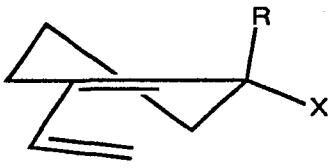


Figure 16: The ground state conformation of the 3-methoxy -1-vinyl cyclohexene (**80b**) optimized by AM1 calculation .

c. Rationalization of the Experimental Results:

Our rationalization of the face selectivity in the conformationally locked dienes of the type **3** and **4** is based solely on steric arguments. We feel that the steric and electronic components of the allylic substituents are well separated for the semicyclic dienes and the steric factor independently controls the face selectivity, as the electronic contribution becomes negligible due to the absence of the free rotation of the allylic center. For example in our experiment, the conformationally locked dienes, unlike the acyclic dienes, can not adopt a *syn-coplanar* orientation of the hetero atom. We postulate that there are two principal reactive

conformations of dienes, **J** where the oxygen is *pseudo-equatorial* to the cyclohexene and **K** where the oxygen is *pseudo-axial*.. Using molecular orbital results for acyclic dienes[15] we postulate that the conformer **K** will have a higher energy of activation for the Diels-Alder transition-state because of unfavorable interactions of the C-O function and the developing bonds in the transition state.



J

K

Thus for dienes with R = H, **J** will be the more reactive conformer. When R = H, X = OH, in a non- hydrogen -bonding solvent, the *syn* face is slightly favored (1.7 : 1) . When a hydrogen-bonding solvent is used, we postulate that the OH becomes a bulkier group and the *anti* face is preferred (4 : 1). If electrostatic repulsions were the force that favored *anti* product then the use of polar solvents should reduce, not increase, the yield of *anti* material, just opposite to our observation.When X = OMe, the face syn to the OMe becomes less reactive because the OMe is a large group towards external approach. As we have already mentioned, we believe a parameter such as the Vogtle-Forster *n* value[105] (see table 6) is a better qualitative descriptor of the volume of a group for our purposes. Recently, Terashima *et al* have also put forward arguments showing that the trimethylsilyloxy group is bigger than the methyl group (*A* value would predict that methyl is bigger than the alkoxy) and this assumption has been used to rationalize the face selectivity in a Diels-Alder reaction which was carried out in connection with the synthesis of a nogalamycin group of antibiotics[107].

In order to obtain further calibration on the diastereoselectivity as well as the comparative steric sizes of different groups (i.e. alkoxy versus methyl), we have designed a set of

allylic dienes where both the faces are blocked by methyl and alkoxy groups towards the approach of the dienophile. In the diene J, when R = Me, X = OH, hydrogen -bonding in DMF increases the size of the OH group so that the syn and anti reactivity are about equal, e. g. the solvated OH group is approximately the size of a Me. When R = Me and X = OMe, the reaction slows dramatically and must be run at 6 Kbar to obtain good yields. We interpret this by arguing that conformer **J**, with the alkoxy group in the more favored electronic orientation, has the *anti* face blocked by CH_3 and syn face blocked by the OMe.The alternate conformer **K** has the *syn* face blocked by the more serious steric effect, but because the OMe is *pseudo-axial*, the *anti-face* reactivity is slowed by adverse electronic effects.

In summarizing our result, we can say that in semicyclic cases, the steric effect is the predominant effect, and irrespective of the dienophile, the *anti* addition should be the major product. Other results including Hehre and Overman's results and the sugar work can be explained by using our reasoning.

B. Conclusion

In conclusion, our rationalization of the π facial discrimination exerted by a hetero atom at the allylic position of a diene is unique and it can be successfully applied in a predictive manner to design organic syntheses. We have postulated two reactive rotamers (**A"** and **B"**), responsible for the diastereoselectivity in acyclic dienes, one being more stable than the other on steric grounds. The major stereodiffentiation comes from the relative difference in energy of activation of the two reactive rotamers in the transition state. For the dienophiles like NPM, maleic anhydride and acrolein , the diene rotamer **A"** reacts through a lower energy in the transition state and the *like* attack becomes more favorable. On the other hand, for the acetylenic dienophiles, the reactive rotamer **B"** reacts faster and stereodiscrimination and the *unlike* attack is preferred.

With the semicyclic dienes, where the allylic substituents can not adopt a preferable orientation, face selectivity is controlled by steric factors alone. We have also postulated

that the A value, a parameter which is popularly used to define the steric size of a group is not correct. We have suggested that a parameter such as the Vogtle-Forster n value is a better qualitative descriptor of the volume of a group for our purposes. Finally, the face selectivity exerted by an allylic substituents in a diene depends on the balance of several factors in the transition state. Therefore a single stereochemical feature of the diene can not be expected to control the face selectivity.

V. Experimental

General Experimental

NMR spectra were recorded on GE QE 300, JEOL FX 400 instruments with tetramethylsilane as the internal standard and $CDCl_3$ as the solvent. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. The high-resolution mass spectra were obtained by the mass spectral facilities at Rockefeller University, New York and the Pennsylvania State University, University Park, PA. High pressure experiments were performed with a LECO TEM-PRES Pressure Generator (Model PG-100 HPC). Melting points were uncorrected and were determined on a Fisher-John melting point apparatus. Thin-layer chromatograms were done on precoated TLC sheets of silica gel 60 F_{254} (E. Merck) and potassium permanganate spray and/or short- and long-wave ultraviolet light was used to visualize the spots. PLC plates were prepared by using Kieselgel 60 PF_{254} (E. Merck), and chromatotron (radial chromatography) plates were prepared by using Kieselgel 60 PF254 gipshaltig (E. Merck). Flash chromatography was performed with silica gel (230-400 mesh) purchased from Aldrich Chemical co. Dry tetrahydrofuran (THF) was obtained by distillation, under nitrogen, from sodium-benzophenone ketyl. Other solvents were purified and dried by using standard procedures.

General Procedure for Determining the Diastereomeric Ratios of the Diels-Alder Adducts:

The diastereomeric ratios for the Diels-Alder adducts were determined from the ^1H NMR examination of the crude reaction mixtures. The integration or the height of the diastereomeric peaks were used to calculate the ratio. The ^1H NMR spectra of the crude reaction mixture are reported in the appendix. The peaks used to determine the diastereomeric ratios are indicated by arrows.

Preparation of 3-hydroxy -1,4 hexadiene (21) [76]:

To a solution of vinylmagnesium bromide (**20**, 44 mL of a 1M solution in THF, 44 mmol) in dry THF (50 mL) was added dropwise (syringe pump) over a period of 20 minutes at 0°C a solution of freshly distilled crotonaldehyde (**19**, 2.45 g, 35 mmol in 40 mL of dry THF). The cooling bath was removed and the reaction mixture was stirred for 1 h. The reaction mixture was quenched with an aqueous solution of NH_4Cl (50 mL) at 0°C . The mixture was brought to room temperature and extracted with ether (3 x 50 mL). The combined organic extracts were washed with saturated brine solution (50 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent gave an oil which was distilled under vacuum to furnish 3-hydroxy -1,4 hexadiene (**21**) as a colorless liquid (2.15 g, 62.7%), bp 45-47° at 20 mm of Hg, lit[76] bp 110-130 (bath) 15 Torr , ^1H NMR (300 MHz, $CDCl_3$) 5.87 (m, 1H), 5.68 (m, 1H), 5.49 (m, 1H), 5.23 (d, 1H , J = 17 .27Hz), 5.1 (d, 1H, J = 10.33 Hz), 4.55 (br t, 1H), 2.67 (br s ,1H), 1.69 (dd, 3H, J = 6.48, 0.89 Hz); IR ($CHCl_3$) 3600, 2910, 2850, 960cm^{-1}.

Rearrangement of 3-hydroxy-1,4-hexadiene (21) to 2-hydroxy-3, 5-hexadiene (12a)[77]: A mixture of 3-hydroxy-1,4-hexadiene (**21**, 2g, 20.4 mmol) and dil. hydrochloric acid (0.1N, 15mL) were shaken vigorously for five minutes in a stoppered glass bottle. Anhydrous K_2CO_3 (345 mg) was added at once and the resulting mixture was shaken vigorously for 1 minutes. The solution was saturated with salt (NaCl) and extracted from ether (3 x 30 mL). The combined extract was dried over $MgSO_4$ and evaporation of the solvent furnished 2-hydroxy-3,5-hexadiene (**12a**) as a colorless liquid which was further purified by vacuum distillation, b.p. 50-54° at 20 mm of Hg, lit [77] 75-76° at 30 mm of Hg (1.4g, 70%) . ^1H NMR (300 Mz) 6.39-6.21 (m, 2H), 5.79 (dd, 1H, J = 15, 6.31 Hz), 5.26 (app d, 1H , J = 17.31 Hz), 5.14 (app d, 1H, J = 10.54

Hz), 4.4 (m, 1H), 1.33 (d, 3H, J = 6.34 Hz); IR ($CHCl_3$) 3600, 3450, 2970,1610, 1360, 1130, 910 cm^{-1}.

Preparation of 5-((Trimethylsilyl)oxy)-1,3-hexadiene(12b):

BSA (*bis* trimethyl silylacetamide, 1.5 mL, 6 mmol) was added dropwise to neat ice cooled alcohol 2-hydroxy-3,5-hexadiene (**12a**, 501 mg, 5.1 mmol) and after addition, the cooling bath was removed. The mixture was stirred overnight. The silylated product was purified by flash chromatography (petroleum ether : EtOAc 95 : 5). The purified product, 5-((Trimethylsilyl)oxy)-1,3-hexadiene (**12b**) was isolated as a colorless oil (571 mg, 65.8 %). ^1H NMR (300 Mz) 6.37-6.25 (m, 1H), 6.17-6.09 (m, 1H), 5.69 (dd, 1H, J = 15.18, 6.1 Hz), 5.17 (app d, 1H , J = 16.47 Hz), 5.06 (app d, 1H, J = 10.83 Hz), 4.32 (m 1H), 1.23 (d, 3H, J = 6.32 Hz), 0.11 (s, 9H); IR ($CHCl_3$) 2910, 1370, 1250, 910 cm^{-1}.

Preparation of 5-((t-Butyl-dimethylsilyl)oxy)-1,3-hexadiene (12c):

A mixture of the alcohol, 2-hydroxy -3,5-hexadiene (**12a**, 203 mg, 2.07 mmol), DBU (317 mg, 2.08 mmol) and t-butyldimethylsilyl chloride (333 mg, 2.2 mmol) in CH_2Cl_2 (6 mL) [78] was kept at 40° under nitrogen for 18h . The reaction mixture was diluted with CH_2Cl_2 (25 mL), washed three times with water (10 mL each) and finally washed with brine solution (20 mL). After drying with anhydrous $MgSO_4$, excess of solvent was evaporated and the crude 5-((t-butyl-dimethylsilyl)oxy)-1,3-hexadiene (**12c**) was purified by flash chromatography (Pet. ether : EtOAc 9 : 1) giving a colorless oil (279 mg, 63.5%). ^1H NMR (300 MHz, $CDCl_3$) 6.42-6.25 (m, 2H), 5.74 (dd, 1H, J = 15.16, 5.54 Hz), 5.21 (app d, 1H , J = 18 Hz), 5.08 (app d, 1H, J = 10.10 Hz), 4.38 (m, 1H), 1.26 (d, 3H, J = 6.36 Hz), 0.94 (s, 9H), 0.05 (s, 6H).

Preparation of 2-Hydroxy-3, 5-heptadiene (13a) [79]:

To a solution of methylmagnesium bromide (34 mL of a 1.5 M solution in toluene : THF 75 : 25, 51 mmol) in dry THF (100 mL) was added dropwise at 0°C a solution of freshly distilled sorbic aldehyde (**22**, 4g, 41.66 mmol in 40 mL of dry THF). After 1 h, an aqueous solution of NH_4Cl (60 mL) was added slowly. The solution was brought to room temperature and was extracted with diethyl ether (3 x 75 mL). Combined organic extracts were washed with brine (60 mL) and dried over anhydrous $MgSO_4$. Evaporation of solvent gave an oil which was distilled under vacuum to furnish 2-hydroxy-3,5-heptadiene (**13a**) as a colorless liquid (3.97 g, 85.2 %, bp 84°/20 mm of Hg) lit [79] bp : 78° /20 mm of Hg): ^1H NMR (300 MHz, $CDCl_3$) 6.16-5.98 (m, 2H), 5.98-5.5 (m, 2H), 4.35 (overlaping dq, 1H), 2.05 (br s, 1H), 1.74 (d, 3H, J = 5.64Hz), 1.26 (d, 3H, J = 6.36) ; IR ($CHCl_3$) 3600, 2950, 1590, 980 cm^{-1}.

Preparation of 2-((Trimethylsilyl)oxy)-3, 5-heptadiene (13c):

BSA (3.5 mL, 14.15 mmol) was added dropwise to neat ice cooled alcohol 2-hydroxy -3,5-heptadiene (**13a**, 1.21 g, 10.8 mmol) and after addition, the cooling bath was removed. The mixture was stirred overnight. The silylated product was purified by flash chromatography (petroleum ether : EtOAc 95 : 5). The silyl ether , 2-((trimethylsilyl)oxy) -3,5-heptadiene (**13c**) was isolated as a colorless oil (1.69 g, 85 %): ^1H NMR (300 MHz, $CDCl_3$) 6.12-5.97 (m, 2H), 5.72-5.51 (m, 2H), 4.31 (m, 1H), 1.74 (d, 3H, J = 6.43 Hz), 1.22 (d, 3H, J = 6.36 Hz), 0.11 (s, 9H); IR ($CHCl_3$) 2960, 1500, 1250, 910 cm^{-1}.

Diels-Alder Reactions of 2-Hydroxy-3,5-hexadiene (12a) with Maleic anhydride (15):

A mixture of 2-hydroxy -3,5-hexadiene (**12a**, 208 mg, 2.12 mmol) and maleic anhydride (203 mg, 2.07 mmol) in dry benzene (4 mL) was stirred (under nitrogen) at room

temperature for 3 days.The solvent was removed and the product was kept under high vacuum . The diastereomeric ratio was determined from the ^1H NMR (300 MHz) of the crude product and was found to be 2.7:1. The ^1H NMR also showed the presence of a trace of unreacted dienophile. The diastereomeric lactonic acid mixture **25a** and **26a** (initial adducts **23a** and **24a** were unstable) was not separable and was isolated as a white solid (335 mg, 82.5%).

Esterification of Lactonic Acid 25a and 26a:

A portion of the mixture (33.5 mg, 0.17 mmol) was dissolved in Et_2O (10 mL) and to it, a solution of diazomethane in ether (10 mL) was added dropwise till the yellow color persisted. Evaporation of the solvent gave the lactone mixture (**25b** and **26b**) as a crude yellow solid (34.5 mg, yield 96.6%) which also could not be separated by chromatography. Crystallization from water gave the pure lactone **25b** as white needles (12 mg), mp 153°, lit[75] mp 151°.

Lactone 25b: ^1H NMR (300 MHz) 5.96-5.89 (m, 1H, C_5-H), 5.69-5.64 (m, 1H, C_4-H), 4.42 (dq, $J_{Me,3}$ = 6.56Hz, $J_{3,9}$ =1.01 Hz C_3-H), 3.82 (s, 3H, -OCH_3), 3.66(dd,1H, $J_{7,8}$ = 4.08 Hz, $J_{8,9}$ = 7.85 Hz, C_8-H), 2.90 - 2.78 (m, 2H, C_7-H and C_9-H), 2.42 - 2.36 (m, 2H, -CH_2-), 1.48 (d,3H, $J_{Me,3}$ = 6.56 Hz, -CH_3); IR ($CHCl_3$) 1765, 1725 cm^{-1}.

Diels-Alder Reactions of 2-((Trimethylsilyl)oxy)-3,5-hexadiene (12b) with Maleic anhydride (15): A mixture of 2-((trimethylsilyl)oxy)-3,5-hexadiene (**12b**, 190 mg, 1.11 mmol) and maleic anhydride (104 mg, 1.06 mmol) in dry benzene (3 mL) was stirred (under nitrogen) at room temperature for 5 days. The solvent was removed and

the diastereomeric ratio was found to be 4 : 1 . The concentrated reaction mixture was subjected to preparative thin layer chromatography (Pet. ether : EtOAc 4:1) to furnish a white solid which was identified as the mixture of lactones **25a** and **26a** respectively (171.4 mg, 82.5%) from the ^{1}H NMR spectrum. Thus, the initial adducts **23b** and **24b** were unstable to chromatographic separation.

Diels-Alder Reactions of 2-((t-Butyldimethylsilyl)oxy)-3,5-hexadiene (12c) with Maleic anhydride (15):

A mixture of 2-((t-butyldimethylsilyl)oxy)-3,5-hexadiene (**12c**, 279 mg, 1.31 mmol) and maleic anhydride (98 mg, 1.31 mmol) in dry benzene (4 mL) was stirred (under nitrogen) at room temperature for 7 days. The solvent was removed and the diastereomeric ratio was was found to be 4.5:1. The concentrated reaction mixture was purified and separated by flash chromatography (Pet. ether: EtOAc 4:1) to furnish the unreacted diene (18 mg), the pure major diastereoisomer **23c** (112 mg, 27.6%), the pure minor adduct **24c** (25 mg, 6.15%) and a mixture of the adducts **23c** and **24c** (111 mg, 27.3%). The major adduct (**23c**) was isolated as a crystalline solid, m.p. 66-68^o whereas the minor adduct **24c** was obtained as a syrupy liquid.

Major Adduct 23c: ^{1}H NMR (300 MHz) 6.04 (m, 1H, C_6-H), 5.88 (m, 1H, C_5-H), 4.47 (overlapping dq, 1H, $J_{Me,10}$= 5.95 Hz, C_{10}-H), 3.82 (dd, 1H, J = 5.17 and 9.67 Hz, C_9-H), 3.47 (m, 1H, C_8-H), 2.76 (Overlapping ddd, 1H, -CH_2-), 2.32 - 2.16 (m, 2H, -CH_2- and C_4-H), 1.29 (d, 3H, $J_{Me,10}$ = 5.99 Hz, -CH_3) 0.93 (s, 9H, Si-C(CH_3)$_3$), 0.19 (s, 3H, Si-CH_3), 0.16 (s, 3H, Si-CH_3); IR ($CHCl_3$) 1765 cm^{-1}.

Minor Adduct 24c: ^{1}H NMR (300 MHz) _6.17 (m,1H, C_6-H), 6.05 (m, 1H, C_5-H), 4.37 (m, 1H, C_{10}-H), 3.43 (m, 2H, C_8-H and C_9-H), 2.69 (Overlapping dd, -CH_2-),

2.31-2.18 (m, 2H, -C$\underline{H}_2$- and C_4-$\underline{H}$), 1.4 (d, 3H, $J_{Me,10}$ = 5.99 Hz, -C$\underline{H}_3$), 0.92 (s, 9H, Si-C(C$\underline{H}_3$)$_3$), 0.18 (s, 3H, Si- C$\underline{H}_3$), 0.15 (s, 3H, Si-C$\underline{H}_3$).

Hydrolysis of the Major Silyl Adduct 23c: A mixture of **23c** (175 mg, 0.56 mmol) and of Dowex 50W-X-8 resin (50 mg) in MeOH (7 mL) was stirred for 48 hours. The reaction was followed by tlc. The solution was filtered and evaporated to give a white crystalline solid. Crude ^{1}H NMR showed the formation of a mixture of the lactone ester **25b** and the lactonic acid **25a**. The lactone **25b** was purified by PLC (Pet. ether; EtOAc 1.5:1) to furnish a solid (41 mg, 34%) which was crystallized from water to give colorless crystals m.p. 152°. This product has identical IR and NMR with the earlier sample of **25b**.

Diels-Alder Reactions of 2-Hydroxy-3,5-heptadiene (13a) with Maleic anhydride (15): A mixture of 2-hydroxy -3,5-heptadiene (**13a**, 115 mg, 1.02 mmol) and maleic anhydride (103 mg, 1.05 mmol) in $CHCl_3$ (3 mL) was stirred under reflux for 3 days. The solvent was removed and the product was kept under high vacuum . The diastereomeric ratio was determined from the ^{1}H NMR (300 MHz) of the crude product and was found to be 2.5:1. The ^{1}H NMR of the adducts **29** and **30** were identical to the *like* and *unlike* products respectively, reported by the French workers from the same reactions[29].

Diels-Alder Reactions of 2-Hydroxy-3,5-hexadiene (12a) with N-Phenyl maleimide (16):

A mixture of 2-hydroxy -3,5-hexadiene (**12a**, 98 mg, 1 mmol) and N-phenylmaleimide (173 mg, 1 mmol) in dry benzene (3 mL) was stirred (under nitrogen) at room temperature. After 12h, a white solid was precipitated out. The stirring was continued for 3 days. The solid was filtered and was washed with benzene (120.8 mg). The mother liquor was concentrated and the ^{1}H NMR (300 MHz) spectrum of it showed the formation of a

mixture of the lactones **33** and **34** . The ^1H NMR spectrum of the filtered solid also showed it to be mixture of lactones **33** and **34** and the diastereomeric ratio was identical in each case and was found to be 1.3 : 1. The tlc of the solid product showed no separation of the diastereomers in different solvent systems. The mother liquor was subjected to purification by PLC (petroleum ether : EtOAc 4 : 1) to furnish more amount of the lactone mixture (22.7 mg, a combined yield of 53%). Attempted separation of both the lactones by fractional crystallization also failed.

Diels-Alder Reactions of 2-((Trimethylsilyl)oxy)-3,5-hexadiene (12b) N-Phenylmaleimide (16): A mixture of 2-((trimethylsilyl)oxy)-3, 5-hexadiene (**12b**, 347 mg, 2.04 mmol) and N-phenylmaleimide (341 mg, 1.97 mmol) in dry benzene (3 mL) was stirred (under nitrogen) at room temperature for 5 days. The solvent was removed and the diastereomeric ratio was found to be 3.5 : 1. The crude mixture was subjected to separation by flash chromatography (Pet. ether: EtOAc 4 : 1). The first fraction was the pure major adduct **31b** which was obtained as a colorless syrup (440 mg, 65.1%). The second fraction was a mixture of the major (**31b**) and the minor adduct (**32b**) which was isolated as a colorless syrup (78.4 mg, 11.6%). The minor adduct **32b** was obtained as an yellow syrup along with the unreacted N-phenylmaleimide (157 mg) . The minor adduct could not be further purified.

Major Adduct 31b: ^1H NMR (300 MHz): 7.5 - 7.2 (m, 5H, Ar$\underline{H}$), 6.07 - 5.99 (m, 1H, C_6-$\underline{H}$), 5.90 - 5.85 (m, 1H, C_5-$\underline{H}$), 4.68 (dq, 1H, J = 6.00 and 10.47 Hz, C_{10}-$\underline{H}$), 3.70 (dd, 1H, J = 8.85 and 4.90 Hz, C_9-$\underline{H}$), 3.33 (overlapping ddd, 1H, C_8-$\underline{H}$), 2.83 (dd, 1H, J = 7.30 and 14.85 Hz, -C$\underline{H}_2$-), 2.31 - 2.24 (m, 2H, -C$\underline{H}_2$- and C_4-$\underline{H}$), 1.30 (d, 3H, $J_{Me,10}$ = 6.02 Hz, -C$\underline{H}_3$), 0.23 (s, 9H, -Si (C$\underline{H}_3$)$_3$); IR ($CHCl_3$) 1700 cm-1 high resolution mass spectrum calcd for $C_{21}H_{25}NO_3Si$ 343.1604, found 343.1594.

Minor adduct 32b: ^{1}H NMR (300 MHz) 7.54 -7.23 (m, 5H, Ar<u>H</u>), 6.10 - 6.02 (m, 2H, C_6-<u>H</u> and C_5-<u>H</u>), 4.5 (overlapping dq, 1H, $J_{Me,10}$ = 5.92 Hz, C_{10}-<u>H</u>), 3.39 - 3.35 (m, 2H, C_9-<u>H</u> and C_8-<u>H</u>) 2.82 (overlapping ddd, 1H, -C<u>H</u>$_2$-), 2.32 - 2.24 (m, 2H, -C<u>H</u>$_2$- and C_4-<u>H</u>), 1.47 (d, 3H, $J_{Me,10}$ = 5.92 Hz, -C<u>H</u>$_3$), 0.19 (s, 9H, -Si(C<u>H</u>$_3$)$_3$); high resolution mass spectrum calcd for $C_{19}H_{25}NO_3Si$ 343.1604, found 343.1599.

Hydrolysis and Lactonization of the Major Silyl Adduct 31b: A solution of adduct **31b** (303 mg, .88 mmol) in MeOH (3 mL) along with 2-3 drops of a saturated oxalic acid solution was stirred and the course of the reaction was followed by tlc. After 0.5h, excess of methanol was removed by rotary evaporator and the remaining pasty mass was purified by passing through a short column of florisil. The column was eluted with EtOAc and concentration of the eluent gave the crude lactone **33** which was further purified by crystallization to give a solid as colorless needles, m.p. 220^0. (207 mg, 86.8%). The concentrated mother liquor (37 mg, 15.51%) was not further separated.

Major Lactone 33: ^{1}H NMR (400 MHz): 9.83 (br, 1H, N<u>H</u>Ar), 7.59-7.06 (m, 5H, Ar<u>H</u>), 5.95 (ddd, 1H, J = 9.77, 3.05, 2.44 Hz, C_5-<u>H</u>), 5.65 (d, 1H, J = 10.38 Hz, C_4-<u>H</u>), 4.47 (dq, 1H, $J_{Me,3}$ = 6.10 Hz, $J_{3,9}$ = 1.71 Hz C_3-<u>H</u>), 3.52 (dd, 1H, J = 7.33 and 6.72 Hz, C_8-<u>H</u>), 2.9-2.85 (m, 2H, C_7-<u>H</u> and C_9-<u>H</u>), 2.47-2.39 (m, 2H, -C<u>H</u>$_2$-), 1.44 (d, 3H, $J_{Me,3}$ = 6.10 Hz, -C<u>H</u>$_3$ at C_3); IR ($CHCl_3$): 1745, 1670 cm^{-1}; Anal. calcd. for $C_{16}H_{17}NO_3$: C, 70.84; H, 6.27; N, 5.16. Found C, 70.75; H, 6.23; N, 5.11.

Hydrolysis and Lactonization of the Minor Silyl Adduct 32b: A solution of adduct **32b** (157 mg, 0.45 mmol) in MeOH (3 mL) along with 2-3 drops of a saturated oxalic acid solution was stirred for 3h. The reaction mixture was cooled, excess methanol

was removed and the crude product was passed through a short column of florisil and eluted with EtOAc. The concentrated mass was purified by chromatotron (Pet ether EtOAc 3 :1) to give a mixture of the alcohol **32b** and the lactone **34** as a syrup (90 mg, 73.8%). The second fraction was the unreacted N-phenylmaleimide (26 mg). The ^1H NMR of the purified mixture showed that alcohol **32b** was unstable and it slowly cyclized to the lactone **34**. The mixture was warmed in MeOH for complete cyclization of the alcohol **32b**. Finally, the lactone **34** was crystallized from methanol to furnish a white solid m.p. 205°.

Minor Lactone 34: ^1H NMR (300 MHz)): 10.03 (br, 1H, NHAr), 7.66-7.11 (m, 5H, ArH), 6.12 (m, 1H, C_5-H), 5.72 (dd, 1H, J = 10.24 and 2.11 Hz, C_4-H), 4.77 (dq, 1H, $J_{Me,3}$ = 6.51 Hz, $J_{3,9}$ = 4.85 Hz, C_3-H), 3.54 (dd, 1H, J=6.68, and 2.85 Hz, C_8-H), 3.19 (m, 1H, C_9-H), 2.94 (ddd, 1H, J = 5.70, 2.88 and .78 Hz, C_7-H), 2.56-2.49 (m, 2H, -CH_2-), 1.49 (d, 3H, $J_{Me,3}$ = 6.51 Hz, CH_3 at C_3); IR ($CHCl_3$) 1745, 1670 cm-1; Anal. calcd. for $C_{16}N_{17}NO_3$: C, 70.84; H, 6.27; N, 5.16. Found C, 71.00; H, 6.09; N, 5.08.

Diels-Alder Reactions of 2-hydroxy-3,5-heptadiene (13a) with N-Phenyl maleimide (16): A mixture of 2-hydroxy-3, 5-heptadiene (**13a**, 224 mg, 2 mmol) and N-phenylmaleimide (276 mg, 1.6 mmol) in dry benzene (3 mL) was stirred (under nitrogen) at room temperature for 5 days. The solvent was removed the ^1H NMR (300 MHz) spectrum showed the presence of three products, where the major adduct **35a** slowly cyclized to the bicyclic lactone **37**. The diastereomeric ratio was found to be 1.7 : 1. The crude mixture was kept in the freezer and the major lactone **37** was crystallized out as a colorless solid (153 mg). The solid was filtered washed with petroleum ether : EtOAc and the mother liquor was concentrated and subjected to separation by multiple elution on PLC (CH_2Cl_2: Acetone 19:1). The major alcohol was unstable under the chromatographic

condition and was completely cyclized to the major lactone **37**. The first fraction was the bicyclic lactone **37** (24 mg, combined yield 38.8%) which was recrystallized from EtOAc to give colorless cubes, m.p. 125° . The second fraction was a mixture of the lactone **37** and the minor alcohol **36a** (83 mg, 18.2%) was isolated a gummy mass. The last fraction was the minor adduct **36a**, which was a stable alcohol and was isolated as a waxy solid (97 mg, 21.27%).

Major Lactone 37: ^{1}H NMR (400 MHz): 9.98 (br, 1H, -NHAr), 7.58 - 7.06 (m, 5H, ArH), 5.89 (m, 1H, C_5-H), 5.57 (d br, $J_{4,5}$ = 10.38 Hz, C_4-H), 4.4 (dq, 1H, $J_{Me,3}$ = 6.71 Hz, $J_{3,9}$ = 2.44 Hz, C_3-H), 3.38 (dd, 1H, $J_{8,9}$ = 7.93 Hz, $J_{8,7}$ = 4.27 Hz, C_8-H), 3.01 (dd, 1H, $J_{7,6}$= 5.50 Hz, $J_{7,8}$= 4.27 Hz C_7-H), 2.80 (m, 2H, C_9-H and C_6-H), 1.43 (d, 3H, $J_{Me,3}$ = 6.71 Hz, -CH_3 at C_3), 1.13 (d, 3H, $J_{Me,6}$=7.32, -CH_3 at C_6) IR ($CHCl_3$): 3420, 3330, 1755, 1675 cm-^{1}; Anal. calcd. for $C_{17}H_{19}NO_3$: C, 71.57; H, 6.66; N, 4.91. Found C, 71.38; H, 7.05; N, 4.97.

Minor Adduct 36d: ^{1}H NMR (400 MHz): 7.46-7.15 (m, 5H, ArH), 6.27 (m, 1H, C_6-H), 5.84 (m, 1H, C_5-H), 4.45 (dq, 1H, $J_{Me,10}$ = 6.1 Hz, $J_{10,4}$ = 3.05 Hz, C_{10}-H), 3.66 (d, 1H, J = 2.45 Hz, -OH), 3.38 (dd, 1H, $J_{9,4}$ = 8.55 Hz, $J_{9,8}$ = 5.50 Hz, C_9-H), 3.23 (overlapping dd, 1H, C_8-H), 2.54 (m, 1H, C_4-H), 2.26 (br m, 1H, C_7-H), 1.46 (d, 3H, $J_{Me,7}$ = 7.32 Hz, -CH_3 at C_7), 1.36 (d, 3H, $J_{Me,10}$ = 6.11 Hz, -CH_3 at C_{10}); IR ($CHCl_3$): 3450, 1700 cm-^{1}; high resolution mass spectrum calcd for $C_{17}H_{19}NO_3$ 285.1365, found 285.1365.

Lactonization of the Adduct Alcohol 36a: A solution of adduct **36a** (95 mg, 0.33 mmol) in MeOH (3 mL) along with 2-3 drops of a saturated oxalic acid solution was

refluxed for 2h. The course of the reaction was followed by tlc. The reaction mixture was cooled, excess methanol was removed by rotary evaporator and the remaining pasty mass was dissolved in EtOAc and passed through a short column of florisil. The column was eluted with EtOAc and concentration of the eluent gave the crude mass which was kept in the freezer overnight. The lactone **38** was separated out as a solid which was filtered and repeatedly washed with Pet ether : EtOAc (65 mg). The lactone **38** was recrystallized from EtOAc to give white needles, m.p. 188°. The mother liquor was concentrated and subjected to separation by PLC (CH_2Cl_2 : Acetone 19:1) to give an additional amount of the minor lactone **38** (9.8 mg, a combined yield of 78.7%) and the unreacted staring alcohol **36d** (7 mg, 7.4%).

Lactone 38: ^{1}H NMR (400 MHz): 10.77 (br, 1H, -NHAr), 7.64-7.08 (m, 5H, ArH), 6.08 (dd, 1H, J = 10.38, 3.05 Hz, C_5-H), 5.57 (br d, 1H, J =10.38 Hz, C_4-H), 4.71 (dq, 1H, $J_{Me,3}$ = 6.11 Hz, $J_{3,9}$ = 3.66 Hz, C_3-H), 3.43 (dd, 1H, $J_{8,9}$ = 7.33 Hz, $J_{8,7}$ = 3.66 Hz, C_8-H), 3.15 (dd, 1H, $J_{7,6}$ = 6.10 Hz, $J_{7,8}$ = 3.66 Hz, C_7-H), 3.10 (m, 1H, C_9-H), 2.86 (m, 1H, C_6-H), 1.47 (d, 3H, $J_{Me,3}$ = 6.71 Hz, -CH_3 at C_3), 1.11 (d, 3H, $J_{Me,6}$=7.32 Hz, CH_3 at C_6); IR ($CHCl_3$): 3300, 3260, 1745, 1660 cm-1; Anal. calcd. for $C_{17}H_{19}NO_3$: C, 71.57; H, 6.66; N, 4.9. Found C, 71.39; H, 6.95; N, 4.89.

Diels-Alder Reactions of 2-((Trimethylsilyl)oxy)-3,5-heptadiene (13b) with N-Phenylmaleimide (16)[26]: A mixture of 2-((trimethylsilyl)oxy)-3,5-heptadiene (**13c** 344 mg, 1.87 mmol) and N-Phenylmaleimide (304 mg, 1.75 mmol) in dry benzene (5 mL) was stirred (under nitrogen) at room temperature for 10 days. The products were purified and separated by PLC (Pet. ether: EtOAc 4 : 1) . The major product **35c** was isolated as a solid which was crystallized from Pet.ether : EtOAc to furnish white needles, m.p. 135° (407 mg, 65.14%). The minor silyl adduct **36c** was isolated as a gummy

yellow mass along with N-phenylmaleimide (approximately 1 : 1 mixture) and could not be further purified (98.4 mg).

Major Silyl Adduct 35c: ^{1}H NMR (400 MHz) 7.42-7.13 (m, 5H, Ar$\underline{H}$), 5.75 (m, 2H, C_6-$\underline{H}$ and C_5-$\underline{H}$) 4.68 (overlapping dq, 1H, $J_{Me,10}$ = 6.10 Hz, C_{10}-$\underline{H}$), 3.62 (dd, 1H, J = 4.88 and 8.55 Hz, C_9-$\underline{H}$) 3.13 (dd, 1H, J = 7.94 and 8.54 Hz, C_8-$\underline{H}$), 2.49 (m, 1H, C_7-$\underline{H}$), 2.20 (m, 1H, C_4-$\underline{H}$), 1.40 (d, 3H, $J_{Me,7}$ = 7.33 Hz, -C$\underline{H}_3$ at C_7), 1.24 (d, 3H, $J_{Me,10}$ = 6.1 Hz, -C$\underline{H}_3$ at C_{10}), 0.15 (s, 9H, -Si(C$\underline{H}_3$)$_3$); IR (CCl_4): 1710 cm^{-1}; high resolution mass spectrum calcd for $C_{20}H_{27}NO_3Si$ 357.1761, found 357.1740.

Minor Silyl Adduct 36c: ^{1}H NMR (400 MHz) 7.43-7.14 (m, 5H, Ar$\underline{H}$) 5.97 (ddd, 1H, J=9.16, 6.10, 3.15 Hz, C_6-$\underline{H}$), 5.74 (ddd, 1H, J=9.15, 6.10, 3.05 Hz, C_5-$\underline{H}$), 4.48 (overlapping dq, 1H, C_{10}-$\underline{H}$), 3.31 (dd, 1H, J = 8.55 and 5.50 Hz, C_9-$\underline{H}$), 3.17 (dd, 1H, J = 8.55 and 7.32 Hz, C_8-$\underline{H}$), 2.49 (m, 1H, C_7-$\underline{H}$), 2.20 (m, 1H, C_4-$\underline{H}$), 1.44 (d, 3H, $J_{Me,7}$ = 7.32 Hz, -C$\underline{H}_3$ at C_6), 1.41 (d, 3H, $J_{Me,10}$=6.1 Hz, -C$\underline{H}_3$ at C_{10}), 0.13 (s, 9H, -Si(C$\underline{H}_3$)$_3$); high resolution mass spectrum calcd for $C_{20}H_{27}NO_3Si$ 357.1761, found 357.1763.

Hydrolysis and Cyclization of the Major Silyl Adduct 35c by Tetrabutylammonium Fluoride:

To a solution of dry the silyl ether adduct **35c**(100 mg, 0.28 mmol) in dry THF (2 mL)was added a solution of tetrabutylammonium fluoride (0.4 mL, 1M solution in THF, 0.4 mmol) at room temperature and the resulting solution was stirred overnight. The solvent was evaporated and the crude mass was passed through a short column of florisil to give a syrupy mass. The thin layer chromatography of the crude mass showed the formation of two new products. The two products were separated by PLC (Petroleum ether : EtOAc 4 : 1) and the major product was the lactone **37** (26 mg, 32.5%) whose identity was

established from the ^1H NMR spectrum and melting point. The minor product **39** was isolated as a white solid (20 mg, 25%) which was crystallized from EtOAc to give colorless crystals, mp. 197°.

Lactone 39: ^1H NMR (400 MHz): 7.52 - 7.08 (m, 6H, ArH, -NHAr)), 5.75 (m, 1H, C_5-H), 5.64 (d br, $J_{4,5}$ = 10.37 Hz, C_4-H), 4.26 (dq, 1H, $J_{Me,3}$ = 6.11 Hz, $J_{3,9}$ = 7.93 Hz, C_3-H), 3.21 (dd, 1H, $J_{8,9}$ = 9.16 Hz, $J_{8,7}$ = 10.38 Hz, C_8-H), 2.72 (m, 1H, C_9-H), 2.62 (m, 1H, C_6-H), 2.12 (dd, 1H, $J_{7,6}$= 9.16 Hz, $J_{8,7}$ = 10.39 Hz C_7-H), 1.46 (d, 3H, $J_{Me,3}$ = 6.1 Hz, -CH_3 at C_3), 1.12 (d, 3H, $J_{Me,6}$=7.32, -CH_3 at C_6) IR ($CHCl_3$): 1755, 1675 cm^{-1}; Anal. calcd. for $C_{17}H_{19}NO_3$: C, 71.57; H, 6.66; N, 4.91. Found C, 71.55; H, 6.74 ; N, 4.91.

Hydrolysis and Lactonization of the Major Silyl Adduct 35c by Acid: A solution of adduct **35c** (120 mg, 0.33 mmol) in MeOH (3 mL) along with 2-3 drops of a saturated oxalic acid solution was stirred for 3h. The course of the reaction was followed by tlc which showed the formation of both , the alcohol and the lactone. The reaction mixture was refluxed for 15 minutes and cooled to room temperature. Excess methanol was removed by rotary evaporator and the remaining pasty mass was dissolved in EtOAc and passed through a short column of florisil. The column was eluted with EtOAc and concentration of the eluent gave the crude lactone **37** which was purified by PLC (CH_2Cl_2 : acetone 19 :1) to give a white solid (94 mg, 98%). The identity of the product was established from the ^1H NMR spectrum and melting point which was identical to the lactone **37** obtained from the reaction of the diene **13a** with NPM.

Hydrolysis and Cyclization of the Minor Silyl Adduct 36c by Tetrabutylammonium Fluoride:

To a solution of the minor silylether adduct **36c** (50 mg, 0.14 mmol) in dry THF (1.5 mL) was added a solution of tetrabutylammonium fluoride (0.2 mL, 1M solution in THF, 0.2 mmol) at room temperature and the resulting solution was stirred overnight. The solvent was evaporated and the crude mass was passed through a short column of florisil. Thin layer chromatography of the crude mass showed the formation two new products. The two products were separated by PLC (Petroleum ether : EtOAc 4 : 1) and the major product was a white solid (11 mg, 27.5 %) which was identical to the lactone **38**, obtained from the reaction of 2-hydroxy 3,5-heptadiene (**13a**) with NPM (**16**). The minor product was the epimerized lactone **41** which was isolated as a white solid (9 mg, 22.5%). Lactone **41** was crystallized from EtOAc as white needles, m.p. 209°.

Lactone 41: ^{1}H NMR (400 MHz): 7.68 - 7.07 (m, 6H, Ar<u>H</u>, -N<u>H</u>Ar)), 5.88 (d, 1H, $J_{4,5}$ = 10.37 Hz, C_5-<u>H</u>), 5.66 (d, $J_{4,5}$ = 10.37 Hz, C_4-<u>H</u>), 4.74 (dq, 1H, $J_{Me,3}$ = 6.71 Hz, $J_{3,9}$ = 6.7 Hz, C_3-<u>H</u>), 3.20 (m, 2H, C_7-<u>H</u>, C_8-<u>H</u>), 2.58 (m, 1H, C_6-<u>H</u>), 2.47 (m, 1H, C_9-<u>H</u>)), 1.39 (d, 3H, $J_{Me,3}$ = 6.71 Hz, -C<u>H</u>$_3$ at C_3), 1.15 (d, 3H, $J_{Me,6}$=7.32, -C<u>H</u>$_3$ at C_6) IR ($CHCl_3$): 1755, 1675 cm^{-1}.

Hydrolysis and Cyclization of the Minor Silyl Adduct 36c in Acid Medium:

A solution of the NPM contaminated adduct **36c** (45 mg) in MeOH (3 mL) along with 2-3 drops of a saturated oxalic acid solution was refluxed for 4h. The course of the reaction was followed by tlc. The reaction mixture was cooled, excess methanol was removed by rotary evaporator and the remaining pasty mass was dissolved in EtOAc and passed through a short column of florisil. The column was eluted with EtOAc and concentration of the eluent gave the crude product which was separated by PLC (Pet. ether: EtOAc 4:1)

to give the pure lactone **38** (13 mg, 49.2%) as a white solid which was identical in all respects to the lactone **38** which was obtained earlier from the lactonization of minor adduct **36a**. Recovered N-phenylmaleimide was also isolated (12 mg, 26.6%) which had contaminated adduct **36c**.

Interconversion of lactone 37 to lactone 39:

Sodium methoxide was prepared by dissolving sodium metal (approximately 10 mg of sodium) in absolute methanol (2 mL). A solution of the lactone **37** (14 mg, 0.05 mmol) was added (solid) the resulting solution was stirred for 2h. The tlc analysis showed the disappearance of the starting material and the formation of a new product . The solution was neutralized by adding oxalic acid solution dropwise and the excess of MeOH was removed by rotary evaporator. The product was extracted from EtOAc (2 x 10 mL) . After drying over anhydrous Na_2SO_4, the excess of the solvent was removed to give a syrup . which was purified by crystallization (acetone : carbon tetrachloride) to give a solid, mp 197° (7.1 mg, 50.7%). The product was identical to the lactone **39** which was obtained from the hydrolysis of the silylether **35c** with tetrabutylammonium fluoride.

Interconversion of lactone 38 to lactone 41:

A solution of the lactone **38** (5 mg, 0.17 mmol) in absolute methanol (0.5 mL)was added dropwise to a solution of sodium methoxide (prepared by dissolving approximately 5 mg of sodium metal in 1 mL of absolute methanol). The resulting solution was stirred at room temperature for 0.5h and similar work up as already described in the previous experiment resulted the formation of the lactone **41**, which was isolated as a white solid (3.4 mg, 68%). This was identical to the previous sample of the lactone **41**.

Attempted Oxidation of the Adduct Alcohol 36a:

A mixture of the adduct alcohol **36a** (15 mg, 0.05 mmol) and PDC (28 mg, 0.07 mmol) in

dry CH_2Cl_2 (4 mL) was stirred at room temperature for 6h. The solvent was removed and the crude mass was subjected to PLC separation (CH_2Cl_2 : acetone 96 : 4) to give two products. The ^1H NMR major product (9.6 mg 64%) was identical to the lactone **38** and the minor product was the unreacted staring alcohol **36a** (3.3 mg, 22%).

Attempted Oxidation of the Adduct Mixture 35a and 36a:

A mixture of 2-hydroxy-3,5-heptadiene (**13a**, 114 mg, 1.01 mmol) and N-phenylmaleimide (176 mg, 1.01 mmol) in dry benzene (3 mL) was stirred (under nitrogen) at room temperature for 5 days. The solvent was removed and the crude products were purified by chromatotron (Pet ether : EtOAc 4 : 1) to get rid of unreacted diene. The purified adduct mixture was obtained as an yellow syrup (203 mg) which contained the unreacted NPM. The adduct mixture (100 mg) was dissolved in dry CH_2Cl_2 (10mL) and to it PDC (220 mg, 0.58 mmol) was added and the resulting mixture was stirred for 6h. The solvent was evaporated and the crude mass was passed through a bed of florisil and eluted with diethyl ether. The eluents were concentrated to give an yellow mass and the ^1H NMR of the mixture showed it to be a mixture of lactones **37** and **38** and a trace of the unreacted alcohol **36a**.

Diels-Alder Reactions of 2-Hydroxy-3,5-heptadiene (13a) with 4-phenyl-1, 2, 4-triazolidine-3, 5-dione (18):

To a cooled solution (-78°) of 4-phenyl-1,2,4-triazolidine-3, 5-dione (**18**, 43.75 mg, 0.25 mmol) in 4 mL of THF: CH_2Cl_2 (1:1) was added dropwise a solution of 2-hydroxy 3,5-heptadiene (**13a**, 28 mg, 0.25 mmol) in a solution of THF: CH_2Cl_2 (1:1) (3 mL). The color of the solution was slowly discharged and after 15 minutes, the cooling bath was removed. The solution was stirred for another 15 minutes and excess of solvent was

evaporated. ^1H NMR of the crude product showed the formation of two products in a ratio of 1 : 2.7. The products were separated by PLC (Pet. ether: EtOAc, 1.5:1) to give two fractions (56.5 mg and 13.2 mg respectively) . Both the fractions were subjected to chromatographic separation separately. The major fraction, on PLC separation (Et_2O developed twice) gave the major adduct **58a** (30 mg, 41.8%) as a colorless syrup and the minor adduct **57a** (13.1 mg). The minor fraction gave an additional amount of the minor adduct **57a** (7.2 mg, a combined yield of 28.3%) on PLC separation (CH_2Cl_2 : Ether 1 : 1) which was a colorless syrup. A third product was also isolated (4.8 mg, 6.7%).

Minor Adduct 57a: ^1H NMR (400 MHz) 7.48-7.19 (m, 5H, Ar$\underline{H}$), 5.97 (ddd, 1H, J = 10, 4.88 and 2.44 Hz, C_7-$\underline{H}$), 5.67 (ddd, 1H, J=10.38, 2.44 and 1.83 Hz, C_6-$\underline{H}$), 4.78 (d, 1H, J=10.99 Hz, -O$\underline{H}$), 4.55 (m, 1H, C_8-$\underline{H}$), 4.48 (m, 1H, C_5-$\underline{H}$), 4.05 (m, 1H, C_{10}-$\underline{H}$), 1.34 (d, 3H, $J_{Me,8}$ = 6.1 Hz, -C$\underline{H}_3$ at C_8), 1.19 (d, 3H, $J_{Me,10}$ = 6.72 Hz, -C$\underline{H}_3$ at C_{10}); IR ($CHCl_3$) 3400, 1690 cm-1; high resolution mass spectrum calcd for $C_{15}H_{17}N_3O_3$ 287.1271, found 287.1278.

Major Adduct 58a: ^1H NMR (400 MHz): 7.45-7.19 (m, 5H, Ar$\underline{H}$), 5.86 (m, 2H, C_6-$\underline{H}$ and C_7-$\underline{H}$), 4.44 (m, 1H, C_8-$\underline{H}$), 4.38 (m, 1H, C_5-$\underline{H}$), 4.22 (m, 1H, C_{10}-$\underline{H}$), 3.18 (br s, 1H, -O$\underline{H}$), 1.45 (d, $J_{Me,8}$ = 6.71 Hz, -C$\underline{H}_3$ at C_8), 1.18 (d, 3H, $J_{Me,10}$ = 6.72 Hz, -C$\underline{H}_3$ at C_{10}); high resolution mass specrum calcd for $C_{15}H_{17}N_3O_3$ 287.1271, found 287.1275.

3rd isomer: A syrup, ^1H NMR (400 MHz): 7.52-7.23 (m, 5H, Ar$\underline{H}$), 6.02 (m, 1H,

C_7-H), 5.83 (ddd, 1H, J =10.38, 3.66 and 1.83 Hz, C_6-H), 4.69 (m, 1H, C_8-H), 4.57 (m, 1H, C_5-H), 4.24 (m, 1H, C_{10}-H), 3.2 (br, 1H, -OH), 1.37 (dd, 3H, J = 6.71 and 6.10 Hz, -CH_3 at C_8), 1.20 (dd, 3H, J=6.71 and 6.10 Hz, -CH_3 at C_{10}); high resolution mass spectrum calcd for $C_{15}H_{17}N_3O_3$ 287.1271, found 287.1272.

Diels-Alder Reactions of 2-((Trimethylsilyl) oxy)3,5-heptadiene (13c) with 4-phenyl-1, 2, 4-triazolidine-3, 5-dione:

To a cooled solution (-78°) of 4-phenyl-1,2,4-triazolidine-3, 5-dione (**18**, 59 mg, 0.33 mmol) in 4 mL of THF: CH_2Cl_2 (1:1) was added dropwise a solution of 2-((trimethylsilyl) oxy)3,5-heptadiene (**13c**, 62 mg, .33 mmol) in of THF: CH_2Cl_2 (1:1) (3 mL). The color of the solution was slowly discharged and after 20 minutes, the cooling bath was removed. The solution was stirred for another 30 minutes and excess of solvent was evaporated. ^{1}H NMR of the crude product showed the formation of two products in a ratio of 1 : 5.5. The crude products were subjected to separation by PLC (Pet. ether: EtOAc, 4 : 1) . The major product **58b** was isolated as a white solid, m.p. 109° (69.5 mg, 58.7%). The minor isomer **57b** was isolated as a syrup (13 mg, 11%).

Minor Silyl Adduct 57b: Pasty mass, ^{1}H NMR (400 MHz): 7.52-7.24 (m, 5H, ArH), 6.00-5.91 (m, 2H, C_7-H and C_6-H), 4.69 (m, 1H, C_{10}-H), 4.49 (m, 1H, C_8-H), 4.37 (m, 1H, C_5-H), 1.47 (d, 3H, $J_{Me,8}$ = 6.59 Hz, -CH_3 at C_8), 1.11 (d, 3H, $J_{Me,10}$ = 6.59 Hz, -CH_3 at C_{10}), 0.13 (s, 9H, -Si(CH_3)$_3$); high resolution mass spectrum calcd for $C_{17}H_{22}N_3O_3Si(M^+$-Me) 344.1431, found 344.1437.

Major Silyl Adduct 58b: A white solid m.p. 109°, ^{1}H NMR (400 MHz): 7.5-7.24 (m, 5H, ArH), 5.94 (m, 2H, C_6-H and C_7-H), 4.58 (m, 1H, C_{10}-H), 4.47 (m, 1H,

C_8-H), 4.37 (m, 1H, C_5-H), 1.55 (dd, 3H, J = 6.71 and 6.71 Hz, -CH_3 at C_8), 1.23 (dd, 3H, J = 6.71 and 6.10 Hz, -CH_3 at C_{10}, 0.07 (s, 9H, -Si(CH_3)$_3$). Anal. calcd. for $C_{18}H_{25}N_3O_3Si$: C, 60.16; H, 6.96; N, 11.69. Found C, 60.22; H, 6.98; N, 11.71.

Hydrolysis of the Minor Silyl Adduct 57b: A solution of adduct **57b** (15.1 mg, .04 mmol) in MeOH (1 mL) along with 1 drop of a saturated oxalic acid solution was refluxed for 2h. The course of the reaction was followed by tlc. The reaction mixture was cooled, excess methanol was removed by rotary evaporator and the remaining pasty mass was dissolved in EtOAc and passed through a short column of florisil. The column was eluted with EtOAc and concentration of the eluent gave the crude product which was purified by PLC (Pet. ether: EtOAc 1.5 : 1) to furnish a colorless syrup (10.2 mg, 84.5%). This product was identical to the minor adduct **57a** obtained from the reaction of diene **13a** and **18**.

Hydrolysis of the Major Silyl Adduct 58b: A solution of the adduct **58b** (72 mg, 0.2 mmol) in MeOH (1.5 mL) along with 1 drops of a saturated oxalic acid solution was refluxed for 2h. The course of the reaction was followed by tlc. Similar work up as described already in the hydrolysis of 57b furnished a colorless syrup (51.5 mg, 89.5%) as a colorless syrup which was crystallized from Petroleum ether : EtOAc to give a white solid. The resulting product was identical in all respects to the major adduct **58a**, obtained from the reaction of the diene **13a** and **18**.

Lactonization of the Major Alcohol Adduct 58a : To an ice cooled stirred suspension of NaH (from 10 mg of 50% dispersion in mineral oil, 0.2 mmol) in dry THF (3 mL) under nitrogen was added dropwise a solution of the major adduct alcohol **58a** (30 mg., 0.10 mmol) in dry THF (3 mL). After the addition, the cooling bath was removed and after one hour the reaction was quenched with an aqueous solution of NH_4Cl. The

solution was extracted with ether (2 x 15 mL) dried over Na_2SO_4. Evaporation of the solvent gave a pasty mass which was subjected to PLC (Pet. ether: EtOAc 1.5:1). A white crystalline solid (9 mg, 30%) was obtained to give the carbamate **59** as colorless crystals m.p. 190°,

The Carbamate 59: ^{1}H NMR (400 MHz): 7.46-7.02 (m, 5H, Ar<u>H</u>), 6.09 (ddd, 1H, J=10.99, 3.66 and 1.83 Hz, C_5-<u>H</u>), 5.73 (br d, 1H, C_4-<u>H</u>), 4.98 (m, 1H, C_6-<u>H</u>), 4.86 (dq, 1H, $J_{Me,3}$ = 6.71 Hz, $J_{3,9}$ = 7.32 Hz, C_3-<u>H</u>), 4.33 (ddd, 1H, J = 7.32, 3.66 and 1.83 Hz, C_9-<u>H</u>). 1.48 (d, 3H, $J_{Me,3}$ = 6.72 Hz, -C<u>H</u>$_3$ at C_3), 1.38 (d, 3H, $J_{Me,6}$ = 6.71 Hz, -C<u>H</u>$_3$ at C-6); IR ($CHCl_3$): 3420, 1785, 1685 cm-^{1}; Anal. calcd. for $C_{15}H_{17}N_3O_3$: C, 62.71; H, 5.92; N, 14.63. Found C, 62.63; H, 5.84; N, 14.59.

Diels-Alder Reactions of 2-hydroxy-3,5-heptadiene (13a) with DMAD (17): A solution of 2-hydroxy-3,5-heptadiene (**13a**, 560 mg, 5 mmol) and dimethyl acetylene dicarboxylate (**17**, 724 mg, 5.11 mmol) in benzene (10 mL) was kept under reflux for 48 h. The reaction mixture was cooled to room temperature and excess of solvent was removed. The ^{1}H NMR spectrum of the crude sample showed the formation of two diastereoisomers in a ratio of 1 : 2.7. The crude mixture was subjected to radial chromatography ($CHCl_3$) to get rid of unreacted dimethyl acetylenedicarboxylate and the aromatic product. The adducts **67** and **68** were isolated as an inseparable colorless oil (908.6 mg, 71.5%).

Hydrogenation of the mixture 67 and 68: Adduct mixture **67** and **68** (59 mg, 0.23 mmol) along with Pt/C catalyst (15 mg) in EtOAc (10 mL) was kept under hydrogen. After 6 h only one double bond equivalent of H_2 was taken up. Filtration of the

catalyst and evaporation of the solvent gave a syrupy liquid (59 mg). The crude alcoholic mixture was separated by PLC (Pet. ether : Ether 3:1) to furnish alcohol **69** (10.8 mg, 18.2%) and of alcohol **70** (45.6 mg, 76.7%) .

Adduct alcohol 69: ^{1}H NMR (400 MHz): 3.80 (m, 1H, C_7-H), 3.73 (s, 6H, 2 x OCH_3), 2.64-2.58 (br m, 2H, C_3-H and C_6-H), 1.75-1.63 (m, 4H, -CH_2-CH_2), 1.20 (d, 3H, $J_{Me,7}$ = 6.71 Hz, -CH_3 at C_7), 1.10 (d, 3H, $J_{Me,6}$ = 6.71 Hz, -CH_3 at C-6); high resolution mass spectrum calcd for $C_{12}H_{16}O_4$ (M^+-MeOH) 224.1048, found 224.1034.

Adduct alcohol 70: A colorless syrup, ^{1}H NMR (400 MHz): 3.98 (dq, 1H, C_7-H), 3.77 (s, 3H, -OCH_3), 3.70 (s, 3H, -OCH_3), 2.69-2.67 (br, m, 1H, C_3-H) 2.49-2.45 (br, m, 1H, C_6-H), 2.18 (br, 1H, -OH), 1.84-1.77 (m, 1H) and 1.68-1.58 (m, 3H, -CH_2-CH_2-), 1.17 (d, 3H, $J_{Me,7}$ = 6.10 Hz, -CH_3 at C_7), 1.11 (d, 3H, $J_{Me,6}$ = 7.32 Hz, -CH_3 at C_6); high resolution mass spectrum calcd for $C_{12}H_{16}O_4$(M^+-MeOH) 224.1048, found 224.1030.

Lactonization of the Minor Alcoholic Adduct 69: A solution of adduct **69** (10.8 mg, 0.04 mmol) in MeOH (1 mL) along with 1 drop of a saturated oxalic acid solution was refluxed for 1.5h. The course of the reaction was followed by tlc. The reaction mixture was cooled, excess methanol was removed by rotary evaporator and the remaining pasty mass was dissolved in EtOAc and passed through a short column of florisil. The product was purified by PLC (Pet. ether: EtOAc 1.5 : 1) to furnish the minor lactone **71** as a gum (7.9 mg, 73.1%) which was crystallized from Pet. ether : EtOAc to give the lactone **71** as colorless crystals m.p. 97°.

Minor Lactone 71: ^{1}H NMR (400 MHz): 4.10 (dq, 1H, $J_{3,9}$ = 9.15 Hz, $J_{Me,3}$ = 6.1

Hz, C_3-H), 3.81 (s, 3H, -COOCH_3), 2.77 (ddd, 1H, J = 9.15, 4.27 and 3.05 Hz, C_9-H), 2.45 (m, 1H, C_6-H), 1.90-1.84 (m, 1H, -CH_2 -CH_2-), 1.76-1.55 (m, 2H, -CH_2 -CH_2), 1.46 (d, 3H, $J_{Me,3}$ = 6.1 Hz, -CH_3 at C_3), 1.35-1.10 (m, 1H, -CH_2 -CH_2), 1.07 (d, 3H, $J_{Me,6}$ = 6.71 Hz, -CH_3 at C_6); IR ($CHCl_3$): 1755, 1725 cm^{-1}; Anal. cald. for $C_{17}H_{19}NO_3$: C, 64.28; H, 7.14. Found C, 64.36; H, 7.28.

Lactonization of the Major Adduct Alcohol 70: A solution of adduct **70** (45.6 mg, 0.17 mmol) in MeOH (2 mL) along with 1-2 drops of a saturated oxalic acid solution was refluxed for 1.5h. The course of the reaction was followed by tlc. The reaction mixture was cooled, excess methanol was removed by rotary evaporator and the remaining pasty mass was dissolved in EtOAc and passed through a short column of florisil. The product was purified by PLC (Pet. ether: EtOAc 1.5 : 1) to furnish the major lactone **72** as a colorless syrup (34.6 mg, 75.8%) which was crystallized out in the freezer. The solid was filtered and washed with Pet. ether : EtOAc to give the lactone **72** as colorless crystals, m.p. 76°.

Major Lactone 72: ^{1}H NMR (400 MHz): 4.80 (dq, 1H, $J_{3,9}$ = 7.93 Hz, $J_{Me,3}$ = 6.11 Hz, C_3-H), 3.79 (s, 3H, -COOCH_3), 3.01 (ddd, 1H, J = 7.93, 4.89 and 3.06 Hz, C_9-H), 2.76 (m, 1H, C_6-H), 1.81-1.64 and 1.41-1.29 (m, 4H, -CH_2-CH_2-), 1.19 (d, 3H, $J_{Me,3}$=6.11 Hz, -CH_3 at C_3), 1.07 (d, 3H, $J_{Me,6}$ = 6.71 Hz, -CH_3 at C_6); IR ($CHCl_3$): 1755, 1725 cm^{-1}; Anal. calcd. for $C_{17}H_{19}NO_3$: C, 64.28; H, 7.14. Found C, 63.93; H, 7.15.

Diels-Alder Reactions of 3-Methyl-1,4,6-heptatriene (14) with Maleic anhydride (15): A mixture of 3-methyl-1,4,6-heptatriene (**14**, 115 mg, 1. 06 mmol)

and maleic anhydride (108 mg, 1.1 mmol) in dry benzene (4 mL) was kept under reflux for 2 days. The solvent was removed the ^1H NMR (400 MHz) spectrum showed the presence of two products in a ratio of 63 : 37 the mixture was purified by PLC (Pet. ether : EtOAc 4 : 1) to furnish an inseparable mixture of adducts **74** and **75** as a white solid , mp 60° (178 mg , 81.5%) .The mixture was not further characterized.

Diels-Alder Reactions of 3-Methyl-1,4,6-heptatriene (14) with N-Phenyl maleimide (15): A mixture of 3-methyl-1,4,6-heptatriene (**14**, 59 mg, 0.54 mmol) and N-phenylmaleimide (89 mg, 0.51 mmol) in dry benzene (2 mL) was kept under reflux for 2 days. The solvent was removed the ^1H NMR (400 MHz) spectrum showed the presence of two products in a ratio of 45 : 55. The concentrated mass was subjected to separation by PLC (Pet. ether : EtOAc) which furnished two products in equal amounts. The product **77** was isolated as a foamy solid (53 mg, 37 %) whereas the the product **76** was isolated as syrupy mass (61, mg, 42.5 %).

Adduct 77: ^1H NMR (400 MHz, $CDCl_3$) 7.37-7.09 (m, 5H, Ar<u>H</u>), 5.93 (m, 2H, C<u>H</u>=C<u>H</u>), 5.76 (ddd, 1H, J = 17.7, 8.55, 1.83 Hz, C<u>H</u>=CH_2), 5.25 (app d, J = 17 Hz, CH=C<u>H</u>H), 5.05 (app d, J = 9.05 Hz, CH=CH<u>H</u>), 3.36 (dd, 1H, J = 9.16, 4.88 Hz, C<u>H</u>CO), 3.18 (dt, 1H, J = 9.16, 2.22 Hz, CH2-C<u>H</u>-CO), 3.01(dq, 1H, J = 6.71, 3.05 Hz, C<u>H</u>CH_3), 2.71 (m, 1H, =CH-C<u>H</u>), 2.15 and 1.93 (m, 2H, C<u>H</u>$_2$), 1.04 (d, 3H, J = 6.71 Hz, CH_3).

Adduct 76: ^1H NMR (400 MHz, $CDCl_3$) 7.38-7.09 (m, 5H, Ar<u>H</u>), 5.87 (d, 2H, J = 3.66 Hz, C<u>H</u>=C<u>H</u>), 5.56 (overlapping ddd, 1H, C<u>H</u>=CH_2), 5.02 (app d, J = 17.09 Hz, CH=C<u>H</u>H), 4.94 (app d, J = 10.37 Hz, CH=CH<u>H</u>), 3.38 (dd, 1H, J = 9.15, 5.50 Hz, C<u>H</u>CO), 3.22 (dt, 1H, J = 9.15, 1.22 Hz, CH2-C<u>H</u>-CO), 2.83 (dq, 1H, J = 6.71, 2.44 Hz, C<u>H</u>CH_3), 2.73 (m, 1H, =CH-C<u>H</u>), 2.14 and 1.97 (m, 2H, C<u>H</u>$_2$), 1.2 (d, 3H, J =

6.71 Hz, $C\underline{H}_3$).

Diels-Alder Reactions of 3-Methyl-1,4,6-heptatriene (14) with DMAD (18): A mixture of 3-methyl-1,4,6-heptatriene (**14**, 112 mg, 1.03 mmol) and DMAD (131 mg, 1.04 mmol) in dry benzene (3 mL) was kept under reflux for 2 days. The solvent was removed the ^1H NMR (400 MHz) spectrum showed the presence of two products in a ratio of 52 : 48. the mixture was purified by chromatotron (Pet. ether : CH_2Cl_2 2 : 1) to furnish an inseparable mixture of adducts **78** and **79** as a colorless syrup (195 mg, 81%). The mixture was not further characterized.

Preparation of 3-vinylcyclohexenone (83)[90]: To a solution of vinylmagnesium bromide (45 mL of a 1M solution in THF, 45 mmol) in dry THF (50 mL) was added dropwise over a period of 15 minutes at 0°C, a solution of 3-ethoxy-2-cyclohexenone (**82**, 5.16g, 36.9 mmol in 45 mL of dry THF). The cooling bath was removed and the reaction mixture was stirred for 1 h. The reaction mixture was quenched with dil. H_2SO_4 (0.1N, 50 mL) extracted with ether (3 x 50 mL). The combined organic extracts were washed with saturated brine solution (50 mL) and dried over anhydrous $MgSO_4$. Evaporation of solvent gave an oil which was distilled under vacuum to furnish 3-vinylcyclohexenone (**83**), bp. 38-40°/.01 mm of Hg lit[90] bp 50°/0.01 Torr (3.14 g (69.8 %) . ^1H NMR (300 MHz, $CDCl_3$) 6.56 (dd, J = 10.73, 17.54 Hz, =CHC=), 5.98 (br s, C=CH), 5.72 (d, J = 17.61 Hz, C=C$\underline{H}$H), 5.5 (d, J = 10.70 Hz, =CH$\underline{H}$), 2.53-2.4 and 2.12-2.06 (2 m, 3 x CH_2).

Preparation of 3-Vinyl-2-cyclohexen-1-ol (80a)[91]: To a suspension of $LiAlH_4$ (1.82g, 48 mmol) in anhydrous ether (50 mL) at 0°C was added dropwise a solution of 3-vinylcyclohexenone[90] (**83**, 3.5g, 28.68 mmol) in anhydrous ether (50 mL). After the

addition, the cooling bath was removed and the mixture was stirred at room temperature for 5 h. The mixture was treated sequentially with ethyl acetate (3.7 mL) and 10% aqueous KOH (11 mL) and then stirred for 30 min. Then the mixture was filtered and insoluble aluminum salt was repeatedly washed with ether. The combined filtrate was dried with anhydrous $MgSO_4$ and evaporation of the solvent furnished a colorless oil. The crude product was purified by distillation (bp. 47-48°/.01 mm of Hg) to give 3.1 g (87.5%) of 3-Vinyl-2-cyclohexen-1-ol (**80a**).

3-Vinyl-2-cyclohexen-1-ol (80a): ^1H NMR (300 MHz, $CDCl_3$) 6.39 (dd, J = 10.74, 17.54 Hz, =CHC=), 5.8 (br s, C=CH), 5.24 (d, J = 17.48 Hz, C=C<u>H</u>H), 5.09 (d, J = 10.83 Hz, =CH<u>H</u>), 4.3 (br s, C<u>H</u>OH), 2.3-1.4 (m, OH & 3 x CH_2); IR ($CHCl_3$) 3595, 3410, 2925, 1650, 1610, 1440, 1050, 855 cm^{-1}.

Preparation of 3-Methoxy-1-vinylcyclohexene (80b): To a mixture of NaH (50% dispersion in mineral oil, 720 mg, 15 mmol) and DMSO (5 mL) was added dropwise a solution of **80a** (1.22 g, 9.83 mmol) in DMSO (3 mL). The mixture was stirred for a period of 1 h after which CH_3I (3.0 mL, 45 mmol) was added dropwise and the resulting mixture was stirred overnight. The mixture was poured into water (50 mL) and extracted from EtOAc (3 x 20 mL). The combined extract was washed with brine (20 mL) and dried over anhydrous $MgSO_4$. After the removal of solvent, the crude product was subjected to flash chromatography (petroleum ether : EtOAc 8 : 2) to give 883 mg (65%) of 3-methoxy -1-vinylcyclohexene (**80b**) as a colorless oil which was further purified by short path distillation (bath temp. 70-75° C at 20 mm of Hg).

3-Methoxy-1-vinylcyclohexene (80b): ^1H NMR (300 MHz, $CDCl_3$) 6.4 (dd, J = 10.76, 17.53 Hz, =CHC=), 5.84 (br s, C=CH), 5.23 (d, J = 17.31 Hz, C = C<u>H</u>H), 5.07 (d, J = 10.76 Hz, =CH<u>H</u>), 3.90 (br s, CHOMe), 3,42 (s, OMe) 2.2 (m, 2H), 1.88 (m,

2H), 1.65 (m, 2H); IR ($CHCl_3$) 2940, 2880, 1670, 1610, 1375, 1090 cm^{-1}; high resolution mass calcd for $C_9H_{14}O$ (M^+) 138.1045, found 138.1041.

Preparation of 3-((Trimethylsilyl)oxy)-1-vinylcyclohexene (80c): BSA (1.8 mL, 7.28 m mol) was added dropwise to neat ice cooled alcohol **80a** (400 mg, 3.22 mmol) and after addition, the cooling bath was removed. The mixture was stirred overnight. The silylated product was purified by flash chromatography (petroleum ether : EtOAc 9 : 1). 3-((trimethylsilyl)oxy)-1- vinyl cyclohexene (**80c**) was isolated as a colorless oil (454 mg, 71.9%).

3-((Trimethylsilyl)oxy)-1-vinylcyclohexene (80c): ^1H NMR (300 MHz, $CDCl_3$) 6.37 (dd, J = 10.75, 17.5 Hz, =CHC=), 5.67 (br s, C=CH), 5.19 (d, J = 17.71 Hz, C=C<u>H</u>H), 5.04 (d, J = 10.71 Hz, =CH<u>H</u>), 4.36 (m, $CHOSiMe_3$), 2.15 (m, 2H), 1.91 (m, 2H), 1.63 (m, 2H), .18 (s, 9H); IR ($CHCl_3$) 2945, 2880, 1610, 1450, 1070, 1010 cm^{-1}; high resolution mass calcd for $C_{11}H_{20}OSi$ (M^+) 196.1284, found 196.1278.

Preparation of 3-Vinyl-1-methyl-2-cyclohexen-1-ol (81a). To a solution of methylmagnesium bromide (5 mL of a 3M solution in ether, 15 mmol) in dry THF (30 mL) was added dropwise at 0°C a solution of 3-vinylcyclohexenone (**83**, 1.51g, 12.37 mmol in 15 mL of dry THF). After 1 h, an aqueous solution of NH_4Cl (50 mL) was added slowly. The mixture was brought to room temperature and extracted from ether (3 x 50 mL). The combined organic extracts were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. Evaporation of solvent gave an oil which was distilled under vacuum to furnish 3-vinyl -1-methyl-2-cyclohexen-1-ol (**81a**) as a colorless liquid (1.3g, 76.5%, bp 49°/.2 mm of Hg).

3-Vinyl-1-methyl-2-cyclohexen-1-ol (81a): ^{1}H NMR (300 MHz, $CDCl_3$) 6.35 (dd, J = 10.74, 17.55 Hz, =CHC=), 5.65 (br s, C=CH), 5.24 (d, J = 17.56 Hz, C=C<u>H</u>H), 5.07 (d, J = 10.76 Hz, =CH<u>H</u>), 2.2-2.07 & 1.8-1.6 (m, OH & 3 X CH_2); IR ($CHCl_3$) 3600, 3450, 1610, 1450, 1380, 1060 cm^{-1}; high resolution mass calcd for $C_9H_{14}O$ (M^+) 138.1045, found 138.1044.

Preparation of 3-Methoxy-3-methyl-1-vinylcyclohexene (81b): To a mixture of KH (35% dispersion in mineral oil, 457 mg, 4 mmol) and dry THF (10 mL) was added dropwise a solution of **81a** (442 mg, 3.2 mmol) in dry THF (3 mL). The resulting mixture was stirred for 1 h and CH_3I (1 mL, 15 mmol) was added dropwise. After one hour, the reaction mixture was poured into water (10 mL) with caution and extracted from EtOAc (3 X 15 mL). The combined extract was washed with brine (15 mL) and dried over anhydrous $MgSO_4$. After solvent evaporation, the crude product was purified by flash chromatography (petroleum ether : EtOAc 9 : 1) to give 3-methoxy-3-methyl-1-vinyl cyclohexene (**81b**) as a colorless oil (298 mg, 67.6%).

3-Methoxy-3-methyl-1-vinylcyclohexene (81b): ^{1}H NMR (300 MHz, $CDCl_3$) 6.39 (dd, J = 10.66, 17.65 Hz, =CHC=), 5.63 (br s, C=C<u>H</u>), 5.23 (d, J = 17.55 Hz, C=C<u>H</u>H), 5.07 (d, J = 10.78 Hz, =CH<u>H</u>), 3.24 (s, OCH_3) 2.2 -2.1 and 1.97-1.44 (m, 6H), 1.30 (s, CH_3); IR ($CHCl_3$) 2950, 1610, 1455, 1375, 1110, 1070 cm^{-1}; high resolution mass calcd for $C_{10}H_{16}0$ (M^+) 152.1201, found 152.1201.

Preparation of 3-((Trimethylsilyl)oxy)-3-methyl-1-vinylcyclohexene (81c): BSA (.5 ml, 2 mmol) was added dropwise to neat ice cooled alcohol **81a** (130 mg, .94 m mol) at 0°C. Work up as described for the preparation of **80c** gave 3-((trimethylsilyl)

oxy)-3-methyl-1-vinyl cyclohexene (**81c**) as a colorless oil (123 mg, 66.7%).

3-((Trimethylsilyl)oxy)-3-methyl-1-vinylcyclohexene (81c): ^{1}H NMR (300 MHz, $CDCl_3$) 6.36 (dd, J = 10.7, 17.48 Hz, =CHC=), 5.68 (br s, C=CH), 5.22 (d, J = 17.21 Hz, C=C<u>H</u>H), 5.06 (d, J = 10.74 Hz, =CH<u>H</u>), 2.4-2.0 (m, 2H), 1.88-1.79 (m, 2H), 1.7-1.5 (m, 2H), 1.35 (s, Me), 0.13 (s, 9H); IR ($CHCl_3$) 2950, 1610, 1450, 1030, 910 cm^{-1};

Diels-Alder Reaction of 3-Vinyl-2-cyclohexen-1ol (80a) with N-Phenyl maleimide: A solution of alcohol **80a** (256 mg, 2.06 m mol) and N-phenylmaleimide (357 mg, 2.06 m mol) in dry benzene (4 mL) was stirred at room temperature for 3 days. ^{1}H NMR and tlc of the crude product showed the formation of three products. The reaction mixture was refluxed for 3 h and the NMR of the crude product showed only two products, which were separated by radial chromatography (CH_2Cl_2 : acetone 19 : 1). The first fraction was a tricyclic lactone **86** (242 mg, 39.5%)which was crystallized from acetone : water to give colorless needles, mp 240°. The second fraction was the *anti* alcohol **85a** obtained as a foamy solid (207 mg, 33.8%) . When the reaction product was concentrated without reflux the *syn* alcohol **84a** was crystallized out in the freezer. The crystals were filtered and washed with benzene to give pure **84a**, mp 163-64°.

***Syn* Adduct Alcohol 84a** : ^{1}H NMR (300 MHz, $CDCl_3$) 7.55-7.3 (m, PhH), 5.84 (br s, C=CH), 4.34 (br d, C<u>H</u>OH), 3.43 (app t, J = 9.19 Hz, COCH), 3.24 (dt, J = 9.9 & 3.23 Hz, COC<u>H</u>-CH_2), 2.83 (m, 2H), 2.6-2.4 (m, 2H), 2.2-1.5 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) 178.90, 177.99, 134.66, 132.39, 129.04, 128.39, 126.69, 119.97, 69.17, 41.02, 40.13, 36.69, 36.11, 33.25, 23.33, 20.99; IR ($CHCl_3$) 3300, 1710, 1600, 1560, 1390 cm^{-1}; Anal. calcd for $C_{18}H_{19}NO_3$: C, 72.72; H, 6.39; N, 4.71. Found: C, 72.52; H, 6.53; N, 4.74.

***Anti* Adduct Alcohol 85a** : ^{1}H NMR (300 MHz, $CDCl_3$) 7.6-7.2 (m, PhH), 5.65 (br s, C=CH), 4.16 (m, C<u>H</u>OH), 3.71 (m, COC<u>H</u> & O<u>H</u>), 3.20 (Overlapping ddd, COC<u>H</u>-CH_2), 2.51 (m, 2H), 2.3-2.1 (m, 2H), 1.85-1.5 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) 178.66, 178.37, 139.08, 131.75, 129.12, 128.65, 126.69, 118.32, 69.70, 44.55, 40.66, 39.54, 32.89, 31.61, 24.72, 22.11; IR ($CHCl_3$) 3450, 1700, 1390, 1140 cm^{-1}; high resolution mass calcd for $C_{18}H_{18}NO_3$ (M^+-H) 296.1286, found 296.1282.

Tricyclic Lactone 86: ^{1}H NMR (300 MHz, $CDCl_3$) 10.1 (br s, NH), 7.7-7.1 (m, PhH), 5.76 (br s, C=CH), 4.78 (app d, J = 3.04 Hz, CHOCO), 3.43 (dd, J = 5.7, 2.8 Hz, CHCO), 3.04 (m, 1H), 2.96 (dt, J = 8.5, 2.8 Hz, NHCOC<u>H</u>CH_2), 2.7-1.5 (series of m, 8H); IR ($CHCl_3$) 3300, 1745, 1675, 1600, 1550, 1440 cm^{-1}; Anal. calcd for $C_{18}H_{19}NO_3$: C, 72.72; H, 6.39; N, 4.71. Found: C, 72.66; H, 6.49; N, 4.63.

Diels-Alder Reaction of 3-Methoxy-1-vinylcyclohexene (80b) with N-Phenyl maleimide:

A solution of methyl ether **80b** (181 mg, 1.31 mmol) and N-phenylmaleimide (266 mg, 1.53 mmol) in dry benzene (3 mL) was stirred at room temperature for 3 days.. The reaction mixture was concentrated and the ^{1}H NMR showed the formation of two adducts. The products were separated by radial chromatography (petroleum ether : $CHCl_3$: acetone 50 : 48 : 2). The major adduct (**85b**) was obtained as a solid (309 mg, 75.86%) which was crystallized from petroleum ether : EtOAc to give colorless crystals (mp 96°). The minor adduct (**84b**) was isolated along with a trace of N-Phenylmaleimide (28.2 mg, 6.9 %) which was crystallized from petroleum ether : EtOAc as colorless crystals (mp 120°C).

***Anti* Adduct 85b (Major)**: ^{1}H NMR (300 MHz, $CDCl_3$) 7.6 - 7.2 (m, PhH), 5.64 (br

s , =CH), 4.33 (ddd, J = 11.0, 9.84, 4.58 Hz, C<u>H</u>OCH$_3$), 3.65 (dd, J = 8.52, 5.9 Hz, COCH), 3.51 (s, OCH$_3$), 3.26 (overlapping dt, CH$_2$C<u>H</u>CO), 2.71 (m, =CHC<u>H</u>H), 2.6 - 1.2 (m, 8H); ^{13}C NMR (75 MHz, CDCl$_3$) 179.13, 177.54, 140.62, 129.06, 128.48, 126.52, 119.01, 76.38, 56.4, 43.36, 40.60, 29.13, 27.64, 25.18, 20.19; IR (CHCl$_3$) 1700, 1490, 1380, 1320 cm^{-1}; Anal. calcd for $C_{19}H_{21}NO_3$: C, 73.71; H, 6.75; N, 4.50. Found: C,73.32; H, 6.69; N, 4.55.

***Syn* Adduct 84b (Minor)**: ^{1}H NMR (300 MHz, CDCl$_3$) 7.5- 7.2 (m, PhH), 5.64 (br s , =CH), 3.90 (d, J = 2.33 Hz, C<u>H</u>OCH$_3$), 3.32 (app t, J = 9.7 Hz, COCH), 3.14 (dt, J = 4.4, 9.9 Hz CH$_2$C<u>H</u>CO), 3.03 (s, OCH$_3$), 2.75 (d, J = 9.59 Hz , allylic CH), 2.66 (br d, J = 18.03 Hz, =CHC<u>H</u>H), 2.49-1.2 (m, 7H); ^{13}C NMR (75 MHz, CDCl$_3$) 135.18, 134.21, 129.14, 128.88, 127.95, 126.04, 118.22, 76.61, 55.36, 40.72, 39.34, 36.96, 36.69, 27.26, 23.42, 21.24; IR (CHCl$_3$) 1700, 1490, 1440, 1380 cm^{-1}; high resolution mass calcd for $C_{19}H_{21}NO_3(M^+)$ 311.1522, found 311.1516.

Conversion of 85a to 85b: A mixture of alcohol adduct **84a** (50 mg, 0.16 mmol), Ag$_2$O (42 mg, 0.18 mmol), K$_2$CO$_3$ (23 mg, 0.16 mmol), MeI (0.4 mL 22.8 mmol) and dry CHCl$_3$ (2 mL) was stirred at room temperature for 4 days. After filtration and solvent evaporation , the crude mass was subjected to PLC separation (petroleum ether : EtOAc 1:1) to give **85b** (19 mg, 36.4%) and 9.3 mg of recovered alcohol **84a**.

Diels-Alder Reaction of 3-((Trimethylsilyl)oxy)-1-vinylcyclohexene (80c) with N-Phenylmaleimide (16):

A solution of silyl ether **80c** (355 mg, 1.81 m mol) and N-phenylmaleimide (365.5 mg, 2.11 mmol) in dry benzene (6 mL) was stirred at room temperature for 4 days. Solvent was

removed and the ^1H NMR spectrum of the reaction mixture showed the formation of two adducts. The crude reaction mixture was purified by radial chromatography ($CHCl_3$: acetone 95 : 5). The inseparable mixture of diastereomers **84c** and **85c** were obtained as a colorless oil (471 mg, 70.5 %). Major adduct **12c**: ^1H NMR (300 MHz, $CDCl_3$) 7.5- 7.2 (m, PhH), 5.63 (br s , =CH), 4.89 (ddd, J = 11.2, 9.4, 4.7 Hz, C<u>H</u>OSiCH_3), 3.54 (dd, J = 8.58, 5.25 Hz, COCH), 3.26 (m, CH_2C<u>H</u>CO), 2.71 (m, =CHC<u>H</u>H), 2.4 - 1.3 (m, 8H), 0.22 (s, $SiMe_3$).

Hydrolysis of Silyl adduct mixture 84c and 85c:

To a methanolic solution (10 mL) of the silylated adduct mixture **84c** and **85c** (450 mg, 1.21 m mol) was added few drops of saturated oxalic acid solution. After two hours of stirring at room temperature, solvent was removed and the resulting product was dried. The crude mass was passed through a short column of florisil and eluted with EtOAc. Removal of solvent gave a pasty mass (281 mg, 78%). The ^1H NMR of the product was identical with anti alcoholic adduct **85a**. A trace amount of tricyclic lactone **13** was also detected in the ^1H NMR spectrum.

Diels-Alder Reaction of 3-Vinyl-2-cyclohexen-1-ol (80a) with DMAD (17):

A solution of alcohol **80a** (136.4 mg, 1.1 mmol) and dimethyl acetylenedicarboxylate (213 mg, 1.5 mmol) in dry benzene (4 mL) was kept under reflux for 40 h. ^1H NMR of the concentrated product showed the formation of two adducts along with some aromatic products. The mixture was separated by radial chromatography ($CHCl_3$) to furnish major adduct **88a** (189.37 mg, 64. 37%) and minor adduct **87a** (52.6 mg, 18%).

***Anti* Adduct 88a (Major):** ^1H NMR (300 MHz, $CDCl_3$) 5.50 (br s, C=CH), 3.79 (s, OCH_3), 3.82 (s, OCH_3), 3.51 (overlapping ddd, C<u>H</u>OH), 3.16 (m, =CHC<u>H</u>H and allylic

CH), 2.9 (m, =CHCHH), 2.44 - 1.22 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) 172.23, 168.57, 137.81, 135.95, 131.20, 117.05, 76.33, 53.23, 53.03, 49.48, 37.19, 35.39, 28.47, 25.95. high resolution mass calcd for $C_{14}H_{17}O_5$ (M^+-H) 265.1075, found 265.1071.

***Syn* Adduct 87a (Minor):** ^1H NMR (300 MHz, $CDCl_3$) 5.65 (br s, C=CH), 4.11 (br s, CHOH) 3.9 (s, OCH_3) 3.86 (s, OCH_3), 3.3 - 2.9 (m, =CHCH2 and allylic CH), 2.6 - 1.57 (m, 7H); high resolution mass calcd for $C_{14}H_{17}O_5$ (M^+) 266.1154, found 266.1149.

Diels-Alder Reaction of 3-((Trimethylsilyl)oxy)-1-vinylcyclohexene (80c) with DMAD (17):

A solution of silyl ether **6c** (202 mg, 1.03 mmol) and dimethyl acetylenedicarboxylate (257 mg, 1.81 mmol) in dry benzene (4 mL) was kept under reflux for 3 days. ^1H NMR of the concentrated crude product showed the formation of two adducts. The products were separated by flash chromatography ($CHCl_3$) to give minor adduct **87b** (7.25 mg, 2%), major adduct **88b** (172.52 mg, 49.5%) and mixture of **87b** and **88b** (15.15 mg, 4.35%).

***Anti* Adduct 88b (Major)** : ^1H NMR (300 MHz, $CDCl_3$) 5.46 (br s, =CH), 3.78 (s, OCH_3), 3.77 (s, OCH_3),3.43 (dt, J = 10.4, 3.99 Hz,CHOSiMe$_3$), 3.20 (m, =CHCHH and allylic CH),2.83 (m,=CHCHH), 2.28-1.25 (series of m, 6H), 0.11 (s, $SiMe_3$); IR ($CHCl_3$) 1725, 1440, 1270, 1105 cm^{-1}.

***Syn* Adduct 87b**: ^1H NMR (300 MHz, $CDCl_3$) 5.53 (br s, =CH), 4.2 (br s CHOSiMe$_3$), 3.8 (s, 2XOCH_3), 3.12 (m, =CHCHH and allylic CH),2.9 (m,=CHCHH), 2.35-1.57 (series of m, 6H), 0.063 (s,$SiMe_3$); high resolution mass calcd for $C_{17}H_{27}O_5Si$

(M^++ H) 339.1627, found 339. 1628.

Hydrolysis of Major Silyl adduct 88b:

A methanolic solution (1 mL) of the silyl adduct **15b** (30 mg, 0.08 mmol) was stirred at room temperature along with few drops of saturated oxalic acid solution for .5 h. Similar work up as described for the hydrolysis of **84c** and **85c** gave adduct alcohol (19.7 mg, 83.5%) as a colorless syrup which was identical to the *anti* alcohol adduct **88a**, obtained from the reaction of **80a** with DMAD (**17**).

Diels-Alder Reaction of 3-Vinyl-2-cyclohexen-1ol (80a) with 4-Phenyl-1, 2, 4- triazoline-3,5 -dione (18):

A solution of alcohol **80a** (92.7 mg, 0.74 mmol) in 2 mL of dry THF : CH_2Cl_2 (1 : 1) was added dropwise to a solution (2 mL) of 4-Phenyl-1, 2, 4- triazoline-3,5 -dione (130 mg, 0.74 mmol) in dry THF : CH_2Cl_2 (1 : 1) at -78°C. The resulting solution was stirred for 15 minutes, the cooling bath was removed and the solution was stirred for an additional 15 minutes. The solvent was removed and ^1H NMR showed the formation of a single adduct. The concentrated product was dissolved in CH_2Cl_2 (1 mL) and passed through a short column of silica gel. The column was eluted with CH_2Cl_2 and on solvent removal the cycloadduct **89** was obtained as a solid (179 mg, 80.9%). The adduct was crystallized from water : acetone to give white crystalline solid (mp 205-06°C).

***Anti* Adduct 89**: ^1H NMR (300 MHz, $CDCl_3$) 7.58-7.3 (m, PhH), 5.76 (br s, =CH), 5.34 (d, J = 3.21 Hz, OH), 4.32 (d, J = 8.79, allyic CH), 4.18 (overlapping qd, =CH-C$\underline{H}_2$N), 3.81 (m, C$\underline{H}$OH), 2.46 (m, 1H), 2.25 (m, 1H), 1.9 (m, 1H), 1.64 (m, 1H), 1.39 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 134.07, 129.28, 129.24, 128.48, 125.79, 125.72, 125.67, 114.46, 74.26, 64.2, 43.0, 34. 07, 33.94, 24.15; IR ($CHCl_3$)

3350, 1700, 1499, 1460 cm^{-1}; Anal. calcd for $C_{16}H_{17}N_3O_3$: C, 64.2; H, 5.68; N, 14.04. Found: C, 63.96; H, 5.80; N, 13.87.

Diels-Alder Reactions of 3-Vinyl-1-methyl-2-cyclohexen-1-ol (81a) with N-Phenylmaleimide (16):

A solution of alcohol **81a** (226 mg, 1.63 m mol) and N-phenylmaleimide (283 mg, 1.63 m mol) in dry benzene (3 mL) was stirred at room temperature. After a few hours the tricyclic lactone (**92**) started separating out as a white solid.The reaction was continued for three days. The crude mixture was concentrated and ^1H NMR of the mixture showed the formation of two products. To the concentrated product benzene (5 mL) was added and the insoluble lactone (**92**) was filtered, washed with benzene and crystallized from acetone : water as colorless needles, mp 213°C. ^1H NMR of the mother liquor showed a mixture of two adducts which were separated by PLC (petroleum ether : EtOAc 3 : 1) to give the tricyclic lactone **92** (19 mg, combined yield 66.9%) and the minor adduct alcohol **91a** (27 mg, 5.3%).

Tricyclic Lactone 92: ^1H NMR (300 MHz, $CDCl_3$) 10.1 (br s, NH), 7.7-7.1 (m, PhH), 5.75 (br s, C=CH), 3.73 (dd, J = 5.75, 2.8 Hz, COCH), 2.92 (dt, J = 8.5, 2.75 Hz, NHCOC<u>H</u>CH_2), 2.82 (br s, OCCHC<u>H</u>), 2.8-1.5 (series of m, 8H), 1.54 (s, CH_3); IR ($CHCl_3$) 3305, 1740, 1670, 1600, 1555, 1445 cm^{-1}; Anal. calcd for $C_{19}H_{21}NO_3$: C, 73.31; H, 6.75; N, 4.50. Found: C,73.54; H, 6.70; N, 4.52.

***Anti* Adduct 91a (Minor)** : ^1H NMR (300 MHz, $CDCl_3$) 7.6-7.3 (m, PhH), 5.74 (br s, C=CH), 4.76 (s, OH), 3.68 (app t, J = 8.9 Hz, COCH), 3.12 (ddd, J = 15.8, 8.9, 6.9 Hz, COC<u>H</u>CH_2), 2.95 (d, J = 9.41 Hz, allylic CH), 2.59 (m, COCHC<u>H</u>H), 2.41-1.39 (m, 6H), 1.24 (s, CH_3); IR ($CHCl_3$) 3420, 1700, 1600, 1490, 1395 cm^{-1}; high resolution mass calcd for $C_{19}H_{20}NO_3$ (M^+-H) 310.1443, found 310.1438.

Diels-Alder Reaction of 3-Methoxy-3-methyl-1-vinylcyclohexene (81b) with N-Phenyl maleimide (16):

A solution of methyl ether **81b** (290 mg, 1.9 mmol) and N-phenylmaleimide (330 mg, 1.9 mmol) in dry CH_2Cl_2 (2.5 mL)was taken into a disposable syringe (3 mL). The air bubbles inside the syringe were removed and the needle of the syringe was replaced by a teflon cap which was tightly closed and covered with parafilm. The syringe was dropped into the high pressure body of LECO high pressure generator (which contained caster oil) and pressure was applied (6 Kbar) to the system. The reaction was continued under high pressure for 5 days. The system was depressurized and the syringe containing the reaction mixture was removed and washed with petroleum ether to get rid of the oil. The reaction mixture was concentrated and the ^1H NMR of the mixture showed the formation of two products. The concentrated mixture was dissolved in a minimum amount of EtOAc and was cooled overnight in the freezer. The major adduct **91b** crystallized out as a solid which was filtered (234 mg) and was recrystallized from petroleum ether : EtOAc to furnish colorless crystals (mp. 122°C). The mother liquor was concentrated and subjected to separation by radial chromatography (petroleum ether : $CHCl_3$: acetone 50 : 48 : 2) to give additional amount of **91b** (56.1 mg, combined yield of 46.9%). The other fraction was the minor adduct **90b** (115 mg, 18.6%) which was isolated along with a trace of NPM.

Major Adduct 91b: ^1H NMR (300 MHz, $CDCl_3$) 7.6-7.24 (m, PhH), 5.7 (br s, C=CH), 3.49 (dd, J = 8.39, 5.49 Hz,COCH), 3.32 (dt, J = 8.7, 2.16 Hz, COC<u>H</u>CH_2), 3.23 (s, OCH_3), 2.79 (ddd, J = 16.17, 6.08, 1.98 Hz, =CHC<u>H</u>H), 2.63(app d, J = 5.35 Hz, allylic CH), 2.46-1.39 (m, 7H), 1.59 (s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 179.09, 177.56, 140.27, 132.14, 129.16, 128.52, 126.42, 119.81, 76.78, 48.5, 45.65, 42.14, 40.95, 31.81, 31.15, 24.02, 21.39, 20.31; IR ($CHCl_3$) 1710, 1500, 1450, 1390 cm^{-1};

high resolution mass calcd for $C_{20}H_{24}NO_3$ (M^+ + H) 326.1756; found 326.1756.

Minor Adduct 90b: ^1H NMR (300 MHz, $CDCl_3$) 7.6-7.3 (m, PhH), 5.7 (br s, C=CH), 3.46 (dd, J = 8.97, 7.59, Hz, COCH), 3.32 (dt, J = 8.3, 3.44 Hz, $COC\underline{H}CH_2$), 3.13 (s, OCH_3), 2.8 (m, 1H), 2.56 (app d, J = 7.69 Hz, allylic CH), 2.5-1.4 (m, 7H), 1.38 (s, CH_3); IR ($CHCl_3$) 1710, 1495, 1450, 1385 cm^{-1}; high resolution mass calcd for $C_{20}H_{24}NO_3$ (M^+ + H) 326.1756; found 326.1750.

Diels-Alder Reaction of 3-((Trimethylsilyl)oxy)-3-Methyl-1 -Vinyl cyclohexene (81c) with N- Phenylmaleimide (16) :

A solution of silyl ether **81c** (123 mg, 0.59 mmol) and N-phenylmaleimide (102 mg, 0.59 mmol) in dry benzene (2 mL) was stirred for 5 days. The reaction mixture was concentrated and the ^1H NMR showed the formation of two products. PLC separation (Pet. ether : EtOAc 8 : 2).furnished two fractions. The major fraction was a mixture of adducts **90c** and **91c** (113 mg, 50%) which could not be further separated. The second fraction was the unreacted NPM (37 mg) .

Hydrolysis of Silyl Adduct Mixture 90c and 91c:

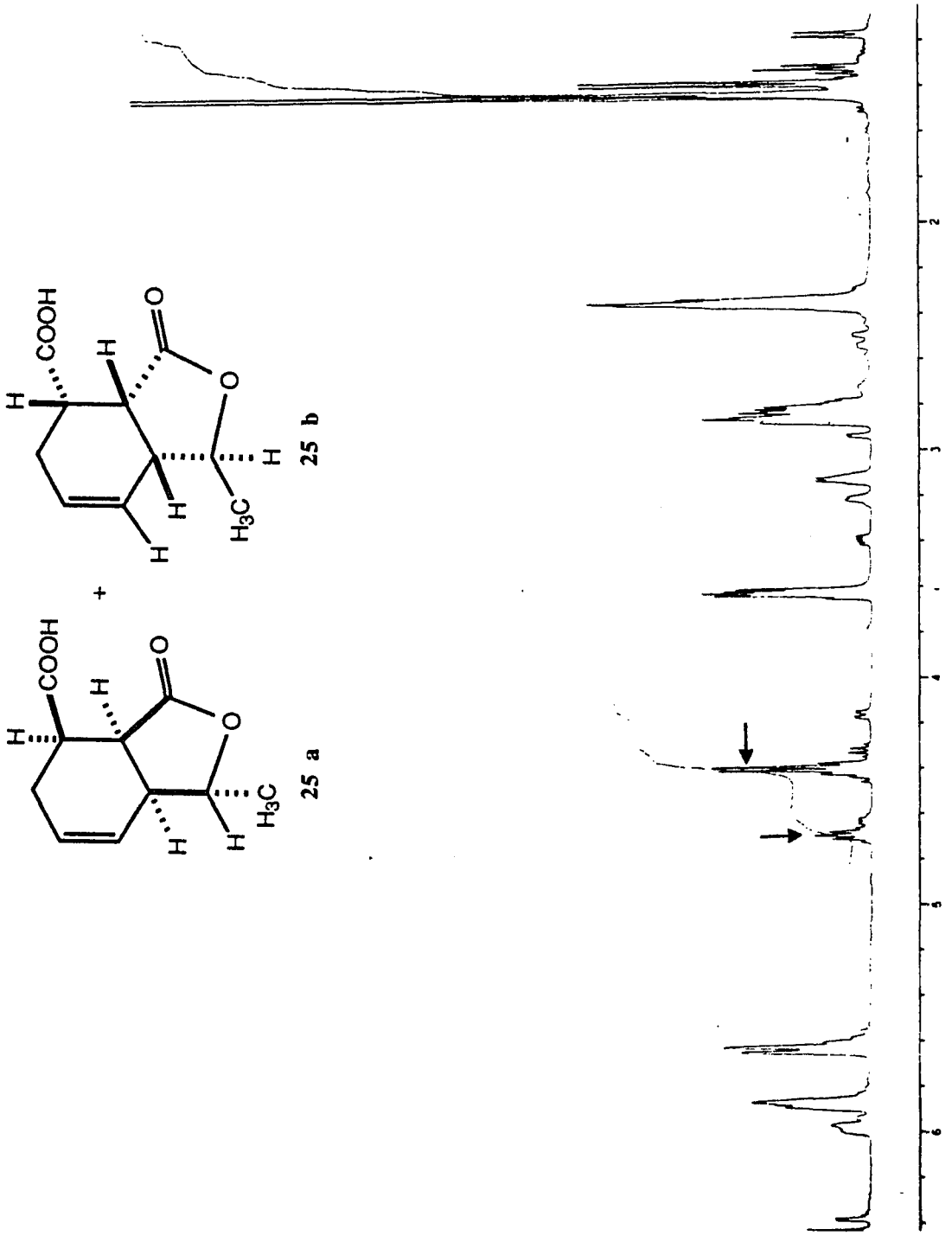
To a methanolic solution (2 mL) of silyl adduct mixture **90c** and **91c** (113 mg, 0.29 mmol) was added a few drops of saturated oxalic acid solution and the solution was stirred for 0.5h. Solvent was removed and the resulting mass was dried under vacuum. The crude mixture was separated by PLC (CH_2Cl_2 : EtOAc 9 : 1) to give the tricyclic lactone **19** (16.1 mg, 17.5%) and the *anti* alcohol **91a** (68 mg, 74.1%).

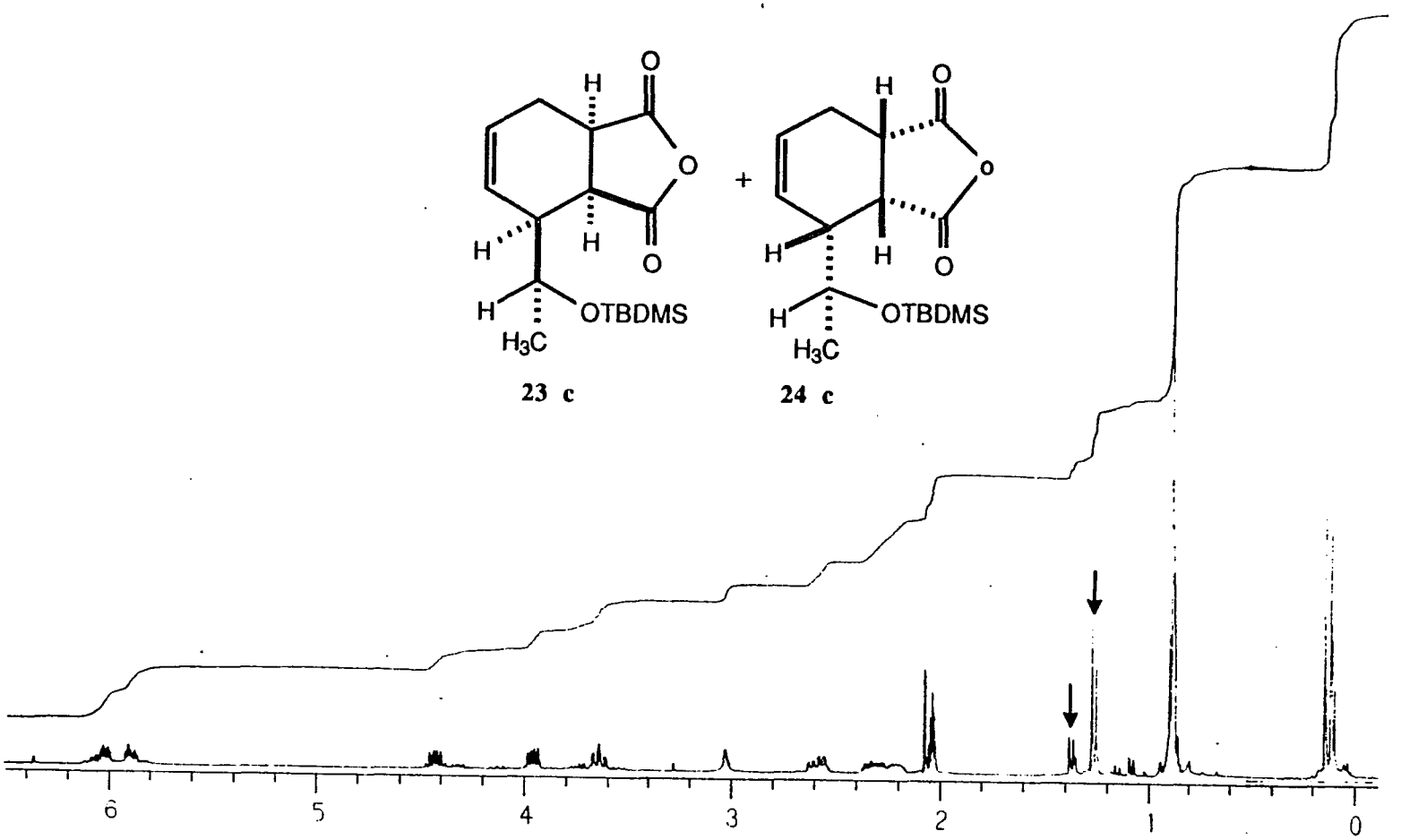
Lactonization of 91a:

A methanolic solution (1 mL) of the *anti* alcohol **91a** (27 mg, 0.08 mmol) along with a

few drops of saturated oxalic acid solution was kept under reflux for 72h. Solvent was removed and the crude mixture was purified by passing through a short column of florisil and by eluting with EtOAc. Evaporation of solvent furnished a pasty mass and ^{1}H NMR showed a mixture of products. The major product was identical to the tricyclic lactone **92**. The mixture was not further separated.

VI. Appendix





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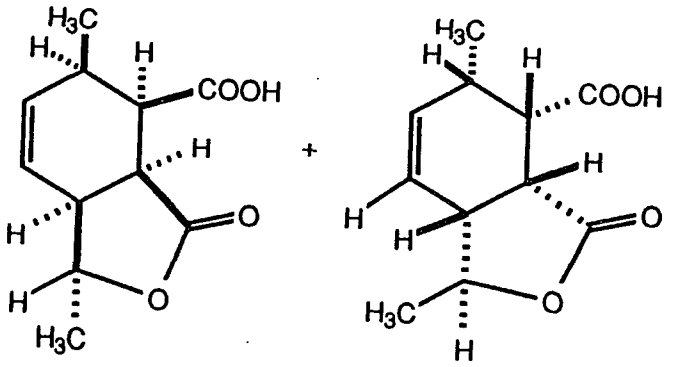

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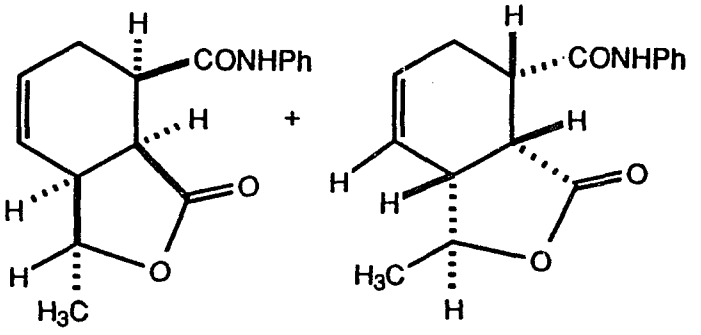

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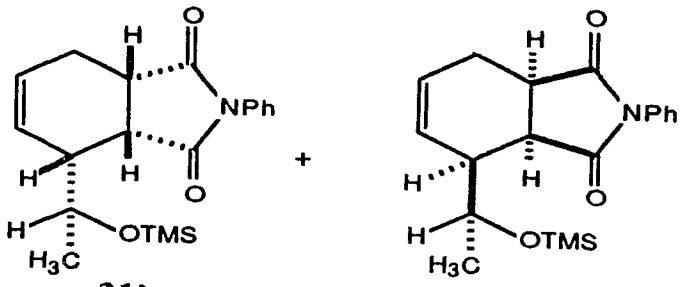
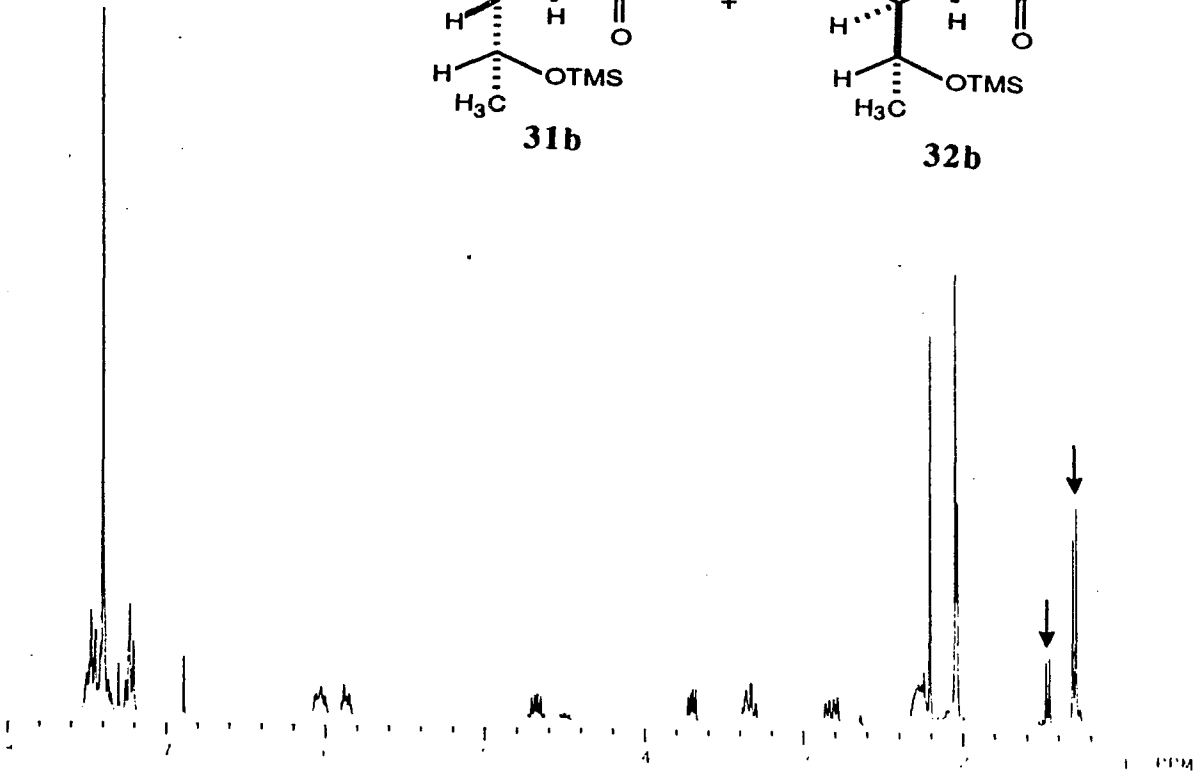
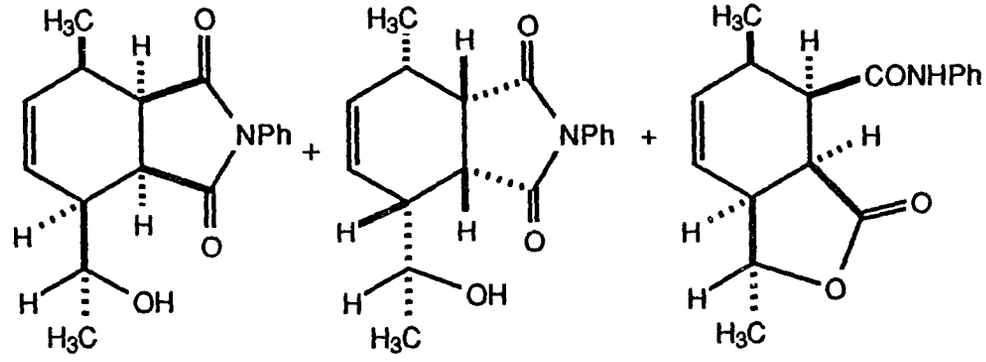


31b + 32b

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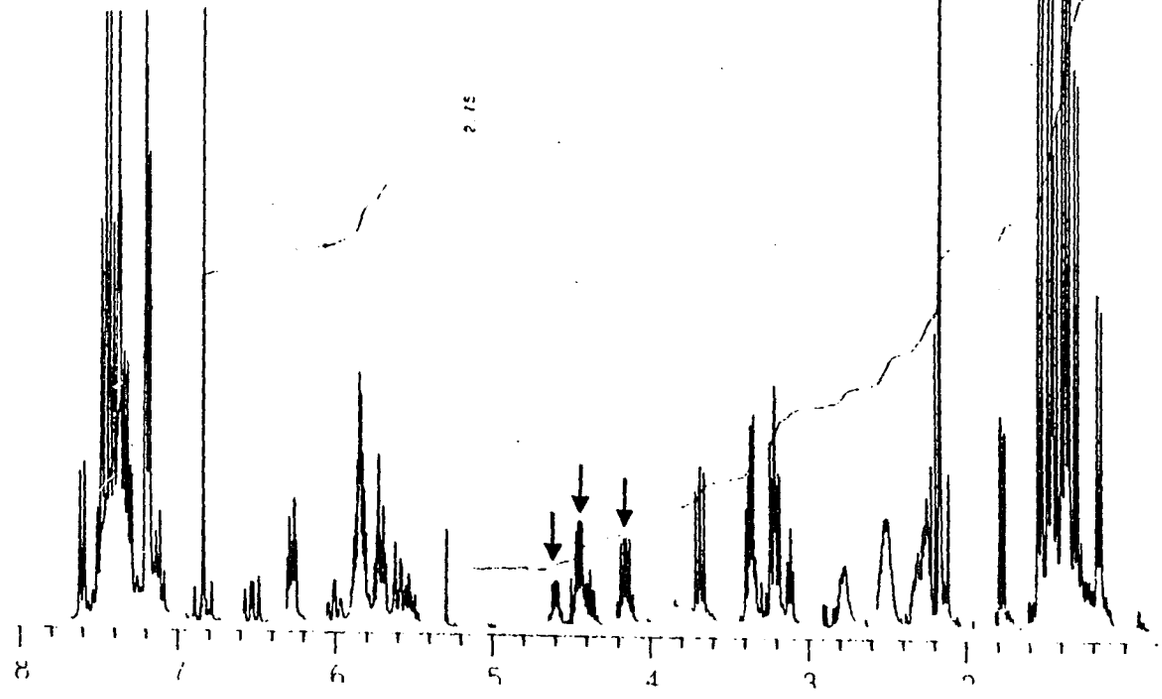
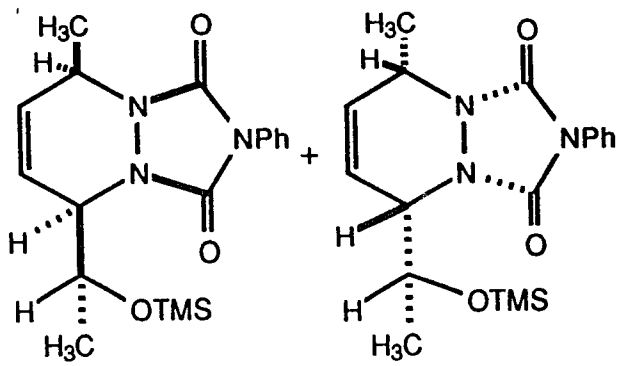
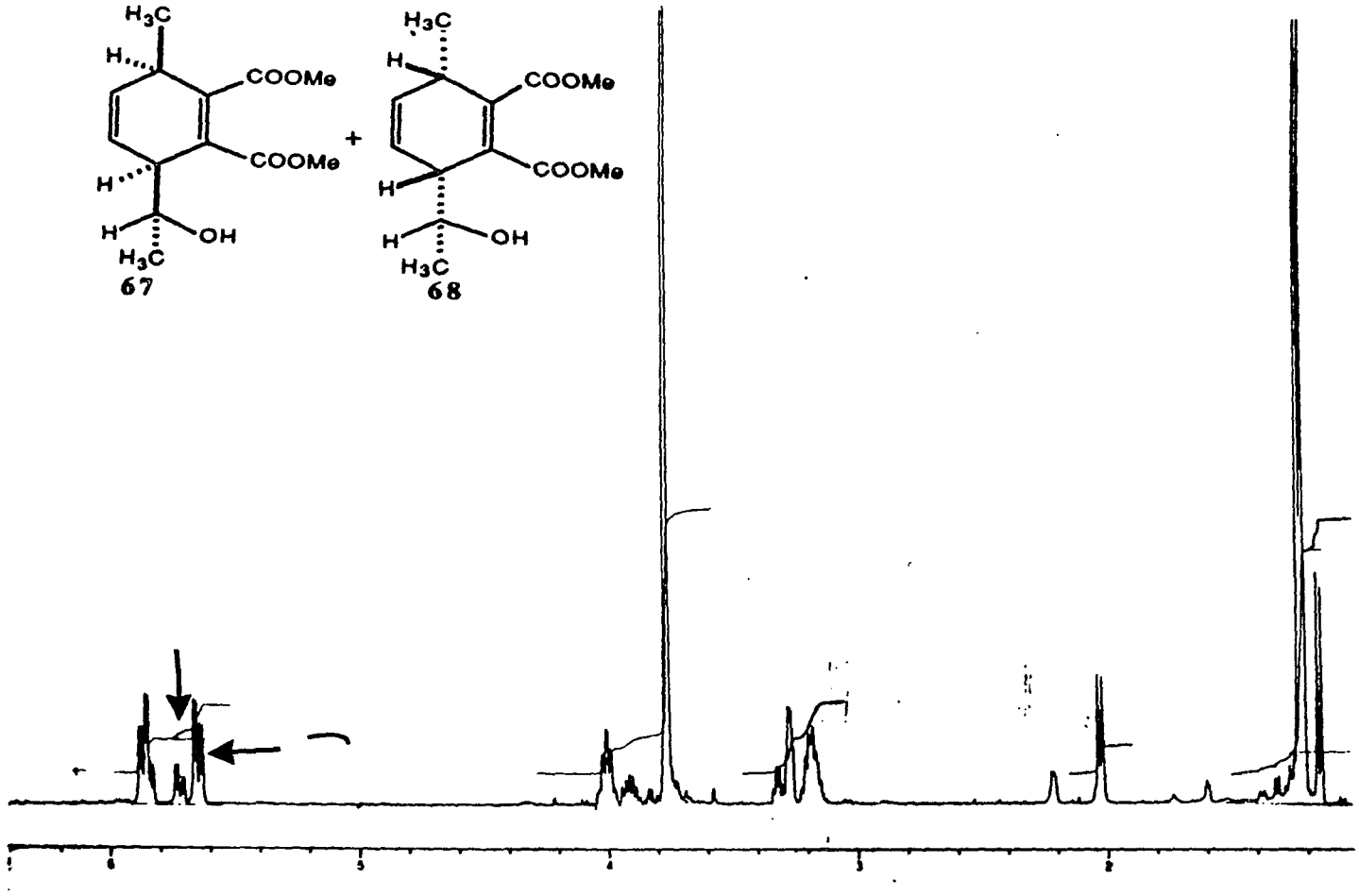
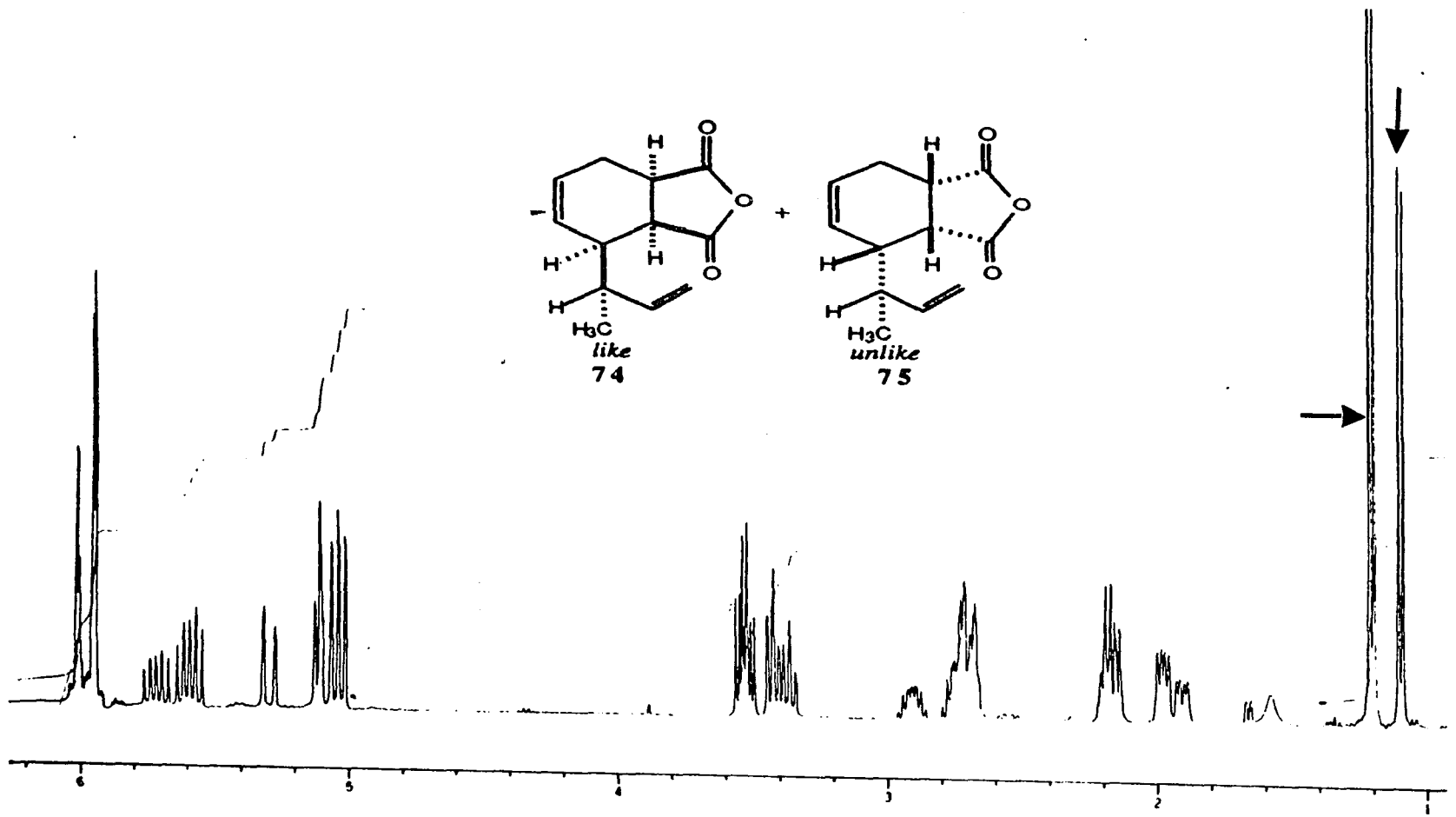
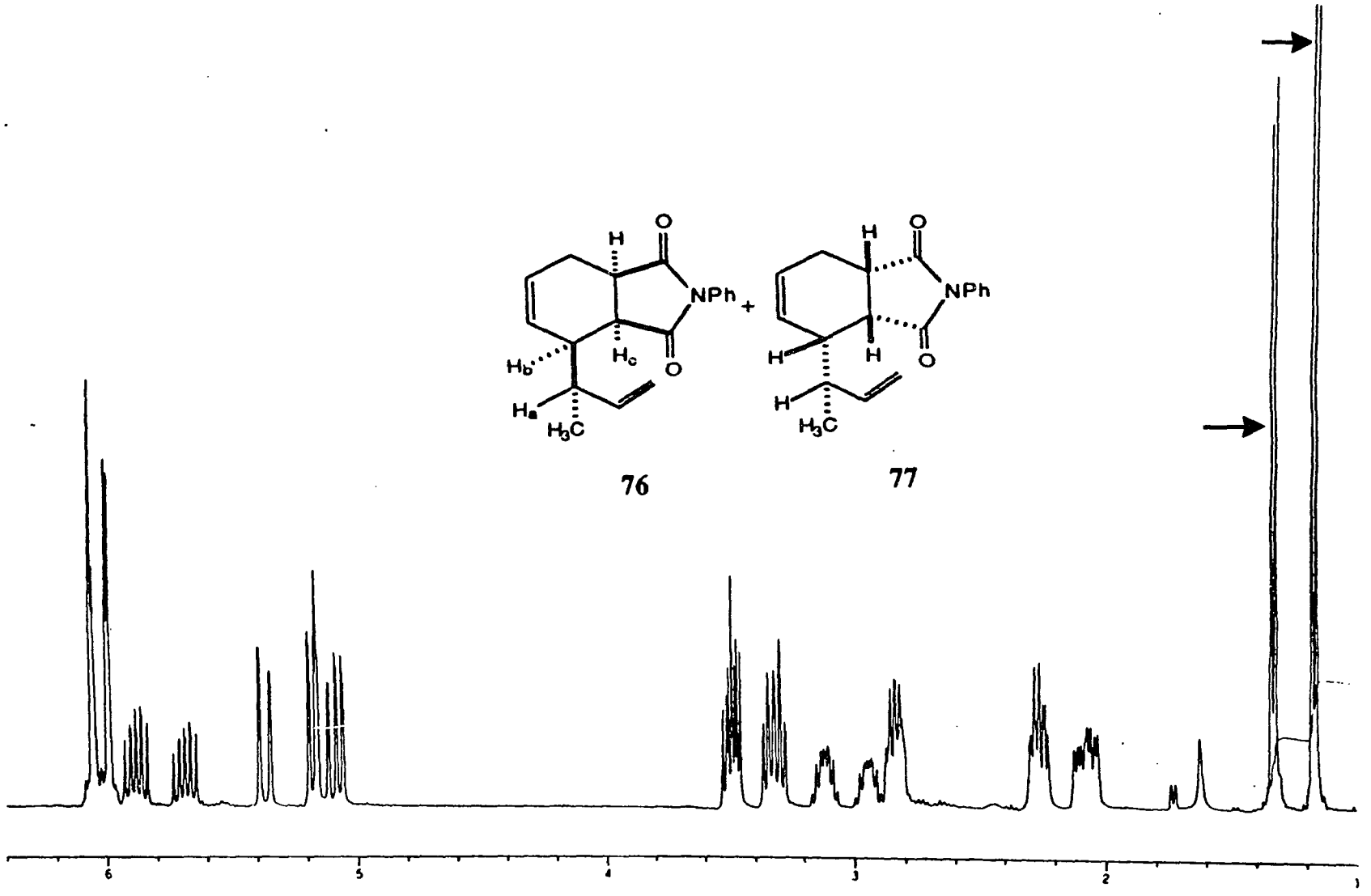




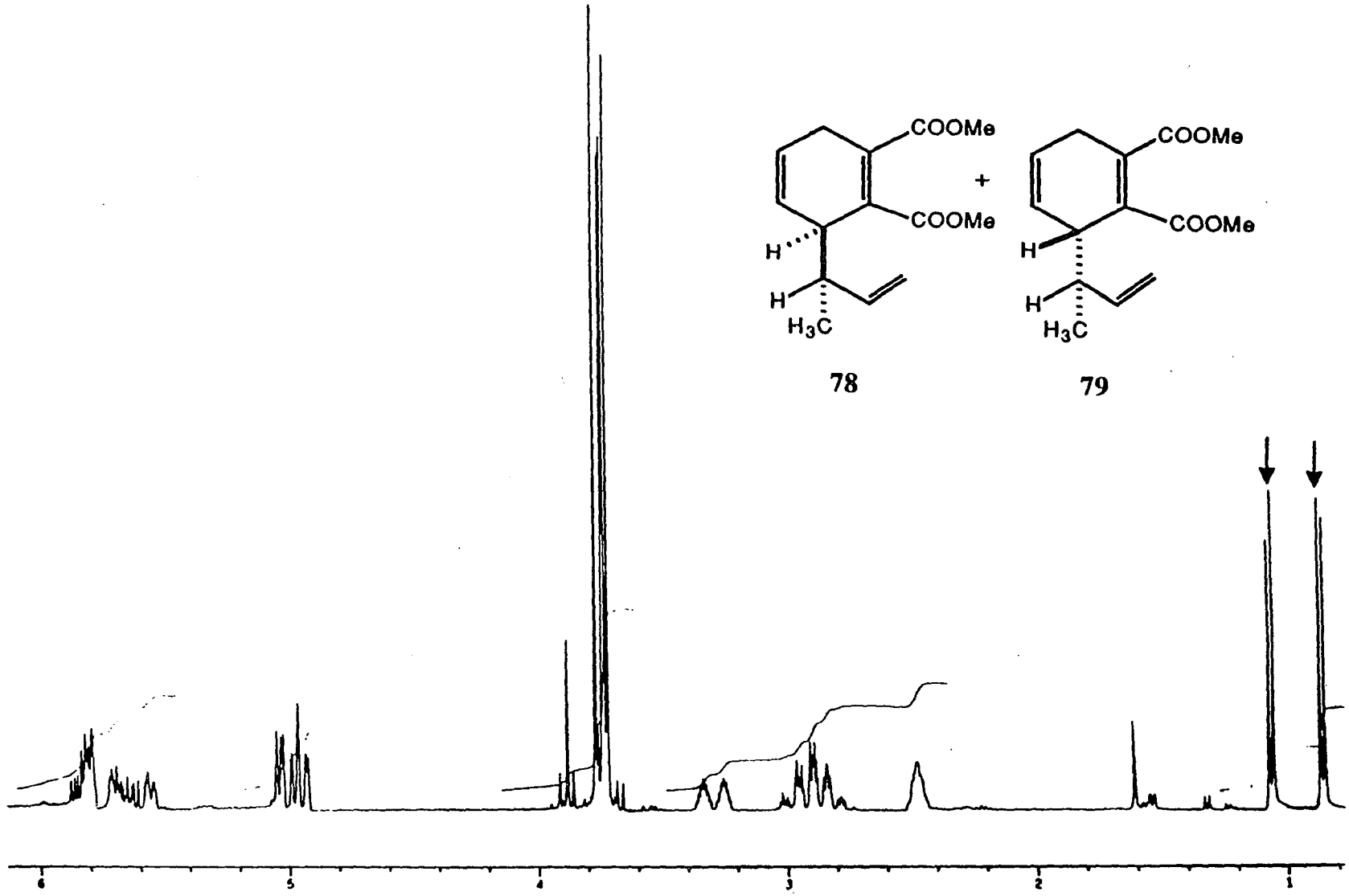
57b **58b**


H3C
COOMe
COOMe
H
H
OH
H3C
67
+
H3C
H
COOMe
COOMe
H
H
OH
H3C
68

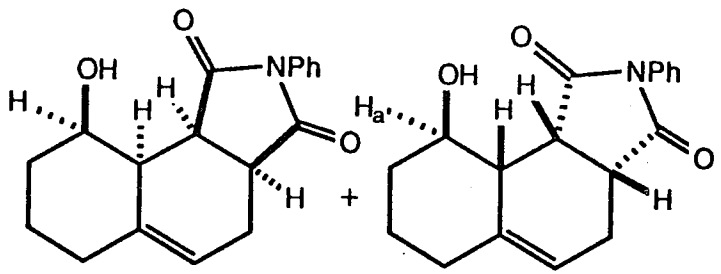

H
O
O
O
H
H
H
H3C
like
74
+
H
O
O
O
H
H
H
H3C
unlike
75
6
5
4
3
2
1



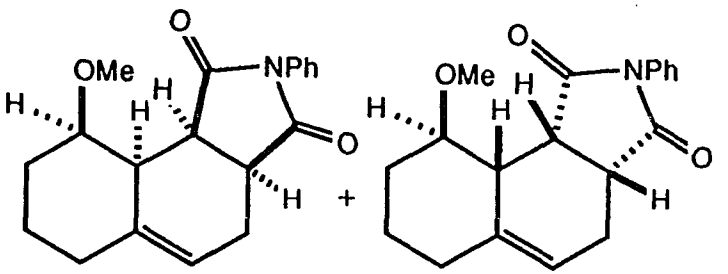
76 **77**



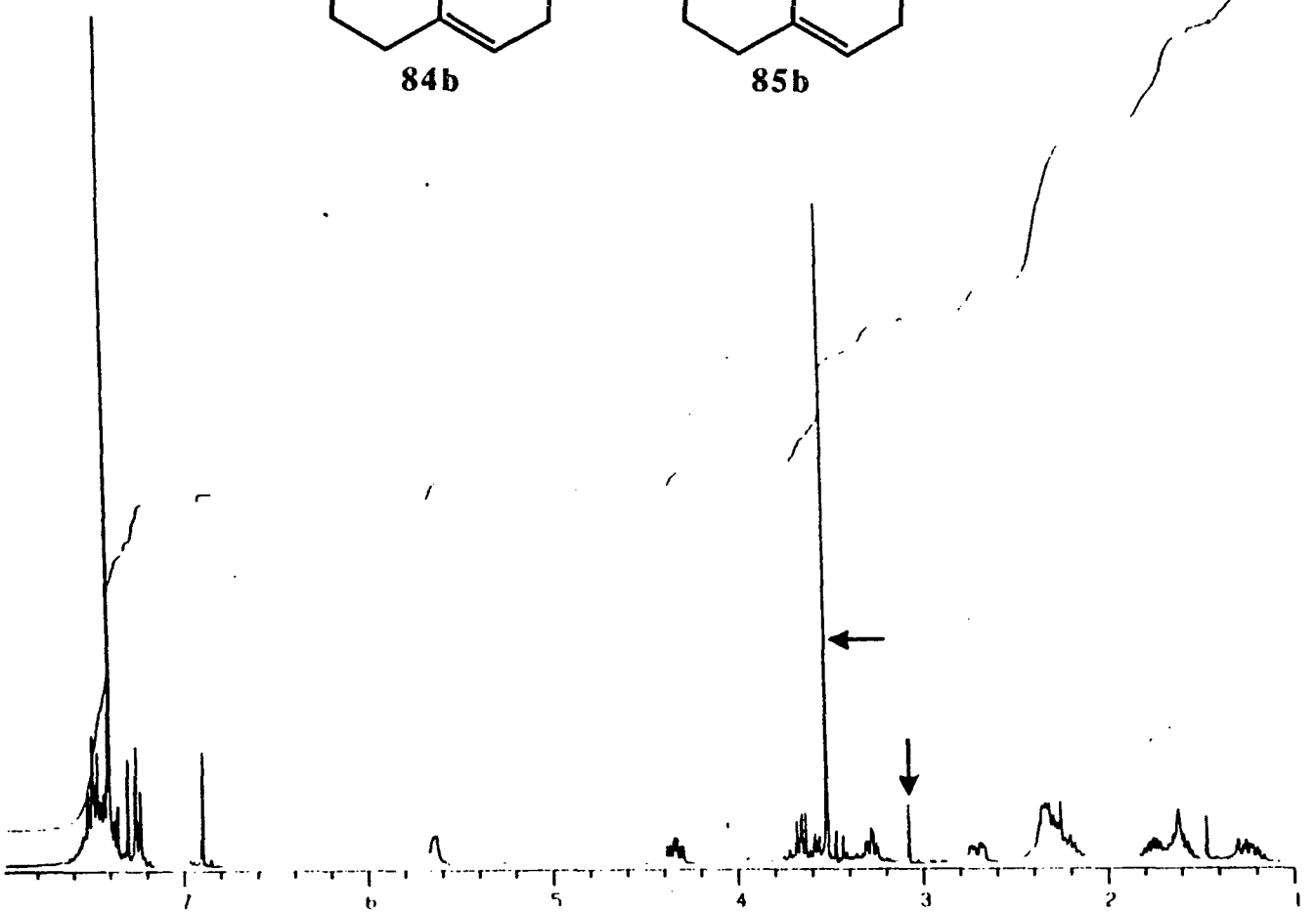
78 79

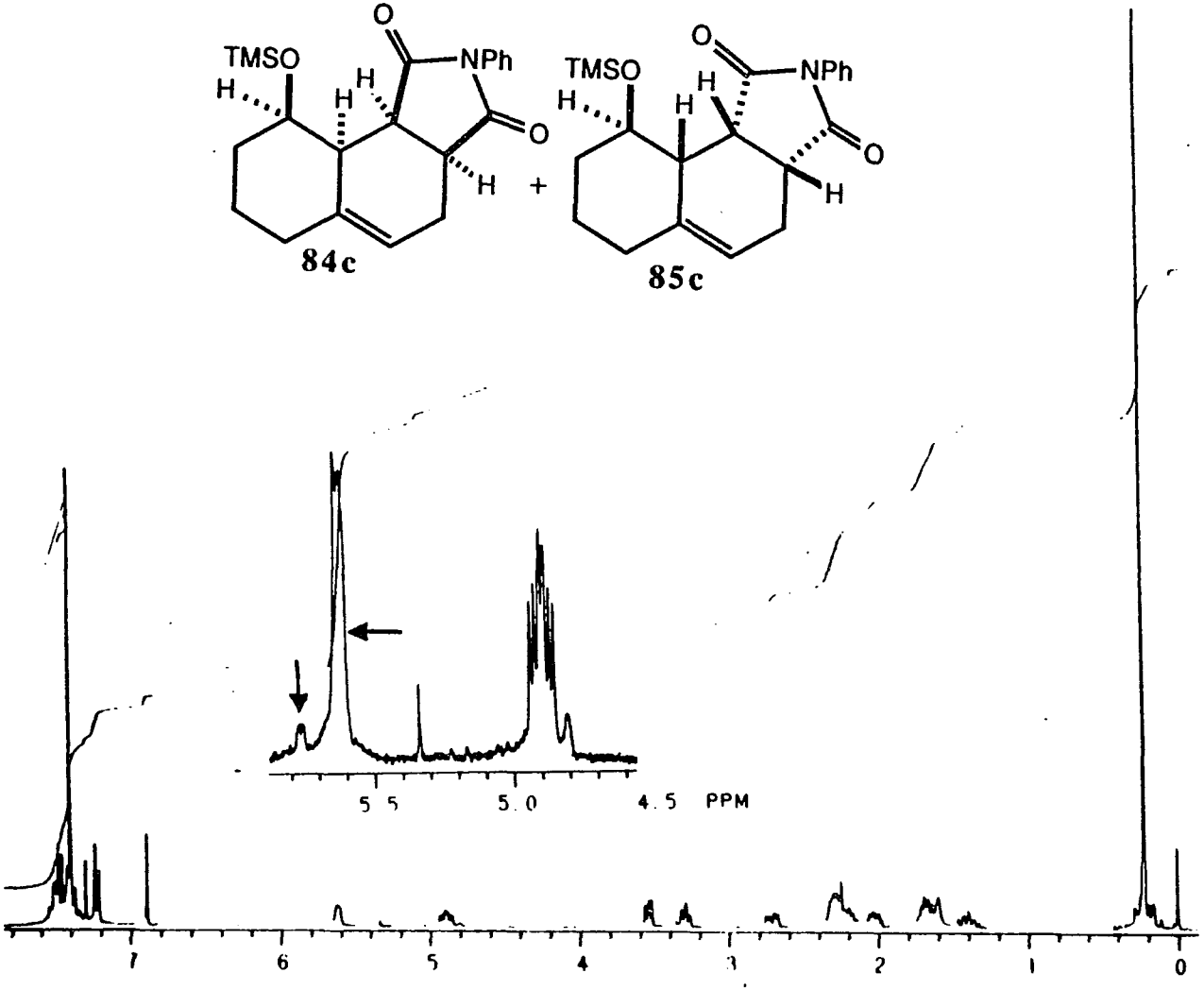


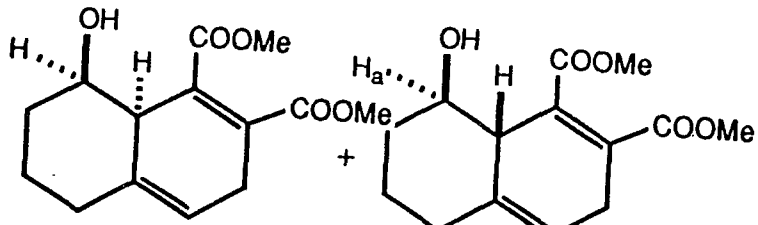
84a **85a**



84b **85b**

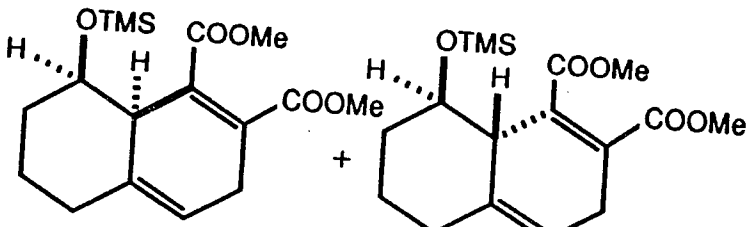



TMSO
H
H
O
NPh
O
H
84c
+
TMSO
H
H
O
NPh
O
H
85c
5.5
5.0
4.5 PPM
7
6
5
4
3
2
1
0

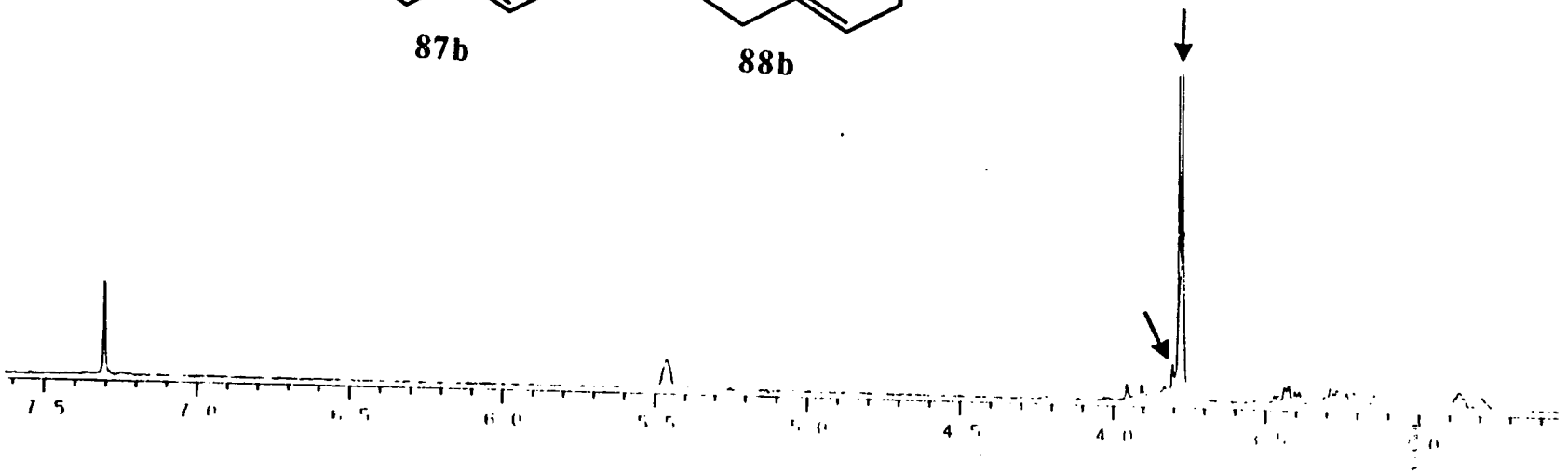


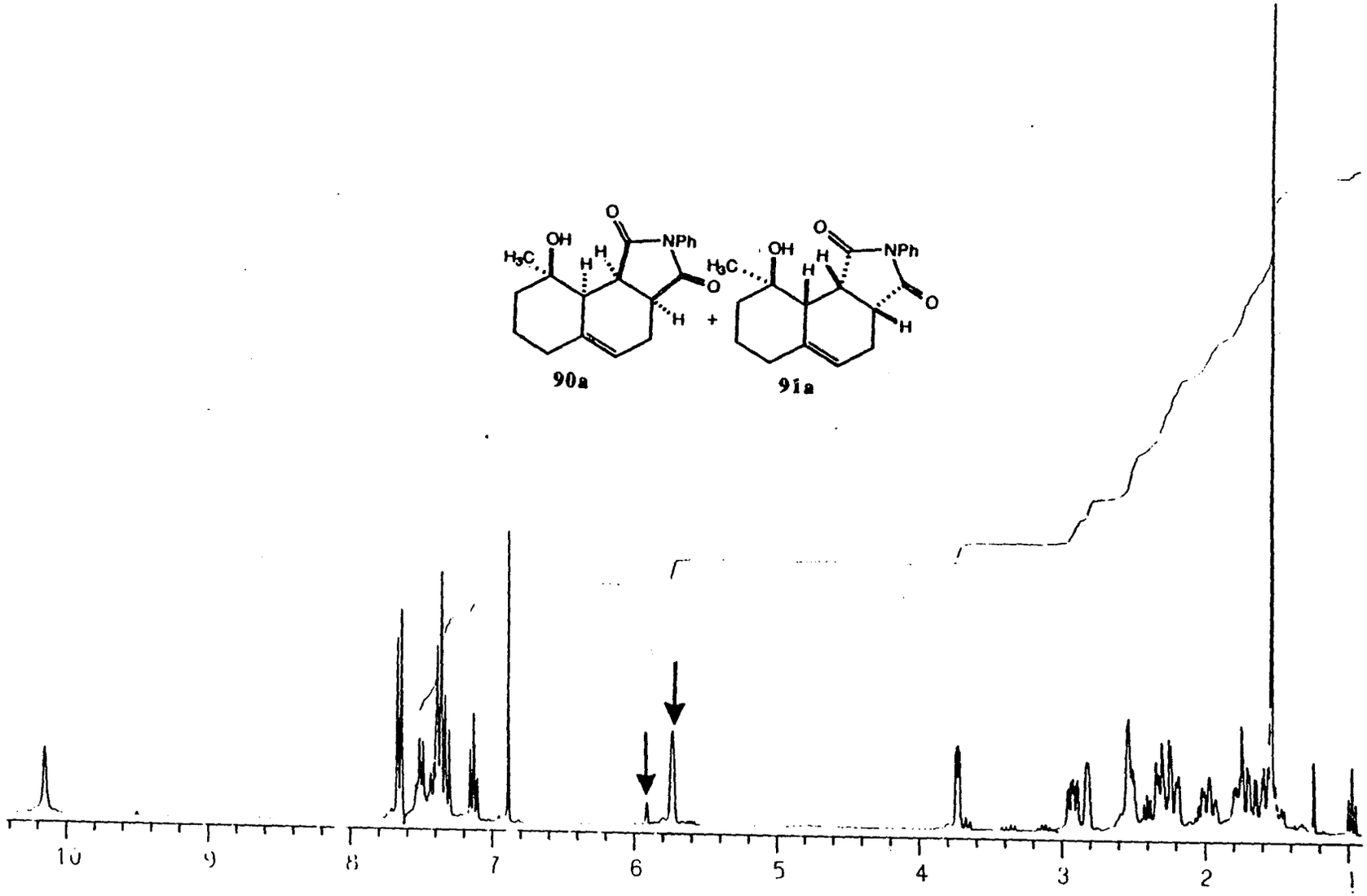
87a

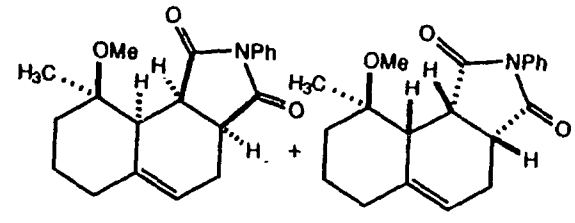
88a



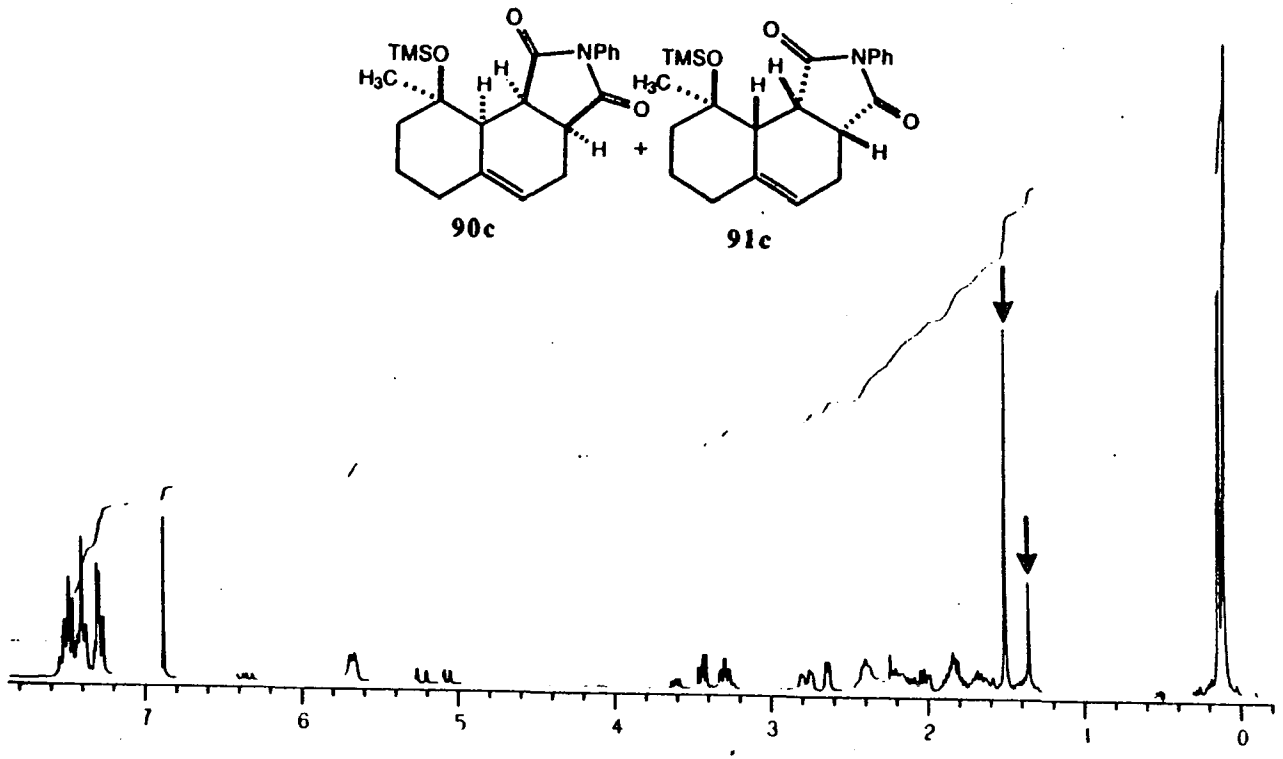
87b **88b**

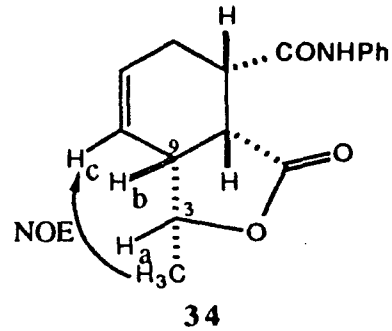



OH
H3C
H
O
NPh
O
H
H
90a
+
OH
H3C
H
O
NPh
O
H
H
91a
10
9
8
7
6
5
4
3
2
1

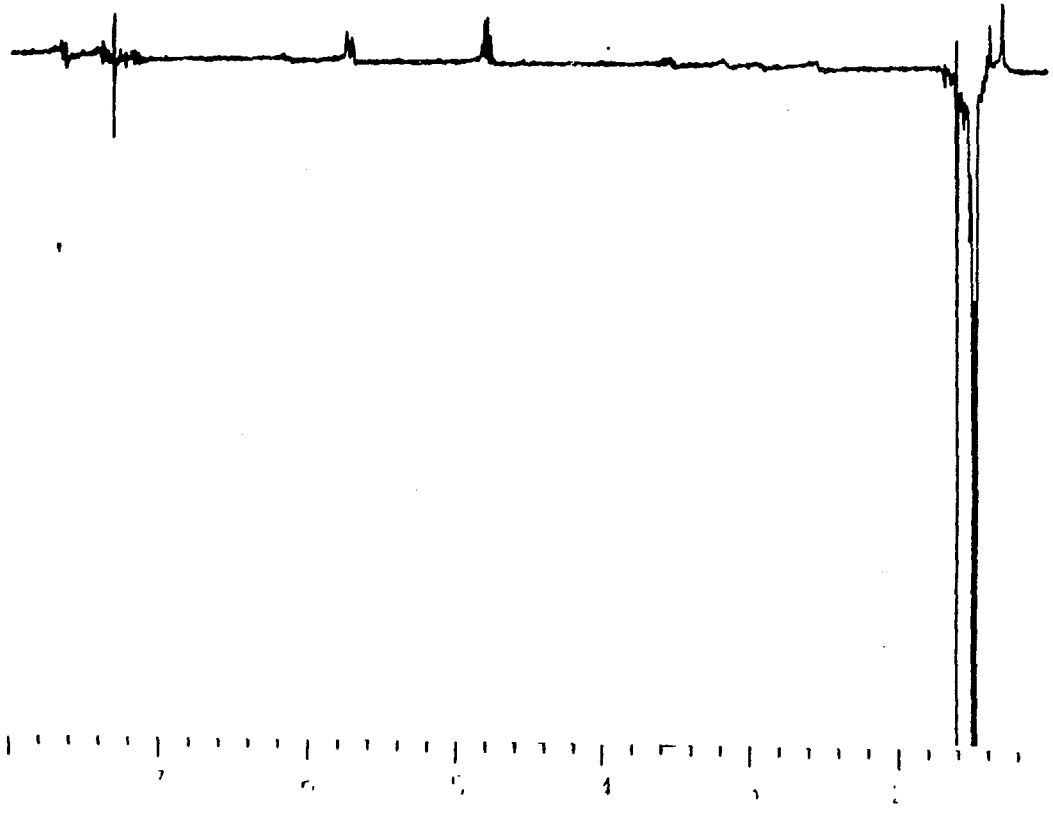


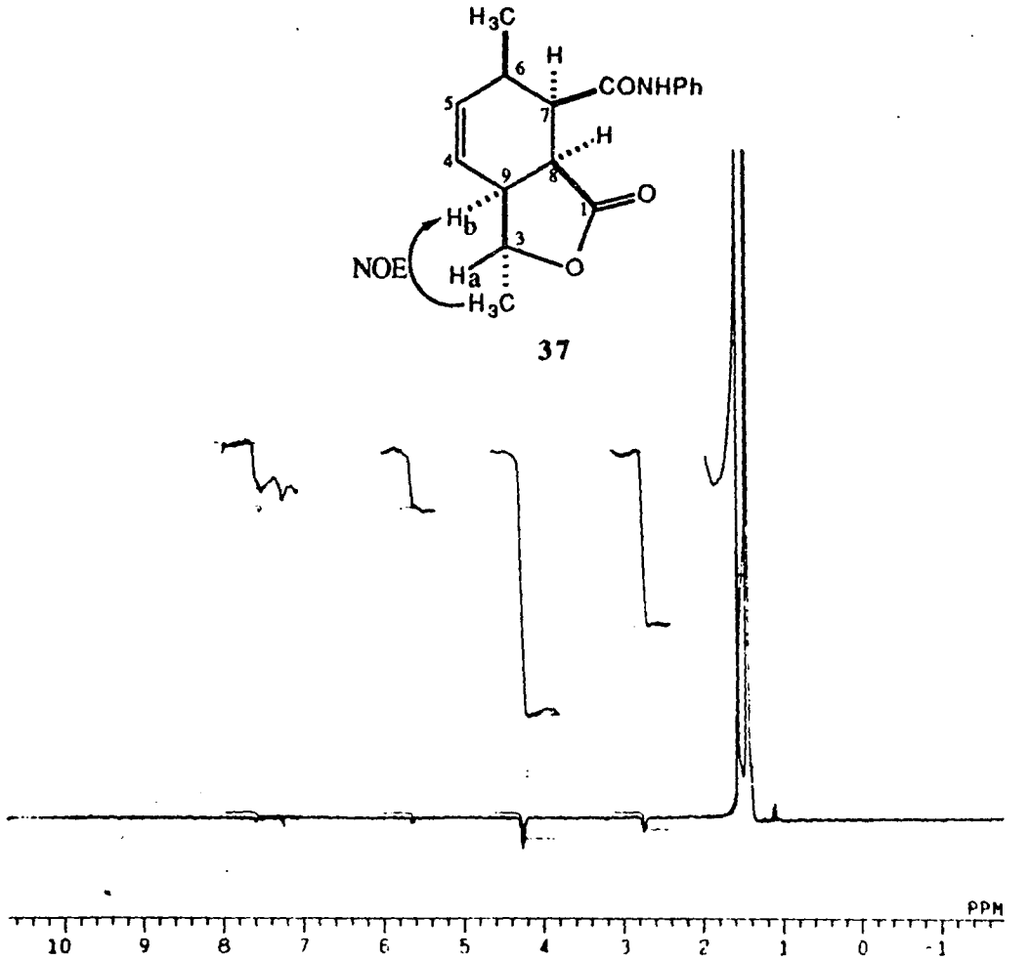
90b **91b**

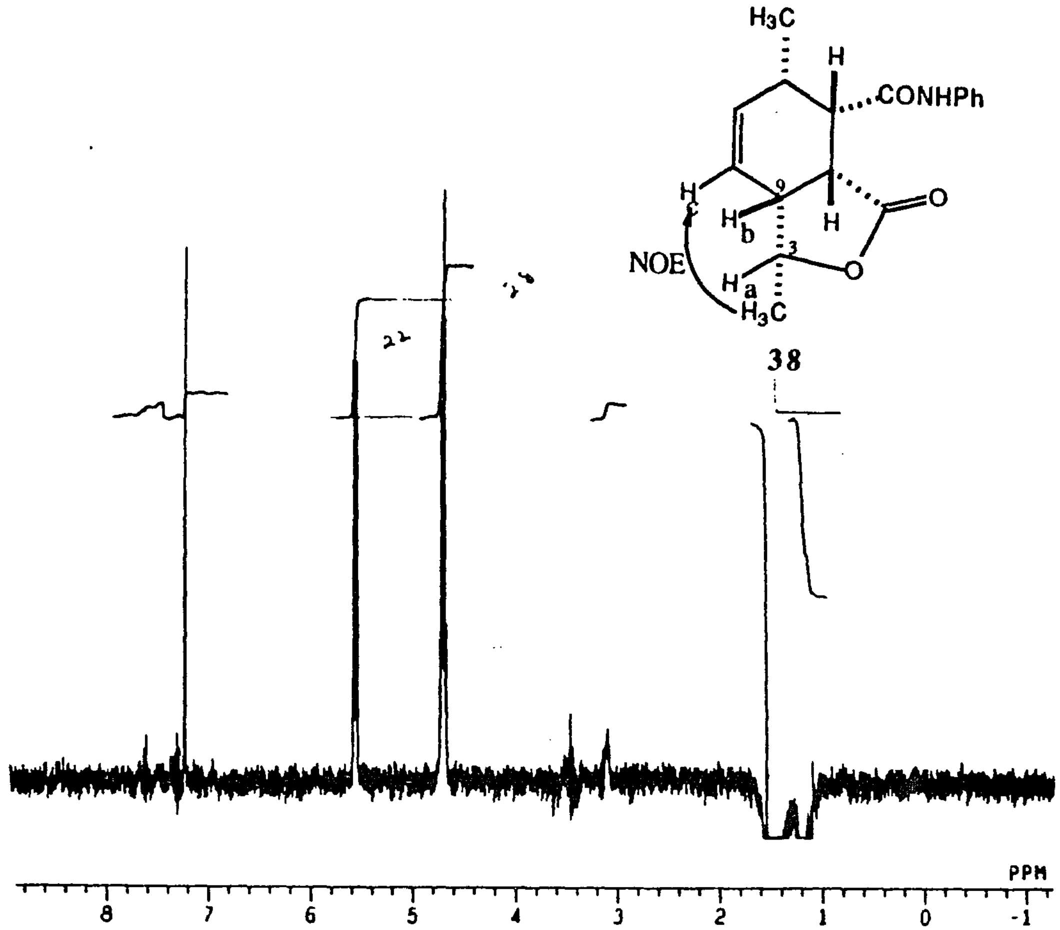

TMSO
H3C
H
O
NPh
O
H
H
+
TMSO
H3C
H
O
NPh
O
H
H
90c
91c
7
6
5
4
3
2
1
0



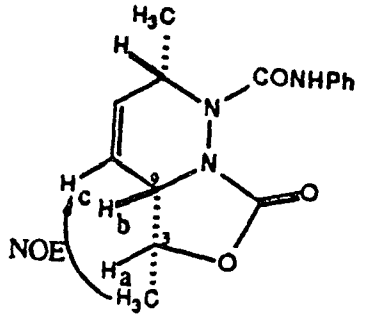
34




H3C
H
CONHPh
H
O
O
Hb
NOE
Ha
H3C
37
PPM
10
9
8
7
6
5
4
3
2
1
0
-1

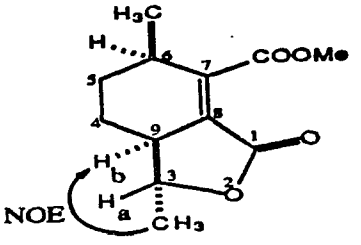


38

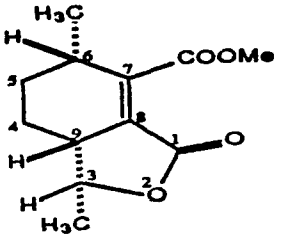


unlike

59

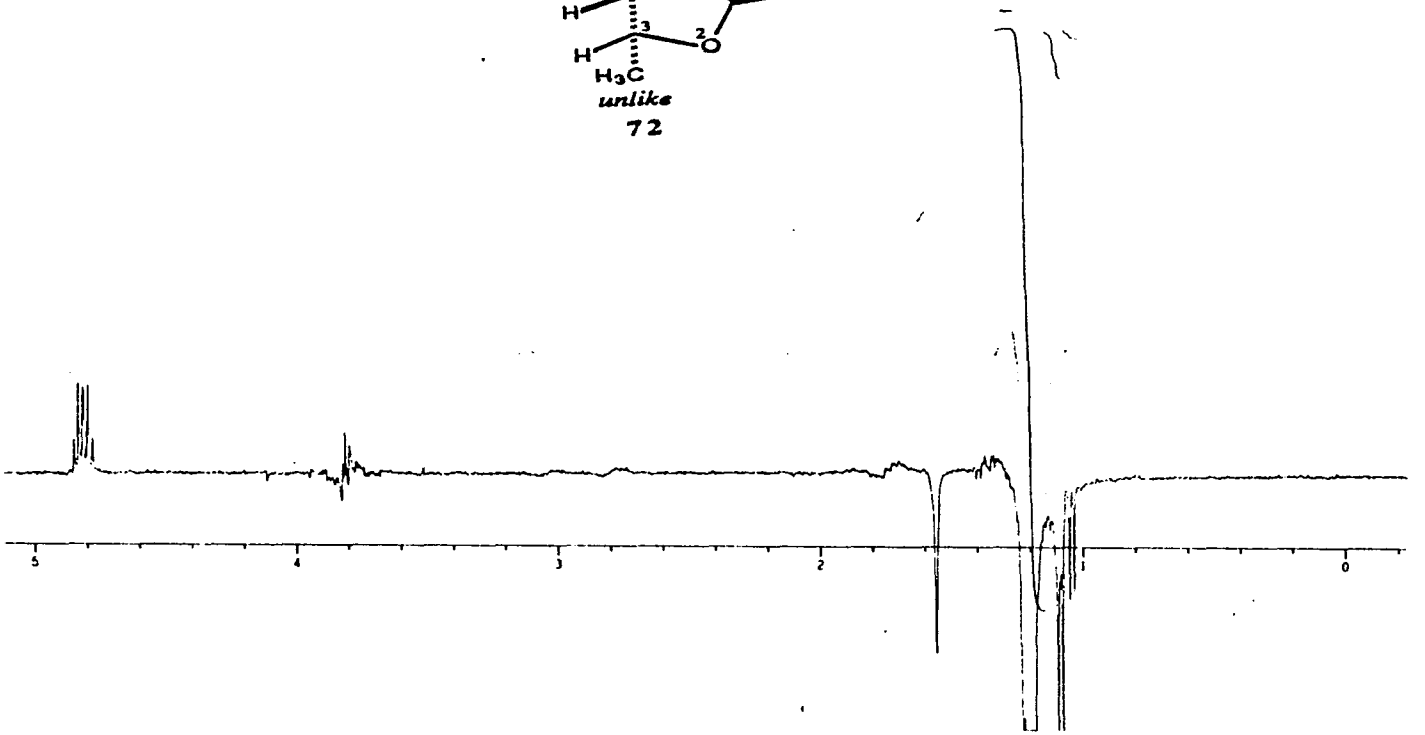


like
71



unlike

72



VI. References:

1. Weinreb, S. M, Staib, R. R. *Tetrahedron.* **1982**, *38*, 3087.
2. Petrzilka, M.; Grayson, J. I. *Synthesis*, **1981**, 753.
3. Sauer, J.Sustmann, R. *Angew Chem. Int. Ed. Engl.*. **1980**, 779.
4 Wollweber, H. *Diels-Alder-Reaktion*, Thieme, Stuttgart 1972.
5. Wollweber, H. in Houben-Weyl, Methoden der Organischen Chemie, 4th Edn., Muller, Ed., vol. 5/1c, Thieme, Stuttgart 1972.
6. Sauer, J. *Angew Chem. Int. Ed. Engl.*. **1966**, 76.
7. Diels, O.; Alder, K. *Justus Leibigs Ann. Chem.*. **1928**, *460*, 98.
8. Fleming, I. in Frontier Orbitals and Organic Chemical Reactions, John Wiley and Sons, London, 1978.
9. Woodward, R. B. Hoffmann, R. *Angew. Chem.* **1969**, 797.
10. Anh, N. T. *Tetrahedron.* **1973**, *29*, 3227.
11. (a) Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381.(b) Kahn, S. D.; Pau, C. F.; Hehre, W. J. *Ibid*, **1986**, *108*, 7396. (c) Kahn, S. D.; Hehre, W. J. *Ibid*, **1986**, *108*, 7399.
12. Dewar, M. J. S, Healy, E. F. *J. Am. Chem. Soc.* **1984**,*106*, 7127 and references therein.
13. Houk, K. N.; Lin, Y-T.; Brown, F. K. *J. Am. Chem. Soc.* **1986**, *108*, 554.
14. For reviews see: *Asymmetric Synthesis*, Ed.; Morrision, J.D., Academic: New York, **1984**; Vol. *1-5*.
15. Helmchen, G.; Karge, R.; Weetman, J. *Modern Synthetic Methods*, Scheffold, R., Ed.; Springer Verlag : New York, 1986; p 261.
16. Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew Chem. Int. Ed. Engl.*. **1985**, 10-13.
17. Paquette, L. A. *Asymmetric Synthesis*, Ed.; Morrision, J.D., Academic: New York,

1984; Vol.*3B* , p 445.

18. Oppolzer, W. *Angew Chem. Int. Ed. Engl.*. **1984**, 876.
19. Wurzinger, H. *Kontakte* (Merck, Darmstadt), **1984**, No.2, p.3.
20. Welzel, P.*Nachr. Chem. Techn. Lab.* **1983**, 979.
21. Mori, Y. *J. Synth. Org. Chem. Jpn.* **1982**, *40* , 321.
22. Morrison, J. D.; Mosher,H. S.; *Asymmetric Organic Reactions, Am. Chem. Soc., Washington D.C.* **1976**, p. 252-257.
23. Franck, R. W.; John, T. V. *J. Org. Chem.* **1980**, *45*, 1170.
24. Franck, R. W.; John, T. V.; Olejniczak, K *J. Am. Chem. Soc.* **1982**,*104*, 1106.
25. Franck, R. W.; John, T. V. *J. Org. Chem.* **1983**, *48*, 3269.
26. Franck, R. W.; Argade, S.; Subramanian, C. S.; Frechet, D. M. *Tetrahedron Lett.* **1985**, *26*, 3187.
27. Tripathy, R.; Franck, R. W.; Onan, K. D. *J. Am. Chem. Soc.*, **1988**,*110*, 3257.
28. Gree, R.; Kessabi, J.; Mosset, P.; Martelli, J.; Carrie, R. *Tetrahedron Lett.* **1984**, *25*, 3697.
29. Kessabi, J. Thesis; Dr. IIIeme Cycle, L' Universite de Rennes, 1985.
30. Messager, J. C.; Toupet, L. *Acta Crystallogr., Sect. B: Struct. Sci.* **1986**, *B42*, 371.
31. Kozikowski, A. P.; Nieduzak, T. R.; Springer, J. P.*Tetrahedron Lett.* **1986**, *27* , 819.
32. Kozikowski, A. P.; Jung, S. H.; Springer, J. P. *J. Chem. Soc., Chem. Commun.* **1986**, 1350.
33. Kozikowski, A. P.; Nieduzak, T. R.; Konoike,T.; Springer, J. P.*J.Am.Chem. Soc.* **1987**, *109*, 5167.
34. Kozikowski, A. P.; Konoike, T.; Nieduzak, T. R.*J.Chem. Soc., Chem. Commun.* **1988**, 167.

35. McDougal, P.; Rico, J. G.; Van Derveer, D. *J. Org. Chem.*. **1986**, *51*, 4492.

36. Reitz, A. B.; Jordan, A. D., Jr.; Maryanoff, B. E. *J. Org. Chem.* **1987**, *52*, 4800.

37. Fisher, M.J.; Hehre, W. J.; Kahn, S. D.; Overman, L. E.. *J. Am. Chem. Soc* .**1988**, *110*, 4625.

38. I. Fleming. *Pure and Appl. Chem.* **1988**, *60*, 71.

39. Sun, K-M.; Giuliano, R. M.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 4774.

40. Giuliano, R. M.; Buzby, J. H. Carbohydr. Res. 1986, 158, C1.

41. Lipshutz, B. H; Nguyen, S. L; Elworthy; T. R. *Tetrahedron*, **1988**, *44*, 3364.

42. Lopez, J. C.; Lameignere, E.; Lukacs, G. *J.Chem. Soc., Chem. Commun.* **1988**, 706.

43. Jones, D. W.*J.Chem. Soc., Chem. Commun.* **1980**, 739.

44. Winstein, S.; Shavatsky, M.; Norton, C.; Woodward, R. B. *J. Am. Chem. Soc* .**1955**, *77*, 4183.

45. (a) Williamson, K. L.; Hsu, Y.-F.; Lacko, R.; Youn, C.N. *J. Am. Chem. Soc* .**1969**, *91*, 6129. (b) Williamson, K. L.; Hsu, Y.L. *Ibid.* **1970**, *92*, 7385.

46. Breslow, R.; Hoffman, J. M., Jr.; Perchonock, C.*Tetrahedron Lett.* **1973**, 3723.

47. Fleming, I.; Williams, R. V. *J. Chem. Soc.; Perkin Trans. 1* , **1981**, 684.

48. Macaulay, J. B.; Fallis, A. G. *J. Am. Chem. Soc.* **1988**, *110*, 4074 and references there in.

49. Mant, L.; Peters, J. A.; Prazeres, M.A. *Recl. Trav. Chim. Pays-Bas* 1985, 104, 205.

50. Primeau, J. L.; Anderson, R. C. Fraser-Reid, B.*J. Am. Chem. Soc.* **1983**, *105*, 5874.

51. Jurczak, J.; Tkacz, M. *Synthesis* , **1979**, 42.

52. Schmidlin, T.; Burckhardt, P. E.; Waspe- Sarcevic, N.; Tamm, C. *Helv. Chim. Acta*

1983, *66*, 450.

53. Horton, D.W.; Machinami, T.; Takagi, Y. *Carbohydr. Res.* **1983**, *121*, 135.
54. For a review and computational studies on hetero atom substituted double bonds see (a) Kahn, S. D.; Pau, C. F.; Chamberlin, A. R; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650.(b) Kahn, S. D.; Hehre, W. J. *Ibid*, **1987**, *109*, 666. (c) Chamberlin, A. R; Mulholland, R. L.; Kahn, S. D.; Hehre, W. J. *Ibid*, **1987**,*109*, 672.
55. (a) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, 4733.(b) Chantemps, P.; Pierre, J-L.*Tetrahedron.* **1976**, *32*, 549. (c) Tanaka, S.; Yamamoto, H.; Nozaki, H.; Sharpless, K. B.; Michaelson, R. C.; Cutting, J. D. *J. Am. Chem. Soc.* **1974**, *96*, 5254.
56. (a) Stork, G.; Kahn, M.*Tetrahedron Lett.* **1983**,*3951*. (b) Cha, J. K.; Christ, W. J.; Kishi, Y.*Tetrahedron*, **1984**, *40*, 2247.
57. Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487.
58. Cherest, M.; Felkin, H.; Prudent, N.*Tetrahedron Lett.* **1968**, *2199*.
59. Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* 1977, *1*, 61.
60. (a) Heathcock, C. H. in Comprehensive Carbanion Chemistry,Buncel, E., Durst, T.; Ed. Elsevier, Amsterdam, 1984, 177. (b) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353.
61. (a) Caramella, P.; Rondan, N.G.; Paddon-Row, M.N.; Houk, K. N.*J. Am. Chem. Soc.* **1981**, *103*, 2438. (b) Paddon-Row, M.N.; Rondan, N.G.Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162.
62. Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.
63. (a) Srivastava, S.; le Noble, W. J. , *J. Am. Chem. Soc.* **1987**, *109*, 5874. (b) Johnson, C.R.; Tait, B. D.; Cieplak, A.S. *Ibid*, **1987**, *109*, 5875. (c) Laube, A. S.; Stilz, H.U. *Ibid*, **1987**,*109*, 5876. (d) Chung, W-S.; Turro, N. J., Srivastava, S.;

Li, H.; le Noble, W. J. *Ibid*, , **1988**, *110*, 7832.

64. For a review, see: Karabatsos, G. J.; Fenoglio, D. J. *Top. Stereochem.* **1970**, *5*, 167.

65. Though in the ground state, the *s-trans* form of the dienes are always the energy minimum, for the sake of convenience, the *s-cis* forms are shown.

66. Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1984**, *49*, 2672.

67. Seebach, D.; Prelog , V. *Angew Chem. Int. Ed. Engl.*. **1982**, *21* , 654.

68. Part of the confusion about the rules for face selectivity stems from the 1984 report (ref. 28) where the selectivity was reported to be *like*, but as corrected in 1986 (ref. 29 and 30), the outcome was in fact from *unlike* approach.

69. Fleming, I.; Lewis, J. L. *J. Chem. Soc., Chem. Commun.*,**1985**, 149.

70. McGarvey, G.J.; Williams, J. M., *J. Am. Chem. Soc.* **1985**, *107*, 1435.

71. The concept regarding the rotamers was put forward by prof. R. Whitney, Queens University.

72. Houk, K. N.; Moses, S. R.; Wu, Y. D.; Rondan, N. G.; Jager, V.; Schohe, R.; Fronczek, F.R. *J. Am. Chem. Soc.* **1984**, *106*, 3380.

73. Kaila, N., Franck, R. W.; Dannenberg, J.J. manuscript submitted.

74. Kahn, S. D.; Hehre, W. J.*J. Am. Chem. Soc.* **1987**, *109*, 663.

75. Heilbron, I. M.; Jones, E. R. H.; McCombie, J. T.; Weedon, B. C. L. *J. Chem. Soc*. **1945**, 88.

76. Oppolzer, W.; Snowden, R.L.; Simmons, D.P. *Helv. Chim. Acta*, **1981**, *64*, 2002.

77. Shackelford, J. M.; Schwartzman, L. H. *J. Org. Chem.* **1962**, 1047.

78. Azipurua, J. M.; Palomo, C. *Tetrahedron Lett.*, **1985**, *26*, 475.

79. Braude, E. A.; Coles, J. A.; *J. Chem. Soc.*, **1951**, 2085.

80. Noggle, J. H.; Schirmer, R. E. in Nuclear Overhauser Effect, Academic Press, New York, **1970**.

81. Rahman, A. in Nuclear Magnetic Resonance, Springer-Verlag, New York, **1986**.

82. The x-ray was done by Prof. K. Onan at Northeastern University.

83. Watson, W. H.; Galloy, J.; Bartlett, P. D.; Roof, A. A. M. *J. Am. Chem. Soc.* **1981**, *103*, 2022.

84. Trost, B. M.; Lynch, J.; Renaut, P. *Tetrahedron Lett.*, **1985**, *26*, 6313.

85. White, J. D.; Sheldon B. C. *J. Org. Chem.* **1981**, *46*, 2273.

86. These results are known via personal communication between Prof. Franck and Prof. Fleming. He has also provided his rationalization regarding the change in the face selectivity by going from NPM to DMAD (lmanuscript submitted).

87. Prof. Fleming has also kindly provided us the x-ray for the the lactone **71**, which confimed our structure. He has also proved the stereochemistry in his silyl series by converting compound **73** (scheme 11) to our lactone **71**.

88. They have used 2-methyl-3-trimethylsilyl-3-butenal as the substrate for the nucleophilic addition to carbonyl group. Sato, F.; Kusakabe, M.; Kobayashi, Y. *J. Chem. Soc., Chem. Commun.*, **1984**, 1130.

89. Saga, M. *Japan. Kokai JP* 48/54200 [73/54200], 30 Jul **1973**, 4 pp.

90. Grewe, R.; Nolte, E.; Rotzoll, R-H.; *Chem. Ber.* **1956**, *89*, 600.

91. (a) Strekowski, L.; Kong, S.; Battiste, M. A. *J. Org. Chem.* **1988**, *53*, 901. (b) Hayakawa, K.; Ohsuti, S.; Kanematsu, K. *Tetrahedron Lett.*. **1986**, *27*, 947.

92. Hall, S. E.; Roush, R. *J. Org. Chem.* **1982**, *47*, 4611.

93. Seebach, D. Stucky, G. *Angew Chem. Int. Ed. Engl.*. **1988**, *217*, 1351.

94. Curran, D. P.; Kim, B.H. *Synthesis*, **1986**, *108* , 1094.

95. Vedejs, E.; McClure, C. K. *J. Am. Chem. Soc* .**1986**, *108*, 1094.

96. Kozikowski and McDougal have used the perpendicular rotamers for the allylic dienes to rationalize the experimental results. However, we are using the

syn-coplanar or *anti-coplanar* models as suggested by the AM1 calculations (ref. 73).

97. Carrupt, P. A.; Berchier, F.; Vogel, P. *Helv. Chim. Acta* , **1985**, *68*, 1716.
98. (a) Kaftory, M.; Peled, M.; Ginsburg, D. *Helv. Chim. Acta* , **1979**, *62*, 1326. (b) Ginsburg, D. *Tetrahedron*, **1983**, *39*, 2095.
99. Jensen, F.; Foote, C. S.*J. Am. Chem. Soc* .**1987**, *109*, 6376.
100. Clennan, E. L.; Earlywine, A. D. *J. Am. Chem. Soc* .**1987**, *109*, 7104.
101. Winstein, S.; Hollness, N.J.*J. Am. Chem. Soc.* **1955**, *77*, 5562.
102. Hirsch, J. A. *Topics in Stereochem.* **1967**, *1*, 199
103. Fraser-Reid, B. *Acc Chem. Res.* **1985**, *18*, 347.
104. Paquette, L. A.; Lin, H-S, Gunn, B. P.; Coghlan, M. J.*J. Am. Chem. Soc* . **1988**, *110*, 5818.
105. Forster, H.; Vogtle F. *Angew Chem. Int. Ed. Engl.*. **1977**, 429 and references there in.
106. Seebach, D.; Zimmermann, J.; Gysel, U.; Ziegler, R.; Ha, T-K. *J. Am. Chem. Soc.* **1988**, *110*, 4763.
107. Kawasaki, M.; Matsuda, F.; Terashima, S. *Tetrahedran*, **1988**, *44*, 5727.