Chapter - I

CHAPTER - 1

THE DIELS-ALDER REACTION

I) INTRODUCTION

There is a large body of chemical reactions of olefinic compounds which do not involve ionic or free radical intermediates and which are remarkably insensitive to the presence or absence of solvents and catalysts. Many of these reactions are characterized by the making and breaking of two or more bonds in a single concerted step through cyclic transition states where in all first - order bonding changes occur. Because of their cyclic transition - states, they are known as pericyclic reactions. They are initiated by heat (thermolysis) or light (photolysis) and are highly stereospecific. Cycloaddition reaction is one of the pericyclic reactions. The thermal reaction between conjugated diene and a dienophile to give a cyclic product is an example of [4 + 2] π cycloaddition reaction and is known as Diels-Alder reaction.

II) CONSERVATION OF MOLECULAR ORBITAL SYMMETRY

In 1965, Woodward and Hoffmann offered a reasonable explanation for pericyclic reactions based on the principle of 'Conservation of Orbital Symmetry'.[1-4].

This principle states that the orbital symmetry is conserved in concerted reactions.

The essential feature of the reaction is the simultaneous overlapping of the participating bond orbitals such that they may pass smoothly over into the bond orbitals of the product. This transformation of reactant orbitals into product orbitals pass through a transition state of merging orbitals. The basic principle guiding these reactions is that the transition state will be of relatively low energy and the reaction favoured as long as the symmetry of the reactant orbitals is retained or conserved in passing to product orbitals. The reaction will be disfavoured if reactant and product orbitals are not the same. This may be understood in an alternative way by noting that only if some bonding character is retained through the transition will the activation energy be low and the reaction favoured. This retention of bonding character occurs only if orbital symmetry is conserved.

The symmetry of the involved orbital is a guide to whether this bonding character will be maintained during a given reaction. Hence when the symmetry of reactant and product orbital is same that is orbital symmetry is conserved in the reaction, the reaction is said to be symmetry allowed or energetically favoured. When symmetry is not retained, the reaction is symmetry forbidden or energetically disfavoured. Reactions which are symmetry forbidden can often occur any way but only under higher energy conditions, either by a different mechanism, a nonconcerted, free radial mechanism with several steps.

III) CORRELATION DIAGRAM AND FMO METHOD

The most familier example of a cycloaddition reaction is the Diels-Alder reaction which involves the formation of a cyclic compound from an alkene and a diene (Chart-I).

The reaction consist in the addition of a system of m π electrons to a system of n π electrons thereby forming a cyclic compound. They offer a versatile route of synthesis of a cyclic compounds with a high degree of stereoselectivity under thermal or photochemical conditions. Depending upon the number of π electrons participating in the process, these reactions are termed (m + n) or (m + n +...) cycloaddition reactions.

The thermal (4 + 2)πcycloaddition has been known as Diels-Alder reaction. In this reaction dienophile (alkene) is activated by electron withdrawing substituents such as - COOH, - COOR, -COR, - NO_2, - CN and - SO_2. Some reactive dienes do not require activated dienophile. Dienes are activated by electron donating substituents. Ex. - 1, 3 butadiene is less reactive than most of its mono, di and trimethyl derivatives. However, in the case of the tetramethyl butadienes, steric hindrance decreases reactivity.

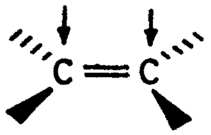
a) Stereochemical modes of Cycloaddition : Suprafacial and Antarafacial processes :

Since in a typical cycloaddition reaction, there is addition of two systems containing double bonds, it is logical to expect the addition to occur on the same or the opposite side of the system. Furthermore, as both the π systems are undergoing addition, it is necessary to specify these modes of addition on each of them. These different modes have been termed suprafacial-s (on the same side) and antarafacial-a (on the opposite side) (Chart-1).

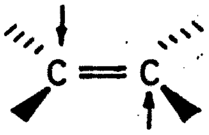
This specification is usually made by placing a suitable subscript (s or a) after the number referring to the π - component. The Diels-Alder reaction may be considered as a process involving 2S + 4S cycloaddition as shown in Chart-1.

CHART - 1

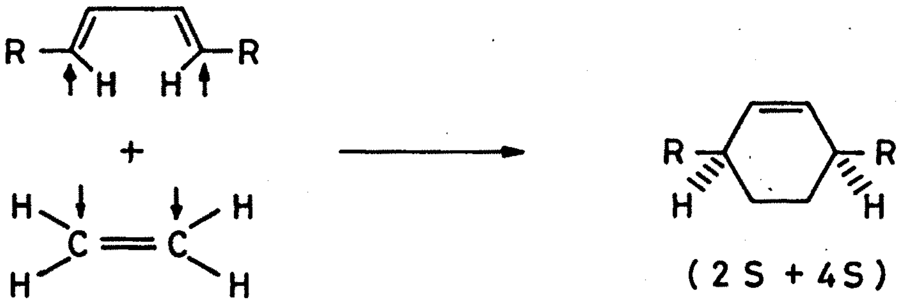
Diels alder reaction



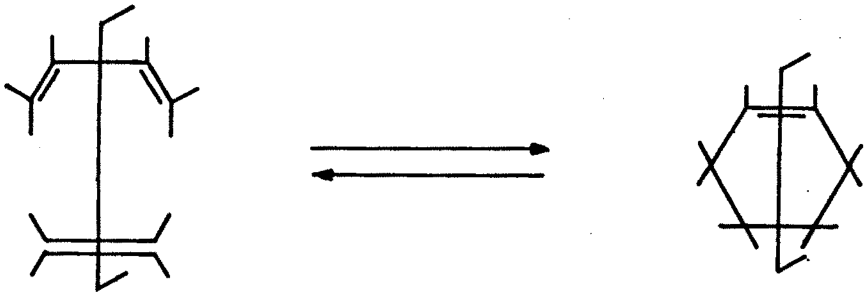
Suprafacial



Antarafacial



Supra – Supra addition



Plane of symmetry

b) Orbital Symmetry in Diels-Alder reaction :

Correlation diagram :

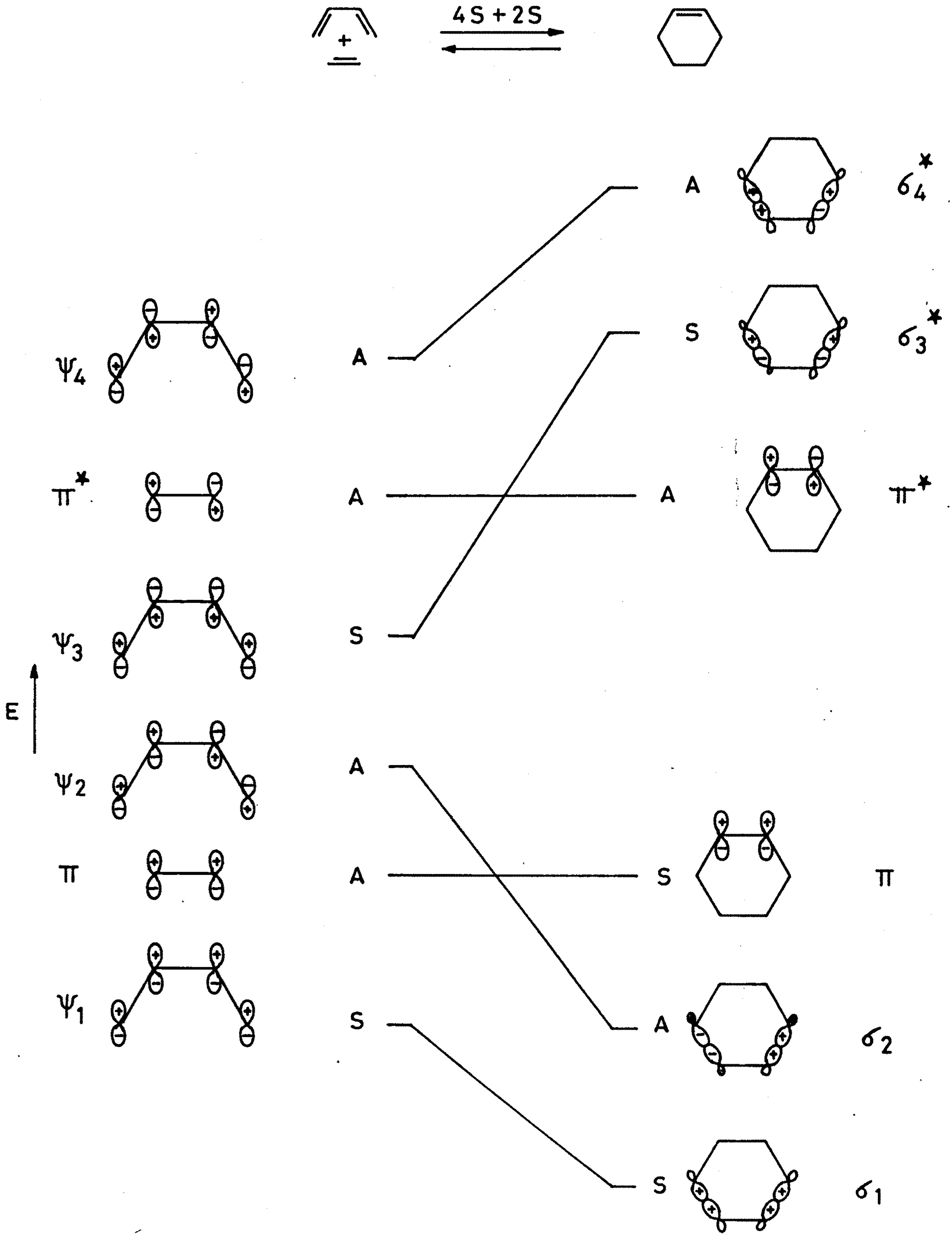
A correlation diagram may be constructed for the Diels-Alder reaction which is a 4S + 2S cycloaddition reaction. In this case there is only a single vertical plane of symmetry bisecting the carbon framework of two reactants and the product (Chart-1).

In this transformation, we have to consider six orbitals each of the reactants and the product. The ground state orbitals of the reactants are ψ_1 ψ_2 (of butadiene) and π (of ethylene) while ψ_3 , π^* and ψ_4 are the corresponding antibonding orbitals. Similarly, the ground state orbitals of cyclohexene are represented by σ_1, σ_2 and π , the remaining three orbitals are antibonding. All these orbitals along with their symmetry properties are shown in (Chart-2) correlation diagram.

It becomes immediately clear from an inspection of the above diagram that there is a smooth transformation of the reactant orbitals into the product orbitals.

$$\psi_1^2 \quad \pi^2 \quad \psi_2^2 \text{ ------> } \sigma_1^2 \, \sigma_1^2 \quad \pi^2$$

CHART - 2



Correlation diagram for 4S + 2S cycloaddition (Diels-Alder) and the reverse process.

The Diels-Alder reaction is therefore, a thermally allowed process. On the other hand, photochemical transformation is not possible as the first excited state of the reactant does not correlate with the first excited state of the product. Rather it correlates with the upper excited state of the product.

$$\psi_1^2 \pi^2 \psi_2 \psi_3 \qquad \sigma_1^2 \sigma_2^2 \pi \sigma_3^*$$

Hence there is a symmetry - imposed barrier to photochemical reaction of (4S + 2S) type.

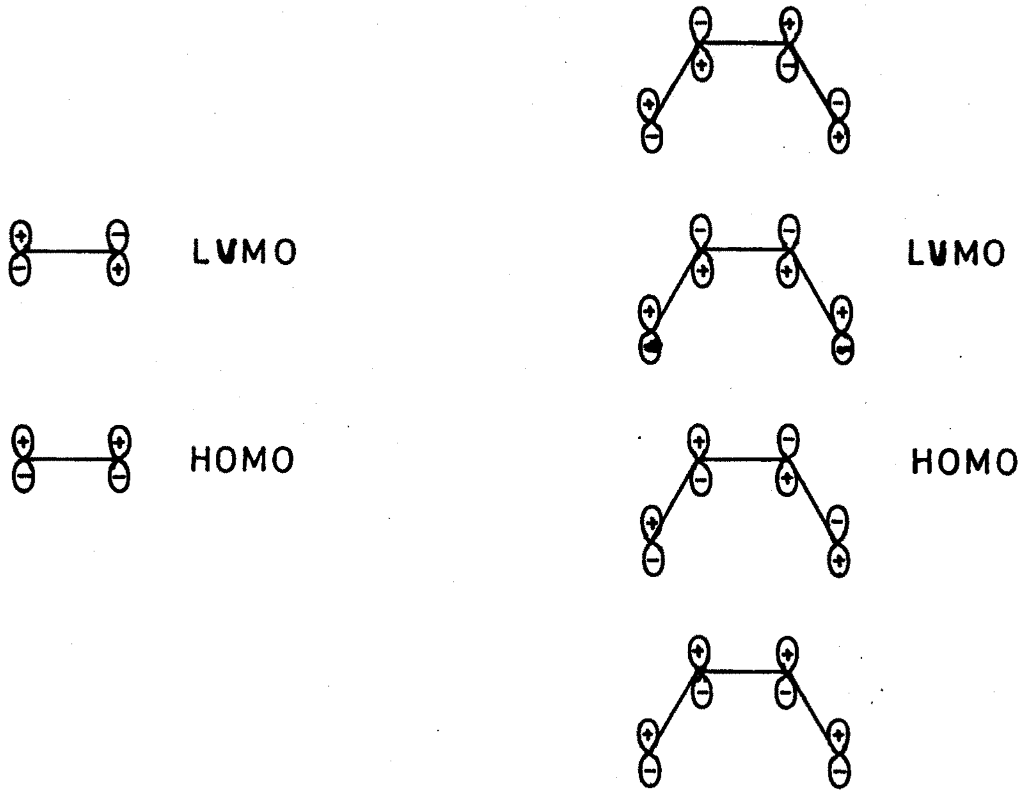
c) **Frontier Molecular Orbital (FMO) Method** :

An alternative approach to determine whether or not a cycloaddition reaction is allowed depends upon the symmetry properties of the highest occupied molecular orbital (HOMO) of one reactant and the lowest vacant molecular orbital (LVMO) of the other. A favourable interaction is possible only when the signs of the coefficients of HOMO and LVMO are the same.

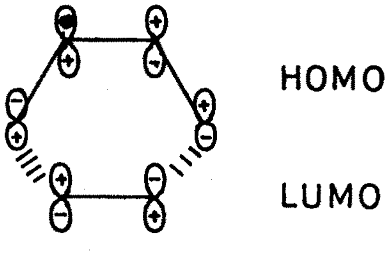
A Diels-Alder reaction is analyzed by a consideration of the molecular orbitals of ethylene and butadiene (Chart-3).

CHART - 3

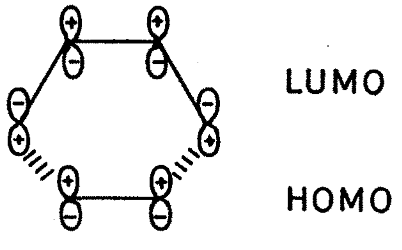
FMO Method



Orbitals of Ethylene and Butadiene



Δ allowed



Δ allowed

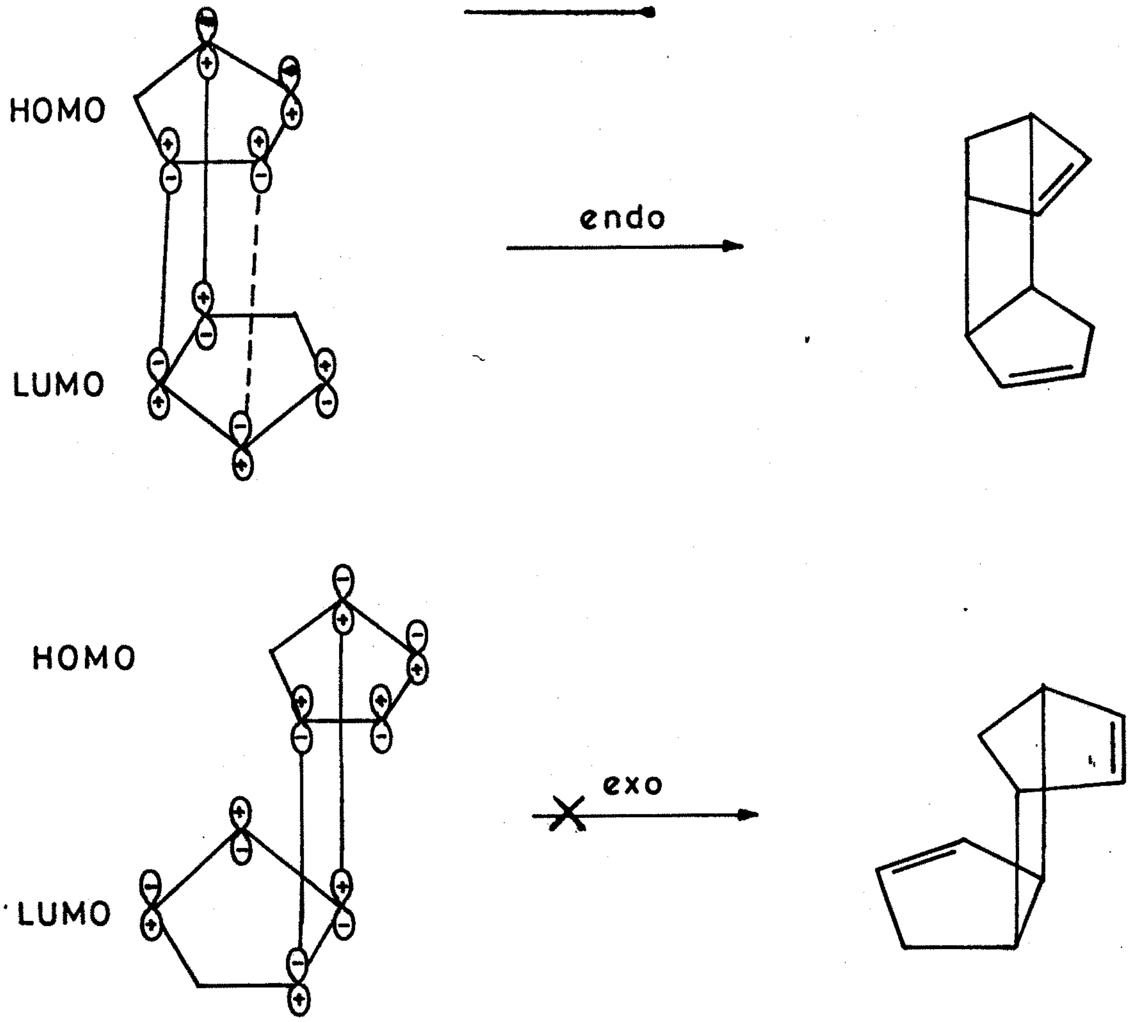
Since signs of the 1, 4 - lobes of butadiene HOMO match those in the LVMO of ethylene, the addition is thermally allowed (Chart-3).

We reach a similar conclusion by considering the signs of butadiene LVMO and HOMO of ethylene (Chart-3).

No such correspondence is obtained by the irradiation of the reactants and consequently the Diels-Alder reaction is a photochemically forbidden process.

An interesting example of the role of frontier orbital in determining the product is the Diels-Alder reaction of cyclopentadiene forming dicyclopentadiene - (Chart-4). Invariably, the endo dimer is formed rather than the exo. This is due to the favourable secondary forces as a result of interaction of frontier orbitals of diene and dienophile components which lower the energy of the transition state. In Chart-4 orbitals involved in actual bonding are connected by full lines and the secondary interactions shown by broken lines. An inspection of the transition states reveals that these interactions are present in the endo transition state while they are absent in the exo. Thus, the endo transition state for this reaction is stabilized vis-a-vis the exo and, therefore, the endo attack should

CHART — 4



Orbital interaction in Diels-Alder reaction of Cyclopentadiene.

Supra — Supra
Symmetry forbidden

Supra — Antara
Symmetry allowed

Thermal (2 + 2) Cycloaddition

i + j	Thermal	Photochemical
4 n	Supra - antara Antara - Supra	Supra — Supra antara - antara
4n + 2	Supra — Supra Antara — antara	Supra — antara Antara — Supra

Woodward Hoffmann rules for (i + j) cycloadditions.

be favoured. However in some cases steric factors may be of a greater magnitude than this effect.

Thus, in summary, cycloaddition reaction is suprafacial with respect to both components. For (4+2) cycloadditions, the stereochemistry shows that this is indeed the case. As far as orbital symmetry is concerned thermal (2 + 2) cycloaddition could occur if it were suprafacial with respect to one component and antarafacial with respect to other (Chart-4).

IV) ORIENTATION IN ADDITION TO ACYCLIC DIENES

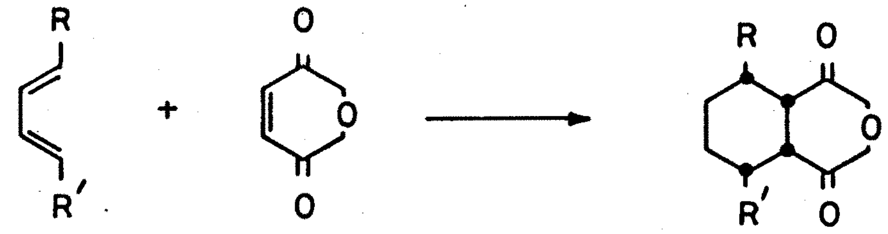
According to endo addition rule, the adducts of trans - 1 and 4 - substituted dienes with simple dienophiles be completely cis - substituted cyclohexenes[5] (Chart-5).

All cis adducts are prone to isomerize to their more stable trans isomers under vigorous conditions. At low temperature and in the absence of equilibrating catalysts, the cis isomer predominates, however, there are exceptions.

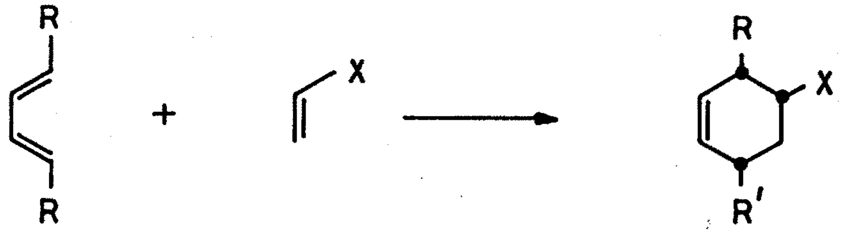
a) The effect of substituents :

The effect of substituents in unsymmetrical dienophiles in addition to unsymmetrical acyclic dienes

CHART -5

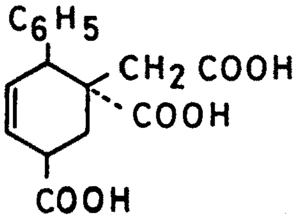


R	R′
CH_3	H
C_2H_5	H
$OCOCH_3$	H
CH_3	CH_3
COOR	COOR

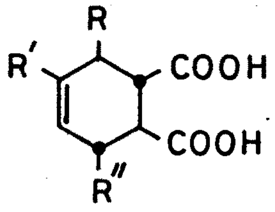


R	R′	X
CH_3	H	$COOCH_3$
CH_3	H	CN
$OCOCH_3$	H	COOH
COOH	CH_3	COOH
COOH	H	COOH

Addition to acrylic acid and its derivatives.



(1)



(2)

would be valuable. The addition of itaconic acid to 5-phenyl - 2, 4 - pentadienoic acid gave the adduct (5.1) in which the carboxymethyl group appears to be cis to the diene substituents.[6] 1-Acetoxy- 1, 3 - butadiene and fumaric acid give a mixture of both possible adducts in unspecified yield and 1-phenyl- 1, 3-butadiene and 4,4,4 - triflurocrotonic acid afford a 1:1 ratio of stereoisomeric adducts.[7] The reaction of fumaryl chloride with several 2-substituted 1- phenyl-1, 3-butadienes has been shown to give adducts of configuration (5.2) [R = C_6H_5, R" = H, R' = CH_3, C_2H_5 and $COOCH_3$], but its addition to 1, 2- diphenyl - 1, 3-butadiene appears to yield the other possible configuration.

Alder and his co-workers studied the addition of fumaric acid derivatives to several unsymmetrically 1,4-disubstituted dienes. Methyl-5-phenyl-2, 4-pentadienoate, 1- phenyl- 1, 3- pentadiene and trans, cis- 2, 4- hexadiene, all gave mixtures of both adducts in unequal amounts, but only in last case major product was (5.2) [R = R" = CH_3, R' = H].

b) Explanation of Orientation (Regioselectivity) :

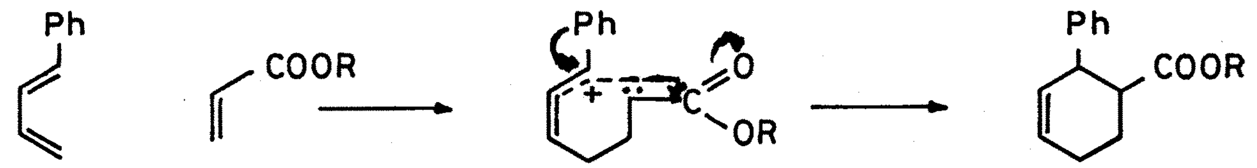
Two different orientations are possible in a diene addition involving substituted reaction components. Thus, a 1-substituted diene with a monosubstituted dienophile may form a ortho and a meta adduct, the same dienophile with a 2- substituted diene can yield a meta and a para adduct. Actually, it has been observed that 1-substituted dienes form preferentially ortho adducts, whereas with 2-substituted derivatives para adducts are favoured.

These results could be regarded as being consistent with a mechanism involving a polar intermediate in which the substituents may conjugate with the adjacent charged atoms (6.3).

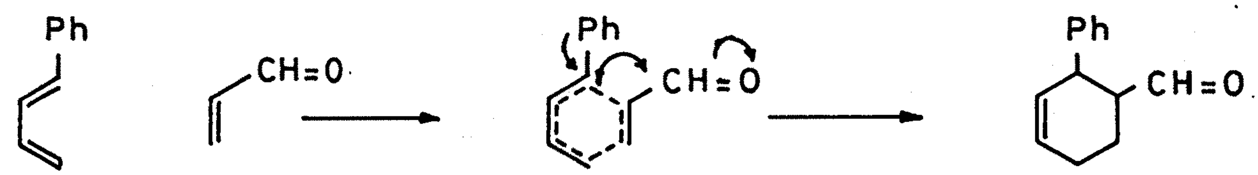
However, the regioselectivity of a diene addition may be better explained by a concerted mechanism. The transition state of a diene addition may be regarded as a six π - electron system, similar to that of benzene, except for the fact that beside p- π overlap, p-σ overlap must also be considered (6.4).

As in benzene, substituents in ortho and para will be better conjugated than those in meta. These qualitative aspects regarding the regioselectivity of the reaction have been treated more quantitatively by quantum mechanical methods. The generalised frontier orbital method based on empirical and calculated

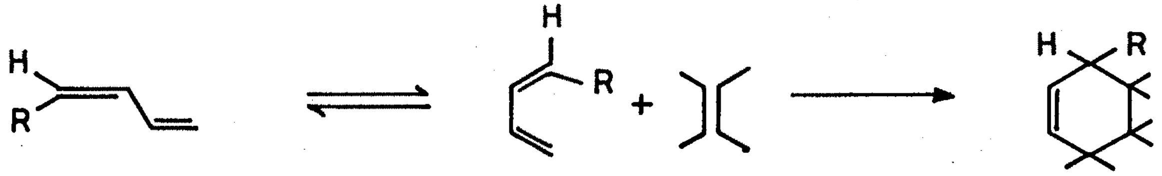
CHART – 6



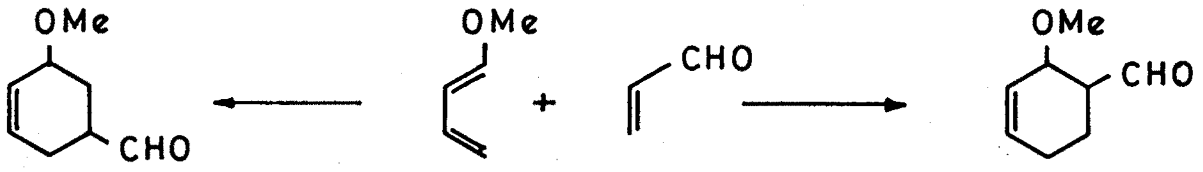
(3)



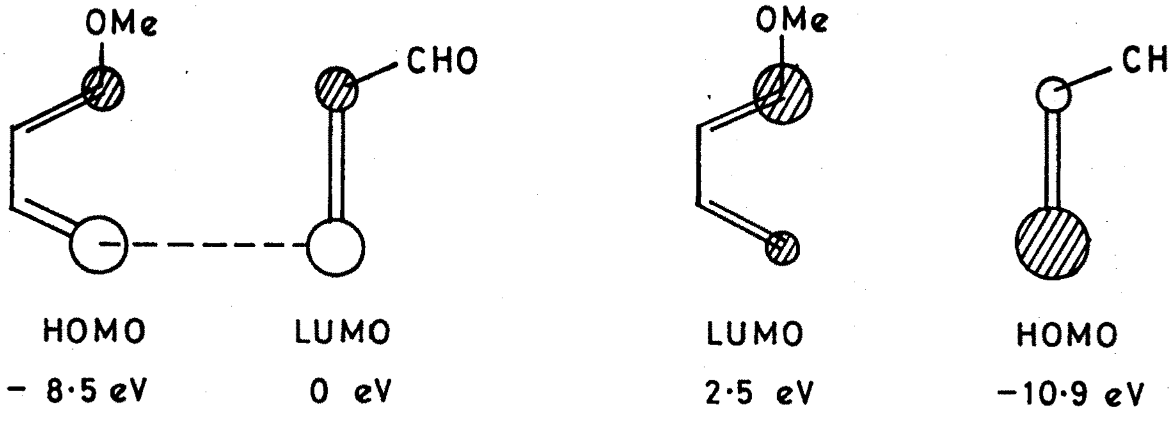
(4)



(5)



(6)



Coefficients of methoxybutadiene and acrolein

[The larger circle indicates a larger coefficient] energies of frontier orbitals as well as on the coefficients of the HOMO and LVMOs, may well account for the observed regioselectivity.

c) <u>Diene reactivity</u> :

In order to participate in a synchronous Diels-Alder reaction, dienes must adopt a cisoid gemoetry about the bond, which for an acyclic diene is less stable than the S- trans conformation.

In cis -1 -substituted dienes (6.5), the S-cis conformation must be disfavoured with respect to the S-cis form of the corresponding trans isomer, due to nonbonding interactions between the substituent and the 4- hydrogen. In a concerted reaction, the trans isomer should be therefore more reactive than the cis derivatives. No large differences in reactivity may be expected in a non-synchronous reaction.

When polar effects are considered, distinction must be made between diene addition with normal electron demand and inverse electron demand. In the former reaction more frequently encountered, the diene component is electron rich, whereas the dienophile is electron-deficient. Electron repellent substituents in the diene will favour the reaction, while electron withdrawing groups will decrease the rate. Indeed, in the reaction with maleic anhydride, in dioxane at 30°C, 2-methylbutadiene is twice as reactive as butadiene, whereas the latter, under similar conditions, reacts 10 times faster than 2-chlorobutadiene. In the Diels-Alder reaction with inverse electron demand, the diene is the electron deficient component. Electron withdrawing substituents, such as in hexachlorocyclopentadiene, will determine the electron-acceptor character of the diene component.

d) Dienophile reactivity :

The reactivity of the dienophile depends on the electron demand of the reaction. In a diene addition with normal electron demand, electron withdrawing groups in the dienophile will accelerate the reaction rate. Thus, tetracyanoethylene, a dienophile with typical electron - withdrawing groups is 4.6×10^8 fold as reactive as cyclopentadiene, an electron-rich dienophile. For simple alkenes, this difference must be still larger.

e) Frontier - Orbital concept :

Regioselectivity can be explained by using the Frontier - Orbital concept.[8] The coefficient of the atomic orbitals in the diene and dienophile influence the regioselectivity.

Ex : Methoxybutadiene gives 'Ortho' adduct rather than the 'Meta' adduct with acrolein (6.6).

In methoxy butadiene and acrolein the coefficients are as shown in Chart-6.

The important low energy interaction in this reaction (electron rich diene and electro-poor dienophile) will be between the HOMO of the diene (E_ν) and LUMO Es of the dienophile (E_ν - Es = 8.5 eV) and not the other way round (E_ν - Es = 13.4 eV).

In substituted dienes and dienophiles the coefficients are not equal at each end. This is indicated in Chart-6, by the size of the cirlce. By considering butadiene, allyl cation and allyl anion as references it is possible to calculate the coefficients of atomic orbitals in the molecular orbitals of any conjugated system.

By taking HOMO (diene) / LUMO (dienophile) interaction, by considering the coefficients of $\ddot{X}$ (an electron - donating group) substituted diene and Z (an electron - withdrawing group) substituted olefin and by allowing large large and small small - interactions to predominate we get expected 'Ortho' product in the reaction of methoxy butadiene and acrolein.

Chart-7 and 8 show the coefficients and energies of variously substituted olefins and dienes.

Chart-10 gives the regioselectivity in Diels-Alder reaction predicted by considering only the Frontier orbital contribution by using the coefficients and energies given in Charts-7 to 9.

Examination of energies reveals that in the reaction with usual dienophiles like  all types of dienes have the HOMO diene / LUMO dienophile as the most favourable interaction. When the dienophile is electron rich like  in all cases the most favourable interaction is now LUMO diene / HOMO dienophile, suggesting that such reactions could be considered as Diels-Alder reactions of opposite electron demand. This would be obvious for cases of dienes like b and e where the difference between the two types of interaction (column 2 - column 3) is large (4 and 3.6 respectively). When the diene has a weak donar (Ex. a and d) this difference (column 2 - column 3) is smaller (1.7 and 1.8 respectively). With dienes of greater electron density, Ex. c and f the interaction difference (column 2 - column 3) is very small (0.0 and 0.4 respectively).

Examination of these results suggest that the nature of dienophile controls, the nature of the important interaction. If the dienophile has a strong withdrawer, the important interaction in all cases is HOMO diene / LUMO dienophile. When the dienophile has strong donar, the opposite interaction is important in all cases.

It is then interesting to see the results in case of dienes with weak donors like . In this system the important interaction is HOMO diene / LUMO dienophile in four out of six cases. The only exception being dienes (b and e) which have electron withdrawer in them. Such Diels-Alder reactions are additional examples of reactions involving inverse electron demand.

To predict the regioselectivity one must first decide which is the low energy interaction (HOMO diene/ LUMO - dienophile or LUMO diene / HOMO dienophile). Once this is decided then regiochemistry is predicted by looking in Charts-7 to 9. The product being predicted by allowing large large and small small interactions to predominate.

In short,

C -

Extra conjugation	raises the energy of the HOMO. lowers the nergy of the LUMO.

Z -

An electron - withdrawing group lowers the energy of the HOMO.

lowers the energy of the LUMO.

$\ddot{X}$ -

An electron donating group raises the energy of the HOMO.

raises the energy of the LUMO.

In the example given in chart-11 one case in which two different products are predicted by considering different interactions is explained.

Chart-12 shows some of the examples[8] showing the regioselectivity observed in variously substituted butadienes and olefins.

V) STEREOCHEMISTRY

The structure of the Diels-Alder adduct can be sometimes accurately predicted considering polar effects in the components (for the regiospecificity) as well as the rules established by Alder and Stein (for the stereospecificity).[9]

CHART - 7

Coefficients and energies of dienophiles

a) for LUMO b) for HOMO

Coefficients indicated by the size of the circles.

Energies given by figures in the brackets in eV.

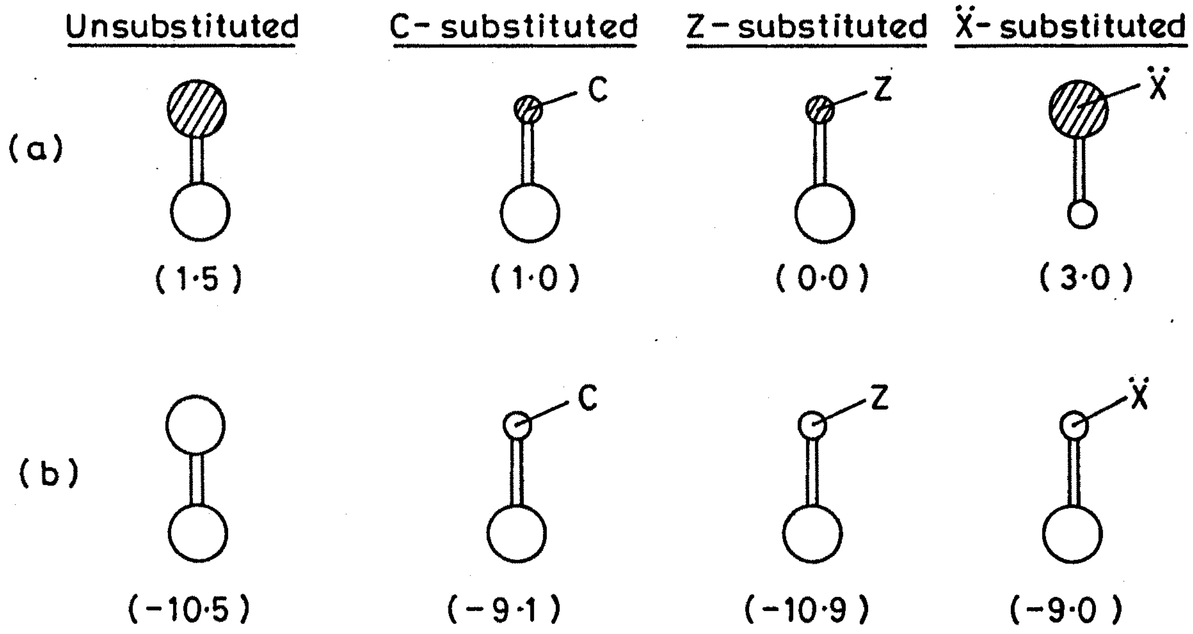


CHART- 8

Coefficients and energies of 1-substituted dienes

a) For LUMO b) For HOMO.

Coefficients indicated by size of the circles.

Energies given by figures in the brackets in eV.

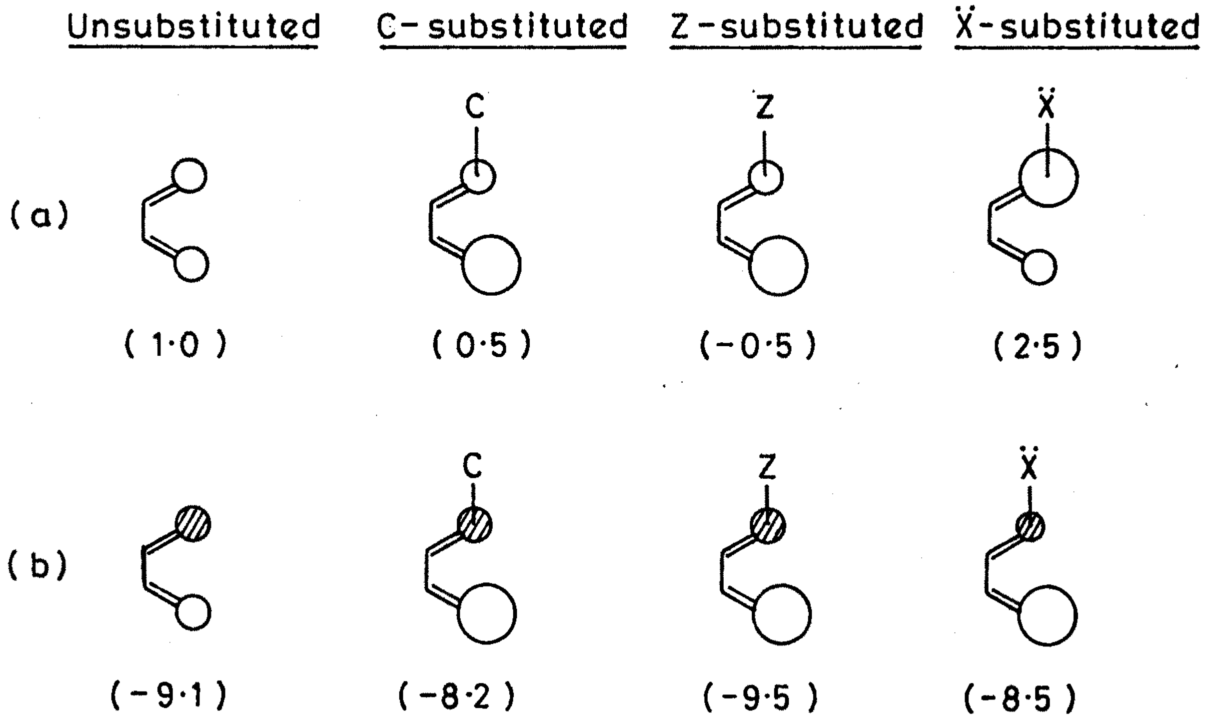


CHART- 9

Coefficients and energies of 2-substituted dienes

a) For LUMO b) For HOMO

Coefficients indicated by size of the circles.

Energies given by figures in the brackets in eV.

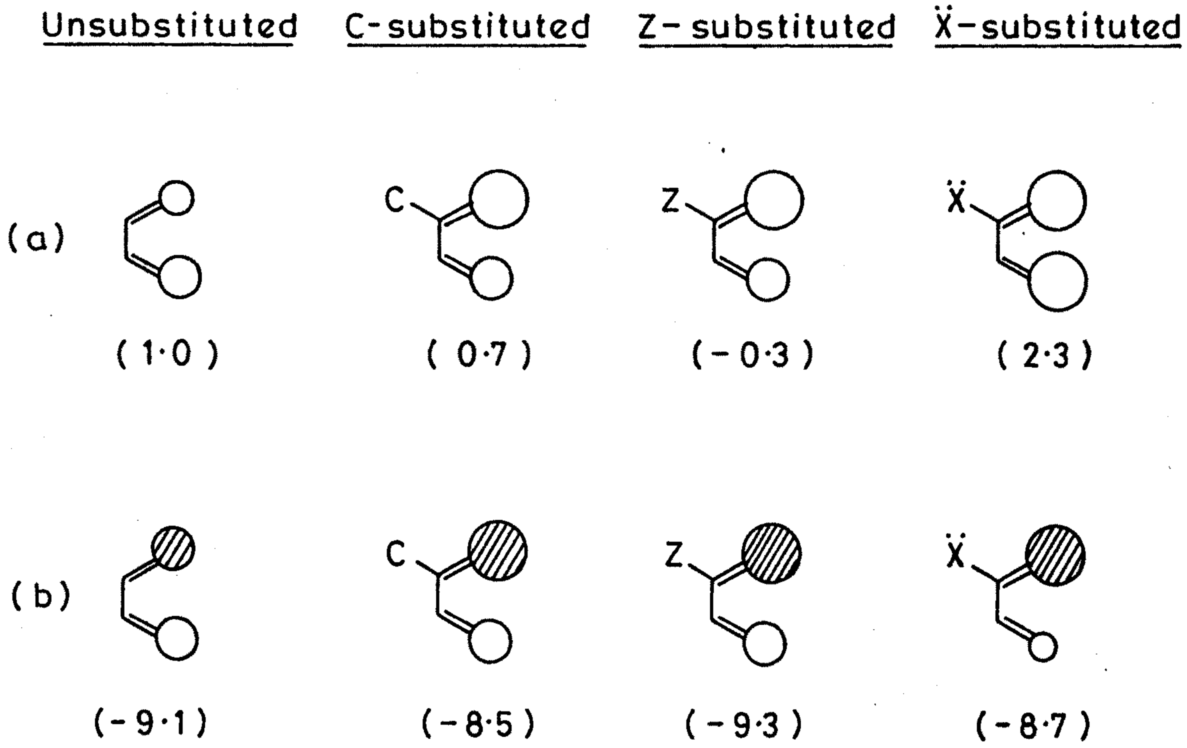
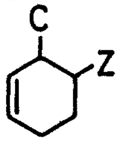
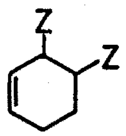
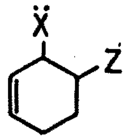
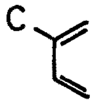
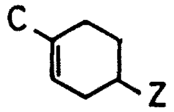
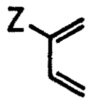
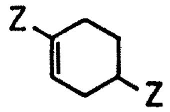
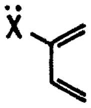
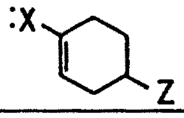
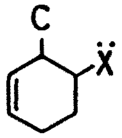
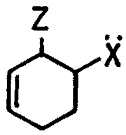
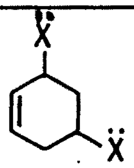
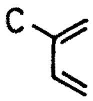
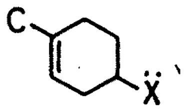
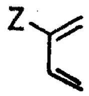
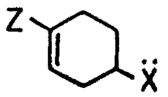


CHART - 10

Expected regioselectivity of diels alder reactions considering the frontier orbital concept.

	Dienophile	Energy	Gap	Diene	Product expected
		A	B		
Group 1		8·2	11·4	a 	 m
		9·5	10·4	b 	 m
		8·5	13·4	c 	 n
		8·5	12·6	d 	 m
		9·3	10·6	e 	 m
		8·7	13·2	f 	 n
		11·2	9·5	a 	 o
		12·5	8·5	b 	 o
Group 2		11·5	11·5	c 	 m⁺
		11·5	9·7	d 	 o
		12·3	8·7	e 	 o

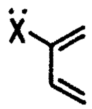
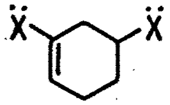
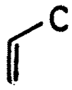
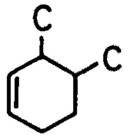
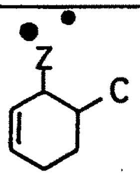
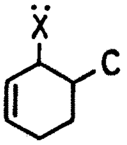
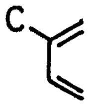
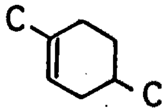
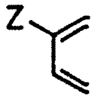
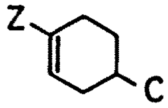
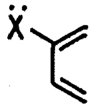
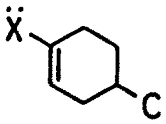
	Dienophile	Energy Gap		Diene	Product expected
		A	B		
		11·7	11·3	f 	 m+
Group 3		9·2	9·6	a 	 m
		10·5	8·6	b 	 m+
		9·5	11·6	c 	 n
		9·5	9·8	d 	 m
		10·3	8·8		 m+
		9·7	11·4		 n

CHART- 11

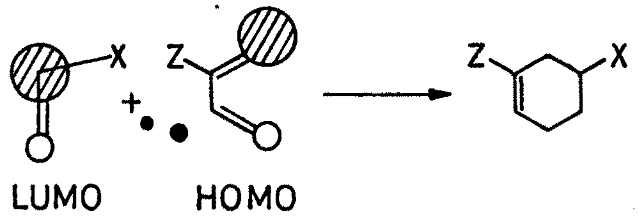
A : HOMO diene/LUMO dienophile

B : LUMO diene/HOMO dienophile

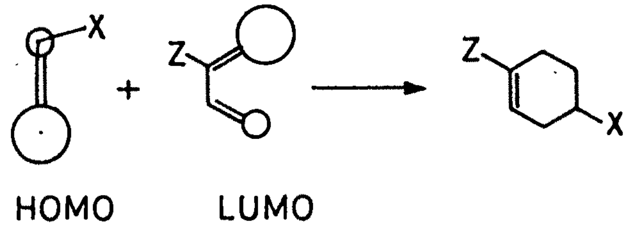
m : It is interesting that in these cases the interaction may be HOMO diene/LUMO dienophile or LUMO diene/HOMO dienophile, the regiochemistry comes out to be the same. For the purpose of exactness in the cases marked with +, the orientation should be predicted by considering LUMO diene and HOMO dienophile.

n : In these cases the correct regiochemistry indicated by considering HOMO diene/LUMO dienophile which is the low energy interaction. The reverse consideration would give '<u>meta</u>' like product.

o : In these cases the correct regiochemistry can be obtained by considering LUMO diene/HOMO dienophile. This interaction is indeed the low energy interaction. Consideration of opposite interaction gives '<u>meta</u>' like product.



Interaction energy 12·3 HOMO diene/ LUMO dienophile



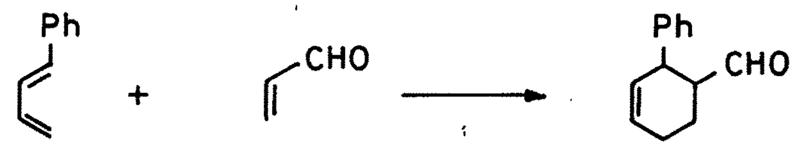
Interaction energy LUMO diene/ HOMO dienophile

Observed regioselectivity from chart IV

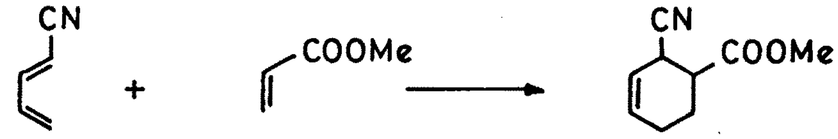
CHART - 12

Examples from group 1

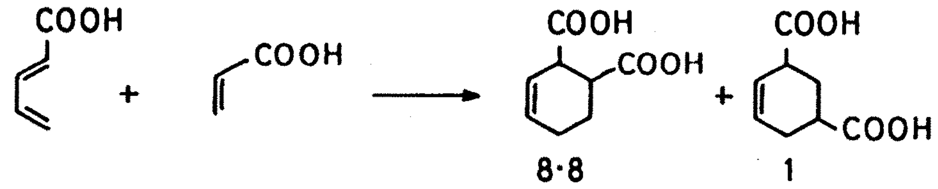
Type a (1)



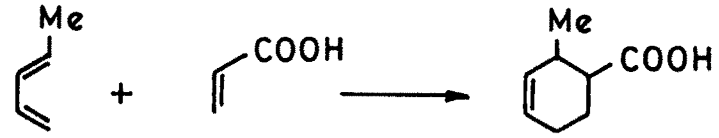
Type b (1)



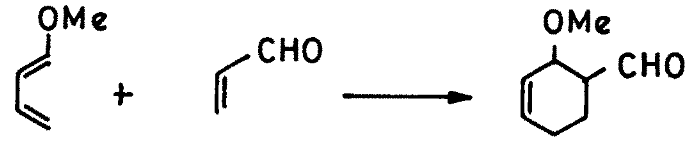
(2)*



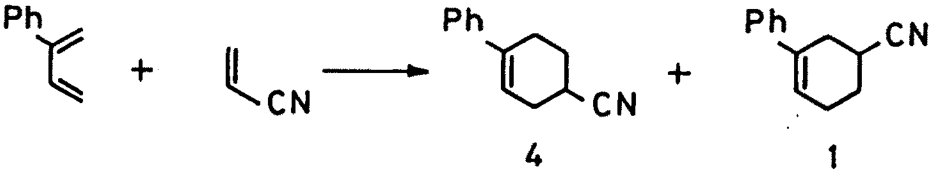
Type c (1)



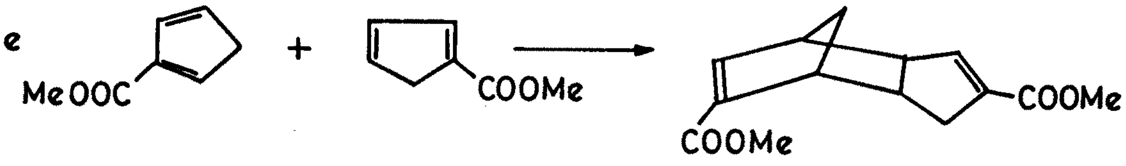
(2)



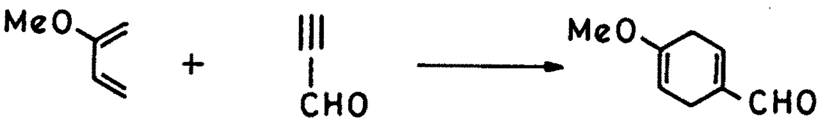
Type d*



Type e

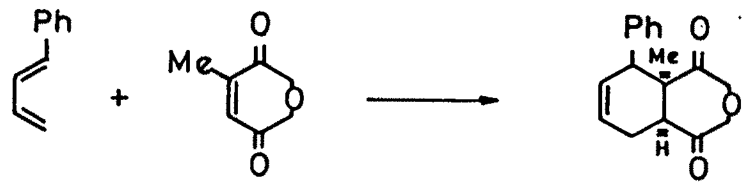


Type f

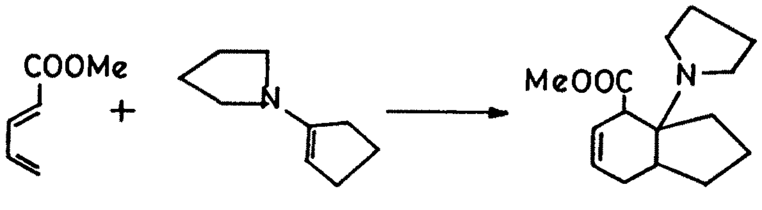


Examples from group 2

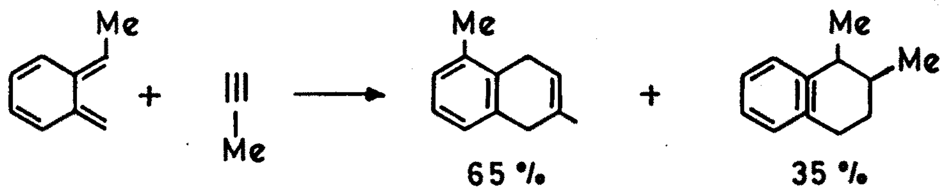
Type a



Type b

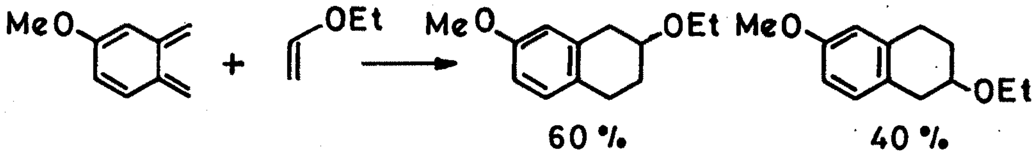


Type C*



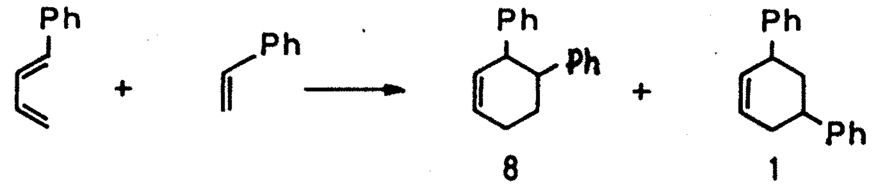
Type d, e Not known

Type f*



Examples from group 3

Type a (1)*



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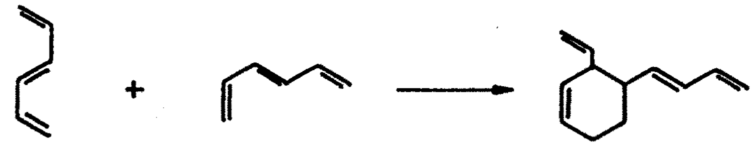

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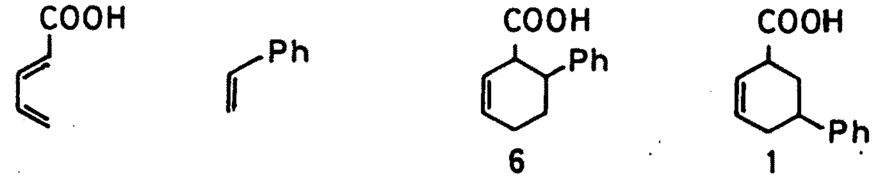
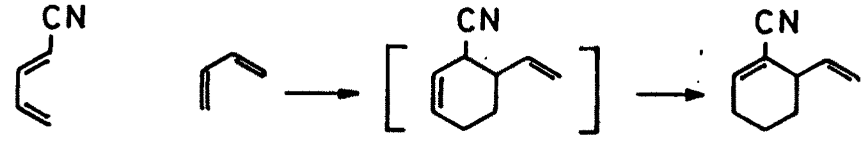


(2)



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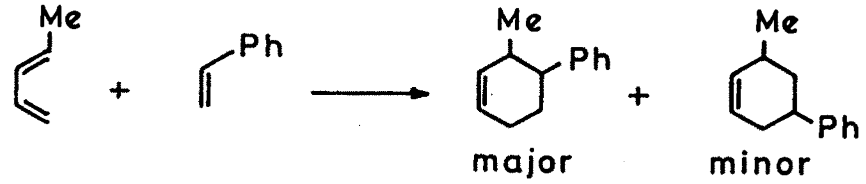
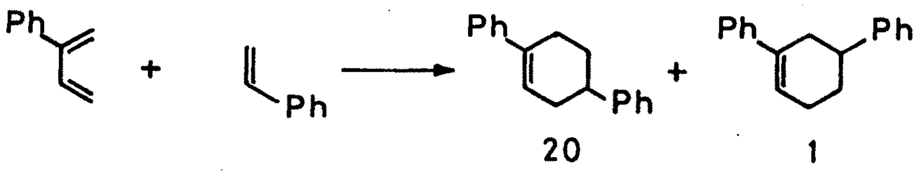
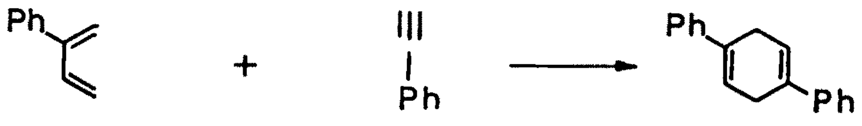
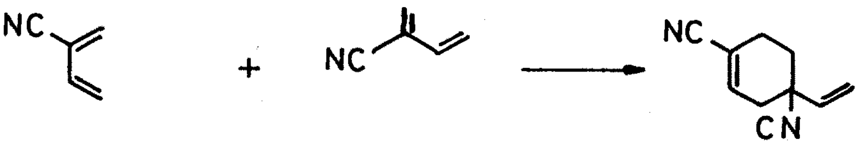


Type d*

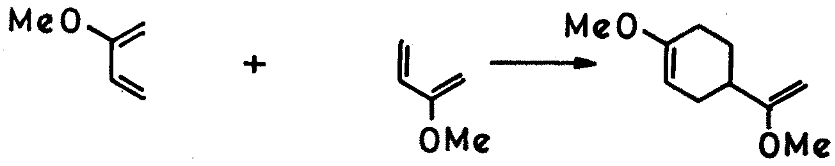




Type e



Type f



* Major product is the product expected from the frontier orbital concept while minor product is not explained by this concept.

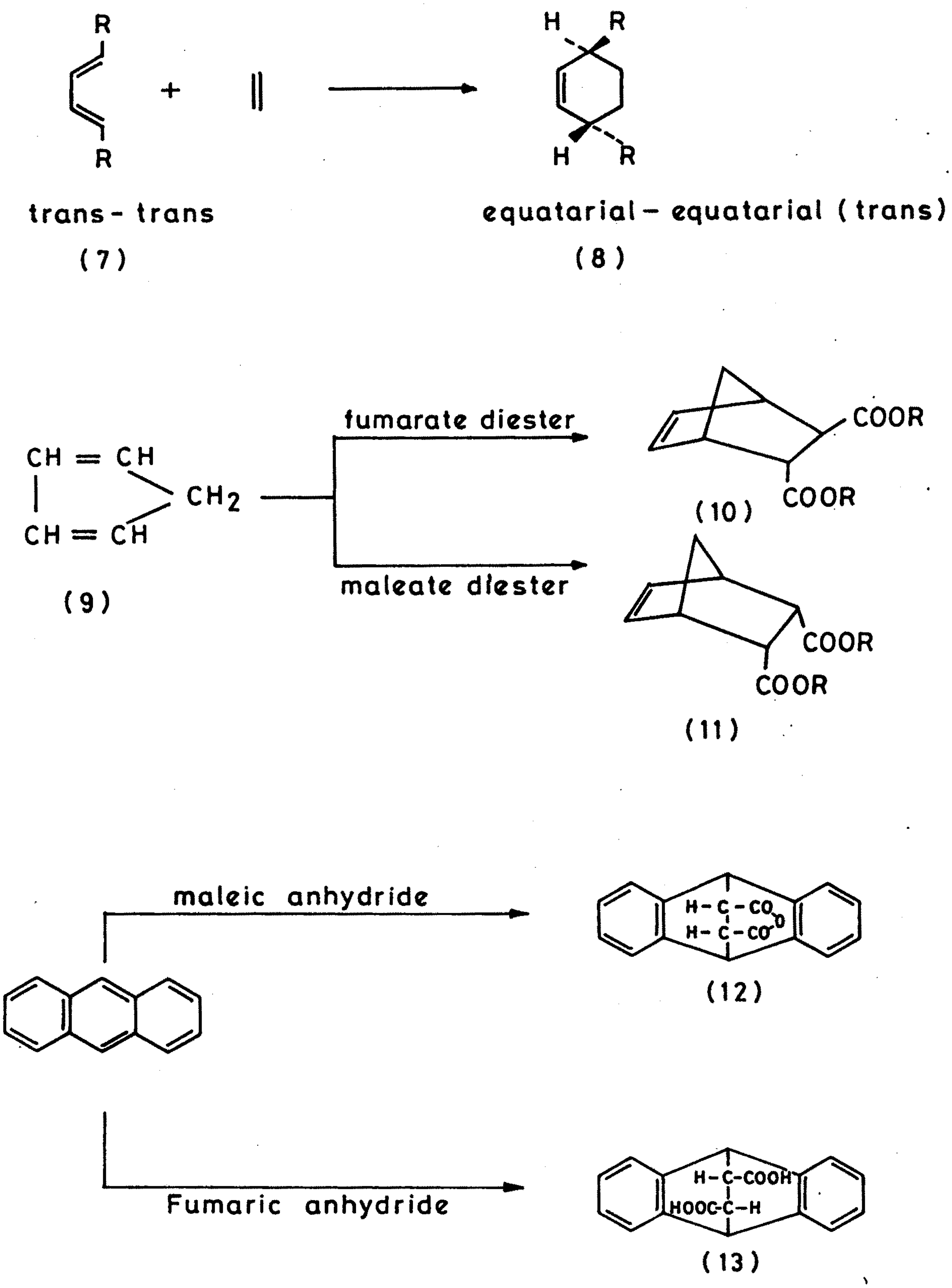
The rule of cis addition : The relative orientation of substituents in both components of a diene adition is preserved in the resulted adduct. Thus, a 1, 4 - trans disubstituted diene (13.7), will form a cyclohexene derivative (13.8) having the two substituents in equatorial - equatorial positions (trans). A diene, Ex : cyclopentadiene will react with the two isomers of a 1, 2 - disubstituted dienophile yielding a cis (13.11) and a trans (13.10) adduct respectively.

a) Stereochemical selectivity of the reaction :

The Diels-Alder reaction exhibits pronounced stereochemical selectivity.[10] The configuration of a given adduct conforms to the following general principles[11], commonly known as the Alder rules.

1. The addition of a dienophile to diene is a purely cis addition. The relative positions of substituents in the dienophile is retained in the adduct. Ex : maleic anhydride reacts with anthracene to yield the cis - anhydride adduct (12), while fumaric acid yields the trans - dicarboxylic acid adduct [12] (13).

CHART - 13


R
R
+
H
R
H
R
trans - trans
(7)
equatarial - equatarial (trans)
(8)
CH = CH
CH = CH
CH2
(9)
fumarate diester
maleate diester
COOR
COOR
(10)
COOR
COOR
(11)
maleic anhydride
H - C - CO
H - C - CO
O
(12)
Fumaric anhydride
H-C-COOH
HOOC-C-H
(13)

2. In the reaction of maleic anhydride with a cyclic diene such as cyclopentadiene, two modes of addition are theoretically possible, leading to the formation of an 'endo' configuration (14) or an 'exo' configuration (15) respectively. Actually, the endo configuration is produced exclusively. This 'one-sided' addition indicates that immediately before combination the components must always be oriented in exactly the same manner with respect to each other, that is of the two possible orientations, A and B, A is favoured.

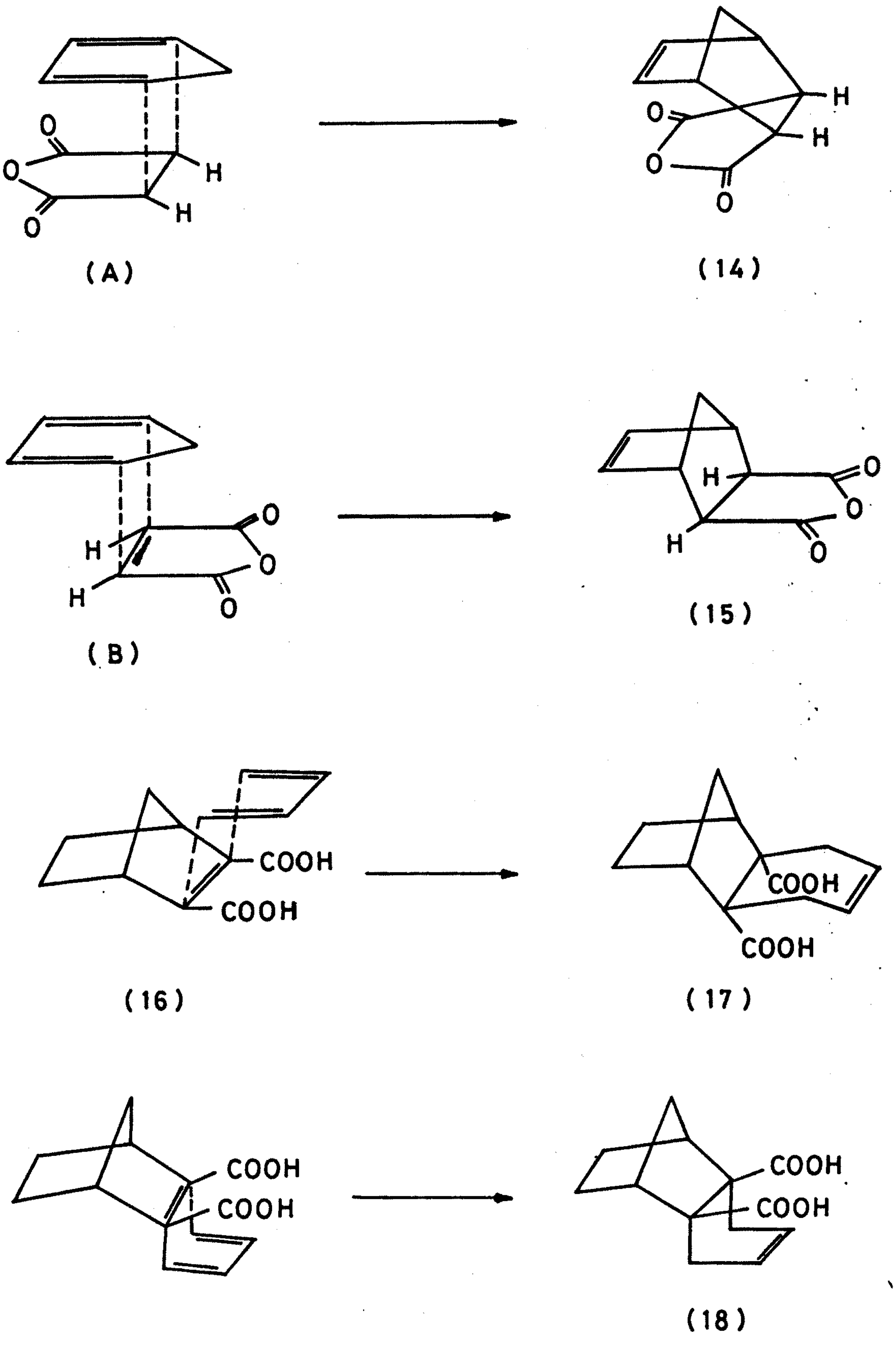
The favoured orientation (A) corresponds to the maximum accumulation of double bonds (the double bonds of the carbonyl groups are included in this consideration). It has been calculated that the attracting forces between the two molecules are greater in the endo orientation than in the exo orientation. Investigation of the behaviour of substituted fulvenes towards maleic anhydride demonstrated in a striking manner that accumulation of unsaturation is truely the criterion for the steric course of the reaction. It should be pointed out, however that when the dienophile has no activating unsaturation it is no longer valid to speak of "maximum accumulation of double bonds" and orientation of the components to give an endo configuration must be attributed to some other factors. According to Alder the unshared electrons on an oxygen, nitrogen or halogen atom may be considered equivalent to unsaturation and in a broader sense the presence of unshared electrons governs the spatial arrangement of the components before addition.

3. The steric course of most Diels-Alder reactions is controlled by the aforementioned generalizations. When however, the dienophile is an asymmetrically substituted maleic acid, such as 3, 6- endomethylene - 3,4,5,6 - tetrahydrophthalic acid (16), there are theoretically two additional steric selectivity of the reaction holds, for, of the two possible configurations (17) and (18) only (17) is produced.

b) <u>**Formation of Stereoisomeric adducts**</u> :

The addition reactions of ethylenic and acetylenic dienophiles show stereo - chemical selectivity. A cis dienophile yields a cis adduct, while a trans adduct results from the trans-form, Ex.: The adduct (m.p. 191°C) from cis-o-methoxycinnamic acid

CHART – 14



(A) (14)

(B) (15)

(16) (17)

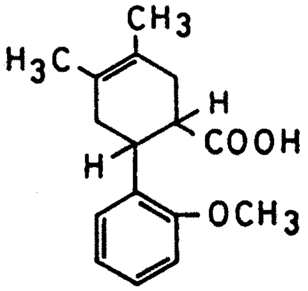
(18)

and 2, 3- dimethylbutadiene is the cis compound (19) and the adduct (m.p. 159-159.5°C) from trans-o-methoxycinnamic acid is the trans compound (20).

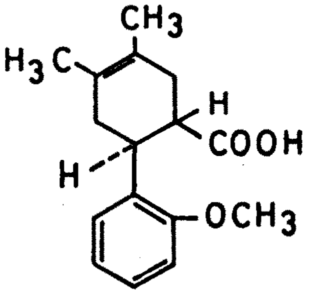
c) **Formation of structurally isomeric adducts** :

Two structural isomers (21) and (22) are possible when an unsymmetrical diene and an unsymmetrical dienophile interact. Unfortunately the structures of the adducts have been rigidly established in only seven instances : acrolein + 1-phenyl butadiene, acrolein and methyl - 3, 4- dihydro - 1 - naphthoate + 2-ethoxy and 2 - methoxy butadiene, 2, 6-dimethoxy - 4 -n-amylcinnamic acid + isoprene and derivatives of sorbic acid + acrylyl chloride and vinyl phenyl ketone. Acrolein and 1- phenylbutadiene gives (23). 2-Methoxybutadiene (and 2-ethoxybutadiene) with acrolein give rise to a single product (24). On the other hand, 2,6-dimethoxy- 4 - n - amyl cinnamic acid and isoprene when heated, usually yields (25), although in a single experiment that could not be duplicated the isomeric adduct was formed. The principal product formed from acrylyl chloride and derivatives of sorbic acid is (26) (79%), as established by conversion to 4-methyl isophthalic acid. The orientation of ethyl sorbate and vinyl phenyl ketone, before reaction, must be just the

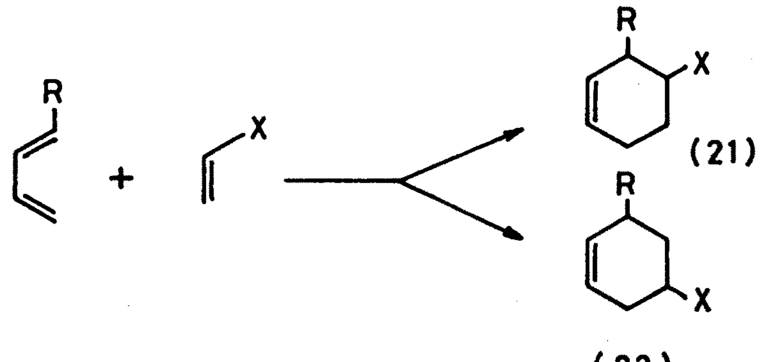
CHART – 15



(19)

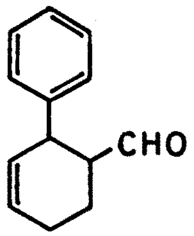


(20)

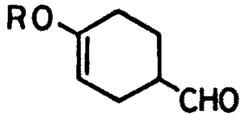


(21)

(22)



(23)



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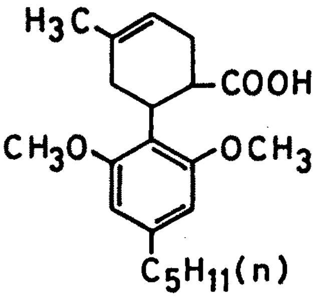
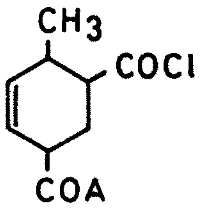
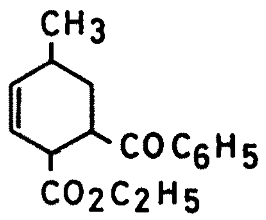


(25)

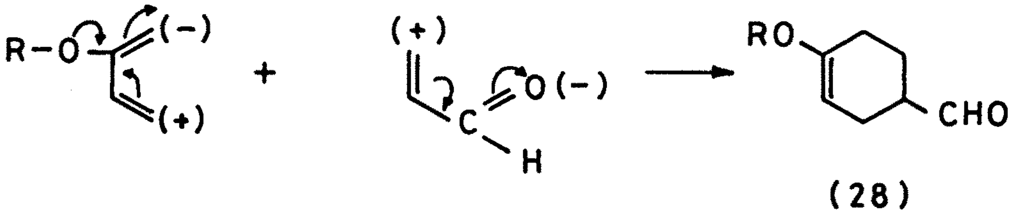


A = Cl - OCH_2CH_2Cl

(26)



(27)



(28)

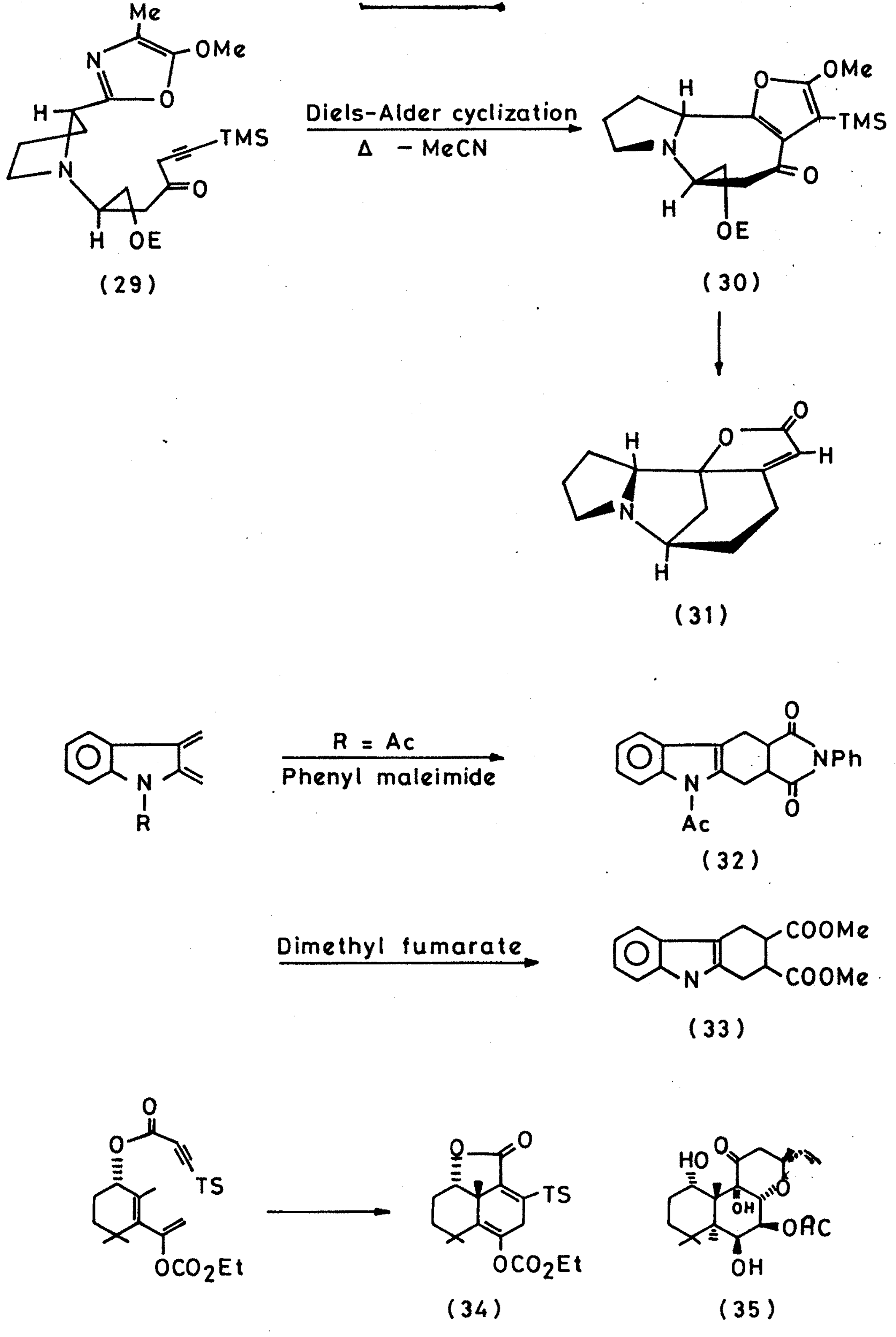
reverse of the previous case, for the main product (70%) is (27), it was smoothly converted to β- methylanthraquinone by a three step reaction.[13]

It has been suggested that the Diels-Alder reaction is probably initiated by a coupling of the more anionoid end of the diene system with a cationoid carbon of the dienophile. The reactions of 2-alkoxy-butadienes with acrolein are in agreement with this hypothesis and may be formulated as (28). The Alder rule correctly predicts the formation of isomer (23) from the interaction of 1-phenyl butadiene and acrolein. It seems likely that steric and Alder effects as well as electronic effect influence the course of the reactions.

d) **Steric approach control** :

The final principle[1] which governs the configuration of Diels-Alder adducts arises in additions of asymmetric dienes and dienophiles. The rule enunciates the natural expectation that the diene should add from the less hindered side of the dienophile, where such a choice exists and that the dienophile should likewise approach the less hindered face of the diene.

CHART – 16


Me
OMe
N
O
H
N
TMS
O
H
OE
(29)
Diels-Alder cyclization
Δ − MeCN
H
O
OMe
TMS
N
O
H
OE
(30)
O
H
O
H
N
H
(31)
N
R
R = Ac
Phenyl maleimide
O
NPh
N
Ac
O
(32)
Dimethyl fumarate
COOMe
N
COOMe
(33)
O
O
TS
OCO$_2$Et
O
O
TS
OCO$_2$Et
(34)
HO
O
O
OH
OAc
OH
(35)

VI) SYNTHETIC APPLICATIONS OF DIELS-ALDER REACTION :

The reaction between a conjugated diene and a dienophile to form a substituted cyclohexene was correctly formulated by Diels and Alder in 1928. The widespread utility of the reaction rests not only on in its ability to form six membered ring compounds and molecules but also on its remarkable stereospecificity.

In the addition of a 1, 4- disubstituted diene to a 1, 2- disubstituted olefin, Ex. : no less than eight racemic products could conceivably be formed, the number is doubled by considering in addition, the alternate structural orientation. Yet the usual result of the reaction is the obtention of one or at the most two stereoisomers. In recent years, the selectivity of diene addition has been exploited in stereospecific syntheses of a number of natural products. Ex.: cholestanol[14], cortisone[15], reserpine[16], estrone[17], yohimbine[18], cantharidin[19] etc.

A few recent examples are given in the following pages.

Peter Jacobi and Coworkers[20] synthesized stereospecifically (-) Norsecurinine (31), an alkaloid which acts as inhibitor of the acetylcholinesterase system and produces a stimulant effect in the central nervous system with lower toxicity. Diels-Alder cyclization of (29) afforded (30) which on six steps gives (31).

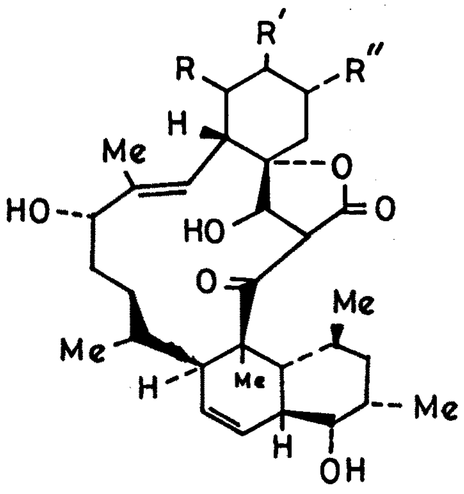
Vice and coworkers[21] achieved the regioselectivity of intermolecular cycloaddition of indole anologs with unsymmetrical dienophiles in the synthesis of complex indole alkaloids (32), (33).

The enantioselective synthesis of key intermediate (34) for the total synthesis of Forskolin (35) has been developed by Corey and coworkers[22]. (35) is an activator of cyclase and promise to be useful in medicine.

The enantioselective and diastereoselective synthesis of the top and bottom half fragment of Kijanolide (36), tetronolide (37), chlorothricolide (38) which are novel antitumor antibiotics was done by Roush and coworkers[23] via the highly regio and stereoselective Diels-Alder reaction.

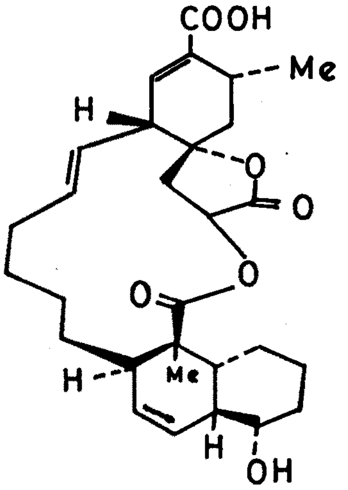
Anthracycline antibiotics have emerged as effective drugs for human cancers. The synthetically useful intermediate (41) can be synthesized by Faujan and coworkers[24] via Diels-Alder reaction of (39) and (40).

CHART - 17

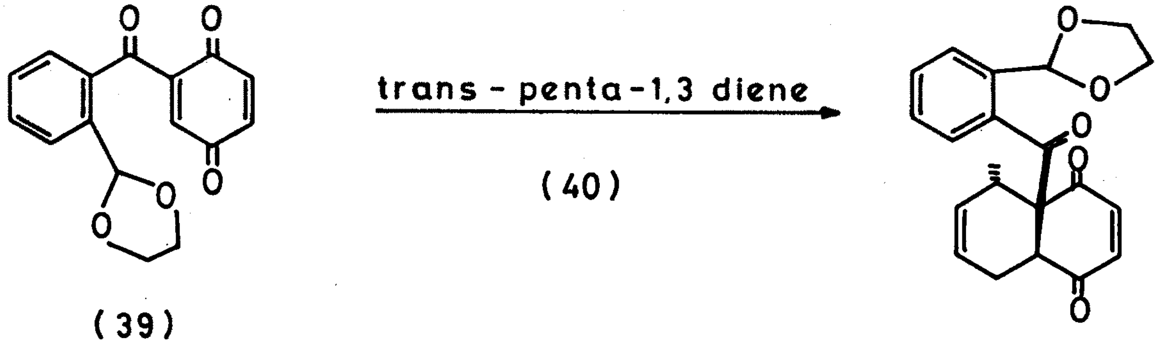


(36) R = H, R' = CH_2OH R" = Me

(37) OH H CHO

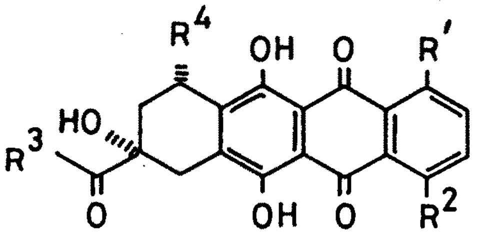


(38)



(39)

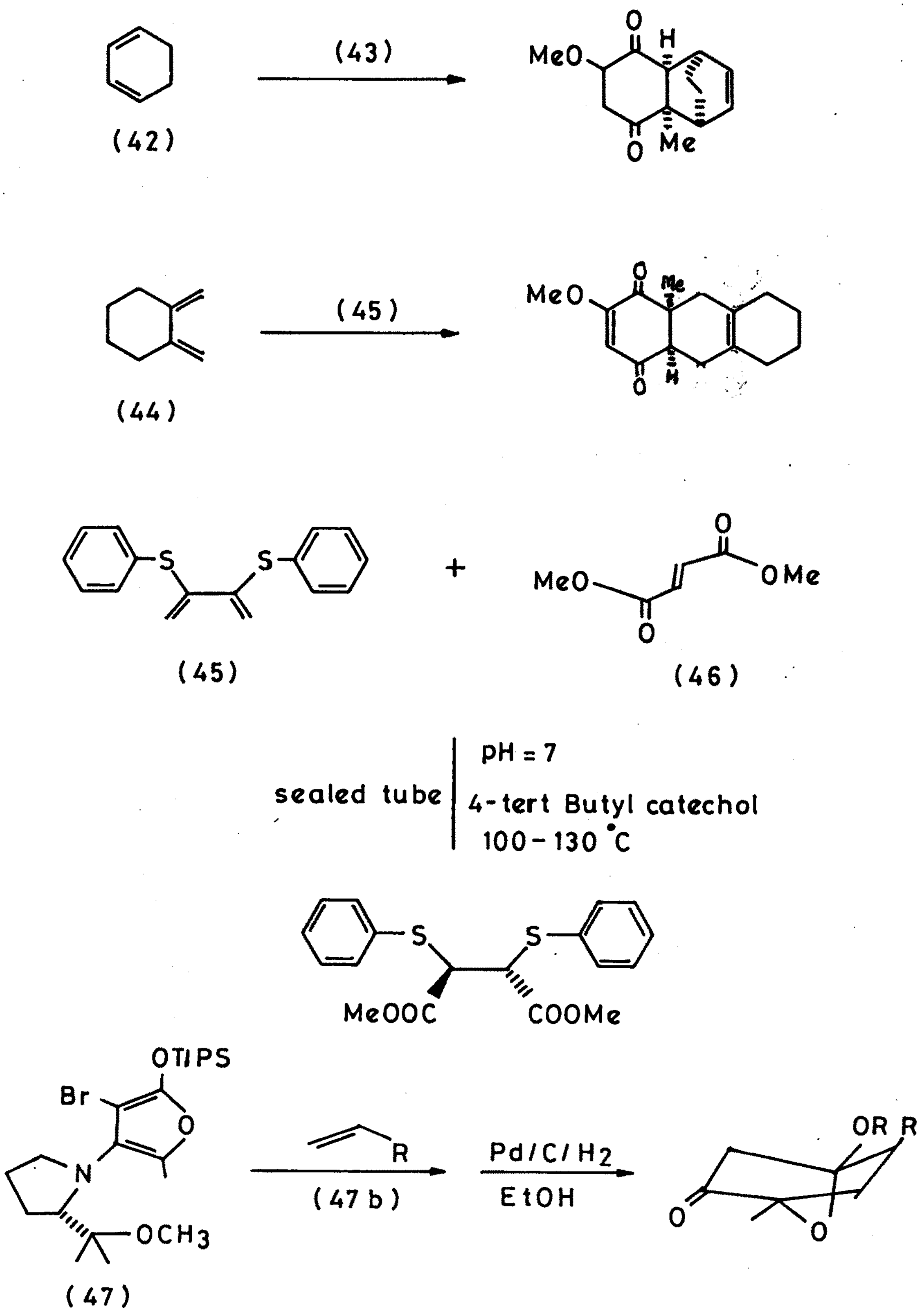
(41)



Aglycone

A

CHART – 18


(42)
(43)
MeO
O
H
O
Me
(44)
(45)
MeO
O
Me
O
H
S
S
+
MeO
O
OMe
O
(45)
(46)
sealed tube
pH = 7
4-tert Butyl catechol
100 – 130 °C
S
S
MeOOC
COOMe
OTIPS
Br
O
N
OCH3
(47)
R
(47 b)
Pd/C/H2
EtOH
OR R
O
O

Engler and coworkers[25] obtained quantitative yield of enantiomerically pure adduct of 2- methoxy-6-methyl (43) and 2-methoxy-5- methyl - 1, 4- benzoquinone (44) with various substituted dienes (42), (44).

Jaeger and coworkers[26] have carried out regioselective Diels-Alder reaction of surfactant - 1,3-diene (45) with surfactant dienophile (46).

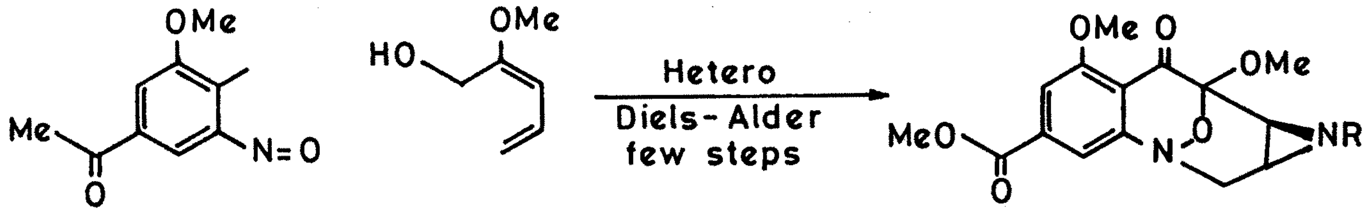
Schlessinger and coworkers[27] observed that the furan derivatives (47) undergo Diels-Alder reaction with dienophilic species (47_b) in excellent yield. The oxobicyclic adducts are useful in chemical transformation in natural product synthesis.

Benbow and coworkers[28] observed the hetero D.A. reaction of diphenyl nitroso compounds (48) which give an intermediate (49) in the total synthesis of mitomycin K (50) useful as antitumor agent.

Enantioselective synthesis of the bottom half of chlorotoricolide (51) by intramolecular D.A. reaction was done by Roush.[29]

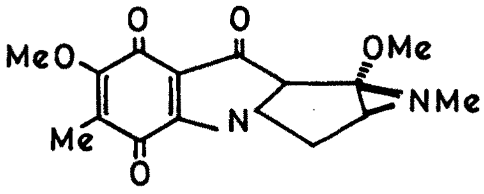
5-(1-methyloxy)-2 (5H)-furanone (52), (54) were used as a chiral dienophile in D.A. reaction[30] with several cyclic and acyclic dienes to give

CHART – 19

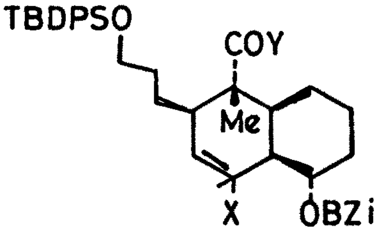


(48)

(49)



(50)



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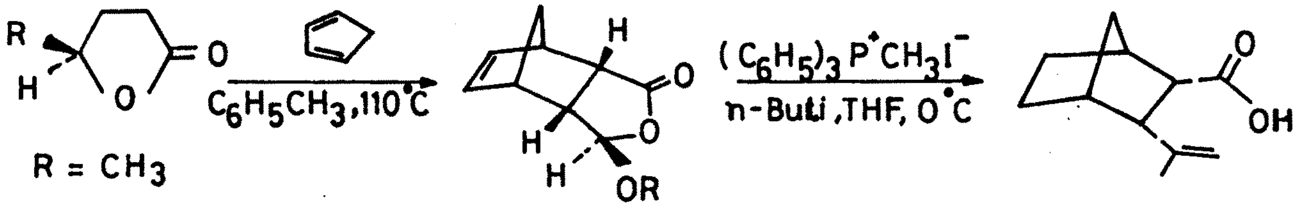
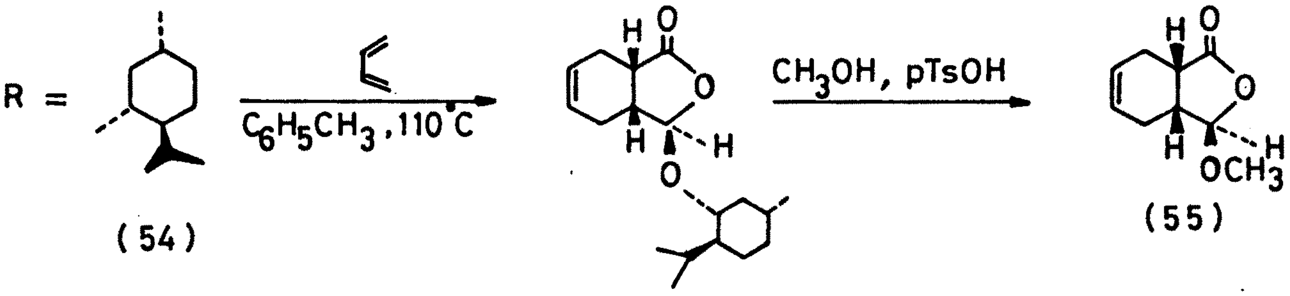


(52)

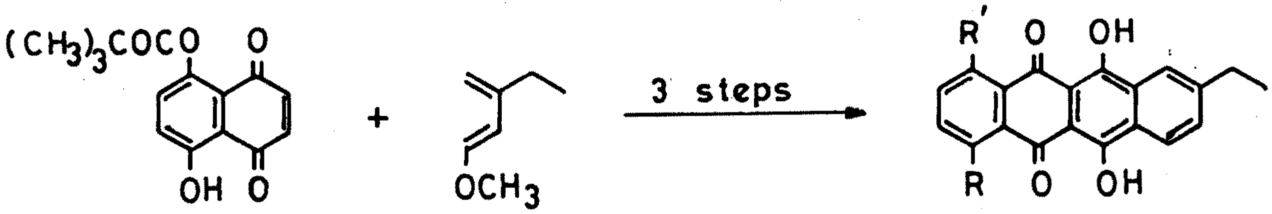
(53)



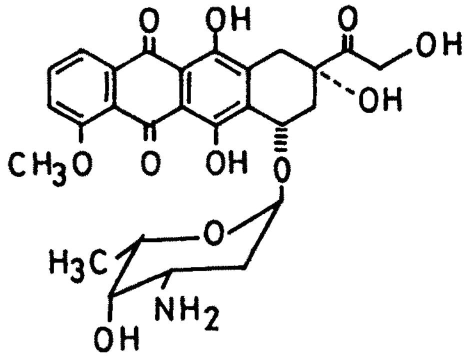
(54)

(55)

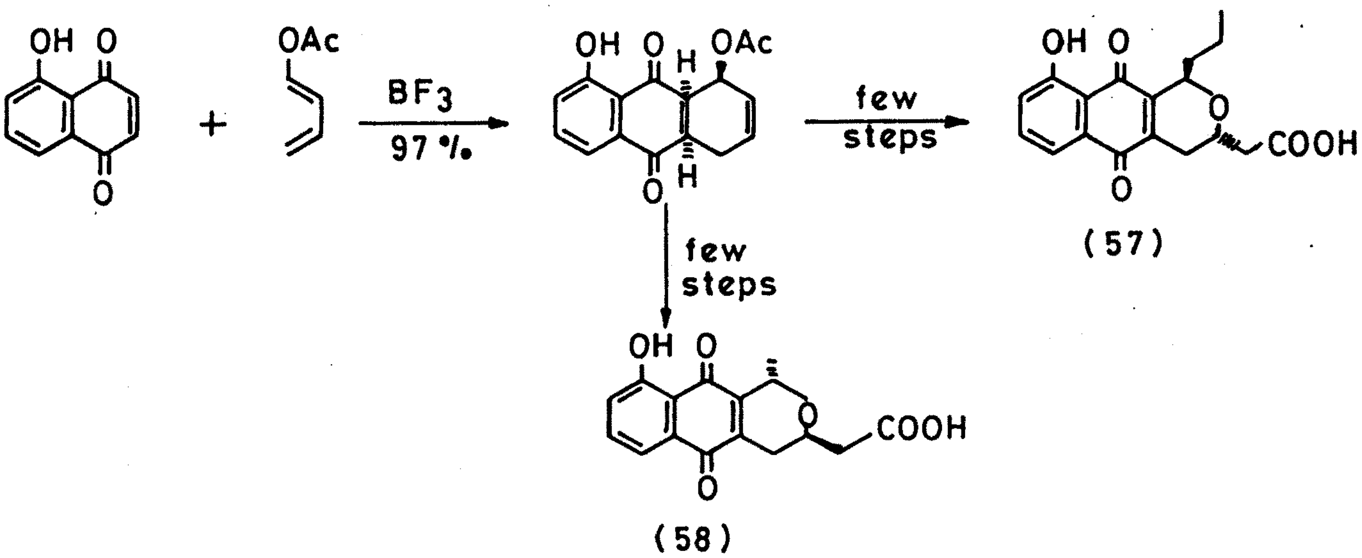
CHART - 20



(56a)



(56 b)



(57)

(58)

enantiomerically pure products (53) and (55). (53) acid is the key intermediate in natural product synthesis shown by Magnus and coworkers.[31]

Kelly and coworkers[32] carried out regiospecific approach to Adriamycinone via D.A. reaction of substituted naphthaquinones (56_a). Adriamycin (56_b) and its analogues are effective against human cancers.

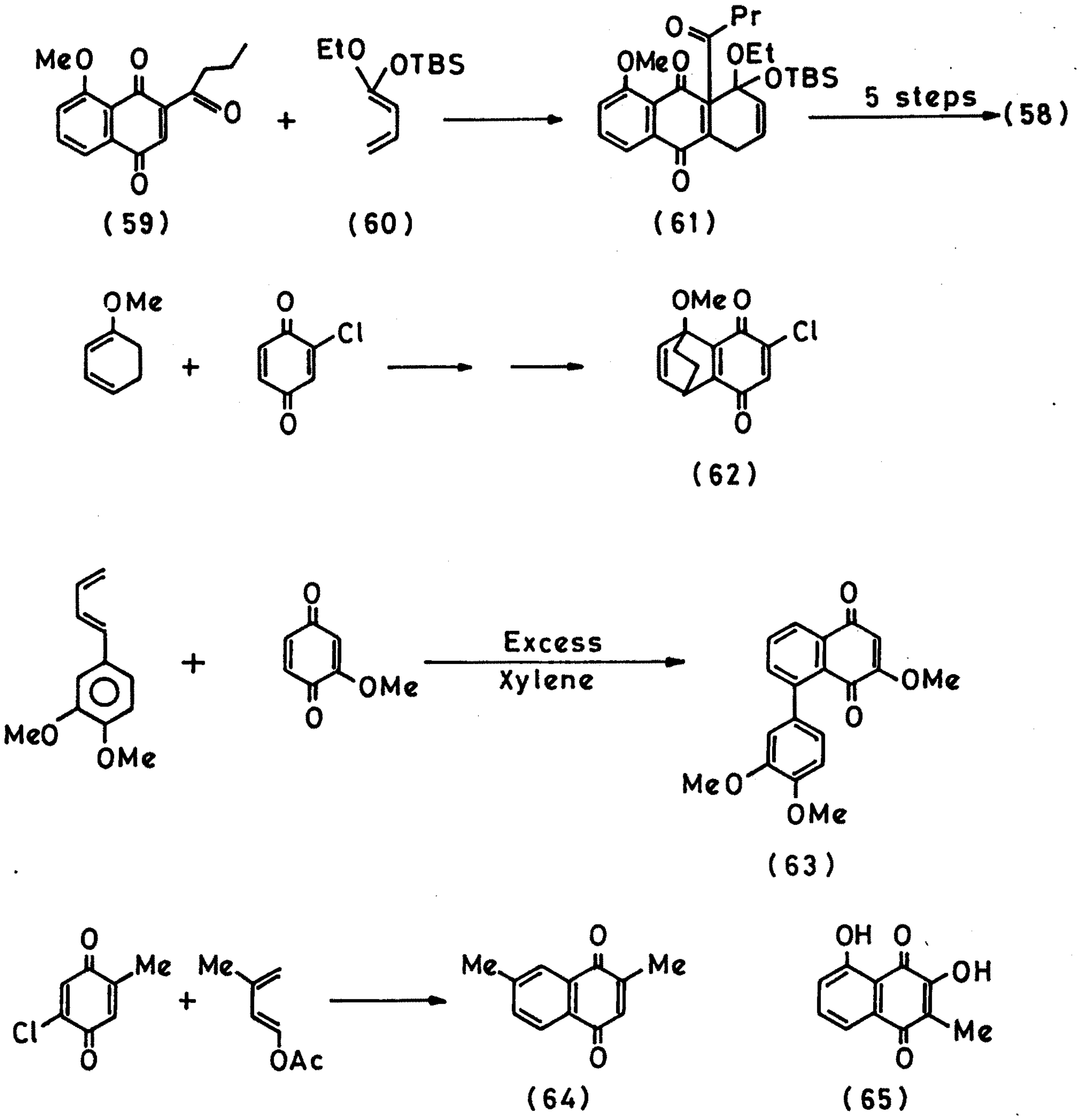
The cyclohexene ring of D.A. adduct of 1-acetoxy-butadiene and Juglone is useful in synthesis of Deoxyfrenolicin (57) and nanomycin-A[33] (58) possesing antifungal and antibiotic activity.

The butanoylquinone (59) and diene (60) gave intermediate (61) in the synthesis of nanomycin-A (58) showed by Li and coworkers.[34]

The regioselective addition of cyclohexadiene to chlorobenzoquinone lead to quinone (62) showed by Giles and coworkers.[35] The other natural naphthaquinones are cassumunaquinone[36] (63), droserone[37] (64), chimaphilin[38] (65).

The cyctotoxically active triptolide (67) synthesis includes an intermediate (66) via D.A. reaction by Tamelen and coworkers.[39] D.A. reaction was

CHART – 21



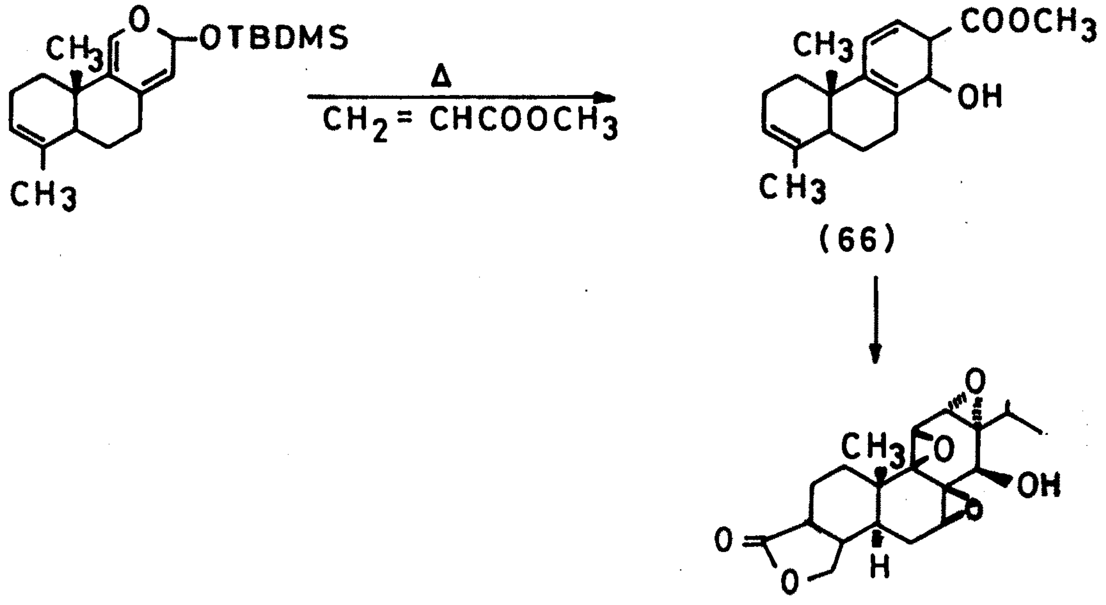
(59) (60) (61)

(62)

(63)

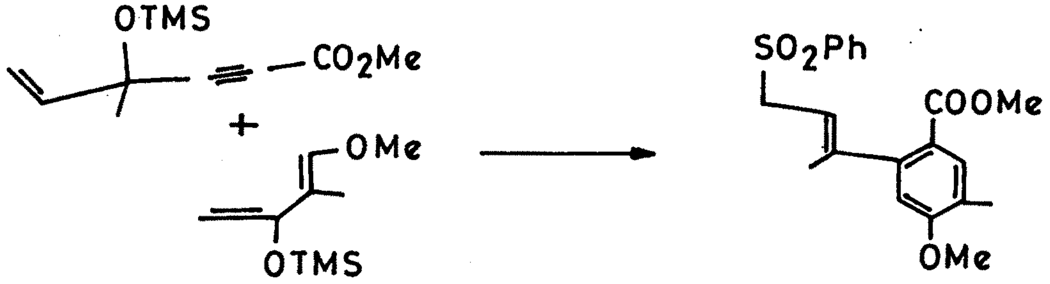
(64) (65)

CHART – 22



(66)

(67)



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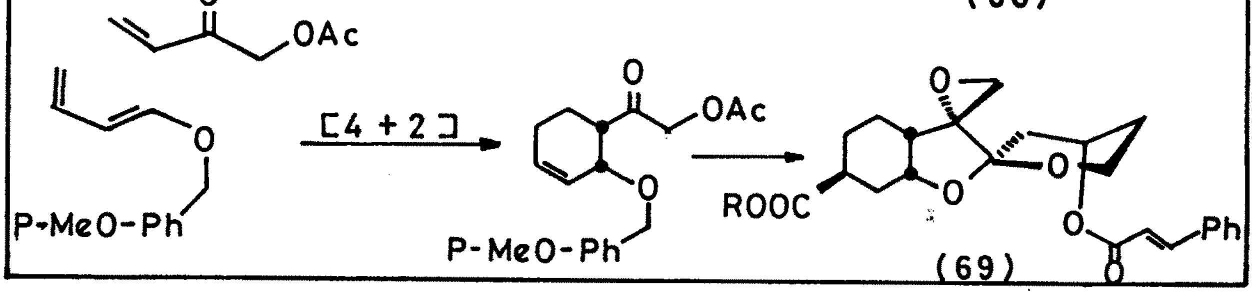


(69)

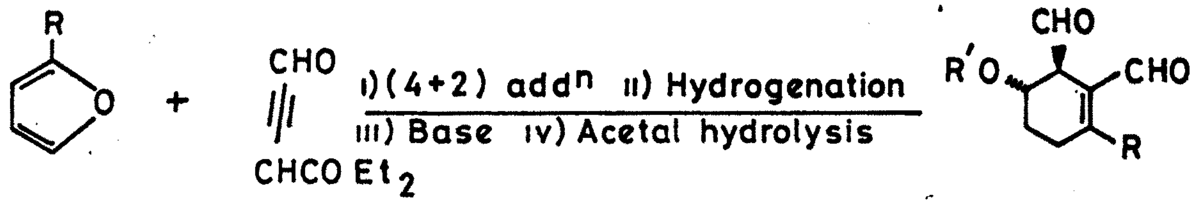
used to assemble an aromatic ring precursor after few steps into desired fragment of milbemycin β_3[40] (68) which is a antihelmintic, insecticidal, acaricidal drug. Phyllanthocin (69) is a aglycone of the potent antileukemic compound phyllanthoside synthesized by Burke and coworkers.[41]

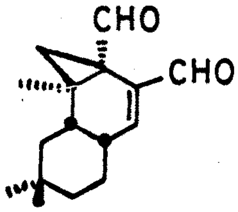
Jorgen and coworkers[42] showed synthetic route via D.A. reaction to biologically active terpenoids isovelleral (70), merulidial (71), polygodial (72), scalaradial. Bracher[43] obtained the synthetic product by D.A. reaction in the synthesis of cleistopholine (73) and streptonigrin[44] having antibiotic and antitumor activity.

The intramolecular D.A. reaction of conjugated enynes provides an efficient and general route to aromatic and dihydroaromatic compounds.[45]

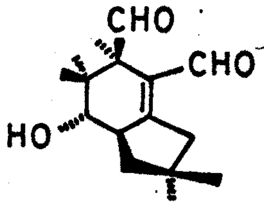
The other physiologically active compounds synthesized via D.A. reaction are paclitaxel, docetaxel[46] having antitumor activity, Quassinoids[47] having antineoplastic, antiviral, antimalarial activity. Stachenone[48], a naturally occuring diterpene[49], an insect sex pheromone, 1, 7- dioxospiro [5, 5] undecane[50] (75), indole alkaloids - tubersonine[51] (76), vindoline[51] (78), tanshinones[52] (77), Ochromycinone[53], aphidicolin.[54]

CHART - 23





(70)



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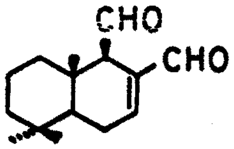

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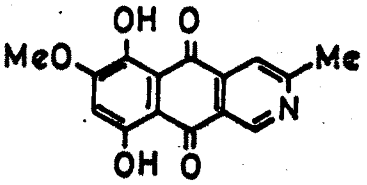

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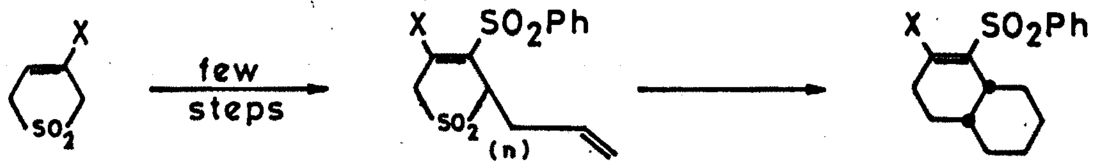
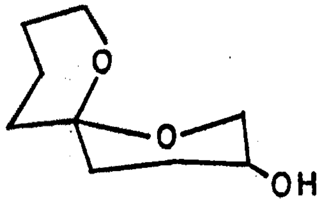


(74)

CHART — 24



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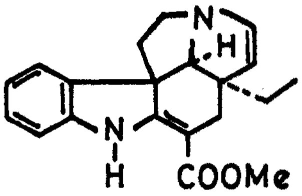
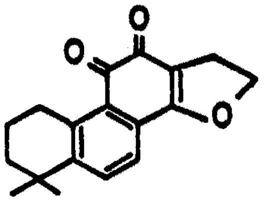


(76)



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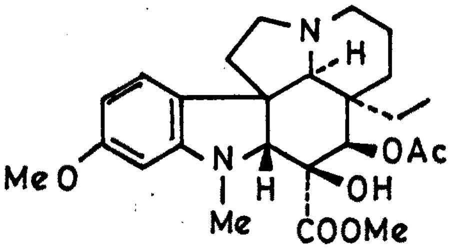

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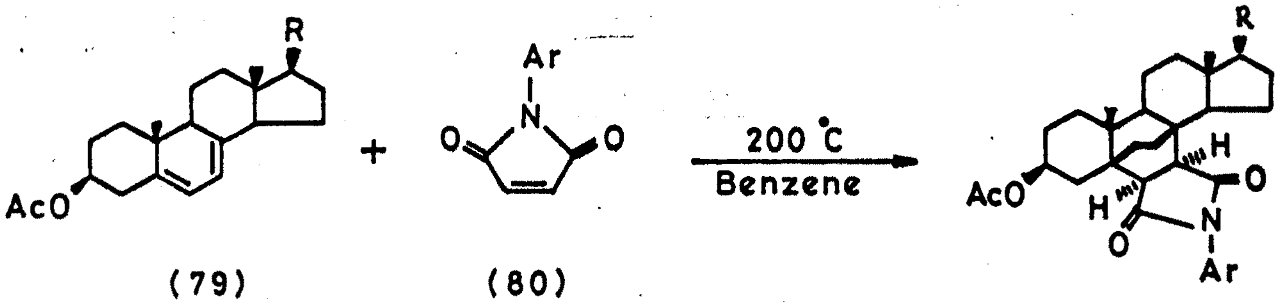

(79) (80)

Intramolecular D.A. reaction of sulfone - substituted 3 - sulfolenes produces trans ring fused hydronaphthalene products[55] (74). Holmes and coworkers[56] prepared polycyclic compounds (81) and (82), promising precursors for the highly biologically active natural product aphidicolin (83) and stemodine (84). Kraus and Krolski[57] have also applied D.A. reaction of 5- arylidene meldrum's acid into the synthesis of the ACE ring of quassimarin (85). Leigh and coworkers[58] have done the reaction between N- phenylmaleimide (79) and 7- dehydrocholesteryl acetate (80).

Asymmetric induction : According to steric approach control, the addition of a planer addend to an asymmetric one to create a new asymmetric center in nonstatistical ratio. Koroleve and Mur[1] found that after adding, 1, 3- butadiene to the mono or di-l-menthyl esters of fumaric acid, saponification of adducts gave optically active 4- cyclohexene- 1, 2- dicarboxylic acid (86). Similarly, the reaction of maleic anhydride with l-menthyl sorbate, followed by hydrolysis, afforded the partially active triacid (87). The reaction represents a potentially powerful method for the determination of absolute configuration of a variety of adducts.

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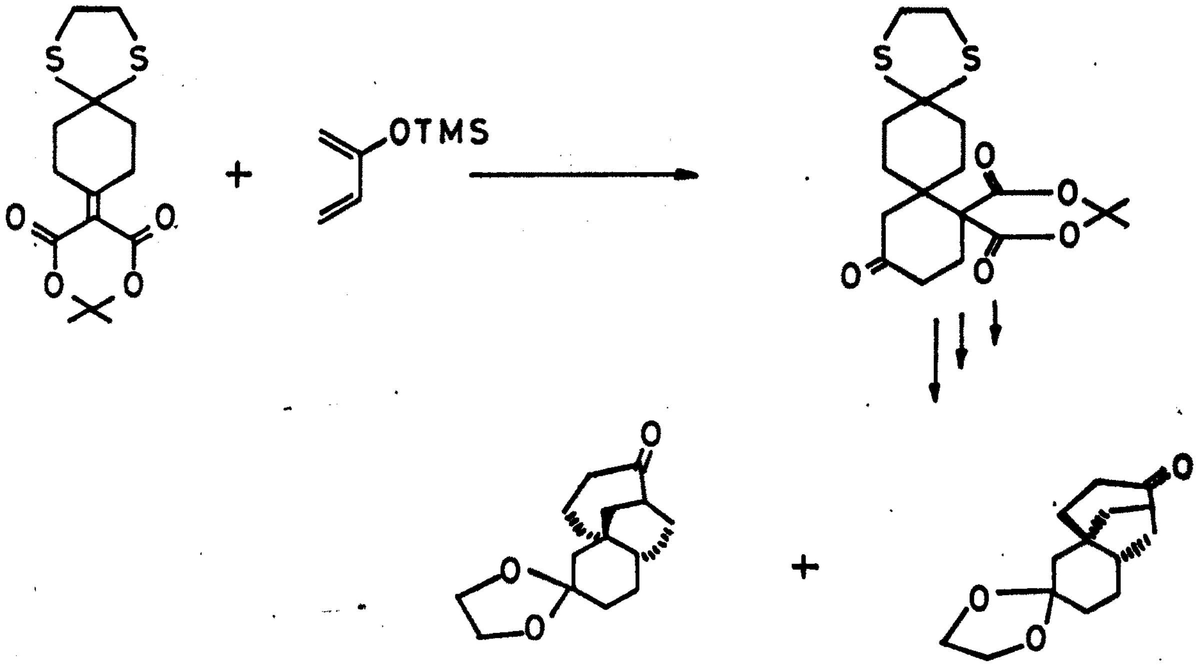
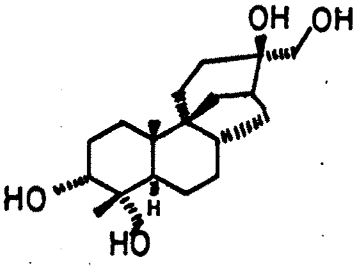
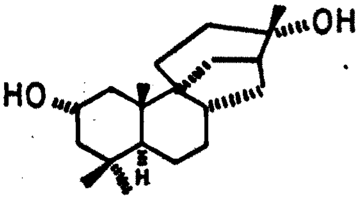
CHART - 25



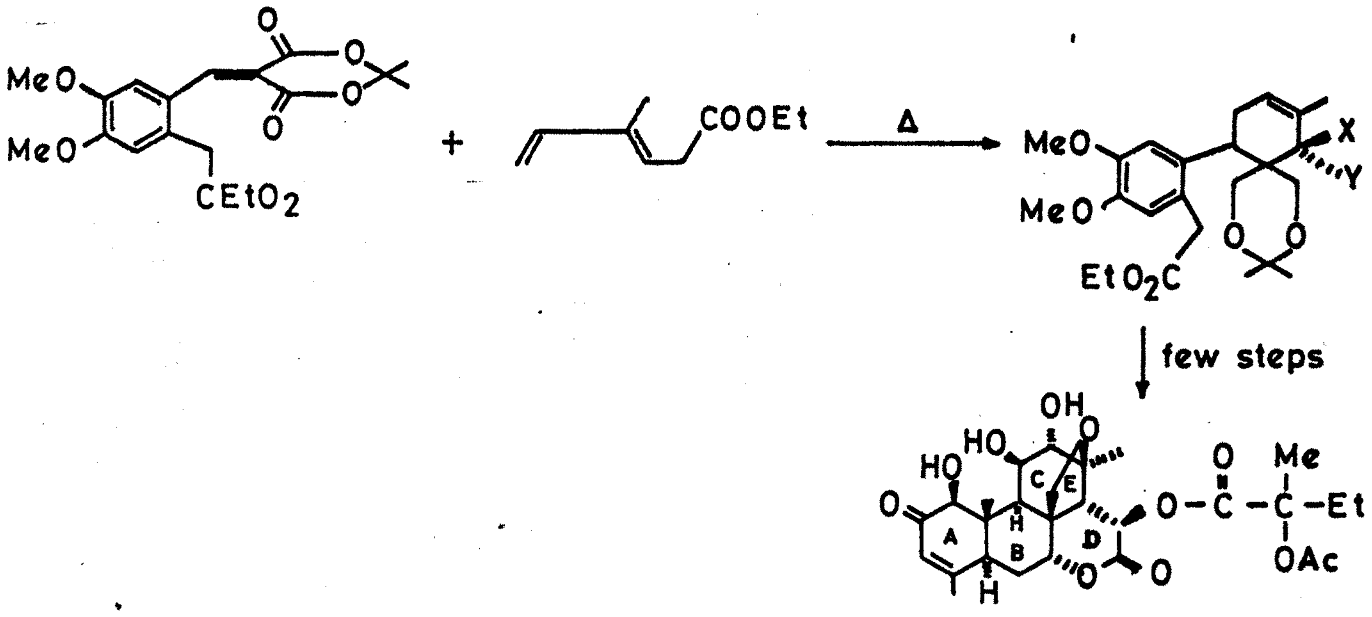


(83)

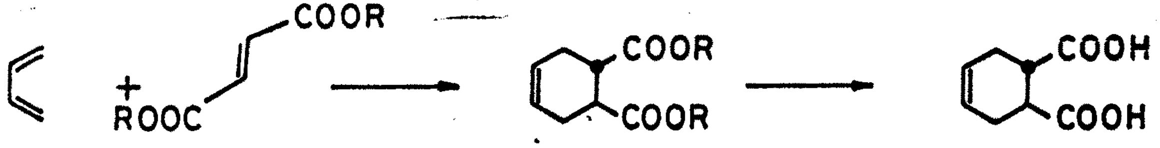


(84)

CHART — 26

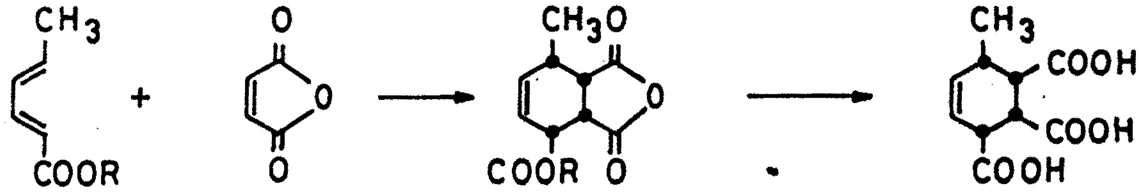


(85)



(86)

$[\alpha]_D = +11{\cdot}65^\circ$



R = l-menthyl

(87)

$[\alpha]_D = -2^\circ$

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