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Intramolecular [4 + 2] Cycloaddition

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The results of studies in intramolecular [4 + 2] cycloaddition carried out in recent years are surveyed. The synthetic possibilities of this reaction for the preparation of natural products and its high stereoselectivity and regioselectivity are demonstrated. The differences and similarities between intramolecular and intermolecular [4 + 2] cycloaddition reactions are elucidated.
The bibliography includes 207 references.

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I. INTRODUCTION

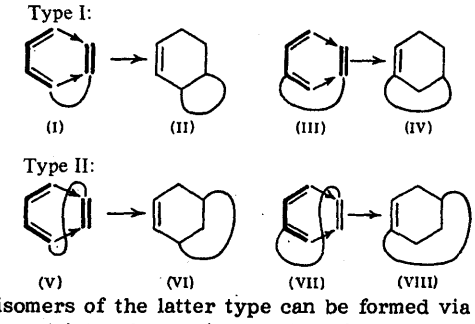
The study of the intramolecular[4 + 2]cycloaddition {IAMC[4 + 2]} reaction has attracted much attention by investigators[1-3] owing to the specific possibilities of the synthesis of polycyclic natural products, in particular sesquiterpenes, antibiotics, alkaloids, vitamins, etc., with its aid[4] and also because of its high stereoselectivity and regioselectivity which makes it possible to synthesise many skeletal structures which are difficult to obtain by other methods.[5-11] Although it is believed[1-3] that the first IAMC[4 + 2] reaction was described in 1953 by Alder,[12] who discovered the diene synthesis in 1928,[13] one should note that it was known as early as 1948 in relation to the Diels–Alder intramolecular reaction of cyclooctatetraene.[14] The existing reviews in the literature[1-3] devoted to the IAMC[4 + 2] reaction cover the period between 1953 and 1978. After the appearance of these reviews, the number of publications on this field increased greatly. In these communications attention was concentrated on the treatment of the mechanism of this type of cycloaddition characterised by the concerted but non-synchronous formation of bonds, by supra- and also antara-facial interactions of the orbitals, the reactivity and selectivity of the interacting components, the influence of the side chain linking the diene and the dienophile on the structure of the transition state (TS), the influence of catalysts on the stereoselectivity and regioselectivity of the reaction, etc.

These and other problems are important for the elucidation of the mechanism of the Diels–Alder reaction in general and the IAMC[4 + 2] reaction in particular. In the present review we attempted to examine these problems concentrating attention on the publications covering the period 1979–1983.

II. CHARACTERISTIC FEATURES OF INTRAMOLECULAR-[4 + 2]CYCLOADDITION

1. Stereoselectivity and Regioselectivity

Depending on the site where the dienophile fragment is linked to the diene fragment, the IAMC[4 + 2] reaction can lead to the formation of different isomers.[15] The different orientations of the reacting fragments in the TS [(I) or (V), (III) or (VII)] create additional possibilities for the formation of different regioisomers [(II) and (VI), (IV) and (VIII)]:



Regioisomers of the latter type can be formed via four pathways: (a) by the *s*,*s*-interaction of the HOMO of the diene and the LUMO of the dienophile; (b) by the *a*,*a*-interaction of the LUMO of the diene and the HOMO of the dienophile; (c) by the *a*,*a*-interaction of the HOMO of the diene and the LUMO of the dienophile; (d) by the *s*,*s*-interaction of the LUMO of the diene and the HOMO of the dienophile (Fig.1). However, the *s*,*s*-interactions (a) and (d) are geometrically unfavourable compared with the *s*,*s*-interactions for the TS (I) and (III).

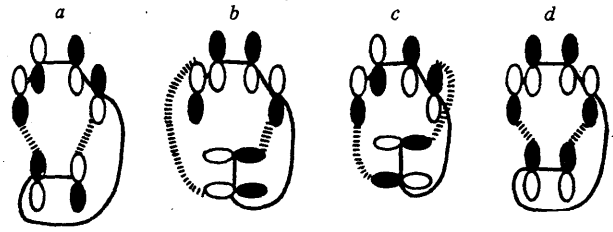
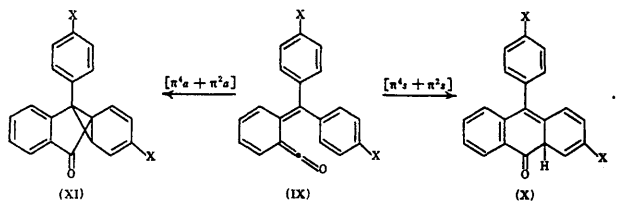


Figure 1. The possible pathways in the interaction of the diene and dienophile orbitals on formation of the regioisomers (VI) and (VIII).

It is noteworthy that, by virtue of the presence of bridging chains of atoms between the diene and dienophile fragments, the TS for the IAMC[4 + 2] is electronically asymmetric and

the coefficients of the atomic orbitals of the diene and dienophile fragments should be different. This determines the *s,s*- or *a,a*-interaction between the diene and dienophile orbitals[16] and also the regioselectivity of the cycloaddition. The higher coefficients for C(4) and C(2′) and also for C(1) and C(1′) favour the *a,a*-interaction of the orbitals, while the higher coefficients for C(1) and C(2′) or C(1′) and C(4) favour the *s,s*-interaction, which is a feature distinguishing the regioselectivity of the IAMC[4 + 2] from the intermolecular [4 + 2]cycloaddition {IRMC[4 + 2]} (Fig. 2).

Thus knowing the structure of the final adduct, the HOMO and LUMO energies of the diene and the dienophile, and the coefficients of the atomic orbitals, it is possible to infer readily the pathway followed in the interaction of the orbitals. As an example, one may quote the IAMC[4 + 2] of the triene (IX), where norcaradiene (XI) was discovered instead of the expected product (X):[17,18]

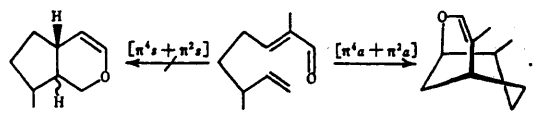


(XI) (IX) (X)

The introduction of the electron-donating dimethylamino-substituent X increases the coefficient of the HOMO in the *p*-position in the benzene ring. On the other hand, the central carbon atom of the keten group, located in the plane of the π* orbitals, is electrophilic, so that the cycloaddition entails the formation of a bond between this atom and the *p*-carbon atom of the *NN*-dimethylaminophenyl group (Fig. 3).

Calculation of the total energy and of the coefficients of the frontier orbitals of the atoms in terms of the CNDO/2 approximation demonstrated that the HOMO of *NN*-dimethylaniline and the LUMO of the unsaturated keten differ little as regards energy and that the interaction between the corresponding fragments therefore gives rise to additional stabilisation in the TS in the cyclisation of the triene (IX).

The IAMC[4 + 2] of 2,6-dimethylocta-2,7-dienal (XII) using BF_3 as the catalyst affords a 47% yield of *exo*-4,8-dimethyl-2-oxabicyclo[3.3.1]non-3-ene (XIII), which is an intermediate in the synthesis of iridiomyrmycene—the insecticidal iridoid isolated from *Iridomyrmex himilus*:[19]



(XIV) (XII) (XIII)

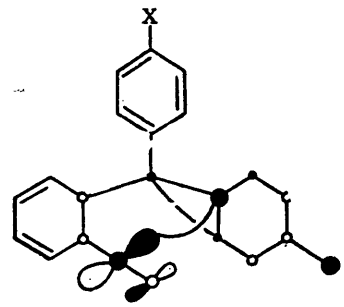


Figure 3. The antarafacial interaction of the orbitals in compound (IX).

The catalyst apparently reduces the LUMO of the dienal in this reaction as a consequence of the formation of the complex[20] and thus favours the *a,a*-interaction of diene and dienophenyl orbitals, which results in the formation of the product (XIII) and not (XIV).

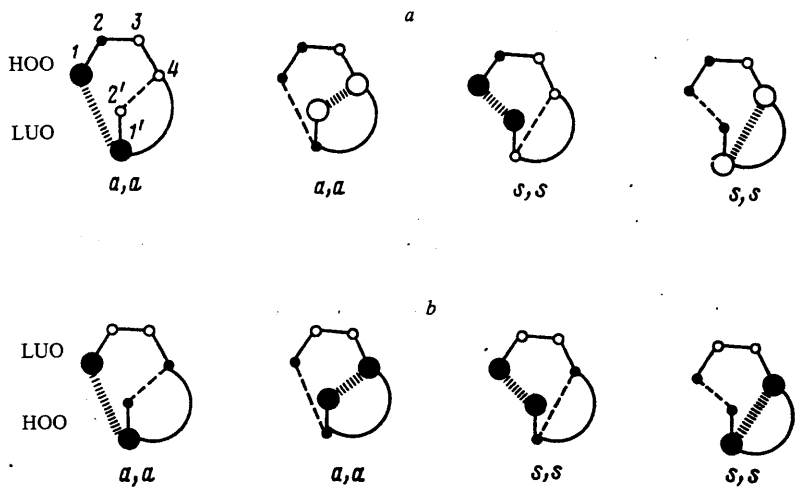
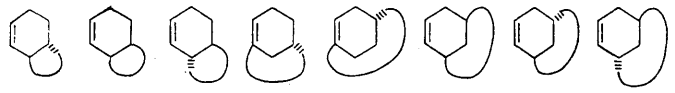
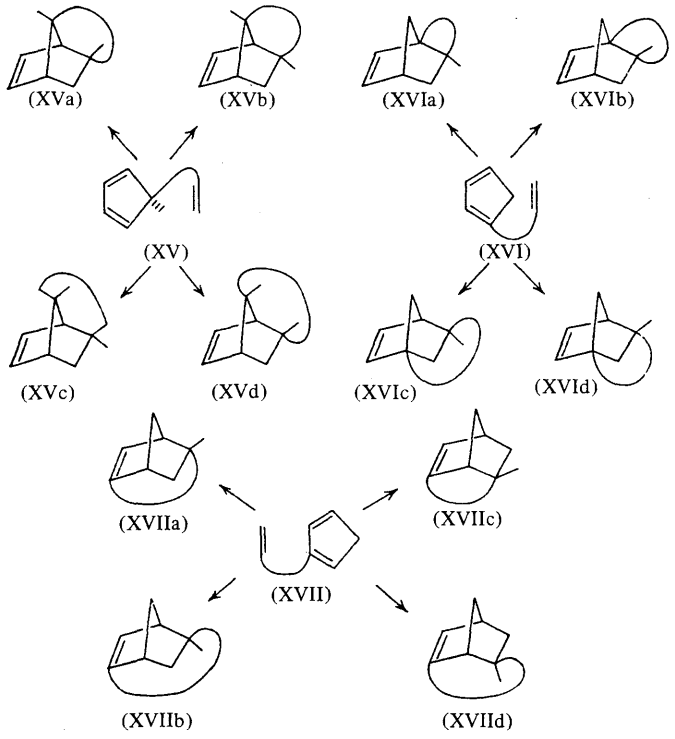


Figure 2. The regiospecificity in IAMC[4 + 2]; schematic representation of the atomic coefficients of the diene (*a*) and dienophile (*b*) orbitals.

The structure of the TS in the cycloaddition reaction and the establishment of a particular configuration in the junction of the rings (*cis*- or *trans*-, *endo*- or *exo*-) undoubtedly depend on the *E*- or *Z*-configuration of the initial trienes. The trienes containing the buta-1,3-diene fragments can give rise to eight stereoisomers when account is taken of the *trans*- and *cis*-junctions in the adducts:



For the triene consisting of cyclopentadiene and ethylene fragments, one may expect formally the formation of twelve structures:

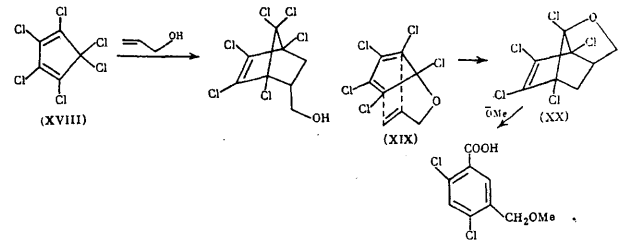


In contrast to the other structures, the formation of the isomers (XVa), (XVd), (XVIc), (XVIIb), and (XVIId) requires the twisting of the linking bridge chain.

2. Structure and Reactivity

It is self-evident that the structure of the substrate not only influences the stereochemistry of the reaction but also determines the substrate reactivity in the reactions investigated and the reactivities of the given reactant in different reaction series are therefore different. This leads to the question of the difference between the reactivities of the same diene in the IAMC[4 + 2] and IRMC[4 + 2] processes.

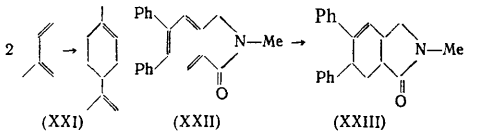
It is known[21] that the IRMC[4 + 2] of hexachlorocyclopentadiene (XVIII) to allyl alcohol proceeds under fairly severe conditions (125 °C, two days, sealed tube), while 5-allyloxy-1,2,3,4,5-pentachlorocyclopentadiene (XIX), obtained by nucleophilic substitution in the diene (XVIII) on treatment with allyl alcohol, is converted spontaneously into the final product (XX) at room temperature:[22]



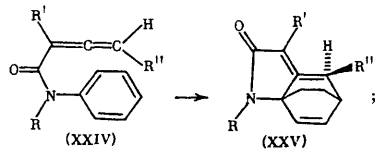
A new rearrangement was observed on treatment of compound (XX) with sodium methoxide.[23]

The presence of substituents in the dienophile component of the triene does not prevent the occurrence of the IAMC[4 + 2] reaction. In this case steric factors probably predominate.

It is known[25] that the entropies of activation for pericyclic reactions, including IRMC[4 + 2], play a major role and that an increase of their negative values indicates a greater order in the system. It was expected that the TS in the IAMC[4 + 2] reaction would be more ordered than for the IRMC[4 + 2] reaction. However, there are virtually no suitable examples of such a comparison in the literature. Comparison of the $\Delta S^{\neq}$ for the dimerisation of isoprene and the IAMC[4 + 2] reaction of compound (XXII) to give the product (XXIII) showed that the value of $\Delta S^{\neq}$ obtained for the dimerisation of isoprene is more negative than for the reaction (XXII) → (XXIII) (−41 and −14.4 e.u. respectively), which is unexpected[2] and is apparently due to the non-synchronous formation of bonds in the IAMC[4 + 2].[26–29]

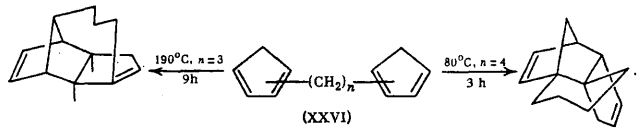


The IAMC[4 + 2] of the allene fragment to the benzene ring in compound (XXIV) proceeds readily with formation of the product (XXV), although such a thermal reaction is forbidden for IRMC[4 + 2]:[30]



R = Me, H, Ph;
R' = Me, H, $SiMe_3$;
R'' = H, $SiMe_2Ph$.

It is essential to take into account the fact that IAMC[4 + 2] does not always proceed at a higher rate than IRMC[4 + 2]. For example, the dimerisation of cyclopentadiene takes place readily at room temperature,[31] but the IAMC [4 + 2] of the polymethylenecyclopentadienes (XXVI, $n = 0 - 12$),[32] requires more severe conditions:



It follows from the data in Table 1 and the information contained in the earlier reviews[1–3] that the reactivity of the trienes is significantly determined by the length and conformational characteristics of the bridge chain linking the diene and dienophile fragments in the triene.

III. THE FORMATION OF ANNELATED SYSTEMS

1. The 6/5-Annelated System

Vigorous study of the formation of the 6/5-annelated cyclic system (condensed rings consisting of six- and five-membered fragments) is being prosecuted mainly by three groups of investigators.[39–44,49–53]

In order to study the possibility of the total synthesis of (±)-dendrobine, the stereochemistry of the IAMC[4 + 2] of methyl (*E*,*E*,*E*)- and (*Z*,*E*,*E*)-6-alkoxy-11-methyldodeca-2,7,9-trienoates (XXVII) and (XXVIII) was examined:[39]

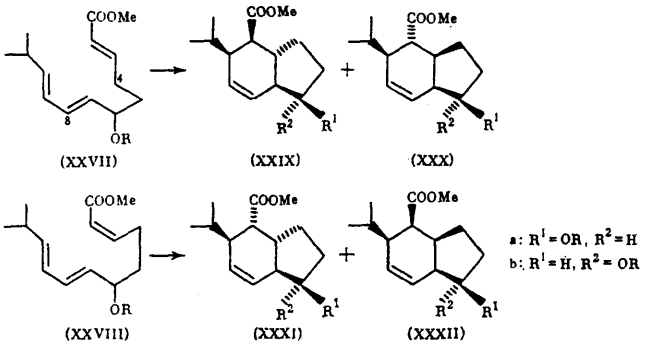
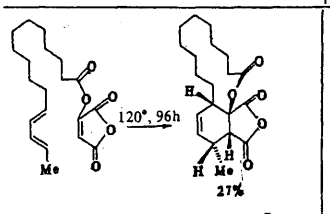
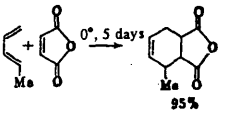
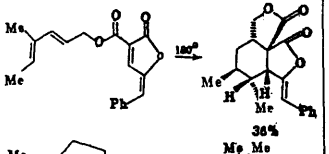
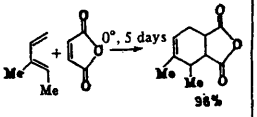
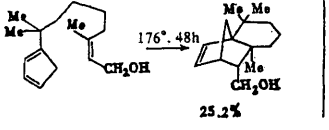
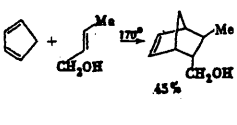
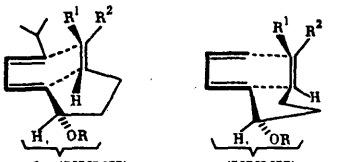


Table 1. The influence of the side chain connecting the diene and the dienophile on the parameters of IAMC[4 + 2] compared with IRMC[4 + 2].

IAMC[4 + 2]	Refs.	IRMC[4 + 2]	Refs.
	[33]		[36]
	[34]		[37]
	[35]		[38]

It was established that in all cases *trans*-hexahydroindene rings [compounds (XXIX) and (XXXI)] are formed to a greater extent than the *cis*-isomers (XXX) and (XXXII). A decrease of the reaction temperature favours the formation of the *trans*-isomers (XXIX) and (XXXI). The TS in the boat form, which leads to the formation of the isomers (XXXIIa, b) is unfavourable owing to the steric interaction between the H atoms of the C(8) atom and the OR group, which accounts for the ratio (XXX)/(XXXII) found in the reaction products. Analysis of the molecular model showed that such geometry is more readily achieved in the TS leading to the *trans*-joined products [*endo*-(XXVII) and *exo*-(XXVIIIa)] than in the TS leading to the *cis*-joined products [*exo*-(XXVII) and *endo*-(XXVIIIa)].



endo-(XXVII) *exo*-(XXVII)
exo-(XXVIIIa) *endo*-(XXVIIIa)

This effect is believed to be sufficiently large to compete with Alder's *endo*-rule in determining the stereochemical consequences of the cyclisation of the triene (XXVIIIa).

The predominance of the *trans*-isomers (XXXVII), (XXXVIII), (XXXIX), and (XL) is also observed in the IAMC[4 + 2] of methyl deca-2,7,9-trienoates (XXXIII), (XXXIV), (XXXV), and (XXXVI) (Table 2).[40,41]

Table 2. IAMC[4 + 2] of methyl deca-2,7,9-trienoates.[40,41]

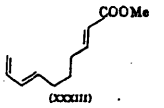
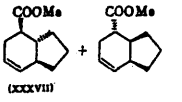
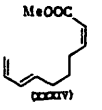
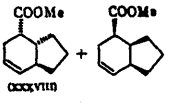
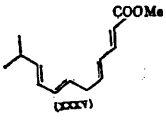
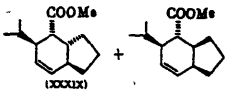
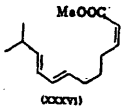
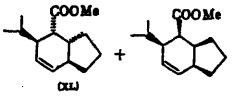
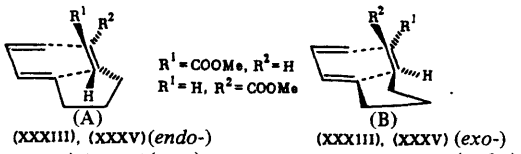
Trienes	Conditions	Products	Yield, %	*trans*/*cis*
 (XXXIII)	150°, 24h	 (XXXVII)	65	60:40
 (XXXIV)	180°, 5h	 (XXXVIII)	75	65:35
 (XXXV)	150°, 40h	 (XXXIX)	72	72:28
 (XXXVI)	180°, 5h	 (XL)	75	67:33

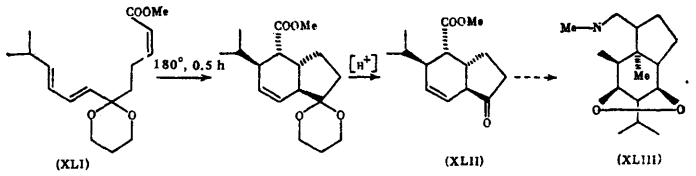
Table 2 shows that the selectivity for the *trans*-joined adducts does not in essence depend on the stereochemistry of the dienophile and the *endo*-rule is undoubtedly a consequence of the cyclisation of the trienes (XXXIV) and (XXXVI). The secondary orbital interaction does not influence the consequences of the cyclisation of the *trans*-trienes (XXXIII) and (XXXV), since it stabilises the *endo*-TS. The breakdown of the *endo*-rule may be a consequence of the strain in the TS (B) compared with (A), which hinders the formation of the boat conformation of the cyclohexene ring in the TS (B).

Furthermore, steric interactions between the hydrogen atoms of the methylene group in the 4-position and of the methylidyne group in the 8-position are observed only for

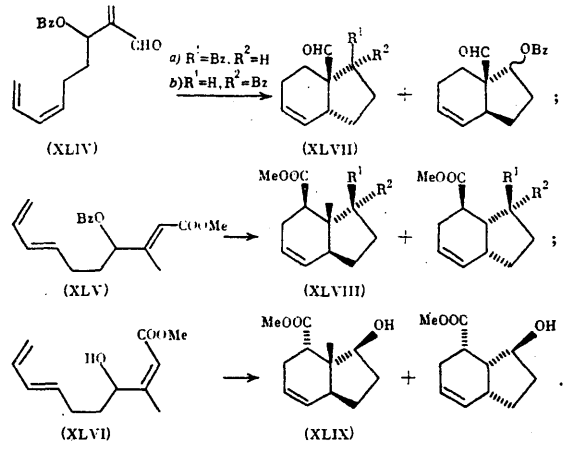
the TS (B), where these atoms are in the eclipsed positions.



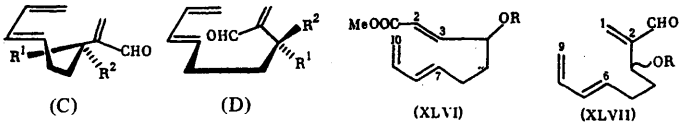
The unusual *trans*-stereoselectivity of the IAMC[4 + 2] for the triene (XLI) ensured the success of the key stage in the improved synthesis of hexahydroindenone (XLII), which is a precursor of dendrobine (XLIII): [42,43]



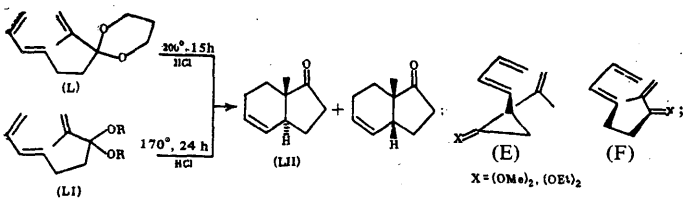
The IAMC[4 + 2] of the angularly methyl-substituted trienes (XLV) and (XLVI) also gives rise predominantly to the *trans*-isomers (XLVIII) and (XLIX); [44] the adducts obtained are important structural elements in the synthesis of derivatives of vitamin D:



It is of interest that the cyclisation of compound (XLIV) exhibits the opposite behaviour—preferential *cis*-selectivity. The main product derived from the triene (XLIV) is obtained from the TS (C) in which the aldehyde group occupies an *exo*-position relative to the diene. However, the *cis*-joined TS (C) is energetically less favourable than the *trans*-(D). It has been established that the LUMO coefficients for C(1) and C(9) are higher than for C(2) and C(6). This fact is crucial in the formation of the *cis*-isomer (XLVII) and the concerted rather than the synchronous interaction of the orbitals of the diene in the dienophile is therefore preferable.

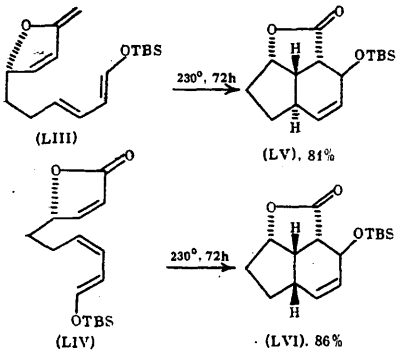


The preferable formation of the angularly substituted *trans*-hydroindenone (LII), containing an oestrogen fragment, is observed in the thermolysis of the trienes (L) and (LI): [45,46]

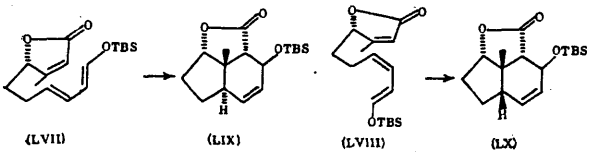


The *endo*-TS (E) is characterised by an appreciable steric hindrance owing to the interaction between one of the alkoxy-groups and the butadiene system, where the corresponding *exo*-TS (F) is more stable.

The *trans*-hydroindene system, which is a synthon for 11-deoxyprostaglandin and 11-ketosteroid, has been synthesised from the triene (LIII) and (LIV): [47]

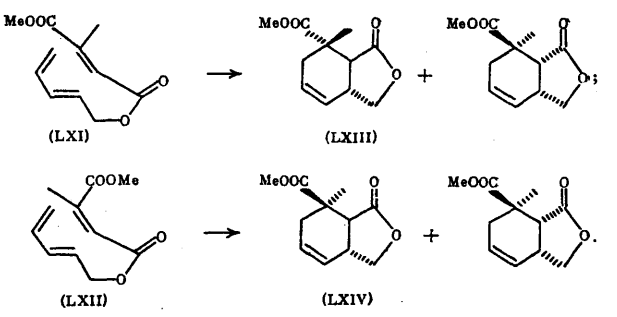


It is of interest that the *E*,*E*-triene (LIII) affords only the *trans*-product (LV), while the cyclisation of the *E*,*Z*-triene (LIV) leads exclusively to the *cis*-isomer (LVI). The results of investigations have demonstrated the preferential *exo*-orientation of the butenolide fragment in the TS for the cyclisation reaction. The angularly methyl-substituted analogues of these trienes also react entirely stereoselectively, i.e. *E*,*E*-(LVII) → (LIX) and *E*,*Z*-(LVIII) → (LX):



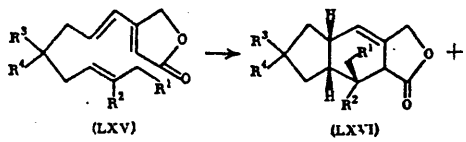
It has been suggested that the rigid structure of the butenolide promotes the necessary orientation of the dienophile in the TS in view of the stereoselectivity of the IAMC[4 + 2] reaction.

The IAMC[4 + 2] of the esters of mesoconic acid (LXI) and sorbyl citraconate (LXII) gives rise preferentially to the *trans*-isomers (LXIII) and (LXIV): [48]



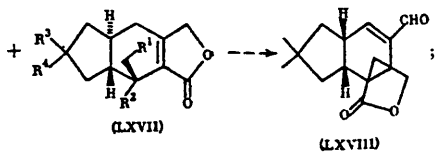
The *trans*:*cis*-ratio is 4.3:1.

The *trans*-stereoselectivity of the cyclisation is also observed in the IAMC[4 + 2] of the triene (LXV), which leads to the synthesis of marasmic acid (LXVIII)—a sesquiterpene antibiotic: [49–51]



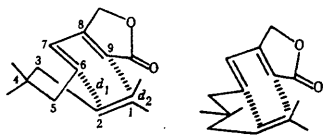
(LXV) (LXVI)

$R^3 = R^4 = Me$
$R^1 = COOMe, CN, COOBu$
$R^2 = H, COOMe, CN$



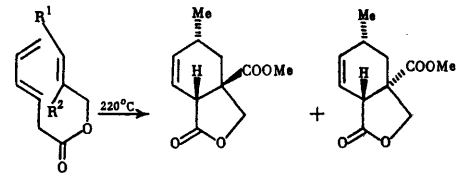
(LXVII) (LXVIII)

The main requirement for the formation of *trans*-hydroindenes is the non-bonding interaction of the diene and dienophile fragments, which leads to an asymmetric TS. The secondary orbital interaction is energetically incapable of overcoming the unfavourable non-bonding interactions in the TS, which leads to the *cis*-isomer:

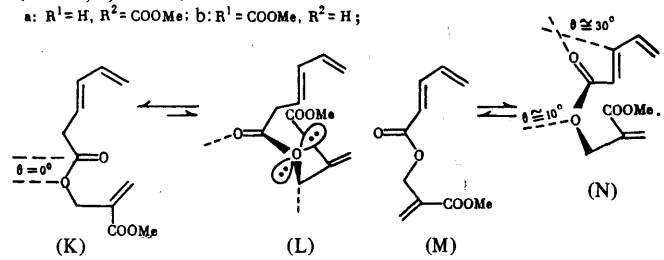


The absence of a steric effect of the substituents on the stereochemistry of the cyclisation can be accounted for by the asymmetric TS in which the distance d_1 between the C(6) and C(2) atoms is smaller than the distance d_2 between the C(9) and C(1) atoms. This is due to the greater coefficients of the MO at C(2) than at C(1) as a consequence of the strong polarisation of the dienophile fragment of the molecule by the substituents at C(1). Kinetic data have shown that the rate of cyclisation is strongly influenced by the nature of the substituents in the triene. The higher rate of cyclisation when the substituent COOR is used at C(1) compared with CN is consistent with literature data[52] concerning the influence of the substituents (COOR > CN) on the rate of IRMC[4 + 2]. The relatively smaller increase of the rate of reaction by the second substituent COOR at C(1) compared with CN can be explained by the steric inhibition of the resonance as a consequence of the impossibility of a coplanar disposition of the two COOR groups and the C=C bond. It is assumed that the lower rate of cyclisation of the triene (LXV, $R^3 = R^4 = Me$) to the *trans*-hydroindene (LVII) compared with the corresponding *cis*-isomer is due to the fact that the introduction of the methyl groups into the connecting chain increases the fraction of the cisoid conformers with a disposition of the diene and dienophile favourable for cyclisation, which decreases $\Delta S^{\neq}$ by approximately 3 e.u.

The influence of the structure of the connecting chain on the formation of products has also been demonstrated in relation to the reactions of the trienes (LXIXa, b).[53] In both cases the IAMC[4 + 2] led to γ-lactones instead of the expected δ-lactones and the nature of the rearrangement is obscure:

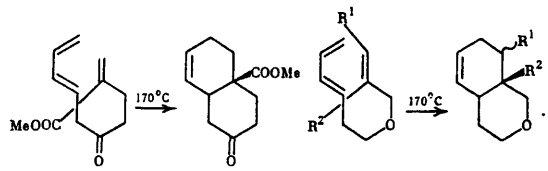


(LXIXa, b) (LXXa)
a: $R^1 = H$, $R^2 = COOMe$; b: $R^1 = COOMe$, $R^2 = H$;



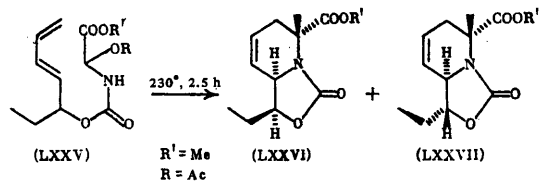
(K) (L) (M) (N)

It is believed that the rearrangement of the double bonds in the trienes (LXIXa, b) is the rate-limiting stage of the reaction. In the case of the TS (L) the dihedral angle between the π-system of the CO group and the unshared electron pair of oxygen should be 90°, which prevents the overlap of diene and dienophile orbitals. On the other hand, in the case of the TS (N) there are no such limitations and the IAMC[4 + 2] takes place readily. In order to confirm this, the IAMC[4 + 2] of the model compounds (LXXI) and (LXXIII), in which there is no ester group and hence there is no orbital interaction between the π-system of CO and the unshared electron pair at the oxygen atom, has been carried out. As was to be expected, this results in the formation of the cyclisation products (LXXII) and (LXXIV), which indicates the decisive role of the above interactions in the stereocontrol of the IAMC[4 + 2]:



(LXXI) (LXXII) (LXXIII) (LXXIV)

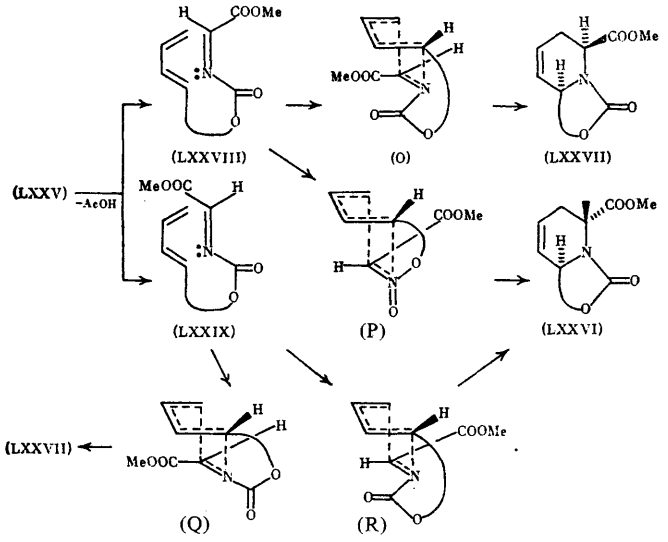
In order to synthesise the spermidine alkaloids such as palustrine and anhydrocannabisativine, the IAMC[4 + 2] reactions of the triene (LXXV) have been investigated and it has been shown that its thermolysis proceeds entirely stereoselectively with formation of a mixture of the *trans*-products (LXXVI) and (LXXVII): [54–56]



(LXXV) (LXXVI) (LXXVII)
$R' = Me$
$R = Ac$

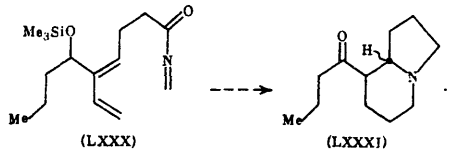
The yield is 59% and the isomer ratio is 55–45. It is assumed that the precursors of the products (LXXVI) and (LXXVII) may be the Z-imine (azamaleate) (LXXVIII) or the E-imine (azafurmarate) (LXXIX) obtained by the elimination of AcOH in the thermolysis of the diene (LXXV); the imines

give rise to the corresponding cycloaddition products:

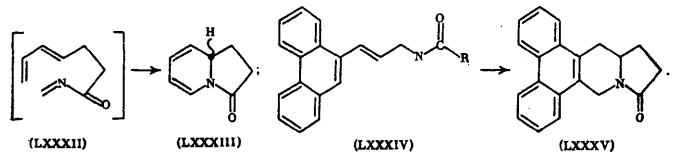


In contrast to Roush's hypotheses, the authors of the above studies[54–56] assume that the length of the bridging chain does not influence the stereochemistry of the final products and the *exo*-azamaleate TS (P) is energetically preferable to the TS (O). The TS (O) does not lead to the expected product; for this reason, the formation of the azamaleate in this process is rejected; the authors[54–56] suggest that the secondary orbital interaction between the CO group at the nitrogen atom and the diene component of the molecule is responsible for the stereocontrol of the cyclisation and that the latter proceeds via the azafumarate (LXXIX), which leads to the TS (I).

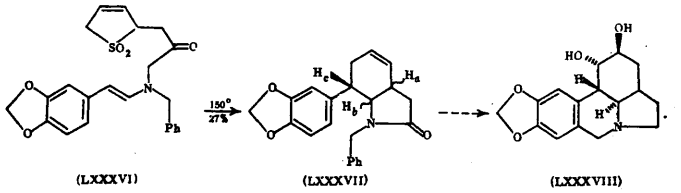
The IAMC[4 + 2] of the suggested intermediate dieneacylimine (LXXX) is the key stage in the synthesis of the alkaloid eleokanine A (LXXXI):[57]



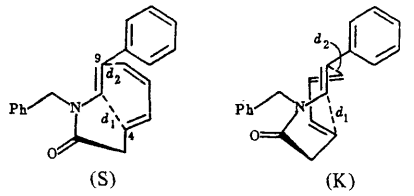
Two indolizidine alkaloids—α-coniceine (LXXXIII) and tylophorine (LXXXV)—have also been synthesised by the IAMC[4 + 2] of the trienes (LXXXII) and (LXXXIV):[58]



The *trans*-stereoselectivity of the cyclisation has been also observed in the synthesis of the antibiotic lycorine (LXXXVIII) from the triene (LXXXVI), as described by Martin et al:[59]

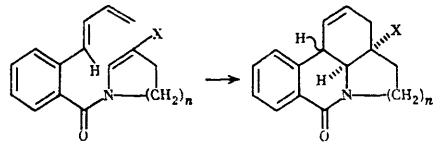


In order to interpret the stereochemical consequences, models of the concerted cycloaddition with an asymmetric biradical or zwitter-ionic TS have been considered.



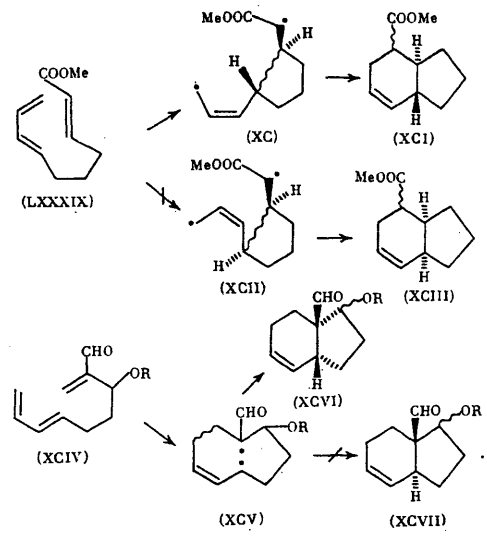
The relative rate of cycloaddition depends on the stabilisation of the radical centre by neighbouring groups. If the aryl substituent at C(9) stabilises the free radical to a greater extent than the nitrogen atom at C(8), the formation of the C(4)–C(8) bond will be preceded by the formation of the C(1)–C(9) bond, i.e. $d_2 < d_1$ for the TS (K). Thus one can predict the stereochemistry of the cyclisation; in the case considered the *trans*-stereoselectivity of the reaction is observed and the TS (S) should lead to a *cis*-joined product.

The galanthan system, which constitutes the nucleus in many *Amaryllidacaea* alkaloids, has been synthesised with the aid of IAMC[4 + 2] in accordance with the scheme[60]



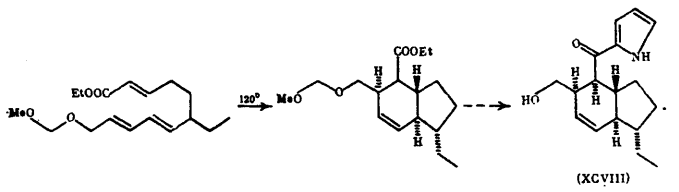
$n = 1, 2$; X = COOMe.

The biradical character of the TS in the IAMC[4 + 2] reaction has also been investigated in relation to the trienes (LXXXIX) and (XCIV):[61]



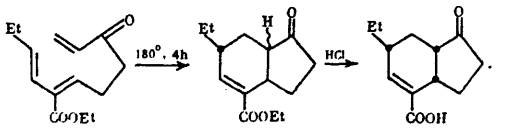
The preferential formation of the *trans*-isomer (XCI) from the triene (LXXXIX) and the *cis*-isomer (XCVI) from the triene (XCIV) can be accounted for by a concerted rather than synchronous TS in the cyclisation reaction; in particular, the "zigzag" TS (XCII) is energetically more favourable than the TS (XC). If the bonds are formed non-synchronously in the cyclisation of the triene (XCIV), then the TS should assume the configuration of a nine-membered ring. This is a state in which the steric strain in the formation of *cis*-hydroindene is reduced to a minimum.

The "right-hand" half of the new ionophore antibiotic X-14547A (XCVIII) is obtained in a high yield [62] from the *trans*-hydroindene:



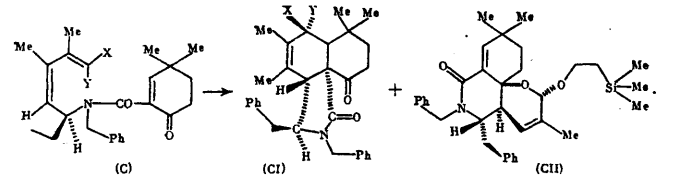
(XCVIII)

(±)-Coronafacic acid (XCIX), isolated from the culture medium of *Pseudomonas coronafacience*, is a structural fragment of the phytotoxin coronatine and is obtained from the hydroindene system in an overall yield of 7%: [63,64]



(XCIX)

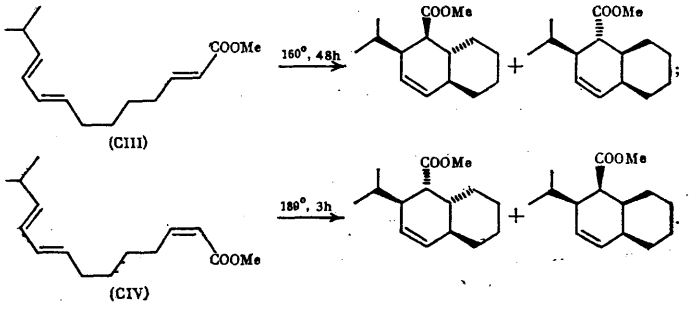
IAMC[4 + 2] constitutes a novel method of synthesis of chiral compounds; in particular the cyclisation of the chiral trienes (C a, b) (a: X = Y = H; b: X = $OCH_2CH_2SiMe_3$; Y = H or $OCH_2CH_2SiMe_3$) proceeds stereo- and enantioselectively, [65-67] as a result of which the product (CIa, X = Y = H) is obtained from the triene (Ca), while the triene (Cb) gives rise to a mixture of the products (CIa, X = CH_2 – CH_2SiMe_3, Y = H) and (CII), which are precursors of cytochalasin *C*:



(C) (CI) (CII)

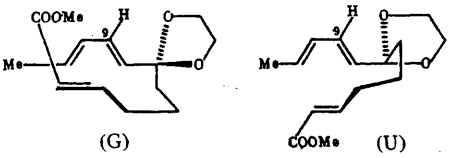
2. The 6/6-Annelated System

The formation of the 6/6-annelated system is to some extent stereochemically different from the formation of the 6/5-system. In the total synthesis of chlorothricin, it was observed that the IAMC[4 + 2] of the 2,8,10-trienoates (CIII) and (CIV) leads preferentially to *cis*-joined products: [68]



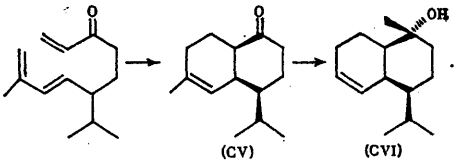
(CIII) (CIV)

Examination of Dreiding molecular models of the *cis*- and *trans*-TS (G) and (U) showed that the eclipsed 1,3-interaction between the H atom at C(9) and the OR group at C(7) develops in the *trans*-TS (G), while it is absent in the *cis*-TS (U). This interaction explains fairly satisfactorily the increasing selectivity also for other undecatrienes having substituents at C(7).



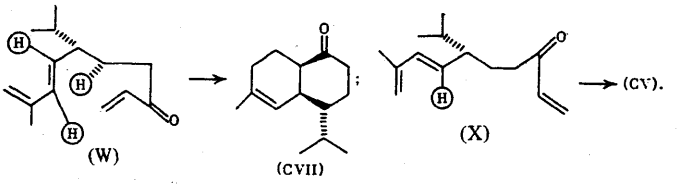
(G) (U)

The synthesis of a crystalline sesquiterpene alcohol (±)-torreyol (CVI) also proceeds via the formation of the *cis*-joined product (CV): [69]



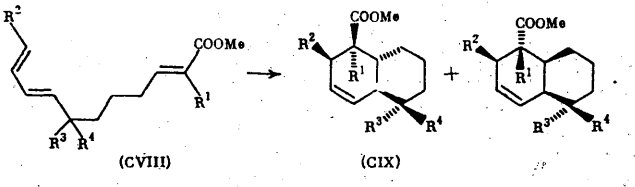
(CV) (CVI)

The formation of the *cis*-isomer (CV) and not the *trans*-isomer (CVII) can be accounted for by the steric hindrance in the TS (W) ("chair"), because the isopropyl group is in the *syn*-position relative to the angular H atom; on the other hand, in the TS (X) ("boat") such hindrance is absent:



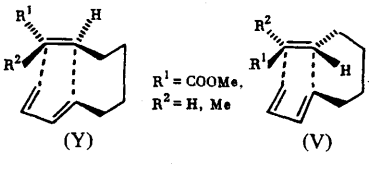
(W) (CVII) (X) (CV).

The characteristics of the stereochemistry of the IAMC[4 + 2] of various trienes (CVIII, R^1 = Me, R^2 = H, Me, R^3 = R^4 = OAlk, R^3 + R^4 = OCH_2CH_2O) make it possible to synthesise the chlorothricolide (CIX)—a fragment of the molecule of chlorothricin produced by a culture of *Streptomyces antibioticus*: [70]



(CVIII) (CIX)

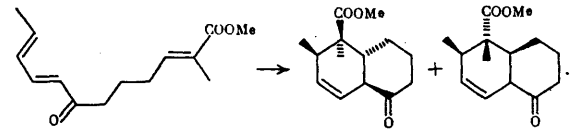
The following features were demonstrated: (a) the somewhat unexpected preferential formation of *cis*-joined products; (b) the absence of a dependence of the reaction selectivity on the stereochemistry of the dienophiles; (c) the independence of the stereochemical reaction pathway of the secondary orbital interaction. In most cases the main products are formed via a TS of type (Y). Consequently the *endo*-group breaks down in the reactions of *E,E,E*-trienes:



(Y) (V)

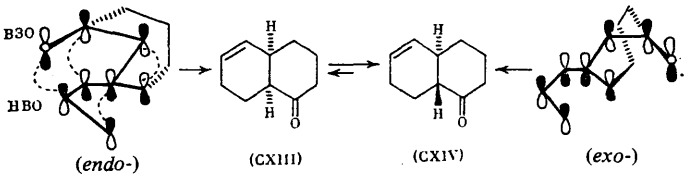
It has been established that the cyclisation is kinetically controlled. One should therefore assume that the *cis*-joined TS (Y) has a somewhat lower energy than the *trans*-joined TS (V) (by 1.0–1.2 kcal mol^{-1}). In all cases the selectivity depends strongly on fine steric conformational effects. Another well known factor influencing the stereochemical

consequences of the IAMC[4 + 2] is the nature of the hybridisation of the atoms or atomic groups in the chain connecting the diene and the dienophile.[71] The sp^2-hybridised atoms in the allyl position in the diene increase the coplanarity of the latter in the reaction TS; thus the orbitals overlap along the reaction coordinate. The sp^2-hybridisation in the allyl position in the diene leads to a result opposite to that of the sp^3-hybridisation, which has been confirmed[71] in relation to the cyclisation of the diene (CX):



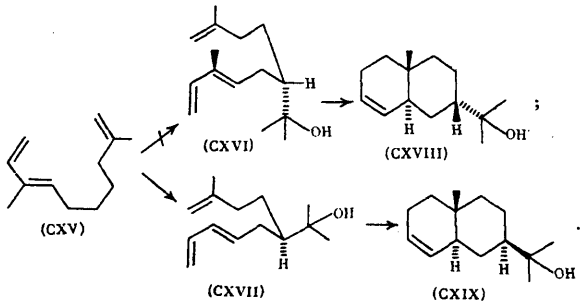
(CX) (CXI) (CXII)

The (CXI):(CXII) ratio is 65:35. Inspection of Dreiding models suggested that the C=O group becomes coplanar with the butadiene fragment; thus the above configuration can be readily obtained only for the transoid disposition, which leads to the preferential formation of the *trans*-joined product (CXI). In order to explain this, the secondary orbital interaction favouring the *endo*-TS has been invoked to account for this phenomenon in a number of other similar examples.[72] The transition from compound (CXIII) to the product (CXIV), which constitutes a kinetically controlled reaction, ensures the preferential *endo*-stereoselectivity of the cyclisation with respect to the C=O group:



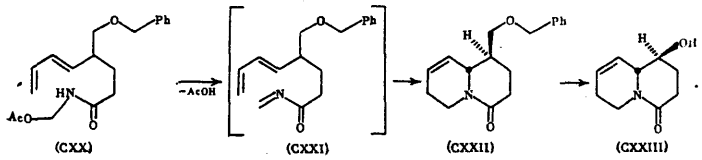
(*endo*-) (CXIII) (CXIV) (*exo*-)

The preferential formation of *trans*-joined rings has been observed in the synthesis of the crystalline sesquiterpene alcohol α-eudesmol (CXIX) from the triene (CXV) with the aid of IAMC[4 + 2].[73] By virtue of the axial position of the hydroxyisopropyl fragment in the TS (CXVI), a steric interaction of this fragment with the remainder of the molecule is observed, which does not occur at all in the case of (CXVII):



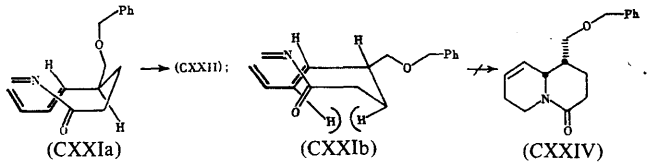
(CXV) (CXVI) (CXVIII) (CXVII) (CXIX)

In the effective synthesis of epilupinine (CXXIII), which belongs to the class of quinolizidine alkaloids, it was discovered[74] that the IAMC[4 + 2] of the triene (CXX) proceeds strictly stereoselectively via the imino-reaction pathway proposed previously:[54–56]



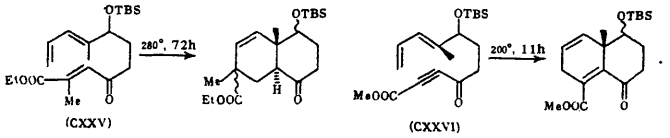
(CXX) (CXXI) (CXXII) (CXXIII)

It has been suggested that the imine (CXXI) cyclises via the TS (CXXIa). Both in the TS (CXXIa) and the TS (CXXIb), the *endo*-disposition of the C=O group is observed, so that the bulky OCH_2Ph group occupies a quasi-equatorial position in the lactone ring. In the TS (CXXIa) the connecting chain assumes a quasi-boat form and such TS leads precisely to the product (CXXII). On the other hand, the lactam ring in the TS (CXXIb) assumes a quasi-chair conformation and the corresponding product (CXXIV) is not detected. Examination of the model shows that in the quasi-chair TS (CXXIb) an unfavourable non-bonding interaction takes place between the hydrogen atom in the vinyl component of the diene and the quasi-axial hydrogen atom in the connecting chain:



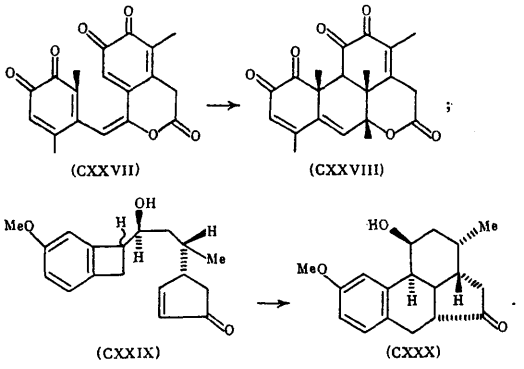
(CXXIa) (CXXIb) (CXXIV)

The *trans*-joined decalin system containing an angular methyl group, which is a structural component of terpenoids and steroid natural products, can be readily obtained[75] from the triene (CXXV) and the tetraene (CXXVI):



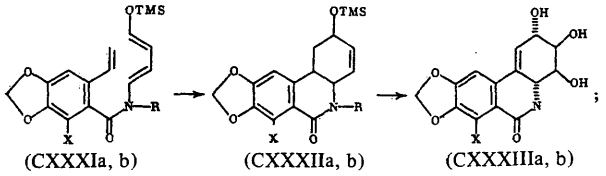
(CXXV) (CXXVI)

The diterpenoid compound quassin (CXXVIII), which contains seven asymmetric centres, can be synthesised stereoselectively from the *o*-quinone (CXXVII) by means of IAMC[4 + 2].[76] Compounds of this type are dehydrated terpenes with a high oxygen content and are present in the plants *Simaroubaceae*. Another possible pathway leading to the synthesis of compound (CXXVIII) involves[77] IAMC[4 + 2] of the benzocyclobutene derivative (CXXIX), whose product (CXXX) is converted into quassin via several stages: (CXXVII)



(CXXVII) (CXXVIII) (CXXIX) (CXXX)

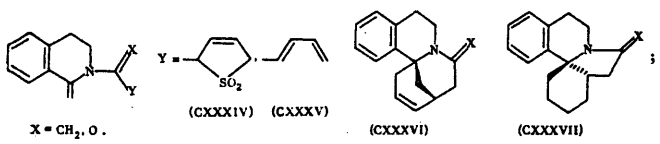
Licoricidin (CXXIIIa) and narciclasine (CXXIIIb) are of considerable interest because of their biological activity; in particular, they inhibit protein synthesis and exhibit a powerful antitumour activity. They can be readily synthesised[78] from the trienes (CXXXIa, b) by IAMC[4 + 2]:



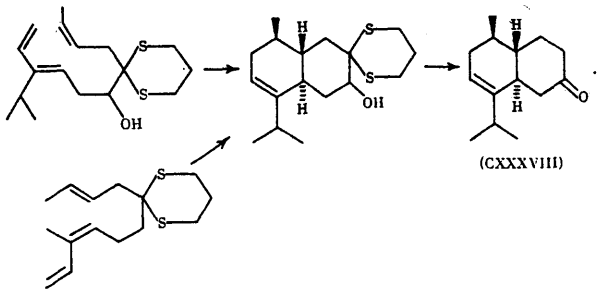
(CXXXIa, b) (CXXXIIa, b) (CXXXIIIa, b)

a: X = H; b: X = OH.

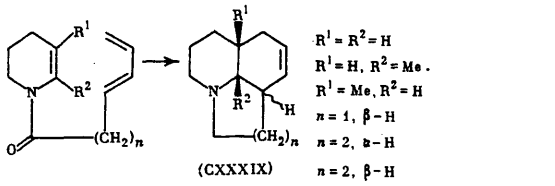
The IAMC[4 + 2] reactions of the enamines and enamides (CXXXIV) and (CXXXV) have been investigated[79,80] in order to develop a new method of synthesis of alkaloids with a tetracyclic spiran skeleton, which is characteristic of erythrin alkaloids; however, instead of the expected compound (CXXXVII), the reaction resulted in the formation of the bridged adducts (CXXXVI):



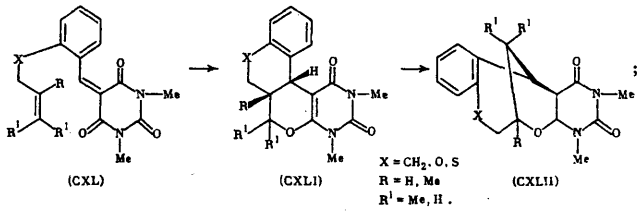
trans-Stereoselectivity of cyclisation has been observed in the synthesis of the cadalane sesquiterpene epizonarene (CXXXVIII) with the aid of IAMC[4 + 2]:[81]



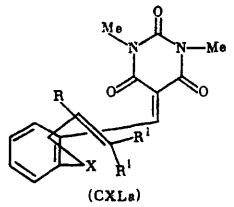
However, the *cis*-joined products (CXXXIX) are formed in the synthesis of *Aspidosperma* alkaloids:[82]



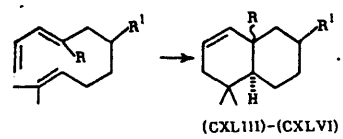
The thermolysis of the trienes (CXL) yields 20:1 mixtures of the products (CXLI) and (CXLII):[83]



The formation of the bridged product (CXLII) shows that the TS (CXL) has the conformation (CXLa):



A short synthesis of (±)-ambrinol (one of the components of ambergris) with the aid of IAMC[4 + 2] leads to four possible stereoisomers, namely (CXLIII, R = α-H, R^1 = H), (CXLIV, R = β-H, R^1 = Me), (CXLV, R = α-Me, R^1 = H), and (CXLVI, R = α-Me, R^1 = Me), among which compounds (CXLIII) and (CXLIV) possess the strong scent of ambergris:[84]



The IAMC[4 + 2] of the triene (CXLVII) proceeds stereoselectively with the preferential formation of compound (CXLVIII), which is converted into the angularly substituted *trans,anti,trans*-perhydrophenanthrene—(±)-fichtelite (CXLIX):[85]

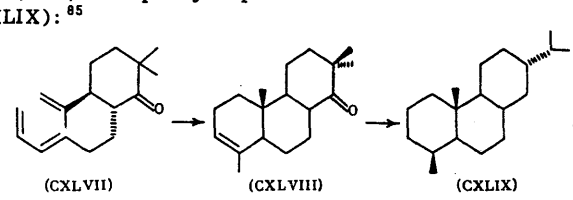
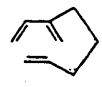
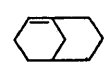
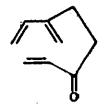
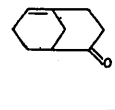
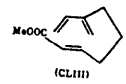
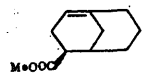
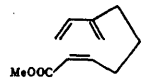
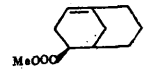
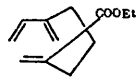
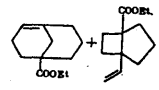


Table 3. Data for the IAMC[4 + 2] of certain trienes leading to the formation of strained bicyclo[*n*.3.1]alkenes.[15]

Initial triene	Conditions	Products	Yield, %
	420°, 23 s		32
	395°, 18 s		72
 (CLIII)	318°, 18 s		76
 (CLIV)	365°, 12 s		—
	390°, 12 s		50

The formation of bridged bicyclo[*n*.3.1]alkenes with the double bond at the bridgehead conflicts with the Bredt prohibition,[86] but, when IAMC[4 + 2] is used, this prohibition sometimes loses its force.[15] However, it has been shown that the reactivity of the triene (CL) in cyclisation is greater than that of the triene (CLI), which has been attributed to the excess strain in compound (CLII). Cycloaddition takes place with formation of the *trans*-cyclooctene ring:

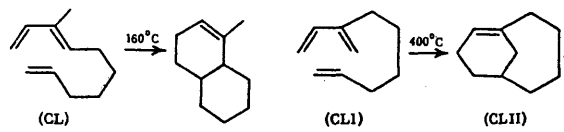
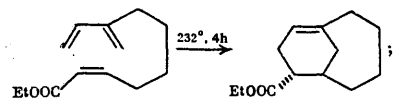
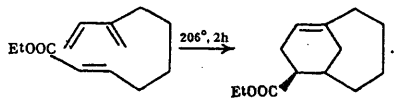


Table 3 shows that the two isomeric trienes *E*-(CLIII) and *Z*-(CLIV) give rise to the same bridged olefin. Kinetic studies have demonstrated that electron-accepting groups accelerate the reaction and that the latter proceeds *exo*-stereoselectively. The cyclisation of compounds *Z*-(CLV) and *E*-(CLVII), leading to the isomeric olefins (CLVI) and (CLVIII), is particularly interesting:



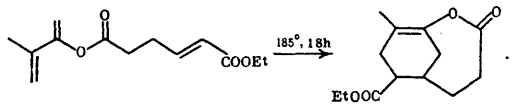
(CLV) (CLVI), 65%



(CLVII) (CLVIII), 80%

These isomers can be readily distinguished on the basis of physicochemical and spectroscopic data. The ratio $k_{(CLV)}/k_{(CLVII)} = 13$ (201 °C) shows that the secondary orbital interaction cannot determine the stereoselectivity of this type of IAMC[4 + 2].

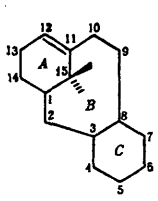
The IAMC[4 + 2] reaction of ethyl 1-methylene-2-methyl-(propenyl)hex-2-enedioate (CLIX), leading to the formation of the bridged enol lactone (CLX) in a high yield, has also been investigated: [87]



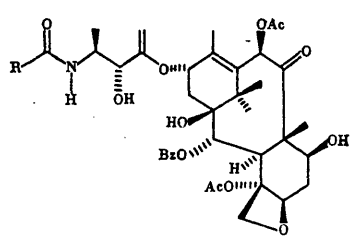
(CLIX) (CLX), 78%

3. The 6/<6-Annelated System

It is noteworthy that this system is rarely encountered; despite this, it has attracted the attention of organic chemists, since representatives of compounds of this class exhibit unique properties. For example, taxane diterpenes, isolated from certain *Taxus* species, contain the unusual tricyclic carbon skeleton (CLXI), in which the eight-membered *B* ring is sterically strained. [88] Taxol (CLXII) and cephalomannine (CLXIII) exhibit extremely high antileukaemic and antitumour activities.

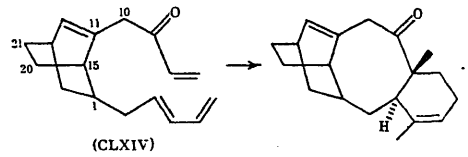


(CLXI)



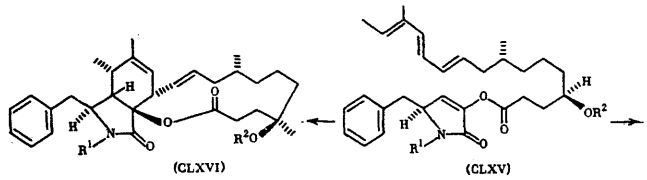
(CLXII) R = Ph
(CLXIII) R = —CMe=CHMe

Although the difficulty of effecting the closure of the *B* ring makes it difficult to obtain compounds of this kind, the IAMC[4 + 2] of the triene (CLXIV) takes place readily. The closure of the B ring is facilitated by the rigid disposition of the five carbon atoms C(2), C(1), C(15), C(11), and C(10), which is due to the fixed boat conformation of the *A* ring: [89]

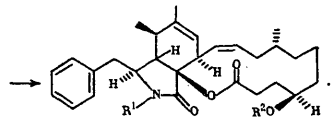


(CLXIV)

The formation of the macrocyclic lactam ring is one of the complex tasks in the synthesis of cytochalasin *B* and related compounds. [90] The above product has been successfully synthesised in the two stereoisomeric forms (CLXVI) and (CLXVII) by the application of a novel and simple procedure involving the IAMC[4 + 2] of the triene (CLXV): [91]



(CLXVI) (CLXV)

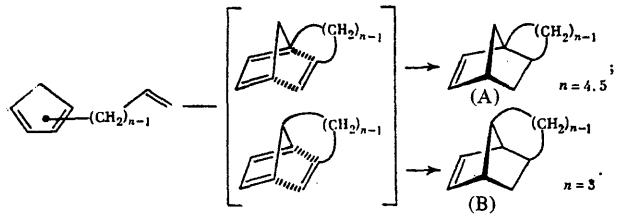


(CLXVII)

IV. THE FORMATION OF BRIDGED CYCLIC SYSTEMS FROM ENDOCYCLIC DIENES

1. Cyclopenta-1,3-diene and Furan

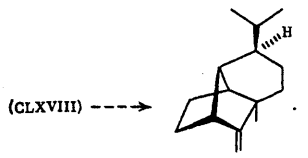
Experiments have shown that, depending on the length of the chain connecting the diene and the dienophile, the IAMC[4 + 2] of alkenylcyclopentadienes yields only two types of tricyclic adducts, (A) and (B), out of the possible twelve isomeric forms: [92,93]



It is remarkable that, when $n = 4$ or 5, then IAMC[4 + 2] leads specifically to a structure of type (A) [via the 1-(*n*-alkenyl)-isomer], while $n = 3$ affords exclusively tricyclo[4.3.0.0^{3,7}]non-4-ene [type (B)] via the 5-(*n*-alkenyl)-isomer.

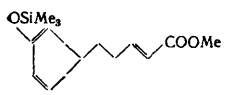
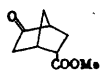
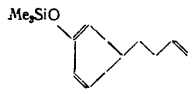
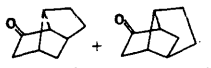
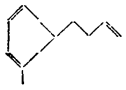
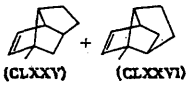
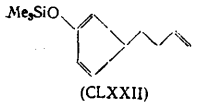
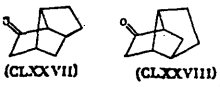
The IAMC[4 + 2] of certain alkenylcyclopentadienes has been carried out [94] (Table 4). The formation of only one regioisomer (CLXVIII) from the triene (CLXIX) is fully consistent with the prediction based on the frontier molecular orbital theory. [95] The cycloaddition of the trienes (CLXX), (CLXXI), and (CLXXII) is extremely important, since the unusual instance, where the formation of the products (CLXXIII), (CLXXV) and (CLXXVII) rules out the biradical cyclisation mechanism, is demonstrated here. [96] It is noteworthy that the precursors of compounds (CLXXIII),

(CLXXIV), (CLXXVI) and (CLXXVIII) are unstable and are converted into a stable form at the instant of their synthesis. The sesquiterpene tricyclic hydrocarbon (±)-sativene (CLXXIX) is readily and stereoselectively synthesised from compound (CLXVIII) in 32% yield: [97]



(CLXXIX)

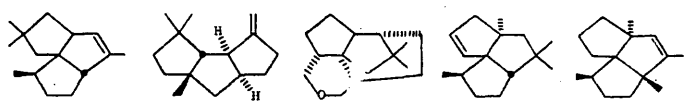
Table 4. Data for the IAMC[4 + 2] of the alkenylcyclopentadienes (CLXX), (CLXXI), (CLXXII), and (CLXIX). [94]

Trienes	Conditions	Products	Yield, %
 (CLXIX)	110°, 3 days	 (CLXVIII) 100 : 0	95
 (CLXX)	250°, 24 h	 (CLXXIII) (CLXXIV) 54 : 46	72
 (CLXXI)	250°, 24 h	 (CLXXV) (CLXXVI) 73 : 27	30
 (CLXXII)	250°, 24 h	 (CLXXVII) (CLXXVIII) 78 : 22	77

The influence of oxygen-containing substituents in the side chain on the reactivity in the IAMC[4 + 2] of the 5-(spiro-2,4-hepta-4,6-dien-1-yl)pent-2-enoates (CLXXIX)–(CLXXXIV) has been discussed in detail. [98]

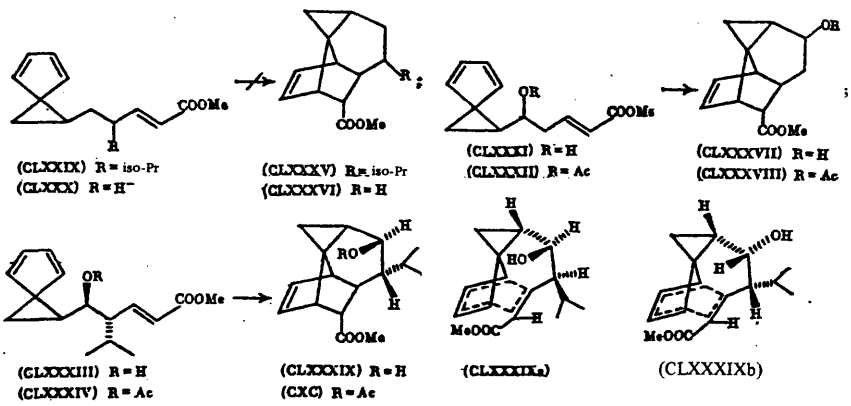
The compounds obtained are intermediates in the synthesis of sesquiterpenes—sinularene, longifolene, sativene, etc. It was observed that the trienes (CLXXIX) and (CLXXX) do not cyclise in the course of 65 h at 195 °C, while the trienes (CLXXXI) and (CLXXXII) are converted into compounds (CLXXXVII) and (CLXXXVIII) in 60% yield after 6 h at 180 °C. It is of interest that the simultaneous employment of both substituents (OR and iso-Pr) in the side chain does not suppress the cyclisation under these conditions. It has been established that, in the presence of oxygen-containing substituents, the dienophile component of the triene is oriented relative to the plane of the cyclopentadiene ring in a way ensuring a position favouring cyclisation. This has been confirmed by the analysis of the ^{1}H NMR spectra of the initial trienes: it was found that the signals of the β-hydrogen atoms in the dienophile component resonate about 5.0 p.p.m. instead of the usual range 6.5–7.5 p.p.m., which indicates the shielding of these atoms by the cyclopentadiene ring. This type of phenomenon has not been observed for the trienes (CLXXIX) and (CLXXX). In the cyclisation of the trienes (CLXXXIII) and (CLXXXIV), only one TS (CLXXXIXb) is actually produced of the two possible TS (CLXXXIXa) and (CLXXXIXb). The formation of one isomer can be accounted for by the unfavourable interactions between the isopropyl group and the *exo*-hydrogen atom in the TS (CLXXXIXa). However, the cause of the appearance of conformations suitable for IAMC[4 + 2] when oxygen-containing substituents in the C(5) position are used remains unknown.

In order to synthesise polyquinane natural products, in particular pentalenene (CXCI), capnellene (CXCII), quadrone (CXCIII), silphinene (CXCIV), and isocomene (CXCV), a study has been made of the IAMC[4 + 2] reactions of several alkenylcyclopentadienes (n = 4). [99]

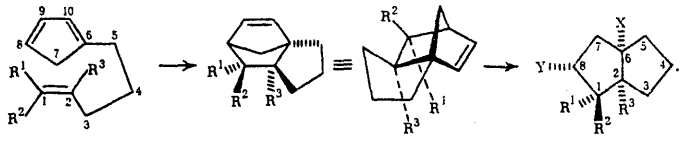


(CXCI) (CXCII) (CXCIII) (CXCIV) (CXCV)

The basic skeleton of these compounds, namely the bicyclo[3.3.0]octane ring (CXCVII), is readily produced by the cleavage of the double bond in the adducts obtained by the



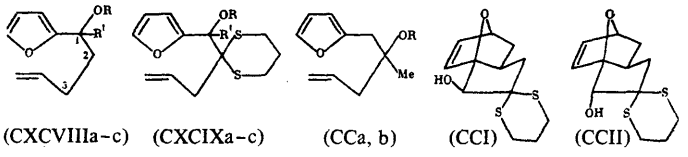
IAMC[4 + 2] of the trienes (CXCVI):



(CXCVI) (CXCVII)

It has been established that, under the conditions of the *trans*-disubstitution in the dienophile component, the reaction proceeds fairly readily and with a high yield of products. In each case two epimeric compounds are produced. Geminal substitution in the C(4) position in the side chain greatly accelerates the IAMC[4 + 2], which indicates the appearance of the TS conformation favourable for the interaction of the diene and dienophile components of the trienes. The stereochemistry of the adducts has been investigated using the nuclear Overhauser effect.

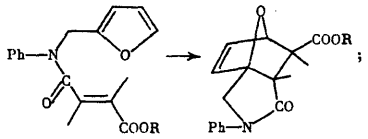
In contrast to alkenylcyclopentadienes, in the case of alkenylfurans the stereochemistry of the junction between the rings formed between the diene and ene fragments is more definite owing to the absence of 1,5-migration in the furane ring.[100] The influence of substituents and solvents on the IAMC[4 + 2] reaction where the α-substituted furan ring is used as the diene component has been investigated.[101] For this purpose, a study has been made of the cyclisation of compounds [CXCVIII, R = R′ = H (a); R = $PhCH_2$, R′ = H (b); R = H, R = Me (c)], [CXCIX, R = R′ = H (a); R = Bz, R′ = H (b); R = H, R′ = Me (c)], and [CC, R = $PhCH_2$ (a); R′ = H (b)]:



(CXCVIIIa-c) (CXCIXa-c) (CCa, b) (CCI) (CCII)

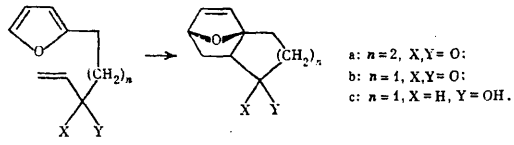
It has been shown that the trienes (CXCVIIIa-c), which have no substituents at the C(1) atom in the side chain, do not undergo the IAMC[4 + 2] reaction. Thermolysis of the trienes takes place *exo*-stereoselectively. The mixture of the (CCa) epimers used gives rise to only traces of the four isomeric reaction products. The triene (CCb) proved to be unreactive under these conditions. The presence of the dithian ring at the C(2) atom in the side chain of compound (CXCIXa) promotes the successful occurrence of the reaction, as a result of which one obtains a mixture of the epimers (CCI) and (CCII) in 63% yield. Geminal substituents at the C(1) atom greatly influence the yield and rate of reaction; thus the presence of the Me and OH geminal groups in the triene (CXCIXc) appreciably accelerates the rate of reaction, while the replacement of the OH group by the ester group in compound (CXCIXb) retards the cyclisation compared with the triene (CXCIXa). The low yield of products in the cyclisation in water compared with the reaction in other solvents can be accounted for by micelle formation. Thus the rate of reaction and the yield of products obtained from α-alkenylfurans greatly depend on the nature of the substituents in the bridging carbon chain; a correct choice of substituents makes it possible to obtain a five-membered carbon ring with a high yield.

The kinetics of the cyclisation of the triene (CCIII) has been investigated spectroscopically;[29] the activation parameters found ($E_A^{\neq}$ = 72.5 kJ mol^{-1}, $\Delta H^{\neq}$ = 69.8 kJ mol^{-1}, $\Delta S^{\neq}$ = −62 J mol^{-1} K^{-1}, and $\Delta V^{\neq}$ = −25 cm^3 mol^{-1}) show that the bulk of the TS in the IAMC[4 + 2] diminishes with increase of pressure to a lesser extent than in the case of IRMC[4 + 2].



(CCIII)
R = H, Et.

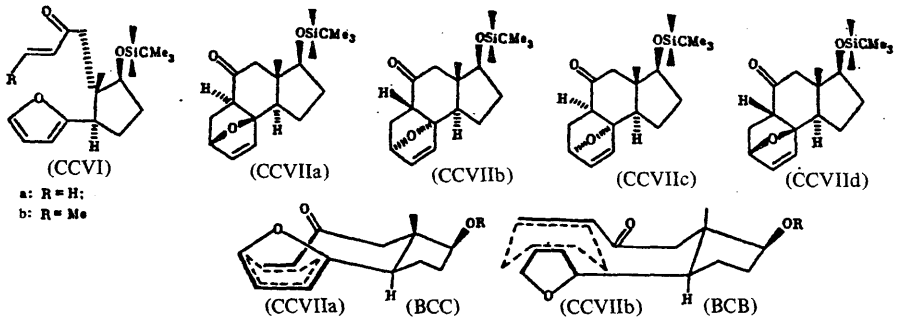
The IAMC[4 + 2] reaction of the trienes (CCIVa-c) has been used to develop a new method of synthesis of corticosteroids and certain characteristic features of this cyclisation have been discovered:[102,103]



a: n = 2, X,Y = O;
b: n = 1, X,Y = O;
c: n = 1, X = H, Y = OH.

(CCIVa-c) (CCVa-c)

A series of model experiments established that, in order to construct the simple oxatricyclo[$6.2.1.0^{1,6}$]undecene system (CCVa, n = 2), it is essential to activate the dienophile in the triene (CCIVa). Indeed the ketone (CCIVa) is readily converted into the corresponding *exo*-adduct (CCVa), while the replacement of the C=O group by OH in the initial triene prevents the IAMC[4 + 2]:



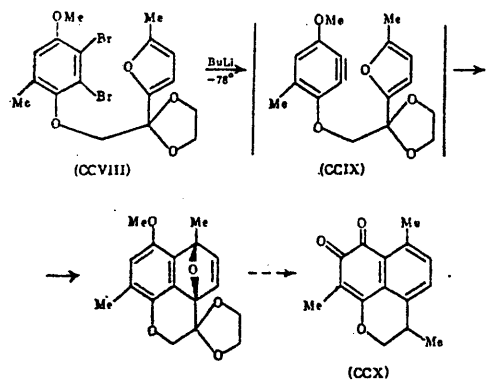
(CCVI)
a: R = H;
b: R = Me

(CCVIIa) (CCVIIb) (CCVIIc) (CCVIId)

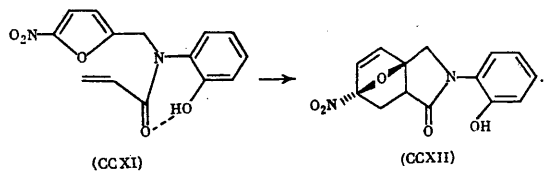
(CCVIIa) (BCC) (CCVIIb) (BCB)

Only the products (CCVIIa) and (CCVIIb) are formed in proportions of 1:8 and in an overall yield of 61% in the thermolysis of compound (CCVIa) out of the four possible isomers (CCVIIa–d). Under these conditions, the methyl-substituted triene (CCVIb) does not react. The formation of only the *exo*-adducts (CCVIIa) and (CCVIIb) in this reaction is not surprising, since the structures of the adducts (CCVIIc) and (CCVIId) are more distorted.[104] It is of interest that at low temperatures the adduct (CCVIIb) is formed preferentially. Investigation revealed that the TS from which the product (CCVIIa) is obtained has the boat-chair-chair (BCC) conformation. Calculation of the force field showed that the boat-chair-boat (BCB) conformation is preferable in cyclododecane, which suggests that the TS for the reaction has the preferred BCB conformation.

Mansonone-E (CCX) isolated from the wood of *Mansonia altissima*, which is an *o*-naphthoquinone widely distributed in nature, can be smoothly synthesised from compound (CCVIII);[105] the key stage in the synthesis is the IAMC[4 + 2] of the intermediate triene (CCIX) containing the furan and benzene fragments:

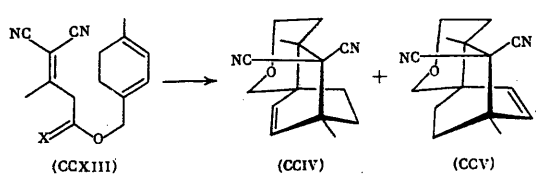


The IAMC[4 + 2] of the triene (CCXI) affords the product (CCXII) in a satisfactory yield,[106] the stereospecificity of the reaction being determined by the intramolecular hydrogen bond between the amide C=O group and the phenolic hydroxyl:



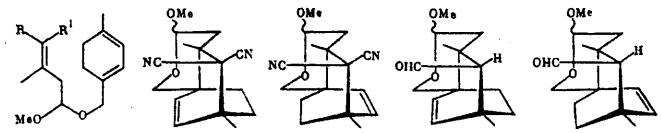
2. Cyclohexa-1,3-diene

Alkenylcyclohexa-1,3-dienes also enter smoothly into the IAMC[4 + 2] reaction. It has been established that the triene (CCXIII, X = H_2) readily gives rise to the cyclisation products (CCXIV) and (CCXV) in proportions of 2.2:1:[107]



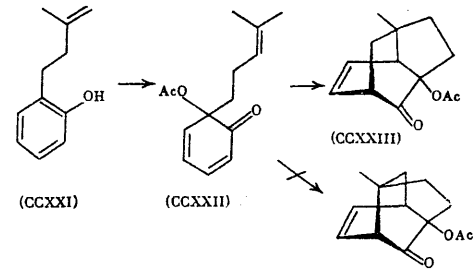
However, its nearest homologue (CCXIII, X = O) does not cyclise under these conditions but polymerises.

The thermolysis of the triene (CCXVIa) at 210 °C in the course of 22 h produces smoothly a mixture of the cyclic products (CCXVII) and (CCXVIII) in proportions of 1.8:1 in 80% yield. It is of interest that in both cases the axial disposition of the OMe group is preferred (*a*:*e* = 2.75:1). Cyclisation is possible also in the presence of only one electron-accepting group. For example, the IAMC[4 + 2] of the *E*-aldehydoacetal (CCXVIb) affords the products (CCXIX) and (CCXX) in proportions of 12.8:1 (*a*:*e* = 1:1 in both cases). The desired product is not formed in the IAMC[4 + 2] of the corresponding *E*-ester (CCXVIc); instead methanol is eliminated from the acetal and an inactive tetraene is therefore generated:

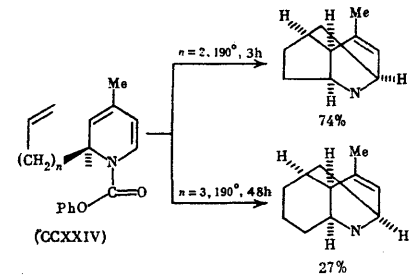


a: R = R^1 = CN;
b: R = CHO, R^1 = H;
c: R = COOEt, R^1 = H

Vessely oxidation of *o*-isopentenylphenol (CCXXI) by $Pb(OAc)_4$ in acetic acid gives rise to the substituted cyclohexa-2,4-dienone (CCXXII), which is converted into isotwist-8-en-2-one (CCXXIII), without isolation, on heating in boiling xylene:[108]



The IAMC[4 + 2] reaction of the dihydropyridines (CCXXIV) has been used to synthesise the various *cis*-decahydroquinoline alkaloids such as gephyrotoxin:[109]

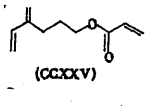
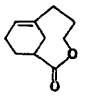
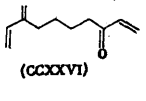
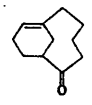
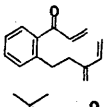
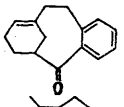
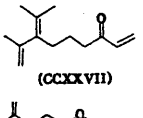
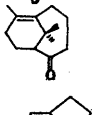
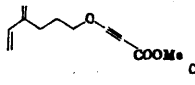
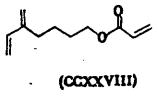
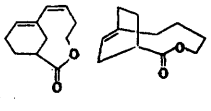


V. CATALYTIC INTRAMOLECULAR [4 + 2]CYCLOADDITION

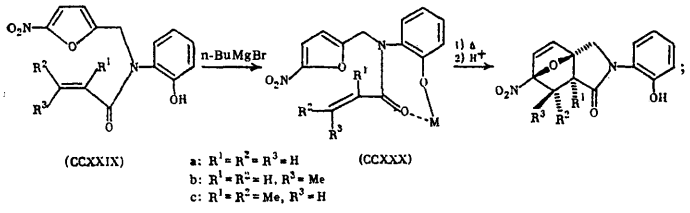
Lewis acids have been used as catalysts in order to increase the rate of pericyclic reactions.[110,111] The catalytic effect of Lewis acids is effectively manifested also in intramolecular Diels–Alder reactions, where fairly severe conditions are required in many instances to achieve regio- and stereo-specificity.[112] For example, the IAMC[4 + 2] of compounds in which the dienophile component is attached to the diene component in the 2-position, leading to the formation of strained bridged cycloalkenes, requires a high temperature.[15] Various Lewis acids have been used in the IAMC[4 + 2] reaction of 4-methylenehex-5-enyl acrylate

(CCXXV). This triene undergoes thermal cyclisation at 139 °C ($\tau_{1/2}$ = 1.8 h). The complex formed between the triene and the Lewis acid is 10^4 times more reactive than the triene itself; this is comparable with the increase of the rate of the IRMC[4 + 2] catalysed by Lewis acids (10^5 at 21 °C).[113] The rate of the catalytic reaction of the triene (CCXXV) is slightly influenced by the polarity of solvents; on passing from pentanes to methylene chlorides, the rate changes only slightly ($k_{CH_2Cl_2}/k_{C_5H_{12}}$ = 2.8). Table 5 presents data on the catalytic IAMC[4 + 2] of certain trienes. It is of interest that the methylated trienone (CCXXVII) is much more reactive than the non-methylated homologue (CCXXVI) under catalytic conditions. This finding conflicts with the result of thermal cyclisation, where the trienone (CCXXVI) is more reactive than compound (CCXXVII). A high reactivity is manifested by dienes when electron-accepting dienophiles are employed in catalytic processes.[114] However, Lewis acids influence only insignificantly the regioselectivity of the IAMC[4 + 2] reaction.[115] The thermal cyclisation of the triene (CCXXVIII) (180 °C, 12 h) affords a mixture of the 1,3- and 1,4-adducts in proportions of 10:1. In the presence of Et_2AlCl (1 equivalent), the cyclisation is completed after 1 h at 21 °C with formation of the same products in proportions of 81:19. The slight change of regioselectivity in favour of the 1,4-isomer agrees with the predictions of the frontier molecular orbital theory.[116] It has also been discovered that the regioselectivity of the IAMC[4 + 2] reaction depends little on temperature.

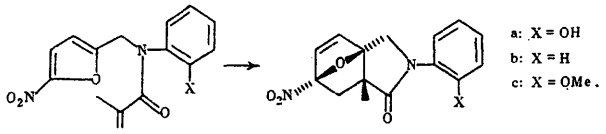
Table 5. Data for the catalytic IAMC[4 + 2] of certain trienes.[112]

Trienes	Products	Conditions	Yield, %
 (CCXXV)		21°, 4 h	85
 (CCXXVI)		21°, 2 h	75
		21°, 1 h	71
 (CCXXVII)		21°, 5 min	70
		21°, 12 h	85
 (CCXXVIII)		21°, 1 h	90

As a result of its aromaticity, furan is a relatively unreactive diene and the IRMC[4 + 2] reaction of nitrofuran with electron-accepting dienophiles should be even more difficult.[114] Despite such an unfavourable combination of the diene and dienophile, the IAMC[4 + 2] of the trienes (CCXXIX) can be achieved readily after treatment with butylmagnesium bromide:[117]

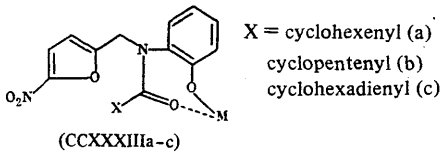


The formation of the complex (CCXXX) as a result of the intramolecular coordination between the phenoxide and amide groups leads to the mutual approach of the diene and dienophile fragments, favouring cyclisation. Subsequently this reaction was investigated in the absence of Grignard reagents, the substituent in the benzene ring being varied:



(CCXXXIa-c) (CCXXXIIa-c)

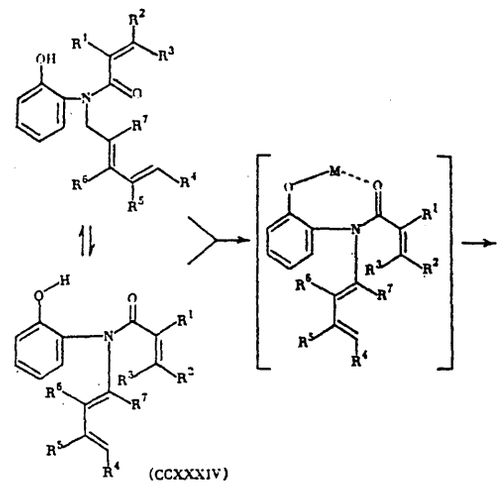
After 7 h in benzene, the product (CCXXIIa) is obtained in 75% yield, while the yields of the products (CCXXXIIb) and (CCXXXIIc) are only 30 and 11% respectively. The shift of the absorption by the C=O group in the IR spectrum confirmed the presence of an intramolecular hydrogen bond between the hydroxyl proton and the C=O group in the initial compound (CCXXXIa), which leads to the coplanarity of the dienophile part of the molecule and hence to an increase of the reaction rate. The solvation effects have only a slight influence on the yield and rate of the cyclisation reaction. One of the main factors determining the course of the cycloaddition is the steric hindrance in the dienophile component of the triene.



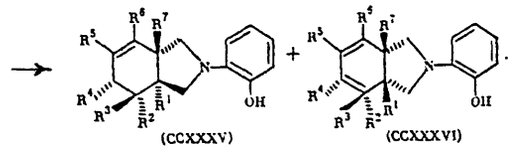
(CCXXXIIIa-c)

Examination of molecular models shows that the axial proton in the cyclohexene ring of cyclohexene-1-carboxamide (CCXXXIIIa) hinders the approach of the cyclohexene ring to the furan ring, which has not been observed for the trienes (CCXXXIIIb) and (CCXXXIIIc). It has been shown that molybdenum and tungsten complexes of the type $[MCl(CO)_2(\eta^3\text{-allyl})(NCMe)_2]$ appreciably accelerate this reaction.[118] The steric structures of the products have been established by NMR using the nuclear Overhauser effect; the *exo*-configuration with the *anti*-position of the Me group relative to its bridging oxygen atom has been attributed to them.

The IAMC[4 + 2] reaction between acyclic diene and αβ-unsaturated amide fragments has been thoroughly investigated[118,120] using intramolecular coordination with participation of metal salts:

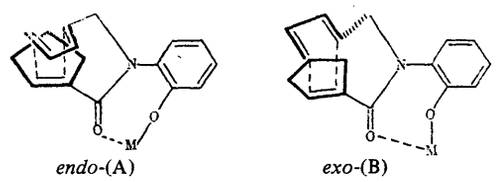


(CCXXXIV)



(CCXXXV) (CCXXXVI)

When magnesium salts are used, the IAMC[4 + 2] of *N*-(*trans*,*trans*-alka-2,4-dienyl)-*N*-(2-hydroxyphenyl)acrylamide derivatives (CCXXXIV) is greatly accelerated and the corresponding products (CCXXXV) and (CCXXXVI) are obtained in high yields; the *exo* : *endo* isomer ratio is approximately 3 : 2. The analogous reaction with *N*-(*trans*,*trans*-alka-2,4-dienyl)-*N*-(2-hydroxyphenyl)cyclopentene-1-carboxamide results in the preferential formation (from 60 : 40 to 85 : 15) of *trans*-joined *exo*-products in a satisfactory yield. The addition of 4-t-butylcatechol in catalytic amounts to the reaction mixture inhibits the polymerisation process. The preferential formation of the *exo*-products is not surprising because, on coordination of phenol to the magnesium salts, the coordination of magnesium to the oxygen of the C=O group makes the molecular conformation more rigid and the TS (A) in the *endo*-cyclisation becomes more strained than the *exo*-TS (B):

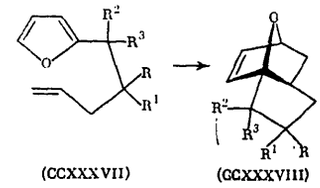


endo-(A) *exo*-(B)

When strong Lewis acids such as aluminium or tin salts are used, a balance between the steric control and control by secondary orbital interaction is observed, so that two products are obtained in almost identical amounts, as in the non-catalytic reaction.

It has been shown[40,41] that the thermal cyclisation of methyl deca-2,7(*E*),9-trienoates (XXXIII)–(XXXV) produces the preferentially *trans*-joined hexahydroindenes (XXXVIIa)–(XL) (Table 2). The catalytic cyclisation of the *trans*-decatrienoates (XXXIII) and (XXXV) using Lewis acids such as $AlCl_3$, $EtAlCl_2$, Et_2AlCl, $BF_3.Et_2O$, etc. proceeds fully stereospecifically with formation of *trans*-joined products.[115] However, this procedure is not feasible for *cis*-decatrienoates, i.e. the stereoselectivity of the catalytic cyclisation of these compounds hardly differs from that of the thermal cyclisation. The lack of a change in the stereoselectivity of the cyclisation of the trienes (XXXIV) and (XXXVI) can be explained by the fact that the enhancement of the secondary orbital interaction between the ester carbonyl group and the Lewis acid is insufficient to overcome the hindrance to the formation of the *trans*-TS.

The thermal cyclisation of the methyl esters of the (*E*,*E*,*E*)- and (*Z*,*E*,*E*)-12-methyltrideca-2,8,10-trienoic acids (CIII) and (CIV) proceeds non-stereospecifically with formation of 50 : 50 mixtures of *cis*- and *trans*-joined products. In the presence of Lewis acids (Et_2AlCl), the stereoselectivity and the yield of products changed to a significant extent.[68] The acid-catalysed cyclisation proceeds mainly with formation of *endo*-products, since the stereocontrol of the reaction is due to the secondary orbital interaction. β-Cyclodextrin has been used successfully as the catalyst in the IAMC[4 + 2] of 1-(2-furyl)-1-hydroxy-2-R,2-R′-pent-4-ene (CCXXXVII) which resulted in the formation of a mixture of the products (CCXXXVIIIa) and (CCXXXIIIb) in an overall yield of 91%:[121]



(CCXXXVII) (GCXXXVIII)

a: $RR^1 = S(CH_2)_3$, $R^2 = H$, $R^3 = OH$
b: $RR^1 = S(CH_2)_3$, $R^2 = OH$, $R^3 = H$.

Thus the data published in recent years permit the conclusion that IAMC[4 + 2] is of enormous interest and we hope that further development of this unique field of chemistry will lead to extensive possibilities for the specific synthesis of the most important natural products and their analogues.

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During the preparation of the manuscript for the press, a fairly large number of publications devoted to IAMC[4 + 2] appeared.[122–207] One of these is a review[122] which deals with the latest advances in the intramolecular Diels–Alder reaction and its application to the synthesis of complex natural products. In particular the synthesis of the bicyclo[4.3.0]nonene, bicyclo[4.4.0]decene, and bicyclo-[5.4.0]undecene systems and bridged bicyclo[*n*.3.1]alkenes is discussed. In contrast to the above review,[122] in the present review attention has been concentrated on the discussion of the synthesis of products from the corresponding trienes and on catalytic IAMC[4 + 2].

The main trend in other investigations[123–207] involved the study of the stereo- and regio-selectivities of IAMC[4 + 2] for the construction of the basic skeletons of natural products using various synthetic procedures, in particular catalysts of various type, an activated double bond, bulky substituents at chiral centres, etc.

The vigorous growth of the number of publications on the IAMC[4 + 2] reaction during such a brief period (1984–1985) again indicates the timely and promising nature of this branch of organic chemistry.

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