Stereochemical Aspects of the Intramolecular Diels–Alder Reaction

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1 Introduction

Since its discovery nearly 60 years ago,[1] the Diels–Alder reaction has become one of the most commonly used stratagems in organic chemistry. The ability to generate simultaneously up to four chiral centres in a highly stereoselective and largely predictable fashion has resulted in its application to numerous synthetic challenges, often difficultly accessible by other means. The intramolecular version of this process, although over thirty years younger than its bimolecular counterpart,[2] has similarly enjoyed widespread use in the construction of polycyclic ring systems with high levels of stereocontrol.

Whilst the last ten years have seen a large number of additions to the review literature covering the intramolecular Diels–Alder (IMDA) reaction,[3] these have largely simply catalogued published examples of the reaction, classifying cyclization substrates according to such structural features as the nature of substituents on the diene and dienophilic groups, the nature and presence of substituents in the linking chain, and the incorporation of heteroatomic groups in the linking chain. The present review sets out to assess critically the effect of such parameters on the stereochemical outcome of the IMDA reaction, including a brief discussion of some recent theoretical work in the area. Although it is clearly outside the scope of this review to analyse exhaustively all the known examples of the IMDA reaction, particular emphasis has been placed on those instances where the observed reactivity serves to highlight and exemplify an emerging stereochemical trend. As a corollary of this selective analysis, examples of the reaction in which stereochemistry is not apparent, or where the observed selectivity results purely as a consequence of some obvious structural feature have been omitted. The use of the IMDA reaction in steroid synthesis, amply reviewed elsewhere, has not been covered in detail. Because the last major reviews appeared in 1984, all the relevant literature since that date has been reviewed.

[1] O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, 1928, **460**, 98.
[2] (a) G. Brieger, *J. Am. Chem. Soc.*, 1963, 3783; (b) L. H. Klemm and K. W. Gopinath, *Tetrahedron Lett.*, 1963, **4**, 1243; (c) H. O. House and T. H. Cronin, *J. Org. Chem.*, 1965, **30**, 1061.
[3] (a) W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, 1977, **16**, 10; (b) W. Oppolzer, *Synthesis*, 1978, 798; (c) R. L. Funk and K. P. C. Vollhardt, *Chem. Soc. Rev.*, 1980, **9**, 41; (d) G. Brieger and J. N. Bennett, *Chem. Rev.*, 1980, **80**, 63; (e) D. F. Taber, 'Intramolecular Diels–Alder Reactions and Alder Ene Reactions', Springer Verlag, New York, 1984; (f) E. Ciganek, *Org. React.*, 1984, **32**, 1; (g) A. G. Fallis, *Can. J. Chem.*, 1984, **62**, 183; (h) M. P. Edwards, Ph.D thesis, University of London, 1982. For a review on mechanistic aspects of the Diels–Alder reaction, see R. Sustmann and J. Sauer, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 779.

Since the large majority of recorded uses of the IMDA reaction has resulted in the construction of bicyclo[4.3.0] and bicyclo[4.4.0] ring systems, rather than the possible (though rarely observed) bridged isomers, the review is split into two main sections dealing with each of these topics; further classification into carbo- and heterocyclic ring synthesis is made within each category.

2 Carbocyclic Systems

A. Bicyclo[4.4.0]decanes.—IMDA reactions of 1,3,9-decatrienes may proceed *via* four distinct transition states, giving rise to product types as depicted below. It should be noted that the terms *endo-* and *exo-* refer to the orientation of the dienophile-activating group with respect to the diene function.


X = dienophile - activating group
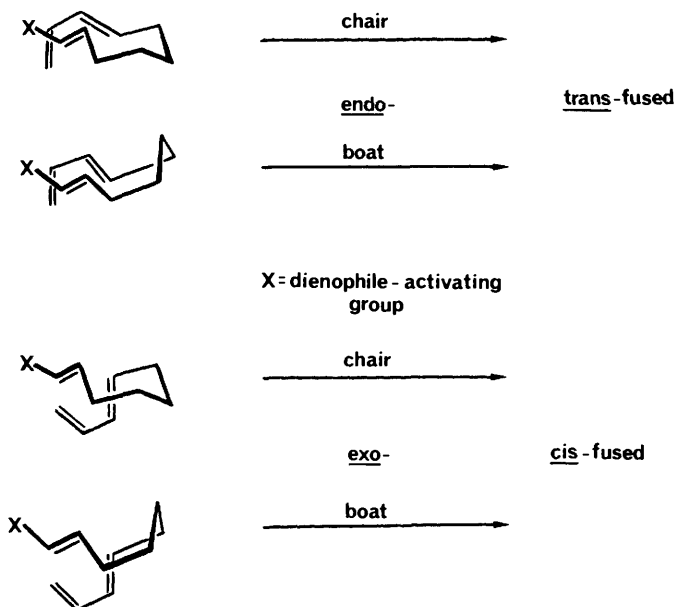
(i) *Unsubstituted and Terminally Substituted Trienes.* Despite the simplicity and ready availability of the IMDA reaction substrate, studies on the cyclization of (*E*)-deca-1,3,9-triene (1) have only recently appeared.[4] Houk and Lin observed that (1) cyclized with very low levels of stereocontrol to give mixtures of *cis-* and *trans*-fused bicyclo[4.4.0]dec-2-ene, with product ratios tending towards unity with increasing temperature (equation 1).


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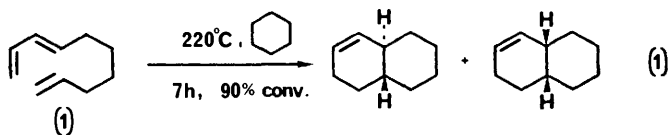
[4] Y.-T. Lin and K. N. Houk, *Tetrahedron Lett.*, 1985, **26**, 2269.

The small preference for the formation of the *cis*-fused product in these reactions, taking into account their irreversibility[5] suggests the activation energy for formation of the *trans*-product to be some 0.3 kcal mol^{-1} higher than for the *cis*-isomer, as predicted by calculations.[6,7] Theoretical methods showed the *trans*-isomer to be 2 kcal mol^{-1} more stable than the *cis*-,[8] suggesting that product stabilities may be of limited use in predicting the stereochemical course of IMDA reactions.

Substitution of an electron-withdrawing group at the dienophile terminus of 1,3,9-decatriene had little effect on the observed stereoselectivity of the cyclization, although lower temperatures were required for the reaction to proceed, presumably due to a lowering of the energy of the dienophile LUMO[9] by the ester function (equations 2 and 3).[10]

$$E = CO_2CH_3$$
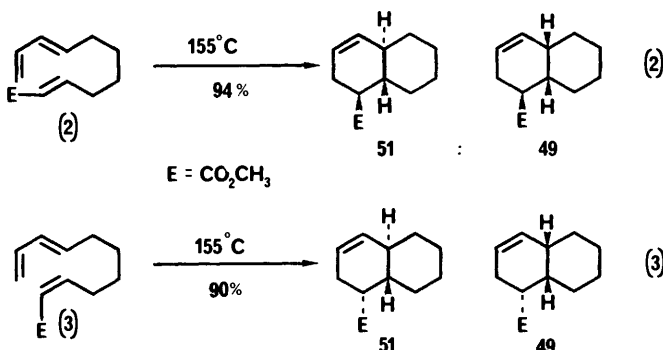
Dienophile geometry exerted no effect on the product ratio, the marginally major product resulting from a chair-like *endo*-transition-state for the cyclization of the *E,E*-triene (2), and from a chair-like *exo*-transition-state for the isomeric triene (3) (Scheme 1).
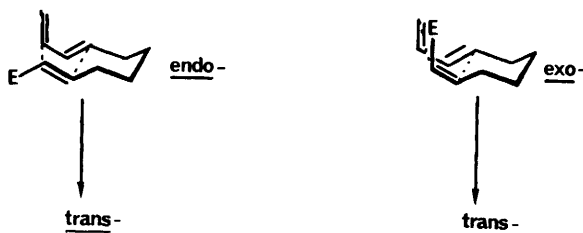
Scheme 1

Secondary orbital interactions are clearly unimportant in determining product

[5] Products were recovered unchanged after resubjection to thermolysis conditions.

[6] C. C. Browne and F. D. Rossini, *J. Phys. Chem.*, 1960, **64**, 927.

[7] S.-J. Chang, D. McNally, S. Shary-Tehrany, M. J. Hickey, and R. H. Boyd, *J. Am. Chem. Soc.*, 1970, **92**, 3109.

[8] N. L. Allinger, *J. Am. Chem. Soc.*, 1977, **99**, 8127.

[9] I. Fleming, 'Frontier Orbitals and Organic Chemical Reactions', Wiley, Chichester, 1978.

[10] W. R. Roush and S. E. Hall, *J. Am. Chem. Soc.*, 1981, **103**, 5200.

ratios in these kinetically controlled processes, demonstrating the limited use of the *endo*-rule in predicting the outcome of thermal reactions. This parallels similar observations in the bimolecular case, where *endo*-selectivity falls rapidly with increasing temperature.[11,12] Attempts to increase the proportion of the product arising from an *endo*-transition-state by Lewis acid catalysis resulted only in diene polymerization.

Addition of an alkyl substituent to the diene terminus of methyl 2,8,10-decatrienoates left the product ratio from *E,E,E*-isomer (4) unchanged, although the geometric isomer (5) showed a small bias towards the formation of the *trans*-fused product (equations 4 and 5).[13]

$$\xrightarrow[\text{69%}]{160°\text{C, 48h}}$$

50 : 50 (4)

$$E = CO_2CH_3$$

$$\xrightarrow[\text{71%}]{180°\text{C, 3h}}$$

55 : 45 (5)
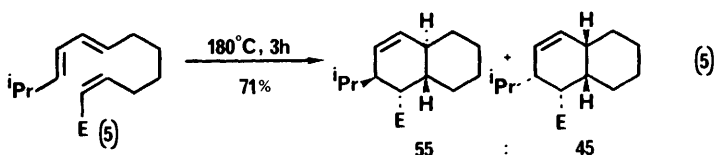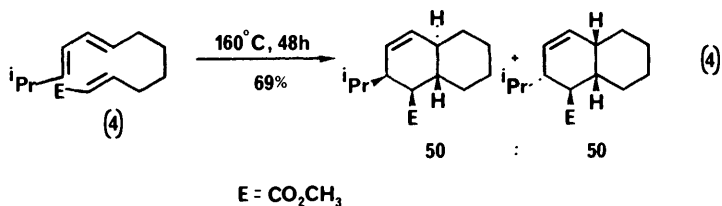
This small difference in selectivity between (4) and (5) may point towards non-bonded interactions between the terminal diene substituent and the ester grouping in the *endo*-transition-state leading to the *cis*-fused bicyclic system from (5) (Scheme 2).

$$\xrightarrow{\text{disfavoured}} \underline{\text{cis}}\text{- product}$$
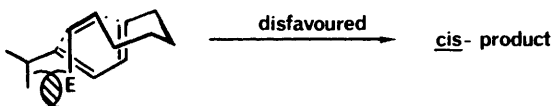
Scheme 2

Much more pronounced *cis*-selectivity was observed in the cyclization of the terminally substituted decatrienoate ester (6) in which formation of the *trans*-isomer was disfavoured by similar steric effects in the *endo*-transition-state (equation 6).[14]
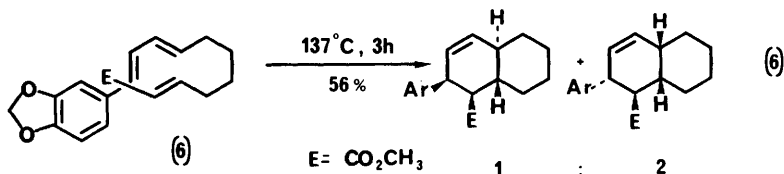
The triene (7), in which an electron-rich diene and an electron-deficient

[11] J. Sauer, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 16.
[12] J. G. Martin and R. K. Hill, *Chem. Rev.*, 1961, **61**, 537.
[13] W. R. Roush and H. R. Gillis, *J. Org. Chem.*, 1982, **47**, 4825.
[14] B. S. Joshi, N. Viswanathan, D. H. Gawad, V. Balakrishnan, and W. Philipsborn, *Helv. Chim. Acta*, 1975, **58**, 2295.

137°C , 3h

56 %
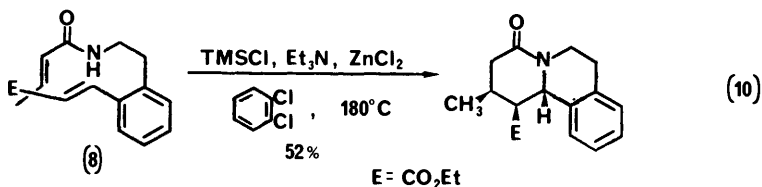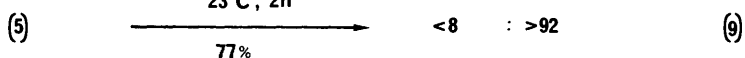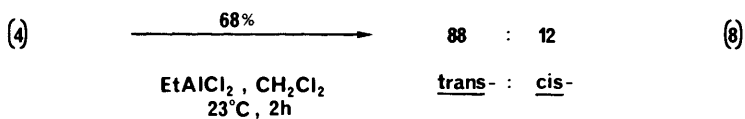
(6)

(6)

E= CO₂CH₃   1 : 2

E = CO_2CH_3 1 : 2

dienophile are present in the cyclization substrate showed a slight preference for formation of the *trans*-isomer, seemingly at variance with the result shown in equation 6 (equation 7).[15]

40°C

benzene

(7)

(7)

E = CO₂Et   55 : 45

E = CO_2Et 55 : 45
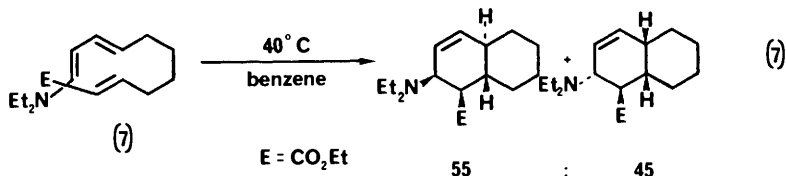
From a comparison of the thermal conditions required to effect cyclization of trienes (2) and (3), (4) and (5), and (7), it can be seen that a bulky terminal diene substituent attenuates IMDA reactivity whilst a strongly electron-donating group has a rate-enhancing effect. The slight bias towards reaction *via* an *endo*-transition-state exhibited by triene (7) may reflect the involvement of secondary orbital interactions at lower temperatures.

Unlike unsubstituted trienes (2) and (3), (4) and (5) reacted with high stereoselectivity when treated with Lewis acids (equations 8 and 9).[13]

endo-Specificity resulting from Lewis acid-enhanced secondary orbital interactions was also exploited in the cyclization of α,β-unsaturated amide (8) in the presence of zinc chloride (equation 10).[16]

(4)   68%   88 : 12   (8)

EtAlCl₂ , CH₂Cl₂
23°C , 2h

EtAlCl₂ , CH₂Cl₂
23°C , 2h   trans- : cis-

(5)   77%   <8 : >92   (9)

TMSCl, Et₃N, ZnCl₂

(8)   180°C   52%   (10)

E= CO₂Et   E = CO_2Et

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[15] T.-C. Wu and K. N. Houk, *Tetrahedron Lett.*, 1985, **26**, 2293.
[16] M. Ihara, T. Kirihara, A. Kawaguchi, K. Fukumoto, and T. Kametani, *Tetrahedron Lett.*, 1984, **25**, 4541.

Zinc may serve the additional role of forming a chelate-type structure *via* co-ordination of the heterodienol ether and ester carbonyl oxygens as shown in Scheme 3.
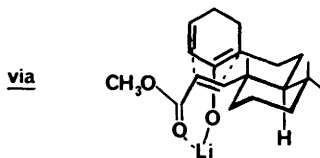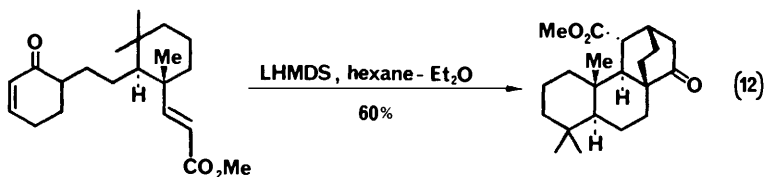
Lithium-chelated species such as (9a) have been invoked to account for the *trans*-specificity observed in the cyclization of the enone (9) (equation 11).[17]


Scheme 3

$$(11)$$
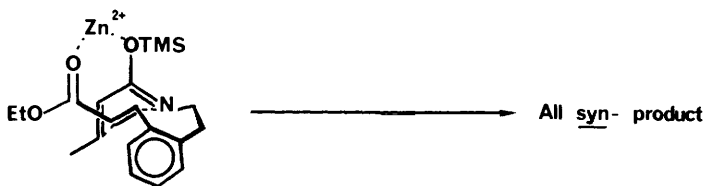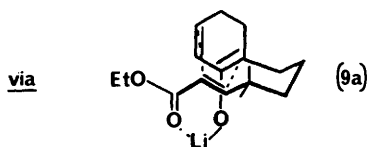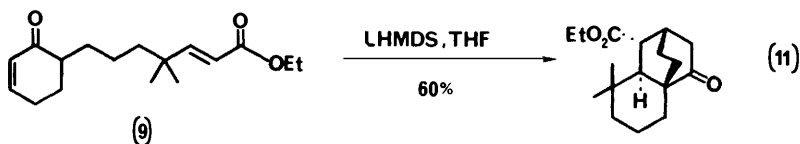
When a *trans*-fused cyclohexane ring was incorporated into the tether connecting diene and dienophile, the resulting 1,2-diequatorial arrangement of the


$$(12)$$

[17] M. Ihara, M. Toyota, K. Fukumoto, and T. Kametani, *Tetrahedron Lett.*, 1984, **25**, 2167; *ibid.*, 1984, **25**, 3235.

ring gave a product arising from attack by the α,β-unsaturated ester moiety at a single diastereoface of the dienolate (equation 12).[18]

Lewis acid-catalysed IMDA reactions *via endo*-transition states have found application in asymmetric synthesis where extremely mild conditions and highly ordered, reactive intermediates are essential prerequisites for efficient diastereofacial selection.[19] Cyclization of optically pure triene (10) occurred with complete *endo*- and very high diastereofacial selectivity to yield the *trans*-fused product (11) (equation 13).[20]
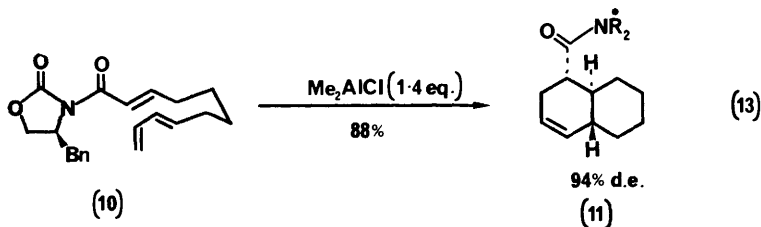

Shielding of one face of the rigid chelated intermediate (12) as a result of π-stacking interactions between the aromatic group at the 4-position of the chiral oxazolidone function and the dienophile was used to explain the observed selectivity. Thermal reaction of (10) gave a 1:1 mixture of *cis*- and *trans*-bicyclic products.
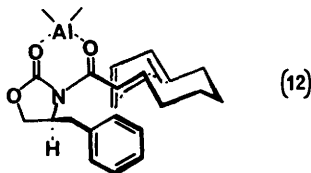
Similar high levels of stereocontrol have been realized through the use of optically pure camphor-derived *N*-acyl sultams in asymmetric IMDA reactions.[21]

Substitution of an electron-withdrawing group at the diene terminus gave a 1:1 mixture of *cis*- and *trans*-cyclization products, whilst attempted Lewis acid-catalysed cycloaddition of triene (13) resulted in polymerization (equation 14).[22]
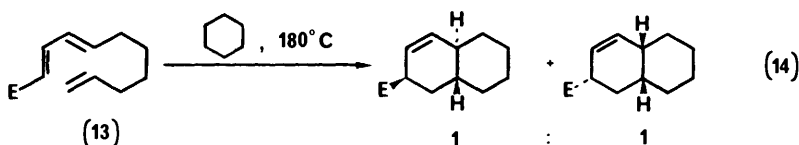
[18] M. Ihara, M. Toyota, K. Fukumoto, and T. Kametani, *Tetrahedron Lett.*, 1985, **26**, 1537.
[19] For a review of the asymmetric Diels–Alder reaction, see W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 876.
[20] D. A. Evans, K. T. Chapman, and J. Bisaha, *Tetrahedron Lett.*, 1984, **25**, 4071.
[21] W. Oppolzer and D. Dupuis, *Tetrahedron Lett.*, 1985, **26**, 5437.
[22] K. N. Houk and Y.-T. Liu, *Tetrahedron Lett.*, 1985, **26**, 2517.

The smaller effect of the presence of an electron-withdrawing group on the diene rather than the dienophile terminus was attributed to the smaller effect of such a group on the HOMO coefficients of the diene than on the LUMO coefficients of the dienophile[23,24] (*vide infra*).

The presence of an electron-withdrawing group within the chain linking diene and dienophile caused a bias towards *cis*-fused products arising *via* an *endo*-transition-state (equation 15).[25]
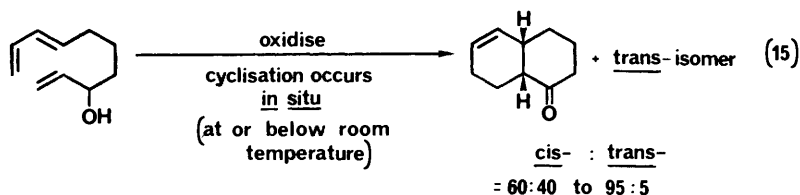
Since some of the oxidation reactions were carried out in acidic media, it seems probable that enhanced secondary orbital interactions arising from protonation of the ketone oxygen were responsible for the observed *endo*-selectivity. Placement of an isopropyl group on the dienophile terminus resulted in complete *endo*-selectivity, presumably due to unfavourable non-bonded interactions between the alkyl substituent and the diene in the alternative *exo*-transition-state. In contrast, fluoride-initiated cyclization of tetraene (14) gave the *trans*- decalone (15) as the sole product (equation 16),[26] presumably as a consequence of base-catalysed isomerization of the initially-formed *cis*-fused isomer.
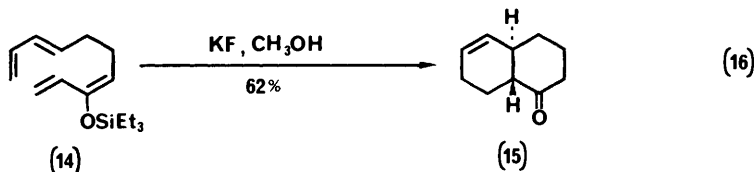
The observation that the analogous reaction in [$^2H_4$]methanol did not result in any deuterium incorporation in (15) would seem to be at variance with the proposed intermediacy of ketone (16), however.
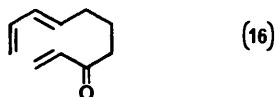
Trienes containing an internal dienophile-activating group and possessing an

[23] K. N. Houk, *J. Am. Chem. Soc.*, 1973, **95**, 4092.
[24] K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *J. Am. Chem. Soc.*, 1973, **95**, 7301.
[25] J.-L. Gras and M. Bertrand, *Tetrahedron Lett.*, 1979, **20**, 4549. See also: O. P. Vig, I. R. Trehan, and R. Kumar, *Ind. J. Chem., Sect. B*, 1977, **15**, 319; O. P. Vig, I. R. Trehan, N. Malik, and R. Kumar, *ibid.*, 1978, **16**, 449.
[26] W. Oppolzer and R. L. Snowden, *Tetrahedron Lett.*, 1976, **17**, 4187.

allenic terminal diene substituent showed enhanced *cis-/endo*-selectivity when the IMDA reaction was carried out in the presence of a Lewis acid (equation 17).[27]

(17)
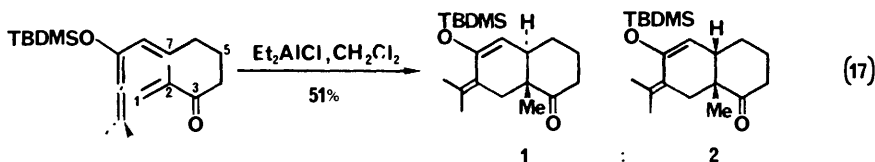
The analogous thermal reaction gave a 1:1 mixture of products. Although this method accomplished the introduction of an angular methyl group in the *trans*-fused product, substitution of a methyl group at C-7 resulted in preferential [1,5] sigmatropic hydrogen shift[28] to give the conjugated triene. Tetraenes in which the allenic double bond is within the incipient 6-membered ring underwent IMDA reactions in which a single isomer was formed, regardless of whether the dienophile-activating group was at the chain terminus or within the newly formed cycle. Thus (17) cyclized to give only two out of four possible diastereomeric products (equation 18).[29]

(18)
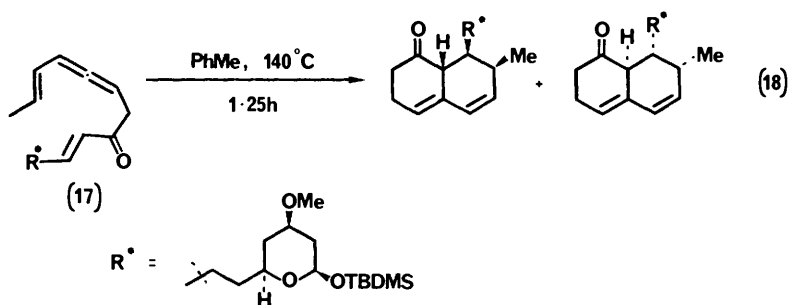
Allenic tetraene (18) similarly gave a single diene upon thermolysis (equation 19).[30]


(19)
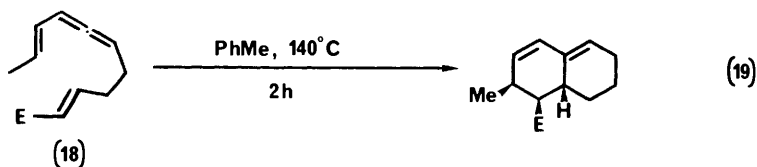
Presumably the alternative transition-state (19) leading to the isomeric product

[27] H. J. Reich and E. K. Eisenhart, *J. Org. Chem.*, 1984, **49**, 5282.
[28] W. H. Okamura, *Acc. Chem. Res.*, 1983, **16**, 81 and references cited therein.
[29] G. E. Keck and D. F. Kachensky, *J. Org. Chem.*, 1986, **51**, 2487. For closely related work see: E. A. Deutsch and B. B. Snider, *J. Org. Chem.*, 1982, **47**, 2682; *Tetrahedron Lett.*, 1983, **24**, 3071.
[30] B. B. Snider and B. W. Burbaum, *J. Org. Chem.*, 1983, **48**, 4370.

(19)　　(20)
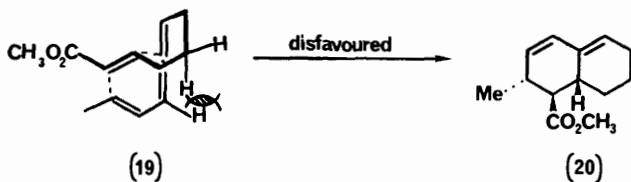
(20) was disfavoured due to non-bonded interactions between H-5 and H-9.

(ii) *Trienes Containing Internal Olefin Substituents.* In sharp contrast to 1,3,9-decatriene, 3-methyl-1,3,9-decatriene cyclized at 160 °C to give *trans*-2-methyl-bicyclo[4.4.0]dec-2-ene as the only product in 95% yield.[31] Addition of a further methyl substituent at the 9-position of the triene substrate severely attenuated reactivity; whilst the *trans*-fused ring system was the only cycloadduct isolated, the low (30%) yield presumably arose from competing polymerization/decomposition of starting material under the somewhat harsh reaction conditions. The exclusive formation of *trans*-product may be attributed to the development of severe non-bonded interactions in the transition-state (21) leading to the *cis*-isomer.


(21)
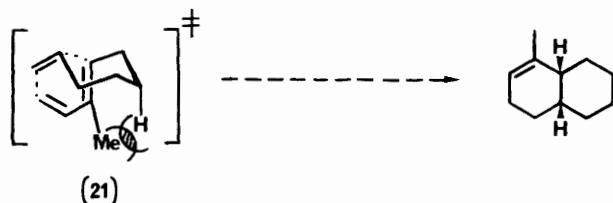
Although substituted triene (22) gave predominantly the *trans*-fused bicyclic

(22)　　100°C , ∼ 10h　　72%　　4 : 1　(20)

(23)　　180°C , 24h　　moderate yield　　1 : 2　(21)
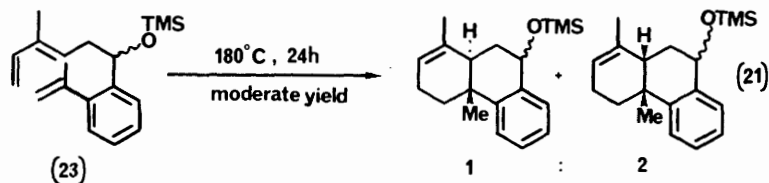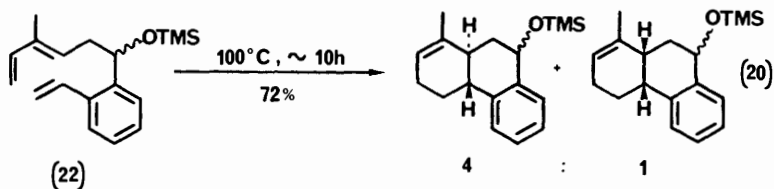
[31] S. R. Wilson and D. T. Mao, *J. Am. Chem. Soc.*, 1978, **100**, 6289. See also S. R. Wilson and J. C. Huffman, *J. Org. Chem.*, 1980, **45**, 560.

product upon thermolysis (equation 20), the methylated analogue (23) yielded more of the corresponding *cis*-isomer (equation 21).[32]

The tendency towards formation of the *cis*-product when the dienophile was internally substituted may indicate the presence of non-bonded interactions between the C-3 and C-9 methyl groups in the transition-state (24) giving rise to the *trans*-fused product; the presence of the fused benzene ring forces the linking chain to adopt a boat-like conformation.
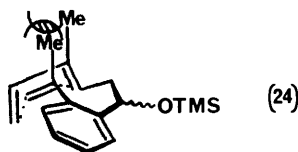

O-Quinodimethane species (25) and (26) reacted to give *trans*-fused tricyclic species with varying stereoselectivity depending on whether or not the internal dienophile was activated (equations 22 and 23).[33]
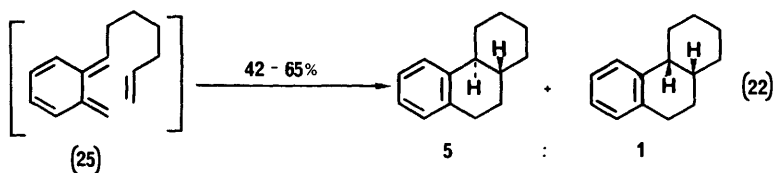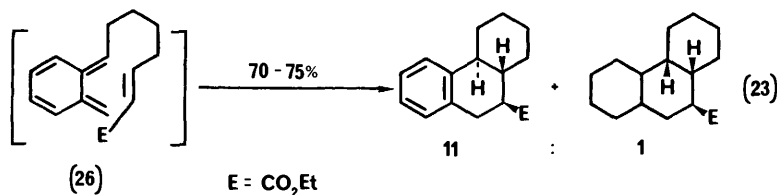
The highly reactive triene (27) cyclized at low temperatures to yield exclusively the *trans*-fused tricycle, formation of the *cis*-isomer being disfavoured by non-bonded interactions between the axial C-6 proton and the methylene bridge linking
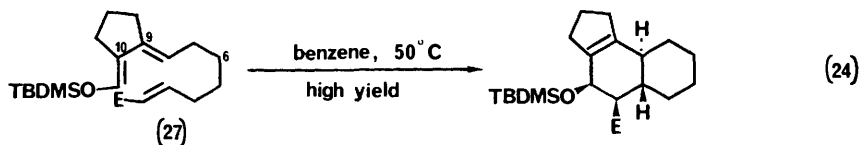
[32] S. R. Wilson and D. T. Mao, *J. Org. Chem.*, 1979, **44**, 3093. For a counter-example see D. F. Taber and S. A. Saleh, *J. Am. Chem. Soc.*, 1980, **102**, 5085. See also S. R. Wilson and R. N. Misra, *J. Org. Chem.*, 1980, **45**, 5079.
[33] K. C. Nicolaou, W. E. Barnette, and P. Ma, *J. Org. Chem.*, 1980, **45**, 1463.

C-9 and C-10 (equation 24)[34] in a transition-state in which a chair-like linking chain is oriented *exo-* with respect to the diene.

Cyclization of tetraene (28) occurred with regioselectivity depending on the nature of the carboxyl function and the solvent to give only *trans*-fused products (equation 25).[35]

$$E = CO_2Et$$

(28)   (29)   (30)

3   :   1
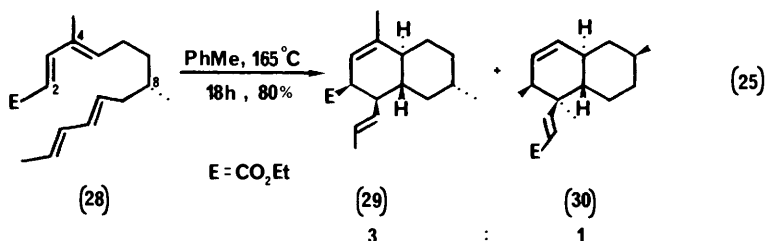
When the cyclization was carried out in boiling water, a 2:3 mixture of (29) and (30) was obtained. This was ascribed to coiling of the lipophilic non-carboxylated diene moiety[36] so as to adopt a conformation disposed towards diene-like rather than dienophilic reactivity. If the free acid or sodium salt corresponding to (28) was cyclized in boiling water, the products corresponding to (29) and (30) were formed in a ratio of 1:8. The predominant formation of (29) in toluene reflects the decreased dienophilic reactivity of trisubstituted olefins. A single diastereomer of (29) arose from the preferred transition-state in which the C-8 methyl group was equatorial in a chair-like linking chain (*vide infra*).

Greater flexibility in this approach may be realized by the use of a *removable* bulky C-3 diene substituent. Thus cyclization of (31) at elevated temperatures gave a single *trans*-fused diastereomer (32) (equation 26).[37]


(31)   (32)

(33)
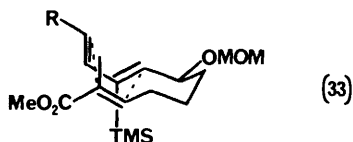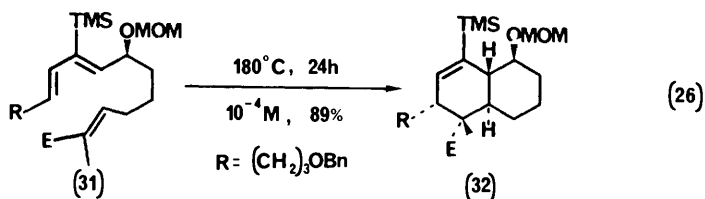
[34] A. P. Kozikowski and S. H. Jung, *Tetrahedron Lett.*, 1986, **27**, 3227.

[35] D. R. Williams, R. D. Gaston, and I. B. Horton III, *Tetrahedron Lett.*, 1985, **26**. 1391. D. R. Williams, M. C. Bremner, D. L. Brown, and J. d'Antoniono, *J. Org. Chem.*, 1985, **50**, 2807.

[36] D. C. Rideout and R. Breslow, *J. Am. Chem. Soc.*, 1980, **102**, 7816.

[37] R. K. Boeckman, jun. and T. E. Barta, *J. Org. Chem.*, 1985, **50**, 3241.

The *trans-* and diastereospecificity resulted from the favouredness of transition-state (33) in which non-bonded interactions and $A_{1,3}$ strain[38] were minimized by the equatorial disposition of the OMOM group in the chair-like linking chain. Although triene (31) was much less reactive towards cyclization than the 'desilylated' analogue,[10] the observed specificity represented a 600-fold increase (*vide infra*). Removal of the trimethylsilyl stereocontrol group was readily accomplished in high yield. Use of bromine instead of silicon at the appropriate position of the diene was less effective in controlling the stereochemistry at the ring junction, although *cis-*and *trans-*products (34) and (35) were both formed as single diastereomers (equation 27).[39]

$$E = CO_2Me$$
$$R = CH=CHCH_2OTMS$$

(34)   (35)

55   :   45

(27)
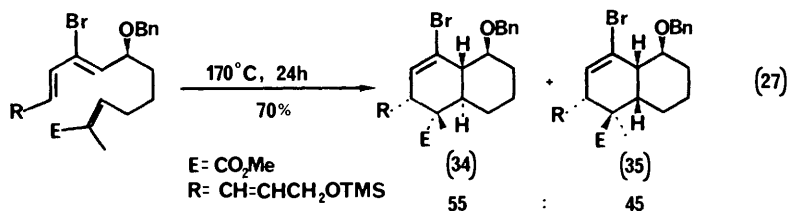
Formation of *cis-*fused (35) may proceed *via* a transition-state (36) in which the benzyloxy group is axial, presumably so as to minimize non-bonded interactions with the bulky halogen. Alternatively a boat-like transition-state (37) may be implicated (*vide infra*).

(36)   (37)
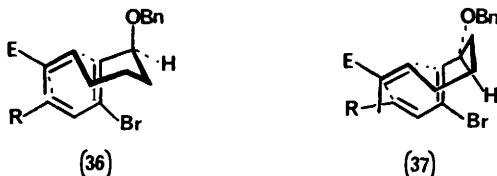
(iii) *Trienes With Substituents on the Linking Chain.* Substituents within the tether linking diene and dienophile may influence the diastereoselectivity of dienophile addition to the non-equivalent diene faces. Triene (38) derived from $(3R)$-$(+)$-citronellol gave a 1:1 mixture of *cis-* and *trans-*fused products upon thermolysis, each as a single diastereomer (equation 28).[40]
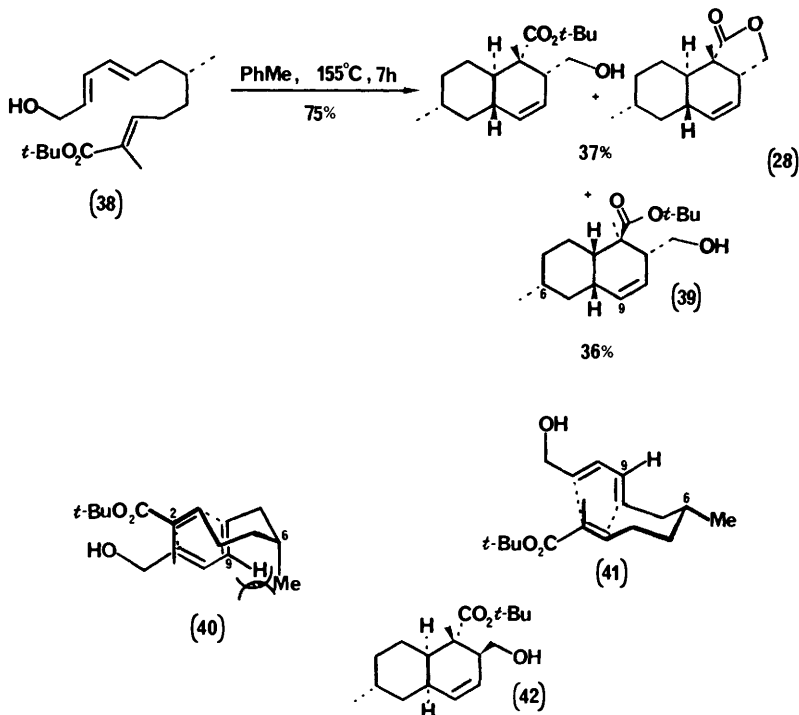
The assignment of structure (39) is however questionable, since it would arise *via* a transition-state (40) in which the C-6 methyl group experiences serious non-bonded interactions with H-9. A likely alternative is (42), arising from the more favoured transition-state (41), although formation of (39) could arguably proceed through a boat-like transition-state in which the C-6 methyl group is pseudo-equatorial.

Heterodiene (43) displayed similar diastereospecificity in giving a product

[38] F. Johnson, *Chem. Rev.*, 1968, **68**, 375.
[39] W. R. Roush and M. Kageyama, *Tetrahedron Lett.*, 1985, **26**, 4327.
[40] T. K. M. Shing, *J. Chem. Soc., Chem. Commun.*, 1986, 49.

PhMe, 155°C, 7h

75%

(38)

H CO$_2$t-Bu
OH

37%

(28)

O O

+

O Ot-Bu
OH

6
H 9
(39)

36%

t-BuO$_2$C 2
HO
6
9 H
Me

(40)

OH
9 H
6
t-BuO$_2$C Me

(41)

H CO$_2$t-Bu
OH
H
(42)

bearing an equatorial substituent in the newly formed saturated ring (equation 29).[41]

180°C

92%

(43)

H
O
H

(29)
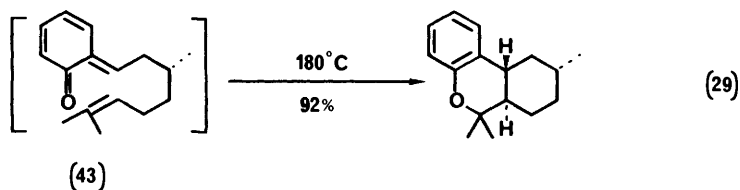
Cyclization of dimethylated triene (44) proceeded to give exclusively the product in which the methyl substituents in the newly formed ring were equatorial (equation 30).[42]

Contrastingly, when the substituents at the corresponding positions were connected to each other, cyclization occurred *via* a transition-state in which these groups were necessarily 1,3-diaxial (equation 31).[43]
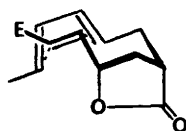
[41] J. J. Talley, *J. Org. Chem.*, 1985, **50**, 1695. See also: G. Sheldrick, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 134; L. Tietze and G. V. Kiedrowski, *Tetrahedron Lett.*, 1981, **22**, 219.

[42] A. Ichihara, H. Kawagishi, N. Tokugawa, and S. Sakamura, *Tetrahedron Lett.*, 1986, **27**, 1347.
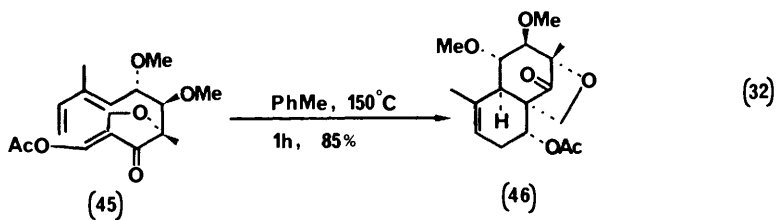
[43] A. Davidson, C. D. Floyd, A. J. Jones, and P. L. Myers, *J. Chem. Soc., Chem. Commun.*, 1985, 1662.

$$\text{(30)}$$

$$E = CO_2Et$$

via

$$\text{(31)}$$
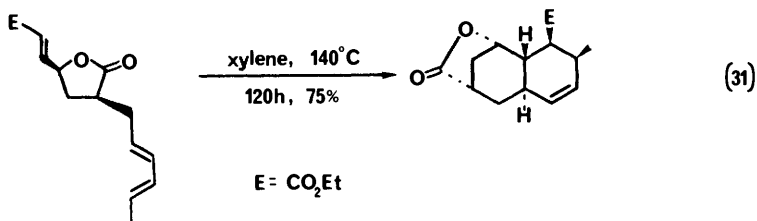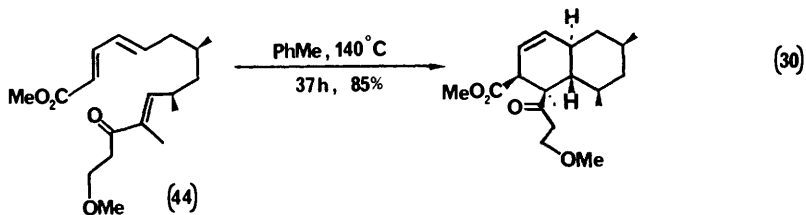
The cyclic triene (45) gave exclusively the *cis*-fused tricycle (46) upon thermolysis, in keeping with some other trienes bearing an internal dienophile-activating group (*vide supra*) (equation 32).[44]

$$\text{(32)}$$

The observed stereospecificity for the *endo*-transition-state, in spite of the proximity of the axial C-6 methoxy function to the C-3 methyl substituent, may indicate more serious non-bonded interactions between the latter and the C-5 methoxy and C-9 substituents in the alternative *exo*-arrangement, as described above (Scheme 4).
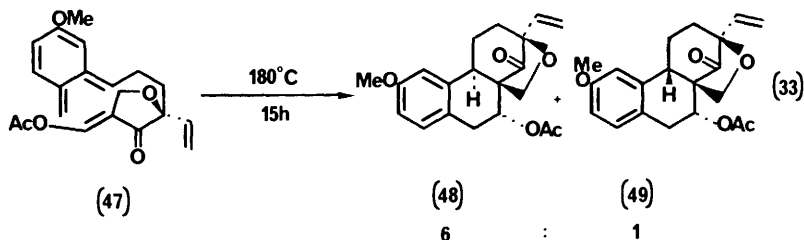
When the C-3 diene substituent formed part of a flat, conjugated π-system as in

[44] K. Shishido, K. Takahashi, Y. Oshio, K. Fukumoto, T. Kametani, and T. Honda, *Tetrahedron Lett.*, 1986, **27**, 1339.
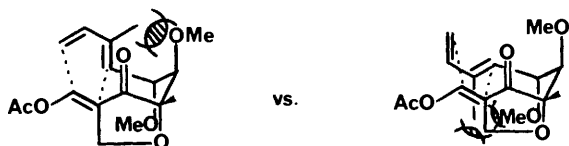
Scheme 4

(47), selectivity was reversed, with the ratio of *exo-* to *endo*-cyclization products (48) and (49) reflecting the differing steric demand of the group (equation 33).[45]


$$(33)$$

If the C-6 methoxyl group in (45) was replaced by a much more sterically demanding pivaloyloxy group as in (50), only the *trans*-fused tricyclic product (51) was formed upon Lewis acid-catalysed cyclization (equation 34).[46]

$$(34)$$
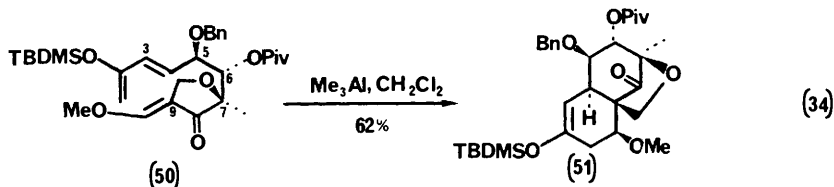
The oxaethano bridge linking C-7 and C-9 in (50) ensured that the bulky C-6 substituent was constrained in an axial disposition. Lewis acid complexation of the enone oxygen may also have served to destabilize the *endo*-transition-state *via* Lewis acid–diene non-bonded interactions.

Incorporation into a rigid cyclic system of substituents bearing a vicinal


$$(35)$$
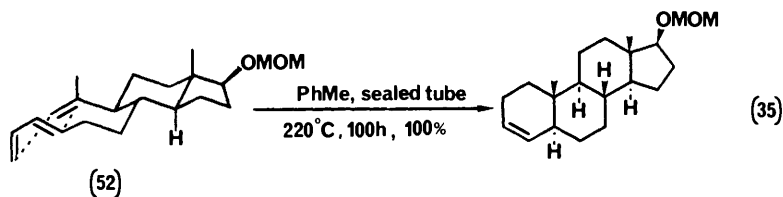
[45] K. Shishido, T. Saitoh, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Chem. Commun.*, 1983, 852; *J. Chem. Soc., Perkin Trans. 1*, 1984, 2139.
[46] R. H. Schlessinger, J.-W. Wong, M. A. Poss, and J. P. Springer, *J. Org. Chem.*, 1985, **50**, 3950.

relationship resulted in cyclization of the steroidal intermediate (52) to give almost entirely the *trans*-fused product (equation 35).[47]

The minor (*ca.* 20%) amounts of *cis*-fused products probably arose from contamination of starting material by some *Z*-triene (*vide infra*). Oxidation of allylic alcohol (53) using Jones's reagent gave the corresponding enone which spontaneously cyclized under the reaction conditions (equation 36).[48]

$$H_2Cr_2O_7, Et_2O$$
$$0°C, 87%$$

(36)

9 : 1
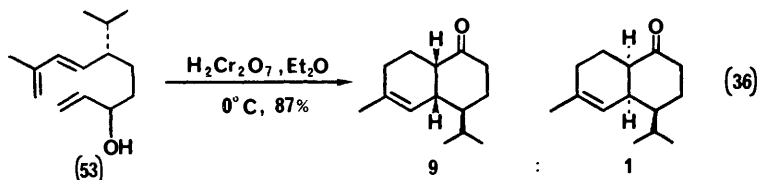
Whilst the *endo*-specificity resulted from secondary orbital interactions becoming significant under the acidic conditions,[49] the observed diastereoselectivity indicates a boat-like transition-state in which the bulky isopropyl group is pseudoequatorially disposed (Scheme 5).

product   disfavoured

Scheme 5
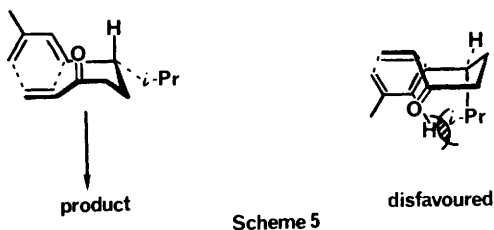
Almost complete *endo*-selectivity was observed in the cyclization of bicyclic triene (54) in the presence of acid (equation 37).[50]

TFA, -78°C
70%

(37)

+ epimer at C - •
(96 : 4)
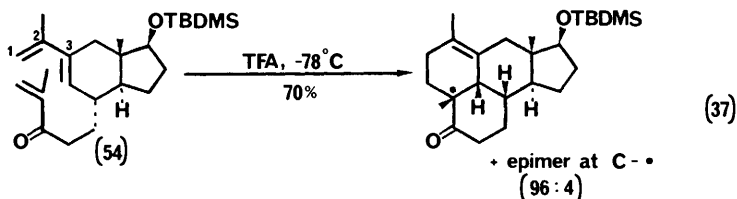
When carried out under thermal conditions, the cyclization gave a 3:2 ratio of products, which may imply non-bonded interactions between the dienophile methyl substituent and the methylene unit attached to C-3. Cyclization onto the α-face of the diene resulted from the α-disposition of the side-chain bearing the dienophilic group.

[47] M. Ihara, I. Sudow, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1986, 117; *J. Org. Chem.*, 1985, **50**, 144.
[48] D. F. Taber and B. P. Gunn, *J. Am. Chem. Soc.*, 1979, **101**, 3992.
[49] K. N. Houk and R. W. Strozier, *J. Am. Chem. Soc.*, 1973, **95**, 4094.
[50] G. Stork, G. Clark, and C. S. Shiner, *J. Am. Chem. Soc.*, 1981, **103**, 4948.

Cyclization of the furan (55) was found to be reversible: the ratio of (56) to (57) after six days at room temperature was 8:1 (61% conversion), whereas heating in boiling benzene for the same time gave a 1:9 product ratio (50% conversion) (Scheme 6).[51]

Scheme 6
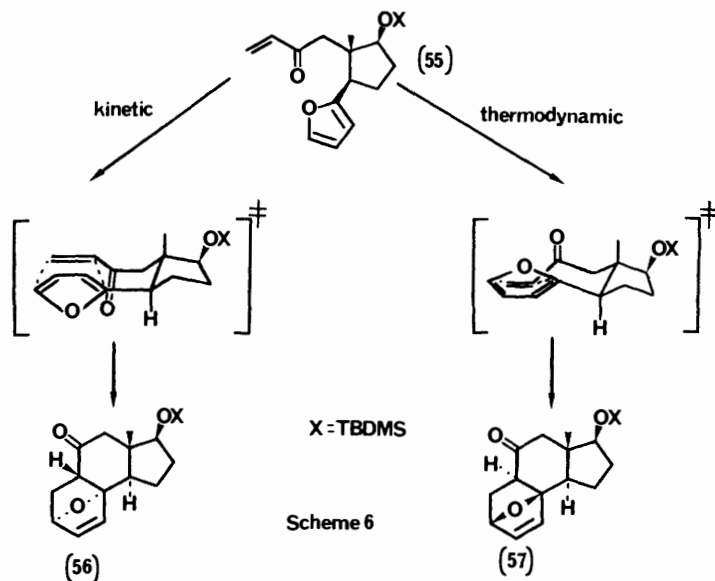
Due to the presence within the linking chain of the dienophile-activating group, bond formation between the diene and dienophile termini is at a more advanced stage than internal bond formation in the transition-state. Calculations show[52] that the most stable conformation of the resulting pseudo-ten-membered ring is the boat–chair–boat arrangement giving rise to the kinetic product (56). The reversible nature of the reaction precludes formation of the highly strained products arising from *endo*-addition of the enone to the furan. This concept of asynchronous bond formation in Diels–Alder reactions will be discussed in more detail below. Strikingly, cyclization of the free alcohol corresponding to (55) was effected by shaking in cold water for 10 min to give exclusively the kinetic product.[53]

Thermolysis of the 3-substituted triene (58) gave a 3.5:1 ratio of *trans*- and *cis*-fused products in which the *trans*-product consisted mainly of the isomer bearing the axial oxygen substituent (equation 38).[54]

Use of Lewis acid catalysts resulted in the exclusive formation of (59). The

[51] L. A. Van Royen, R. Mijngheer, and P. J. de Clercq, *Tetrahedron Lett.*, 1982, **23**, 3283; *Bull. Soc. Chem. Belg.*, 1984, **93**, 1019. See also P. J. de Clercq and L. A. Van Royen, *Synth. Commun.*, 1979, **9**, 771.

[52] J. B. Hendrickson, *J. Am. Chem. Soc.*, 1964, **86**, 4854; *ibid.*, 1967, **89**, 7036.

[53] L. A. Van Royen, R. Mijngheer, and P. J. de Clercq, *Tetrahedron Lett.*, 1983, **24**, 3145; *Tetrahedron*, 1985, **41**, 4667.

[54] R. L. Funk and W. E. Zeller, *J. Org. Chem.*, 1982, **47**, 180.
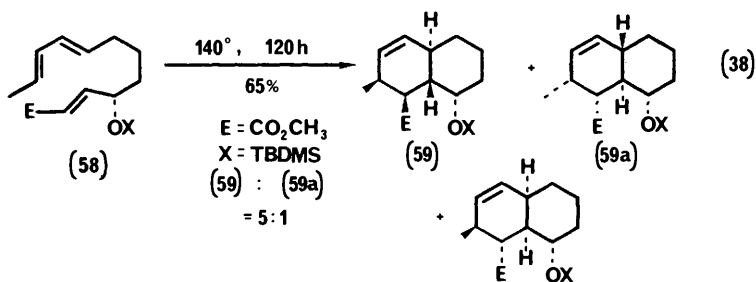
preference to form the product in which the t-butyldimethylsilyloxy group is axial was ascribed to a minimization of non-bonded interactions between H-2 and the H-4 substituent, and to the involvement of a transition-state in which the C-4–O bond is orthogonal to the plane of the adjacent double bond, thereby maximizing $\sigma^*_{C-O}-\pi^*$ overlap and lowering the energy of the dienophile LUMO. With an aldehyde group at the dienophile terminus, Lewis acid-catalysed cyclization proceeded extremely rapidly at low temperatures to give the *trans*-fused isomer with an axial oxygen substituent as the only product.[55] Similar reactivity was displayed when the substituent was allylic with respect to the diene (equation 39), although the nature of the oxygen protecting group had a profound effect on the observed diastereoselectivity (equation 40).
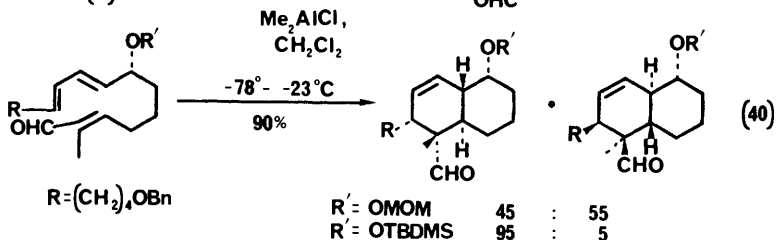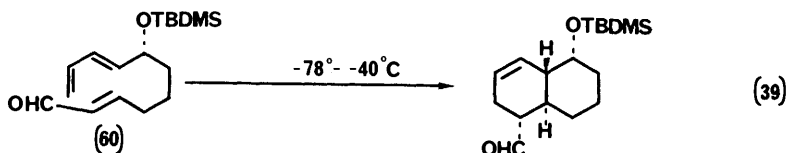

Thermal reactions of carboxylic esters corresponding to (60) gave mixtures of *cis*- and *trans*-fused isomers depending on dienophile geometry. Thus whilst both *E*- and *Z*-dienophilic trienes cyclized to give predominantly *cis*-fused products in which the preference was for an axial C-7 substituent, *E*-dienophilic trienes showed

[55] (a) J. A. Marshall, J. E. Audia, J. Grote, and B. G. Shearer, *Tetrahedron*, 1986, **42**, 2893; (b) J. A. Marshall, J. E. Audia, and J. Grote, *J. Org. Chem.*, 1984, **49**, 5277. See also M. Hirama and M. Uei, *J. Am. Chem. Soc.*, 1982, **104**, 4251.

a tendency towards equatorial C-7 substitution in the *trans*-isomers, and the *Z*-isomers towards axial groups at this position.[10] All of the observed selectivities were low, however. The presence of two oxygen substituents at the 7-position resulted in the predominant formation of *cis*-fused products (equation 41).

(41)

1 : 4
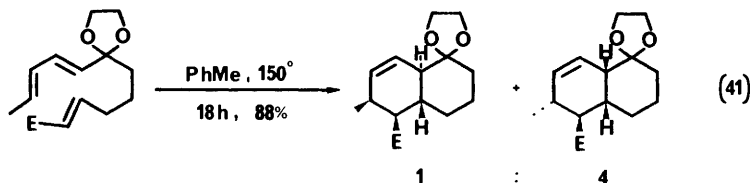
Presumably $A_{1,3}$ strain in the transition-state (61) leading to the *trans*-product disfavours its formation.

(61)
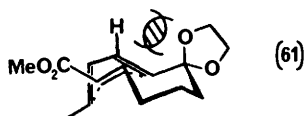
Cyclization of diene (62) gave a *ca.* 2:1 mixture of *trans*- and *cis*-products (equation 42).[10] Coplanarity of the C–O bond with the diene favours the *trans*-transition-state and lowers the energy of the diene HOMO, explaining the decreased reactivity of (62).

(42)

65 : 35

conjugated
isomers
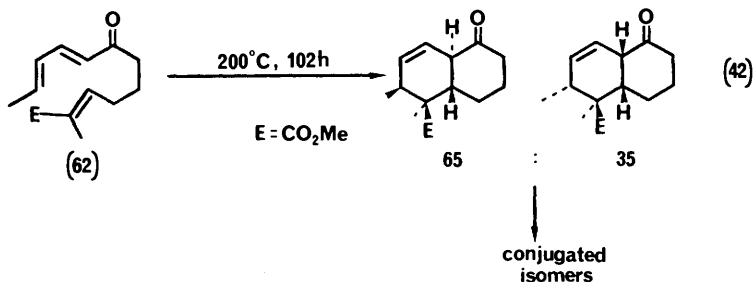
The acetylenic ester (63) cyclized to give a *ca.* 2:1 mixture of diastereomers (equation 43).[56]

The major product presumably arose from a minimization of steric effects in the necessarily boat-like transition-state (64).

A methyl substituent at the C-4 position of enal (65) exerted a powerful directing influence on the mode of cyclization in the presence of Lewis acid (equation 44).[57]

Addition of a C-2 methyl substituent did not affect this specificity, although the more substituted triene was less reactive than (65). The tendency for the C-4

[56] S. E. Hall and W. R. Roush, *J. Org. Chem.*, 1982, **47**, 4611. For a related case in which no diastereoselectivity was observed, see S. D. Burke, T. H. Powner, and M. Kageyama, *Tetrahedron Lett.*, 1983, **24**, 4529.

[57] J. A. Marshall, J. E. Audia, and J. Grote, *J. Org. Chem.*, 1986, **51**, 1155.
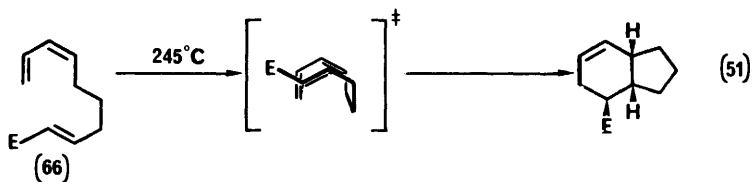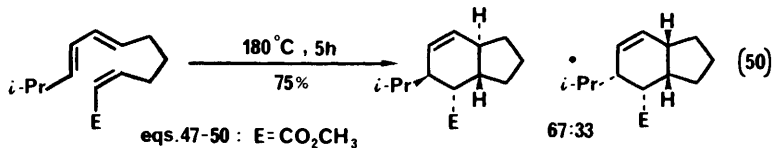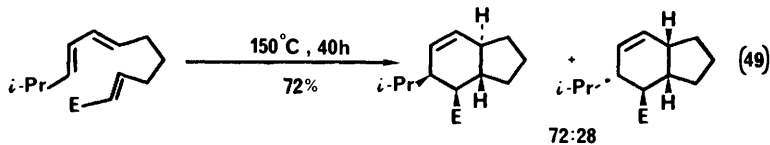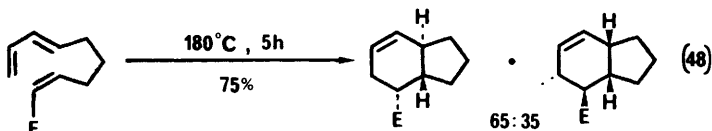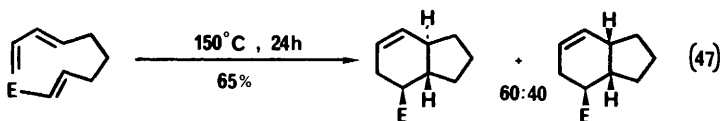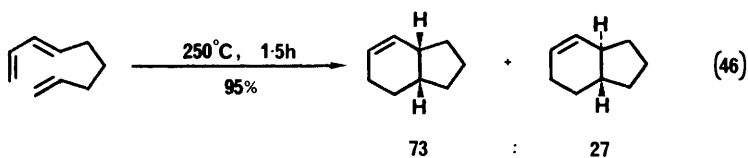
$$(43)$$

$$(64)$$

$$(44)$$
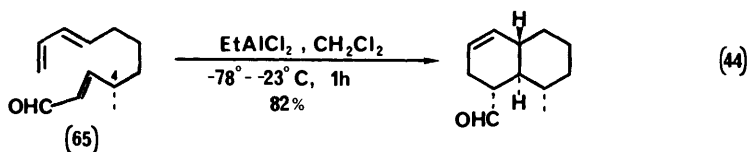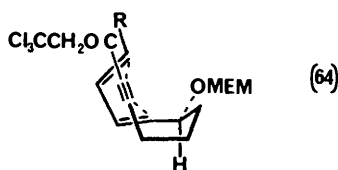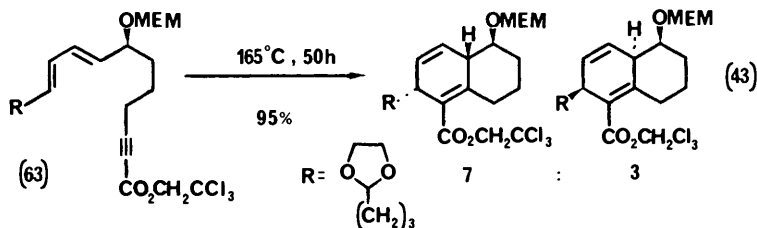
substituent to adopt an equatorial disposition was unchanged by the presence of an axial methyl group at C-6 (equation 45).

$$(45)$$
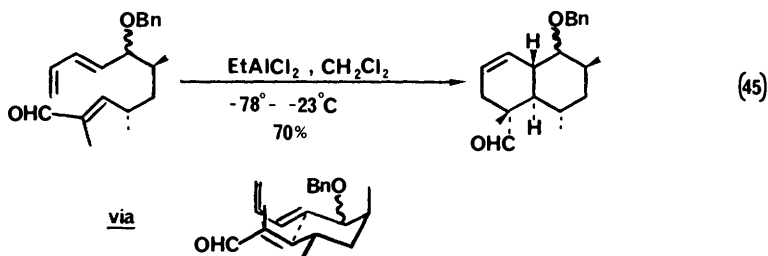
The observed stereoselectivity was correctly predicted by calculations of the energies of the diastereomeric *trans*-products, implying a late or product-like transition-state.

B. Bicyclo[4.3.0]nonanes.—1,3,8-Nonatrienes may cyclize *via* two alternative transition states to form *trans*- or *cis*-fused bicyclo[4.3.0] products.

(i) *Unsaturated and Terminally-substituted Trienes.* Unlike the unsubstituted higher homologue, (*E*)-1,3,8-nonatriene cyclized with moderate selectivity to form a *ca.* 3:1 mixture of *cis*- and *trans*-fused products (equation 46).[4]

207

X = dienophile - activating group

$$73 : 27 \tag{46}$$

$$60:40 \tag{47}$$

$$65:35 \tag{48}$$

$$72:28 \tag{49}$$

$$67:33 \tag{50}$$

eqs. 47-50 : E = CO$_2$CH$_3$

(66)

$$\tag{51}$$

208
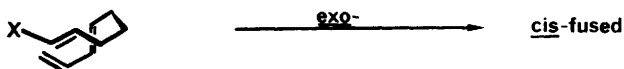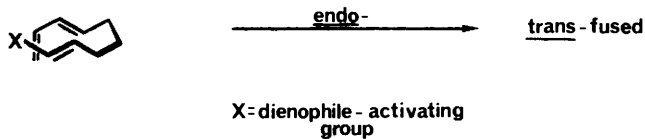
Whilst the major isomer is thermodynamically more favoured, the kinetically controlled nature of the cyclization was demonstrated by the recovery of unchanged bicyclic products after separation and re-subjection to the thermolysis conditions. With a terminal carboxylic ester as the dienophile-activating group, *trans*-selectivity was observed (equations 47 and 48);[58] the presence of a terminal diene substituent resulted in a small increase in the proportion of *trans*-product formed (equations 49 and 50).

As with the decatriene case, dienophile geometry did not greatly affect the stereoselectivity of cyclization. *E,Z*-Diene (66) gave only the *cis*-fused isomer upon thermolysis, reacting at a rate comparable to that of the corresponding *E,E*-geometric isomer (equation 51).[2c] The latter result contrasted with the differing reactivities in intermolecular Diels–Alder reactions which was used as a means of obtaining pure (66) from a mixture with the *E,E*-isomer. Cyclization of the nitrotriene (67) proceeded more rapidly and with greater *trans*-selectivity than the corresponding carboxylic ester, though the *Z,E,E*-isomer gave a *ca.* 1:1 mixture of products (equations 52 and 53).[59]
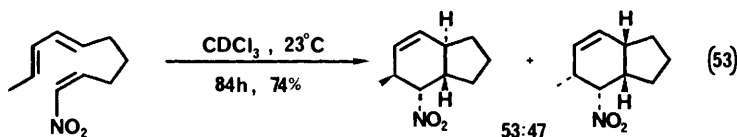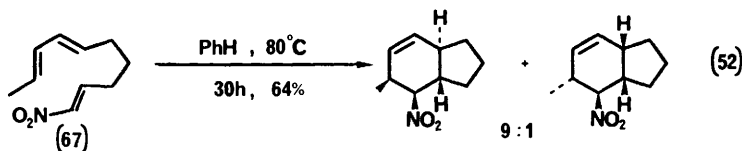
Lewis acid-catalysed IMDA reaction of *E,E*-triene (68) resulted in exclusive formation of the *trans*-fused bicyclic product (equation 54) whereas the *E,Z*-isomer (69) cyclized in low yield with poor stereoselectivity (equation 55).[58b,60]

The same trends were observed for the less reactive trienes in which the diene was terminally substituted, and reflect the insufficient magnitude of Lewis acid-
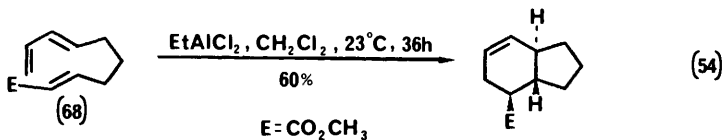
[58] (a) W. R. Roush, A. I. Ko, and H. R. Gillis, *J. Org. Chem.*, 1980, **45**, 4264; (b) W. R. Roush, H. R. Gillis, and A. I. Ko, *J. Am. Chem. Soc.*, 1982, **104**, 2269.

[59] M. J. Kurth, M. J. O'Brien, H. Hope, and M. Yanuck, *J. Org. Chem.*, 1985, **50**, 2626.

[60] W. R. Roush and H. R. Gillis, *J. Org. Chem.*, 1980, **45**, 4267.

$$(55)$$
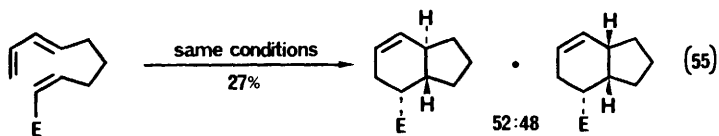
enhanced secondary orbital interactions to overcome the tendency of 1,3,8-nonatrienes with this substitution pattern to form *trans*-fused products.

Lewis acid-mediated cyclization of the enamide (69) occurred with good stereoselectivity, again presumably *via* a chelated intermediate (*vide supra*) (equation 56).[61]
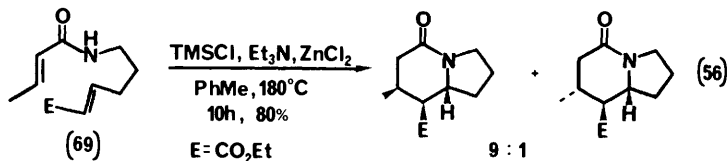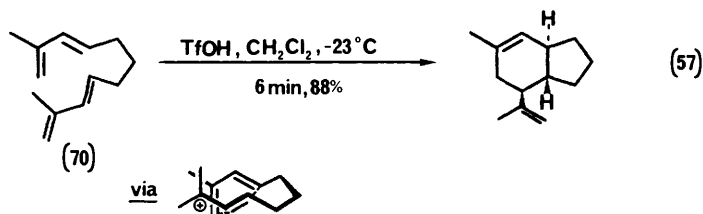

$$(56)$$

Brønsted acid-catalysed cyclization of tetraene (70) gave a single bicyclic diene *via* an *endo*-transition-state (equation 57),[62] although a stepwise, cationic mechanism may also explain this transformation.

$$(57)$$

A related transition-state was invoked to explain the exclusive formation of the *trans*-fused product in the hydrofluoric acid-mediated cyclization of (71) (equation 58).[63]

$$(58)$$
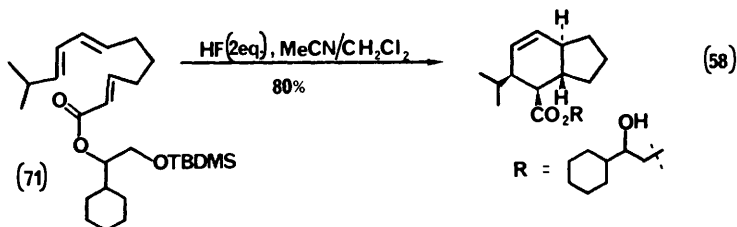
[61] M. Ihara, T. Kirihara, K. Fukumoto, and T. Kametani, *Heterocycles*, 1985, **23**, 1097.

[62] P. G. Gassman and D. A. Singleton, *J. Am. Chem. Soc.*, 1984, **106**, 6085.

[63] W. R. Roush, H. R. Gillis, and A. P. Essenfeld, *J. Org. Chem.*, 1984, **49**, 4674.

The failure of the methyl ether corresponding to (71) (TBDMS = Me) to cyclize under the same conditions indicated the intermediacy of a 1,3-dioxolenium cation which directed the subsequent *endo*-specific ring closure (Scheme 7).
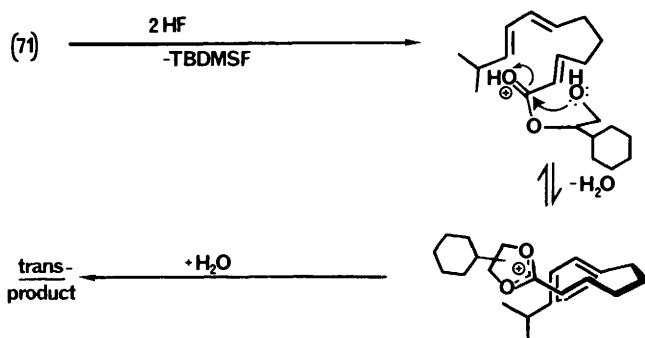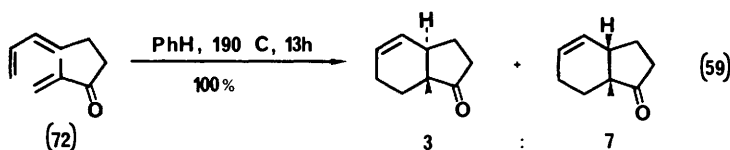

Scheme 7

(ii) *Trienes Containing Internal Olefin Substituents.* Substituted trienone (72) was first reported[64] to give only the *cis*-fused indenone upon thermolysis, although a later paper[65] described more modest selectivity (equation 59).

The non-coplanarity of the carbonyl group with the dienophile in the conformation required for orbital overlap with the diene to occur was used to account for the high temperatures needed to effect cyclization, although the C-8 methyl group may also attenuate reactivity. The preponderance of *cis*-fused product resulted from more advanced peripheral carbon–carbon bond formation in the transition-state, which adopts the more stable *cis*-skewed conformation of the pseudo-nine-membered ring (*vide infra*). The tendency towards predominant
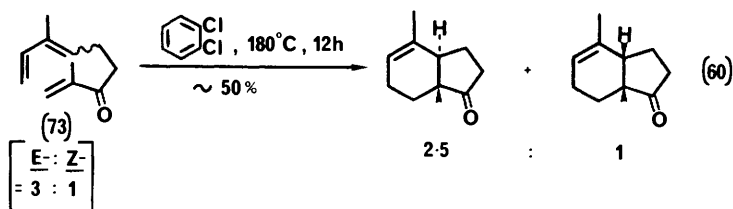
[64] J. J. S. Bajorek and J. K. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1559.
[65] M. E. Jung and K. M. Halweg, *Tetrahedron Lett.*, 1981, **22**, 3929.

formation of *cis*-products from trienes having an internal dienophile activating group was reversed, however, in the case of triene (73) (equation 60).[66]

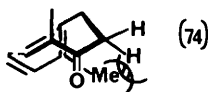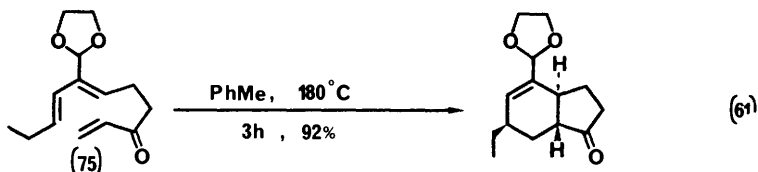Since the *Z*-isomer of (73) may only form the *cis*-fused product upon cyclization (*vide supra*), the *E*-isomer actually gave a 20:1 ratio of *trans*- to *cis*-fused products, a consequence of unfavourable non-bonded interactions in the transition-state (74) leading to the latter.

Similar reactivity was exhibited by the triene (75) substituted at C-3 of the diene (equation 61).[67]

The related substrate (76) showed much lower stereoselectivity in favour of the *cis*-isomer (equation 62).[68]
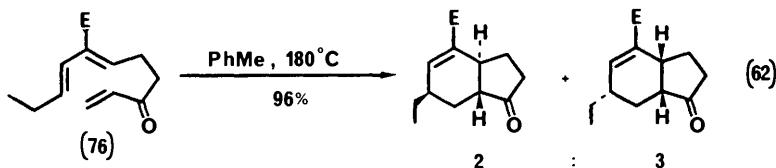
The greater proportion of *cis*-product formed from cyclization of (76) than from (75) presumably reflects the smaller steric bulk of an ethyl ester relative to a 1,3-dioxolane. Activation of the dienophile by two electron-withdrawing groups gave mixtures of *trans*- and *cis*-products with ratios depending on dienophile geometry (equations 63 and 64).[69]

The higher proportion of *cis*-product in the cyclization mixture of (77) may point towards steric interactions between the diene and the dienophile acetyl and methyl substituents in the *trans*-transition-state. The highly reactive doubly-activated triene (78) cyclized at low temperatures to give almost exclusively the *trans*-fused tricyclic product (equation 65).[34]

[66] (a) K. Shishido, K. Airoya, K. Fukumoto, and T. Kametani, *Tetrahedron Lett.*, 1986, **27**, 1167. However, a *trans*:*cis* ratio of 3:7 has also been claimed for this cyclization; (b) D. F. Taber, C. Campbell, B. P. Gunn, and I.-C. Chiu, *Tetrahedron Lett.*, 1981, **22**, 5141. For a very recent example of high *trans*-selectivity resulting from a C-3 diene methyl substituent, see K. Takada, M. Sato, and E. Yoshii, *Tetrahedron Lett.*, 1986, **27**, 3903.

[67] A. Ichihara, R. Kimura, S. Yamada, and S. Sakamura, *J. Am. Chem. Soc.*, 1980, **102**, 6353.

[68] M. E. Jung and K. M. Halweg, *Tetrahedron Lett.*, 1981, **22**, 2735.

[69] P. D. Williams and E. LeGoff, *Tetrahedron Lett.*, 1985, **26**, 1367.

$$61°C, 72h \atop 87\% \quad (63)$$

$$83 : 17$$

$$110°C, 180h \quad (64)$$

$$(77) \quad 50 : 50$$

$$50°C, 3h \atop > 70\% \quad trans\text{-}:cis\text{-} \atop =20:1 \quad (65)$$

$$(78)$$
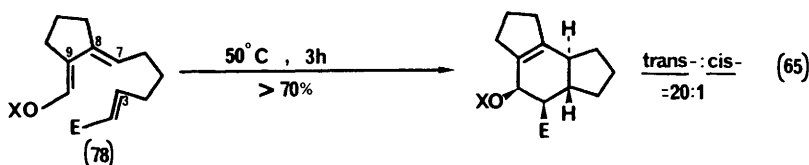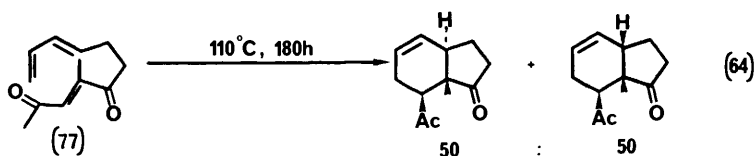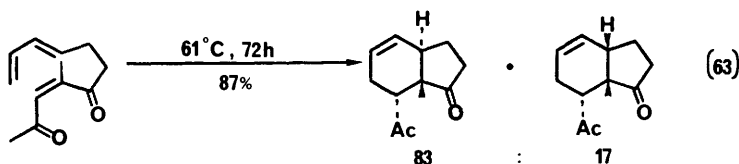
The high selectivity resulted from non-bonded interactions between the C-8–C-9 trimethylene bridge and the linking chain disfavouring the *cis*-transition-state, and from advanced internal (*i.e.* C-3–C-7) bond formation in the transition-state favouring the *trans*-pseudo-cyclopentane ring.

(iii) *Trienes Containing Substituents in the Linking Chain.* Trienes which are disubstituted alpha to the dienophile exhibit enhanced *trans*-selectivity as a consequence of unfavourable steric buttressing between the bulky geminal substituents and the group at C-3 of the diene. Thus, ketal (79) afforded a *ca.* 2.5:1 mixture of *trans*- and *cis*-products upon thermolysis in contrast with the related enone (*vide supra*) (equation 66).[65]

$$PhMe, 170°C, 24h \atop 98\% \quad (66)$$

$$(79) \quad 72 : 28$$
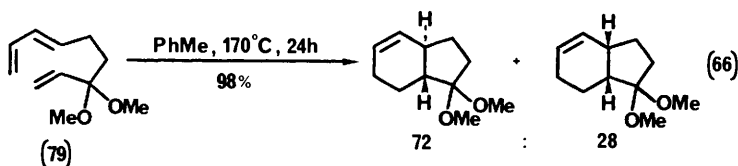
The 1,3-dioxane corresponding to (79) gave a similar product mixture,[70] whilst a related 1,3-dithiane was less stereoselective (equation 67).[71]

[70] S. A. Bal and P. Helquist, *Tetrahedron Lett.*, 1981, **22**, 3933.
[71] M. E. Jung and K. M. Halweg, *Tetrahedron Lett.*, 1984, **25**, 2121.
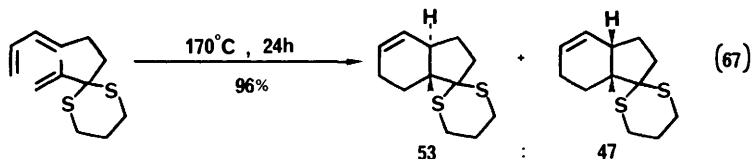
Dienophile-activated trienes bearing single substituents on the position allylic to the dienophile give mixtures of diastereomers on cyclization. *E,E*-Triene (80) showed moderate *trans*-selectivity, although diastereoselectivity for both isomers was poor (equation 68).[72]

In contrast, *E,Z*-triene (85) showed enhanced *trans*-selectivity with both products being formed as single diastereomers (equation 69).[72]

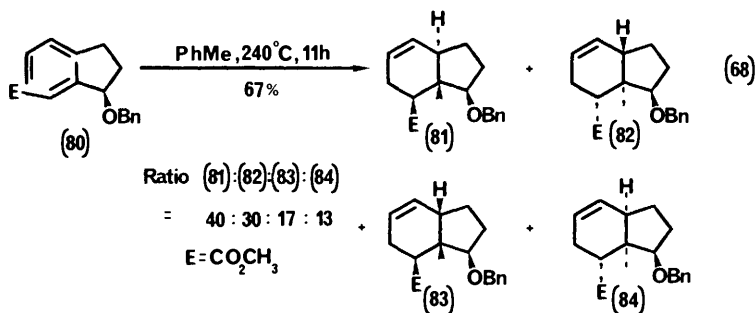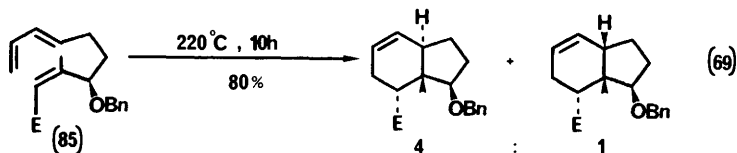The diastereospecificity clearly resulted from a minimization of $A_{1,3}$ strain between the ester and benzyloxy groups (Scheme 8).

Such interactions are absent in the case of *E,E*-triene (80), accounting for the low diastereoselectivity; the poorer *trans*-selectivity may be a consequence of non-bonded interactions between the diene and the ester and the C-3 methyl substituent in the *endo*-transition-state (*cf.* equations 63 and 64). Activation of the dienophile by an internal electron-withdrawing substituent which was not part of the linking chain gave predominantly the *cis*-product [66b,72] despite the presence of a C-3 diene methyl substituent in one of the cases studied.

Thermolysis of the substituted cyclopentenone (86) gave exclusively the product in which the newly formed ring junction was *cis*-oriented (equation 70).[73]

[72] W. R. Roush and S. M. Peseckis, *J. Am. Chem. Soc.*, 1981, **103**, 6696.
[73] M. Ihara, A. Kawaguchi, M. Ihichiro, K. Fukumato, and T. Kametani, *J. Chem. Soc., Chem. Commun.*, 1986, 671.

E=CO$_2$CH$_3$

product   **Scheme 8**

(70)
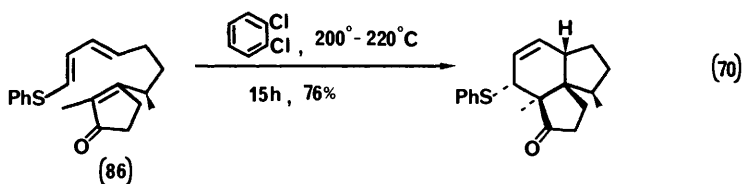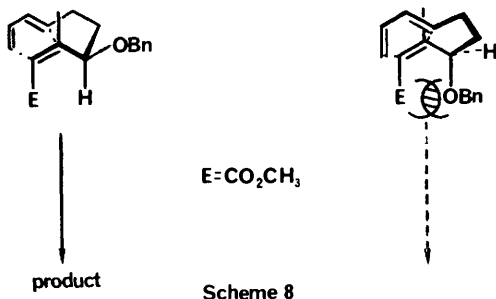
This result contrasts with the normally observed tendency for trienes having this substitution pattern to form *trans*-ring fusions (*e.g.* equation 65), and may be due to interactions between the diene and the cyclopentenone ring disfavouring the expected *endo*-transition-state (87). A$_{1,3}$ strain in the diastereomeric *exo*-transition-state (88) precludes its involvement, and (89) is the preferred conformation.
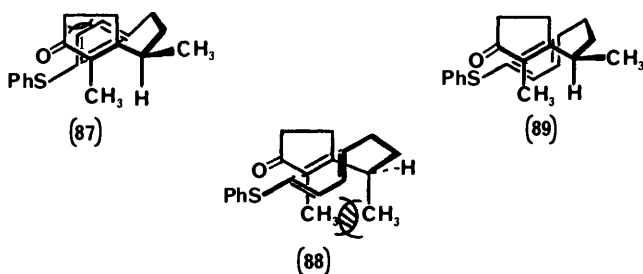
The thermal IMDA reaction of (90), in which the dienophilic group has the *Z*-geometry gave exclusively the product of *exo*-addition with a *trans*-ring-fusion,

(71)

215
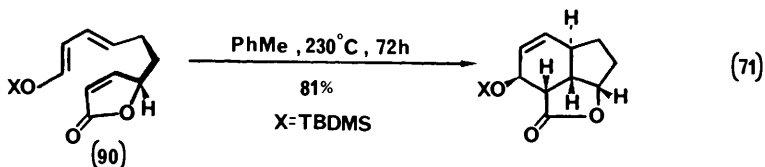
the diastereofacial specificity of addition being determined by the stereochemistry at C-4 (equation 71).[74]

The *E,Z*-triene corresponding to (90) predictably gave the all *cis*-fused product (91) upon thermolysis.

Enone (92) gave the *endo*-product (93) as a single isomer upon prolonged heating at high temperatures (equation 72).[75]
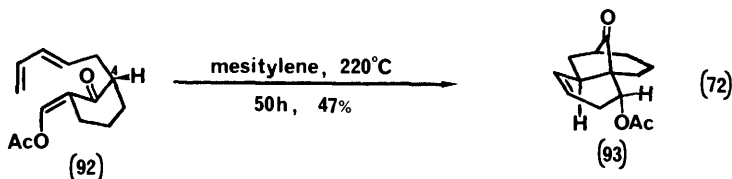
C-4 stereochemistry determined the diastereospecificity, whilst *endo*-selectivity was enhanced by diene–trimethylene ring steric interactions in the alternative *exo*-transition-state.

Trienes substituted in the position allylic to the diene cyclize to give mixtures of *trans*- and *cis*-fused bicyclic products with varying diastereoselectivity. The terminally substituted triene (94) cyclized under therma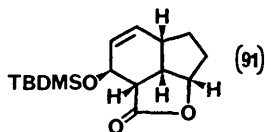l conditions to give mostly the *trans*-product with moderate diastereoselectivity for both *trans*- and *cis*-isomers (equation 73).[76]
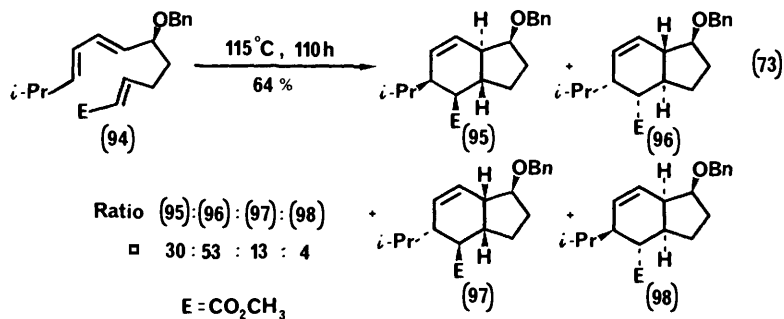
[74] S. D. Burke, D. R. Magnin, J. A. Oplinger, J. P. Baker, and A. Abdelmagid, *Tetrahedron Lett.*, 1984, **25**, 19.

[75] K. Shishido, K. Hiroya, Y. Ueno, K. Fukumoto, T. Kametani, and T. Honda, *J. Chem. Soc., Perkin Trans. 1*, 1986, 829; *Chem. Lett.*, 1984, 1653; K. Shishido, K. Hiroya, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1986, 837.

[76] W. Roush, *J. Org. Chem.*, 1979, **44**, 4008; *J. Am. Chem. Soc.*, 1978, **100**, 3599; 1980, **102**, 1390.

The preferred *trans*-diastereomer resulted from destabilizing $A_{1,3}$ strain in the alternative transition-state leading to (95), the same reason accounting for the 3:1 ratio of (97):(98) (Scheme 9).

E=CO$_2$Me

(96) (95) (97) (98)
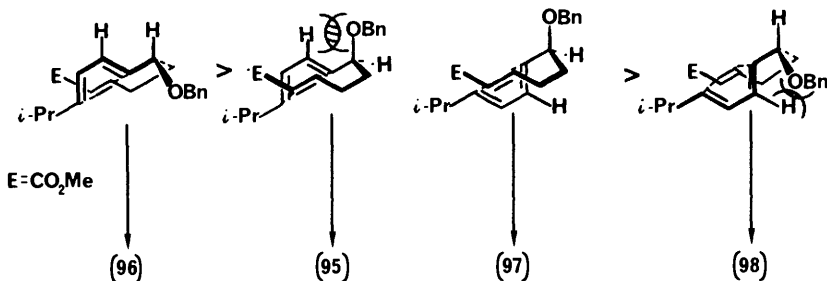
Scheme 9

Cyclization of the isomeric substrate (99) again gave mixtures of products although the predominant *trans*-product was that in which the benzyloxy group was pseudo-axial. Similar product ratios were obtained upon thermolysis of *E,E*-nitrotriene (100), and with a benzenesulphonyl group alpha to the diene complete *trans*-selectivity was realized with a 9:1 diastereomeric ratio (equation 74),[89] although the major product possessed a pseudo-equatorial benzenesulphonyl group.
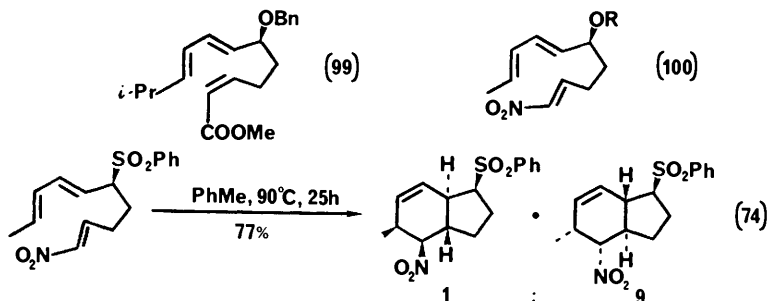
Alkyl substituents at the diene allylic position also have a diastereo-directing influence on IMDA reactions. Triene (101) cyclized to give predominantly the *trans*-fused product in which the ethyl group was pseudo-equatorial, other isomers forming less than 10% of the product mixture (equation 75).[77]

endo-Selectivity was better with R = MEM than TBDPS,[77a] pointing towards the significance of non-bonded interactions between the terminal diene substituent

[77] (a) M. P. Edwards, S. V. Ley, and S. G. Lister, *Tetrahedron Lett.*, 1981, **22**, 361; (b) K. C. Nicolaou and R. L. Magolda, *J. Org. Chem.*, 1981, **46**, 1506; (c) W. R. Roush and A. G. Myers, *ibid.*, 1981, **46**, 1509. See also S. R. Attah-Poku, F. Chau, V. K. Yadav, and A. G. Fallis, *J. Org. Chem.*, 1985, **50**, 3418.

$$R = TBDPS, MEM$$
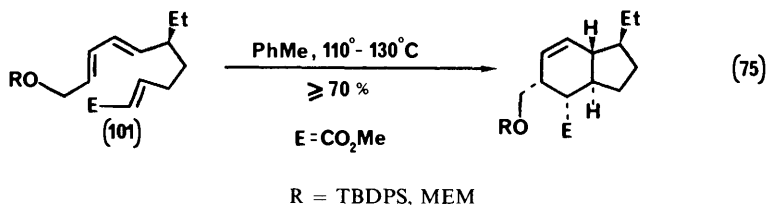
and the ester in the *endo*-transition state. Substitution of a bulky trimethylsilyl group at C-8 resulted in diastereo- and *endo*-specific cyclization *via* a transition-state (102) in which $A_{1,3}$ strain and non-bonded interactions were minimized.[37]
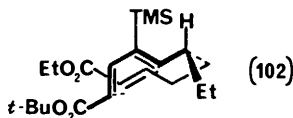
(iv) *Trienes with geminal Substituents in the Linking Chain.* 1,3,8-Nonatrienes geminally substituted at the 6-position display enhanced reactivity in relation to the unsubstituted analogues. Trienes (103) underwent thermal IMDA reactions to give solely the *trans*-fused isomers (equation 76).[78]

Isomerization of the double bond occurred under the reaction conditions to give the thermodynamically more stable isomer in which the unsaturation was 'opposite' the *trans*-ring fusion.[79] The rate of cyclization was observed to be approximately four times greater than in the unsubstituted case, reflecting the sm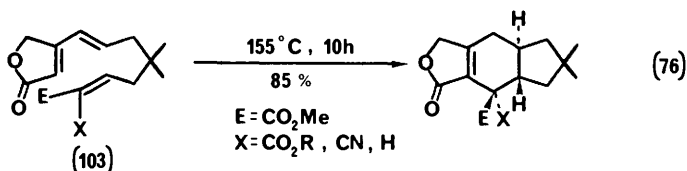aller population of unreactive rotameric forms as a result of steric interactions with the geminal substituents. Interestingly, addition of a second ester group to (103) (X = COOR) resulted in a surprisingly small increase in the rate of cyclization; this was interpreted in terms of non-coplanarity of the two ester π-systems (steric inhibition of resonance). The use of very bulky *E*-dienophilic esters did not affect the *trans*-specificity, indicating the unimportance of non-bonded interactions between the ester and the butenolide methylene, in contrast to some of the findings described above. This was interpreted in terms of the asymmetric stretch mode of the asynchronicity of the IMDA reaction (*vide infra*). In contrast, the substituted *Z*-dienophilic triene (104) gave a 1:1 mixture of *cis*- and isomerized *trans*-products (equation 77).[80]

[78] R. K. Boeckman, jun. and S. S. Ko, *J. Am. Chem. Soc.*, 1982, **104**, 1033.
[79] (a) R. Burcourt, *Bull. Soc. Chim. Fr.*, 1963, 1262; (b) A. A. Akhrem and A. Yu Titov, 'Total Steroid Synthesis', Plenum Press, New York, 1970, pp. 48–50.
[80] R. K. Boeckman, jun. and S. S. Ko, *J. Am. Chem. Soc.*, 1980, **102**, 7146.

$$\text{(77)}$$
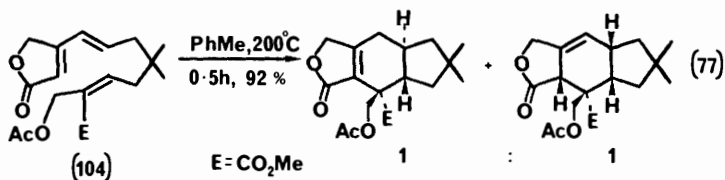
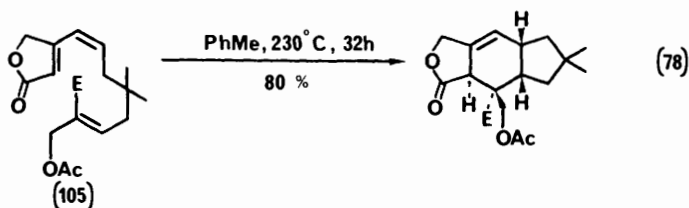The formation of some *cis*-fused product may indeed indicate non-bonded interactions between the acetoxymethyl group and the butenolide methylene in the *exo*-transition-state giving rise to the *trans*-fused product. Pure *cis*-fused tricyclic lactone was formed when the triene (105) was heated (equation 78).[81]

$$\text{(78)}$$

Compound (105) cyclized about forty times more slowly than the isomeric (104), although [1,5] sigmatropic hydrogen shifts[28] did not compete significantly with the cyclization. That the position of the geminal substituents on the chain linking diene and dienophile is important was demonstrated by a comparison of the rates of cyclization of the substituted cyclopentadienes[82] (106) and (107) (equations 79).[83]

$$\text{(79)}$$
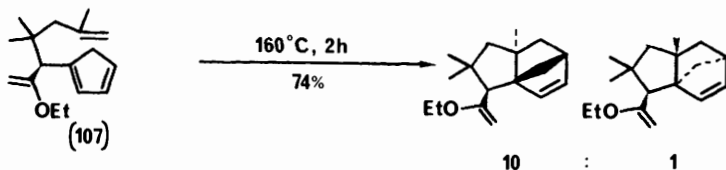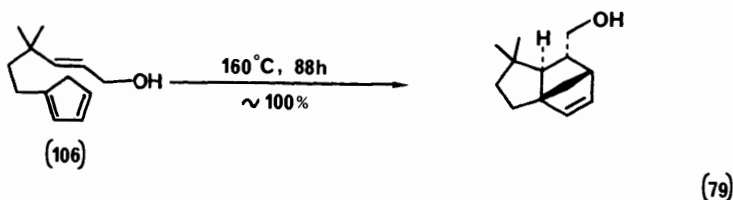
The stereocontrolling influence of the ethoxyvinyl group allylic to the diene may

[81] R. K. Boeckman, jun. and T. R. Alessi, *J. Am. Chem. Soc.*, 1982, **104**, 3216.

[82] D. D. Sternbach, J. W. Hughes, and D. F. Burdi, *J. Org. Chem.*, 1984, **49**, 201.

[83] (a) D. D. Sternbach, J. W. Hughes, D. F. Burdi, and R. M. Forstot, *Tetrahedron Lett.*, 1983, **24**, 3295; (b) D. D. Sternbach, J. W. Hughes, D. F. Burdi, and B. A. Banks, *J. Am. Chem. Soc.*, 1985, **107**, 2149.

be rationalized by a consideration of the diastereomeric transition-states (108) and (109), of which (108) is preferred due to minimization of $A_{1,3}$ strain.

(108)   (109)

Whilst the substituted cyclopentadienes (106) may clearly isomerize *via* [1,5] hydrogen shifts, only the isomers shown undergo IMDA reactions. The exclusive formation of isomers in which the linking chain is *exo-* with respec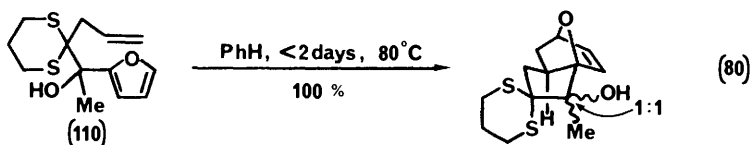t to the diene is similarly well-established.[84] Similar effects ascribable to geminal C-6 substituents were observed in the IMDA reactions of 2-substituted furans. The 1,3-dithiane function in (110) was crucial to IMDA reactivity, as its replacement with a benzyloxy and a methyl group rendered the furan unreactive (equation 80).[85]

(80)

Catalysis of the reaction in aqueous medium using β-cyclodextrin may have been a result of the forced proximity of the reacting centres in the catalyst cavity or of inclusion of the 1,3-dithiane group, generating the effect of two extremely bulky geminal substituents.[86] The unique ability of the 1,3-dithiane moiety to accelerate these reactions may stem from its rigidity, and from the larger C–S bond length and smaller Van der Waals radius of sulphur *versus* methyl, thereby minimizing non-bonded interactions with the substituent alpha to the diene.[87]

Cyclization studies of the furan (111) yielded information about the relative stereo-directing tendencies of substituents alpha to the diene and dienophile (equation 81).[88]

(81)

(111)   (112)
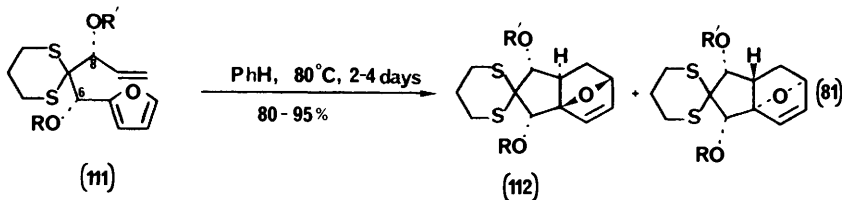
[84] (a) E. J. Corey and R. S. Glass, *J. Am. Chem. Soc.*, 1967, **89**, 2600; (b) E. G. Breitholle and A. G. Fallis, *Can. J. Chem.*, 1976, **54**, 1991; *J. Org. Chem.*, 1978, **43**, 1964.
[85] D. D. Sternbach and D. M. Rossana, *Tetrahedron Lett.*, 1982, **23**, 303.
[86] D. D. Sternbach and D. M. Rossana, *J. Am. Chem. Soc.*, 1982, **104**, 5853.
[87] D. D. Sternbach, D. M. Rossana, and K. D. Onan, *Tetrahedron Lett.*, 1985, **26**, 591.
[88] D. D. Sternbach, D. M. Rossana, and K. D. Onan, *J. Org. Chem.*, 1984, **49**, 3427.

Less sterically demanding R and R′ groups gave mixtures of diastereomeric tricyclic products, but bulky groups such as tetrahydropyran-2-yl and benzyl promoted the exclusive formation of (112) *via* a transition-state (113) in which the C-8 substituent was pseudo-equatorial.

(113)   (114)
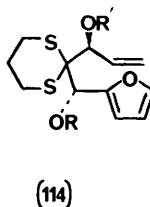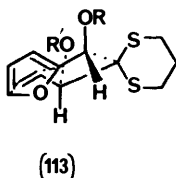
A similar preference for a pseudo-equatorial OR′ group was displayed by the isomeric furan (114).

It may be seen from the examples cited that bicyclo[4.4.0] and -[4.3.0] carbocyclic systems may be obtained with high levels of stereocontrol by the cyclization of an appropriately designed triene precursor. A summary of the general stereochemical features of these reactions is presented below.

Bicyclo[4.4.0] *systems.*

(i) Thermal cyclization reactions of unsubstituted or terminally substituted 1,3,9-decatrienes exhibit low stereoselectivities.

(ii) For thermal reactions, product ratios are essentially independent of dienophile geometry; secondary orbital interactions do not control product stereochemistry.

(iii) Lewis acid- and metal enolate-mediated cyclization reactions of trienes containing an electron-withdrawing group on the dienophile are highly stereoselective, giving rise to products formed *via* transition-states in which the dienophile-activating and diene groups are *endo*. Product ratios are governed by dienophile geometry, and secondary orbital interactions between the diene and the dienophile account for the observed stereoselectivities.

(iv) 1,3,9-Decatrien-8-ones cyclize readily at low temperatures to give *cis*-fused bicyclic ketones formed *via* an *endo*-transition-state.

(v) Bulky C-3 diene substituents promote high *trans*-selectivity.

(vi) 1,3,9-Decatrienes possessing substituents at both C-3 and C-9 are less reactive than the monosubstituted analogues.

(vii) Trienes substituted in the chain linking diene and dienophile generally cyclize *via* a transition-state in which the substituents are equatorially disposed in a chair-like linking chain. However, oxygen substituents positioned allylically with respect to the diene or dienophile frequently adopt a pseudo-axial disposition.

Bicyclo[4.3.0] *systems.*

  (i) Unsubstituted 1,3,8-nonatrienes cyclize under thermal conditions with moderate selectivity to give predominantly the *cis*-fused isomer. Addition of an electron-withdrawing dienophile substituent reverses the observed selectivity, independently of dienophile geometry.
 (ii) Highly reactive dienophile-activated trienes (and less reactive substrates in the presence of Lewis acids) exhibit high *trans*-selectivity if the geometry of the dienophile is *E*; *Z*-dienophiles show low selectivity.
(iii) Trienes substituted at C-3 of the diene show enhanced *trans*-selectivity.
 (iv) Trienes with substituents which are allylic with respect to the diene or dienophile generally give products in which the substituent is pseudo-equatorial.
  (v) Geminal substitution alpha to the dienophile results in slightly enhanced *trans*-selectivity relative to the unsubstituted analogues.
 (vi) Geminal substitution beta to the dienophile increases triene reactivity.

Both 1,3,9-decatrienes and 1,3,8-nonatrienes possessing a diene group having a *Z*-internal double bond invariably cyclize to give exclusively *cis*-fused products.

3 Heterocyclic Systems

A. Nitrogen-containing Heterocycles.—(i) *Bicyclo*[4.4.0] *Systems.* Oppolzer first observed the stereocontrolling influence of the hybridization of the atoms in the chain linking the diene and dienophile in IMDA reaction substrates. Thus the urethane (115)[89] cyclized to give exclusively the *cis*-fused *N*-carbomethoxy-hexahydroquinoline (equation 82) whilst the amide (116) gave a mixture of *trans*- and *cis*-products (equation 83).[90]

$$\text{(82)}$$

$$\text{(83)}$$
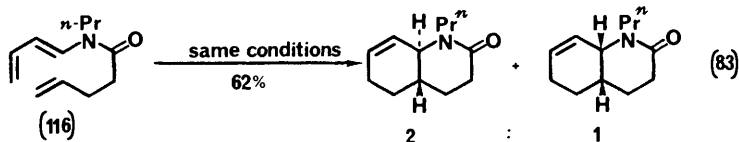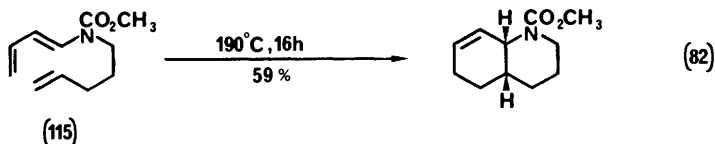
Placement of a methyl group on the dienophile terminus of (115) slowed down the cyclization such that elimination became significantly competitive. It was

[89] W. Oppolzer and W. Frostl, *Helv. Chim. Acta*, 1975, **58**, 587.
[90] W. Oppolzer and W. Frostl, *Helv. Chim. Acta*, 1975, **58**, 590. For a related example in which chain substituents caused formation of the *cis*-isomer exclusively, see P. Magnus and P. M. Cairns, *J. Am. Chem. Soc.*, 1986, **108**, 217.

argued that the favourable conformations in which all the diene and amide orbitals were such as to favour *endo*-cyclization to the *cis*-product from (115), and *exo*-cyclization of (116) to the *trans*-fused isomer. The latter cyclization was said to be less selective due to the *endo*-effect, which would lead to the formation of the *cis*-ring-fusion. These arguments are questionable, however; *endo*-effects due to secondary orbital interactions are unimportant in determining the stereochemistry of cyclizations at such elevated temperatures. If orbital overlap of the nitrogen lone pair with the amide carbonyl introduces some trigonal character at nitrogen, then the favoured transition-states are those in which the C-4 diene proton is vicinally eclipsed by a less sterically demanding acyl, rather than an alkyl carbon atom (Scheme 10).

Scheme 10

cis-   trans-
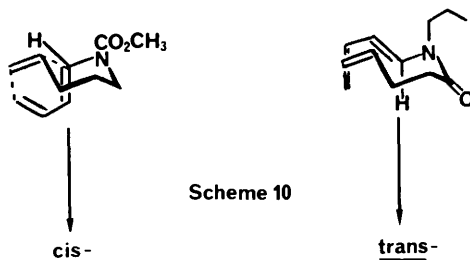
The observed stereoselectivity was utilized in the synthesis of a pumiliotoxin-C precursor in which the observed diastereospecificity implied a boat-like transition-state (117) (equation 84),[91] although the low yield of the cyclization reaction precludes unambiguous assignment of this conformation.
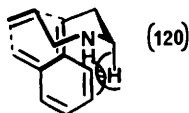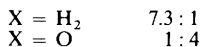

$$\text{PhMe , 215°C , 20h, } 25\%$$ (84)
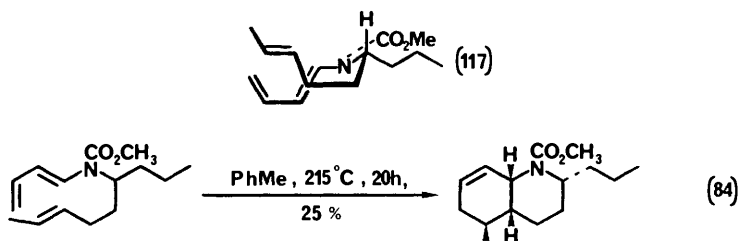
Cyclization of *O*-quinodimethanes formed during thermolysis of benzo-cyclobutanes gave varying amounts of *cis*- and *trans*-products depending on the position and oxidation state of the nitrogen-containing function in the linking chain (equations 85 and 86).[92]

The greater *trans*-selectivity realized from cyclization of (119) ($X = H_2$) than from (118) ($X = Y = H_2$) may arise from the greater degree of steric buttressing between the incipient aromatic ring and a methylene rather than an $-NH-$ group at this position, as in (120).

[91] W. Oppolzer, W. Frostl, and H. P. Weber, *Helv. Chim. Acta*, 1975, **58**, 593. For application to a synthesis of ($\pm$)-chelidonine, see W. Oppolzer and K. Keller, *J. Am. Chem. Soc.*, 1971, **93**, 3836.
[92] W. Oppolzer, *Tetrahedron Lett.*, 1974, **15**, 1001.

(85)

(118)

$$X = Y = H_2 \qquad 2.7 : 1$$
$$X = O, Y = H_2 \qquad 1 : 5.2$$
$$X = H_2, Y = O \qquad 1 : 2$$

(86)

(119)

$$X = H_2 \qquad 7.3 : 1$$
$$X = O \qquad 1 : 4$$

(120)
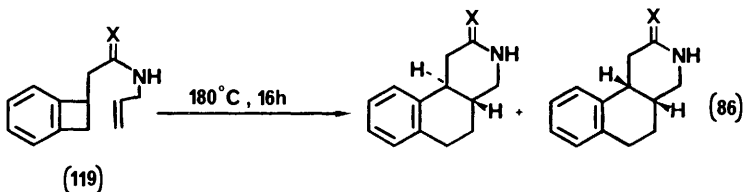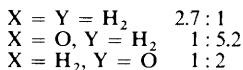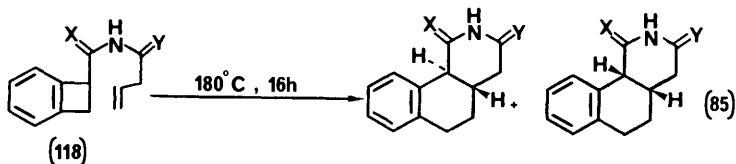
In contrast to (118) (X = O, Y = H$_2$), dienamide (121) gave the *trans*-fused bicyclic amide upon thermolysis, isomerization to the more stable conjugated enamide taking place *in situ* (equation 87).[93]

(87)

DMSO, 190°C, 24h

65-81%

R = Me, Et, *i*-Pr

Ar = MeO

(121)
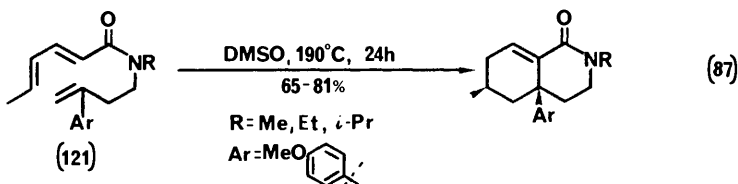
Thermolysis of the *E,Z,E*-diene (122) predictably gave exclusively the *cis*-fused product with the observed diastereoselectivity resulting from the preferred equatorial disposition of the C-6 methyl substituent.[94]

(ii) *Bicyclo*[4.3.0] *Systems.* Thermolysis of the benzocyclobutane (123) resulted in exclusive formation of the *cis*-fused γ-lactam, paralleling the trend observed for the higher homologues (equation 88).[95]

[93] S. Handa, K. Jones, C. G. Newton, and D. J. Williams, *J. Chem. Soc., Chem. Commun.,* 1985, 1362.
[94] S. Wattanasin, F. G. Kathawala, and R. K. Boeckman, jun. *J. Org. Chem.,* 1985, **50**, 3810.
[95] W. Oppolzer, *J. Am. Chem. Soc.,* 1971, **93**, 3833.

$$(88)$$
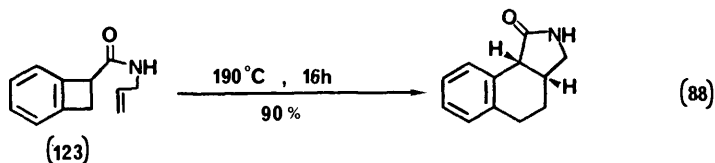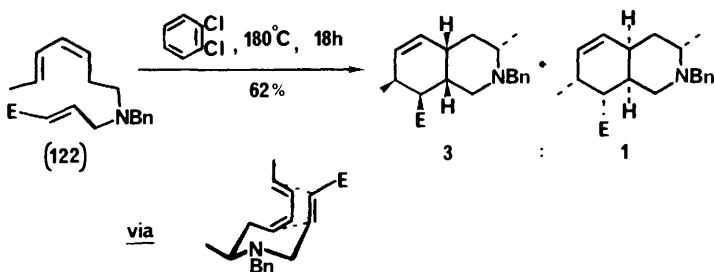
In contrast to the analogous six-membered-ring-forming reaction,[91] amide (124) gave predominantly the *cis*-fused product (equation 89).[96]

$$(89)$$

The lower temperatures required for cyclization of (124) reflect the higher energy of the diene HOMO in the intermediate *O*-quinodimethane, presumably as a result of the absence of delocalization of the nitr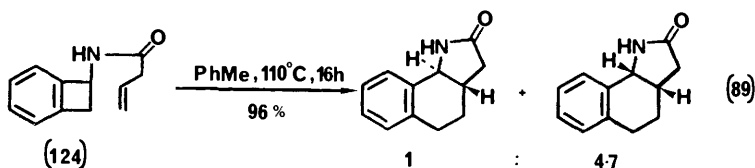ogen lone pair into the carbonyl double bond in the conformation required for cyclization to occur. The intermediacy of an *O*-quinodimethane species was established by observing the rate of racemization of optically active (124).

As expected, terminally activated amide dienophiles show increased reactivity and *trans*-selectivity. The highly reactive amide (125) cyclized spontaneously upon formation at 0 °C, giving exclusively the *trans*-product resulting from an *endo*-transition-state (equation 90).[97]

$$(90)$$
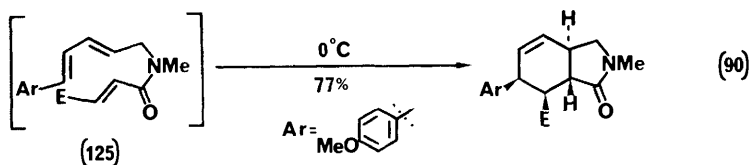
[96] W. Oppolzer. *J. Am. Chem. Soc.*, 1971, **93**, 3834.

[97] H. W. Gschwend and H. P. Meier. *Angew. Chem., Int. Ed. Engl.*, 1972, **11**, 294.

The less activated triene (126) gave mostly *trans*-product upon heating in boiling benzene (equation 91).

$$\text{(91)}$$

15 : 2
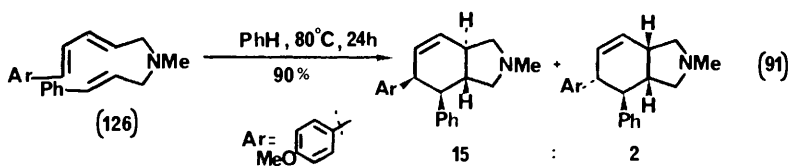
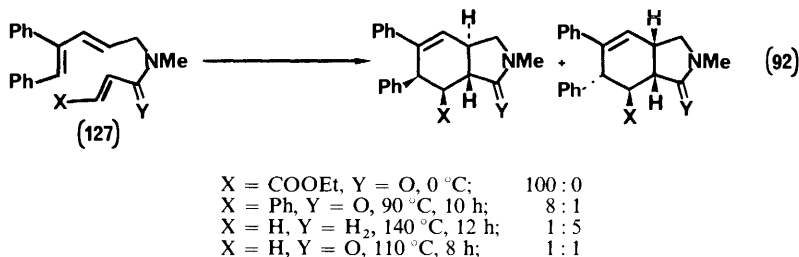With 1,2-diaryl dienes (127), similar trends in reactivity were observed, with activating groups on the dienophile promoting increased *trans*-selectivity (equation 92).[98]

$$\text{(92)}$$

X = COOEt, Y = O, 0 °C;	100 : 0
X = Ph, Y = O, 90 °C, 10 h;	8 : 1
X = H, Y = H$_2$, 140 °C, 12 h;	1 : 5
X = H, Y = O, 110 °C, 8 h;	1 : 1

When the *N*-methyl group in (127) (X = COOEt, Y = O) was replaced with a proton, reactivity decreased sharply. In general, large groups on the amide nitrogen lowered activation energies for the cyclization reactions, presumably by disfavouring unreactive rotamers as discussed above. The comparatively unreactive nature of acrylamides not possessing a terminal dienophile-activating group was ascribed to the non-coplanarity of the C=C and C=O double bonds, thereby causing an increase in the LUMO energy of the dienophile, with consequently poorer HOMO diene–LUMO dienophile overlap.

As with the all-carbon analogues, substituents in the chain linking the diene and dienophile exert a considerable stereocontrolling influence on IMDA reactions. Cyclization of the *Z*-diene (128) gave a single product with complete absolute stereochemical control at the three newly-formed chiral centres (equation 93).[99]

$$\text{(93)}$$
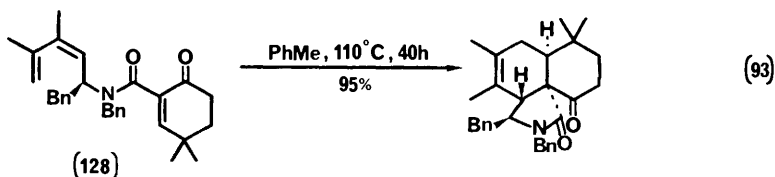
[98] H. W. Gschwend, A. O. Lee, and H. P. Meier, *J. Org. Chem.*, 1973, **38**, 2169.
[99] S. G. Pyne, M. J. Hensel, S. R. Byrn, A. T. McKenzie, and P. L. Fuchs, *J. Am. Chem. Soc.*, 1980, **102**, 5960. For applications to cytochalasin total synthesis, see: S. G. Pyne, M. J. Hensel, and P. L. Fuchs, *J. Am. Chem. Soc.*, 1982, **104**, 5719; S. G. Pyne, D. C. Spellmeyer, S. Chen, and P. L. Fuchs, *ibid.*, 1982, **104**, 5728. Also see M. Yoshioka, H. Nakai, and N. Ohno, *ibid.*, 1984, **106**, 1133.

Consideration of the two possible diastereomeric transition-states reveals considerable non-bonded interactions between the pseudo-axial benzyl group and the diene terminus in the transition-state (129) leading to the unobserved isomer (130).

(129) (130)
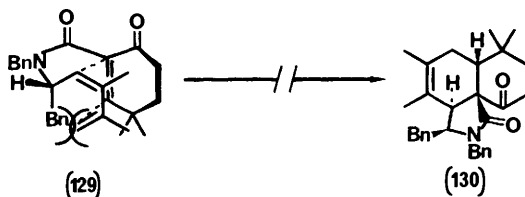
Interestingly, the *E*-triene corresponding to (128) was totally inert to cyclization under the conditions employed. This result serves to demonstrate the utility of *Z*-trienes in securing complete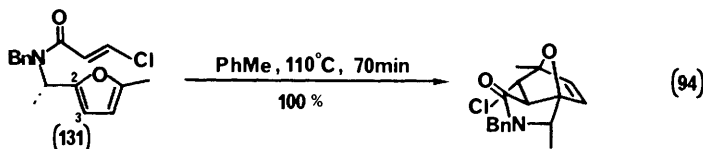 *cis*- and extremely high diastereoselectivity by maximizing non-bonded interactions in the undesired transition-state.

Similar diastereospecificity was displayed when the furan (131) cyclized under relatively mild conditions to give a single *exo*-diastereomer (equation 94).[100]

A strong preference for transition-state (132) was implied by this result; addition of a methoxyl substituent at C-3 of the furan rendered the cyclization completely non-diastereoselective in accord with this model.

(132)

High diastereoselectivity may be attained by the use of removable chiral groups, enabling access to IMDA products with high optical purity. Thus the *R*-phenylglycinol-derived amide (133) underwent internal cycloaddition upon formation of its magnesium salt to give the cyclized product in 76% diastereomeric excess (equation 95).[101]

Chelation by magnesium between the hydroxyl and carbonyl oxygens served the dual purpose of rendering the two faces of the internal dienophile diastereotopic, and accelerating the reaction by increasing the proportion of reactive s-*cis*-rotameric forms.[102]

[100] M. E. Jung and L. J. Street, *J. Am. Chem. Soc.*, 1984, **106**, 8327.

[101] T. Mukaiyama and N. Iwasawa, *Chem. Lett.*, 1981, 29.

[102] T. Mukaiyama, T. Tsuji, and N. Iwasawa, *Chem. Lett.*, 1979, 697.

(95)
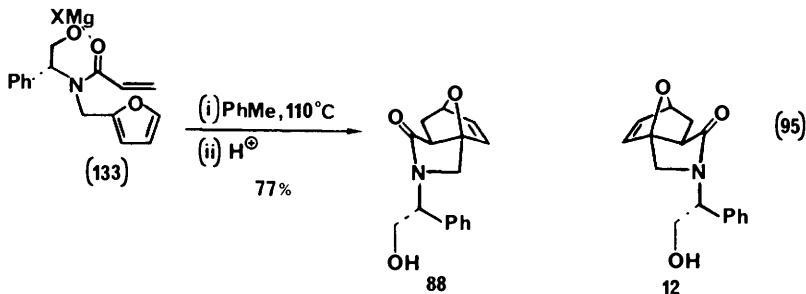
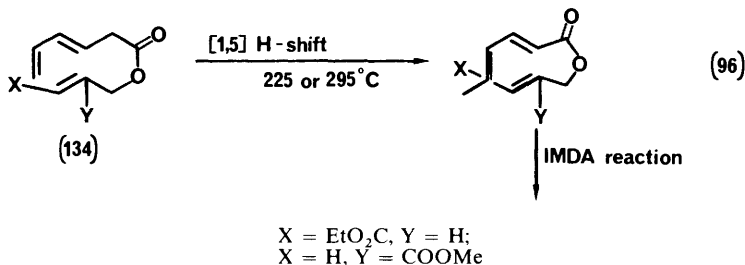**B. Oxygen-containing Heterocycles.**—(i) *Bicyclo*[4.4.0] *Systems*. Trienes (134) containing an ester grouping in the chain linking diene and dienophile were found to be resistant to cyclization, instead isomerizing to the conjugated ester prior to IMDA reaction (equation 96).[103]

(96)

$$X = EtO_2C, Y = H;$$
$$X = H, Y = COOMe$$

The unreactive nature of (134) was explained in terms of an unfavourable lack of overlap of the ester oxygen non-bonding electrons with the carbonyl group in the reactive conformation (135) required for cyclization to occur.[104] That an ester group was the cause of this lack of reactivity, as opposed to solely an ether oxygen, a carbonyl group, or an unusually facile [1,5] hydrogen shift was established by the ready cyclization of trienes (136), (137), and (138) (equations 97, 98, and 99).

(135)
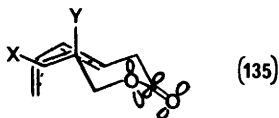
Electron-withdrawing groups on the internal dienophile carbon atom caused preferential formation of the *cis*-fused isomers as previously observed.

[103] R. K. Boeckman, jun. and D. M. Demko. *J. Org. Chem.*, 1982, **47**, 1789.
[104] M. Simonetta and S. Carra, 'General and Theoretical Aspects of the –COOH and –COOR Groups' in 'The Chemistry of Carboxylic Acids and Esters', ed. S. Patai, Wiley, New York, 1969, p. 13.

$$(97)$$

(136)   30 : 70

$$(98)$$

(137)   60 : 40

E = COOEt

$$(99)$$

(138)   25 : 75
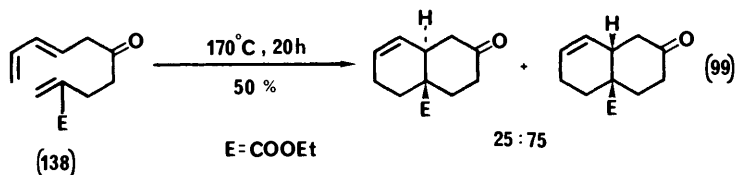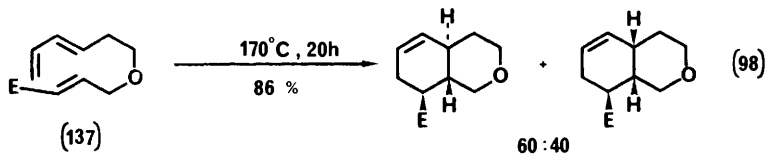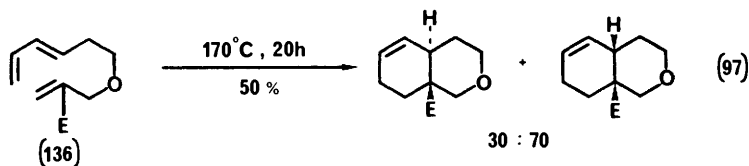
Cyclization of the cyclic trienes (139) occurred *via* approach of the dienophilic group to a single face of the diene to give product mixtures which varied according to the geometry and substitution of the enone moiety (equation 100).[105]
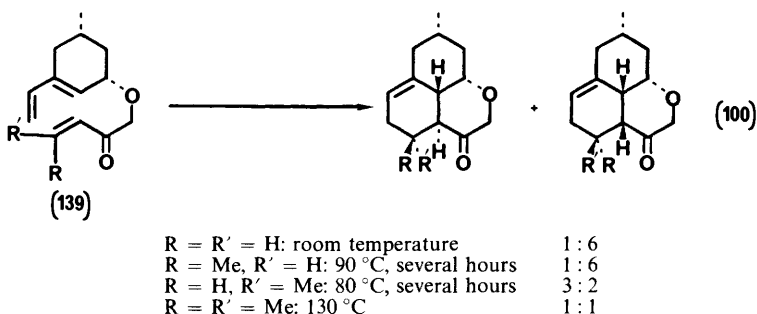

$$(100)$$

(139)

R = R′ = H: room temperature	1 : 6
R = Me, R′ = H: 90 °C, several hours	1 : 6
R = H, R′ = Me: 80 °C, several hours	3 : 2
R = R′ = Me: 130 °C	1 : 1

The *Z*-enone (139) (R = Me, R′ = H) surprisingly gave the *endo*-product predominantly, despite the expected diene–β-methyl non-bonded interactions in the transition state.

Equally striking was the preferred cyclization of (139) (R = H, R′ = Me) to give the *exo*-cycloadduct. Here again, steric interactions appeared to be maximized in the transition-state leading to the preferred product. Whilst the predominance of *cis*-product from cyclization of (139) (R = R′ = H) would be predicted on the basis of secondary orbital interactions at room temperature, the observed

[105] S. J. Hecker and C. H. Heathcock, *J. Org. Chem.*, 1985, **50**, 5159.

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selectivities for the substituted trienes are somewhat puzzling. As expected, disubstitution at the dienophile terminus caused a decrease in reactivity. The acetylenic ketone (140) cyclized at a slower rate than the enones (139) due to the unfavoured boat-like transition-state adopted as a consequence of the linearity of the dienophile (equation 101).
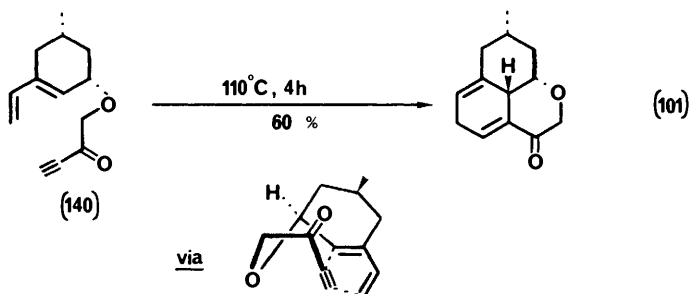
A boat-like transition-state was invoked to explain the diastereospecific formation of the *cis*-fused tricyclic aldehyde upon thermolysis of aldehyde (141) (equation 102).[106]
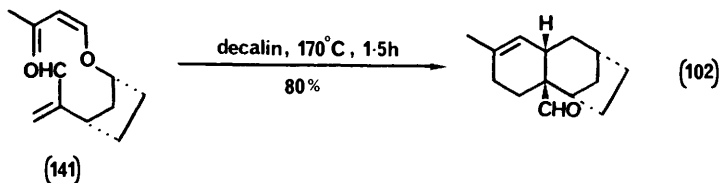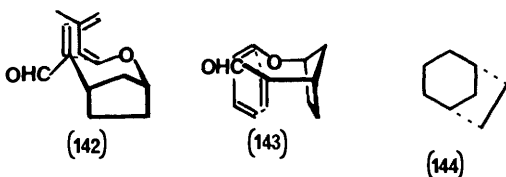

Of the two possible transition-states for the cyclization of (141), (143) was clearly preferred, with the incipient heterocyclic ring adopting a boat-form.


Comparison was made between the implied transition-state conformation and the preferred conformation of the hydrocarbon (144), which suggested that the alternative transition-state (142) would be lower in energy. Since bond formation between the terminal carbon atoms of the diene and dienophile would be expected

[106] M. Koreeda and J. I. Luengo, *J. Org. Chem.*, 1984, **49**, 2079.

to be at a more advanced stage in the transition-state for cyclization of (141) (*vide infra*), a consideration of the preferred conformations of 1,3- bridged ten-membered rings might have been more instructive.

Cyclization of the heterodienophilic triene (145) occurred readily at or below room temperature to give the *endo*-product exclusively (equation 103).[107]

$$(103)$$

$$(145)$$
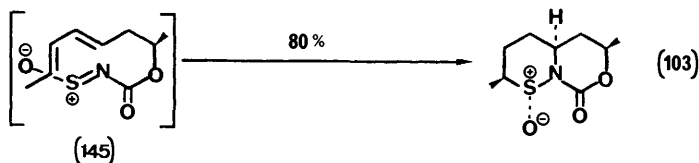
The methyl group in the linking chain accounted for the diastereospecificity; the reaction proceeded *via* a boat-like transition-state (146) in which the methyl group was pseudo-equatorial, 1,2-eclipsing interactions disfavouring the alternative chair-like arrangement (147).[108]

$$(146)$$

$$(147)$$

(ii) *Bicyclo*[4.3.0] *Systems.* Cyclic ethers have been generated with high stereo-selectivity *via* the IMDA reaction. The silylated triene (148) gave only the *exo*-product upon heating in toluene (equation 104).[109]

$$(104)$$

$$(148)$$
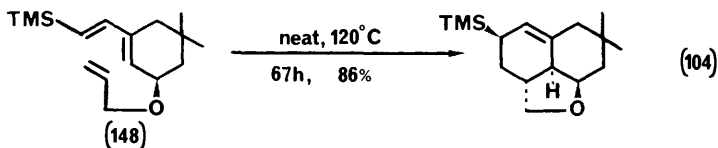
Whilst replacing the geminal methyl groups on the cyclohexane ring with hydrogen atoms had no effect on the reactivity of (148), increasing substitution on the dienophilic group slowed cyclization considerably, with elimination of allylic alcohol increasing significantly.

Cyclization of the related triene (149) also proceeded predominantly *via* an *exo*-transition-state (equation 105).[110]

Allenyl ethers were shown to be more reactive than the isomeric propargylic compounds. Thus (150) underwent base-catalysed isomerization and *in situ*

[107] S. W. Remizewski, R. R. Whittle, and S. M. Weinreb, *J. Org. Chem.*, 1984, **49**, 3243.
[108] For a review of the intramolecular imino Diels–Alder reaction, see S. M. Weinreb, *Acc. Chem. Res.*, 1985, **18**, 16.
[109] S. D. Burke, S. M. Smith Strickland, and T. H. Powner, *J. Org. Chem.*, 1983, **48**, 454.
[110] R. L. Funk, C. J. Mossman, and W. E. Zeller, *Tetrahedron Lett.*, 1984, **25**, 1655.

(105)
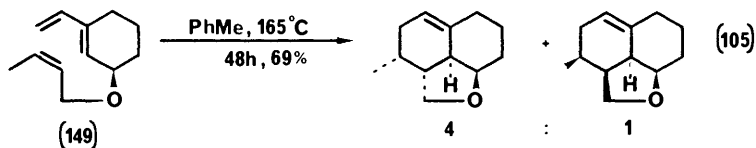
cyclization to give the enol ether product, which was subsequently converted into the tricyclic lactone (151) (equation 106).[111]

(106)

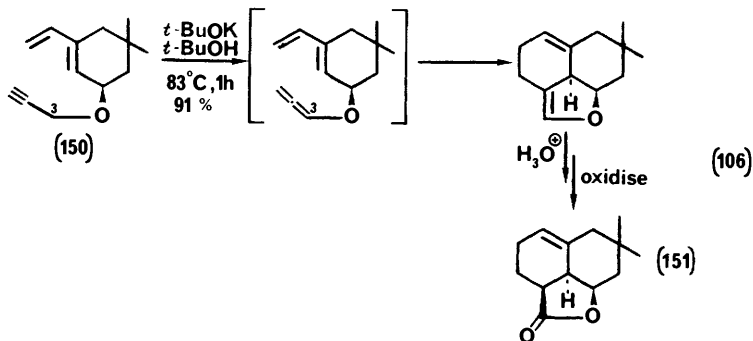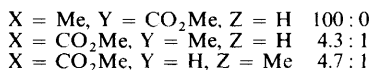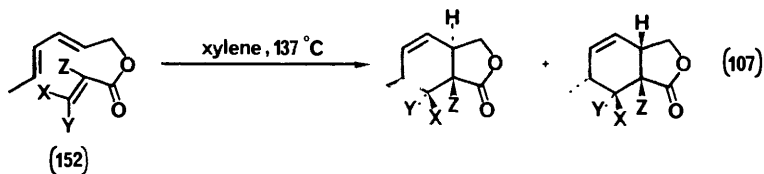The increased reactivity of the allenic intermediate resulted from the absence of non-bonded interactions between H-3 and the cyclohexane ring.[112]

Cyclization of the trienes (152) showed a general tendency towards the formation of *trans*-fused γ-lactones (equation 107).[113]

(107)

$$
\begin{array}{llll}
X = Me, & Y = CO_2Me, & Z = H & 100:0 \\
X = CO_2Me, & Y = Me, & Z = H & 4.3:1 \\
X = CO_2Me, & Y = H, & Z = Me & 4.7:1
\end{array}
$$

Compound (152) (X = Me, Y = CO$_2$Me, Z = H) in which the dienophile activating groups were *syn* to each other was the most reactive isomer; an increase in the steric bulk of the Z-substituent had a negative effect on the rate of cyclization. Anomalously, with a carboxylic *acid* group at the Y-position, the *cis*-

[111] K. Hayakawa, S. Oshuki, and K. Kanematsu, *Tetrahedron Lett.*, 1986, **27**, 947. See also K. Hayakawa, Y. Yamaguchi, and K. Kanematsu, *Tetrahedron Lett.*, 1985, **26**, 2689.

[112] K. Hayakawa, M. Yodo, S. Oshuki, and K. Kanematsu, *J. Am. Chem. Soc.*, 1984, **106**, 6735.

[113] J. D. White and B. G. Sheldon, *J. Org. Chem.*, 1981, **46**, 2273; J. D. White, B. G. Sheldon, B. A. Solheim, and J. Clardy, *Tetrahedron Lett.*, 1978, **19**, 5189.

fused product was obtained exclusively, albeit in low yield. Reversibility of the IMDA reaction was tentatively put forward to explain this peculiarity.[114]

The sorbic acid derivative (153) gave almost entirely the *trans*-fused product upon heating (equation 108).[103]

$$135\,^{\circ}C\,,\;15.5h\qquad79\%\qquad\qquad9\;:\;1\qquad(108)$$
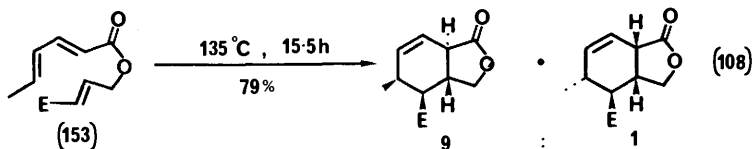
Cyclization occurred readily in spite of a lowering of the diene HOMO energy due to coplanarity and overlap of the diene with the ester carbonyl. This overlap reduces the demand for ester-oxygen–carbonyl overlap, though molecular models showed the ester-oxygen lone-pair to be skewed only slightly away from the conformation in which maximum overlap could take place. Although cyclization may only take place *via* the disfavoured s-*cis*-conformation of the ester linkage the energy barrier to rotation about the CO–O bond is sufficiently small so as not to impede the IMDA reactions.[115]

Although the singly-activated ester (154) failed to cyclize upon heating due to competing elimination and polymerization processes, the mixed fumaric ester (155) gave a single cycloadduct (equation 109),[109] formed *via* an *exo*-transition-state with respect to the internal ester.

(154)

$$PhH,\;120\,^{\circ}C,\;90h\qquad80\%\qquad F=CO_2Et\qquad(109)$$

(155)
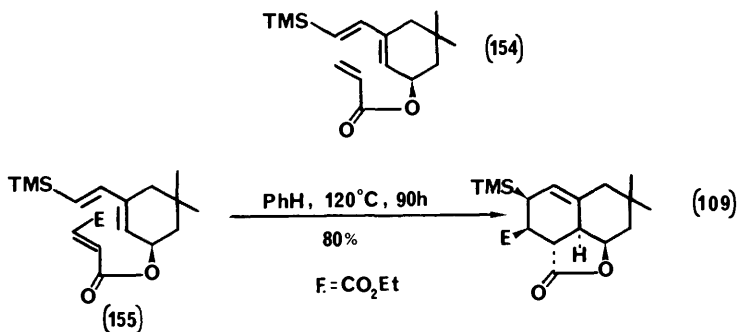
Similar results were obtained for the more sterically demanding trienes (156)[116,117] and (157).[118]

[114] For similar anomalous behaviour, see A. Ingendoh, J. Becher, H. Clausen, and H. C. Nielsen, *Tetrahedron Lett.*, 1985, **26**, 1249.

[115] See reference 13 of reference 103.

[116] P. R. Jenkins. K. A. Menear, P. Barraclough, and M. S. Nobbs, *J. Chem. Soc., Chem. Commun.*, 1984, 1423.

[117] P. Magnus, C. Walker, P. R. Jenkins, and K. A. Menear, *Tetrahedron Lett.*, 1986, **27**, 651.

[118] F. E. Ziegler, B. H. Jaynes, and M. T. Saindane, *Tetrahedron Lett.*, 1985, **26**, 3307. For a related approach to the forskolin ring system, see: K. C. Nicolaou and W. S. Li, *J. Chem. Soc., Chem. Commun.*, 1985, 421.
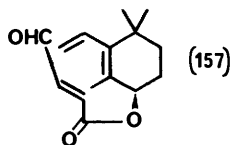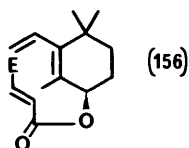
The maleic acid derivative (158) cyclized to give two *endo*-(with respect to the internal ester) isomers (equation 110).[116,117]
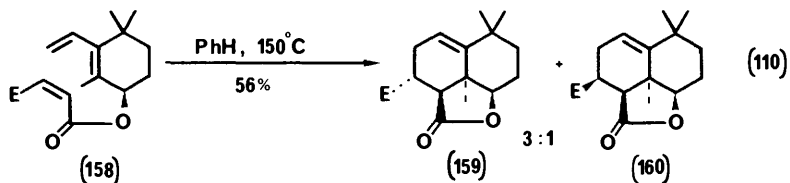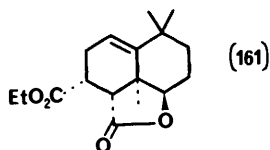
Whilst (160) clearly resulted from an *endo*-transition state, (159) would appear to be the product of dienophile isomerization prior to cyclization. The non-identity of (159) with the cyclization product of (156) clearly disproved this; (159) was shown

by deuterium incorporation studies to be the epimerization product of the initially formed *exo*-product (161).[117]

Singly-activated dienophilic trienes with an ester group forming part of the linking chain may undergo IMDA reactions if sufficiently vigorous conditions are employed. The substituted acrylate (162) formed a three-component mixture of cycloadducts upon prolonged thermolysis (equation 111).[119]
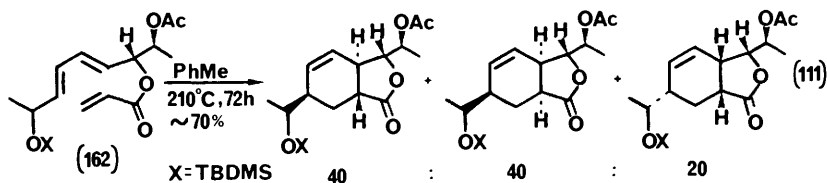
The 60:40 *cis–trans* product-ratio was in keeping with other cyclizations of trienes with internally substituted dienophilic groups. The diastereospecificity of formation of the *trans*-isomer was a consequence of $A_{1,3}$ strain in the alternative transition state (163).

[119] J. D. White, E. G. Nolen, jun., and C. H. Miller, *J. Org. Chem.*, 1986, **51**, 1150.

(163)
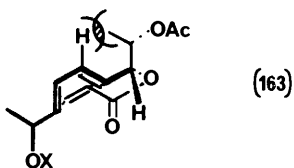
The moderate selectivity associated with cyclization to the *cis*-isomer nevertheless parallels that observed in carbocyclic bicyclo[4.3.0] systems (*vide supra*).

Summary.
Whilst the cyclization reactions of trienes containing heteroatoms in the linking chain exhibit many of the stereochemical features of the all-carbon substrates, several additional trends may be summarized as follows.

Bicyclo[4.4.0] *systems*

(i) The presence of an amide group within the linking chain has a variable effect on the observed selectivity, depending on its position relative to the diene and dienophile.
(ii) Trienes containing non-conjugated ester groups are unreactive, and isomerize prior to cyclization.

Bicyclo[4.3.0] *systems*

(i) Amides in which either the nitrogen atom or the carbonyl group is conjugated with the diene exhibit *cis*-selectivity.
(ii) Amides and esters which are conjugated with the dienophile double bond exhibit *trans*-selectivity which increases with terminal dienophile activation; the absence of such activation gives rise to zero or moderate *cis*-selectivity. Amines and ethers show stereoselectivities similar to the all-carbon substrates.

4 Theoretical Aspects
It is abundantly clear from the foregoing discussion that a delicate and subtle balance of structural factors affects the stereochemical outcome of the IMDA reactions of triene substrates. Although secondary orbital interactions may become significant at low temperatures and in the presence of Lewis and Brønsted acids, the *endo*-'rule' is of very limited use in predicting isomer distributions in the thermal reactions discussed above. Careful consideration of parameters such as diene/ dienophile substitution, length of the linking chain, and the nature of any heteroatomic functionality present is essential to an understanding of the observed stereoselectivities. Central to this understanding is an appropriate assessment of those steric interactions which are important in determining the energy of the transition-state.

The concept of the 'concerted but non-synchronous' reaction pathway is a useful one in deciding which transition-state interactions are important. In this model, transition-state bonding is considered to be at a more advanced stage between those two atoms which have the largest coefficient of the frontier molecular orbital.[23] Thus A will cyclize *via* a transition-state in which peripheral bond formation is more advanced and B *via* a more internally bonded transition-state.


EDG = electron-donating group

EWG = electron-withdrawing group
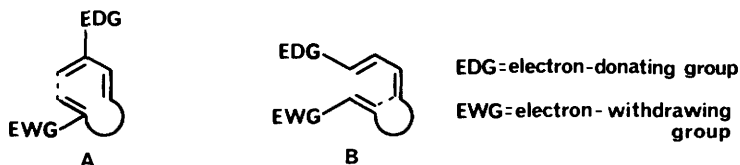
This model does not imply a stepwise reaction; the reaction is concerted in that the two bonds are *initiated* simultaneously,[113] but asynchronous by virtue of the differing rates of formation of the peripheral and internal bonds along the reaction co-ordinate. Two modes of asynchronicity have been put forward to explain some of the stereochemical features of IMDA reactions, and these are outlined below.

A. Asymmetric Stretch Asynchronicity.—Considering a triene with a substitution

pattern as in B above. Asymmetric stretch asynchronicity would mean that the internal termini of the diene and the dienophile have moved together concomitant with a moving apart of the peripheral atoms. Consequently, the transition-state has more of the character of the ring formed by connecting the internal termini. This explains why 1,3,8-nonatrienes substituted as in B give predominantly *trans*-fused products,[58,59] since the most stable pseudo-five-membered transition-state is that in which the diene and dienophile are *anti* with respect to each other. The moving apart of the peripheral termini has been used to explain the unimportance of the steric bulk of the ester alkyl group R in determining the stereospecificity of cyclization of (103) (X = H) to give purely *trans*-products *via* an *endo*-transition-state.[78]


(103) (X = H)
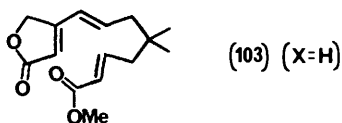
Conversely, 1,3,8-nonatrienes with internal dienophile-activating groups display more nine-membered ring character in the transition-state, giving predominantly *cis*-fused products due to the greater stability of a *cis*-skewed nine-membered ring.[64,65,66b,68,72,80] A consideration of the thermodynamic stabilities of cyclodecane conformers accounted for the kinetic cyclization of (55) *via* the most favoured [52] boat–chair–boat transition-state.[51,53]
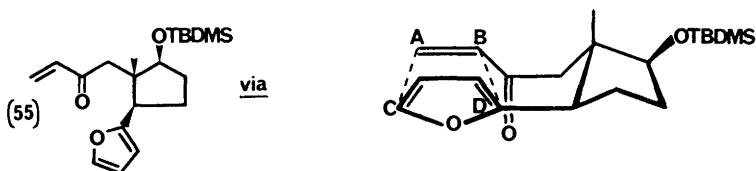
In the transition-state, peripheral bonding between A and C is more advanced, so the resulting structure acquires some of the character of a ten- rather than a six-membered ring. Conversely, with 1,3,9-decatrienes substituted as in **B**, the linking chain adopts the most stable chair-like conformation as a result of its pseudo-six-membered ring character. This explains the stereocontrolling influence of substituents in the linking chain which adopt the more stable equatorial disposition.[40-42]

B. Twist Asynchronicity.—In this mode, supported by force-field calculations,[120] twisting occurs about the bond which is the more fully formed in the transition-state. In the case of a 1,3,8-nonatriene substituted as in **B**, twisting occurs about the incipient C-4–C-8 bond which is more fully formed in the transition-state.
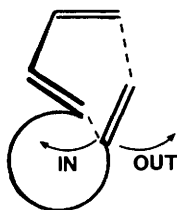
The torque generated by the distortion of the incipient five-membered ring is such as to reduce the C-5–C-4–C-8–C-7 dihedral angle (N) to as near zero as possible. If twisting about C-4–C-8 occurs as a result of this torque, it may be seen that the dienophile twists in an *exo*-direction, away from the diene. With the arrangement D leading to the *cis*-fused product, the torque is such as to reduce angle N as before but concomitantly with a twisting of the dienophile *endo* with respect to the diene, such as to increase non-bonded interactions. Thus transition state C is favoured over D, and *trans*-product predominates. Similar arguments apply to trienes with internal dienophile activating groups.

With a tetramethylene linking chain, as in the case of 1,3,9-decatrienes with terminal dienophile-activating groups, there is very little torque about C-4–C-9,

[120] F. K. Brown and K. N. Houk, *Tetrahedron Lett.*, 1985, **26**, 2297.
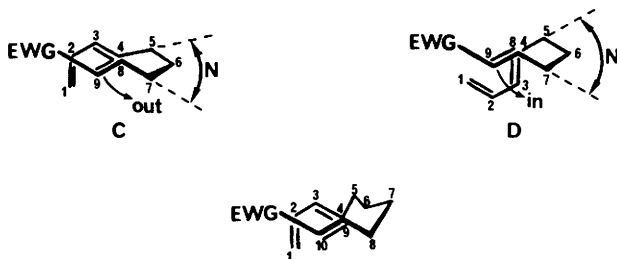
and very slight changes in stereoselectivity occur upon substitution of an electron-withdrawing group at C-10.

Clearly, such notions of asynchronous bond formation must be used with caution when predicting cyclization stereochemistries, as non-bonded interactions and electronic effects may be such as to stabilize or destabilize one or other of the transition-states to such an extent that product distributions are changed or even reversed[121] from those predicted by these models. Nevertheless, the concept of concerted but non-synchronous bond-formation provides a complementary insight into the stereocontrolling factors in intramolecular Diels–Alder reactions.

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[121] Compare references 65 and 66, for example.