The Intramolecular Diels–Alder Reaction

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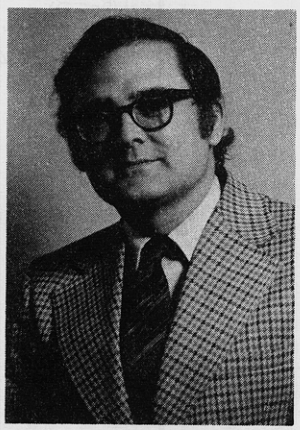
Contents



Gottfried Brieger is Professor of Chemistry at Oakland University. He was born in Berlin, Germany, and received his undergraduate training at Harvard College and his Ph.D at the University of Wisconsin with Professor E. E. van Tamelen. During 1972–1973, he was a senior Fulbright Fellow at Heidelberg University.

Janet N. Bennett, a native Michigander, received her undergraduate training at Albion College and her M.S. with G. Brieger at Oakland University, where she is currently a lecturer.

I. Introduction

Since its formulation in 1928,[1] the Diels–Alder reaction has remained remarkably useful in the armamentum of the synthetic organic chemist. Especially for the synthesis of polycyclic natural products, it presents an unrivalled opportunity for the regioselective and stereospecific introduction of multiple centers of configuration. Alternately, Diels–Alder adducts have been successfully used to generate synthons for the solution of other synthetic tasks.

In recent years, it has become increasingly clear that the intramolecular $[4\pi + 2\pi]$ reaction can be used effectively to synthesize a variety of interesting bridged polycyclic species, including many natural products. In properly designed systems, added advantages accrue in terms of ease of reaction and regio- and stereoselectivity.

The synthetic uses of the intramolecular Diels–Alder (IMDA) reaction have been reviewed recently,[2,3] but in view of the rapid development of the field, an update is provided here. The tables included here represent a reasonably complete index of reactions known to date.

Selected examples from the newer literature will be discussed with emphasis on the relationship of structure to reactivity, regioselectivity, and stereoselectivity.

II. Historical Review

The first example of an IMDA appears to be the unpublished result quoted by Alder,[4] which converted 1,4-pentadiene and dimethyl acetylenedicarboxylate, via an unisolated ene adduct, to a bicyclo[4.1.0]heptane derivative.

Subsequent isolated reports[5,6–8] appear to be of a more incidental nature until 1963, when two reports appeared which deliberately sought to apply the IMDA to natural product synthesis. One involved an attempted synthesis of longifolene[9] (eq 1); the other[10] included a simple synthesis of a podophyllotoxin degradation product (eq 2). General contributions to the reaction mechanism were made in 1965.[11] Methyl *trans,trans*- and *trans,cis*-2,7,9-decatrienoates cyclize regiospecifically and stereospecifically to form tetrahydroindans **1** and **2**. Noteworthy is the formation of the regio isomers which are not favored in the corresponding intermolecular analogue. It was also noted that reaction with maleic anhydride, when offered as a competitive dienophile, predominated over the entropically favorable intramolecular reaction. Further, it was found that reducing the bridge to two carbon atoms, as in the corresponding nonatrienes, did not lead to any intramolecular adducts.

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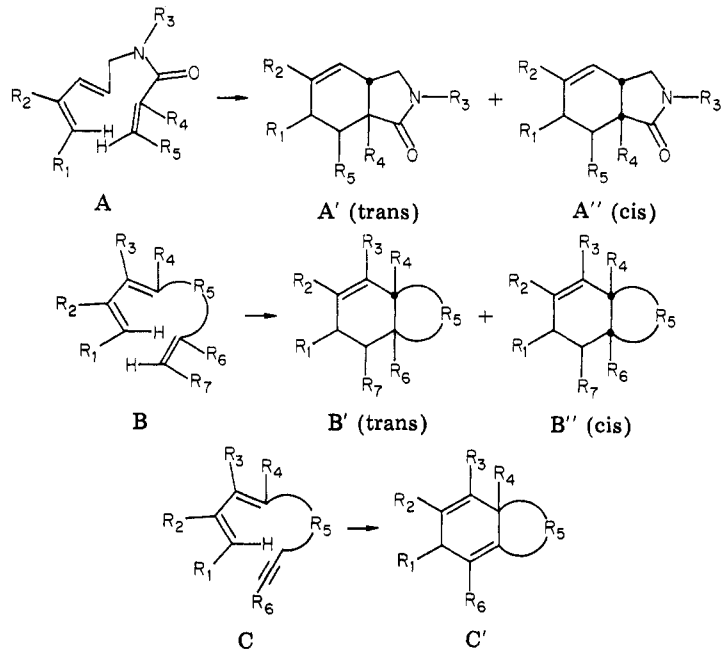
TABLE I.[a] IMDA Reactions of Open-Chain Molecules



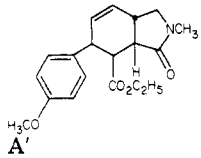
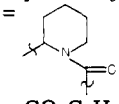
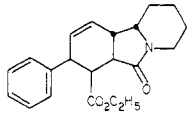
skeletal type (A, B, or C)	product	(a) reference (b) yield (c) reaction conditions (d) comments
1. A skeleton $R_1 = p\text{-}C_6H_5OCH_3$; $R_2 = H$; $R_3 = CH_3$; $R_4 = H$; $R_5 = CO_2C_2H_5$	**A′ 	(a) *90a (b) 77% (c) 0 °C, CH_2Cl_2/pyridine, 1 h (d) 3 in bridge
2. A skeleton $R_1 = p\text{-}C_6H_5OCH_3$; $R_2 = H$; $R_3 = CH_3$; $R_4 = H$; $R_5 = C_6H_5$	A′ A″	(a) *90a (b) 79%; 10.5% (c) 0 °C, CH_2Cl_2/pyridine, 1 h (d) 3 in bridge
3. B skeleton $R_1 = C_6H_5$; $R_2 = H$; $R_3 = H$; $R_4 = H$; $R_5 =$  $R_6 = H$; $R_7 = CO_2C_2H_5$	B′ **B″ 	(a) *90b (b) 70%; 1-3% (c) 0 °C (d) 3 in bridge
4. A skeleton $R_1 = R_2 = C_6H_5$; $R_3 = CH_3$; $R_4 = H$; $R_5 = CO_2C_2H_5$	A′	(a) *91 (b) 63% (c) 0 °C (d) 3 in bridge
5. A skeleton $R_1 = R_2 = C_6H_5$; $R_3 = R_4 = H$; $R_5 = CO_2C_2H_5$	A′	(a) *91 (b) 58% (c) 110 °C (d) 3 in bridge
6. A skeleton $R_1 = R_2 = C_6H_5$; $R_3 = CH_3$; $R_4 = H$; $R_5 = C_6H_5$	A′ A″	(a) *91 (b) 8:1; % unknown (c) 90 °C (d) 3 in bridge
7. A skeleton $R_1 = R_2 = C_6H_5$; $R_3 = CH_3$; $R_4 = R_5 = H$; and (C=O) is CH_2	A′ A″	(a) *91 (b) 16%; 84% (c) 140 °C, 12 h (d) 3 in bridge
8. A skeleton $R_1 = R_2 = C_6H_5$; $R_3 = CH_3$; $R_4 = R_5 = H$	A′ A″	(a) *91 (b) 42%; 40% (c) 25-110 °C, 8 h, toluene (d) 3 in bridge
9. B skeleton $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$; $R_5 = C{=}O$ / $N(CH_2CH{=}CH_2)CH_2$ $R_6 = R_7 = H$	B′ B″	(a) 13 (b) 2:1; 80% (c) 156 °C, 3 h, DMF (d) 3 in bridge

TABLE I (*Continued*)

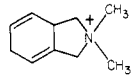
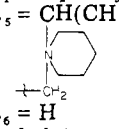
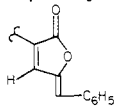
	skeletal type (A, B, or C)	product	(a) reference (b) yield (c) reaction conditions (d) comments
10.	C skeleton (ammonium cation) $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = CH_2N(CH_3)_2CH_2$; $R_6 = H$	***C′* 	(a) 14a (b) yield not given (c) not mentioned (d) 3 in bridge
11.	C skeleton (ammonium cation) $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = CH(CH_2{=}CH_2)$  $R_6 = H$	C′	(a) 14b (b) 70% (c) sealed tube, 100 °C, 90 h, DMF (d) 3 in bridge
12.	A skeleton $R_1 = R_2 = H$; $NR_3 = CH_2$; $R_4 = CH_3$; $R_5 = H$	A″	(a) *92 (b) 30% (c) 190 °C, 13 h (d) 3 in bridge
13.	C skeleton $R_1 = H$; $R_2 = CH_3$; $R_3 =$ $R_4 = H$; $R_5 + R_6 +$ dieno- phile = $C(CH_3)_2CH_2CH_2CN$	C′	(a) *93 (b) yield not given (c) *hν* initially, then 500 °C (d) 3 in bridge
14.	A skeleton $R_1 = R_2 = CH_3$; $N + R_3 = O$; $R_4 + R_5$ + dienophile = 	A″	(a) *94 (b) 32% (c) 180 °C, 2.5 h, *o*-dichlorobenzene (d) 3 in bridge, part of natural, product skeleton, (cytochalasins)
15.	B skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = CH_2N(COR')CH_2$; $R' = C(CH_3)_3$ or CF_3 $R_6 = R_7 = H$	B″	(a) 15 (b) almost quantitative (c) 90–95 °C (d) 3 in bridge
16a. (3)	B skeleton $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$; $R_5 = CON{=}C[N(CH_3)_2]$; $R_6 = CH_3$; $R_7 = H$	B″	(a) 16 (b) 77.8% (c) 171–172 °C, acetonitrile (d) 3 in bridge
16b.	B skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = CON{=}C[N(CH_3)_2]$; $R_6 = CH_3$; $R_7 = H$	B″	(a) 16 (b) 69.9% (c) 171–172 °C, acetonitrile (d) 3 in bridge
16c.	B skeleton $R_1 = R_3 = R_4 = H$; $R_2 = CH_3$; $R_5 = CON{=}C[N(CH_3)_2]$; $R_6 = CH_3$; $R_7 = H$	B″	(a) 16 (b) 62.8% (c) 171–172 °C, acetonitrile (d) 3 in bridge
16d.	B skeleton $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$; $R_5 = CON{=}C[N(CH_3)_2]$; $R_6 = C_6H_5$; $R_7 = H$	B″	(a) 16 (b) 65.7% (c) 171–172 °C, acetonitrile (d) 3 in bridge
17a.	B skeleton $R_1 = R_2 = R_4 = H$; $R_3 = CH_3$; $R_5 = (CH_2)_4$; $R_6 = R_7 = H$	B″	(a) 18a (b) 95% (c) 160 °C (d) 4 in bridge
17b.	B skeleton $R_1 = R_2 = R_4 = H$; $R_3 = CH_3$; $R_5 = CH_2C(R'R'')CH_2CH_2$; $R' = OH$ (axial); $R'' = H$ (equatorial); $R_6 = CH_3$; $R_7 = H$	B″	(a) 18a (b) 24% (axial); 33% (equatorial) (c) 160 °C (d) 4 in bridge
17c.	B skeleton $R_1 = R_2 = R_4 = H$; $R_3 = CH_3$; $R_5 = (CH_2)_4$; $R_6 = CH_3$; $R_7 = H$	B″	(a) 18a (b) 30% (c) 190 °C/toluene (d) 4 in bridge
17d. (8)	B skeleton $R_1 = R_2 = R_4 = H$; $R_3 = CH_3$; $R_5 = CH_2C(R'R'')CH_2CH_2$; $R' = OSiMe_3$ (axial); $R'' = H$ (equatorial); $R_6 = CH_3$; $R_7 = H$	B′ B″	(a) 18a (b) 34% trans-axial; 54% trans-equatorial; 5% cis-equatorial (c) 200 °C, 100 h, toluene (d) 4 in bridge; several steps to (±)-selina-3,7-diene
18. (12)	B skeleton $R_1 = CH(CH_3)_2$; $R_2 = R_3 =$ $R_4 = H$; $R_5 =$ $CH(OSiMe_3)CH_2CH_2$; $R_6 = H$; $R_7 = CO_2CH_3$	B′ B″	(a) 19 (b) 72.5%; 10.5% (c) refluxing toluene, 85 h (d) 3 in bridge; (±)-dendrobine is obtained from B′

TABLE I (*Continued*)

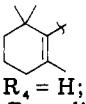
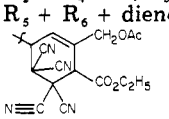
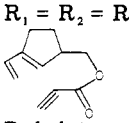
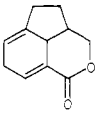
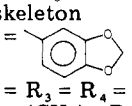
	skeletal type (A, B, or C)	product	(a) reference (b) yield (c) reaction conditions (d) comments
19.	B skeleton	B″	(a) 21
(20)	$R_1 = R_3 = R_4 = H$; $R_2 = CH_3$; $R_5 = CH[CH(CH_3)_2]CH_2CH_2CH(OH)$-; $R_6 = R_7 = H$	upon cyclization, CHOH → C=O	(b) 87% (c) oxidation by $H_2Cr_2O_7$, 0 °C 25 min, ether (d) 4 in bridge; several steps to (±)-torreyol
20.	B skeleton	B′	(a) 22
(24)	$R_1 = CO_2CH_2CH_3$; $R_5 = COCH_2CH_2CH(CH_3)$; $R_6 = CH_3$; $R_7 = H$	B″	(b) 54–93% (c) 250 °C, 6 h, toluene (d) 4 in bridge; valencane skeleton is obtained from B′; eremophilane skeleton is obtained from B″
21.	B skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = (CH_2)_3$; $R_6 = H$; $R_7 = CO_2CH_3$	B′ B″	(a) *11 (b) good yield, % unknown (c) temperature not given (d) 3 in bridge
22.	C skeleton $R_1 =$  $R_2 = R_4 = H$; $R_3 = CH_3$; $R_5 + R_6$ + dienophile = 	C′	(a) *95 (b) 73.3% (c) 80 °C (d) 3 in bridge
23.	B skeleton $R_1 = CH(CH_3)_2$; $R_2 = R_3 = H$; $R_4 = CH_3$; $R_5 = CH(CN)CH_2CH_2$; $R_6 = H$; $R_7 = CO_2CH_3$	B″	(a) *96 (b) 49% (c) 180 °C (d) 3 in bridge; basic skeleton to 8-epidendrobine
24.	B skeleton $R_1 = R_2 = R_4 = H$; $R_3 = OSiEt_3$; $R_5 = (CH_2)_3$; $R_6 = R_7 = H$	B″	(a) *97 (b) 55% (c) 160 °C (d) 3 in bridge
25.	B skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = N(CO_2CH_3)CH_2CH_2$; $R_6 = R_7 = H$	B″	(a) *98 (b) 38% (c) 160 °C, 16 h, toluene (d) 3 in bridge
26.	B skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = (CH_2)_3C=O$ $R_6 = R_7 = H$	B′	(a) *97 (b) 62% (c) 0 °C (d) 4 in bridge
27.	B skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = N(CO_2CH_3)(CH_2)_3$; $R_6 = R_7 = H$	B″	(a) *98 (b) 84% (c) 190 °C, 24 h, toluene (d) 4 in bridge
28.	B skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = N(COCH_3)(CH_2)_3$; $R_6 = R_7 = H$	B″	(a) *98 (b) 59% (c) 190 °C, 16 h, toluene (d) 4 in bridge
29.	B skeleton $R_1 = R_2 = R_3 = R_4 = R_6 = H$; $R_5 = N(COCH_3)(CH_2)_3$; $R_7 = CH_3$	B″	(a) *98 (b) 36% (c) 205 °C, 22 h, toluene (d) 4 in bridge
30.	B skeleton $R_1 = R_2 = R_3 = R_4 = R_6 = H$; $R_5 = N(CO_2CH_3)CH(CH_2CH_2CH_3)(CH_2)_2$; $R_7 = CH_3$	B″	(a) *99 (b) 25% (c) 215 °C, 20 h, 5% toluene solution, sealed tube (d) 4 in bridge; several steps to (±)-pumiliotoxin C
31.	C skeleton $R_1 = R_2 = R_4 = H$; 		(a) *100 (b) 70% (c) 135 °C, 20 h, acetic anhydride (d) 4 in bridge; several steps to basic configuration of A and B ring of gibberellic acid 22
32.	B skeleton $R_1 =$  $R_2 = R_3 = R_4 = H$; $R_5 = (CH_2)_3$; $R_6 = H$; $R_7 =$ 	B″	(a) *101 (b) 33% (c) 110 °C (d) 4 in bridge; cyclopiperstachine

TABLE I (*Continued*)

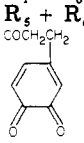
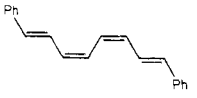
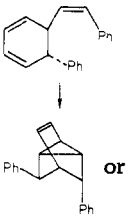
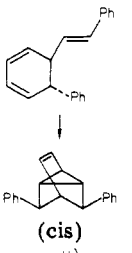
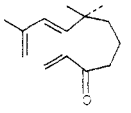
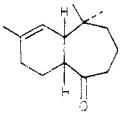
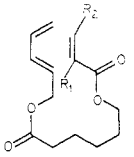
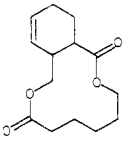
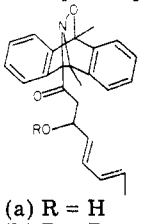
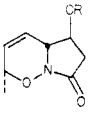
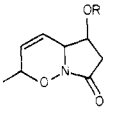
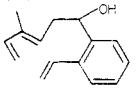
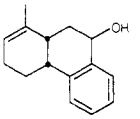
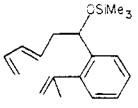
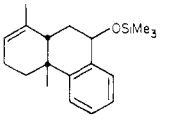
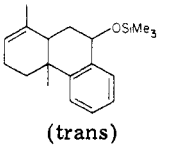
	skeletal type (A, B, or C)	product	(a) reference (b) yield (c) reaction conditions (d) comments
33.	B skeleton $R_1 = C_6H_5$; $R_2 = R_3 = R_4 = H$; $R_5 + R_6 + R_7$ + dienophile = 	B′	(a) *102 (b) 37% (c) 25 °C, $NaIO_4$ (d) 4 in bridge; synthesis of lachnanthocarpone
	exceptions to skeleton		
34.		 (trans)  (cis)	(a) 103 (b) 26% (trans); 20% (cis) (c) 175 °C (d) 1 in bridge
35.			(a) *104 (b) 70% (c) 110 °C, $AlCl_3$ (d) 5 in bridge; β-himachalene; several steps to *dl*-α-himachalene
36.	 (a) $R_1 = R_2 = H$ (b) $R_1 = CH_3$ $R_2 = CO_2CH_3$, CH_3	 (cis and trans)	(a) *105 (b) 77% (c) 205 °C, benzonitrile (d) diene and dienophile are separated by 10 atoms
37. (5)	 (a) R = H (b) R = D (c) R = Ac (d) R = $SiMe_2$-*t*-Bu	 (cis)  (trans)	(a) 17 (b) quantitative 66:33 (a) 66:33 (b) 43:57 (c) 41:59 (d) (c) refluxing benzene, 5 h (d) 3 in bridge
38a.			(a) 18b (b) 72% (c) 100 °C, 2 h (d) 4 in bridge
38b.		 (cis)  (trans)	(a) 18b (b) 43%; cis/trans 2:1 (c) 180 °C, 24 h (d) 4 in bridge

TABLE I (*Continued*)

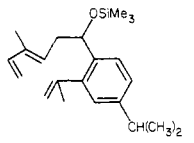
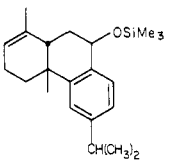
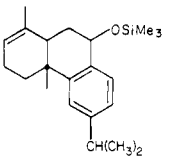
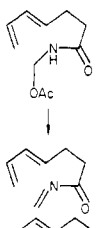
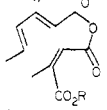
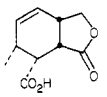
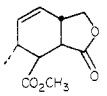
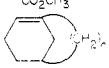
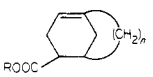
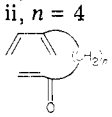
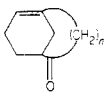
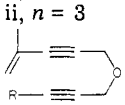
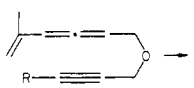
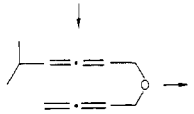
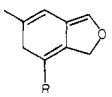
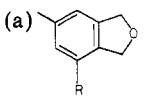
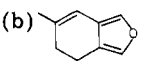
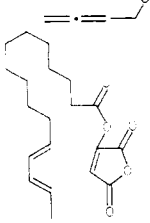
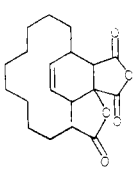
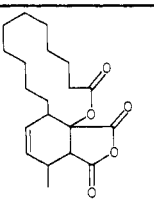
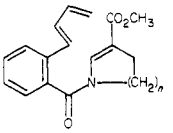
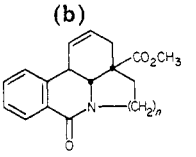
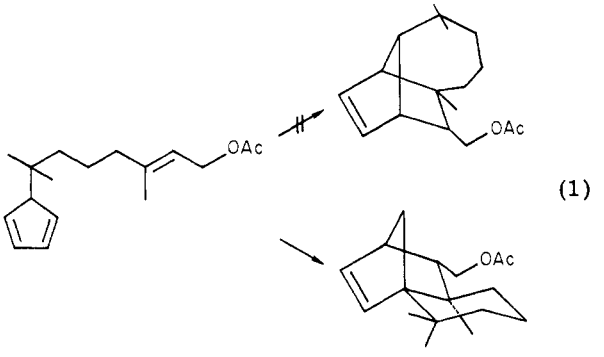
exceptions to skeleton	product	(a) reference (b) yield (c) reaction conditions (d) comments
38c. 	 (cis)  (trans)	(a) 18b (b) 77%; cis/trans 1:1 (c) 180 °C, 22 h (d) 4 in bridge
39. (17) 		(a) 20 (b) 73% (c) toluene solution of methylol acetate was passed through a 15-cm column of glass helices; 370–390 °C (d) 3 in birdge; several steps to δ-coniceine
40. (27) (28)  R = H or CH_3	 	(a) 23 (b) 60% (R = H); 40% (R = CH_3) (c) refluxing xylene, 15 h (d) 3 in bridge
41a. (33) (34)  i, n = 3 ii, n = 4		(a) 24 and 25 (b) 28% (i); 55% (ii) (c) 405 °C (i), 455 °C (ii) (d) bridgehead alkene, 3 in bridge (n = 3), 4 in bridge (n = 4)
41b.  R = CH_3 or CH_2CH_3 i, n = 3 ii, n = 4		(a) 24 and 25 (b) 76% (i); 90% (ii) (c) 320 °C (i), 420 °C (ii) (d) bridgehead alkene, 3 in bridge (n = 3), 4 in bridge (n = 4)
41c.  i, n = 2 ii, n = 3		(a) 24 and 25 (b) 70% (i); 80% (ii) (c) 385 °C (i), 398 °C (ii) (d) bridgehead alkene, 3 in bridge (n = 2), 4 in bridge (n = 3)
42.   R = H or C_6H_5 	 (a)  (b) 	(a) 65 (b) 15% (R = H) (a); 11% (R = C_6H_5) (a); 55% (R = H) (b) (c) KO-t-Bu t-BuOH room temperature (d) 3 in bridge
43. (37) 	 (a)	(a) 26 (b) 5% (a), 27% (b) (c) refluxing toluene, 96 h (d) 12 in bridge

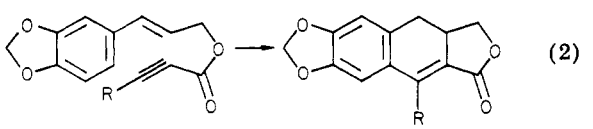
TABLE I (*Continued*)

exceptions to skeleton	product	(a) reference (b) yield (c) reaction conditions (d) comments
	 (b)	
44.  (a) $n = 1$ (b) $n = 2$	 (a) $n = 1$ (b) $n = 2$	(a) 106 (b) 84% (a), 74% (b) (c) refluxing *o*-dichlorobenzene 2.5 h (a) 3.5 h (b) (d) 4 in bridge

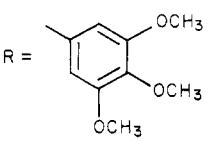
[a] In this and the following table, the following obtains: (1) The IMDA reactions in the tables are numbered sequentially. A number in parentheses under the reaction number designates that this structure and the following reaction are discussed in the text. (2) The product letter preceded by a double asterisk indicates that this particular IMDA adduct is illustrated below. (3) A reference number preceded by an asterisk designates that this IMDA reaction has been previously reviewed. (4) The counting for the number of bridge atoms is carried out in the following manner: if the precursor for the IMDA adduct is an open-chain triene, the numbering commences at the first atom adjacent to the diene and ends at the last atom preceding the dienophile; if the precursor for the IMDA adduct is an endocyclic diene, the numbering commences at the atom which is both adjacent to the diene and correspondingly branches to the dienophile and ends at the last atom adjacent to the dienophile.

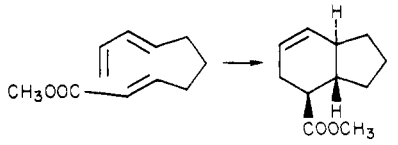


(1)

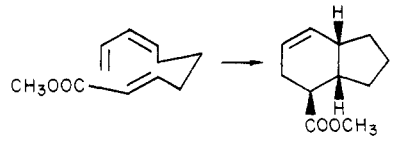


(2)





1



2

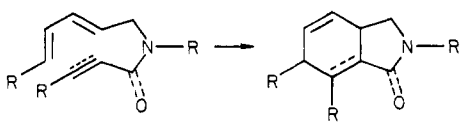
Finally, an early study[12] in 1967 provided information on the intramolecular reactivity of several cyclohexadienes. This report not only provided an indication that strained ring systems could indeed be formed but yielded useful thermodynamic data on the vinylcyclohexadiene–tricyclo[3.2.1.$0^{2,7}$]oct-3-ene equilibrium.

Subsequent development of the field has been reviewed.[2,3] We will present current developments based on the major structural types of dienes reported to date: acyclic dienes, endocyclic 5-ring dienes, endocyclic 6-ring dienes, endocyclic dienes in rings >6, endo,exo dienes, for both aromatic and alicyclic systems, Claisen rearrangement systems, and *o*-quinodimethanes.

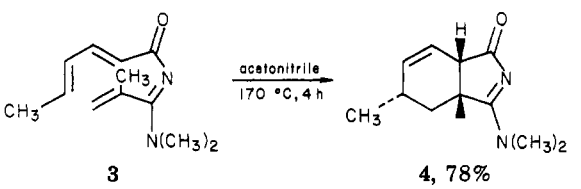
III. Major Reaction Types

A. Acyclic Dienes

Interest has continued in the cyclization of readily available *N*-allyl and *N*-propargyl amides according to eq 3, with the



(3)

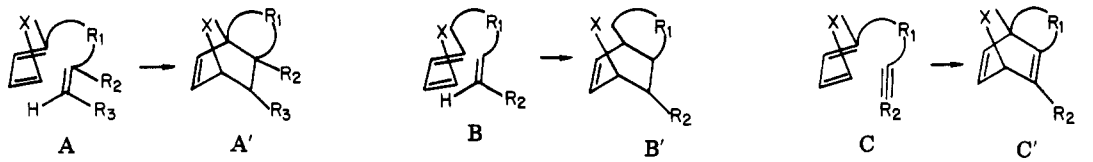


3 4, 78%

formation of substituted isoindolenes.[13-15] These reactions are not stereospecific, and epimerization must also be considered. On the other hand, an acylamidine (**3**) has been cyclized successfully and leads to the thermodynamically favored product **4** exclusively.

The acylnitroso group is a reactive dienophile, but like other nitroso compounds is inherently unstable. 9,10-Dimethylanthracene was used as a temporary protecting group to circumvent this difficulty; it formed the starting material **5**, which on thermolysis regenerated the nitroso group and cyclized quantitatively to **6** and **7**.

TABLE II: IMDA Reactions of Endocyclic Dienes of 5-Membered Rings



X = CH_2, S, or O

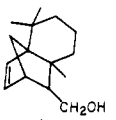
	skeletal type (A, B, or C)	product	(a) reference (b) yield (c) reaction conditions (d) comments
45.	A skeleton X = CH_2; R_1 = $C(CH_3)_2CH_2CH_2CH_2$; R_2 = CH_3; R_3 = CH_2OH	**A' 	(a) *9 (b) 25.2% (c) 176 °C, 48 h, pseudocumene (d) 4 in bridge
46a. (42)	A skeleton goes to B; X = CH_2; R_1 = $(CH_2)_2$; R_2 = H		(a) 28 (b) 44.5% (c) 180 °C, 4 h, benzene, sealed tube (d) isomerization from 1 to 5 position affords 3 atoms in the bridge
46b.	A skeleton X = CH_2; R_1 = $(CH_2)_3$; R_2 = R_3 = H	A'	(a) 28 (b) 77% (c) 180 °C, 4 h, benzene, sealed tube (d) 3 in bridge
46c.	A skeleton X = CH_2; R_1 = $(CH_2)_4$; R_2 = R_3 = H	A'	(a) 28 (b) 73% (c) 180 °C, 4 h, benzene, sealed tube (d) 4 in bridge
47.	B skeleton X = CH_2; R_1 = $(CH_2)_2$; R_2 = H; R_3 = CH_3	**B' 	(a) 107 (b) yield not given (c) heat, $N(n\text{-}C_4H_9)_3$ (d) isomerization from 1 to 5 position affords 3 atoms in the bridge
48.	A skeleton X = CH_2; R_1 = $(CH_2)_3$; R_2 = R_3 = H	A'	(a) *108 (b) yield not given (c) heat, $N(n\text{-}C_4H_9)_3$ (d) 3 in bridge
49.	A skeleton X = O; R_1 = CH_2NHCO; R_2 = H; R_3 = COOH, C_6H_5, *p*-tolyl, or CH_3	A'	(a) 34a (b) 35% (c) room temperature, ethanol (d) 3 in bridge
50.	A skeleton X = O; R_1 = $CH_2N(C_6H_5)CO$; R_2 = H; R_3 = COOH	A'	(a) 34b (b) 96% (c) room temperature, ethanol (d) 3 in bridge
51.	A skeleton X = O; R_1 = $CH_2N(C_6H_5)CH_2$; R_2 = R_3 = H	A'	(a) 6 (b) 51% (c) room temperature (d) 3 in bridge
52.	A skeleton X = O (ammonium salt) R_1 = $CH_2N(R'R'')CH_2$; R_2 = R_3 = H R' = CH_3, CH_2CH_3, C_6H_5, CH_2CN; R'' = CH_3, CH_2CH_3; R'R''N = piperidine or morpholino	A'	(a) 34c (b) 90-97% (c) heat (d) 3 in bridge
53.	A skeleton X = O (ammonium salt) R_1 = $CH_2N(R'R'')$; R_2 = H; R_3 = H, CH_3, $CH{=}CH_2$, C_6H_5; R' = R'' = CH_3, CH_2CH_3; R'R''N = piperidino or morpholino	A'	(a) 34c (b) 85-93% (c) heat (d) 3 in bridge

TABLE II (*Continued*)

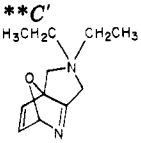
	skeletal type (A, B, or C)	product	(a) reference (b) yield (c) reaction conditons (d) comments
54.	C skeleton X = O (ammonium salt) $R_1 + R_2$ + dienophile = $CH_2N(CH_2CH_3)_2$ $CH_2C{\equiv}N$	**C′ 	(a) 34c (b) 90% (c) heat (d) 3 in bridge
55.	A skeleton X = O (ammonium salt) $R_1 + R_2 + R_3$ + dienophile = $CH_2N(CH_2CH_3)_2CH_2$-$C(OCH_3){=}O$	A′	(a) 34c (b) 85% (c) heat (d) 3 in bridge
56.	C skeleton X = O (ammonium salt) $R_1 + R_2$ + dienophile = $CH_2N(CH_3)_2CH_2$-$CH_2C{\equiv}N$	C′	(a) 34c (b) 90% (c) heat (d) 4 in bridge
57.	A skeleton X = S (ammonium salt) $R_1 = CH_2N(CH_3)_2CH_2$; R_2 = H, CH_3, H; R_3 = H, H, C_6H_5	A′	(a) 35 (b) 85-90% (c) heat (d) 3 in bridge
58.	C skeleton X = S (ammonium salt) $R_1 = CH_2N(CH_3)_2CH_2$; R_2 = H or CH_3	C′	(a) 35 (b) 85% (c) heat (d) 3 in bridge
59.	A skeleton X = O $R_1 = CH_2N(COR')CH_2$; R′ = $C(CH_3)_3$ or CF_3 $R_2 = R_3$ = H	A′	(a) 15 (b) almost quantitative (c) 90-95 °C (d) 3 in bridge
60. (53)	C skeleton X = CH_2 $R_1 = C(OCH_2C{\equiv}CH)_2OCH_2$; R_2 = H	C′	(a) 33 (b) quantitative (c) room temperature, 7 days, $CHCl_3$ (d) 3 in bridge
61a.	A. skeleton X = O $R_1 = CH_2N(CH_3)$ $C{=}O$ $R_2 = R_3$ = H	A′	(a) 36a (b) quantitative (c) refluxing benzene, 6 days (d) 3 in bridge
61b.	A skeleton X = O $R_1 = CH_2N(CH_3)$ $C{=}O$ $R_2 = CH_3$; R_3 = H	A′	(a) 36a (b) quantitative (c) refluxine benzene, 5 days (d) 3 in bridge
61c.	A skeleton X = O $R_1 = CH_2N(CH_3)$ $C{=}O$ R_2 = H; $R_3 = CH_3$	A′	(a) 36a (b) 40% (c) refluxing benzene, 14 days (d) 3 in bridge
61d.	A skeleton X = O $R_1 = CH_2CH_2N(CH_3)$ $C{=}O$ $R_2 = R_3$ = H	A′	(a) 36a (b) quantitative (c) refluxing benzene, 4 days (d) 4 in bridge
61e.	A skeleton X = O $R_1 = CH_2CH_2N(CH_3)$ $C{=}O$ R_2 = H; $R_3 = CH_3$	A′	(a) 36a (b) 12% (c) refluxing benzene (d) 4 in bridge

TABLE II (*Continued*)

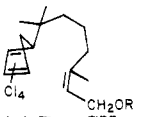
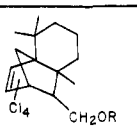
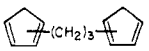
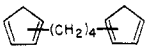
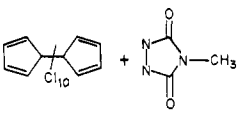
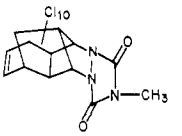
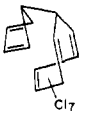
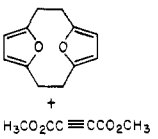
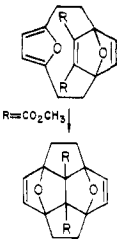
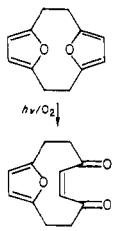
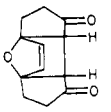
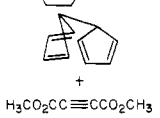
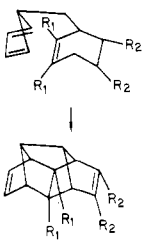
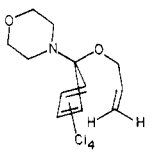
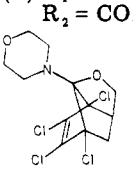
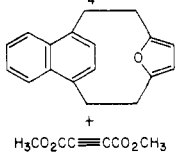
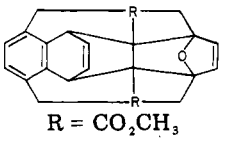
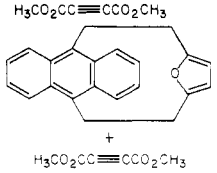
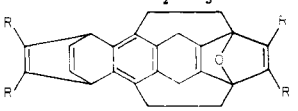
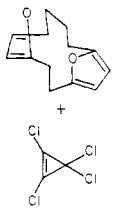
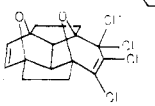
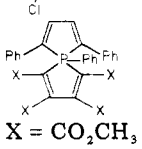
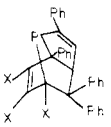
	skeletal type (A, B, or C)	product	(a) reference (b) yield (c) reaction conditons (d) comments
61f.	A skeleton X = O R_1 = $CH_2CH_2CH_2N(CH_3)$ C=O $R_2 = R_3 = H$	A′	(a) 36a (b) 45% (c) refluxing benzene (d) 5 in bridge
62.	A skeleton X = O $R_1 = CON(CH_3)CH_2$; $R_2 = R_3 = H$	A′	(a) 36a (b) quantitative (c) refluxing benzene, 6 days (d) 3 in bridge
63.	A skeleton X = O $R_1 = (CH_2)_3N(CH_2C_6H_5)$ C=O $R_2 = R_3 = H$	A′	(a) 36a (b) 75% (c) refluxing benzene (d) 5 in bridge
64.	A skeleton X = O $R_1 = CH_2C(CO_2Et)_2CH_2$; $R_2 = R_3 = H$	A′	(a) 36a (b) 40% (c) refluxing benzene, 5 days (d) 3 in bridge
65.	A skeleton X = O $R_1 = CH_2N(CH_3)$ C=O $R_2 = C_6H_5$; $R_3 = H$	A′	(a) 36b (b) 48% (c) 120 °C, sealed tube, 15 h, benzene (d) 3 in bridge
	exceptions to skeleton		
66. (40)	similar to A skeleton  (a) R = CH_3 (b) R = $CH_2C_6H_5$		(a) 27 (b) 70-80% (a), 41% (b) (c) refluxing decalin, 5 h (d) 4 in bridge
67. (44)	similar to A skeleton 		(a) 29 (b) 74% (c) 155 °C, sealed tube 50 h, xylene (d) 3 in bridge; several steps to (±)-cedrol; several steps to (±)-cedrene
68a. (46)			(a) 30 (b) quantitative (c) 190 °C, sealed tube, 9 h, benzene (d) 4 in bridge
68b. (46)			(a) 30 (b) quantitative (c) refluxing benzene, 3 h (d) 4 in bridge
69. (49)			(a) 31 (b) 63% (c) refluxing ethyl acetate, 3 days (d) 3 in bridge; D-A followed by IMDA
70. (51)			(a) 32 (b) 60% (c) diethyl ether, room temperature, 6 h (d) 4 in bridge
71.			(a) *38 (b) quantitative (c) 105 °C (d) 3 in bridge; D-A followed by IMDA

TABLE II (*Continued*)

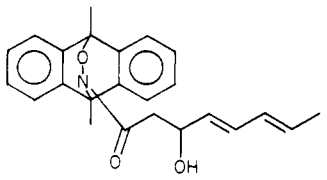
exception to skeleton	product	(a) reference (b) yield (c) reaction conditions (d) comments
72. 		(a) *7 (b) 42% (c) $h\nu/O_2$ (d) 3 in bridge
73. 	 (a) R_1=CO_2CH_3, R_2 = H (b) R_1 = H, R_2 = CO_2CH_3	(a) *109 and *110 (b) 3:2 between a and b (c) 78 °C, THF (d) 3 in bridge; D-A followed by IMDA
74. 		(a) *5 (b) 42% (c) room temperature, 4 weeks (d) 3 in bridge
75. 	 R = CO_2CH_3	(a) 39 (b) 30% (c) 100 °C 20 h (d) 5 in bridge; D-A followed by IMDA
76. 	R = CO_2CH_3 	(a) 40 (b) 36% (c) heated with dimethyl acetylenedicarboxylate (d) 5 in bridge; D-A followed by IMDA
77. 		(a) 111 (b) quantitative (c) 80 °C refluxing benzene (d) 3 in bridge; D-A followed by IMDA
78. (71)  X = CO_2CH_3	 X = CO_2CH_3	(a) 41 (b) 23% (c) refluxing $CHCl_3$, 4 h (d) 1 in bridge

Increasing the bulk of the hydroxyl substituent by forming various ethers changed the proportion of stereoisomers somewhat. Thus, the corresponding dimethyl *tert*-butylsilyl ether gave a product ratio of 41% **6** to 59% **7**.[17]

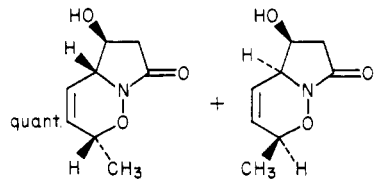
The outstanding versatility of the IMDA is exemplified by the recent syntheses of several natural products, including selina-3,7(11)-diene[18a] dendrobine,[19] δ-coniceine, tylophorine,[20] and (±)-torreyol.[21]

It was noted in the critical intramolecular step of the selinadiene synthesis that the reaction of **8** was stereoselective, leading primarily to the trans-fused isomer. The small amount of cis may certainly have resulted from partial isomerization of the starting diene during the long reaction period.

In the synthesis of (±)-dendrobine,[19] a hydrindene system is created according to eq 4. Here we note the formation of both cis- and trans-fused rings. The distribution of products would indicate a relatively small energy difference between the two systems, perhaps approximating that of the *cis–trans*-hydrindene difference of ca. 1.0 kcal/mol. In any case, there is no evidence that equilibrium values have been reached.

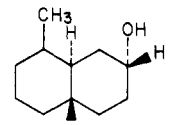


5

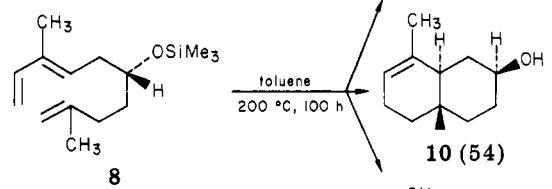


6 (66)* 7 (33)

(parenthesized number without % denotes relative yields)

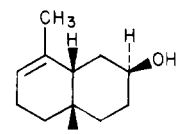


9 (34)

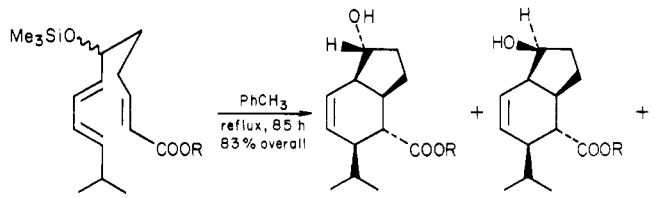


8

10 (54)

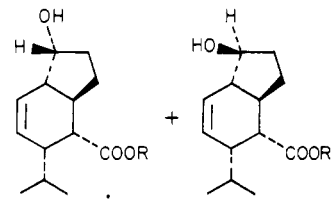


11 (6)

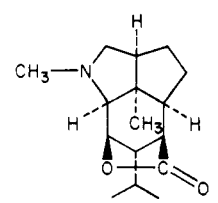


12

13 (9.5) 14 (1.0)



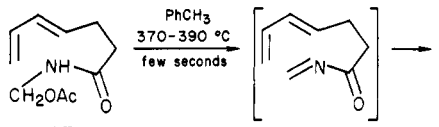
15 (39) 16 (33.5)



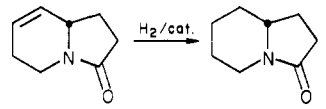
(4)

(±)-dendrobine

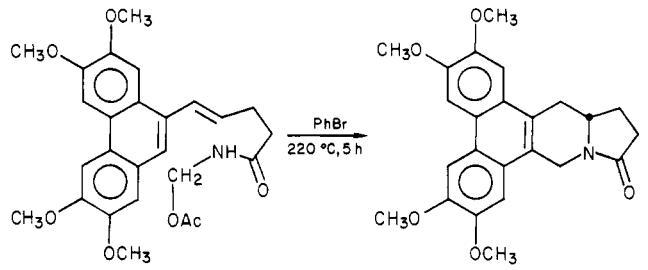
Two indolizidine alkaloids, δ-coniceine and tylophorine, were recently synthesized in excellent yields from their corresponding acyclic precursors **17** and **19**.[20] Presumably, the unstable acyl imine **18** is formed as an intermediate.



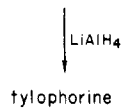
17 18



73% δ-coniceine

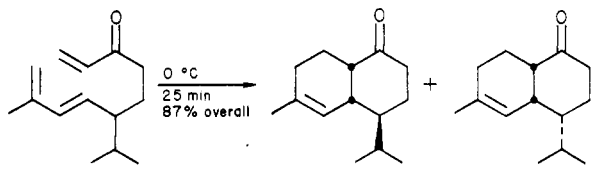


19 50%

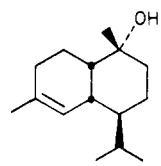


tylophorine

The synthesis of (±)-torreyol (**23**) is a more conventional application to the construction of an octalin skeleton, but the synthesis, although stereoselective, might well have been accomplished expeditiously by a conventional intermolecular DA.[21]

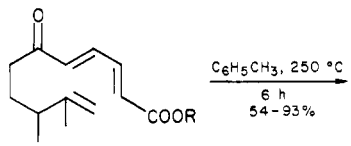


20 21 (9) 22 (1)

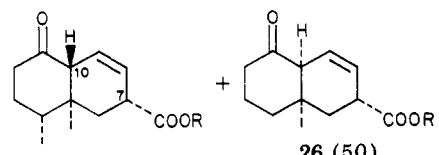


23

An entry to the eremophilane and valencane ring systems is provided by the IMDA of **24**, which cyclizes stereoselectively to **25** to **26**.[22] Due to rapid epimerization at C-10, the reaction



24



25 (50) 26 (50)

can be controlled to give almost exclusively the more stable **26**. This constitutes a synthesis of the eremophilane ring system.

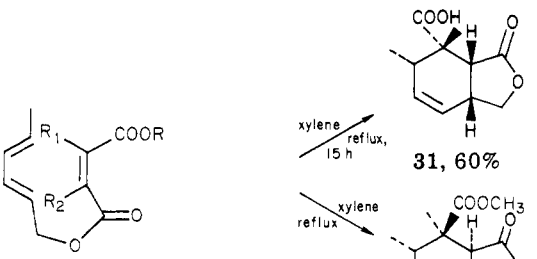
A secondary epimerization at C-7 allows the creation of the valencane stereochemistry.

Subtle influences of substituents were discovered in the in-

tramolecular cyclization of the isomeric sorbyl citraconates and mesaconates.[23] Thus, the half-ester **27** cyclized exclusively in the endo mode to **31**, whereas the corresponding ester **28** cyclized exclusively in the exo mode to **32**. An explanation is offered in terms of the lesser steric hindrance for the ester in the exo arrangement. It may also be that the carboxyl proton is attracted preferentially to the dienic system, thus facilitating endo overlap.

The fact that esters **29** and **30** do not react, even at 180 °C, is surprising, but is further discussed under Regioselectivity.

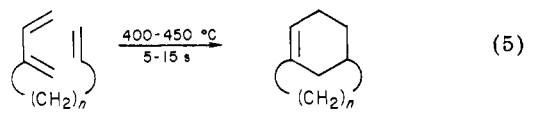
A most interesting development in the field has been the discovery that rather strained bridgehead alkenes can be formed via flash pyrolysis of certain trienes, as in eq 5.[24]



27, R = H; R_1 = Me; R_2 = H
28, R = Me; R_1 = Me; R_2 = H
29, R = Me; R_1 = H; R_2 = Me
30, trans, R = CH_3; R_1 = H; R_2 = Me

31, 60%

32, 40%



(5)

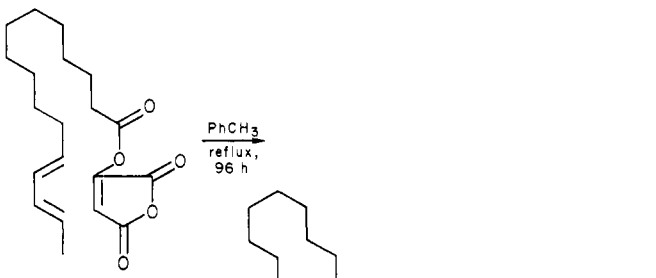
33, n = 3
34, n = 4

35, n = 3 (16%)
36, n = 4 (55%)

Thermodynamic data have been obtained on one of the simple systems, (n = 3), and, surprisingly, the reaction is exothermic by 18.3 kcal. The entropic factor is rather low (−29 eu), leading to an equilibrium constant of 0.28 at 427 °C.

Thus, the considerable strain in the product does not preclude its formation. In fact, the reaction can be carried out in solution when activating substituents are present on either side of the dienophile.[25]

Macrocyclic applications of the reaction have been reported in preliminary studies directed toward the synthesis of cytochalasans, fungal metabolites containing a 14-membered lactone ring fused to an isoindolene skeleton.[26] The model reaction using **37** with high dilution, as illustrated below, proved to be both stereo- and regioselective, forming macrolactones **38** and **39** in the indicated yields.



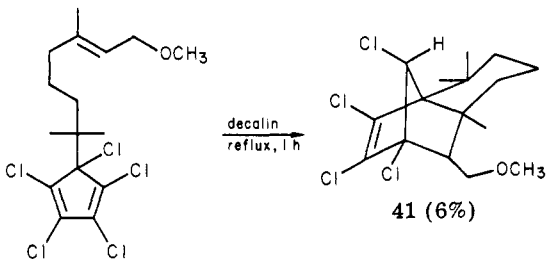
37

38 (27%)

39 (5%)
(stereochemistry unknown)

B. Endocyclic 5-Ring Dienes

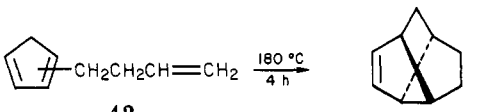
The enhanced reactivity of cyclopentadiene and its derivatives was utilized in early studies of the IMDA in an approach to longifolene.[9] Recently, this study was repeated with a perchlorocyclopentadienyl ring system (**40**) in an attempt to prevent the initial rearrangement to a 2-substituted cyclopentadiene derivative. Even here, however, an unexpected isomerization involving hydrogen abstraction led to the indicated product, **41**, rather than the longifolene skeleton.[27]



40

41 (6%)

The reactions of alkenylcyclopentadienes have been extended. While allylcyclopentadiene does not give any intramolecular products, butenylcyclopentadiene (**42**) provides a convenient route to brexene (**43**). Longer chains give the expected

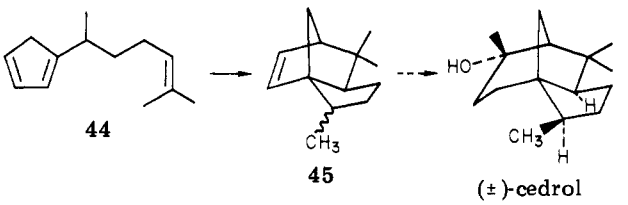


42

43 (quantitative)

bridgehead products.[28]

(±)-Cedrol and (±)-cedrene have been synthesized from appropriately substituted cyclopentadienes. The reaction apparently proceeded via a regioselective exo addition in **44** to give **45**.[29]

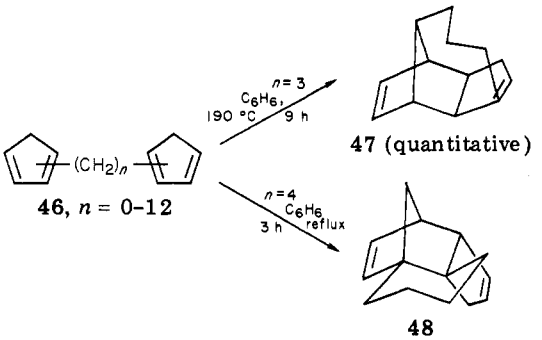


44

45

(±)-cedrol

Polymethylenebiscyclopentadienes (**46**, n = 0 ... 12) have also been studied.[30] Remarkably, in this series, only the compounds with n = 3 or 4 produced any intramolecular products. With a three-carbon bridge, the bridgehead diene **47** was formed resulting from an exo addition of a 1,3″ isomer. This is unusual in that considerably less strained exo and endo isomers can be envisaged. For n = 4 the expected bridgehead derivative **48** is formed.

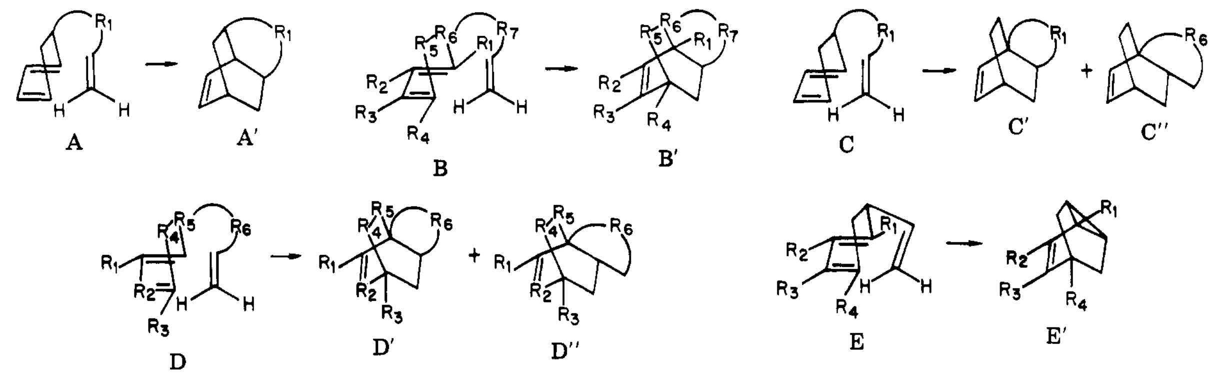


46, n = 0–12

47 (quantitative)

48

TABLE III: IMDA Reactions of Endocyclic Dienes of 6-Membered Rings



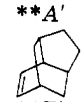
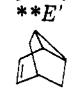
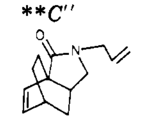
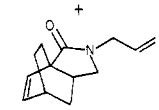
	skeletal type (A, B, C, D, or E)	product	(a) reference (b) yield (c) reaction conditions (d) comments
79a.	A skeleton $R_1 = (CH_2)_2$	***A′* 	(a) *12 (b) 71.9% (c) 200 °C (d) 3 in bridge
79b.	E skeleton $R_1 = R_2 = R_3 = R_4 = H$	***E′* 	(a) *12 (b) 13.2% (c) 200 °C (d) 1 in bridge
79c.	A skeleton $R_1 = CH_2$	A′	(a) *12 (b) 33.4% (c) 200 °C (d) 2 in bridge
80.	C skeleton $R_1 = C(O)N(CH_2CH{=}CH_2)CH_2$	***C′* ***C″*  + 	(a) 13 (b) 80% (c) 156 °C, 1.5 h (d) 3 in bridge
81a.	A skeleton $R_1 = (CH_2)_3$	A′	(a) *42a (b) 72.7% (c) 210 °C, 21 h (d) 4 in bridge
81b.	C skeleton $R_1 = (CH_2)_3$	C′ C″	(a) *42b (b) 5.9% (C′), 21.4% (C″) (c) 210 °C, 21 h (d) 3 in bridge
82a.	A skeleton $R_1 = C(O)CH_2CH_2$ or $C(CH_2)CH_2CH_2$	A′	(a) *42b (b) 37% (c) 227–232 °C, 50 h (d) 4 in bridge; isomerizes to form C skeleton in 82b
82b.	C skeleton $R_1 = C(O)CH_2CH_2$ or $C(CH_2)CH_2CH_2$	C′ C″	(a) *42b (b) 11% (C′), 43% (C″) (c) 227–232 °C, 50 h (d) 3 in bridge
83.	E skeleton (1) *1,2,2,1*, $R_1 = R_4$ (2) *1,2,1,2*, $R_2 = R_4$ (3) *2,1,1,2*, $R_2 = R_3$ (4) 2,1,2,1, $R_1 = R_3$ *1* / *2* (a) C_6H_5 / H (b) CO_2CH_3 / CH_3 (c) CO_2CH_2-CH_3 / C_4H_9 (d) CO_2CH_3 / C_6H_5	E′ 1a 1b, 2b 1c, 2c 1d–4d	(a) 44 (b) 25% (1a), 87% (1b, 2b), 80% (1c, 2c), 76% (1d–4d) (c) 180 °C (d) 1 in bridge
84.	E skeleton $R_1 = CO_2CH_3$; $R_2 = R_4 = H$; $R_3 = CO_2H$	E′	(a) 45 (b) 70% (c) heat (d) 1 in bridge

TABLE III (*Continued*)

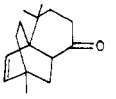
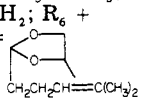
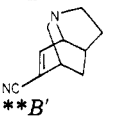
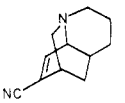
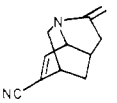
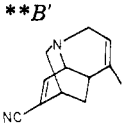
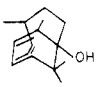
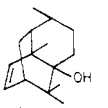
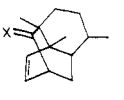
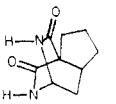
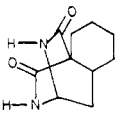
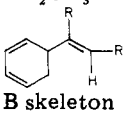
skeletal type (A, B, C, D, or E)	product	(a) reference (b) yield (c) reaction conditions (d) comments
85. D skeleton R_1 = H; R_2 = CH; R_3 = CH_3; R_4 = R_5 = CH_2; R_6 = $C(CH_3)_2CH_2CH_2$ C(O)	**D′ 	(a) 46 (b) 49% (c) heat (d) 4 in bridge
86. D skeleton (67) R_1 = R_2 = H; R_3 = CH_3; R_4 = R_5 = CH_2; R_6 + dienophile = 	D′ D″	(a) 47 (b) 55% (c) 250 °C, sealed tube, 24 h, mesitylene (d) 3 in bridge; several steps to khusimone
87a. B skeleton (69a) R_1 = R_2 = R_4 = H; R_3 = CN; R_5 = CH_2; R_6 = N; R_7 = $(CH_2)_2$	**B′ 	(a) 48 (b) 48% (c) 110 °C, 17 h, toluene (d) 3 in bridge
87b. B skeleton (69b) R_1 = R_2 = R_4 = H; R_3 = CN; R_5 = CH_2; R_6 = N; R_7 = $(CH_2)_3$	**B′ 	(a) 48 (b) 8% (c) 207 °C, 15 h, tetralin (d) 4 in bridge
87c. B skeleton (69c) R_1 = R_2 = R_4 = H; R_3 = CN; R_5 = CH_2; R_6 = N; R_7 = $CH_2C(CH_2)CH_2$	**B′ 	(a) 48 (b) 10% (c) 138–140 °C, 4 h, xylene (d) 3 in bridge
87d. B skeleton (69d) R_1 = R_2 = R_4 = H; R_3 = CN; R_5 = CH_2; R_6 = N; R_7 = CH_2CH=$C(CH_3)$	**B′ 	(a) 48 (b) 7% (c) 207 °C, 2 h, tetralin (d) 4 in bridge
88. B skeleton 	**B′ 	(a) *112 (b) 30% (c) 280 °C, 24 h, decalin/5% KO-*t*-Bu (d) 4 in bridge; racemic patchouli alcohol
89. B skeleton R_1 = CH_3; R_2 = R_3 = R_4 = H; R_5 = $C(CH_3)_2$; R_6 = CH_2; R_7 = $C(O)CH_2$	B′	(a) 113 (b) 84% (c) passage through GLC (d) 3 in bridge
90. B skeleton R_1 = CH_3; R_2 = R_3 = R_4 = H; R_5 = C(O) or $C(CH_2)$; R_6 = $C(CH_3)$; R_7 = $CH_2CH_2CH(CH_3)$	**B′ 	(a) *114 (b) 11.4% overall (c) 430 °C, GLC (d) 4 in bridge; norseyshellanone, R_5 = C(O); seychellene, R_5 = $C(CH_2)$
91. B skeleton R_1 = R_3 = H; R_2 = R_4 = CH_3; R_5 = C(O); R_6 = $C(CH_3)$; R_7 = OC(O)	B′	(a) *115 (b) yield not given (c) 70 °C (d) 3 in bridge
92a. D skeleton R_1 = OH; R_2 = N; R_3 = H; R_4 = NH; R_5 = C(O); R_6 = $(CH_2)_3$	**D′ 	(a) *116 (b) 100% (c) 200 °C, 5 h, DMF (d) 3 in bridge
92b. D skeleton R_1 = OH; R_2 = N; R_3 = H; R_4 = NH; R_5 = C(O); R_6 = $(CH_2)_4$	**D′ 	(a) *116 (b) 100% (c) 200 °C, 5 h, DMF (d) 4 in bridge
93. E skeleton R_1 = R_2 = R_3 = R_4 = H; R = CO_2CH_3 	E′	(a) *117a (b) yield not given (c) 48-h reflux (d) 1 in bridge
94. B skeleton R_1 = R_3 = R_4 = H; R_2 = CO_2CH_3; R_5 = CH_2; R_6 = $C(CH_3)$; R_7 + dienophile = $C(CH_3)$=CH_2	B′	(a) 117b (b) 10% (c) 100 °C, 17 h, benzene (d) 1 in bridge

TABLE III (*Continued*)

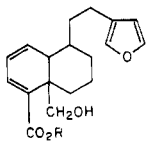
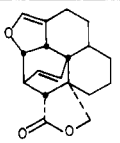
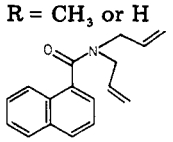
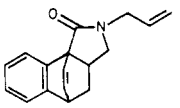
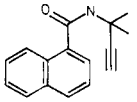
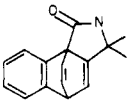
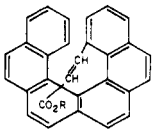
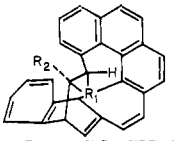
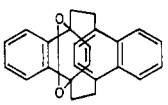
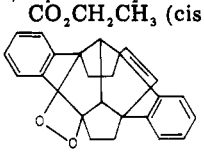
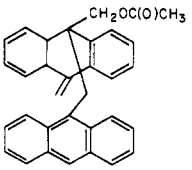
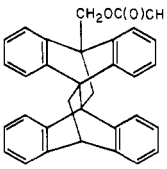
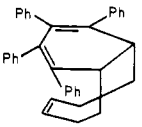
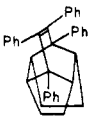
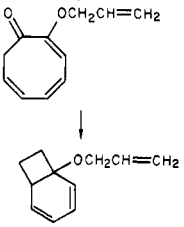
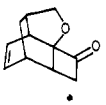
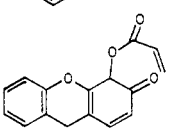
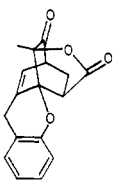
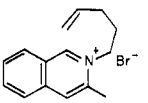
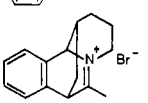
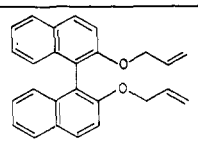
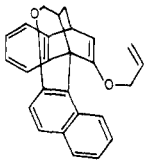
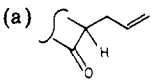
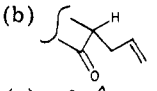
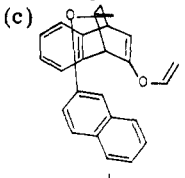
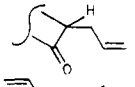
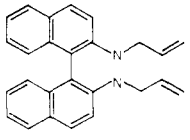
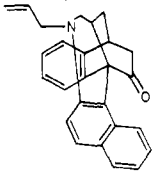
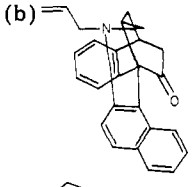
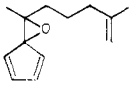
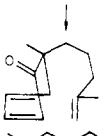
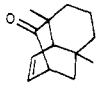
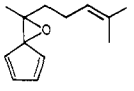
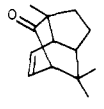
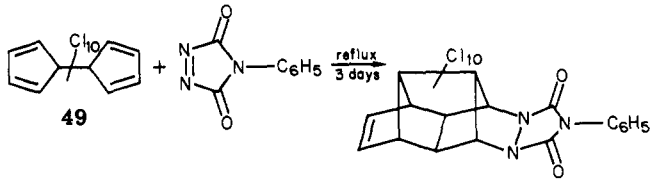
	exceptions to skeleton	product	(a) reference (b) yield (c) reaction conditions (d) comments
95. (71)	 R = CH_3 or H		(a) 49 (b) 90% (c) refluxing diglyme, 48 h, N_2 (d) 5 in bridge
96a. (76a)			(a) 13 (b) 70% (c) 218 °C, 3.5 h (d) 3 in bridge
96b. (76b)			(a) 13 (b) 76% (c) 218 °C, 3 h (d) 3 in bridge
97. (78)	 R = CH_2CH_3	 (a) R_1 = $CO_2CH_2CH_3$; R_2 = H (trans) (b) R_1 = H; R_2 = $CO_2CH_2CH_3$ (cis)	(a) 50a (b) 80% (a), 20% (b) (c) 12-h reflux in solution of $(EtO)_2P(O)CH_2CO_2Et$ (d) 5 in bridge; helicene skeleton
98. (80)			(a) 50b (b) 20% (c) $h\nu$ initially; 58 °C (d) 3 in bridge
99. (82)			(a) 51 (b) 92% (c) refluxing benzene and ethanol with KO-*t*-Bu, 1 h (d) 4 in bridge
100. (84)			(a) 52 (b) good yield, % not given (c) reflux temperature of tetracyclone and cyclooctadiene (d) 3 in bridge; one step synthesis
101. (86)			(a) 53 (b) 74% (c) 195 °C (d) 3 in bridge
102.			(a) *115 (b) 23% (c) 80 °C (d) 3 in bridge; nucleus of both morellin and gambogic acid
103.			(a) 118 (b) 46% (c) 240 °C, 24 h (d) 3 in bridge

TABLE III (*Continued*)

exceptions to skeleton	product	(a) reference (b) yield (c) reaction conditions (d) comments
104. 	 (a)  (b)  (c)  	(a) 119 (b) 44% (a), 3% (b), 19% (c) (c) 215 °C, 16 h (d) 4 in bridge
105. 	(a)  (b) 	(a) 120 (b) 28% (a), 10% (b) (c) 230 °C, 2-(methylamino)ethanol and water (d) 4 in bridge
106a.  		(a) 121 (b) 71% (c) 270–280 °C 2 h, toluene (d) 4 in bridge
106b.  		(a) 121 (b) 55% (c) 270–280 °C, 2 h, toluene (d) 3 in bridge

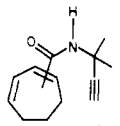
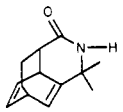
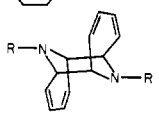
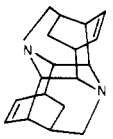
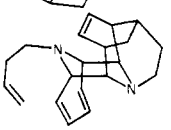
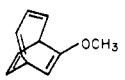
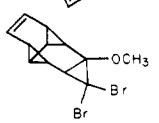
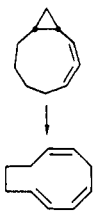
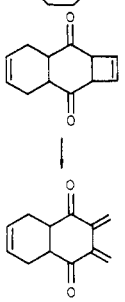
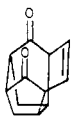
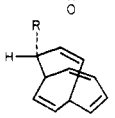
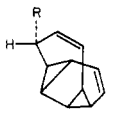
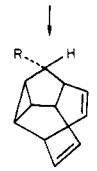
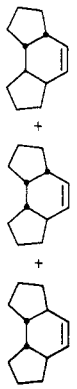
It should be noted that **47** is the thermodynamic product, since unheated samples of the 1,3-bis(cyclopentadienyl)propane show the presence of other isomers as well.

The biscyclopentadiene **46**, $n = 0$, is subject to an interesting IMDA which has been quaintly termed a "domino" DA reaction.[31] The perchloro analogue **49**, although resistant to all conventional dienophiles, finally succumbed to *N*-methyltriazolinedione to give the adduct **50**.



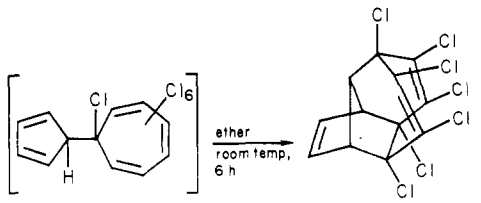
49 **50** (67%)

TABLE IV: IMDA Reactions of Endocyclic Dienes Larger Than Six

skeletal type	product	(a) reference (b) yield (c) reaction conditions (d) comments
107. 		(a) 13 (b) 78% (c) 218 °C, 3 h (d) 4 in bridge
108. (88a) (88b)  (a) R = $CH_2CH{=}CH_2$ (b) R = $CH_2CH_2CH{=}CH_2$	(a)  (b) 	(a) 54a and b (b) 30% (a), 27% (b) (c) 180 °C, sealed tube, 2-3 h (d) 4 in bridge
109. (90) 		(a) 55 (b) 29.8%, (c) 25 °C and dibromocyclopropanation (d) 1 in bridge
110. (92) 		(a) 56 (b) 50% (c) 250 °C, 45 s, Ar (d) 1 in bridge
111. (94) 		(a) 57 (b) yield not available (c) 480 °C (d) 3 in bridge
112.  R = *p*-nitrobenzoate	 	(a) 122 (b) yield not given (c) 1,8-bis(dimethylamino)naphthalene, 70% aqueous Me_2CO (d) 1 in bridge
113. 		(a) 58 (b) quantitative (c) 200 °C, Cp_2TiCl_2-$LiAlH_4$ (d) 3 in bridge

An interesting reaction takes place during the preparation of the chlorofulvalene derivative **51** from perchlorocycloheptatriene and sodium cyclopentadienide. Instead of obtaining this derivative or the fugitive hexachlorofulvalene, an IMDA supervenes and **52** is formed in 60% yield.[32]

Finally we note that the isomeric mixture of the tri(2-propynyl)

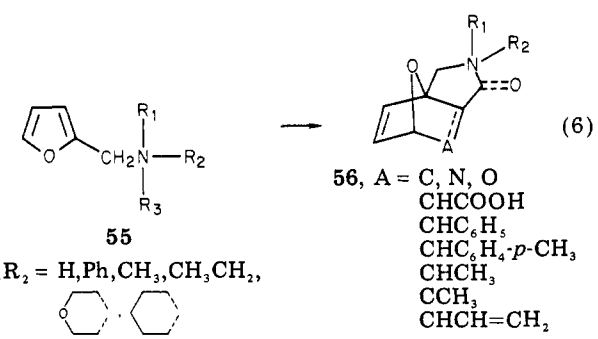


51 52 (60%)

ortho ester of cyclopentadienecarboxylic acid **53** cyclizes quantitatively to form **54**, a bridgehead alkene which appears quite strained.[33]

53 54 (quantitative)

Five-membered heterodienes are expected to be much less reactive, although one of the earliest reports includes the cyclization of a furan derivative.[6] Since that time, numerous other cases have been reported of cyclizations involving a variety of furfuryl derivatives of the type shown in eq 6.[34a-d] A related thiophene case has also been reported.[35]



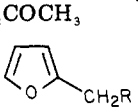
(6)

55

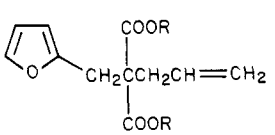
R_1, R_2 = H, Ph, CH_3, CH_3CH_2,

R_3 = $COCH{=}CHCOOH$
$COCH{=}CHC_6H_5$
$COCH{=}CHC_6H_4$-*p*-CH_3
$COCH{=}CHCH_3$
$CH_2C{\equiv}N$
$CH_2C{\equiv}CH$
$CH_2C{\equiv}CCH_3$
$CH{=}CHCH{=}CH_2$
CH_2COCH_3

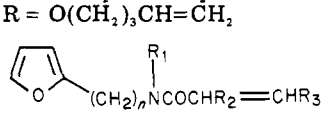
56, A = C, N, O
$CHCOOH$
CHC_6H_5
CHC_6H_4-*p*-CH_3
$CHCH_3$
CCH_3
$CHCH{=}CH_2$



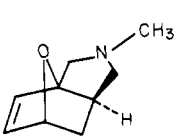
57a, R = $COOCH_2CH{=}CH_2$
b, R = $COOCH_2C(COOR){=}CH_2$
c, R = $NHCOCH{=}CH_2$
d, R = $OCOCH{=}CH_2$
e, R = $OCH_2CH{=}CH_2$
f, R = $O(CH_2)_3CH{=}CH_2$



59

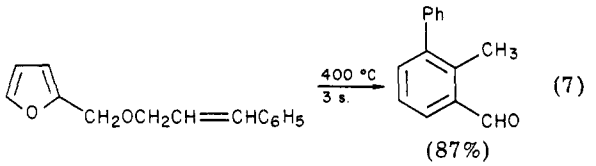


58, n = 1-3



60

Unusual steric effects appear to play a significant role in the cyclization of furan derivatives. Thus, neither furfurylacetic acid derivatives **57a–c** nor furfuryl alcohol derivatives **57d–f** appear to cyclize,[36,37] with the possible exception of furfuryl cinnamyl ether, which gives 2-methyl-3-phenylbenzaldehyde in high yield on flow pyrolysis at 400 °C,[37] as in eq 7. A mechanism involving

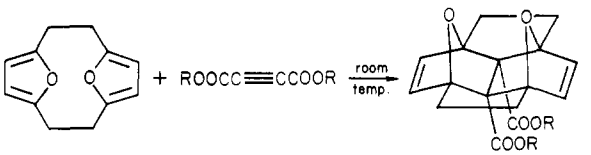


(87%) (7)

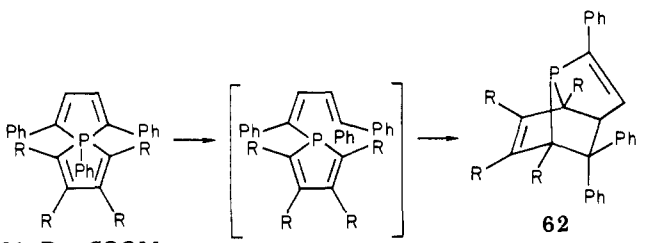
an intermediate DA adduct seems most plausible.

On the other hand, tertiary amine derivatives **58** did cyclize more or less readily, as well as **59** containing a fully substituted carbon atom in the side chain.[36a] The products, at least in the cases involving the formation of five-membered bridgehead rings, appear to be regiospecific exo additions as in **60**.

The "domino" reaction has also been carried out with a furanoid cyclophane[38] and predictable extensions to hybrid systems such as the 1,4-naphtho- and 9,10-anthraceno[2.2]-furanophanes have been carried out.[39,40]



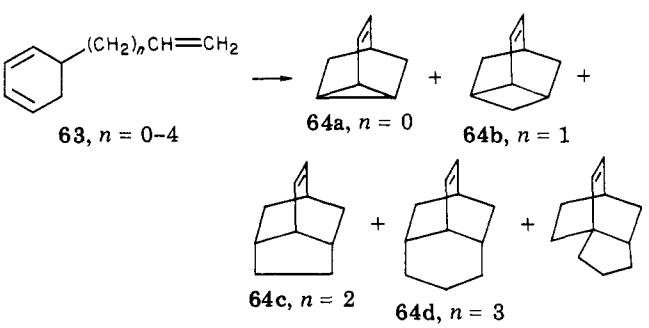
Another more complex example is the rearrangement of the spirophosphole **61** to **62**, which presumably occurs via an open-chain intermediate.[41]



61, R = COOMe 62

C. Endocyclic 6-Ring Dienes

The cyclizations of a series of alkenylcyclohexadienes (**63**) has been reported. Structures have not yet been determined for the example where n = 4, however.[42a,b,43]



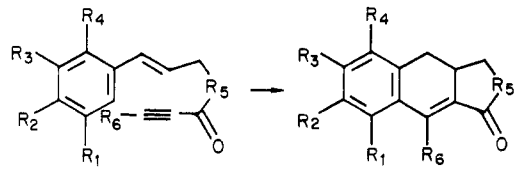
63, n = 0-4 64a, n = 0 64b, n = 1 64c, n = 2 64d, n = 3

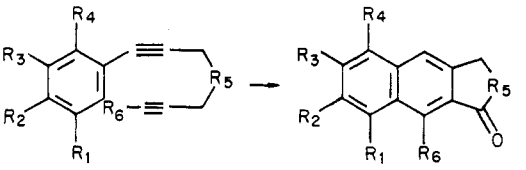
Two facile entries into the series with n = 2 have been noted. The mixed oligomerization of butadiene and substituted alkynes produces suitable precursors, albeit as a mixture of isomers. These cyclize readily to the corresponding tricyclo[2.2.2.$0^{2,6}$]-oct-7-enes.[44]

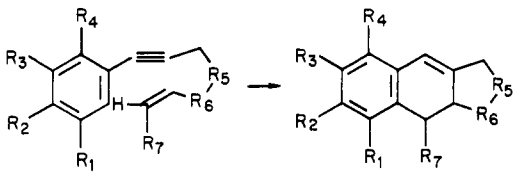
Similarly, addition of dienes to coumalic acid or methyl coumalate eventually produces tricyclooctenes, presumably via unisolated vinylcyclohexadiene intermediates.[45]

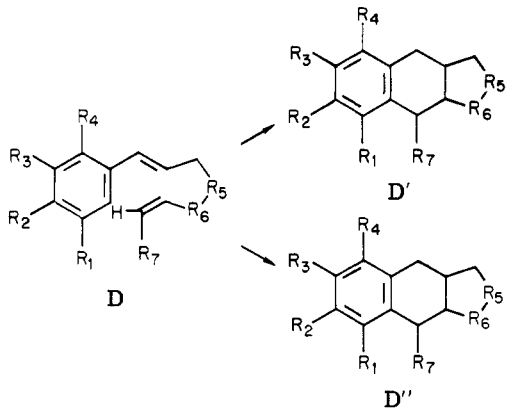
More specific use of the reaction was made in a synthesis of a thujopsene derivative useful in fragrances. Thus, cyclization of ketone **65** proceeded readily to give a mixture of **66a** and **66b**. That these were indeed the kinetic products was shown by equilibrium of either isomer to the same 3:1 mixture.[46]

TABLE V: IMDA Reactions of Endo,exo Dienes









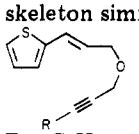
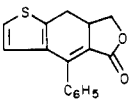
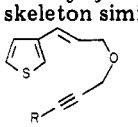
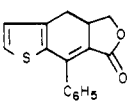
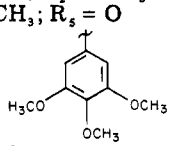
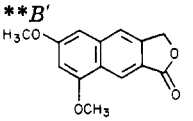
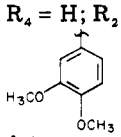
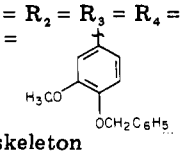
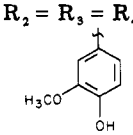
	skeletal type (A, B, C, or D)	product	(a) reference (b) yield (c) reaction conditions (d) comments
114a.	skeleton similar to A  R = C_6H_5		(a) 64 (b) 24% (c) refluxing Ac_2O (d) 3 in bridge
114b.	skeleton similar to A  R = C_6H_5		(a) 64 (b) 10% (c) refluxing Ac_2O (d) 3 in bridge
115.	A skeleton R_1 = H; R_2 and R_3 form: OCH_2O; R_4 = OCH_3; R_5 = O R_6 = 	A'	(a) *123b (b) 60% (c) refluxing Ac_2O (d) 3 in bridge
116.	B skeleton $R_1 = R_2 = OCH_3$; $R_2 = R_4$ = H; R_5 = O; R_6 = H	**B' 	(a) *123c (b) 10% (c) refluxing Ac_2O (d) 3 in bridge
117.	B skeleton $R_1 = R_4$ = H; R_2 and R_3 form: OCH_2O; R_5 = O; R_6 = H or R_6 as in reaction 115 above	B'	(a) *123c and *10 (b) 3% (c) refluxing Ac_2O (d) 3 in bridge
118.	A skeleton $R_1 = R_4$ = H; $R_2 = R_3 = OCH_3$; R_5 = O; R_6 = 	A'	(a) *123a (b) 18% (c) refluxing DMF (d) 3 in bridge
119a.	A skeleton $R_1 = R_2 = R_3 = R_4$ = H; R_5 = O; R_6 = 	A'	(a) 123d (b) 29-39% (c) refluxing Ac_2O (d) 3 in bridge
119b.	A skeleton $R_1 = R_2 = R_3 = R_4$ = H; R_5 = O; R_6 = 	A'	(a) 123d (b) 29-39% (c) refluxing Ac_2O (d) 3 in bridge

TABLE V (*Continued*)

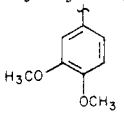
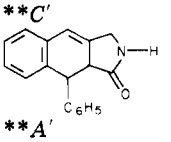
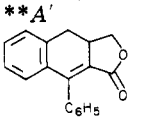
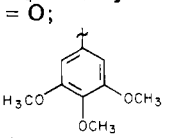
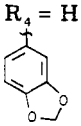
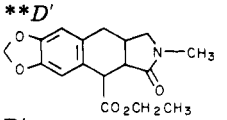
	skeletal type (A, B, C, or D)	product	(a) reference (b) yield (c) reaction conditions (d) comments
119c.	A skeleton $R_1 = R_4 = H$; $R_2 = OCH_2C_6H_5$; $R_3 = OCH_3$; $R_5 = O$; R_6 = 	A′	(a) 123d (b) 29-39% (c) refluxing Ac_2O (d) 3 in bridge
120a.	A skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = NH$; $R_6 = C_6H_5$	A′	(a) 123e (b) 80% (c) refluxing Ac_2O (d) 3 in bridge
120b.	B skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = NH$; $R_6 = C_6H_5$	B′	(a) 123e (b) 66% (c) refluxing Ac_2O (d) 3 in bridge
120c.	C skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = NH$; $R_6 = CO$; $R_7 = C_6H_5$	**C′ 	(a) 123e (b) 23% (c) refluxing Ac_2O (d) 3 in bridge
121a. (104)	A skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = O$; $R_6 = C_6H_5$	**A′ 	(a) 63 and 123a (b) 46% (c) refluxing Ac_2O (d) 3 in bridge
121b.	B skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = O$; $R_6 = C_6H_5$	B′	(a) 63 (b) 39% (c) refluxing Ac_2O (d) 3 in bridge
122.	A skeleton $R_1 = R_4 = H$; $R_2 + R_3$ form: OCH_2O; $R_5 = O$; R_6 = 	A′	(a) 63 (b) 39% (c) refluxing Ac_2O (d) 3 in bridge
123.	B skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = O$; $R_6 = H$	B′	(a) *123c (b) 2% (c) refluxing Ac_2O (d) 3 in bridge
124a.	A skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = NCH_2C_6H_5$ $R_6 = C_6H_5$	A′	(a) 123e (b) quantitative (c) refluxing Ac_2O (d) 3 in bridge
124b.	B skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = NCH_2C_6H_5$; $R_6 = C_6H_5$	B′	(a) 123e (b) 14% (c) refluxing Ac_2O (d) 3 in bridge
125a.	B skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = NCH_2C_6H_5$; $R_6 = C_6H_5$	B′	(a) *123f (b) 14% (c) refluxing Ac_2O (d) 3 in bridge
125b.	A skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = NCH_2C_6H_5$; $R_6 = C_6H_5$	A′	(a) *123f (b) 29% (c) refluxing Ac_2O (d) 3 in bridge
126.	A skeleton $R_1 = R_4 = H$; $R_2 = R_3 = OCH_3$; $R_5 = O$; R_6 = 	A′	(a) 124 (b) 9% (c) refluxing Ac_2O (d) 3 in bridge; synthesis of (±)-collinusin and justicidin B
127.	D skeleton $R_1 = R_4 = H$; $R_2 + R_3$ form; OCH_2O; $R_5 = NCH_3$; $R_6 = CO$; $R_7 = CO_2CH_2CH_3$	**D′ 	(a) *125 (b) 56% (c) refluxing toluene, 8 h, N_2 (d) 3 in bridge
128.	D skeleton $R_1 = R_3 = R_4 = H$; $R_2 = Cl$; $R_6 = CH_2$; $R_7 = p$-chlorobenzene	D′	(a) *125 (b) yield not given (c) 180 °C, *o*-dichlorobenzene (d) 3 in bridge

TABLE V (*Continued*)

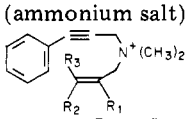
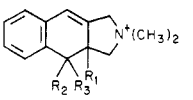
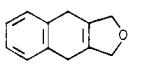
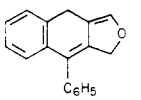
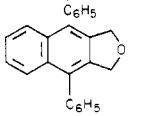
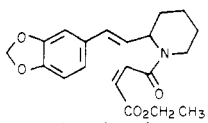
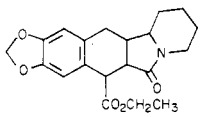
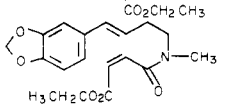
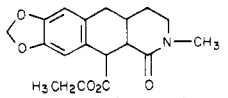
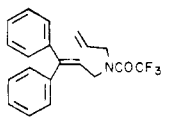
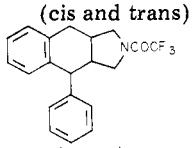
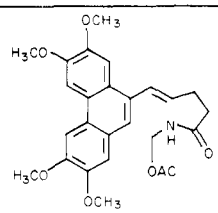
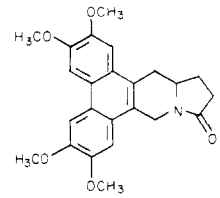
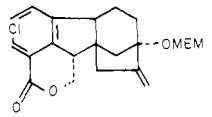
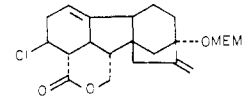
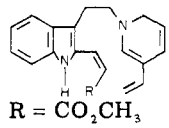
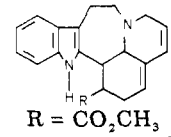
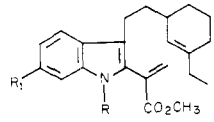
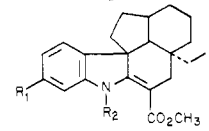
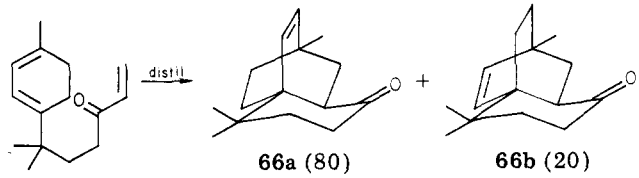
	skeletal type (A, B, or C)	product	(a) reference (b) yield (c) reaction conditions (d) comments
129.	D skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = NCH_2C_6H_5$; $R_6 = CO$; $R_7 = C_6H_5$	D′	(a) *126 (b) 48% (c) 180 °C, 6 days, *o*-dichlorobenzene (d) 3 in bridge
130a.	D skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = NCOCF_3$; $R_6 = CH_2$; $R_7 = H$	D′ D″	(a) *126 (b) 20.33% (D′), 40.67% (D″) (c) 235 °C, 20 h (d) 3 in bridge
130b.	D skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = NCOCF_3$; $R_6 = CH_2$; $R_7 = C_6H_5$	C′	(a) *126 (b) 78% (c) 180 °C, 20 h (d) 3 in bridge
131.	basic C skeleton (ammonium salt)  (a) $R_1 = R_2 = R_3 = H$ (b) $R_1 = H$; $R_2 = CH_3$; $R_3 = H$ (c) $R_1 = H$; $R_2 = H$; $R_3 = CH_3$ (d) $R_1 = H$; $R_2 = C_6H_5$; $R_3 = H$	(a) 	(a) 127 (b) 65% (a), 80% (b), 40% (c), 100% (d) (c) aqueous NaOH (d) 3 in bridge
132a. (106)	C skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = O$; $R_6 = CH_2$; $R_7 = H$	C′ (i) (ii) 	(a) 65 (b) 55% (i), 28 (ii) (c) 55 °C, KO-*t*-Bu (d) 3 in bridge; adduct forms after isomerization of triple bond to allene system
132b.	C skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = O$; $R_6 = CH_2$; $R_7 = C_6H_5$	(i)  (ii) 	(a) 65 (b) 52% (i), 30% (ii) (c) 55 °C, KO-*t*-Bu (d) 3 in bridge; adduct forms after isomerization of triple bond to allene system
132c.	C skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = O$; $R_6 = CH_2$; $R_7 = C_6H_5$	C′	(a) 65 (b) 97% (c) 55 °C, KO-*t*-Bu (d) 3 in bridge
132d.	C skeleton $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = O$; $R_6 = CH_2$; $R_7 = H$	C′	(a) 65 (b) 77% (c) 55 °C, KO-*t*-Bu (d) 3 in bridge
	exceptions to skeleton		
133a.	skeleton similar to C but with trans (=) $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = NH$; $R_6 = CO$; $R_7 = C_6H_5$	C′	(a) 123e (b) 75% (c) refluxing Ac_2O (d) 3 in bridge
133b.	skeleton similar to C but with trans (=) $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = NCH_2C_6H_5$; $R_6 = CO$; $R_7 = C_6H_5$	C′	(a) 123e (b) 17% (c) refluxing Ac_2O (d) 3 in bridge
134.			(a) *125 (b) 37% (c) refluxing CH_3CN, 15 min, N_2 (d) 3 in bridge
135.		 (cis and trans)	(a) *125 (b) 11% (cis), 27% (trans) (c) refluxing *o*-dichlorobenzene (d) 4 in bridge
136.		 (trans)	(a) *126 (b) 48% (trans) (c) 180 °C, 6 days (d) 3 in bridge

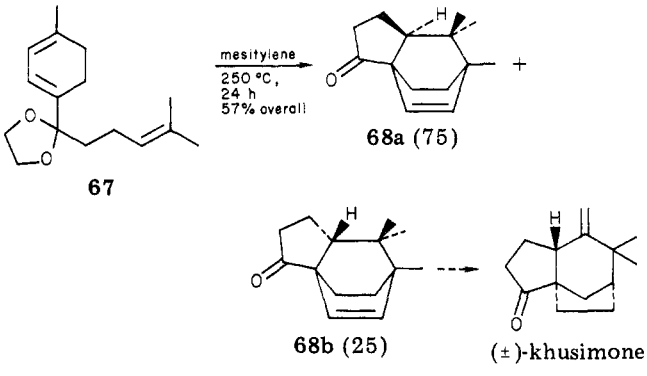
TABLE V (*Continued*)

	exceptions to skeleton	product	(a) reference (b) yield (c) reaction conditions (d) comments
137. (19)			(a) 19 (b) 50% (c) 220 °C, 5 h, bromobenzene (d) 3 in bridge; several steps to tylophorine
138. (97)			(a) 59a and b (b) 55% (c) 160 °C, sealed tube, 45 h, benzene/propylene oxide (d) 4 in bridge synthesis of gibberellic acid
139.	 $R = CO_2CH_3$	 $R = CO_2CH_3$	(a) *128 (b) 28% (c) 100 °C, EtOAc solution (d) 5 in bridge
140. (99a)	 (a) $R_1 = H; R_2 = H$ (b) $R_1 = OCH_3; R_2 = H$ (c) $R_1 = H; R_2 = CH_3$	 (a) $R_1 = H; R_2 = H$ (b) $R_1 = OCH_3; R_2 = H$ (c) $R_1 = H; R_2 = CH_3$	(a) 60, 61, and 62 (b) 55% (a), 92% (b), 56% (c) (c) formed in situ, 118 h, toluene (a); 72 h, toluene (b); 72 h, toluene (c) (d) 3 in bridge; (±)-vincadifformine is formed from (a); (±)-ervinceine is formed from (b); minovine is formed from (c)



65 66a (80) 66b (20) (quantitative)

Khusimone, a norsequiterpene component of Vetiver oil, has been prepared by an IMDA of intermediate **67** to **68a** and **68b**. Further acid-catalyzed rearrangement as well as a difficult photochemically generated endo–exo isomerization of the double bond are required to complete the synthesis.[47]

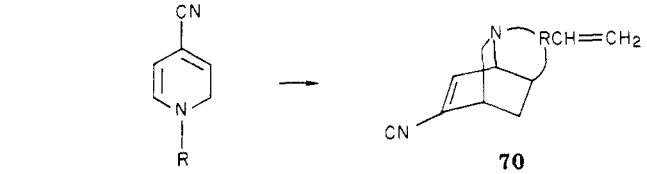


67 68a (75) 68b (25) (±)-khusimone

Work has also continued on dihydropyridines of type **69**. Modest yields of the adducts corresponding to type **70** were obtained, partly due to the competitive formation of dimers.[48]

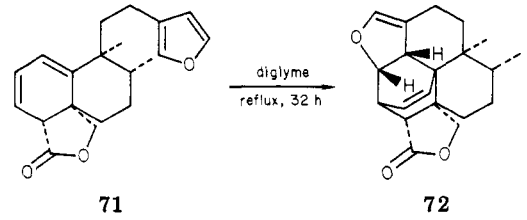
Here must also be included an unusual transformation of a naturally occurring furanoid diterpene. Upon heat treatment of its methyl ether, **71** is formed; this isomerizes and then undergoes an IMDA, in which the furan ring serves as a dienophile to form **72**.[49] This reaction, with inverse electron demand, has only been observed with *o*-quinone and furan.

The IMDA of a dihydropyridine derivative is involved in the

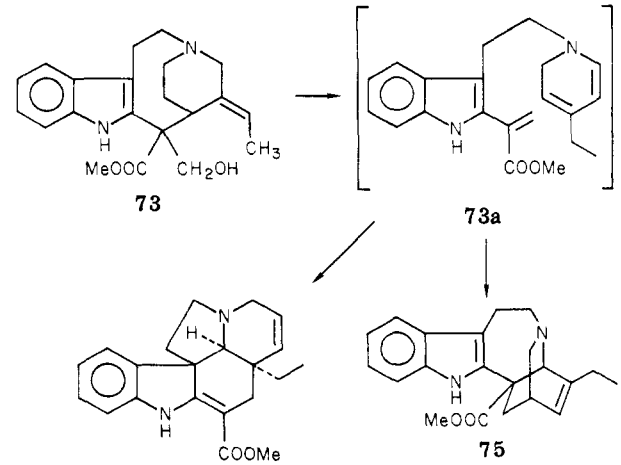


69a, R = $CH_2CH_2CH{=}CH_2$
b, R = $(CH_2)_3CH{=}CH_2$
c, R = $CH_2C(=CH_2)CH{=}CH_2$
d, R = $CH_2CH{=}C(CH_3)CH{=}CH_2$

70

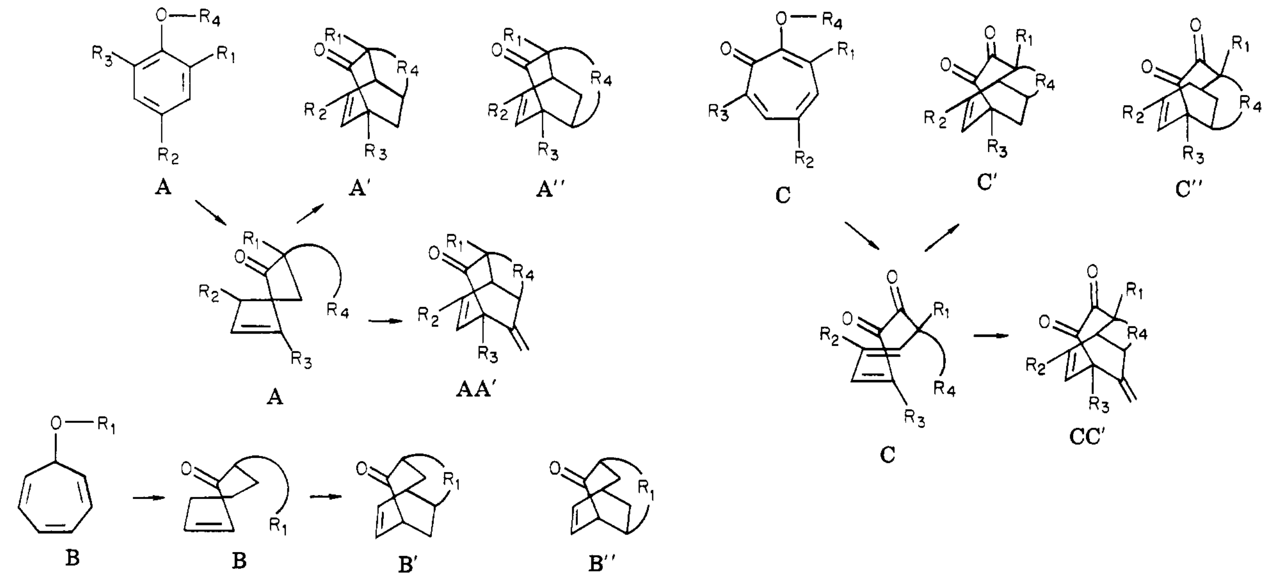


71 72



73 73a 74 75

TABLE VI. IMDA Reactions of Claisen Rearrangement Products



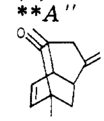
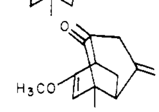
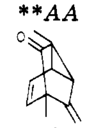
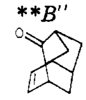
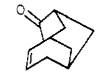
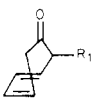
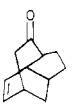
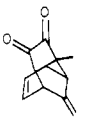
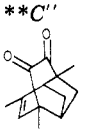
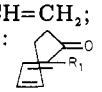
	skeletal type (A, B, or C)	product	(a) reference (b) yield (c) reaction conditions (d) comments
141a.	A skeleton $R_1 = R_3 = CH_3$, R_2 = (i) CH_3; (ii) OCH_3; $R_4 = CH_2C(CH_2)CH{=}CH_2$	(i) ***A'* A'' (ii) A' ***A''*  	(a) 129a (b) (i) 12% (A'), 44% (A'') (ii) 18% (A'), 54% (A'') (c) (i) 80 °C, benzol, 24 std 50 °C, benzol/16 std (ii) 80 °C, benzol/36 std (d) 3 in bridge
141b.	A skeleton $R_1 = R_3 = CH_3$; R_2 = H; $R_4 = CH_2CH_2CH{=}CH_2$	A'	(a) 129 a (b) 8% (c) 110 °C, toluene (d) 3 in bridge
142.	A skeleton $R_1 = R_3 = CH_3$; R_2 = H; $R_4 = CH_2C{\equiv}CH$ triple bond forms allene system = • =	***AA'* 	(a) 129 b (b) yield not given (c) heat (d) 1 in bridge
143.	A skeleton $R_1 = R_3 = CH_3$; R_2 = H or CH_3; $R_4 = R_5$ $\equiv - R_6$	AA'	(a) 129 b (b) yield not given (c) reaction conditions, not given (d) 1 in bridge
144.	A skeleton $R_1 = R_2 = R_3 = CH_3$; $R_4 = COOCH{=}CH_2$	A'	(a) 129 c (b) 41% (c) 80 °C, refluxing benzene (d) 3 in bridge
145. (113a)	A skeleton $R_1 = R_2 = R_3 = CH_3$; $R_4 = CH_2CH{=}CHCH{=}CH_2$	A' A''	(a) *129d and 67 (b) 4.3% (A'), 12.5% (A'') (c) heat (d) 4 in bridge
146. (113b)	A skeleton $R_1 = R_3 = CH_3$; R_2 = H; $R_4 = CH_2CH{=}C(CH_3)$ $CH{=}CH_2$	A' A''	(a) *130 and 67 (b) 60% (c) 75-80 °C (d) 4 in bridge; several steps to (±)-seychellene
147. (111)	B skeleton $R_1 = CH_2CH{=}CH_2$	***B'* ***B''*  	(a) 66a and b (b) 41% (B'), 41% (B'') (c) 200 °C, 24 h (d) 3 in bridge

TABLE VI. (*Continued*)

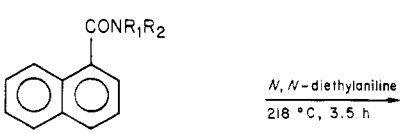
skeletal type (A, B, or C)	product	(a) reference (b) yield (c) reaction conditions (d) comments
148a. B skeleton $R_1 = CH_2CH_2CH{=}CH_2$	B′ B″	(a) 131a (b) 58% (B′), 18% (B″) (c) 200–210 °C, neat or in heptane (d) 4 in bridge; isomerizes to 148b
148b.  $R_1 = CH_2CH_2CH{=}CH_2$		(a) 131a (b) 24% (c) 200–210 °C, neat or in heptane (d) 3 in bridge
149a. C skeleton $R_1 = CH_3$; $R_2 = R_3 = H$; $R_4 = CH_2C{\equiv}CH$; R_4 isomerizes to form allene system; = • =	**CC′ 	(a) 68 (b) 80% (c) refluxing nonane (d) 1 in bridge; position of CH_3 makes IMDA more favored than in reaction 149b
149b. C skeleton $R_1 = R_2 = H$; $R_3 = CH_3$; $R_4 = CH_2C{\equiv}CH$; R_4 isomerizes to form allene system; = · =	CC′	(a) 68 (b) yield not given (small) (c) refluxing nonane (d) 1 in bridge
150. C skeleton $R_1 = R_2 = R_3 = CH_3$; $R_4 = CH_2CH{=}CH_2$	C′ **C″ 	(a) 131b (b) yield not given (c) 160 °C, then 240 °C (d) 2 in bridge
151. B skeleton $R_1 = (CH_2)_3CH{=}CH_2$; isomerizes to: 		(a) 131c (b) 77% (c) 200–205 °C, 24 h, heptane (d) 3 in bridge
152. B skeleton $R_1 = CH_2CH{=}CH_2$; all carbon analogue	**(*i*) (i) forms before Claisen rearrangement B′ B″ 	(a) 132 (b) 15% (*i*), 20% (B′), 65% (B″) (c) 215 °C, 4 days, heptane (d) 3 in bridge; all carbon analogue
153. A skeleton $R_1 = R_2 = R_3 = CH_3$; $R_4 = (CH_2)_3CH{=}CH_2$	A′	(a) 67 (b) 6.8% (c) 50 °C (d) 4 in bridge
154. B skeleton R_1 = 		(a) 133 (b) 21% (c) 200–205 °C, 24 h, heptane (d) 4 in bridge
155. A skeleton $R_1 = R_2 = R_3 = CH_3$; R_4 = 		(a) 67 (b) 26% (c) 50 °C (d) 4 in bridge

thermal transformation of the alkaloid stemmadenine **73**, which gives **74** and **75**, albeit in low yields. Most plausible is the formation of intermediate **73a**, which can cyclize in two modes, with the dihydropyridine moiety serving as diene to form the Iboga-type structure **75**, or, functioning as a dienophile, leading to the Aspidosperma representative **74**. These reactions have been reviewed previously.[3] Syntheses specifically based on the latter principle will be discussed under Endo,exo Systems.

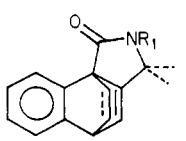
Other sources for endocyclic 6-member dienes are aromatic compounds, as well as valence tautomers. A few cases of IMDA utilizing such structures have been reported.

No benzenoid system has as yet been reacted via an IMDA, but the more reactive naphthalene derivatives **76a,b** do cyclize.[13]

Rather more complex products result from a hexahelicene derivative, **78**, which gave **79a,b** in the indicated yields.[50a] A secondary product of the autoxidation of [2.2]paracyclonaphthane **80** is **81**,[50b] and an IMDA is involved in the final step of a synthesis of lepidopterene (**83**) from **82**.[51]



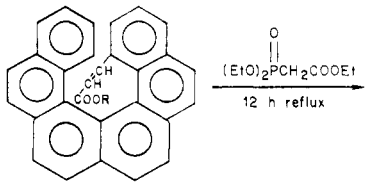
76a, R_1, $R_2 = CH_2CH{=}CH_2$
b, $R_1 = H$; $R_2 = Me_2CC{\equiv}CH$



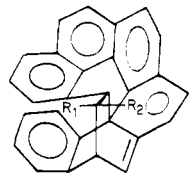
77a (70%)
b (76%)

Cage compound **85** is formed from **84** which itself is readily available from a Diels–Alder reaction of tetracyclone and 1,5-cyclooctadiene.[52]

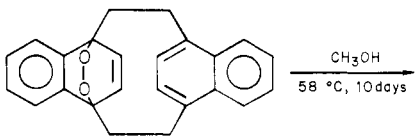
Cyclooctapolyenes form a convenient source of cyclo-



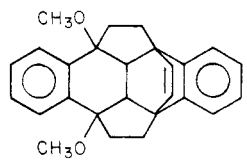
78



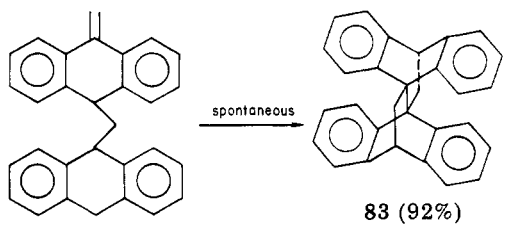
79a, R_1 = COOMe; R_2 = H (80%)
b, R_1 = H; R_2 = COOMe (20%)



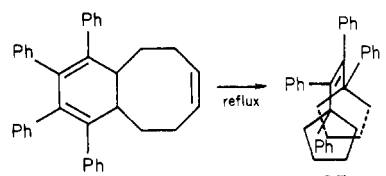
80



81 (20%)

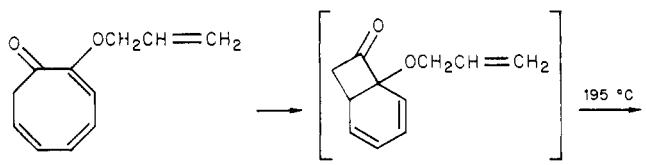


82 83 (92%)

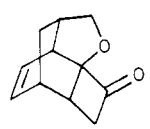


84 85

hexadienes by valence tautomerization. Thus, **86** readily forms **87** via **86a**.[53]



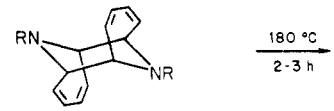
86 86a



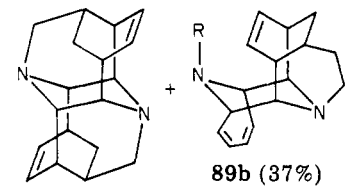
87 (74%)

D. Endocyclic Dienes in Rings >6

There are as yet few examples of IMDA's involving larger rings. With the exception of the Claisen rearrangement products of troponoid derivatives, we note the following examples. Dimers of azepins **88a,b** cyclize in modest yields to form the indicated structures, whose stereochemistry, although plausibly based on model studies, remain to be secured.[54a,b]

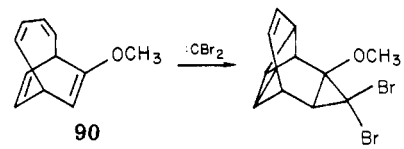


88a, R = $CH_2CH=CH_2$
b, R = $CH_2CH_2CH=CH_2$



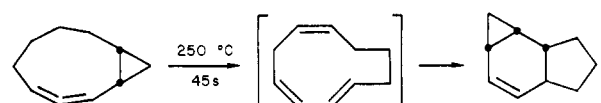
89a (30%) 89b (37%)

The bicyclotetraene **90**, although clearly arranged for an IMDA, normally does not cyclize due to the strain introduced by the presence of two cyclopropane rings. However, the addition of dibromocarbene leads to the formation of **91** rather than the expected adduct.[55]



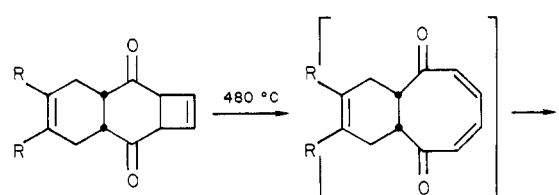
90 91

A trans,cis,cis isomer of 1,3,6-cyclodecatriene is the most likely precursor of the stereospecifically formed product **93** from the pyrolysis of allene **92**.[56]

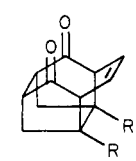


92 93

Valence isomerization of **94** provides the same ring system as **85** with the diene and dienophile reversed, leading to a related cage structure, **95**.[57]



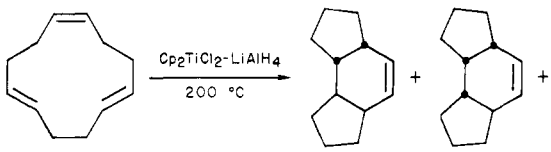
94



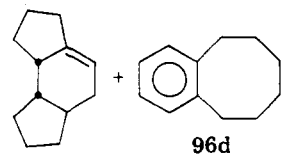
95

IMDA reactions are also undoubtedly the basis of a series of transformations of *cis,trans,trans*-dodeca-1,5,9-triene. When this olefin was treated with Cp_2TiCl_2–$LiAlH_4$ at 200 °C four products, **96a–d**, were formed as indicated. All can readily be accounted for by considering the corresponding conjugated isomers of CDT.[58]

The indicated products **96a** and **96b** would be formed stereospecifically from *cis,trans,cis*- or *cis,cis,trans*-1,6,8-cyclododecatriene and *trans,trans,cis*- or *trans,cis,trans*-1,6,8-cyclododecatrienes, respectively. **96c** could originate from **96b** by an additional hydrogen migration or conceivably from cis,-trans,trans- or trans,trans,trans-1,6,8 isomers, followed by hydrogen shifts.



96a 96b



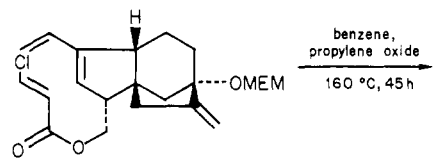
96c 96d

E. Endo,exo Dienes

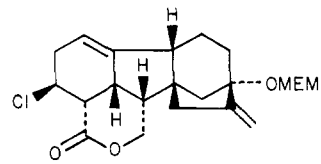
1. Alicyclic Systems

There are as yet few representatives of IMDA reactions involving alicyclic systems with endo,exo dienes. However, the examples cited indicate the substantial promise which these systems have for natural product synthesis.

Thus, a key step in the recently announced synthesis of gibberellic acid was the intramolecular endo cyclization of **97** to give **98**. The presence of propylene oxide as an HCl scavenger was crucial to the success of this reaction.[59a,b]

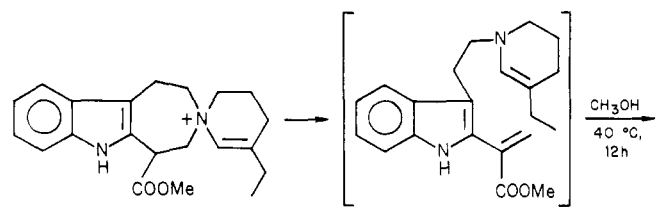


97

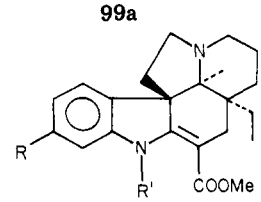


98 (55%)

As mentioned earlier, alkaloid synthesis will prove to be a fertile field for the application of the IMDA reaction. In fact, a synthesis based on exactly this principle for the alkaloid vincadifformine (**100**) has been reported by the in situ generation of intermediate **99a** from **99**. The biosynthetic route thus gains considerable plausibility, considering the excellent yield and mild conditions required.[60]



99 99a



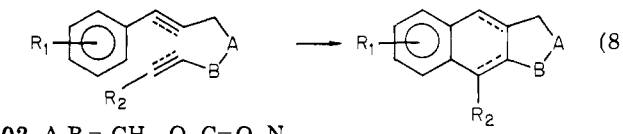
100, R,R′ = H; vincadifformine
101, R = OCH_3; R′ = H; ervinceine

Successful syntheses of related alkaloids, such as ervinceine (**101**), have also been reported.[61]

Generation of the same intermediates from a tetrahydrocarboline precursor has led to alternate syntheses of the same alkaloids, and additionally to minovine **100** (R′ = CH_3).[62]

2. Aromatic Systems

Styrene and its congeners have often been used as dienes, and in fact one of the first IMDA reactions reported was that of a styrene derivative, which gave the derivative of a natural product.[10] Considerable flexibility is available in terms of substituents for the general reaction depicted in eq 8.

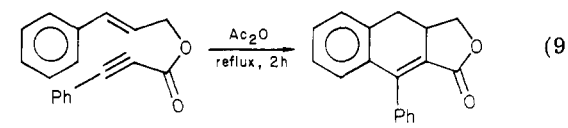


(8)

102, A,B = CH_2, O, C=O, N 103

In other words, tricyclic lactones, lactams, ethers, and amines are the typical products. The all-carbon analogue has evidently not been prepared.

A typical example would be the cyclization of cinnamyl propiolate as shown in eq 9.[63]

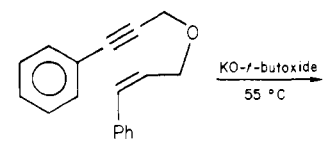


(9)

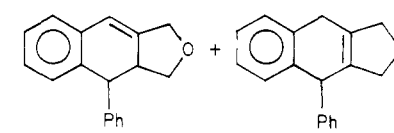
104 105 (46%)

In place of the benzene ring, thiophene has also been used; however, yields are rather modest.[64] The reaction is clearly capable of considerable extension.

There is also evidence, in the presence of base, for the intermediate formation and cyclization of allenes derived from the corresponding alkynes under rather mild conditions. Thus, the ether **106** cyclizes smoothly in the presence of strong base to **107a** and **107b**. A corresponding aliphatic example reinforces the intermediacy of allenes.[65]

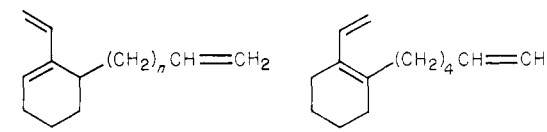


106

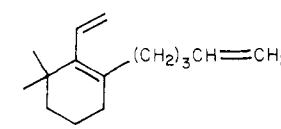


107a (55%) + 107b (28%)

The search for new approaches to a variety of polycyclic ring systems in natural products prompted a study of the cyclization of **108**, **109**, and **110**. At temperatures up to 250 °C, there was no indication of any IMDA, however.



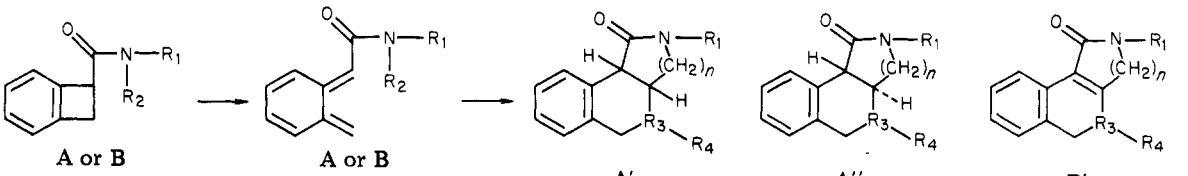
108, n = 2-4 109



110

The failure of these cyclizations may be superficially attributed to steric effects and lack of activation in the dienophile.

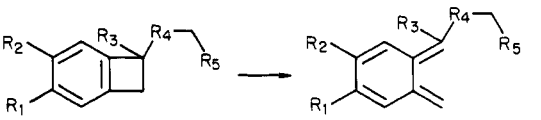
TABLE VII: IMDA Reactions of *o*-Quinodimethanes



A or B A or B A' (cis) A'' (trans) B'

A skeleton contains a double bond in R_2
B skeleton contains a triple bond in R_2

A' and A'' are formed from a double bond in R_2; B' is formed from a triple bond in R_2; N and C=O can switch positions, and R_1 changes with N substituent



C C

(for structures formed from C, note illustrated reaction products)

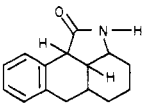
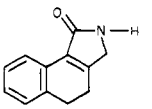
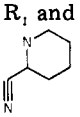
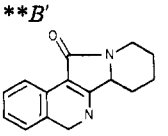
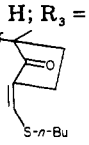
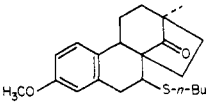
	skeletal type (A, B, or C)	product	(a) reference (b) yield (c) reaction conditions (d) comments
156.	A skeleton R_1 = H; R_2 = (a)  or (b)  R_3 = CH; R_4 = H	**A' (b) 	(a) *134a (b) 70% (a), 77% (b) (c) boiling *o*-dichlorobenzene (d) 3 in bridge
157.	B skeleton R_1 = H; R_2 = $CH_2C{\equiv}CH$; R_3 = CH; R_4 = H	**B' 	(a) *134a (b) 95% (c) refluxing bromobenzene, 16 h (d) 3 in bridge
158.	A skeleton R_1 = CH_3; R_2 = $CH_2C{=}O$ R_3 = O; R_4 = no substituent	A' A''	(a) *134b (b) 25% (c) 155 °C, 23 h (d) 3 in bridge
159.	A skeleton R_1 = H; R_2 = $CH_2C{=}NOCH_3$ R_3 = N; R_4 = OCH_3	A' A''	(a) *134b (b) 68% (c) 155 °C, 20 h (d) 3 in bridge
160.	B skeleton R_1 = CH_3; R_2 = $CH_2C{\equiv}N$; R_3 = N; R_4 = no substituent	B'	(a) *134b (b) 76% (c) 180 °C, 16 h (d) 3 in bridge
161.	B skeleton R_1 and R_2 form:  R_3 = N; R_4 = no substituent	**B' 	(a) *134b (b) 87% (c) 155 °C (d) 3 in bridge
162.	A skeleton R_1 = H; R_2 = (a) $CH_2CH{=}CH$ (b) $(CH_2)_2CH{=}CH_2$ (c) $(CH_2)_3CH{=}CH_2$ R_3 = CH; R_4 = H	A'	(a) *134a (b) 80% (a and b), 20% (c) (c) 190 °C, 16 h (d) 3 in bridge (a), 4 in bridge (b), 5 in bridge (c)
163.	A skeleton R_1 = H; R_2 = $CH_2CH{=}CH_2$; R_3 = CH; R_4 = H C=O and N exchange positions	A' A''	(a) *134c (b) 79.2% (A'), 16.8% (A'') (c) refluxing toluene, 16 h (d) 3 in bridge
164a. (118)	C skeleton R_1 = OCH_3; R_2 = H; R_3 = H; R_4 = CH_2; R_5 = 		(a) 69 (b) 65% (c) 180 °C, 13 h, *o*-dichlorobenzene/N_2 (d) 4 in bridge

TABLE VII (*Continued*)

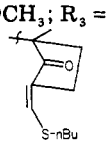
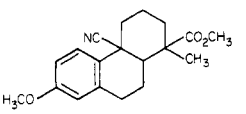
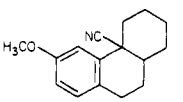
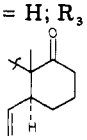
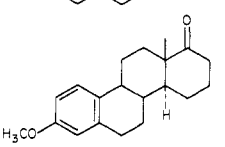
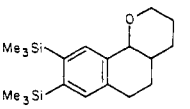
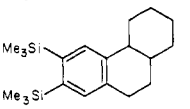
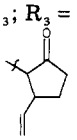
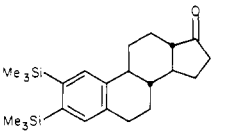
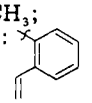
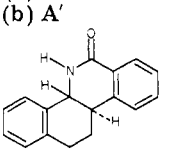
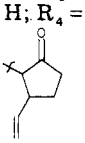
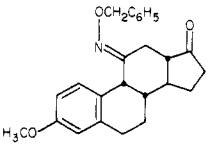
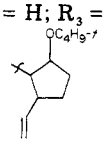
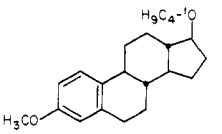
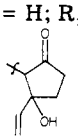
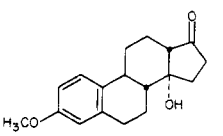
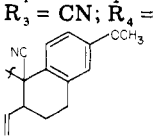
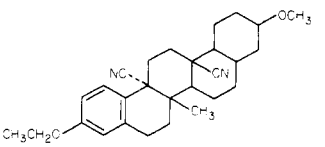
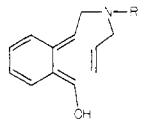
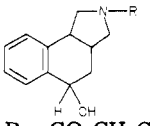
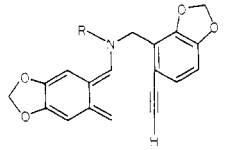
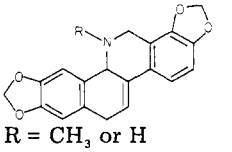
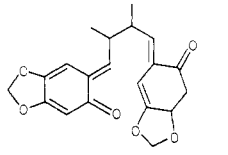
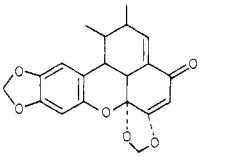
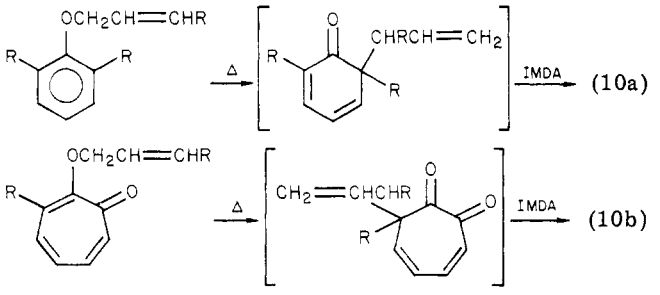
skeletal type (A, B, or C)	product	(a) reference (b) yield (c) reaction conditions (d) comments
164b. C skeleton $R_1 = H; R_2 = OCH_3; R_3 = H;$ $R_4 = CH_2; R_5 =$ 	same as in 164a above except $R_1 = H$ and $R_2 = OCH_3$	(a) 69 (b) 78.9% (c) 180 °C, 6 h, *o*-dichlorobenzene/N_2 (d) 4 in bridge
165. C skeleton (120) $R_1 = OCH_3; R_2 = H; R_3 = CN;$ $R_4 = CH_2; R_5 =$ $C(CH_3)(CH{=}CH_2)CO_2CH_3$		(a) 70 (b) 52% (c) 180-230 °C, 3 h (d) 4 in bridge
166. C skeleton (122) $R_1 = H; R_2 = OCH_3; R_3 = CN;$ $R_4 = CH_2; R_5 = CH_2CH_2CH{=}CH_2$		(a) 71 (b) 80% (c) 180 °C, 6 h, *o*-dichlorobenzene (d) 4 in bridge
167. C skeleton $R_1 = OCH_3; R_2 = H; R_3 = H;$ $R_4 = CH_2; R_5 =$ 		(a) *72a and 72b (b) 95% (c) boiling *o*-dichlorobenzene, 4 h (d) 4 in bridge; *o*-methyl-*D*-homoestrone
168a. C skeleton $R_1 = R_2 = SiMe_3; R_3 = H; R_4 = O;$ $R_5 = CH_2CH_2CH{=}CH_2$		(a) 73a (b) 60% (trans) (c) refluxing decane, 30 h (d) 4 in bridge
168b. C skeleton $R_1 = R_2 = SiMe_3; R_3 = H;$ $R_4 = CH_2; R_5 = CH_2CH_2CH{=}CH_2$		(a) 73a (b) 75% (trans), 5% (cis) (c) refluxing decane, 30 h (d) 4 in bridge
169. C skeleton (127) $R_1 = R_2 = SiMe_3; R_3 = H;$ $R_4 = CH_2; R_5 =$ 		(a) 73b (b) 71% (c) refluxing decane, N_2 (d) 4 in bridge
170. A skeleton R_1 = (a) H; (b) CO_2CH_3; R_2 in both a and b is:  $R_3 = CH; R_4 = H$ N and C=O exchange positions	(a) ***A''* (b) *A'* 	(a) *74a (b) 90% (A''-a), 78% (A'-b) (c) 180 °C (d) 4 in bridge
171. C skeleton $R_1 = OCH_3; R_2 = H;$ $R_3 = H; R_4 = C(NOCH_2C_6H_5)$ $R_5 =$ 		(a) 74b (b) 50% (cis-anti-trans) (c) 140 °C, 6 h, *o*-dichlorobenzene/Ar (d) 4 in bridge
172. C skeleton $R_1 = OCH_3; R_2 = H; R_3 = H;$ $R_4 = CH_2; R_5 =$ 		(a) 75 (b) 84% (c) 180 °C, 3 h, *o*-dichlorobenzene/N_2 (d) 4 in bridge; several steps to estradiol
173. C skeleton $R_1 = OCH_3; R_2 = H; R_3 = H;$ $R_4 = CH_2; R_5 =$ 		(a) 76 (b) 45% (c) 180 °C; 4 h, *o*-dichlorobenzene/N_2 (d) 4 in bridge; synthesis of 14α-hydroxy-estrone
174. C skeleton (130) $R_1 = OCH_2CH_3; R_2 = H;$ $R_3 = CN; R_4 = CH_2; R_5 =$ 		(a) 77a and b (b) 58% (c) 210-215 °C, 3 h, toluene, sealed tube (d) 4 in bridge; related to triterpenoids alnusenone and friedelin

TABLE VII (*Continued*)

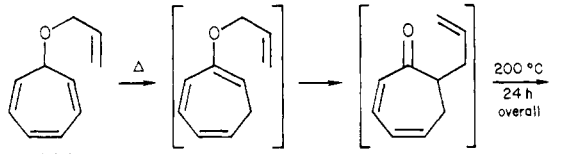
exceptions to skeleton	product	(a) reference (b) yield (c) reaction conditions (d) comments
175.  R = $CO_2CH_2CH_3$	 R = $CO_2CH_2CH_3$	(a) *134d (b) 51.75% (cis), 17.25% (trans) (c) $h\nu$ greater than 300 nm (d) 3 in bridge
176.  R = CH_3 or H	 R = CH_3 or H	(a) *74a (b) 73% (c) 120 °C, 1 h, *o*-xylene (d) 4 in bridge; R = CH_3 for *dl*-chelidonine; R = H for *dl*-norchelidonine
177. 		(a) *135a and b (b) 46% (c) 25 °C (d) 4 in bridge; synthesis of carpanone

F. Claisen Rearrangement Systems

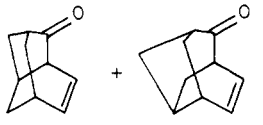
Cyclohexadiene systems are accessible from Claisen rearrangements of the corresponding phenolic ethers, as well as from tropone and tropolone derivatives as indicated in eq 10a and 10b.



Heat transforms these intermediates to a variety of complex tricyclics. Illustrative are the thermal rearrangements of 7-allyloxycycloheptatriene (**111**) which leads ultimately to the tricyclic ketones **112a** and **112b**. Here a series of 1,5 hydrogen



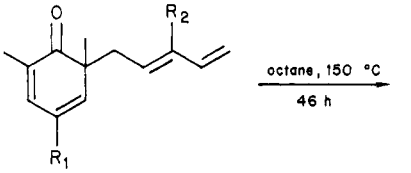
111 111a 111b



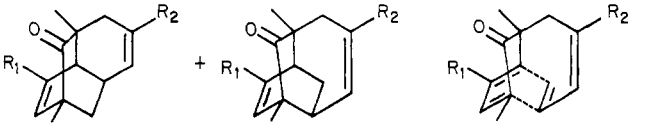
112a (50) 112b (50)

shifts to **111b** must precede the intramolecular reaction, since the products can only be derived from this isomer.[66a,b] It is interesting to note here that the reaction is not regiospecific, as is the case for the corresponding cyclohexadiene system, where, even upon increase of the dienophile bridge length, regiospecificity persists.

On the other hand, this is also not the case when 6-pentadienylcyclohexadienones **113a** and **113b** are cyclized. The kinetic products are **114a–d**. Here there are several IMDA possibilities since in fact either component could react as diene or dienophile. The observed results are explained on the basis



113a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$

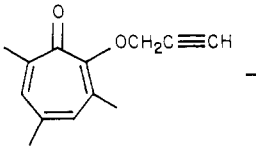


114a (5%) **b** (15%) **114c** (35%) **d** (44%) **115**

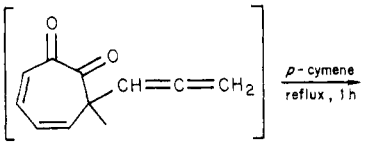
that there is least perturbation of the butadienyl π system in the transition state **115**.[67]

Product **114a** could in principle be obtained from the reaction path in which the cyclohexadienone acts as dienophile. This pathway should be energetically favored. As the authors point out, the question could possibly be resolved through the use of optically active dienone **115**, since the two pathways would essentially lead to enantiomeric structures.

A final example indicates the unusual synthesis of the barbaralane skeleton via the IMDA of the troponoid allene **116a**.[68]



116



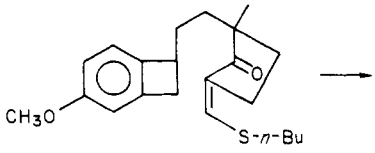
116a **117** (80%)

G. *o*-Quinodimethanes

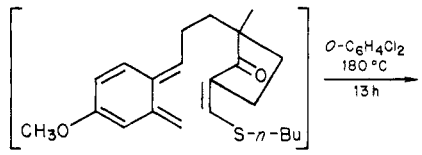
Considerable new work has appeared on the synthetic applications of *o*-quinodimethanes, generated thermally from in-

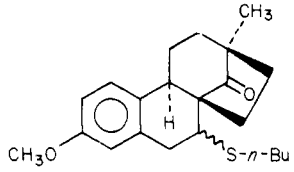
termediate benzocyclobutenes, in the IMDA reaction. Thus, reports have appeared describing the synthesis of diterpenes, diterpene alkaloids, and steroids and approaches to pentacyclic triterpenes.

The carbon skeleton of hibaeol has been prepared stereospecifically from **118**.[69]



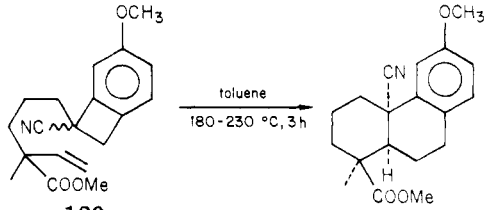
118





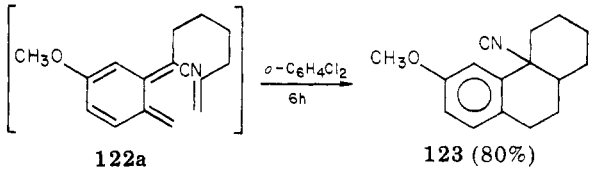
119 (65%)

A related synthesis with a bridgehead cyano group in **120** produces the diterpenoid alkaloid intermediate **121**.[70]

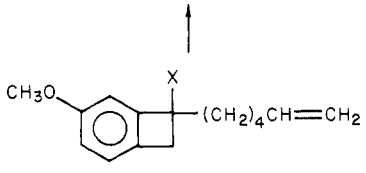


120 **121** (40-50%)

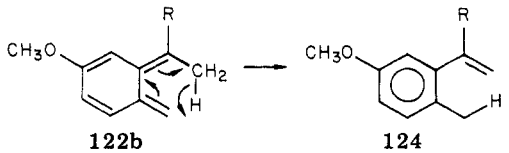
The subtleties involved in the introduction of angular substituents are well illustrated by a related study on the potential cyclization of **122**. Except for the case where X = CN, the competitive [1,5] sigmatropic hydrogen migration predominates as in **122b** and styrenes are formed instead.[71]



122a **123** (80%)



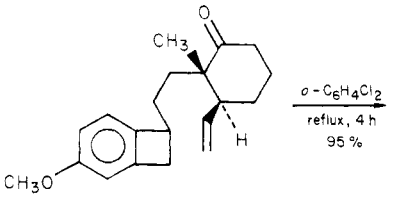
122, X = CN, CH_2CN, CH_3



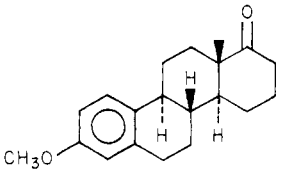
122b **124**

Considerable effort has gone into the application of this pathway to steroid synthesis. The initial targets, of necessity, were the aromatic steroids, estrone and estradiol.

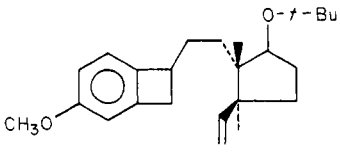
Initial difficulties in coupling the desired synthons led to a synthesis of *D*-homoestrone via **125**.[72] However, a novel alternative approach to the same intermediate via the cobalt-complex-catalyzed oligomerization of **126** and TMSA leads to **127**, which can be isolated or cyclized in situ to **128**.[73a,b] Notable in these and related cases is the stereoselective formation of the trans,anti configuration. In order to achieve a cis B–C ring juncture, change of hybridization at C-11 from sp^3 to sp^2 is required.



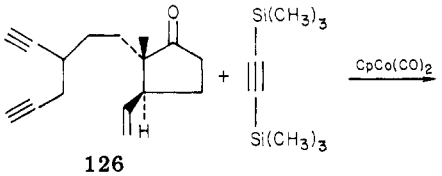
125



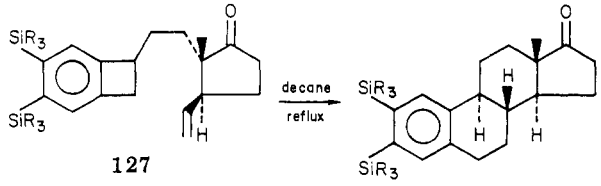
D-homoestrone methyl ether



129

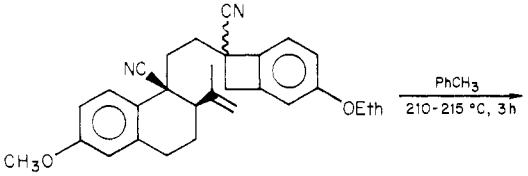


126

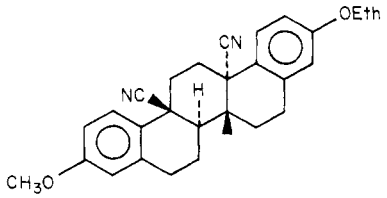


127 **128** (71%)

Estradiol diether is formed quite readily from **129**;[75] 14α-hydroxyestrone methyl ether has been prepared by an analogous route as well.[76] Extension of the method to the pentacyclic triterpenoid skeletons has also been reported. An inital intermolecular–intramolecular bis addition of isoprene to a bis-benzocyclobutene failed. However a separate synthesis of the partially cyclized intermediate **130** gave the desired product stereoselectively in respectable yield.[77] The product **131** is related to the pentacyclic triterpenoids alnusenone and friedelin.



130



131 (58%)

Since it is not possible to discuss all known IMDA reactions at this point, additional examples may be found in the Tables I–VII.

IV. Structure and Reactivity

As is evident from the previous discussion and the tables, most major classes of dienes and dienophiles have been investigated in the IMDA.

Of the various dienic systems reported thus far, perhaps the least explored are the endo,exo dienes. Anthracene, naphthalene, and related aromatic systems have also seen only limited use. On the other hand, acyclic dienes, endocyclic dienes, styrenes, and *o*-quinodimethanes have seen extensive use.

Does the IMDA confer significant advantages over the corresponding intermolecular reaction? From the available data one must conclude that, in spite of the entropic assistance available in the IMDA, no intramolecular reactions have been reported for systems which will not react intermolecularly.

A good case in point is the reaction of furan and its derivatives. While a number of substituted furans, such as 2-methylfuran or furfuryl alcohol and its derivatives, do react more or less readily with active dienophiles such as maleic anhydride,[78] others, such as furfural and methyl furoate, will not react, even under the very favorable conditions of ultrahigh pressure (15 kbar) and room temperature.[79] Neither are the intramolecular reactions of **54a,b** successful.

If we examine the dienophilic contributions to the reaction, an advantage is seen in the IMDA of unactivated structures such as **8**, **33**, **40**, **42**, **44**, **63**, **67**, **122**, **125**, **130**, and others. The corresponding intermolecular reactions occur in generally poorer yields.[78] An instructive comparison is the bimolecular reaction of geraniol with cyclopentadiene, which yields an adduct in only 4% yield after 48 h at 170 °C. The corresponding IMDA, shown in eq 1, is virtually quantitative under identical conditions.[9,80]

One of the most striking observations in the IMDA is the fact that considerable strain can be accommodated in the product. Of course this is in part a reflection on the kinetically controlled pathway which is generally observed. Compounds such as **35**, **36**, **47**, **54**, **64a,b**, and **91** can be cited as examples. Strain energies have been estimated for some of these compounds and are on the order of 12 kcal/mol for **35**,[81] 37.7 kcal for **64a**,[12] and 55 kcal for **91**.[55] Thus, even substantial ring strain does not appear to be a deterrent to the IMDA.

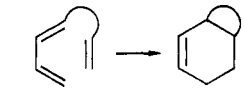
It is therefore of considerable interest to note that strain in medium rings, which is presumably primarily due to nonbonded and transannular interactions, may have a major influence on the success or failure of an IMDA. The strain energies for medium-size rings are known (maximum ~14.6 kcal/mol) for C_9 and C_{10}.[82] These strain energies are certainly within the range quoted above for known strained IMDA products. It is an experimental fact, however, that very few IMDAs have been reported with bridge sizes greater than three or four atoms (C, N, O). In fact, the exceptions are **37** (12 atoms), **58** (n = 3) (5 atoms), and (in Tables I–VII) **35**, **61f**, **63**, **95**, **97**, **162c** (5 atoms), and **36** (10 atoms).

In model studies deliberately designed to give maximum opportunity for an IMDA with longer chain lengths, as in **46**, there was no indication of any product in the range n = 5–12. Since the strain occasioned by nonbonded interactions in the products seems insufficient to account for this finding, we believe that the nonbonded interactions are nevertheless sufficient to prevent the initial approach of the diene to the dienophile prior to the formation of the transition state.

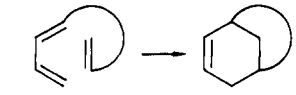
We conclude that the structural limitations previously uncovered in the intermolecular Diels–Alder reaction still hold for the IMDA, but that improved yields may be obtained, especially for the reaction of unactivated dienophiles.

V. Regioselectivity

The question of regioselectivity in the IMDA has been inadequately explored up to this point. We refer here of course not to the selectivity involved in an exo–endo sense, but rather addition in a quasi "ortho" or "meta" sense, as in **132** and **133**.



132



133

Few of the systems reported so far appear to have even the minimal bridge length requirements for structures of type **133** and, as has been pointed out in the previous section, chains longer than three or four atoms apparently do not react. Nevertheless, especially in bridged systems such as **64c**, the possibility for a "meta" type product exists, although it is not found in the unsubstituted system (note, however, **35**, **36**).

On introduction of a carbonyl group in the bridge, however, such as in **113a,b**, this type of product is indeed found, and in fact is favored over the "ortho" adduct. On increase of the dienone ring size to seven, the reaction becomes unselective and **112a** and **112b** are formed in equal amounts. Inclusion of nitrogen in the diene system as in **69** does not change this picture.

o-Quinodimethanes, such as those derivable from **120**, **122**, **125**, and **130**, could conceivably form regioisomers, but the transoid arrangement of the connecting chain certainly makes this very unlikely and, in fact, no regioisomers are observed.

We note finally the special cases involving natural products, such as **72**, **74**, **75**, and **99a**. Here models suggest the possibility of regioisomers, yet none have been reported. Since the starting materials are quite complex, however, the possibility of the formation of a small amount of regioisomers can probably not be excluded.

The most clearcut example of regioselectivity is the formation of the macrocyclic lactones **38** and **39**.

Recently, frontier molecular orbital theory has been applied with considerable success to the problem of regio- and stereoselectivity in pericyclic reactions including the Diels–Alder reaction.[83] In particular, the qualitative predictive value of FMO has been verified for over 100 Diels–Alder reactions.[84]

Application of this method to some of the intramolecular reactions discussed in this review gives the following results.[85] Thus, for compounds of type **55**, **71**, **113**, and **73a** (with dihydropyridine moiety acting as diene) using standard Hückel parameters, the observed major orientation is predicted. Furthermore, the lack of reactivity of **29** and **30** is also predicted because the preferred frontier orbital interaction is sterically unlikely.

Before we can conclude, however, that this method is generally valid, one should note that the method does not predict the observed product from **73a** when the dihydropyridine moiety is reacting as a dienophile. Application to the macrocyclic systems **37** shows that the product formed in the lesser amount is actually the preferred initial product. Finally there is no indication that the two orientations observed in equal yield from **111** could be expected. The preferred product, based on FMO calculations, is **112a**. Of course it is not clear whether the products reported in these cases are the kinetic products, a prerequisite for the application of these calculations.

A question which remains unanswered is the application of the method to cases where the main frontier orbital interactions

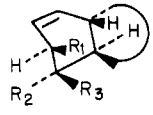
are disallowed due to steric interference. In any case, the method does appear to have some validity and predictive value for IMDAs as well, even though success or failure, as well as any quantitative conclusions, is as yet unwarranted.

VI. Stereochemistry

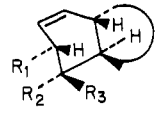
Probably the most attractive feature of the IMDA is the opportunity to control the stereochemistry of the products at four centers or even more, if substitutents in the bridging chain are considered.

We consider first the formal exo–endo addition mode.

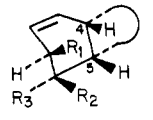
Starting with a defined geometry for the diene and dienophile, we can derive the stereochemistry of the developing centers, provided the mode of addition (exo–endo) is known or predictable. The possible modes of addition and their stereochemical consequences are illustrated in structures **134a** through **137b**.



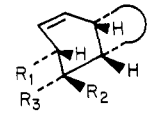
cis,trans, **134a** "exo"



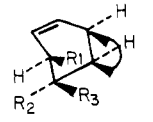
trans,trans, **134b** "exo"



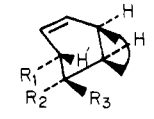
cis,trans, **135a** "endo"



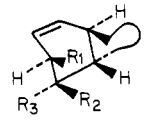
trans,trans, **135b** "endo"



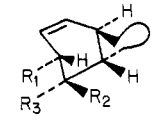
cis,cis, **136a** "exo"



trans,cis, **136b** "exo"



cis,cis, **137a** "endo"



trans,cis, **137b** "endo"

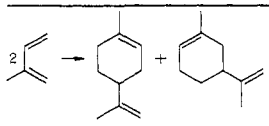
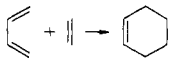
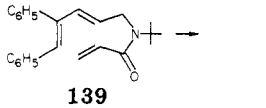
From these diagrams it may be seen that exo addition of a trans-oriented side chain (relative to the diene) leads to trans-fused ring systems, as in **134a,b**, which is also true of endo addition for a cis-oriented chain, as in **137a,b**. Conversely, endo addition of a trans chain leads to cis-ring fusion (**135a,b**) as does the addition of a cis chain in the exo mode (**136a,b**).

Naturally, depending on the nature of the diene, not all configurations are allowed. Thus, 1-substituted cyclohexadienes as well as cyclopentadienes and related heterocycles like furan cannot utilize configurations **136** and **137**.

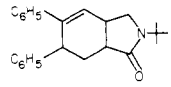
Further conclusions, previously noted,[3] suggest that the endo-cis modes (**137a,b**) are rather strained, and therefore make the exo addition modes more likely. Further inspection of structures **135a,b** also suggest an eclipsed arrangement along the developing bond between atoms 4 and 5, again favoring an exo addition mode, rather than the generally preferred endo mode noted in intermolecular reactions.

In fact, of the several examples reviewed here, **9**, **10**, **41**, **45**, **48**, **56**, **60**, **72**, **74**, **75**, **89a,b**, **100**, **101**, **125**, **128** and **130** all are exclusively exo products. Endo addition is noted exclusively or at least to some extent in examples **4**, **15**, **16**, **21**, **22**, **26**, **31**, **38**, **66b** and **68b**. All of these examples have in common the presence of a carbonyl group in the bridge, and provide additional clearcut examples of the dramatic directional effect which an sp^2 substitution on the bridge can exert on the steric outcome.

TABLE VIII

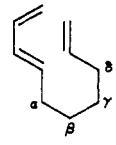
reaction	$\Delta G^{\ddagger}$, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	P, atm	ref
	33.0	18.8	−41.0	1	87
	29.2	21.7	−22.0	8140	87
	27.5				86
	25.3	2.10	−14.4		88

139



The presence of other substituents on the bridge has less obvious effects. Thus, increasing the bulk of an OH substituent in the side chain of **5** by forming its dimethyl-tert-butylsilyl ether did in fact produce a modest increase in product **7**.

If we consider what has been reported for substituents in the positions α–δ indicated in structure **138**, we observe the following results. On examining the stereochemistry of the side-chain group relative to the nearest bridgehead group, we find a consistent preference for a cis relationship, as exemplified by **10** (β), **14** and **15** (α), **21** (α), **25** and **26** (δ), **121** (δ) and **128** (δ). These results are at least indicative of a possible trend.



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VII. Thermodynamics

Since the Diels–Alder reaction is basically an exothermic reaction,[86] we are primarily interested in the changes that occur in the activation parameters on transition from an inter- to an intramolecular reaction. Unfortunately, no data are available for closely parallel systems, and we must base the comparison on more general models.

Preliminary thermodynamic data are available on the interesting reaction depicted in eq 5, **33** → **35**, but the activation parameters have not yet been determined.

As a basic system for an intramolecular reaction we will cite the dimerization of isoprene to dipentene (Table VIII, eq 1). While this is not the simplest system, it does represent the case of an unactivated dienophile reacting with a relatively inert diene. Further the reaction has been studied in some detail. The activation parameters for this reaction and other systems to be discussed are given in Table VIII.

It will be noted that the free energy of activation is rather high, even more so than the classic reaction of butadiene with ethylene. Also, as expected, the entropy of activation is rather negative, reflecting the highly ordered transition state.

If we compare the activation parameters for structure **139**, we see that the principal change in parameters is the change in entropy, which is less negative by a substantial amount. The free-energy change, compared to the butadiene–ethylene value, is not very dramatic.

It is also interesting to note here the well-known effect of

pressure on the Diels–Alder reaction. No instances of pressure applied to IMDA reactions have been reported so far. However, we note that the effect of approximately 8000 atm simulates the effect of intramolecularity in the isoprene system by approximately halving the entropy. The effect of pressure on reactivity, regioselectivity, and stereochemistry is well documented for the intermolecular reaction, and will undoubtedly find application in the IMDA as well.[89]

VIII. Conclusions and Prospects

The intramolecular Diels–Alder reaction has become a most versatile method for the synthesis of polycyclic structures, particularly natural products. Of particular interest is the selective introduction of stereochemistry. However, there are also opportunities to limit the number of possible isomers, compared to the intermolecular reaction, by the selective coupling of reactants. The synthesis of alkaloids and steroids, in particular, should be facilitated by the use of this approach.

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